Syntheses of 2-(3,4-Dimethoxyphenyl)ethylamine Derivatives and Their Antiulcer Activities

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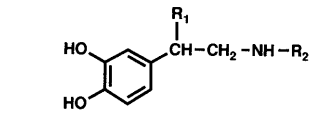
A series of acyl derivatives of 2-(3,4-dimethoxyphenyl)ethylamine (4) were synthesized and evaluated for their effectiveness to prevent water-immersion stress-induced gastric ulceration when given intraperitoneally to rats. Among them *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-phenylaminoacetamide hydrochloride (15) had significant antiulcer activity. Further modification of the four parts of 15 revealed that only the introduction of a carbamoyl group into 2- or 3-position of the phenylamino part gave compounds (49—51, 54 and 55) which retained antiulcer activity comparable to the lead compound. However, the compounds (49—51 and 54) did not exert a prophylactic effect when administered orally except for the 3-substituted bezamide derivative 55. Alkyl substitution on the nitrogen of benzamide gave 3-[[[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]amino-*N*-methylbenzamide (66, DQ-2511) and the related compounds (67, 70, 74 and 77) which all had potent antiuler activities at oral doses of 50—400 mg/kg.

Keywords 2-phenylethylamine derivative; 2-carbamoylphenylacetamide; 3-carbamoylphenylacetamide; benzamide; antiulcer activity; water-immersion stress-induced gastric ulceration; cysteamine-induced duodenal ulceration; rat

On the basis of considerable evidence regarding to the etiology and pathophysiology of peptic ulcer disease, it is generally accepted that peptic ulcerogenesis most likely results from an imbalance between the aggressive gastric secretion and the natural mucosal resistance of the upper gastrointestinal tract against acid peptic injury.[1] Consequently, drugs which can either suppress the gastric secretion or enhance the mucosal defensive factors have been developed and used for therapy of the disease.[2] For example, cimetidine and ranitidine are potent H_2-antagonists[3] and sucralfate enhances mucosal defense (cimetidine: reference drug in this study). In addition, attention has been recently focused on the development of antiulcer drugs with dual effects on gastric secretion and mucosal resistance.

Several neuro-transmitters such as dopamine **1**, epinephrine **2** and norepinephrine **3** have been demonstrated to modulate both the aggressive and defensive mechanisms in the upper gastrointestinal tract, although their precise roles in the pathogenesis of peptic ulcer have not been fully clarified.[4] These neuro-transmitters share the 2-phenylethylamino moiety on their chemical structures (Fig. 1) leading us to design chemical modification of 2-phenylethylamines. We found that *N*-acyl derivatives of 2-phenylethylamines affect gastrointestinal function. Therefore, we



dopamine **1** $R_1=R_2=H$

epinephrine **2** $R_1=OH$, $R_2=Me$

norepinephrine **3** $R_1=OH$, $R_2=H$

Fig. 1

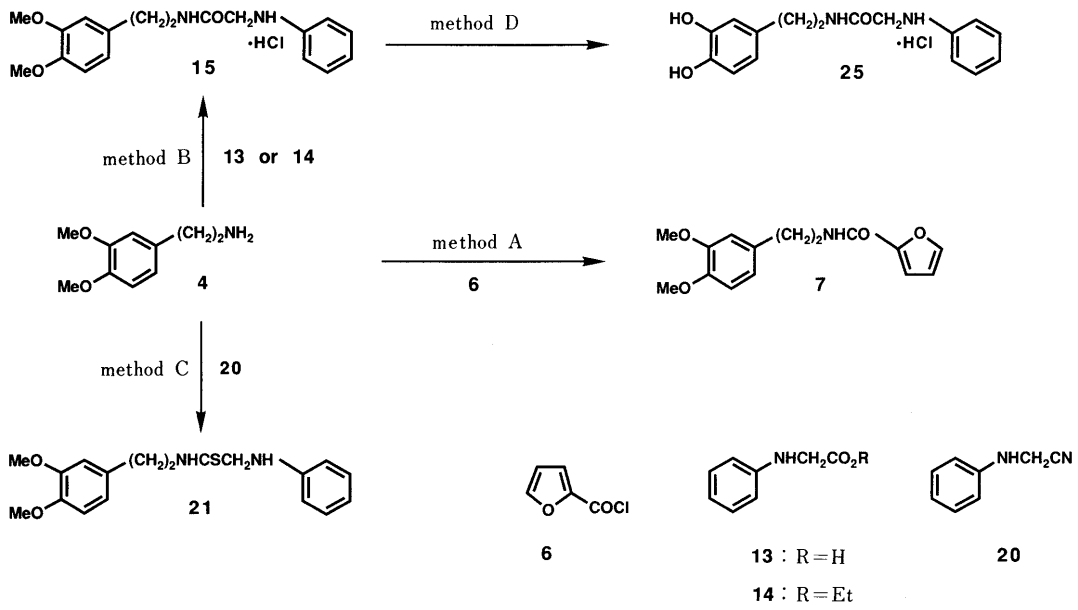
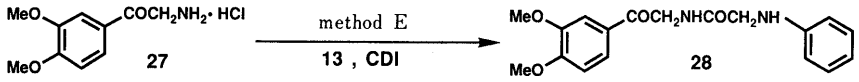


Chart 1



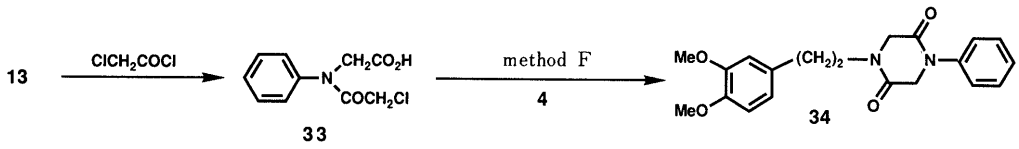


Chart 2

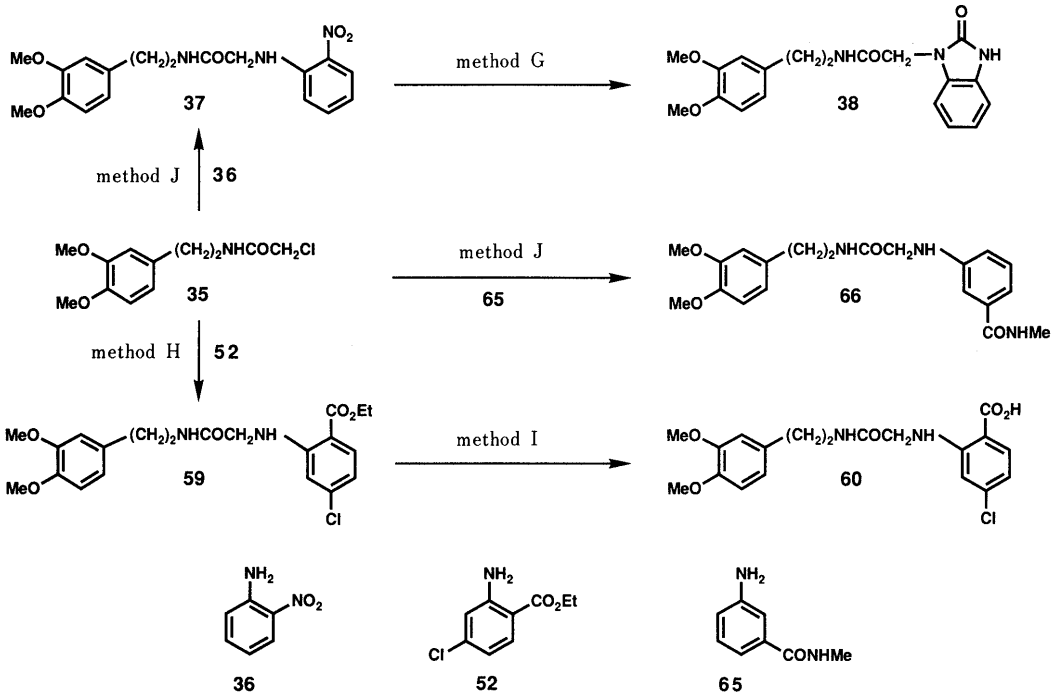


Chart 3

synthesized a series of variously modified amides in order to investigate their properties of antiulcer effect. This paper describes the syntheses of these amides and their antiulcer activities in rats.

Chemistry The synthetic routes to **7**, **15**, **21** and **25** are shown in Chart 1. Compound **7** was synthesized by reaction of amine **4** with furoyl chloride **6**[5] in the presence of triethylamine (Et_3N) in $CHCl_3$ at room temperature (method A). Compound **15** was prepared by fusing a mixture of **4** and either 2-(phenylamino)acetic acid **13** or its ethyl ester **14** at 145 °C under nitrogen (method B). A mixture of **4** and phenylaminoacetonitrile **20**[6] in EtOH saturated with H_2S at 0—5 °C was heated at 100 °C in a sealed tube to give thioamide **21** (method C). Demethylation of **15** with BBr_3 in $CHCl_3$ at −60 °C afforded the dihydroxy derivative **25** (method D).

Chart 2 describes the syntheses of **28** and **34**. The condensation of phenacylamine **27**[7] and **13** in dry tetrahydrofuran (THF) with *N*,*N*′-carbonyldiimidazole (CDI) gave *N*-(phenylcarbonylmethyl)acetamide **28** (method E). The chloroacetyl derivative **33**[8] was prepared by acylation of **13** with chloroacetyl chloride, and the mixture of **4** and **33** was heated at 130 °C under nitrogen to provide the cyclized compound **34**.

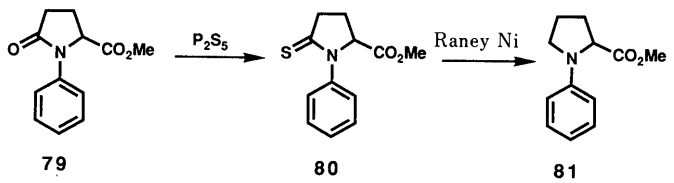


Chart 4

The syntheses of **38**, **59**, **60** and **66** are shown in Chart 3. The nitro compound **37** was catalytically reduced to the amine which was cyclized with trichloromethyl chloroformate (TCF) to afford **38** (method G). Compound **59** was synthesized by melting a mixture of 2-chloro-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (**35**)[9] and ethyl 2-amino-4-chlorobenzoate (**52**) (method H), and hydrolyzed to give the benzoic acid **60** (method I). A mixture of **35**, 3-amino-*N*-methylbenzamide (**65**),[10] NaI, $CaCO_3$ and *N*,*N*-dimethylformamide (DMF) was heated at 50 °C to give **66** (method J).

Ester **81**, which was the intermediate of **32**, was prepared as shown in Chart 4. Thioamidation of pyrrolidone **79**[11]

with P_2S_5 in pyridine afforded **80** which was desulfurized with Raney Ni in boiling 80% EtOH to give **81**.

Pharmacological Evaluation and Discussion

All of the synthesized compounds which are listed in Tables I—V were evaluated for activities against water-immersion stress-induced gastric ulceration when given intraperitoneally or orally to rats.[12]

Table I indicates that the 2-(phenylamino)acetyl derivative of 2-(3,4-dimethoxyphenyl)ethylamine **15** has more potent activity than various other amides (**5**, **7**—**12** and **16**—**19**). The exchange of the carbamoyl group of **15** for thiocarbamoyl caused a drastic decrease in the activity. On the basis of these data, *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-phenylaminoacetamide **15** was selected as the lead compound for further improvement. Structure **15** was divided into four parts (A, B, C and D) as shown in Fig. 2, and each of them was modified systematically to search for more active compounds.

At first, modifications of part A and B were undertaken, and the structures and activities of these compounds are shown in Table II. Compounds **22**—**25** in which the 3,4-dimethoxyphenyl part A was replaced by some other groups were synthesized. Compounds **22**—**25** were ineffective against ulceration. Based on these observations, we selected the 3,4-dimethoxyphenyl group as part A. Compounds **26**, **28** and **30** in which the ethylamino part B was exchanged for various alkylamino groups (methylamino, carbonylmethylamino or *N*-ethyl substituted ethylamino) were inactive. The tetrahydronaphthylamino derivative **29**, in which the conformation of the ethylamino part was restricted, was also inactive. Therefore it was considered that the ethylamino group was the most suitable for part B. The aminoacetyl part C was cyclized to give **31**, **32**, **34** and **38**. They were less effective than **15** (Table III). These results suggested that the introduction of additional cyclic structures into part C was not useful, and that the most desirable structure for moiety A–B–C was the [[[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]amino unit. Consequently, A–B–C moiety of **15** was fixed, and various substituents were introduced into the part D phenyl ring to search for more effective compounds.

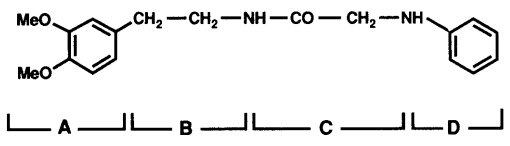
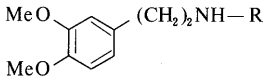


Fig. 2

Table IV shows compounds with variously substituted phenyl groups and their activities when they were administrated intraperitoneally to rats. Many active compounds were obtained by introduction of substituents into the phenyl group. Compounds **49**—**51**, **54**, **55** and **64** bearing a carbamoyl or sulfamoyl group showed especially potent activity. Concerning compounds with a 4-carbamoyl substituted phenyl, a more active compound was not found, and the introduction of additional substituents (chloro or methoxy group) also failed to improve activity. In the case of compounds bearing a carbamoyl group in the 2-position of the phenyl ring, different results were obtained. Compound **48** without additional

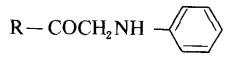
TABLE I. Acyl Derivatives of 2-(3,4-Dimethoxyphenyl)ethylamine and Their Antiulcer Activities (i.p.)

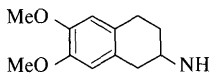


Compd. No.	R	Method[a] (Yield (%))	mp (°C)	Formula	Analysis (%) Calcd (Found)			% inhibition[b]	
					C	H	N	100	200 mg/kg i.p.
5	COC_6H_5	A (76)	85—88	$C_{17}H_{19}NO_3$	71.56 (71.47	6.71 6.60	4.91 4.75)		0
7	CO-2-furyl	A (73)	86—87	$C_{15}H_{17}NO_4$	65.44 (65.58	6.22 6.25	5.09 5.19)	6	
8	CO-2-thienyl	A (80)	104—105	$C_{15}H_{17}NO_3S$	61.83 (61.99	5.88 5.92	4.81 5.04)	3	
9[c]	$COCH_2C_6H_5$	A (77)	102—104	$C_{18}H_{21}NO_3$					−18
10[d]	$COCH_2SC_6H_5$	B (75)	75—76	$C_{18}H_{21}NO_3S$					−0.4
11	$COCH_2CH_2OC_6H_5$	B (35)	77—79	$C_{19}H_{23}NO_4$	69.28 (69.02	7.04 6.93	4.25 4.26)		5
12[e]	$COCH_2NHCOC_6H_5$	B (15)	109—110	$C_{19}H_{22}N_2O_4 \cdot H_2O$				9	
15	$COCH_2NHC_6H_5$	B (52)	160—170 (dec.)	$C_{18}H_{22}N_2O_3 \cdot HCl$	61.62 (61.68	6.61 6.58	7.98 7.92)	42[g]	
16	$COCH_2NH$-2-pyridyl	B (46)	97—98	$C_{17}H_{21}N_3O_3$	64.75 (64.67	6.71 6.75	13.32 13.41)	23	
17	$COCH_2NHC_6H_{11}$	H (63)	203—205 (dec.)	$C_{18}H_{28}N_2O_3 \cdot HCl$	60.58 (60.71	8.19 8.31	7.85 7.90)	−14	
18	$COCH_2$-1-pyrrolyl	B (53)	134—135	$C_{16}H_{20}N_2O_3$	66.65 (66.60	6.99 7.03	9.72 9.66)	−22[f]	
19	$COCH_2$-1-pyrrolidinyl	H (46)	70	$C_{16}H_{24}N_2O_3$	65.73 (65.89	8.27 8.03	9.58 9.40)	−6	
21	$CSCH_2NHC_6H_5$	C (21)	110—111	$C_{18}H_{22}N_2O_2S$	65.43 (65.66	6.71 6.69	8.48 8.46)	7	

a) See text. *b*) Protective activities against 20 h water-immersion stress-induced gastric ulceration in rats ($n=7$). *c*) Known compound.[13] *d*) Known compound.[14] *e*) Known compound.[9] *f*) $p<0.05$, *g*) $p<0.01$ *vs.* control.

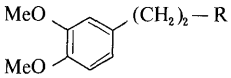
TABLE II. Compounds Obtained by Modification of Moiety A and B, and Their Antiulcer Activities (i.p.)

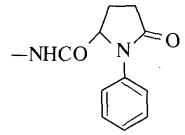
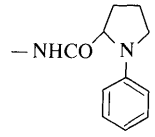
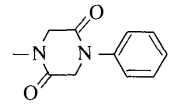
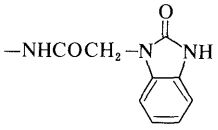


Compd. No.	R	Method[a] (Yield (%))	mp (°C)	Formula	Analysis (%) Calcd (Found)			% inhibition[b]
					C	H	N	100 mg/kg i.p.
22	$C_6H_5CH_2CH_2NH$	B (29)	134—175 (dec.)	$C_{16}H_{18}N_2O \cdot HCl$	66.09 (66.10	6.59 6.57	9.63 9.62)	18
23	$3,4\text{-}(OCH_2O)C_6H_3CH_2CH_2NH$	B (55)	150—160 (dec.)	$C_{17}H_{18}N_2O_3 \cdot HCl$	60.99 (60.73	5.72 5.61	8.37 8.76)	−20
24	$4\text{-}MeOC_6H_4CH_2CH_2NH$	I (48)	83—84	$C_{17}H_{20}N_2O_2$	71.81 (71.39	7.09 7.03	9.85 10.32)	13
25	$3,4\text{-}(OH)_2C_6H_3CH_2CH_2NH$	D (56)	175—182 (dec.)	$C_{16}H_{18}N_2O_3 \cdot HCl$	59.54 (59.20	5.93 6.16	8.68 8.85)	−10
26	$3,4\text{-}(MeO)_2C_6H_3CH_2NH$	H (59)	147—157 (dec.)	$C_{17}H_{20}N_2O_3 \cdot HCl$	60.62 (60.72	6.28 6.37	8.32 8.34)	−1
28	$3,4\text{-}(MeO)_2C_6H_3COCH_2NH$	E (75)	159	$C_{18}H_{20}N_2O_4$	65.84 (66.19	6.14 6.19	8.53 8.33)	1
29		E (29)	107—108	$C_{20}H_{24}N_2O_3$	70.57 (70.69	7.11 7.12	8.23 8.11)	−2
30	$3,4\text{-}(MeO)_2C_6H_3CH_2CH_2NEt$	H (66)	98—99	$C_{20}H_{26}N_2O_3$	70.15 (70.42	7.65 7.64	8.18 8.06)	10

a) See text. *b*) Protective activities against 20 h water-immersion stress-induced gastric ulceration in rats ($n=7$).

TABLE III. Compounds Obtained by Modification of Moiety C and Their Antiulcer Activities (i.p.)



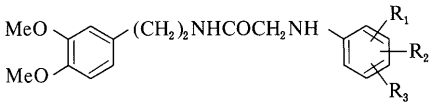
Compd. No.	R	Method[a] (Yield (%))	mp (°C)	Formula	Analysis (%) Calcd			Found			% inhibition[b]
					C	H	N	C	H	N	100 mg/kg i.p.
31		B (41)	121—122	$C_{21}H_{24}N_2O_4$	68.46	6.57	7.60	68.70	6.78	7.74	15
32		B (30)	Oil	$C_{21}H_{26}N_2O_3$	71.16	7.39	7.90	71.03	7.29	8.05	26
34		F (22)	142—143	$C_{20}H_{22}N_2O_4$	67.78	6.26	7.90	67.41	6.15	7.78	15
38		G (67)	198—200	$C_{19}H_{21}N_3O_4$	64.21	5.96	11.82	64.26	6.02	11.75	20

a) See text. *b*) Protective activities against 20 h water-immersion stress-induced gastric ulceration in rats ($n=7$).

substituents was inactive, but many effective compounds were found when further chloro or methoxy groups were introduced into the phenyl moiety. On the other hand, the compound possessing a 3-carbamoyl group was significantly more active without other substituents on the phenyl group. It was discovered that compounds containing 2-, 3- or 4-carbamoyl substituted phenyl had quite different effects against ulceration. Among these benzamide derivatives, **55** was the most effective at an intraperitoneal dose of 100 mg/kg.

Usually antiulcer agents are administered orally for treatment of gastric ulcers, so it is desirable to identify orally active compounds. The intraperitoneally active compounds (**49**—**51**, **54**—**56** and **64**) were examined for their antiulcer effect at oral doses of 100, 200 and 400 mg/kg. In this evaluation only **55** was effective at a dose of 400 mg/kg, and other compounds were entirely devoid of activity. It was then proposed that alkyl substitution (methyl, ethyl, isopropyl, 2-hydroxyethyl group *etc.*) on the ni-

TABLE IV. Compounds Obtained by Modification of Moiety D and Their Antiulcer Activities (i.p.)

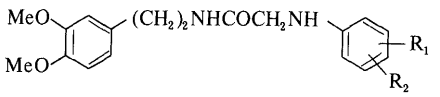


Compd. No.	R_1	R_2	R_3	Method[a] (Yield (%))	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	% inhibition[b] 50	100 mg/kg i.p.
39	2-Cl	H	H	H (44)	68—70	$C_{18}H_{21}ClN_2O_3$	61.98 (61.78	6.07 6.07	8.03 8.03)		22
40	3-Cl	H	H	H (47)	140—160 (dec.)	$C_{18}H_{21}ClN_2O_3 \cdot HCl$	56.11 (56.45	5.76 5.80	7.27 7.40)		36[f]
41	4-Cl	H	H	H (36)	155—165 (dec.)	$C_{18}H_{21}ClN_2O_3 \cdot HCl$	56.11 (56.25	5.76 5.72	7.27 7.25)		25
42	4-F	H	H	H (43)	135—155 (dec.)	$C_{18}H_{21}FN_2O_3 \cdot HCl$	58.62 (58.78	6.01 6.15	7.60 7.72)		20[e]
43	4-MeO	H	H	H (23)	140—163 (dec.)	$C_{19}H_{24}N_2O_4 \cdot HCl$	59.92 (59.67	6.62 6.71	7.36 7.63)		20
44	4-Me	H	H	H (26)	132—145 (dec.)	$C_{19}H_{24}N_2O_3 \cdot HCl$	62.55 (62.68	6.91 7.00	7.68 7.63)		15
45	4-$CONH_2$	H	H	H (16)	155—165 (dec.)	$C_{19}H_{23}N_3O_4 \cdot HCl$	57.94 (57.78	6.14 6.21	10.67 10.61)		20[e]
46	4-$CONH_2$	3-Cl	H	H (45)	175—184 (dec.)	$C_{19}H_{22}ClN_3O_4 \cdot HCl$	53.28 (53.61	5.41 5.42	9.81 9.82)	17	14
47	4-$CONH_2$	2-Cl	5-MeO	H (17)	206—208	$C_{20}H_{24}ClN_3O_5$	56.94 (56.76	5.73 5.76	9.96 10.00)	8	21[e]
48	2-$CONH_2$	H	H	H (58)	149—151	$C_{19}H_{23}N_3O_4$	63.85 (63.61	6.49 6.52	11.76 11.60)	8	12
49	2-$CONH_2$	3-Cl	H	H (32)	171—172	$C_{19}H_{22}ClN_3O_4$	58.24 (58.35	5.66 5.66	10.72 10.73)	22[e]	33[e]
50	2-$CONH_2$	4-Cl	H	H (46)	169—170	$C_{19}H_{22}ClN_3O_4$	58.24 (58.14	5.66 5.55	10.72 10.67)	21	34[f]
51	2-$CONH_2$	5-Cl	H	H,J (29)	168—169	$C_{19}H_{22}ClN_3O_4$	58.24 (58.26	5.66 5.59	10.72 10.70)	18	38[f]
53	2-$CONH_2$	4-MeO	H	H (74)	104—107	$C_{20}H_{25}N_3O_5$	62.00 (61.86	6.50 6.30	10.85 10.80)	20[e]	17[e]
54	2-$CONH_2$	5-MeO	H	H (31)	151—152	$C_{20}H_{25}N_3O_5$	62.00 (61.79	6.50 6.52	10.85 11.12)	30	44[e]
55[c]	3-$CONH_2$	H	H	J (55)	140—155 (dec.)	$C_{19}H_{23}N_3O_4 \cdot HCl$	57.94 (57.64	6.14 6.08	10.67 10.77)	18	53[f]
56[d]	3-$CONH_2$	H	H	J (48)	133—135	$C_{19}H_{23}N_3O_4$	63.85 (63.59	6.49 6.40	11.76 11.71)	8	15
57	3-$CONH_2$	4-Cl	H	H (67)	147—162 (dec.)	$C_{19}H_{22}ClN_3O_4 \cdot HCl$	53.28 (53.27	5.41 5.50	9.81 9.80)	16[e]	35
58	3-$CONH_2$	6-Cl	H	H (71)	166—168	$C_{19}H_{22}ClN_3O_4$	58.24 (58.05	5.66 5.63	10.72 10.52)	8	16
59	2-CO_2Et	5-Cl	H	H (40)	141—142	$C_{21}H_{25}ClN_2O_5$	59.93 (60.06	5.99 6.10	6.66 6.82)		16[e]
60	2-CO_2H	5-Cl	H	I (92)	170—171	$C_{19}H_{21}ClN_2O_5 \cdot 1/2\,H_2O$	56.79 (57.04	5.52 5.39	6.97 6.96)		20
61	3-CO_2Me	H	H	J (45)	118—119	$C_{20}H_{24}N_2O_5$	64.50 (64.73	6.50 6.56	7.52 7.37)		−1
62	3-CO_2H	H	H	I (54)	154—156	$C_{19}H_{22}N_2O_5$	63.68 (63.89	6.19 6.13	7.82 7.64)		1
63	2-SO_2NH_2	5-Cl	H	J (24)	170—171	$C_{18}H_{22}ClN_3O_5S$	50.52 (50.14	5.18 5.20	9.82 9.63)		18[e]
64	3-SO_2NH_2	H	H	J (67)	140—141	$C_{18}H_{23}N_3O_5S$	54.95 (54.92	5.89 6.10	10.68 10.38)		47[e]

a) See text. *b*) Protective activities against 20 h water-immersion stress-induced gastric ulceration in rats ($n=7$). *c*) Hydrochloride of **56**. *d*) Compound **56** showed 56% inhibition of ulceration at a dose of 200 mg/kg. *e*) $p<0.05$, *f*) $p<0.01$ *vs.* control.

trogen of the benzamide unit might give more effective compounds. Table V shows benzamide derivatives and their antiulcer activities at oral doses of 50, 100, 200 and 400 mg/kg. By this modification we obtained several more active compounds (**66**, **67**, **69**—**72**, **74** and **77**), and many of them exhibited potent activity even at a dose of 50 mg/kg. The corresponding nonsubstituted benzamide derivative **55** ($ID_{50}=260$ mg/kg *p.o.*) had merely one fourth of the antiulcer activity of *N*-methylbenzamide **66** ($ID_{50}=63.0$ mg/kg *p.o.*). In general, it was ascertained that the introduction of lower alkyl groups on nitrogen of the benzamide unit gave significant improvement in activity. Comparing the effects of *N*-alkyl substitution (**66**, **67** and **68**), methyl and ethyl substitutions gave better activity than

TABLE V. Benzamide Derivatives and Their Antiulcer Activities (*p.o.*)



Compd. No.	R_1	R_2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	% inhibition[a] mg/kg *p.o.* 50	100	200	400	ID_{50}[b] mg/kg *p.o.*
49	2-$CONH_2$	3-Cl								17	17	16	
50	2-$CONH_2$	4-Cl								2	−7	−2	
51	2-$CONH_2$	5-Cl								2	2	−9	
54	2-$CONH_2$	5-MeO								26	8	9	
55	3-$CONH_2$	H								33	42	60[f]	260 (76.5—911)
56	3-$CONH_2$	H								30	21	39	
64	3-SO_2NH_2	H								−29	30	−15	
66	3-CONHMe	H	51	93—96[c]	$C_{20}H_{25}N_3O_4$	64.67 (64.59)	6.78 (6.83)	11.31 (11.30)	46[f]	60[f]	72[f]	72[f]	63.0 (21.1—188)
67	3-CONHEt	H	45	99—101	$C_{21}H_{27}N_3O_4$	65.44 (65.55)	7.06 (7.17)	10.90 (10.78)	30[e]	53[f]	63[f]	86[f]	97.0 (45.1—209)
68	3-$CONHCHMe_2$	H	35	109—111	$C_{22}H_{29}N_3O_4$	66.15 (65.90)	7.32 (7.30)	10.52 (10.40)	−1	32	38	44[f]	
69	3-$CONHCH_2CH_2OH$	H	72	Glass	$C_{21}H_{27}N_3O_5$	62.83 (63.18)	6.78 (6.87)	10.47 (10.48)	30	59[f]	59[f]	55[f]	140 (53.4—367)
70	3-$CONMe_2$	H	31	Glass	$C_{21}H_{27}N_3O_4$	65.44 (65.08)	7.06 (7.08)	10.90 (10.76)	39[f]	55[f]	64[f]	65[f]	105 (33.3—331)
71	3-CO-R_3[d]	H	70	Glass	$C_{23}H_{29}N_3O_5$	64.62 (64.66)	6.84 (7.02)	9.83 (9.74)	10	53[f]	86[f]	66[f]	136 (70.8—261)
72	2-CONHMe	H	40	123—124	$C_{20}H_{25}N_3O_4$	64.67 (64.56)	6.78 (6.79)	11.31 (11.17)	−5	33	51[f]	63[f]	205 (79.5—529)
73	2-CONHMe	5-Cl	21	128—130	$C_{20}H_{24}ClN_3O_4$	59.19 (59.46)	5.96 (6.04)	10.35 (10.44)	16	31	32	35	
74	2-CONHMe	5-MeO	45	128—129	$C_{21}H_{27}N_3O_5$	62.83 (62.85)	6.78 (6.79)	10.47 (10.35)	33[e]	36[f]	69[f]	71[f]	125 (56.1—279)
75	2-$CONMe_2$	5-MeO	34	106—107	$C_{22}H_{29}N_3O_5$	63.60 (63.78)	7.03 (7.20)	10.11 (10.10)	−49	−96	−33	9	
76	2-CO-R_3[d]	5-MeO	42	78—82	$C_{24}H_{31}N_3O_6 \cdot H_2O$	60.62 (60.91)	6.99 (7.10)	8.84 (8.81)	−9	−24	30	7	
77	2-CONHMe	4-MeO	43	114—116	$C_{21}H_{27}N_3O_5$	62.83 (63.12)	6.78 (6.79)	10.47 (10.43)	45[f]	41[f]	65[f]	72[f]	120 (49.8—289)
78	4-CONHMe	H	64	167—169	$C_{20}H_{25}N_3O_4$	64.67 (64.71)	6.78 (6.79)	11.31 (11.26)	7	24	47[f]	46[f]	
Cimetidine									31	46	74[f]		105 (50.0—221)

Compounds (**66**—**78**) were synthesized by method J. *a*) Protective activities against 7 h water-immersion stress-induced gastric ulceration in rats ($n=7$). *b*) 95% confidence interval is in parentheses. *c*) Recrystallized from MeOH–Et_2O. The isomorphic crystalline forms (mp 130 °C, recrystallized from EtOH–Et_2O) showed almost identical profiles of biological activities. *d*) R_3 = 1-morpholino. *e*) $p<0.05$, *f*) $p<0.01$ *vs.* control.

TABLE VI. Solubilities in Water and the *AUC* of **55**, **56** and **66**

Compound	Solubility (mg/ml) 25 °C	37 °C	*AUC*[a] (h·μg/ml)
55[b]	1.07	2.60	24.08± 3.02
56	0.56	1.08	10.63± 4.75
66	5.31	8.85	43.87±13.57

a) All values are mean±S.D. in rats ($n=7$). *b*) Initially compound **55** dissolved to the extent of 5—10 mg/ml in water at 25 or 37 °C, but the solubility rapidly decreased after 1—2 min because of the formation of the trihydrate of **56**. The solubility was constant at the values shown in the table after 30 min.

isopropyl.

We speculated that the increased activities of these compounds achieved by modifications of the lead compound might result from improvement in their absorption. In order to confirm this, first a comparison of the solubilities of *N*-unsubstituted benzamide **55** (hydrochloride of **56**), **56**[15] and *N*-methylbenzamide **66** was made. The solubility of **66** in water was nine times greater than **56**, and **55** had twice that of **56** (Table VI). It was presumed that this considerable difference in solubilities between these compounds probably causes a large difference in their bioavailabilities. After each of the three compounds **55**, **56** and **66** was given orally to rats, their serum concentrations were monitored over 7 h. The area under the serum concentration *vs.* time curve (*AUC*) of **66** was about four times as much as that of **56**, and **55** had twice the *AUC* of **56** (Table VI). These results showed that the antiulcer effects of these compounds bear close relationships to their bioavailabilities and that improved activities of compounds possessing *N*-alkylbenzamide groups depend on their increased absorption and water solubility. Introduction of alkyl groups on the nitrogen of these benzamides proved useful for the search for more orally absorbable compounds.

It was also found that 3-[[[2-(3,4-dimethoxyphenyl)-ethyl]carbamoyl]methyl]amino-*N*-methylbenzamide (**66**, DQ-2511) was effective to prevent duodenal ulcer formation induced by cysteamine, at an oral dose of 300 mg/kg.[16] According to Szabo's work,[17] dopamine agonists including bromocriptine, lergotrile and apomorphine significantly suppressed cysteamine-induced doudenal ulceration indicating this model of experimental ulcers susceptible to dopaminergic drugs. It has also been reported that DQ-2511 inhibits gastric acid secretion and enhances gastric mucosal defense factors.[16] The precise mechanism of DQ-2511 still remains to be elucidated.

There was no obvious adverse or toxic symptoms observed in preclinical studies with DQ-2511. Anti-gastric ulcer study is in progress in clinical phase II.

Experimental

Chemistry Melting points were taken in open capillary tubes on a melting point apparatus (Yamato Scientific Co., Ltd.) and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-20B (60 MHz) or Hitachi R-40 (90 MHz) instrument using dimethyl sulfoxide-d_6 (DMSO-d_6) or $CDCl_3$ as a solvent and Me_4Si as an internal standard, and spectra of all compounds were consistent with their structures. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; br, broad; d, doublet; dd, double doublets; t, triplet; q, quartet; m, multiplet. Elemental analyses were performed with a Yanaco MT-3 analyzer.

Mathod A. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]furan-2-carboxamide (7) To a mixture of 2-(3,4-dimethoxyphenyl)ethylamine (**4**) (2.7 g, 0.015 mol), Et_3N (1.6 g, 0.015 mol) and $CHCl_3$ (30 ml) was added dropwise 2-furoyl chloride **6** (2.0 g, 0.015 mol) at room temperature. After stirring for 2 h, the reaction mixture was washed successively with 1 N HCl, 5% aqueous Na_2CO_3 and water. The $CHCl_3$ solution was dried and evaporated to dryness. The solid was recrystallized from a mixture of acetone and Et_2O to give 3.0 g (73%) of **7** as colorless crystals, mp 86—87 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.83 (2H, t, J=8 Hz), 3.65 (2H, q, J=7 Hz), 3.85 (3H, s), 3.86 (3H, s), 6.20—6.40 (1H, br), 6.45 (1H, dd, J=2, 4 Hz), 6.78 (3H, br s), 7.06 (1H, d, J=4 Hz), 7.32 (1H, br).

Method B. 2-Phenylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide Hydrochloride (15) A mixture of compound ethyl 2-(phenylamino)acetate (**14**) (1.1 g, 0.0061 mol) and **4** (3.4 g, 0.019 mol) was heated at 145 °C for 12 h under nitrogen. After cooling, the reaction mixture was dissolved in $CHCl_3$ and the solution was washed with 1% aqueous Na_2CO_3, water and dried. The solvent was removed and the residue was dissolved in MeOH containing 10% HCl. The solvent was evaporated and the resulting solid was recrystallized from a mixture of MeOH and Et_2O to give 1.1 g (52%) of **15** as colorless crystals, mp 160—170 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.68 (2H, t, J=8 Hz), 3.10—3.60 (2H, br), 3.77 (6H, s), 3.88 (2H, br s), 6.53—7.55 (8H, m), 8.08—8.51 (1H, br).

Method C. 2-Phenylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]thioacetamide (21) A solution of **4** (4.2 g, 0.023 mol) and 2-(phenylamino)acetonitrile (**20**) (2.7 g, 0.020 mol) in EtOH (10 ml) was saturated with H_2S at 0—5 °C. The mixture was heated at 100 °C in a sealed tube for 8 h, and concentrated to give a brown precipitate. The precipitate was chromatographed on silica gel eluting with $CHCl_3$. The eluate was evaporated and the solid was recrystallized from EtOH to give 1.4 g (21%) of **21** as colorless crystals, mp 110—111 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.72 (2H, t, J=7 Hz), 3.65 (3H, s), 3.69 (3H, s), 3.83 (2H, q, J=7 Hz), 4.05 (2H, s), 6.10—7.20 (8H, m), 8.80—8.33 (1H, br).

Method D. 2-Phenylamino-*N*-[2-(3,4-dihydroxyphenyl)ethyl]acetamide Hydrochloride (25) Compound **15** (30.0 g, 0.086 mol) was dissolved in $CHCl_3$ (500 ml) and washed with 5% aqueous NaOH, water and dried. The solution was evaporated to give 25.7 g of the solid of 2-phenylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide. The solid (19.0 g, 0.060 mol) was dissolved in CH_2Cl_2 (500 ml) and BBr_3 (61.0 g, 0.24 mol) was added dropwise at −60 °C. The solution was then stirred at room temperature for 1 h. The reaction mixture was poured into ice-water and the aqueous layer was separated from the organic layer. The aqueous solution was chromatographed on Amberlite IR120 eluting with 5% HCl. The eluate was concentrated under reduced pressure to give 11.0 g (56%) of **25** as colorless crystals, mp 175—182 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.30—2.82 (2H, br), 3.03—3.60 (2H, br), 3.98 (2H, s), 6.34—6.93 (3H, m), 7.07—7.63 (5H, m), 8.30—8.66 (1H, br).

Method E. 2-Phenylamino-*N*-(3,4-dimethoxyphenylcarbonylmethyl)acetamide (28) To a solution of 2-(phenylamino)acetic acid (**13**) (0.78 g, 0.0050 mol) in dry THF (20 ml) was added CDI (0.96 g 0.0055 mol) at 0—5 °C and the mixture was stirred for 2 h. *N*-(3,4-Dimethoxyphenylcarbonylmethyl)amine hydrochloride (**27**) (0.69 g, 0.0030 mol) and Et_3N (0.30 g, 0.0030 mol) were added to the mixture at −10 °C. After stirring for 1.5 h, the mixture was allowed to stand overnight at 0—5 °C, poured into water and extracted with $CHCl_3$. The extract was washed with 5% aqueous $NaHCO_3$, water and dried. The solvent was distilled off. The residue was chromatographed on silica gel eluting with $CHCl_3$. The eluate was concentrated to dryness and the solid was recrystallized from benzene to give 0.68 g (69%) of **28** as colorless crystals, mp 159 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.85 (2H, s), 3.89 (3H, s), 3.91 (3H, s), 4.00—4.50 (2H, br), 4.71 (2H, d, J=5 Hz), 6.50—7.77 (8H, m).

Method F. 1-[2-(3,4-Dimethoxyphenyl)ethyl]-2,5-dioxo-4-phenylpiperazine (34) A mixture of 2-[*N*-(2-chloroacetyl)-*N*-phenylamino]acetic acid (**33**) (2.0 g, 0.0090 mol) and **4** (3.3 g, 0.018 mol) was melted at 130 °C and stirred for 1 h under nitrogen. After cooling, the reaction mixture was dissolved in $CHCl_3$ and the solution was washed with 1 N HCl, water and dried. The solvent was removed and Et_2O was added to the residue to give crystals which were recrystallized from EtOH to give 0.70 g (22%) of **34** as colorless crystals, mp 142—143 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.89 (2H, t, J=7 Hz), 3.71 (2H, t, J=8 Hz), 3.88 (6H, s), 4.00 (2H, s), 4.30 (2H, s), 6.80 (3H, br s), 7.01—7.55 (5H, m).

Method G. 2-(2,3-Dihydro-2-oxo-1*H*-benzimidazol-1-yl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (38) A solution of **37** (4.8 g, 0.013 mol) in dioxane (100 ml) was hydrogenated in the presence of PtO_2 (0.2 g), and the catalyst was removed by filtration. A solution of Et_3N (2.1 g, 0.020 mol) in dioxane (150 ml) was added to the filtrate, and then TCF (2.0 g, 0.010 mol) was added dropwise to the mixture under cooling in an ice-water bath. The reaction mixture was evaporated to dryness and water was added to the residue. The precipitate was collected and washed with water and Et_2O. The solid was recrystallized from MeOH to give 3.2 g (67%) of **38** as colorless crystals, mp 198—200 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.69 (2H, t, J=7 Hz), 3.15—3.60 (2H, br), 3.85 (3H, s), 3.89 (3H, s), 4.42 (2H, s), 6.62—7.15 (7H, m), 8.23 (1H, t, J=5 Hz).

Method H. Ethyl 4-Chloro-2-[[[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]aminobenzoate (59) A mixture of chloride **35** (2.6 g, 0.010 mol) and **52** (4.0 g, 0.020 mol) was heated at 160 °C with stirring for 5 h under nitrogen. After cooling, benzene was added to the reaction mixture and insoluble material was filtered off. The filtrate was concentrated to dryness. The residue was chromatographed on neutral alumina eluting with a mixture of benzene and cyclohexane (1 : 1), and subsequently with $CHCl_3$. The $CHCl_3$ eluting fraction was concentrated, and the solid was recrystallized from EtOH to give 1.7 g (40%) of **59** as colorless crystals, mp 141—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3 H, t, J=7 Hz), 2.69 (2H, t, J=7 Hz), 3.47 (2H, q, J=7 Hz), 3.79 (6H, s), 3.85 (2H, br s), 4.30 (2H, q, J=7 Hz), 6.40—7.95 (3H, m), 8.07—8.40 (1H, br).

Method I. 4-Chloro-2-[[[(2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]aminobenzoic Acid Hemihydrate (60) Compound **59** (0.37 g, 0.00088 mol) was added to 1 N NaOH (10 ml) and the solution was refluxed for 40 min. After cooling, insoluble material was filtered off. The filtrate was acidified with concentrated HCl and extracted with AcOEt. The organic layer was washed with water and dried. The solvent was removed and the crystals were recrystallized from a mixture of acetone and water to give 0.32 g (92%) of **60** as off-white crystals, mp 170—171 °C. ^{1}H-NMR (acetone-d_6) δ: 2.75 (2H, t, J=7 Hz), 3.51 (2H, q, J=7 Hz), 3.80 (6H, s), 3.99 (2H, br d, J=5 Hz), 6.60—6.98 (5H, m), 8.00 (1H, d, J=9 Hz).

Method J. 3-[[[2-(3,4-Dimethoxyphenyl)ethyl]carbamoyl]methyl]amino-*N*-methylbenzamide (66) A mixture of chloride **35** (68.6 g, 0.27 mol), 3-amino-*N*-methylbenzamide (**65**) (40.0 g, 0.27 mol), NaI (39.9 g, 0.27 mol), $CaCO_3$ (53.8 g, 0.54 mol) and DMF (250 ml) was stirred at 50 °C for 7 h. After cooling, insoluble material was removed by filtration and the filtrate was concentrated. The residue was extracted with $CHCl_3$ and the extract was washed with 5% aqueous Na_2SO_3, brine and dried. The solvent was distilled off. The residue was dissolved in MeOH and concentrated HCl was added. The mixture was concentrated and EtOH was added. The precipitate was collected and washed with a mixture of EtOH and Et_2O (1 : 2) and dried. The filtrate was suspended in CH_2Cl_2 and 10% aqueous Na_2CO_3 was added to make the solution alkaline. The organic layer was separated from the aqueous layer and washed with brine. The organic layer was dried and the solvent was removed. To the residue was added a mixture of MeOH and Et_2O, and the resulting solid was collected. The solid was recrystallized from a mixture of MeOH and Et_2O to give 51.0 g (51%) of **66** as colorless crystals, mp 93—96.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.60 (2H, t, J=7 Hz), 2.72 (3H, d, J=5 Hz), 3.27 (2H, q, J=7 Hz), 3.63 (2H, d, J=6 Hz), 3.69 (6H, s), 5.97 (1H, t, J=6 Hz), 6.49—7.22 (7H, m), 7.76 (1H, br), 8.13 (1H, br).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(2-nitrophenylamino)acetamide (37)** Essentially the same procedure as described in method J was used to prepare **37** from chloride **35** and 2-nitroaniline **36**. Compound **37** was obtained as orange crystals (61%), mp 114 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.74 (2H, t, J=7 Hz), 3.57 (2H, q, J=7 Hz), 3.85 (6H, s), 4.00 (2H, d, J=6 Hz), 6.26—7.70 (7H, m), 8.00—8.48 (2H, br). *Anal.* Calcd for: $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.04; H, 5.90; N, 11.50.

Methyl 1-Phenyl-2-pyrrolidinecarboxylate (81) A mixture of methyl 1-phenyl-5-oxo-2-pyrrolidinecarboxylate (**79**) (6.5 g, 0.030 mol), P_2S_5 (8.0 g, 0.036 mol) and pyridine (50 ml) was refluxed for 1 h. The reaction

mixture was poured into hot water, and the resulting precipitate was collected by filtration. The filtrate was evaporated and the residue was extracted with $CHCl_3$. The solution was washed with water, dried and concentrated to give an oil. The previously obtained precipitate and the oil were combined, chromatographed on silica gel eluting with $CHCl_3$. The eluate was evaporated to give 2.5 g of methyl 1-phenyl-5-thioxo-2-pyrrolidinecarboxylate (**80**) as pale yellow crystals, mp 121—122 °C.

To a solution of **80** in 80% EtOH (200 ml) was added Raney Ni (W-4) (2.0 g) and the resulting suspension was refluxed for 3 h under stirring. The solution was separated from Ni and MeOH (200 ml) was added to the Ni and refluxed. The MeOH solution was separated. The solution was added to the aqueous EtOH solution described above and evaporated. The residue was dissolved in $CHCl_3$ and dried. The solvent was removed to give 2.0 g of an oil. The oil was chromatographed on silica gel eluting with $CHCl_3$ to give 1.3 g (21%) of colorless oil **81**. ^{1}H-NMR (DMSO-d_6) δ: 1.72—2.35 (4H, m), 3.60—3.04 (2H, m), 3.63 (3H, s), 4.00—4.30 (1H, m), 7.32—6.32 (5H, m). *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.87; H, 7.26; N, 7.20.

Pharmacology. Measurement of Antiulcer Activity Male Donryu rats (330—390 g) were used and stress ulcers were induced by the method of Takagi and Okabe.[12] Thirty min after intraperitoneal or oral administration of test drugs, the rats were immobilized in wire cages and immersed into a water bath (21 ± 1 °C) vertically to the level of xiphoid process. They were sacrificed 20 or 7 h after the immersion and the stomach was removed. Each stomach was filled with approximately 10 ml of a 5% formalin solution and immersed in the same solution for 10 to 20 min. The stomach was subsequently opened along the greater curvature and was examined for lesions. The severity of the lesions was quantitated as an ulcer index which was the sum of the length (mm) of each lesion.

Statistical Analysis Statistical significance was assessed using one-way analysis of variance and multiple comparison by Fischer. The Litchfield and Wilcoxon test[18] was used to calculate ID_{50} values and 95% confidence limits for antiulcer effect.

Measurement of Solubility Compound **55**, **56** or **66** was added to 7 ml of distilled water at 25 or 37 °C in a glass-stoppered tube, and then the tube was immediately shaken vigorously for 30 s. The glass tubes were allowed to stand at 25 or 37 °C with vigorous shaking for 30 s at 3 min intervals. After 30 min, an aliquot of each suspension was filtered (0.8 μm pore membrane filter) to obtain a clear solution (*ca.* 0.5 ml). A constant volume of each filtrate was pipetted, and was diluted with distilled water to prepare sample solutions of spectrophotometry. The solubility of each compound was determined by measuring the absorbance at 221 nm using a Hitachi 557 Double Wavelength Double Beam Spectrophotometer, and comparison with a calibration curve.

Measurement of Serum Concentration Male Donryu rats weighing 270 to 340 g were used. All animals were fasted for 24 h prior to drug administration. Each compound was given orally to the animals at a dose of 300 mg/kg as a suspension in a 0.5% aqueous sodium carboxymethylcellulose solution. The blood samples were collected from the tail veins at 1, 4 and 7 h, and centrifuged to obtain a serum sample. To 0.2 ml of the serum were added 1.8 ml of 0.1 M phosphate buffer (pH = 7.0). After the addition of 5 ml of $CHCl_3$ containing 1 μg of internal standard (compound **51**), the mixture was shaken and centrifuged. The organic layer was transferred into another tube and evaporated to dryness under a nitrogen stream at room temperature. The residue was dissolved in 0.2 ml of MeOH and 10 μl of the solution was injected onto the HPLC column. HPLC was carried out on equipment consisting of a Hitachi 635 pump and a variable wavelength UV-VIS detector. A reversed-phase column, 150 × 4.0 mm i.d., packed with Nucleosil $_5C_{18}$ (Machrey-Nagel), and 50% MeOH as an eluent were used for chromatographic analysis. The flow rate was 1.0 ml/min and the detector was set at 277 nm. The *AUC* was calculated by the trapezoidal rule.

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