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A Novel Class of Antiulcer Agents. 4-Phenyl-2-(1-piperazinyl)quinolines

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The synthesis of a novel class of antiulcer agents, the substituted 4-phenyl-2-(1-piperazinyl)quinolines, and their pharmacological activities (inhibitory effects on hypothermia induced by reserpine and on gastric ulcers induced by stress or ethanol) are described. These compounds can be classified into three groups (a group predominantly effective on the stress-induced ulcer, one effective on both the stress- and ethanol-induced ulcers, and one selectively effective on the ethanol-induced ulcer), with regard to antiulcer activity. The inhibitory effect on stress-induced ulcer was found to be in close relation to the antagonism of hypothermia. The structure–activity relationships in these compounds are described. Among the compounds, 2-(4-ethyl-1-piperazinyl)-4-phenylquinoline dimaleate (9, AS-2646) showed a potent inhibition of stress-induced ulcer and gastric acid secretion, possively through action on the central nervous system, and it was selected for clinical evaluation.

Keywords antiulcer agent; anti-stress ulcer activity; gastric antisecretion; anti-reserpine activity; 4-phenyl-2-(1-piperazinyl-quinoline; 2-(4-ethyl-1-piperazinyl)-4-phenylquinoline dimaleate

It is generally believed that peptic ulcer results from an imbalance between acid and pepsin on the one hand, and mucosal resistance on the other. In the past decade, many antisecretory agents, such as histamine H_2-receptor antagonists, selective muscarinic M_1-receptor antagonists, and H^+/K^+-adenosine triphosphatase (ATPase) inhibitors, have been introduced for the therapy of ulcers or are undergoing clinical trials. These agents exert their effects at peripheral sites.

On the other hand, some antidepressants have recently attracted interest in this field,[1] because these centrally acting agents have been found to show antiulcer activity in experimental models and in clinical studies, as exemplified by the tricyclic antidepressants, desmethylimipramine,[2] trimipramine,[3] imipramine,[4] doxepine,[5] and mianserin.[6] Some of them possess gastric acid antisecretory activity. These agents seem to exert their antiulcer or antisecretory effects through a central mechanism, which remains to be fully elucidated. Lippmann and Seethaler suggested that the blockade of norepinephrine (NE) reuptake correlates with the inhibition of gastric secretion and reserpine-induced ulcer.[7] Alhaider *et al.* suggested that the reversal of reserpine-induced hypothermia correlates with the inhibition of NE reuptake in a series of 2-substituted 4-phenylquinolines.[8] We have previously reported some 4-phenyl-2-(1-piperazinyl)quinoline derivatives, which showed antidepressant-like activity in animal tests.[9] Among these compounds, the N-ethyl derivative (**9**) has a pharmacological profile similar to that of tricyclic antidepressants, with a potency stronger than that of imipramine.[10] These compounds may exhibit practically useful antiulcer and/or gastric antisecretory effects.

This paper describes the synthesis of new derivatives of 4-phenyl-2-(1-piperazinyl)quinoline, having various substituents on the terminal piperazine nitrogen and especially on the 4-phenyl group, and their antiulcer effects (preventive activities against two types of ulcer induced by restraint and water-immersion stress and by ethanol), along with their antagonistic effect on hypothermia induced by reserpine. The structure–activity relationships for these compounds are also described. Among the compounds, 2-(4-ethyl-1-piperazinyl)-4-phenylquinoline dimaleate (**9**, AS-2646) was selected for clinical evaluation as a promising potential antiulcer agent.

Chemistry

The synthetic scheme is outlined in Chart 1. Catalytic hydrogenation of 2-nitrobenzophenones (**1b**, **c**, **e**), followed by acetylation with acetic anhydride (Ac_2O) and sodium acetate (NaOAc), gave the 2-acetylaminobenzophenones (**4a**—**c**, **e**) in more than 80% yield (procedure A). Analogous compounds (**4d**, **f**, **g**) were prepared by the Grignard reaction of 2-methyl-4*H*-3,1-benzoxazin-4-one with the substituted phenyl bromides (**3d**, **f**, **g**) (procedure B), but the yields were not satisfactory. According to the synthetic route described previously,[9] **4a**—**g** were cyclized to the 4-phenylcarbostyrils (**5a**—**g**) (Table I) with sodium methylate ($NaOCH_3$). The chlorination of **5a**—**g** with thionyl chloride ($SOCl_2$) and *N*,*N*-dimethylformamide (DMF) in chloroform ($CHCl_3$) at 50 °C for 30 min, easily afforded **6a**—**g** (Table I) in 86—99% yield. This method of chlorination seems to be more advantageous than that employing phosphorus oxychloride,[9] especially in a large scale preparation, because of the low reaction temperature and short reaction time. The aminolysis of **6a**—**g** with various piperazines (procedure C) afforded the target compounds (**7**—**31**) (52—97% yield), among which some compounds were obtained by subsequent alkylation of the terminal piperazine nitrogen (procedure D) (Table II). In this study, compound **9**, previously reported as AD-1308[9,10] (dihydrochloride), was converted into the dimaleate salt with a new registration number (AS-2646) because of the hygroscopic character of AD-1308.

Pharmacological Results and Discussion

Compounds **7**—**31** were examined in mice at the dose of 100 mg/kg, *p.o.* for antagonistic effect on hypothermia induced by reserpine, and the results are summarized in Table II. Among them, **7**—**11** with no substituent on the 4-phenyl group, are known to show potent effects in this test.[9] Introduction of 4-OCH_3, 4-F, or 4-CH_3 onto the 4-phenyl group retained high (**12**—**16**, **24**) to moderate (**18**, **19**, **25**) potency. Compounds having a 4-chloro substituent showed a decreased potency, which ranged from moderate

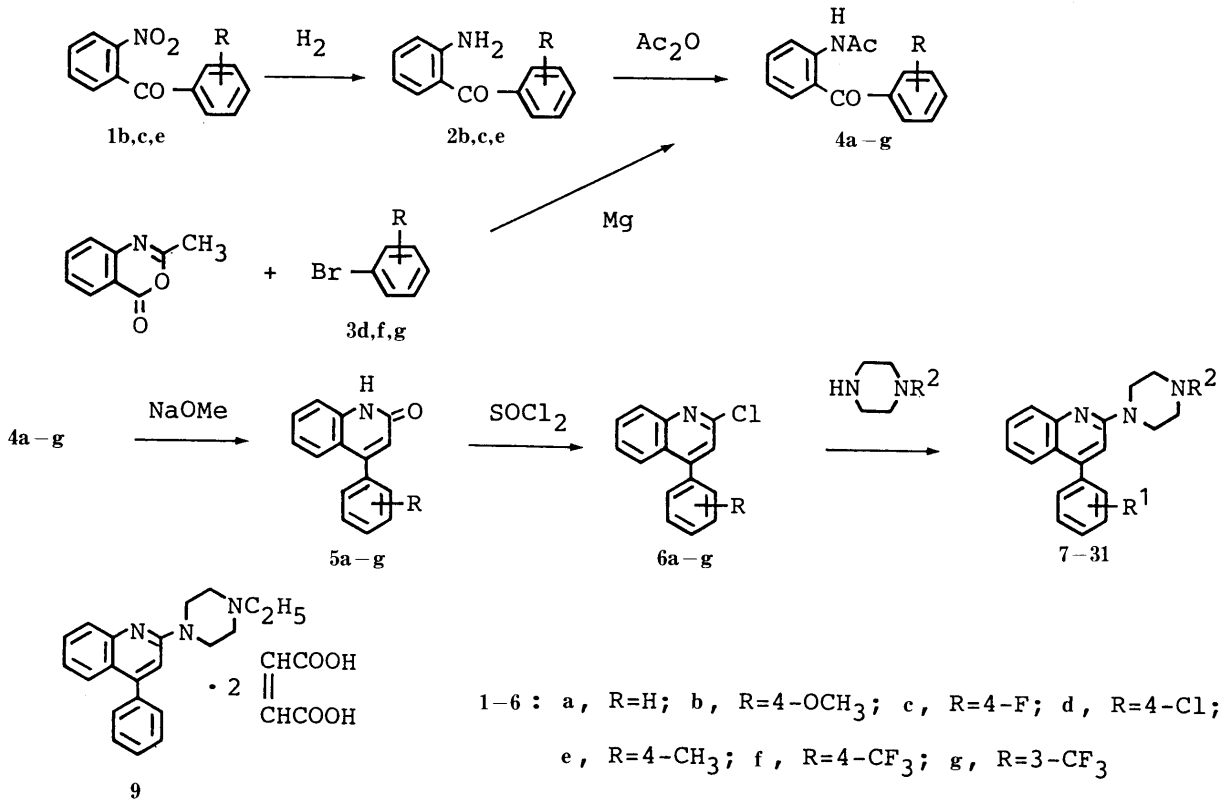
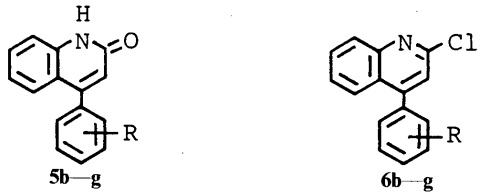


Chart 1

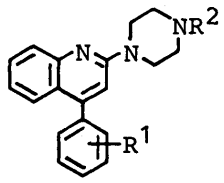
TABLE I. Physical Properties of Intermediates **5** and **6**



Compd.	R	Yield (%)	mp (°C) Solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	Cl	F	N
5b	4-OCH_3	67	239—241[b] EA–H	$C_{16}H_{13}NO_2$	76.48 (76.47	5.21 5.13			5.57 5.45)
5c	4-F	84	247—248 C–E	$C_{15}H_{10}FNO$	75.30 (75.07	4.21 4.25		7.94 7.68	5.86 5.88)
5d	4-Cl	95	250—251 C–E	$C_{15}H_{10}ClNO$	70.46 (70.29	3.94 3.95	13.86 13.79		5.48 5.40)
5e	4-CH_3	72	248—249 C–EA	$C_{16}H_{13}NO$	81.68 (81.87	5.57 5.66			5.95 5.94)
5f	4-CF_3	13[c]	254—255 C–EA	$C_{16}H_{10}F_3NO$	66.44 (66.30	3.48 3.59		19.70 19.89	4.84 4.86)
5g	3-CF_3	18[c]	237 C–EA	$C_{16}H_{10}F_3NO$	66.44 (66.50	3.48 3.64		19.70 19.52	4.84 4.55)
6b	4-OCH_3	91	157—158[d] EA–H	$C_{16}H_{12}ClNO$	71.25 (71.07	4.48 4.33	13.14 13.37		5.19 5.09)
6c	4-F	86	118 E–A	$C_{15}H_9ClFN$	69.91 (70.14	3.52 3.30	13.76 13.78	7.37 7.24	5.44 5.45)
6d	4-Cl	99	148—149[e] C–H	$C_{15}H_9Cl_2N$	65.72 (66.00	3.31 3.22	25.86 25.58		5.11 5.04)
6e	4-CH_3	95	78—79[f] E–H	$C_{16}H_{12}ClN$	75.74 (76.00	4.77 4.92	13.97 13.95		5.52 5.50)
6f	4-CF_3	86	138—139 C–H	$C_{16}H_9ClF_3N$	62.46 (62.52	2.95 3.14	11.52 11.68	18.52 18.26	4.55 4.57)
6g	3-CF_3	95	118—120 C–H	$C_{16}H_9ClF_3N$	62.46 (62.52	2.95 3.14	11.52 11.68	18.52 18.26	4.55 4.57)

a) Recrystallization solvents: EA, ethyl acetate; H, hexane; C, $CHCl_3$; E, Et_2O; A, EtOH. *b*) Lit. mp 235—237 °C.[23] *c*) Yield from the corresponding **3**. *d*) Lit. mp 154—158 °C.[23] *e*) Lit. mp 153—154 °C.[24] *f*) Lit. mp 80—82 °C.[24]

TABLE II. Physical and Pharmacological Properties of 4-Phenyl-2-piperazinylquinolines



7—31

Compd.	R^1	R^2	Proceed[a] Yield (%)	mp (°C) Solvent[b]	Formula	Analysis (%) Calcd (Found) C	H	Cl	F	N	% inhibition[c] RES	SUL[d]	EUL[d]
7[g]	H	H	C 80	178—180 W	$C_{19}H_{19}N_3 \cdot MA$[j]	68.13 (67.98	5.72 5.66			10.36 10.35)	78[h]	72[e,i]	33
8[g]	H	CH_3			$C_{21}H_{21}N_3$						72	85[e]	41
9[g]	H	C_2H_5	C 87	189—190 W	$C_{19}H_{19}N_3 \cdot 2MA$	63.38 (63.51	5.69 5.50			7.65 7.63)	91	90[e,i]	35
10[g]	H	CH_2CH_2OH			$C_{21}H_{23}N_3O \cdot 2HCl \cdot 7/4\,H_2O$						56	56[e]	22
11[g]	H	CH_2Ph			$C_{20}H_{25}N_3 \cdot 1/6\,H_2O$						69	70[e]	NT[k]
12	4-OCH_3	H	C 67	96—98 E–H	$C_{20}H_{21}N_3O \cdot 1/5\,H_2O$	74.37 (74.54	6.68 6.64			13.01 12.97)	72[l]	72[e]	23
13	4-OCH_3	C_2H_5	C 83	184—185 W–M–EA	$C_{22}H_{25}N_3O \cdot 2MA$	62.17 (61.94	5.74 5.53			7.25 7.14)	97	71[e]	38
14	4-OCH_3	CH_2CH_2OH	C 52	163—164 M–EA	$C_{22}H_{25}N_3O_2 \cdot 2MA$	60.50 (60.38	5.58 5.75			7.01 7.09)	81	64[e]	23
15	4-F	H	C 80	139 C–E	$C_{19}H_{18}FN_3 \cdot 1/4\,H_2O$	73.17 (73.22	5.98 6.09		6.09 5.90	13.47 13.23)	87	69[e]	19
16	4-F	CH_3	C 97	210—220 A	$C_{20}H_{20}FN_3 \cdot 2HCl \cdot H_2O$	58.25 (58.03	5.87 5.64	17.20 17.15	4.61 4.68	10.19 10.00)	109	66[e]	19
17	4-F	C_2H_5	D 83	230—235 A	$C_{21}H_{22}FN_3 \cdot 2HCl \cdot H_2O$	59.16 (59.45	6.15 6.23	16.63 16.74	4.46 4.26	9.86 9.93)	48	68[e]	52
18	4-F	CH_2CH_2OH	C 97	210—218 A–EA	$C_{21}H_{22}FN_3O \cdot 2HCl$	59.44 (59.10	5.70 5.65	16.71 16.47	4.48 4.57	9.90 9.84)	66	65[e,i]	80[e]
19	4-F	$(CH_2)_3OH$	D 67	175—177 M–EA	$C_{22}H_{24}FN_3O \cdot 2MA$	60.30 (60.00	5.40 5.38		3.18 3.13	7.03 6.95)	60	62[f]	69[f]
20	4-F	$CH_2C_6H_5$	D 83	154—155 E	$C_{26}H_{24}FN_3$	78.56 (78.29	6.09 6.19		4.78 4.91	10.57 10.60)	45	25	−9
21	4-Cl	H	C 64	185—186 W–M–EA	$C_{19}H_{18}ClN_3 \cdot MA$	62.80 (62.76	5.04 4.90	8.06 8.16		9.55 9.43)	64	66[e]	87[e]
22	4-Cl	C_2H_5	C 65	187—189 W–M–EA	$C_{21}H_{22}ClN_3 \cdot 2MA$	59.64 (59.41	5.18 5.24	6.07 6.08		7.20 6.97)	45	54[e]	89[e]
23	4-Cl	CH_2CH_2OH	C 88	178—180 W–M–EA	$C_{21}H_{22}ClN_3O \cdot 2MA$	58.05 (57.82	5.04 5.12	5.91 6.08		7.00 6.93)	7	36	76[e]
24	4-CH_3	H	C 93	168—169 M–EA	$C_{20}H_{21}N_3 \cdot 2MA \cdot 1/4\,H_2O$	62.27 (62.39	5.51 5.26			7.78 7.77)	114	86[e]	56
25	4-CH_3	CH_2CH_2OH	C 86	169—170 M–EA	$C_{22}H_{25}N_3O \cdot 2MA$	62.17 (62.08	5.74 5.75			7.25 7.28)	51	70[e]	64[e]
26	4-CH_3	C_4H_9	D 50	190 M–EA	$C_{24}H_{29}N_3 \cdot 2MA$	64.96 (64.94	6.30 6.12			7.10 7.16)	27	41[f]	NT[k]
27	4-CF_3	C_2H_5	C 91	182—183 W–M–EA	$C_{22}H_{22}F_3N_3 \cdot 2MA$	58.35 (58.15	4.90 5.00		9.23 8.96	6.80 6.86)	−31	44[f]	57
28	4-CF_3	CH_2CH_2OH	C 81	174—175 W–M–EA	$C_{22}H_{22}F_3N_3O \cdot 2MA$	56.87 (56.69	4.77 4.93		9.00 9.03	6.63 6.62)	7	42[f]	87[f]
29	3-CF_3	H	C 65	159—160 M–EA	$C_{20}H_{18}F_3N_3 \cdot 2MA$	57.05 (57.29	4.45 4.51		9.67 9.50	7.13 7.27)	−14	4	84[f]
30	3-CF_3	C_2H_5	C 58	168—169 M–IP	$C_{22}H_{22}F_3N_3 \cdot 2MA$	58.35 (58.40	4.90 5.15		9.23 9.43	6.80 6.85)	−55	20	64[f]
31	3-CF_3	CH_2CH_2OH	C 67	143—144 M–EA	$C_{22}H_{22}F_3N_3O \cdot 2MA$	56.87 (57.08	4.77 5.07		9.00 9.34	6.63 6.70)	−33	−3	75[f]

a) See the corresponding procedure under Experimental. *b*) Recrystallization solvents: W, H_2O; M, MeOH; IP, isopropyl alcohol. See also footnote *a* in Table I. *c*) RES = inhibitory effect on the reserpine-induced hypothermia in mice at 100 mg/kg *p.o.*; SUL = inhibitory effect on the stress-induced ulcer in rats at 10 mg/kg *p.o.*; EUL = inhibitory effect on the ethanol-induced ulcer in rats at 10 mg/kg *p.o.* *d*) Mean value from five determinations. The homogeneity in variance was verified by the F test. The significance of differences between means was verified by using Student's *t* test. When the variance was not homogeneous, the significance of difference between means was verified by the Aspin–Welch method. *e*) $p < 0.01$. *f*) $0.01 < p < 0.05$ *vs.* respective control value by Student's *t* test. *g*) These compounds have been reported[9]; **7** and **9** were reported as the free base and dihydrochloride, respectively. *h*) Result for the free base. *i*) Drug given at 5 mg/kg. *j*) Maleic acid. *k*) Not determined. *l*) Drug given at 50 mg/kg.

(**21**) to inactive (**23**). On the other hand, interestingly, substitution with 4- or 3-CF_3 resulted in a complete loss of this effect (**27**—**31**).

The effects of **7**—**31** on the ulcer induced by restraint and water-immersion stress (stress-ulcer), and on the ulcer induced by ethanol (ethanol-ulcer), were evaluated in rats at the dose of 10 mg/kg, *p.o.* (Table II). The former ulcer is considered to be caused by the disturbance in brain catecholamine metabolism,[11] and the latter is employed for estimating gastric cytoprotective activity.[12] From the viewpoint of antiulcerogenic effects, most of the compounds could be classified into three groups. The first group of compounds, having a phenyl (**7**—**11**) or 4-methoxyphenyl group (**12**—**14**), showed moderate to potent activity in inhibiting the stress-ulcer and did not show any significant effect on the ethanol-ulcer. Some 4-fluorophenyl derivatives (**15**, **16**) also belong to this group. These compounds characteristically exhibited a potent activity in the reserpine-hypothermia test. The second group of compounds, having a 4-fluorophenyl (**17**—**19**), 4-chlorophenyl (**21**, **22**), or 4-methylphenyl group (**24**, **25**) exhibited approximately similar inhibitory potency on both ulcers. Moderate (**17**—**19**, **21**, **25**) to weak (**22**) effects on the hypothermia were generally observed in this group of compounds. An exception is the highly potent compound **24**. The third group of compounds, represented by the 3-trifluoromethyl-substituted compounds (**29**—**31**), showed a potent effect only on the ethanol-ulcer, in contrast to those of the first group. Compound **23** is included in this group. This group of compounds exhibited no inhibitory effect on the hypothermia. Compounds **27** and **28** seem to be marginal cases that could fit into group 2 or group 3. As an exception to this classification scheme, **20** did not show a potent effect on either type of ulcer. Generally, compounds without a substituent on the terminal piperazine nitrogen showed appreciable antiulcer and anti-reserpine activities, and the introduction of a substituent did not result in significantly more active compounds. An exception is the inactive compound **20**. With regard to the substituents on the 4-phenyl group, compounds in group 1 (stress > ethanol) had 4-phenyl substituents of H, 4-OCH_3 and 4-F (NH and NCH_3 substituents). Compounds in group 2 (stress = ethanol) had 4-phenyl substituents of 4-F (for nitrogen substituents larger than methyl except for benzyl), 4-Cl (for NH and NC_2H_5 substituents) and 4-CH_3 (NH and NCH_2CH_2OH substituents). The compounds in group 3 (stress < ethanol) had a 3-CF_3 and a 4-Cl (for CH_2CH_2OH substituent). Overall, it appears that good activity against stress-ulcer and weak to marginal activity against ethanol-ulcer is associated with an electron-donating or a weakly electron-withdrawing group on the 4-phenyl ring. An electron-withdrawing group increases the activity against ethanol-ulcer and decreases the activity against stress-ulcer. This effect is maximal for the 3-CF_3 group. The inhibitory effect on stress-ulcer correlates with potent to moderate antagonism of hypothermia. Conversely, potent inhibition of ethanol-ulcer correlates with inactivity or a moderate effect on hypothermia.

On the basis of the above results, 2-(4-ethyl-1-piperazinyl)-4-phenylquinoline dimaleate (**9**), which was most effective on the stress-ulcer, was selected for further evaluation, including studies of its effects on the two ulcer models previously discussed and on basal gastric acid secretion in rats. The ED_{50} values calculated in each test are shown in Table III, comparing with those of cimetidine, a histamine H_2-antagonistic antisecretory agent, and imipramine, a tricyclic antidepressant with antisecretory and anti-ulcer effects,[4] as reference agents. In inhibiting the stress-ulcer, **9** showed a marked potency (ED_{50}, 1.2 mg/kg, *p.o.*) and was about 22 and 3 times more potent than cimetidine and imipramine, respectively. At higher dose, **9** was effective on the ethanol-ulcer, which suggested that **9** has some gastric cytoprotective activity.[13] Compound **9** strongly inhibited the acid secretion of pylorus-ligated rats (ED_{50}, 2.8 mg/kg, *p.o.*) and was about 10 and 1.5 times more potent than cimetidine and imipramine, respectively.

TABLE III. Antiulcer and Gastric Antisecretory Activities of **9**, Cimetidine and Imipramine

Compd.	ED_{50} (mg/kg, *p.o.*)		
	Stress-ulcer	Ethanol-ulcer	Gastic acid secretion
9	1.2 (0.4—3.2)[a]	20.5 (10.9—38.4)	2.8 (0.7—12.0)
Cimetidine	26.3 (9.1—75.8)	> 100	27.4 (12.5—59.9)
Imipramine	3.8 (1.6—8.8)	NT[b]	4.1 (2.0—8.5)

a) 95% confidence limits. *b*) Not tested.

As discussed above, **9** and its analogs (**7**, **8**, **10**—**16**, **24**) exhibited marked anti-reserpine activities, which are in close relation to the potent inhibitions of the stress-ulcer. A significant inhibition by **9** of the stress-ulcer seems to be substantially related to its antisecretory activity. On the other hand, Karasawa *et al.* demonstrated that antidepressant-like effects of **9** are mediated through the action of this compound on the brain noradrenergic neuronal system.[10] Considering these findings, it is suggested that the effects of **9** may be accounted for by a central mechanism. This is supported by the facts that 1) when administered intracerebrobentricularly, **9** showed far greater potency (ED_{50}, 0.08 mg/kg) in inhibiting basal gastric acid secretion than when given *p.o.* or i.v.; 2) **9** potently inhibited gastric acid hypersecretion induced by 2-deoxy-D-glucose, a centrally acting secretagogue, and by the restraint and water-immersion stress at low doses (0.5—2 mg/kg, *p.o.* and 0.2—1 mg/kg, i.d., respectively), while higher doses were required to inhibit the hypersecretion induced by peripherally acting secretagogues such as carbachol, histamine and pentagastrin, and by electrical vagus nerve stimulation at the cervical level.[14] Anticholinergic and antihistaminic activities (*in vitro*) of **9** were weak and were about one-sixteenth and one-hundredth those of imipramine, respectively. Details of the pharmacology and mechanism of action of **9** will be published elsewhere.

In conclusion, we have described a novel class of antiulcer agents, the 4-phenyl-2-(1-piperazinyl)quinoline derivatives. Among them, compound **9** (AS-2646) was considered to be of value as a potential antiulcer agent on the basis of its efficient antiulcer and gastric antisecretory activities. It was selected for clinical trials to evaluate its therapeutic usefulness against peptic ulcers.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra were taken with a Varian XL-300 spectrometer with tetramethylsilane (TMS) as an internal reference. Organic extracts were dried over Mg_2SO_4.

2-Acetylamino-4′-fluorobenzophenone (4c) (Procedure A) A mixture of 2-nitrobenzoic acid (46 g, 0.275 mol) and PCl_5 (57.3 g, 0.275 mol) was stirred at 50 °C for 30 min. It was concentrated *in vacuo*, and the residue was dissolved in fluorobenzene (80 ml). To this solution, $AlCl_3$ (55 g, 0.41 mol) was added at 0—10 °C during 1 h. After being stirred for an additional 1 h, the reaction mixture was poured onto ice and water, and extracted with EtOAc. The extract was washed with water, dried and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–hexane (1 : 1), and crystallized from ether–hexane to give **1c** (42.5 g, 63%), mp 111—112 °C, (lit.[15] mp 127—128 °C). *Anal.* Calcd for $C_{13}H_8FNO_3$: C, 63.68; H, 3.29; F, 7.75; N, 5.71. Found: C, 63.83; H, 3.24; F, 7.73; N, 5.52. Compound **1c** (48.6 g, 0.21 mol) was dissolved in EtOH (300 ml) and hydrogenated in the presence of 5% Pd–C (3 g). The catalyst was removed by filtration, and the filtrate was evaporated. The crystalline residue was recrystallized from $CHCl_3$ to give **2c** (39.8 g, 86%), mp 127—128 °C, (lit.[16] mp 124—125 °C). *Anal.* Calcd for $C_{13}H_{10}FNO$: C, 72.55; H, 4.68; F, 8.83; N, 6.51. Found: C, 72.78; H, 4.79; F, 8.93; N, 6.73. Compound **2c** was treated with Ac_2O and NaOAc as described previously[9] to give the acetate **4c** (92%), mp 102 °C ($CHCl_3$–EtOH) (lit.[17] mp 85.5—87.5 °C). *Anal.* Calcd for $C_{15}H_{12}FNO_2$: C, 70.03; H, 4.70; F, 7.38; N, 5.43. Found: C, 70.30; H, 5.00; F, 7.43; N, 5.62. Compounds **1b** and **1e** were similarly prepared. **1b**: 73% yield, mp 86—90 °C (ether–hexane) (lit.[18] mp 94 °C). **1e**: 35% yield, mp 154—155 °C (ether–hexane) (lit.[18] mp 155 °C). Compounds **2b** and **2e** were similarly prepared in quantitative yields except for recrystallization, and the crude materials were used for the next step. Compounds **4a**,[9] **4b** and **4e**, were similarly prepared. **4b**: 89% yield, mp 107—108 °C (ether–hexane) (lit.[17] mp 115.5—118.5 °C). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.37; H, 5.80; N, 5.44. **4e**: 88% yield, mp 117—118 °C (EtOAc–hexane) (lit.[17] mp 113—115.5 °C). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.90; H, 6.02; N, 5.50.

2-Acetylamino-4′-chlorobenzophenone (4d) (Procedure B) 2-Methyl-4*H*-3,1-benzoxazin-4-one was treated with 4-chlorophenylmagnesium bromide, according to the precedure described,[19] gave **4d** (45% yield), mp 134—135 °C (EtOAc–EtOH). *Anal.* Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; Cl, 12.95; N, 5.12. Found: C, 65.87; H, 4.38; Cl, 13.02; N, 4.97. Compounds **4f** and **4g** were similarly prepared and the crude materials were used for the next step.

4-Phenylcarbostyril (5a) (General Procedure) A mixture of **4a** (17.7 g, 0.08 mol), 28% $NaOCH_3$ solution (41 g, 0.24 mol), and EtOH (50 ml) was stirred under reflux for 1 h. The reaction mixture was cooled and poured onto ice and water. The resulting solid was collected and dissolved in $CHCl_3$. The solution was washed with dilute HCl, followed with water, dried, and evaporated. The residue was recrystallized from $CHCl_3$–ether to give **5a**[9] (15 g, 78%). Compounds **5b**—**g** were prepared similarly and the results are listed in Table I.

2-Chloro-4-phenylquinoline (6a) (General Procedure) A mixture of **5a** (11.1 g, 0.05 mol), $CHCl_3$ (20 ml), $SOCl_2$ (7.7 g, 0.065 mol), and DMF (4 ml) was stirred at 50 °C for 30 min. The reaction mixture was cooled and poured onto ice and water. The organic layer was separated, washed with water, dried, and evaporated to give the crystalline residue, which was recrystallized from hexane to give **6a**[9] (11.4 g, 95%). Compounds **6b**—**g** were similarly prepared and the results are listed in Table I.

2-(4-Ethyl-1-piperazinyl)-4-phenylquinoline Dimaleate (9) The preparation of this compound (as the dihydrochloride) by the reaction of **6a** with piperazine followed by ethylation with ethyl iodide, has been described.[9] Another method is as follows (Procedure C): A mixture of **6a** (4.8 g, 0.02 mol) and *N*-ethylpiperazine (6.8 g, 0.06 mol) was stirred at 130 °C for 2 h. The reaction mixture was diluted with water, basified with dilute NaOH, and extracted with ether. The organic layer was washed with water, dried and evaporated. The residual oil was chromatographed on silica gel (10 g) with $CHCl_3$–MeOH (100 : 1). The eluate was treated with a solution of maleic acid in MeOH to form the maleate. Recrystallization from water gave **9** (7.7 g, 70%) (Table II). ^{1}H-NMR (as the free base) (300 MHz, $CDCl_3$) δ: 1.15 (3H, t, J=7.2 Hz, $CH_2\underline{CH}_3$), 2.48 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 2.59 (4H, m, 3- and 5-H of piperazine), 3.81 (4H, m, 2- and 6-H of piperazine), 6.91 (1H, s, 3-H), 7.16 (1H, ddd, J=8.3, 6.9, 1.3 Hz, 6-H), 7.53 (1H, ddd, J=8.4, 6.9, 1.5 Hz, 7-H), 7.62 (1H, ddd, J=8.3, 1.5, 0.6 Hz, 5-H), 7.77, (1H, ddd, J=8.4, 1.3, 0.6 Hz, 8-H), 7.4—7.55 (5H, m, C_6H_5). ^{13}C-NMR (as the maleate) (300 MHz, DMSO-d_6) δ: 155.62 (2), 110.00 (3), 147.35 (4 or 8a), 121.53 (4a), 125.03 (5), 122.29 (6), 129.58 (7), 126.72 (8), 149.42 (8a or 4), 137.75 (1′), 128.51 (2′, 6′), 129.23 (3′, 5′), 128.37 (4′), 50.16 (piperazine 2, 6), 41.92 (piperazine 3, 5), 50.78 ($\underline{C}H_2$), 8.94 ($\underline{C}H_3$), 132.98 (maleic acid $\underline{C}H$=), 166.85 (maleic acid $\underline{C}OOH$). Compounds **12**—**16**, **18**, **21**—**25** and **27**—**31** were prepared similarly (see Table II). Compound **7**, reported previously as the free base, was converted into the maleate in a usual manner (Table II).

4-(4′-Fluorophenyl)-2-[4-(3-Hydroxypropyl)-1-piperazinyl]quinoline Dimaleate (19) (Procedure D) A mixture of **15** (1.23 g, 0.004 mol, as the free base), 3-chloropropyl alcohol (0.38 g, 0.004 mol), Na_2CO_3 (0.42 g, 0.004 mol), and 2-butanone (10 ml) was stirred under reflux for 20 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, dried, and evaporated. The residue was treated in the same manner as described for **9** to give **19** (1.6 g, 67%) (Table II). Compounds **17**, **20** and **26** were prepared similarly (see Table II).

Pharmacological Methods. Animals and Materials Male Std-Wistar rats (180—270 g) and male Std-ddY mice (20—25 g) were used in the experiments. Drugs were dissolved or suspended in 0.5% aqueous tragacanth and administered orally to groups of five animals each. All doses of the compounds are expressed as the form (salt or base) indicated in Table II.

Effect on the Ulceration Induced by Exposure to Restraint and Water-Immersion Stress Rats were fed until just before the experiment. The rats were individually immobilized in each compartment of the stress cage. The cage was immersed vertically in a water bath at 23 °C to the heigh of the xiphoid process of the rat according to the method of Takagi *et al.*[20] After 20 h, the rats were killed. The stomachs were removed and cut open along the greater curvature. The maximum diameter of each lesion was measured with a dissecting microscope (×12). The sum of the length (mm) of each lesion was used as the ulcer index. Test compounds were administered orally 30 min before the immersion. The inhibitory rate was calculated as follows: [(UI in control group − UI in treated group)/(UI in control group)] × 100 (%), where UI means ulcer index (mean value). The ED_{50} value (the dose required for 50% reduction of the ulcer index) and 95% confidence limits were calculated according to the method of Litchfield and Wilcoxon.[21]

Effect on the Ulceration Induced by Ethanol This test was carried out according to the method of Robert *et al.*[12] Rats were fasted for 24 h and then given absolute ethanol (1 ml) orally. One hour later, the animals were killed. The stomachs were removed and cut open along the greater curvature. The length (mm) of each lesion in the glandular portion was measured using a dissecting microscope (×12). The sum of the length (mm) of each lesion was used as an ulcer index. Test compounds were administered orally 30 min before the administration of ethanol. The inhibitory rate, the ED_{50} value and 95% confidence limits were calculated as described above.

Effect on Gastric Acid Secretion in Pylorus-ligated Rats Rats were fasted for 24 h with free access to water in wire-bottomed cages. These rats were anesthetized with ether, and a 2 cm midline incision was made caudal from the xiphoid process. The stomach was gently exposed and the pylorus was ligated with surgical silk. The incision was immediately closed. Exactly 4 h following the ligation, the rats were killed, and the stomachs were removed. A small incision was made in the stomach with a fine pair of scissors and the gastric content was allowed to drain into a graduated centrifuge tube. The content was centrifuged at 3000 rpm for 15 min. The secretory volume was determined by subtracting the sediment from the total volume. An aliquot of 1 ml was taken from each sample, diluted with distilled water (9 ml), and titrated to pH 7.0 with 0.02 N NaOH using an autotitrator (Toa Electronics, AUT-1). Test compounds were administered orally 30 min before the ligation. The ED_{50} value (the dose required for 50% inhibition of acid secretion) and the 95% confidence limits were calculated as described above.

Effect on Hypothermia Induced by Reserpine This experiment was carried out according to the method of Askew.[22] Each test compound was given orally, followed by an injection of reserpine, 5 mg/kg i.p. The rectal temperature of each mouse was measured 4 h later with a thermister (Shibaura Electric, BMG III-30). The inhibitory rate was determined as follows: [[(RT in reserpine + drug group) − RT in reserpine group]/(RT in tragacanth group − RT in reserpine group)] × 100 (%), where RT means rectal temperature (mean value).

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