2-Mercapto-3-pyridinol and the substituted nitrohalobenzenes were obtained commerically, with one exception. 4-Chloro-3-nitrobenzenesulfonamide was obtained from 4-chloro-3-nitrobenzenesulfonyl chloride (Aldrich) by reaction with concentrated aqueous ammonia. The following examples illustrate the general methods.

7-(Trifluoromethyl)-1-azaphenoxathiin (2). Triethylamine (50 mL) was added to a stirred mixture of 2-mercapto-3-pyridinol (12.7 g 0.1 mol), 4-chloro-3-nitrobenzotrifluoride (22.56 g, 0.1 mol), and dry DMF (200 mL), and the mixture was boiled under reflux for 18 h. The cooled mixture was poured into H_2O (700 mL) and extracted with Et_2O (2 × 600 mL). The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo. The residue was crystallized from 95% EtOH as pale yellow needles: mp 87–88 °C; IR (Nujol) 1610, 1570, 1500 cm^{-1}; NMR ($CDCl_3$) δ 8.35 (dd, J = 4.5 and 1.5 Hz, H-2), 7.17 (m, 5 H); MS M^+ 269 (100%). Anal. ($C_{12}H_6NOSF_3$) C, H, N.

7-Methoxy-1-azaphenoxathiin (7). 2-Mercapto-3-pyridinol (12.7 g, 0.1 mol) in dry DMF (50 mL) was added dropwise to a suspension of NaH (4.8 g, 0.2 mol) in DMF (200 mL) at 5 °C. 4-Chloro-3-nitroanisole (18.8 g, 0.1 mol) was added, and the mixture was stirred and heated under reflux for 18 h. The cooled mixture was poured into H_2O (900 mL) and extracted with Et_2O (2 × 600 mL). The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residual brown oil solidified overnight and was crystallized twice from hexane (charcoal) to give the product as fawn needles: mp 75–76 °C; NMR (Me_2SO-d_6) δ 8.38 (dd, J = 4.5 and 1.5 Hz, H-2), 7.5–6.8 (m, 5 H), 3.78 (s, 3 H); MS M^+ 231 (100%). Anal. ($C_{12}H_9NO_2S$) C, H, N.

7-(Trifluoromethyl)-1-azaphenoxathiin 10,10-Dioxide (8). Compound 2 (2.69 g, 0.01 mol) was added to a mixture of HOAc (50 mL) and 12% H_2O_2 (10 mL), and the mixture was stirred and boiled under reflux for 15 min. The reaction mixture was diluted with H_2O (50 mL) and allowed to cool. The colorless product was collected by filtration and crystallized from EtOH as needles: mp 180–181 °C; IR (Nujol) 1580, 1560 cm^{-1}; NMR (Me_2SO-d_6) δ 8.74 (dd, J = 4.5 and 1.5 Hz, H-2), 8.35 (d, J = 8 Hz, 1 H), 8.0 (m, 4 H); MS M^+ 301 (100%). Anal. ($C_{12}H_6NO_3SF_3$) C, H, N.

Pharmacological Methods. Compounds were administered either intraperitoneally (ip) or orally (po) to male, albino CFI mice (18–22 g), male Charles River (CD) rats (200–300 g, behavioral and toxicity studies), or male Long–Evans rats (200–300 g, muricide) in a methylcellulose suspension. The initial screening dose was 30 mg/kg, except for muricide (10 or 20 mg/kg).

(a) Antagonism of Methamphetamine Aggregate Toxicity.[10] Groups of 10 mice were kept in a plastic cage (11 × 26 ×13 cm) and treated with test drug po 30 min prior to ip administration of 15 mg/kg methamphetamine hydrochloride. ED_{50}, the dose required to protect 50% of the animals from death, was determined from mortality 4 h after methamphetamine injection.

(b) Reversal of Tetrabenazine-Induced Ptosis.[11] Groups of five mice were treated po with test drug 30 min prior to ip administration of 30 mg/kg tetrabenazine methanesulfonate. The size of the palpebral opening was evaluated at 30 min. The ED_{50} represents the dose required for half the mice to show a 50% increase in size of palpebral opening with respect to control.

(c) Inhibition of Muricidal Behavior.[12] Test drug was administered ip to groups of five rats, and mice were presented at 30 min. The ED_{50} reflects the dose at which half the rats failed to kill.

(d) Antagonism of Pentylenetetrazole-Induced Convulsions.[13] Groups of five mice were treated po with test drug 30 min before ip treatment with 150 mg/kg of pentylenetetrazole. Animals were observed for convulsions for 60 min. The ED_{50} reflects a 50% decrease in the number of animals convulsing.

(e) **Antagonism of Acetic Acid Writhing.**[14,15] Groups of five mice were treated po with test drug 15 min before ip dosing with 10 mL of 0.6% aqueous HOAc solution. The animals were observed for writhing behavior for a 10-min period beginning 3 min after treatment with HOAc. An animal was considered protected if the number of writhes was decreased 50% or more from control. The ED_{50} is expressed as the dose required to protect 50% of the treated mice.

(f) Biochemical Studies. The method of Hendley[9] was used.

(g) Behavioral and Acute Toxicity Studies. The test drugs were evaluated by the method of Irwin.[8] Groups of three mice were treated with test drug at 10, 30, 100, and 300 mg/kg and observed in comparison with controls 60 min later. Delayed toxicity was assessed at 24 h.

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Inhibition of Histamine-Induced Gastric Secretion by Flavone-6-carboxylic Acids[1]

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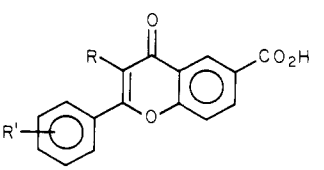
Twenty-five flavone-6-carboxylic acids were synthesized and tested as to their ability to inhibit histamine-induced gastric acid secretion in the rat. 3-Isopropoxy-4′-methoxyflavone-6-carboxylic acid (41) showed consistent oral activity while being devoid of any other noteworthy pharmacological effects. In vitro, this compound was found to be inactive as a histamine H_2 antagonist, and its mode of action remains unknown.

During the course of our investigation into the antiallergic activity of xanthone-2-carboxylic acids,[2,3] we became interested in substituted flavone-6-carboxylic acids (1), in



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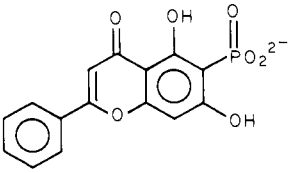

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which the relative positions of the pyrone carbonyl and the carboxy group would be the same as in xanthone-2-

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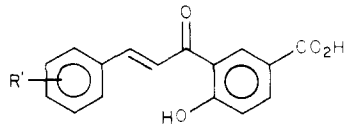
Table I. 2-Hydroxychalcone-5-carboxylic Acids



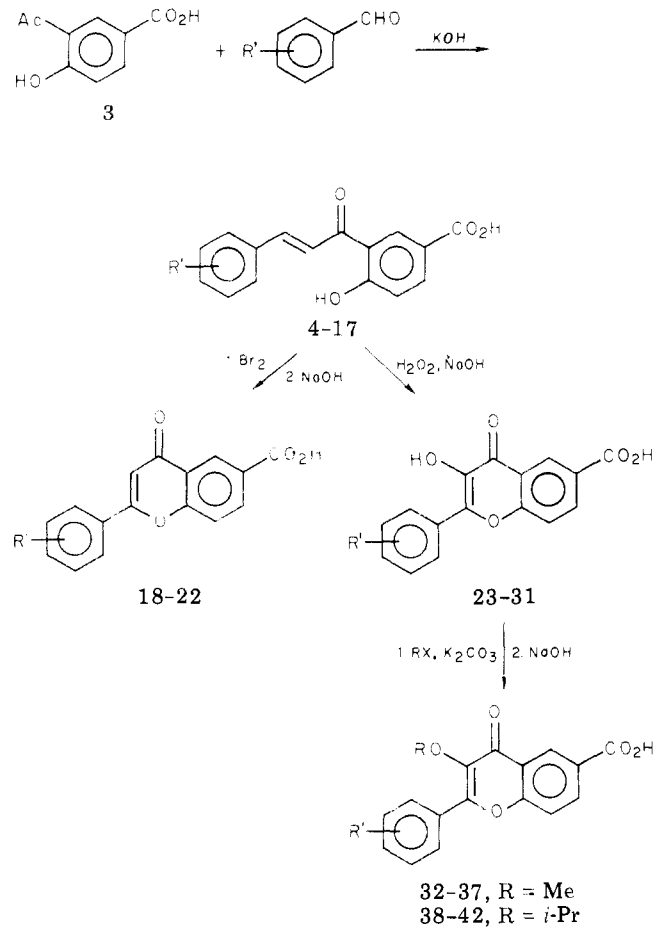
no.	R'	mp, °C	formula[a]	% yield
4	2'-Me	228-230	$C_{17}H_{14}O_4$	76
5	4'-Me	240-242	$C_{17}H_{14}O_4$	79
6	4'-*i*-Pr	200-203	$C_{19}H_{18}O_4$	68
7	4'-OC_6H_{13}	187	$C_{22}H_{24}O_5$	68
8	3'-OMe	231	$C_{17}H_{14}O_5$	66
9	4'-OMe	242	$C_{17}H_{14}O_5$[b]	66
10	3',4',5'-$(OMe)_3$	224-225	$C_{19}H_{18}O_7$	79
11	4'-OEt	224-225	$C_{18}H_{16}O_5$	86[c]
12	4'-OC_6H_{13}	181-183	$C_{22}H_{24}O_5$	68
13	4'-F	250	$C_{16}H_{11}O_4F$	51
14	4'-Cl	292-294	$C_{16}H_{11}O_4Cl$	64
15	2'-Br	265-266	$C_{16}H_{11}O_4Br$	63
16	4'-$MeSO_2$	262-264	$C_{17}H_{14}O_6S$	62
17	4'-CO_2H	351-353	$C_{17}H_{12}O_6$	61

[a] All compounds were analyzed for C and H. [b] Reference 15. [c] Yield of crude material with mp 216-218 °C.

carboxylic acid. A report that baicalein 6-phosphate (**2**) possesses antianaphylactic properties[4] seemed to make this a particularly worthwhile endeavor. However, examination of a selected group of varyingly substituted flavone-6-carboxylic acids in the rat passive cutaneous anaphylaxis assay revealed that these compounds were at best equivalent to the reference standard, disodium cromoglycate. In view of the current state of the art,[5] these findings must be considered rather disappointing. Nevertheless, a recent report on this subject[6] apparently confirms our own results. Surprisingly, routine pharmacological testing revealed that many of the flavone-6-carboxylic acids inhibited histamine-induced gastric acid secretion in the rat.

Chemistry. Base-promoted condensation of the requisite benzaldehydes with 3-acetyl-4-hydroxybenzoic acid (**3**) provided the desired chalcone derivatives **4**–**17** (Table I). Bromination of these chalcones, followed by treatment of the resulting dibromides with KOH (Emilewicz–von Kostanecki cyclization[7]), gave the flavone-6-carboxylic acids **18**–**22** (Table II). When the chalcones were subjected to the Algar–Flynn–Oyamada reaction,[8,9] the corresponding flavon-3-ols **23**–**31** were obtained (Table II). The latter were readily transformed into the 3-methoxy (**32**–**37**) and 3-isopropoxy (**38**–**42**) analogues (Table II) as shown in Scheme I.

Scheme I



Results and Discussion

No clear structure–activity relationship emerged from the data (Table II) obtained in the gastric acid secretion inhibition assay (see Experimental Section). Compounds with fairly large lipophilic groups, such as *n*-hexyl (**19**) or *n*-hexyloxy (**28** and **35**) in the 4' position were either inactive or stimulated gastric secretion. The latter was also true for **24** and **29**, which are very insoluble even in the form of their sodium or potassium salts. The nature of this stimulatory effect has not been elucidated. Compounds containing a variety of groups, such as $MeSO_2$, CO_2H, halo, and MeO, in the 4' position showed gastric acid secretion inhibitory activity, which was not influenced to any great extent by substitution at C-3. Thus, the 4'-MeO derivatives **20** (R = H), **26** (R = OH), **34** (R = MeO), and **41** (R = *i*-Pr) were all active. In addition, the few chalcone intermediates tested in this assay also displayed some degree of activity.

Although not confirmed experimentally by us, the 6-carboxy group seems to be required, since two series of benzopyrans substituted with either 2-furyl[10] or 2-thienyl[11] instead of phenyl, but lacking the CO_2H group, were not capable of inhibiting histamine-induced gastric secretion.

When tested orally in a rat ligated stomach preparation (see Experimental Section), only **41** was consistenty active (Table III), with a potency of approximately one-half that of the reference standard, metiamide. The rather low acute oral toxicity of **41** [LD_{50} (rat) = 1480 mg/kg] makes this an attractive candidate for evaluation in other species. In vitro testing revealed that **41** was not a histamine H_2 antagonist.[12] In addition, **41** given intraperitoneally to mice at doses of up to 300 mg/kg produced no pupillary mydriasis. Absence of mydriasis indicates that this agent is devoid of anticholinergic activity. Structurally, flavones like **41** and particularly their chalcone intermediates are reminiscent of the histidine decarboxylase inhibitor leca-

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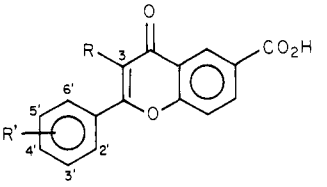
Table II. Gastric Antisecretory Activity of Flavone-6-carboxylic Acids



no.	R	R'	mp, °C	formula[a]	method	crystn solvent[b]	% yield	dose,[c] mg/kg sc	% inhibn of total acid output (rat)[d]
18	H	4'-*i*-Pr	258-260	$C_{19}H_{16}O_4$[e]	A	D	56	80	19[f]
19	H	4'-C_6H_{13}	214-216	$C_{22}H_{22}O_4$[g]	A	E	84	80	2[f]
20	H	4'-MeO	348	$C_{17}H_{12}O_5$[h]	A	D	45	80	13
21	H	4'-F	305-307	$C_{16}H_9O_4F$	A	F	54	80	21
22	H	4'-$MeSO_2$	372	$C_{17}H_{12}O_6S$	A	G	62	70	41
23	OH	2'-Me	270-271	$C_{17}H_{12}O_5$	B	E	80	80	15
24	OH	4'-Me	354-356	$C_{17}H_{12}O_5$	B	F	68	80	−6[i]
25	OH	4'-*i*-Pr	302-303	$C_{19}H_{16}O_5$	B	F	46	80	24
26	OH	4'-MeO	341-343	$C_{17}H_{12}O_6$[h]	B	F	51	80	24
27	OH	3',4',5'-$(OMe)_3$	316-318	$C_{19}H_{16}O_8$	B	G	67	80	24
28	OH	4'-$C_6H_{13}O$	252-253	$C_{22}H_{22}O_6$	B	F	71	80	−11[i]
29	OH	4'-Cl	329-330	$C_{16}H_9O_5Cl$	B	F	61	80	−19[i]
30	OH	2'-Br	285-287	$C_{16}H_9O_5Br$	B	E	69	80	22
31	OH	4'-CO_2H	408-410	$C_{17}H_{10}O_7$	B	G	56	80	23
32	OMe	4'-Me	247	$C_{18}H_{14}O_5$	C	D	76	80	4
33	OMe	4'-*i*-Pr	215	$C_{20}H_{18}O_5$	C	E	64	80	18
34	OMe	4'-MeO	252	$C_{18}H_{14}O_6$	C	D	66	80	22
35	OMe	4'-$C_6H_{13}O$	206-207	$C_{23}H_{24}O_6$	C	E	91	76	−12[i]
36	OMe	4'-F	276-278	$C_{17}H_{11}O_5F$	C	D	83	70	4[f]
37	OMe	4'-Cl	297-299	$C_{17}H_{11}O_5Cl$	C	F	88	80	34
38	O-*i*-Pr	4'-Me	256	$C_{20}H_{18}O_5$	C	D	70	80	8
39	O-*i*-Pr	4'-*i*-Pr	219	$C_{22}H_{20}O_5$	C	E	76	80	20
40	O-*i*-Pr	3'-MeO	188-189	$C_{20}H_{18}O_6$	C	E	83	66	12
41	O-*i*-Pr	4'-MeO	262-264	$C_{20}H_{18}O_6$	C	E	79	80	35
42	O-*i*-Pr	4'-EtO	274	$C_{21}H_{20}O_6$	C	E	75	60	18
burimamide[j]								90	49

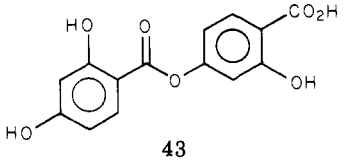
[a] All compounds were analyzed for C and H. [b] D = EtOH; E = EtOH-H_2O; F = THF-EtOH; G = DMF-AcOH. [c] All compounds were converted into Na salts prior to testing. [d] Ten rats per compound unless indicated otherwise. [e] Reference 6. [f] Only nine rats were used. [g] C: calcd, 75.41; found, 74.81. [h] Reference 16. [i] Compound stimulates gastric secretion. [j] *N*-Methyl-*N'*-[4-(4(5)-imidazolyl)butyl]thiourea.

Table III. Inhibition of Gastric Acid Secretion by 41 Given Orally

compd	dose, mg/kg po	no. of rats	gastric juice: $\bar{X}$ vol, mL ± SD	mequiv of HCl: $\bar{X}$/100 g ± SD	% inhibn of total acid output
41	control	10	4.66 ± 1.9	0.248 ± 0.114	
	50	10	5.13 ± 1.6	0.238 ± 0.077	4
	100	10	5.16 ± 1.0	0.226 ± 0.080	9
	150	8	4.80 ± 2.4	0.161 ± 0.128	34[a]
	200	10	3.68 ± 1.7	0.101 ± 0.086	59[a]
metiamide[b]	control	10	4.82 ± 2.2	0.273 ± 0.073	
	75	10	2.99 ± 1.7	0.148 ± 0.010	46[a]
	150	10	1.70 ± 0.5	0.064 ± 0.021	76[a]

[a] $p < 0.05$. [b] *N*-Methyl-*N'*-[2-[[(5-methylimidazol-4-yl)methyl]thio]ethyl]thiourea.

noric acid[13] (**43**). However, a compound of this type would



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presumably not be active against exogenous histamine. Thus, the mode of action of **41** remains unknown.

Experimental Section

Melting points were determined in a Mel-Temp apparatus and are uncorrected. The IR spectra were measured on a Perkin-Elmer Model 267 grating infrared spectrophotometer as Nujol mulls. The UV spectra were recorded in methanol solution with a Perkin-Elmer UV–visible spectrophotometer. The NMR spectra were measured with a Varian T-60 NMR spectrometer in $CDCl_3$ or Me_2SO-d_6 solutions, using Me_4Si as internal standard. Silica gel GF (0.25 mm; Analtech, Inc.) plates were used for thin-layer chromatography, eluting with a toluene–THF–AcOH (30:3:1) mixture. The plates were visualized with UV light or a ceric sulfate [10 g of $Ce(SO_4)_2$ in 1 L of 35% H_2SO_4] spray. All starting benzaldehydes are known.

3-Acetyl-4-hydroxybenzoic Acid (3). The following procedure was judged more convenient than the one published,[14] since it obviates the use of nitrobenzene. Ethyl 4-acetoxybenzoate (58 g, 0.278 mol), $AlCl_3$ (117 g, 0.875 mol), and KCl (32.2 g, 0.29 mol) were mixed in a 2-L three-neck round-bottom flask. With ov-

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erhead stirring, the mixture was heated at 155–160 °C (oil bath temperature) for 1 h, during which time a solid, brown foamy mass formed and stirring was no longer possible. After cooling (ice bath), the reaction mixture was digested with 1100 mL of 2 N HCl. EtOH (220 mL) was then added, and the resulting suspension was refluxed for 0.5 h to complete hydrolysis of the Et ester. The crude product was isolated by suction filtration of the cooled reaction mixture, washing well with H_2O and drying. Recrystallization of the combined crude material from seven such runs from THF–EtOH (charcoal) gave 167.4 g of **3**, mp 243 °C (lit. mp 241–242 °C). A second crop (37.9 g; mp 221–228 °C), obtained on concentration of the mother liquid, was further purified by dissolution in aqueous $NaHCO_3$, extraction with ether, and treatment of the aqueous phase with charcoal. After acidification with 2 N HCl, the precipitate was filtered off, washed with H_2O, dried, and recrystallized from THF–EtOH: yield 27.9 g; mp 243 °C. Evaporation of the combined mother liquids to dryness, followed by purification as described for the second crop, gave an additional 20.8 g (mp 243 °C) after two recrystallizations from THF–EtOH (total yield 64%).

2-Hydroxychalcone-5-carboxylic Acids 4–17 (Table I). To an ice-cooled solution of 3-acetyl-4-hydroxybenzoic acid (**3**; 5.0 g, 27.8 mmol) and the required benzaldehyde (30.0 mmol) in EtOH (75 mL) was added 40% KOH (25 mL). The resulting dark red solution was stirred under N_2 at ambient temperature until reaction was complete as judged by TLC; this usually required 1–2 days. Thereafter, the reaction mixture was slowly poured into excess 6 N HCl, and the resulting yellow precipitate was filtered off, washed with H_2O, and dried. The crude materials were recrystallized from THF–EtOH, except **7** (EtOH–H_2O) and **17** (DMF–AcOH). Condensation of 4-fluorobenzaldehyde with **3** as described led to a mixture of the desired fluorochalcone **13** and the ethoxy analogue **11**. Formation of the latter could be suppressed using dioxane as solvent instead of EtOH.

Method A. Flavone-6-carboxylic Acids 18–22 (Table II). Bromine (2.72 g, 17 mmol) was added to a solution of the chalcone (15 mmol) in AcOH (150 mL). After the solution was stirred at ambient temperature for 3 h, 1% aqueous $NaHSO_3$ (250 mL) was added slowly. The resulting precipitate was filtered off, washed with H_2O, and suspended in EtOH (100 mL). KOH (2.94 g, 52.5 mmol) dissolved in H_2O (50 mL) was added, and stirring was continued for 4 h. The reaction mixture was acidified with 2 N HCl, and the precipitate formed was filtered off, washed with water, dried, and recrystallized (Table II).

Method B. 3-Hydroxyflavone-6-carboxylic Acids 23–31 (Table II). To an ice-cooled solution of the chalcone (30 mmol) and NaOH (5.2 g, 130 mmol) in EtOH (200 mL) and H_2O (100 mL) was added 30% H_2O_2 (11.4 mL, 100 mmol). The reaction mixture was stirred at 0 °C for 2 h and then at ambient temperature for 16 h. The crude flavonols which separated on acidification (2 N HCl) were filtered off, washed with H_2O, dried, and recrystallized from the solvents listed in Table II.

Method C. 3-Methoxy- and 3-Isopropoxyflavone-6-carboxylic Acids 32–42 (Table II). A mixture of the 3-hydroxyflavone-6-carboxylic acid (10.0 mmol), MeI or *i*-PrBr (50.0 mmol), K_2CO_3 (6.9 g, 50.0 mmol), and DMF (75 mL) was stirred at ambient temperature for 24 h. The reaction mixture was then poured into 750 mL of H_2O containing concentrated HCl (10 mL) and extracted with CH_2Cl_2 (150 mL × 2). The organic phase was washed with H_2O (50 mL × 5), dried ($MgSO_4$), filtered, and concentrated to a small volume. This solution was passed through a short column of alumina ("Woelm", activity II, neutral), eluting with CH_2Cl_2. The combined eluates were evaporated to dryness, and the residue was refluxed with NaOH (0.6 g, 15.0 mmol) in 80% aqueous EtOH (100 mL) for 30 min. Acidification (2 N HCl), suction filtration, and recrystallization provided the alkoxyflavonecarboxylic acids (Table II).

Pharmacology. Male albino rats (Hilltop, Sprague–Dawley derived) in a weight range of 200 to 240 g were used. The animals were starved for 48 h but allowed access to water ad libitum. The animals were divided into groups of 10. The compounds under study were administered either subcutaneously or orally by gavage in a volume of 1 mL/kg. A comparable control group was given saline. Thirty minutes later, each animal was anesthetized with ether, and the gastrointestinal tract was ligated just caudad to the pyloric sphincter.[17] Immediately after surgery, each animal was given 2.5 mg/kg of histamine subcutaneously; this was repeated at 15-min intervals for 3 h. The animals were then sacrificed and the stomachs removed. The stomach content was aspirated and the volume recorded. An aliquot (1.0 mL or less qs with distilled water) of gastric juice was titrated against 0.02 N NaOH to pH 7.0 ± 0.1. Total acid output (mequiv of H^+/100 g) was determined. Drug-treated animals were compared to controls with respect to H^+ secretion; percent mean inhibition in comparison to controls for each experiment was derived, and tests for statistically significant differences in mean values were obtained by an analysis of variance.

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