hydrogenated at 40 psi in the presence of 25 mg of 1,5-cyclooctadienerhodium(I) chloride dimer and 70 mg of (–)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ("(–)-DIOP", Alfa). Hydrogen uptake was complete after 3 h. The mixture was diluted with 10 mL of ether, cooled to 0 °C, and filtered to remove the product. The crude product was recrystallized three times from aqueous acetic acid to give a single, pure diastereomer, identified as the D,D isomer [1(*S*)-[(benzyloxycarbonyl)amino]ethyl](2(*R*)-carbomethoxy-1-*n*-propyl)phosphinic acid (11): TLC (system 2) R_f 0.70; ^{1}H NMR (CD_3OD) δ 1.2 (d, 3 H), 1.3 (dd, 3 H), 1.8 (m, 1 H), 2.2 (m, 1 H), 2.9 (m, 1 H), 3.7 (s, 3 H), 4.0 (m, 1 H), 5.1 (dd, 1 H), 7.3–7.5 (m, 6 H); MS (NIFAB), *m/e* 342 (M – H); $[\alpha]_D$ +30.1° (CH_3OH, *c* 0.3).

(1(*S*)-Aminoethyl)(2(*R*)-carboxy-1-*n*-propyl)phosphinic Acid (12b). [1(*S*)-[(Benzyloxycarbonyl)amino]ethyl](2(*R*)-carbomethoxy-1-*n*-propyl)phosphinic acid (11) was converted according to method A to give the title compound **12b** as a single diastereomer in 60% yield: TLC (system 2) R_f 0.35; ^{1}H NMR (D_2O) δ 1.27 (d, 3 H), 1.38 (dd, 3 H), 1.68 (m, 1 H), 2.10 (m, 1 H), 2.81 (m, 1 H), 3.25 (m, 1 H); MS (NIFAB), *m/e* 194 (M – H).

(1(*S*)-Aminoethyl)(2(*S*)-carboxy-1-*n*-propyl)phosphinic Acid (12a). This chirally pure diastereomer was isolated by HPLC separation of methyl[1(*S*)-[(benzyloxycarbonyl)amino]-ethyl](2(*RS*)-carbomethoxy-1-propyl)phosphinate (**7n**) on a RP-18 (E. Merck) semipreparative column, eluting with H_2O (73%) and acetonitrile (27%) and giving diastereomers A and B. Each diastereomer was deprotected according to method A to give two pure diastereomers as determined by HPLC. Diastereomer A (t_R 29.5 min) gave on deprotection compound **12b** (NMR, MS, HPLC) and diastereomer B gave the *S,S* compound **12a** having TLC, NMR, and MS data identical with that of **12b**.

Benzyl [1(*S*)-[(Benzyloxycarbonyl)amino]ethyl](2(*R*)-carbomethoxy-1-propyl)phosphinate (13). A solution of compound 11 (0.342 g, 1 mmol) in THF (2 mL) at room temperature was treated with benzyl alcohol (0.134 mL 1.3 mmol), followed by dicyclohexylcarbodiimide (0.22 g, 1.1 mmol) and 4-(dimethylamino)pyridine. The mixture was stirred at room temperature for 6 h; then, an additional 0.22 g of DCC was added, and the reaction stirred overnight at room temperature. The mixture was diluted with ether (20 mL) and filtered, and the filtrate was washed with HCl (0.1 N), aqueous sodium bicarbonate (1%), and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (silica, 9:1 EtOAc–CH_3CN) to give the title compound (0.338 g, 78%) as an 8:1 mixture of diastereomers at phosphorus. The major component was isolated by preparative HPLC (silica, EtOAc) to give **13** (0.25 g) as a single diastereomer.

Crystals suitable for X-ray were obtained by slow, room temperature evaporation of a 10-mg sample of **13** in 250 μL of ether: TLC (silica; $CHCl_3$–MeOH–H_2O–HOAc, 100:20:3:0.5) R_f 0.87; ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3 H), 1.32 (q, 3 H), 1.83 (m, 1 H), 2.33 (m, 1 H), 2.82 (m, 1 H), 3.55 (s, 3 H), 4.10 (m, 1 H), 5.1 (m, 4 H), 5.62 (d, 1 H), 7.3 (br s, 10 H); MS (FAB), *m/e* 434 (M + 1).

X-ray Crystal Structure Analysis of 13. Suitable crystals of **13** ($C_{22}H_{28}NO_6P$) for X-ray diffraction studies formed from ether with space group symmetry of *P*1 and cell constants of a = 10.482 (2) Å, b = 11.254 (3) Å, c = 5.479 (4) Å, α = 91.58 (3)°, β = 92.63 (3)°, and γ = 117.68 (2)° for Z = 1 and a calculated density of 1.261 g/cm^3. Of the 1524 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 1433 reflections were observed [$I > 3\sigma(I)$]. The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[22] Both phenyl groups were found to be disordered. This disordering was modeled by two separate positions for each phenyl group with occupancies of 0.5. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.064. Tables V–VII containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Tables VI and VII only contain bond distances and angles for one set of phenyl positions. Figure 2 is a computer generated perspective drawing of **13** from the final X-ray coordinates showing the absolute stereochemistry.

Registry No. **3a**, 115047-74-0; **3b**, 113592-15-7; **3c**, 113592-18-0; **3d**, 113592-20-4; **3e**, 115047-75-1; **3f**, 113592-22-6; **3g**, 115047-76-2; **3h**, 113592-24-8; **3i**, 113592-29-3; **3j**, 113592-31-7; **3k**, 113592-33-9; **3l**, 113592-36-2; (I)-4, 76437-21-3; (*R*)-4, 115115-40-7; (*S*)-4, 115115-41-8; (±)-**5**, 113592-12-4; (*R*)-**5**, 113592-76-0; (*S*)-**5**, 113592-51-1; **7a**, 113592-14-6; **7b**, 113592-16-8; **7c**, 113592-19-1; **7d**, 113592-21-5; **7e**, 115047-81-9; **7f**, 113592-23-7; **7g**, 115047-82-0; **7h**, 113592-25-9; **7i**, 113592-30-6; **7j**, 113592-32-8; **7k**, 113592-35-1; **7l**, 113592-38-4; **9**, 115047-83-1; **10**, 115047-84-2; **11**, 115047-85-3; **13**, 115047-86-4; methyl acrylate, 96-33-3; methyl methacrylate, 80-62-6; methyl 2-ethylacrylate, 2177-67-5; methyl 2-propylacrylate, 3070-66-4; methyl 2-(methylthio)acrylate, 43228-10-0; methyl 2-butylacrylate, 3070-68-6; methyl 2-isobutylacrylate, 3070-69-7; methyl 2-heptylacrylate, 91213-29-5; methyl 2-benzylacrylate, 3070-71-1; methyl 2-(2-phenylethyl)acrylate, 113592-34-0; methyl 2-(3-phenylpropyl)acrylate, 88465-93-4; L-alanyl-L-alanine ligase, 9023-63-6; 2-trimethylphosphonoacrylate, 55168-74-6; fluoro-D-alanine, 35455-20-0; 1-aminoethylphosphonic acid, 16606-65-8; 1-aminoethylphosphonous acid, 65576-94-5; D-alanyl-D-alanine, 923-16-0; D-cycloserine, 68-41-7; 1-(carbobenzoxyamino)propanephosphinic acid, 115047-79-5; 1-(carbobenzoxyamino)propanephosphinic acid methyl ester, 115075-80-4.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **13** (3 pages). Ordering information is given on any current masthead page.

Synthesis of (Aryloxy)alkylamines. 1. Novel Antisecretory Agents with H^+K^+-ATPase Inhibitory Activity

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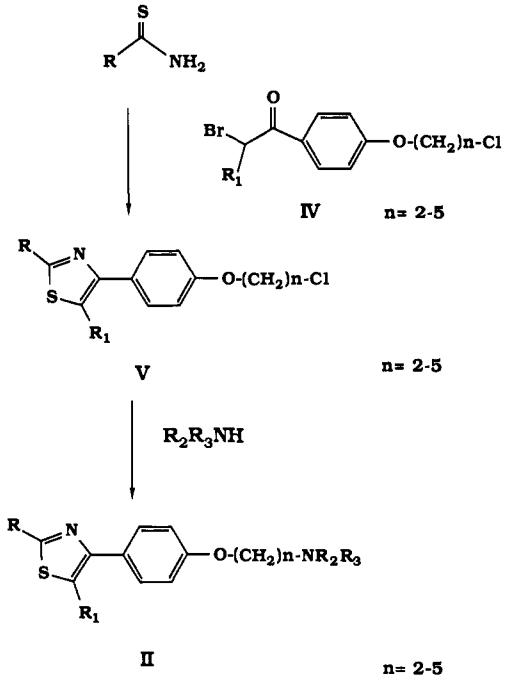
A series of heterocyclic (aryloxy)alkylamines of structures II and III were prepared and found to possess gastric antisecretory activity. Of the variety of substituted thiazoles, benzoxazoles, and benzothiazoles prepared, thiazole **18**, benzoxazole **32**, and benzothiazole **47** exhibited gastric antisecretory potency comparable to that of ranitidine in vivo in the pylorous ligated rat model. In an isolated rabbit parietal system, the series of thiazoles, benzoxazoles, and benzothiazoles also demonstrated similar potency to that of ranitidine toward the inhibition of both histamine-stimulated and dcAMP-stimulated uptake of amino[^{14}C]pyrine. These compounds inhibited the H^+K^+-sensitive ATPase enzyme in isolated gastric microsomes. A direct correlation existed between inhibition of ^{14}C uptake, in vivo antisecretory activity, and inhibition of the H^+K^+-ATPase enzyme. The more potent antisecretory compounds **18**, **32**, and **47** were also the more potent enzyme inhibitors. These data suggest that the mechanism responsible for the observed in vitro and in vivo gastric antisecretory activity, in these series of compounds, is a consequence of the inhibition of the H^+K^+-sensitive ATPase enzyme.

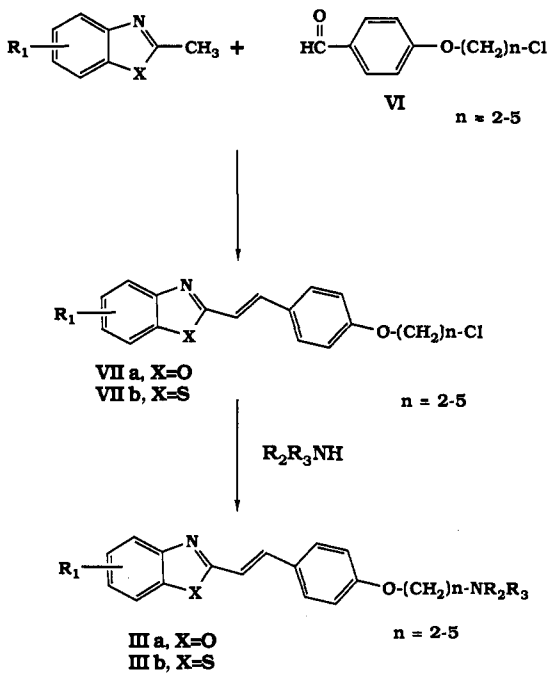
Peptic ulcer disease results from the failure of tissues to resist the corrosive effects of gastric acid and pepsin.[1] This imbalance in the hemostatic mechanism often can be restored by reducing the exposure of these tissues to gastric

0022-2623/88/1831-1778$01.50/0

Scheme I

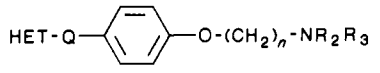


Scheme II

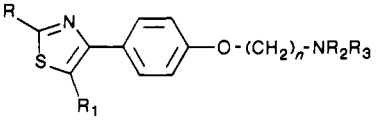


acid. Therefore, the most effective therapies are those that reduce the secretion of acid from gastric parietal cells. This can be accomplished by inhibition of the parietal cell surface receptors: e.g. histamine H_2 receptors, acetylcholine receptors, or gastrin receptors.[2] Antihistamines such as cimetidine[3] and ranitidine[4] that inhibit histamine action at the H_2-receptor site are effective in the treatment of peptic ulcer but may also cause, to a limited extent and predominantly with cimetidine, various central nervous system (CNS) disturbances, such as confusion and seizures, particularly in elderly patients. Recently, inhibition of the parietal cell specific H^+K^+-sensitive ATPase enzyme by the clinical candidate omeprazole[5] has been demonstrated as an effective inhibitor of gastric acid secretion. The unique feature of a H^+K^+-ATPase inhibitor, such as omeprazole, is that acid secretion is blocked at the final process in acid production regardless of what agent stimulates acid secretion.[6] Clinically, omeprazole does not appear to possess the CNS side effects associated with cimetidine or ranitidine and has been shown to control gastric secretion in Zollinger–Ellison syndrome better than high doses of the H_2 blockers.[7] Therefore, a gastric antisecretory compound that acts via inhibition of the H^+K^+-ATPase enzyme could be a good therapeutic agent.

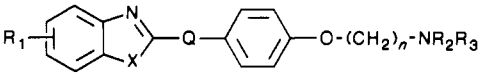
In our laboratories, we developed a synthetic program to prepare various heterocyclic aryloxyalkylamines of general structure I. Our aim was to probe pharmacological activity in these systems by first focusing on the heterocyclic moiety, while maintaining a constant (aryloxy)alkylamine portion. Once an area of interest was established, we then explored the effects on biological activity of altering the spacer Q (i.e. carbonyl, direct bond, ethylene linkage) and, finally, of varying the (aryloxy)alkylamine moiety. The derivatives were examined in a wide variety of pharmacological and biochemical assays in order to evaluate their potential pharmacological utility. This had led to the development of an interesting series of CNS agents, which is the subject of a subsequent paper,[8] as well as the compounds discussed herein. As a result of this process, a series of substituted thiazoles (II) and benzoxazoles and benzothiazoles (III) that possess very interesting gastric antisecretory activity was discovered.



I



II



III

Chemistry

The preparation of a variety of substituted thiazole derivatives (II) was achieved by the condensation of an appropriately substituted thioamide with an α-halo ketone[9] derivative IV to give a [4-(chloroalkoxy)phenyl]-2-substituted-thiazole V (Scheme I). Initial attempts to condense substituted thioamides with α-bromo-4-hydroxyacetophenone resulted in low yields of the expected (4-hydroxyphenyl)-2-substituted-thiazoles. When the free phenol of 4-hydroxyacetophenone was protected as a chloroalkoxy group, as in intermediate IV, greatly improved yields of the thioamide condensation resulted.

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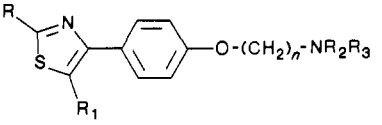
(9) Schwarz, G. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 332.

Table I. Substituted Thiazoles

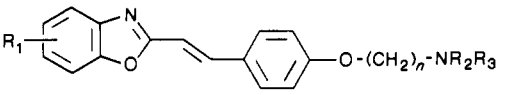


R_1 = H unless otherwise specified

compd	R	n	NR_2R_3	empirical formula[a]	mp,[b] °C	yield,[c] %
1	CH_3	3	NBu_2	$C_{21}H_{32}N_2OS \cdot 2HCl$	120–2	16
2	C_6H_5	3	NBu_2	$C_{26}H_{34}N_2OS \cdot HCl$	131–4	75
3	C_6H_5, R_1 = CH_3	3	NBu_2	$C_{27}H_{36}N_2OS \cdot 2HCl \cdot {}^1/_2H_2O$	102–4	73
4	C_6H_5, R_1 = CH_2CH_3	3	NBu_2	$C_{28}H_{38}N_2OS \cdot HCl \cdot {}^3/_2H_2O$	128–31	83
5	4-Cl-C_6H_4	3	NBu_2	$C_{26}H_{33}ClN_2OS \cdot HCl$	150–2	34
6	4-MeO-C_6H_4	3	NBu_2	$C_{27}H_{36}N_2O_2S \cdot 2HCl \cdot {}^1/_2H_2O$	67–70	33
7	4-Me-C_6H_4	3	NBu_2	$C_{27}H_{36}N_2OS \cdot 2HCl$	144–7	44
8	4-CF_3-C_6H_4	3	NBu_2	$C_{27}H_{33}F_3N_2OS \cdot HCl \cdot H_2O$	148–150	24
9	3,5-$(MeO)_2$-C_6H_3	3	NBu_2	$C_{28}H_{38}N_2O_3S \cdot HCl \cdot H_2O$	139–143	30
10	3-pyridyl	3	NBu_2	$C_{25}H_{33}N_3OS \cdot 2HCl \cdot 2H_2O$	199–202	36
11	C_6H_5	2	NBu_2	$C_{25}H_{32}N_2OS \cdot HCl$	129–131	30
12	C_6H_5	4	NBu_2	$C_{27}H_{36}N_2OS \cdot HCl$	132–4	74
13	C_6H_5	5	NBu_2	$C_{28}H_{38}N_2OS \cdot HCl \cdot H_2O$	88–90	58
14	C_6H_5	3	NEt_2	$C_{22}H_{26}N_2OS \cdot HCl \cdot H_2O$	156–8	40
15	C_6H_5	3	NPr_2	$C_{24}H_{30}N_2OS \cdot HCl \cdot {}^1/_2H_2O$	154–6	48
16	C_6H_5	3	pyrrolidine	$C_{22}H_{24}N_2OS \cdot HCl$	214–7	46
17	C_6H_5	3	piperidine	$C_{23}H_{26}N_2OS \cdot HCl$	218–221	38
18	C_6H_5	3	imidazole	$C_{21}H_{19}N_3OS \cdot HCl \cdot H_2O$	173–7	67
19	C_6H_5	3	triazole	$C_{20}H_{18}N_4OS \cdot HCl$	197–8	37
20	C_6H_5	4	imidazole	$C_{22}H_{21}N_3OS \cdot HCl \cdot {}^1/_2H_2O$	178–180	53
21	4-CF_3-C_6H_4	3	imidazole	$C_{22}H_{18}F_3N_3OS \cdot HCl$	180–3	69
22	3-pyridyl	3	imidazole	$C_{20}H_{18}N_4OS \cdot HCl$	159–163	51

[a] All compounds exhibited satisfactory (±0.4%) elemental analysis as salts. [b] Recrystallized from acetone. [c] Procedure A in the Experimental Section.

Table II. Substituted Benzoxazoles



compd	R_1	n	NR_2R_3	empirical formula[a]	mp,[b] °C	yield,[c] %
23	H	3	NBu_2	$C_{26}H_{34}N_2O_2 \cdot HCl$	153–4	75
24	5-Me	3	NBu_2	$C_{27}H_{36}N_2O_2 \cdot 2HCl$	143–4	68
25	6-MeO	3	NBu_2	$C_{27}H_{36}N_2O_3 \cdot HCl$	151–2	8
26	H	3	NEt_2	$C_{22}H_{26}N_2O_2 \cdot HCl$	225–6	85
27	H	3	NPr_2	$C_{24}H_{30}N_2O_2 \cdot 2HCl \cdot H_2O$	172–3	40
28	H	3	imidazole	$C_{21}H_{19}N_3O_2 \cdot HCl \cdot {}^1/_2H_2O$	235–6	63
29	H	2	NBu_2	$C_{25}H_{32}N_2O_2 \cdot HCl$	176–7	54
30	H	4	NBu_2	$C_{27}H_{36}N_2O_2 \cdot HCl \cdot H_2O$	172–4	11
31	H	4	NEt_2	$C_{23}H_{28}N_2O_2 \cdot HCl \cdot H_2O$	219–220	12
32	H	4	NPr_2	$C_{25}H_{32}N_2O_2 \cdot 2HCl$	152–3	30
33	H	4	pyrrolidine	$C_{23}H_{26}N_2O_2 \cdot HCl \cdot H_2O$	229–232	55
34	H	4	piperidine	$C_{24}H_{28}N_2O_2 \cdot HCl$	230–2	42
35	H	4	imidazole	$C_{22}H_{21}N_3O_2 \cdot HCl \cdot H_2O$	205–7	40
36	H	5	imidazole	$C_{23}H_{23}N_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$	220–2	37

[a] All compounds exhibited satisfactory (±0.4%) elemental analysis as salts. [b] Recrystallized from acetone. [c] Procedure B in the Experimental Section.

Subsequent displacement of the alkyl chloride of IV, employing a variety of amines, gave the desired product II. The substituted thiazoles prepared are summarized in Table I.

The benzoxazole and benzothiazole derivatives (III, Q = ethenyl) were prepared by a Knoevenagel-type condensation[10] of 2-methyl-1,3-benzoxazole or 2-methyl-1,3-benzothiazole with the appropriately substituted 4-(chloroalkoxy)benzaldehyde VI (Scheme II). The condensation was performed with an excess of aqueous sodium hydroxide in DMSO, and none of the intermediate alcohol was observed. This condensation failed with 4-hydroxybenzaldehyde, with decomposition of the starting benzaldehyde, possibly due to the drastic basic conditions needed for the reaction. As noted in the case of the thiazoles, when the free phenol was protected as the chloroalkoxy group VI, condensation gave desired styrenes VIIa or VIIb smoothly and in good yields. Surprisingly, the chloride was not displaced by the hydroxide in the reaction, though in the cases where the side chain contained three methylene units, varying amounts (10–20%) of allylic products were observed due to dehydrohalogenation. Subsequent displacement of chloride in VIIa or VIIb with a variety of amines yielded IIIa and IIIb, respectively. The benzothiazole derivatives (IIIc) (X = S, Q = direct bond) were prepared by the condensation of 2-aminothiophenol with the appropriately substituted benzoyl chloride VIII. Subsequent chloride displacement with an amine produced the desired products (Scheme III). The benzoxazoles and benzothiazoles prepared are summarized in Tables II and III.

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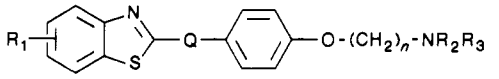
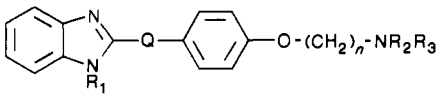
Table III. Substituted Benzothiazoles



compd	R_1	Q	n	NR_2R_3	empirical formula[a]	mp,[b] °C	yield,[c] %
37	H	ethenyl	3	NBu_2	$C_{26}H_{34}N_2OS\cdot2HCl\cdot2H_2O$	181–2	66
38	5-Me	ethenyl	3	NBu_2	$C_{27}H_{36}N_2OS\cdot2HCl$	194–5	40
39	6-MeO	ethenyl	3	NBu_2	$C_{27}H_{36}N_2O_2S\cdot2HCl\cdot{}^1/_2H_2O$	190–4	52
40	5-Cl	ethenyl	3	NBu_2	$C_{26}H_{33}ClN_2OS\cdot2HCl$	176–7	41
41	H	ethenyl	3	NEt_2	$C_{22}H_{26}N_2OS\cdot2HCl\cdot{}^1/_2H_2O$	187–8	24
42	H	ethenyl	3	NPr_2	$C_{24}H_{30}N_2OS\cdot2HCl\cdot H_2O$	135–7	57
43	H	ethenyl	3	piperidine	$C_{23}H_{26}N_2OS\cdot HCl\cdot{}^3/_2H_2O$	215–7	51
44	H	ethenyl	3	imidazole	$C_{21}H_{19}N_3OS\cdot2HCl$	231–2	35
45	H	ethenyl	2	NBu_2	$C_{25}H_{32}N_2OS\cdot2HCl\cdot{}^1/_2H_2O$	172–3	36
46	H	ethenyl	4	NEt_2	$C_{23}H_{28}N_2OS\cdot2HCl\cdot2H_2O$	205–7	31
47	H	ethenyl	4	NPr_2	$C_{25}H_{32}N_2OS\cdot HCl\cdot{}^1/_2H_2O$	155–6	35
48	H	ethenyl	4	pyrrolidine	$C_{23}H_{26}N_2OS\cdot HCl\cdot{}^1/_2H_2O$	220–2	33
49	H	ethenyl	4	imidazole	$C_{22}H_{21}N_3OS\cdot HCl\cdot H_2O$	214–7	46
50	H	bond	3	NBu_2	$C_{24}H_{32}N_2OS\cdot2HCl\cdot{}^1/_2H_2O$	136–7	35[d]
51	H	bond	3	NPr_2	$C_{22}H_{28}N_2OS\cdot2HCl\cdot{}^1/_2H_2O$	142–3	19[d]

[a] All compounds exhibited satisfactory (±0.4%) elemental analysis as salts. [b] Recrystallized from acetone. [c] Procedure B in the Experimental Section except where noted. [d] Procedure C in the Experimental Section.

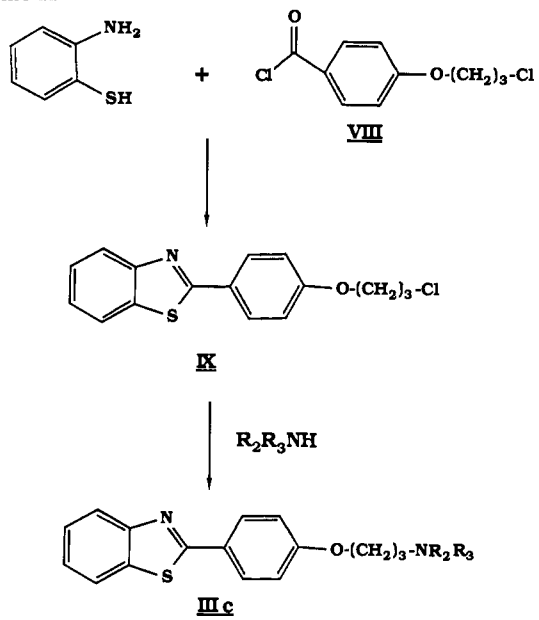
Table IV. Substituted Benzimidazoles



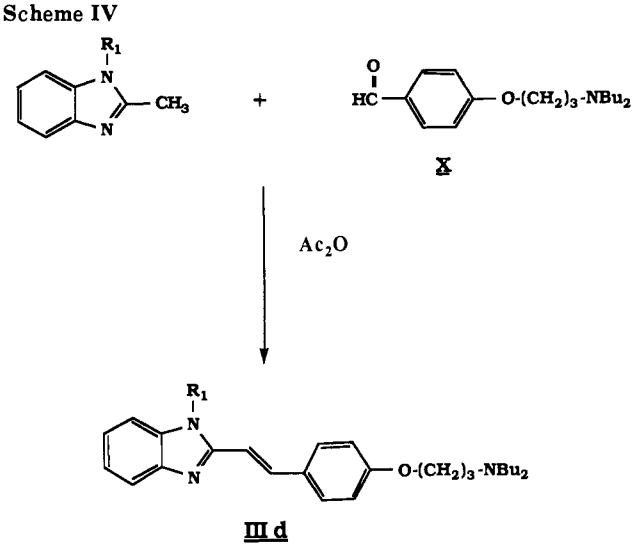
compd	R_1	Q	n	NR_2R_3	empirical formula[a]	mp,[b] °C	yield,[c] %
52	H	ethenyl	3	NBu_2	$C_{26}H_{35}N_3O\cdot C_4H_4O_8\cdot H_2O$	200–2	13
53	CH_3	ethenyl	3	NBu_2	$C_{27}H_{37}N_3O\cdot C_4H_4O_8\cdot H_2O$	201–2	8
54	H	bond	3	NBu_2	$C_{24}H_{33}N_3O\cdot3HCl\cdot{}^1/_2H_2O$	215–8[e]	30[d]

[a] All compounds exhibited satisfactory (±0.4%) elemental analysis as salts. [b] Recrystallized from petroleum ether except where noted. [c] Procedure D in the Experimental Section except where noted. [d] Procedure E in the Experimental Section. [e] Recrystallized from methanol–ether.

Scheme III



Scheme IV



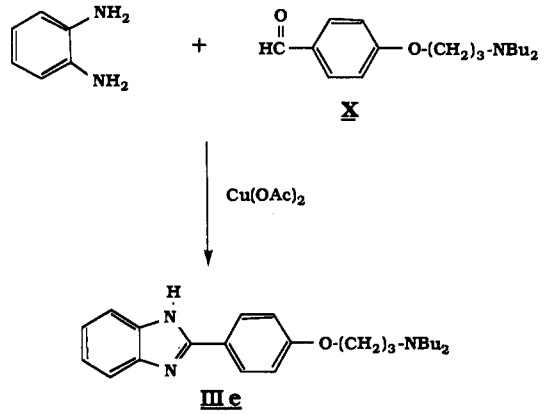
The corresponding 1,3-benzimidazole derivatives (IIId,e, X = NR_1, NH) were prepared to complete our structure–activity relationships (SAR) studies. The benzimidazoles (IIId, Q = ethenyl), were synthesized by the condensation of 2-methyl-1,3-benzimidazole with the substituted benzaldehyde X in acetic anhydride[11] (Scheme IV). The 4-[3-(dibutylamino)propoxy]benzaldehyde X was derived from the benzaldehyde VI by dibutylamine displacement of the chloride. Benzimidazole (IIIe, Q = direct bond) was produced by condensing 1,2-phenylenediamine with X in the presence of copper acetate (Scheme V). The benzimidazoles prepared are summarized in Table IV.

Results and Discussion

Of the variety of substituted thiazoles, benzoxazoles, and benzothiazoles prepared, many were found to possess both in vitro and in vivo gastric antisecretory activity. The in vitro antisecretory activity was measured indirectly by using isolated rabbit parietal cells, which were stimulated by either exogeneous histamine or dibutyryl cyclic adenosine 3′,5′-monophosphate (dcAMP). Accumulation of the radiolabeled marker amino[^{14}C]pyrine (^{14}C-AP) was used

(11) Sullivan, W. R. *J. Med. Chem.* **1970**, *13*, 784.

Scheme V



as an indirect measurement of parietal cell stimulation.[12] Compounds were evaluated for their ability to inhibit histamine stimulation, which elicits secretion via a histamine mechanism, and dcAMP stimulation, which is suggestive of an internal cellular mechanism of ^{14}C-AP uptake. The in vivo antisecretory activity was determined in the 4 h pylorous ligated rat by the method of Shay.[13] The antisecretory activity for these compounds is summarized in Tables V and VI and is compared to known antisecretory standards, cimetidine,[3] ranitidine,[4] and omeprazole.[5]

In the substituted thiazole series (Table V), the 2-position of the thiazole ring was altered while the 4-[3-(dibutylamino)propoxy]phenyl group was maintained as the (aryloxy)alkylamino side chain. Placement of a phenyl group in the 2-position (**2**) produced a compound that was more potent than cimetidine both in vitro and in vivo in our antisecretory assays whereas methyl substitution in the 2-position (**1**) gave little activity. Methyl or ethyl substitution (**3**, **4**) at the 5-position maintained activity for the inhibition of ^{14}C-AP uptake but diminished the in vivo potency. Substitution on the phenyl ring in **2** regardless of electron-withdrawing or electron-donating groups (**5–9**) or replacement of the phenyl moiety with pyridine (**10**) lessened potency in both in vitro and in vivo assays.

The effects of varying the length of the side chain (n) were next explored while the phenyl group at the 2-position and a terminal dibutylamino group (**11–13**) were maintained. Results obtained by lengthening or shortening the side chain can be summarized as follows: four methylene (**12**) and five methylene (**13**) unit separations are equivalent and more potent than the two methylene (**11**) unit separation, while the three methylene unit side chain (**2**) possessed the best in vitro and in vivo antisecretory activity.

Variation of the alkylamino group, while maintaining a phenyl group in the 2-position and a propylene side chain separation, was then studied. A variety of dialkylamine (**14**, **15**), cycloalkylamine (**16**, **17**), and heterocyclic amine (**18**, **19**) derivatives were prepared, and all possessed activity greater than that of cimetidine for the inhibition of ^{14}C-AP uptake. Replacement of the dibutylamino group with an imidazole group (**18**) resulted in a compound with significantly improved potency both in vitro and in vivo and approximately equal to that of ranitidine.

Since the imidazole group was superior as an amine terminus in this series of compounds, the effects of side-chain length and substituents on the phenyl ring were restudied for this amine substitution. Similar to our earlier observation, lengthening the side chain separation to four methylene units (**20**) decreased both the in vitro and in vivo activity. Substituents on the phenyl ring (**21**) or replacement of the phenyl ring with a 3-pyridyl group (**22**) also resulted in decreased potency. The compound with the best antisecretory profile in the thiazole series (**18**) was chosen for further study in dogs.

Table V. Antisecretory Activity of Various Substituted Thiazoles

compd	inhibn of ^{14}C-AP uptake[a] vs histamine	inhibn of ^{14}C-AP uptake[a] vs cAMP	inhibn of H^+K^+-ATPase[b]	inhibn of total acid secretion[c]
1	1.5	8.4	22%	8%
2	0.45	0.42	47%	75%, ED_{50} = 17.0 (14.3–20.7)
3	0.27	0.23	65%	36%
4	0.34	0.24	5%	NT[f]
5	2.1	1.8	55%	40%
6	0.48	0.23	33%	4%
7	1.5	3.0	24 μM	41%
8	2.9	2.0	11 μM	40%[d]
9	0.26	0.54	30%	17%
10	1.65	0.88	20 μM	19%
11	0.31	0.35	44%	41%
12	0.13	0.12	64%	56%
13	0.49	0.86	58%	54%
14	0.12	0.09	47 μM	82%[d]
15	0.23	0.18	60%	94%[d]
16	0.39	<10	32 μM	36%
17	0.11	0.05	34 μM	46%
18	0.08	0.02	18 μM	91%, ED_{50} = 5.1 (3.6–6.6)
19	10.0	NT[f]	36%	72%[e]
20	0.82	0.31	0%	31%[d]
21	0.37	0.62	>100	27%
22	3.3	3.0	>100	53%
cimetidine	0.82	>100		ED_{50} = 32 (27–39)
ranitidine	0.04	>100		ED_{50} = 9.1 (7.5–11.3)
omeprazole	0.25 ± 0.07	0.28 ± 0.07	3.3 ± 0.33 μM	ED_{50} = 7.1 (6.1–8.2)

[a] Inhibition of ^{14}C-AP uptake as IC_{50} values in micromolar concentration as determined in the isolated rabbit parietal cell preparation. All values are the mean ± 15% (n = 4). [b] Inhibition of H^+K^+-ATPase enzyme at 100 μM except where IC_{50} values (μM) are noted. All values are the mean ± 15% (n = 4). [c] Inhibition of total acid secretion in pylorous-ligated rats at 20 mg/kg (id) except where noted. Values are the mean ± 15% (n = 10); 95% fiducial limits in brackets. [d] Dose of 40 mg/kg (id). [e] Dose of 10 mg/kg (id). [f] Not tested.

In the benzoxazole and benzothiazole series (Table VI), a different story unfolds. All of the compounds were more potent in vitro (^{14}C-AP uptake assay) than cimetidine. Substitution on the benzoxazole or benzothiazole ring (**24–25**, **38–40**) does not influence this activity, in contrast to the thiazole series. When the ethylene spacer was removed (Q = direct bond) (**51**), the in vivo antisecretory potency was reduced compared to that of the corresponding styryl counterpart (**42**).

Variation of the alkylamino group while maintaining a propylene side chain separation was studied (**26–28**, **41–44**). Similar to the thiazole derivatives, introduction of the imidazole group as the amine (**28**, **44**) retained cimetidine-like potency for the inhibition of ^{14}C-AP uptake. However, in sharp contrast to the thiazole derivatives, compounds **28** and **44** failed to achieve the in vivo ranitidine-like potency as observed for compound **18**.

Similar to the thiazole series, lengthening the alkoxy side chain to four methylene units in the benzoxazole series (**30**) enhanced the inhibition of ^{14}C-AP uptake potency, yet reduced the in vivo potency. Substituting a variety of amines while the butylene side chain was maintained (**30–35**, **46–49**) indicated that the dipropylamino substi-

(12) Soll, A. H. *Am. J. Physiol.* **1980**, *238*, G366.
(13) Shay, H.; Sun, D. C. H.; Gruenstein, M. *Gastroenterology* **1954**, *26*, 906.

Table VI. Antisecretory Activity of Various Benzoxazoles, Benzothiazoles, and Benzimidazoles

compd	inhibn of ^{14}C-AP uptake[a] vs histamine	inhibn of ^{14}C-AP uptake[a] vs cAMP	inhibn of H^+K^+-ATPase[b]	inhibn of total acid secretion[c]
23	0.15	0.15	17%	96%[d]
24	0.26	0.34	27 μM	88%[d]
25	0.08	0.05	26 μM	64%[d]
26	0.32	0.98	20%	54%[d]
27	0.22	0.35	25 μM	77%
28	0.29	0.25	64 μM	26%
29	0.26	0.54	43%	43%
30	0.18	<10	20 μM	14%[d]
31	0.08	0.12	74 μM	31%
32	0.39	0.11	21 μM	90%, ED_{50} = 11.5 (9.6–14.2)
33	0.17	0.24	84 μM	24%[d]
34	0.17	0.33	40 μM	42%
35	0.27	0.33	30 μM	14%
36	0.28	0.23	13 μM	45%
37	0.25	0.26	18 μM	40%
38	0.29	0.53	52%	14%
39	0.26	0.46	60 μM	31%
40	0.40	0.50	52%	26%[d]
41	0.37	0.15	54 μM	71%[d]
42	0.21	0.14	67%	42%
43	0.18	0.21	35 μM	32%
44	0.13	0.34	0%	22%
45	0.43	0.60	43%	14%
46	0.18	0.35	44 μM	52%
47	0.03	0.12	21 μM	93%,[d] ED_{50} = 13.6 (10.1–19.7)
48	0.16	0.26	17 μM	20%
49	0.20	0.26	22%	17%[d]
50	0.25	2.6	18 μM	NT[e]
51	0.21	0.14	67%	42%[d]
52	2.3	1.5	54 μM	2.8%[d]
53	0.8	2.6	88 μM	1.6%
54	1.8	1.2	17 μM	24%[d]
cimetidine	0.82	>100		ED_{50} = 32 (27–39)
ranitidine	0.04	>100		ED_{50} = 9.1 (7.5–11.3)
omeprazole	0.25 ± 0.07	0.28 ± 0.07	3.3 ± 0.33 μM	ED_{50} = 7.1 (6.1–8.2)

[a] Inhibition of ^{14}C-AP uptake as IC_{50} values in micromolar concentration as determined in the isolated rabbit parietal cell preparation. All values are the mean ± 15% (n = 4). [b] Inhibition of H^+K^+-ATPase enzyme at 100 μM except where IC_{50} values (μM) are noted. All values are the mean ± 15% (n = 4). [c] Inhibition of total acid secretion in pylorous-ligated rats at 20 mg/kg (id) except where noted. Values are the mean ± 15% (n = 10); 95% fiducial limits in brackets. [d] Dose of 40 mg/kg (id). [e] Not tested.

tution in both the benzoxazole and benzothiazole series produced compounds (**32**, **47**) that possessed in vivo potency similar to ranitidine. In contrast to the above, benzoxazole and benzothiazole derivatives, benzimidazoles **52–54** had no in vivo antisecretory activity even at 40 mg/kg.

These series of thiazoles, benzoxazoles, and benzothiazoles possessed good activity for inhibition of ^{14}C-AP uptake stimulated by either histamine or dcAMP. Inhibition of the dcAMP response suggests that these compounds may exert their antisecretory activity via an internal mechanism of action, e.g. inhibition of the H^+K^+-sensitive ATPase enzyme. To further characterize this potential mechanism of action, these compounds were evaluated as H^+K^+-ATPase enzyme inhibitors.[14]

Within the series of thiazoles, benzoxazoles, and benzothiazoles, a good overall correlation is observed between the inhibition of ^{14}C-AP uptake, in vivo total acid secretion, and inhibition of the H^+K^+-sensitive ATPase enzyme. The more potent compounds, from our previous discussion, in each of these series (**18**, **32**, **47**) were also more potent as H^+K^+-ATPase inhibitors with IC_{50} values of 18, 21, and 21 μM, respectively. The benzimidazole **54** also possessed an IC_{50} value of 17 μM as a H^+K^+-ATPase inhibitor; however, the lack of in vivo antisecretory activity suggests that this compound may be either a nonspecific enzyme inhibitor or have poor bioavailability.

Although a good overall correlation exists between the inhibition of ^{14}C-AP uptake in parietal cells as stimulated by dcAMP and the inhibition of the H^+K^+-sensitive ATPase enzyme, some exceptions to this correlation may be noted. In each series, there were compounds that were potent inhibitors of dcAMP-stimulated ^{14}C-AP uptake but weak H^+K^+-ATPase inhibitors (**4**, **23**, **42**). Likewise, there were compounds that were potent inhibitors of the H^+K^+-ATPase enzyme but weak inhibitors of dcAMP stimulated ^{14}C-AP uptake (**16**, **30**, **50**). These deviant results do not alter the overall correlation between the two assays and are difficult to explain.

Although compounds **18**, **32**, and **47** are 5–6 times less potent than omeprazole as inhibitors of H^+K^+-ATPase, further studies are necessary to determine whether these compounds are reversible binding agents, unlike omeprazole which is irreversible. The data suggest that the mechanism of action for the observed gastric antisecretory activity of the thiazoles, benzoxazoles, and benzothiazoles could be related to their H^+K^+-sensitive ATPase inhibition and not to inhibition of the histamine H_2 receptor. Further studies in dogs to characterize their antisecretory profile are currently in progress.

Experimental Section

Melting point determinations were done on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer IR8 and are reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker WP-100 (100 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield relative to tetramethylsilane as standard. Mass spectra (MS) were obtained on a Finnigan-MAT Model 8230 instrument. Combustion analyses were ±0.4% of theory unless otherwise noted. Compounds in the tables were prepared according to the general procedures described. Physical properties of the compounds are summarized in Tables I–IV.

Procedure A. 4-(3-Chloropropoxy)acetophenone. To a mixture of 4-hydroxyacetophenone (50.7 g, 0.37 mol) and 1-bromo-3-chloropropane (160 mL, 1.5 mol) in methanol (250 mL) was added portionwise potassium hydroxide (63 g, 1.12 mol). The mixture was stirred at reflux for 24 h, cooled to room temperature, filtered through Celite, and evaporated in vacuo. The residual semisolid was diluted with diethyl ether (500 mL) and washed with H_2O (2 × 300 mL). The ether solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give the title compound as a liquid in 68% yield (53.3 g). ^{1}H NMR ($CDCl_3$): δ 7.98–7.89 (d, J = 8.9 Hz, 2 H), 7.02–6.92 (d, J = 8.9 Hz, 2 H), 4.16 (t, J = 5.9 Hz, 2 H), 3.75 (t, J = 6.4 Hz, 2 H), 2.52 (s, 3 H), 2.34–2.16 (m, 2 H).

α-Bromo-4-(3-chloropropoxy)acetophenone (IV). To a stirred solution of the above compound (53.3 g, 0.25 mol) in diethyl ether (250 mL) was slowly added bromine (13.0 mL, 0.25 mol), and the mixture was allowed to stir at room temperature for 16 h. The dark mixture was poured into an aqueous saturated sodium bicarbonate solution (300 mL), and the organic layer was separated. The ether layer was washed with an aqueous saturated sodium bicarbonate solution (300 mL) and with water (300 mL) and was dried over $MgSO_4$. The solution was filtered and evaporated in vacuo to yield IV (64.4 g, 88%) as a dark oil. ^{1}H NMR ($CDCl_3$): δ 7.96 (d, J = 8.9 Hz, 2 H), 6.95 (d, J = 8.9 Hz, 2 H), 4.41 (s, 2 H), 4.19 (t, 2 H), 3.75 (t, 2 H), 2.26 (m, 2 H).

2-Substituted 4-[4-(3-Chloropropoxy)phenyl]thiazole (V). A mixture of IV (26 g, 89 mmol) and thiobenzamide (R = Ph, 12

(14) Wallmark, B.; Jaresten, B. M.; Larsson, H.; Ryberg, B.; Brandstrom, A.; Fellenius, E. *Am. J. Physiol.* **1983**, *245*, G64.

g, 89 mmol) in ethanol (150 mL) was stirred at reflux for 3 h, cooled to room temperature, and filtered to give V (R = Ph, R_1 = H, n = 3) (17.6 g, 56%) as a brown solid, mp 72–75 °C. IR (KBr): 1610 cm^{-1}. MS: 330 (M^+). ^1H NMR ($CDCl_3$): δ 7.95 (m, 4 H), 7.33 (m, 4 H), 6.98 (d, J = 8 Hz, 2 H), 4.17 (t, J = 5.9 Hz, 2 H), 3.78 (t, J = 5.9 Hz, 2 H), 2.25 (m, 2 H). Anal. ($C_{18}H_{16}ClNOS$) H, N; C: calcd, 65.54; found, 64.86.

4-[4-[3-(Dibutylamino)propoxy]phenyl]-2-phenylthiazole (2). A suspension of V (R = Ph, R_1 = H) (5.6 g, 17.1 mmol) in dibutylamine (60 mL) was stirred at 120 °C for 5 h. The excess dibutylamine was removed by distillation, and the resulting oil was flash chromatographed (SiGel, 9:1 CH_2Cl_2–MeOH) to give the free base of the title compound as an oil. The HCl salt was prepared by addition of concentrated HCl to a solution of the free base in methanol; concentration and recrystallization from acetone yielded **2** (2.58 g, 75%) as an off-white solid, mp 131–134 °C. IR (KBr): 2030, 1615 cm^{-1}. MS: 422 (M^+). ^1H NMR (CD_3OD): δ 8.00–7.57 (m, 8 H), 7.14–7.05 (m, 2 H), 4.20 (t, J = 5.8 Hz, 2 H), 3.21 (m, 6 H), 2.28 (m, 2 H), 1.85–1.34 (m, 8 H), 1.01 (m, 6 H).

Procedure B. 4-(3-Chloropropoxy)benzaldehyde (VI, *n* = 3). To a suspension of sodium hydride (50% in oil, 3.9 g, 82 mmol) in dimethylformamide (100 mL) was added the 4-hydroxybenzaldehyde (5.0 g, 41 mmol). The mixture was stirred at room temperature under an atmosphere of nitrogen for 1 h and then was treated dropwise with 1-bromo-3-chloropropane (8.1 mL, 82 mmol). The mixture was stirred at room temperature for 12 h, quenched with methanol, and filtered through Celite. The filtrate was dissolved in diethyl ether (500 mL), washed with water (3 × 200 mL), and dried over Na_2SO_4. The ether layer was concentrated to give 6.1 g (80%) of VI (n = 3) as a yellow liquid. ^1H NMR ($CDCl_3$): δ 9.95 (s, 1 H), 7.85 (d, J = 8.1 Hz, 2 H), 7.01 (d, J = 8.1 Hz, 2 H), 4.21 (t, J = 5 Hz, 2 H), 3.81 (t, J = 5 Hz, 2 H), 1.26 (m, 2 H).

(*E*)-2-[2-[4-(3-Chloropropoxy)phenyl]ethenyl]benzoxazole (VIIa, *n* = 3). To a solution of VI (n = 3, 5.0 g, 25 mmol) and 2-methylbenzoxazole (3.1 mL, 25 mmol) in dimethyl sulfoxide (25 mL) was added a 50% aqueous sodium hydroxide solution (15 mL). The solution was stirred at room temperature for 24 h and diluted with ice water (1.0 L), and the resulting precipitate was collected by filtration. The precipitate was washed with water and was dried in vacuo to give VIIa (n = 3, 6.4 g, 79%) as a yellow solid, mp 82–83 °C. IR (KBr): 1600 cm^{-1}. MS: 313 (M^+). ^1H NMR ($CDCl_3$): δ 7.88–6.79 (m, 10 H), 4.19 (t, J = 5 Hz, 2 H), 3.79 (t, J = 5 Hz, 2 H), 2.31 (m, 2 H). Anal. ($C_{18}H_{16}ClNO_2$) C, H, N.

In a similar manner, (*E*)-2-[2-[4-(3-chloropropoxy)phenyl]-ethenyl]benzothiazole (VIIb, n = 3), by using 2-methyl-1,3-benzothiazole, was prepared as a yellow solid, mp 97–99 °C. ^1H NMR ($CDCl_3$): δ 8.15–6.91 (m, 10 H), 4.15 (t, J = 5.2 Hz, 2 H), 3.81 (t, J = 5.2 Hz, 2 H), 2.21 (m, 2 H).

(*E*)-2-[2-[4-[3-(Dibutylamino)propoxy]phenyl]ethenyl]-benzoxazole (23). A solution of VIIa (n = 3, 6.0 g, 19 mmol) in 60 mL of dibutylamine was heated to 150 °C for 12 h. The excess dibutylamine was removed by distillation, and the resulting oil was purified by flash chromatography (SiGel, 9:1 $CHCl_3$–MeOH) to give 5.8 g (75%) of the free base of the title compound. The HCl salt was prepared by the addition of concentrated HCl to a solution of the free base in methanol; concentration and recrystallization from acetone gave **23** as a yellow solid, mp 153–154 °C. IR (KBr): 3400, 1595 cm^{-1}. MS: 406 (MH^+). ^1H NMR ($CDCl_3$): δ 7.99–6.81 (m, 10 H), 4.15 (t, J = 5 Hz, 2 H) 3.09 (m, 6 H), 2.44 (m, 2 H), 1.99–0.87 (m, 16 H). Anal. ($C_{26}H_{34}N_2O_2$) C, H, N.

(*E*)-2-[2-[4-[3-(Dibutylamino)propoxy]phenyl]ethenyl]-benzothiazole (37), mp 181–182 °C. IR (KBr): 3400, 1595 cm^{-1}. MS: 422 (M^+). ^1H NMR ($CDCl_3$): δ 7.88–6.81 (m, 10 H), 4.12 (t, J = 5.3 Hz, 2 H), 3.02–2.59 (m, 6 H), 2.25–0.84 (m, 16 H). Anal. ($C_{26}H_{34}N_2OS \cdot 2HCl \cdot 2H_2O$) C, H, N.

Procedure C. 4-(3-Chloropropoxy)benzoic Acid. To a suspension of sodium hydride (50%, 8.0 g, 164 mmol) in dimethylformamide (200 mL) was added 4-hydroxybenzoic acid (10.0 g, 82 mmol) portionwise. The mixture was stirred at room temperature for 2 h, treated with 1-chloro-3-bromopropane (16 mL, 164 mmol), and allowed to stir at room temperature for 48 h. The mixture was quenched with methanol, acidified with concentrated HCl, and filtered through Celite. The filtrate was diluted with diethyl ether (500 mL), washed with H_2O (3 × 200 mL), and dried over Na_2SO_4. The ether solution was concentrated to give 4-(3-chloropropoxy)benzoic acid (1.1 g, 6%) as an off-white solid, mp 136–138 °C. ^1H NMR (DMSO): δ 12.00 (s, 1 H), 7.88 (d, J = 8.8 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 2 H), 4.24 (t, J = 5.0 Hz, 2 H), 3.54 (t, J = 5.1 Hz, 2 H), 2.23 (m, 2 H).

2-[4-[3-(Dibutylamino)propoxy]phenyl]benzothiazole (50). To a solution of the above benzoic acid (10 g, 47 mmol) in anhydrous tetrahydrofuran (50 mL) was added oxalyl chloride (4.0 mL, 47 mmol) dropwise. The reaction was heated to 50 °C for 2 h, concentrated, and then treated with a solution of 2-aminothiophenol (5.0 mL, 47 mmol) in tetrahydrofuran (20 mL). The solution was stirred until it solidified. The resulting precipitate was filtered and recrystallized from methylene chloride–hexanes to give 1.1 g (67%) of IX as a yellow solid. ^1H NMR ($CDCl_3$): δ 8.21–6.79 (m, 8 H), 4.19 (m, 2 H), 3.68 (m, 2 H), 2.21 (m, 2 H).

The title compound was prepared as described above with IX (1.0 g, 3.1 mmol) and dibutylamine (5.0 mL) as starting materials to produce 0.42 g (35%) of **50**, which was converted to the HCl salt, mp 136–137 °C. IR (KBr): 3400, 1600 cm^{-1}. MS: 379 (M^+). ^1H NMR ($CDCl_3$): δ 8.42–6.85 (m, 8 H), 4.21 (t, J = 5.1 Hz, 2 H), 3.12 (m, 6 H), 1.99–0.85 (m, 16 H). Anal. ($C_{24}H_{32}N_2OS \cdot 2HCl \cdot {}^1/_2H_2O$) C, H, N.

Procedure D. 4-[3-(Dibutylamino)propoxy]benzaldehyde (X). A solution of the chloride VI (n = 3, 8.0 g, 38 mmol) in dibutylamine (50 mL) was heated to 150 °C for 12 h. The excess dibutylamine was removed in vacuo, and the resulting oil was chromatographed (SiGel, 9:1 CH_2Cl_2–MeOH) to give 7.5 g (65%) of X as a thick yellow oil. ^1H NMR ($CDCl_3$): δ 9.21 (s, 1 H), 7.88 (d, J = 8.8 Hz, 2 H), 7.10 (d, J = 8.8 Hz, 2 H), 4.11 (t, 2 H), 2.65 (m, 6 H), 1.98–0.91 (m, 18 H).

(E)-2-[2-[4-[3-(Dibutylamino)propoxy]phenyl]ethenyl]-benzimidazole (52). To a solution of the aldehyde X (2.6 g, 9.0 mmol) in acetic anhydride (1 mL) was added 2-methyl-1,3-benzimidazole in 2 mL of acetic anhydride. The solution was heated to 125 °C for 16 h and then was concentrated. The residue was dissolved in methylene chloride and washed with aqueous sodium bicarbonate solution and brine, and the organic layer was evaporated in vacuo. The crude material was chromatographed (Flash, SiGel, 9:1 CH_2Cl_2–Et_2O) to give the free base of the title compound as an oil (0.46 g, 13%). The oxalate salt was prepared by the addition of anhydrous oxalic acid to a solution of the free base in methanol; collection of the precipitate and recrystallization from petroleum ether gave **52** as a white solid, mp 200–202 °C. MS: 406 (MH^+). ^1H NMR ($CDCl_3$): δ 7.60–7.05 (m, 11 H), 4.12 (t, J = 5 Hz, 2 H) 3.11 (m, 6 H), 2.10 (m, 2 H), 1.50–0.90 (m, 14 H). Anal. ($C_{26}H_{35}N_3O \cdot C_4H_4O_8 \cdot H_2O$) C, H, N.

Procedure E. 2-[4-[3-(Dibutylamino)propoxy]phenyl]-benzimidazole (54). To a suspension of copper acetate (2.4 g, 12 mmol) in water (20 mL) was added a solution of 1,2-phenylenediamine (0.65 g, 6.0 mmol) in methanol (20 mL) followed by the aldehyde X (1.75 g, 6.0 mmol). The mixture was heated to reflux for 30 min, and the methanol was removed in vacuo. A 2 N HCl solution (20 mL) was added and heated to 60 °C for 2 h. The reaction was cooled to 0 °C, treated with 2 N sodium hydroxide (21 mL), dissolved in methylene chloride, and washed with aqueous sodium bicarbonate solution and brine, and the organic layer was evaporated in vacuo. The crude material was chromatographed (Flash, SiGel, 9:1 CH_2Cl_2–Et_2O) to give the free base of the title compound as a solid (0.63 g, 8%). The HCl salt was prepared by the addition of concentrated HCl to a solution of the free base in methanol and recrystallized from methanol–ether to yield **54** as a white solid, mp 215–218 °C. MS: 380 (MH^+). ^1H NMR ($CDCl_3$): δ 8.20–7.25 (m, 9 H), 4.20 (t, J = 5 Hz, 2 H) 3.11 (m, 6 H), 2.21 (m, 2 H), 1.53–0.90 (m, 14 H). Anal. ($C_{24}H_{33}N_3O \cdot 3HCl \cdot {}^1/_2H_2O$) C, H, N.

Isolated Rabbit Parietal Cell Assay. Inhibition of acid secretion was measured indirectly in vitro with an isolated rabbit parietal cell preparation.[15] Parietal cells were isolated from the fundic mucosa of rabbit stomachs by a four-stage collagenase digestion process. The supernatant fraction from the last two

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stages contained the individual parietal cells. The cell suspension was centrifuged and reconstituted in a modified Hank's buffer to contain 2–3 × 10^6 cells/mL. The cells were then tested for their ability to accumulate amino[^{14}C]pyrine (^{14}C-AP). Parietal cells were incubated with 0.23 μCi of ^{14}C-AP, 1 × 10^{-6} M histamine or 3 × 10^{-4} M dibutyryl cAMP, 1 × 10^{-5} M isobutylmethylxanthine, and test compound in 0.02 mL of dimethyl sulfoxide with a final incubation volume of 2.0 mL. The flasks were incubated at 37 °C, aliquots were taken, and cell pellets were collected by centrifugation. Pellets were solubilized with Protosol (New England Nuclear), and radioactivity was determined by liquid scintillation spectrometry. Data are expressed as the concentration of drug required to inhibit the histamine or dibutyryl cAMP response. The data reported is the mean of four experiments with confidence limits ±15%.

Isolated H^+K^+-ATPase Assay. The inhibition of parietal cell H^+K^+-ATPase was determined with microsomal preparations obtained from the fundic mucosa from New Zealand white rabbits.[16,17] Fundic mucosa were homogenized in a modified Tris buffer consisting of 250 mM sucrose, 0.2 mM EDTA, and 5.0 mM Tris, adjusted to pH 7.4 with HCl. The H^+K^+-ATPase enzyme activity was measured in a 1-mL incubation volume containing 50 mM Tris pH 7.4, 2 mM $MgCl_2$, 2 mM Na_2ATP, with or without 20 mM KCl and vehicle control (dimethyl sulfoxide) or test compound added in a 0.02-mL volume. Typically, 20–50 mg of membrane protein was added, and the tubes were preincubated with test compound for 10 min at 37 °C. Substrate, Na_2ATP, was then added, and the tubes were incubated for another 15 min at 37 °C. The reaction was stopped by the addition of 14% trichloroacetic acid (1 mL), and the samples were centrifuged at 2000*g* for 10 min. The amount of inorganic phosphate present in an aliquot of supernatant was determined.[18] The H^+K^+-ATPase activity was determined after correcting for basal (Mg^{2+} only) enzyme activity present in membrane preparation.[15] The data reported is the mean of four experiments with confidence limits ±15%.

Pylorous-Ligated Rat Assay. The in vivo antisecretory activity was determined in pylorus-ligated rats. Male Charles River rats weighing 150–300 g were deprived of food but not water for 18–24 h prior to use. The rats were weighed and anesthetized with ether, and the pylorus was ligated according to the method of Shay.[13] Treatment or vehicle control was then administered intraduodenally (id). Rats were housed two per cage and sacrificed with CO_2 4 h after ligation. The stomachs were removed and rinsed, and the contents were emptied into a graduated centrifuge tube. The tubes were centrifuged, the volume of gastric juice was recorded, and any samples obviously contaminated by feces, food, or blood were eliminated. A 1-mL aliquot of gastric juice was titrated with 0.1 N NaOH to a pH of 7.0–7.4, and the total amount of acid secreted was determined. ED_{50} values and 95% confidence limits for total acid output were determined from the least-squares regression.[19] The data reported is the mean from 10 animals with confidence limits ±20% and are quantal numbers.

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Registry No. 1, 114979-74-7; 1·2HCl, 114979-18-9; **2**, 114979-75-8; **2**·HCl, 114979-19-0; **3**, 114995-25-4; **3**·2HCl, 114979-20-3; 4, 114979-76-9; 4·HCl, 114979-21-4; **5**, 114979-77-0; **5**·HCl, 114979-22-5; **6**, 114979-78-1; **6**·2HCl, 114979-23-6; **7**, 114979-79-2; **7**·2HCl, 114979-24-7; **8**, 114979-80-5; **8**·HCl, 114979-25-8; **9**, 114979-81-6; **9**·HCl, 114979-26-9; **10**, 114979-82-7; **10**·2HCl, 114979-27-0; 11, 114979-83-8; 11·HCl, 114979-28-1; **12**, 114979-84-9; **12**·HCl, 114979-29-2; **13**, 114979-85-0; **13**·HCl, 114979-30-5; 14, 114979-86-1; 14·HCl, 114979-31-6; **15**, 114979-87-2; **15**·HCl, 114979-32-7; **16**, 114979-88-3; **16**·HCl, 114979-33-8; **17**, 114979-89-4; **17**·HCl, 114979-34-9; **18**, 114979-90-7; **18**·HCl, 114979-35-0; **19**, 114979-91-8; **19**·HCl, 114979-36-1; **20**, 114979-92-9; **20**·HCl, 114979-37-2; **21**, 114979-93-0; **21**·HCl, 114995-24-3; **22**, 114979-94-1; **22**·HCl, 114979-38-3; **23**, 114979-95-2; **23**·HCl, 114979-39-4; **24**, 114979-96-3; **24**·2HCl, 114979-40-7; **25**, 114979-97-4; **25**·HCl, 114979-41-8; **26**, 114979-98-5; **26**·HCl, 114979-42-9; **27**, 114979-99-6; **27**·2HCl, 114979-43-0; **28**, 114980-00-6; **28**·HCl, 114979-44-1; **29**, 114980-01-7; **29**·HCl, 114979-45-2; **30**, 114980-02-8; **30**·HCl, 114979-46-3; **31**, 114980-03-9; **31**·HCl, 114979-47-4; **32**, 114980-04-0; **32**·2HCl, 114979-48-5; **33**, 114980-05-1; **33**·HCl, 114979-49-6; **34**, 114980-06-2; **34**·HCl, 114979-50-9; **35**, 114980-07-3; **35**·HCl, 114979-51-0; **36**, 114980-08-4; **36**·2HCl, 114979-52-1; **37**, 114980-09-5; **37**·2HCl, 114979-53-2; **38**, 114980-10-8; **38**·2HCl, 114979-54-3; **39**, 114980-11-9; **39**·2HCl, 114979-55-4; **40**, 114980-12-0; **40**·2HCl, 114979-56-5; **41**, 114980-13-1; 41·2HCl, 114979-57-6; **42**, 114980-14-2; **42**·2HCl, 114979-58-7; **43**, 114980-15-3; **43**·HCl, 114979-59-8; **44**, 114980-16-4; 44·2HCl, 114979-60-1; **45**, 114980-17-5; **45**·2HCl, 114979-61-2; **46**, 114980-18-6; **46**·2HCl, 114979-62-3; **47**, 114980-19-7; **47**·HCl, 114979-63-4; **48**, 114980-20-0; **48**·HCl, 114979-64-5; **49**, 114980-21-1; **49**·HCl, 114979-65-6; **50**, 114995-26-5; **50**·2HCl, 114979-66-7; **51**, 114995-27-6; **51**·2HCl, 114979-67-8; **52**, 114979-68-9; **52**·2$C_2H_2O_4$, 114979-69-0; **53**, 114979-70-3; **53**·2$C_2H_2O_4$, 114979-71-4; **54**, 114980-22-2; **54**·3HCl, 114979-72-5; IV, 114604-68-1; V (R = Ph, *n* = 3), 114979-73-6; VI (*n* = 3), 82625-25-0; VIIa (*n* = 3), 114980-24-4; VIIb (*n* = 3), 114980-25-5; IX, 114980-28-8; X, 114980-27-7; H_3CCSNH_2, 62-55-5; Cl-*p*-$C_6H_4CSNH_2$, 2521-24-6; MeO-*p*-$C_6H_4CSNH_2$, 2362-64-3; Me-*p*-$C_6H_4CSNH_2$, 2362-62-1; F_3C-*p*-$C_6H_4CSNH_2$, 72505-21-6; HO-*p*-$C_6H_4COCH_2CH_3$, 70-70-2; HO-*p*-$C_6H_4COCH_2CH_2CH_3$, 1009-11-6; $BrCH_2CH_2Cl$, 107-04-0; $Br(CH_2)_4Cl$, 6940-78-9; $Br(CH_2)_5Cl$, 54512-75-3; 4-hydroxyacetophenone, 99-93-4; 1-bromo-3-chloropropane, 109-70-6; thiobenzamide, 2227-79-4; 4-(3-chloropropoxy)acetophenone, 91427-23-5; 3,5-dimethoxythiobenzamide, 114980-23-3; 3-pyridylthioamide, 4621-66-3; 4-hydroxybenzaldehyde, 123-08-0; 2-methylbenzoxazole, 95-21-6; 2-methyl-1,3-benzothiazole, 120-75-2; 5-methylbenzoxazole, 10531-78-9; 6-methoxybenzoxazole, 114980-26-6; 4-(3-chloropropoxy)benzoic acid, 65136-52-9; 4-hydroxybenzoic acid, 99-96-7; 2-aminothiophenol, 137-07-5; 2-methyl-1,3-benzimidazole, 615-15-6.

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