113859-31-7; **13b**, 113859-32-8; **13d**, 113859-33-9; **13e**, 113859-34-0; **13f**, 113859-35-1; **13g**, 113859-36-2; $EtOCH_2COCH_2COOEt$, 41051-14-3; $H_2NC(=NH)NH_2 \cdot Y_2H_2CO_3$, 593-85-1; diethyl (*p*-aminobenzoyl-L-glutamate, 13702-52-8.

Supplementary Material Available: Tables listing UV spectral data for pyrido[2,3-*d*]pyrimidines (**11b–g** and **1b,d–g**) and also ^1H NMR parameters for **11b–g** (2 pages). Ordering information is given on any current masthead page.

Substituted 2-[(2-Benzimidazolylsulfinyl)methyl]anilines as Potential Inhibitors of H^+/K^+ ATPase

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A series of substituted 2-[(2-benzimidazolylsulfinyl)methyl]anilines were synthesized as potential inhibitors of the acid secretory enzyme H^+/K^+ ATPase. Substitutions on the aniline nitrogen atom resulted in potent enzyme inhibition in vitro but weak activity in gastric fistula dogs. Electron-donating substituents on the aniline ring enhanced in vitro and in vivo potency relative to the unsubstituted analogue. The potency showed a correlation to the calculated pK_a of the aniline nitrogen atom. Substitutions on the aniline and benzimidazole rings did not further enhance potency. Di- and trisubstituted aniline derivatives were potent inhibitors of the enzyme system. The preferred combination of substituents were a methoxy group on the benzimidazole ring and a single alkyl group on the aniline ring. One such compound, **76**, was an effective inhibitor of acid secretion in the dog and was selected for further pharmacological study.

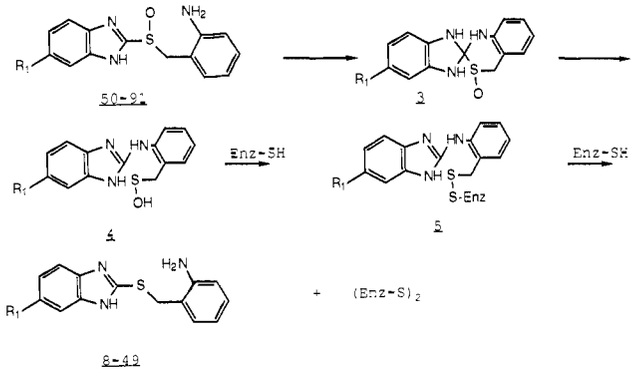
Investigations into the mechanism of gastric acid secretion and the design of new therapeutic agents were greatly stimulated following the discovery of histamine-2 antagonists as therapeutic agents for peptic ulcer disease. The identification of H^+/K^+ ATPase as the proton pump in the parietal cell soon led to the first series of inhibitors of the enzyme, omeprazole (**1**) and timoprazole (**2**).[1-3] Our interest in inhibitors of gastric acid secretion led us to explore structural modifications of substituted benzimidazole derivatives.

The mechanism of omeprazole's inhibitory action on the ATPase was reported recently.[4] In the presence of acid, **1** is transformed into a sulfenic acid, which ultimately oxidizes the enzyme to an inactive disulfide. During the process, **1** becomes reduced to its sulfide precursor. Although reduced **1** retains no in vitro activity, it has been shown in vivo that oxidation of sulfide to **1** occurs.[5]

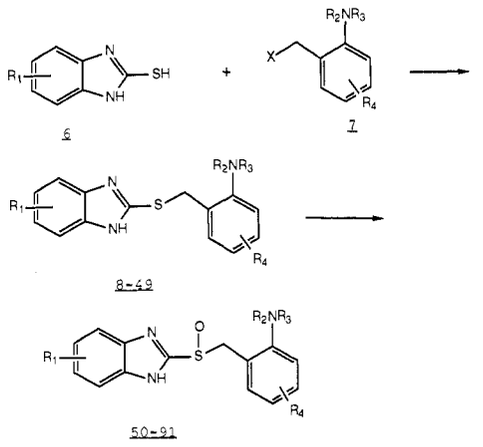
The in vitro inhibitory activity of substituted benzimidazoles was shown to be profoundly influenced by substituents on the benzimidazole and pyridine rings.[6] Thus the rate of decomposition of the sulfoxide should correlate with the basicity of the pyridine nitrogen, and the subsequent stability of the cyclic intermediate should be influenced by the benzimidazole ring substituent.

In view of the dependence on a weakly basic center situated proximal to the sulfoxide group, we replaced the pyridine ring of omeprazole and some analogues with substituted aniline groups (Table I). The observation that many of these aniline-derived compounds were potent inhibitors of H^+/K^+ ATPase was expected on the basis of a mechanistic pathway analogous to that of omeprazole.

Scheme I



Scheme II



A sulfenic acid **4** should be formed by acid-induced decomposition of sulfoxides **50–91** to form the sulfides **8–49** and oxidized enzyme via the covalently bound intermediate **5** (Scheme I). The synthesis of a similar series of compounds was recently disclosed in a patent,[7] and the bio-

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(7) Okabe, S.; Satoh, M.; Yamakura, T.; Nomura, Y.; Hayashi, M., to Nippon Chemifar, Belgian Patent No. BE 903128, 1986; *Chem. Abstr.* **1986**, *105*, 133 881*w*.

0022-2623/88/1831-1215$01.50/0

Table I. Biological Activities of 2-[(2-Benzimidazolylsulfinyl)methyl]anilines

compd	H^+/K^+ ATPase IC_{50}, μM	gastric fistula dog, % inhibn at 3 mg/kg, id (N)[a]
50	4.3	53 ± 17.6 (3)
51	11.0	78 ± 11.3 (3)
52	24.0	ND[b]
53	7.4	60[c] (1)
54	7.9	ND
55	12.0	ND
56	4.4	37 ± 18.3 (3)
57	13.5	44[c] (1)
58	120.0	ND
59	>100	37[c] (1)
60	0.6	21 ± 10.4 (3)
61	0.7	14[c] (1)
62	0.7	44 ± 18.2 (3)
63	2.1	67[c] (1)
64	3.2	44 ± 17.9 (3)
65	2.0	62 ± 24.8 (3)
66	3.9	21 ± 12.0 (3)
67	2.6	19 ± 18.3 (3)
68	1.6	37[c] (1)
69	9.3	68 (2)
70	>100	24[c] (1)
71	25.0	ND
72	24.0	13[c] (1)
73	>100	16 (2)
74	>100	7 ± 7.0 (3)
75	>100	28 ± 13.6 (3)
76	4.2	80 ± 3.6 (4)
77	5.4	72 ± 6.3 (3)
78	5.3	ND
79	>100	ND
80	8.5	ND
81	0.8	ND
82	0.8	*d*
83	0.6	79 ± 2.4 (3)
84	60	ND
85	6.4	ND
86	1.5	ND
87	0.7	ND
88	16.0	ND
89	0.2	53 ± 23.2 (3)
90	2.7	ND
91	2.1	31 ± 30.3 (3)
omeprazole	2.0	97 ± 1.8 (3)
timoprazole	130.0	68 ± 14.4 (3)

[a] SEM calculated for three or more experiments. [b] ND = not determined. [c] Compound administered intravenously. [d] Lethal at 10 mg/kg, id.

logical activity of **61** was described.[8]

Chemistry

Alkylation of 2-mercaptobenzimidazole **6** with a (halomethyl)- or (hydroxymethyl)aniline **7** under neutral or acidic conditions gave the desired sulfides **8–49** (Scheme II, Table II). The reaction solvent, EtOH or *i*-PrOH, was chosen so that the product **8** as the hydrohalide precipitated and could be isolated by filtration. This was important because acidic solutions of **8** decomposed rapidly. The hydrohalide salts of **8** were neutralized by direct addition to aqueous K_2CO_3, and the free bases were isolated by extraction with methylene chloride. Oxidation of **8–49** with *m*-chloroperbenzoic acid in chloroform or methylene chloride was conveniently carried out at 0 °C to give the sulfoxides **50–91**, respectively (Table III). Overoxidation to form sulfones occurred infrequently, but chromatographic separation provided sulfoxides free of sulfone contaminants.

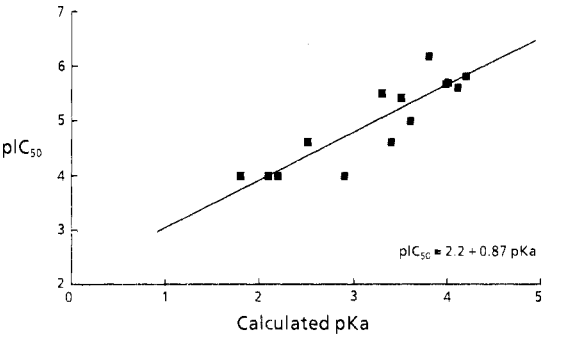

Figure 1. Correlation of calculated pK_a and pIC_{50} values for compounds **62–75** ($r^2 = 0.78$, $p < 0.001$).

The substituted 2-mercaptobenzimidazoles were either purchased or synthesized by known methods.[9] The substituted anilines were synthesized by known or modified methods. Refluxing solutions of (chloromethyl)- or (bromomethyl)aniline hydrohalides and 2-mercaptobenzimidazole in EtOH or *i*-PrOH provided sulfides as dihydrohalides (method A). Similarly, (hydroxymethyl)aniline and 2-mercaptobenzimidazole in HOAc containing H_2SO_4 gave sulfides, albeit in lower yields (method B). Solutions of the sulfides in methylene chloride or chloroform were treated with *m*-chloroperbenzoic acid at 0 °C to afford the sulfoxides in good yields (method C). The phthalimide-protected *o*-toluidine was brominated with NBS, and the crude bromide allowed to react with 2-mercaptobenzimidazole. The sulfide was oxidized with *m*-chloroperbenzoic acid, and the phthalimide group was removed with hydrazine hydrate to give the desired sulfoxide in good yields (method D). The *N*-pivaloylaniline derivative was metalated with *n*-butyllithium. The lithiated aromatic was allowed to react with DMF at −5 °C, and the resulting aldehyde was reduced with $NaBH_4$ to the benzyl alcohol derivative. Refluxing a solution of the benzyl alcohol derivative in concentrated HCl served to hydrolyze the pivaloylamide and convert the benzyl alcohol to the requisite chloromethyl aniline (method E). The *N*-arylphthalimide was hydroxymethylated directly with paraformaldehyde and gaseous HCl in concentrated H_2SO_4 (method F).

Results

Many of the aniline derivatives showed good activity in the in vitro H^+/K^+ ATPase inhibition assay. It was assumed that the mechanism of action must be similar to that of omeprazole, because of the dependence on acid activation prior to addition of the enzyme to the medium.[10] Single substituents on the benzimidazole ring (compounds **51–56**) had little additional effect on the enzyme inhibitory activity relative to the unsubstituted compound **50**. Benzimidazole rings containing two substituents (**57** and **58**) were less active than **50**. Both **57** and **58** were not very soluble in the assay medium, possibly accounting for the reduced activity.

Substitutions on the aniline nitrogen (**60** and **61**) by methyl groups sharply enhanced enzyme inhibition activity, whereas acetylation (**59**) markedly diminished activity. This observation suggests that the acid-induced rearrangement is triggered by protonation of the adjacent aniline nitrogen atom, and as the pK_a of the basic center

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Table II. 2-[(1*H*-Benzimidazol-2-ylthio)methyl]anilines

compd	R_1	R_2	R_3	R_4	method	% yield[a]	mp, °C (solv)[b]	formula	anal.[c]
8	H	H	H	H	a	20, 11 (method B)	146–148 (B)	$C_{14}H_{13}N_3S$	CHNS
9	5-MeO	H	H	H	A	20	140–142 (D)	$C_{15}H_{15}N_3OS$	CHNS
10	5-EtO	H	H	H	A	75	87–89 (C)	$C_{16}H_{17}N_3OS \cdot H_2O$	CHNS
11	4-Me	H	H	H	A	23	125–127 (C)	$C_{15}H_{15}N_3S$	CHNS
12	5-Me	H	H	H	A	61	244–293 (C)	$C_{15}H_{15}N_3S$	CHNS
13	5-Cl	H	H	H	A	63	240–280 (H)	$C_{14}H_{12}ClN_3S$	C[d]HNS
14	5-CF_3	H	H	H	A	37	156, br (C)	$C_{15}H_{12}F_3N_3S$	CHFNS
15	5,6-Me_2	H	H	H	A	60	(E)	$C_{16}H_{17}N_3S$	C[e]HNS
16	5,6-$(MeO)_2$	H	H	H	A	86	218–223 (N)		
17	H	Ac	H	H	A[f]	28	217–222 (B)	$C_{16}H_{15}N_3OS$	CHNS
18	H	Me	H	H	A[g]	55	109–112 (L)	$C_{15}H_{15}N_3S$	CHNS
19	H	Me	Me	H	a	63	167–170 (N)	$C_{16}H_{17}N_3S$	CHNS
20	H	H	H	3′-Me	A[h]	67	155, br (F)	$C_{15}H_{15}N_3S$	CHNS
21	H	H	H	4′-Me	A[i]	52	127–131 (F)	$C_{15}H_{15}N_3S$	CHNS
22	H	H	H	6′-Me	A[j]	48	130–134 (P)	$C_{15}H_{15}N_3S$	CHNS
23	H	H	H	4′-Et	E[k]	33	111–112 (D)	$C_{16}H_{17}N_3S$	CHNS
24	H	H	H	6′-Et	E[l]	65	(gum)	$C_{16}H_{17}N_3S$	C[m]HNS
25	H	H	H	4′-*n*-Bu	E[n]	13	108–109 (K)		
26	H	H	H	4′-MeO	A[o]	52	206–208 (J)	$C_{15}H_{15}N_3OS \cdot 2HCl$	CHCl[p]NS
27	H	H	H	6′-MeO	A[q]	52	130, br (F)	$C_{15}H_{15}N_3OS \cdot 0.5H_2O$	C[r]HN[s]S
28	H	H	H	4′-Cl	A[t]	21	114–118 (F)	$C_{14}H_{12}ClN_3S$	CHClNS
29	H	H	H	4′-F	*a*	15			
30	H	H	H	5′-Cl	A[u]	26	158–161 (B)	$C_{14}H_{12}ClN_3S$	CHClNS
31	H	H	H	4′-CF_3	*a*	29	130–137 (C)	$C_{15}H_{12}F_3N_3S$	CHFNS
32	H	H	H	4′-CO_2Et	A[v]	38	174–176 (H)	$C_{17}H_{17}N_3O_2S$	CHNS
33	H	H	H	6′-CO_2Me	A[w]	65	122–130 (L)	$C_{16}H_{15}N_3O_2S \cdot {}^1/_4H_2O$	CHNS[x]
34	5-MeO	H	H	4′-Me	A	44	128, br (C)	$C_{16}H_{17}N_3OS$	C[y]HNS
35	5-MeO	H	H	6′-Me	A	49	132–134 (K)	$C_{16}H_{17}N_3OS$	CHNS
36	5-EtO	H	H	4′-Me	A	54	(C)		
37	5-MeO	H	H	4′-CO_2Et	A	25	140–146 (K)	$C_{18}H_{19}N_3O_3S$	CHNS
38	5-CF3	H	H	6′-MeO	A	66	130–148 (K)	$C_{16}H_{14}F_3N_3OS$	CHFNS
39	H	H	H	3′,6′-Me_2	E[z]	69	215–295 (C)	$C_{16}H_{17}N_3S$	C[aa]HNS
40	H	H	H	4′,6′-Me_2	A[bb]	49	139–141 (D)	$C_{16}H_{17}N_3S$	C[cc]HNS
41	H	H	H	5′,6′-Me_2	E[dd]	75	150, br	$C_{16}H_{17}N_3S$	CHN[ee]S
42	H	H	H	4′-Cl, 6′-Me	E[ff]	55		$C_{15}H_{14}ClN_3S$	CHClN
43	H	H	H	5′-Cl, 6′-Me	E[gg]	58	153–155 (H)	$C_{15}H_{14}ClN_3S$	C[hh]HClN
44	5-CF_3	H	H	3′,6′-Me_2	E	69	(gum)		
45	5-Me	H	H	5′,6′-Me_2	E	73	(C)	$C_{17}H_{19}N_3S$	CHN[ii]S
46	H	H	H	3′,4′,5′-Me_3	F[jj]	35	269–271 (D)	$C_{25}H_{21}N_3O_2S$	CHNS
47	H	H	H	3′,5′-Me_2	a	43	240–244 (E)	$C_{25}H_{21}N_3O_3S$	CHNS
48	H	H	H	3′-Me, 4′-Cl, 6′-MeO	E[kk]	68	146–148 (C)	$C_{16}H_{16}ClN_3OS$	CHClNS
49	5-MeO	H	H	3′,5′-Me_2, 4′-MeO	F	35	133–142 (J)	$C_{26}H_{23}N_3O_4S$	CHNS

[a] See the Experimental Section. Compounds in Table II were prepared by method A unless otherwise indicated. [b] Recrystallization solvent: A = $CHCl_3$, B = MeCN, C = CH_2Cl_2, D = Et_2O, E = MeOH, F = none, G = $CHCl_3$/EtOH, H = CH_2Cl_2/MeOH, I = H_2NNH_2/H_2O, J = Et_2O/MeOH, K = Et_2O/hexane, L = CH_2Cl_2/Et_2O, M = NH_3/h_2O, N = *i*-PrOH, P = CH_2Cl_2/hexane. [c] Elemental analyses are within ±0.4% of the calculated values unless otherwise noted. [d] C: calcd, 58.03; found, 57.33. [e] C: calcd, 67.81; found, 67.21. [f] From *N*-acetyl-2-(hydroxymethyl)benzenamine, ref 17. [g] From *N*-methyl-2-(hydroxymethyl)benzenamine, ref 18. [h] From 2-amino-6-methylbenzoic acid, ref 14. [i] From 2-(hydroxymethyl)-4-methylbenzenamine, ref 19. [j] From 2-amino-3-methylbenzoic acid, ref 14. [k] From 4-ethylbenzenamine, ref 14. [l] From 2-ethylbenzenamine, ref 14. [m] C: Calcd, 67.81; found, 67.23. [n] From 4-*n*-butylbenzenamine, ref 14. [o] From 5-methoxy-2-nitrobenzaldehyde, ref 20. [p] Cl: calcd, 19.79; found, 19.09. [q] From 6-methoxy-2-nitrobenzaldehyde, ref 20. [r] C: calcd, 61.20; found, 61.79. [s] N: calcd, 14.27; found, 14.72. [t] From 4-chloro-2-(hydroxymethyl)benzenamine, ref 21. [u] From 5-chloro-2-(hydroxymethyl)benzenamine, ref 21. [v] From ethyl 4-amino-3-(chloromethyl)benzoate, ref 22. [w] From methyl 2-amino-3-(chloromethyl)benzoate, ref 22. [x] S: calcd, 10.08; found, 9.67. [y] C: calcd, 64.19; found, 63.71. [z] From 2,5-dimethylbenzenamine, ref 14. [aa] C: calcd, 67.81; found, 67.20. [bb] From 2,4-dimethyl-6-(hydroxymethyl)benzenamine, ref 23. [cc] C: calcd, 67.81; found, 67.20. [dd] From 2,3-dimethylbenzenamine, ref 14. [ee] N: calcd, 14.83; found, 14.40. [ff] From 4-chloro-2-methylbenzenamine, ref 14. [gg] From 3-chloro-2-methylbenzenamine, ref 24. [hh] C: calcd, 59.30; found, 59.80. [ii] N: calcd, 14.13; found, 13.62. [jj] From 3,4,5-trimethylbenzenamine, ref 25. [kk] From 2-methoxy-4-chloro-5-methylbenzenamine, ref 14.

increases, the efficiency of the sulfoxide rearrangement is enhanced. The hypothesis is supported by the good inhibitory activity for anilines substituted on the ring by electron-donating substituents (**62–69**), intermediate activity for electronegative substituents (**70–72**), and poor activity for the electron-withdrawing groups (**73–75**). For compounds **62–75**, a linear regression analysis of calculated[11] pK_a against pIC_{50} shows a high degree of correlation ($r^2 = 0.78$, $p < 0.001$, Figure 1).

Monosubstitution on the benzimidazole and aniline rings (**76–80**) showed activity similar to that seen for the unsubstituted benzimidazole derivatives. Disubstitution on the aniline ring by two methyl groups (**81–83**) showed pronounced activity, whereas the chloro- and methyl-substituted derivatives (**84** and **85**) were not as effective. The benzimidazole substituted derivatives (**86** and **87**) were not distinguishable from the benzimidazole unsubstituted analogues.

The trisubstituted aniline derivatives (**88–90**) were of interest because **89** and **91** contained the substitution pattern of omeprazole. The 5-methoxy derivative **91** displayed good enzyme inhibitory activity.

The activity of the anilines in the histamine-stimulated gastric fistula dog was diminished, in general, with respect to omeprazole. One compound, **76**, was selected for further study.

The lack of correlation of the in vitro and in vivo tests suggested that the bioavailability of the aniline derivatives was not as good as omeprazole. Attempts to increase ab-

(11) The σ constant for the sulfinyl group was calculated from the observed pK_a of omeprazole, and the remaining substituent constants used were those of Hammett. The pK_a's were calculated from $pK_a = 3.60 - 2.88\sum\sigma_R$.

Table III. 2-[(1*H*-Benzimidazol-2-ylsulfinyl)methyl]anilines

compd	R_1	R_2	R_3	R_4	% yield[a]	mp, °C (solv)[b]	formula	anal.[c]
50	H	H	H	H	60	164–165 (A)	$C_{14}H_{13}N_3OS \cdot {}^1/_2H_2O$	CHNS
51	5-MeO	H	H	H	49	152–153 (B)	$C_{15}H_{15}N_3O_2S$	CHNS
52	5-EtO	H	H	H	81	154–155 (A)	$C_{16}H_{17}N_3O_2S$	CHNS
53	4-Me	H	H	H	75	*d* (C)	$C_{15}H_{15}N_3OS \cdot {}^1/_2H_2O$	CHNS
54	5-Me	H	H	H	87	171–172 (A)	$C_{15}H_{15}N_3OS$	CHNS
55	5-Cl	H	H	H	67	165–166 (A)	$C_{14}H_{12}ClN_3OS$	C[e]HNS
56	5-CF_3	H	H	H	43	152–152.5 (D)	$C_{15}H_{12}F_3N_3OS$	CHFNS
57	5,6-Me_2	H	H	H	38	179–181 (E)	$C_{16}H_{17}N_3OS \cdot {}^1/_4H_2O$	C[f]HNS
58	5,6-$(MeO)_2$	H	H	H	30	130–139 (D)	$C_{16}H_{17}N_3O_3S$	C[g]HNS
59	H	Ac	H	H	80	201–202.5 (D)	$C_{16}H_{15}N_3O_2S$	CHNS
60	H	Me	H	H	39	117–120 (F)	$C_{15}H_{15}N_3OS \cdot H_2O$	CHNS
61	H	Me	Me	H	53	107–109 (D)	$C_{16}H_{17}N_3OS$	CHNS
62	H	H	H	3′-Me	54	152–153 (A)	$C_{15}H_{15}N_3OS \cdot {}^1/_4H_2O$	CHNS
63	H	H	H	4′-Me	85	147–153 (D)	$C_{15}H_{15}N_3OS$	C[h]HNS
64	H	H	H	6′-Me	53	156–157 (G)	$C_{15}H_{15}N_3OS$	CHNS
65	H	H	H	4′-Et	68	155–156 (C)	$C_{16}H_{17}N_3OS$	CHNS
66	H	H	H	6′-Et	73	*i* (F)	$C_{16}H_{17}N_3OS$	CHNS
67	H	H	H	4′-*n*-Bu	68	146–148 (C)	$C_{18}H_{21}N_3OS$	CHNS
68	H	H	H	4′-MeO	49	152–153 (C)	$C_{15}H_{15}N_3O_2S$	C[f]HNS
69	H	H	H	6′-MeO	59	141–143 (C)	$C_{15}H_{15}N_3O_2S \cdot {}^1/_2H_2O$	CHNS
70	H	H	H	4′-Cl	25	210–211 (H)	$C_{14}H_{12}ClN_3OS$	CHClN
71	H	H	H	4′-F	10	184–185 (I)	$C_{14}H_{12}FN_3OS$	CHFN
72	H	H	H	5′-Cl	88	173.5–175.5 (A)	$C_{14}H_{12}ClN_3OS$	C[k]HClNS
73	H	H	H	4′-CF_3	84	185–187 (A)	$C_{15}H_{12}F_3N_3OS$	C[f]HFNS
74	H	H	H	4′-CO_2Et	63	192–194 (A)	$C_{17}H_{17}N_3O_3S \cdot {}^1/_2H_2O$	CHNS
75	H	H	H	6′-CO_2Me	31	158–161 (J)	$C_{16}H_{15}N_3O_3S \cdot H_2O$	CH[m]NS
76	5-MeO	H	H	4′-Me	70	148–149 (D)	$C_{16}H_{17}N_3O_2S$	CHNS
77	5-MeO	H	H	6′-Me	75	142–144 (C)	$C_{16}H_{17}N_3O_2S$	CHNS
78	5-EtO	H	H	4′-Me	14	152–153 (D)	$C_{17}H_{19}N_3O_2S$	C[n]HNS
79	5-MeO	H	H	4′-CO_2Et	44	200[o] (B)	$C_{18}H_{19}N_3O_4S$	CHNS
80	5-CF_3	H	H	6′-MeO	6	170 (K)	$C_{16}H_{14}F_3N_3O_2S$	CHFNS
81	H	H	H	3′,6′-Me_2	40	144–145 (L)	$C_{16}H_{17}N_3OS \cdot H_2O$	CHNS
82	H	H	H	4′,6′-Me_2	66	144–146 (D)	$C_{16}H_{17}N_3OS \cdot {}^1/_2H_2O$	CHNS
83	H	H	H	5′,6′-Me_2	43	160[o] (H)	$C_{16}H_{17}N_3OS \cdot {}^1/_4H_2O$	C[p]HNS
84	H	H	H	4′-Cl, 6′-Me	22	168–169 (C)	$C_{15}H_{14}ClN_3OS \cdot {}^1/_2H_2O$	CHNS
85	H	H	H	5′-Cl, 6′-Me	30	169–170 (F)	$C_{15}H_{14}ClN_3OS \cdot {}^1/_2H_2O$	CHNS
86	5-CF_3	H	H	3′,6′-Me_2	21	137[o] (B)	$C_{17}H_{16}F_3N_3OS$	CHFNS
87	5-Me	H	H	5′,6′-Me_2	16	141–143 (C)	$C_{17}H_{19}N_3OS \cdot {}^1/_2H_2O$	C[q]HN[r]S
88	H	H	H	3′,4′,5′-Me_3	75[s]	145[o] (M)	$C_{17}H_{19}N_3OS \cdot {}^1/_2H_2O$	CHNS
89	H	H	H	3′,5′-Me_2, 4′-MeO	90[s]	198.5–201 (D)	$C_{17}H_{19}N_3O_2S$	CHNS
90	H	H	H	3′-Me, 4′-Cl, 6′-MeO	57	163–164 (A)	$C_{16}H_{16}ClN_3O_2S$	CHClN[t]S
91	5-MeO	H	H	3′,5′-Me_2, 4′-MeO	68[s]	149–155 (M)	$C_{18}H_{21}N_3O_3S$	CHNS

[a] See the Experimental Section. Compounds in Table III were prepared by method C unless otherwise indicated. [b] Recrystallization solvent: A = $CHCl_3$, B = MeCN, C = CH_2Cl_2, D = Et_2O, E = MeOH, F = none, G = $CHCl_3$/EtOH, H = CH_2Cl_2/MeOH, I = H_2NNH_2/H_2O, J = Et_2O/MeOH, K = Et_2O/hexane, L = CH_2Cl_2/Et_2O, M = NH_3/H_2O, N = *i*-PrOH, P = CH_2Cl_2/hexane. [c] Elemental analyses are within ±0.4% of the calculated values unless otherwise noted. [d] Slowly liquified above 100 °C. [e] C: calcd, 54.99; found, 54.40. [f] C: calcd, 63.24; found, 62.80. [g] C: calcd, 57.99; found, 57.44. [h] C: calcd, 63.14; found, 61.44. [i] Foamed at 150 °C. [j] C: calcd, 59.78; found, 59.01. [k] C: calcd, 54.99; found, 54.37. [l] C: calcd, 53.09; found, 52.39. [m] H: calcd, 4.35; found, 4.78. [n] C: calcd, 61.98; found, 61.38. [o] Decomposed. [p] C: calcd, 63.24; found, 62.72. [q] C: calcd, 63.33; found, 63.74. [r] N: calcd, 13.03; found, 12.54. [s] Method D. [t] N: calcd, 60.15; found, 59.71.

sorption by increasing the lipopohilicity of the substituents (**67**, R^4 = *n*-Bu) were not successful. The possibility that the aniline derivatives undergo a metabolic transformation has not been ruled out.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian FT-80 spectrometer in $CDCl_3$ or DMSO-d_6. UV and IR spectra were consistent with the structures described, and all spectra were recorded by A. J. Damascus. Elemental analyses were determined by E. Zielinski of Searle Research and Development Laboratories, Skokie, IL, and are within ±0.4% of the calculated values unless otherwise indicated.

Biology. Preparation of H^+/K^+ ATPase from Canine Gastric Mucosa. H^+/K^+ ATPase was prepared from canine fundic mucosa by the method of Lee et al.[12] with modification. The mixed glandular mucosal scrapings were homogenized in a medium containing 10 mM Tris·HCl (pH 7.5) and 250 mM sucrose (Tris·HCl–sucrose medium) with a Waring commercial blender and again with a Teflon–glass homogenizer. The crude microsomes were isolated as sediment from centrifugation of the homogenate between 20000*g* for 20 min and 150000*g* for 90 min. The crude microsomes were resuspended in Tris·HCl sucrose medium and further centrifuged for 60 min at 250000*g* over a sucrose step gradient. The microsomes, retained at the interface between 15% and 30% sucrose, were collected, lyophilized, and stored at −20 °C prior to use in the H^+/K^+ ATPase assay. The lyophilized microsomal suspension was permeable to K^+, because it exhibited equivalent K^+-stimulated ATPase activity in the presence or absence of the K^+-ionophore valinomycin.

ATPase Assay. ATPase was assayed in a final volume of 2 mL of incubation medium containing 20 mM Mes-Tris (pH 6.0), 5 mM $MgCl_2$, 25 mM sucrose, and 4 mM Tris-ATP with or without 20 mM KCl. Lyophilized microsomal suspensions equivalent to 25 μg of protein were preincubated for 30 min at 37 °C with a test compound in the incubation medium but without Tris-ATP. The reaction was initiated by adding Tris-ATP, and at 30 min the inorganic phosphate released into the medium form ATP was determined according to the method of Chandrarajan and Klein.[13] The H^+/K^+ ATPase activity represents the difference between the K^+-stimulated and basal ATPase activities, which were 5–10 and 40–50 μmol of P_i/mg of protein h, respectively. The IC_{50} values (the concentration necessary to inhibit 50% of the H^+/K^+

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ATPase activity) for test compounds were obtained by linear regression analysis of data from two separate experiments, each performed in duplicate.

Gastric Antisecretory Studies. Adult female beagles, weighing 6–12 kg, were prepared surgically with gastric fistulas for collection of secretions and cannulae for intraduodenal administration of compound. This route was chosen because of the acid lability of many of the compounds. The dogs were allowed 3–4 weeks to recover from surgery and were trained to stand quietly in Pavlov supports. Studies were done in conscious animals that had been fasted 18 h prior to each experiment. Dogs were rested for at least 2 weeks to allow for complete recovery of secretory function.

Following a 30-min basal secretion period, compounds were administered at a dose of 3 mg/kg into the duodenal cannula through a specially constructed dosing plug 30 min after compound administration. A histamine infusion of 15 μg/kg per h was started, and collections of gastric secretions were made every 30 min for 4 h.

Total acidity of gastric samples was determined by titrating with 0.1 N NaOH solution to pH 7.0 (Radiometer, Copenhagen). Mean percent inhibition of total acid output (TAO) was calculated for the 4-h experimental period. In most cases three animals were used for these determinations.

Chemistry. 2-[(1*H*-Benzimidazol-2-ylthio)methyl]-*N*,*N*-dimethylaniline (19). Method A. A mixture of 2.20 g (14.6 mmol) of 2-mercaptobenzimidazole and 2-(chloromethyl)-*N*,*N*-dimethylaniline[14] in 120 mL of absolute EtOH was stirred under N_2 for 2 h. A solid (4.8 g) was collected by filtration, washed with EtOH, and air-dried. The solid was partitioned between aqueous K_2CO_3 and dichloromethane. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to dryness. Recrystallization from MeCN gave 2.3 g of a white solid. A second crop was obtained from the MeCN liquors (0.7 g). The two crops were combined and recrystallized from *i*-PrOH, giving **19** as an analytically pure solid, mp 167–170 °C. Anal. ($C_{16}H_{17}N_3S$) C, H, N, S.

2-[(1*H*-Benzimidazol-2-ylthio)methyl]aniline (8). Method B. A mixture of 9.0 g (60 mmol) of 2-mercaptobenzimidazole and 4.9 g (40 mmol) of 2-aminobenzyl alcohol[14] were heated at 84 °C in a mixture of 45 mL of glacial HOAc and 12.0 g (120 mmol) of H_2SO_4. After 2 h, an additional 1.0 g of 2-aminobenzyl alcohol and 1 g of H_2SO_4 were added. After 1 h, the reaction mixture was cooled and poured into cold (ca. 0 °C) water containing excess NaOH. The resultant gummy precipitate was extracted (four times) with CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and recrystallized from MeCN to give 950 mg (9%) of **8**. Column chromatography of the material contained in the liquors on silica gel gave additional material (1.1 g). The total yield was 20% as an analytically pure solid, mp 146–148 °C. Anal. ($C_{14}H_{13}N_3S$) C, H, N, S.

2-[(1*H*-Benzimidazol-2-ylsulfinyl)methyl]aniline Hemihydrate (50). Method C. To a solution of **8** (830 mg, 3.25 mmol) in $CHCl_3$ at −10 °C was added a solution of 85% *m*-chloroperbenzoic acid (662 mg, 3.25 mmol) in 10 mL of $CHCl_3$ during a period of 10 min. After 30 min, the reaction was quenched with 4 drops of Me_2S, and the solution was concentrated in vacuo. The solid residue was washed sequentially with $CHCl_3$ and Et_2O and then air-dried to give 550 mg of **50**, mp 164–165 °C. Anal. ($C_{14}H_{13}N_3OS \cdot {}^1/_2H_2O$) C, H, N, S.

***N*-(4-Fluoro-2-methylphenyl)phthalimide. Method D.** A mixture of 4-fluoro-2-methylaniline[15] (1.33 g, 10.6 mmol) and phthalic anhydride (1.57 g, 10.6 mmol) was heated at 160 °C for 0.5 h. The solid that resulted upon cooling was washed with MeOH and air-dried, affording 1.96 g of the title compound, mp 189.5–190.5 °C. Anal. ($C_{15}H_{10}NFO_2$) C, H, N, F.

***N*-[2-[(2-Benzimidazolylthio)methyl]-4-fluorophenyl]phthalimide.** A solution of *N*-(4-fluoro-2-methylphenyl)-phthalimide (567 mg, 2.22 mmol), *N*-bromosuccinimide (435 mg, 2.45 mmol), and benzoyl peroxide (59 mg, 0.25 mmol) was irradiated with a sunlamp for 1 h. The mixture was filtered, and the filtrate was evaporated in vacuo to give the bromide as a semisolid. A mixture of 2-mercaptobenzimidazole and the bromide was refluxed in 2-propanol for 1.5 h. Upon cooling, the solid was removed by filtration and washed with cold 2-propanol and Et_2O. After drying, 190 mg of the title compound was obtained.

2-[(2-Benzimidazolylsulfinyl)methyl]-4-fluoroaniline (71). To a solution of *N*-[2-[(2-benzimidazolylthio)methyl]-4-fluorophenyl]phthalimide (104 mg, 0.248 mmol) in CH_2Cl_2 (60 mL) was added a solution of 85% *m*-chloroperbenzoic acid (53 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) at −5 °C. The mixture was stirred for 20 min, 1 drop of Me_2S was added, and the solution was concentrated in vacuo. The residue was washed with Et_2O and dried, giving 119 mg of an oily solid sulfoxide, which was homogeneous by TLC. The sulfoxide was stirred in EtOH (5 mL) with H_2N-$NH_2 \cdot H_2O$ (0.14 mL) at room temperature for 3 h. The solid that formed was removed by filtration, and the filtrate was concentrated in vacuo. The residue was washed with 3% NH_4OH and water and was air-dried to give 50 mg of **71**, mp 184–185 °C. Anal. ($C_{14}H_{12}N_3FOS$) C, H, N, F.

2-(Chloromethyl)-4-(trifluoromethyl)aniline Hydrochloride. Method E. To a solution of 10.0 g (62 mmol) of 4-(trifluoromethyl)aniline[14] and 6.6 g (65 mmol) of triethylamine in 100 mL of CH_2Cl_2 at 0 °C was added dropwise 7.9 g (65 mmol) of pivaloyl chloride. After being stirred overnight, the mixture was poured into water. The aqueous layer was washed with additional CH_2Cl_2, and the organic layers were combined. The organic extracts were washed with three portions of water, dried over $MgSO_4$, filtered, and concentrated in vacuo to dryness. The residue was recrystallized from hexane, giving 14.2 g of the acylated aniline derivative. A mixture of 17.2 g of the N-acylated aniline derivative and 24 mL of TMEDA was stirred in Et_2O cooled to −5 °C, to which was added dropwise 100 mL of *n*-BuLi in hexane (1.55 M). The mixture was allowed to warm to room temperature, stirred for 4 h, and then recooled to −5 °C. DMF (15 mL) was added dropwise, and the mixture was stirred for 1 h. The reaction mixture was partitioned between water and Et_2O. The water layer was separated and washed with additional Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give an oil. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 12.9 g of N-acylated 2-amino-5-(trifluoromethyl)benzaldehyde as a solid. The benzaldehyde derivative (6.3 g) was converted to the corresponding benzyl alcohol derivative by reaction in 60 mL of EtOH with 1.05 g of $NaBH_4$, added as a solution in 10 mL of aqueous 0.6 N NaOH. The reaction mixture was acidified with dilute HCl and concentrated in vacuo to dryness. The residual solid was washed thoroughly with water and air-dried, giving 6.2 g of the benzyl alcohol derivative. A solution of 3.0 g of the benzyl alcohol derivative in 30 mL of dioxane was heated at about 80 °C for 4 h with 40 mL of concentrated HCl. Upon cooling, the reaction mixture was concentrated to dryness under a stream of N_2. The residue was washed thoroughly with Et_2O, giving 3.0 g of title compound.

2-[(2-Benzimidazolylthio)methyl]-4-(trifluoromethyl)-aniline (31) and 2-[(2-benzimidazolylsulfinyl)methyl]-4-(trifluoromethyl)aniline (73) were prepared by methods A and C, respectively.

***N*-[3,5-Dimethyl-2-(hydroxymethyl)-4-methoxyphenyl]phthalimide. Method F.** A solution of *N*-(4-methoxy-3,5-dimethylphenyl)phthalimide[16] (5.0 g, 17.8 mmol) and paraformaldehyde (3.0 g, 100 mmol) in H_2SO_4 (100 mL) was cooled to 0 °C, and HCl gas was introduced for 5 min. The mixture was stirred at 0 °C for 45 min and then was poured into ice, and the

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resulting solid product was isolated by filtration. The solid was washed with water and dried in vacuo to provide 5.4 g of colorless solid, identified as the benzyl alcohol derivative, mp 267–271 °C. Anal. ($C_{18}H_{17}NO_4$) C, H, N.

2-[(2-Benzimidazolylthio)methyl]-3,5-dimethyl-4-methoxyaniline (47) and 2-[(2-benzimidazolylsulfinyl)methyl]-3,5-dimethyl-4-methoxyaniline (89) were prepared by methods A and C, respectively.

Registry No. **6** (R_1 = H), 583-39-1; **6** (R_1 = 5-OMe), 37052-78-1; **6** (R_1 = 5-OEt), 55489-15-1; **6** (R_1 = 4-Me), 27231-33-0; **6** (R_1 = 5-Me), 27231-36-3; **6** (R_1 = 5-Cl), 25369-78-2; **6** (R_1 = 5-CF_3), 86604-73-1; **6** (R_1 = 5,6-$(Me)_2$), 3287-79-4; **6** (R_1 = 5,6-$(OMe)_2$), 74004-74-3; **7** (R_2, R_3, R_4 = H, X = OH), 5344-90-1; **7** (R_2, R_3, R_4 = H, X = Cl), 114059-99-3; **7** (R_2 = Ac, R_3, R_4 = H, X = Cl), 90562-37-1; **7** (R_2 = Me, R_3, R_4 = H, X = Cl), 100376-52-1; **7** (R_2, R_3 = Me, R_4 = H, X = Cl), 106771-59-9; **7** (R_2, R_3 = H, R_4 = 3-Me, X = Cl), 114060-00-3; **7** (R_2, R_3 = H, R_4 = 4-Me, X = Cl), 114060-01-4; **7** (R_2, R_3 = H, R_4 = 6-Me, X = Cl), 88301-86-4; **7** (R_2, R_3 = H, R_4 = 4-Et, X = Cl), 114060-02-5; **7** (R_2, R_3 = H, R_4 = 4-Et, X = Cl)·HCl, 106746-71-8; **7** (R_2, R_3 = H, R_4 = 6-Et, X = Cl), 88301-87-5; **7** (R_2, R_3 = H, R_4 = 6-Et, X = Cl)·HCl, 88301-76-2; **7** (R_2, R_3 = H, R_4 = 4-*n*-Bu, X = Cl), 114060-03-6; **7** (R_2, R_3 = H, R_4 = 4-*m*-Bu, X = Cl)·HCl, 106746-85-4; **7** (R_2, R_3 = H, R_4 = 4-MeO, X = Cl), 114060-04-7; **7** (R_2, R_3 = H, R_4 = 4-MeO, X = Cl)·2HCl, 114060-05-8; **7** (R_2, R_3 = H, R_4 = 6-MeO, X = Cl), 88301-88-6; **7** (R_2, R_3 = H, R_4 = 4-Cl, X = Cl), 114060-06-9; **7** (R_2, R_3 = H, R_4 = 5-Cl, X = Cl), 95304-97-5; **7** (R_2, R_3 = H, R_4 = 4-CF_3, X = Cl), 114060-07-0; **7** (R_2, R_3 = H, R_4 = 4-CO_2Et, X = Cl), 114060-08-1; **7** (R_2, R_3 = H, R_4 = 6-CO_2Me, X = Cl), 88301-89-7; **7** (R_2, R_3 = H, R_4 = 3,6-$(Me)_2$, X = Cl), 114060-09-2; **7** (R_2, R_3 = H, R_4 = 3,6-$(Me)_2$, X = Cl)·HCl, 106746-89-8; **7** (R_2, R_3 = H, R_4 = 4,6-$(Me)_2$, X = Cl), 114060-10-5; **7** (R_2, R_3 = H, R_4 = 5,6-$(Me)_2$, X = Cl), 114060-11-6; **7** (R_2, R_3 = H, R_4 = 5,6-$(Me)_2$, X = Cl)·HCl, 106746-87-6; **7** (R_2, R_3 = H, R_4 = 4-Cl, 6-Me, X = Cl), 114060-12-7; **7** (R_2 = H, R_3 = COBu-*t*, R_4 = 4-CF_3, X = OH), 106746-82-1; **7** (R_2, R_3 = H, R_4 = 4-CF_3, X = Cl)·HCl, 106746-83-2; **7** (R_2, R_3 = H, R_4 = 4-Cl, 6-Me, X = Cl)·HCl, 106746-91-2; **7** (R_2, R_3 = H, R_4 = 5-Cl, 6-Me, X = Cl), 114060-13-8; **7** (R_2, R_3 = H, R_4 = 5-Cl, 6-Me, X = Cl)·HCl, 114060-14-9; **7** (R_2, R_3 = H, R_4 = 3-Me, 4-Cl, 6-OMe, X = Cl), 114060-15-0; **7** (R_2, R_3 = H, R_4 = 3-Me, 4-Cl, 6-OMe, X = Cl)·HCl, 106746-92-3; **8**, 104340-33-2; **9**, 106747-44-8; **10**, 106746-78-5; **11**, 106747-42-6; **12**, 106746-76-3; **13**, 106746-77-4; **14**, 106746-79-6; **15**, 106747-43-7; **16**, 106747-01-7; **17**, 106747-41-5; **18**, 104340-35-4; **19**, 104340-38-7; **20**, 106746-61-6; **21**, 106746-63-8; **22**, 106746-65-0; **23**, 106746-70-7; **24**, 111881-58-4; **25**, 106746-84-3; **26**, 106746-58-1; **27**, 106746-60-5; **28**, 106747-47-1; **30**, 106747-48-2; **31**, 106746-80-9; **32**, 106746-98-9; **33**, 106746-97-8; **34**, 106746-68-3; **35**, 106746-69-4; **36**, 106746-93-4; **37**, 106747-00-6; **38**, 106746-96-7; **39**, 106746-88-7; **40**, 106746-66-1; **41**, 106746-86-5; **42**, 106746-90-1; **43**, 114060-16-1; **44**, 106746-95-6; **45**, 106746-94-5; **46**, 114060-17-2; **47**, 106746-74-1; **48**, 106785-95-9; **49**, 114060-18-3; **50**, 104340-34-3; **51**, 106747-08-4; **52**, 106747-23-3; **53**, 106747-06-2; **54**, 106747-21-1; **55**, 106747-22-2; **56**, 106747-24-4; **57**, 106747-07-3; **58**, 106747-37-9; **59**, 106747-05-1; **60**, 104340-37-6; **61**, 100924-68-3; **62**, 106747-14-2; **63**, 106747-15-3; **64**, 106747-16-4; **65**, 114060-19-4; **66**, 106771-58-8; **67**, 106747-26-6; **68**, 106747-12-0; **69**, 106747-13-1; **70**, 106747-10-8; **71**, 106747-38-0; **72**, 106747-11-9; **73**, 106747-25-5; **74**, 106747-35-7; **75**, 106747-34-6; **76**, 106747-18-6; **77**, 106747-19-7; **78**, 106747-30-2; **79**, 106747-36-8; **80**, 106747-33-5; **81**, 106785-96-0; **82**, 106747-17-5; **83**, 106747-27-7; **84**, 106747-28-8; **85**, 114060-20-7; **86**, 106747-32-4; **87**, 106747-31-3; **88**, 106747-39-1; **89**, 106747-20-0; **90**, 106747-29-9; **91**, 106747-40-4; ATPase, 9000-83-3; *N*-(4-fluoro-2-methylphenyl)phthalimide, 106747-02-8; 4-fluoro-2-methylaniline, 452-71-1; phthalic anhydride, 85-44-9; *N*-[2-[(2-benzimidazolylthio)methyl]-4-fluorophenyl]phthalimide, 106771-57-7; *N*-[4-fluoro-2-(bromomethyl)phenyl]phthalimide, 106747-03-9; *N*-[2-[(2-benzimidazolylsulfinyl)methyl]-4-fluorophenyl]phthalimide, 106747-04-0; 4-(trifluoromethyl)aniline, 455-14-1; pivaloyl chloride, 3282-30-2; *N*-pivaloyl-4-(trifluoromethyl)aniline, 25617-34-9; *N*-pivaloyl-2-amino-5-(trifluoromethyl)benzaldehyde, 106746-81-0; *N*-(4-methoxy-3,5-dimethylphenyl)phthalimide, 106746-72-9; *N*-[3,5-dimethyl-2-(hydroxymethyl)-4-methoxyphenyl]phthalimide, 106746-73-0; 4-methoxy-3,5-dimethylbenzenamine, 39785-37-0; omeprazole, 73590-58-6; timoprazole, 57237-97-5; 4-ethylbenzenamine, 589-16-2; 2-ethylbenzenamine, 578-54-1; 4-*n*-butylbenzenamine, 104-13-2; 2,5-dimethylbenzenamine, 95-78-3; 2,3-dimethylbenzenamine, 87-59-2; 4-chloro-2-methylbenzenamine, 95-69-2; 3-chloro-2-methylbenzenamine, 87-60-5; 3,4,5-trimethylbenzenamine, 1639-31-2; 2-methoxy-4-chloro-5-methylbenzenamine, 6376-14-3; *N*-(3,4,5-trimethylphenyl)-phthalimide, 40101-22-2; *N*-[2-(hydroxymethyl)-3,4,5-trimethylphenyl]phthalimide, 114060-21-8.

(Imidazo[1,2-*a*]pyrimidin-2-yl)phenylmethanones and Related Compounds as Potential Nonsedative Anxiolytics

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Several series of heterocyclic carboxylic esters were found to be active in the benzodiazepine receptor binding assay, a typical example being ethyl 7-ethyl-5-methoxyimidazo[1,2-*a*]quinoline-2-carboxylate (**4b**) with an IC_{50} of 150 nM. The corresponding phenylmethanone **5d** was more potent with an IC_{50} of 14 nM and was orally active in animal models thought to predict anxiolytic effects. The synthesis of a large number of compounds resulted in the optimization of this activity in a series of (imidazo[1,2-*a*]pyrimidin-2-yl)phenylmethanones of which compounds **7e**, **8b**, **8h**, **8j**, and **8k** were equipotent with chlordiazepoxide while exhibiting reduced anticonvulsant activity, little or no muscle relaxation, and negligible sedative effects.

A current goal of antianxiety research is the discovery of potent anxiolytic agents which do not possess sedative side effects. Part of this endeavor has been to find compounds which lack the benzodiazepine structure but which nevertheless bind potently to the benzodiazepine receptor. A separation of antianxiety activity from muscle relaxation, sedation, and hypnotic effects might then be achieved by partial intrinsic activity at the receptor complex.[1]

With this aim we routinely screened all compounds synthesized for a variety of objectives in our laboratories for their ability to displace [^{3}H]flunitrazepam from rat-brain preparations. One of these compounds, ethyl 4,5-

(1) (a) Haefely, W. In *Clinical Neuropharmacology*; Raven: New York, 1984; Vol. 7, Suppl 1, p 658. (b) Williams, M. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1984**, *8*, 209.

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