Synthesis and Structure–Activity Relationships of Substituted 2-[(2-Imidazolylsulfinyl)methyl]anilines as a New Class of Gastric H^+/K^+-ATPase Inhibitors. II

Tomio YAMAKAWA,*[,a] Hitoshi MATSUKURA,[a] Yutaka NOMURA,[a] Mitsuko YOSHIOKA,[a] Mitsuo MASAKI,[a] Hiroyuki HARADA,[b] and Susumu OKABE[b]

Research Laboratories, Nippon Chemiphar Co., Ltd.,[a] 1–22, Hikokawato, Misato, Saitama 341, Japan and Department of Applied Pharmacology, Kyoto Pharmaceutical University,[b] Misasagi, Yamashina, Kyoto 607, Japan. *Received September 17, 1991*

A series of 2-[(2-imidazolylsulfinyl)methyl]anilines (2) having various substituents on their imidazole and aniline rings was synthesized and examined for their H^+/K^+-ATPase (adenosine triphosphatase) inhibitory effects and antisecretory activity against histamine-stimulated gastric acid secretions in Heidenhain pouch dogs. Although substitutions on the imidazole ring did not enhance biological activity, substitution on the aniline ring by electron-donating substituents potently enhanced the enzyme inhibitory activity and also showed an inhibitory effect on histamine-stimulated gastric acid secretion after oral administration. In particular, the *in vitro* activity of the dimethyl (2u—w) and trimethyl (2ac) derivatives was about 10 times that of omeprazole. Also, 4-methyl (2k), 4-methoxy-5-methyl (2y) and 3,5-dimethyl-4-methoxy (2ab) derivatives showed a potent antisecretory effect of more than 80% after oral administration at 6 mg/kg. Although these aniline derivatives have relatively low stabilities in aqueous solution, replacement of the isobutyl group at the aniline nitrogen atom with *N*-(2-methoxyethyl) group enhanced the stability.

Keywords 2-[(2-imidazolylsulfinyl)methyl]aniline; H^+/K^+-ATPase inhibitor; antisecretory effect; stability; structure–activity relationship

A previous paper[1] described *N*-substituted 2-[(2-imidazolylsulfinyl)methyl]anilines as a new class of H^+/K^+-ATPase (adenosine triphosphatase) inhibitors. Of these, the imidazolylsulfinyl compounds having monoalkyl or monoalkoxyalkyl substituent on the aniline nitrogen atom showed a potent enzyme inhibitory activity and antisecretory effect in histamine-stimulated Heidenhain pouch dogs after intravenous (i.v.) administration. It has been reported that the *in vitro* and *in vivo* activities of 2-[(2-benzimidazolylsulfinyl)methyl]pyridines[2] and 2-[(2-benzimidazolylsulfinyl)methyl]anilines[3] were markedly influenced by substitutions on the benzimidazole and pyridine or aniline rings. Our continued interest in the structure–activity relationships of 2-[(2-imidazolylsulfinyl)methyl]anilines led us to explore the substitutions on the imidazole or aniline ring.

In this paper, we report the synthesis and pharmacological activities of 2-[(2-imidazolylsulfinyl)methyl]anilines having various substituents on the imidazole or aniline ring. We also discuss the relationships between H^+/K^+-

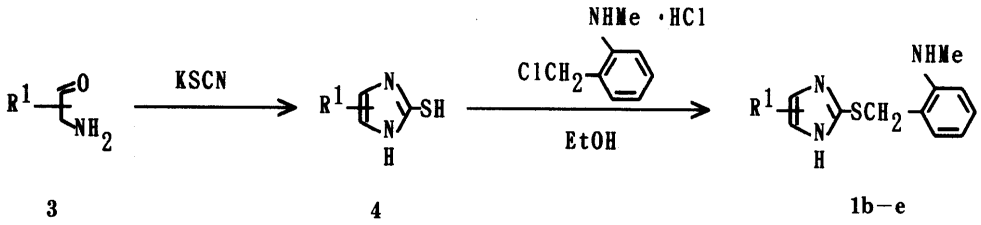

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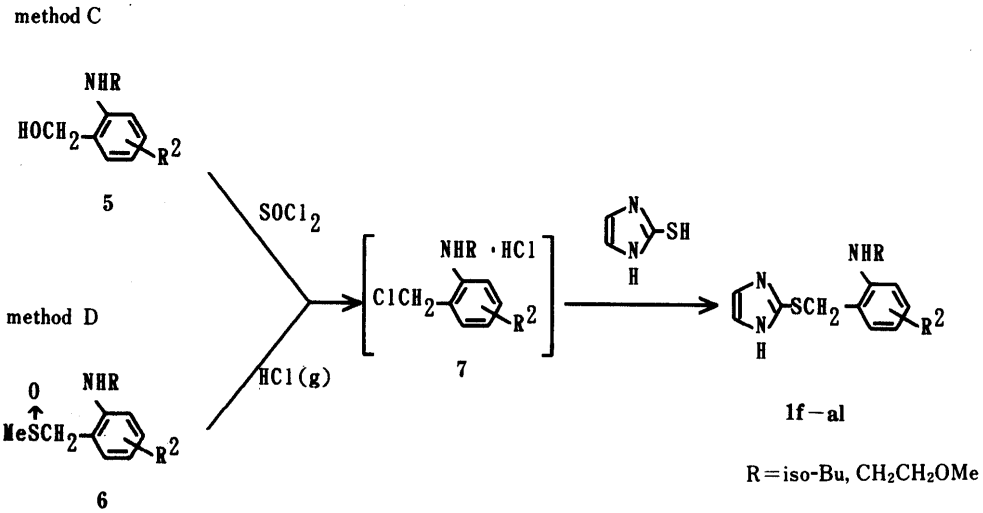
Chart 1



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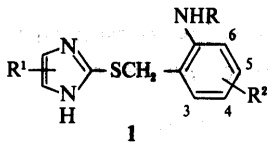
R=iso-Bu, CH_2CH_2OMe

Chart 2

TABLE I. Substituted 2-[(2-Imidazolylthio)methyl]anilines (**1**)



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Compd. No.	R	R^1	R^2	Method[a]	Yield[b] (%)	Appearance	mp (°C)	HR-MS Found	HR-MS (Calcd)	^{1}H-NMR[c] δ ($CDCl_3$), (J=Hz)
1b	Me	4-Me	H	C	100	Brown oil	—	233.0985	(233.0987)	2.20 (3H, s), 2.83 (3H, s), 4.13 (2H, s), 6.4—7.2 (5H,m)
1c	Me	4-Me, 5-Et	H	C	41	Gray powder	118—119	261.1302	(261.1301)	1.14 (3H, t, 7), 2.12 (3H, s), 2.49 (2H, q, 7), 2.81 (3H, s), 4.09 (2H, s), 6.4—7.3 (4H, m)
1d	Me	4-Ph	H	C	80	Pale brown oil	—	295.1142	(295.1144)	3.72 (3H, s), 4.14 (2H, s), 6.3–7.7 (10H, m)
1e	Me	4,5-$(CH_2)_4$–	H	C	53	Pale brown prisms	142—143.5	273.1299	(273.1301)	1.6—2.0 (4H, m), 2.3—2.8 (4H, m), 2.80 (3H, s), 4.13 (2H, s), 6.4—7.3 (4H, m)
1g	iso-Bu	H	3-OMe	C	28	White powder	ND	ND		0.99 (6H, d, 7), 1.94 (1H, m), 2.91 (2H, d, 7), 3.79 (3H, s), 4.36 (2H, s), 6.25 (1H, d, 8), 6.28 (1H, d, 8), 7.01 (2H, s), 7.09 (1H, t, 8)
1h	iso-Bu	H	4-OMe	C	34	Pale brown powder	96—97	291.1403	(291.1406)	0.99 (6H, d, 7), 1.92 (1H, m), 2.90 (2H, d, 7), 3.66 (3H, s), 4.17 (2H, s), 6.4—6.8 (3H, m), 7.03 (2H, bs)
1i	iso-Bu	H	6-OMe	C	49	Pale yellow powder	56—57	291.1406	(291.1406)	1.02 (6H, d, 7), 1.89 (1H, m), 2.85 (2H, d, 7), 3.83 (3H, s), 4.19 (2H, s), 6.5—7.2 (3H, m), 6.99 (2H, s)
1j	iso-Bu	H	3-Me	C	30	Pale brown prism	112.5—114	275.1452	(275.1457)	0.98 (6H, d, 7), 1.93 (1H, m), 2.18 (3H, s), 2.90 (2H, d, 7), 4.27 (2H, s), 6.49 (2H, d, 8), 7.04 (1H, t, 8), 7.04 (2H, s)
1k	iso-Bu	H	4-Me	C	42	Pale gray powder	97.5—98.5	275.1456	(275.1457)	0.96 (6H, d, 7), 1.6—2.1 (1H, m), 2.15 (3H, s), 2.90 (2H, d, 7), 4.17 (2H, s), 6.3—7.1 (3H, m), 7.02 (2H, s)
1l	iso-Bu	H	5-Me	C	68	Pale yellow oil	—	ND		0.99 (6H, d, 7), 1.94 (1H, m), 2.27 (3H, s), 2.94 (2H, d, 7), 4.19 (2H, s), 6.2—6.5 (2H, m), 6.81 (1H, d, 7), 7.03 (2H, s)
1m	iso-Bu	H	6-Me	C	68	Pale brown powder	ND	ND		1.02 (6H, d, 7), 1.90 (1H, m), 2.29 (3H, s), 2.80 (2H, d, 7), 4.21 (2H, s), 6.6—7.1 (5H, m)
1n	iso-Bu	H	4-F	C	71	Pale yellow prism	100.5—101.5	279.1195	(279.1206)	0.99 (6H, d, 7), 1.92 (1H, m), 2.89 (2H, d, 7), 4.16 (2H, s), 6.3—7.1 (3H, m), 7.05 (2H, s)
1o	iso-Bu	H	5-F	C	47	White powder	181—183	279.1180	(279.1206)	0.98 (6H, d, 7), 1.93 (1H, m), 2.90 (2H, d, 7), 4.18 (2H, s), 6.0—6.9 (3H, m), 7.05 (2H, s)
1p	iso-Bu	H	3-Cl	C	57	White powder	114.5—115.5	295.0909	(295.0911)	0.99 (6H, d, 7), 1.95 (1H, m), 2.89 (2H, d, 6), 4.48 (2H, s), 6.49 (1H, dd, 1, 8), 6.66 (1H, dd, 1, 8), 7.04 (1H, t, 8), 7.04 (2H, s)
1q	iso-Bu	H	4-Cl	C	45	White prism	99—102	295.0909	(295.0911)	0.96 (6H, d, 6), 1.92 (1H, m), 2.89 (2H, d, 7), 4.15 (2H, s), 6.3—7.2 (3H, m), 7.04 (2H, s)
1r	iso-Bu	H	5-Cl	C	69	White powder	121.5—123.5	295.0909	(295.0911)	1.01 (6H, d, 7), 1.96 (1H, m), 2.95 (2H, d, 7), 4.12 (2H, s), 6.46 (1H, dd, 2, 8), 6.56 (1H, d, 2), 6.80 (1H, d, 8), 7.02 (2H, s)
1s	iso-Bu	H	4-OCF_3	C	81	White powder	105—106.5	345.1171	(345.1124)	0.98 (6H, d, 6), 1.93 (1H, m), 2.92 (2H, d, 7), 4.17 (2H, s), 6.54 (1H, d, 9), 6.6—7.1 (2H, m), 7.04 (2H, s)
1t	iso-Bu	H	4-NO_2	C	83	Yellow prism	157.5—159.5	306.1152	(306.1151)	1.00 (6H, d, 7), 2.00 (1H, m), 3.10 (2H, d, 7), 4.24 (2H, s), 6.57 (1H, d, 9), 7.03 (2H, s), 7.82 (1H, d, 2), 7.98 (1H, dd, 2, 9)
1u	iso-Bu	H	3,4-Me_2	D	94	White powder	ND	ND		0.99 (6H, d, 7), 1.95 (1H, m), 2.13 (3H, s), 2.17 (3H, s), 2.89 (2H, d, 7), 4.32 (2H, s), 6.35 (1H, d, 7), 6.90 (1H, d, 7), 7.00 (2H, s)
1v	iso-Bu	H	4,5-Me_2	D	97	White powder	ND	ND		0.98 (6H, d, 7), 1.95 (1H, m), 2.08 (3H, s), 2.19 (3H, s), 2.91 (2H, d, 7), 4.18 (2H, s), 6.44 (1H, s), 6.70 (1H, s), 7.03 (2H, s)
1w	iso-Bu	H	3,5-Me_2	D	69	White powder	104—105	289.1613	(289.1614)	0.98 (6H, d, 7), 1.92 (1H, m), 2.14 (3H, s), 2.23 (3H, s), 2.89 (2H, d, 7), 4.24 (2H, s), 6.32 (2H, s), 7.03 (2H, s)
1x	iso-Bu	H	4-OMe, 3-Me	D	59	White powder	ND	ND		0.98 (6H, d, 7), 1.95 (1H, m), 2.11 (3H, s), 2.87 (2H, d, 7), 3.73 (3H, s), 4.28 (2H, s), 6.47 (1H, d, 9), 6.75 (1H, d, 9), 7.03 (2H, s)
1y	iso-Bu	H	5-Me, 4-OMe	D	72	White powder	ND	ND		1.05 (6H, d, 7), 1.95 (1H, m), 2.18 (3H, s), 2.90 (2H, d, 7), 3.62 (3H, s), 4.18 (2H, s), 6.44 (1H, s), 6.70 (1H, s), 7.02 (2H, s)
1z	iso-Bu	H	5-F, 4-OMe	D	78	White powder	122.5—123.5	309.1313	(309.1312)	1.00 (6H, d, 7), 1.6—2.1 (1H, m), 2.88 (2H, d, 7), 3.72 (3H, s), 4.16 (2H, s), 6.40 (1H, d, 14), 6.58 (1H, d, 9), 7.05 (2H, s)
1aa	iso-Bu	H	3,5-F_2	D	71	White powder	130.5—133	297.1110	(297.1112)	0.98 (6H, d, 7), 1.95 (1H, m), 2.88 (2H, d, 7), 4.29 (2H, s), 5.9—6.1 (2H, m), 7.04 (2H, s)
1ab	iso-Bu	H	3,5-Me_2, 4-OMe	D	87	White powder	121.5—123.5	319.1721	(319.1720)	1.00 (6H, d, 7), 1.93 (1H, m), 2.14 (3H, s), 2.24 (3H, s), 2.87 (2H, d, 6), 3.59 (3H, s), 4.26 (2H, s), 6.32 (1H, s), 7.03 (2H, s)
1ac	iso-Bu	H	3,4,5-Me_3	D	65	White powder	ND	ND		0.97 (6H, d, 7), 1.95 (1H, m), 2.07 (3H, s), 2.13 (3H, s), 2.23 (3H, s), 2.87 (2H, d, 7), 4.38 (2H, s), 6.36 (1H, s), 7.03 (2H, s)

TABLE I. (continued)

Compd. No.	R	R^1	R^2	Method[a]	Yield[b] (%)	Appearance	mp (°C)	HR-MS Found	HR-MS (Calcd)	^{1}H-NMR[c] δ ($CDCl_3$), (J=Hz)
1ae	CH_2CH_2OMe	H	4-OMe	D	69	Pale yellow powder	99.5—100.5	293.1198	(293.1199)	3.31 (2H, t, 5), 3.42 (3H, s), 3.65 (3H, s), 3.70 (2H, t, 5), 4.10 (2H, s), 6.4—6.9 (3H, m), 7.01 (2H, s)
1af	CH_2CH_2OMe	H	3-Me	C	68	White prism	91—92.5	277.1235	(277.1250)	2.21 (3H, s), 3.32 (2H, t, 5), 3.42 (3H, s), 3.71 (2H, t, 5), 4.20 (2H, s), 6.3—7.1 (3H, m), 7.03 (2H, s)
1ag	CH_2CH_2OMe	H	4-Me	C	76	Pale brown powder	90.5—91.5	277.1232	(277.1250)	2.15 (3H, s), 3.35 (2H, t, 5), 3.43 (3H, s), 3.72 (2H, t, 5), 4.11 (2H, s), 6.4—7.0 (3H, m), 7.01 (2H, s)
1ah	CH_2CH_2OMe	H	5-F	C	61	Colorless oil	—	281.0996	(281.0999)	3.34 (2H, t, 5), 3.45 (3H, s), 3.74 (2H, t, 5), 4.10 (2H, s), 6.1—6.4 (2H, m), 6.6—6.9 (1H, m), 7.05 (2H, s)
1ai	CH_2CH_2OMe	H	3-Me, 4-OMe	D	96	Pale brown powder	ND	ND		2.14 (3H, s), 3.28 (2H, t, 5), 3.44 (3H, s), 3.73 (3H, s), 3.73 (2H, t, 5), 4.21 (2H, s), 6.50 (1H, d, 8), 6.74 (1H, d, 8), 7.03 (2H, s)
1aj	CH_2CH_2OMe	H	4-OMe, 5-Me	D	79	White powder	ND	ND		2.15 (3H, s), 3.40 (2H, t, 5), 3.44 (3H, s), 3.63 (3H, s), 3.72 (2H, t, 5), 4.09 (2H, s), 6.43 (1H, s), 6.50 (1H, s), 7.01 (2H, s)
1ak	CH_2CH_2OMe	H	4-OMe, 5-F	D	78	White powder	117.5—118.5	311.1107	(311.1105)	3.29 (2H, t, 5), 3.44 (3H, s), 3.6—3.8 (2H, m), 3.70 (3H, s), 4.07 (2H, s), 6.2—6.6 (2H, m), 7.01 (2H, s)
1al	CH_2CH_2OMe	H	3,5-Me_2, 4-OMe	D	75	White powder	113—115.5	321.1512	(321.1512)	2.16 (3H, s), 2.24 (3H, s), 3.30 (2H, t, 5), 3.42 (3H, s), 3.60 (3H, s), 3.67 (2H, t, 5), 6.42 (1H, s), 7.04 (2H, s)

ND: Not determined. *a*) Method C, $SOCl_2$; method D, HCl (g). *b*) Yields have not been optimized. *c*) Solvent for **1y** was $CDCl_3/CD_3$ OD=1/1 (v/v).

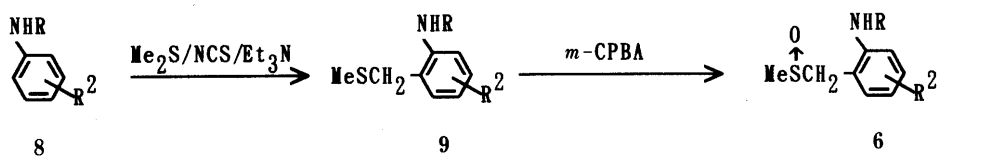


Chart 3

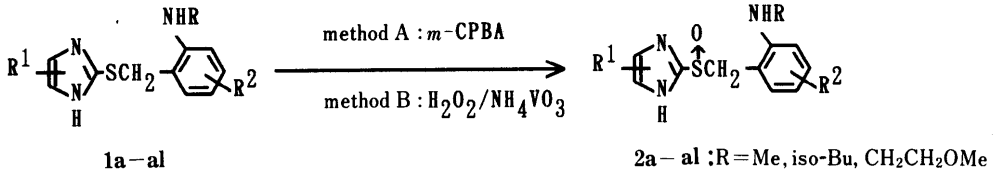


Chart 4

ATPase inhibitory activity (pH 6.0 and 7.4), antisecretory effects and stability in aqueous solutions (pH 3.0, 5.0, 7.0).

Synthesis

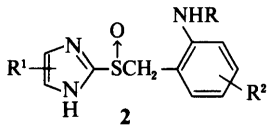
The substituted 2-mercaptoimidazoles (**4**) were prepared from 2-aminoketones (**3**) and potassium thiocyanate.[4] Condensation of **4** with 2-methylaminobenzyl chloride in EtOH at room temperature gave the corresponding sulfides (**1b—e**) in good yields as shown in Chart 1. The yield and chemical data of the sulfides (**1b—e**) are summarized in Table I.

The substituted 2-isobutylamino or 2-(2-methoxyethyl)-aminobenzyl chloride hydrochlorides (**7**), unstable key intermediates, were synthesized by two methods as shown in Chart 2. Most monosubstituted derivatives were prepared by the chlorination of corresponding benzyl alcohols (**5**) with $SOCl_2$, and then condensed with 2-mercaptoimidazole to give the sulfides (**1**) (method C). Monosubstituted 2-aminobenzyl alcohols (**5**) were synthesized by known or modified methods from the corresponding anthranilic acids. All di-or trisubstituted 2-aminobenzyl chlorides were synthesized from corresponding 2-methylsulfinylmethylanilines (**6**) with gaseous HCl,[5] and then condensed with 2-mercaptoimidazole (method D). The yield and chemical data of the sulfides (**1g—ac, 1ae—al**) are summarized in Table I.

2-Methylsulfinylmethylanilines (**6**) were synthesized using the pathway shown in Chart 3. Di- or trisubstituted anilines prepared by known methods were methylthiomethylated at the 2-position on the aniline ring with dimethylsulfide and *N*-chlorosuccinimide (NCS) in the presence of triethylamine.[6] In unsymmetrical anilines, a mixture of regioisomers was produced which could not be separated by column chromatography on silica gel. Accordingly, after oxidation of the crude mixture with *m*-chloroperbenzoic acid (*m*-CPBA), each regioisomer was isolated by column chromatography.

Sulfinyl compounds (**2**) were synthesized by low temperature oxidation of the corresponding sulfides (**1**) with *m*-CPBA (method A) or with H_2O_2 catalyzed by NH_4VO_3 in a mixed solvent (CH_2Cl_2–MeOH–AcOH) (method B) as shown in Chart 4. Utility of the latter oxidation method was previously reported.[1] The yield and chemical data of the sulfoxides (**2b—e, g—ac, ae—al**) are summarized in

TABLE II. Substituted 2-[(2-Imidazolylsulfinyl)methyl]anilines (**2**): Synthesis



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Compd. No.	Method[a]	Yield[b] (%)	Appearance	Recrystn.[c] solv.	mp (°C)	IR ν cm^{-1} (S→O)	HR-MS Found	HR-MS (Calcd)	^{1}H-NMR (Solvent)[e] δ (J=Hz)
2b	A	36	White prisms	a	143—146	1005	247.0937	(247.0937)	(c) 2.19 (3H, s), 2.69 (3H, d, 4), 4.41 (2H, s), 5.66 (1H, br), 6.3—7.2 (5H, m), 13.0 (1H, br)
2c	A	42	White prisms	a	120	1030	277.1234	(277.1250)	(b) 1.12 (3H, m), 2.14 (3H, s), 2.50 (2H, q, 8), 2.69 (3H, s), 4.24 (1H, d, 14), 4.44 (1H, d, 14), 4.9 (1H, br), 6.4—7.4 (4H, m)
2d	A	50	Pale yellow prisms	a	145—146	1005	311.1101	(311.1090)	(c) 2.69 (3H, s), 4.45 (1H, d, 13), 4.63 (1H, d, 13), 5.7 (1H, br), 6.2—8.0 (10H, m), 13.3 (1H, br)
2e	A	25	White prisms	a	142—144	1040	289.1246	(289.1250)	(a) 1.6—2.1 (4H, m), 2.4—2.8 (4H, m), 2.78 (3H, s), 4.22 (1H, d, 14), 4.40 (1H, d, 14), 6.4—7.3 (4H, m)
2g	B	21	White powder	b	116	1020	307.1355	(307.1356)	(b) 0.97 (6H, d, 7), 1.87 (1H, m), 2.7—3.0 (2H, br), 3.72 (3H, s), 4.38 (1H, d, 13), 4.79 (1H, d, 13), 6.26 (1H, d, 8), 6.33 (1H, d, 8), 7.16 (1H, t, 8), 7.19 (2H, s)
2h	A	49	Pale brown powder	a	137—138	1020	307.1354	(307.1356)	(a) 1.02 (6H, d, 7), 1.92 (1H, m), 2.84 (2H, d, 7), 3.65 (3H, s), 4.31 (1H, d, 13), 4.58 (1H, d, 13), 6.3—6.9 (3H, m), 7.24 (2H, s)
2i	A	47	White powder	b	109—112	1050	307.1358	(307.1356)	(a) 0.99 (6H, d, 6), 1.82 (1H, m), 2.84 (2H, d, 7), 3.84 (3H, s), 4.39 (1H, d, 13), 4.63 (1H, d, 13), 6.3—6.9 (3H, m), 7.21 (2H, s)
2j	A	40	White powder	b	140—142	1020	291.1408	(291.1406)	(a) 1.02 (6H, d, 7), 1.93 (1H, m), 2.23 (3H, s), 2.89 (2H, d, 7), 4.44 (1H, d, 14), 4.66 (1H, d, 14), 6.58 (2H, d, 8), 7.11 (1H, t, 8), 7.28 (2H, s)
2k	A	42	Pale yellow powder	b	138—139	1020	291.1406	(291.1406)	(a) 1.00 (6H, d, 6), 1.7—2.1 (1H, m), 2.14 (3H, s), 2.85 (2H, d, 7), 4.16 (1H, d, 15), 4.34 (1H, d, 15), 6.4—7.0 (3H, m), 6.63 (2H, s)
2l	B	30	Pale yellow powder	a	144.5—145	1025	291.1403	(291.1406)	(a) 1.02 (6H, d, 7), 1.93 (1H, m), 2.26 (3H, s), 2.88 (2H, d, 7), 4.28 (1H, d, 14), 4.51 (1H, d, 14), 6.2—6.5 (2H, m), 6.70 (1H, d, 7), 7.23 (2H, s)
2m	B	41	White powder	a	144—147	1025	291.1405	(291.1406)	(a) 1.04 (6H, d, 7), 1.89 (1H, m), 2.30 (3H, s), 2.74 (2H, d, 7), 4.39 (1H, d, 13), 4.62 (1H, d, 13), 6.5—7.3 (3H, m), 7.21 (2H, s)
2n	B	71	White powder	a	150—151	1020	295.1155	(295.1156)	(a) 1.02 (6H, d, 7), 1.92 (1H, m), 2.85 (2H, d, 7), 4.31 (1H, d, 14), 4.54 (1H, d, 14), 6.4—7.0 (3H, m), 7.25 (2H, s)
2o	B	79	Pale yellow powder	a	158—160	1020	295.1155	(295.1156)	(a) 1.02 (6H, d, 7), 1.94 (1H, m), 2.89 (2H, d, 7), 4.29 (1H, d, 14), 4.50 (1H, d, 14), 6.0—6.9 (3H, m), 7.25 (2H, s)
2p	B	69	White powder	a	163—164.5	1020	311.0861	(311.0860)	(a) 1.02 (6H, d, 7), 1.94 (1H, m), 2.89 (2H, d, 7), 4.71 (2H, s), 6.60 (1H, dd, 1, 8), 6.74 (1H, dd, 1, 8), 7.14 (1H, t, 8), 7.28 (2H, s)
2q	B	83	Pale brown powder	b	151—154	1020	311.0858	(311.0860)	(c) 0.94 (6H, d, 7), 1.87 (1H, m), 2.83 (2H, br), 4.52 (2H, s), 6.4—7.2 (3H, m), 7.29 (2H, s)
2r	B	71	White powder	a	173	1020	311.0861	(311.0860)	(c) 0.95 (6H, d, 7), 1.89 (1H, m), 2.84 (2H, br), 4.44 (1H, d, 13), 4.46 (1H, d, 13), 4.46 (1H, dd, 2, 8), 6.43 (1H, dd, 1, 8), 6.49 (1H, d, 1), 6.74 (1H, d, 8), 6.9—7.5 (2H, s)
2s	B	65	White powder	a	141—142	1030	361.1072	(361.1073)	(a) 1.02 (6H, d, 6), 1.92 (1H, m), 2.89 (2H, d, 7), 4.28 (1H, d, 14), 4.52 (1H, d, 14), 6.4—7.1 (3H, m), 7.23 (2H, s)
2t	B	37	Yellow prism	b	215—220	1025	322.1102	(322.1101)	(c) 0.94 (6H, d, 7), 1.92 (1H, m), 3.02 (2H, d, 6), 4.62 (2H, s), 6.66 (1H, d, 9), 7.27 (2H, s), 7.65 (1H, d, 3), 7.96 (1H, dd, 3, 9)
2u	A	34	White powder	b	126—128	1045	305.1560	(305.1563)	(c) 0.95 (6H, d, 6), 1.90 (1H, m), 2.07 (3H, s), 2.13 (3H, s), 2.75 (2H, d, 6), 4.40 (1H, d, 14), 4.70 (1H, d, 14), 6.40 (1H, d, 7), 6.95 (1H, d, 7), 7.32 (2H, s)
2v	A	29	White powder	b	129—131	1020	305.1561	(305.1563)	(a) 1.02 (6H, d, 7), 1.90 (1H, m), 2.20 (3H, s), 2.25 (3H, s), 2.87 (2H, d, 6), 4.39 (1H, d, 14), 4.58 (1H, d, 14), 6.41 (2H, s), 7.28 (2H, s)
2w	A	17	White powder	b	129—131	1020	305.1561	(305.1563)	(a) 1.02 (6H, d, 6), 1.90 (1H, m), 2.20 (3H, s), 2.25 (3H, s), 2.87 (2H, d, 6), 4.39 (1H, d, 14), 4.58 (1H, d, 14), 6.41 (2H, s), 7.28 (2H, s)
2x	A	55	Pale yellow powder	b	127—128	1020	321.1511	(321.1512)	(b) 0.97 (6H, d, 6), 1.95 (1H, m), 2.13 (3H, s), 2.80 (2H, d, 6), 3.75 (3H, s), 4.48 (1H, d, 14), 4.70 (1H, d, 14), 6.54 (1H, d, 9), 6.81 (1H, d, 9), 7.22 (2H, s)
2y	A	26	Pale yellow powder	b	138—139	1000	321.1509	(321.1512)	(a) 0.99 (6H, d, 6), 1.95 (1H, m), 2.15 (3H, s), 2.84 (2H, d, 6), 3.62 (3H, s), 4.27 (1H, d, 14), 4.57 (1H, d, 14), 6.28 (1H, s), 6.52 (1H, s), 7.23 (2H, s)
2z	A	57	White powder	b	123.5—124	1030	325.1261	(325.1261)	(a) 1.01 (6H, d, 7), 1.91 (1H, m), 2.81 (2H, d, 6), 3.69 (3H, s), 4.27 (1H, d, 14), 4.53 (1H, d, 14), 6.4—6.5 (2H, m), 7.25 (2H, s)
2aa	A	32	White powder	b	168.5—169	1020	313.1058	(313.1061)	(a) 1.02 (6H, d, 7), 1.94 (1H, m), 2.87 (2H, d, 7), 4.43 (1H, d, 14), 4.47 (1H, d, 14), 6.1—6.2 (2H, m), 7.26 (2H, s)
2ab	A	38	White powder	b	112—114	1030	335.1667	(335.1669)	(a) 1.02 (6H, d, 7), 1.91 (1H, m), 2.15 (3H, s), 2.27 (3H, s), 2.85 (2H, d, 7), 3.63 (3H, s), 4.43 (1H, d, 14), 4.60 (1H, d, 14), 6.43 (1H, s), 7.28 (2H, s)
2ac	A	12	Pale brown powder	a	126—128	1010	319.1717	(319.1720)	(a) 1.02 (6H, d, 7), 1.95 (1H, m), 2.12 (3H, s), 2.17 (3H, s), 2.27 (3H, s), 2.85 (2H, d, 7), 4.41 (1H, d, 14), 4.63 (1H, d, 14), 6.45 (1H, s), 7.27 (2H, s)
2ae	A	34	Pale brown powder	b	123.5—124.5	1015	309.1150	(309.1149)	(b) 3.20 (2H, m), 3.38 (3H, s), 3.60 (2H, m), 3.61 (3H, s), 4.22 (1H, d, 14), 4.57 (1H, d, 14), 6.35 (1H, d, 3), 6.62 (1H, d, 9), 6.76 (1H, dd, 3, 9), 7.17 (2H, s)
2af	B	69	White powder	a	129—132	1020	293.1198	(293.1199)	(a) 2.22 (3H, s), 3.1—3.8 (4H, m), 3.42 (3H, s), 4.39 (1H, d, 14), 4.62 (1H, d, 14), 6.4—7.2 (3H, m), 7.27 (2H, s)

TABLE II. (continued)

Compd. No.	Method[a]	Yield[b] (%)	Appearance	Recrystn.[c] solv.	mp (°C)	IR ν cm^{-1} (S→O)	HR-MS Found	HR-MS (Calcd)	^{1}H-NMR (Solvent)[e] δ (J=Hz)
2ag	B	66	Pale brown powder	a	147—149	1020	293.1200	(293.1199)	(a) 2.14 (3H, s), 3.24 (2H, t, 5), 3.43 (3H, s), 3.64 (2H, t, 5), 4.30 (1H, d, 13), 4.50 (1H, d, 13), 6.4—7.1 (3H, m), 7.23 (2H, s)
2ah	A	28	Pale brown powder	b	125.5—126.5	1000	297.0950	(297.0948)	(b) 3.22 (2H, t, 5), 3.41 (3H, s), 3.5—3.8 (2H, m), 4.20 (1H, d, 14), 4.47 (1H, d, 14), 5.53 (1H, br), 6.1—6.4 (3H, m), 7.15 (2H, s)
2ai	A	22	Pale brown powder	b	110—111	1020	323.1304	(323.1305)	(a) 1.00 (6H, d, 6), 2.13 (3H, s), 3.1—3.2 (2H, m), 3.42 (3H, s), 3.68 (2H, t, 5), 3.76 (3H, s), 4.35 (1H, d, 14), 4.65 (1H, d, 14), 6.60 (1H, d, 8), 6.85 (1H, d, 8), 7.25 (2H, s)
2aj	A	31	Pale green powder	b	112—114	1000	323.1303	(323.1305)	(a) 2.15 (3H, s), 3.27 (2H, t, 5), 3.43 (3H, s), 3.62 (3H, s), 3.62 (2H, t, 5), 4.26 (1H, d, 14), 4.55 (1H, d, 14), 6.27 (1H, s), 6.58 (1H, s), 7.22 (2H, s)
2ak	A	39	White powder	b	126.5—127	1020	327.1056	(327.1054)	(b) 3.19 (2H, t, 5), 3.43 (3H, s), 3.5—3.8 (2H, m), 3.69 (3H, s), 4.26 (1H, d, 14), 4.51 (1H, d, 14), 6.4—6.6 (2H, m), 7.23 (2H, s)
2al	A	37	Pale brown powder	b	110—111	1020	337.1461	(337.1461)	(a) 2.15 (3H, s), 2.26 (3H, s), 3.23 (2H, t, 5), 3.42 (3H, s), 3.63 (3H, s), 3.67 (2H, t, 5), 4.39 (1H, d, 14), 4.61 (1H, d, 14), 6.46 (1H, s), 7.27 (2H, s)

a) Method A, *m*-CPBA oxidation; method B, H_2O_2/NH_4VO_3 oxidation. *b*) Yields from sulfide have not been optimized. *c*) a, this compound was crystallized with addition of aqueous NH_4Cl solution to the NaOH solution of this compound; b, chloroform–ether–hexane. *d*) Compounds decompose on melting; clearly defined melting points are not always obtainable. *e*) As the solvent of ^{1}H-NMR: a, $CDCl_3/CD_3OD=1:1$ (v/v); b, $CDCl_3$; c, DMSO-d_6.

Table II.

Results and Discussion

2-[(2-Imidazolylsulfinyl)methyl]-*N*-methylanilines in which imidazole rings were substituted with alkyl (**2b**, **c**, **e**) or an aryl (**2d**) group were initially synthesized and evaluated for inhibitory activity of H^+/K^+-ATPase prepared from rabbit stomach (pH 6.0 and 7.4) and of histamine-stimulated gastric acid secretion in Heidenhain pouch dogs after intravenous administration (3 mg/kg). The results are summarized in Table III. Introduction of substituents on the imidazole ring markedly reduced the potency in both *in vitro* enzyme inhibitory activity and gastric antisecretory effect compared with the unsubstituted compound (**2a**). IC_{50} value for **2a** was 2.8 μg/ml, whereas the phenyl derivative (**2d**) had no inhibitory activity even at 100 μM. Although the compounds with little or no activity in the *in vitro* H^+/K^+-ATPase inhibition assay are known to be stable in aqueous solution,[1,3] the stability of **2b**—**e** at pH 3.0, 5.0 and 7.0 was the same level as that of **2a** or omeprazole.

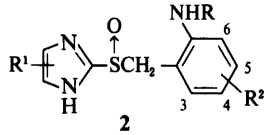
The effects of substitutions on the aniline ring were also investigated by introducing mono-, di- and trisubstituents to *N*-isobutyl-2-[(2-imidazolylsulfinyl)methyl]aniline, which has demonstrated a satisfactory pharmacological activity and stability as described.[1] H^+/K^+-ATPase inhibitory activity, antisecretory effects and half-lives in aqueous solution of the synthesized compounds are summarized in Table III. Single substitution on the aniline ring by electron-donating groups such as methoxy or methyl groups enhanced the *in vitro* activity compared with the unsubstituted compound (**2f**), with the exception of substitution at 6-position (**2i**, **m**). Furthermore, these active compounds showed inhibitory effects on gastric acid secretion in histamine-stimulated Heidenhain pouch dogs when administered by i.v. injection (3 mg/kg). The results for **2i** and **2m** are similar to those for omeprazole analogues with the substituent at the 6-position on the pyridine ring. It can be assumed that the decrease of inhibitory potency observed for **2i** and **2m** is due to steric hindrance in the process leading to inhibition.

In contrast, the introduction of electronegative substituents such as fluorine (**2n**, **o**) or chlorine (**2p**—**r**) or an electron-withdrawing substituent such as trifluoromethoxy (**2s**) or nitro groups (**2t**) markedly decreased activities both *in vitro* and *in vivo* (i.v.) compared with unsubstituted compounds (**2f**), with the exception of 5-fluoro substituted compound (**2o**). These observations suggest that the basicity at the aniline nitrogen atom markedly influences pharmacological activities.

Compounds which showed potent antisecretory activities after i.v. administration were further investigated after oral administration (10 and, or 6 mg/kg). Unsubstituted compound (**2f**) was not very effective, whereas the compound with 4-methoxy (**2h**), 3-methyl (**2j**), 4-methyl (**2k**) or 5-fluoro (**2o**) substituents showed inhibitory effects of more than 50% at 10 mg/kg. Compound **2k** had the highest activity, 84%, even at 6 mg/kg. The compounds which showed potent *in vivo* activity, however, were less stable than omeprazole in an acidic solution, whereas the half-lives of the other inactive compounds were more than 1 h at pH 5.0.

Di- or trisubstituted compounds (**2u**—**ac**) by methoxy and methyl group and fluorine on the aniline ring showed pronounced *in vitro* activity, with the exception of the 3,5-difluoro substituted derivative (**2aa**). Although dimethyl (**2u**—**w**) and trimethyl (**2ac**) substitution potently enhanced enzyme inhibition at pH 6.0 (10 times higher than that of omeprazole), the antisecretory effects of these compounds after oral administration were not as potent as expected. The methoxy- and methyl-substituted derivatives (**2x**, **y**, **ab**) were of interest, because **2ab**, in particular, contained the substitution pattern of omeprazole. These compounds displayed high potency after oral administration (6 mg/kg) in histamine-stimulated gastric acid secretion. However, most compounds with potent inhibitory effects on gastric acid secretion after oral administration were quite unstable in aqueous solution even at pH 7.0. Such compounds became increasingly difficult to isolate and handle following final-stage oxidation of the sulfide. The only relatively stable compound was the 3-methyl-4-methoxy substituted aniline (**2x**).

TABLE III. Substituted 2-[(2-Imidazolylsulfinyl)methyl]anilines (**2**): Activity and Stability



2

Compd. No.	R	R^1	R^2	H^+/K^+ ATPase IC_{50} (μM)		Heidenhain pouch inhibn· at i.v. %	at *p.o.* %		$T_{1/2}$ (h)		
				pH 6.0	pH 7.4	3 mg/kg	10 mg/kg	6 mg/kg	pH 3.0	pH 5.0	pH 7.0
2a	Me	H	H	2.8	44	82			0.04	0.93	35
2b	Me	4-Me	H	12	62	50			0.03	0.72	31
2c	Me	4-Me, 5-Et	H	12	74	26			0.04	0.67	37
2d	Me	4-Ph	H	>100	>100	32			0.07	1.73	14
2e	Me	4,5-$(CH_2)_4$–	H	24	>100	53			0.04	0.74	33
2f	iso-Bu	H	H	12	100	81	NE		0.03	0.93	63
2g	iso-Bu	H	3-OMe	2.5	20	97			<0.006	0.08	3.6
2h	iso-Bu	H	4-OMe	1.5	29	81	53	NE	0.02	0.23	6.8
2i	iso-Bu	H	6-OMe	19	300		Ne		0.92	1.55	67
2j	iso-Bu	H	3-Me	1.2	6.5	78	80		0.009	0.08	4.1
2k	iso-Bu	H	4-Me	3.6	16	97	100	84	0.01	0.22	14
2l	iso-Bu	H	5-Me	<1.0	9.4	87[a]		33	<0.005	0.04	2.2
2m	iso-Bu	H	6-Me	21	>300	30		NE	0.36	2.07	81
2n	iso-Bu	H	4-F	39	58	26			0.14	4.61	97
2o	iso-Bu	H	5-F	29	>300	97	78	26	0.01	0.87	37
2p	iso-Bu	H	3-Cl	56	61	NE			0.11	7.06	121
2q	iso-Bu	H	4-Cl	90	42	NE			0.22	8.32	18
2r	iso-Bu	H	5-Cl	>100	>300	22			0.09	3.48	43
2s	iso-Bu	H	4-OCF_3	>100	>300	NE			0.67	19.7	20
2t	iso-Bu	H	4-NO_2	>100	>300	NE			c)	c)	c)
2u	iso-Bu	H	3,4-Me_2	0.36	2.4	76	28		—	0.02	1.10
2v	iso-Bu	H	4,5-Me_2	0.29	2.1		31		—	0.02	0.70
2w	iso-Bu	H	3,5-Me_2	0.16	0.84	91	68	41	—	—	0.20
2x	iso-Bu	H	4-OMe, 3-Me	4.2	28			63	0.02	0.15	4.95
2y	iso-Bu	H	5-Me, 4-OMe	0.70	6.9		100	91	—	—	0.42
2z	iso-Bu	H	5-F, 4-OMe	1.7	13			68	—	0.07	2.60
2aa	iso-Bu	H	3,5-F_2	>300	>300			NE	0.29	7.62	131
2ab	iso-Bu	H	3,5-Me_2, 4-OMe	0.35	2.1	84[a]	100	95	—	0.01	0.46
2ac	iso-Bu	H	3,4,5-Me_3	0.42	0.60	100	100	26	—	—	0.08
2ad	CH_2CH_2OMe	H	H	43	180	89	NE		0.15	4.59	175
2ae	CH_2CH_2OMe	H	4-OMe	16	64			76	0.13	0.88	43
2af	CH_2CH_2OMe	H	3-Me	4.4	26	89	NE		0.01	0.33	18
2ag	CH_2CH_2OMe	H	4-Me	25	>300	85	100	66[b]	0.05	1.63	58
2ah	CH_2CH_2OMe	H	5-F	45	230			18	0.03	0.93	63
2ai	CH_2CH_2OMe	H	3-Me, 4-OMe	17	160			65	0.09	0.80	32
2aj	CH_2CH_2OMe	H	4-OMe, 5-Me	1.0	16			100	—	0.07	1.9
2ak	CH_2CH_2OMe	H	4-OMe, 5-F	7.2	64	81		97	0.01	0.40	14
2al	CH_2CH_2OMe	H	3,5-Me_2, 4-OMe	0.46	11		100	66	—	0.06	2.3
Omeprazole				3.8	54	95	100		0.05	0.34	27

NE: not effective. *a*) Inhibition at 1 mg/kg. *b*) Inhibition at 3 mg/kg. *c*) Insoluble in the test solution.

It was earlier reported[1] that the compounds substituted with alkoxyalkyl groups at the aniline nitrogen atom possessed higher stability than alkyl substituted compounds. To increase stability, *N*-(2-methoxyethyl)anilines with desirable substituents such as methoxy and methyl groups and fluorine were synthesized and tested for stability and pharmacological activities. The data are summarized in Table III. The stability of all *N*-(2-methoxyethyl) derivatives in the respective solutions (pH 3.0, 5.0 and 7.0) increased compared with the corresponding *N*-isobutyl derivatives, as expected. The 4-methoxy (**2ae**) and 3-methyl-4-methoxy (**2ai**) derivatives showed twice the stability of omeprazole at pH 3.0. However, in the *in vitro* test, *N*-(2-methoxyethyl) derivatives were less active than the corresponding *N*-isobutyl derivatives. In the inhibitory effects on gastric acid secretion *N*-(2-methoxyethyl) derivatives were similar to *N*-isobutyl derivatives, although the potency differed depending on the compound.

The results obtained from *N*-isobutyl and *N*-(2-methoxyethyl)derivatives indicated a distinct correlation in the potency of *in vitro* inhibitory activity and the half-lives in aqueous solution. A similar correlation has been previously reported.[1] These results also indicate that there is a lack of correlation in inhibitory effect on gastric acid secretion by intravenous administration and oral administration, which might be due to a difference in the absorption of the compounds. Thus the plasma concentrations were measured 2 h after oral administration of the compounds (10 mg/kg). The plasma concentration of the unsubstituted compound (**2f**), which showed no activity after oral administration, was 50 ng/ml, whereas that of

the 4-methyl derivative (**2k**) which had a potent activity, was 1700 ng/ml.

Thus, a series of 2-[(2-imidazolylsulfinyl)methyl]anilines (**2**) with electron-donating substituents on the aniline moiety have been identified as attractive antisecretory agents.

Experimental

Melting points (mp) determined with a Yamato MP-21 apparatus were uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-50 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-FX90Q or JEOL JNM-EX400 NMR spectrometer with tetramethylsilane as the internal standard. High resolution mass spectra (HR-MS) were obtained on a JEOL JMS-SX102 mass spectrometer.

2-Methylaminobenzyl chloride hydrochloride was prepared by $LiAlH_4$-reduction of the commercially available methyl *N*-methylanthranilate followed by chlorination with thionyl chloride. Chemical data of **1a**, **1f**, **1ad**, **2a**, **2f** and **2ad** were reported previously.[1]

General Procedure for the Preparation of Substituted 2-Isobutylaminobenzyl Alcohols (5) A mixture of methyl 5-methylanthranilate (5.0 g, 30 mmol), K_2CO_3 (4.97 g) and isobutyryl chloride (3.38 g, 36 mmol) in benzene (50 ml) was refluxed for 2 h. The reaction mixture was cooled to room temperature and then cold water was added. The benzene layer was separated, washed with 6 N HCl and saturated NaCl solution, and then dried with anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to yield 7.0 g (99%) of methyl 2-isobutyrylamino-5-methylbenzoate as an analytically pure solid. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J=7 Hz), 2.31 (3H, s), 2.60 (1H, m), 3.91 (3H, s), 7.30 (1H, dd, J=2, 9 Hz), 7.82 (1H, d, J=2 Hz), 8.62 (1H, d, J=9 Hz). HR-MS m/z Calcd for $C_{13}H_{17}NO_3$: 235.1209. Found: 235.1206. A solution of methyl 2-isobutyrylamino-5-methylbenzoate (3.52 g, 15 mmol) in tetrahydrofuran (THF, 10 ml, dried by Al_2O_3) was added dropwise over 15 min to a suspension of $LiAlH_4$ (1.14 g, 30 mmol) in THF (35 ml, dried by Al_2O_3) with ice-water cooling. The mixture was then stirred at 0 °C for 30 min and heated at 50 °C for 1 h. The reaction mixture was cooled and the reaction was quenched with saturated aqueous Na_2SO_4. The insoluble solid was removed by filtration and the filtrate was concentrated to give 2-isobutylamino-5-methylbenzyl alcohol (**5k**) (2.7 g, yield 93%) as a pale brown oil. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (6H, d, J=7 Hz), 1.6—2.1 (1H, m), 2.22 (3H, s), 2.91 (2H, d, J=7 Hz), 4.58 (2H, s), 6.4—7.1 (3H, m). The other benzyl alcohols were obtained by a procedure similar to that described for **5k**.

General Procedure for the Preparation of Substituted 2-Methylsulfinylmethylanilines (6) NCS (6.69 g, 50 mmol) was added in portions at 0—5 °C to a stirred solution of *N*-isobutyl-4-methoxy-3,5-dimethylaniline (7.0 g, 33 mmol) and dimethylsulfide (3.6 ml) in CH_2Cl_2 (140 ml) over a period of 10 min. After stirring for an additional 10 min, Et_3N (7.0 ml) was added and the mixture was stirred under reflux for 1 h. The organic layer was washed with 5% Na_2CO_3 solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography (silica gel, acetone–hexane) gave 6.61 g (purity 82%, containing acetone, yield 61%) of *N*-isobutyl-4-methoxy-3,5-dimethyl-2-methylthiomethylaniline as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (6H, d, J=6 Hz), 1.94 (1H, m), 2.06 (3H, s), 2.27 (6H, s), 2.91 (2H, d, J=7 Hz), 3.62 (3H, s), 3.74 (2H, s), 3.9—4.3 (1H, br), 6.35 (1H, s). *m*-CPBA (purity 85%, 2.07 g, 10.3 mmol) was added in portions with stirring to a solution of *N*-isobutyl-4-methoxy-3,5-dimethyl-2-methylthiomethylaniline (3.31 g, 10 mmol) in a mixed solvent of $CHCl_3$ (30 ml) and MeOH (3 ml) over a period of 15 min with ice water cooling. After 15 min, the reaction was quenched with 5% Na_2CO_3 solution and the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by chromatography (silica gel, AcOEt–hexane) gave 1.91 g (66%) of *N*-isobutyl-4-methoxy-3,5-dimethyl-2-methylsulfinylmethylaniline (**6ab**) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (6H, d, J=6 Hz), 1.90 (1H, m), 2.20 (3H, s), 2.27 (3H, s), 2.60 (3H, s), 2.83 (2H, d, J=6 Hz), 3.63 (3H, s), 3.97 (1H, d, J=14 Hz), 4.17 (1H, d, J=14 Hz), 5.01 (1H, br), 6.41 (1H, s).

The other substituted 2-methylsulfinylmethylanilines were obtained by a procedure similar to that described for **6ab**.

General Procedure for the Preparation of Substituted 2-[(2-Imidazolylthio)methyl]anilines (1) [Method C] A solution of 2-isobutylamino-5-methylbenzyl alcohol (**5k**) (2.7 g, 13.9 mmol) in CH_2Cl_2 (29 ml) was cooled to 0 °C and $SOCl_2$ (1.22 ml, 18.6 mmol) in CH_2Cl_2 (5 ml) was added dropwise over a period of 10 min. After 30 min, the reaction mixture was concentrated *in vacuo* and the resultant gummy precipitate was added to 2-mercaptoimidazole (2.0 g, 20 mmol) and EtOH (29 ml). The mixture was stirred at room temperature for 1 h. After removal of the solvent, CH_2Cl_2 and a saturated $NaHCO_3$ solution were added. The organic layer was separated, washed with saturated NaCl and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the addition of Et_2O–hexane (2:1) followed by filtration of the precipitate gave 1.6 g (42%) of 2-[(2-imidazolylthio)methyl]-*N*-isobutyl-4-methylaniline (**1k**) as a pale gray powder.

Compounds **1g—j**, **l—t** and **af—ah** were obtained by a procedure similar to that described for **1k**. mp, HR-MS and ^{1}H-NMR are given in Table I.

General Procedure for the Preparation of Substituted 2-[(2-Imidazolylthio)methyl]anilines (1) [Method D] HCl gas was bubbled into a stirred solution of *N*-isobutyl-4-methoxy-3,5-dimethyl-2-methylsulfinylmethylaniline (**6ab**) (1.91 g, 6.7 mmol) in CH_2Cl_2 (20 ml) for 10 min with ice water cooling. After stirring for an additional 10 min, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 again. The resultant brown solution was added dropwise to a solution of 2-mercaptoimidazole (2.0 g, 20 mmol) in 20 ml of EtOH over a period of 10 min with stirring. After 30 min, the solvent was evaporated and CH_2Cl_2 and 5% Na_2CO_3 solutions were added. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, AcOEt–hexane) and crystallization from Et_2O–hexane gave 1.87 g (87%) of 2-[(2-imidazolylthio)methyl]-*N*-isobutyl-4-methoxy-3,5-dimethylaniline (**1ab**) as a white powder.

Compounds **1u—aa**, **ac**, **ae** and **ai—al** were obtained by a procedure similar to that described for **1ab**. mp, HR-MS and ^{1}H-NMR are given in Table I.

General Procedure for the Preparation of Substituted 2-[(2-Imidazolylsulfinyl)methyl]anilines (2) by Method A *m*-CPBA (purity 80%, 0.77 g, 3.6 mmol) was added portionwise to a solution of 2-[(2-imidazolylthio)-methyl]-*N*-isobutyl-4-methylaniline (**1k**) (1.0 g, 3.4 mmol) in $CHCl_3$ (10 ml) at 0—5 °C. The mixture was stirred for 30 min then $CHCl_3$ and saturated $NaHCO_3$ solutions were added. The $CHCl_3$ layer was separated, washed successively with 0.1 N NaOH (10 ml) and then extracted twice with 1 N NaOH (10 ml) to transfer the reaction product into the aqueous fraction. The combined extract was made ammonia-alkaline by the addition of 20% NH_4Cl solution. The gummy precipitate left after the ammonia-alkaline solution was dissolved in $CHCl_3$ and the solution was then washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 440 mg (42%) of 2-[(2-imidazolylsulfinyl)methyl]-*N*-isobutyl-4-methylaniline (**2k**) as a pale yellow powder.

Compounds **2b—e**, **h—j**, **u—ae** and **ah—al** were obtained by a procedure similar to that described for **2k**. mp, HR-MS, IR (S→O) and ^{1}H-NMR are given in Table II.

General Procedure for the Preparation of Substituted 2-[(2-Imidazolylsulfinyl)methyl]anilines (2) [Method B] A mixture of 5-fluoro-2-[(2-imidazolylthio)methyl]-*N*-isobutylaniline (**1o**) (2.0 g, 7.2 mmol), $CHCl_3$ (20 ml), MeOH (20 ml), and 2.0 ml of AcOH was stirred for 30 min at room temperature. The resultant solution of **1o** was cooled with ice water to below 5 °C and 35% H_2O_2 (3.0 ml) and NH_4VO_3 (40 mg) were added. The mixture was stirred for about 2.5 h at a temperature between −3 and 3 °C. The precipitate deposited after the addition of 5% Na_2CO_3 solution was filtered, washed with water and CH_2Cl_2 and dissolved in 2 N NaOH (30 ml). The alkaline solution was washed with $CHCl_3$ and then 1 N NH_4Cl (90 ml) was added. The separated precipitate was filtered, washed with water and dried *in vacuo* at room temperature overnight to give 1.68 g (79%) of 5-fluoro-2-[(2-imidazolylsulfinyl)-methyl]-*N*-isobutylaniline (**2o**) as a pale yellow powder.

Compounds **2g**, **l—n**, **p—t**, **af** and **ag** were obtained by a procedure similar to that described for **2o**. mp, HR-MS, IR (S→O) and ^{1}H-NMR are given in Table II.

Assay Procedure for Antisecretory Effect in Histamine-stimulated Heidenhain Pouch Dogs after Oral Administration Beagles of both sexes (12—14 kg) with Heidenhain pouch were fasted for 18 h before experiments. Histamine dihydrochloride was continuously administered i.v. at a dose of 160 μM/kg/h. Gastric juice was collected at 15 min intervals and the volume was determined. Acid concentration was measured by titration with 0.1 N NaOH to pH 7.0. Test compounds were administered *p.o.* 2 h before the initiation of histamine administration. The percentage inhibition of acid output was determined 1 h after administration of histamine by comparison with the control value.

Another Assay Procedure H^+/K^+-ATPase inhibitory activity, anti-

secretory effect in histamine-stimulated Heidenhain pouch dogs after i.v. administration and stability in aqueous solution (pH 3.0, 5.0 and 7.0) were tested using reported methods.[1)]

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