Efficient Synthesis and Gastric (H^+/K^+)-ATPase-Inhibitory Activity of 2-Aryl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazoles

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A series of 2-aryl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazoles (1, 2) was prepared by condensation of 5-acylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-ones (9, 10) with ammonium acetate under azeotropic reaction conditions. Various congeners, *N*-methyl and *N*-phenyl analogues (3—5), 4,5-dihydro-1*H*-thieno[2,3-*e*]benzimidazoles (6), 4,5-dihydro-1*H*-thieno[2,3-*g*]benzoxazoles (7), and 4,5-dihydro-1*H*-thieno[2,3-*g*]benzothiazoles (8), were also prepared. Several compounds in this series were shown to be K^+-competitive inhibitors of the gastric (H^+/K^+)-ATPase and more potent inhibitors than SK&F-96067, 3-butyryl-8-methoxy-4-(2-tolylamino)quinoline, on pentagastrin-stimulated acid secretion in chronic gastric fistula rats after intraduodenal administration.

Key words (H^+/K^+)-ATPase inhibitor; 4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole; gastric acid

Gastric (H^+/K^+)-ATPase, the proton pump of the parietal cell, is responsible for the final step of acid secretion in the stomach.[1] Sustained suppression of gastric acid secretion by irreversible proton pump inhibitors, *e.g.* omeprazole, has been associated with the formation of gastric carcinoids owing to hypergastrinemia in long-term carcinogenicity studies.[2,3] With this background, we were interested in reversible (H^+/K^+)-ATPase inhibitors as shorter-acting inhibitors of gastric acid secretion and as potential therapies for acid-related gastrointestinal disorders. Such compounds are expected to have the potential to combine profound inhibition of acid secretion, elicited by all stimuli, with the dosing flexibility available with the short-acting H_2-receptor antagonists.

In a search for reversible inhibitors of the enzyme, we found that 2-aryl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazoles (**1**) potently inhibit pentagastrin-stimulated acid secretion in chronic gastric fistula rats after intraduodenal administration. We describe herein an efficient synthetic approach to **1** and its congeners (**2**—**8**) (Fig. 1), and their inhibitory activities on gastric (H^+/K^+)-ATPase and pentagastrin-stimulated acid secretion.

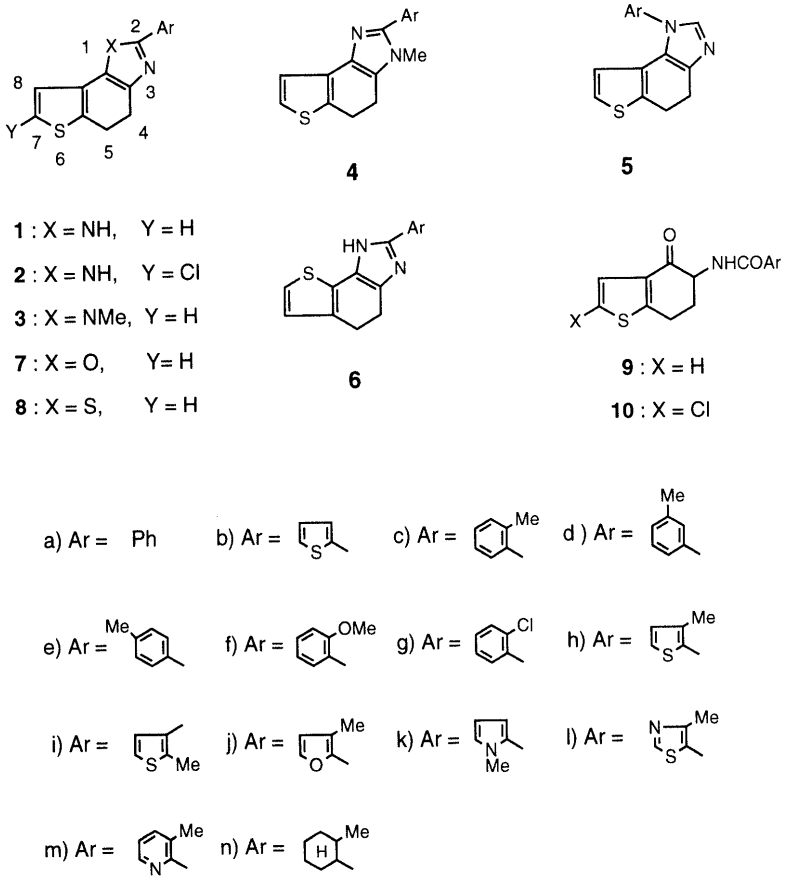

Fig. 1

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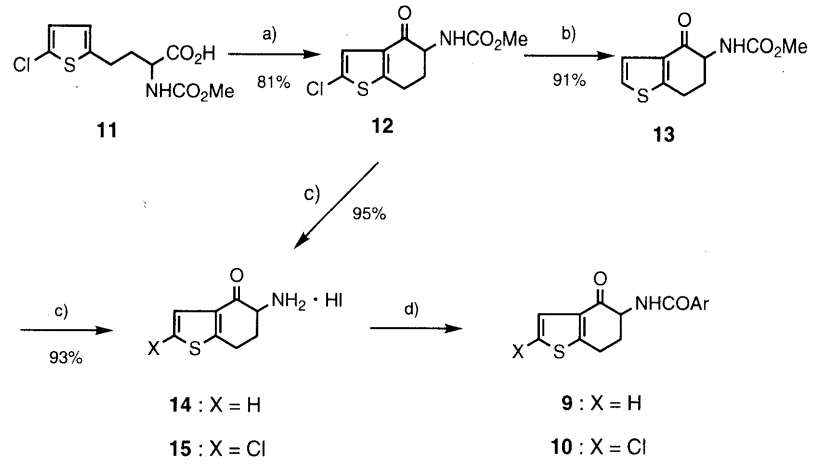
Chemistry

The imidazole nucleus is generally prepared by the condensation of α-acylamino ketone with ammonium acetate ($AcOH \cdot NH_3$) in acetic acid (AcOH)[4] or α-halo ketone with amidine,[5,6] though there are few reports on the synthesis of **1** from either ketone. We successfully constructed the 4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole nucleus (**1**) by the condensation of 5-acylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-ones (**9**) with $AcOH \cdot NH_3$ under azeotropic reaction conditions.

The requisite α-acylamino ketones (**9**) were prepared from 4-(5-chlorothiophen-2-yl)-2-methoxycarbonylaminobutyric acid (**11**),[7] by a four-step reaction sequence as illustrated in Chart 1. Intramolecular Friedel–Crafts acylation of **11** followed by dehalogenation with palladium–charcoal (Pd–C) provided 5-methoxycarbonylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one (**13**). Removal of the methoxycarbonyl group of **13** with iodotrimethylsilane (Me_3SiI)[8] and acylation of the resulting amine (**14**) gave 5-acylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-ones (**9**) in good yields. Similarly, treatment of 2-chloro-5-methoxycarbonylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one (**12**) with Me_3SiI followed by acylation gave **10**.

First, condensation of **10a** with $AcOH \cdot NH_3$ in AcOH was taken as a model for construction of the imidazole nucleus and investigated under reflux. The dehydrogenated product (**17**)[9] resulting from further oxidation of the desired 4,5-dihydro product **2a** by air was isolated in 33% yield in addition to **2a** (16% yield). When the reaction was run under an argon atmosphere, the formation of **17** was largely prevented, but no increase in the yield of **2a** was observed. The reaction in a sealed tube at elevated temperature (200 °C) gave similar results. From the above results, it appears that the water generated in the reaction hydrolyzes the intermediary enamine (**16**) and consequently decreases the formation of **2a** (Chart 2).

In order to remove the resulting water, the condensation was examined under azeotropic reaction conditions. The desired product (**2a**) was obtained in 91% yield when the reaction was carried out in refluxing xylene in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) using a Dean–Stark distillation head under an argon atmosphere. Several examples of the preparation of 2-aryl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazoles (**1**—**3**) from α-acylamino ketones (**9**, **10**) with $AcOH \cdot NH_2R$ are summarized in Table 1. Construction of the imidazole nucleus (**1**) from arylcarboxamides (**9c**, **9f**—**m**) bearing an *ortho*-substituent in the aryl moiety also proceeded smoothly (entries 2, 5—12).[10] 1-Methyl imidazoles (**3**) were also prepared by the reaction of **9** with $AcOH \cdot NH_2Me$ (entries 15, 16).



Reagent : a) 1) $(COCl)_2$, 2) $AlCl_3$ in CH_2ClCH_2Cl; b) 10% Pd-C, HCO_2H, Et_3N in MeOH; c) Me_3SiI; d) ArCOCl, Et_3N.

Chart 1

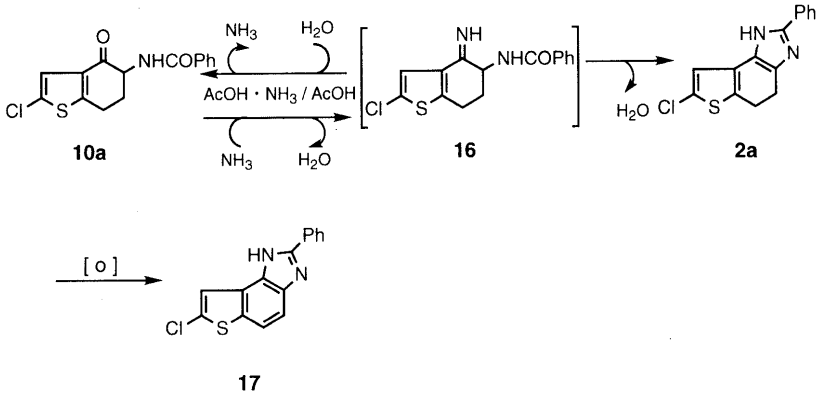
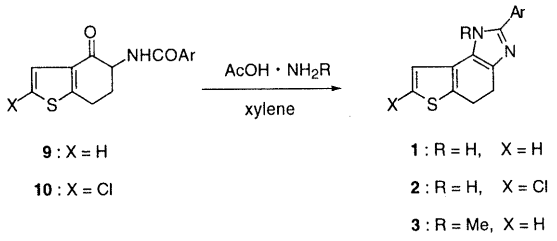


Chart 2

3-Methyl analogues (**4**) were obtained by methylation of **1** with methyl iodide (CH_3I). Treatment of **1b** with CH_3I and sodium hydride (NaH) gave **4b** as a sole product in 40% yield, whereas methylation of **1a**, which was prepared by catalytic hydrogenolysis of **2a** in 79% yield, afforded a mixture of **3a** (29% yield) and **4a** (35% yield).

Table 1. Condensation of α-Acylamino Ketone (**9**, **10**) with AcOH·NH_2R



9 : X = H
10 : X = Cl

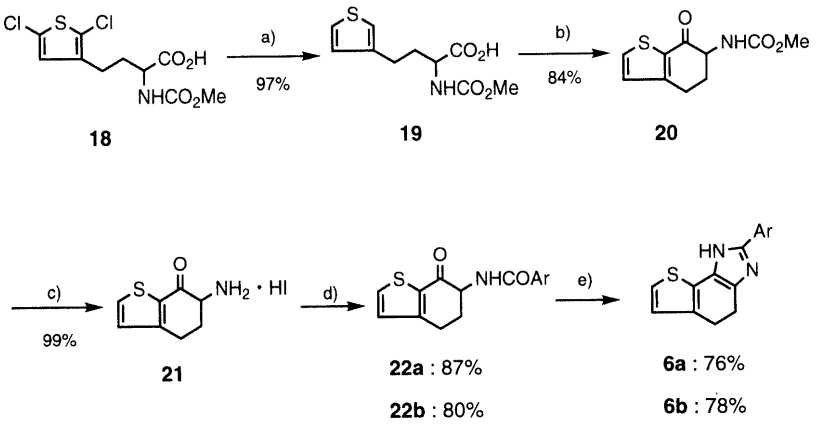
1 : R = H, X = H
2 : R = H, X = Cl
3 : R = Me, X = H

Entry	Starting ketone	Product	Yield (%)	Entry	Starting ketone	Product	Yield (%)
1	**9b**	**1b**	91	9	**9j**	**1j**	65
2	**9c**	**1c**	79	10	**9k**	**1k**	66
3	**9d**	**1d**	73	11	**9l**	**1l**	82
4	**9e**	**1e**	69	12	**9m**	**1m**	78
5	**9f**	**1f**	80	13	**9n**	**1n**	74
6	**9g**	**1g**	60	14	**10a**	**2a**	76
7	**9h**	**1h**	64	15	**9a**	**3a**	65
8	**9i**	**1i**	89	16	**9b**	**3b**	84

The method for construction of the dihydrobenzimidazole nucleus (**1**—**3**) from **9** and **10** was successfully applied to the preparation of 2-aryl-4,5-dihydro-1*H*-thieno[2,3-*e*]benzimidazoles (**6**) as depicted in Chart 3. Hydrogenolysis of **18** and intramolecular Friedel–Crafts acylation of **19** gave α-methoxycarbonylamino ketone (**20**). Removal of the methoxycarbonyl group from **20** followed by acylation afforded the amide (**22**). Treatment of **22** with $AcOH \cdot NH_3$ gave **6** in good yields.

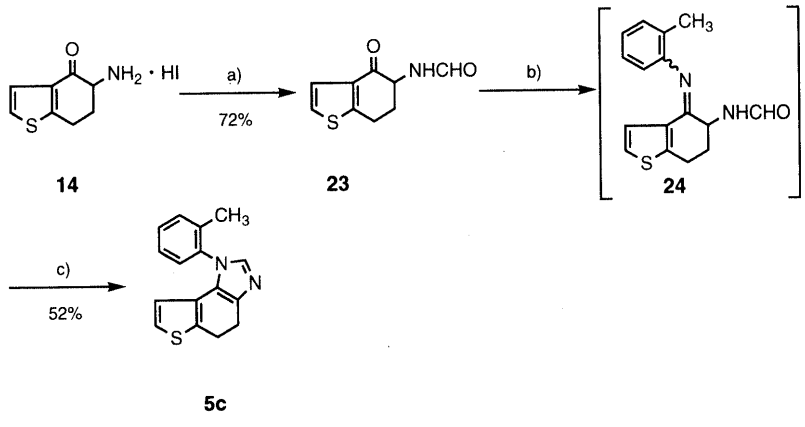
N-Tolyl imidazole (**5c**) was prepared from **14** as shown in Chart 4. After formylation of **14**, the resulting formate (**23**) was converted into the intermediary imine (**24**) according to a slightly modified Love's method.[11] Intramolecular condensation of **24** with phosphorus pentachloride (PCl_5) gave **5c**.

4,5-Dihydro-1*H*-thieno[2,3-*g*]benzoxazoles (**7**) and 4,5-dihydro-1*H*-thieno[2,3-*g*]benzothiazoles (**8**) were also prepared from **9** in high yields by treatment with $POCl_3$ and Lawesson's reagent, respectively (Chart 5).



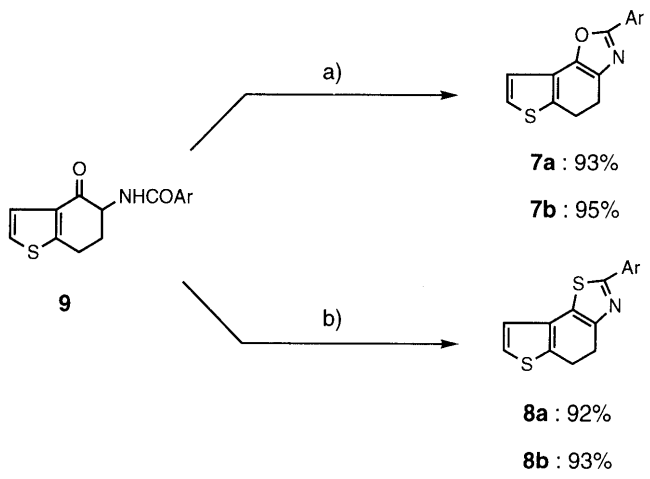
Reagent : a) 10%Pd-C, $HCO_2H \cdot NH_3$, K_2CO_3 in EtOH; b) 1) $(COCl)_2$, 2) $AlCl_3$ in CH_2ClCH_2Cl;
c) Me_3SiI; d) ArCOCl, Et_3N; e) $AcOH \cdot NH_3$, *p*-TsOH in xylene

Chart 3



Reagent : a) Ac_2O, HCO_2H, Et_3N; b) *o*-Toluidine, H_2SO_4, $(EtO)_4Si$;
c) PCl_5 in $CHCl_3$

Chart 4



Reagent : a) $POCl_3$; b) Lawesson's reagent in xylene

Chart 5

Table 2. Biological Activity of **1**—**8** and SK&F-96067

Compd.	(H^+/K^+)-ATPase inhibition:[a] % inhibition at 10 μM (IC_{50})	Rat gastric secretion:[b] % inhibition at 10 mg/kg, id[c]	Compd.	(H^+/K^+)-ATPase inhibition:[a] % inhibition at 10 μM (IC_{50})	Rat gastric secretion:[b] % inhibition at 10 mg/kg, id[c]
1a	48	++(75)	**2a**	27	±
1b	61 (3 μM)	+	**3a**	25	N.E.
1c	69 (5 μM)	++(91)	**3b**	32	N.E.
1d	48	±	**4a**	10	±
1e	52	±	**4b**	21	N.E.
1f	48	±	**5c**	29	N.E.
1g	30	+	**6a**	14	N.E.
1h	58 (8 μM)	++(99)	**6b**	16	±
1i	60 (6 μM)	++(96)	**7a**	6	N.E
1j	16	+	**7b**	11	N.E.
1k	43	++(80)	**8a**	35	N.E.
1l	5	±	**8b**	37	N.E.
1m	35	±	**SK&F-96067**	73 (3 μM)	++ (81)
1n	26	±			

a) Inhibition of K^+-stimulated gastric (H^+/K^+)-ATPase activity. *b*) Inhibition of pentagastrin-stimulated gastric acid secretion in chronic gastric fistula rats after intraduodenal administration. *c*) ++: inhibition ≧70%, +: 70% > inhibition ≧50%, ±: 50% > inhibition ≧30%, N. E.: inhibition < 30%.

Results and Discussion

Effects of **1** and its congeners (**2**—**8**) were assayed according to the following protocols, as described previously.[12-14] The *in vitro* screening for inhibition of K^+-stimulated ATPase activity was performed by the use of canine gastric microsomes at pH 6.8. The synthesized compounds (**1**—**8**) were evaluated for the potential to inhibit pentagastrin-induced acid secretion in chronic gastric fistula rats after intraduodenal administration. Biological results are listed in Table 2, including those for SK&F-96067,[15] known to be a potent and reversible (H^+/K^+)-ATPase inhibitor.

From the structure–activity relationship studies on 2-aryl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazoles (**1**), the C_2-aryl group of **1** was found to be essential for both (H^+/K^+)-ATPase-inhibitory activity and intraduodenal antisecretory activity. Lack of aromaticity of the C_2-aryl group and transposition of the aryl group to the N_1-atom of **1** caused a marked decrease in the activity (**1n**, **5c**), while the imidazole (**1c**) having an aryl substituent at the C_2-position showed potent activities *in vitro* and *in vivo*. A remarkable enhancement of *in vivo* activity was observed by the introduction of a methyl group at the *ortho* position of the C_2-aryl ring of **1**. In particular, 4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole having a 2-tolyl (**1c**), 3-methylthienyl (**1h**), or 2-methylthiophen-3-yl (**1i**) group at the C_2-position exhibited higher antisecretory activity than did SK&F-96067. The time courses of mean percent inhibition of pentagastrin-induced acid secretion in chronic gastric fistula rats after intraduodenal administration of the imidazoles (**1c**, **1h**, **1i**) are shown in Fig. 2.

Some minor modifications of the imidazole ring and thiophene ring of **1** were examined further. Introduction of a methyl group at the N-atom of the imidazole nucleus (**3a, b**, **4a, b**) and displacement of the S-atom and C_8-sp^2 carbon of **1** (**6a, b**) significantly reduced the *in vitro* and *in vivo* activities. Conversion of the imidazole ring of **1** into an oxazole (**7a, b**) or thiazole ring (**8a, b**) also caused a marked decrease in activities. Of the compounds evaluated *in vitro*, 2-thienyl-4,5-dihydro-1*H*-thieno[3,2-*e*]-benzimidazole (**1b**) strongly inhibited (H^+/K^+)-ATPase and the IC_{50} value of **1b** for the enzyme was about the same as that of SK&F-96067. Steady-state enzyme kinetic experiments with **1b** were performed at pH 6.8. As shown in Fig. 3, the data were well fitted by three straight lines, indicating a competitive pattern of inhibition. This implies that **1b** is a reversible inhibitor with respect to the activating cation, K^+.

Although some of the 2-aryl-4,5-dihydro-1*H*-thieno-[3,2-*e*]benzimidazoles were found to be potent and reversible inhibitors of (H^+/K^+)-ATPase, they showed unfavorable side effects at higher doses. Therefore, we are continuing studies on optimization of our lead compounds (**1**).

Experimental

General Procedure All the melting points are uncorrected. Infrared (IR) spectra were taken with a Hitachi IR-215 or an Analect FX-6200 FT-IR spectrophotometer. NMR spectra were recorded with a JEOL JNM-FX-200 or a JEOL JNM-GSX-400 spectrometer. Chemical shifts are given as d values from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triple triplet, ddd = double double doublet, ddt = double double triplet, dddd = double double double doublet, dddt = double double double triplet, br = broad, br d = broad doublet, and m = multiplet. Mass spectra (EI-MS, FAB-MS) were recorded with a Finnigan Mat INCOS 50 or a JEOL JMS-HX 100 mass spectrometer. Microanalyses were performed on a Perkin-Elmer 2400 C, H, N, analyzer, a Yokogawa IC-100 ion chromatographic analyzer, and a Hitachi Z-8000 atomic absorption spectrophotometer. Silica Gel 60 K-230 (230—400 mesh) (Katayama) was used for flash column chromatography.

Materials Methoxycarbonylaminobutyric acids (**11**, **18**) were prepared according to the method described in the previous paper.[8]

Preparation of 4,5-Dihydro-1*H*-thieno[3,2-*e*]benzimidazoles (1—3) and 4,5-Dihydro-1*H*-thieno[2,3-*e*]benzimidazoles (6) Dihydrobenzimidazoles (**1**—**3**, **6**) were prepared by condensation of amides (**9**, **10**, **22**) with $AcOH \cdot NH_2R$ using a Dean-Stark distillation head under an argon atmosphere. The general procedure is exemplified by the preparation of **2a** from **10a**.

7-Chloro-2-phenyl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole (2a) A mixture of **10a** (1.98 g, 6.5 mmol), 95% $AcOH \cdot NH_3$ (20 g, 0.25 mol), and *p*-$TsOH \cdot H_2O$ (128 mg, 0.67 mmol) in xylene (40 ml) was degassed with

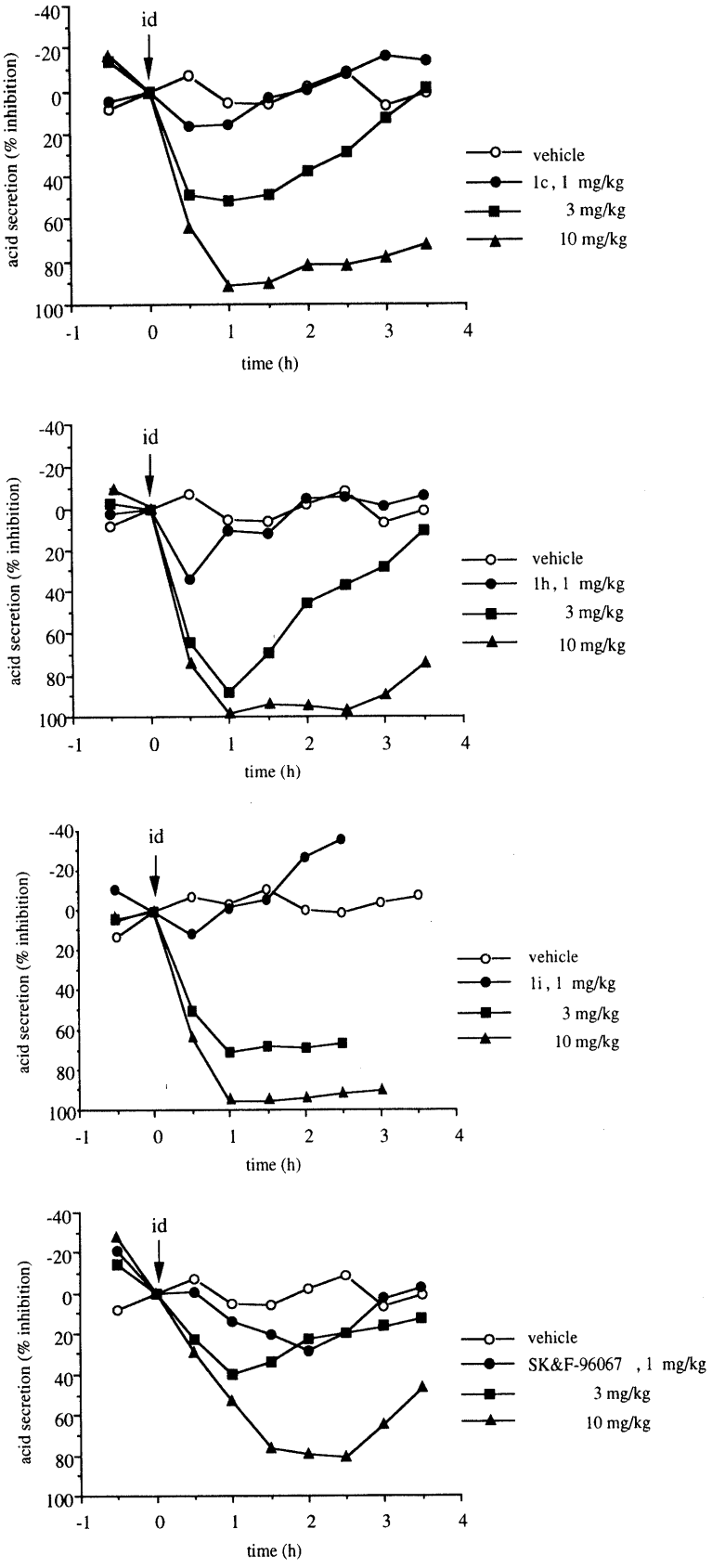


Fig. 2. The Time Course of Mean Percent Inhibition of Pentagastrin-Stimulated Gastric Acid Secretion in Chronic Gastric Fistula Rats Following an Intraduodenal Bolus Injection of **1c**, **1h**, **1i**, or SK&F-96067

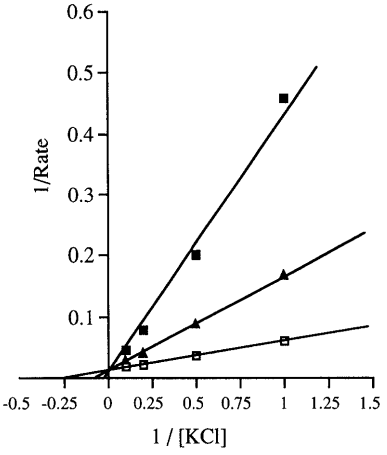


Fig. 3. (H^+/K^+)-ATPase Activity Was Determined at pH 6.8 in the Presence of 2 mM Na_2ATS and 1 to 10 mM KCl

Compound **1b** was present at 0 μM (□), 5 μM (▲) or 10 μM (■).

argon and refluxed for 4 h using a Dean–Stark distillation head. The xylene was removed by distillation and saturated $NaHCO_3$ solution was added to the residue. The mixture was extracted with AcOEt. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with $CHCl_3$–AcOEt (2:1) gave **2a** (1.69 g, 91%), mp 225—227 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.88—3.09 (4H, m, 4-H, 5-H), 7.20 (1H, s, 8-H), 7.32 (1H, tt, J=7.3, 1.5 Hz, 4′-H), 7.45 (2H, ddd, J=8.5, 7.3, 1.5 Hz, 3′-H, 5′-H), 7.90 (2H, dt, J=8.5, 1.5 Hz, 2′-H, 6′-H), 12.5 (1H, br, NH). IR (Nujol) cm^{-1}: 3080. EI-MS m/z: 286, 288 (3:1, M^+). *Anal.* Calcd for $C_{15}H_{11}ClN_2S$: C, 62.82; H, 3.87; N, 9.77; Cl, 12.36; S, 11.18. Found: C, 62.75; H, 3.69; N, 9.68; Cl, 12.39; S, 11.28.

2-Thienyl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole (1b) This compound was obtained from **9b** with AcOH·NH_3 in 76% yield, mp 271—273 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.8—3.0 (2H, m), 3.04—3.11 (2H, m), 7.11 (1H, dd, J=4.9, 3.5 Hz, 4′-H), 7.20 (1H, d, J=4.9 Hz, 8-H), 7.36 (1H, d, J=4.9 Hz, 5′-H), 7.47 (1H, d, J=3.5 Hz, 3′-H), 7.47 (1H, d, J=4.9 Hz, 7-H). IR (Nujol) cm^{-1}: 3110. EI-MS m/z: 258 (M^+). *Anal.* Calcd for $C_{13}H_{10}N_2S_2$: C, 60.44; H, 3.90; N, 10.84; S, 24.82. Found: C, 60.70; H, 3.89; N,11.09; S, 24.58.

2-(2-Tolyl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1c) This compound was obtained from **9c** with AcOH·NH_3 in 79% yield, mp >300 °C (MeOH–iso-PrOH). ^{1}H-NMR (DMSO-d_6) δ: 2.53 (3H, s, 2′-Me), 3.08—3.16 (2H, m), 3.21—3.28 (2H, m), 7.41—7.49 (2H, m, 3′-H, 5′-H), 7.52 (1H, d, J=5.2 Hz, 8-H), 7.56 (1H, dt, J=1.5, 7.5 Hz, 4′-H), 7.60 (1H, d, J=5.2 Hz, 7-H), 7.66 (1H, dd, J=7.5, 1.5 Hz, 6′-H). IR (Nujol) cm^{-1}: 3060. EI-MS m/z: 266 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2S$·HCl: C, 63.46; H, 4.99; N, 9.25; Cl, 11.71; S, 10.59. Found: C, 63.33; H, 4.91; N, 9.14; Cl, 11.80; S, 10.50.

2-(3-Tolyl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1d) This compound was obtained from **9d** with AcOH·NH_3 in 73% yield, mp >300 °C (MeOH–iso-PrOH). ^{1}H-NMR (DMSO-d_6) δ: 2.37 (3H, s, 3′-Me), 2.89—2.96 (2H, m), 3.05—3.11 (2H, m), 7.13 (1H, br d, J=7.5 Hz, 4′-H), 7.30 (1H, d, J=5.2 Hz, 8-H), 7.32 (1H, t, J=7.5 Hz, 5′-H), 7.36 (1H, d, J=5.2 Hz, 7-H), 7.74 (1H, br d, J=7.5 Hz, 6′-H), 7.79 (1H, br, 2′-H). IR (Nujol) cm^{-1}: 3040. EI-MS m/z: 266 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2S$·HCl: C, 63.46; H, 4.99; N, 9.25; Cl, 11.71; S, 10.59. Found: C, 63.20; H, 4.93; N, 9.14; Cl, 11.67; S, 10.52.

2-(4-Tolyl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1e) This compound was obtained from **9e** with AcOH·NH_3 in 69% yield, mp >300 °C (MeOH–iso-PrOH). ^{1}H-NMR (DMSO-d_6) δ: 2.41 (3H, s, 4′-Me), 3.07—3.14 (2H, m), 3.19—3.26 (2H, m),7.45 (2H, d, J=8 Hz, 3′-H, 5′-H), 7.51 (1H, d, J=5.2 Hz, 8-H), 7.67 (1H, d, J=5.2 Hz, 7-H), 8.12 (2H, d, J=8 Hz, 2′-H, 6′-H). IR (Nujol) cm^{-1}: 3330, 3060. EI-MS m/z: 266 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2S$·HCl·H_2O: C, 59.90; H, 5.34; N, 8.73; Cl, 11.05; S, 9.99. Found: C, 59.91; H, 5.26; N, 8.62; Cl, 10.99; S, 9.99.

2-(2-Methoxyphenyl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole (1f) This compound was obtained from **9f** with AcOH·NH_3 in 80% yield, mp 156.5—159 °C (dec.) (AcOEt–hexane). ^{1}H-NMR (DMSO-d_6) δ: 2.93—3.00 (2H, m), 3.04—3.11 (2H, m), 3.96 (3H, s, OMe), 7.02 (1H, dt, J=7.5, 1.0 Hz, 5′-H), 7.14 (1H, dd, J=7.5, 1.0 Hz, 3′-H), 7.27—7.35 (3H, m, 7-H, 8-H, 4′-H), 8.09 (1H, dd, J=7.5, 1.7 Hz, 6′-H), 11.72 (1H, br, NH). IR (Nujol) cm^{-1}: 3120. EI-MS m/z: 282 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; S, 11.36. Found: C, 68.21; H, 4.96; N, 9.87; S, 11.14.

2-(2-Chlorophenyl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1g) This compound was obtained from **9g** with AcOH·NH_3 in 60% yield, mp >300 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.10—3.17 (2H, m), 3.22—3.29 (2H, m), 7.53 (1H, d, J=5.2 Hz, 8-H), 7.58 (1H, d, J=5.2 Hz, 7-H), 7.62 (1H, dt, J=1.4, 7.5 Hz, 5′-H), 7.70 (1H, dt, J=1.8, 7.5 Hz, 4′-H), 7.77 (1H, dd, J=7.5, 1.4 Hz, 3′-H), 7.90 (1H, dd, J=7.5, 1.8 Hz, 6′-H). IR (Nujol) cm^{-1}: 3060. EI-MS m/z: 286 (M^+). *Anal.* Calcd for $C_{15}H_{11}ClN_2S$·HCl: C, 55.74; H, 3.74; N, 8.67; Cl, 21.94; S, 9.92. Found: C, 55.73; H, 3.66; N, 8.64; Cl, 21.94; S, 10.08.

2-(3-Methylthienyl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1h) This compound was obtained from **9h** with AcOH·NH_3 in 64% yield, mp >300 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.48 (3H, s, 3′-Me), 3.06—3.13 (2H, m), 3.19—3.26 (2H, m), 7.17 (1H, d, J=5 Hz, 4′-H), 7.51 (1H, d, J=5.2 Hz, 8-H), 7.59 (1H, d, J=5.2 Hz, 7-H), 7.87 (1H, d, J=5 Hz, 5′-H). IR (Nujol) cm^{-1}: 3070, 3090. EI-MS m/z: 272 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2S_2$·HCl: C, 54.44; H, 4.24; N, 9.07; Cl, 11.48; S, 20.76. Found: C, 54.23; H, 4.18; N, 8.97; Cl, 11.78; S, 20.51.

2-(2-Methylthiophen-3-yl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1i) This compound was obtained from **9i** with AcOH·NH_3 in 89% yield, mp 269—270 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.72 (3H, s, 2′-Me), 3.07—3.14 (2H, m), 3.20—3.27 (2H, m), 7.47 (1H, d, J=5.3 Hz), 7.51 (1H, d, J=5.2 Hz, 8-H), 7.58 (1H, d, J=5.2 Hz, 7-H), 7.59 (1H, d, J=5.3 Hz). IR (Nujol) cm^{-1}: 3060. EI-MS m/z: 272 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2S_2$·HCl: C, 54.44; H, 4.24; N, 9.07; Cl, 11.48; S, 20.76. Found: C, 54.47; H, 4.12; N, 9.09; Cl, 11.59; S, 20.70.

2-(3-Methylfuran-2-yl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1j) This compound was obtained from **9j** with AcOH·NH_3 in 65% yield, mp 242—245 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.39 (3H, s, 3′-Me), 3.00—3.12 (2H, m), 3.15—3.26 (2H, m), 3.52 (2H, br, NH·HCl), 6.71 (1H, d, J=1.8 Hz, 4′-H), 7.50 (1H, d, J=4.9 Hz, 8-H), 7.56 (1H, d, J=4.9 Hz, 7-H). IR (Nujol) cm^{-1}: 3070, 3080, 3140. EI-MS m/z: 256 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2OS$·HCl: C, 57.43; H, 4.48; N, 9.57; Cl, 12.11; S, 10.95. Found: C, 57.14; H, 4.40; N, 9.54; Cl, 12.36; S, 11.02.

2-(1-Methylpyrrol-2-yl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1k) This compound was obtained from **9k** with AcOH·NH_3 in 66% yield, mp 260—261 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 3.05—3.13 (2H, m), 3.18—3.25 (2H, m), 3.95 (3H, s, N-Me), 6.24 (1H, dd, J=3.9, 2.6 Hz, 4′-H), 6.85 (1H, dd, J=3.9, 1.8 Hz, 3′-H), 7.16 (1H, dd, J=2.6, 1.8 Hz, 5′-H), 7.50 (1H, d, J=5.2 Hz, 8-H), 7.65 (1H, d, J=5.2 Hz, 7-H). IR (Nujol) cm^{-1}: 3070, 3130. EI-MS m/z: 255 (M^+). *Anal.* Calcd for $C_{14}H_{13}N_3S$·HCl: C, 57.63; H, 4.83; N, 14.40; Cl, 12.15; S, 10.99. Found: C, 57.37; H, 4.81; N, 14.30; Cl, 11.87; S, 10.80.

2-(4-Methyl-1,3-thiazol-5-yl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1l) This compound was obtained from **8l** with AcOH·NH_3 in 82% yield, mp 298—300 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.64 (3H, s, 4′-Me), 3.06—3.13 (2H, m), 3.19—3.26 (2H, m), 7.51 (1H, d, J=5.3 Hz, 8-H), 7.53 (1H, d, J=5.3 Hz, 7-H), 9.28 (1H, s, 2′-H). IR (Nujol) cm^{-1}: 3050. EI-MS m/z: 273 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3S_2$·HCl: C, 50.39; H, 3.90; N, 13.56; Cl, 11.44; S, 20.70. Found: C, 50.63; H, 3.96; N, 13.36; Cl, 11.57; S, 20.41.

2-(3-Methylpyrid-2-yl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1m) This compound was obtained from **9m** with AcOH·NH_3 in 78% yield, mp 254—256 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.70 (3H, s, 3′-Me), 3.10—3.17 (2H, m), 3.20—3.28 (2H, m), 7.51 (1H, d, J=5.1 Hz, 8-H), 7.57 (1H, dd, J=7.7, 4.7 Hz, 5′-H), 7.64 (1H, d, J=5.1 Hz, 7-H), 7.93 (1H, dd, J=7.7, 1.1 Hz, 4′-H), 8.65 (1H, dd, 6′-H). IR (Nujol) cm^{-1}: 3060. EI-MS m/z: 267 (M^+). *Anal.* Calcd for $C_{15}H_{13}N_3S$·HCl: C, 59.30; H, 4.64; N, 13.83; Cl, 11.67; S, 10.55. Found: C, 59.33; H, 4.58; N, 13.75; Cl, 11.95; S, 10.78.

***cis*-2-(2-Methylcyclohexyl)-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (1n)** This compound was obtained from **9n** with AcOH·NH_3 in 74% yield, mp 227—229 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.76 (3H, d, J=7.1 Hz, 2′-Me), 1.28—1.54 (3H, m), 1.56—1.68 (2H, m), 1.76—2.02 (3H, m), 2.32—2.43 (1H, m, 2′-$H_{eq.}$), 2.98—3.04 (2H, m), 3.13—3.20 (2H, m), 3.26 (1H, dt, J=12.2, 4 Hz, 1′-$H_{ax.}$), 7.48 (1H, d, J=5.1 Hz, 8-H), 7.52 (1H, d, J=5.1 Hz, 7-H). IR (Nujol) cm^{-1}: 3150. EI-MS m/z: 272 (M^+). *Anal.* Calcd for $C_{16}H_{20}N_2S$·HCl: C, 62.22; H,

6.85; N, 9.07; Cl, 11.48; S, 10.38. Found: C, 62.24; H, 6.91; N, 9.04; Cl, 11.37; S, 10.32.

1-Methyl-2-phenyl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (3a) This compound was obtained from **9a** with AcOH·NH_2Me in 65% yield, mp 255—257 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 3.06—3.13 (2H, m), 3.19—3.26 (2H, m), 4.00 (3H, s, 1-Me), 7.57 (1H, d, J=5.3 Hz, 8-H), 7.62 (1H, d, J=5.3 Hz, 7-H), 7.67—7.72 (3H, m, 3′-H, 4′-H, 5′-H), 7.80—7.85 (2H, m, 2′-H, 6′-H). IR (Nujol) cm^{-1}: 3050, 3120. EI-MS *m/z*: 266 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2S$·HCl: C, 63.46; H, 4.99; N, 9.25; Cl, 11.71; S, 10.59. Found: C, 63.34; H, 4.99; N, 9.11; Cl, 11.50; S, 10.48.

1-Methyl-2-thienyl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole Hydrochloride (3b) This compound was obtained from **9b** with AcOH·NH_2Me in 84% yield, mp 256—258 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 3.03—3.10 (2H, m), 3.16—3.23 (2H, m), 4.07 (3H, s, 1-Me), 7.39 (1H, dd, J=5.1, 3.8 Hz, 4′-H), 7.56 (1H, d, J=5.3 Hz, 8-H), 7.61 (1H, d, J=5.3 Hz, 7-H), 7.91 (1H, dd, J=3.8, 1.2 Hz, 3′-H), 8.07 (1H, dd, J=5.1, 1.2 Hz, 5′-H). IR (Nujol) cm^{-1}: 3050, 3110. EI-MS *m/z*: 272 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2S_2$·HCl: C, 54.44; H, 4.24; N, 9.07; Cl, 11.48; S, 20.76. Found: C, 54.66; H, 4.17; N, 8.95; Cl, 11.47; S, 20.48.

2-Phenyl-4,5-dihydro-1*H*-thieno[2,3-*e*]benzimidazole (6a) This compound was obtained from **22a** with AcOH·NH_3 in 76% yield, mp 223—226 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.85—3.0 (4H, m, 4-H, 5-H), 6.96 (1H, d, J=4.9 Hz, 6-H), 7.22 (1H, d, J=4.9 Hz, 7-H), 7.31 (1H, tt, J=7.3, 1.3 Hz, 4′-H), 7.40—7.47 (2H, m, 3′-H, 5′-H), 7.90—7.94 (2H, m, 2′-H, 6′-H). IR (Nujol) cm^{-1}: 3100. EI-MS *m/z*: 252 (M^+). *Anal.* Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10; S, 12.71. Found: C,71.18; H, 4.83; N, 10.95; S, 12.61.

2-Thienyl-4,5-dihydro-1*H*-thieno[2,3-*e*]benzimidazole Hydrochloride (6b) This compound was obtained from **22b** with AcOH·NH_3 in 78% yield, mp 294—296 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.9—3.16 (4H, m, 4-, 5-H), 7.07 (1H, d, J=4.9 Hz, 6-H), 7.30 (1H, dd, J=5, 3.6 Hz, 4′-H), 7.51 (1H, d, J=4.9 Hz, 7-H), 7.90 (1H, dd, J=5, 1.2 Hz, 5′-H), 8.05 (1H, dd, J=3.6, 1.2 Hz, 3′-H). IR (Nujol) cm^{-1}: 3100. EI-MS *m/z*: 258 (M^+). *Anal.* Calcd for $C_{13}H_{10}N_2S_2$·HCl: C, 52.96; H, 3.76; N, 9.50; Cl, 12.03; S, 21.75. Found: C, 52.83; H, 3.72; N, 9.25; Cl, 12.23; S, 21.88.

Preparation of 5-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one Hydriodide (14) *N*,*N*-dimethylformamide (DMF) (0.5 ml) was added to a solution of **11** (178.8 g, 0.64 mol) and oxalyl chloride (89.4 g, 0.7 mol) in 1,2-dichloroethane (2 l) at room temperature. The mixture was stirred for 4 h at the same temperature, then $AlCl_3$ (203 g, 1.5 mol) was added portionwise at −23 °C. The whole was stirred for 1 h at the same temperature, poured into ice-water, and extracted with AcOEt (6 l). The extract was washed with brine, saturated $NaHCO_3$ solution, and brine, then dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give **12** (135.5 g, 81%), mp 97.5—99 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.02 (1H, dq, J=5, 13 Hz, 6-$H_{ax.}$), 2.7—2.9 (1H, m, 6-$H_{eq.}$), 2.96—3.29 (2H, m, 7-H), 3.72 (3H, s, COOMe), 4.39 (1H, dt, J=13, 5 Hz, 5-H), 5.74 (1H, br, NH), 7.18 (1H, s, 2-H). IR (Nujol) cm^{-1}: 3330, 1695, 1680. EI-MS *m/z*: 259, 261 (3 : 1, M^+). *Anal.* Calcd for $C_{10}H_{10}ClNO_3S$: C, 46.25; H, 3.88; N, 5.39; Cl, 13.65; S, 12.35. Found: C, 46.14; H, 3.79; N, 5.11; Cl, 13.86; S, 12.40.

A solution of **12** (25.1 g, 97 mmol) in MeOH (500 ml) containing Et_3N (20 g, 198 mmol) was hydrogenated over 10% Pd–C (4 g) at room temperature for a day under atmospheric pressure of hydrogen. After removal of the catalyst by filtration and evaporation of the solvent *in vacuo*, the residue was taken up in AcOEt, washed with 5% HCl and brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give **13** (19.8 g, 91%), mp 104—105 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.1 (1H, m, 6-$H_{ax.}$), 2.8—2.9 (1H, m, 6-$H_{eq.}$), 3.13—3.29 (2H, m, 7-H), 3.72 (3H, s, COOMe), 4.41 (1H, dt, J=13, 5 Hz, 5-H), 5.8 (1H, br, NH), 7.12 (1H, d, J=5.3 Hz, 2-H), 7.38 (1H, d, J=5.3 Hz, 3-H). IR (Nujol) cm^{-1}: 3330, 1695, 1670. EI-MS *m/z*: 225(M^+). *Anal.* Calcd for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.21; H, 4.80; N, 6.24; S, 14.42.

Me_3SiI (34 g, 170 mmol) was added to a solution of **13** (19.7 g, 87 mmol) in alcohol-free $CHCl_3$ (200 ml), and then the reaction mixture was refluxed under an argon atmosphere. After 3 h, the reaction was quenched by addition of MeOH (15 ml) at 0 °C. The resulting precipitates were collected by filtration and washed with $CHCl_3$ to give **14** (24.1 g, 93%), mp 218—219 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.11—2.27 (1H, m, 6-$H_{ax.}$), 2.41—2.5 (1H, m, 6-$H_{eq.}$), 3.15—3.34 (2H, m, 7-H), 4.37 (1H, br d, J=12.5 Hz, 5-H), 7.35 (1H, d, J=5.4 Hz), 7.52 (1H, d, J=5.4 Hz), 8.33 (3H, br, NH_2·HI). IR (Nujol) cm^{-1}: 1670. EI-MS *m/z*: 167 (M^+). *Anal.* Calcd for C_8H_9NOS·HI: C, 32.56; H, 3.42; N, 4.75; I, 43.00; S, 10.86. Found: C, 32.34; H, 3.34; N, 4.61; I, 43.12; S, 10.61.

Preparation of 5-Amino-2-chloro-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one Hydriodide (15) Me_3SiI (48.4 g, 242 mmol) was added to a solution of **12** (31.4 g, 121 mmol) in alcohol-free $CHCl_3$ (300 ml), and then the reaction mixture was refluxed under an argon atmosphere. After 2 h, the reaction was quenched by addition of MeOH (20 ml) at 0 °C. The resulting precipitates were collected by filtration and washed with $CHCl_3$ to give **15** (37.8 g, 95%), mp 231.5—232 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.07—2.28 (1H, m, 6-$H_{ax.}$), 2.36—2.52 (1H, m, 6-$H_{eq.}$), 3.12—3.22 (2H, m, 7-H), 4.35 (1H, br d, J=13.2 Hz, 5-H), 7.38 (1H, s, 3-H), 8.32 (3H, br, NH_2·HI). IR (Nujol) cm^{-1}: 1685, 1680. EI-MS *m/z*: 201, 203 (3 : 1, M^+). *Anal.* Calcd for C_8H_8ClNOS·HI: C, 29.15; H, 2.75; N, 4.25; Cl, 10.76; I, 38.50; S, 9.73. Found: C, 28.89; H, 2.63; N, 4.08; Cl, 10.63; I, 38.79; S, 9.53.

Preparation of 6-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-7-one Hydriodide (21) A mixture of **18** (23.25 g, 74.5 mmol), HCO_2H·NH_3 (71.64 g, 1.14 mol), K_2CO_3 (31.12 g, 224 mmol), and 10% Pd–C (5.1 g) in EtOH (500 ml) was refluxed for 18 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in H_2O, acidified with 10% HCl, and extracted with AcOEt. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with $CHCl_3$–MeOH (50 : 1) gave **19** (17.53 g, 97%) as a powder. ^{1}H-NMR (DMSO-d_6) δ: 1.75—2.1 (2H, m, 3-H), 2.64 (2H, t, J=7.8 Hz, 4-H), 3.55 (3H, s, CO_2Me), 3.8—4.0 (1H, m, 2-H), 6.98 (1H, dd, J=4.9, 1.5 Hz, 4′-H), 7.14 (1H, dd, J=2.9, 1.5 Hz, 2′-H), 7.45 (1H, dd, J=4.9, 2.9 Hz, 5′-H), 7.52 (1H, d, J=7.8 Hz, NH), 12.60 (1H, s, CO_2H). IR (Nujol) cm^{-1}: 3420, 1745, 1725, 1680. EI-MS *m/z*: 243, 245 (3 : 1, M^+).

The Friedel–Crafts acylation of **19** and removal of the methoxycarbonyl group of **20** with Me_3SiI were carried out under conditions similar to those described for the preparation of **14**. The Friedel–Crafts acylation of the acid chloride, derived from **19** (16.65 g, 68.4 mmol), with $AlCl_3$ (20.8 g, 156 mmol) gave **20** (12.92 g, 84%), mp 145—146 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.02 (1H, tt, J=13, 8.7 Hz, 5-$H_{ax.}$), 2.73—2.81 (1H, m, 5-$H_{eq.}$), 3.03 (2H, dd, J=8.5, 3.5 Hz, 4-H), 3.73 (3H, s, COOMe), 4.47 (1H, dt, J=13.2, 4.8 Hz, 6-H), 5.75 (1H, br, NH), 6.98 (1H, d, J=4.9 Hz, 3-H), 7.68 (1H, d, J=4.9 Hz, 2-H). IR (Nujol) cm^{-1}: 3310, 1695, 1660. FAB-MS *m/z*: 226 (MH^+). *Anal.* Calcd for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.31; H, 4.96; N, 6.13; S, 13.96.

Treatment of **20** (7.01 g, 31.1 mmol) with Me_3SiI (12.6 g, 63.0 mmol) gave **21** (9.10 g, 99%), mp 233—234 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.02—2.23 (1H, m, 5-$H_{ax.}$), 2.34—2.50 (1H, m, 5-$H_{eq.}$), 2.9—3.15 (2H, m, 4-H), 4.38—4.46 (1H, m, 6-H), 7.21 (1H, d, J=5 Hz, 3-H), 8.16 (1H, d, J=5 Hz, 2-H), (3H, b, NH_2·HI). IR (Nujol) cm^{-1}: 1655. EI-MS *m/z*: 167 (M^+). *Anal.* Calcd for C_8H_9NOS·HI: C, 32.56; H, 3.42; N, 4.75; I, 43.00; S,10.86. Found: C, 32.45; H, 3.33; N, 4.55; I, 43.01; S, 10.62.

Preparation of 5-Acylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-ones (9, 10) and 6-Acylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-7-ones (22) The amides (**9, 10, 22**) were prepared by treatment of amines (**14, 15, 21**) with acyl halides in the presence of Et_3N. The general procedure is exemplified by the preparation of **10a** from **15**.

***N*-(2-Chloro-4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) Benzamide (10a)** Under an argon atmosphere, a solution of Et_3N (3.53 g, 34.9 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a suspension of **15** (4.15 g, 12.6 mmol) and benzoyl chloride (2.69 g, 19.1 mmol) in CH_2Cl_2 (30 ml) under ice-cooling. The reaction mixture was stirred for 1 h, then poured into ice-water. The CH_2Cl_2 layer was washed with 10% HCl, brine, saturated $NaHCO_3$ solution, and brine, then dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from AcOEt–MeOH to give **10a** (3.5 g, 91%), mp 183.5—184.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (1H, ddt, J=13.3, 5, 12.5 Hz, 6′-$H_{ax.}$), 2.98—3.13 (2H, m, 6′-$H_{eq.}$, 7′-$H_{eq.}$), 3.27 (1H, ddd, J=17.4, 12.5, 4.7 Hz, 7′-$H_{ax.}$), 4.77 (1H, dt, J=13.3, 4.7 Hz, 5′-H), 7.22 (1H, s, 3′-H), 7.24 (1H, br, NH), 7.43—7.57 (3H, m, 3-H, 4-H, 5-H), 7.84—7.88 (2H, m, 2-H, 6-H). IR (Nujol) cm^{-1}: 3410, 1660, 1650. EI-MS *m/z*: 306, 308 (3 : 1, MH^+). *Anal.* Calcd for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96; N, 4.58; Cl, 11.59; S, 10.49. Found: C, 58.77; H, 3.91; N, 4.50; Cl, 11.64; S, 10.55.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) Benzamide (9a)** This compound was obtained from **14** with benzoyl chloride in 76% yield, mp 211—213.5 °C (tetrahydrofuran (THF)–MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (1H, ddt, J=13.1, 5, 12.5 Hz, 6′-$H_{ax.}$), 3.05 (1H, ddt,

J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.21 (1H, ddd, J=17.4, 5, 2.4 Hz, 7′-$H_{eq.}$), 3.32 (1H, dddd, J=17.4, 12.5, 4.5, 0.8 Hz, 7′-$H_{ax.}$), 4.79 (1H, dt, J=13.1, 4.5 Hz, 5′-H), 7.14 (1H, dd, J=5.3, 0.8 Hz), 7.32 (1H, br d, J=4.5 Hz, NH), 7.41 (1H, d, J=5.3 Hz), 7.43—7.57 (3H, m, 3-H, 4-H, 5-H), 7.85—7.90 (2H, m, 2-H, 6-H). IR (Nujol) cm^{-1}: 3290, 1685, 1635. EI-MS m/z: 271 (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.28; H, 4.73; N, 5.13; S, 11.61.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 2-Thiophenecarboxamide (9b)** This compound was obtained from **14** with thenoyl chloride in 77% yield, mp 179—181 °C (THF–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (1H, ddt, J=13.2, 5.3, 12.5 Hz, 6′-$H_{ax.}$), 3.03 (1H, ddt, J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.20 (1H, ddd, J=17.5, 5.3, 2.4 Hz, 7′-$H_{eq.}$), 3.31 (1H, dddd, J=17.5, 12.5, 4.5, 0.8 Hz, 7′-$H_{ax.}$), 4.76 (1H, dt, J=13.2, 4.5 Hz, 5′-H), 7.10 (1H, dd, J=5, 3.7 Hz, 4-H), 7.14 (1H, dd, J=5.3, 0.8 Hz), 7.17 (1H, br, NH), 7.41 (1H, d, J=5.3 Hz), 7.51 (1H, dd, J=5, 1.2 Hz, 5-H), 7.61 (1H, dd, J=3.7, 1.2 Hz, 3-H). IR (Nujol) cm^{-1}: 3300, 1680, 1630. FAB-MS m/z: 278 (MH^+). *Anal.* Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.29; H, 4.00; N, 5.05; S, 23.12. Found: C, 56.27; H, 3.92; N, 4.95; S, 23.23.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 2-Tolylamide (9c)** This compound was obtained from **14** with 2-tolyl chloride in 79% yield, mp 188.5—191.5 °C (THF–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (1H, ddt, J=13.2, 5.2, 12.4 Hz, 6′-$H_{ax.}$), 2.51 (3H, s, 2′-Me), 3.05 (1H, dddd, J=12.4, 5, 4.5, 2.4 Hz, 6′-$H_{eq.}$), 3.22 (1H, ddd, J=17.3, 5.2, 2.4 Hz, 7′-$H_{eq.}$), 3.34 (1H, ddd, J=17.3, 12.4, 4.5 Hz, 7′-$H_{ax.}$), 4.82 (1H, dt, J=13.2, 5 Hz, 5′-H), 6.87 (1H, br, NH), 7.15 (1H, d, J=5.2 Hz), 7.21—7.26 (2H, m, 3-H, 5-H), 7.35 (1H, dt, J=1.5, 7.5 Hz, 4-H), 7.40 (1H, d, J=5.2 Hz), 7.50 (1H, dd, J=7.5, 1.5 Hz, 6-H). IR (Nujol) cm^{-1}: 3360, 1680, 1630. EI-MS m/z: 285 (M^+). *Anal.* Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.37; H, 5.22; N, 4.72; S, 11.22.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 3-Tolylamide (9d)** This compound was obtained from **14** with 3-tolyl chloride in 71% yield, mp 148—151 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (1H, ddt, J=13.1, 5.2, 12.6 Hz, 6′-$H_{ax.}$), 2.42 (3H, s, 3′-Me), 3.05 (1H, dddd, J=12.6, 5, 4.5, 2.4 Hz, 6′-$H_{eq.}$), 3.21 (1H, ddd, J=17.5, 5.2, 2.4 Hz, 7′-$H_{eq.}$), 3.33 (1H, ddd, J=17.5, 12.4, 4.5 Hz, 7′-$H_{ax.}$), 4.78 (1H, dt, J=13.1, 5 Hz, 5′-H), 7.15 (1H, bd, J=5.5 Hz), 7.28 (1H, br, NH), 7.33—7.36 (2H, m, 4-H, 5-H), 7.41 (1H, d, J=5.5 Hz), 7.67—7.69 (2H, m, 2-H, 6-H). IR (Nujol) cm^{-1}: 3300, 1690, 1630, 1610. EI-MS m/z: 285 (M^+). *Anal.* Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.29; H, 5.24; N, 4.71; S, 10.94.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 4-Tolylamide (9e)** This compound was obtained from **14** with 2-tolyl chloride in 74% yield, mp 189—190 °C (THF–MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (1H, ddt, J=13.2, 5.2, 12.1 Hz, 6′-$H_{ax.}$), 2.41 (3H, s, 4′-Me), 3.05 (1H, dddd, J=12.1, 5, 4.5, 2.4 Hz, 6′-$H_{eq.}$), 3.20 (1H, ddd, J=17.4, 5.2, 2.4 Hz, 7′-$H_{eq.}$), 3.32 (1H, dddd, J=17.4, 12.1, 4.5, 0.8 Hz, 7′-$H_{ax.}$), 4.78 (1H, dt, J=13.2, 5 Hz, 5′-H), 7.14 (1H, dd, J=5.2, 0.8 Hz), 7.26 (2H, d, J=8.1 Hz, 3-H, 5-H), 7.41 (1H, d, J=5.2 Hz), 7.77 (2H, d, J=8.1 Hz, 4-H). IR (Nujol) cm^{-1}: 3300, 1680, 1630. EI-MS m/z: 285 (M^+). *Anal.* Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.12; H, 5.27; N, 4.74; S, 11.22.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 2-Methoxybenzamide (9f)** This compound was obtained from **14** with 2-methoxybenzoyl chloride in 85% yield, mp 155—156.5 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (1H, ddt, J=13.2, 5.3, 12.5 Hz, 6′-$H_{ax.}$), 3.07 (1H, ddt, J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.19 (1H, ddd, J=17.5, 5.3, 2.4 Hz, 7′-$H_{eq.}$), 3.32 (1H, dddd, J=17.5, 12.5, 4.5, 0.7 Hz, 7′-$H_{ax.}$), 4.85 (1H, dt, J=13.2, 4.5 Hz, 5′-H), 7.01 (1H, dd, J=8.3, 1.0 Hz, 3-H), 7.09 (1H, ddd, J=7.8, 7.4, 1.0 Hz, 5-H), 7.14 (1H, dd, J=5.3, 0.7 Hz), 7.42 (1H, d, J=5.3 Hz), 7.47 (1H, ddd, J=8.3, 7.4, 1.9 Hz, 4-H), 8.22 (1H, dd, J=7.8, 1.9 Hz, 6-H), 9.08 (1H, br, NH). IR (Nujol) cm^{-1}: 3340, 1690, 1630. EI-MS m/z: 301(M^+). *Anal.* Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.73; H, 4.96; N, 4.49; S, 10.36.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 2-Chlorobenzamide (9g)** This compound was obtained from **14** with 2-chlorobenzoyl chloride in 81% yield, mp 207.5—209 °C (THF–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.11 (1H, ddt, J=13.2, 5.3, 12.5 Hz, 6′-$H_{ax.}$), 3.08 (1H, ddt, J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.22 (1H, ddd, J=17.5, 5.3, 2.4 Hz, 7′-$H_{eq.}$), 3.32 (1H, dddd, J=17.5, 12.5, 4.5, 0.5 Hz, 7′-$H_{ax.}$), 4.83 (1H, dt, J=13.2, 4.5 Hz, 5′-H), 7.14 (1H, dd, J=5.3, 0.5 Hz), 7.31—7.45 (3H, m, 3-H, 4-H, 5-H), 7.33 (1H, br, NH), 7.40 (1H, d, J=5.3 Hz), 7.7—7.74 (1H, m, 6-H). IR (Nujol) cm^{-1}: 3340, 1675, 1640. FAB-MS m/z: 306 (MH^+). *Anal.* Calcd for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96; N, 4.58; Cl, 11.59; S, 10.49. Found: C, 58.77; H, 3.89; N, 4.51; Cl, 11.75; S, 10.52.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 3-Methylthiophene-2-carboxamide (9h)** This compound was obtained from **14** with 3-methylthenoyl chloride in 92% yield, mp 144—146 °C (THF–iso-PrOH). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (1H, ddt, J=13.1, 5.3, 12.5 Hz, 6′-$H_{ax.}$), 2.59 (3H, s, 3-Me), 3.04 (1H, ddt, J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.20 (1H, ddd, J=17.5, 5.3, 2.4 Hz, 7′-$H_{eq.}$), 3.30 (1H, ddd, J=17.5, 12.5, 4.5 Hz, 7′-$H_{ax.}$), 4.75 (1H, dt, J=13.1, 4.5 Hz, 5′-H), 6.91 (1H, d, J=5.1 Hz, 4-H), 7.14 (1H, d, J=5.4 Hz), 7.05 (1H, br, NH), 7.32 (1H, d, J=5.1 Hz, 5-H), 7.40 (1H, d, J=5.4 Hz). IR (Nujol) cm^{-1}: 3300, 1680, 1630. EI-MS m/z: 291 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO_2S_2$: C, 57.71; H, 4.50; N, 4.81; S, 22.01. Found: C, 57.58; H, 4.39; N, 4.64; S, 21.72.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 2-Methylthiophene-3-carboxamide (9i)** This compound was obtained from **14** with 3-(2-methylthiophene)carbonyl chloride in 79% yield, mp 159—159.5 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (1H, ddt, J=13, 5.3, 12.5 Hz, 6′-$H_{ax.}$), 2.76 (3H, s, 2-Me), 3.02 (1H, dddt, J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.20 (1H, ddd, J=17.5, 5.3, 2.4 Hz, 7′-$H_{eq.}$), 3.31 (1H, ddd, J=17.5, 12.5, 4.5 Hz, 7′-$H_{ax.}$), 4.75 (1H, dt, J=13, 4.5 Hz, 5′-H), 6.98 (1H, br, NH), 7.05 (1H, d, J=5.4 Hz, 4-H), 7.14 (1H, d, J=5.3 Hz), 7.25 (1H, d, J=5.4 Hz, 5-H), 7.40 (1H, d, J=5.3 Hz). IR (Nujol) cm^{-1}: 3320, 1680, 1630. EI-MS m/z: 291 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO_2S_2$: C, 57.71; H, 4.50; N, 4.81; S, 22.01. Found: C, 57.73; H, 4.41; N, 4.75; S, 21.89.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 3-Methylfuran-2-carboxamide (9j)** This compound was obtained from **14** with 2-(3-methylfuroyl) chloride in 72% yield, mp 169—169.5 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (1H, ddt, J=13, 5.5, 12.5 Hz, 6′-$H_{ax.}$), 2.41 (3H, s, 3-Me), 2.97 (1H, ddt, J=12.5, 2.5, 4.5 Hz, 6′-$H_{eq.}$), 3.19 (1H, ddd, J=17.5, 5.5, 2.5 Hz, 7′-$H_{eq.}$), 3.29 (1H, dddd, J=17.5, 12.5, 4.5, 0.8 Hz, 7′-$H_{ax.}$), 4.76 (1H, ddd, J=13, 5.3, 4.5 Hz, 5′-H), 6.35 (1H, d, J=1.5 Hz, 4-H), 7.13 (1H, dd, J=5.3, 0.8 Hz), 7.35 (1H, d, J=1.5 Hz, 5-H), 7.35 (1H, br, NH), 7.41 (1H, d, J=5.3 Hz). IR (Nujol) cm^{-1}: 3320, 1680, 1640. EI-MS m/z: 275 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09; S, 11.65. Found: C, 60.88; H, 4.74; N, 5.03; S, 11.63.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 1-Methylpyrrole-2-carboxamide (9k)** This compound was obtained from **14** with 2-(1-methylpyrrole)carbonyl chloride in 44% yield, mp 166—167 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (1H, ddt, J=13, 5.3, 12.5 Hz, 6′-$H_{ax.}$), 2.95 (1H, dddt, J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.18 (1H, ddd, J=17.5, 5.3, 2.4 Hz, 7′-$H_{eq.}$), 3.28 (1H, dddd, J=17.5, 12.5, 4.5, 0.5 Hz, 7′-$H_{ax.}$), 3.95 (3H, s, 1-Me), 4.72 (1H, dt, J=13, 4.5 Hz, 5′-H), 6.11 (1H, dd, J=3.9, 2.6 Hz, 4-H), 6.71—6.75 (2H, m, 3-H, 5-H), 6.97 (1H, br, NH), 7.13 (1H, dd, J=5.3, 0.5 Hz), 7.40 (1H, d, J=5.3 Hz). IR (Nujol) cm^{-1}: 3320, 1680, 1640. EI-MS m/z: 274 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.30; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.17; H, 5.12; N, 10.09; S, 11.59.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 4-Methyl-1,3-thiazole-5-carboxamide (9l)** This compound was obtained from **14** with 5-(4-methyl-1,3-thiazole)carbonyl chloride in 79% yield, mp 175—176.5 °C (MeOH–CH_3CN). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (1H, ddt, J=13, 5.4, 12.5 Hz, 6′-$H_{ax.}$), 2.81 (3H, s, 4-Me), 3.04 (1H, ddt, J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.22 (1H, ddd, J=17.5, 5.4, 2.4 Hz, 7′-$H_{eq.}$), 3.32 (1H, dddd, J=17.5, 12.5, 4.5, 0.8 Hz, 7′-$H_{ax.}$), 4.75 (1H, dt, J=13, 4.5 Hz, 5′-H), 7.07 (1H, br, NH), 7.16 (1H, dd, J=5.3, 0.8 Hz), 7.41 (1H, d, J=5.3 Hz), 8.75 (1H, s, 2-H). IR (Nujol) cm^{-1}: 3260, 1685, 1625. EI-MS m/z: 292 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O_2S_2$: C, 53.40; H, 4.14; N, 9.58; S, 21.93. Found: C, 53.28; H, 4.05; N, 9.52; S, 21.80.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 3-Methylpyridine-2-carboxamide (9m)** This compound was obtained from **14** with 2-(3-methylpyridine)carbonyl chloride in 46% yield, mp 168.5—170 °C (AcOEt–iso-Pr_2O). ^{1}H-NMR ($CDCl_3$) δ: 2.16 (1H, ddt, J=13.1, 5.3, 12.5 Hz, 6′-$H_{ax.}$), 2.75 (3H, s, 3-Me), 2.92 (1H, ddt, J=12.5, 2.4, 4.5 Hz, 6′-$H_{eq.}$), 3.21 (1H, ddd, J=17.5, 5.3, 2.4 Hz, 7′-$H_{eq.}$), 3.31 (1H, ddd, J=17.5, 12.5, 4.5 Hz, 7′-$H_{ax.}$), 4.73 (1H, br, NH), 4.81 (1H, dt, J=13.1, 4.5 Hz, 5′-H), 7.13 (1H, d, J=5.3 Hz), 7.33 (1H, dd, J=7.7, 4.6 Hz, 5-H), 7.43 (1H, d, J=5.3 Hz), 7.60 (1H, dd, J=7.7, 1.0 Hz, 4-H), 8.46 (1H, dd, J=4.6, 1.0 Hz, 6-H). IR (Nujol) cm^{-1}: 3325, 1680, 1650. EI-MS m/z: 286(M^+). *Anal.* Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.93; N, 9.78; S, 11.20. Found: C, 62.72; H, 4.85; N, 9.72; S, 11.29.

***N*-(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl) 2-Methylcyclohexanecarboxamide (9h: a Mixture of *cis*- and *trans*-Isomers)** This

compound was obtained from **14** with 2-methylcyclohexanecarbonyl chloride in 64% yield, mp 125—128 °C (AcOEt–iso-Pr_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.92—0.96 (3H, m, 2-Me), 1.2—2.01 (9H, m, 2-H, 3-H, 4-H, 5-H, 6-H), 2.08—2.31 (1H, m, 1-H), 2.38—2.48 (1H, m, 6′-$H_{ax.}$), 2.84—2.93 (1H, m, 6′-$H_{eq.}$), 3.14 (1H, ddd, J=17.5, 5.2, 2.4 Hz, 7′-$H_{eq.}$), 3.25 (1H, dddd, J=17.5, 12.5, 4.5, 1.2 Hz, 7′-$H_{ax.}$), 4.62 (1H, dt, J=13.2, 5 Hz, 5′-H), 6.47—6.60 (1H, m, NH), 7.12 (1H, d, J=5.2 Hz), 7.38 (1H, dd, J=5.2, 1.2 Hz). IR (Nujol) cm^{-1}: 3310, 1700, 1685, 1645, 1630. EI-MS m/z: 291 (M^+). *Anal.* Calcd for $C_{16}H_{21}NO_2S$: C, 65.94; H, 7.26; N, 4.81; S, 11.00. Found: C, 65.84; H, 7.26; N, 4.75; S, 10.92.

***N*-(7-Oxo-4,5,6,7-tetrahydrobenzo[*b*]-thiophen-6-yl) Benzamide (22a)** This compound was obtained from **21** with benzoyl chloride in 87% yield, mp 212—214 °C (THF). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (1H, ddt, J=12.7, 5.6, 11.6 Hz, 5′-$H_{ax.}$), 2.99 (1H, ddt, J=12.7, 2.5, 4.5 Hz, 6′-$H_{eq.}$), 3.0—3.2 (2H, m, 4′-H), 4.86 (1H, dt, J=13.2, 4.8 Hz, 6′-H), 7.00 (1H, d, J=4.9 Hz, 3′-H), 7.25 (1H, br, NH), 7.43—7.56 (3H, m, 3-H, 4-H, 5-H), 7.60 (1H, d, J=4.9 Hz, 2′-H), 7.85—7.99 (2H, m, 2-H, 6-H). IR (Nujol) cm^{-1}: 3280, 1670, 1635. EI-MS m/z: 271 (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.35; H, 4.78; N, 5.09; S, 11.58.

***N*-(7-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-6-yl) 2-Thiophenecarboxamide (22b)** This compound was obtained from **21** with thenoyl chloride in 80% yield. mp 195.5—196 °C (MeOH–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (1H, ddt, J=12.5, 5.9, 11.2 Hz, 5′-$H_{ax.}$), 2.95 (1H, ddt, J=12.5, 2.5, 4.5 Hz, 6′-$H_{eq.}$), 3.0—3.18 (2H, m, 4′-H), 4.83 (1H, dt, J=13.2, 4.7 Hz, 6′-H), 7.00 (1H, d, J=4.9 Hz, 3′-H), 7.10 (1H, dd, J=5, 3.7 Hz, 4-H), 7.13 (1H, br, NH), 7.50 (1H, dd, J=5, 1.2 Hz, 5-H), 7.61 (1H, dd, J=3.7, 1.2 Hz, 3-H), 7.70 (1H, d, J=4.9 Hz, 2′-H). IR (Nujol) cm^{-1}: 3270, 1675, 1665, 1620. EI-MS m/z: 277 (M^+). *Anal.* Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.30; H, 4.00; N, 5.05; S, 23.12. Found: C, 56.20; H, 3.90; N, 4.97; S, 22.98.

Preparation of 2-Phenyl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole (1a) Dechlorination of **2a** was carried out under conditions similar to those described for the preparation of **13**. Hydrogenation of **2a** (1.21 g, 4.2 mmol) over 10% Pd–C followed by treatment with HCl–MeOH gave **1a**·HCl (965 mg, 79%), mp >300 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.07—3.32 (4H, m, 4-H, 5-H), 7.52 (1H, d, J=5 Hz, 8-H), 7.56—7.67(3H, m, 3′-H, 4′-H, 5′-H), 7.71 (1H, d, J=5 Hz, 7-H), 8.20—8.32 (2H, m, 2′-H, 6′-H). IR (Nujol) cm^{-1}: 3080. EI-MS m/z: 252 (M^+). *Anal.* Calcd for $C_{15}H_{12}N_2S$·HCl: C, 62.39; H, 4.54; N, 9.70; Cl, 12.28; S, 11.10. Found: C, 62.42; H, 4.39; N, 9.65; Cl, 12.21; S, 11.14.

Preparation of 3-Methyl-2-thienyl-4,5-dihydro-1*H*-thieno[3,2-*e*]-benzimidazole (4b) CH_3I (684 mg, 4.82 mmol) was added to a solution of the sodio derivative of **1b** prepared from 62.7% NaH (176 mg, 4.60 mmol) in DMF (20 ml) under ice-cooling. The reaction mixture was stirred for 5 h at the same temperature, poured into ice-water, and extracted with AcOEt. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from MeOH–iso-Pr_2O to give **4b** (373 mg, 40%), mp 205.5—207 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.98 (2H, t, J=8 Hz, 4-H), 3.11 (2H, t, J=8 Hz, 5-H), 3.73 (3H, s, 3-Me), 7.16 (1H, dd, J=5.1, 3.7 Hz), 7.20 (1H, d, J=5.1 Hz, 8-H), 7.33 (1H, d, J=5.1 Hz, 7-H), 7.44 (1H, dd, J=3.7, 1.1 Hz, 3′-H), 7.58 (1H, dd, J=5.1, 1.1 Hz, 5′-H) (upon irradiation of 3-Me, 8.2% and 15.2% nuclear Overhauser effects were observed on the methylene at the 4-position and a proton at the 3′-position, respectively). EI-MS m/z: 272 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2S_2$: C, 61.73; H, 4.44; N, 10.28; S, 23.54. Found: C, 61.98; H, 4.35; N, 10.24; S, 25.30.

3-Methyl-2-phenyl-4,5-dihydro-1*H*-thieno[3,2-*e*]benzimidazole (4a) Methylation of **1a** was carried out under conditions similar to those described above. Treatment of **1a** with NaH and CH_3I gave a mixture of **3a** and **4a**. After column chromatography on silica gel (2:1 hexane–AcOEt as an eluent), **4a** was isolated in 35% yield together with **3a** in 29% yield, mp 270—271 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 3.12—3.19 (2H, m), 3.24—3.31 (2H, m), 3.81 (3H, s, NMe), 7.53 (1H, d, J=5.3 Hz, 8-H), 7.57 (1H, d, J=5.3 Hz, 7-H), 7.67—7.72 (3H, m, 3′-H, 4′-H, 5′-H), 7.84—7.88 (2H, m, 2′-H, 6′-H). EI-MS m/z: 266 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2S$·HCl: C, 63.46; H, 4.99; N, 9.25; Cl, 11.71; S, 10.59. Found: C, 63.51; H, 4.99; N, 9.16; Cl, 11.62; S, 10.55.

Preparation of 1-(2-Tolyl)-4,5-dihydro-1*H*-thieno[3,2-e]benzimidazole (5c) A solution of acetic-formic anhydride, prepared from formic acid (1.8 g, 40 mmol) and acetic anhydride (2.9 g, 28 mmol), was added to a suspension of **14** (7.10 g, 24 mmol) in THF (50 ml) under ice-cooling. The mixture was stirred for 10 min, and then a solution of Et_3N (9.5 g, 94 mmol) in THF (30 ml) was added. The reaction mixture was stirred for 3 h at room temperature, poured into ice-water and extracted with AcOEt. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give **23** (3.37 g, 72%), mp 100—102 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (1H, ddt, J=13, 5.5, 12.5 Hz, 6′-$H_{ax.}$), 2.94 (1H, dddd, J=12.5, 5, 4.5, 2.5 Hz, 6′-$H_{eq.}$), 3.18 (1H, ddd, J=17.4, 5.5, 2.5 Hz, 7′-$H_{eq.}$), 3.27 (1H, dddd, J=17.4, 12.5, 4.5, 0.8 Hz, 7′-$H_{ax.}$), 4.67 (1H, ddt, J=13, 1.2, 5 Hz, 5′-H), 6.75 (1H, br, NH), 7.14 (1H, dd, J=5.3, 0.8 Hz), 7.38 (1H, d, J=5.3 Hz), 8.34 (1H, t, J=1.2 Hz, CHO). IR (Nujol) cm^{-1}: 3370, 1690, 1660. EI-MS m/z: 195 (M^+). *Anal.* Calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17; S, 16.42. Found: C, 55.26; H, 4.71; N, 7.23; S, 16.50. A drop of concentrated H_2SO_4 was added to a mixture of **23** (1.50 g, 7.7 mmol), *o*-toluidine (900 mg, 8.4 mmol), and tetraethoxysilane (7.5 ml), and the whole was stirred for 5 h at 140—150 °C under an argon atmosphere, then diluted with AcOEt (50 ml). The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. A solution of the residue in $CHCl_3$ (25 ml) was added dropwise to a suspension of PCl_5 (1.5 g, 7.2 mmol) in $CHCl_3$ (50 ml) at room temperature. The mixture was stirred for 15 h, then the reaction was quenched with water. The $CHCl_3$ layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$ as an eluent), and recrystallized from AcOEt–hexane to give **5c** (1.07 g, 52%), mp 156—158 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s, 2′-Me), 3.02—3.09 (2H, m), 3.12—3.19 (2H, m), 5.99 (1H, d, J=5.2 Hz), 6.88 (1H, d, J=5.2 Hz), 7.27—7.47 (4H, m, 3′-H, 4′-H, 5′-H, 6′-H), 7.35 (1H, s, 2-H). EI-MS m/z: 266 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52; S, 12.04. Found: C, 72.26; H, 5.07; N, 10.42; S, 11.86.

Preparation of 2-Phenyl-4,5-dihydro-1*H*-thieno[2,3-*g*]benzoxazole (2a) A mixture of **9a** (1.60 g, 5.90 mmol) and $POCl_3$ (20 g, 130 mmol) was refluxed for 1 h under an argon atmosphere, and then evaporated *in vacuo*. The residue was suspended in water, neutralized with 10% NH_4OH, and then extracted with AcOEt–THF. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Recrystallization of the residue from AcOEt gave **7a** (1.39 g, 93%), mp 166—167 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.96 (2H, t, J=8.8 Hz, 4-H), 3.19 (2H, t, J=8.8 Hz, 5-H), 7.25 (1H, d, J=5.2 Hz, 8-H), 7.46—7.57 (4H, m, 3′-H, 4′-H, 5′-H, 7-H), 7.97—8.02 (2H, m, 2′-H, 6′-H). EI-MS m/z: 253 (M^+). *Anal.* Calcd for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.53; S, 12.66. Found: C, 71.16; H,4.20; N, 5.55; S, 12.70.

2-Thienyl-4,5-dihydro-1*H*-thieno[2,3-*g*]benzoxazole (7b) Employing the procedure described above, **7b** was obtained from **9b** with $POCl_3$ in 95% yield, mp 143—144.5 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 2.94 (2H, t, J=8.7 Hz, 4-H), 3.18 (2H, t, J=8.7 Hz, 5-H), 7.22 (1H, dd, J=5, 3.6 Hz, 4′-H), 7.22 (1H, d, J=5.2 Hz, 8-H), 7.49 (1H, d, J=5.2 Hz, 7-H), 7.68 (1H, dd, J=3.6, 1.2 Hz, 3′-H), 7.75 (1H, dd, J=5, 1.2 Hz, 5′-H). EI-MS m/z: 259 (M^+). *Anal.* Calcd for $C_{13}H_9NOS_2$: C, 60.21; H, 3.50; N, 5.40; S, 24.72. Found: C, 59.97; H, 3.40; N, 5.37; S, 24.58.

Preparation of 2-Phenyl-4,5-dihydro-1*H*-thieno[2,3-*g*]benzothiazole (8a) A mixture of **9a** (1.33 g, 4.90 mmol) and Lawesson's reagent (2.58 g, 6.38 mmol) in xylene (50 ml) was refluxed for 19 h under an argon atmosphere and the xylene was evaporated *in vacuo*. The residue was taken up in AcOEt, washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (7:1 hexane–AcOEt as an eluent), and then recrystallized from AcOEt–hexane to give **8a** (1.21 g, 92%), mp 97.5—98.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.13—3.16 (4H, m, 4-H, 5-H), 7.14 (1H, d, J=5.4 Hz, 8-H), 7.45—7.53 (4H, m, 3′-H, 4′-H, 5′-H, 7-H), 7.90—7.94 (2H, m, 2′-H, 6′-H). EI-MS m/z: 269 (M^+). *Anal.* Calcd for $C_{15}H_{11}NS_2$: C, 66.88; H, 4.12; N, 5.20; S, 23.81. Found: C, 66.84; H,4.06; N, 5.09; S, 23.76.

2-Thienyl-4,5-dihydro-1*H*-thieno[2,3-*g*]benzothiazole (8b) Employing the procedure described above, **8b** was obtained from **9b** with Lawesson's reagent in 93% yield, mp 92—93.5 °C (AcOEt–hexane). ^{1}H-NMR (DMSO-d_6) δ: 3.05—3.18 (4H, m, 4-H, 5-H), 7.15 (1H, d, J=5.1 Hz, 8-H), 7.17 (1H, dd, J=5.1, 3.7 Hz, 4′-H), 7.46 (1H, d, J=5.1 Hz, 7-H), 7.61 (1H, dd, J=3.7, 1.2 Hz, 3′-H), 7.69 (1H, dd, J=5.1, 1.2 Hz, 5′-H). EI-MS m/z: 275 (M^+). *Anal.* Calcd for $C_{13}H_9NS_3$: C, 56.69; H, 3.29; N, 5.09; S,34.93. Found: C, 56.88; H, 3.13; N, 5.03; S, 34.80.

Biology. K^+-Stimulated ATPase Activity The gastric (H^+/K^+)-ATPase was isolated from canine gastric mucosa as reported in the literature.[12] Mongrel dogs of either sex were anesthetized with sodium

pentobarbital and exsanguinated. The fundus of the stomach was isolated. The mucosa was scraped off and homogenized in a medium consisting of 0.25 M sucrose, 1 mM EDTA and 5 mM Tris/HCl (pH 6.8) using a Polytron (Kinematica, Littau, Switzerland). The homogenate was centrifuged differentially to harvest the microsomal fraction. The crude microsomes suspended in 0.25 M sucrose were layered over 7.5% Ficoll (w/w) in 0.25 M sucrose and centrifuged at 100000 × *g* for 3 h. The microsomal band appearing at the interface of the sucrose and Ficoll was collected, diluted with 0.25 M sucrose and stored at −80 °C until use. The activity of (H^+/K^+)-ATPase was measured as follows: The reaction mixture contained, in a total volume of 1 ml, 5 mM $MgCl_2$, 70 mM Tris/HCl buffer (pH 6.8), 2 mM Na_2ATP, and a test compound in the presence or absence of 5 mM KCl and 5 μg/ml nigercin. The enzyme (20 μg protein/ml) was used to start the incubation. The reaction was stopped by adding 1 ml of 12% (w/v) trichloroacetic acid. After the end of incubation (20 min, 37 °C), liberated inorganic phosphate was measured.[13] (H^+/K^+)-ATPase activity was calculated from the difference between ATPase activities with or without KCl and nigercin.

Rat Gastric Secretion *In vivo* testing for gastric antisecretory activity was carried out in chronic gastric fistula rats.[14] Under sodium pentobarbital anesthesia, a plastic cannula was inserted into the forestomach. A polyethylene tube for administration of test compounds was inserted into the upper part of the duodenum and held in place by a ligature, and the other end was subcutaneously led to the neck. One week of recovery was allowed before experiments. Conscious rats were placed in Bollman cages and gastric acid secretion was stimulated by administration of pentagastrin (100 μg/kg/h) *via* the tail vein. After 1.5 h, compounds were administered as an intraduodenal bolus injection. Percentage inhibition was calculated from a comparison of the acid secretion at peak inhibition compared to the secretion immediately prior to administration.

References and Notes

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