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Discovery of a Novel Pyrrole Derivative 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine Fumarate (TAK-438) as a Potassium-Competitive Acid Blocker (P-CAB)

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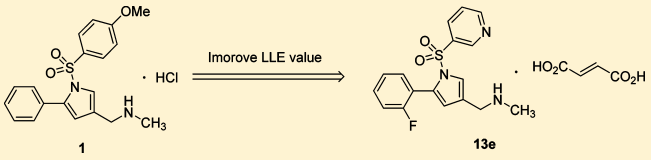
Supporting Information

ABSTRACT: In our pursuit of developing a novel and potent potassium-competitive acid blocker (P-CAB), we synthesized pyrrole derivatives focusing on compounds with low log *D* and high ligand-lipophilicity efficiency (LLE) values. Among the compounds synthesized, the compound **13e** exhibited potent H^+,K^+-ATPase inhibitory activity and potent gastric acid secretion inhibitory action in vivo. Its maximum efficacy was more potent and its duration of action was much longer than those of proton pump inhibitors (PPIs). Therefore, compound **13e** (1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate, TAK-438) was selected as a drug candidate for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer, and other acid-related diseases.



INTRODUCTION

Current therapies for gastroesophageal reflux disease (GERD), peptic ulcer, and other acid-related diseases either prevent the stimulation of parietal cells (e.g., H_2 receptor antagonists, H2RAs) or inhibit gastric H^+,K^+-ATPase (e.g., proton pump inhibitors, PPIs).[1] After PPIs are transformed to their activated form in acidic conditions, they inhibit gastric H^+,K^+-ATPase activity by forming covalent bonds with the H^+,K^+-ATPase and suppress gastric acid secretion.[2,3] Despite the potent inhibitory activities of PPIs against acid secretion and their worldwide clinical application, it is suggested that the treatment with PPIs can be further improved or enhanced in several aspects such as cytochrome P450 (CYP) polymorphism.[4] The potassium-competitive acid blocker (P-CAB), a new class of acid suppressant, inhibits gastric H^+,K^+-ATPase activity by reversible and K^+-competitive ionic binding to the enzyme.[5] In comparison with PPIs, P-CAB is supposed to offer alternative therapeutic advantages such as better symptom control and faster healing of GERD, peptic ulcer, and other acid-related diseases. Over the past 2 decades, various companies have focused on developing P-CAB as an acid suppressant.[6] Several structural types such as imidazopyridines (SCH28080,[7] AZD0865,[8] and PF-03716556[9]), pyrimidines (YH1885[10]), imidazonaphthyridines (soraprazan[11]), and pyrrolopyridazines (CS-526[12]) have been investigated as P-CAB, but their insufficient efficacy or hepatic toxicity has limited their clinical developments. More recently, 1*H*-pyrrolo[2,3-*c*]pyridines,[13,14] tetrahydrochromenoimidazoles,[15] imidazoles,[16] and a new type of imidazopyridine[17] have been discovered.

We have revealed that novel pyrrole derivatives represented by compound **1** as P-CAB showed not only potent and selective H^+,K^+-ATPase inhibitory activity in vitro but also antisecretory activities in histamine-stimulated gastric acid secretion in rats and Heidenhain-pouch dogs.[18] Moreover, the duration of action of compound **1** in Heidenhain-pouch dog was much longer than that of lansoprazole (LPZ). These results encouraged us to further investigate the derivatives of compound **1**. Despite the optimum in vitro and in vivo results, overall DMPK and safety profiles required improvements. To aid the selection of better profiles, an estimation of druglikeness was carried out using ligand-lipophilicity efficiency (LLE = $pIC_{50} - \log D$). LLE is a parameter used in drug design and drug discovery to evaluate the quality of compounds and to estimate their druglikeness based on their linking potency and lipophilicity.[19] We focused on identifying high LLE compounds because they were expected to have potent activity, low lipophilicity, and preferable properties as drug candidates. The preferred substitution pattern of pyrrole for potent inhibitory activity consists of the arylsulfonyl group at the 1-position, the

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methylaminomethyl group at the 3-position, and the aryl group at the 5-position attached to the pyrrole ring. From our plausible binding model of H^+,K^+-ATPase with compound **1**, it was indicated that there was a small polar space around the arylsulfonyl group that can establish direct or water-mediated polar interactions with the neighboring Thr815, Phe897, and Asn898 residues as shown by a blue circle in Figure 1 (left).

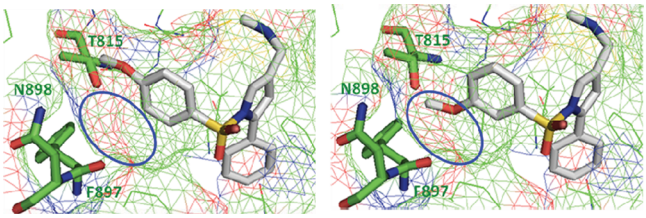
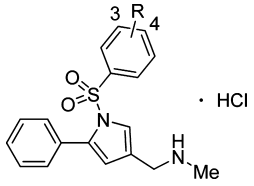


Figure 1. Plausible binding models of compounds **1** (left) and **2** (right) with H^+,K^+-ATPase. Blue circles show the polar space.

From this point of view, 3-methoxy derivative **2** was expected to demonstrate a better fit for the cavity as circled in Figure 1 (right). This hypothesis was confirmed by the result that compound **2** showed 3-fold higher H^+,K^+-ATPase inhibitory activity than compound **1** (Table 1). The methylsulfonyl derivative **3** exhibited 2- to 3-fold lower inhibitory activity probably because of steric hindrance between the estimated polar cavity and methylsulfonyl group (Table 1). These findings indicated that the polar cavity is not very large and prompted us to replace the phenyl ring with heteroaromatic rings such as thiophene or pyridine to acquire polar interactions and to decrease log *D* values. Herein, we report the synthesis, in vitro H^+,K^+-ATPase inhibitory activities, and in vivo anti-secretory activities of pyrrole derivatives.

Table 1. Effects of Substituents on 1-Phenylsulfonyl Group on H^+,K^+-ATPase Inhibitory Activities



compd	R	H^+,K^+-ATPase IC_{50} (nM)[a]
1	4-OMe	30 (19–47)
2	3-OMe	11 (6.1–18)
3	3-SO_2Me	78 (49–120)

[a]Inhibitory activity against H^+,K^+-ATPase. Data are from duplicate experiments. IC_{50} values and 95% confidence limits are calculated from the concentration–response curves generated by nonlinear regression using the program GraphPadPrism (GraphPad Software, San Diego, CA). The confidence limits are shown in parentheses.

CHEMISTRY

The conversion of 1-arylsulfonyl group was accomplished by starting from 5-aryl-1*H*-pyrrole-3-carbaldehyde derivatives **7**, and their synthetic methods are shown in Scheme 1. The 5-aryl-1*H*-pyrrole-3-carbaldehydes (**7a–c**) were synthesized from the corresponding α-bromoacetophenone derivatives **4**, which were commercially available or prepared via bromination of the acetophenone derivatives. Condensation of compound **4** with ethyl cyanoacetate gave intermediate **5**, which was cyclized under acidic conditions followed by dehalogenation to afford 5-arylpyrrole-3-carboxylic acid ester derivatives **6** in moderate yields. Subsequently, the ester group was reduced to a hydroxymethyl group in good yield by using diisobutylaluminum hydride, and the hydroxyl group was oxidized to a formyl group with tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide in moderate yield. However, the 2-methylphenyl derivative **7d** was obtained in very low yield because undesirable furan formation was favored in the acid-catalyzed cyclization step.[20] In order to avoid this problem, compound **7d** was synthesized from pyrrole **8**. Protection of the 1-position of pyrrole by the triisopropylsilyl group followed by Vilsmeier formylation and deprotection gave pyrrole-3-carbaldehyde (**10**). It is reported that this nucleophilic attack on compound **9** occurs predominantly at the 3-position because of the steric hindrance of the triisopropylsilyl group.[21,22] Bromination of **10** by NBS gave the 5-bromopyrrole derivative **11**, which underwent Suzuki–Miyaura coupling reaction with 2-methylphenylboronic acid to give the desired compound **7d** in moderate yield. 2-Bromophenylboronic acid instead of 2-methylphenylboronic acid was used to obtain **7e**.

Compound **7** was sulfonylated by arylsulfonyl chloride in the presence of a base to afford the corresponding sulfonyl derivative **12**. In some cases, addition of 15-crown-5 was essential for this reaction. It is considered that 15-crown-5 enhanced the reactivity of the sodium amide of **7**. The formyl group of compound **12** was converted to methylaminomethyl moiety by reductive amination reaction using methylamine hydrochloride or 40% methylamine methanol solution and sodium tetrahydroborate. These compounds were isolated in crystalline form as hydrochloride or fumarate (Scheme 2).

The formyl derivative **7a** was converted to *N*-Boc-protected methylaminomethyl derivative **14** by reductive amination and followed by treatment with $(Boc)_2O$ before sulfonylation (Scheme 3). Sulfonylation of compound **14** was performed in the same manner as previously described to yield the 1-arylsulfonylated pyrroles **15**. 6-Chloro-3-pyridyl derivative **15c** was transformed to **15d** and **15e** by Pd-catalyzed methylation and cyanation, respectively. The compounds **15** were finally deprotected by treatment with hydrogen chloride to give compounds **16** as hydrochlorides.

The conversion of the 5-aryl group was also accomplished by using Suzuki–Miyaura coupling reaction starting from compound **18** (Scheme 4). Reductive amination of compound **11**, *N*-Boc protection, and sulfonylation were conducted in the same manner as previously described. Suzuki–Miyaura coupling of compound **18** with various arylboronic acids gave corresponding compounds **19** in moderate to good yields. Finally, deprotection of compounds **19** and subsequent salt formation in a similar manner afforded compounds **20**.

RESULTS AND DISCUSSION

The synthesized compounds were evaluated for their H^+,K^+-ATPase inhibitory activities at pH 6.5, log *D* values at pH 7.4, LLE values, and inhibitory activities on histamine-induced gastric acid secretion in anesthetized rats (1 mg/kg, iv). In in vivo tests, the compounds were administered intravenously (1 mg/kg), and the total acid secretion for 3 h after histamine injection was compared to that of vehicle.

At first, we focused on the effects of replacement of the phenylsulfonyl group with the heteroarylsulfonyl group at the 1-position of the pyrrole ring; the results are summarized in Table 2. The 2-thienyl derivative **13a** was about 3-fold less

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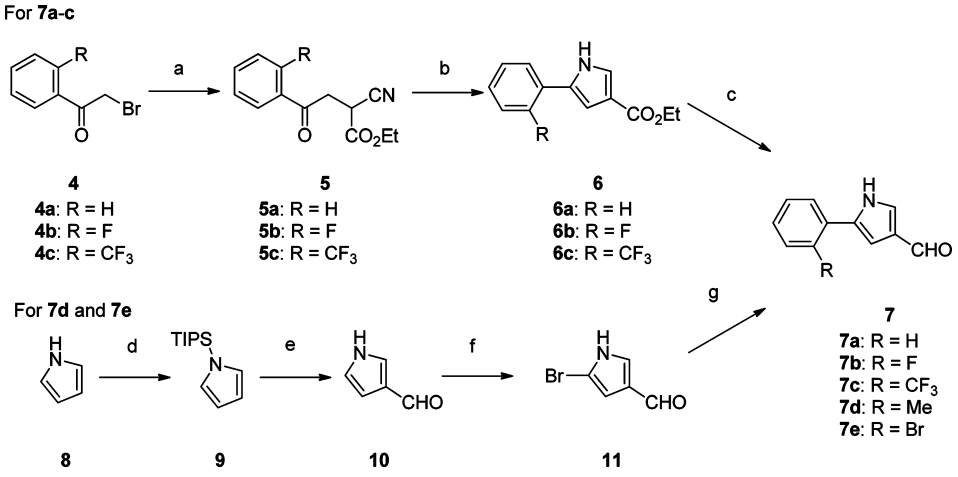
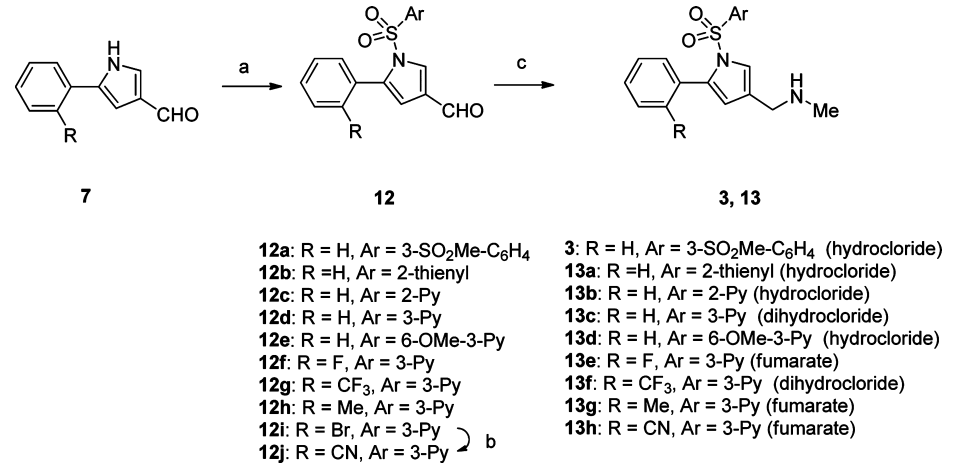
Scheme 1[a]



[a]Reagents and conditions: (a) ethyl cyanoacetate, K_2CO_3, acetone, rt, 18 h, 66−100%. (b) (i) 4 N HCl−EtOAc or HCl(g), EtOAc, rt, 3 h. (ii) H_2, 10%Pd−C, EtOH. rt, 24 h, 18−62%. (c) (i) 1.5 mol/L diisobutylaluminum hydride in toluene, THF, −78 °C, 1 h. (ii) MNO, TPAP, 4 Å molecular sieves, MeCN, rt, 1.5 h, 60−62%. (d) NaH, TIPSCl, THF, 0 °C, 1.5 h, quant. (e) (i) Vilsmeier reagent, CH_2Cl_2, reflux, 30 min; (ii) 1 N NaOH aq, H_2O, rt, 2 h, 38%. (f) NBS, THF, −70 °C, 1 h, then −10 °C, 2 h, 51%. (g) R-C_6H_4-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME−H_2O, 105 °C, 24 h, 32−69%.

Scheme 2[a]



[a]Reagents and conditions: (a) NaH, 15-crown-5, $ArSO_2Cl$, THF, rt, 15 min, 17−100%. (b) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, microwave, 100 W, 4.5 min, 63%. (c) (i) methylamine hydrocloride, $NaBH_3CN$, THF, rt, 18 h, or 40% $MeNH_2$ in MeOH, THF, rt, 30 min, then $NaBH_4$, MeOH, rt, 10 min; (iii) 4 N HCl−EtOAc, EtOH, or fumaric acid, EtOH, EtOAc, rt, 10 min, 10−83%.

active than 3-thienyl derivative **16a**. Compound **13b** bearing a 2-pyridylsulfonyl group exhibited lower H^+,K^+-ATPase inhibitory activity, while 3-pyridylsulfonyl derivative **13c** showed potent inhibition comparable with that of 3-thienyl derivative **16a**. These results are consistent with our proposed model, which suggests that not only aromatic groups but also heteroaromatic ones at the 1-position can maintain potency. Sulfur and nitrogen atoms on 3-thienyl and 3-pyridyl derivatives (**16a** and **13c**) appear to occupy a more favorable position than those of 2-thienyl and 2-pyridyl derivatives (**13a** and **13b**) to have polar interactions with the neighboring residues of H^+,K^+-ATPase. Among these four compounds, the 3-pyridyl derivative **13c** exhibited the highest LLE (7.1), reflecting its high potency and low log *D* (0.7), and relatively potent inhibitory activity in vivo. Hence, we further tested the effects of the substituents on the 3-pyridine ring. Compared to compound **13c**, methoxy derivative **13d** showed more potent inhibitory activity in vitro and vivo, but methyl and cyano derivatives (**16b** and **16c**) exhibited less potent H^+,K^+-ATPase inhibitory activities. Even though potent inhibitory activity in rats was observed for compound **13d**, we selected the 3-pyridylsulfonyl derivative **13c** as a lead compound for further optimization based on its higher LLE.

Next, we evaluated the effects of substituents on a phenyl ring at the 5-position in 3-pyridylsulfonyl derivatives, and the results are shown in Table 3. The in vitro activities of 2- and 3-fluoro derivatives (**13e** and **20b**) were similar to that of an unsubstituted phenyl derivative **13c**, while 4-fluoro derivative **20a** exhibited about 3-fold lower activity. Among these three compounds, 2-fluoro compound **13e** demonstrated the highest LLE and the most potent inhibitory activity in vivo. Hence, we focused on substitution at the 2-position of the phenyl group. The chloro derivative **20c** showed similar in vitro activity, but methyl and trifluoromethyl derivatives (**13g** and **13f**) had

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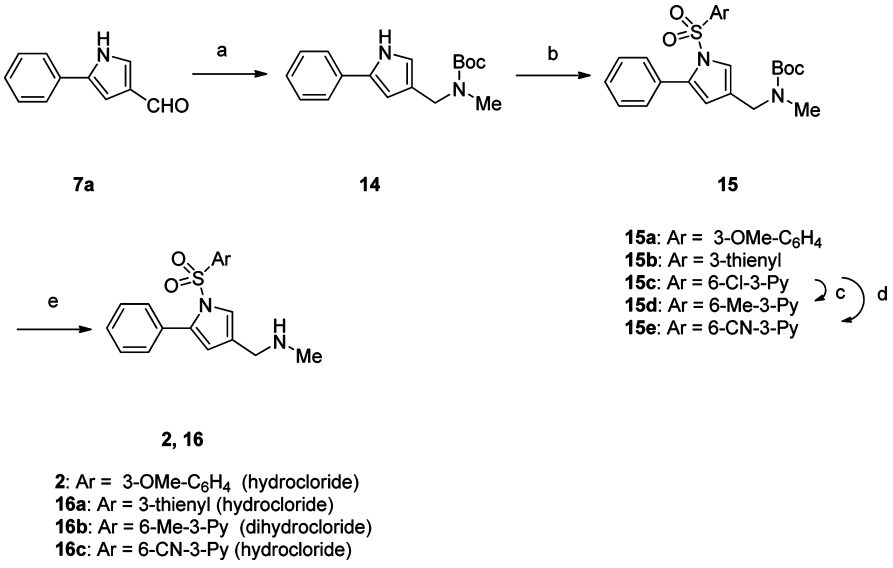
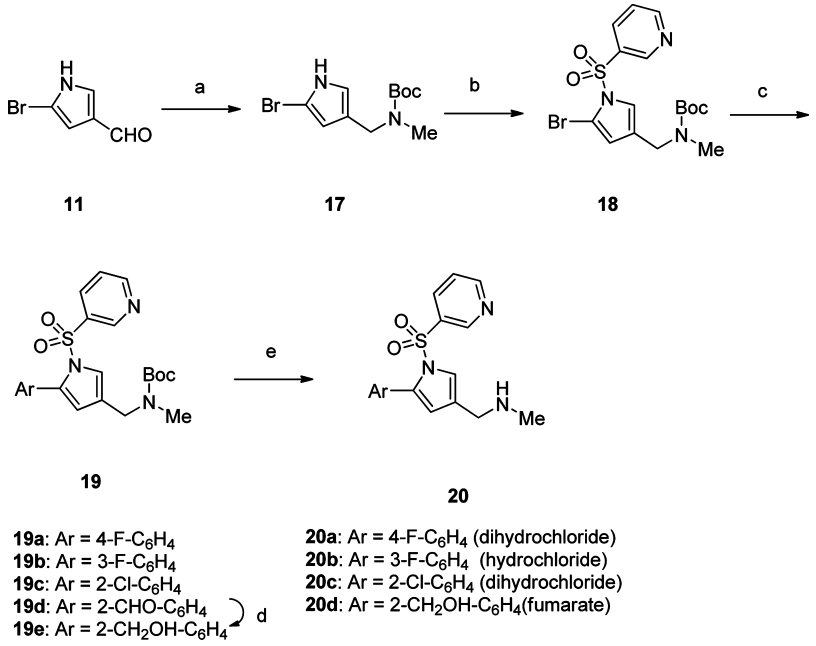
Scheme 3[a]



[a]Reagents and conditions: (a) (i) 40% $MeNH_2$ in MeOH, THF, MeOH, rt, 30 min; (ii) $NaBH_4$, MeOH, rt, 10 min; (iii) $(Boc)_2O$, EtOAc, rt, 1.5 h, 64%. (b) NaH, 15-crown-5, $ArSO_2Cl$, THF, rt, 30 min, 20−100%. (c) $MeB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 90 °C, 72 h, 36%. (d) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 100 °C, 2 h, 72%. (e) 4 N HCl−EtOAc, MeOH or EtOH, rt, 3 h, 28−78%.

Scheme 4[a]



[a]Reagents and conditions: (a) (i) 40% $MeNH_2$ in MeOH, THF, MeOH, rt, 30 min; (ii) $NaBH_4$, MeOH, rt, 10 min; (iii) $(Boc)_2O$, EtOAc, rt,1.5 h, 61%. (b) NaH, 15-crown-5, 3-pyridinesulfonyl chloride hydrochloride, THF, rt, 2 h, 85%. (c) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 105 °C, 1 h, or $ArB(OH)_2$, $Pd_2(dba)_3$, (*S*)-Phos, Na_2CO_3, toluene, 120 °C, 17 h 48−64%. (d) $NaBH_4$, MeOH, 0 °C, 30 min, 60%. (e) 4 N HCl−EtOAc, EtOH, rt, 3 h, or (i) TFA, rt, 1 h, (ii) $NaHCO_3$ aq; (iii) fumaric acid, EtOAc, EtOH, 35−67%.

slightly lower activities than compound **13e**. Although the in vitro H^+,K^+-ATPase inhibitory activities of these two compounds (**13g** and **13f**) were about 3- to 5-fold lower than that of compound **13c**, the former showed higher in vivo potency; however, the reason for this difference is unclear. Introduction of polar substituents such as cyano (**13h**) or hydroxymethyl (**20d**) resulted in a decrease of H^+,K^+-ATPase inhibitory activity. On the basis of these results, including H^+,K^+-ATPase inhibitory activity, LLE, and in vivo potency, compound **13e** was selected for further evaluation.

Compound **13e** was orally absorbed in rats and dogs, and it was further evaluated in in vivo studies. It inhibited basal gastric acid secretion in pylorus-ligated rats following po administration in a dose-dependent manner, and complete inhibition was observed at a dose of 4 mg/kg. LPZ, a typical PPI, also inhibited gastric acid secretion, but it did not show complete inhibition even at 8 mg/kg.[23] The effects of compound **13e** and

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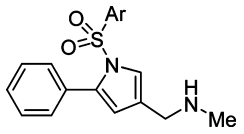
Table 2. Effects of Arylsulfonyl Group on Porcine H^+,K^+-ATPase Activity, log *D*, LLE, and Inhibitory Activity on Histamine-Induced Gastric Acid Secretion in Anesthetized Rats



compd	Ar	H^+,K^+-ATPase IC_{50} (nM)[a]	log *D* [b]	LLE	in vivo (% inhibition)[c]
1	4-OMe-C_6H_4	30 (19−47)	1.5	6.0	95
13a	2-thienyl	51 (31−83)	1.2	6.1	69
16a	3-thienyl	16 (8−33)	1.1	6.7	55
13b	2-Py	170 (140−200)	0.7	6.1	NT[d]
13c	3-Py	16 (12−20)	0.7	7.1	85
16b	6-Me-3-Py	34 (27−43)	1.0	6.6	83
13d	6-OMe-3-Py	13 (8.5−21)	1.7	6.2	95
16c	6-CN-3-Py	110 (61−210)	1.4	5.6	17

[a]Inhibitory activity against H^+,K^+-ATPase. Data are from duplicate experiments. IC_{50} values and 95% confidence limits are calculated from the concentration−response curves generated by nonlinear regression using the program GraphPadPrism (GraphPad Software, San Diego, CA). The confidence limits are shown in parentheses. [b]Measured at pH 7.4. [c]Histamine-induced acid secretion in rats (1 mg/kg, iv). [d]NT means not tested.

LPZ on histamine-stimulated gastric acid secretion in Heidenhain-pouch dogs are shown in Figure 2. Gastric acid secretion was completely inhibited at a dose of 1 mg/kg po, and the inhibitory effect was observed even after 2 days from the administration. The maximum efficacy and the duration of action of compound **13e** were more and much longer, respectively, than those of LPZ for the same applied dose. This result indicates that the pharmacological effect of compound **13e** is superior to that of LPZ. This compound showed limited CYP polymorphism (data not shown), which would also be another advantage against LPZ. Owing to its high LLE resulting from its high in vitro activity and low log *D*, the overall DMPK and safety profiles of compound **13e** were better than those of compound **1**. On the basis of these findings,

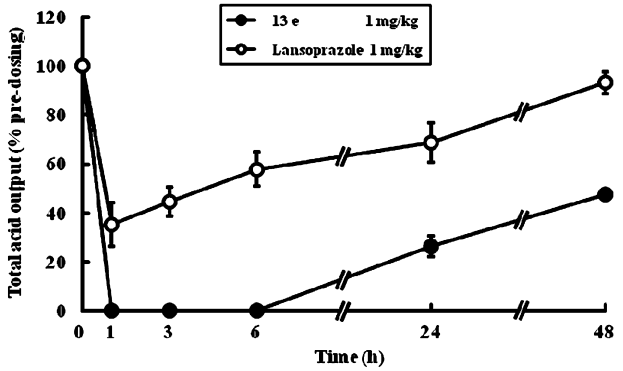


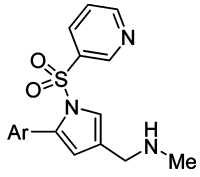
Figure 2. Effects of **13e** and lansoprazole on histamine-stimulated gastric acid secretion in Heidenhain-pouch dogs.

compound **13e** was selected as a promising candidate for the clinical study of GERD, peptic ulcer, and other acid-related diseases.

CONCLUSION

A series of *N*-(5-aryl-1-arylsulfonyl-1*H*-pyrrole-3-yl)methyl-*N*-methylmethanamine derivatives were synthesized. Further, the compounds were evaluated for their inhibitory activities on H^+,K^+-ATPase in vitro and on histamine-induced gastric acid secretion in rats. Their LLE (pIC_{50} − log *D*) values were also calculated using their measured log *D* values. Our focus is to identify high LLE compounds because they are expected to possess favorable properties and can serve as clinical candidates. In order to acquire polar interactions and reduce log *D* values, polar substituents or heteroaromatic groups were introduced at the 1-position of the pyrrole ring. We discovered that the 3-pyridylsulfonyl group had favorable in vitro and in vivo activities, and it also had a high LLE. Furthermore, unlike substitution at other positions, fluoro substitution at the 2-position of the phenyl ring at the 5-position enhanced the LLE values and in vivo antisecretory activities of the compounds. Among the synthesized derivatives, the representative compound **13e** showed potent H^+,K^+-ATPase inhibitory activity in vitro, the highest LLE, and potent inhibitory activities on

Table 3. Effects of Substituents at 5-Position on Porcine H^+,K^+-ATPase Activity, log *D*, LLE, and Inhibitory Activity on Histamine-Induced Gastric Acid Secretion in Anesthetized Rats



compd	Ar	H^+,K^+-ATPase IC_{50} (nM)[a]	log *D* [b]	LLE	in vivo (% inhibition)[c]
13e	2-F-C_6H_4	19 (1.7−23)	0.4	7.3	98
20b	3-F-C_6H_4	20 (13−29)	1.0	6.7	92
20a	4-F-C_6H_4	46 (37−57)	1.0	6.3	85
20c	2-Cl-C_6H_4	17 (14−19)	0.7	7.1	97
13g	2-Me-C_6H_4	46 (41−52)	1.0	6.3	95
13f	2-CF_3-C_6H_4	75 (44−130)	0.8	6.3	92
13h	2-CN-C_6H_4	230 (180−310)	−0.2	6.8	68
20d	2-CH_2OH-C_6H_4	2200 (1600−3000)	−0.3	6.0	NT[d]

[a]Inhibitory activity against H^+,K^+-ATPase. Data are from duplicate experiments. IC_{50} values and 95% confidence limits are calculated from the concentration−response curves generated by nonlinear regression by using the program GraphPadPrism (GraphPad Software, San Diego, CA). The confidence limits are shown in parentheses. [b]Measured at pH 7.4. [c]Histamine-induced acid secretion in rats (1 mg/kg, iv). [d]NT means not tested.

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EXPERIMENTAL SECTION

General Methods. Melting points were determined on a Yanagimoto micromelting point apparatus or Büchi B-545 and are uncorrected. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-300 or a Bruker AV-300M spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard. Coupling constants (J) are reported in hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; br, broad; d, doublet; t, triplet; m, multiplet. Microwave was irradiated with a CEM Discover microwave focused chemical synthesis reactor. TLC analyses were carried out on Merck Kieselgel 60 F254 plates or Fuji Silysia Chemical Ltd. Chromatorex NH-TLC plates. Silica gel column chromatography was performed using Merck 0.063−0.200 mm silica gel 60 and Fuji Silysia Chemical Ltd. 100−200 mesh Chromatorex NH silica DM1020. Purity (>95%) of the all tested compounds was determined by elemental analysis or HPLC−UV analysis. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd. and are within 0.4% of the theoretical values. HPLC−UV analysis for purity confirmation was performed with the following parameters: analytical column YMC-UltraHT C18, 2 μm, 2.0 mm × 30 mm (from YMC Co., Ltd.); mobile phase A, 50 mM ammonium acetate solution; mobile phase B, acetonitrile; linear gradient of 5% mobile phase B to 85% for 4 min with flow rate of 0.7 mL/min; interval time, 1 min; column temperature, 40 °C; injection volume, 5 μL; compound concentration, about 0.1 mg/mL in water/acetonitrile (1:1); detection wavelength, average 230−280 nm. HRMS analysis was carried out by Takeda Analytical Laboratories, Ltd. 2-Bromo-1-(2′-fluorophenyl)ethanone (**4b**) and 2-bromo-1-[(2′-trifluoromethyl)phenyl]ethanone (**4c**) were prepared in a similar manner as reported.[24,25]

1-{1-[(3-Methoxyphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (2). This compound was prepared from **15a** using a similar procedure described later as for the preparation of **13a**. Pale-purple crystals, mp 167−169 °C (68%). ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H), 3.68 (s, 3H), 3.97 (s, 2H), 6.44 (d, J = 1.9 Hz, 1H), 6.76−6.77 (m, 1H), 7.00−7.04 (m, 1H), 7.15−7.18 (m, 2H), 7.24−7.28 (m, 1H), 7.34−7.47 (m, 4H), 7.73 (d, J = 1.9 Hz, 1H). Anal. ($C_{19}H_{21}ClN_2O_3S$) C, H, N.

***N*-Methyl-1-(1-{[3-(methylsulfonyl)phenyl]sulfonyl}-5-phenyl-1*H*-pyrrol-3-yl)methanamine hydrochloride (3).** Compound **3** was prepared from compound **12a** using a similar procedure described later as for the preparation of compound **13a**. Colorless crystals, mp 208−210 °C (83%). ^{1}H NMR (DMSO-d_6) δ: 2.49 (s, 3H), 3.26 (s, 3H), 3.98 (s, 2H), 6.49 (d, J = 1.8 Hz, 1H), 7.13−7.17 (m, 2H), 7.34−7.46 (m, 3H), 7.77−7.87 (m, 4H), 8.25−8.29 (m, 1H), 9.08 (br, 2H). Anal. ($C_{19}H_{21}ClN_2O_4S_2$) C, H, N.

Ethyl 2-Cyano-4-oxo-4-phenylbutanoate (5a). Potassium carbonate (13.8 g, 99.8 mmol) was added to ethyl cyanoacetate (37 mL, 348 mmol), and the mixture was stirred at 40−45 °C for 45 min. A solution of **4a** (10.0 g, 50.2 mmol) in acetone (100 mL) was added dropwise over 30 min. After the dropwise addition was completed, the mixture was stirred at room temperature for 18 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Excess ethyl cyanoacetate contained in the obtained oil was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane−ethyl acetate, 8:1 to 1:1) to give 10.4 g (90%) the title compound as a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, J = 7.2 Hz, 3H), 3.55 (dd, J = 16.0, 5.6 Hz, 1H), 3.80 (dd, J = 16.0, 7.0 Hz, 1H), 4.16 (dd, J = 7.0, 5.6 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 7.40−7.70 (m, 3H), 7.90−8.00 (m, 2H).

Compounds **5b** and **5c** were prepared from compounds **4b** and **4c** using a similar procedure as for the preparation of compound **5a**.

Ethyl 2-Cyano-4-(2-fluorophenyl)-4-oxobutanoate (5b). An oil (~100%). ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, J = 7.2 Hz, 3H), 3.55−3.80 (m, 2H), 4.11 (t, J = 6.0 Hz, 1H), 4.24−4.34 (m, 2H), 7.15−7.29 (m, 2H), 7.55−7.62 (m, 1H), 7.94 (dt, J = 7.5, 1.8 Hz, 1H).

Ethyl 2-Cyano-4-oxo-4-[(2-trifluoromethyl)phenyl]-butanoate (5c). An oil (66%). ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, J = 7.2 Hz, 3H), 3.34−3.46 (m, 1H), 3.59−3.70 (m, 1H), 4.08−4.22 (m, 1H), 4.32 (q, J = 7.2 Hz, 2H), 7.57−7.80 (m, 4H).

Ethyl 5-Phenyl-1*H*-pyrrole-3-carboxylate (6a). Hydrogen chloride gas (28 g) was bubbled through a solution of **5a** (5.0 g, 21.6 mmol) in tetrahydrofuran (60 mL) under ice-cooling, and the mixture was stirred at room temperature for 3 h. Then nitrogen gas was introduced to substitute HCl gas and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 6:1) to give 4.24 g (79%) of ethyl 2-chloro-5-phenyl-1*H*-pyrrole-3-carboxylate. ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, J = 6.8 Hz, 3H), 4.33 (q, J = 6.8 Hz, 2H), 6.87 (d, J = 3.2 Hz, 1H), 7.20−7.60 (m, 5H), 8.79 (br, 1H). To a solution of ethyl 2-chloro-5-phenyl-1*H*-pyrrole-3-carboxylate (8.5 g, 34.0 mmol) in ethanol (50 mL) was added 10% palladium carbon (50% wet, 0.5 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 9:1 to 1:1) to give 4.50 g (62%) the title compound as a colorless solid, mp 148−150 °C. ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, J = 7.2 Hz, 3H), 4.31 (q, J = 7.2 Hz, 2H), 6.91 (m, 1H), 7.20−7.70 (m, 6H), 8.77 (br, 1H).

Compounds **6b** and **6c** were prepared from compounds **5b** and **5c** using a similar procedure as for the preparation of compound **6a**.

Ethyl 5-(2-Fluorophenyl)-1*H*-pyrrole-3-carboxylate (6b). A brown solid, mp 84−86 °C (18%). ^{1}H NMR ($CDCl_3$) δ: 1.67 (t, J = 7.2 Hz, 3H), 4.31 (q, J = 7.2 Hz, 2H), 7.03−7.05 (m, 1H), 7.08−7.25 (m, 3H), 7.49−7.50 (m, 1H), 7.58−7.66 (m, 1H), 9.22 (brs, 1H).

Ethyl 5-[(2-Trifluoromethyl)phenyl]-1*H*-pyrrole-3-carboxylate (6c). Colorless crystals, mp 180−181 °C (51%). ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, J = 7.2 Hz, 3H), 4.31 (q, J = 7.2 Hz, 2H), 6.81 (s, 1H), 7.42−7.61 (m, 5H), 8.69 (br, 1H).

5-Phenyl-1*H*-pyrrole-3-carbaldehyde (7a). To a solution of **6a** (2.16 g, 10.0 mmol) in tetrahydrofuran (100 mL) was added dropwise a 1.5 mol/L solution of diisobutylaluminum hydride in toluene (24 mL, 36 mmol) at −78 °C over 10 min. The mixture was further stirred at −78 °C for 1 h. Water (2 mL) was added dropwise over 2 min, and the mixture was further stirred at room temperature for 1 h. To the reaction mixture were added Celite and anhydrous magnesium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give 1.51 g (87%) of (5-phenyl-1*H*-pyrrol-3-yl)methanol. ^{1}H NMR (DMSO-d_6) δ: 4.34 (d, J = 5.4 Hz, 2H), 4.60 (t, J = 5.4 Hz, 1H), 6.45−6.46 (m, 1H), 6.74 (br, 1H), 7.11−7.15 (m, 1H), 7.31−7.35 (m, 2H), 7.57−7.59 (m, 2H), 11.05 (s, 1H). To a solution of (5-phenyl-1*H*-pyrrol-3-yl)methanol (1.51 g, 8.72 mmol) in acetonitrile (45 mL) were added tetra-*n*-propylammonium perruthenate (0.46 g, 1.31 mmol), *N*-methylmorpholine *N*-oxide (2.36 g, 20.2 mmol), and 4 Å molecular sieves (4.5 g), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 4:1 to 1:1) to give 0.92 g (62%) of the title compound as a pale-yellow powder, mp 137−139 °C. ^{1}H NMR ($CDCl_3$) δ: 6.95 (m, 1H), 7.29−7.32 (m, 1H), 7.40−7.44 (m, 2H), 7.50−7.52 (m, 3H), 9.02 (br, 1H), 9.84 (s, 1H).

Compounds **7b** and **7c** were prepared from compounds **6b** and **6c** using a similar procedure as for the preparation of compound **7a**.

5-(2-Fluorophenyl)-1*H*-pyrrole-3-carbaldehyde (7b). Yellow crystals, mp 130−131 °C (60%). ^{1}H NMR ($CDCl_3$) δ: 7.07−7.28 (m, 4H), 7.52−7.54 (m, 1H), 7.61−7.67 (m, 1H), 9.49 (brs, 1H), 9.86 (s, 1H).

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5-[2-(Trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde (7c). Colorless crystals (61%). ^{1}H NMR ($CDCl_3$) δ: 6.79−6.81 (m, 1H), 7.46−7.78 (m, 5H), 9.13 (br, 1H), 9.82 (s, 1H).

5-(2-Methylphenyl)-1*H*-pyrrole-3-carbaldehyde (7d). Compound **11** (100 mg, 0.57 mmol), 2-methylphenylboronic acid (94 mg, 0.69 mmol), and sodium carbonate (146 mg, 1.38 mmol) were suspended in a mixed solvent of 1,2-dimethoxyethane (5 mL) and water (2 mL), and the mixture was sufficiently degassed under a nitrogen atmosphere. Tetrakis(triphenylphosphine)palladium (33 mg, 0.029 mmol) was added, and the mixture was further degassed and refluxed at 105 °C for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 8:1 to 3:1) to give 72 mg (68%) of the title compound as colorless crystals. ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H), 6.75−6.76 (m, 1H), 7.24−7.35 (m, 4H), 7.49−7.51 (m, 1H), 8.80 (brs, 1H), 9.84 (s, 1H).

Compound **7e** was prepared using a similar procedure as for the preparation of compound **7d** using 2-bromophenylboronic acids.

5-(2-Bromophenyl)-1*H*-pyrrole-3-carbaldehyde (7e). Colorless crystals (32%). ^{1}H NMR ($CDCl_3$) δ: 6.94−6.95 (m, 1H), 7.16−7.22 (m, 1H), 7.34−7.39 (m, 1H), 7.49−7.54 (m, 2H), 7.63−7.66 (m, 1H), 9.28 (br, 1H), 9.85 (s, 1H).

1*H*-Pyrrole-3-carbaldehyde (10). To a suspension of sodium hydride (60% dispersion in oil, 13.7 g, 285 mmol) in tetrahydrofuran (450 mL) was slowly added pyrrole (**8**) (17.4 g, 259 mmol) at 0 °C. The mixture was stirred at the same temperature for 1.5 h. To the mixture was slowly added triisopropylsilyl chloride (50 g, 259 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for another 1.5 h. To the reaction mixture was added ice−water, and it was extracted with diethyl ether. The extract was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 57.7 g (quant) of 1-(triisopropylsilyl)pyrrole (**9**) as a yellow oil. To a suspension of Vilsmeier reagent (36.5 g, 285 mmol) in dichloromethane (500 mL) was added a solution of **9** (57.7 g) in dichloromethane (30 mL) in one portion at 0 °C. The mixture was refluxed for 30 min and then cooled to 0 °C. The obtained solid was collected by filtration and washed with diethyl ether. The solid was dissolved in water (50 mL). To the solution was added 1 N sodium hydroxide solution (500 mL), and the mixture was stirred for 2 h. The resulting mixture was extracted with chloroform and ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give 9.4 g (38%) of the title compound as a pale brown solid, mp 60−61 °C. ^{1}H NMR ($CDCl_3$) δ: 6.68−6.70 (m, 1H), 6.83−6.85 (m, 1H), 7.44−7.46 (m, 1H), 9.09 (br, 1H), 9.81 (s, 1H).

5-Bromo-1*H*-pyrrole-3-carbaldehyde (11). To a solution of compound **10** (19.1 g, 200 mmol) in tetrahydrofuran (300 mL) was slowly added a solution of *N*-bromosuccinimide (35.8 g, 201 mmol) in *N*,*N*-dimethylformamide (100 mL) at −70 °C, and the mixture was stirred at the same temperature for 1 h, then warmed to −10 °C during 2 h. After the mixture was stirred at the same temperature for 30 min, ice−water was added and extracted with ethyl acetate. The extract was successively washed with 10% citiric acid solution, 6% sodium hydrogen carbonate solution, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give 17.7 g (51%) of the title compound as a pale brown solid, mp 125−128 °C. ^{1}H NMR ($CDCl_3$) δ: 6.65−6.67 (m, 1H), 7.38−7.40 (m, 1H), 8.80 (brs, 1H), 9.71 (s, 1H).

1-{[3-(Methylsulfonyl)phenyl]sulfonyl}-5-phenyl-1*H*-pyrrole-3-carbaldehyde (12a). Sodium hydride (60% in oil, 212 mg, 5.30 mmol) was washed with hexane twice and suspended in tetrahydrofuran (10 mL). To the suspension was added a solution of **7a** (602 mg, 3.52 mmol) in tetrahydrofuran (10 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. 15-Crown-5 (1.05 mL, 5.34 mmol) and a solution of (3-methylsulfonyl)benzenesulfonyl chloride (1.36 g, 5.34 mmol) in tetrahydrofuran (5 mL) were added at 0 °C, and the reaction mixture was stirred at room temperature for 15 min. Water was added, and the mixture was extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate solution, water, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 1:1) to give 943 mg (69%) of the title compound as a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.98 (s, 3H), 6.61 (d, J = 1.8 Hz, 1H), 7.16−7.20 (m, 2H), 7.30−7.36 (m, 2H), 7.41−7.47 (m, 1H), 7.57−7.59 (m, 2H), 7.92−7.94 (m, 1H), 8.10−8.13 (m, 2H), 9.90 (s, 1H).

Compounds **12b−i** were prepared from **7a−e** using a similar procedure as for the preparation of compound **12a** using the corresponding sulfonyl chlorides.

5-Phenyl-1-(2-thienylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (12b). Colorless crystals, mp 93−94 °C (57%). ^{1}H NMR ($CDCl_3$) δ: 6.59 (d, J = 1.8 Hz, 1H), 6.90 (dd, J = 4.9, 3.9 Hz, 1H), 7.05 (dd, J = 3.9, 1.4 Hz, 1H), 7.24−7.45 (m, 5H), 7.62 (dd, J = 4.9, 1.4 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 9.88 (s, 1H).

5-Phenyl-1-(pyridin-2-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (12c). A yellow oil (45%). ^{1}H NMR ($CDCl_3$) δ: 6.58 (d, J = 2.1 Hz, 1H), 7.05−7.09 (m, 2H), 7.22−7.25 (m, 2H), 7.31−7.39 (m, 2H), 7.43−7.48 (m, 1H), 7.63−7.69 (m, 1H), 8.19 (d, J = 2.1 Hz, 1H), 8.60−8.62 (m, 1H), 9.90 (s, 1H).

5-Phenyl-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (12d). A brown solid (75%). ^{1}H NMR ($CDCl_3$) δ: 6.60 (d, J = 1.8 Hz, 1H), 7.15−7.19 (m, 2H), 7.25−7.37 (m, 3H), 7.42−7.48 (m, 1H), 7.53−7.57 (m, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.49−8.50 (m, 1H), 8.74−8.76 (m, 1H), 9.90 (s, 1H).

1-[(6-Methoxypyridin-3-yl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carbaldehyde (12e). An oil (17%). ^{1}H NMR ($CDCl_3$) δ: 3.95 (s, 3H), 6.59−6.62 (m, 2H), 7.19−7.44 (m, 6H), 8.08−8.10 (m, 2H), 9.88 (s, 1H).

5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (12f). Colorless crystals, mp 105−107 °C (82%). ^{1}H NMR ($CDCl_3$) δ: 6.68 (d, J = 1.8 Hz, 1H), 6.99−7.05 (m, 1H), 7.16−7.19 (m, 2H), 7.35−7.39 (m, 1H), 7.45−7.51 (m, 1H), 7.69−7.73 (m, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.58−8.59 (m, 1H), 8.81−8.83 (m, 1H), 9.91 (s, 1H).

1-(Pyridin-3-ylsulfonyl)-5-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde (12g). Colorless crystals (∼100%). ^{1}H NMR ($CDCl_3$) δ: 6.69 (d, J = 1.8 Hz, 1H), 7.34−7.38 (m, 1H), 7.44−7.48 (m, 1H), 7.61−7.69 (m, 4H), 8.16 (d, J = 1.8 Hz, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.81 (m, 1H), 9.91 (s, 1H).

5-(2-Methylphenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (12h). A red oil (80%). ^{1}H NMR ($CDCl_3$) δ: 1.82 (s, 3H), 6.56 (d, J = 1.5 Hz, 1H), 6.87−6.90 (m, 1H), 7.11−7.19 (m, 2H), 7.30−7.39 (m, 2H), 7.56−7.60 (m, 1H), 8.15 (d, J = 1.5 Hz, 1H), 8.52−8.53 (m, 1H), 8.80−8.82 (m, 1H), 9.92 (s, 1H).

5-(2-Bromophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (12i). A pale-yellow solid (91%). ^{1}H NMR ($CDCl_3$) δ: 6.66 (d, J = 1.5 Hz, 1H), 7.31−7.40 (m, 4H), 7.48−7.52 (m, 1H), 7.66−7.71 (m, 1H), 8.15 (d, J = 1.8 Hz, 1H), 8.55 (d, J = 2.7 Hz, 1H), 8.82−8.84 (m, 1H), 9.92 (s, 1H).

2-[4-Formyl-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-2-yl]-benzonitrile (12j). A mixture of **12i** (102 mg, 0.26 mmol), zinc cyanide (61.0 mg, 0.52 mmol), and tetrakis(triphenylphosphine)-palladium (60.0 mg, 0.052 mmol) in *N*,*N*-dimethylformamide (2 mL) was microwaved (100 W, 4 min 30 s). Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 4:1 to 2:1) to give 97.4 mg (63%) of the title compound as a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ: 6.79 (d, J = 1.8 Hz, 1H), 7.41−7.51 (m, 2H), 7.58−7.78 (m, 4H), 8.17 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 2.7 Hz, 1H), 8.84−8.86 (m, 1H), 9.91 (s, 1H).

***N*-Methyl-1-[5-phenyl-1-(2-thienylsulfonyl)-1*H*-pyrrol-3-yl]-methanamine Hydrochloride (13a).** To a solution of **12b** (180 mg, 0.57 mmol) in methanol (20 mL) was added a 40% methylamine methanol solution (220 mg, 2.16 mmol) at room temperature, and the mixture was stirred for 30 min. Sodium borohydride (64 mg, 1.69

mmol) was added at room temperature, and the mixture was stirred for 10 min. Then 1 mol/L hydrochloric acid (20 mL) was added, and the mixture was stirred for 5 min. The reaction mixture was basified with a saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane−ethyl acetate, 1:4 to 0:1), and the obtained oil was dissolved in ethyl acetate (5 mL). A 4 mol/L hydrogen chloride−ethyl acetate solution (1 mL) was added, and the mixture was concentrated under reduced pressure. The residue was crystallized from ethyl acetate to give 171 mg (82%) of the title compound as colorless crystals. ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H), 3.98 (s, 2H), 6.49 (d, J = 1.8 Hz, 1H), 7.12 (dd, J = 5.0, 3.9 Hz, 1H), 7.22−7.25 (m, 2H), 7.32 (dd, J = 3.9, 1.4 Hz, 1H), 7.36−7.46 (m, 3H), 7.69 (d, J = 1.8 Hz, 1H), 8.08 (dd, J = 5.0, 1.4 Hz, 1H), 9.10 (br, 2H). Anal. ($C_{16}H_{17}ClN_2O_2S_2$) C, H, N.

Compounds **13b−d** and **13f** were prepared from compounds **12c−e** and **12g** using a similar procedure as for the preparation of compound **13a**.

***N*-Methyl-1-[5-phenyl-1-(pyridin-2-ylsulfonyl)-1*H*-pyrrol-3-yl]methanamine Hydrochloride (13b).** Colorless crystals, mp 162−164 °C (31%). ^{1}H NMR (DMSO-d_6) δ: 2.54 (s, 3H), 4.02 (s, 2H), 6.43 (brs, 1H), 7.03−7.06 (m, 2H), 7.24−7.29 (m, 2H), 7.33−7.38 (m, 1H), 7.55−7.56 (m, 1H), 7.70−8.74 (m, 2H), 7.95−8.01 (m, 1H), 8.67−8.68 (m, 1H), 8.85 (br, 2H). Anal. ($C_{17}H_{18}ClN_3O_2S$) C, H, N.

***N*-Methyl-1-[5-phenyl-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methanamine Dihydrochloride (13c).** A solid, mp 188−189 °C (29%). ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H), 3.97−4.00 (s, 2H), 6.50 (s, 1H), 7.14−7.16 (m, 2H), 7.35−7.45 (m, 3H), 7.62−7.70 (m, 1H), 7.78−7.83 (m, 2H), 8.47−8.48 (m, 1H), 8.84−8.86 (m, 1H), 9.08 (br, 2H), 1H not detected. Anal. ($C_{17}H_{19}Cl_2N_3O_2S$) C, H, N.

1-{1-[(6-Methoxypyridin-3-yl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}-*N*-methylmethanamine Hydrochloride (13d). A solid, mp 204−206 °C (58%). ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H), 3.90 (s, 3H), 3.98 (s, 2H), 6.45 (s, 1H), 6.91−6.94 (m, 1H), 7.16−7.18 (m, 2H), 7.36−7.45 (m, 3H), 7.59−7.63 (m, 1H), 7.72 (s, 1H), 8.09−8.10 (m, 1H), 8.91 (br, 2H). Anal. ($C_{18}H_{20}ClN_3O_3S{\cdot}0.25H_2O$) C, H, N.

***N*-Methyl-1-{1-(pyridin-3-ylsulfonyl)-5-[2-(trifluoromethyl)-phenyl]-1*H*-pyrrol-3-yl}methanamine Dihydrochloride (13f).** Pale-red crystals, mp 209−210 °C (69%). ^{1}H NMR (DMSO-d_6) δ: 2.47 (t, J = 5.5 Hz, 3H), 4.00 (t, J = 5.5 Hz, 2H), 6.60 (d, J = 1.8 Hz, 1H), 7.18−7.21 (m, 1H), 7.63−7.81 (m, 4H), 7.91−8.00 (m, 2H), 8.58 (d, J = 1.8 Hz, 1H), 8.90−8.92 (m, 1H), 9.48−9.57 (m, 2H), 1H not detected. Anal. ($C_{18}H_{18}Cl_2F_3N_3O_2S{\cdot}2.0H_2O$) C, H, N.

1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine Fumarate (13e). Compound **12f** (1.52 g, 8.03 mmol) was dissolved in methanol (30 mL). A 40% methylamine methanol solution (3.57 g, 35.0 mmol) was added at room temperature, and the mixture was stirred for 30 min. Sodium borohydride (523 mg, 13.8 mmol) was added at room temperature, and the mixture was stirred for 10 min. Then 1 mol/L hydrochloric acid (50 mL) was added and the mixture was stirred for 5 min. The reaction mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (ethyl acetate−methanol, 1:0 to 7:3) to give 1.30 g of a free base of the title compound as a pale-yellow oil. The obtained free base (750 mg) was dissolved in ethyl acetate (30 mL). A solution of fumaric acid (278 mg, 2.40 mmol) in methanol (3 mL) was added dropwise at room temperature. After the mixture was stirred for 30 min, the obtained crystals were collected by filtration and washed with ethyl acetate to give 912 mg (74%) of the title compound as colorless crystals, mp 201−203 °C. ^{1}H NMR (DMSO-d_6) δ: 2.43 (s, 3H), 3.87 (s, 2H), 6.47 (s, 2H), 6.49 (d, J = 1.8 Hz, 1H), 7.07−7.13 (m, 1H), 7.19−7.26 (m, 2H), 7.49−7.56 (m, 1H), 7.59−7.64 (m, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.86−7.90 (m, 1H), 8.56−8.57 (m, 1H), 8.87−8.89 (m, 1H), 3H not detected. Anal. ($C_{21}H_{20}FN_3O_6S$) C, H, N.

Compounds **13g** and **13h** were prepared from compounds **12h** and **12j** using the same procedure as for the preparation of compound **13e**.

***N*-Methyl-1-[5-(2-methylphenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methanamine Fumarate (13g).** Colorless crystals, mp 207−210 °C (56%). ^{1}H NMR (DMSO-d_6) δ: 1.81 (s, 3H), 2.45 (s, 3H), 3.88 (s, 2H), 6.33 (d, J = 1.8 Hz, 1H), 6.46 (s, 2H), 6.83−6.85 (m, 1H), 7.12−7.22 (m, 2H), 7.32−7.37 (m, 1H), 7.57−7.61 (m, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.78−7.82 (m, 1H), 8.44−8.45 (m, 1H), 8.87−8.89 (m, 1H), 3H not detected. Anal. ($C_{22}H_{23}N_3O_6S$) C, H, N.

2-{4-[(Methylamino)methyl]-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-2-yl}benzonitrile Fumarate (13h). Colorless crystals, mp 202−203 °C (38%). ^{1}H NMR (DMSO-d_6) δ: 2.39 (s, 3H), 3.82 (s, 2H), 6.47 (s, 2H), 6.58 (d, J = 1.8 Hz, 1H), 7.34−7.36 (m, 1H), 7.59−7.76 (m, 4H), 7.84−7.89 (m, 2H), 8.53 (d, J = 2.4 Hz, 1H), 8.87−8.89 (m, 1H), 3H not detected. Anal. ($C_{22}H_{20}N_4O_6S$) C, H, N.

***tert*-Butyl Methyl[(5-phenyl-1*H*-pyrrol-3-yl)methyl]-carbamate (14).** To a solution of **7a** (0.92 g, 5.37 mmol) in methanol (92 mL) was added 40% methylamine solution (1.26 g, 12.3 mmol) at room temperature, and the mixture was stirred for 30 min. To the reaction mixture was added sodium borohydride (305 mg, 8.06 mmol) at room temperature, and the mixture was stirred for 10 min. Water (200 mL) was added, and the mixture was further stirred for 1 h. Brine (50 mL) was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in acetonitrile (48 mL), and di-*tert*-butyl dicarbonate (1.41 g, 6.46 mmol) was added dropwise at room temperature. The mixture was stirred for 1.5 h and partitioned between water and ethyl acetate. The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 9:1 to 4:1) to give 0.99 g (64%) of the title compound as colorless crystals, mp 100−102 °C. ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9H), 2.84 (s, 3H), 4.30 (s, 2H), 6.45 (s, 1H), 6.75 (s, 1H), 7.18−7.22 (m, 1H), 7.34−7.38 (m, 2H), 7.44−7.46 (m, 2H), 8.37 (br, 1H).

Compounds **15a−c** were prepared using a similar procedure as for the preparation of compound **12a** using compound **14** and corresponding sulfonyl chlorides.

***tert*-Butyl ({1-[(3-Methoxyphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methyl)methylcarbamate (15a).** An oil (~100%). ^{1}H NMR ($CDCl_3$) δ: 1.46 (s, 9H), 2.80 (s, 3H), 3.64 (s, 3H), 4.22 (brs, 2H), 6.19 (s, 1H), 6.74−6.75 (m, 1H), 6.94−7.02 (m, 2H), 7.16−7.35 (m, 7H).

***tert*-Butyl {[5-Phenyl-1-(3-thienylsulfonyl)-1*H*-pyrrol-3-yl]-methyl}methylcarbamate (15b).** A yellow oil (58%). ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.82 (brs, 3H), 4.22 (brs, 2H), 6.11 (s, 1H), 6.87−6.89 (m, 1H), 7.22−7.33 (m, 7H), 7.40−7.41 (m, 1H).

***tert*-Butyl ({[1-(6-Chloropyridin-3-yl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methyl)methylcarbamate (15c).** A solid, mp 114−115 °C (32%). ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.82 (s, 3H), 4.23 (s, 2H), 6.16 (s, 1H), 7.23−7.49 (m, 8H), 8.28 (s, 1H).

***tert*-Butyl Methyl({[1-(6-methylpyridin-3-yl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methyl)carbamate (15d).** Under an argon atmosphere, a mixture of **15c** (100 mg, 0.22 mmol), methylboronic acid (14 mg, 0.23 mmol), tetrakis(triphenylphosphine)palladium (25 mg, 0.022 mmol), potassium carbonate (90 mg, 0.65 mmol), and dioxane (3 mL) was stirred at 80 °C for 24 h. Methylboronic acid (14 mg, 0.23 mmol) and tetrakis(triphenylphosphine)palladium (25 mg, 0.022 mmol) were added, and the mixture was stirred at 90 °C for 24 h. Methylboronic acid (14 mg, 0.23 mmol), tetrakis-(triphenylphosphine)palladium (25 mg, 0.022 mmol), potassium carbonate (90 mg, 0.65 mmol), and dioxane (2 mL) were added, and the mixture was stirred at 90 °C for 24 h. The reaction mixture was diluted with ethyl acetate, washed successively with saturated aqueous sodium hydrogen carbonate solution, water, and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel

column chromatography (hexane−ethyl acetate, 19:1 to 1:1) to give 85.8 mg (36%) of the title compound as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.46 (s, 9H), 2.58 (s, 3H), 2.81 (s, 3H), 4.20−4.23 (m, 2H), 6.13 (s, 1H), 7.07−7.10 (m, 1H), 7.24−7.42 (m, 7H), 8.39 (s, 1H).

***tert*-Butyl ({[1-(6-Cyanopyridin-3-yl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methyl)methylcarbamate (15e).** Under an argon atmosphere, a mixture of **15c** (153 mg, 0.33 mmol), zinc(II) cyanide (77 mg, 0.66 mmol), tetrakis(triphenylphosphine)palladium (77 mg, 0.066 mmol), and *N*,*N*-dimethylformamide (6 mL) was stirred at 100 °C for 2 h. The reaction mixture was diluted with ethyl acetate, washed successively with a saturated aqueous sodium hydrogen carbonate solution, water, and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 4:1) to give 107 mg (72%) of the title compound as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.83 (s, 3H), 4.22 (brs, 2H), 6.17 (s, 1H), 7.19−7.23 (m, 2H), 7.28−7.29 (m, 1H), 7.32−7.44 (m, 3H), 7.59−7.67 (m, 2H), 8.54−8.55 (m, 1H).

***N*-Methyl-1-{1-[(6-methylpyridin-3-yl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methanamine Dihydrochloride (16b).** Compound **15d** (113 mg) was dissolved in ethanol (2 mL). A 4 mol/L hydrogen chloride−ethyl acetate solution (1 mL) was added, and the mixture was stirred at room temperature for 1 h. The solvent was concentrated under reduced pressure, and the residue was recrystallized from ethanol to give the title compound (yield 40 mg, 38%), mp 204−206 °C. ^{1}H NMR (DMSO-d_6) δ: 2.50−2.53 (m, 6H), 3.97−3.99 (m, 2H), 6.46 (s, 1H), 7.16−7.18 (m, 2H), 7.38−7.44 (m, 4H), 7.65−7.75 (m, 2H), 8.34 (s, 1H), 8.98 (br, 2H), 1H not detected. Anal. ($C_{18}H_{21}Cl_2N_3O_2S$) C, H, N.

Compounds **16a** and **16c** were prepared from compounds **15b** and **15e** using a similar procedure as for the preparation of compound **16b**.

***N*-Methyl-1-[5-phenyl-1-(3-thienylsulfonyl)-1*H*-pyrrol-3-yl]-methanamine Hydrochloride (16a).** Pale-purple crystals, mp 211−214 °C (28%). ^{1}H NMR (DMSO-d_6) δ: 2.52 (s, 3H), 3.98 (s, 2H), 6.45 (d, J = 1.8 Hz, 1H), 6.99 (dd, J = 5.2, 1.4 Hz, 1H), 7.16−7.19 (m, 2H), 7.34−7.45 (m, 3H), 7.69 (d, J = 1.8 Hz, 1H), 7.74 (dd, J = 5.2, 3.0 Hz, 1H), 7.98 (dd, J = 3.0, 1.4 Hz, 1H). HPLC purity 98.15% (220 nM), 97.76% (254 nM). ESI-HRMS calcd for $C_{16}H_{16}N_2O_2S_2$ m/z 333.0726 (M + H), found 333.0707 (M + H).

5-({4-[(Methylamino)methyl]-2-phenyl-1*H*-pyrrol-1-yl}-sulfonyl)pyridine-2-carbonitrile Hydrochloride (16c). A solid, mp 226−227 °C (38%). ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H), 3.98 (s, 2H), 6.52 (s, 1H), 7.15−7.17 (m, 2H), 7.37−7.47 (m, 3H), 7.79 (s, 1H), 8.04−8.07 (m, 1H), 8.22−8.24 (m, 1H), 8.61−8.62 (m, 1H), 9.03 (br, 2H). Anal. ($C_{18}H_{17}ClN_4O_2S$) C, H, N.

***tert*-Butyl [(5-Bromo-1*H*-pyrrol-3-yl)methyl]-methylcarbamate (17).** This compound was prepared from compound **11** using a similar procedure as for the preparation of compound **14**. A pale-yellow oil (61%). ^{1}H NMR ($CDCl_3$) δ: 1.48 (s, 9H), 2.79 (s, 3H), 4.17 (s, 2H), 6.09 (brs, 1H), 6.64 (brs, 1H), 8.07 (br, 1H).

***tert*-Butyl {[5-Bromo-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-methyl}methylcarbamate (18).** To a suspension (10 mL) of sodium hydride (60% in oil, 204 mg, 5.10 mmol) in tetrahydrofuran was added a solution of **17** (410 mg, 1.42 mmol) in *N*,*N*-dimethylformamide (3 mL) at 0 °C, and 15-crown-5 (938 mg, 4.26 mmol) and pyridin-3-ylsulfonyl chloride hydrochloride (456 mg, 2.13 mmol) were added at the same temperature. After the mixture was stirred at room temperature for 2 h, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution, water, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 8:1 to 3:1) to give 522 mg (85%) of the title compound as a pale-yellow powder. ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.80 (brs, 3H), 4.18 (brs, 2H), 6.28 (brs, 1H), 7.35 (brs, 1H), 7.48−7.52 (m, 1H), 8.18−8.22 (m, 1H), 8.85−8.88 (m, 1H), 9.12−9.13 (m, 1H).

Compounds **19a−c** were prepared using a similar procedure as for the preparation of compound **7d** using compound **18** and corresponding boronic acids.

***tert*-Butyl {[5-(4-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate (19a).** A pale-yellow oil (94%). ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.81 (brs, 3H), 4.22 (brs, 2H), 6.12 (brs, 1H), 7.00−7.06 (m, 2H), 7.18−7.31 (m, 4H), 7.56−7.60 (m, 1H), 8.54−8.55 (m, 1H), 8.73−8.75 (m, 1H).

***tert*-Butyl {[5-(3-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate (19b).** A pale-yellow oil (90%). ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.81 (brs, 3H), 4.22 (brs, 2H), 6.16 (brs, 1H), 6.93−7.11 (m, 3H), 7.27−7.32 (m, 3H), 7.59−7.63 (m, 1H), 8.58 (d, J = 2.1 Hz, 1H), 8.73−8.75 (m, 1H).

***tert*-Butyl {[5-(2-Chlorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate (19c).** A pale-blue oil (53%). ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.84 (brs, 3H), 4.26 (brs, 2H), 6.20 (d, J = 1.8 Hz, 1H), 7.26−7.36 (m, 6H), 7.65−7.71 (m, 1H), 8.58−8.59 (m, 1H), 8.75−8.79 (m, 1H).

***tert*-Butyl {[5-(2-Formylphenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate (19d).** Compound **18** (430 mg, 0.85 mmol) was dissolved in toluene (10 mL), and the mixture was sufficiently degassed. Dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)-phosphine (66 mg, 0.16 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (37 mg, 0.040 mmol) were added at room temperature. The mixture was stirred for 30 min with deaeration, and a 2 mol/L aqueous sodium carbonate solution (1.2 mL) and (2-formylphenyl)boronic acid (180 mg, 1.20 mmol) were added. After further stirring at room temperature for 15 min, the mixture was heated to 120 °C over 1 h and further stirred for 16 h. The reaction mixture was cooled to room temperature. Water was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 4:1 to 1:1) to give 218 mg (48%) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.86 (s, 3H), 4.27 (brs, 2H), 6.23 (brs, 1H), 7.09−7.11 (m, 1H), 7.28−7.33 (m, 1H), 7.43 (d, J = 1.2 Hz, 1H), 7.53−7.61 (m, 3H), 7.96−7.99 (m, 1H), 8.49−8.50 (m, 1H), 8.75−8.77 (m, 1H), 9.61−9.62 (m, 1H).

***tert*-Butyl ({5-[2-(Hydroxymethyl)phenyl]-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl}methyl)methylcarbamate (19e).** Compound **19d** (218 mg, 0.48 mmol) was dissolved in tetrahydrofuran (2 mL), and sodium borohydride (24 mg, 0.63 mmol) and methanol (1 mL) were added at 0 °C. After the mixture was stirred at the same temperature for 30 min, water was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane−ethyl acetate, 1:1 to 1:3) to give 132 mg (60%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.46 (s, 9H), 2.10−2.15 (m, 1H), 2.85 (s, 3H), 4.25 (brs, 2H), 4.30−4.38 (m, 2H), 6.12 (d, J = 1.5 Hz, 1H), 6.69−6.72 (m, 1H), 7.13−7.18 (m, 1H), 7.30−7.35 (m, 2H), 7.44−7.49 (m, 1H), 7.59−7.62 (m, 2H), 8.50 (d, J = 2.4 Hz, 1H), 8.76−8.78 (m, 1H).

Compounds **20a−c** were prepared from **19a−c** using a similar procedure as for the preparation of compound **16a**.

1-[5-(4-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine Dihydrochloride (20a). Colorless crystals, mp 184−187 °C (40%). ^{1}H NMR (DMSO-d_6) δ: 2.47−2.51 (m, 3H), 3.97 (t, J = 6.0 Hz, 2H), 6.52−6.53 (m, 1H), 7.15−7.26 (m, 4H), 7.57−7.61 (m, 1H), 7.79−7.85 (m, 2H), 8.00 (d, J = 2.4 Hz, 1H), 8.85−8.87 (m, 1H), 9.22 (br, 2H), 1H not detected. Anal. ($C_{17}H_{18}Cl_2FN_3O_2S{\cdot}H_2O$) C, H, N.

1-[5-(3-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine Hydrochloride (20b). Colorless crystals, mp 206−210 °C (35%). ^{1}H NMR (DMSO-d_6) δ: 2.49−2.51 (m, 3H), 3.97 (s, 2H), 6.57 (d, J = 1.8 Hz, 1H), 6.98−7.02 (m, 2H), 7.27−7.33 (m, 1H), 7.40−7.47 (m, 1H), 7.58−7.62 (m, 1H), 7.80−7.87 (m, 2H), 8.54 (d, J = 2.7 Hz, 1H), 8.86−8.88 (m, 1H), 9.06 (br, 2H). Anal. ($C_{17}H_{17}ClFN_3O_2S$) C, H, N.

1-[5-(2-Chlorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine Dihydrochloride (20c). Colorless crystals, mp 210−214 °C (46%). ^{1}H NMR (DMSO-d_6) δ: 2.50 (br, 3H), 4.01 (t, J = 6.0 Hz, 2H), 5.40 (1H, br), 6.55 (d, J = 2.1 Hz, 1H), 7.13−7.16 (m, 1H), 7.35−7.40 (m, 1H), 7.47−7.51 (m, 2H), 7.61−7.65 (m, 1H), 7.84−7.93 (m, 2H), 8.57 (d, J = 2.1 Hz, 1H), 8.89−8.91 (m, 1H), 9.23 (br, 2H). Anal. ($C_{17}H_{18}Cl_3N_3O_2S\cdot0.5H_2O$) C, H, N.

(2-{4-[(Methylamino)methyl]-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-2-yl}phenyl)methanol Fumarate (20d). Compound **19e** (132 mg, 0.29 mmol) was dissolved in trifluoroacetic acid (1 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was basified with a saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by basic silica gel column chromatography (ethyl acetate−methanol, 1:0 to 9:1) to give 60.3 mg of a free base of the title compound as a colorless oil. A solution of the obtained free base in ethyl acetate (5 mL) was added to a solution of fumaric acid (19.6 mg, 0.17 mmol) in methanol (2 mL), and the mixture was concentrated under reduced pressure. The residue was recrystallized from ethanol to give 48 mg (35%) of the title compound as a colorless crystals, mp 193−196 °C. ^{1}H NMR (DMSO-d_6) δ: 2.42 (s, 3H), 3.83 (s, 2H), 4.00 (s, 2H), 6.35 (d, J = 1.5 Hz, 1H), 6.46 (s, 2H), 6.81−6.83 (m, 1H), 7.17−7.22 (m, 1H), 7.41−7.50 (m, 2H), 7.55−7.60 (m, 1H), 7.65 (s, 1H), 7.75−7.78 (m, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.86 (d, J = 4.8 Hz, 1H), 4H not detected. Anal. ($C_{22}H_{23}N_3O_7S$), C, H, N.

Binding Models. The homology model of the luminal region of H^+,K^+-ATPase was constructed from the crystal structure of Ca^{2+}-ATPase (PDB code 1IWO[26]) by using SCWRL, version 2.9.[27] Compounds **1** and **2** were docked into the cavity affirmed in the H^+,K^+-ATPase model by using GOLD, version 2.1.2.[28]

Proton Potassium Adenosine Triphosphatase (H^+,K^+-ATPase) Inhibitory Activity Test. Accordinpg to the method of Wallmark et al.,[29] a gastric mucosal membrane microsomal fraction was prepared from the stomach of swine. First, the stomach was removed, washed with tap water, and immersed in 3 mol/L brine, and the surface of the mucosal membrane was wiped with a paper towel. The gastric mucosal membrane was detached, chopped, and homogenized in a 0.25 mol/L saccharose solution (pH 6.8) containing 1 mmol/L EDTA and 10 mmol/L tris-hydrochloric acid using polytron (Kinematica). The obtained homogenate was centrifuged at 20000g for 30 min and the supernatant was centrifuged at 100000g for 90 min. The precipitate was suspended in 0.25 mol/L saccharose solution, superimposed on a 0.25 mol/L saccharose solution containing 7.5% Ficoll, and centrifuged at 100000g for 5 h. The fraction containing the interface between the both layers was recovered, and centrifugally washed with 0.25 mol/L saccharose solution. The obtained microsomal fraction was used as a proton, potassium adenosine triphosphatase standard product. To 40 μL of a 50 mmol/L HEPES-Tris buffer (5 mmol/L magnesium chloride, 10 mmol/L potassium chloride, 10 μmol/L valinomycin, pH 6.5) containing 2.5 μg/mL (based on the protein concentration) of the enzyme standard product was added a test compound (5 μL) dissolved in a 10% aqueous dimethyl sulfoxide solution, and the mixture was incubated at 37 °C for 30 min. The enzyme reaction was started by adding 5 μL of a 2 mmol/L adenosine triphosphate Tris salt solution (50 mmol/L HEPES-Tris buffer (5 mmol/L magnesium chloride, pH 6.5)). The enzyme reaction was carried out at 37 °C for 20 min, and 15 μL of a malachite green solution (0.12% malachite green solution in sulfuric acid (2.5 mol/L), 7.5% ammonium molybdate, and 11% Tween 20 were mixed at a ratio of 100:25:2) was added to quench the reaction. After the mixture was allowed to stand at room temperature for 15 min, the resulting reaction product of inorganic phosphorus with malachite green was colorimetrically determined at a wavelength of 610 nm. In addition, the amount of the inorganic phosphoric acid in the reaction solution free of potassium chloride was measured in the same manner, which was subtracted from the inorganic phosphoric acid amount in the presence of potassium chloride to determine the H^+,K^+-ATPase activity. The inhibitory rate (%) was determined from the activity value of the control and the activity values of various concentrations of the test compound, and the 50% inhibitory concentration (IC_{50}) of the H^+,K^+-ATPase activity was determined.

Inhibiton of Histamine-Stimulated Acid Secretion in Anesthetized Rats (iv). Seven-week-old male Jcl:Sprague Dawley (SD) rats were used. The animals were fasted for 24 h but had free access to water before the experiment. The pylorus was ligated after anesthetization with urethane (1.2 g/kg, ip), and the abdomen was closed. Drugs and the vehicle were given intravenously just after the pylorus ligation. Three minutes later, histamine·2HCl (30 mg/kg per 10 mL) was injected subcutaneously. Three hours after histamine administration, the rats were sacrificed by CO_2 asphyxiation and the stomachs were removed. The gastric contents were collected and centrifuged at 3000 rpm for 10 min. The volume of each sample was measured and the acid concentration was determined by automatic titration to pH 7.0 with 0.1 mol/L NaOH (COM-555SC; Hiranuma Sangyo Co., Ltd., Japan), and the total acid output during the 3 h period (μequiv/(3 h)) was calculated.

Histamine-Stimulated Acid Secretion in Heidenhain Pouch Dogs. Drugs and the vehicle were given orally (0.2 mL/kg) to the dogs in a blind manner. Histamine·2HCl (30 μg/kg) was injected subcutaneously 1 day before and 1, 3, 6, 24, and 48 h after drugs and the vehicle administration. The gastric juice from the pouch was collected continuously for three consecutive 30 min periods after each dosing with histamine·2HCl. The volume of gastric juice was measured, and the acid concentration was determined by automatic titration to pH 7.0 with 0.1 mol/L NaOH solution (COM-555SC; Hiranuma Sangyo Co., Ltd., Japan). The total acid output during the 90 min period (μequiv/(90 min)) from each time was calculated and expressed as a percentage of the predosing value measured 1 day before the administration.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Elemental analysis data for compounds **2**, **3**, **13**, **16**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; LLE, ligand-lipophilicity efficiency; LPZ, lansoprazole

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