Bioorganic & Medicinal Chemistry 20 (2012) 3925–3938

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Discovery, synthesis, and biological evaluation of novel pyrrole derivatives as highly selective potassium-competitive acid blockers

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ARTICLE INFO

Article history:
Received 23 February 2012
Revised 5 April 2012
Accepted 6 April 2012
Available online 14 April 2012

Keywords:
Pyrrole
H^+,K^+-ATPase
Potassium-competitive acid blocker

ABSTRACT

To discover a gastric antisecretory agent more potent than existing proton pump inhibitors, novel pyrrole derivatives were synthesized, and their H^+,K^+-ATPase inhibitory activities and inhibitory action on histamine-stimulated gastric acid secretion in rats were evaluated. Among the compounds synthesized, compound **17a** exhibited selective and potent H^+,K^+-ATPase inhibitory activity through reversible and K^+-competitive ionic binding; furthermore, compound **17c** exhibited potent inhibitory action on histamine-stimulated gastric acid secretion in rats and Heidenhain pouch dogs.

1. Introduction

The inhibition of gastric acid secretion is the cornerstone of the treatment of gastroesophageal reflux diseases, peptic ulcer, and other acid-related diseases.[1,2] The development of histamine H_2 receptor antagonists (H_2RAs) in the 1970s represented the first major advancement in the treatment of acid-related diseases. However, H_2RAs have a relatively short duration of action, their effect on meal-stimulated acid secretion is weak, and their antisecretory effect is diminished after repeated administration.[3]

The development of proton pump inhibitors (PPIs) provided effective management for patients with erosive esophagitis, and meta-analysis revealed that PPIs are superior to H_2RAs for the treatment of erosive esophagitis.[4] PPIs have been extensively prescribed in a wide range of acid-related disorders, including non-erosive esophagitis, peptic ulcer, nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal injury, and upper abdominal bleeding. Although the efficacy of PPIs has been established, their efficacy can be improved in terms of acid lability, delayed onset of action, variations of efficacy among patients largely because of CYP2C19 metabolism, and insufficient inhibition of nocturnal acid breakthrough.[5–9] Studies are being performed to develop an acid suppressant for improved therapy. Although several pharmaceutical companies have attempted to develop a new class of acid suppressants, the potassium-competitive acid blockers (P-CABs) that inhibit gastric H^+,K^+-ATPase activity through reversible and K^+-competitive ionic binding (Fig. 1),[10] all agents except revaprazan are not used clinically because of their insufficient efficacy or hepatic toxicity.[11–16]

We performed high-throughput screening (HTS) for H^+,K^+-ATPase inhibitory activity to discover a effective gastric antisecretory agent with novel chemical structure and safe toxicological profile, which led to the discovery of a pyrrole derivative **1** as an inhibitor. The pyrrole derivative **1** showed relatively weak H^+,K^+-ATPase inhibitory activity with an IC_{50} of 540 nM but had a novel and quite unique structure (Fig. 2). We believed that this simple pyrrole derivative with a strong basic moiety has a great potential as an unprecedented gastric antisecretory agent. In this paper, we report the discovery, synthesis, and structure–activity relationships (SAR) of pyrrole derivatives.

2. Chemistry

Synthesis of key intermediates such as **4**, **5a**, **5b,** and **8** was performed as shown in Scheme 1. Condensation of commercially available α-bromoacetophenone **2** with ethyl cyanoacetate gave **3**, which was cyclized under acidic condition to afford **4**, followed by dehalogenation to give pyrrole-3-carboxylic acid ester **5a**. The carboxylic acid **5b** was obtained by alkaline hydrolysis of the ester **5a**. The ester group of **5a** was reduced to hydroxymethyl group

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http://dx.doi.org/10.1016/j.bmc.2012.04.014

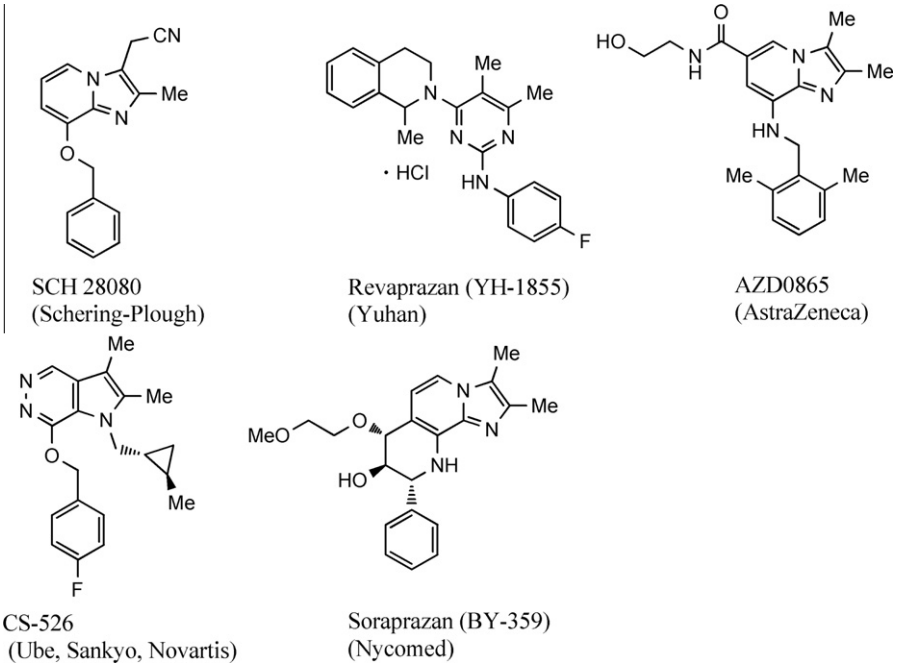

Figure 1. Structures of some reported potassium-competitive acid blockers.

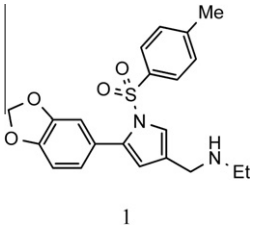

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Figure 2. Discovery of a novel pyrrole derivative.

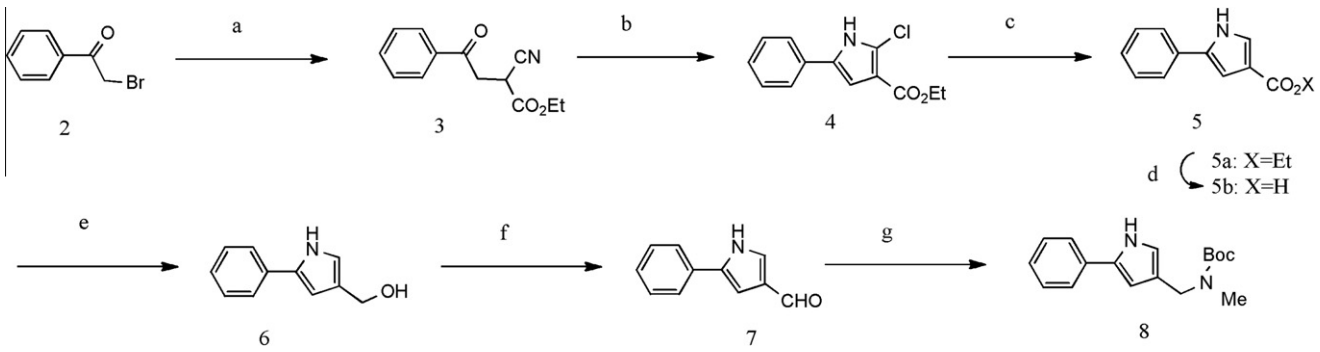
using diisobutylaluminum hydride (DIBAL-H) and then was oxidized using tetra-*n*-propylammonium perruthenate and *N*-methylmorpholine-*N*-oxide to give a formyl compound **7**. The formyl compound **7** thus obtained was converted to **8** by reductive amination and subsequent treatment with $(Boc)_2O$.

Compounds **16** and **17a–h** were synthesized from **5a**, **8,** or **12a** as shown in Scheme 2. Sulfonylation or benzylation of **5a** under basic condition followed by treatment with DIBAL-H afforded the corresponding alcohols **10**, which were then oxidized to formyl compounds **11** using the same method as that used for **7**. The compounds obtained by this reaction were converted by reductive amination to compound **16** and **17a–e** with *N*-ethyl or *N*-methyl methanamine moiety, respectively.

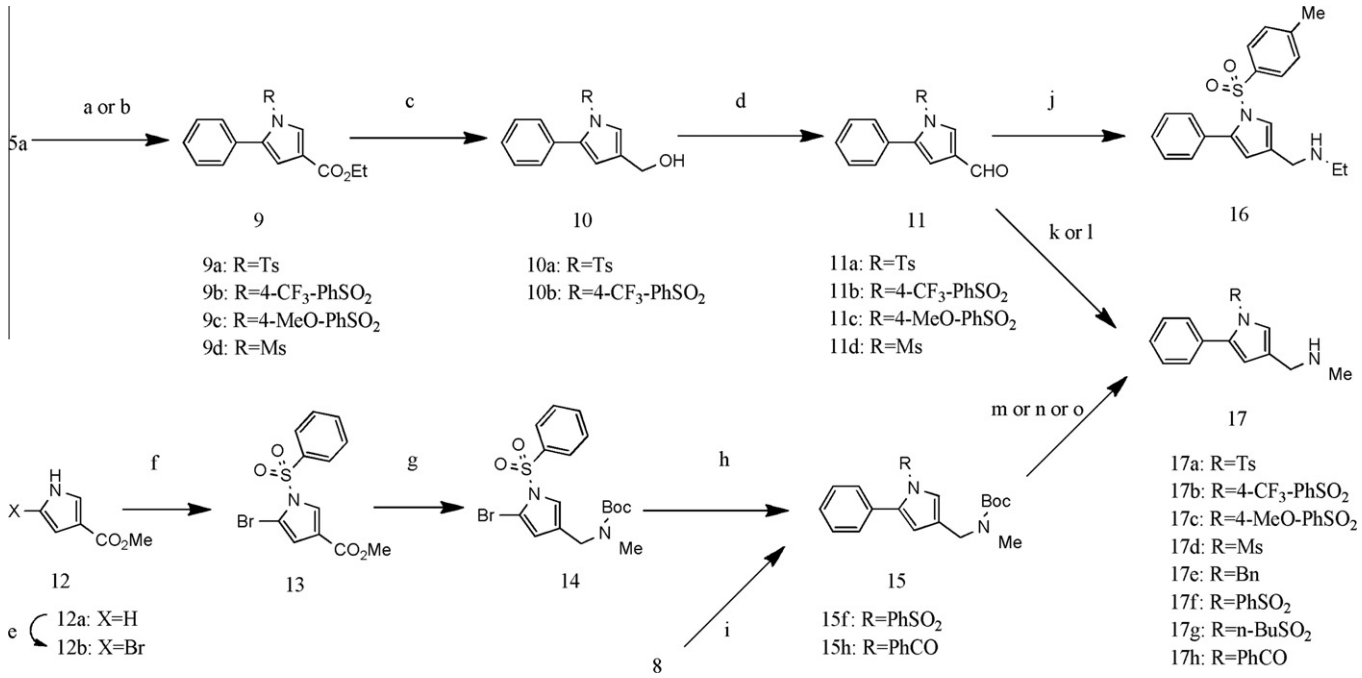
Bromination of commercially available pyrrole derivative **12a** using *N*-bromosuccinimide (NBS) in the presence of pyridine gave **12b**; subsequent treatment with benzenesulfonyl chloride under basic condition gave **13** followed by conversion to **14** using a method similar to that shown in Scheme 1. The compound **14** obtained by this reaction was converted to **15f** by Suzuki–Miyaura coupling reaction using phenylboronic acid, and subsequent treatment with strong acid afforded **17f**.

Sulfonylation or benzoylation of **8** under basic condition followed by deprotection with strong acid yielded **17g** and **17h**, respectively. These compounds were isolated as oxalate or fumarate for their evaluation as a solid.

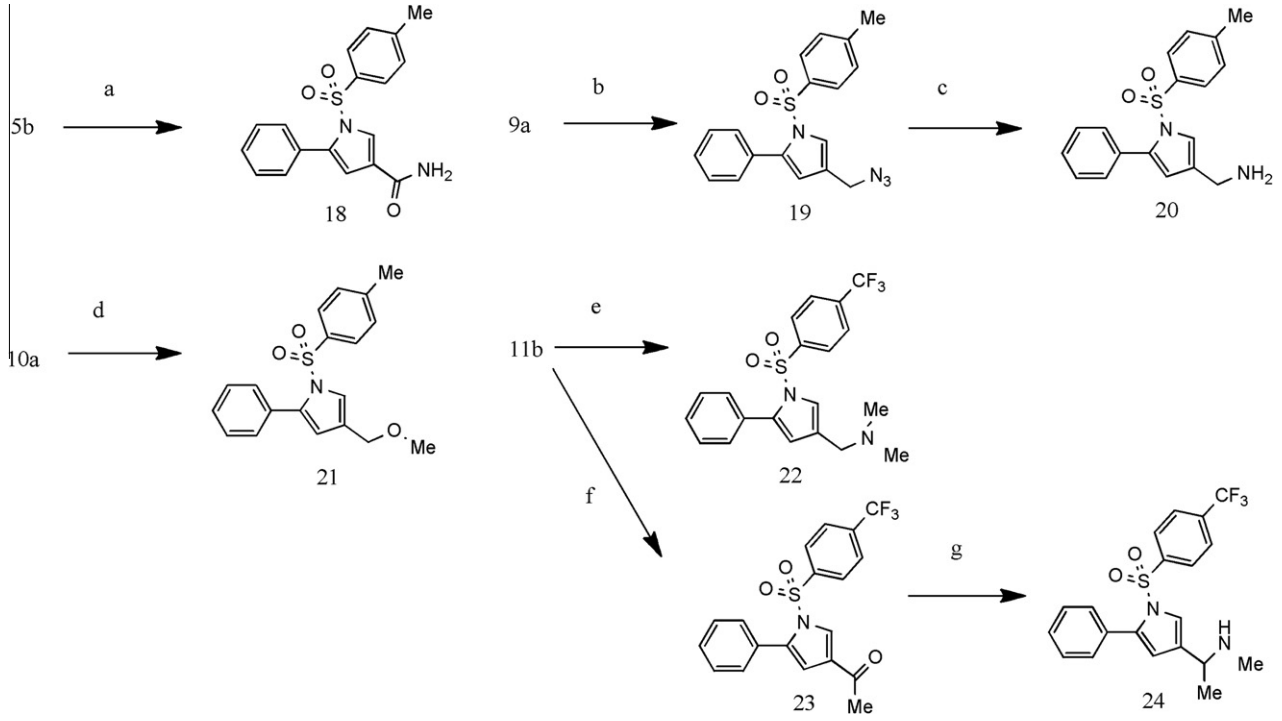
Compounds **18**, **20**, **21**, **22**, and **24** were synthesized from intermediates **5b**, **9a**, **10a** or **11b** as shown in Scheme 3. Reaction of **5b** with 4-toluenesulfonyl chloride (TsCl) followed by addition of ammonia solution at room temperature afforded amide **18**. Reduction of ester **9a** with DIBAL-H provided the corresponding alcohol, and subsequent conversion to azide using the 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and *n*-Bu_4NN_3 system[17] followed by



Scheme 1. Reagents and conditions: (a) ethyl cyanoacetate, K_2CO_3, acetone, rt; (b) HCl (g), THF, rt; (c) H_2, 10% Pd–C, EtOH, rt; (d) 8 N NaOH, MeOH, THF, 55 °C; (e) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C; (f) MNO, TPAP, MS4 Å, MeCN, rt; (g) (1) 40% $MeNH_2$ in MeOH, rt; (2) $NaBH_4$, rt; (3) $(Boc)_2O$, MeCN, rt.



Scheme 2. Reagents and conditions: (a) NaH, RCl, DMF, rt; (b) NaH, BnBr, DMF, rt; (c) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C; (d) MNO, TPAP, MS4 Å, MeCN, rt; (e) NBS, Py, THF, −20 °C; (f) NaH, $PhSO_2Cl$, DMF, rt; (g) (1) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C; (2) MNO, TPAP, MS4 Å, MeCN, rt; (3) $MeNH_2$-HCl, $NaBH_3CN$, MeOH, rt; (4) $(Boc)_2O$, EtOAc, rt; (h) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 105 °C; (i) NaH, 15-crown-5, RCl, DMF, rt; (j) $EtNH_2$-HCl, MS4 Å, $NaBH_3CN$, MeOH, rt; (k) (1) $MeNH_2$-HCl, MS4 Å, $NaBH_3CN$, MeOH, rt; (2) 4 N HCl/EtOAc, EtOAc; (l) (1) 40% $MeNH_2$ in MeOH, MeOH, $NaBH_4$, rt; (2) 4 N HCl/EtOAc, EtOAc; (m) 4 N HCl/EtOAc, EtOAc, rt; (n) (1) 4 N HCl/EtOAc, EtOAc, 60 °C; (2) $(COOH)_2$, EtOAc, Et_2O; (o) (1) 4 N HCl/EtOAc, MeOH, rt; (2) fumaric acid, MeOH, EtOAc.



Scheme 3. Reagents and conditions: (a) (1) NaH, TsCl, DMF, rt; (2) 25% NH_3, rt; (b) (1) DIBAL-H, THF, rt; (2) DDQ, PPh_3, *n*-Bu_4NN_3, CH_2Cl_2, rt; (c) (1) 10% Pd–C, H_2, AcOH, MeOH, rt; (2) 4 N HCl/EtOAc, EtOAc; (d) NaH, MeI, DMF, rt; (e) (1) 2 M Me_2NH/THF, MeOH, rt; (2) $NaBH_4$, rt; (3) 4 N HCl /EtOAc, EtOAc; (f) (1) MeMgBr, THF, ether, 10 °C; (2) MnO_2, CH_2Cl_2, rt; (g) (1) 40% $MeNH_2$ in MeOH, MS4 Å, EtOH, 70 °C; (2) $NaBH_4$, rt; (3) 4 N HCl/EtOAc, EtOAc.

hydrogenation reaction gave primary amine **20**. Methyl ether **21** was obtained by methylation of alcohol **10a** under basic condition.

Reductive amination of **11b** with dimethylamine yielded **22**. Formyl group of **11b** was also converted to acetyl group by using Grignard reaction and subsequent oxidation. The product obtained by this reaction, **23**, was converted to **24** by reductive amination.

Replacements of the phenyl group at 5-position of the pyrrole ring with *n*-butyl and cyclopropyl group were achieved as shown

in Scheme 4. Condensation of **25** with 1-iodobutane followed by cyclization with ethyl acrylate afforded **27**, and subsequent reaction with benzenesulfonyl chloride gave **28**. Suzuki–Miyaura coupling reaction of **13** with cyclopropylboronic acid gave **29**. The esters **28** and **29** thus obtained were converted to **30a** and **30b**, respectively, using a method similar to that shown in Scheme 2.

Introduction of substituents into the pyrrole ring at 2- and 4-positions was achieved as shown in Scheme 5.

Condensation of **2** with ethyl acetoacetate followed by cyclization using ammonium acetate in acetic acid yielded **31**, which was reacted with benzenesulfonyl chloride followed by reduction and subsequent oxidation reaction to give formyl compound **33a**.

Sulfonylation of chlorinated compound **4** under basic condition did not yield **32**, but the addition of 15-crown-5 as an additive gave good yields (81%) of **32**. Then, **32** was converted to **33b** by reduction and subsequent oxidation reaction.

Bromination of commercially available **35** with NBS followed by sulfonylation and Suzuki–Miyaura coupling reaction with boronic acid afforded 4-methylated ester intermediate **38**. Subsequent treatments of **33a**, **33b**, and **38** in a manner similar to that for the transformation of **11** or **9** into **17** yielded the target compounds **34a**, **34b,** and **39**, respectively.

3. Results and discussion

The compounds synthesized were evaluated for their H^+,K^+-ATPase inhibitory activities at pH 6.5 according to their IC_{50} values (in vitro), and some of the compounds were investigated for their inhibitory effects on histamine-induced gastric acid secretion in anesthetized rats (in vivo). In vivo test was performed by intravenous administration of 10 mg/kg or 1 mg/kg of the compound, and the total acid output for 3 h after histamine injection was compared to that obtained after administration of the vehicle. The results of in vitro and in vivo evaluation are shown in Tables 1–3.

Firstly, the 1,3-benzodioxol-5-yl group at the 5-position of pyrrole ring was replaced by a phenyl group to simplify its SAR study (Table 1). The result showed that such a replacement maintained the enzymatic inhibitory potency of **1** (**1**, IC_{50} = 540 nM and **16**, IC_{50} = 650 nM).

Secondly, the effects of basic moiety on the 3-position of the pyrrole ring were carefully investigated because this compound might be characterized as a new type of inhibitor having a strong basic moiety.

Compound **17a** with *N*-methylaminomethyl substituent at 3-position of the pyrrole ring showed much greater in vitro inhibitory activity than compound **16** having *N*-ethylaminomethyl substituent (**16**, IC_{50} = 650 nM and **17a**, IC_{50} = 55 nM). In addition, **17a** showed considerably potent in vivo inhibitory activity (**16**, 53% inhibition at 10 mg/kg, iv and **17a,** 66% inhibition at 1 mg/kg, iv).

On the other hand, the compounds with a non-basic moiety, such as **18** and **21**, showed very low inhibitory activities (IC_{50} >10000 nM). Furthermore, in vitro activities of non-substituted methanamine **20** (IC_{50} = 860 nM), *N,N*-dimethyl methanamine **22** (IC_{50} = 710 nM), and *N*-methyl ethanamine **24** (IC_{50} = 2300 nM) showed significantly weaker activities than those of *N*-methyl methanamine derivatives (**17a** and **17b**) despite their comparable basicity. On the basis of these results, a basic moiety at 3-position of the pyrrole ring was a requisite for the inhibitory activity and substitution of *N*-methyl methanamine was supposed to be the most optimized structure.

Thirdly, we investigated the effects of conversion at 1- and 5-position of the pyrrole ring, and the results are shown in Table 2.

Replacement of *p*-toluenesulfonyl group at 1-position of the pyrrole ring with alkylsulfonyl group (**17d**, IC_{50} >10000 nM and **17g**, IC_{50} = 830 nM) showed low in vitro activities. The compounds having a benzyl group (**17e**, IC_{50} = 510 nM) and a benzoyl group (**17h**, IC_{50} >10000 nM) also had weaker in vitro activities than sulfonyl analogues.

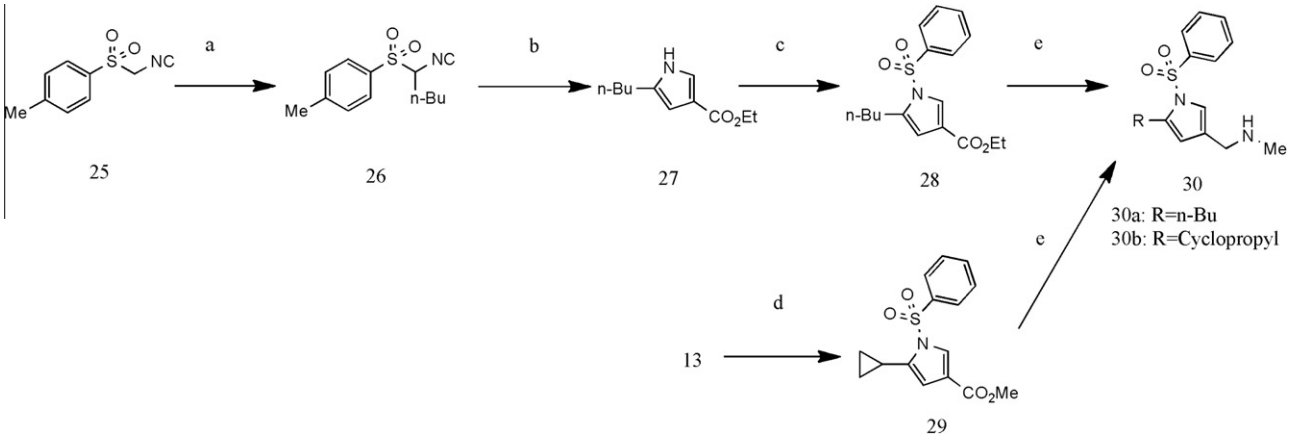
In addition, conversion of phenyl group at 5-position of the pyrrole ring to an alkyl group (**30a**, IC_{50} = 250 nM and **30b**, IC_{50} = 1500 nM) decreased activities.

On the other hand, compounds with a sulfonyl moiety and an aromatic moiety in both 1- and 5-positions, such as **17c** (IC_{50} = 30 nM), showed strong in vitro activity. Especially non-substituted compound (**17f**, IC_{50} = 9.4 nM) on 1-benzenesulfonyl ring had the most potent in vitro activity. We also investigated the effects of a substituent on 1-benzenesulfonyl and 5-phenyl ring, and many compounds showed potent in vitro activities.

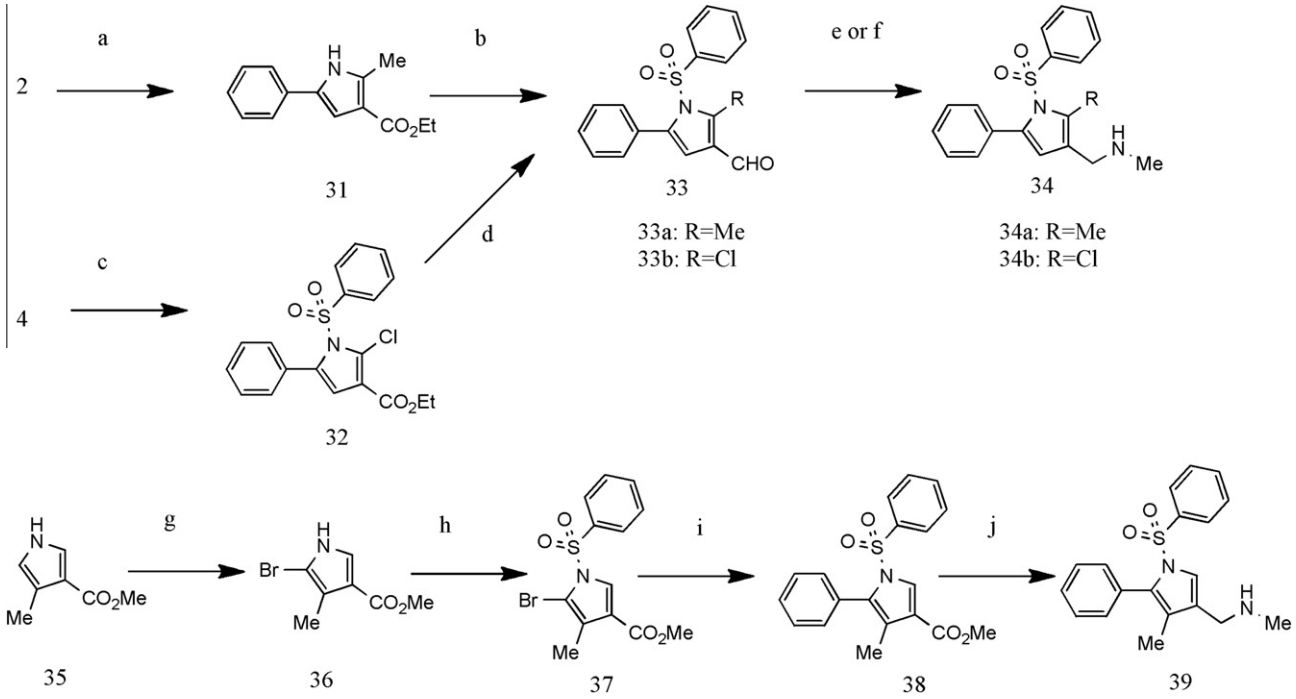
Our results demonstrated that a sulfonyl moiety and an aromatic moiety at 1- and 5-position of the pyrrole ring were very important for their potent H^+,K^+-ATPase inhibitory activities. In fact, compound **17c** and **17f** exhibited excellent inhibition of histamine-stimulated gastric acid secretion in rats (95% and 96% inhibition at 1 mg/kg, iv, respectively) according to their in vitro activities.

Finally, we investigated the effects of substituents at 2- and 4-positions of the pyrrole ring on inhibitory activities, and the results are shown in Table 3.

Compounds **34a** (IC_{50} = 25 nM), **34b** (IC_{50} = 40 nM), and **39** (IC_{50} = 29 nM) retained strong H^+,K^+-ATPase inhibitory activities. However, the non-substituted compound **17f** (IC_{50} = 9.4 nM) had

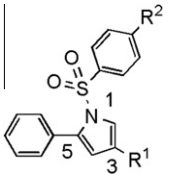


Scheme 4. Reagents and conditions: (a) 1-iodobutane, TBAI, 30% NaOH, CH_2Cl_2, rt; (b) CH_2=$CHCO_2Et$, *t*-BuOK, THF, rt; (c) NaH, $PhSO_2Cl$, THF, rt; (d) cyclopropylboronic acid, $Pd(OAc)_2$, PCy_3, K_3PO_4, H_2O, toluene, 100 °C; (e) (1) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C; (2) TPAP, MNO, MS4 Å, MeCN, rt; (3) 2 M $MeNH_2$ in THF, rt; (4) $NaBH_4$, MeOH, rt; (5) 4 N HCl/EtOAc, EtOAc.



Scheme 5. Reagents and conditions: (a) (1) NaH, $MeCOCH_2CO_2Et$, DMF, rt; (2) $AcONH_4$, AcOH, 80 °C; (b) (1) NaH,$PhSO_2Cl$, DMF, rt; (2) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C; (3) MNO, TPAP, MS4 Å, MeCN, rt; (c) NaH, THF, 15-crown-5, Ph-SO_2Cl, rt; (d) (1) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C; (2) MNO, TPAP, MS4 Å, MeCN, rt; (e) (1) $MeNH_2$-HCl, MS4 Å, $NaBH_3CN$, MeOH, rt; (2) 4 N HCl/EtOAc, EtOAc; (f) (1) 40% $MeNH_2$ in MeOH, MeOH, $NaBH_4$, rt; (2) 4 N HCl/EtOAc, EtOAc; (g) NBS, Py, THF, 5 °C; (h) NaH, $PhSO_2Cl$, DMF, rt; (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 105 °C; (j) (1) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C; (2) MNO, TPAP, MS4 Å, MeCN, rt; (3) $MeNH_2$-HCl, $NaBH_3CN$, MeOH, rt; (4) 4 N HCl/EtOAc, EtOAc.

Table 1
Effects of benzodioxol moiety at 5-position, substituent at 1-position (R^2) and basic moiety at 3-position (R^1) on inhibitory activities



Compound	R^1	R^2	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo acid secretion in rats (1 mg/kg, iv, % inhibition)
1			540	39 (10 mg/kg, iv)[a]
16		Me	650	53 (10 mg/kg, iv)[a]
17a		Me	55	66
18		Me	>10,000	NT[b]
21		Me	>10,000	−3 (10 mg/kg, iv)[a]
20		Me	860	NT[b]
17b		CF_3	110	73
22		CF_3	710	59 (10 mg/kg, iv)[a]
24		CF_3	2300	−4

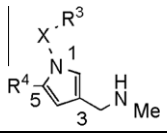
[a] Acid secretion in rats (10 mg/kg, iv, % inhibition).
[b] Not tested.

the most potent in vitro and in vivo activities, and a substituent at 2- or 4-position did not improve the activity.

Because compound **17a** was quite stable in acidic conditions, which was different from that of conventional PPIs, we investigated the mode of action of **17a** for inhibition of gastric H^+,K^+-ATPase activity.

The effect of washout on the inhibition of H^+,K^+-ATPase activity by compound **17a,** and Lineweaver–Burk plots of K^+ concentration

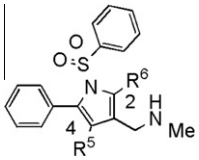
Table 2
Effects of sulfonyl moiety at 1-position (X and R^3) and aromatic moiety at 5-position (R^4) on inhibitory activities



Compound	R^3	X	R^4	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo acid secretion in rats (1 mg/kg, iv, % inhibition)
17a	4-Me-Ph	SO_2	Ph	55	66
17d	Me	SO_2	Ph	>10,000	27 (10 mg/kg, iv)[a]
17g	*n*-Bu	SO_2	Ph	830	NT[b]
17e	Ph	CH_2	Ph	510	84 (10 mg/kg, iv)[a]
17h	Ph	CO	Ph	>10,000	NT[b]
30a	Ph	SO_2	*n*-Bu	250	−8
30b	Ph	SO_2	Cyclopropyl	1500	NT[b]
17c	4-MeO-Ph	SO_2	Ph	30	95
17f	Ph	SO_2	Ph	9.4	96

[a] Acid secretion in rats (10 mg/kg, iv, % inhibition).
[b] Not tested.

Table 3
Effect of substituents (R^5 and R^6) on pyrrole ring on inhibitory activities



Compound	R^5	R^6	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo acid secretion in rats (1 mg/kg, iv, % inhibition)
34a	H	Me	25	77
34b	H	Cl	40	49
39	Me	H	29	95

versus H^+, K^+-ATPase activity in the presence of a various concentration of **17a** are shown in Figures 3 and 4, respectively.

Our results showed that **17a** inhibited gastric H^+,K^+-ATPase activity through reversible and K^+-competitive ionic binding.

We also evaluated the Na^+,K^+-ATPase inhibitory activities of the newly identified potent compounds (**17a**, **17c**, **17f, 34a**, **34b**, and **39**) to examine their selectivity. The IC_{50} values of Na^+,K^+-ATPase inhibitory activities were more than 10000 nM for all these compounds. These compounds showed high selectivity for H^+,K^+-ATPase.

Because compound **17c** showed good physicochemical properties in addition to promising activity, this compound was selected for further investigation of biological activities.

We investigated the effect of compound **17c** on histamine-stimulated gastric acid secretion in Heidenhain pouch dogs by oral administration. We compared the results with those of lansoprazole, a typical PPI (Fig. 5). Compound **17c** completely inhibited gastric acid secretion after oral administration at 1 mg/kg, and its duration of action was longer than that of lansoprazole; a distinct suppression of acid secretion was observed even after 24 h after the administration.

To understand the high potency of compound **17a** as a P-CAB, we constructed a binding model of compound **17a** with H^+,K^+-ATPase and compared its effect with that of SCH 28080,[11] which is a prototype P-CAB. The homology model of the luminal region of H^+,K^+-ATPase was constructed from the crystal structure of Ca^{2+}-ATPase (PDB ID, 1IWO[18]) by using SCWRL ver. 2.9.[19] Each of compound **17a** and SCH 28080 was docked into the cavity affirmed in the H^+,K^+-ATPase model by using GOLD ver. 2.1.2[20] and then the docking model obtained was minimized energetically by Discover3 ver. 98.0 (InsightII, version 2000.1. Accelrys Inc., San Diego, CA, USA). The binding models of each compound with H^+,K^+-ATPase are shown in Figure 6. These binding models indicate that pyrrole derivative **17a** binds to the enzyme in a quite different manner from that of SCH 28080. We assumed that the tosyl group of compound **17a** binds tightly to the space near Tyr928 by π–π interaction with the side chain of Tyr928, and the compound **17a** forms 2 hydrogen bonds with the side chains of both Tyr925 and Tyr928. Further, the phenyl group at 5-position of the pyrrole ring interacts with the side chain of Phe124 with a CH–π interaction. Furthermore, the *N*-methyl methanamine moiety at 3-position of the pyrrole ring forms a hydrogen bond with the main chain of Val331 and

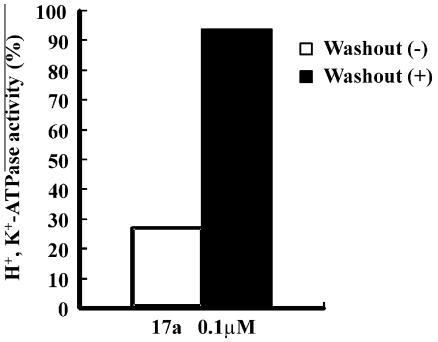


Figure 3. Effect of washout on the inhibition of H^+,K^+-ATPase by compound **17a**. The activity of the H^+,K^+-ATPase was measured with and without washout of compound **17a**. Data with or without washout were expressed as percentage of the H^+,K^+-ATPase activity in control ($n = 2$).

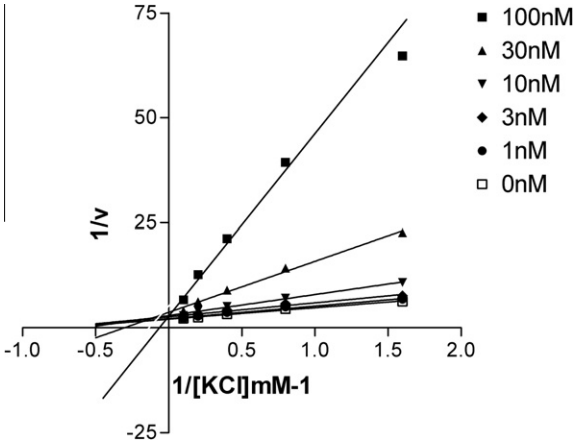


Figure 4. Lineweaver–Burk plots of K^+ concentration versus H^+,K^+-ATPase activity in the presence of a various concentration of **17a**.

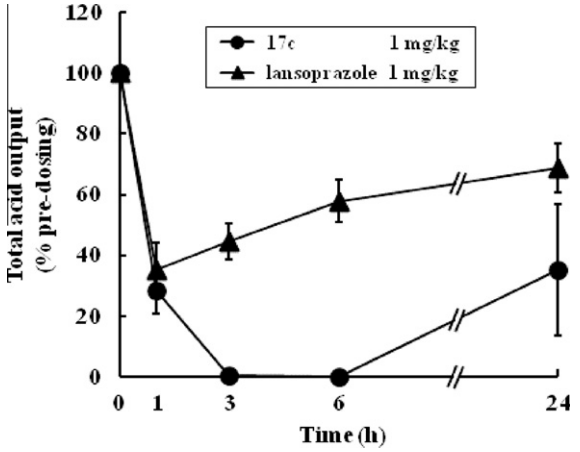


Figure 5. Effects of **17c** and lansoprazole given orally on histamine-stimulated gastric acid secretion in Heidenhain-pouch dogs.

is considered to occupy the predicted cation flow channel quite efficiently. Therefore, the phenylsulfonyl moiety at 1-position, the *N*-methyl methanamine moiety at 3-position, and phenyl moiety at 5-position of the pyrrole ring were assumed to be important for the H^+,K^+-ATPase inhibitory activity. On the other hand, the benzyloxy group of SCH 28080 interacts with Phe124, but π–π interaction around Tyr928 and hydrogen bonds between Tyr925, Tyr928, and Val331 are not observed in the case of SCH 28080.

These findings suggested that our pyrrole derivatives might have a potential of being developed as a new type of P-CAB.

4. Conclusions

In conclusion, we synthesized novel pyrrole derivatives and evaluated their SAR for inhibitory activities on H^+,K^+-ATPase in vitro and in vivo using an acid secretion model in rats. Our results showed that *N*-methyl methanamine moiety at 3-position on the pyrrole ring was the most suitable and two aromatic moieties at 1- and 5-positions on pyrrole ring were very important for potent H^+,K^+-ATPase inhibitory activities of these pyrrole derivatives.

Among the compounds synthesized, compound **17a** exhibited selective and potent H^+,K^+-ATPase inhibitory activity as a P-CAB, and compound **17c** exhibited potent inhibitory actions on histamine-stimulated gastric acid secretion in rats and Heidenhain pouch dogs.

Further investigation followed by optimization of the drug metabolism and other pharmacokinetic profile based on **17c** may lead to the development of a new type of P-CAB having long duration of action in humans.

5. Experimental section

Melting points were determined on a Yanagimoto micro melting point apparatus or Büche B-545 and were not corrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-200, a Varian Mercury-300, a Jeol JNM-AL400 or a Bruker AV-300 M spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra (HRMS) experiments were carried out by Takeda Analytical Laboratories, Ltd. All MS experiments were performed using electrospray ionization (ESI) in positive or negative ion mode. Elemental analyses were also obtained from Takeda Analytical Laboratories, LTD. TLC analyses were carried out on Merck Kieselgel 60 F_{254} 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, Fuji Silysia Chemical Ltd 100–200 mesh Chromatorex NH silica DM1020 or Purif-Pack (SI 60 lM or NH 60lM, Fujisilysia, Ltd). Commercial reagents and solvents were used without additional purification.

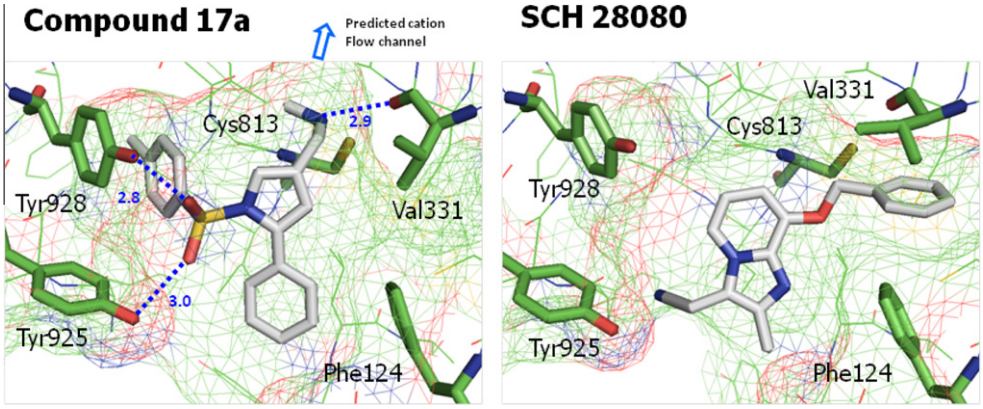


Figure 6. Binding models of compound **17a** and SCH 28080 with H^+,K^+-ATPase. Several residues near compound **17a** are shown in stick representations. Three hydrogen bonds between compound **17a** and H^+,K^+-ATPase are shown in blue dash lines. The distances (Å) between heavy atoms participating in these hydrogen bonds are also described in blue letters. The predicted cation flow channel is indicated by the blue arrow.

5.1. Ethyl 2-cyano-4-oxo-4-phenylbutanoate (3)

Potassium carbonate (13.8 g, 99.8 mmol) was added to ethyl cyanoacetate (37 mL, 348 mmol), and the mixture was stirred at 40 °C for 45 min. A solution of **2** (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 EtOAc. The extract was washed with brine, dried over Na_2SO_4, 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/EtOAc = 8/1–1/1) to give **3** (10.4 g, 90%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ: 1.35 (3H, t, J = 7.2 Hz), 3.55 (1H, dd, J = 16.0, 5.6 Hz), 3.80 (1H, dd, J = 16.0, 7.0 Hz), 4.16 (1H, dd, J = 7.0, 5.6 Hz), 4.31 (2H, q, J = 7.2 Hz), 7.40–7.70 (3H, m), 7.90–8.00 (2H, m).

5.2. Ethyl 2-chloro-5-phenyl-1*H*-pyrrole-3-carboxylate (4)

HCl gas (28 g) was bubbled through a solution of **3** (5.0 g, 21.6 mmol) in THF (60 mL) under ice-cooling, and the mixture was stirred at room temperature for 3 h. Then, N_2 gas was introduced to substitute HCl gas and then the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6/1) to give **4** (4.24 g, 79%) as a solid: ^{1}H NMR ($CDCl_3$) δ: 1.37 (3H, t, J = 6.8 Hz), 4.33 (2H, q, J = 6.8 Hz), 6.87 (1H, d, J = 3.2 Hz), 7.20–7.60 (5H, m), 8.79 (1H, br).

5.3. Ethyl 5-phenyl-1*H*-pyrrole-3-carboxylate (5a)

To a solution of **4** (8.5 g, 34.0 mmol) in EtOH (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/EtOAc = 9/1–1/1) to give **5a** (4.50 g, 62%) as colorless crystals: mp 148–150 °C; ^{1}H NMR ($CDCl_3$) δ: 1.36 (3H, t, J = 7.2 Hz), 4.31 (2H, q, J = 7.2 Hz), 6.91 (1H, m), 7.20–7.70 (6H, m), 8.77 (1H, br).

5.4. 5-Phenyl-1*H*-pyrrole-3-carboxylic acid (5b)

To a solution of **5a** (700 mg, 3.25 mmol) in MeOH (30 mL) and THF (30 mL) was added dropwise 1 N NaOH (30 mL), and the mixture was stirred at 60 °C for 2 h. To this mixture was added dropwise 8 N NaOH (30 mL) at 55 °C, and then the mixture was stirred overnight at 55 °C. The mixture was concentrated under reduced pressure to half volume at 60 °C, and then acidified with 6 N HCl. The resulting insoluble product was collected by filtration and rinsed with H_2O to give **5b** (462 mg, 76%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ: 6.83 (m, 1H), 7.10–7.27 (m, 1H,), 7.31–7.49 (m, 3H), 7.54–7.84 (m, 2H), 11.84 (br, 2H).

5.5. (5-Phenyl-1*H*-pyrrol-3-yl)methanol (6)

To a solution of **5a** (2.16 g, 10.0 mmol) in THF (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 **6** (1.51 g, 87%) as a solid. ^{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).

5.6. 5-Phenyl-1*H*-pyrrole-3-carbaldehyde (7)

To a solution of **6** (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 molecular sieves 4 Å powder (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/EtOAc = 4/1–1/1) to give **7** (0.92 g, 62%) as pale yellow crystals: mp 137–139 °C; ^{1}H NMR ($CDCl_3$) δ: 6.95 (1H, m), 7.29–7.32 (1H, m), 7.40–7.44 (2H, m), 7.50–7.52 (3H, m), 9.02 (1H, br), 9.84 (1H, s).

5.7. *tert*-Butyl methyl[(5-phenyl-1*H*-pyrrol-3-yl)methyl]-carbamate (8)

To a solution of **7** (0.92 g, 5.37 mmol) in MeOH (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 EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in acetonitrile (48 mL), and di-*tert*-butyl bicarbonate (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 EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1–4/1) to give **8** (0.99 g, 64%) as colorless crystals: mp 100–102 °C; ^{1}H NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.84 (3H, s), 4.30 (2H, s), 6.45 (1H, s), 6.75 (1H, s), 7.18–7.22 (1H, m), 7.34–7.38 (2H, m), 7.44–7.46 (2H, m), 8.37 (1H, br).

5.8. Ethyl 1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carboxylate (9a)

Sodium hydride (60% in oil, 408 mg, 10.2 mmol) was suspended in DMF (5 mL). To the suspension was added a solution of **5a** (2.0 g, 9.3 mmol) in DMF (5 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. A solution of 4-methylbenzenesulfonyl chloride (1.94 g, 10.2 mmol) in DMF (5 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 1 h. Water was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6/1–1/1) to give **9a** (2.90 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.36 (3H, t, J = 7.2 Hz), 2.36 (3H, s), 4.31 (2H, q, J = 7.2 Hz), 6.52 (1H, d, J = 1.8 Hz), 7.05–7.40 (9H, m), 8.07 (1H, d, J = 1.8 Hz).

Compounds **9b**–**d** were prepared from **5a** in a manner similar to that described for compound **9a**.

5.9. Ethyl 5-phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrole-3-carboxylate (9b)

A colorless oil (77%): ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J = 7.1 Hz), 3.80 (2H, q, J = 7.1 Hz), 6.56 (1H, d, J = 2.0 Hz), 7.16 (2H, d, J = 7.3 Hz), 7.29–7.41 (3H, m), 7.44 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.6 Hz), 8.09 (2H, d, J = 2.0 Hz).

5.10. Ethyl 1-[(4-methoxyphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carboxylate (9c)

A colorless oil (97%): ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.4 Hz), 3.82 (3H, s), 4.30 (2H, q, J = 7.4 Hz), 6.51 (1H, d, J = 1.8 Hz), 6.74 (2H, d, J = 9.0 Hz), 7.15–7.40 (7H, m), 8.07 (1H, d, J = 1.8 Hz).

5.11. Ethyl 1-(methylsulfonyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (9d)

Colorless crystals (57%): mp 125–126 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J = 6.8 Hz), 2.91 (3H, s), 4.31 (2H, q, J = 6.8 Hz), 6.69 (1H, d, J = 2.2 Hz), 7.20–7.55 (5H, m), 7.92 (1H, d, J = 2.2 Hz).

5.12. {1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}-methanol (10a)

To a solution of **9a** (2.85 g, 7.7 mmol) in THF (30 mL) was added dropwise a 1.5 mol/L solution of diisobutylaluminum hydride in toluene (12.8 mL, 19.3 mmol) at −78 °C over 30 min. The mixture was further stirred at −78 °C for 1 h, 1 N HCl (20 mL) was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc = 6/1–1/1) to give **10a** (2.29 g, 91%) as a pale-brown oil: ^{1}H NMR ($CDCl_3$) δ: 2.35 (3H, s), 4.55 (2H, d, J = 4.8 Hz), 6.19 (1H, d, J = 2.2 Hz), 7.09 (2H, d, J = 8.4 Hz), 7.15–7.45 (8H, m).

5.13. (5-Phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrol-3-yl)methanol (10b)

Compound **10b** was prepared from **9b** using a similar procedure as for the preparation of compound **10a**. A pale red solid (88%): ^{1}H NMR ($CDCl_3$) δ: 4.58 (2H, s), 6.23 (1H, d, J = 1.7 Hz), 7.19–7.22 (2H, m), 7.29–7.33 (2H, m), 7.37–7.43 (2H, m), 7.45 (2H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.3 Hz).

5.14. 1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carbaldehyde (11a)

To a solution of **10a** (1.50 g, 4.6 mmol) in acetonitrile (10 mL) were added tetra-*n*-propylammonium perruthenate (150 mg, 0.43 mmol), *N*-methylmorpholine *N*-oxide (932 mg, 6.9 mmol) and molecular sieves 4 Å powder (1.5 g), and the mixture was stirred at room temperature for 1 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/EtOAc = 6/1–1/1) to give **11a** (1.23 g, 82%) as a pale-brown oil: ^{1}H NMR ($CDCl_3$) δ: 2.37 (3H, s), 6.55 (1H, d, J = 2.2 Hz), 7.05–7.50 (9H, m), 8.10 (1H, d, J = 2.2 Hz).

5.15. 5-Phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrole-3-carbaldehyde (11b)

Compound **11b** was prepared from **10b** in a manner similar to that described for compound **11a**. A colorless solid (68%): ^{1}H NMR ($CDCl_3$) δ 6.60 (1H, d, J = 1.7 Hz), 7.13–7.16 (2H, m), 7.29–7.33 (2H, m), 7.41–7.45 (3H, m), 7.58 (2H, d, J = 8.6 Hz), 8.12 (1H, d, J = 2.0 Hz), 9.90 (1H, s).

5.16. 1-[(4-Methoxyphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carbaldehyde (11c)

Compound **11c** was prepared from **9c** in a manner similar to that described for compound **10a** and **11a**. A pale red oil (65%): ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 6.55 (1H, d, J = 1.8 Hz), 6.74 (2H, d, J = 8.8 Hz), 7.15–7.45 (7H, m), 8.10 (1H, d, J = 1.8 Hz), 9.87 (1H, s)

5.17. 1-(Methylsulfonyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (11d)

Compound **11d** was prepared from **9d** in a manner similar to that described for compound **10a** and **11a**. A colorless solid (51%): ^{1}H NMR ($CDCl_3$) δ 2.95 (3H, s), 6.73 (1H, d, J = 1.8 Hz), 7.40–7.60 (5H, m), 7.96 (1H, d, J = 1.8 Hz), 9.89 (1H, s).

5.18. Methyl 5-bromo-1*H*-pyrrole-3-carboxylate (12b)

A solution of methyl 1*H*-pyrrole-3-carboxylate (4.48 g, 35.8 mmol) in THF (70 mL) was cooled to −78 °C, *N*-bromosuccinimide (6.30 g, 35.4 mmol) was added, pyridine (five drops) was added, and the mixture was left standing in a freezer (−20 °C) for 3 days. The reaction mixture was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc = 9/1–1/1) to give **12b** (3.59 g, 49%) as a pale-yellow solid: ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 6.58 (1H, m), 7.36 (1H, m), 8.60 (1H, br s).

5.19. Methyl 5-bromo-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (13)

Sodium hydride (60% in oil, 1.11 g, 27.8 mmol) was washed with hexane, and suspended to DMF (50 mL). To the suspension was slowly added a solution of **12b** (5.06 g, 24.8 mmol) in DMF (10 mL) at 0 °C. After stirring at room temperature for 30 min, a solution of benzenesulfonyl chloride (3.3 mL, 25.8 mmol) in DMF (5 mL) was added at 0 °C, and the mixture was stirred at room temperature for 30 min, poured into ice water and extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1–1/1) to give **13** (8.46 g, 99%) as crystals: mp 70–72 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (3H, s), 6.68 (1H, d, J = 2.1 Hz), 7.55–7.60 (2H, m), 7.67–7.72 (1H, m), 7.96–7.99 (2H, m), 8.08 (1H, d, J = 2.1 Hz).

5.20. *tert*-Butyl {[5-bromo-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-methyl} methylcarbamate (14)

Compound **14** was prepared from **13** in a manner similar to that described for compounds **6, 7** and **8**. A colorless solid (51%): ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.79 (3H, br s), 4.17 (2H, br s), 6.24 (1H, br s), 7.35 (1H, br s), 7.51–7.57 (2H, m), 7.62–7.68 (1H, m), 7.90–7.94 (2H, s).

5.21. *tert*-Butyl methyl{[5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methyl} carbamate (15f)

A mixture of **14** (1.04 g, 2.42 mmol), phenylboronic acid (448.2 mg, 3.68 mmol), Na_2CO_3 (770.8 mg, 7.27 mmol) and tetrakis (triphenylphosphine) palladium (421.1 mg, 0.36 mmol) in DME (25 mL) and H_2O (25 mL) was stirred at 105 °C for 12 h under Ar_2 atmosphere. After cooling, a solution of $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, water, brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give **15f** (0.97 g, 94%) as crystals: mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 2.80 (3H, br s), 4.22 (2H, br s),

6.09 (1H, br s), 7.19–7.23 (2H, m), 7.26–7.38 (8H, m), 7.47–7.53 (1H, m).

5.22. *tert*-Butyl [(1-benzoyl-5-phenyl-1*H*-pyrrol-3-yl)methyl]-methylcarbamate (15h)

To a suspension of NaH (60% in oil, 97 mg) in THF (10 mL) was added a solution of **8** (483 mg, 1.69 mmol), 15-crown-5 (447 mg) and BzCl (261 mg) at 0 °C. The mixture was stirred at room temperature for 1 h, diluted with H_2O, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 9/1–4/1) to give **15h** (210 mg, 32%) as a pale red oil: ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.85 (3H, s), 4.26 (2H, s), 6.37 (1H, s), 6.96 (1H, s), 7.18–7.28 (5H, m), 7.37–7.42 (2H, m), 7.51–7.56 (1H, m), 7.74–7.77 (2H, m).

5.23. *N*-({1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methyl) ethanamine (16)

Compound **11a** (300 mg, 0.92 mmol) was dissolved in methanol (30 mL), and molecular sieves 4 Å powder (600 mg), ethylamine hydrochloride (376 mg, 4.61 mmol) and sodium cyano borohydride (69 mg, 1.10 mmol) were added to the mixture. The reaction mixture was stirred at room temperature for 1 h. The mixture was filtered with Celite and the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 6/1–1/1) to give **16** (50 mg, 15%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.13 (3H, t, J = 7.0 Hz), 2.35 (3H, s), 2.68 (2H, q, J = 7.0 Hz), 3.64 (2H, s), 6.15 (1H, d, J = 1.8 Hz), 7.08 (2H, d, J = 8.2 Hz), 7.20–7.40 (9H, m); HRMS (ESI) calcd for $C_{20}H_{22}N_2O_2S$ $(M+H)^+$ m/z 355.1475, found m/z 355.1440.

5.24. *N*-Methyl-1-{1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methanamine hydrochloride (17a)

Free base of compound **17a** was prepared from **11a** and methyl ammonium chloride using a similar procedure as for the preparation of compound **16**. A brown oil (7%): ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s), 2.44 (3H, s), 3.59 (2H, s), 6.13 (1H, d, J = 1.8 Hz), 7.08 (2H, d, J = 8.0 Hz), 7.20–7.40 (9H, m).

Obtained free base of **17a** (213 mg, 242 mg) was dissolved in EtOAc (5 mL each). A 4 N HCl/EtOAc solution (0.3 mL each) was added, and the each mixture was stirred at room temperature for 15 min. After combined, the resulting mixture was concentrated under reduced pressure. The residue was crystallized from EtOAc to give **17a** (428 mg, 85%) as a pale red solid: ^{1}H NMR (DMSO-d_6) δ 2.35 (3H, s), 2.50 (3H, s), 3.97 (2H, s), 6.43 (1H, d, J = 1.8 Hz), 7.13–7.43 (9H, m), 7.70 (1H, s), 8.98 (2H, br s); Anal. Calcd for $C_{19}H_{21}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43. Found: C, 60.44; H, 5.72; N, 7.26.

5.25. *N*-Methyl-1-(5-phenyl-1-{[4-(trifluoromethyl)phenyl]-sulfonyl}-1*H*-pyrrol-3-yl)methanamine hydrochloride (17b)

Compound **11b** (65 mg) was dissolved in MeOH (5 mL). 40% methylamine methanol solution (50 mg) was added at room temperature and the mixture was stirred for 15 min. To the reaction mixture was added sodium borohydride (24 mg) at room temperature and the mixture was stirred for 10 min 1 N HCl (5 mL) was added, and the mixture was stirred for 5 min. The mixture was basified with a saturated aqueous sodium hydrogen carbonate and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 4:1 to EtOAc) and the obtained oil was dissolved in ethyl acetate (5 mL). 4 N HCl/EtOAc (1 mL) was added and the mixture was concentrated under reduced pressure. The residue was crystallized from EtOAc to give **17b** (50 mg, 68%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 2.50–2.51 (3H, m), 3.99 (2H, s), 6.48 (1H, s), 7.13–7.15 (2H, m), 7.35–7.38 (2H, m), 7.42–7.46 (1H, m), 7.61 (2H, d, J = 8.3 Hz), 7.78–7.78 (1H, m), 7.92 (2H, d, J = 8.5 Hz), 9.03 (2H, br); HRMS (ESI) calcd for $C_{19}H_{17}F_3N_2O_2S$ $(M+H)^+$ m/z 395.1036, found m/z 395.1012.

5.26. 1-{1-[(4-Methoxyphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (17c)

Compound **17c** was prepared from **11c** using a similar procedure as for the preparation of compound **17a**. Pale red crystals (54%): mp 185–188 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (3H, s), 3.80 (3H, s), 3.98 (2H, s), 6.45 (1H, d, J = 2.2 Hz), 6.74 (2H, d, J = 7.0 Hz), 7.10–7.40 (7H, m), 7.64 (1H, d, J = 2.2 Hz), 9.82 (2H, br); Anal. Calcd for $C_{19}H_{21}ClN_2O_3S$: C, 58.08; H, 5.39; N, 7.13. Found: C, 58.13; H, 5.49; N, 6.78.

5.27. *N*-Methyl-1-[1-(methylsulfonyl)-5-phenyl-1*H*-pyrrol-3-yl]methanamine hydrochloride (17d)

Compound 1**7d** was prepared from **11d** using a similar procedure as for the preparation of compound **17a**. Colorless crystals (55%): mp 183–185 °C; ^{1}H NMR (DMSO-d_6) δ 2.54 (3H, s), 3.22 (3H, s), 4.00 (2H, s), 6.53 (1H, m), 7.45 (5H, m), 7.51 (1H, m), 9.09 (2H, br); Anal. Calcd for $C_{13}H_{17}ClN_2O_2S$: C, 51.91; H, 5.70; N, 9.31. Found: C, 51.91; H, 5.62; N, 9.13.

5.28. 1-(1-Benzyl-5-phenyl-1*H*-pyrrol-3-yl)-*N*-methylmethanamine (17e)

Compound 1**7e** was prepared from **5a** using a similar procedure as for the preparation of compounds **9a** (benzyl bromide was used instead of TsCl), **10a**, **11a** and **16** (methyl ammonium chloride was used instead of ethyl ammonium chloride). A colorless oil (34%): ^{1}H NMR ($CDCl_3$) δ 2.49 (3H, s), 3.65 (2H, s), 5.09 (2H, s), 6.23 (1H, d, J = 2.1 Hz), 6.66 (1H, d, J = 2.1 Hz), 7.02 (2H, d, J = 6.3 Hz), 7.20–7.40 (8H, m); HRMS (ESI) calcd for $C_{19}H_{20}N_2$ $(M+H)^+$ m/z 277.1699, found m/z 277.1670.

5.29. *N*-Methyl-1-[5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-methanamine hydrochloride (17f)

To a solution of **15f** (637 mg, 1.49 mmol) in MeOH (10 mL) was added 4 N HCl/EtOAc (4 mL), the mixture was stirred at room temperature for 3 h. The mixture was treated with active carbon, filtrated and the filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOH to give **17f** (394 mg, 73%) as crystals: mp 229–231 °C; ^{1}H NMR ($CDCl_3$) δ 2.55 (3H, s), 3.98 (1H, s), 6.47 (1H, d, J = 1.8 Hz), 7.12–7.15 (2H, m), 7.23–7.37 (7H, m), 7.47–7.53 (1H, m), 7.65 (1H, d, J = 1.8 Hz), 9.83 (2H, br s); Anal. Calcd for $C_{18}H_{19}ClN_2O_2S$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.40; H, 5.29; N, 7.61.

5.30. 1-[1-(Butylsulfonyl)-5-phenyl-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hemi oxalate (17g)

To a solution of **8** (70 mg, 0.244 mmol) in DMF (7 mL) was added sodium hydride (60% in oil, 98 mg) at room temperature

and the mixture was stirred at room temperature for 30 min. Butane-1-sulfonyl chloride (230 mg) was added, and the resulting mixture was stirred over night, poured into H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1–4:1) and the resulting oil was dissolved in MeOH (5 mL) and 4 N HCl/EtOAc (1 mL) was added. The mixture was stirred at 60 °C for 20 min, concentrated under reduced pressure, basified with a solution of $NaHCO_3$, and extracted with EtOAc. Oxalic acid (10 mg) was added to the extract, and the mixture was concentrated under reduced pressure. The residue was crystallized from Et_2O/EtOAc to give **17g** (17.9 mg, 21%) as a pale violet solid: ^{1}H NMR (DMSO-d_6) δ 0.75 (3H, t, J = 7.2 Hz), 1.14–1.38 (4H, m), 2.56 (3H, s), 3.21 (2H, t, J = 7.2 Hz), 4.01 (2H, s), 6.48 (1H, s), 7.44 (5H, br), 7.48 (1H, s); HRMS (ESI) calcd for $C_{16}H_{22}N_2O_2S$ $(M+H)^+$ m/z 307.1475, found m/z 307.1446.

5.31. {4-[(Methylamino)methyl]-2-phenyl-1*H*-pyrrol-1-yl}-(phenyl)methanone fumarate (17h)

To a solution of **15h** in EtOAc (2 mL) and MeOH (1 mL) was added dropwise 4 N HCl/EtOAc (2 mL) at room temperature. After stirring for 4 h at room temperature, the mixture was concentrated under reduced pressure. The residue was basified with a Na_2CO_3 solution, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 3/1–1/3) and the obtained oil was dissolved in EtOAc (5 mL). To this solution was added a solution of fumaric acid (37 mg) in MeOH (2 mL), and the mixture was concentrated under reduced pressure. The residue was crystallized with EtOH to give **17h** (66 mg, 30%) as a pale red solid: ^{1}H NMR (DMSO-d_6) δ 2.47 (3H, s), 3.86 (2H, s), 6.43 (2H, s), 6.60–6.61 (1H, m), 7.20–7.32 (6H, m), 7.51–7.56 (2H, m), 7.65–7.67 (1H, m), 7.77–7.78 (2H, m); Anal. Calcd for $C_{13}H_{17}ClN_2O_2S$ 0.5EtOH: C, 67.12; H, 5.87; N, 6.52. Found: C, 67.04; H, 5.55; N, 6.67.

5.32. 1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carboxamide (18)

To a solution of **5b** (200 mg, 1.07 mmol) in DMF (5 mL) was added NaH (60% in oil, 107 mg) at 0 °C. The mixture was stirred at room temperature, and tosyl chloride (448 mg, 2.35 mmol) was added. After stirring at room temperature for 1 h, 25% NH_3 solution (1 mL) was added, and the mixture was stirred at room temperature for 1 h. After dilution with H_2O, the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1–1:1) and crystallized from hexane/iPr_2O to give **18** (32 mg, 9%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 5.64 (2H, br), 6.40 (1H, d, J = 2.2 Hz), 7.05–7.45 (9H, m), 7.98 (1H, d, J = 2.2 Hz); Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.38; H, 4.74; N, 8.15.

5.33. 4-(Azidomethyl)-1-[(4-methylphenyl)sulfonyl]-2-phenyl-1*H*-pyrrole (19)

To a solution of **9a** (500 mg, 1.35 mmol) in THF (10 mL) was added dropwise 1.5 M DIBAL-H in toluene (2.70 mL, 4.06 mmol) at −78 °C, and the mixture was stirred at room temperature for 30 min. 1 N HCl (6 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 15 min and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. A solution of the residue in CH_2Cl_2 (2 mL) was added to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (612 mg, 2.7 mmol), triphenylphosphine (532 mg, 2.03 mmol) and tetra-*n*-butylammoniumazide (768 mg, 2.7 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1–1/1) to give **19** (233 mg, 49%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s), 4.48 (2H, s), 6.19 (1H, d, J = 2.2 Hz), 7.09 (2H, d, J = 8.6 Hz), 7.15–7.40 (8H, m), 7.46 (1H, d, J = 2.2 Hz).

5.34. 1-{1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methanamine hydrochloride (20)

To a solution of **19** (230 mg, 0.563 mmol) in MeOH (10 mL) was added 10% palladium carbon (50% water-containing product, 150 mg), and the mixture was stirred under H_2 atmosphere at room temperature for 18 h. To the reaction mixture was added acetic acid (1 mL), and the mixture was stirred under a H_2 atmosphere at room temperature for 18 h. The reaction mixture was filtrated, and a solution of $NaHCO_3$ was added to the filtrate, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 9/1 to EtOAc), and the obtained oil was dissolved in EtOAc (5 mL), 4 N HCl/EtOAc (0.5 mL) was added, and the mixture was concentrated under reduced pressure. The residue was crystallized from EtOAc to give **20** (10 mg, 4%) as colorless crystals: mp 198–201 °C; ^{1}H NMR (DMSO-d_6) δ 2.35 (3H, s), 3.89 (2H, s), 6.39 (1H, d, J = 1.8 Hz), 7.10–7.20 (2H, m), 7.22–7.50 (7H, m), 7.66 (1H, d, J = 1.8 Hz), 8.20 (3H, br); Anal. Calcd for $C_{18}H_{19}ClN_2O_2S$ 0.25H_2O: C, 58.85; H, 5.35; N, 7.63. Found: C, 58.61; H, 5.45; N, 7.36.

5.35. 4-(Methoxymethyl)-1-[(4-methylphenyl)sulfonyl]-2-phenyl-1*H*-pyrrole (21)

To a solution of **10a** (200 mg, 0.61 mmol) in DMF (1 mL) was added NaH (60% in oil, 37 mg, 0.92 mmol) and MeI (57 μL, 0.92 mmol) at 0 °C. After being stirred at room temperature for 1 h, 1 N HCl (5 mL) was added to the mixture. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1–1:1) to give **21** (105 mg, 50%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s), 3.36 (3H, s), 4.30 (2H, s), 6.16 (1H, d, J = 1.8 Hz), 7.06–7.40 (10H, m); HRMS (ESI) calcd for $C_{19}H_{19}NO_3S$ $(M+H)^+$ m/z 342.1158, found m/z 342.1141.

5.36. *N*,*N*-Dimethyl-1-(5-phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrol-3-yl) methanamine hydrochloride (22)

Using **11b** (80 mg), 2 M dimethylamine in THF solution (1 mL) and sodium borohydride (24 mg), a similar procedure as the preparation of compound **17b** was performed to give **22** (59 mg, 63%) as colorless crystals: mp 185–188 °C; ^{1}H NMR (DMSO-d_6) δ 2.67 (6H, s), 4.12 (2H, s), 6.56–6.56 (1H, m), 7.15–7.17 (2H, m), 7.34–7.38 (2H, m), 7.42–7.46 (1H, m), 7.63 (2H, d, J = 8.3 Hz), 7.85 (1H, d, J = 1.7 Hz), 7.92 (2H, d, J = 8.3 Hz), 10.68 (1H, br); Anal. Calcd for $C_{20}H_{20}ClF_3N_2O_2S$ 0.5H_2O: C, 52.92; H, 4.66; N, 6.17. Found: C, 53.24; H, 4.63; N, 5.82.

5.37. 1-(5-Phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrol-3-yl)ethanone (23)

To a solution of 1 M MeMgBr in THF (16 mL, 16 mmol) and Et_2O (16 mL) was added dropwise a solution of **11b** (600 mg,

1.58 mmol) in THF (4 mL) and Et_2O (4 mL) at 10 °C. The mixture was stirred at 10 °C for 1 h, and then poured into ice water. The resulting mixture was poured into a saturated solution of NH_4Cl, and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give pale brown oil (0.63 g). To a solution of the obtained oil in CH_2Cl_2 (30 mL) was added MnO_2 (2.77 g, 31.9 mmol) at room temperature. The mixture was stirred at room temperature for 4 h, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1–4:1) to give **23** (461 mg, 74%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 2.49 (3H, s), 6.57 (1H, d, J = 1.9 Hz), 7.12–7.16 (2H, m), 7.28–7.33 (2H, m), 7.39–7.41 (1H, m), 7.43 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz), 8.06 (1H, d, J = 1.9 Hz).

5.38. *N*-Methyl-1-(5-phenyl-1-{[4-(trifluoromethyl)phenyl]-sulfonyl}-1*H*-pyrrol-3-yl)ethanamine hydrochloride (24)

A mixture of **23** (200 mg, 0.51 mmol), 40% $MeNH_2$ in MeOH (400 mg, 5.2 mmol) and MS4A in EtOH (10 mL) was stirred at 70 °C for 1.5 h, and then cooled to room temperature. $NaBH_4$ (58 mg, 1.53 mmol) was added at room temperature, and the mixture was stirred for 1.5 h, quenched with 1 N HCl (50 mL). The resulting mixture was stirred for 30 min, basified with a saturated solution of $NaHCO_3$, and then extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/MeOH = EtOAc to 4:1) and the obtained oil was dissolved in ethyl acetate (5 mL). 4 N HCl/EtOAc (1 mL) was added and the mixture was concentrated under reduced pressure. The residue was crystallized from iPr_2O/EtOAc to give **24** (52 mg, 23%) as colorless crystals: mp 205–208 °C; ^{1}H NMR (DMSO-d_6) δ 1.52 (3H, d, J = 6.7 Hz), 2.37 (3H, s), 4.28 (1H, q, J = 6.7 Hz), 6.55 (1H, s), 7.14–7.45 (5H, m), 7.63 (2H, d, J = 8.4 Hz), 7.78 (1H, s), 7.92 (2H, d, J = 8.4 Hz); Anal. Calcd for $C_{20}H_{20}ClF_3N_2O_2S$ 0.5H_2O: C, 52.92; H, 4.66; N, 6.17. Found: C, 53.19; H, 4.53; N, 6.05.

5.39. 1-[(1-Isocyanopentyl)sulfonyl]-4-methylbenzene (26)

A mixture of *p*-toluenesulfonylmethyl isocyanide **25** (9.75 g, 50 mmol), tetrabutylammonium iodide (3.69 g, 10 mmol), 1-butyl iodide (11.3 mL, 100 mmol), CH_2Cl_2 (100 mL) and 30% NaOH solution (100 mL) was stirred at room temperature for 12 h. The mixture was diluted with water (200 mL), and then extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained gum-like residue was extracted three times with diethyl ether (100 mL). The extract was concentrated under reduced pressure to give **26** (10.8 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.91–0.97 (3H, m), 1.32–1.66 (4H, m), 1.80–1.90 (1H, m), 2.10–2.25 (1H, m), 2.49 (3H, s), 4.42–4.47 (1H, m), 7.41–7.51 (2H, m), 7.86–7.88 (2H, m).

5.40. Ethyl 5-butyl-1*H*-pyrrole-3-carboxylate (27)

A solution of **26** (10.8 g, 43.0 mmol) and ethyl acrylate (4.78 mL, 43.0 mmol) in THF (120 mL) was added dropwise to a suspension of potassium *tert*-butoxide (5.79 g, 51.6 mmol) in THF (80 mL) while stirring at room temperature over 1 h. The mixture was further stirred at room temperature for 30 min, and then diluted with water, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19/1–4/1) to give **27** (6.56 g, 78%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.89–0.95 (3H, m), 1.24–1.45 (5H, m), 1.55–1.65 (2H, m), 2.55–2.60 (2H, m), 4.23–4.30 (2H, m), 6.33 (1H, s), 7.30 (1H, s), 8.11 (1H, br).

5.41. Ethyl 5-butyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (28)

To a solution of **27** (978 mg, 5.0 mmol) in THF (50 mL) was added sodium hydride (60% in oil, 240 mg, 6.0 mmol) under Ar atmosphere. After stirring at room temperature for 30 min, benzenesulfonyl chloride (0.77 mL, 6.0 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was poured into H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19/1–4/1), and the obtained solid was washed with hexane to give **28** (780 mg, 47%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.84–0.89 (3H, m), 1.26–1.37 (5H, m), 1.47–1.55 (2H, m), 2.59–2.64 (2H, m), 4.25–4.32 (2H, m), 6.37 (1H, m), 7.52–7.66 (3H, m), 7.79–7.82 (2H, m), 7.92 (1H, s).

5.42. Methyl 5-cyclopropyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (29)

A mixture of **13** (2.11 g, 6.13 mmol), cyclopropylboronic acid (683 mg, 7.95 mmol), palladium(II) acetate (69 mg, 0.31 mmol), tricyclohexylphosphine (174 mg, 0.62 mmol) and tripotassium phosphate (4.55 g, 21.5 mmol) in toluene (27 mL) and water (1.3 mL) was stirred at 100 °C for 4 h under Ar atmosphere. After cooled to room temperature, the reaction mixture was diluted with H_2O (50 mL), and the mixture was extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1–4/1) to give **29** (406 mg, 22%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.30–0.36 (2H, m), 0.71–0.77 (2H, m), 2.00–2.08 (1H, m), 3.79 (3H, s), 6.19 (1H, s), 7.51–7.56 (2H, m), 7.63–7.66 (1H, m), 7.85–7.88 (2H, m), 7.94 (1H, s).

Compounds **30a** and **30b** were prepared form **28** and **29**, respectively using a similar procedure as for the preparation of compound **17b** from **9b**.

5.43. 1-[5-Butyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (30a)

Colorless crystals (53%): mp 139–140 °C; ^{1}H NMR (DMSO-d_6) δ 0.79–0.85 (3H, m), 1.24–1.48 (4H, m), 2.48 (3H, s), 2.58–2.63 (2H, m), 3.91 (2H, s), 6.25 (1H, s), 7.54 (1H, s), 7.66–7.88 (5H, m), 8.91 (2H, br); Anal. Calcd for $C_{16}H_{23}ClN_2O_2S$: C, 56.04; H, 6.75; N, 8.17. Found: C, 55.97; H, 6.97; N, 8.15.

5.44. 1-[5-Cyclopropyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (30b)

Colorless crystals (40%): mp 198–199 °C; ^{1}H-NMR (DMSO-d_6) δ 0.22–0.27 (2H, m),0.75–0.81 (2H, m), 1.97–2.05 (1H, m), 2.47 (3H, s), 3.87 (2H, s), 6.09 (1H, s), 7.55 (1H, s), 7.66–7.91 (5H, m), 8.92 (2H, br); Anal. Calcd for $C_{15}H_{19}ClN_2O_2S$ 0.5H_2O: C, 53.64; H, 6.00; N, 8.34. Found: C, 53.88; H, 5.71; N, 8.10.

5.45. Ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (31)

A solution of ethyl acetoacetate (13.02 g, 100 mmol) in DMF (40 mL) was added dropwise to a stirred suspension of NaH (60% in oil, 2.88 g) at 0 °C. The mixture was stirred at 0 °C for 20 min, and then a solution of phenacyl bromide **2** (20.0 g, 100 mmol) in DMF (20 mL) was added dropwise slowly. The reaction mixture was stirred at room temperature for 1.5 h, poured into ice water, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to

give ethyl 2-acetyl-4-oxo-4-phenylbutanoate (32.4 g, crude) as an oil. A mixture of thus obtained oil (32.4 g) and $AcONH_4$ (11.6 g) in AcOH (150 mL) was stirred at 80 °C for 20 h. The reaction mixture was concentrated under reduced pressure, and the residue was taken up EtOAc, washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1–7/2) to give **31** (15.6 g, 68%) as a solid: ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J = 7.0 Hz), 2.59 (3H, s), 4.30 (2H, q, J = 7.0 Hz), 6.84 (1H, d, J = 2.8 Hz), 7.18–7.27 (1H, m), 7.36 (2H, t, J = 7.7 Hz), 7.43–7.51 (2H, m), 8.52 (1H, br).

5.46. Ethyl 2-chloro-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (32)

To a solution of **4** (1.0 g, 4.0 mmol) in THF (40 mL) was added sodium hydride (60% in oil, 488 mg) at room temperature and the mixture was stirred for 30 min. 15-Crown-5 (2.65 g) was added dropwise and the mixture was stirred at room temperature for 30 min. To this mixture was added benzenesulfonyl chloride (1.84 g), and the mixture was further stirred at room temperature for 24 h, poured into H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 17:3) to give **32** (1.27 g, 81%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.2 Hz), 4.27 (2H, q, J = 7.2 Hz), 6.55 (1H, s), 7.38–7.50 (7H, m), 7.60–7.71 (3H, m).

5.47. 2-Methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (33a)

Compound **33a** was prepared from **31** in a manner similar to that described for compound **9a**, **10a** and **11a**. A colorless oil (6%): ^{1}H NMR ($CDCl_3$) δ 2.88 (3H, s), 6.47 (1H, s), 7.18–7.61 (10H, m), 10.00 (1H, s).

5.48. 2-Chloro-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (33b)

Compound **33b** was prepared from **32** in a manner similar to that described for compound **10a** and **11a**. A colorless oil (41%): ^{1}H NMR ($CDCl_3$) δ 6.52 (1H, s), 7.32–7.52 (7H, m), 7.62–7.69 (3H, m), 9.93 (1H, s).

5.49. *N*-Methyl-1-[2-methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl] methanamine hydrochloride (34a)

Compound **34a** was prepared from **33a** in a manner similar to that described for compound **17a**. Colorless crystals (35%): mp 183–184 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (3H, s), 2.50 (3H, s), 3.91 (2H, s), 6.40 (1H, s), 7.22–7.28 (2H, m), 7.34–7.49 (5H, m), 7.57 (2H, t, J = 7.8 Hz), 7.72 (1H, t, J = 6.8 Hz), 8.84 (2H, br s); Anal. Calcd for $C_{19}H_{20}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43. Found: C, 60.38; H, 5.59; N, 7.23.

5.50. 1-[2-Chloro-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (34b)

Compound **34b** was prepared from **33b** in a manner similar to that described for compound **17b**. Colorless crystals (61%): mp 180–182 °C; ^{1}H NMR (DMSO-d_6) δ 2.43 (3H, s), 3.89 (2H, s), 6.61 (1H, s), 7.36–7.46 (5H, m), 7.62–7.69 (4H, m), 7.75–7.82 (1H, m), 8.97 (2H, br); Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_2S$: C, 54.41; H, 4.57; N, 7.05. Found: C, 54.30; H, 4.57; N, 7.01.

5.51. Methyl 5-bromo-4-methyl-1*H*-pyrrole-3-carboxylate (36)

To a solution of methyl 4-methyl-1*H*-pyrrole-3-carboxylate **35** (5.0 g, 35.9 mmol) in THF (60 mL) was added NBS (6.39 g, 35.9 mmol) at −78 °C. After being stirred 15 min at −78 °C, pyridine (five drops) was added, and the mixture was stood at 5 °C for 18 h in a refrigerator. The mixture was concentrated under reduced pressure, diluted with H_2O, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1–2/1) to give **36** (4.05 g, 52%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.23 (3H, s), 3.80 (3H, s), 7.35–7.40 (1H, m), 8.45 (1H, br).

5.52. Methyl 5-bromo-4-methyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (37)

Compound **37** was prepared from **36** in a manner similar to that described for compound **13**. A brown solid (69%): ^{1}H NMR ($CDCl_3$) δ 2.11 (3H, s), 3.79 (3H, s), 7.45–7.70 (3H, m), 7.85–7.95 (2H, m), 8.06 (1H, s).

5.53. Methyl 4-methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (38)

Compound **38** was prepared from **37** in a manner similar to that described for compound **15a**. A pale yellow oil (87%): ^{1}H NMR ($CDCl_3$) δ 1.98 (3H, s), 3.85 (3H, s), 6.98 (2H, d, J = 8.4 Hz), 7.20–7.60 (8H, m), 8.08 (1H, s).

5.54. *N*-Methyl-1-[4-methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methanamine hydrochloride (39)

Compound **39** was prepared from **38** in a manner similar to that described for compound **10a**, **11a** and **17a**. Colorless crystals (20%): mp 186–187 °C; ^{1}H NMR (DMSO-d_6) δ 1.78 (3H, s), 2.58 (3H, s), 3.99 (2H, s), 6.95–7.10 (2H, m), 7.20 (1H, m), 7.30–7.65 (6H, m), 7.70–7.90 (2H, m), 8.91 (2H, br); Anal. Calcd for $C_{19}H_{21}ClN_2O_2S$ $0.5H_2O$: C, 59.13; H, 5.95; N, 7.26. Found: C, 59.50; H, 5.52; N, 7.32.

5.55. Measurement of H^+,K^+-ATPase activity

According to the method of Wallmark et al.,[21] a gastric mucosal microsomal fraction was prepared from the stomach of porcine. First, the stomach was removed, washed with tap water, immersed in 3 mol/L NaCl solution, and the surface of the mucosa was wiped with a paper towel. The gastric mucosa was detached, chopped, and homogenized in a homogenizing buffer consisting of 0.25 mol/L saccharose, 1 mmol/L EDTA and 10 mmol/L Tris HCl pH 6.5 using polytron (Kinematica). The obtained homogenate was centrifuged at 20,000*g* for 30 min and the supernatant was centrifuged at 100,000*g* for 90 min. The precipitate was suspended in a homogenizing buffer and layered over 7.5% (w/w) Ficoll in a homogenizing buffer, and centrifuged at 100,000*g* for 5 h. The microsomal fraction appearing at the interface between the both layers was collected and centrifuged at 100,000*g* for 90 min. The pellet was collected and suspended in a homogenizing buffer to give a concentration of 0.5 mg of protein per mL. The resulting suspension was stored at −80 °C until use and used as the gastric microsomes. The obtained microsomal fraction was used as H^+,K^+-ATPase standard product. Protein was determined with a protein assay kit (Bio-Rad, Hercules, CA, USA) using bovine serum albumin as a standard.

The activity of H^+,K^+-ATPase from the porcine stomach was measured as follows: the enzyme mixture contained, in volume of 40 μL, 50 mmol/L HEPES-Tris pH 6.5 containing 5 mmol/L $MgCl_2$, 10 μmol/L of valinomycin in 0.1% DMSO solution and 0.1 μg of the

gastric microsomes as a enzyme source in the presence or absence of 10 mmol/L KCl. The 5 μL of various concentration of the test compound in 10% DMSO solution, was added to the enzyme mixture and incubated at 37 °C for 30 min. The enzyme reaction was started by adding 5 μL of a 2 mmol/L ATP solution. The reaction was stopped with 15 μL malachine green reagents (0.12% malachite green: 7.5% hexaammonium heptamolybdate: 11% Tween 20 = 100:25:2). After allowing 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 620 nm. The ATPase activity was determined by the inorganic phosphate released from ATP hydrolysis according to the method of Fiske and Subbarow.[22] The activity of H^+,K^+-ATPase was calculated from the difference between ATPase activities with or without K^+. The inhibitory effects of the test compounds were expressed as percentage inhibition with respect to the K^+-stimulated H^+, K^+-ATPase activity in the control. The values of IC_{50} were calculated using sigmoidal dose response equation in GraphPad Prism (GraphPad Software Inc., San. Diego, CA, USA).

5.56. Inhibition test of histamine-stimulated acid secretion in anesthetized rats

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 min later, histamine 2HCl (30 mg/kg/10 mL) was injected subcutaneously. Three h 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 (μEq/3 h) was calculated.

5.57. Washout reversibility test on the inhibition of H^+,K^+-ATPase

Gastric microsomes were incubated with 0.1 μM compound (final concentration of DMSO was 1%) at 37 °C for 30 min in assay buffer consisting of 50 mmol/L HEPES-Tris buffer pH 6.5, 5 mmol/L $MgCl_2$, 10 mmol/L KCl, and then aliquots of the reaction mixture were taken to determine H^+,K^+ ATPase activity. From the remaining reaction mixture, the compound was washed out by ultrafiltration through 30 kDa cut-off membranes. Residues were resuspended in the same volume of the assay buffer without the compound. The reaction was initiated by the addition of 2 mmol/L ATP and the reaction mixture was incubated at 37 °C for 20 min. The reaction was stopped with malachite green reagents (0.12% malachite green: 7.5% hexaammonium heptamolybdate: 11% tween 20 = 100:25:2). The ATPase activity was determined by the inorganic phosphate released from ATP hydrolysis according to the method of Fiske and Subbarow.[22] The K^+-stimulated H^+,K^+-ATPase activity obtained with 1% DMSO solution was calculated as 100% control. Data were expressed as percentage of the ATPase activity in vehicle with or without washout.

5.58. Measurement of Na^+,K^+-ATPase inhibitory activity

The activity of Na^+,K^+-ATPase from porcine cerebral cortex (Sigma) was measured as described for H^+,K^+-ATPase except the components of the enzyme mixture that contained in volume of 40 μL, 4 μg of Na^+,K^+-ATPase, 50 mmol/L Tris-HEPES (pH 7.5), 2 mmol/L $MgCl_2$ with or without 100 mmol/L NaCl and 10 mmol/L KCl.

5.59. Inhibiton test of 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 and 24 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 (μEq/90 min) from each time was calculated and expressed as a percentage of the pre-dosing value measured 1 day before the administration.

Acknowledgments

The authors thank Dr. Akihiro Tasaka and Dr. Akio Miyake for helpful discussions.

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