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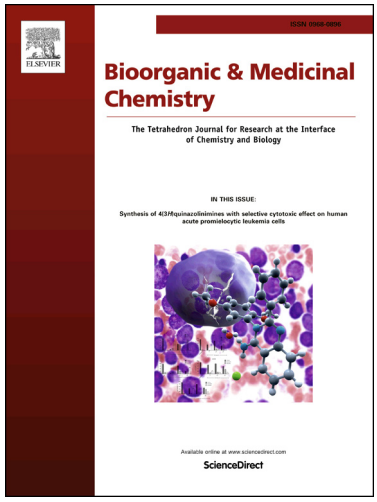

Exploration of pyrrole derivatives to find an effective potassium-competitive acid blocker with moderately long-lasting suppression of gastric acid secretion

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Exploration of pyrrole derivatives to find an effective potassium-competitive acid blocker with moderately long-lasting suppression of gastric acid secretion

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Keywords: Potassium-competitive acid blocker; transfer behavior to the stomach; rapid onset, moderately long-lasting acid suppression

Abbreviations: absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox), area under the curve (AUC), benzyl mercaptan (BnSH), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), hepatic cytochrome P450 2C19 (CYP2C19), hepatic cytochrome P450 3A4 (CYP3A4), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), differential scanning calorimetry (DSC), 2,4-dimethoxybenzyl (DMB), 4-dimethylaminopyridine (DMAP), dimethyl sulfoxide (DMSO), di-*tert*-butyl dicarbonate (Boc_2O), drug metabolism and pharmacokinetics (DMPK), electrospray ionization (ESI), half-maximal inhibitory concentration (IC_{50}), high-performance liquid chromatography (HPLC), high-resolution mass spectrometry (HRMS), human ether-a-go-go-related gene (hERG), intravenous injection (iv), liquid chromatography with tandem mass spectrometry (LC/MS/MS), lithium diisopropylamide (LDA), melting point (mp), methoxy (MeO), *N*-chlorosuccinimide (NCS), per os (po), potassium-competitive acid blocker (P-CAB), proton pump inhibitor (PPI), pyridyl (Py), room temperature (rt), tetrahydrofuran (THF), thermogravimetry-differential thermal analysis (TG-DTA), thin-layer chromatography (TLC)

Abstract

With the aim to discover a novel excellent potassium-competitive acid blocker (P-CAB) that could perfectly overcome the limitations of proton pump inhibitors (PPIs), we tested various approaches

based on pyrrole derivative **1** as a lead compound. As part of a comprehensive approach to identify a new effective drug, we tried to optimize the duration of action of the pyrrole derivative. Among the compounds synthesized, fluoropyrrole derivative **20j**, which has a 2-F-3-Py group at position 5, fluorine atom at position 4, and a 4-Me-2-Py sulfonyl group at the first position of the pyrrole ring, showed potent gastric acid-suppressive action and moderate duration of action in animal models. On the basis of structural properties including a slightly larger Clog P value (1.95), larger log D value (0.48) at pH 7.4, and fairly similar pKa value (8.73) compared to those of the previously optimized compound **2a**, compound **20j** was assumed to undergo rapid transfer to the stomach and have a moderate retention time there after single administration. Therefore, compound **20j** was selected as a new promising P-CAB with moderately long duration of action.

1. Introduction

Gastric H^+,K^+-ATPase is the key enzyme at the final step of gastric acid secretion. Its inhibition is thought to be especially effective for control of gastric acid secretion; accordingly, the development of H^+,K^+-ATPase inhibitors for the treatment of acid-related diseases has attracted considerable interest.[1]

Proton pump inhibitors (PPIs) such as lansoprazole, omeprazole, rabeprazole, and pantoprazole inhibit gastric H^+,K^+-ATPase by covalently binding to its sulfhydryl group, resulting in inhibition of gastric acid secretion.[2–6] Although PPIs are now the mainstay of therapy for acid-related diseases, there are several limitations in terms of acid lability, delayed onset of action, variations of efficacy among patients (largely because of CYP2C19-mediated metabolism), and insufficient inhibition of nocturnal acid breakthrough.[7–11]

Potassium-competitive acid blockers (P-CABs), a new class of acid suppressors with a mode of action different from that of PPIs, are expected to offer some therapeutic benefits such as better symptom control and faster remission of gastroesophageal reflux disease and of other acid-related diseases. P-CABs, as the name suggests, inhibit H^+,K^+-ATPase activity in gastric parietal cells reversibly and in a potassium-competitive manner.[12]

In our previous paper,[13] we have reported that compound **2a**, as a novel P-CAB that has quite low lipophilicity and excellent ADME-Tox parameters, has a potent H^+,K^+-ATPase inhibitory activity in vitro and potent and long-lasting inhibition of histamine-induced gastric acid secretion in rats and Heidenhain pouch dogs.[13] Judging by the finding that compound **2a** inhibits histamine-stimulated gastric acid secretion by approximately 80% in Heidenhain pouch dogs even after 48 h of oral administration at a dose of 0.8 mg/kg, compound **2a** was hypothesized to exert stronger and much longer inhibition in humans as compared to PPIs. Actually, it holds great promise as a new P-CAB with unusually long duration of action.

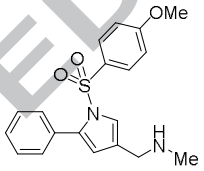
On the other hand, there is a possibility that the duration of action of compound **2a** in humans cannot

be deduced from the animal data, and we were slightly concerned about a risk of too long duration of action of compound **2a** in humans. Therefore, with the aim to discover a novel excellent P-CAB that would perfectly overcome the limitations of PPIs, we started to study how to precisely control the duration of action of pyrrole compounds. Major factors affecting the duration of gastric acid suppression were found to be H^+,K^+-ATPase inhibitory activity in vitro and in vivo, the pattern of distribution to the stomach, and effectiveness of elimination (clearance) from the stomach, but the contribution rates of such factors were estimated to depend on the overall physicochemical properties of a compound in question.

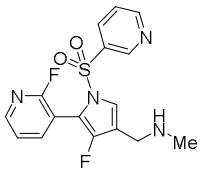
Therefore, to understand the duration of gastric-acid-suppressive activity comprehensively, we decided to evaluate not only basic physicochemical properties such as lipophilicity, basicity, and membrane penetration, which should determine tissue distribution, but also the actual concentration in the stomach.

Consequently, gastric and plasma concentration profiles after intravenous administration of compound **2a** were determined by means of cassette dosing experiment, and it turned out that this compound remains in the stomach at rather high concentrations after 24 h in spite of elimination from blood plasma. In addition, compound **2a** showed significantly more effective transfer to (and retention in) the stomach as compared to pyrrole lead compound **1** (Table 1).[14]

Table 1 A series of properties of lead compound **1** and previously optimized P-CAB **2a**



1



2a

Compound	Clog P	log D	pKa	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content % control at 100 μM	hERG % inhibition at 10 μM	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng·h/mL or ng·h/g) in rat plasma and stomach after intravenous administration at a dose of 0.2 mg/kg (as free base)									
								C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
								plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach
1	3.88	1.54	9.48	30	95	(22.1)[b]	89.1	17.2	361.4	7.3	387.7	2.9	244	0	0	56	3730
2a	1.45	0.04	8.54	49	98	100.2	39.8	51.5	602.2	15	752.1	0	628.6	0	130.5	54	10277

[a] All values are averages of three rats.

[b] ATP content at 30 μM (% control)

Because of the above-mentioned concerns, we started searching for a new P-CAB that has low lipophilicity, excellent ADME-Tox parameters like compound **2a**, and moderately long duration of acid suppression (Figure 1), on the basis of the hypothesis that compound **2a** may show a little excessive duration of action in humans. Consequently, we succeeded in identifying a novel

fluoropyrrole derivative by further modifications.

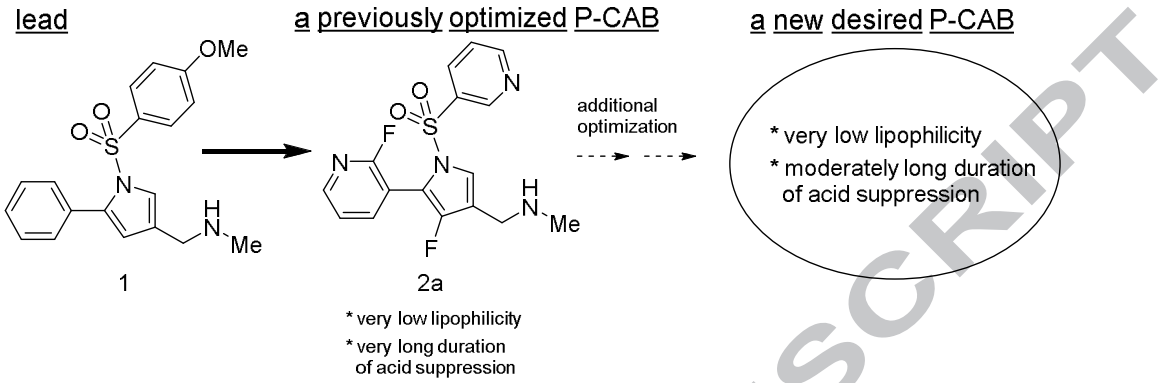
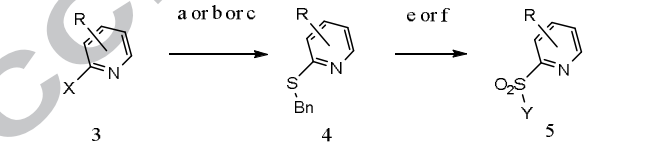


Figure 1. An outline of the search for a new P-CAB with desirable properties.

Herein we report exploration of compounds and identification of a novel fluoropyrrole derivative as a P-CAB with optimal duration of action.

2. Chemistry

Synthesis of several commercially unavailable 2-pyridyl sulfonylation reagents was accomplished as shown in Scheme 1. Condensation of commercially available 2-halopyridines **3** with benzyl thiol by means of a nucleophilic aromatic substitution reaction or a palladium coupling reaction yielded corresponding 2-benzylthiopyridines **4**. 6-MeO derivative **4h** was obtained from compound **4b** via a substitution reaction with sodium methoxide. Subsequent oxidation of **4** with *N*-chlorosuccinimide (NCS) afforded corresponding sulfonyl halides **5**. Reaction products of **4a** and **4d** were too unstable to be isolated as sulfonyl chlorides; therefore, they were isolated as stable sulfonyl fluoride derivatives **5a** and **5d** after treatment with potassium fluoride.

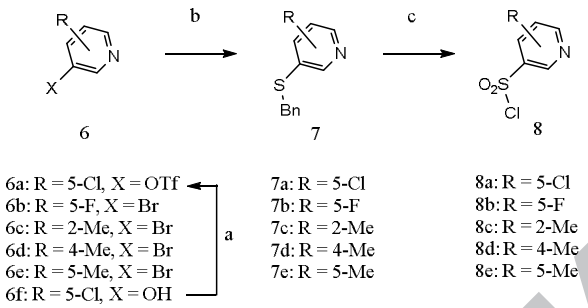


Scheme 1. Reagents and conditions: (a) BnSH, NaH, THF, rt or 60 °C; (b) BnSH, K_2CO_3, DMSO, 150 °C; (c) BnSH, $Pd_2(dba)_3$, Xantphos, i-Pr_2NEt, toluene, 80 °C; (d) NaOMe, MeOH, 60 °C; (e)

NCS, AcOH, H_2O, then KF, rt; (f) NCS, AcOH, H_2O, rt.

Synthesis of several commercially unavailable sulfonylation reagents for 3-pyridyl derivatives was accomplished as shown in Scheme 2.

Condensation of commercially available or prepared compounds **6** with benzyl mercaptan via a palladium coupling reaction gave corresponding **7**. As for triflate derivative **6a**, it was obtained from compound **6f** under basic conditions with a good yield. Subsequent oxidation of compounds **7** afforded compounds **8** in a manner similar to the approach described above.



Scheme 2. Reagents and conditions: (a) N-Phenyl-bis(trifluoromethanesulfonimide), Et_3N, THF, rt; (b) BnSH, $Pd_2(dba)_3$, Xantphos, iPr_2NEt, toluene, 80 °C; (c) NCS, AcOH, H_2O, rt.

Synthesis of fluoropyrrole derivatives **20** was accomplished by starting from commercially available **9**, and the synthesis method is shown in Scheme 3.

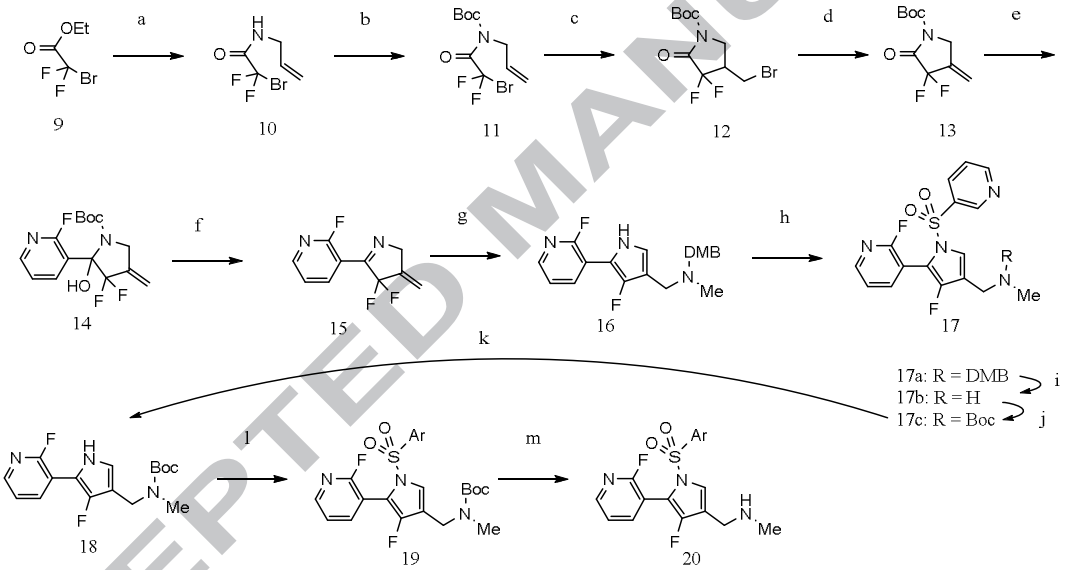
Initially, the introduction of a fluorine group into the pyrrole ring at position 4 was performed by directly applying fluorination reactions to several pyrrole intermediates, but these methods were not practical because the fluorination reaction step poses many difficult problems such as a low yield and selectivity, the need for precise column chromatography, and the use of an expensive fluorination reagent. To solve these problems, we attempted to develop an effective method for synthesis of fluoropyrrole derivatives without direct fluorination of the pyrrole ring. As a result, we succeeded in the development of a novel method for synthesis of fluoropyrroles, consisting of key reactions such as a nucleophilic reaction with the carbonyl group of a lactam using pyridyl lithium and a novel allyl rearrangement reaction (S_N2' reaction) accompanied by desorption of the fluorine group and double-bond transposition.

As for the synthesis of compound **12,** it was successfully achieved by a method similar to the one described in the literature.[15] Condensation of compound **9** with allylamine under neat conditions gave amide compound **10**, which was reacted with Boc_2O in the presence of *N*,*N*-dimethyl-4-aminopyridine to obtain Boc-protected compound **11**, followed by cyclization to produce difluorolactam **12**.

Compound **12** was treated under basic conditions to obtain **13** followed by a nucleophilic addition reaction with lithiated fluoropyridine to produce **14**, which was then subjected to a deprotection reaction accompanied by dehydration under acidic conditions to obtain **15** with a moderate yield. Compound **15** was converted to **16** by means of a novel S_N2' reaction, and subsequent sulfonylation of **16** in the presence of 15-crown-5 under basic conditions yielded **17a**. We then used a deprotection reaction to prepare compound **17b** (free base of compound **2a**).

Protection of **17b** with Boc_2O afforded **17c**, which was followed by desulfonylation in the presence of a strong base to obtain key intermediate **18**. Compound **18** was then sulfonylated using various sulfonylation agents **5** and **8** to produce compounds **19**, and subsequent treatment with a strong acid afforded corresponding target compounds **20**.

As for compounds **1** and **2a** described above and compounds **2b–e** to be discussed later, they were prepared using a procedure similar to a method reported elsewhere.[13,14]



19a: Ar = 2-thienyl
19b: Ar = 2-fulyl
19c: Ar = 3-furyl
19d: Ar = 2-Py
19e: Ar = 6-MeO-2-Py
19f: Ar = 4-MeO-2-Py
19g: Ar = 5-MeO-2-Py
19h: Ar = 3-Me-2-Py
19i: Ar = 6-Me-2-Py
19j: Ar = 4-Me-2-Py
19k: Ar = 6-F-2-Py
19l: Ar = 5-F-2-Py
19m: Ar = 2-Cl-3-Py
19n: Ar = 5-Cl-3-Py
19o: Ar = 5-F-3-Py
19p: Ar = 2-Me-3-Py
19q: Ar = 4-Me-3-Py
19r: Ar = 5-Me-3-Py
19s: Ar = 6-Me-3-Py

20a: Ar = 2-thienyl
20b: Ar = 2-fulyl
20c: Ar = 3-fulyl
20d: Ar = 2-Py
20e: Ar = 6-MeO-2-Py
20f: Ar = 4-MeO-2-Py
20g: Ar = 5-MeO-2-Py
20h: Ar = 3-Me-2-Py
20i: Ar = 6-Me-2-Py
20j: Ar = 4-Me-2-Py
20k: Ar = 6-F-2-Py
20l: Ar = 5-F-2-Py
20m: Ar = 2-Cl-3-Py
20n: Ar = 5-Cl-3-Py
20o: Ar = 5-F-3-Py
20p: Ar = 2-Me-3-Py
20q: Ar = 4-Me-3-Py
20r: Ar = 5-Me-3-Py
20s: Ar = 6-Me-3-Py

Scheme 3. Reagents and conditions: (a) allylamine, rt; (b) Boc_2O, DMAP, MeCN, rt; (c) CuBr,

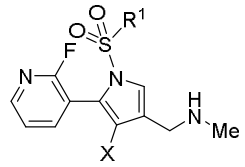
2,2′-bipyridyl, 1,2-dichloroethane, 80 °C; (d) DBU, THF, 0 °C, then rt; (e) LDA, 2-fluoropyridine, THF, −78 °C; (f) HCl, AcOH, rt; (g) NaH, DMB, THF, 0 °C; (h) NaH, 15-crown-5, pyridine-3-sulfonyl chloride, THF, 0 °C; (i) (1) $ClCO_2CH(Cl)CH_3$, THF, 0 °C; (2) Et_3N, THF, 65 °C; (3) EtOH, reflux; (4) 1 mol/L NaOH, $NaHCO_3$, H_2O, EtOAc, rt; (j) Boc_2O, THF, rt; (k) 1 mol/L NaOH, iPrOH, THF, rt; (l) NaH, 15-crown-5, Ar-sulfonyl chloride or Ar-sulfonyl fluoride, THF, rt; (m) 4 mol/L HCl/EtOAc, iPrOH or EtOH, EtOAc, rt, or (1) 4 mol/L HCl/EtOAc, iPrOH or EtOH, EtOAc, rt; (2) $NaHCO_3$, EtOAc; (3) fumaric acid or succinic acid, EtOH or MeOH, EtOAc.

3. Results and discussion

The compounds synthesized were evaluated for their Clog P values, log D values at pH 7.4, and H^+,K^+-ATPase-inhibitory activities at pH 6.5 by their IC_{50} value (in vitro), and many of the compounds were also analyzed for their inhibitory effects on histamine-induced gastric acid secretion in anesthetized rats (in vivo), effects on cellular ATP content (cytotoxicity), hERG-inhibitory activity, and inhibition of CYP3A4 activity. An in vivo assay was conducted by intravenous administration of the compound at 1 mg/kg, and the total acid output for 3 h after histamine injection was compared with that after administration of vehicle. The log D values were measured at pH 7.4 with relative retention time to standard compounds of high-performance liquid chromatography (HPLC) analysis.[16] We also evaluated concentration of the compounds in plasma and stomach after intravenous administration at a dose of 0.2 mg/kg (as free base) in cassette dosing experiments on rats. To extrapolate the onset and duration profile of the compounds, drug concentrations at 10 min and at 1, 4, and 24 h (C_{10min}, C_{1h}, $C_{4h,}$ and C_{24h}) after intravenous administration were measured in plasma (ng/mL) and stomach (ng/g). In addition, the area under the curve (AUC) was calculated in plasma (ng·h/mL) and stomach (ng·h/g) as an indicator of stomach transfer behavior. The results are shown in Tables 1–4.

First, we examined the effects of the fluorine group at position 4 and the effects of the binding site for heteroaromatics at the first position of the pyrrole ring to assess the possibility of our desired properties by means of several potent compounds reported in our previous paper.[13] The results are summarized in Table **2**.

Table 2 Effects of a fluorine group at position 4 (X) and of a binding site for heteroaromatics at the first position (R^1) of the pyrrole ring on activities and various properties of pyrrole compounds



Compound	2a	2b	2c	2d	2e	20a	20b	20c	20d
X	F	H	H	H	H	F	F	F	F
R^1	3-Py	3-Py	3-thienyl	2-thienyl	2-Py	2-thienyl	2-furyl	3-furyl	2-Py

Compound	Clog P	log D	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content % control at 100 μM	hERG % inhibition at 10 μM	CYP3A4 % inhibition at 10 μM	Rat cassette dosing[a] Concentrations in rat plasma (ng/mL) and stomach (ng/g) after intravenous administration at a dose of 0.2 mg/kg (as free)									
								C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
								plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach
2a	1.45	0.04	49	98	100.2	39.8	14.4	51.5	602.2	15	752.1	0	628.6	0	130.5	54	10277
2b	1.21	–0.85	210	96	85.7	4.4	4.2	37.1	420	8.4	532.2	0	540.9	0	19.6	35	7646
2c	2.28	–0.83	32	98	64	60	1.4	23.5	406.7	8.9	613.7	0	639.6	0	41.7	29	9152
2d	2.28	–0.69	32	96	74.9	63	NT[b]	20.8	522.3	8.8	592.4	0	210.3	0	0	27	3815
2e	1.21	0.05	120	81	78.6	NT[b]	–9.7	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
20a	2.52	0.54	72	98	77.5	56.1	20.5	36.6	411.5	12.2	954.8	0	826.7	0	17.4	42	11717
20b	1.98	0.2	79	75	90.8	28.7	5.6	26.5	592.5	6.5	706.3	0	253.6	0	0	26	4566
20c	1.98	0.45	60	95	100.5	44.5	12.8	37.4	635.4	11.5	687.7	0	193.8	0	0	41	3865
20d	1.45	0.44	97	95	94.8	9	7.7	36	616.7	7.9	809.2	0	337.1	0	2.1	33	5757

[a] All values are averages of three rats.

[b] Not tested

Unfluorinated 3-pyridyl derivative **2b** ($AUC_{stomach}$ = 7646 ng·h/mL) showed significantly lower AUC in the stomach as compared to fluorinated derivative **2a** ($AUC_{stomach}$ = 10227 ng·h/g). In addition, the maximal concentration time of compound **2b** in the stomach after intravenous administration was 4 h as compared to 1 h for compound **2a**. Such a difference in the pattern of transfer to the stomach was assumed to be mainly based on membrane penetration which is determined by physicochemical properties including log D (lipophilicity) and pKa (basicity) values.

In our previous paper, it took 150–180 min for pH of a gastric perfusate to reach its maximum value after intravenous administration of compound **2b** in contrast to the rapid onset of pharmacological action of compound **2a**.[13] These experimental results on difference in the stomach concentration between compounds **2b** and **2a** could explain the difference in the pH behavior of gastric perfusate during histamine stimulation in anesthetized rats. It is likely that compound **2a** (with a fluorine group introduced at position 4 of the pyrrole ring) caused both rapid transfer and quite long retention in the stomach because of its suitable balance of moderate log D (0.04) and pK_a (8.54) values. Unfluorinated 3-thienyl derivative **2c** ($AUC_{stomach}$ = 9152 ng·h/g) showed a similar pattern of transfer to the stomach as compared to **2b.** Although its AUC in the stomach was a little smaller, the maximal concentration time in the stomach for **2c** after intravenous administration was the same as

that of **2b** and equaled 4 h. Therefore, the actual onset of pharmacological action of compound **2c** after single administration was also presumed to be not rapid as in **2b**. On the other hand, unfluorinated 2-thienyl derivative **2d** ($AUC_{stomach}$ = 3815 ng·h/g) showed much lower AUC in the stomach as compared to **2c**.

These results encouraged us to continue exploration of additional 4-fluorinated compounds that have a heteroaromatic sulfonyl group at position 1. Although there were no gastric-transfer data regarding unfluorinated 2-pyridyl derivative **2e**, we could assume that the relatively low in vivo activity of compound **2e** (IC_{50} = 120 nM, 81% inhibition at 1 mg/kg, iv) might be caused by its lower AUC in the stomach as compared to compound **2b** (IC_{50} = 210 nM, 96% inhibition at 1 mg/kg, iv, $AUC_{stomach}$ = 7646 ng·h/g). In such a case, the pyrrole derivative was expected to show both rapid transfer to the stomach and increasing AUC in the stomach after introduction of a fluorine group at position 4.

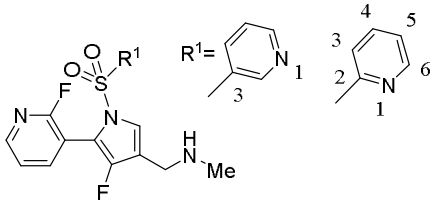
On the basis of these findings and a hypothesis, we decided to design and explore some additional 4-fluorinated pyrrole derivatives that are expected to show moderate gastric transfer. 4-Fluorinated 2-thienyl derivative **20a** ($AUC_{stomach}$ = 11717 ng·h/g) had much higher AUC in the stomach than unfluorinated **2d** did. In addition, the maximal drug concentration time for compound **20a** in the stomach after intravenous administration was 1 h (rapid onset of action might be expected), and the residual level of compound **20a** in the stomach 24 h after intravenous administration was much lower than that of compound **2a**. Unfortunately, compound **20a** seemed to be out of the acceptable range in terms of hERG-inhibitory activity.

4-Fluorinated furyl derivatives **20b** ($AUC_{stomach}$ = 4566 ng·h/g) and **20c** ($AUC_{stomach}$ = 3865 ng·h/g) were within a tolerable range in terms of hERG inhibition, but 2-furyl compound **20b** did not have strong in vivo activity. On the other hand, 3-furyl compound **20c** showed strong in vivo activity (95% inhibition at 1 mg/kg, iv). Judging by its gastric transfer properties, it was expected to show both rapid onset of acid suppression after single administration and moderate duration of action.

4-Fluorinated 2-pyridyl derivative **20d** ($AUC_{stomach}$ = 5757 ng·h/g) was found to have enhanced activities both in vitro and in vivo (IC_{50} = 97 nM, 95% inhibition at 1 mg/kg, iv) as compared to those of unfluorinated **2e,** as expected. Moreover, compound **20d** actually has excellent ADME-Tox parameters including hERG-inhibitory activity in addition to its good gastric transfer properties, resembling our desired properties. Therefore, we selected **20d** as a lead compound for further optimization.

Second, we analyzed several analogs of compound **20d** in detail to understand the comprehensive potential of 2-pyridyl derivatives at position 1, and the results are summarized in Table 3.

Table 3 Effects of substituent introduction into the 2-pyridyl group at the first position (R^1) of the pyrrole ring on activities and various properties of pyrrole compounds



Compond	R^1	Compond	R^1
2a	3-Py	20h	3-Me-2-Py
20d	2-Py	20i	6-Me-2-Py
20e	6-MeO-2-Py	20j	4-Me-2-Py
20f	4-MeO-2-Py	20k	6-F-2-Py
20g	5-MeO-2-Py	20l	5-F-2-Py

Compound	Clog P	log D	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content % control at 100 μM	hERG % inhibition at 10 μM	CYP3A4 % inhibition at 10 μM	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng·h/mL or ng·h/g) in rat plasma and stomach after intravenous administration at a dose of 0.2 mg/kg (as free base)									
								C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
								plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach
2a	1.45	0.04	49	98	100.2	39.8	14.4	51.5	602.2	15	752.1	0	628.6	0	130.5	54	10277
20d	1.45	0.44	97	95	94.8	9	7.7	36	616.7	7.9	809.2	0	337.1	0	2.1	33	5757
20e	2.21	1.03	150	98	69.8	82.3	55.8	43.5	772.8	14.9	1255	0	970.8	0	47.9	50	14434
20f	1.81	0.51	140	95	84.5	38.7	19	37.2	617.2	10.1	773.4	0	268.3	0	8.8	38	4964
20g	1.81	0.64	280	95	80	17.6	7.7	54.2	623.5	13.1	806.2	0	426.5	0	0	52	6761
20h	1.95	0.32	510	54	79.1	NT[b]	29	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
20i	1.95	0.71	210	91	83.8	13.9	22.9	41.7	1083.9	10.3	999.2	0	527	0	3.3	41	8550
20j	1.95	0.48	73	92	85.5	45.1	4.3	39.4	946.9	8.1	926.6	0	681.7	0	28.9	35	10378
20k	1.62	0.7	240	NT	74	NT[b]	46	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
20l	1.62	0.42	100	87	86.5	NT[b]	21.7	25	369.3	5	525.7	0	346.7	0	0	22	5179

[a] All values are averages of three rats.

[b] Not tested

Although compound **20d** remained in the stomach for 24 h after intravenous administration, its residual concentration seemed to be quite small in terms of our drug concept implying long-lasting acid suppression for 24 h. The introduction of a methoxy (MeO) group into the 2-pyridyl (Py) moiety of **20d** maintained strong in vivo activity in spite of weaker in vitro activity. 6-MeO-2-Py derivative **20e** ($AUC_{stomach}$ = 14434 ng·h/g) showed better gastric transfer than **20d** did. Nonetheless, an unacceptable hERG-inhibitory activity was observed, unfortunately.

4-MeO-2-Py derivative **20f** ($AUC_{stomach}$ = 4964 ng·h/g) showed better gastric transfer properties regarding its residual level in the stomach after 24 h, accompanied by acceptable hERG inhibition, and moreover, it appeared to have moderate duration of acid suppression.

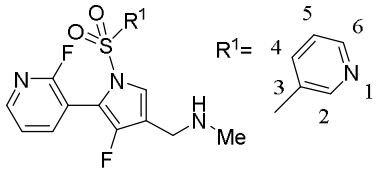
On the other hand, 5-MeO-2-Py derivative **20g** ($AUC_{stomach}$ = 6761 ng·h/g) was not detected in the stomach after 24 h in spite of a slight increase in AUC in the stomach. Compound **20g** was presumed to have faster clearance from the stomach than **20d** did. As for the introduction of a methyl group into the 2-pyridyl moiety of **20d**, 3-Me-2-Py derivative **20h** did not show strong activities either in vitro or in vivo, but both 6-Me-2-Py derivative **20i** ($AUC_{stomach}$ = 8550 ng·h/g) and 4-Me-2-Py

derivative **20j** ($AUC_{stomach}$ = 10378 ng·h/g) exerted relatively good activities accompanied by acceptable ADME-Tox parameters and a moderate stomach concentration.

Unfortunately, in the case of the introduction of a fluorine group into the 2-pyridyl moiety of **20d**, 6-F-2-Py derivative **20k** strongly inhibited CYP3A4, and 5-F-2-Py derivative **20l** did not show good in vivo activity in spite of its in vitro activity similar to that of **20d**.

Finally, we evaluated several analogs of compound **2a** to elucidate the effects of substituents in the 3-pyridyl group at position 1 on such properties as lipophilicity and basicity (Table 4).

Table 4 Effects of substituent introduction into the 3-pyridyl group at position 1 (R^1) of the pyrrole ring on activities and various properties of pyrrole compounds



Compond	R^1	Compond	R^1
2a	3-Py	20p	2-Me-3-Py
20m	2-Cl-3-Py	20q	4-Me-3-Py
20n	5-Cl-3-Py	20r	5-Me-3-Py
20o	5-F-3-Py	20s	6-Me-3-Py

Compound	Clog P	log D	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content % control at 100 μM	hERG % inhibition at 10 μM	CYP3A4 % inhibition at 10 μM	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng·h/mL or ng·h/g) in rat plasma and stomach after intravenous administration at a dose of 0.2 mg/kg (as free base)									
								C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
								plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach
2a	1.45	0.04	49	98	100.2	39.8	14.4	51.5	602.2	15	752.1	0	628.6	0	130.5	54	10277
20m	2.19	0.75	390	NT[b]	86.9	NT[b]	53.1	28	539	10.1	722.1	0	427.4	0	0	33	6568
20n	2.19	1.44	160	NT[b]	66.9	NT[b]	45.9	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
20o	1.62	0.83	200	99	88.9	22.7	27	43	330.4	8.3	605.5	0	425.2	0	38.3	38	6599
20p	1.95	0.48	210	92	97.4	14.8	30.1	25.3	507	8	577	0.3	299.7	0	0	32	4806
20q	1.95	0.43	120	98	90.9	28.2	40	50.1	359.6	8.4	618.5	0	250.7	0	0	41	4248
20r	1.95	0.61	140	87	86.9	NT[b]	49.7	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
20s	1.95	0.62	180	97	76.7	24.8	–1.2	40.1	671.5	10.8	1124	0	1182.8	0	219.1	41	18284

[a] All values are averages of three rats.

[b] Not tested

The introduction of a substituent into the 3-pyridyl moiety of compound **2a** reduced in vitro activities in any cases of chlorination, fluorination, or methylation. In addition, both 2-Cl-3-Py derivative **20m** and 5-Cl-3-Py derivative **20n** inhibited CYP3A4 activity beyond our acceptable level. In contrast, 5-F-3-Py derivative **20o** ($AUC_{stomach}$ = 6559 ng·h/g) showed promising gastric transfer behavior and acceptable toxicity parameters accompanied by strong in vivo activity. 2-Me-3-Py derivative **20p** ($AUC_{stomach}$ = 4806 ng·h/g) and 4-Me-3-Py derivative **20q** ($AUC_{stomach}$ = 4248 ng·h/g) both had good ADME-Tox parameters, but we assumed that the duration of acid suppression was probably too short from the standpoint of their gastric transfer in rats. Although 5-Me-3-Py

derivative **20r** did not exert enough in vivo activity in addition to unacceptable CYP3A4 inhibition, 6-Me-3-Py derivative **20s** ($AUC_{stomach}$ = 18284 ng·h/g) showed strong in vivo acid suppression accompanied by acceptable toxicity parameters. Nevertheless, its AUC in the stomach was much larger than that of compound **2a** in rats, and its residual level in the stomach at 24 h after administration was also obviously too high.

To clarify the actual pH profile in the stomach, we evaluated the effects of compounds **20c**, **20d**, **20e**, **20f**, **20g**, **20i**, **20j**, **20o,** and **20s** on the pH of a gastric perfusate under conditions of histamine stimulation in anesthetized rats (Figure 2).

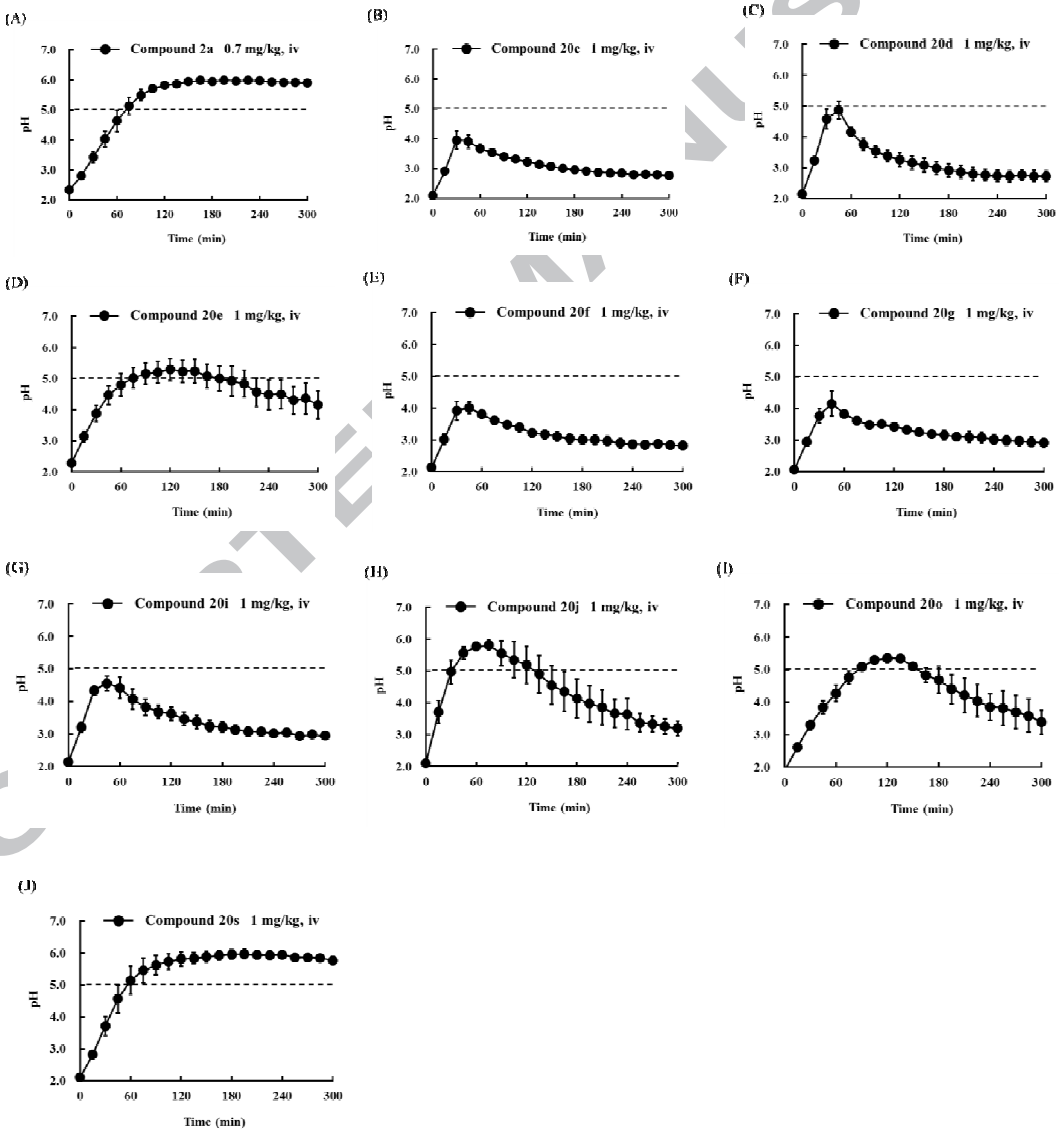


Figure 2. Effects of intravenous administration of compounds **2a** (A)[13], **20c** (B), **20d** (C), **20e** (D), **20f** (E), **20g** (F), **20i** (G), **20j** (H), **20o** (I), and **20s** (J) on the pH of gastric perfusate under conditions of histamine stimulation in anesthetized rats. Each data point represents mean ± SE from three to six rats.

The pH value of saline under these experimental conditions was 6.0 to 6.3. Intravenous infusion of histamine 2HCl at 8 mg/kg/h stimulated gastric acid secretion and decreased pH of the gastric perfusate to ~2.

In our previous study, intravenous administration of compound **2a** at a dose of 0.7 mg/kg caused a relatively rapid increase in pH of the gastric perfusate to ~6, and the effect was sustained for more than 5 h after administration (Figure 2A).[13] In contrast, intravenous administration of selected compounds clearly changed the pH profile of the gastric perfusate of compound **2a** at a dose of 1 mg/kg except for compound **20s**.

Compounds **20c**, **20f**, **20g**, and **20i** caused a rapid elevation of perfusate pH after intravenous administration at 1 mg/kg, but the perfusate pH did not reach 5 obviously in any case (Figure 2B, E, F, and G). On the other hand, intravenous administration of **20d**, **20e**, **20j**, **20o**, or **20s** at a dose of 1 mg/kg increased pH of the gastric perfusate to ~5 or greater.

Compound **20d** caused rapid elevation of perfusate pH to approximately 5 after the administration of **20d** at 1 mg/kg, whereas perfusate pH rapidly decreased thereafter (Figure 2C). Compound **20d** seemed to clearly have short duration of acid suppression in line with our assumption from gastric transfer properties such as AUC in the stomach and the residual level after 24 h. Compound **20e** unfortunately possessed unacceptable parameters in terms of CYP3A4 and hERG inhibition (Table 3), but had a strong pH-increasing effect and, moreover, showed a certain level of sustained action accompanied by significantly shorter duration of action relative to compound **2a** (Figure 2D).

Compound **20j**, which possessed acceptable ADME-Tox parameters, rapidly increased pH of the gastric perfusate to approximately 6, and the effect moderately diminished thereafter (Figure 2H). Although compound **20o** showed declining behavior similar to that of **20j**, the elevation of perfusate pH by **20o** exceeded only 5, and furthermore, the onset of acid suppression was not so rapid. Its characteristic pH behavior may also be due to some extent to the gastric concentration after intravenous administration and the AUC in the stomach (Table 4).

As for compound **20s**, rapid onset of pharmacological action, and rather long-lasting acid suppression were observed as in compound **2a**. Judging by the gastric transfer properties of this compound (Table 4), further long-lasting acid suppression may be assumed. According to these results, compound **20j**, which showed moderate duration of action in rats, was selected for further analysis. We studied the effects of oral administration of compound **20j** in rats and dogs (Figures 3 and 4). As shown in Figure 3, compound **20j** inhibited histamine-stimulated gastric acid secretion in

anesthetized rats in a dose-dependent manner.

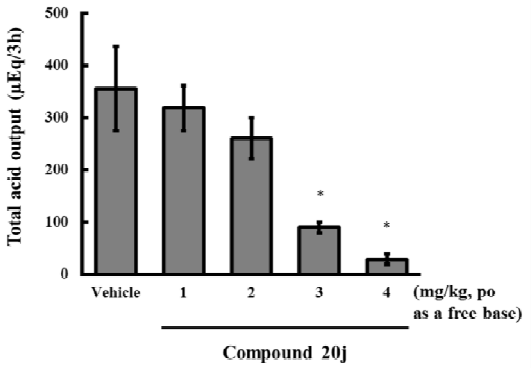


Figure 3. Effects of oral administration of compound **20j** on histamine-stimulated gastric acid secretion in anesthetized rats. Each column represents mean ± SE from seven or eight rats. Statistical significance of the difference was determined by the one-tailed Shirley-Williams test; $*p < 0.025$ compared to vehicle.

Compound **20j** also completely inhibited histamine-stimulated gastric acid secretion in Heidenhain pouch dogs after oral administration at a dose of 1 mg/kg (Figure 4A). Its duration of action was much longer than that of lansoprazole at 3 mg/kg, po (Figure 4B[13]), but significantly shorter than that of compound **2a** (Figure 4C[13]). Moreover, its effect was obviously longer as compared to that of unmethylated compound **20d** at 1 mg/kg, po (Figure 4D), and its distinct acid suppression was observed even 24 h after the administration.

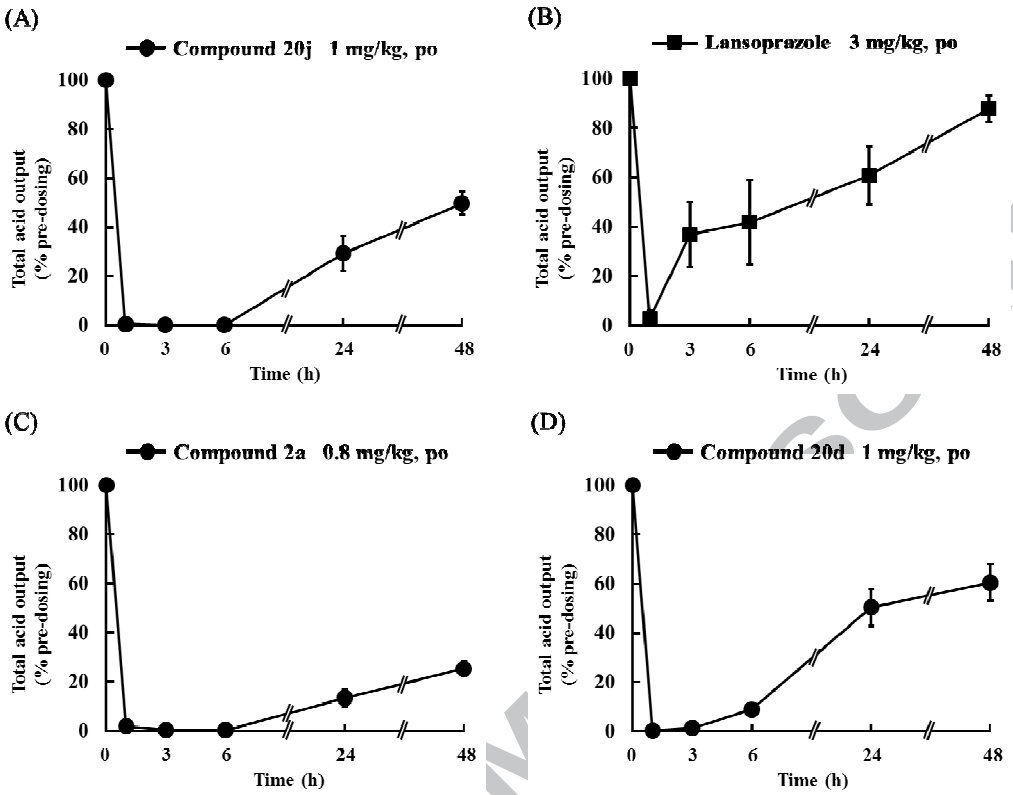
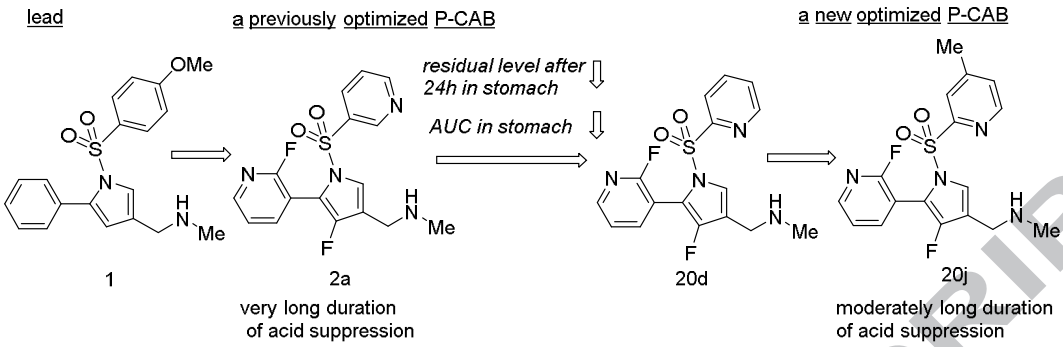


Figure 4. Effects of oral administration of compound **20j** (A), lansoprazole (B),[13] compound **2a** (C),[13] and compound **20d** (D) on histamine-stimulated gastric acid secretion in Heidenhain pouch dogs. Each data point represents mean ± SE from three or four dogs.

Compound **20j** was designed to have weak lipophilic properties (Clog P = 1.95) and moderate basicity; the log D value was 0.48 at pH 7.4 and pKa (acid dissociation constant) of the side chain amino group portion was 8.73. On the basis of these physicochemical properties such as the log D value (0.48 at pH 7.4) increased by the 5-Me-2-Py group and similar pK_a (8.73) after the introduction of fluorine as compared to compound **2a**, compound **20j** was presumed to have rapid onset and moderate duration of action after single administration because of rapid transfer into the acidic secretory canaliculi in the stomach and remaining there over an appropriate period (Figure 5).



Compound	Clog P	log D (pH 7.4)	pKa	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng·h/mL or ng·h/g) in rat plasma and stomach after intravenous administration at a dose of 0.2 mg/kg (as free base)									
						C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
						plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach	plasma	stomach
1	3.88	1.54	9.48	30	95	17.2	361.4	7.3	387.7	2.9	244	0	0	56	3730
2a	1.45	0.04	8.54	49	98	51.5	602.2	15	752.1	0	628.6	0	130.5	54	10277
20d	1.45	0.44	NT[b]	97	95	36	616.7	7.9	809.2	0	337.1	0	2.1	33	5757
20j	1.95	0.48	8.73	73	92	39.4	946.9	8.1	926.6	0	681.7	0	28.9	35	10378

[a] All values are averages of three rats.

[b] Not tested

Figure 5. Identification of a novel potent P-CAB called **20j**, which has moderately long duration of acid suppression

These results indicate that the pharmacological effect of compound **20j** is superior to that of lansoprazole. This new compound also showed good acid resistance and limited susceptibility to CYP polymorphism (data not shown) unlike lansoprazole. Furthermore, the overall DMPK and safety profiles of **20j** were excellent as in compound **2a**.

Additionally, compound **20j** was expected to have equal or slightly shorter duration of action in humans as compared with **TAK-438**,[17–21] which was recently launched in Japan for the treatment of gastric ulcer, duodenal ulcer, erosive esophagitis, prevention of low-dose aspirin- or non-steroidal anti-inflammatory drug-induced ulcer recurrence, and as an adjunctive therapy for *Helicobacter pylori* eradication, judging by **20j**'s pharmacological effects in rats and Heidenhain pouch dogs.

On the basis of these findings, compound **20j**, which has physicochemical properties different from those of **TAK-438** (e.g., in terms of lipophilicity and basicity), could be a promising alternative as a P-CAB, if the need arises.

4. **Conclusion**

We synthesized novel pyrrole derivatives that show moderate duration of acid suppression—in

accordance with our hypothesis based on previously optimized compound **2a**—and we evaluated their potency including stomach transfer and safety profiles. Our initial plan for identification of a desired compound with moderate duration of action involved studying both the effects of a fluorine group at position 4 and of hetero-aromatic groups at position 1 of the pyrrole ring regarding the stomach concentration behavior. Consequently, we found that the pyrrole compound that has both a fluorine group at position 4 and a 2-pyridyl sulfonyl group at position 1 possesses potentially favorable properties. Eventually, our experiments revealed that the combination of 2-F-3-Py group at position 5, a fluorine group at position 4, and 4-Me-2-Py sulfonyl group at the first position of the pyrrole ring was probably the most suitable for both potent activity and moderately long duration of action accompanied by low lipophilicity and acceptable ADME-Tox parameters.

Thus, identified compound **20j** showed potent H^+,K^+-ATPase inhibitory activity in vitro and potent moderately long-lasting inhibitory effects on histamine-stimulated gastric acid secretion in rats and Heidenhain pouch dogs. We succeeded in identifying a new P-CAB with moderately long duration of action as a possible alternative to TAK-438 if the need arises.

5. Experimental section

Experimental procedures and characterization data for all synthetic intermediates are reported in Supplementary data.

5.1. General

The pKa values were measured by pH-metric assays using a Sirius T3 system (Sirius Analytical Ltd., UK). The assay measures the concentration of H^+ ions in solution between pH 2 and 12 using a pH electrode (Ag/AgCl). Melting points were determined on a Yanagimoto micro melting point apparatus or Büche B-545 or by differential scanning calorimetry (DSC) or TG-DTA analyses. DSC analyses were conducted using a DSC1 system (Mettler Toledo, Switzerland). The thermograms were obtained at a temperature of 25–300 °C and a heating rate of 5 °C/min under nitrogen gas at a flow rate of 40 mL/min. The powders (~1 mg) were weighed in an aluminum pan, crimped, and then placed in the thermal analysis chamber. TG-DTA analyses were carried out by Sumika Chemical Analysis Service, Ltd. Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian Gemini-200, Varian Mercury-300, and Bruker AV-300M 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 spectrometry (HRMS) experiments were carried out by Sumika Chemical Analysis Service, Ltd. All MS experiments were conducted using electrospray ionization (ESI) in positive or negative ion mode. Elemental analyses were obtained from Takeda Analytical Laboratories, Ltd., or Sumika Chemical Analysis Service, Ltd. Thin-layer

chromatography (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 run 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 μM or NH 60 μM, Fuji Silysia Chemical, Ltd.). Commercial reagents and solvents were used without additional purification.

5.2.

*1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(thiophen-2-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine hydrochloride (**20a**)*

To a solution of compound **19a** (276 mg, 0.59 mmol) in EtOAc (2 mL) and iPrOH (1 mL) was added 4 mol/L HCl/EtOAc (5 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from EtOH to obtain compound **20a** as colorless crystals (168 mg, 70%): mp 196 °C; ^{1}H-NMR (DMSO-d_6) δ 2.56 (3H, s), 4.05 (2H, s), 7.22 (1H, dd, *J* = 5.1 Hz, 4.0 Hz), 7.48–7.56 (2H, m), 7.85 (1H, d, *J* = 5.5 Hz), 7.93 (1H, ddd, *J* = 9.5 Hz, 7.5 Hz, 2.0 Hz), 8.18 (1H, dd, *J* = 4.9 Hz, 1.3 Hz), 8.40 (1H, dq, *J* = 4.9 Hz, 0.9 Hz), 9.12 (2H, brs); Anal. Calcd for $C_{15}H_{14}ClF_2N_3O_2S_2$: C, 44.39; H, 3.48; N, 10.35. Found: C, 44.31; H, 3.41; N, 10.35.

5.3.

*1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(furan-2-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine hydrochloride (**20b**)*

Compound **20b** was prepared from **19b** following a similar procedure as for the preparation of compound **20a** from **19a**. Colorless crystals (77%): mp 229 °C; ^{1}H-NMR (DMSO-d_6) δ 2.58 (3H, s), 4.07 (2H, s), 6.77 (1H, dd, *J* = 3.8 Hz, 1.7 Hz), 7.17 (1H, d, *J* = 3.8 Hz), 7.50 (1H, ddd, *J* = 7.1 Hz, 5.2 Hz, 1.4 Hz), 7.80 (1H, d, *J* = 5.5 Hz), 7.94 (1H, ddd, *J* = 9.3 Hz, 7.5 Hz, 1.6 Hz), 8.13 (1H, s), 8.40 (1H, d, *J* = 4.3 Hz), 9.04 (2H, brs); Anal. Calcd for $C_{15}H_{14}ClF_2N_3O_3S$: C, 46.22; H, 3.62; N, 10.78. Found: C, 46.08; H, 3.50; N, 10.65.

5.4.

*1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(furan-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine hydrochloride (**20c**)*

Compound **20c** was prepared from **19c** following a similar procedure as for the preparation of compound **20a** from **19a**. Colorless crystals (76%): mp 234 °C; ^{1}H-NMR (DMSO-d_6) δ 2.57 (3H, s), 4.05 (2H, s), 6.72 (1H, dd, *J* = 1.9 Hz, 0.8 Hz), 7.49 (1H , ddd, *J* = 7.3 Hz, 5.0 Hz, 1.7 Hz), 7.85 (1H, d, *J* = 5.7 Hz), 7.91 (1H, ddd, *J* = 9.6 Hz, 7.5 Hz, 1.9 Hz), 7.96 (1H, t, *J* = 1.9 Hz), 8.33 (1H, dd, *J* = 1.5 Hz, 0.8 Hz), 8.36–8.41 (1H, m), 9.32 (2H, brs); Anal. Calcd for $C_{15}H_{14}ClF_2N_3O_3S$: C, 46.22; H,

3.62; N, 10.78. Found: C, 46.26; H, 3.58; N, 10.80.

5.5.

*1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-2-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine hydrochloride (**20d**)*

To a solution of compound **19d** (221 mg, 0.477 mmol) in EtOAc (2 mL) and EtOH (2 mL) was added 4 mol/L HCl/EtOAc (4 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from EtOH/EtOAc (1/3) to obtain compound **20d** as colorless crystals (175 mg, 92%): mp 187–188 °C; ^{1}H-NMR (DMSO-d_6) δ 2.56 (3H, s), 4.06 (2H, s), 7.42–7.48 (1H, m), 7.72–7.92 (4H, m), 8.07–8.15 (1H, m), 8.33–8.38 (1H, m), 8.70–8.74 (1H, m), 9.18 (2H, brs); Anal. Calcd for $C_{16}H_{15}ClF_2N_4O_2S$: C, 47.94; H, 3.77; N, 13.98. Found: C, 48.01; H, 3.74; N, 14.04.

5.6.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-methoxypyridin-2-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methyl methanamine hydrochloride (**20e**)*

Compound **20e** was prepared from **19e** following a similar procedure as for the preparation of compound **20a** from **19a**. Colorless crystals (51%): mp 202–204 °C; ^{1}H-NMR (DMSO-d_6) δ 2.58 (3H, s), 3.79 (3H, s), 4.08 (2H, s), 7.21 (1H, d, J = 8.4 Hz), 7.32 (1H, d, J = 6.9 Hz), 7.42–7.46 (1H, m), 7.81–7.89 (2H, m), 7.94 (1H, dd, J = 8.4 Hz, 6.9 Hz), 8.33–8.35 (1H, m), 8.96 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_3S$: C, 47.39; H, 3.98; N, 13.00. Found: C, 47.27; H, 3.90; N, 13.00.

5.7.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methoxypyridin-2-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methyl methanamine hydrochloride (**20f**)*

Compound **20f** was prepared from **19f** following a similar procedure as for the preparation of compound **20a** from **19a**. Colorless crystals (79%): mp 205–208 °C; ^{1}H-NMR (DMSO-d_6) δ 2.57 (3H, s), 3.87 (3H, s), 4.06 (2H, s), 7.17 (1H, d, J = 2.3 Hz), 7.33 (1H, dd, J = 5.7 Hz, 2.7 Hz), 7.46 (1H, ddd, J = 6.9 Hz, 5.2 Hz, 1.5 Hz), 7.80 (1H, d, J = 5.7 Hz), 7.89 (1H, ddd, J = 9.3 Hz, 7.6 Hz, 1.7 Hz), 8.30–8.39 (1H, m), 8.51 (1H, d, J = 5.7 Hz), 9.01 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_3S$: C, 47.39; H, 3.98; N, 13.00. Found: C, 47.47; H, 3.97; N, 12.97.

5.8.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-methoxypyridin-2-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methyl methanamine hydrochloride (**20g**)*

Compound **20g** was prepared from **19g** following a similar procedure as for the preparation of

compound **20a** from **19a**. Colorless crystals (88%): mp 229–233 °C; ^{1}H-NMR (DMSO-d_6) δ 2.54 (3H, s), 3.91 (3H, s), 4.03 (2H, s), 7.38–7.46 (1H, m), 7.51–7.58 (1H, m), 7.62–7.70 (1H, m), 7.75–7.87 (2H, m), 8.33 (1H, dt, *J* = 4.7 Hz, 0.8 Hz), 8.36 (1H, d, *J* = 3.0 Hz), 9.20 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_3S$: C, 47.39; H, 3.98; N, 13.00. Found: C, 47.35; H, 4.27; N, 12.77.

5.9.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(3-methylpyridin-2-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine fumarate (**20h**)*

To a solution of compound **19h** (107 mg, 0.223 mmol) in EtOAc (2 mL) and iPrOH (1 mL) was added 4 mol/L HCl/EtOAc (3 mL), and the mixture was stirred at room temperature for 1 h, and then concentrated under reduced pressure. A solution of $NaHCO_3$ was added to the residue, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by basic silica gel column chromatography (n-hexane/EtOAc = 4/1–1/1), and then the obtained oil (45 mg) was dissolved in EtOAc (2 mL). A solution of fumaric acid (13.6 mg, 0.117 mmol) in EtOH (2 mL) was added at room temperature, and the mixture was concentrated under reduced pressure. The residue was crystalized from EtOH/EtOAc (1/10) to produce compound **20h** as colorless crystals (51 mg, 46%): mp 150 °C; ^{1}H-NMR (DMSO-d_6) δ 2.35 (3H, s), 2.38 (3H, s), 3.73 (2H, s), 6.53 (2H, s), 7.32–7.39 (1H, m), 7.48 (1H, d, *J* = 5.7 Hz), 7.63 (1H, dd, *J* = 7.8 Hz, 4.4 Hz), 7.74–7.83 (1H, m), 7.93 (1H, d, *J* = 7.6 Hz), 8.27 (1H, d, *J* = 4.2 Hz), 8.41 (1H, d, *J* = 4.5 Hz), 3H not detected. Anal. Calcd for $C_{21}H_{20}F_2N_4O_6S$: C, 51.01; H, 4.08; N, 11.33. Found: C, 50.70; H, 4.16; N, 11.19.

5.10.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-methylpyridin-2-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine hydrochloride (**20i**)*

Compound **20i** was prepared from **19i** following a similar procedure as for the preparation of compound **20a** from **19a**. Colorless crystals (53%): mp 217–220 °C; ^{1}H-NMR (DMSO-d_6) δ 2.49 (3H, s), 2.54 (3H, s), 4.04 (2H, s), 7.43–7.48 (1H, m), 7.58–7.64 (2H, m), 7.79 (1H, d, *J* = 5.4 Hz), 7.88–7.99 (2H, m), 8.34–8.35 (1H, m), 9.21 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_2S$: C, 49.22; H, 4.13; N, 13.51. Found: C, 49.23; H, 4.11; N, 13.49.

5.11.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-2-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine succinate (**20j**)*

To a solution of compound **19j** (333 mg, 0.696 mmol) in EtOAc (2 mL) and iPrOH (1 mL) was added 4 mol/L HCl/EtOAc (3 mL), and the mixture was stirred at room temperature for 1 h, and then

concentrated under reduced pressure. The residue was crystalized from EtOAc, and the obtained crystals were recrystallized from EtOAc/EtOH (5/1) to produce 1-{4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylm ethanamine hydrochloride (191 mg, 66 % from **19j**) as colorless crystals; mp 181–185 °C; ^{1}H-NMR (DMSO-d_6) δ 2.37 (3H, s), 2.56 (3H, s), 4.05 (2H, s), 7.45 (1H, ddd, *J* = 7.3 Hz, 5.0 Hz, 1.7 Hz), 7.54 (1H, s), 7.59–7.66 (1H, m), 7.77–7.90 (2H, m), 8.33–8.40 (1H, m), 8.55 (1H, d, *J* = 4.9 Hz), 9.11 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_2S$: C, 49.22; H, 4.13; N, 13.51. Found: C, 49.30; H, 4.42; N, 13.61.

A solution of $NaHCO_3$ was added to the crystals (751 mg, 1.81 mmol), and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford 1-{4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylm ethanamine (647 mg, 62% from **19j**) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 2.38 (3H, s), 2.45 (3H, s), 3.64 (2H, s), 7.23–7.30 (2H, m), 7.33 (1H, d, *J* = 5.7 Hz), 7.36 (1H, s), 7.88 (1H, ddd, *J* = 9.3 Hz, 7.4 Hz, 1.9 Hz), 8.22–8.29 (1H, m), 8.45 (1H, d, *J* = 4.5 Hz), 1H not detected.

The obtained oil (189 mg, 0.50 mmol) was dissolved in EtOAc (2 mL). A solution of succinic acid (59 mg, 0.50 mmol) in EtOH (2 mL) was added at room temperature, and the mixture was concentrated under reduced pressure. The resulting solid was recrystallized from EtOH/H_2O (10/1) to obtain compound **20j** as colorless crystals (232 mg, 58% from **19j**): mp 166–168 °C; ^{1}H-NMR (DMSO-d_6) δ 2.34 (3H, s), 2.36 (4H, s), 2.37 (3H, s), 3.66 (2H, s), 7.39–7.49 (2H, m), 7.52 (1H, s), 7.55–7.63 (1H, m), 7.86 (1H, ddd, *J* = 9.5 Hz, 7.4 Hz, 1.9 Hz), 8.34 (1H, ddd, *J* = 4.9 Hz, 1.9 Hz, 0.9 Hz), 8.54 (1H, d, *J* = 4.9 Hz), 3H not detected. Anal. Calcd for $C_{21}H_{22}F_2N_4O_6S$: C, 50.80; H, 4.47; N, 11.28. Found: C, 50.77; H, 4.52; N, 11.37.

5.12.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-fluoropyridin-2-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine hydrochloride (**20k**)*

Compound **20k** was prepared from **19k** following a similar procedure as for the preparation of compound **20d** from **19d**. Colorless crystals (53%): mp 215–218 °C; ^{1}H-NMR (DMSO-d_6) δ 2.58 (3H, s), 4.08 (2H, s), 7.44–7.48 (1H, m), 7.65–7.78 (3H, m), 7.87–7.92 (1H, m), 8.28–8.37 (2H, m), 8.85 (2H, brs); Anal. Calcd for $C_{16}H_{14}ClF_3N_4O_2S$: C, 45.88; H, 3.37; N, 13.38. Found: C, 45.51; H, 3.38; N, 13.26.

5.13.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-fluoropyridin-2-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine hydrochloride (**20l**)*

Compound **20l** was prepared from **19l** following a similar procedure as for the preparation of compound **20a** from **19a**. Colorless crystals (51%): mp 200–204 °C; ^{1}H-NMR (DMSO-d_6) δ 2.58 (3H, s), 4.07 (2H, s), 7.41–7.49 (1H, m), 7.80 (1H, d, *J* = 5.5 Hz), 7.82–7.91 (2H, m), 8.05 (1H, dt, *J* = 8.6 Hz, 2.8 Hz), 8.36 (1H, ddd, *J* = 4.9 Hz, 1.9 Hz, 0.9 Hz), 8.78 (1H, d, *J* = 2.8 Hz), 8.97 (2H, brs); Anal. Calcd for $C_{16}H_{14}ClF_3N_4O_2S$: C, 45.88; H, 3.37; N, 13.38. Found: C, 45.95; H, 3.46; N, 13.43.

5.14.

*1-{1-[(2-Chloropyridin-3-yl)sulfonyl]-4-fluoro-5-(2-fluoropyridin-3-yl)-1H-pyrrol-3-yl}-N-methylmethanamine hydrochloride (**20m**)*

Compound **20m** was prepared from **19m** following a similar procedure as for the preparation of compound **20d** from **19d**. Colorless crystals (90%): mp 219 °C; ^{1}H-NMR (DMSO-d_6) δ 2.59 (3H, s), 4.09 (2H, s), 7.40–7.48 (1H, m), 7.52 (1H, dd, *J* = 8.0 Hz, 4.5 Hz), 7.72–7.79 (1H, m), 7.81–7.91 (1H, m), 7.93–8.02 (1H, m), 8.32–8.36 (1H, m), 8.75 (1H, dd, *J* = 4.7 Hz, 1.7 Hz), 9.21 (2H, brs). Anal. Calcd for $C_{16}H_{14}Cl_2F_2N_4O_2S$: C, 44.15; H, 3.24; N, 12.87. Found: C, 43.98; H, 3.41; N, 12.86.

5.15.

*1-{1-[(5-Chloropyridin-3-yl)sulfonyl]-4-fluoro-5-(2-fluoropyridin-3-yl)-1H-pyrrol-3-yl}-N-methylmethanamine hydrochloride (**20n**)*

Compound **20n** was prepared from **19n** following a similar procedure as for the preparation of compound **20a** from **19a**. Colorless crystals (95%): mp 211–216 °C; ^{1}H-NMR (DMSO-d_6) δ 2.57 (3H, s), 4.05 (2H, s), 7.52 (1H, ddd, *J* = 7.3 Hz, 5.1 Hz, 1.9 Hz), 7.93 (1H, ddd, *J* = 9.6 Hz, 7.5 Hz, 2.0 Hz), 8.01 (1H, d, *J* = 5.5 Hz), 8.11 (1H, t, *J* = 2.2 Hz), 8.43 (1H, ddd, *J* = 4.9 Hz, 1.8 Hz, 0.8 Hz), 8.57 (1H, d, *J* = 2.1 Hz), 9.05 (1H, d, *J* = 2.1 Hz), 9.33 (2H, brs); Anal. Calcd for $C_{16}H_{14}Cl_2F_2N_4O_2S$: C, 44.15; H, 3.24; N, 12.87. Found: C, 44.20; H, 3.56; N, 12.90.

5.16.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-fluoropyridin-3-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine hydrochloride (**20o**)*

Compound **20o** was prepared from **19o** following a similar procedure as for the preparation of compound **20a** from **19a**. Colorless crystals (65%): mp 228–233 °C; ^{1}H-NMR (DMSO-d_6) δ 2.57 (3H, s), 4.05 (2H, s), 7.51 (1H, ddd, *J* = 7.4 Hz, 5.1 Hz, 1.9 Hz), 7.92 (1H, ddd, *J* = 9.5 Hz, 7.6 Hz, 1.9 Hz), 8.01 (1H, d, *J* = 5.3 Hz), 8.05 (1H, dt, *J* = 7.7 Hz, 2.4 Hz), 8.36–8.46 (1H, m), 8.49 (1H, s), 9.03 (1H, d, *J* = 2.7 Hz), 9.36 (2H, brs); Anal. Calcd for $C_{16}H_{14}ClF_3N_4O_2S$: C, 45.88; H, 3.37; N, 13.38. Found: C, 45.94; H, 3.35; N, 13.47.

5.17.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(2-methylpyridin-3-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine fumarate (**20p**)*

Compound **20p** was prepared from **19p** following a similar procedure as for the preparation of compound **20h** from **19h**. Colorless crystals (85%): mp 182–185 °C; ^{1}H-NMR (DMSO-d_6) δ 2.41 (3H, s), 2.49 (3H, s), 3.77 (2H, s), 6.53 (2H, s), 7.31 (1H, dd, *J* = 8.1 Hz, 4.7 Hz), 7.42 (1H, ddd, *J* = 7.2 Hz, 5.1 Hz, 1.7 Hz), 7.47 (1H, dd, *J* = 8.3 Hz, 1.5 Hz), 7.71 (1H, d, *J* = 5.7 Hz), 7.84 (1H, ddd, *J* = 9.6 Hz, 7.5 Hz, 1.9 Hz), 8.28–8.34 (1H, m), 8.73 (1H, dd, *J* = 4.7 Hz, 1.7 Hz), 3H not detected; Anal. Calcd for $C_{21}H_{20}F_2N_4O_6S$: C, 51.01; H, 4.08; N, 11.33. Found: C, 51.06; H, 4.10; N, 11.37.

5.18.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-3-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine fumarate (**20q**)*

Compound **20q** was prepared from **19q** following a similar procedure as for the preparation of compound **20h** from **19h**. Colorless crystals (78%): mp 205–208 °C; ^{1}H-NMR (DMSO-d_6) δ 2.33 (3H, s), 2.40 (3H, s), 3.76 (2H, s), 6.53 (2H, s), 7.43 (1H, ddd, *J* = 7.3 Hz, 5.1 Hz, 1.8 Hz), 7.52 (1H, d, *J* = 5.1 Hz), 7.72 (1H, d, *J* = 5.7 Hz), 7.85 (1H, ddd, *J* = 9.5 Hz, 7.4 Hz, 1.9 Hz), 8.14 (1H, s), 8.32 (1H, ddd, *J* = 4.9 Hz, 1.9 Hz, 0.9 Hz), 8.70 (1H, d, *J* = 5.1 Hz), 3H not detected; Anal. Calcd for $C_{21}H_{20}F_2N_4O_6S$: C, 51.01; H, 4.08; N, 11.33. Found: C, 50.95; H, 4.11; N, 11.37.

5.19.

*1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-methylpyridin-3-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine fumarate (**20r**)*

Compound **20r** was prepared from **19r** following a similar procedure as for the preparation of compound **20h** from **19h**. Colorless crystals (76%): mp 178–182 °C; ^{1}H-NMR (DMSO-d_6) δ 2.33 (3H, s), 2.35 (3H, s), 3.70 (2H, s), 6.54 (2H, s), 7.50 (1H, ddd, *J* = 7.3 Hz, 5.1 Hz, 1.9 Hz), 7.63–7.71 (2H, m), 7.90 (1H, ddd, *J* = 9.6 Hz, 7.5 Hz, 2.0 Hz), 8.36–8.41 (1H, m), 8.42 (1H, d, *J* = 2.3 Hz), 8.76 (1H, d, *J* = 1.3 Hz), 3H not detected; Anal. Calcd for $C_{21}H_{20}F_2N_4O_6S$: C, 51.01; H, 4.08; N, 11.33. Found: C, 50.88; H, 4.06; N, 11.31.

5.20.

*Bis{1-[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(6-methypyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine}fumarate (**20s**)*

Compound **20s** was prepared from **19s** following a similar procedure as for the preparation of compound **20h** from **19h**. Colorless crystals (70%): mp 192–195 °C; ^{1}H-NMR (DMSO-d_6) δ 2.30 (3H, s), 2.56 (3H, s), 3.61 (2H, s), 6.51 (1H, s), 7.45–7.53 (2H, m), 7.60 (1H, d, *J* = 5.7 Hz), 7.79

(1H, dd, J = 8.3 Hz, 2.3 Hz), 7.91 (1H, ddd, J = 9.6 Hz, 7.5 Hz, 1.9 Hz), 8.35–8.40 (1H, m), 8.48 (1H, d, J = 2.3 Hz), 2H not detected; Anal. Calcd for $C_{19}H_{18}F_2N_4O_4S$: C, 52.29; H, 4.16; N, 12.84. Found: C, 52.32; H, 4.28; N, 12.86.

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

Measurement of H^+,K^+-ATPase activity was done using the method described elsewhere.[14]

5.22. An assay of inhibition of acid secretion in anesthetized rats by intravenous administration

This assay was performed using the method described elsewhere.[14]

5.23. An assay of inhibition of acid secretion in anesthetized rats by oral administration

This assay was conducted in a manner similar to a method reported elsewhere.[13] A test compound at doses of 1, 2, 3, or 4 mg/kg (as the free base) or vehicle was administered orally 1 h before pylorus ligation and histamine 2HCl (30 mg/kg, subcutaneous) administration. Gastric contents were collected 3 h after histamine administration, and the total acid output was calculated.

5.24. Measurement of pH of a gastric perfusate under conditions of histamine stimulation in anesthetized rats

This assay was performed by the method described elsewhere.[13]

5.25. An assay of inhibition of acid secretion in Heidenhain pouch dogs

This assay was performed by the method described elsewhere.[13]

5.26. A pharmacokinetic experiment in rats

Test compounds were administered intravenously via cassette dosing to fasted male Sprague-Dawley rats. After that, blood and the stomach were collected. The blood samples were centrifuged to obtain the plasma fraction. The plasma and a 20% stomach homogenate in saline were deproteinized with acetonitrile containing an internal standard. After centrifugation, the supernatant was diluted and centrifuged again. The compound concentrations in the supernatant were measured by LC/MS/MS.

5.27. A cytotoxicity assay

This assay was carried out by the method described elsewhere.[13]

5.28. Whole-cell patch-clamp for a hERG inhibition assay

This assay was conducted using a procedure described elsewhere.[13]

5.29. Measurement of CYP3A4-inhibitory activity

This activity of test compounds was evaluated by incubating 100 μmol/L testosterone with 10 nmol/L CYP3A4 derived from CYP3A4-expressing insect cells (BD Bioscience) in the presence of 10 μmol/L test compound. The reaction mixture was incubated for 15 min at 37 °C. The concentration of 6β-hydroxytestosterone was measured by means of an HPLC system equipped with an ultraviolet light detector.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version.

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Graphical Abstract

Exploration of pyrrole derivatives to find an effective potassium-competitive acid blocker with moderately long-lasting suppression of gastric acid secretion

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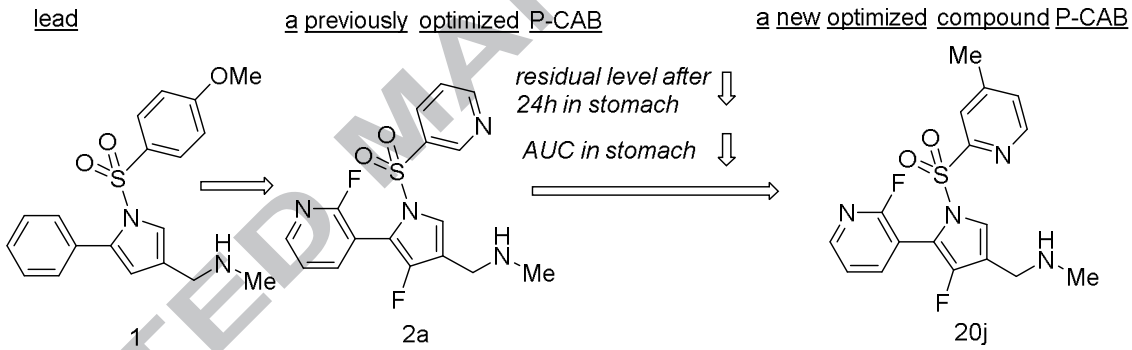

	1	2a	20j
Clog P	3.88	1.45	1.95
log D (pH 7.4)	1.54	0.04	0.48