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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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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 C log 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

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

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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]

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 (Fig. 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.

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.

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

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

Compound	ClogP	LogD	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	10,277

[a] All values are averages of three rats.
[b] ATP content at 30 μM (% control).