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Novel 1*H*-pyrrolo[2,3-*c*]pyridines as acid pump antagonists (APAs)

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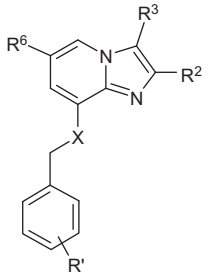
ABSTRACT

A series of 1*H*-pyrrolo[2,3-*c*]pyridines as acid pump antagonists (APAs) was synthesized and the inhibitory activities against H^+/K^+ ATPase isolated from hog gastric mucosa were determined. After elaborating on substituents at N1, C5, and C7 position of 1*H*-pyrrolo[2,3-*c*]pyridine scaffold, we have observed that compounds **14f** and **14g** are potent APAs with H^+/K^+ ATPase IC_{50} = 28 and 29 nM, respectively.

Gastroesophageal reflux disease (GERD) is a common acid-related disorder that occurs in approximately 10–20% of Western people and about 5% of people in Asia, it is defined as at least a weekly episode of heartburn and/or acid regurgitation.[1] The severity of the symptoms and esophageal mucosal damage were correlated well with the exposure of the esophagus to gastric acid.[2] Therefore, acid suppression is considered as the first-line therapy for GERD, and many drugs that suppress the acid secretion are now available. These conventional agents are histamine 2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs). Presently, PPIs are recognized as the 'treatment of choice' in most countries.[3] However, PPIs still continue to have their set of limitations. The currently available PPIs require around 3–5 days to achieve maximum acid inhibition at existent therapeutic doses, primarily due to their chemical structures and irreversible inhibition of H^+/K^+ ATPase.[4] Failure to demonstrate a sustained acid inhibition throughout the day and night, in spite of twice daily administration, and nocturnal acid breakthrough (NAB) are found to be common in patients taking PPIs.[5] Therefore, many novel strategies to address the unmet needs of existent PPI therapy have been investigated, and acid pump antagonists (APAs) could play a promising role, as they provide faster onset and longer duration of action than conventional PPIs by virtue of their ability to reversibly bind to the proton pump.[6]

APAs are lipophilic and weak bases that have diverse structures such as, imidazopyridines, pyrimidines, imidazonaphthyridines, quinolines, etc.[6] The APAs studied most extensively so far rely on substituted imidazo[1,2-*a*]pyridine derivatives (**1**) (Fig. 1). And they



1

R^2 = substituted small alkyl, etc.
R^3 = substituted small alkyl, etc.
R^6 = H, amide, etc.
R' = alkyl, halogen, etc.
X = O, N, etc.

Figure 1. Structure of imidazo[1,2-*a*]pyridine APAs **1**.

were shown to inhibit the gastric acid secretion by reversible and K^+ competitive binding to H^+/K^+ ATPase, and they also displayed excellent antisecretory properties.[7–9]

In the course of our efforts to develop novel and potent APAs, we were able to identify APAs that have a novel heterocyclic scaffold different from the well-known imidazo[1,2-*a*]pyridine. Here, we report the synthesis and pharmacological evaluation of 1*H*-pyrrolo[2,3-*c*]pyridine derivatives of the general formula **2** as APAs (Fig. 2).

Reaction of commercially available 2-chloro-3-nitropyridine **3** with respective benzyl alcohols using tris[2-(2-methoxyethoxy)-ethyl]amine (TDA) as a phase transfer catalyst led to 2-benzyloxy

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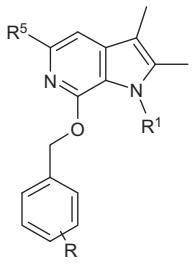


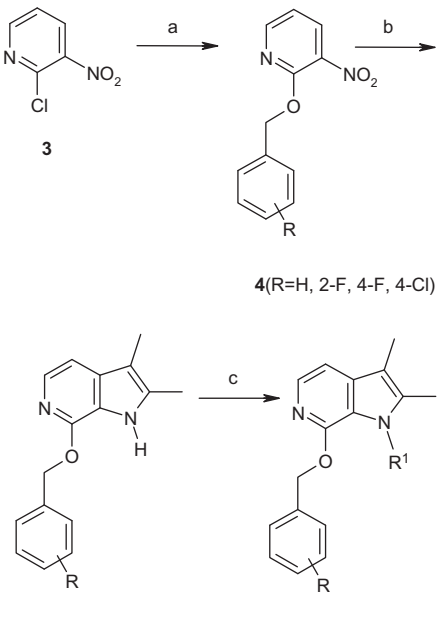
2

R^1 = H, substituted alkyl, alkenyl, benzyl, etc.
R^5 = H, amide
R = H, F, Cl

Figure 2. Structure of 1*H*-pyrrolo[2,3-*c*]pyridine APAs **2**.

substituted 3-nitropyridines **4** in good yield (84–95%). Subsequently, substituted 1*H*-pyrrolo[2,3-*c*]pyridines **5** was prepared by Bartoli reaction as described in the literature.[10] Reaction of 2-benzyloxy substituted 3-nitropyridines **4** with 1-methyl-1-propenyl magnesium bromide 0.5 M in anhydrous THF under nitrogen atmosphere at −78 °C provided 7-benzyloxy substituted 1*H*-pyrrolo-[2,3-*c*]pyridines **5** in moderate yield (12–39%). After deprotonation of 7-benzyloxy substituted 1*H*-pyrrolo[2,3-*c*]pyridines **5** with potassium *t*-butoxide and 18-crown-6, transformation with respective substituted alkyl or benzyl halide afforded corresponding N-1-alkylated pyrrolo[2,3-*c*]pyridine derivatives **6** in moderate to good yield (41–76%, Scheme 1).

5-Amide substituted 1*H*-pyrrolo[2,3-*c*]pyridine derivatives were obtained starting from commercially available 2,6-dichloro-



3

4(R=H, 2-F, 4-F, 4-Cl)

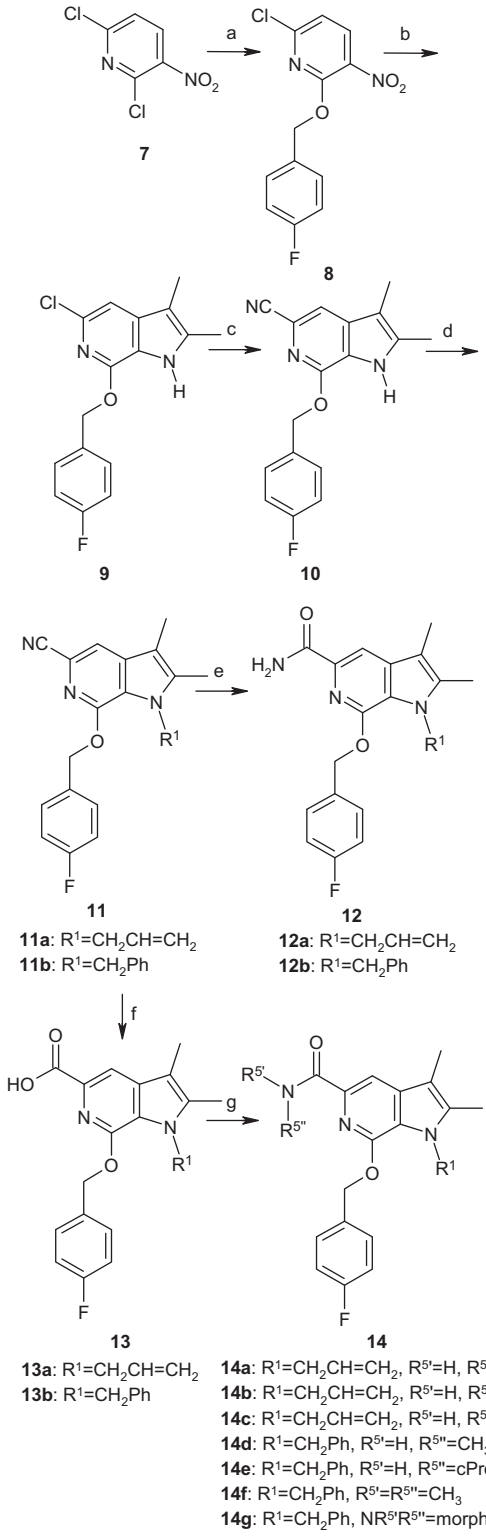
5

5a: R=H
5b: R=2-F
5c: R=4-F
5d: R=4-Cl

6

6a: $R^1 = CH_2CH{=}CH_2$, R = 4-F
6b: $R^1 = CH_2CH(CH_3)_2$, R = 4-F
6c: $R^1 = CH_2CH(CH_3)_2$, R = 4-Cl
6d: $R^1 = CH_2CH_2CH_3$, R = 4-F
6e: $R^1 = CH_2$[1,3]dioxolane, R = 4-F
6f: $R^1 = CH_2$cPro, R = 4-F
6g: $R^1 = CH_2Ph$, R = 4-Cl

Scheme 1. Reagents and conditions: (a) benzyl alcohols, TDA, KOH, K_2CO_3, toluene, rt, 40 min, 84–95%; (b) 1-methyl-1-propenyl magnesium bromide, THF, −78 °C, 1 h, 12–39%; (c) alkyl halide, KO^{t}Bu, 18-crown-6, THF, rt, 12 h, 41–76%.



7

8

9

10

11

11a: $R^1 = CH_2CH{=}CH_2$
11b: $R^1 = CH_2Ph$

12

12a: $R^1 = CH_2CH{=}CH_2$
12b: $R^1 = CH_2Ph$

13

13a: $R^1 = CH_2CH{=}CH_2$
13b: $R^1 = CH_2Ph$

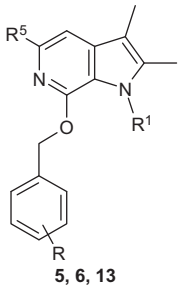
14

14a: $R^1 = CH_2CH{=}CH_2$, $R^{5'}$=H, $R^{5''}$=CH_3
14b: $R^1 = CH_2CH{=}CH_2$, $R^{5'}$=H, $R^{5''}$=cPro
14c: $R^1 = CH_2CH{=}CH_2$, $R^{5'}$=H, $R^{5''}$=4-pyridyl
14d: $R^1 = CH_2Ph$, $R^{5'}$=H, $R^{5''}$=CH_3
14e: $R^1 = CH_2Ph$, $R^{5'}$=H, $R^{5''}$=cPro
14f: $R^1 = CH_2Ph$, $R^{5'}$=$R^{5''}$=CH_3
14g: $R^1 = CH_2Ph$, $NR^{5'}R^{5''}$=morpholinyl

Scheme 2. Reagents and conditions: (a) benzyl alcohol, TDA, KOH, K_2CO_3, toluene, rt, 40 min, 69%; (b) 1-methyl-1-propenyl magnesium bromide, THF, −78 °C, 1 h, 30%; (c) CuCN, DMF, 160 °C, 2 days, 15%; (d) alkyl halide, NaH, DMF, rt, 45–60%; (e) KOH, EtOH/H_2O, reflux, 2 h, 80–84%; (f) KOH, EtOH/H_2O, reflux, 3 days, 75–80%; (g) EDC, HOBT, DIPEA, $R^{5'}R^{5''}$ NH, CH_2Cl_2, overnight, 50–77%.

3-nitropyridine **7** (Scheme 2). 5-Chloro-7-(4-fluorobenzyloxy)-2,3-dimethyl-1*H*-pyrrolo[2,3-*c*]pyridine intermediate **9** was synthesized following the same procedures as shown in Scheme 1. For the introduction of nitrile group at C5, compound of formula **9** was

Table 1
H^+/K^+ ATPase inhibition assay results for **5**, **6**, **12**, and **14**



5, 6, 13

Compds	R^1	R^5	R	H^+/K^+ ATPase IC_{50} (μM)
5a	H	H	H	50.9%[a]
5b	H	H	2-F	32.1%[a]
5c	H	H	4-F	60.3%[a]
6a	$CH_2CH{=}CH_2$	H	4-F	0.125
6b	$CH_2CH(CH_3)_2$	H	4-F	0.196
6c	$CH_2CH(CH_3)_2$	H	4-Cl	0.205
6d	$CH_2CH_2CH_3$	H	4-F	0.302
6e	CH_2[1,3] dioxolane	H	4-F	0.173
6f	CH_2cPro	H	4-F	0.181
6g	CH_2Ph	H	4-Cl	0.187
12a	$CH_2CH{=}CH_2$	$CONH_2$	4-F	80.3%[a]
12b	CH_2Ph	$CONH_2$	4-F	16.1%[a]
14a	$CH_2CH{=}CH_2$	$CONH(CH_3)$	4-F	78.4%[a]
14b	$CH_2CH{=}CH_2$	CONH(cPro)	4-F	0.408
14c	$CH_2CH{=}CH_2$	CONH(4-pyridyl)	4-F	0.735
14d	CH_2Ph	$CONH(CH_3)$	4-F	39.4%[b]
14e	CH_2Ph	CONH(cPro)	4-F	0.738
14f	CH_2Ph	$CON(CH_3)_2$	4-F	0.028
14g	CH_2Ph	CO(morpholinyl)	4-F	0.029

[a] Inhibition percentage at 4 μM.
[b] Inhibition percentage at 1 μM.

treated with excess copper (I) cyanide in DMF at 160 °C. The low yield (15%) for **10** was to due to the low reactivity of Cl at C5. Deprotonation of **10** with NaH, and subsequent reaction with respective substituted alkyl or benzyl halide afforded N-1-alkylated derivatives **11** (45–60%). The hydrolysis of **11** under basic condition yielded carboxylic acid derivatives **13** via carboxamides (**12**, $R^{5\prime} = R^{5\prime\prime} = H$) in good yield (75–80%). Finally, coupling of compounds of formula **13** with respective amines using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole hydrate (HOBT), and diisopropylethylamine (DIPEA) led C5-amide substituted derivatives **14** (50–77%).

Table 1 enlists the inhibitory activities of 1*H*-pyrrolo [2,3-*c*]pyridines **5**, **6**, **12**, **14** against H^+/K^+ ATPase isolated from hog gastric mucosa.[11]

The inhibitory activity against H^+/K^+ ATPase of compounds without substituents at N1 and C5 ($R^1 = R^5 = H$) was evaluated as a starting point. Compounds **5a–c** were shown to have near micromolar inhibitory concentration. After exploring the substituents of benzyloxy groups at C7 to improve inhibitory activity against H^+/K^+ ATPase, we discovered the compound of formula **5c** which substituted by 4-fluorobenzyloxy group at C7 of 1*H*-pyrrolo[2,3-*c*]-pyridine (R = 4-F) with moderately increased inhibitory activity (inhibition percentage at 4 μM = 60.3%) compared to other substituents (R = H and 2-F), indicating that the substituents at *para*-position of the benzyloxy group are favored. And the replacement of F with Cl at *para*-position of the benzyloxy group had no notable change in the inhibitory activity against H^+/K^+ ATPase exemplified by compounds **6b** and **6c** (IC_{50} = 0.196 and 0.205 μM, respectively).

Therefore, with F at *para*-position of the benzyloxy group of 1*H*-pyrrolo[2,3-*c*]pyridines held constant (R = 4-F), we further elaborated on the effect of substituents at N1 on the inhibitory activity against H^+/K^+ ATPase (**6a–b**, **6d–f**). By alkylating at N1, compounds with significantly increased inhibitory activity were obtained. Compounds **6a–b** and **6d–f** were shown to have dramatically increased activity compared to that of the compound of formula **5c** devoid of substituent at N1 ($R^1 = H$). Among them, **6a** substituted by allyl group at N1 showed much higher activity (IC_{50} = 0.125 μM) than other compounds **6b**, **6d**, **6e**, and **6f** substituted with alkyl groups of the same length at N1, which means that the substituents with sp^2 character at N1 of 1*H*-pyrrolo[2,3-*c*]pyridine are favored. The same trend was also exhibited by compounds **6c** ($R^1 = CH_2CH(CH_3)_2$) and **6g** ($R^1 = CH_2Ph$). Moderate improvement in inhibitory activity against H^+/K^+ ATPase was made by **6g** substituted by benzyl group at N1 compared to that of **6c** (IC_{50} = 0.187 and 0.205 μM, respectively).

Based on the results above, we focused on the substitution at C5. Various C5-amide substituted 1*H*-pyrrolo[2,3-*c*]pyridines (R = 4-F,

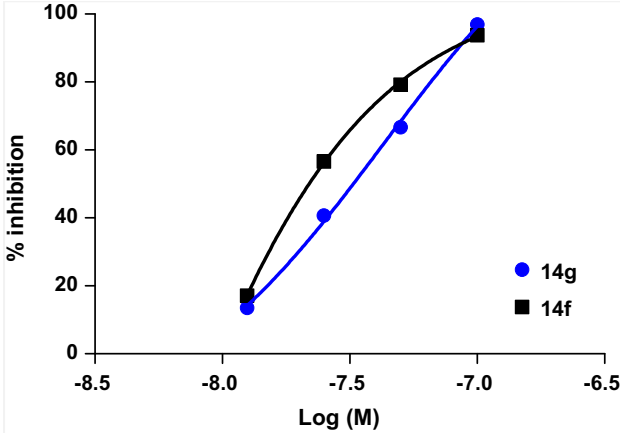


Figure 3. Dose-dependent inhibitions of H^+/K^+ ATPase by 1*H*-pyrrolo[2,3-*c*]pyridine APAs **14f** and **14g**.

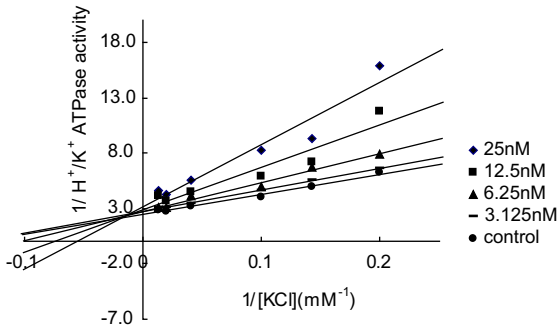


Figure 4. Lineweaver–Burk plot showing H^+/K^+ ATPase activity versus K^+ concentration for various concentrations of **14f**.

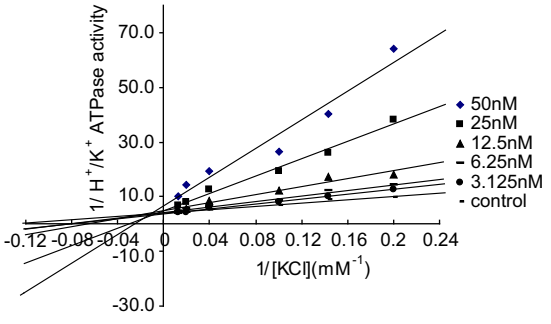


Figure 5. Lineweaver–Burk plot H^+/K^+ ATPase activity versus K^+ concentration for various concentrations of **14g**.

R^1 = allyl or benzyl) were synthesized and their inhibitory activity against H^+/K^+ ATPase was tested. C5-primary amide (R^5 = $CONH_2$) and secondary amide (R^5 = $CONH(CH_3)$, CONH(cPro), and CONH(4-pyridyl)) substituted 1*H*-pyrrolo[2,3-*c*]pyridines **12a**, **14a**, **14b**, and **14c** were shown to have lower inhibitory activity than that of unsubstituted one **6a**. However, it was notable that C5-secondary amide substituted compounds were more potent than C5-primary amide substituted compounds: **14b** (R^5 = CONH(cPro)), and **14c** (R^5 = CONH(4-pyridyl)) were shown to have more improved inhibitory activity than **12a** (R^5 = $CONH_2$, IC_{50} = 0.408 and 0.735 μM, vs inhibition percentage at 4 μM = 80.3%). A similar trend was also observed for N-1-benzyl substituted 1*H*-pyrrolo[2,3-*c*]pyridines **12b** (R^5 = $CONH_2$), **14d** (R^5 = $CONH(CH_3)$) and **14e** (R^5 = CONH(cPro)). Therefore, C5-tertiary amide substituted 1*H*-pyrrolo[2,3-*c*]pyridines was expected to show more improved inhibitory activity against H^+/K^+ ATPase compared to C5-secondary amide substituted ones, which were proved by the compounds **14f** and **14g**. Compounds **14f** (R^5 = $CON(CH_3)_2$) and **14g** (R^5 = CO(morpholinyl)) showed dose-dependent inhibitory activity against H^+/K^+ ATPase with IC_{50} = 28 and 29 nM, respectively (Fig. 3).

Compounds **14f** and **14g** inhibited H^+/K^+ ATPase activity in a K^+-competitive manner with K_i = 13.6 and 10.7 nM, respectively (Figs. 4 and 5).[12] The Lineweaver–Burk plots showed H^+/K^+ ATPase activity versus K^+ concentration for various concentrations of **14f** and **14g**, and demonstrated a common intercept with the *Y*-axis, which is characteristic of competitive inhibition.

In summary, we have prepared a series of novel 1*H*-pyrrolo [2,3-*c*]pyridines as APAs. Optimization of substituents at N1, C5, and C7 led to some potent 1*H*-pyrrolo[2,3-*c*]pyridines APAs. Especially, compounds **14f** and **14g** were shown to have excellent inhibitory activity against H^+/K^+ ATPase (IC_{50} = 28 and 29 nM, respectively). Therefore, compounds **14f** and **14g** are promising leads for further development as APAs, and this series of 1*H*-pyrrolo[2,3-*c*]pyridine derivatives would be explored for further optimization.

Acknowledgment

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11. Ion-leaky membrane vesicle enriched in gastric H^+/K^+-ATPase was derived from pig stomach as per the method described by Saccomani et al. with suitable modifications (Saccomani, G.; Stewart, H. B.; Show, D.; Lewin, M.; Sachs, G. *Biochem. Biophy. Acta* **1977**, *465*, 311). The inhibitory effects of the K^+ specific H^+/K^+-ATPase activity was calculated based on the difference between the activity of H^+/K^+-ATPase activity with and without K^+ ion. The lyophilized vesicle in 5 mM pipes/Tris buffer (pH 6.1) was pre-incubated in the presence of various concentrations of compounds. After 5 min of preincubation, negative and positive buffers were respectively added to the previous reaction mixture. As a substrate ATP was added to the reaction buffer, and incubated for 30 min at 37 °C. Enzymatic activity was stopped by adding colorimetric reagent and the amount of mono phosphate (P_i) in the reaction was measured at 620 nm using the micro plate reader. The difference between the P_i production with and without K^+ is taken as K^+ stimulated H^+/K^+-ATPase activity. The IC_{50}s of test compounds were calculated from each % inhibition value of compounds using the method as described be Litchfield–Wilcoxon (Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, 95).
12. The inhibition kinetics were determined in relation to the activation of H^+/K^+-ATPase activity by K^+. The lyophilized vesicle in 5 mM pipes/Tris buffer (pH 6.1) was pre-incubated in the presence of various concentrations of compounds. Compounds were examined for its ability to inhibit the generation of inorganic phosphate induced by various concentrations of KCl. The difference between the P_i production with K^+ and without K^+ is taken as K^+ stimulated H^+/K^+-ATPase activity. The K^+-stimulated H^+/K^+-ATPase activities were analyzed by Lineweaver–Burk plot.