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Evaluation of basic, heterocyclic ring systems as templates for use as potassium competitive acid blockers (pCABs)

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ABSTRACT

A variety of basic, heterocyclic templates has been reported as potassium-competitive, acid pump antagonists. Herein, we report a comparison of potencies of these templates and others to establish which offers the best start point for further systematic optimisation. Modifications were carried out to improve the developability profile of the more potent 1*H*-pyrrolo[2,3-*c*]pyridine template, affording molecules with improved overall in vitro characteristics versus the reported clinical candidate AR-H047108, and comparable to the clinically efficacious AZD-0865.

Potassium-competitive acid blockers (pCABs), also known as acid pump antagonists (APAs), have become a focus of attention as a means of achieving rapid but potentially long-lasting inhibition of gastric acid secretion. Unlike the irreversible proton pump inhibitors (PPIs) they do not require acid activation and would be expected to be significantly more stable than PPIs under all physiological conditions. Thus, their pharmacokinetic half life can be significantly longer allowing active drug species to be present whenever parietal cells become activated. Therefore, full acid suppression from first dose together with long duration of action are expected to be key features of these reversible inhibitors. Furthermore, the potential use of mildly basic molecules as pCABs may lead to accumulation in the acidic parietal cell, leading to similar concentrations to those delivered by PPIs, affording additional opportunities for selectivity, potency and duration of action.[1]

A number of basic heterocyclic molecules (e.g., **1–5**; Fig 1) have been reported as pCABs and some progressed to clinical trials. Indeed AZD-0865 **(3)** has been reported to show the desired rapid onset and long duration of acid suppression in GERD patients with excellent effect on clinical outcome comparable to that of the PPI esomeprazole.[2] The relative in vitro profiles of these pCABs has not previously been reported, however our own comparison suggests their in vitro developability profiles may not always be optimal, for example, CS526 (**1**) and AR-H047108 (**2**) show significant CyP450 interaction (Table 1). In this Letter, we describe work to evaluate related compounds having different heterocyclic cores to gain a deeper understanding of which template(s) may offer the best start-points for potential optimisation. We then describe optimisation of the physico-chemical properties of one of the more potent templates, the 1*H*-pyrrolo[2,3-*c*]pyridines, to achieve potent compounds with at least comparable in vitro profiles to those of previously reported clinical candidate pCABs, (**1**–**4**).

To aid the selection of templates for further optimisation, an evaluation of heterocyclic biaryl ring systems was carried out having a range of pK_a's and bearing key functionality identified from previously reported work.[16–19]

Previously reported SAR in the imidazo[1,2-*a*]pyridine series[6] indicates the 2,6-dialkyl benzylamino substituent to give enhanced potency. This has been rationalised by modelling[20] of analogues of analogues of SCH28080 and the conformationally restricted tricyclic analogue Soraprazan (**4**) (reported H^+/K^+ ATPase pIC_{50} 7.0)[10] which suggests the preferred orientation of the pendant phenyl ring is orthogonal to the core imidazopyridine ring.

Reported SAR[17,19,21] also indicates that the 2,3-dimethyl substitution in the imidazo[1,2-*a*]pyridine template (e.g., **5**) also gives enhanced potency (1000× relative to the 2,3-unsubstituted analogue). The benzylamine at the 8-position of this compound (H^+/K^+ ATPase pIC_{50} 9.1) is more potent than the corresponding 8-benzyloxy analogue[22] (**6**, H^+/K^+ ATPase pIC_{50} 7.6). To allow direct comparison of potencies, 2,3-dimethyl substitution of the core template (generalised nomenclature) and 8-(2,6-dimethyl benzyl) amino substituents were used as standard groups on the range of alternative templates evaluated.

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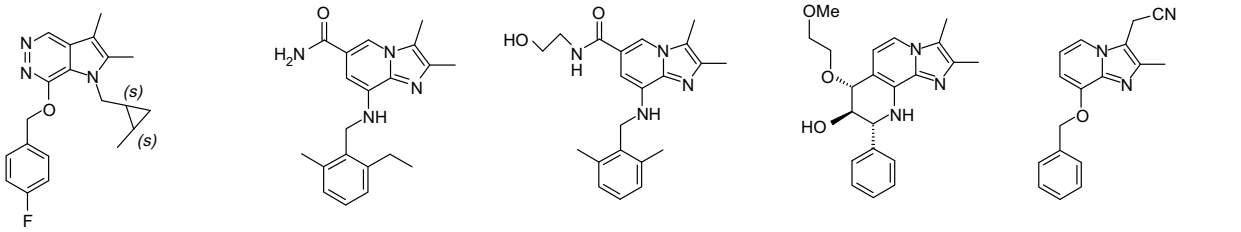


Figure 1. Examples of basic heterocyclic pCABs.[3–14]

Table 1
GSK data on reported pCABs

	H^+/K^+ATPase pIC_{50}	Parietal cells:[15] pIC_{50}	CYP450 IC_{50} (μM) 1A2, 2C9, 2C19, 2D6, 3A4[a](DEF), 3A4(7BQ)	Time dependent inhibition[b,c] (TDI) 3A4, 2D6 IC_{50},	CLi (ml/min/kg.) Rat, Dog, Hu.
(1)	6.8	6.55	1.2, 0.8, 5.1, 4.4, 6.0, 14	1.2 (DEF), 0.6	30, 38, 16
(2)	7.0	7.63	4.3, 3.6, >20, 9.2, 3.8, 3.9	0.4 (DEF), —	14, 3, 6.5
(3)	6.5	7.25	>50, 31, >100, 58, 9, 12	3.9 (DEF)/10 (7BQ), 1.0	4, 0.9, 1.3
(5)	7.4	7.78	2.0, 54, >100, >100, 82, 9, 12	1.7 (DEF), —	8.5, —, 8.0

[a] 3A4 DEF assay uses diethoxyfluorescein as CYP 3A4 substrate. The 3A4 7BQ assay uses 7-benzyloxyquinoline.
[b] IC_{50} fold change from $t = 0$ to 10 min when pre-incubation of 10 min before IC_{50} determination.
[c] A twofold increase in IC_{50} (TDI >2) is considered as a positive result, TDI at CYP 1A2, 2C9 and 3A4 7BQ were not measured in this project.

Of the various templates evaluated (Table 2), only the 1*H*-pyrrolo[2,3-*c*]pyridine (**18**)[23] gave, in our hands, comparable potency to the imidazo[1,2-*a*]pyridine (**5**), however the pyrrolo[1,2-*a*]pyrazine (**8**) and the imidazo [1,2-*a*]pyrazine[24] (**9**) also have potency levels that may be of interest for further optimisation. Though the inhibitory activity of the imidazo[1,2-*a*]pyridine is reported to reside in the positively charged protonated form,[25] hence a smaller percentage of the less basic compounds is protonated under the conditions of the H^+/K^+ATPase inhibition (pH 7.4) it appears that basicity per se is not sufficient for activity (e.g., **14** is only weakly active) (Table 2).

We were unable to derive a correlation of H^+/K^+ATPase inhibition (measured at pH 7.4) with pK_a. This was further complicated by the finding that a number of analogues were poorly soluble making pK_a measurement difficult. Also, we obtained poor predictions for pK_a of these systems using calculated methods.[27] As the position of the most basic centre in the 1*H*-pyrrolo[2,3-*c*]pyridine (**18**) is expected to be at the pseudo aminopyridyl centre, it suggests that the precise position of the basic centre relative to the pendant aryl ring may not be critical for potency (e.g., **5** vs **18**), but a basic nitrogen at generic positions 1 or 7 (see figure Table 2 for numbering system) appears optimal for good activity. Introduction of an additional nitrogen atom in position 5 (e.g., **11**, **12**, **14**) appears to be less tolerated and nitrogen at position 1 gives higher potency than at position 3 when having a basic nitrogen at position 7 (cf. **17** vs **18**).

An attempt to derive a CoMFA model[28,29] in order to further explain this data was unsuccessful as all statistical measures indicated no relationship between activity and CoMFA electrostatic or steric fields.

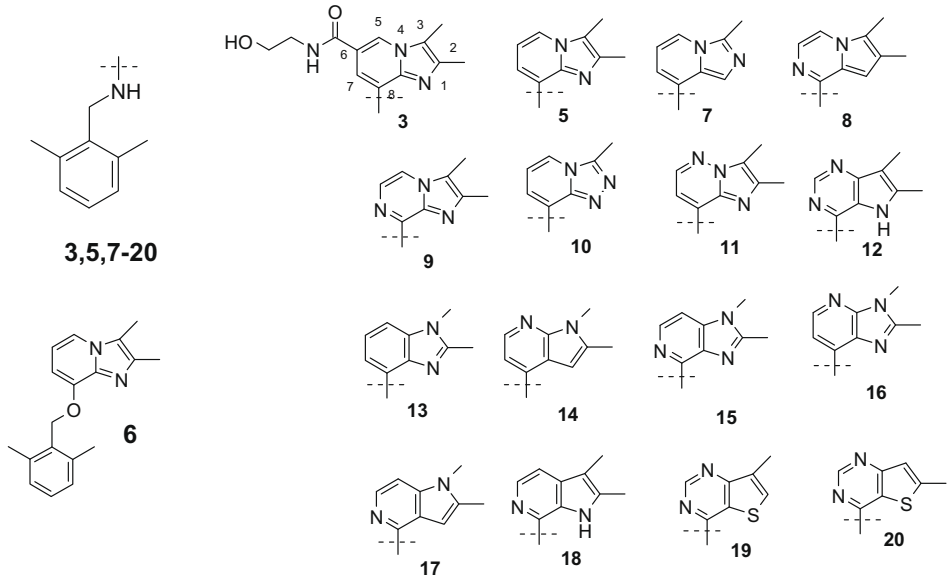
Evaluation of the in vitro DMPK profiles (Table 2) of the most active analogues (H^+/K^+ ATPase pIC_{50} >6.8) indicated that these minimally substituted analogues all had poor P450 profiles and, or high intrinsic clearance. However, the in vitro DMPK profile of AZD-0865 (**3**) versus unsubstituted compound (**5**) suggests these profiles can be improved by appropriate substitution. We also expected reduction in lipophilicity to improve overall developability characteristics including P450 inhibition and intrinsic clearance (CLi), and reduction in basicity to improve CyP450 2D6 profile in particular.[30]

Having established 1*H*-pyrrolo[2,3-*c*]pyridine (**18**) as the only one from those evaluated having comparable potency to the imidazo[1,2-*a*]pyridine template (**5**), further SAR evaluation of (**18**) was carried out. The effect of methyl substituents in the 2,3-positions on the heterocyclic ring and the influence of the 2,6-dimethyl groups on the benzyl substituent were first examined to establish if the SAR in the 1*H*-pyrrolo[2,3-*c*]pyridine series matched that of the imidazo[1,2-*a*]pyridine series (Table 3).

Replacement of the methyl substituent (R^2) with hydrogen to give (**21**) gave only a minor decrease in potency compared to the 2,3-dimethyl analogue (**18**) whereas removal of both methyl groups at C2,C3 (**22**) reduced potency more substantially, suggesting C3 methyl is the key substituent for potency. Removal of the 2,6-dimethyl groups on the benzyl substituent (**23**) gave approximately 10-fold reduction in potency (relative to **18**), presumably because the orthogonal conformation of the benzyl substituent is no longer as preferred.[31]

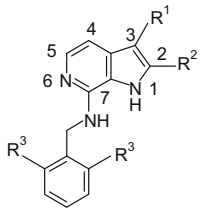
Our strategy to improve the developability profile of the 1*H*-pyrrolo[2,3-*c*]pyridine (**18**) initially focused on substitution at the C5 position with suitable heteroaromatic and heterocyclyl groups to modulate overall properties, a strategy which we have also shown to be successful in the imidazo[1,2-*a*]pyridine template.[21] Although C5 substitution reduced the potency relative to the unsubstituted analogue (**18**), an effect also observed with the corresponding substitution in the imidazo[1,2-*a*]pyridine series,[21] we were encouraged to find that H^+/K^+ ATPase-inhibitory potencies, comparable to that of (**3**) were still obtained for some analogues, with significant inhibition of histamine-induced parietal cell acid secretion (Table 4). Moreover, reducing basicity (see

Table 2
H^+/K^+ATPase potency and invitro DMPK profiles for range of templates evaluated



Ex	H^+/K^+ATPase pIC_{50}	Parietal cell pIC_{50}	pK_a	CHI Log D^{26} pH 7.4	CYP450 IC_{50} (μM) 1A2, 2C9, 2C19, 2D6, 3A4(DEF), 3A4(7BQ)	CLi (ml/min/kg.) Rat, Dog, Hu
3	6.5	7.25	6.27	2.14	50, 31, >100, 58, 9, 12	4, 0.9, 1.3
5	9.1		7.28	4.20	3.9, 3.9, 1.9, 2.7, 5.5, 9.6	50, 28, 7.6
6	7.6		7.41	3.38	0.7, 16, 6.2, 2.3, 5.5, 18	
7	4.1		6.03			
8	7.6	6.85	7.92	3.54	6.1, 14, 4.7, <0.1, 4.7, 1.6	50, —, 11
9	7.1	6.55		3.40		
10	4.0	IA@1 μM		3.50		
11	6.1			3.53		
12	5.9	7.2		2.53	>100, >100, >10, 0.3, 8.8, >100	9.0, —, 2.8
13	5.5	7.35			2.1, 8.8, 9.2, 35, 13, 9	47, —, 8.0
14	4.8	36%@50 μM	7.42	3.28		
15	5.3	7.13	7.49	2.09	31, 68, 27, <0.1, 12, 21	14, 6.5, 3.4
16	4.5		5.81	2.27		
17	6.8	22%@50 μM	9.14	2.04	41,66, 6.9, <0.1, 3.1, 4.3	28, 17, 3.8
18	9.4	7.15		2.29	14, 33, 1.8, <0.1, 9.0, 9.6	50, 19, 5
19	<4					
20	<4					

Table 3
Further SAR for substitution of 1*H*-pyrrolo[2,3-*c*]pyridine series

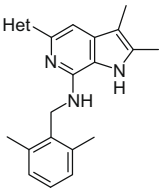


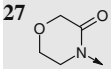
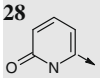
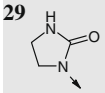
Ex	R^1	R^2	R^3	pK_a	H+/K+ATPase pIC_{50}	Parietal cell[15] % inhib. @50 nM
18	Me	Me	Me	nd	9.4	67.3
21	Me	H	Me	8.71	9.0	92.5
22	H	H	Me	8.63	6.8	nd
23	Me	Me	H	8.79	8.4	98.5

24, 27, 28) significantly improved the CYP450 2D6 inhibition profile as expected and gave only minor reductions in cell potency albeit a more significant decrease in H^+/K^+ ATPase-inhibitory potencies were observed. We were also pleased to find that intrinsic clearance was also reduced by substitution at C5 (compared to **18**), for example, **24**, **25**, and **27**.

Achieving potency as well as developability properties within an appropriate range in the pyrrolo[2,3-*c*]pyridine template,

Table 4
Profiles of 5 substituted 1*H*-pyrrolo[2,3-*c*]pyridines

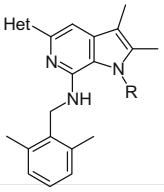


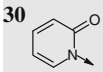
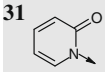
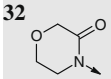
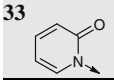
Het	H^+/K^+ATPase pIC_{50}	pK_a	CHI Log *D* pH 7.4	Parietal cell assay pIC_{50}	CYP450 IC_{50} (μM) 1A2, 2C9, 2C19, 2D6, 3A4(DEF), 3A4(7BQ)	CLi (ml/min/kg.) Rat, Hu
18 H	9.4	nd	2.30	7.1	14, 33, 1.8, <0.1, 9.0, 9.6	50, 19, 5
24 	7.4	4.71	3.18	nd	29, 3.3, 20, >33, 3, 90	2.9, 2.7
25 Ph	6.3	Insuff. Sol.[a]	5.31	6.5	3.7, 6.7, 0.3, 0.6, 7.7, 6.6	3.9, <0.5
26 	7.4	6.32	3.77	6.8	26, 1.4, 6.4, 1.9, 1.0, 1.8	nd
27 	5.9	Insuff. Sol.[a]	2.83	6.7	35, 61, 66, 25, 22, 22	4.3, 1.6
28 	5.1	Insuff. Sol.[a]	4.12	6.5	>100, 2.3, 62,60, 1.3, 2.2	nd
29 	6.5	nd	2.54	6.8	22, 2.7, 8.2, 0.7, 1.6, 1.6	6.0, 1.3

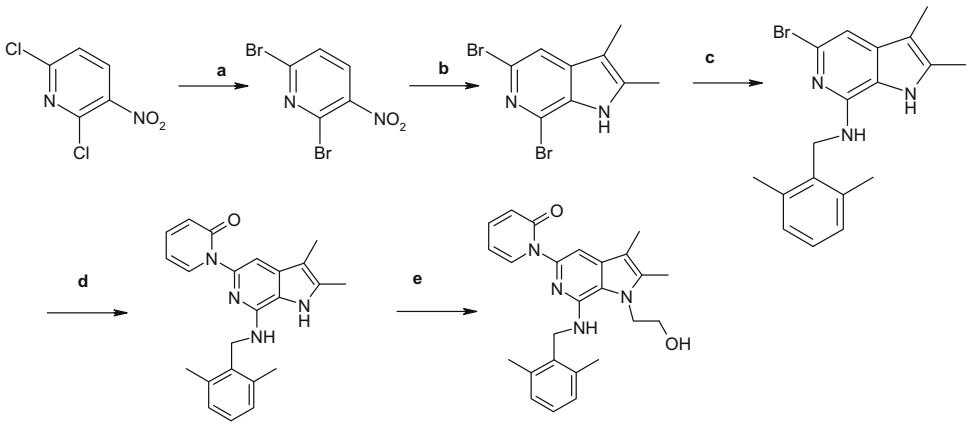
[a] Examples 25, 27, 28 were insufficiently soluble for pK_a's to be determined.

merely by modification at C5 alone proved elusive; we therefore investigated further modification. A useful synthetic handle in this regard is the N1-position. (Table 5). N1 ethyl substitution on the C5 pyridone to give (**30**), maintained potency. Although N1 allyl (**33**) is potent versus H^+/K^+ ATPase, it is poorly active in the cell assay. In both examples, intrinsic clearance is increased and overall CyP450 profile is poorer relative to the unsubstituted N1 analogue (**27**), possibly due to an increase in lipophilicity. We found that substitution with the more hydrophilic 2-hydroxyethyl group (e.g., **31**, **32**) was tolerated and gave

Table 5
Profiles of 1,5 disubstituted 1*H*-pyrrolo[2, 3-*c*]pyridines



Het	R	H^+/K^+ATPase pIC_{50}	pK_a	CHI Log *D* pH 7.4	Parietal cell assay pIC_{50}	CYP450 IC_{50} (μM) 1A2, 2C9, 2C19, 2D6, 3A4(DEF), 3A4(7BQ)	CLi (ml/min/kg.) Rat, Hu
30 	Et	7.4	4.0	3.9	6.7	65, 0.7, 6.5, 18, 2.9, —	41, 22
31 	$(CH_2)_2OH$	6.8	4.5	3.12	6.6	>100, 11.4, 40, 45.5, 5.6, —	21.9,12.1
32 	$(CH_2)_2OH$	6.6	5.4	2.93	7.1	>100, 13, >100, 36, 6.0, 11	6.5,6.9
33 	$CH_2CH{=}CH_2$	7.5	4.0	4.06	I.A@300 nM	62,0.5,6.0,26,2.4,—	20,13



Scheme 1. Preparation of 1,5-disubstituted 1*H*-pyrrolo[2,3-*c*]pyridine (**31**). Reagents and conditions: (a) Br_2, AcOH, 50 °C, (88%); (b) 3-bromo2-butene, Mg/THF, 0 °C (22%) (c) 2,6-dimethylbenzylamine, potassium carbonate 190 °C, (80%); (d) 2-pyridone, copper iodide, cesium carbonate, 1,2-dimethylethylamine, NMP, (31%). (e) (i) sodium hydride, (ii) 2-[(2-bromoethyl)oxy]tetrahydro-2*H*-pyran, DMF, (iii) tosic acid, methanol (44%).

improved CyP450 profiles. Compound **32** was of particular interest as it showed a good balance of in vitro PK characteristics, with H^+/K^+ATPase and cell potency and an overall in vitro profile comparable to that of previously reported clinical candidates such as (**2**) and (**3**).

The synthesis of (**31**) is representative of the approach taken for the preparation of this class of compound and is outlined in Scheme 1. Thus the commercially available 2,6-dichloro-3-nitropyridine was converted to the corresponding dibromide which was followed by Bartoli azaindole formation.[32] Reaction with 2,6-dibromobenzylamine gave selective displacement of the C7 bromide. Displacement of the C5 bromide with pyridinone using Ullman conditions,[33] followed by N1 alkylation with 2-[(2-bromoethyl)oxy]tetrahydro-2*H*-pyran then removal of the THP protecting group to yield the desired compound (**31**).

In conclusion, evaluation of potency and in vitro DMPK profiles of a range of bicyclic templates has shed light on SAR and key requirements for potency. Although no clear correlations between the range of 5,6 ring system templates and potencies could be derived, SAR suggests weak basicity is required for activity and that a heteroatom basic centre is best tolerated at positions 1 and 7 (generalised nomenclature).

The imidazo[1,2-*a*]pyridine template (**5**) and the 1*H*-pyrrolo[2,3-*c*]pyridine (**18**) were identified as being the most potent templates and we have demonstrated that the in vitro DMPK profile of the parent 1*H*-pyrrolo[2,3-*c*]pyridine (**18**) can be improved by suitable substitution at C5 and N1 in order to modify pK_a and lipophilicity. In particular the 1*H*-pyrrolo[2,3-*c*]pyridine compound (**32**) has been identified as having a similar overall in vitro profile to that of the reported clinical candidate imidazo[1,2-*a*]pyridine, AZD-0865 (**3**). Further profiling and modifications of compound (**32**) will be reported in a later publication.

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