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Orally active C-6 heteroaryl- and heterocyclyl-substituted imidazo[1,2-*a*]pyridine acid pump antagonists (APAs)

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ABSTRACT

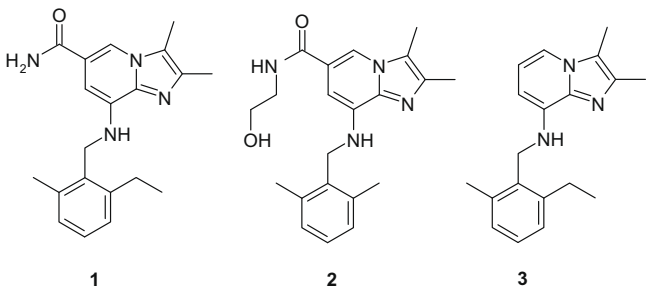
Acid pump antagonists (APAs) such as the imidazo[1,2-*a*]pyridine AZD-0865 **2** have proven efficacious at low oral doses in acid related gastric disorders. Herein we describe some of the broader SAR in this class of molecule and detail the discovery of an imidazo[1,2-*a*]pyridine **15** which has excellent efficacy in animal models of gastric acid secretion following oral administration, as well as a good overall developability profile. The discovery strategy focuses on use of heteroaryl and heterocyclic substituents at the C-6 position and optimization of developability characteristics through modulation of global physico-chemical properties.

Acid pump antagonists (APAs, also known as potassium-competitive acid blockers or P-CABs) are reversible inhibitors of the H^+/K^+ ATPase responsible for the acidification of the stomach. They are expected to have similar efficacy but faster onset in the treatment of gastric acid-related disorders compared with the current gold standard proton pump inhibitors (PPIs), which bind irreversibly to the same enzyme.[1]

Imidazo[1,2-*a*]pyridine derivatives such as AR-HO47108 **1** or AZD-0865 **2** (Fig. 1) attracted our attention since they are reported to have shown efficacy in animal models of gastric acid secretion and in the clinic at low oral doses.[2] Although recent reports indicate toxicity issues have been reported for **1**,[3] a detailed SAR and broader evaluation of analogues in this C6-substituted imidazo[1,2-*a*]pyridine series has not previously been reported.

Our own in vitro exploration of these compounds showed that the amide functionality at C-6 in **1** and **2** leads to a drop in enzyme potency compared to the parent compound **3**. However, the in vitro clearance and CYP450 inhibition profiles were improved (Table 1). We hypothesized that these improvements were primarily due to a reduced lipophilicity (CHI log *D*) or to reduced electron density at key regions of the molecule (as evidenced by reduced pK_a of **1** (6.2) versus **3** (7.0)—this may also partly explain the reduced enzyme potency).[5] We therefore decided to explore other means of modulating these features by C-6 modification. Our investigations quickly focused on C6-heteroaryl and heterocyclic functionality.[6] As described herein, we subsequently expanded the SAR elsewhere in the template to fine-tune the overall properties.

Tetra-substituted imidazo[1,2-*a*]pyridines of structure **4** can be readily obtained (Scheme 1) from commercially available 2-amino pyridines. Reductive amination (X = NH_2) led to key intermediates **5**. Regioselective substitution of the C-8 substituent (**4**, X = Br) with *p*-methoxybenzyl alcohol gave phenol **6** after deprotection. This was alkylated to give intermediate **7**. In the case of C-linked C-8 substituents, the Suzuki coupling using arylethenyl boronic acid was carried out prior to hydrogenation and C-6 bromination to give **8** followed by reaction with an alpha-bromo ketone to give the C-8 carbon linked intermediate **9**. Intermediates **5**, **7** or **9** were further functionalized at the C-6 position using Ullman or Buchwald chem-



1 2 3

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

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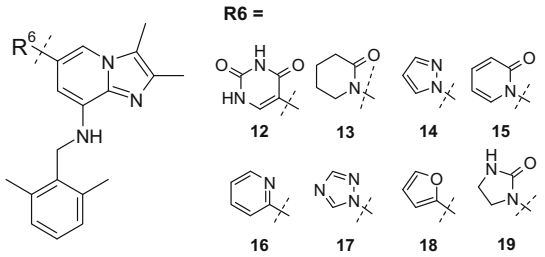
Table 1
In vitro profile of reference APAs and C6-modified imidazo[1,2-*a*]pyridines

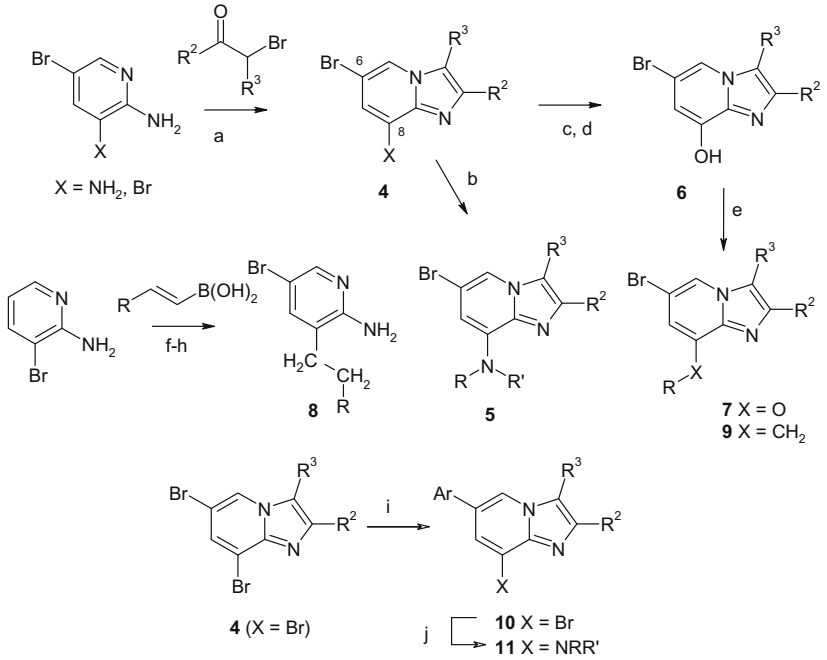


Compd	H^+/K^+ ATPase pIC_{50}	Parietal cell %I[a]	Rat H^+ secretion %I[b]	Rat [Bl][b] (μM)	Cli (r,d,h) ml/min/g liver[c]	CYP IC_{50} (μM)[4] 1A2, 2C9, 2C19, 2D6, 3A4 (DEF, 7BQ)	CHI log *D* @ pH 7.4[d]
1	7.0	107	94*	0.14	14, 3.0, 6.5	4.3, 3.6, 20, 9.2, 3.8, 3.9	2.52
2	6.5	~100	98	0.62	4, 0.9, 1.3	>100, 14, >100, 46, 8.4, 14	2.14
3	8.2	94	82 (*45)	0.015	>50, —, 12	1.5, 1.5, 0.5, 1.1, 4.7, 6.3	4.32
12	8.4	1	2	0.019	38, 0.9, 2.9	26, 3.4, 17, 39, 1.7, 2.6	1.8
13	8.3	113	85	0.072	19, <0.5, 2.9	>100, 14, 34, 41, 6.8, 22	2.79
14	8.1	104	94	0.604	8.2, 4.0, 2.9	35, 0.86, 9.3, 11, 2.9, 2.1	3.60
15	7.9	93	93 (*84)	0.125	6.0, 1.0, 1.9	100, 17, >50, 97, 13, 48	2.67
16	7.4	22	28	0.355	13, 2, 3.3	>100, 0.63, 5.2, 1.7, 1.3, 1.8	4.11
17	7.6	117	92 (*83)	0.716	6.9, 2.7, 2.0	13, 2.5, 16, 17, 17, 6.7	3.07
18	6.5	11	24	0.490	6.2, 1.9, 1.7	1.3, 3.2, 13, 2.2, 1.8, 1.5	4.63
19	6.9	1[e]	40[f]	0.041	45, 4.8, 4.9	>100, 5.8, >100, >100, 6.5, 5.3	2.62

[a] % Inhibition of pentagastrin stimulated accumulation of ^{14}C-aminopyrine by 50 nM compound.
[b] As for Tables 4–6, 70 min following 3 mg/kg dose (or * 1 mg/kg) in pentagastrin stimulated acid secretion in rat. See Ref. 8 for procedure. Concentration of compound in rat blood ([Bl]) was determined in parallel.
[c] Intrinsic clearance in rat (r), dog (d) and human (h) liver microsomes.
[d] Chromatographic hydrophobicity index, measured at pH 7.4. pK_a were in general not determined as a result of poor solubility—calculated log *D* and pK_a using eg the ACD software generally resulted in poor predictions in this series of analogues.
[e] 107% at 150 nM.
[f] 92% I @ 10 mg/kg p.o. Nd = not determined.

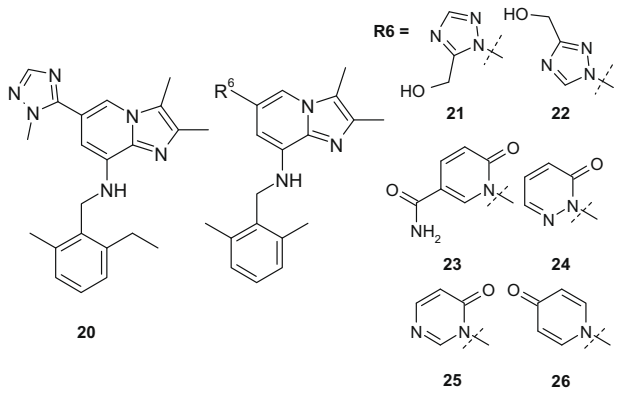
istry to give the desired APAs.[7] Alternatively, amine C-8 substituent could be introduced via Buchwald coupling after introduction of the C-6 substituent (**4**→**10**→**11**).

A range of heteroaryl/heterocyclyl substituents at C-6 gave acceptable H^+/K^+ ATPase inhibition (see representative examples Table 1) and some even gave improved inhibition compared with



Scheme 1. Access to C-6 heteroaryl/heterocyclyl imidazo[1,2-*a*]pyridines. Reagents and conditions: (a) NMP, 180 °C, microwave or EtOH, reflux; (b) R–X, X = Cl or Br, Na_2CO_3, KI, DMF; (c) PMB-OH, NaH, DMF, 0–90 °C; (d) CH_2Cl_2, CF_3COOH, 25 °C; (e) NaH, DMF, 25 °C then R–X, X = Cl, Br; (f) $Pd(PPh_3)_4$, K_2CO_3, dioxan, reflux; (g) Pd/C, H_2 (1 atm), MeOH, 25 °C; (h) Br_2, CH_2Cl_2, 25 °C; (i) Ar-H, CuI, Cs_2CO_3, trans 1,2-diaminocyclohexane, DMF, 120 °C or ArH, $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, dioxane, reflux; (j) NHRR′, $Pd_2(dba)_3$, dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, *t*BuONa, dioxane, 120 °C, microwave irradiation.

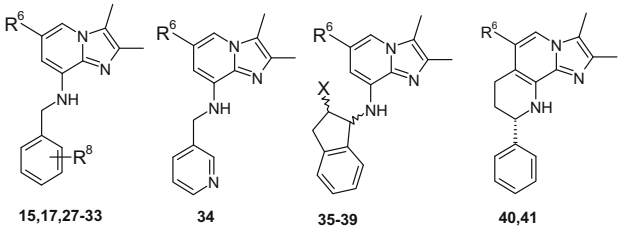
Table 2
SAR at C-6 from leads **15** and **17**



Compd	H^+/K^+ ATPase pIC_{50}	Parietal cell pIC_{50}	Rat H^+ secretion %I[a]	Cli (r,h,d) ml/min/g liver	CYP IC_{50} (μM) 2C9, 3A4 (DEF, 7BQ)	CHI log *D* @ pH 7.4
15	7.9	7.3	93	6.0, 1.0, 1.9	17, 13, 48	2.67
17	7.6	7.2	92	6.9, 2.7, 2.0	13, 17, 6.7	3.07
20	7.0	7.1	88	31, 1.7, 6.7	3.2, 7.5, 13	3.09
21	7.6	7.0	95	5.4, 1.3, 1.6	6.5, 16, 21	2.26
22	7.5	6.8	93	4.6, <0.4, 1.3	8.6, 13, 15	2.16
23	7.1	6.5	8	4.9, 0.7, 1.7	19, 7.2, 14	1.71
24	7.8	7.3	92	9.6, 0.7, 1.8	4.2, 7.2, 8.5	2.47
25	7.0	7.2	Nd	2.5, 0.5, 1.4	4.7, 2.1, 4.8	2.33
26	6.7	[b]	0	2.5, 1.0, 0.5	17, 16, 28	1.58

Nd = not determined.
[a] 3 mg/kg oral dose.
[b] 42% and 97% I @150 and 500 nM respectively.

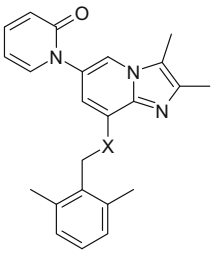
Table 3
SAR at C-8 from leads **15** and **17**



Compd	R^6	R^8	X	H^+/K^+ ATPase pIC_{50}	Rat H^+ secretion%I (3 mg/kg po)	CYP IC_{50} (μM) 2C9, 3A4 (DEF, 7BQ)	CHI log *D* pH 7.4
15	2-Pyridone	2,6-diCH_3	—	7.9	93[d]	17, 13, 48	2.67
17	1,2,4-Triazole	2,6-diCH_3	—	7.6	92	13, 17, 6.7	3.07
27	2-Pyridone	2-CH_3	—	7.2	68	10, 7.2, 17	2.11
28	1,2,4-Triazole	2-CH_3	—	6.3	Nd	2.9, 17, 3.8	2.30
29	2-Pyridone	2-Cl-4-F	—	7.0	57	3.7, 3.4, 13	2.26
30	1,2,4-Triazole	2-Cl-4-F	—	6.3	76	1.1, 5.2, 2.9	2.61
31	2-Pyridone	H	—	5.8	Nd	13, 19, 24	1.87
32	2-Pyridone	2-MeO	—	5.3	Nd	5.6, 4.6, 4.2	1.93
33	2-Pyridone	3-Me	—	4.7	Nd	Nd	2.17
34	2-Pyridone	—	—	<4	Nd	Nd	0.73
35	2-Pyridone	—	H[a]	7.1	100	23, 13, 36	2.33
36	1,2,4-Triazole	—	H[a]	6.9	92	4.6, 5.1, 5.5	2.72
37	2-Pyridone	—	H[b]	5.6	44	2.5, 18, 86	2.36
38	2-Pyridone	—	OH[c]	6.4	84[e]	97, 62, >100	1.55
39	1,2,4-Triazole	—	OH[c]	6.8	Nd	5.3, 3.1, 15	1.71
40	2-Pyridone	—		6.2	Nd	5.6, 7.7, A[f]	3.35
41	1,2,4-Triazole	—		6.6	Nd	14, 0.7, 2.6	2.27

Nd = not determined.
[a] (*R*) Isomer.
[b] (*S*) Isomer.
[c] Most active *trans* isomer.
[d] 84% at 1 mg/kg.
[e] 21% at 1 mg/kg.
[f] Enzyme activation.

Table 4
Influence of the C-8 linker



15, 42-43

Compd	X	H^+/K^+ ATPase pIC_{50}	Rat H^+ secretion %I (3, 1 mg/kg po)	Cli (r,h,d) ml/min/g liver	CYP IC_{50} (μM) 2C9,3A4 (DEF, 7BQ)	CHI log *D* pH 7.4
15	NH	7.9	93, 84	6.0, 1.0, 1.9	17, 13, 48	2.67
42	O	7.4	81, 41	15, 0.5, 4.4	21, 9.2, 21	2.12
43	CH_2	5.9	nd	42, —, 24	4.2, 10, 31	2.61

1 and **2**. We were encouraged to find that some also gave good inhibition of pentagrastin-stimulated acid secretion in the rat following oral administration.[8] It was clear that good in vivo activity required good H^+/K^+ ATPase and parietal cell inhibitory activity as well as good in vivo blood concentrations.

It is also apparent from Table 1 that: (a) CYP450 liabilities (mainly 2C9 and 3A4) are associated with compounds of higher CHI log *D*,[9] (b) reducing (e.g., **12**) or increasing (e.g., **16**) CHI log *D* too far results in poor cellular penetration and so poor parietal cell inhibition, (c) there is a cross-species difference in magnitude of intrinsic clearance, (d) the lowest rat blood concentrations following oral dosing are largely associated with the highest intrinsic clearance, (e) intrinsic clearance differences are driven partly but not solely by CHI log *D* differences—this may also result from liabilities due to some of the substituents themselves, or to less beneficial electronic effects on the overall template.

We next investigated the SAR of the two overall best molecules, **15** and **17**, seeking to optimize further their physicochemical properties. We initially looked at close analogues of the C6-pyridone or triazole, respectively (examples are shown in Table 2), specifically those bearing substituted 1,2,4-triazoles, substituted 2-pyridones or close analogues of the 2-pyridone motif. These afford further evidence that the H^+/K^+ ATPase enzyme tolerates broad substitution at C6, and indeed some also give cell and in vivo potency. Compounds with lowered CHI log *D* again gave somewhat improved CYP450 inhibition and intrinsic clearance profiles; however, if lowered too far (e.g., as in **23** and **26**), poor cell penetration and so poor cell and in vivo acid suppression again resulted.

None of the modified C6-substituted analogues afforded improvement over the progenitor **15** or **17**. We therefore broadened our SAR investigation of these two compounds to other positions in the molecule.

In line with previously published SAR in related systems there was a strong requirement at C8 for *ortho*-lipophilic-substituted phenyl for good enzyme activity (compare **15**, **17** and **27–30** with 31–**33** as well as **31** with **34**) indicating the orthogonal relative orientation of this substituent relative to the heterocyclic scaffold (Table 3).[10]

Thus, whilst they reduce CHI log *D*, replacements for the *ortho*-dialkyl substituents were detrimental to in vitro and in vivo potency, and also gave no additional benefit to CYP450 profiles (or intrinsic clearance—data not shown). Introducing specific constraints via cyclization from the linker nitrogen atom to the potentially metabolically vulnerable benzylic position gave potent inhibitors in vitro (compare **35**, **36** and **38**, **39** vs **37**) and in vivo (inhibitor **36**) although no improvement in overall profile. Introduction of an hydroxy group (compound **38**) improved CYP450 profile as expected due to lower CHI log *D*, but had a detrimental effect on in vitro and in vivo potency. Locking the conformation of the C-8 aryl substituent and blocking the benzylic position alternatively via cyclization to the imidazo[1,2-*a*]pyridine ring (see **40** and **41** as examples) has been reported[11] to give potent inhibitors, but in our hands, resulted in inferior in vitro potency and developability profiles compared to **15** or **17**.

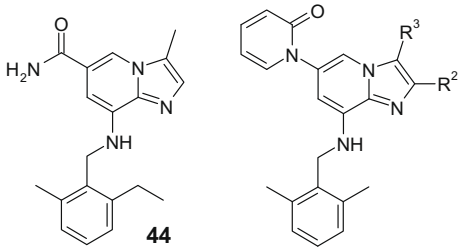
The role of the C-8 linker atom was also investigated. Compounds with heteroatom linkers were more active than their alkane counterpart (Table 4) and also of superior CYP450 and intrinsic clearance profiles. The difference in profile between **15** and **42** is representative of what was observed between most NH- and O-linked analogues (data for other compounds not shown) whatever the nature of the C-6 substituent: despite their lower CHI log *D*, the latter were in general of similar CYP450 profiles but had slightly inferior rat and human intrinsic clearance profiles which may go some way to explain their poorer in vivo potency.

At the C-2 and C-3 positions very few modifications were tolerated (Table 5): our early SAR investigation of **1** suggested that a methyl substituent at C-2 was essential for good activity (compare activity of **44** and **1**) and introduction of an hydrophilic substituent at this position was poorly tolerated (compare activity of **15** and **45**) hence no further modification was attempted in this position. C-3 Hydroxymethyl (**47**), hydrogen (**46**) or halogen (**48**) were the only methyl-replacements at this position to give sub-micromolar in vitro activity (data for other analogues including methoxymethyl, carboxy-amides, aminomethyl, not shown).[12] **46** gave comparable in vivo activity to **15**. The lower CHI log *D*-hydroxymethyl derivative **47** (by analogy with AZD-0865 (**1**),[2a] a possible metabolite of **15**) showed inferior in vivo potency.

The compounds which showed the most appropriate overall profiles were progressed to oral PK studies in rat and dog (Table 6). Despite the differences in in vitro clearance rates, the in vivo PK data in both rat and dog were in broad agreement with each other. Oral bioavailabilities were in line with the blood clearance rates which in turn, together with volumes of distribution, are largely predicted by CHI log *D* values. Compound **15** proved to have the best balance between in vitro and in vivo potency and DMPK profile.

In summary, the C6-heteroaryl/heterocyclyl-substituted imidazo[1,2-*a*]pyridine template affords a good start-point for the identification of gastric acid suppressing molecules. The overall developability, cellular potency and in vivo performance of such molecules can be tuned to a large extent by targeting appropriate

Table 5
SAR at the C-2 and C-3 positions



Compd	R^2	R^3	H^+/K^+ ATPase pIC_{50}	Rat H^+ secretion %I (3, 1 mg/kg po)
1	—	—	7.0	—, 94
44	—	—	5.7	nd
15	CH_3	CH_3	7.9	93, 84
45	CH_2OH	CH_3	5.4	nd
46	CH_3	H	6.4	92, 90
47	CH_3	CH_2OH	6.9	90, 27
48	CH_3	Cl	6.1	nd

Table 6
In vivo pharmacokinetic data for selected APAs

Compd	CLb[a] (mL/min/kg)		Vss[a] (L/kg)		$T_{1/2}$[a] (h)		Fpo[b] (%)	
	Rat (n = 1 or 3)*	Dog (n = 1 or 3)*	Rat	Dog	Rat	Dog	Rat (n = 3)	Dog (n = 3)
15	48 ± 2[c]	21 ± 8[c]	1.3 ± <0.1	3.7 ± 0.9	0.5 ± <0.1	2.5 ± 0.4	33 ± 5	61 ± 28
17	83 ± 16	50 ± 7	3.5 ± 1.4	6.6 ± 0.8	nd	2.3 ± 0.2	21 ± 3	12 ± 5
21	55		1.5		0.5		13 ± 11	
35	90		1.8		0.3		nd	
46	58		1.8		0.5		18 ± 6	
47	37 ± 2	10	1.0 ± 0.1	1.1	5.3	1.6	28 ± 9	36

[a] 1 mg free base/kg/h iv dose (solution in 0.9% w/v saline containing 10% w/v hydroxylpropyl-β-cyclodextrin and 2% v/v DMSO).
[b] 3 mg free base/kg p.o. dose (suspended in 1% w/v methylcellulose).
[c] iv formulation: 0.9% w/v saline.
* Standard deviations given when n = 3.

physicochemical properties. As a result we have succeeded in identifying compounds which inhibit acid secretion at low oral doses in the rat with good in vitro and in vivo DMPK profile in both rat and dog. Amongst them, inhibitor **15** proved to have the best overall profile. Further acid suppression studies and characterization of this derivative will be reported in due course.

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4. 3A4 DEF assay uses Diethoxyfluorescein as CYP 3A4 substrate. The 3A4 7BQ assay uses 7-Benzyloxyquinoline.
5. The active form of the inhibitor is known to be the protonated imidazopyridine and the pIC_{50} determination is done at pH 7.4. See: (a) Wallmark, B.; Briving, C.; Fryklund, J.; Munson, K.; Jackson, R.; Mendlein, J.; Rabon, E.; Sachs, G. *J. Biol. Chem.* **1987**, *262*, 2077; (b) Briving, C.; Andersson, B.-M.; Nordberg, P.; Wallmark, B. *Biochim. Biophys. Acta* **1988**, *946*, 185.
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7. The conditions of reactions were identical to conditions (i), Scheme 1.
8. Typically groups of male Wistar rats weighing 150 ± 20 g are fasted overnight prior to use in groups of 3. Test substance or vehicle (2% tween80 + 98% water) is administrated by oral gavage at 60 min before challenge with pentagastrin (5 μg/kg i.p.). Gastric acidity in individual samples (mEq HCl/ml) is titrated 10 min later. For procedures used in in vitro assays, see: Bamford, M. J.; Elliott, R. L.; Giblin, G. M. P.; Naylor, A.; Witherington, J.; Panchal, T. A.; Demont, E. H. PCT Int. Appl., WO 2006100119A1, 2006.
9. This trend was observed with most of the compounds in this series, hence only IC_{50}s against 2C9, 3A4 DEF and 7BQ are reported in the rest of the manuscript.
10. For first report of SAR in the imidazo[1,2-*a*]pyridine series, see: Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S.; Wong, S.-C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; Steinberg, M.; McPhail, A. T. *J. Med. Chem.* **1985**, *28*, 876.
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12. The same trend is observed in the C-6 triazole series (data not shown). Kaminski et al. have reported activity with a $-CH_2-CN$ or NH_2 groups but have shown that these substituents can lead to liver toxicity: see Kaminski, J. J.; Perkins, D. G.; Frantz, J. D.; Solomon, D. M.; Elliott, A. J.; Chiu, P. J. S.; Long, J. F. *J. Med. Chem.* **1987**, *30*, 2047–2051. and references cited therein.