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# Discovery of biaryl inhibitors of $H^+/K^+$ ATPase

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ABSTRACT

We report the identification of a novel biaryl template for $H^+/K^+$ ATPase inhibition. Evaluation of critical SAR features within the biaryl imidazole framework and the use of pharmacophore modelling against known imidazopyridine and azaindole templates suggested that the geometry of the molecule is key to achieving activity. Herein we present our work optimising the potency of the molecule through modifications and substitutions to each of the ring systems. In particular sub-micromolar potency is achieved with **(4b)** presumably through a proposed intramolecular hydrogen bond that ensures the required imidazole basic centre is appropriately located.



Reversible imidazopyridine $H^+/K^+$ ATPase inhibitors (acid pump antagonists, APAs) such as AR-HO47108 **(1a)** ($H^+/K^+$ ATPase $pIC_{50}$ 7.0) have become a focus of attention as a means of achieving rapid and potentially long-lasting inhibition of gastric acid secretion. Unlike the irreversible proton pump inhibitors (PPIs) that are the current gold standard for treatment of GERD (GastroEsophageal Reflux Disease) they do not require acid activation and would be expected to be significantly more stable than PPIs under physiological conditions. Thus, their pharmacokinetic half life can be significantly longer allowing active drug species to be present whatever the activation state of the target parietal cells. Thus full acid suppression from first dose, together with long duration of action is expected to be a key feature of reversible inhibitors.[1–4]

The geometry of the pendant phenyl ring perpendicular to the central core ring system is a key factor in potency against $H^+/K^+$ ATPase, as is the presence of small lipophilic substituents at the imidazopyridine C2 and C3 positions[5–7](Fig. 1). Also it has been shown that the protonated form of the molecule binds to the pump. In addition it has been suggested that mildly basic molecules can accumulate within the parietal cell[8], giving higher local concentrations and hence an increased functional potency. As an extension of our work exploring basic 6,5 bicyclic ring systems as acid pump antagonists[9,10] we identified an alternative template containing the critical SAR features necessary for activity in other templates.[11,12] The biarylimidazole template **(2c)** was designed to include these features and lack the benzylamine substituent of the imidazopyridine series, a substituent which we postulated may be susceptible to metabolism. In Figure 1, **(2c)** shows an excellent superimposition with the potent imidazopyridine compound **(1b)** ($H^+/K^+$ ATPase $pIC_{50}$ 7.1) as an alternative to the benzylamino-2,3-dimethylimidazopyridine template, recently reported to be associated with signals of toxicity in clinical studies.[13,14]

Variation of substituents on $Ar^1$ of **(2)** (Table 1) demonstrated a modest increase in potency with one or two *ortho* substituents **(2a–d)**. This reflects the increased orthogonality of the biaryl system as a result of increased steric interaction between the substituents and the core ring protons. The dimethyl analogue **(2c)** shows approximately the same potency as both its monomethyl **(2b)** and diethyl **(2d)** analogues suggesting scope for further exploration exists. The methyl thiophene ring system **(2e)** was less potent than its phenyl analogue.

Insertion of a one or two atom linker between the two phenyl rings **(2f–j)** had a detrimental effect on potency. This was also the case with the *ortho* **(2k)** and *para* **(2l)** directly linked biaryl species.

Next we evaluated imidazole substitution patterns and alternative heterocycles in order to investigate how the planarity of the molecule and the location of the basic centre (the imidazole nitrogen atom) affected the potency (Table 2).

Removal of, or increasing the size of the $R^2$ and $R^3$ methyl groups **(3a–b)** or replacement with benzimidazole **(3c)** gave lower potency compounds, suggesting that there is a steric constraint at

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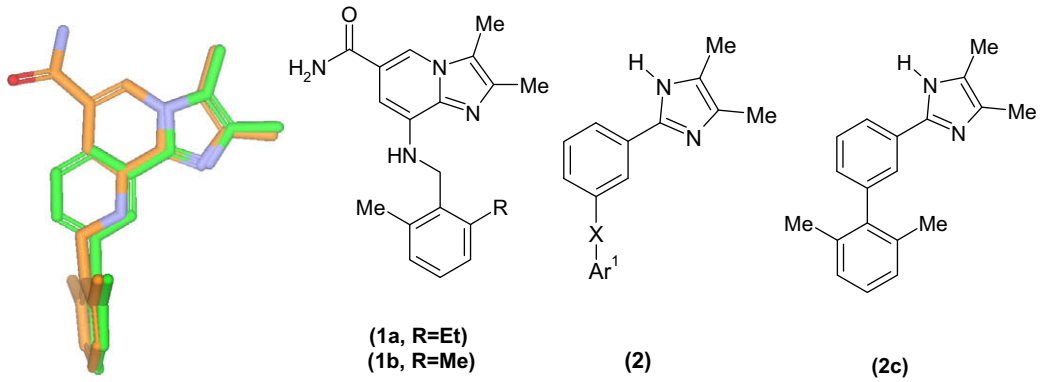



**Figure 1.** Overlay of imidazopyridine (**1b**) with biaryl imidazole (**2c**).

**Table 1**

| Ex | X | $Ar^1$ | $H^+/K^+$ ATPase $pIC_{50}$ |
|---|---|---|---|
| **2a** | — | Ph | 4.7 |
| **2b** | — | 2-Me-Ph | 5.1 |
| **2c** | — | 2,6-diMe-Ph | 5.2 |
| **2d** | — | 2,6-diEt-Ph | 5.1 |
| **2e** | — | 3-Me-thiophen-4-yl | 4.8 |
| **2f** | NH | 2,6-diMe-Ph | 4.9 |
| **2g** | *(trans)*-CH=CH | Ph | 4.4 |
| **2h** | $CH_2CH_2$ | Ph | 4.3 |
| **2i** | NHCH2 | 2,6-diMe-Ph | 4.3 |
| **2j** | CONH | Ph | 4.0 |
| **2k** | *Ortho* | Ph | 4.2 |
| **2l** | *Para* | 2,6-diMe-Ph | 4.4 |

$pIC_{50}$ values are reported as mean of >2 experiments.

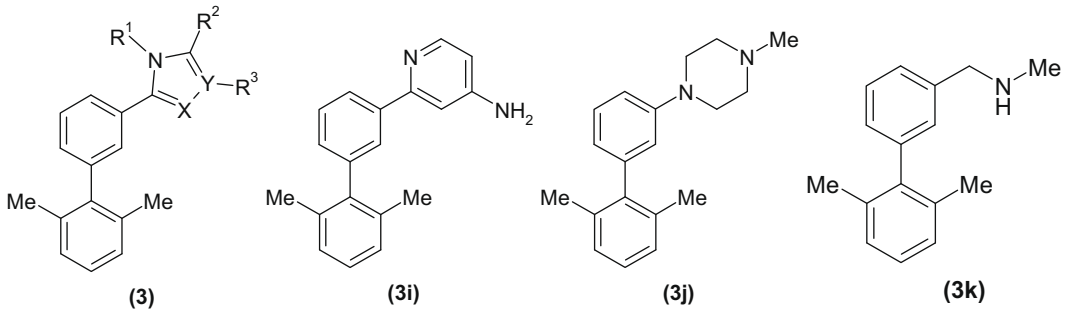
these positions (comparable to SAR in the imidazopyridine series). Methyl $R^1$ substitution with unsubstituted imidazole is tolerated (**3d**) with a twist being induced by the steric clash between the *(N1)* substituent and the core ring protons.[15] The addition of methyl substituents $R^2$ and $R^3$ result in reduced potency (**3e**), possibly due to the ring twist causing the $R^2$ and $R^3$ methyl groups to adopt a more unfavourable orientation. Larger $R^1$ substituents such as the *n*-propyl moiety also give lower potency (**3f**) again suggesting steric constraints.

Isomeric imidazoles (**3g**) and (**3h**) also proved to be inadequate replacements for imidazole (**2c**). Similarly, replacement of the imidazole ring with either pyridine (**3i**) or piperazine (**3i**) ring systems or with alkyl amines (**3j**) gave compounds with reduced potency.

Having shown that a loss of co-planarity between the 4,5-dimethylimidazole and core ring was detrimental to activity we turned our attention to the core phenyl ring, exploring additional substituents and alternative ring systems (Table 3).

Thus we introduced the 2- and 6-methoxy substituents (**4a,b**) in order to lock the system by means of an intramolecular hydrogen bond between the hydrogen atom of the imidazole moiety and the oxygen atom of the methoxy group. This provided a potentially better mimic of the imidazopyridine by fixing the basic imid-

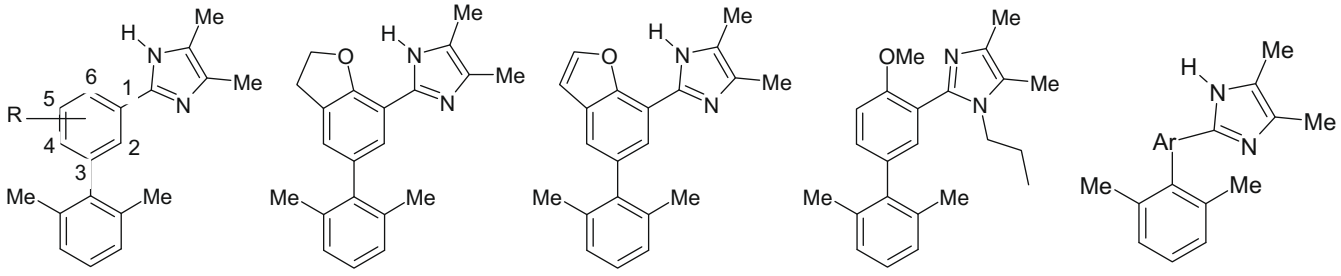
**Table 2**




| Ex | X | Y | $R^1$ | $R^2$ | $R^3$ | $H^+/K^+$ ATPase $pIC_{50}$ |
|---|---|---|---|---|---|---|
| **2c** | N | C | H | Me | Me | 5.2 |
| **3a** | N | C | H | H | H | 4.5 |
| **3b** | N | C | H | Et | Et | 4.8 |
| **3c** | N | C | H | Ph | | 4.4 |
| **3d** | N | C | Me | H | H | 5.2 |
| **3e** | N | C | Me | Me | Me | 4.6 |
| **3f** | N | C | *n*-Pr | H | H | 4.3 |
| **3g** | CH | N | — | Me | Me | 4.8 |
| **3h** | CH | N | Me | H | — | 4.4 |
| **3i** | | | | | | 4.5 |
| **3j** | | | | | | 4.4 |
| **3k** | | | | | | 4.3 |

$pIC_{50}$ values are reported as mean of >2 experiments.

**Table 3**



(4) (4l) (4m) (4p) (5)

| Ex | R | $H^+/K^+$ ATPase $pIC_{50}$ | Ex | R | $H^+/K^+$ ATPase $pIC_{50}$ | Ex | Ar | $H^+/K^+$ ATPase $pIC_{50}$ |
|---|---|---|---|---|---|---|---|---|
| **4a** | 2-OMe | <4.0 | **4i** | 6-$OCHF_2$ | 5.0 | **2c** | Ph | 5.2 |
| **4b** | 6-OMe | 6.1 | **4j** | 6-$OCH_2CO_2Me$ | 5.9 | **5a** | 2,5-Furanyl | 4.9 |
| **4c** | 4-OMe | 4.9 | **4k** | 6-$OCH_2CONH_2$ | 5.7 | **5b** | 2,5-Thienyl | 4.1 |
| **4d** | 4-Me | 4.9 | **4l** | — | 5.5 | **5c** | 2,4-Furanyl | <4.0 |
| **4e** | 5,6-DiMeO | 4.6 | **4m** | — | 5.4 | **5d** | 2,4-Thienyl | 4.5 |
| **4f** | 6-OH | 5.7 | **4n** | 6-OMe-pyrid-5-yl* | 4.8 | | | |
| **4g** | 6-OEt | 5.6 | **4o** | Pyrid-4-yl | <4.0 | | | |
| **4h** | 6-OBn | 5.3 | **4p** | — | 4.9 | | | |

$pIC_{50}$ values are reported as mean of >2 experiments.
* No *ortho* methyl substituents on phenyl ring.

azole nitrogen atom to a single tautomer. Whilst the 2-methoxy compound (**4a**) showed a complete loss of activity, the addition of the 6-methoxy substituent gave a compound **(4b)** with submicromolar activity. The methoxy regioisomer **(4c)** was also lower in potency than the unsubstituted compound **(2c)**. Other substituents such as methyl and dimethoxy **(4d–e)** also reduced potency suggesting substitution at the 4- and 5- positions is disfavoured.

We hypothesised that a key factor governing potency was the position of the basic imidazole *N-1*. Assuming intramolecular hydrogen bonding locks the imidazole tautomer in place the basic nitrogen atom in the 6-methoxy compound **(4b)** superimposes well with the basic centre in the more potent imidazopyridine series which may account for the increase in potency. However the basic centre in the 2-methoxy analogue **(4a)** is likely to be located over the imidazopyridine ring fused nitrogen atom (Fig. 1) which would appear to be disfavoured. Exploration of other oxygen containing groups that could maintain this putative hydrogen bond **(4f–k)** showed that other substituents are tolerated. The presence of a carboxylate functionality **(4k–l)** *beta* to the oxygen is also tolerated and could provide a handle for further optimisation.

The appropriate dihydrobenzofuran **(4l)**, benzofuran **(4m)** and pyridine **(4o)** core ring systems gave less potent compounds than the phenyl core **(4b)**. However the methoxypyridine **(4n)** is equipotent with its unsubstituted phenyl equivalent **(2a)**. Alkylation of the imidazole at *N-1* **(4p)** unsurprisingly resulted in a significant loss of potency possibly through the loss of co-planarity and hydrogen bonding between the imidazole and core ring systems that is predicted by modelling[16] and the steric clash outlined previously.

Five-membered ring systems **(5a–d)** proved poor replacements for the central phenyl ring, which is reflected by the poorer overlays with the imidazopyridine template (Fig. 2).

In conclusion we have been able to develop the biarylimidazole framework to yield a compound with submicromolar activity against the gastric $H^+/K^+$ ATPase **(4b)** which removes one of the potentially problematic structural features in the imidazopyridine series (i.e. the benzylamine functionality). Key components of the activity have been shown to be the geometry of each of the pendant rings relative to the core in order to fit within a tight binding pocket, which was influenced by a putative hydrogen bond accepting methoxy substituent. The methoxy group also appears to have a vector appropriate to allow access to the area of the pharmacophore occupied by the amide substituent in the imidazopyridines **(1a–b)**. This could provide a handle to introduce appropriate functionalities to modify the pharmacokinetic properties of the molecule. The template therefore affords an interesting starting point for further optimisation which will be reported in due course.

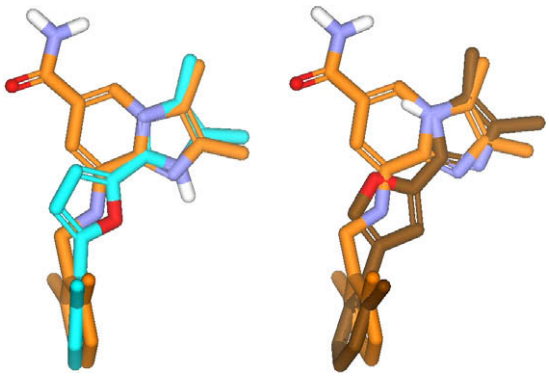
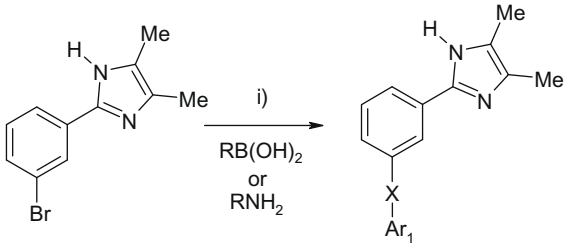
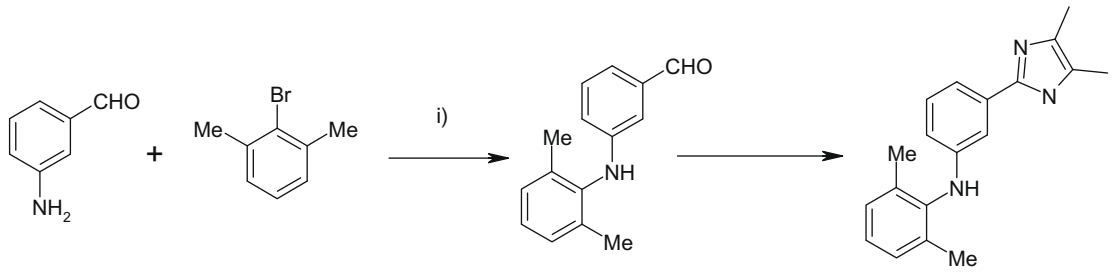


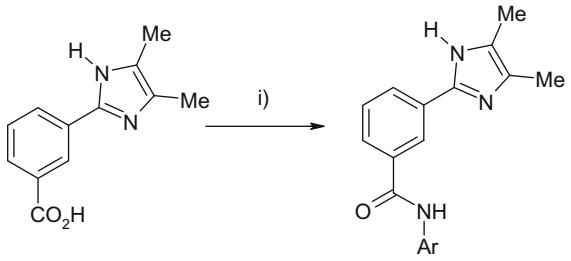
**Figure 2.** Overlays of imidazopyridine **(1b)** with biaryl imidazoles **(5a)** and **(5c)**.




**Scheme 1.** Reagents and conditions: (i) boronic acid (2 equiv), $Pd(dppf)Cl_2$ (0.1 equiv), 2 M $Na_2CO_3$ (3 equiv), DMF, microwave (μW), 100 °C, 3 h or amine (2 equiv), CuI (0.2 equiv), $Cs_2CO_3$ (2 equiv), DMF, μW, 220 °C, 10 h.



**Scheme 2.** Reagents and conditions: (i) ArBr, aldehyde (3 equiv) $Pd_2(dba)_3$ (0.1 equiv), BINAP (0.1 equiv), NaO*t*Bu (1.4 equiv), toluene, 100 °C, 16 h.



**Scheme 3.** Reagents and conditions: (i) biarylcarboxylate, ArNH2 (1.1 equiv), HOBT (2 equiv), triethylamine (3 equiv), resin bound DCC (1.1 equiv), NMP, 20 °C, 16 h.

Synthesis of substituted aromatic ring systems Ar[1] **(2)**[17] was readily achieved via coupling of appropriate phenyl **(2a–e, k–l)** or vinyl boronic acids (**2g**) or amines (**2i**) with 2-(3-bromophenyl)-4,5-dimethyl-1*H*-imidazole, which was in turn synthesised from 3-bromobenzaldehyde using the conditions of Wolkenberg et al.[18] (Scheme 1). Ethyl linked compound **(2h)** was synthesised by reduction of **(2g)** using 10% Pd/C and hydrogen in ethanol.

Nitrogen linked compound **(2f)** was synthesised from intermediate generated from a palladium mediated coupling of 3-aminobenzaldehyde and 2-bromo-1,3-dimethylbenzene followed by imidazole ring formation as outlined above (Scheme 2).

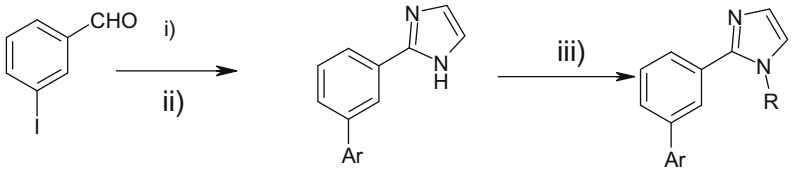
Biaryl carboxylic acid was generated from the methyl ester by refluxing in 5 M HCl for 16 h. In turn the ester was synthesised using the conditions of Wolkenberg et al. This intermediate was then coupled with appropriate anilines to yield the amide linked analogues **(2j)** (Scheme 3).

Biarylimidazoles **(3a–e,h)** were synthesised via Suzuki reaction of 3-bromophenylboronic acid with the appropriate bromoimidazole followed by a second Suzuki coupling to form the biaryl bond as described in Scheme 1. Biarylimidazole **(3g)** was prepared in the same manner though the bromoimidazole was generated from the equivalent dibromoimidazole following literature precedent.[19] *n*-Propyl analogue **(3f)** was synthesised by alkylation of the unsubstituted imidazole (Scheme 4).

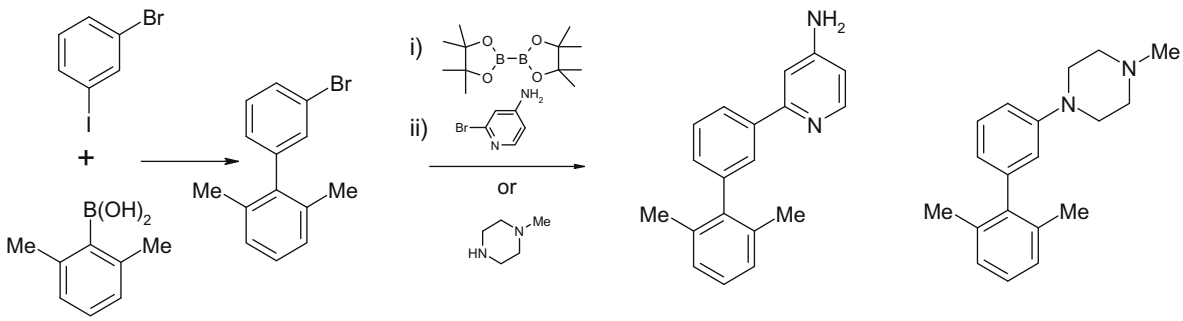
The pyridine analogue **(3i)** was synthesised via an anhydrous Suzuki reaction between 2-bromo-4-pyridinamine and 2-(2′,6′-dimethyl-3-biphenylyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Scheme 5). The latter was generated by Suzuki reaction between (2,6-dimethylphenyl)boronic acid and 1-bromo-3-iodobenzene and a subsequent palladium mediated halogen-metal exchange with pinacoldiborane.

The piperazine compound **(3j)** was obtained by Buchwald coupling between 3′-bromo-2,6-dimethylbiphenyl (described in synthesis of **3i** above) and 1-methylpiperazine

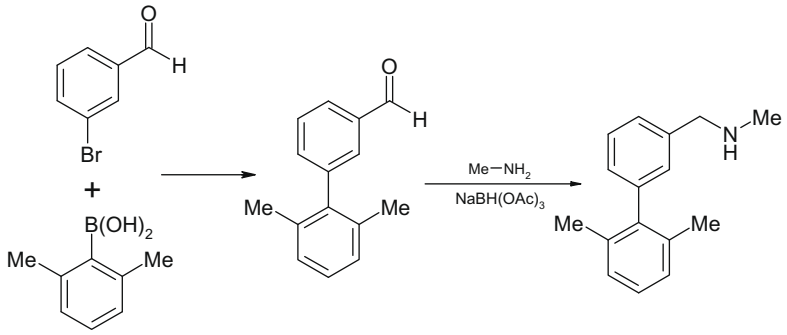
The alkyl amine **(3k)** was synthesised via a reductive amination between 2′,6′-dimethyl-3-biphenylcarbaldehyde which was in turn synthesised by a Suzuki reaction between 3-bromobenzaldehyde and (2,6-dimethylphenyl)boronic acid followed by a reductive



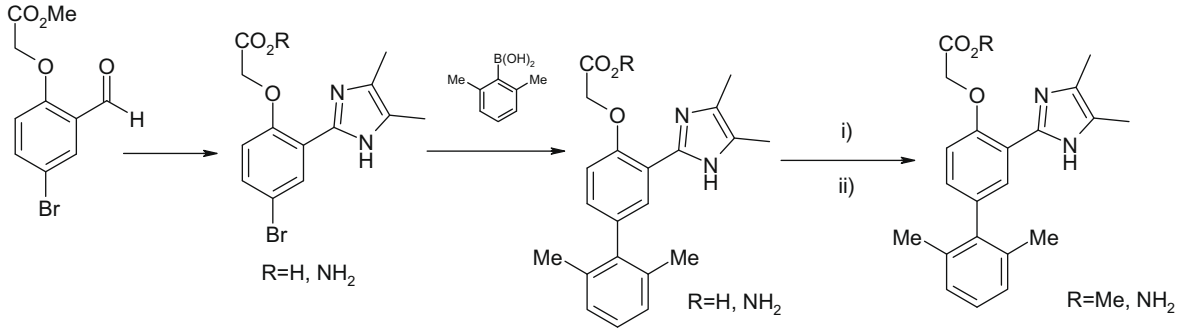
**Scheme 4.** Reagents and conditions: (i) $NH_4OH$ (10 equiv), glyoxal (10 equiv), ethanol, 20 °C, 16 h; (ii) $ArB(OH)_2$ (1.2 equiv), $Na_2CO_3$ (4 equiv), $Pd(PPh_3)_4$ (0.1 equiv), 1:1 dioxan/water, 100 °C, 48 h; (iii) R–I (2 equiv), NaH (2 equiv), THF, 20 °C, 16 h.



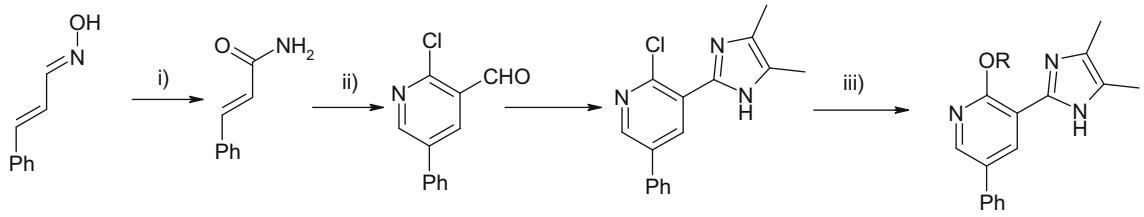
**Scheme 5.** Reagents and conditions: (1) pinacoldiborane (1.1 equiv), $Pd(dppf)Cl_2$ (0.06 equiv), dppf (0.06 equiv), KOAc (3 equiv), dioxan, 80 °C, 90 h; (2) 2-bromo-4-aminopyridine (1.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), $Cs_2CO_3$ (2 equiv), 99:1 toluene/ethanol, μW, 100 °C, 90 min or Amine (2 equiv) $Pd(OAc)_2$ (0.05 equiv), BINAP (0.15 equiv), $Cs_2CO_3$ (1.5 equiv), dioxan, 100 °C, 16 h.



**Scheme 6.** Reagents and conditions: methylamine (2 equiv), $NaBH(OAc)_3$ (2 equiv), AcOH (cat), DCM, 20 °C, 16 h.



**Scheme 7.** Reagents and conditions: (i) oxalyl chloride (1.1 equiv), DCM, 20 °C, 2 h; (ii) methanol or 2 M methanolic ammonia.



**Scheme 8.** Reagents and conditions: (i) $PCl_5$ (1 equiv), diethyl ether, 20 °C, 5 h; (ii) $POCl_3$ (8 equiv), DMF (12 equiv), 90 °C, 6 h; (iii) NaOR (10 equiv), methanol, 65 °C, 24 h.

amination with methylamine using sodium triacetoxyborohydride as the reducing agent (Scheme 6).

Compounds **(4a–e, g–i, l–m, o, 5a–d)** were synthesised using the same methodology outlined in Scheme 1. The phenolic analogue **(4f)** was generated from the benzyl derivative **(4h)** using the hydrogenation conditions for **(2h)** above.

The carboxylate compounds **(4j–k)** were made from the starting methyl ester following conditions outlined in Scheme 1. The ester was transformed into a mixture of carboxylic acid and amide during imidazole formation and the desired compounds were obtained after treatment with oxalyl chloride and quenching in methanol or methanolic ammonia as appropriate (Scheme 7).

Alkoxypyridine compound **(4n)** was synthesised by building up the core pyridine ring, imidazole formation as described in the literature and subsequent alkoxide displacement of a chloropyridine (Scheme 8).

*(N1)*-Alkylated methoxy derivative **(4p)** was synthesised using conditions outlined in Scheme 4.

## Acknowledgements

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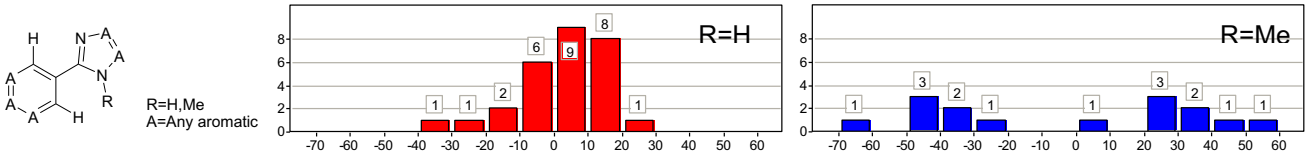
15. A search of the Cambridge crystallography database with the following query retrieved a total of 43 hits where the twist between the two rings is more pronounced with R = Me than R = H.




16. Structures were optimised with MMFF94x force field and superimposed by maximising volume overlap (rigid-body fit) within MOE (CCG).
17. All novel compounds gave satisfactory $^{1}$H NMR and LC/MS data in full agreement with their proposed structures.
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