

# Synthesis of a Novel Library of 1-Substituted Pyrido[1,2-*a*]benzimidazoles

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The reactivity and synthesis of new analogues of pyrido[1,2-*a*]benzimidazoles have been explored. Twenty-three derivatives bearing phenoxy, thiophenoxy, aniline, and aryl groups at the 1-position were successfully synthesised in 25–91 % yield, via nucleophilic substitution, Buchwald–Hartwig amination, and Suzuki coupling type processes. Solvent free synthetic protocols were employed to achieve the nucleophilic substitution of anilines with electron donating groups or moderately electron withdrawing groups on a sterically demanding intermediate (**7a**). An unusual polycyclic heterocycle was identified as a side-product during this work: a dimeric bis(pyrido[1,2-*a*]benzimidazole).

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## Introduction

Pyrido[1,2-*a*]benzimidazoles are tricyclic derivatives of benzimidazole that contain a fused pyridyl ring (Fig. 1). First described by Morgan in 1937,<sup>[1]</sup> the highly conjugated aromatic system is of interest in materials science, and has found applications in fluorescence.<sup>[2]</sup> The pyrido[1,2-*a*]benzimidazole motif is also an important structure in medicinal chemistry: a diversity of biological applications are recognised, including the semi-synthetic antibiotic Rifaximin,<sup>[3]</sup> and a variety of antineoplastic, analgesic,<sup>[4]</sup> anti-bacterial,<sup>[5]</sup> anti-fungal,<sup>[6]</sup> anti-malarial,<sup>[7]</sup> and anticancer agents (e.g. **2–6**).<sup>[8–10]</sup>

While the heteroarene cores of **1–6** are essential for achieving potent biological activity in each case, the peripheral substituents are also important.<sup>[7,8]</sup> For example, compounds **4** and **5** displayed quite different activity and selectivity patterns against leukemia cell lines in vitro.<sup>[11]</sup> It is particularly notable that replacing the chlorine atom in **6** with an aniline group in **5** gave a significant enhancement in anti-leukemia activity.<sup>[1,9]</sup> Thus, methods for systematically derivatising a particular position of the pyrido[1,2-*a*]benzimidazole core are of great value for providing compounds for biological screening and structure–activity relationship studies. In this context, we report herein the synthesis of a small library of pyrido[1,2-*a*]benzimidazole derivatives bearing a variety of substituents at position 1.

To investigate the potential anti-cancer activity of novel pyrido[1,2-*a*]benzimidazole derivatives, we desired to synthesise a series of highly substituted analogues **8** and **9** (Scheme 1), containing various phenoxy, thiophenoxy, aniline, and aryl

groups at position 1. We aimed to access these compounds through aromatic nucleophilic substitution and Suzuki coupling of the corresponding 1-chloro derivatives **7** (Scheme 1). Compound **7** was previously shown to undergo aromatic nucleophilic substitution reactions, but with aliphatic amines as the nucleophiles.<sup>[6]</sup> At the outset of this study it was expected that the substitutions with less nucleophilic aromatic amines and coupling with aryl boronic acids would pose more of a challenge, and substitutions with oxygen or sulfur based nucleophiles may be more straightforward despite a lack of literature precedent for such transformations.

## Results and Discussion

### Preparation of Starting Materials

The synthesis of pyrido[1,2-*a*]benzimidazoles is well documented. The most common route involves [3 + 3] cyclocondensation of C2 methylene-containing benzimidazoles with appropriate bielectrophiles.<sup>[11]</sup> More recently, other strategies including multicomponent reactions and copper-catalysed reactions<sup>[12]</sup> have also been developed, contributing to a flourishing body of research in this area. The requisite starting materials for this study **7a,b** were readily obtained through a two-step sequence (Scheme 2).<sup>[2,13,14]</sup> Thus, [3 + 3] cyclocondensation of benzimidazoleacetonitrile **11** with substituted ethyl acetoacetate derivatives **10a,b** afforded the 1-oxo compounds **12a,b** in high yield, and subsequent chlorination with POCl<sub>3</sub> delivered the desired compounds **7a,b** in multigram quantities.<sup>[2]</sup>

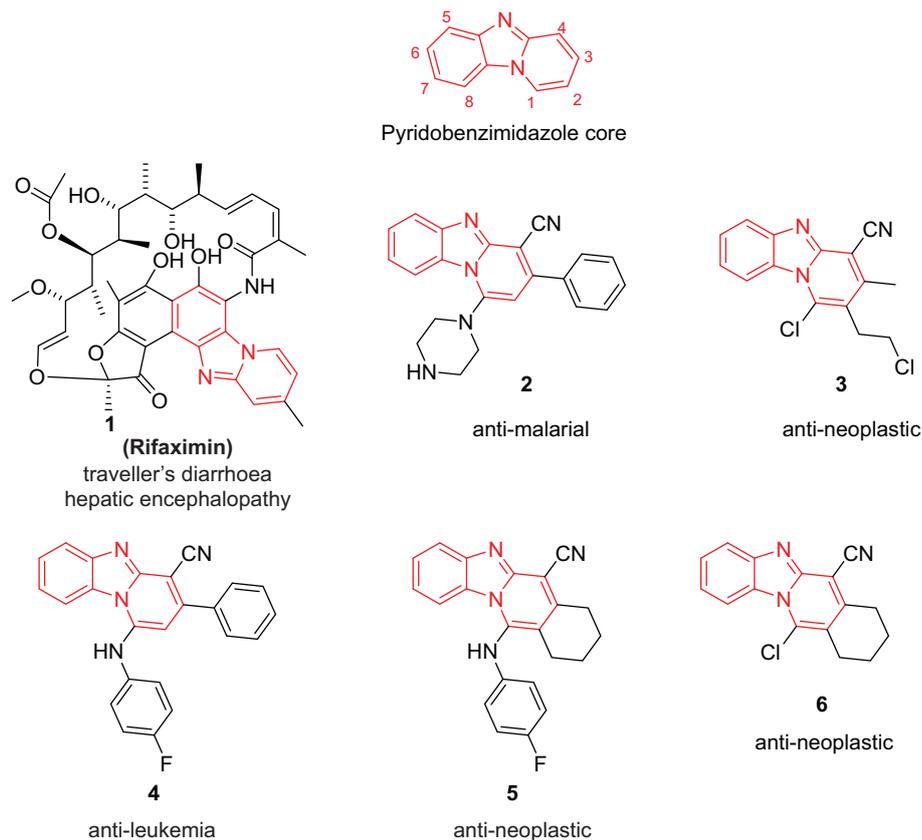
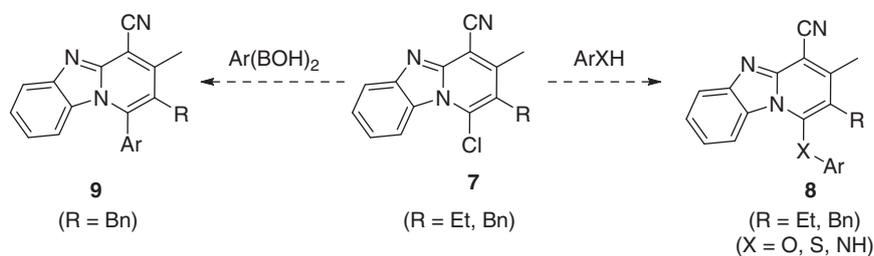
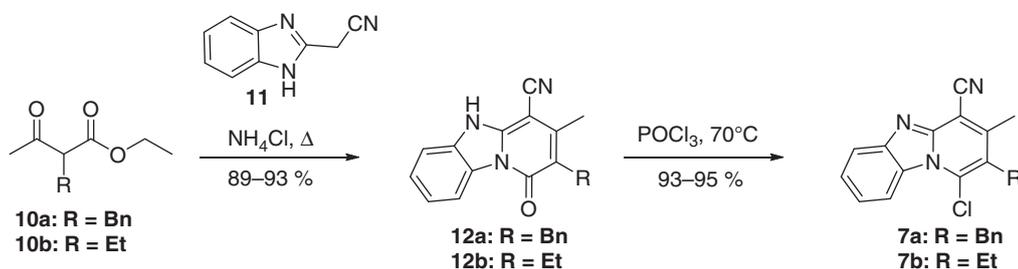


Fig. 1. Some examples of medicinally important pyrido[1,2-*a*]benzimidazole derivatives.



Scheme 1. Strategy for synthesising a library of 1-substituted pyrido[1,2-*a*]benzimidazole derivatives.



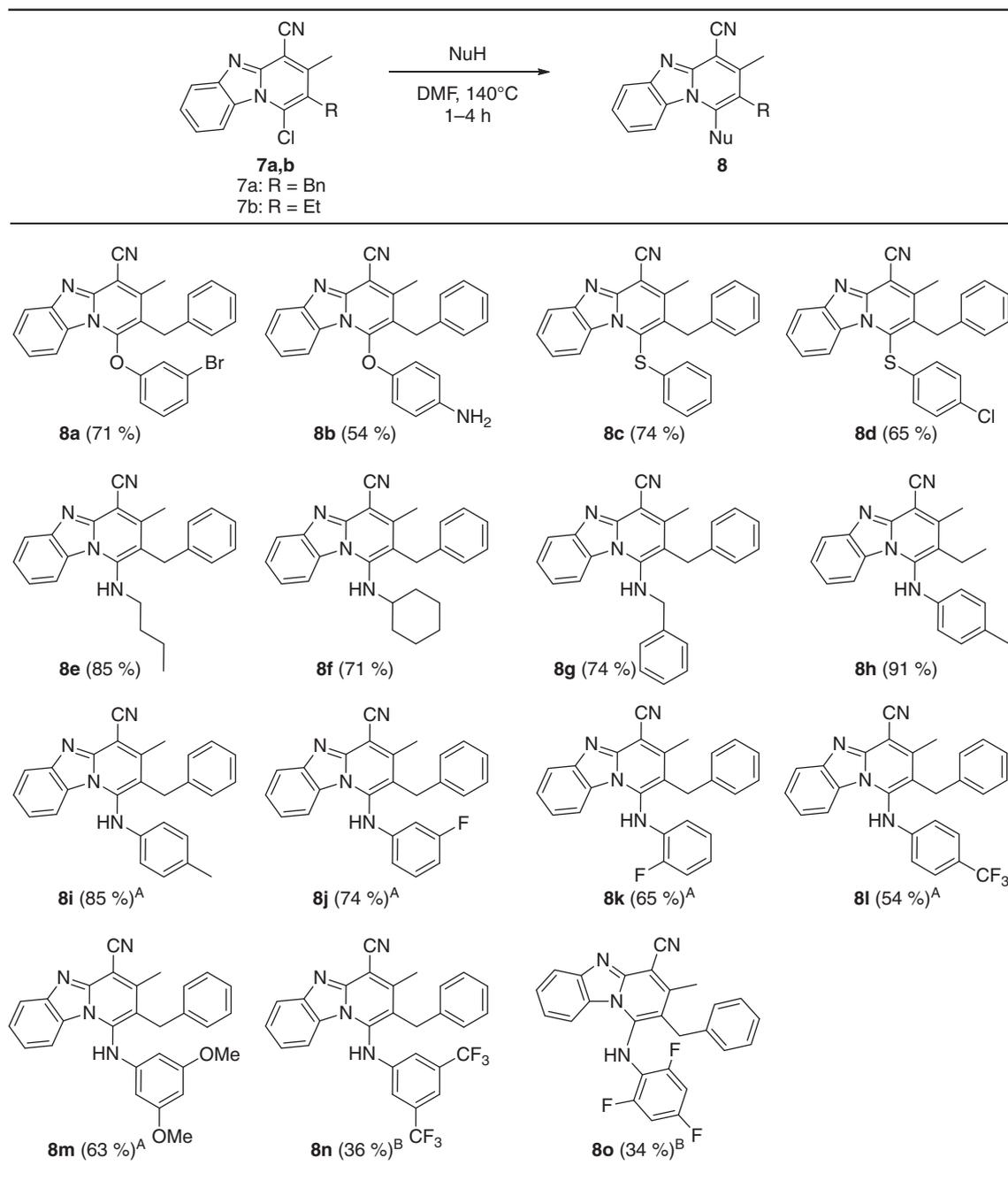
Scheme 2. Synthesis of the starting materials **7a,b**.

### Aromatic Nucleophilic Substitution Reactions

With the precursors **7a,b** in hand, their reactivity towards nucleophiles was then investigated (Table 1). A variety of phenols, thiophenols, and aliphatic amines were found to successfully react with **7a**, giving the desired products **8a–g** in

moderate to good yields under conditions identical to those previously reported for aliphatic amine nucleophiles.<sup>[6]</sup> Attention was next turned towards the use of aromatic amines **8h–o** (Table 1). It was found that *p*-toluidine reacted efficiently with **7b** to give the desired product **8h** in excellent yield, despite the

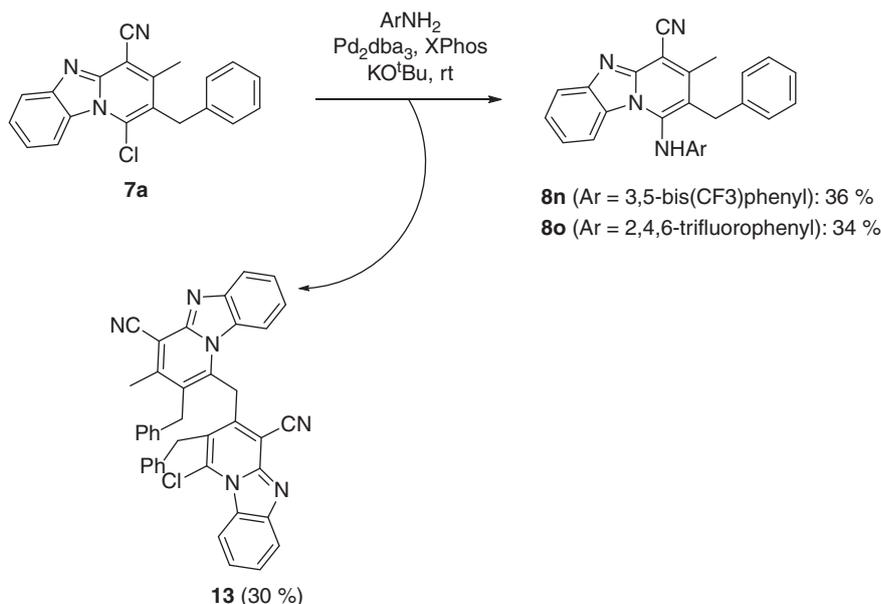
Table 1. Aromatic nucleophilic substitution reactions

<sup>A</sup>Reaction performed neat at 120°C.<sup>B</sup>Reaction performed using Buchwald coupling.

lower nucleophilicity. To investigate whether the reduced steric demand of the ethyl substituent of **7b** was contributing to the efficiency of this reaction, substrate **7a** was trialed in the same process. However, in this case no reaction was observed under the standard conditions, or even under a variety of other conditions including the use of a higher-boiling solvent, addition of strong base, microwave assisted heating,<sup>[15,16]</sup> or ultrasonic irradiation.

Finally, it was discovered that the desired compound **8i** could be obtained in high yield through heating a mixture of **7a** and

*p*-toluidine in the absence of solvent (Table 1).<sup>[17]</sup> Solvent-free synthetic protocols are popular in modern organic synthesis for two reasons: first, there are environmental benefits from avoiding the use of organic solvents; and second, the rates of reactions can be significantly increased.<sup>[18]</sup> The substitution reaction to give **8i** (Table 1) proved that solvent-free conditions are ideal for the synthesis of 1-anilino-pyrido[1,2-*a*]benzimidazoles. The reaction gave moderate to high yields with anilines bearing electron-donating or moderately electron-withdrawing groups **8i–m**. An additional benefit was the ease of work-up: the reaction



**Scheme 3.** Buchwald–Hartwig amination reactions and the dimeric structure **13** that was isolated as a major side-product.

mixtures were simply triturated with hexane, filtered, and the solid residue subjected to chromatography on silica gel.

However, the strongly electron deficient<sup>[19]</sup> substrates 3,5-bis(trifluoromethyl)aniline **8n** and 2,4,6-trifluoroaniline **8o** were found to be unreactive even in the absence of solvent. Thus, other methods were needed to be explored for such substrates.

#### Buchwald–Hartwig Amination Reactions

Over the past two decades, palladium-catalysed C–N bond formation (the Buchwald–Hartwig amination reaction)<sup>[19–21]</sup> has become the method of choice for synthesising targets that contain aromatic moieties linked by a nitrogen atom. The palladium-catalysed approach is highly versatile, allowing most aryl halides (including chlorides, bromides, and iodides) to be successfully coupled with a wide range of amines (primary, secondary, electron-deficient, and heterocyclic amines).<sup>[22]</sup> Recent investigations have shown that the use of tris(dibenzylideneacetone)dipalladium(0) (Pd<sub>2</sub>dba<sub>3</sub>) and [2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl] (XPhos)<sup>[23]</sup> provides an excellent catalytic system for the coupling of aryl chlorides with aniline derivatives,<sup>[24–26]</sup> sometimes even at room temperature.<sup>[27,28]</sup> Hence, this catalyst system was chosen for this research.

When compound **7a** was treated with strongly electron deficient aniline derivatives in the presence of Pd<sub>2</sub>dba<sub>3</sub>, XPhos, and KO<sup>t</sup>Bu at room temperature, the desired products **8n** and **8o** were isolated in 34–36% yield (Scheme 3). Higher temperatures did not increase the yields, but instead led to complex product mixtures. Nevertheless the Buchwald–Hartwig approach was found to provide a convenient route to otherwise inaccessible pyrido[1,2-*a*]benzimidazoles.

In an attempt to rationalise the modest yields of the Buchwald–Hartwig amination, one major side product **13**, was carefully isolated in 30% yield (Scheme 3). It seems that under the strongly basic reaction conditions (KO<sup>t</sup>Bu, 3 equiv.), deprotonation of the methyl group of **7a** and subsequent nucleophilic

attack onto another molecule of **7a** affords the dimeric structure **13**. In addition, besides **13**, further oligomers and/or coupling products are possible, and this can explain the modest yields of the desired products **8n** and **8o**.

#### Suzuki Coupling Reactions

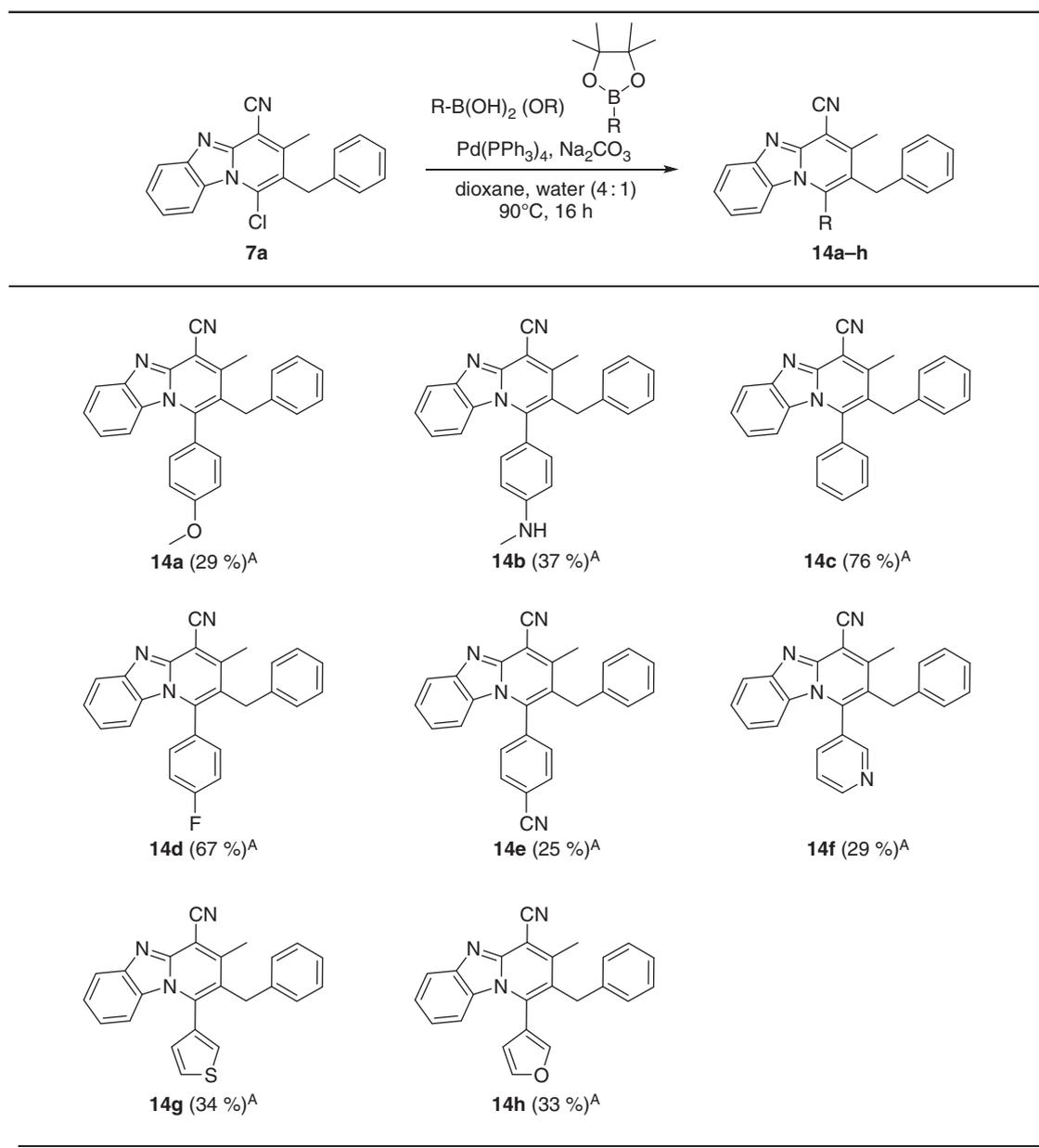
Having developed methods for aromatic nucleophilic substitution of **7a** with diverse nucleophiles (Schemes 2 and 3), efforts were next directed towards the formation of a carbon–carbon bond with **7a**. The Suzuki coupling reaction was employed to achieve the formation of the C–C bond. This palladium catalysed cross-coupling reaction between the organic halides or triflates and organoboron compounds is a powerful and general methodology for C–C bond formation. It offers several advantages, such as being largely unaffected by the presence of water and tolerates a broad range of functional groups.

Compound **7a** was treated with a variety of aromatic boronic acids or boronic acid esters in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and Na<sub>2</sub>CO<sub>3</sub> at 90°C to afford the desired products **14a–h** in moderate to good yields (25–76%) after column chromatography and crystallisation (Table 2). One major side product formed was the dimer of **7a** (Compound **13**). The structures of the compounds **14a** (Fig. 2), **14d** (Fig. 3), and **13** (Fig. 4) were confirmed by X-ray crystallography.<sup>[29]</sup>

#### Conclusion

The chemistry of pyrido[1,2-*a*]benzimidazoles has been explored. Various 1-phenoxy, 1-thiophenoxy, 1-anilino, and 1-aryl derivatives have been synthesised from the 1-chloro precursors via either aromatic nucleophilic substitution processes or, for strongly electron deficient 1-anilino derivatives, Buchwald–Hartwig amination and Suzuki coupling conditions. The synthetic methods developed herein will underpin the ongoing development of this important class of heterocycles for future applications in medicine and materials science.

Table 2. Synthesis of compounds 14a–h using Suzuki coupling



<sup>A</sup>Isolated yields after column chromatography and recrystallization.

## Experimental

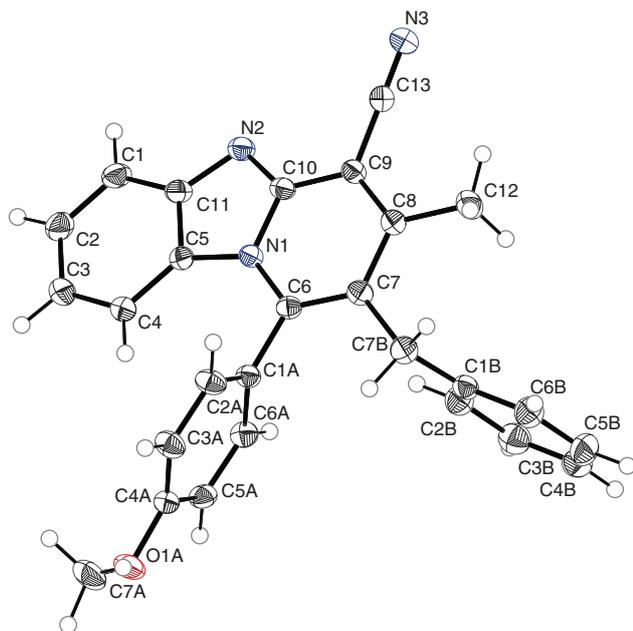
### General

The solvents and reagents were purchased from commercial sources (Combi-Blocks, Sigma Aldrich) and used without purification. The reactions were monitored by TLC (thin-layer chromatography) using Merck SilicaGel 60 254 plates, and UV light (254 nm) was used for visualisation. Grace Davison LC60A 40–63  $\mu\text{m}$  silica gel columns were used as the stationary phase for column chromatography and the mobile phase was varied depending upon the polarity of the compounds. The melting points were measured using a Mel-Temp melting point apparatus and a Thermo Nicolet 370 FT-IR spectrometer was used to record the infrared spectra. High-resolution mass spectrometry (HRMS) was performed at the Bioanalytical Mass Spectrometry Facility, UNSW using the electrospray ionisation (ESI) method.  $^1\text{H}$  and  $^{13}\text{C}$

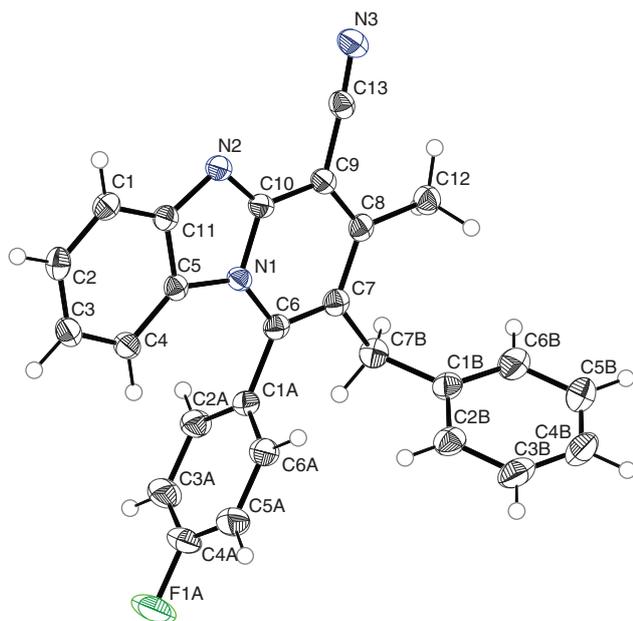
NMR spectra were recorded at room temperature in deuterated solvents using Bruker Avance 300, 400, or 600 MHz instruments. Tetramethylsilane was used as the internal standard and the chemical shifts ( $\delta$ ) are reported in parts per million (ppm).

### 2-Benzyl-1-(3-bromophenoxy)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (8a)

A mixture of compound 7a (100 mg, 0.30 mmol) and *m*-bromophenol (85.2 mg, 0.45 mmol) in DMF (10 mL) was heated at reflux for 4 h. The crude product was purified by flash chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound 8a as a yellow solid (100.0 mg, 71%). Mp 207–209°C.  $\delta_{\text{H}}$  (300 MHz, DMSO-*d*<sub>6</sub>) 7.92 (dt, *J* 8.3, 1.0, 1H), 7.83 (dt, *J* 8.4, 1.0, 1H), 7.59–7.46 (m, 3H), 7.29 (ddd, *J* 8.3, 7.2, 1.1, 1H), 7.26–7.10 (m, 7H), 3.98 (s, 2H), 2.52 (d, *J* 2.3, 3H).  $\delta_{\text{C}}$



**Fig. 2.** ORTEP diagram of 2-benzyl-1-(4-methoxyphenyl)-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile.

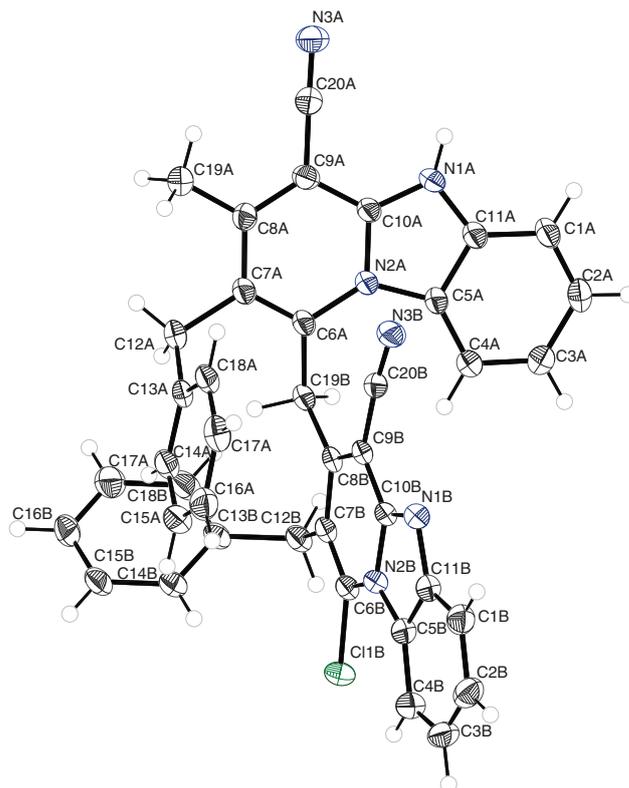


**Fig. 3.** ORTEP diagram of 2-benzyl-1-(4-fluorophenyl)-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile.

(75 MHz, DMSO-*d*<sub>6</sub>) 154.3, 152.0, 146.7, 146.2, 144.1, 137.8, 133.3, 128.5, 127.9, 127.4, 126.4, 122.1, 121.8, 119.2, 117.6, 116.3, 115.3, 114.7, 112.6, 97.65, 30.5, 19.2.  $\nu_{\max}$  (KBr)/cm<sup>-1</sup> 3063, 3022, 2229, 1635, 1596, 1499, 1385, 1369, 1306, 1272, 1249, 1230, 1198, 1171, 1115, 1103, 954, 935, 849, 775, 745, 698. HRMS (+ESI) *m/z* 468.0703, [M + H]<sup>+</sup>; calcd for [C<sub>26</sub>H<sub>18</sub>BrN<sub>3</sub>O + H] 468.0711.

**1-(4-Aminophenoxy)-2-benzyl-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (**8b**)**

A mixture of compound **7a** (100 mg, 0.30 mmol) and 4-amino phenol (49.3 mg, 0.45 mmol) in DMF (4 mL) was heated at



**Fig. 4.** ORTEP diagram of 2-benzyl-1-((2-benzyl-1-chloro-4-cyanobenzoyl)methyl)-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile.

reflux for 4 h. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexane (10–90%) to afford compound **8b** as a yellow solid (54.1 mg, 54%). Mp 227–229°C.  $\delta_{\text{H}}$  (600 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 7.99 (dt, *J* 8.4, 1.0, 1H), 7.94 (dt, *J* 8.3, 1.0, 1H), 7.53 (ddd, *J* 8.3, 7.2, 1.1, 1H), 7.29–7.21 (m, 3H), 7.23–7.16 (m, 1H), 7.07 (ddt, *J* 7.5, 1.3, 0.7, 2H), 6.75–6.69 (m, 2H), 6.62–6.56 (m, 2H), 3.99 (s, 2H), 3.76–3.54 (br s, 2H), 2.57 (s, 3H).  $\delta_{\text{C}}$  (150 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 152.09, 148.48, 148.19, 147.42, 145.11, 144.10, 138.39, 129.02, 128.47, 128.29, 126.91, 126.71, 122.44, 120.06, 116.61, 116.28, 115.73, 115.45, 112.99, 98.73, 31.43, 19.73.  $\nu_{\max}$  (KBr)/cm<sup>-1</sup> 3452, 3357, 3030, 2229, 1626, 1481, 1443, 1382, 1307, 1231, 1180, 1021, 921, 819, 726. HRMS (+ESI) *m/z* 405.1710, [M + H]<sup>+</sup>; calcd for [C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>O + H] 405.1709.

**2-Benzyl-3-methyl-1-(phenylthio)benzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (**8c**)**

A mixture of compound **7a** (100 mg, 0.30 mmol) and thiophenol (56.9 mg, 0.45 mmol) in DMF (10 mL) was heated at reflux for 4 h. The crude product was purified by flash chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **8c** as a yellow solid (90.5 mg, 74%). Mp 242–244°C.  $\delta_{\text{H}}$  (300 MHz, DMSO-*d*<sub>6</sub>) 8.71 (dt, *J* 8.7, 0.9, 1H), 7.90 (ddd, *J* 8.3, 1.2, 0.7, 1H), 7.52 (ddd, *J* 8.2, 7.1, 1.1, 1H), 7.34–7.11 (m, 11H), 4.55 (s, 2H), 2.56 (s, 3H).  $\delta_{\text{C}}$  (75 MHz, DMSO-*d*<sub>6</sub>) 149.2, 146.2, 143.8, 138.2, 135.0, 132.7, 131.2, 130.2, 130.0, 128.6, 127.9, 127.0, 126.4, 126.3, 126.2, 121.9, 119.2, 116.9, 115.0, 105.0, 102.8, 100.1, 35.6, 19.9.  $\nu_{\max}$  (KBr)/cm<sup>-1</sup> 3410, 3072, 3021, 2226, 1602, 1585, 1454, 1442, 1393, 1387, 1298, 1190, 1076, 1004, 822, 760, 742. HRMS (+ESI) *m/z* 428.1187, [M + Na]<sup>+</sup>; calcd for [C<sub>26</sub>H<sub>19</sub>N<sub>3</sub>S + Na] 428.1197.

2-Benzyl-1-((4-chlorophenyl)thio)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**8d**)

A mixture of compound **7a** (100 mg, 0.30 mmol) and *p*-chlorothiophenol (72.3 mg, 0.45 mmol) in DMF (10 mL) was heated at reflux for 4 h. The crude product was purified by flash chromatography using 2 : 3 ethyl acetate/hexane to afford compound **8d** as a yellow solid (86.2 mg, 65%). Mp 244–246°C.  $\delta_{\text{H}}$  (300 MHz, DMSO- $d_6$ ) 8.66 (dt, *J* 8.7, 1.0, 1H), 7.91 (dt, *J* 8.3, 1.0, 1H), 7.52 (ddd, *J* 8.2, 7.1, 1.1, 1H), 7.37–7.09 (m, 10H), 4.52 (s, 2H), 2.55 (s, 3H).  $\delta_{\text{C}}$  (75 MHz, DMSO- $d_6$ ) 148.9, 144.3, 138.2, 134.5, 131.9, 131.7, 131.0, 130.2, 129.9, 128.6, 128.1, 127.8, 126.4, 126.0, 121.9, 119.5, 116.6, 115.0, 103.1, 34.2, 19.8.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3422, 3079, 3024, 2223, 1620, 1584, 1466, 1452, 1444, 1372, 1387, 1298, 1195, 1086, 1007, 823, 761, 743, 730. HRMS (+ESI) *m/z* 440.0981, [M + H]<sup>+</sup>; calcd for [C<sub>26</sub>H<sub>18</sub>ClN<sub>3</sub>S + H] 440.0988.

2-Benzyl-1-(butylamino)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**8e**)

A mixture of compound **7a** (100 mg, 0.30 mmol) and *n*-butylamine (33.0 mg, 0.45 mmol) in DMF (10 mL) was heated to 80°C for 4 h. The reaction mixture was cooled to room temperature. Water (30 mL) was added to precipitate a yellow solid which was collected by filtration. The crude product was recrystallised from acetone to afford compound **8e** as a yellow solid (95 mg, 85%). Mp 179–181°C.  $\delta_{\text{H}}$  (300 MHz, acetone- $d_6$ ) 8.29 (ddd, *J* 8.4, 1.2, 0.7, 1H), 7.82 (ddd, *J* 8.2, 1.2, 0.7, 1H), 7.53 (ddd, *J* 8.3, 7.2, 1.2, 1H), 7.40–7.27 (m, 3H), 7.27–7.18 (m, 3H), 5.36 (t, *J* 6.8, 1H), 4.36 (d, *J* 1.0, 2H), 3.23–3.11 (m, 2H), 2.58 (s, 3H), 1.74–1.61 (m, 2H), 1.25 (dq, *J* 14.7, 7.4, 2H), 0.81 (t, *J* 7.3, 3H).  $\delta_{\text{C}}$  (75 MHz, acetone- $d_6$ ) 151.3, 149.1, 146.3, 140.2, 130.2, 129.6, 128.7, 127.3, 126.4, 121.5, 120.0, 117.0, 116.7, 112.1, 95.4, 48.2, 33.1, 32.9, 20.8, 19.8, 14.0.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3241, 3091, 3050, 2952, 2866, 2216, 1707, 1628, 1595, 1369, 1311, 1133, 765. HRMS (+ESI) *m/z* 369.2068, [M + H]<sup>+</sup>; calcd for [C<sub>24</sub>H<sub>24</sub>N<sub>4</sub> + H] 369.2079.

2-Benzyl-1-(cyclohexylamino)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**8f**)

A mixture of compound **7a** (100 mg, 0.30 mmol) and cyclohexylamine (52.0 mg, 0.45 mmol) in DMF (10 mL) was heated to 80°C for 4 h. The reaction mixture was cooled to room temperature and water (30 mL) was added to precipitate a yellow solid which was collected by filtration. The crude product was recrystallised from acetone to afford compound **8f** as a yellow solid (84.5 mg, 71%). Mp 256–257°C.  $\delta_{\text{H}}$  (300 MHz, DMSO- $d_6$ ) 8.26 (d, *J* 8.4, 1H), 7.89–7.81 (m, 1H), 7.54 (ddd, *J* 8.2, 7.2, 1.0, 1H), 7.38 (ddd, *J* 8.4, 7.2, 1.2, 1H), 7.34–7.24 (m, 2H), 7.24–7.19 (m, 1H), 7.16–7.10 (m, 2H), 6.04 (d, *J* 10.4, 1H), 4.29 (s, 2H), 3.27–3.06 (m, 1H), 2.51 (m, 1H), 2.41 (s, 3H), 1.85 (d, *J* 12.2, 2H), 1.63 (d, *J* 11.4, 2H), 1.46 (t, *J* 11.5, 3H), 1.16–0.82 (m, 2H).  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3373, 3021, 2847, 2366, 2217, 1627, 1595, 1476, 1446, 1306, 737, 720, 698. HRMS (+ESI) *m/z* 403.1910, [M + H]<sup>+</sup>; calcd for [C<sub>27</sub>H<sub>26</sub>N<sub>4</sub> + H] 403.1923.

2-Benzyl-1-(benzylamino)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**8g**)

A mixture of compound **7a** (100 mg, 0.30 mmol) and benzylamine (48.4 mg, 0.45 mmol) in DMF (10 mL) was heated to 80°C for 4 h. The reaction mixture was cooled to room temperature. Water (30 mL) was added to precipitate a yellow solid which was collected by filtration. The crude product was recrystallised from

acetone to afford compound **8g** as a yellow solid (89.9 mg, 74%). Mp 234–236°C.  $\delta_{\text{H}}$  (300 MHz, DMSO- $d_6$ ) 8.31 (d, *J* 8.4, 1H), 7.87 (d, *J* 8.1, 1H), 7.55 (ddd, *J* 8.2, 7.1, 1.1, 1H), 7.39–7.14 (m, 7H), 7.14–7.06 (m, 2H), 7.06–6.97 (m, 2H), 6.64 (d, *J* 6.9, 1H), 4.28 (d, *J* 6.2, 2H), 3.92 (s, 2H), 2.35 (s, 3H).  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3373, 3021, 2847, 2366, 2217, 1627, 1595, 1476, 1446, 1306, 737, 720, 689. HRMS (+ESI) *m/z* 403.1910, [M + H]<sup>+</sup>; calcd for [C<sub>27</sub>H<sub>22</sub>N<sub>4</sub> + H] 403.1923.

2-Ethyl-3-methyl-1-(*p*-tolylamino)benzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**8h**)

A mixture of compound **7b** (100 mg, 0.36 mmol) and *p*-toluidine (57.3 mg, 0.54 mmol) in DMF (10 mL) was heated to 80°C for 48 h. The reaction mixture was cooled to room temperature. Water (30 mL) was added to precipitate a yellow solid which was collected by filtration. The crude product was recrystallised from acetone to afford compound **8h** as a yellow solid (110.5 mg, 91%).  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.94 (dd, *J* 8.2, 1.0, 1H), 7.79 (dd, *J* 8.4, 1.0, 1H), 7.43 (ddd, *J* 8.2, 7.1, 1.0, 1H), 7.10 (ddd, *J* 8.4, 7.1, 1.1, 1H), 7.00 (d, *J* 8.3, 2H), 6.47 (d, *J* 8.3, 2H), 6.06 (bs, 1H), 2.93 (s, 3H), 2.71 (q, *J* 7.5, 2H), 2.24 (s, 3H), 1.24 (t, *J* 7.5, 3H).  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 150.1, 149.2, 146.5, 144.6, 142.2, 140.0, 138.8, 131.6, 128.6, 128.5, 126.0, 121.6, 120.9, 120.8, 119.5, 116.0, 20.6, 19.1, 18.9, 14.3.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3296, 2849, 2533, 2225, 1635, 1585, 1511, 1478, 1457, 1370, 1307, 1273, 1215, 1220, 1165, 1010, 814, 757. HRMS (+ESI) *m/z* 341.1760, [M + H]<sup>+</sup>; calcd for [C<sub>22</sub>H<sub>20</sub>N<sub>4</sub> + H] 341.1766.

2-Benzyl-3-methyl-1-(*p*-tolylamino)benzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**8i**)

A mixture of compound **7a** (100 mg, 0.30 mmol) and *p*-toluidine (323.4 mg, 3.02 mmol) was heated to 120°C for 1 h. The crude material was purified by flash chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **8i** as a yellow solid (103.3 mg, 85%).  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 8.17 (br s, 1H), 8.02 (dd, *J* 8.4, 1.0, 1H), 7.82 (dd, *J* 8.2, 1.0, 1H), 7.45 (ddd, *J* 8.2, 7.2, 1.0, 1H), 7.17–7.26 (m, 5H), 7.13 (ddd, *J* 8.4, 7.2, 1.0, 1H), 6.99 (d, *J* 8.12, 2H), 6.67 (d, *J* 8.44, 2H), 4.28 (s, 2H), 2.57 (s, 3H).  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 150.1, 149.2, 146.8, 145.3, 144.6, 143.4, 142.2, 141.2, 140.0, 138.8, 131.6, 128.6, 128.5, 126.0, 121.6, 120.9, 120.8, 119.5, 117.3, 116.0, 112.4, 105.6, 33.7, 20.6, 18.9.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3396, 2839, 2543, 2215, 1645, 1595, 1510, 1480, 1467, 1422, 1370, 1307, 1283, 1265, 1240, 1165, 1080, 814, 757. HRMS (+ESI) *m/z* 403.1914, [M + H]<sup>+</sup>; calcd for [C<sub>27</sub>H<sub>22</sub>N<sub>4</sub> + H] 403.1923.

2-Benzyl-1-((3-fluorophenyl)amino)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**8j**)

A mixture of compound **7a** (100 mg, 0.30 mmol) and *m*-fluoroaniline (335.2 mg, 3.02 mmol) was heated to 120°C for 1 h. The crude material was purified by flash chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **8j** as a yellow solid (90.8 mg, 74%). Mp 234–236°C.  $\delta_{\text{H}}$  (300 MHz, acetone- $d_6$ ) 8.57 (s, 1H), 8.04 (dt, *J* 8.5, 1.0, 1H), 7.82 (dt, *J* 8.2, 1.0, 1H), 7.46 (ddd, *J* 8.3, 7.1, 1.1, 1H), 7.19 (m, 7H), 6.69–6.55 (m, 3H), 4.30 (s, 2H), 2.57 (s, 3H).  $\delta_{\text{C}}$  (75 MHz, acetone- $d_6$ ) 166.5, 163.2, 151.4, 148.1, 146.6, 146.5, 145.9, 139.9, 139.6, 132.2, 132.1, 129.8, 129.4, 128.8, 127.1, 126.5, 122.2, 120.3, 120.1, 116.8, 116.0, 111.4, 111.3, 107.9, 107.6, 102.7, 102.3, 100.6, 55.0, 33.3, 19.8.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3405, 3365, 2220, 1610, 1560, 1476, 1453, 1420, 1389, 1374, 1230, 1200, 1163,

1124, 1045, 845, 740. HRMS (+ESI)  $m/z$  429.1486,  $[M + Na]^+$ ; calcd for  $[C_{26}H_{19}FN_4 + Na]$  429.1491.

*2-Benzyl-1-((2-fluorophenyl)amino)-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (8k)*

A mixture of compound **7a** (100 mg, 0.30 mmol) and *o*-fluoroaniline (335.2 mg, 3.02 mmol) was heated to 120°C for 1 h. The crude material was purified by column chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **8k** as a yellow solid (80.8 mg, 65 %). Mp 226–228°C.  $\delta_H$  (300 MHz, acetone- $d_6$ ) 8.16 (br s, 1H), 7.97 (dt,  $J$  8.4, 1.0, 1H), 7.84 (ddd,  $J$  8.3, 1.2, 0.7, 1H), 7.48 (ddd,  $J$  8.3, 7.2, 1.1, 1H), 7.31–7.11 (m, 7H), 6.92–6.78 (m, 2H), 6.58–6.45 (m, 1H), 4.30 (s, 2H), 2.60 (s, 3H).  $\delta_C$  (75 MHz, acetone- $d_6$ ) 154.3, 151.4, 151.1, 148.1, 145.9, 139.9, 139.7, 132.4, 132.3, 130.0, 129.4, 128.9, 127.2, 126.6, 126.0, 125.9, 122.2, 122.0, 121.9, 120.8, 120.3, 116.8, 116.5, 116.5, 116.2, 116.0, 33.3, 19.9.  $\nu_{max}$  (KBr)/ $cm^{-1}$  3531, 3385, 2233, 1618, 1599, 1591, 1477, 1448, 1433, 1292, 1374, 1304, 1231, 764, 699. HRMS (+ESI)  $m/z$  429.1486,  $[M + Na]^+$ ; calcd for  $[C_{26}H_{19}FN_4 + Na]$  429.1491.

*2-Benzyl-3-methyl-1-((4-(trifluoromethyl)phenyl)amino)benzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (8l)*

A mixture of compound **7a** (100 mg, 0.30 mmol) and *p*-(trifluoromethyl)aniline (0.49 g, 3.02 mmol) was heated to 120°C for 3 h. The crude material was purified by flash chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **8l** as a yellow solid (74.4 mg, 54 %). Mp 226–228°C.  $\delta_H$  (300 MHz, acetone- $d_6$ ) 8.77 (br s, 1H), 8.01 (ddd,  $J$  8.5, 0.7, 1H), 7.85 (ddd,  $J$  8.3, 1.2, 0.7, 1H), 7.55–7.42 (m, 3H), 7.29–7.11 (m, 6H), 6.96 (dt,  $J$  8.2, 0.8, 2H), 4.29 (d,  $J$  0.7, 2H), 2.59 (s, 3H).  $\delta_C$  (75 MHz, acetone- $d_6$ ) 151.4, 148.1, 148.0, 146.0, 139.6, 139.4, 129.8, 129.5, 128.9, 127.9, 127.9, 127.2, 126.6, 122.3, 122.1, 120.9, 120.4, 116.6, 115.9, 115.2, 101.1, 33.4, 19.8.  $\nu_{max}$  (KBr)/ $cm^{-1}$  3384, 3133, 3064, 3024, 2931, 2222, 1622, 1527, 1495, 1408, 1371, 1354, 1321, 1260, 1200, 1184, 1109, 1064, 970, 848, 757, 738. HRMS (+ESI)  $m/z$  479.1465,  $[M + Na]^+$ ; calcd for  $[C_{27}H_{19}F_3N_4 + Na]$  479.1460.

*2-Benzyl-1-((3,5-dimethoxyphenyl)amino)-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (8m)*

A mixture of compound **7a** (100 mg, 0.30 mmol) and 3,5-dimethoxyaniline (51.7 mg, 3.02 mmol) was heated to 120°C for 3 h. The crude product was purified by flash chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **8m** as a yellow solid (85.3 mg, 63 %). Mp 244–246°C.  $\delta_H$  (300 MHz, acetone- $d_6$ ) 8.22 (br s, 1H), 8.10 (ddd,  $J$  8.5, 1.1, 0.7, 1H), 7.83 (ddd,  $J$  8.3, 1.2, 0.7, 1H), 7.48 (ddd,  $J$  8.3, 7.2, 1.1, 1H), 7.30–7.14 (m, 6H), 6.03 (t,  $J$  2.1, 1H), 5.96 (d,  $J$  2.2, 2H), 4.29 (d,  $J$  0.8, 2H), 3.63 (s, 6H), 2.57 (s, 3H).  $\delta_C$  (75 MHz, acetone- $d_6$ ) 163.2, 151.5, 148.1, 146.4, 145.9, 140.5, 139.9, 130.1, 129.4, 128.9, 127.2, 126.5, 122.1, 120.2, 120.1, 117.0, 116.1, 94.3, 93.3, 55.5, 33.4, 19.8.  $\nu_{max}$  (KBr)/ $cm^{-1}$  2898, 2603, 2220, 1605, 1545, 1524, 1493, 1446, 1423, 1354, 1305, 1207, 1158, 1051, 823, 740, 678. HRMS (+ESI)  $m/z$  471.1791,  $[M + Na]^+$ ; calcd for  $[C_{28}H_{24}N_4O_2 + Na]$  471.1797.

*General Procedure A: Buchwald–Hartwig Amination*

An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd<sub>2</sub>dba<sub>3</sub>

(1 mol-%) and XPhos (5 mol-%). If the aryl halide (1.0 mmol), amine (1.1–1.5 mmol), or base (1.5–4.0 mmol) were solids, they were also added at this time. The Schlenk tube was evacuated and backfilled with argon or nitrogen (this sequence was repeated three times) and then capped with a rubber septum. If the aryl halide, amine or base were liquids, they were added to the Schlenk tube at this time along with the solvent. The reaction mixture was allowed to stir at room temperature for 1 h and quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane mixtures).

*2-Benzyl-1-((3,5-bis(trifluoromethyl)phenyl)amino)-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (8n)*

Following the general procedure A, compound **7a** (100 mg, 0.30 mmol) was reacted with 3,5-bis(trifluoromethyl)aniline (103.8 mg, 0.45 mmol) in the presence of potassium *tert*-butoxide (107.7 mg, 0.96 mmol). The crude material was purified by column chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **8n** as a yellow solid (57.0 mg, 36 %). Mp 236–238°C.  $\delta_H$  (600 MHz, acetone- $d_6$ ) 8.04 (dt,  $J$  8.5, 1.0, 1H), 7.86 (dt,  $J$  8.2, 1.0, 1H), 7.48 (ddd,  $J$  8.3, 7.2, 1.1, 1H), 7.42–7.34 (m, 3H), 7.22–7.15 (m, 5H), 7.15–7.09 (m, 1H), 4.31 (s, 2H), 2.62 (s, 3H).  $\delta_C$  (150 MHz, acetone- $d_6$ ) 151.36, 148.16, 146.86, 145.93, 139.56, 138.80, 133.42, 129.78, 129.39, 128.84, 127.15, 126.66, 125.17, 123.37, 122.44, 121.22, 120.39, 116.34, 115.95, 115.30, 113.73, 33.40, 19.  $\nu_{max}$  (KBr)/ $cm^{-1}$  3326, 3195, 3022, 2917, 2855, 2227, 1614, 1562, 1466, 1453, 1327, 774, 749. HRMS (+ESI)  $m/z$  547.1337,  $[M + Na]^+$ ; calcd for  $[C_{28}H_{18}F_6N_4 + Na]$  547.1333.

*2-Benzyl-3-methyl-1-((2,4,6-trifluorophenyl)amino)benzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (8o)*

Following the general procedure A, compound **7a** (100 mg, 0.30 mmol) was reacted with 2,4,6-trifluoroaniline (66.6 mg, 0.45 mmol) in the presence of potassium *tert*-butoxide (107.7 mg, 0.96 mmol). The crude material was purified by column chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **8o** as a yellow solid (45.4 mg, 34 %). Mp 230–232°C.  $\delta_H$  (600 MHz, acetone- $d_6$ ) 8.34 (d,  $J$  8.4, 1H), 7.82 (dt,  $J$  8.2, 1.0, 1H), 7.51 (ddd,  $J$  8.3, 7.2, 1.1, 1H), 7.25 (ddd,  $J$  8.4, 7.2, 1.2, 1H), 7.18–7.10 (m, 3H), 7.03–6.98 (m, 2H), 6.74 (t,  $J$  8.9, 2H), 4.17 (s, 2H), 2.56 (s, 3H).  $\delta_C$  (150 MHz, acetone- $d_6$ ) 158.01, 156.41, 155.37, 153.81, 153.75, 153.71, 153.65, 150.75, 147.89, 139.21, 130.56, 129.20, 128.15, 126.95, 126.67, 122.05, 118.90, 116.98, 116.39, 101.32, 33.10, 19.53.  $\nu_{max}$  (KBr)/ $cm^{-1}$  3431, 3358, 2224, 1610, 1593, 1492, 1475, 1448, 1423, 1346, 1189, 892, 742, 689. HRMS (+ESI)  $m/z$  465.1296,  $[M + Na]^+$ ; calcd for  $[C_{26}H_{17}F_3N_4 + Na]$  465.1303.

*2-Benzyl-1-((2-benzyl-1-chloro-4-cyanobenzo[4,5]imidazo[1,2-*a*]pyridin-3-yl)methyl)-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (13)*

Following the general procedure, compound **7a** (100 mg, 0.30 mmol) was reacted with 2,4,6-trifluoroaniline (66.6 mg, 0.45 mmol) in the presence of potassium *tert*-butoxide (107.7 mg, 0.96 mmol). The crude material was purified by column chromatography on silica gel using 2 : 3 ethyl acetate/hexane to afford compound **13** as a yellow solid (60.1 mg, 30 %).

Mp 240–242°C.  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.63 (dt,  $J$  8.6, 0.9, 1H), 8.04 (dt,  $J$  8.3, 1.0, 2H), 7.64 (ddd,  $J$  8.3, 7.2, 1.1, 1H), 7.49 (ddd,  $J$  8.6, 7.2, 1.2, 1H), 7.43 (ddd,  $J$  8.2, 6.6, 1.5, 1H), 7.21–7.06 (m, 5H), 7.04–6.89 (m, 5H), 6.85–6.78 (m, 2H), 4.99–4.79 (m, 2H), 4.45 (d,  $J$  16.9, 1H), 4.12–3.84 (m, 3H), 2.59 (s, 3H).  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 148.28, 146.47, 146.16, 145.35, 144.83, 142.86, 137.67, 136.35, 135.02, 134.74, 130.35, 129.27, 129.22, 128.77, 127.76, 127.33, 127.28, 127.14, 126.80, 126.04, 123.36, 123.02, 121.99, 121.17, 120.99, 119.47, 115.88, 114.94, 113.23, 112.07, 102.83, 100.85, 35.22, 34.81, 34.01, 19.68.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3444, 3308, 3177, 2217, 1647, 1644, 1615, 1590, 1502, 1455, 1400, 1325, 1270, 1178, 738, 707. HRMS (+ESI)  $m/z$  627.2056  $[\text{M} + \text{H}]^+$ ; calcd for  $[\text{C}_{40}\text{H}_{27}\text{ClN}_6 + \text{H}]$  627.2064.

#### General Procedure B: Suzuki Coupling Reaction

To a stirred solution of intermediate **7a** (100 mg, 0.30 mmol) in dioxane (4 mL) in a re-sealable Schlenk tube, was added boronic acid (0.60 mmol) followed by  $\text{Na}_2\text{CO}_3$  (95.8 mg, 0.90 mmol) dissolved in water (1 mL) at room temperature and the reaction mixture was purged with argon for 10 min.  $\text{Pd}(\text{PPh}_3)_4$  (34.8 mg, 0.03 mmol) was then added and the reaction mixture purged with argon for the second time for 5 min. The reaction mixture was sealed and heated at 90°C for 16 h. The reaction mixture was cooled to room temperature, water added (20 mL), and the mixture extracted with EtOAc (2 × 25 mL). The organic layers were combined, washed with brine solution (15 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure products that were recrystallised from EtOAc/acetonitrile to obtain pure compounds as yellow solids.

#### 2-Benzyl-1-(4-methoxyphenyl)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**14a**)

Following the general procedure B, compound **7a** (100 mg, 0.30 mmol) was reacted with 4-methoxyphenylboronic acid (91.6 mg, 0.60 mmol) in the presence of  $\text{Na}_2\text{CO}_3$  (95.8 mg, 0.90 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (34.8 mg, 0.03 mmol). The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure product, which was then recrystallised from EtOAc/acetonitrile to afford pure compound **14a** as a yellow solid (35.1 mg, 29%). Mp 296–298°C.  $\delta_{\text{H}}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.93–7.87 (m, 1H), 7.42 (ddd,  $J$  8.3, 7.2, 1.1, 1H), 7.33–7.28 (m, 2H), 7.28–7.16 (m, 3H), 7.13–7.06 (m, 2H), 7.01–6.94 (m, 3H), 6.14–6.09 (m, 1H), 3.93 (s, 2H), 3.91 (s, 3H), 2.52 (s, 3H).  $\delta_{\text{C}}$  (100 MHz,  $\text{CD}_2\text{Cl}_2$ ) 161.7, 150.1, 147.1, 145.4, 143.7, 139.4, 130.5, 129.1, 127.9, 126.8, 126.1, 125.0, 121.6, 121.3, 120.1, 115.7, 115.6, 115.1, 101.5, 55.9, 34.8, 19.9.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  2929, 2221, 1594, 1490, 1442, 1292, 1243, 1028, 834, 735. HRMS (+ESI)  $m/z$  404.1756  $[\text{M} + \text{H}]^+$ ; calcd for  $[\text{C}_{27}\text{H}_{21}\text{N}_3\text{O} + \text{H}]$  404.1757.

#### 2-Benzyl-3-methyl-1-(4-(methylamino)phenyl)benzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**14b**)

Following the general procedure B, compound **7a** (100 mg, 0.30 mmol) was reacted with 4-aminophenylboronic acid pinacol ester (140.5 mg, 0.60 mmol) in the presence of  $\text{Na}_2\text{CO}_3$  (95.8 mg, 0.90 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (34.8 mg, 0.03 mmol). The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure product, which was then recrystallised from EtOAc/acetonitrile to afford pure compound **14b** as a yellow solid

(45.2 mg, 37%). Mp 269–271°C.  $\delta_{\text{H}}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.89 (dt,  $J$  8.2, 1.0, 1H), 7.42 (ddd,  $J$  8.2, 7.1, 1.1, 1H), 7.30–7.22 (m, 2H), 7.22–7.11 (m, 3H), 7.03–6.95 (m, 3H), 6.78–6.73 (m, 2H), 6.31 (dt,  $J$  8.5, 1.0, 1H), 4.23 (q,  $J$  5.2, 1H), 3.98 (s, 2H), 2.91 (d,  $J$  5.1, 3H), 2.50 (s, 3H).  $\delta_{\text{C}}$  (100 MHz,  $\text{CD}_2\text{Cl}_2$ ) 151.4, 150.2, 147.3, 145.4, 144.7, 139.7, 130.7, 130.0, 129.0, 128.0, 126.7, 125.9, 121.4, 121.3, 120.6, 120.0, 115.8, 115.5, 113.1, 101.1, 34.9, 30.6, 19.9.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3435, 3026, 2922, 2222, 1611, 1491, 1441, 1396, 1262, 1180, 824, 739. HRMS (+ESI)  $m/z$  403.1916  $[\text{M} + \text{H}]^+$ ; calcd for  $[\text{C}_{27}\text{H}_{22}\text{N}_4 + \text{H}]$  403.1917.

#### 2-Benzyl-3-methyl-1-phenylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**14c**)

Following the general procedure B, compound **7a** (100 mg, 0.30 mmol) was reacted with phenyl boronic acid (73.5 mg, 0.60 mmol) in the presence of  $\text{Na}_2\text{CO}_3$  (95.8 mg, 0.90 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (34.8 mg, 0.03 mmol). The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure product, which was then recrystallised from EtOAc/acetonitrile to afford pure compound **14c** as a yellow solid (85.1 mg, 76%). Mp 263–265°C.  $\delta_{\text{H}}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.91 (dt,  $J$  8.3, 1.0, 1H), 7.71–7.64 (m, 1H), 7.61 (ddt,  $J$  8.5, 6.7, 1.4, 2H), 7.42 (ddd,  $J$  8.8, 7.6, 1.3, 3H), 7.29–7.15 (m, 3H), 7.02–6.96 (m, 2H), 6.94 (ddd,  $J$  8.5, 7.1, 1.2, 1H), 5.94 (dt,  $J$  8.6, 0.9, 1H), 3.92 (s, 2H), 2.53 (s, 3H).  $\delta_{\text{C}}$  (100 MHz,  $\text{CD}_2\text{Cl}_2$ ) 150.1, 147.1, 145.4, 143.6, 139.3, 133.0, 131.0, 130.4, 130.3, 129.2, 129.1, 127.9, 126.8, 126.1, 121.6, 120.9, 120.2, 115.6, 114.9, 101.7, 54.4, 54.1, 54.0, 53.8, 53.8, 53.6, 53.3, 34.8, 19.9.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  2917, 2225, 1742, 1628, 1595, 1483, 1446, 1306, 1206, 775, 735, 713. HRMS (+ESI)  $m/z$  374.1649  $[\text{M} + \text{H}]^+$ ; calcd for  $[\text{C}_{26}\text{H}_{19}\text{N}_3 + \text{H}]$  374.1651.

#### 2-Benzyl-1-(4-fluorophenyl)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**14d**)

Following the general procedure B, compound **7a** (100 mg, 0.30 mmol) was reacted with 4-fluorophenyl boronic acid (84.6 mg, 0.60 mmol) in the presence of  $\text{Na}_2\text{CO}_3$  (95.8 mg, 0.90 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (34.8 mg, 0.03 mmol). The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure product, which was then recrystallised from EtOAc/acetonitrile to afford pure compound **14d** as a yellow solid (78.0 mg, 67%). Mp 276–278°C.  $\delta_{\text{H}}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.92 (dt,  $J$  8.2, 1.0, 1H), 7.44 (ddd,  $J$  8.2, 7.1, 1.1, 1H), 7.42–7.36 (m, 2H), 7.34–7.16 (m, 5H), 7.02–6.92 (m, 3H), 6.04 (dt,  $J$  8.6, 0.9, 1H), 3.91 (s, 2H), 2.54 (s, 3H).  $\delta_{\text{C}}$  (100 MHz,  $\text{CD}_2\text{Cl}_2$ ) 165.6, 163.1, 150.0, 147.0, 145.5, 142.5, 139.1, 131.5, 131.4, 130.3, 129.1, 129.0, 129.0, 127.9, 126.9, 126.2, 121.8, 121.3, 120.4, 117.7, 117.4, 115.5, 114.7, 102.0, 34.7, 19.9.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3032, 2931, 2223, 1601, 1485, 1447, 1367, 1294, 1219, 1018, 836, 750, 695. HRMS (+ESI)  $m/z$  392.1556  $[\text{M} + \text{H}]^+$ ; calcd for  $[\text{C}_{26}\text{H}_{18}\text{FN}_3 + \text{H}]$  392.1557.

#### 2-Benzyl-1-(4-cyanophenyl)-3-methylbenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**14e**)

Following the general procedure B, compound **7a** (100 mg, 0.30 mmol) was reacted with 4-cyanophenyl boronic acid (88.6 mg, 0.60 mmol) in the presence of  $\text{Na}_2\text{CO}_3$  (95.8 mg, 0.90 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (34.8 mg, 0.03 mmol). The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure

product, which was then recrystallised from EtOAc/acetonitrile to afford pure compound **14e** as a yellow solid (30.6 mg, 25%). Mp 289–292°C.  $\delta_{\text{H}}$  (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 7.96–7.86 (m, 3H), 7.62–7.52 (m, 2H), 7.44 (ddd, *J* 8.3, 7.2, 1.1, 1H), 7.32–7.18 (m, 3H), 7.00 (ddd, *J* 8.5, 7.2, 1.2, 1H), 6.96–6.87 (m, 2H), 5.96 (dt, *J* 8.6, 0.9, 1H), 3.86 (s, 2H), 2.53 (s, 3H).  $\delta_{\text{C}}$  (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 149.9, 146.7, 145.4, 141.2, 138.7, 137.1, 134.1, 130.4, 130.0, 129.2, 127.8, 127.1, 126.4, 122.1, 121.1, 120.5, 118.2, 115.3, 115.2, 114.3, 102.4, 34.7, 19.9.  $\nu_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3031, 2224, 1592, 1488, 1447, 1300, 1266, 1182, 1022, 844, 756, 696. HRMS (+ESI) *m/z* 399.1603 [M + H]<sup>+</sup>; calcd for [C<sub>27</sub>H<sub>18</sub>N<sub>4</sub> + H] 399.1604.

#### 2-Benzyl-3-methyl-1-(pyridin-3-yl)benzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (**14f**)

Following the general procedure B, compound **7a** (100 mg, 0.30 mmol) was reacted with 3-pyridinyl boronic acid (74.1 mg, 0.60 mmol) in the presence of Na<sub>2</sub>CO<sub>3</sub> (95.8 mg, 0.90 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (34.8 mg, 0.03 mmol). The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure product, which was then recrystallised from EtOAc/acetonitrile to afford pure compound **14f** as a yellow solid (32.2 mg, 29%). Mp 253–256°C.  $\delta_{\text{H}}$  (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 8.90 (dd, *J* 4.9, 1.7, 1H), 8.65 (dd, *J* 2.2, 0.9, 1H), 7.93 (dt, *J* 8.3, 1.0, 1H), 7.74 (ddd, *J* 7.8, 2.3, 1.7, 1H), 7.55 (ddd, *J* 7.9, 4.9, 0.9, 1H), 7.44 (ddd, *J* 8.2, 7.1, 1.1, 1H), 7.29–7.20 (m, 3H), 7.02–6.91 (m, 3H), 5.99 (dt, *J* 8.6, 0.9, 1H), 3.90 (s, 2H), 2.56 (s, 3H).  $\delta_{\text{C}}$  (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 152.2, 149.8, 149.7, 146.9, 145.5, 140.3, 138.8, 137.1, 130.3, 129.2, 129.2, 128.2, 127.9, 127.1, 126.3, 124.7, 122.0, 121.9, 120.6, 115.3, 114.4, 102.5, 34.8, 19.9.  $\nu_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3024, 2915, 2222, 1590, 1507, 1443, 1299, 1183, 1021, 815, 733. HRMS (+ESI) *m/z* 375.1604 [M + H]<sup>+</sup>; calcd for [C<sub>25</sub>H<sub>18</sub>N<sub>4</sub> + H] 375.1604.

#### 2-Benzyl-3-methyl-1-(thiophen-3-yl)benzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (**14g**)

Following the general procedure B, compound **7a** (100 mg, 0.30 mmol) was reacted with 3-thienylboronic acid (77.2 mg, 0.60 mmol) in the presence of Na<sub>2</sub>CO<sub>3</sub> (95.8 mg, 0.90 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (34.8 mg, 0.03 mmol). The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure product, which was then recrystallised from EtOAc/acetonitrile to afford pure compound **14g** as a yellow solid (39.3 mg, 34%). Mp 268–270°C.  $\delta_{\text{H}}$  (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 7.91 (dt, *J* 8.3, 1.0, 1H), 7.67 (dd, *J* 5.0, 2.9, 1H), 7.52–7.40 (m, 2H), 7.29–7.20 (m, 3H), 7.14 (dd, *J* 5.0, 1.3, 1H), 7.10–6.90 (m, 3H), 6.11 (dt, *J* 8.5, 1.0, 1H), 4.00–3.87 (m, 2H), 2.52 (s, 3H).  $\delta_{\text{C}}$  (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 149.7, 147.0, 145.4, 139.4, 139.1, 132.7, 130.3, 129.1, 128.9, 128.1, 127.9, 127.2, 126.9, 126.2, 122.1, 121.8, 120.2, 115.5, 114.6, 101.9, 34.9, 19.8.  $\nu_{\text{max}}$  (KBr)/cm<sup>-1</sup> 2221, 1589, 1542, 1489, 1442, 1347, 1303, 1078, 830, 741, 692. HRMS (+ESI) *m/z* 380.1215 [M + H]<sup>+</sup>; calcd for [C<sub>24</sub>H<sub>17</sub>N<sub>3</sub>S + H] 380.1215.

#### 2-Benzyl-1-(furan-3-yl)-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (**14h**)

Following the general procedure B, compound **7a** (100 mg, 0.30 mmol) was reacted with 3-furanylboronic acid (67.5 mg, 0.60 mmol) in the presence of Na<sub>2</sub>CO<sub>3</sub> (95.8 mg, 0.90 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (34.8 mg, 0.03 mmol). The residue obtained was purified by silica gel column chromatography using methanol/dichloromethane (0–10%) to afford impure product, which was

then recrystallised from EtOAc/acetonitrile to afford pure compound **14h** as a yellow solid (36.1 mg, 33%). Mp 252–254°C.  $\delta_{\text{H}}$  (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 7.92 (dt, *J* 8.2, 1.0, 1H), 7.78 (t, *J* 1.7, 1H), 7.61 (dd, *J* 1.6, 0.9, 1H), 7.48 (ddd, *J* 8.2, 7.1, 1.1, 1H), 7.32–7.18 (m, 3H), 7.13 (ddd, *J* 8.5, 7.1, 1.2, 1H), 7.03–6.95 (m, 2H), 6.81 (dt, *J* 8.6, 0.9, 1H), 6.57 (dd, *J* 1.9, 0.9, 1H), 4.11–3.90 (m, 2H), 2.52 (s, 3H).  $\delta_{\text{C}}$  (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 149.5, 147.0, 145.4, 142.4, 139.4, 135.9, 130.4, 129.2, 127.9, 126.9, 126.2, 122.9, 121.8, 120.3, 117.6, 115.5, 115.1, 111.7, 102.1, 35.0, 19.9.  $\nu_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3108, 2222, 1588, 1489, 1447, 1364, 1302, 1189, 1157, 1084, 939, 873, 739. HRMS (+ESI) *m/z* 364.1443 [M + H]<sup>+</sup>; calcd for [C<sub>24</sub>H<sub>17</sub>N<sub>3</sub>O + H] 364.1444.

### Supplementary Material

<sup>1</sup>H and <sup>13</sup>C NMR spectra of all synthesised compounds are available on the Journal's website.

### Conflicts of Interest

The authors declare no conflicts of interest.

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- [29] Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 2006266 (**14a**), CCDC 2006267 (**14d**) and CCDC 2017491 (**13**). X-Ray crystal structures were obtained by Donald Craig, Crystallography Laboratory, UNSW Analytical Centre, Sydney, Australia.