$ZrCl_4$-catalysed synthesis of new 4-(2-hydroxyphenyl)pyrazolo[3,4-*b*]pyridine derivatives

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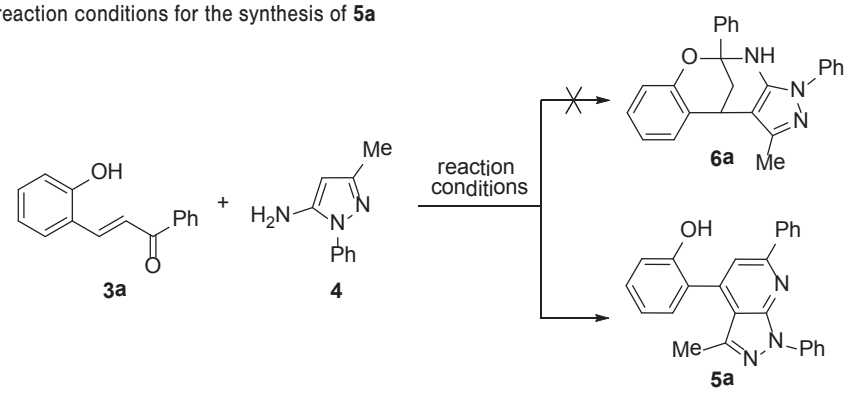
In the presence of a catalytic amount of zirconium(IV) chloride, an efficient synthesis of new 4-(2-hydroxyphenyl)pyrazolo[3,4-*b*]pyridines has been developed by the reaction 2-hydroxychalcones with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine in refluxing ethanol. All these novel compounds have been characterised by ^{1}H NMR, ^{13}C NMR, HRMS, IR spectra and X-ray crystallographic analysis.

Keywords: zirconium(IV) chloride, 2-hydroxychalcones, pyrazolo[3,4-*b*]pyridines, aromatisation

Functionalised pyrazolo[3,4-*b*]pyridines have attracted ever-increasing attention as they are widely present in numerous natural products, anxiolytic targets (such as cartazolate, etazolate and tracazolate)[1,2] and fluorescent dyes.[3] Therefore, a variety of methods have been reported for the preparation of pyrazolo[3,4-*b*]pyridine derivatives, most of them involving the multicomponent reactions of aldehydes, 5-aminopyrazoles and highly active methylene compounds catalysed by acetic acid,[4,5] L-proline[6,7] or microwave irradiation.[8] As a mild Lewis acid catalyst, zirconium(IV) chloride ($ZrCl_4$) has the advantage of low cost and low toxicity, but it has been rarely utilised in catalytic organic synthesis.[9–11] Recently, we have developed an efficient method for the synthesis of coumarin- and cyclohexandione-fused 2,8-oxazabicyclo[3.3.1]nonanes by the three-component reaction of 2-hydroxychalcones, 4-hydroxycoumarin/1,3-cyclohexandiones and aqueous ammonia.[12–14] On the basis of the possible intermolecular Michael addition/amination/intramolecular bicyclisation domino reaction mechanism and excellent nucleophilicity of 5-aminopyrazoles, we expected to be able to synthesise the pyrazole-fused 2,8-oxazabicyclo[3.3.1]nonane **6a** from 2-hydroxychalcone **3a** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **4**. However, it was found that the expected product did not form, and the reaction gave 4-(2-hydroxyphenyl)pyrazolo[3,4-*b*]pyridine **5a** in excellent yield in the presence of $ZrCl_4$ (Table 1).

Table 1 Optimisation of reaction conditions for the synthesis of **5a**



Entry[a]	Catalyst[b]	Solvent	Temp/°C	Yield/%[c]
1	$InBr_3$	EtOH	Reflux	20
2	AcOH	EtOH	Reflux	Trace
3	L-proline	EtOH	Reflux	<5
4	H_3PO_4	EtOH	Reflux	50
5	AgOTf	EtOH	Reflux	Trace
6	$In(OTf)_3$	EtOH	Reflux	<5
7	$ZnCl_2$	EtOH	Reflux	Trace
8	I_2	EtOH	Reflux	89
9	$ZrCl_4$	EtOH	Reflux	92
10[d]	$ZrCl_4$	EtOH	Reflux	76
11[e]	$ZrCl_4$	EtOH	Reflux	35
12	$ZrCl_4$	EtOH	40	<5
13	$ZrCl_4$	EtOH	25	0
14	$ZrCl_4$	MeOH	Reflux	75
15	$ZrCl_4$	MeCN	Reflux	85
16	$ZrCl_4$	Toluene	80	81
17	$ZrCl_4$	DMSO	80	24
18	$ZrCl_4$	DMF	80	20

[a]All reactions were performed with **3a** (0.5 mmol), **4** (0.5 mmol) in an appropriate solvent (5 mL) for 10 h. [b]0.25 equiv. of catalyst was employed in these reactions unless mentioned. [c]Isolated yield. [d]0.2 equiv. of catalyst was employed. [e]0.1 equiv. of catalyst was employed.

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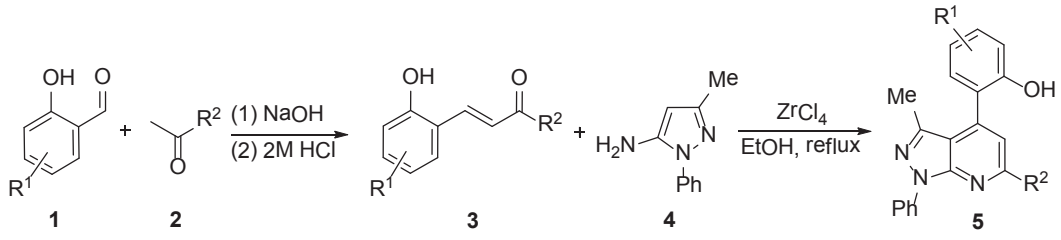

a R^1 = H, R^2 = C_6H_5 (**5a**, 92%)
b R^1 = H, R^2 = 4-CH_3-C_6H_4 (**5b**, 85%)
c R^1 = H, R^2 = 4-CH_3O-C_6H_4 (**5c**, 91%)
d R^1 = H, R^2 = 4-HO-C_6H_4 (**5d**, 60%)
e R^1 = H, R^2 = 4-F-C_6H_4 (**5e**, 85%)
f R^1 = H, R^2 = 4-Cl-C_6H_4 (**5f**, 83%)
g R^1 = H, R^2 = 4-Br-C_6H_4 (**5g**, 80%)
h R^1 = H, R^2 = 2-naph (**5h**, 81%)
i R^1 = H, R^2 = 2-furyl (**5i**, 85%)
j R^1 = H, R^2 = 2-thienyl (**5j**, 91%)
k R^1 = H, R^2 = 2-pyridyl (**5k**, 62%)
l R^1 = H, R^2 = Me (**5l**, 65%)
m R^1 = H, R^2 = $CH{=}C(CH_3)_2$ (**5m**, 53%)
n R^1 = 4-OMe, R^2 = C_6H_5 (**5n**, 82%)
o R^1 = 5-Cl, R^2 = C_6H_5 (**5o**, 89%)
p R^1 = 5-Br, R^2 = C_6H_5 (**5p**, 85%)

Scheme 1 Synthesis of pyrazolo[3,4-*b*]pyridines.

Initially, a reaction of 2-hydroxychalcone, synthesised by the condensation of salicylaldehyde (**1a**) with acetophenone (**2a**) according to known methods,[15] with **4** was carried out under varied conditions for the attempted preparation of **6a** (Table 1 and Scheme 1). It was found that the hydroxy group did not participate in the cyclisation reaction, and **5a** was obtained in 20% yield in refluxing ethanol using $InBr_3$ as the catalyst (entry 1). The structure was confirmed by means of ^{1}H NMR, ^{13}C NMR, HRMS and IR spectra. Frequently used catalysts (such as AcOH and L-proline) for the synthesis of pyrazolo[3,4-*b*] pyridines were ineffective for this reaction (entries 2 and 3). After screening the catalysts H_3PO_4, AgOTf, $In(OTf)_3$, $ZnCl_2$, iodine and $ZrCl_4$, the latter proved to be the most efficient affording **5a** in 92% isolated yield (entries 4–8). The amount of $ZrCl_4$, nature of the solvent (MeOH, MeCN, toluene, DMSO and DMF) and reaction temperature (40 °C and 25 °C) were also examined, and it was shown that 0.25 equiv. of catalyst in refluxing ethanol was the optimal reaction condition (entries 9–18).

We also attempted the $ZrCl_4$-catalysed reaction of **1a**, **2a** and **4** in refluxing ethanol in a one-pot procedure, but **5a** was obtained in only 45% yield. The low yield was probably attributed to the relatively low activity of acetophenone compared with the reported highly active methylene compounds.[4–7] In view of the facile synthesis of 2-hydroxychalcones, a variety of substituted derivatives were used to react with **4** under the optimal conditions, and the results are summarised in Scheme 1. It was observed that the substrates in which R^1 = H and R^2 was a phenyl ring bearing an electron-donating substituent (–CH_3 and –OCH_3) afforded the corresponding products **5b** and **5c** in 85% and 91% yields respectively. The 4-(hydroxyphenyl) substrate **3d** provided **5d** in 60% yield. Halogen atom substituted substrates (–F, –Cl and –Br) also gave the target products **5e**–**g** in good yields (80–85%). The structures of **5e** and **5g** were further confirmed by X-ray crystallographic analysis (Fig. 1).

The crystal data of compound **5e** (CCDC 1041603): $C_{25}H_{18}FN_3O{\cdot}C_6H_{12}$, M = 479.58, crystal system: monoclinic, space group: P2(1)/c, lattice parameters: a = 11.1099(17) Å, b = 11.3558(18) Å, c = 21.839(3) Å, α = 90°, β = 104.529(3)°, γ = 90°, V = 2667.1(7) Å^3, Z = 4, D_c = 1.194 g cm^{-3}, F000 = 1016, final R indices [I > 2sigma(I)]: R^1 = 0.0566, wR^2 = 0.1520.

The crystal data of compound **5g** (CCDC 1041604): $C_{25}H_{18}BrN_3O{\cdot}C_6H_{12}$, M = 540.49, crystal system: monoclinic, space group: P2(1)/n, lattice parameters: a = 10.8901(19) Å, b = 11.0738(19) Å, c = 22.857(4) Å, α = 90°, β = 95.749(3)°, γ = 90°, V = 2742.6(8) Å^3, Z = 4, D_c = 1.309 g cm^{-3}, F000 = 1120, final R indices [I > 2sigma(I)]: R^1 = 0.0502, wR^2 = 0.1290.

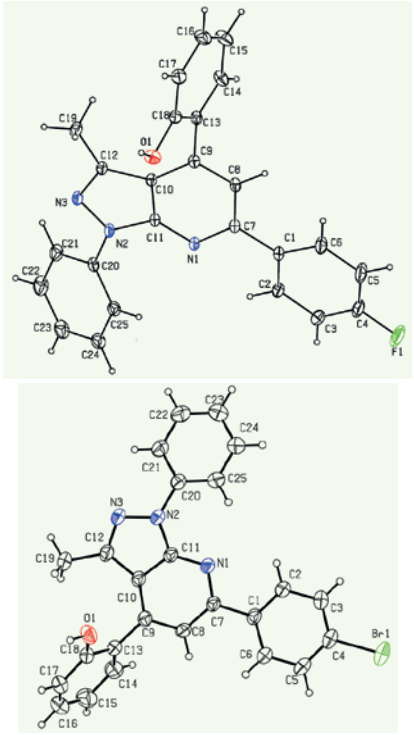

Fig. 1 X-ray structures of **5e** and **5g** (solvent *n*-hexane was omitted for clarity)

This transformation was also suitable for the naphthalene-linked ring and heterocyclic substrates (furan, thiophene and pyridine), delivering **5h**–**k** in 62–91% yields. In addition, the alkyl substrates **3l** and **3m** were also effective for this transformation with the isolation of **5l** and **5m** in 65% and 53% yields respectively. Moreover, 4-methoxy-, 5-chloro- and 5-bromo-substituted (R^1) 2-hydroxychalcones also furnished **5n**–**p** in excellent yields (82–89%).

A literature survey indicated that 4,7-dihydro-pyrazolo[3,4-*b*] pyridines have been prepared from 5-aminopyrazoles and chalcones in DMF, which can be subsequently dehydrogenated to aromatic pyrazolo[3,4-*b*]pyridines upon treatment with *N*-bromosuccinimide.[16] This reaction has also been performed in an ionic liquid, leading to the pyrazolo[3,4-*b*]pyridines in good yield.[17] However, no 2-hydroxyphenyl-substituted

pyrazolo[3,4-*b*]pyridines have been reported. We now describe the successful development of a $ZrCl_4$-catalysed reaction for the synthesis of novel 4-(2-hydroxyphenyl)pyrazolo[3,4-*b*]pyridine derivatives from easily available 2-hydroxychalcones and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine in refluxing ethanol. All of these hitherto unknown compounds were characterised by means of their ^{1}H NMR, ^{13}C NMR, HRMS and IR spectra. In addition, the structures of **5e** and **5g** were confirmed by single crystal X-ray diffraction analysis. The main advantages of this approach are the wide scope of substrates and functional group tolerances.

Experimental

All the chemicals were commercially available and used without further purification. All the organic solvents were dried and freshly distilled before use. ^{1}H and ^{13}C NMR spectra were recorded using Bruker AV 300 MHz spectrometers with $CDCl_3$ or DMSO-d_6 as the solvent. High resolution mass spectra (EI) were recorded using a Waters GCT Premier. IR spectra were obtained as KBr pellet samples using a Nicolet 5700 FTIR spectrometer. Melting points were determined using an uncorrected X-4 apparatus. The X-ray crystal structure determination was performed using a Bruker Smart Apex CCD system. 2-Hydroxychalcones **3** were synthesised by the condensation of salicylaldehyde with acetophenones according to known methods.[15,18,19]

Synthesis of 1H-pyrazolo[3,4-b]pyridines **5***; general procedure*

A mixture of the 2-hydroxychalcone derivatives (**3**, 0.5 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**4**, 0.5 mmol) and $ZrCl_4$ (29 mg, 0.125 mmol) was heated under reflux in anhydrous ethanol (5 mL). When the reactant disappeared (10 h, monitored by TLC), the mixture was cooled to room temperature and purified by column chromatography using petroleum ether–ethyl acetate as the eluent to deliver compounds **5**. Characterisation data of all new compounds are as follows.

*2-(1,6-Diphenyl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)phenol* (**5a**): White solid; 174 mg, yield 92%; m.p. 218–220 °C. IR (KBr) ν_{max}/cm^{-1} 3445, 1596, 1499, 1279, 1156, 1098, 1037, 862, 755; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (s, 1H), 8.38 (d, *J* = 8.3 Hz, 2H), 8.28–8.25 (m, 2H), 7.71 (s, 1H), 7.63–7.48 (m, 5H), 7.39–7.31 (m, 3H), 7.06–6.97 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.8, 154.6, 150.7, 144.2, 143.0, 139.3, 138.4, 130.6, 130.3, 129.7, 129.2, 128.9, 127.4, 125.3, 124.2, 120.2, 119.2, 115.8, 115.6, 114.7, 13.5; HRMS (EI): *m/z* calcd for $C_{25}H_{20}N_3O$: 378.1601; found: 378.1602 [M + H]$^+$.

*2-(3-Methyl-1-phenyl-6-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl) phenol* (**5b**): White solid; 167 mg, yield 85%; m.p. 210–212 °C. IR (KBr) ν_{max}/cm^{-1} 3432, 1580, 1501, 1446, 1346, 1280, 1155, 1035, 863, 753; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.2 Hz, 2H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.53–7.48 (m, 3H), 7.40–7.34 (m, 1H), 7.30–7.25 (m, 4H), 7.07–7.00 (m, 2H), 5.61 (s, 1H), 2.41 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 152.8, 151.4, 142.9, 141.2, 139.8, 139.5, 136.0, 130.5, 130.3, 129.5, 128.9, 127.5, 125.4, 124.2, 121.0, 120.7, 116.0, 115.6, 114.1, 21.3, 13.7; HRMS (EI): *m/z* calcd for $C_{26}H_{22}N_3O$: 392.1757; found: 392.1758 [M + H]$^+$.

*2-[6-(4-Methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridin-4-yl]phenol* (**5c**): White solid; 186 mg, yield 91%; m.p. 186–188 °C. IR (KBr) ν_{max}/cm^{-1} 3447, 1602, 1426, 1240, 1182, 1038, 830, 749; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.38 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.9 Hz, 2H), 7.65–7.57 (m, 3H), 7.39–7.30 (m, 3H), 7.11–6.97 (m, 4H), 3.84 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.7, 155.6, 154.6, 150.7, 144.0, 143.0, 139.4, 130.8, 130.6, 130.2, 129.2, 128.8, 125.2, 124.4, 120.1, 119.2, 115.6, 115.1, 114.3, 114.2, 55.3, 13.5; HRMS (EI): *m/z* calcd for $C_{26}H_{22}N_3O_2$: 408.1707; found: 408.1708 [M + H]$^+$.

*2-(6-(4-Hydroxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridin-4-yl)phenol* (**5d**)**:** White solid; 118 mg, yield 60%; m.p. 194–196 °C. IR (KBr) ν_{max}/cm^{-1} 3442, 1643, 1383, 1163, 756; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (br, 1H), 9.85 (br, 1H), 8.38 (d, *J* = 7.9 Hz, 2H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.62–7.57 (m, 3H), 7.38–7.29 (m, 3H), 7.05–6.90 (m, 4H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.2, 156.0, 154.6, 150.8, 143.8, 142.9, 139.5, 130.5, 130.2, 129.2, 128.9, 125.1, 124.4, 120.0, 119.1, 115.7, 115.6, 114.8, 113.9, 13.5; HRMS (EI): *m/z* calcd for $C_{25}H_{20}N_3O_2$: 394.1550; found: 394.1553 [M + H]$^+$.

*2-[6-(4-Fluorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridin-4-yl]phenol* (**5e**): White solid; 168 mg, yield 85%; m.p. 198–199 °C. IR (KBr) ν_{max}/cm^{-1} 3446, 1644, 1504, 1445, 1229, 1157, 1097, 841, 757; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (s, 1H), 8.38–8.31 (m, 4H), 7.71–7.70 (m, 1H), 7.62–7.56 (m, 2H), 7.39–7.30 (m, 5H), 7.06–6.97 (m, 2H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.2 (d, $^1J_{C\text{-}F}$ = 245.6 Hz), 154.7, 154.5, 150.6, 144.2, 143.0, 139.3, 134.8 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 130.6, 130.3, 129.6 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 129.1, 125.3, 124.2, 120.2, 119.1, 115.8 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 115.6, 114.6, 13.5; HRMS (EI): *m/z* calcd for $C_{25}H_{19}FN_3O$: 396.1507; found: 396.1513 [M + H]$^+$.

*2-[6-(4-Chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridin-4-yl]phenol* (**5f**): White solid; 171 mg, yield 83%; m.p. 210–211 °C. IR (KBr) ν_{max}/cm^{-1} 3442, 1644, 1595, 1499, 1443, 1392, 1343, 1093, 826, 753; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37–8.34 (m, 2H), 8.14–8.09 (m, 2H), 7.57–7.49 (m, 4H), 7.47–7.39 (m, 2H), 7.34–7.29 (m, 2H), 7.13–7.04 (m, 2H), 5.12 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 152.6, 151.4, 142.9, 141.5, 139.5, 137.3, 135.8, 130.7, 130.3, 129.0, 128.8, 125.6, 123.9, 121.0, 120.9, 116.0, 115.6, 114.5, 13.8; HRMS (EI): *m/z* calcd for $C_{25}H_{19}ClN_3O$: 412.1211; found: 412.1213 [M + H]$^+$.

*2-[6-(4-Bromophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridin-4-yl]-phenol* (**5g**): White solid; 182 mg, yield 80%; m.p. 219–220 °C. IR (KBr) ν_{max}/cm^{-1} 3439, 1633, 1590, 1500, 1445, 1399, 1349, 1069, 865, 755; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (s, 1H), 8.36–8.33 (m, 2H), 8.22 (d, *J* = 8.6 Hz, 2H), 7.75–7.72 (m, 3H), 7.62–7.57 (m, 2H), 7.40–7.31 (m, 3H), 7.06–6.97 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.1, 155.0, 151.1, 144.9, 143.5, 139.7, 138.1, 132.4, 131.1, 130.8, 129.9, 129.7, 125.9, 124.6, 123.9, 120.8, 119.7, 116.2, 116.1, 115.4, 14.0; HRMS (EI): *m/z* calcd for $C_{25}H_{19}BrN_3O$: 456.0706; found: 456.0706 [M + H]$^+$.

*2-[(3-Methyl-6-naphthalen-2-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridin-4-yl]phenol* (**5h**): White solid; 173 mg, yield 81%; m.p. 220–222 °C. IR (KBr) ν_{max}/cm^{-1} 3438, 1737, 1596, 1496, 1444, 1369, 1283, 859, 750, 699; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.92 (s, 1H), 8.54–8.47 (m, 3H), 8.18–8.13 (m, 2H), 8.06–8.03 (m, 1H), 7.98 (s, 1H), 7.72–7.62 (m, 4H), 7.47–7.39 (m, 3H), 7.14–7.05 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.7, 154.6, 150.7, 144.2, 143.0, 139.4, 135.7, 133.5, 133.1, 130.6, 130.3, 129.2, 128.8, 128.5, 127.6, 127.1, 127.0, 126.5, 125.3, 124.7, 124.3, 120.2, 119.2, 116.0, 115.6, 114.7, 13.5; HRMS (EI): *m/z* calcd for $C_{29}H_{22}N_3O$: 428.1757; found: 428.1757 [M + H]$^+$.

*2-(6-Furan-2-yl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)phenol* (**5i**): White solid; 156 mg, yield 85%; m.p. 225–228 °C. IR (KBr) ν_{max}/cm^{-1} 3441, 1598, 1497, 1442, 1387, 1293, 1156, 868, 750; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.38–8.35 (m, 2H), 7.94–7.93(m, 1H), 7.60–7.52 (m, 3H), 7.41–7.29 (m, 4H), 7.06–6.96 (m, 2H), 6.73–6.72 (m, 1H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.5, 152.8, 150.5, 147.7, 145.1, 144.1, 143.1, 139.3, 130.5, 130.4, 129.2, 125.3, 123.9, 120.0, 119.2, 115.6, 114.5, 114.1, 112.6, 111.0, 13.5; HRMS (EI): *m/z* calcd for $C_{23}H_{18}N_3O_2$: 368.1394; found: 368.1400 [M + H]$^+$.

*2-(3-Methyl-1-phenyl-6-thiophen-2-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)phenol* (**5j**): Yellow solid; 175 mg, yield 91%; m.p. 225–227 °C. IR (KBr) ν_{max}/cm^{-1} 3437, 1644, 1582, 1440, 1356, 1291, 1155, 1094, 859, 754; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 2H), 7.68–7.66 (m, 1H), 7.53–7.25 (m, 7H), 7.13–7.02 (m, 3H), 5.50 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 152.1, 150.9, 144.8, 143.1, 141.4, 139.4, 130.6, 130.3, 128.9, 128.7, 128.2, 126.2, 125.4, 123.9, 120.72, 120.68, 116.1, 114.4, 114.2, 13.7; HRMS (EI): *m/z* calcd for $C_{23}H_{18}N_3OS$: 384.1165; found: 384.1166 [M + H]$^+$.

*2-(3-Methyl-1-phenyl-6-pyridin-2-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)phenol* (**5k**): Yellow solid; 117 mg, yield 62%; m.p. 238–239 °C. IR (KBr) ν_{max}/cm^{-1} 3438, 1590, 1498, 1277, 1147, 1099, 1036, 749; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.7 Hz, 2H), 8.28 (d, *J* = 7.7 Hz, 2H), 8.09 (s, 1H), 7.71–7.49 (m, 4H), 7.37–7.28 (m, 2H), 7.19–7.17 (m, 2H), 7.07–6.96 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 154.7, 153.3, 150.8, 148.5, 143.2, 142.1, 139.5, 137.1, 130.4, 128.9, 125.4, 124.2, 124.1, 121.9, 120.8, 120.4, 116.5, 116.4, 115.8, 13.8; HRMS (EI): *m/z* calcd for $C_{24}H_{19}N_4O$: 379.1553; found: 379.1550 $[M + H]^+$.

*2-(3,6-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)phenol* (**5l**): White solid; 103 mg, yield 65%; m.p. 209–211 °C. IR (KBr) ν_{max}/cm^{-1} 3427, 1597, 1343, 1222, 1150, 1089, 1023, 906, 858, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.6 Hz, 2H), 7.51–7.45 (m, 2H), 7.38–7.32 (m, 1H), 7.27–7.16 (m, 2H), 7.04–6.99 (m, 2H), 6.86 (s, 1H), 5.81 (s, 1H), 2.63 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 152.8, 150.9, 142.9, 140.9, 139.2, 130.4, 130.1, 128.9, 125.6, 123.9, 121.3, 120.5, 118.7, 116.2, 113.4, 24.8, 13.6; HRMS (EI): *m/z* calcd for $C_{20}H_{18}N_3O$: 316.1444; found: 316.1439 $[M + H]^+$.

*2-[3-Methyl-6-(2-methylpropenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]phenol* (**5m**): White solid; 94 mg, yield 53%; m.p. 146–148 °C. IR (KBr) ν_{max}/cm^{-1} 3436, 1644, 1567, 1496, 1431, 1387, 1151, 878, 754; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28–8.25 (m, 2H), 7.51–7.45 (m, 2H), 7.39–7.34 (m, 1H), 7.28–7.21 (m, 2H), 7.06–7.00 (m, 2H), 6.92 (d, *J* = 1.2 Hz, 1H), 6.42 (d, *J* = 1.2 Hz, 1H), 5.45–5.31 (m, 1H), 2.31 (s, 3H), 2.21 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 152.7, 151.1, 143.9, 142.8, 140.2, 139.4, 130.4, 130.2, 128.8, 125.4, 124.4, 124.0, 121.1, 120.6, 119.8, 116.0, 112.9, 28.1, 20.6, 13.7; HRMS (EI): *m/z* calcd for $C_{23}H_{22}N_3O$: 356.1757; found: 356.1757 $[M + H]^+$.

*5-Methoxy-2-(1,6-diphenyl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)phenol* (**5n**): Yellow solid; 167 mg, yield 82%; m.p. 222–223 °C. IR (KBr) ν_{max}/cm^{-1} 3446, 1626, 1507, 1397, 1304, 1260, 1156, 1030, 811, 756; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.8 Hz, 2H), 8.14 (d, *J* = 6.9 Hz, 2H), 7.54–7.45 (m, 6H), 7.30–7.28 (m, 1H), 7.20–7.17 (m, 1H), 6.64–6.60 (m, 2H), 5.56 (s, 1H), 3.85 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 157.1, 153.8, 151.5, 143.0, 141.2, 139.5, 138.9, 131.0, 129.6, 129.0, 128.8, 127.6, 125.5, 121.0, 116.6, 116.1, 114.6, 106.9, 101.5, 55.4, 13.9; HRMS (EI): *m/z* calcd for $C_{26}H_{22}N_3O_2$: 408.1707; found: 408.1706 $[M + H]^+$.

*4-Chloro-2-(1,6-diphenyl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)phenol* (**5o**): Yellow solid; 183 mg, yield 89%; m.p. 218–220 °C. IR (KBr) ν_{max}/cm^{-1} 3438, 1648, 1569, 1496, 1151, 1020, 875, 759; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14(s, 1H), 8.38–8.28 (m, 4H), 7.76(s, 1H), 7.63–7.51 (m, 5H), 7.46–7.41 (m, 2H), 7.36–7.31 (m, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 153.7, 150.6, 142.8, 142.4, 139.3, 138.2, 129.94, 129.90, 129.7, 129.2, 128.9, 127.4, 126.0, 125.4, 122.7, 120.2, 117.2, 115.8, 114.4, 13.5; HRMS (EI): *m/z* calcd for $C_{25}H_{19}ClN_3O$: 412.1211; found: 412.1214 $[M + H]^+$.

*4-Bromo-2-(1,6-diphenyl-3-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl)phenol* (**5p**): Yellow solid; 194 mg, yield 85%; m.p. 220–223 °C. IR (KBr) ν_{max}/cm^{-1} 3434, 1644, 1589, 1496, 1151, 1114, 876, 805, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29–8.26 (m, 2H), 8.11–8.08 (m, 2H), 7.52–7.27 (m, 9H), 6.68 (d, *J* = 8.7 Hz, 1H), 6.07 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 152.0, 151.4, 142.6, 139.6, 139.4, 138.6, 133.3, 132.7, 129.8, 129.0, 128.9, 127.6, 126.1, 121.0, 117.9, 115.7, 113.9, 112.7, 13.8; HRMS (EI): *m/z* calcd for $C_{25}H_{19}BrN_3O$: 456.0706; found: 456.0704 $[M + H]^+$.

Electronic Supplementary Information

Copies of the ^{1}H and ^{13}C NMR spectra of **5a–p** and full details of the X-ray bond lengths and bond angles for **5e** and **5g** are available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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