Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 307

The acid-catalysed synthesis of 7-azaindoles from 3-alkynyl-2-aminopyridines and their antimicrobial activity†

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Received 3rd September 2013,
Accepted 7th November 2013

DOI: 10.1039/c3ob41798k

www.rsc.org/obc

The synthesis of 7-azaindoles from 3-alkynyl-2-aminopyridines using acidic conditions, namely, a mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA), is described. This methodology resulted in the synthesis of fifteen 7-azaindoles, with most containing substituents at the 2- and 5-positions. The majority of these were tested for antimicrobial activity against a range of bacteria and yeasts. The 7-azaindoles displayed the best activity against the yeasts, particularly against *Cryptococcus neoformans*, where activities as low as 3.9 μg ml^{-1} were observed.

Introduction

The azaindoles are a growing class of indole isosteres that possess promising biological profiles. For example, the natural product variolin B **1** (Fig. 1) isolated from an extremely rare Antarctic sponge is a promising anti-cancer agent.[1]

Other examples include the synthetic azaindole derivative of rebeccamycin, known as diazarebeccamycin **2**, which has also been shown to exhibit promising anticancer activity,[2] and 6-azaindole **3** which has demonstrated activity as an inhibitor of HIV-1 attachment to CD_4^+ T cells.[3]

The synthesis of 7-azaindoles is often accomplished by initial Sonogashira coupling of a 3-halosubstituted-2-aminopyridine as shown in Scheme 1.[4] The intermediate alkynylpyridines are then exposed to a variety of different reaction conditions and reagents to afford the desired azaindoles. Many methods have been developed for this step and include the use of cesium- or potassium-containing bases such as potassium hydride, potassium *t*-butoxide or cesium *t*-butoxide[5a–d] or even bases such as DBU[5e] and triethylamine.[5f] Metal-containing catalysts have also been used for this purpose and include amongst others, the use of copper,[6a] an indium salt[6b] or even gold catalysts.[6c] The Cacchi reaction in the presence of a palladium catalyst[6d] has also been successfully used to facilitate both the Sonogashira coupling reaction and the azaindole

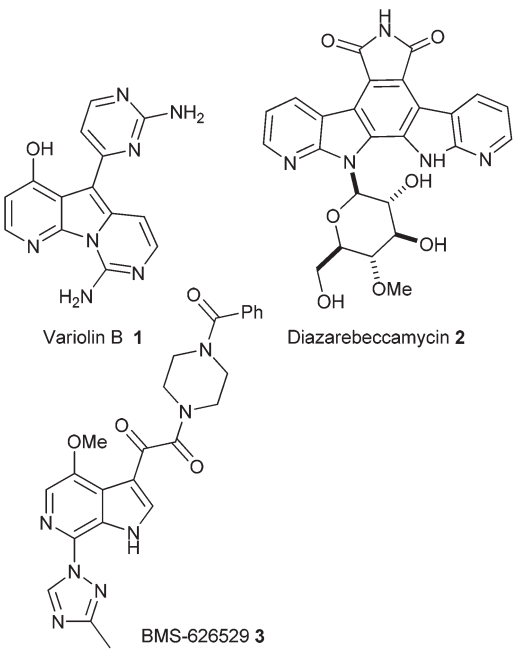
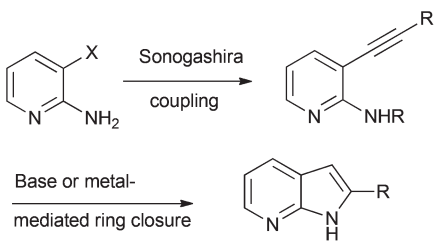


Fig. 1 Examples of biologically active azaindoles.



Scheme 1

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†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra are provided. See DOI: 10.1039/c3ob41798k

ring forming step to produce 2,3-disubstituted azaindoles directly from the aminopyridines. Even the use of microwaves in the presence of water with[7a] or without[7b] added salts has been reported.

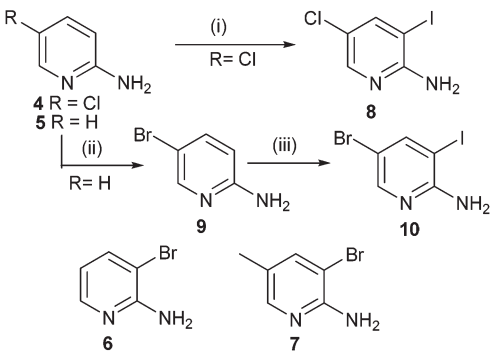
As a result of our interest in the synthesis of indole-containing compounds and their antibacterial and antifungal activity,[8] we initiated a programme directed towards the synthesis of the related compounds, azaindoles. The specific goal described in this publication was to attempt to develop versatile and cheap conditions for the synthesis of 7-azaindoles from the corresponding Sonogashira coupled 3-alkynyl-2-aminopyridine precursors. Thereafter, as azaindoles have interesting biological profiles, we wished to ascertain if the 7-azaindoles we had synthesized would display activity against a range of bacterial and yeast cell lines.

Results and discussion

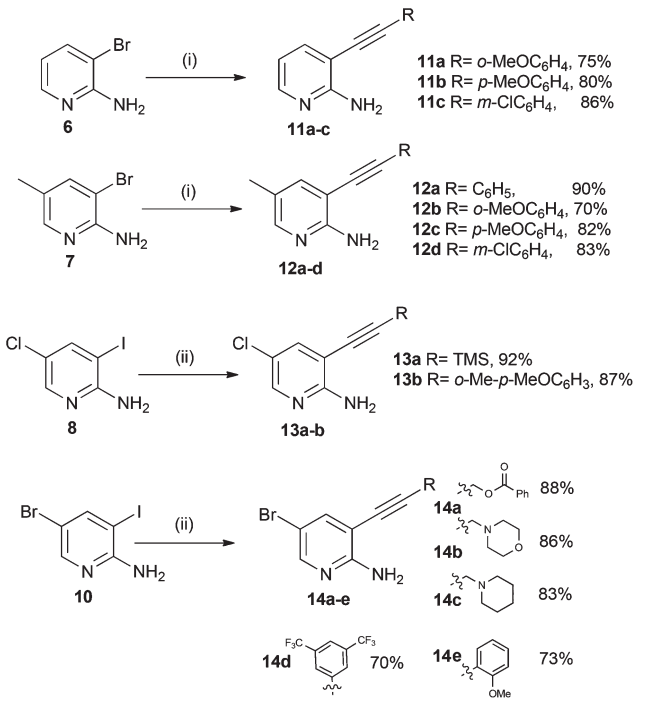
Initially the required halogenated substituted pyridines were prepared or obtained from commercial sources. 5-Chloro-2-aminopyridine **4**, 2-aminopyridine **5**, 3-bromo-2-aminopyridine **6** and 5-methyl-2-amino-3-bromopyridine **7** were obtained from Sigma-Aldrich. 5-Chloro-2-aminopyridine **4** was treated with I_2 in the presence of Ag_2SO_4[9] in ethanol to afford the 3-iodo substituted aminopyridine **8** in good yield.

Finally, 5-bromo-3-iodopyridin-2-amine **10** was prepared by initially treating 2-aminopyridine **5** with NBS[10] in MeCN to afford 5-bromo-2-aminopyridine **9**. Then **9** was subjected to potassium iodate, I_2 and a mixture of H_2SO_4, acetic acid and water[6a] to provide 5-bromo-3-iodopyridin-2-amine **10** in good yield (Scheme 2).

We were now in a position to attempt the Sonogashira coupling reaction, for which we believed that coupling would take place at the more reactive iodine substituent in substrates **8** and **10**, or at the bromine in the case of aminopyridines **6** and **7**. The 2-amino-3-halogen containing pyridines were treated with catalytic tetrakis(triphenylphosphine)palladium(0), copper(I) iodide, triethylamine as a base and a range of acety l-enes to afford the desired compounds (**11–14**) in good to excellent yield as shown in Scheme 3.



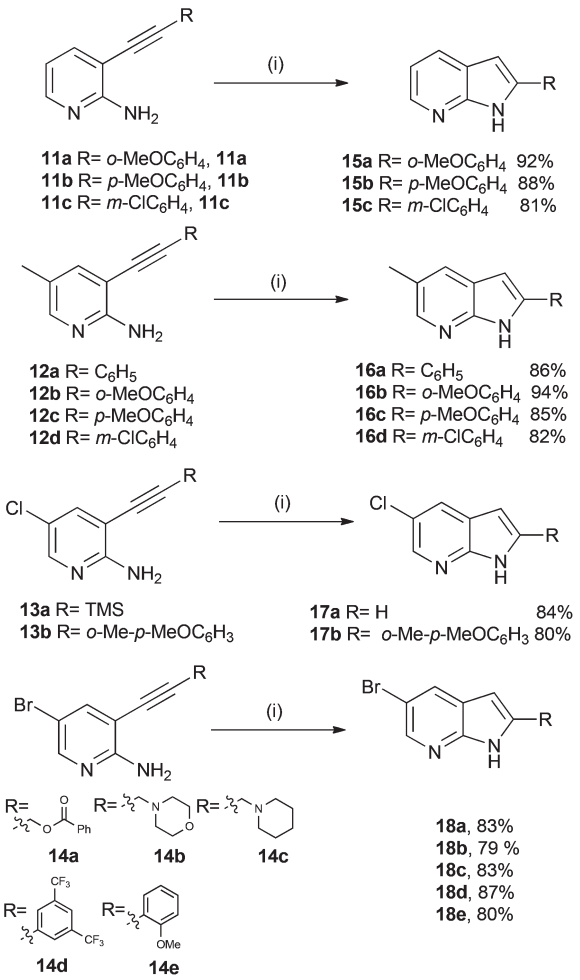
Scheme 2 *Reagents and conditions*: (i) I_2, Ag_2SO_4, EtOH, rt, 86%; (ii) NBS, MeCN, rt, 98%; (iii) I_2, KIO_3, H_2SO_4, AcOH, H_2O, 80 °C, 90%.



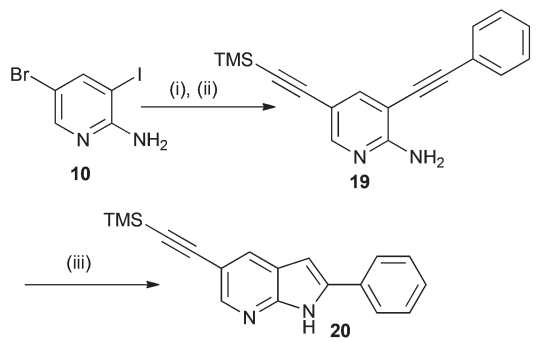
Scheme 3 *Reagents and conditions*: (i) RC≡CH, Et_3N, CuI, cat. $Pd(PPh_3)_4$, THF, 70 °C; (ii) RC≡CH Et_3N, CuI, cat. $Pd(PPh_3)_4$, THF, rt.

The stage was now set to attempt the formation of the pyrrole ring in order to assemble the 7-azaindole nucleus. For this step we wished to investigate if it was possible to use acidic conditions to affect the ring closure. A variety of acids (HCl, H_2SO_4, AcOH and trifluoroacetic acid (TFA)) were initially used. The use of TFA seemed to be promising as a small amount of azaindole was forming but the conversion rate was estimated to be only 10%. Since there are examples in the literature[4] of the corresponding amide (rather than amine) undergoing ring closure to afford azaindoles, we thought that the addition of trifluoroacetic anhydride (TFAA) to the reaction mixture containing TFA might improve the rate, conversion and yield of the desired azaindoles. After much experimentation we found that in the presence of 1 equivalents of TFA and 1.3 equivalents of TFAA in MeCN as a solvent and heating to reflux for 8 h, the substrate afforded the desired azaindoles (**15–18**) in generally excellent yields (Scheme 4).

As one final example we wished to take advantage of the different reactivity of the halogens on substrate **10** to establish if it was possible to introduce two different alkyne substituents using different temperatures. Hence as shown in Scheme 5, **10** was treated under Sonogashira reaction conditions with phenylacetylene initially at room temperature. After TLC showed that the starting material had all been consumed, the solvent was evaporated under reduced pressure and the crude material was then subjected to the same palladium catalyst using trimethylsilylacetylene as the alkyne coupling partner. After the reaction was deemed to be complete by TLC, work-up of the reaction and analysis of the product by NMR spectroscopy showed that two different alkyne substituents were present on



Scheme 4 *Reagents and conditions*: (i) TFA, TFAA, MeCN, 100 °C.



Scheme 5 *Reagents and conditions*: (i) Ph-C≡CH, Et_3N, CuI, Pd-$(PPh_3)_4$, THF, rt; (ii) TMS-C≡CH, Et_3N, CuI, $Pd(PPh_3)_4$, THF, 70 °C. 85% over two steps; (iii) TFA, TFAA, MeCN, 100 °C, 91%.

the 3,5-substituted aminopyridine **19**. Presumably, this is due to the different reactivities of the iodine and bromine substituents in the two Sonogashira reactions. Exposure of **19** to our acid mediated reaction conditions for azaindole formation resulted in the formation of the desired azaindole **20** in excellent yield.

As we now had a series of substituted azaindoles on hand they were quantitatively evaluated for antimicrobial activity (Table 1). While compound **16b** showed promising antibacterial activity (7.8 μg ml^{-1}) against *Pseudomonas aeruginosa*, many of the azaindoles showed very good and selective anti-yeast activity, particularly against *Cryptococcus neoformans*, where all compounds showed noteworthy inhibitory values of between 3.9–15.6 μg ml^{-1}. Previous studies on the antimicrobial effects of other azaindole derivatives include the quantitative study by Kumaran *et al.*,[11] and the promising antifungal effects found by Lebouvier.[12] Previous antimicrobial studies on azaindoles for activity against *Cryptococcus neoformans* is, however, lacking and the promising activity noted here warrants further examination, particularly, given that increased reports of infections from *Cryptococcus neoformans* show that this represents a major health threat for HIV infected patients.[13,14] Newer antifungals to combat this opportunistic pathogen will certainly be beneficial in future treatments, particularly with emerging trends of resistance evident.

In summary, to the best of our knowledge this is the first report outlining the synthesis of azaindoles from 3-alkynyl-2-aminopyridines under acidic conditions. The azaindoles synthesized display significant anti-yeast activity.

Experimental

^1H NMR and ^{13}C NMR spectra were recorded either on a Bruker AVANCE 300 spectrometer or a Bruker AVANCE III 500 spectrometer. All chemical shift values are reported in parts per million referenced against TMS which is given an assignment of zero parts per million. Coupling constants (*J*-values) are given in hertz (Hz). All mass spectroscopy data were collected on a Waters Acquity UPLC system coupled to a Waters HDMS G1 QTOF mass spectrometer. UPLC settings: analytical column: BEH C18 150 × 2.1 mm; column temperature: 60 °C; mobile phase: 90% water (0.1% formic acid): 5% acetonitrile; flow rate: 0.4 ml min^{-1}. MS settings: mode: VTOF; ionisation: ESIPos and ESINeg; scan range: 100–1000 Da; scan speed: 0.1 second; run time: 10 min. Infrared spectra were recorded on a Bruker Tensor 27 standard system spectrometer with diamond ATR attachment. Macherey-Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel column chromatography with various EtOAc and hexane mixtures as the mobile phase. TLC was performed on aluminum-backed Macherey-Nagel Alugram Sil G/UV254 plates pre-coated with 0.25 mm silica gel 60. The following acetylenes are commercially available: phenylacetylene, trimethylsilylacetylene, 2-ethynylanisole, 4-ethynylanisole, 1-ethynyl-4-methoxy-2-methylbenzene, 1-ethynyl-3,5-bis(trifluoromethyl)benzene and propargylbenzoate. The remaining two acetylenes 1-(prop-2-ynyl)piperidine and 4-(prop-2-ynyl)morpholine were prepared according to ref. 15 and 16.

5-Chloro-3-iodo-2-aminopyridine 8

To a solution of 2-amino-5-chloropyridine **4** (0.700 g, 5.45 mmol) in ethanol was added silver sulfate (1.699 g,

Table 1 Antimicrobial and antifungal activity of selected azaindoles (μg ml^{-1})

Compound	*Pseudomonas aeruginosa* NCTC 9027	*Escherichia coli* ATCC 8739	*Klebsiella pneumoniae* ATCC 8739	*Staphylococcus aureus* ATCC25923	*Enterococcus faecalis* ATCC 29212	*Cryptococcus neoformans* ATCC 90112	*Candida tropicalis* ATCC 201380	*Candida albicans* ATCC 10231
15a	31.3	62.5	31.3	31.3	93.8	**4.0**	**5.9**	**7.8**
15b	31.3	62.5	31.3	31.3	125.0	**7.8**	31.3	**15.6**
15c	31.3	31.3	23.5	31.3	62.5	**15.6**	31.3	31.3
16a	31.3	31.3	31.3	62.5	250.0	**7.8**	31.3	**15.6**
16b	7.8	62.5	31.3	31.3	125.0	**3.9**	31.3	31.3
16c	31.3	46.9	31.3	31.3	62.5	**7.8**	**15.6**	31.3
17a	31.3	62.5	31.3	62.5	125.0	**15.6**	**15.6**	31.3
17b	31.3	31.3	31.3	250.0	125.0	**15.6**	**15.6**	250.0
18a	31.3	31.3	46.9	31.3	250.0	**7.8**	15.6	23.5
18b	31.3	31.3	31.3	62.5	62.5	**8.0**	31.3	31.3
18c	31.3	31.3	31.3	62.5	62.5	**15.6**	31.3	31.3
18d	62.5	31.3	62.5	31.3	250.0	**15.6**	31.3	**15.6**
18e	62.5	31.3	31.3	62.5	250.0	**15.6**	31.3	**15.6**
20	46.9	250.0	31.3	250.0	125.0	**3.9**	31.3	31.3
Control[a]	0.3	0.6	0.6	0.6	0.3	0.8	2.5	2.5

[a] Control for bacteria, ciprofloxacin; for the yeasts, amphotericin.

5.45 mmol) in one portion followed by the addition of iodine (1.383 g, 5.45 mmol) portionwise. The heterogeneous mixture was stirred at rt until determined complete by TLC. After the reaction was complete, the mixture was filtered through celite or silica gel and the ethanol removed under reduced pressure. The resulting crude material was re-dissolved in dichloromethane and washed with a saturated solution of aqueous sodium thiosulfate. The separated dichloromethane layer was removed under reduced pressure and the resulting solid was purified by silica gel chromatography to give 2-amino-5-chloro-3-iodopyridine **8**[9] (1.189 g 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 2.2, 1H), 7.84 (d, J = 2.2, 1H), 5.06 (s, 2H).

5-Bromo-2-aminopyridine 9

2-Aminopyridine **5** (2.600 g, 0.0276 mol) was dissolved in dry MeCN (100 ml), treated with *N*-bromosuccinimide (5.219 g, 0.0293 mol) and stirred for 2 h at rt. The solvent was removed and the resulting cream white solid purified by flash chromatography to give 2-amino-5-bromopyridine **9**[10] as a white solid (4.692 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.48 (dd, J = 8.7, 2.4, 1H), 6.41 (d, J = 8.7, 1H), 4.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.36, 148.88, 140.49, 110.42, 108.56.

5-Bromo-3-iodo-2-aminopyridine 10

A mixture of 2-amino-5-bromopyridine **9** (45.00 g, 0.260 mol), iodic acid (11.86 g, 0.0676 mol), iodine (26.40 g, 0.104 mol), sulfuric acid (4.50 ml), acetic acid (150 ml) and water (30 ml) was heated to 80 °C for 8 h. After this time, the reaction mixture was concentrated under vacuum and then made basic with an aqueous 12 M sodium hydroxide solution. The basic solution was extracted with dichloromethane, washed with a saturated solution of sodium thiosulfate and then brine, dried over $MgSO_4$ and then the organic solvent was removed under vaccum. The resulting cream white solid was purified by flash chromatography to give 2-amino-5-bromo-3-iodopyridine **10**[6a] as a white solid (70.11 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.95 (s, 1H), 5.03 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.75, 148.72, 148.57, 107.58, 77.93.

General procedure for the Sonogashira reaction to synthesize 11a–c and 12a–d

To a flame-dried round-bottom flask under a nitrogen or argon atmosphere containing 2-amino-3-bromopyridine derivative (**6** and **7**) was added CuI (2 mol%) and $Pd(PPh_3)_4$ (2 mol%) in one portion followed by the addition of the degassed alkyne solution in THF (20 ml). Triethylamine (5 ml) was then added and the reaction mixture was stirred at 70 °C until no starting material was present as monitored by thin layer chromatography (TLC). After this time, the reaction was quenched with a saturated aqueous ammonium chloride and was then extracted with either dichloromethane or ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered through either silica or celite and the excess solvent was removed on a rotary evaporator, followed by purification using flash chromatography (30% EtOAc–hexane) to yield the desired products **11a–c** and **12a–d**.

3-[(2-Methoxyphenyl)ethynyl]pyridin-2-amine 11a. Using 2-amino-3-bromopyridine (0.450 g, 2.60 mmol), 1-ethynyl-2-methoxybenzene (0.343 g, 2.60 mmol), CuI (9.91 mg, 0.0520 mmol) and $Pd(PPh_3)_4$ (0.0612 g, 0.0520 mmol) the product **11a** was obtained as a cream white solid (0.351 g, 75%). Mp: 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 5.0, 1.6, 1H), 7.57 (dt, J = 13.5, 6.7, 1H), 7.46 (dd, J = 7.6, 1.6, 1H), 7.32 (td, J = 8.4, 1.7, 1H), 6.98–6.89 (m, 2H), 6.62 (dd, J = 7.5, 5.0, 1H), 5.34 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.92, 159.17, 147.83, 138.83, 132.44, 129.95, 120.65, 113.27, 112.09, 110.53, 103.46, 92.26, 89.30, 55.82. IR (cm^{-1}) 3298 (NH str.), 2997 (CH str.), 2312 (alkyne), 1619 (C=N), 1580

(C═C), 1181 (C–O). HRMS (ES^+) Calculated for $C_{14}H_{13}N_2O$ $[M + H]^+$: 225.1028, found 225.1032.

3-[(4-Methoxyphenyl)ethynyl]pyridin-2-amine 11b. Using 2-amino-3-bromopyridine (0.450 g, 2.60 mmol), 1-ethynyl-4-methoxybenzene (0.350 g, 2.60 mmol), CuI (9.91 mg, 0.0520 mmol) and $Pd(PPh_3)_4$ (0.0612 g, 0.0520 mmol) the product 3-[(4-methoxyphenyl)ethynyl]pyridin-2-amine **11b** (0.389 g, 80%) was obtained as a cream white solid. Mp: 159–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J = 4.9, 1.5, 1H), 7.57 (dd, J = 7.5, 1.7, 1H), 7.50–7.41 (m, 2H), 6.93–6.83 (m, 2H), 6.63 (dd, J = 7.5, 5.0, 1H), 5.05 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.93, 158.75, 147.69, 139.71, 133.01, 114.79, 114.13, 113.57, 103.54, 95.49, 83.14, 55.34; IR (cm^{-1}) 3245 (NH str.), 2986 (CH str.), 2359 (alkyne), 1619 (C═N), 1558 (C═C), 1144 (C–O). HRMS (ES^+) Calculated for $C_{14}H_{13}N_2O$ $[M + H]^+$: 225.1028, found 225.1039.

3-[(3-Chlorophenyl)ethynyl]pyridin-2-amine 11c. Using 2-amino-3-bromopyridine (0.450 g, 2.60 mmol), 1-ethynyl-3-chlorobenzene (0.354 g, 2.60 mmol), CuI (9.91 mg, 0.0520 mmol) and $Pd(PPh_3)_4$ (0.0612 g, 0.0520 mmol) the product **11c** (0.373 g, 86%) was obtained as a cream white solid. Mp: 117–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.60 (d, J = 7.3, 1H), 7.51 (s, 1H), 7.40 (d, J = 7.2, 1H), 7.37–7.27 (m, 2H), 6.67 (s, 1H), 5.10 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.72, 148.28, 140.23, 134.37, 131.34, 129.72, 129.61, 128.91, 124.40, 113.66, 102.65, 94.04, 85.60; IR (cm^{-1}) 3326 (NH str.), 3003 (CH str.), 2219 (alkyne), 1627 (C═N), 1565 (C═C), 1198 (C–O); HRMS (ES^+) Calculated for $C_{13}H_{10}N_2Cl$ $[M + H]^+$: 229.0533, found 229.0542.

5-Methyl-3-(phenylethynyl)pyridin-2-amine 12a. Starting with 2-amino-3-bromo-5-methylpyridine (0.450 g, 2.41 mmol), phenylacetylene (0.2455 g, 2.41 mmol), CuI (9.18 mg, 0.0482 mmol) and $Pd(PPh_3)_4$ (0.0557 g, 0.0482 mmol) the product **12a**[5c] (0.450 g, 90%) was obtained as a cream white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 1.6, 1H), 7.57–7.49 (m, 2H), 7.47 (d, J = 1.9, 1H), 7.38 (dd, J = 6.5, 2.7, 3H), 4.97 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.86, 147.82, 140.62, 131.47, 128.57, 128.45, 122.77, 122.55, 102.87, 95.30, 84.58, 17.27.

3-[(2-Methoxyphenyl)ethynyl]-5-methylpyridin-2-amine 12b. Using 2-amino-3-bromo-5-methylpyridine (0.450 g, 2.41 mmol), 1-ethynyl-2-methoxybenzene (0.3177 g, 2.41 mmol), CuI (9.18 mg, 0.0482 mmol) and $Pd(PPh_3)_4$ (0.0557 g, 0.0482 mmol), the product 3-((2-methoxyphenyl)-ethynyl)-5-methylpyridin-2-amine **12b** (0.404 g, 70%) was obtained as a cream white solid. Mp: 120–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.49–7.39 (m, 2H), 7.31 (d, J = 1.7, 1H), 6.94 (ddd, J = 22.1, 11.0, 4.6, 2H), 5.16 (s, 2H), 3.92 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.90, 157.30, 147.73, 139.55, 132.45, 129.87, 122.17, 120.62, 112.19, 110.53, 103.13, 92.05, 89.43, 55.80, 17.29; IR (cm^{-1}) 3301 (NH str.), 3001 (CH str.), 2212 (alkyne), 1639 (C═N), 1594 (C═C), 1179 (C–O); HRMS (ES^+) Calculated for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1184, found 239.1198.

3-[(4-Methoxyphenyl)ethynyl]-5-methylpyridin-2-amine 12c. Using 2-amino-3-bromo-5-methylpyridine (0.450 g, 2.41 mmol), 1-ethynyl-4-methoxybenzene (0.3177 g, 2.41 mmol), CuI (9.18 mg, 0.0482 mmol) and $Pd(PPh_3)_4$ (0.0557 g, 0.0482 mmol), the desired product **12c** (0.472 g, 82%) was obtained as a cream white solid. Mp: 94–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 1.6, 1H), 7.46–7.43 (m, 2H), 7.42 (d, J = 1.9, 1H), 6.91–6.85 (m, 2H), 4.92 (s, 2H), 3.82 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.87, 156.86, 147.56, 140.38, 132.97, 122.51, 114.90, 114.12, 103.24, 95.30, 83.30, 55.33, 17.26; IR (cm^{-1}) 3276 (NH str.), 2987 (CH str.), 2238 (alkyne), 1618 (C═N), 1564 (C═C), 1170 (C–O); HRMS (ES^+) Calculated for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1184, found 239.1185.

3-[(3-Chlorophenyl)ethynyl]-5-methylpyridin-2-amine 12d. Using 2-amino-3-bromo-5-methylpyridine (0.450 g, 2.41 mmol), 1-ethynyl-3-chlorobenzene (0.328 g, 2.41 mmol), CuI (9.18 mg, 0.0482 mmol) and $Pd(PPh_3)_4$ (0.0557 g, 0.0482 mmol), the product **12d** (0.482 g, 83%) was obtained as a cream white solid. Mp: 104–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.50 (s, 1H), 7.45 (s, 1H), 7.39 (d, J = 7.3, 1H), 7.31 (dt, J = 13.3, 6.8, 2H), 4.93 (s, 2H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.84, 148.16, 140.86, 134.35, 131.31, 129.70, 129.58, 128.84, 124.49, 122.68, 102.36, 93.87, 85.78, 17.25; IR (cm^{-1}) 3347 (NH str.), 3005 (CH str.), 2259 (alkyne), 1624 (C═N), 1590 (C═C), 1176 (C–O); HRMS (ES^+) Calculated for $C_{14}H_{12}N_2Cl$ $[M + H]^+$: 243.0689, found 243.0705.

General procedure for the Sonogashira reaction to synthesize 13a–b and 14a–e

To a flame-dried round-bottom flask under a nitrogen or argon atmosphere containing 2-amino-3-iodopyridine derivative **9** and **10** was added CuI (2 mol%) and $Pd(PPh_3)_4$ (2 mol%) in one portion followed by the addition of the degassed alkyne solution in THF (20 ml). Triethylamine (5 ml) was then added and the reaction mixture was stirred at rt, until no starting material was present as monitored by thin layer chromatography (TLC). After this time, the reaction was quenched with a saturated aqueous ammonium chloride and was extracted with either dichloromethane or ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered through either silica or celite and the excess solvent was removed on a rotary evaporator, followed by purification using flash chromatography (30% EtOAc–hexane) to yield the desired products **12a–b** and **14a–e**.

5-Chloro-3-[(trimethylsilyl)ethynyl]pyridin-2-amine 13a. Using 2-amino-3-iodo-5-chloropyridine (4.475 g, 17.6 mmol), trimethylsilylacetylene (8.626 g, 88.1 mmol), CuI (0.06704 g, 0.352 mmol) and $Pd(PPh_3)_4$ (0.4068 g, 0.352 mmol) **13a** (3.626 g, 92%) was obtained as a cream white solid[17] (0.2153 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 2.4, 1H), 7.51 (d, J = 2.5, 1H), 5.06 (s, 2H), 0.27 (s, 9H).

5-Chloro-3-[(4-methoxy-2-methylphenyl)ethynyl]pyridin-2-amine 13b. Using 2-amino-3-iodo-5-chloropyridine (0.300 g, 1.19 mmol), 1-ethynyl-4-methoxy-2-methylbenzene (0.1740 g, 1.19 mmol), CuI (4.517 mg, 0.0237 mmol) and $Pd(PPh_3)_4$ (0.4068 g, 0.0237 mmol) the product **13b** was produced (0.2834 g, 87%) as a cream white solid. Mp: 127–130 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.55 (s, 1H), 7.41 (d, J = 8.4, 1H), 6.79 (s, 1H), 6.74 (d, J = 8.4, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.17, 156.92, 145.88, 141.88, 138.66, 133.38, 120.18, 115.32, 114.26, 111.56, 105.04, 95.67, 85.77, 55.31, 21.18; IR (cm^{-1}) 3368 (NH str.), 2989 (CH str.), 2287 (alkyne), 1605 (C═N), 1558 (C═C), 1164 (C–O); HRMS (ES^+) Calculated for $C_{15}H_{14}N_2ClO$ $[M + H]^+$: 273.0795, found 273.0801.

3-(2-Amino-5-bromopyridin-3-yl)prop-2-yn-1-yl benzoate 14a. Using 2-amino-3-iodo-5-bromopyridine (2.600 g, 8.70 mmol), prop-2-yn-1-yl benzoate (1.672 g, 16.4 mmol), CuI (33.14 mg, 0.174 mmol) and $Pd(PPh_3)_4$ (0.2011 g, 0.174 mmol) **14a** (2.546 g, 88%) was obtained as a brown solid. Mp: 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11–8.02 (m, 3H), 7.63–7.53 (m, 2H), 7.45 (t, J = 7.6, 2H), 5.23 (s, 2H), 5.14 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.30, 158.39, 149.54, 142.34, 133.77, 130.12, 129.63, 128.80, 106.91, 103.77, 90.95, 81.23, 53.41; IR (cm^{-1}) 3249 (NH str.), 2989 (CH str.), 2312 (alkyne), 1629 (C═N), 1548 (C═C), 1173 (C–O); HRMS (ES^+) Calculated for $C_{15}H_{12}N_2O_2Br$ $[M + H]^+$: 331.0082, found 331.0080.

5-Bromo-3-(3-morpholinoprop-1-yn-1-yl)pyridin-2-amine 14b. Starting with 2-amino-3-iodo-5-bromopyridine (3.000 g, 10.0 mmol), 4-(prop-2-yn-1-yl)morpholine (1.253 g, 10.0 mmol), CuI (38.23 mg, 0.201 mmol) and $Pd(PPh_3)_4$ (0.2320 g, 0.201 mmol), the product 5-bromo-3-(3-morpholinoprop-1-yn-1-yl)pyridin-2-amine **14b** (2.541 g, 86%) was obtained as a brown solid. Mp: 115–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 2.4, 1H), 7.57 (d, J = 2.4, 1H), 5.14 (s, 2H), 3.80–3.66 (m, 4H), 3.53 (s, 2H), 2.66–2.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.94, 148.74, 142.22, 107.06, 104.78, 91.93, 80.05, 67.05, 52.68, 48.38; IR (cm^{-1}) 3310 (NH str.), 2959 (CH str.), 2291 (alkyne), 1630 (C═N), 1572 (C═C), 1132 (C–O); HRMS (ES^+) Calculated for $C_{12}H_{15}N_3BrO$ $[M + H]^+$: 296.0398, found 296.0420.

5-Bromo-3-[3-(piperidin-1-yl)prop-1-yn-1-yl]pyridin-2-amine 14c. Using 2-amino-3-iodo-5-bromopyridine (3.000 g, 10.0 mmol), 1-(prop-2-yn-1-yl)piperidine (1.235 g, 10.0 mmol), CuI (38.23 mg, 0.201 mmol) and $Pd(PPh_3)_4$ (0.2320 g, 0.201 mmol) the product **14c** (2.451 g, 83%) was obtained as brown solid. Mp: 79–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 2.4, 1H), 7.57 (d, J = 2.4, 1H), 5.15 (s, 2H), 3.50 (s, 2H), 2.52 (m, 4H), 1.61 (dt, J = 11.0, 5.6, 4H), 1.42 (d, J = 5.1, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.99, 148.50, 142.11, 107.04, 105.15, 92.92, 79.53, 53.75, 48.81, 26.16, 24.09; IR (cm^{-1}) 3262 (NH str.), 2988 (CH str.), 2259 (alkyne), 1639 (C═N), 1558 (C═C); HRMS (ES^+) Calculated for $C_{13}H_{17}N_3Br$ $[M + H]^+$: 294.0606, found 294.0613.

3-[(3,5-Bis(trifluoromethyl)phenyl)ethynyl]-5-bromopyridin-2-amine 14d. Using 2-amino-3-iodo-5-bromopyridine (1.500 g, 5.02 mmol), 1-ethynyl-3,5(trifluoromethyl)benzene (1.235 g, 10.0 mmol), CuI (19.12 mg, 0.100 mmol) and $Pd(PPh_3)_4$ (0.1160 g, 0.100 mmol) the product **14d** (1.436 g, 70%) was obtained as white crystals. Mp: 194–196 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 2.4, 1H), 7.94 (s, 2H), 7.86 (s, 1H), 7.74 (d, J = 2.4, 1H), 5.10 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.71, 150.16, 142.56, 132.76, 132.49, 131.74, 131.72, 124.92, 124.25, 122.64, 122.08, 107.59, 103.59, 93.49, 86.93; IR (cm^{-1}) 3309 (NH str.), 2995 (CH str.), 2319 (alkyne), 1629 (C═N), 1571 (C═C); HRMS (ES^+) Calculated for $C_{15}H_8N_2BrF_6$ $[M + H]^+$: 408.9775, found 408.9778.

5-Bromo-3-[(2-methoxyphenyl)ethynyl]pyridin-2-amine 14e. Using 2-amino-3-iodo-5-bromopyridine (2.500 g, 8.36 mmol), 1-ethynyl-2-methoxybenzene (1.105 g, 8.36 mmol), CuI (31.84 mg, 0.167 mmol), $Pd(PPh_3)_4$ (0.1932 g, 0.167 mmol) furnished the product **14e** as a cream white solid (2.013 g, 83%). Mp: 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 2.3, 1H), 7.67 (d, J = 2.3, 1H), 7.46 (dd, J = 7.5, 1.5, 1H), 7.40–7.29 (m, 1H), 7.00–6.91 (m, 2H), 5.51 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.00, 157.82, 148.21, 140.39, 132.47, 130.34, 120.70, 111.56, 110.55, 106.69, 105.26, 93.51, 88.04, 55.81; IR (cm^{-1}) 3310 (NH str.), 3002 (CH str.), 2358 (alkyne), 1627 (C═N), 1571 (C═C), 1181 (C–O); HRMS (ES^+) Calculated for $C_{14}H_{12}N_2BrO$ $[M + H]^+$: 303.0133, found 303.0147.

General method for the synthesis of azaindoles 15a–c, 16a–d, 17a–b and 18a–e

The corresponding 2-amino-3-ethynylpyridine derivatives (40–200 mg) **11a–c**, **12a–d**, **13a–b** and **14a–e** were dissolved in MeCN. To the resulting solution was added trifluoroacetic acid (1 eq.) in one portion followed by the addition of trifluoroacetic anhydride (1.3 eq.) dropwise. The resulting mixture was then heated to reflux for 8 h and was allowed to cool to rt. The solvent was then removed on a rotary evaporator and the resulting crude material was re-dissolved in dichloromethane and washed with aqueous sodium carbonate (10%). The separated and dried ($MgSO_4$) organic phase was purified by flash silica chromatography using ethyl acetate–hexane mixture (10–50%) gave desired azaindoles **15a–c**, **16a–d**, **17a–d** and **18a–e** in good yields.

2-(2-Methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine 15a. The product **15a** was produced as a cream white solid (0.1236 g, 92%). Mp: 125–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.30–8.20 (m, 1H), 7.93–7.87 (m, 1H), 7.84 (dd, J = 7.7, 1.5, 1H), 7.36–7.27 (m, 1H), 7.12–6.98 (m, 3H), 6.84 (d, J = 1.6, 1H), 3.98 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.08, 148.60, 142.91, 136.27, 129.31, 128.23, 128.04, 121.46, 120.66, 120.05, 116.14, 111.91, 98.09, 55.76; IR (cm^{-1}) 3234 (NH str.), 2933 (CH str.), 1626 (C═N), 1578 (C═C), 1179 (C–O); HRMS (ES^+) Calculated for $C_{14}H_{13}N_2O$ $[M + H]^+$: 225.1028, found 225.1042.

2-(4-Methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine 15b. The product **15b** was furnished as a cream white solid (0.1542 g, 88%). Mp: 182–184 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.35 (s, 1H), 8.25 (d, J = 3.3, 1H), 7.92 (d, J = 7.7, 1H), 7.82 (d, J = 8.8, 2H), 7.15–6.97 (m, 3H), 6.67 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.83, 149.92, 141.64, 139.57, 128.25, 127.21, 125.15, 122.56, 116.06, 114.52, 96.24, 55.44; IR (cm^{-1}) 3281 (NH str.), 2986 (CH str.), 1671 (C═N), 1594 (C═C), 1176 (C–O); HRMS (ES^+) Calculated for $C_{14}H_{13}N_2O$ $[M + H]^+$: 225.1028, found 225.1035.

2-(3-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine 15c. The azaindole **15c** was produced as a cream white solid (0.08213 g,

81%). Mp: 205–207 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.82 (s, 1H), 8.37 (s, 1H), 7.98 (d, J = 7.9, 1H), 7.86 (s, 1H), 7.72 (d, J = 7.5, 1H), 7.44 (t, J = 7.9, 1H), 7.37 (d, J = 7.8, 1H), 7.14 (s, 1H), 6.82 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.76, 143.05, 137.60, 135.14, 134.05, 130.36, 129.12, 128.18, 125.73, 123.79, 122.03, 116.56, 98.53; IR (cm^{-1}) 3255 (NH str.), 2987 (CH str.), 1631 (C=N), 1588 (C=C); HRMS (ES^+) Calculated for $C_{13}H_{10}N_2Cl$ $[M + H]^+$: 229.0533, found 229.0536.

5-Methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine 16a. The product **16a** was formed as a cream white solid[15] (86%). ^{1}H NMR (500 MHz, DMSO) δ 11.98 (s, 1H), 8.07 (d, J = 1.3, 1H), 7.93 (d, J = 7.5, 2H), 7.72 (s, 1H), 7.46 (t, J = 7.7, 2H), 7.34 (t, J = 7.4, 1H), 6.84 (d, J = 1.8, 1H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 148.33, 143.62, 138.25, 131.71, 128.84, 127.83, 127.56, 125.19, 124.37, 120.73, 96.49, 18.09.

2-(2-Methoxyphenyl)-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 16b. The desired azaindole **16b** was furnished as a cream white solid (0.1001 g, 94%). Mp: 169–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.10 (s, 1H), 7.83 (dd, J = 7.8, 1.6, 1H), 7.69 (s, 1H), 7.33–7.26 (m, 1H), 7.05 (ddd, J = 13.7, 10.3, 4.6, 2H), 6.75 (d, J = 2.0, 1H), 3.98 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.99, 147.26, 143.95, 136.31, 129.14, 128.10, 127.97, 125.04, 121.45, 120.41, 120.14, 111.91, 97.37, 55.75, 18.60; IR (cm^{-1}) 3240 (NH str.), 2981 (CH str.), 1624 (C=N), 1579 (C=C), 1178 (C–O); HRMS (ES^+) Calculated for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1184, found 269.1190.

2-(4-Methoxyphenyl)-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 16c. The product **16c** was produced as a cream white solid (0.1011 g, 85%). Mp: 245–247 °C; ^{1}H NMR (500 MHz, MeOD) δ 7.99 (s, 1H), 7.78 (d, J = 8.8, 2H), 7.75 (s, 1H), 7.04 (d, J = 8.8, 2H), 6.64 (s, 1H), 3.87 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 161.32, 149.06, 143.26, 140.97, 129.54, 129.51, 127.96, 126.28, 126.05, 115.41, 96.61, 55.83, 18.50; IR (cm^{-1}) 3298 (NH str.), 2972 (CH str.), 1635 (C=N), 1575 (C=C), 1168 (C–O); HRMS (ES^+) Calculated for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1184, found 239.1190.

2-(3-Chlorophenyl)-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 16d. The product **16d** was formed as a cream white solid (0.1012 g, 82%). Mp: 239–242 °C; ^{1}H NMR (500 MHz, DMSO) δ 12.07 (s, 1H), 8.10 (s, 1H), 8.03 (s, 1H), 7.90 (d, J = 7.7, 1H), 7.75 (s, 1H), 7.48 (t, J = 7.6, 1H), 7.39 (d, J = 7.8, 1H), 6.97 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 148.34, 144.28, 136.55, 133.85, 133.80, 130.69, 127.90, 127.46, 124.75, 124.63, 123.76, 120.52, 97.78, 18.07; IR (cm^{-1}) 3347 (NH str.), 2947 (CH str.), 1630 (C=N), 1587 (C=C); HRMS (ES^+) Calculated for $C_{14}H_{12}N_2Cl$ $[M + H]^+$: 243.0689, found 243.0697.

5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine 17a. The azaindole **17a** was yielded as a cream white solid[16] (0.1032 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.89 (s, 1H), 8.29 (d, J = 2.0, 1H), 7.94 (d, J = 2.0, 1H), 7.46–7.35 (m, 1H), 6.62–6.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.94, 141.20, 128.27, 126.86, 123.80, 121.28, 100.59; IR (cm^{-1}) 3288 (NH str.), 2969 (CH str.), 1629 (C=N), 1553 (C=C).

5-Chloro-2-(4-methoxy-2-methylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine 17b. The desired product **17b** was produced as a yellow solid (0.08109 g, 80%). Mp: 209–211 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.10 (s, 1H), 7.88 (s, 1H), 7.47 (d, J = 8.2, 1H), 6.89 (s, 2H), 6.44 (s, 1H), 3.88 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.87, 147.00, 140.74, 140.15, 137.90, 130.45, 127.34, 124.29, 123.95, 122.37, 116.68, 111.72, 99.84, 55.36, 21.28; IR (cm^{-1}) 3210 (NH str.), 2989 (CH str.), 1637 (C=N), 1571 (C=C), 1182 (C–O). HRMS (ES^+) Calculated for $C_{15}H_{14}N_2ClO$ $[M + H]^+$: 273.0795, found 273.0803.

(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl benzoate 18a. The azaindole **18a** was formed as a cream white solid (0.4211 g, 83%). Mp: 181–184 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.33 (s, 1H), 8.27 (d, J = 2.2, 1H), 8.15 (d, J = 2.2, 1H), 8.10–8.07 (m, 2H), 7.64 (t, J = 7.5, 1H), 7.50 (t, J = 7.8, 2H), 6.60 (s, 1H), 5.52 (s, 2H); ^{13}C NMR (126 MHz, MeOD) δ 167.67, 148.54, 144.41, 137.76, 134.49, 132.25, 131.11, 130.77, 130.71, 129.68, 123.83, 112.41, 101.66, 60.78; IR (cm^{-1}) 3368 (NH str.), 3000 (CH str.), 1605 (C=N), 1559 (C=C), 1164 (C–O); HRMS (ES^+) Calculated for $C_{15}H_{12}N_2BrO_2$ $[M + H]^+$: 331.0082, found 331.0100.

4-[(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl]morpholine 18b. The product **18b** formed as a cream white solid (0.159 g, 79%). Mp: 189–192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.37 (d, J = 2.1, 1H), 7.97 (d, J = 2.0, 1H), 6.28 (s, 1H), 3.78–3.70 (m, 6H), 2.59–2.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.70, 142.96, 138.67, 130.56, 123.04, 111.75, 99.65, 67.19, 56.72, 54.07; IR (cm^{-1}) 3223 (NH str.), 2969 (CH str.), 1640 (C=N), 1573 (C=C), 1140 (C–O); HRMS (ES^+) Calculated for $C_{12}H_{15}N_3BrO$ $[M + H]^+$: 296.0398, found 296.0401.

5-Bromo-2-(piperidin-1-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridine 18c. The azaindole **18c** was furnished as a cream white solid (0.1131 g, 83%). Mp: 194–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.35 (d, J = 2.1, 1H), 7.94 (d, J = 2.0, 1H), 6.23 (s, 1H), 3.65 (s, 2H), 2.43–2.38 (m, 4H), 1.66–1.53 (m, 4H), 1.46 (d, J = 4.9, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.50, 142.89, 139.93, 130.25, 123.12, 111.74, 98.93, 57.02, 55.11, 26.28, 24.55; IR (cm^{-1}) 3217 (NH str.), 2989 (CH str.), 1631 (C=N), 1572 (C=C); HRMS (ES^+) Calculated for $C_{13}H_{13}N_3Br$ $[M + H]^+$: 294.0606, found 294.0621.

2-[3,5-Bis(trifluoromethyl)phenyl]-5-bromo-1*H*-pyrrolo[2,3-*b*]-pyridine 18d. The azaindole **18d** was produced as a white solid (0.1009 g, 78%). Mp: 251–253 °C; ^{1}H NMR (500 MHz, acetone) δ 11.69 (s, 1H), 8.60 (s, 2H), 8.33 (d, J = 2.2, 1H), 8.21 (d, J = 2.2, 1H), 8.03 (s, 1H), 7.30 (s, 1H), 6.43 (s, 1H); ^{13}C NMR (126 MHz, acetone) δ 149.39, 145.63, 137.75, 134.97, 132.78, 131.55, 126.75, 126.72, 125.47, 123.56, 123.30, 122.19, 112.87, 100.82; IR (cm^{-1}) 3293 (NH str.), 2952 (CH str.), 1641 (C=N), 1576 (C=C); HRMS (ES^+) Calculated for $C_{15}H_8N_2BrF_6$ $[M + H]^+$: 408.9775, found 408.9764.

5-Bromo-2-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine 18e. The desired product **18e** was produced as a cream white solid (0.1069, 80%). Mp: 196–197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.30 (d, J = 1.7, 1H), 8.02 (d, J = 1.6, 1H), 7.84 (dd, J = 7.8, 1.6, 1H), 7.43–7.32 (m, 1H), 7.17–7.02 (m, 2H), 6.78 (d, J = 2.1, 1H), 4.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.08, 146.82, 143.27, 137.88, 129.87, 129.80, 128.24, 122.21, 121.55, 119.34, 111.96, 97.29, 55.81; IR (cm^{-1}) 3229 (NH str.), 2955 (CH str.), 1624 (C=N), 1576 (C=C), 1160

(C–O); HRMS (ES^+) Calculated for $C_{14}H_{12}N_2BrO$ $[M + H]^+$: 303.0133, found 303.0146.

3-(Phenylethynyl)-5-[(trimethylsilyl)ethynyl]pyridin-2-amine 19. To a flame-dried round-bottom flask under an argon atmosphere containing 2-amino-3-iodopyridine derivative **10** (1.379 g, 4.61 mmol) was added CuI (0.01756 g, 2 mol%) and $Pd(PPh_3)_4$ (0.1066 g, 2 mol%) in one portion followed by the addition of a degassed phenylacetylene solution in THF (0.4702 g, 4.61 mmol). Triethylamine (5 ml) was then added and the reaction mixture was stirred at rt, until no starting material was present as monitored by thin layer chromatography (TLC). After this time, the reaction was quenched with a saturated aqueous ammonium chloride and was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered through either silica or celite and the excess solvent was removed on a rotary evaporator. The resulting crude material was taken up in dry THF (20 ml) and treated with trimethylsilylacetylene (5 ml), Et_3N (5 ml), CuI (17.56 mg), $Pd(PPh_3)_4$ (0.1066 g) and the reaction mixture was heated to 70 °C. After 8 h the reaction mixture was worked up as described previously, followed by purification using flash chromatography (30% EthOAc–hexane) to afford **19** as a yellowish solid (1.139 g, 85%). Mp: 155–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 1.9, 1H), 7.71 (d, J = 2.1, 1H), 7.57–7.46 (m, 2H), 7.37 (dd, J = 9.6, 6.1, 3H), 5.34 (d, J = 23.2, 2H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.79, 151.11, 142.72, 131.56, 128.89, 128.53, 122.35, 109.63, 102.85, 101.84, 95.90, 94.99, 83.38, 0.01; IR (cm^{-1}) 3283 (NH str.), 2956 (CH str.), 2144 (alkyne), 1625 (C═N), 1583 (C═C); HRMS (ES^+) Calculated for $C_{18}H_{18}N_2Si$ $[M + H]^+$: 291.2238, found 291.2237.

2-Phenyl-5-[(trimethylsilyl)ethynyl]-1*H*-pyrrolo[2,3-*b*]pyridine 20. The forgoing 2-amino-3-ethynylpyridine derivative **19** (0.5513 g, 1.90 mmol) was dissolved in MeCN. To the resulting solution was added trifluoroacetic acid (0.2164 g, 0.15 ml, 1.90 mmol) in one portion followed by the addition of trifluoroacetic anhydride (0.5187 g, 0.35 ml, 2.47 mmol) dropwise. The resulting mixture was then heated to reflux for 8 h and then allowed to cool to rt. The solvent was then removed on a rotary evaporator and the resulting crude material was re-dissolved in dichloromethane and washed with aqueous sodium carbonate (10%). Purification by flash silica using ethyl acetate–hexane mixture (10–50%) gave 2-phenyl-5-[(trimethylsilyl)ethynyl]-1*H*-pyrrolo[2,3-*b*]pyridine **20** (0.4236 g, 91%). Mp: 255–258 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.56 (s, 1H), 8.40 (d, J = 1.7, 1H), 8.05 (d, J = 1.6, 1H), 7.85–7.76 (m, 2H), 7.53 (t, J = 7.7, 2H), 7.47–7.38 (m, 1H), 6.75 (d, J = 2.0, 1H), 0.30 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.74, 146.08, 140.24, 131.93, 131.78, 129.19, 128.64, 125.75, 121.46, 112.42, 103.65, 97.73, 94.57, 0.06; IR (cm^{-1}) 3249 (NH str.), 2957 (CH str.), 1609 (C═N), 1586 (C═C); HRMS (ES^+) Calculated for $C_{18}H_{19}N_2Si$ $[M + H]^+$: 291.1318, found 291.1327.

Antimicrobial activity

The substituted azaindoles were quantitatively evaluated for antimicrobial activity using the minimum inhibitory concentration (MIC) assay.[18] The azaindoles were tested against a number of reference test organisms including Gram-positive (*Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 25923), Gram-negative (*Pseudomonas aeruginosa* NCTC 9027, *Escherichia coli* ATCC 8739 and *Klebsiella pneumoniae* ATCC 13883) and yeasts (*Candida tropicalis* ATCC 201380, *Candida albicans* ATCC 10231 and *Cryptococcus neoformans* ATCC 90112). The positive control used for the bacteria was ciprofloxacin, while that used for the yeasts was amphotericin. The solvent (acetone) was included in the assay as a negative control. All antimicrobial assays were undertaken at least in duplicate or triplicate where necessary.

Acknowledgements

This work was supported by the National Research Foundation (NRF, GUN 2053652 and IRDP of the NRF (South Africa) for financial support provided by the Research Niche Areas programme), Pretoria, and the University of the Witwatersrand (Science Faculty Research Council). We also gratefully acknowledge the NRF scarce skills programme and the CSIR scholarship scheme for generous funding to TCL. Dr R Mampa (University of the Witwatersrand) and Dr P Steenkamp (CSIR, Pretoria) are thanked for providing the NMR and HRMS MS spectroscopy services, respectively.

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