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A highly effective synthesis of 2-alkynyl-7-azaindoles: Pd/C-mediated alkynylation of heteroaryl halides in water

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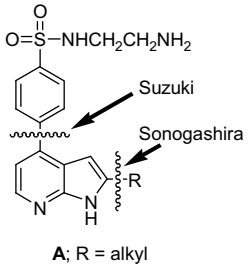
ABSTRACT

The reaction of 4-chloro-2-iodo-7-azaindole with terminal alkynes was investigated using 10% Pd/C–PPh_3–CuI as a catalyst system in water. This study afforded a new, mild and selective process for the preparation of 2-alkynyl-4-chloro-7-azaindole in good yields via C–C bond forming reaction. The resulting chloro derivative can be functionalized further via another Pd-mediated C–C bond forming reaction with arylboronic acid.

1. Introduction

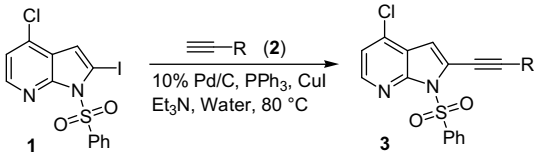
7-Azaindole (1*H*-pyrrolo[2,3-*b*]pyridine), a member of azaindole family, is considered as a bioisostere of indole or purine moiety and constitutes core subunits in many bioactive molecules.[1] Though unlike indoles their occurrence is less common in natural products synthesis of 7-azaindoles, however, attracted considerable interest due to their physicochemical and pharmacological properties. For example, 2-substituted 4-aryl-7-azaindoles represented by general structure **A** (Fig. 1) have been reported as inhibitors of kinase activity.[2] Also, 7-azaindoles have been explored as inhibitors[3a] of PDE-4 that are useful for the potential treatment of rheumatoid arthritis, COPD (chronic obstructive pulmonary disease), asthma and rhinitis.[3b] A retrosynthetic analysis revealed that compound **A** can be prepared via a combination of Sonogashira and Suzuki coupling reactions as shown in Figure 1.



A; R = alkyl

Figure 1. 7-Azaindole derivatives of pharmacological interest and strategy for their synthesis.

While a number of conventional methods are available for the synthesis of 2-substituted 7-azaindoles recent advances in transition-metal catalyzed reactions however have enabled chemists to develop a range of novel and efficient methodologies.[1,4] These include (i) construction of the five-membered ring via a two-step process, i.e., Sonogashira coupling followed by cyclization of the resulting alkyne and (ii) transition-metal mediated functionalization at C-2 of 7-azaindole ring. Thus, Pd-mediated coupling of 2-iodo-7-azaindole has been carried out with (i) $ArB(OH)_2$ (Suzuki reaction, 49–86% yield), (ii) aryl-, vinyl- and allylstannanes (Stille coupling, 49–84% yield) and (iii) $RCH{=}CH_2$ (Heck reaction, 52–92% yield) to afford 2-substituted derivatives.[5] Surprisingly, Sonogashira coupling of 2-iodo-7-azaindole with terminal alkynes is less common and has not been explored as a general methodology for the synthesis of 2-substituted 7-azaindoles earlier. Due to our continued interest in the Pd/C-mediated alkynylation of heteroaryl halides via C–C bond forming reactions[6–9] we now wish to report a highly efficient and practical method for the synthesis of 2-alkynyl-7-azaindoles (**3**) from 2-iodo-7-azaindole (**1**) and terminal alkynes (**2**) using 10% Pd/C–PPh_3–CuI as a catalyst system in water (Scheme 1).



Scheme 1. Pd/C-mediated alkynylation of 2-iodo-7-azaindole (**1**) in water.

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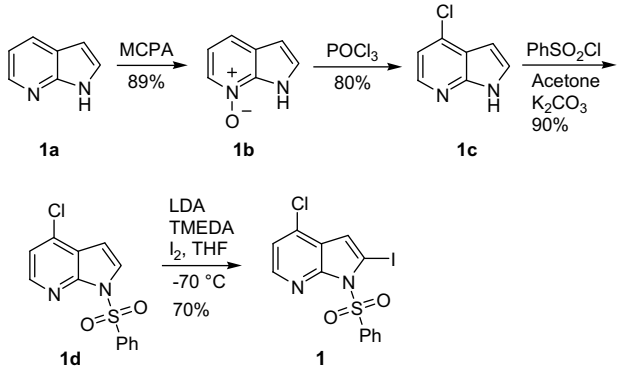
2. Results and discussion

We selected 1-benzenesulfonyl-4-chloro-2-iodo-7-azaindole (**1**) as our starting material with the aim that chloro group of the resultant product can be exploited for further functionalization towards the synthesis of **A** (Fig. 1). Compound **1** was prepared by treating 4-chloro-7-azaindole[10,11] (**1c**) with benzenesulfonyl chloride in the presence of K_2CO_3 followed by iodination of the resulting compound **1d** in the presence of LDA (lithium diisopropylamide) and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) at a low temperature (Scheme 2). Compound **1c** in turn can be prepared from **1a** according to a known procedure.[10]



Scheme 2. Pd/C-mediated alkynylation of 2-iodo-7-azaindole (**1**) in water.

We then examined the reaction of **1** with a terminal alkyne, i.e., but-3-yn-1-ol (**2a**) using 10% Pd/C–PPh_3–CuI as a catalyst system (Table 1). Initially, a number of organic solvents including water were examined to identify a suitable solvent for the present C–C bond forming reaction between **1** and **2a**. These reactions were generally carried out at 80 °C and monitored by TLC until the halide (**1**) disappeared completely. Among the solvents examined, the use of DMF (entry 1, Table 1) and acetonitrile (entry 2, Table 1) in the presence of Et_3N provided the desired product **3a** albeit in moderate yields. However, the use of water increased the yield significantly and **3a** was isolated in 85% yield within 3 h (entry 3, Table 1). Yield was decreased when Et_3N was replaced by other bases such as 2-ethanolamine (entry 4, Table 1) and DIPA (entry 5, Table 1). Thus, because of easy availability of water and more importantly, to omit the use of environmentally harmful and expensive organic solvents we choose to use water as a solvent for our further studies. Accordingly, a variety of terminal alkynes (**2a**–**j**) were coupled with **1** and results of this study are summarized in Table 2.

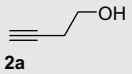
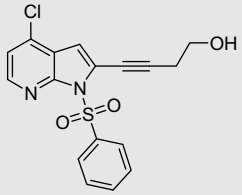
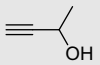
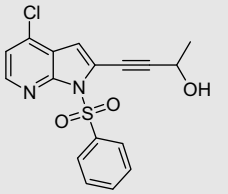
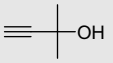
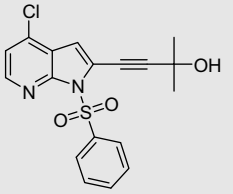
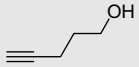
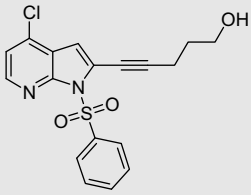
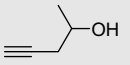
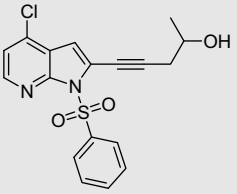
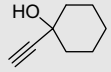
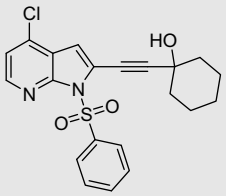
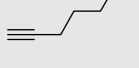
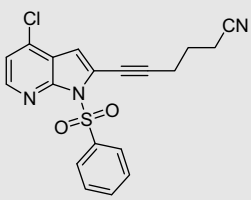
As can be seen from Table 2 the reaction proceeded well with both aliphatic (entries 1–7, Table 2) and aromatic alkynes (entries 8–10, Table 2). A cyano group on the alkyl side chain (entry 7, Table 2) or a free amine on the aromatic ring (entry 10, Table 2) was well tolerated. All the reactions were generally completed within 3–8 h irrespective of the nature of substituents present in the terminal

Table 1
Effect of bases/solvents on the coupling reaction of 1-benzenesulfonyl-2-iodo-7-azaindole (**1**) with but-3-yn-1-ol (**2a**)[a]

Entry	Solvent; base	Time (h)	Yield[b] (%)
1	DMF; Et_3N	12.0	55
2	CH_3CN; Et_3N	10.0	60
3	H_2O; Et_3N	3.0	85
4	H_2O; 2-aminoethanol	36.0	30
5	H_2O; DIPA	36.0	20

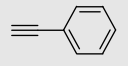
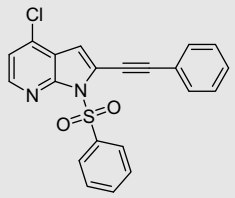
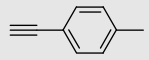
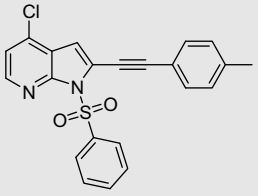
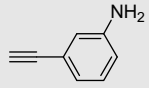
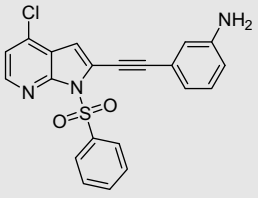
[a] All reactions were carried out by using **1** (1.0 equiv), **2** (1.5 equiv), 1:4:2 ratio of 10% Pd/C–PPh_3–CuI and a base (5.0 equiv) at 80 °C.
[b] Isolated yields.

Table 2
Pd/C-mediated synthesis of 2-alkynyl 7-azaindoles (**3**) in water[a]

Entry	Alkynes (**2**)	Products (**3**)		Reaction Time (h)	Yield[b] (%)
1	 **2a**		**3a**	3.0	85
2	 **2b**		**3b**	3.5	75
3	 **2c**		**3c**	3.0	70
4	 **2d**		**3d**	4.0	80
5	 **2e**		**3e**	3.0	80
6	 **2f**		**3f**	5.0	60
7	 **2g**		**3g**	3.0	80

(*continued on next page*)

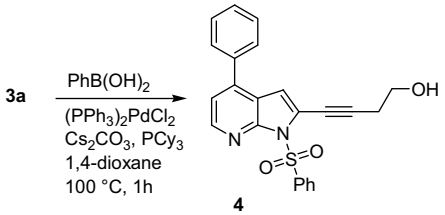
Table 2 (*continued*)

Entry	Alkynes (**2**)	Products (**3**)	Reaction Time (h)	Yield[b] (%)
8	 **2h**	 **3h**	8.0	81
9	 **2i**	 **3i**	6.0	85
10	 **2j**	 **3j**	4.0	90

[a] All reactions were carried out by using **1** (1.0 equiv), **2** (1.5 equiv), 1:4:2 ratio of 10% Pd/C–PPh_3–CuI and Et_3N (5 equiv) in water at 80 °C.
[b] Isolated yields.

alkynes (**2a**–**j**) affording the desired products (**3a**–**j**) in good to excellent yields.

We have shown that 1-benzenesulfonyl-4-chloro-2-iodo-7-azaindole (**1**) participated in Pd/C-mediated C–C bond forming reactions smoothly with a variety of commercially available alkynes in water. The process allowed selective replacement of iodo group by an acetylenic moiety to provide the chloro derivative **3**. Since preparation of compound **A** (Fig. 1) requires installation of an appropriate aryl group at the C-4 position of **3** hence we examined the coupling reaction of **3a** with phenyl boronic acid under Suzuki condition. To our delight the reaction proceeded smoothly without affecting the other functional groups present in **3a** and afforded the desired product **4** in 65% yield (Scheme 3). Notably, this is the first example of Suzuki coupling reaction[12] where 4-chloro derivative of 2-alkynyl-7-azaindole was employed as a halide component.



Scheme 3. Suzuki coupling of **3a** with phenyl boronic acid.

3. Conclusion

In conclusion, we have developed a novel and easy access to 2-alkynyl-7-azaindoles, synthesis of which may be tedious or cumbersome via other routes. A combination of Pd/C-mediated selective alkynylation of 4-chloro-2-iodo-7-azaindole followed by Suzuki coupling of the resulting chloro derivative provided the desired product. A detailed study was carried out on the alkynylation step. Thus, 2-iodo-7-azaindole was reacted with a variety of terminal alkynes in the presence of 10% Pd/C–PPh_3–CuI as a catalyst system in water to provide the corresponding 2-alkynyl derivatives. Further application of this methodology is under active investigation.

4. Experimental

4.1. General

Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^1H and ^{13}C NMR spectra were determined in DMSO-d_6 solution using 400 and 200 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.0) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as br (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on an FTIR spectrometer. Melting points were determined by using thermal analysis and differential scanning calorimetry (DSC) was generated with the help of DSC-60A detector. MS spectra were obtained on a mass spectrometer. Chromatographic (HPLC) purity was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength and retention times. All the reagents used are commercially available except compound **1** that was prepared according to a known procedure[10,11] described below.

4.2. General procedure for the preparation of 7-azaindole *N*-oxide 3-chlorobenzoate (1b)

To a solution of 7-azaindole (10.0 g, 0.084 mol) in DME/heptane (1:2, 150 mL) was added 3-chloroperbenzoic acid (85 wt %, 2.66 g, 0.101 mol) portion wise at 8 °C. Precipitation of solid was observed and the resulting slurry was stirred at room temperature for 2.5 h. The solid separated was filtered, washed with DME/heptane (1:2, 50 mL) and dried to afford the desired product as off white solid (21.9 g, 89.2 %); mp 144–146 °C (lit[10] 142–145 °C); ^1H NMR (DMSO-d_6, 400 MHz) δ13.22 (br s, 1H), 12.53 (s, 1H), 8.16 (d, J=6.2 Hz, 1H), 7.86–7.93 (m, 2H), 7.63–7.72 (m, 2H), 7.54 (t, J=8.0 Hz, 1H), 7.46 (d, J=3.0 Hz, 1H), 7.07 (dd, J=6.3 and 1.4 Hz, 1H), 6.58 (d, J=3.1 Hz, 1H), 6.39 (d, J=3.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 102.6, 116.5, 120.6, 124.4, 126.9, 128.2, 129.2, 130.9, 131.5, 132.5, 133.3, 133.7, 138.6, 166.5.

4.3. General procedure for the preparation of 4-chloro-7-azaindole (1c)

A mixture of 7-azaindole *N*-oxide 3-chlorobenzoate (**1b**) (20.0 g, 0.068 mol) in $POCl_3$ (0.506 mol) was heated at 85–90 °C for 18.0 h. The solution was cooled to 50 °C and $POCl_3$ was distilled off under vacuum. The residue was dissolved in acetonitrile (50.0 mL) and quenched with slow addition of water (50.0 mL) maintaining the temperature below 50 °C. The mixture was then basified to pH ~9 by using a 50% aqueous solution of NaOH. The slurry was cooled to room temperature, and the solid precipitated was filtered, washed with water (50.0 mL) and dried under vacuum to afford the desired product as off white solid (8.4 g, 80.0 %). Mp 175–177 °C (lit.[10] 172–175 °C); ^1H NMR (DMSO-d_6, 400 MHz) δ12.07 (s, 1H), 8.18 (d, J=5.2 Hz, 1H), 7.59 (d, J=3.2 Hz, 1H), 7.16 (d, J=5.2 Hz, 1H), 6.50 (d, J=3.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 97.9, 115.1, 118.6, 127.2, 134.0, 143.1, 149.0; Mass (ES) m/z 293 (M+1, 100%).

4.4. General procedure for the preparation of 4-chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1d)

To a mixture of 4-chloro-7-azaindole (**1b**) (6.0 g, 0.039 mol) and K_2CO_3 (13.45 g, 0.097 mol) in acetone (180.0 mL) was added $PhSO_2Cl$ (13.77 g, 0.058 mol) drop wise at 0 °C. The reaction mixture was stirred for 1.0 h at same temperature and then refluxed for 24.0 h. The solution was filtered at 30 °C, the filtrate was collected and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (120 mL), washed with water (2×30 mL) followed by saturated brine (2×25 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product isolated was purified by column chromatography on silica gel using 25% ethyl acetate/*n*-hexane to afford the desired product as off white solid (10.4 g, 90.0%); mp 120 °C; R_f (20% acetone/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.34 (d, *J*=5.2 Hz, 1H), 8.13–8.11 (m, 2H), 8.04 (d, *J*=3.6 Hz, 1H), 7.76–7.62 (m, 3H), 7.48 (d, *J*=5.0 Hz, 1H), 6.88 (d, *J*=4.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 103.3, 119.2, 121.2, 127.5 (2C), 127.9, 129.6 (2C), 134.8, 135.5, 137.0, 145.5, 146.8; IR (cm^{-1}, KBr) 3144, 1368, 1173; Mass (ES) *m*/*z* 293 (M+1, 100%); HPLC 97.9%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 21.53 min; HRMS (ESI) calcd for $C_{13}H_{10}N_2O_2SCl$ $(M+H)^+$ 293.0110, found 293.0111.

4.5. General procedure for the preparation of 4-chloro-2-iodo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1)

LDA was freshly prepared by adding *n*-butyl lithium (0.018 mol) drop wise to a solution of diisopropyl amine (0.018 mol) in THF (250.0 mL) at −40 °C. A mixture of **1d** (5.0 g, 0.017 mol) and TMEDA (0.017 mol) in THF (100.0 mL) was cooled to −70 °C separately. Freshly prepared LDA solution was then added drop wise to it at −70 °C. After 1.0 h, a solution of iodine in THF was added drop wise at −70 °C. After completion of the reaction, the mixture was quenched with ammonium chloride solution and extracted with ethyl acetate (3×250 mL). The combined organic layer was washed with saturated aq NaCl (2×100 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography on silica gel using 30% ethyl acetate/*n*-hexane to afford the desired product as an off white solid (5.0 g, 70.0 %); mp 135 °C. R_f (25% acetone/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.19 (d, *J*=5.3 Hz, 1H), 8.0 (dd, *J*=7.3 and 1.5 Hz, 2H), 7.73–7.66 (m, 3H), 7.56 (d, *J*=5.3 Hz, 1H), 7.19 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 82.85, 117.0, 119.5, 122.3, 127.3 (2C), 129.6 (2C), 133.4, 134.9, 137.5, 144.9, 149.2; IR (cm^{-1}, KBr) 3122, 1350, 1154; Mass (ES) *m*/*z* 418.0 (M+1, 100%); HPLC 98.1%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 23.5 min; HRMS (ESI): calcd for $C_{13}H_9N_2O_2SCl$ $(M+H)^+$ 418.9121, found 418.9122.

4.6. General procedure for the preparation of 2-alkynyl 7-azaindoles (3)

A mixture of compound **1** (300.0 mg, 0.71 mmol), 10% Pd/C (37.98 mg, 0.03 mmol), PPh_3 (37.37 mg, 0.14 mmol), CuI (13.58 mg, 0.07 mmol) and Et_3N (3.58 mmol) in water (8.0 mL) was stirred for 1.0 h under nitrogen. The acetylenic compound **2** (1.07 mmol) was added and the mixture was stirred according to the conditions mentioned in Table 2. After completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and filter through Celite. Filtrate was collected and extracted with ethyl acetate (2×50 mL). The organic layers were collected, combined, washed with saturated aqueous NaCl solution (2×25 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product isolated was purified by column chromatography on silica gel using hexane–ethyl acetate to afford the desired product.

4.7. 4-(4-Chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)but-3-yn-1-ol (3a)

This compound was obtained as light yellow solid; mp 134–135 °C; R_f (35% acetone/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.39 (d, *J*=5.4 Hz, 1H), 8.09 (dd, *J*=7.3 and 1.5 Hz, 2H), 7.72 (m, 1H), 7.62 (m, 2H), 7.48 (d, *J*=5.4 Hz, 1H), 7.07 (s, 1H), 4.98 (t, *J*=5.9 Hz, 1H), 3.68 (m, 2H), 2.72 (t, *J*=6.8 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.8, 59.2, 71.3, 99.3, 110.2, 119.8 (2C), 121.9, 127.2 (2C), 129.6 (2C), 134.8, 134.9, 137.8, 146.3, 147.5; IR (cm^{-1}, KBr) 3432, 3019, 2235, 1216; Mass (ES) *m*/*z* 361.0 (M+1, 100%); HPLC 98.3%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 18.2 min; HRMS (ESI): calcd for $C_{17}H_{14}N_2O_3SCl$ $(M+H)^+$ 361.0414, found 361.0420.

4.8. 4-(4-Chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)but-3-yn-2-ol (3b)

This compound was obtained as low melting solid; R_f (30% acetone/*n*-hexane) 0.35; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.41 (d, *J*=5.4 Hz, 1H), 8.08 (dd, *J*=7.3 and 1.5 Hz, 2H), 7.76–7.66 (m, 3H), 7.49 (d, *J*=5.2 Hz, 1H), 7.12 (s, 1H), 5.68 (d, *J*=5.4 Hz, 1H), 4.71 (m, 1H), 1.48 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.9, 56.9, 72.5, 102.7, 110.7, 119.8, 119.9, 121.4 (2C), 125.1 (2C), 129.7, 134.9, 135.1, 137.7, 146.6, 147.7; IR (cm^{-1}, $CHCl_3$) 3685, 3019, 2400, 1215; Mass (ES) *m*/*z* 361.0 (M+1, 100%); HPLC 98.1%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 15.52 min; HRMS (ESI): calcd for $C_{17}H_{14}N_2O_3SCl$ $(M+H)^+$ 361.0414, found 361.0416.

4.9. 4-(4-Chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-2-methylbut-3-yn-2-ol (3c)

This compound was obtained as low melting yellow solid; R_f (35% acetone/*n*-hexane) 0.4; ^{1}H NMR (DMSO-d_6, 400 MHz) 8.42 (d, *J*=5.4 Hz, 1H), 8.08 (dd, *J*=7.3 and 1.2 Hz, 2H), 7.74–7.63 (m, 3H), 7.52 (d, *J*=5.1 Hz, 1H), 7.11 (s, 1H), 5.56 (br s, 1H), 1.56 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) 30.3, 31.0, 70.9, 85.6, 105.2, 110.0, 119.8, 119.9, 121.5, 127.1 (2C), 129.7 (2C), 134.9, 135.0, 137.8, 146.6, 147.7; IR (cm^{-1}, KBr) 3425, 2924, 2247, 1366, 1186; Mass (ES) *m*/*z* 375.0 (M+1, 100 %); HPLC 97.6%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 19.9 min; HRMS (ESI): calcd for $C_{18}H_{16}N_2O_3SCl$ $(M+H)^+$ 375.0570, found 375.0579.

4.10. 5-(4-Chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)pent-4-yn-1-ol (3d)

This compound was obtained as low melting brown solid; R_f (35% acetone/*n*-hexane) 0.35; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.39 (d, *J*=5.4 Hz, 1H), 8.04 (dd, *J*=7.3 and 1.5 Hz, 2H), 7.72–7.61 (m, 3H), 7.48 (d, *J*=5.1 Hz, 1H), 7.07 (s, 1H), 3.57 (m, 3H), 2.63 (t, *J*=6.9 Hz, 2H), 1.75 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.8, 22.0, 59.3, 70.6, 101.2, 110.1, 119.8 (2C), 122.0, 127.1 (2C), 129.7 (2C), 134.8, 134.9, 137.8, 146.3, 147.6 IR (cm^{-1}, $CHCl_3$) 3647, 3020, 2233, 1215; Mass (ES) *m*/*z* 375.0 (M+1, 100%); HPLC 97.8%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/

5, flow: 1.0 mL/min, UV 220 nm, retention time 18.9 min; HRMS (ESI): calcd for $C_{18}H_{16}N_2O_3SCl$ $(M+H)^+$ 375.0570, found 375.0575.

4.11. 5-(4-Chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)pent-4-yn-2-ol (3e)

This compound was obtained as white solid, mp 111–112 °C; R_f (30% acetone/*n*-hexane) 0.35; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.39 (d, J=5.4 Hz, 1H), 8.09 (dd, J=8.3 and 1.2 Hz, 2H), 7.72–7.61 (m, 3H), 7.48 (d, J=5.3 Hz, 1H), 7.08 (s, 1H), 4.94 (d, J=4.4 Hz, 1H), 3.94 (m, 1H), 2.65 (m, 2H), 1.27 (d, J=6.1 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 22.8, 29.8, 64.9, 71.8, 99.0, 110.3, 119.8 (2C), 122.1, 127.2 (2C), 129.6 (2C), 134.8, 134.9, 137.8, 146.3, 147.5; IR (cm^{-1}, KBr) 3436, 2925, 2233, 1360, 1178; Mass (ES) m/z 375.0 (M+1, 100%); HPLC 97.9%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 19.5 min; HRMS (ESI): calcd for $C_{18}H_{16}N_2O_3SCl$ $(M+H)^+$ 375.0570, found 375.0575.

4.12. 1-((4-Chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)ethynyl)cyclohexanol (3f)

This compound was obtained as low melting brown solid; R_f (30% acetone/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) 8.41 (d, J=5.4 Hz, 1H), 8.08 (dd, J=8.3 and 1.2 Hz, 2H), 7.73–7.63 (m, 3H), 7.49 (d, J=5.3 Hz, 1H), 7.10 (s, 1H), 5.65 (s, 1H), 1.41–2.08 (m, 10H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 22.5 (2C), 24.6, 24.8, 67.0, 67.4, 72.8, 104.5, 110.7, 119.9 (2C), 121.6, 127.1 (2C), 129.7 (2C), 134.9 (2C), 137.8, 146.5, 147.6; IR (cm^{-1}, $CHCl_3$) 3427, 3019, 2400, 2222, 1215; Mass (ES) m/z 415.0 (M+1, 100%); HPLC 98.6%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 23.1 min; HRMS (ESI): calcd for $C_{21}H_{20}N_2O_3SCl$ $(M+H)^+$ 415.0883, found 415.0864.

4.13. 6-(4-Chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)hex-5-ynenitrile (3g)

This compound was obtained as low melting brown solid; R_f (20% acetone/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) 8.39 (d, J=5.1 Hz, 1H), 8.05 (dd, J=8.4 and 1.2 Hz, 2H), 7.62–7.75 (m, 3H), 7.49 (d, J=5.3 Hz, 1H), 7.14 (s, 1H), 2.40 (t, J=7.0 Hz, 2H), 1.92 (t, J=7.0 Hz, 2H), 1.75 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.6, 23.6, 23.7, 76.6, 98.9, 110.8, 119.8, 119.9, 120.1, 121.7, 127.2 (2C), 129.7 (2C), 134.9 (2C), 137.7, 146.5, 147.6; IR (cm^{-1}, KBr) 2924, 2247, 1186, 1215; Mass (ES) m/z: 384.0 (M+1, 100%); HPLC 98.7%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 21.8 min; HRMS (ESI): calcd for $C_{19}H_{15}N_3O_2SCl$ $(M+H)^+$ 384.0574, found 384.0573.

4.14. 4-Chloro-2-(phenylethynyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3h)

This compound was obtained as white solid, mp 165 °C; R_f (20% acetone/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) 8.43 (d, J=5.4 Hz, 1H), 8.10 (dd, J=7.3 and 1.5 Hz, 2H), 7.73–7.69 (m, 5H), 7.50–7.56 (m, 4H), 7.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 74.6, 98.0, 111.2 (2C), 119.9 (2C), 121.1, 121.2, 127.1 (2C), 128.9 (2C), 129.8 (2C), 131.3 (2C), 134.9, 135.2, 137.7, 146.8, 147.8; IR (cm^{-1}, KBr) 3428, 2096, 2400, 1638, 1196; Mass (ES) m/z: 393 (M+1, 100%); HPLC 97.7%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 26.7 min; HRMS (ESI): calcd for $C_{21}H_{14}N_2O_2SCl$ $(M+H)^+$ 393.0465, found 393.0459.

4.15. 4-Chloro-1-(phenylsulfonyl)-2-(*p*-tolylethynyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3i)

This compound was obtained as yellow solid; mp 205 °C; R_f (20% acetone/*n*-hexane) 0.35; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.40 (d, J=5.4 Hz, 1H), 8.10 (dd, J=8.4 and 1.2 Hz, 2H), 7.54–7.72 (m, 5H), 7.45 (d, J=4.9 Hz, 1H), 7.32 (d, J=8.0 Hz, 2H), 7.17 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 73.1, 97.8, 110.1 (2C), 118.2 (2C), 121.8, 121.9, 127.6 (2C), 128.8 (2C), 128.9 (2C), 130.7 (2C), 135.1, 135.5, 137.2, 144.3, 145.9; IR (cm^{-1}, KBr) 3118, 2210, 1383, 1183; Mass (ES) m/z: 407 (M+1, 100%); HPLC 98.3%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 27.98 min; HRMS (ESI): calcd for $C_{22}H_{15}N_2O_2SCl$ $(M+H)^+$ 407.0621, found 407.0621.

4.16. 3-((4-Chloro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)ethynyl)aniline (3j)

This compound was obtained as light green solid; mp 190 °C; R_f (40% acetone/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.42 (d, J=5.4 Hz, 1H), 8.08 (dd, J=7.3 and 1.2 Hz, 2H), 7.73–7.64 (m, 3H), 7.51 (d, J=5.4 Hz, 1H), 7.26 (s, 1H), 7.12 (t, J=8.0 Hz, 1H), 6.86 (s, 1H), 6.79 (d, J=7.6 Hz, 1H), 6.68 (d, J=8.1 Hz, 1H), 5.32 (br s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 78.2, 99.3, 110.7, 115.9 (2C), 118.8, 119.9, 120.0, 121.6 (2C), 127.1 (2C), 129.4, 129.8 (2C), 134.9 (2C), 135.1, 137.7, 146.6, 147.8; IR (cm^{-1}, KBr) 3447, 3358, 3030, 2205, 1377, 1190; Mass (ES) m/z: 408 (M+1, 100%); HPLC 97.6%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 18.2 min; HRMS (ESI): calcd for $C_{21}H_{15}N_3O_2SCl$ $(M+H)^+$ 408.0574, found 408.0586.

4.17. Preparation of 4-phenyl-2-(phenylethynyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (4)

A mixture of **3a** (0.254 mmol), aq Cs_2CO_3 (1.0 mmol), PCy_3 (0.012 mmol) and $(PPh_3)_2PdCl_2$ (0.012 mmol) in 1,4-dioxane (2.0 mL) was stirred for 10 min under nitrogen. Then phenyl boronic acid (0.381 mmol) was added and the mixture was stirred at 100 °C for 1.0 h. After completion of the reaction, the mixture was cooled to room temperature and extracted with ethyl acetate (3×20 mL). The organic layers were collected, combined, washed with saturated aq NaCl (2×5 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography on silica gel using 30% ethyl acetate/hexane to afford the desired product as white solid; mp 142 °C; R_f (40% acetone/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.4 (d, J=5.6 Hz, 1H), 8.09 (m, 3H), 7.62–7.77 (m, 5H), 7.49 (d, J=5.2 Hz, 2H), 7.10 (s, 1H), 5.0 (t, J=5.6 Hz, 1H), 3.68 (m, 2H), 2.73 (t, J=6.8 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.8, 59.3, 71.7, 98.3, 112.0, 118.3, 118.6, 121.4, 127.2 (2C), 128.3 (2C), 129.0 (2C), 129.5 (2C), 134.6 (2C), 136.2, 138.1, 141.6, 145.9, 145.8; IR (cm^{-1}, KBr) 3432, 3019, 2238, 1210; Mass (ES) m/z 403.0 (M+1, 100%); HPLC 98.1%, column: Luna C 18 (150×4.6 mm), mobile phase A: 0.05% TFA in water; mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/5, 25/85, 30/95, 31/5, flow: 1.0 mL/min, UV 220 nm, retention time 22.1 min; HRMS (ESI): calcd for $C_{23}H_{19}N_2O_3S$ $(M+H)^+$ 403.1116, found 403.1132.

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