Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Synthesis and biological evaluation of 2,3-Bis(het)aryl-4-azaindoles Derivatives as protein kinases inhibitors

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Content

General methods.

^{1}H NMR and ^{13}C NMR spectra were recorded on a broker DPX 250 or 400 MHz instrument using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in parts per million (δ scale) and all coupling constant (J) values are in Hertz (Hz). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sept (septuplet), m (multiplet) and dd (doublet doublet). Melting points are uncorrected. IR absorption spectra were obtained on a Perkin Elmer PARAGON 1000 PC and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. HRMS were performed by the Centre Commun de Spectrométire de Masse (Clermont Ferrand, France). Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualized by UV light at 254 nm and 356 nm and revealed with $KMnO_4$ solution. Column chromatographies were performed using silica gel 60 (0.063 – 0.200 mm, Merck).

Synthesis of ketones 8 to 16.

General procedure A: To a solution of picoline **II** (10.0 mmol) and ester **III** (10.0 mmol) in 20 mL of anhydrous THF at 0°C was added dropwise a solution of LiHMDS 1M in THF (20.0 mmol) for 15 minutes. The resulting solution was stirred at room temperature over night under N_2 atmosphere. Then, the solvent was evaporated under reduce pressure and the residue was diluted in AcOEt. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated. To cleave the TBS group, the crude product was diluted in 60 mL of THF and treated by a solution of TBAF 1M in THF (20.0 mmol). The reaction was stirred for 2 h at room temperature and concentrated. Ketones **8** to **16** was purified by chromatography on a silica gel using a mixture of petroleum ether/AcOEt allowing an effective separation.

1-(2-Hydroxyphenyl)-2-(pyridine-4-yl)ethanone (9).

Compound **9** was obtained as a yellow solid in 41% yield following the general procedure A. R_f (AcOEt): 0.26; mp: 78°C; IR (ATR diamond): ν (cm^{-1}) 994, 1160, 1220, 1271, 1333, 1413, 1488, 1604, 1638, 1720; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 4.30 (s, 2H), 6.92 (ddd, 1H, J = 8.1, 7.2 and 1.2 Hz), 7.00 (d, 1H, J = 8.4 Hz), 7.20 (d, 2H, J = 5.8 Hz), 7.50 (ddd, 1H, J = 8.4, 7.2 and 1.6 Hz), 7.79 (dd, 1H, J = 8.1 and 1.6 Hz), 8.58 (d, 2H, J = 5.8 Hz), 12.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 44.5 (CH_2), 119.0 (C_q), 119.1 (CH_{aro}), 119.4 (CH_{aro}), 125.0 ($2CH_{aro}$), 130.2 (CH_{aro}), 137.2 (CH_{aro}), 143.0 (C_q), 150.2 ($2CH_{aro}$), 163.1 (C_q), 202.1 (C=O); MS (IS) : m/z = 214.0 $[MH]^+$.

1-(3-Hydroxyphenyl)-2-(pyridine-4-yl)ethanone (10).

Compound **10** was obtained as a yellow solid in 56% yield following the general procedure A. R_f (AcOEt): 0.32; mp: 210°C; IR (ATR diamond): ν (cm^{-1}) 1185, 1252, 1274, 1318, 1377, 1426, 1477, 1584, 1611, 1681, 2603, 2678; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 4.46 (s, 2H), 7.08 (dd, 1H, J = 8.0 and 2.4 Hz), 7.31 (d, 2H, J = 5.7 Hz), 7.35 – 7.43 (m, 2H), 7.56 (d, 1H, J = 7.8 Hz), 8.54 (d, 2H, J = 5.7 Hz), 9.87 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 44.0 (CH_2), 114.4 (CH_{aro}), 119.3 (CH_{aro}), 120.6 (CH_{aro}), 125.4 ($2CH_{aro}$), 129.9 (CH_{aro}), 137.6 (C_q), 144.2 (C_q), 149.3 ($2CH_{aro}$), 157.6 (C_q), 196.4 (C=O); MS (IS) : m/z = 214.0 $[MH]^+$.

1-(4-Hydroxyphenyl)-2-(pyridine-4-yl)ethanone (11).

Compound **11** was obtained as a yellow solid in 67% yield following the general procedure A. R_f (AcOEt): 0.25; mp: 235°C; IR (ATR diamond): ν (cm^{-1}) 988, 1013, 1163, 1205, 1234, 1260, 1295, 1323, 1393, 1427, 1512, 1577, 1605, 1669, 2492, 2563; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 4.39 (s, 2H), 6.92 (d, 2H, J = 8.7 Hz), 7.31 (d, 2H, J = 5.9 Hz), 7.98 (d, 2H, J = 8.7 Hz), 8.52 (d, 2H, J = 5.9 Hz), 10.49 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 43.4 (CH_2), 115.3 ($2CH_{aro}$), 125.3 ($2CH_{aro}$), 127.8 (C_q), 131.0 ($2CH_{aro}$), 144.7 (C_q), 149.3 ($2CH_{aro}$), 162.3 (C_q), 194.6 (C=O); MS (IS) : m/z = 214.0 $[MH]^+$.

1-(3-Fluorophenyl)-2-(pyridine-4-yl)ethanone (12).

Compound **12** was obtained as a white solid in 55% yield following the general procedure A without TBAF treatment. R_f (AcOEt/PE 2/3): 0.27; mp: 60°C; IR (ATR diamond): ν (cm^{-1}) 1001, 1061, 1148, 1247, 1323, 1422, 1443, 1588, 1687; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 4.27 (s, 2H), 7.19 (d, 2H, J = 4.7 Hz), 7.25 – 7.35 (m, 1H), 7.42 – 7.52 (m, 1H), 7.63 –

7.71 (m, 1H), 7.78 (d, 1H, J = 7.7 Hz), 8.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 44.9 (CH_2), 115.4 (d, CH_{aro}, J = 22 Hz), 120.9 (d, CH_{aro}, J = 22 Hz), 124.4 (d, CH_{aro}, J = 3 Hz), 125.1 ($2CH_{aro}$), 130.7 (d, CH_{aro}, J = 8 Hz), 138.4 (d, C_q, J = 6 Hz), 143.1 (C_q), 150.3 ($2CH_{aro}$), 163.1 (d, C_q, J = 249 Hz), 194.8 (d, C=O, J = 2 Hz); MS (IS) : m/z = 216.0 $[MH]^+$.

1-(6-Hydroxynaphthalen-2-yl)-2-(pyridine-4-yl)ethanone (13).

Compound **13** was obtained as a yellow solid in 53% yield following the general procedure A. R_f (AcOEt): 0.20; mp: >250°C; IR (ATR diamond): ν (cm^{-1}) 983, 1156, 1256, 1343, 1399, 1425, 1472, 1580, 1654, 1652, 2653, 2705; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 4.55 (s, 2H), 7.13 – 7.21 (m, 2H), 7.33 (d, 2H, J = 5.8 Hz), 7.78 -8.00 (m, 3H), 8.50 (d, 2H, J = 5.8 Hz), 8.56 – 8.69 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 44.0 (CH_2), 109.1 (CH_{aro}), 118.3 (CH_{aro}), 120.6 ($2CH_{aro}$), 124.7 (CH_{aro}), 126.6 (CH_{aro}), 129.6 (CH_{aro}), 130.9 (C_q), 131.3 (CH_{aro}), 131.8 (C_q), 133.4 (C_q), 144.7 (C_q), 149.3 ($2CH_{aro}$), 158.1 (C_q), 194.6 (C=O); MS (IS) : m/z = 264.0 $[MH]^+$.

1-(3,5-Dihydroxyphenyl)-2-(pyridine-4-yl)ethanone (14).

Compound **14** was obtained as a yellow solid in 22% yield following the general procedure A. R_f (AcOEt): 0.10; mp: 205°C; IR (ATR diamond): ν (cm^{-1}) 1190, 1255, 1280, 1310, 1370, 1420, 1470, 1580, 1634, 1682, 2650, 2692; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 4.34 (s, 2H), 6.47 (s, 1H), 6.86 (d, 2H, J = 2.0 Hz), 7.25 (d, 2H, J = 5.6 Hz), 8.49 (d, 2H, J = 5.6 Hz), 9.69 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 43.9 (CH_2), 106.2 ($2CH_{aro}$), 107.4 (CH_{aro}), 125.3 ($2CH_{aro}$), 138.1 ($2C_q$), 144.3 (C_q), 149.3 ($2CH_{aro}$), 158.7 (C_q), 196.3 (C=O); MS (IS) : m/z = 230.0 $[MH]^+$.

1-(3-Hydroxyphenyl)-2-(pyridine-3-yl)ethanone (15).

To a solution of DIPA (380 µL, 2.68 mmol) in 2 mL of anhydrous THF at 0°C was added dropwise *n*-BuLi 1.6 M in hexane (1.70 mL, 2.72 mmol) and the resulting solution was stirred for 30 minutes. At the same temperature, a solution of 3-picoline (261 µL, 2.68 mmol) in 2 mL of anhydrous THF was introduced under N_2 atmosphere. 30 minutes later, the mixture was cooled at -78°C and a solution of ester **3** (650 mg, 2.44 mmol) in 3 mL of THF was added. The reaction was stirred at room temperature for 1 h. Then, the solvent was evaporated under reduce pressure and the residue was diluted in AcOEt. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated. To cleave the TBS group, the crude product was diluted in 15 mL of THF and treated by a solution of TBAF 1M in THF (3.00 mL, 3.00 mmol). The reaction was stirred for 2 h at room temperature and concentrated. Ketone **15** was purified by chromatography on a silica gel using a mixture of petroleum ether/AcOEt (3/7) and was obtained as a white solid in 31% yield. R_f (AcOEt/PE 8/2): 0.30; mp: 152°C; IR (ATR diamond): ν (cm^{-1}) 1158, 1175, 1249, 1273, 1326, 1427, 1453, 1585, 1674, 2613, 2691; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 4.46 (s, 2H), 7.09 (dd, 1H, J = 8.0, 1.8 Hz), 7.35 – 7.46 (m, 3H), 7.58 (d, 1H, J = 7.8 Hz), 7.69 (d, 1H, J = 7.8 Hz), 8.46 – 8.53 (m, 2H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 41.8 (CH_2), 114.4 (CH_{aro}), 119.3 (CH_{aro}), 120.5 (CH_{aro}), 123.2 (CH_{aro}), 129.8 (CH_{aro}), 131.0 (C_q), 137.5 (CH_{aro}), 137.6 (C_q), 147.6 (CH_{aro}), 150.8 (CH_{aro}), 157.6 (C_q), 197.0 (C=O); MS (IS) : m/z = 214.0 $[MH]^+$.

1-(3-Hydroxyphenyl)-2-(pyridine-2-yl)ethanone (16).

Compound **16** was obtained as a white solid in 56% yield following the general procedure A. It was isolated in the mixture of two inseparable rotamers in proportions of 65:35. R_f (AcOEt/PE 1/1): 0.40; mp: 187°C; IR (ATR diamond): ν (cm^{-1}) 1010, 1151, 1174, 1249, 1270, 1330, 1453, 1590, 1675, 2617; ^{1}H NMR (250 MHz, DMSO-d_6): minority rotamer δ (ppm) 6.32 (s, 1H), 6.82 – 6.88 (m, 1H), 7.14 – 7.24 (m, 1H), 7.26 - 7.42 (m, 4H), 7.80 – 7.87 (m, 1H), 8.44 (d, 1H, J = 4.9 Hz), 9.58 (s, 1H), 15.34 (br s, 1H). Majority rotamer δ (ppm)

4.51 (s, 2H), 7.06 (dd, 1H, J = 8.0 and 2.4 Hz), 7.25 – 7.42 (m, 4H), 7.53 (d, 1H, J = 7.7 Hz), 7.77 (dd, 1H, J = 7.6 and 1.8 Hz), 8.51 (d, 1H, J = 4.8 Hz), 9.83 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): two inseparable rotamers δ (ppm) 47.7 (CH_2), 93.8 (CH), 112.0 (CH_{aro}), 114.5 (CH_{aro}), 116.0 (CH_{aro}), 116.4 (CH_{aro}), 119.0 (CH_{aro}), 119.4 (CH_{aro}), 120.3 (CH_{aro}), 121.8 (CH_{aro}), 121.9 (CH_{aro}), 124.4 (CH_{aro}), 129.4 (CH_{aro}), 129.8 (CH_{aro}), 136.5 (CH_{aro}), 137.3 (C_q), 137.8 (C_q), 137.9 (CH_{aro}), 144.3 (CH_{aro}), 149.0 (CH_{aro}), 155.8 (C_q), 157.4 (C_q), 157.6 (C_q), 157.8 (C_q), 163.2 (C_q), 196.9 (C=O); MS (IS) : m/z = 214.0 $[MH]^+$.

Fisher reaction.

General procedure B: A solution of 5-Hydrazinyl-2-methoxypyridine **17** (139 mg, 1.00 mmol), ketone **8-16** (1.00 mmol) and PTSA (476 mg, 2.50 mmol) in 15 mL of toluene was heated at reflux for 12 h with vigorous stirring. Then, the reaction was concentrated and the crude product was solubilized in CH_2Cl_2. The organic layer was washed with a saturated solution of $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and evaporated. 4-azaindoles **18** to **26** was purified by chromatography on a silica gel using a mixture of petroleum ether/AcOEt allowing an effective separation.

5-Methoxy-2-phenyl-3-(pyridin-4-yl)-4-azaindole (18).

Compound **18** was obtained as a yellow solid following the general procedure B in 52% yield. R_f (AcOEt/PE 3/1): 0.40; mp: 272°C; IR (ATR diamond): ν (cm^{-1}) 992, 1005, 1040, 1107, 1169, 1198, 1263, 1290, 1403, 1463, 1490, 1594; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.95 (s, 3H), 6.72 (d, 1H, J = 8.7 Hz), 7.48 – 7.57 (m, 5H), 7.62 – 7.65 (m, 2H), 7.81 (d, 1H, J = 8.7 Hz), 8.50 (d, 2H, J = 5.9 Hz), 11.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 52.7 (CH_3), 105.8 (CH_{aro}), 108.9 (C_q), 122.8 (CH_{aro}), 123.4 ($2CH_{aro}$), 125.0 (C_q), 128.7 (CH_{aro}), 128.8 ($2CH_{aro}$), 128.9 ($2CH_{aro}$), 132.1 (C_q), 138.6 (C_q), 140.7 (C_q), 141.9 (C_q), 149.2 ($2CH_{aro}$), 159.6 (C_q); HRMS (EIMS): *m/z* calcd for $C_{19}H_{16}N_3O$: 302.1293 $[M+H]^+$, found: 302.1312.

2-(2-Hydroxyphenyl)-5-methoxy-3-(pyridin-4-yl)-4-azaindole (19).

Compound **19** was obtained as a yellow solid following the general procedure B in 9% yield. R_f (AcOEt/PE 8/2): 0.24; mp: 260°C; IR (ATR diamond): ν (cm^{-1}) 1020, 1069, 1100, 1195, 1215, 1268, 1284, 1402, 1439, 1579, 1604, 3332; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.94 (s, 3H), 6.66 (d, 1H, J = 8.7 Hz), 6.90 (t, 1H, J = 7,3 Hz), 7.00 (d, 1H, J = 8.0 Hz), 7.24 (d, 1H, J = 7.3 Hz), 7.32 (t, 1H, J = 7.3 Hz), 7.68 – 7.75 (m, 3H), 8.38 (d, 2H, J = 5.4 Hz), 9.80 (br s, 1H), 11.67 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 52.7 (CH_3), 105.1 (CH_{aro}), 109.0 (C_q), 116.1 (CH_{aro}), 119.2 (CH_{aro}), 119.7 (C_q), 121.9 ($2CH_{aro}$), 122.5 (CH_{aro}), 124.7 (C_q), 130.4 (CH_{aro}), 131.5 (CH_{aro}), 136.8 (C_q), 140.5 (C_q), 142.7 (C_q), 148.9 ($2CH_{aro}$), 155.4 (C_q), 159.3 (C_q); HRMS (EIMS): *m/z* calcd for $C_{19}H_{16}N_3O_2$: 318.1243 $[M+H]^+$, found: 318.1231.

2-(3-Hydroxyphenyl)-5-methoxy-3-(pyridin-4-yl)-4-azaindole (20).

Compound **20** was obtained as a white solid following the general procedure B in 34% yield. R_f (AcOEt): 0.39; mp: >260°C; IR (ATR diamond): ν (cm^{-1}) 981, 1014, 1070, 1104, 1193, 1214, 1251, 1269, 1400, 1269, 1581, 1603, 3356; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 3.95 (s, 3H), 6.71 (d, 1H, J = 8.7 Hz), 6.85 – 6.91 (m, 1H), 6.93 – 6.99 (m, 2H), 7.32 (t, 1H, J = 7.9 Hz), 7.66 (d, 2H, J = 6.1 Hz), 7.78 (d, 1H, J = 8.7 Hz), 8.50 (d, 2H, J = 6.1 Hz), 9.69 (s, 1H), 11.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 52.7 (CH_3), 105.7 (CH_{aro}), 108.7 (C_q), 115.5 (CH_{aro}), 115.8 (CH_{aro}), 119.4 (CH_{aro}), 122.7 (CH_{aro}), 123.4 ($2CH_{aro}$), 124.8 (C_q), 130.0 (CH_{aro}), 133.4 (C_q), 138.8 (C_q), 140.7 (C_q), 142.0 (C_q), 149.1 ($2CH_{aro}$), 157.6 (C_q), 159.6 (C_q); HRMS (EIMS): *m/z* calcd for $C_{19}H_{16}N_3O_2$: 318.1243 $[M+H]^+$, found: 318.1248.

2-(4-Hydroxyphenyl)-5-methoxy-3-(pyridin-4-yl)-4-azaindole (21).

Compound **21** was obtained as a white solid following the general procedure B in 30% yield. R_f (AcOEt): 0.34; mp: >260°C; IR (ATR diamond): ν (cm^{-1}) 1010, 1025, 1105, 1198, 1218, 1255, 1275, 1404, 1460, 1606, 3270; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.94 (s, 3H), 6.68 (d, 1H, J = 8.6 Hz), 6.90 (d, 2H, J = 8.5 Hz), 7.37 (d, 2H, J = 8.5 Hz), 7.67 (d, 2H, J = 6.0 Hz), 7.76 (d, 1H, J = 8.6 Hz), 8.48 (d, 2H, J = 6.0 Hz), 9.86 (br s, 1H), 11.73 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 52.7 (CH_3), 105.1 (CH_{aro}), 107.9 (C_q), 115.7 ($2CH_{aro}$), 122.4 (CH_{aro}), 122.7 (C_q), 123.2 ($2CH_{aro}$), 124.7 (C_q), 130.2 ($2CH_{aro}$), 139.4 (C_q), 141.0 (C_q), 142.3 (C_q), 149.1 ($2CH_{aro}$), 158.0 (C_q), 159.4 (C_q); HRMS (EIMS): *m/z* calcd for $C_{19}H_{16}N_3O_2$: 318.1243 $[M+H]^+$, found: 318.1225.

2-(3-Fluorophenyl)-5-methoxy-3-(pyridin-4-yl)-4-azaindole (22).

Compound **22** was obtained as a yellow solid following the general procedure B in 30% yield. R_f (AcOEt/PE 2/3): 0.21; mp: >260°C; IR (ATR diamond): ν (cm^{-1}) 779, 807, 828, 976, 1010, 1030, 1107, 1166, 1188, 1267, 1399, 1467, 1492, 1592; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 3.94 (s, 3H), 6.74 (d, 1H, J = 8.7 Hz), 7.27 – 7.42 (m, 3H), 7.50 – 7.60 (m, 1H), 7.62 (d, 2H, J = 6.0 Hz), 7.82 (d, 1H, J = 8.7 Hz), 8.53 (d, 2H, J = 6.0 Hz), 12.00 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 52.7 (CH_3), 106.3 (CH_{aro}), 109.7 (C_q), 115.3 (d, CH_{aro}, J = 22 Hz), 115.4 (d, CH_{aro}, J = 22 Hz), 123.0 (CH_{aro}), 123.7 ($2CH_{aro}$), 125.0 (d, CH_{aro}, J = 3 Hz), 125.1 (C_q), 130.9 (d, CH_{aro}, J = 9 Hz), 134.3 (d, C_q, J = 9 Hz), 136.7 (d, C_q, J = 2 Hz), 140.6 (C_q), 141.6 (C_q), 149.3 ($2CH_{aro}$), 159.7 (C_q), 162.1 (d, C_q, J = 244 Hz); HRMS (EIMS): *m/z* calcd for $C_{19}H_{15}N_3OF$: 320.1199 $[M+H]^+$, found: 320.1214.

2-(3-Hydroxyphenyl)-5-methoxy-3-(pyridin-3-yl)-4-azaindole (25).

Compound **25** was obtained as a yellow solid following the general procedure B in 19% yield. R_f (CH_2Cl_2/EtOH 9/1): 0.43; mp: >260°C; IR (ATR diamond): ν (cm^{-1}) 980, 1038, 1109, 1229, 1271, 1400, 1454, 1467, 1573, 3250; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 3.91 (s, 3H), 6.69 (d, 1H, J = 8.7 Hz), 6.84 (d, 1H, J = 7.7 Hz), 6.89 – 6.97 (m, 2H), 7.28 (t, 1H, J = 7.7 Hz), 7.36 – 7.46 (m, 1H), 7.78 (d, 1H, J = 8.7 Hz), 7.98 (d, 1H, J = 7.7 Hz), 8.44 (d, 1H, J = 4.2 Hz), 8.78 (s, 1H), 9.65 (s, 1H), 11.74 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 52.6 (CH_3), 105.6 (CH_{aro}), 108.5 (C_q), 115.2 (CH_{aro}), 115.4 (CH_{aro}), 119.2 (CH_{aro}), 122.6 (CH_{aro}), 123.2 (CH_{aro}), 124.8 (C_q), 129.9 (CH_{aro}), 130.2 (C_q), 133.4 (C_q), 136.2 (CH_{aro}), 137.5 (C_q), 140.9 (C_q), 146.3 (CH_{aro}), 149.9 (CH_{aro}), 157.6 (C_q), 159.5 (C_q); HRMS (EIMS): *m/z* calcd for $C_{19}H_{16}N_3O_2$: 318.1243 $[M+H]^+$, found: 318.1234.

2-(3-Hydroxyphenyl)-5-methoxy-3-(pyridin-2-yl)-4-azaindole (26).

Compound **26** was obtained as a brown solid following the general procedure B in 34% yield. R_f (CH_2Cl_2/EtOH 9/1): 0.33; mp: 230°C; IR (ATR diamond): ν (cm^{-1}) 1031, 1105, 1199, 1269, 1404, 1476, 1500, 1581, 3308; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.91 (s, 3H), 6.68 (d, 1H, J = 8.6 Hz), 6.78 (d, 1H, J = 7.9 Hz), 6.93 – 6.99 (m, 2H), 7.17 – 7.26 (m, 2H), 7.77 (d, 1H, J = 8.6 Hz), 7.87 (t, 1H, J = 7.7 Hz), 8.12 (d, 1H, J = 7.9 Hz), 8.48 (d, 1H, J = 3.9 Hz), 9.48 (s, 1H), 11.67 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 52.6 (CH_3), 105.3 (CH_{aro}), 112.2 (C_q), 114.9 (CH_{aro}), 115.6 (CH_{aro}), 119.5 (CH_{aro}), 120.8 (CH_{aro}), 122.5 (CH_{aro}), 124.5 (CH_{aro}), 124.6 (C_q), 129.1 (CH_{aro}), 134.1 (C_q), 135.7 (CH_{aro}), 138.8 (C_q), 141.1 (C_q), 148.7 (CH_{aro}), 153.6 (C_q), 157.0 (C_q), 159.4 (C_q); HRMS (EIMS): *m/z* calcd for $C_{19}H_{16}N_3O_2$: 318.1243 $[M+H]^+$, found: 318.1228.

Ether deprotection

General procedure C: To a solution of 4-azaindole **18,22** (0.500 mmol) in 5 mL of CH_3CN were added successively sodium iodide (375 mg, 2.5 mmol) and dropwise chlorotrimethylsilane (320 µL, 2.5 mmol). The resulting solution was heated at reflux for 2 h. The solvent was evaporated and the crude product was purified by chromatography on a silica gel using a mixture of CH_2Cl_2/MeOH allowing an effective separation.

5-Hydroxy-2-phenyl-3-(pyridin-4-yl)-4-azaindole (27).

Compound **27** was obtained as a yellow solid following the general procedure C in 52% yield. R_f (CH_2Cl_2/MeOH 4/1): 0.15; mp: >260°C; IR (ATR diamond): ν (cm^{-1}) 1032, 1136, 1178, 1345, 1406, 1467, 1535, 1650, 3326; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 6.34 (d, 1H, J = 9.0 Hz), 7.37 – 7.47 (m, 7H), 7.42 (d, 1H, J = 9.0 Hz), 8.50 (d, 2H, J = 6.1 Hz), 10.74 (br s, 1H), 12.12 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 107.3 (C_q), 114.2 (CH_{aro}), 119.3 (CH_{aro}), 123.4 ($2CH_{aro}$), 125.4 (C_q), 128.7 (CH_{aro}), 128.8 ($2CH_{aro}$), 128.9 ($2CH_{aro}$), 132.0 (C_q), 138.7 (C_q), 141.1 (C_q), 142.8 (C_q), 149.3 ($2CH_{aro}$), 160.4 (C_q); HRMS (EIMS): *m/z* calcd for $C_{18}H_{14}N_3O$: 288.1137 $[M+H]^+$, found: 288.1153.

2-(3-Fluorophenyl)-5-hydroxy-3-(pyridin-4-yl)-4-azaindole (28).

Compound **28** was obtained as a yellow solid following the general procedure C in 63% yield. R_f (CH_2Cl_2/MeOH 4/1): 0.19; mp: >260°C; IR (ATR diamond): ν (cm^{-1}) 784, 823, 1117, 1190, 1474, 1533, 1572, 1604, 3418; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 6.32 (d, 1H, J = 9.0 Hz), 7.14 – 7.26 (m, 3H), 7.34 – 7.46 (m, 3H), 7.68 (d, 1H, J = 9.0 Hz), 8.50 (d, 2H, J = 5.2 Hz), 10.80 (br s, 1H), 11.94 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 107.3 (C_q), 111.4 (CH_{aro}), 114.6 (d, CH_{aro}, J = 22 Hz), 115.0 (d, CH_{aro}, J = 22 Hz), 112.0 (C_q), 124.3 (d, CH_{aro}, J = 2 Hz), 124.7 ($2CH_{aro}$), 126.3 (CH_{aro}), 130.8 (d, CH_{aro}, J = 8 Hz), 133.6 (C_q), 133.7 (C_q), 134.1 (C_q), 140.9 (C_q), 149.6 ($2CH_{aro}$), 161.4 (C_q), 162.0 (d, C_q, J = 244 Hz); HRMS (EIMS): *m/z* calcd for $C_{18}H_{13}N_3OF$: 306.1043 $[M+H]^+$, found: 306.1060.