

Supporting Information

Microwave-assisted, acetic acid-catalyzed, metal-free synthesis of 5H-pyrazino[2,3-b]indoles via sequential C–C and C–N bond formation

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General experimental methods

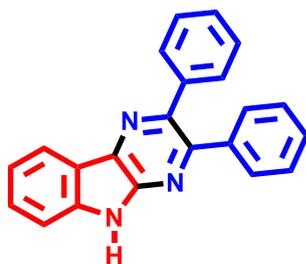
^1H NMR and ^{13}C NMR spectra were obtained on Bruker 400 MHz or 300 MHz instrument at 400 MHz and 100 MHz or 300 MHz and 75 MHz respectively. Chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (tetramethylsilane) reference. Coupling constants (J) are reported in hertz (Hz), and spin multiplicities are represented by the symbols s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Microwave reactions were performed using a commercial microwave reactor (Anton Paar Microwave 200) in sealed reaction vessels at 200 power watt and reaction temperatures were monitored by an equipped IR sensor. X-ray diffraction was done on a Bruker SMART diffractometer equipped with a graphite monochromator and Mo-K α ($\lambda = 0.71073 \text{ \AA}$) radiation. The progress of the reaction was checked by TLC using 300-400 mesh silica gel. Column chromatography was performed using 60-120 mesh silica gel. All the available reagents were purchased from commercial sources and used without purification. The solvents used during reactions were distilled for purity.

Experimental and characterization data

General synthesis of 5H-pyrazino[2,3-b]indoles (4aa-4be):

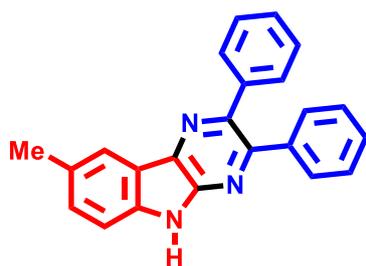
A mixture of isatin (1.0 mmol), benzylamine (2.0 mmol) and Acetic acid (20 mol%) were irradiated in microwave at 150°C for 15 minute. After completion of reaction (followed by TLC), the reaction mixture was diluted with 5 ml dichloromethane and washed with brine (2 \times 10 ml), dried and concentrated under vacuum and the resulting crude product was purified by column chromatography over 60-120 mesh silica gel [ethyl acetate/ petroleum ether (60-80°C)]. No further purification was needed.

2,3-diphenyl-5H-pyrazino[2,3-b]indole (**4aa**):



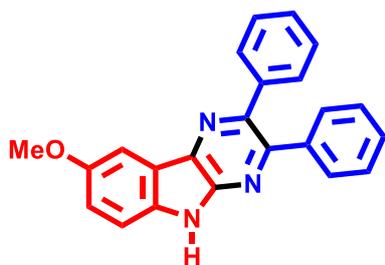
Yield : 85% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 190-192°C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 12.25 (s, 1H) , 8.27 (d, $J = 9$ Hz, 1H), 7.63 (d, $J = 3$ Hz, 2H), 7.46-7.41 (m, 4H) , 7.36- 7.33 (m, 7H) ; ^{13}C NMR (75 MHz, DMSO- d_6) : 148.5 , 145.3 , 144.6 , 141.6 , 140.6 , 140.2 , 133.8 , 130.48 , 130.45 , 129.5 , 128.5 , 128.0 , 121.6, 121.1 , 119.8 112.7 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{16}\text{N}_3[\text{M}+\text{H}]^+$: 322.1344 ; found : 322.1345.

8-methyl-2,3-diphenyl-5H-pyrazino[2,3-b]indole (**4ab**):



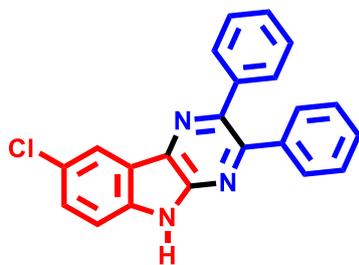
Yield : 80% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 194-196°C ; $^1\text{H NMR}$ (400 MHz, DMSO-d_6) : δ (ppm)= 12.10 (s, 1H) , 8.06 (s, 1H) , 8.52 (d, J = 8 Hz, 1H), 7.45-7.41 (m, 5H) , 7.33 (d, J = 8 Hz, 6H), 2.51 (s, 3H) ; $^{13}\text{C NMR}$ (100 MHz, DMSO-d_6) : 148.2 , 145.1 , 144.7 , 140.6 , 140.3 , 139.9 , 133.7 , 130.9 , 130.5 , 130.4 , 130.1 , 128.44 , 128.41 , 127.9 , 121.2 , 119.9 , 112.5, 21.5 ; HRMS-ESI (m/z): calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_3[\text{M}+\text{H}]^+$: 336.1501 ; found : 336.1505.

8-methoxy-2,3-diphenyl-5H-pyrazino[2,3-b]indole (**4ac**):



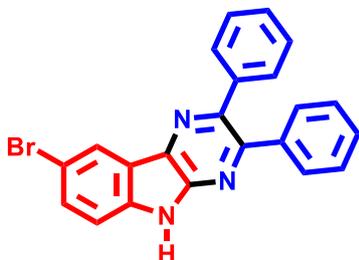
Yield : 81% ; White solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 192-194°C ; $^1\text{H NMR}$ (400 MHz, CDCl_3) : δ (ppm)= 9.88 (s, 1H) , 786 (d, J = 4 Hz, 1H) , 7.48 (t, J = 8 Hz , 4H) , 7.37 (t, J = 8 Hz, 5H) , 7.20-7.17 (M, 2H), 6.89 (d, J = 8 Hz, 1H), 3.95 (s, 3H) ; $^{13}\text{C NMR}$ (100 MHz, CDCl_3) : 154.3 , 145.5 , 144.8 , 144.4 , 138.2 , 138.0 , 135.5 , 135.2 , 134.7, 134.1 , 131.5 , 128.9, 128.7 , 120.4 , 119.7 , 112.7 , 103.2 , 56.0 ; HRMS-ESI (m/z): calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_3\text{O}[\text{M}+\text{H}]^+$: 352.4170 ; found : 352.4176.

8-chloro-2,3-diphenyl-5H-pyrazino[2,3-b]indole (**4ad**) :



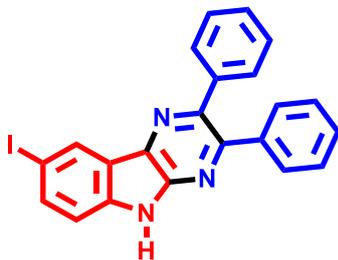
Yield : 86% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 189-191°C ; ^1H NMR (400 MHz, DMSO- d_6) : δ (ppm)= 12.38 (s, 1H) , 8.27 (d, J = 4 Hz, 1H) , 7.63 (s, 2H) , 7.48-7.41 (m, 4H) , 7.38 – 7.31 (m, 6H) ; ^{13}C NMR (100 MHz, DMSO- d_6) : 148.5 , 145.9 , 144.6 , 141.6 , 140.7 , 140.5 , 133.9 , 130.8 , 130.5 , 129.5 , 128.4 , 128.0 , 121.6 , 121.5 , 119.7 , 112.4 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{15}\text{ClN}_3$ $[\text{M}+\text{H}]^+$: 356.0955 ; found : 356.0951.

8-bromo-2,3-diphenyl-5H-pyrazino[2,3-b]indole (**4ae**):



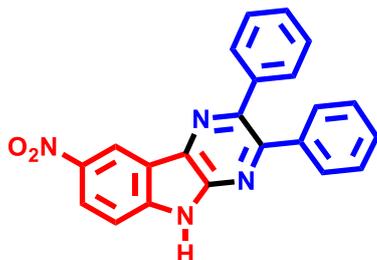
Yield : 84% ; White solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 195-197°C ; ^1H NMR (400 MHz, DMSO- d_6) : δ (ppm)= 12.42 (s, 1H) , 8.38 (d, J = 4 Hz, 1H) , 7.74 (d, J = 8Hz, 1H) , 7.59 (d, J = 8Hz, 1H) , 7.44-7.40 (m, 4H) , 7.35 – 7.32 (m, 7H) ; ^{13}C NMR (100 MHz, DMSO- d_6) : 149.0 , 145.6 , 144.4 , 139.9 , 139.7 , 139.5 , 132.1 , 131.4 , 130.0 , 128.2 , 128.03 , 128.00 , 127.7 , 123.3 , 121.1 , 114.4 , 112.7 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{15}\text{BrN}_3$ $[\text{M}+\text{H}]^+$: 400.0449 ; found : 400.0447.

8-iodo-2,3-diphenyl-5H-pyrazino[2,3-b]indole (**4af**):



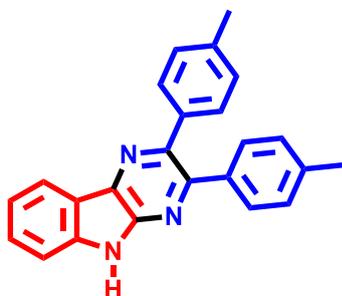
Yield : 82% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 188-190°C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 12.40 (s, 1H) , 8.53 (s, 1H) , 7.89-7.85 (m, 1H) , 7.48 (d, J = 9 Hz, 1H) , 7.44-7.39 (m, 4H) , 7.34-7.31 (m, 6H) ; ^{13}C NMR (100 MHz, DMSO- d_6) : 149.3 , 145.9 , 144.4 , 140.6 , 140.3 , 140.0 , 137.3 , 132.3 , 130.4 , 129.7 , 128.6 , 128.5 , 128.4 , 128.1 , 122.2 , 115.2 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{15}\text{IN}_3$ $[\text{M}+\text{H}]^+$: 448.0311 ; found : 448.0313.

8-nitro-2,3-diphenyl-5H-pyrazino[2,3-b]indole (**4ag**):



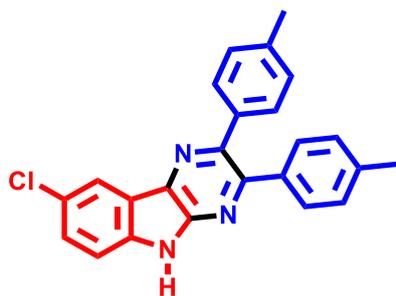
Yield : 70% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 193-195°C ; ^1H NMR (400 MHz, DMSO-d_6) : δ (ppm)= 13.17 (s, 1H) , 9.19 (s,1H) , 8.75 (d, J = 8 Hz, 1H) , 7.78 (d, J = 12Hz, 1H) , 7.41-7.33 (m, 10H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : 150.3 , 149.8 , 149.4 , 145.0 , 142.9 , 138.2 , 138.0 , 134.9 , 133.7 , 132.7 , 129.9 , 128.9 , 126.8 , 124.7 , 119.4 , 117.9 , 114.4 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{15}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 367.1195 ; found : 367.1190.

2,3-di-p-tolyl-5H-pyrazino[2,3-b]indole (**4ah**):



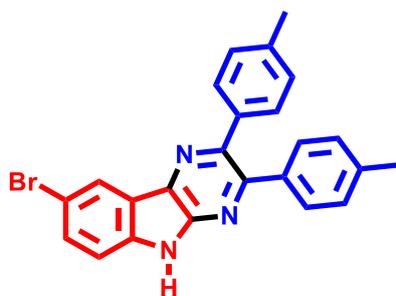
Yield : 79% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 190-192°C ; ^1H NMR (300 MHz, DMSO-d_6) : δ (ppm)= 12.19 (s, 1H) , 8.24 (d, J = 6 Hz, 1H), 7.61 (d, J = 6 Hz, 2H), 7.36-7.31 (m, 5H) , 7.15 (d, J = 6 Hz, 4H), 2.32 (s, 6H) ; ^{13}C NMR (75 MHz, DMSO-d_6) : 148.4 , 145.3 , 144.5 , 141.5 , 137.9 , 137.8 , 137.5 , 137.2 , 133.5, 130.3 , 129.4 , 129.1 , 121.5 , 121.0 , 119.8 , 112.7 , 121.3 ; HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{N}_3$ $[\text{M}+\text{H}]^+$: 350.1657 ; found : 350.1658.

8-chloro-2,3-di-p-tolyl-5H-pyrazino[2,3-b]indole (**4ai**):



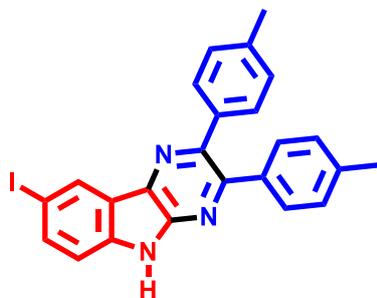
Yield : 82% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 187-189°C ; ^1H NMR (300 MHz, DMSO-d_6) : δ (ppm)= 12.56 (s, 1H) , 8.29 (s,1H) , 7.69(s, 2H) , 7.44-7.39 (m, 4H) , 7.24 (d, J = 9 Hz, 4H) , 2.30 (s, 6H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : 150.7 , 146.6 , 145.9 , 141.8 , 139.1 , 137.9 , 137.4 , 135.2 , 132.5 , 130.4 , 130.3 , 129.2, 129.1 , 127.4 , 123.1 , 120.7 , 115.1 , 21.3 ; HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{ClN}_3$ $[\text{M}+\text{H}]^+$: 384.1268 ; found : 384.1265.

8-bromo-2,3-di-p-tolyl-5H-pyrazino[2,3-b]indole (**4aj**):



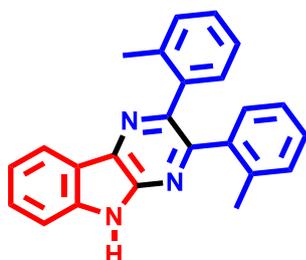
Yield : 78% ; White solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 189-191°C ; $^1\text{H NMR}$ (400 MHz, DMSO-d_6) : δ (ppm)= 12.28 (s, 1H) , 8.51 (s, 1H) , 7.60 (s, 2H) , 7.50 (s, 1H) , 7.26 (t, J = 8 Hz, 4H) , 7.05 (d, J = 8 Hz, 4H) , 2.32 (s, 6H) ; $^{13}\text{C NMR}$ (100 MHz, DMSO-d_6) : 150.1 , 149.8 , 145.6 , 140.2 , 139.1 , 138.7 , 137.8 , 137.3 , 133.3 , 131.7 , 130.9 , 130.4 , 129.9 , 129.6 , 129.2 , 124.8 , 122.6 , 115.6 , 114.8 , 21.2 ; HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{BrN}_3[\text{M}+\text{H}]^+$: 428.0762 ; found : 428.0761.

8-iodo-2,3-di-*p*-tolyl-5H-pyrazino[2,3-*b*]indole (**4ak**):



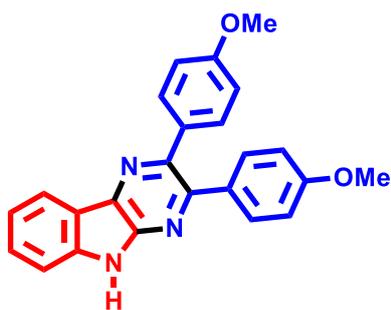
Yield : 77% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 196-198°C ; $^1\text{H NMR}$ (400 MHz, DMSO-d_6) : δ (ppm)= 12.35 (s, 1H) , 8.51 (s, 1H) , 7.88-7.85 (m, 1H) , 7.46 (d, J = 8 Hz, 1H) , 7.31 (t, J = 6 Hz, 4H) , 7.14 (d, J = 6 Hz, 4H) , 2.32 (s, 6H) ; $^{13}\text{C NMR}$ (100 MHz, DMSO-d_6) : 149.3 , 145.9 , 144.4 , 140.5 , 138.0 , 137.6 , 137.3 , 137.2 , 137.1 , 132.0 , 130.30 , 130.26 , 129.6 , 129.12 , 129.08 , 122.3 , 115.1 , 21.3 ; HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{IN}_3[\text{M}+\text{H}]^+$: 476.0624 ; found : 476.0620.

2,3-di-*o*-tolyl-5H-pyrazino[2,3-*b*]indole (**4al**):



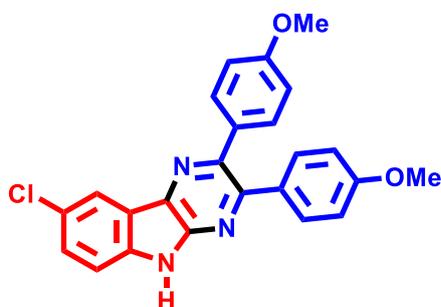
Yield : 78% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 185-187°C ; $^1\text{H NMR}$ (300 MHz, DMSO-d_6) : δ (ppm)= 12.19 (s, 1H) , 8.25 (d, J = 6 Hz, 1H) , 7.64 (d, J = 4 Hz, 2H) , 7.38-7.33 (m, 1H) , 7.19-7.15 (m, 4H) , 7.09-7.04 (m, 4H) , 2.16 (s, 3H) , 2.14 (s, 3H) ; $^{13}\text{C NMR}$ (75 MHz, DMSO-d_6) : 149.5 , 146.1 , 144.2 , 141.5 , 139.6 , 139.3 , 136.6 , 136.4 , 133.5 , 131.1 , 130.8 , 130.5 , 130.4 , 129.5 , 128.4 , 128.1 , 125.5 , 121.5 , 121.1 , 119.8 , 112.7 , 20.2 , 20.1 ; HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{N}_3[\text{M}+\text{H}]^+$: 350.1657 ; found : 350.1658.

2,3-bis(4-methoxyphenyl)-5H-pyrazino[2,3-*b*]indole (**4am**):



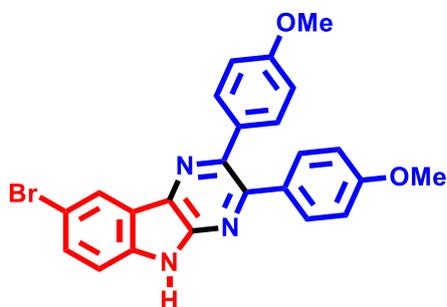
Yield : 68% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 194-196°C ; $^1\text{H NMR}$ (300 MHz, CDCl_3) : δ (ppm)= 11.08 (s, 1H) , 8.38 (s,2H) , 7.57-7.32 (m, 7H), 7.02-6.89 (m, 5H), 6.68 (d, J = 9 Hz, 1H), 3.88 (s, 3H) , 3.86 (s, 3H) ; $^{13}\text{C NMR}$ (75 MHz, CDCl_3) : 159.8 , 159.3 , 147.5 , 145.6 , 144.3 , 140.7 , 134.7 , 132.7 , 132.4 , 131.5 , 131.4 , 128.6 , 121.7 , 120.9 , 120.3 , 114.1 , 113.8 , 111.8 , 55.4 55.3 ; HRMS-ESI (m/z): calcd for $\text{C}_{24}\text{H}_{20}\text{N}_3\text{O}_2[\text{M}+\text{H}]^+$: 382.1556 ; found : 382.1157.

8-chloro-2,3-bis(4-methoxyphenyl)-5H-pyrazino[2,3-b]indole (**4an**):



Yield : 72% ; White solid ; R_f : 0.2 (12% Ethyl Acetate in Petroleum Ether) ; M.P. = 186-188°C ; $^1\text{H NMR}$ (300 MHz, CDCl_3) : δ (ppm)= 11.19 (s, 1H) , 8.48 (s,1H) , 7.57 (d, J = 9 Hz, 2H) , 7.48 (d, J = 6 Hz, 2H) , 7.33 (d, J = 9 Hz, 1H) , 6.97 – 6.6.91 (m, 4H), 6.46 (d, J = 9 Hz, 1H) , 3.90 (s, 3H), 3.85 (s, 3H) ; $^{13}\text{C NMR}$ (75 MHz, CDCl_3) : 161.0 , 160.4 , 149.0 , 146.3 , 145.0 , 138.8 , 134.8 , 132.5 , 132.2 , 131.8 , 131.4 , 128.6 , 126.5 , 121.33 , 121.25 , 117.1 , 116.0 , 114.4 , 55.4 , 55.3 ; HRMS-ESI (m/z): calcd for $\text{C}_{24}\text{H}_{19}\text{ClN}_3\text{O}_2[\text{M}+\text{H}]^+$: 416.1166 ; found : 416.1167.

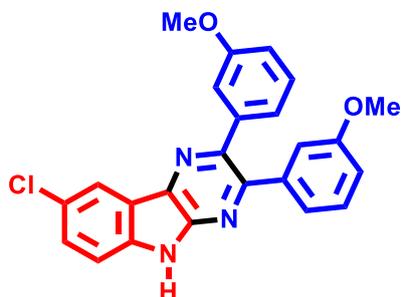
8-bromo-2,3-bis(4-methoxyphenyl)-5H-pyrazino[2,3-b]indole (**4ao**):



Yield : 70% ; Yellow solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 193-195°C ; $^1\text{H NMR}$ (400 MHz, CDCl_3) : δ (ppm)= 11.19 (s, 1H) , 8.48 (s,1H) , 7.75 – 7.57 (m, 5H), 7.18 – 7.12 (m, 4H), 6.66 (d, J = 12 Hz, 1H) , 3.89 (s, 3H), 3.84 (s, 3H) ; $^{13}\text{C NMR}$ (100 MHz, CDCl_3) :

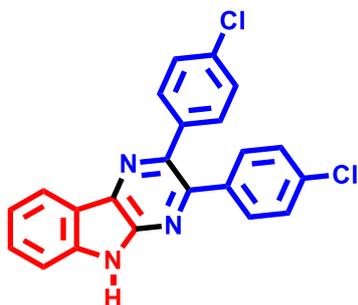
147.0 , 144.5 , 139.0 , 133.6 , 132.3 , 132.2 , 131.5 , ,131.4 , 131.3 , 125.4 , 122.1 , 114.5 , ,114.0 , 113.8 , 113.3 , 55.5 , 55.4 ; HRMS-ESI (m/z): calcd. for C₂₄H₁₉BrN₃O₂[M+H]⁺ : 460.0661; found : 460.0662.

8-chloro-2,3-bis(3-methoxyphenyl)-5H-pyrazino[2,3-b]indole (**4ap**):



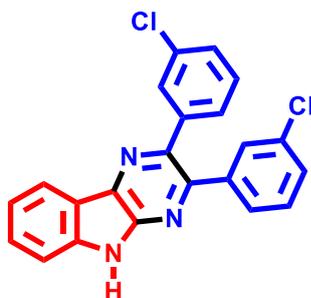
Yield : 78% ; White solid ; R_f : 0.2 (12% Ethyl Acetate in Petroleum Ether) ; M.P. = 190-192°C ; ¹H NMR (300 MHz, DMSO-d₆) : δ (ppm)= 12.46 (s, 1H) , 8.27 (s, 1H), 7.65 (s, 2H), 7.28-7.23 (m, 2H) , 7.02-6.90 (m, 6H) , 3.67 (s, 3H), 3.66 (s, 3H) ; ¹³C NMR (75 MHz, DMSO-d₆) : 159.3 , 149.3 , 145.8 , 144.9 , 141.6 , 141.3 , 139.9 , 132.7 , 129.6 , 129.3 , 125.5 , 122.8 , 121.0 , 120.8 , 115.9 , 115.7 , 114.53 , 114.48 , 113.8 , 55.5 ; HRMS-ESI (m/z): calcd. for C₂₄H₁₉ClN₃O₂[M+H]⁺ : 416.1166 ; found : 416.1164.

2,3-bis(4-chlorophenyl)-5H-pyrazino[2,3-b]indole (**4aq**):



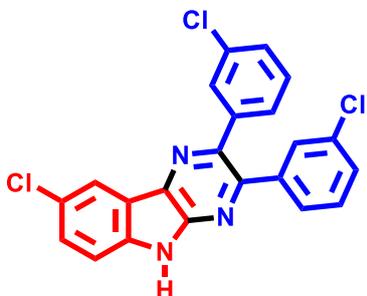
Yield : 87% ; White solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 184-186°C ; ¹H NMR (300 MHz, DMSO-d₆) : δ (ppm)= 12.31 (s, 1H) , 8.26 (d, J = 9 Hz, 1H) , 7.72- 7.60 (m, 3H) , 7.47 (s, 3H), 7.36 -7.30 (m, 3H) ; ¹³C NMR (75 MHz, DMSO-d₆) : 147.2 , 144.7 , 144.0 , 141.9 , 139.3 , 138.8 , 134.3 , 133.6 , 133.0 , , 132.3 , 129.7 , 128.7 , 128.6 , 121.9 , 121.3 , 119.6 , 112.9 ; HRMS-ESI (m/z): calcd. for C₂₂H₁₄Cl₂N₃[M+H]⁺ : 390.0565 ; found : 390.0566.

2,3-bis(3-chlorophenyl)-5H-pyrazino[2,3-b]indole (**4ar**):



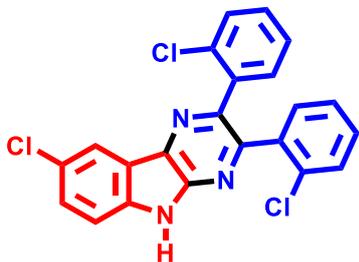
Yield : 84% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 193-195°C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 12.34 (s, 1H) , 8.29 (d, J = 9 Hz, 1H), 7.65 (d, J = 3 Hz, 2H), 7.55 (s, 2H), 7.45-7.30 (m, 7H) ; ^{13}C NMR (75 MHz, DMSO- d_6) : 146.9 , 144.6 , 143.7 , 142.3 , 141.9 , 134.4 , 133.3 , 130.34 , 130.29 , 130.2 , 129.9 , 129.3 , 129.2 , 128.6 , 128.1 , 121.8 , 121.3 , 112.8 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{13}\text{Cl}_2\text{N}_3[\text{M}+\text{H}]^+$: 389.0487 ; found : 389.0488.

8-chloro-2,3-bis(3-chlorophenyl)-5H-pyrazino[2,3-b]indole (**4as**):



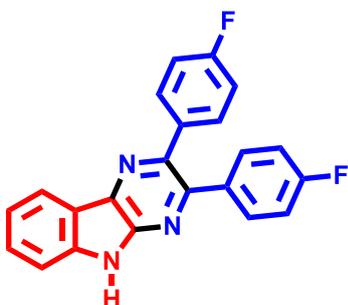
Yield : 85% ; White solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 183-185°C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 12.51 (s, 1H) , 8.27 (s, 1H), 7.65-7.55 (m, 4H) , 7.47-7.28 (m, 6H) ; ^{13}C NMR (75 MHz, DMSO- d_6) : 147.8 , 145.0 , 144.3 , 142.0 , 141.7 , 140.1 , 133.3 , 133.2 , 130.4 , 130.3 , 130.2 , 129.7 , 129.2 , 128.7 , 128.2 , 125.7 , 121.0 , 120.8 , 114.5 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{13}\text{Cl}_3\text{N}_3[\text{M}+\text{H}]^+$: 424.0175 ; found : 424.0179.

8-chloro-2,3-bis(2-chlorophenyl)-5H-pyrazino[2,3-b]indole (**4at**):



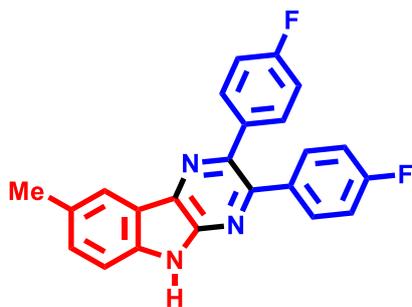
Yield : 87% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 188-190°C ; ^1H NMR (400 MHz, DMSO- d_6) : δ (ppm)= 12.57 (s, 1H) , 8.30 (s, 1H), 7.71 -7.66 (m, 2H) , 7.45 -7.37 (m, 4H) , 7.36 -7.26 (m, 4H) ; ^{13}C NMR (100 MHz, DMSO- d_6) : 148.0 , 144.7 , 144.6 , 140.0 , 138.0 , 137.7 , 133.4 , 133.2 , 132.8 , 130.6 , 130.5 , 129.8 , 129.7 , 127.01 , 126.96 , 125.8 , 121.1 , 120.7 , 114.0 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{13}\text{Cl}_3\text{N}_3[\text{M}+\text{H}]^+$: 424.0175 ; found : 424.0172.

2,3-bis(4-fluorophenyl)-5H-pyrazino[2,3-b]indole (**4au**):



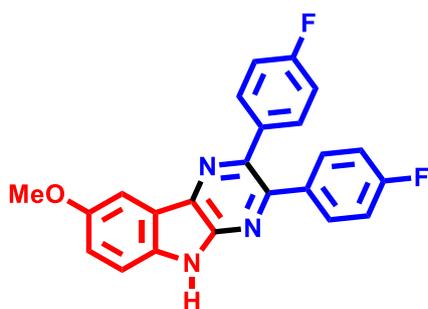
Yield : 85% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 186-188 °C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 12.20 (s, 1H) , 8.26 (d, J = 9 Hz, 1H) , 7.64 (d, J = 3 Hz, 2H) , 7.49- 7.43 (m, 4H) , 7.37 -7.30 (m, 1H), 7.23- 7.17 (m, 4H) ; ^{13}C NMR (75 MHz, DMSO- d_6) : 162.4 (1J = 244.4 Hz) , 147.4 , 144.6 , 144.3 , 141.7 , 136.91 , 136.87 , 136.52 , 136.48 , 133.9 , 133.6 , 132.6 (3J = 12.75 Hz) , 132.5(3J = 8.5 Hz) , 129.6 , 121.6 , 121.2 , 119.7 , 115.5 (2J = 21 Hz) , 115.47(2J = 21.75 Hz) , 112.7 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{14}\text{F}_2\text{N}_3[\text{M}+\text{H}]^+$: 358.3718 ; found : 358.3710.

2,3-bis(4-fluorophenyl)-8-methyl-5H-pyrazino[2,3-b]indole (**4av**):



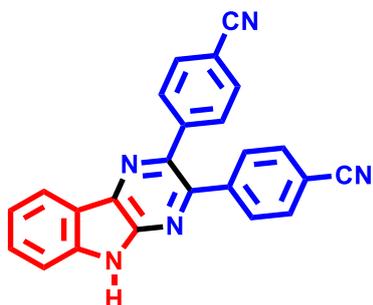
Yield : 83% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 190-192°C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 12.12 (s, 1H) , 8.04 (s, 1H), 7.52-7.41 (m, 6H) , 7.21-7.16 (m, 4H) , 2.49 (s,3H) ; ^{13}C NMR (75 MHz, DMSO- d_6) : 162.4 (1J = 243.75 Hz) , 162.1 (1J = 243.0 Hz) , 160.7 , 160.5 , 147.1 , 144.7 , 144.0 , 139.9 , 137.0 , 136.9 , 136.57 , 136.53 , 133.8 , 132.6 (3J = 9 Hz) , 132.5 (3J = 9 Hz) , 132.49 , 132.4 , 131.0 , 130.1 , 121.3 , 119.8 , 115.5 (2J = 21.75 Hz) , 115.4 (2J = 21.0 Hz), 112.5 , 21.43 ; HRMS-ESI (m/z): calcd. for $\text{C}_{23}\text{H}_{16}\text{F}_2\text{N}_3[\text{M}+\text{H}]^+$: 372.1312 ; found : 372.1325.

2,3-bis(4-fluorophenyl)-8-methoxy-5H-pyrazino[2,3-b]indole (**4aw**):



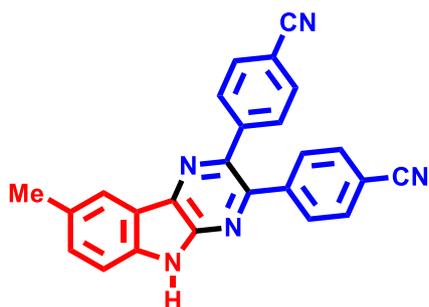
Yield : 82% ; White solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 191-193 °C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 11.97 (s, 1H) , 7.73 (s, 2H), 7.49-7.42 (m, 7H) , 7.38-7.31 (m, 4H), 3.94 (s,3H) ; ^{13}C NMR (75 MHz, DMSO- d_6) : 163.9 , 163.7 , 160.7 , 160.5 , 147.2 , 144.7 , 143.9 , 139.9 , 136.8 , 136.53 , 136.51 , 135.5 , 133.8 , 132.6 , 132.53 , 132.48 , 132.3 , 130.9 , 130.1 , 121.3 , 119.9 , 115.7 , 115.5 , 115.36 , 115.33 , 112.4 , 55.5 ; HRMS-ESI (m/z): calcd. for $\text{C}_{23}\text{H}_{16}\text{F}_2\text{N}_3\text{O}[\text{M}+\text{H}]^+$: 388.1261 ; found : 388.1260.

4,4'-(5H-pyrazino[2,3-b]indole-2,3-diyl)dibenzonitrile (**4ax**):



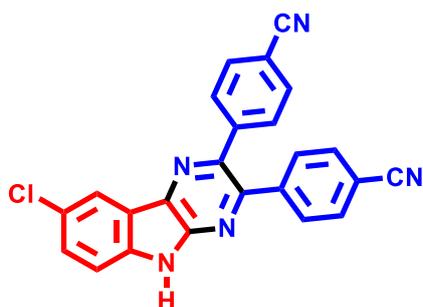
Yield : 84% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 186-188°C ; $^1\text{H NMR}$ (400 MHz, DMSO-d_6) : δ (ppm)= 12.50 (s, 1H) , 8.29 (d, J = 8 Hz, 1H) , 7.87- 7.82 (m, 4H) , 7.68- 7.60 (m, 6H), 7.39 -7.34 (m, 1H) ; $^{13}\text{C NMR}$ (100 MHz, DMSO-d_6) : 146.9 , 144.79 , 144.77 , 144.4 , 143.5 , 142.1 , 134.8 , 132.61 , 132.57 , 131.5 , 130.3 , 122.0 , 121.5 , 119.6 , 119.3 , 119.1 , 114.5 , 113.9 , 113.4 ; HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{14}\text{N}_5[\text{M}+\text{H}]^+$: 372.1249 ; found : 372.1246.

4,4'-(8-methyl-5H-pyrazino[2,3-b]indole-2,3-diyl)dibenzonitrile (**4ay**):



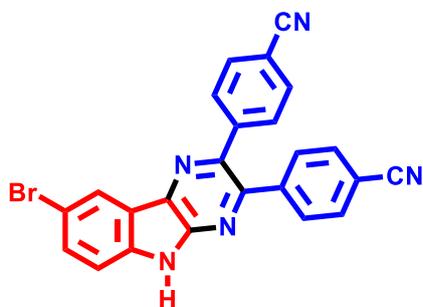
Yield : 82% ; White solid ; R_f : 0.2 (12% Ethyl Acetate in Petroleum Ether) ; M.P. = 194-196°C ; $^1\text{H NMR}$ (400 MHz, DMSO-d_6) : δ (ppm)= 12.54 (s, 1H) , 8.47 (s, 1H) , 7.87- 7.83 (m, 5H) , 7.64- 7.61 (m, 5H), 2.51 (s, 3H) ; $^{13}\text{C NMR}$ (100 MHz, DMSO-d_6) : 147.9 , 144.81 , 144.80 , 144.3 , 144.1 , 140.7 , 133.5 , 132.7 , 132.6 , 131.5 , 124.2 , 121.3 , 119.2 , 119.0 , 115.1 , 113.6 , 111.6 , 111.1 , 21.4 ; HRMS-ESI (m/z): calcd. for $\text{C}_{25}\text{H}_{16}\text{N}_5[\text{M}+\text{H}]^+$: 386.1406 ; found : 386.1402.

4,4'-(8-chloro-5H-pyrazino[2,3-b]indole-2,3-diyl)dibenzonitrile (**4az**):



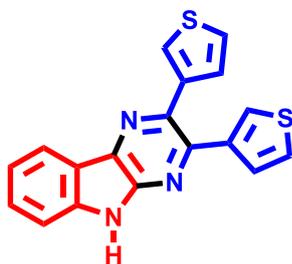
Yield : 86% ; White solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 189-191°C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 12.60 (s, 1H) , 8.34 (s, 1H), 7.86- 7.83 (m, 4H) , 7.66- 7.61 (m, 6H) ; ^{13}C NMR (100 MHz, DMSO- d_6): 147.9 , 145.2 , 144.5 , 144.2 , 144.1 , 140.0 , 133.6 , 132.7 , 132.6 , 131.6 , 130.1 , 126.0 , 121.1 , 120.6 , 119.2 , 119.1 , 114.6 , 111.5 , 111.0 ; HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{13}\text{ClN}_5[\text{M}+\text{H}]^+$: 406.0859 ; found : 406.0853.

4,4'-(8-bromo-5H-pyrazino[2,3-b]indole-2,3-diyl)dibenzonitrile (**4ba**):



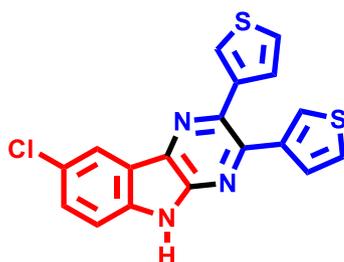
Yield : 85% ; White solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 191-193°C ; ^1H NMR (400 MHz, DMSO- d_6) : δ (ppm)= 12.58 (s, 1H) , 8.44 (s, 1H) , 7.88- 7.84 (m, 5H) , 7.64- 7.61 (m, 5H) ; ^{13}C NMR (100 MHz, DMSO- d_6) : 147.9 , 144.83 , 144.80 , 144.2 , 144.1 , 140.8 , 133.5 , 132.7 , 132.6 , 131.6 , 124.1 , 121.3 , 119.2 , 119.1 , 115.1 , 113.6 , 111.6 , 111.1 ; HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{13}\text{BrN}_5[\text{M}+\text{H}]^+$: 450.0354 ; found : 450.0355.

2,3-di(thiophen-3-yl)-5H-pyrazino[2,3-b]indole (**4bb**):



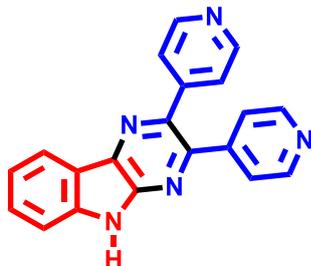
Yield : 76% ; Yellow solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 197-199°C ; ^1H NMR (300 MHz, DMSO- d_6) : δ (ppm)= 12.35 (s, 1H) , 8.21 (d, $J=9$ Hz, 1H) , 7.74-7.60 (m, 4H) , 7.24-6.98 (m, 5H) ; ^{13}C NMR (100 MHz, DMSO- d_6) : 144.7 , 143.2 , 142.6 , 141.8 , 140.3 , 138.3 , 132.5 , 129.8 , 129.7 , 128.8 , 128.6 , 128.5 , 128.1 , 126.8 , 120.9 , 120.7 , 114.5 ; HRMS-ESI (m/z): calcd. for $\text{C}_{18}\text{H}_{12}\text{N}_3\text{S}_2[\text{M}+\text{H}]^+$: 334.0473 ; found : 334.0475.

8-chloro-2,3-di(thiophen-3-yl)-5H-pyrazino[2,3-b]indole (**4bc**):



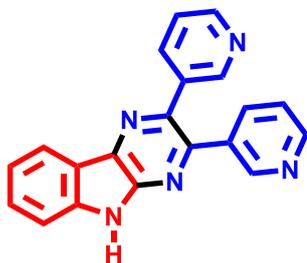
Yield : 76% ; Yellow solid ; R_f : 0.2 (10% Ethyl Acetate in Petroleum Ether) ; M.P. = 196-198°C ; ^1H NMR (300 MHz, DMSO-d_6) : δ (ppm)= 12.53 (s, 1H) , 8.21(s,1H) , 7.76-7.71 (m, 2H) , 7.63-7.62 (m, 1H) , 7.45-7.40 (m, 1H) , 7.20-7.14 (s, 3H) , 7.08 -7.05 (m, 1H) , 7.00 -6.98 (m, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : 144.7 , 143.1 , 142.6 , 141.9 , 140.3 , 138.4 , 132.5 , 129.8 , 129.7 , 128.8 , 128.6 , 128.5 , 128.1 , 125.8 , 120.8 , 120.7 , 114.5 ; HRMS-ESI (m/z): calcd. for $\text{C}_{18}\text{H}_{11}\text{N}_3\text{S}_2[\text{M}+\text{H}]^+$: 368.0083 ; found : 368.0085.

2,3-di(pyridin-4-yl)-5H-pyrazino[2,3-b]indole (**4bd**):



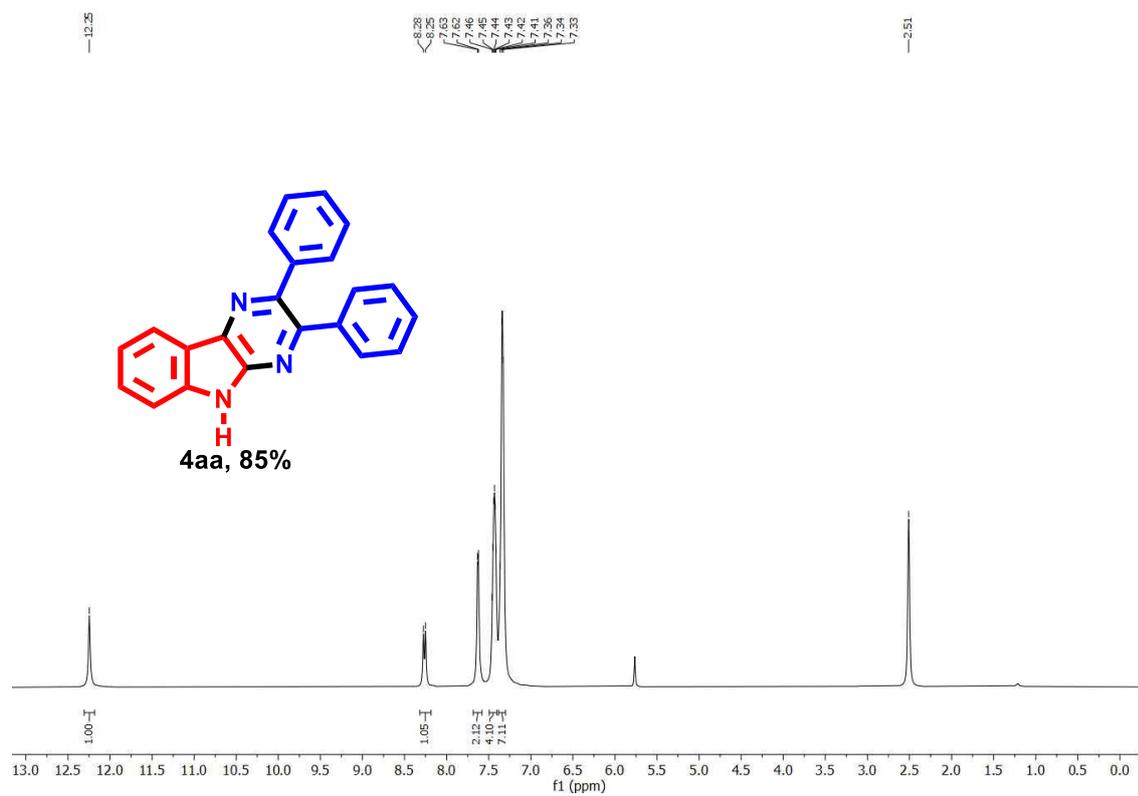
Yield : 81% ; Yellow solid ; R_f : 0.2 (8% Ethyl Acetate in Petroleum Ether) ; M.P. = 199-201°C ; ^1H NMR (300 MHz, DMSO-d_6) : δ (ppm)= 12.47 (s, 1H) , 8.62- 8.56 (m, 4H) , 8.28 (d, J = 9 Hz , 1H), 7.69-7.64 (m, 2H), 7.46-7.43 (m, 5H) ; ^{13}C NMR (75 MHz, DMSO-d_6) : 150.03 , 150.00 , 147.4 , 147.1 , 146.1 , 144.8 , 142.5 , 142.2 , 135.2 , 130.4 , 125.3 , 125.0 , 122.0 , 121.6 , 119.4 , 112.9 ; HRMS-ESI (m/z): calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_5[\text{M}+\text{H}]^+$: 324.3670 ; found : 324.3671.

2,3-di(pyridin-3-yl)-5H-pyrazino[2,3-b]indole (**4be**):

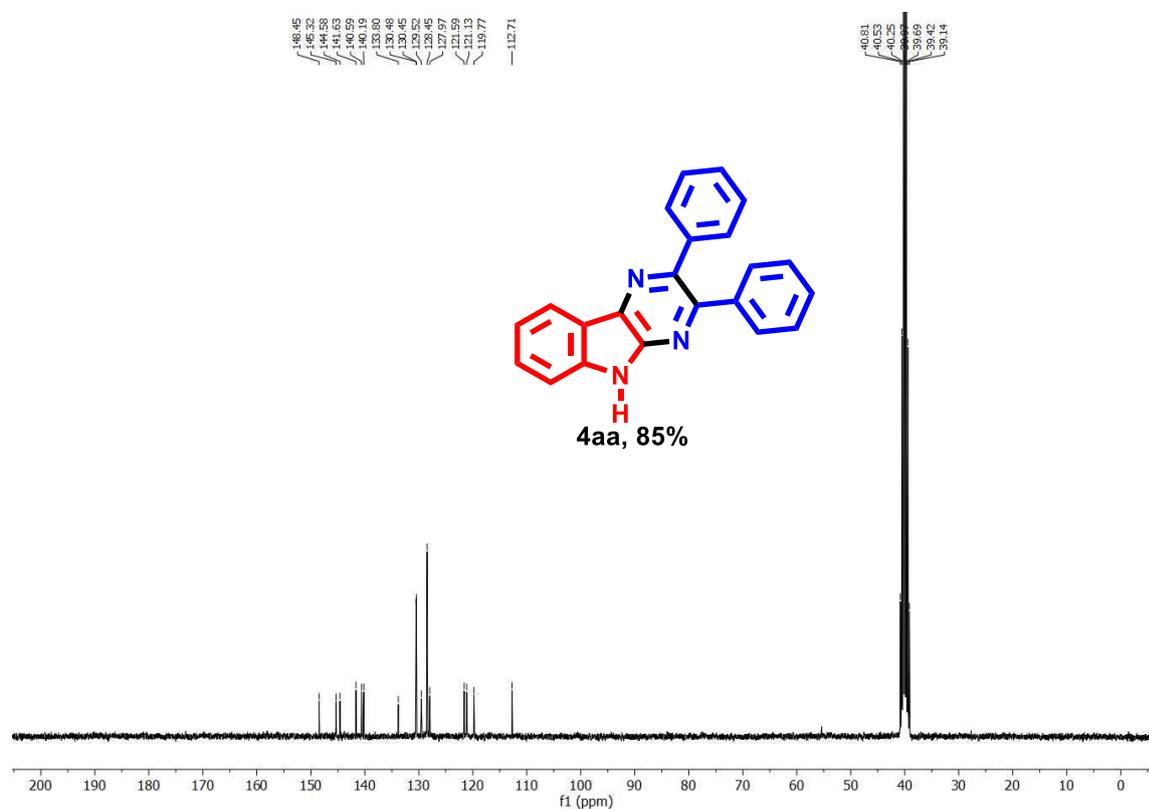


Yield : 80% ; Yellow solid ; R_f : 0.2 (12% Ethyl Acetate in Petroleum Ether) ; M.P. = 200-202°C ; ^1H NMR (300 MHz, DMSO-d_6) : δ (ppm)= 12.40 (s, 1H) , 8.61- 8.56 (m, 4H) , 8.32 (d, J = 9 Hz , 1H), 7.89-7.83 (m, 2H), 7.68-7.63 (m, 2H) , 7.45-7.39 (m, 3H) ; ^{13}C NMR (75 MHz, DMSO-d_6) : 150.5 , 150.4 , 149.4 , 149.0 , 146.0 , 144.5 , 142.6 , 141.9 , 137.0 , 134.7 , 130.1 , 123.6 , 121.9 , 121.4 , 119.5 , 112.8 ; HRMS-ESI (m/z): calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_5[\text{M}+\text{H}]^+$: 324.1249; found : 324.1245.

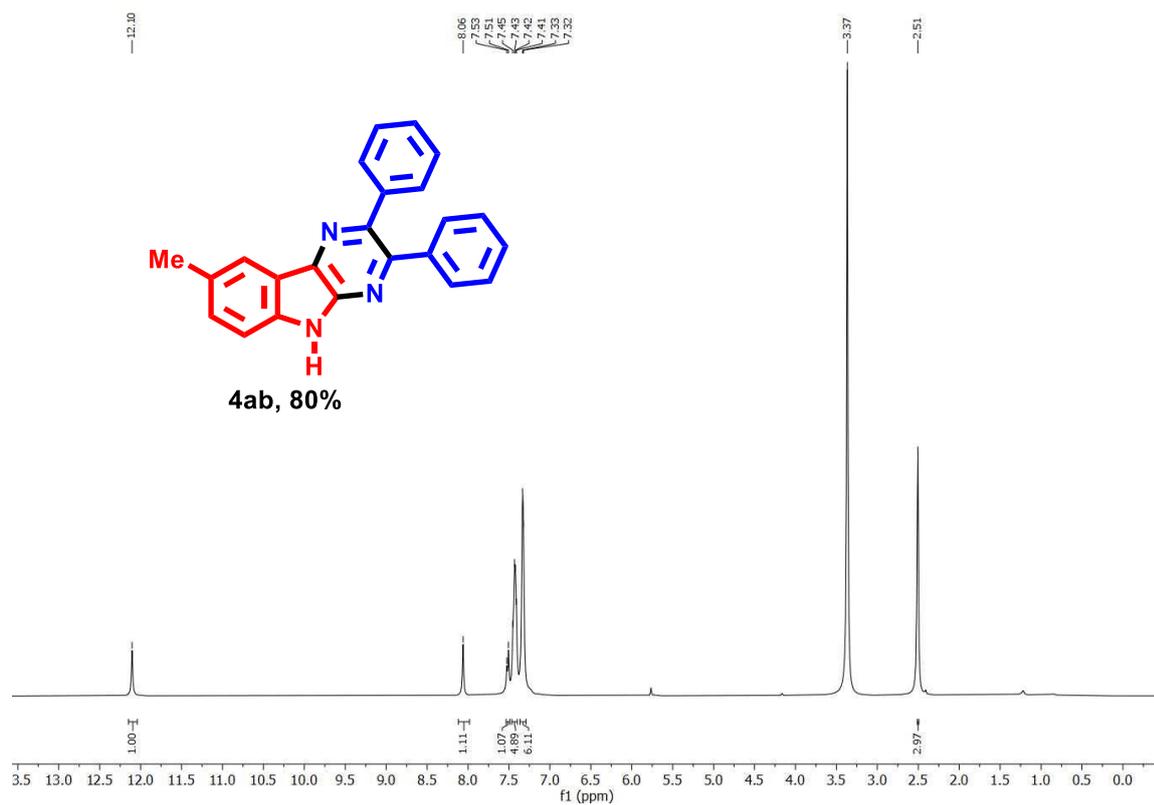
^1H and ^{13}C NMR spectra of compounds (4aa-4be)



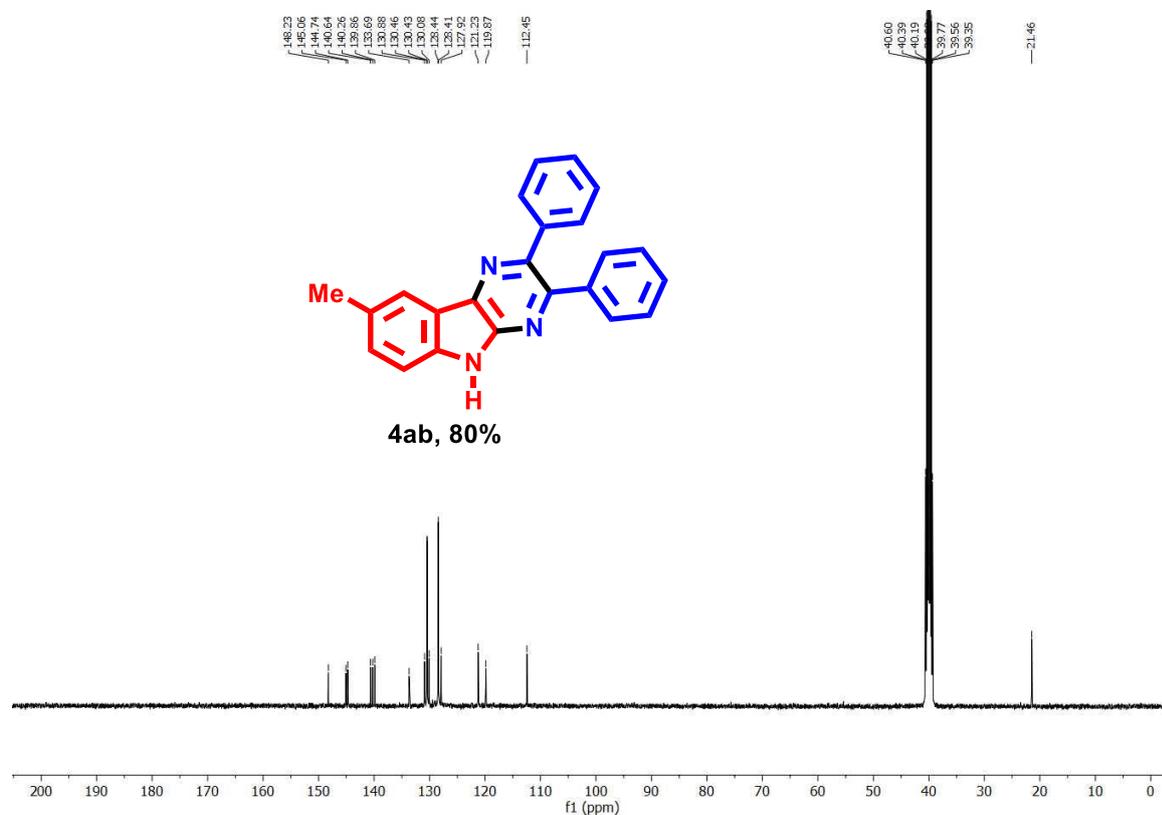
^1H NMR spectrum (300 MHz, DMSO- d_6) of compound 4aa



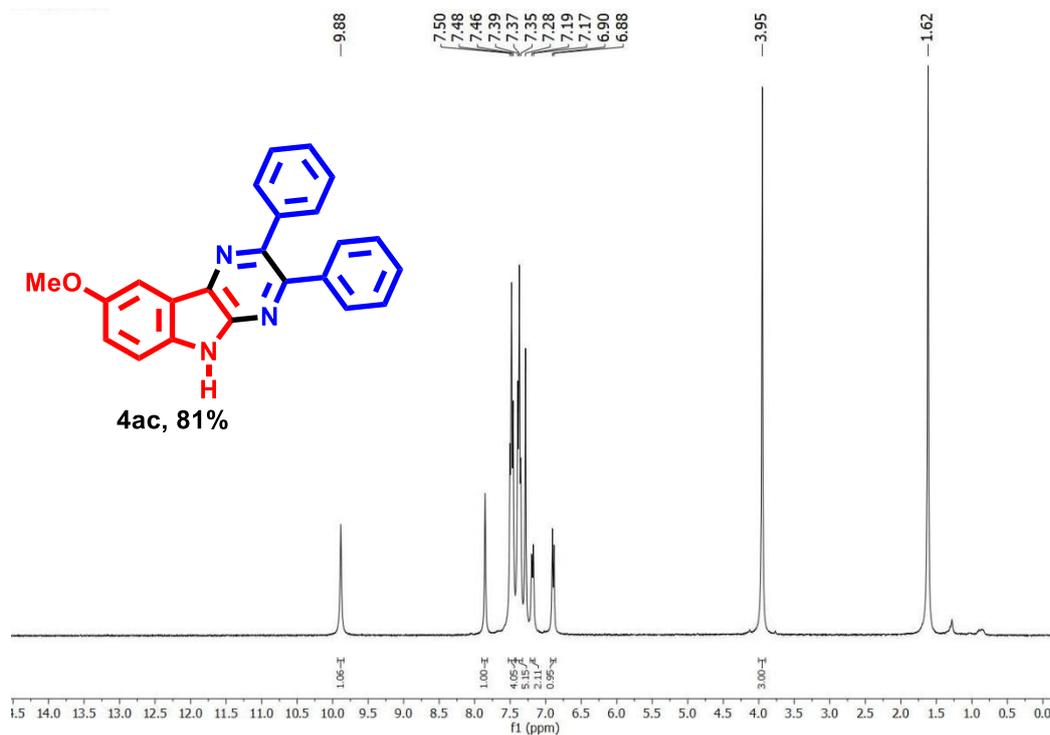
^{13}C NMR spectrum (75 MHz, DMSO- d_6) of compound 4aa



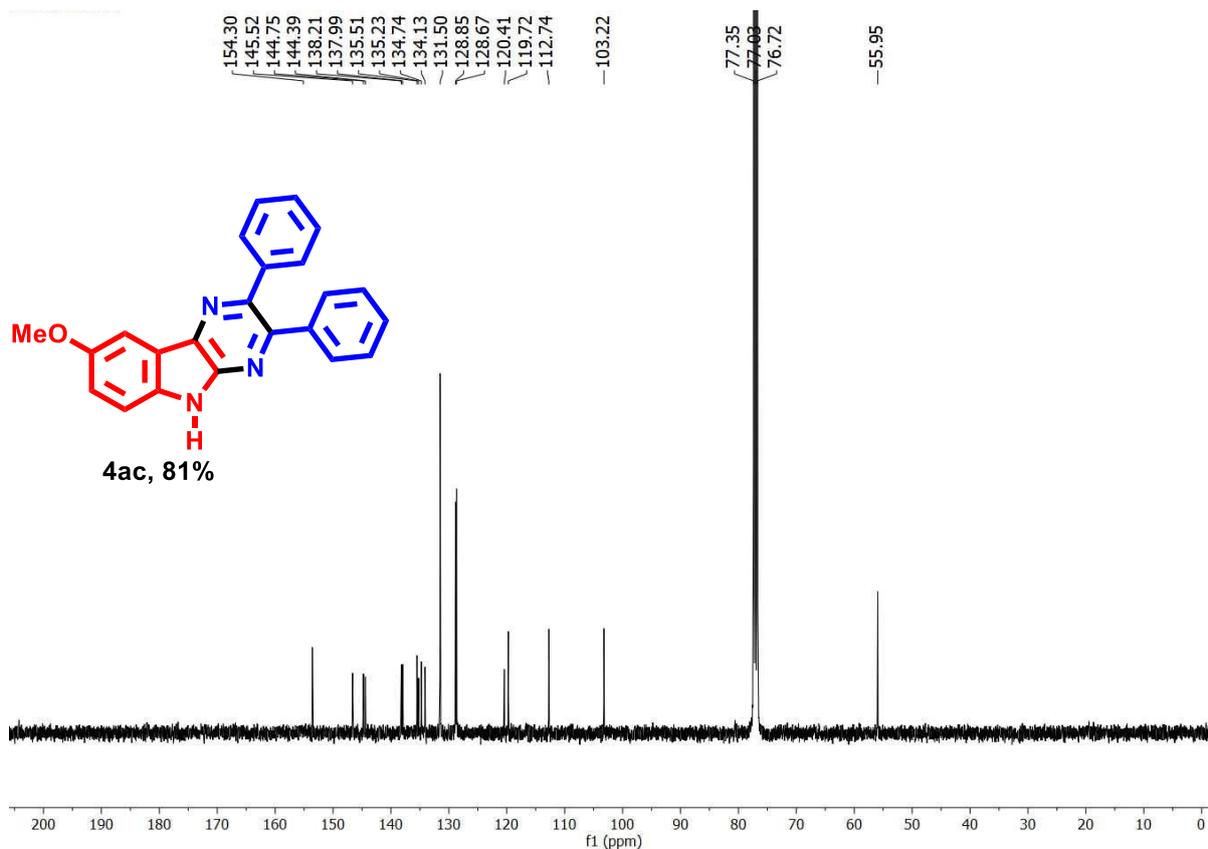
^1H NMR spectrum (400 MHz, DMSO-d_6) of compound **4ab**



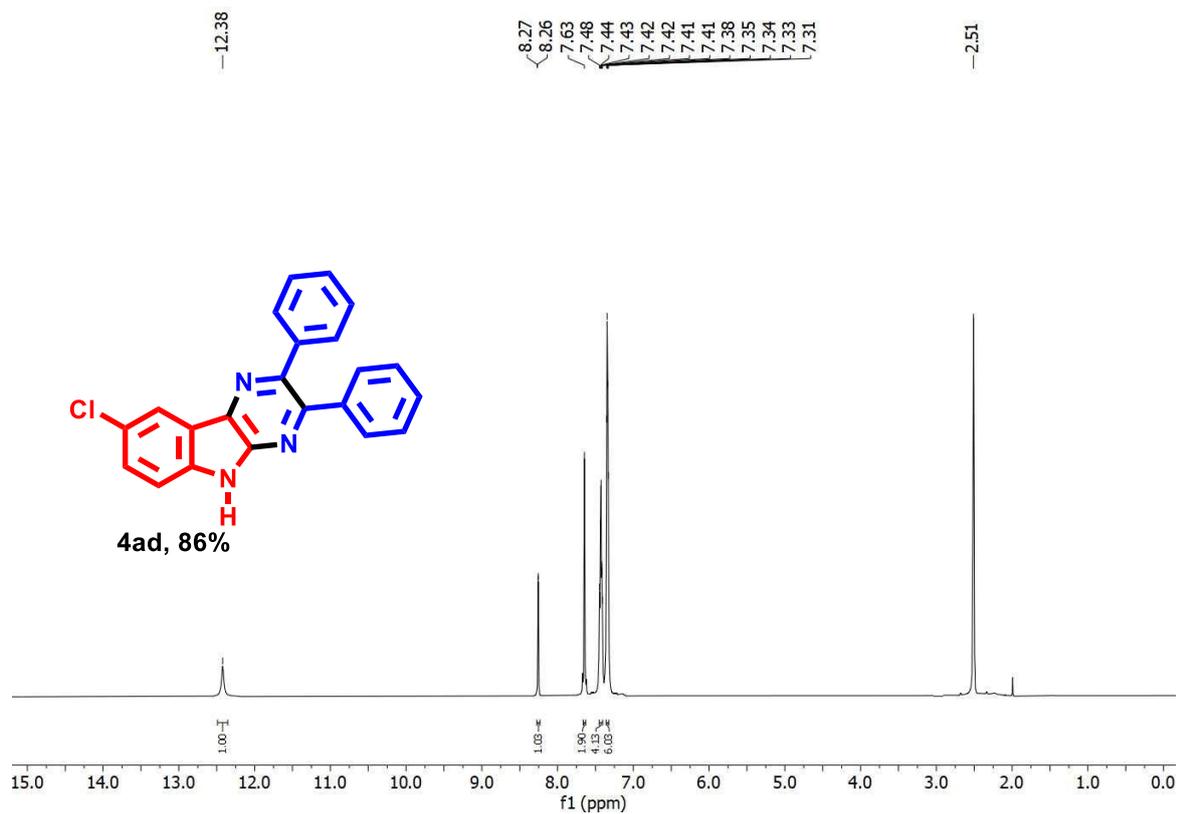
^{13}C NMR spectrum (100 MHz, DMSO-d_6) of compound **4ab**



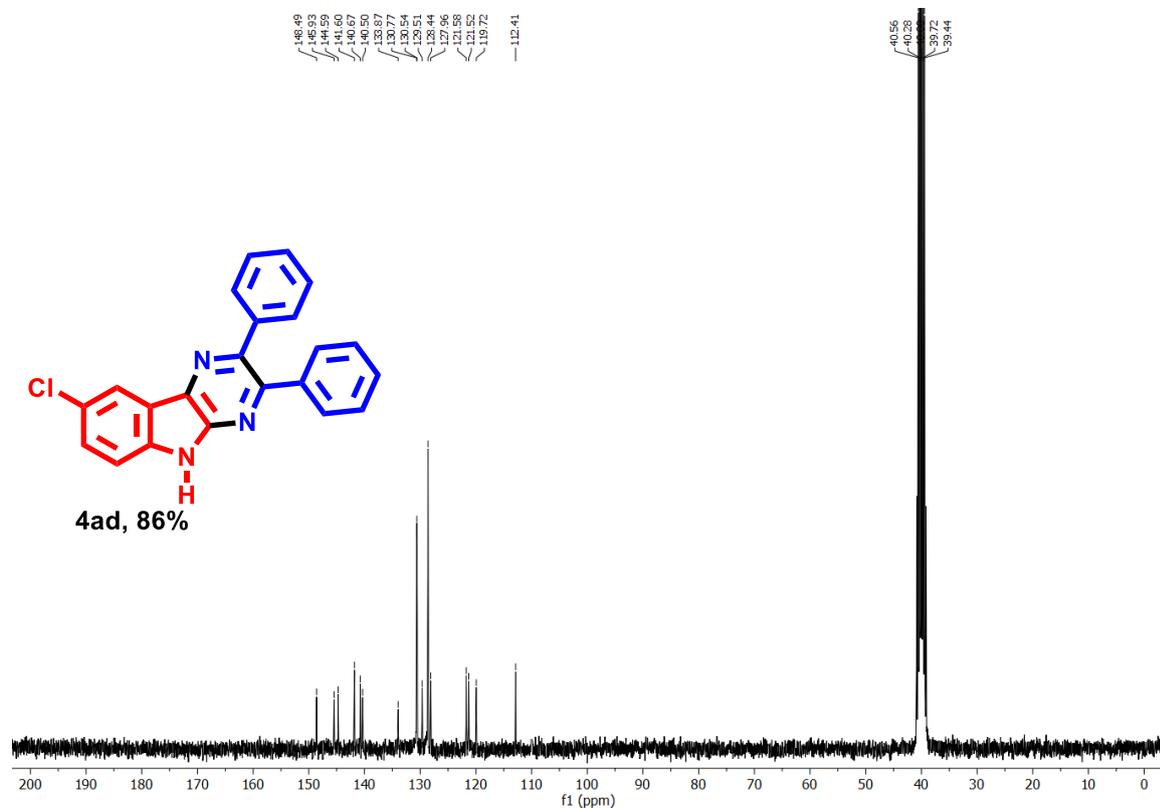
¹H NMR spectrum (400 MHz, CDCl₃) of compound 4ac



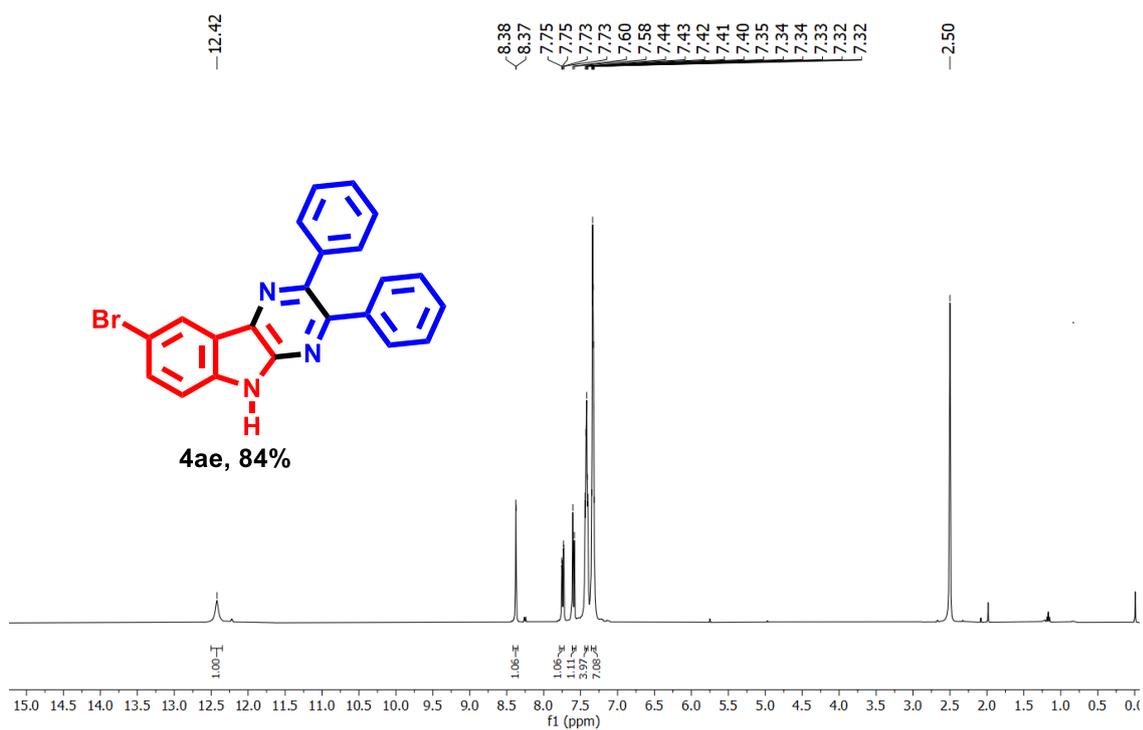
¹³C NMR spectrum (100 MHz, CDCl₃) of compound 4ac



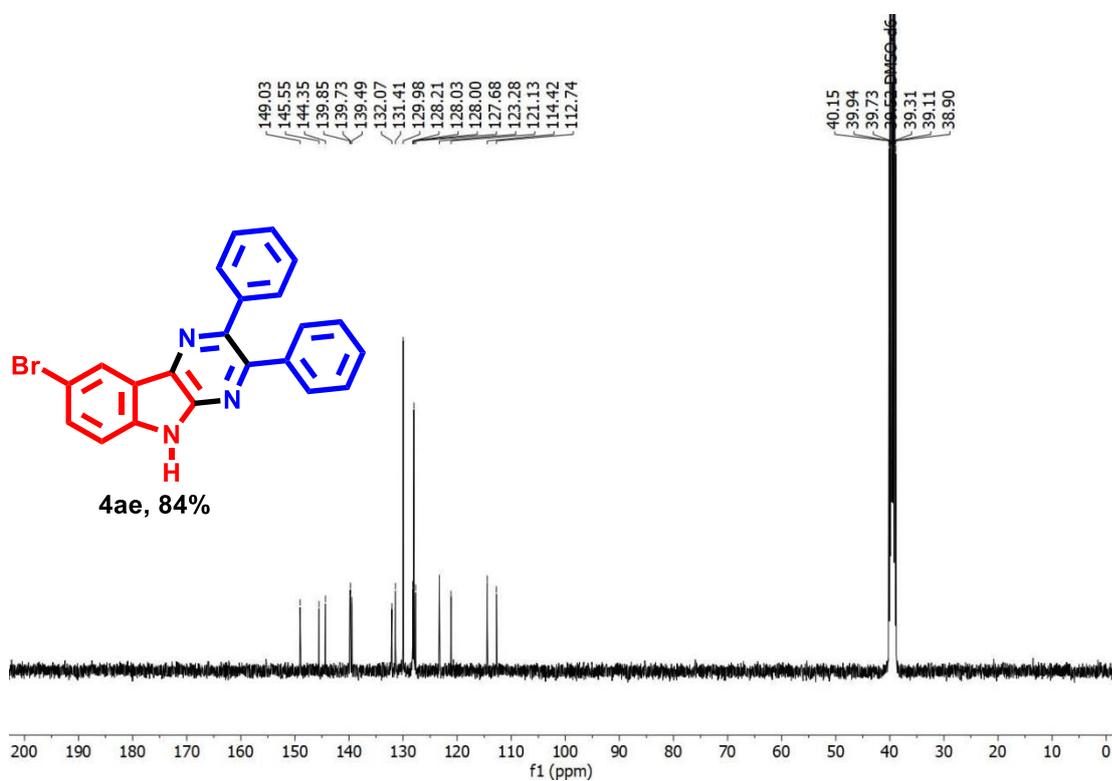
¹H NMR spectrum (400 MHz, DMSO-d₆) of compound 4ad



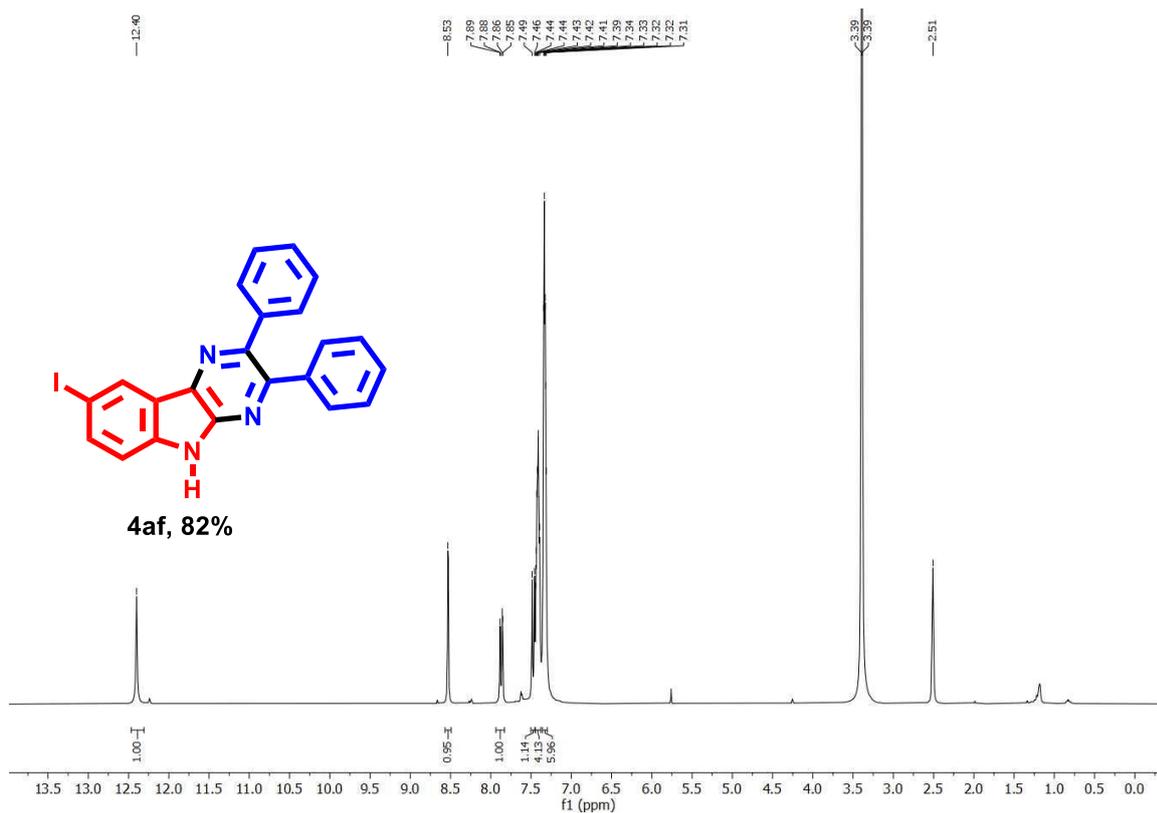
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound 4ad



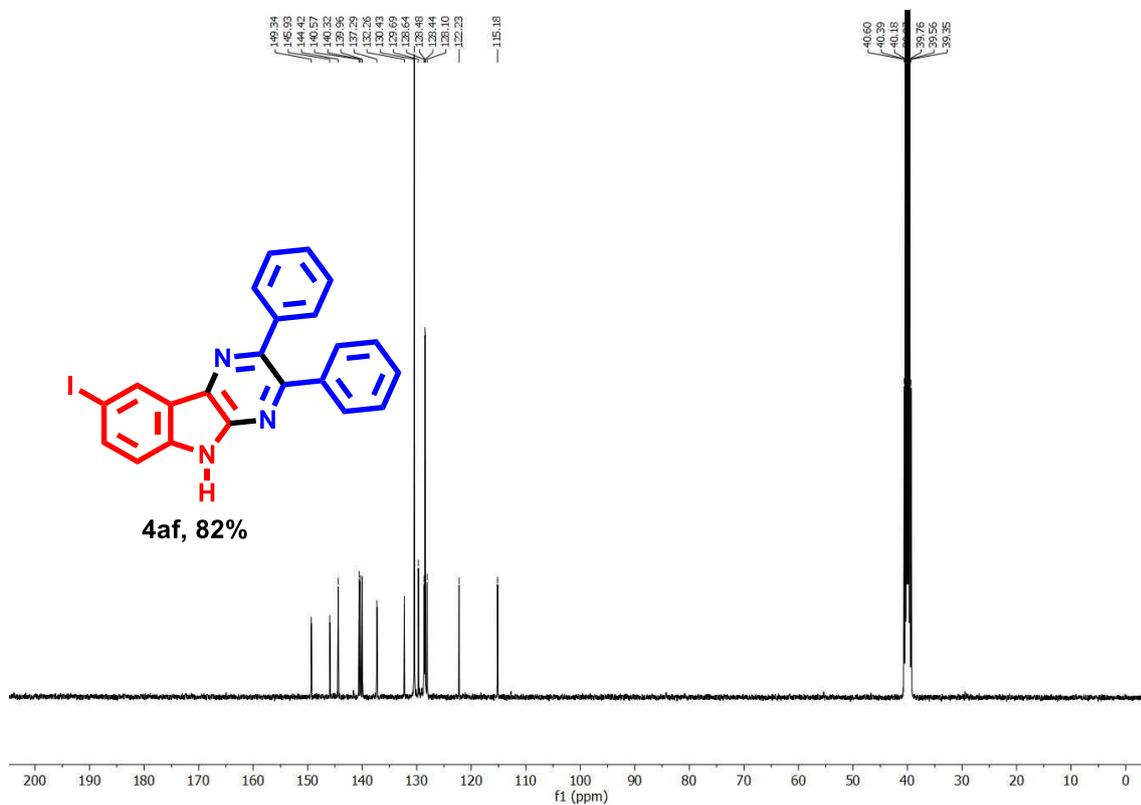
¹H NMR spectrum (400 MHz, DMSO-d₆) of compound **4ae**



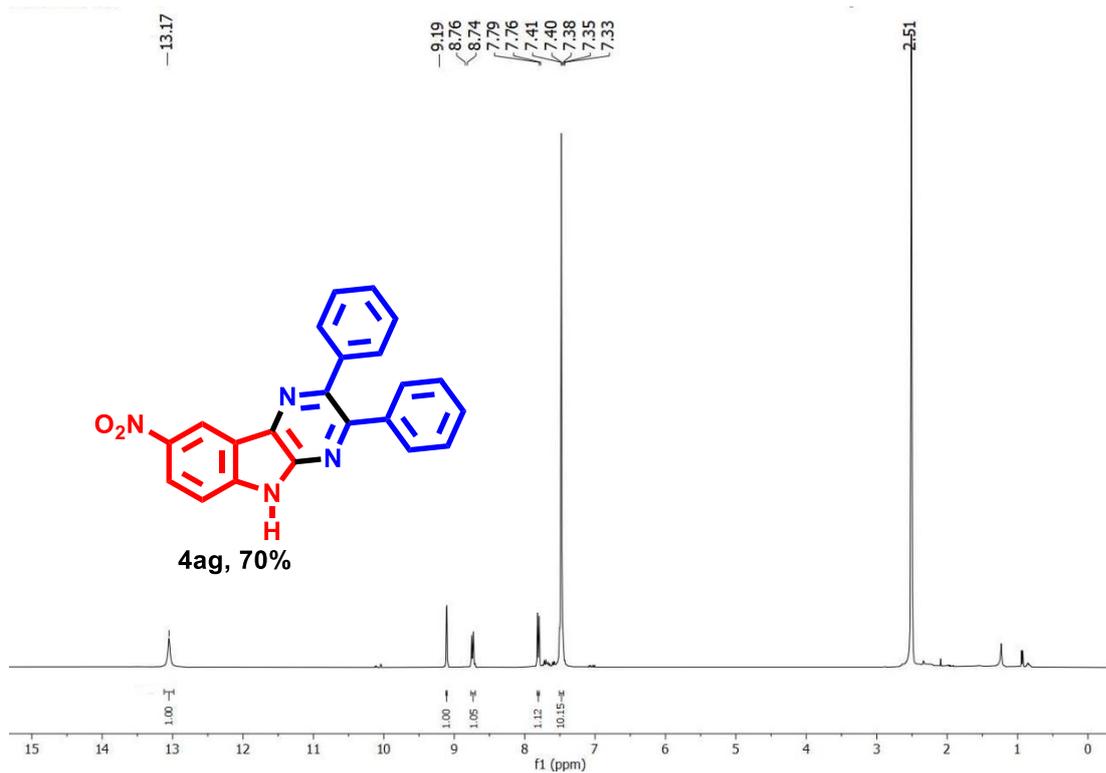
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound **4ae**



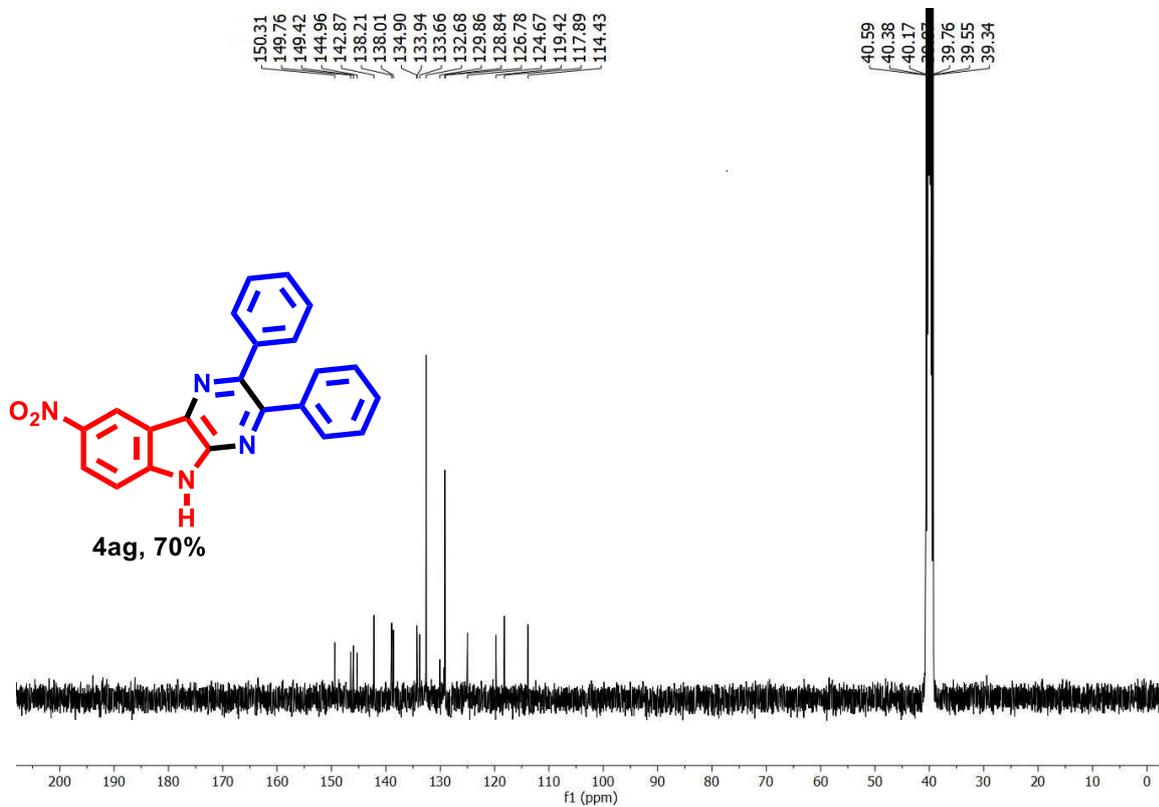
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4af



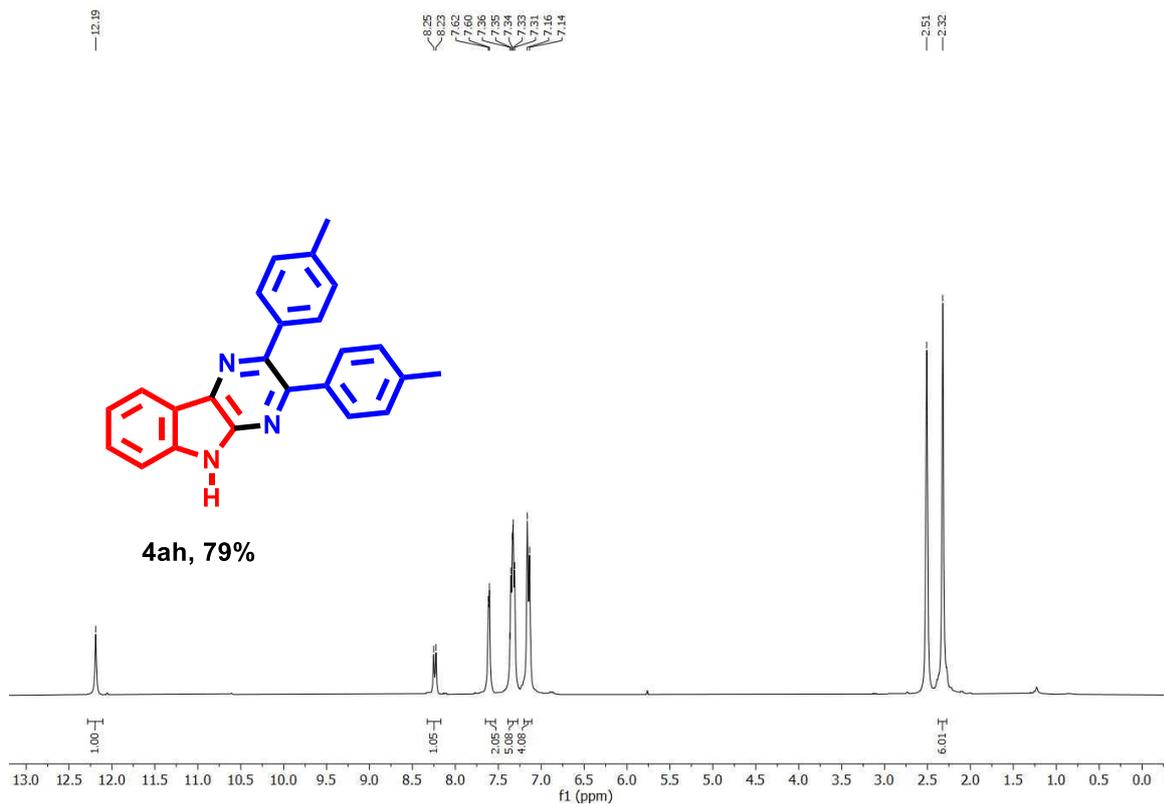
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound 4af



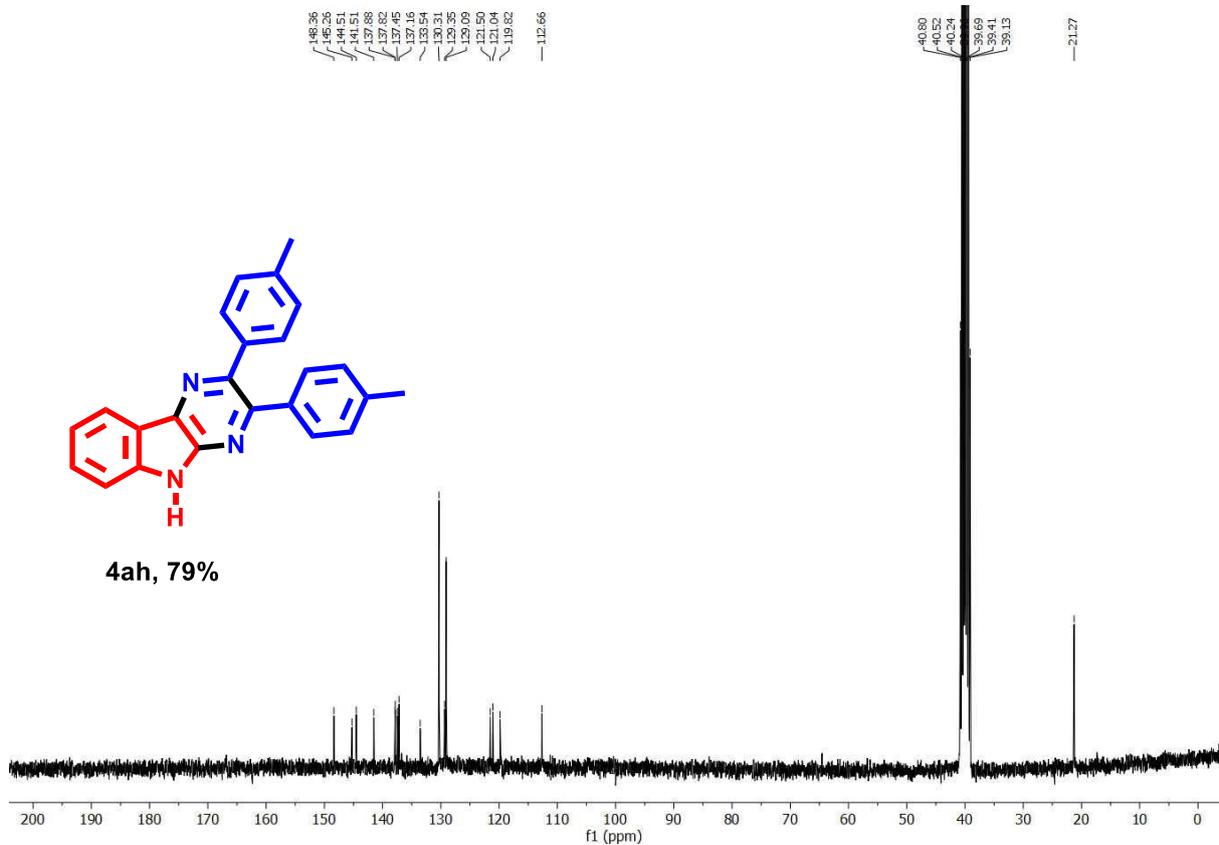
¹H NMR spectrum (400 MHz, DMSO-d₆) of compound 4ag



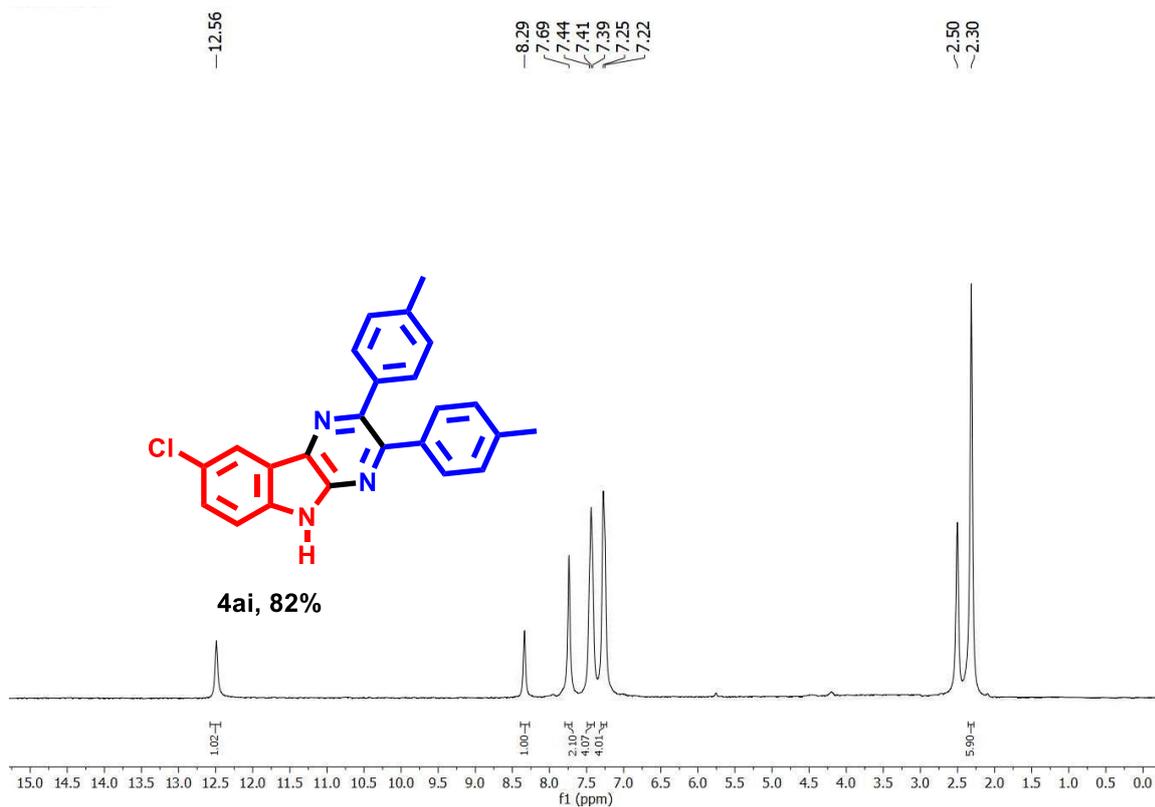
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound 4ag



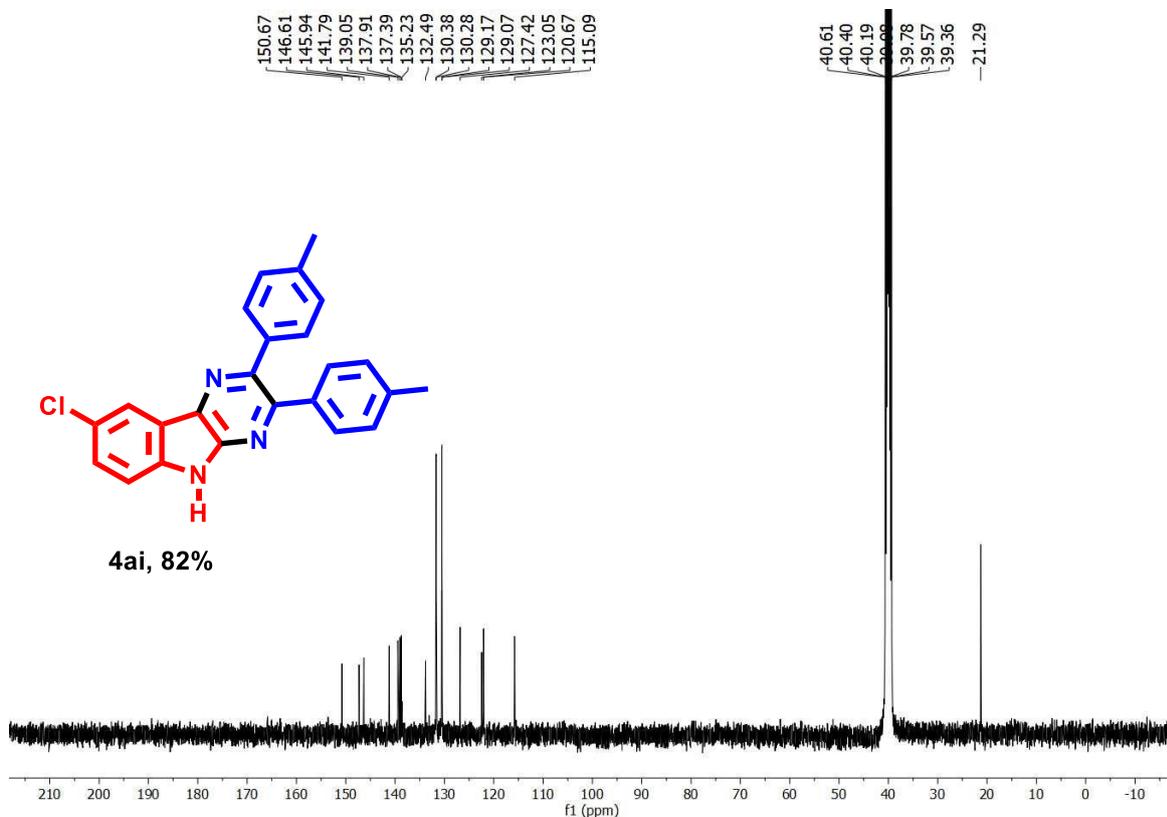
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4ah



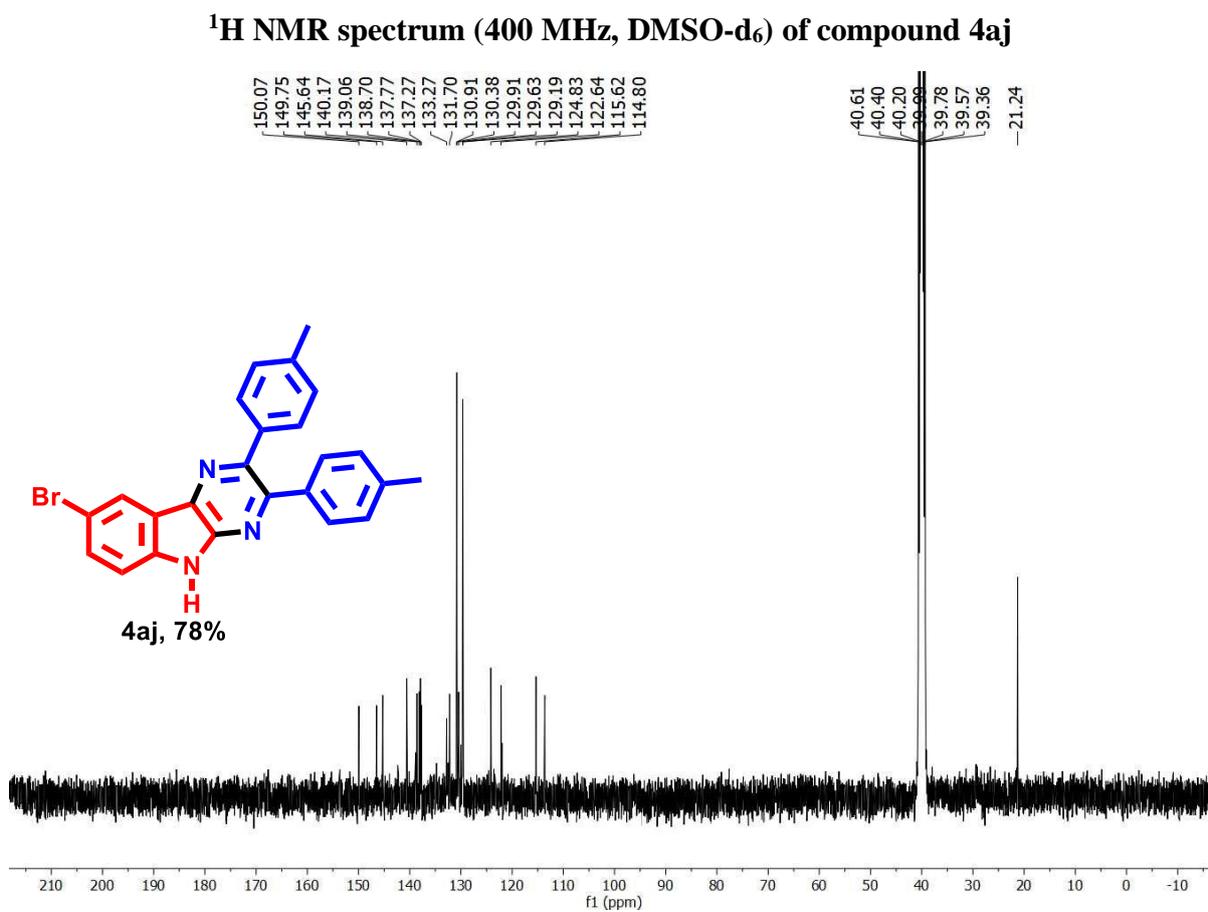
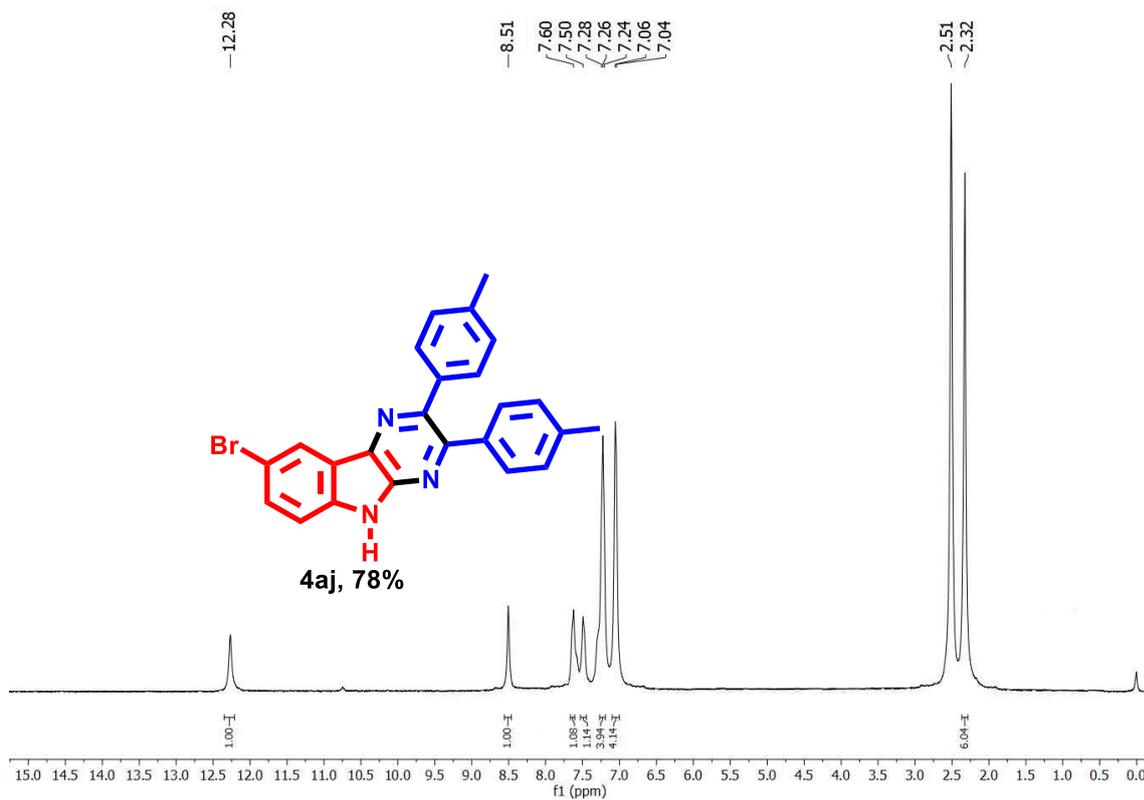
¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4ah

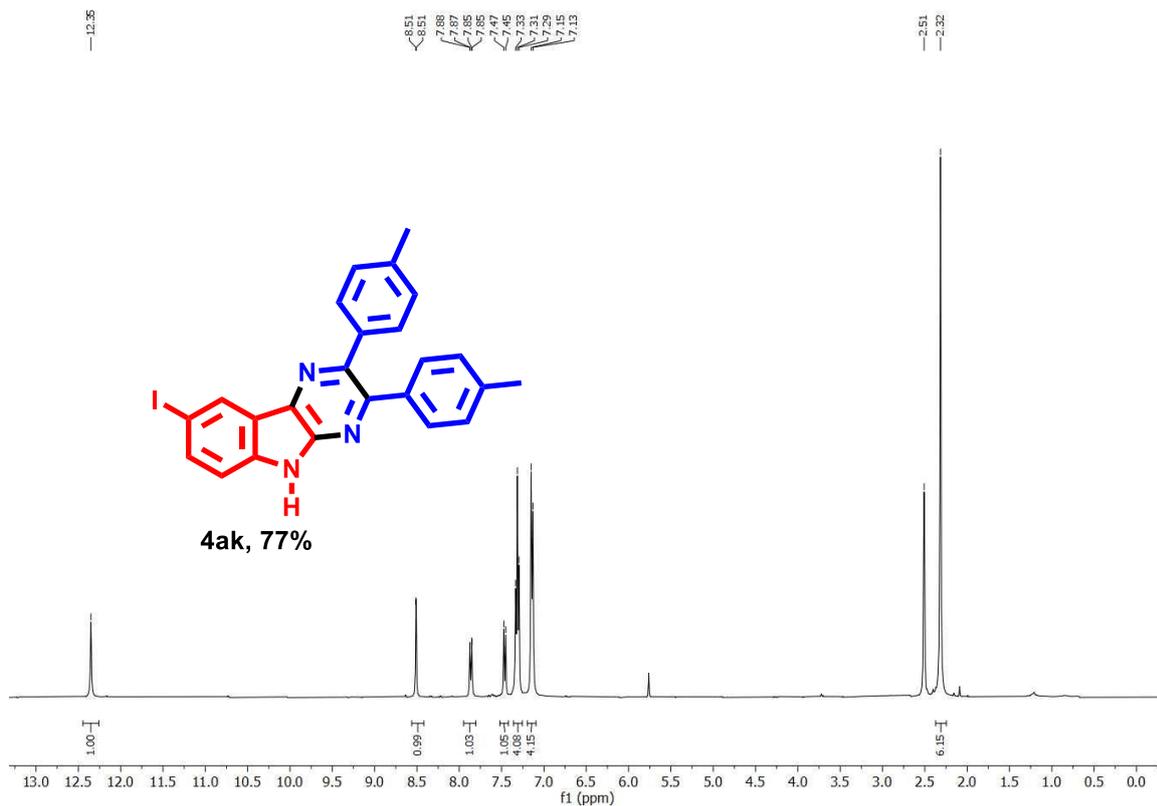


¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4ai

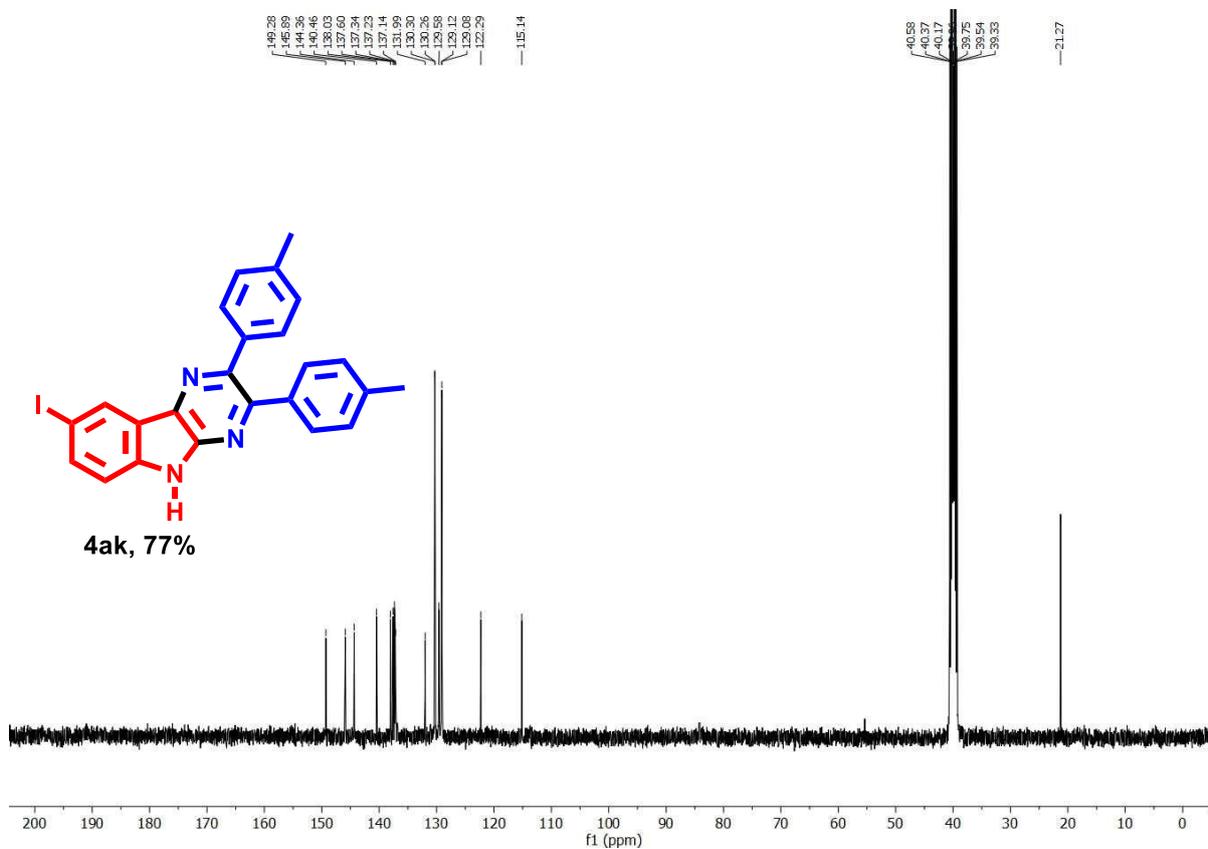


¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound 4ai

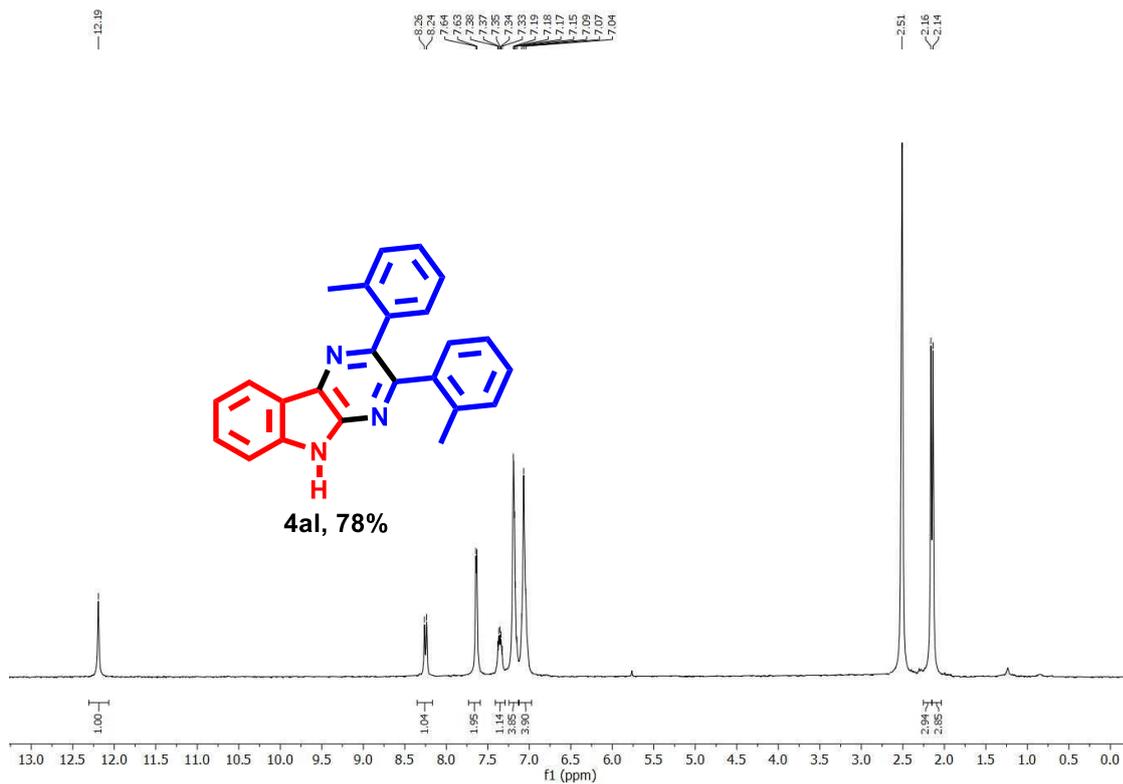




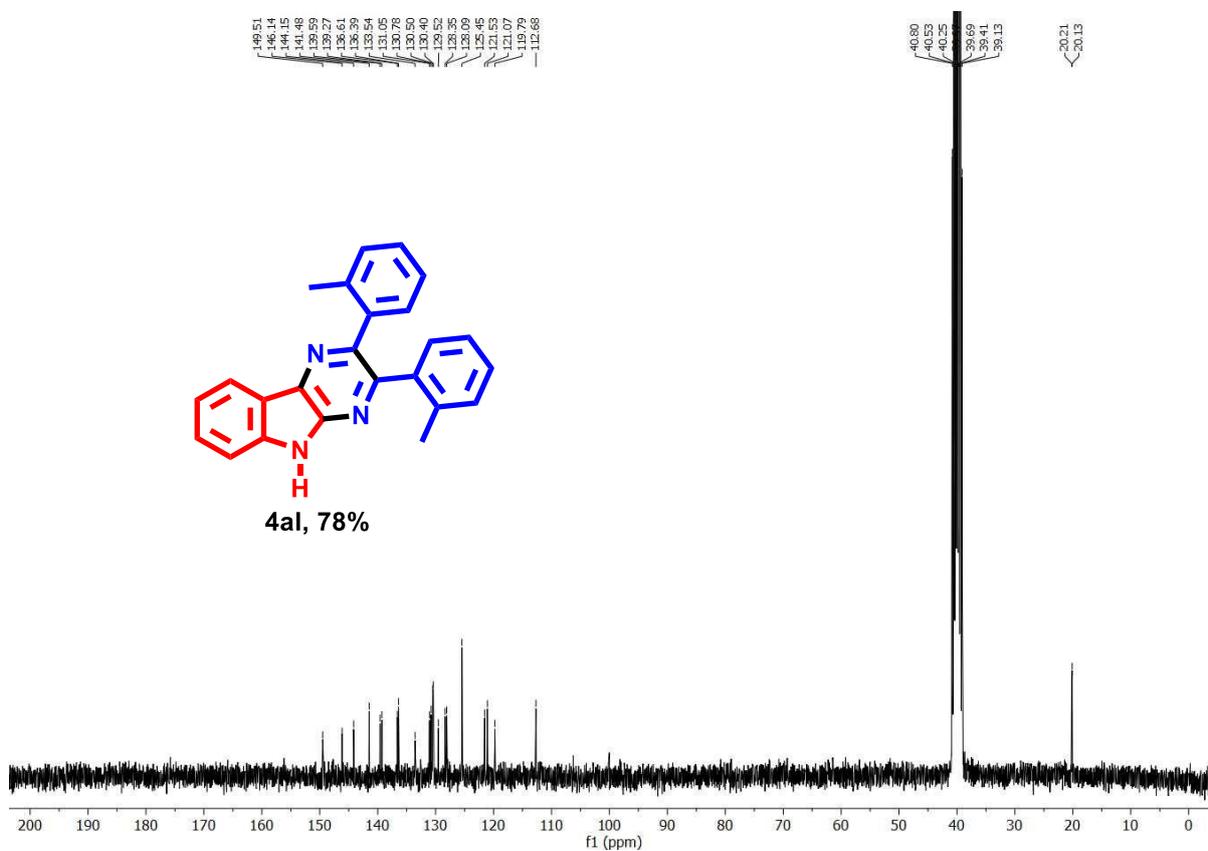
¹H NMR spectrum (400 MHz, DMSO-d₆) of compound 4ak



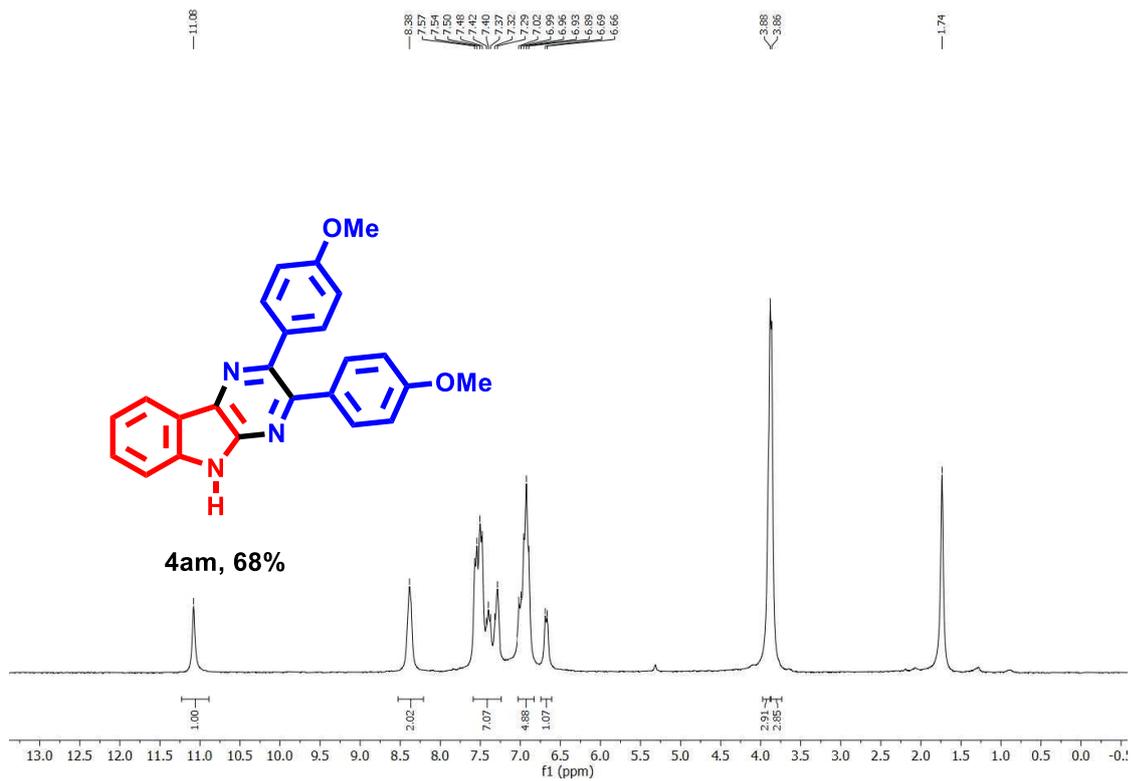
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound 4ak



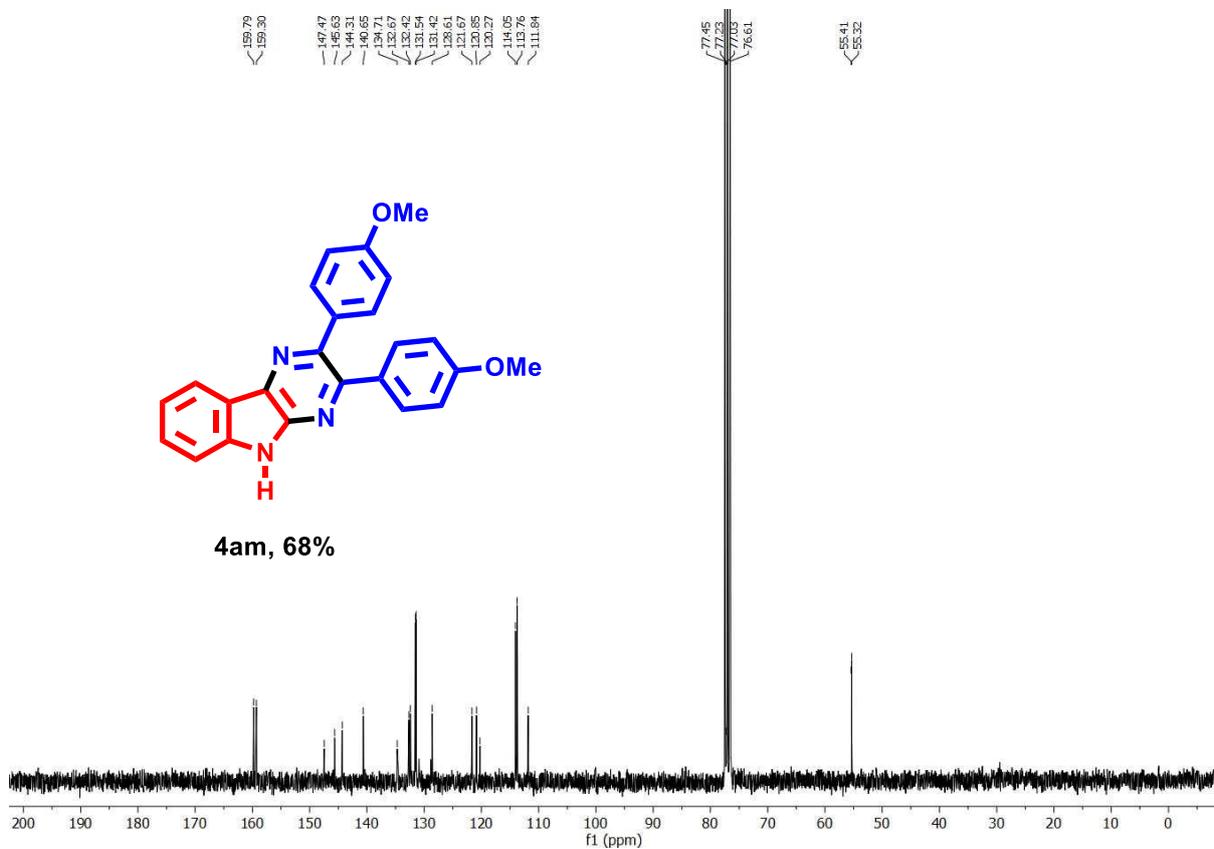
^1H NMR spectrum (300 MHz, DMSO- d_6) of compound 4al



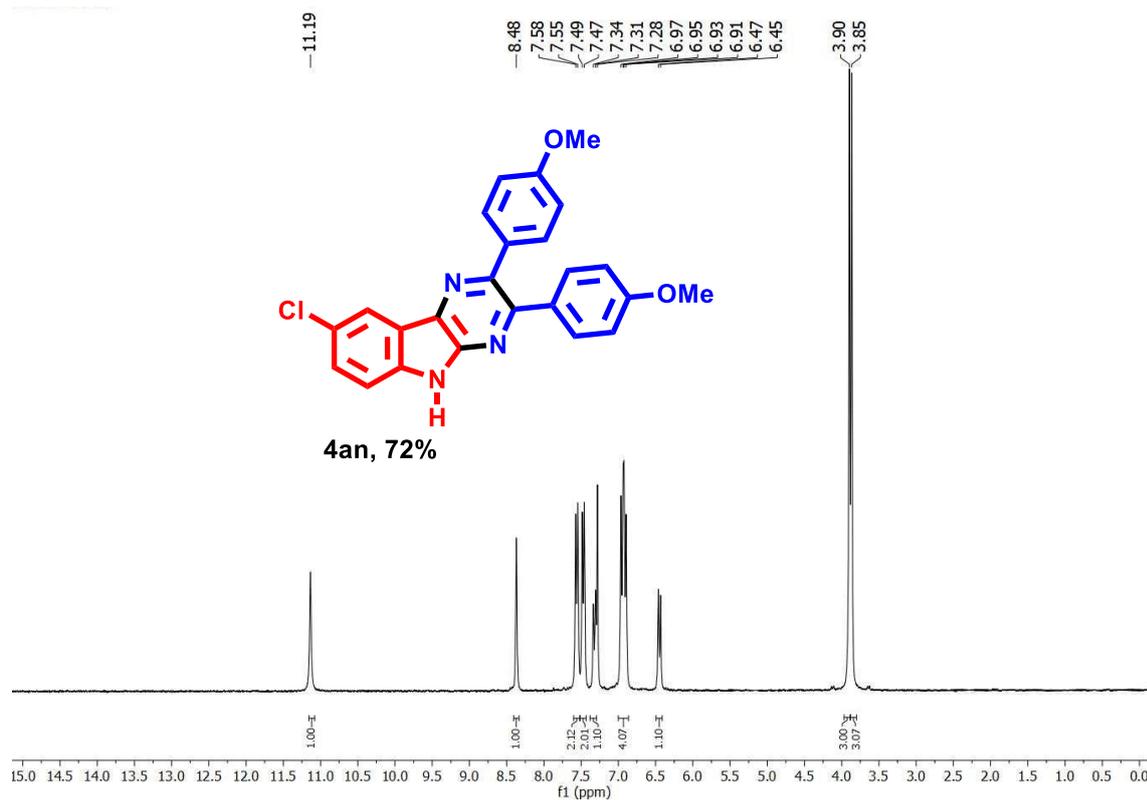
^{13}C NMR spectrum (75 MHz, DMSO- d_6) of compound 4al



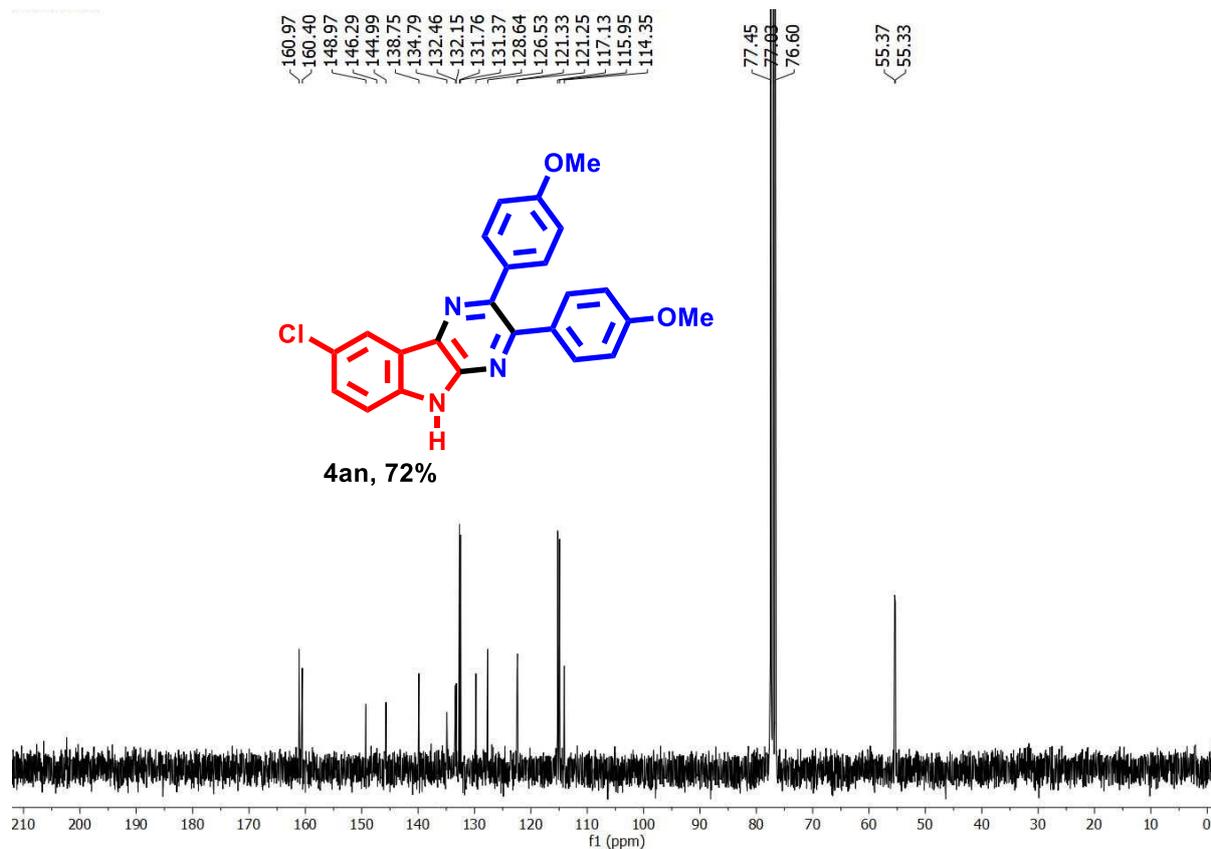
^1H NMR spectrum (300 MHz, CDCl_3) of compound 4am



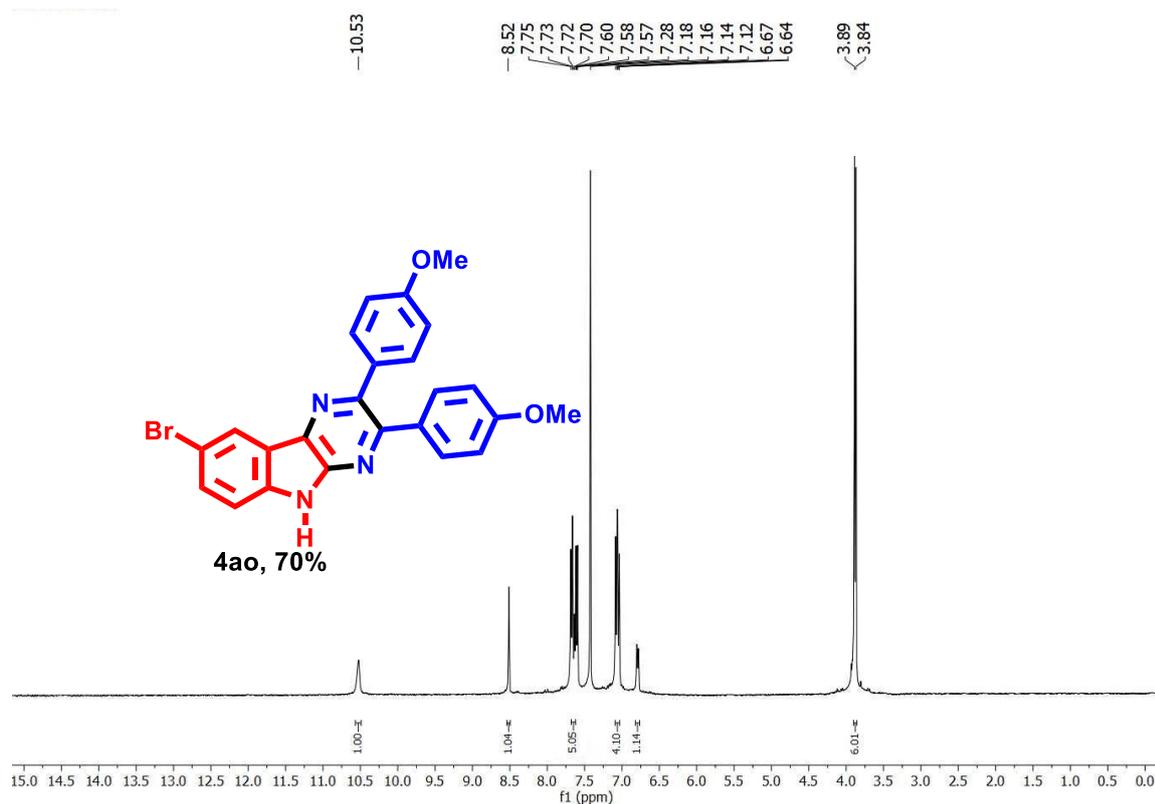
^{13}C NMR spectrum (75 MHz, CDCl_3) of compound 4am



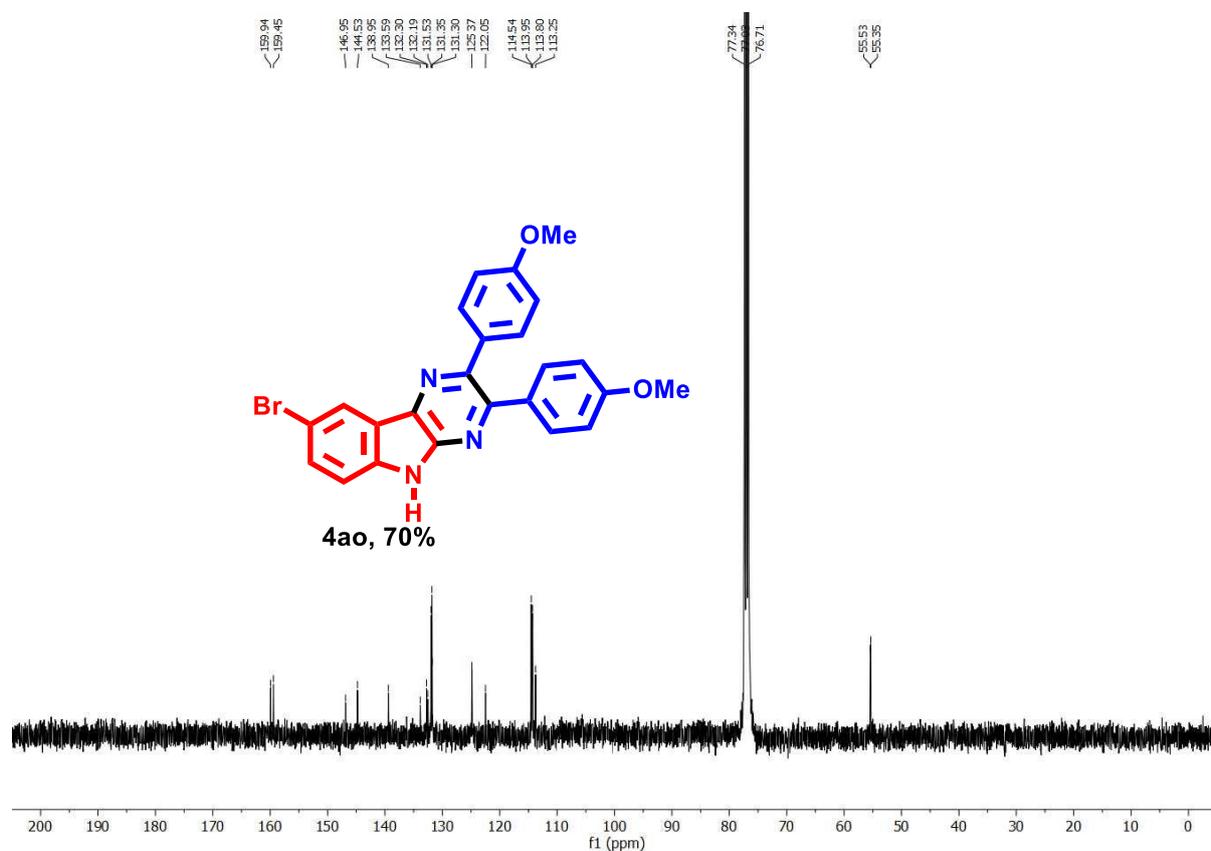
¹H NMR spectrum (300 MHz, CDCl₃) of compound 4an



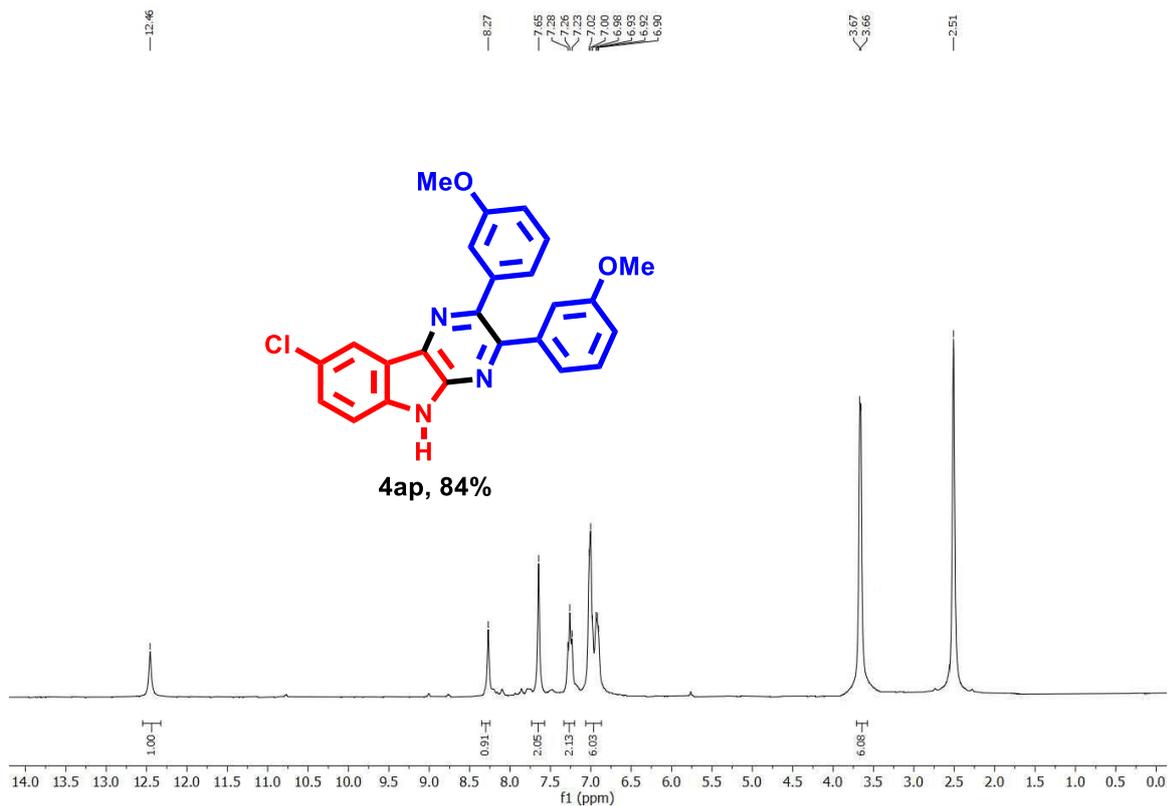
¹³C NMR spectrum (75 MHz, CDCl₃) of compound 4an



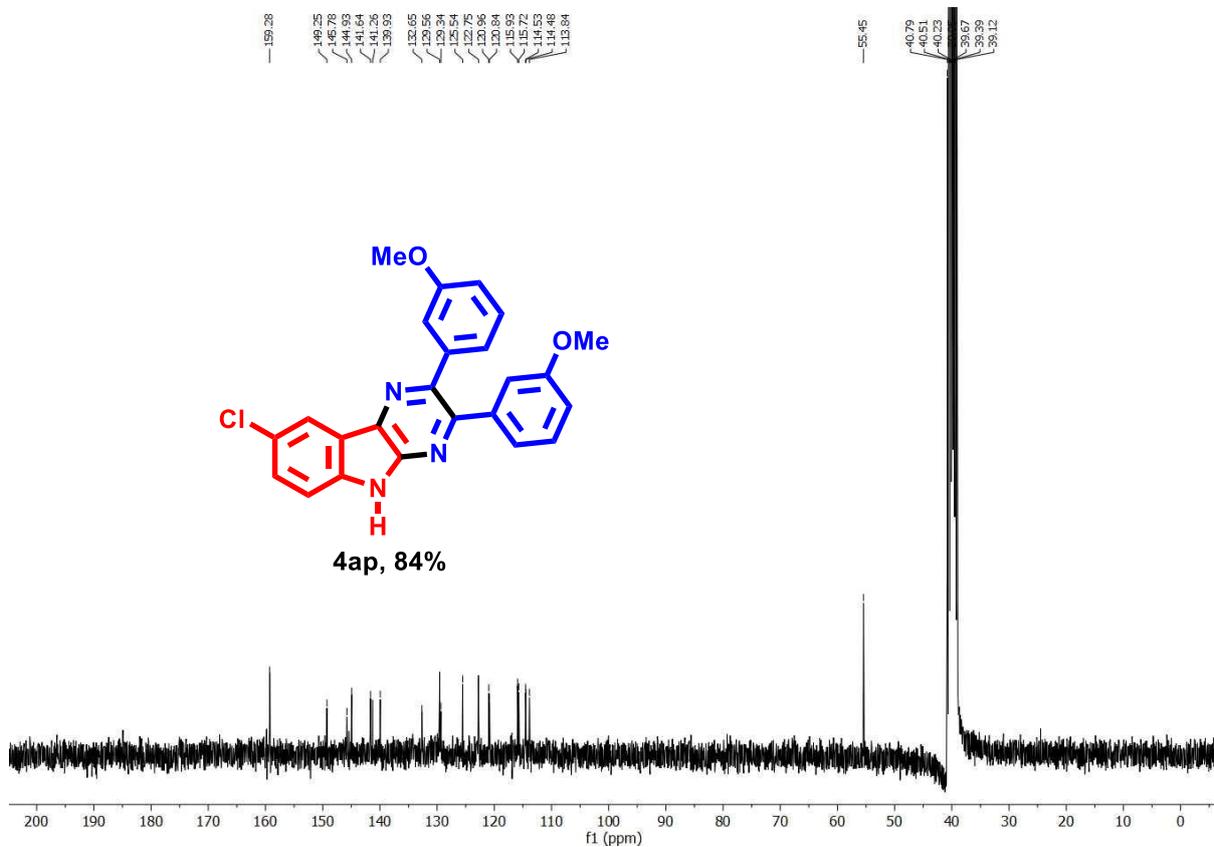
¹H NMR spectrum (400 MHz, CDCl₃) of compound 4ao



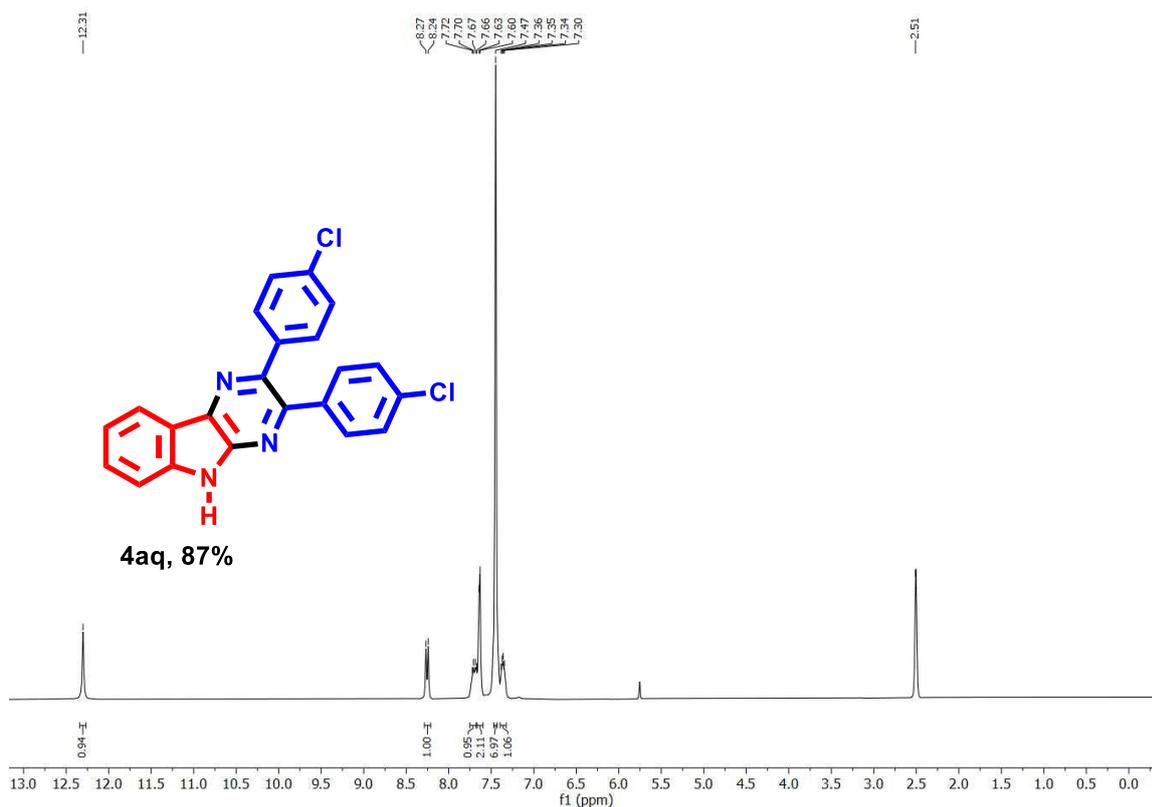
¹³C NMR spectrum (100 MHz, CDCl₃) of compound 4ao



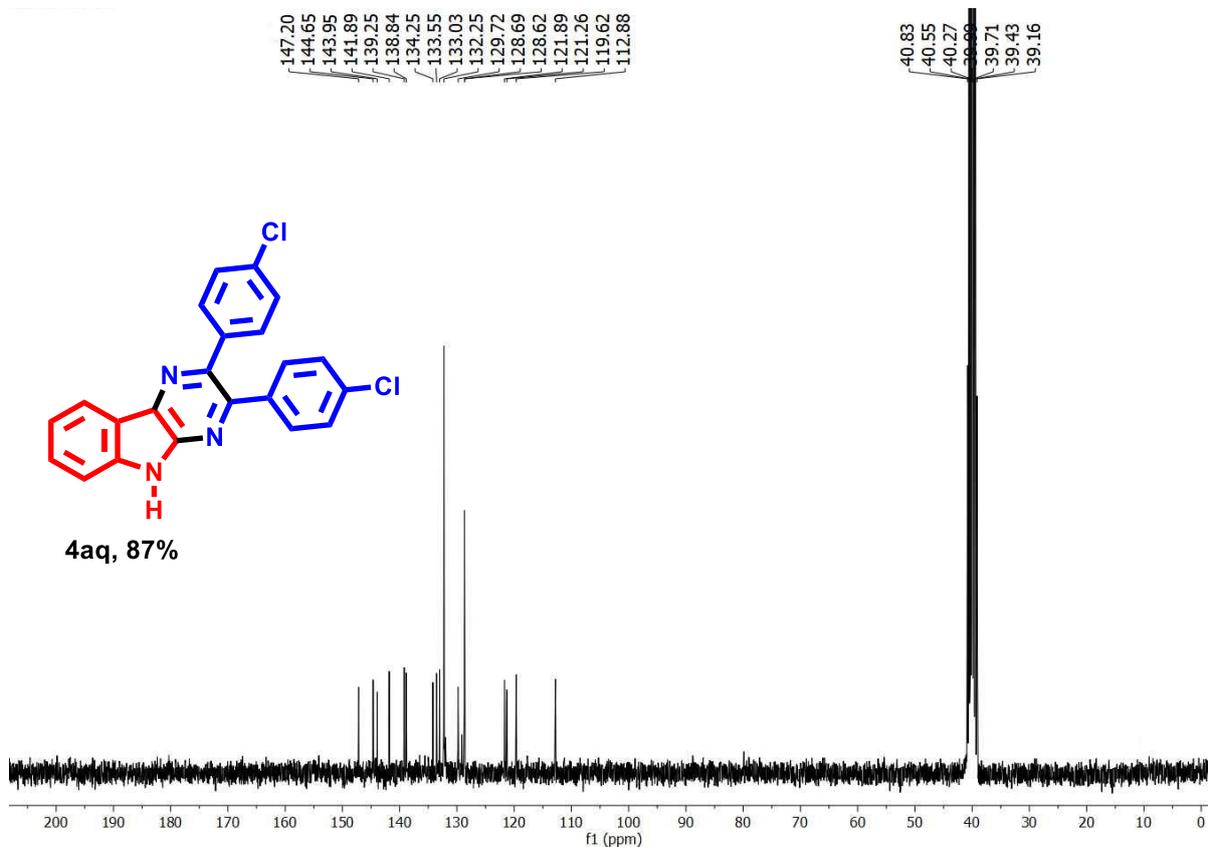
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4ap



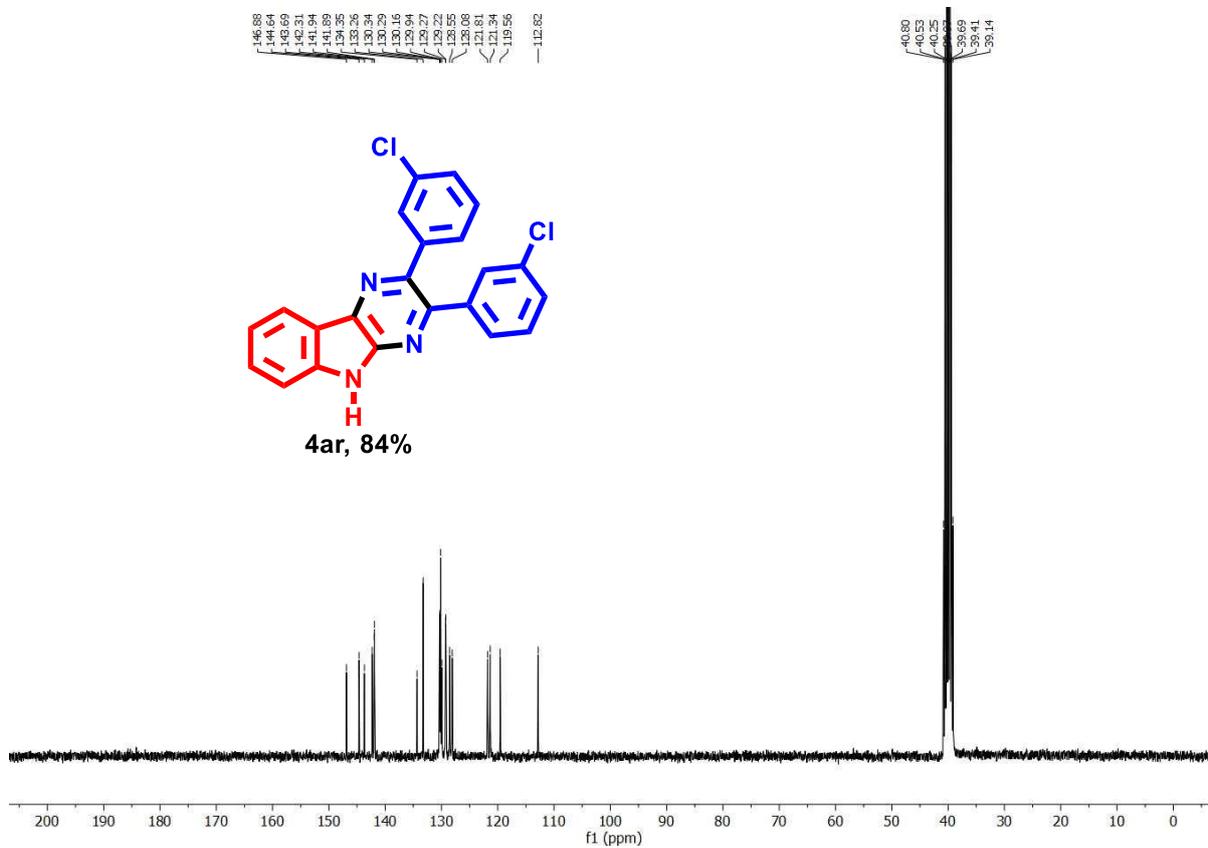
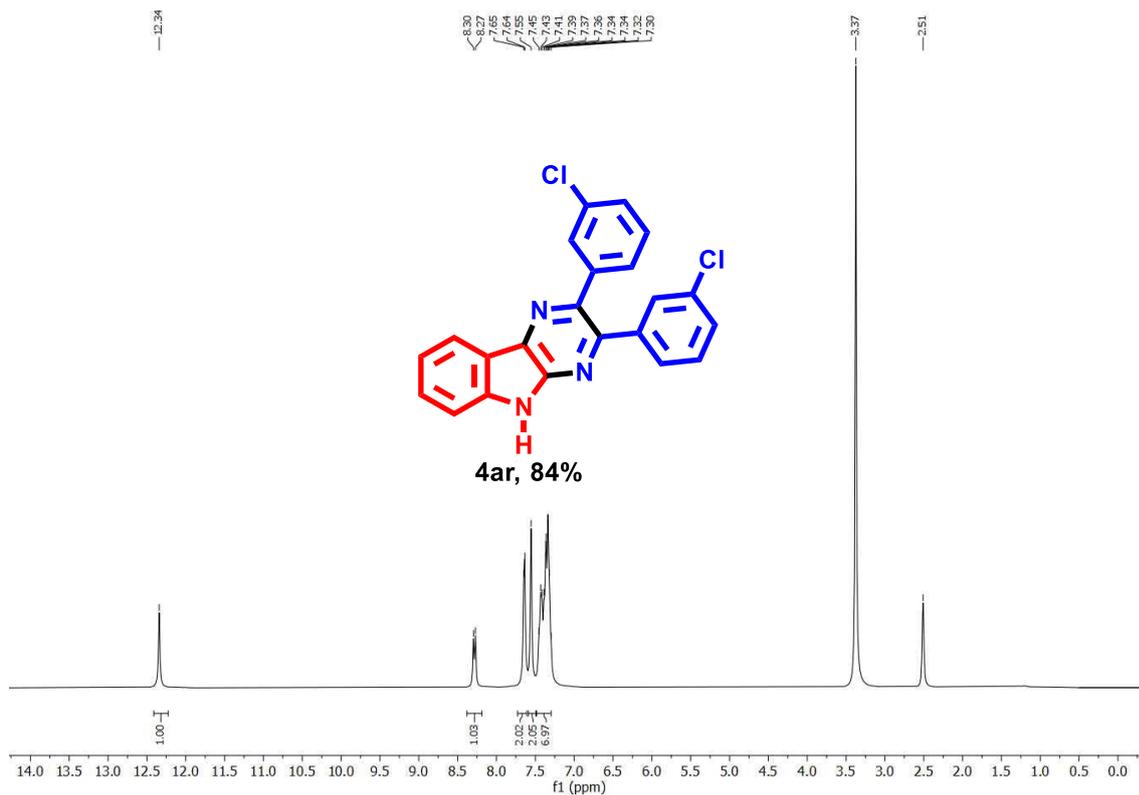
¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4ap

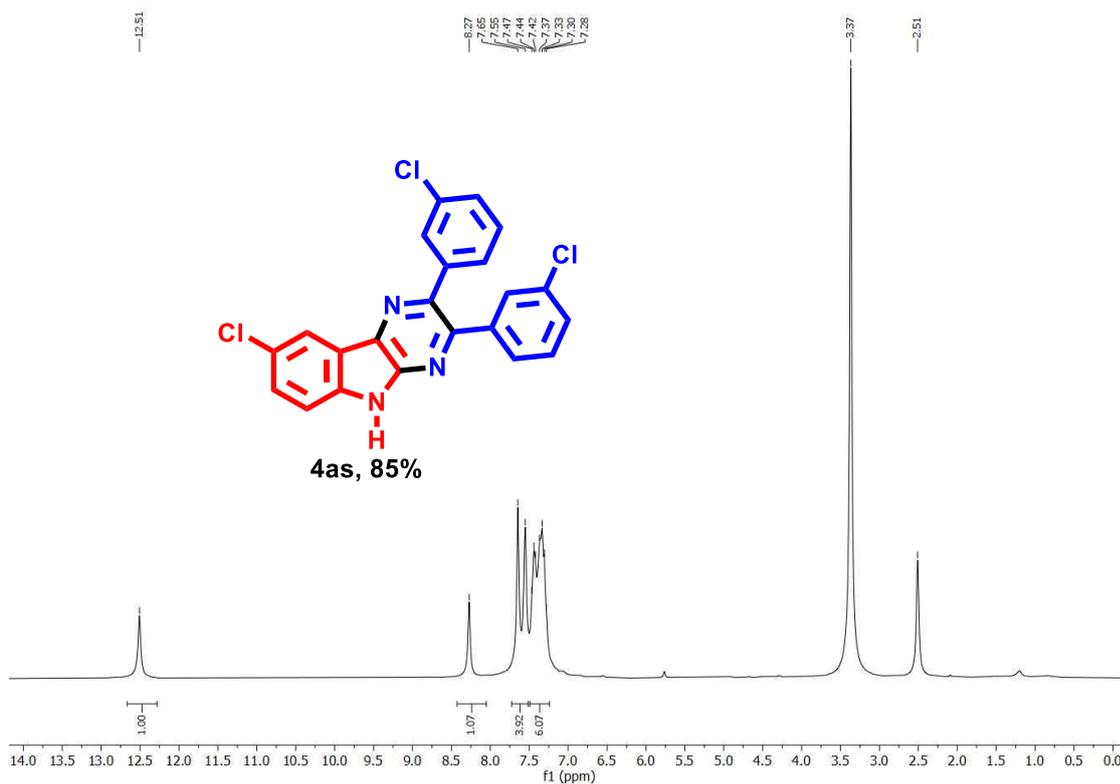


¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4aq

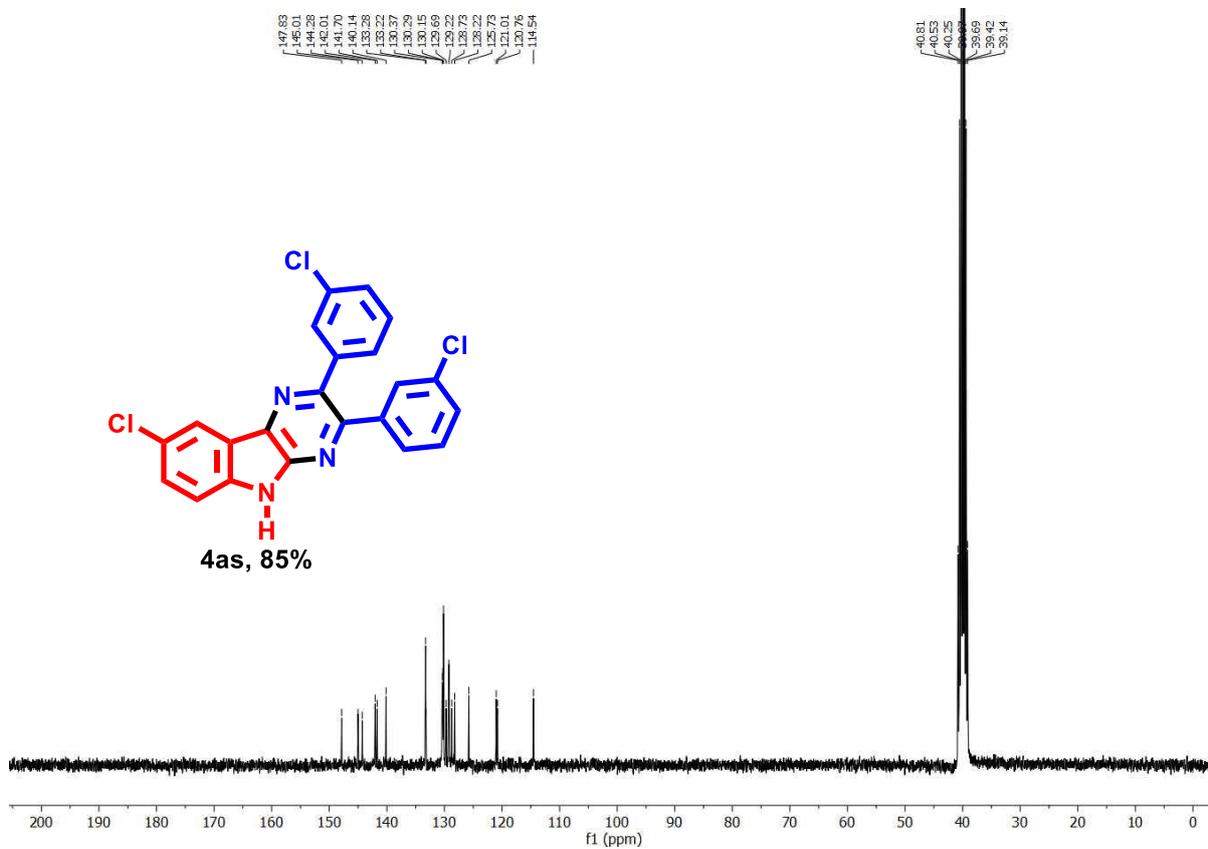


¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4aq

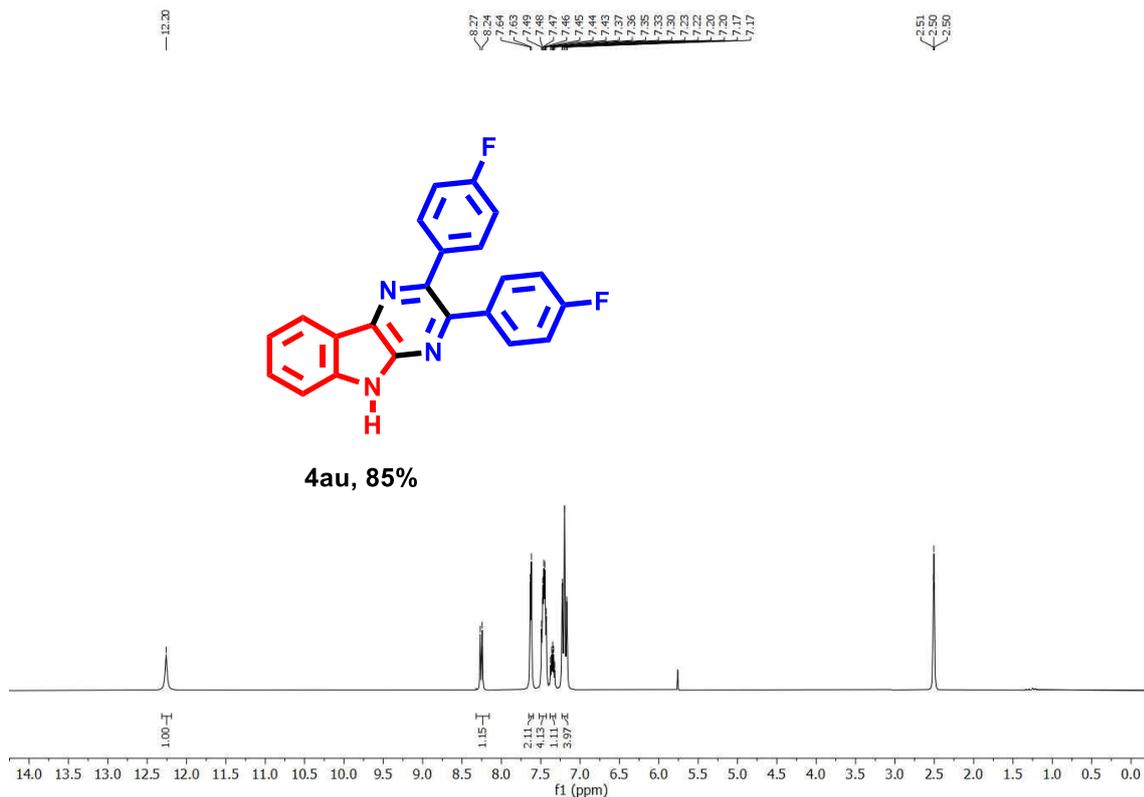




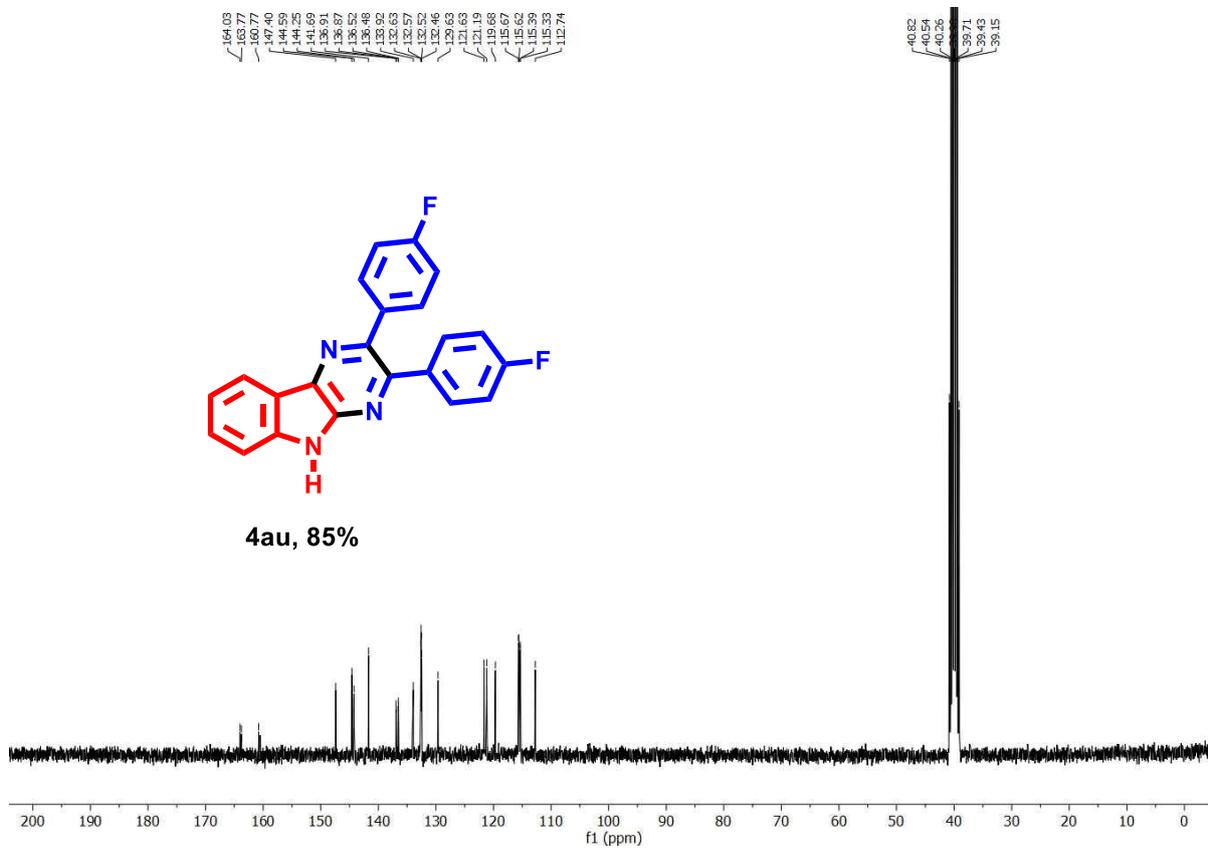
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4as



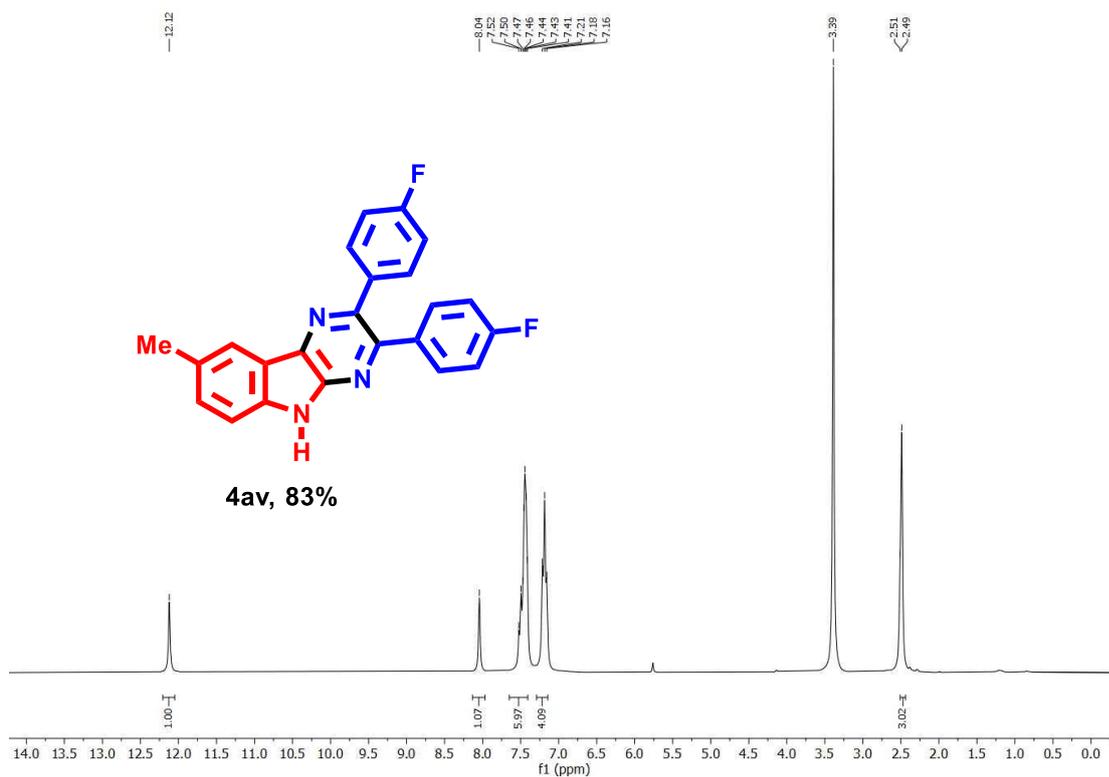
¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4as



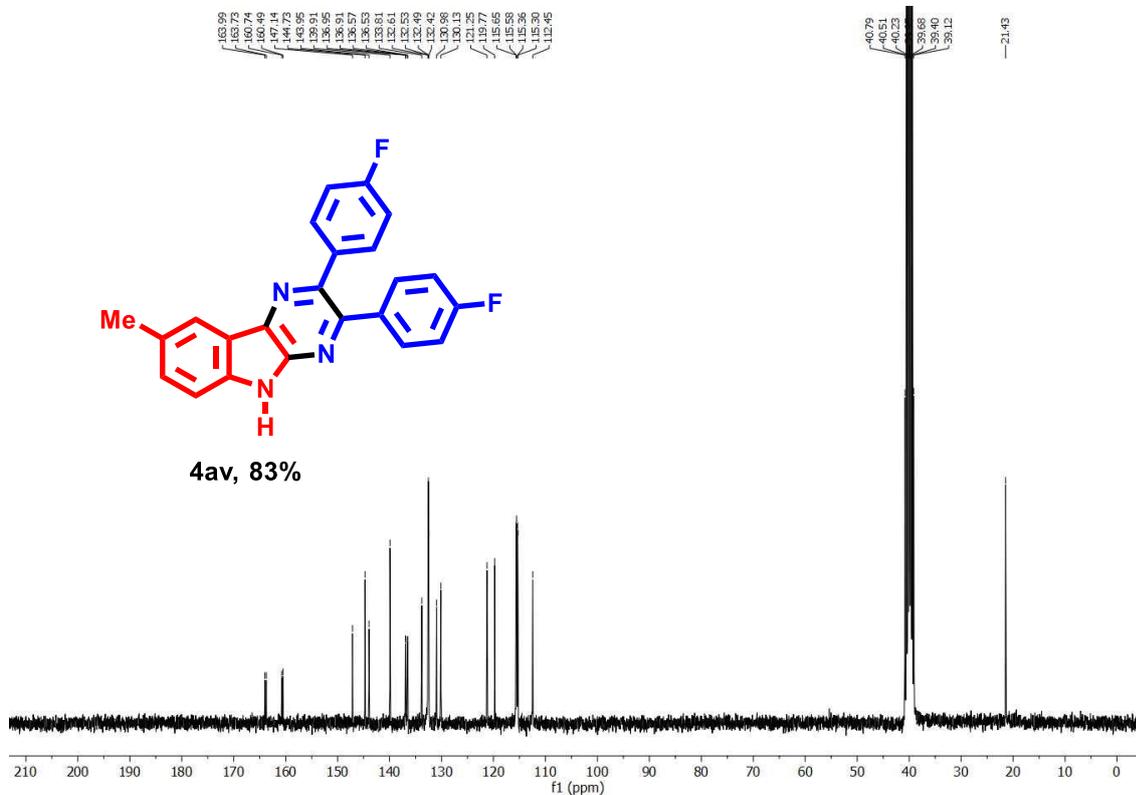
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4au



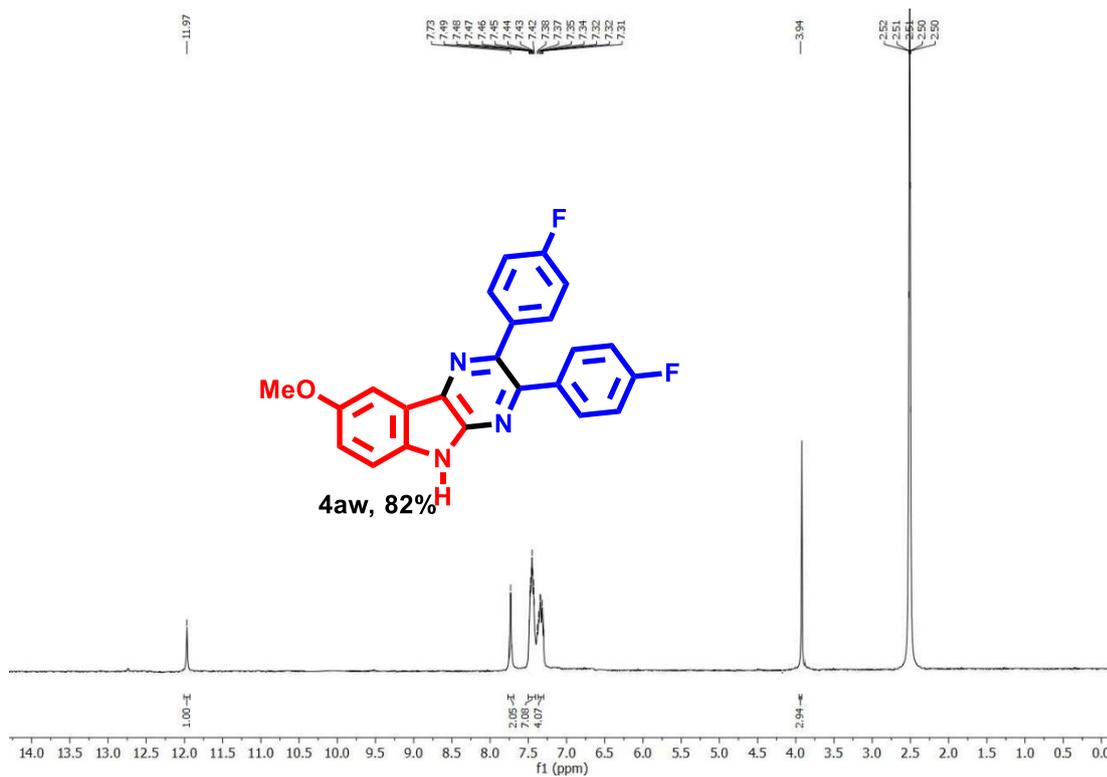
¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4au



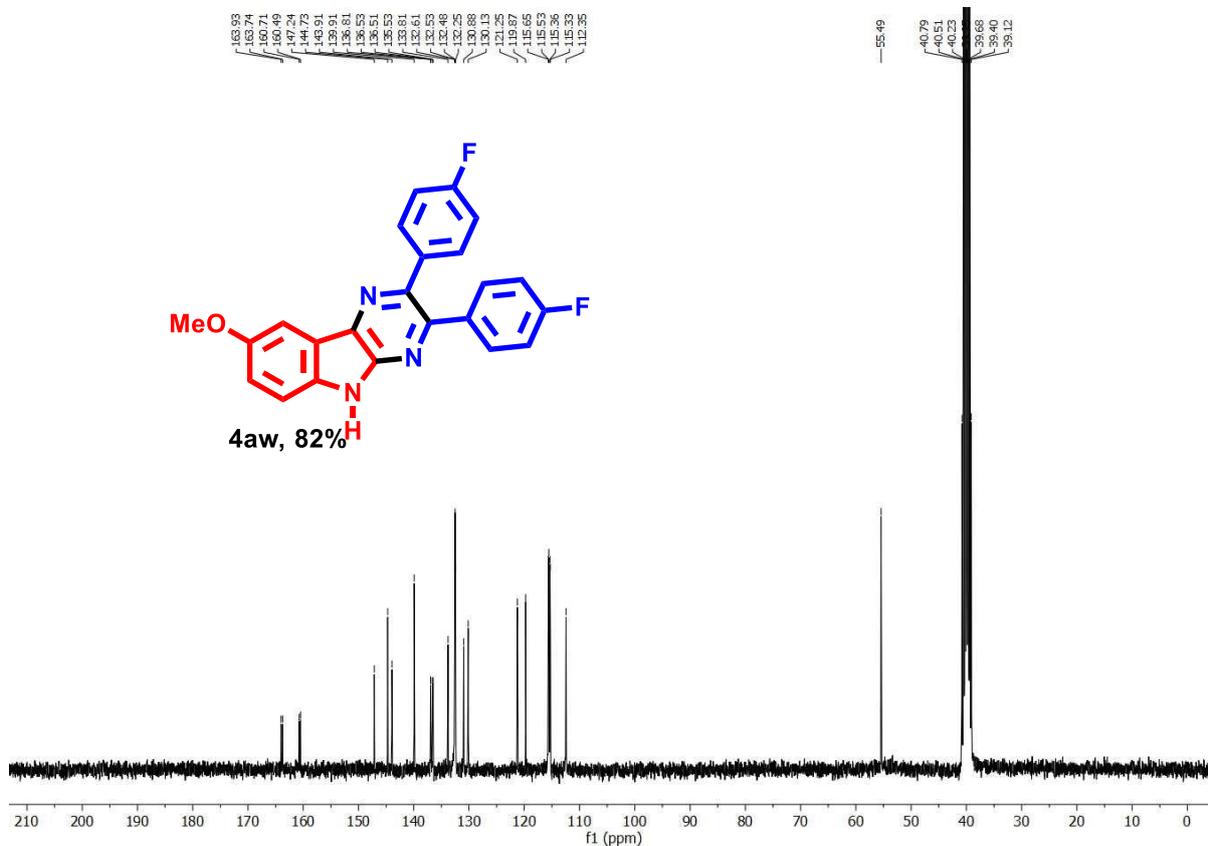
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4av



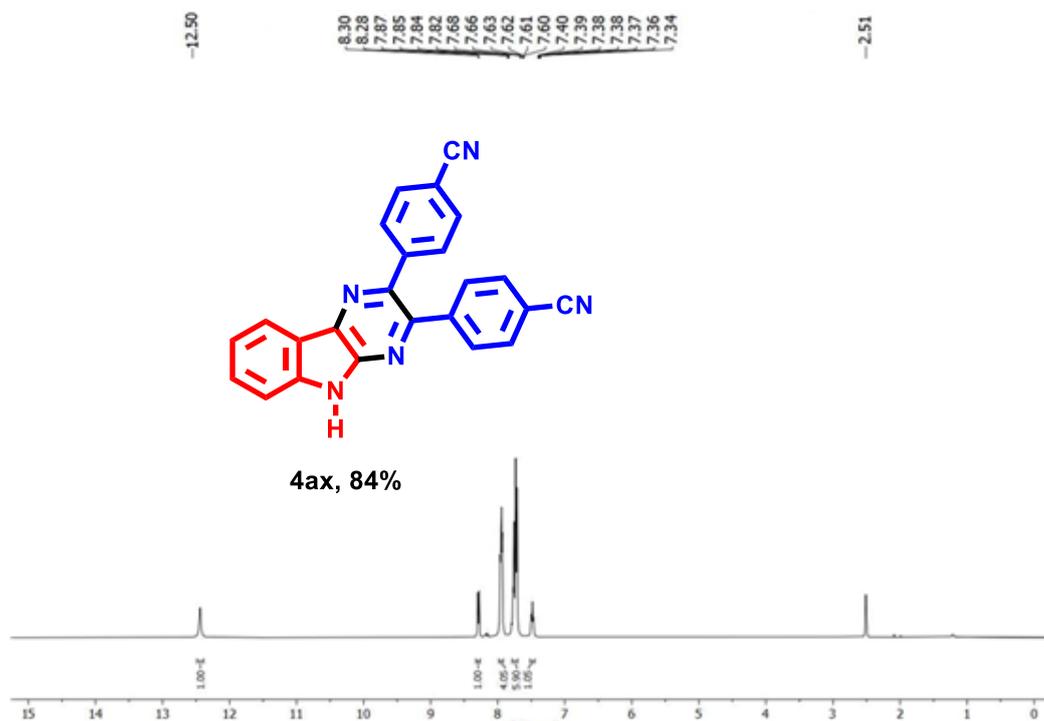
¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4av



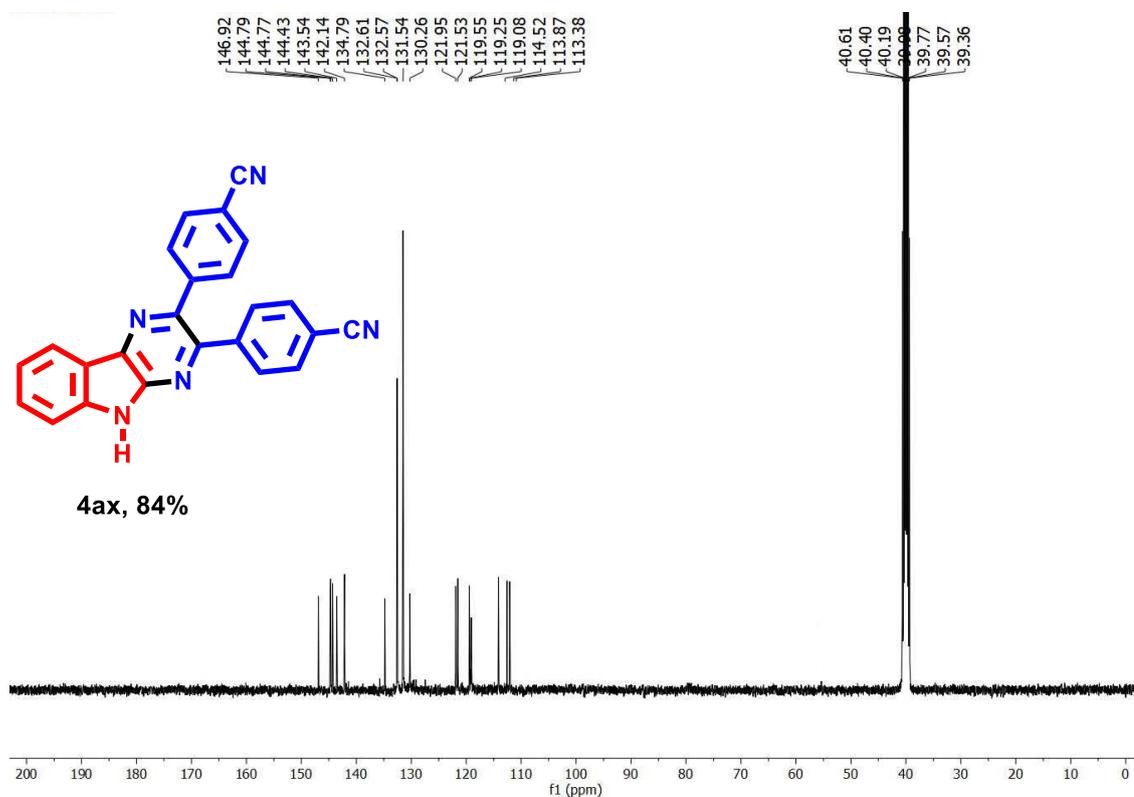
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4aw



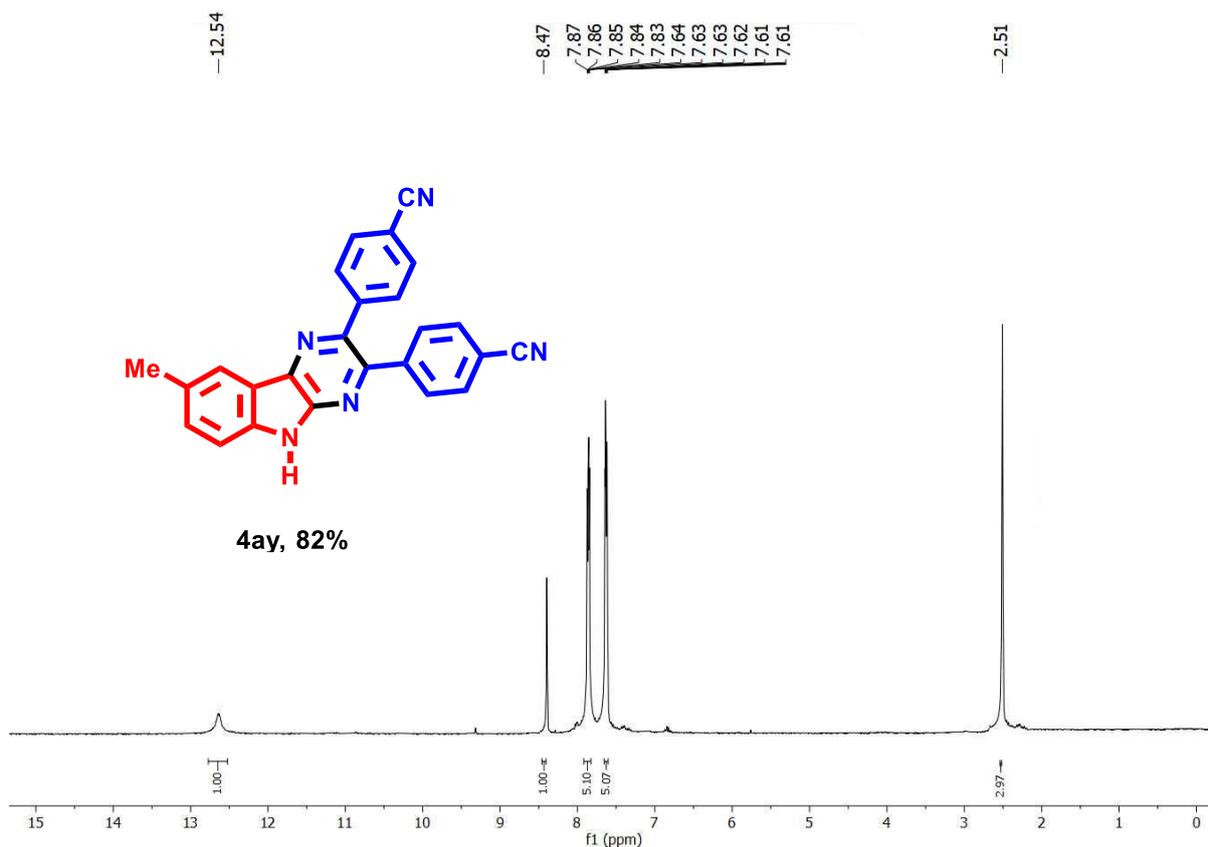
¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4aw



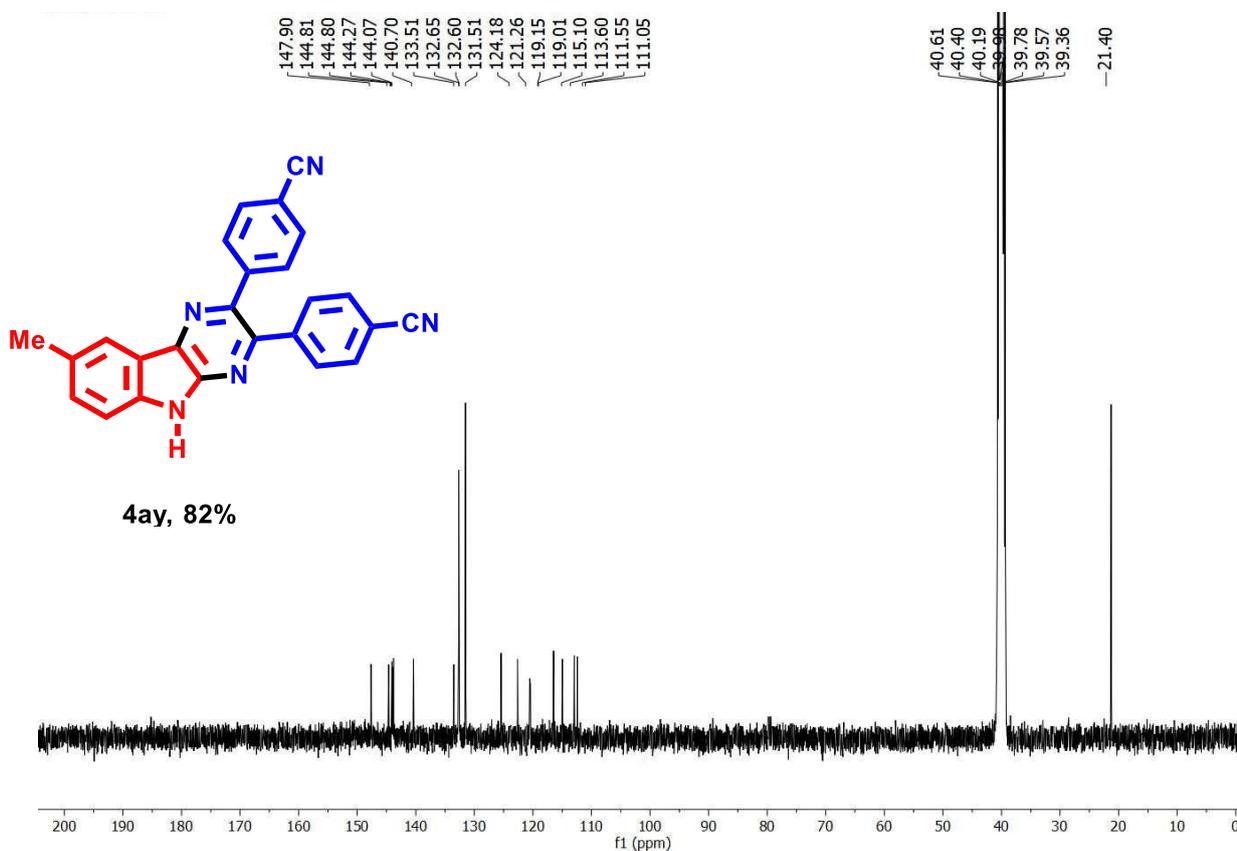
¹H NMR spectrum (400 MHz, DMSO-d₆) of compound 4ax



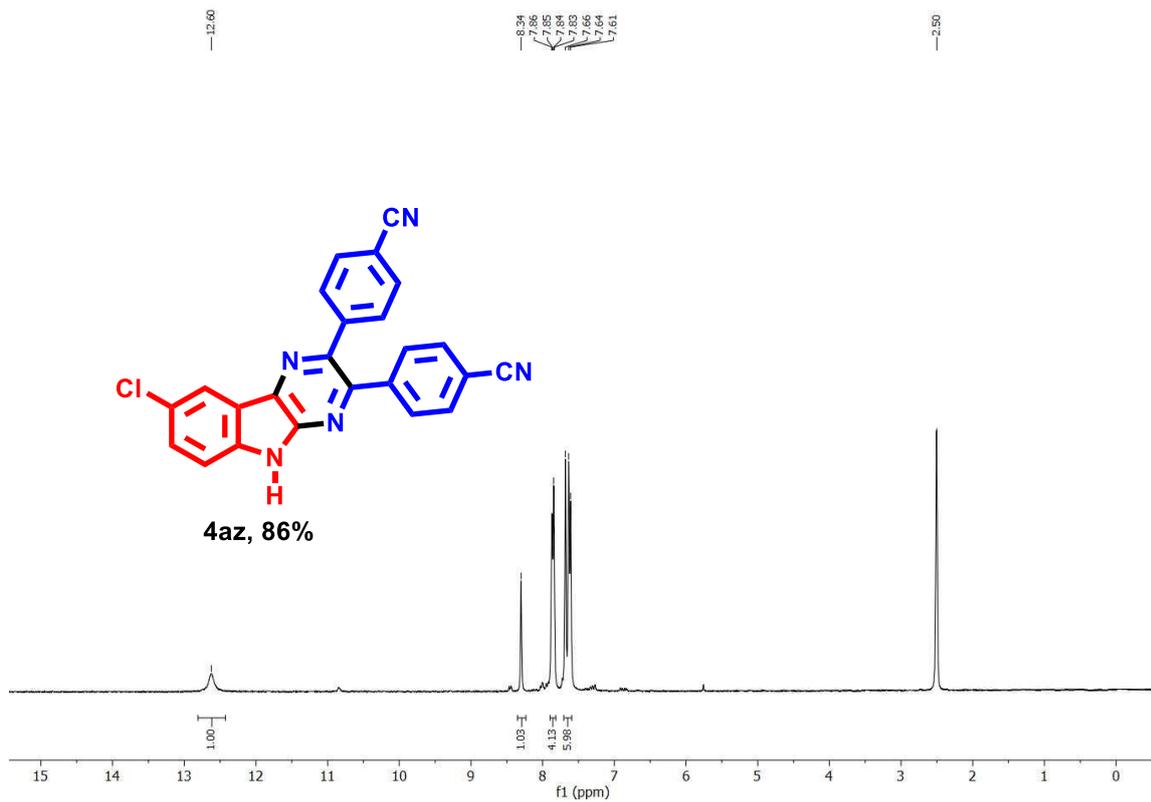
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound 4ax



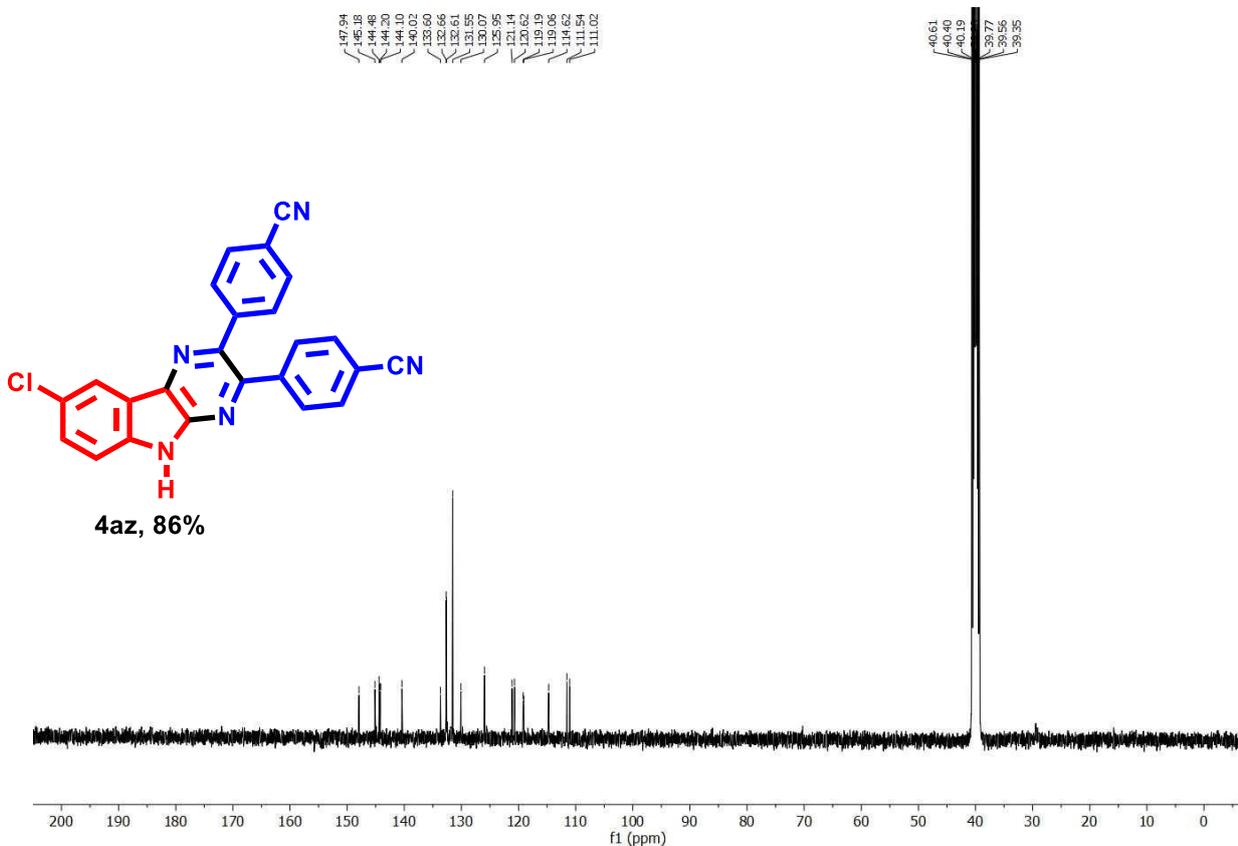
¹H NMR spectrum (400 MHz, DMSO-d₆) of compound **4ay**



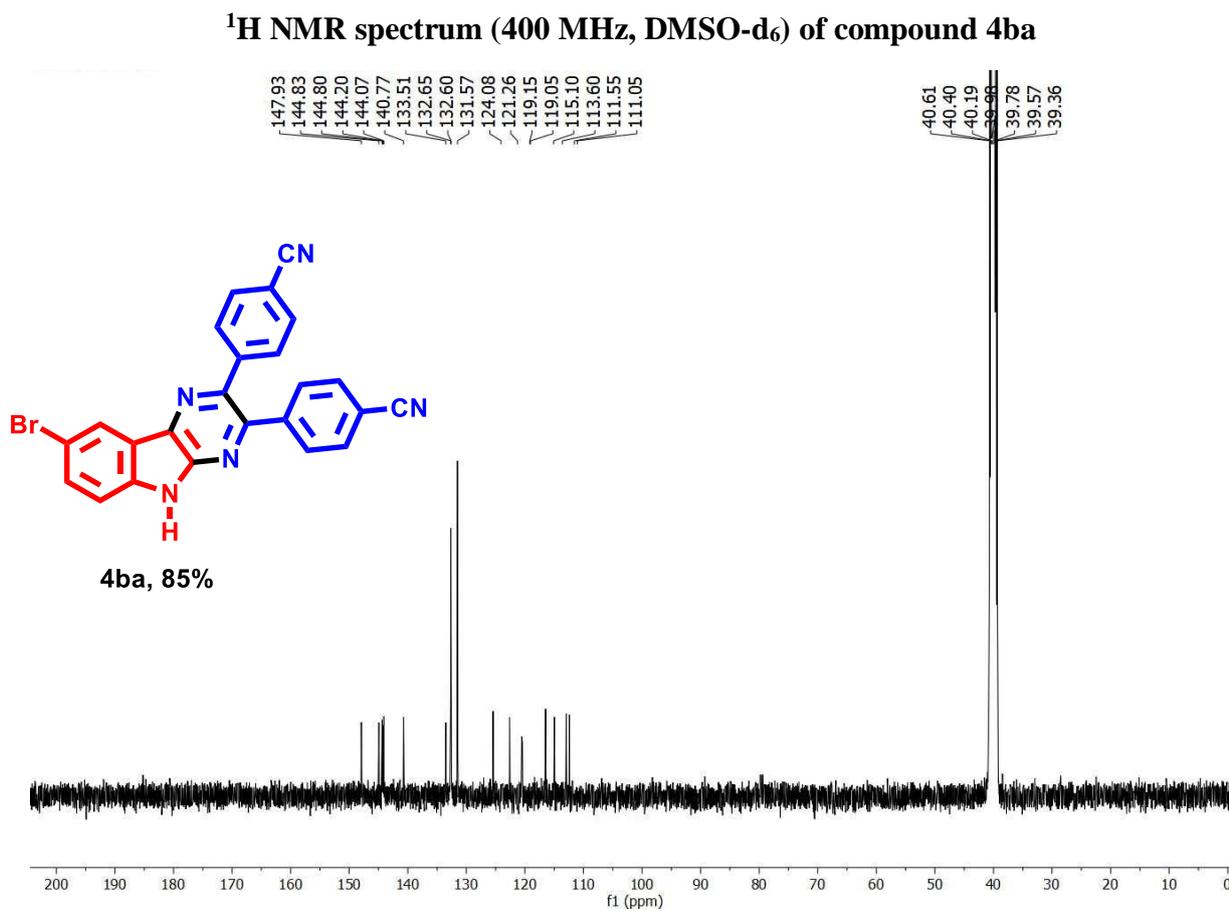
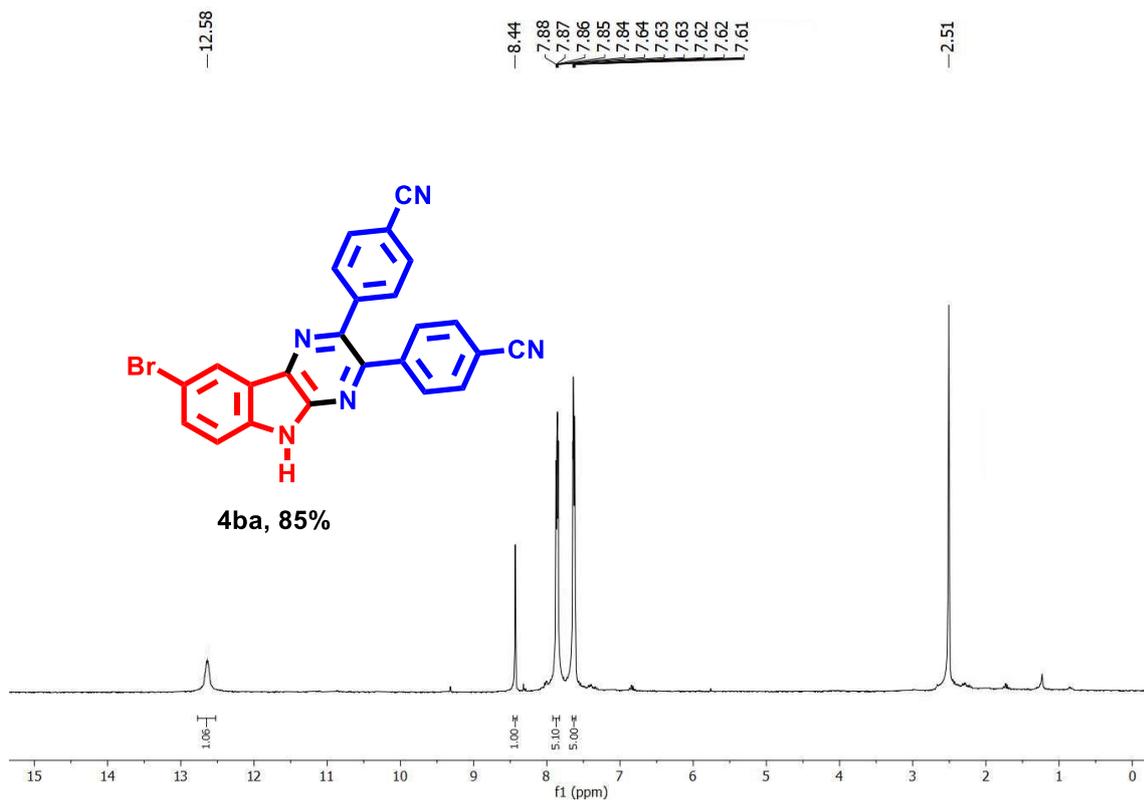
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound **4ay**

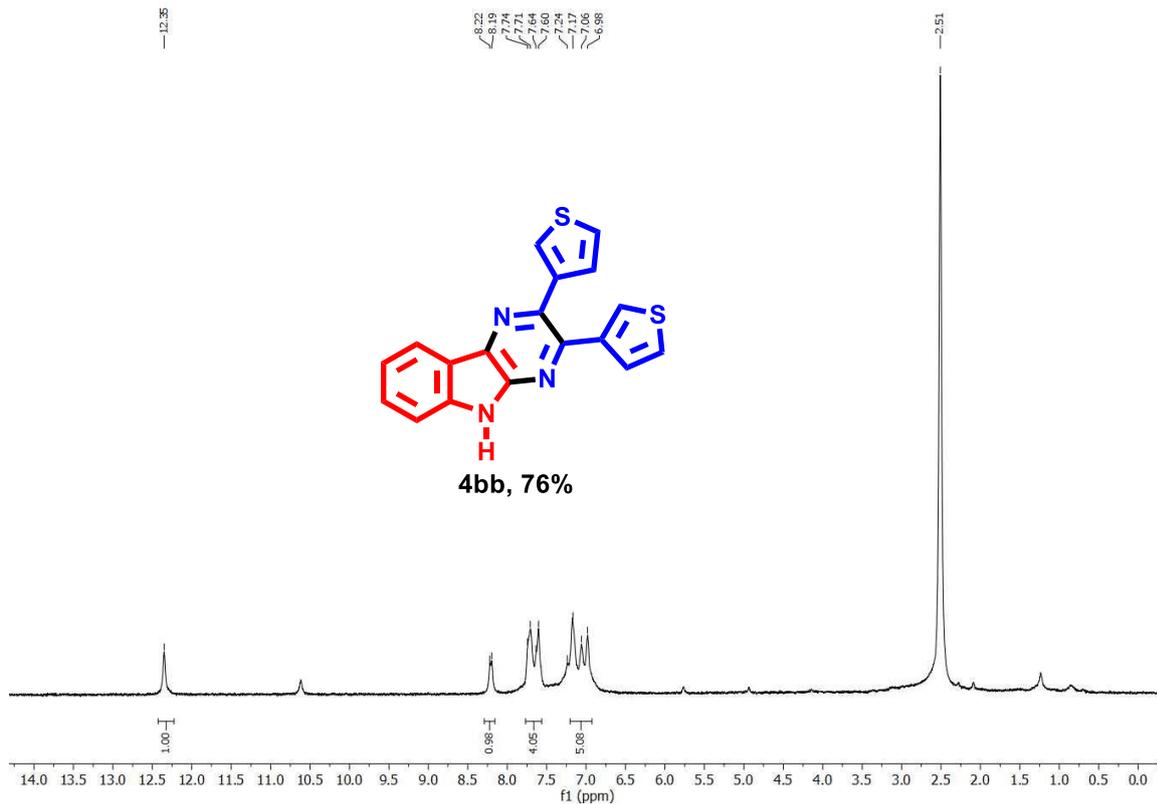


¹H NMR spectrum (300 MHz, DMSO-d₆) of compound **4az**

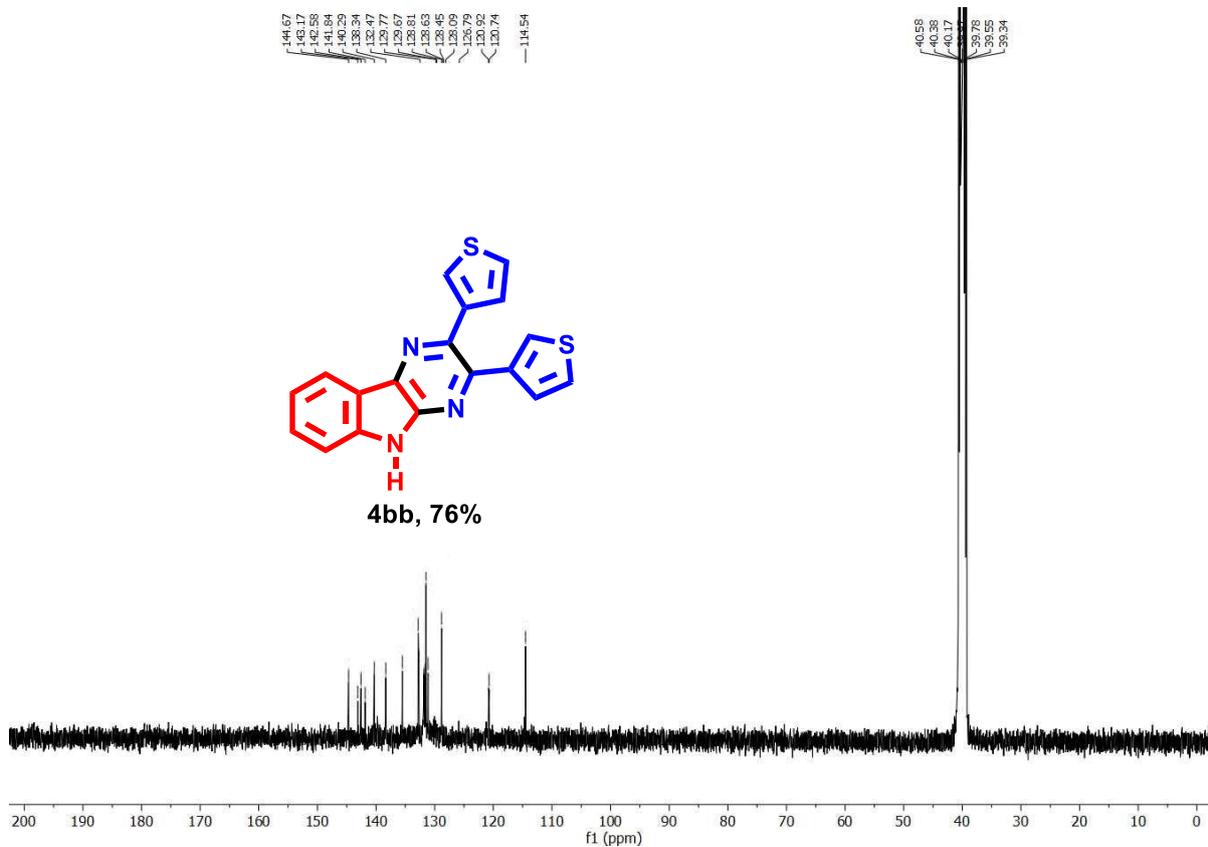


¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound **4az**

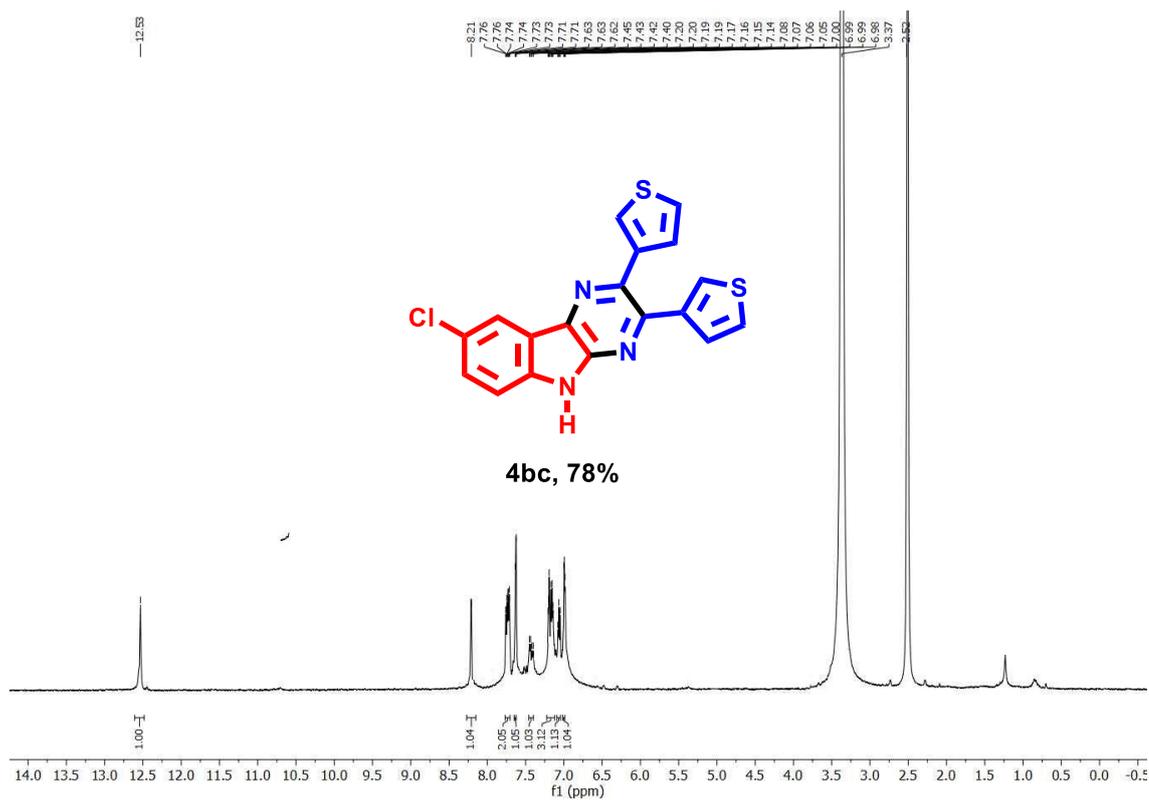




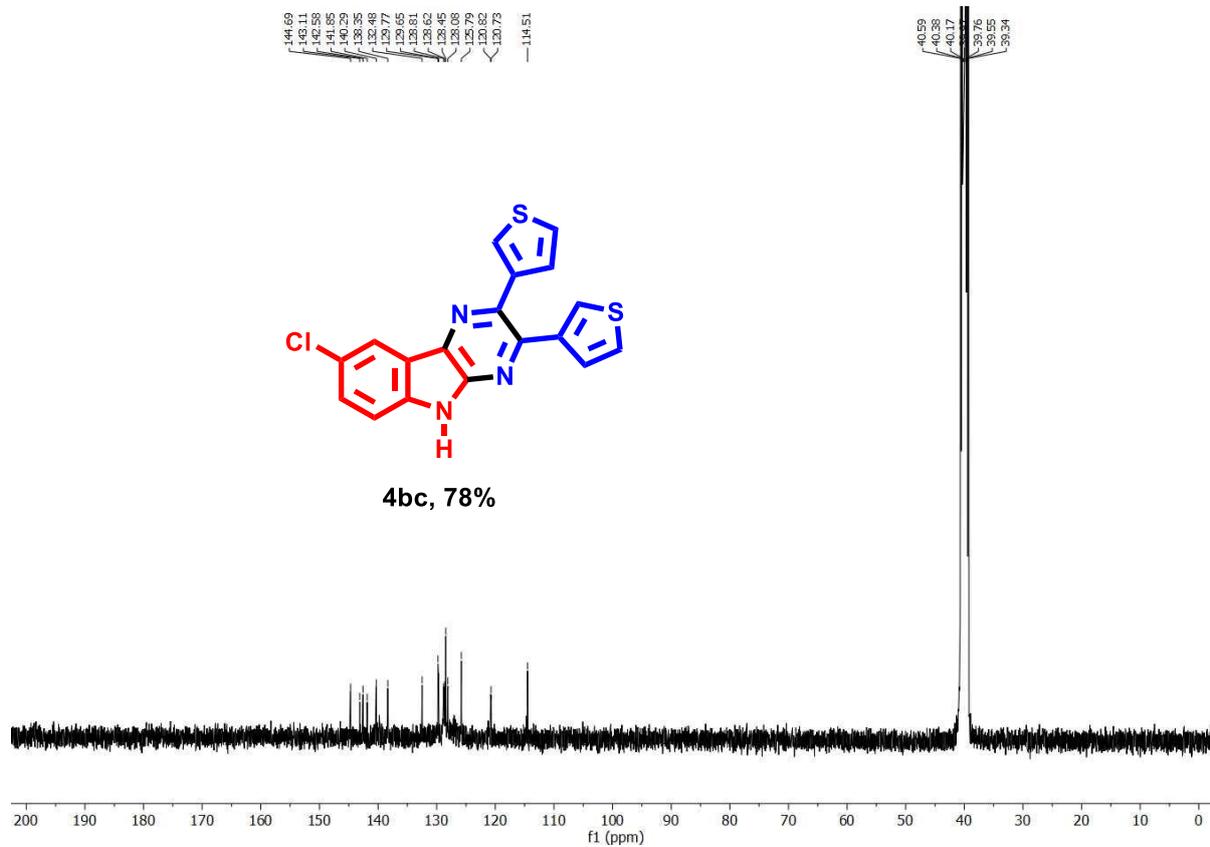
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4bb



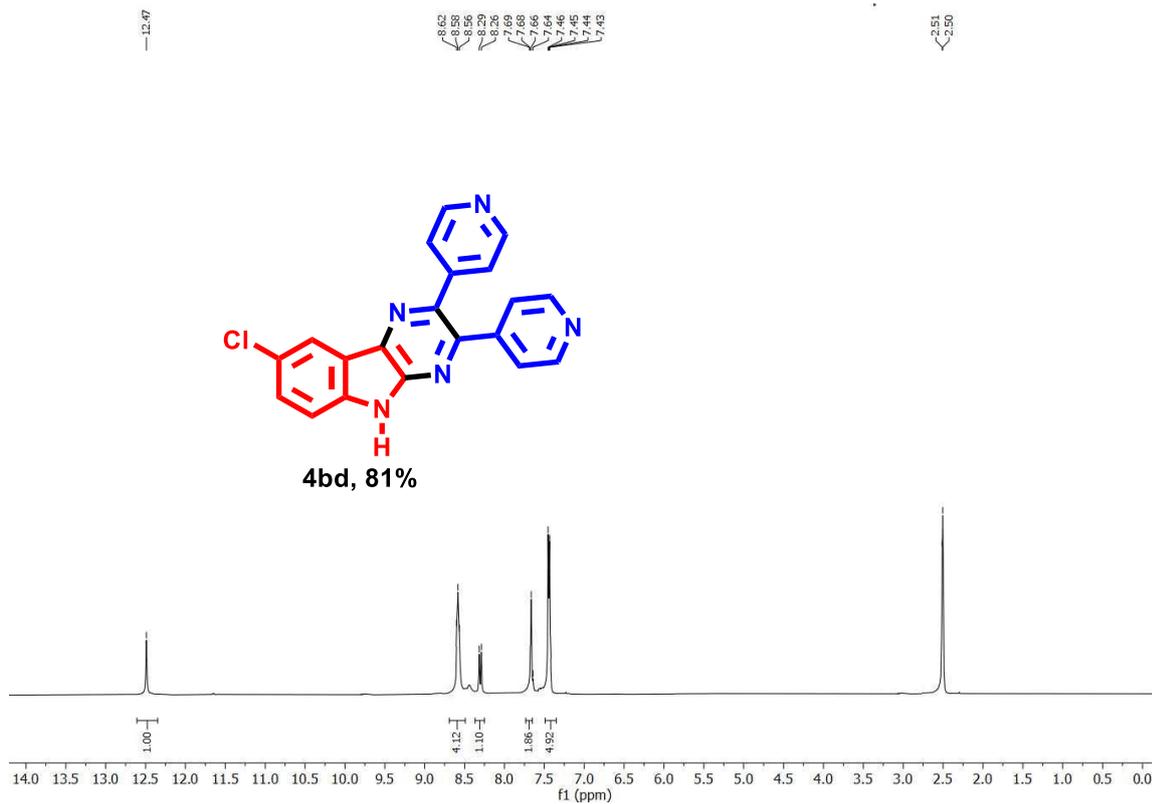
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound 4bb



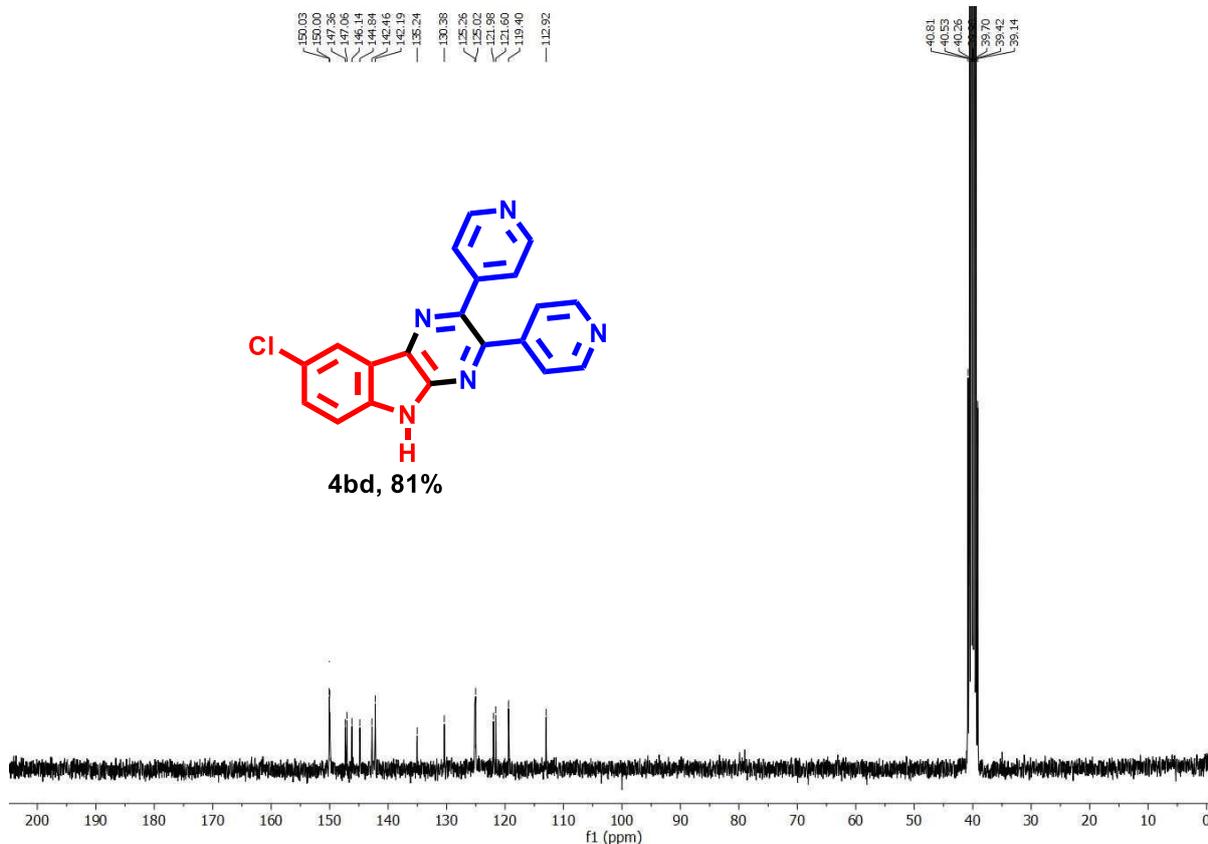
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4bc



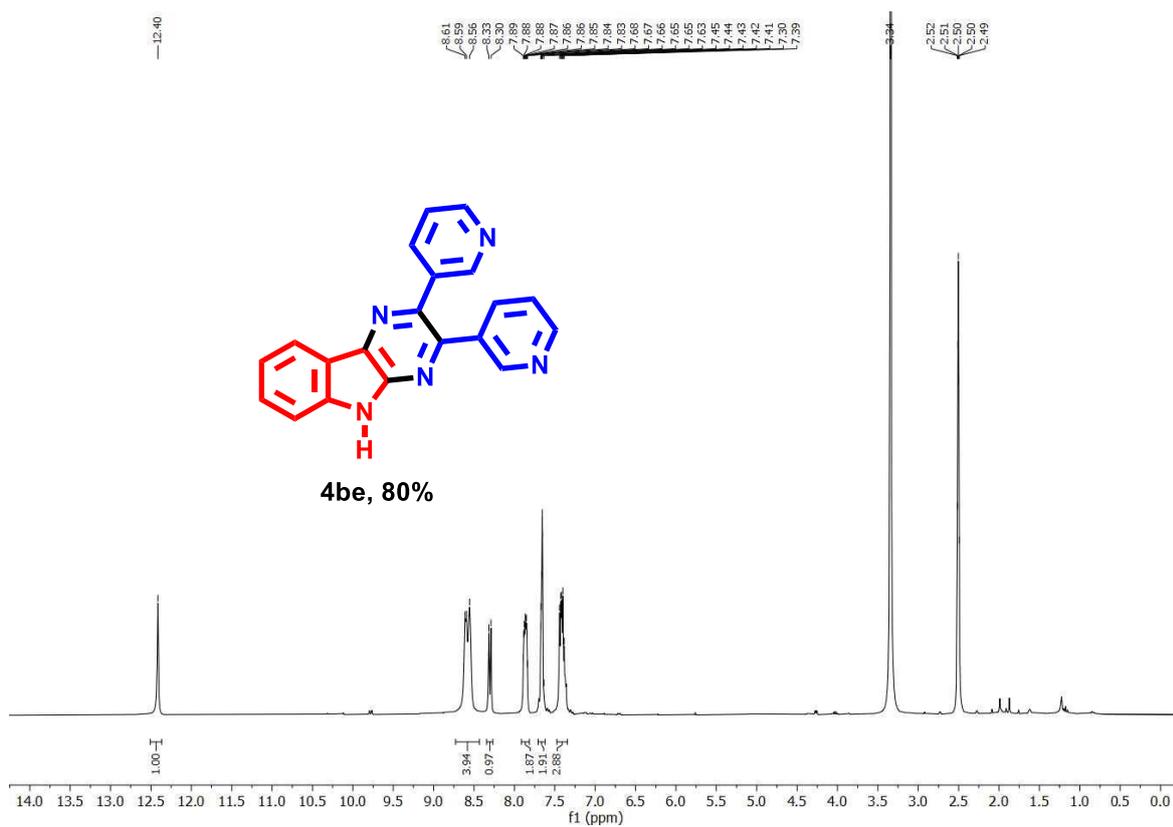
¹³C NMR spectrum (100 MHz, DMSO-d₆) of compound 4bc



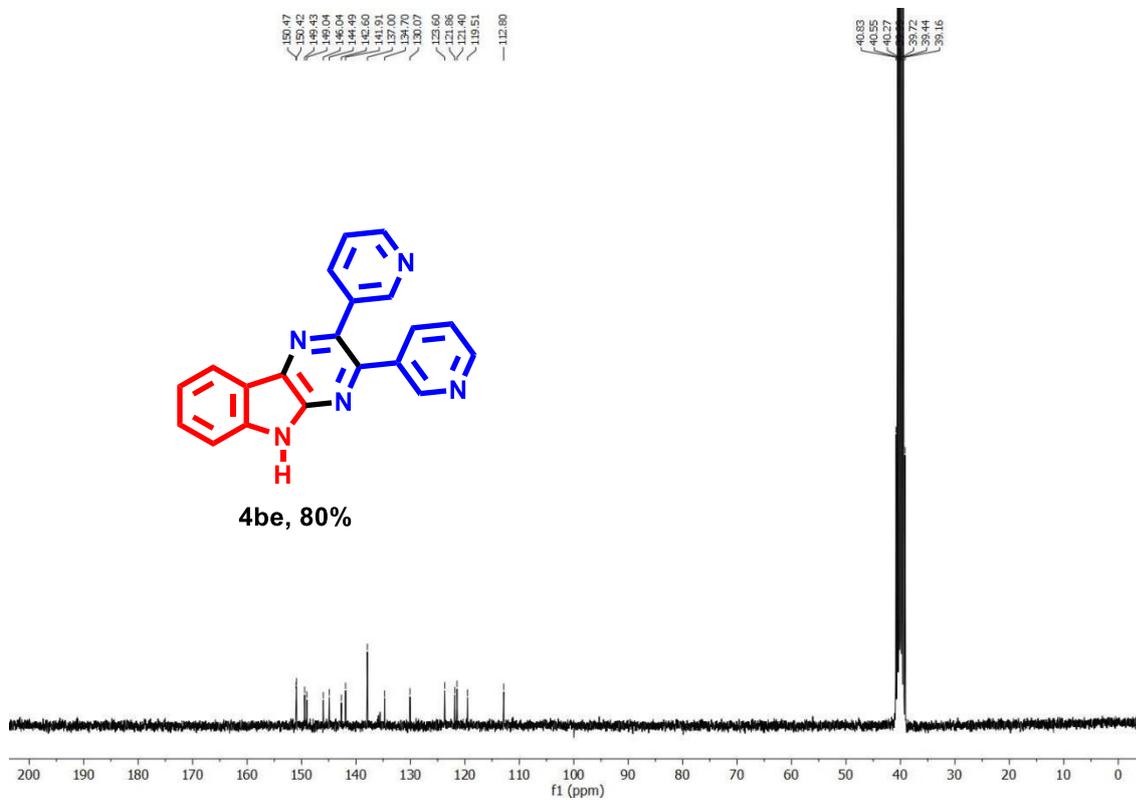
¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4bd



¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4bd

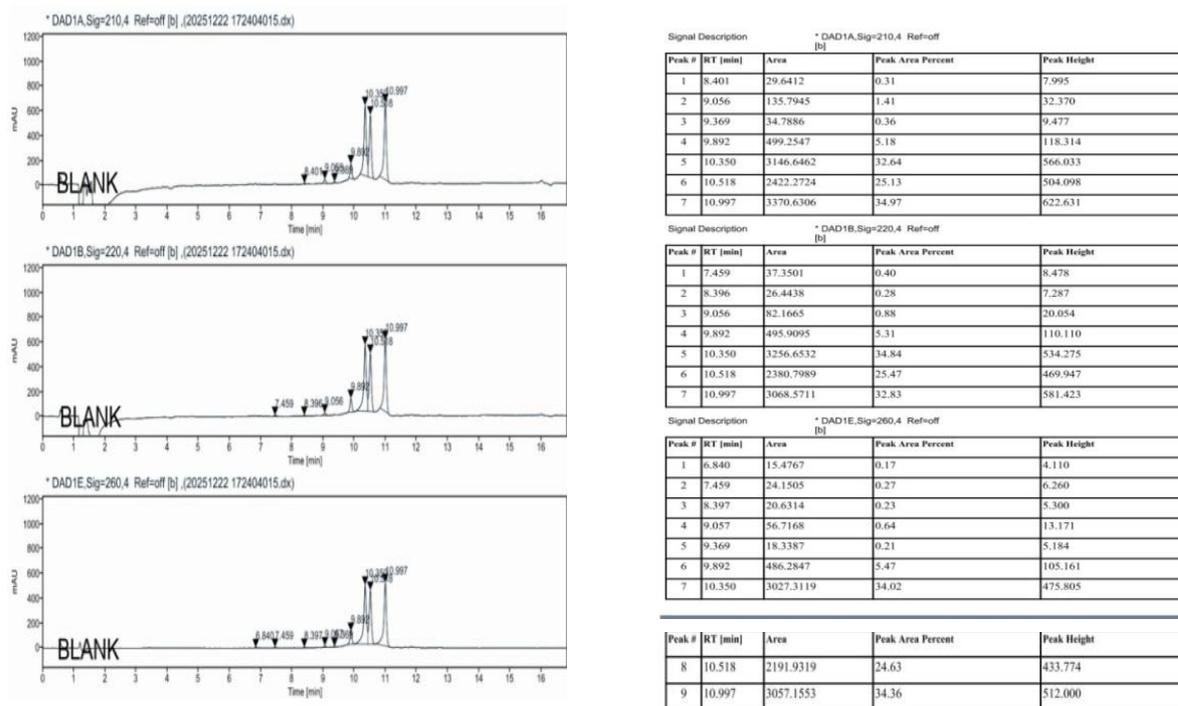
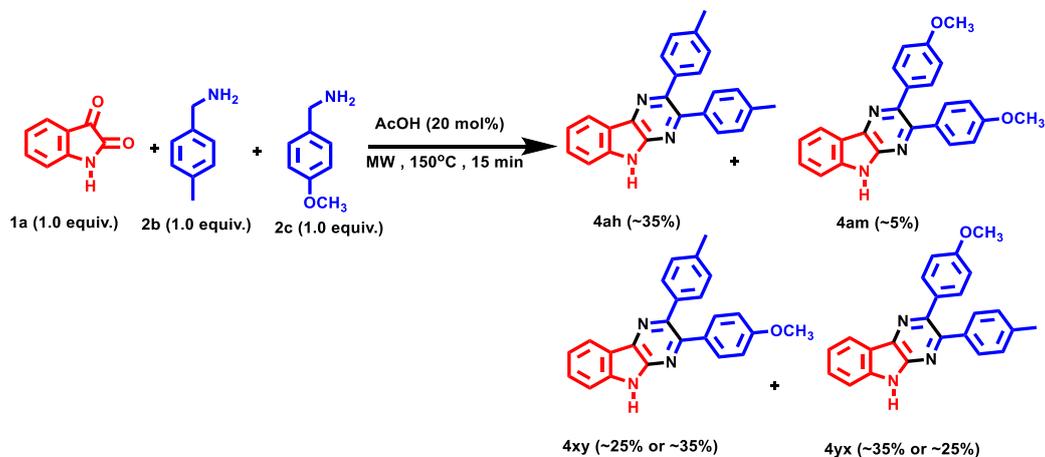


¹H NMR spectrum (300 MHz, DMSO-d₆) of compound 4be

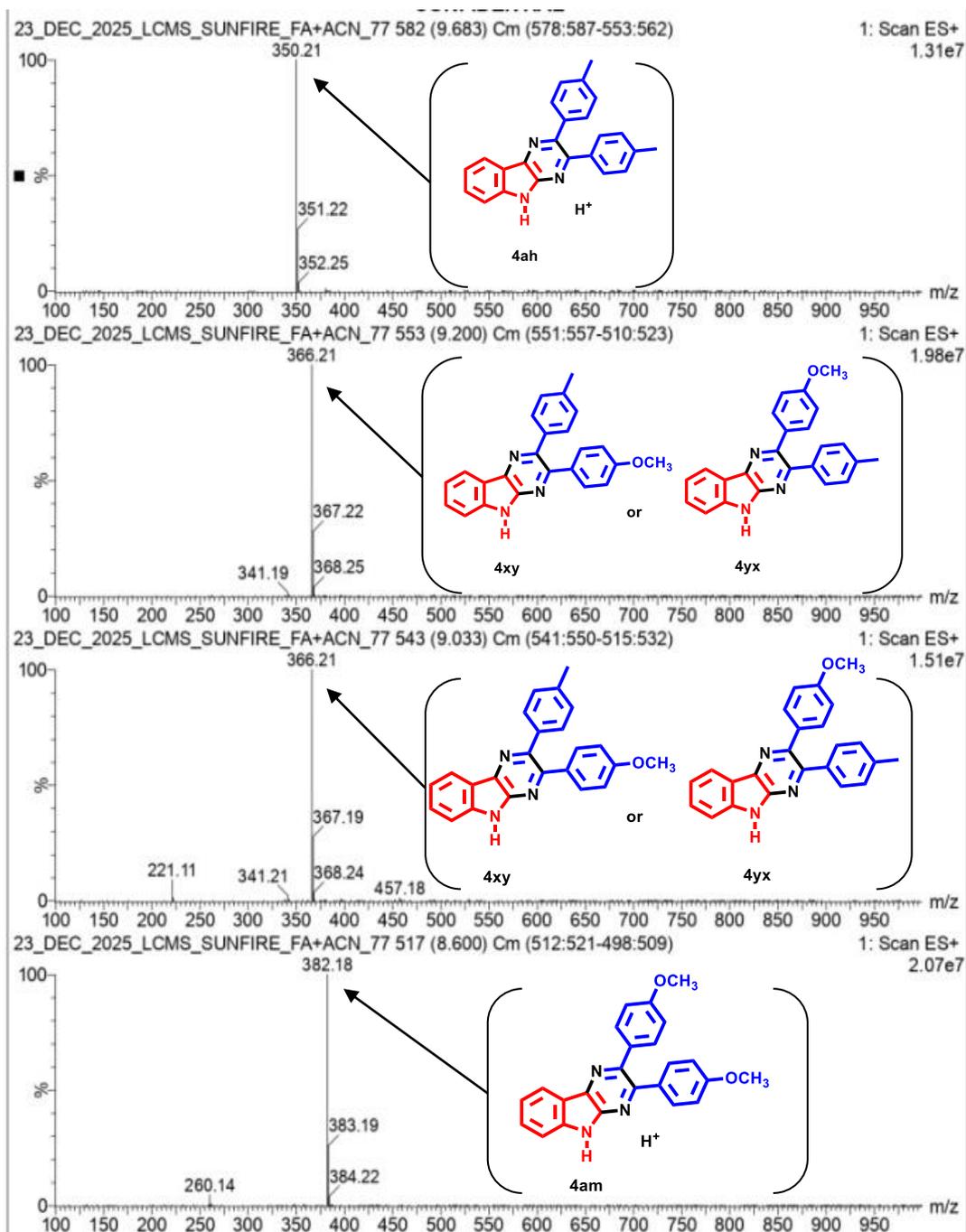


¹³C NMR spectrum (75 MHz, DMSO-d₆) of compound 4be

Crossover Experiment



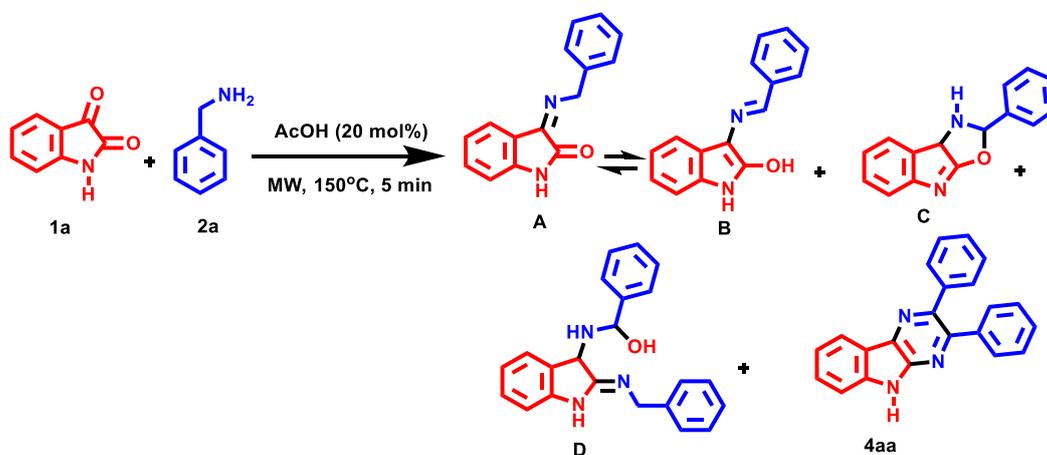
SI Figure 1. HPLC data of crossover experiment



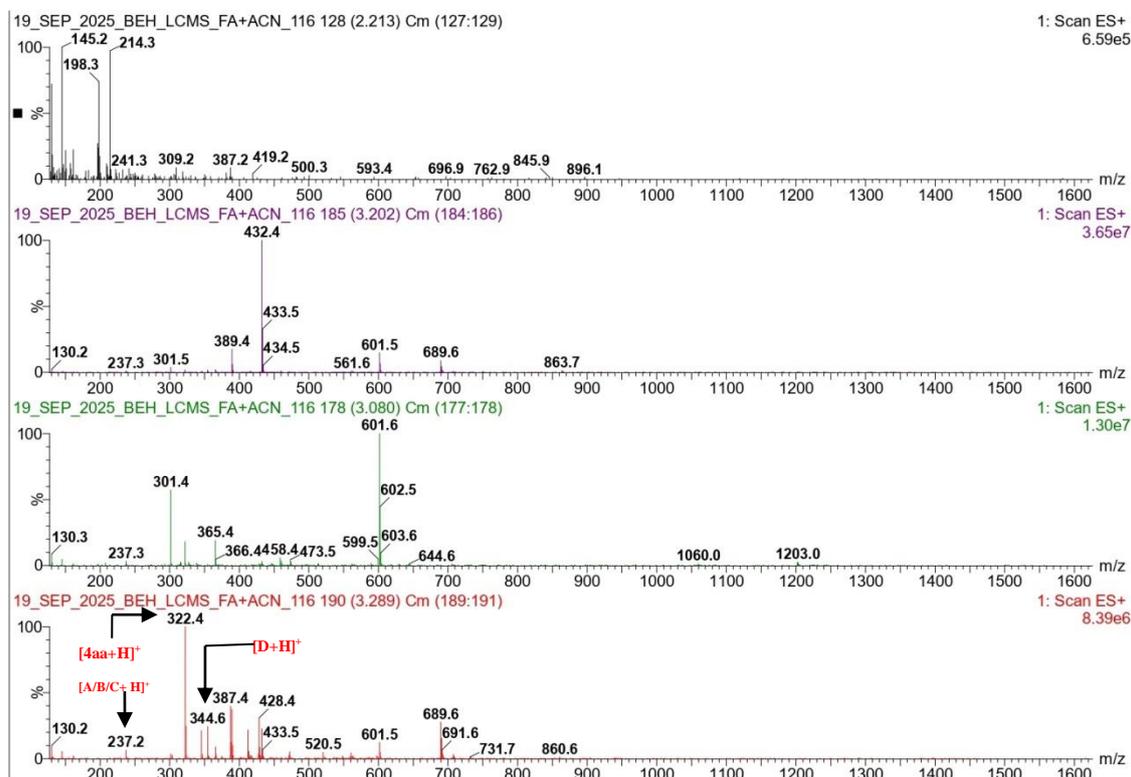
SI Figure 2. The LCMS mass spectroscopy of crossover experiment

Control Experiments

1. LCMS mass spectrum of crude reaction mixture: The reaction was quenched after 5 minute and the compound as well as the intermediates were found using the LCMS mass spectrometry of crude reaction mixture. It was evident from the mass spectrum that the product **4aa** and the intermediates (**A**, **B**, **C** and **D**) were present.



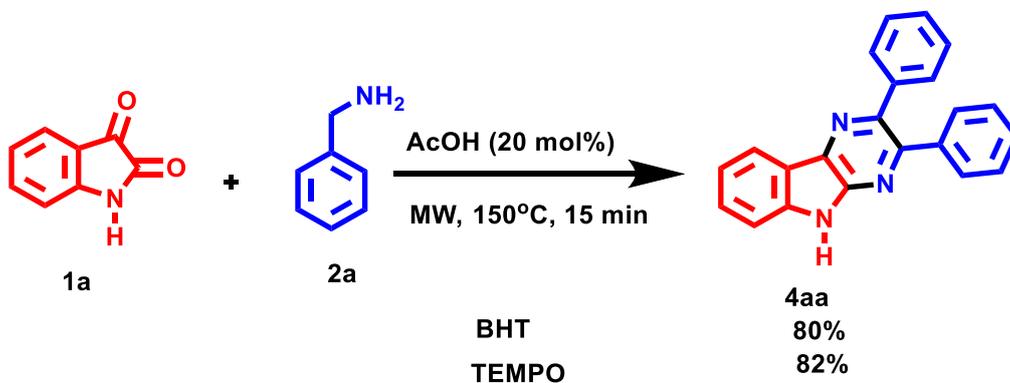
SI Scheme 1. An investigation of reaction after 5 minute under optimized reaction conditions.



SI Figure 3: The LCMS mass spectrometry of crude reaction mixture after 5 minute.

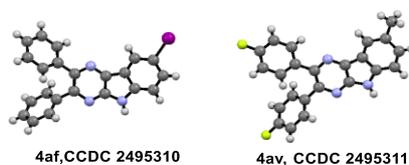
Control experiment carried out in presence of radical scavengers.

We performed the reaction using radical scavengers such as BHT and TEMPO and we ended up getting the product **4aa** in yield of 80% and 82% respectively . This result suggests that the reaction must not go through radical pathway.



SI Scheme 2: Experiment carried out in presence of radical scavengers.

Crystallographic information of 4af and 4av



SI Figure 4 : Ortep diagram of compound 4af and 4av

Crystallographic table

Crystallographic Parameters	4af	4av
Empirical formula	C ₂₂ H ₁₄ N ₃ I	C ₂₃ H ₁₅ F ₂ N ₃
<i>T</i> /K	273.15	273.15
<i>f</i> _w	447.26	371.38
Crystal system	Monoclinic	Orthorhombic
Space Group	<i>P</i> 2 ₁ / <i>n</i>	<i>F</i> dd2
<i>a</i> /Å	11.4350(13)	17.7713(11)
<i>b</i> /Å	9.3584(11)	34.281(2)
<i>c</i> /Å	17.928(2)	12.0694(8)
<i>α</i> /deg	90	90
<i>β</i> /deg	106.062(4)	90
<i>γ</i> /deg	90	90
<i>V</i> /Å ³	1843.6(4)	7352.8(8)
<i>Z</i>	4	16
<i>D</i> _c /Mgm ⁻³	1.611	1.342
<i>μ</i> /mm ⁻¹	1.747	0.095
<i>F</i> (000)	880.0	3072
cryst size/mm ³	0.29 × 0.18 × 0.13	0.28 × 0.20 × 0.14
<i>θ</i> /deg	2.46– 26.94	2.709–27.137
Measured reflns	53404	63451
Unique reflns	4050	4057
^a GOF on <i>F</i> ²	1.093	1.217
<i>R</i> ₁ ^b , <i>wR</i> ₂ ^c [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0445, <i>wR</i> ₂ = 0.0945	<i>R</i> ₁ = 0.0445, <i>wR</i> ₂ = 0.1168
<i>R</i> ₁ , <i>wR</i> ₂	<i>R</i> ₁ = 0.0681, <i>wR</i> ₂ = 0.1187	<i>R</i> ₁ = 0.0760, <i>wR</i> ₂ = 0.1576

^aGOF = {Σ[w(*F*_o²-*F*_c²)²]/(n-p)} 1/2. ^b*R*₁ = Σ [|*F*_o|-*F*_c]/ Σ |*F*_o|. ^c*wR*₂ = [Σ [w(*F*_o²-*F*_c²)²]/ Σ [w(*F*_o²)²]]^{1/2} where w = 1/[σ²(*F*_o²)+(aP)²+bP], P = (*F*_o²+2*F*_c²)/3.

SI Table 1. Crystallographic information of 4af and 4av

Analysis of green chemistry metrics

The following equations have been used for calculating Effective Mass Yield (**EMY**), Atom Economy (**AE**), Carbon Efficiency (**CE**), Reaction Mass Efficiency (**RME**) and **E-factor**. Calculated data for compound **4ah** and **4aq** have been shown in **SI Table 4**.

$$\text{EMY (\%)} = \frac{\text{Mass of the product}}{\text{Mass of the nonbenign reagents}} \times 100$$

$$\text{AE (\%)} = \frac{\text{Molecular weight of the product}}{\text{Total molecular weight of the reactants}} \times 100$$

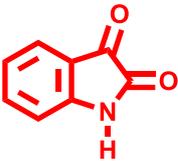
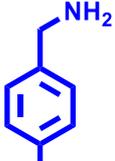
$$\text{CE (\%)} = \frac{\text{Amount of carbon in the product}}{\text{Total carbon present in the reactants}} \times 100$$

$$\text{RME (\%)} = \frac{\text{Mass of the isolated product}}{\text{Total mass of the reactants}} \times 100$$

$$\text{E-factor (g/g)} = \frac{\text{Total mass of wastes}}{\text{Mass of the product}} = \frac{(\text{Mass of raw materials} - \text{mass of product})}{\text{Mass of the the product}}$$

This Work:



Reactants	Amount used for reaction (g) (1.00 mmol)	Molecular weight (MW)	No of C-atom present in reactant
 1a	0.147	147.1330	8
 2b	0.121	121.1830	8
 2d	0.141	141.5980	7

SI Table 2. Data required for Analysis of green chemistry metrics of compound **4ah** and **4aq**

Product	Molecular weight (MW)	Yield (%)	Amount of product (g)	No of C-atom present in product	Mole no of product
4ah	349.4370	79	0.276	24	0.0007898419457
4aq	390.2670	87	0.339	22	0.0008686360876

SI Table 3. Materials and their respective amount used for metrics calculations

Representative calculations of green metrics for 2,3-di-p-tolyl-5H-pyrazino[2,3-b]indole (**4ah**):

$$\text{EMY (\%)} = \frac{\text{Mass of the product}}{\text{Mass of the nonbenign reagents}} \times 100 = \frac{0.276}{0.147+(0.121*2)} \times 100 = 70.95\%$$

$$\text{AE (\%)} = \frac{\text{Molecular weight of the product}}{\text{Total molecular weight of the reactants}} \times 100 = \frac{349.4370}{147.1330 + (121.1830 \times 2)} \times 100 = 89.71\%$$

$$\text{CE (\%)} = \frac{\text{Amount of carbon in the product}}{\text{Total carbon present in the reactants}} \times 100 = \frac{(0.0007898419457 \times 24)}{(0.001 \times 8) + (0.001 \times 16)} \times 100 = 78.98\%$$

$$\text{RME(\%)} = \frac{\text{Mass of the isolated product}}{\text{Total mass of the reactants}} \times 100 = \frac{349.4370}{147.1330 + (121.1830 \times 2)} \times 100 = 89.71\%$$

$$\text{E-factor (g/g)} = \frac{\text{Total mass of wastes}}{\text{Mass of the product}} = \frac{(\text{Mass of raw materials} - \text{mass of product})}{\text{Mass of the the product}} = \frac{0.389 - 0.276}{0.276} = 0.41$$

Product	Yield (%)	EMY (%)	AE (%)	CE (%)	RME (%)	E-factor (g/g)
4ah	79	70.95	89.71	78.98	89.71	0.41
4aq	87	79.02	90.69	86.86	90.69	0.27

SI Table 4. Green Metrics (**EMY**, **AE**, **CE**, **RME** and **E-factor**) for **4ah** and **4aq** compound.