Supporting Information

Aqueous mediated Iodine catalyzed C-N coupling followed by C-C coupling towards 5*H*-pyrazino[2,3-*b*]indoles

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General experimental methods

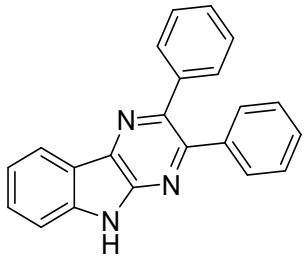
^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker 400 MHz or 300 MHz instrument at 400 MHz and 100 MHz or 300 MHz and 75 MHz respectively. Chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (tetramethylsilane) reference. Coupling constants (*J*) are reported 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). X-ray diffraction was done on a Bruker SMART diffractometer equipped with a graphite monochromator and Mo-Kα (λ = 0.71073 Å) 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-4bi):

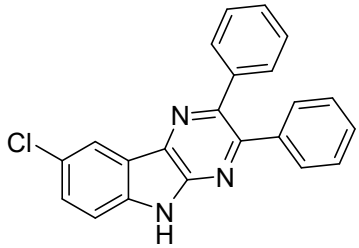
A mixture of isatin (1 mmol), benzylamine (2.2 mmol), ammonium acetate (1.1 equiv.) and iodine (20 mol%) in 0.3 ml water was stirred at 90 ºC for 6 hrs under air. The reaction progress was monitored by TLC. Finally, after completion of the reaction the reaction mixture was diluted with 5 ml dichloromethane and washed with brine (2×10 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**)*



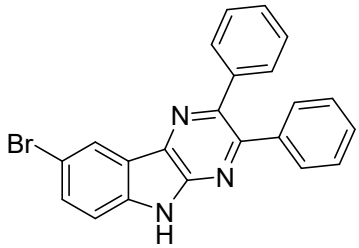
Yield : 81 % ; White solid ; ^{1}H NMR (300 MHz, DMSO-d_6) : δ (ppm) = 12.22 (s, 1H, N-H) , 8.25 (d, *J* = 9 Hz, 1H) , 7.63 (d, *J* = 3 Hz, 2H) , 7.43-7.32 (m, 11H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 148.5, 145.3, 144.6, 141.6, 140.6, 140.2, 133.8, 130.5, 130.4, 129.5, 128.4, 128.0, 121.6, 121.1, 119.8, 112.7 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{16}N_3$ $[M + H]^+$: 322.1344 , found : 322.1332 .

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



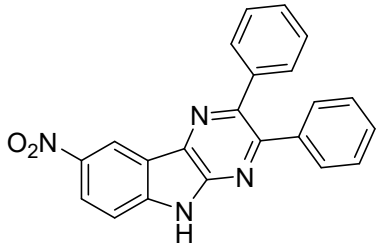
Yield : 86 % ; White solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.42 (s,1H, N-H), 8.26 (d, *J* = 4 Hz, 1H), 7.65 (s, 2H), 7.45-7.41 (m, 4H), 7.35-7.33 (m, 6H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 149.5, 146.0, 145.00, 140.3, 140.0, 139.9, 132.7, 130.5, 130.4, 129.3, 128.7, 128.5, 128.5, 128.1, 125.5, 121.0, 120.8, 114.5 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{15}ClN_3$ $[M + H]^+$: 356.0955 , found : 356.0959 .

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



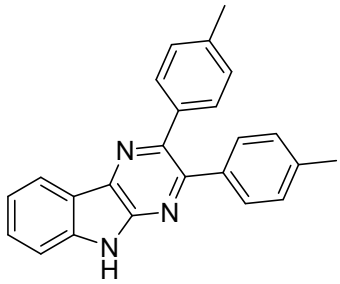
Yield : 85 % ; White solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.43 (s, 1H, N-H), 8.39 (d , *J* = 4 Hz, 1H), 7.45-7.41 (m, 5H), 7.35-7.33 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6) = 149.5, 146.0, 144.8, 140.3, 140.2, 140.0, 132.5, 131.9, 130.4, 128.7, 128.5, 128.5, 128.1, 123.7, 121.6, 114.9, 113.2 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{15}BrN_3$ $[M + H]^+$: 400.0449 , found : 400.0445 .

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



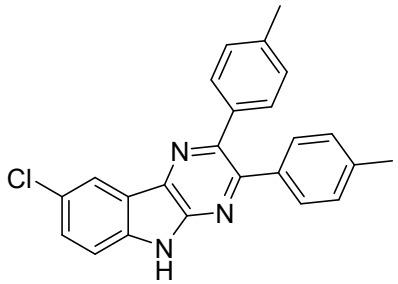
Yield : 65 % ; yellow solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 13.07 (s, 1H, N-H), 9.05 (s, 1H), 8.49 (d, *J* = 8 Hz , 1H) , 7.81 (d, *J* = 12 Hz, 1H), 7.51-7.45 (m, 10H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 149.1, 146.2, 145.7, 145.0, 141.9, 138.6, 138.3, 134.0, 133.9, 133.5, 132.3, 129.8, 128.8, 128.8, 124.7, 119.4, 117.9, 113.5 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{15}N_4O_2$ $[M + H]^+$: 367.1195 , found : 366.1192 .

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



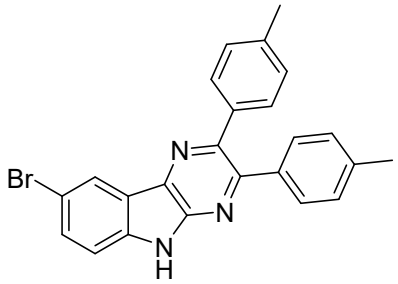
Yield : 78 % ; White solid ; ^{1}H NMR(300 MHz, $CDCl_3$) : δ (ppm) = 10.06 (s, 1H, N-H), 8.40 (d, *J* = 9 Hz, 1H), 7.49-7.43 (m, 5H), 7.34 (d, *J* = 6 Hz, 1H), 7.18 (t, *J* = 9 Hz, 4H), 6.91 (d, *J* = 9 Hz, 1H), 2.41 (d, *J* = 12Hz, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$) = 147.9, 146.0, 144.3, 140.7, 138.2, 137.5, 137.2, 137.1, 134.9, 130.1, 130.1, 129.2, 128.9, 128.7, 121.7, 120.9, 120.3, 111.8, 21.3, 21.3 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{20}N_3$ $[M + H]^+$: 350.1657 , found : 350.1651 .

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



Yield : 81 % ; White solid ; ^{1}H NMR(300 MHz, DMSO-d_6) : δ (ppm) = 12.36 (s, 1H, N-H), 8.21 (s, 1H), 7.61 (s, 2H), 7.34-7.29 (m, 4H), 7.14 (d, *J* = 9 Hz, 4H), 2.31 (s, 6H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 149.4, 145.9, 144.9, 139.8, 138.1, 137.6, 137.4, 137.2, 132.4, 130.3, 130.3, 129.1, 129.1, 125.4, 121.1, 120.7, 111.4, 21.3 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{19}ClN_3$ $[M + H]^+$: 384.1268 , found : 384.1262 .

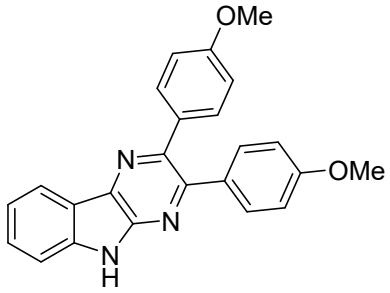
*8-bromo-2,3-di-p-tolyl-5H-pyrazino[2,3-b]indole (**4cb**)*



Yield : 80 % ; White solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.38 (s, 1H, N-H), 8.36 (s, 1H), 7.72 (s, 1H), 7.59 (s, 1H), 7.33 (t, *J* = 8 Hz, 4H), 7.15 (d, *J* = 8 Hz, 4H), 2.3 (s, 6H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 149.4, 146.0, 144.7, 140.1, 138.1, 137.6, 137.4,

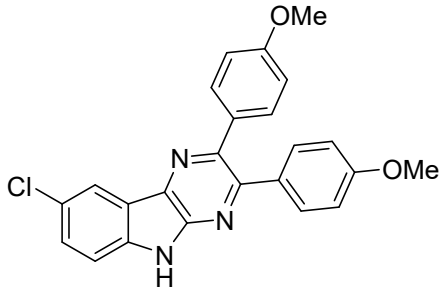
137.2, 132.3, 131.7, 130.3, 130.3, 129.9, 129.1, 129.1, 123.6, 121.6, 114.8, 113.1, 21.3 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{19}BrN_3$ $[M + H]^+$: 428.0762 , found : 428.0761 .

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



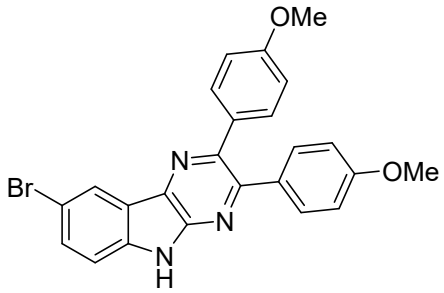
Yield : 85 % ; yellow solid ; ^{1}H NMR(300 MHz, $CDCl_3$) : δ (ppm) = 10.93 (s, 1H, N-H), 8.3 (d, *J* = 9 Hz, 1H), 7.57 (d, *J* = 9 Hz, 2H), 7.50 (d, *J* = 9 Hz , 2H), 7.42-7.37 (m, 1H), 7.32-7.28 (m, 1H) ,6.93 (t, *J* = 9 Hz, 4H),6.63 (d, *J* = 6 Hz, 1H), 3.88 (d, *J* = 9 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) = 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 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{20}N_3O_2$ $[M + H]^+$: 382.1556 , found : 382.1552 .

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



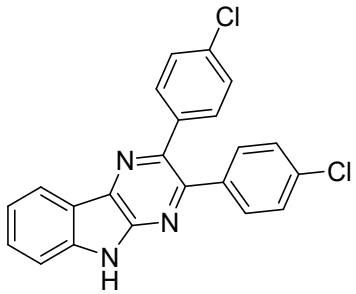
Yield : 77 % ; yellow solid ; ^{1}H NMR(300 MHz, $CDCl_3$) : δ (ppm) = 11.14 (s, 1H, N-H), 8.34 (s, 1H), 7.56 (d, *J* = 6 Hz, 2H), 7.47 (d, *J* = 6 Hz, 2H), 7.32 (d, *J* = 9 Hz, 1H), 6.97-6.90 (m, 4H), 6.45 (d, *J* = 9 Hz, 1H), 3.89 (d, *J* = 9 Hz) ; ^{13}C NMR (75 MHz, $CDCl_3$) = 160.0, 159.4, 148.2, 146.2, 144.6, 138.8, 133.8, 132.3, 132.1, 131.6, 131.4, 128.6, 126.5, 121.3, 121.3, 114.1, 113.8, 113.0, 55.5, 55.3 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{19}ClN_3O_2$ $[M + H]^+$: 416.1166 , found : 416.1165 .

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



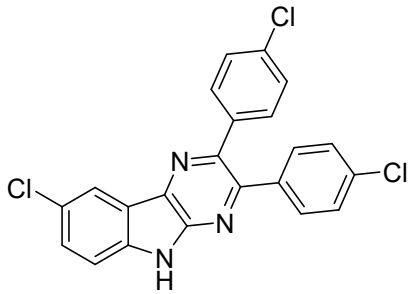
Yield : 74 % ; yellow solid ; ^{1}H NMR(400 MHz, $CDCl_3$) : δ (ppm) = 10.53 (s, 1H, N-H), 8.51 (s, 1H), 7.55- 7.46 (m, 5H), 6.95-6.90 (m , 4H), 6.66 (d, *J* = 12 Hz, 1H), 3.88 (d, *J* = 8 Hz, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$) = 159.9, 159.4, 146.4, 144.3, 139, 133.4, 132.3, 132.1, 131.5, 131.4, 131.3, 124.4, 122.0, 114.0, 113.9, 113.8, 113.3, 55.4, 55.3 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{19}BrN_3O_2$ $[M + H]^+$: 460.0661 , found : 460.0663 .

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



Yield : 84 % ; White solid ; ^{1}H NMR(300 MHz, DMSO-d_6) : δ (ppm) = 12.30 (s, 1H, N-H), 8.26 (d, *J* = 9 Hz, 1H), 7.72-7.62 (m, 3H), 7.44 (s, 7H), 7.36-7.33 (m, 1H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 147.2, 144.6, 143.9, 141.8, 139.2, 138.8, 134.2, 133.6, 133.0, 132.3, 129.8, 129.1, 128.7, 128.7, 121.7, 121.3, 119.6, 112.8 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{14}Cl_2N_3$ $[M + H]^+$: 390.0565 , found : 390.0566 .

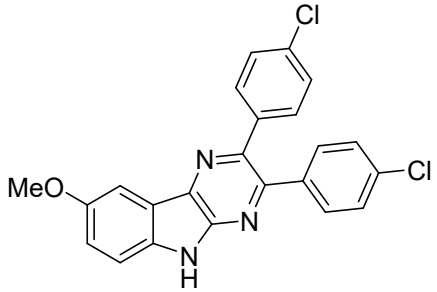
8-chloro-2,3-bis(4-chlorophenyl)-5H-pyrazino[2,3-b]indole ***(4bd)***



Yield : 87 % ; White solid ; ^{1}H NMR(300 MHz, DMSO-d_6) : δ (ppm) = 12.49 (s, 1H, N-H), 8.26 (s, 1H), 7.65 (s, 2H), 7.45-7.44 (m, 8H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 148.2, 145.0, 144.6, 140.1, 138.9, 138.6, 133.7, 133.2, 133.1, 132.3, 129.6, 128.7, 128.7, 125.7,

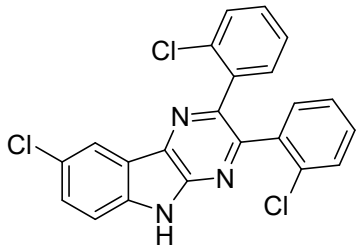
120.9, 120.8, 114.6 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{13}Cl_3N_3$ $[M + H]^+$: 424.0175 , found : 424.0175 .

*2,3-bis(4-chlorophenyl)-8-methoxy-5H-pyrazino[2,3-b]indole (**4ed**)*



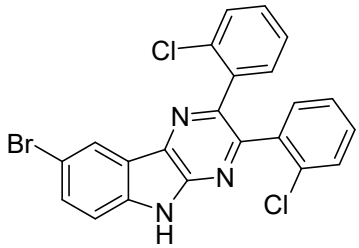
Yield : 78 % ; yellow solid ; ^{1}H NMR(400 MHz, $CDCl_3$) : δ (ppm) = 9.88 (s, 1H, N-H), 7.86 (d, *J* = 4 Hz, 1H), 7.48 (t, *J* = 8 Hz, 4H), 7.37 (t, *J* = 8 Hz,4H), 7.20-7.17 (m, 1H), 6.89 (d, J = 8 Hz, 1H), 3.95 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) = 155.1, 146.6, 144.8, 144.4, 138.2, 138.0, 135.5, 135.2, 134.7, 134.1, 131.5, 128.9, 128.7, 120.4, 119.7, 112.7, 103.2,56.0 ppm ; HRMS-ESI (m/z): calcd for $C_{23}H_{16}Cl_2N_3O$ $[M + H]^+$: 420.0670 , found : 420.0674 .

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



Yield : 82 % ; white solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.57 (s, 1H), 8.30 (d, *J* = 4 Hz, 1H), 7.69 (s, 2H), 7.45-7.39 (m, 4H), 7.37-7.28 (m, 4H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 148.2, 144.8, 144.6, 140.1, 138.1, 137.7, 133.3, 133.2, 132.9, 130.6, 130.5, 129.8, 129.8, 129.6, 127.0, 127.0, 125.8, 121.0, 120.7, 114.6 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{13}Cl_3N_3$ $[M + H]^+$: 424.0175 , found : 424.0472 .

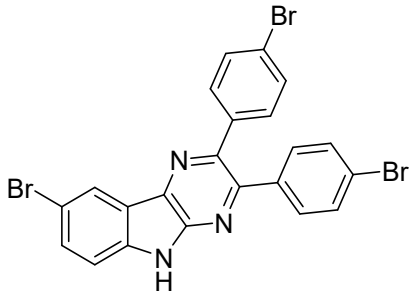
*8-bromo-2,3-bis(2-chlorophenyl)-5H-pyrazino[2,3-b]indole (**4ce**)*



Yield : 80 % ; White solid ; ^{1}H NMR(300 MHz, DMSO-d_6) : δ (ppm) = 12.57 (s, 1H), 8.42 (s, 1H), 7.79 (d, *J* = 6 Hz, 1H), 7.65 (d, *J* = 9 Hz, 1H), 7.45-7.25 (m, 8H) ; ^{13}C NMR (75

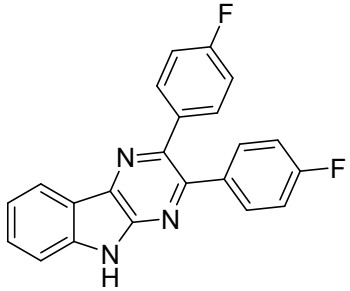
MHz, DMSO-d_6) = 148.3, 144.6, 144.6, 140.3, 138.0, 137.7, 133.3, 133.0, 132.9, 132.4, 130.7, 130.4, 129.8, 129.6, 127.0, 124.0, 121.3, 115.0, 113.5 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{13}BrCl_2N_3$ $[M + H]^+$: 467.9670 , found : 467.9676 .

*8-bromo-2,3-bis(4-bromophenyl)-5H-pyrazino[2,3-b]indole (**4cf**)*



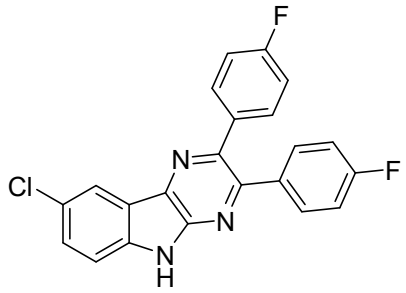
Yield : 81 % ; yellow solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.51 (s, 1H, N-H), 8.38 (s, 1H), 7.77 (d, *J* = 9 Hz, 1H), 7.61-7.57 (m, 5H), 7.40-7.37 (m, 4H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 147.4, 144.6, 144.2, 141.7, 136.9, 136.9, 136.5, 136.5, 133.9, 132.6, 132.6, 132.5, 132.5, 129.6, 121.6, 121.2, 119.7, 115.7, 115.6, 115.4, 115.3, 112.7 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{13}Br_3N_3$ $[M + H]^+$: 555.8660 , found : 555.8665 .

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



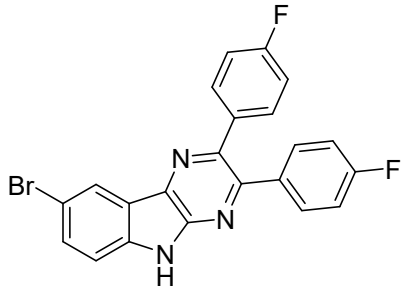
Yield : 86 % ; white solid ; ^{1}H NMR(300 MHz, DMSO-d_6) : δ (ppm) = 12.26 (s, 1H, N-H), 8.26 (d, *J* = 9 Hz, 1H), 7.62 (d, *J* = 3 Hz, 2H), 7.49-7.42 (m, 4H), 7.37-7.32 (m, 1H), 7.24-7.16 (m, 4H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 162.4 (C-F, $1J_{C\text{-}F}$ = 244.5 Hz), 162.2 (C-F, $1J_{C\text{-}F}$ = 243.8 Hz) , 147.4, 144.6, 144.2, 141.7, 136.7 (C-F, $2J_{C\text{-}F}$ = 29.5 Hz), 136.7 (C-F, $2J_{C\text{-}F}$ = 29.3 Hz), 133.9, 132.6, 132.6, 132.5, 132.5, 129.6, 121.6, 121.2, 119.7, 115.5 (C-F, $3J_{C\text{-}F}$ = 21.7 Hz), 115.5 (C-F, $3J_{C\text{-}F}$ = 21.0 Hz), 112.7 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{14}F_2N_3$ $[M + H]^+$: 358.1156 , found : 358.1153 .

*8-chloro-2,3-bis(4-fluorophenyl)-5H-pyrazino[2,3-b]indole (**4bg**)*



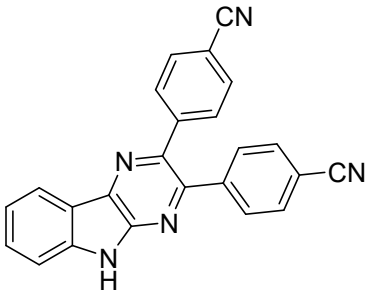
Yield : 88 % ; white solid ; ^{1}H NMR(400 MHz, $CDCl_3$) : δ (ppm) = 10.10 (s, 1H, N-H), 8.38 (d, *J* = 4 Hz, 1H), 7.55-7.52 (m, 2H), 7.50-7.47 (m, 3H), 7.13-7.05 (m, 4H), 6.90 (d, *J* = 8 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) = 163.0 (C-F, $1J_{C\text{-}F}$ = 248 Hz), 162.7 (C-F, $1J_{C\text{-}F}$ = 246 Hz), 147.7, 145.6, 144.6, 138.8, 135.5 (C-F, $2J_{C\text{-}F}$ = 10 Hz), 135.4 (C-F, $2J_{C\text{-}F}$ = 9 Hz), 134.1, 132.0, 132.0, 131.9, 129.4, 127.1, 121.6, 121.3, 115.7 (C-F, $2J_{C\text{-}F}$ = 27 Hz), 115.5 (C-F, $2J_{C\text{-}F}$ = 26 Hz), 112.8 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{13}ClF_2N_3$ $[M + H]^+$: 392.0766 , found : 392.0761 .

*8-bromo-2,3-bis(4-fluorophenyl)-5H-pyrazino[2,3-b]indole (**4cg**)*



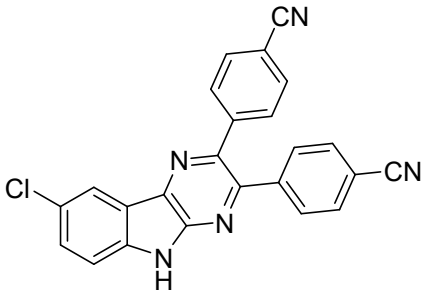
Yield : 85 % ; white solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.54 (s, 1H, N-H), 8.38 (d, *J* = 4 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.60 (d, *J* = 8 Hz, 1H), 7.48-7.43 (m, 4H), 7.23-7.18 (m, 4H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 162.5 (C-F, $1J_{C\text{-}F}$ = 245 Hz), 162.2 (C-F, $1J_{C\text{-}F}$ = 243 Hz), 148.4, 144.9, 144.8, 140.2, 136.5 (C-F, $2J_{C\text{-}F}$ = 35 Hz), 136.4 (C-F, $2J_{C\text{-}F}$ = 35 Hz), 132.6, 132.6, 132.5, 132.0, 123.8, 121.5, 115.6 (C-F, $3J_{C\text{-}F}$ = 22 Hz), 115.5 (C-F, $3J_{C\text{-}F}$ = 22 Hz), 114.9, 113.3 ppm ; HRMS-ESI (m/z): calcd for $C_{22}H_{13}BrF_2N_3$ $[M + H]^+$: 436.0261, found : 436.0265 .

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



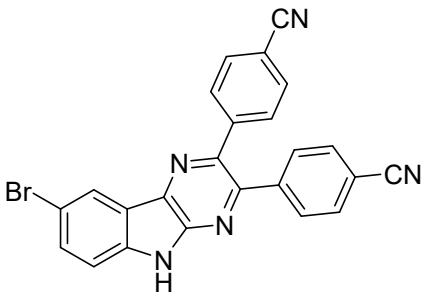
Yield : 87 % ; White solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.44 (s, 1H, N-H), 8.29 (d, *J* = 8 Hz, 1H), 7.86-7.83 (m, 4H), 7.67-7.61 (m, 6H), 7.40-7.36 (m, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 146.9, 144.7, 144.7, 144.3, 143.6, 142.1, 134.8, 132.6, 132.6, 131.5, 130.3, 121.9, 121.5, 119.5, 119.2, 119.0, 112.9, 111.4, 110.9 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{14}N_5$ $[M + H]^+$: 372.1249 , found : 372.1245 .

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



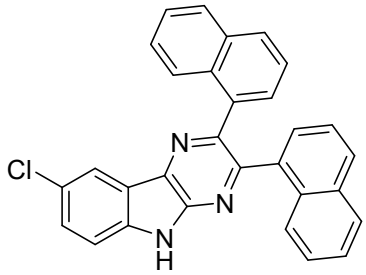
Yield : 89 % ; White solid ; ^{1}H NMR(300 MHz, DMSO-d_6) : δ (ppm) = 12.62 (s, 1H, N-H), 8.30 (s, 1H), 7.86 (d, *J* = 6 Hz, 4H), 7.68 (s, 2H), 7.63 (d, *J* = 9 Hz, 4H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 147.9, 145.1, 144.4, 144.2, 144.1, 140.4,133.7, 132.7, 132.6, 131.5, 130.0 125.9, 121.1, 120.7, 119.2, 119.1,114.7, 111.5, 111.0 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{13}ClN_5$ $[M + H]^+$: 406.0859 , found : 406.0857 .

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



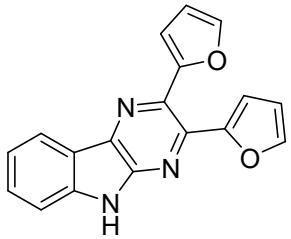
Yield : 86 % ; White solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.64 (s, 1H, N-H), 8.43 (s, 1H), 7.87-7.84 (m, 5H), 7.64-7.61 (m, 5H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 147.9, 144.9, 144.4, 144.2, 144.1, 140.7, 133.5, 132.7, 132.6, 131.5, 124.1, 121.3, 119.2, 119.1, 115.1, 113.6, 111.6, 111.0 ppm ; HRMS-ESI (m/z): calcd for $C_{24}H_{13}BrN_5$ $[M + H]^+$: 450.0354 , found : 450.0352 .

*8-chloro-2,3-di(naphthalen-1-yl)-5H-pyrazino[2,3-b]indole (**4bi**)*



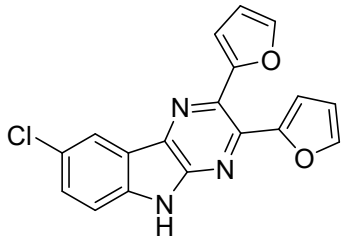
Yield : 83 % ; White solid ; ^{1}H NMR(400 MHz, DMSO-d_6) : δ (ppm) = 12.51 (s, 1H, N-H), 8.29 (s, 1H), 7.84 (d, *J* = 8 Hz, 3H), 7.76 (d, *J* = 8 Hz, 3H), 7.71 (s, 1H), 7.70 (s, 1H), 7.46-7.22 (m, 8H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 150.3, 146.5, 145.0, 140.1, 137.5, 137.1, 133.4, 133.2, 129.5, 128.7, 128.4, 126.5, 126.3, 126.2, 125.6, 125.1, 125.0, 121.1, 121.0, 114.5 ppm ; HRMS-ESI (m/z): calcd for $C_{30}H_{19}ClN_3$ $[M + H]^+$: 456.1268 , found : 456.1267 .

2,3-di(furan-2-yl)-5H-pyrazino[2,3-b]indole (4aj)



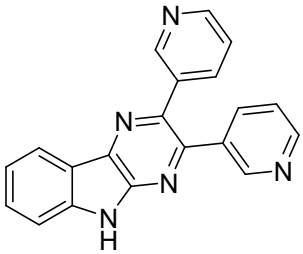
Yield : 71 % ; Yellow solid ; ^{1}H NMR (300 MHz, DMSO-d_6) : δ (ppm) = 10.57 (s, 1H, N-H) , 8.37 (d, *J* = 9 Hz, 2H) , 7.34-7.23 (m, 4H) , 7.04-6.99 (m, 1H) , 6.88 (d, *J* = 9 Hz, 1H), 6.81 (d, *J* = 3 Hz, 1H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 151.2, 147.7, 146.7, 143.1, 130.2, 125.0, 122.7, 121.8, 121.7, 121.3, 119.8, 114.0, 110.2 ppm ; HRMS-ESI (m/z): calcd for $C_{18}H_{11}N_3O_2$[M + H]$^+$: 302.0930 , found : 302.0935 .

8-chloro-2,3-di(furan-2-yl)-5H-pyrazino[2,3-b]indole (4bj)



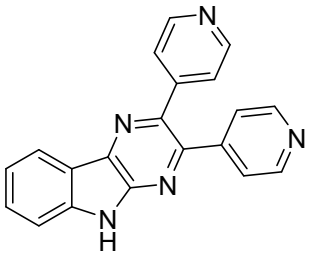
Yield : 74 % ; Yellow solid ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) = 10.72 (s, 1H, N-H) , 8.29 (d, *J* = 12 Hz, 2H) , 7.41-7.30 (m, 3H) , 7.22-7.18 (m, 1H) , 6.89 (d, *J* = 8 Hz, 1H), 6.85-6.84 (m, 1 H), 6.80 (d, J = 8 Hz, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) = 151.0, 148.5, 147.4, 141.7, 129.6, 127.7, 125.8, 125.0, 124.3, 123.4, 122.7, 121.4, 121.2, 114.3, 111.5 ppm ; HRMS-ESI (m/z): calcd for $C_{18}H_{11}ClN_3O_2$[M + H]$^+$: 336.0540 , found : 336.0542 .

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



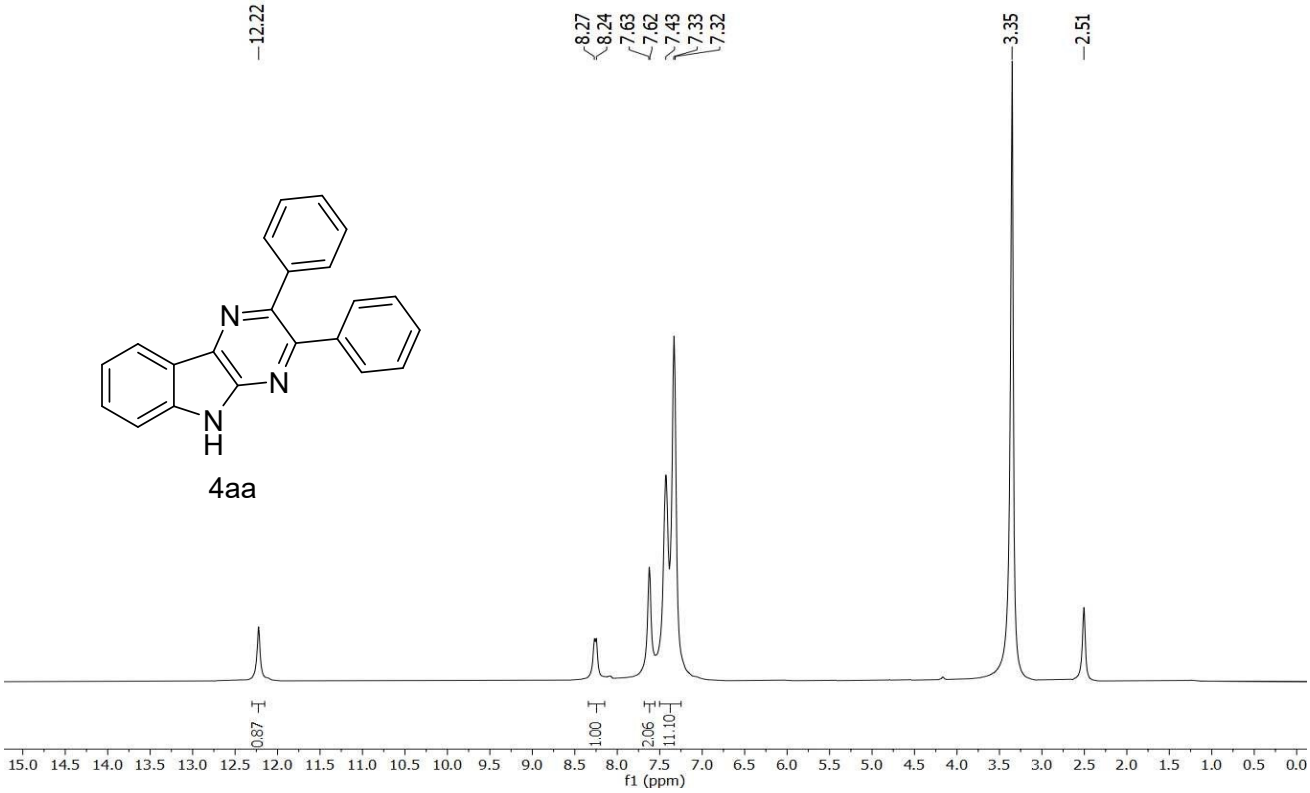
Yield : 74 % ; Yellow solid ; ^{1}H NMR (300 MHz, DMSO-d_6) : δ (ppm) = 10.72 (s, 1H, N-H) , 8.61-8.55 (m, 4 H), 8.31 (d , J = 9 Hz, 1H), 7.88-7.84 (m, 2H), 7.67-7.65 (m, 2H), 7.44-7.38 (m, 3H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 151.0, 150.9, 149.4, 149.0, 146.0, 144.9, 142.7, 141.9, 137.9, 134.7, 130.1, 123.7, 121.9, 121.4, 119.5, 112.9 ppm ; HRMS-ESI (m/z): calcd for $C_{20}H_{13}N_5[M + H]^+$: 324.1249 , found : 324.1245 .

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



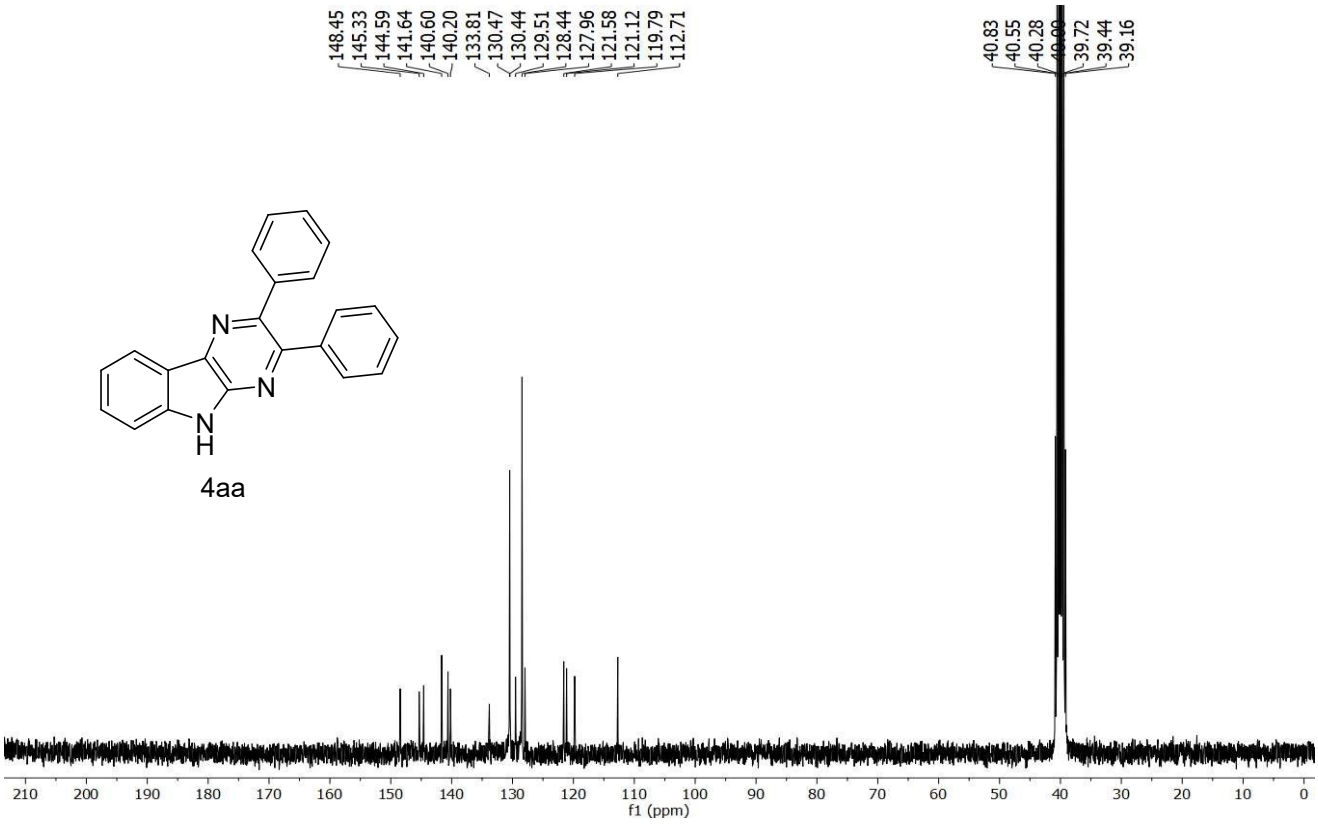
Yield : 74 % ; Yellow solid ; ^{1}H NMR (300 MHz, DMSO-d_6) : δ (ppm) = 12.49 (s, 1H, N-H) , 8.60-8.57 (m , 4H), 8.31 (d, J = 9 Hz, 1H), 7.69-7.68 (m, 2H), 7.45-7.43 (m, 5H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 150.1, 150.0, 147.3, 147.1, 146.2, 144.8, 142.8, 135.0, 130.4, 125.2, 125.0, 122.0, 121.6, 119.4, 113.0 ppm ; HRMS-ESI (m/z): calcd for $C_{20}H_{13}N_5[M + H]^+$: 324.1249 , found : 324.1249 .

^{1}H and ^{13}C NMR spectra of compounds



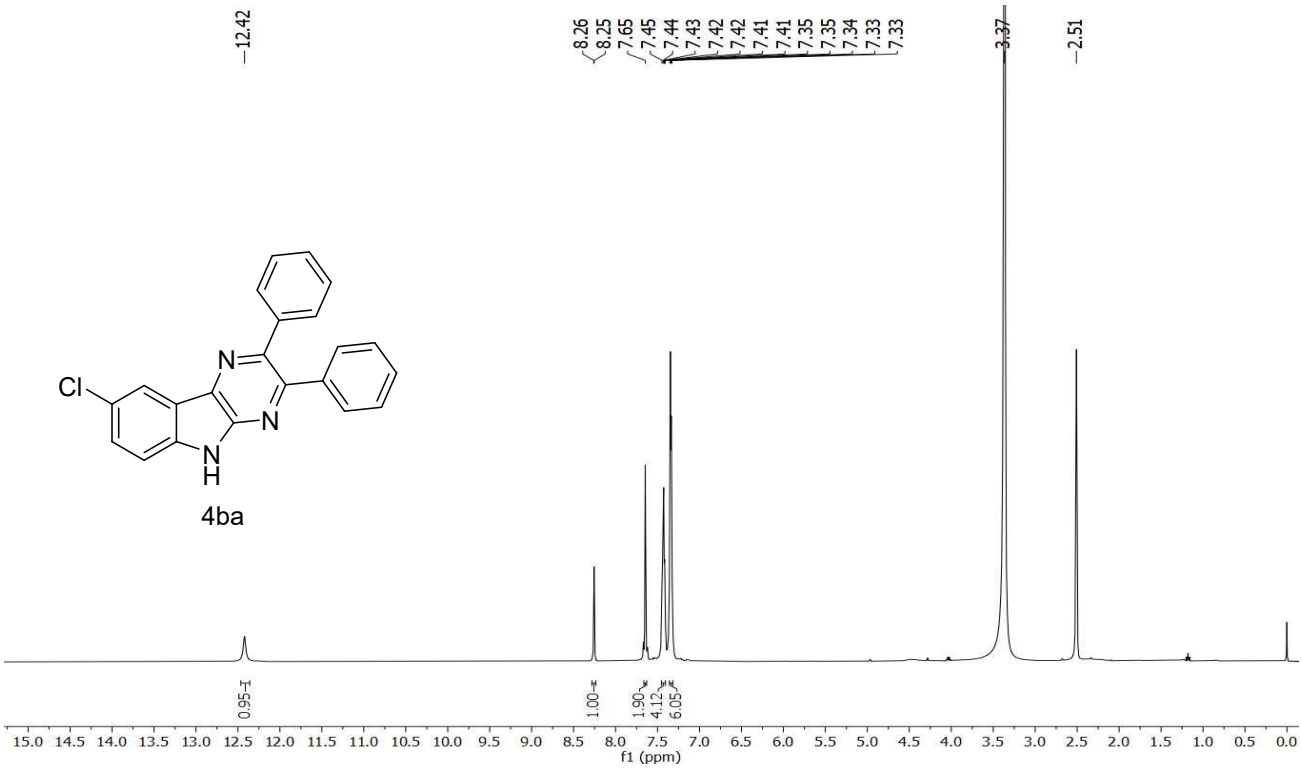
4aa

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

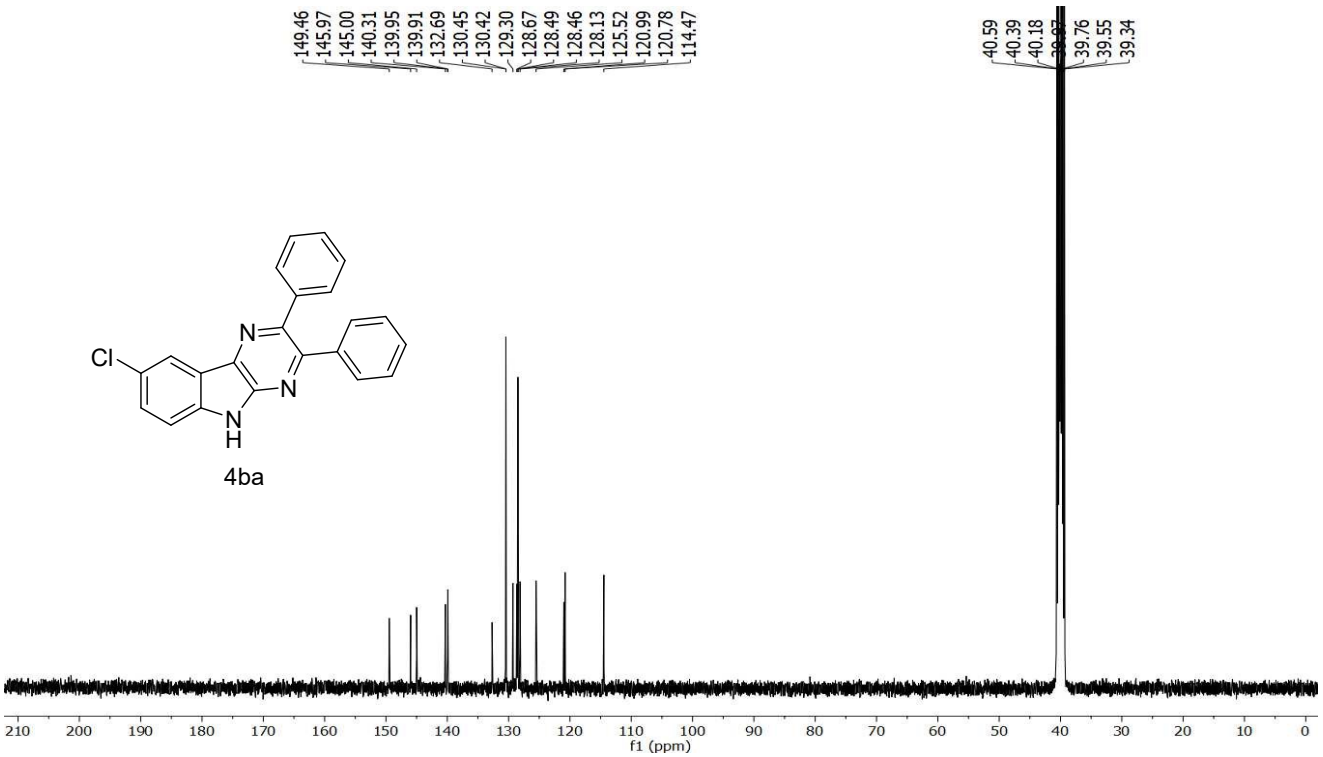


4aa

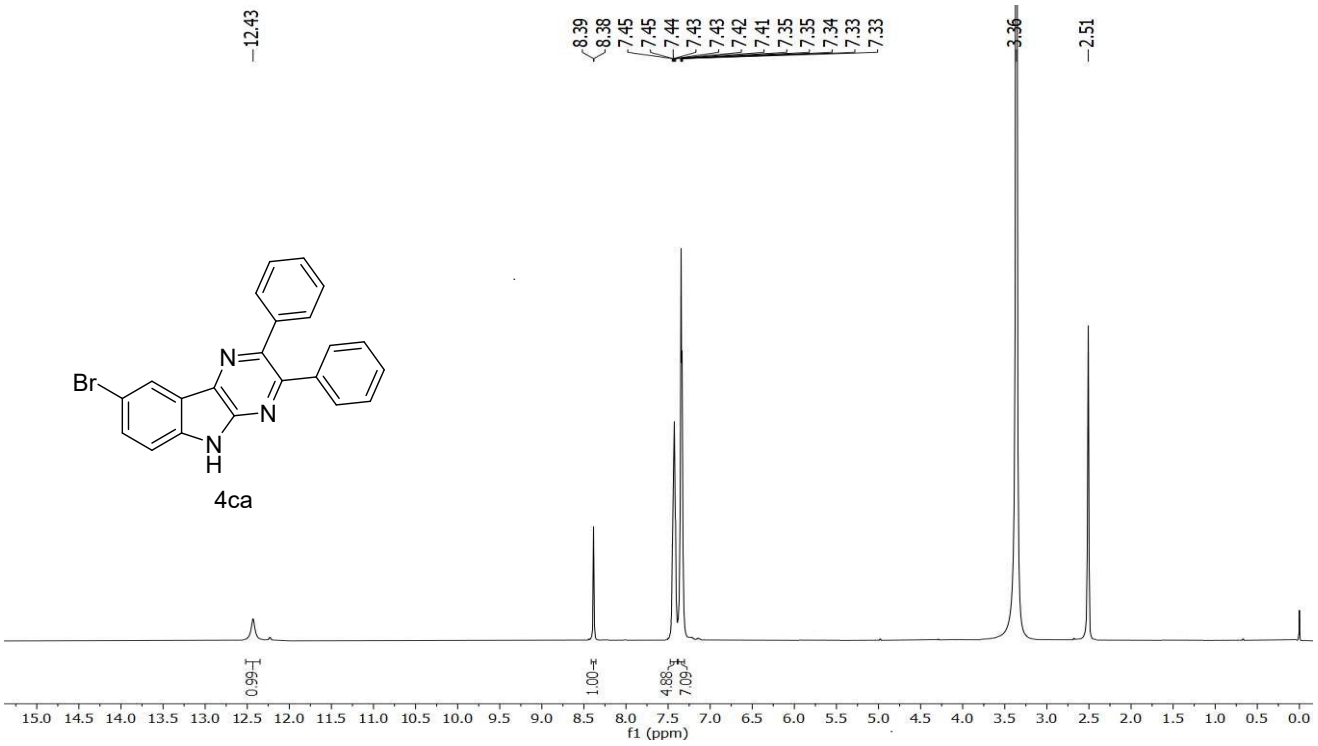
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound 4aa



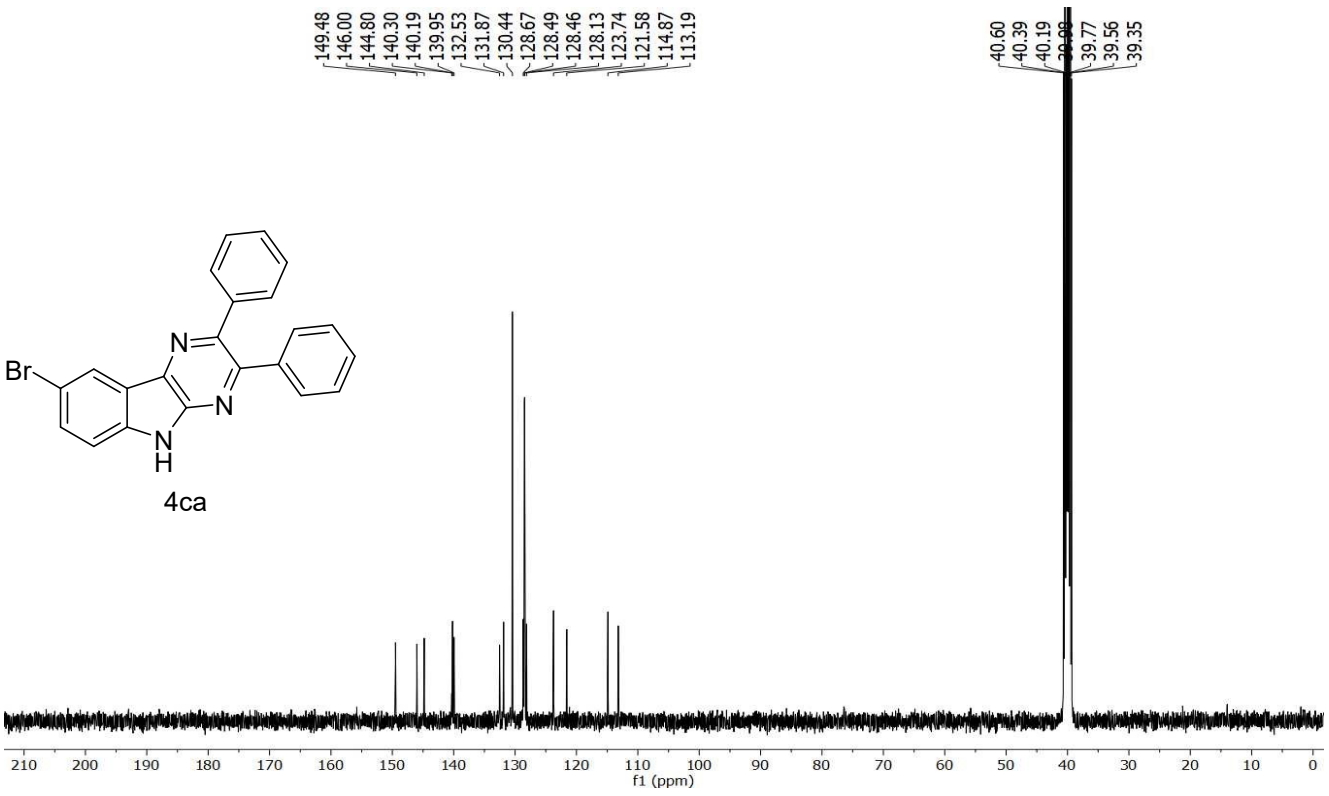
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4ba



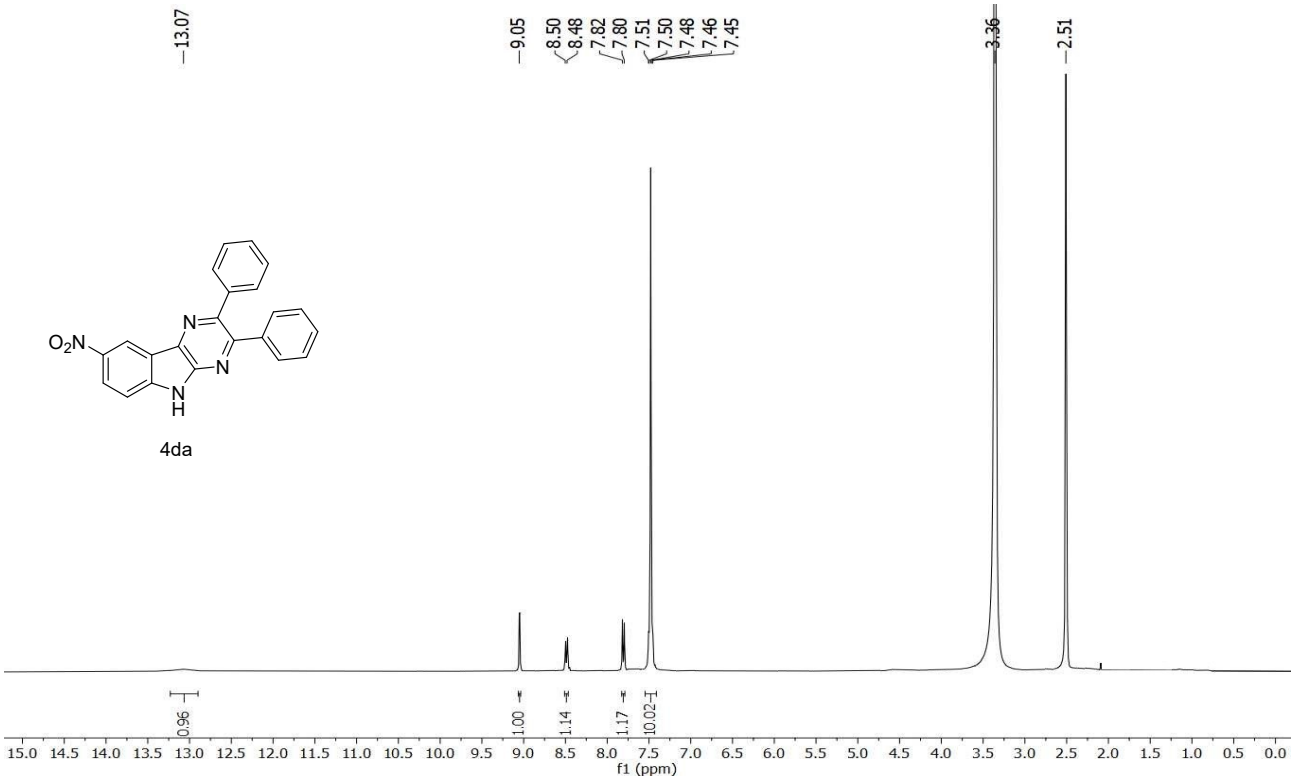
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4ba



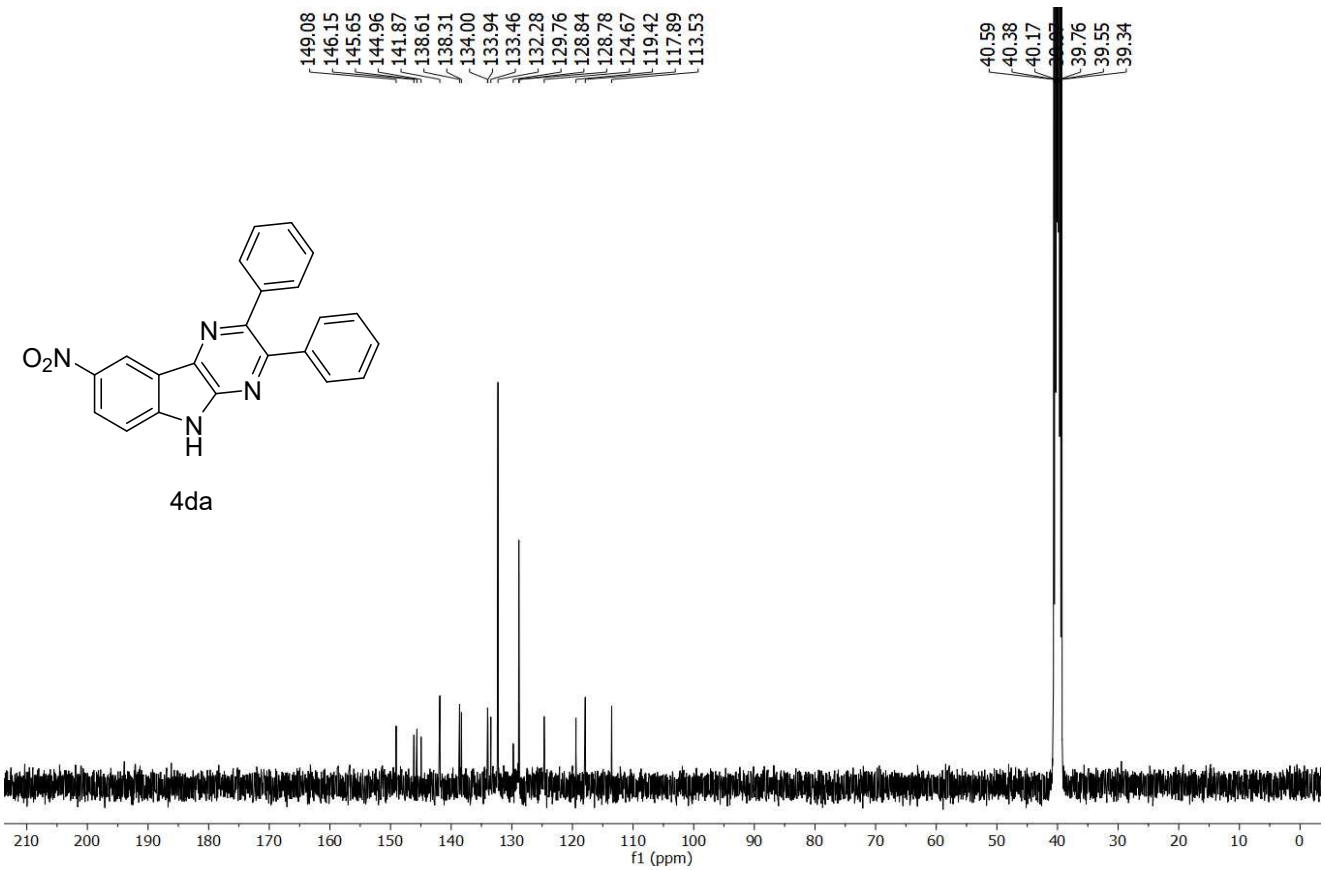
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4ca



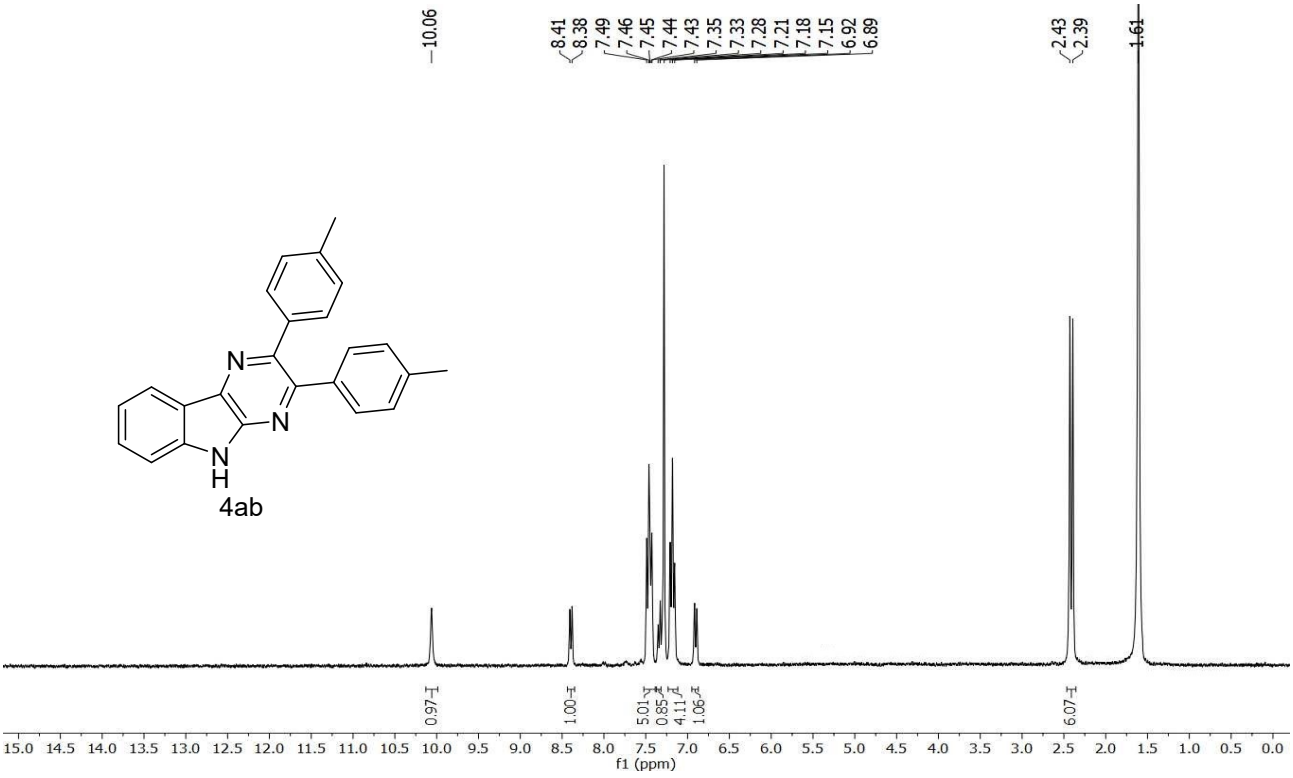
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4ca



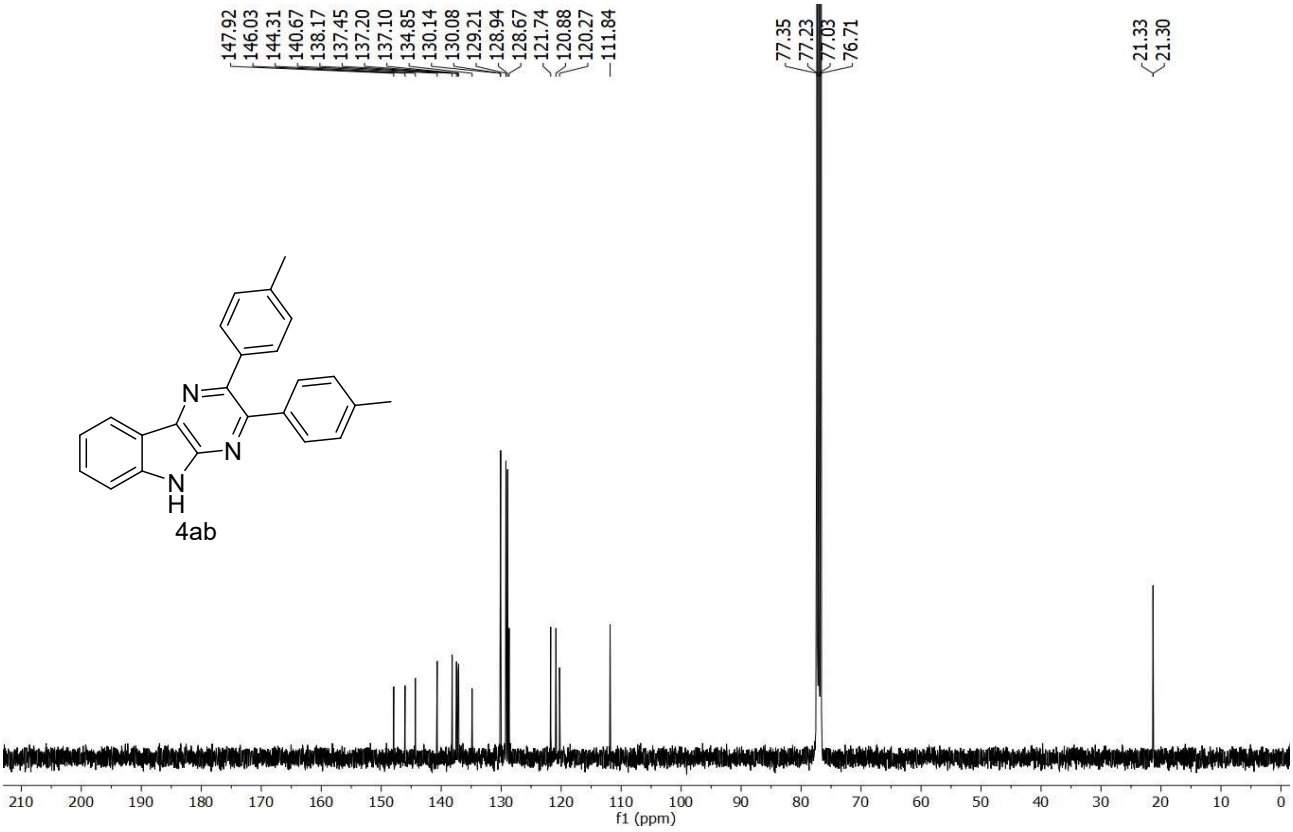
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4da



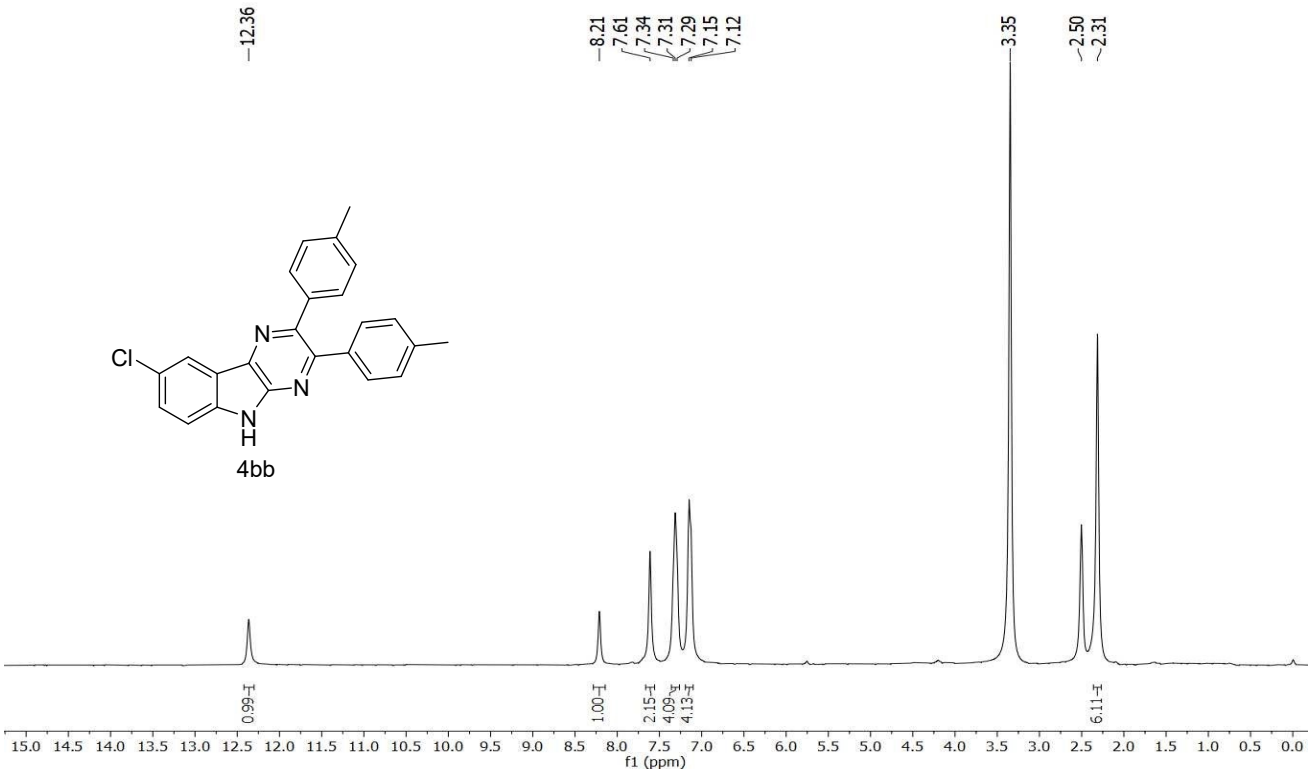
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4da



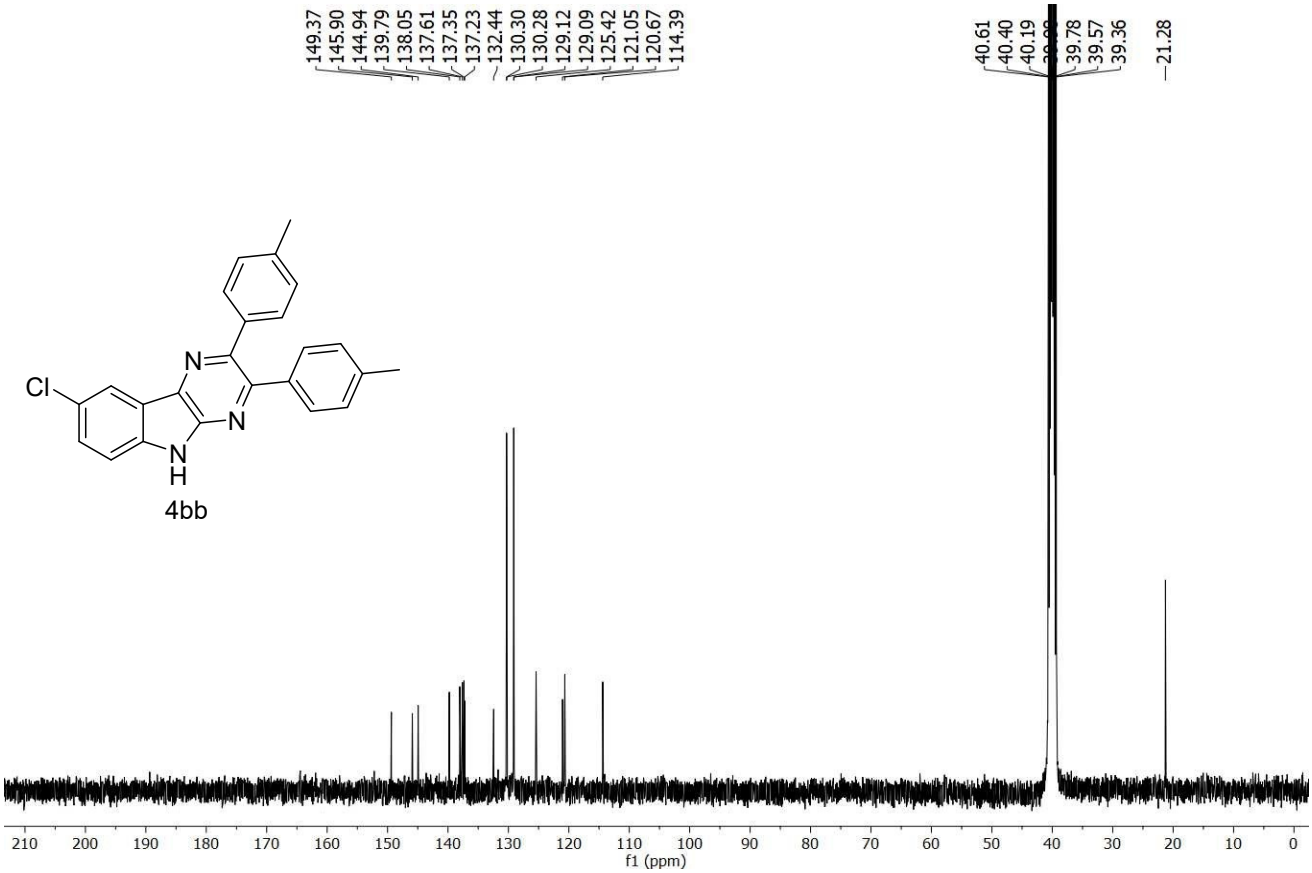
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound 4ab



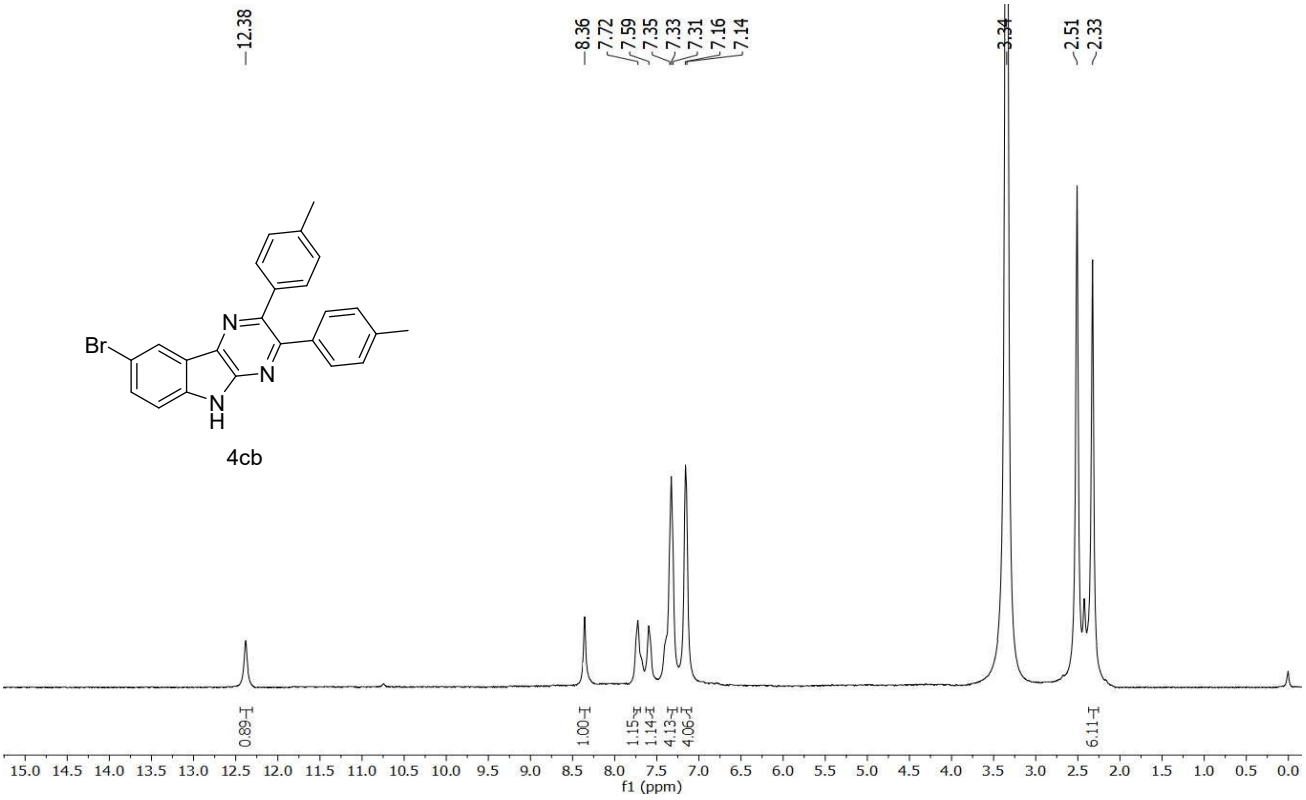
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4ab



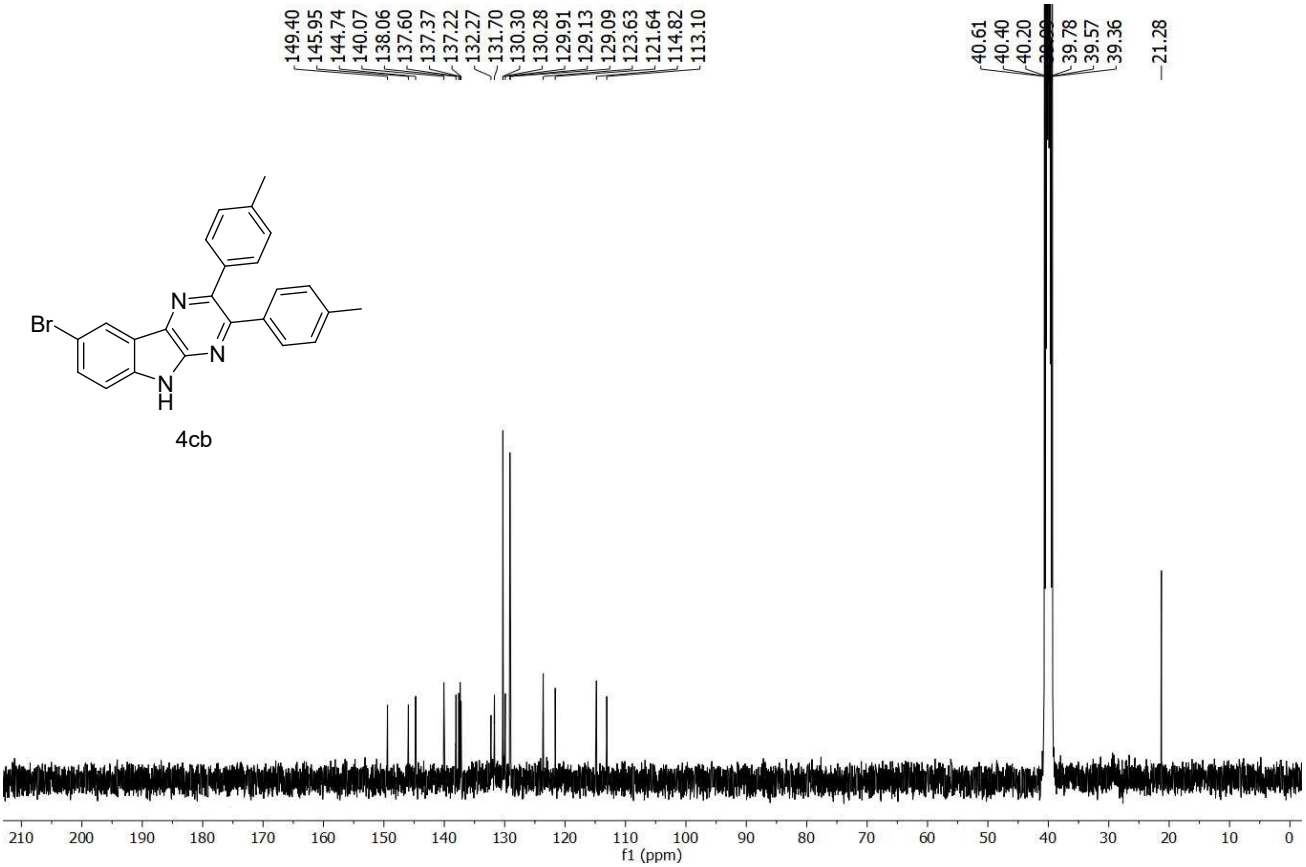
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound 4bb



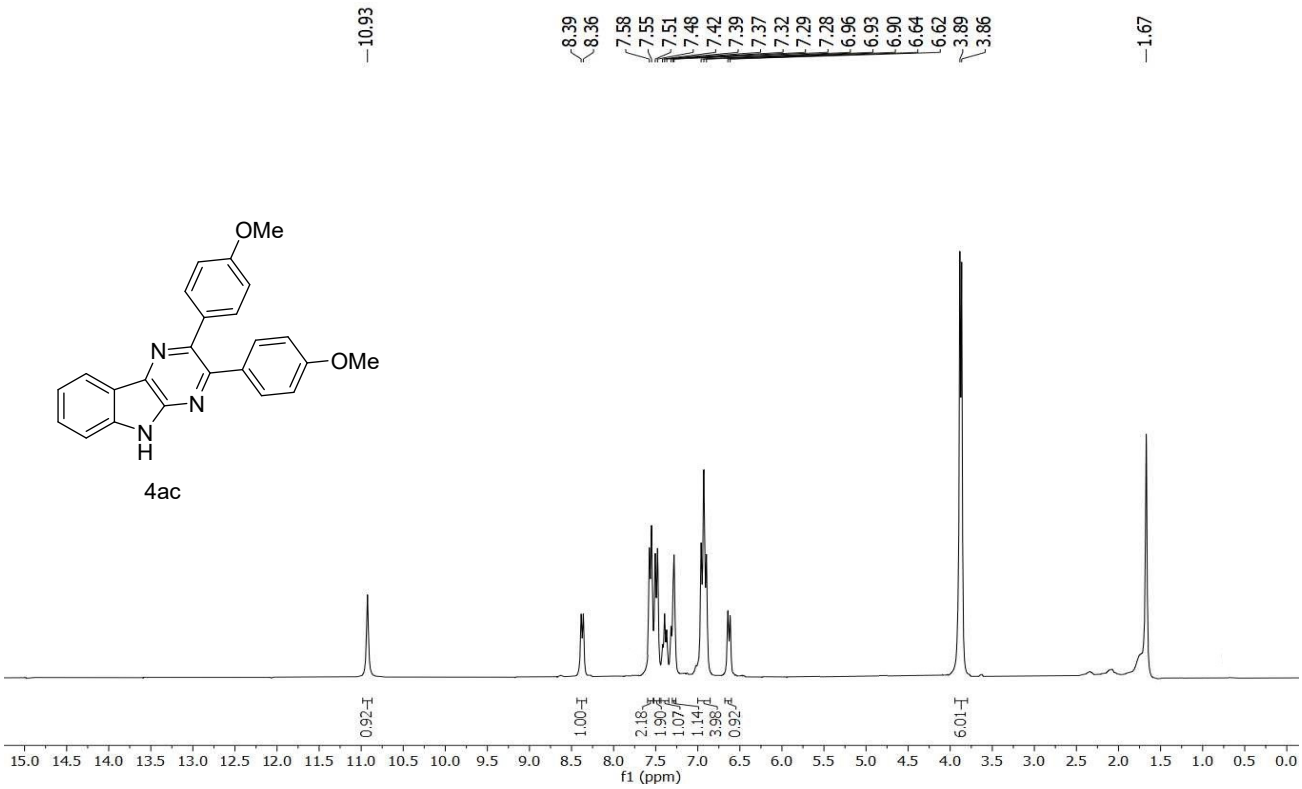
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4bb



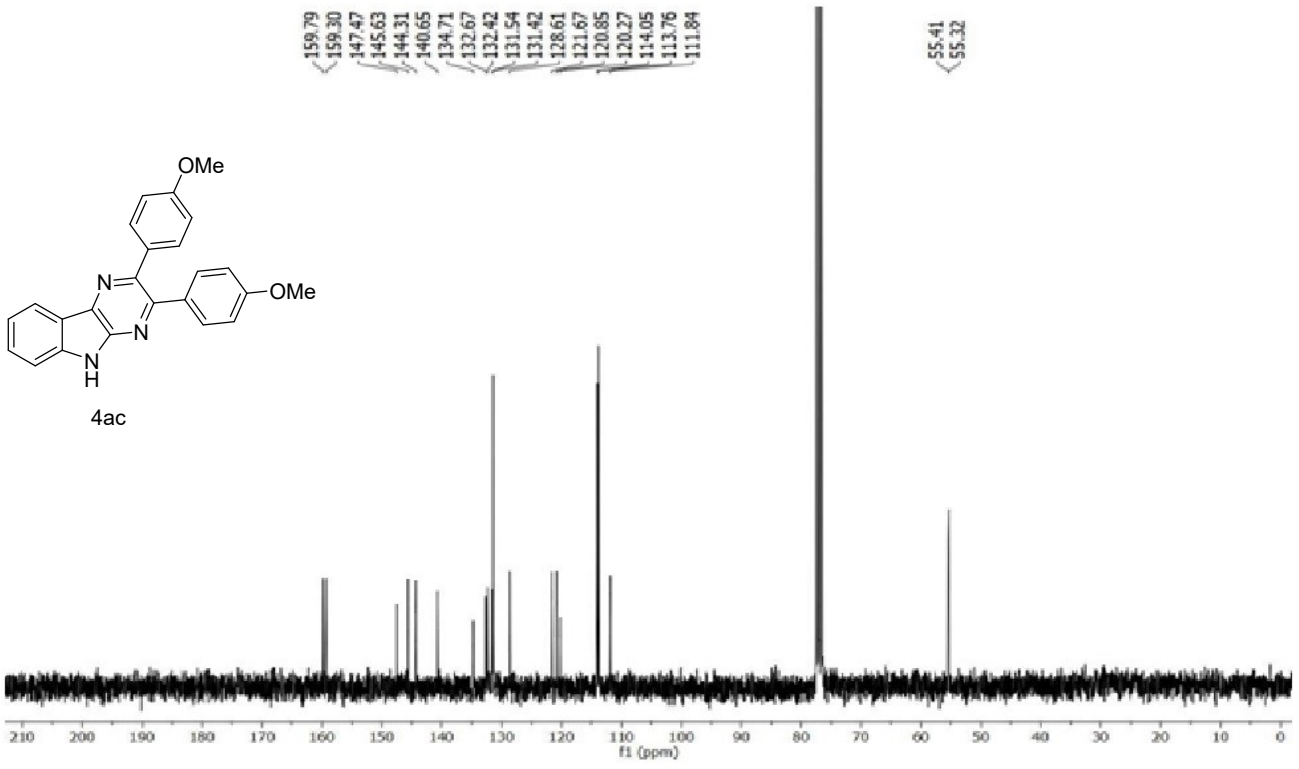
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4cb



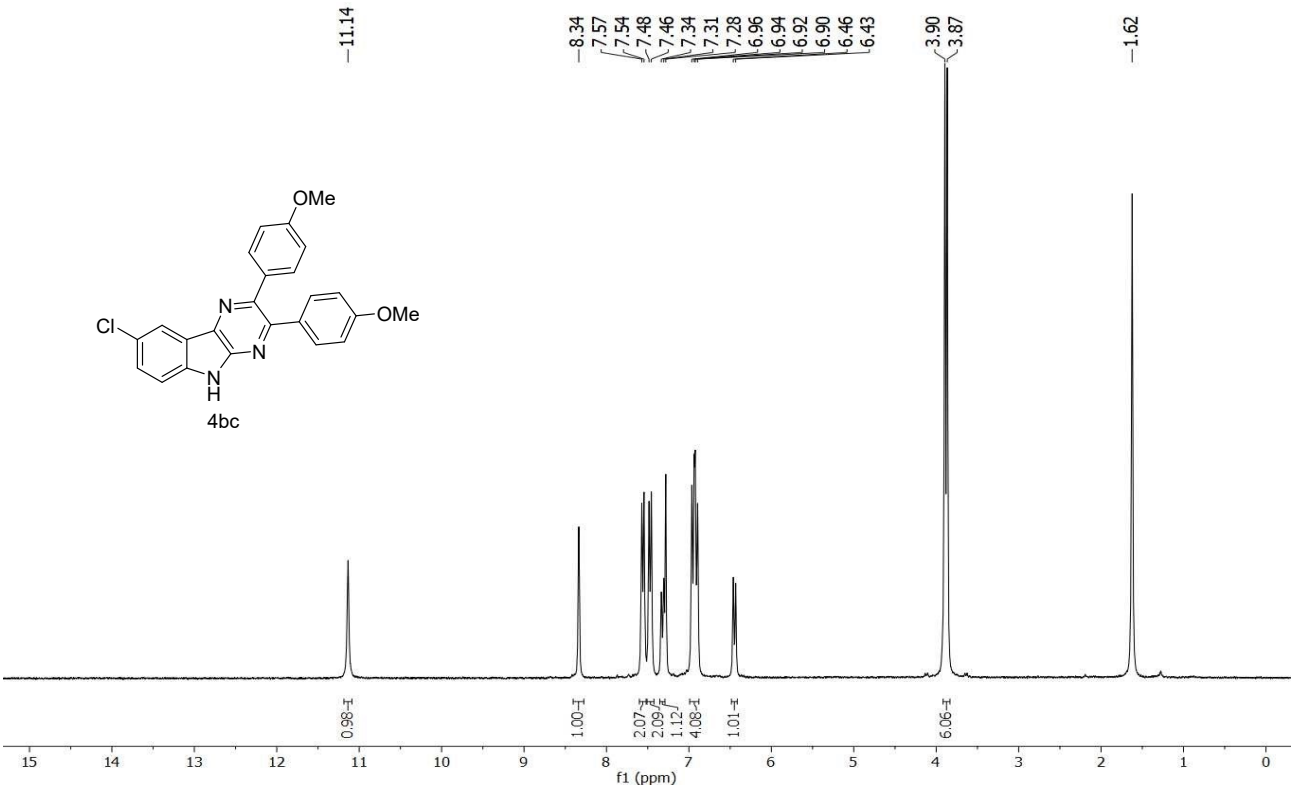
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4cb



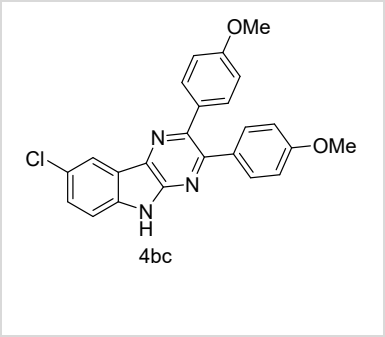
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 4ac



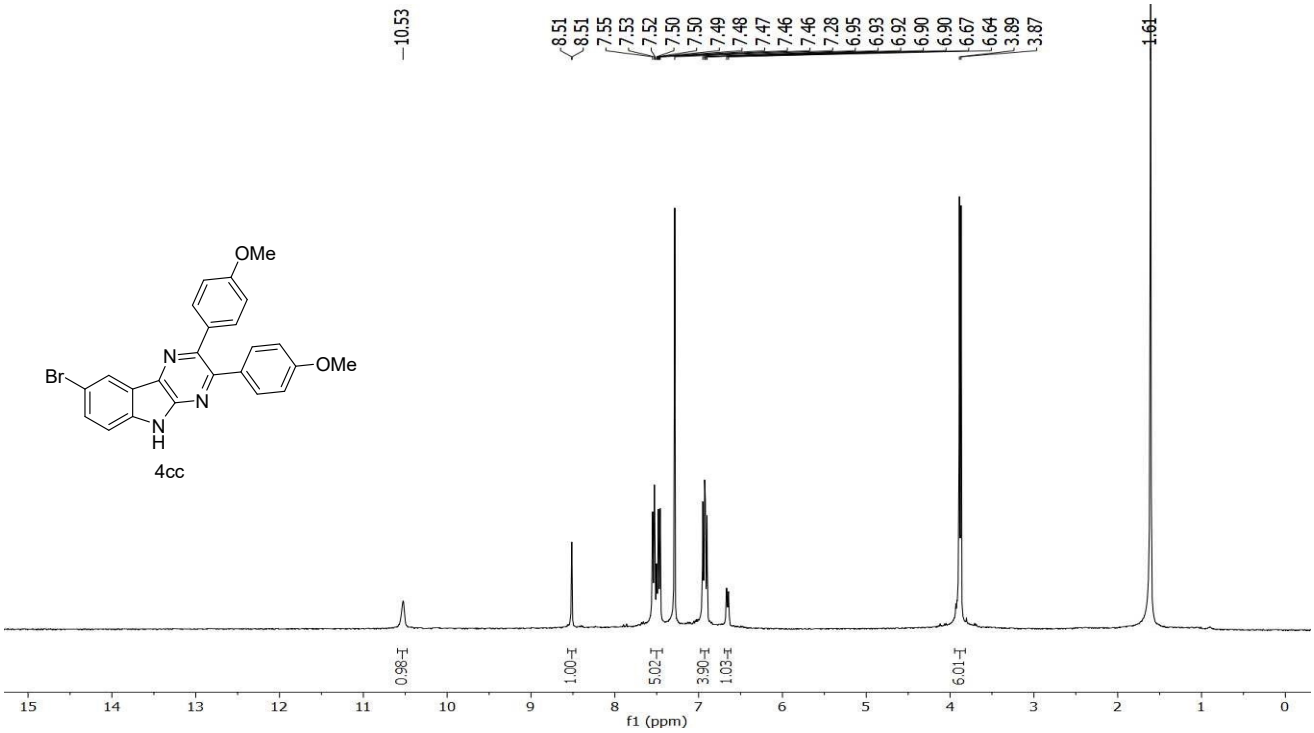
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 4ac



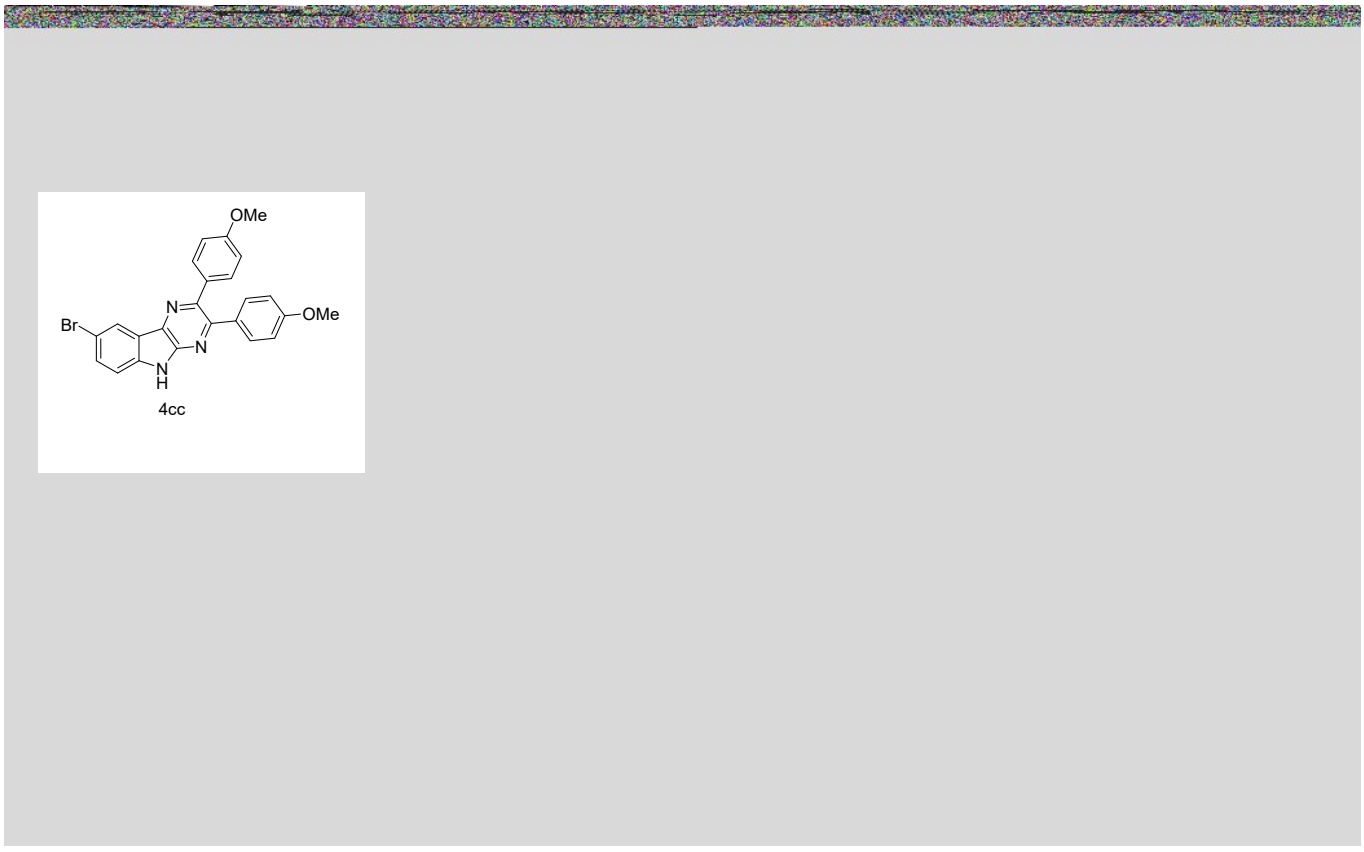
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 4bc



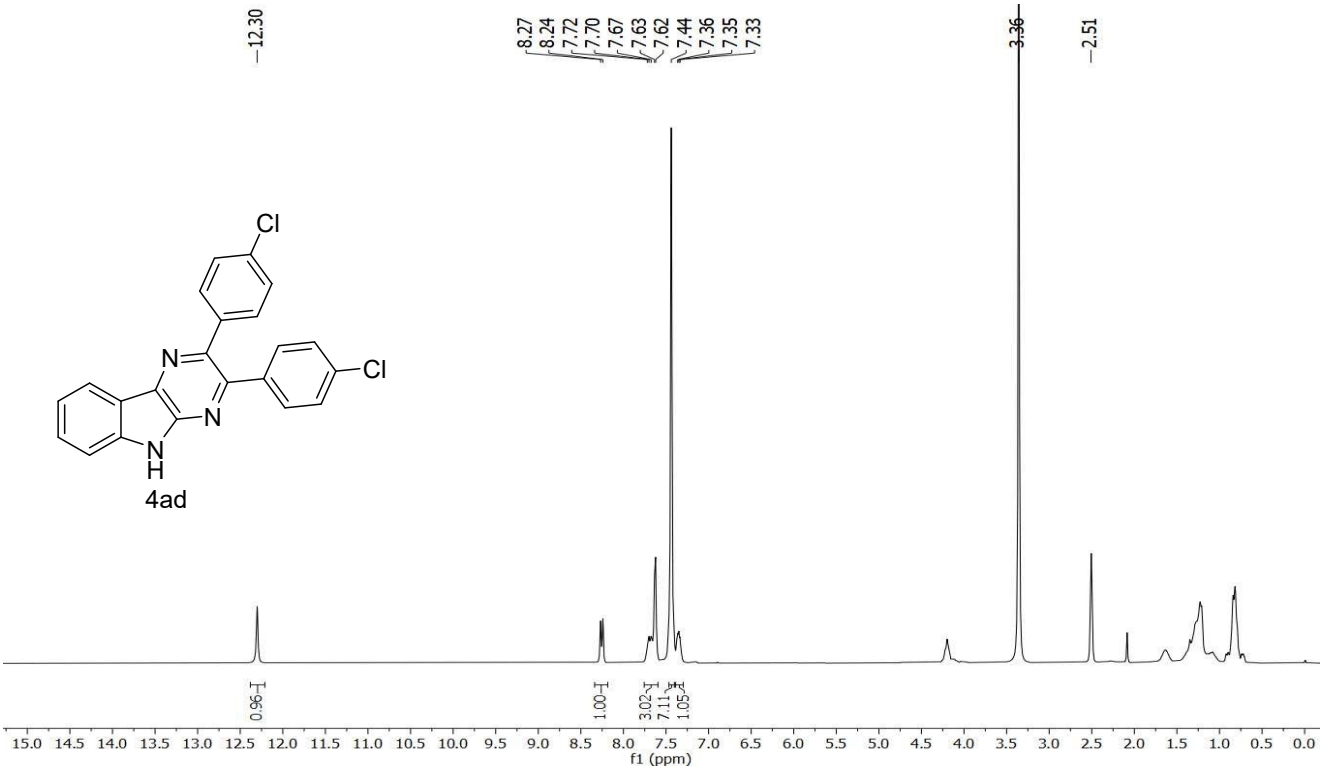
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 4bc



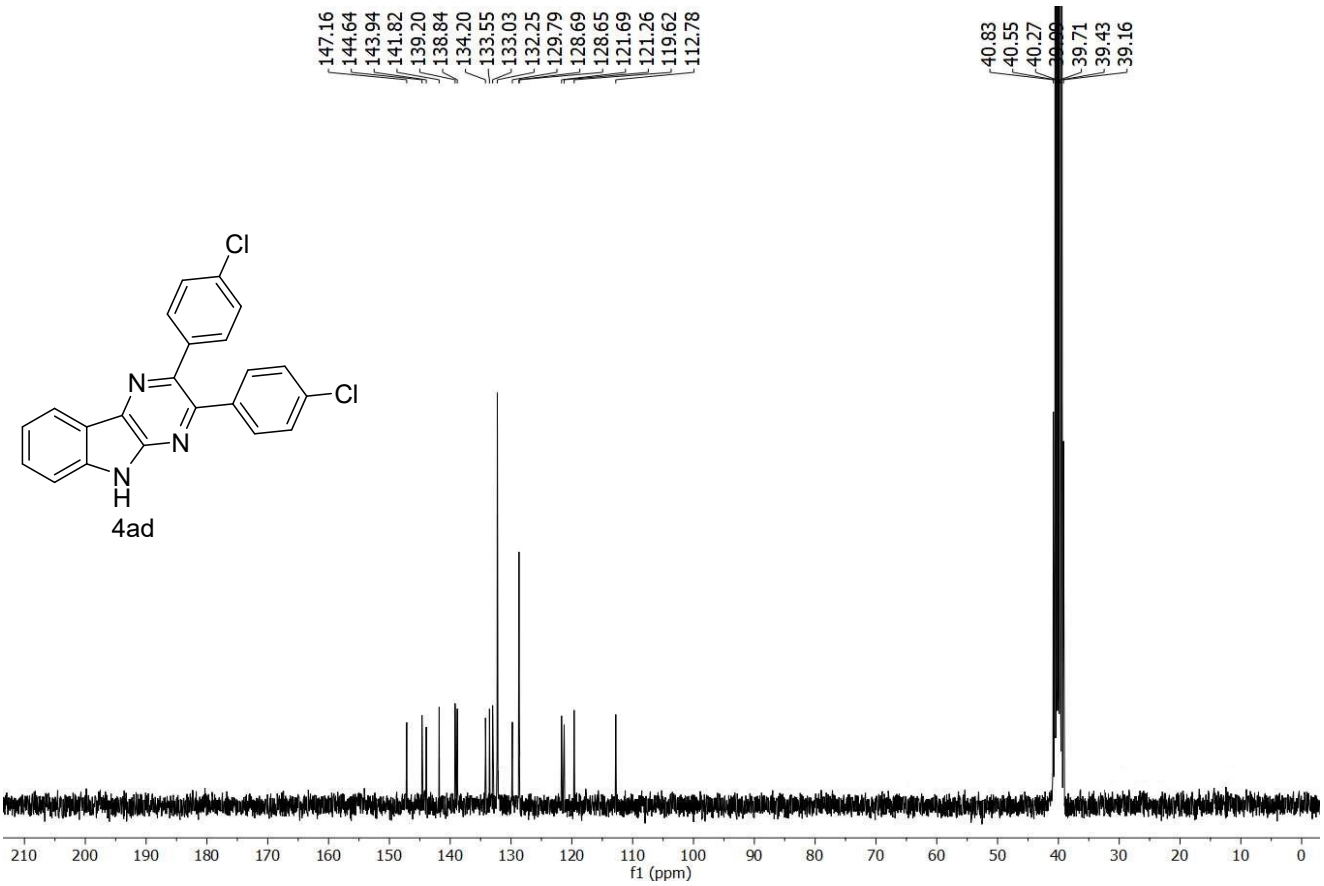
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 4cc



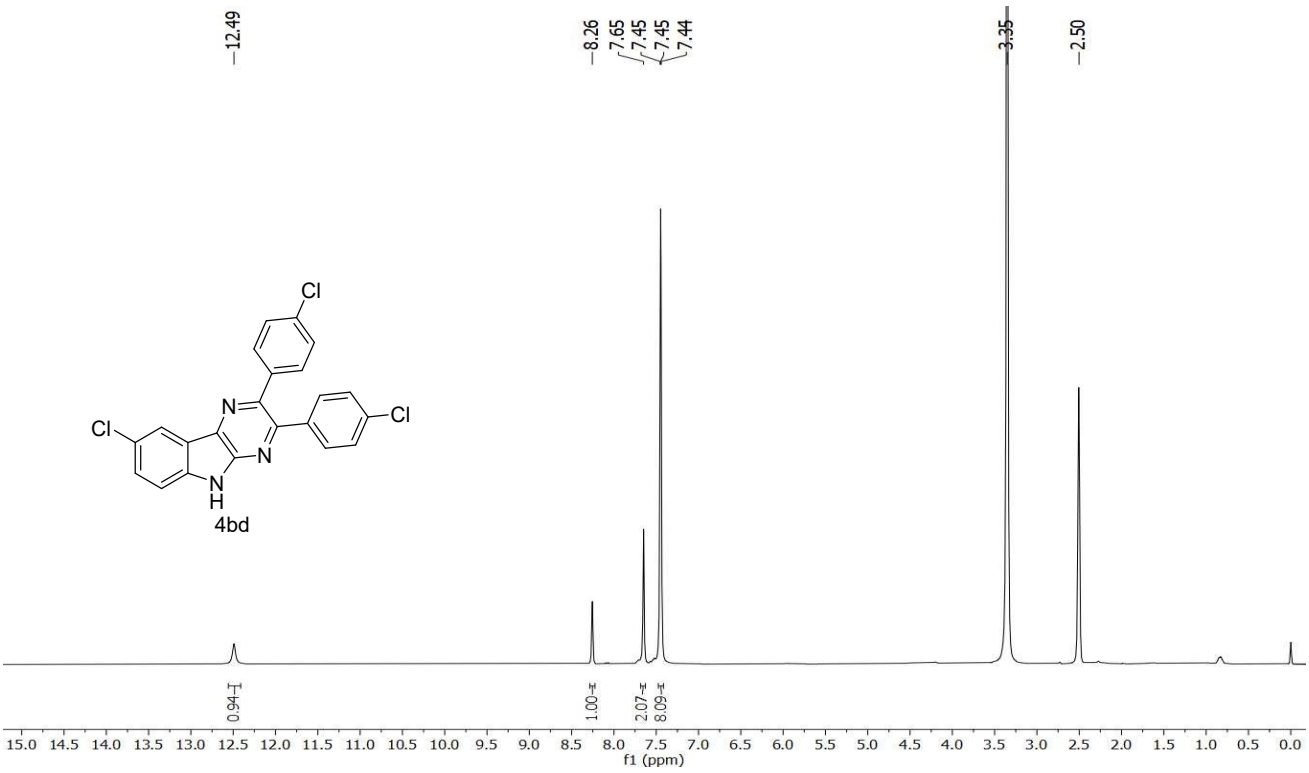
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 4cc



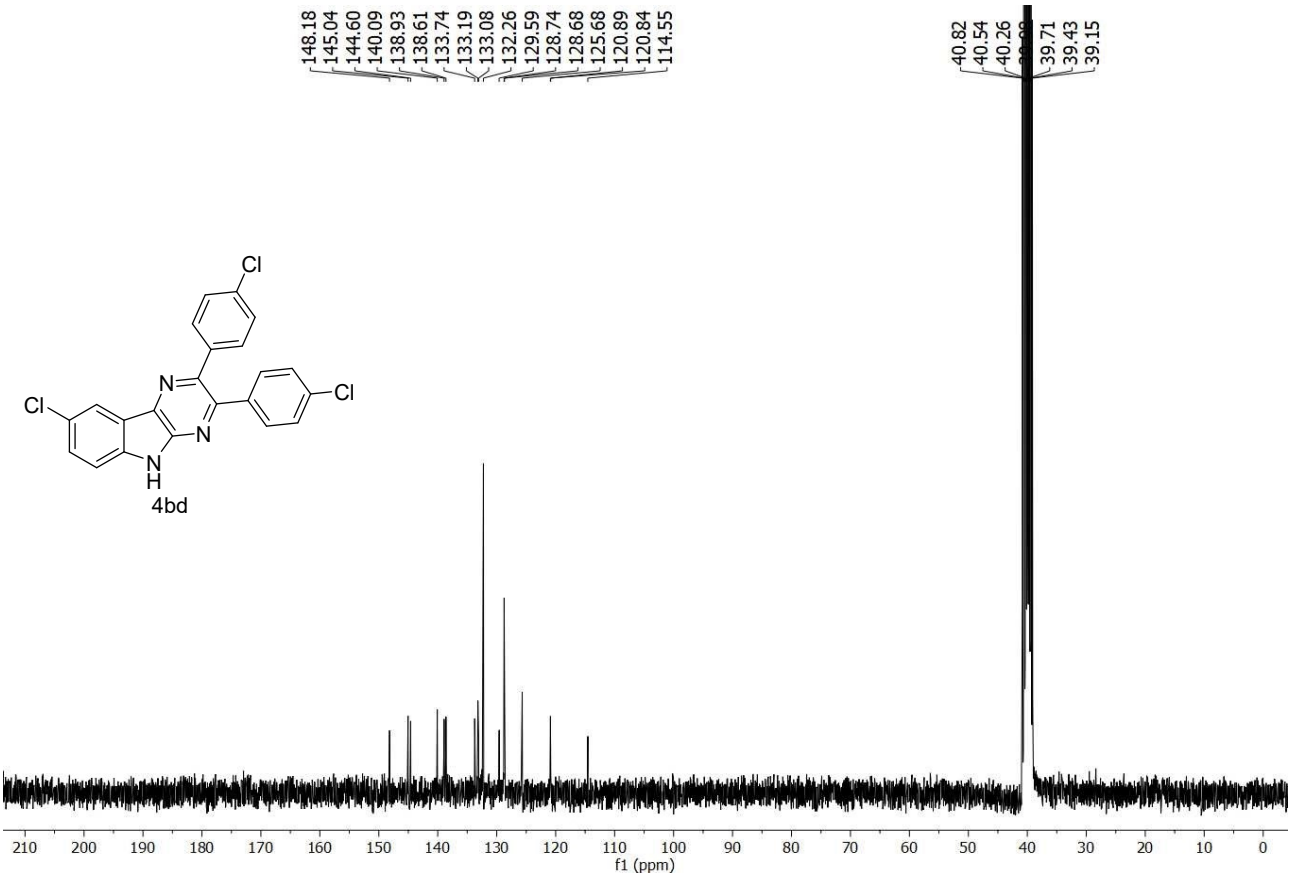
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound 4ad



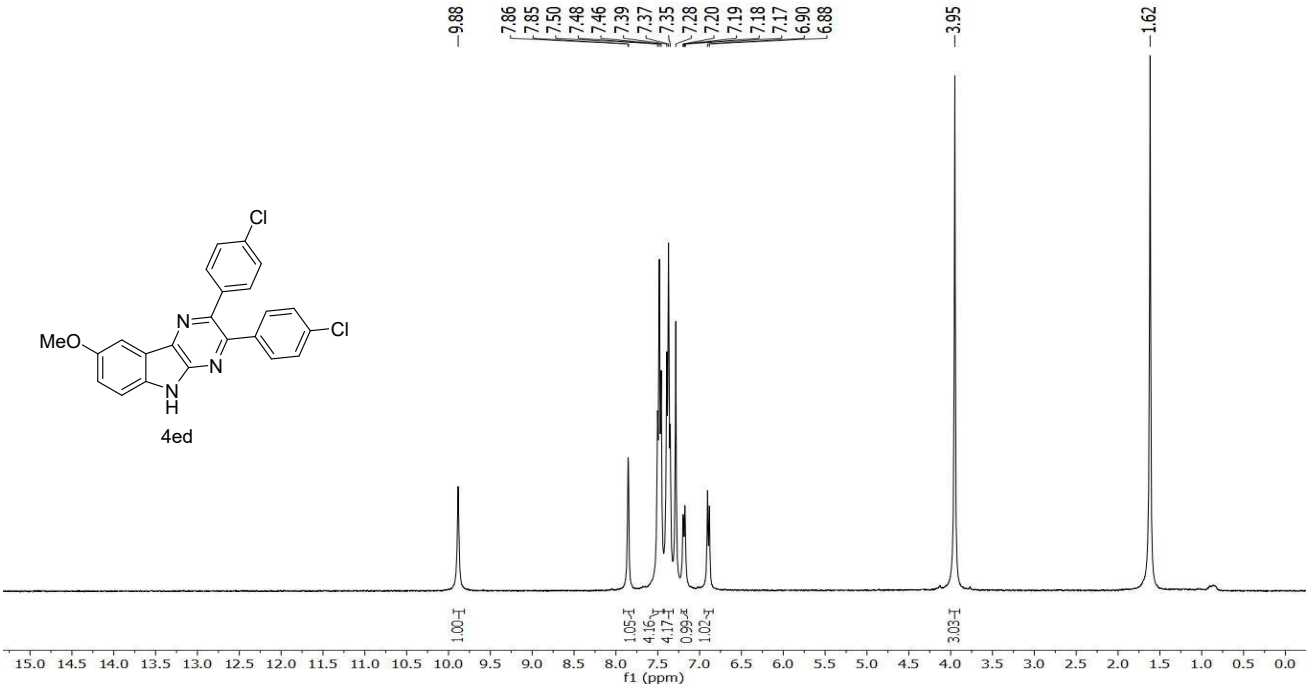
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound 4ad



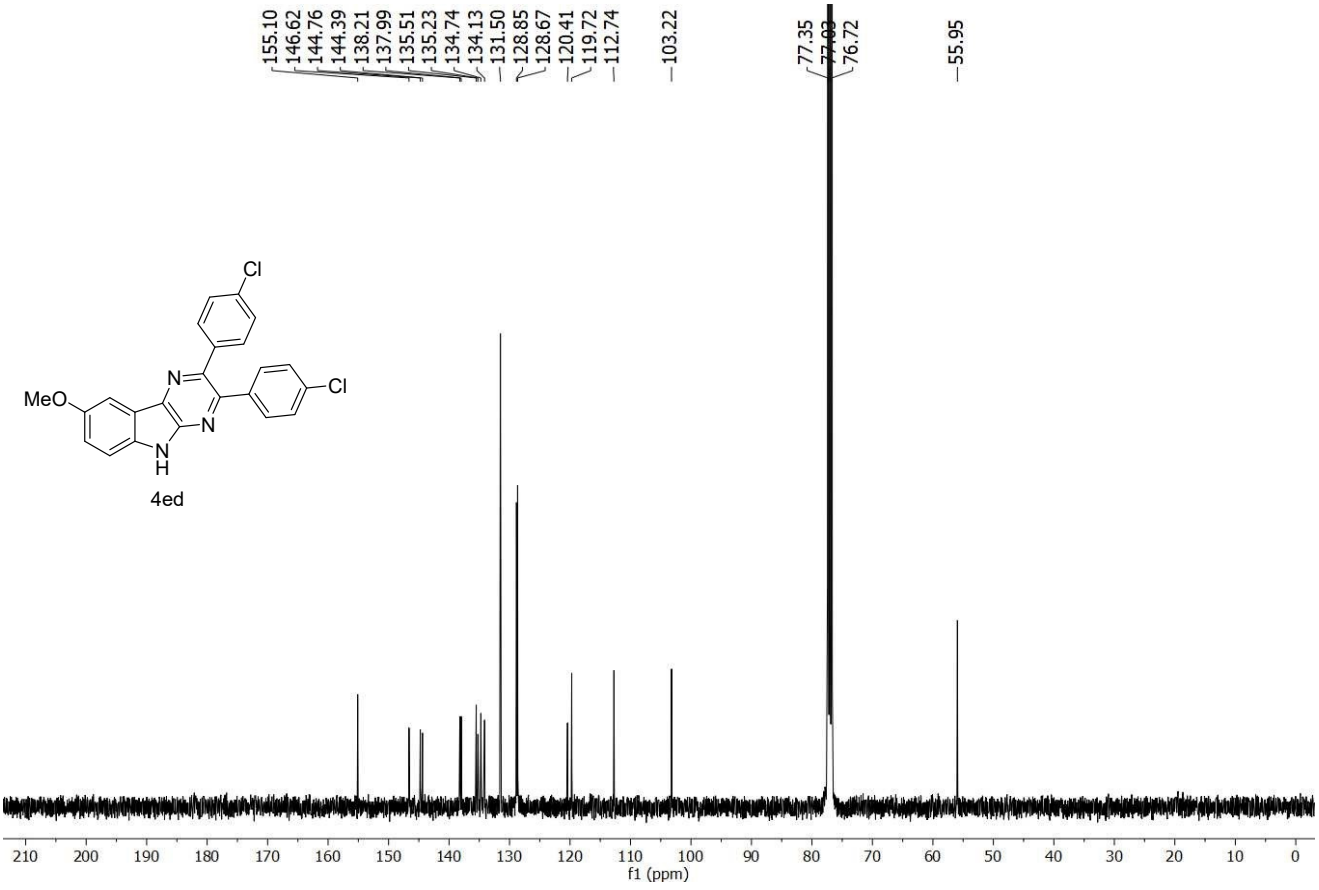
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound 4bd



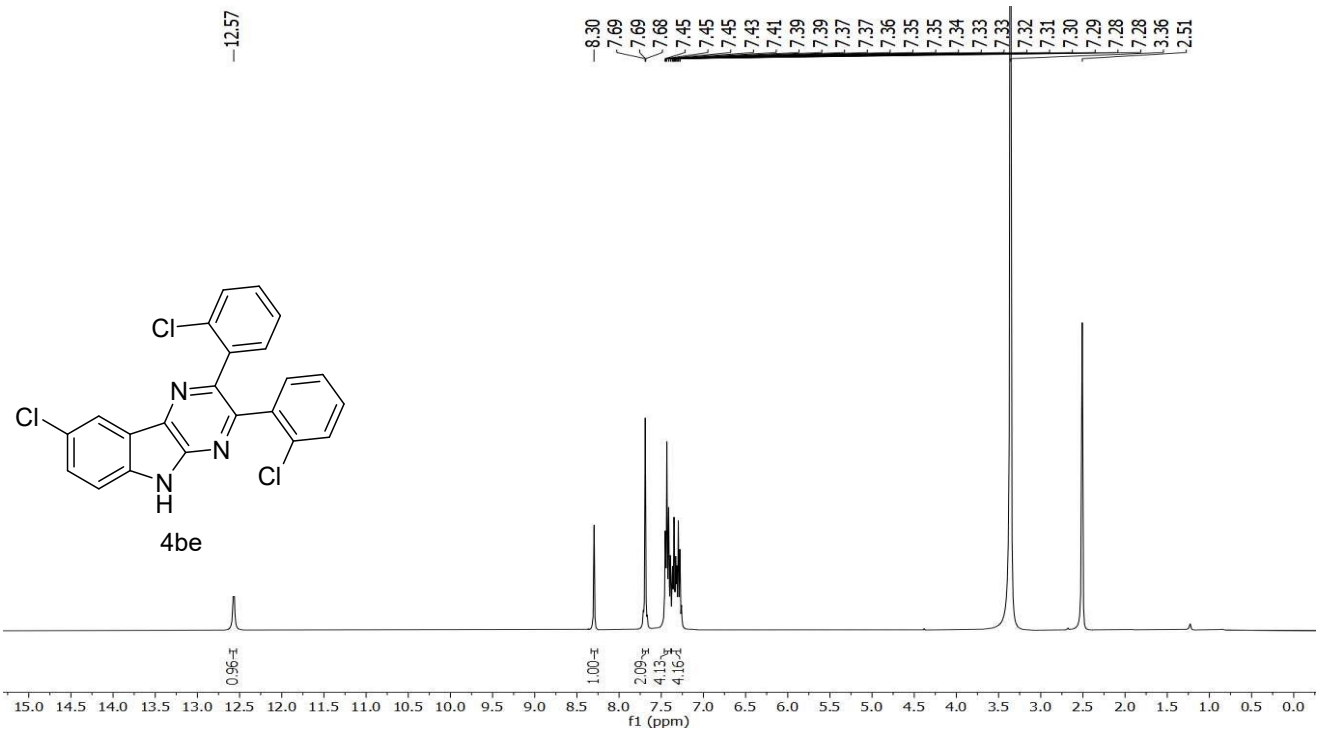
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound 4bd



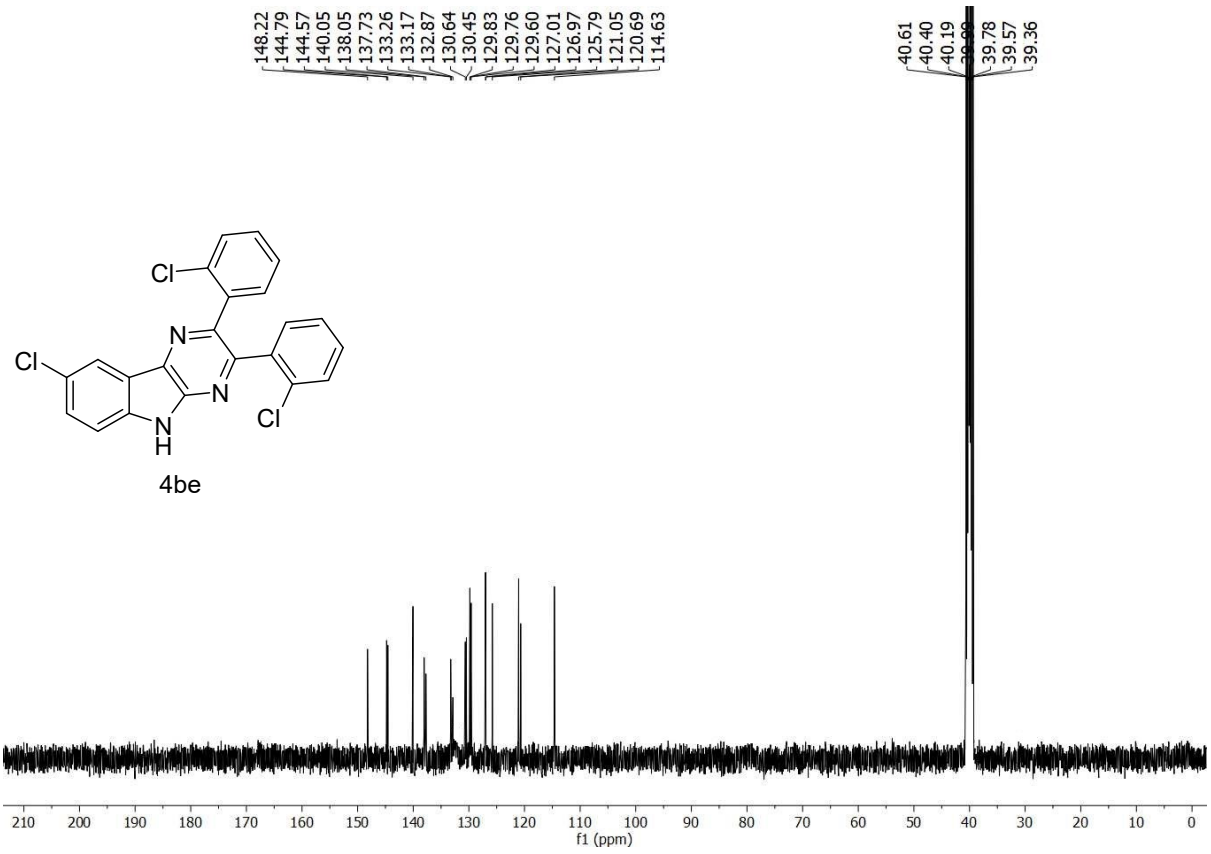
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 4ed



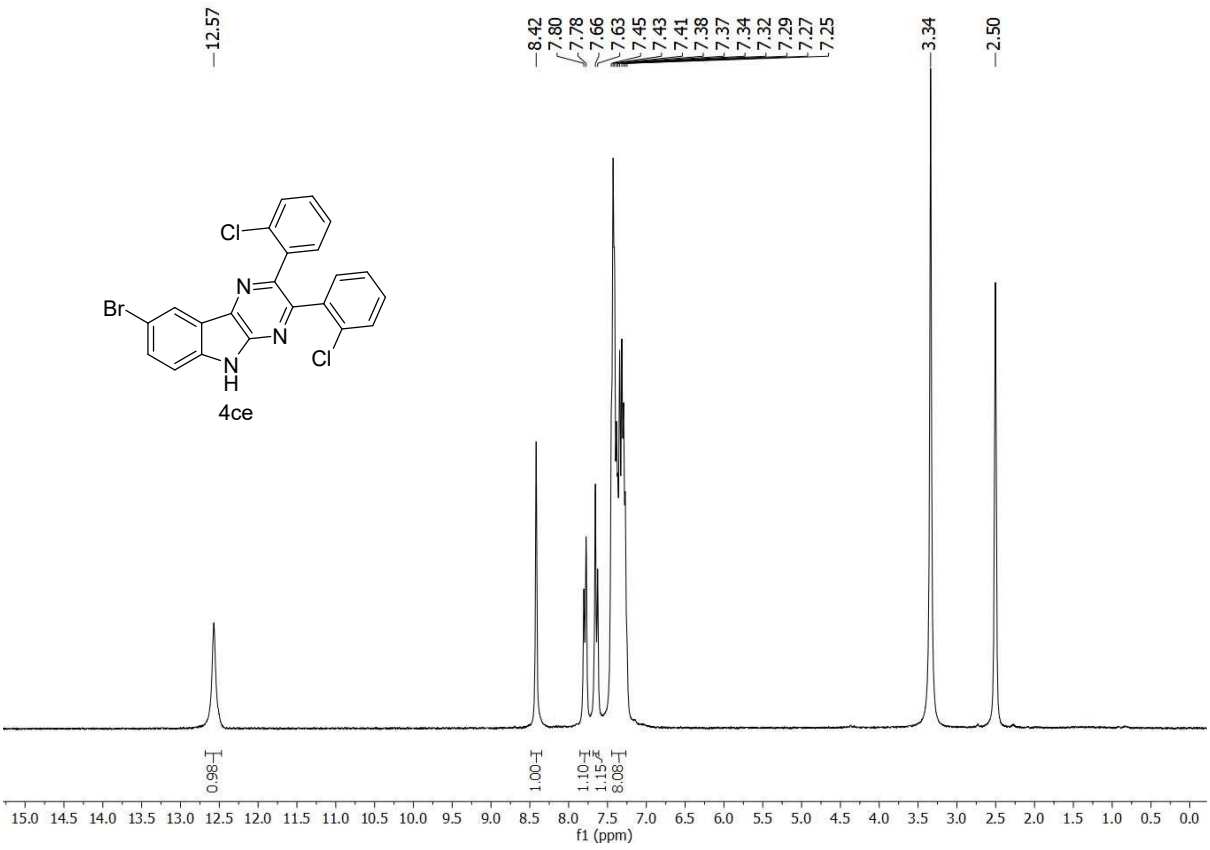
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 4ed



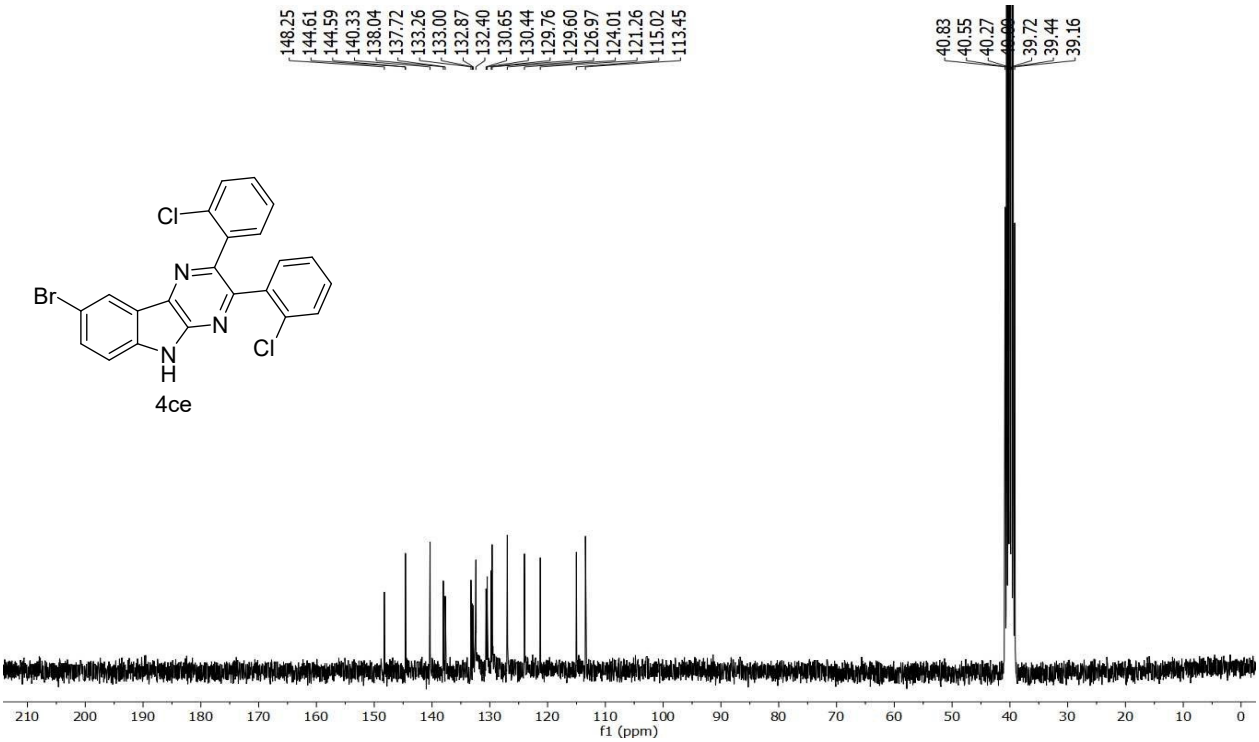
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4be



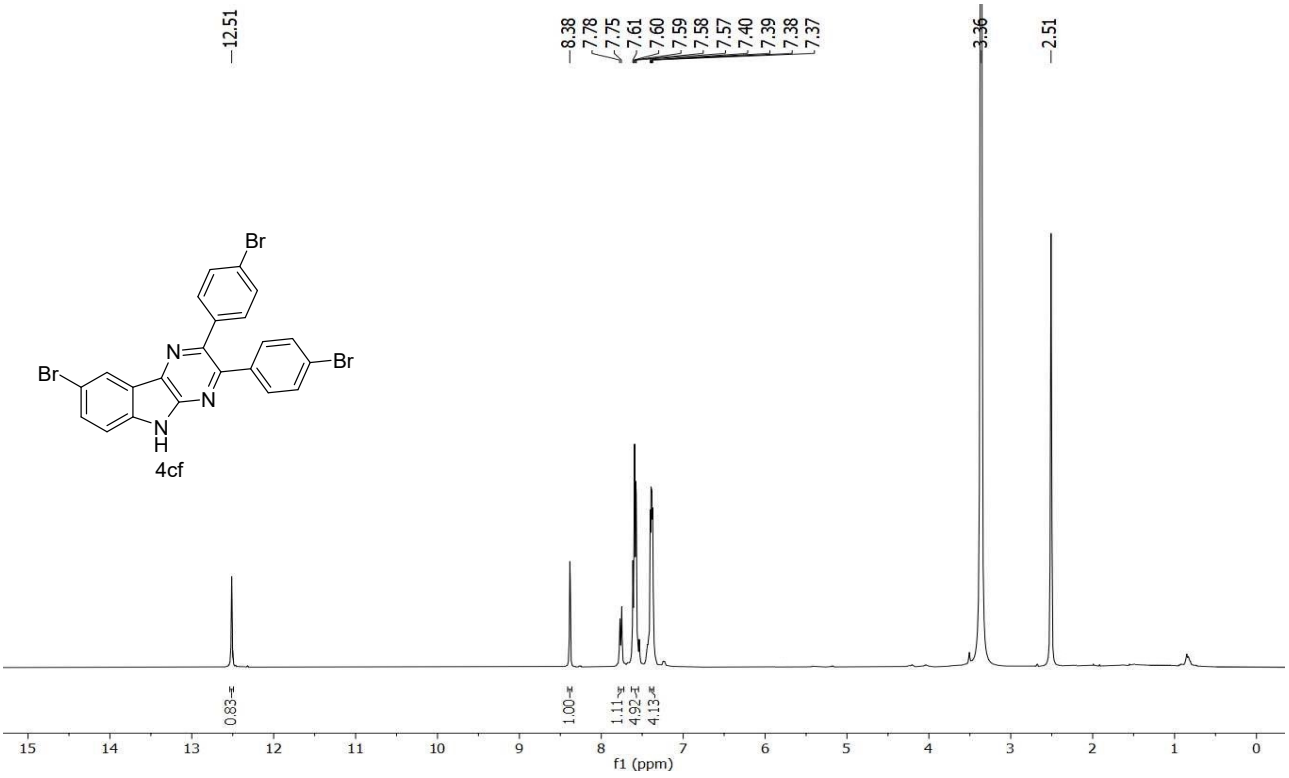
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4be



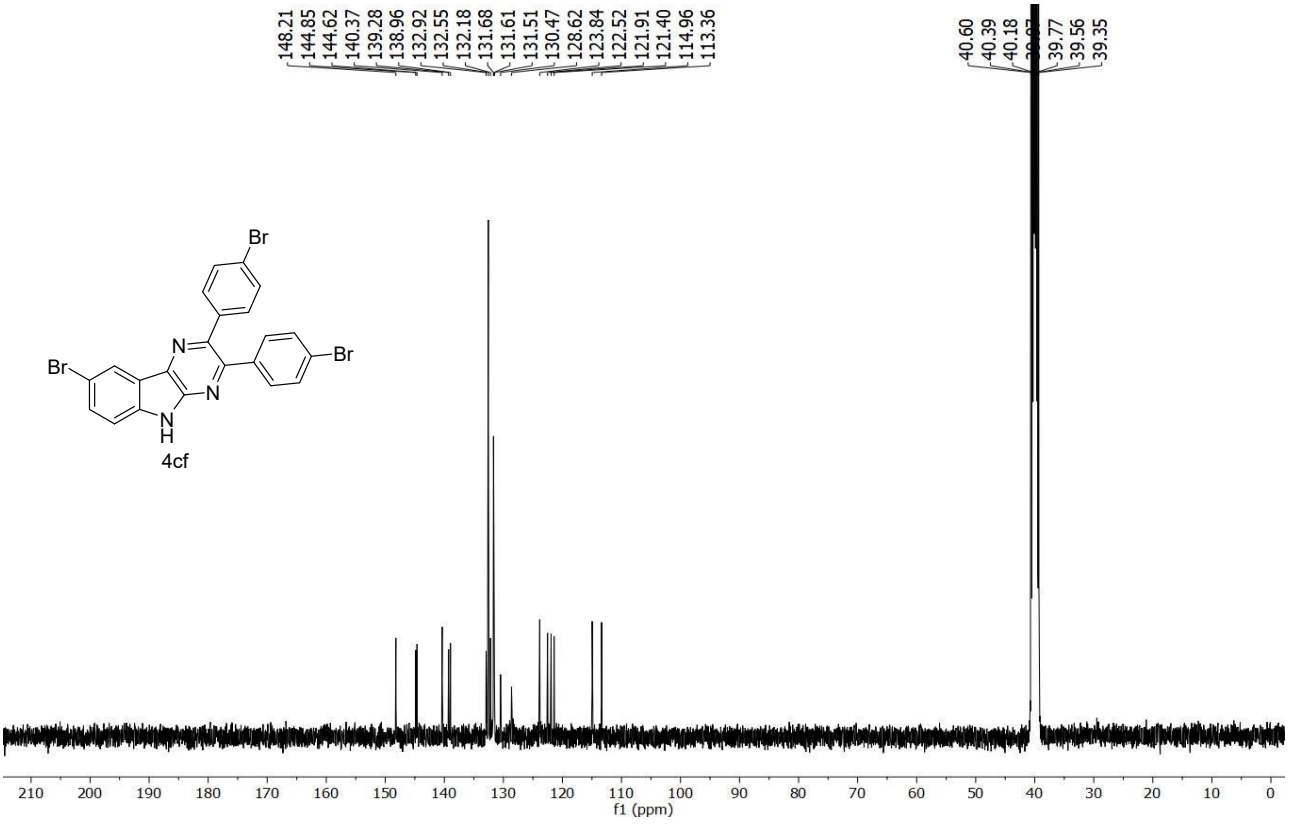
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4ce



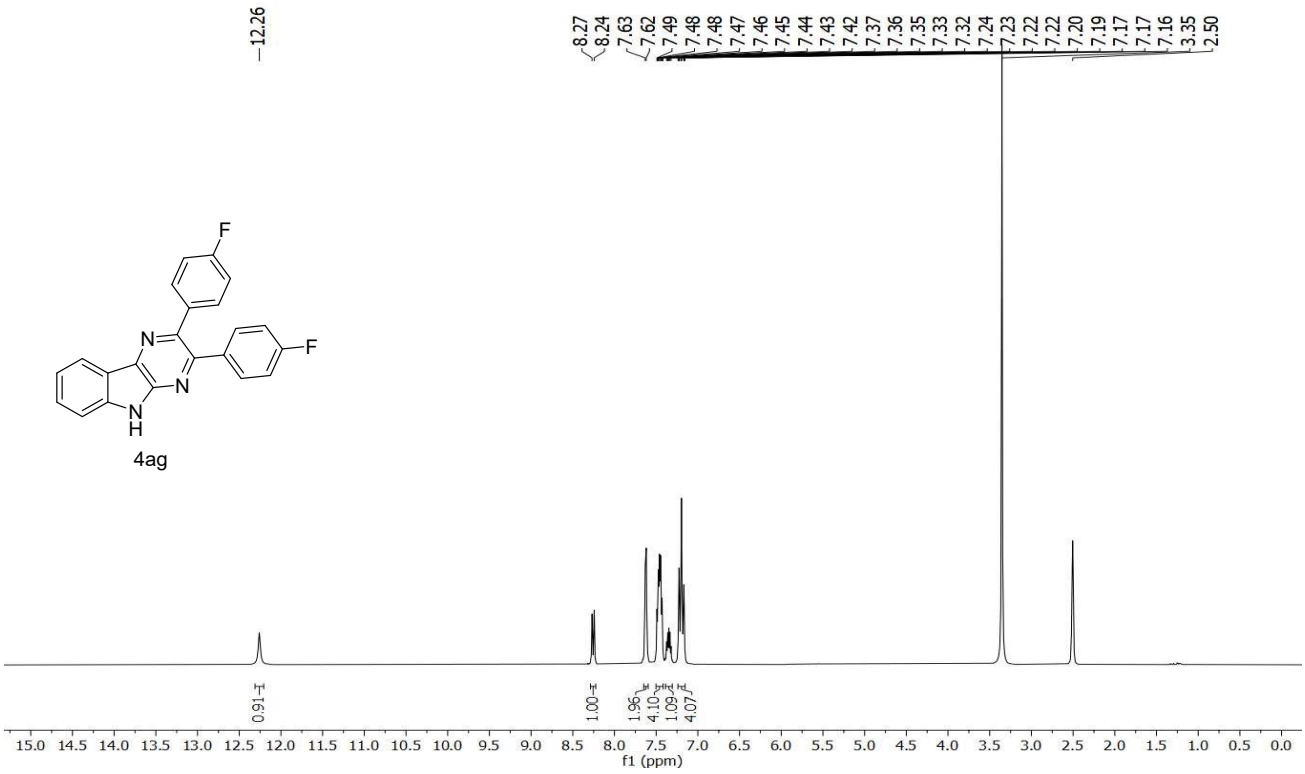
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4ce



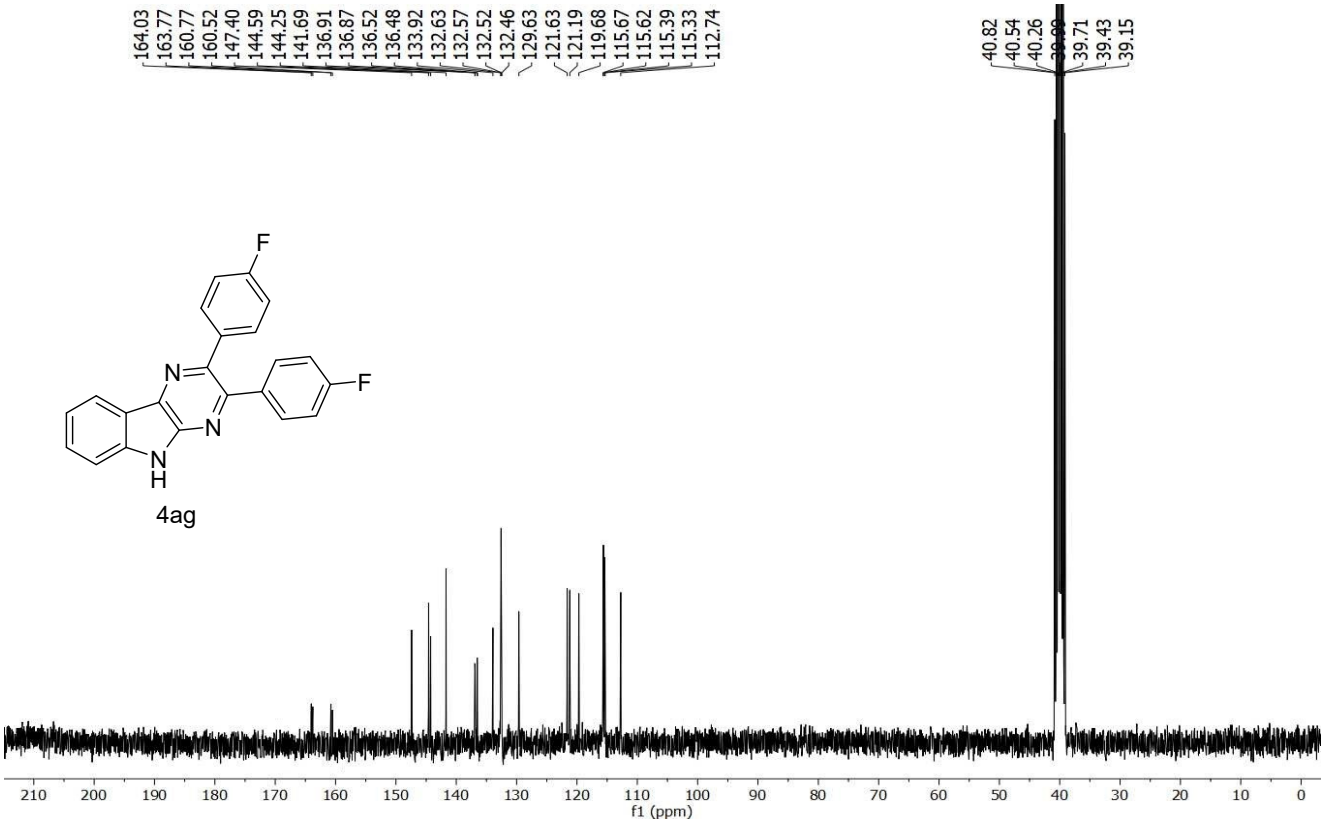
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4cf



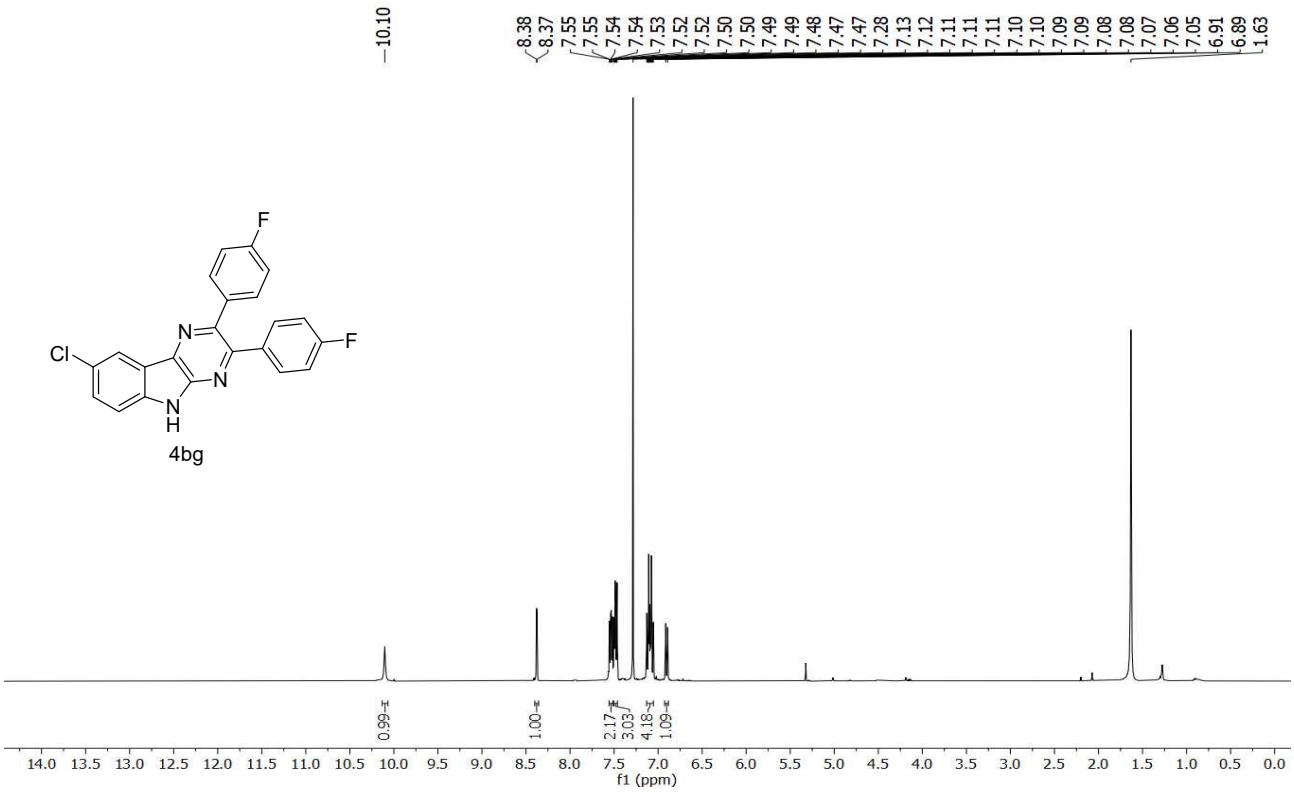
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound 4cf



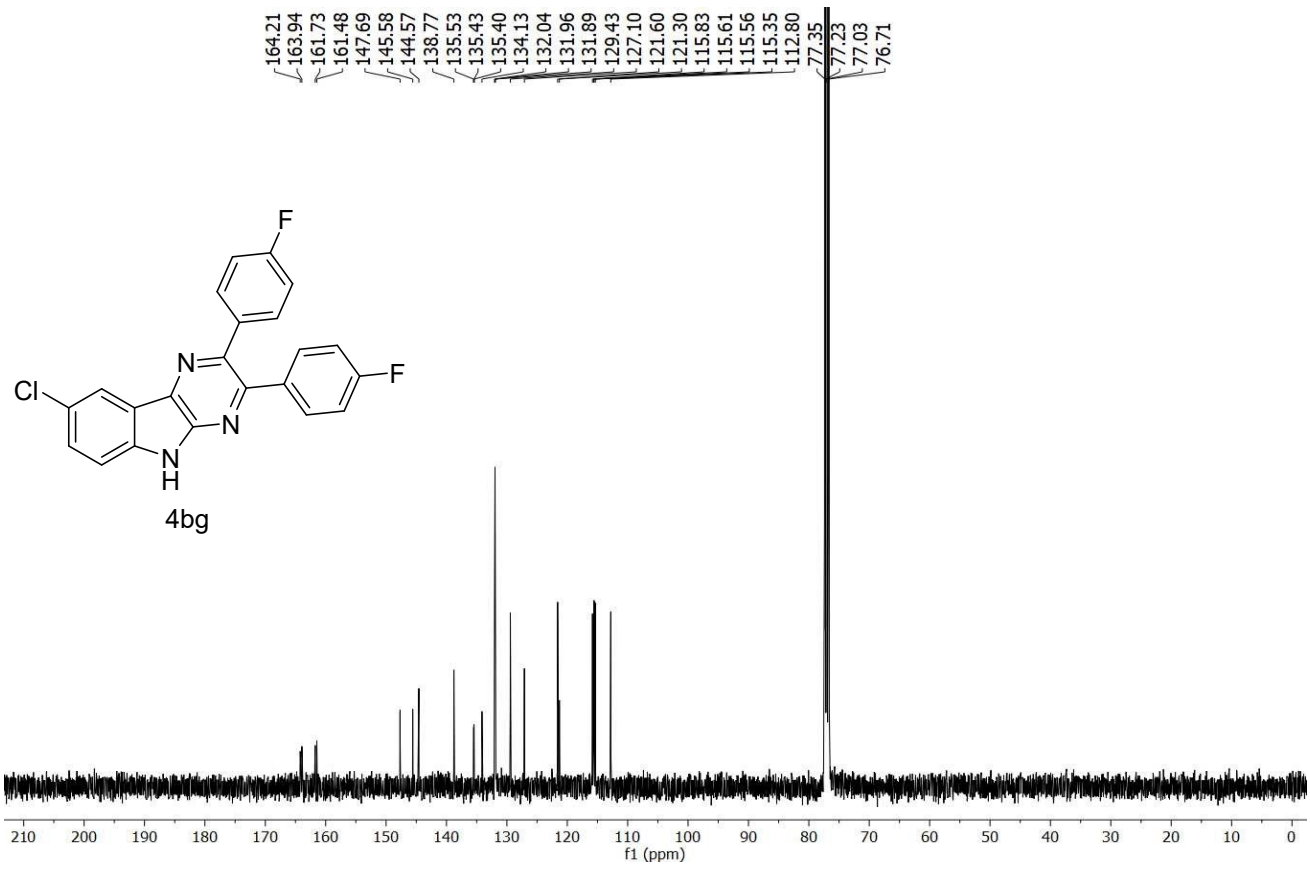
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound 4ag



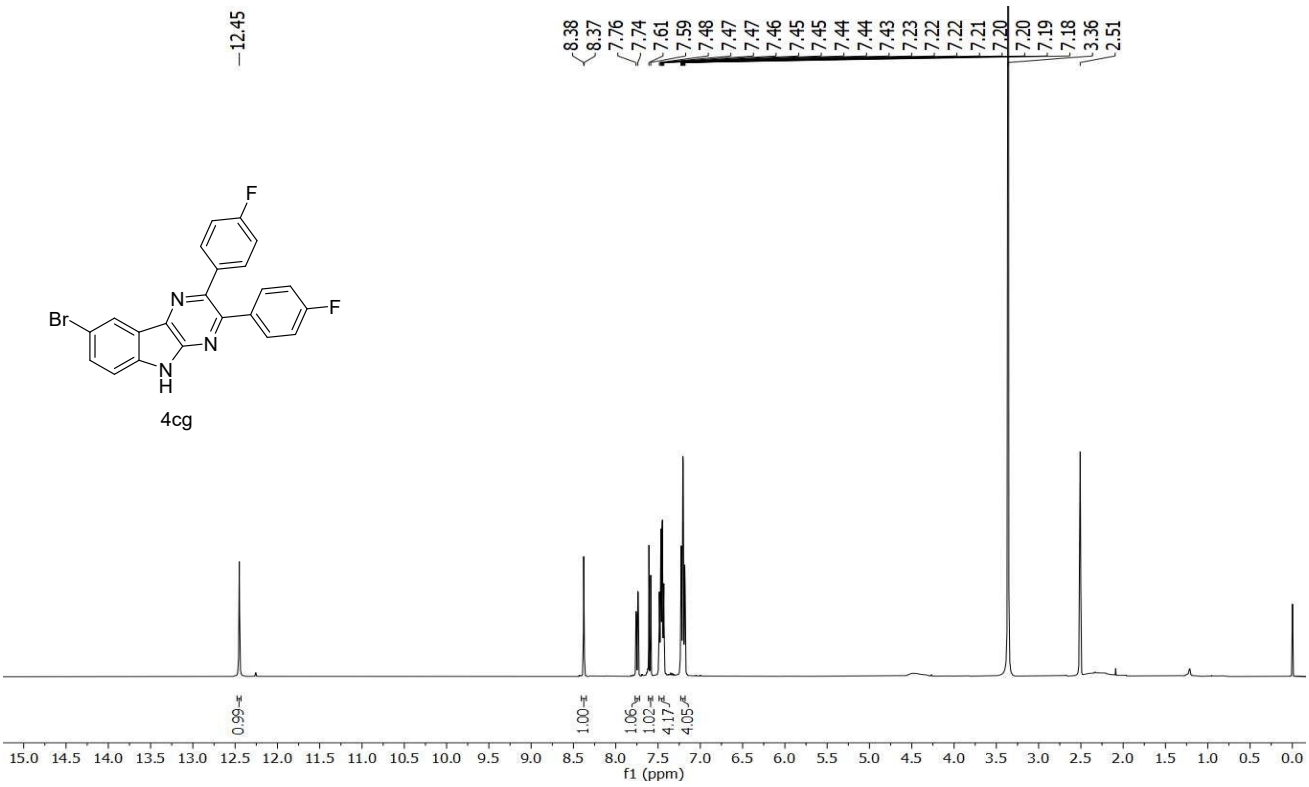
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound 4ag



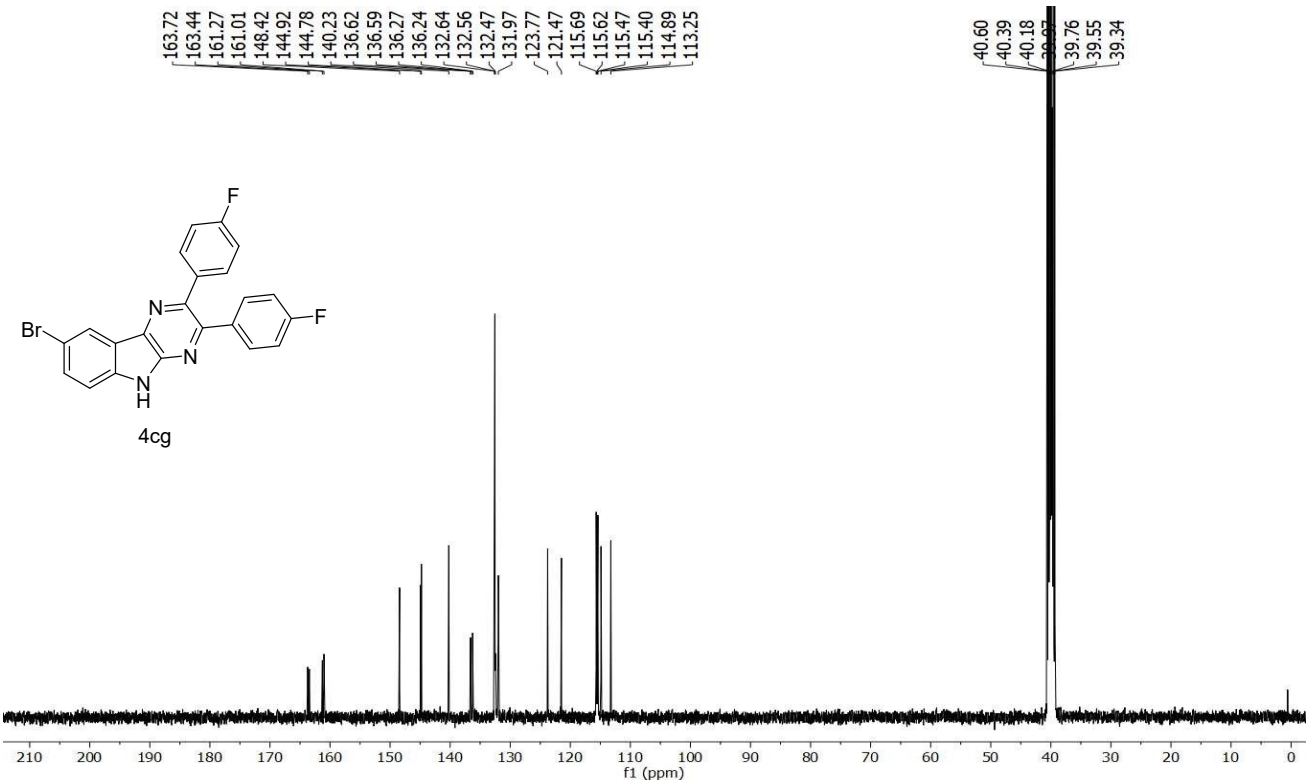
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 4bg



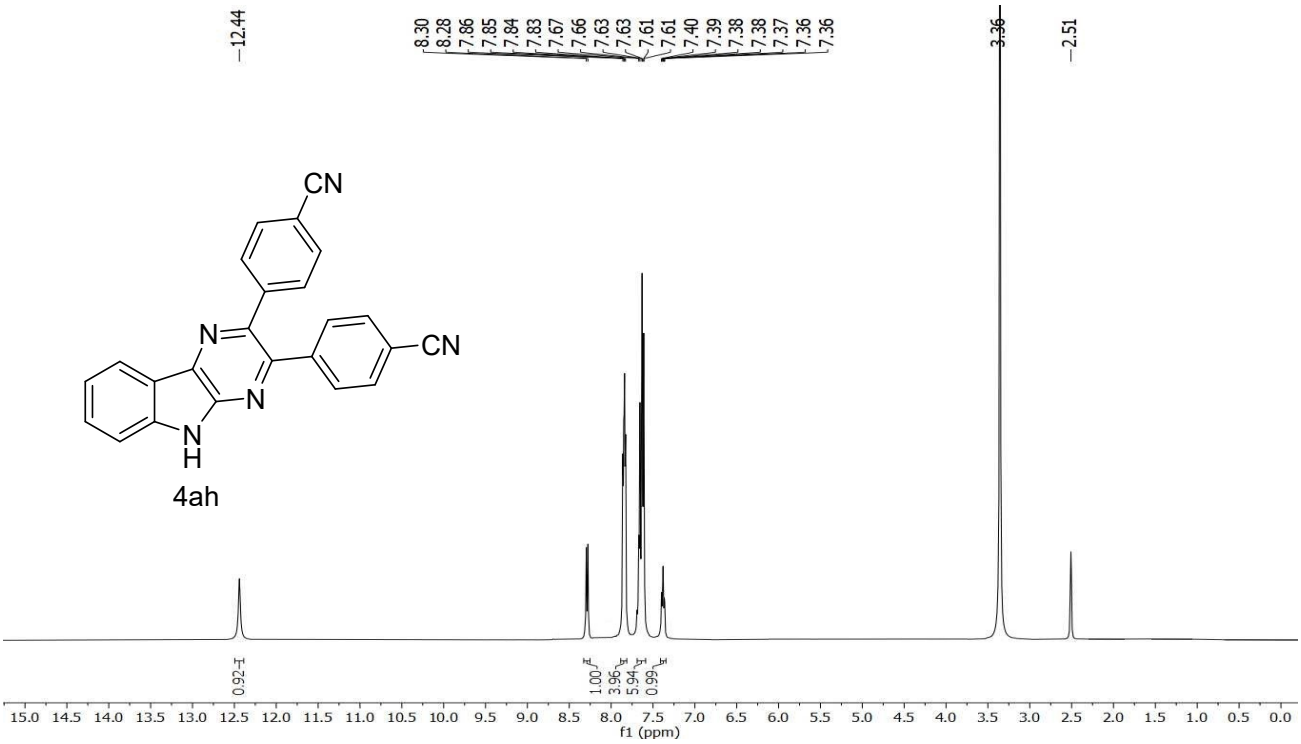
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 4bg



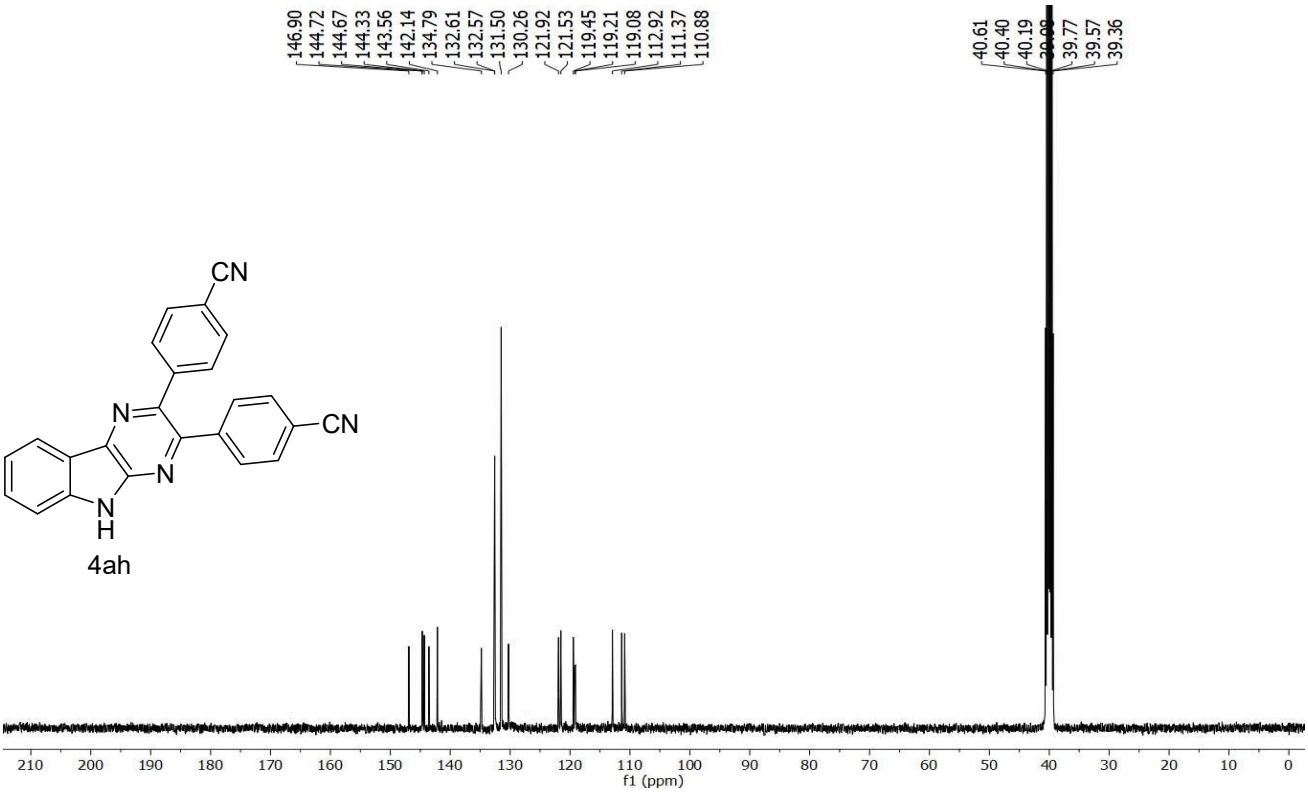
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4cg



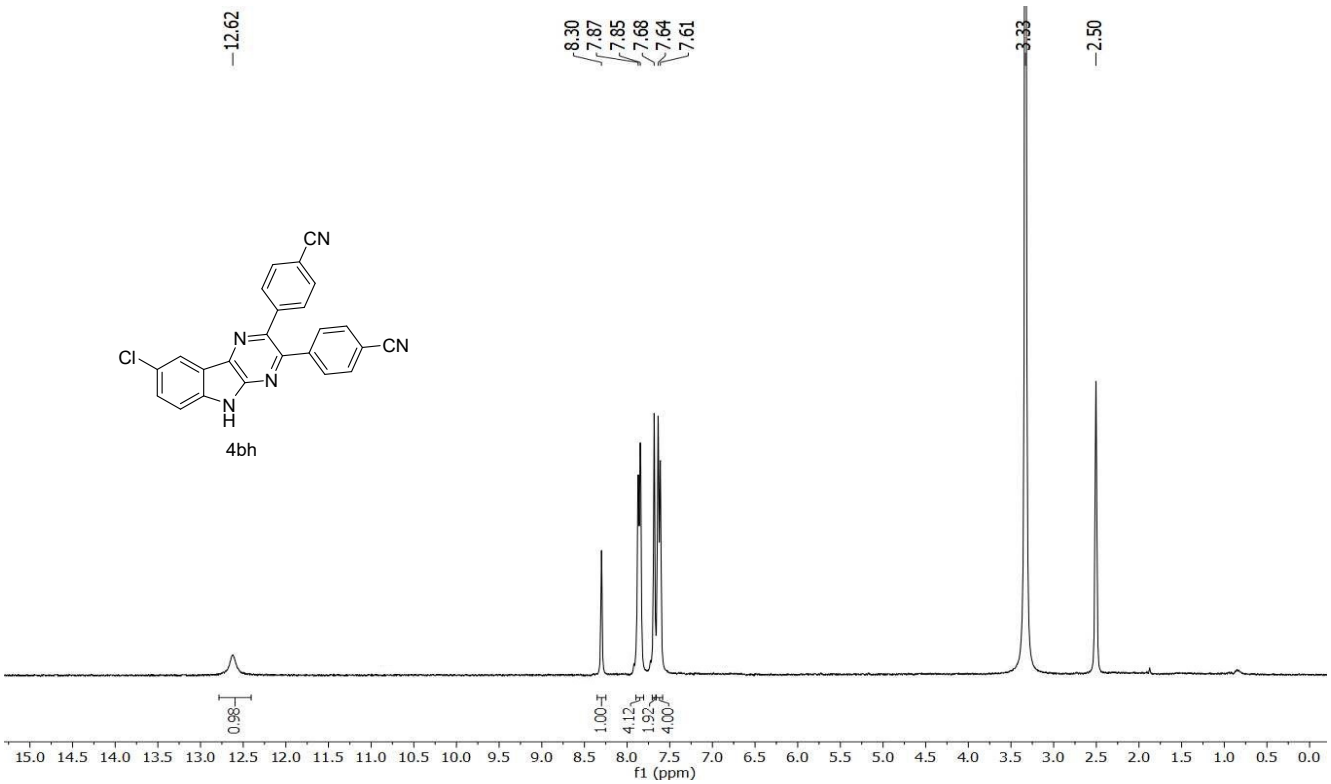
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4cg



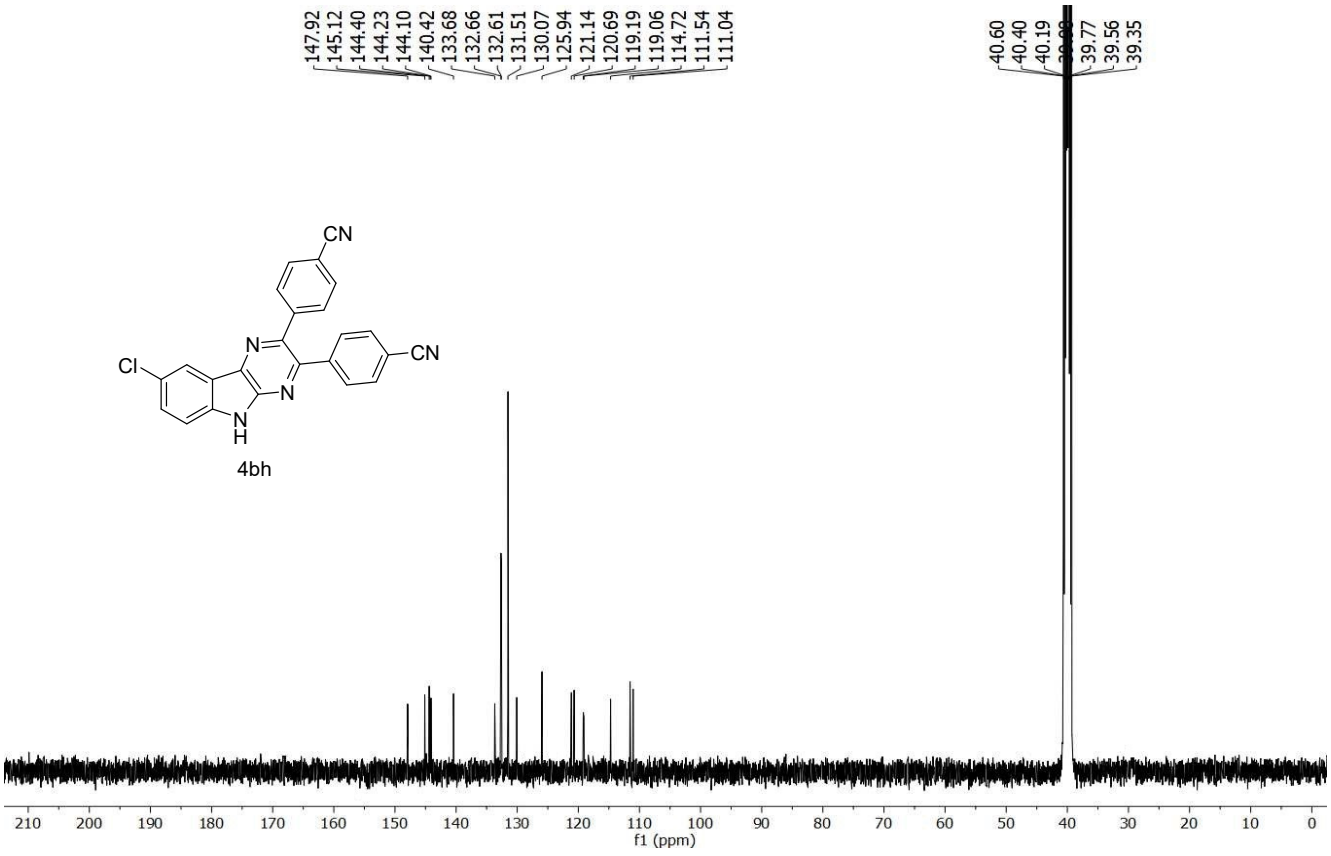
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4ah



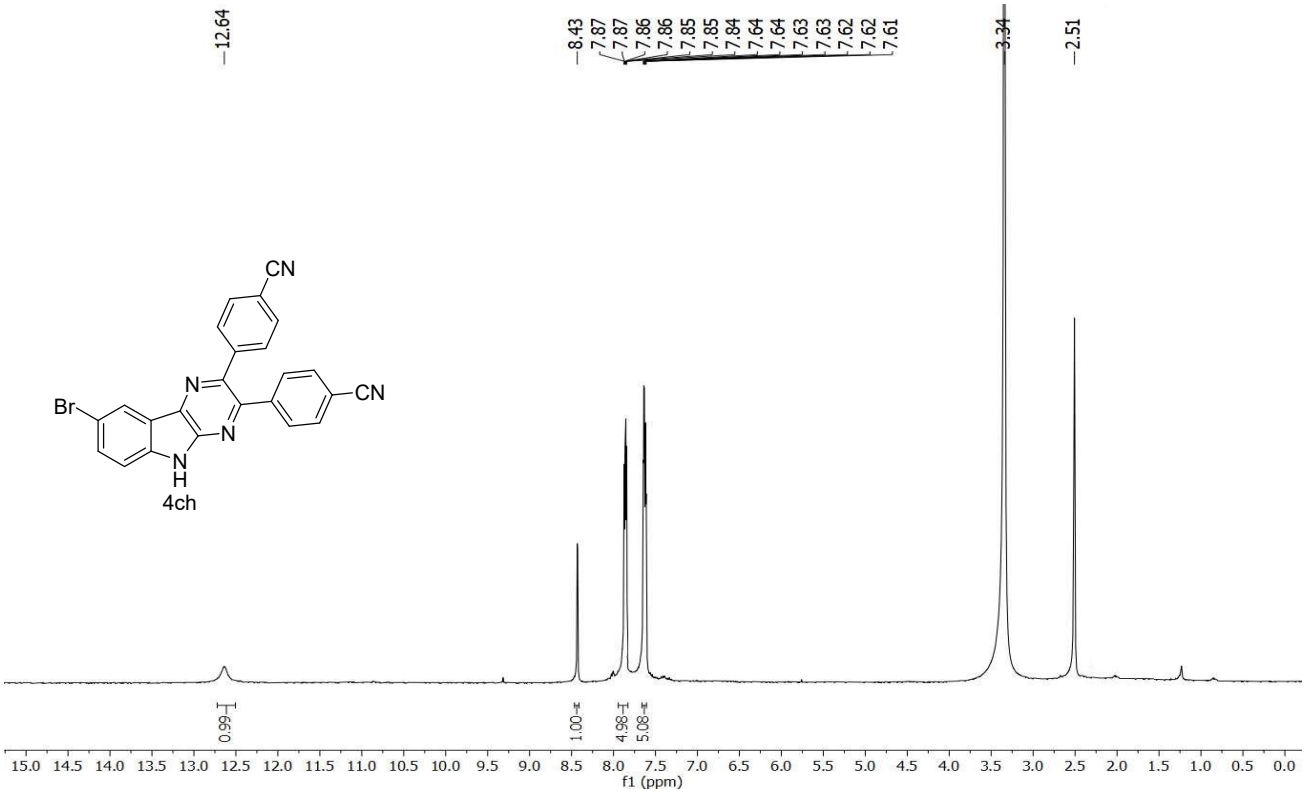
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4ah



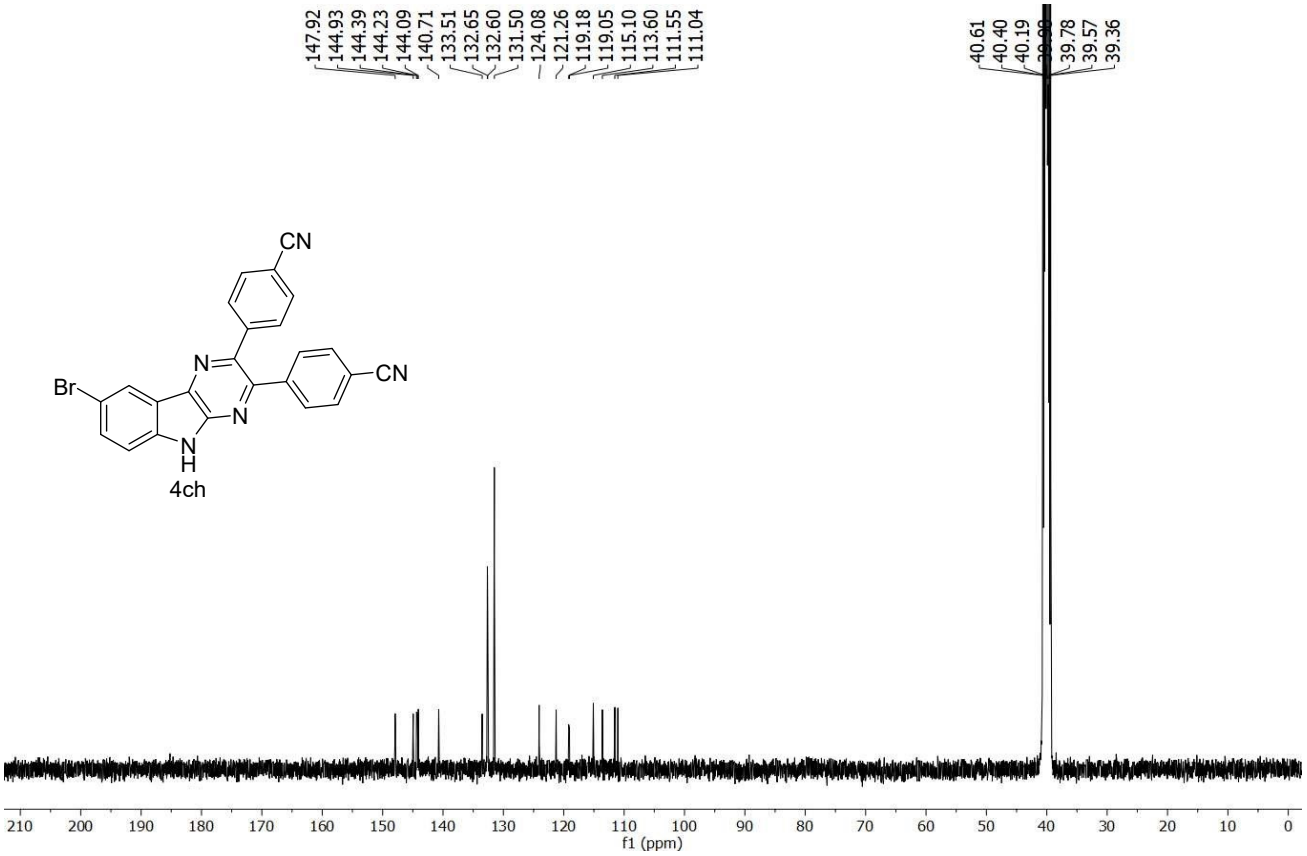
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound 4bh



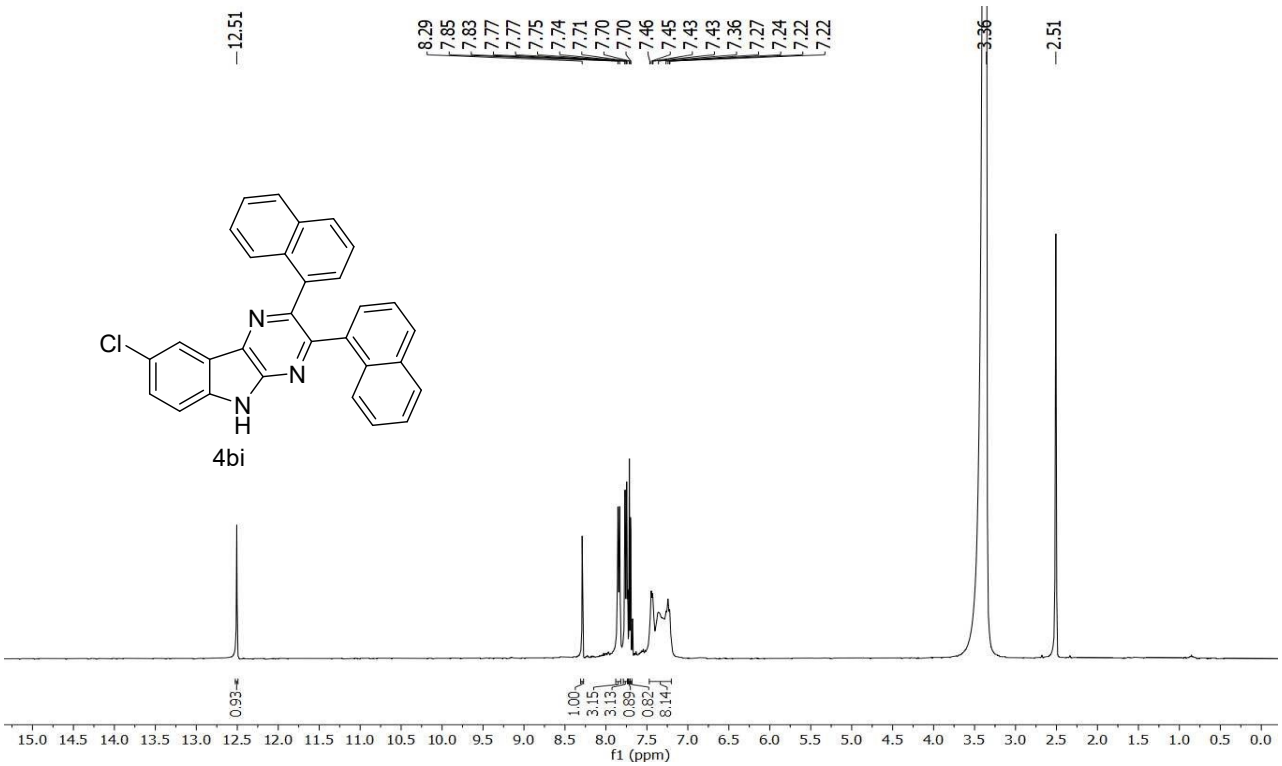
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound 4bh



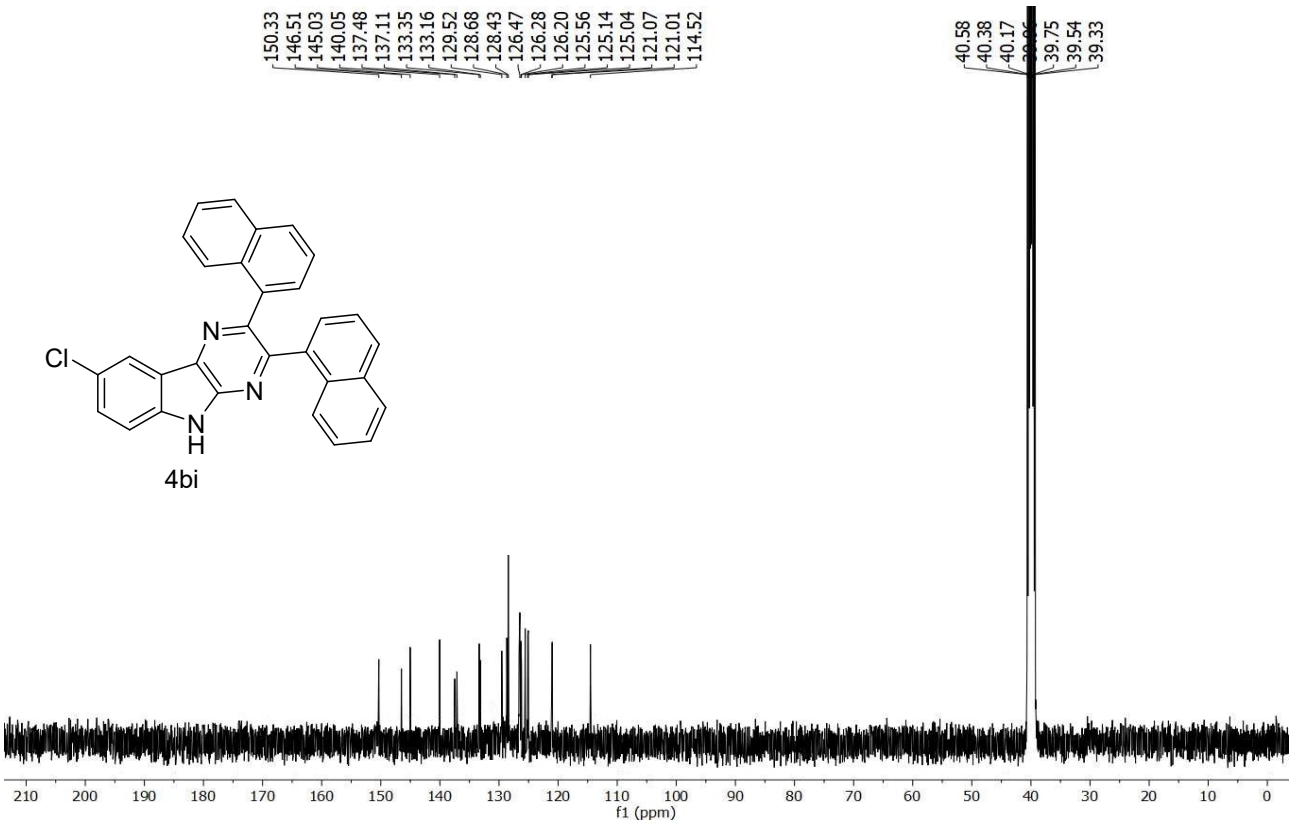
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4ch



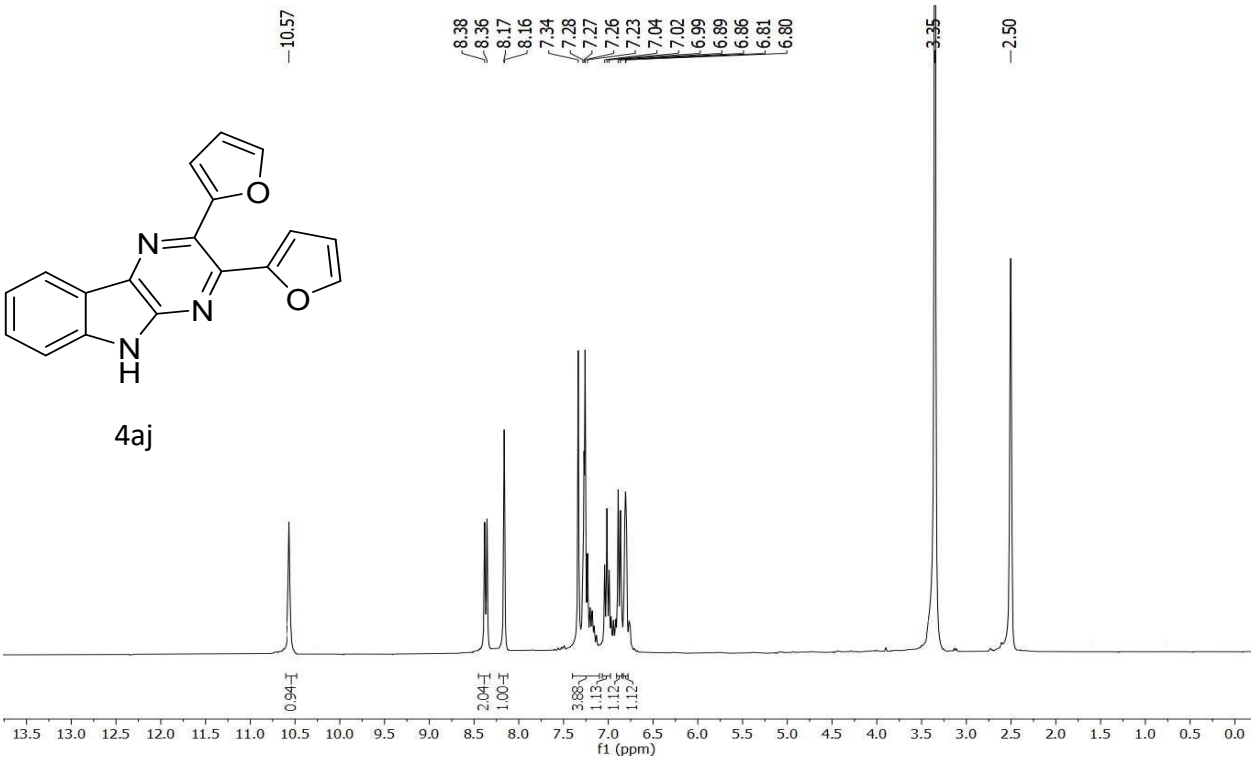
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4ch



^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4bi

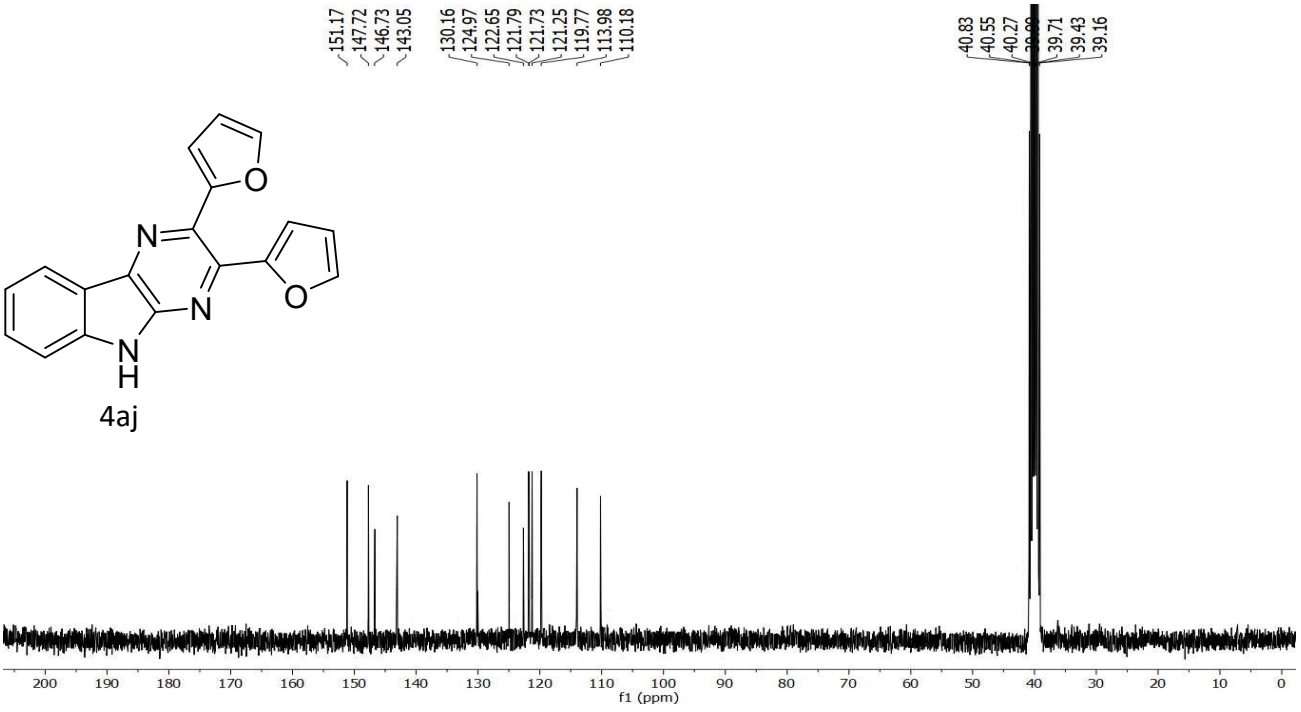


^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4bi



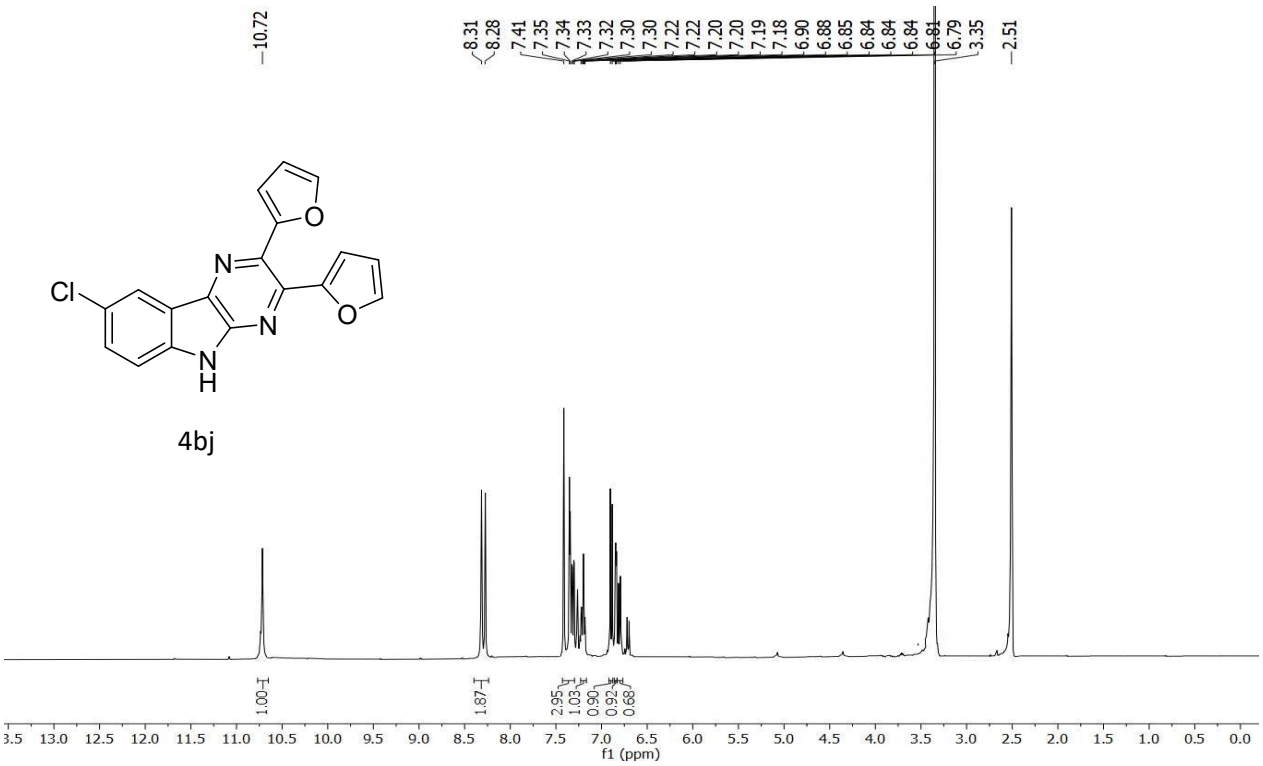
4aj

^{1}H NMR (300 MHz, DMSO-d$_6$) spectrum of compound 4aj

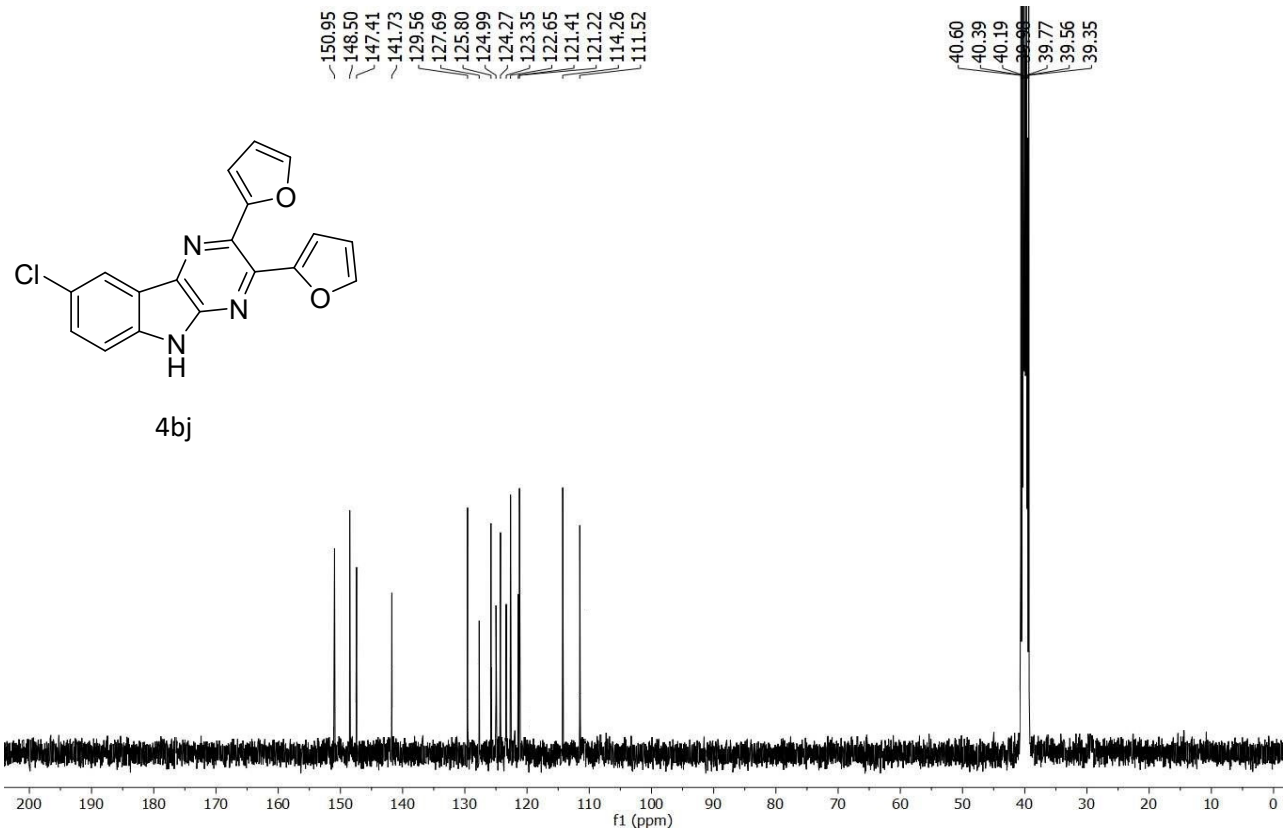


4aj

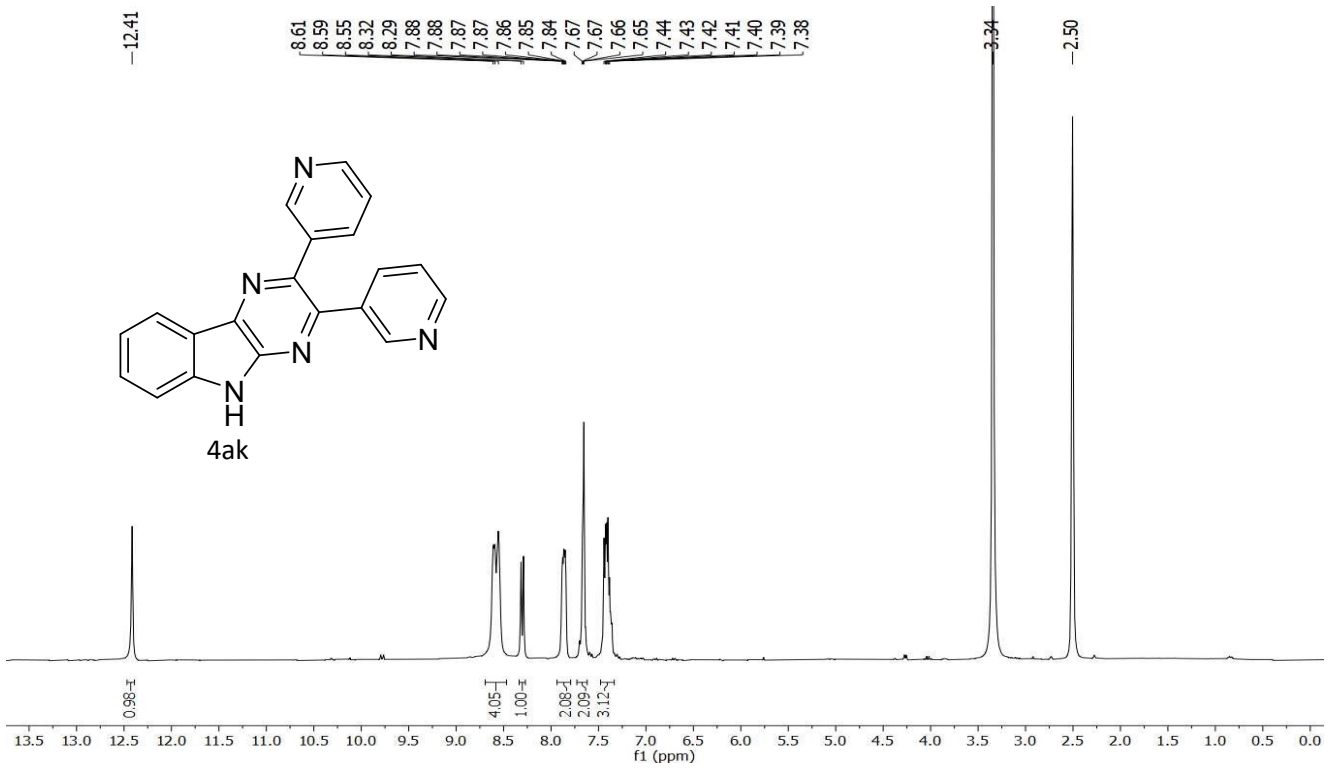
^{13}C NMR (75 MHz, DMSO-d$_6$) spectrum of compound 4aj



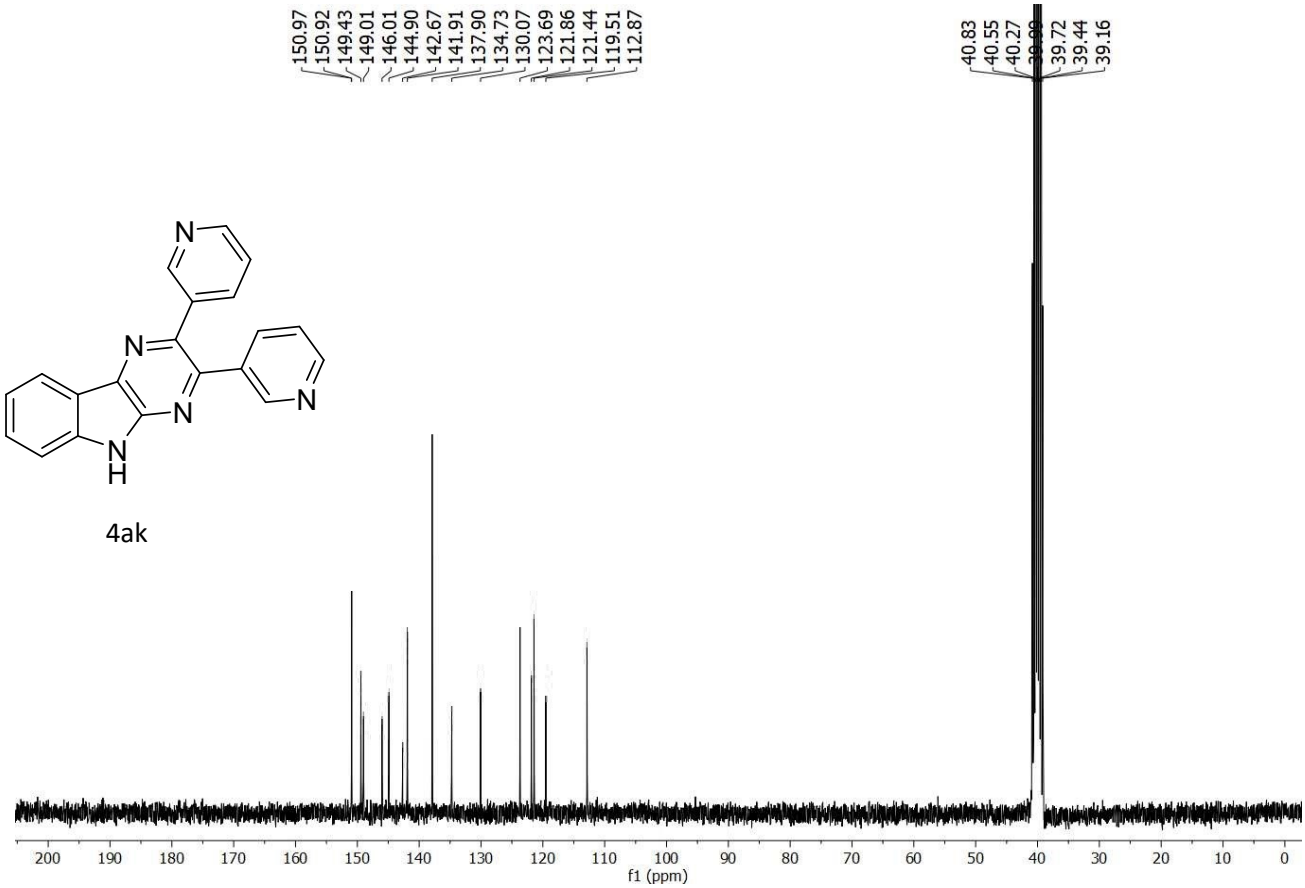
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound 4bj



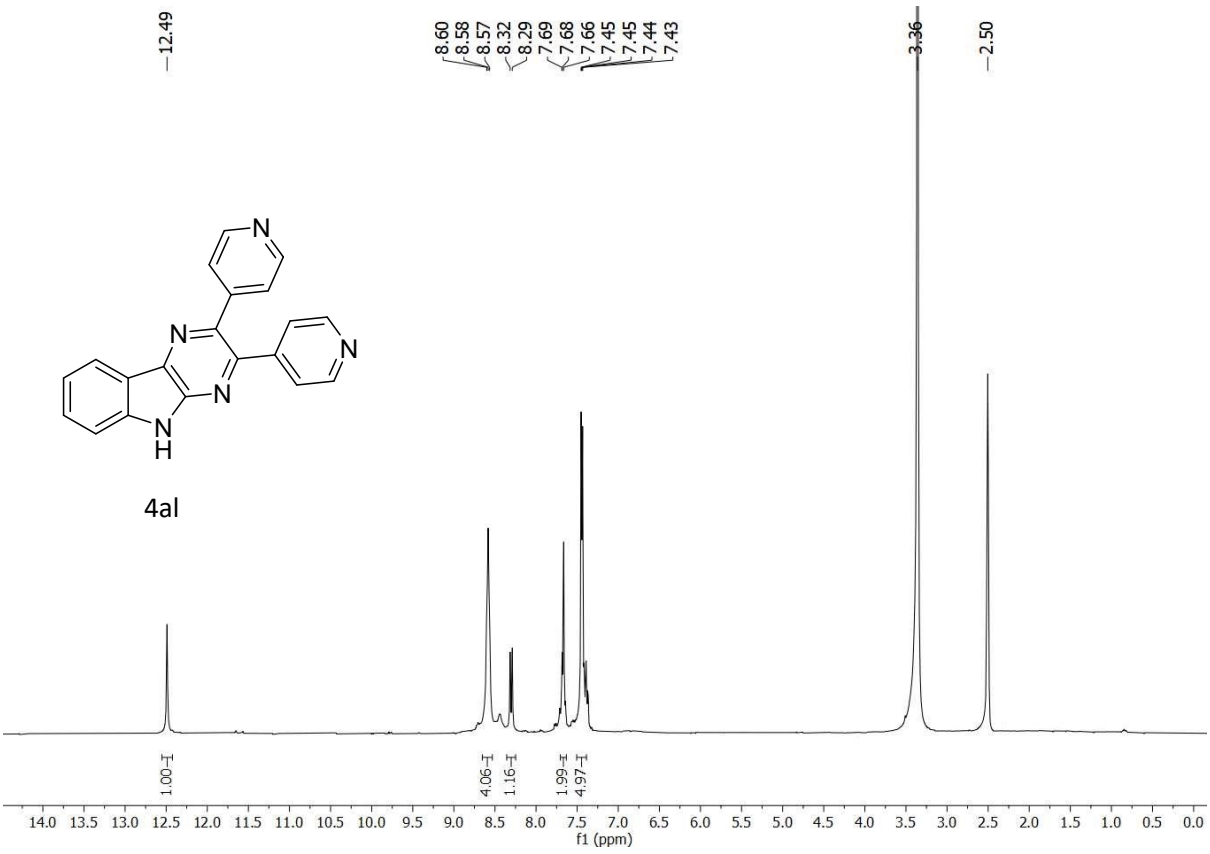
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound 4bj



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

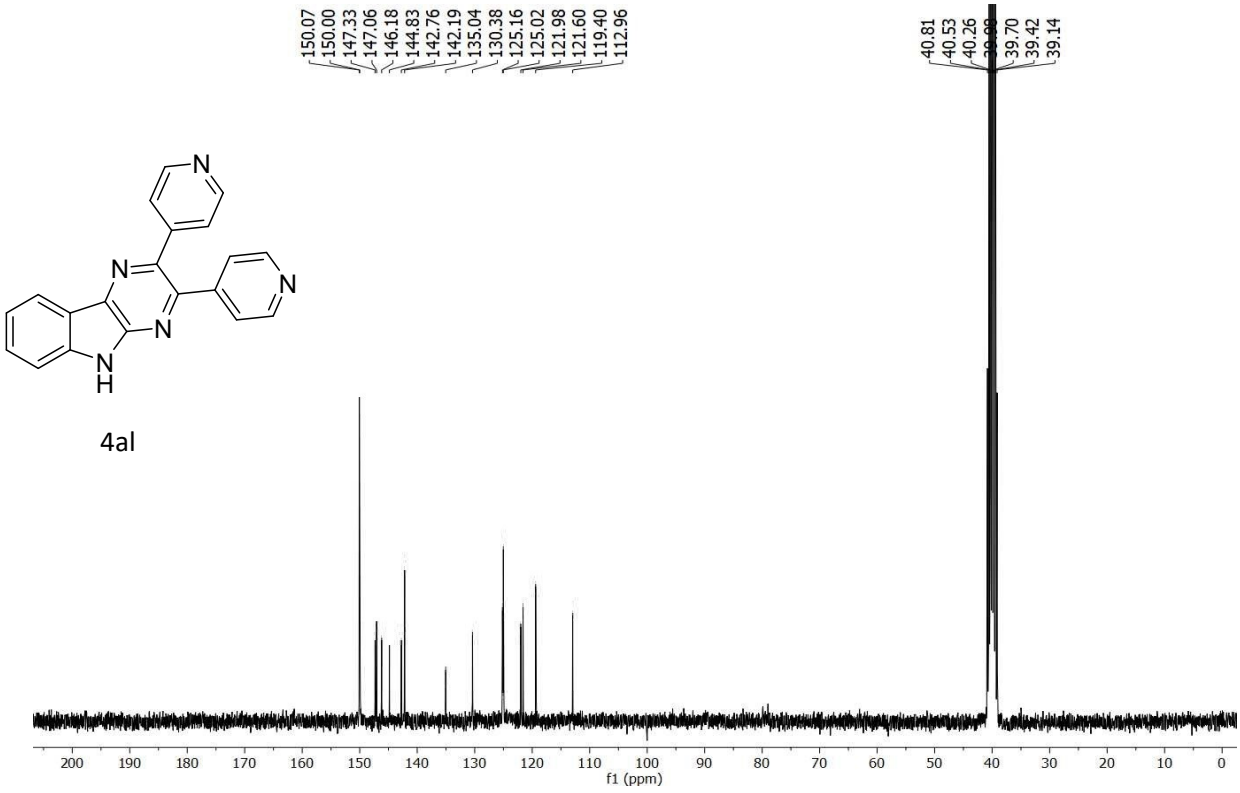


^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound 4ak



4al

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



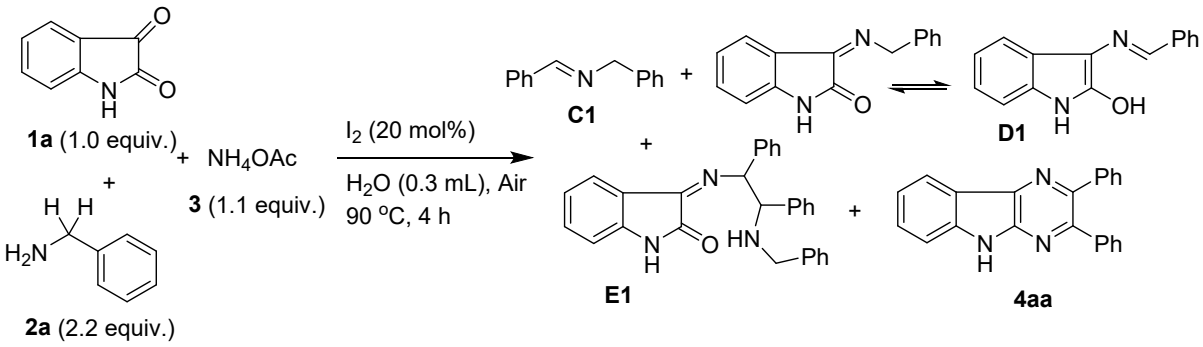
4al

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

Control experiments : Control experiments were carried out to gain more insight into the reaction mechanism (**Scheme SI-1**, **Scheme SI-2**, **Scheme SI-3** and **Scheme SI-5**).

Mass spectrum of raction mixture

The reaction was quenched after 4 hours and the compounds were detected through mass spectrum of the crude reaction mixture (**Scheme SI-1**). From the mass spectrum it was noticeably observed that there is the presence of intermediates (**C1**, **D1** and **E1**) along with the product **4aa** (**Figure SI-1**).



Scheme SI-1 An investigation of the reaction after 4 hours under optimized reaction condition

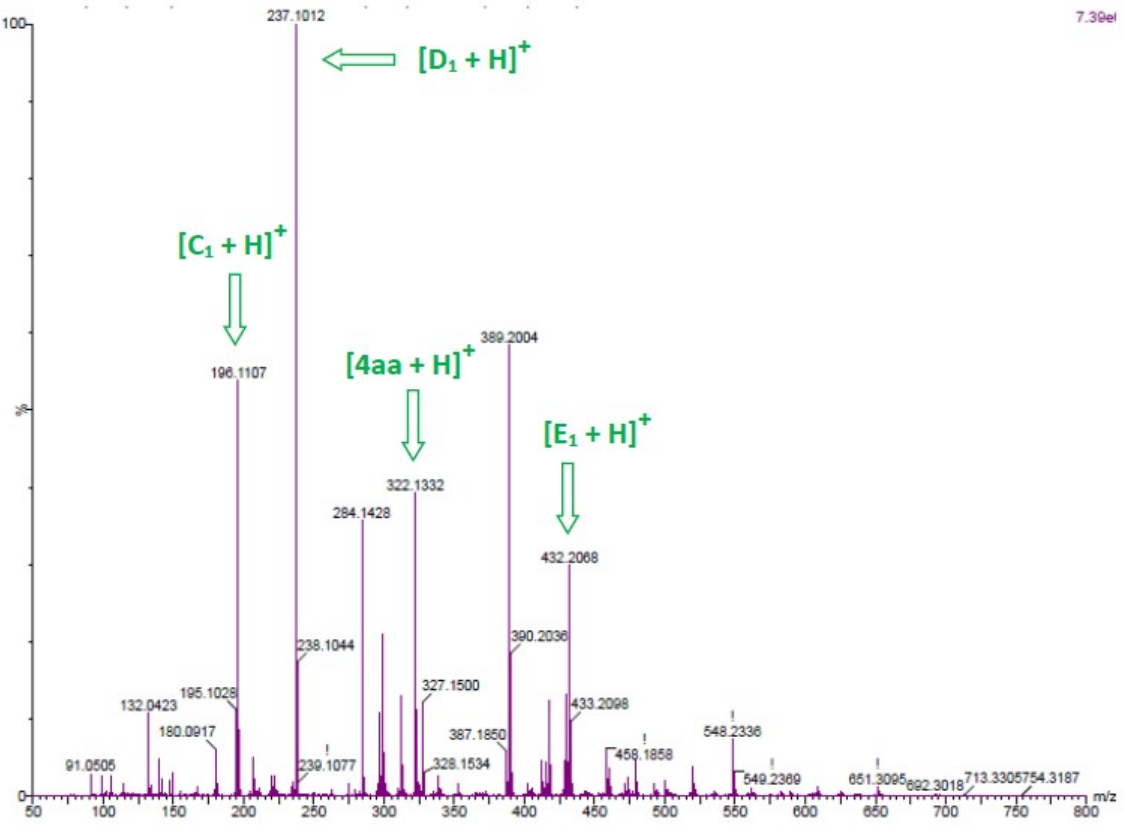
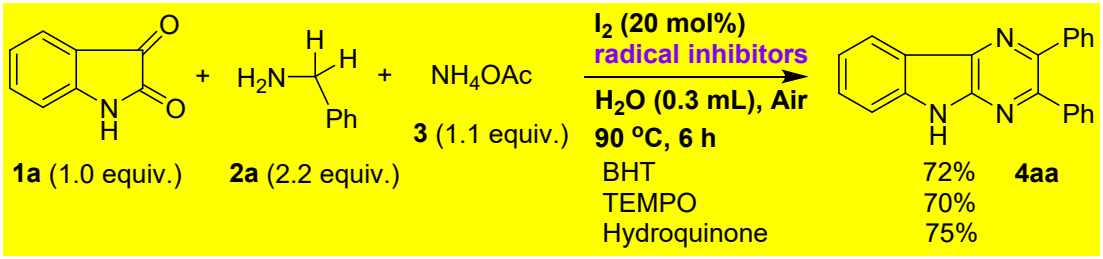


Figure SI-1 The reaction was quenched after 4 hours and the compounds were detected through mass spectra.

Control experiment carried out in presence of radical scavengers.

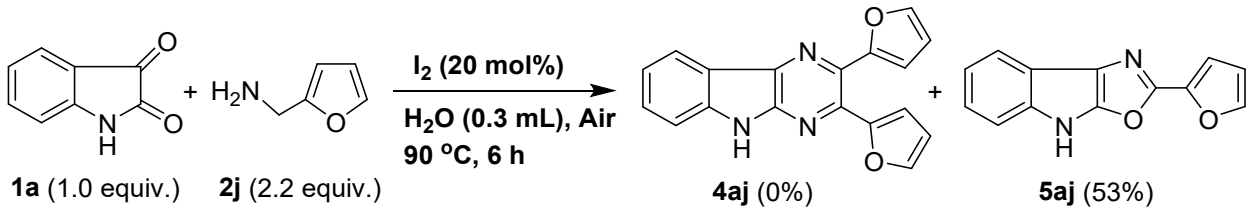
The reaction involving radical scavengers, such as BHT, TEMPO and hydroquinone were also carried out, and we have successfully obtained the product **4aa** in 72%, 70% and 75% yields respectively (**Scheme SI-2**).



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

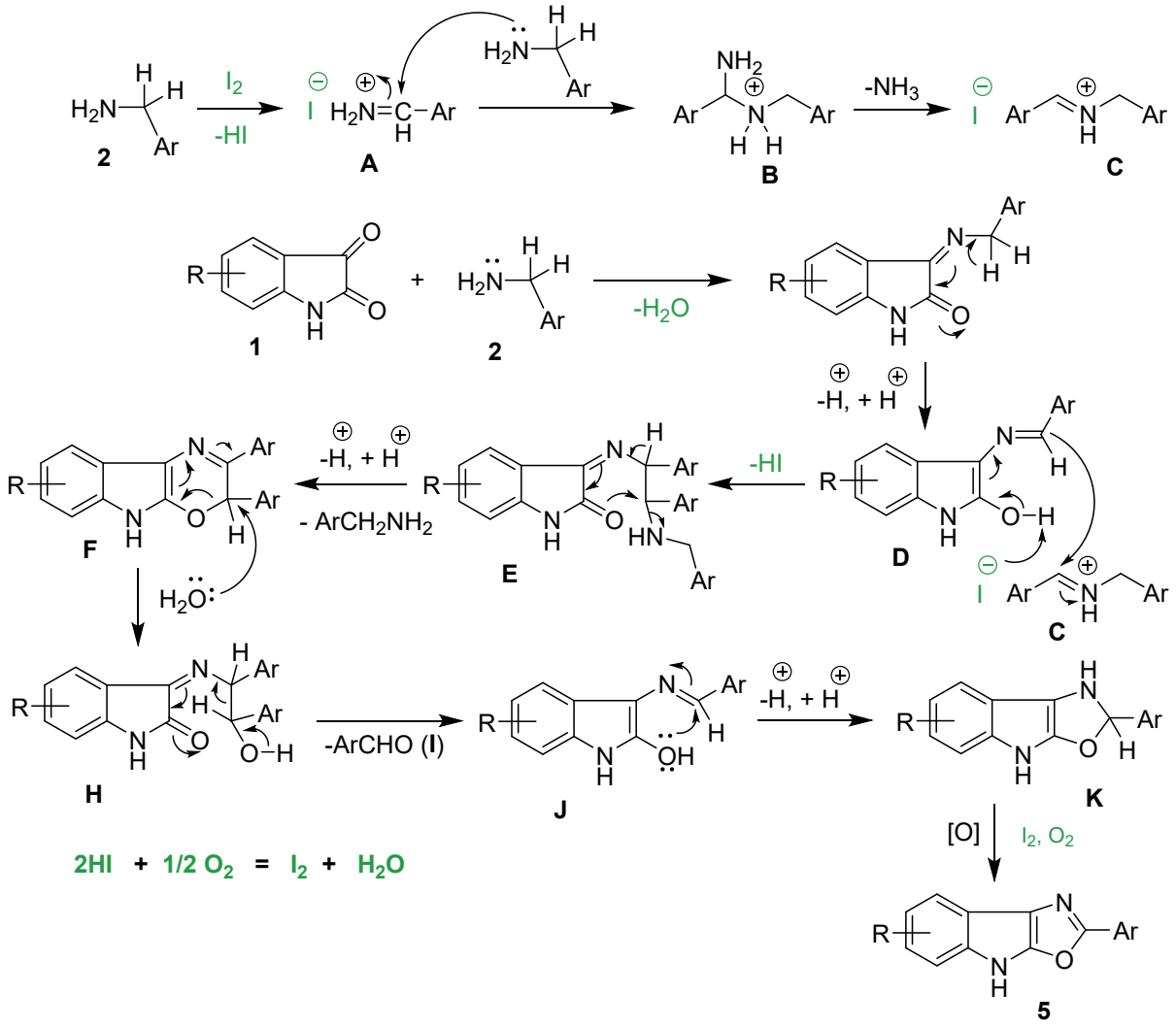
Control experiment carried out without ammonium acetate (NH_4OAc).

The control experiment shown in **Scheme SI-3**, we consider the reaction of isatin **1a** and 2-aminomethylfuran **2j** without NH_4OAc under the optimized reaction condition. Here, we got 53% 4*H*-oxazolo[5,4-*b*]indole **5aj** instead of the desired 5*H*-pyrazino[2,3-*b*]indole **4aj**.



Scheme SI-3 Experiment carried out without ammonium acetate (NH_4OAc)

In the absence of ammonium acetate formation mechanism of 4*H*-oxazolo[5,4-*b*]indole by water given below (**Scheme SI-4**).



Scheme SI-4 Proposed formation mechanism of 4*H*-oxazolo[5,4-*b*]indole by water in the absence of ammonium acetate

In this proposed formation mechanism of 4*H*-oxazolo[5,4-*b*]indole by water in the absence of ammonium acetate (**Scheme SI-4**), we have discussed step by step the formation of 4*H*-oxazolo[5,4-*b*]indole instead of the desired product 5*H*-pyrazino[2,3-*b*]indole. In this case the intermediate **F** decomposed by water and furnished more stable aromatic 4*H*-oxazolo[5,4-*b*]indole **5**. Here, water (H_2O) attack on the intermediate **F** to furnish intermediate **H**. After that, removal of one molecule of aromatic aldehyde from **H** gives the intermediate **J**. Finally **J** undergoes cyclisation to **K** followed by aromatization of 4*H*-oxazolo[5,4-*b*]indole **5.**

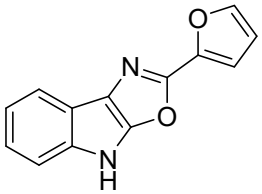
Control experiment carried out with benzyl alcohol 6a or benzaldehyde 7a.

The reaction of isatin **1a** with benzyl alcohol **6a** or benzaldehyde **7a** instead of benzylamine **2a** produces no desired product **4aa** (**Scheme SI-5**). These results imply that, benzyl amine and ammonium acetate both are important to construct the pyrazine ring of 5*H*-pyrazino[2,3-*b*]indole moiety.

Scheme SI-5 Experiment carried out with benzyl alcohol **6a** or benzaldehyde **7a**.

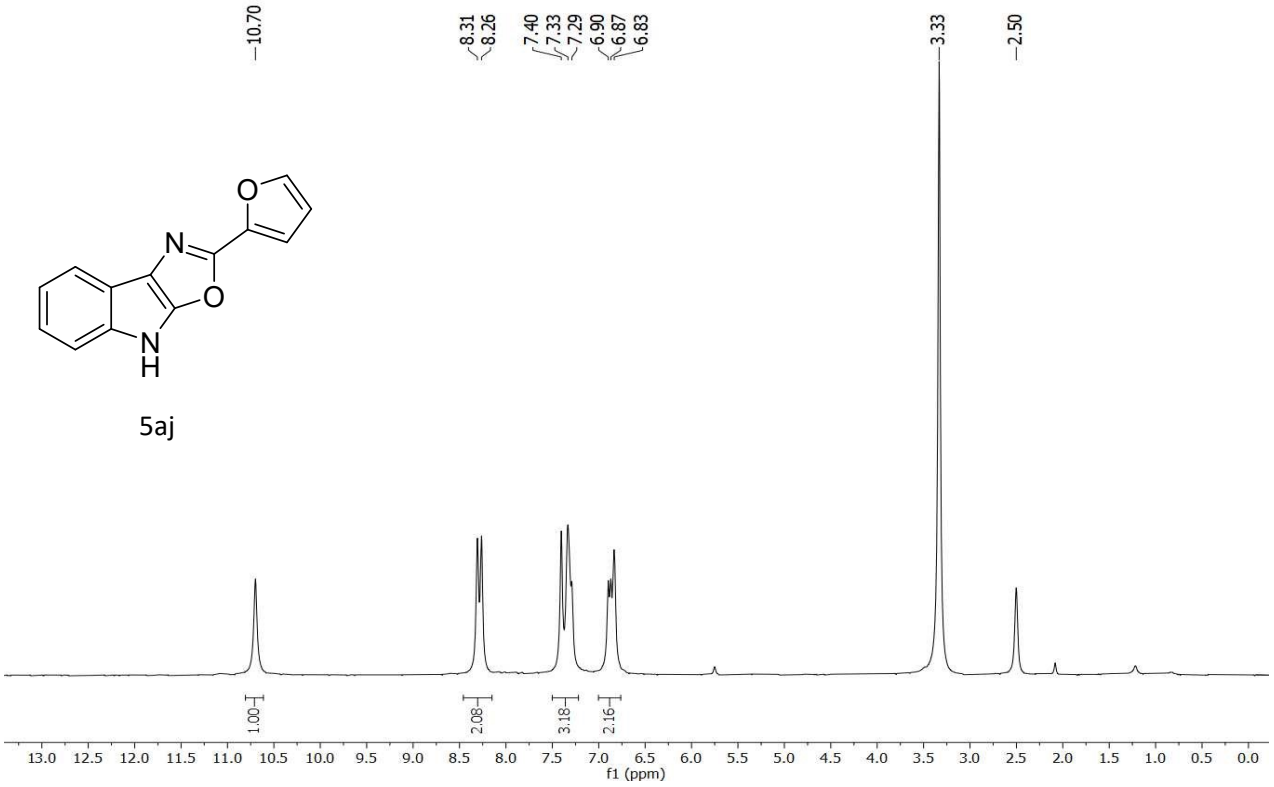
Characterization data of 5aj

2-(furan-2-yl)-4H-oxazolo[5,4-b]indole (**5aj**)



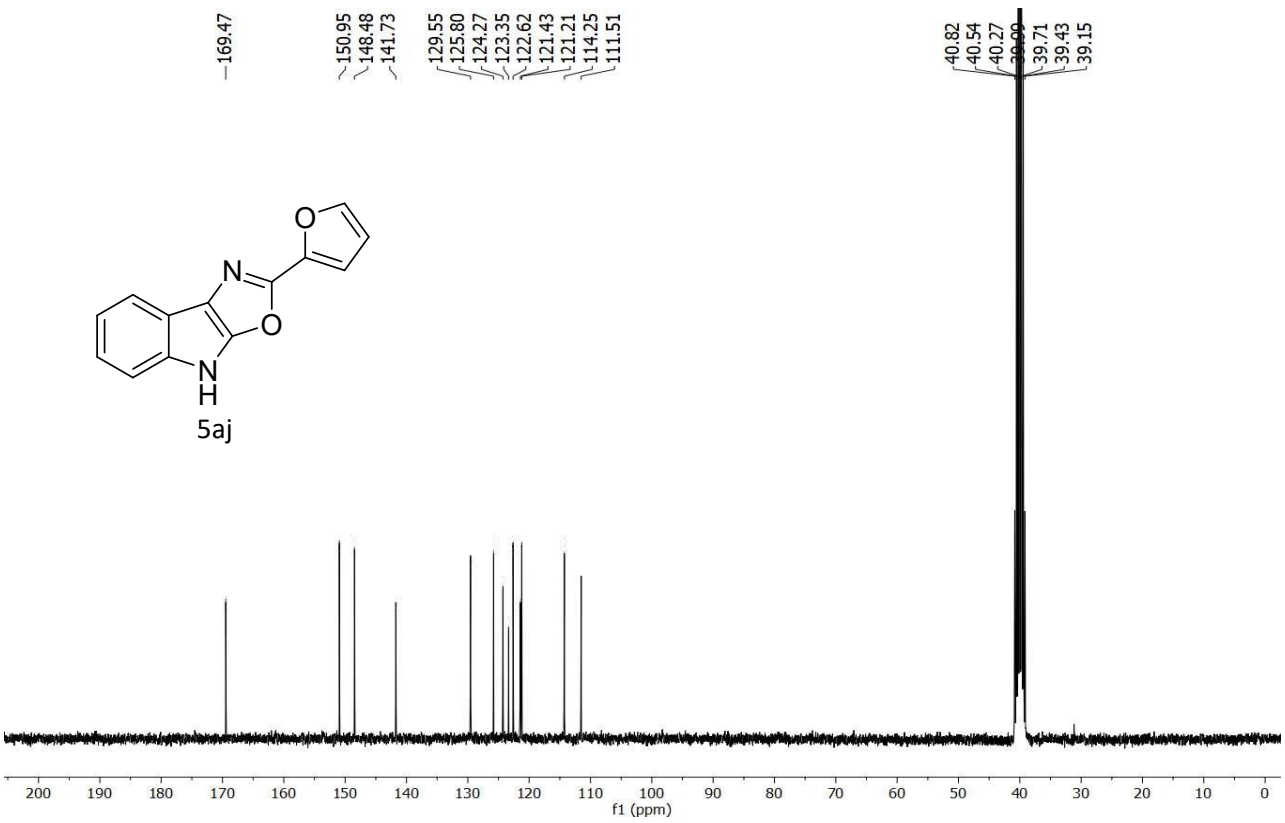
Yield : 54 % ; Yellow solid ; ^{1}H NMR (300 MHz, DMSO-d_6) : δ (ppm) = 10.70 (s, 1H, N-H), 8.29 (d, J = 15 Hz, 2H), 7.40-7.29 (m, 3H), 6.90-6.83 (m, 2H) ; ^{13}C NMR (75 MHz, DMSO-d_6) = 169.5, 151.0, 148.5, 141.7, 129.6, 125.8, 124.3, 123.4, 122.6, 121.4, 121.2, 114.3, 114.5 ppm ; HRMS-ESI (m/z): calcd for $C_{13}H_8N_2O_2$ $[M + H]^+$:225.0664, found :225.0661.

^{1}H and ^{13}C NMR spectra of 5aj



5aj

^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound 5aj



5aj

^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound 5aj

Crystallographic Information of **4ba** and **4ag**

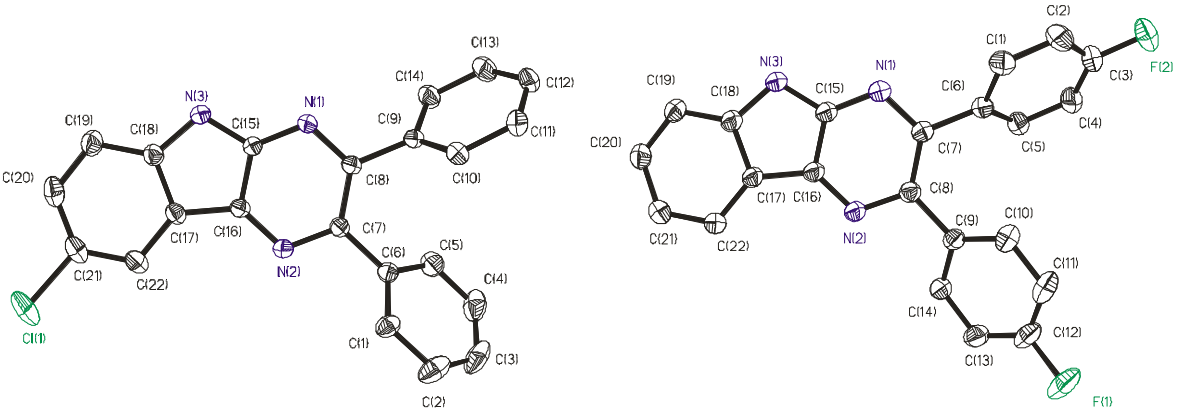


Figure: Molecular geometries of (a) **4ba** and (b) **4ag** in crystals (40% thermal ellipsoids, hydrogen atoms are omitted for clarity).

Crystallographic table

Complexes	**4ba**	**4ag**
CCDC	2246524	2246525
formula	$C_{22}H_{14}N_3Cl$	$C_{22}H_{13}N_3F_2$
fw	355.81	357.35
crystal color	yellow	yellow
crystal system	monoclinic	monoclinic
space group	*C* 2/*c*	*P* 21/*c*
a (Å)	17.4509(7)	9.5735(4)
b (Å)	12.4727(5)	12.6239(5)
c(Å)	17.6236(7)	28.8448(12)
α ( )	90	90
β ( )	112.121(2)	93.918(2)
γ ( )	90	90
V (Å^3)	3553.6(3)	3477.9(2)
Z	8	8
T (K)	273(2)	273(2)
2θ	50.70	47.72
calcd (g cm^{-3})	1.330	1.365
reflections collected	20048	50271
uniquereflections	3136	6482
reflection (I>2σ(I))	2226	4570
λ (Å)/*μ* (mm^{-1})	0.71073 /0.225	0.71073 / 0.097
F(000)	1472	1472
R1[a][I>2σ(I)]/GOF [b]	0.0573/ 1.025	0.0559/ 1.028
R1[a] (all data)	0.0878	0.0861
*w*R2[c] (I>2σ (I))	0.1464	0.1561
no. of parameters/restr.	235/0	487/0
residual density (eÅ^{-3})	0.283	0.188
observation criterion: [a]R1 = $\Sigma\|\|F_o\|-\|F_c\|\|/\Sigma\|F_o\|$. [b]GOF = $\{\Sigma[w(F_o^2-F_c^2)^2]/(n-p)\}^{1/2}$, [c]*w*R2 = $[\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$ where $w = 1/[\sigma^2(F_o^2)+(aP)^2+bP]$, $P = (F_o^2+2F_c^2)/3$.		