Copper(II)-Catalyzed C5 and C7 halogenation of quinolines Using sodium halide under Mild Conditions

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Supporting Information

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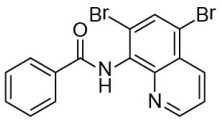
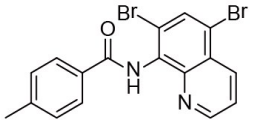
1 Characterization of the products

N-(5,7-dibromoquinolin-8-yl)benzamide (3a)



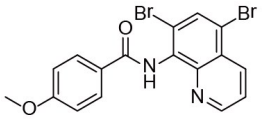
Obtained as a white solid in 85% yield; M.p. 156-157 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.82 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.47 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.08 (d, *J* = 3.3 Hz, 2H), 8.06 (d, *J* = 1.4 Hz, 1H), 7.59-7.56 (m, 1H), 7.53 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.49 (dd, *J* = 10.5, 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.37, 150.56, 143.79, 136.10, 134.43, 134.12, 133.95, 132.29, 128.74, 128.04, 126.89, 122.83, 120.22, 118.91. HRMS (ESI+): Calculated for $C_{16}H_{10}Br_2N_2OH$: $[M+H]^+$ 404.9233, Found 404.9168.

N-(5,7-dibromoquinolin-8-yl)-4-methylbenzamide (3b)



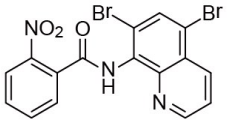
Obtained as a white solid in 86% yield; M.p. 166-167 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.80 (d, *J* = 2.6 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.51 (dd, *J* = 8.4, 3.7 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.36, 150.49, 143.75, 142.84, 136.17, 134.45, 134.22, 131.06, 129.36, 128.08, 126.88, 122.81, 120.35, 118.79, 21.62. HRMS (ESI+): Calculated for $C_{17}H_{12}Br_2N_2OH$: $[M+H]^+$ 418.9389, Found 418.9394.

N-(5,7-dibromoquinolin-8-yl)-4-methoxybenzamide (3c)



Obtained as a white solid in 91% yield; M.p. 82-83 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.82 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.47 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.08 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.53 (dd, *J* = 8.5, 4.2 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.97, 162.88, 150.43, 143.73, 136.18, 134.48, 134.35, 130.01, 126.89, 126.20, 122.78, 120.16, 118.62, 113.91, 55.52. HRMS (ESI+): Calculated for $C_{17}H_{12}Br_2N_2O_2H$: $[M+H]^+$ 434.9339, Found 434.9345.

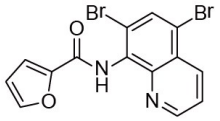
N-(5,7-dibromoquinolin-8-yl)-2-nitrobenzamide (3d)



Obtained as a white solid in 79% yield; M.p. 204-205 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.75 (s, 1H), 8.52 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.11 (d, *J* = 6.0 Hz, 2H), 7.94 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.69-7.63 (m, 1H), 7.59 (dd, *J* = 8.5, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.89, 150.94,

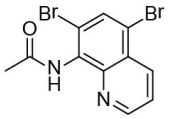
146.56, 143.83, 136.13, 134.37, 133.60, 132.75, 132.59, 131.04, 129.20, 127.00, 124.69, 122.98, 120.62, 119.86. HRMS (ESI+): Calculated for $C_{16}H_9Br_2N_3O_3H$: $[M+H]^+$ 449.9084, Found 449.9090.

***N*-(5,7-dibromoquinolin-8-yl)furan-2-carboxamide (3e)**



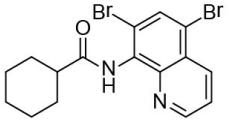
Obtained as a white solid in 73% yield; M.p. 159-160 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.89 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.49 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.09 (s, 1H), 7.59 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.55 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.30 (dd, *J* = 3.5, 0.6 Hz, 1H), 6.58 (dd, *J* = 3.5, 1.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.76, 150.83, 147.71, 144.81, 144.13, 136.08, 134.31, 133.05, 127.01, 122.85, 120.89, 119.57, 116.03, 112.48. HRMS (ESI+): Calculated for $C_{14}H_8Br_2N_2O_2H$: $[M+H]^+$ 394.9026, Found 394.9034.

***N*-(5,7-dibromoquinolin-8-yl)acetamide (3f)**



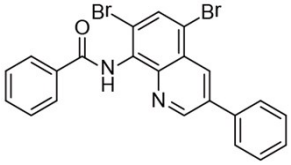
Obtained as a white solid in 85% yield; M.p. 227-228 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.49 (dt, *J* = 11.7, 5.8 Hz, 2H), 8.06 (s, 1H), 7.56 (dd, *J* = 8.5, 4.2 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.70, 146.57, 146.51, 143.99, 136.33, 134.30, 133.70, 127.05, 121.65, 119.61, 23.73. HRMS (ESI+): Calculated for $C_{11}H_8Br_2N_2OH$: $[M+H]^+$ 342.9076, Found 342.9082.

***N*-(5,7-dibromoquinolin-8-yl)cyclohexanecarboxamide (3g)**



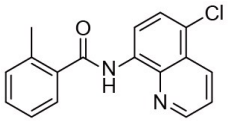
Obtained as a white solid in 89% yield; M.p. 202-203 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.47 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.27 (s, 1H), 8.04 (s, 1H), 7.54 (dd, *J* = 8.5, 4.2 Hz, 1H), 2.52 (tt, *J* = 11.6, 3.5 Hz, 1H), 2.13 (dd, *J* = 13.6, 2.1 Hz, 2H), 1.90-1.85 (m, 2H), 1.74-1.62 (m, 3H), 1.42-1.28 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.12, 150.61, 143.94, 135.98, 134.27, 133.88, 126.87, 122.69, 120.51, 118.79, 45.94, 29.65, 25.82, 25.71. HRMS (ESI+): Calculated for $C_{16}H_{16}Br_2N_2OH$: $[M+H]^+$ 410.9702, Found 410.9710.

***N*-(5,7-dibromo-3-phenylquinolin-8-yl)benzamide (3h)**



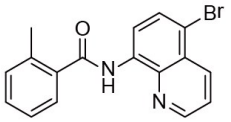
Obtained as a white solid in 81% yield; M.p. 202-203 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, *J* = 13.2 Hz, 2H), 8.59 (d, *J* = 1.8 Hz, 1H), 8.10 (dd, *J* = 9.2, 1.9 Hz, 3H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.56-7.50 (m, 4H), 7.47 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.43, 150.10, 146.56, 142.81, 136.79, 135.73, 134.78, 134.07, 134.00, 133.11, 132.33, 129.41, 128.77, 128.06, 127.56, 126.77, 119.90, 119.11. HRMS (ESI+): Calculated for $C_{22}H_{14}Br_2N_2OH$: $[M+H]^+$ 480.9546, Found 480.9552.

***N*-(5-chloroquinolin-8-yl)-2-methylbenzamide (4ba)**



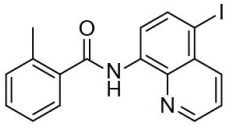
Obtained as a white solid in 40% yield; M.p. 145-146 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.87 (d, *J* = 8.4 Hz, 1H), 8.80 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.55 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.54 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.40 (td, *J* = 7.5, 1.3 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 2.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.09, 148.72, 139.16, 136.80, 136.35, 134.03, 133.41, 131.47, 130.48, 128.26, 127.25, 126.06, 126.00, 124.55, 122.37, 116.46, 20.22. HRMS (ESI+): Calculated for $C_{17}H_{13}ClN_2OH$: $[M+H]^+$ 297.0789, Found 297.0790.

***N*-(5-bromoquinolin-8-yl)-2-methylbenzamide (4bb)**



Obtained as a white solid in 84% yield; M.p. 146-147 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.82 (d, *J* = 8.4 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.51 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.54 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.40 (td, *J* = 7.5, 1.2 Hz, 1H), 7.31 (t, *J* = 8.2 Hz, 2H), 2.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.14, 148.76, 139.29, 136.81, 136.30, 135.98, 134.65, 131.48, 130.92, 130.53, 129.05, 127.25, 126.08, 122.73, 116.99, 114.51, 20.26. HRMS (ESI+): Calculated for $C_{17}H_{13}BrN_2OH$: $[M+H]^+$ 341.0284, Found 341.0287.

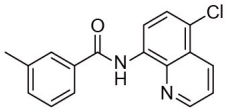
***N*-(5-iodoquinolin-8-yl)-2-methylbenzamide (4bc)**



Obtained as a white solid in 78% yield; M.p. 93-94 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.76-8.70 (m, 2H), 8.41 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.54 (dd, *J* = 7.3, 3.1 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 2H), 2.59 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.23, 148.58, 141.24, 138.89, 138.47, 136.82, 136.26, 135.51, 131.45, 130.54, 129.77, 127.32,

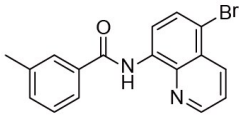
126.04, 123.15, 118.37, 89.62, 20.21. HRMS (ESI+): Calculated for $C_{17}H_{13}IN_2OH$: $[M+H]^+$ 389.0146, Found 389.0153.

_N_-(5-chloroquinolin-8-yl)-3-methylbenzamide (4ca)



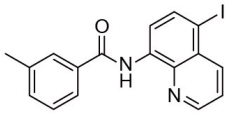
Obtained as a white solid in 41% yield; M.p. 86-87 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.82 (dd, *J* = 5.0, 3.5 Hz, 2H), 8.48 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.84-7.79 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.40-7.33 (m, 2H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.47, 148.66, 139.18, 138.69, 134.82, 133.87, 133.33, 132.73, 128.66, 128.02, 127.23, 125.89, 124.34, 124.18, 122.31, 116.42, 21.47. HRMS (ESI+): Calculated for $C_{17}H_{13}ClN_2OH$: $[M+H]^+$ 297.0789, Found 297.0790.

_N_-(5-bromoquinolin-8-yl)-3-methylbenzamide (4cb)



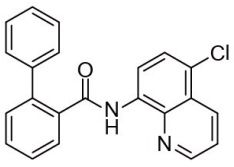
Obtained as a white solid in 84% yield; M.p. 111-112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.83 (dd, *J* = 4.1, 1.2 Hz, 1H), 8.79 (d, *J* = 8.4 Hz, 1H), 8.49 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.86-7.78 (m, 3H), 7.53 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.43-7.36 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.53, 148.72, 139.33, 138.72, 135.93, 134.79, 134.51, 132.79, 130.92, 128.69, 128.05, 127.16, 124.20, 122.69, 116.98, 114.34, 21.52. HRMS (ESI+): Calculated for $C_{17}H_{13}BrN_2OH$: HRMS (ESI+): Calculated for $C_{17}H_{13}BrN_2OH$: $[M+H]^+$ 341.0284, Found 341.0287.

_N_-(5-iodoquinolin-8-yl)-3-methylbenzamide (4cc)



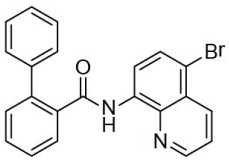
Obtained as a white solid in 78% yield; M.p. 104-105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.80 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.69 (d, *J* = 8.3 Hz, 1H), 8.37 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.89-7.80 (m, 2H), 7.53 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.41 (dt, *J* = 15.1, 7.5 Hz, 2H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.68, 148.78, 140.88, 139.28, 138.74, 138.38, 135.53, 134.86, 132.80, 129.68, 128.69, 128.09, 124.25, 123.18, 118.07, 89.45, 21.48. HRMS (ESI+): Calculated for $C_{17}H_{13}IN_2OH$: $[M+H]^+$ 389.0146, Found 389.0153.

_N_-(5-chloroquinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (4da)



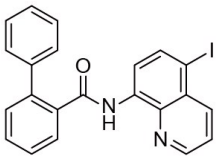
Obtained as a white solid in 38% yield; M.p. 140-141 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.75 (d, *J* = 8.4 Hz, 1H), 8.50 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.41 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.93-7.88 (m, 1H), 7.55 (dd, *J* = 11.2, 5.0 Hz, 2H), 7.51-7.45 (m, 4H), 7.40 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.25 (dd, *J* = 13.7, 5.9 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.75, 148.16, 140.31, 139.98, 138.92, 135.84, 133.83, 133.02, 130.74, 130.70, 129.36, 129.03, 128.42, 127.70, 127.69, 127.12, 125.69, 124.27, 122.09, 116.18. HRMS (ESI+): Calculated for $C_{22}H_{15}ClN_2OH$: $[M+H]^+$ 359.0946, Found 359.0951.

***N*-(5-bromoquinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (4db)**



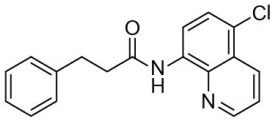
Obtained as a white solid in 81% yield; M.p. 132-133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.47 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.38 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.91 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.50-7.46 (m, 4H), 7.40 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.28-7.24 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.79, 148.20, 140.30, 139.93, 139.05, 135.79, 135.57, 134.45, 130.78, 130.75, 129.39, 129.03, 128.44, 127.72, 126.94, 122.46, 116.72, 114.25. HRMS (ESI+): Calculated for $C_{22}H_{15}BrN_2OH$: $[M+H]^+$ 403.0441, Found 403.0449.

***N*-(5-iodoquinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (4dc)**



Obtained as a white solid in 79% yield; M.p. 154-155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.58 (d, *J* = 8.3 Hz, 1H), 8.47 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.30 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.91 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.56 (dt, *J* = 7.5, 3.8 Hz, 1H), 7.52-7.47 (m, 4H), 7.42 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.92, 148.00, 140.86, 140.32, 139.97, 138.59, 138.32, 135.75, 135.24, 130.73, 130.71, 129.45, 129.34, 129.02, 128.39, 127.68, 127.66, 122.87, 118.14, 89.42. HRMS (ESI+): Calculated for $C_{22}H_{15}IN_2OH$: $[M+H]^+$ 451.0302, Found 451.0309.

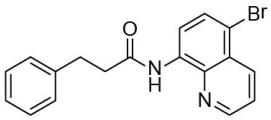
***N*-(5-chloroquinolin-8-yl)-3-phenylpropanamide (4ea)**



Obtained as a white solid in 35% yield; M.p. 108-109 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.78 (d, J = 4.1 Hz, 1H), 8.71 (d, J = 8.4 Hz, 1H), 8.53 (dd, J = 8.5, 1.3 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.55-7.50 (m, 1H), 7.29 (d, J = 4.5 Hz, 4H), 7.22-

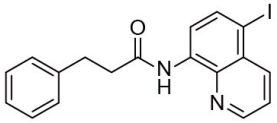
7.17 (m, 1H), 3.14 (t, *J* = 7.8 Hz, 2H), 2.87 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.72, 148.52, 140.66, 138.82, 133.71, 133.39, 128.59, 128.40, 127.25, 126.30, 125.90, 124.21, 122.28, 116.43, 39.69, 31.42. HRMS (ESI+): Calculated for $C_{18}H_{15}ClN_2OH$: $[M+H]^+$ 311.0946, Found 311.0950.

***N*-(5-bromoquinolin-8-yl)-3-phenylpropanamide (4eb)**



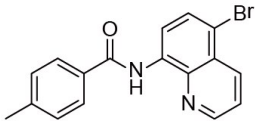
Obtained as a white solid in 88% yield; M.p. 106-107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.50 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.53 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.30-7.28 (m, 4H), 7.22-7.17 (m, 1H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.88 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.79, 148.58, 140.64, 138.97, 135.96, 134.34, 130.93, 128.60, 128.41, 127.15, 126.31, 122.65, 116.98, 114.15, 39.73, 31.40. HRMS (ESI+): Calculated for $C_{18}H_{15}BrN_2OH$: $[M+H]^+$ 355.0441, Found 355.0448.

***N*-(5-iodoquinolin-8-yl)-3-phenylpropanamide (4ec)**



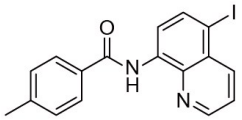
Obtained as a white solid in 82% yield; M.p. 112-113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.73 (d, *J* = 4.1 Hz, 1H), 8.56 (d, *J* = 8.2 Hz, 1H), 8.36 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.55-7.50 (m, 1H), 7.33-7.27 (m, 4H), 7.21 (d, *J* = 4.3 Hz, 1H), 3.14 (t, *J* = 7.8 Hz, 2H), 2.89 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.83, 148.65, 140.76, 140.63, 138.88, 138.29, 135.32, 129.58, 128.59, 128.40, 126.31, 123.14, 117.89, 89.21, 39.76, 31.40. HRMS (ESI+): Calculated for $C_{18}H_{15}IN_2OH$: $[M+H]^+$ 403.0302, Found 403.0309.

***N*-(5-bromoquinolin-8-yl)-4-methylbenzamide (4fb)**



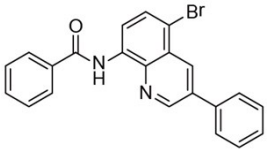
Obtained as a white solid in 84% yield; M.p. 169-170 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.79 (d, *J* = 8.4 Hz, 1H), 8.48 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.30, 148.70, 142.55, 139.38, 135.93, 134.59, 132.00, 130.95, 129.50, 127.29, 127.19, 122.68, 116.90, 114.22, 21.59. HRMS (ESI+): Calculated for $C_{17}H_{13}BrN_2OH$: $[M+H]^+$ 341.0284, Found 341.0287.

***N*-(5-iodoquinolin-8-yl)-4-methylbenzamide (4fc)**



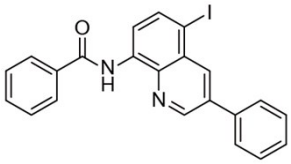
Obtained as a white solid in 82% yield; M.p. 171-172 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.79 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.69 (d, *J* = 8.3 Hz, 1H), 8.35 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.52 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.39, 148.77, 142.57, 140.78, 139.33, 138.36, 135.61, 132.06, 129.66, 129.51, 127.32, 123.17, 117.90, 89.29, 21.56. HRMS (ESI+): Calculated for $C_{17}H_{13}IN_2OH$: $[M+H]^+$ 389.0146, Found 389.0153.

_N_-(5-bromo-3-phenylquinolin-8-yl)benzamide (4gb)



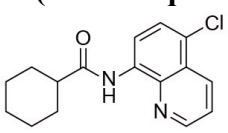
Obtained as a white solid in 83% yield; M.p. 135-136 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.66 (s, 1H), 9.09 (d, *J* = 2.1 Hz, 1H), 8.80 (d, *J* = 8.4 Hz, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.08-8.06 (m, 2H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.75-7.73 (m, 2H), 7.57-7.53 (m, 5H), 7.48 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.40, 148.20, 138.36, 137.16, 135.66, 134.83, 134.45, 133.19, 132.06, 131.42, 129.36, 128.88, 128.64, 127.60, 127.31, 127.03, 116.92, 114.64. HRMS (ESI+): Calculated for $C_{22}H_{15}BrN_2OH$: $[M+H]^+$ 403.0441, Found 403.0449.

_N_-(5-iodo-3-phenylquinolin-8-yl)benzamide (4gc)



Obtained as a white solid in 57% yield; M.p. 143-144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 9.06 (d, *J* = 2.1 Hz, 1H), 8.70 (d, *J* = 8.3 Hz, 1H), 8.50 (d, *J* = 2.1 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.10-8.07 (m, 2H), 7.77-7.74 (m, 2H), 7.61-7.55 (m, 5H), 7.49 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.48, 148.30, 146.56, 138.80, 138.30, 138.12, 137.12, 136.23, 135.47, 134.87, 132.08, 129.39, 128.89, 128.65, 127.64, 127.34, 117.85, 89.82. HRMS (ESI+): Calculated for $C_{22}H_{15}IN_2OH$: $[M+H]^+$ 451.0302, Found 451.0309.

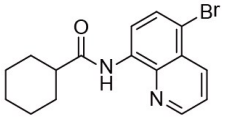
_N_-(5-chloroquinolin-8-yl)cyclohexanecarboxamide (4ha)



Obtained as a white solid in 38% yield; M.p. 64-65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.85 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.54 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 8.5, 4.2 Hz, 1H), 2.48 (tt, *J* = 11.7,

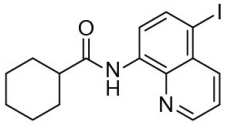
3.5 Hz, 1H), 2.10 (dd, *J* = 13.5, 2.0 Hz, 2H), 1.93-1.86 (m, 2H), 1.65 (qd, *J* = 12.4, 3.2 Hz, 2H), 1.46-1.22 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.79, 148.53, 139.03, 133.94, 133.33, 127.24, 125.87, 123.95, 122.22, 116.32, 46.84, 29.72, 25.77, 25.74. HRMS (ESI+): Calculated for $C_{16}H_{17}ClN_2OH$: $[M+H]^+$ 289.1102, Found 289.1102.

***N*-(5-bromoquinolin-8-yl)cyclohexanecarboxamide (4hb)**



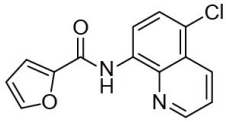
Obtained as a white solid in 83% yield; M.p. 97-98 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.77 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.42 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 8.5, 4.2 Hz, 1H), 2.46 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.08 (dd, *J* = 13.5, 2.0 Hz, 2H), 1.89-1.84 (m, 2H), 1.62 (tt, *J* = 12.5, 6.2 Hz, 2H), 1.45-1.19 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.78, 148.52, 139.05, 135.80, 134.51, 130.84, 127.02, 122.53, 116.83, 113.85, 46.82, 29.71, 25.77, 25.73. HRMS (ESI+): Calculated for $C_{16}H_{17}BrN_2OH$: $[M+H]^+$ 333.0597, Found 333.0599.

***N*-(5-iodoquinolin-8-yl)cyclohexanecarboxamide (4hc)**



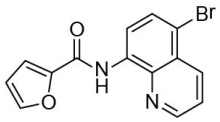
Obtained as a white solid in 85% yield; M.p. 126-127 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.78 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.58 (d, *J* = 8.3 Hz, 1H), 8.37 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.53 (dd, *J* = 8.5, 4.2 Hz, 1H), 3.73 (q, *J* = 7.0 Hz, 1H), 2.50 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.09 (dd, *J* = 13.6, 1.9 Hz, 2H), 1.93-1.85 (m, 2H), 1.64 (qd, *J* = 12.4, 3.2 Hz, 2H), 1.45-1.36 (m, 2H), 1.35-1.29 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.95, 148.48, 140.97, 138.87, 138.38, 135.47, 129.58, 123.02, 118.07, 88.94, 46.85, 29.70, 25.72, 18.43. HRMS (ESI+): Calculated for $C_{16}H_{17}IN_2OH$: $[M+H]^+$ 381.0459, Found 381.0465.

***N*-(5-chloroquinolin-8-yl)furan-2-carboxamide (4ia)**



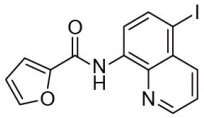
Obtained as a white solid in 29% yield; M.p. 186-187 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.93 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.82 (d, *J* = 8.4 Hz, 1H), 8.59 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.64 (t, *J* = 5.1 Hz, 2H), 7.60 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.31 (dd, *J* = 3.4, 0.5 Hz, 1H), 6.60 (dd, *J* = 3.5, 1.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.34, 148.88, 148.21, 144.63, 139.24, 133.53, 133.41, 127.27, 126.06, 124.65, 122.43, 116.60, 115.35, 112.51. HRMS (ESI+): Calculated for $C_{14}H_9ClN_2O_2H$: $[M+H]^+$ 273.0426, Found 273.0431.

***N*-(5-bromoquinolin-8-yl)furan-2-carboxamide (4ib)**



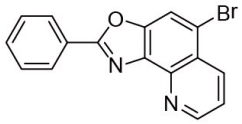
Obtained as a white solid in 71% yield; M.p. 191-192 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.74 (s, 1H), 8.90 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.54 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 0.9 Hz, 1H), 7.59 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.31 (d, *J* = 3.2 Hz, 1H), 6.60 (dd, *J* = 3.5, 1.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.34, 148.90, 148.17, 144.67, 139.32, 136.00, 134.15, 130.94, 127.30, 122.78, 117.14, 115.42, 114.60, 112.55. HRMS (ESI+): Calculated for $C_{14}H_9BrN_2O_2H$: $[M+H]^+$ 316.9920, Found 316.9923.

***N*-(5-iodoquinolin-8-yl)furan-2-carboxamide (4ic)**



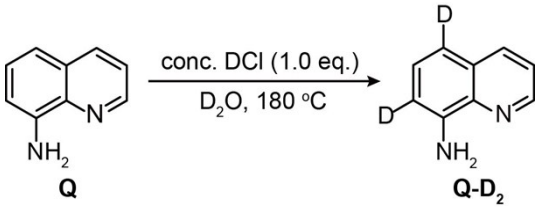
Obtained as a white solid in 63% yield; M.p. 162-163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.74 (s, 1H), 8.83 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.62 (d, *J* = 8.3 Hz, 1H), 8.37 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 0.9 Hz, 1H), 7.54 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.33-7.29 (m, 1H), 6.59 (dd, *J* = 3.5, 1.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.34, 148.91, 148.16, 144.69, 140.77, 139.12, 138.26, 135.07, 129.68, 123.22, 118.07, 115.45, 112.53, 89.73. HRMS (ESI+): Calculated for $C_{14}H_9IN_2O_2H$: $[M+H]^+$ 364.9782, Found 364.9785.

5-bromo-2-phenyloxazolo[5,4-h]quinoline (5a)



Obtained as a white solid in 88% yield; M.p. 153-154 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.11 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.68 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.62 (s, 1H), 8.29-8.26 (m, 2H), 7.80 (dd, *J* = 8.6, 4.2 Hz, 1H), 7.69-7.66 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.95, 152.20, 150.61, 141.15, 137.94, 136.51, 132.55, 129.94, 127.71, 126.68, 125.11, 122.98, 118.49, 116.90. HRMS (ESI+): Calculated for $C_{16}H_9BrN_2OH$: $[M+H]^+$ 324.9971, Found 324.9967.

2 Investigation into the mechanism of reaction

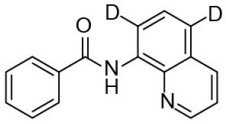


In a 50 mL schlenk tube with a magnetic stir bar, 8-aminoquinoline (288.0 mg, 2.0 mmol) was added, followed by conc. DCl in D_2O (1 equiv, 2.0 mL). The tube was capped and sealed and heated for 12 h at 150 °C. When it was completed, the reaction was cooled to room temperature and diluted with water (25 mL). extracted with EtOAc (10 mL x 3) and the combined organic layer was washed with 1 M $NaHCO_3$ aqueous solution (3 x 15 mL), brine (50 mL), dried with Na_2SO_4, and filtered through a pad of Celite. The solvent was removed under reduced pressure to afford the deuterated aniline product **Q-D$_2$**.

5,7-dideuteroquinolin-8-amine (Q-D$_2$)[1]

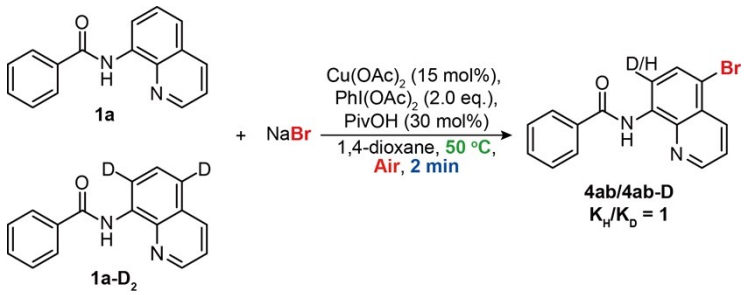
Obtained as a brown solid in 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.03 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.32 (dd, *J* = 8.3, 4.2 Hz, 2H), 5.01 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.28, 143.88, 138.23, 136.14, 128.85, 127.27, 121.29, 116.00, 115.90, 115.71, 115.51, 110.17, 110.10, 109.91, 109.72.

***N*-(5,7-dideuteroquinolin-8-yl)benzamide (1a-D$_2$)[2]**



Obtained as a white solid in 89% yield; M.p. 81-82 °C. ^{1}H NMR (500 MHz, CDCl3) δ 10.69 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.14-8.02 (m, 3H), 7.60-7.48 (m, 4H), 7.39 (dd, J = 8.2, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.33, 148.20, 138.69, 136.28, 135.12, 134.45, 131.79, 128.75, 127.87, 127.25, 127.15, 121.61, 121.35, 121.16, 116.45, 116.25, 116.05.

2.1 KIE experiment



Following the synthetic procedure of compound **3**, the reaction of **1a** (62.0 mg, 0.25 mmol), **1a- D$_2$** (62.5 mg, 0.25 mmol), NaBr (102.0 mg, 2.0 eq), $Cu(OAc)_2$ (13.7 mg, 15 mol%), $PhI(OAc)_2$ (322.0 mg, 2.0 eq) and PivOH (15.3 mg, 30 mol%) in 1,4-dioxane (4.0 mL) at 50 °C under air for 2.0 min produced **4ab**/**4ab-D** (45% yield). ^{1}H NMR analysis of the isolated product demonstrated an 1:1 ratio of H/D at the 7-position of the quinoline (**Figure S1**). The KIE of 1.0 was resolved for the sulfonation reaction, this result indicated that the turnover-limiting step does not involve C-H

activation.

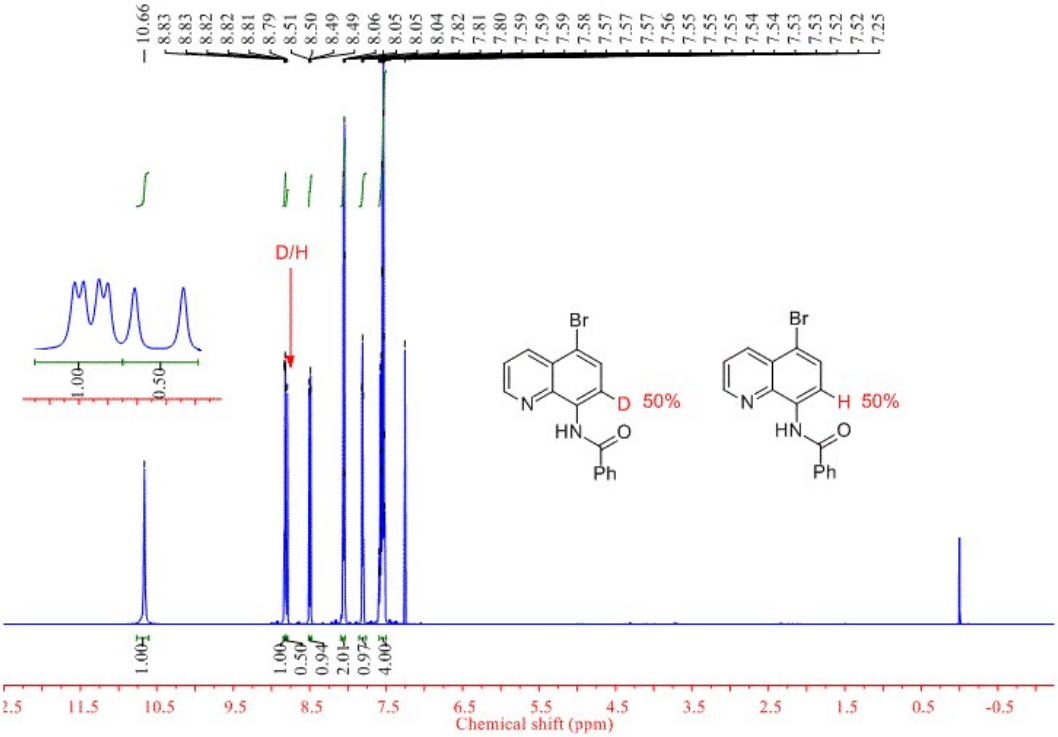
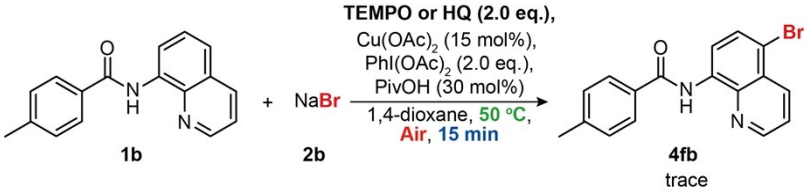


Figure S1 ^{1}H NMR spectrum of product of the KIE experiment.

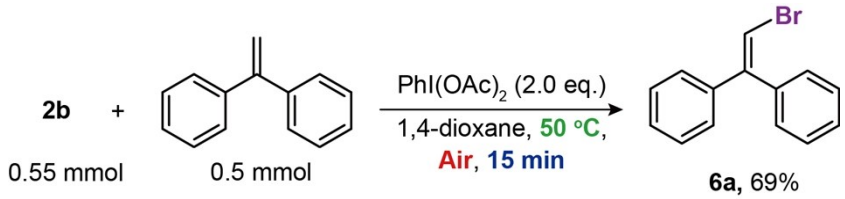
2.2 Radical inhibition experiment

No product was obtained in the presence of the radical inhibitor TEMPO or HQ, which showed that a radical pathway should be involved.

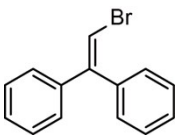


2.3 Radical capture experiment

We try to trap the radical intermediate by using 1,1-diphenylethylene in the reaction. To our delight, we observed the radical coupling product in 69% yield.

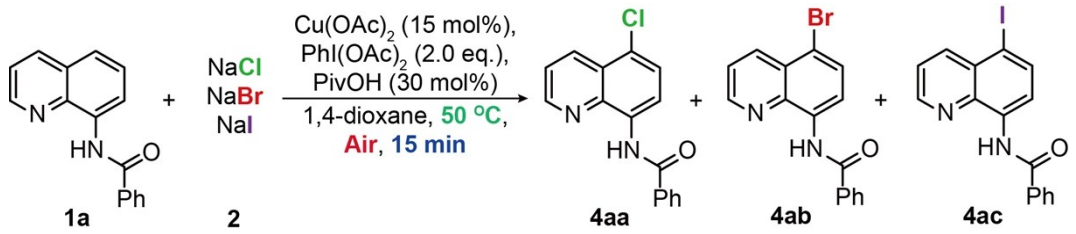


(2-bromoethene-1,1-diyl)dibenzene (6a)



Obtained as a white solid in 69% yield; M.p. 49-50 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.34 (m, 3H), 7.32-7.27 (m, 5H), 7.21 (dt, J = 4.4, 2.9 Hz, 2H), 6.77 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.88, 140.75, 139.11, 129.69, 128.46, 128.26, 128.15, 128.01, 127.65, 105.21. HRMS (ESI+): Calculated for $C_{14}H_{11}BrH$: $[M+H]^+$ 259.0117, Found 259.0091.

2.4 Radical competition experiment



Following the synthetic procedure of compound **3**, the reaction of **1a** (74.4 mg, 0.3 mmol), NaCl (35.1 mg, 2.0 eq), NaBr (61.2 mg, 2.0 eq), NaI (90.0 mg, 2.0 eq), $Cu(OAc)_2$ (8.19 mg, 15 mol%), $PhI(OAc)_2$ (193.2 mg, 2.0 eq) and PivOH (9.18 mg, 30 mol%) in 1,4-dioxane (2.0 mL) at 50 °C under air for 15.0 min produced the halogenated products. ^{1}H NMR analysis of the ratio of **4aa**, **4ab**,**4ac** is 0.18:1:0.85 (**Figure S2**). This result indicated that the order of stability is bromine radical > iodine radical > chlorine radical in this reaction.

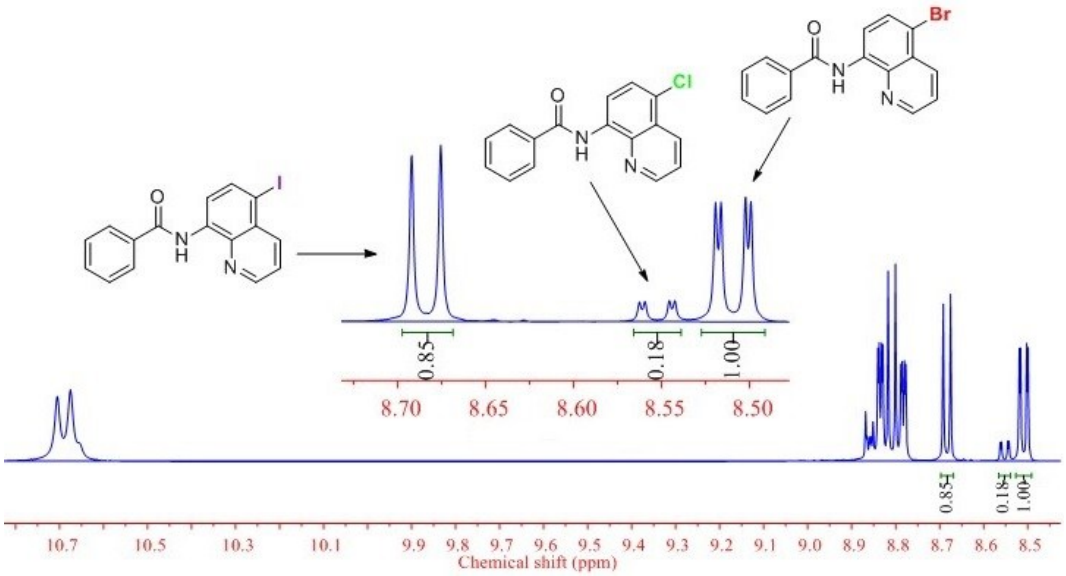


Figure S2 ^{1}H NMR spectrum of product of radical competition experiment.

X-ray Crystal Data for 3a

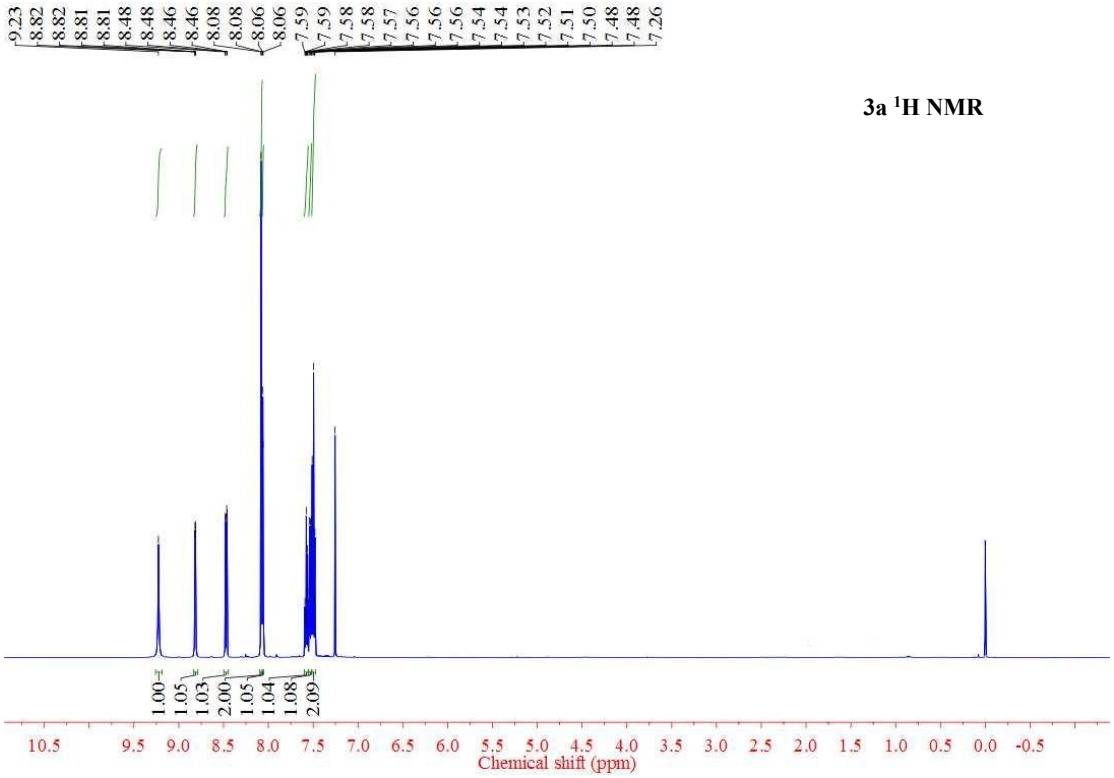
Crystals of **3a** ($C_{16}H_{10}Br_2N_2O$) was recrystallized from ethyl acetate and *n*-hexane. The single yellow transparent granular crystal which was suitable for X-ray diffraction measurements was mounted on a glass fiber. Unit cell measurements and intensity data collections were performed on a Rigaku AFC7R diffractometer with graphite monochromated Mo Ka. The data reduction included a correction for Lorentz

and polarization effects, with an applied multi-scan absorption correction (SADABS). The crystal structure was solved and refined using the SHELXTL-97 program suite. Direct methods yielded all non-hydrogen atoms which were refined with anisotropic thermal parameters. The obtained crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: 1429312 (**3a**, CCDC NO). The crystallographic data and refinement parameters of them are listed in Table S1.

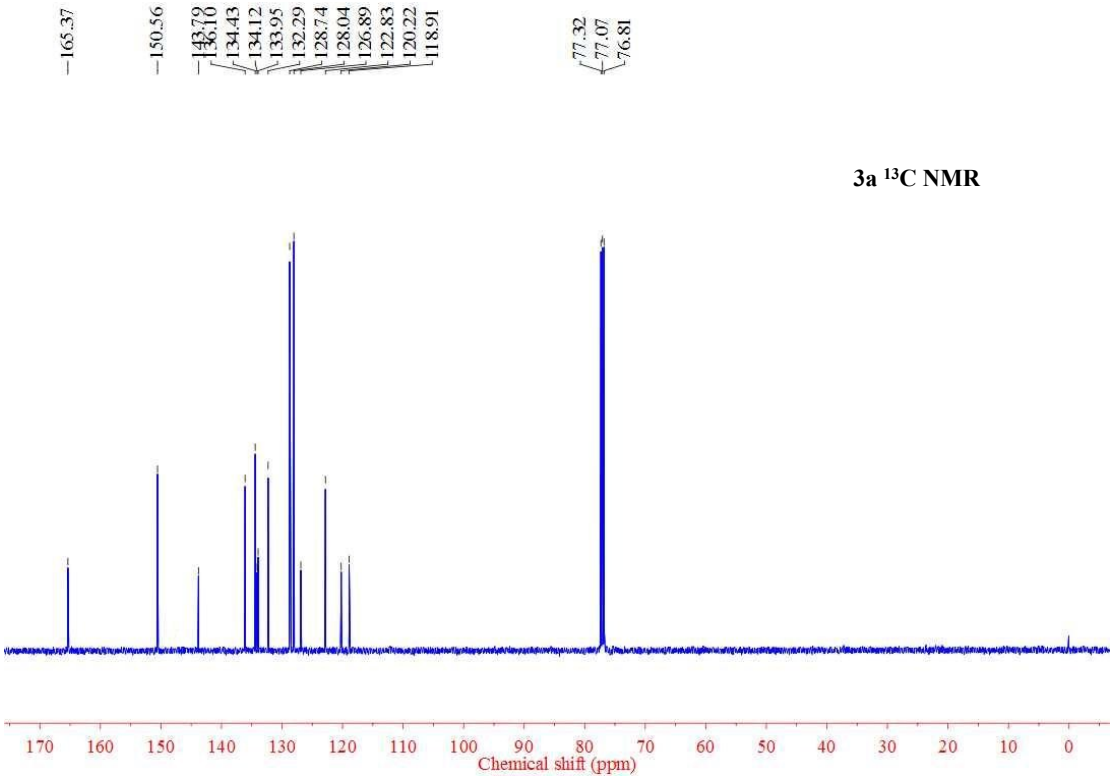
Table S1. Crystallographic data and structure refinement for **3a.**

Empirical formula	$C_{16}H_{10}Br_2N_2O$
Formula weight	406.08
Temperature, K	293(2)
Wavelength, Å	0.71073
Crystal system	Monoclinic
Space group	Pc
Unit cell dimensions	
a, *b*, *c*, Å	8.0468(7), 12.1197(10), 7.5388(7)
α, *β*, *γ*, °	90.00, 91.03, 90.00
Volume, Å^3	735.10(11)
Z	2
Calculated density, Mg/m^3	1.835
Absorption coefficient, mm^{-1}	5.513
F (000)	396
Crystal size, mm	0.22 x 0.21 x 0.20
Theta range for data collection, °	3.04 to 25.10
Limiting indices	-9<=h<=9, -14<=k<=14, -8<=l<=8
Absorption correction	multi-scan
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2595 / 2 / 191
Goodness of fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0595, wR2 = 0.1538
R indices (all data)	R1 = 0.0607, wR2 = 0.1553

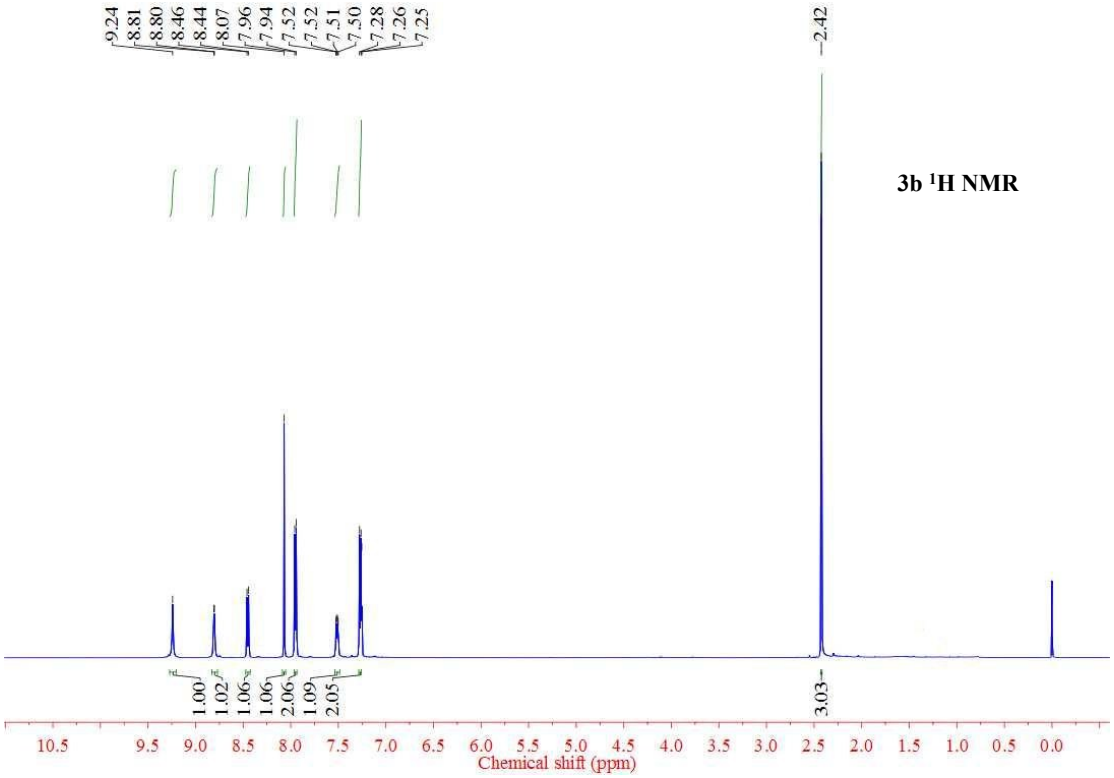
Copies of ^{1}H NMR and ^{13}C NMR Spectra



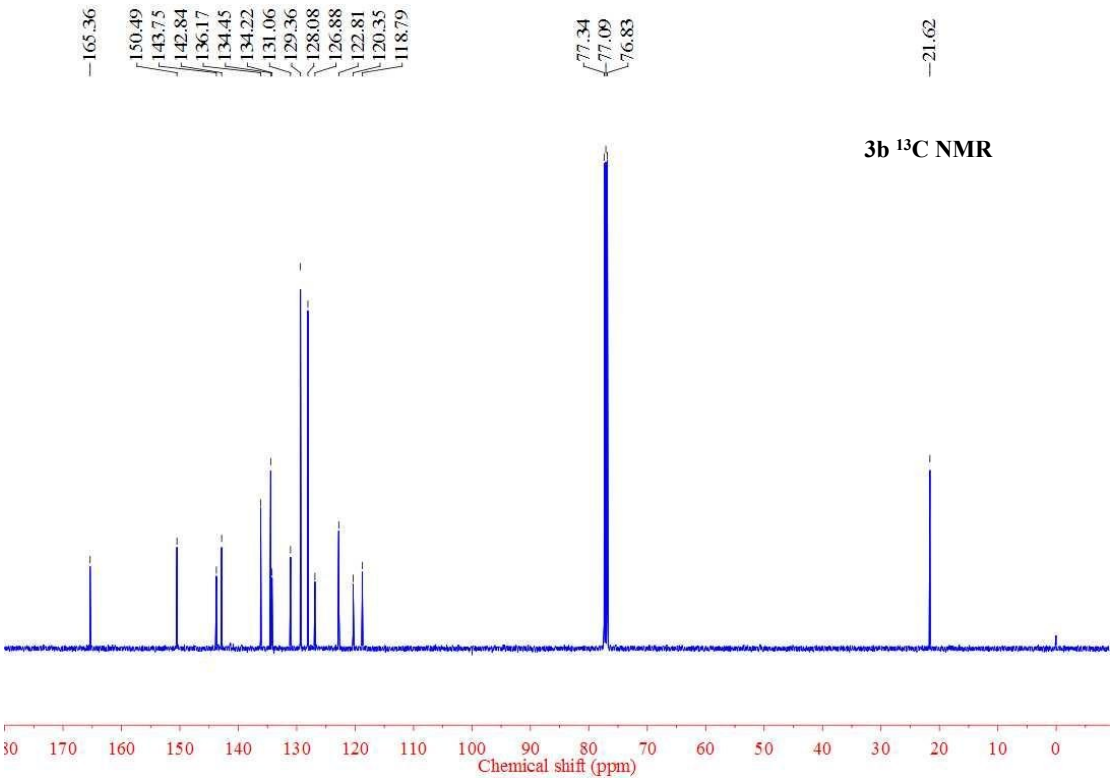
3a ^{1}H NMR



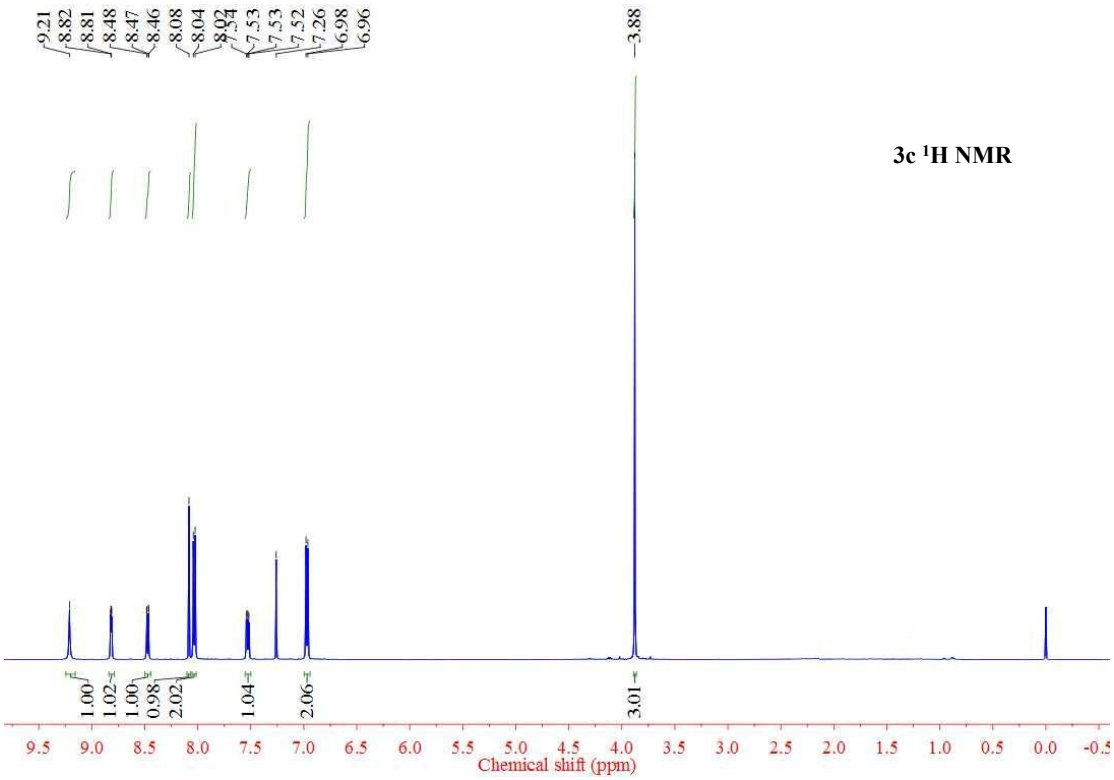
3a ^{13}C NMR



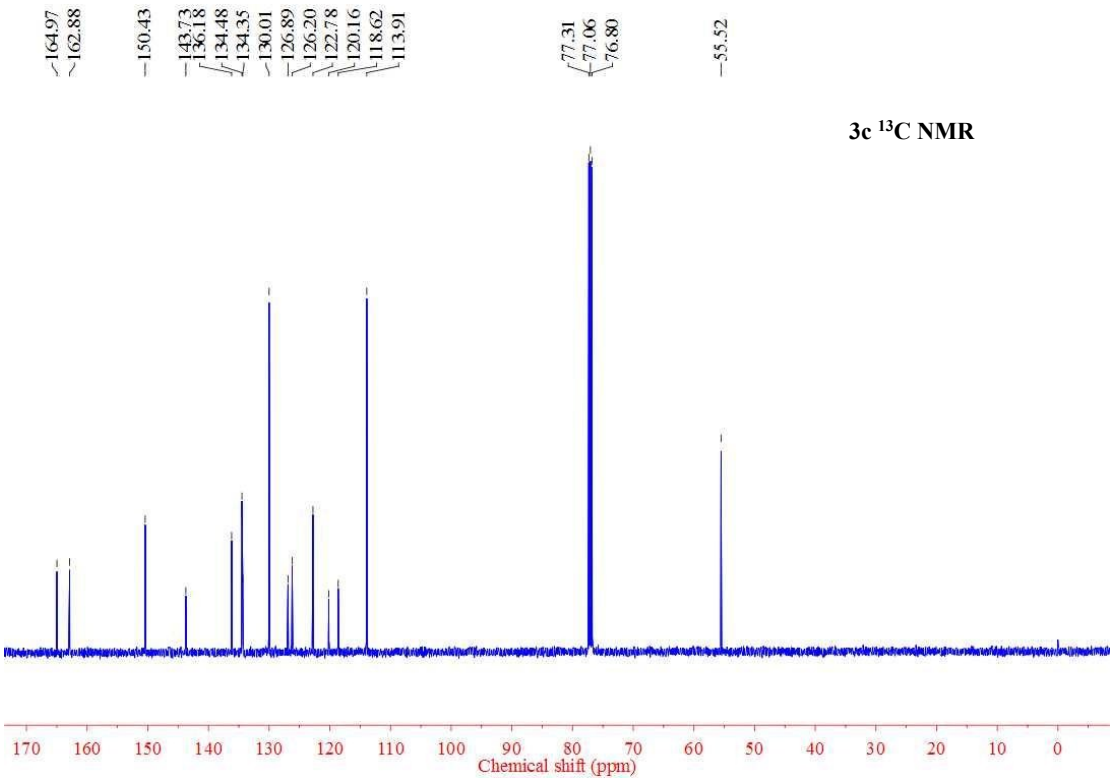
3b ^{1}H NMR



3b ^{13}C NMR



3c ^{1}H NMR



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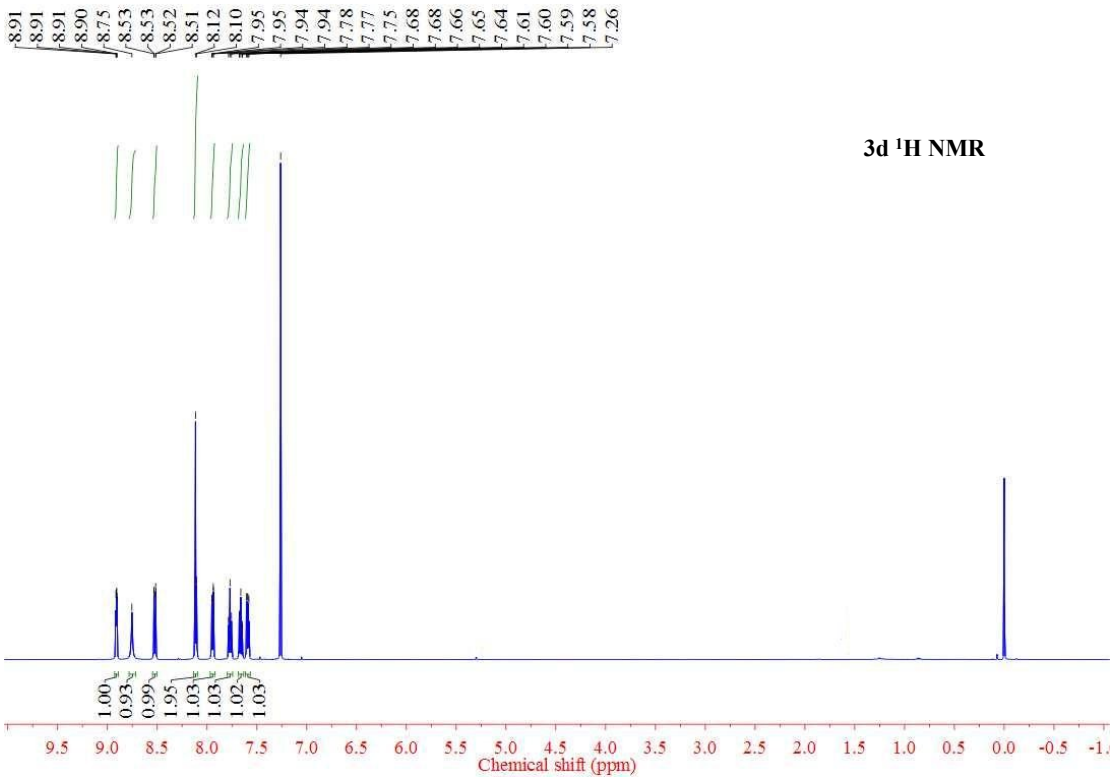

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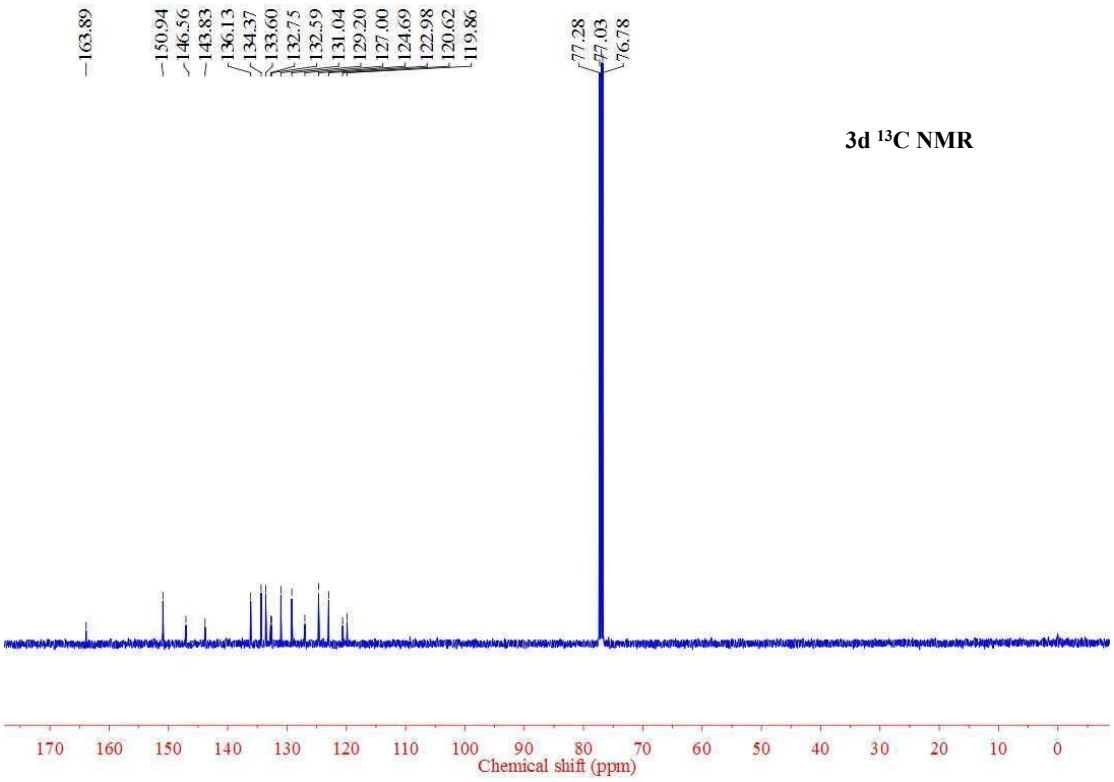

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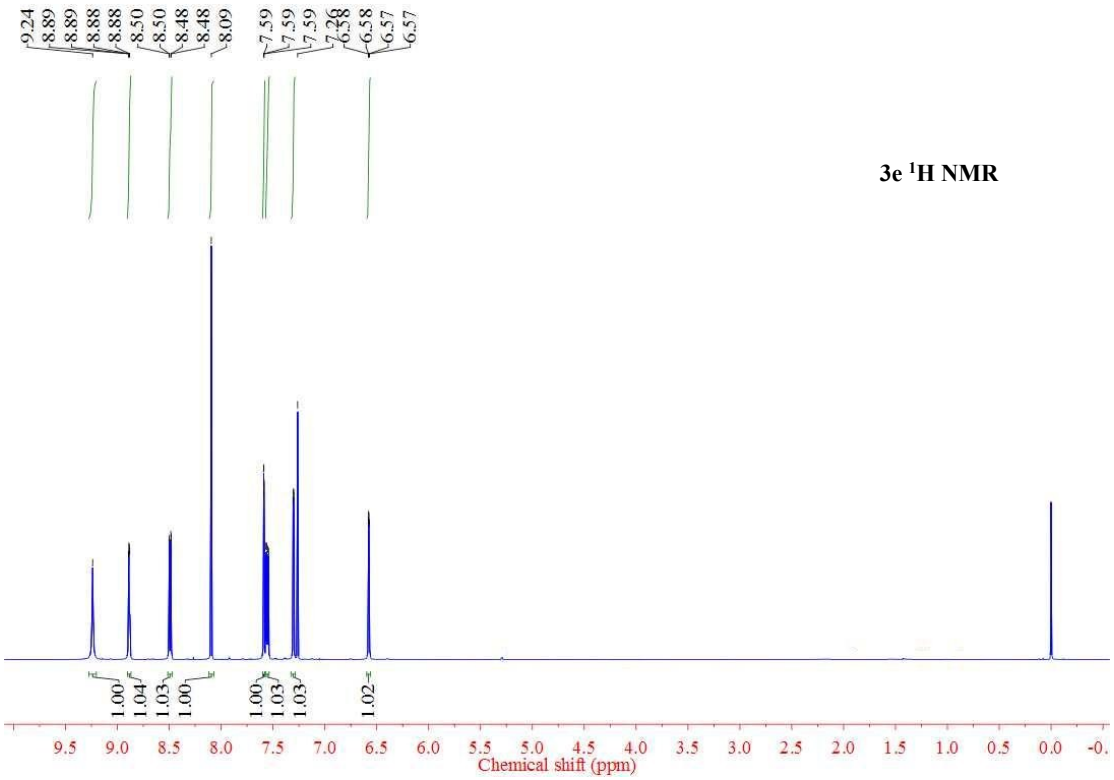
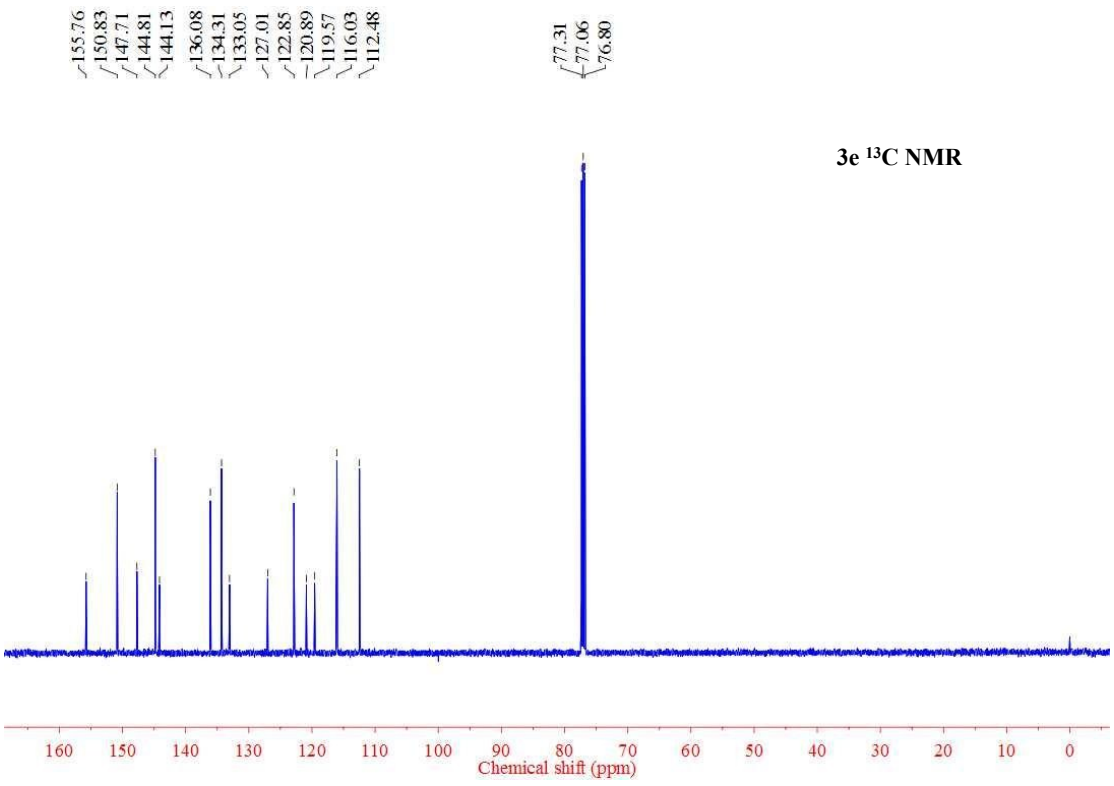


3e ^{1}H NMR



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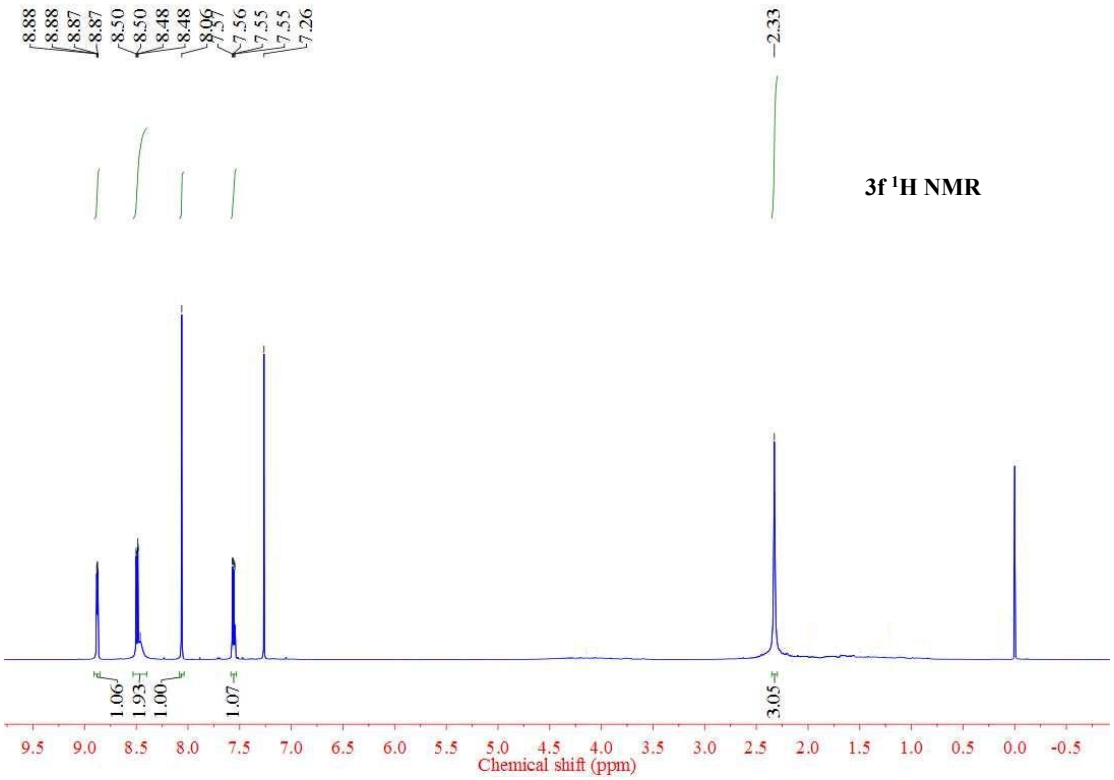

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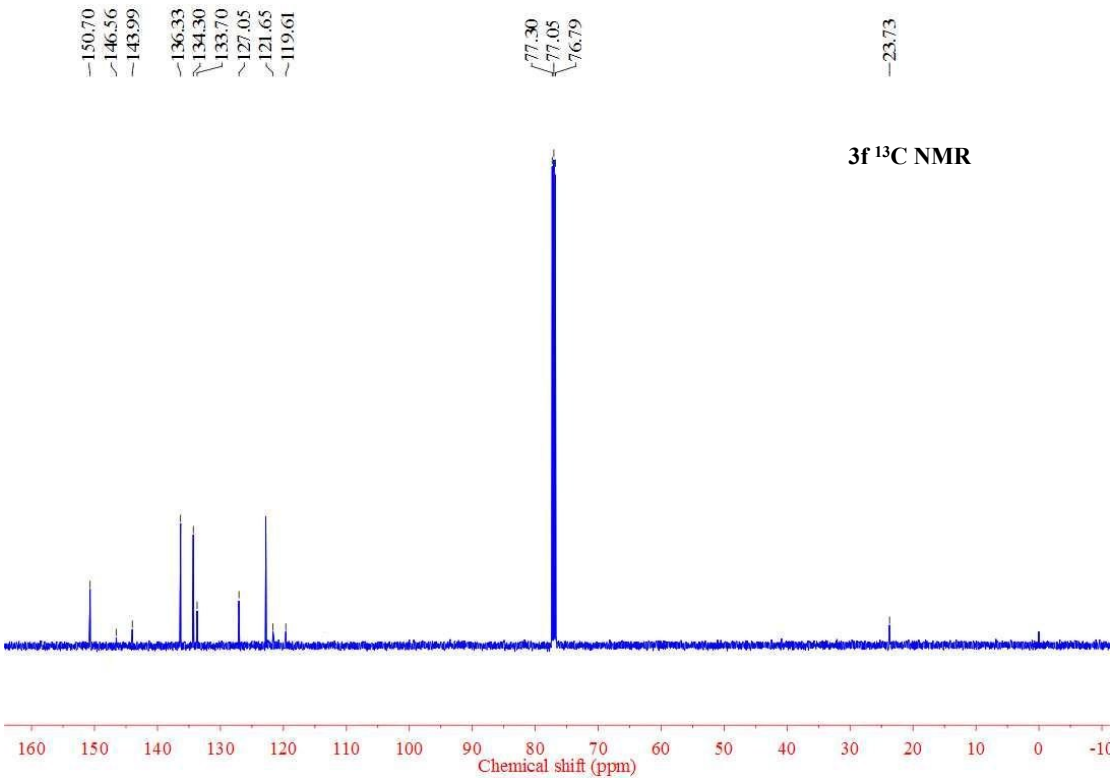

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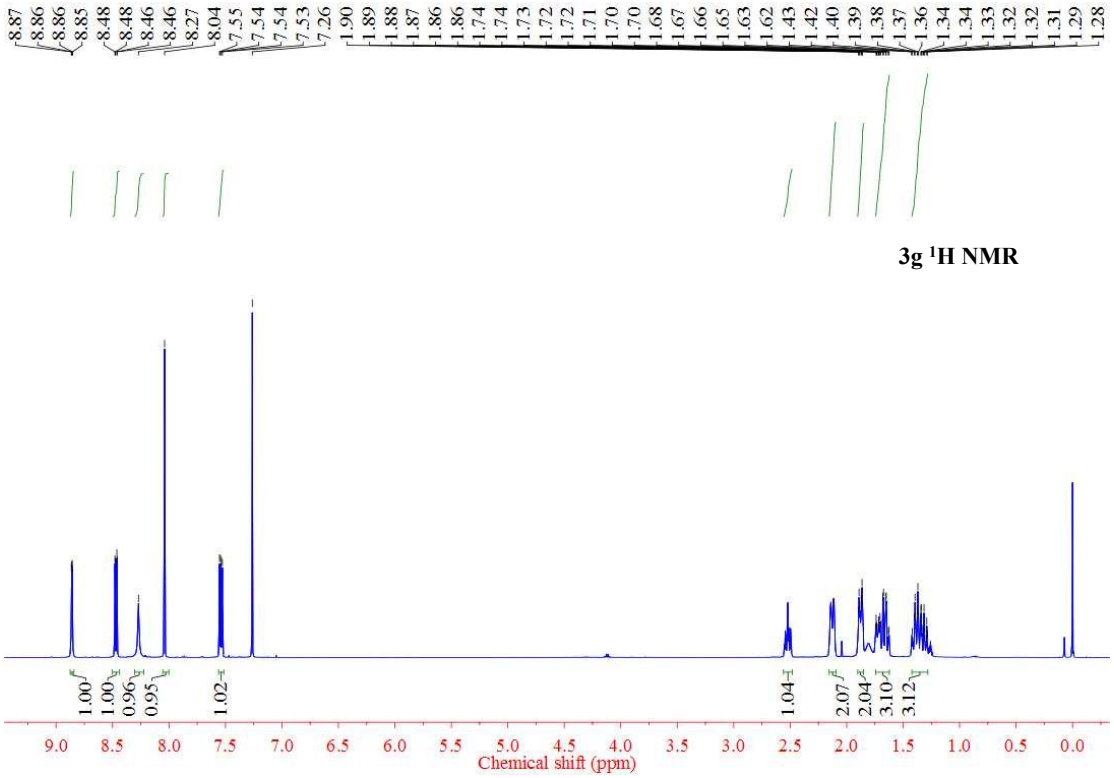

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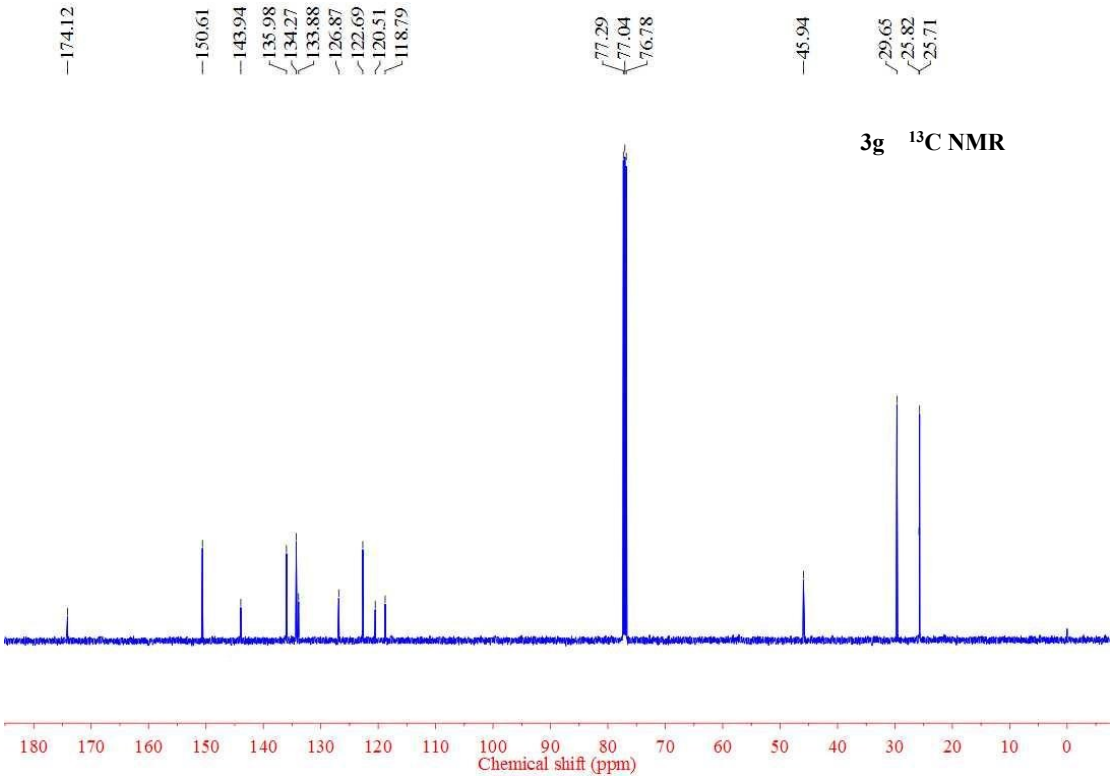

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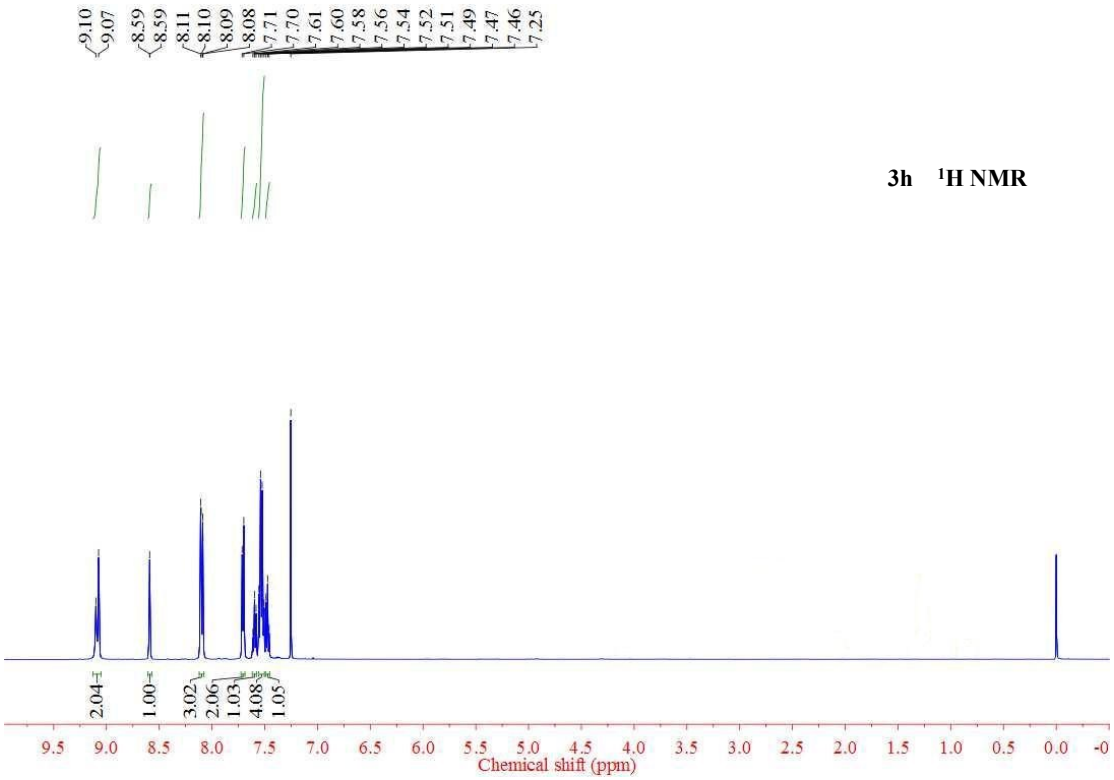

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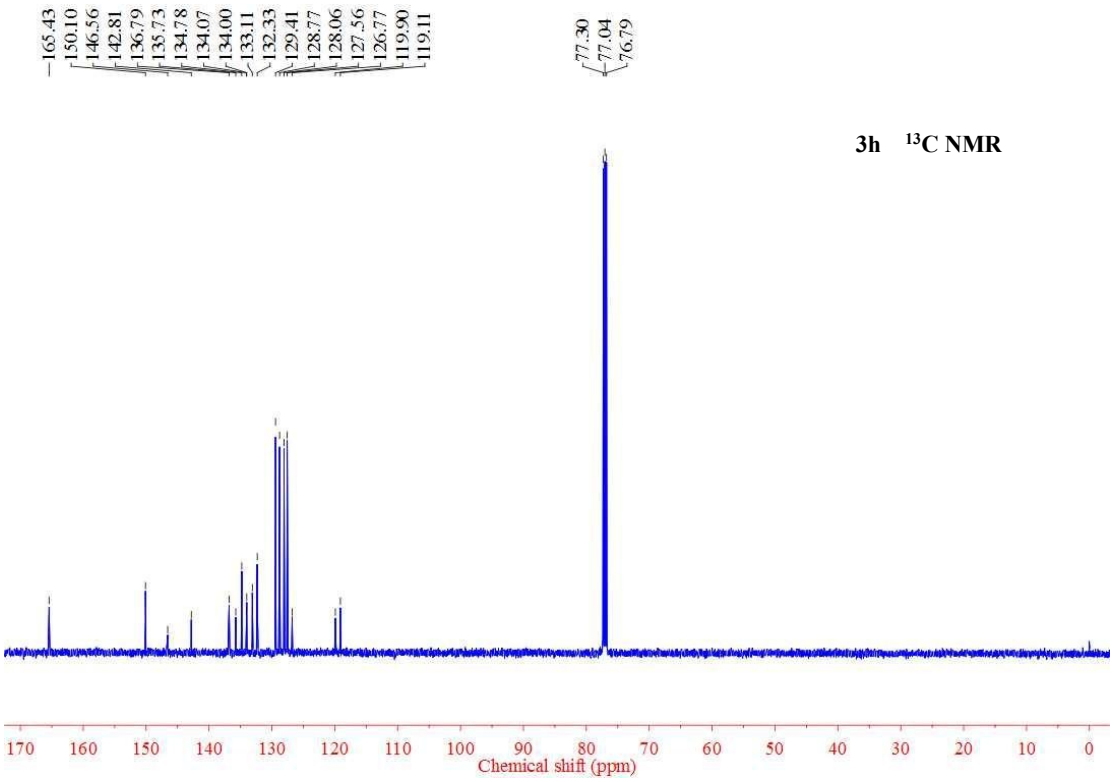

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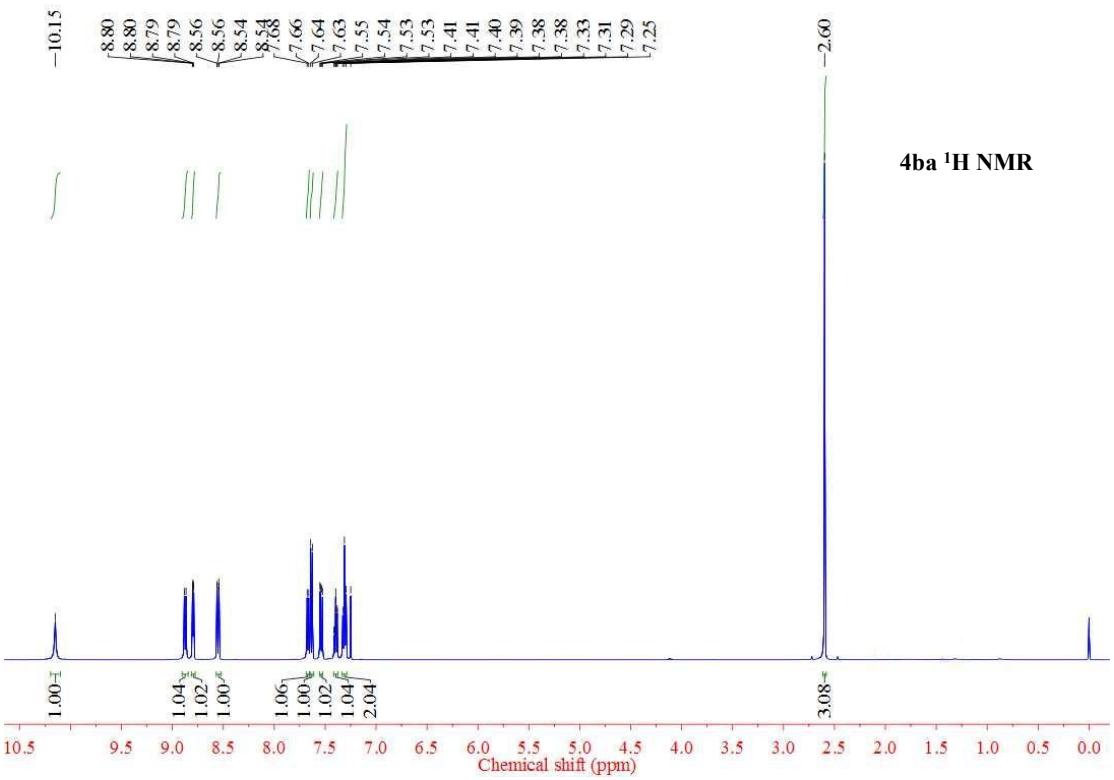

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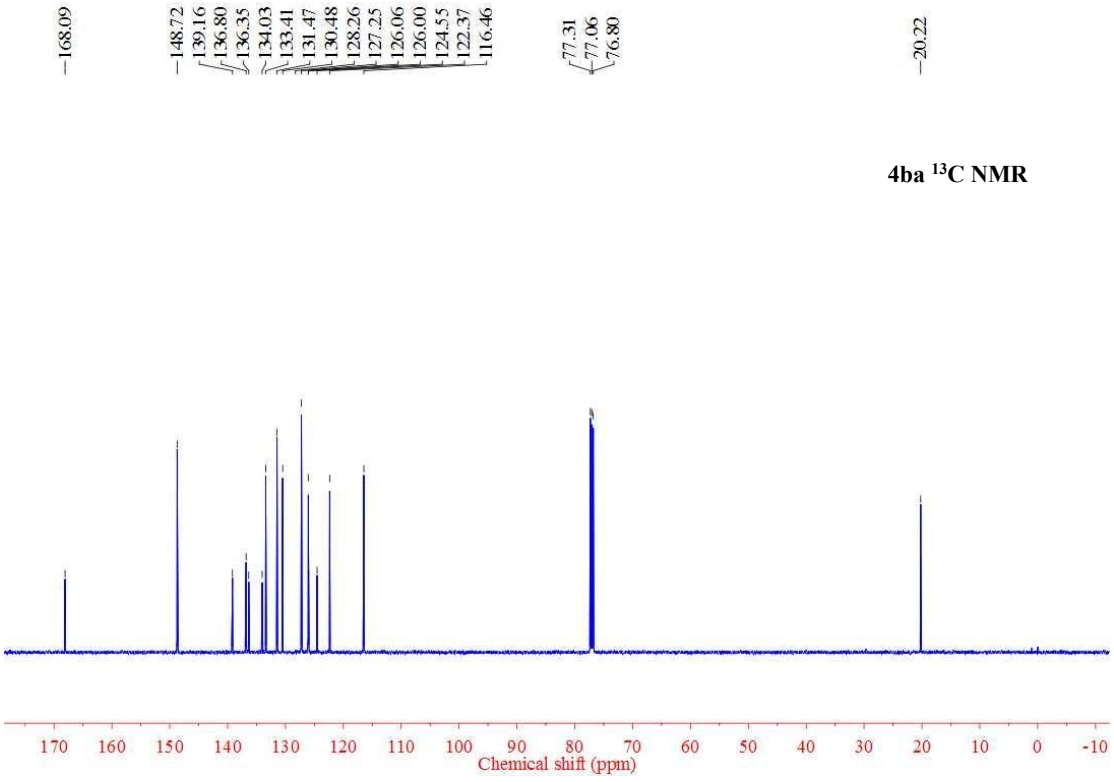

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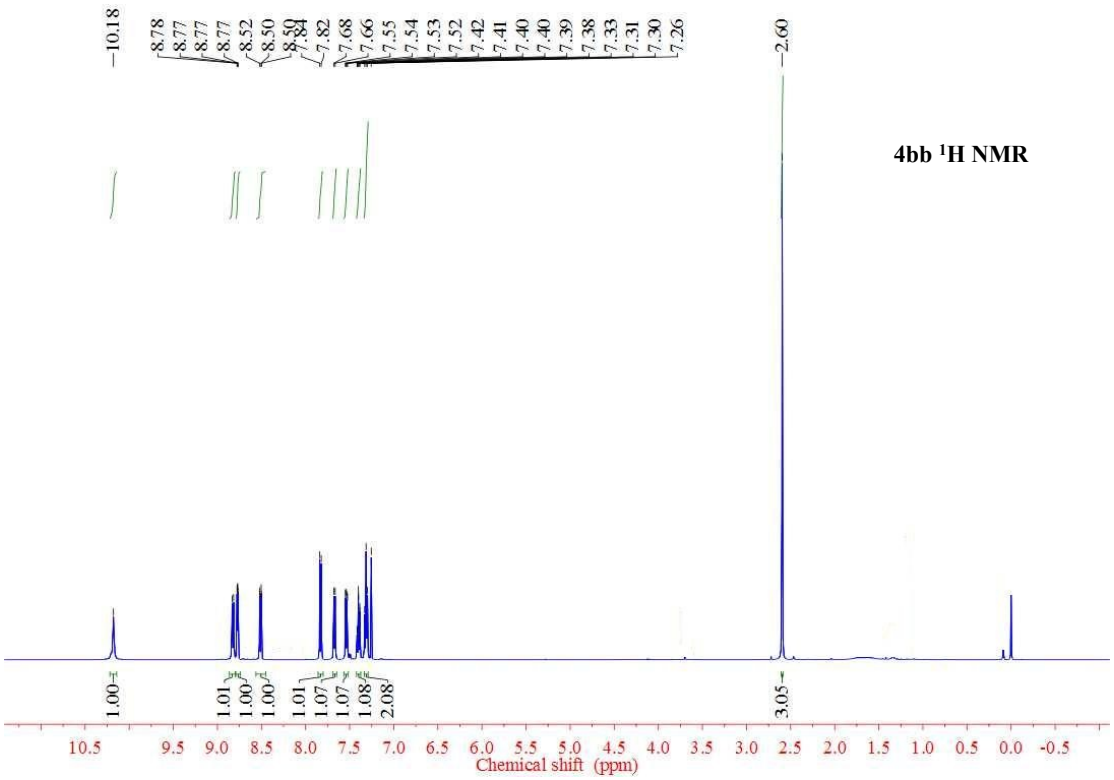

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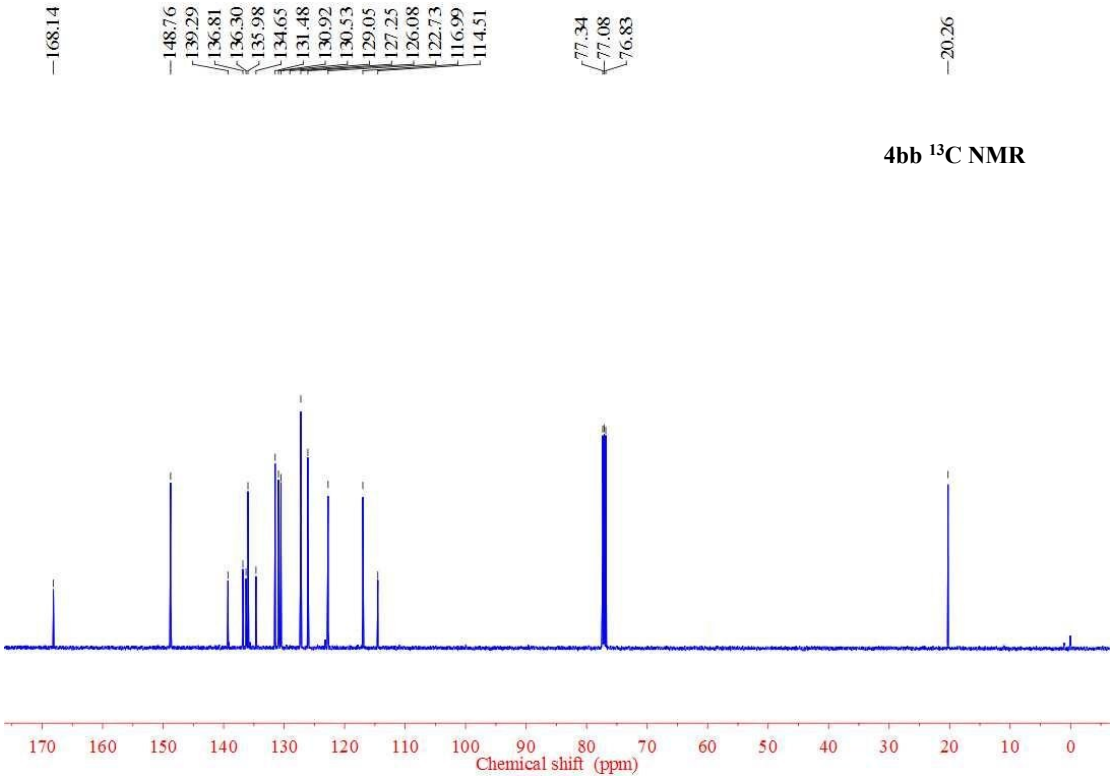

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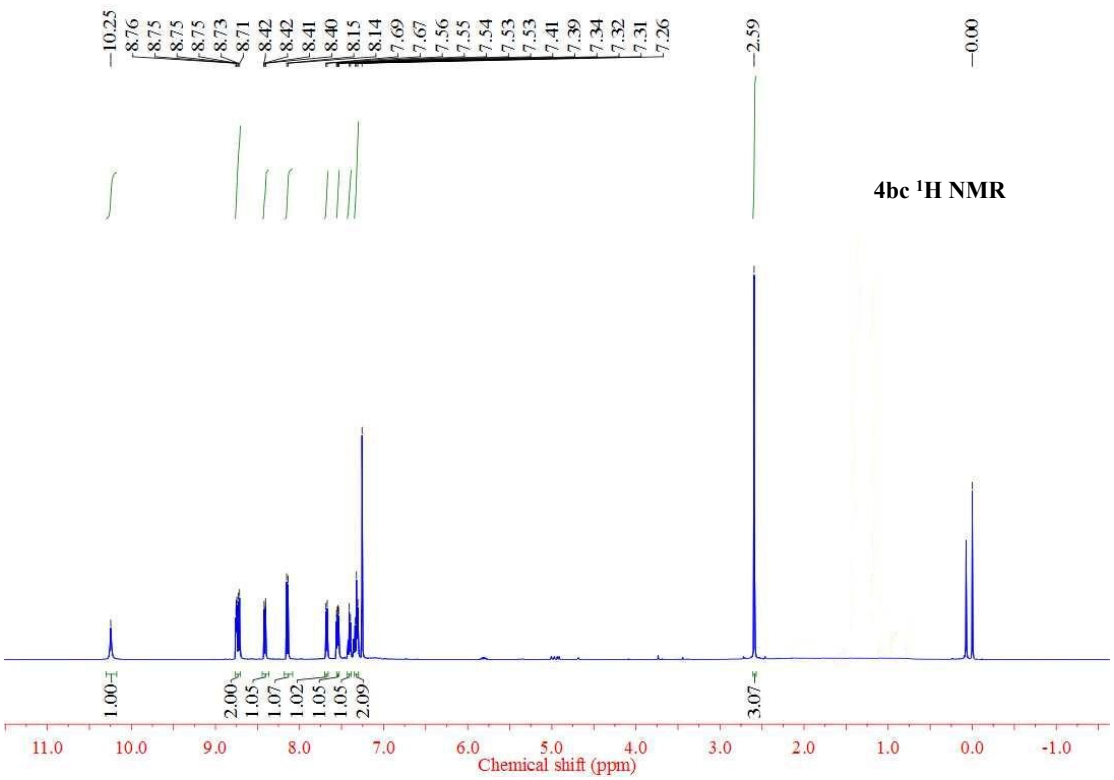

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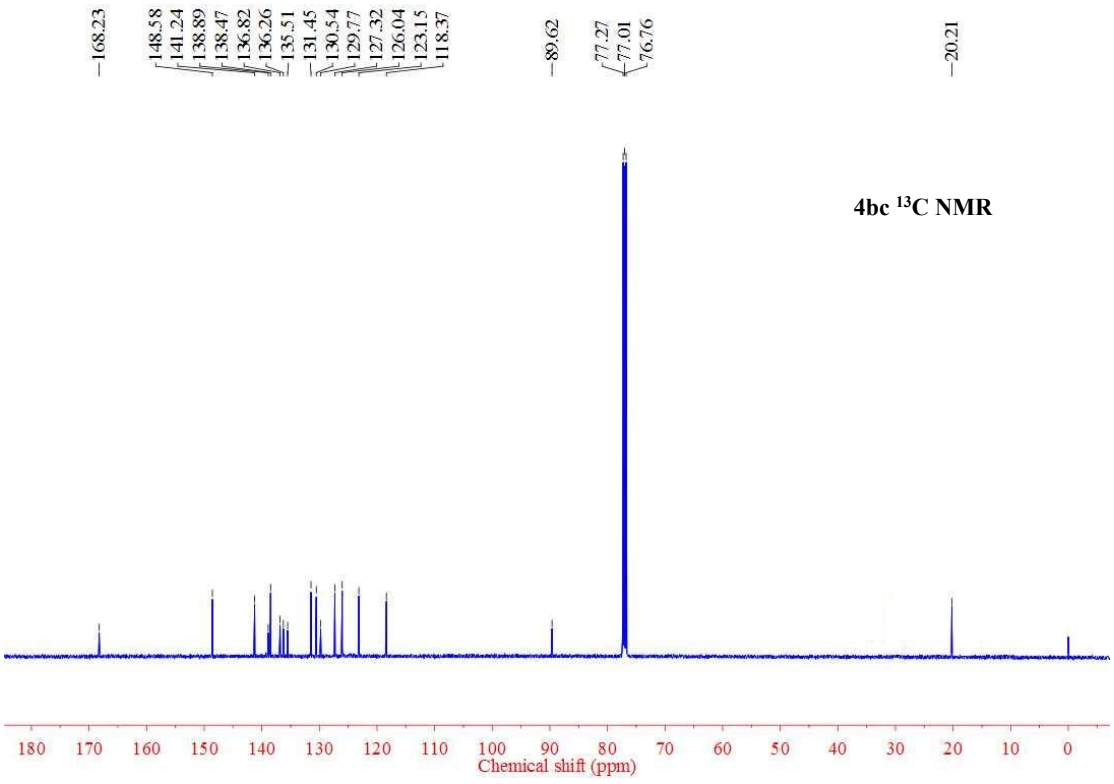

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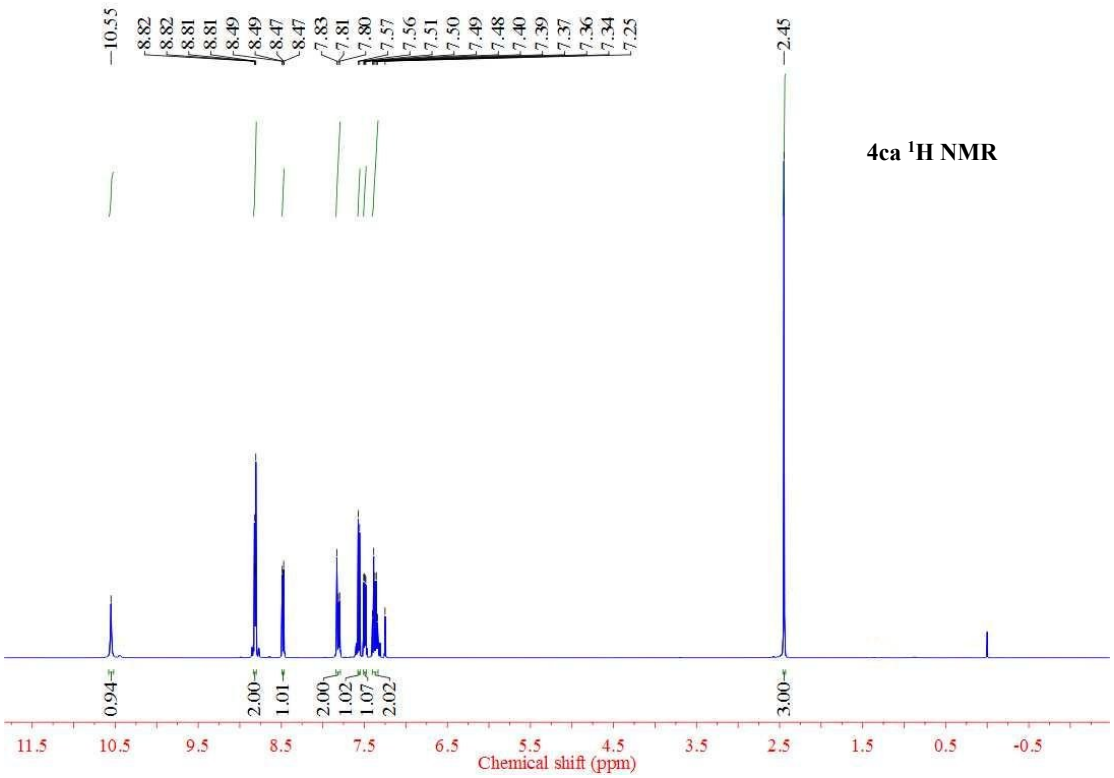

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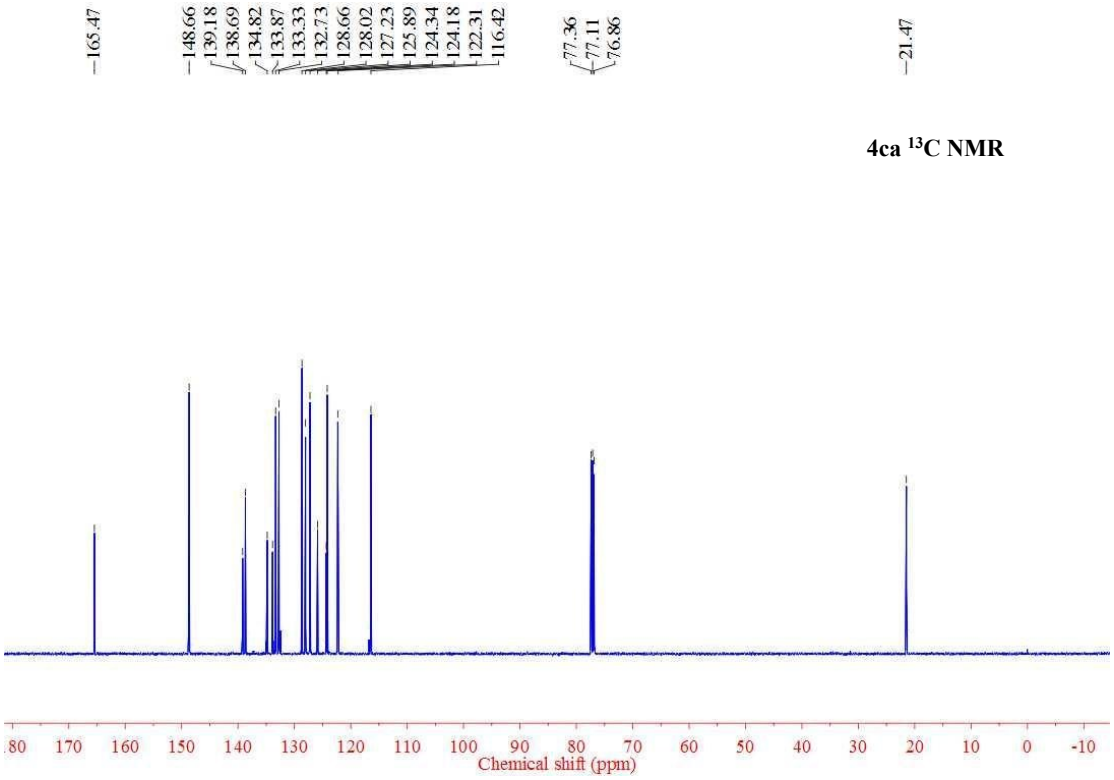

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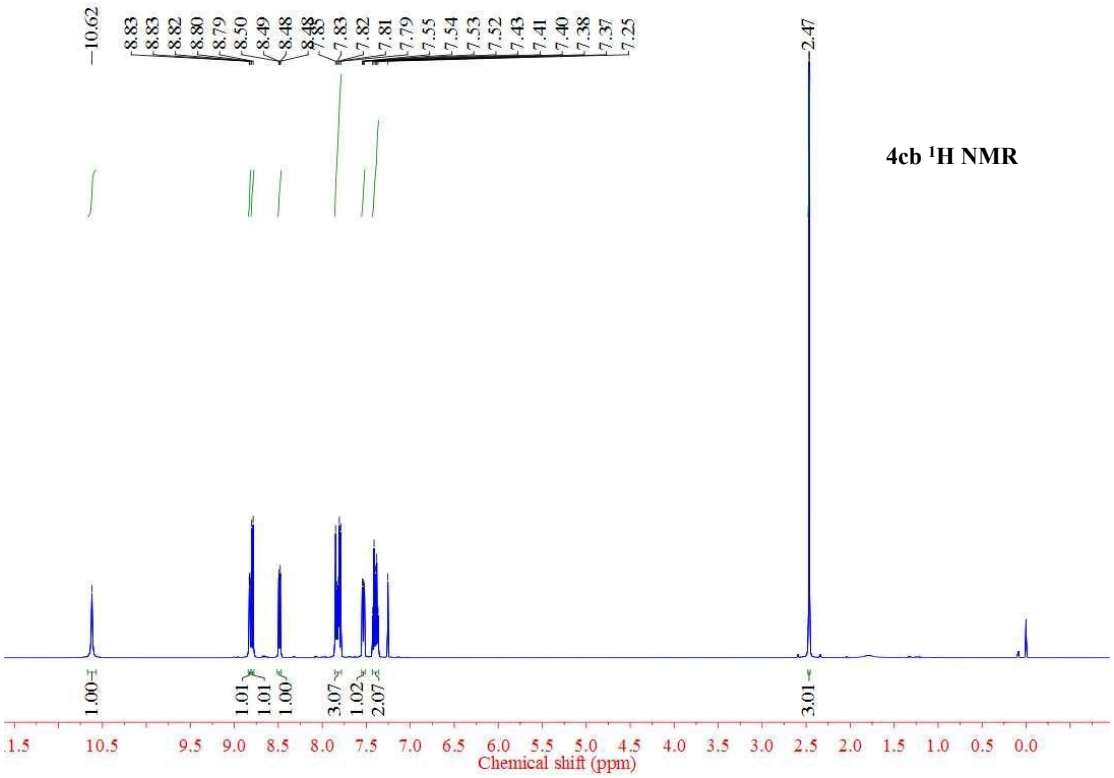

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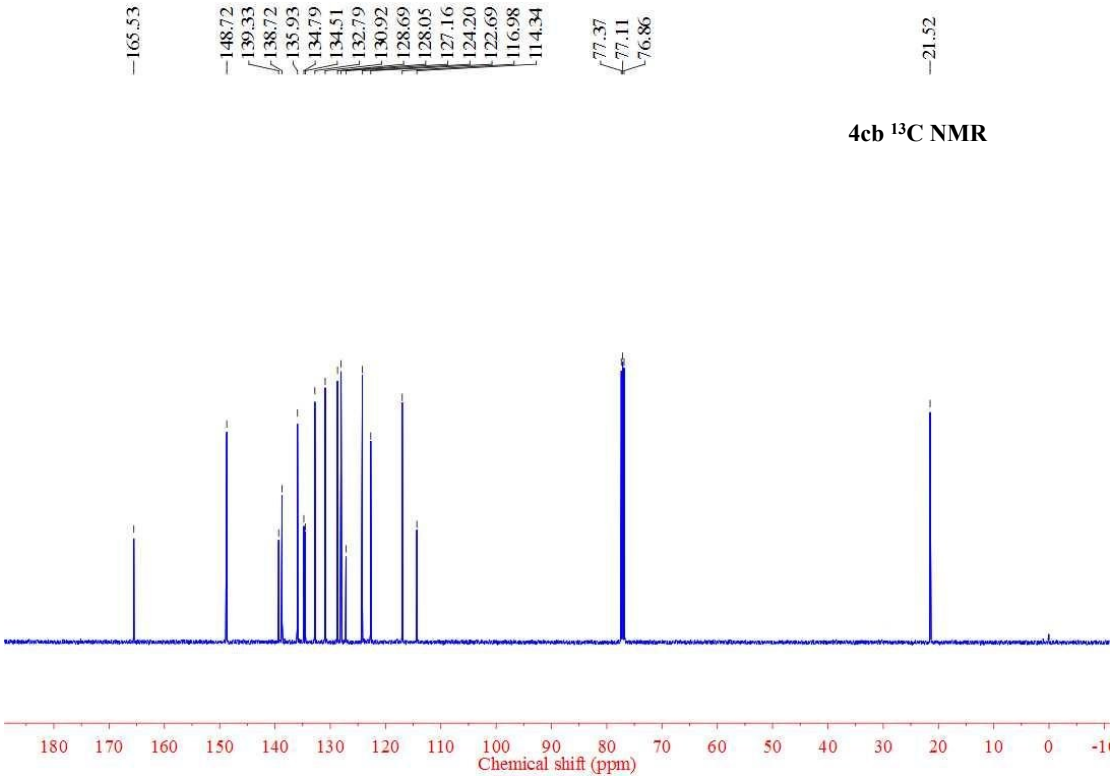

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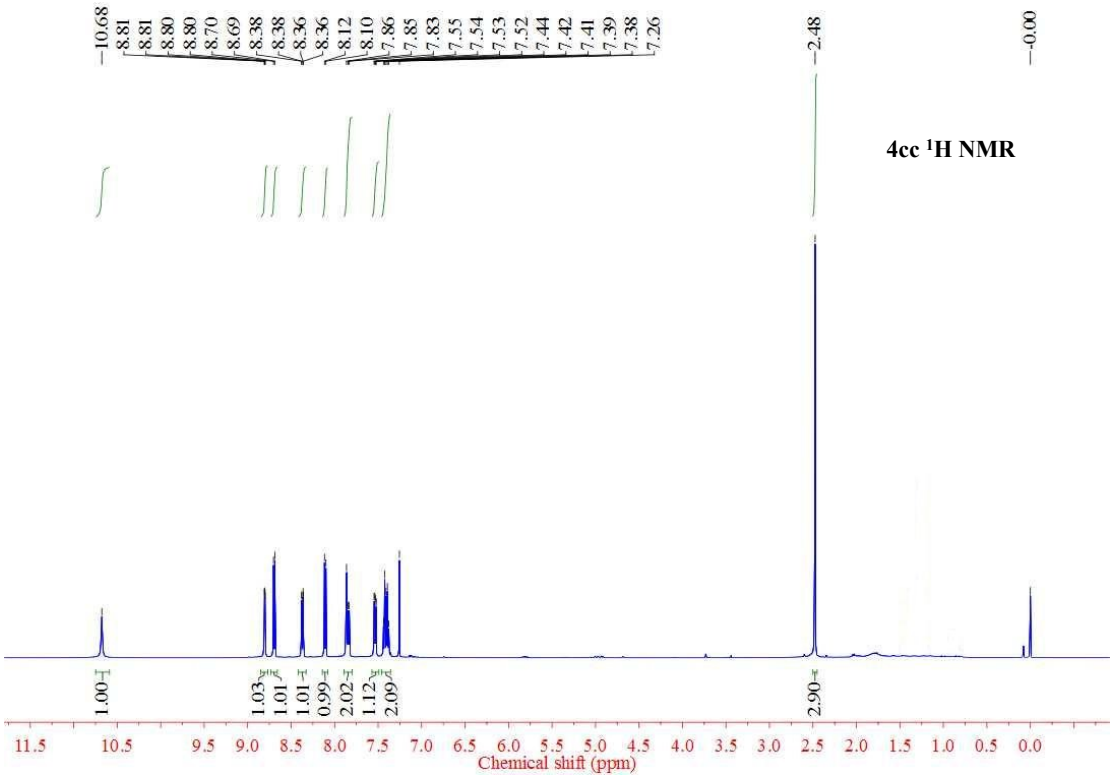

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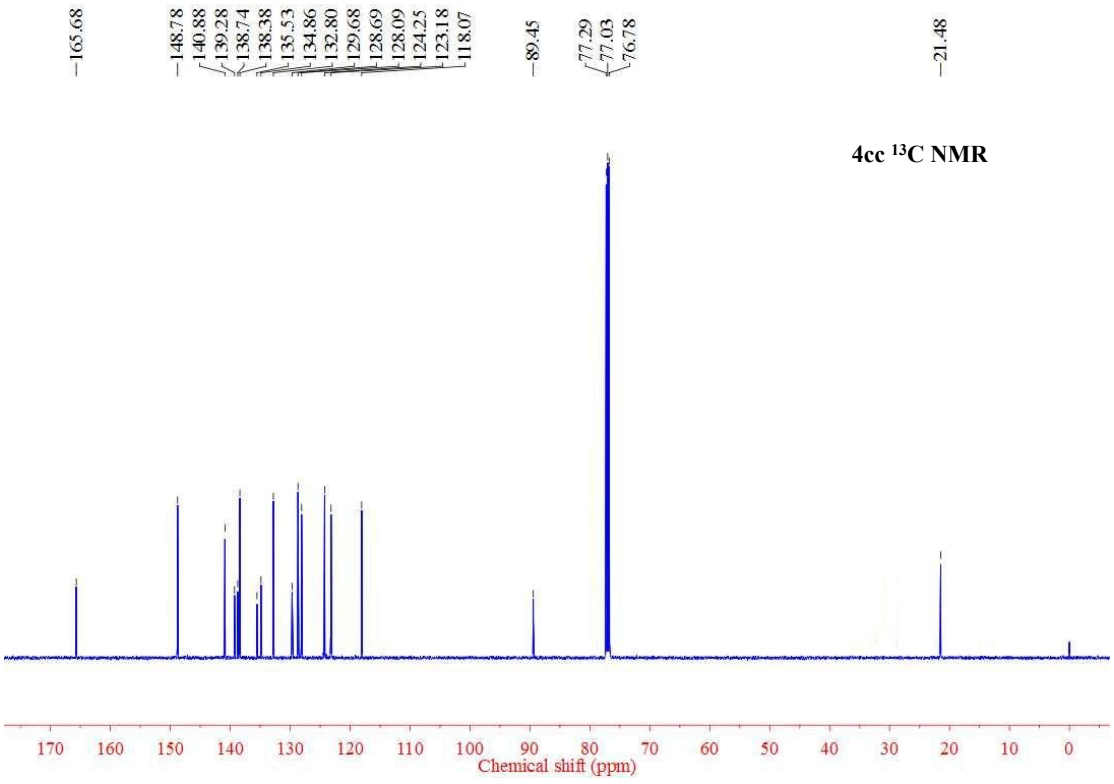

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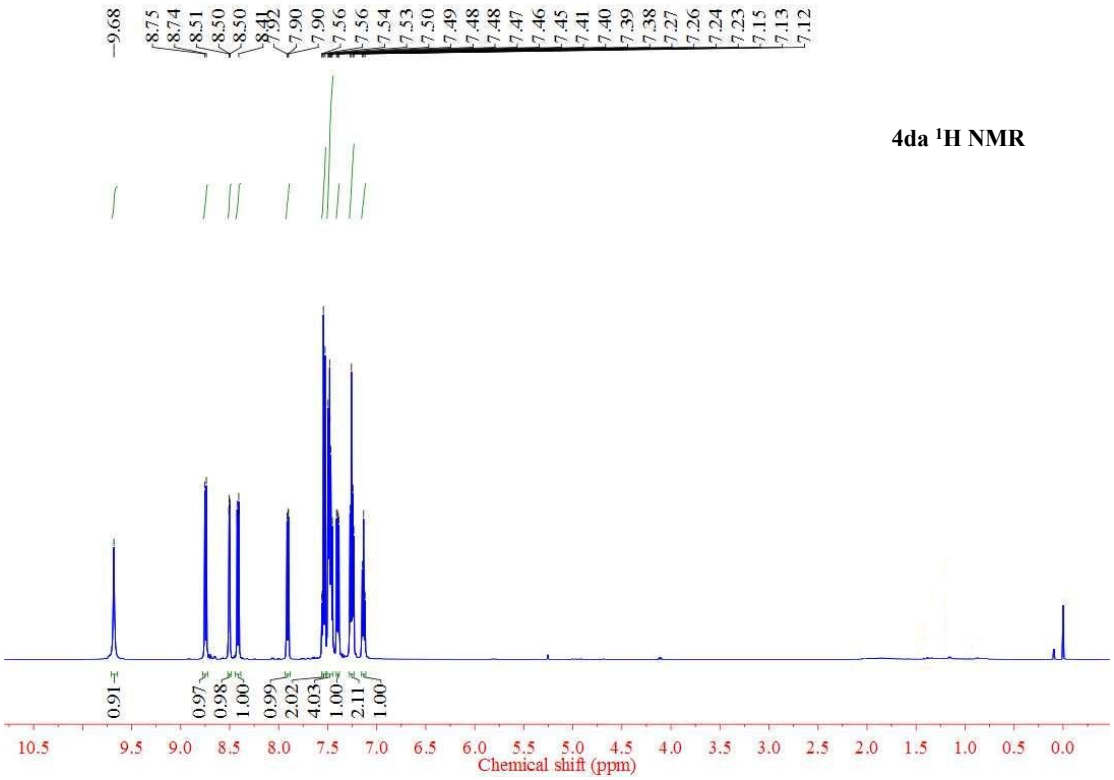

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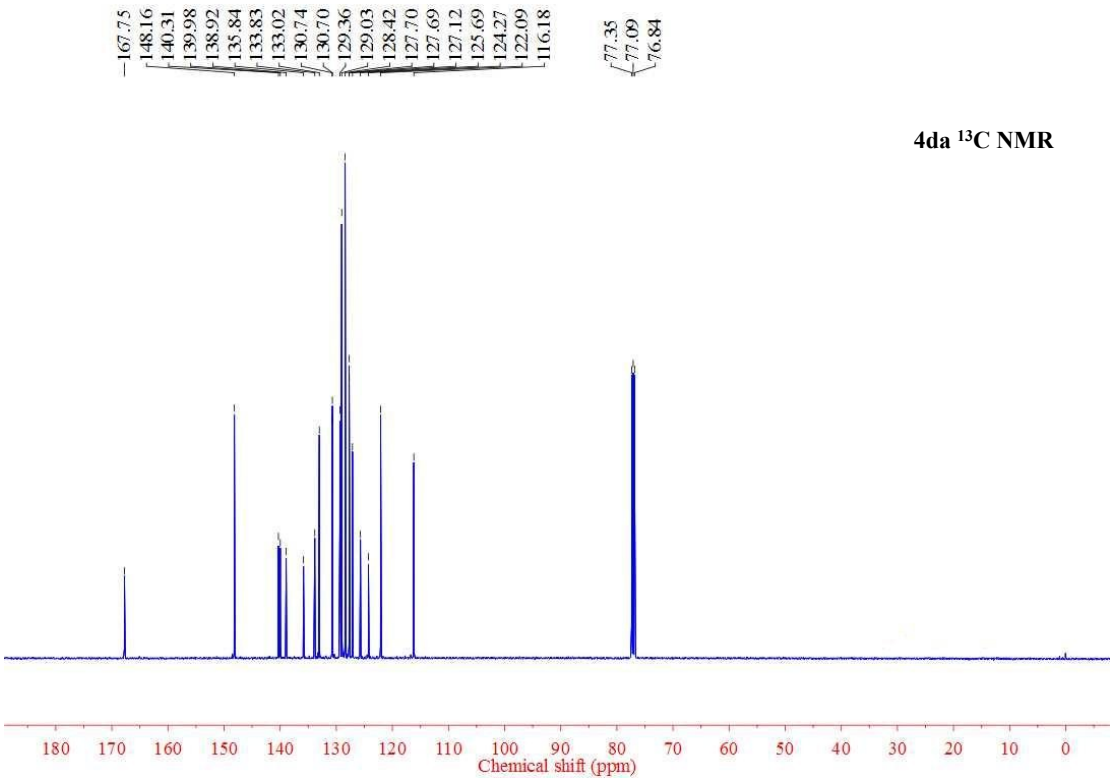

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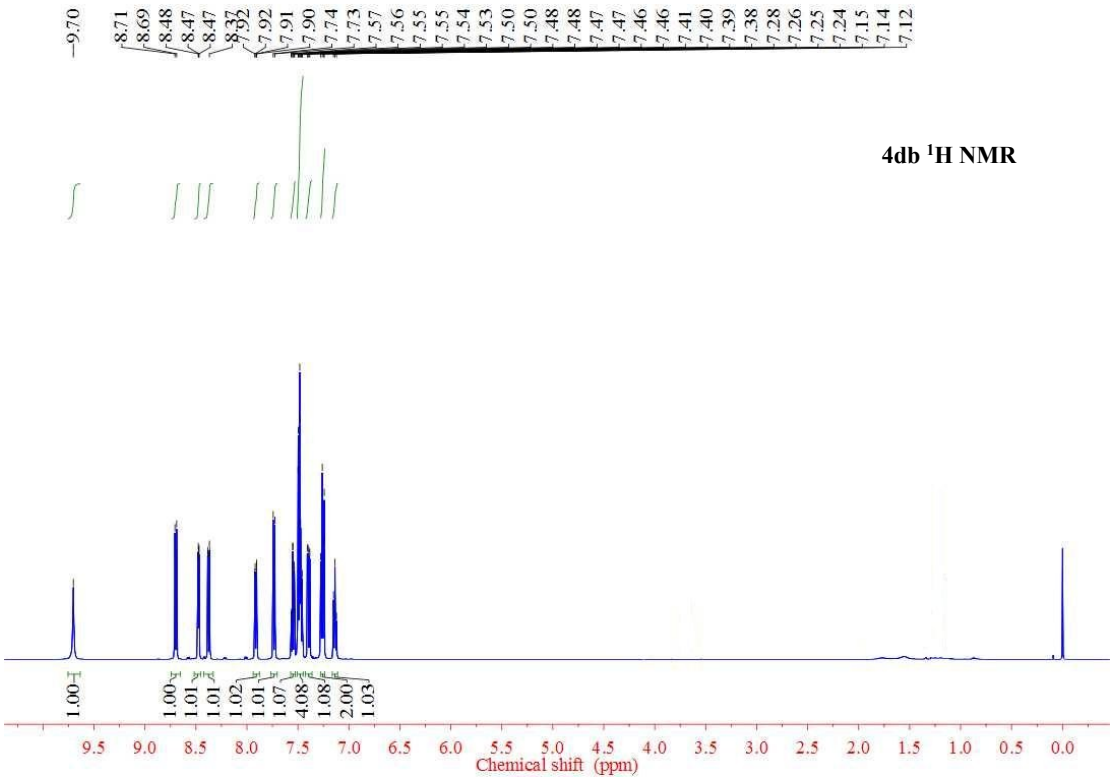

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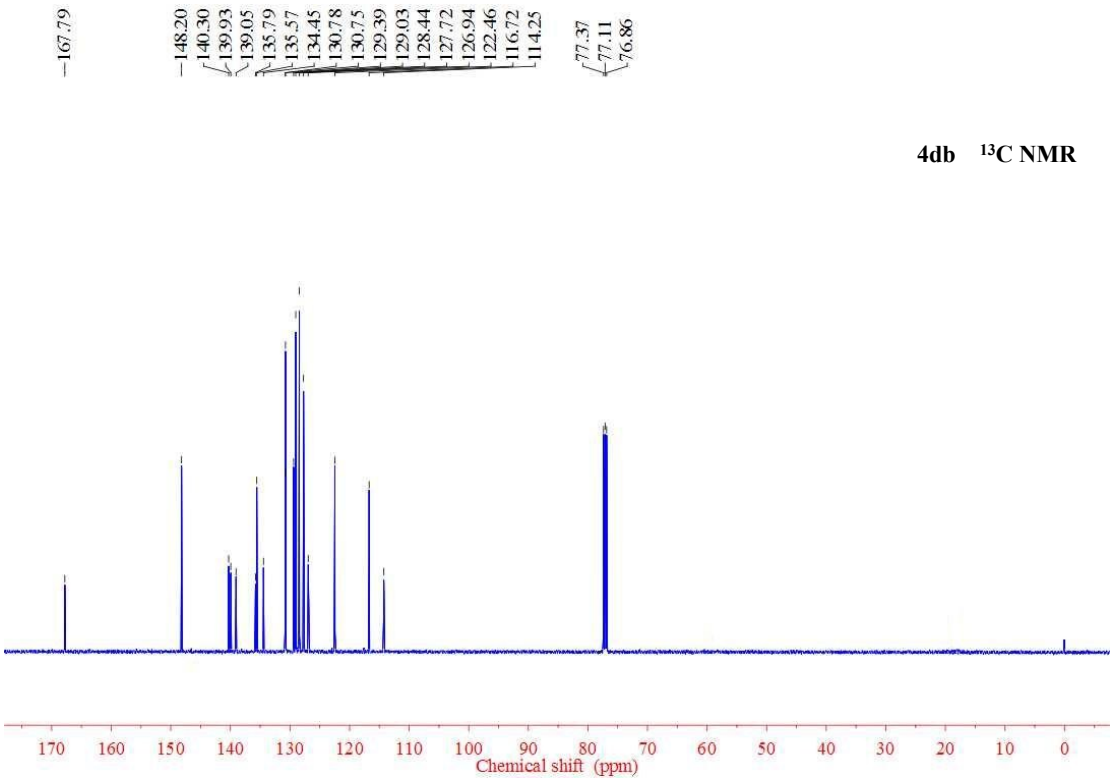

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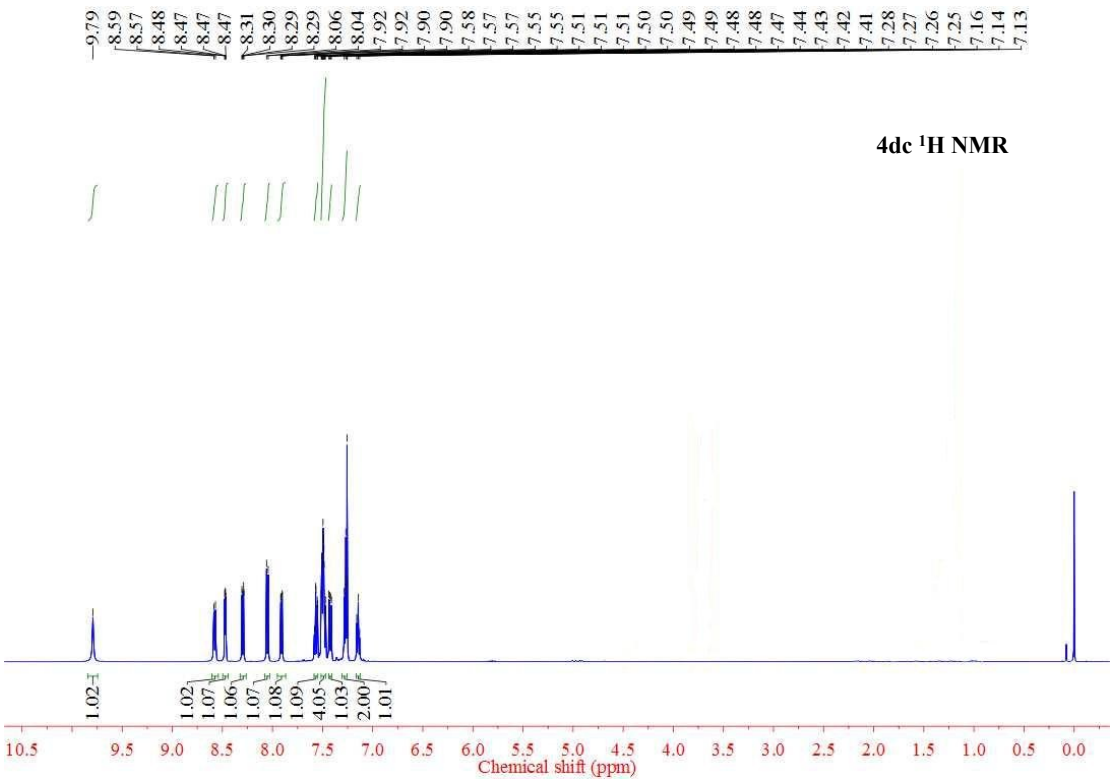

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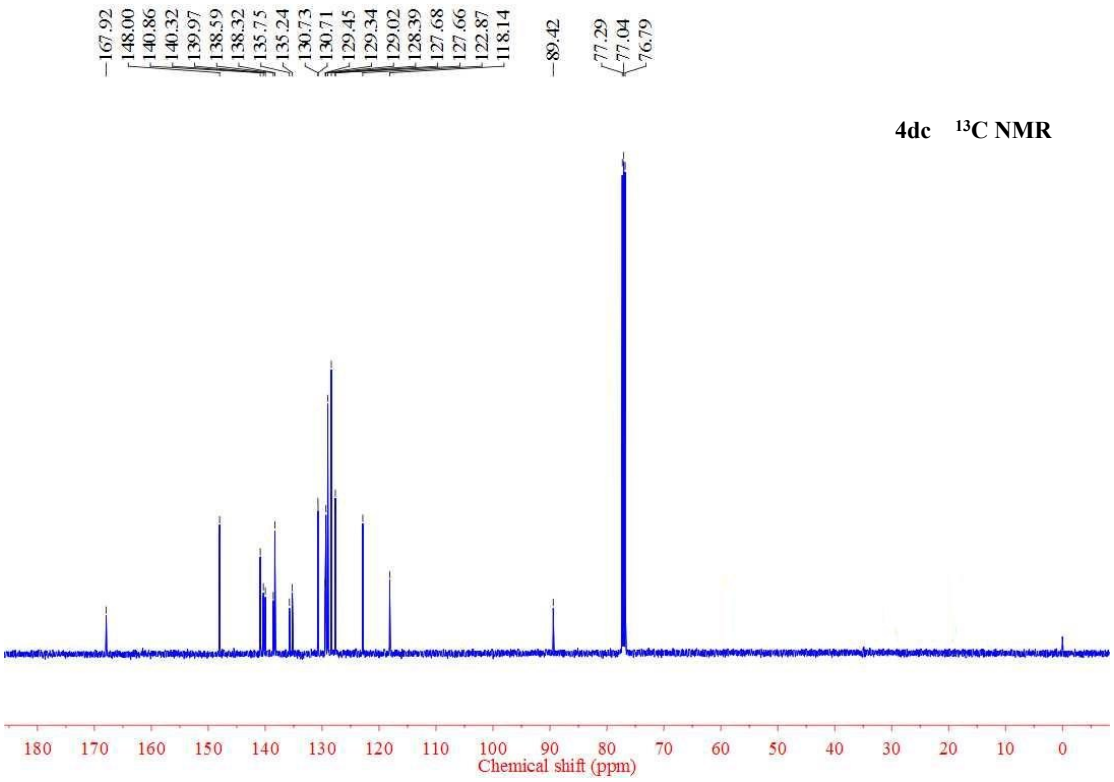
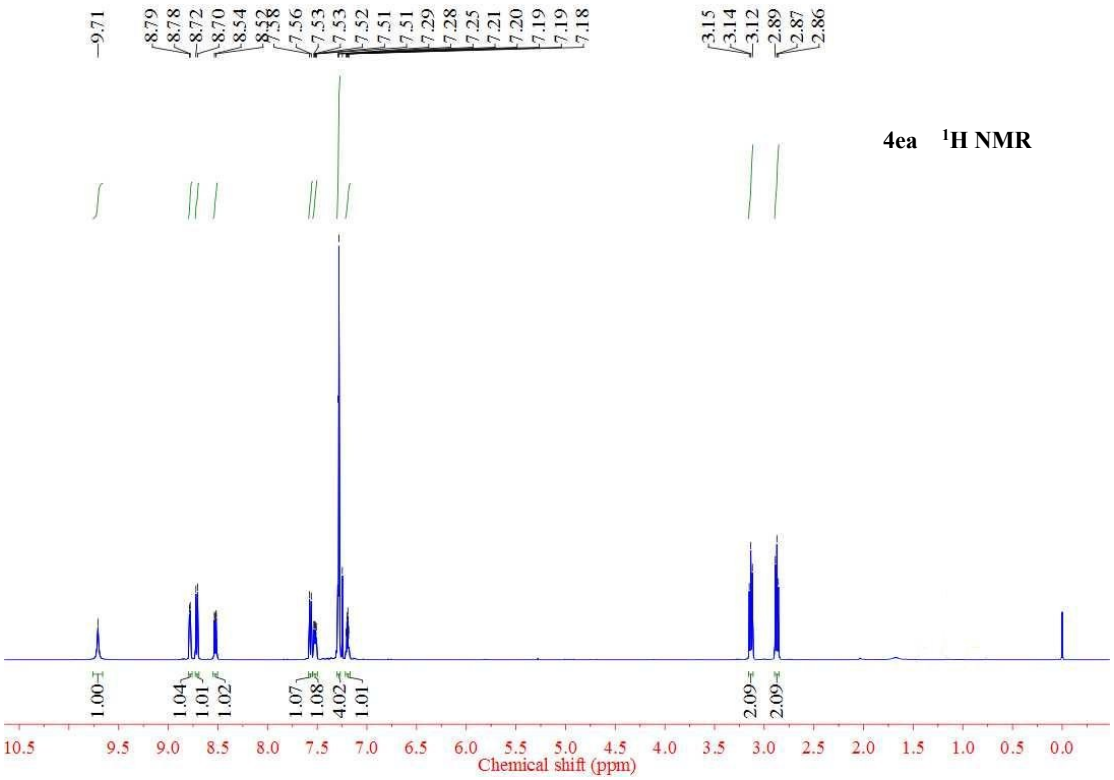
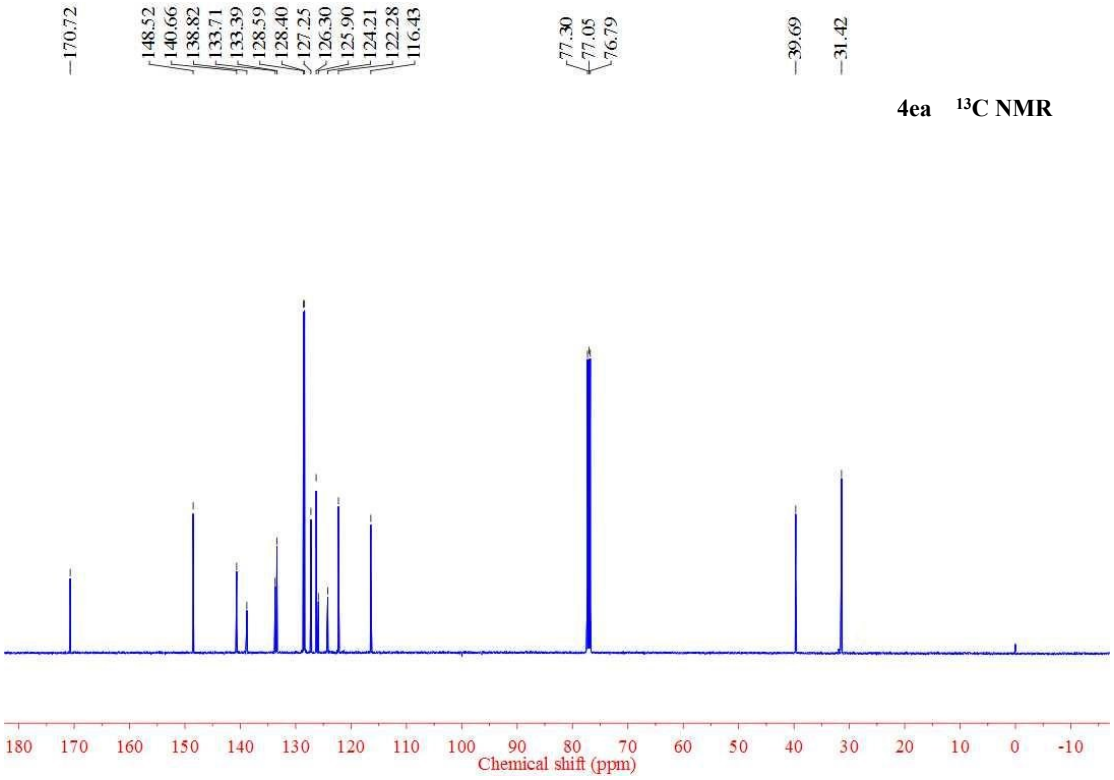


4dc ^{13}C NMR

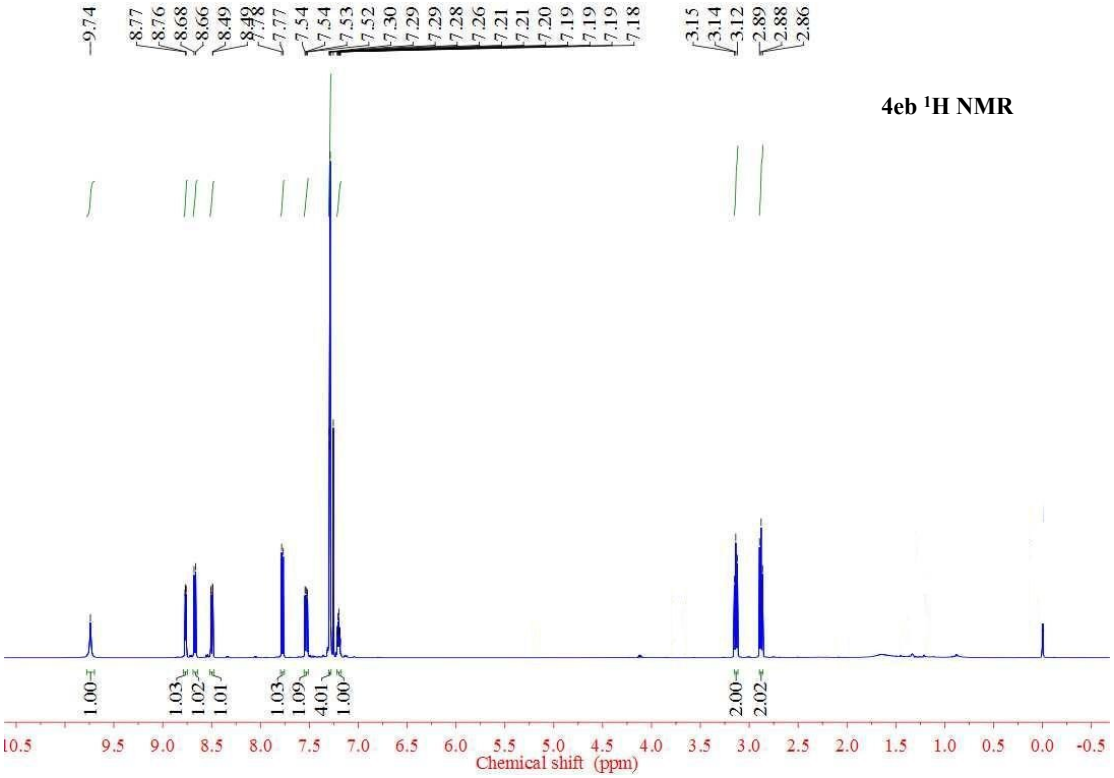


4ea ^{1}H NMR

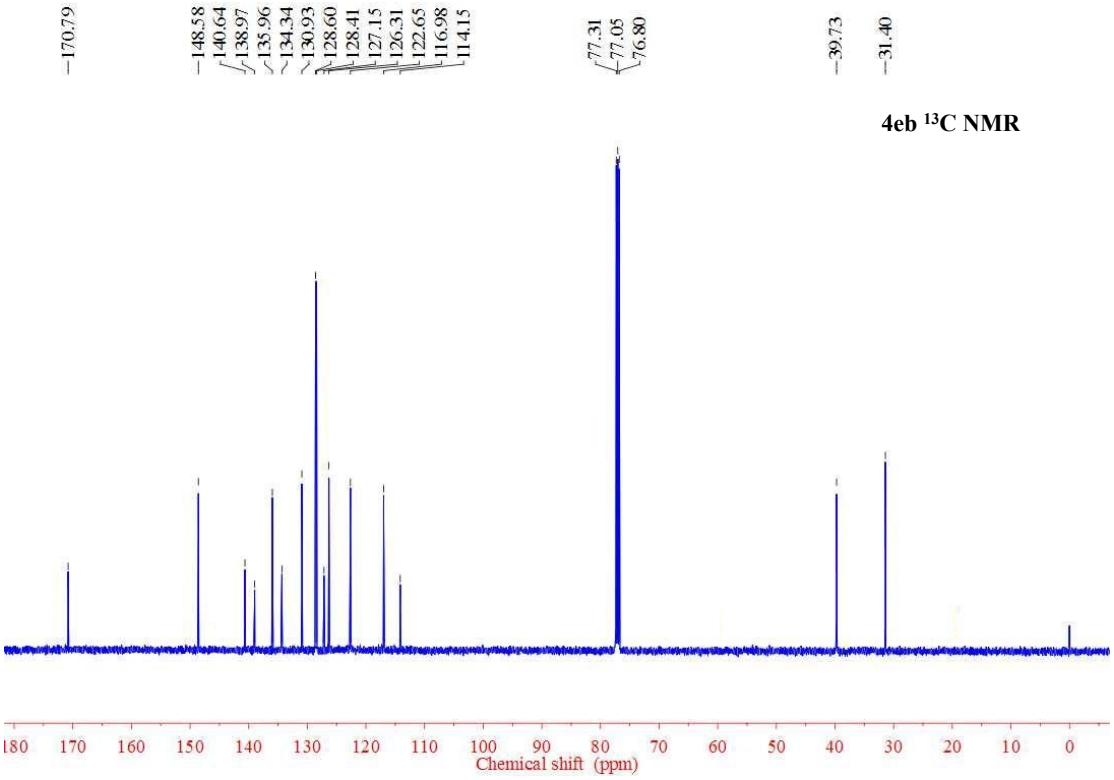


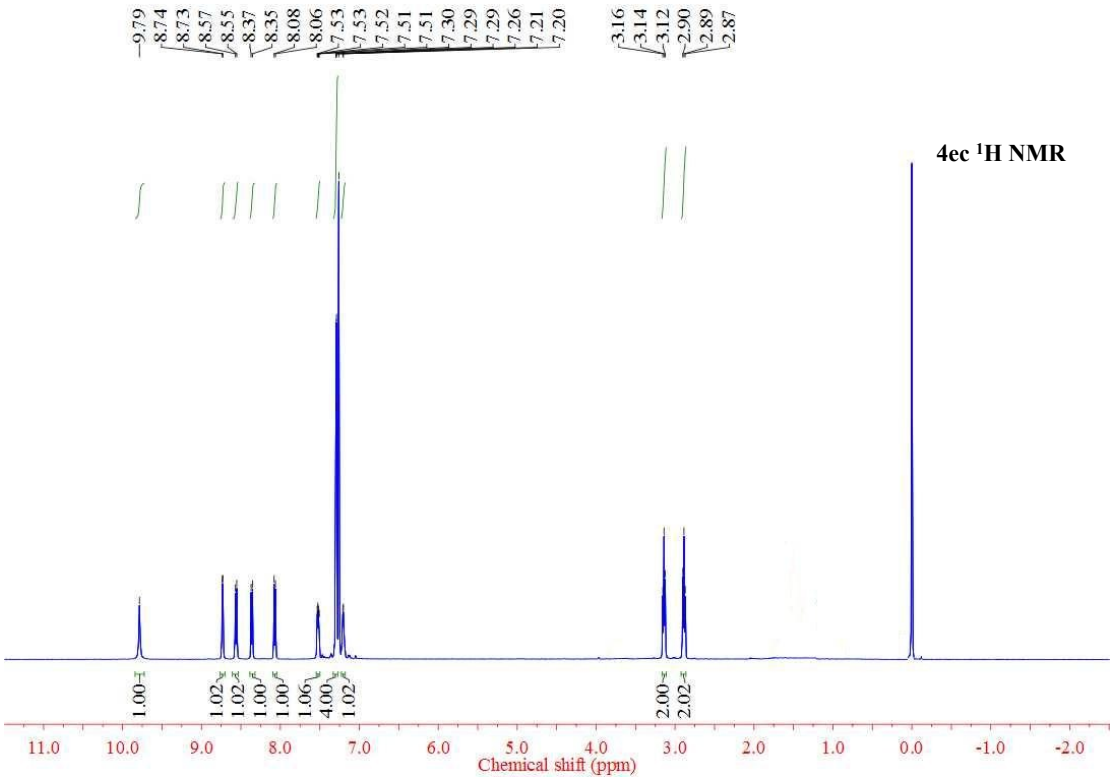
4ea ^{13}C NMR

4eb ^{1}H NMR

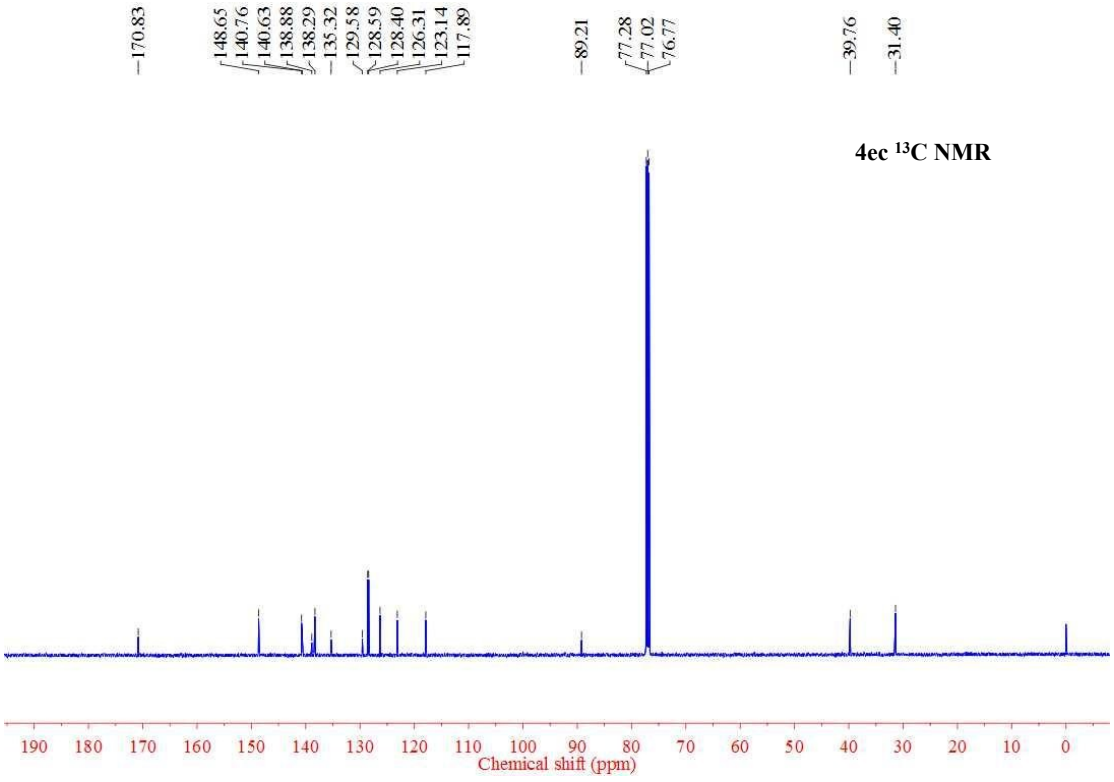


4eb ^{13}C NMR

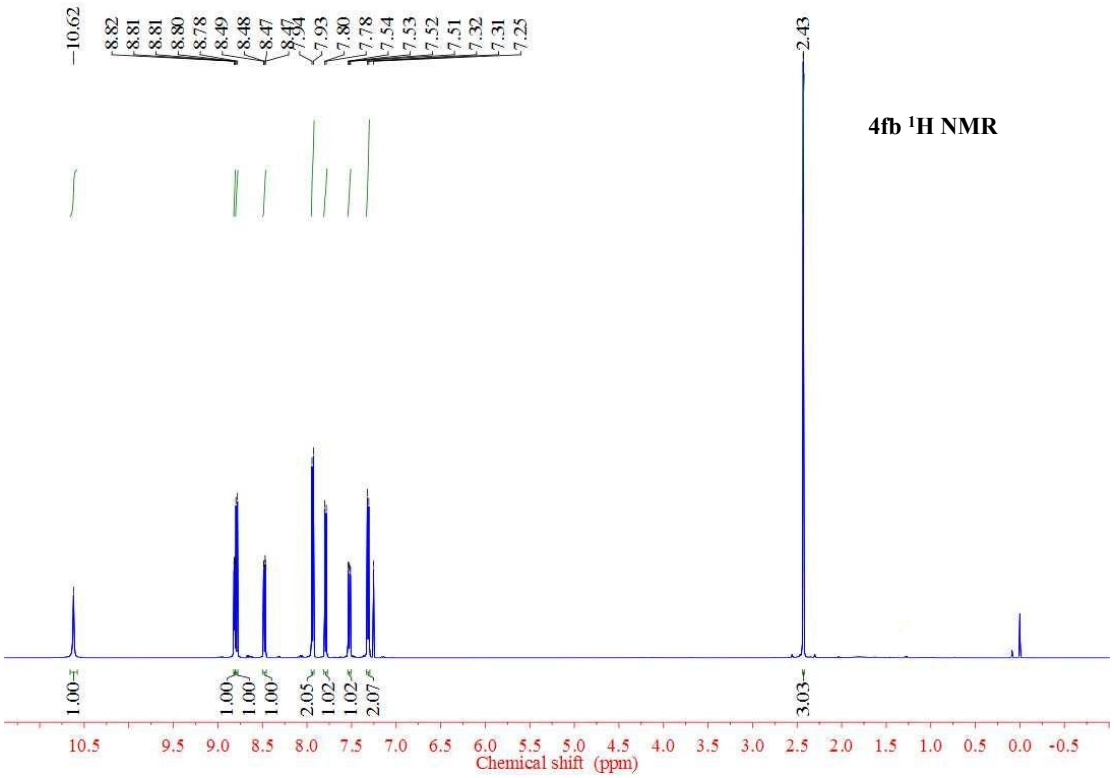




4ec ^{1}H NMR



4ec ^{13}C NMR



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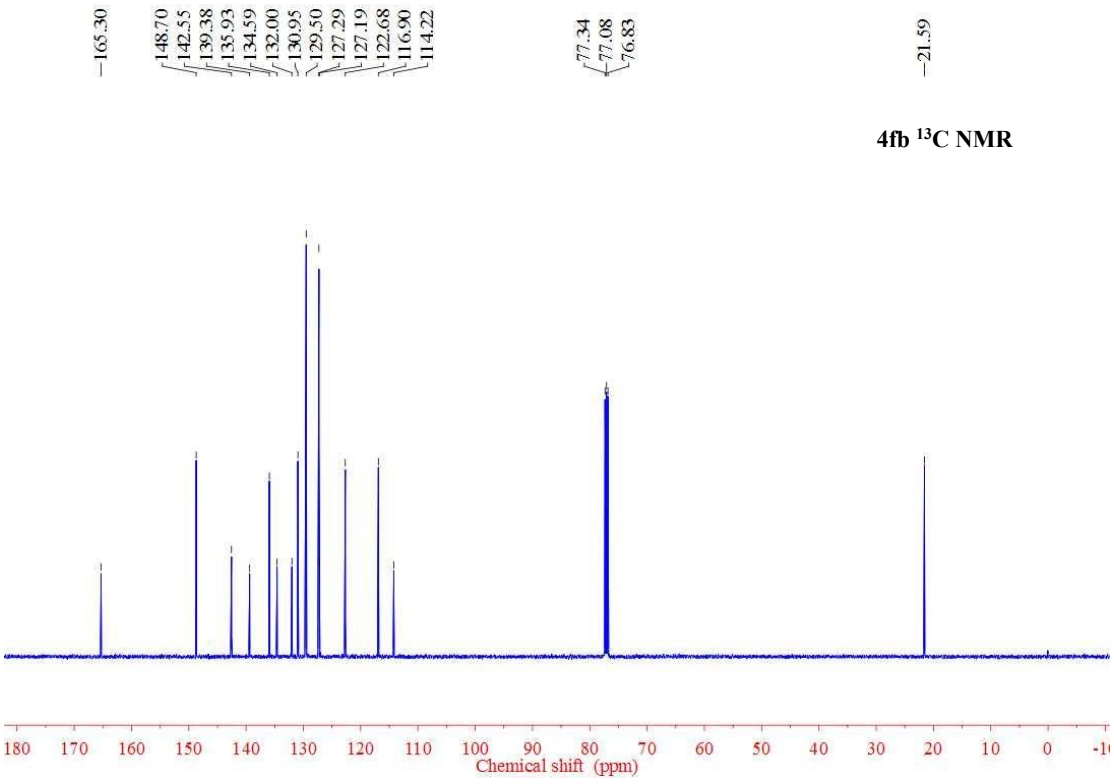

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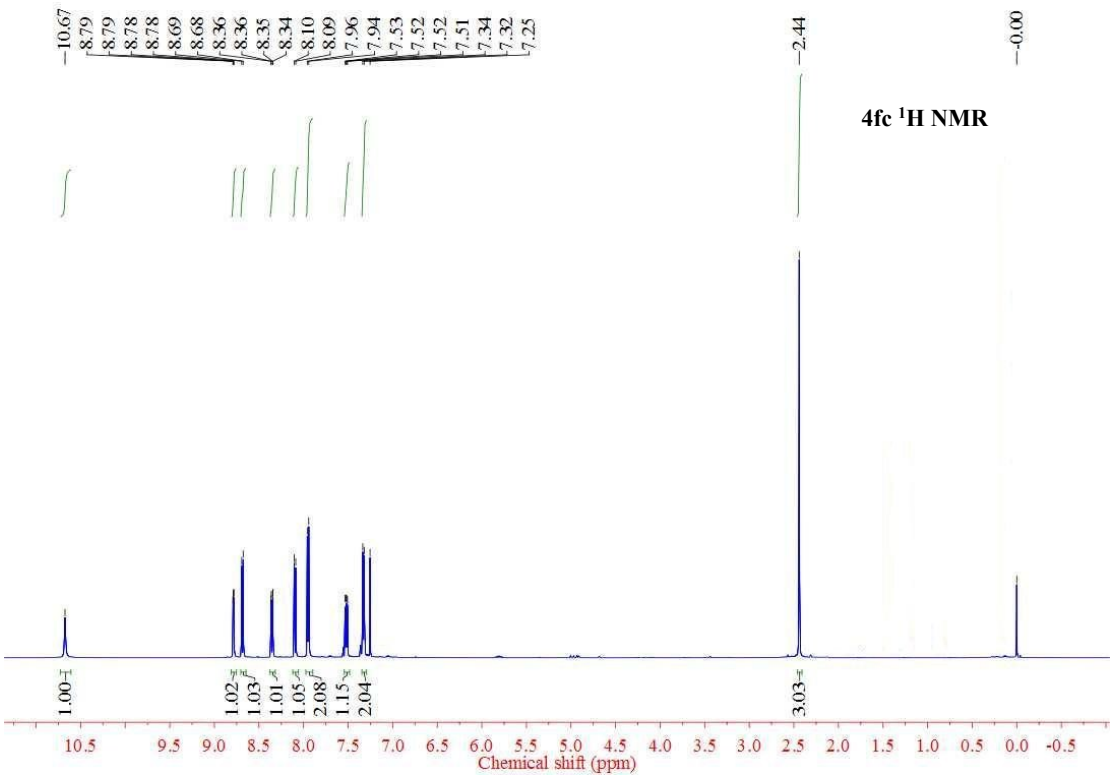

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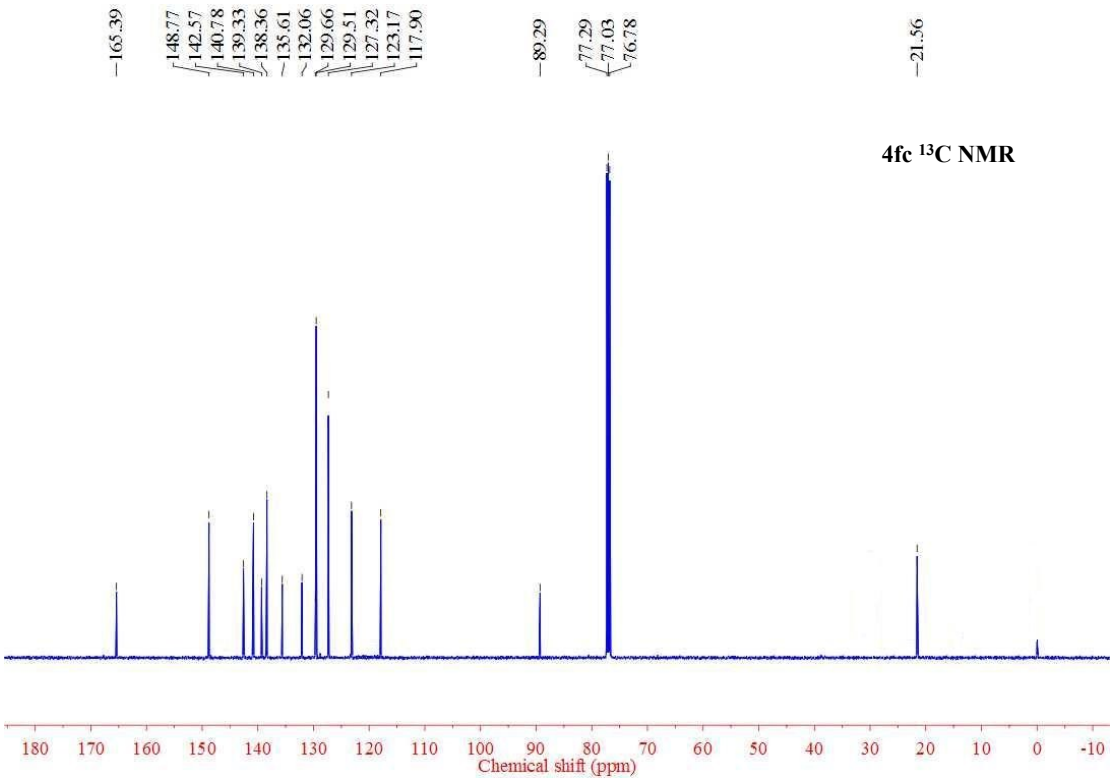

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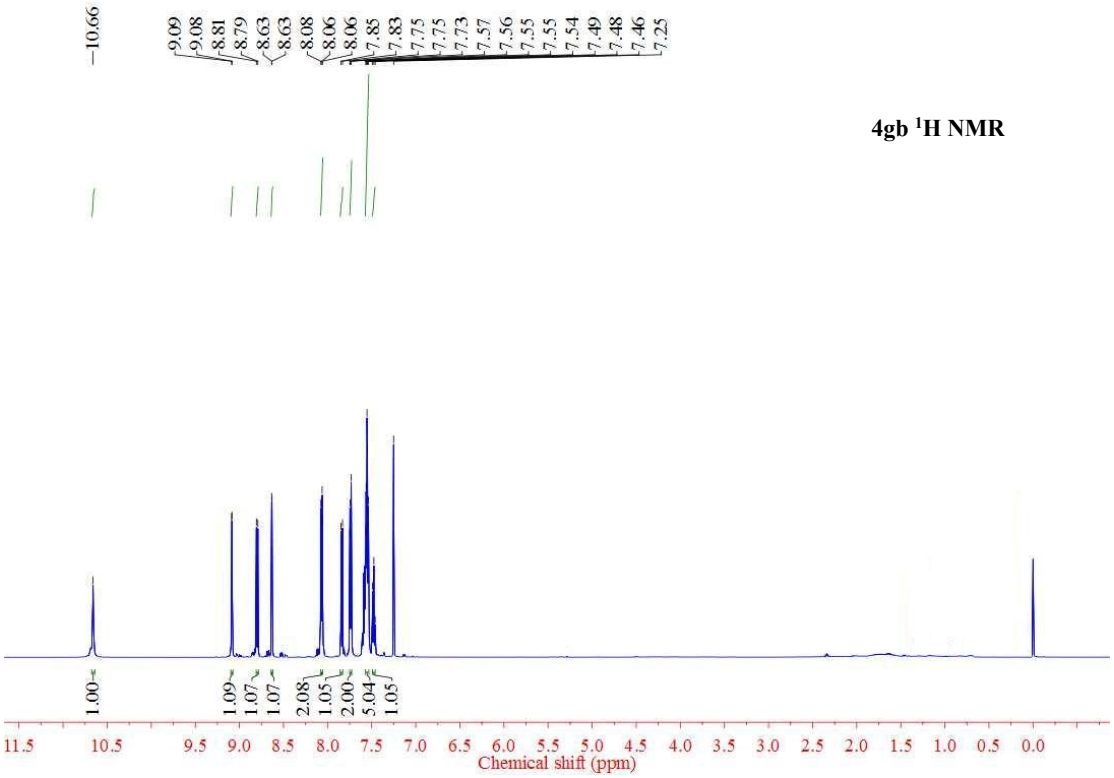
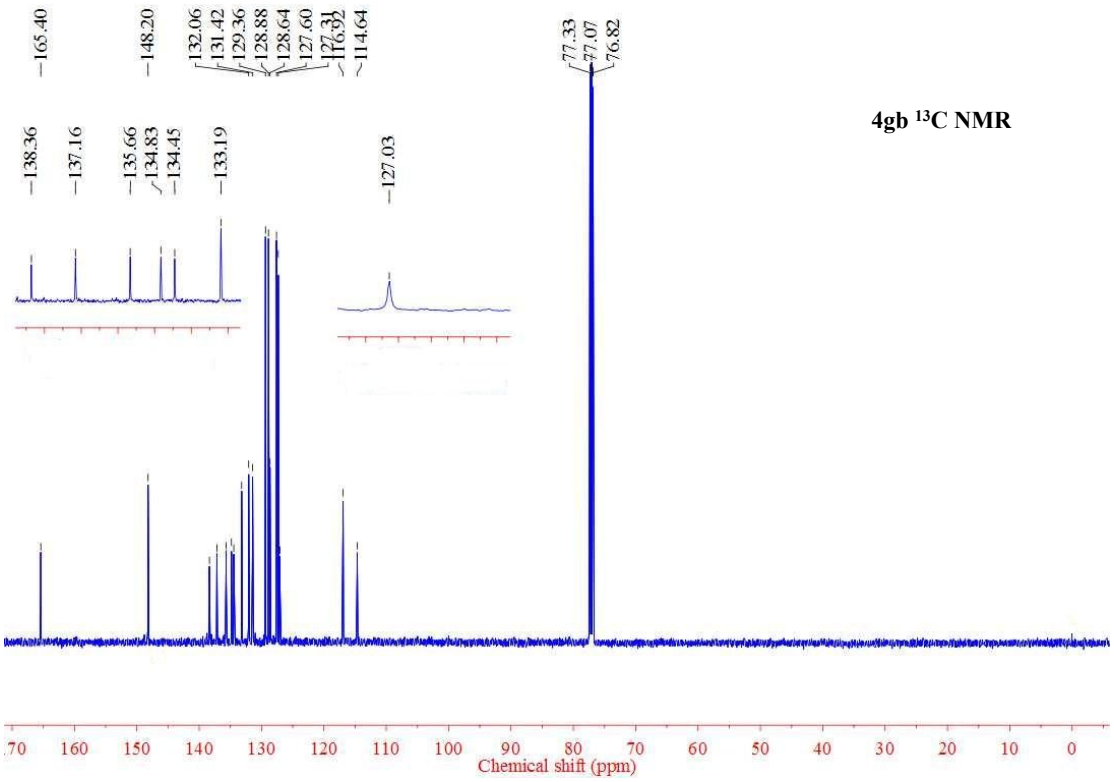


4gb ^{1}H NMR



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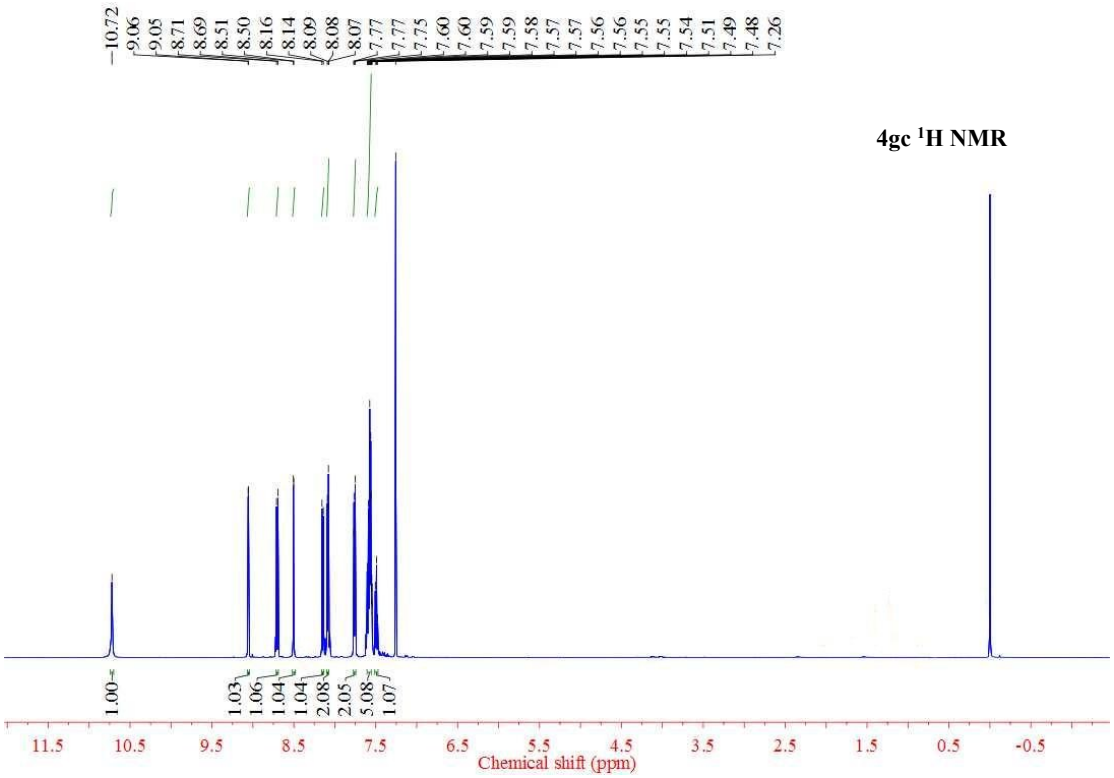

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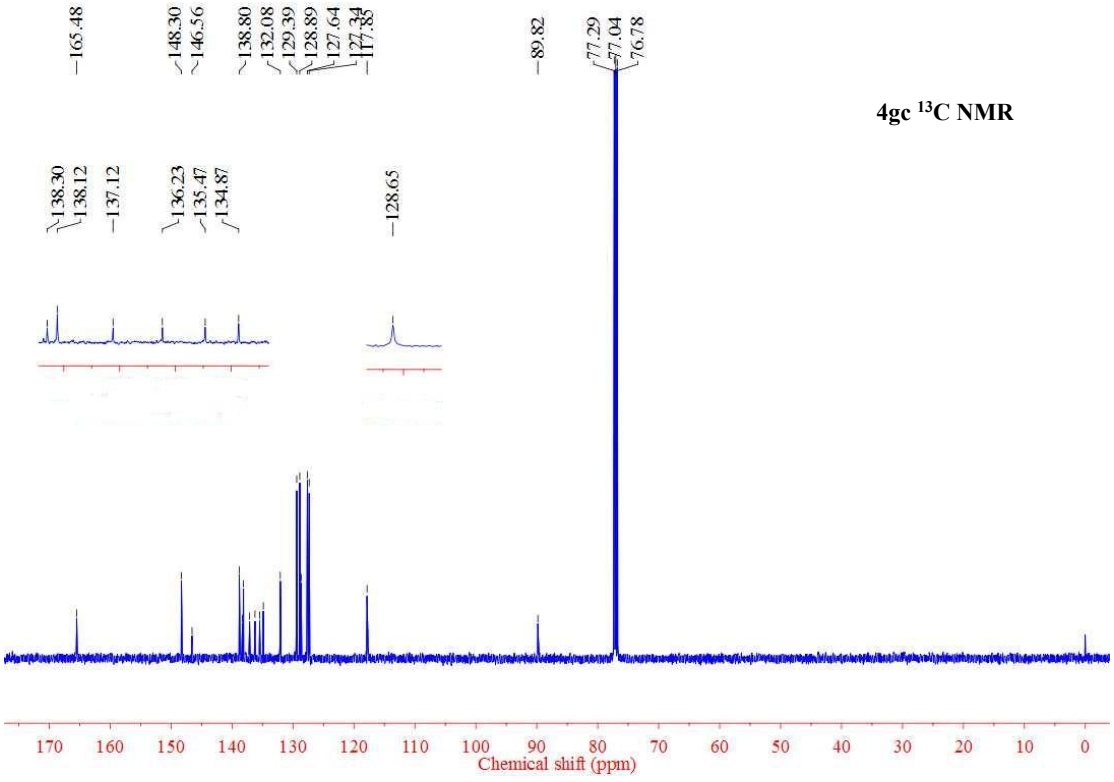

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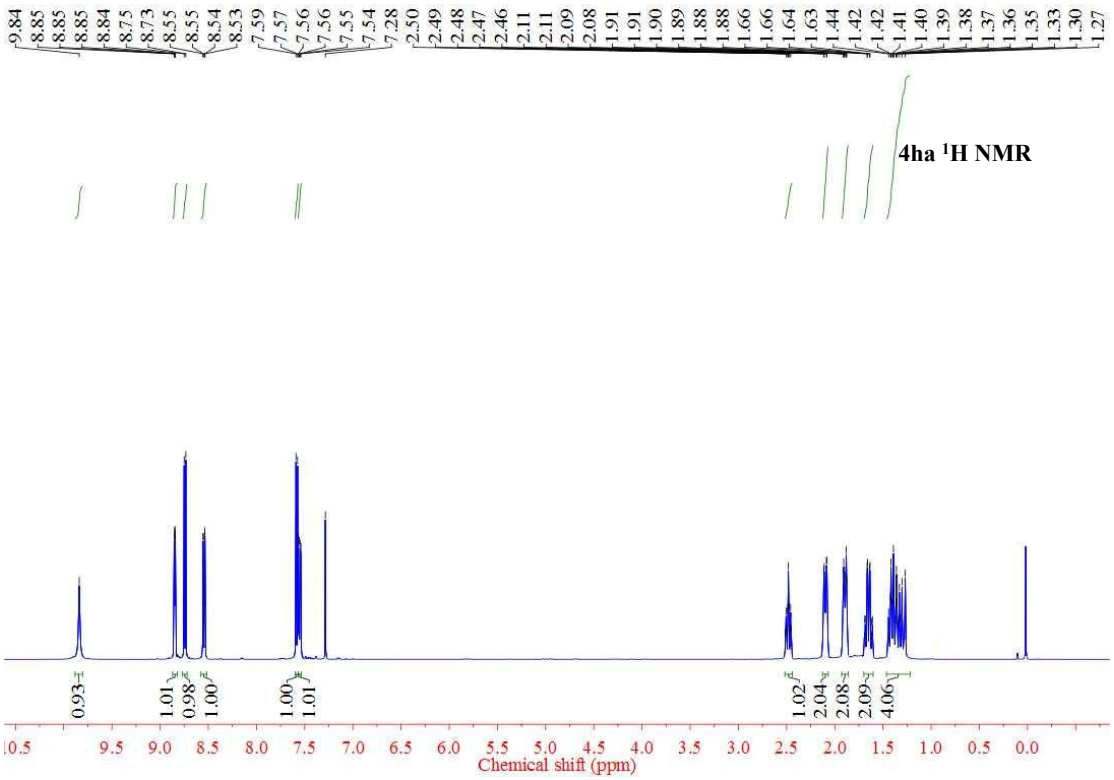
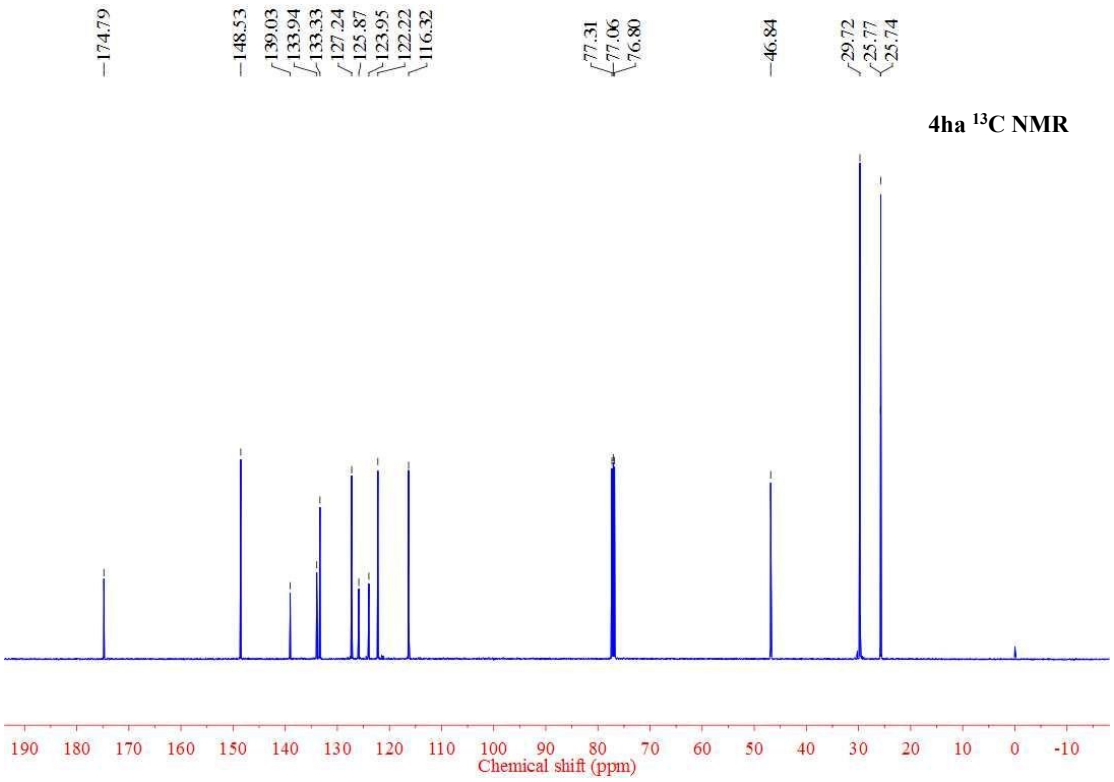


4ha ^{1}H NMR



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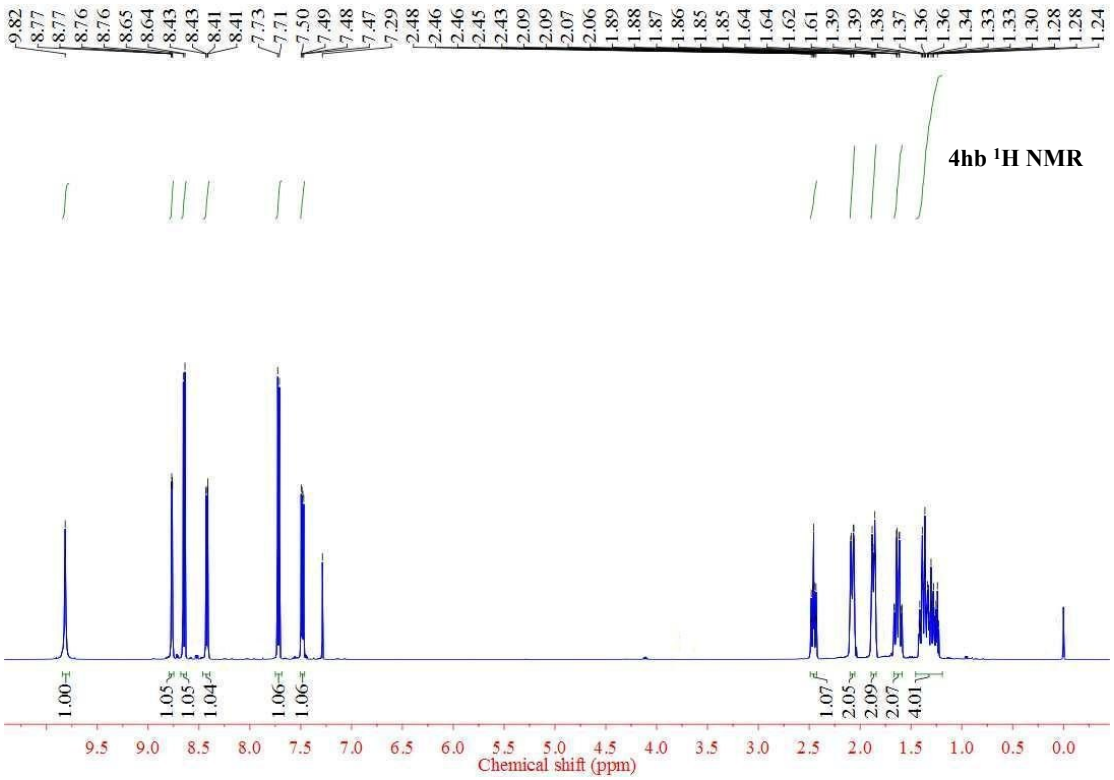

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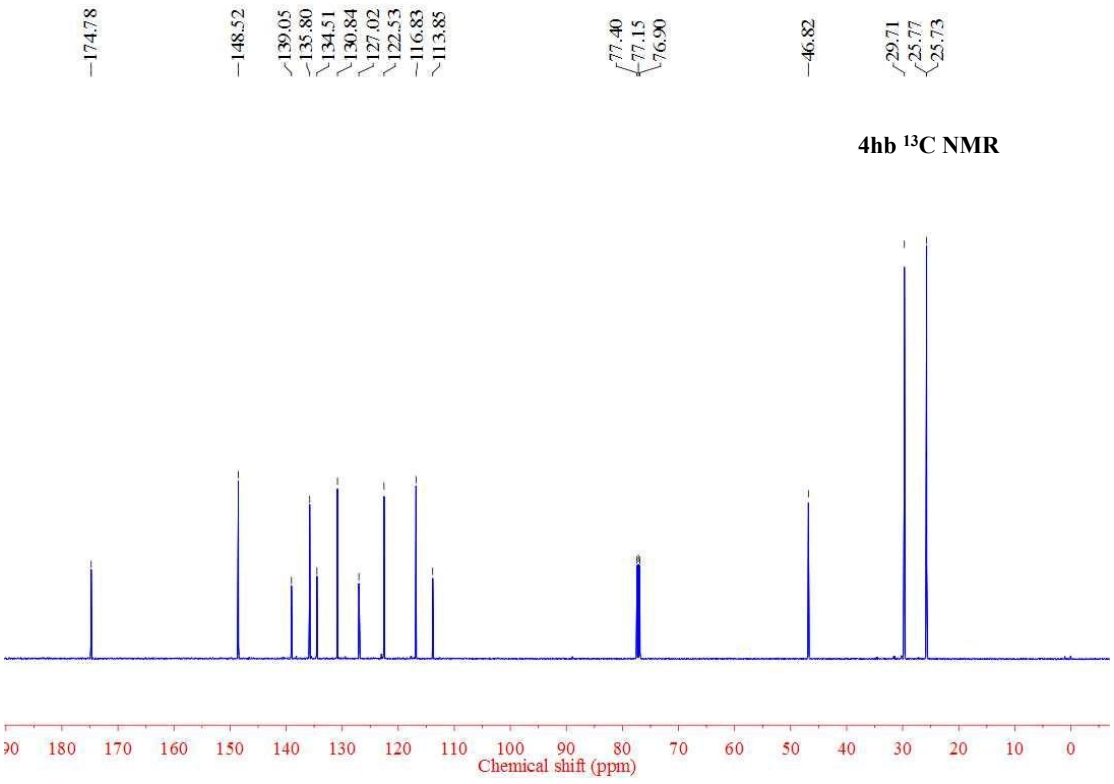

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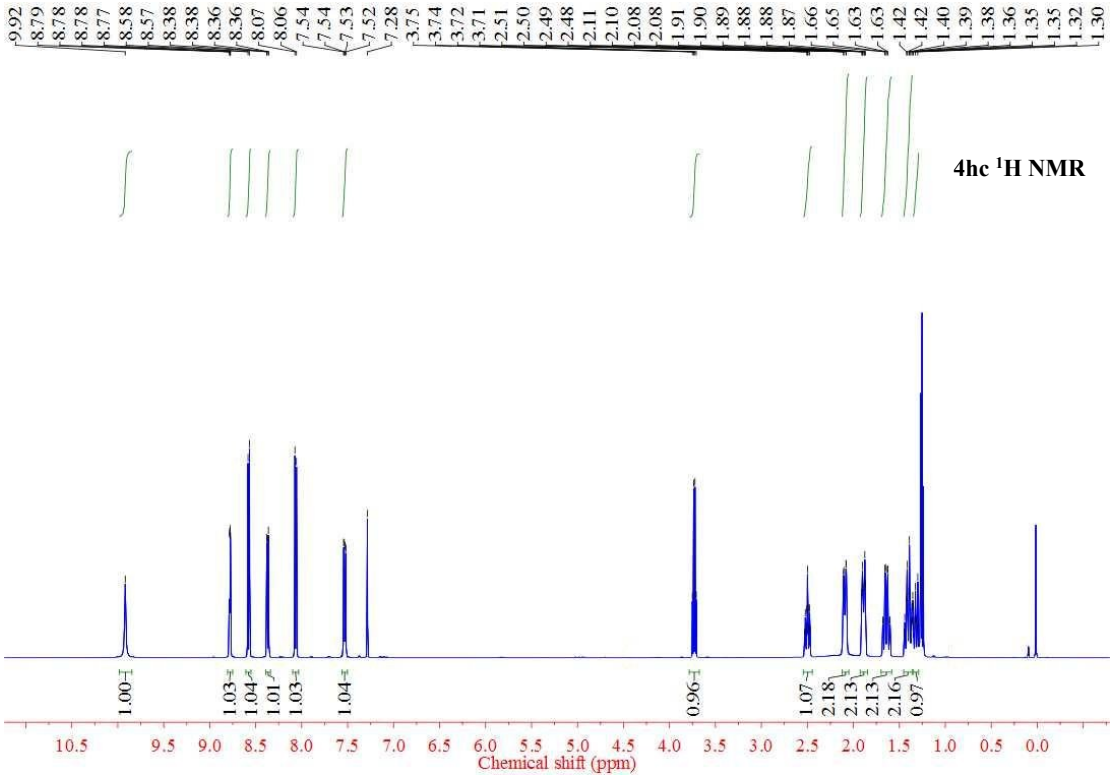
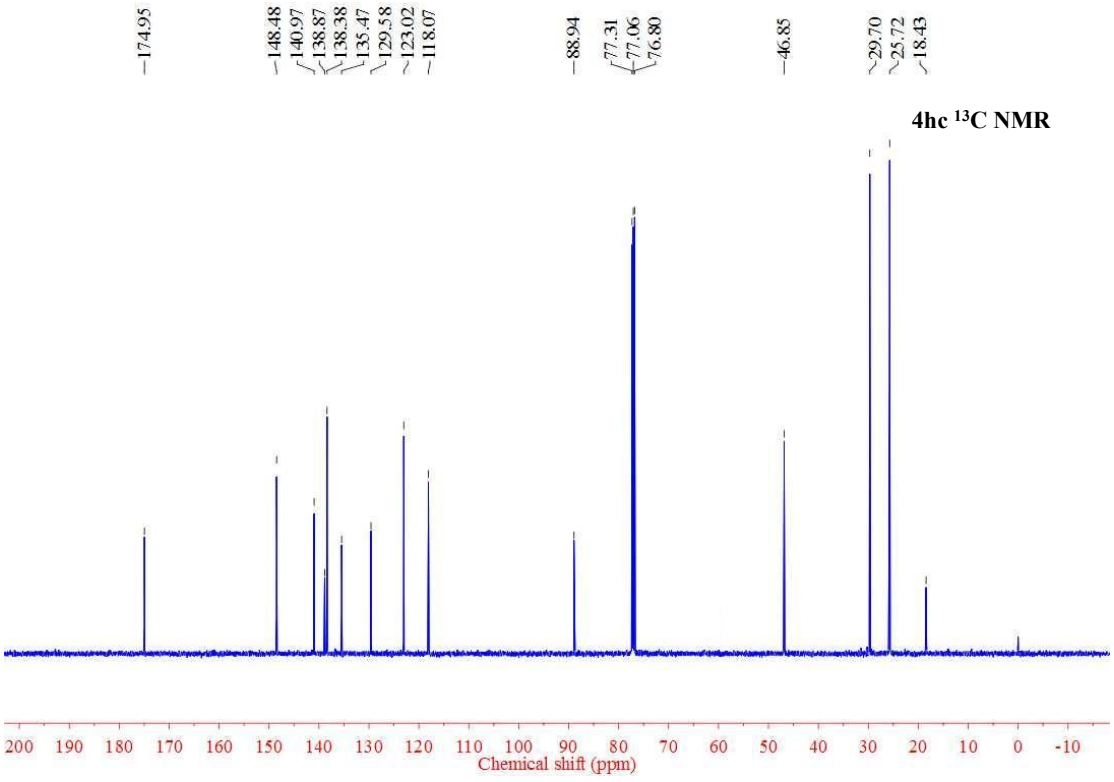
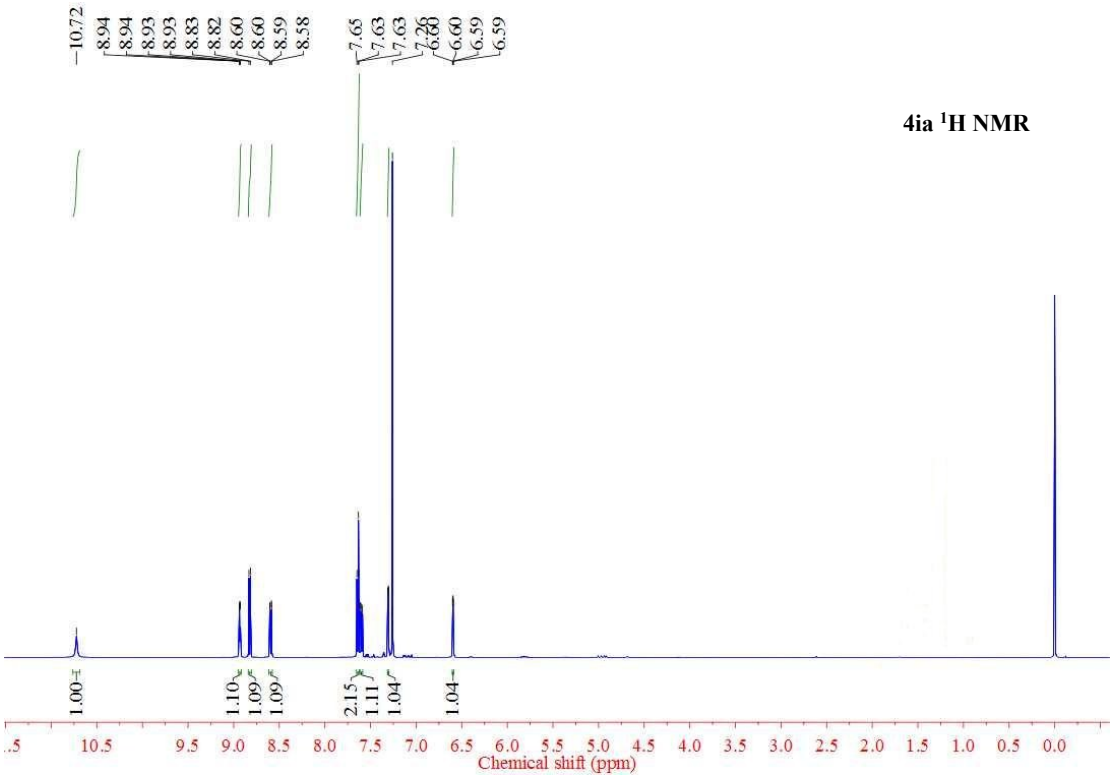


4hc ^{1}H NMR

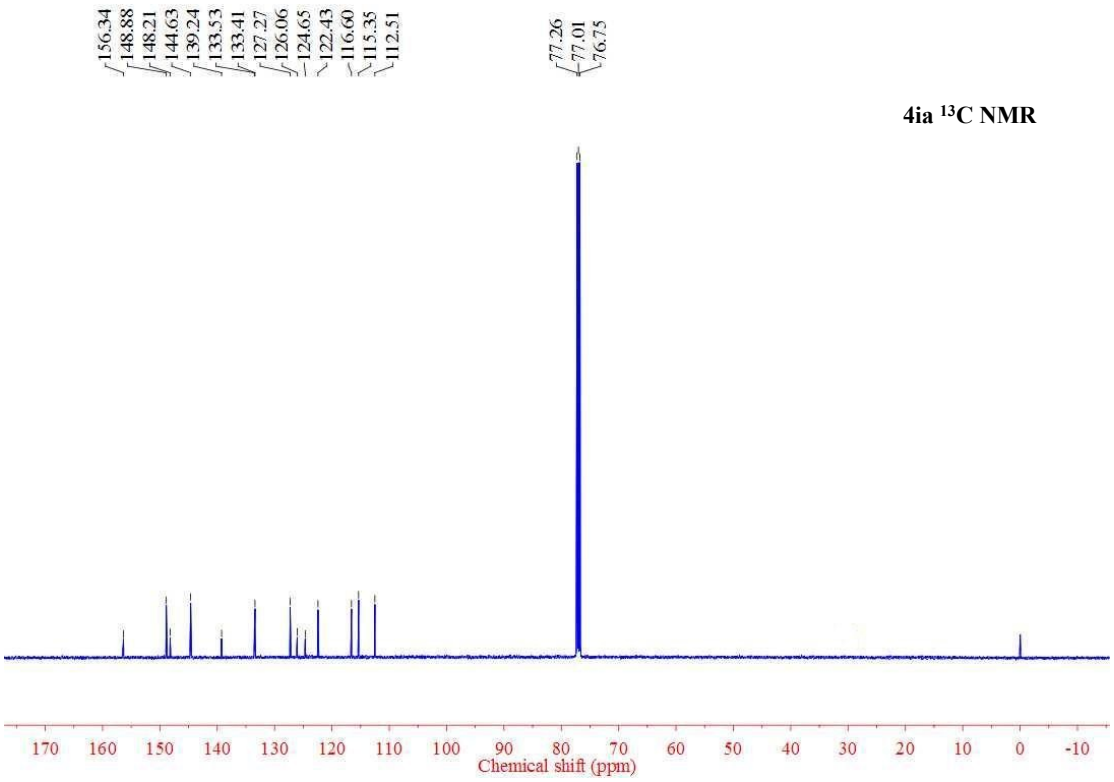


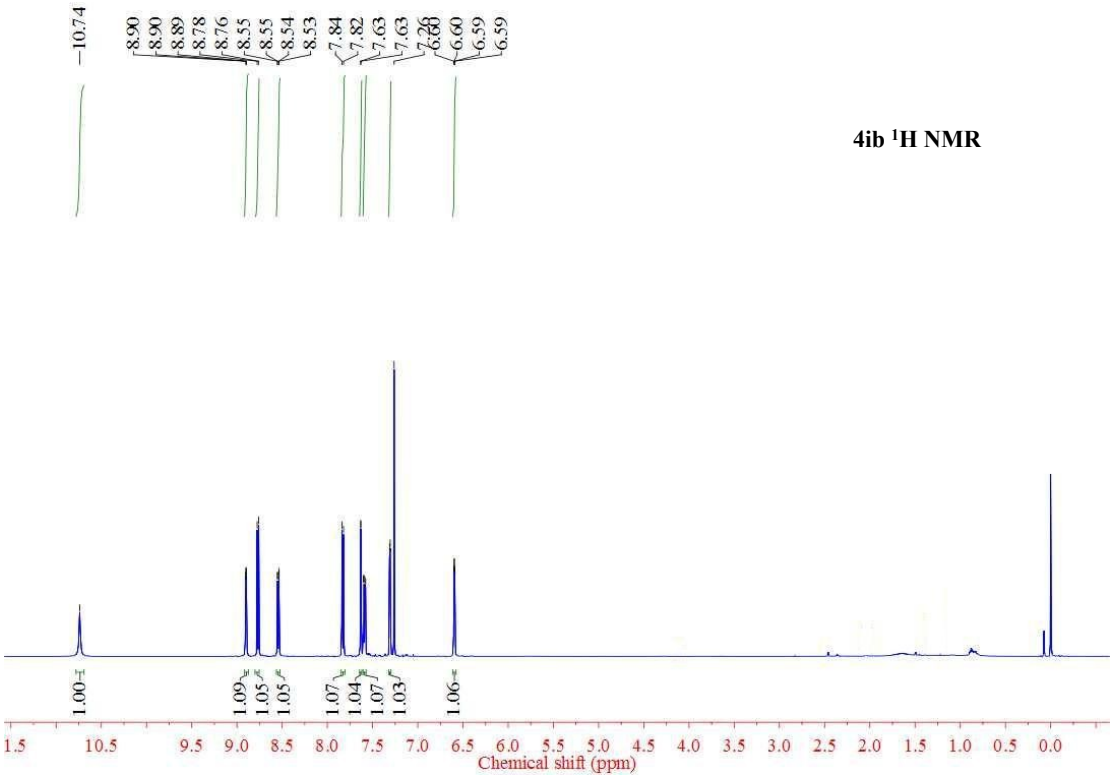
4hc ^{13}C NMR

4ia ^{1}H NMR

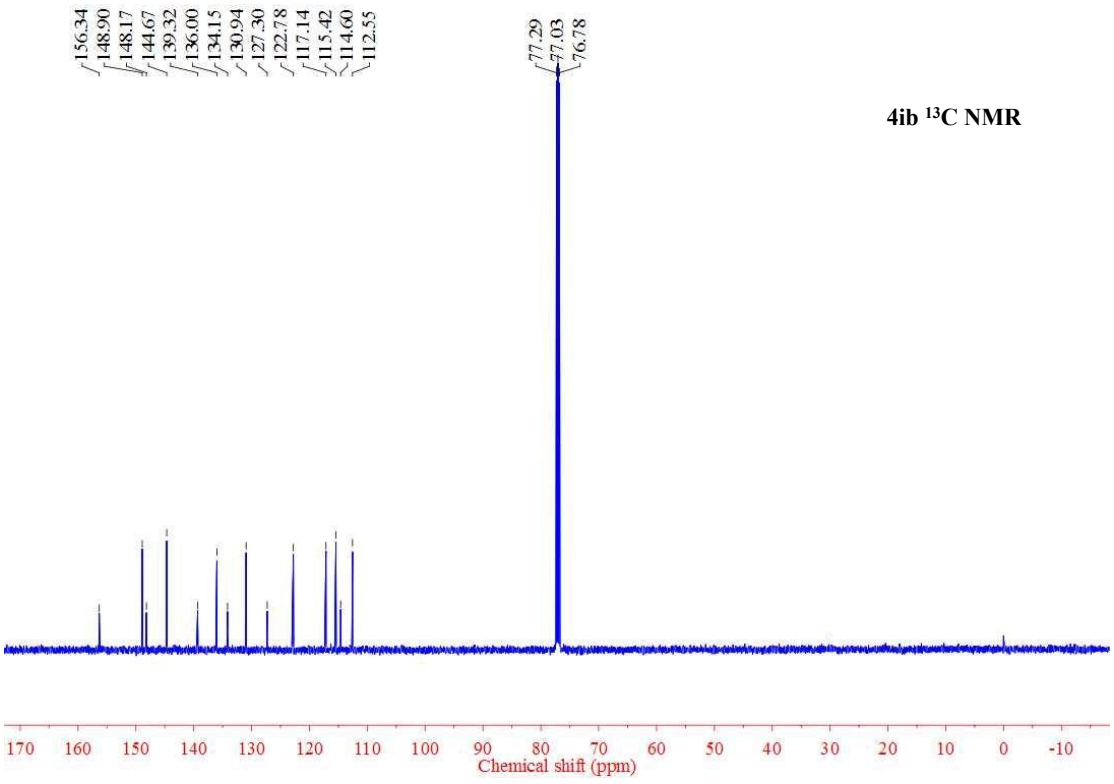


4ia ^{13}C NMR

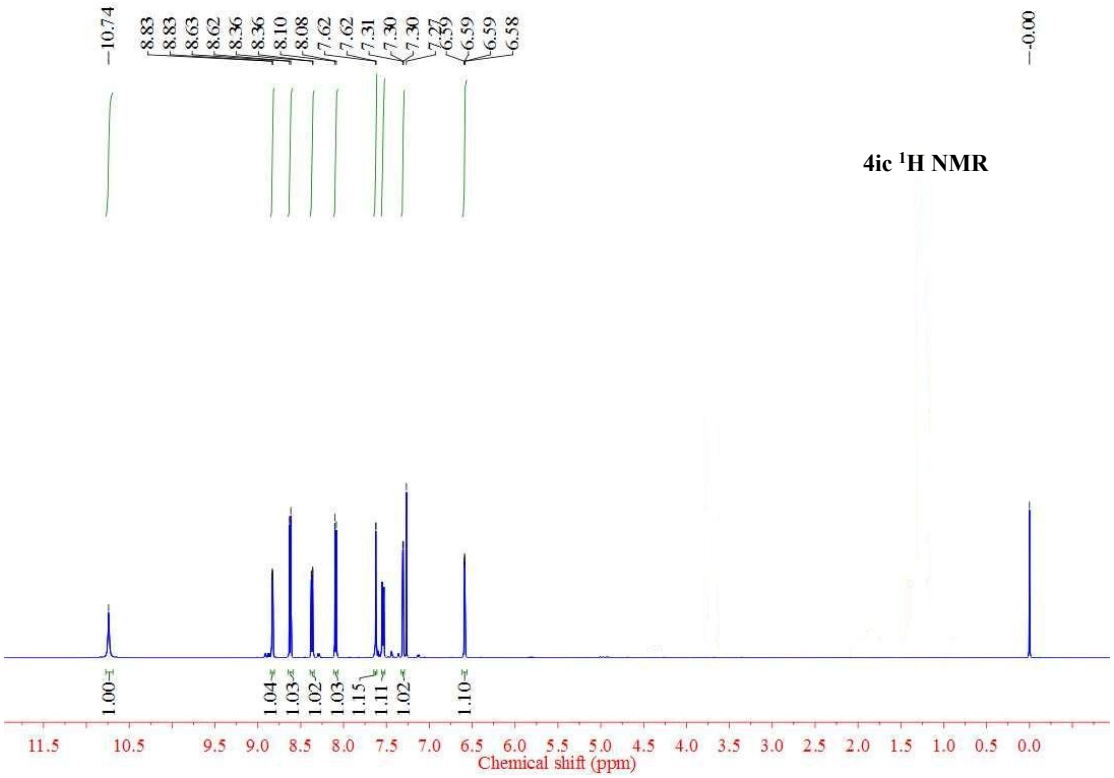




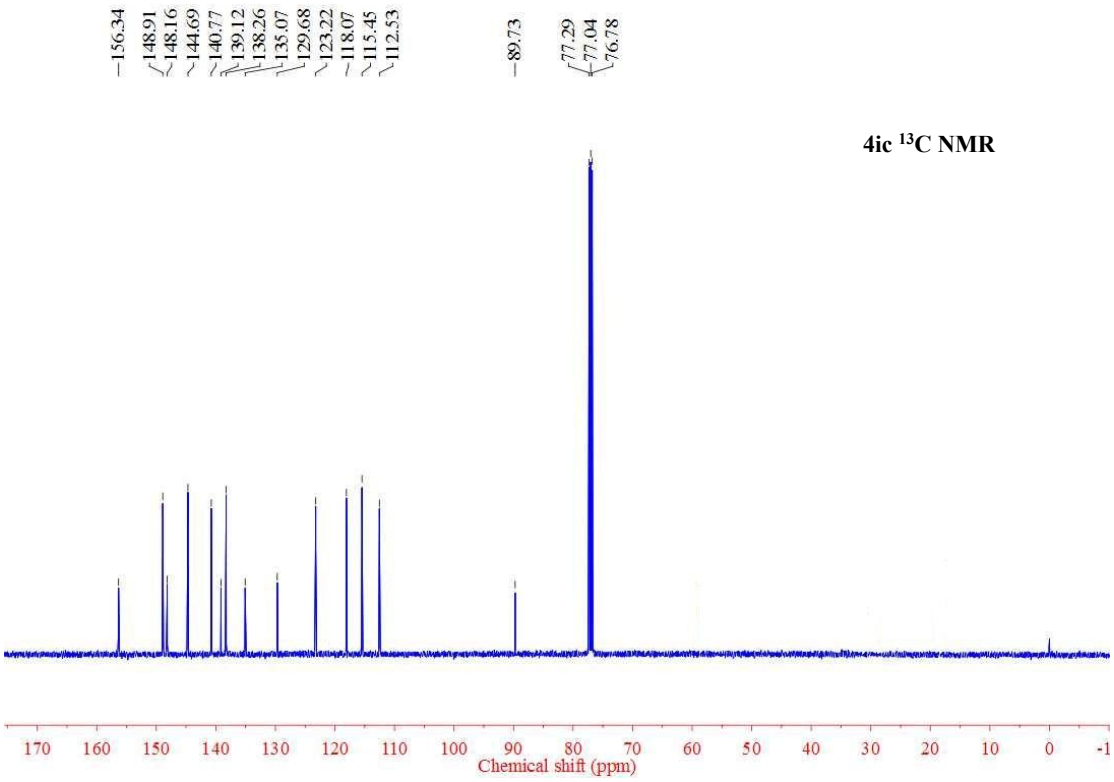
4ib ^{1}H NMR



4ib ^{13}C NMR

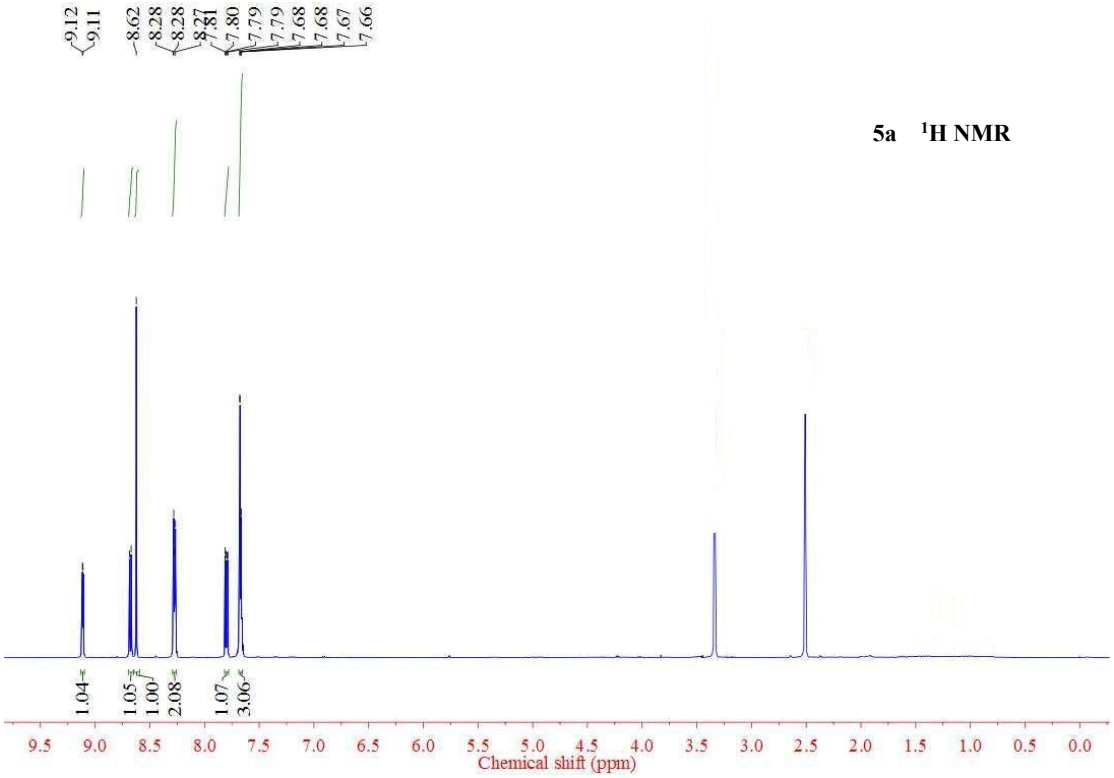


4ic ^{1}H NMR

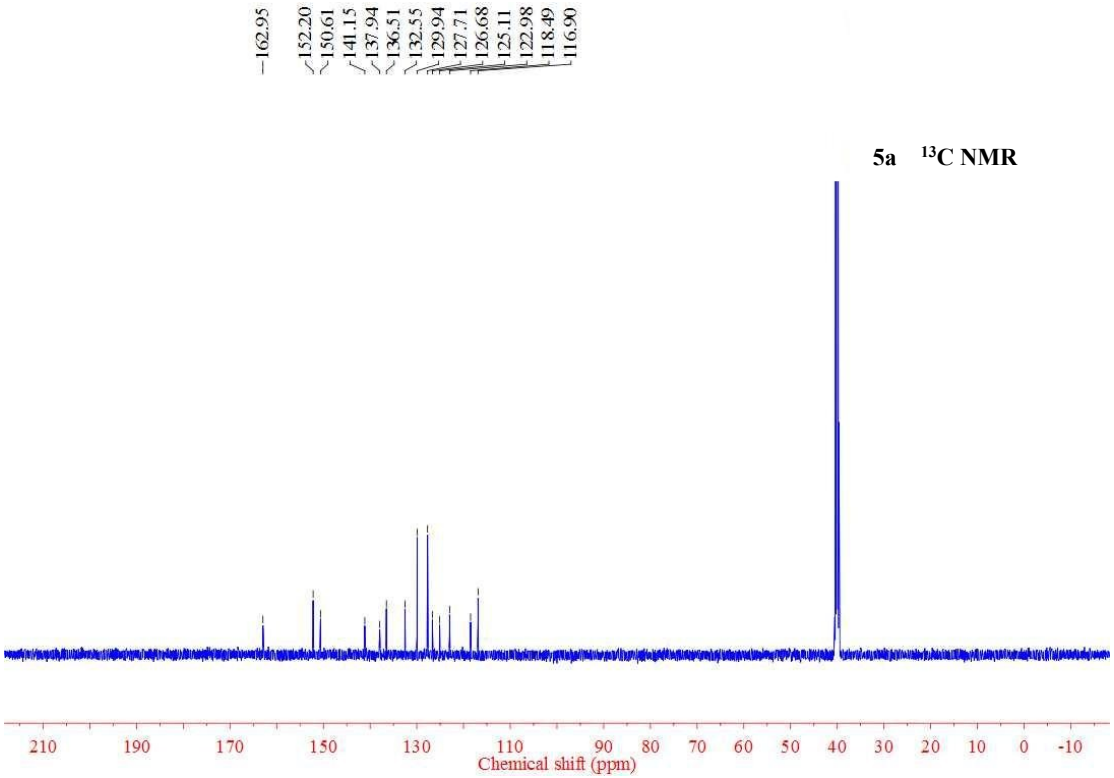


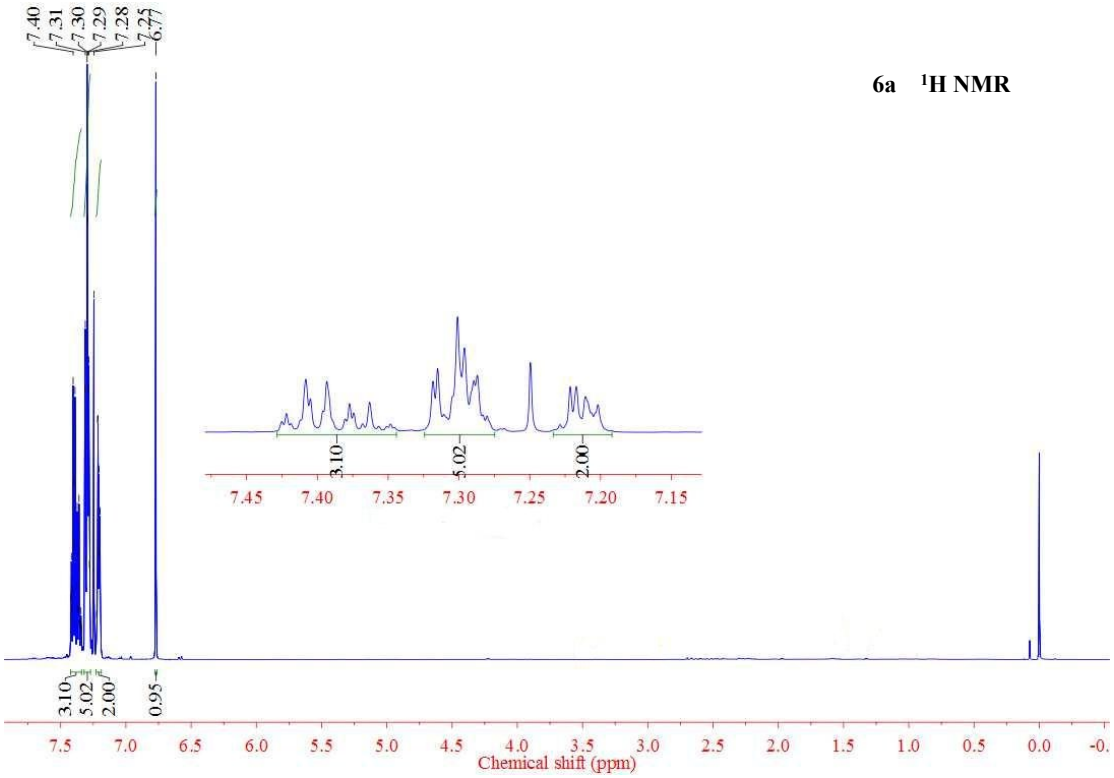
4ic ^{13}C NMR

5a ^{1}H NMR

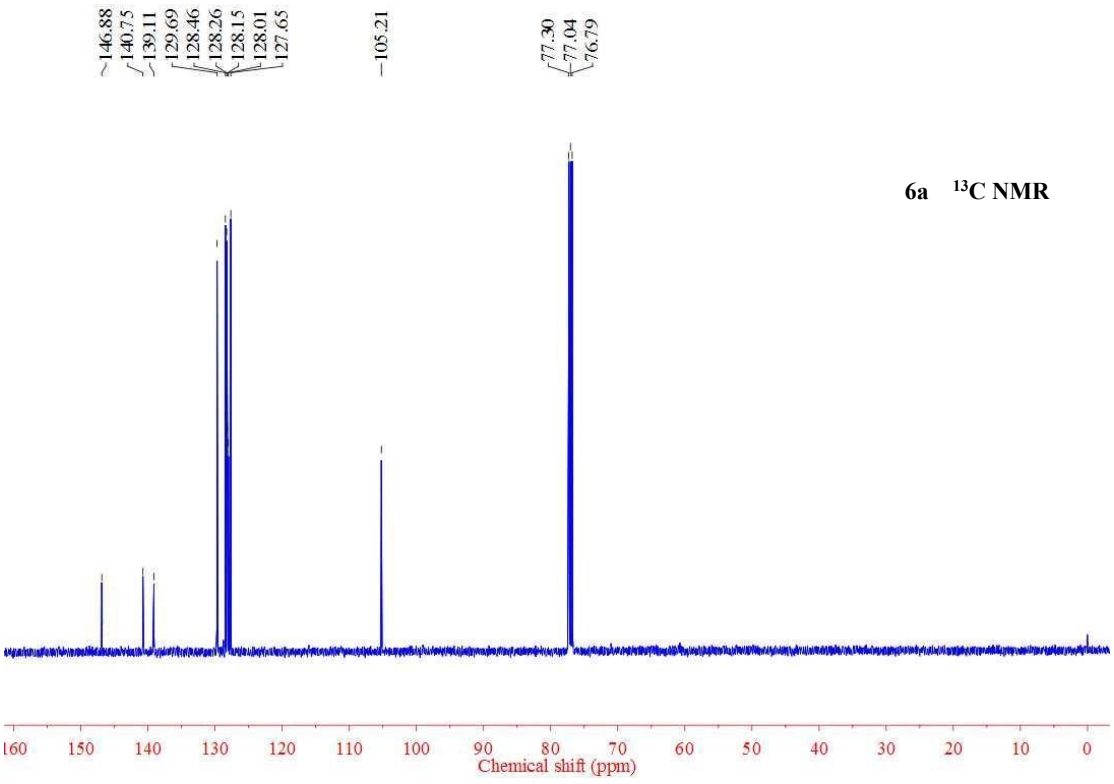


5a ^{13}C NMR

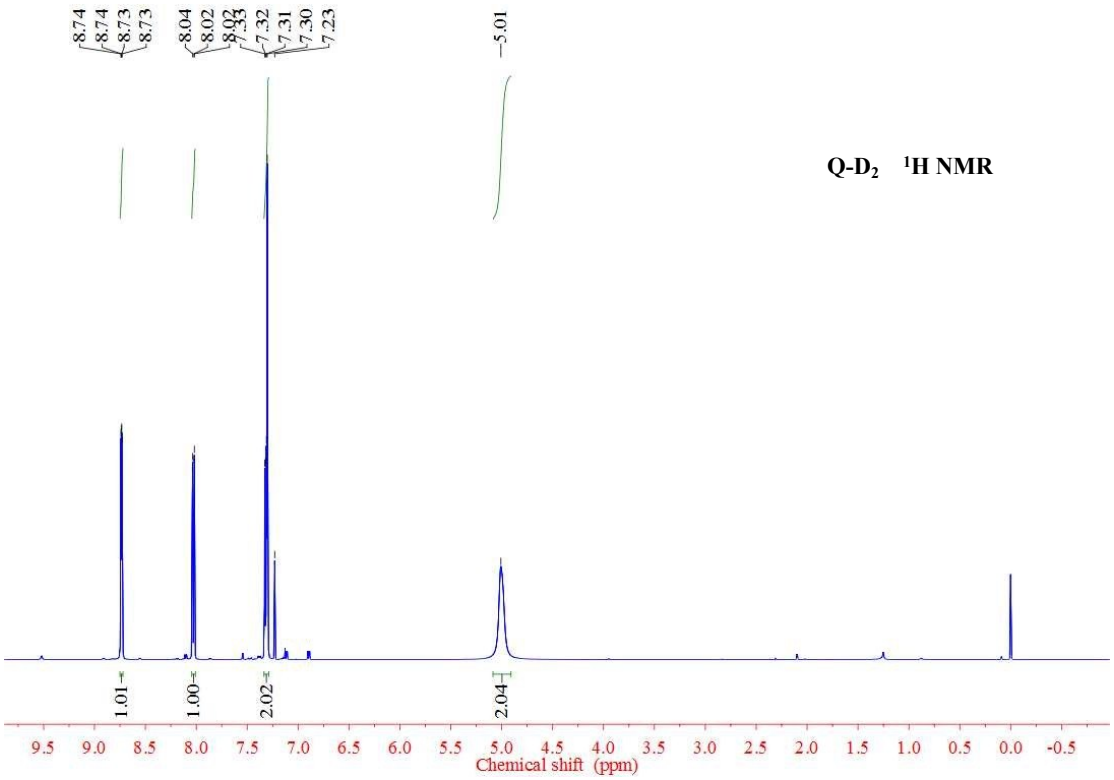




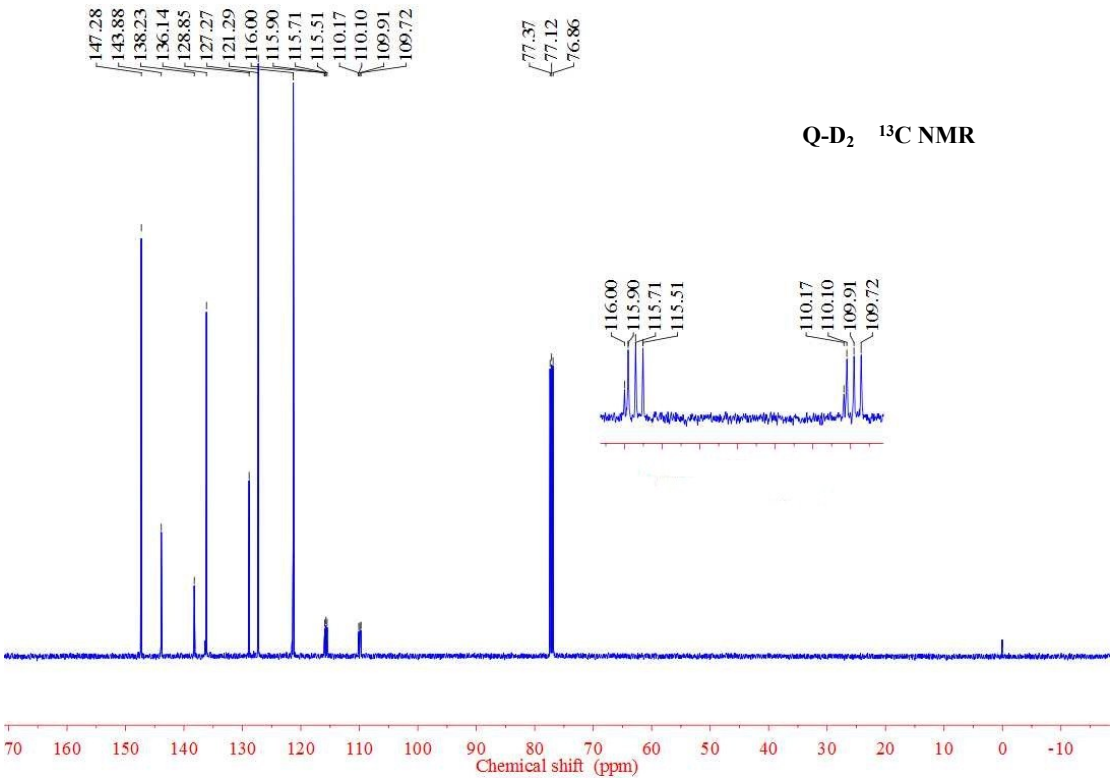
6a ^{1}H NMR



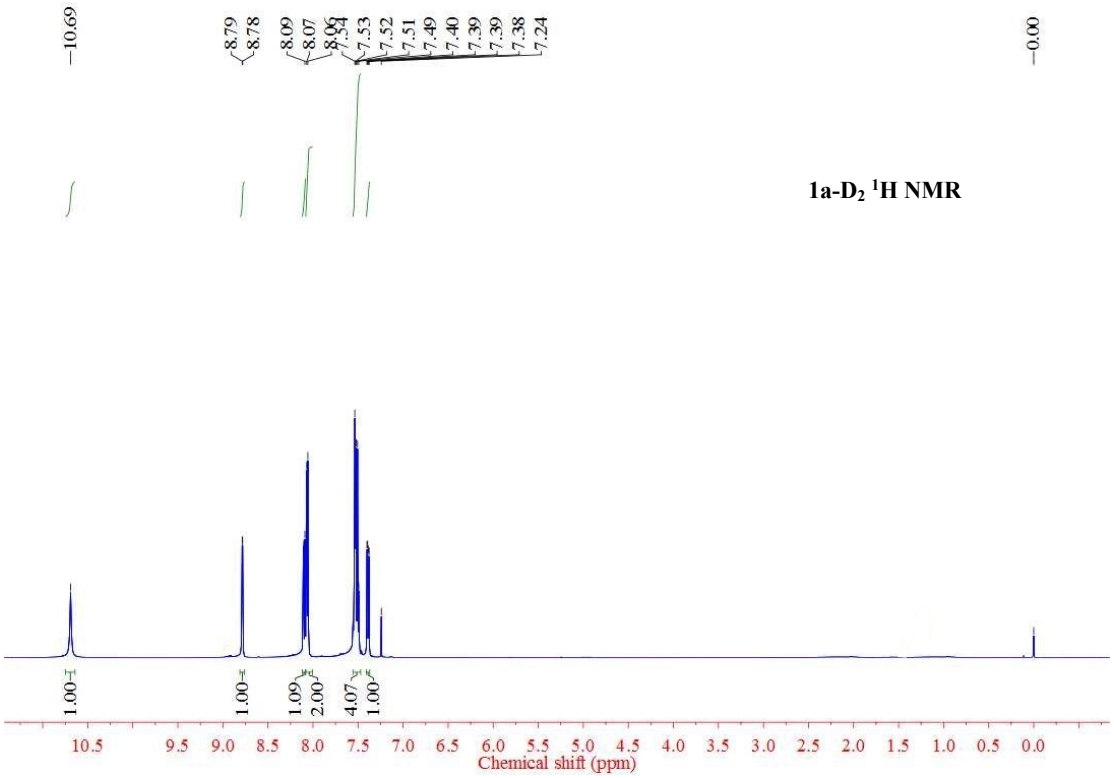
6a ^{13}C NMR



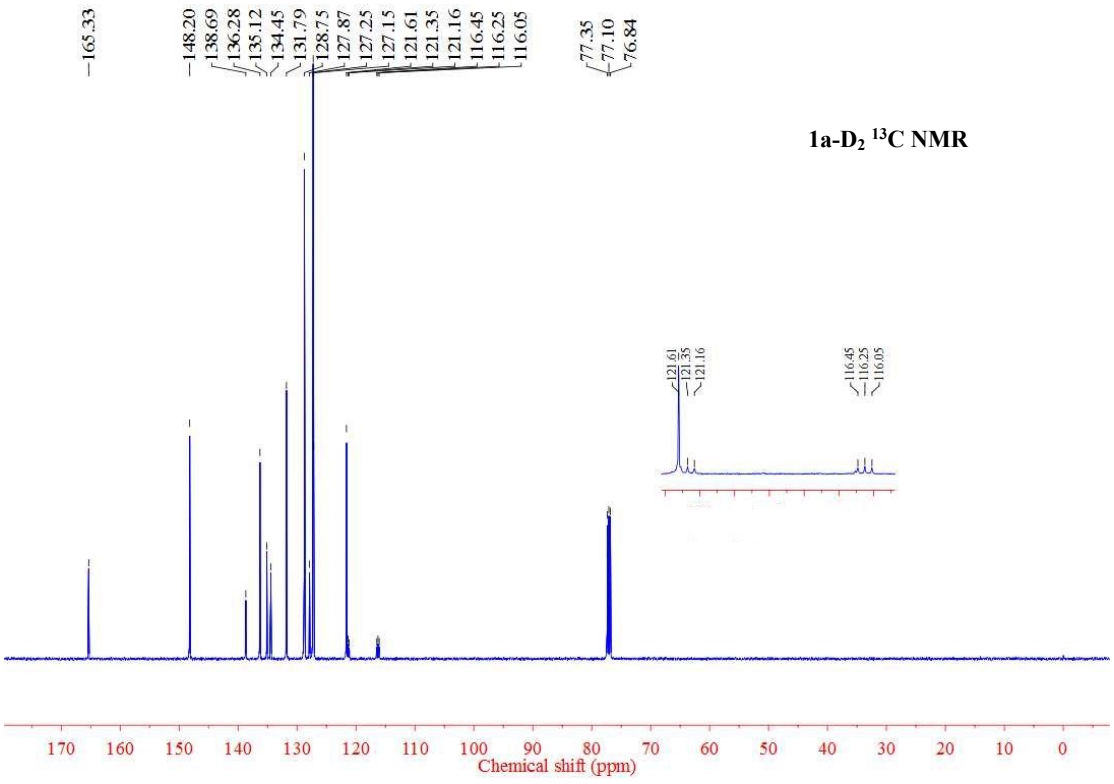
Q-D_2 ^{1}H NMR



Q-D_2 ^{13}C NMR



1a-D$_2$ ^{1}H NMR



1a-D$_2$ ^{13}C NMR

Reference

[1] A. M. Suess, M. Z. Ertem, C. J. Cramer, S. S. Stahl, *J. Am. Chem. Soc*., **2013**, *135*, 9797.

[2] A. Martins, M. Lautens, *Org. Lett*., **2008**, *10*, 4351.