

Catalyst-Free Synthesis of Tetrahydropyrimidines via Formal [3+3]-Cycloaddition of Imines with 1,3,5-Hexahydro-1,3,5-Triazines

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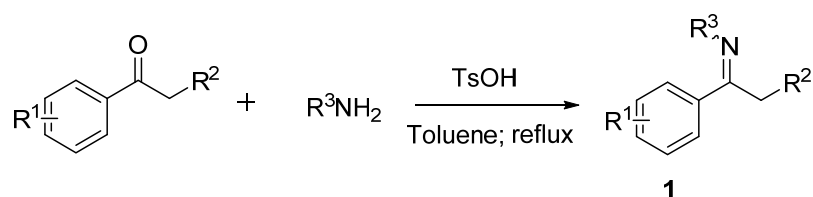
General information

All of the reactions were performed in flame-dried tubes. For column chromatography, 200-300 mesh silica gel was used. ^1H NMR were recorded on Bruker 300 MHz, 400 MHz spectrometer and ^{13}C NMR were recorded on Bruker 75 MHz, 100 MHz or 125MHz spectrometer in CDCl_3 . HRMS were performed on Agilent 6540 Q-TOF mass spectrometer (ESI). Melting points were determined on a SGW X-4B melting point apparatus. Triazines **2** were prepared according to previously reported literature.^[1]

Preparation of substrates

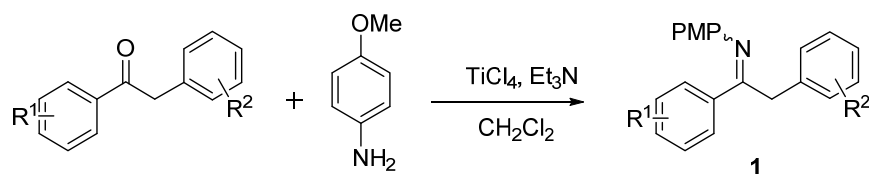
Imines **1** were prepared according to the follow procedure.^[2, 3]

Procedure A:



Ketone (10 mmol, 1 eq), R^3NH_2 (20 mmol, 2 eq), TsOH (1 mmol, 0.1 eq) and toluene (80 mL) were added into a round-bottom flask, the mixture was heated to reflux overnight under Dean-Stark conditions. The reaction mixture was cooled to room temperature. After evaporating the solvents under reduced pressure, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate/ Et_3N =100:1:2) or crystallization from petroleum ether to afford the imine **1**, which was unstable and used directly to next step.

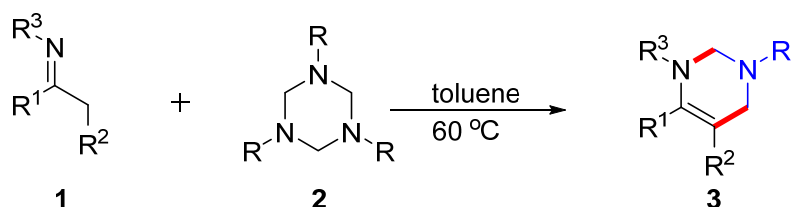
Procedure B:



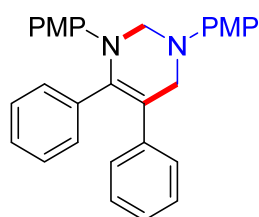
To a solution of 4-Methoxyaniline (27 mmol) and Et_3N (27 mmol) in CH_2Cl_2 (70 mL)

was added dropwise TiCl_4 (1 mL, 9 mmol) at 0 °C under argon atmosphere. After stirring for 30 min, the reaction mixture was allowed to warm to room temperature and a solution of ketone (9 mmol) in CH_2Cl_2 (30 mL) was added dropwisely. The reaction mixture was stirred at 40 °C overnight. The reaction mixture was filtered and washed with EtOAc, the filtrate was concentrated under vacuum to give crude product. The crude product was purified by recrystallization to give imine **1**, which was unstable and used directly to next step.

General procedure for Table 2



To a tube was added **1** (0.3 mmol, 1 eq), **2** (0.33 mmol, 1.1 eq) and toluene (6 mL), the resulting mixture was stirred at 60 °C for 6-18 h. The reaction solution was concentrated and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 80:1-20:1) to give **3**.

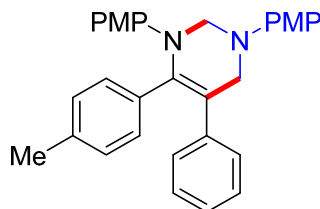


1,3-bis(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3a):

This compound was prepared via general procedure as yellow oil (116 mg, yield: 86%).

^1H NMR (400 MHz, CDCl_3) δ 7.20-7.12 (m, 7H), 7.00-6.96 (m, 3H), 6.94-6.90 (m, 2H), 6.77 (s, 4H), 6.66-6.62 (m, 2H), 4.81 (s, 2H), 4.13 (s, 2H), 3.73 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.52, 153.58, 142.50, 141.14, 140.78, 140.17, 136.84, 130.91, 129.81, 127.99, 127.49, 127.07, 126.08, 125.91, 120.11, 117.68,

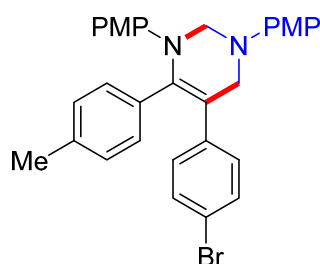
114.56, 113.83, 72.65, 55.67, 55.27, 53.07. HRMS (ESI) calcd. for $C_{30}H_{29}N_2O_2$ $[M+H]^+$: 449.2224, found: 449.2221.



1,3-bis(4-methoxyphenyl)-5-phenyl-6-(p-tolyl)-1,2,3,4-tetrahydropyrimidine (3b):

This compound was prepared via general procedure as yellow oil (121 mg, yield: 87%).

1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.10 (m, 5H), 7.04 (d, $J = 8.0$ Hz, 2H), 6.96-6.89 (m, 2H), 6.80-6.72 (m, 6H), 6.67-6.60 (m, 2H), 4.79 (s, 2H), 4.12 (s, 2H), 3.71 (s, 3H), 3.65 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.48, 153.54, 142.56, 141.33, 140.77, 140.42, 136.71, 133.86, 130.75, 129.79, 128.31, 128.00, 125.97, 125.91, 119.64, 117.61, 114.57, 113.83, 72.63, 55.67, 55.27, 53.09, 21.21. HRMS (ESI) calcd. for $C_{31}H_{30}N_2NaO_2$ $[M+Na]^+$: 485.2199, found: 485.2194.

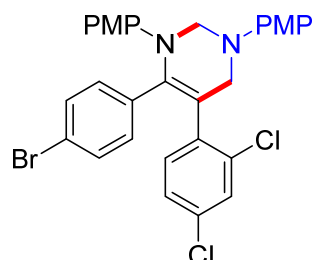


5-(4-bromophenyl)-1,3-bis(4-methoxyphenyl)-6-(p-tolyl)-1,2,3,4-tetrahydropyrimidine (3c):

This compound was prepared via general procedure as yellow oil (130 mg, yield: 80%).

1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, $J = 8.0$ Hz, 2H), 7.01 (t, $J = 8.0$ Hz, 4H), 6.89 (d, $J = 8.0$ Hz, 2H), 6.81 (d, $J = 8.0$ Hz, 2H), 6.75 (s, 4H), 6.63 (d, $J = 8.0$ Hz, 2H), 4.77 (s, 2H), 4.08 (s, 2H), 3.72 (s, 3H), 3.66 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.57, 153.63, 142.40, 141.53, 141.03, 139.37, 137.07, 133.43, 131.30,

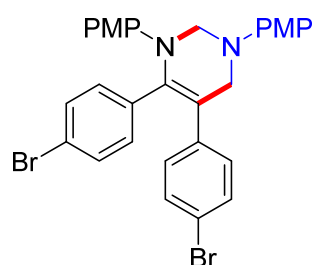
131.05, 130.76, 128.50, 126.02, 119.64, 117.84, 117.71, 114.55, 113.82, 72.53, 55.66, 55.26, 52.80, 21.23. HRMS (ESI) calcd. for $C_{31}H_{30}BrN_2O_2$ $[M+H]^+$: 541.1485, found: 541.1484.



6-(4-bromophenyl)-5-(2,4-dichlorophenyl)-1,3-bis(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine (3d):

This compound was prepared via general procedure as a white solid (114 mg, yield: 64%), mp: 99-101 °C.

1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, $J = 4.0$ Hz, 1H), 7.15-7.09 (m, 4H), 7.02 (d, $J = 8.0$ Hz, 2H), 6.93 (d, $J = 8.0$ Hz, 2H), 6.75 (s, 4H), 6.66 (d, $J = 8.0$ Hz, 2H), 4.87 (d, $J = 12.0$ Hz, 1H), 4.77 (d, $J = 12.0$ Hz, 1H), 4.19 (d, $J = 16.0$ Hz, 1H), 3.82 (d, $J = 16.0$ Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.86, 153.78, 142.20, 141.32, 140.71, 137.33, 135.71, 135.41, 133.50, 133.44, 131.28, 130.85, 129.53, 127.30, 125.91, 121.56, 118.18, 118.03, 114.51, 114.02, 72.81, 55.64, 55.30, 52.63. HRMS (ESI) calcd. for $C_{30}H_{26}BrCl_2N_2O_2$ $[M+H]^+$: 595.0549, found: 595.0545.

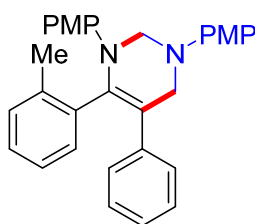


5,6-bis(4-bromophenyl)-1,3-bis(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine (3e):

This compound was prepared via general procedure as a white solid (141mg, yield:

78%), mp: 169-171 °C.

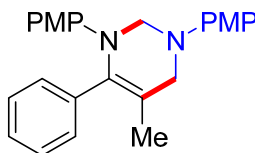
¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 8.0 Hz, 4H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.80-6.71 (m, 4H), 6.65 (d, *J* = 8.0 Hz, 2H), 4.76 (s, 2H), 4.08 (s, 2H), 3.73 (s, 3H), 3.69 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 155.89, 153.79, 142.22, 140.58, 140.45, 138.70, 135.52, 132.41, 131.31, 131.00, 127.53, 126.11, 121.39, 120.17, 119.19, 117.82, 114.58, 113.98, 72.63, 55.65, 55.30, 52.86. HRMS (ESI) calcd. for C₃₀H₂₇Br₂N₂O₂ [M+H]⁺: 605.0434, found: 605.0435.



1,3-bis(4-methoxyphenyl)-5-phenyl-6-(o-tolyl)-1,2,3,4-tetrahydropyrimidine (3f):

This compound was prepared via general procedure as yellow oil (85 mg, yield: 61%).

¹H NMR (400 MHz, CDCl₃) δ 7.14-7.07 (m, 3H), 7.07-7.01 (m, 3H), 6.96-6.91 (m, 1H), 6.88-6.82 (m, 6H), 6.81-6.76 (m, 2H), 6.63-6.57 (m, 2H), 4.89-4.75 (m, 2H), 4.29-4.14 (m, 2H), 3.74 (s, 3H), 3.65 (s, 3H), 2.17 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 155.70, 153.69, 142.75, 140.58, 140.42, 140.00, 137.40, 135.95, 132.45, 130.00, 128.97, 127.72, 127.39, 125.91, 125.74, 124.95, 118.21, 118.09, 114.54, 113.64, 71.57, 55.66, 55.24, 52.68, 20.15. HRMS (ESI) calcd. for C₃₁H₃₀N₂NaO₂ [M+Na]⁺: 485.2199, found: 485.2194.

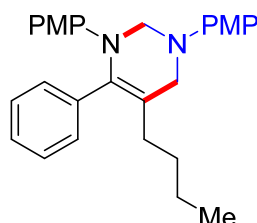


1,3-bis(4-methoxyphenyl)-5-methyl-6-phenyl-1,2,3,4-tetrahydropyrimidine (3g):

This compound was prepared via general procedure as yellow oil (83 mg, yield: 72%).

¹H NMR (400 MHz, CDCl₃) δ 7.45-7.39 (m, 2H), 7.25 (t, *J* = 8.0 Hz, 2H), 7.17 (t, *J* =

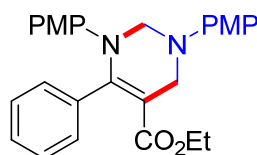
8.0 Hz, 1H), 6.96-6.91 (m, 2H), 6.82-6.77 (m, 2H), 6.76-6.71 (m, 2H), 6.69-6.63 (m, 2H), 4.74 (s, 2H), 3.77 (s, 2H), 3.76 (s, 3H), 3.69 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.20, 153.27, 142.70, 141.82, 137.96, 137.42, 130.02, 127.70, 127.15, 125.28, 117.17, 115.32, 114.53, 113.79, 72.41, 55.68, 55.28, 53.66, 17.54. HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 387.2067, found: 387.2069.



5-butyl-1,3-bis(4-methoxyphenyl)-6-phenyl-1,2,3,4-tetrahydropyrimidine (3h):

This compound was prepared via general procedure as yellow oil (75 mg, yield: 58%).

^1H NMR (300 MHz, CDCl_3) δ 7.38-7.32 (m, 2H), 7.24-7.10 (m, 3H), 6.93-6.86 (m, 2H), 6.79-6.69 (m, 4H), 6.65-6.59 (m, 2H), 4.69 (s, 2H), 3.80 (s, 2H), 3.73 (s, 3H), 3.65 (s, 3H), 2.26-2.14 (m, 2H), 1.61-1.53 (m, 2H), 1.37-1.27 (m, 2H), 0.88 (t, $J = 8.0$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 155.23, 153.27, 142.86, 141.69, 138.44, 137.57, 129.88, 127.66, 127.18, 125.38, 119.92, 117.23, 114.53, 113.75, 72.24, 55.68, 55.26, 51.65, 32.20, 30.96, 22.72, 14.00. HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 429.2537, found: 429.2536.

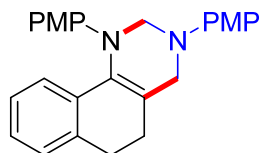


ethyl 1,3-bis(4-methoxyphenyl)-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3i):^[4]

This compound was prepared via general procedure as a white solid (99 mg, yield: 74%).

^1H NMR (400 MHz, CDCl_3) δ 7.13 (s, 5H), 6.92 (d, $J = 12.0$ Hz, 2H), 6.78 (d, $J = 12.0$ Hz, 2H), 6.62 (d, $J = 8.0$ Hz, 2H), 6.52 (d, $J = 8.0$ Hz, 2H), 4.84 (s, 2H), 4.27 (s, 2H),

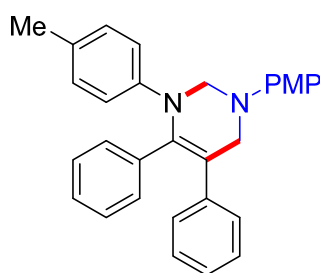
3.90 (q, $J = 8.0$ Hz, 2H), 3.75 (s, 3H), 3.64 (s, 3H), 0.87 (t, $J = 8.0$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.84, 156.70, 154.86, 154.18, 142.39, 138.90, 136.60, 129.76, 128.13, 128.05, 127.45, 119.30, 114.48, 113.68, 102.29, 71.97, 59.39, 55.62, 55.22, 49.66, 13.81.



1,3-bis(4-methoxyphenyl)-1,2,3,4,5,6-hexahydrobenzo[h]quinazoline (3j):

This compound was prepared via general procedure as a white solid (106 mg, yield: 89%), mp: 144-146 °C.

^1H NMR (400 MHz, CDCl_3) δ 7.13 (d, $J = 4.0$ Hz, 1H), 7.10-7.03 (m, 2H), 7.02-6.93 (m, 3H), 6.82-6.74 (m, 4H), 6.71 (d, $J = 8.0$ Hz, 2H), 4.74 (s, 2H), 3.85 (s, 2H), 3.72 (s, 3H), 3.73 (s, 3H), 2.93 (t, $J = 8.0$ Hz, 2H), 2.40 (t, $J = 8.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.15, 153.29, 148.26, 142.61, 142.02, 136.02, 134.85, 131.78, 127.32, 126.57, 126.27, 123.59, 121.74, 116.96, 114.58, 114.28, 72.24, 55.69, 55.43, 52.12, 28.22, 26.20. HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 399.2067, found: 399.2065.

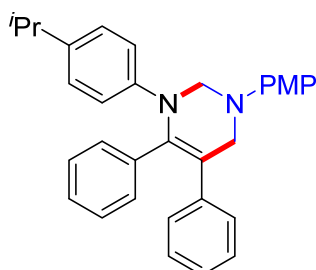


3-(4-methoxyphenyl)-5,6-diphenyl-1-(p-tolyl)-1,2,3,4-tetrahydropyrimidine (3k):

This compound was prepared via general procedure as yellow oil (97 mg, yield: 75%).

^1H NMR (400 MHz, CDCl_3) δ 7.23-7.11 (m, 7H), 7.04-6.96 (m, 3H), 6.93-6.83 (m, 4H), 6.78 (s, 4H), 4.87 (s, 2H), 4.14 (s, 2H), 3.74 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 153.55, 145.17, 142.48, 140.43, 140.15, 136.82, 132.13, 130.83,

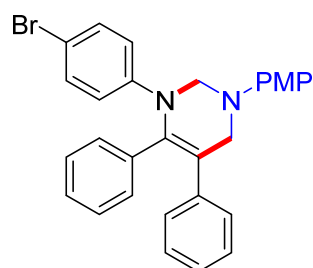
129.81, 129.17, 127.97, 127.48, 127.04, 126.09, 124.24, 120.57, 117.64, 114.53, 72.15, 55.65, 53.21, 20.73. HRMS (ESI) calcd. for C₃₀H₂₉N₂O [M+H]⁺: 433.2274, found: 433.2278.



1-(4-isopropylphenyl)-3-(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3l):

This compound was prepared via general procedure as yellow oil (94 mg, yield: 68%).

¹H NMR (400 MHz, CDCl₃) δ 7.22-7.11 (m, 7H), 7.03-6.98 (m, 3H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.77 (s, 4H), 4.88 (s, 2H), 4.14 (s, 2H), 3.73 (s, 3H), 2.78-2.68 (m, 1H), 1.14 (s, 3H), 1.12 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 153.51, 145.33, 142.93, 142.50, 140.40, 140.19, 136.86, 130.81, 129.81, 128.00, 127.50, 127.03, 126.50, 126.13, 123.92, 120.85, 117.57, 114.51, 71.98, 55.65, 53.30, 33.28, 23.95. HRMS (ESI) calcd. for C₃₂H₃₃N₂O [M+H]⁺: 461.2587, found: 461.2588.

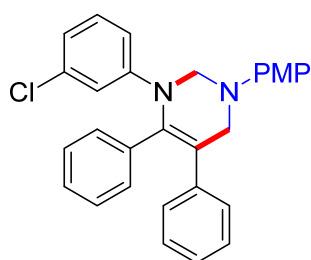


1-(4-bromophenyl)-3-(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3m):

This compound was prepared via general procedure as yellow oil (77 mg, yield: 52%).

¹H NMR (400 MHz, CDCl₃) δ 7.21-7.11 (m, 9H), 7.04-7.97 (m, 3H), 6.80 (d, *J* = 8.0

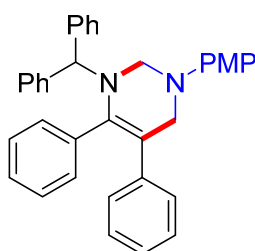
Hz, 2H), 6.78 (s, 4H), 4.88 (s, 2H), 4.14 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 153.85, 146.82, 142.17, 139.71, 139.68, 136.29, 131.52, 130.71, 129.78, 128.08, 127.69, 127.33, 126.39, 125.73, 121.68, 117.97, 115.55, 114.59, 72.03, 55.67, 53.30. HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{26}\text{BrN}_2\text{O}$ $[\text{M}+\text{H}]^+$: 497.1223, found: 497.1221.



1-(3-chlorophenyl)-3-(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3n):

This compound was prepared via general procedure as yellow oil (64 mg, yield: 47%).

^1H NMR (400 MHz, CDCl_3) δ 7.21-7.12 (m, 7H), 7.03-6.98 (m, 3H), 6.96 (d, $J = 8.0$ Hz, 1H), 6.92 (t, $J = 4.0$ Hz, 1H), 6.83-6.74 (m, 6H), 4.90 (s, 2H), 4.15 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 153.89, 148.96, 142.18, 139.67, 139.54, 136.23, 133.98, 130.66, 129.78, 129.37, 128.09, 127.70, 127.35, 126.43, 124.14, 122.69, 122.26, 121.90, 118.08, 114.57, 71.90, 55.65, 53.36. HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{26}\text{ClN}_2\text{O}$ $[\text{M}+\text{H}]^+$: 453.1728, found: 453.1725.

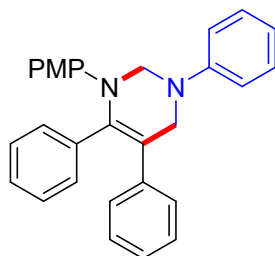


1-benzhydryl-3-(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3o):

This compound was prepared via general procedure as a white solid (110 mg, yield: 72%), mp: 186-188 °C.

^1H NMR (300 MHz, CDCl_3) δ 7.25-7.16 (m, 12H), 7.12-6.99 (m, 8H), 6.76-6.69 (m,

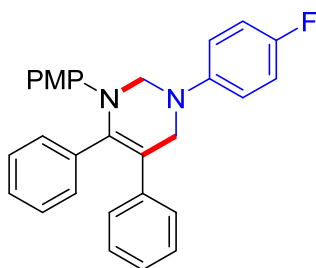
2H), 6.56-6.49 (m, 2H), 5.56 (s, 1H), 4.47 (s, 2H), 3.83 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 153.13, 142.76, 142.63, 140.88, 140.67, 137.07, 130.80, 129.65, 129.02, 128.00, 127.91, 127.72, 127.48, 126.92, 125.49, 116.94, 116.64, 114.32, 66.23, 63.93, 61.29, 55.63, 52.48. HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{33}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 509.2587, found: 509.2589.



1-(4-methoxyphenyl)-3,5,6-triphenyl-1,2,3,4-tetrahydropyrimidine (3p):

This compound was prepared via general procedure as yellow oil (109 mg, yield: 87%).

^1H NMR (400 MHz, CDCl_3) δ 7.24-7.11 (m, 9H), 7.04-6.92 (m, 5H), 6.83-6.75 (m, 3H), 6.71-6.62 (m, 2H), 4.93 (s, 2H), 4.22 (s, 2H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.65, 148.18, 141.02, 140.92, 140.07, 136.78, 130.93, 129.76, 129.21, 128.04, 127.54, 127.18, 126.18, 125.88, 120.26, 119.19, 115.26, 113.93, 70.82, 55.28, 52.00. HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{27}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 419.2118, found: 419.2115.

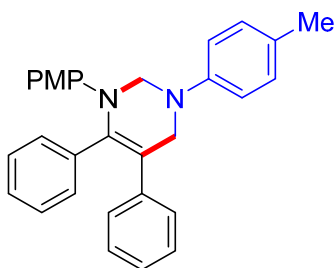


3-(4-fluorophenyl)-1-(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3q):

This compound was prepared via general procedure as yellow oil (92 mg, yield: 70%).

^1H NMR (400 MHz, CDCl_3) δ 7.22-7.12 (m, 7H), 7.03-6.96 (m, 3H), 6.94-6.85 (m,

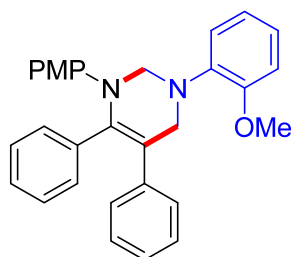
4H), 6.77-6.69 (m, 2H), 6.67-6.61 (m, 2H), 4.85 (s, 2H), 4.16 (s, 2H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.63, 144.80, 144.78, 140.93, 139.98, 136.68, 130.90, 129.76, 128.04, 127.54, 127.18, 126.19, 125.85, 119.95, 117.16, 117.09, 115.70, 115.48, 113.91, 72.00, 55.27, 52.74. HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{26}\text{FN}_2\text{O}$ $[\text{M}+\text{H}]^+$: 437.2024, found: 437.2025.



1-(4-methoxyphenyl)-5,6-diphenyl-3-(p-tolyl)-1,2,3,4-tetrahydropyrimidine (3r):

This compound was prepared via general procedure as yellow oil (114 mg, yield: 88%).

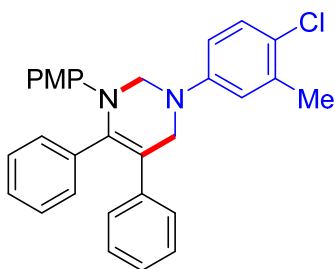
^1H NMR (400 MHz, CDCl_3) δ 7.20-7.09 (m, 7H), 7.01-6.96 (m, 5H), 6.93 (d, $J = 8.0$ Hz, 2H), 6.69 (d, $J = 8.0$ Hz, 2H), 6.63 (d, $J = 8.0$ Hz, 2H), 4.85 (s, 2H), 4.16 (s, 2H), 3.64 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.63, 146.06, 141.08, 140.93, 140.18, 136.87, 130.96, 129.81, 129.72, 128.72, 128.04, 127.54, 127.15, 126.15, 125.95, 120.28, 115.68, 113.91, 71.45, 55.29, 52.43, 20.48. HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 433.2274, found: 433.2275.



3-(2-methoxyphenyl)-1-(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3s):

This compound was prepared via general procedure as colorless oil (104 mg, yield: 77%).

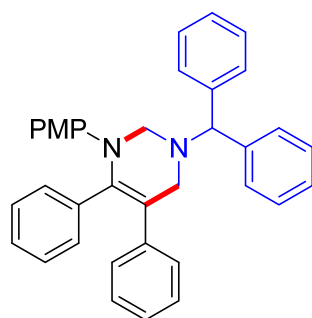
^1H NMR (400 MHz, CDCl_3) δ 7.20-7.10 (m, 7H), 7.06 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.01-6.95 (m, 3H), 6.93-6.85 (m, 2H), 6.84-6.79 (m, 2H), 6.70 (dd, $J = 8.0, 4.0$ Hz, 1H), 6.62-6.55 (m, 2H), 4.87 (s, 2H), 4.20 (s, 2H), 3.64 (s, 3H), 3.44 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 154.86, 152.20, 141.32, 140.40, 138.56, 137.71, 136.91, 130.97, 129.99, 127.94, 127.45, 126.92, 125.92, 125.74, 122.77, 120.74, 119.41, 118.34, 113.37, 111.38, 71.09, 55.32, 55.17, 53.49. HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 449.2224, found: 449.2221.



3-(4-chloro-3-methylphenyl)-1-(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3t):

This compound was prepared via general procedure as yellow oil (109 mg, yield: 78%).

^1H NMR (400 MHz, CDCl_3) δ 7.22-7.11 (m, 7H), 7.03-6.96 (m, 4H), 6.93 (d, $J = 8.0$ Hz, 2H), 6.75 (d, $J = 4.0$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 2H), 6.54 (dd, $J = 8.0, 4.0$ Hz, 1H), 4.86 (s, 2H), 4.16 (s, 2H), 3.67 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 155.73, 147.38, 140.95, 140.76, 139.85, 136.61, 134.80, 131.15, 130.88, 129.69, 128.03, 127.52, 127.20, 126.22, 126.12, 125.81, 120.01, 115.61, 113.97, 113.87, 70.46, 55.28, 52.14, 18.96. HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{28}\text{ClN}_2\text{O}$ $[\text{M}+\text{H}]^+$: 467.1885, found: 467.1884,.

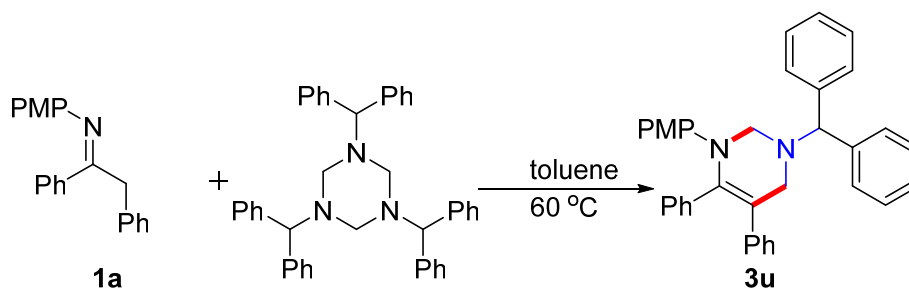


3-benzhydryl-1-(4-methoxyphenyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine (3u):

This compound was prepared via general procedure as a white solid (120 mg, yield: 79%), mp: 200-202 °C.

^1H NMR (400 MHz, CDCl_3) δ 7.24-7.19 (m, 4H), 7.18-7.10 (m, 8H), 7.09-7.02 (m, 3H), 7.00-6.91 (m, 5H), 6.83 (d, $J = 8.0$ Hz, 2H), 6.64 (d, $J = 8.0$ Hz, 2H), 4.56 (s, 1H), 4.21 (s, 2H), 3.72 (s, 3H), 3.50 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.23, 142.46, 141.63, 140.44, 139.88, 137.04, 130.82, 129.80, 128.43, 127.77, 127.64, 127.44, 126.95, 126.85, 125.76, 125.65, 120.73, 113.61, 71.43, 70.98, 55.95, 55.44. HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{33}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 509.2587, found: 509.2589.

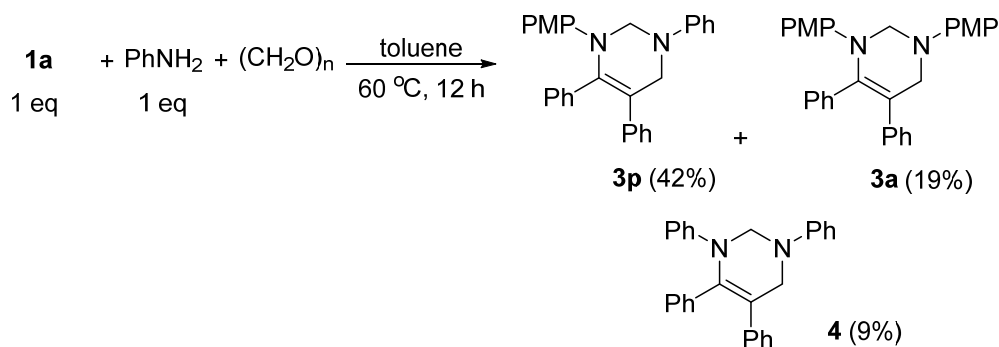
Large scale reaction for Scheme 2



To a flask was added **1a** (5 g, 16.6 mmol), 1,3,5-tribenzhydryl-1,3,5-triazinane (10.7 g, 18.2 mmol) and toluene (300 mL), the resulting solution was stirred at 60 °C for 24 h. The reaction mixture was concentrated, the residue was purified by recrystallization from EtOAc/Hexane to give **3u** as a white solid (6.1 g, yield: 72%).

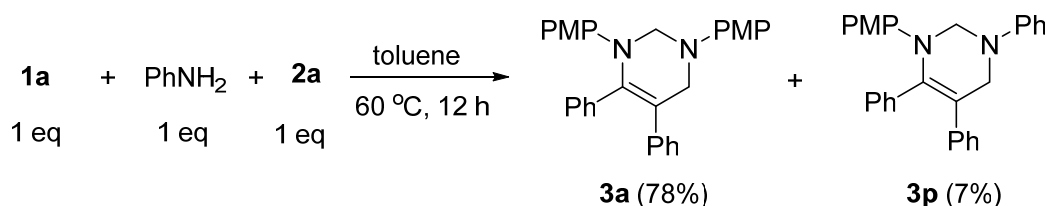
Mechanistic studies for Scheme 3

1. Scheme 3a



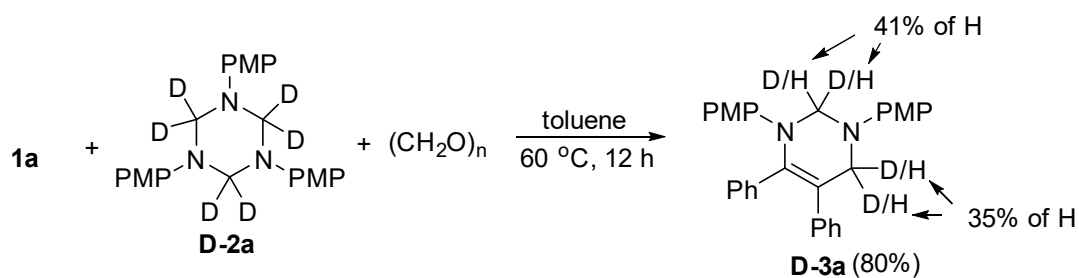
To a tube was added **1a** (0.30 mmol, 1 eq), PhNH₂ (0.30 mmol, 1 eq), (CH₂O)_n (0.63 mmol, 2.1 eq) and toluene (6 mL), the resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 80:1-20:1) to give **3p** (53 mg, yield: 42%), **3a** (26 mg, yield: 19%) as yellow oil and **4** (10 mg, yield: 9%) as yellow oil. Data of **4**: ¹H NMR (400 MHz, CDCl₃) δ 7.21-7.11 (m, 9H), 7.10-7.04 (m, 2H), 7.02-6.92 (m, 5H), 6.87-6.81(m, 1H), 6.80-6.71(m, 3H), 5.01 (s, 2H), 4.21 (s, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 148.05, 147.42, 140.39, 139.94, 136.59, 130.80, 129.73, 129.17, 128.60, 128.05, 127.56, 127.19, 126.28, 124.17, 122.81, 121.10, 119.21, 115.25, 70.10, 52.18. HRMS (ESI) calcd. for C₂₈H₂₅N₂ [M+H]⁺: 389.2012, found: 389.2016.

2. Scheme 3b



To a tube was added **1a** (0.30 mmol, 1 eq), PhNH₂ (0.30 mmol, 1 eq), **2a** (0.30 mmol, 1 eq) and toluene (6 mL), the resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 80:1-20:1) to give **3a** (105 mg, yield: 78%) as yellow oil and **3p** (9 mg, yield: 7%) as yellow oil.

2. Scheme 3c

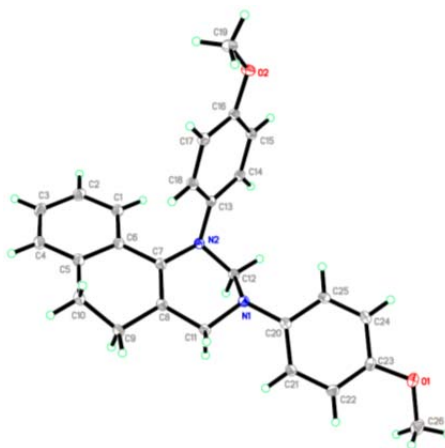


To a tube was added **1a** (0.30 mmol, 1 eq), **D-2a** (0.33 mmol, 1.1 eq), $(\text{CH}_2\text{O})_n$ (0.63 mmol, 2.1 eq) and toluene (6 mL), the resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 80:1-20:1) to give **D-3a** (109 mg, yield: 80%) as yellow oil.

^1H NMR (300 MHz, CDCl_3) δ 7.20-7.10 (m, 7H), 7.01-6.95 (m, 3H), 6.94-6.87 (m, 2H), 6.76 (s, 4H), 6.63 (d, $J = 8.7$ Hz, 2H), 4.81 (s, 0.82H), 4.13 (s, 0.7H), 3.72 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 155.52, 153.55, 142.54, 142.51, 141.14, 141.10, 140.87, 140.83, 140.79, 140.76, 140.18, 136.84, 130.92, 129.80, 127.99, 127.49, 127.08, 126.07, 126.06, 125.92, 125.88, 120.10, 119.90, 117.69, 117.64, 114.57, 113.83, 72.64, 72.58, 55.66, 55.26, 53.08, 53.01. HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{25}\text{D}_4\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 453.2475, found: 453.2478.

X-ray structure of **3j**:

The crystal structures have been deposited at the Cambridge Crystallographic Data Centre (CCDC 1577296, **3j**). The data can be obtained free of charge via the internet at www.ccdc.cam.ac.uk/data_request/cif.



References:

- [1] Zhu, C.; Xu, G.; Sun, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 11867.
- [2] (a) Gautier, F-M.; Jones, S.; Martin, S. J. *Org. Biomol. Chem.* **2009**, *7*, 229. (b) Saito, K.; Horiguchi, K.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *Chem. Eur. J.* **2014**, *20*, 7616. (c) Lu, B.; Wu, J.; Yoshikai, N. *J. Am. Chem. Soc.* **2014**, *136*, 11598.
- [3] Zheng, Y.; Xue, Z.; Liu, L.; Shu, C.; Yuan, W.; Zhang, X. *Org. Biomol. Chem.* **2013**, *11*, 412.
- [4] Cao, H.; Wang, X.; Jiang, H.; Zhu, Q.; Zhang, M.; Liu, H. *Chem. Eur. J.* **2008**, *14*, 11623.

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6.63

4.81

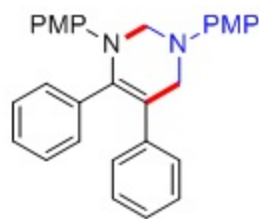
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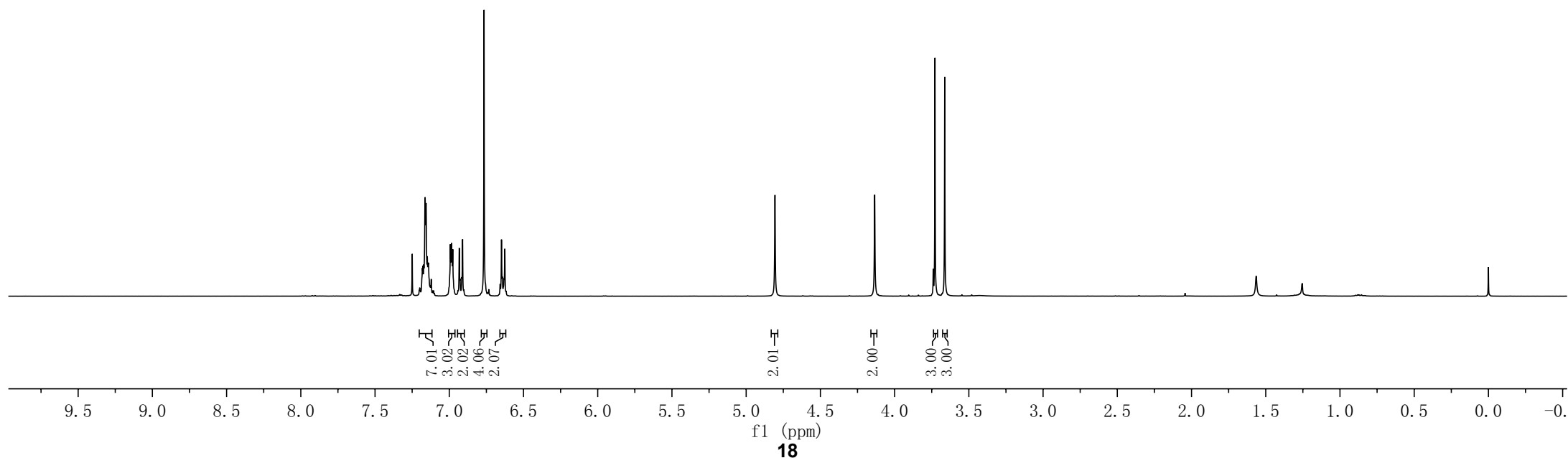
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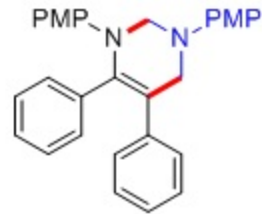
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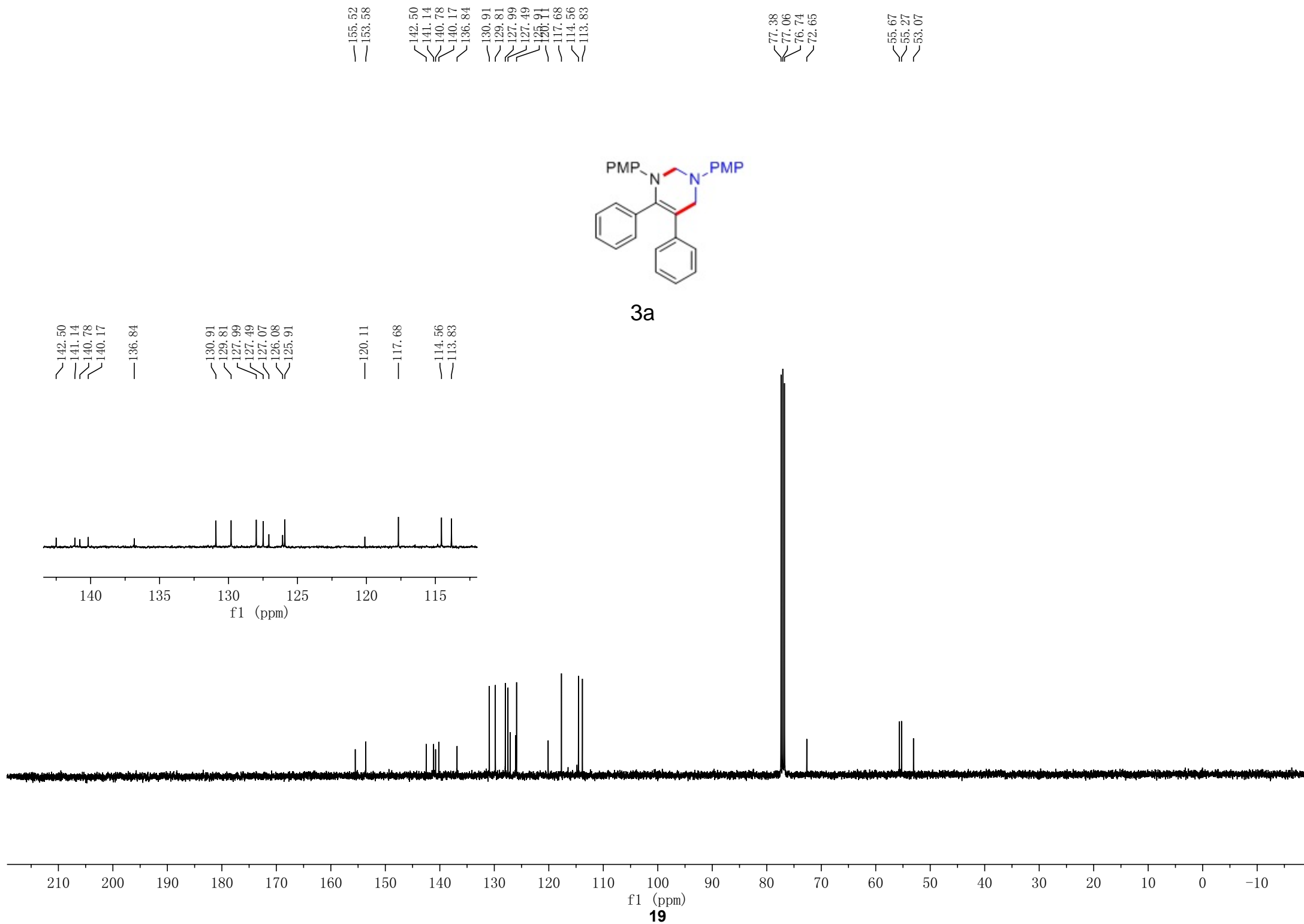


3a





3a



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6.62

— 4.79

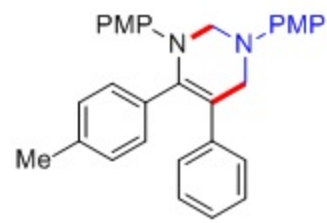
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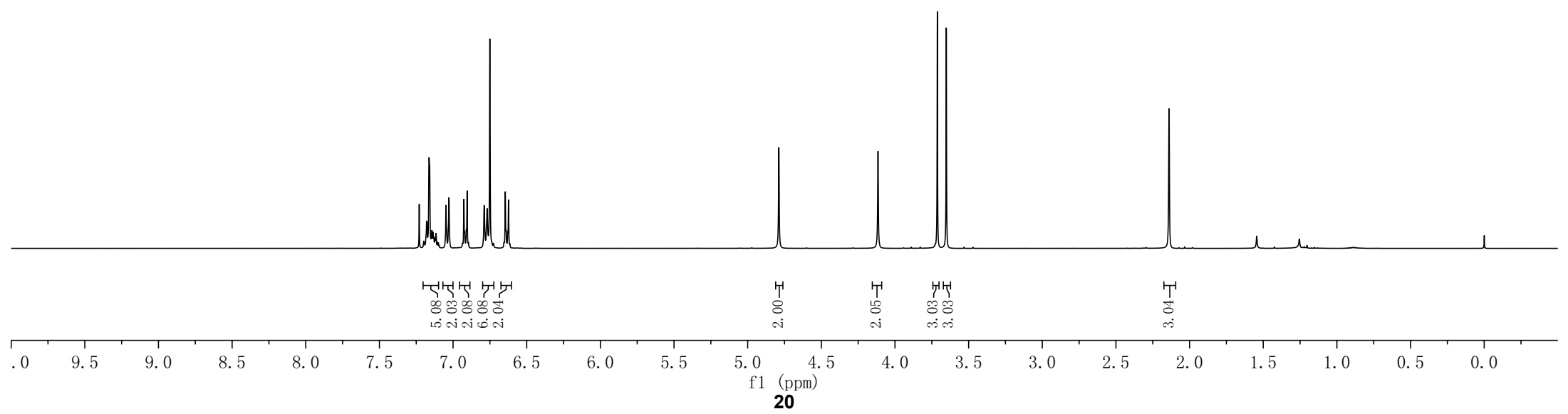
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3b

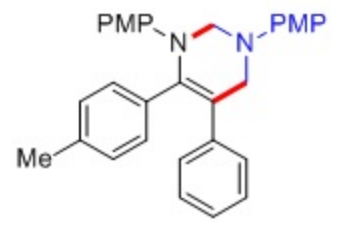


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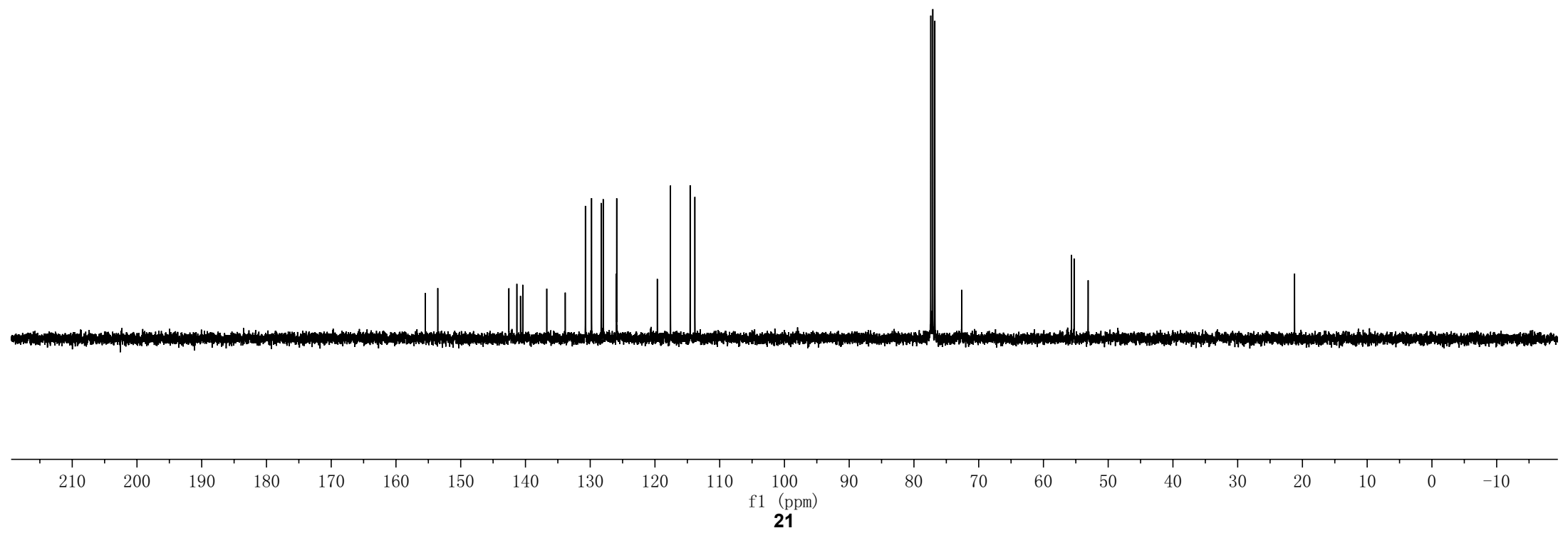
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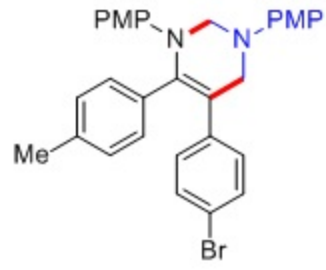
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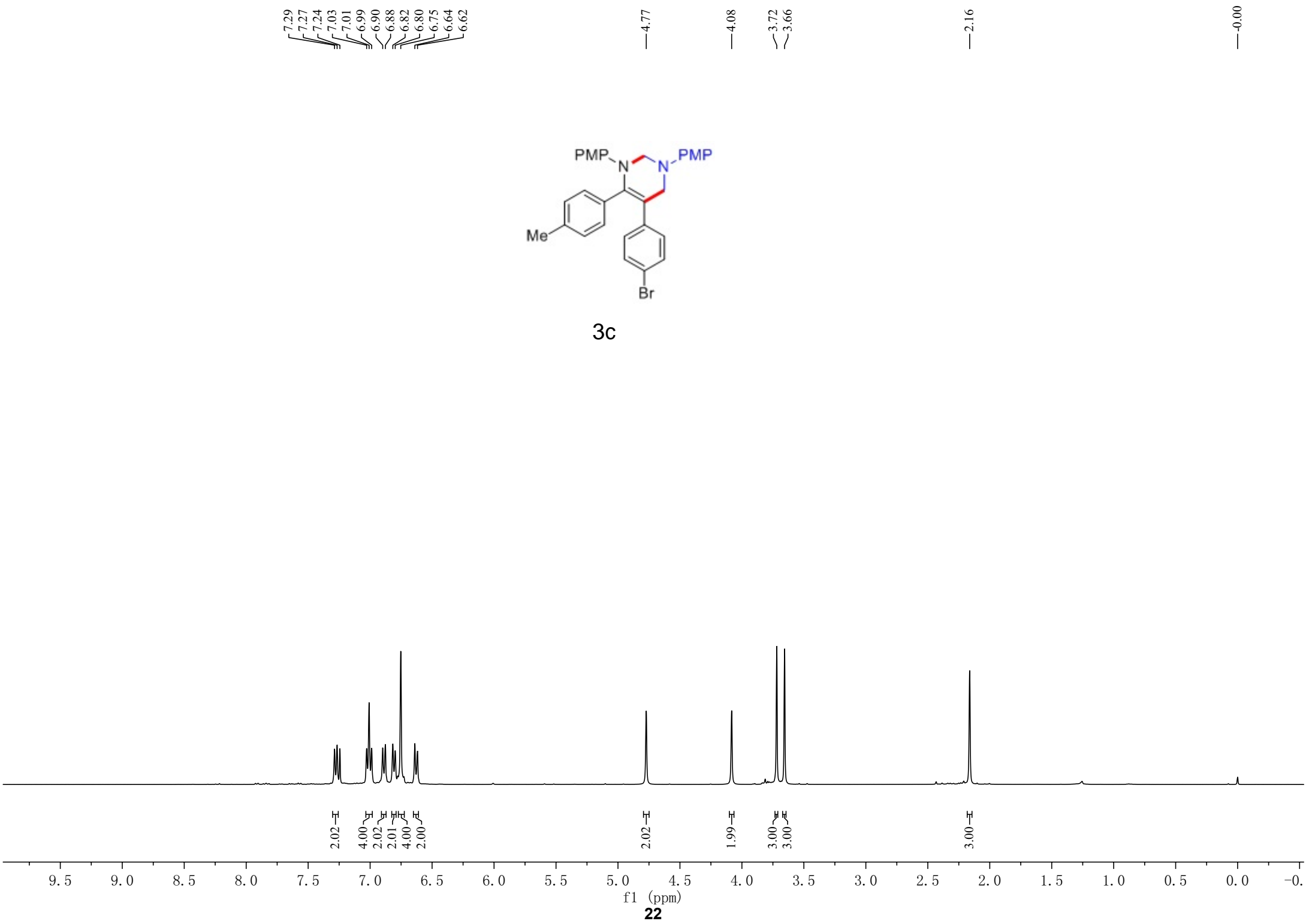


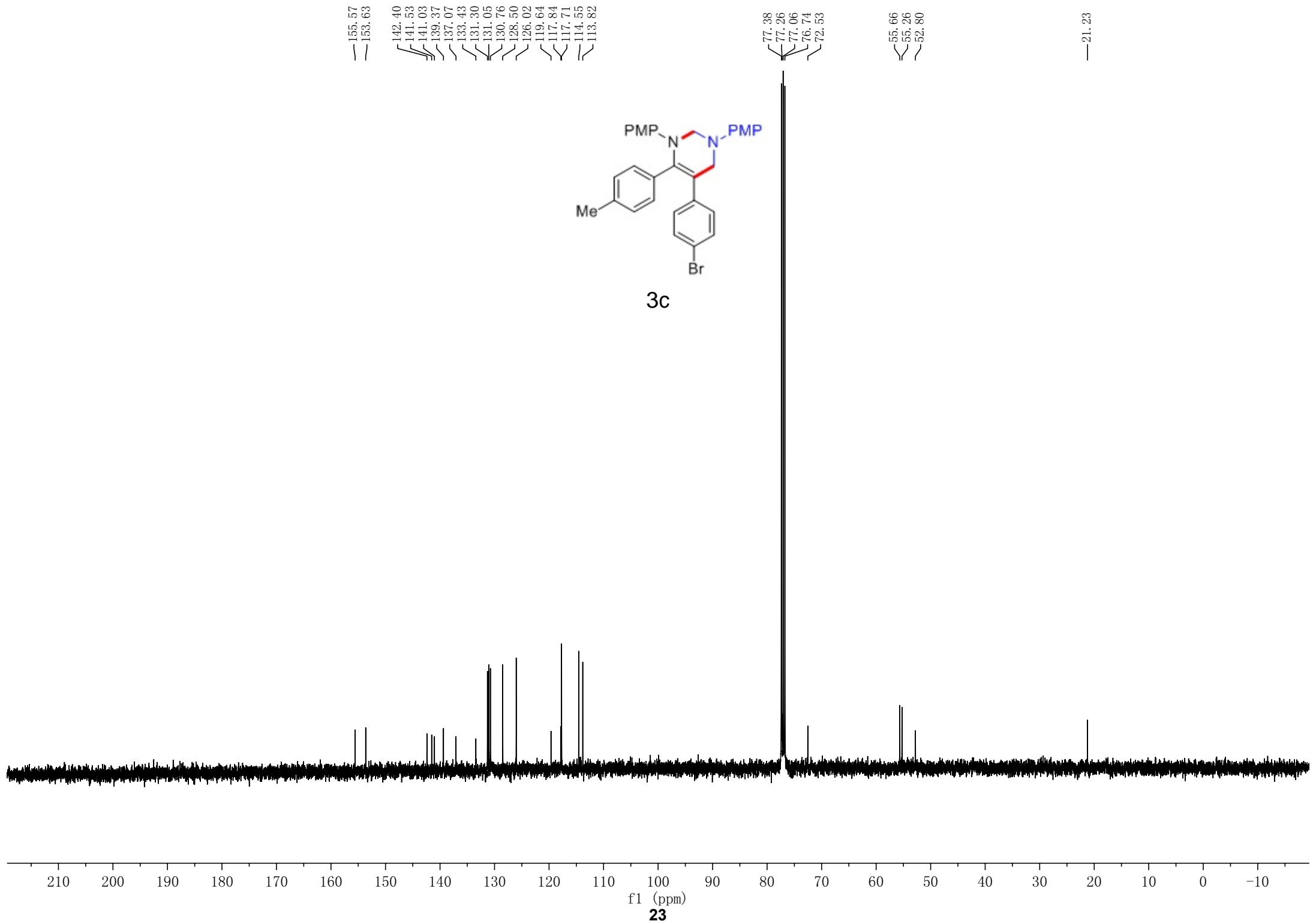
3b





3c





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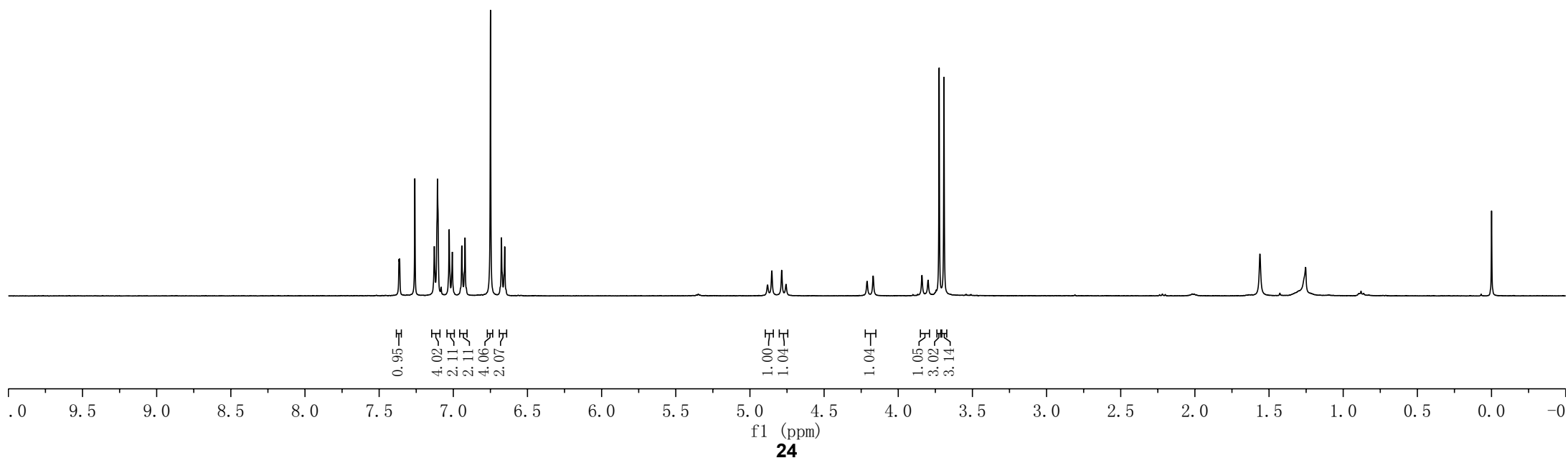
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— 1.56

— 0.00



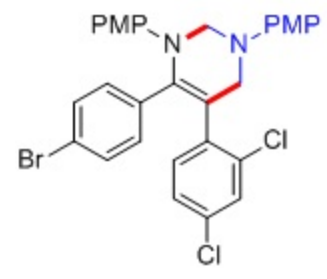
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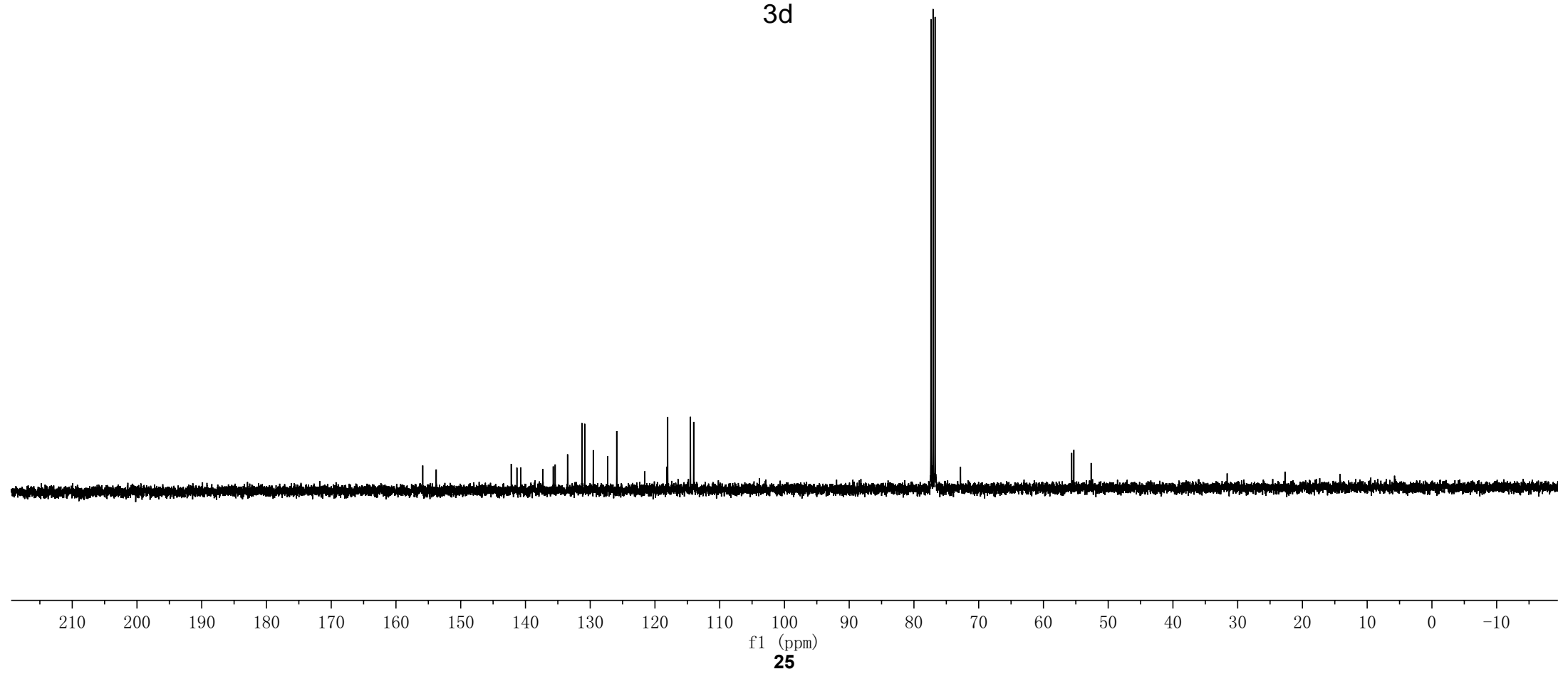
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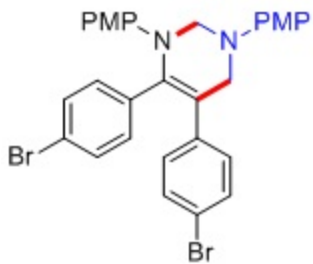
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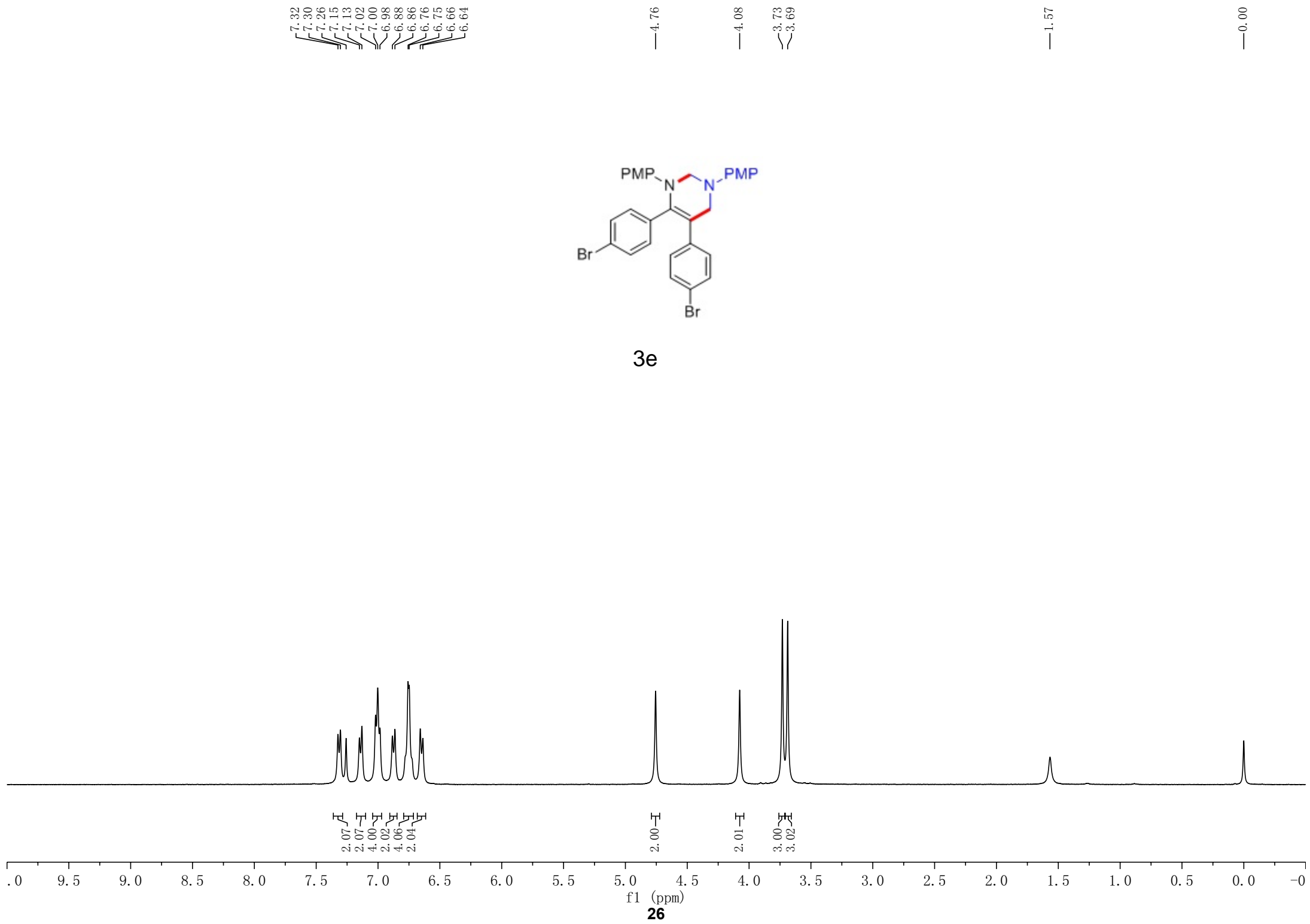


3d





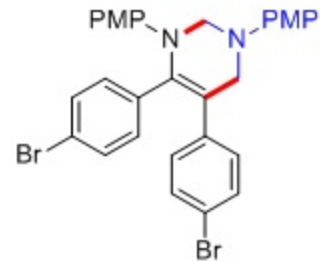
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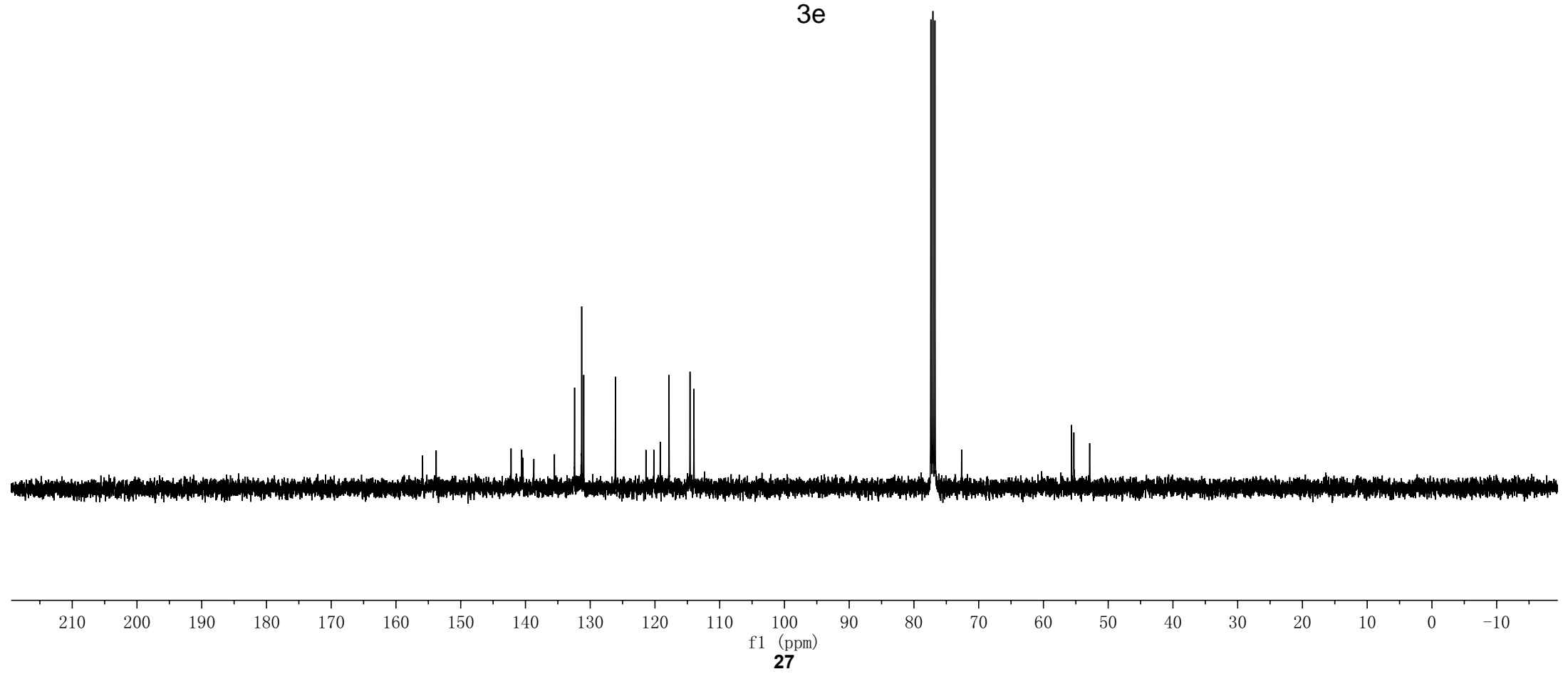
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52.86



3e



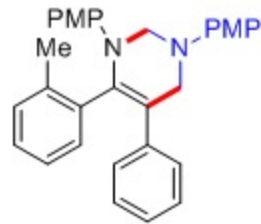
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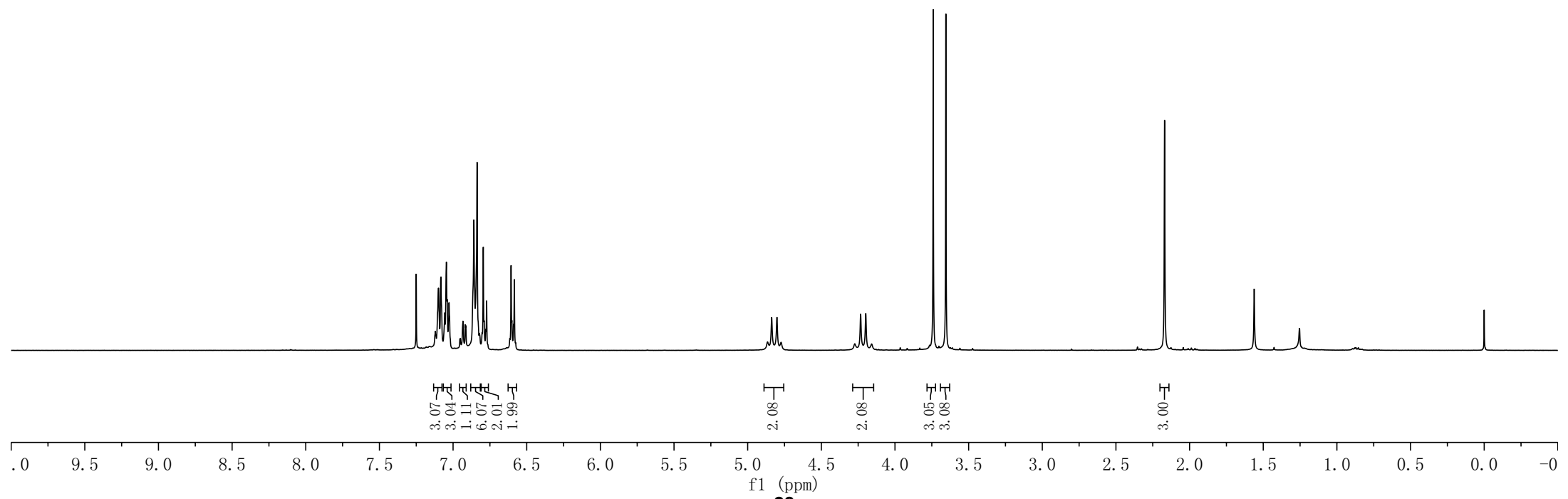
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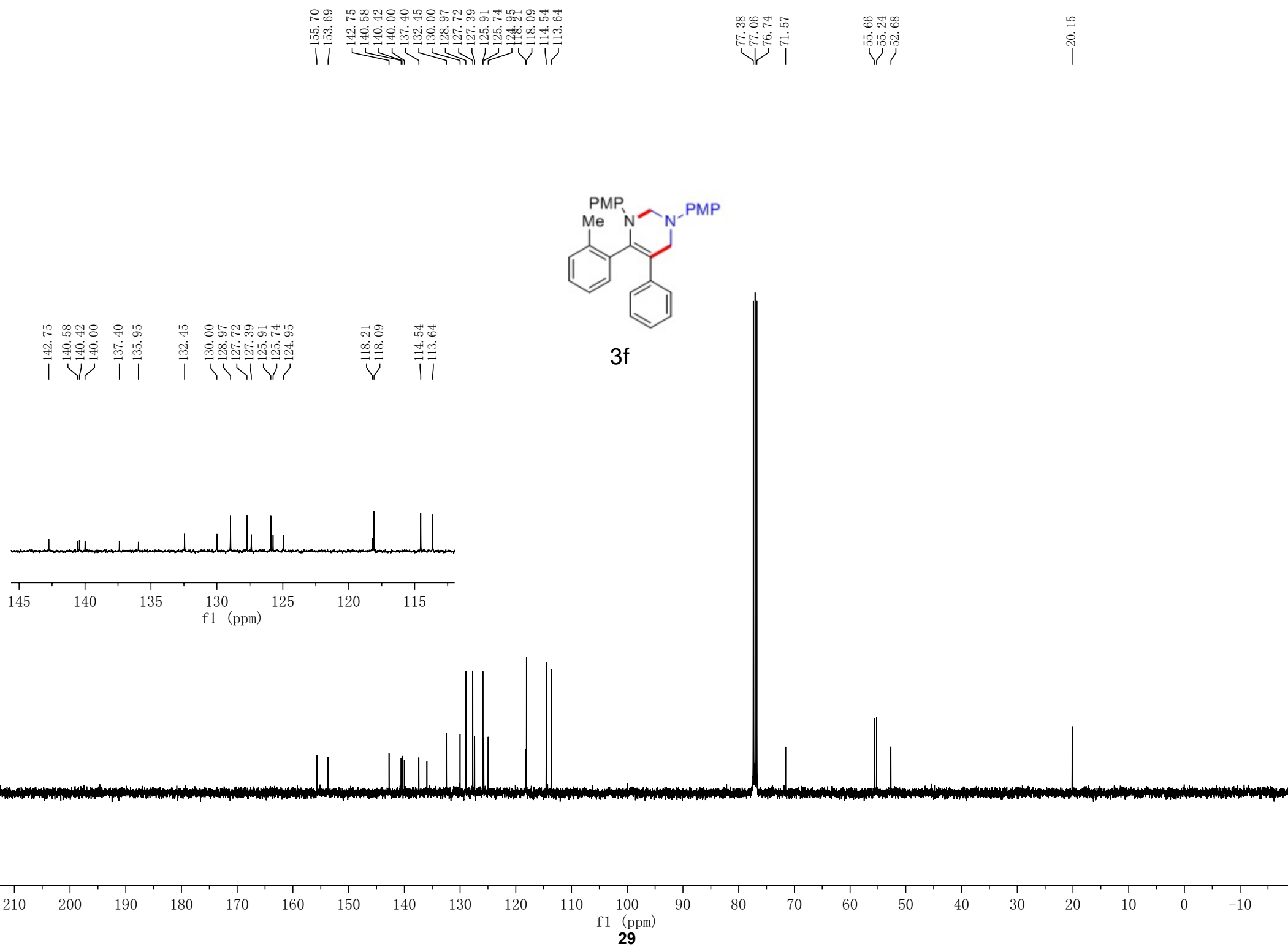
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3f





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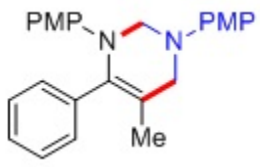
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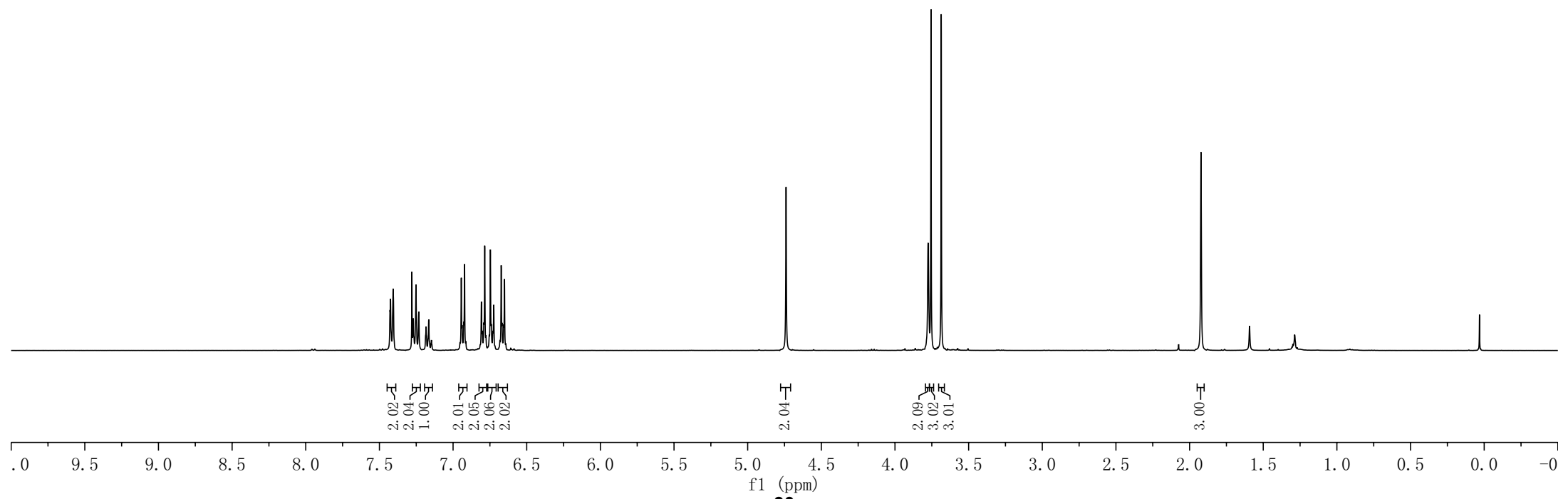
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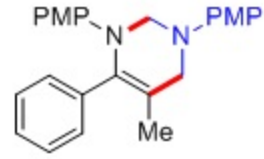
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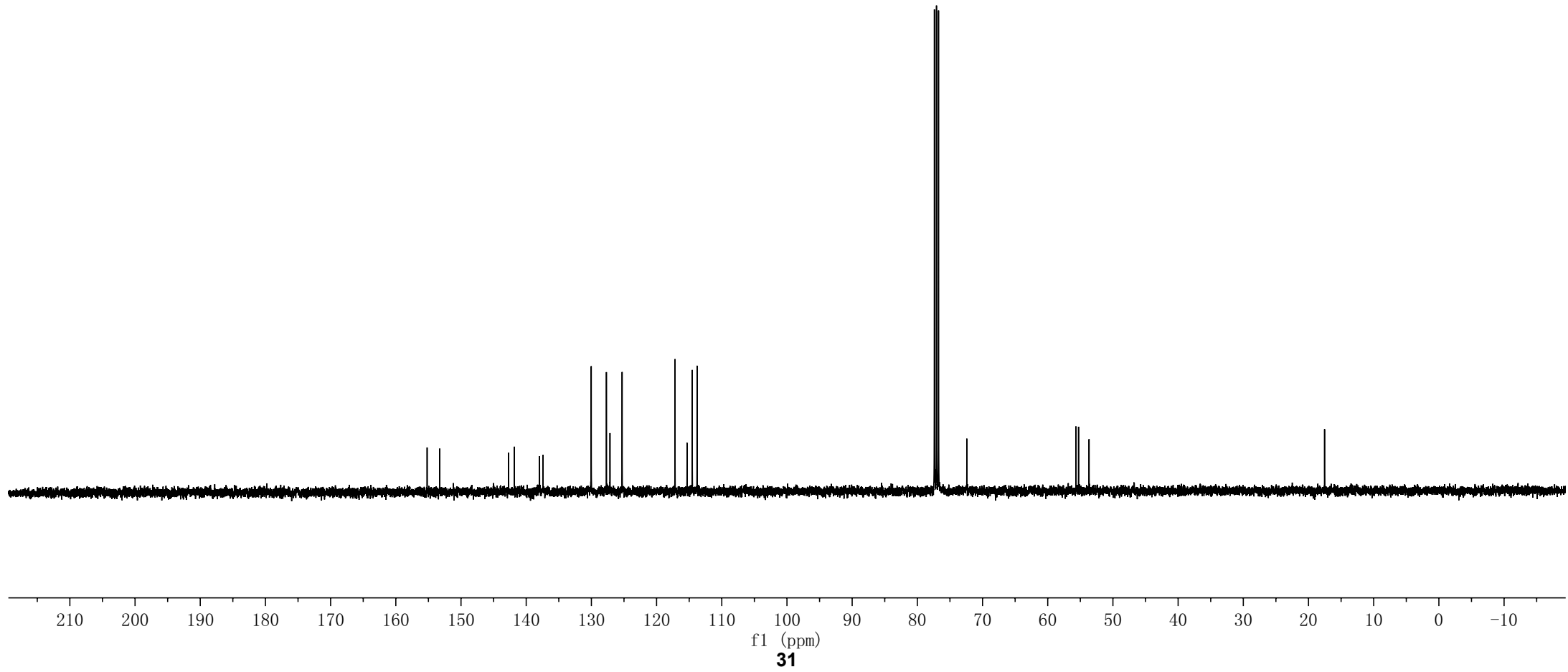
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3g



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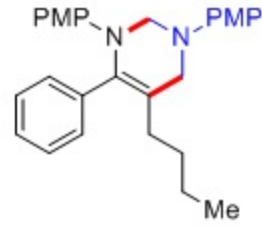
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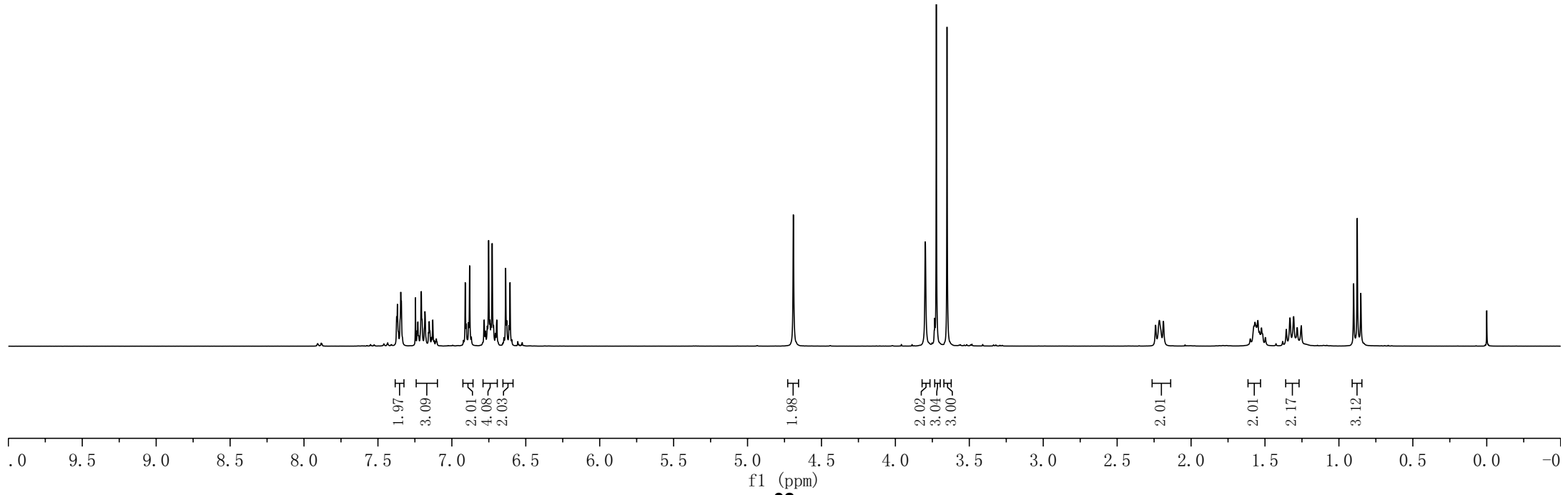
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2.19

1.58
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1.56
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1.52
1.33
1.31
1.28
0.90
0.88
0.85

-0.00



3h



155.23
153.27

142.86
141.69
138.44
137.57

129.88
127.66
127.18
125.38

119.92
117.23
114.53
113.75

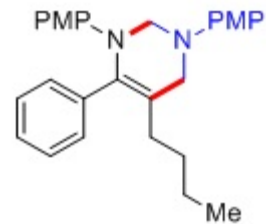
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76.63
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51.65

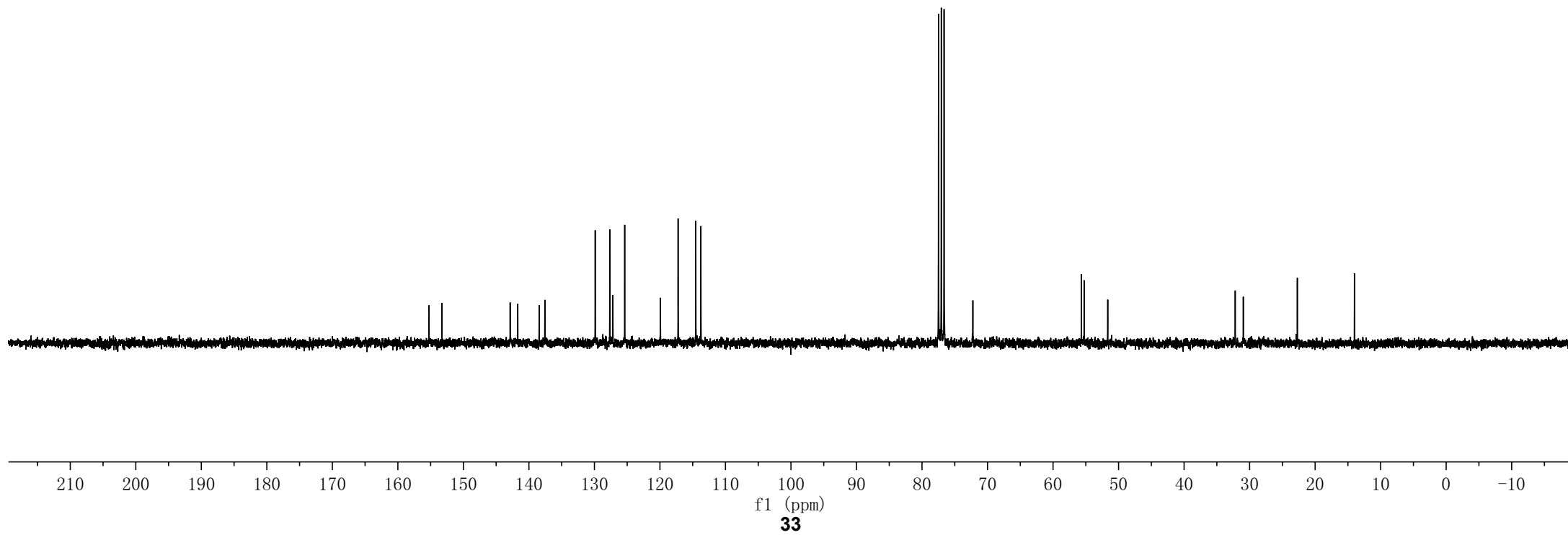
32.20
30.96

22.72

14.00



3h



7.26
7.13
6.93
6.90
6.80
6.77
6.63
6.63
6.61
6.53
6.51

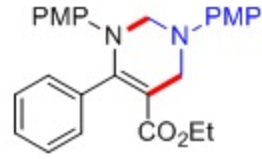
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4.27

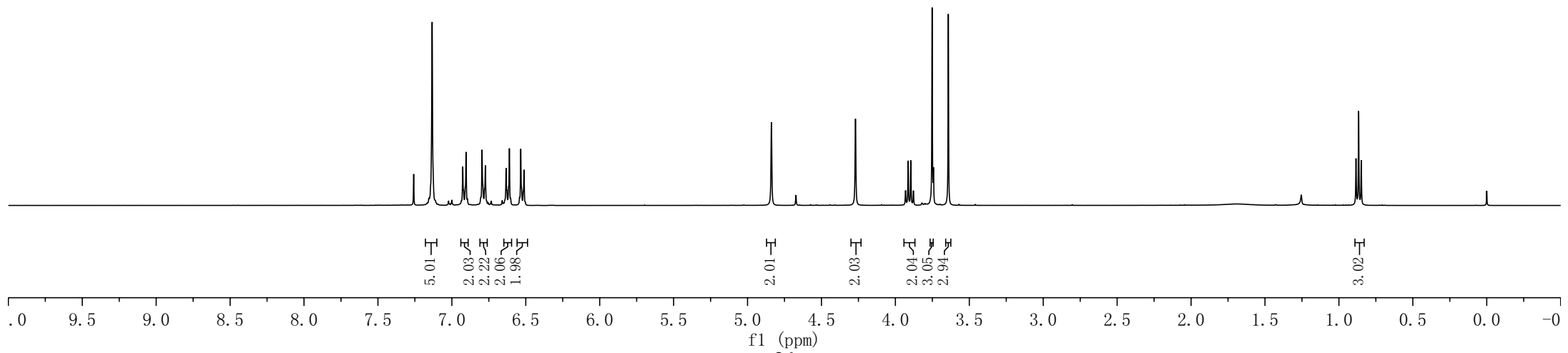
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3.64

0.88
0.87
0.85

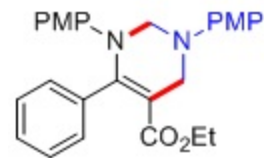
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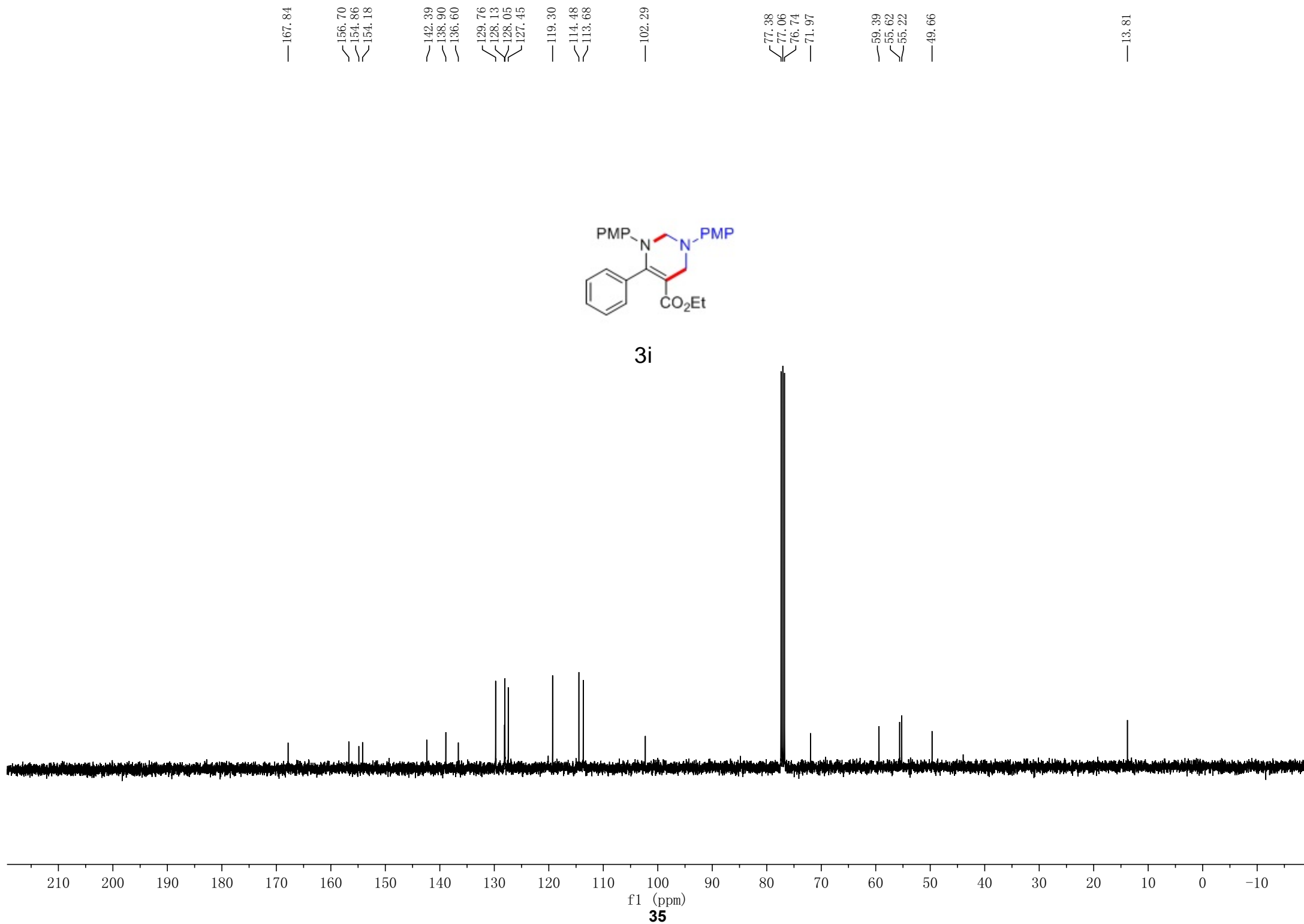
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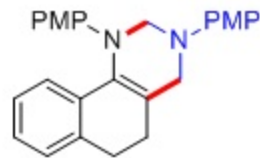


34

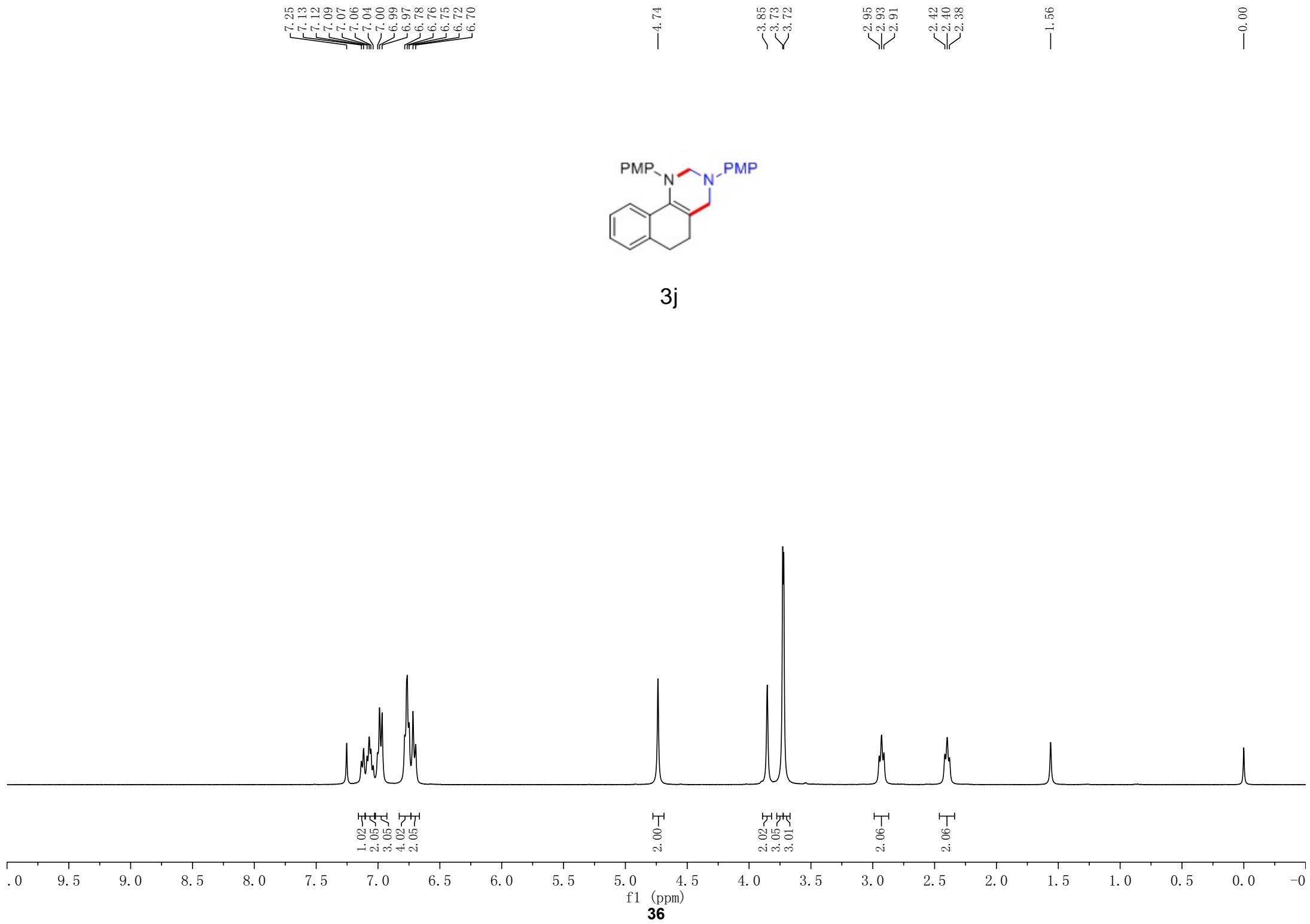


3i





3j

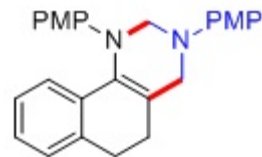


155.15
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148.26
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134.85
131.78
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121.74
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114.58
114.28

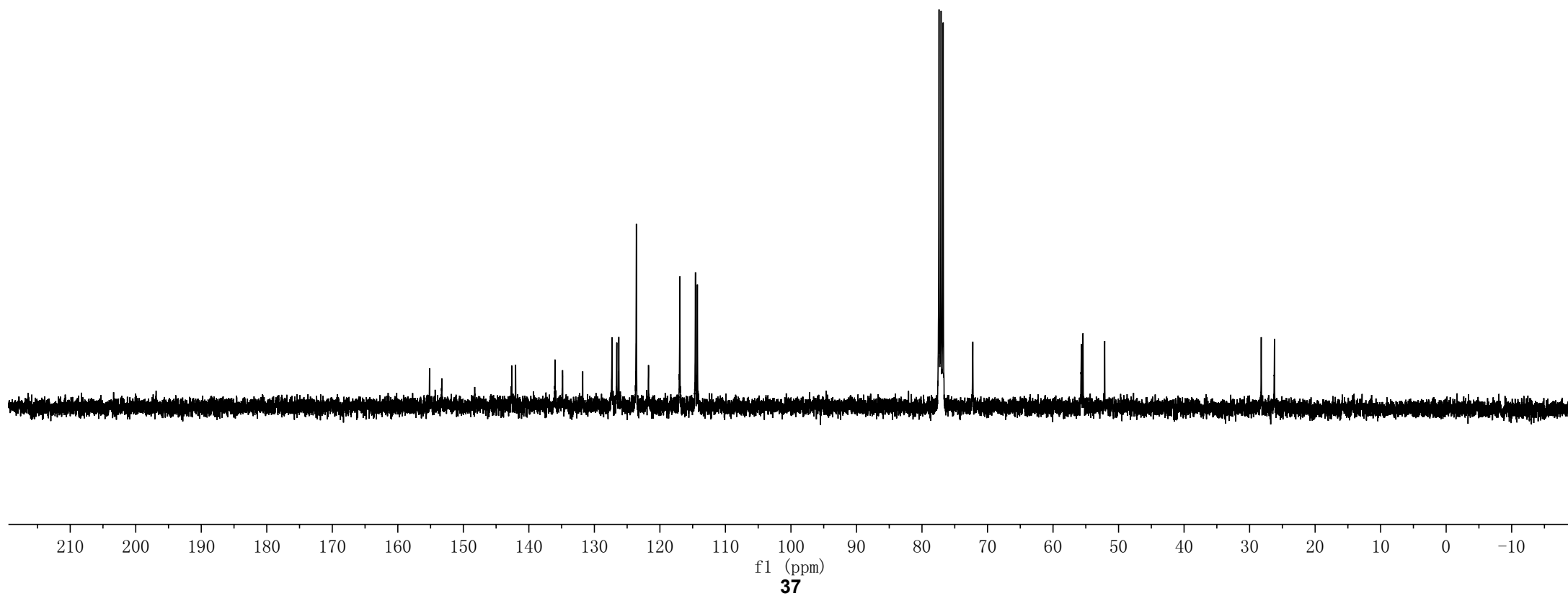
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52.12

28.22
26.20



3j

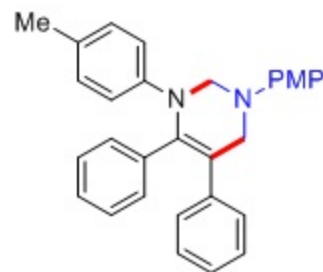


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7.18
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7.15
7.14
7.14
7.01
7.00
6.99
6.91
6.89
6.87
6.85
6.78

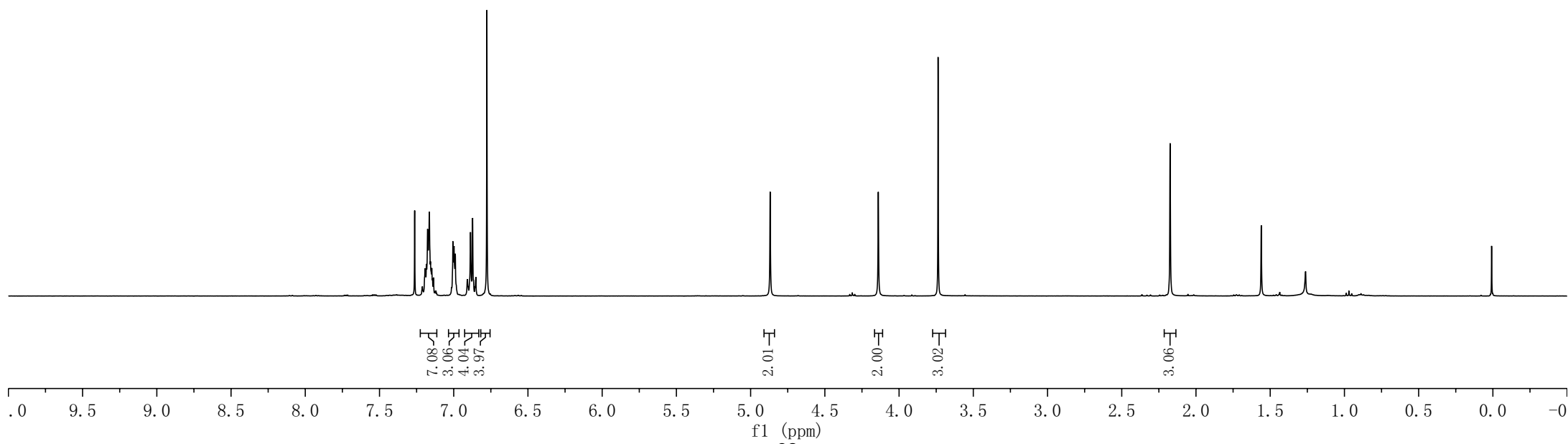
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3.74

2.17
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1.26

0.01



3k



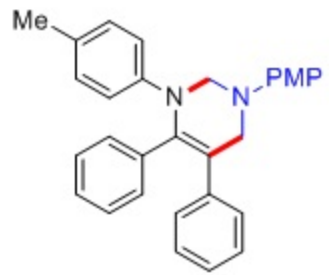
38

153.55
145.17
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127.04
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117.64
114.53

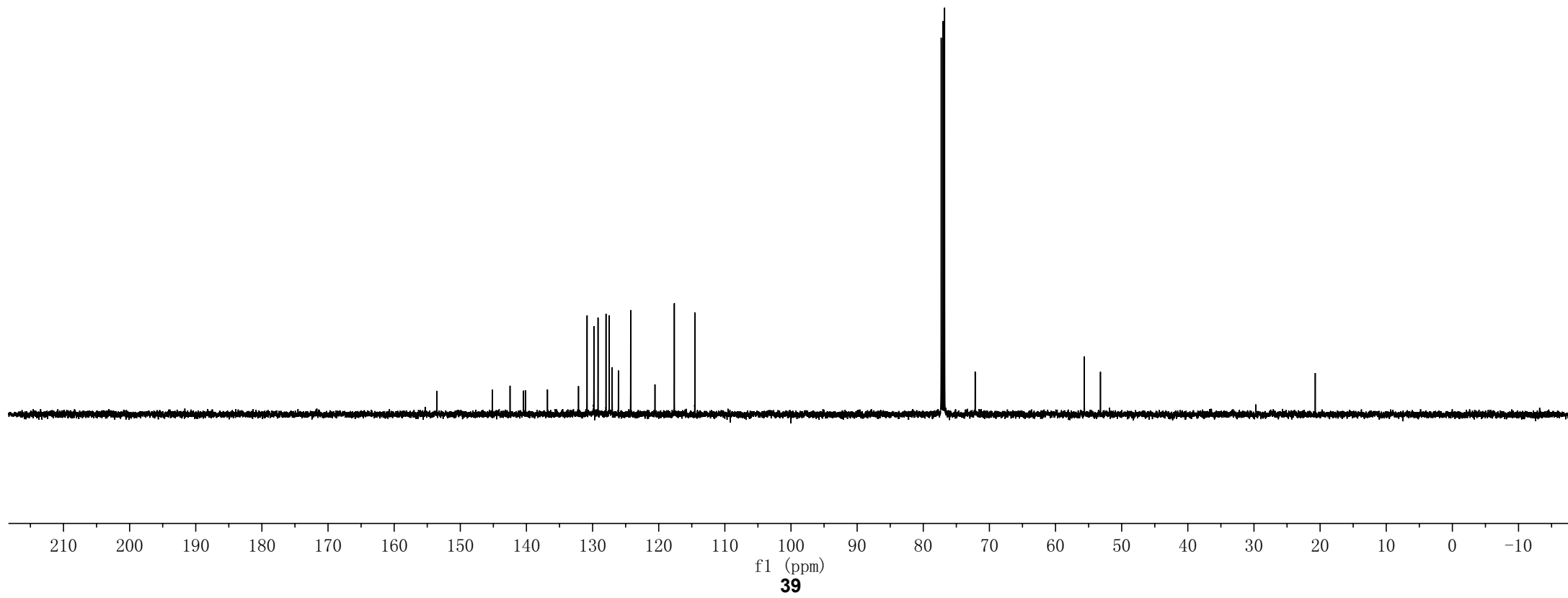
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72.15

55.65
53.21

20.73



3k



7.26
7.21
7.21
7.19
7.18
7.18
7.17
7.16
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7.01
7.00
6.95
6.93
6.89
6.87
6.77

4.88

4.14

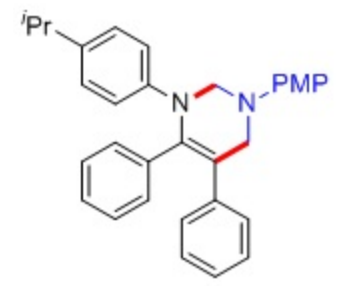
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2.68

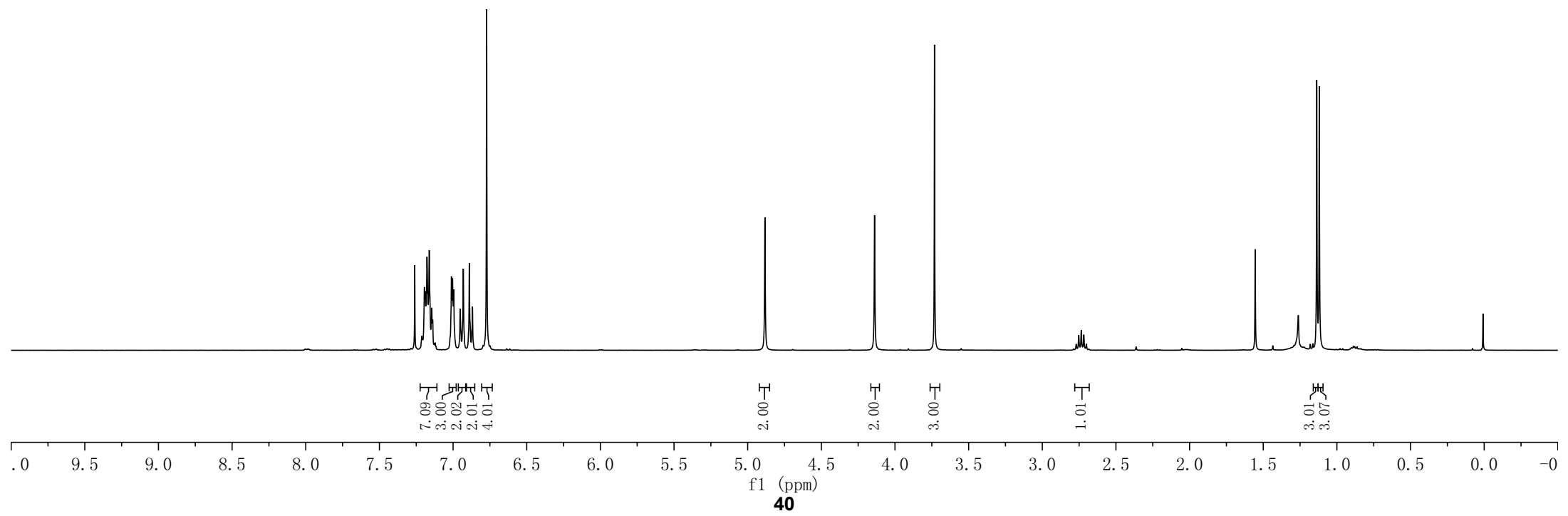
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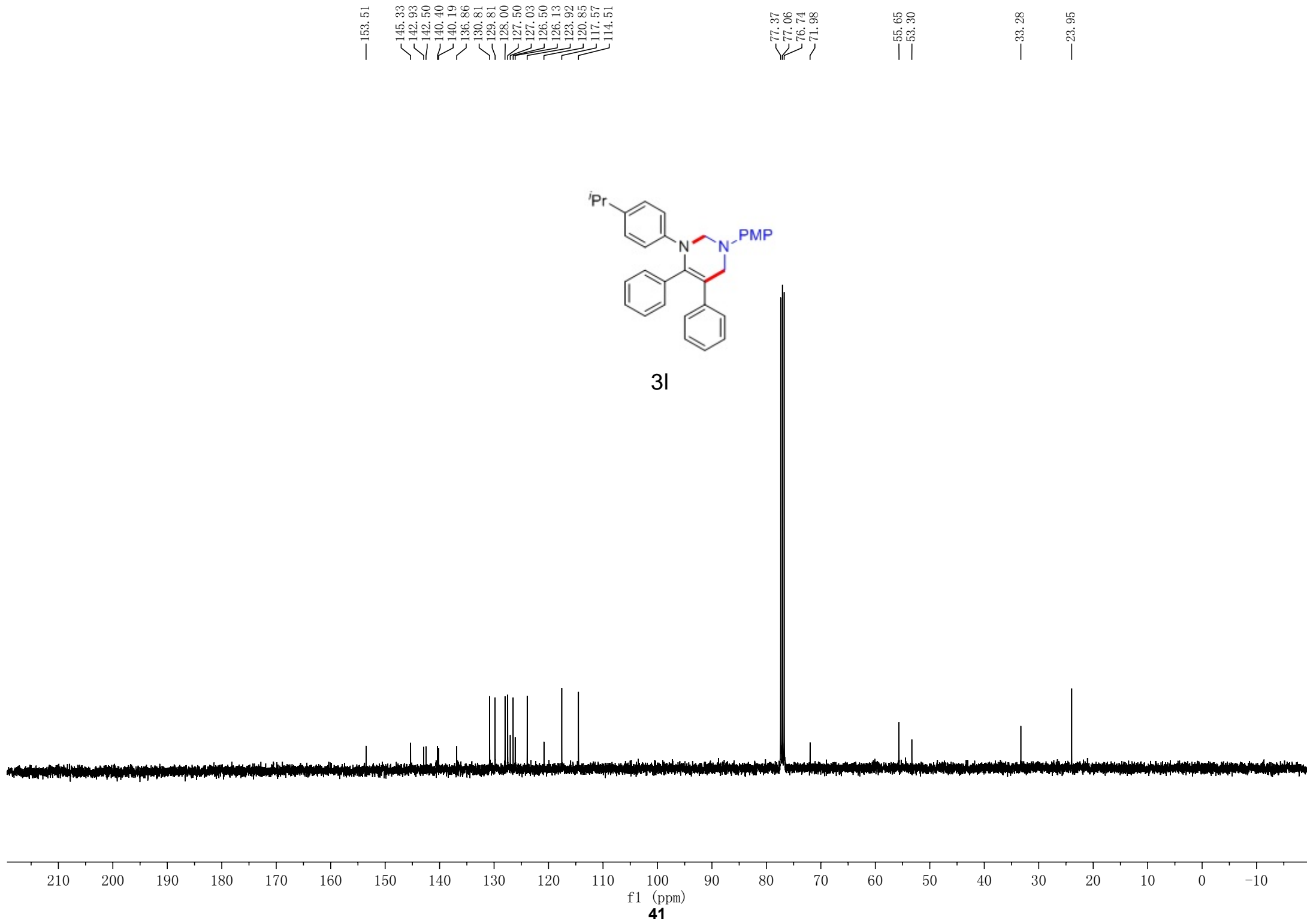
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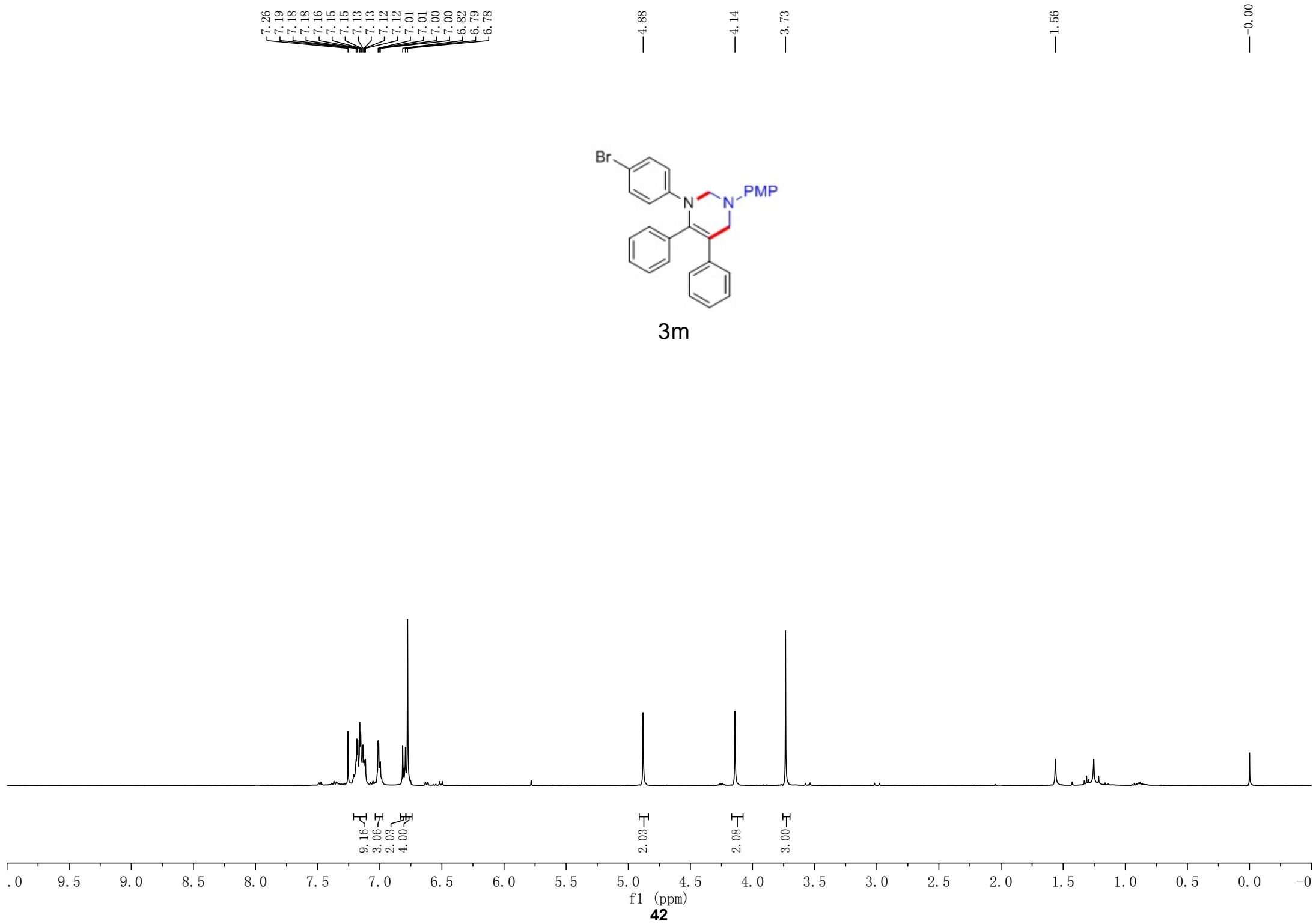
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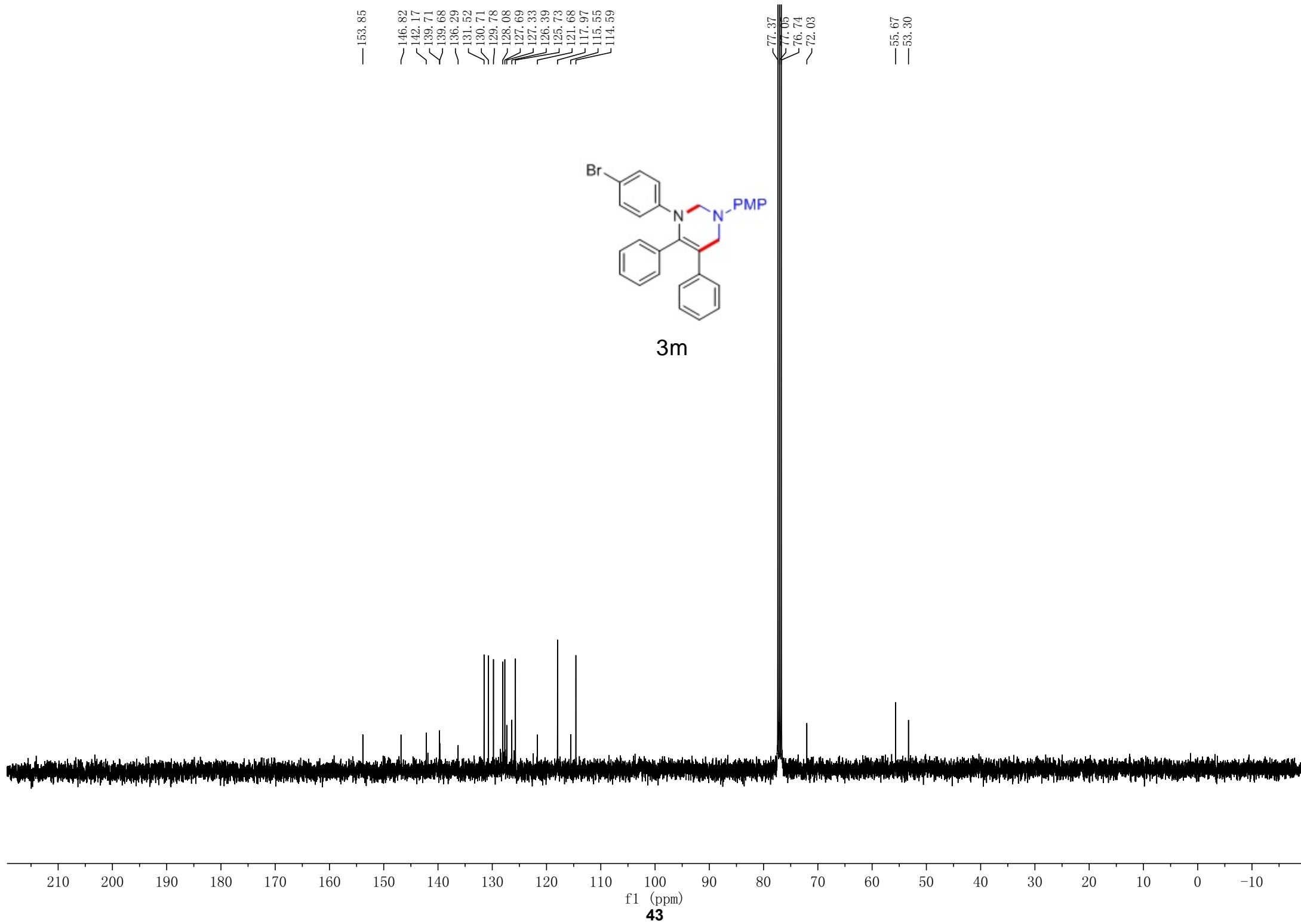


31









7.25
7.20
7.18
7.16
7.15
7.14
7.13
7.13
7.02
7.01
7.00
6.99
6.97
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6.92
6.92
6.82
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6.78
6.76
6.76

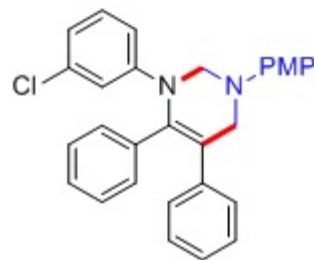
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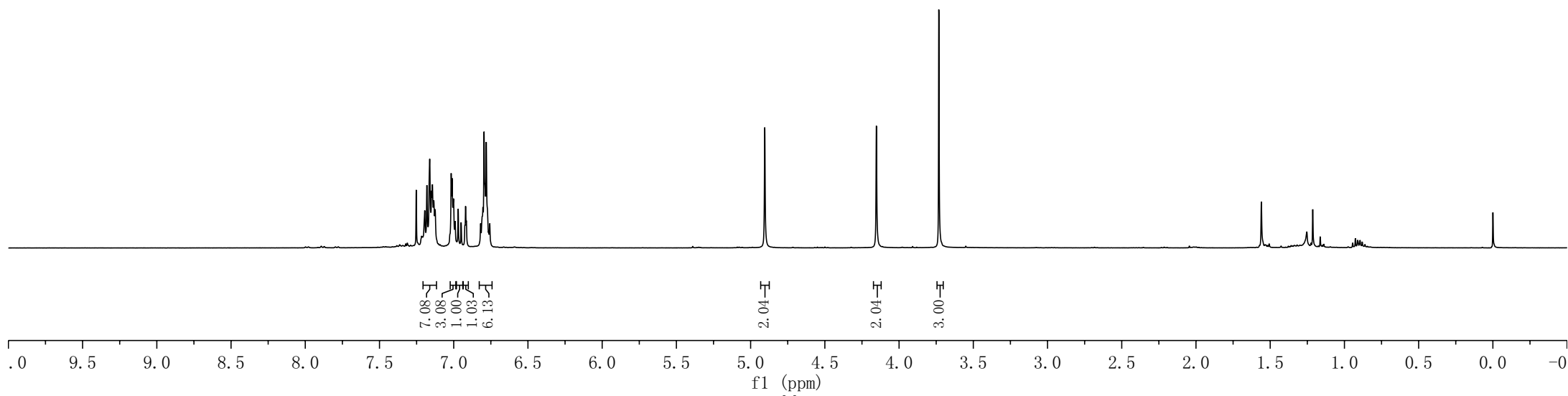
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1.56

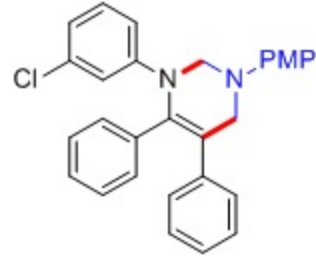
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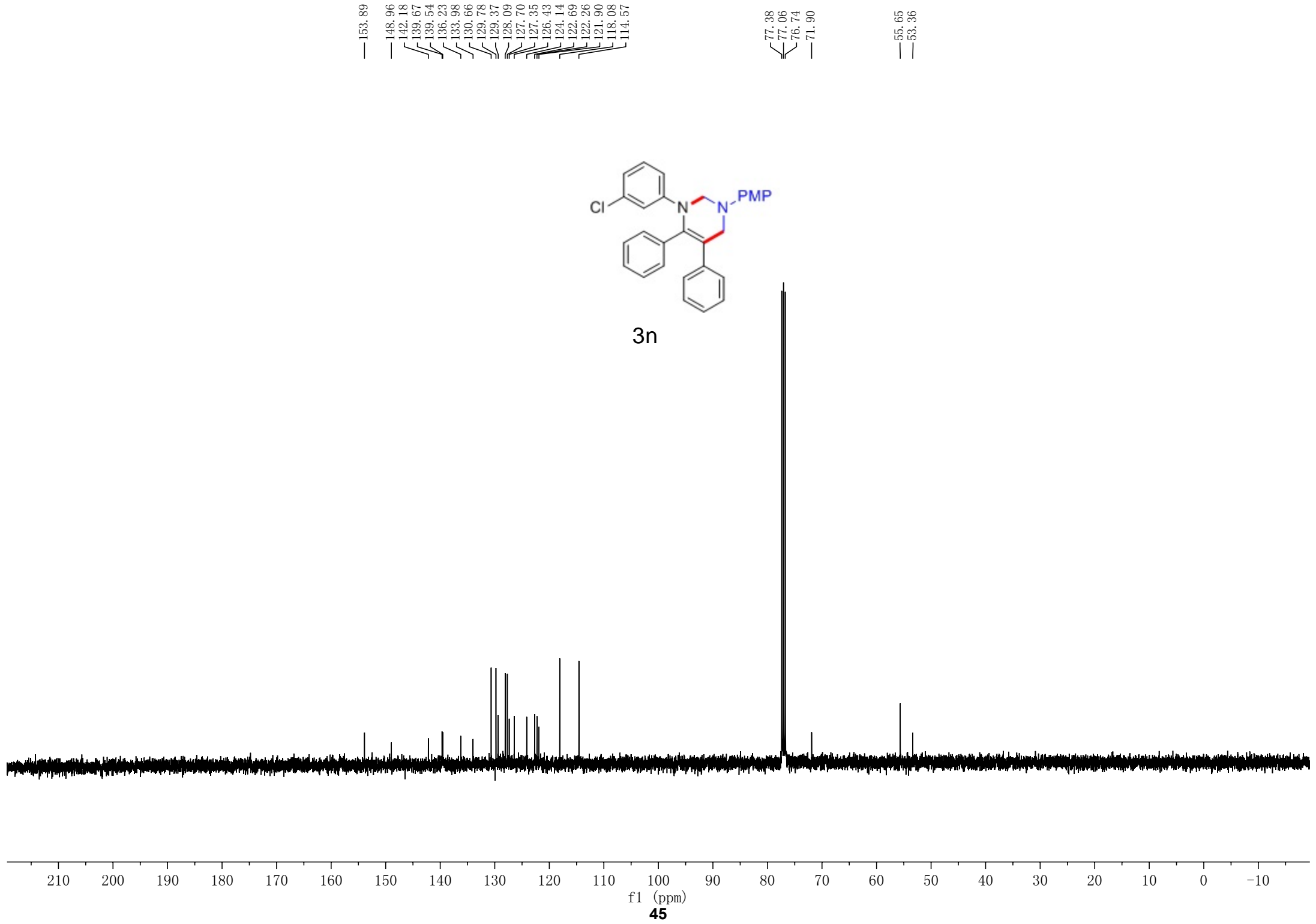
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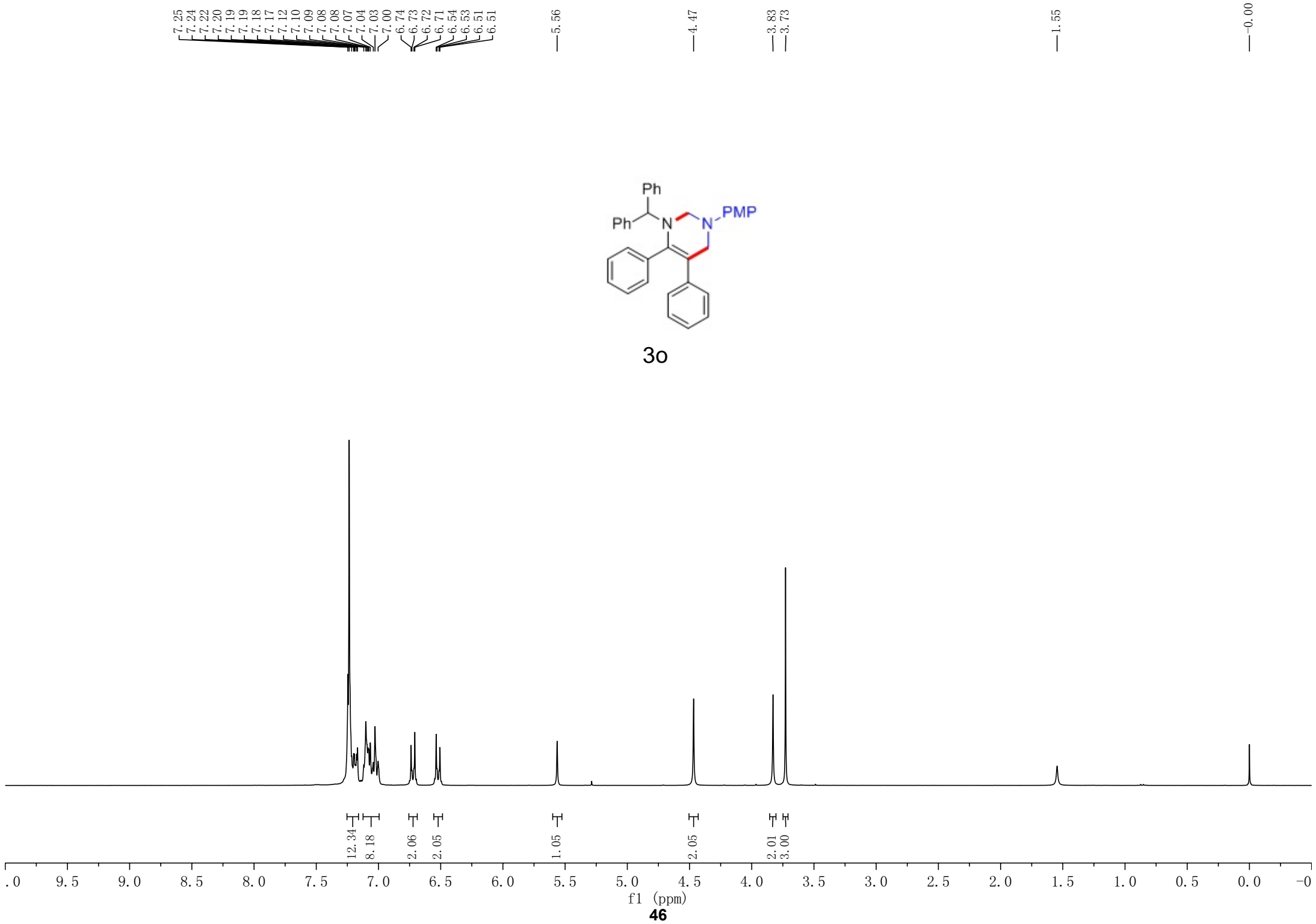


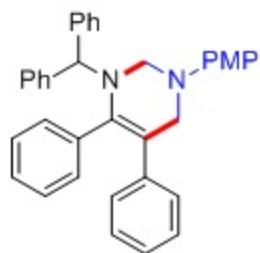
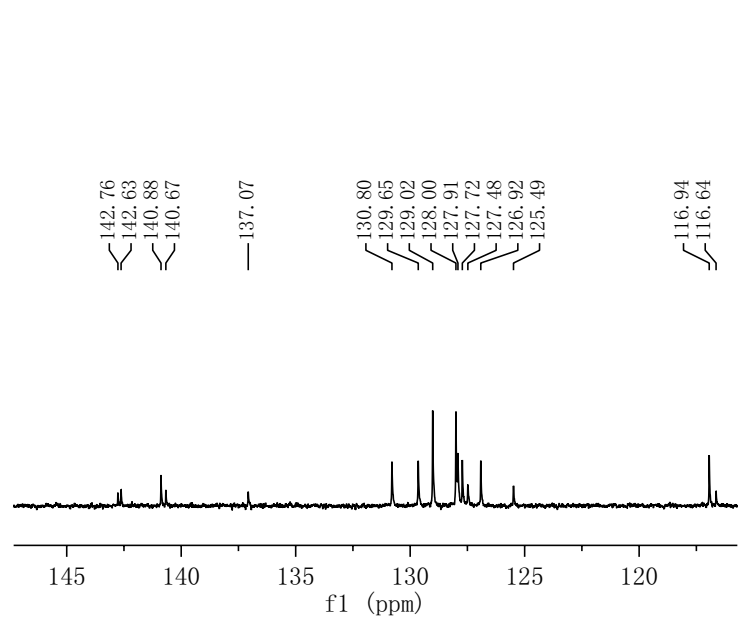
44



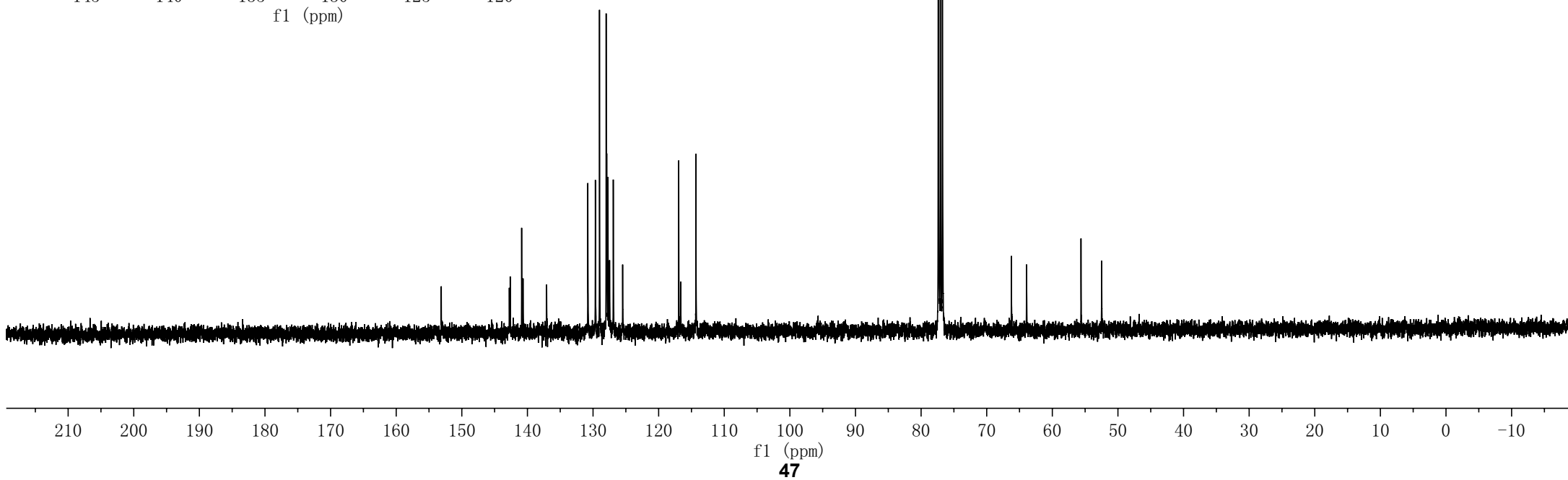
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30



47

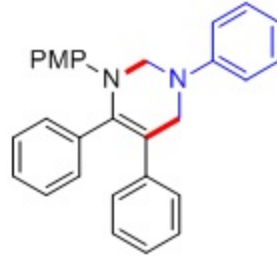
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7.17
7.15
7.14
7.01
7.01
7.00
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6.95
6.81
6.79
6.77
6.67
6.67
6.65
6.65

4.93

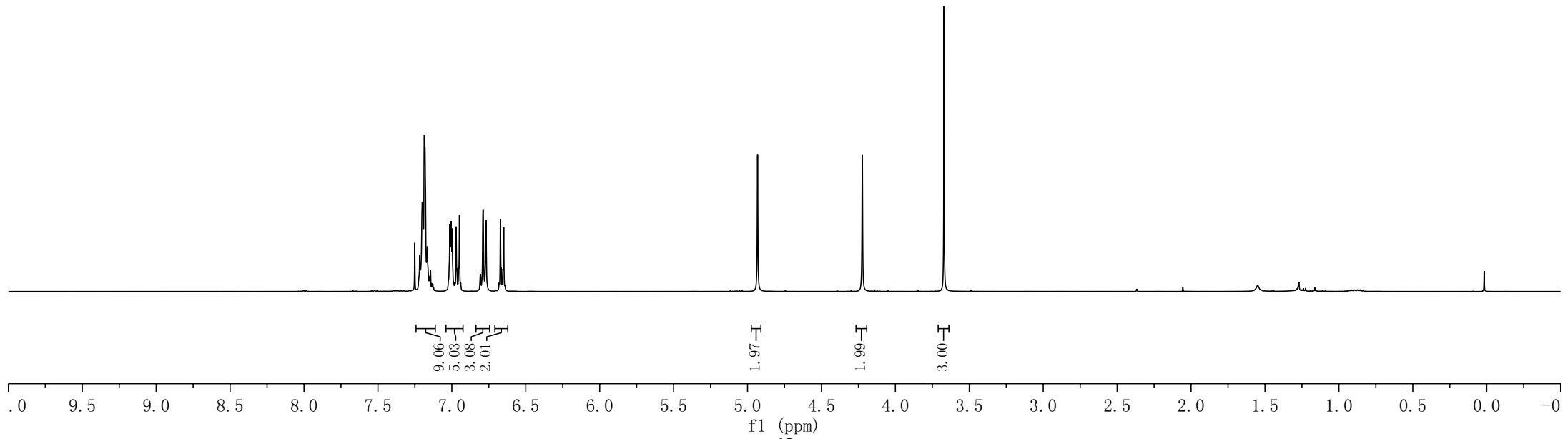
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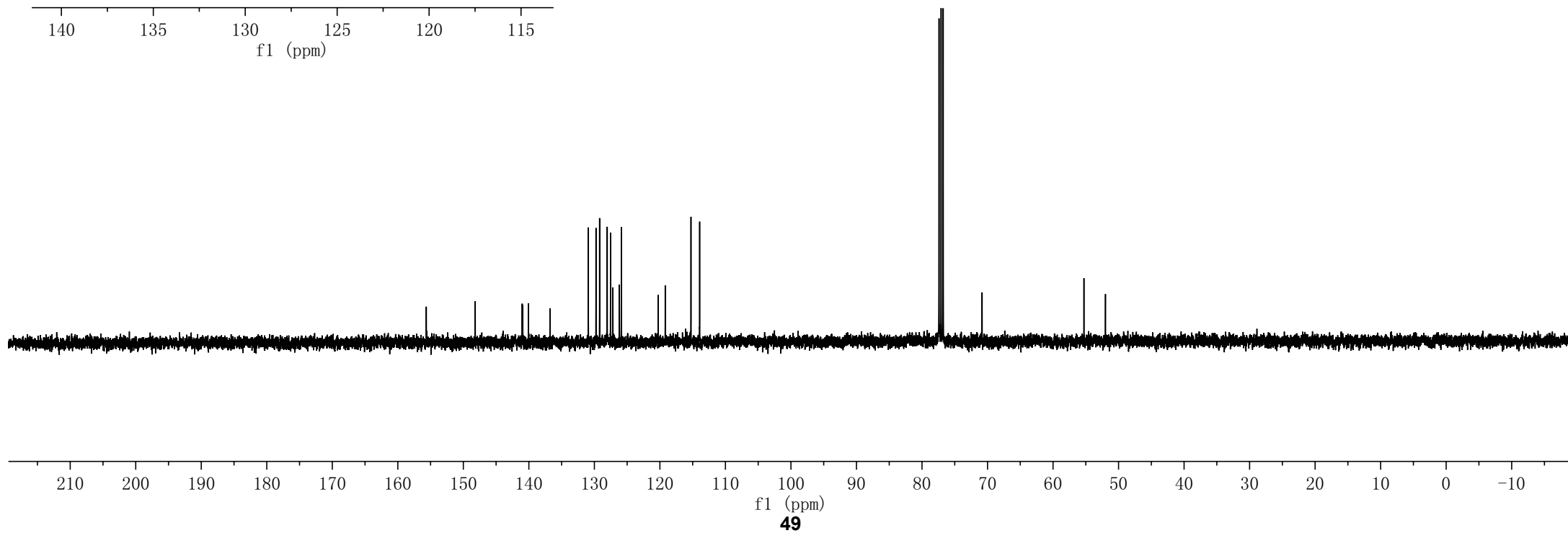
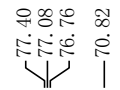
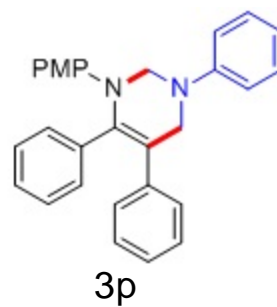
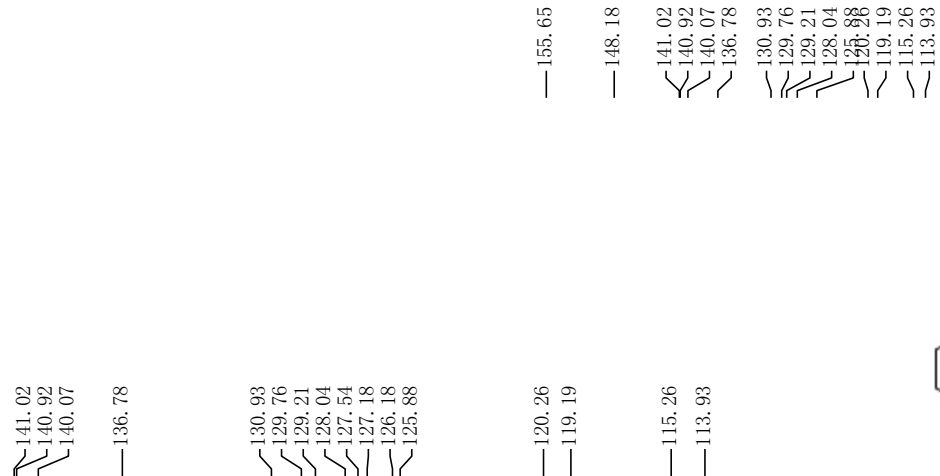
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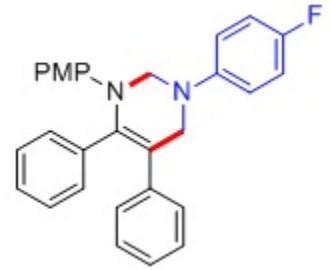
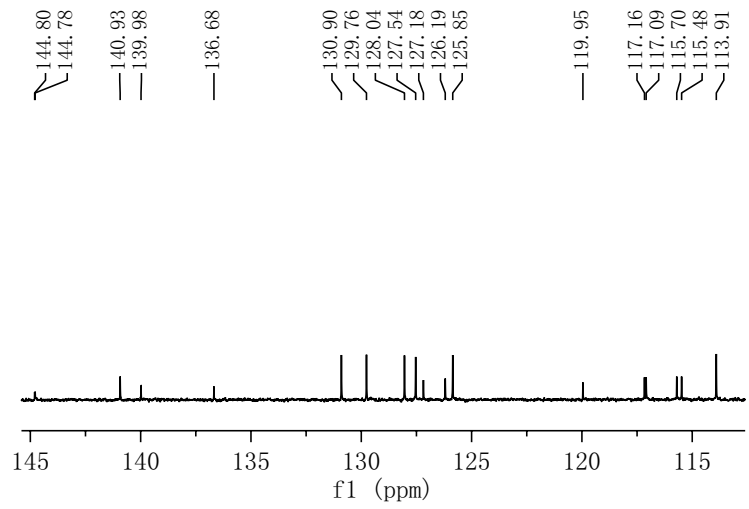
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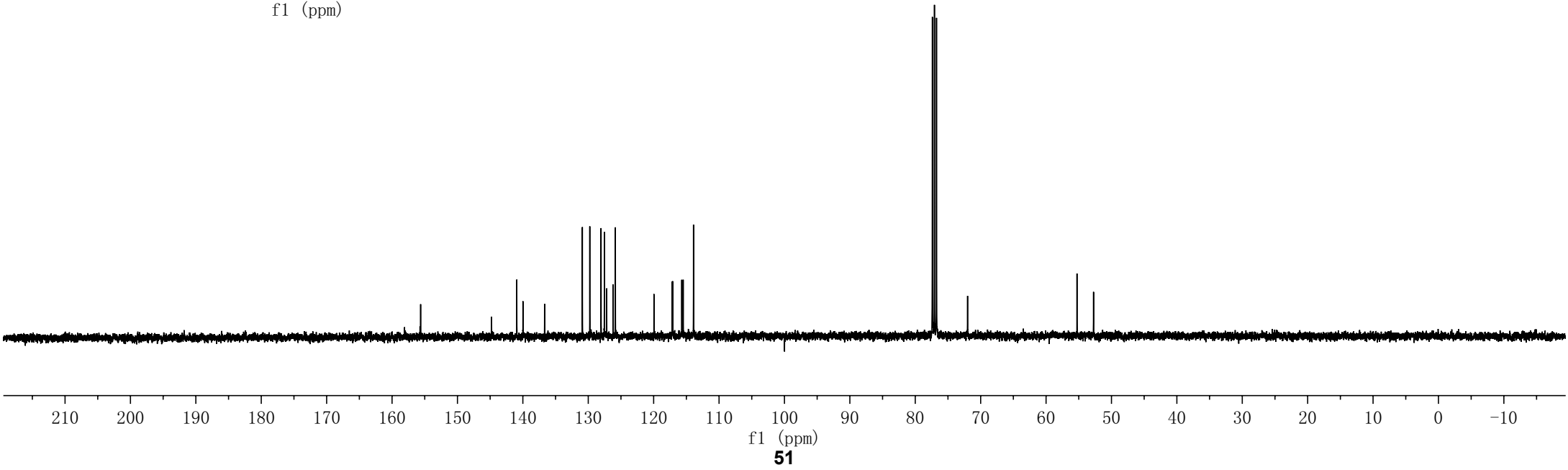
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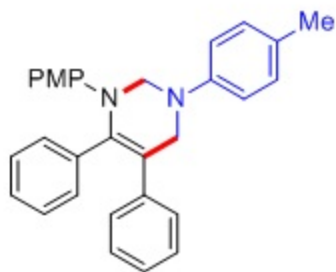


3q



51

7.21
7.17
7.16
7.14
7.14
7.13
7.11
7.00
6.98
6.97
6.94
6.92
6.70
6.67
6.64
6.62



3r

—4.85

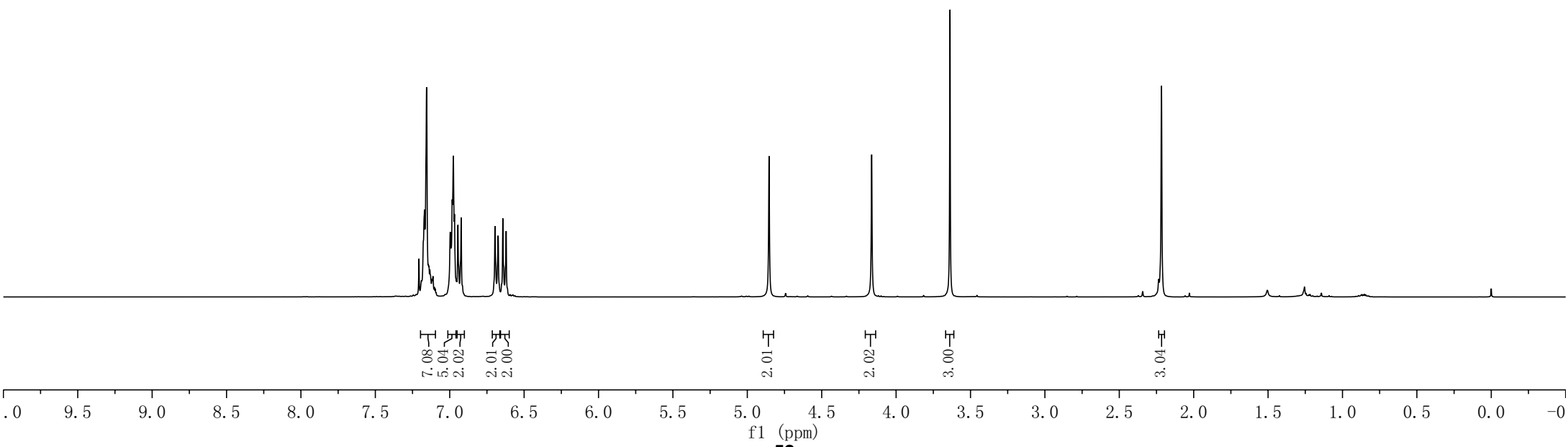
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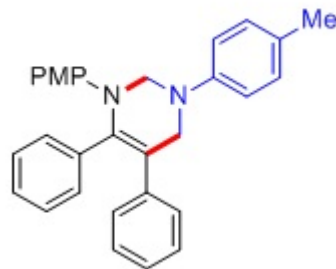
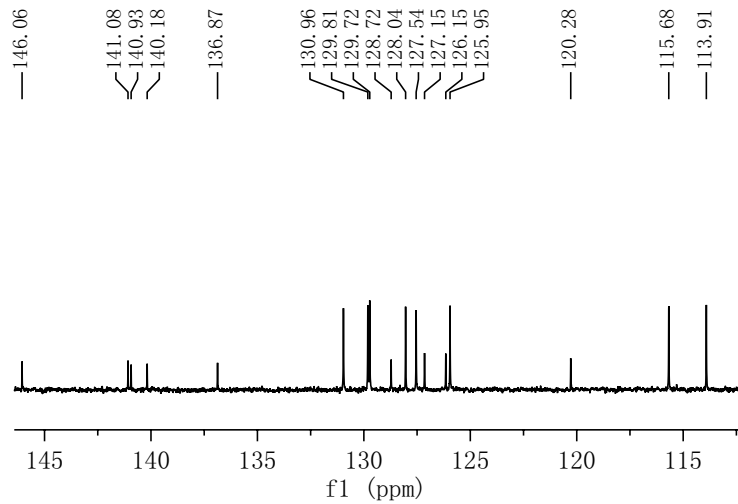
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—2.22

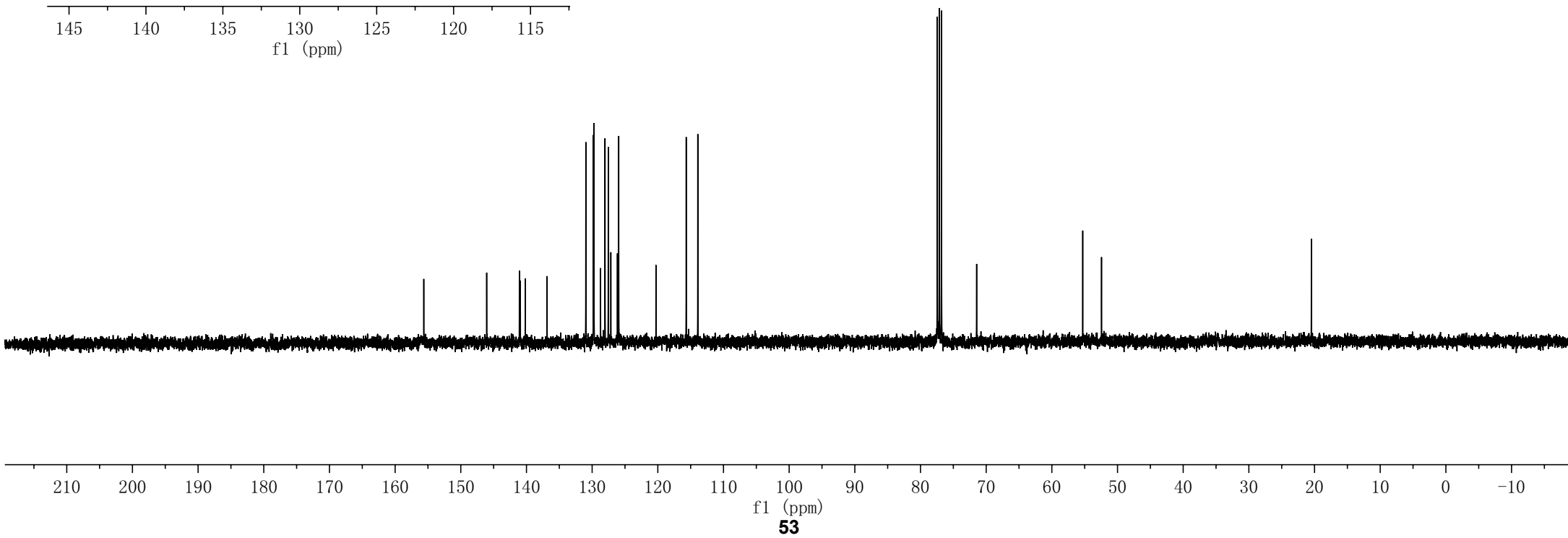
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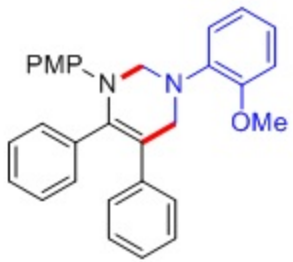




3r



7.25
7.17
7.17
7.16
7.15
7.14
7.13
7.13
7.12
7.11
7.07
7.06
7.05
7.05
6.98
6.98
6.97
6.91
6.90
6.89
6.88
6.87
6.86
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6.81
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6.57
6.57

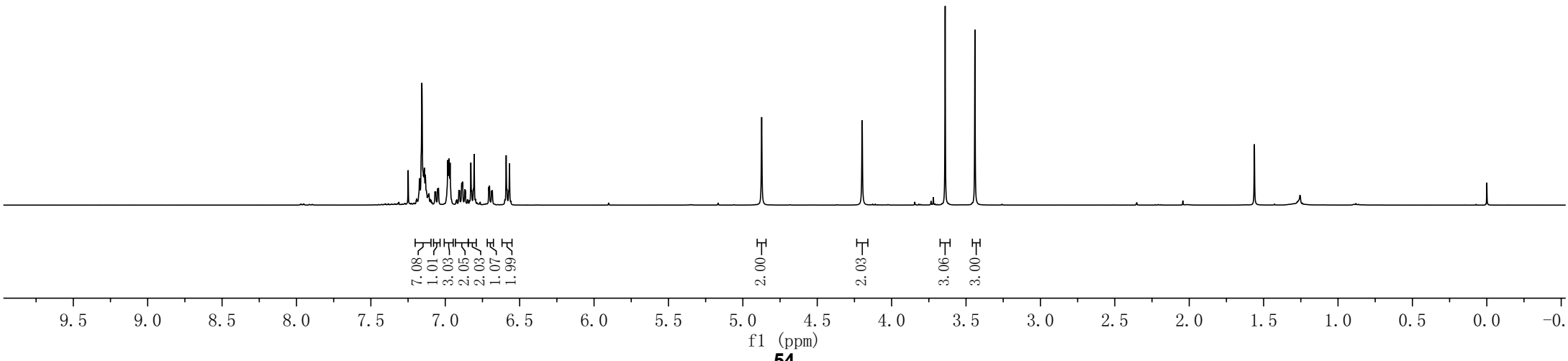


3s

4.87
4.20
3.64
3.44

1.56

0.00



141.32
140.40
138.56
137.71
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126.92
125.92
125.74

122.77
120.74
119.41
118.34

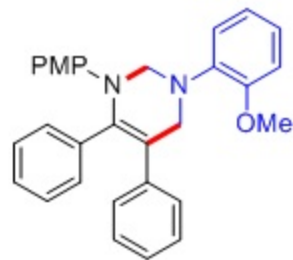
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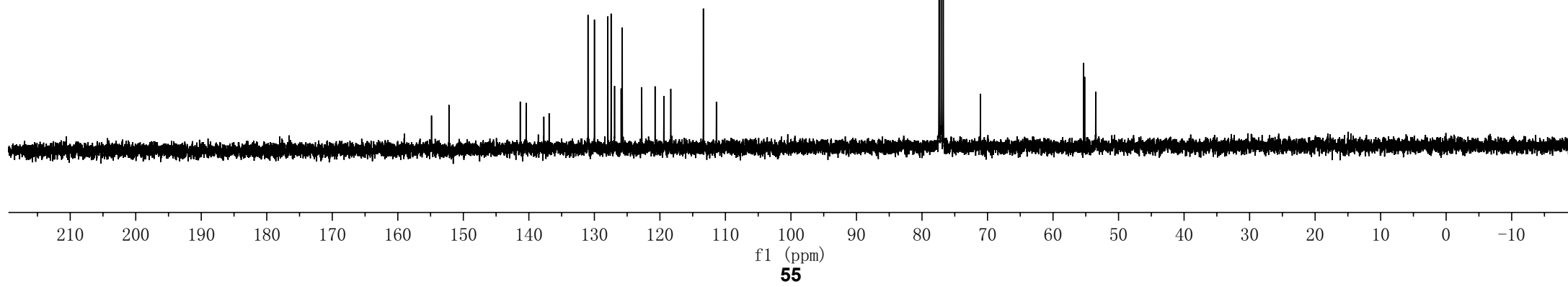
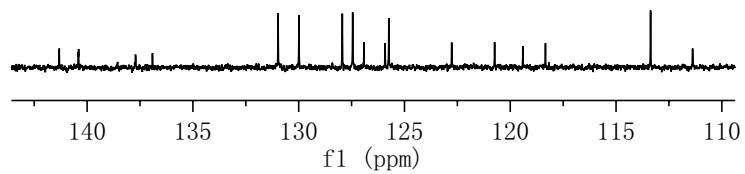
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127.45
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125.74
122.77
119.41
113.37
111.38

77.39
77.07
76.75
71.09

55.32
55.17
53.49



3s



7.25
7.21
7.19
7.17
7.16
7.15
7.14
7.12
7.00
6.99
6.99
6.98
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6.92
6.76
6.75
6.66
6.64
6.55
6.54
6.53
6.52

4.86

4.16

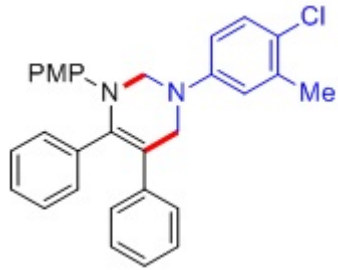
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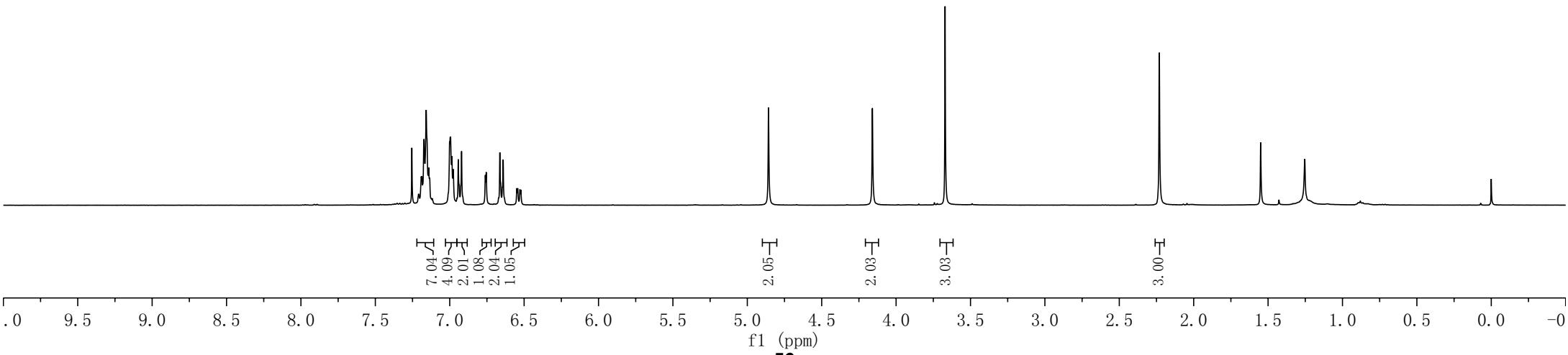
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1.25

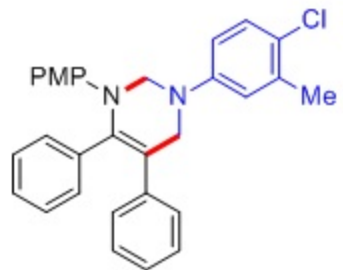
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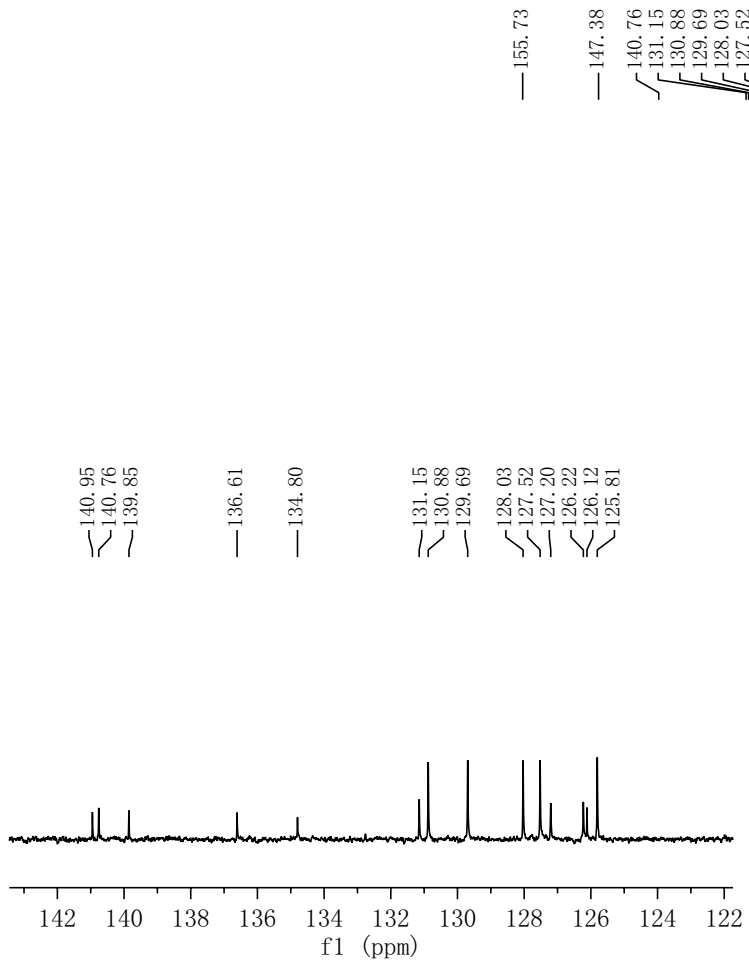
3t



56



3t

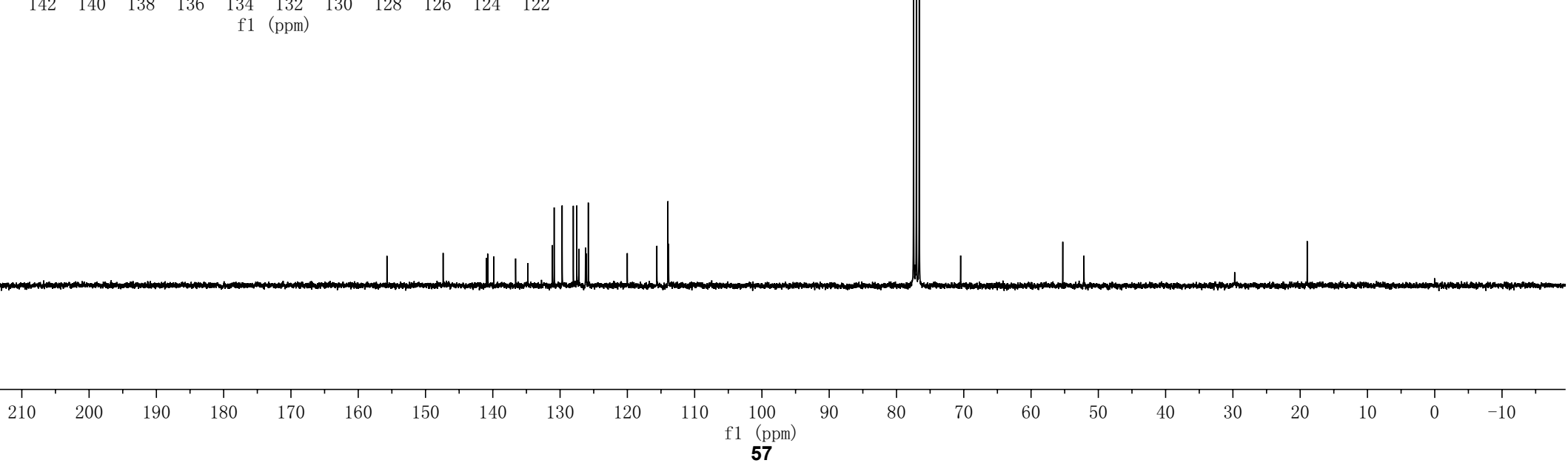


155.73
147.38
140.76
131.15
130.88
129.69
128.03
127.52
127.20
126.22
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115.61
113.97
113.87

77.46
77.04
76.62
70.46

55.28
52.14

18.96

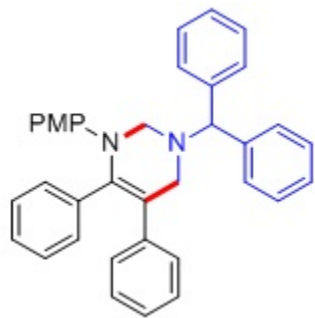


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7.09
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7.07
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6.63

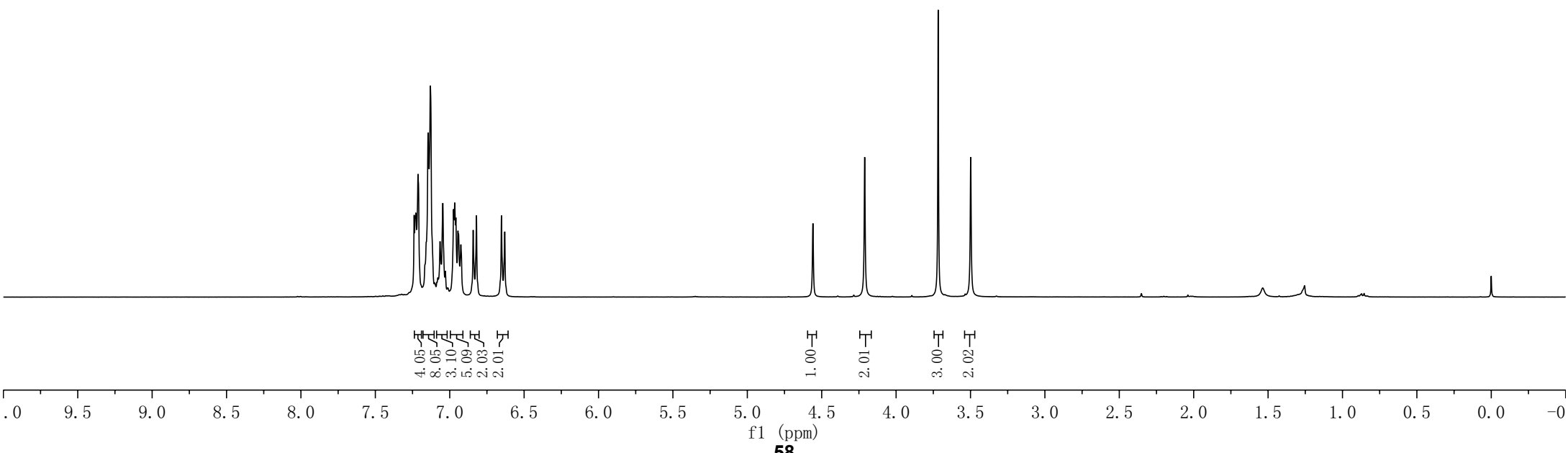
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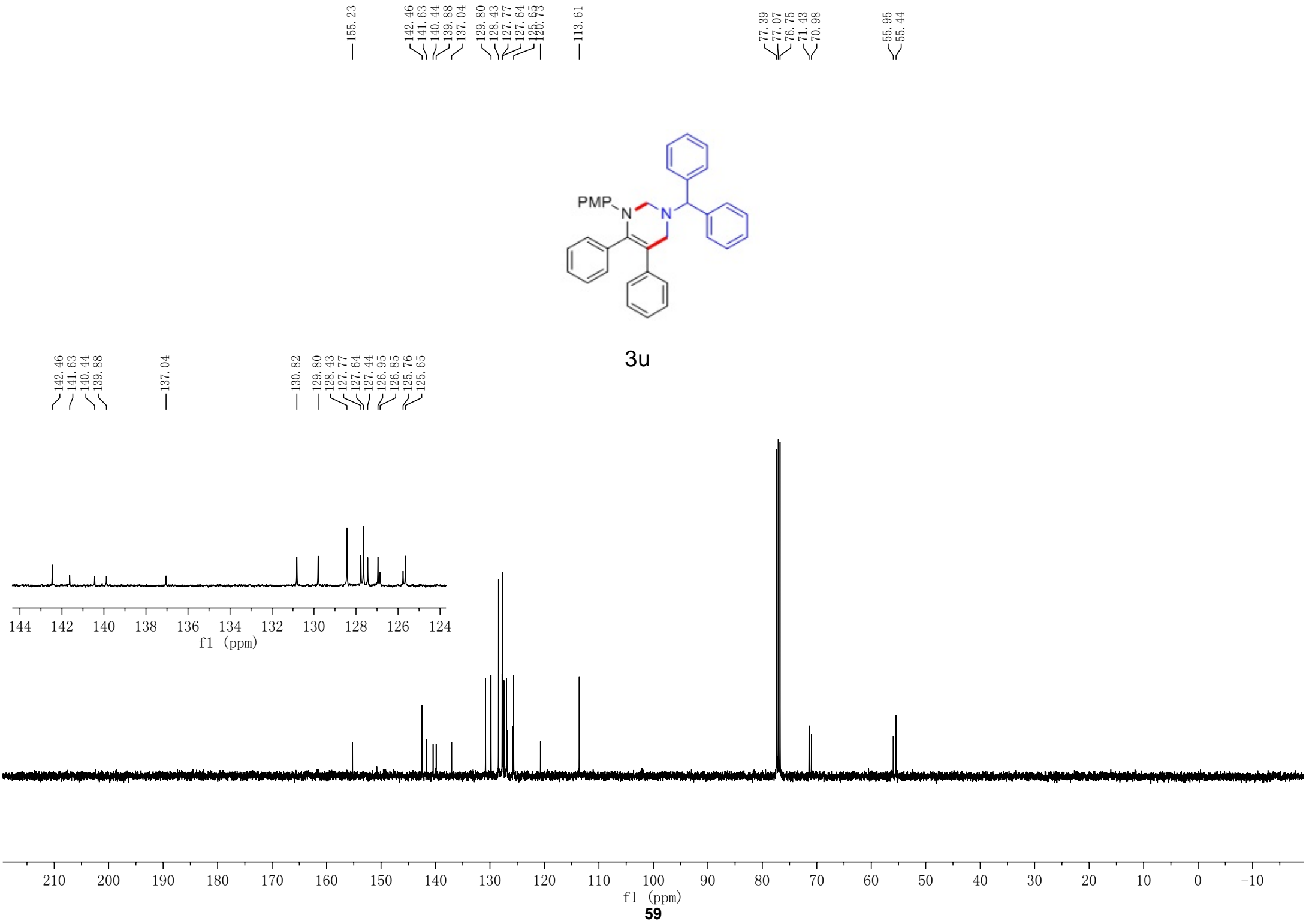
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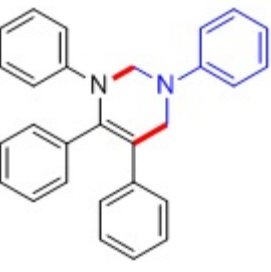


3u





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7.14
7.14
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7.12
7.11
7.10
7.08
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6.75
6.74



4

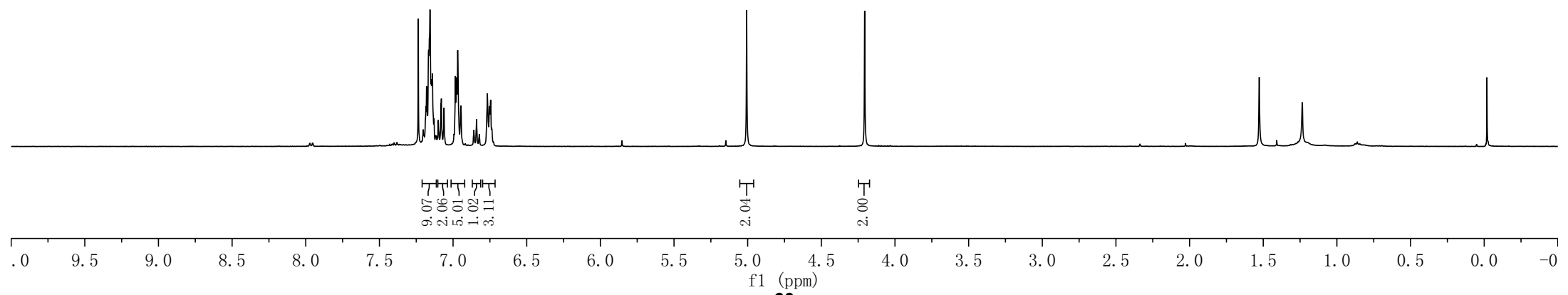
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4.21

1.53

1.23

-0.02

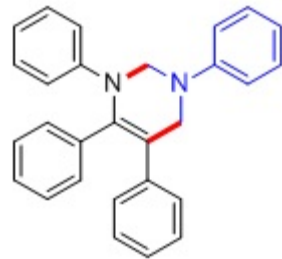


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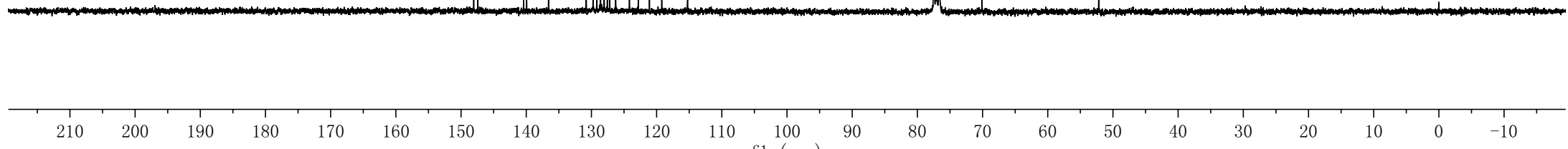
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128.05
127.56
127.19
126.28
124.17
122.81
121.10
119.21
115.25

77.46
77.04
76.62
70.10

52.18



4



61

7.24
7.18
7.17
7.16
7.14
7.12
7.11
6.99
6.98
6.97
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6.90
6.89
6.76
6.64
6.61

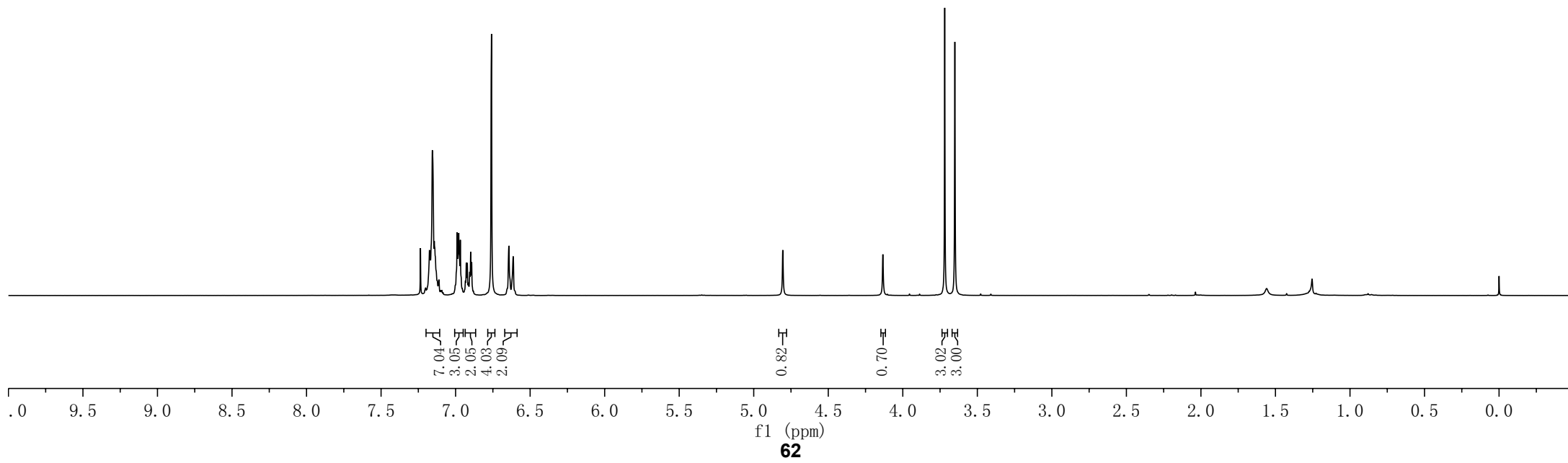
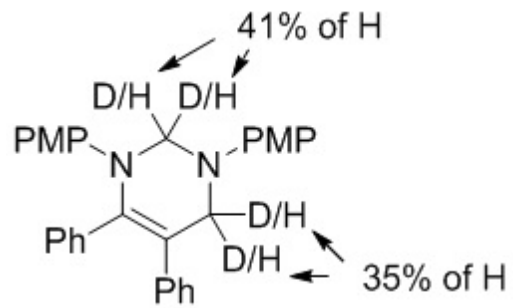
— 4.81

— 4.13

— 3.72
— 3.65

— 1.56

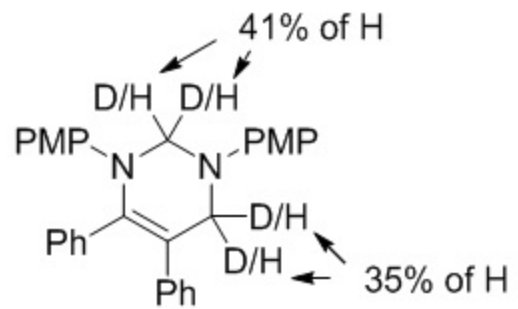
— 0.00



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117.69
117.64
114.57
113.83

77.49
77.07
76.64
72.64
72.58

55.66
55.26
53.08
53.01



D-3a

