Mn(II)-catalysed ortho-alkenylation of aromatic amines and its application in reproductive diseases

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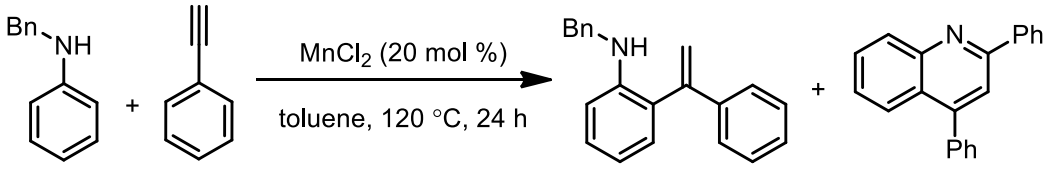
1. General Information

Unless stated otherwise, all reactions were conducted in pressure tubes under N_2. All solvents were received from commercial sources without further purification. Commercially available reagents were used as received. Non-commercially available substrates were synthesized following reported protocols. Thin-layer chromatography (TLC) was visualized using a combination of UV and potassium permanganate staining techniques. Silica gel (particle size 40 – 63 μm) was used for flash column chromatography. NMR spectra were recorded on Bruker AV 400 spectrometer at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR). Proton and carbon chemical shifts are reported relative to the solvent used as an internal reference. High-resolution mass spectra were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource.

2. Reaction Optimization

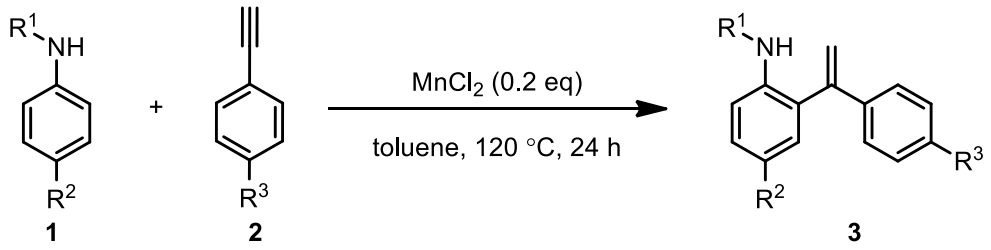


1a **2a** **3a**[a] **3ab**[a]

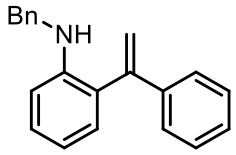
entry	oxidant	yield **3a** (%)[b]	yield **3ab** (%)[b]
1	BPO	0	46
2	H_2O_2	0	25
3	$K_2S_2O_8$	0	53
4	TBHP	0	32
5	PhIO	0	24
6	$NaIO_4$	0	33

Table 1 Effect of oxidants. *N*-benzylaniline (0.2 mmol), Phenylacetylene (0.4 mmol), $MnCl_2$ (0.04 mmol), oxidant (0.2 mmol), toluene (2.0 mL), at 120 °C for 24 h. [a] The reactions were carried out in sealed tubes. [b] Yields were determined by GC analysis.

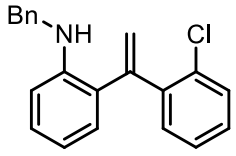
3. Typical Procedure for Synthesis of *O*-alkenyl arylamines.



To a 15 mL pressure tube were added aromatic amine **1** (0.20 mmol), $MnCl_2$ (0.04 mmol, 5 mg), and then toluene (2 mL), aryl acetylene **2** (0.40 mmol) were added. The resulting solution was stirred at 120 ^{o}C for 24 h. After the reaction was completed, the solution was cooled to room temperature, and diluted with ethyl acetate (10 mL). The combined organic phases were washed with brine, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (*n*-Hexane or *n*-Hex/EtOAc = 100:1 to 50:1) to afford the desired product.

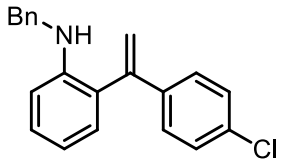


3a: **N-benzyl-2-(1-phenylvinyl)aniline**,[1] White solid (46 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.10 (m, 10H), 7.05 – 6.99 (m, 2H), 6.73 (t, J = 7.4 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.79 (d, J = 1.2 Hz, 1H), 5.37 (d, J = 1.2 Hz, 1H), 4.21 (s, 2H), 4.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 145.2, 139.9, 139.4, 130.7, 129.1, 128.7, 128.6, 128.2, 127.4, 127.1, 127.1, 126.8, 117.0, 116.6, 110.8, 48.0.

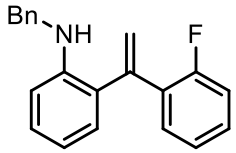


3b: **N-benzyl-2-(1-(2-chlorophenyl)vinyl)aniline**, White solid (55 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.11 (m, 10H), 7.00 (dd, J = 7.6, 1.6 Hz, 1H),

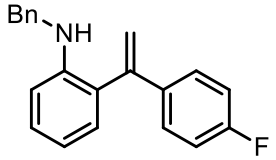
6.68 – 6.66 (m , 2H), 5.73 (d, J = 1.6 Hz, 1H), 5.60 (d, J = 1.6 Hz, 1H), 4.56 (s, 1H), 4.29 – 4.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 140.9, 139.3, 132.6, 130.8, 130.1, 129.7, 128.8, 128.7, 128.5, 127.2, 127.0, 126.7, 121.0, 116.7, 110.9, 48.2; HRMS (ESI) m/z Calcd for $C_21H_{18}ClN$ $[M+H]^+$ 319.1128, Found 319.1131.



3c: **N-benzyl-2-(1-(4-chlorophenyl)vinyl)aniline**,[2] White solid (58 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.19 (m, 8H), 7.10 (dd, J = 7.2, 1.6 Hz, 1H), 7.07 – 7.03 (m, 2H), 6.74 (td, J = 7.2, 0.8 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 5.78 (d, J = 1.2 Hz, 1H), 5.39 (d, J = 1.2 Hz, 1H), 4.23 (s, 2H), 3.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 145.1, 139.2, 138.2, 134.0, 130.5, 129.2, 128.7, 128.5, 128.0, 127.1, 127.1, 126.7, 117.0, 116.9, 110.8, 48.0.

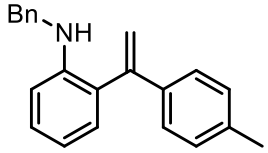


3d: **N-benzyl-2-(1-(2-fluorophenyl)vinyl)aniline**, White solid (50 mg, 82% yiel d). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.03 (m, 11H), 6.72 (td, J = 7.2, 0. 8 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.87 (t, J = 1.2 Hz, 1H), 5.64 (t, J = 1.2 Hz, 1H), 4.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 159.3, 144.9, 141.5 (d, J_{C-F} = 1.0 Hz), 139.3, 130.5 (d, J_{C-F} = 3.0 Hz), 130.1, 129.3 (d, J_{C-F} = 8.4 Hz), 128.9, 128.5, 128.2 (d, J_{C-F} = 12.0 Hz), 127.6, 127.0, 127.0, 124. 1 (d, J_{C-F} = 3.6 Hz), 121.3 (d, J_{C-F} = 6.7 Hz), 116.9, 116.2, 116.0, 110.8, 48.0; HRMS (ESI) m/z Calcd for $C_{21}H_{18}FN$ $[M+H]^+$ 303.1423, Found 303.1427.

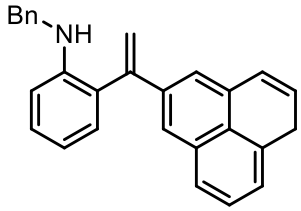


3e: **N-benzyl-2-(1-(4-fluorophenyl)vinyl)aniline**,[2] White solid (51 mg, 84% yie ld). ^{1}H NMR (400 MHz, DMSO): δ 7.32 – 6.94 (m, 11H), 6.72 (t, J = 7.4 H z, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.71 (s, 1H), 5.33 (s, 1H), 4.20 (s, 2H), 4.

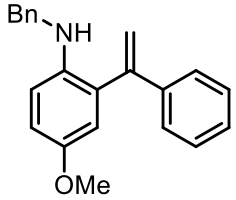
00 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 159.3, 156.8, 141.4, 140.4, 134.5, 131.1 (d, $J_{C\text{-}F}$ = 3.3 Hz), 125.7, 124.4, 123.8, 123.7, 123.6, 122.3, 122.3, 122.2, 112.2, 111.5 (d, $J_{C\text{-}F}$ = 1.4 Hz), 110.8, 110.5, 106.0, 43.2.



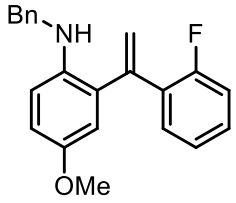
3f: **N-benzyl-2-(1-(p-tolyl)vinyl)aniline**, White solid (46 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.12 (m, 9H), 7.08 – 7.03 (m, 2H), 6.75 (td, J = 7.6, 0.8 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.77 (d, J = 1.6 Hz, 1H), 5.37 (d, J = 1.6 Hz, 1H), 4.23 (s, 2H), 4.09 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 145.2, 139.8, 139.4, 138.2, 130.5, 128.9, 128.5, 128.4, 127.4, 127.0, 126.7, 123.9, 116.8, 116.4, 110.7, 47.9, 21.5; HRMS (ESI) m/z Calcd for $C_{22}H_{21}N$ $[M+H]^+$ 299.1674, Found 299.1680.



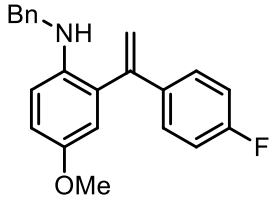
3g: **2-(1-(1H-phenalen-5-yl)vinyl)-N-benzylaniline**, White solid (50 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 – 8.67 (m, 2H), 8.10 (d, J = 7.6 Hz, 1H), 7.83 – 7.81 (m, 1H), 7.76 (s, 1H), 7.69 – 7.57 (m, 3H), 7.49 – 7.42 (m, 1H), 7.24 (dd, J = 7.6, 1.6 Hz, 1H), 7.14 – 7.03 (m, 3H), 6.91 (d, J = 7.2 Hz, 2H), 6.71 – 6.59 (m, 2H), 5.87 (d, J = 2.0 Hz, 1H), 5.73 (d, J = 2.0 Hz, 1H), 4.70 (s, 1H), 4.19 (d, J = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 145.0, 138.9, 131.5, 130.7, 130.5, 130.3, 130.0, 129.3, 128.9, 128.8, 128.4, 127.8, 127.4, 127.0, 126.9, 126.8, 126.7, 126.6, 126.4, 123.0, 122.5, 120.3, 116.9, 111.0, 48.0; HRMS (ESI) m/z Calcd for $C_{28}H_{23}N$ $[M+H]^+$ 373.1830, Found 373.1825.



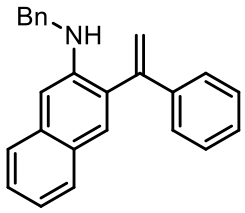
3h: **N-benzyl-4-methoxy-2-(1-phenylvinyl)aniline**,[2] White solid (40 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 5H), 7.23 – 7.17 (m, 3H), 7.05 – 7.01 (m, 2H), 6.80 – 6.76 (m, 2H), 6.58 (d, J = 8.4 Hz, 1H), 5.79 (d, J = 1.2 Hz, 1H), 5.36 (d, J = 1.2 Hz, 1H), 4.16 (s, 2H), 3.77 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 147.0, 139.6, 139.6, 139.6, 128.7, 128.6, 128.4, 128.2, 127.2, 126.9, 126.7, 116.8, 116.5, 114.1, 112.2, 55.8, 48.9.



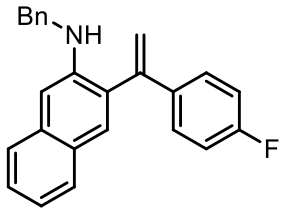
3i: **N-benzyl-2-(1-(2-fluorophenyl)vinyl)-4-methoxyaniline**, White solid (48 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.02 (m, 9H), 6.79 – 6.71 (m, 2H), 6.56 (d, J = 8.8 Hz, 1H), 5.87 (t, J = 1.2 Hz, 1H), 5.63 (t, J = 1.2 Hz, 1H), 4.21 (s, 2H), 3.94 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 159.2, 151.5, 141.4, 139.6, 139.3, 130.5 (d, $J_{C\text{-}F}$ = 3.1 Hz), 129.3 (d, $J_{C\text{-}F}$ = 8.4 Hz), 129.0, 128.5, 127.1, 127.0, 124.1 (d, $J_{C\text{-}F}$ = 3.7 Hz), 121.4 (d, $J_{C\text{-}F}$ = 6.9 Hz), 116.4, 116.3, 116.0, 113.9, 112.2, 55.8, 48.9; HRMS (ESI) m/z Calcd for $C_{22}H_{20}FNO$ $[M+H]^+$ 333.1529, Found 333.1532.



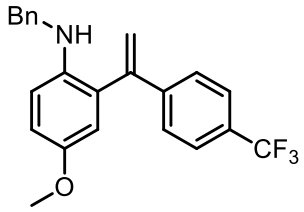
3j: **N-benzyl-2-(1-(4-fluorophenyl)vinyl)-4-methoxyaniline**, White solid (49 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.18 (m, 5H), 7.08 – 7.04 (m, 2H), 7.02 – 6.96 (m, 2H), 6.80 (dd, J = 8.8, 2.8 Hz, 1H), 6.74 (d, J = 2.8 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 5.74 (d, J = 1.2 Hz, 1H), 5.34 (d, J = 0.8 Hz, 1H), 4.18 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 161.6, 151.5, 145.9, 139.5 (d, $J_{C\text{-}F}$ = 4.1 Hz), 135.6 (d, $J_{C\text{-}F}$ = 3.2 Hz), 128.5, 128.4, 128.3, 128.2, 127.1, 127.0, 116.7, 116.2, 116.2, 115.5, 115.3, 114.1, 112.2, 55.8, 48.9; HRMS (ESI) m/z Calcd for $C_{28}H_{23}N$ $[M+H]^+$ 373.1830, Found 373.1823.



3k: **N-benzyl-3-(1-phenylvinyl)naphthalen-2-amine**, White solid (47 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.30 – 7.07 (m, 11H), 6.27 (d, J = 1.2 Hz, 1H), 5.42 (d, J = 1.6 Hz, 1H), 4.58 (s, 1H), 4.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.5, 139.7, 139.2, 133.3, 128.8, 128.6, 128.5, 128.1, 127.9, 127.2, 127.0, 126.4, 126.3, 124.2, 121.8, 119.3, 118.3, 114.1, 48.2; HRMS (ESI) m/z Calcd for $C_{25}H_{21}N$ $[M+H]^+$ 335.1674, Found 335.1679.

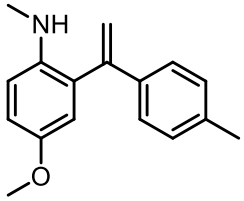


3l: **N-benzyl-3-(1-(4-fluorophenyl)vinyl)naphthalen-2-amine**, White solid (54 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 – 7.67 (m, 2H), 7.55 (d, J = 8.8 Hz, 1H), 7.36 – 7.27 (m, 4H), 7.25 – 7.15 (m, 5H), 7.14 – 7.09 (m, 1H), 6.98 – 6.91 (m, 2H), 6.20 (d, J = 0.8 Hz, 1H), 5.40 (d, J = 0.8 Hz, 1H), 4.57 (s, 1H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 161.6, 143.0, 142.4, 139.6, 135.2 (d, $J_{C\text{-}F}$ = 3.2 Hz), 133.1, 129.0, 128.6, 128.0 128.0, 127.9, 127.2, 127.1, 127.0, 126.8, 126.5, 124.0, 121.9, 118.9, 117.9 (d, $J_{C\text{-}F}$ = 1.5 Hz), 115.6, 115.4, 114.1, 48.2; HRMS (ESI) m/z Calcd for $C_{25}H_{20}FN$ $[M+H]^+$ 353.1580, Found 353.1573.

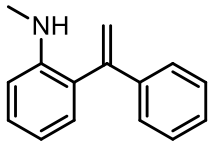


3m: **N-benzyl-4-methoxy-2-(1-(4-(trifluoromethyl)phenyl)vinyl)aniline**, White solid (62 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.0 Hz, 2H),

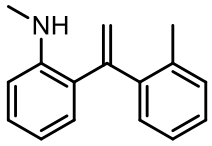
7.44 (d, J = 8.0 Hz, 2H), 7.24 – 7.16 (m, 3H), 7.00 (m, 2H), 6.83 (dd, J = 8.8, 3.2 Hz, 1H), 6.74 (d, J = 2.8 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 5.87 (d, J = 0.8 Hz, 1H), 5.48 (d, J = 1.2 Hz, 1H), 4.16 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 146.0, 143.2, 139.4 (d, $J_{C\text{-}F}$ = 7.7 Hz), 130.1 (q, $J_{C\text{-}F}$ = 32.2 Hz), 128.5, 128.2, 127.8, 127.2, 127.1, 127.0, 125.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 122.8, 120.1, 118.6, 116.8, 114.4, 112.4, 55.8, 48.9, 29.8; HRMS (ESI) m/z Calcd for $C_{23}H_{20}F_3NO$ $[M+H]^+$ 383.1497, Found 383.1488.



3n: **4-methoxy-N-methyl-2-(1-(p-tolyl)vinyl)aniline**, White solid (42 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.09 (m, 4H), 6.79 (dd, J = 8.8, 2.8 Hz, 1H), 6.60 (d, J = 3.2 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 5.58 (d, J = 2.0 Hz, 1H), 5.45 (d, J = 1.6 Hz, 1H), 3.85 (s, 1H), 3.70 (s, 3H), 2.72 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 148.0, 141.7, 141.1, 135.8, 130.7, 129.5, 128.7, 127.8, 126.0, 119.1, 116.3, 113.7, 111.5, 55.8, 31.8, 20.4; HRMS (ESI) m/z Calcd for $C_{17}H_{19}NO$ $[M+H]^+$ 253.1467, Found 253.1474.

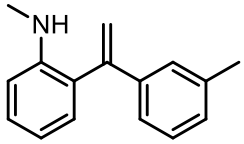


3o: **N-methyl-2-(1-phenylvinyl)aniline**,[3] White solid (31 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.24 (m, 6H), 7.08 (dd, J = 7.6, 1.6 Hz, 1H), 6.74 (td, J = 7.6, 1.2 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 1.2 Hz, 1H), 5.33 (d, J = 1.6 Hz, 1H), 3.71 (s, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 146.7, 139.7, 130.5, 129.1, 128.7, 128.2, 127.3, 126.6, 116.7, 116.4, 110.0, 30.9.

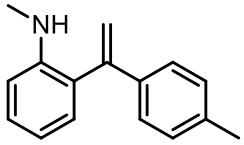


3p: **N-methyl-2-(1-(o-tolyl)vinyl)aniline**,[4] White solid (28 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, J = 6.8, 1.6 Hz, 1H), 7.24 – 7.12 (m, 4H), 6.96 (d, J =

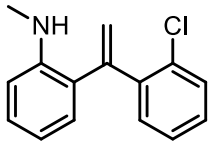
6.8 Hz, 1H), 6.64 (t, J = 7.6 Hz, 2H), 5.58 (d, J = 1.6 Hz, 1H), 5.45 (d, J = 1.6 Hz, 1H), 4.25 (s, 1H), 2.77 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 146.4, 142.1, 135.8, 130.7, 129.8, 129.6, 128.7, 127.7, 127.2, 126.0, 118.7, 116.6, 110.1, 31.0, 20.3.



3q: **N-methyl-2-(1-(m-tolyl)vinyl)aniline**, White solid (29 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.23 (m, 1H), 7.21 – 7.06 (m, 5H), 6.73 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 5.79 (d, J = 1.2 Hz, 1H), 5.31 (d, J = 1.2 Hz, 1H), 3.73 (s, 1H), 2.72 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 146.7, 139.6, 138.1, 130.4, 128.9, 128.9, 128.4, 127.3, 127.1, 123.8, 116.5, 116.1, 109.8, 30.8, 21.5; HRMS (ESI) m/z Calcd for $C_{16}H_{17}N$ $[M+H]^+$ 223.1361, Found 223.1356.

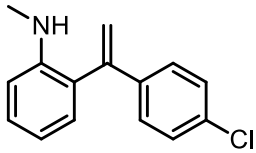


3r: **N-methyl-2-(1-(p-tolyl)vinyl)aniline**,[5] White solid (30 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 5H), 7.05 (dd, J = 7.2, 1.6 Hz, 1H), 6.77 – 6.61 (m, 2H), 5.81 (d, J = 1.2 Hz, 1H), 5.35 (d, J = 1.2 Hz, 1 H), 3.66 (s, 1H), 2.73 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 146.6, 138.0, 136.6, 130.3, 129.3, 128.9, 127.4, 126.4, 116.5, 115.3, 109. 8, 30.8, 21.2.

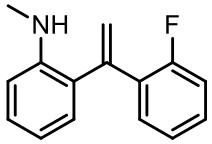


3s: **2-(1-(2-chlorophenyl)vinyl)-N-methylaniline**, White solid (38 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 2H), 7.24 – 7.16 (m, 3H), 6.92 (dd, J = 8.0, 1.6 Hz, 1H), 6.67 – 6.61 (m, 2H), 5.68 (d, J = 1.6 Hz, 1H), 5.61 (d, J = 1.6 Hz, 1H), 4.31 (s, 1H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 145.1, 141.0,

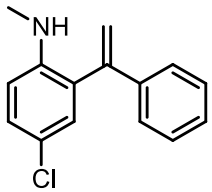
132.5, 130.8, 131.0, 129.5, 128.8, 128.7, 126.9, 126.7, 120.7, 116.4, 110.2, 31.0; HRMS (ESI) m/z Calcd for $C_{15}H_{14}ClN$ $[M+H]^+$ 243.0815, Found 243.0822.



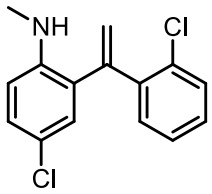
3t: **2-(1-(4-chlorophenyl)vinyl)-N-methylaniline**,[5] White solid (39 mg, 79% yi eld). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.23 (m, 5H), 7.05 (dd, J = 7.6, 1.6 Hz, 1H), 6.74 (td, J = 7.6, 0.8 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 5.81 (d, J = 1.2 Hz, 1H), 5.34 (d, J = 1.2 Hz, 1H), 3.66 (s, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 145.9, 138.0, 133.9, 130.3, 129.2, 128.7, 127.8, 126.6, 116.6, 109.9, 30.7.



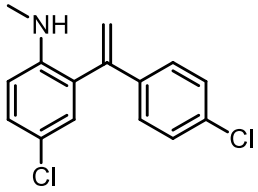
3u: **2-(1-(2-fluorophenyl)vinyl)-N-methylaniline**, White solid (33 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 2H), 7.14 – 7.01 (m, 4H), 6.74 – 6.62 (m, 2H), 5.89 (s, 1H), 5.59 (s, 1H), 3.91 (s, 1H), 2.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 159.3, 146.4, 141.4, 130.4 (d, $J_{C\text{-}F}$ = 3.1 Hz), 129.9, 129.2 (d, $J_{C\text{-}F}$ = 8.4 Hz), 128.9, 127.5, 124.1 (d, $J_{C\text{-}F}$ = 3.7 Hz), 121.2 (d, $J_{C\text{-}F}$ = 7.4 Hz), 116.5, 116.1 (d, $J_{C\text{-}F}$ = 22.8 Hz), 109.9, 30.9; HRMS (ESI) m/z Calcd for $C_{15}H_{14}FN$ $[M+H]^+$ 227.1110, Found 227.1123.



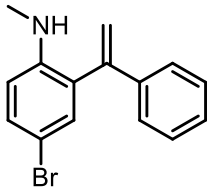
3v: **4-chloro-N-methyl-2-(1-phenylvinyl)aniline**,[5] White solid (29 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 5H), 7.21 (dd, J = 8.8, 2.4 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 5.84 (d, J = 1.2 Hz, 1H), 5.33 (d, J = 1.2 Hz, 1H), 3.69 (s, 1H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 145.3, 138.8, 129.9, 128.7, 128.6, 128.4, 128.4, 126.4, 121.2, 116.9, 110.9, 30.8.



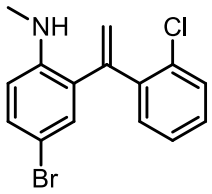
3w: **4-chloro-2-(1-(2-chlorophenyl)vinyl)-N-methylaniline**, White solid (34 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 1H), 7.33 – 7.27 (m, 1H), 7.25 – 7.22 (m, 2H), 7.13 (dd, J = 8.8, 2.8 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.54 (d, J = 8.8 Hz, 1H), 5.68 (d, J = 1.2 Hz, 1H), 5.63 (d, J = 1.2 Hz, 1H), 4.26 (s, 1H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 144.1, 140.3, 132.5, 130.8, 130.1, 129.0, 128.9, 128.4, 128.1, 126.9, 121.5, 121.1, 111.2, 31.1; HRMS (ESI) m/z Calcd for $C_{15}H_{13}Cl_2N$ $[M+H]^+$ 277.0425, Found 277.0436.



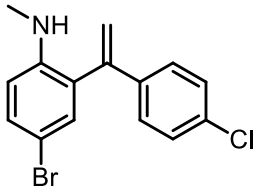
3x: **4-chloro-2-(1-(4-chlorophenyl)vinyl)-N-methylaniline**, White solid (36 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.25 (m, 4H), 7.22 (dd, J = 8.8, 2.4 Hz, 1H), 7.03 (d, J = 2.8 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 5.82 (d, J = 0.8 Hz, 1H), 5.35 (d, J = 0.8 Hz, 1H), 3.64 (s, 1H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.3, 144.1, 140.3, 132.5, 130.8, 130.1, 129.0, 128.9, 128.4, 126.9, 121.5, 111.2, 31.1; HRMS (ESI) m/z Calcd for $C_{15}H_{13}Cl_2N$ $[M+H]^+$ 277.0425, Found 277.0432.



3y: **4-bromo-N-methyl-2-(1-phenylvinyl)aniline**,[5] White solid (33 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 6H), 7.19 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 5.84 (d, J = 1.2 Hz, 1H), 5.33 (d, J = 1.2 Hz, 1H), 3.71 (s, 1H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 145.7, 138.8, 132.6, 131.5, 128.9, 128.7, 128.4, 126.4, 116.9, 111.3, 108.2, 30.7.

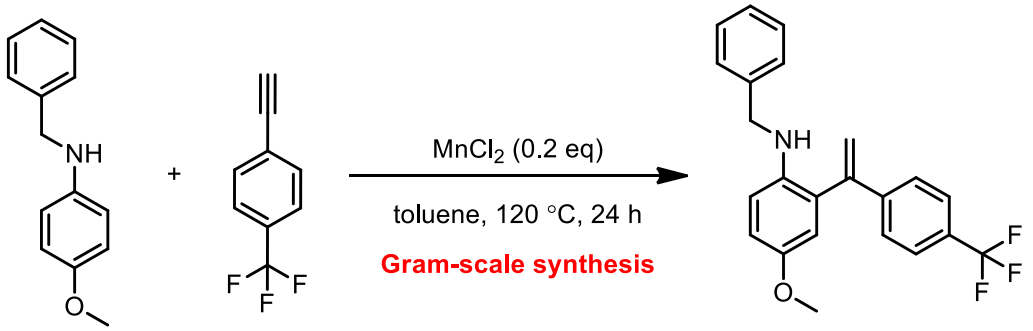


3z: **4-bromo-2-(1-(2-chlorophenyl)vinyl)-N-methylaniline**, White solid (40 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 1H), 7.32 – 7.21 (m, 4H), 7.01 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 5.67 (d, J = 1.6 Hz, 1H), 5.62 (d, J = 1.6 Hz, 1H), 4.27 (s, 1H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 144.0, 140.2, 132.5, 131.6, 131.3, 130.8, 130.1, 129.0, 128.6, 126.9, 121.6, 111.7, 108.2, 31.0; HRMS (ESI) m/z Calcd for $C_{15}H_{13}BrClN$ $[M+H]^+$ 320.9920, Found 320.9913.



3ab: **4-bromo-2-(1-(4-chlorophenyl)vinyl)-N-methylaniline**, White solid (41 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, J = 8.8, 2.4 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.26 – 7.24 (m, 1H), 7.16 (d, J =2.4 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 5.82 (d, J = 1.2 Hz, 1H), 5.34 (d, J = 1.2 Hz, 1H), 3.65 (s, 1H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 144.7, 137.3, 134.2, 132.6, 131.7, 128.8, 128.3, 127.6, 117.3, 111.4, 108.3, 30.7; HRMS (ESI) m/z Calcd for $C_{15}H_{13}BrClN$ $[M+H]^+$ 320.9920, Found 320.9926.

4. Gram-scale Synthesis



According to the typical procedure: To a 250 mL pressure tube were added *N*-benzyl-4-methoxyaniline (5.0 mmol, 1.07 g), $MnCl_2$ (1.0 mmol, 126 mg), and then toluene (20 mL), 1-ethynyl-4-(trifluoromethyl)benzene (10.0 mmol, 1.7 g) were

added. The resulting solution was stirred at 120 ^{o}C for 24 h. After column purification (*n*-Hexane), coupling product was obtained (1.4 g, 73% yield).

5. Biological Activity Evaluation Test in Spermatogenesis

Seven weeks old adult male rats with the C57BL/B6 background (Laboratory Animal Center of Nantong University) was maintained in a 12 h dark/light cycle under temperature at 23 ± 2℃ and relative humidity of 45–55%. These animals were fed with ad libitum access to water and food. One week later, the animals were randomly divided into 5 groups (6 animals per group). Firstly, busulfan was dissolved in dimethyl sulfoxide (DMSO; Sigma, St Louis, MO, USA). Before injection, distilled water was added to obtain final concentrations of 6 mg/mL and all of the groups were received a single injection of 6 mg/kg into each testis in a volume of approximately 25 μL. Secondly, **3m** was dissolved in a mixture of dimethyl sulfoxide and deionized sterile water (1:3, v/v) and was intraperitoneally injected for five days.

Seven days after treatment of busulfan, rats in groups 1 received the normal saline injection, and group 2 received DMSO, serving as the control, while rats in groups 3, 4, 5 received i.p. 1mg/kg, 10 mg/kg, 100 mg/kg of **3m** per day for five days, and then rats (3 animals each group) were sacrificed on 2 weeks and 4 weeks by asphyxiation with CO_2. Epididymis and testis were fixed in 4% paraformaldehyde, then embedded in paraffin, sliced at 4 μm and deparaffinized for hematoxylin and eosin (HE) staining. HE staining was carried out by standard protocol.

6. Possible mechanism.

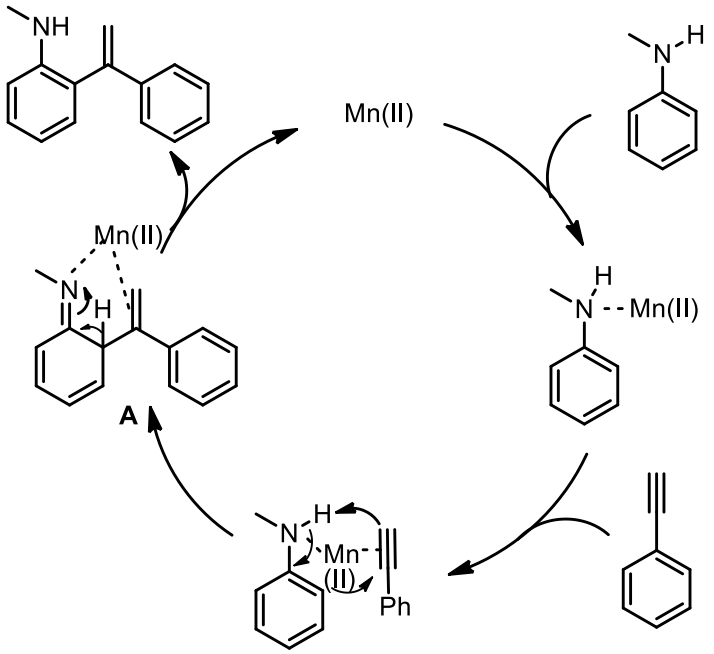


Figure 1 Possible mechanism

References

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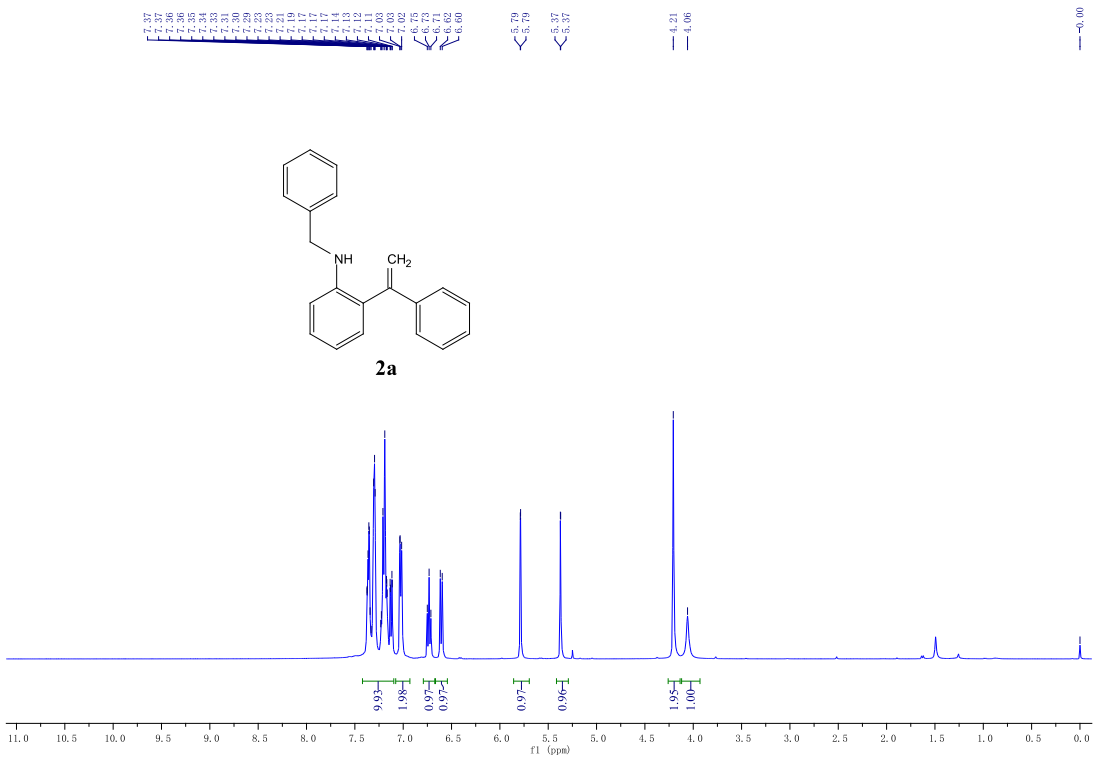
[2]. W. Sun, C. Chen, Y. Qi, J. Zhao, Y. Bao, B. Zhu, *Org. Biomol. Chem*. 2019, ***17***, 8358.

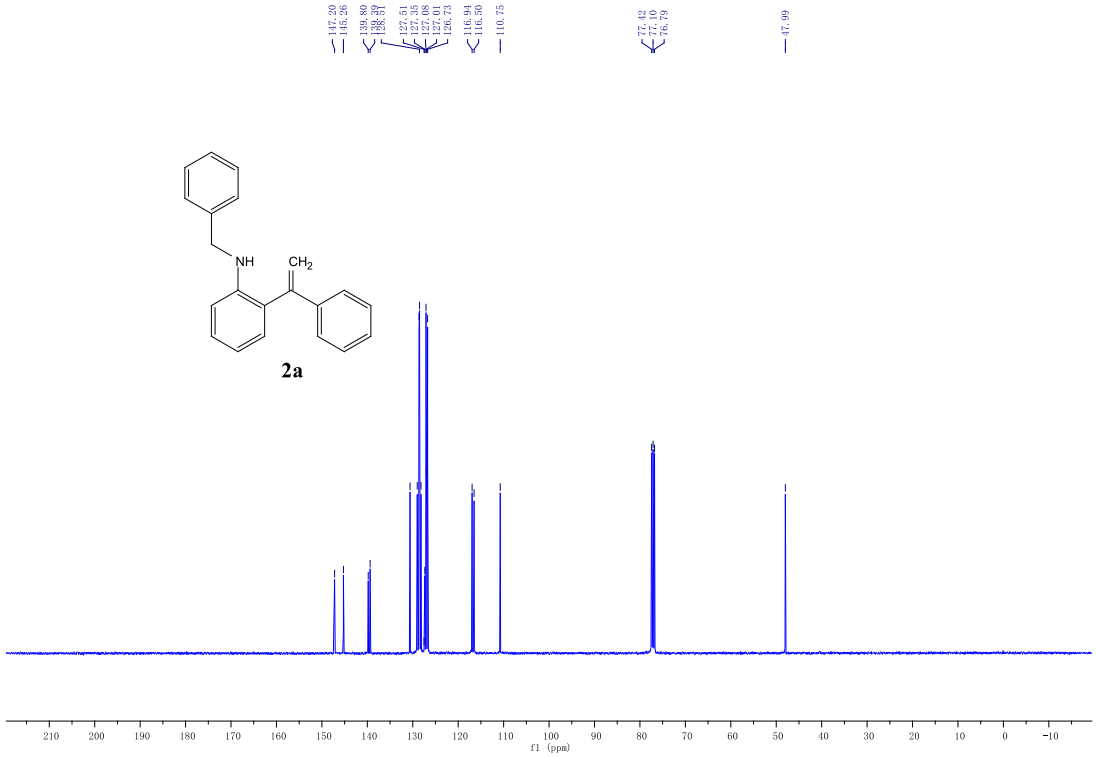
[3]. T. Torigoe, T. Ohmura, M. Suginome, *Angew. Chem. Int. Ed.* 2017, ***56***, 14272.

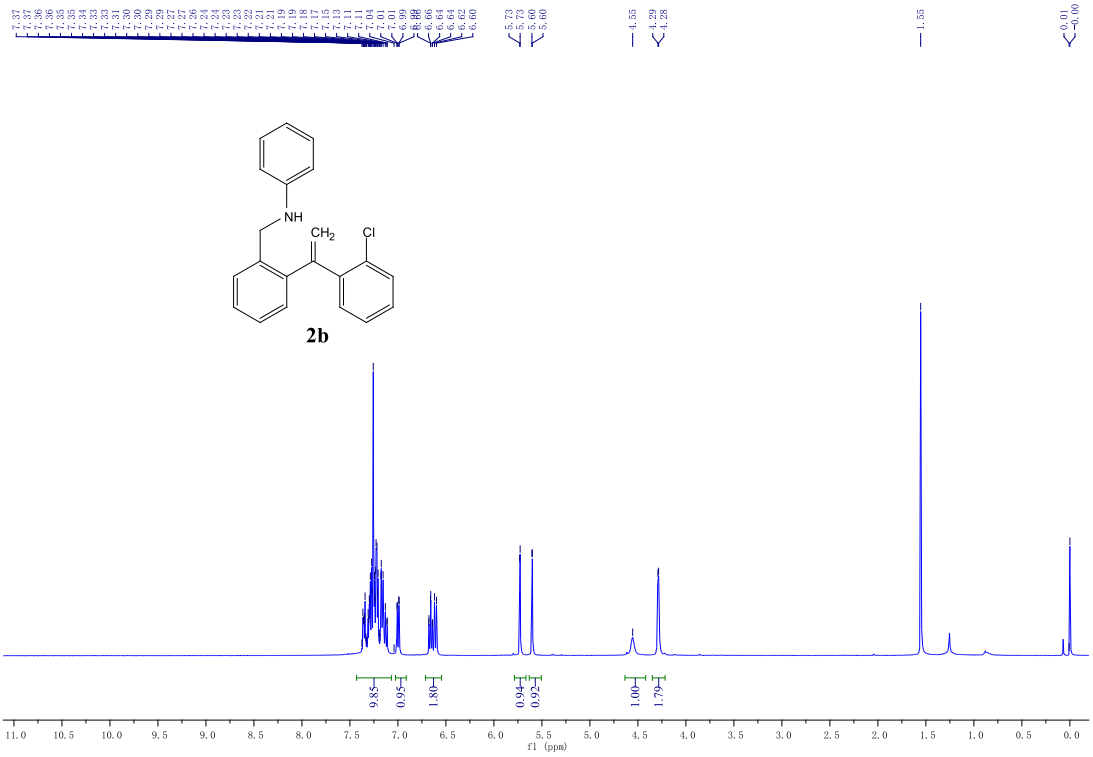
[4]. C. Zhang, X. Wu, C. Wang, C. Zhang, J. Qu, Y. Chen, *Org. Lett.* 2020, ***22***, 6376.

[5]. A. Whyte, K.I. Burton, J. Zhang, M. Lautens, *Angew. Chem. Int. Ed*. 2018, ***57*** 13927.

7. NMR Spectra



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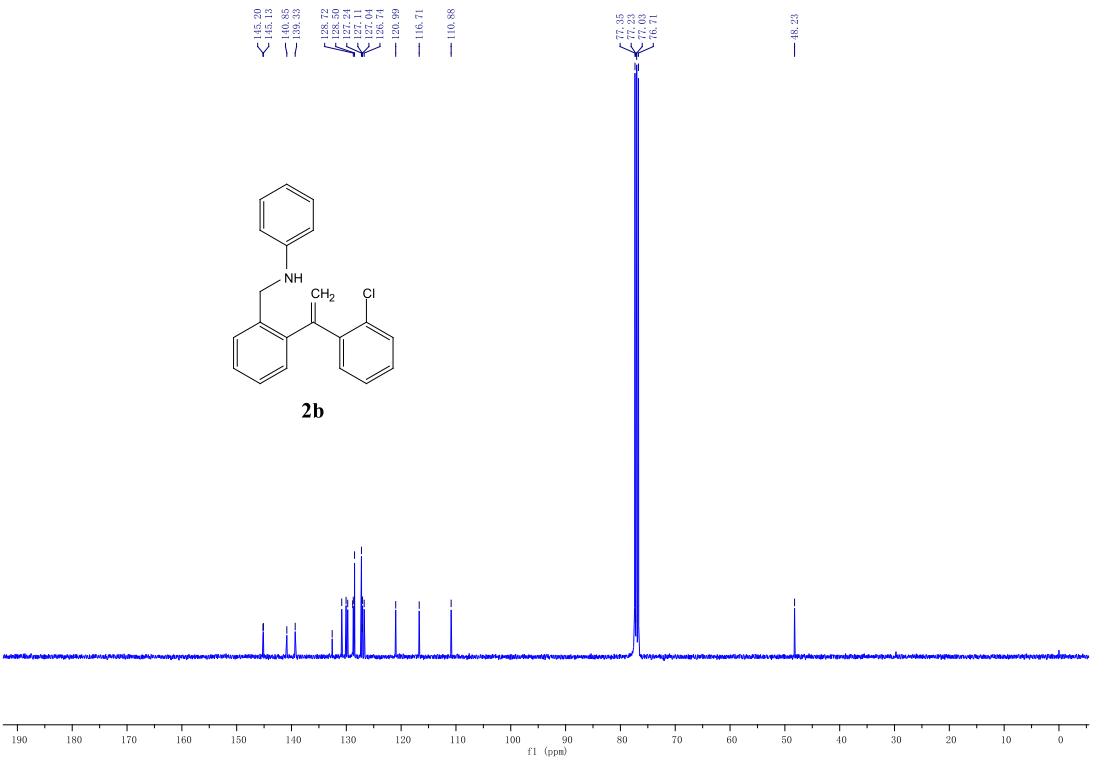
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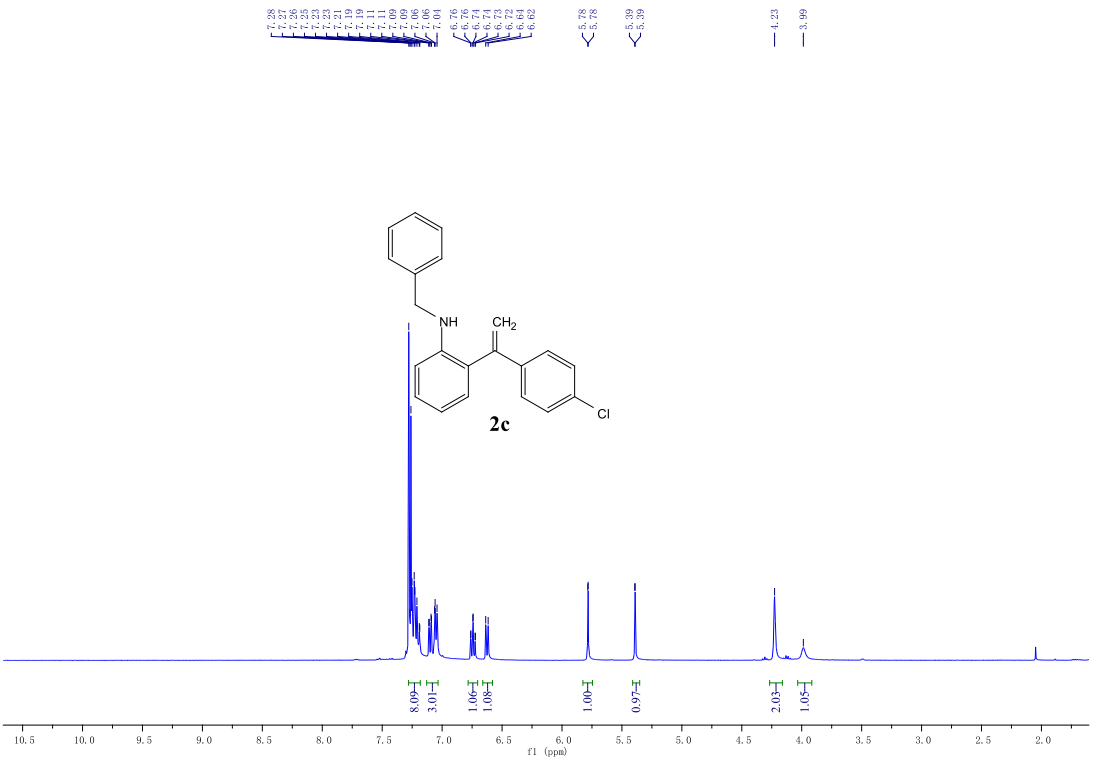
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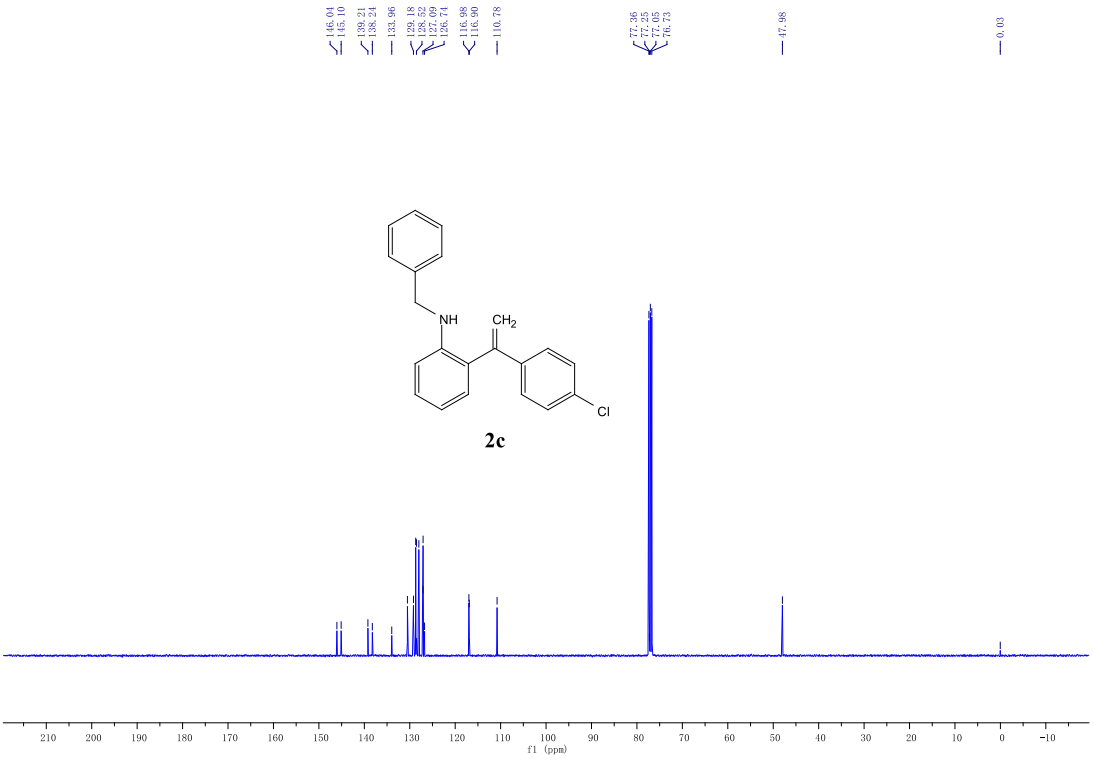
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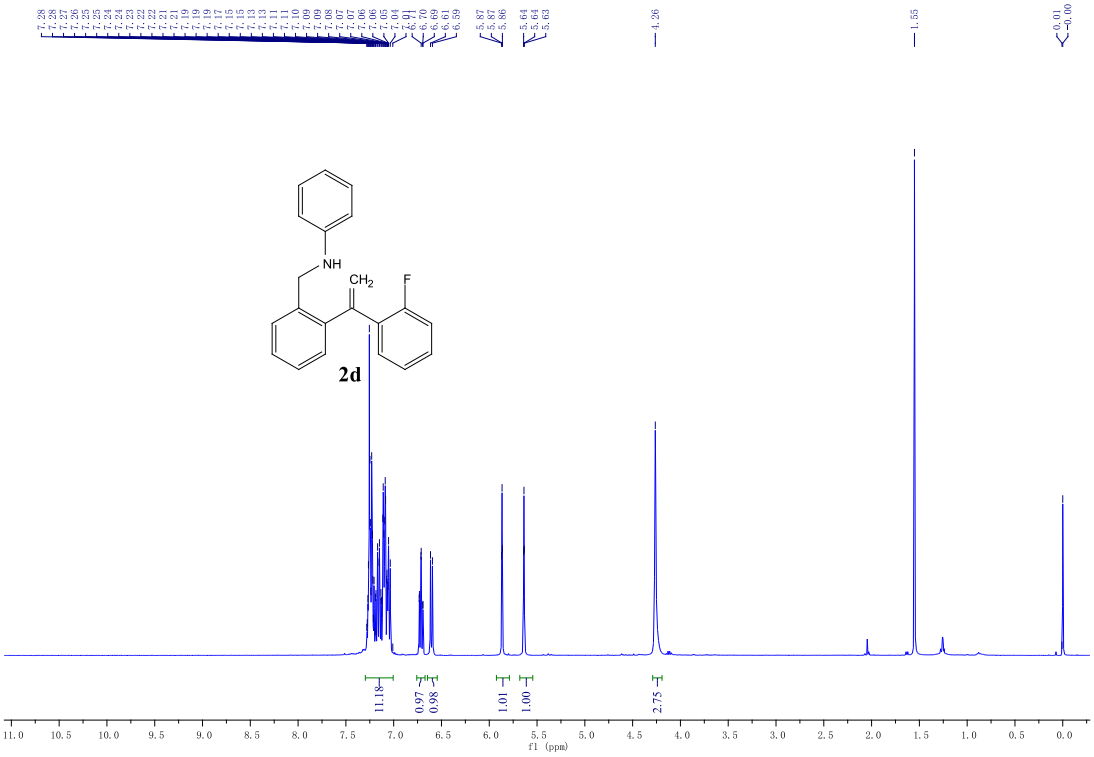
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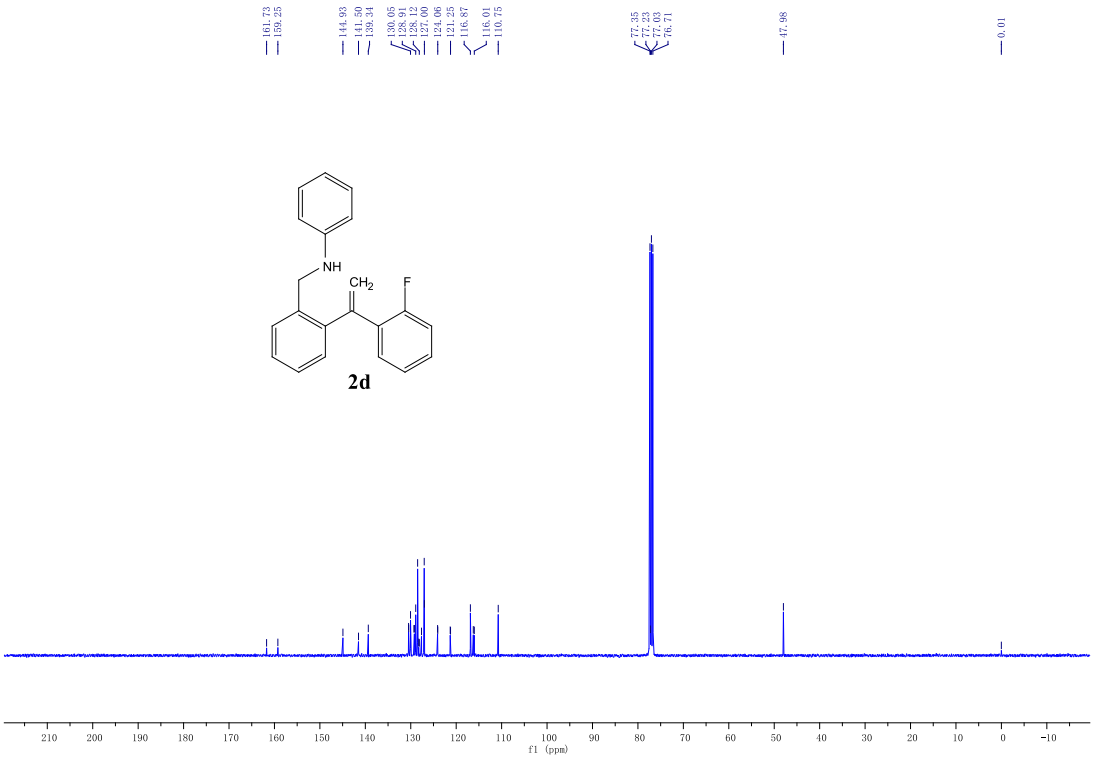
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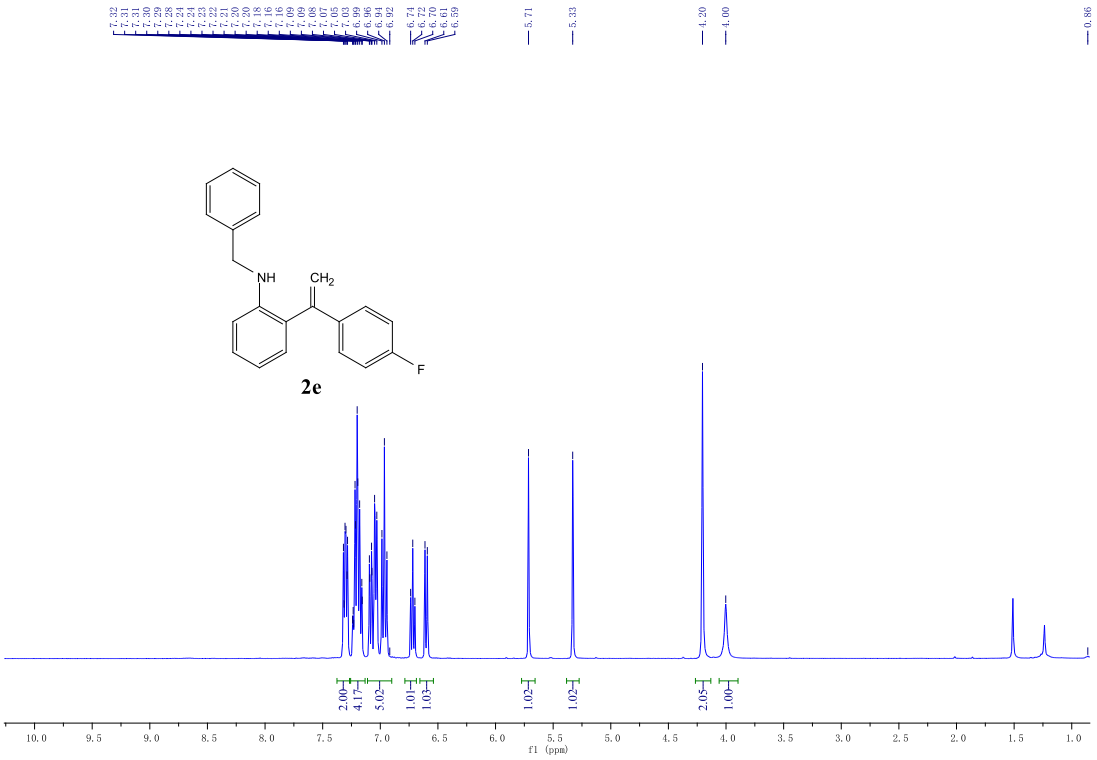
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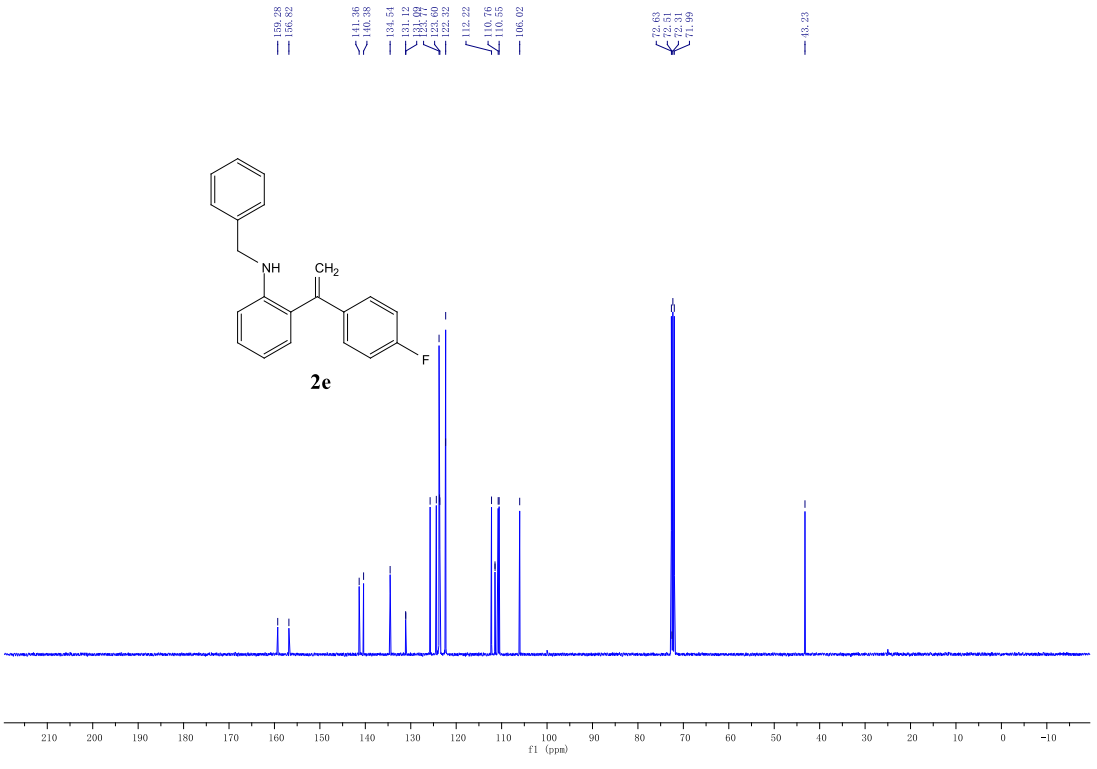
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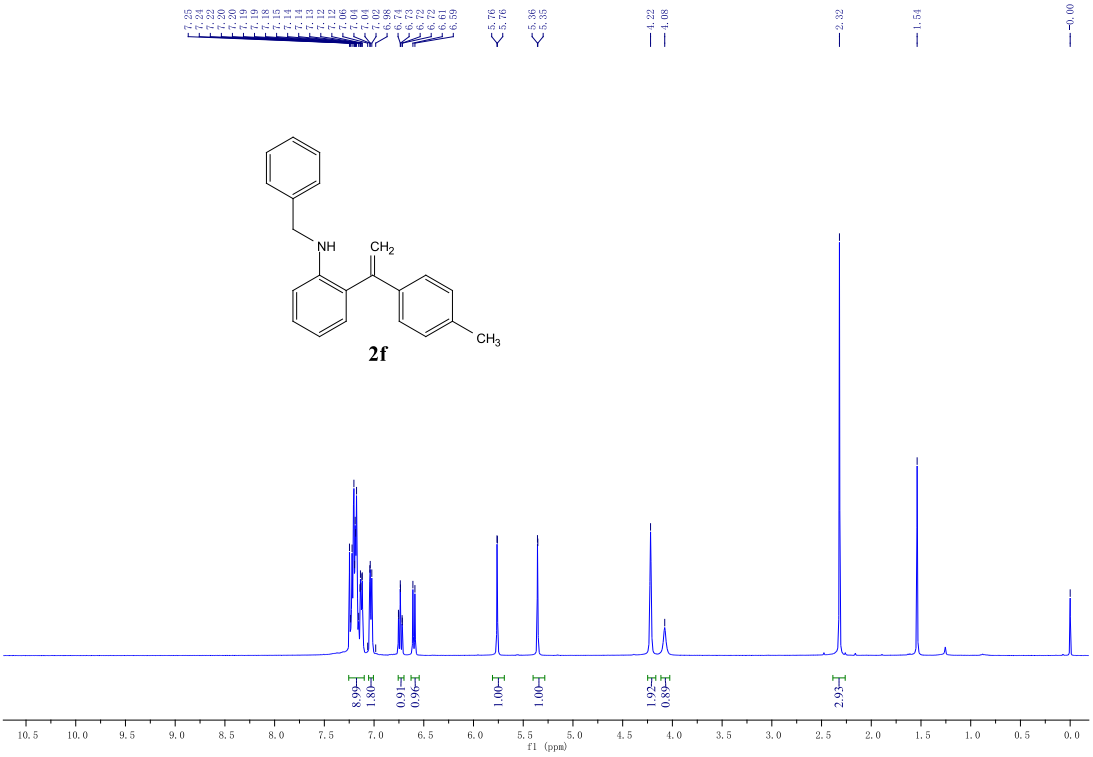
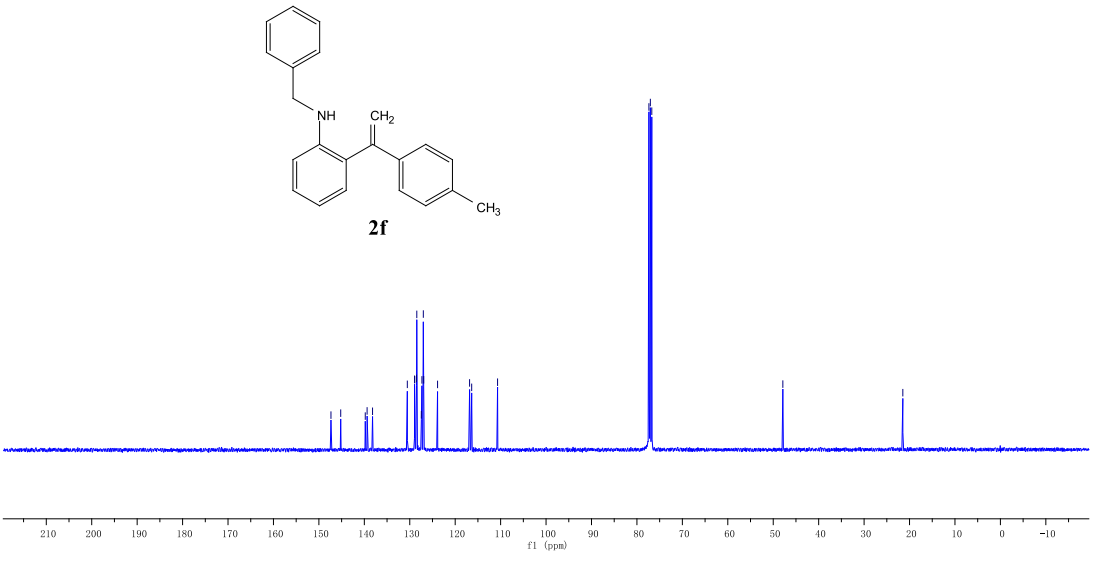
f1 (ppm)


NH
CH2
CH3
2f
f1 (ppm)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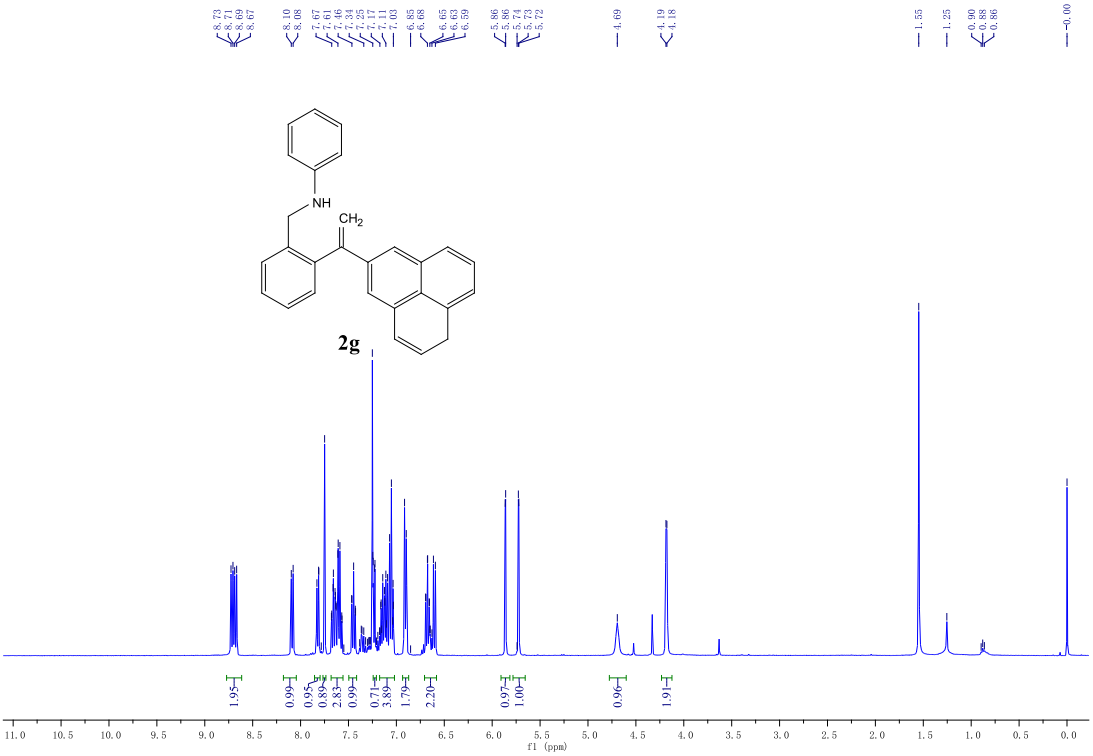
CH2
CH3
2f
f1 (ppm)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7.03
6.85
6.68
6.65
6.63
6.59
5.86
5.86
5.74
5.73
5.72
4.69
4.19
4.18
1.55
1.25
0.90
0.88
0.86
0.00
NH
CH2
2g
1.95
0.99
0.95
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1.00
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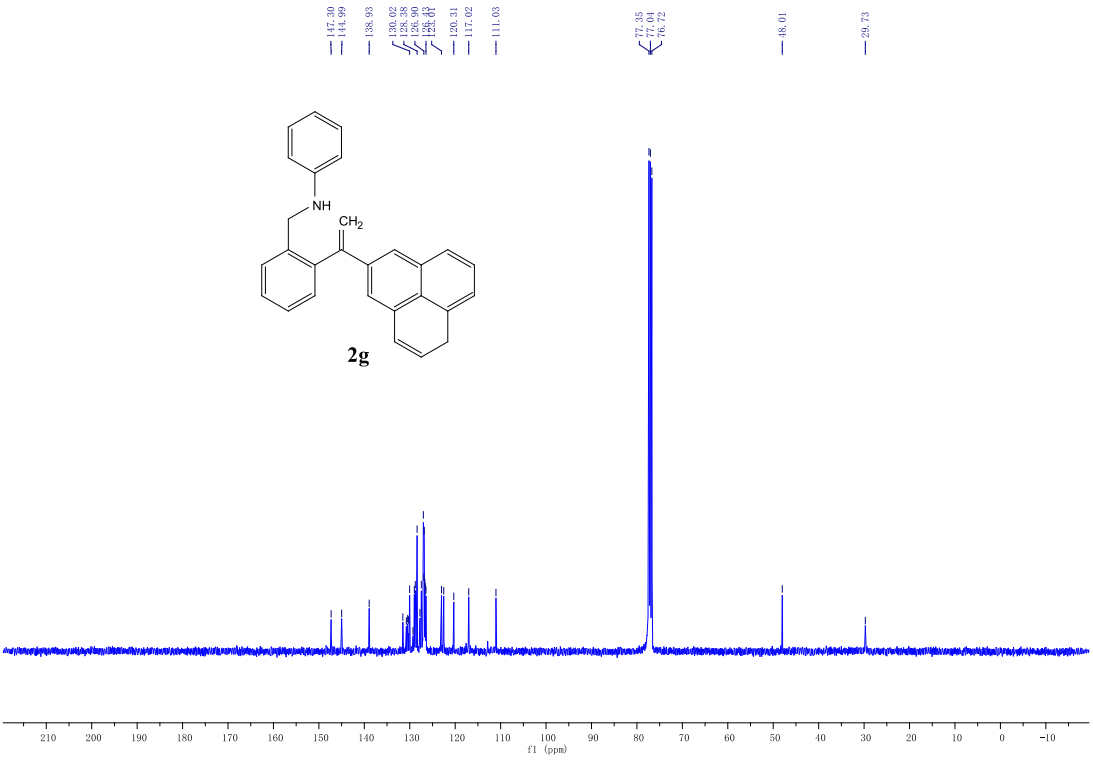
f1 (ppm)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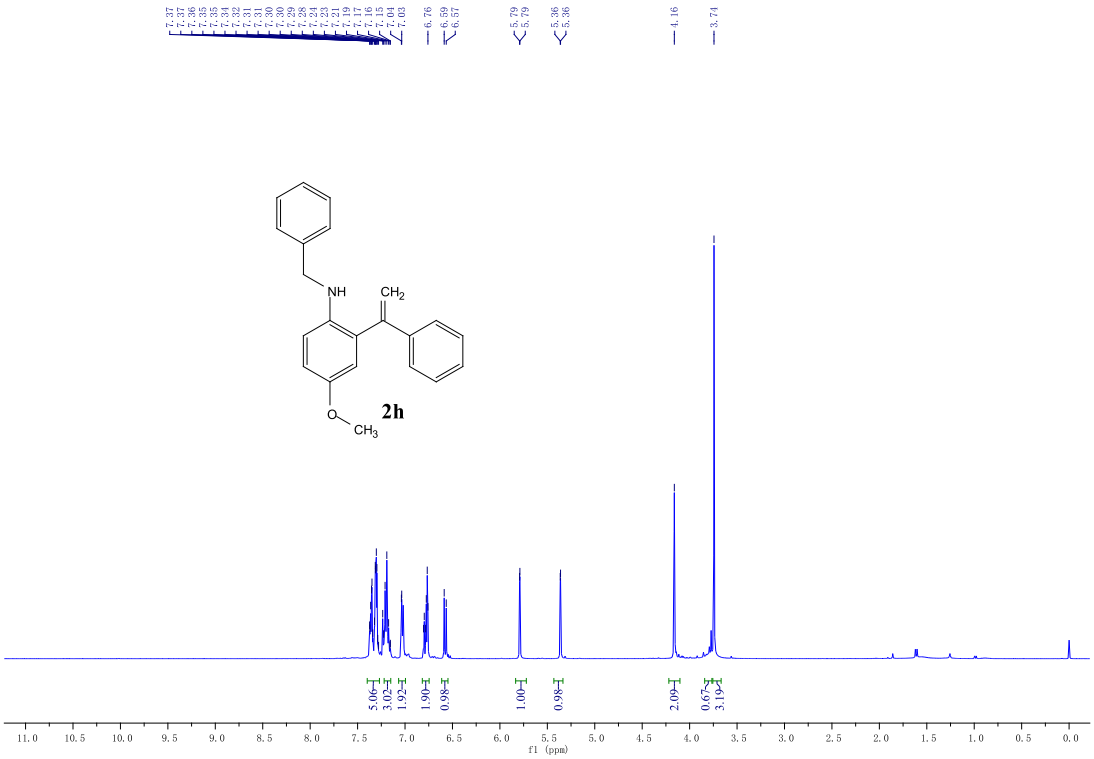
77.04
76.72
48.01
29.73
NH
CH2
2g
f1 (ppm)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7.21
7.19
7.17
7.16
7.15
7.04
7.03
6.76
6.59
6.57
5.79
5.79
5.36
5.36
4.16
3.74
NH
CH2
O
CH3
2h
5.06
3.02
1.92
1.90
0.98
1.00
0.98
2.09
0.67
3.19
11.0
10.5
10.0
9.5
9.0
8.5
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7.0
6.5
6.0
5.5
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2.0
1.5
1.0
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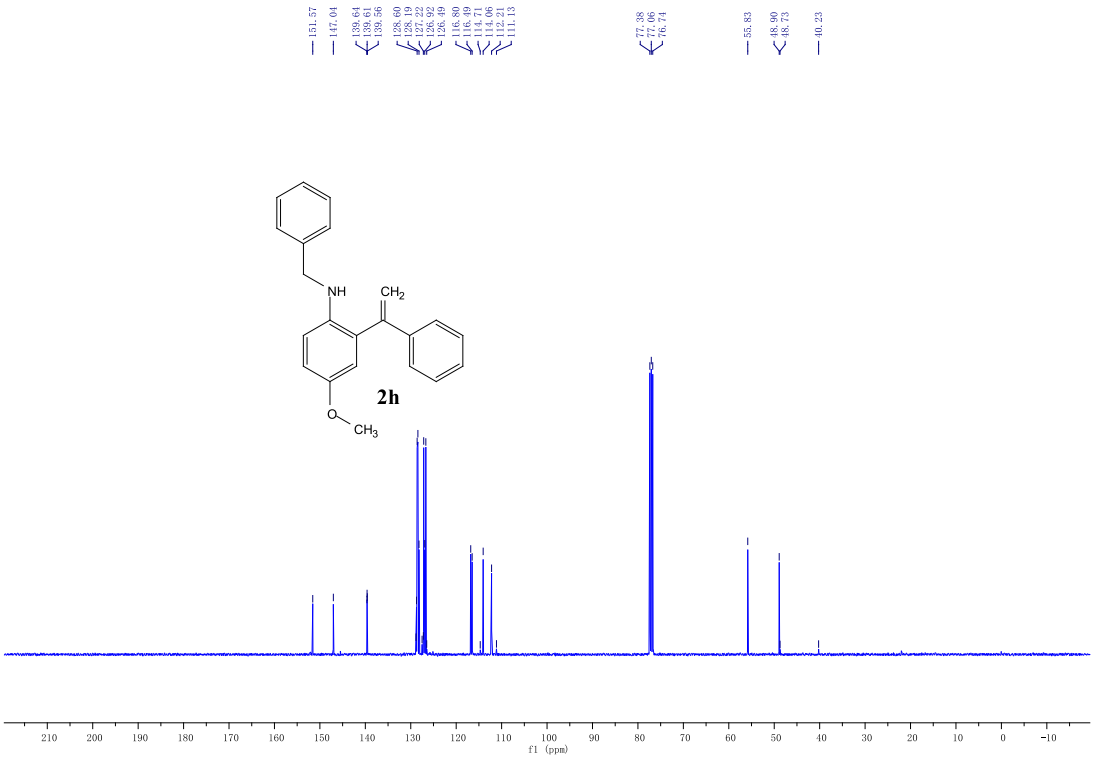
0.0
f1 (ppm)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114.71
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112.21
111.13
77.38
77.06
76.74
55.83
48.90
48.73
40.23
NH
CH2
O
CH3
2h
210
200
190
180
170
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140
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120
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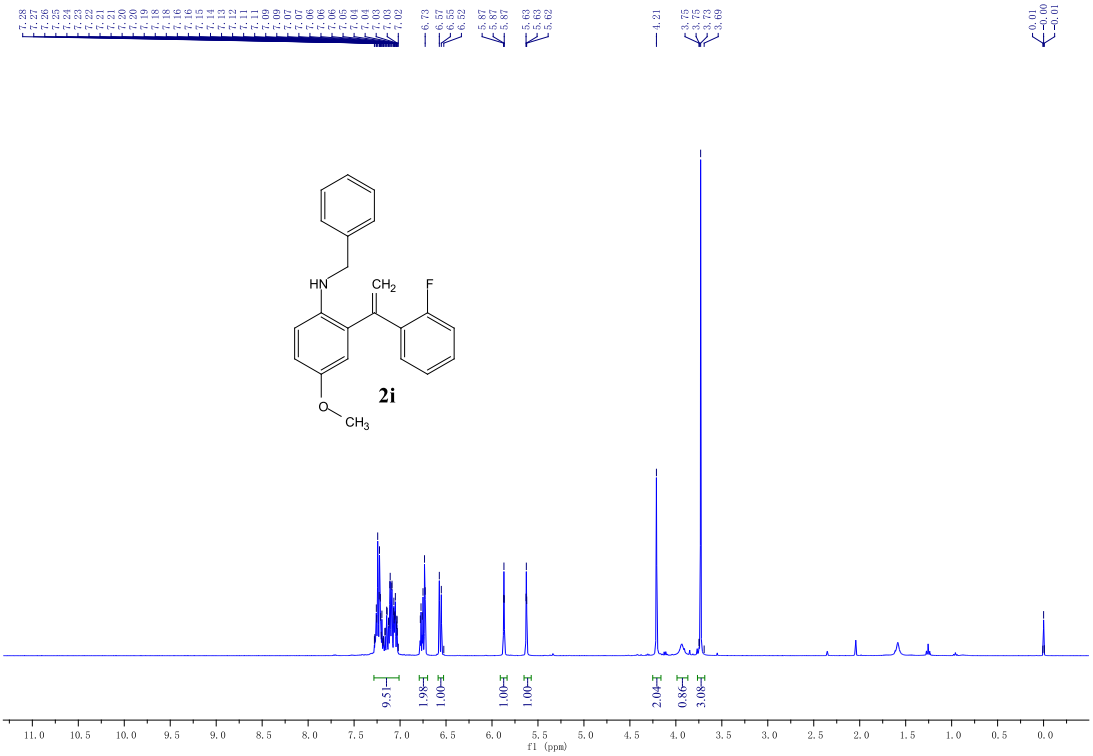
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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CH2
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O
CH3
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1.00
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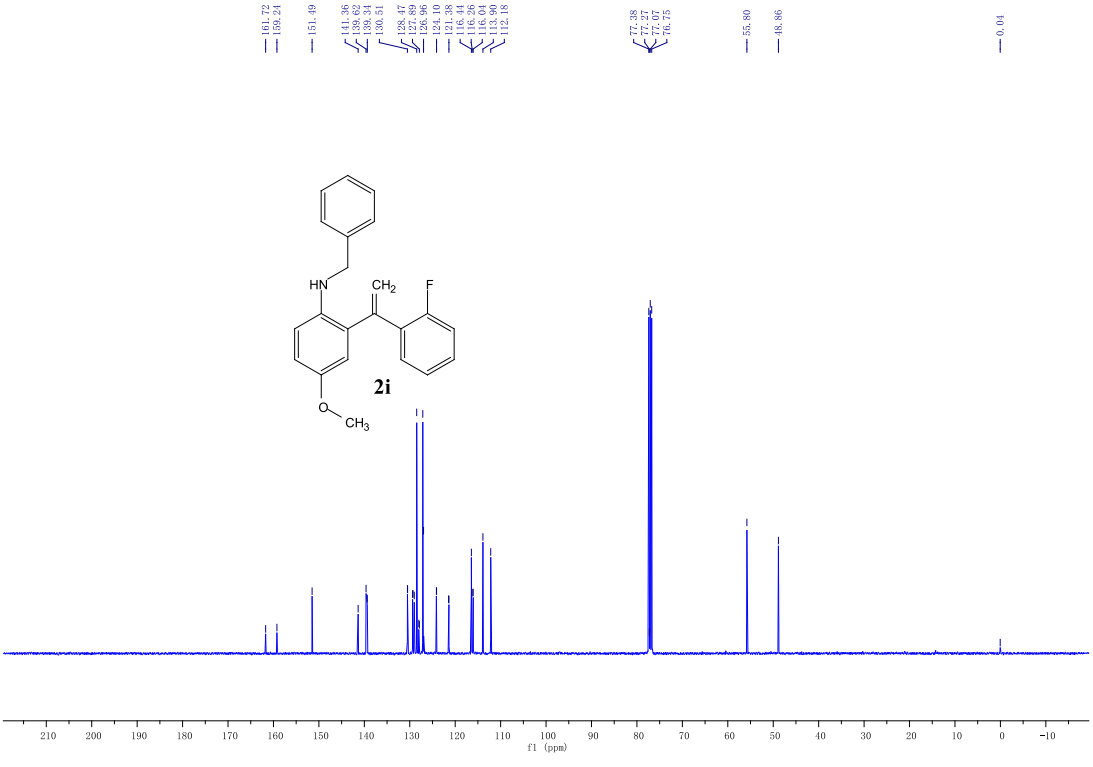
3.08
f1 (ppm)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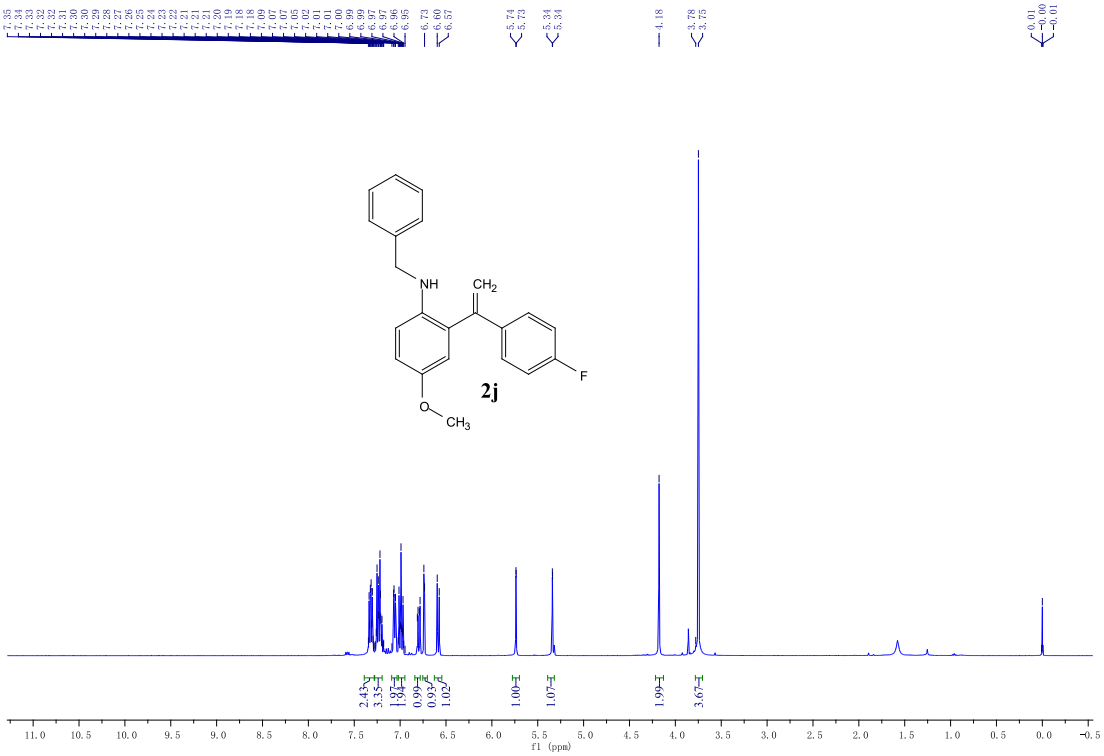
CH2
F
O
CH3
2i
f1 (ppm)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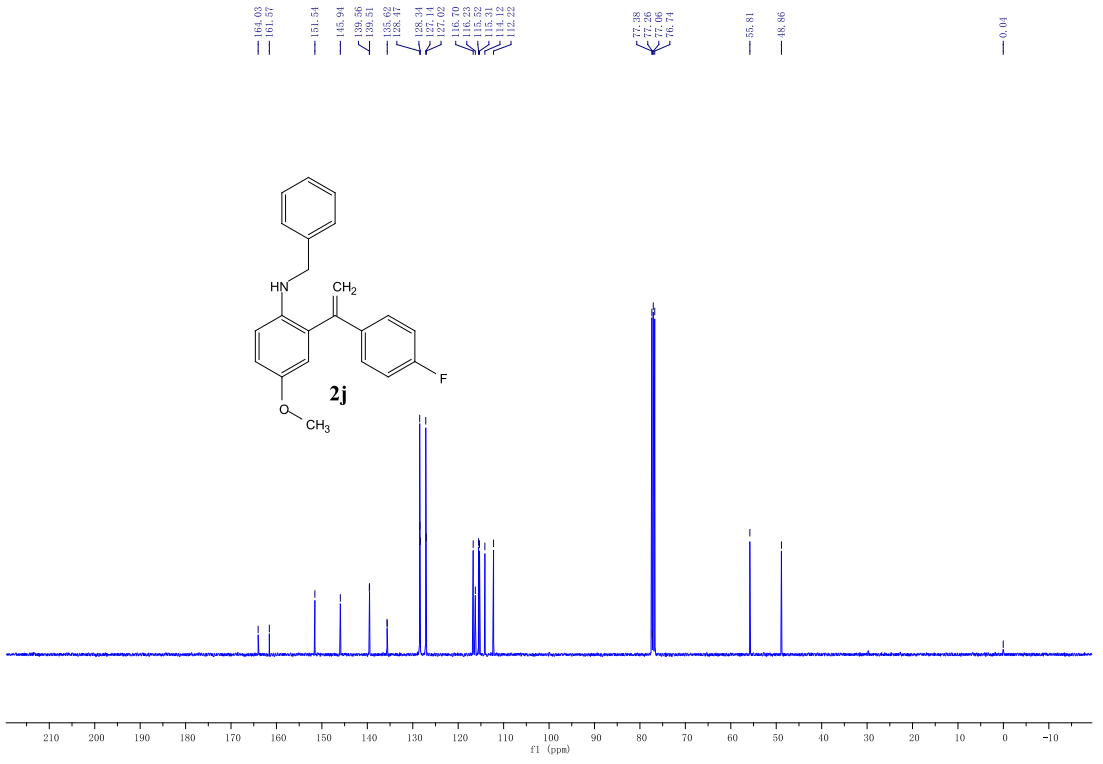
CH2
F
2j
O
CH3
f1 (ppm)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CH2
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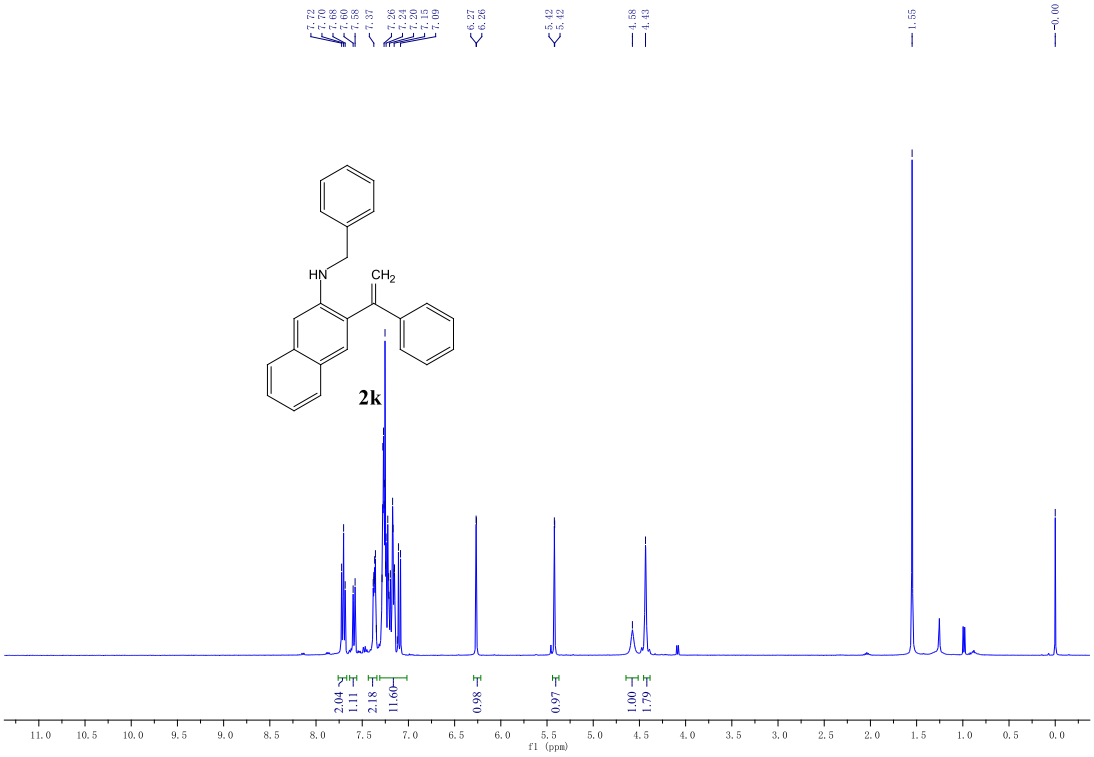
2j
O
CH3
f1 (ppm)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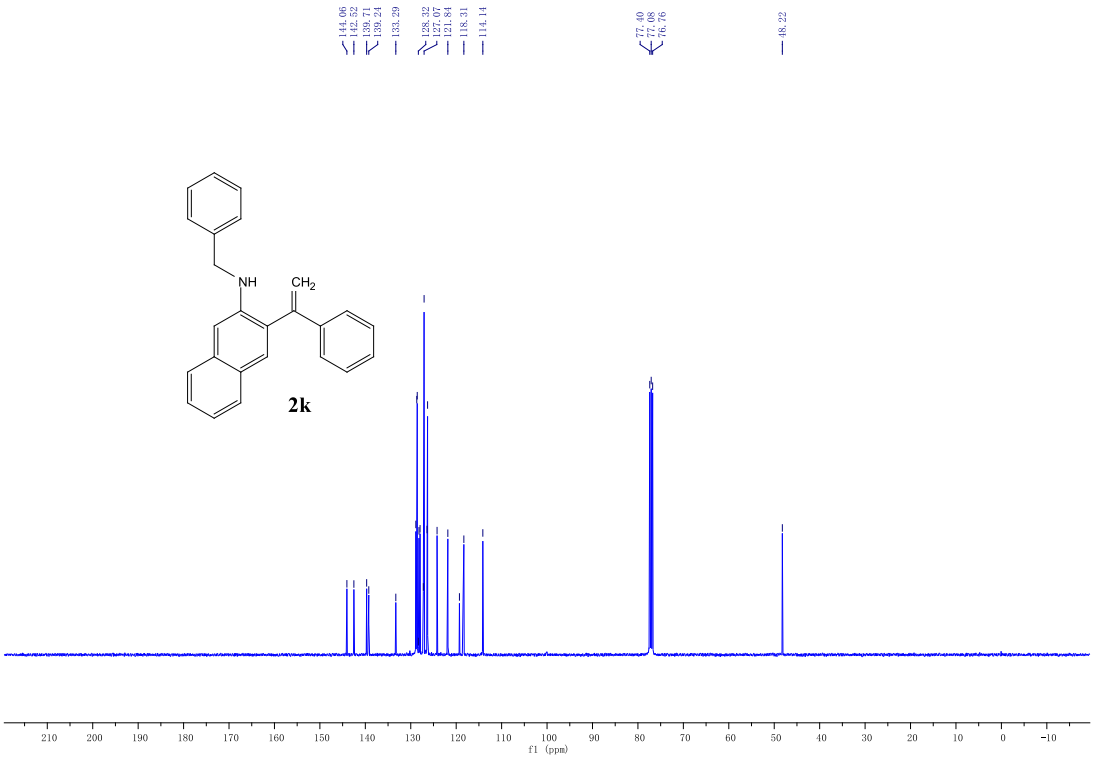
7.26
7.24
7.20
7.15
7.09
6.27
6.26
5.42
5.42
4.58
4.43
1.55
0.00
HN
CH2
2k
2.04
1.11
2.18
11.60
0.98
0.97
1.00
1.79
f1 (ppm)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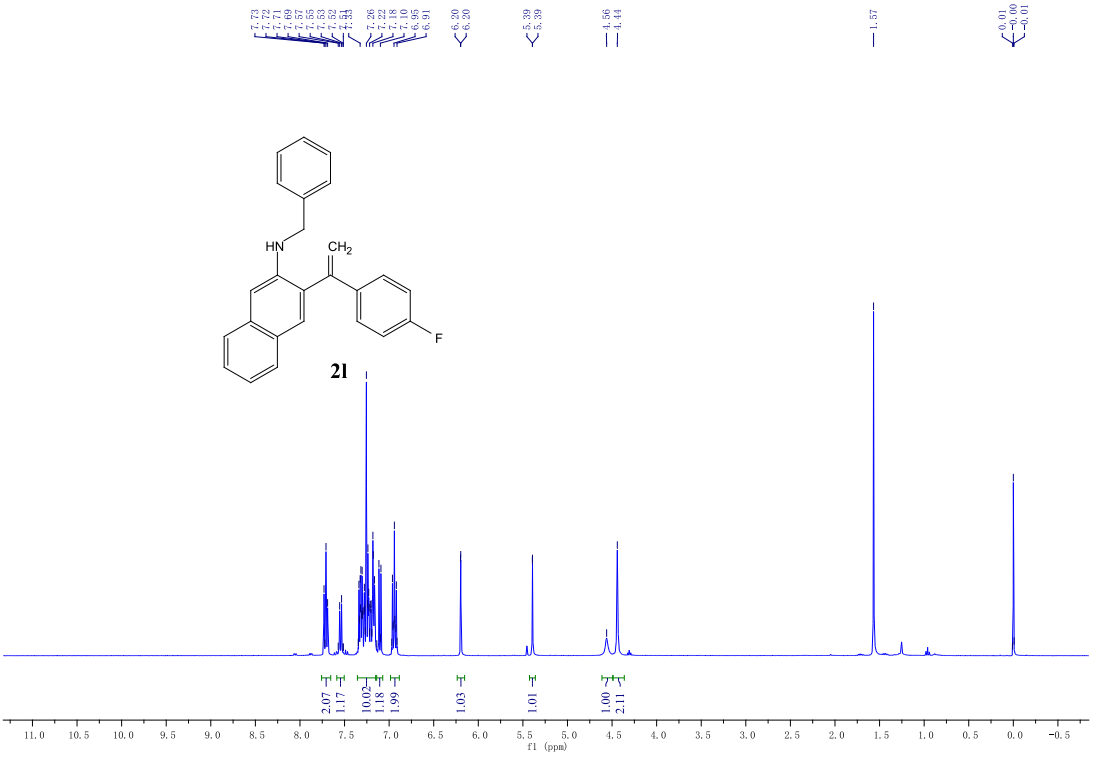
114.14
77.40
77.08
76.76
48.22
NH
CH2
2k
f1 (ppm)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7.25
7.22
7.18
7.10
6.95
6.91
6.20
6.20
5.39
5.39
4.56
4.44
1.57
0.01
0.00
-0.01
HN
CH2
F
21
2.07
1.17
10.02
1.18
1.99
1.03
1.01
1.00
2.11
11.0
10.5
10.0
9.5
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8.5
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7.5
7.0
6.5
6.0
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5.0
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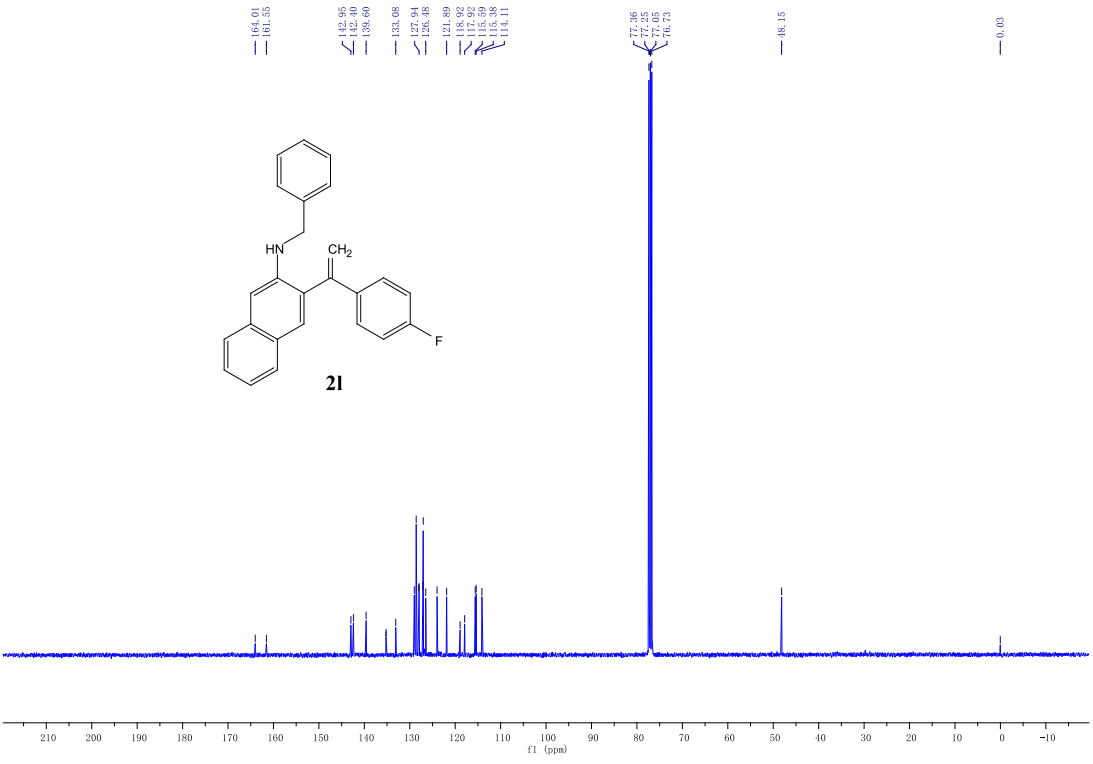
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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115.59
115.38
114.11
77.36
77.25
77.05
76.73
48.15
0.03
HN
CH2
F
21
210
200
190
180
170
160
150
140
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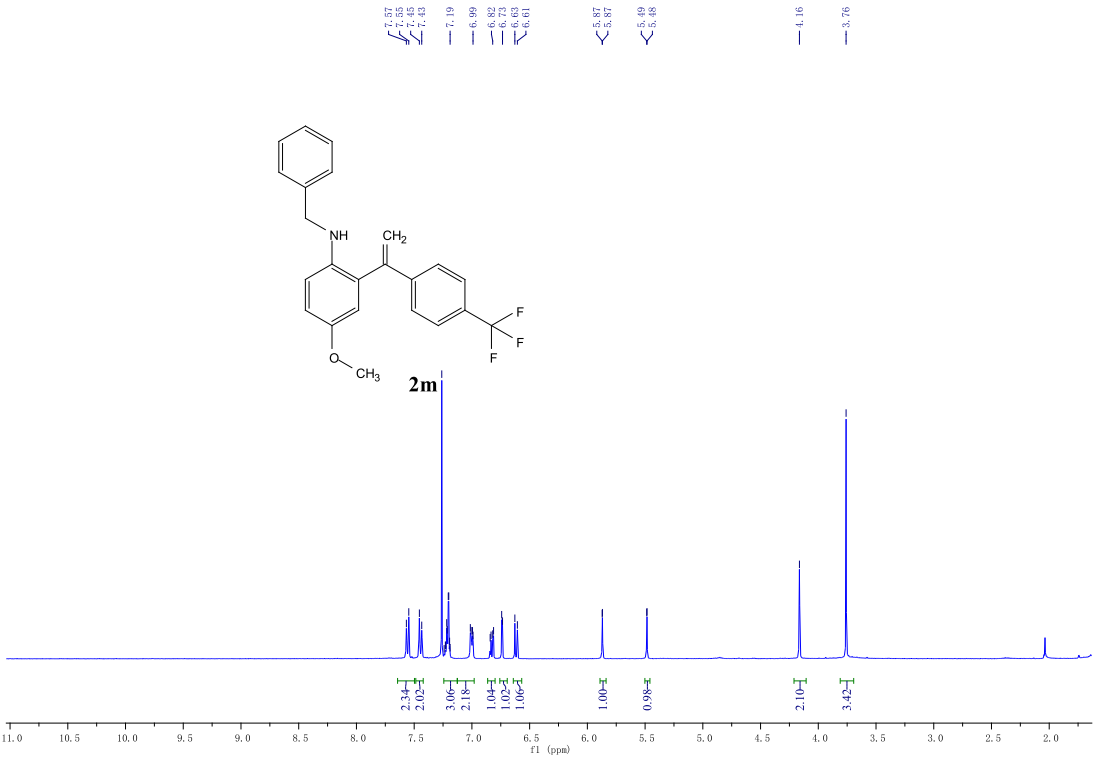
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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6.61
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5.87
5.49
5.48
4.16
3.76
NH
CH2
F
F
F
O
CH3
2m
2.34
2.02
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2.18
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1.06
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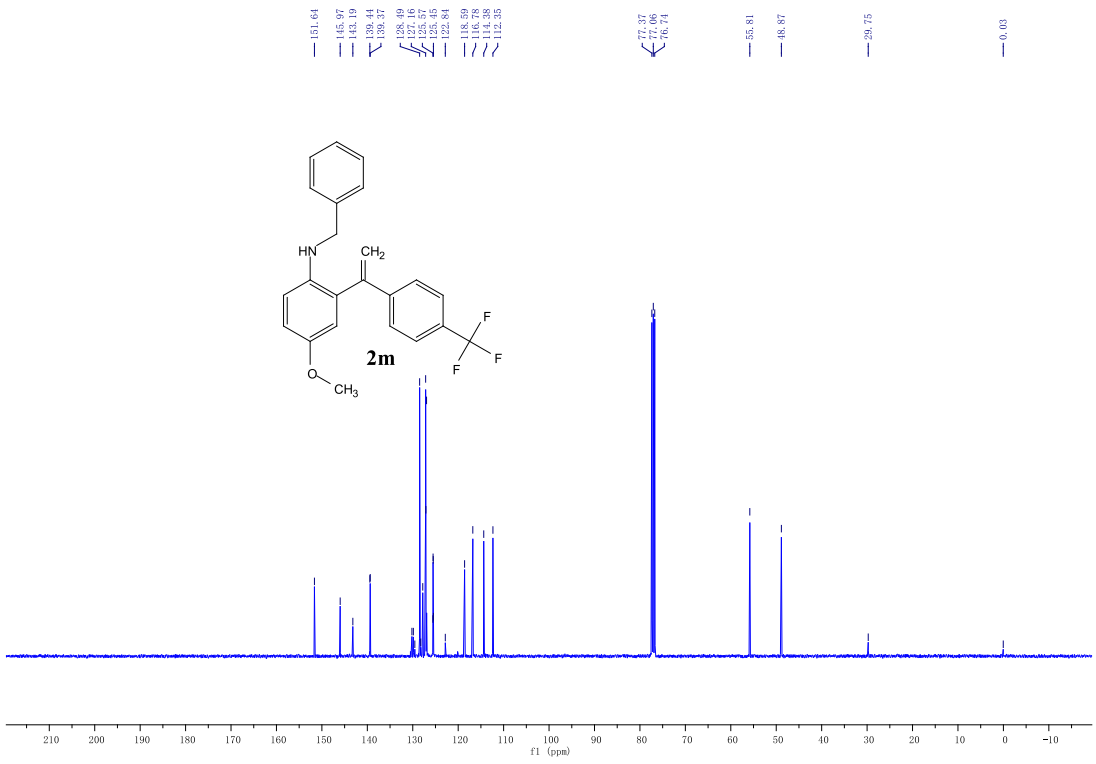
3.42
f1 (ppm)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114.38
112.35
77.37
77.06
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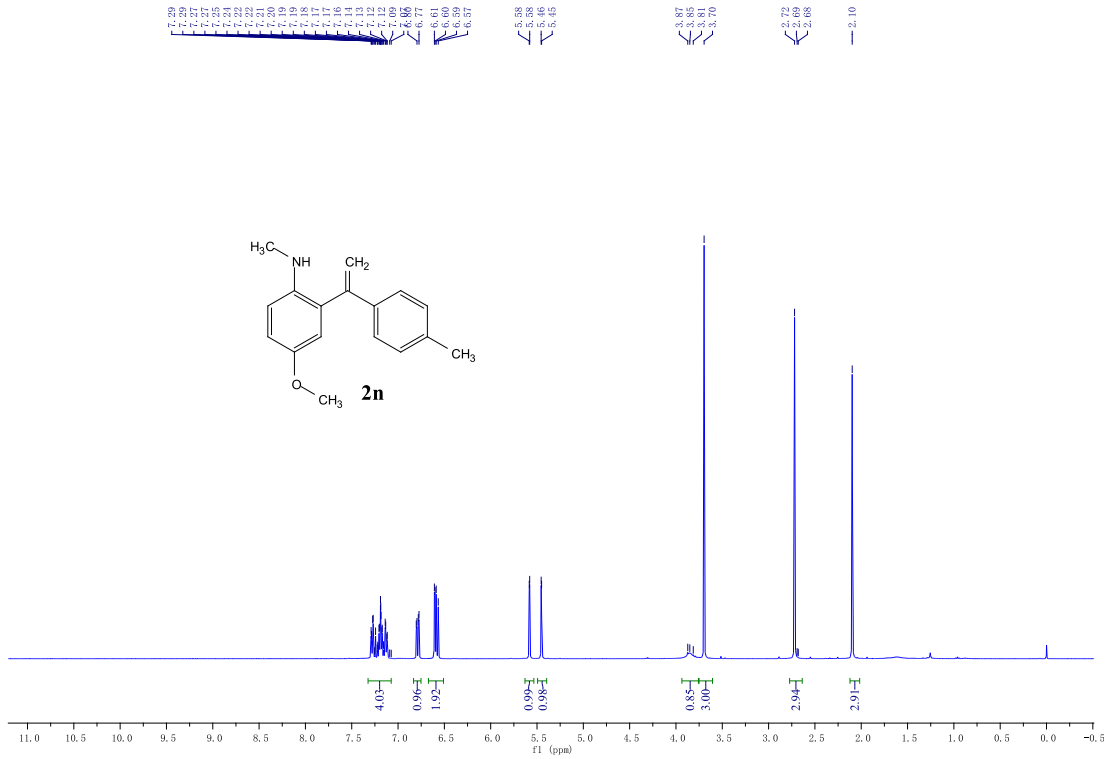
CH2
F
F
F
O
CH3
2m
f1 (ppm)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5.58
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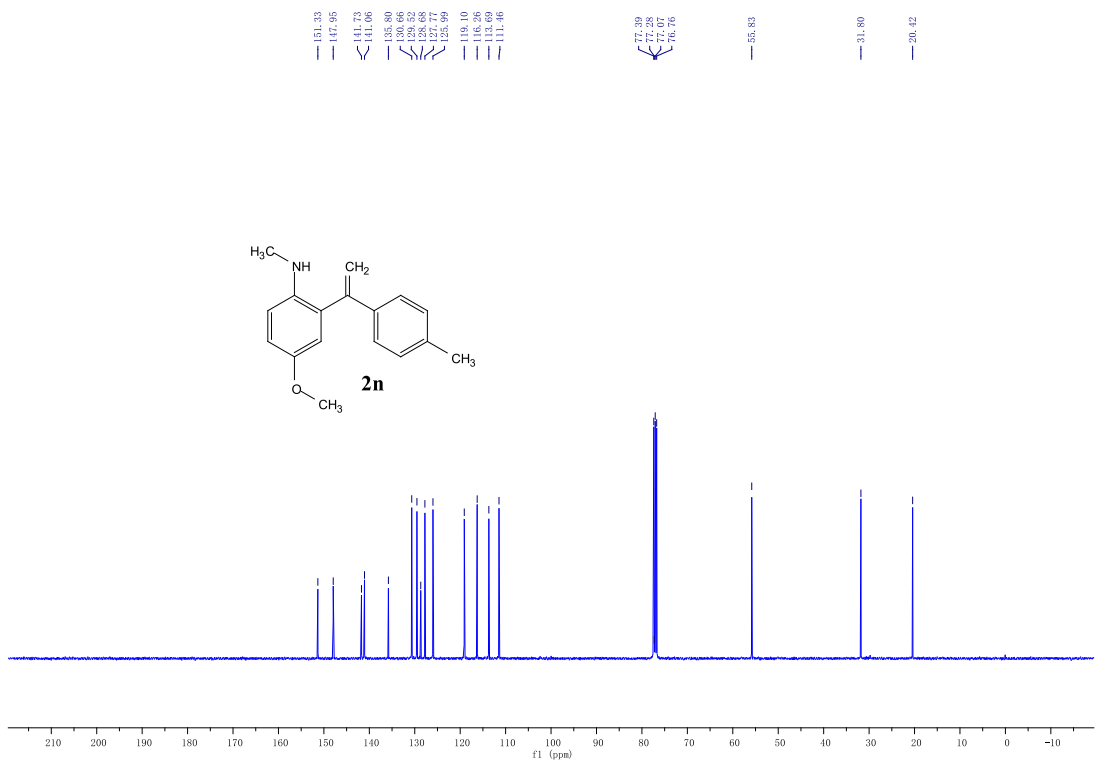
3.85
3.81
3.70
2.72
2.69
2.68
2.10
H3C
NH
CH2
CH3
O
CH3
2n
4.03
0.96
1.92
0.99
0.98
0.85
3.00
2.94
2.91
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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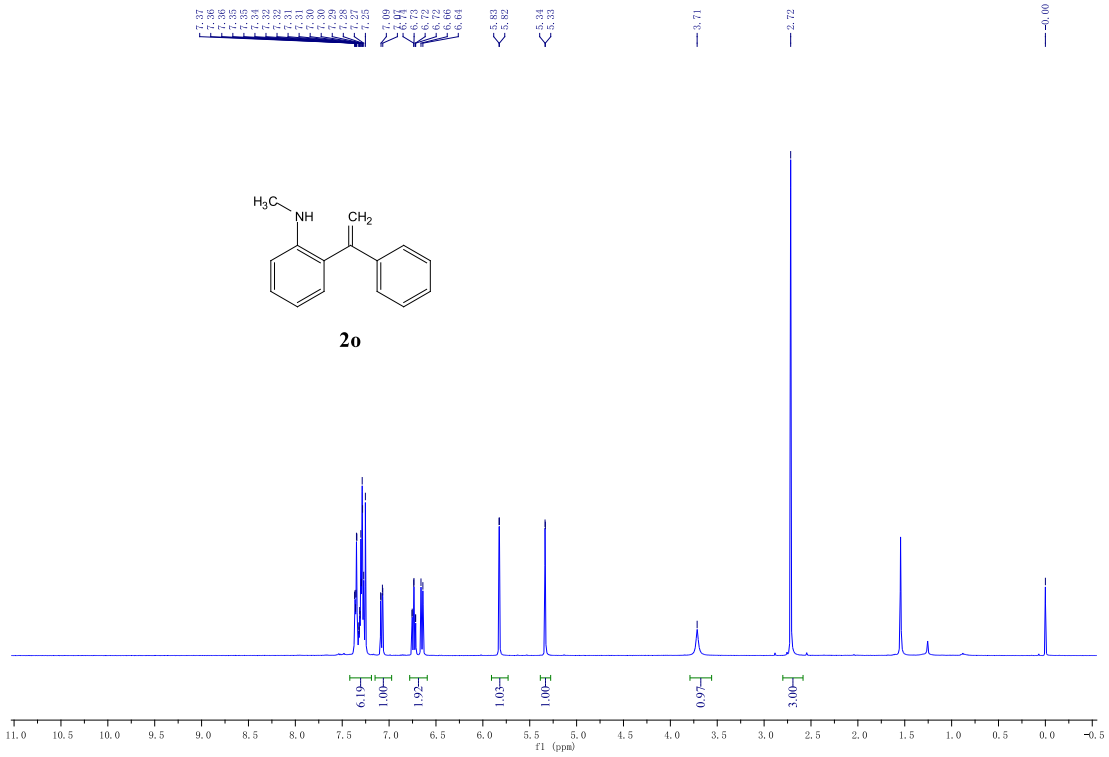
116.26
113.69
111.46
77.39
77.28
77.07
76.76
55.83
31.80
20.42
H3C
NH
CH2
CH3
O
CH3
2n
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.07
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6.73
6.72
6.72
6.66
6.64
5.83
5.82
5.34
5.33
3.71
2.72
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NH
CH2
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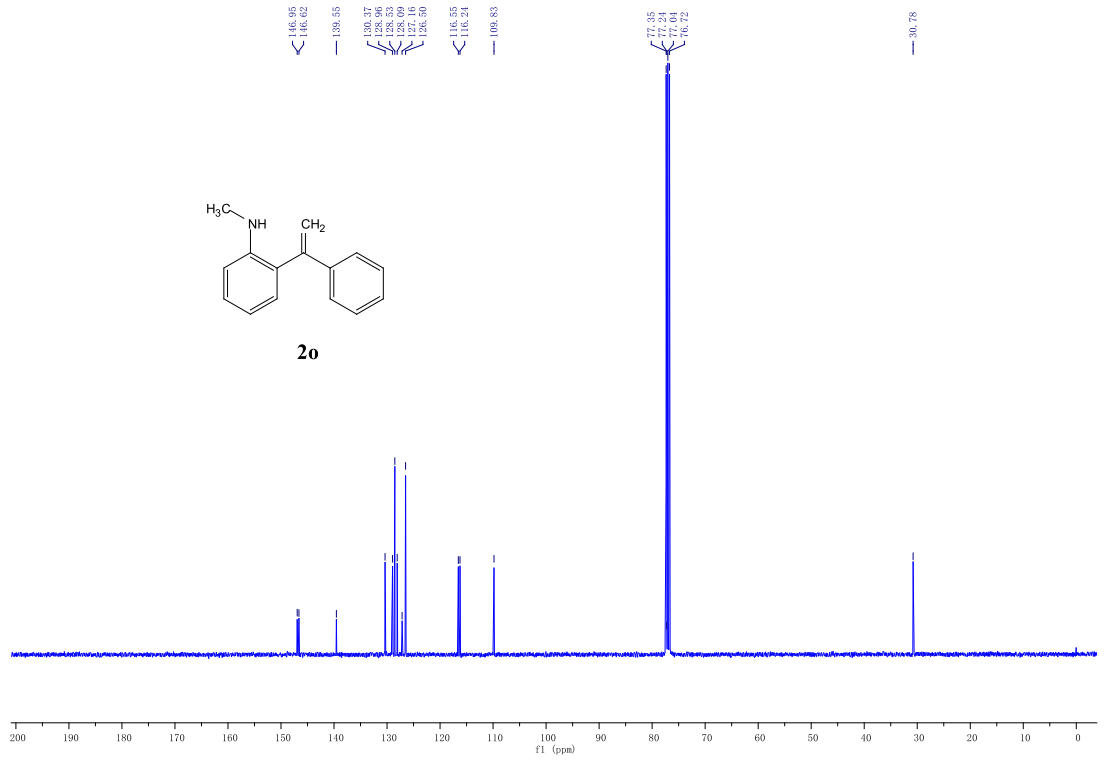
1.92
1.03
1.00
0.97
3.00
f1 (ppm)

2o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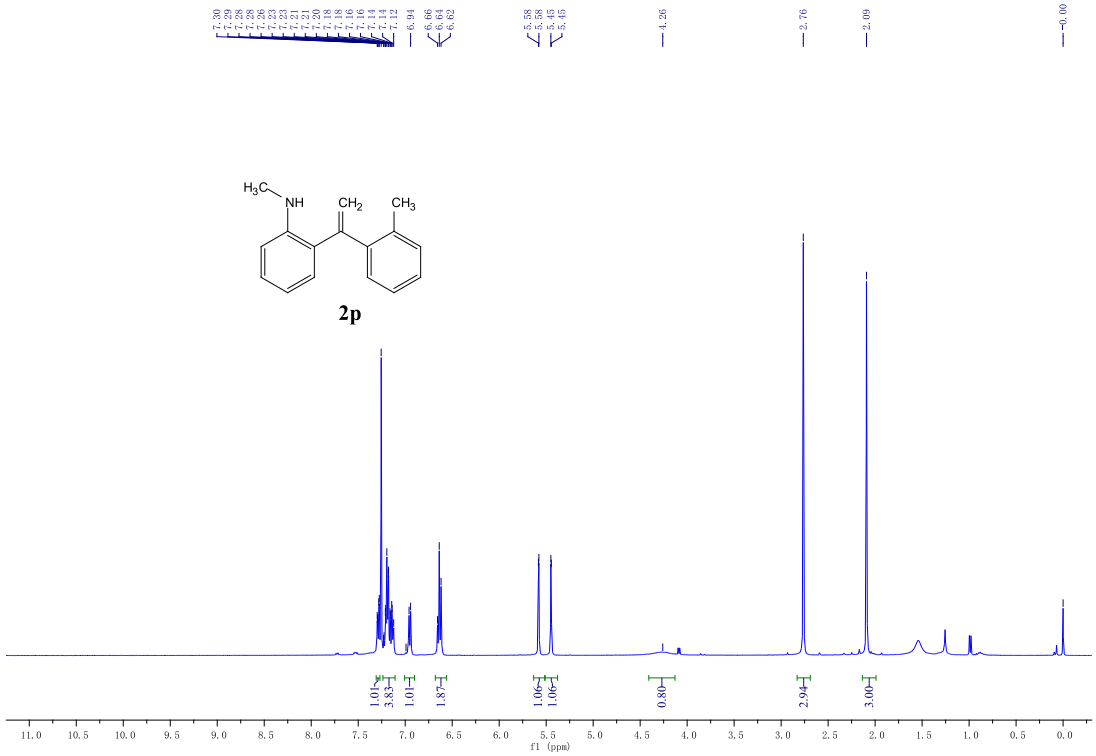
77.24
77.04
76.72
30.78
H3C
NH
CH2
f1 (ppm)

2o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7.12
6.94
6.66
6.64
6.62
5.58
5.58
5.45
5.45
4.26
2.76
2.09
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H3C
NH
CH2
CH3
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1.06
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0.80
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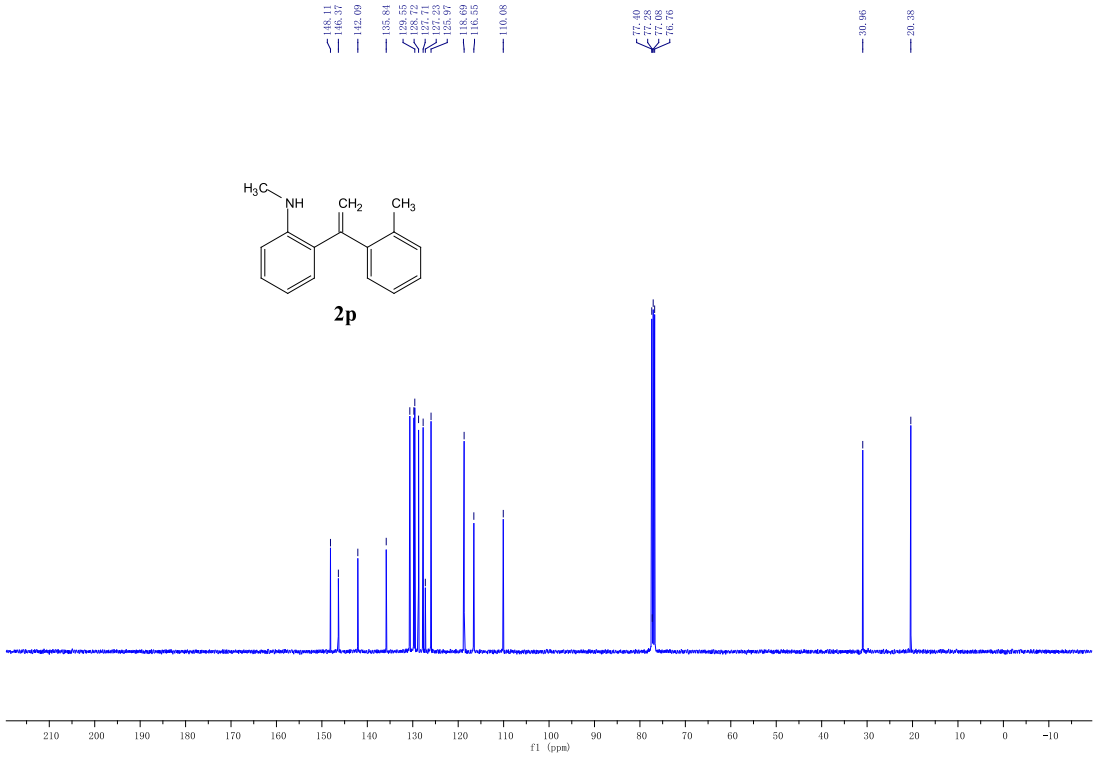
3.00
f1 (ppm)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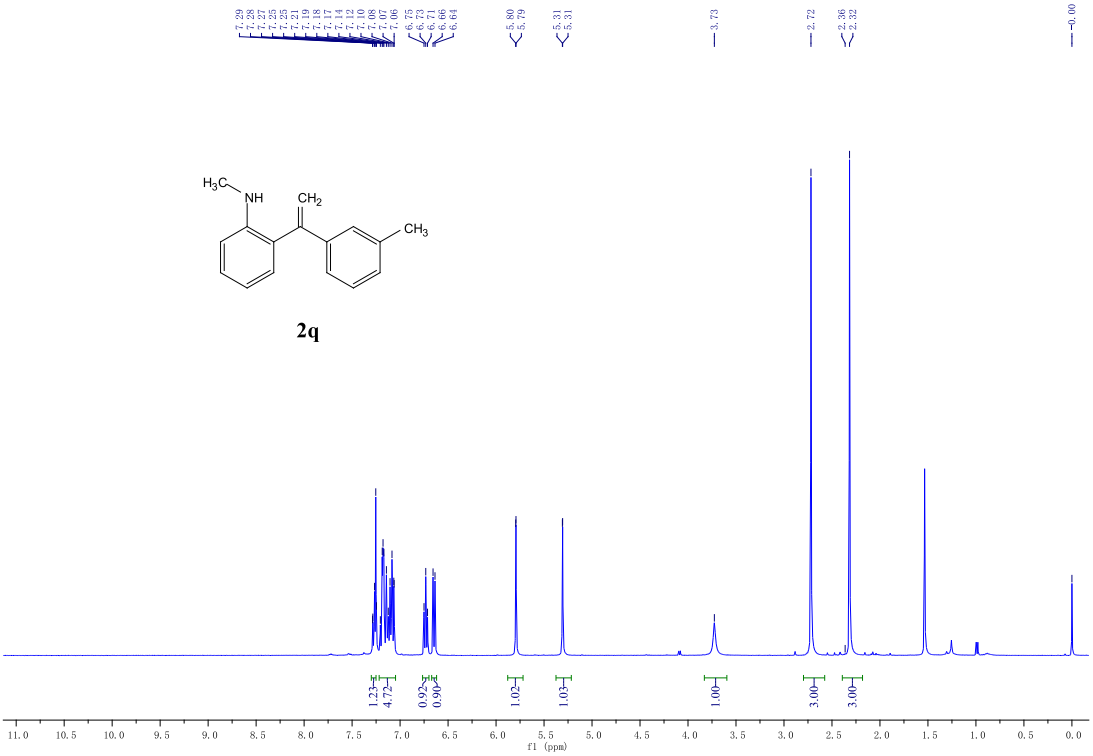
NH
CH2
CH3
2p
f1 (ppm)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7.14
7.12
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6.64
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5.31
3.73
2.72
2.36
2.32
0.00
H3C
NH
CH2
CH3
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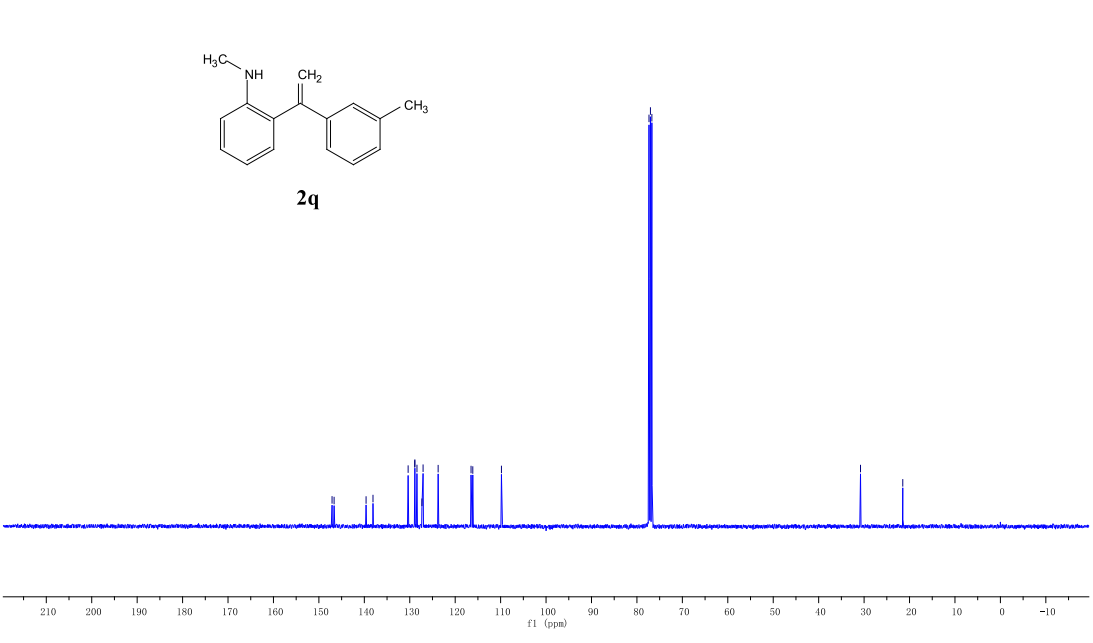
1.03
1.00
3.00
3.00
f1 (ppm)

2q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77.03
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30.79
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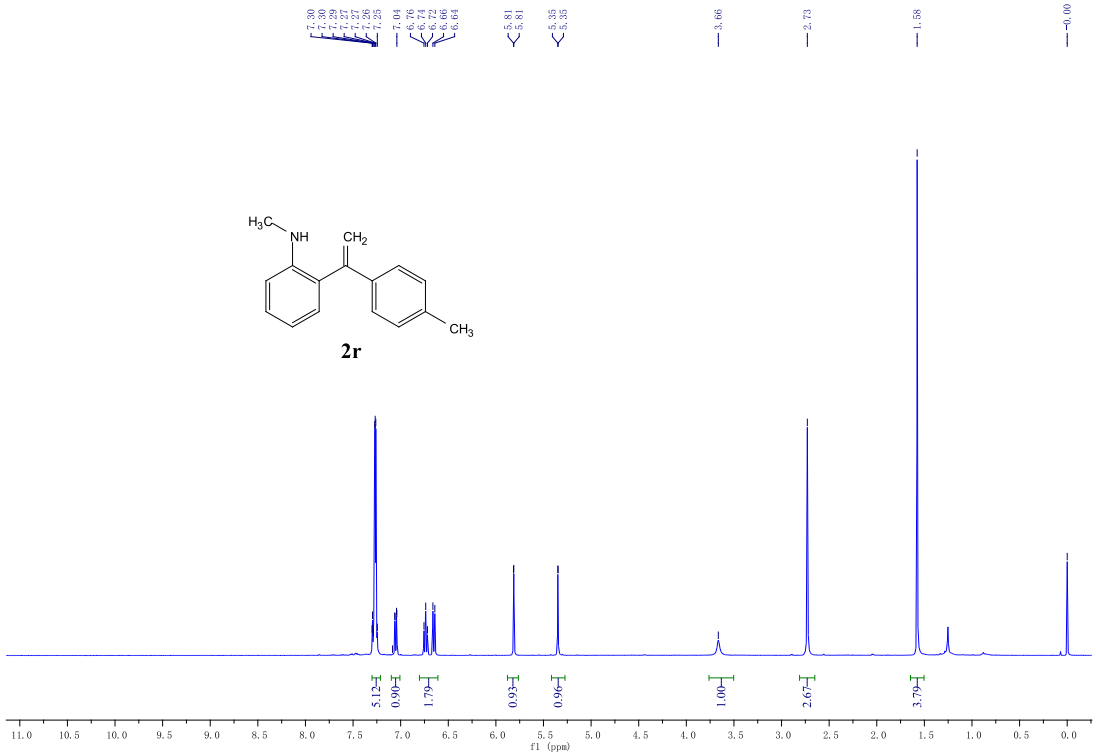
H3C
NH
CH2
CH3
f1 (ppm)

2q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7.26
7.25
7.04
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6.74
6.72
6.66
6.64
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5.81
5.35
5.35
3.66
2.73
1.58
0.00
H3C
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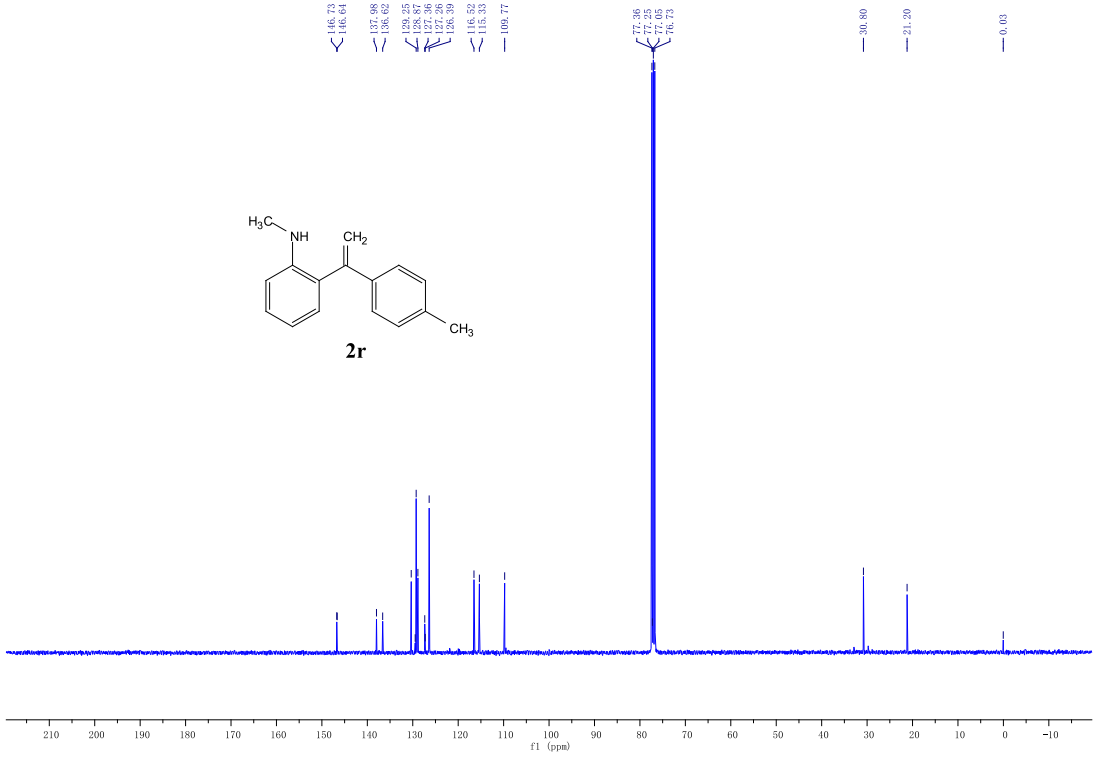
f1 (ppm)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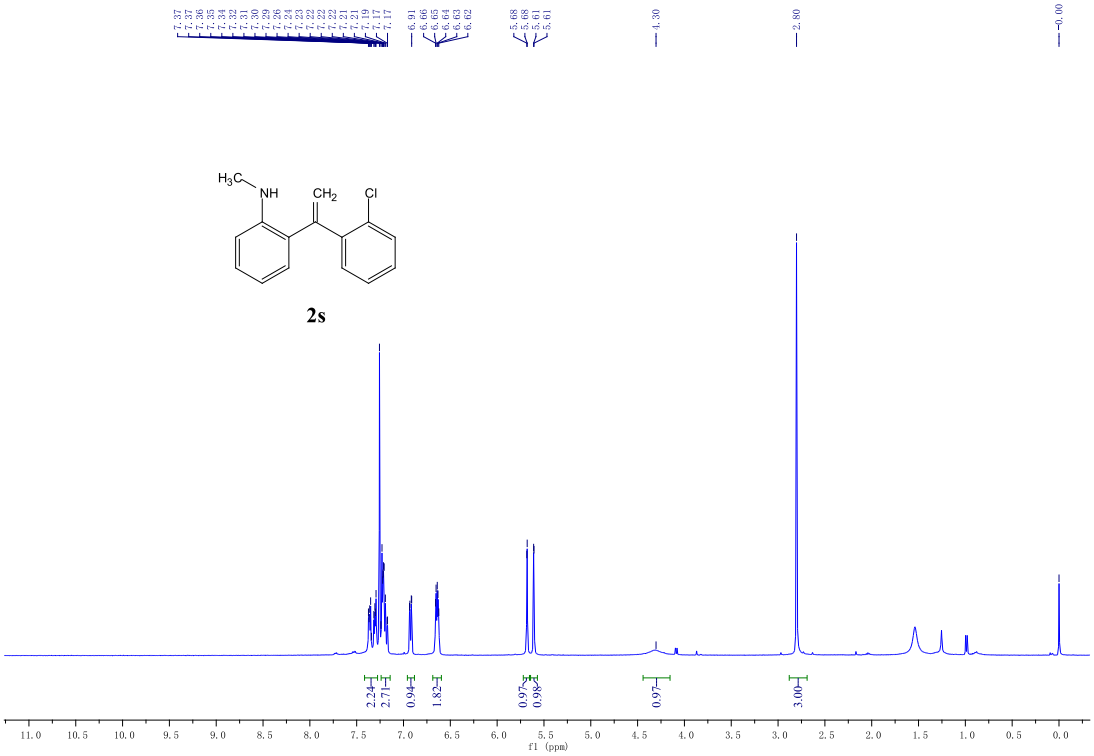
NH
CH2
CH3
2r
f1 (ppm)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7.22
7.21
7.21
7.19
7.17
7.17
6.91
6.66
6.65
6.64
6.63
6.62
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5.61
4.30
2.80
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H3C
NH
CH2
Cl
2s
2.24
2.71
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1.82
0.97
0.98
0.97
3.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
1.5
1.0
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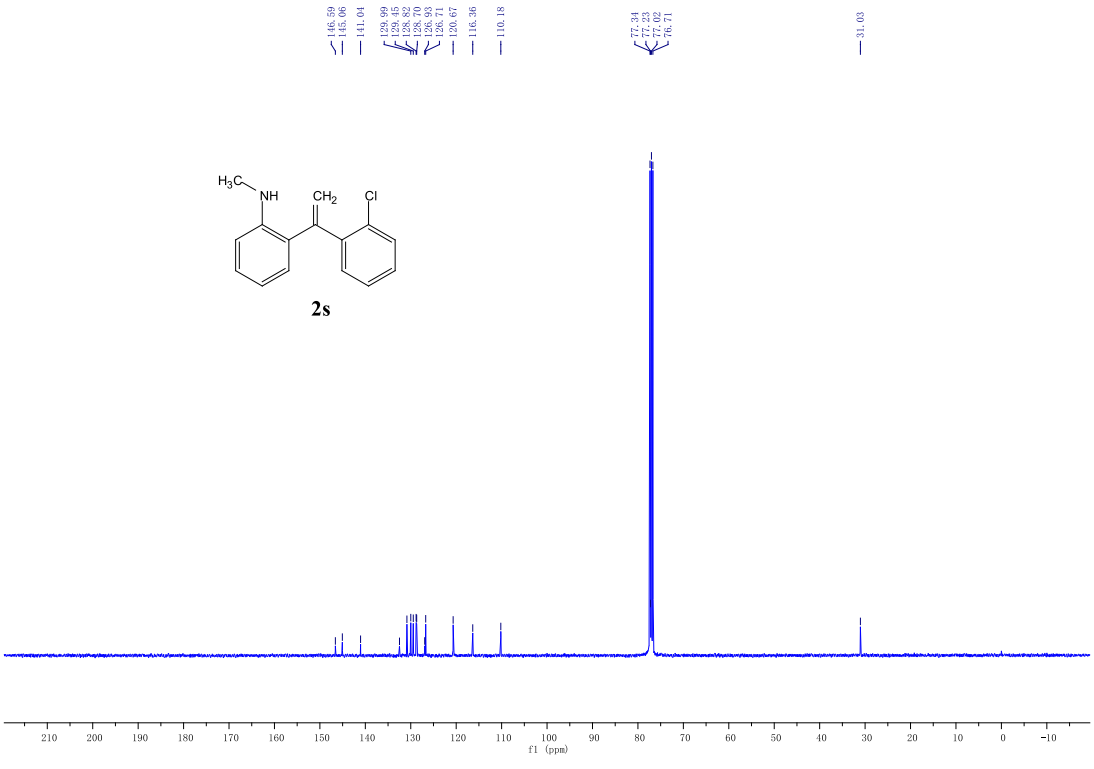
0.0
f1 (ppm)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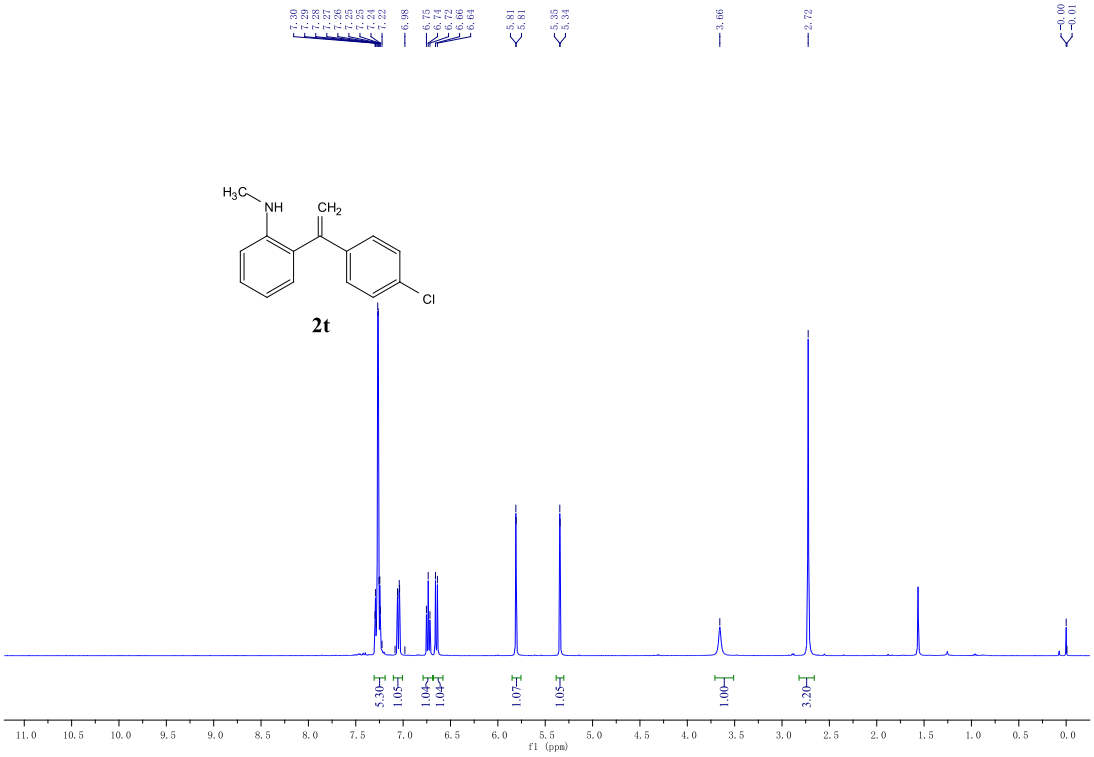
129.99
129.45
128.82
128.70
126.93
126.71
120.67
116.36
110.18
77.34
77.23
77.02
76.71
31.03
H3C
NH
CH2
Cl
2s
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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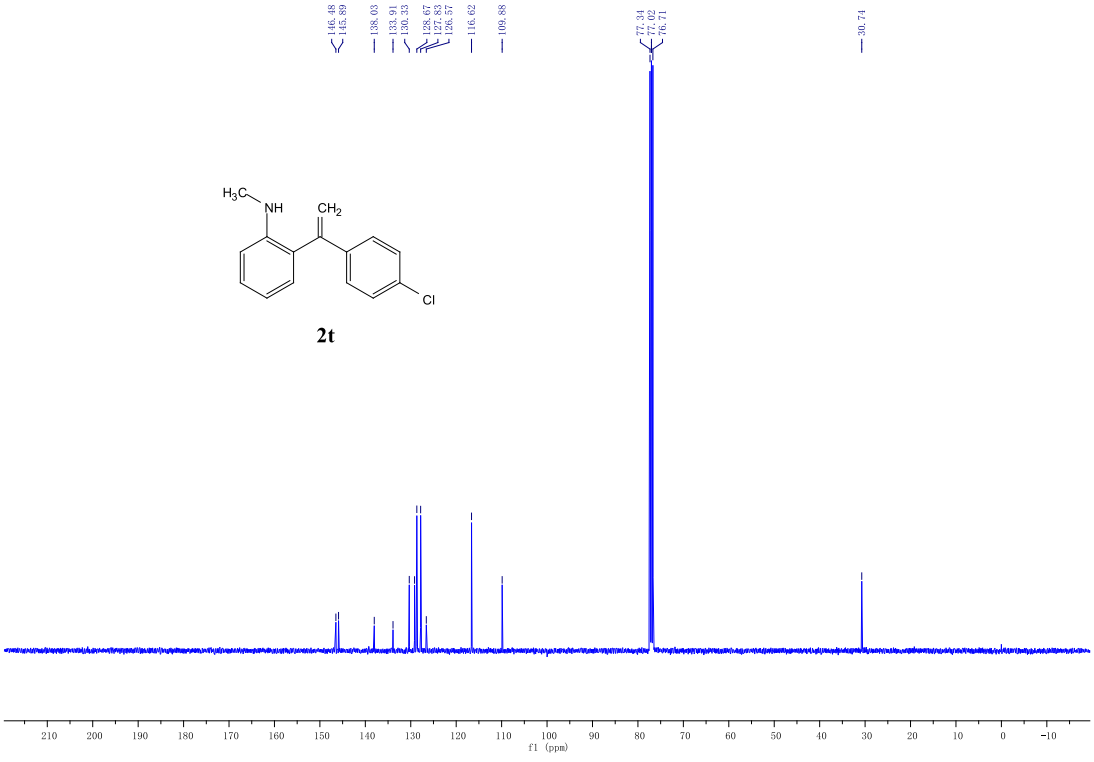
6.74
6.72
6.66
6.64
5.81
5.81
5.35
5.34
3.66
2.72
0.00
-0.01
H3C
NH
CH2
Cl
2t
5.30
1.05
1.04
1.04
1.07
1.05
1.00
3.20
f1 (ppm)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109.88
77.34
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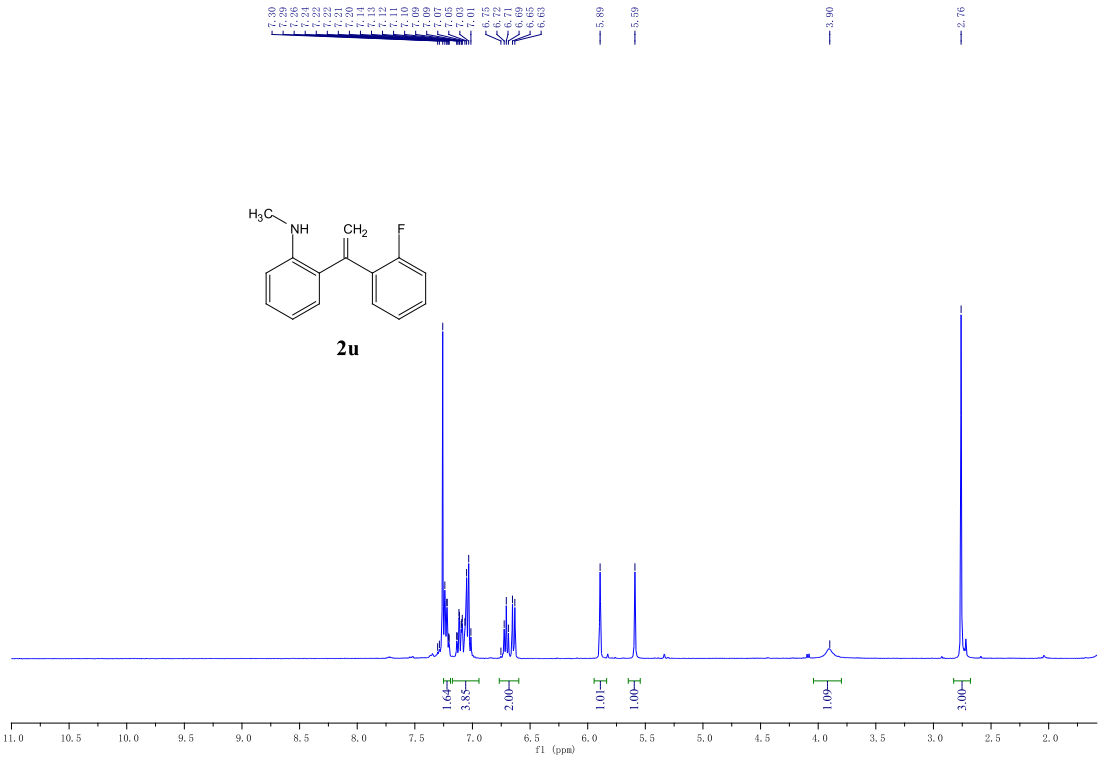
76.71
30.74
H3C
NH
CH2
Cl
2t
f1 (ppm)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7.10
7.09
7.09
7.07
7.05
7.03
7.01
6.75
6.72
6.71
6.69
6.65
6.63
5.89
5.59
3.90
2.76
H3C
NH
CH2
F
1.64
3.85
2.00
1.01
1.00
1.09
3.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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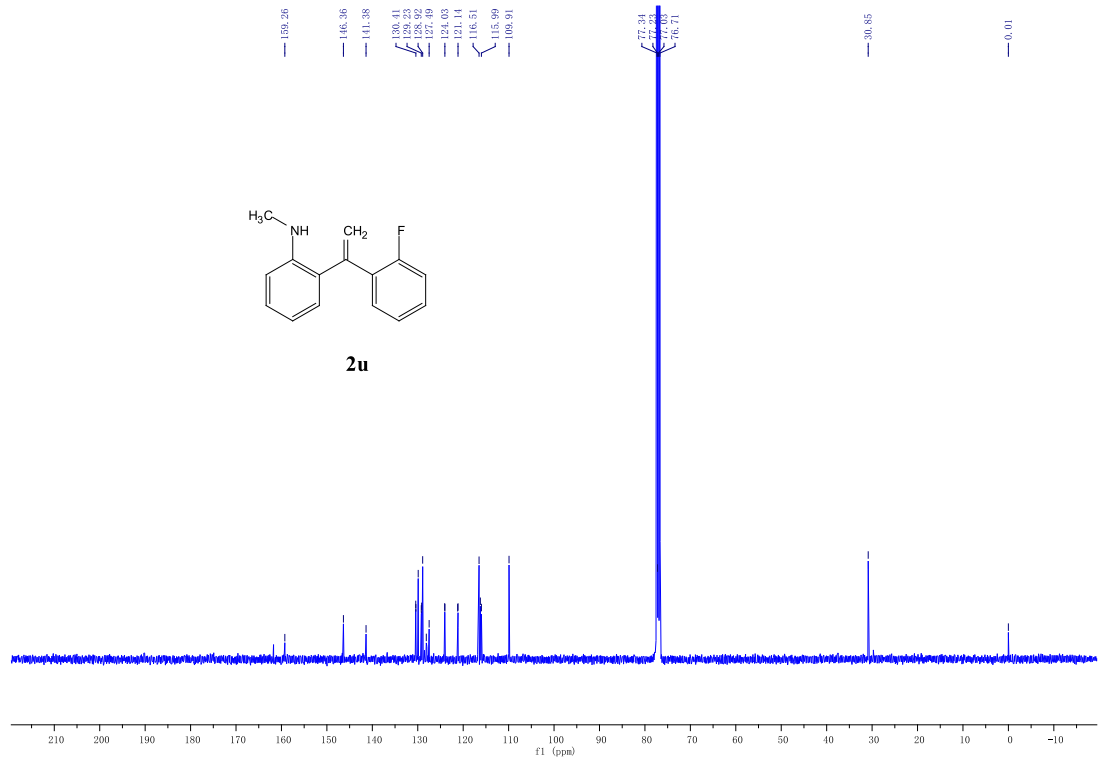
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

2u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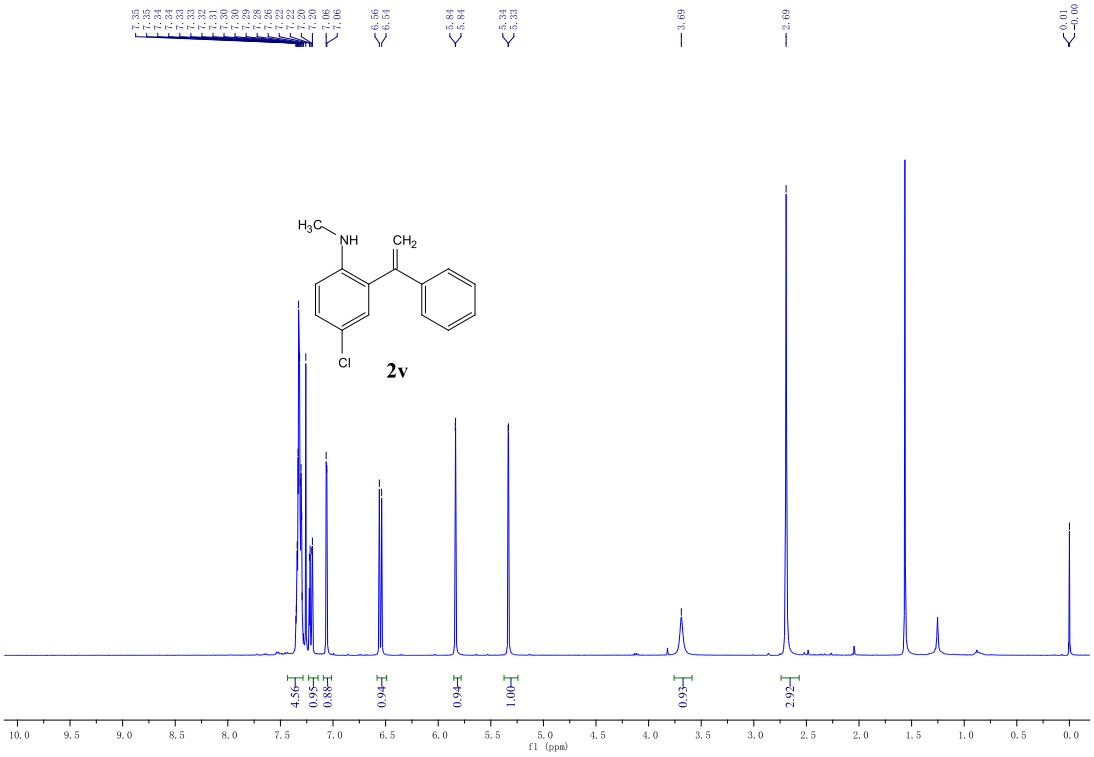
127.49
124.03
121.14
116.51
115.99
109.91
77.34
77.23
77.03
76.71
30.85
0.01
H3C
NH
CH2
F
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

2u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7.26
7.22
7.22
7.20
7.20
7.06
7.06
6.56
6.54
5.84
5.84
5.34
5.33
3.69
2.69
0.01
0.00
H3C
NH
CH2
Cl
2v
4.56
0.95
0.88
0.94
0.94
1.00
0.93
2.92
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
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1.0
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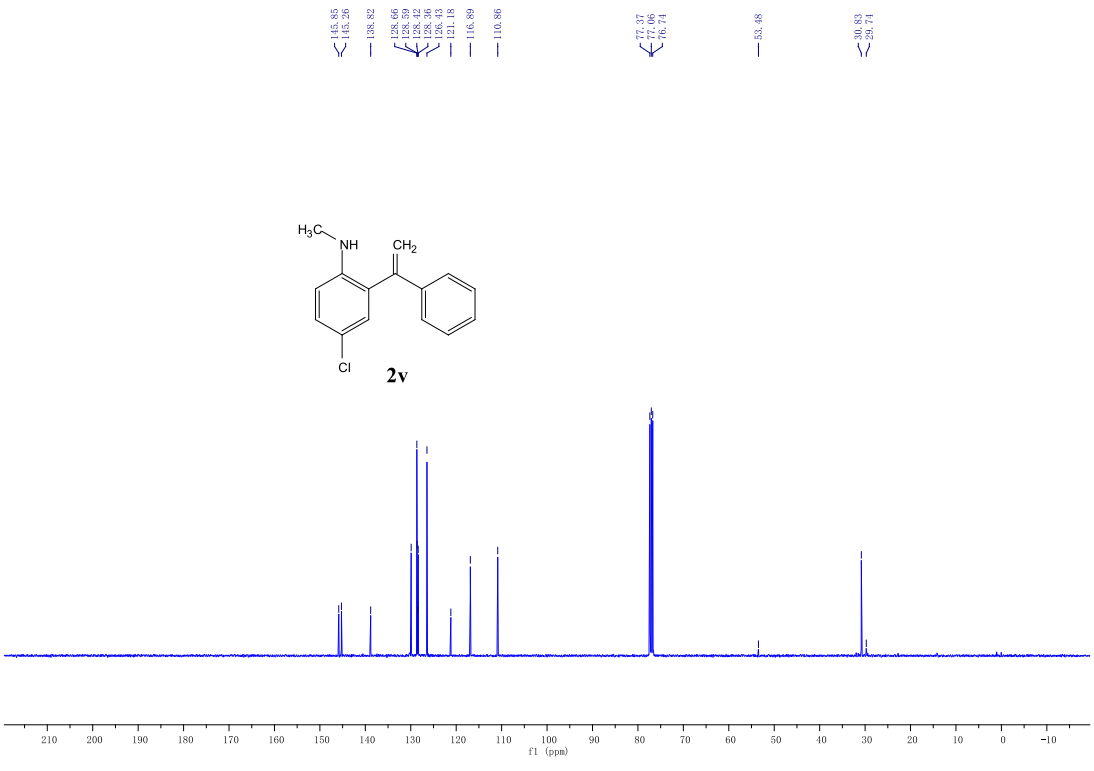
f1 (ppm)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77.37
77.06
76.74
53.48
30.83
29.74
H3C
NH
CH2
Cl
2v
210
200
190
180
170
160
150
140
130
120
110
100
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80
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60
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40
30
20
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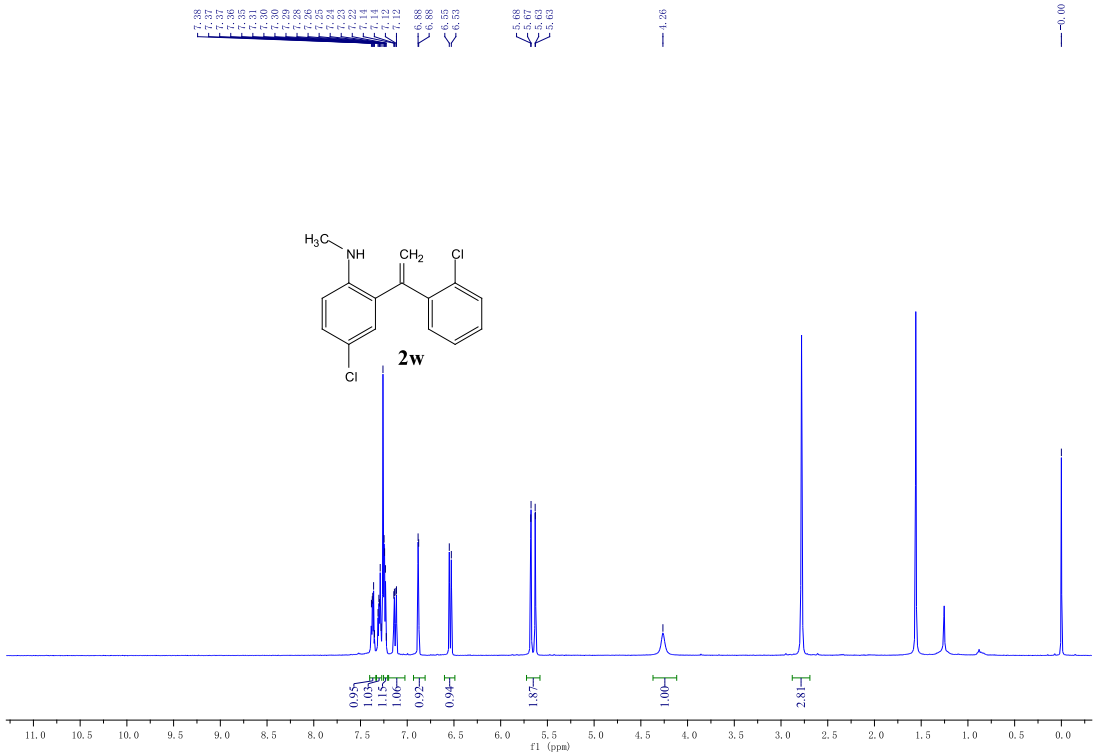
0
-10
f1 (ppm)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7.23
7.22
7.14
7.13
7.12
6.88
6.88
6.55
6.53
5.68
5.67
5.63
5.63
4.26
0.00
H3C
NH
CH2
Cl
Cl
2w
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1.87
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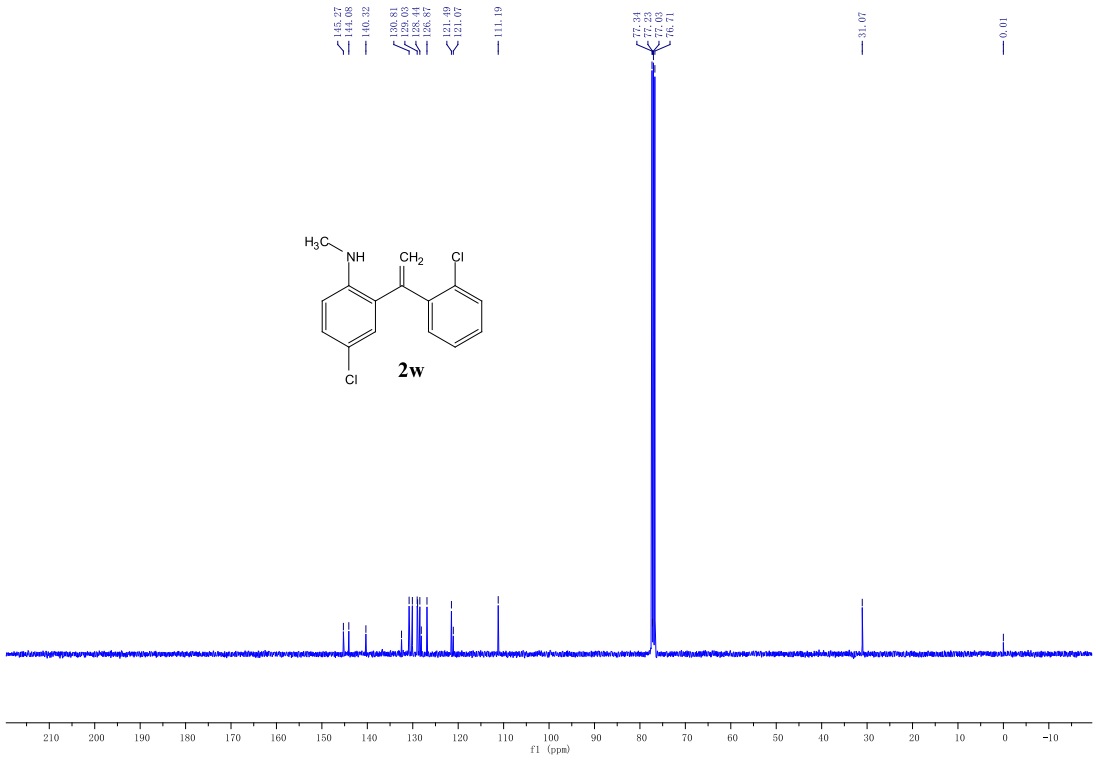
2.81
f1 (ppm)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111.19
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76.71
31.07
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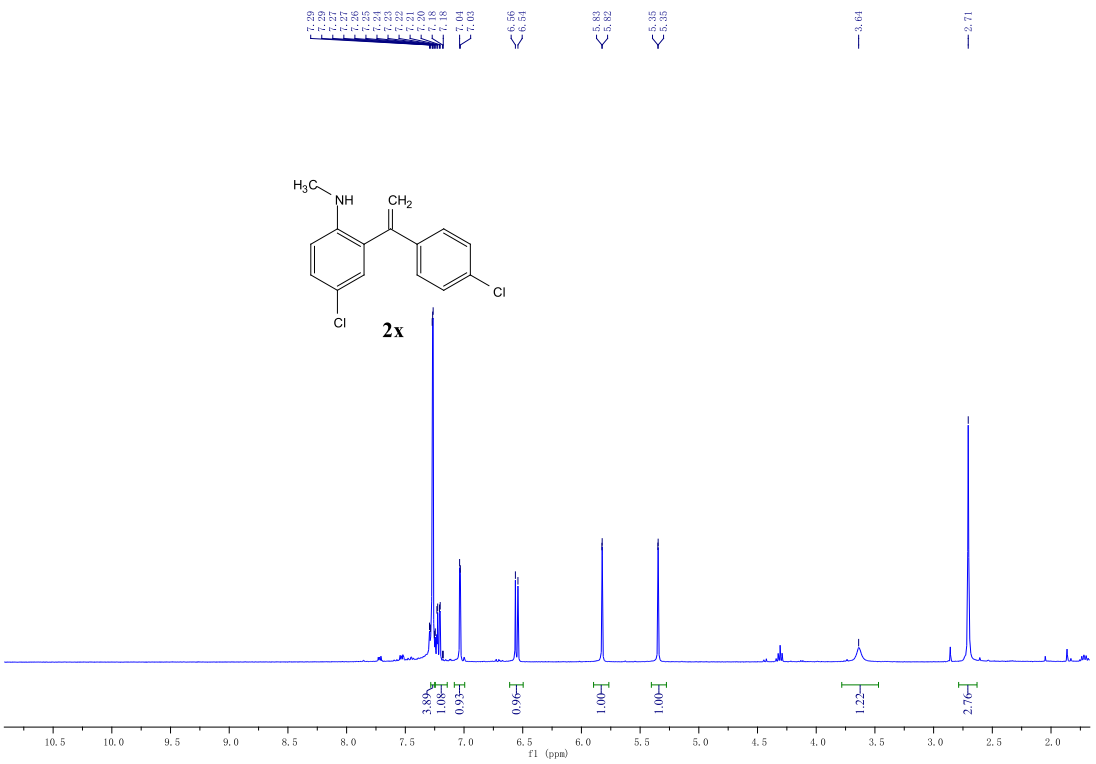
H3C
NH
CH2
Cl
Cl
2w
f1 (ppm)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5.83
5.82
5.35
5.35
3.64
2.71
H3C
NH
CH2
Cl
Cl
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1.08
0.93
0.96
1.00
1.00
1.22
2.76
10.5
10.0
9.5
9.0
8.5
8.0
7.5
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3.0
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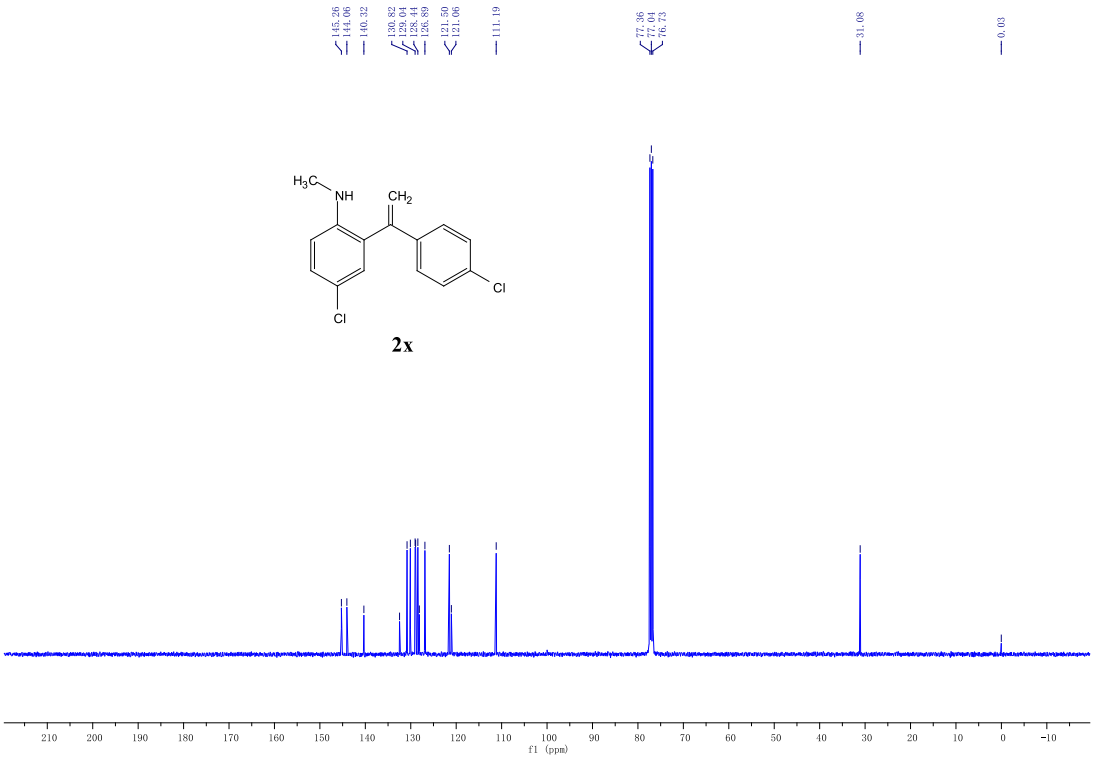
2.0
f1 (ppm)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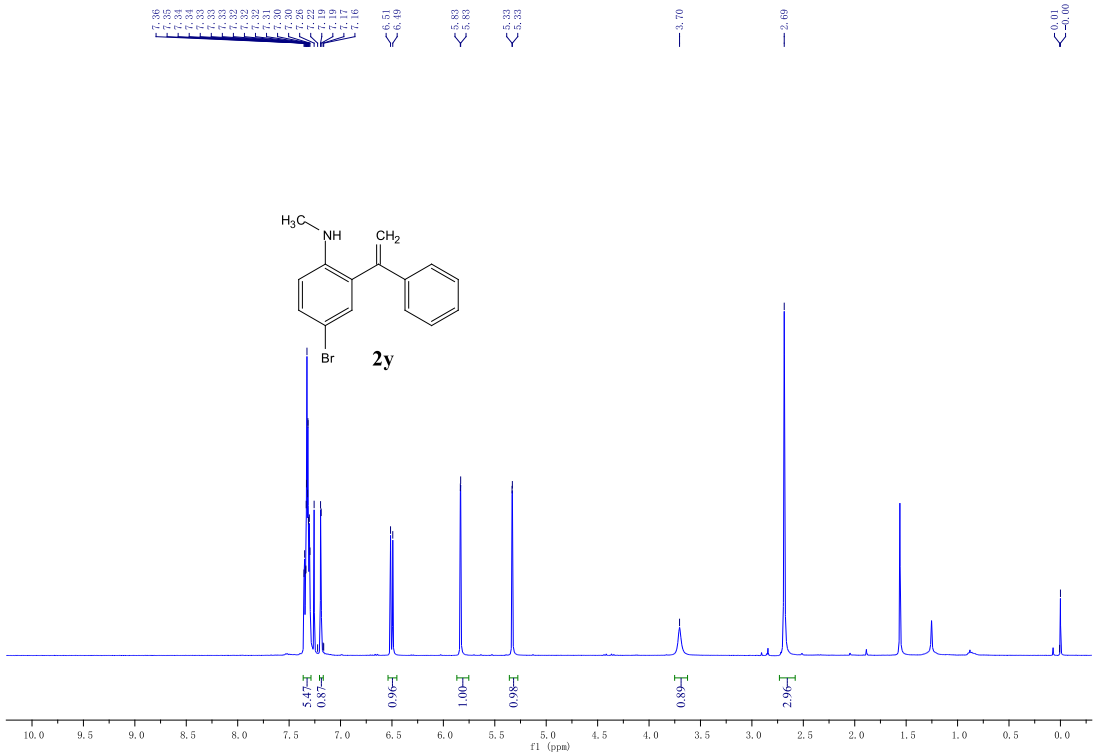
140.32
130.82
129.04
128.44
126.89
121.50
121.06
111.19
77.36
77.04
76.73
31.08
0.03
H3C
NH
CH2
Cl
Cl
2x
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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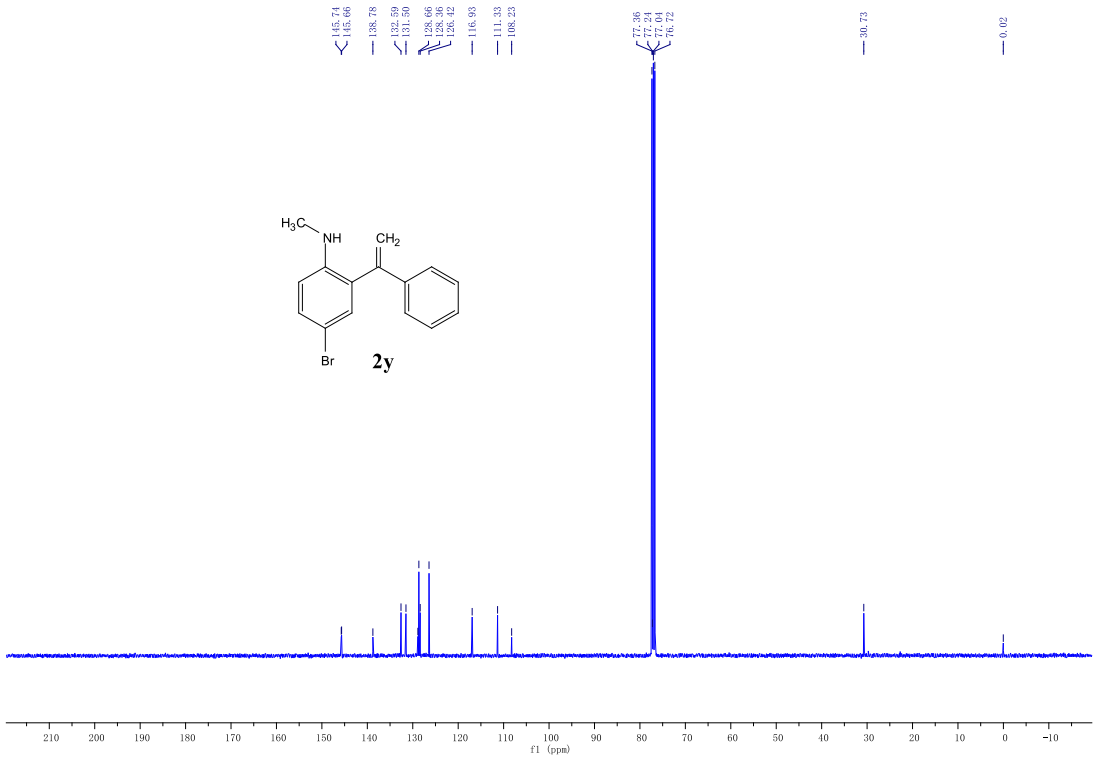
7.22
7.19
7.17
7.16
6.51
6.49
5.83
5.83
5.33
5.33
3.70
2.69
0.01
0.00
H3C
NH
CH2
Br
2y
5.47
0.87
0.96
1.00
0.98
0.89
2.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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77.04
76.72
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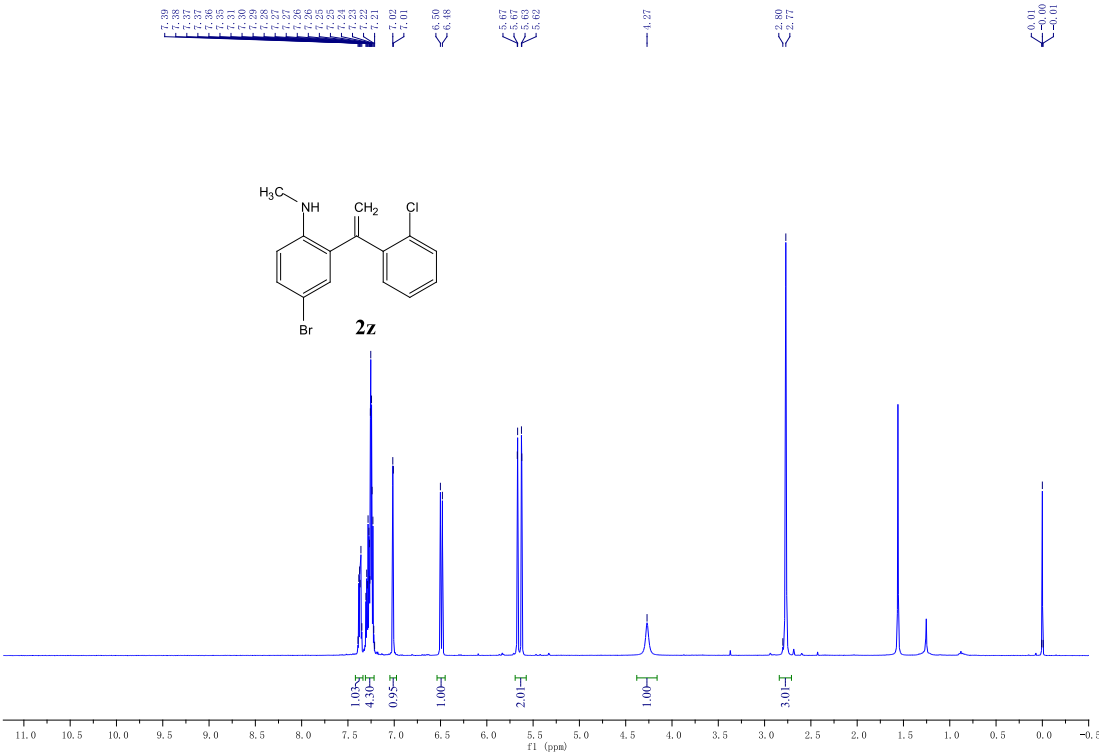
NH
CH2
Br
2y
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.26
7.26
7.25
7.25
7.24
7.23
7.22
7.21
7.02
7.01
6.50
6.48
5.67
5.67
5.63
5.62
4.27
2.80
2.77
0.01
0.00
-0.01
H3C
NH
CH2
Cl
Br
2z
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4.30
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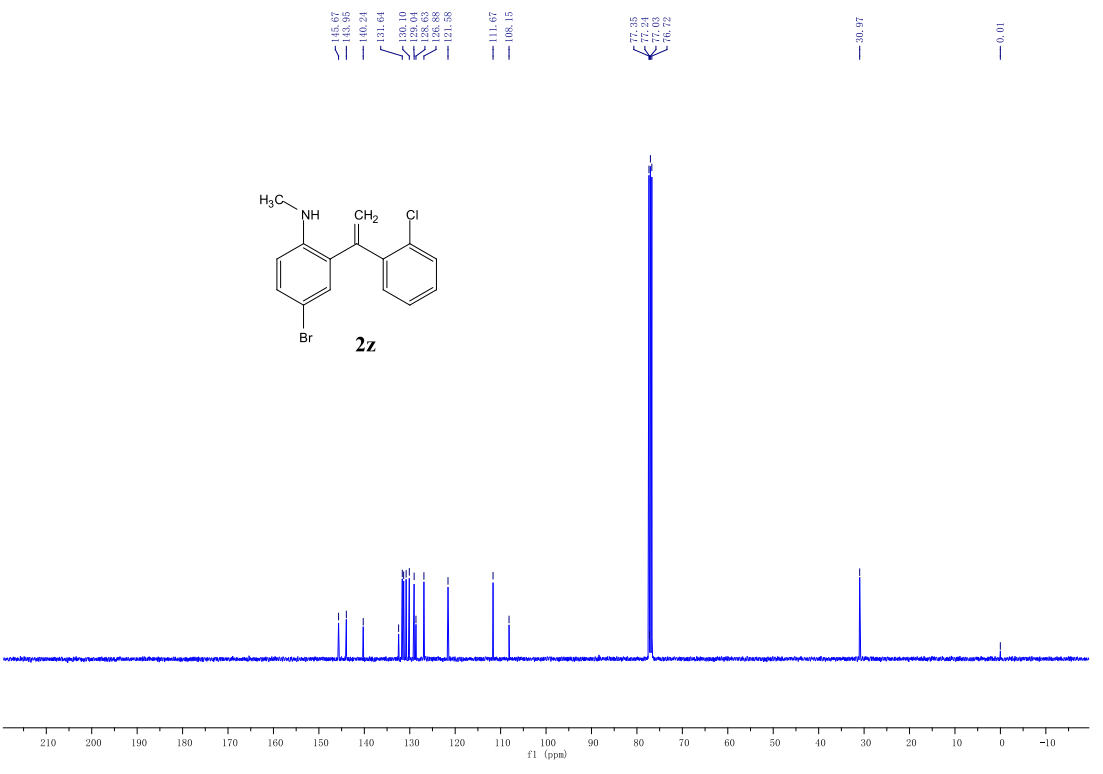
2.01
1.00
3.01
f1 (ppm)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129.04
128.63
126.88
121.58
111.67
108.15
77.35
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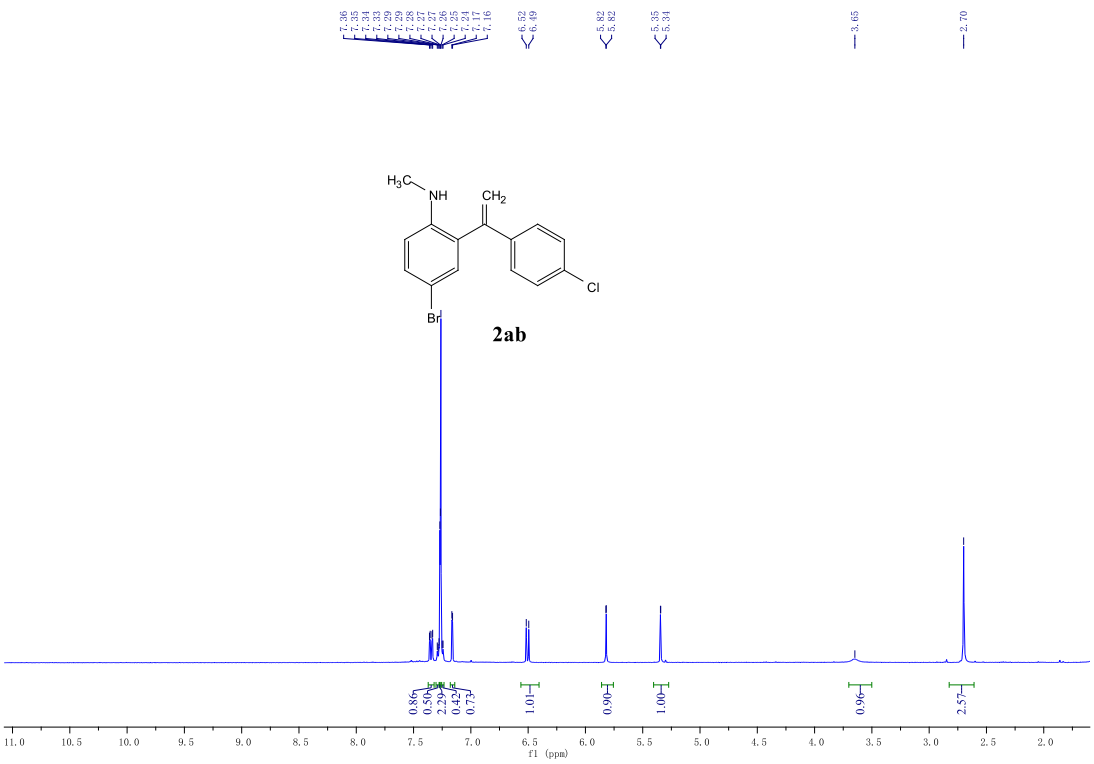
77.03
76.72
30.97
0.01
H3C
NH
CH2
Cl
Br
2z
f1 (ppm)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6.49
5.82
5.82
5.35
5.34
3.65
2.70
H3C
NH
CH2
Cl
Br
2ab
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0.50
2.29
0.42
0.73
1.01
0.90
1.00
0.96
2.57
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10.0
9.5
9.0
8.5
8.0
7.5
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4.0
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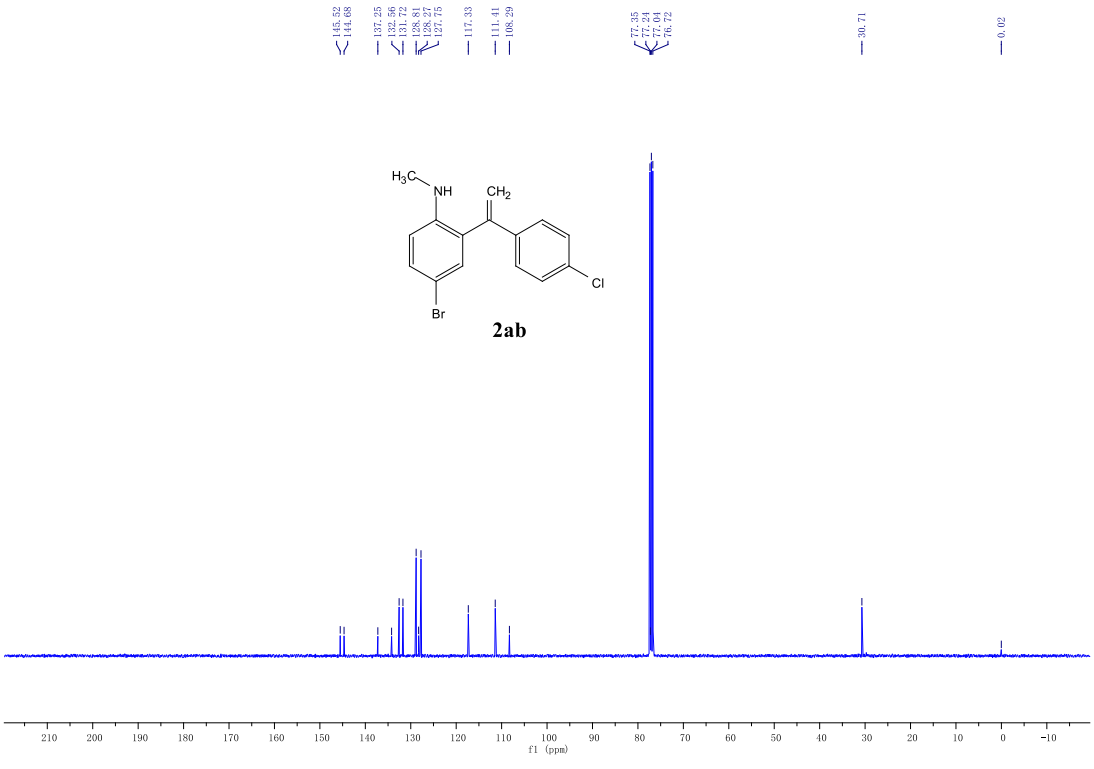
3.0
2.5
2.0
f1 (ppm)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117.33
111.41
108.29
77.35
77.24
77.04
76.72
30.71
0.02
H3C
NH
CH2
Cl
Br
2ab
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)