Supporting Information for

Polyphosphoric acid-promoted one-pot synthesis and neuroprotective effects of flavanones against NMDA-induced injury in PC12 cells†

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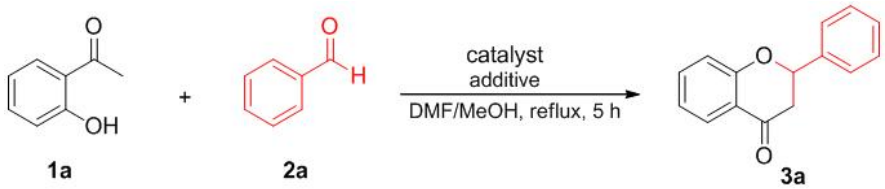
1. General information

Fetal bovine serum (FBS), Dulbecco's modified Eagle's medium (DMEM), penicillin and streptomycin were obtained from Gibco (Gibco, Paisley, UK). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT), NMDA and Fura-2 acetoxymethyl ester (Fluo-2/AM) were purchased from Sigma-Aldrich (Saint Louis, MO, USA). MK-801 was from MCE (Shanghai, China). Unless otherwise noted, all reagents, catalysts and solvents were purchased from commercial suppliers and used without further purification. Column Chromatography was performed with silica gel (200-300 mesh). The IR spectra were recorded with Mattson FTIR spectrometer 5000. Absorption maxima were measured in cm^{-1}. ^{1}H and ^{13}C NMR spectra were achieved on a Bruker AVANCE 600 MHz spectrometer (^{1}H 600 MHz, ^{13}C 151 MHz) in $CDCl_3$. High-resolution mass spectra were measured on a ThermoFish QE Focus facility. Thin-layer chromatographies were done on pre-coated silica gel 60F254 plates (Merck).

2. Optimization of the reaction conditions

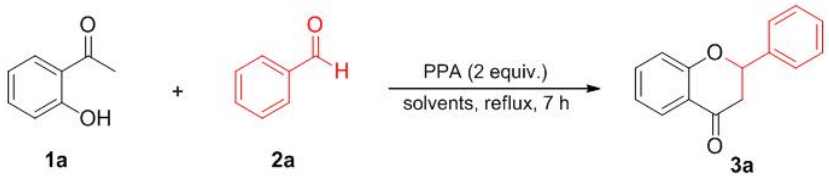
Table S1 Evaluation of catalysts and additive[a]



Entry	Catalyst (4 equiv.)	Additive (1 equiv.)	**3a** (%)[b]
1	PPA	/	50
2	P_2O_5	/	42
3	H_3PO_4	/	3
4[c]	H_2SO_4	/	20
5[c]	PPA	H_2SO_4	27

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), DMF (6.4 mL), MeOH (1.6 mL). [b] Isolated yield. [c] H_2SO_4 (98% concentrated sulfuric acid).

Table S2 Evaluation of solvents[a]

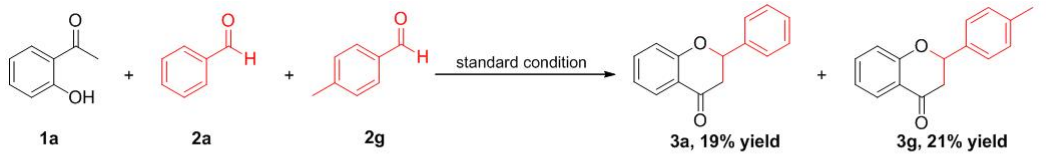


1a 2a 3a

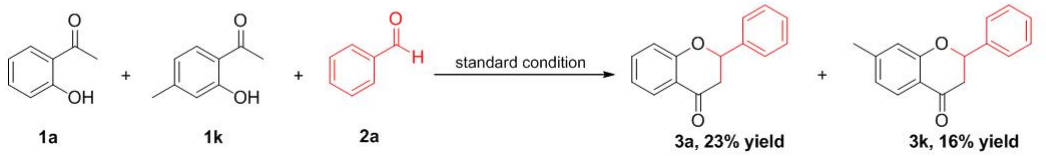
Entry	Solvents		**3a** (%)[b]
	1	2	
1	DMF	/	6
2	/	MeOH	/
2	DMF	EtOH	9
3	DMF	*i*-PrOH	14
4	DMF	*n*-BuOH	59
5	DMF	H_2O	/
6	DMF	AcOH	15
7	DMA	MeOH	11
8	DMSO	MeOH	/
9	1,4-dioxane	MeOH	12
10	acetonitrile	MeOH	35
11	toluene	MeOH	10
12	ether	MeOH	50
13	CCl_4	MeOH	/
14	DMA	EtOH	41
15	DMA	*i*-PrOH	10

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), solvents (8 mL), the volume ratio of solvent 1 to solvent 2 is 4:1. [b] Isolated yield.

3. The crossover experiments[a]



(1)

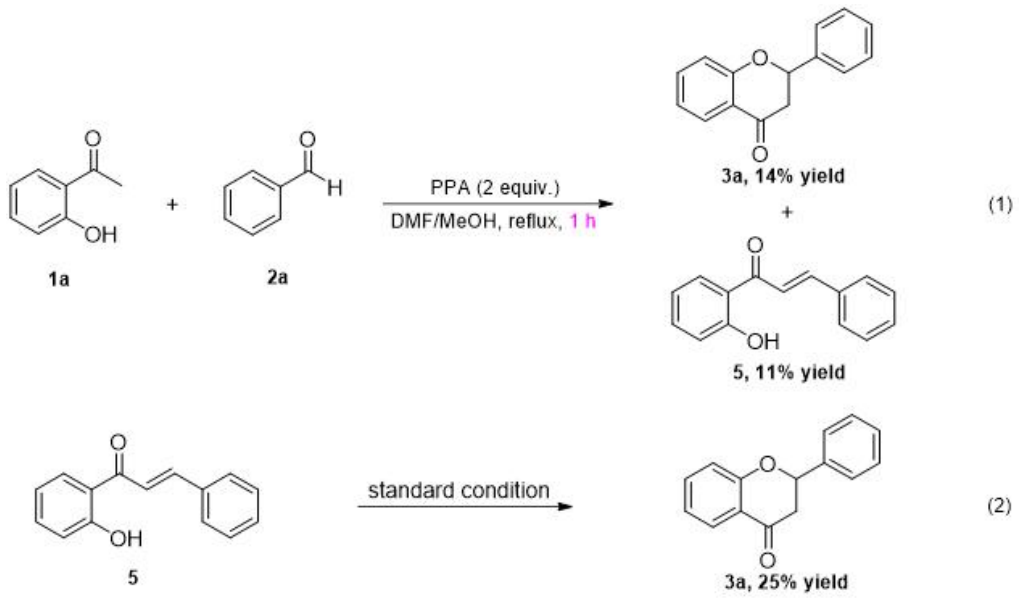


(2)

[a] Yields were determined by ^{1}H NMR with TTCE as internal standard.

4. The control experiments[a]

To get a deeper understanding of the reaction, control experiments were conducted. The reaction afforded a certain amount of chalcone **5**, and the chalcone **5** could be converted to flavanone in 25% yield under the standard condition. These observations excluded the main involvement of the chalcone process.



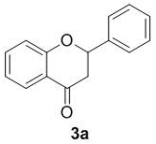
[a] Yields were determined by ^{1}H NMR with TTCE as internal standard.

5. Chemical synthesis

*General procedure for the preparation of products **3a-3q***

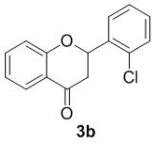
To a stirred solution of DMF (6.4 mL) and MeOH (1.6 mL) was added PPA (0.4 mmol), 2-hydroxyacetophenones **1** (0.2 mmol) and benzaldehydes **2** (0.8 mmol) in 50 mL flask. The reaction mixture was refluxed until the completion of the starting materials as monitored by TLC (7 h). The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, dried over Na_2SO_4 and evaporated. The resulting crude compound was purified by silica gel column chromatography, affording the pure products **3**.

6. Analytical data of the products



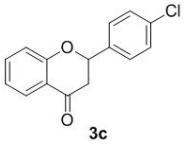
3a

2-phenylchroman-4-one (**3a**). White solid; Yield: 84%; IR (KBr plate): ν_{max} 3062.41, 3038.98, 2898.49, 1690.01, 1605.51, 1228.16, 766.15, 700.31. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.56 – 7.50 (m, 3H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.11 – 7.07 (m, 2H), 5.52 (dd, *J* = 13.4, 2.7 Hz, 1H), 3.13 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.93 (dd, *J* = 16.8, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.91, 161.57, 138.76, 136.17, 128.84, 128.76, 127.06, 126.14, 121.85, 121.61, 118.13, 79.62, 44.69. HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{15}H_{13}O_2$: 225.09101, found, 225.09027.



3b

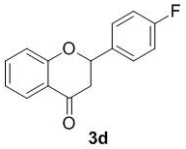
2-(2-chlorophenyl)chroman-4-one (**3b**). White solid; Yield: 69%; IR (KBr plate): ν_{max} 2945.49, 1671.21, 1514.61, 1263.50. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.78 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.3, 1.8 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.35 (td, *J* = 7.7, 1.7 Hz, 1H), 7.14 – 7.09 (m, 2H), 5.91 (dd, *J* = 13.6, 2.7 Hz, 1H), 3.07 (dd, *J* = 16.9, 2.8 Hz, 1H), 2.92 (dd, *J* = 16.9, 13.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.60, 161.57, 136.75, 136.23, 131.66, 129.75, 129.62, 127.46, 127.23, 127.18, 121.86, 120.97, 118.10, 76.52, 43.53.



3c

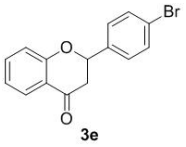
2-(4-chlorophenyl)chroman-4-one (**3c**). Light yellow solid; Yield: 82%; IR (KBr plate): ν_{max} 2900.80, 1698.06, 1471.61, 1303.67, 906.57, 705.54. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.49 – 7.41 (m, 4H), 7.09 (dd, *J* = 14.3, 7.6 Hz, 2H), 5.50 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.07 (dd, *J* = 16.8, 13.2 Hz, 1H), 2.91 (dd, *J* = 16.8, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.56, 161.33, 137.28, 136.33, 134.62, 129.07, 127.53, 127.12, 121.84, 120.91, 118.11,

78.84, 44.62. HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{15}H_{12}O_2Cl$: 225.09101259.05203, found, 259.05090.



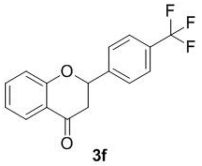
3d

2-(4-fluorophenyl)chroman-4-one (**3d**). White solid; Yield: 73%; IR (KBr plate): ν_{max} 2920.09, 2846.42, 1693.42, 1303.27, 1225.30, 767.39. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.55 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.18 – 7.13 (m, 2H), 7.09 (td, *J* = 8.2, 4.3 Hz, 2H), 5.50 (dd, *J* = 13.3, 2.8 Hz, 1H), 3.09 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.91 (dd, *J* = 16.8, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.75, 162.85(247.64), 161.41, 136.30, 134.60, 128.05(9.06), 127.11, 121.78, 120.91, 118.11, 115.83(21.14), 78.95, 44.69. HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{15}H_{12}O_2F$: 243.08158, found, 243.08136.



3e

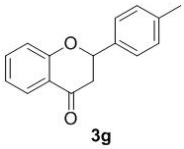
2-(4-bromophenyl)chroman-4-one (**3e**). White solid; Yield: 81%; IR (KBr plate): ν_{max} 3060.48, 2954.41, 2897.38, 1687.97, 1461.31, 1300.16, 821.07, 773.35. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.09 (dd, *J* = 14.7, 7.8 Hz, 2H), 5.48 (d, *J* = 13.1 Hz, 1H), 3.06 (dd, *J* = 16.4, 13.7 Hz, 1H), 2.91 (d, *J* = 16.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.54, 161.30, 137.80, 136.35, 132.03, 127.82, 127.12, 122.74, 121.86, 120.90, 118.12, 78.87, 44.58. HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{15}H_9O_2BrNa$: 322.96781, found, 322.96689.



3f

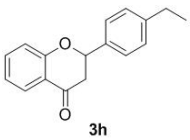
2-(4-(trifluoromethyl)phenyl)chroman-4-one (**3f**). White solid; Yield: 77%; IR (KBr plate): ν_{max} 3058.55, 2908.13, 1932.32, 1681.84, 1466.61, 1325.41, 1113.37, 764.00. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.14 – 7.09 (m, 2H), 5.59 (dd, *J* = 13.2,

2.8 Hz, 1H), 3.07 (dd, *J* = 16.8, 13.2 Hz, 1H), 2.96 (dd, *J* = 16.8, 3.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.19, 161.18, 142.72, 136.41, 130.89(32.72), 127.15, 126.37, 125.88(3.52), 123.92(272.30), 122.00, 120.92, 118.10, 78.77, 44.66. HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{16}H_{12}O_2F_3$: 293.07839, found, 293.07718.



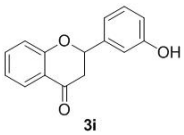
3g

2-(*p*-tolyl)chroman-4-one (**3g**). White solid; Yield: 85%; IR (KBr plate): ν_{max} 3058.55, 3029.62, 2917.18, 2888.84, 1691.98, 1462.34, 1302.70, 762.47. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.53 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.10 – 7.05 (m, 2H), 5.48 (dd, *J* = 13.4, 2.8 Hz, 1H), 3.13 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.90 (dd, *J* = 16.8, 2.8 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.21, 161.66, 138.75, 136.19, 135.76, 129.52, 127.06, 126.22, 121.55, 120.94, 118.17, 79.56, 44.59, 21.23. HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{14}O_2Na$: 261.08860, found, 261.08783.



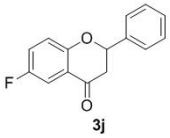
3h

2-(4-ethylphenyl)chroman-4-one (**3h**). White solid; Yield: 87%; IR (KBr plate): ν_{max} 2960.74, 2927.81, 2871.49, 1681.76, 1465.19, 1306.29, 771.34. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.10 – 7.06 (m, 2H), 5.49 (dd, *J* = 13.4, 2.7 Hz, 1H), 3.14 (dd, *J* = 16.8, 13.5 Hz, 1H), 2.91 (dd, *J* = 16.8, 2.8 Hz, 1H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.24, 161.68, 145.10, 136.19, 135.95, 128.36, 127.06, 126.31, 121.55, 120.95, 118.17, 79.61, 44.57, 28.64, 15.54. HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{17}H_{16}O_2Na$: 275.10425, found, 275.10333.



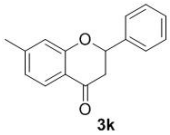
3i

2-(3-hydroxyphenyl)chroman-4-one (**3i**). White solid; Yield: 74%; IR (KBr plate): ν_{max} 3321.00, 3064.33, 2904.27, 1675.69, 1313.57, 1225.45, 769.12, 697.25. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 – 7.94 (m, 1H), 7.57 – 7.52 (m, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 7.7, 6.5 Hz, 2H), 7.03 (dd, *J* = 16.0, 4.9 Hz, 2H), 6.88 (dd, *J* = 8.0, 2.3 Hz, 1H), 5.47 (dd, *J* = 13.3, 2.9 Hz, 1H), 5.38 (s, 1H), 3.09 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.92 (dd, *J* = 16.9, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.24, 161.52, 156.08, 140.53, 136.37, 130.20, 127.09, 121.72, 120.89, 118.39, 118.17, 115.76, 113.09, 79.25, 44.63. HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{12}O_3Na$: 263.06787, found, 263.06702.



3j

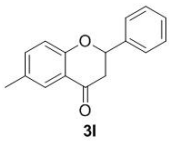
6-fluoro-2-phenylchroman-4-one (**3j**). White solid; Yield: 76%; IR (KBr plate): ν_{max} 3081.69, 3035.41, 2918.66, 2890.77, 1692.64, 1481.01, 1271.87, 900.65, 763.09. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.2, 3.2 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.49 – 7.45 (m, 2H), 7.44 – 7.40 (m, 1H), 7.26 (ddd, *J* = 9.0, 7.7, 3.2 Hz, 1H), 7.07 (dd, *J* = 9.0, 4.2 Hz, 1H), 5.49 (dd, *J* = 13.4, 2.8 Hz, 1H), 3.11 (dd, *J* = 17.0, 13.4 Hz, 1H), 2.94 (dd, *J* = 17.0, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.23, 157.80, 157.79, 157.39(243.11), 138.44, 128.92, 126.16, 123.75(25.67), 121.39(6.04), 119.85(6.04), 112.05(22.65), 79.87, 44.38. HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{15}H_{12}O_2F$: 243.08158, found, 243.08073.



3k

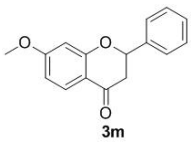
7-methyl-2-phenylchroman-4-one (**3k**). White solid; Yield: 86%; IR (KBr plate): ν_{max} 3068.19, 3037.34, 2892.91, 2854.13, 1689.22, 1614.02, 1292.28, 1154.51, 811.67, 772.18. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.47 (dd, *J* = 10.2, 4.8 Hz, 2H), 7.43 – 7.39 (m, 1H), 6.90 (d, *J* = 7.5 Hz, 2H), 5.49

(dd, *J* = 13.3, 2.8 Hz, 1H), 3.08 (dd, *J* = 16.8, 13.3 Hz, 1H), 2.89 (dd, *J* = 16.8, 2.9 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.70, 161.61, 147.80, 138.91, 128.84, 128.73, 126.95, 126.15, 123.02, 118.72, 118.13, 79.60, 44.64, 21.99. HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{14}O_2Na$: 261.08860, found, 261.08780.



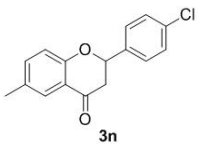
3l

6-methyl-2-phenylchroman-4-one (**3l**). White solid; Yield: 85%; IR (KBr plate): ν_{max} 3029.62, 2919.71, 1696.52, 1489.09, 1290.01, 1228.68, 763.32. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 5.48 (dd, *J* = 13.4, 2.7 Hz, 1H), 3.10 (dd, *J* = 16.9, 13.4 Hz, 1H), 2.90 (dd, *J* = 16.9, 2.8 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.28, 159.66, 138.90, 137.30, 131.10, 128.85, 128.74, 126.62, 126.16, 120.56, 117.93, 79.59, 44.74, 20.45. HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{14}O_2Na$: 261.08860, found, 261.08777.



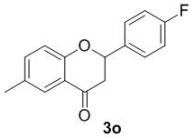
3m

7-methoxy-2-phenylchroman-4-one (**3m**). White solid; Yield: 82%; IR (KBr plate): ν_{max} 2941.52, 2840.63, 1682.09, 1606.79, 1257.99, 699.21. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.47 (dd, *J* = 10.2, 4.8 Hz, 2H), 7.42 (dd, *J* = 8.3, 6.1 Hz, 1H), 6.65 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 5.50 (dd, *J* = 13.3, 2.8 Hz, 1H), 3.86 (s, 3H), 3.07 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.86 (dd, *J* = 16.9, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.62, 166.23, 163.55, 138.81, 128.87, 128.79, 128.79, 126.18, 114.85, 110.30, 100.94, 80.03, 55.67, 44.35. HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{14}O_3Na$: 277.08352, found, 277.08255.



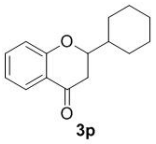
3n

2-(4-chlorophenyl)-6-methylchroman-4-one (**3n**). White solid; Yield: 85%; IR (KBr plate): ν_{max} 2917.93, 1693.94, 1491.77, 1291.52, 822.63. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 1.6 Hz, 1H), 7.46 – 7.41 (m, 4H), 7.37 – 7.34 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.46 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.04 (dd, *J* = 16.8, 13.2 Hz, 1H), 2.88 (dd, *J* = 16.8, 3.0 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.81, 159.40, 137.43, 137.39, 134.53, 131.32, 129.03, 127.52, 126.66, 120.52, 117.88, 78.79, 44.65, 20.45. HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{16}H_{14}O_2Cl$: 273.06768, found, 273.06644.



3o

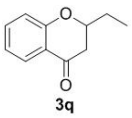
2-(4-fluorophenyl)-6-methylchroman-4-one (**3o**). White solid; Yield: 80%; IR (KBr plate): ν_{max} 2921.90, 2861.85, 1693.16, 1488.55, 1225.09, 834.29. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 1.6 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.17 – 7.12 (m, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.46 (dd, *J* = 13.3, 2.8 Hz, 1H), 3.06 (dd, *J* = 16.8, 13.3 Hz, 1H), 2.88 (dd, *J* = 16.8, 2.9 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.00, 162.81(247.64), 161.99, 137.37, 134.75(3.02), 131.26, 128.03(7.55), 126.65, 120.51, 117.88, 115.79(21.14), 78.90, 44.73, 20.45. HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{16}H_{14}O_2F$: 257.09723, found, 257.09613.



3p

2-cyclohexylchroman-4-one (**3p**). White oil; Yield: 51%; IR (KBr plate): ν_{max} 2926.85, 2853.31, 1692.93, 1464.22, 1310.76, 763.68. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.03 – 6.98 (m, 2H), 4.23 (ddd, *J* = 12.8, 6.0, 3.0 Hz, 1H), 2.72 (ddd, *J* = 19.7, 16.6, 8.0 Hz, 2H), 2.04 – 1.99 (m, 1H), 1.87 – 1.71 (m, 4H), 1.38 – 1.11 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.22, 161.93, 135.93, 126.91, 124.57, 121.04, 117.91, 81.99, 41.78, 40.26, 28.27, 28.20,

26.33, 25.96, 25.90. HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{18}O_2Na$: 253.11990, found, 253.11945.



3q

2-ethylchroman-4-one (**3q**). White oil; Yield: 63%; IR (KBr plate): ν_{max} 2924.69, 2850.79, 1695.05, 1465.04, 1305.37, 1229.18, 764.42. ^1H NMR (600 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H), 7.04 – 6.99 (m, 2H), 4.41 (ddd, *J* = 15.2, 7.4, 5.4 Hz, 1H), 2.73 – 2.69 (m, 2H), 1.97 – 1.88 (m, 1H), 1.81 (dqd, *J* = 14.9, 7.5, 5.4 Hz, 1H), 1.10 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.76, 161.73, 135.98, 126.95, 121.15, 121.01, 117.93, 79.06, 42.56, 27.98, 9.31. HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{11}H_{13}O_2$: 177.09101, found, 177.09073.

7. Biological evaluation

7.1. Cell culture conditions

Differentiated PC12 cells (purchased from Institute of Cell Biology, Chinese Academy of Sciences, Shanghai, China) were cultured in DMEM supplemented with 2.5% fetal bovine serum, penicillin (50 U/mL) and streptomycin (50 mg/L). Cells were cultured in a humidified atmosphere containing 5% CO_2 at 37 °C.

7.2. Protective effects of flavanones against NMDA-induced injury in PC12 cells

PC12 cells were seeded at a density of 4×10^3 cells/well in 200 μL volumes in 96-well plates. After 4 days of incubation, the cells were pretreated with MK-801 and target compounds (final concentrations: 20 μM or 1-40 μM) for 24 h. NMDA (final concentration: 2 mM) was then added for another 6 h. After these treatments, MTT was added to the medium at a final concentration of 0.5 mg/mL. After incubating for an additional 4 h at 37 °C, the medium was replaced by 100 μL DMSO. The absorbance was measured at 490 nm with a microplate reader (Thermo Scientific Varioskan LUX Multimode Reader).

7.3. Evaluation of intracellular Ca^{2+} influx

PC12 cells were subcultured in 6-well plates (2×10^4 cells/well) for 4 days. Cells were treated with 10 μM MK-801 and 40 μM **3m** for 24 h, then treated with 2 mM NMDA for 6 h to induce injury. In the following experiments, cells were washed with

D-PBS and incubated with Fluo-2/AM (2.5 μM) at 37 ºC for 30 min in the dark. Subsequently, cells were washed twice with D-PBS buffer and incubated at 37 ºC for another 10 min. The images were photographed with a fluorescence microscope (Feica AE2000, Germany).

8. Molecular docking study

Docking study of the most active compound **3m** was performed using AutoDock 4 software package. Crystal structure of NMDA receptor in complex with DCKA and glutamate (PDB: 4NF4) was used. For active site docking, a grid box with size 32 × 32 × 32 Å centered at the center of co-crystalized ligand (DCKA) was selected. The pose with the best AutoDock score was chosen for further analysis. Images were rendered using The PyMOL Molecular Graphics System 2.4 and MOE 2020.09.

9. Statistical analysis

Data were presented as mean ± SD. Multiple group difference were evaluated using one-way analysis of variance (ANOVA) followed by the post hoc LSD test. $p < 0.05$ were considered statistically significant.

10. Selected glycine antagonists and docking study of compound 3a

As shown in Fig. S1A, flavanones and most glycine antagonists are of a planar structure. We selected the (*2R*)-**3a** for docking study. The docking results shown that compound **3a** fitted well in the active pocket of NMDA receptor glycine antagonists and exhibited binding energy of -6.26 kcal/mol (Fig. S1B). In the binding mode both compound **3a** and DCKA shown hydrogen bond interactions with THR-126 and ARG-131 (Fig. S1C and D). Similarly to DCKA, compound **3a** also being stabilized by Pi-stacking interaction with PHE-92 (Fig. S1C and D).

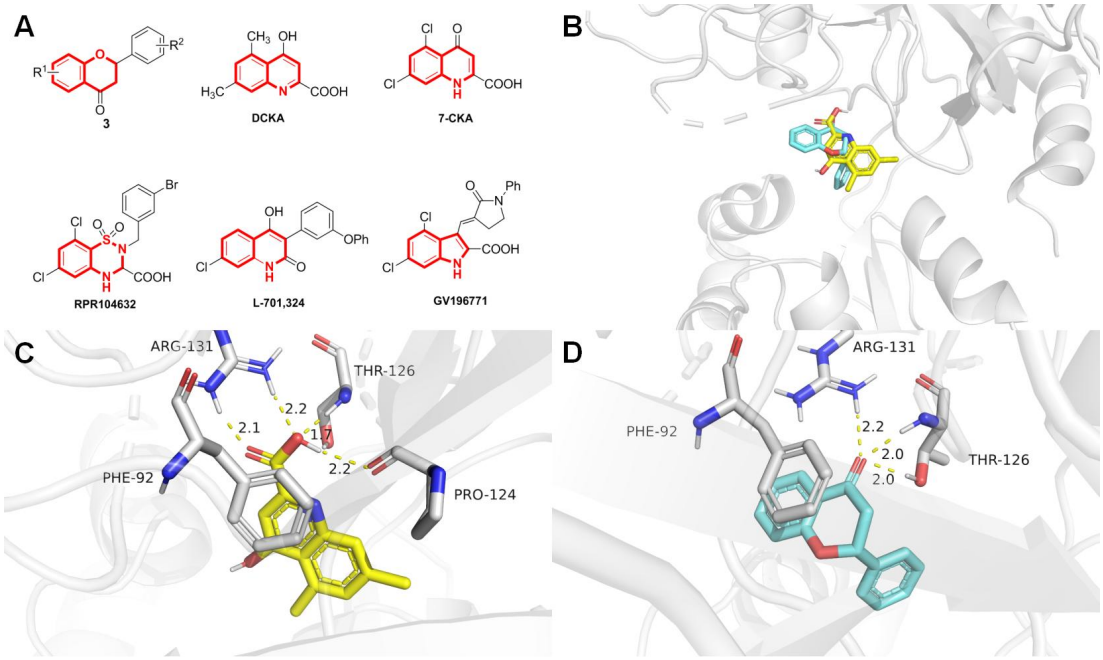
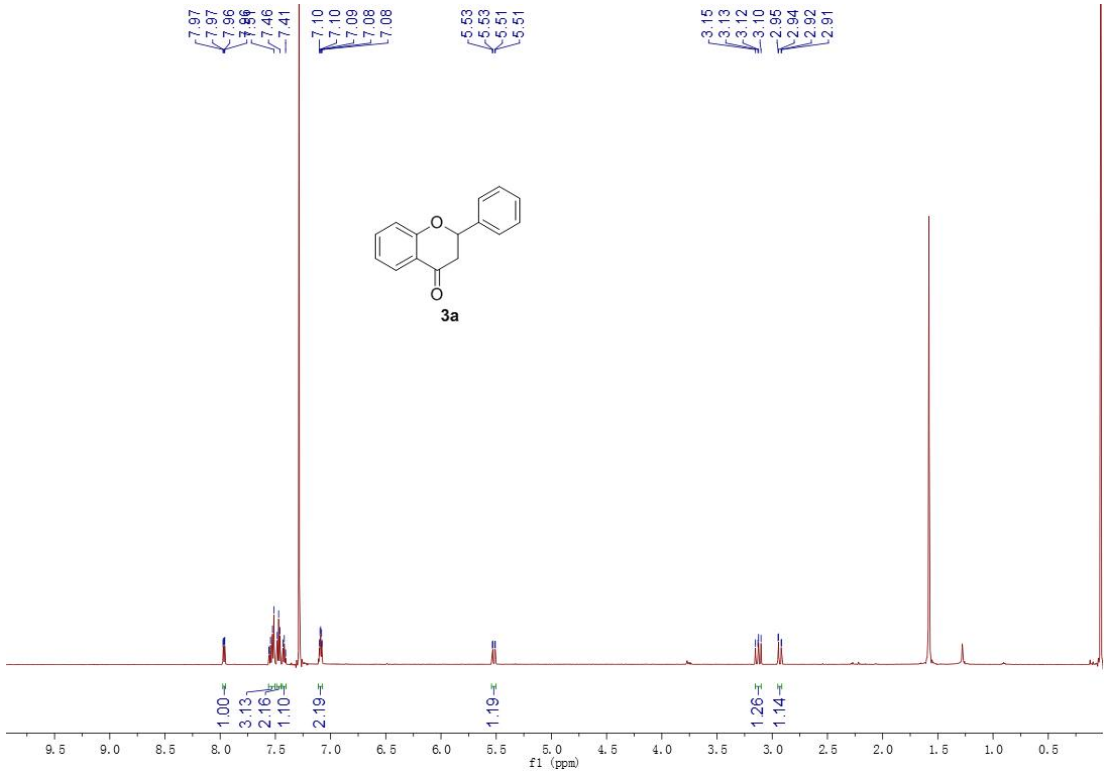
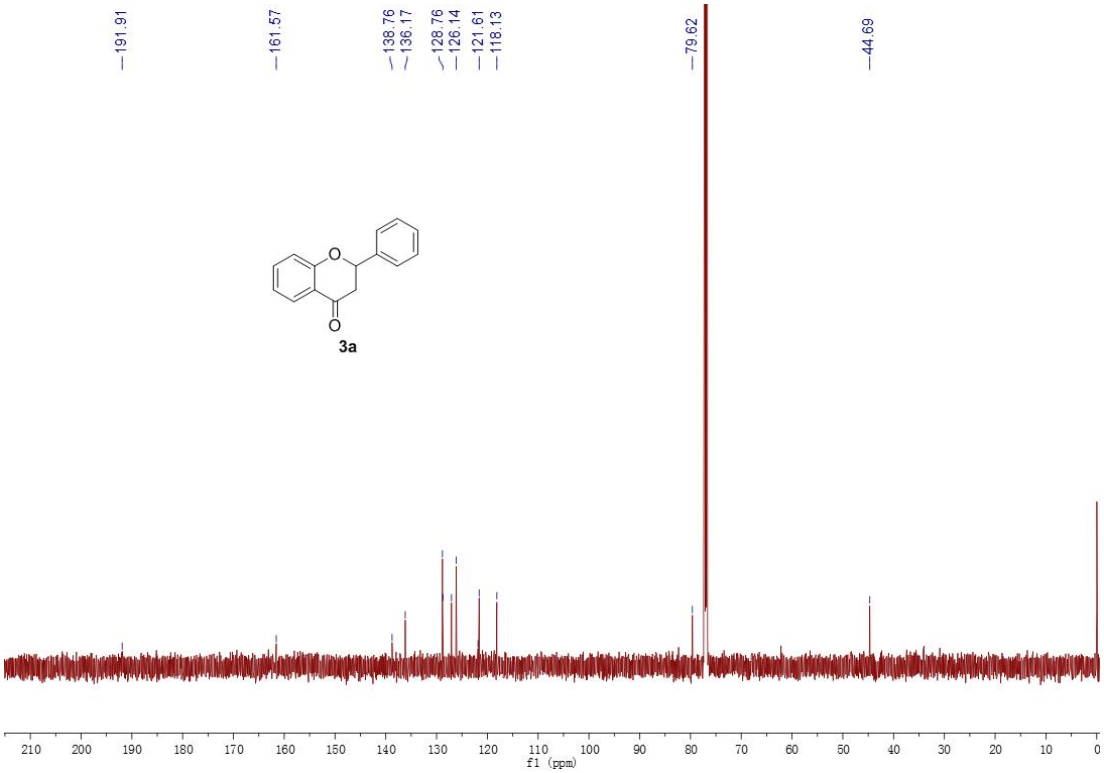
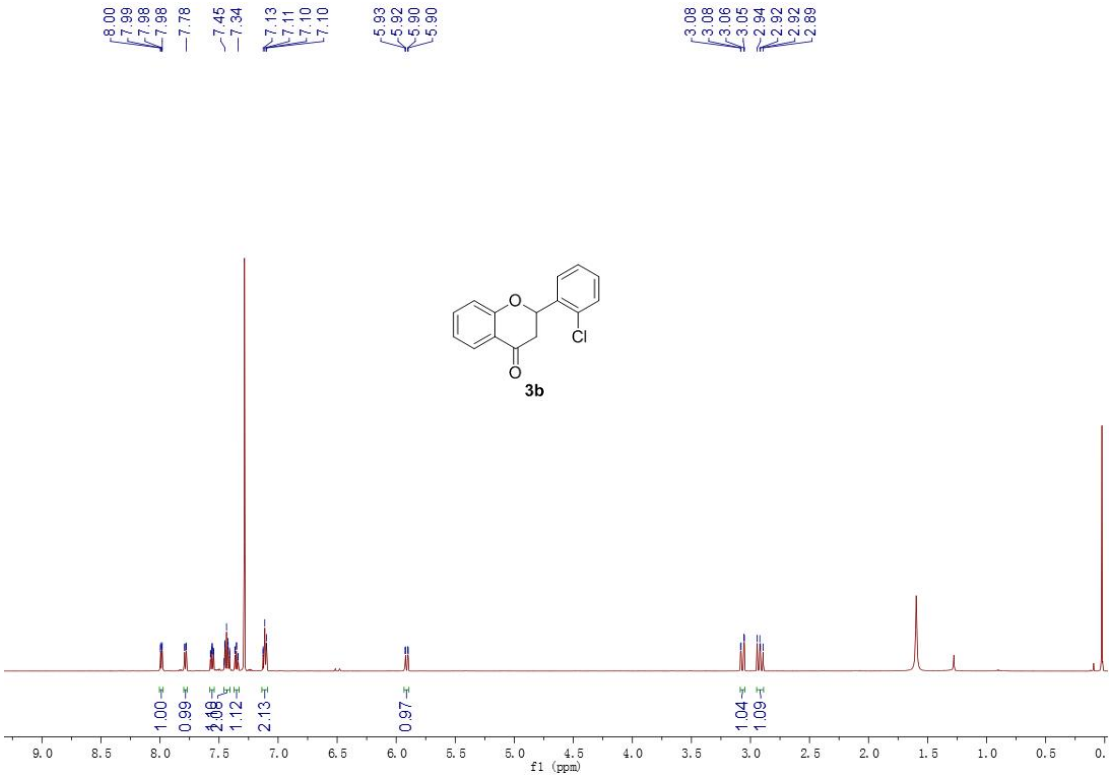


Fig. S1 (A) Flavanones and selected glycine antagonists. (B) Alignment of compound **3a** (cyan) and DCKA (yellow) in the active site. (C) The interactions of DCKA with the active site residues. (D) The interactions of compound **3a** with the active site residues. Hydrogen bond interactions were shown in yellow dotted lines.

11. ^{1}H NMR & ^{13}C NMR spectra of the products



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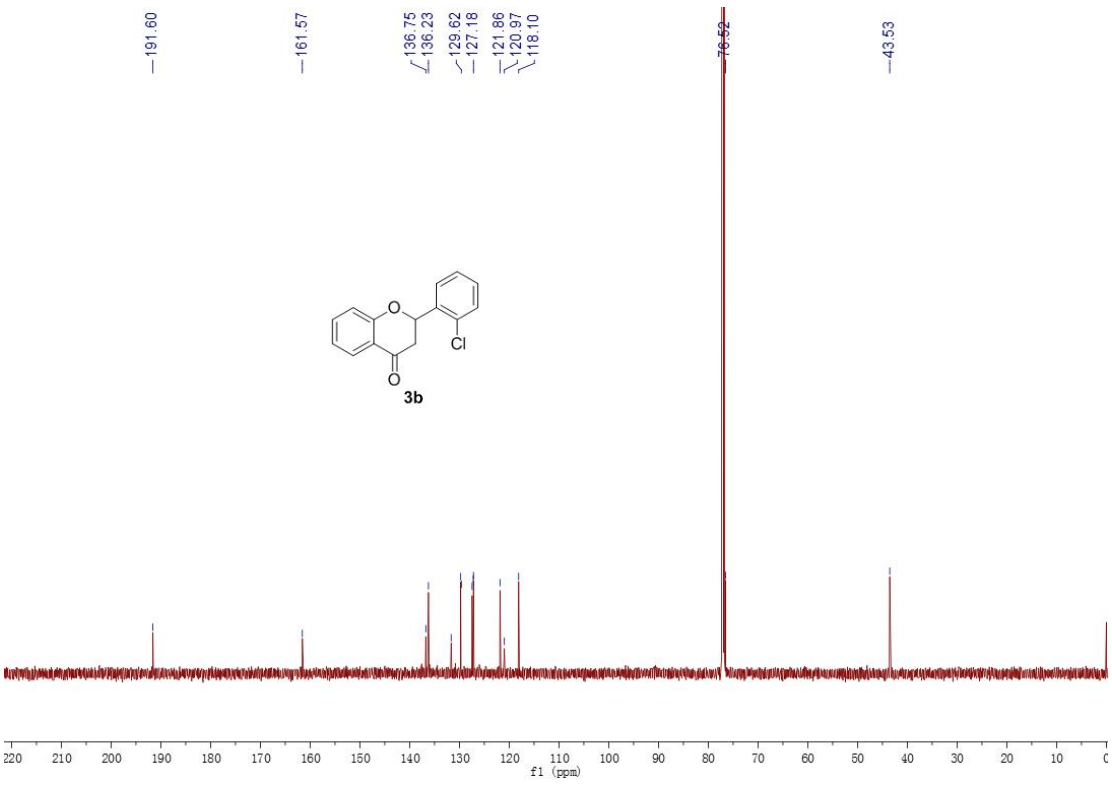
f1 (ppm)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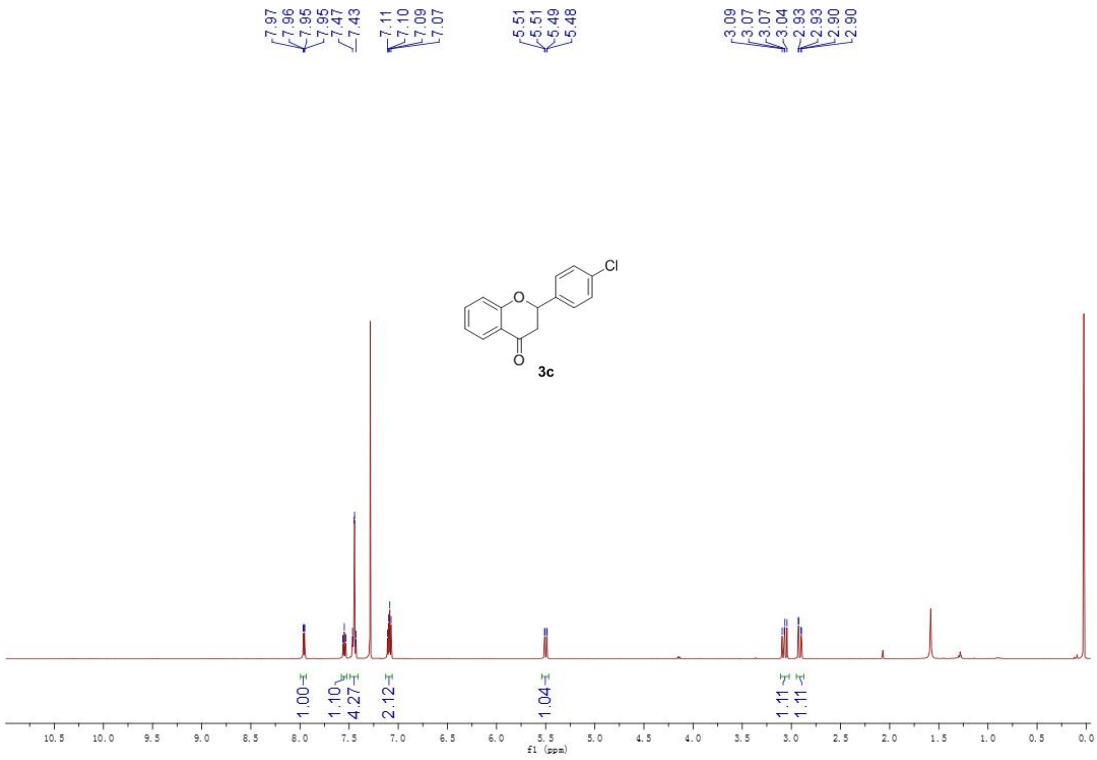
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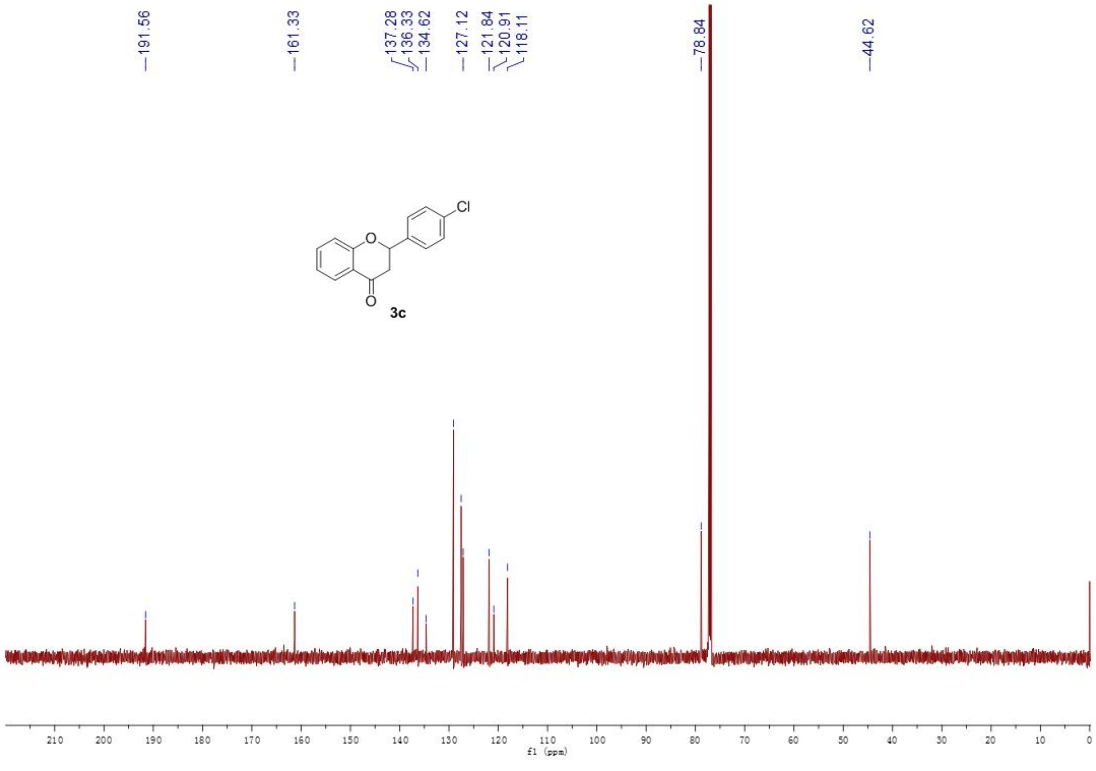
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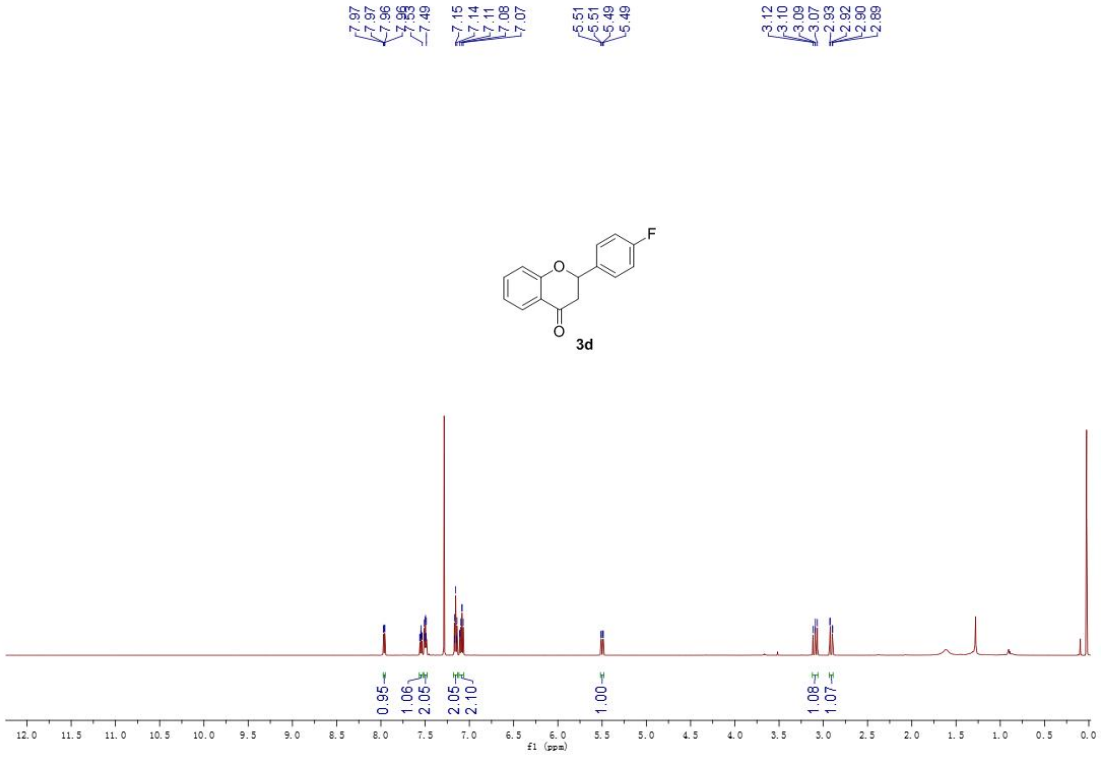
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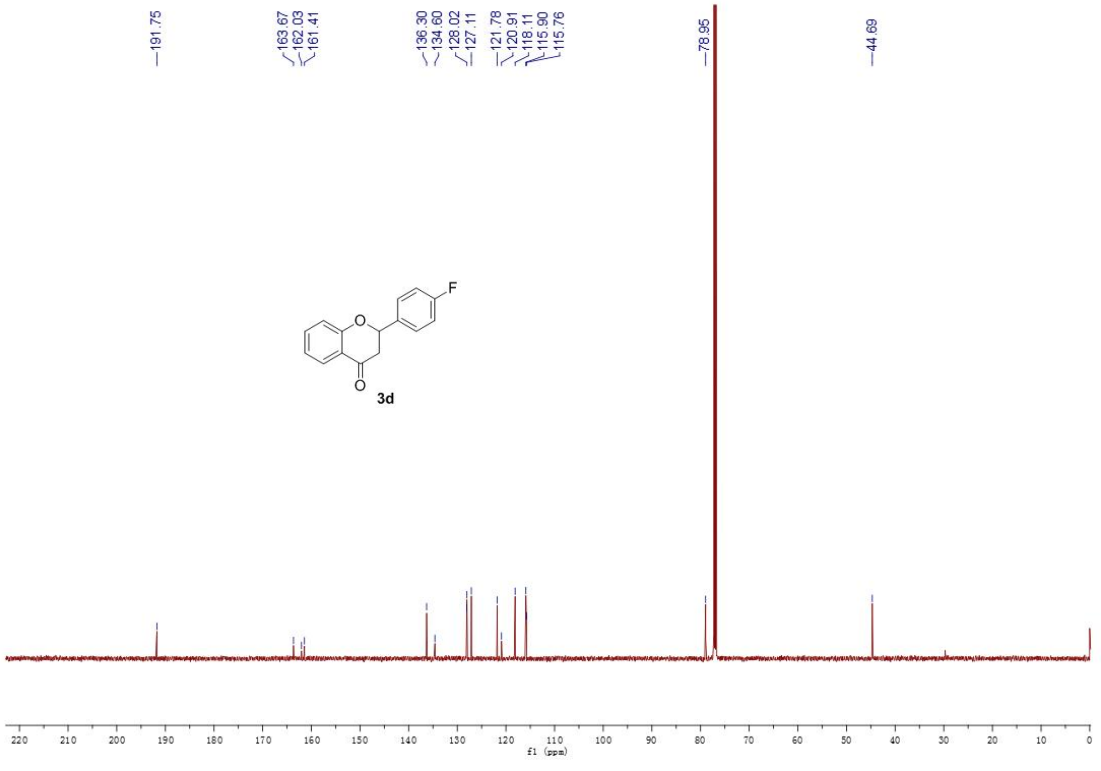
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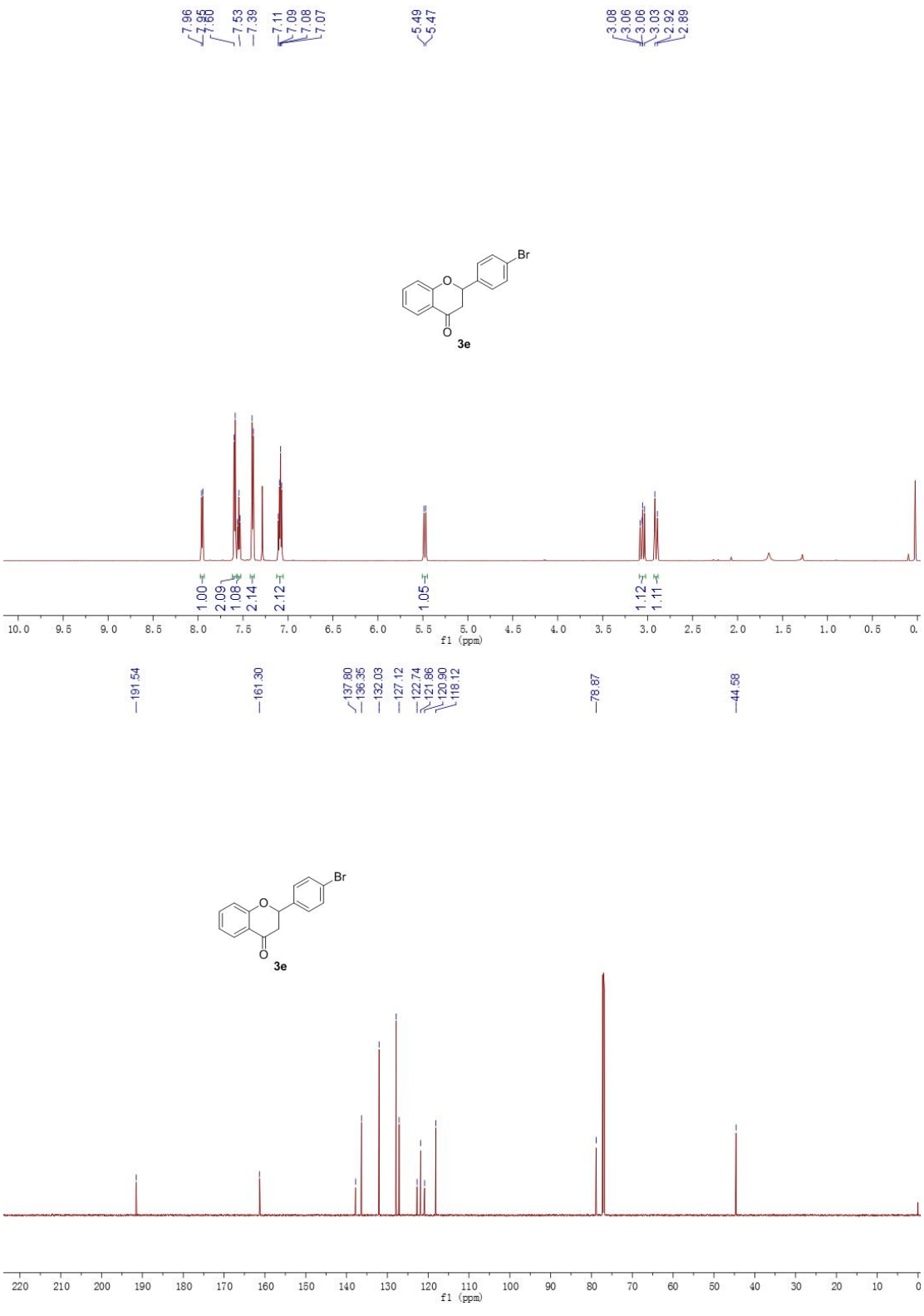
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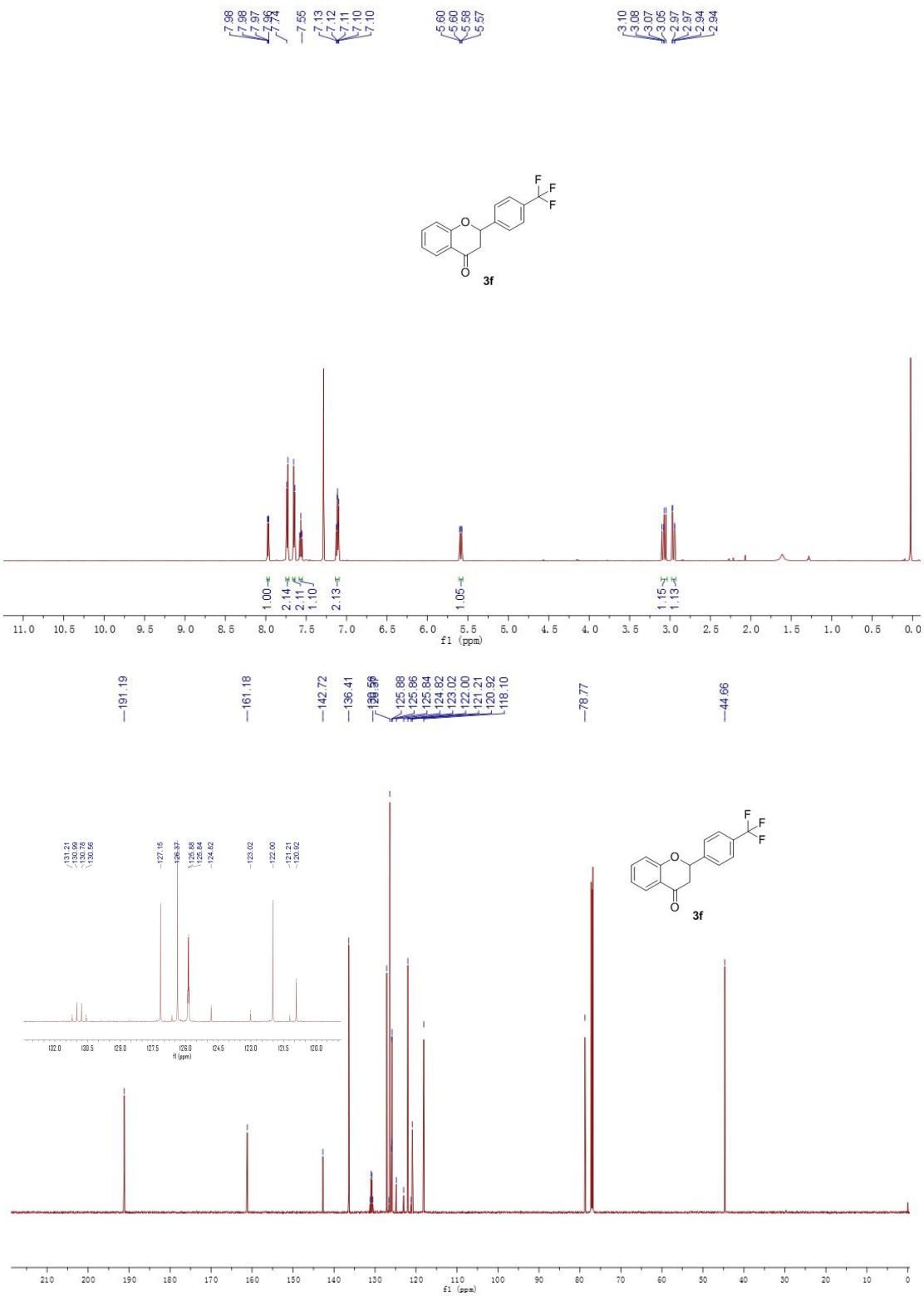
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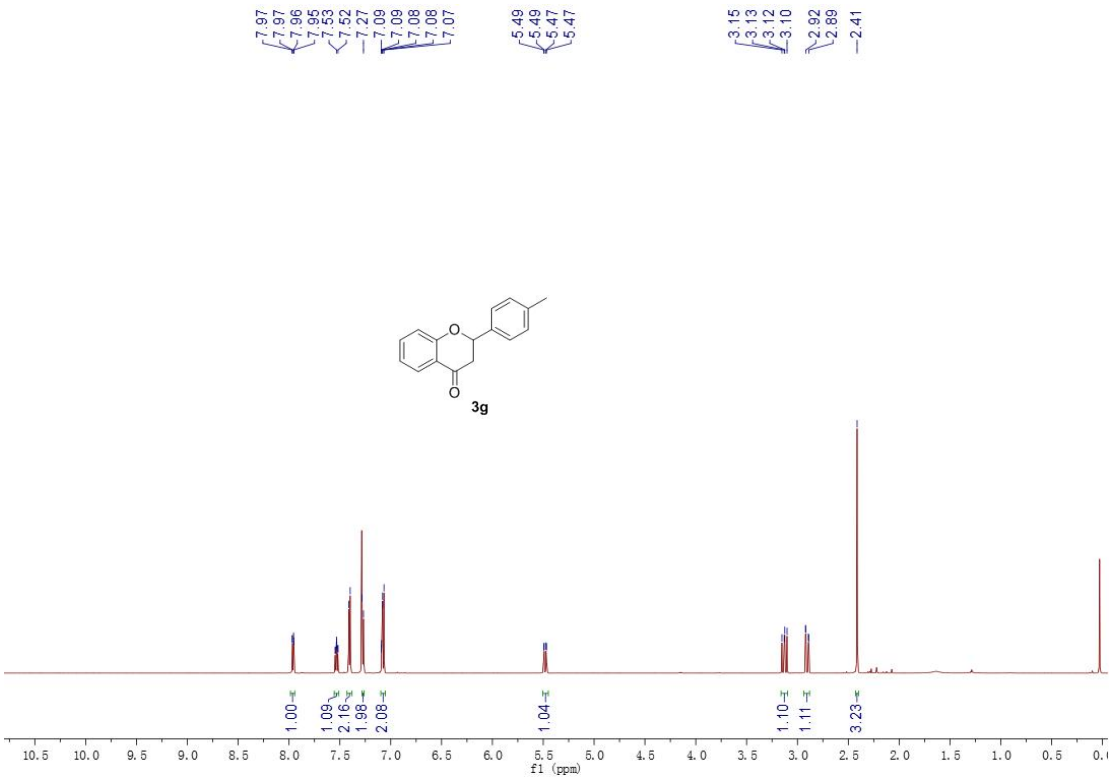
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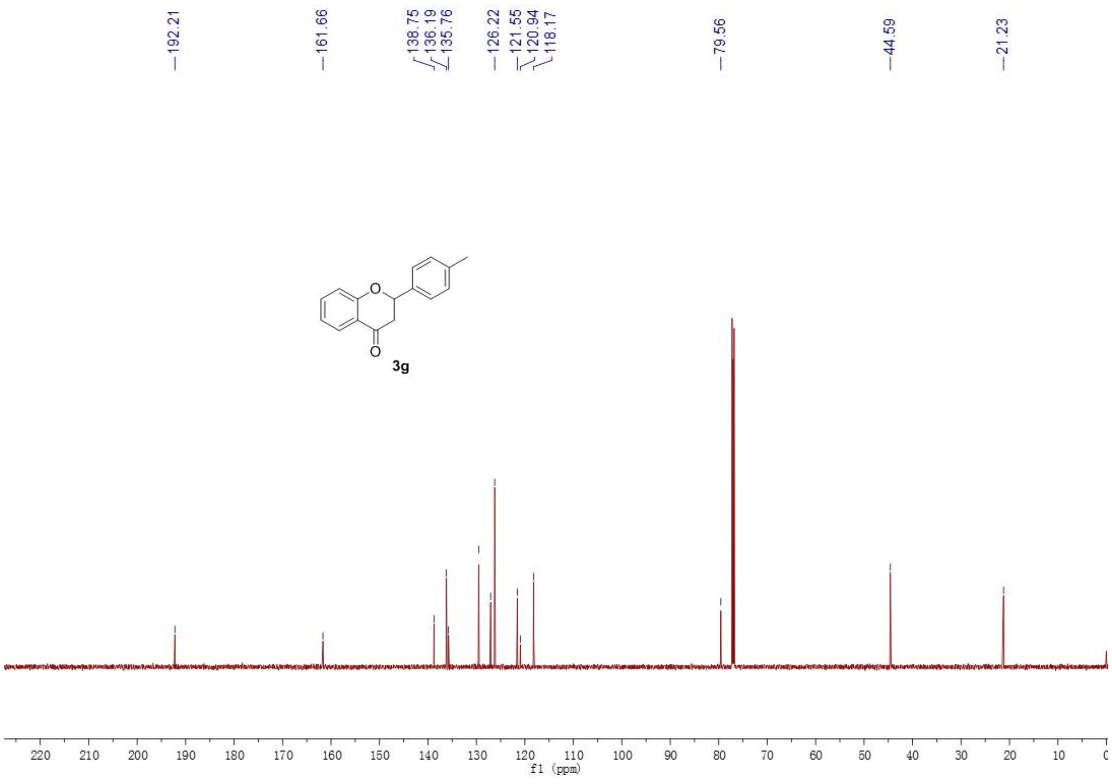
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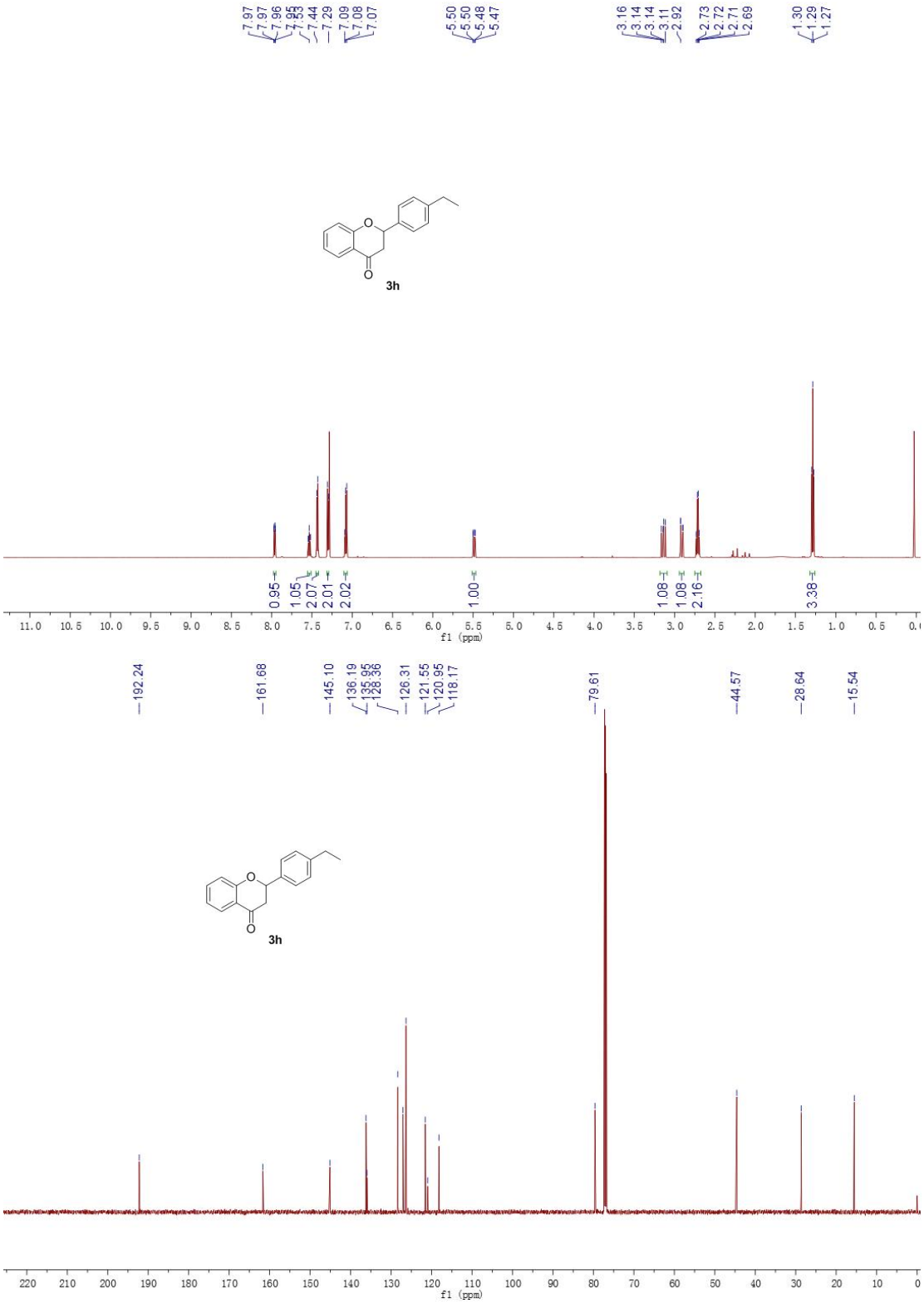
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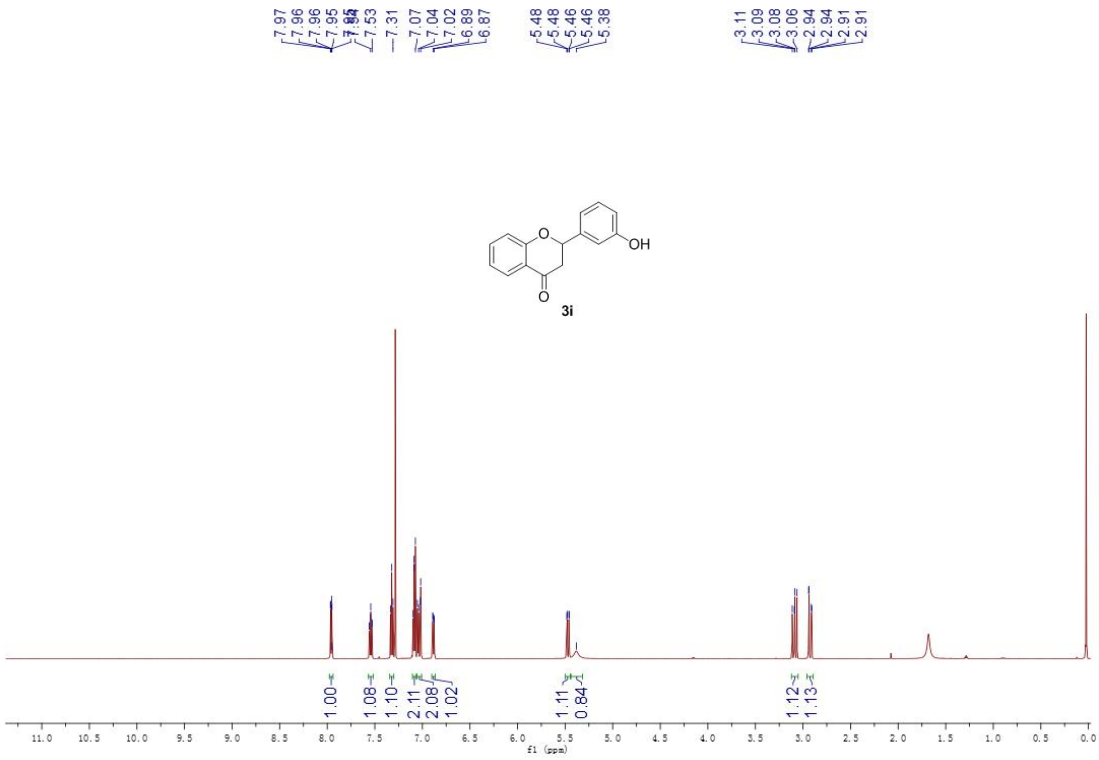
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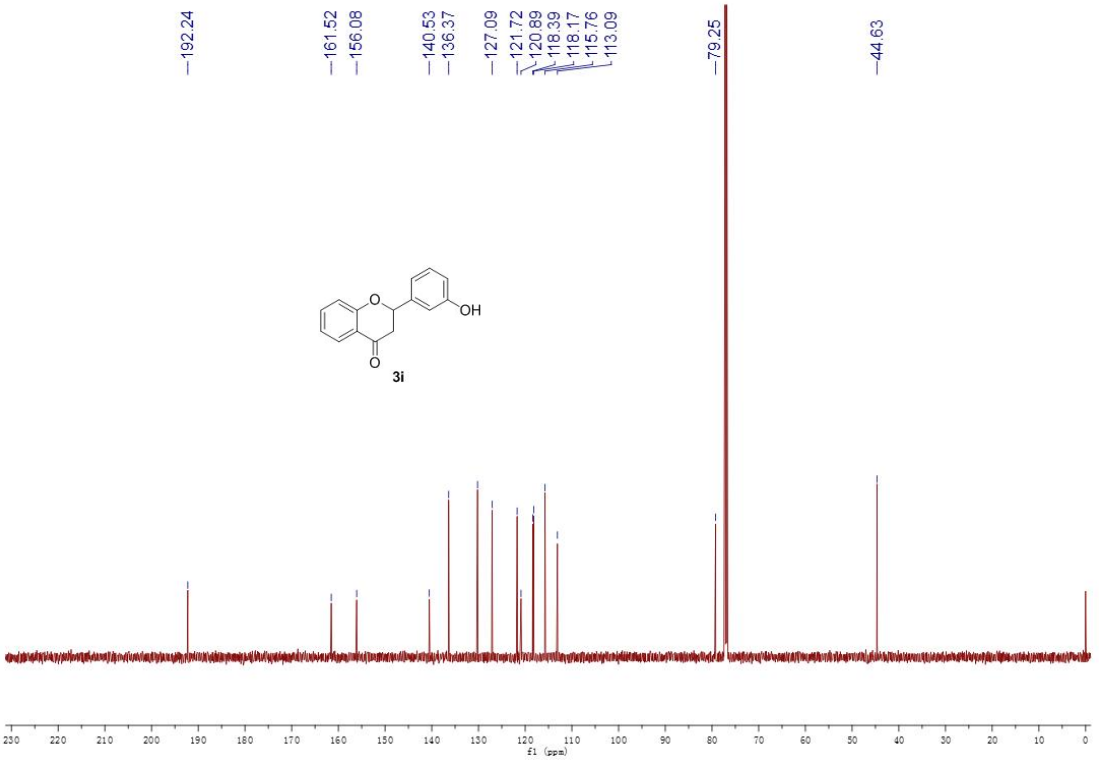
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7.27
7.26
7.26
7.26
7.25
7.25
7.08
7.07
7.07
7.06
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5.48
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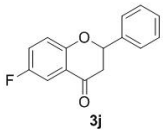
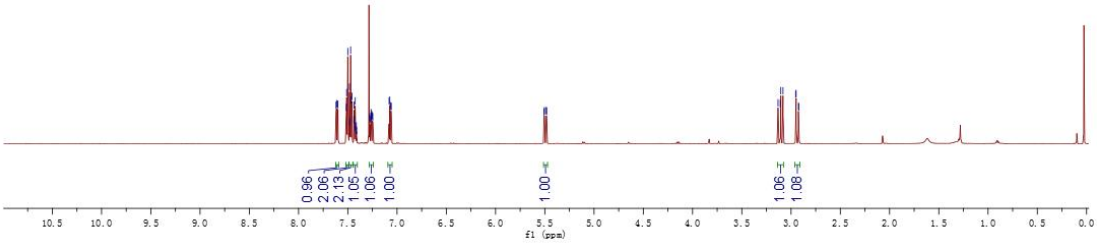
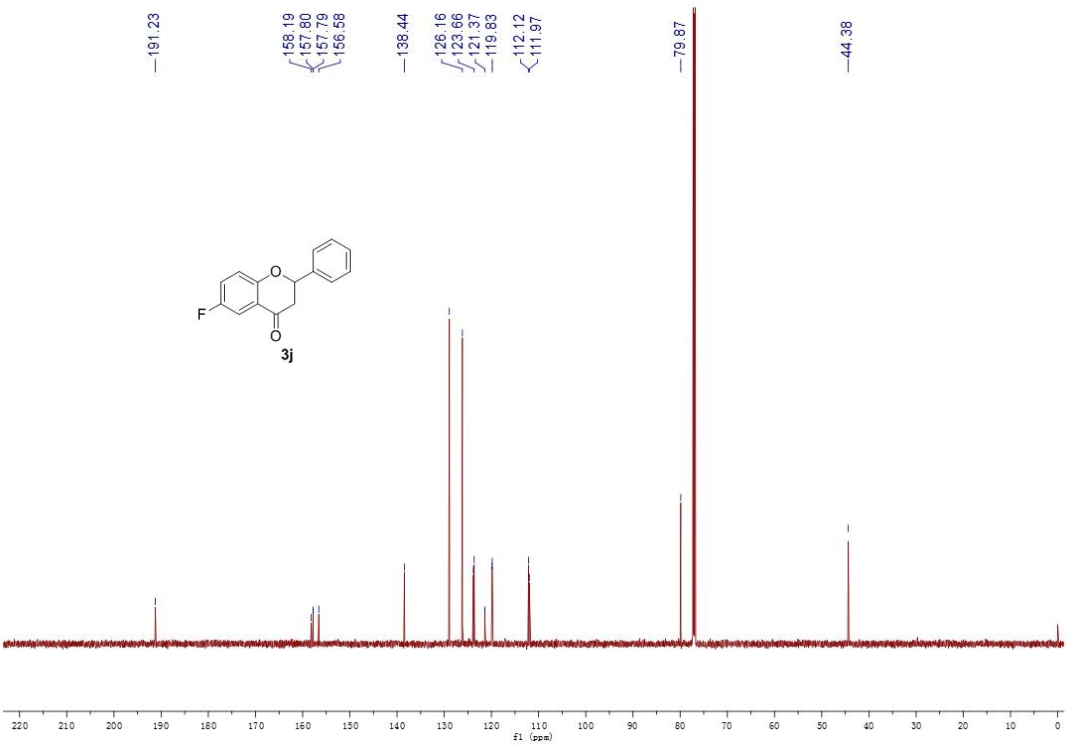
3.11
3.10
3.08
2.95
2.95
2.92
2.92

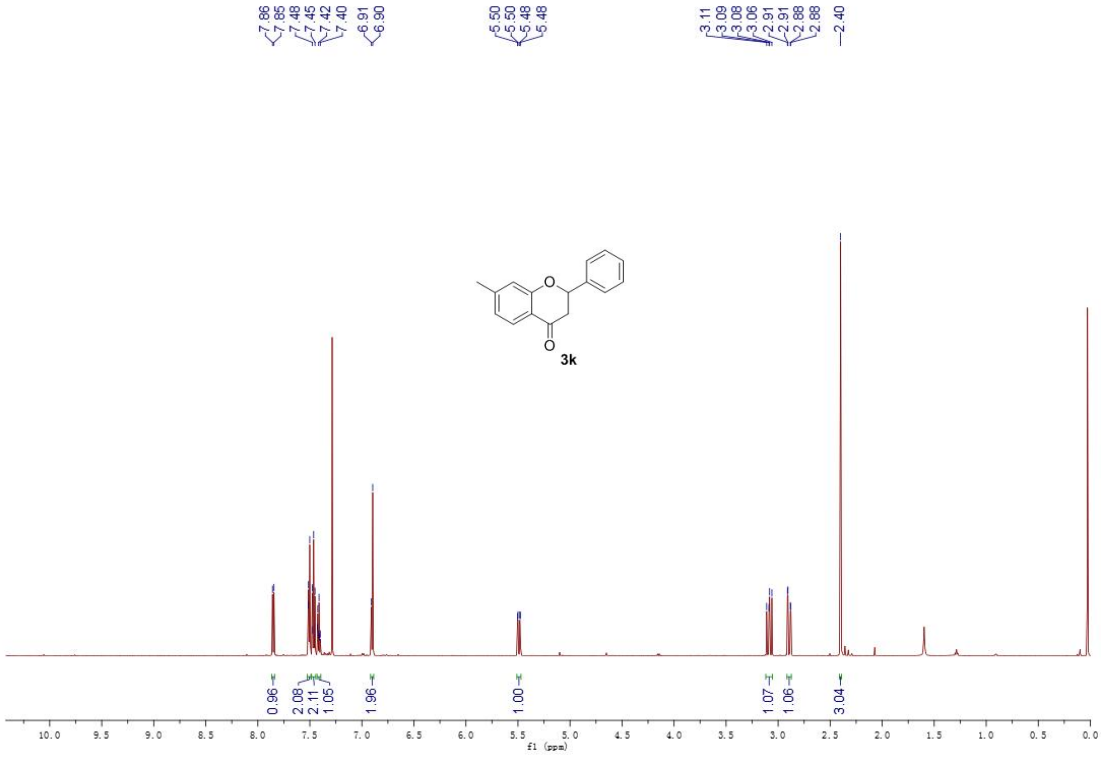

O
F
O

3j


0.96
2.06
2.13
1.05
1.06
1.00
1.00
1.06
1.08
f1 (ppm)


191.23
158.19
157.80
157.79
156.58
138.44
126.16
123.66
121.37
119.83
112.12
111.97
79.87
44.38
O
F
O
f1 (ppm)

3j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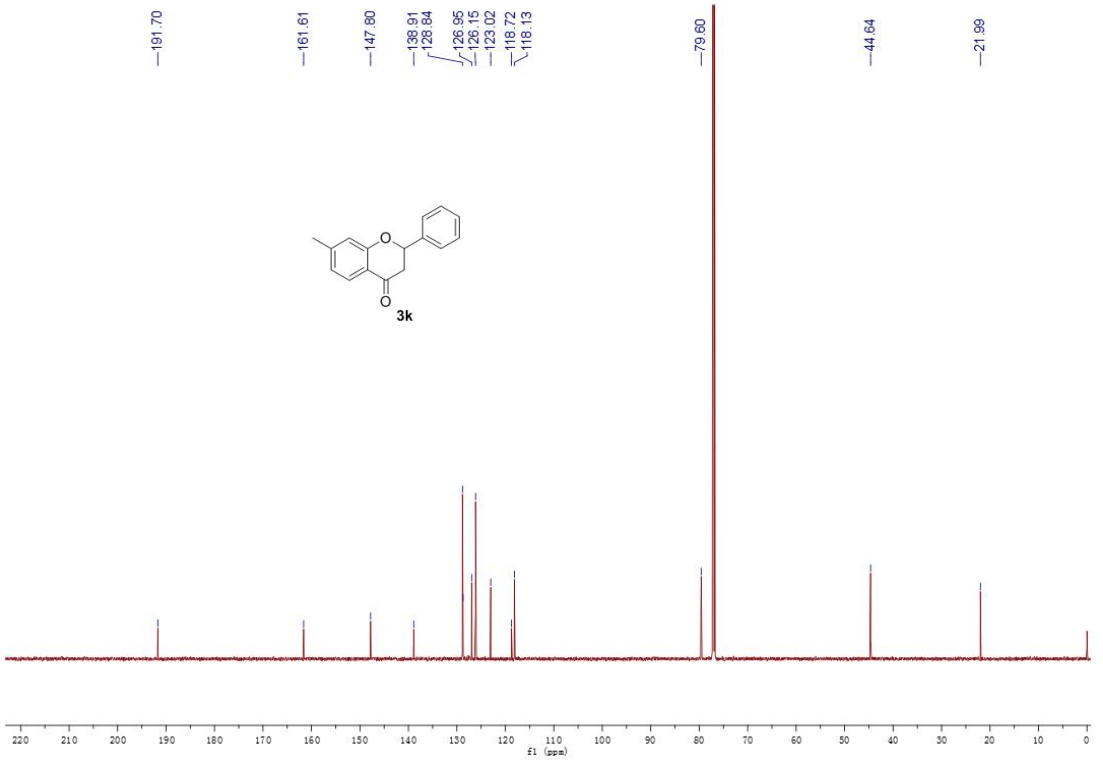
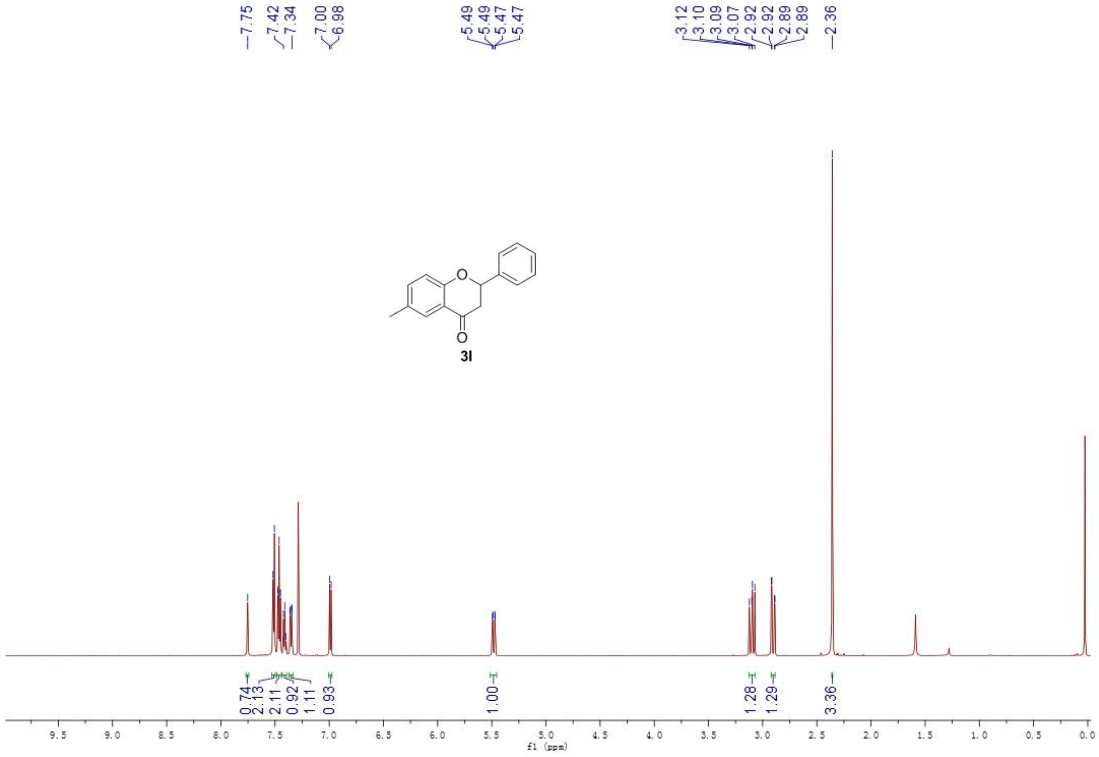
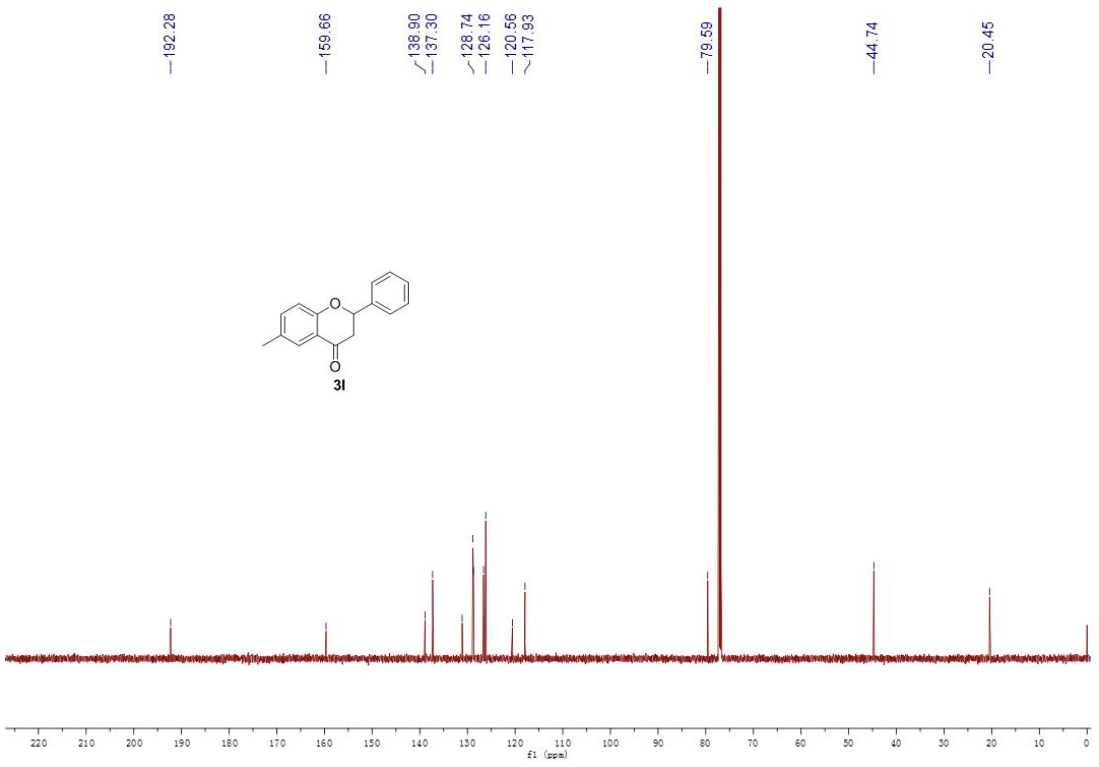
7.85
7.48
7.45
7.42
7.40
6.91
6.90
5.50
5.50
5.48
5.48
3.11
3.09
3.08
3.06
2.91
2.91
2.88
2.88
2.40
3k
0.96
2.08
2.11
1.05
1.96
1.00
1.07
1.06
3.04
f1 (ppm)


191.70
161.61
147.80
138.91
128.84
126.95
126.15
123.02
118.72
118.13
79.60
44.64
21.99
3k
f1 (ppm)


7.75
7.42
7.34
7.00
6.98
5.49
5.49
5.47
5.47
3.12
3.10
3.09
3.07
2.92
2.92
2.89
2.89
2.36
3I
0.74
2.13
2.11
0.92
1.11
0.93
1.00
1.28
1.29
3.36
f1 (ppm)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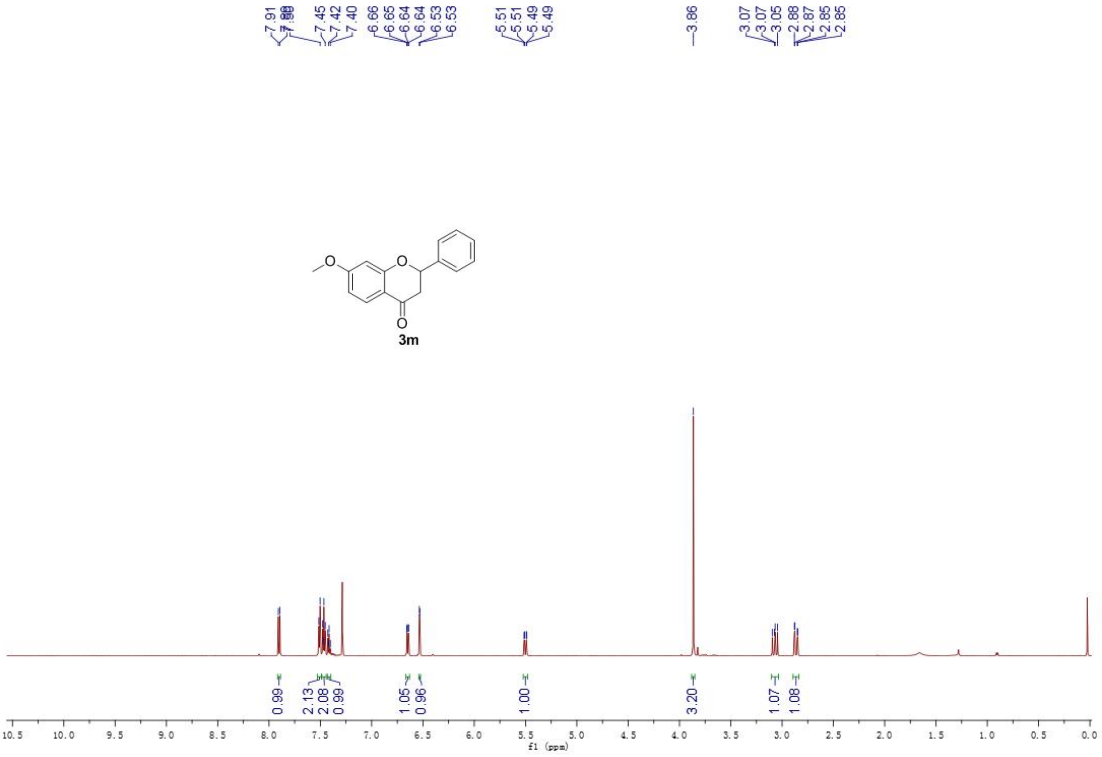
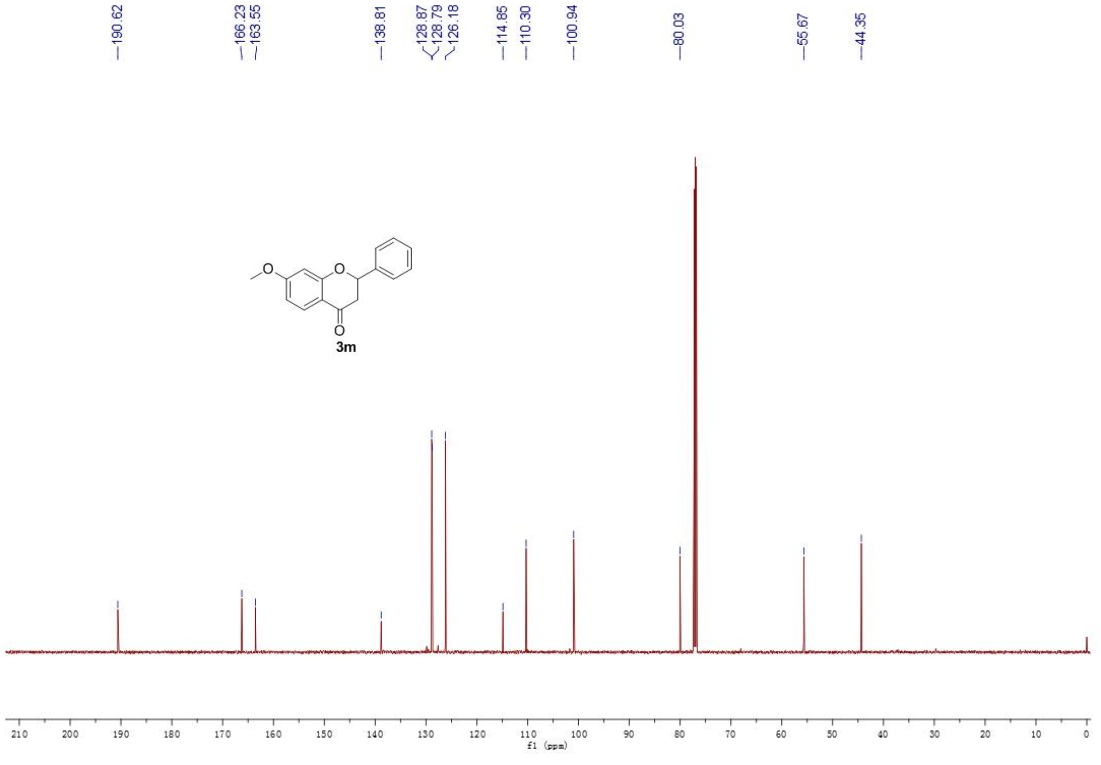
159.66
138.90
137.30
128.74
126.16
120.56
117.93
79.59
44.74
20.45
3I
f1 (ppm)


7.91
7.45
7.42
7.40
6.66
6.65
6.64
6.64
6.53
6.53
5.51
5.51
5.49
5.49
3.86
3.07
3.07
3.05
2.88
2.87
2.85
2.85
3m
0.99
2.13
2.08
0.99
1.05
0.96
1.00
3.20
1.07
1.08
f1 (ppm)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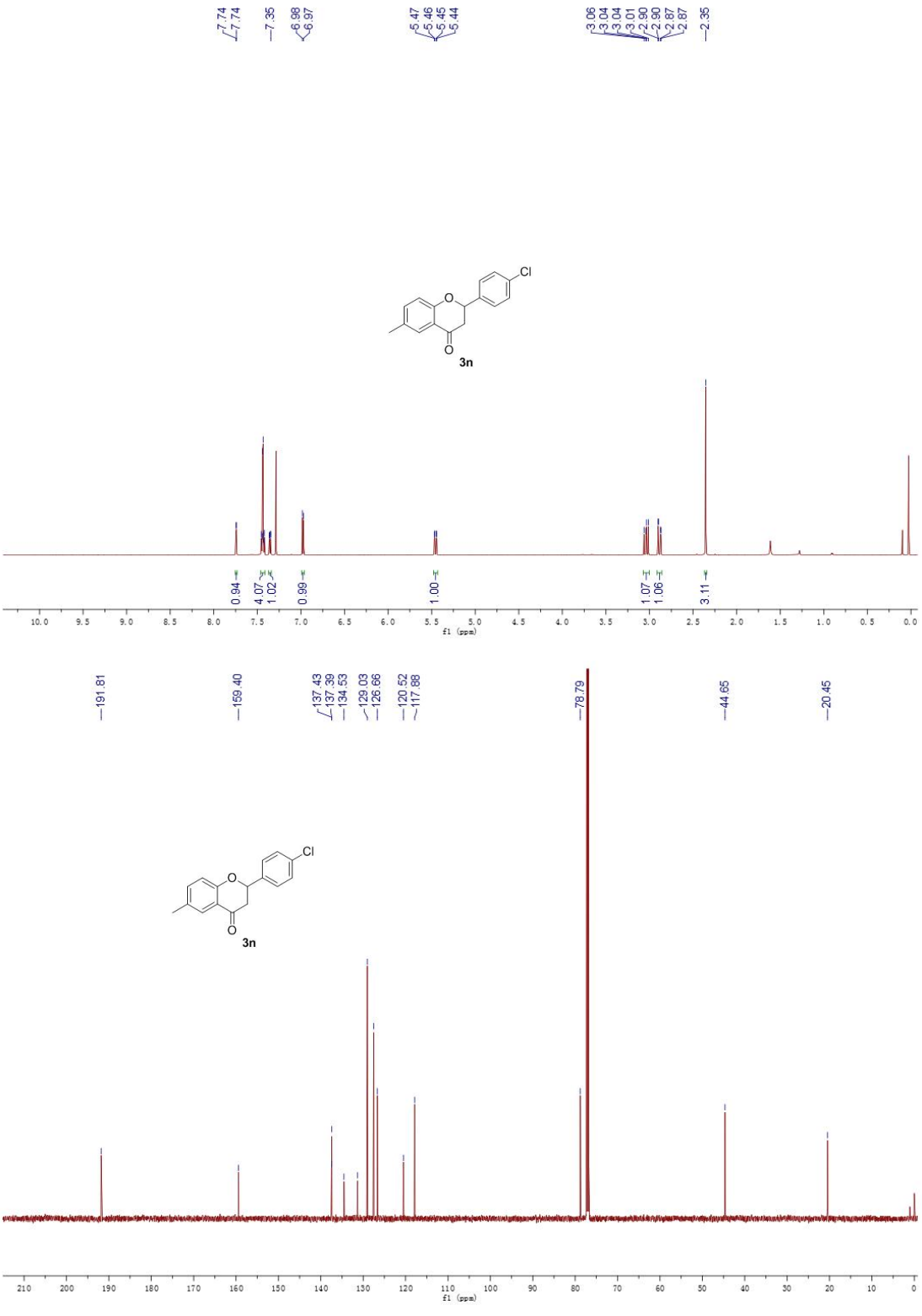
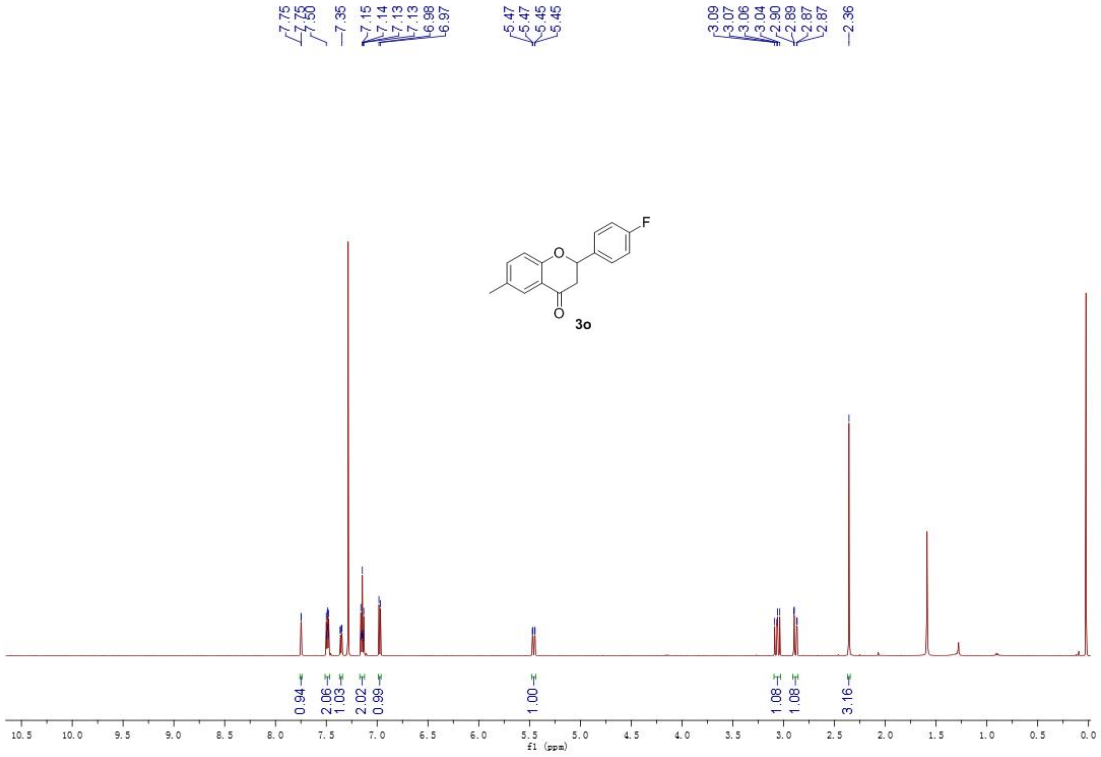
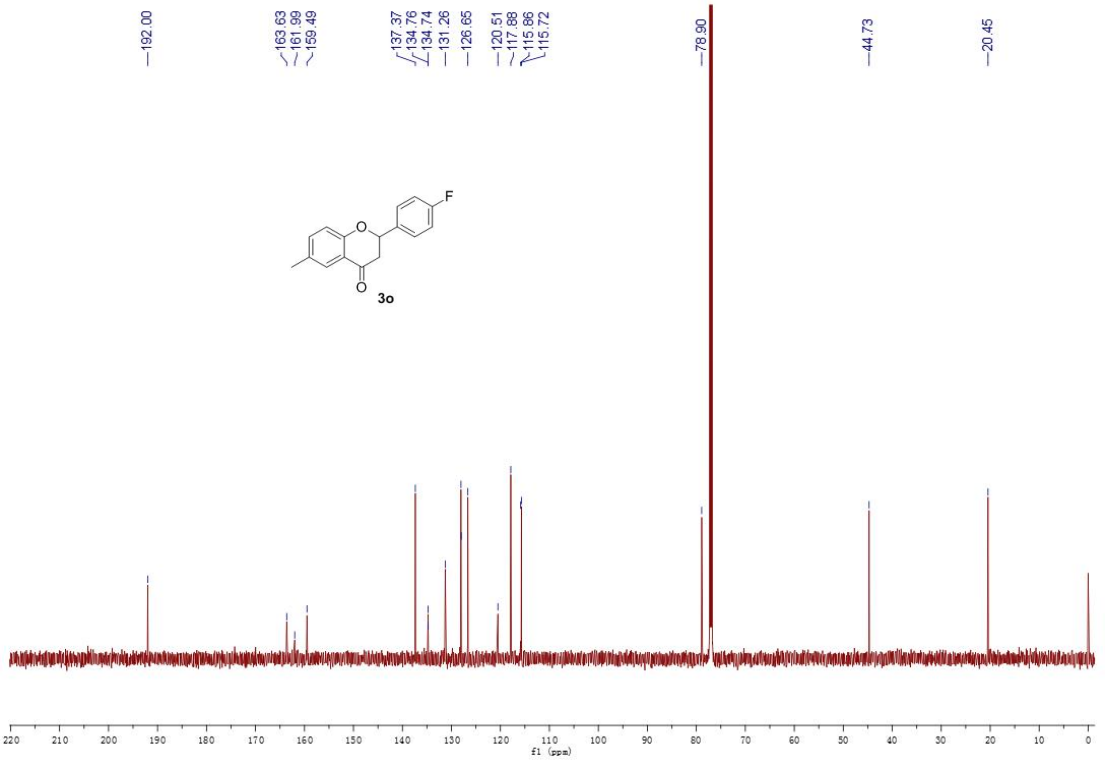
166.23
163.55
138.81
128.87
128.79
126.18
114.85
110.30
100.94
80.03
55.67
44.35
3m
f1 (ppm)


7.74
7.74
7.35
6.98
6.97
5.47
5.46
5.45
5.44
3.06
3.04
3.04
3.01
2.90
2.90
2.87
2.87
2.35
Cl
O
O
3n
0.94
4.07
1.02
0.99
1.00
1.07
1.06
3.11
f1 (ppm)
191.81
159.40
137.43
137.39
134.53
129.03
126.66
120.52
117.88
78.79
44.65
20.45
Cl
O
O
3n
f1 (ppm)


7.75
7.75
7.50
7.35
7.15
7.14
7.13
7.13
6.98
6.97
5.47
5.47
5.45
5.45
3.09
3.07
3.06
3.04
2.90
2.89
2.87
2.87
2.36
F
O
O
3o
0.94
2.06
1.03
2.02
0.99
1.00
1.08
1.08
3.16
f1 (ppm)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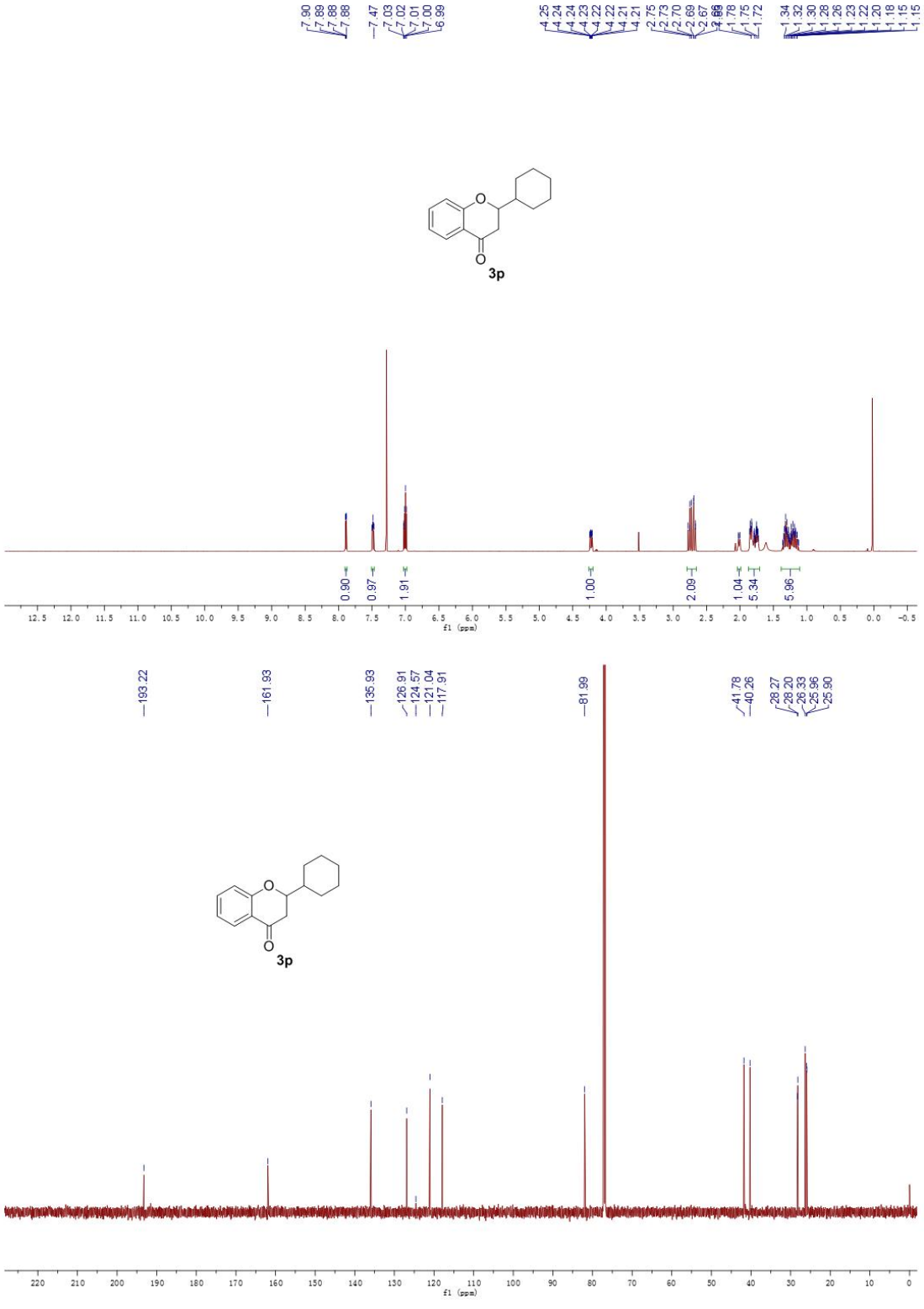
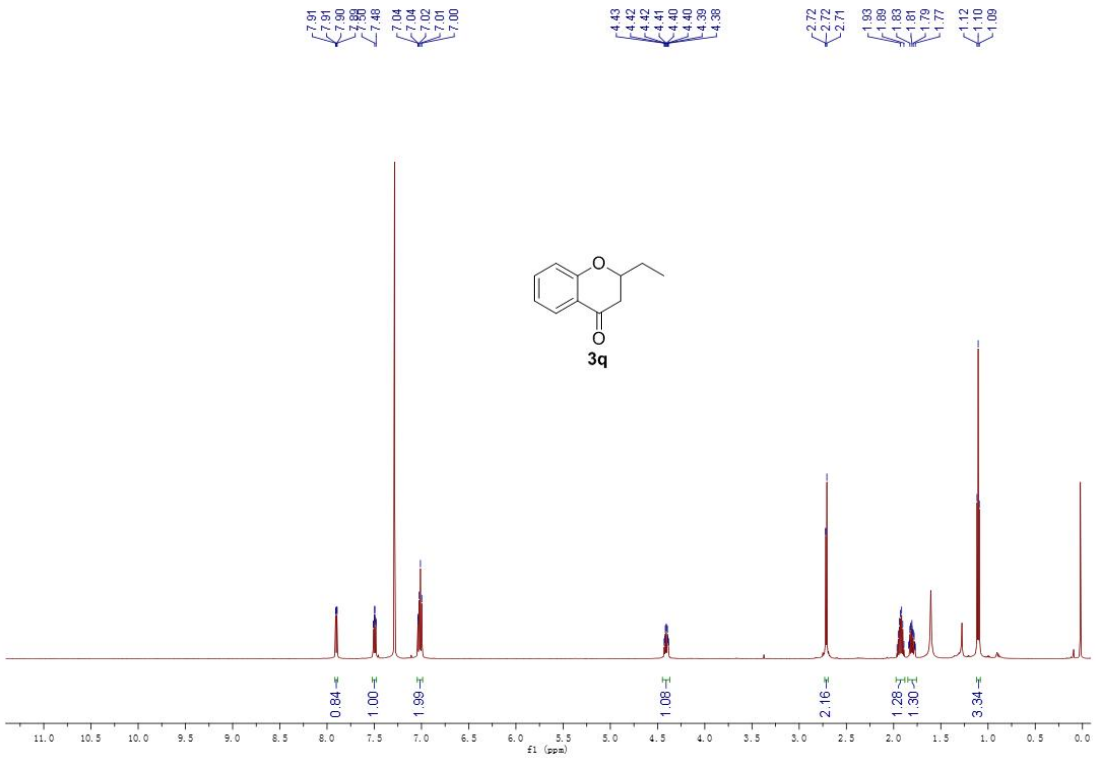
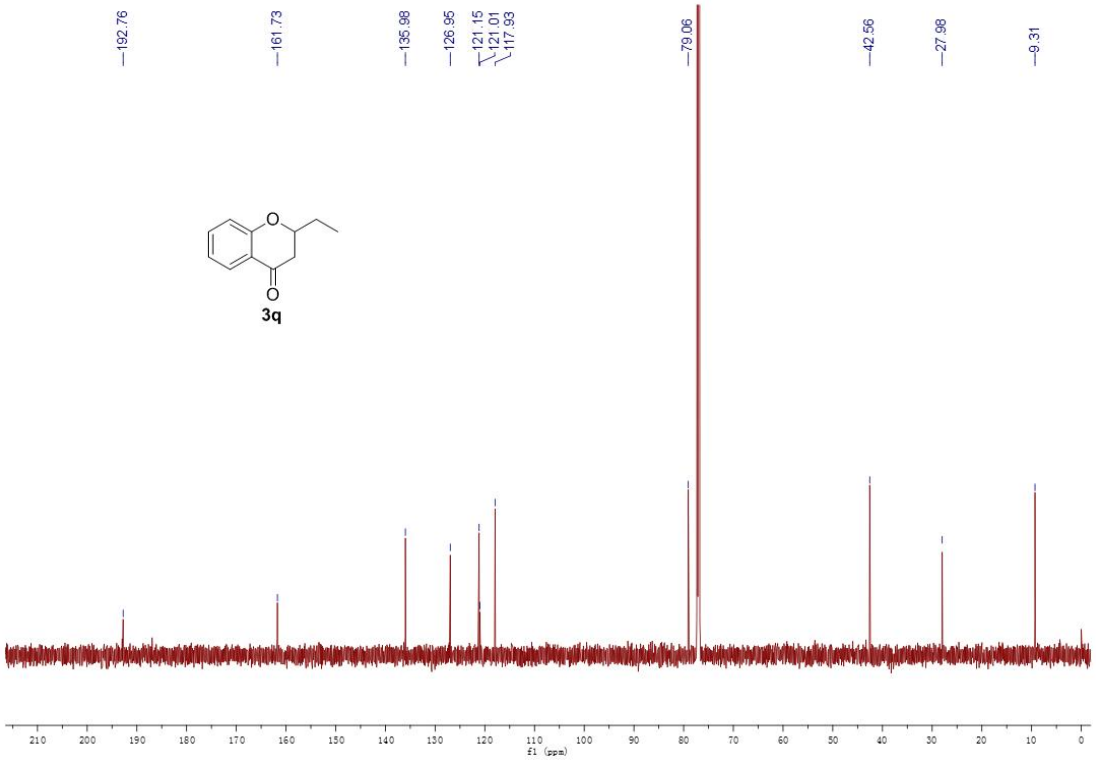
163.63
161.99
159.49
137.37
134.76
134.74
131.26
126.65
120.51
117.88
115.86
115.72
78.90
44.73
20.45
F
O
O
3o
f1 (ppm)


7.90
7.89
7.88
7.88
7.47
7.03
7.02
7.01
7.00
6.99
4.25
4.24
4.24
4.23
4.22
4.22
4.21
4.21
2.75
2.73
2.70
2.69
2.67
1.78
1.75
1.72
1.34
1.32
1.30
1.28
1.26
1.23
1.22
1.20
1.18
1.15
1.15
3p
0.90
0.97
1.91
1.00
2.09
1.04
5.34
5.96
f1 (ppm)
193.22
161.93
135.93
126.91
124.57
121.04
117.91
81.99
41.78
40.26
28.27
28.20
26.33
25.96
25.90
3p
f1 (ppm)


7.91
7.91
7.90
7.48
7.04
7.04
7.02
7.01
7.00
4.43
4.42
4.42
4.41
4.40
4.40
4.39
4.38
2.72
2.72
2.71
1.93
1.89
1.83
1.81
1.79
1.77
1.12
1.10
1.09
3q
0.84
1.00
1.99
1.08
2.16
1.28
1.30
3.34
f1 (ppm)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161.73
135.98
126.95
121.15
121.01
117.93
79.06
42.56
27.98
9.31
3q
f1 (ppm)