

Supplementary Material

Protective Effects of Marine alkaloid Neolamellarin A Derivatives against Glutamate Induced PC12 Cell Apoptosis

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General procedures for the synthesis of important intermediates

The general procedures for the synthesis of important intermediates **4a** - **4e**, **5a** - **5e** and **6a** - **6c** are as follows.

1.1. General procedure for the synthesis of **4a** - **4e**

The substituted phenyl acetaldehydes **3** ^[17] (10 mmol) and benzylamine (1.07 g, 10 mmol) were dissolved in THF (15 mL), and stirred at room temperature for 0.5 h under argon. Then AgOAc (3.34 g, 20 mmol) and NaOAc (1.64 g, 20 mmol) were added, and the mixture was stirred at 60 °C for 8 h. The mixture was cooled down to room temperature, and then the resulting precipitate was filtered and washed with EtOAc. The filtrate was evaporated under reduced pressure and the resulting residue was purified by flash column chromatography (petroleum ether: dichloromethane = 5: 1 to 3: 1) to give the pure compounds **4a** - **4e**.

1.1.1. 1-benzyl-3,4-bis(2-methoxyphenyl)-1*H*-pyrrole (**4a**)

White solid 1.15 g. Yield 62.3%. ¹H NMR (500 MHz, CDCl₃) δ (ppm) 7.37-7.36 (m, 2H), 7.31-7.26 (m, 3H), 7.14-7.13 (m, 4H), 6.91 (s, 2H), 6.82-6.81 (m, 4H), 5.12 (s, 2H), 3.49 (s, 6H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 156.28 (2C), 137.53 (C), 130.44 (2CH), 128.65 (2CH), 127.67 (4CH), 126.60 (2CH), 126.05 (2CH), 121.19 (2C), 120.13 (CH), 119.97 (2C), 110.68 (2CH), 54.96 (CH₂), 53.54 (2CH₃). HRMS (ESI) *m/z*: calcd for M⁺ C₂₅H₂₄O₂N, 370.1802; found, M⁺ 370.1802.

1.1.2. 1-benzyl-3,4-bis(3-methoxyphenyl)-1*H*-pyrrole (**4b**)

White solid 1.04 g. Yield 56.5%. ¹H NMR (500 MHz, CDCl₃) δ (ppm) 7.37-7.35 (m, 2H), 7.33-7.32 (m, 1H), 7.26-7.25 (m, 2H), 7.17-7.14 (dd, *J* = 9.6, 6.2 Hz, 2H), 6.88-6.87 (d, *J* = 7.3 Hz, 2H), 6.83- 6.81(m, 4H), 6.74-6.72 (dd, *J* = 7.3, 2.3 Hz, 2H), 5.09 (s, 2H), 3.68 (s, 6H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 159.27 (2C), 137.26 (C), 137.07 (2C), 129.00 (2CH), 128.80 (2CH), 127.90 (CH), 127.42 (2CH), 123.45 (2C), 120.95 (2CH), 120.70 (2CH), 113.57 (2CH), 111.55 (2CH), 55.02 (CH₂), 53.58 (2CH₃). HRMS (ESI) *m/z*: calcd for M⁺ C₂₅H₂₄O₂N, 370.1802; found, M⁺ 370.1799.

1.1.3. 1-benzyl-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole (**4c**)

White solid 1.34 g. Yield 72.8%. ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.38-7.36 (td, *J* = 7.4, 1.4 Hz, 2H), 7.33-7.31 (m, 1H), 7.27 -7.25 (m, 2H), 7.20-7.19 (d, *J* = 9.44 Hz, 4H), 6.82-6.80 (d, *J* = 9.44 Hz, 4H), 6.74 (d, *J* = 1.6 Hz, 2H), 5.07 (s, 2H), 3.80 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 157.66 (2C), 137.52 (C), 129.40 (4CH), 128.75 (2CH), 128.44 (CH), 127.80 (2C), 127.40 (2CH), 123.00 (2C), 120.02 (2CH), 113.56 (4CH), 55.15 (2CH₃), 53.50 (CH₂). HRMS (ESI) *m/z*: calcd for M⁺ C₂₅H₂₄O₂N, 370.1802; found, M⁺ 370.1798.

1.1.4 1-benzyl-3,4-bis(3,4-dimethoxyphenyl)-1*H*-pyrrole (**4d**)

White solid 1.41 g. Yield 65.4%. ¹H NMR (500 MHz, CDCl₃) δ (ppm) 7.38-7.35 (t, *J* = 7.0 Hz, 2H), 7.32-7.31 (d, *J* = 6.3 Hz, 1H), 7.25 (s, 2H), 6.84-6.82 (d, *J* = 8.1 Hz, 2H), 6.78-6.77 (m, 6H), 5.07 (s, 2H), 3.85 (s, 6H), 3.67 (s, 6H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 148.28 (2C), 147.02 (2C), 137.41 (C), 128.77 (2CH), 128.59 (2C), 127.84 (CH), 127.36 (2CH), 123.16 (2C), 120.39 (2CH), 119.99 (2CH), 111.99 (2CH), 110.93 (2CH), 55.80 (2CH₃), 55.57 (2CH₃), 53.53 (CH₂). HRMS (ESI) *m/z*: calcd for M⁺ C₂₇H₂₈O₄N, 430.2013; found, M⁺ 430.2011.

1.1.5 1-benzyl-3,4-bis(3,4,5-trimethoxyphenyl)-1*H*-pyrrole (**4e**)

White solid 1.98 g. Yield 73.8%. ¹H NMR (500 MHz, CDCl₃) δ (ppm) 7.38-7.36 (dd, *J* = 8.9, 4.0 Hz, 2H), 7.33-7.32 (d, *J* = 6.1 Hz, 1H), 7.26-7.25 (d, *J* = 6.1 Hz, 2H), 6.82 (s, 2H), 6.49 (s, 4H), 5.09 (s, 2H), 3.81 (s, 6H), 3.69 (s, 12H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 152.72 (4C), 137.25 (2C), 136.03 (C), 131.19 (2C), 128.81 (2CH), 127.92 (CH), 127.31 (2CH), 123.48 (2C), 120.19 (2CH), 105.55 (4CH), 60.87 (2CH₃), 55.86 (4CH₃), 53.58 (CH₂). HRMS (ESI) *m/z*: calcd for M⁺ C₂₉H₃₂O₆N, 490.2224; found, M⁺ 490.2214.

1.2. General procedure for the synthesis of **5a** - **5e**

To a mixture of **4a** - **4e** (2.0 mmol) and *t*-BuOK (22.24 g, 20.0 mmol) was successively added THF (12 mL) and DMSO (20 mL) under oxygen atmosphere, then the solution was stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous NH₄Cl solution (30 mL) and extracted with EtOAc (20 \times 3 mL). The organic phase was washed with H₂O (3 \times 30 mL), dried with MgSO₄, and evaporated under reduced pressure and the resulting residue was purified by flash column chromatography (petroleum ether: ethyl acetate = 1: 1) to give the pure compounds **5a** - **5e**.

1.2.1. 3,4-bis(2-methoxyphenyl)-1*H*-pyrrole (**5a**)

White solid 0.49 g. Yield 87.5%. ^1H NMR (600 MHz, CDCl_3) δ 8.33 (s, NH), 7.17–7.14 (m, 4H), 7.01 (d, $J = 2.76$, 2H), 6.85–6.82 (m, 4H), 3.50 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 156.59 (2C), 130.78 (2CH), 126.97 (2CH), 126.07 (2C), 120.31 (2CH), 120.22 (2C), 118.06 (2CH), 110.81 (2CH), 55.13 (CH_3), 55.10 (CH_3). HRMS (ESI) m/z : calcd for M^+ $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}$, 280.1332; found, M^+ 280.1334.

1.2.2. 3,4-bis(3-methoxyphenyl)-1H-pyrrole (**5b**)

Sticky liquid 0.51 g. Yield 89.5%. ^1H NMR (600 MHz, CDCl_3) δ 8.48 (s, NH), 7.21–7.18 (t, $J = 7.9$ Hz, 2H), 6.92–6.90 (m, 4H), 6.86 (s, 2H), 6.77–6.75 (dd, $J = 8.2$, 2.0 Hz, 2H), 3.70 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 159.26 (2C), 137.06 (2C), 129.03 (2CH), 123.36 (2C), 121.10 (2CH), 117.43 (2CH), 113.79 (2CH), 111.58 (2CH), 55.01 (2CH₃). HRMS (ESI) m/z : calcd for M^+ $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}$, 280.1332; found, M^+ 280.1335.

1.2.3. 3,4-bis(4-methoxyphenyl)-1H-pyrrole (**5c**)

White solid 0.52 g. Yield 91.2%. ^1H NMR (600 MHz, CDCl_3) δ 8.26 (s, NH), 7.22–7.20 (d, $J = 8.6$ Hz, 4H), 6.85–6.82 (m, 6H), 3.81 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 157.74 (2C), 129.55 (4CH), 128.33 (2C), 123.00 (2C), 116.72 (2CH), 113.54 (4CH), 55.17 (2CH₃). HRMS (ESI) m/z : calcd for M^+ $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}$, 280.1332; found, M^+ 280.1338.

1.2.4. 3,4-bis(3,4-dimethoxyphenyl)-1H-pyrrole (**5d**)

Yellowish solid 0.63 g. Yield 92.6%. ^1H NMR (500 MHz, CDCl_3) δ (ppm) 8.41 (s, NH), 6.89–6.88 (d, $J = 2.6$ Hz, 2H), 6.87–6.85 (dd, $J = 8.2$, 1.8 Hz, 2H), 6.81–6.80 (m, 4H), 3.87 (s, 6H), 3.69 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm) 148.29 (2C), 147.10 (2C), 128.57 (2C), 123.11 (2C), 120.55 (2CH), 116.72 (2CH), 112.18 (2CH), 110.99 (2CH), 55.81 (2CH₃), 55.57 (2CH₃). HRMS (ESI) m/z : calcd for M^+ $\text{C}_{20}\text{H}_{22}\text{O}_4\text{N}$, 340.1543; found, M^+ 340.1543.

1.2.5. 3,4-bis(3,4,5-trimethoxyphenyl)-1H-pyrrole (**5e**)

Yellowish solid 0.73 g. Yield 91.2%. ^1H NMR (500 MHz, CDCl_3) δ (ppm) 8.52 (s, NH), 6.94–6.93 (d, $J = 2.6$ Hz, 2H), 6.51 (s, 4H), 3.83 (s, 6H), 3.71 (s, 12H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm) 152.75 (4C), 136.13 (2C), 131.25 (2C), 123.44 (2C), 116.95 (2CH), 105.78 (4CH), 60.90 (2CH₃), 55.89 (4CH₃). HRMS (ESI) m/z : calcd for M^+ $\text{C}_{22}\text{H}_{26}\text{O}_6\text{N}$, 400.1755; found, M^+ 400.1759.

1.3. General procedure for the synthesis of acyl chloride **6a** - **6c**

To a solution of the substituted benzoic acid (2.4 mmol) in anhydrous CH_2Cl_2 (10 mL) was added catalytic amount of DMF and oxalyl chloride (0.6 mL, 13.6 mmol) at room temperature under argon atmosphere. After stirring for 2 h, the solvent was removed by vacuum evaporation, and the compounds **6a** - **6c** were directly used without further purification.

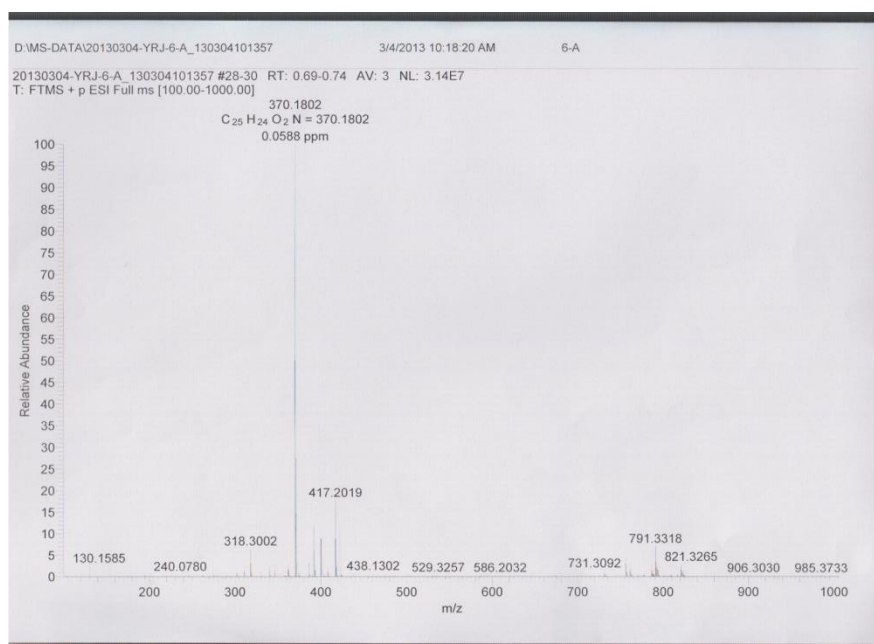


Figure S1. HRMS spectrum of **4a**

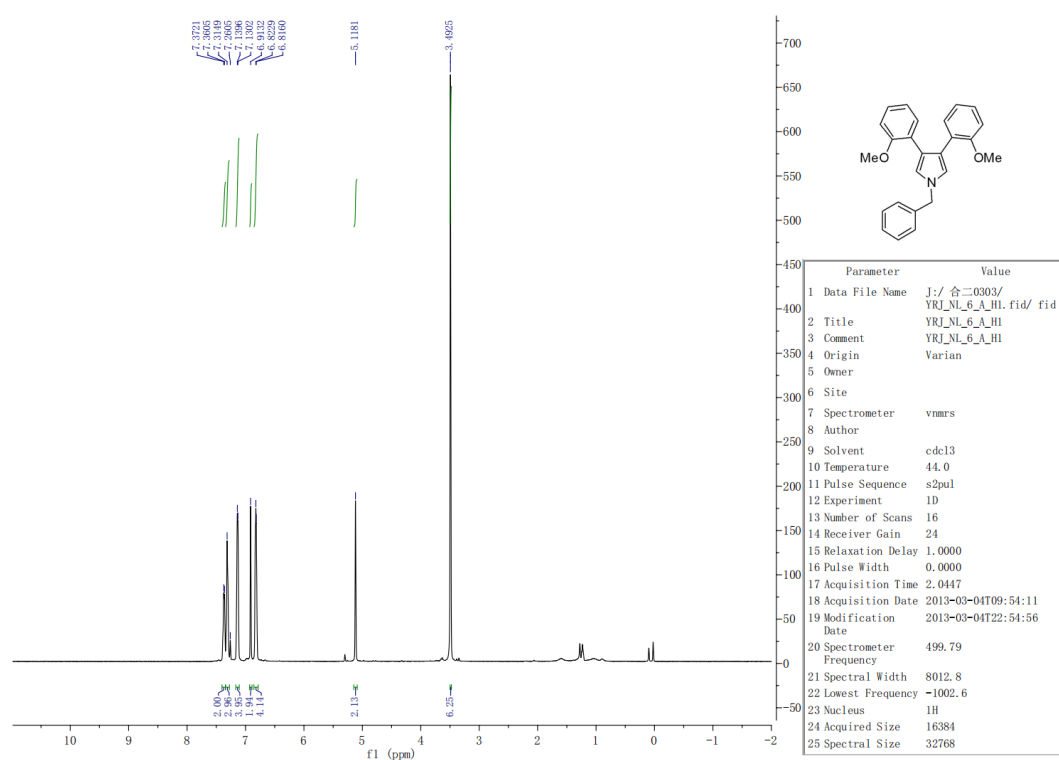


Figure S2. ¹H NMR spectrum of **4a**

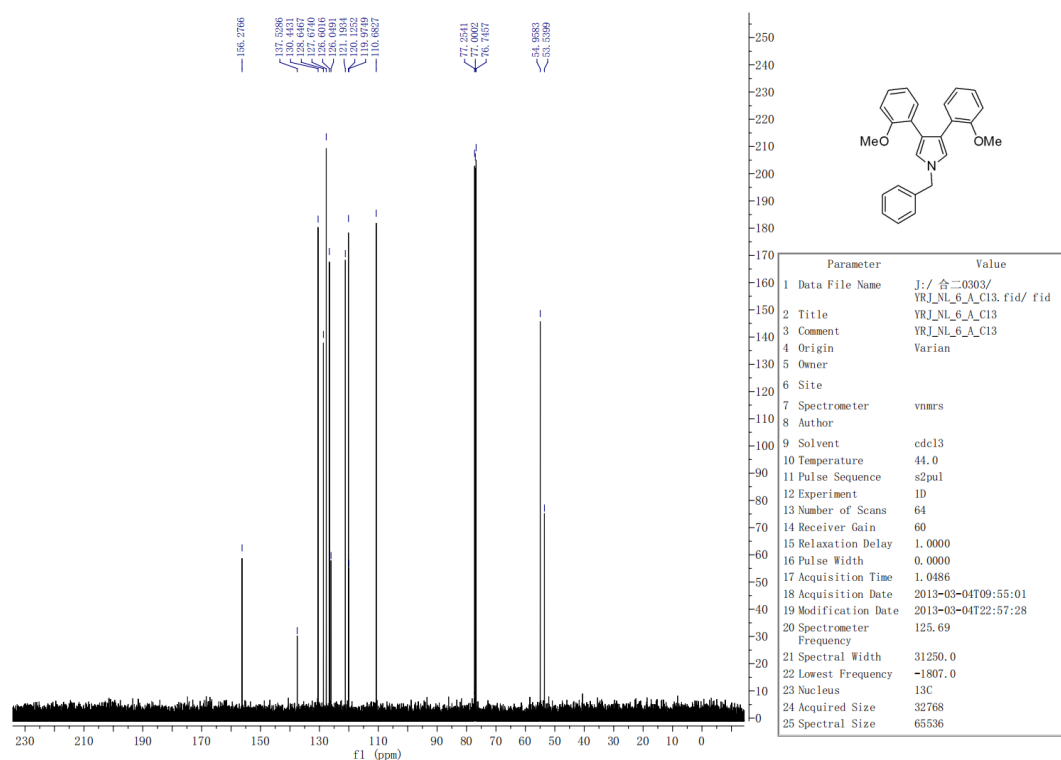


Figure S3. ^{13}C NMR spectrum of 4a

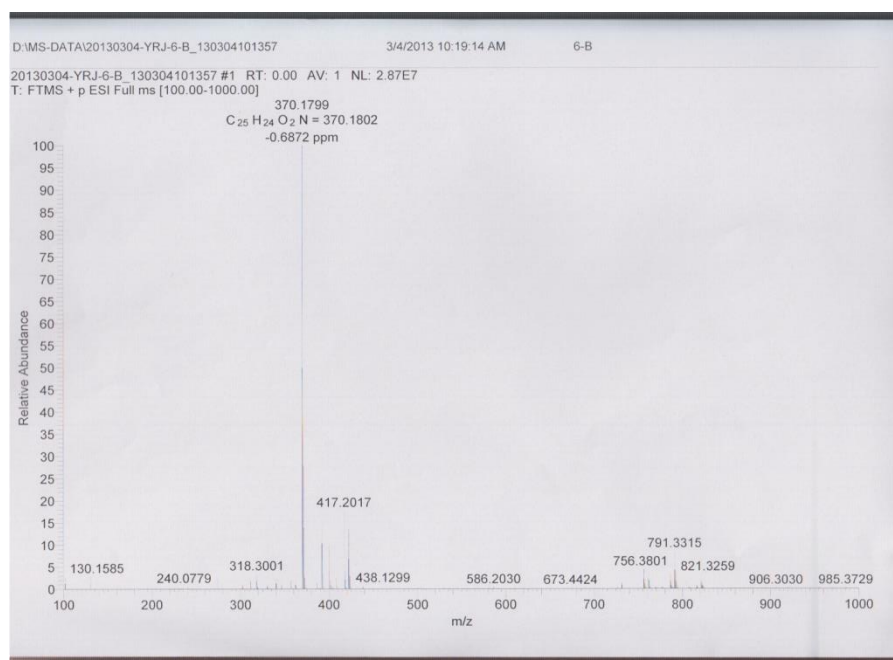


Figure S4. HRMS spectrum of 4b

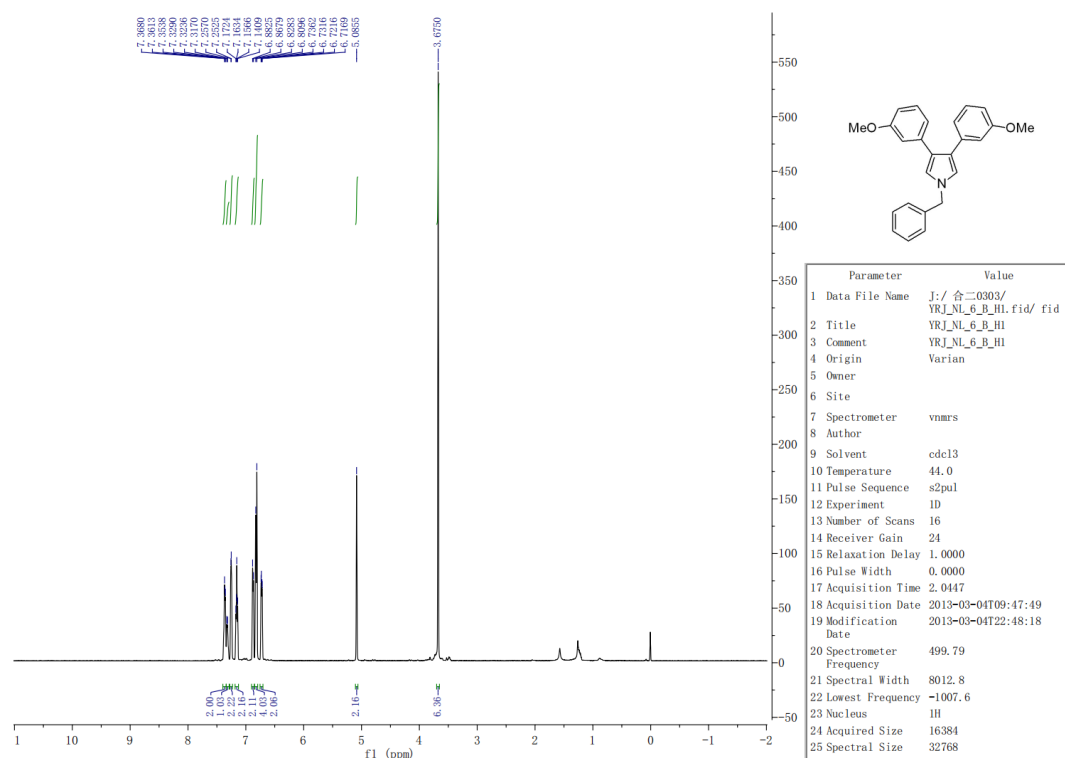


Figure S5. ^1H NMR spectrum of 4b

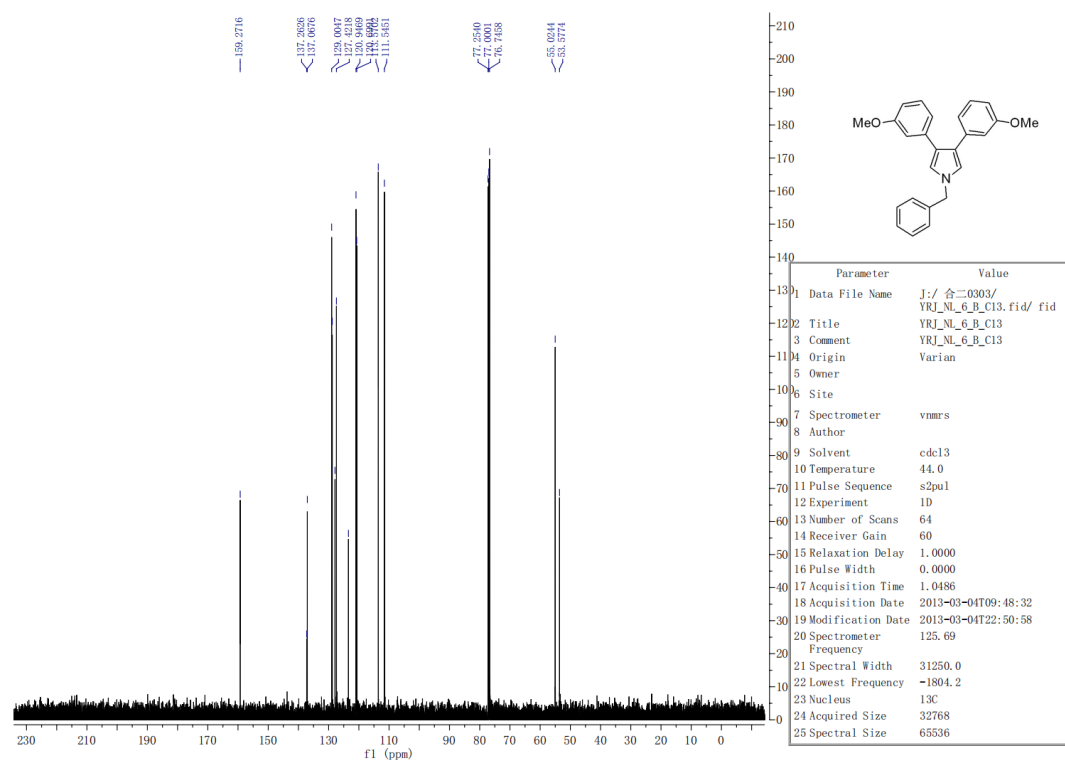


Figure S6. ^{13}C NMR spectrum of 4b

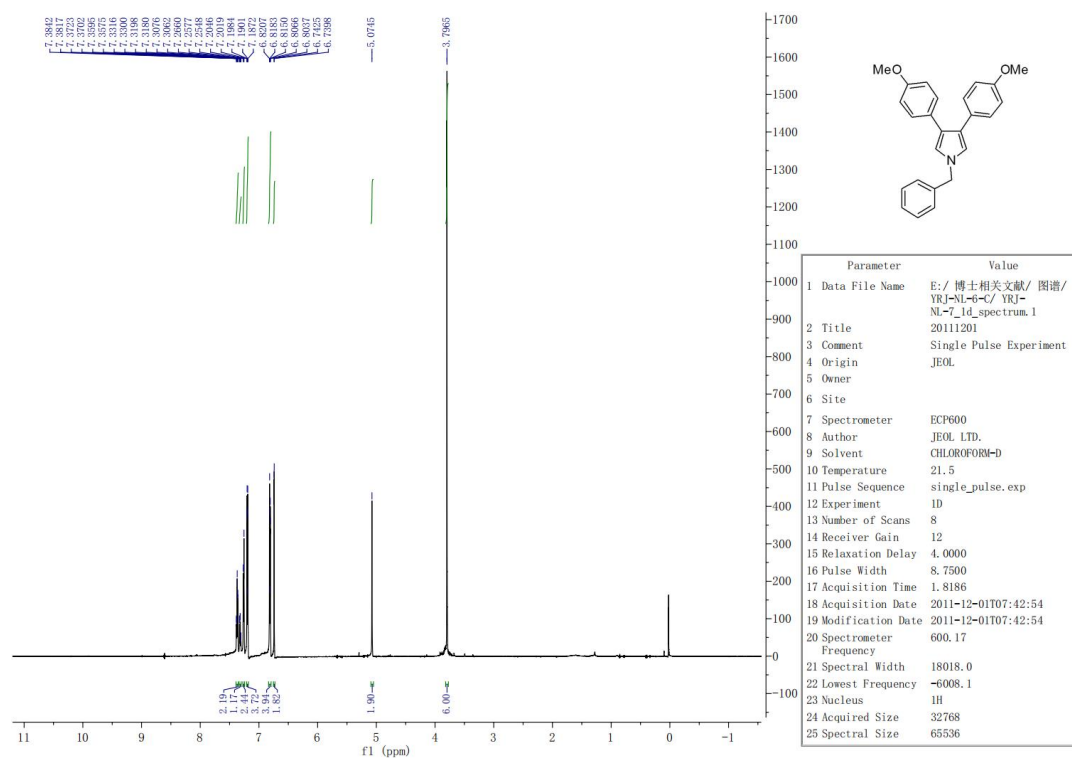


Figure S7. ^1H NMR spectrum of 4c

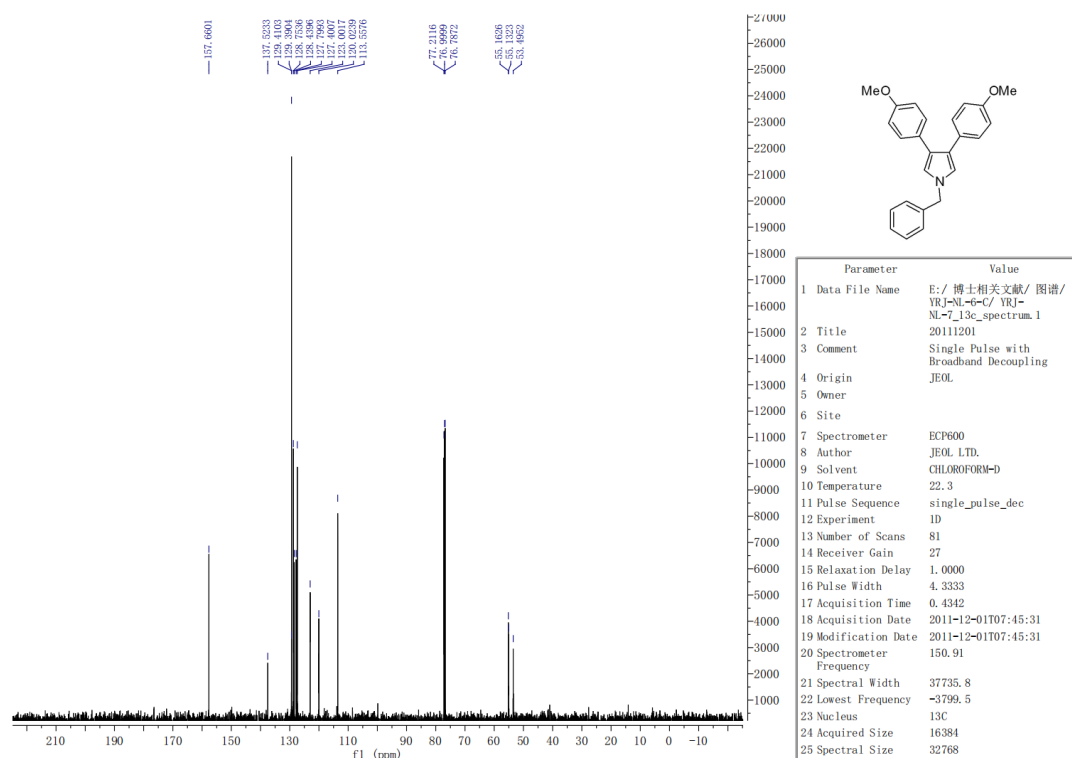


Figure S8. ^{13}C NMR spectrum of 4c

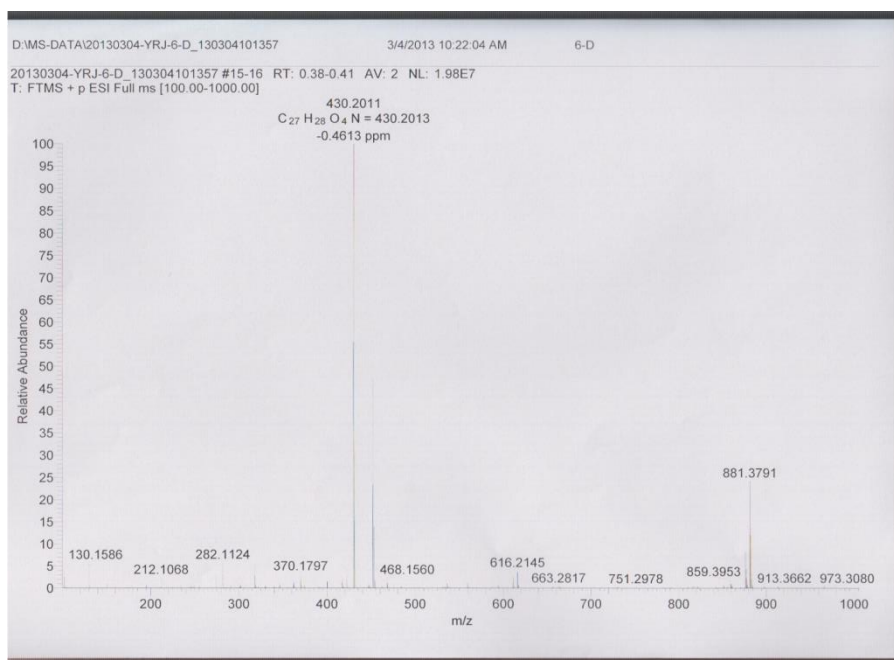


Figure S9. HRMS spectrum of **4d**

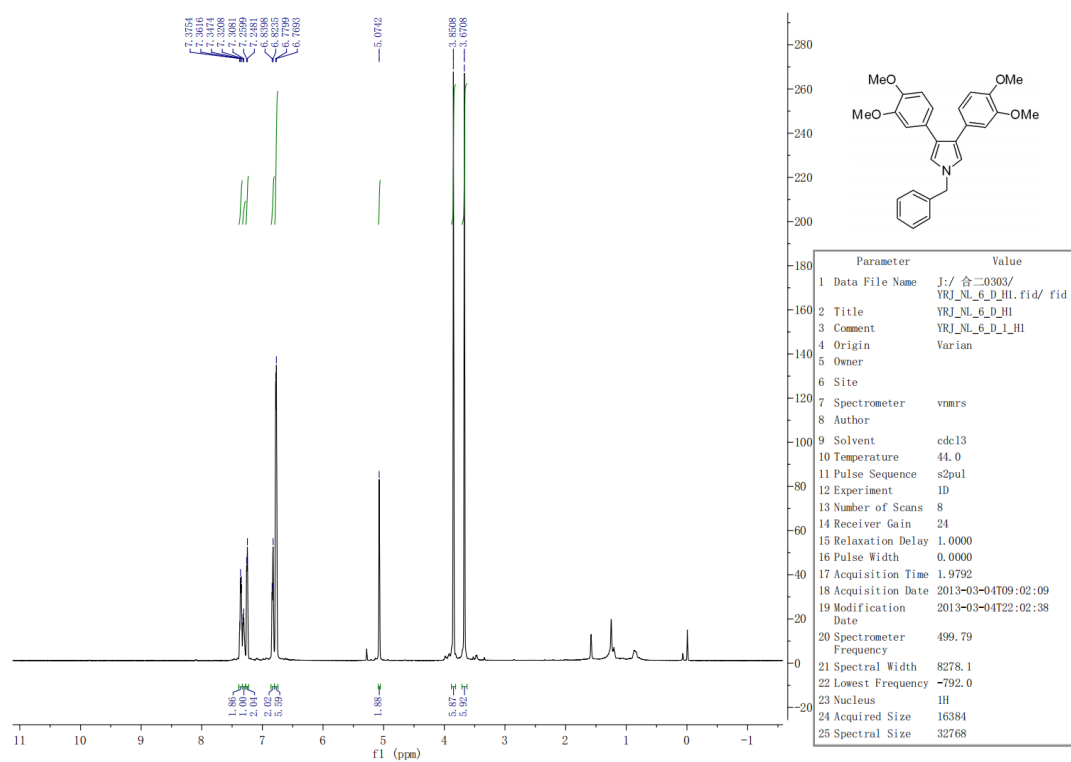


Figure S10. ¹H NMR spectrum of **4d**

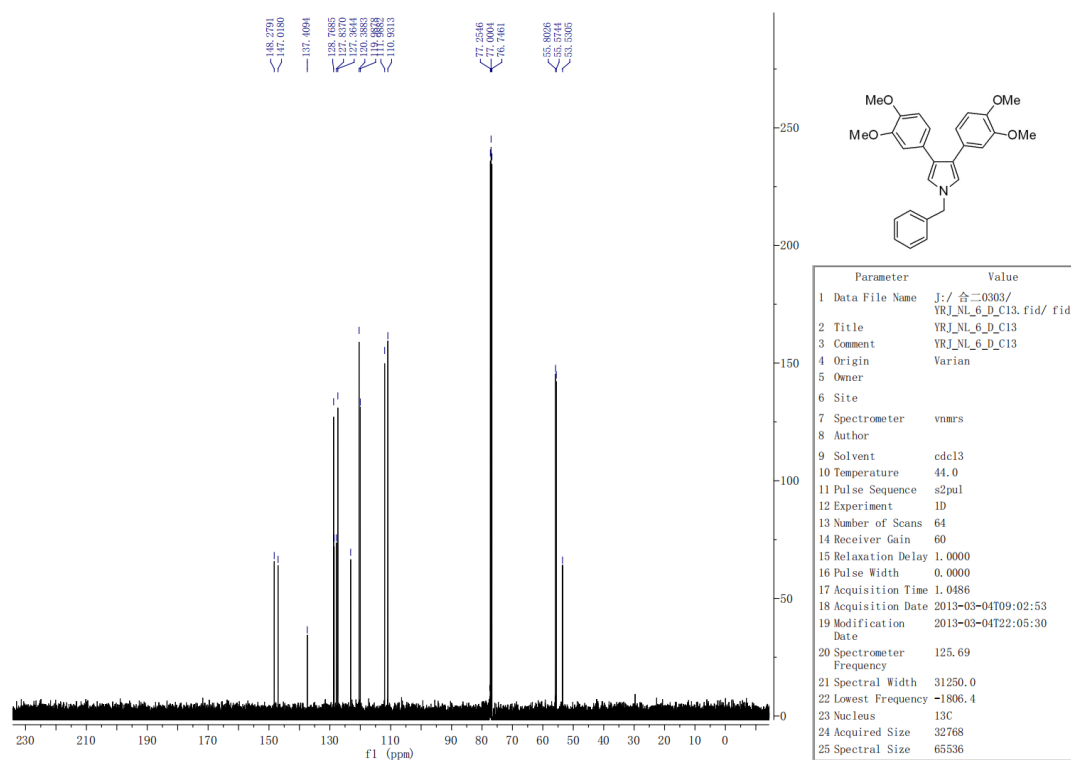


Figure S11. ^{13}C NMR spectrum of **4d**

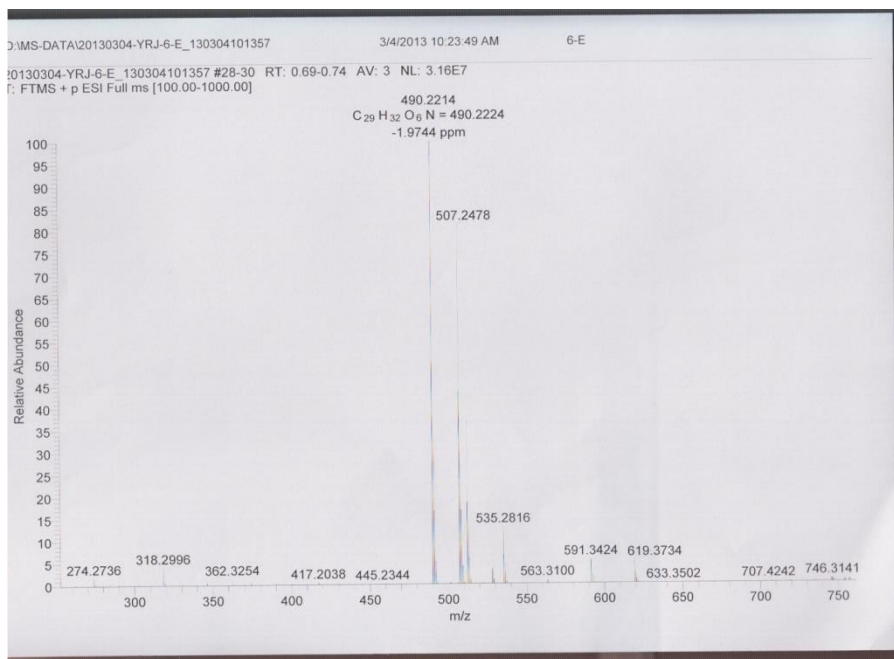


Figure S12. HRMS spectrum of **4e**

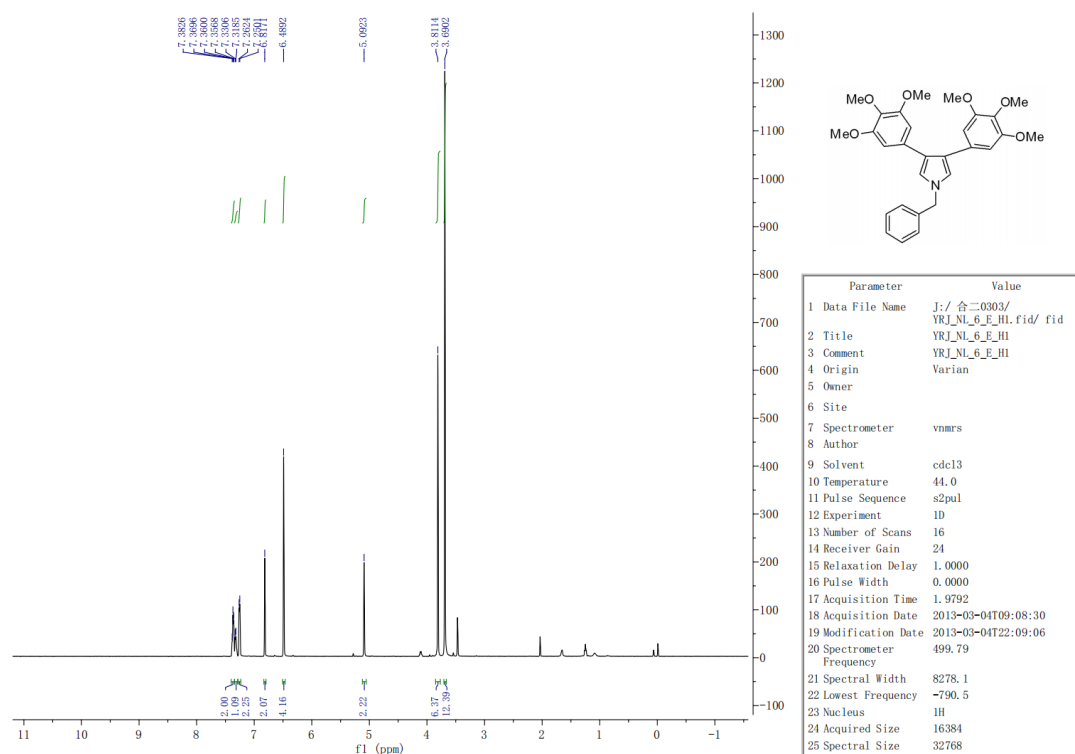


Figure S13. ^1H NMR spectrum of **4e**

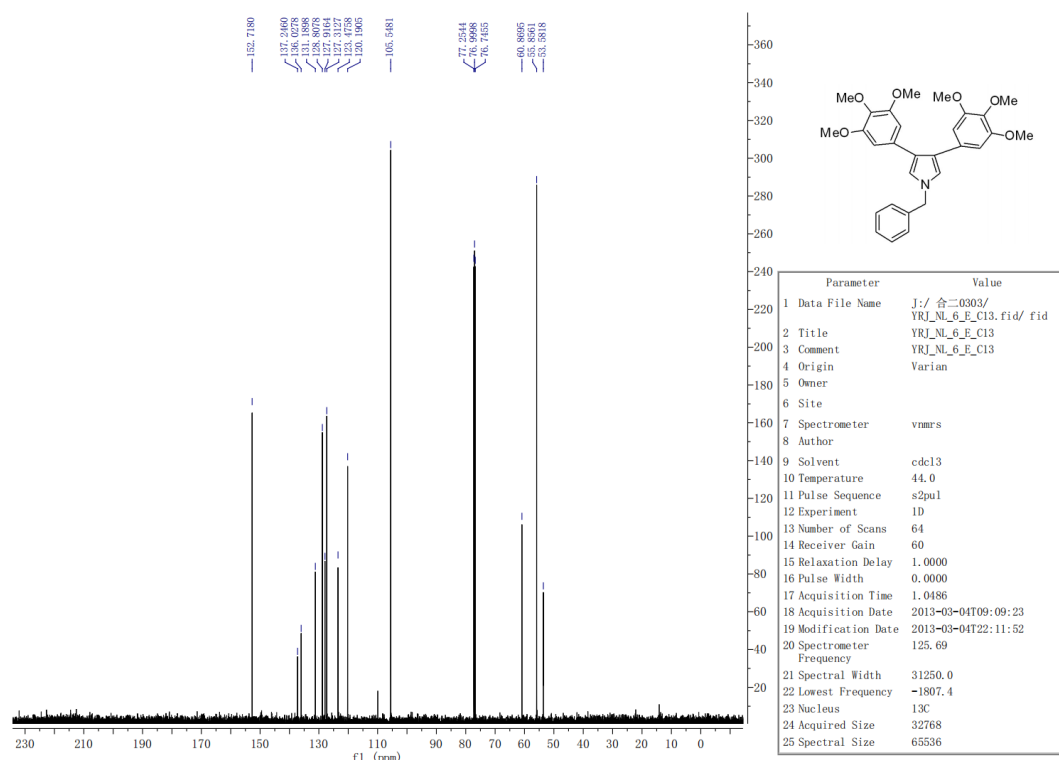


Figure S14. ^{13}C NMR spectrum of **4e**

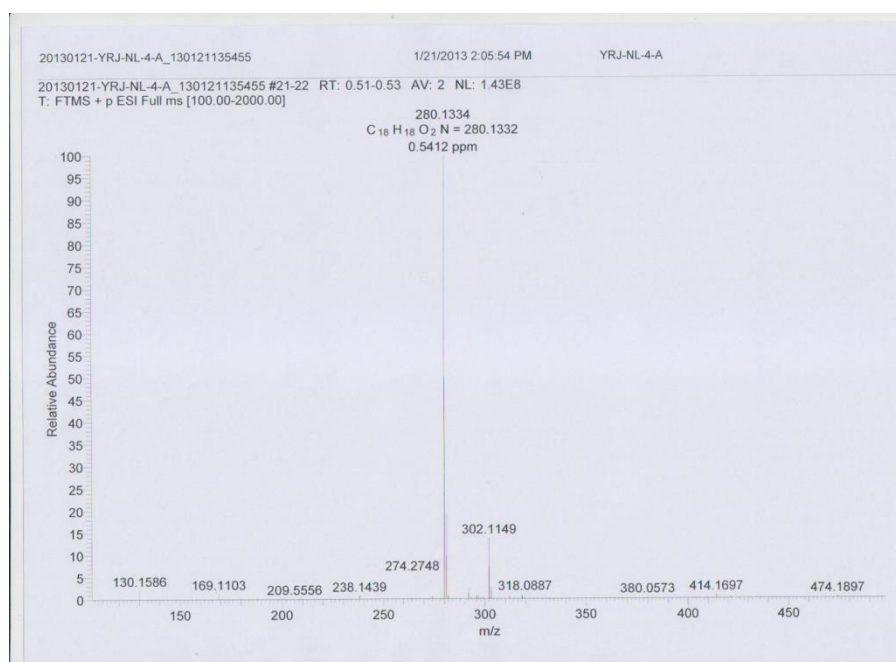


Figure S15. HRMS spectrum of **5a**

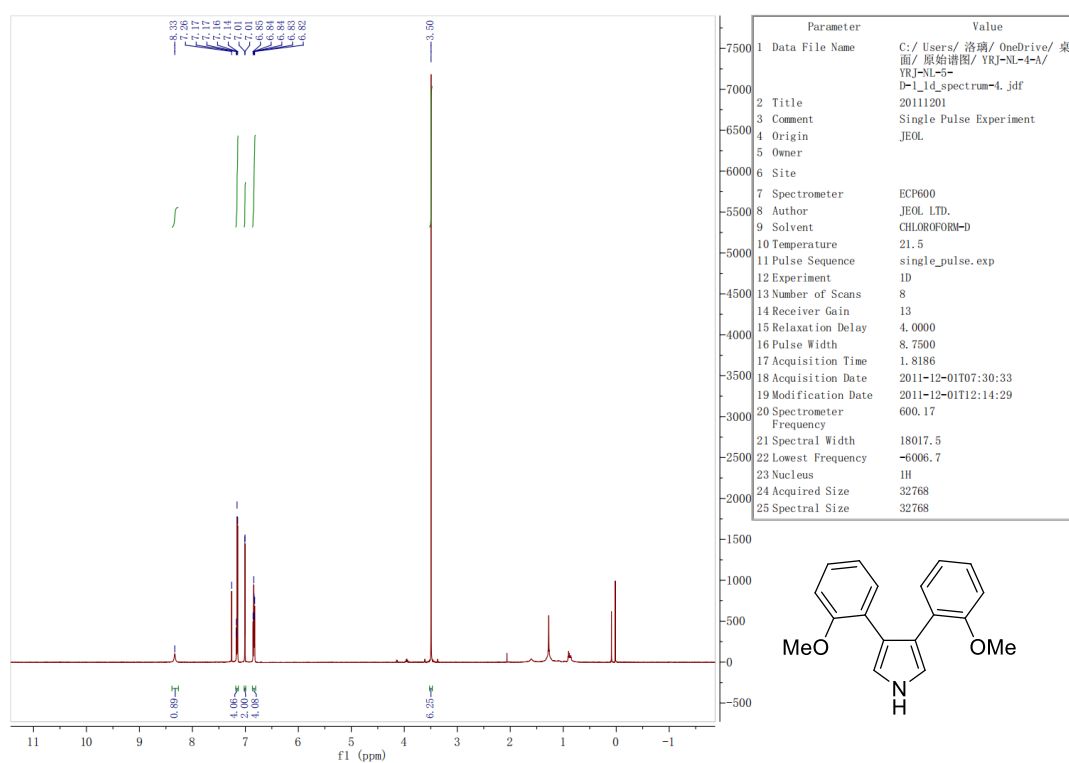


Figure S16. ¹H NMR spectrum of **5a**

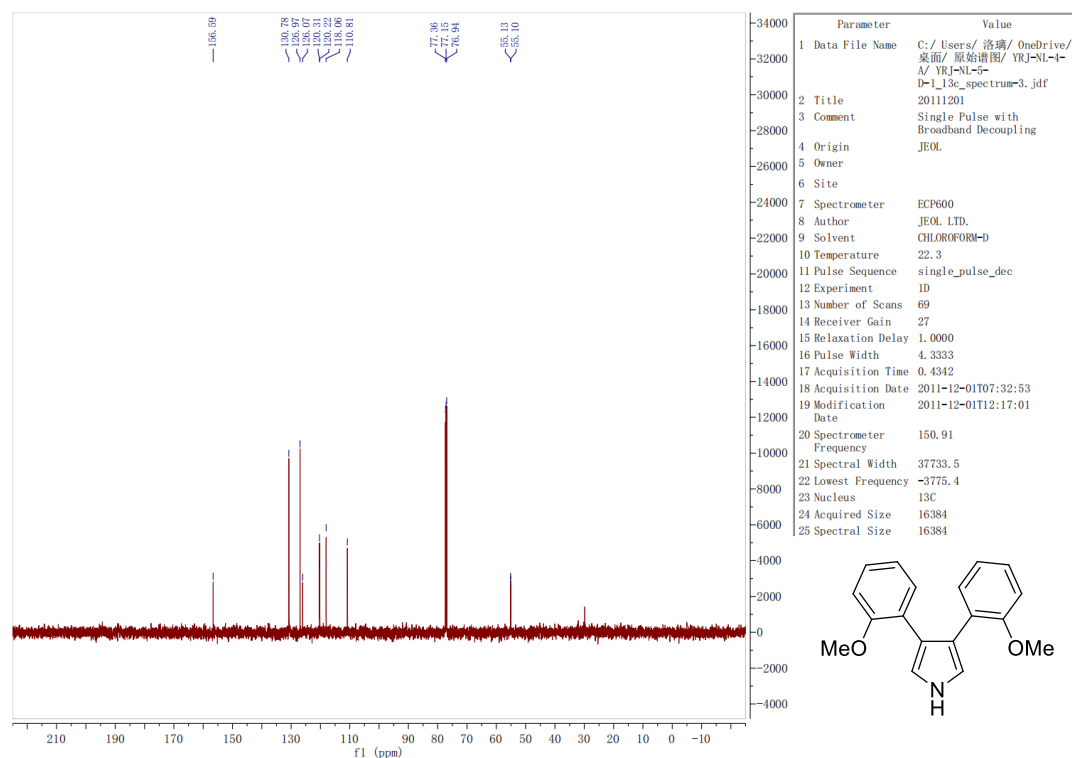


Figure S17. ^{13}C NMR spectrum of **5a**

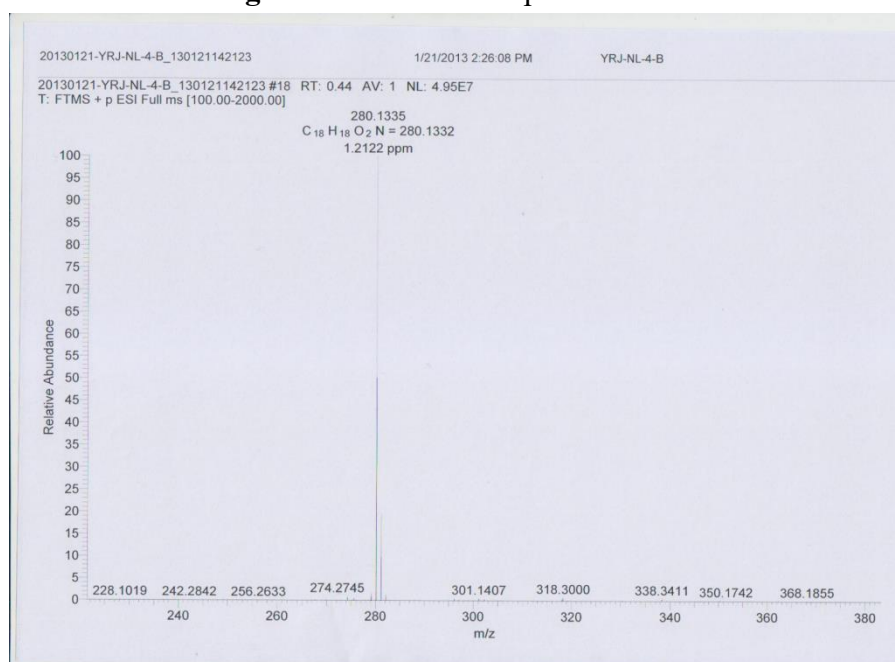


Figure S18. HRMS spectrum of **5b**

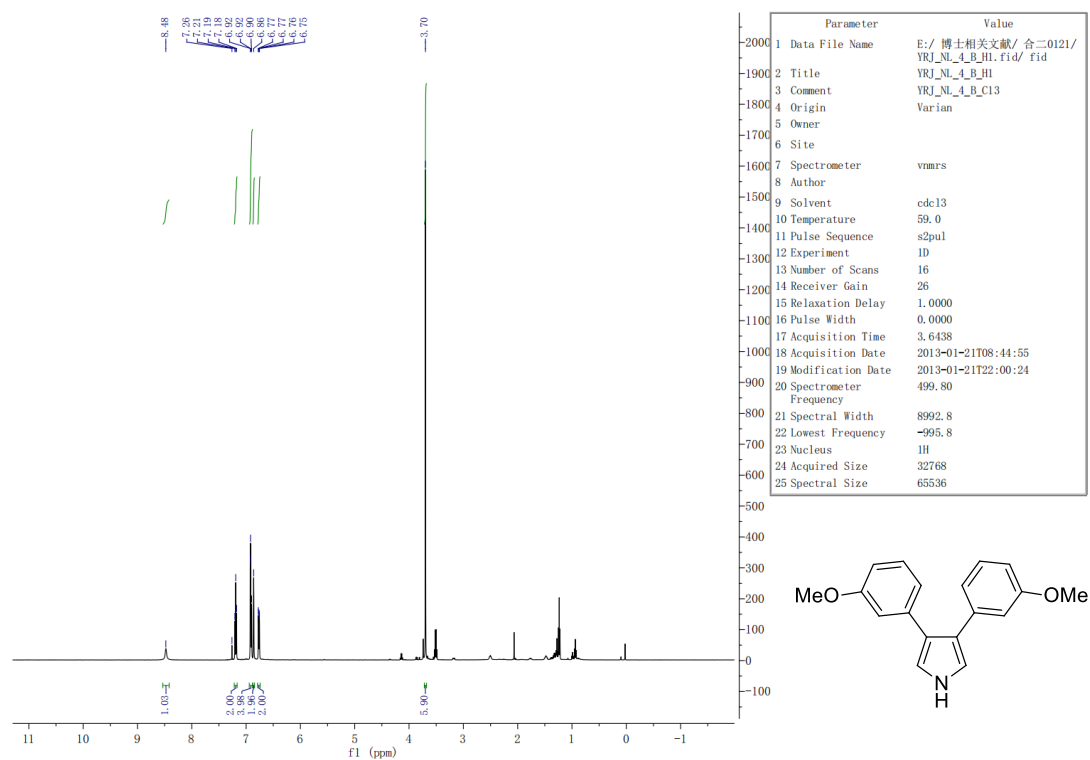


Figure S19. ^1H NMR spectrum of **5b**

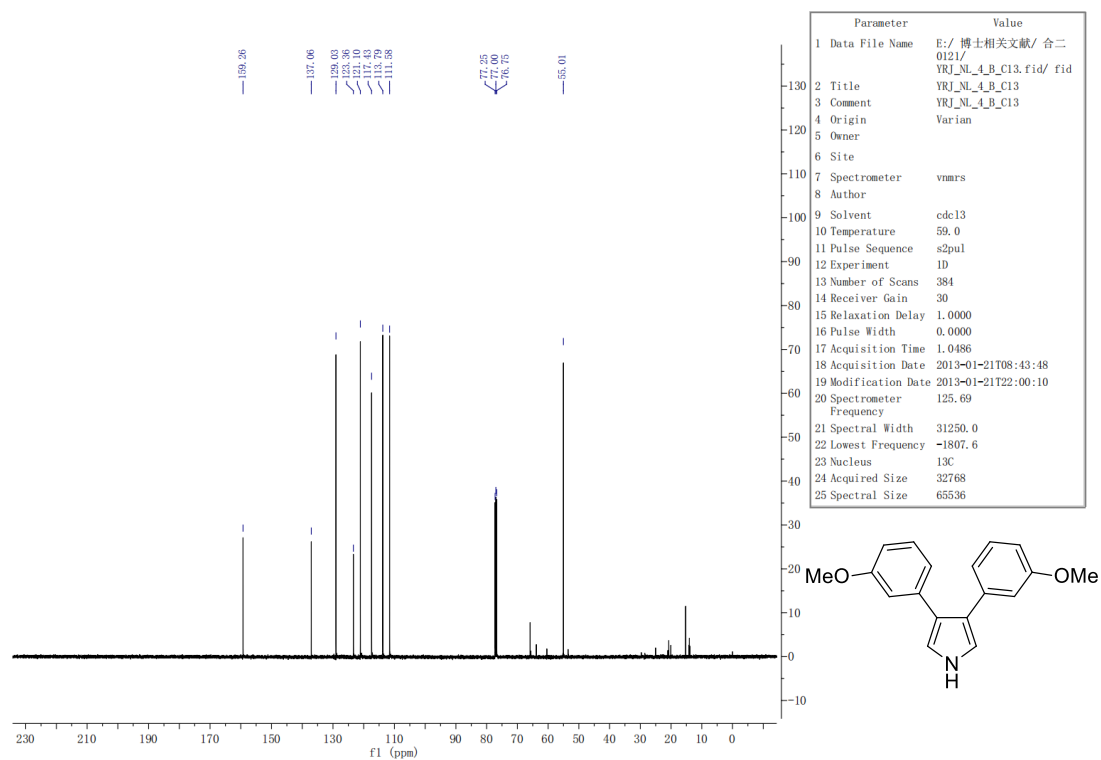


Figure S20. ^{13}C NMR spectrum of **5b**

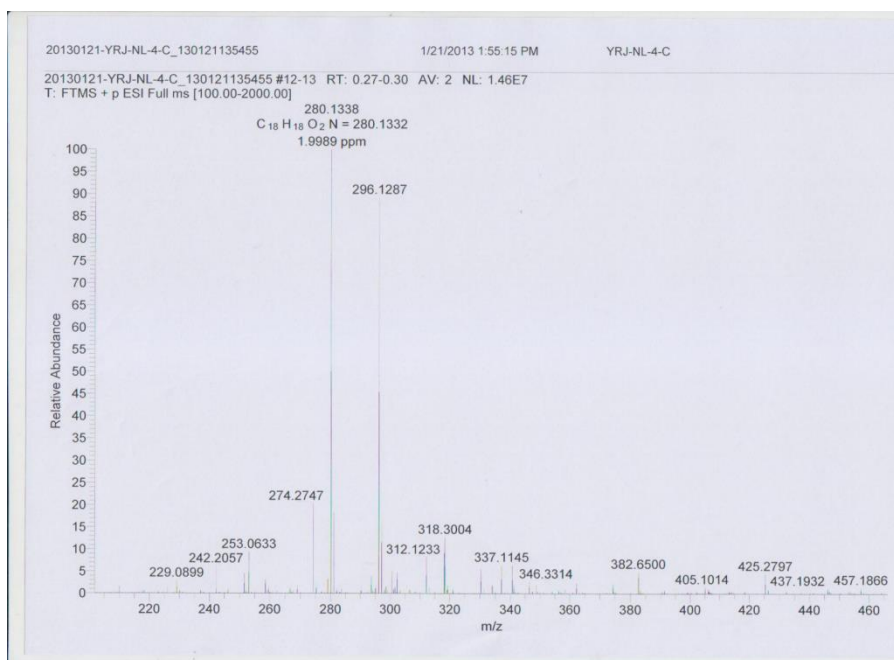


Figure S21. HRMS spectrum of **5c**

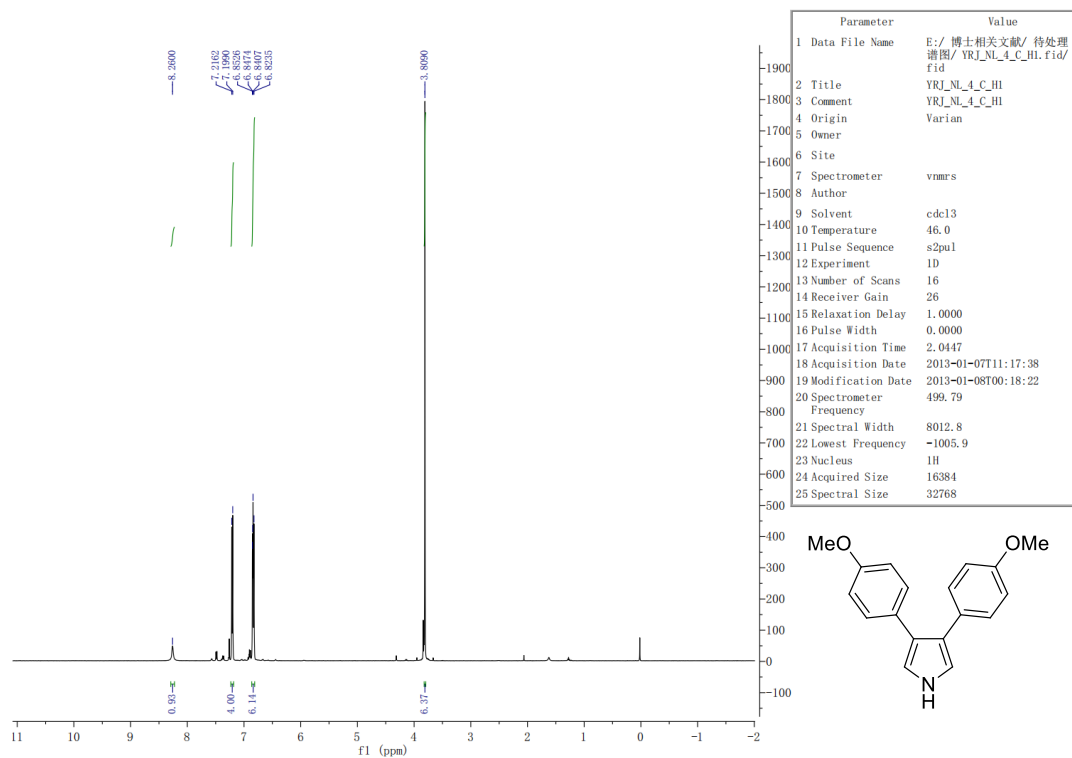


Figure S22. ^1H NMR spectrum of **5c**

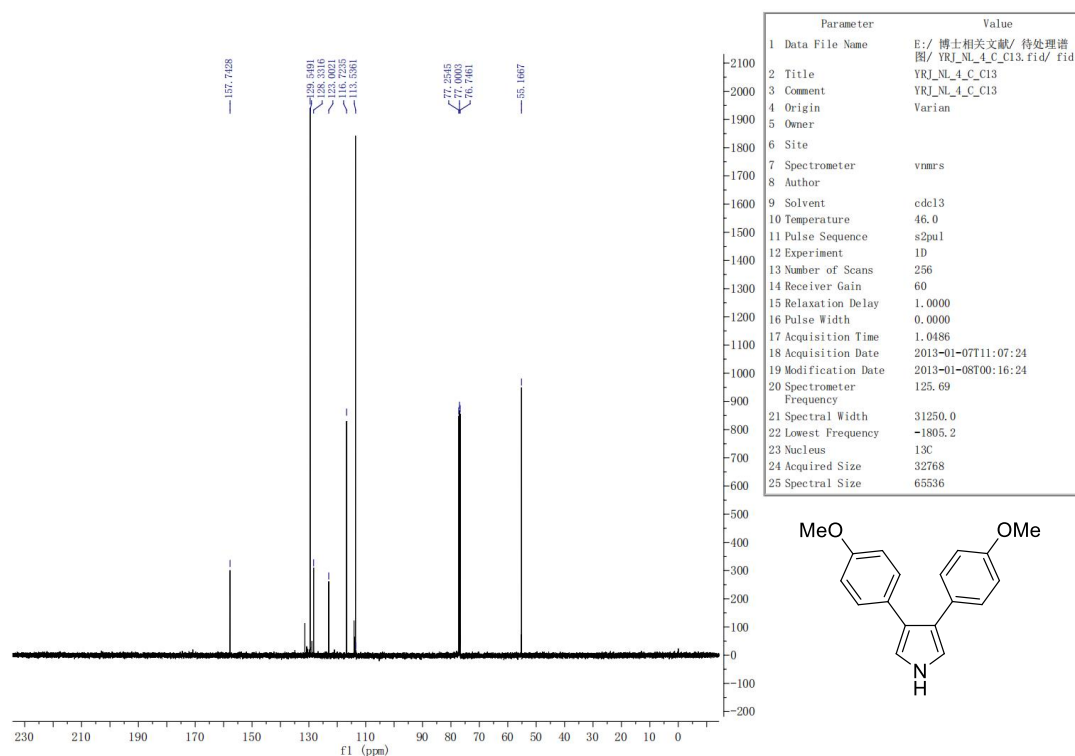


Figure S23. ^{13}C NMR spectrum of **5c**

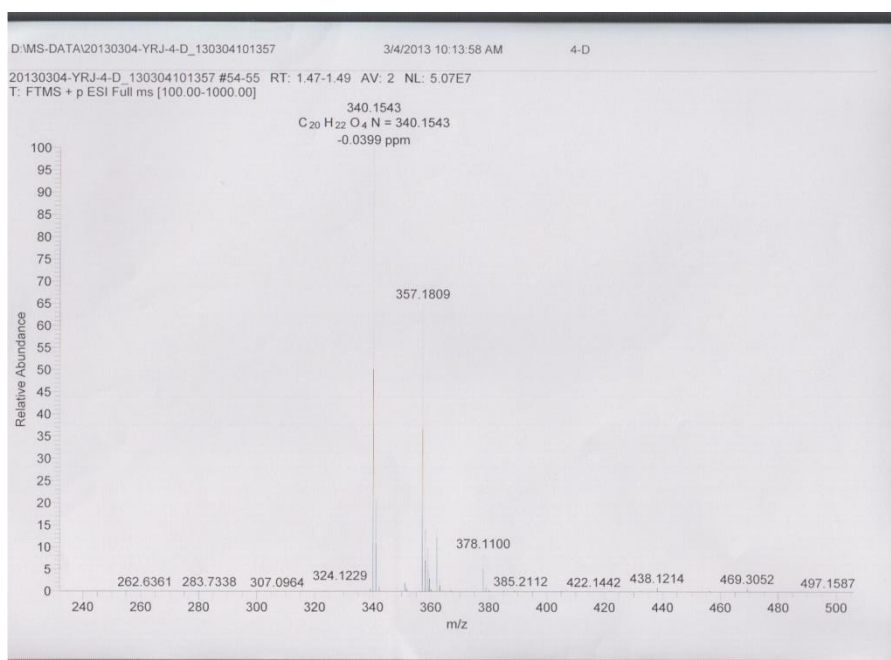


Figure S24. HRMS spectrum of **5d**

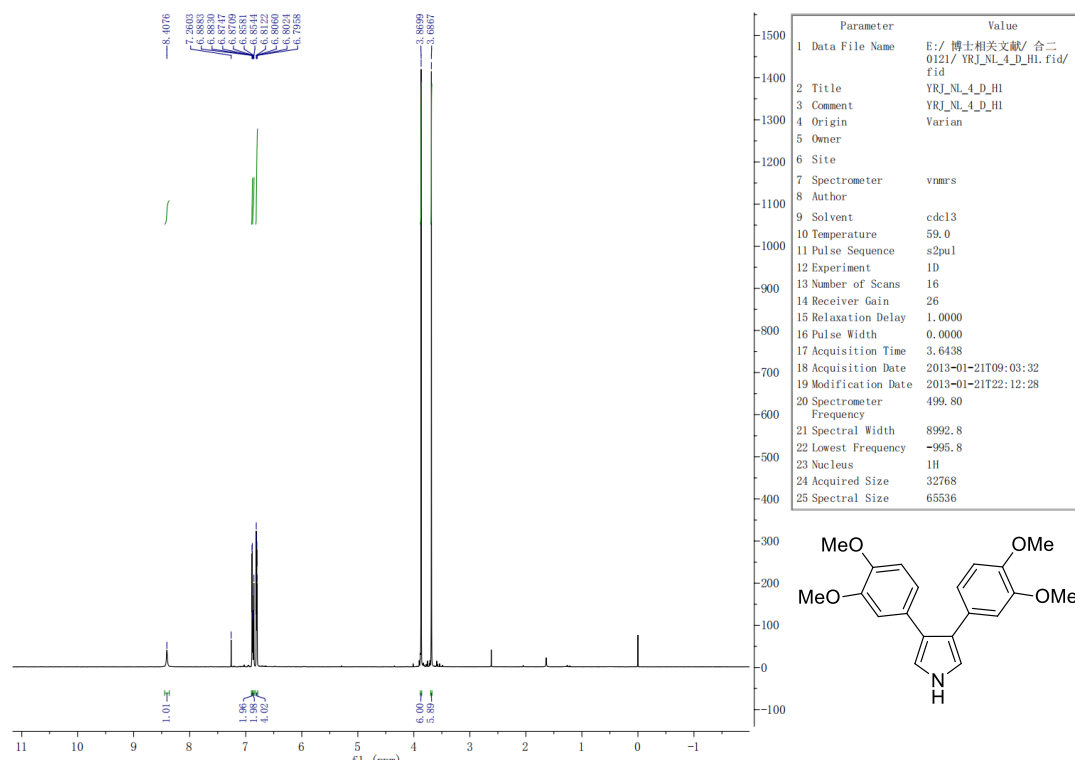


Figure S25. ¹H NMR spectrum of 5d

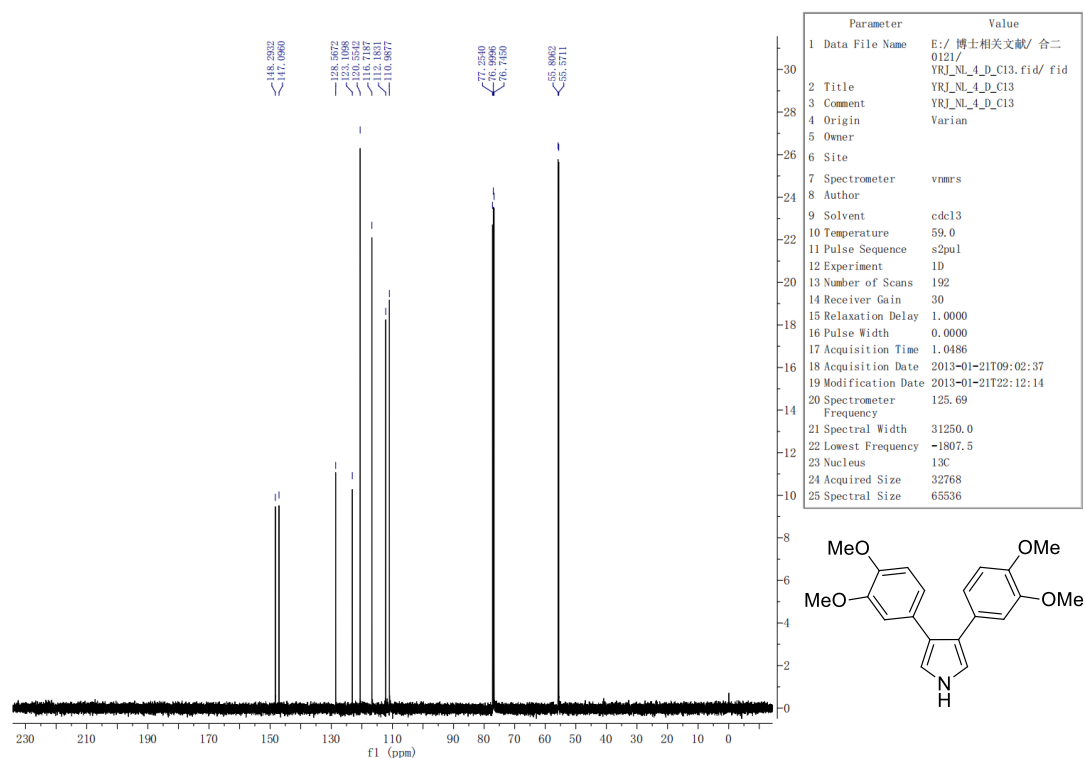


Figure S26. ¹³C NMR spectrum of 5d

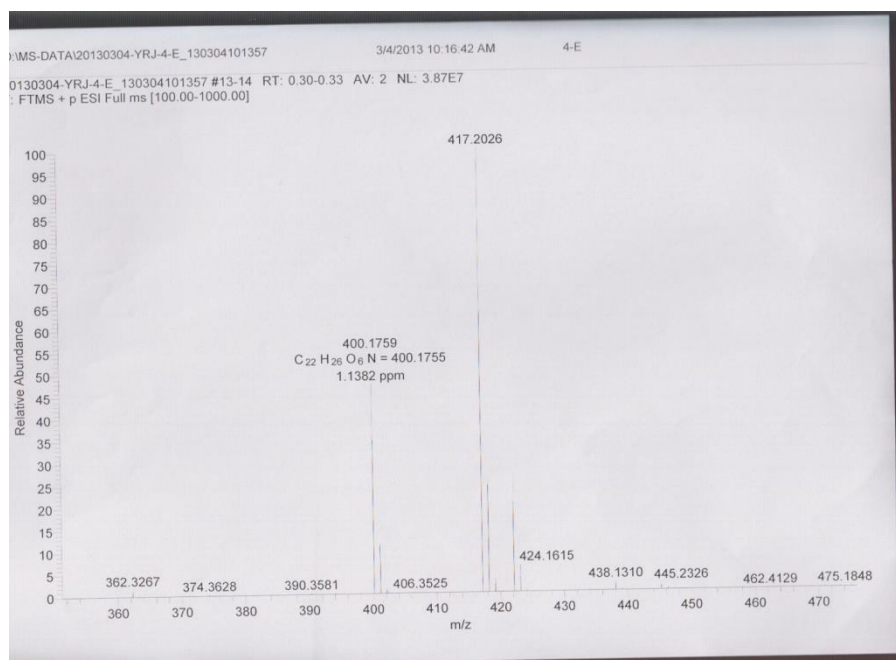


Figure 27. HRMS spectrum of **5e**

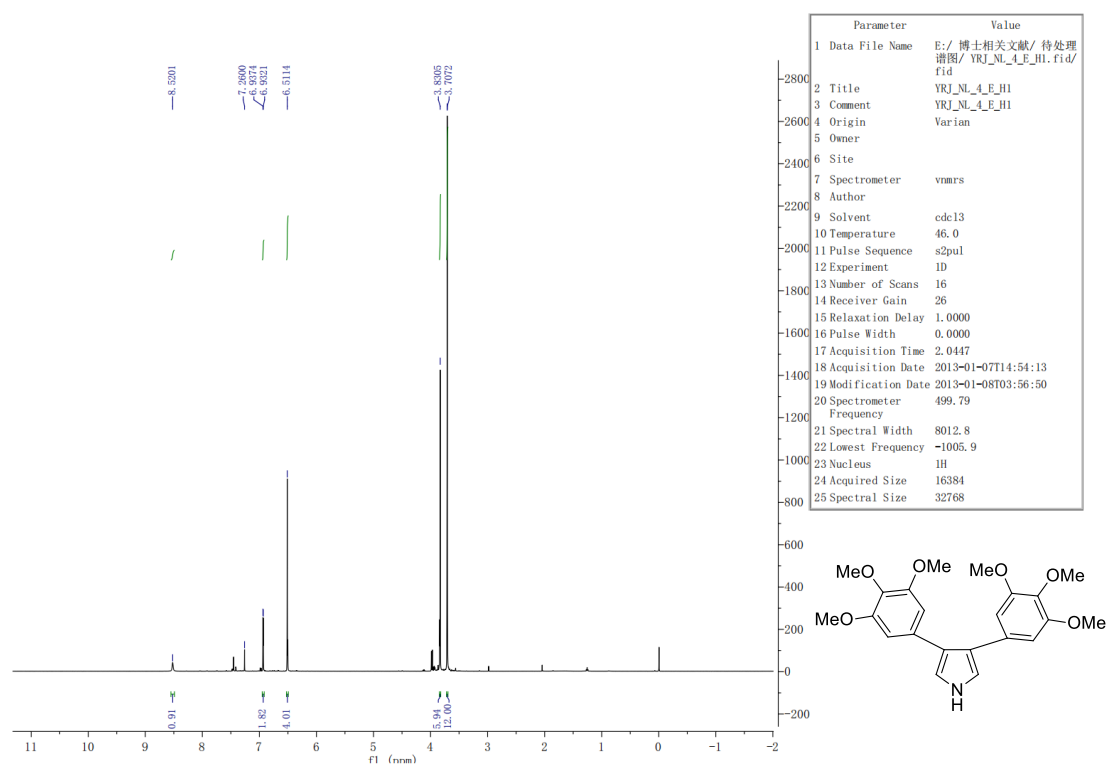


Figure S28. ¹H NMR spectrum of **5e**

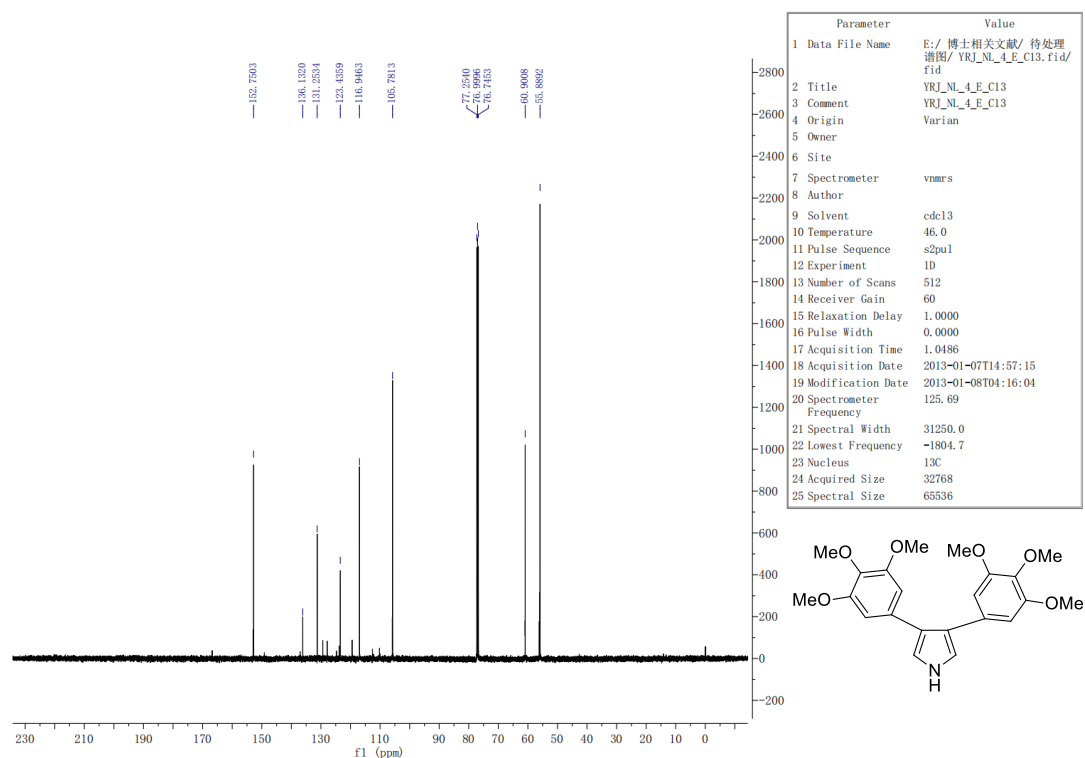


Figure S29. ^{13}C NMR spectrum of **5e**

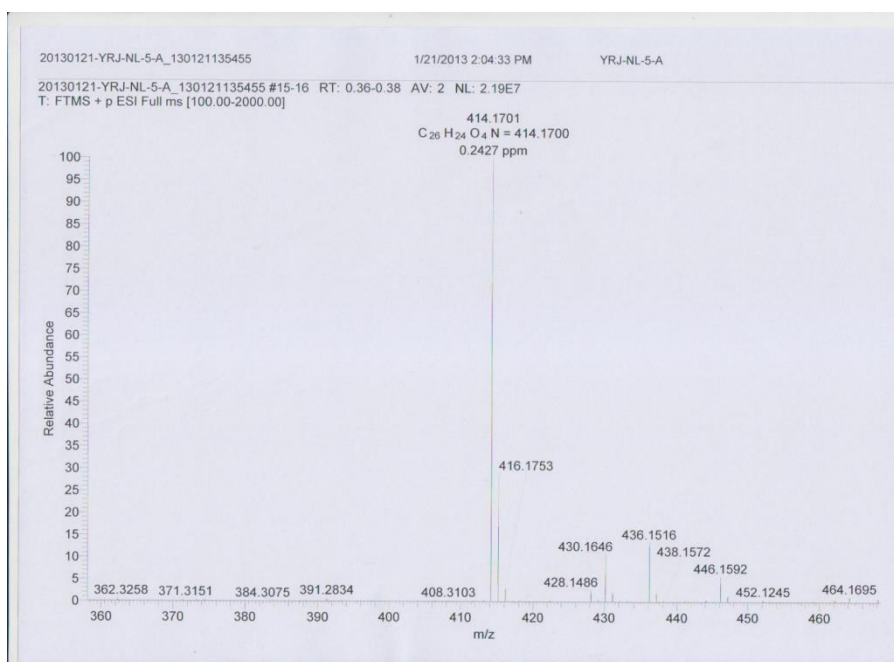


Figure S30. HRMS spectrum of **1a**

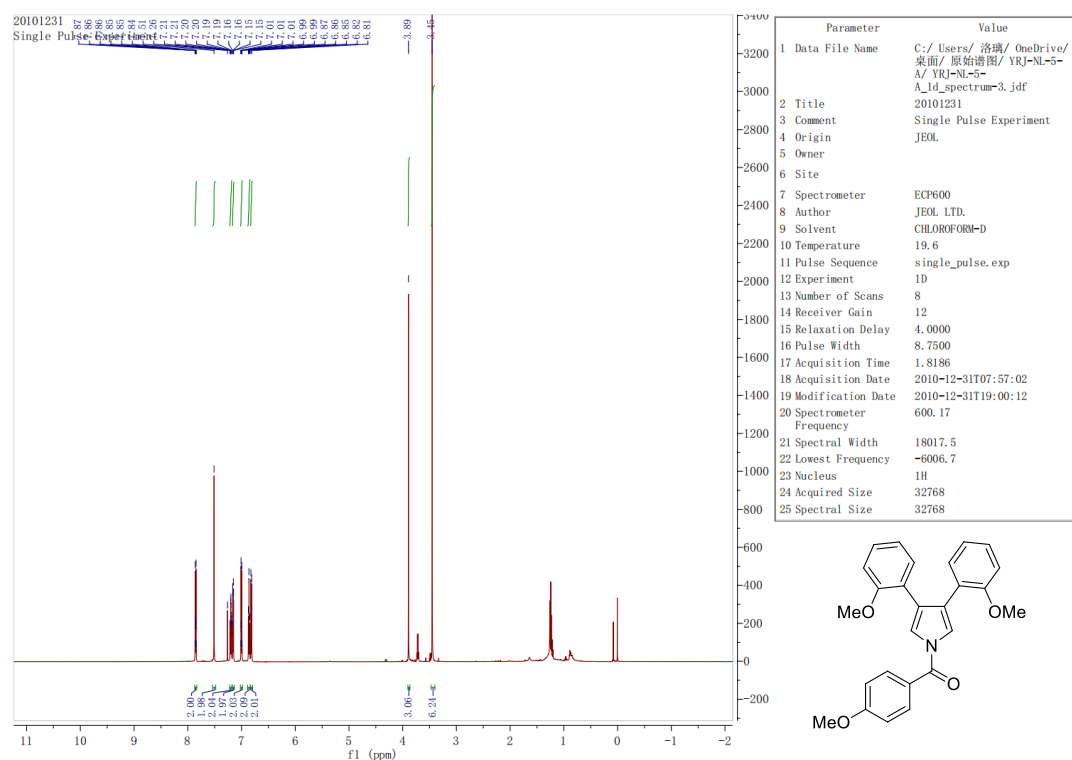


Figure S31. ^1H NMR spectrum of 1a

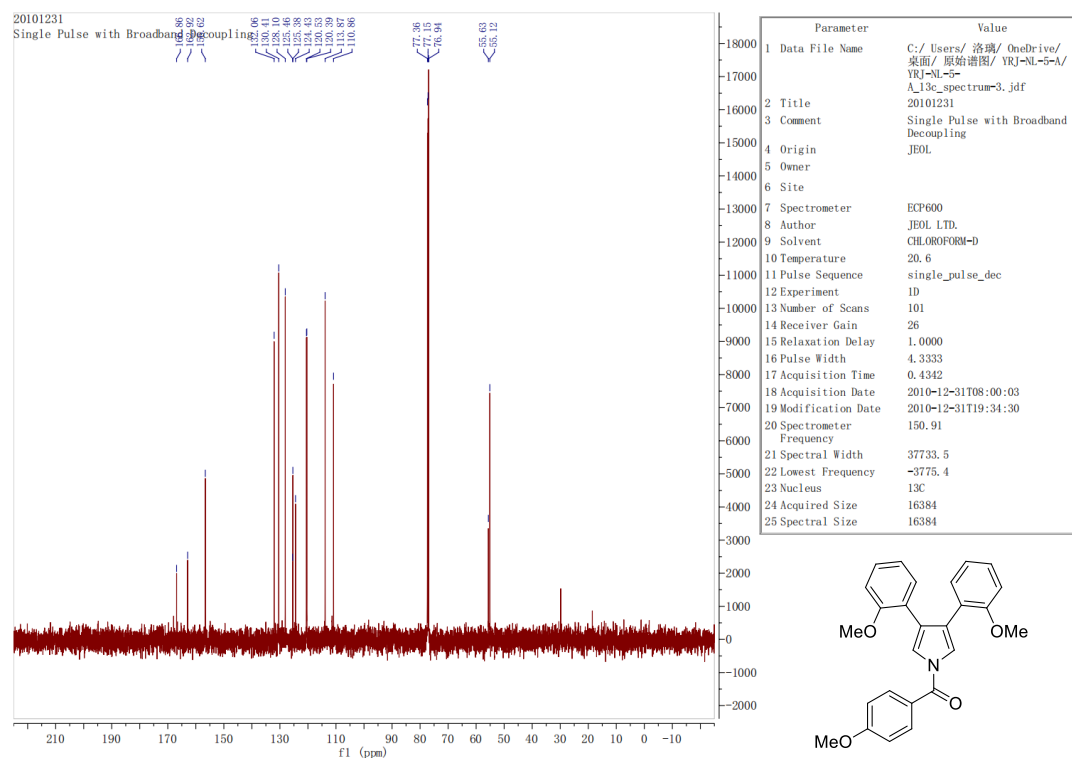
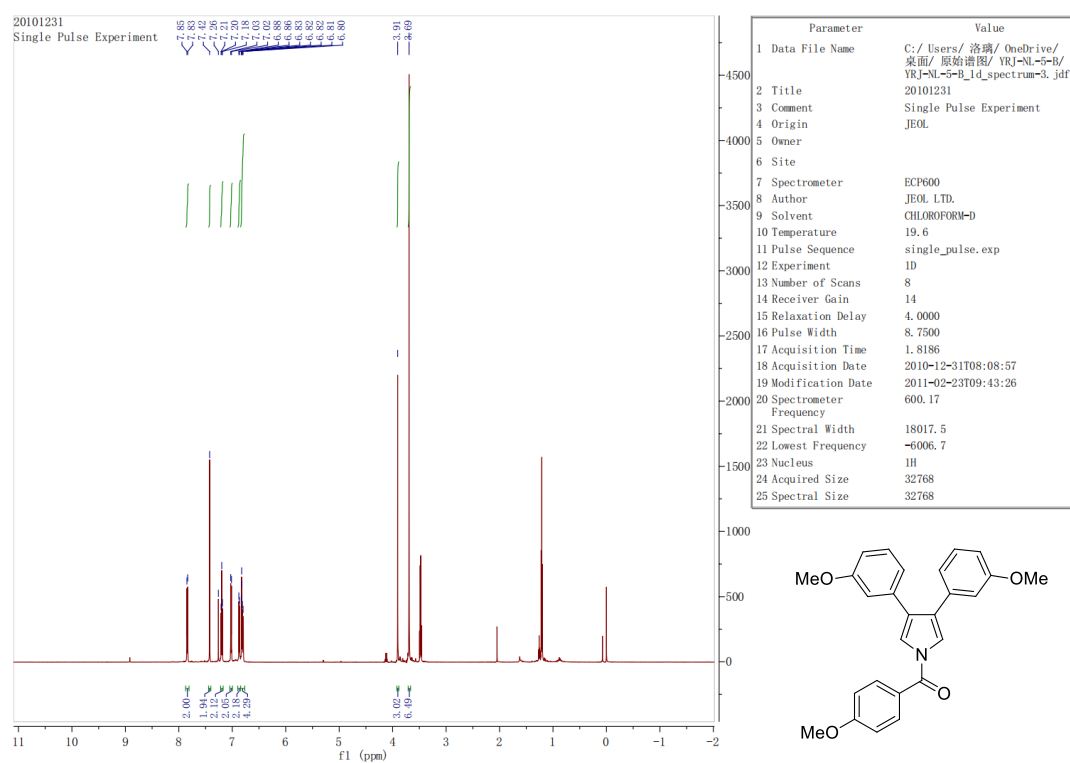
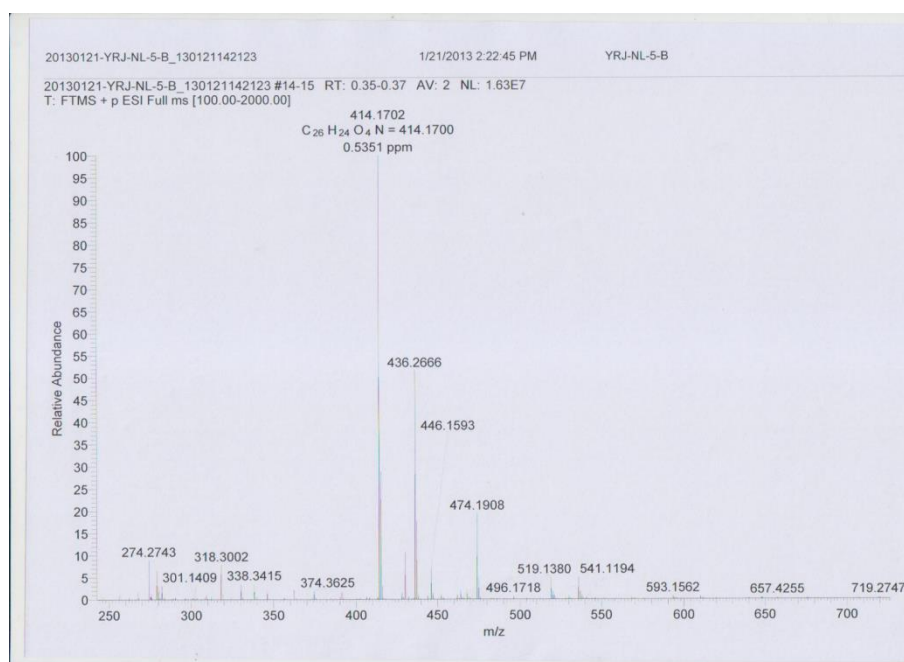


Figure S32. ^{13}C NMR spectrum of 1a



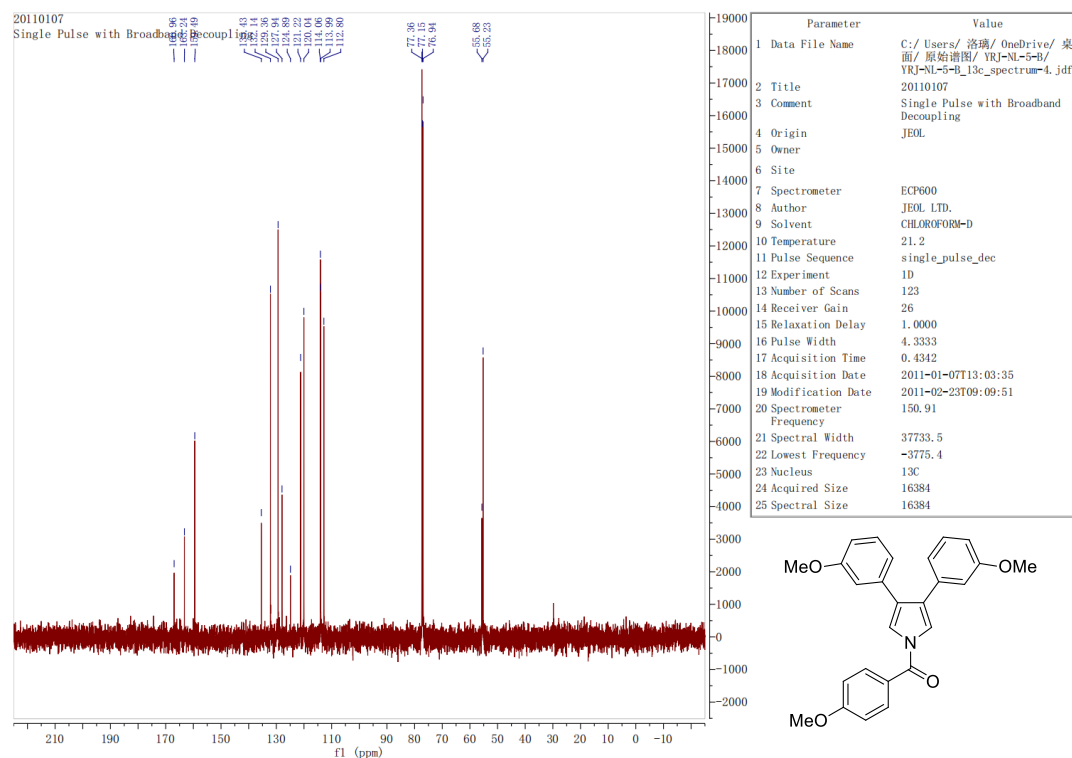


Figure S35. ^{13}C NMR spectrum of **1b**

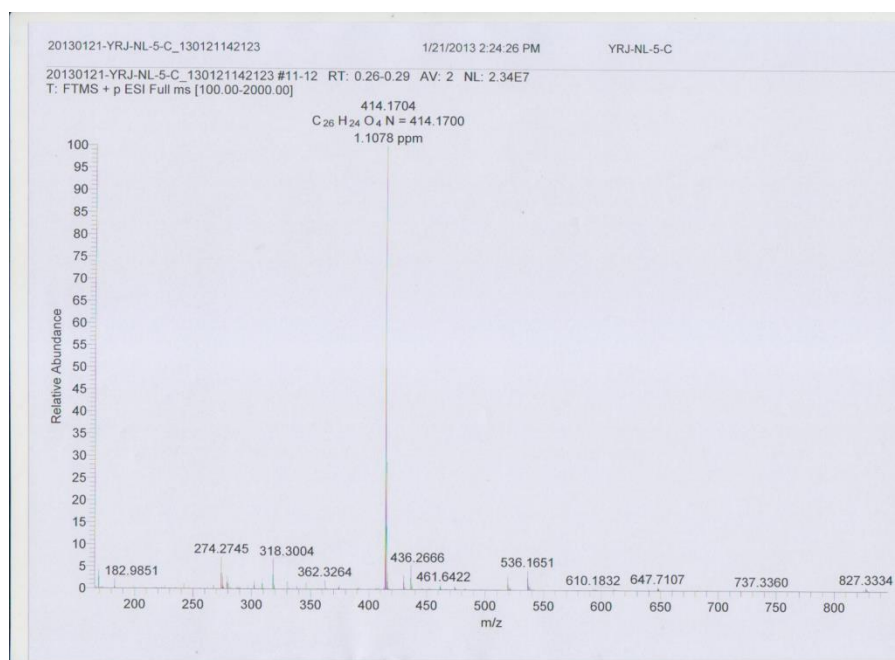
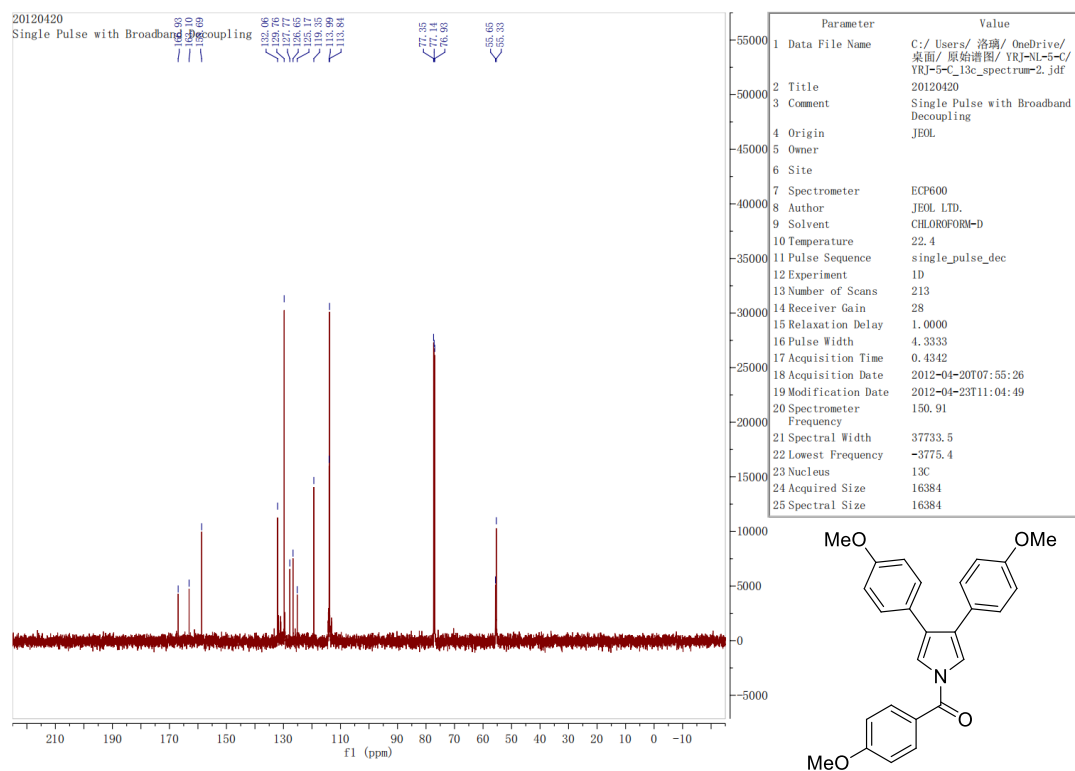
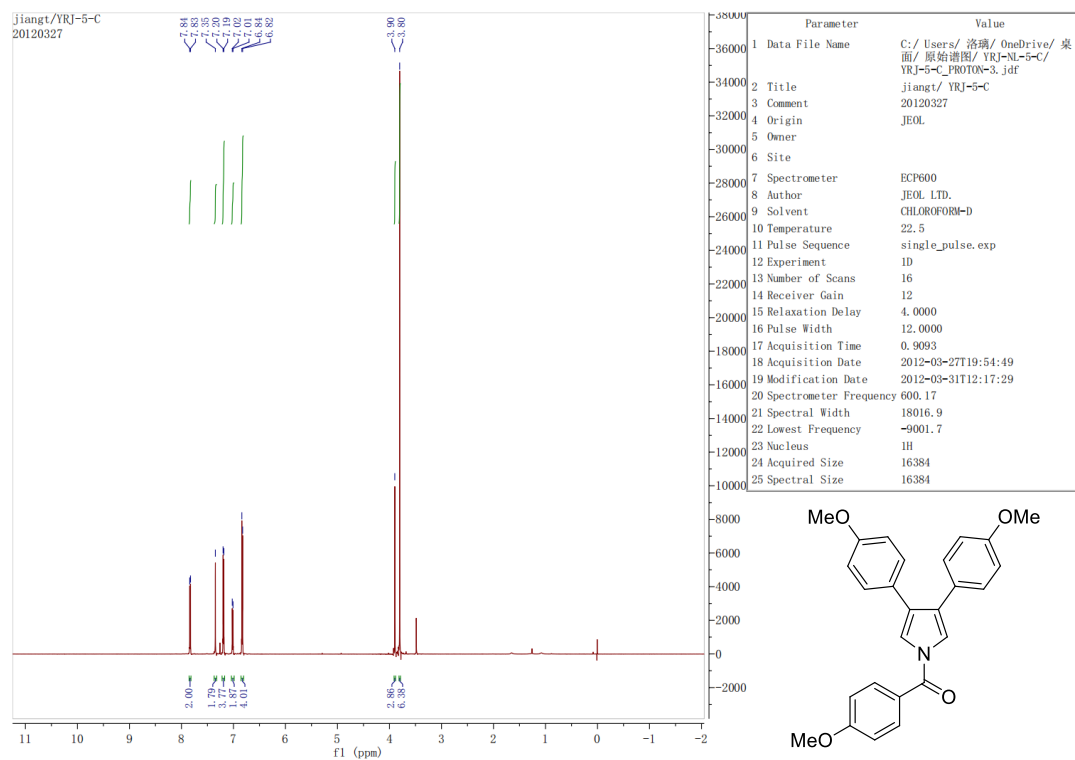


Figure S36. HRMS spectrum of **1c**



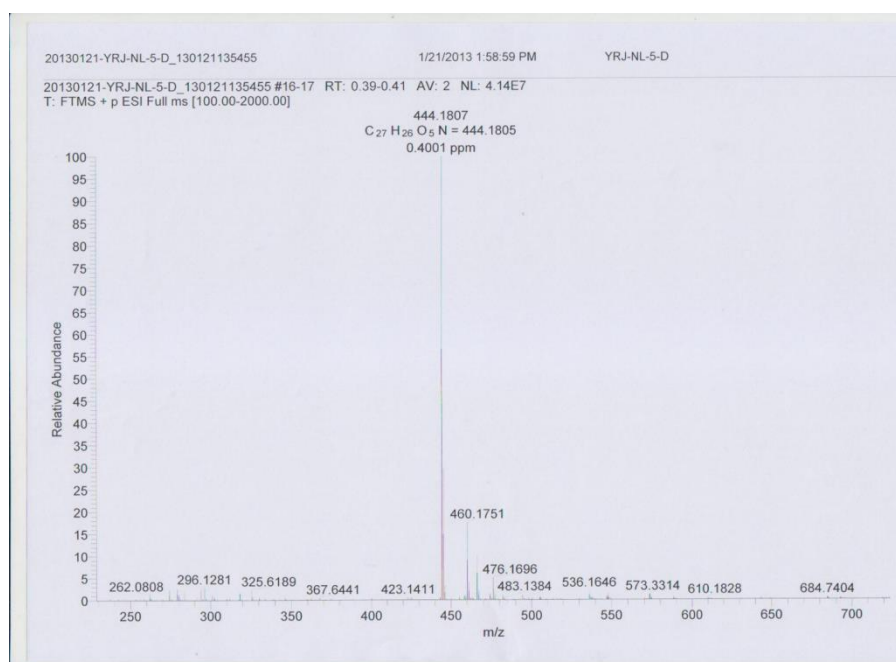


Figure S39. HRMS spectrum of **1d**

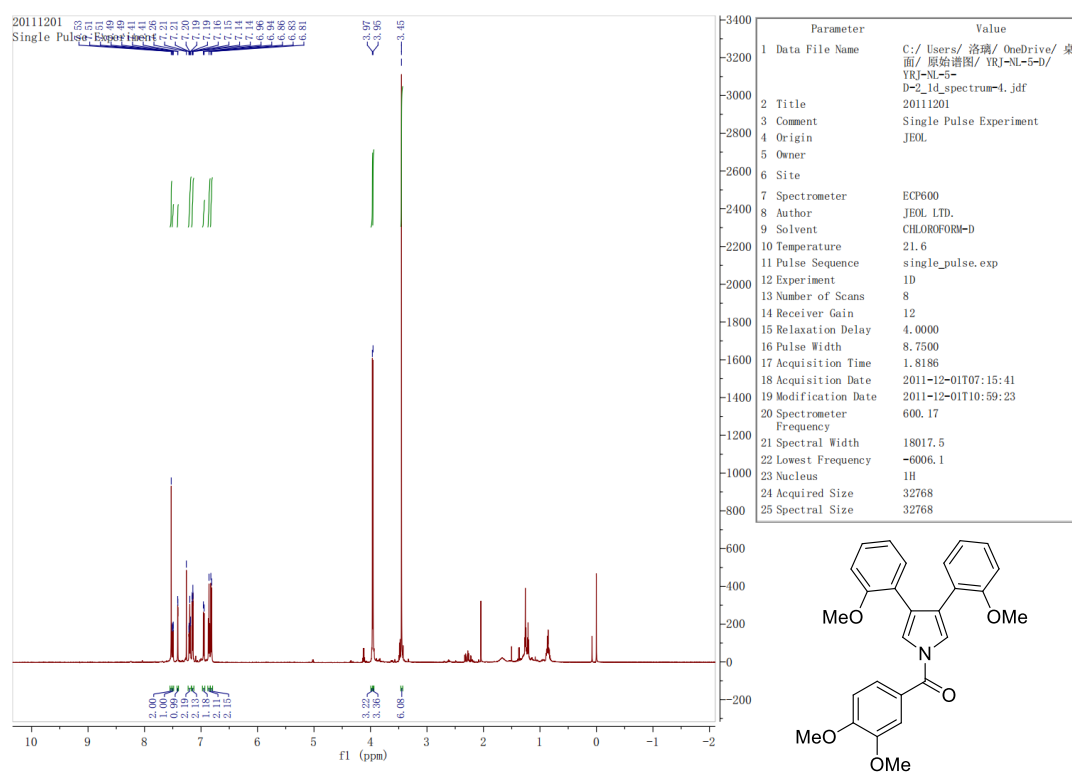


Figure S40. ¹H NMR spectrum of **1d**

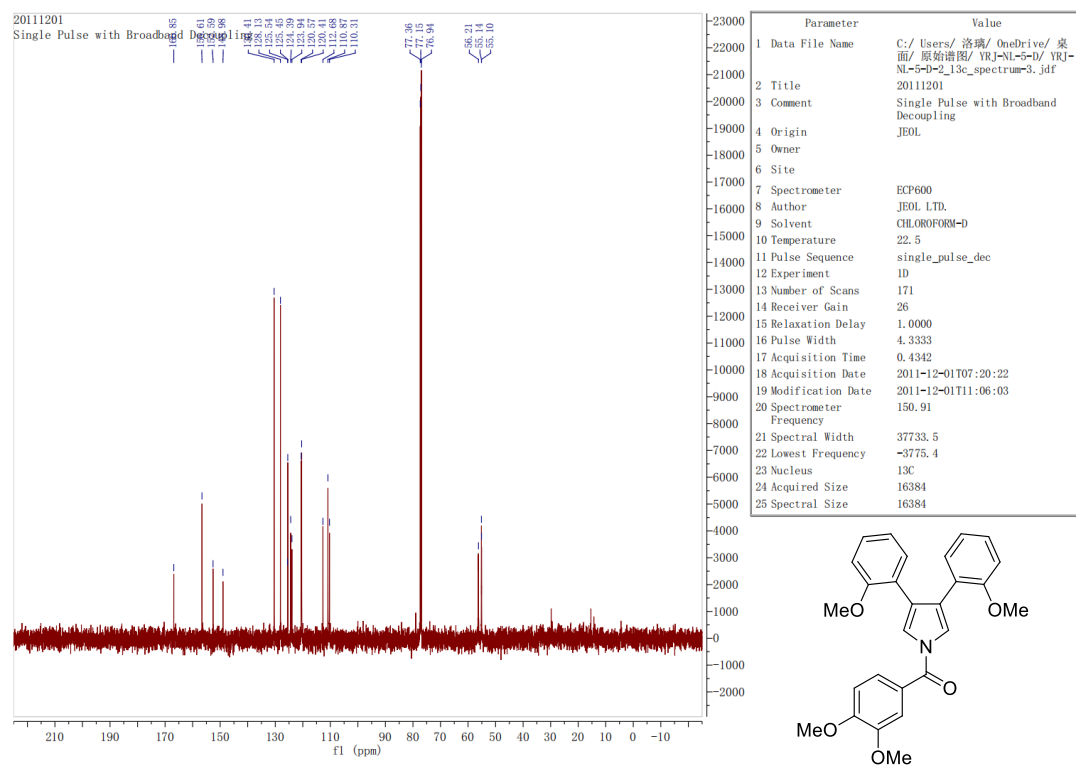


Figure S41. ^{13}C NMR spectrum of 1d

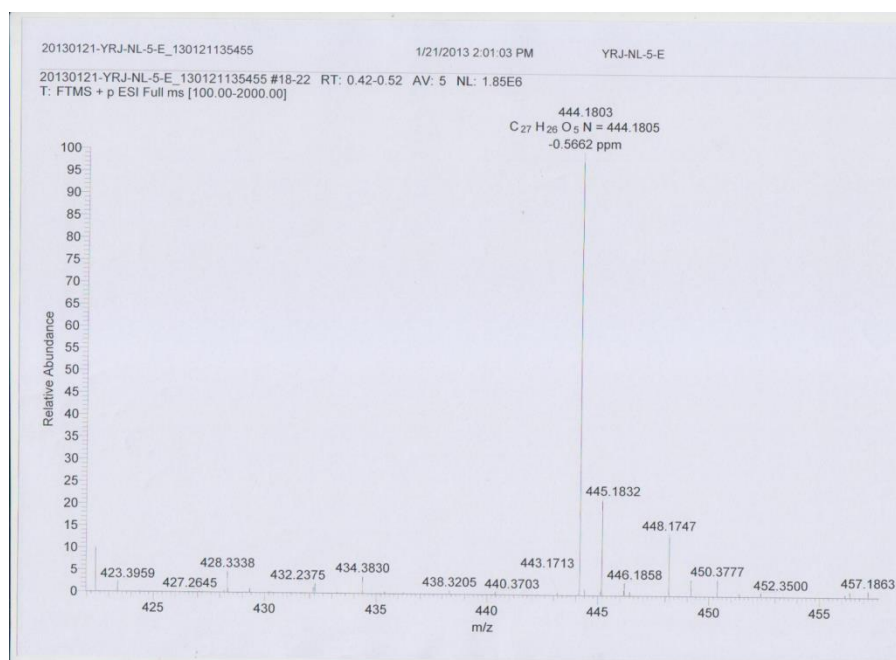


Figure S42. HRMS spectrum of 1e

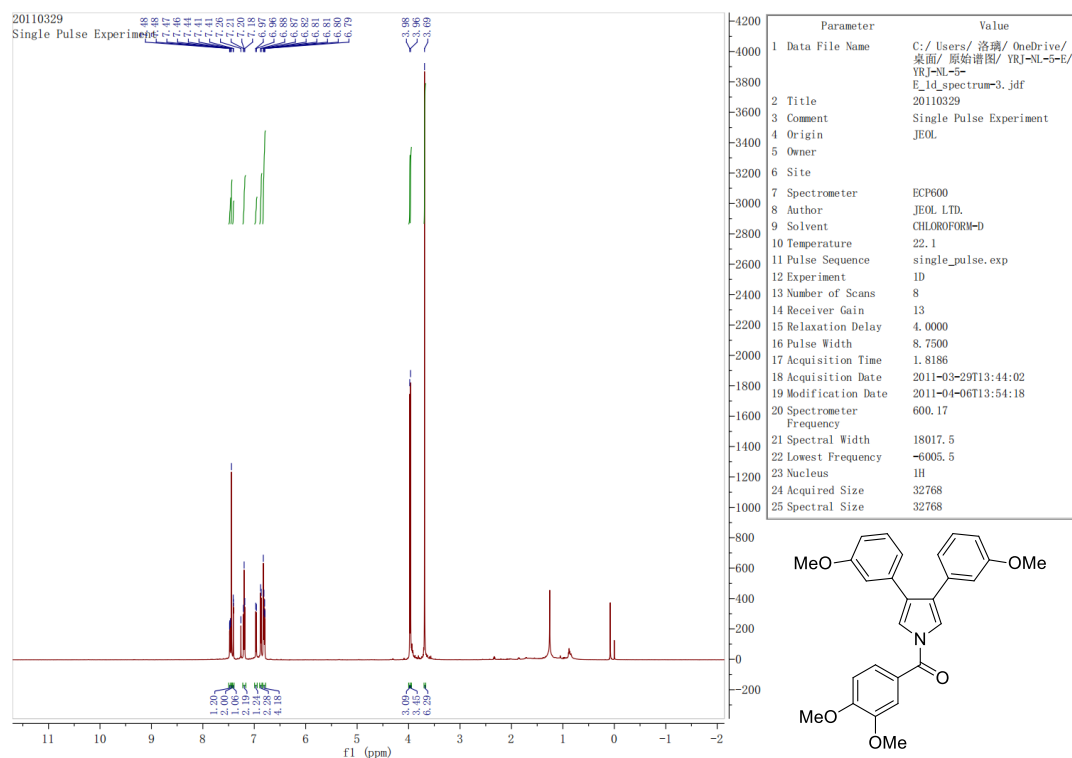


Figure S43. ^1H NMR spectrum of 1e

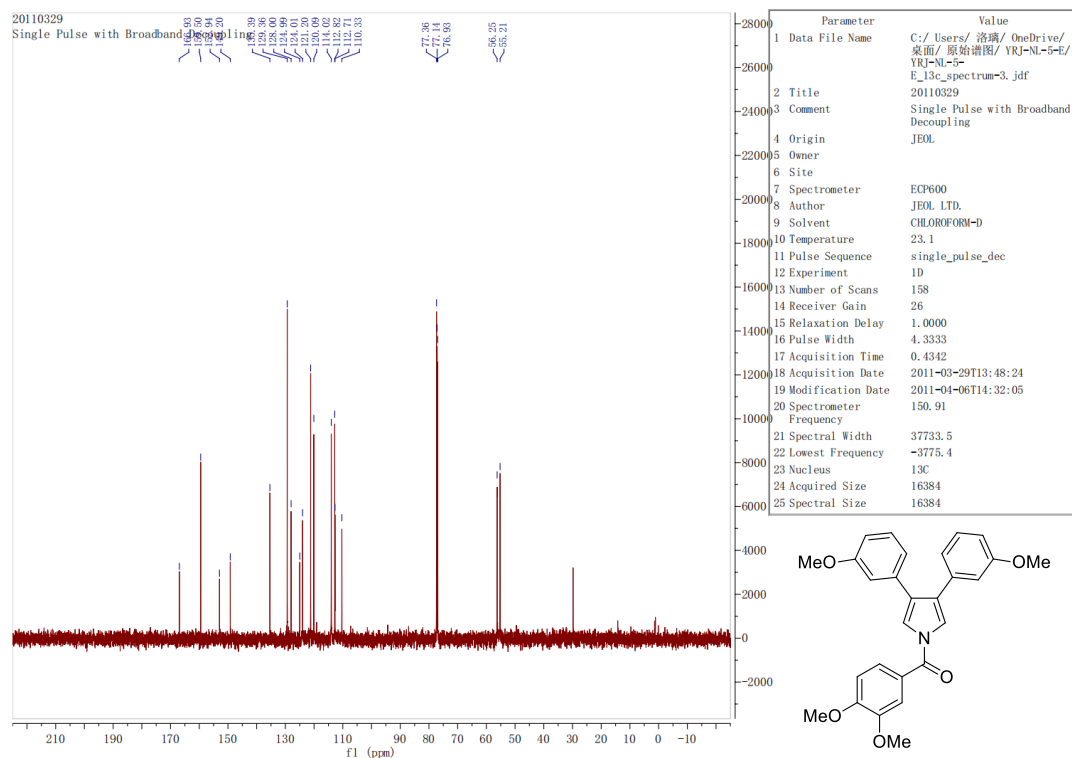


Figure S44. ^{13}C NMR spectrum of 1e

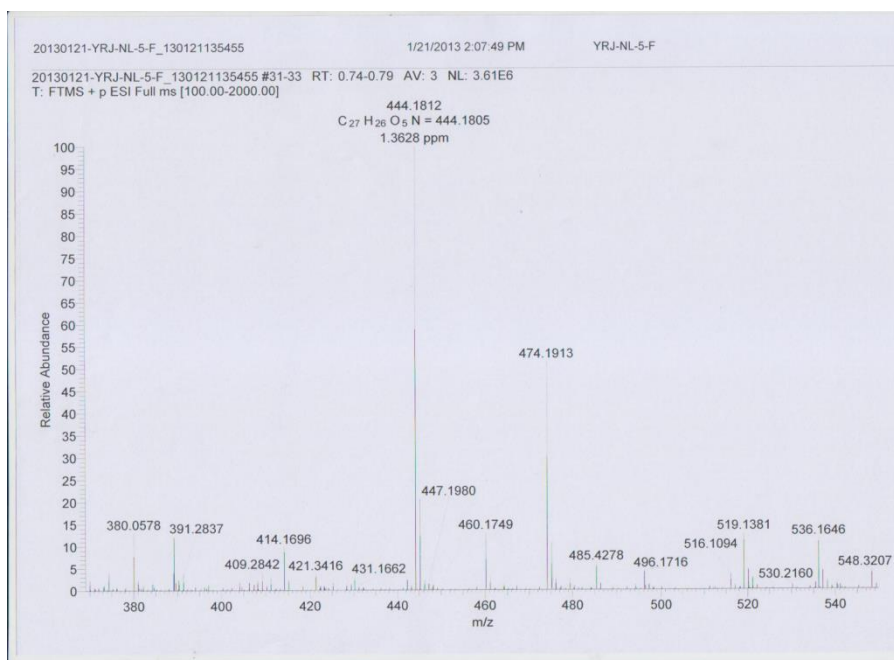


Figure S45. HRMS spectrum of **1f**

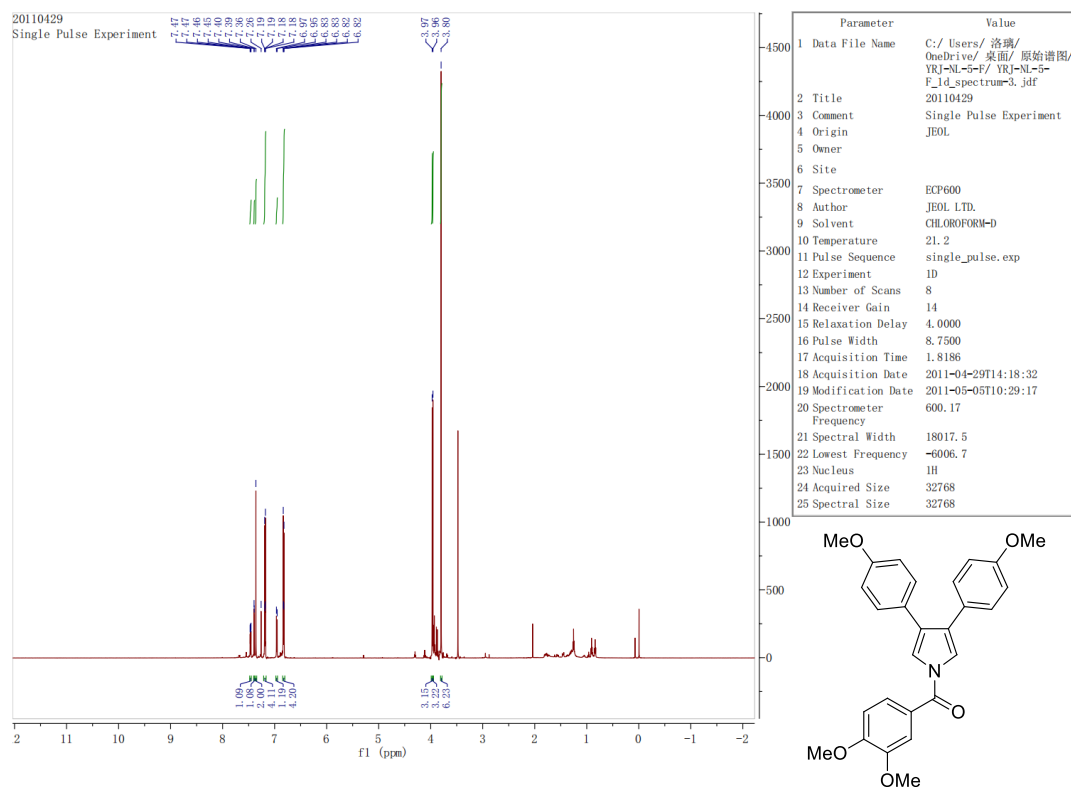


Figure S46. ¹H NMR spectrum of **1f**

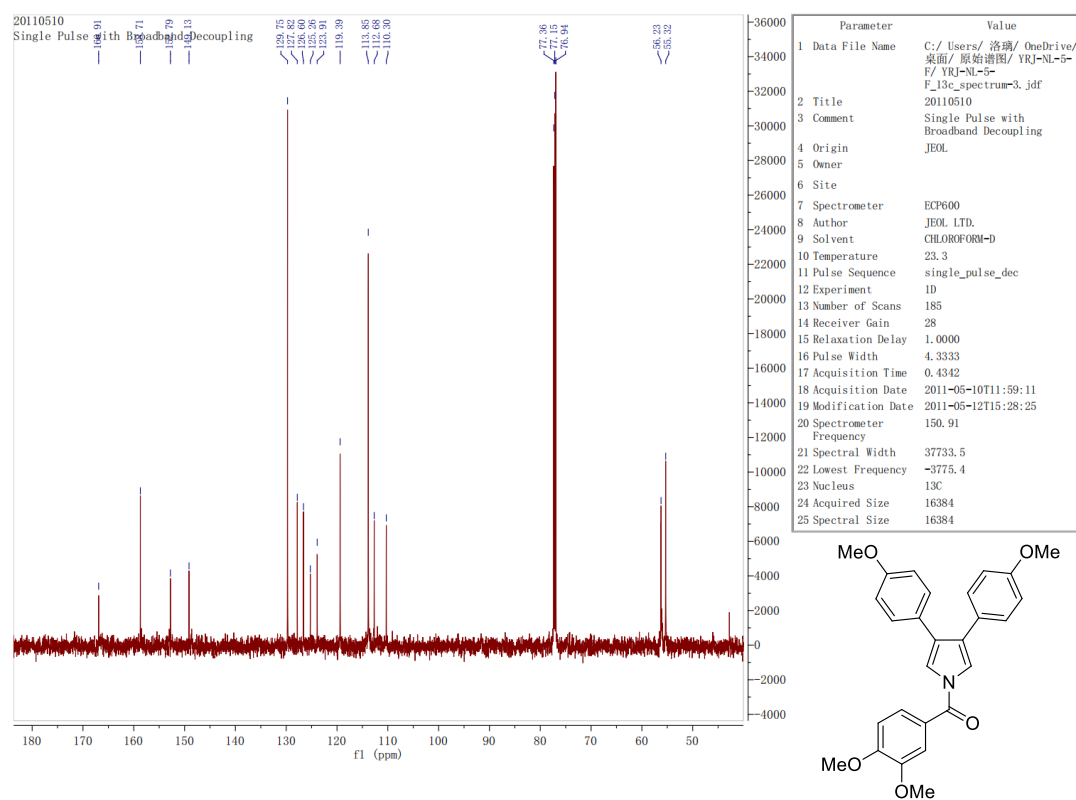


Figure S47. ^{13}C NMR spectrum of **1f**

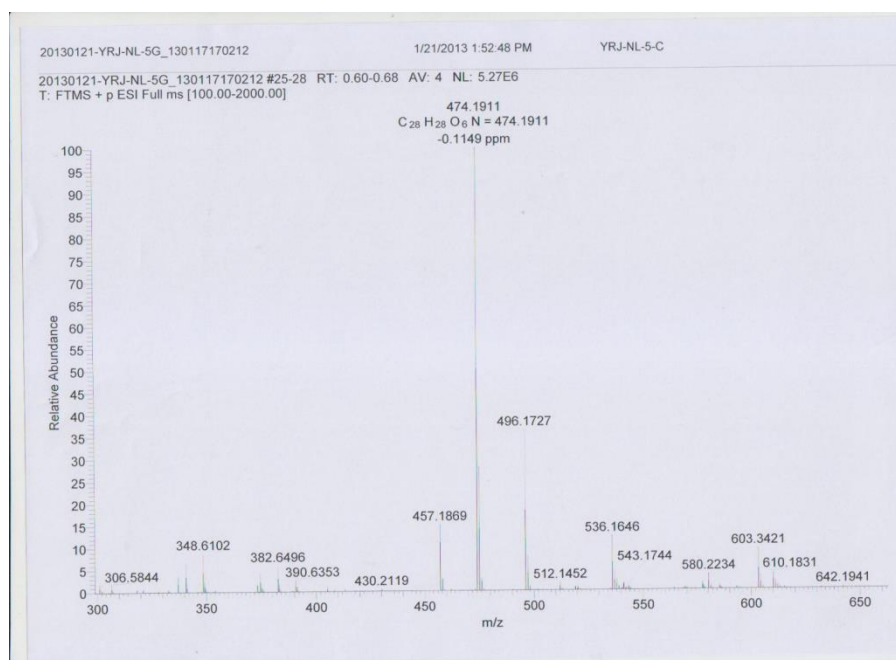


Figure S48. HRMS spectrum of **1g**

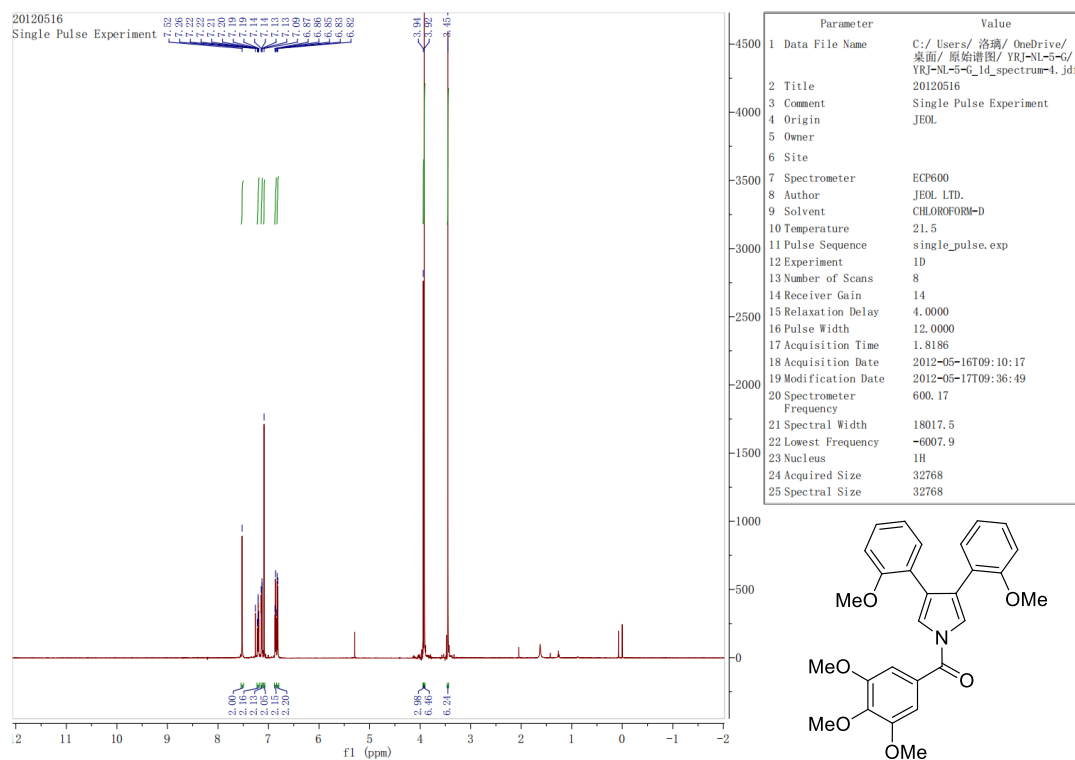


Figure S49. ^1H NMR spectrum of **1g**

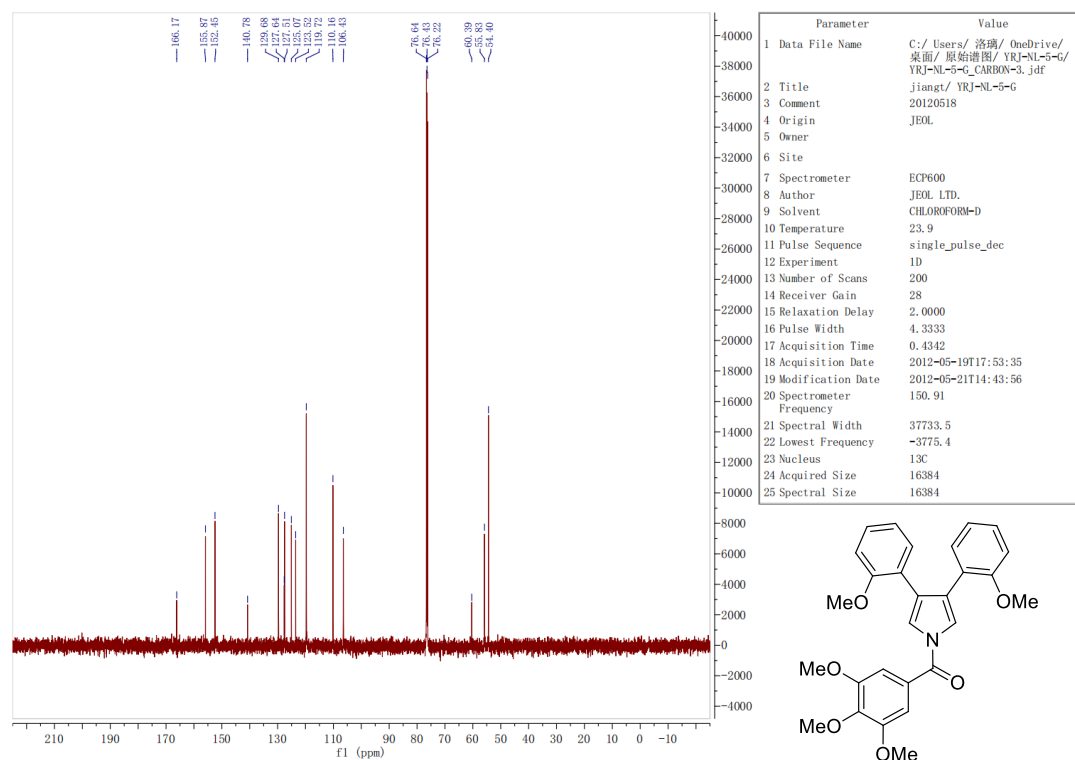


Figure S50. ^{13}C NMR spectrum of **1g**

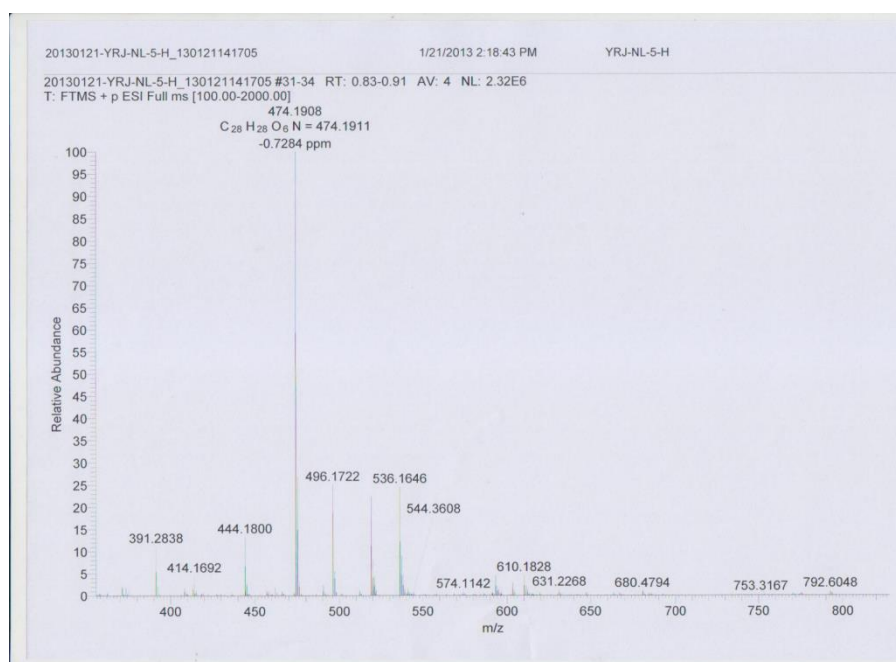


Figure S51. HRMS spectrum of **1h**

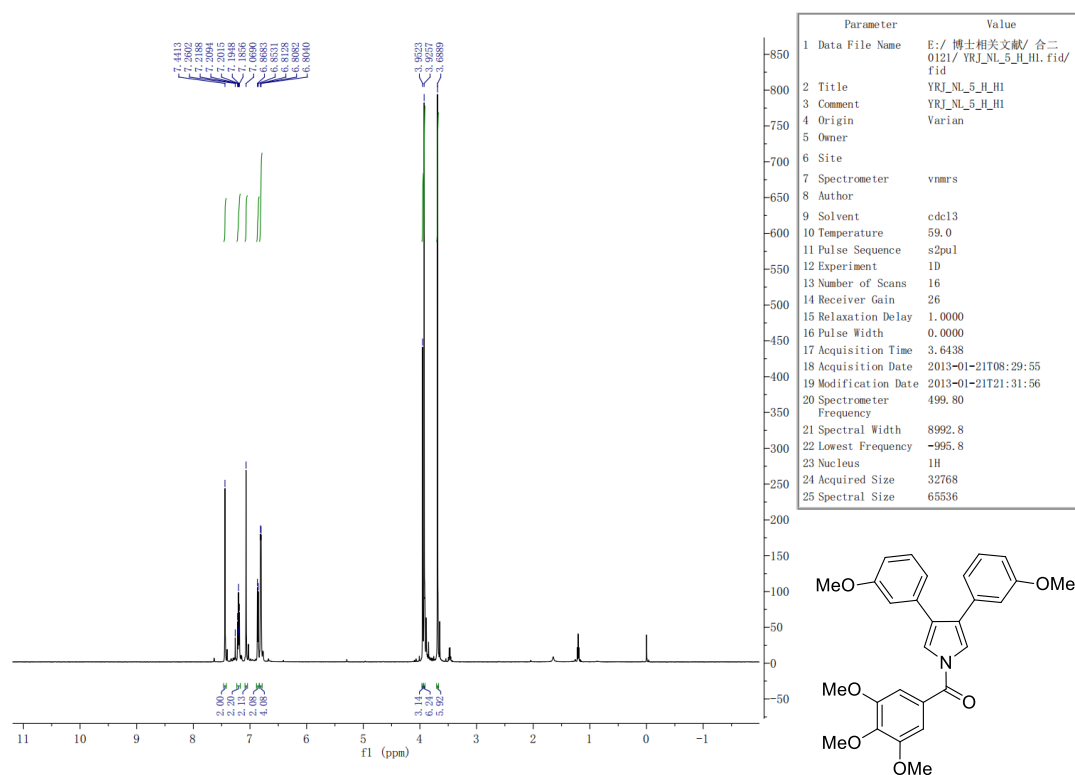


Figure S52. ¹H NMR spectrum of **1h**

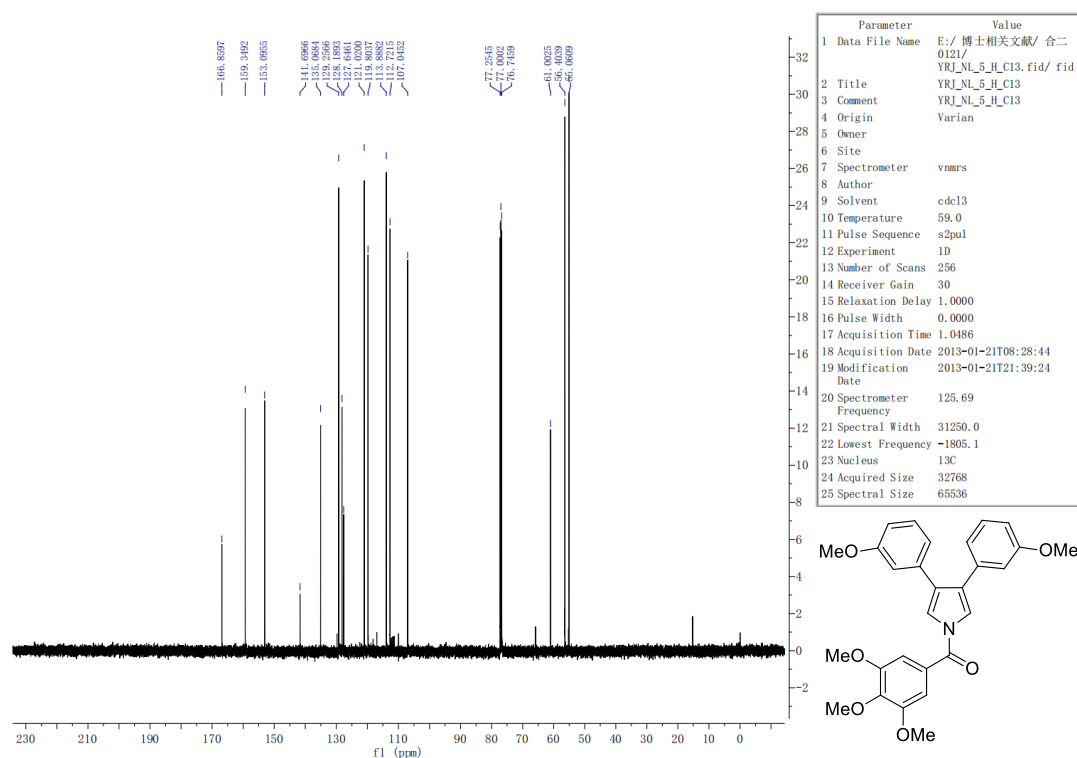


Figure S53. ^{13}C NMR spectrum of **1h**

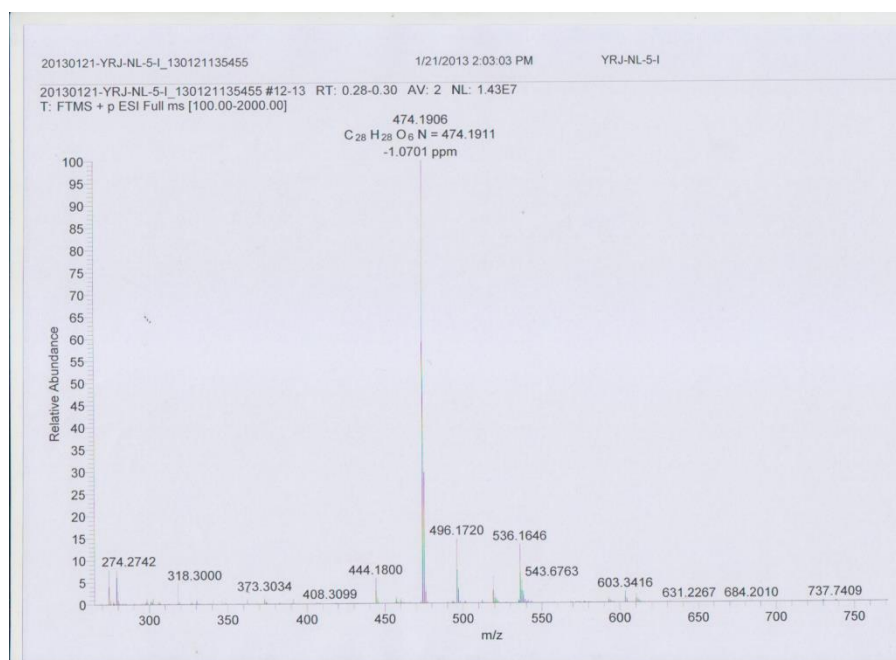


Figure S54. HRMS spectrum of **1i**

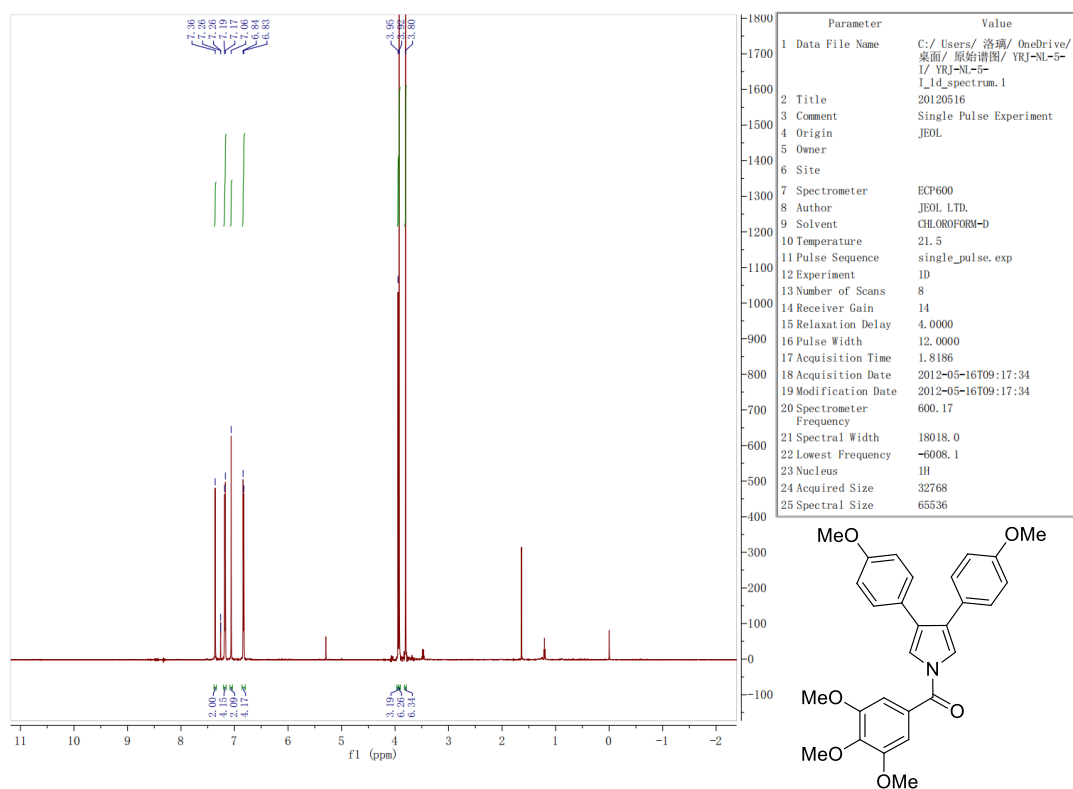


Figure S55. ¹H NMR spectrum of **1i**

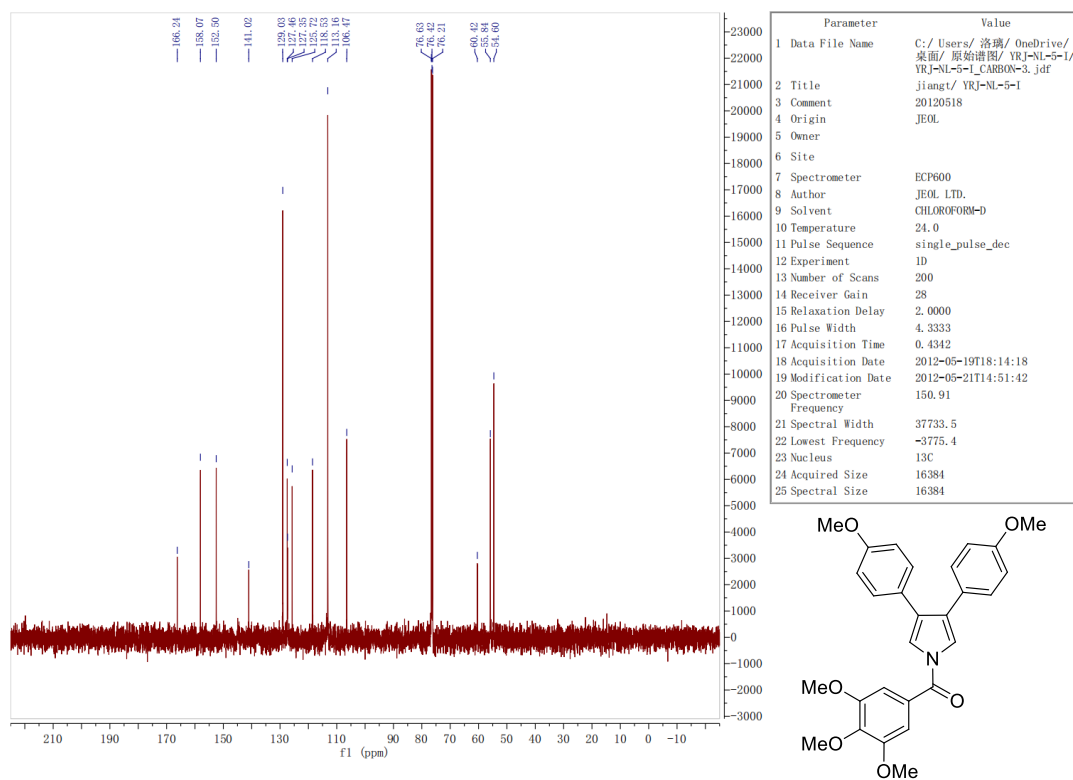


Figure S56. ¹³C NMR spectrum of **1i**

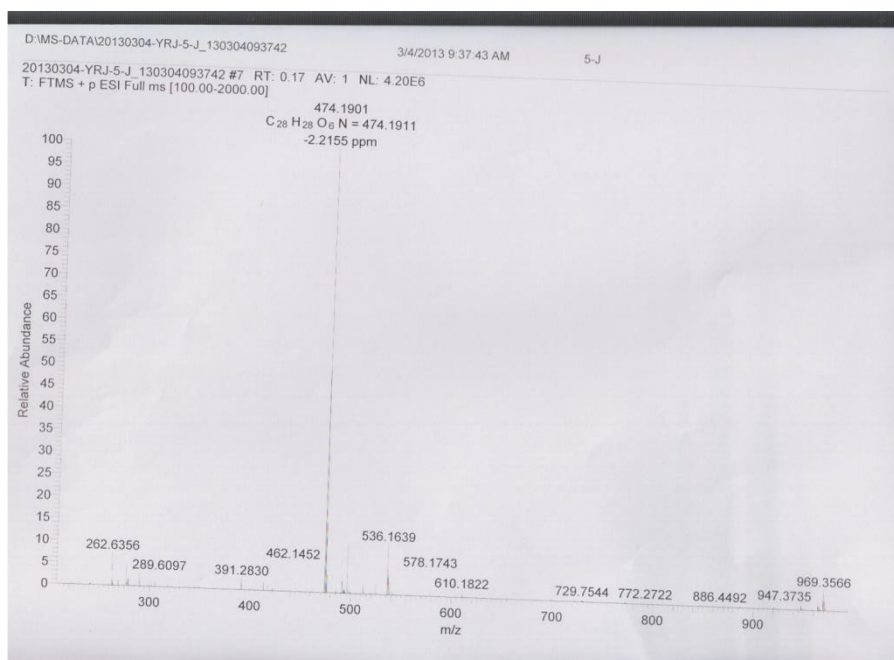


Figure S57. HRMS spectrum of **1j**

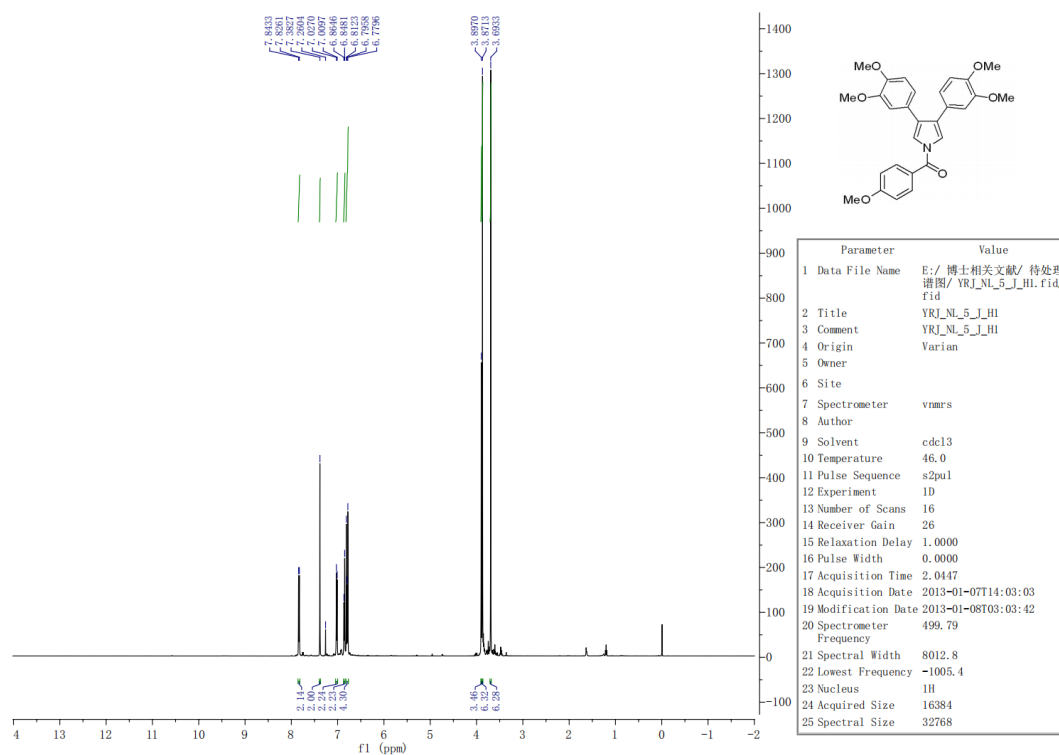


Figure S58. ¹H NMR spectrum of **1j**

YRJ-NL-5-J

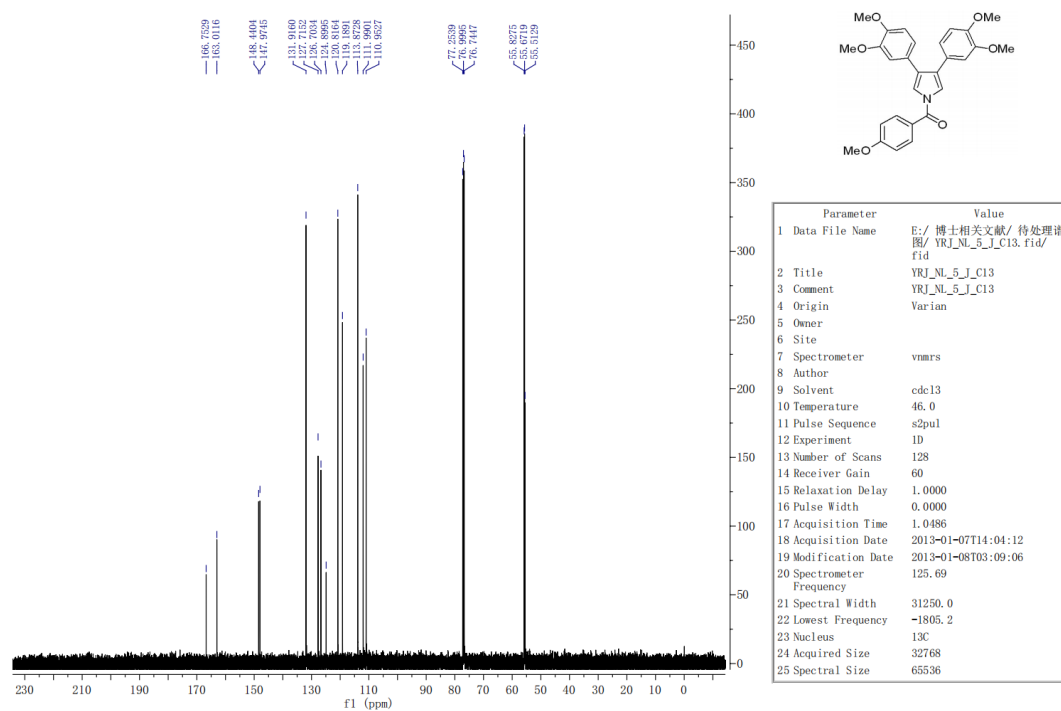


Figure S59. ^{13}C NMR spectrum of 1j

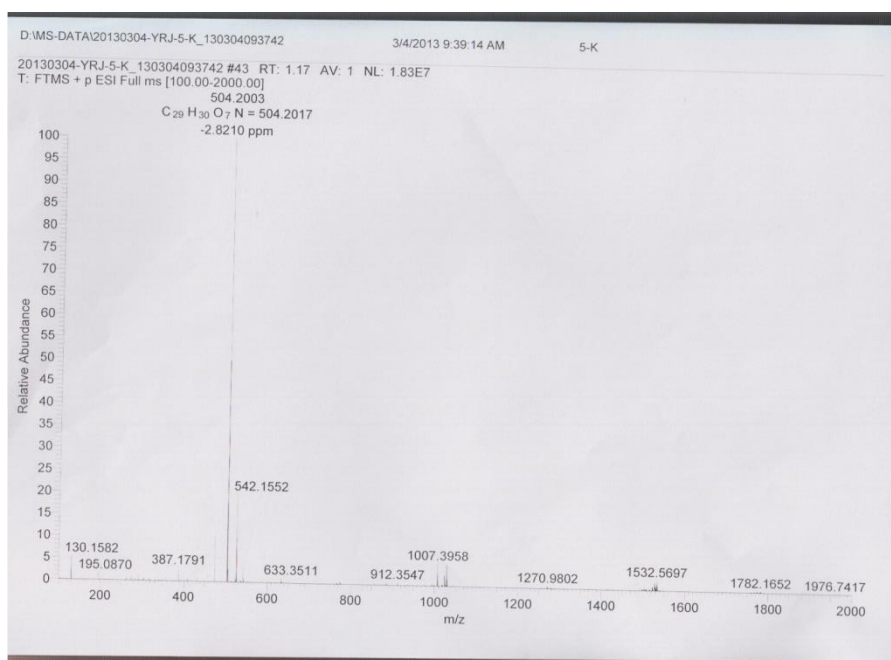


Figure S60. HRMS spectrum of 1k

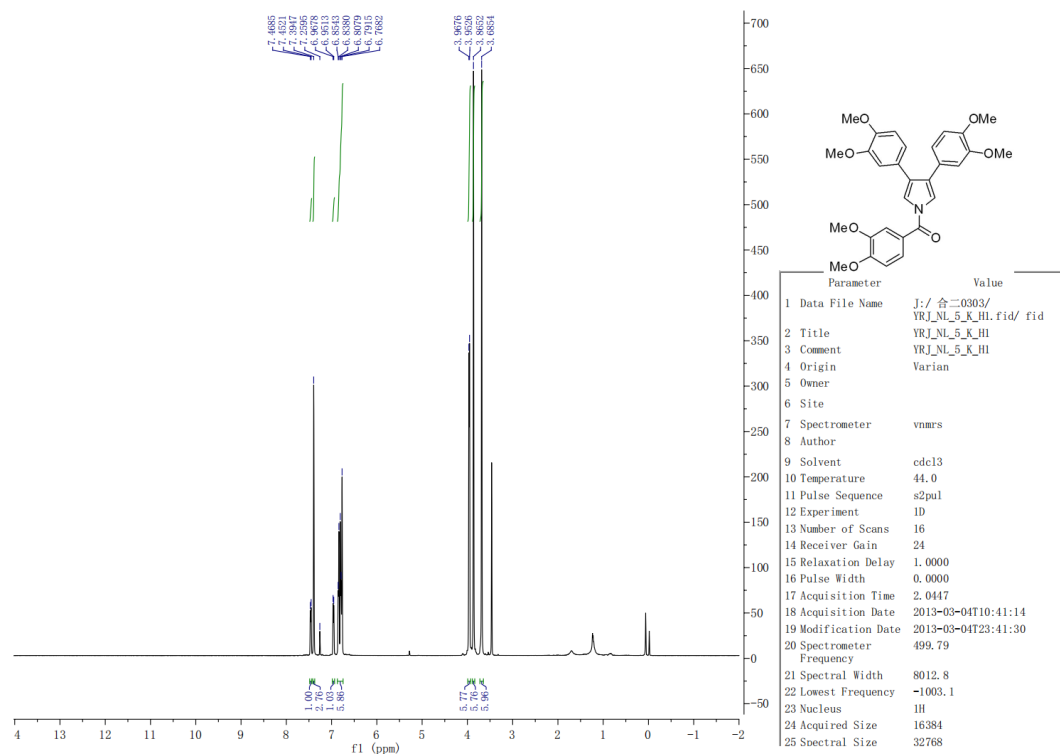


Figure S61. ¹H NMR spectrum of 1k

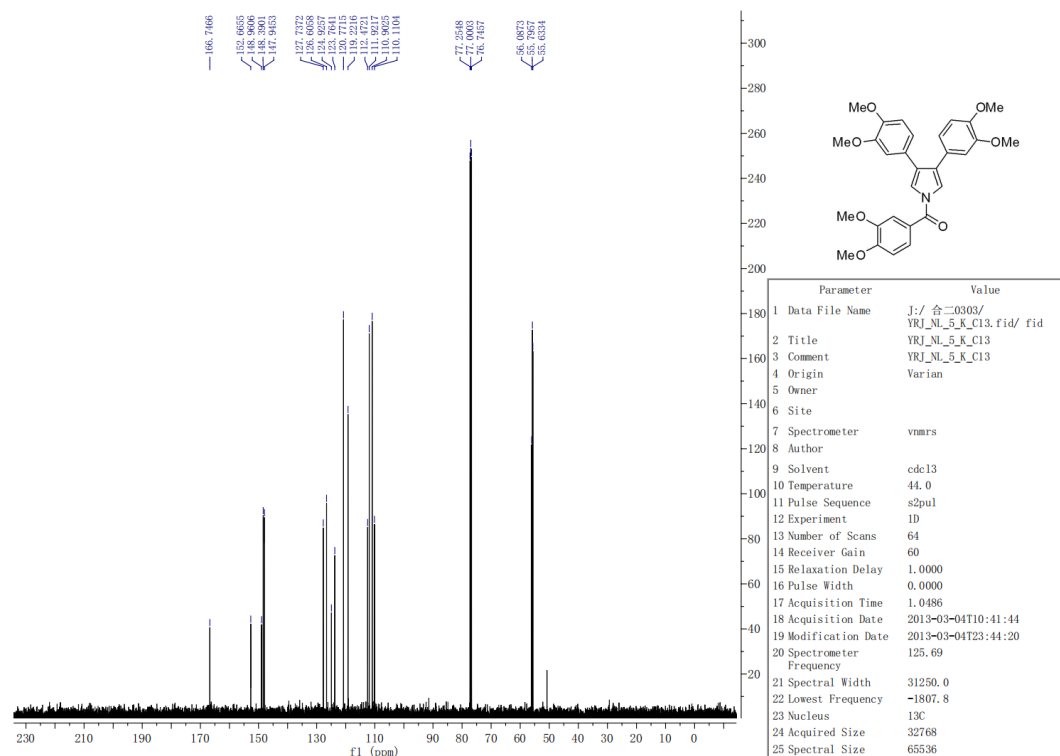
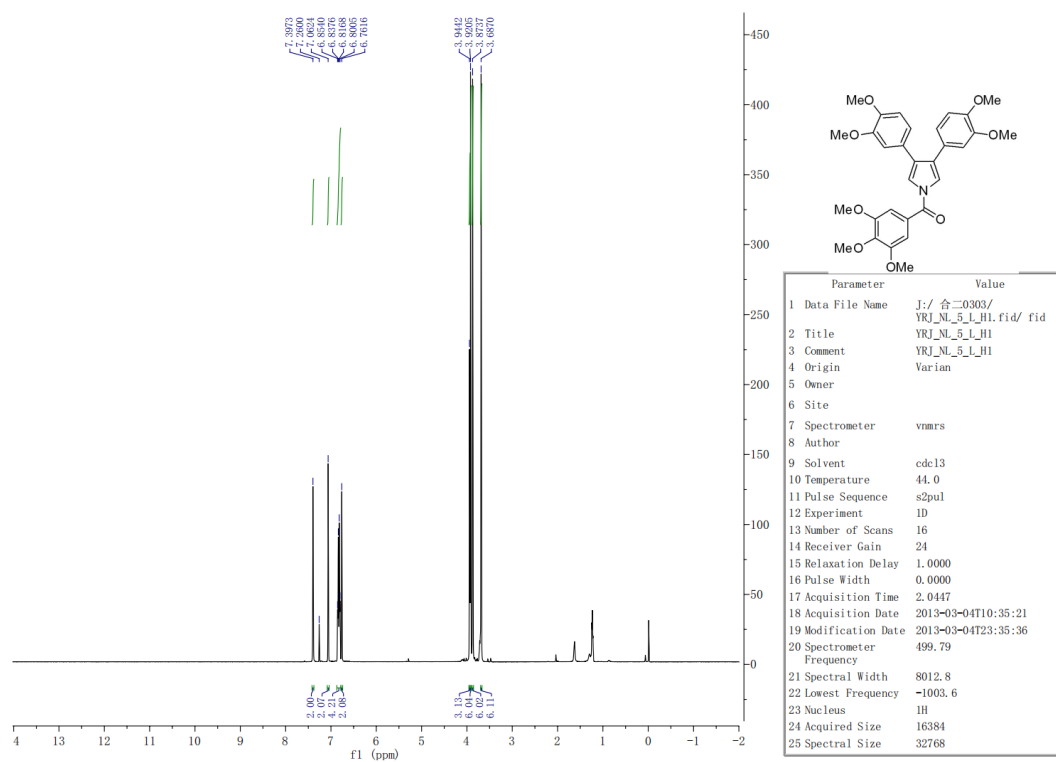
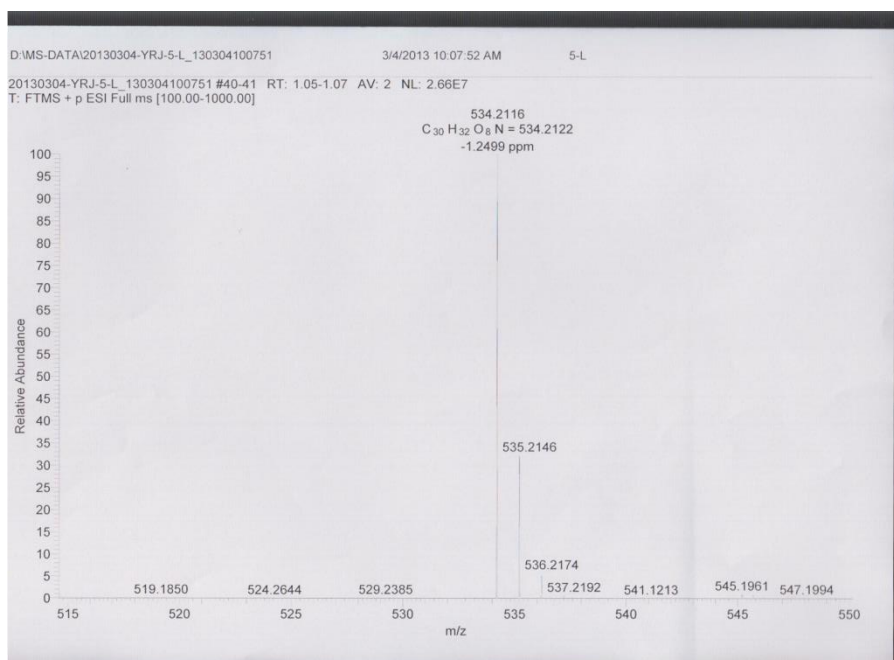


Figure S62. ¹³C NMR spectrum of 1k



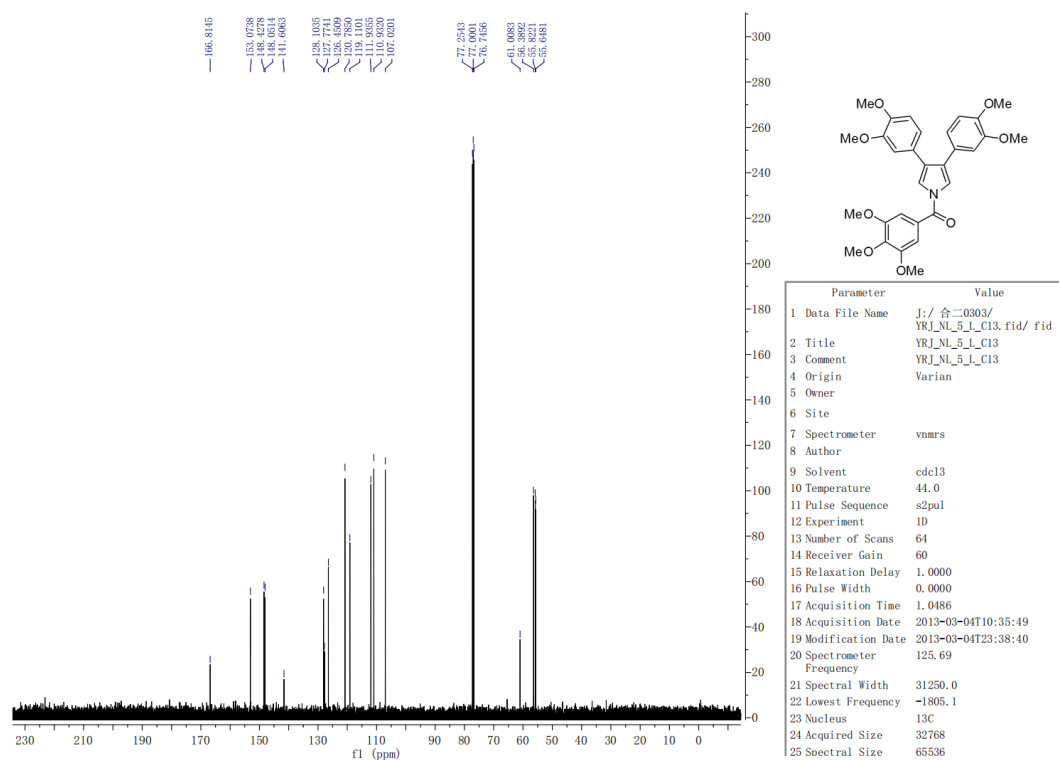


Figure S65. ^{13}C NMR spectrum of **11**

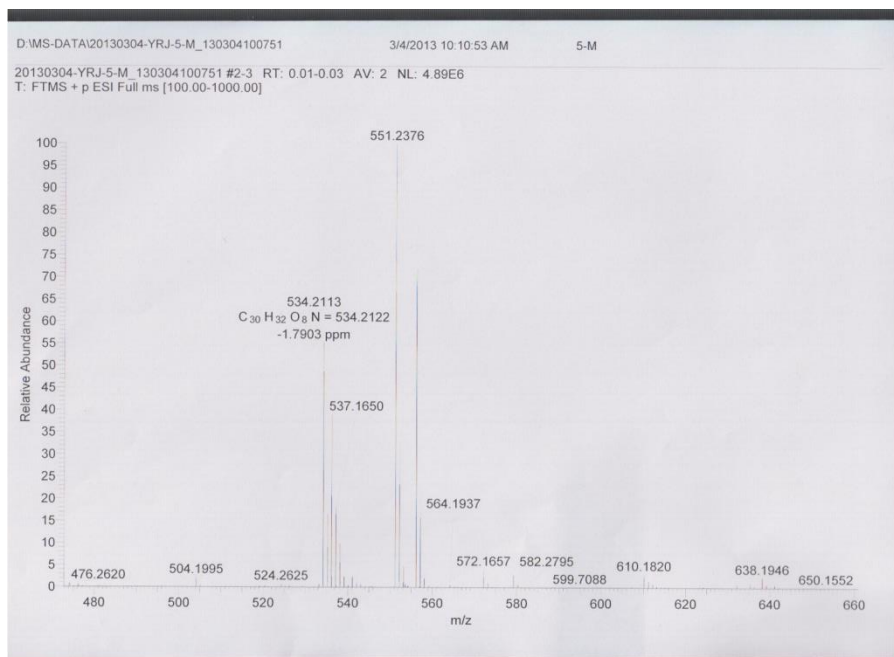


Figure S66. HRMS spectrum of **1m**

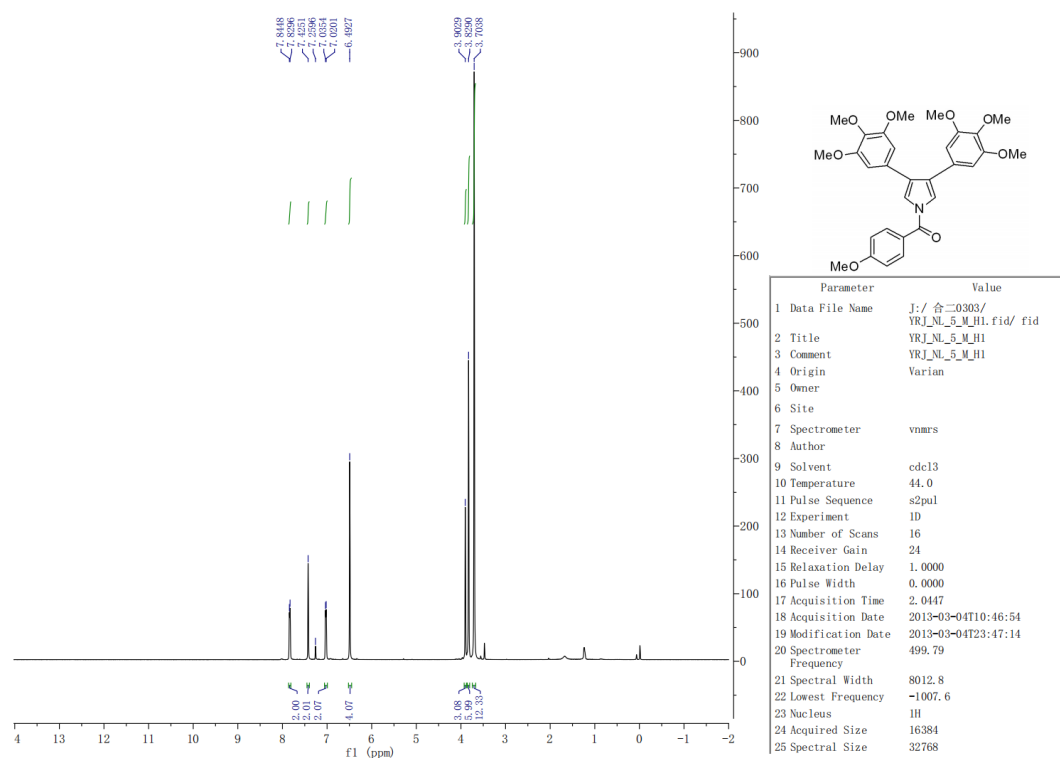


Figure S67. ^1H NMR spectrum of **1m**

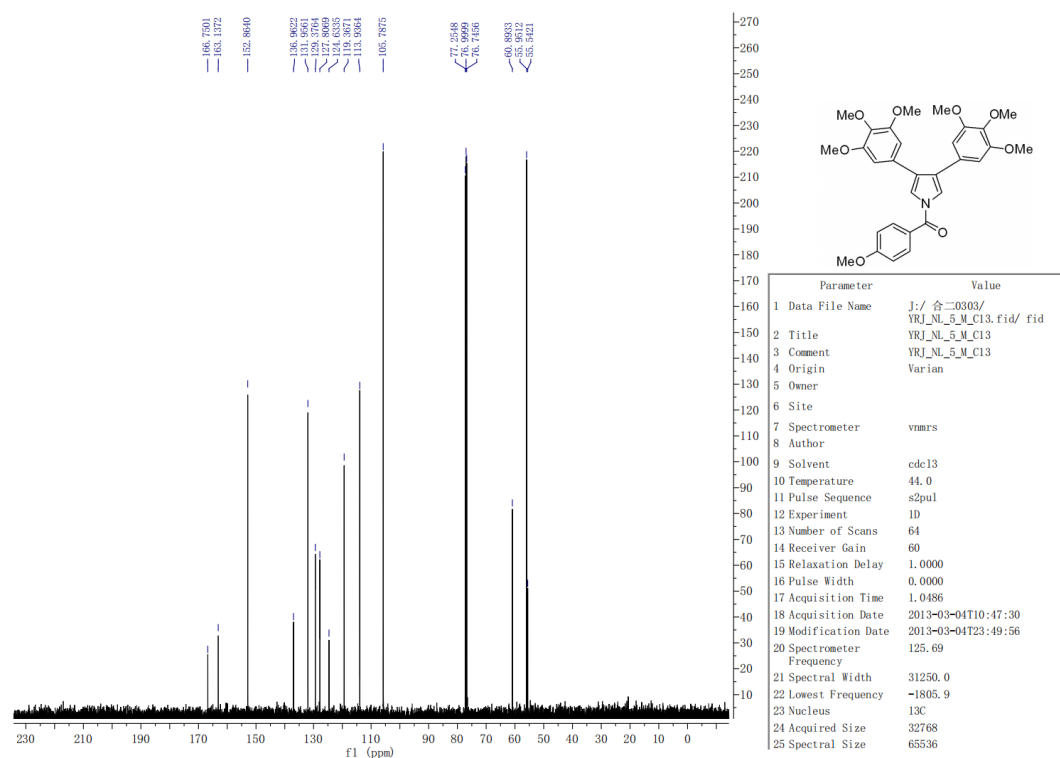


Figure S68. ^{13}C NMR spectrum of **1m**

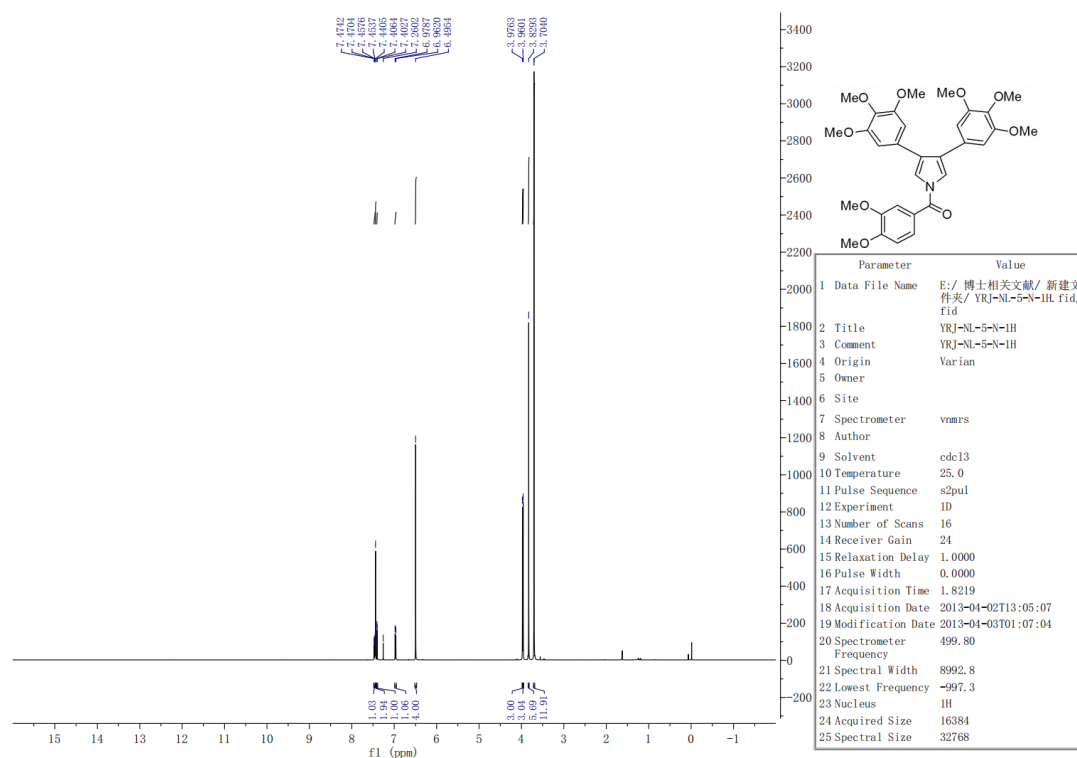


Figure S69. ¹H NMR spectrum of **1n**

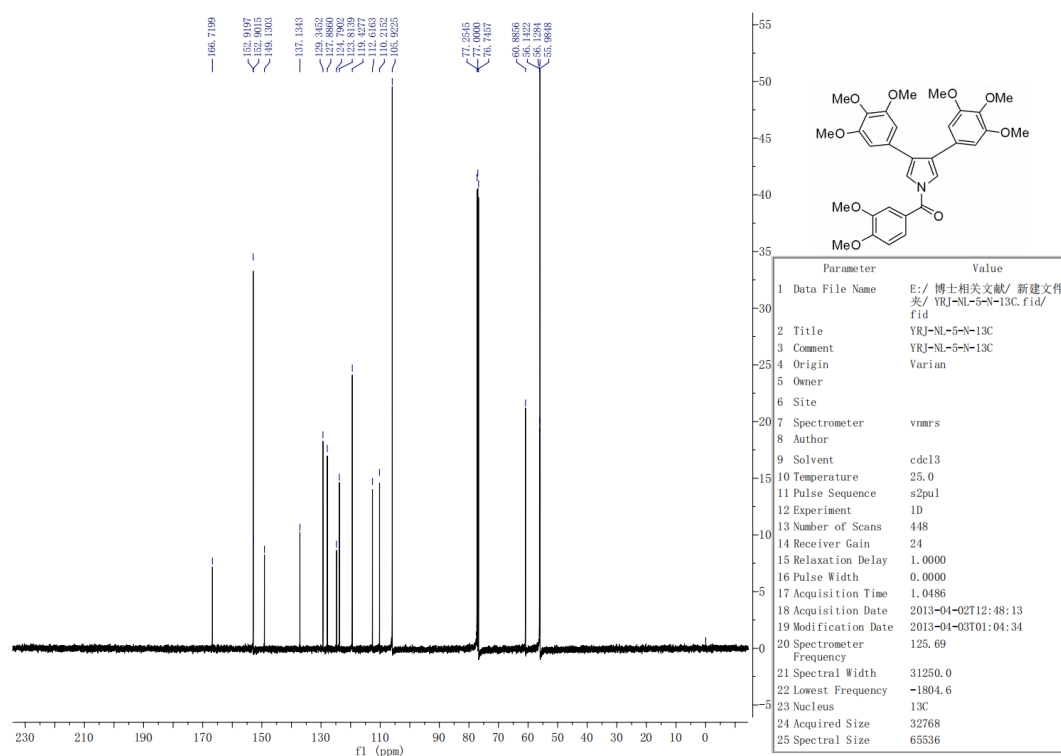


Figure S70. ¹³C NMR spectrum of **1n**

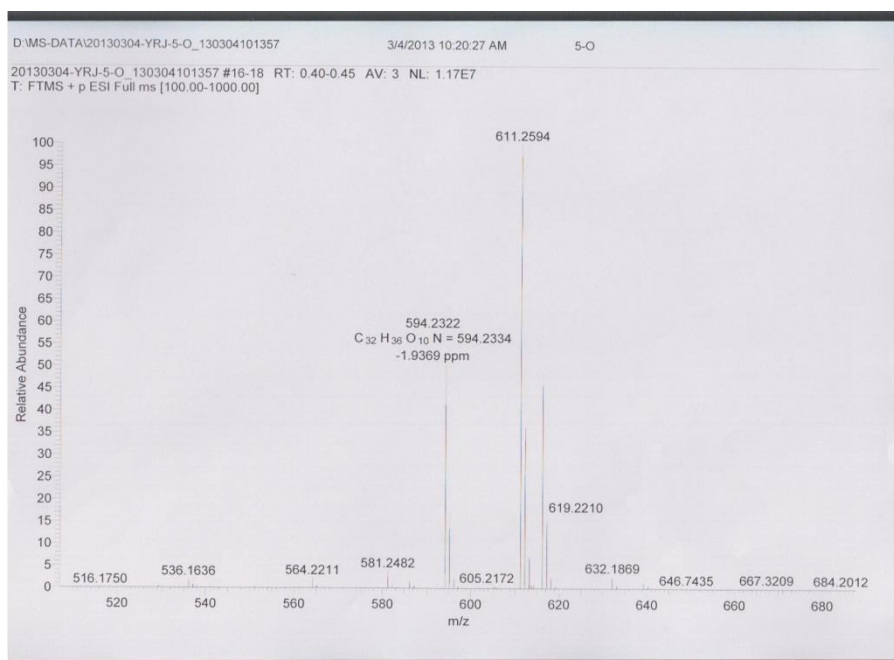


Figure S71. HRMS spectrum of **1o**

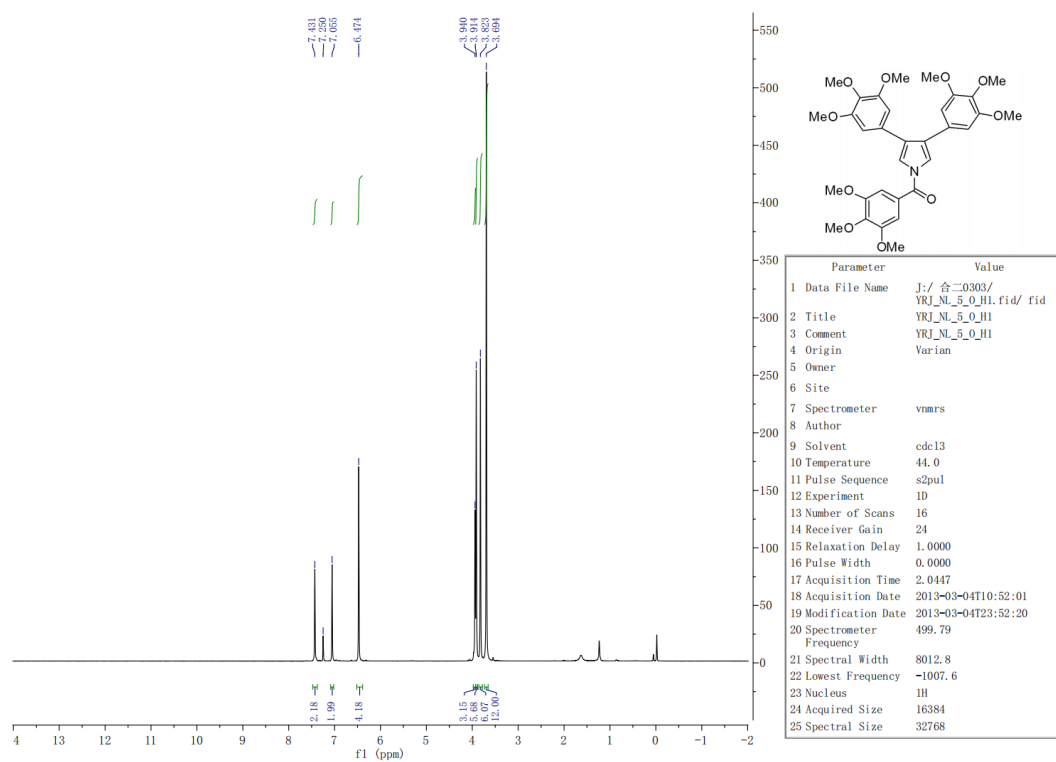


Figure S72. ¹H NMR spectrum of **1o**

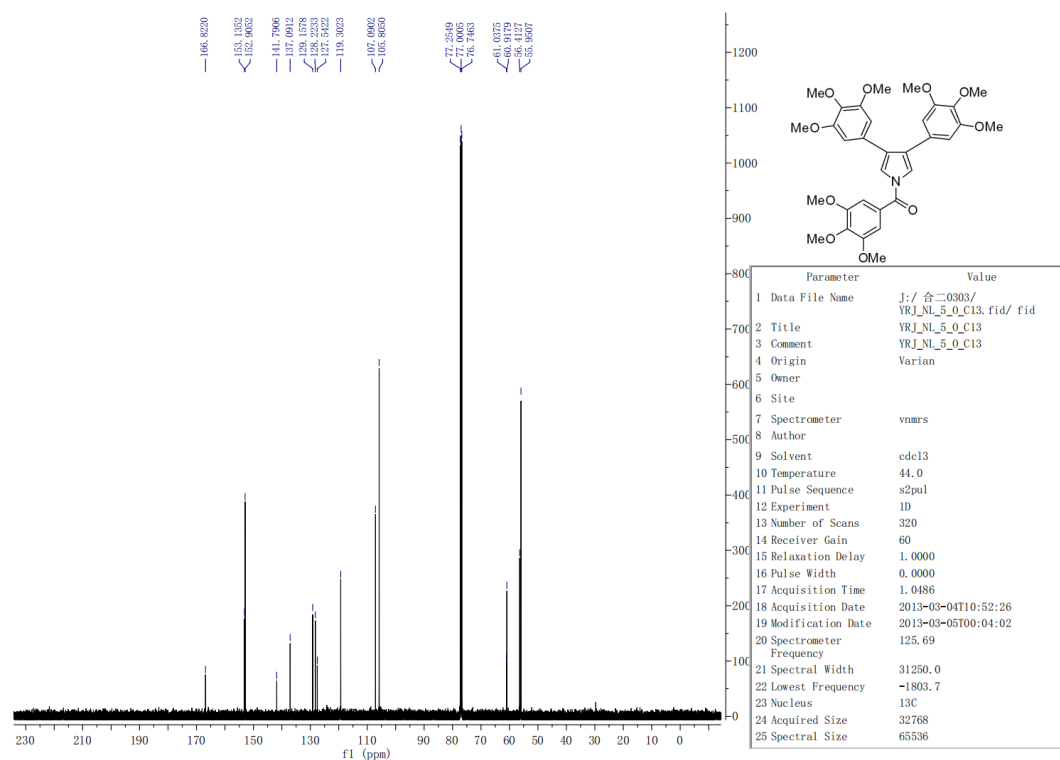


Figure S73. ^{13}C NMR spectrum of **10**

Table S1 The cytotoxicity of the permethylated Neolamellarin A derivatives **1a** - **1o** at gradient concentrations on PC12 cell line

Compound	Concentration (μM)	Cell viability \pm SD (100%) ^a
Blank control		100
1a	2.5	109.55 \pm 2.57
	5	114.88 \pm 2.40
	10	126.65 \pm 2.75
	20	143.33 \pm 1.81
1b	2.5	112.50 \pm 3.35
	5	120.05 \pm 2.51
	10	131.64 \pm 1.91
	20	142.52 \pm 3.84
1c	2.5	117.50 \pm 2.18
	5	126.36 \pm 2.63
	10	144.89 \pm 5.27
	20	162.47 \pm 5.41
1d	2.5	110.87 \pm 6.78
	5	113.82 \pm 1.92
	10	112.02 \pm 3.75
	20	109.71 \pm 3.56
1e	2.5	111.54 \pm 1.93
	5	112.52 \pm 2.73
	10	114.40 \pm 4.32
	20	116.44 \pm 5.44
1f	2.5	105.19 \pm 0.41
	5	118.95 \pm 6.60
	10	126.46 \pm 3.66
	20	128.42 \pm 6.00
1g	2.5	106.50 \pm 2.14
	5	105.91 \pm 3.74
	10	109.93 \pm 2.07
	20	114.22 \pm 3.37
1h	2.5	104.35 \pm 2.67
	5	111.95 \pm 4.52

Compound	Concentration (μM)	Cell viability \pm SD (100%) ^a
1i	10	122.42 \pm 4.50
	20	119.64 \pm 2.05
	2.5	120.04 \pm 4.76
	5	125.62 \pm 4.35
1j	10	126.80 \pm 3.13
	20	114.50 \pm 2.73
	2.5	104.55 \pm 1.85
	5	105.61 \pm 1.26
1k	10	113.76 \pm 2.14
	20	104.89 \pm 3.92
	2.5	106.24 \pm 1.52
	5	104.61 \pm 0.62
1l	10	100.21 \pm 2.89
	20	95.64 \pm 2.10
	2.5	110.38 \pm 2.02
	5	107.82 \pm 3.05
1m	10	116.44 \pm 1.52
	20	115.45 \pm 4.72
	2.5	106.37 \pm 3.19
	5	104.45 \pm 3.68
1n	10	104.40 \pm 4.30
	20	90.56 \pm 3.00
	2.5	103.97 \pm 3.32
	5	101.61 \pm 3.04
1o	10	107.02 \pm 3.76
	20	97.37 \pm 3.06
	2.5	109.02 \pm 3.18
	5	106.50 \pm 3.41
	10	108.77 \pm 0.49
	20	100.00 \pm 3.75

^a Each value was calculated from three independent experiments. The data were shown as mean \pm SD deviation.

Table S2 The neuroprotective activity of the permethylated Neolamellarin A derivatives **1a** - **1o** at gradient concentrations on PC12 cell death induced by glutamate

Compound	Concentration (μ M)	Cell viability \pm SD (100%) ^a
Blank control		100
Negative control (glutamate)	8	35.92 \pm 3.01
HupA (positive control)	100	45.55 \pm 5.77
1a	2.5	43.89 \pm 4.17
	5	45.24 \pm 2.88
	10	50.75 \pm 4.38
	20	51.61 \pm 3.23
1b	2.5	42.68 \pm 3.71
	5	44.48 \pm 6.37
	10	52.20 \pm 7.03
	20	61.68 \pm 8.32
1c	2.5	45.00 \pm 3.53
	5	56.69 \pm 7.06
	10	85.01 \pm 5.22
	20	99.73 \pm 10.49
1d	2.5	50.97 \pm 3.33
	5	50.63 \pm 4.07
	10	67.54 \pm 5.60
	20	79.27 \pm 2.41
1e	2.5	45.51 \pm 4.72
	5	52.75 \pm 2.89
	10	57.28 \pm 7.00
	20	73.87 \pm 3.14
1f	2.5	39.95 \pm 1.59
	5	48.00 \pm 2.39
	10	59.63 \pm 2.53
	20	101.56 \pm 3.79
1g	2.5	46.56 \pm 2.42
	5	40.99 \pm 3.16
	10	53.40 \pm 3.90
	20	55.35 \pm 1.86

Compound	Concentration (μM)	Cell viability ± SD (100%) ^a
1h	2.5	41.51 ± 1.37
	5	51.51 ± 5.10
	10	79.41 ± 3.13
	20	119.20 ± 4.86
1i	2.5	46.35 ± 3.19
	5	57.84 ± 3.70
	10	80.34 ± 6.26
	20	71.75 ± 5.67
1j	2.5	44.40 ± 5.99
	5	36.06 ± 3.52
	10	43.68 ± 4.41
	20	67.64 ± 6.34
1k	2.5	38.24 ± 3.06
	5	45.06 ± 1.49
	10	67.26 ± 2.20
	20	84.79 ± 5.62
1l	2.5	53.15 ± 3.28
	5	43.38 ± 2.35
	10	47.41 ± 4.39
	20	49.26 ± 5.43
1m	2.5	38.38 ± 1.75
	5	50.91 ± 3.36
	10	86.42 ± 5.66
	20	94.21 ± 4.07
1n	2.5	48.27 ± 4.11
	5	65.74 ± 2.95
	10	102.38 ± 7.61
	20	106.31 ± 3.22
1o	2.5	47.09 ± 5.51
	5	50.18 ± 0.79
	10	70.22 ± 6.79
	20	113.90 ± 10.11

^a Each value was calculated from three independent experiments. The data were shown as mean \pm SD deviation.