Supporting Information

The synthesis of *N*, *N*'-Disulfanediyl bis(*N*'-((*E*)-benzylidene) acetohydrazide) from (*E*)-*N*'-Benzylideneacetohydrazide and S_8

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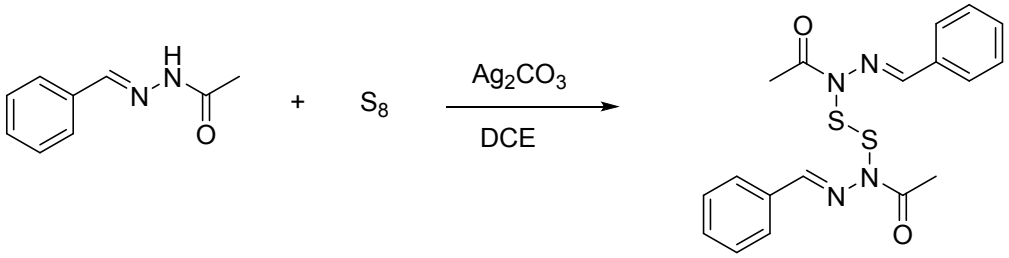
1. General Information

All the chemicals were obtained commercially and used without any prior purification. ^{1}H NMR spectra were recorded on a BrukerAvanceII 400 spectrometer. Compounds for HRMS were analyzed by positive-mode electrospray ionization (ESI) using an Agilent 6530 QTOF mass spectrometer. All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60-90°C) and ethyl acetate. Unless otherwise noted. All compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS, which are consistent with those repored in the literature.

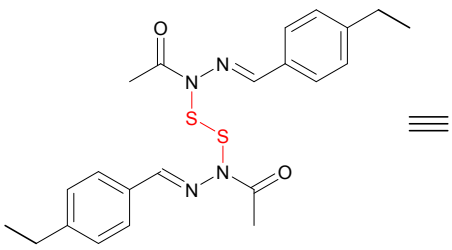
2. Experimental Section

General procedure for Synthesis of *N,N'*-disulfanediylbis(*N'*-((*E*)-benzylidene)acetohydrazide).

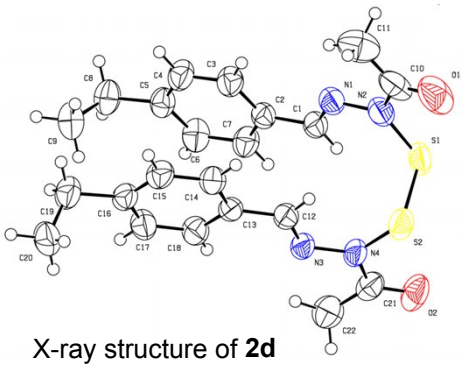


A mixture of the **1a** (0.2 mmol), S_8 (0.3 mmol), Ag_2CO_3 (2.5 equiv.), in CH_2ClCH_2Cl (2. 0 mL) was stirred at round-bottom flask, N_2, 80 °C for 3 h. After cooling down to room temperature and concentrating in vacuum, the residue was purified by flash chromatograph y on a short silica gel to afford the product.

3. Crystal data of 2d



2d

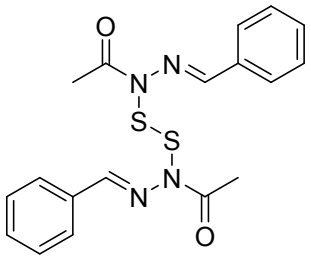


X-ray structure of **2d**
CCDC 2008330

Empirical formula	$C_{22}H_{26}N_4O_2S_2$
Formula weight	442.59
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	P-1
Unit cell dimensions	a = 10.0938 Å □= 90°.
	b = 111.2771 Å □= 90°.
	c = 11.8150 Å □ = 90°.
Volume	1147.4(9) $Å^3$
Z	2
Density (calculated)	1.281 g/cm^3
Absorption coefficient	0.257 mm^{-1}
F(000)	468
Crystal size	0.210 x 0.160 x 0.120 mm^3
Theta range for data collection	2.32 to 28.13°.
Index ranges	-11<=h<=12, -13<=k<=12, -14<=l<=14
Reflections collected	4258
Independent reflections	6883 [R(int) = 0.0192]
Completeness to theta = 25.242°	
Absorption correction	multi-scan
Max. and min. transmission	0.952 and 0.970
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4258 / 0 / 271
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0475, wR2 = 0.1304
R indices (all data)	R1 = 0.0592, wR2 = 0.1429

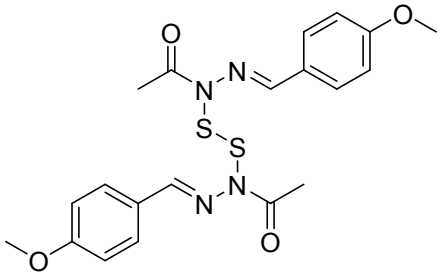
4. Characterization data of the products

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-benzylidene)acetohydrazide) (2a)



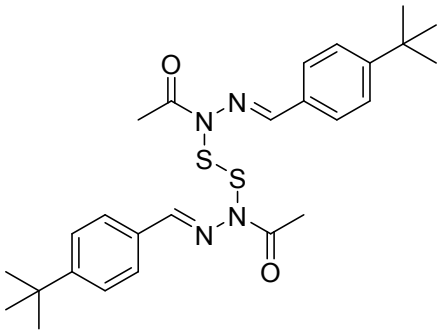
Yellow solid, 27.4 mg, 71 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 81.7-82.9 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (s, 2H), 7.59 – 7.41 (m, 4H), 7.23 – 7.32 (m, 6H), 2.46 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5, 144.94, 132.96, 130.47, 128.73, 127.68, 23.30. **HRMS** (ESI+): Calculated for $C_{18}H_{18}N_4O_2S_2$, $[M+H]^+$ 387.0973. Found 387.0906.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-4-methoxybenzylidene)acetohydrazide) (2b)



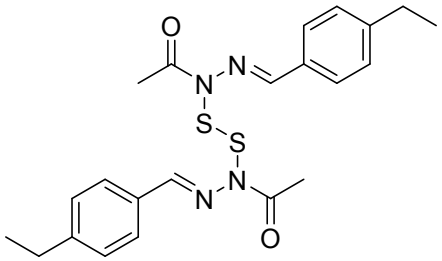
Yellow solid, 29.9 mg, 67 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 131.5-133.6 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (s, 2H), 7.49 (d, J = 6.3 Hz, 4H), 6.84 (d, J = 8.1 Hz, 4H), 3.84 (s, 6H), 2.50 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.65, 161.46, 144.76, 129.22, 125.79, 114.13, 55.38, 23.30. **HRMS** (ESI+): Calculated for $C_{20}H_{22}N_4O_4S_2$, $[M+H]^+$ 447.1173. Found 447.1104.

_N_,_N′_-disulfanediylbis(N'-((E)-4-(tert-butyl)benzylidene)acetohydrazide) (2c)



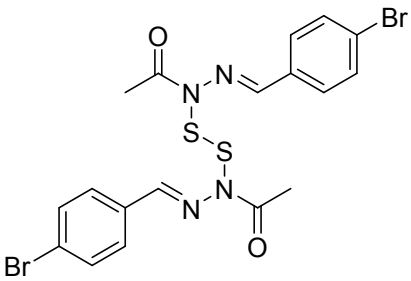
Yellow solid, 30.9 mg, 62 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 109.1-110.4 ℃. **^{1}H NMR** (400 MHz, CDCl3) δ 8.05 (s, 2H), 7.47 – 7.39 (m, 4H), 7.29 (d, *J* = 6.6 Hz, 4H), 2.44 (s, 6H), 1.25 (s, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.69, 153.94, 144.93, 130.24, 127.50, 125.66, 34.92, 31.21, 23.32. **HRMS** (ESI+): Calculated for $C_{26}H_{34}N_4O_2S_2$, $[M+H]^+$ 499.2173. Found 499.2142.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-4-ethylbenzylidene)acetohydrazide) (2d)



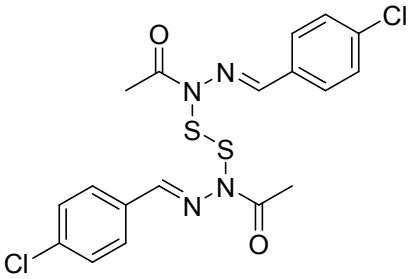
White solid, 27.9 mg, 63 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 118.2-119.7 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.38 (d, *J* = 7.7 Hz, 4H), 7.06 (d, *J* = 7.7 Hz, 4H), 2.57 (q, *J* = 7.6 Hz, 4H), 2.43 (s, 6H), 1.16 (t, *J* = 7.6 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.64, 147.06, 145.08, 130.50, 128.20, 127.73, 28.85, 23.29, 15.41. **HRMS** (ESI+): Calculated for $C_{22}H_{26}N_4O_2S_2$, $[M+H]^+$ 443.1573. Found 443.1564.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-4-bromobenzylidene)acetohydrazide) (2e)



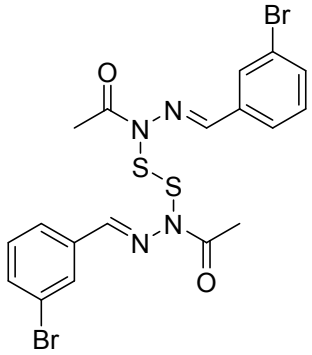
White solid, 33.1 mg, 61 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 156.0-157.4 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.47 (d, *J* = 7.5 Hz, 4H), 7.44 – 7.36 (m, 4H), 2.51 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.50, 143.74, 132.01, 131.86, 128.94, 124.87, 23.25. **HRMS** (ESI+): Calculated for $C_{18}H_{16}Br_2N_4O_2S_2$, $[M+H]^+$ 542.9173. Found 542.9129.

***N*,*N*′-disulfanediylbis(*N*′-((*E*)-4-chlorobenzylidene)acetohydrazide) (2f)**



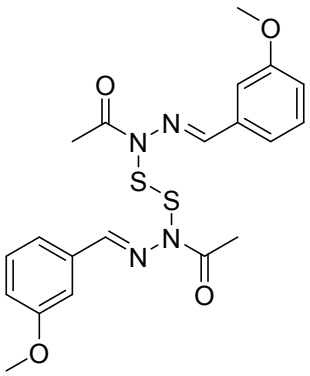
Yellow solid, 30.9 mg, 68 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 129.9-131.4 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.40 (d, *J* = 6.4 Hz, 4H), 7.20 (d, *J* = 7.5 Hz, 4H), 2.42 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.46, 143.64, 136.46, 131.46, 129.03, 128.75, 23.21. **HRMS** (ESI+): Calculated for $C_{18}H_{16}Cl_2N_4O_2S_2$, $[M+H]^+$ 455.0173. Found 455.0125.

***N*,*N*′-disulfanediylbis(*N*′-((*E*)-3-bromobenzylidene)acetohydrazide) (2h)**



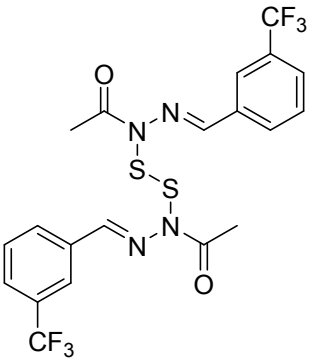
Yellow solid, 30.9 mg, 57 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 166.8-168.2 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (s, 2H), 7.62 (s, 2H), 7.46 – 7.38 (m, 4H), 7.15 (d, *J* = 7.8 Hz, 2H), 2.46 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.29, 143.39, 134.90, 133.40, 130.21, 130.00, 126.44, 123.00, 23.21. **HRMS** (ESI+): Calculated for $C_{18}H_{16}Br_2N_4O_2S_2$, $[M+H]^+$ 542.9173. Found 542.9117.

***N*,*N*′-disulfanediylbis(*N*′-((*E*)-3-methoxybenzylidene)acetohydrazide) (2i)**



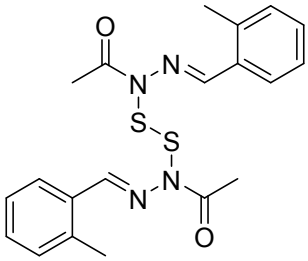
Yellow solid, 27.7 mg, 62 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 122.3-123.7 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 2H), 7.24 (s, 2H), 7.14 – 7.07 (m, 4H), 6.91 (d, *J* = 7.4 Hz, 2H), 3.80 (s, 6H), 2.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.55, 159.79, 144.85, 134.34, 129.70, 120.80, 116.45, 112.03, 55.23, 23.21. **HRMS** (ESI+): Calculated for $C_{20}H_{22}N_4O_4S_2$, $[M+H]^+$447.1173. Found 447.1102.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-3-(trifluoromethyl)benzylidene)acetohydrazide) (2j)



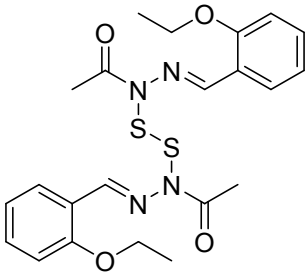
White solid, 30.3 mg, 58 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 181.4-183.2 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (s, 2H), 7.75 (s, 4H), 7.59 (d, *J* = 6.9 Hz, 2H), 7.46 (d, *J* = 6.5 Hz, 2H), 2.56 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.42, 143.35, 133.67, 131.50, 131.17, 130.51, 129.34, 127.04, 126.95, 126.91, 126.88, 125.00, 124.19, 124.15, 124.12, 124.03, 122.29, 23.19. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.95. **HRMS** (ESI+): Calculated for $C_{20}H_{16}F_6N_4O_2S_2$, $[M+H]^+$523.0673. Found 523.0649.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-2-methylbenzylidene)acetohydrazide) (2l)



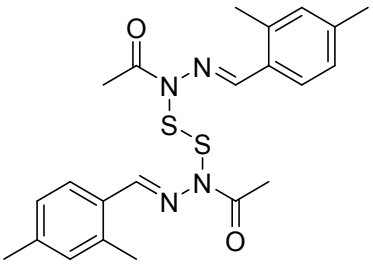
White solid, 26.5 mg, 64 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 138.6-140.0 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (s, 2H), 7.55 (d, *J* = 6.8 Hz, 2H), 7.15 (d, *J* = 7.3 Hz, 2H), 7.06 (t, *J* = 8.1 Hz, 4H), 2.43 (s, 6H), 2.35 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.58, 143.30, 136.34, 129.98, 129.84, 129.11, 126.66, 125.17, 22.34, 18.97. **HRMS** (ESI+): Calculated for $C_{20}H_{22}N_4O_2S_2$, $[M+H]^+$ 415.1273. Found 415.1221.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-2-ethoxybenzylidene)acetohydrazide) (2m)



Yellow solid, 25.6 mg, 54 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 115.5-116.3 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (s, 2H), 7.76 – 7.54 (m, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 4H), 3.98 (q, *J* = 7.0 Hz, 4H), 2.41 (s, 6H), 1.32 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.75, 157.73, 141.19, 131.56, 126.59, 121.80, 120.66, 112.21, 64.16, 23.27, 14.76. **HRMS** (ESI+): Calculated for $C_{22}H_{26}N_4O_4S_2$, $[M+H]^+$ 475.1473. Found 475.1410.

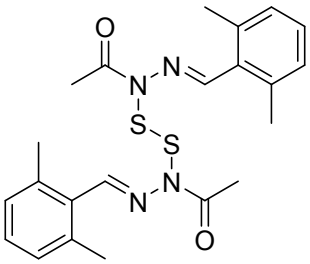
_N_,_N′_-disulfanediylbis(_N′_-((_E_)-2,4-dimethylbenzylidene)acetohydrazide) (2q)



White solid, 28.7 mg, 65 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 133.7-135.5 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.42 (d, *J* = 6.5 Hz, 2H), 6.86 (s, 2H), 6.86

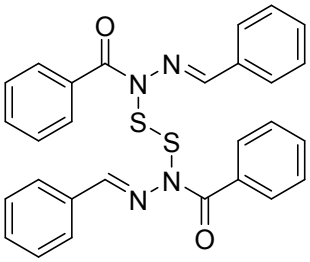
– 6.83 (m, 2H), 2.41 (s, 6H), 2.30 (s, 6H), 2.24 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.62, 143.44, 139.31, 136.25, 130.68, 127.15, 126.79, 125.94, 22.38, 20.30, 18.95. **HRMS** (ESI+): Calculated for $C_{22}H_{26}N_4O_2S_2$, $[M+H]^+$445.1573. Found 445.1525.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-2,6-dimethylbenzylidene)acetohydrazide) (2r)



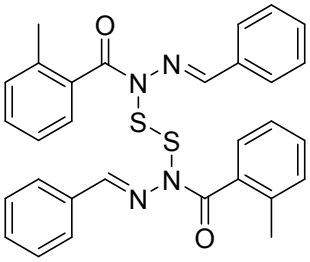
White solid, 27.4 mg, 62 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 120.4-122.2 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63 (s, 2H), 7.12 – 7.08 (m, 2H), 6.99 (d, *J* = 7.5 Hz, 4H), 2.37 (s, 12H), 2.34 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.79, 144.88, 138.05, 129.75, 129.44, 128.97, 23.39, 21.55. **HRMS** (ESI+): Calculated for $C_{22}H_{26}N_4O_2S_2$, $[M+H]^+$ 443.1573. Found 443.1538.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-benzylidene)benzohydrazide) (2s)



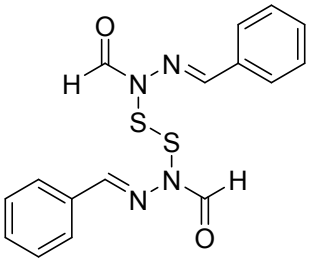
White solid, 33.2 mg, 65 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 78.1-79.9 ℃. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.47 (s, 2H), 7.66 (d, *J* = 7.6 Hz, 4H), 7.59 – 7.54 (m, 2H), 7.53 – 7.40 (m, 8H), 7.39 – 7.27 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 171.52, 145.64, 134.84, 133.42, 131.57, 130.82, 129.82, 129.16, 128.07. **HRMS** (ESI+): Calculated for $C_{28}H_{22}N_4O_2S_2$, $[M+H]^+$ 511.1273. Found 511.1270.

_N_,_N′_-disulfanediylbis(_N′_-((_E_)-benzylidene)-2-methylbenzohydrazide) (2t)



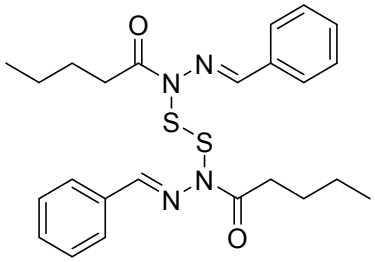
White solid, 30.1 mg, 56 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 96.9-98.0 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (s, 2H), 7.28 (s, 2H), 7.27 – 7.19 (m, 4H), 7.14 (ddd, *J* = 10.7, 7.5, 4.3 Hz, 8H), 7.09 (d, *J* = 9.2 Hz, 4H), 2.23 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.09, 145.03, 135.92, 135.30, 132.87, 130.34, 129.89, 129.56, 128.60, 127.78, 127.34, 125.25, 19.71. **HRMS** (ESI+): Calculated for $C_{30}H_{26}N_4O_2S_2$, $[M+H]^+$ 539.1573. Found 539.1574.

***N*,*N′*-disulfanediylbis(*N′*-((*E*)-benzylidene)formohydrazide) (2u)**



White solid,17.5 mg, 49 % yield (eluent: ethyl acetate / petroleum ether = 1:8); m.p.: 141.1-142.2 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.85 (s, 2H), 8.11 (s, 2H), 7.48 (d, *J* = 7.3 Hz, 4H), 7.29 – 7.22 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.56, 146.75, 132.15, 130.85, 128.71, 127.94. **HRMS** (ESI+): Calculated for $C_{16}H_{14}N_4O_2S_2$, $[M+H]^+$ 359.0673. Found 359.0875.

***N*,*N′*-disulfanediylbis(*N′*-((*E*)-benzylidene)pentanehydrazide) (2v)**

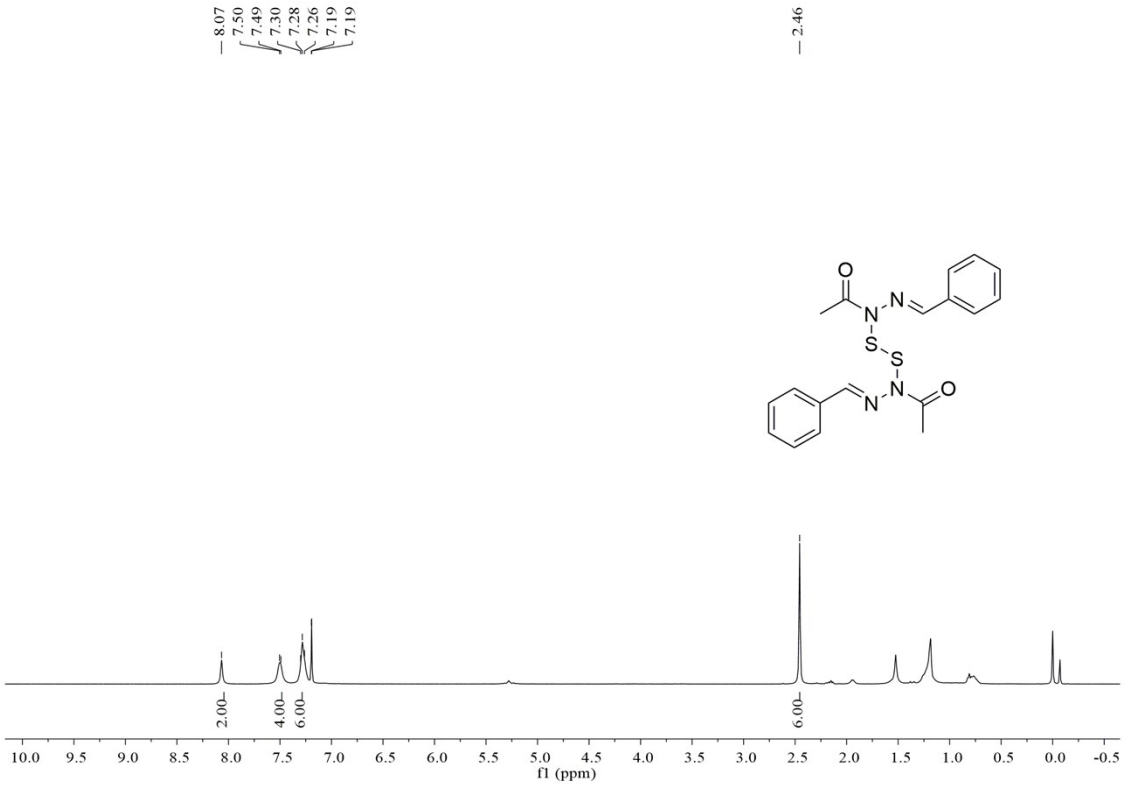


White solid, 25.4 mg, 54 % yield (eluent: ethyl acetate / petroleum ether = 1:10); m.p.: 132.8-134.4 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (s, 2H), 7.54 – 7.41 (m, 4H), 7.26 (d, *J* = 7.3 Hz, 6H), 2.81 (t, *J* = 7.5 Hz, 4H), 1.59 (d, *J* = 8.3 Hz, 4H), 1.33 (q, *J* = 7.5 Hz, 4H), 0.86 (t, *J* = 7.3 Hz,

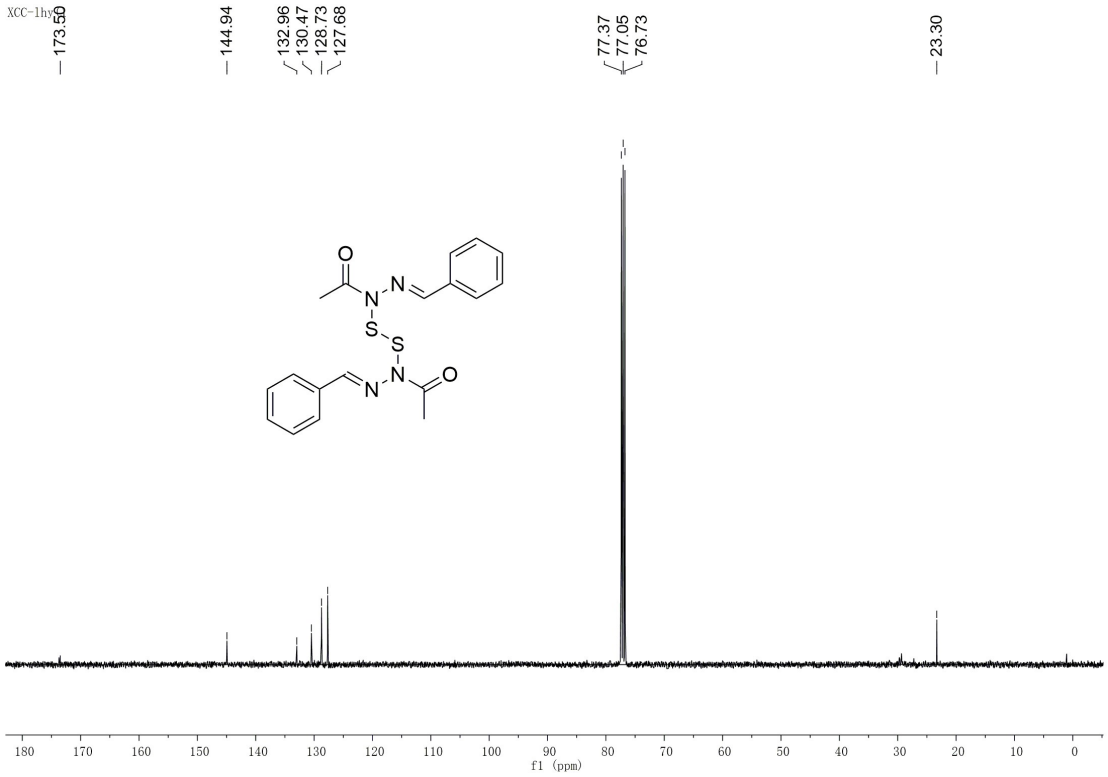
6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.99, 143.55, 132.11, 129.28, 127.65, 126.59, 34.23, 25.99, 21.46, 12.89. **HRMS** (ESI+): Calculated for $C_{24}H_{30}N_4O_2S_2$, $[M+H]^+$ 471.1873. Found 471.1870.

5. ^{1}H and ^{13}C NMR spectra of the products

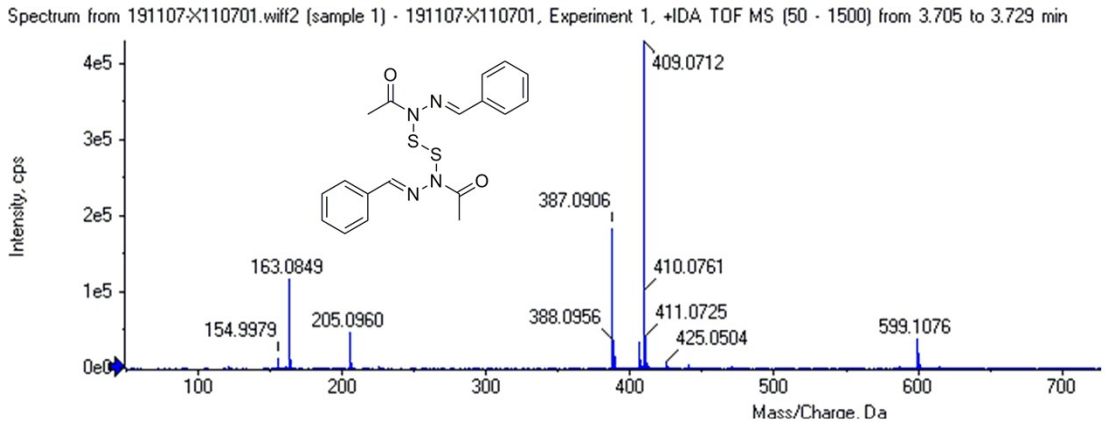
2a ^{1}H NMR



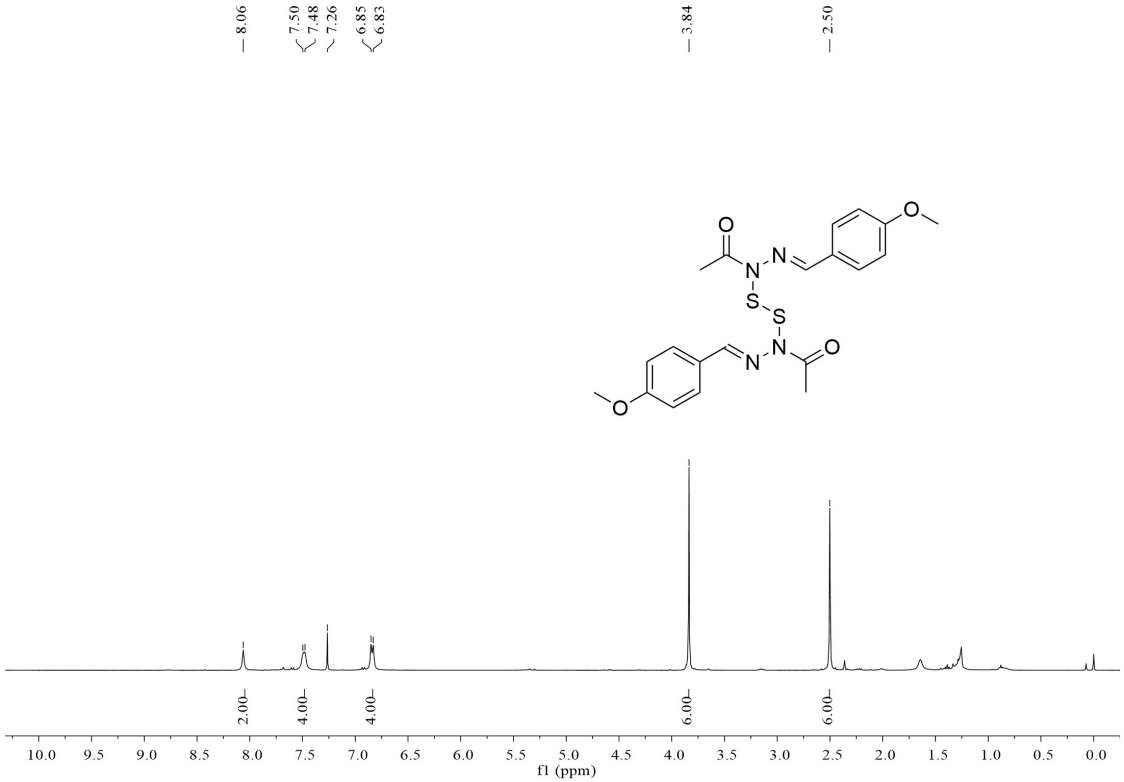
2a ^{13}C NMR



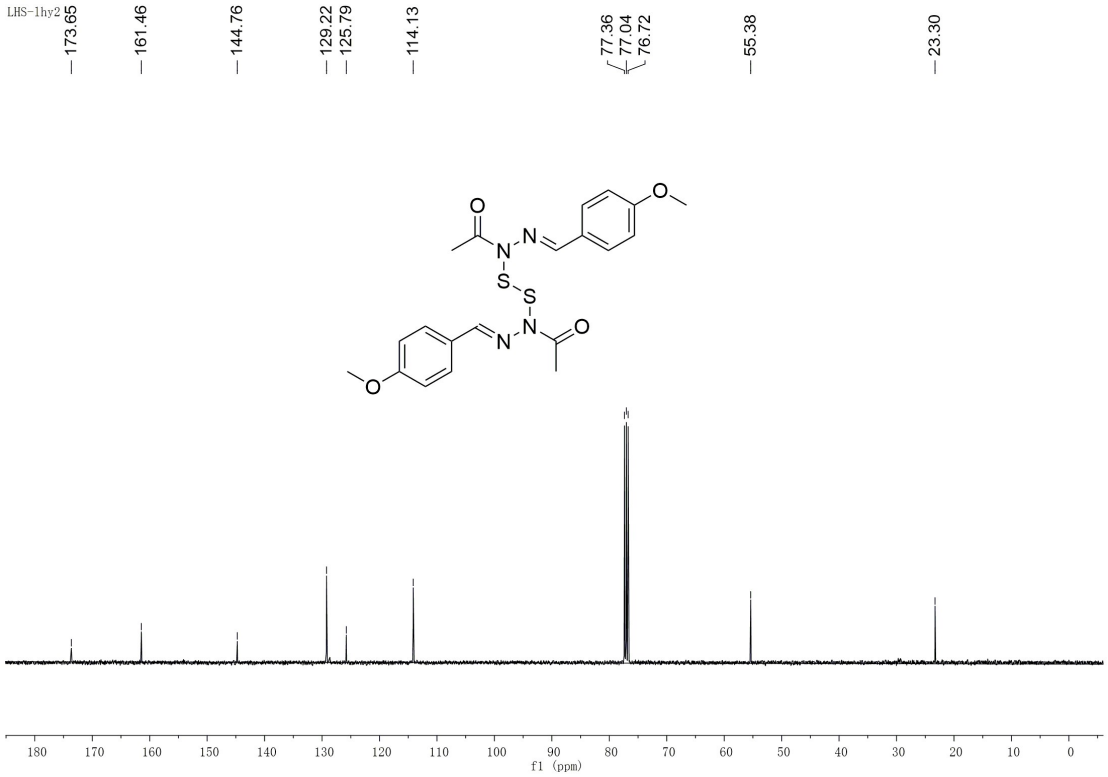
2a MS


Spectrum from 191107-X110701.wiff2 (sample 1) - 191107-X110701, Experiment 1, +IDA TOF MS (50 - 1500) from 3.705 to 3.729 min
Intensity, cps
4e5
3e5
2e5
1e5
0e0
409.0712
387.0906
163.0849
410.0761
154.9979
205.0960
388.0956
411.0725
425.0504
599.1076
100
200
300
400
500
600
700
Mass/Charge, Da

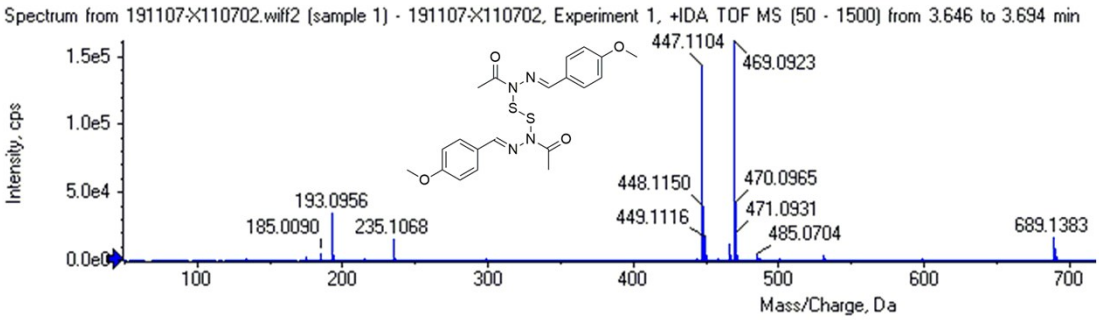
2b ^{1}H NMR


8.06
7.50
7.48
7.26
6.85
6.83
3.84
2.50
2.00
4.00
4.00
6.00
6.00
f1 (ppm)

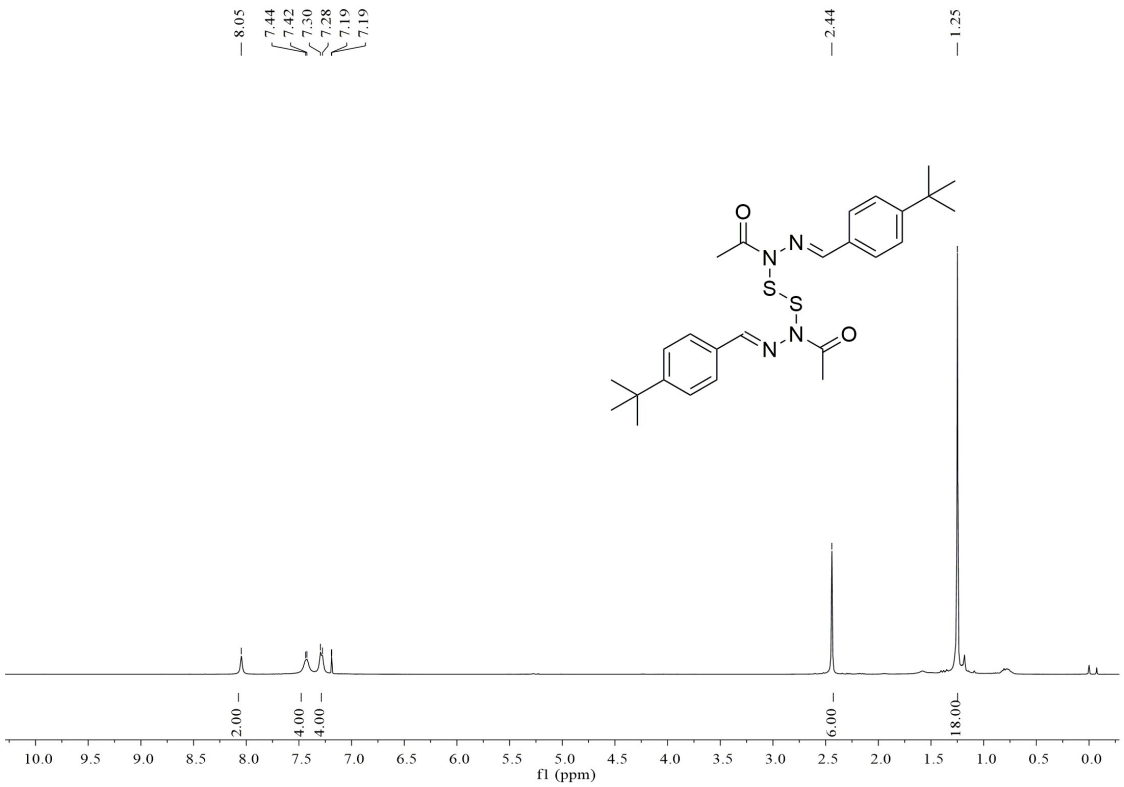
2b ^{13}C NMR



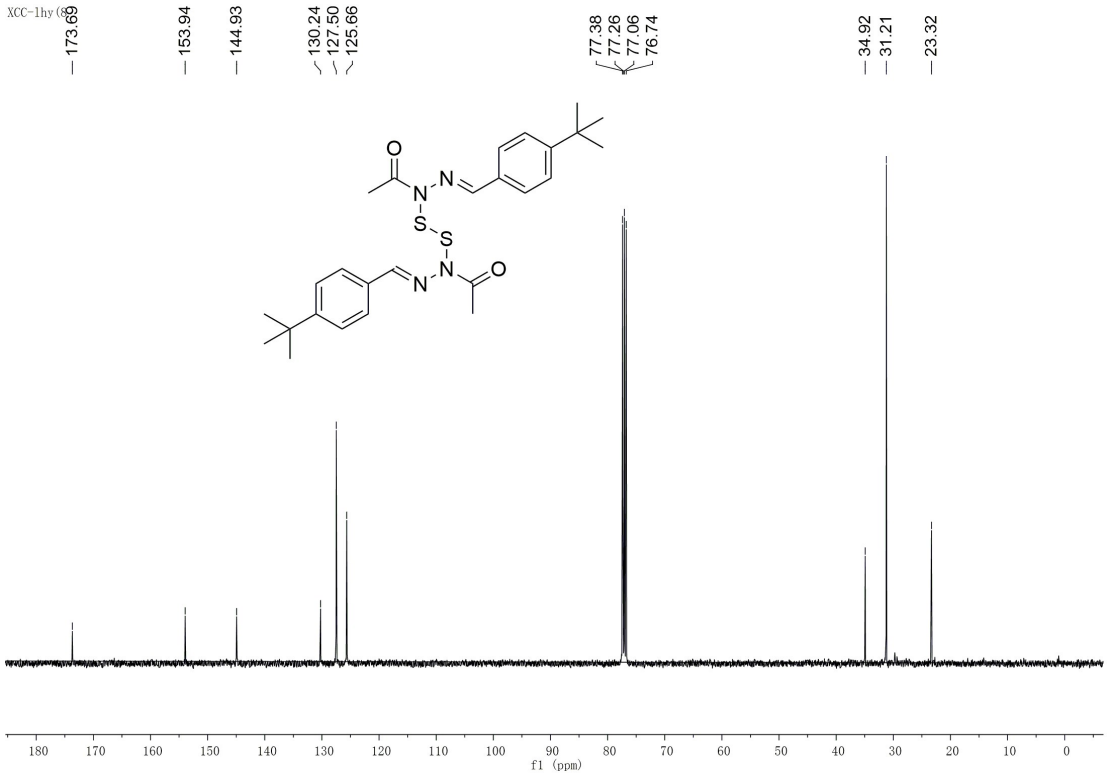
2b MS



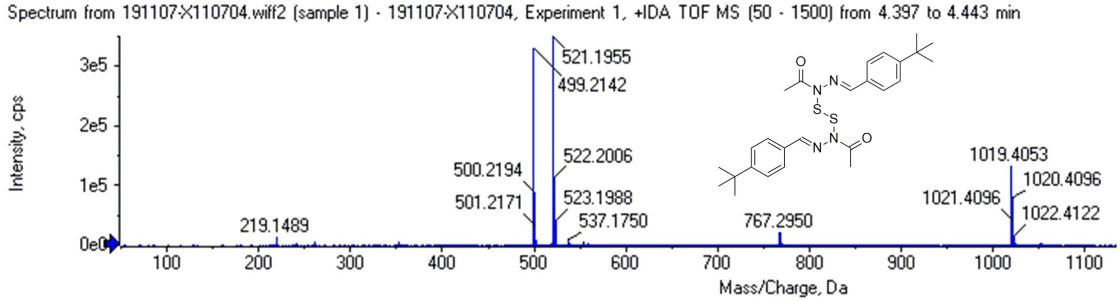
2c ^{1}H NMR


8.05
7.44
7.42
7.30
7.28
7.19
7.19
2.44
1.25
2.00
4.00
4.00
6.00
18.00
f1 (ppm)

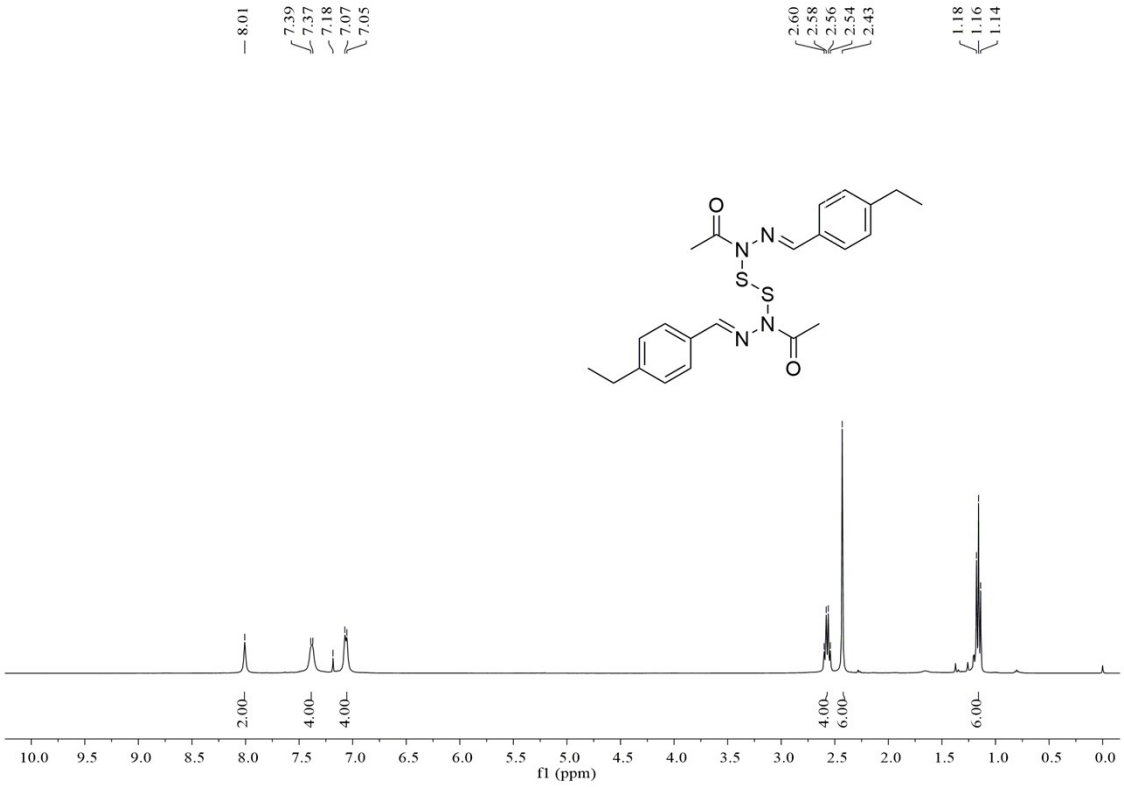
2c ^{13}C NMR


173.69
153.94
144.93
130.24
127.50
125.66
77.38
77.26
77.06
76.74
34.92
31.21
23.32
f1 (ppm)

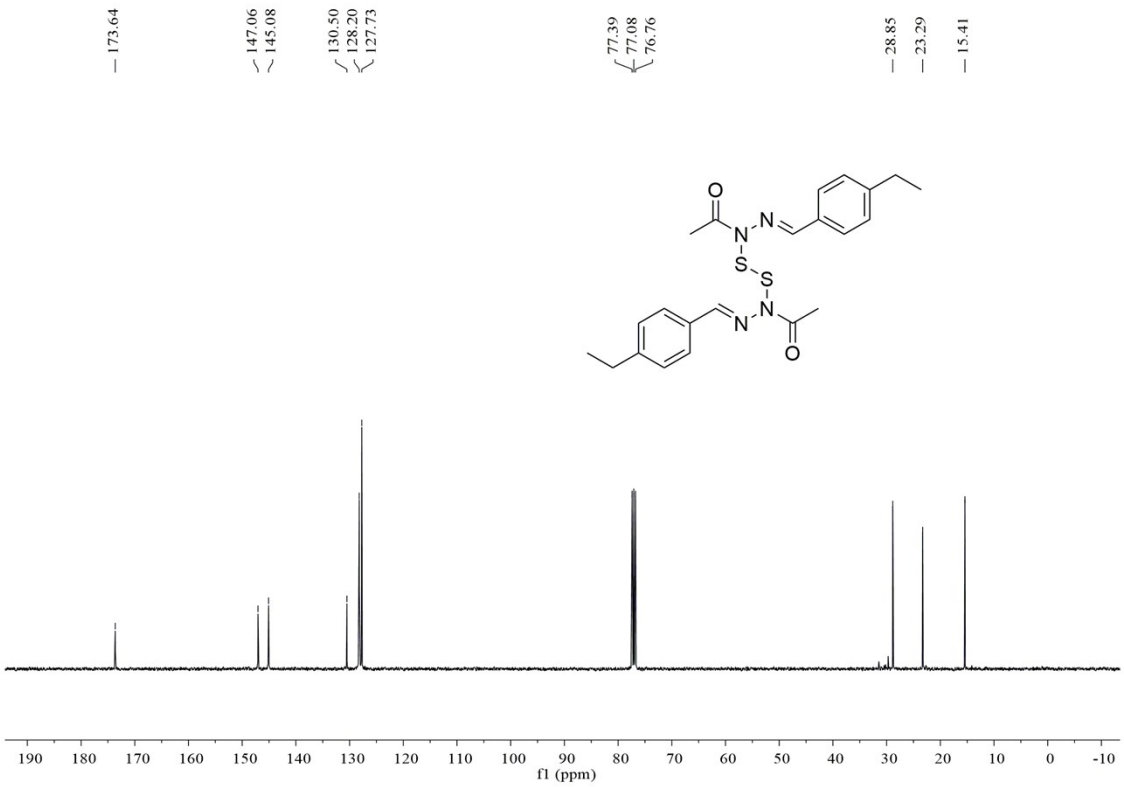
2c MS



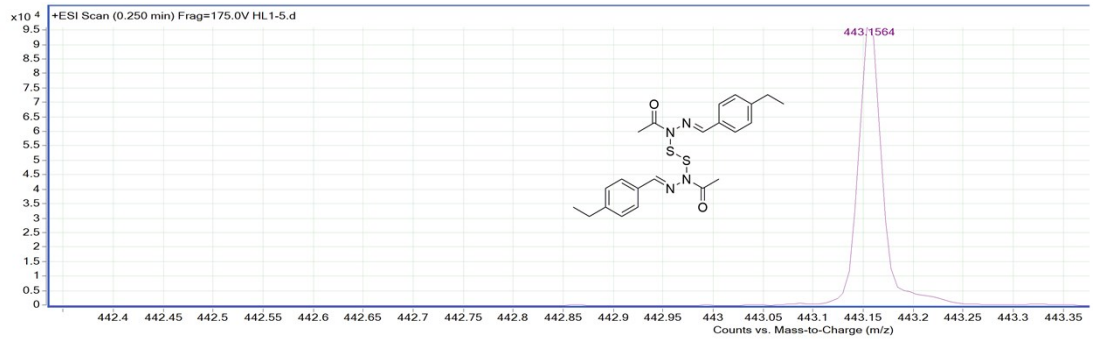
2d ^{1}H NMR



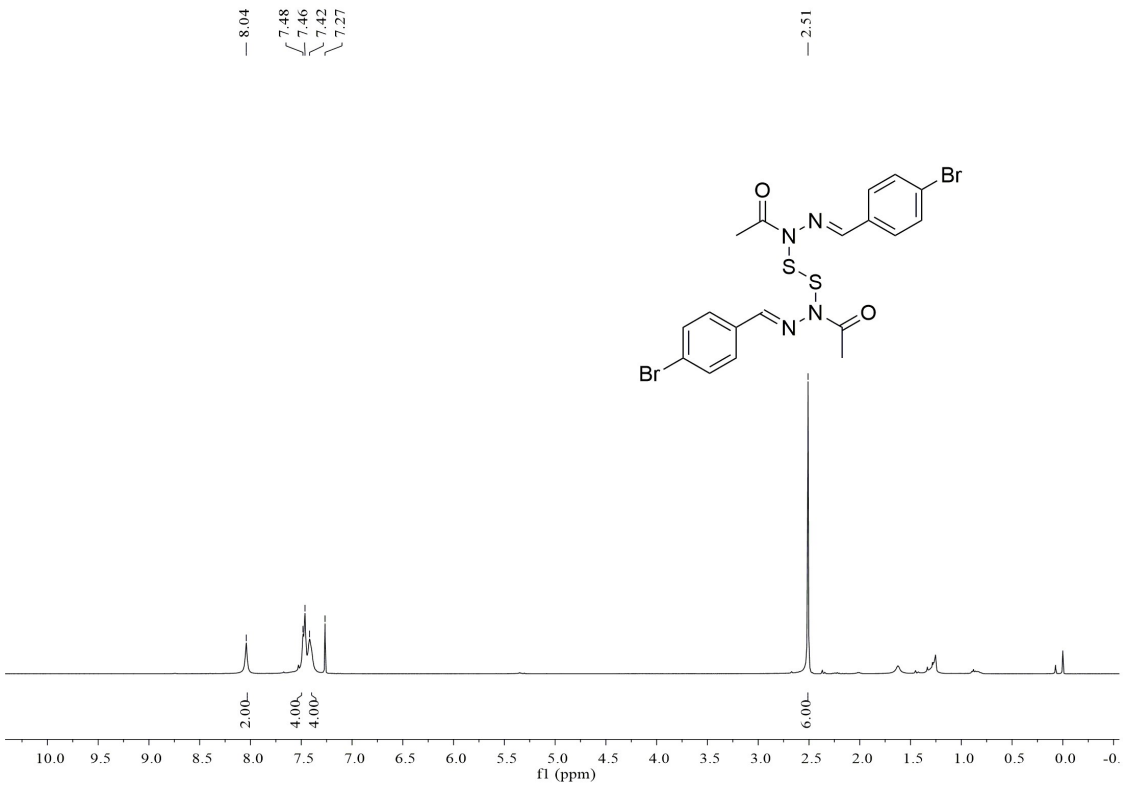
2d ^{13}C NMR



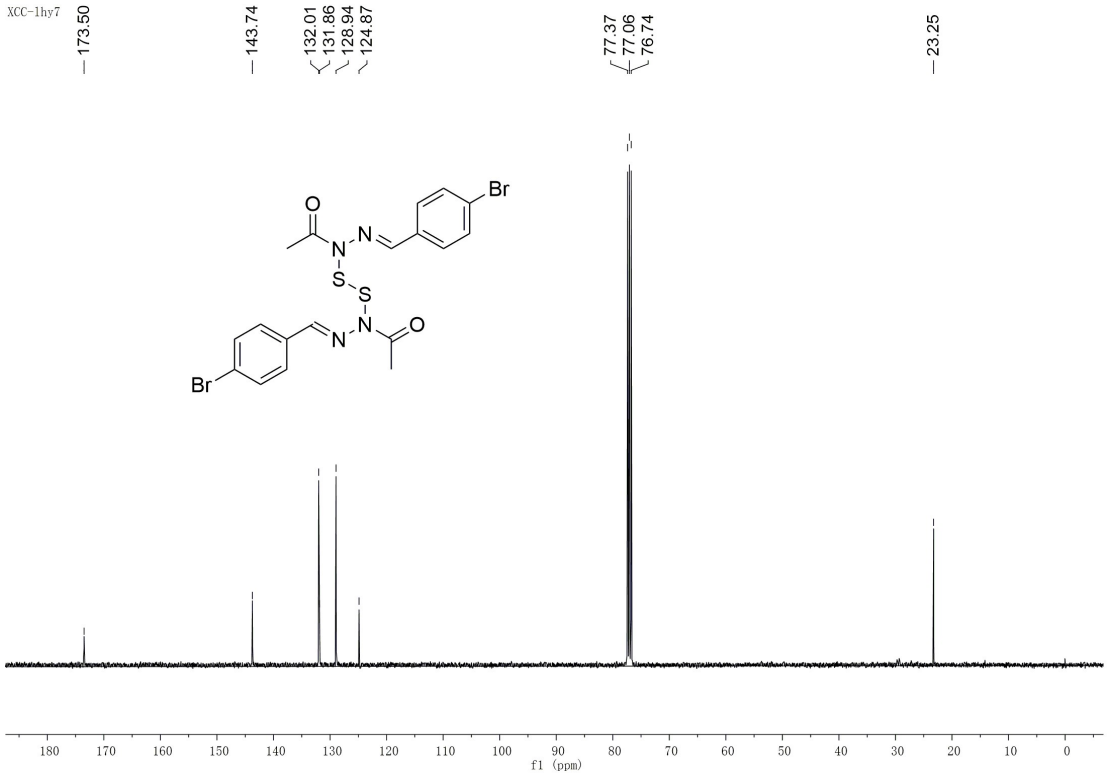
2d MS



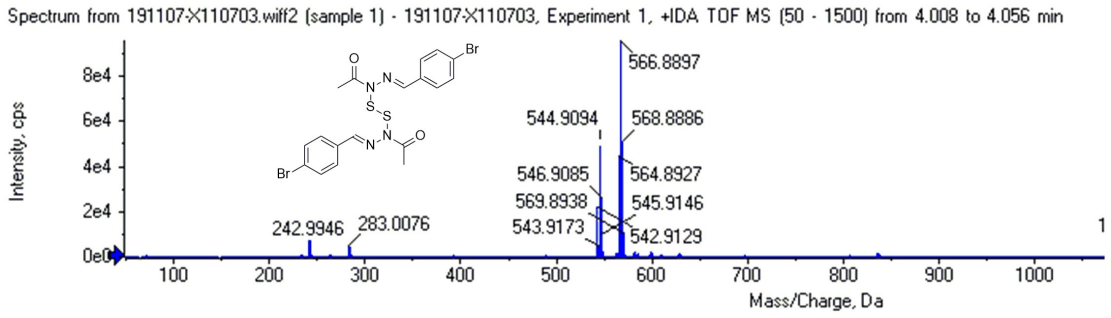
2e ^{1}H NMR



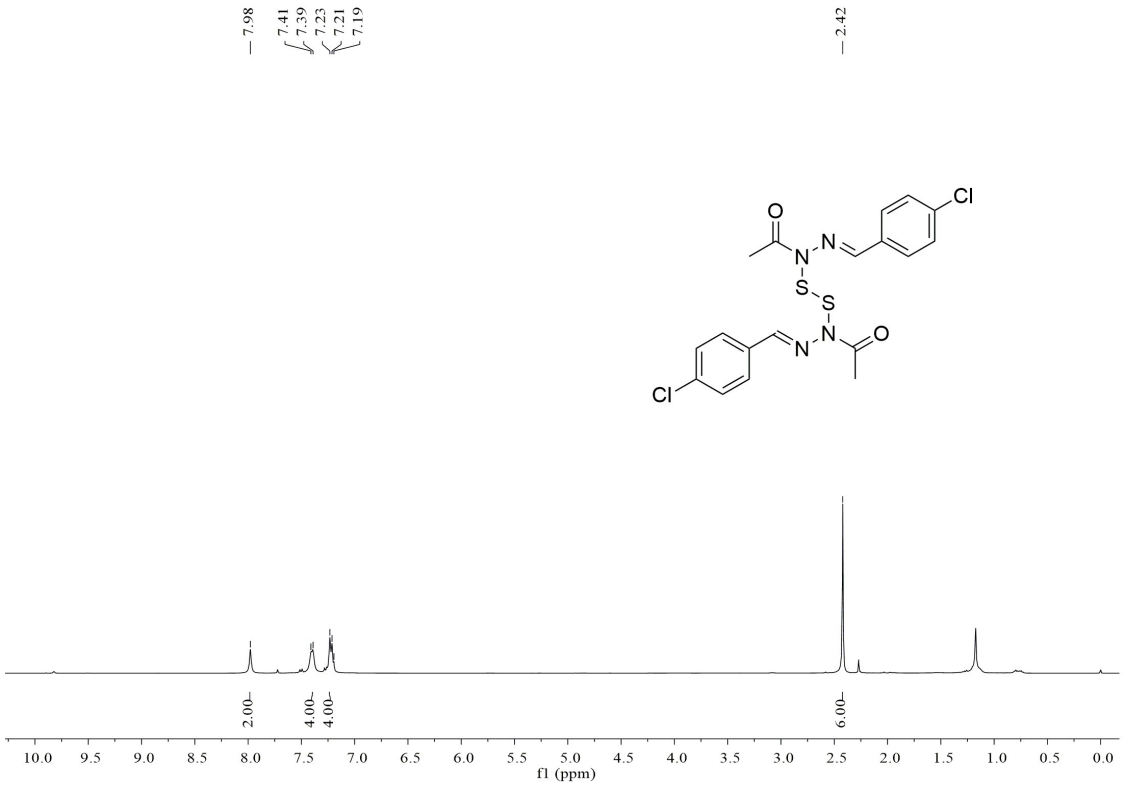
2e ^{13}C NMR



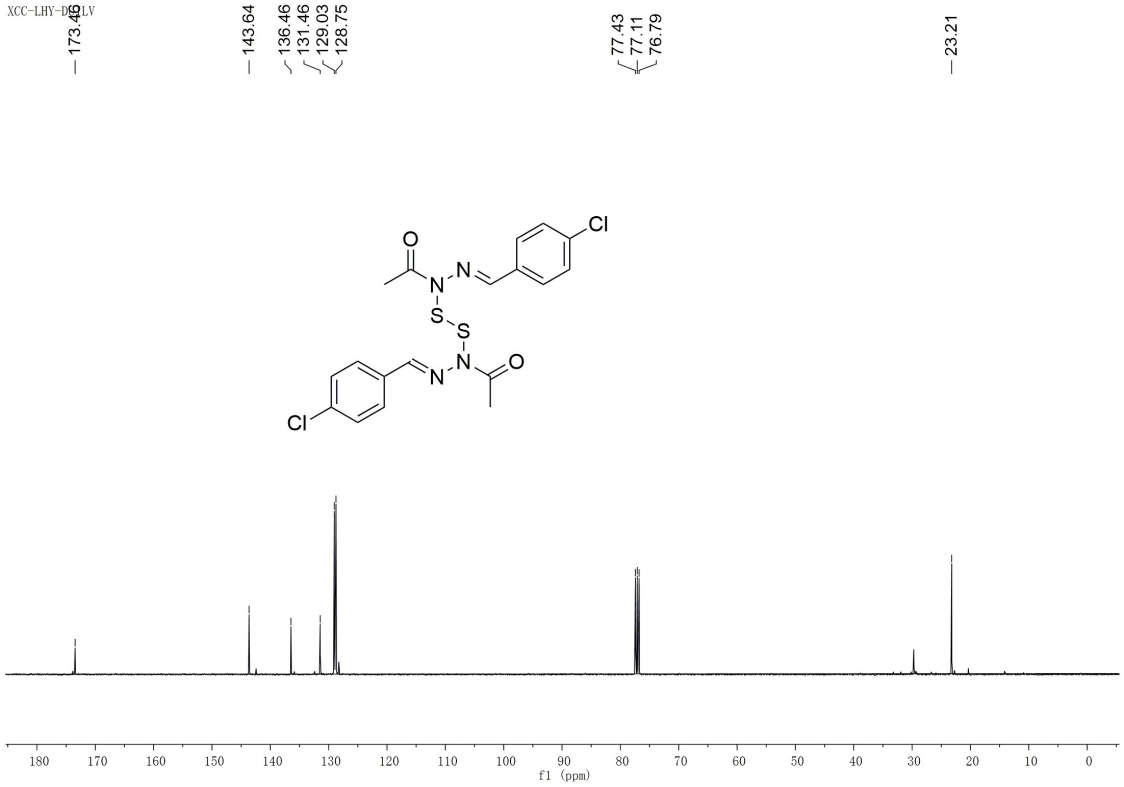
2e MS


Spectrum from 191107-X110703.wiff2 (sample 1) - 191107-X110703, Experiment 1, +IDA TOF MS (50 - 1500) from 4.008 to 4.056 min
Intensity, cps
8e4
6e4
4e4
2e4
0e0
566.8897
544.9094
568.8886
546.9085
564.8927
569.8938
545.9146
543.9173
542.9129
242.9946
283.0076
Br
Br
100
200
300
400
500
600
700
800
900
1000
Mass/Charge, Da

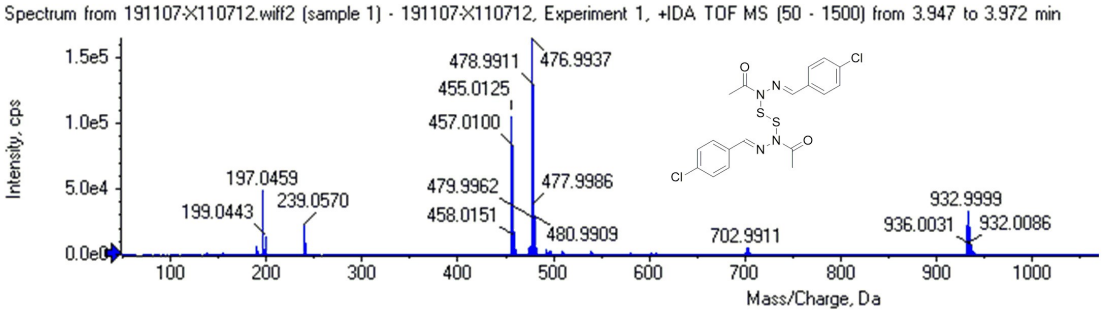
2f ^{1}H NMR


7.98
7.41
7.39
7.23
7.21
7.19
2.42
Cl
Cl
2.00
4.00
4.00
6.00
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)

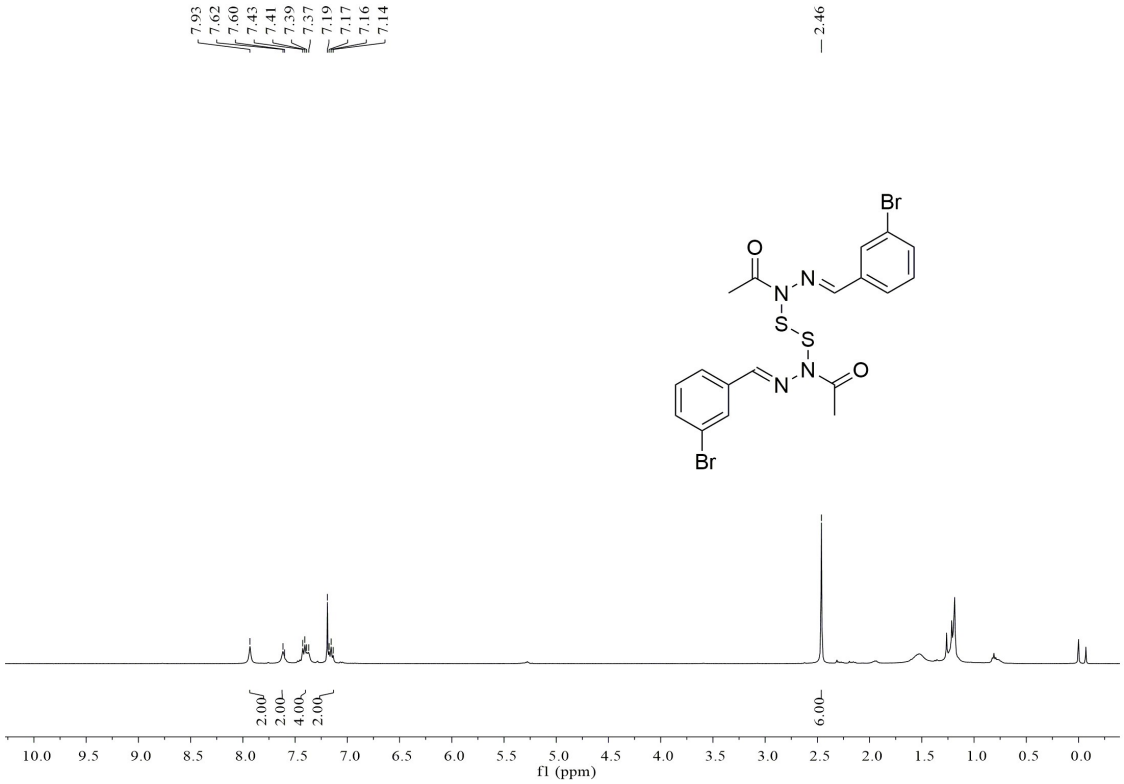
2f ^{13}C NMR



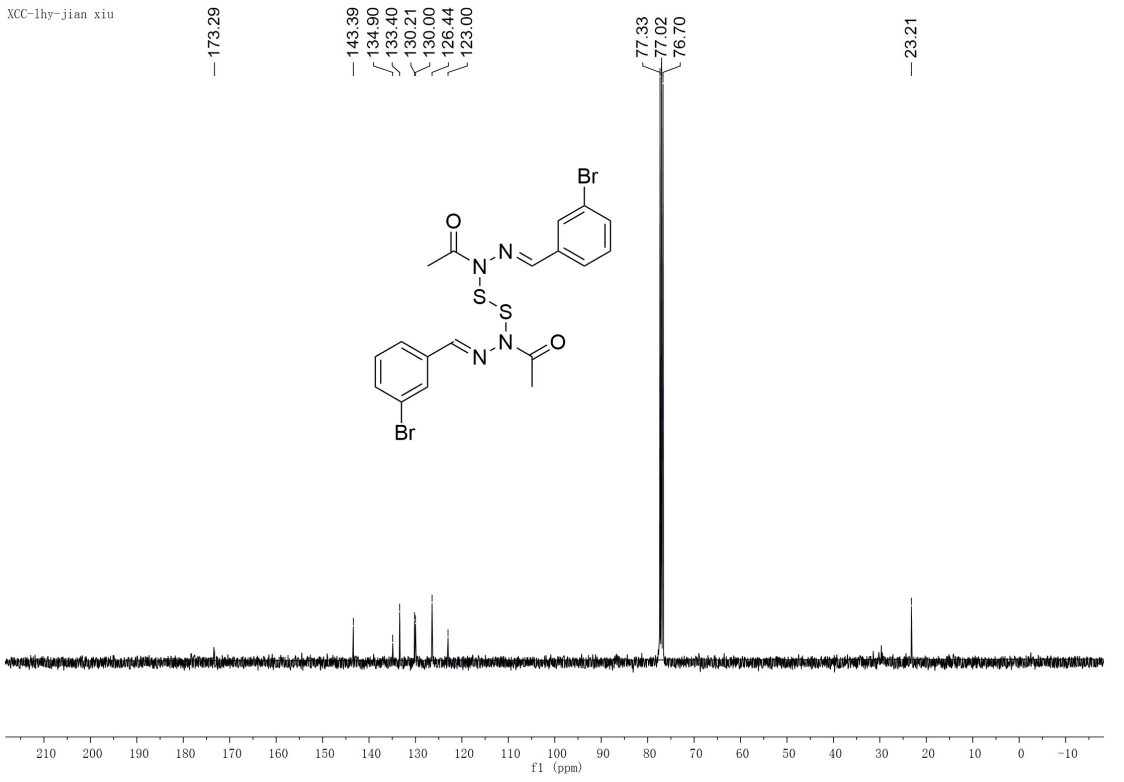
2f MS



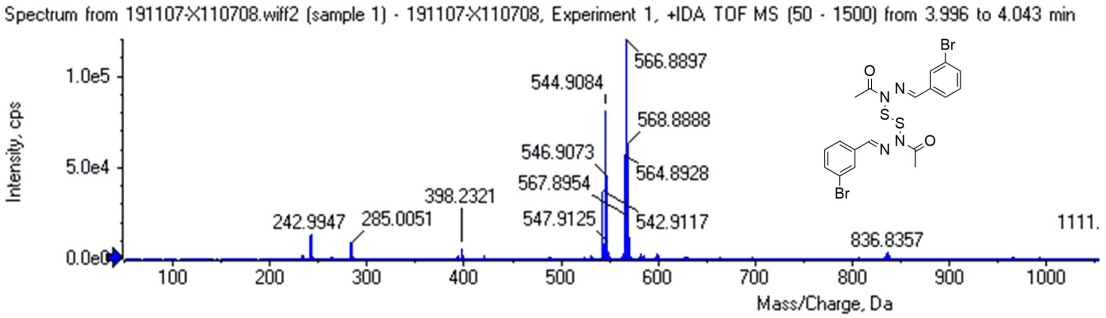
2h ^{1}H NMR



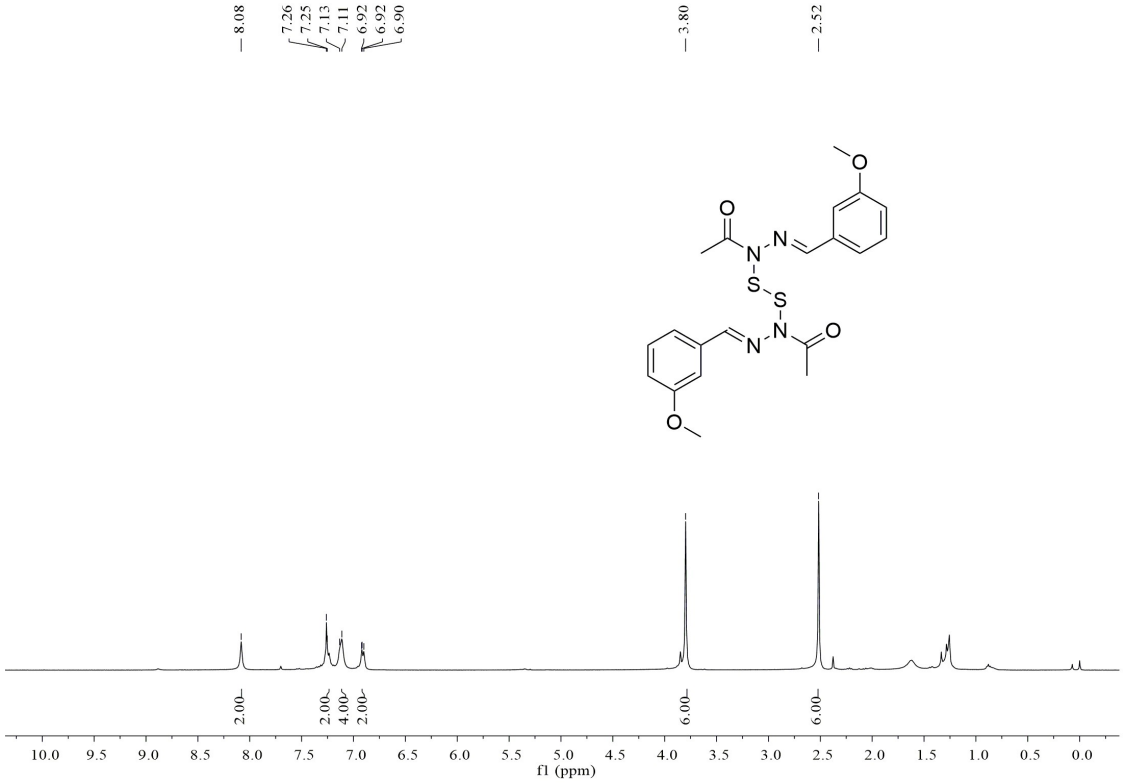
2h ^{13}C NMR



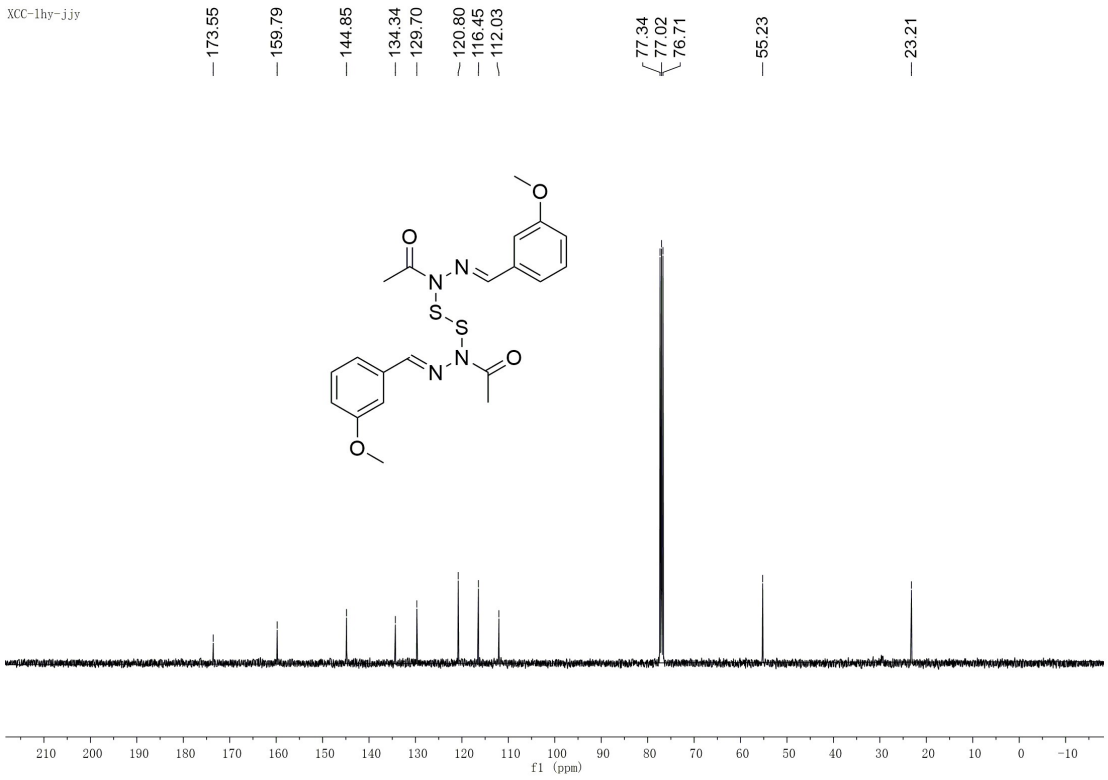
2h MS



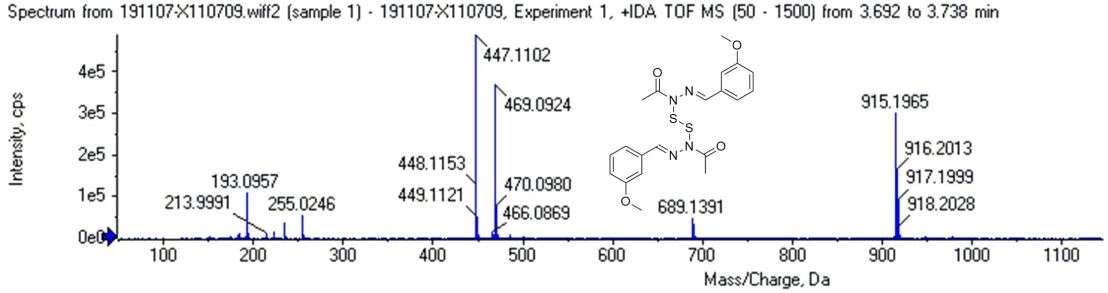
2i ^{1}H NMR



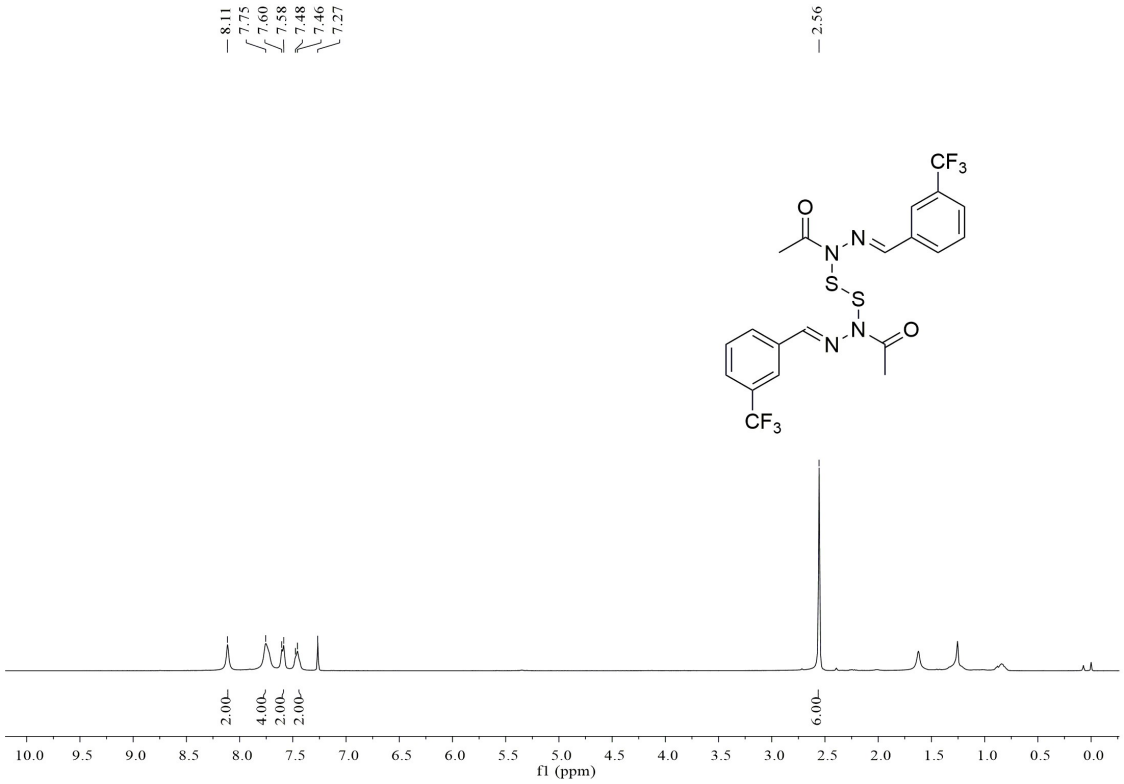
2i ^{13}C NMR



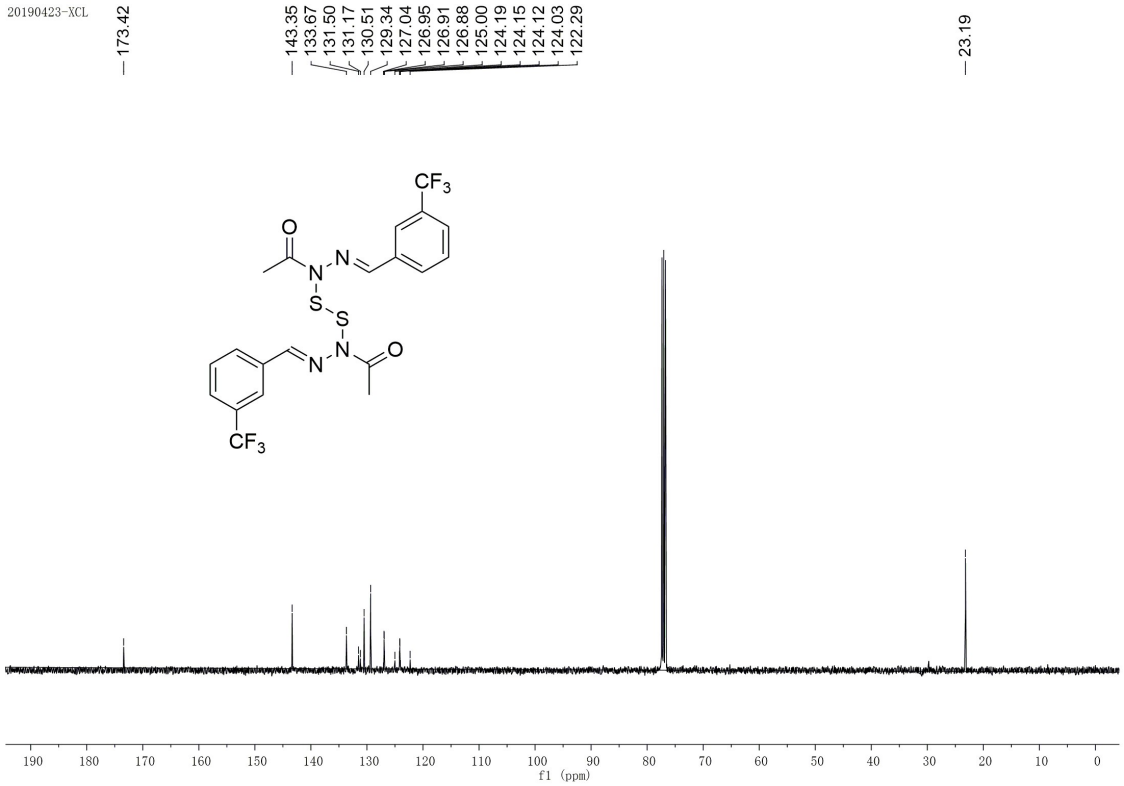
2i MS



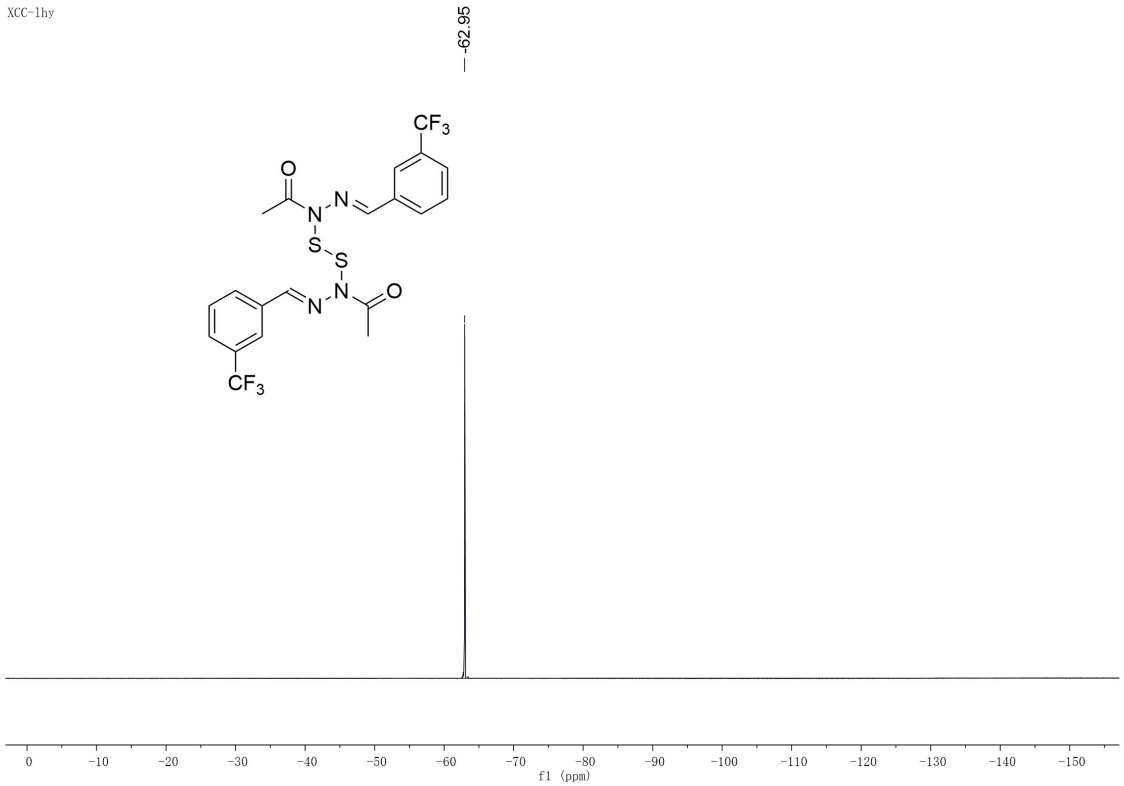
2j ^{1}H NMR



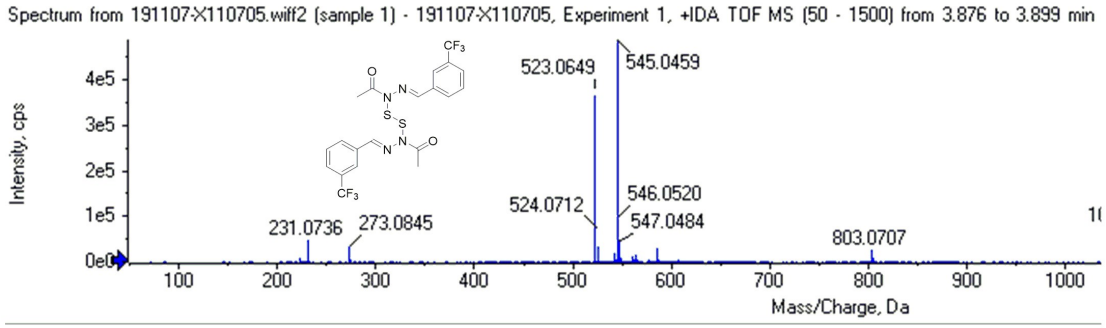
2j ^{13}C NMR



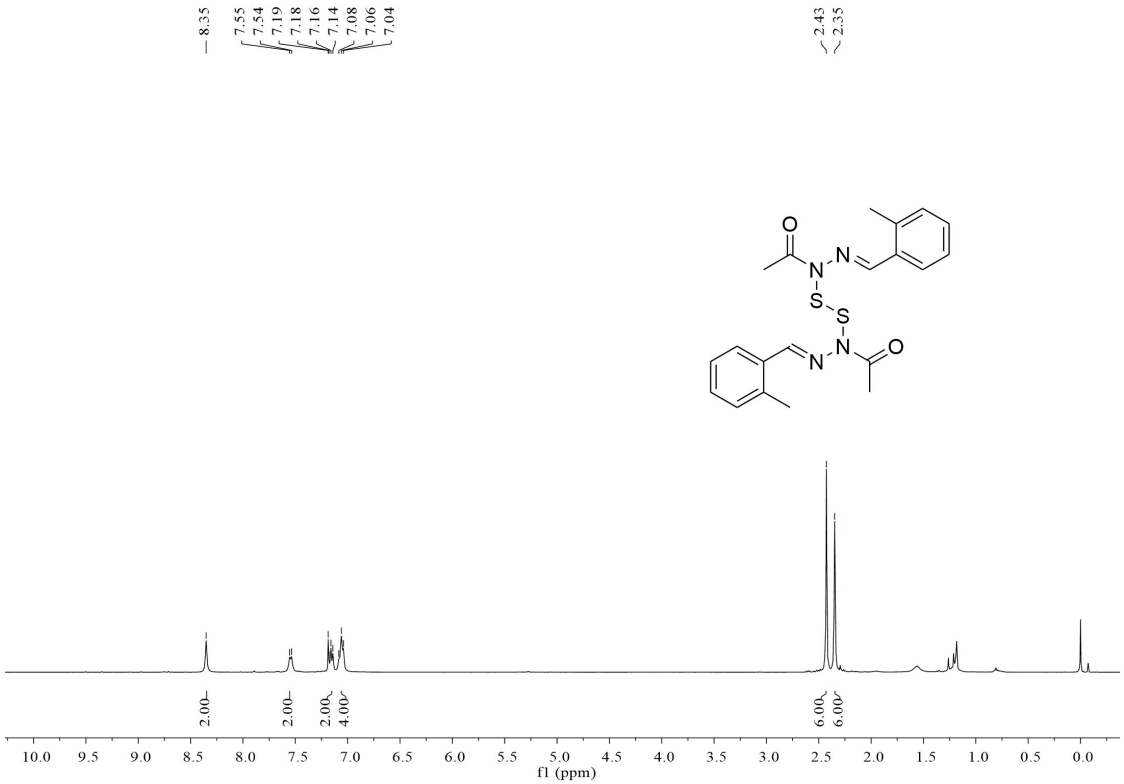
2j ^{19}F NMR



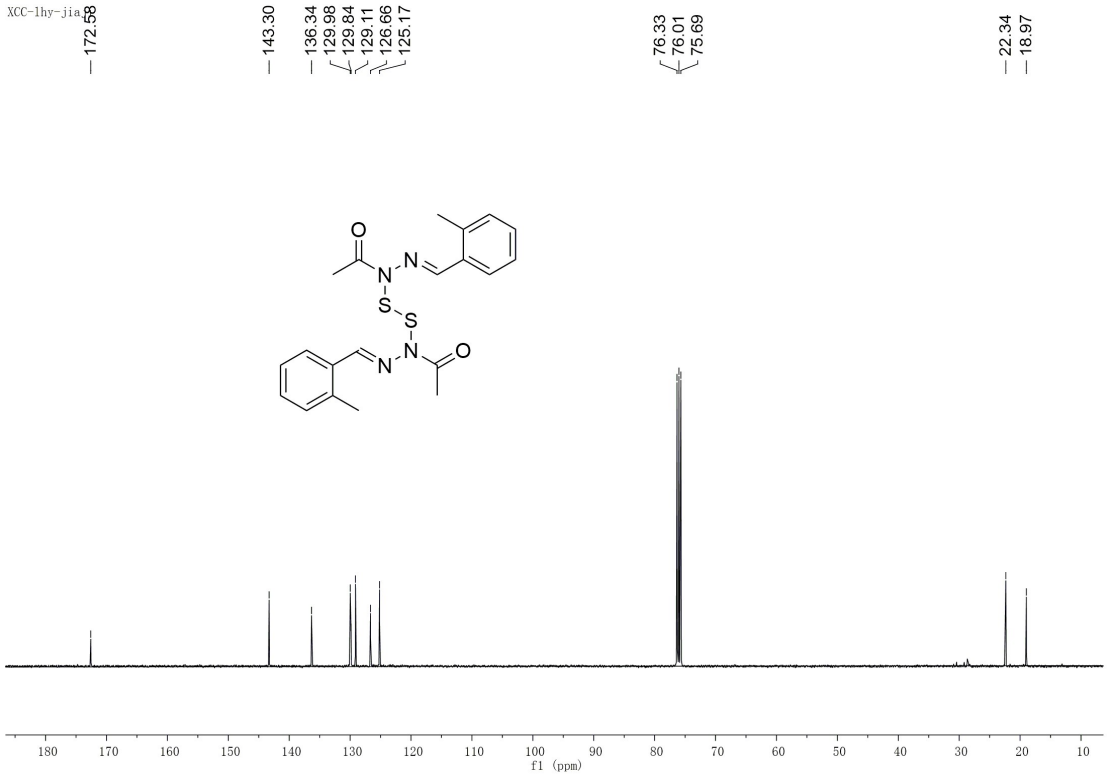
2j MS



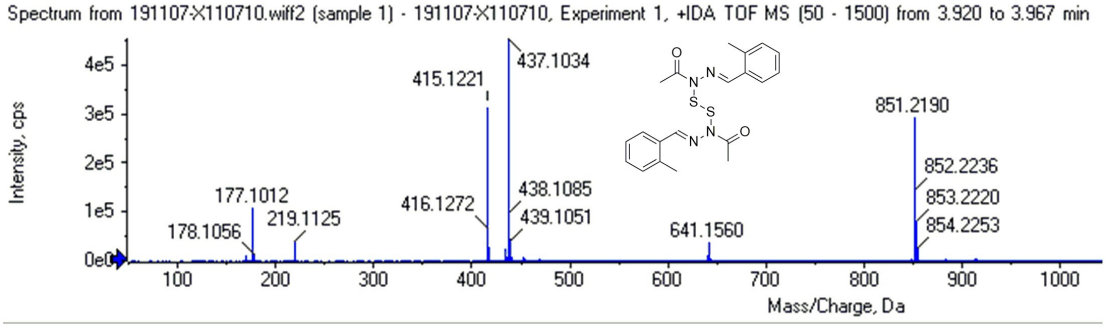
2l ^{1}H NMR



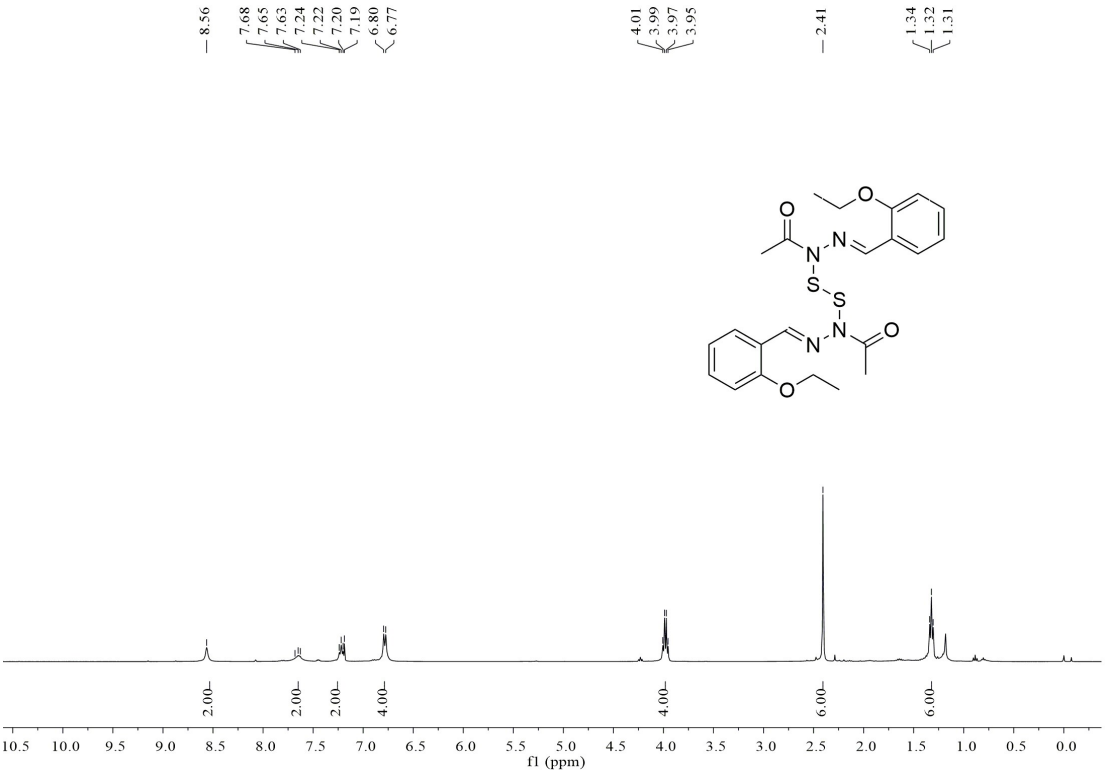
2l ^{13}C NMR



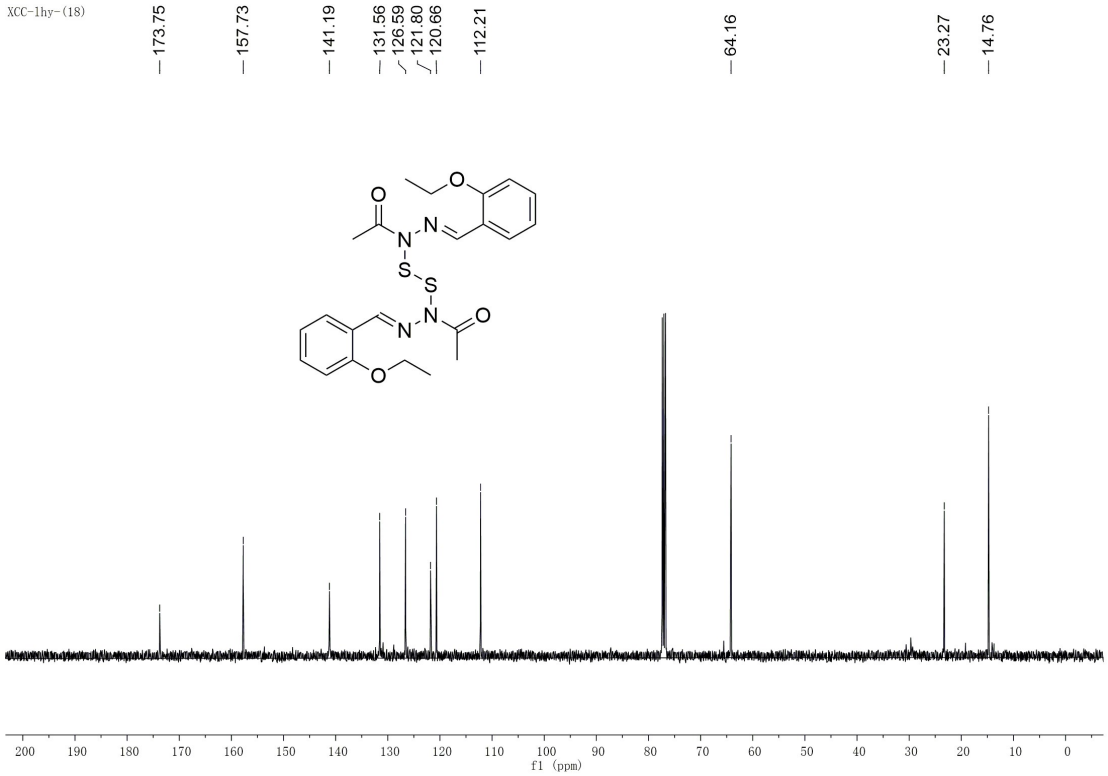
2l MS



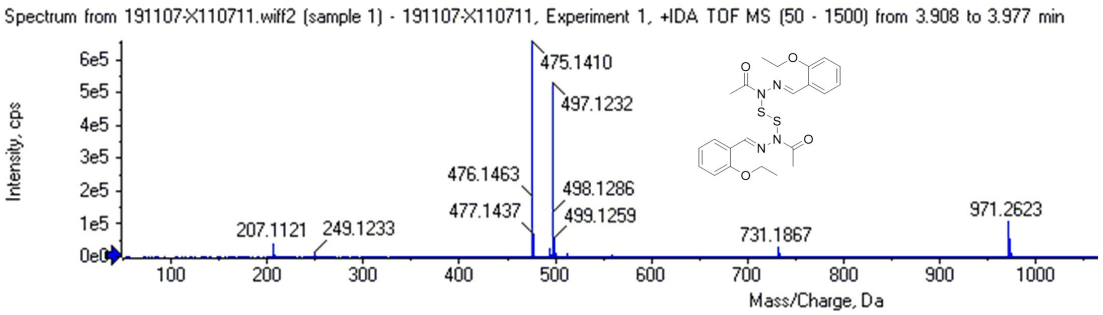
2m ^{1}H NMR



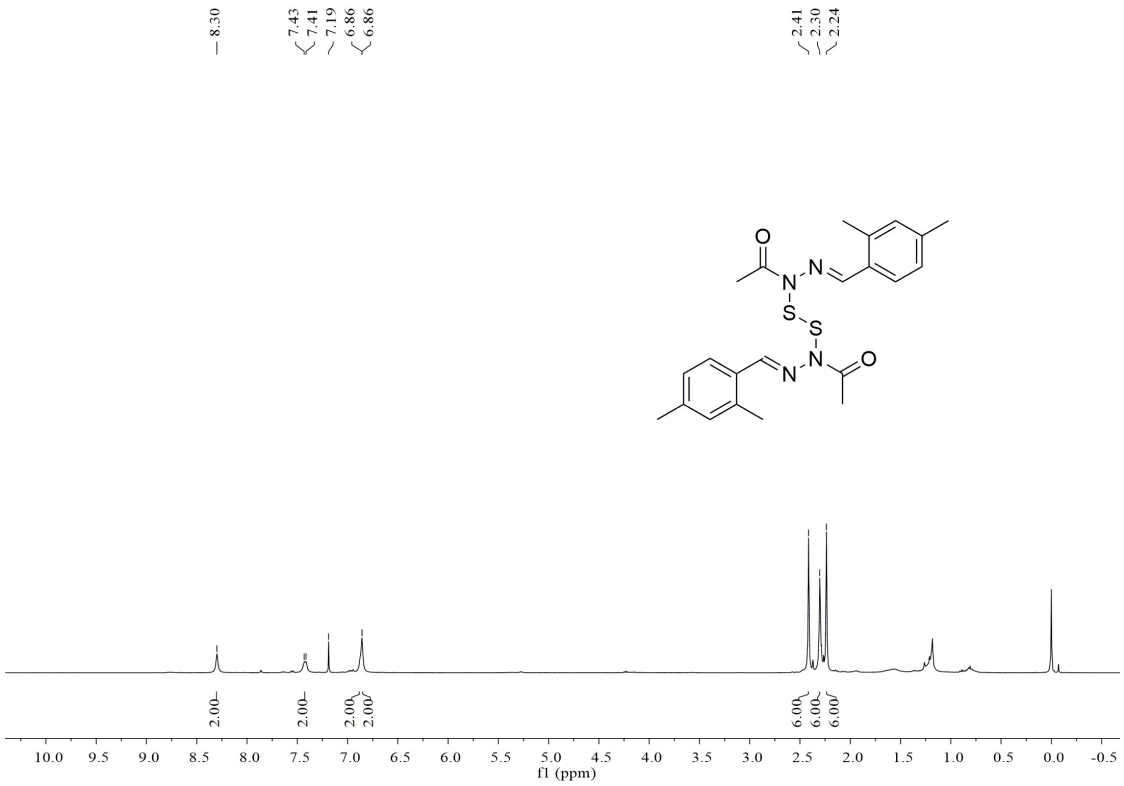
2m ^{13}C NMR



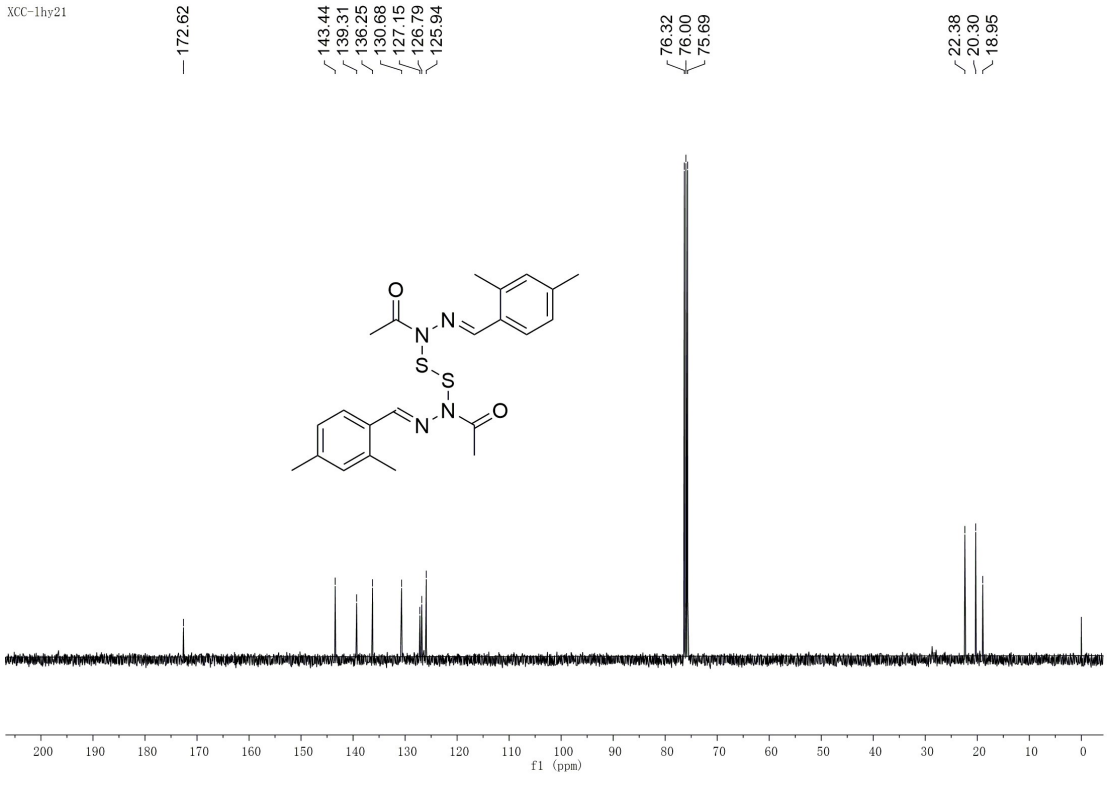
2m MS



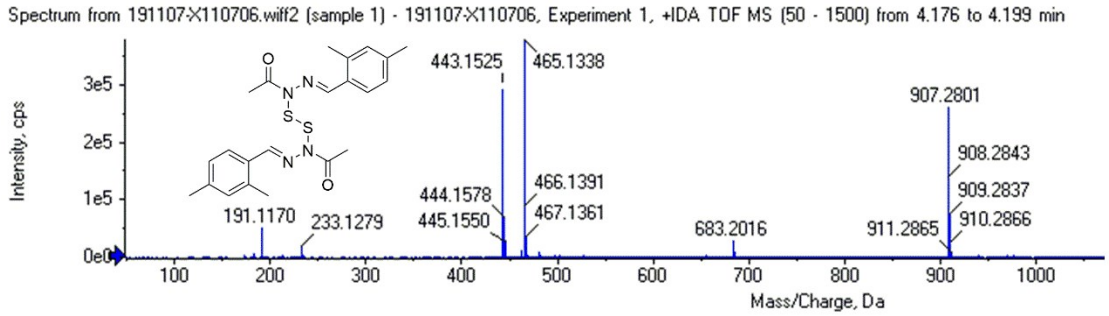
2q ^{1}H NMR



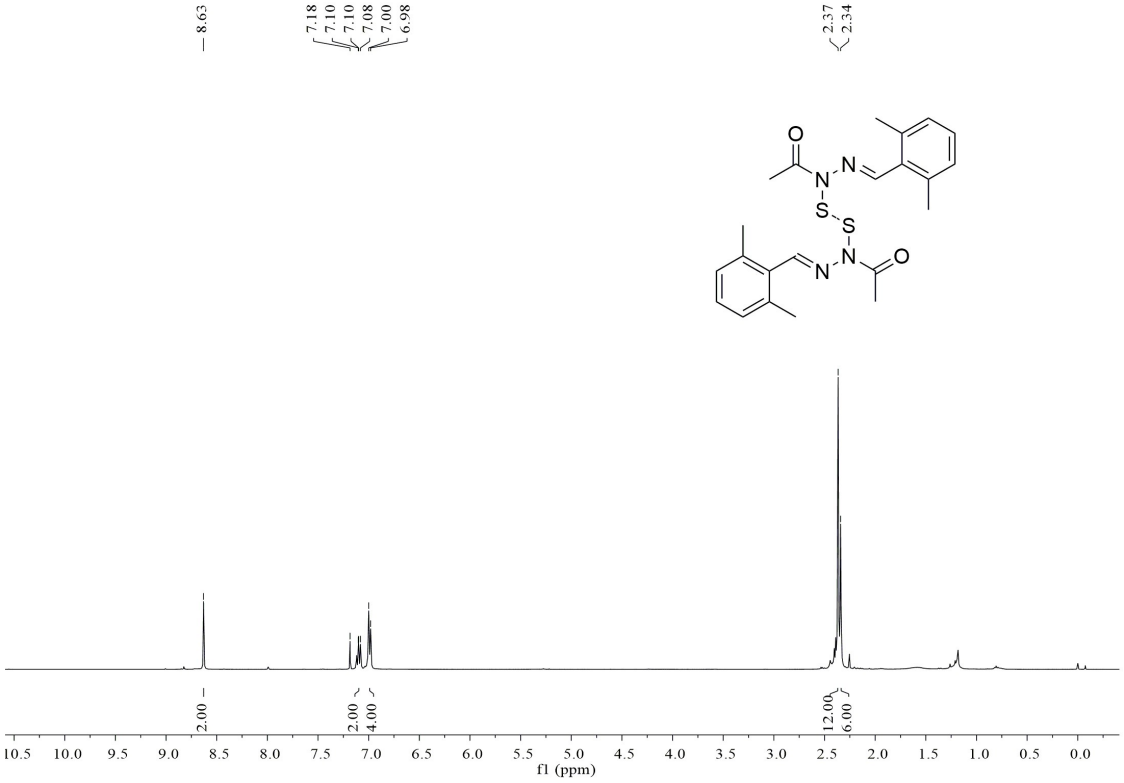
2q ^{13}C NMR



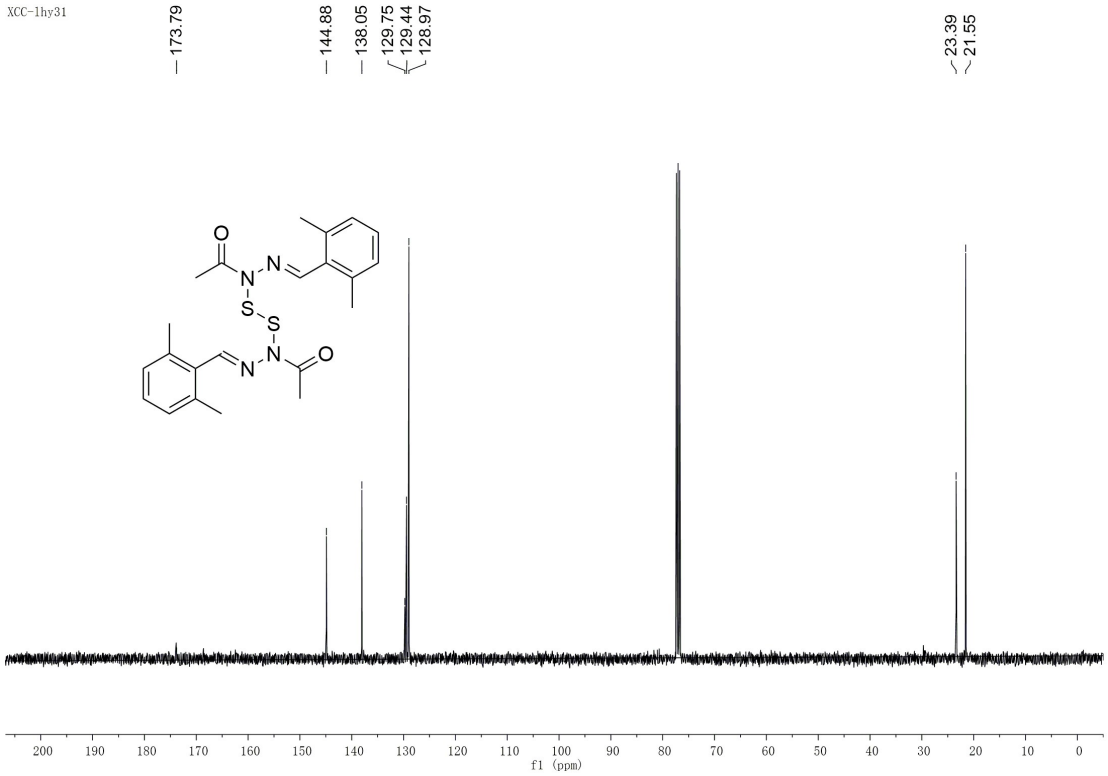
2q MS



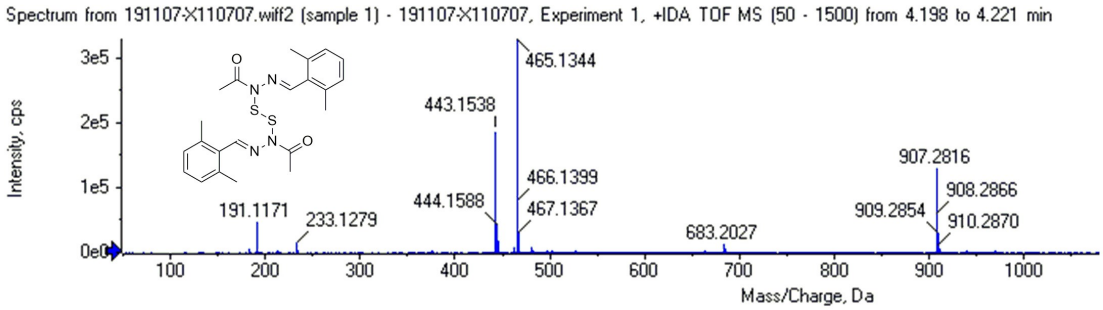
2r ^{1}H NMR



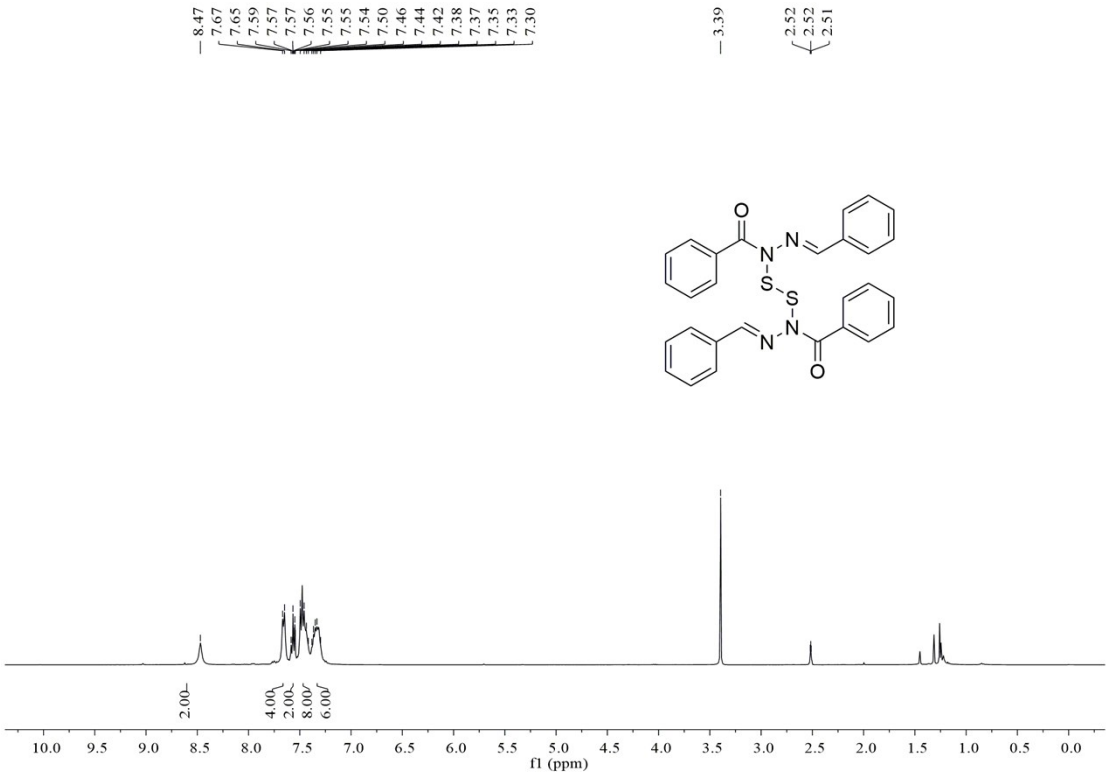
2r ^{13}C NMR



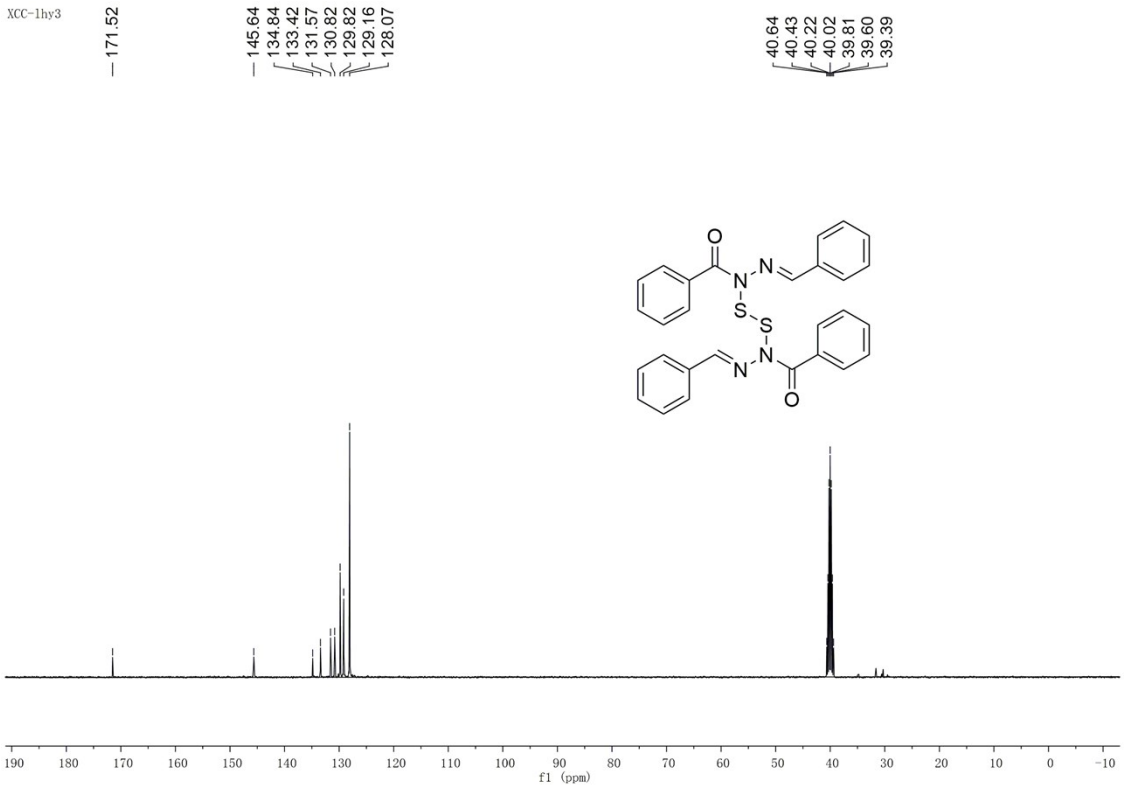
2r MS



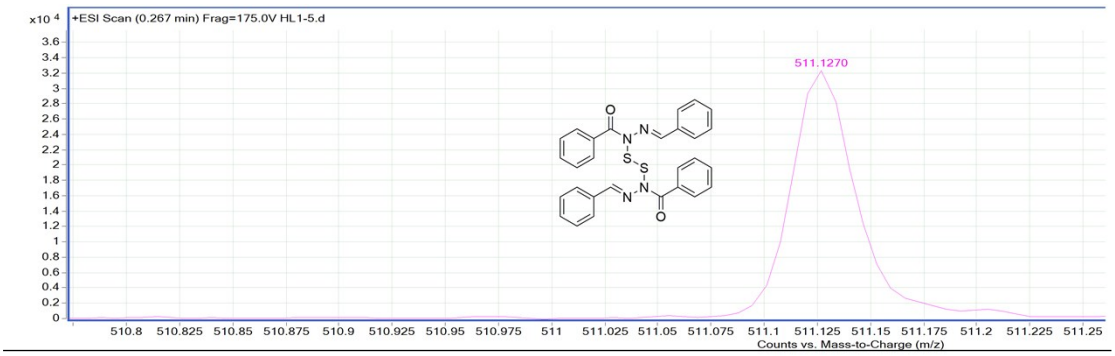
2s ^{1}H NMR (DMSO)



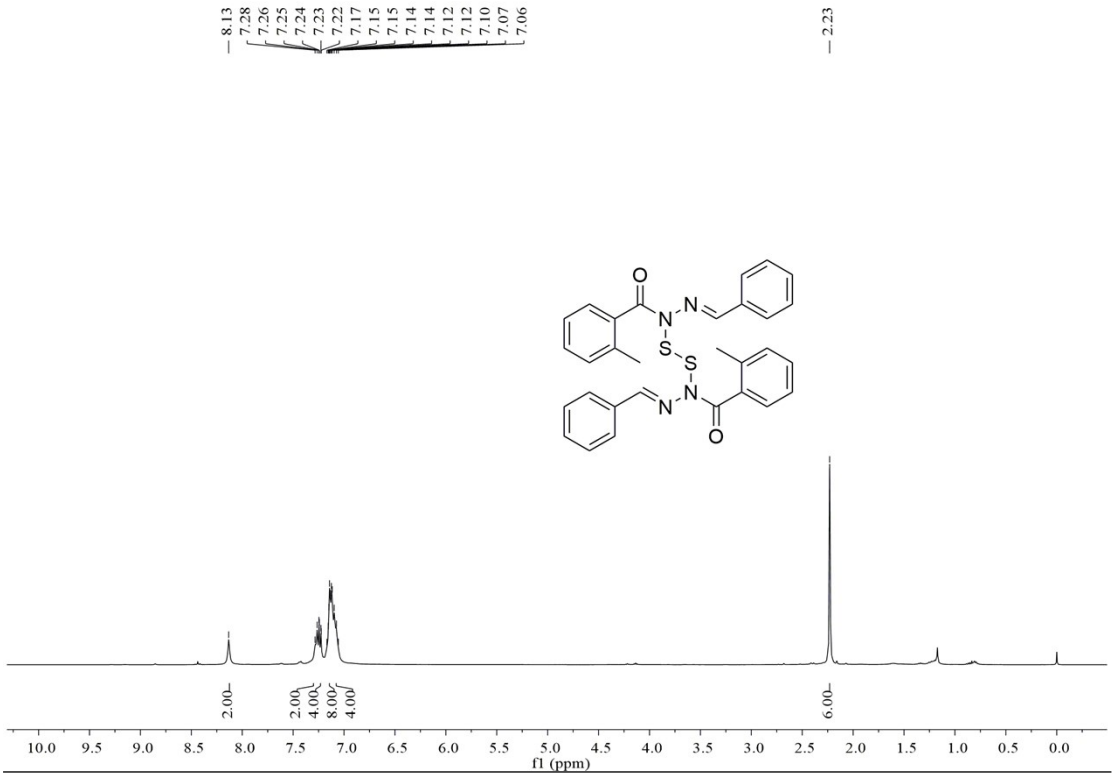
2s ^{13}C NMR



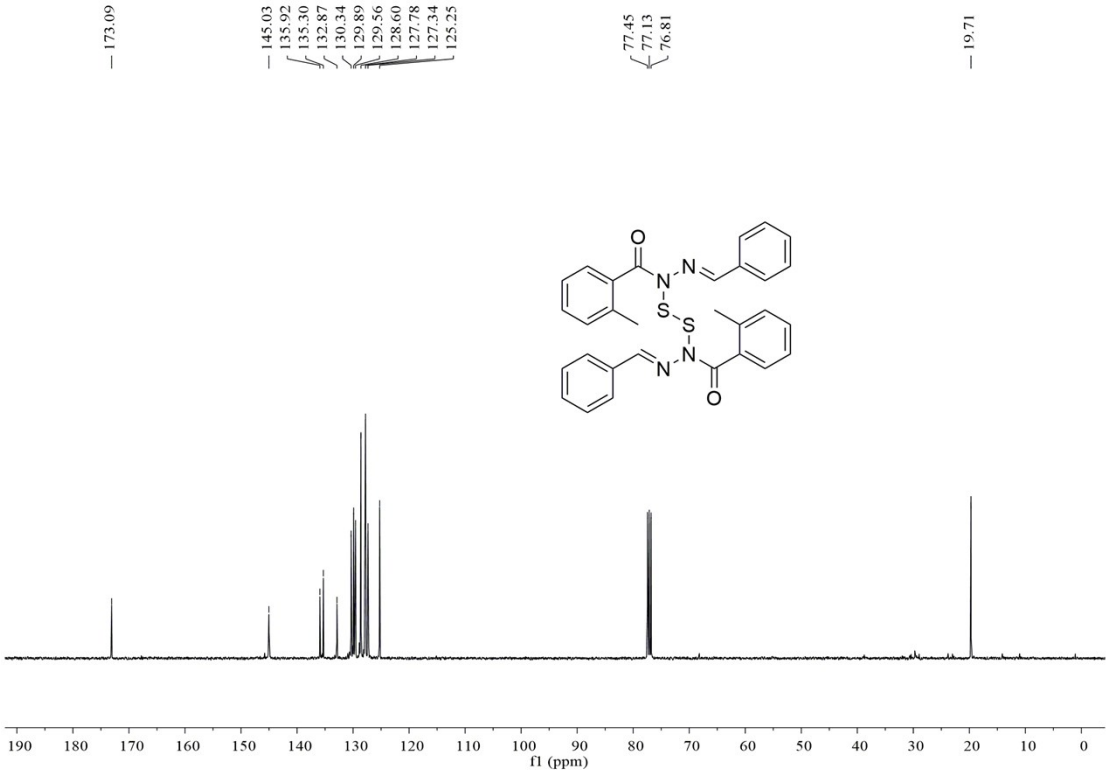
2s MS



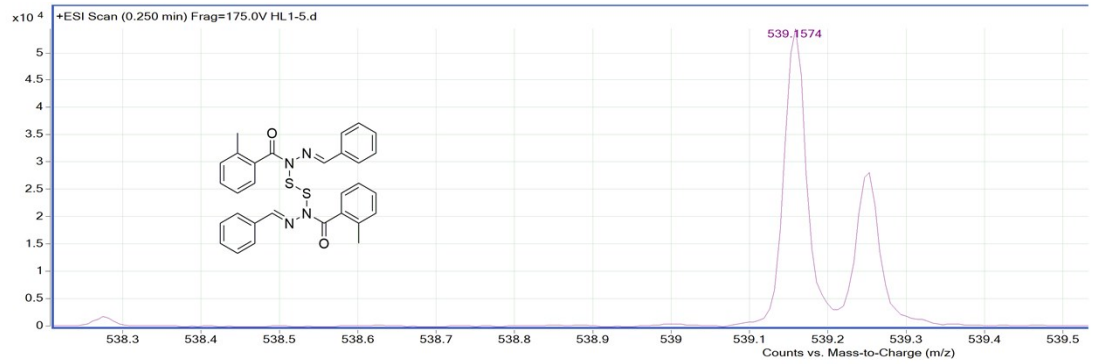
2t ^{1}H NMR



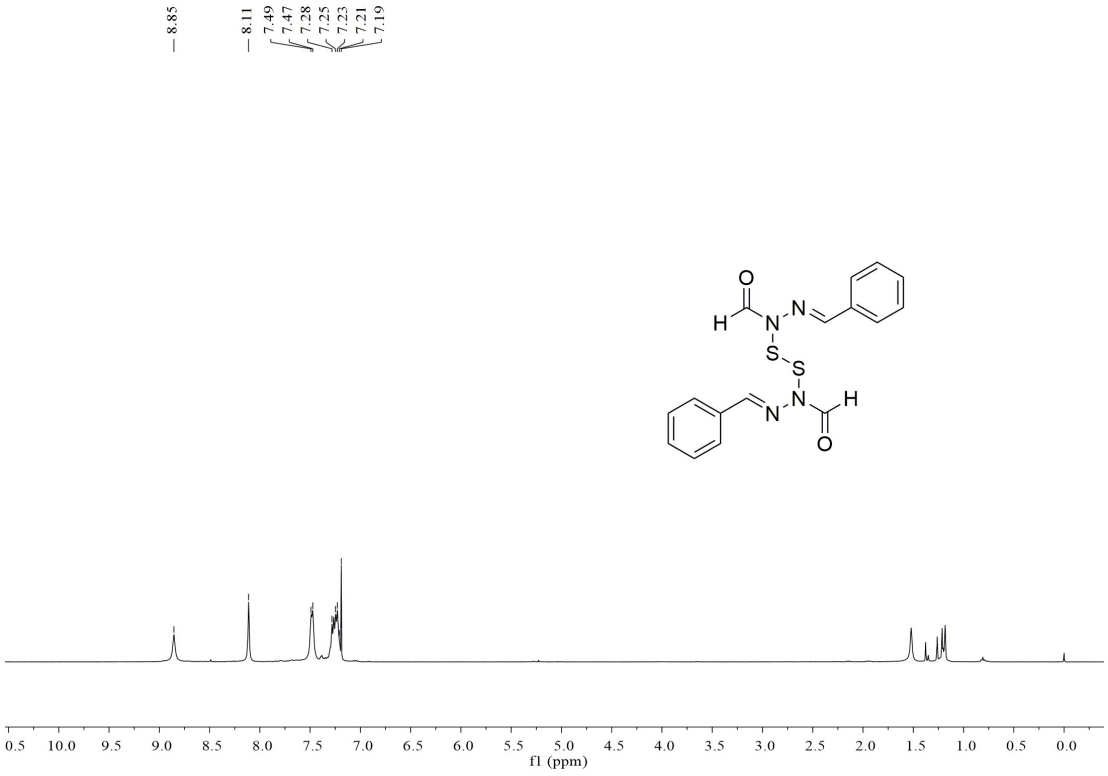
2t ^{13}C NMR



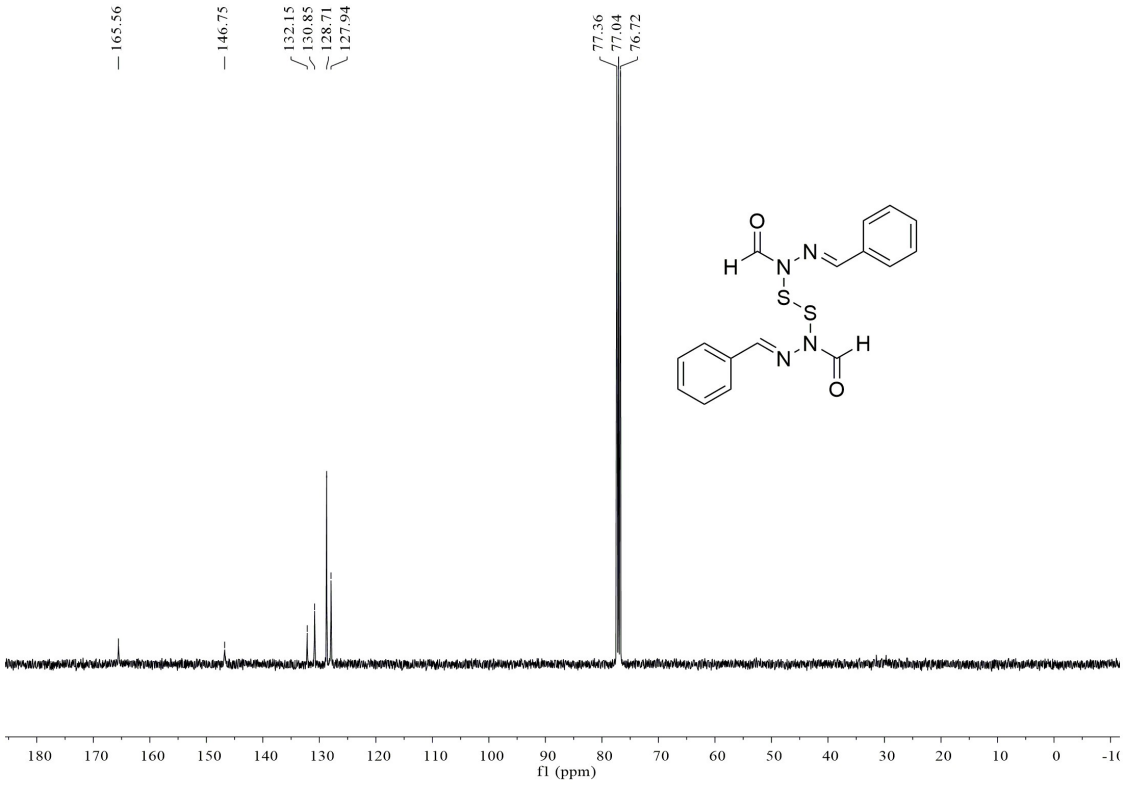
2t MS



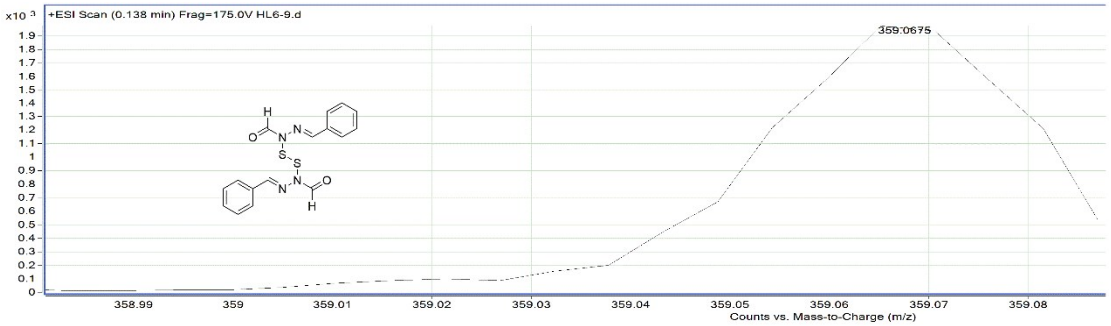
2u ^{1}H NMR



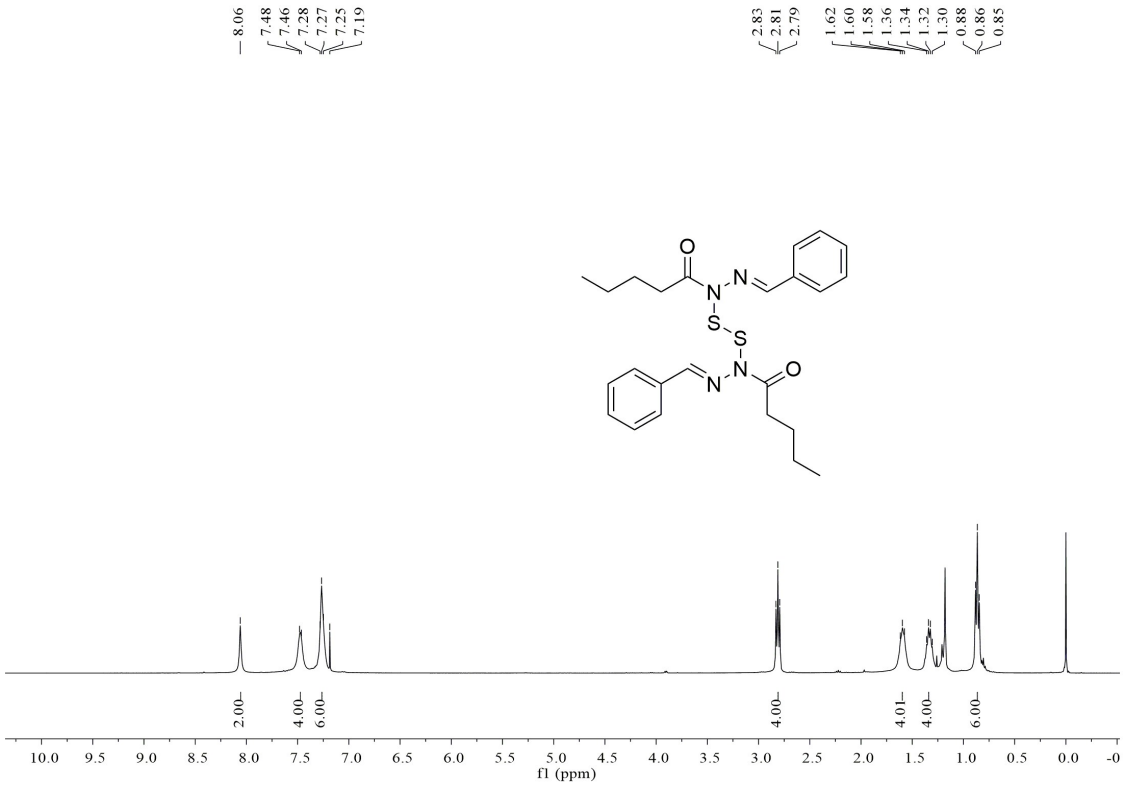
2u ^{13}C NMR



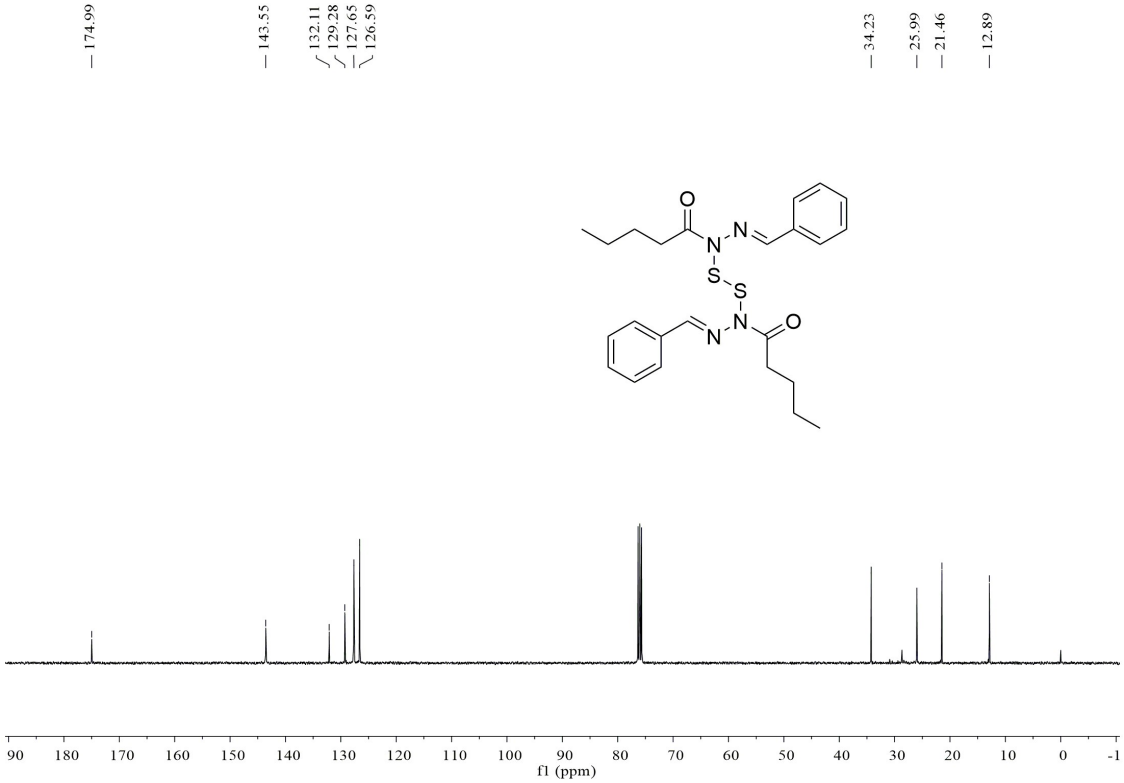
2u MS



2v ^{1}H NMR



2v ^{13}C NMR



2v MS