Supporting information

Synthesis and structure-activity relationship studies of water-soluble β-cyclodextrin-glycyrrhetinic acid conjugates as potential anti-influenza virus agents

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1. Synthesis of compounds **7, 8, 14-17** and **36**

1.1 1H-benzotriazol-1-yl 3β-hydroxy-11-oxo-olean-12-en-30-oate (**7**)[1]

To a solution of glycyrrhetinic acid **1** (4 g, 8.51 mmol) and TBTU (4 g, 12.4 mmol) in dry tetrahydrofuran (80 mL), DIPEA (2 mL, 1.21 mmol) was added. After continuous stirring at room temperature for 24 h, the solvent was removed by steaming. The residue was purified by column chromatography to give 4.5 g (90%) of compound **7** as a canary yellow solid. R_f = 0.13 (petroleum ether:ethyl acetate= 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, 1H, *J* = 8.4 Hz), 7.55 (t, 1H, *J* = 7.2 Hz), 7.42 (t, 1H, *J* = 7.4 Hz), 7.33 (d, 1H, *J* = 8.3 Hz), 5.68 (s, 1H), 3.21 (dd, 1H, *J* = 10.8, 5.4 Hz), 2.74 (td, 1H, *J* = 13.5, 3.4 Hz), 2.32 (s, 1H), 2.14–0.94 (m, other aliphatic ring protons), 1.56, 1.41, 1.13, 1.11, 0.99, 0.91, 0.78 (s, each 3H, 7 × CH_3), 0.68 (d, 1H, *J* = 11.6 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ 199.94, 172.53, 167.70, 143.49, 128.93, 128.84, 128.52, 124.83, 120.55, 78.64, 61.80, 55.26, 48.20, 45.34, 44.33, 43.13, 40.83, 39.07, 39.04, 37.70, 37.03, 32.68, 31.94, 31.11, 28.49, 28.03, 27.96, 27.16, 26.29, 23.42, 18.50, 17.07, 16.28, 15.52

1.2 (N-prop-2-yn-1-yl) (3*β*,20*β*)-3-hydroxy-11-oxo-olean-12-en-29-amide (**8**)[2]

To a solution of compound **7** (505 mg, 0.85 mmol) and 69 μL propargyl amine (1.27 mmol) in DMF(15mL) was added Na_2CO_3 (361 mg, 1.62 mmol). The resulting solution was stirred vigorously for 24 h at room temperature. The solvent was removed by steaming. The residue was purified by column chromatography to give 223 mg (51%) of compound **8** as a white solid. R_f = 0.33 (petroleum ether:ethyl acetate = 1:1);^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (t, 1H, *J* = 4.2 Hz), 5.68 (s, 1H), 4.11 (dd, 1H, *J* = 17.4, 2.9 Hz), 4.02 (dd, 1H, *J* = 17.3, 2.9 Hz), 3.22 (dd, 1H, *J* = 10.2, 5.8 Hz), 2.78 (td, 1H, *J* = 13.4, 3.4 Hz), 2.33 (s, 1H), 2.24 (t, 1H, *J* = 2.8 Hz), 2.17–0.94 (m, other aliphatic ring protons), 1.37, 1.13 (s, each 3H, 2 × CH_3), 1.12 (s, 6H, 2 × CH_3), 1.00, 0.81, 0.80 (s, each 3H, 3 × CH_3), 0.69 (d, 1H, *J* = 11.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.11, 175.46, 168.99, 128.54, 79.73, 78.76, 71.67, 61.81, 54.94, 48.02, 45.34, 43.51, 43.17, 41.79, 39.16, 39.12, 37.33, 37.07, 32.75, 31.89, 31.43, 29.30, 28.38, 28.09, 27.28, 26.45, 26.37, 23.33, 18.66, 17.46, 16.34

1.3 6^A-*O*-(*p*-Toluenesulfonyl)-*β*-CD **(14)**[3]

β-CD (10.0g, 8.8 mmol) was suspended in 70 mL of water, and NaOH (1.06 g, 26.4 mmol) in 3.0 mL of water was added dropwise over 10 min. The suspension became homogeneous after the addition was complete. *p*-Toluenesulfonyl chloride (1.68 g, 8.8 mmol) in 4.0 mL CH_3CN was added dropwise over 20 min. A white precipitate was visible immediately after the start of the addition. The reaction mixture was stirred another 2 h at room temperature and then filtered. The filtrate was acidified to about pH 6-7 with 1N HCl and the product allowed to precipitate at 4°C overnight. The resulting white precipitate was recovered by suction filtration to provide 1.65 g of crude product. Recrystallization of hot water afforded **2** (1.07 g) as a white solid in 9.4% yield. R_f = 0.52 (*i*-PrOH:NH_4OH:H_2O = 5:2:2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (d, 2H, J = 7.6 Hz, 2 × arom-H), 7.42 (d, 2H, J = 7.5 Hz, 2 × arom-H), 5.70 (br s, 14H, 14 × OH), 4.83 (br s, 5H, 5 × H_1), 4.75 (br s, 2H, 2 × H_1), 4.30-4.33 (m, 2H), 4.16-4.19 (m, 2H), 3.20-3.64 (m, 44H, overlaps with HOD), 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.78, 132.70, 129.86, 127.55, 102.23, 101.97, 101.92, 101.28, 81.67, 81.57, 81.51, 81.44, 81.20, 80.80, 73.06, 72.93, 72.73, 72.69, 72.43, 72.37, 72.16, 72.04, 71.88, 69.68, 68.91, 59.93, 59.83, 59.81, 59.55, 59.30, 21.18; ESI-HRMS Calcd for $C_{49}H_{80}NO_{37}S$ $[M+NH_4]^+$: 1306.4124. Found 1306.4128.

1.4 6^A-Azido-6^A-deoxy-per-*O*-acetyl-*β*-CD **(16)**[4, 5]

6^A-*O*-(p-tolsulfonyl)-*β*-CD (1.01 g, 0.78 mmol) was suspended in water (50 mL), NaN_3 (0.153 g, 0.24 mmol) was added. The reaction was carried out with stirring at 80°C for 12 h. The mixture was cooled to room temperature and poured into acetone (200 mL). The resulting precipitate was filtrated and dried in vacuo to give the azide product as a white power (0.736 g, 81%). R_f = 0.37 (*i*-PrOH:NH_4OH:H_2O = 5:2:2).

To a solution of 6^A-azido-6^A-deoxy-*β*-CD (160 mg, 0.14 mmol) in pyridine (2 mL) was added 16.8 mg of DMAP (0.14 mmol) and 1 mL Ac_2O at room temperature. The reaction mixture was stirred for 18 h under nitrogen. The solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2:CH_3OH = 30:1) to give 237 mg (86%) of compound **4** as a white foam. R_f = 0.57 (CH_2Cl_2:CH_3OH = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13-5.27 (m, 7H, 7 × H_3), 5.07 (d, 1H, J = 3.9 Hz, H_1), 5.00-5.04 (m, 5H, 5 × H_1), 4.93 (d, 1H, J = 3.8 Hz, H_1), 4.68-4.77 (m, 7H, 7 × H_2), 4.45-4.54 (m, 6H, 6 × H_6), 3.98-4.25 (m, 13H, 6 × H_6, 7 × H_4), 3.60-3.73 (m,

9H, 2 × H_6, 7 × H_5), 1.95-2.08 (m, 60H, 20 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.57, 170.54, 170.51, 170.47, 170.43, 170.34, 170.32, 170.24, 170.21, 170.19, 170.07, 169.25, 169.21, 169.20, 169.17, 169.15, 96.81, 96.75, 96.59, 96.53, 96.40, 96.35, 77.21, 76.68, 76.54, 76.37, 76.28, 71.11, 70.89, 70.76, 70.63, 70.54, 70.37, 70.19, 70.13, 69.95, 69.72, 69.50, 69.38, 69.27, 69.25, 62.52, 62.44, 62.31, 50.53, 20.67, 20.59; ESI-HRMS Calcd for $C_{82}H_{113}N_4O_{54}$ $[M+NH_4]^+$: 2017.6214. Found 2017.6179; $C_{82}H_{109}N_3NaO_{54}$ $[M+Na]^+$: 2022.5768. Found 2022.5705; $C_{82}H_{110}KN_3O_{54}$ $[M+H+K]^+$: 2039.5591. Found 2039.5624.

1.5 6^A-Azido-per-*O*-methyl-β-CD **(17)**[4, 5]

To a solution of the azide product (365 mg, 0.31 mmol) in dried DMF (10 mL) was added 372 mg (60%, 9.3 mmol) of NaH at 0°C under nitrogen. After the reaction mixture was stirred at 0°C for 1 h, 0.72 mL of CH_3I (8.1 mmol) was added. The reaction mixture was stirred at 0°C for 1 h and then kept at room temperature for another 12 h under nitrogen. CH_3OH was added dropwise to quench the reaction and the solvent was removed in vacuo. The residue dissolved with CH_2Cl_2, washed with brine, dried with Na_2SO_4, filtrated and the solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2:CH_3OH = 40:1) to give 280 mg (62%) of **3** as a white foam. R_f = 0.63 (CH_2Cl_2:CH_3OH = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08-5.13 (m, 6H, 6 × H_1), 5.05 (d, 1H, J = 3.7 Hz, H_1), 3.41-3.94 (m, 33H), 3.72 (m, 1H, $H_{6\beta}{}^A$), 3.64 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.62 (2 × s, 15H, 5 × OCH_3), 3.62 (m, 1H, $H_{6\alpha}{}^A$), 3.50 (2 × s, 6H, 2 × OCH_3), 3.49 (s, 9H, 3 × OCH_3), 3.48 (s, 6H, 2 × OCH_3), 3.38 (s, 3H, OCH_3), 3.37 (s, 15H, 5 × OCH_3), 3.14-3.19 (m, 7H, 7 × H_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.34, 99.12, 98.97, 98.86, 98.39, 82.10, 82.06, 82.00, 81.91, 81.87, 81.80, 81.74, 81.72, 81.43, 80.37, 80.27, 80.22, 80.18, 80.11, 80.01, 71.57, 71.45, 71.43, 71.37, 71.27, 71.13, 71.01, 70.96, 70.89, 70.84, 61.49, 61.45, 61.42, 61.39, 61.32, 61.30, 58.99, 58.96, 58.91, 58.64, 58.56, 58.52, 58.51, 58.45, 58.41, 52.07; ESI-HRMS Calcd for $C_{62}H_{113}N_4O_{34}$ $[M+NH_4]^+$: 1457.7231. Found 1457.7279; $C_{62}H_{109}N_3NaO_{34}$ $[M+Na]^+$: 1462.6785. Found 1462.6831; $C_{62}H_{109}N_3O_{34}K$ $[M+K]^+$: 1478.6519. Found 1478.6588.

1.6 3β-hydroxy-11-oxo-18β-olean-12-en-30-oic acid benzyl ester (**36**)[6]

To a solution of glycyrrhetinic acid **1** (1.05 g, 2.20 mmol) in DMF (20 mL) was added 367 mg of K_2CO_3 (2.6 mmol) and 320 μL benzyl bromide (2.60 mmol). The resulting solution was stirred vigorously for 24 h at 60°C. The solvent was removed by steaming. The residue was purified by reverse column chromatography to give 1.10 g (89%) of compound **36** as a white solid. R_f = 0.15 (petroleum ether:ethyl acetate = 1:1);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.32 (m, 5H), 5.54 (s, 1H), 5.20 (d, 1H, J = 12.2 Hz), 5.09 (d, 1H, J = 12.2 Hz), 3.22 (dd, 1H, J = 10.6, 5.4 Hz), 2.78 (td, 1H, J = 13.5, 3.6 Hz), 2.31 (s, 1H), 2.03–0.92 (m, other aliphatic ring protons), 1.34, 1.15, 1.13, 1.10, 1.00, 0.80, 0.73 (s, each 3H, 7 × CH_3), 0.68 (d, 1H, J = 10.1 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ 200.14, 176.21, 169.01, 136.13, 128.62, 128.53, 128.30, 128.25, 78.75, 66.23, 61.79, 54.94, 48.21, 45.35, 43.99, 43.17, 41.08, 39.14, 37.65, 37.07, 32.77, 31.78, 31.17, 28.42, 28.30, 28.11, 27.31, 26.47, 26.41, 23.36, 18.68, 17.49, 16.38, 15.60

Reference:

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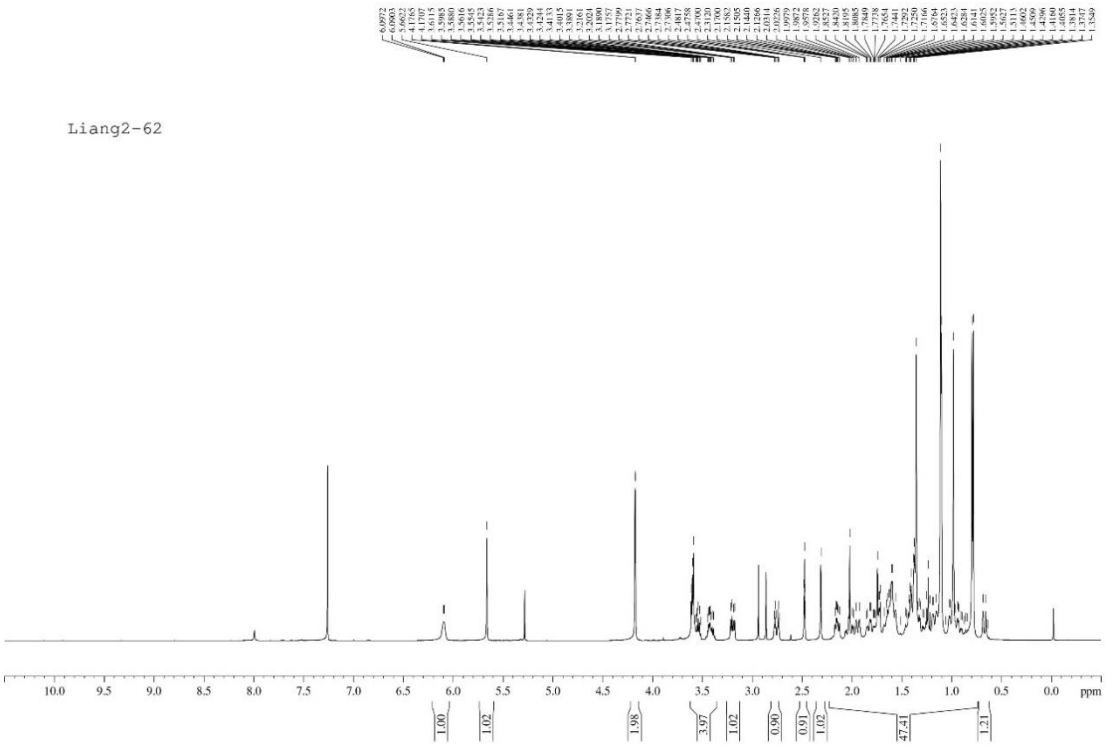
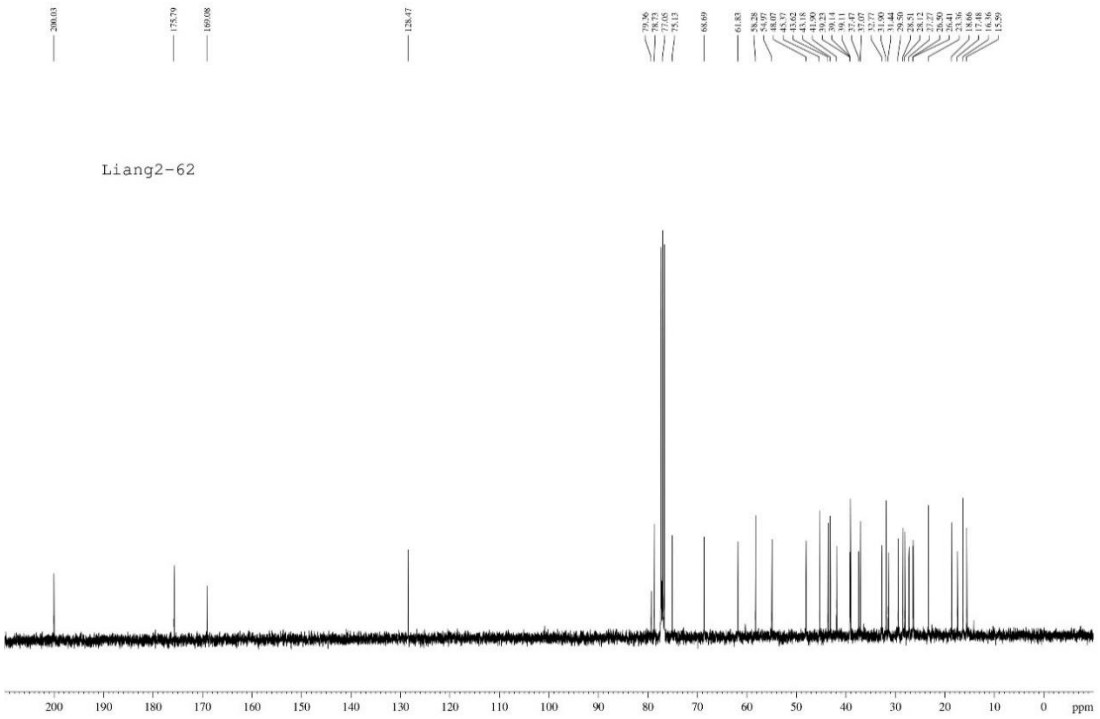
2. Selected 1H, 13C NMR and HRMS spectra

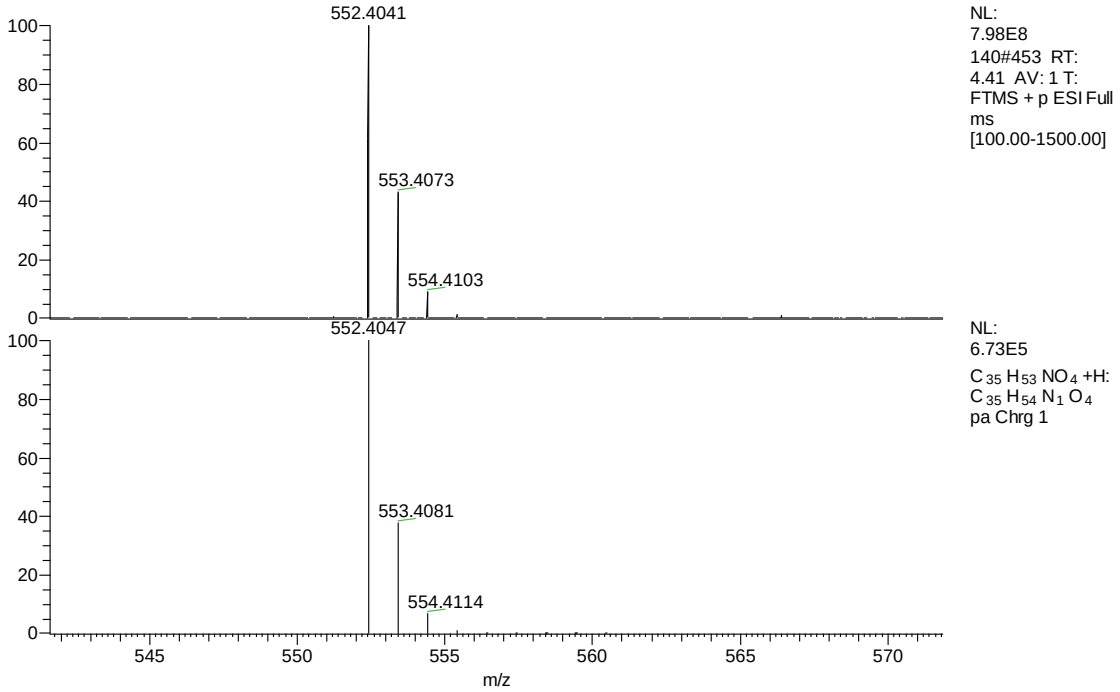
^{1}H NMR of compound **9**



^{13}C NMR of compound **9**



HRMS of compound **9**



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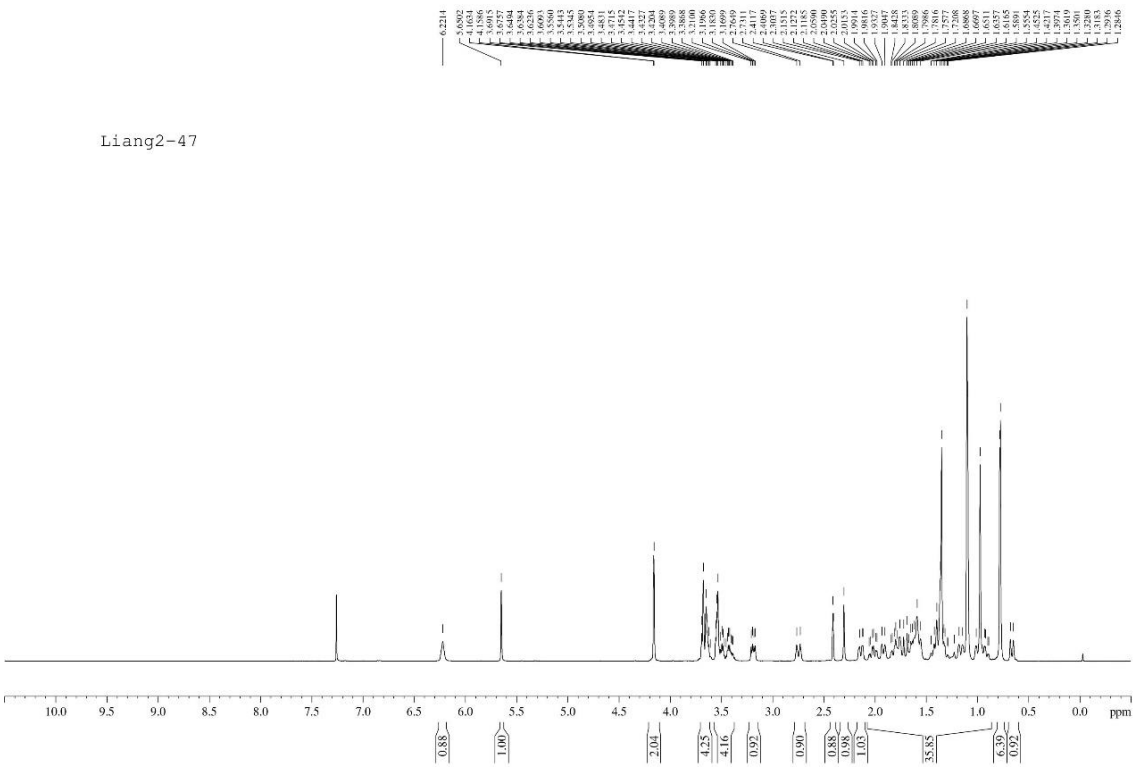

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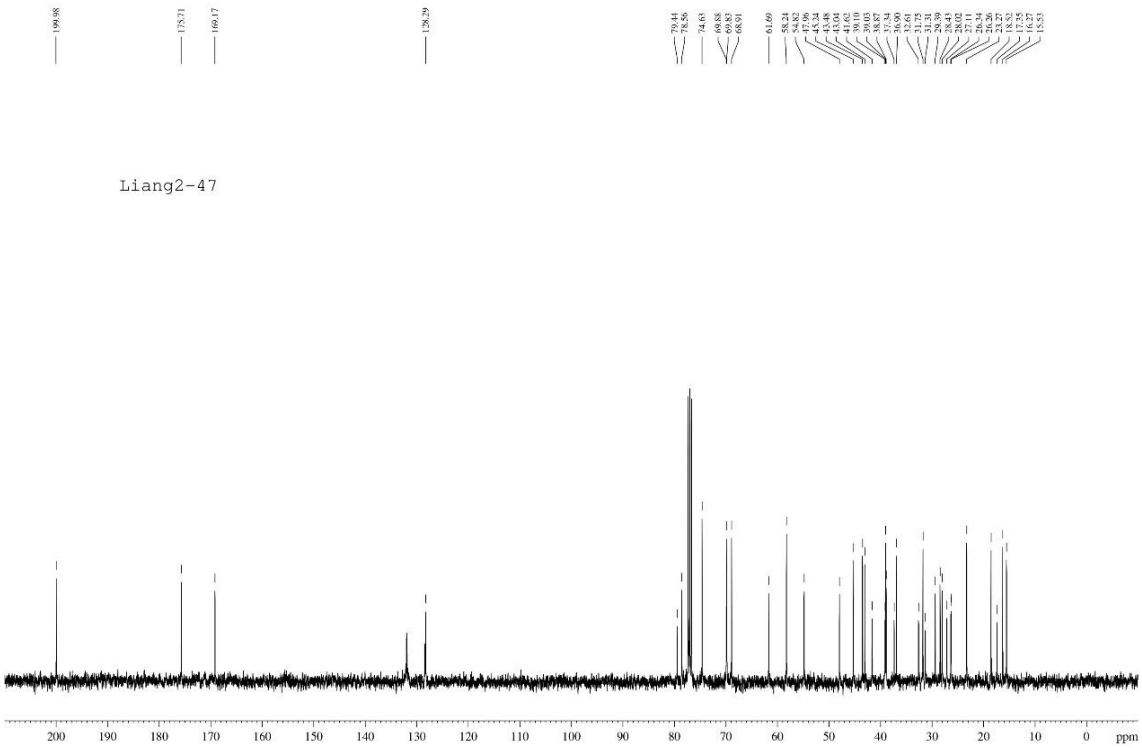

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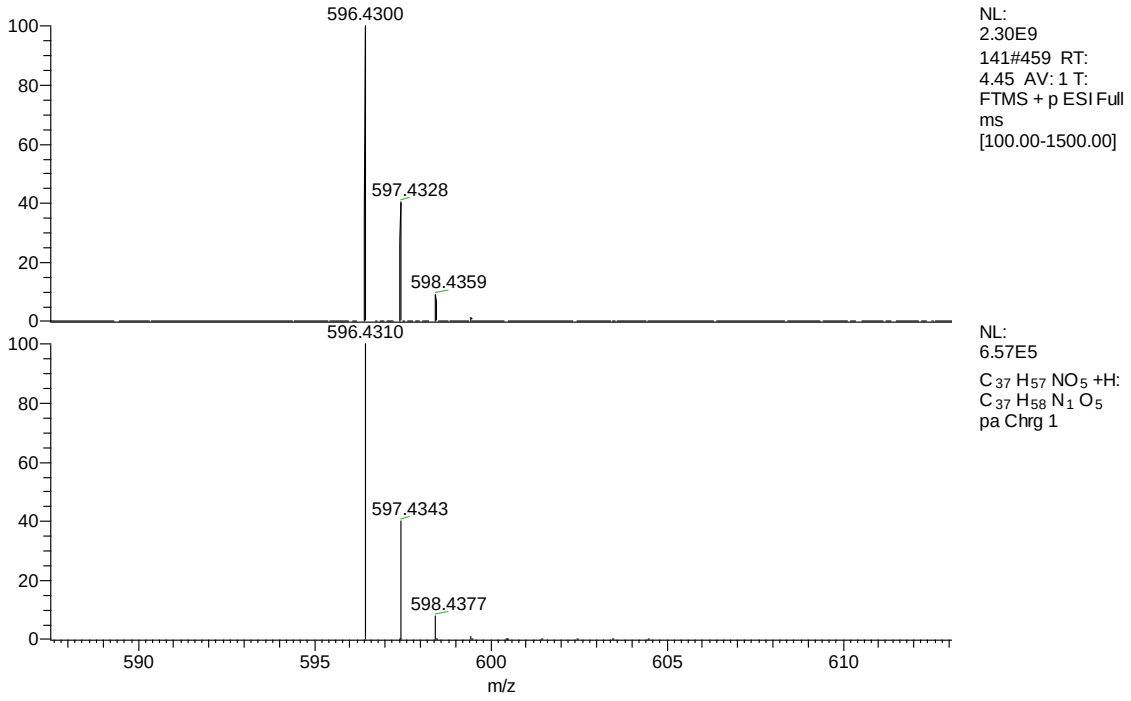

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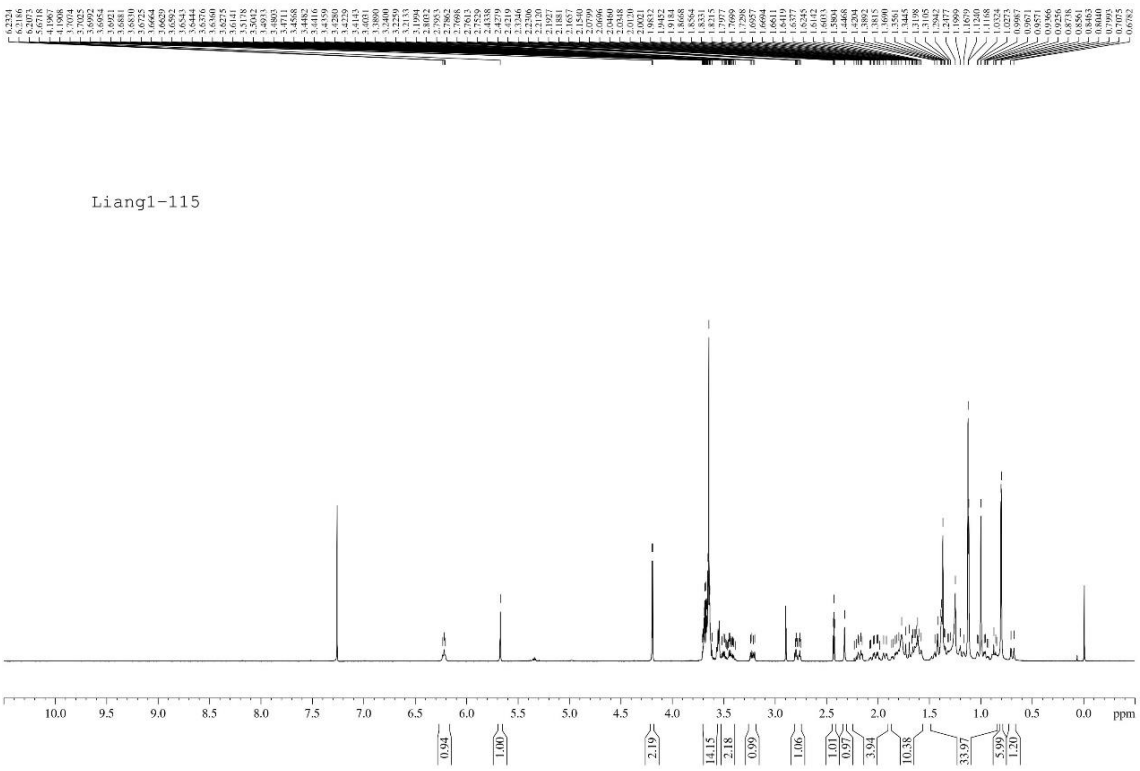

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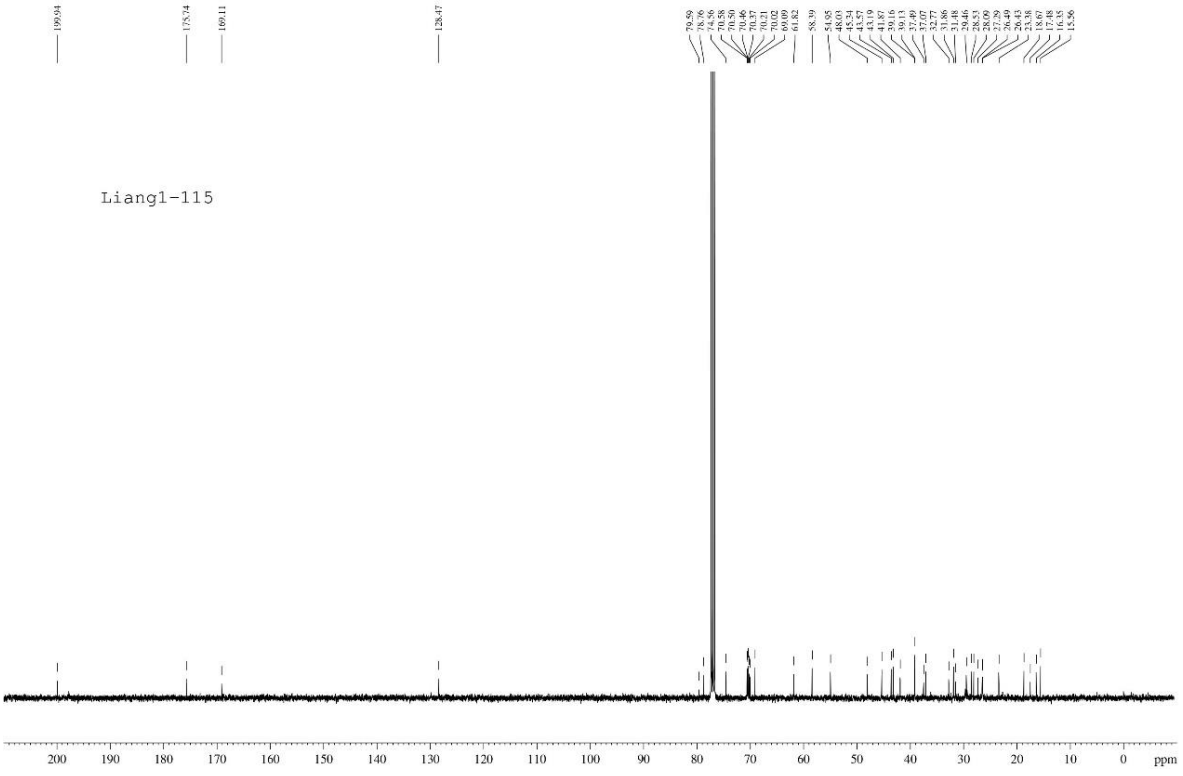

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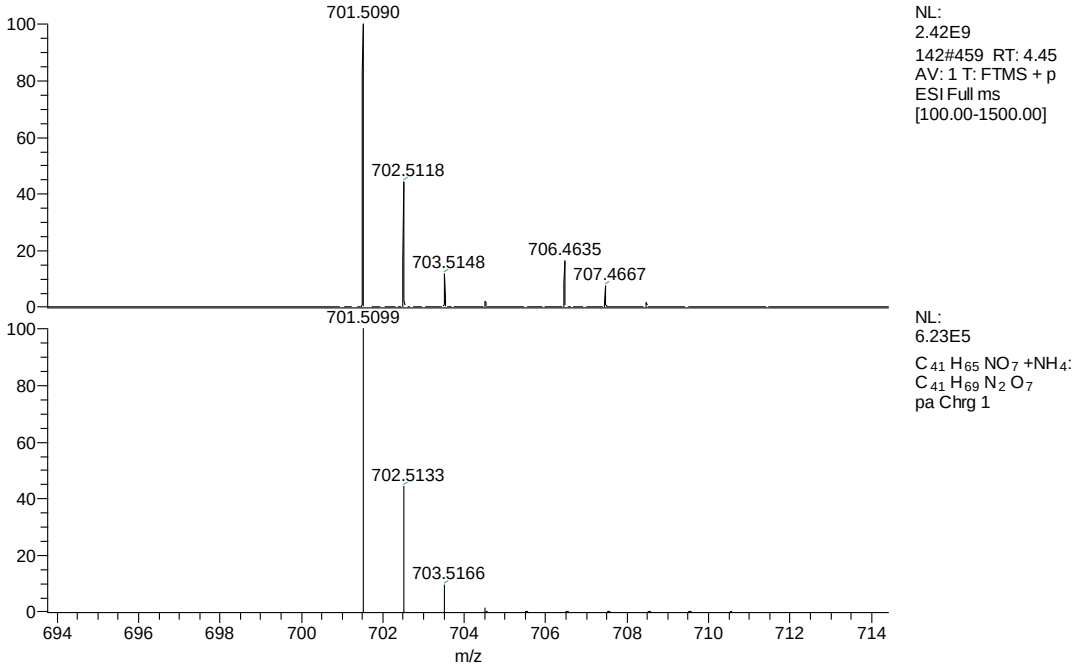

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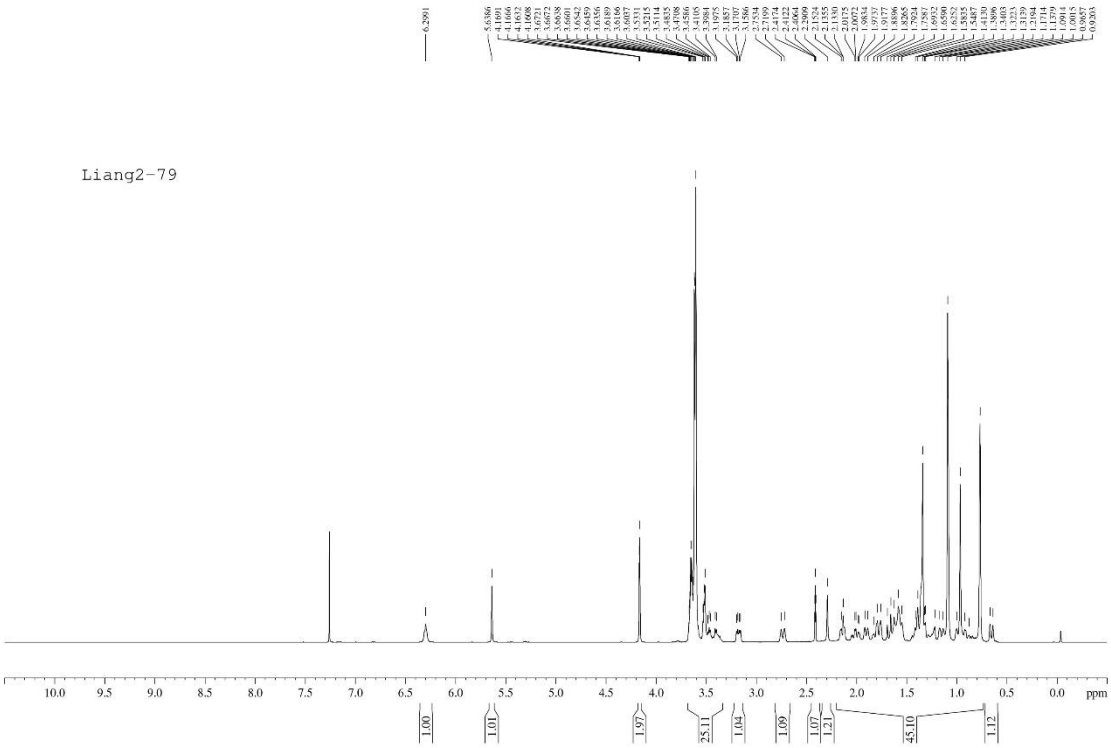

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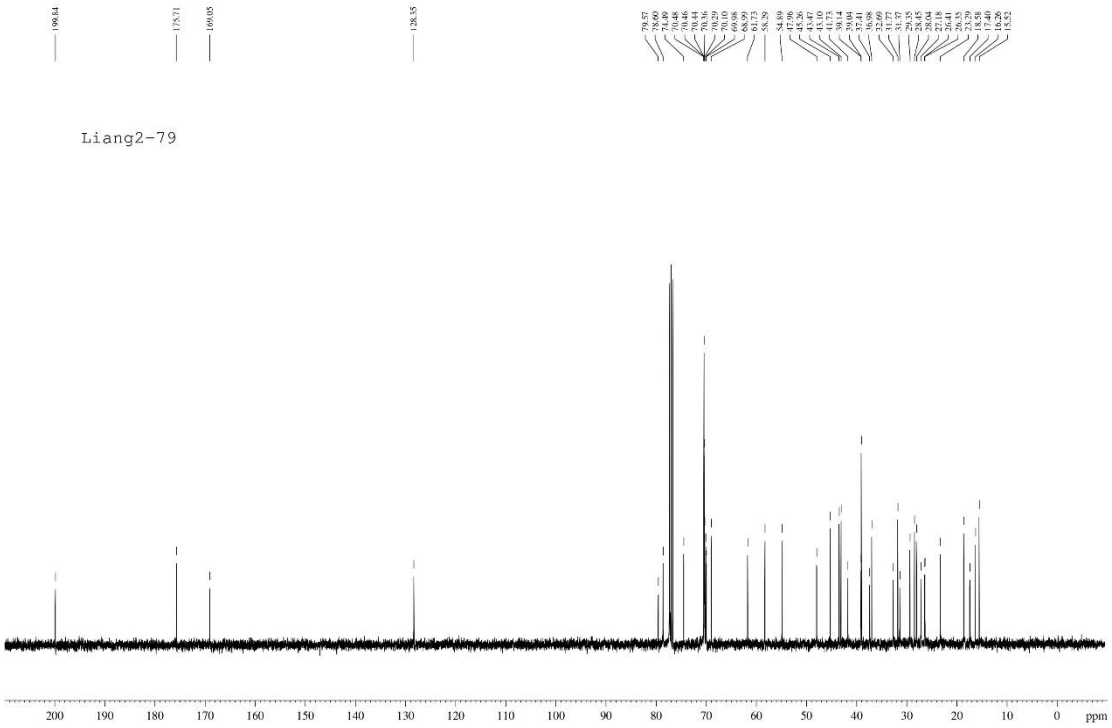

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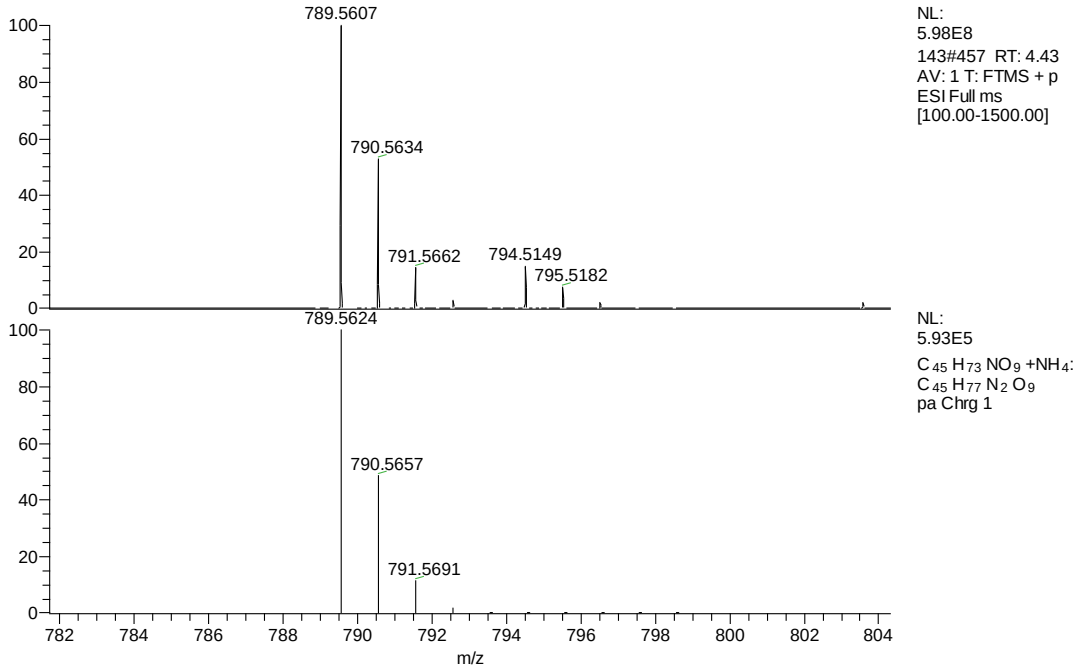
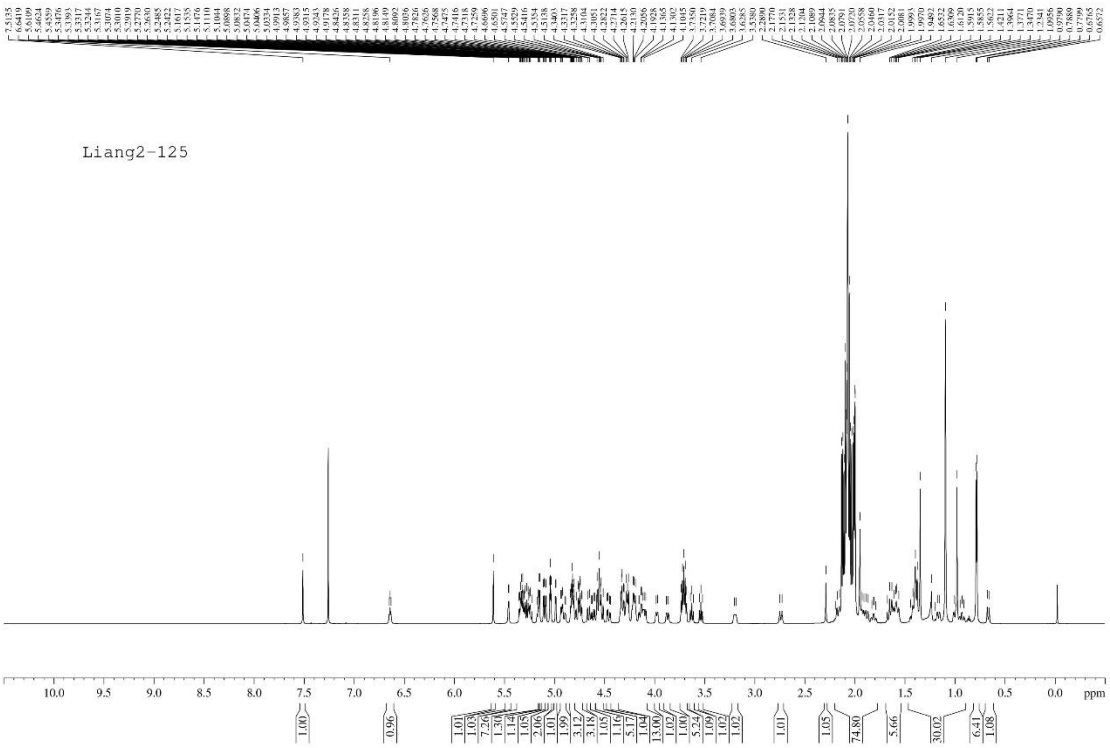


^{1}H NMR of compound **18**



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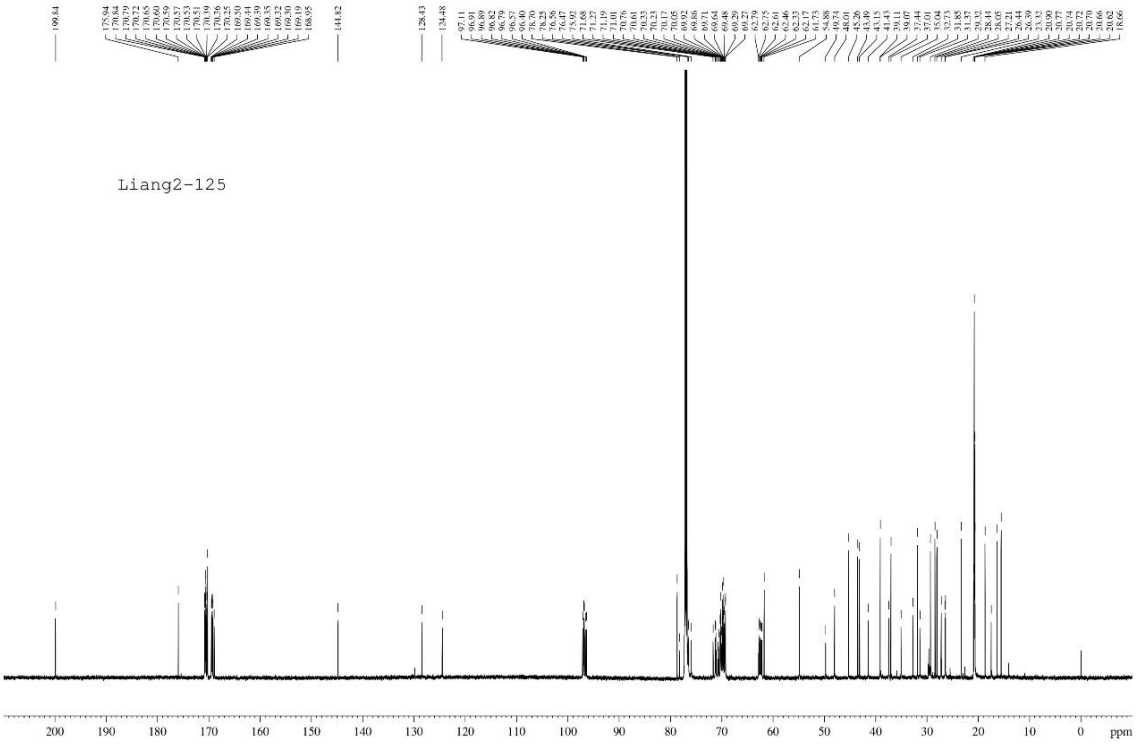
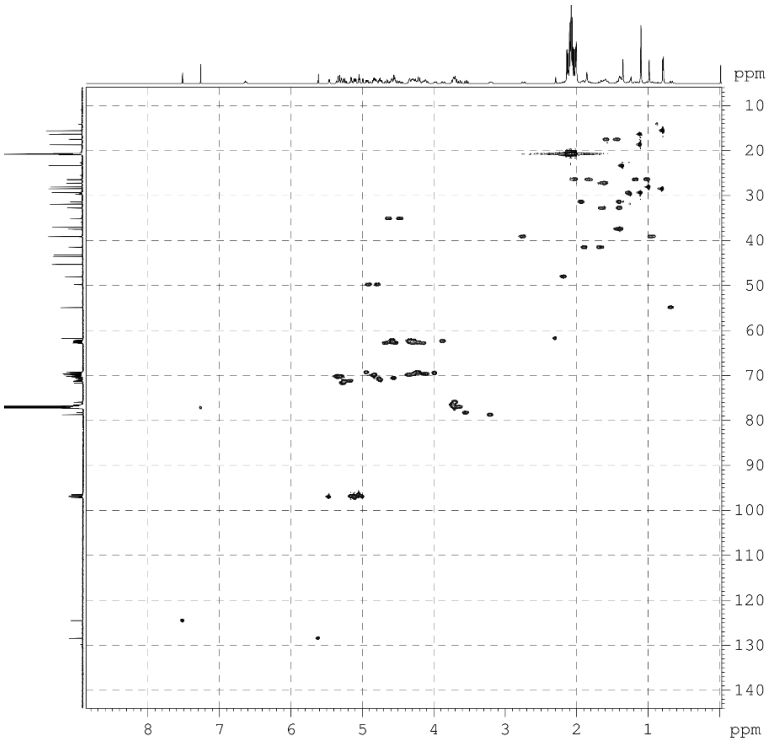


HSQC of compound **18**



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PROCNO	1
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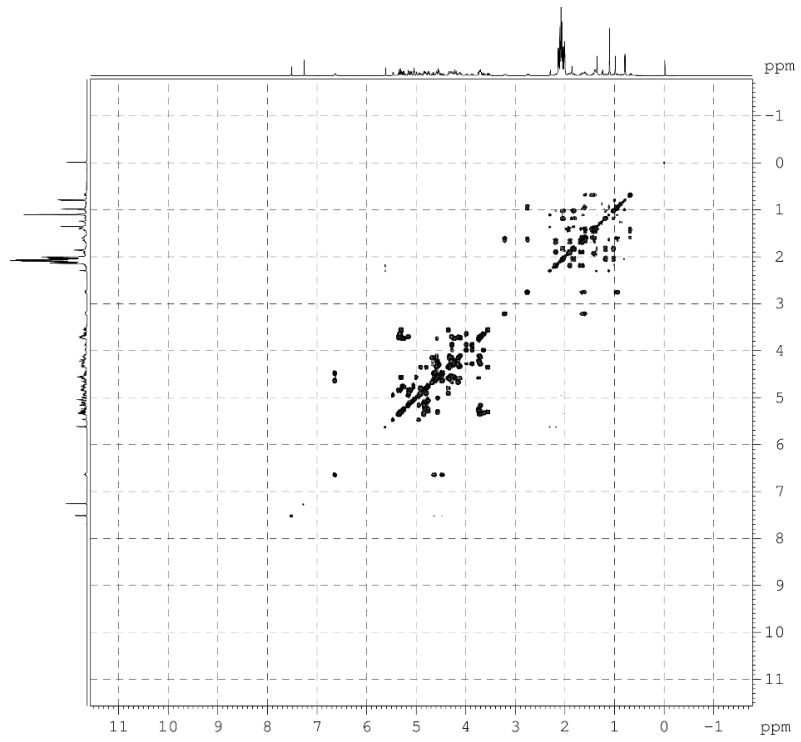
PULPROG	hsqcetgp
TD	2048
SOLVENT	CDCl3
NS	6
DS	16
SWH	5341.880
FIDRES	2.608340
AQ	0.1917428
RG	2050
DW	93.600
DE	6.50
TE	196.6

H-H COSY of compound **18**



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TD	2048
SOLVENT	CDCl3
NS	6
DS	16
SWH	5341.880
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RG	2050
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DE	6.50
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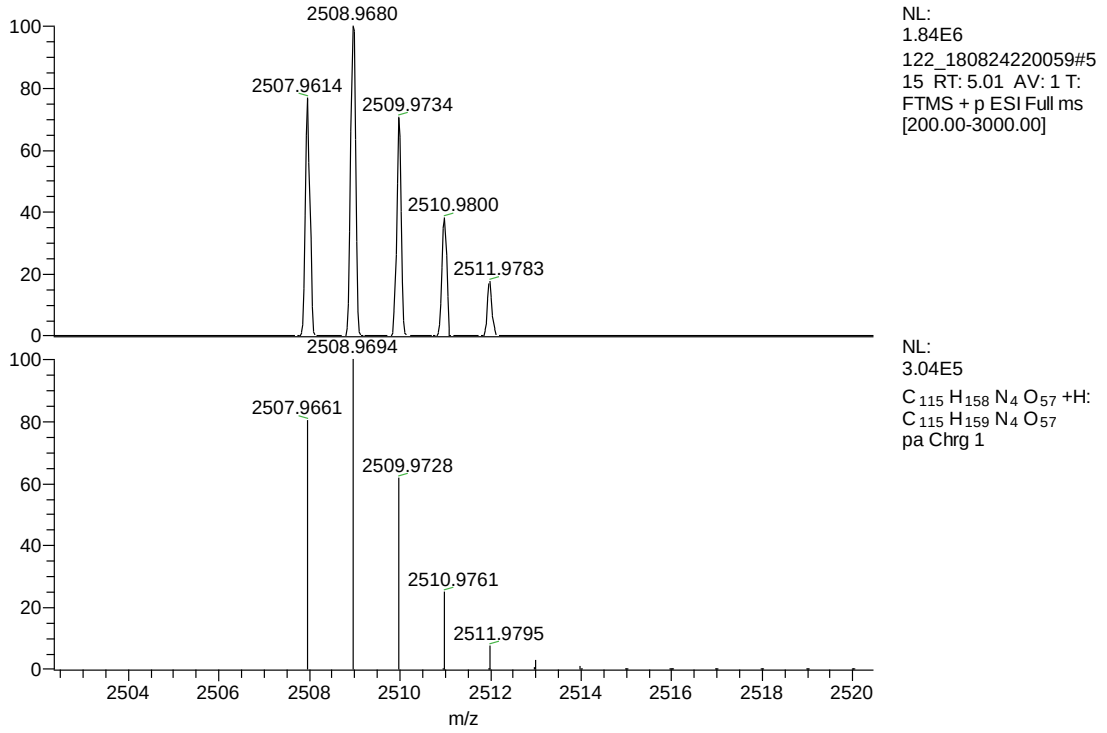
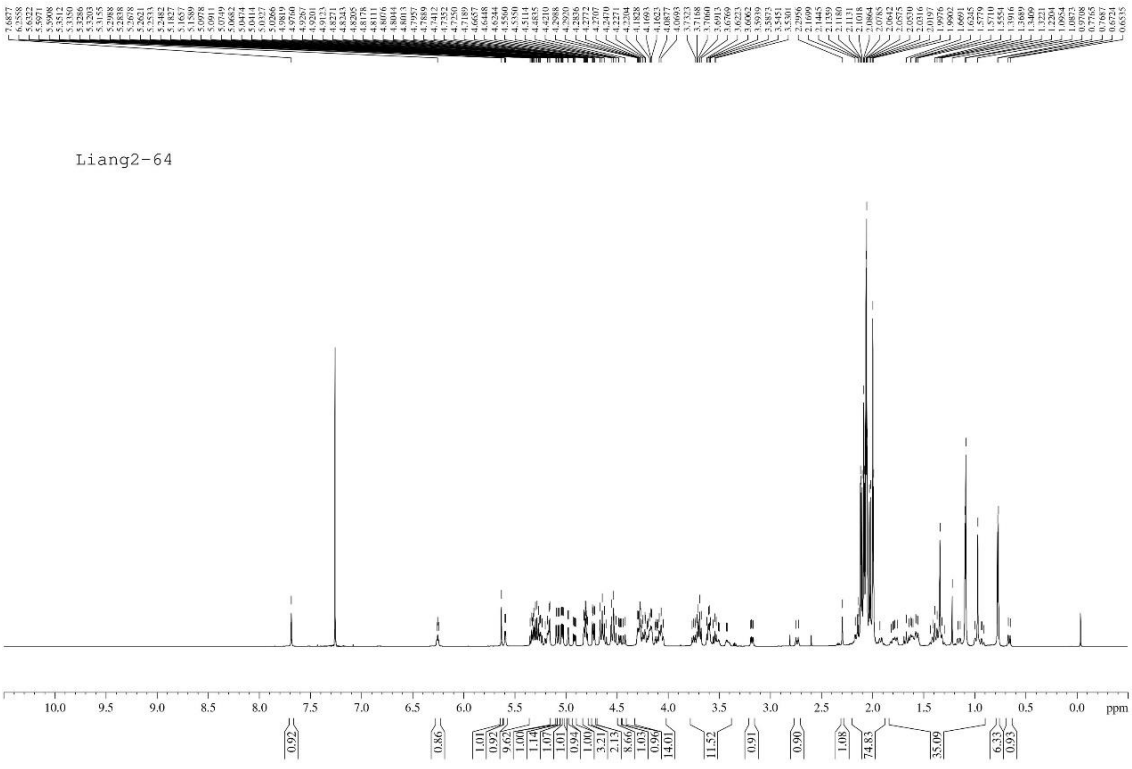
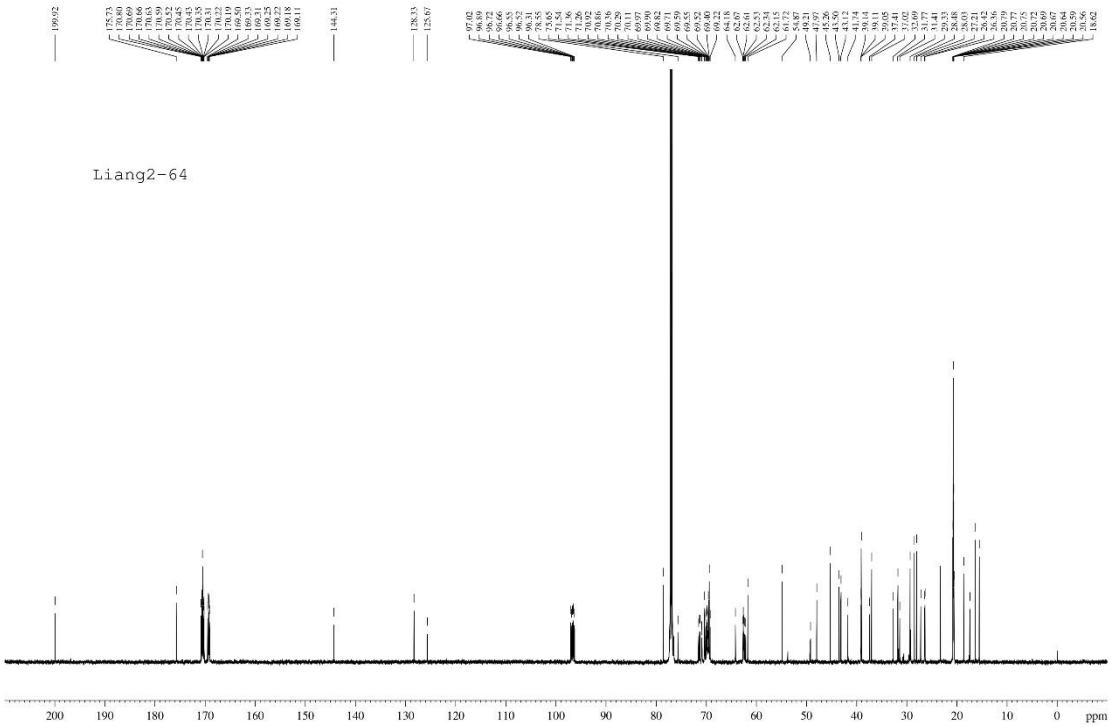
HRMS of compound **18**



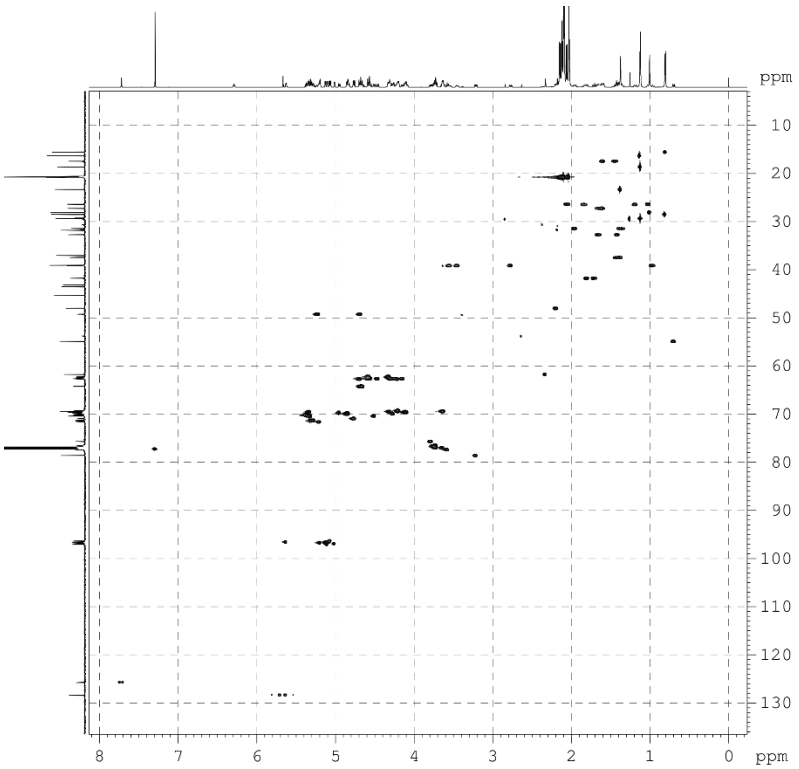
^{1}H NMR of compound **19**



^{13}C NMR of compound **19**



HSQC of compound **19**



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TD	2048
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NS	8
DS	16
SWH	5647.590
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AQ	0.1813663
RG	203
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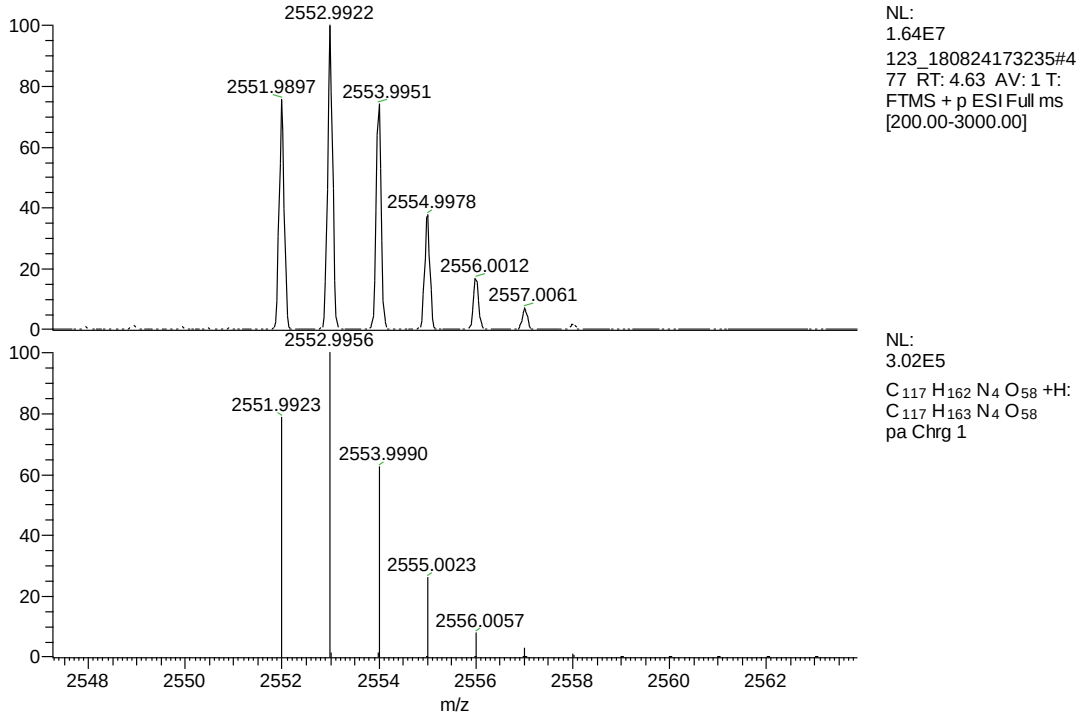
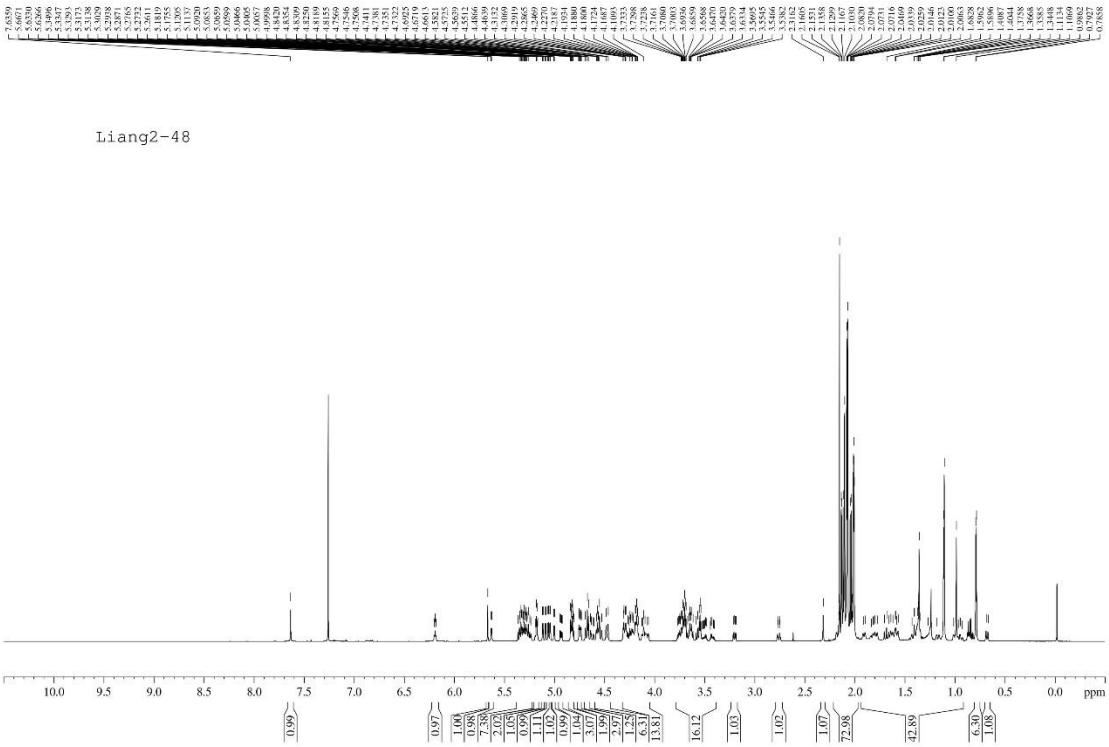
TE	300.4

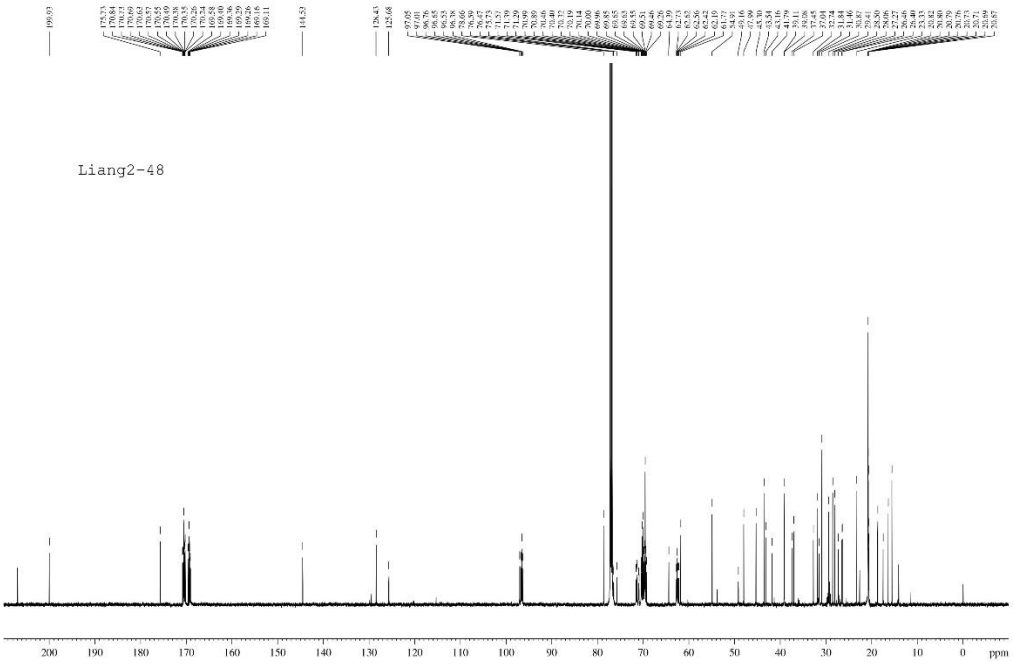
HRMS of compound **19**



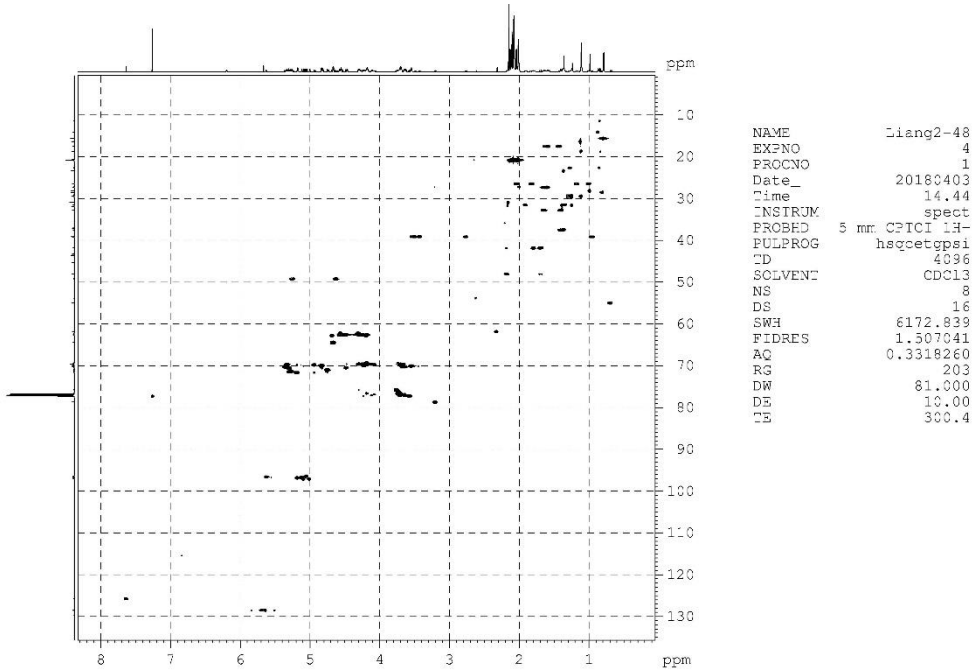
^{1}H NMR of compound **20**



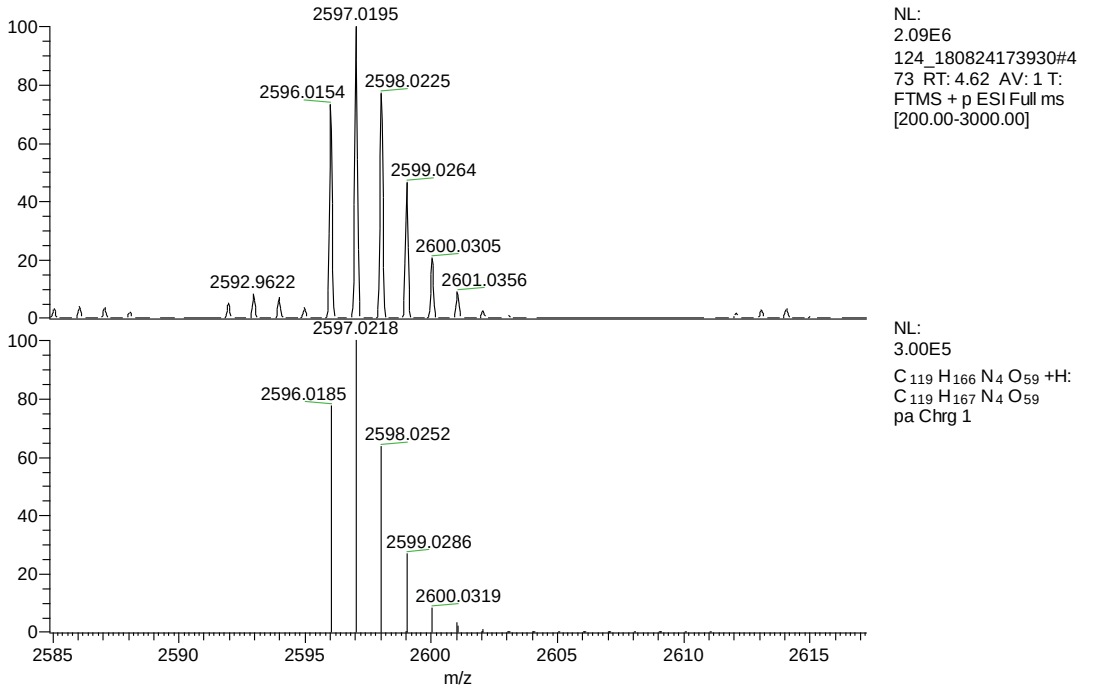
^{13}C NMR of compound **20**



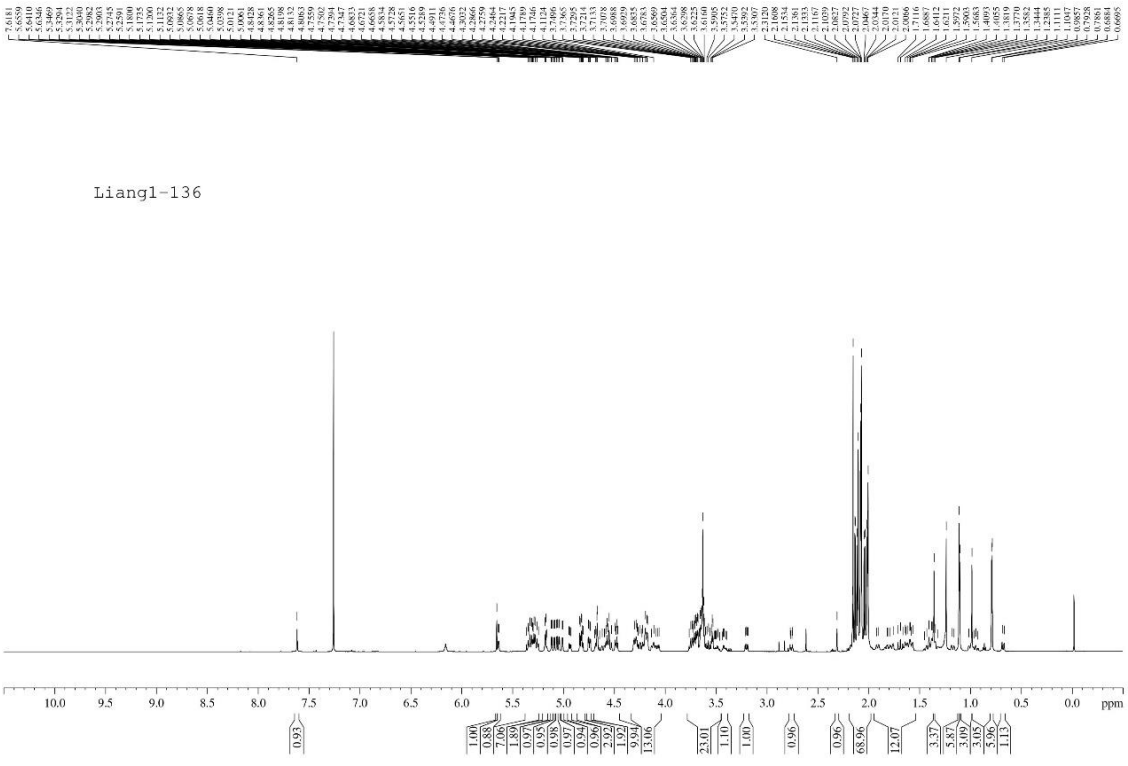
HSQC of compound **20**



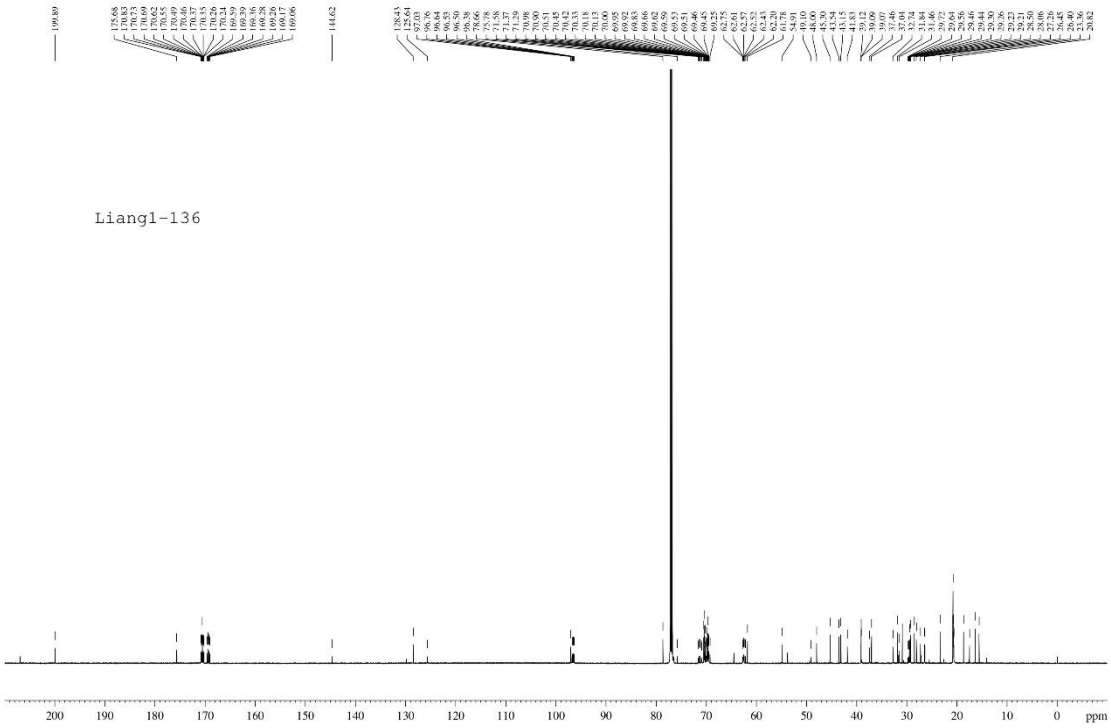
HRMS of compound **20**



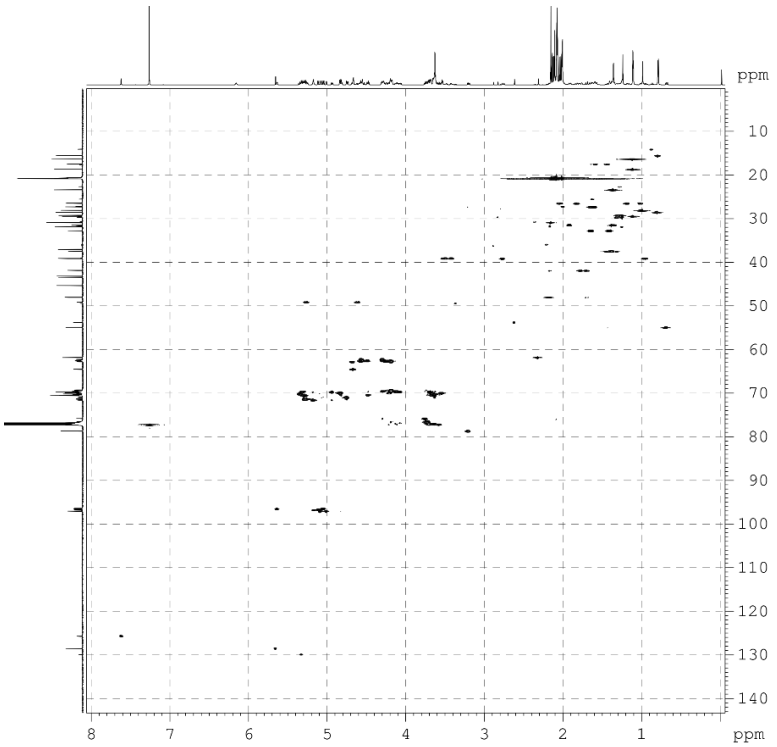
^{1}H NMR of compound **21**



^{13}C NMR of compound **21**

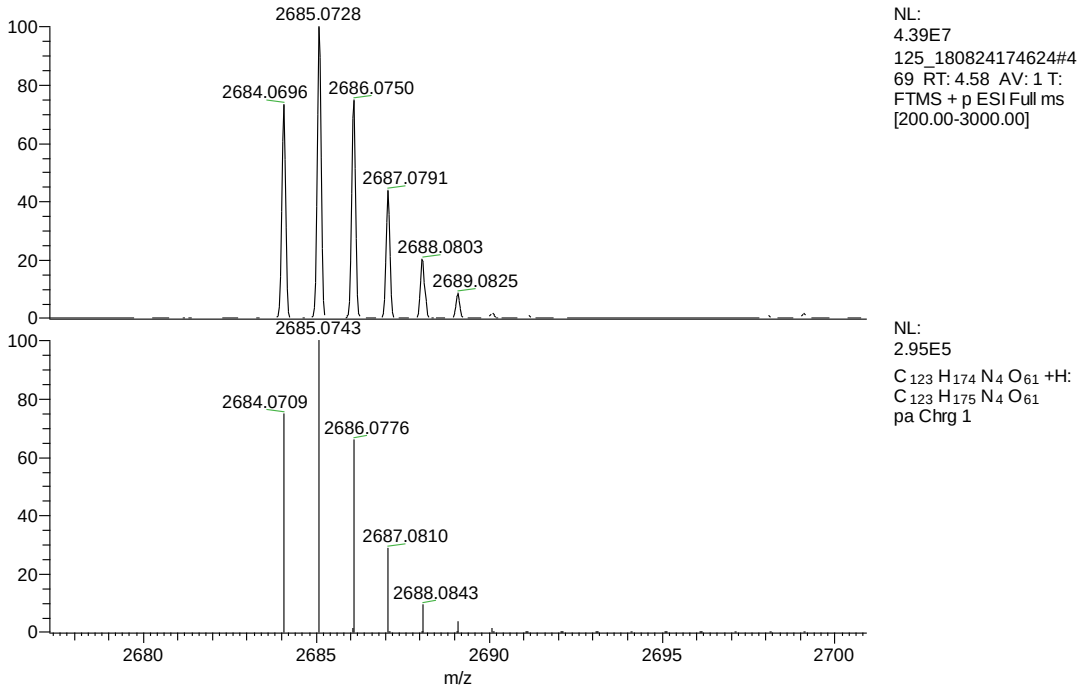


HSQC of compound **21**

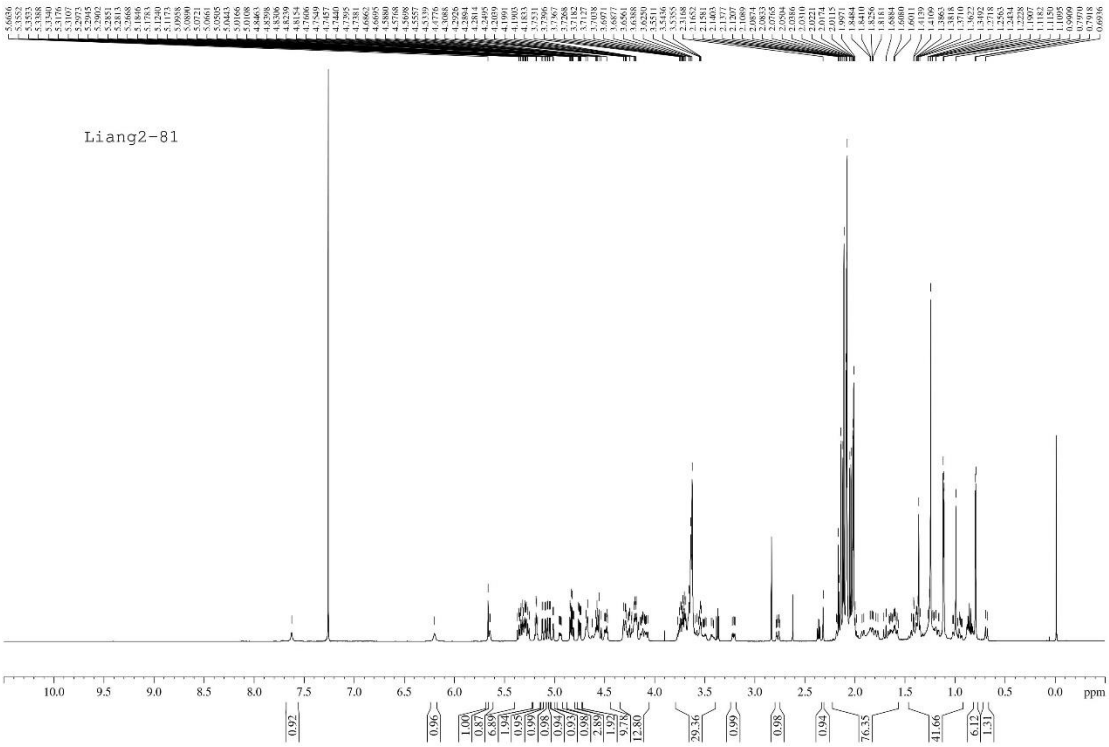


NAME	Liang1-136
EXPNO	4
PROCNO	1
Date_	20171117
Time	11.59
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	hsqcetgpsi
TD	2048
SOLVENT	CDCl3
NS	4
DS	16
SWH	5980.861
FIDRES	2.920342
AQ	0.1712628
RG	203
DW	83.600
DE	10.00
TE	300.4

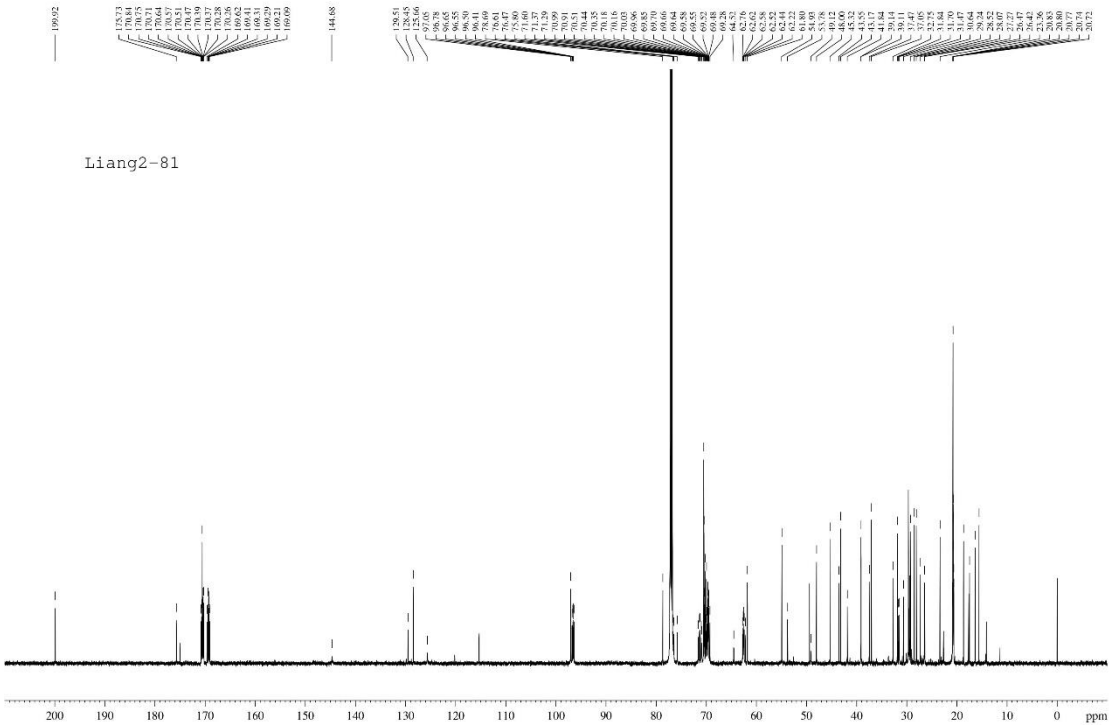
HRMS of compound **21**



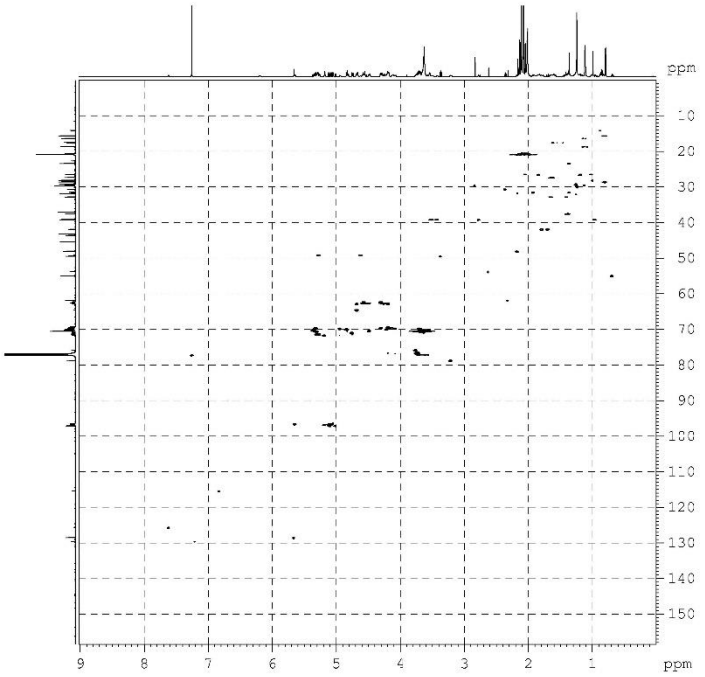
^{1}H NMR of compound **22**



^{13}C NMR of compound **22**

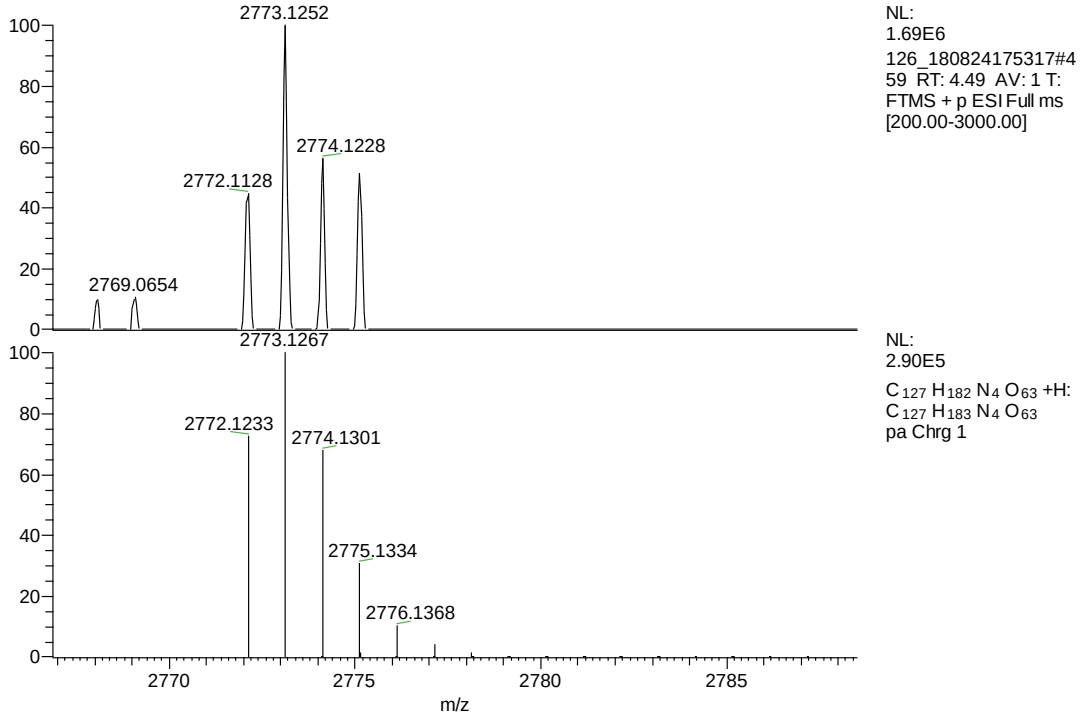


HSQC of compound **22**

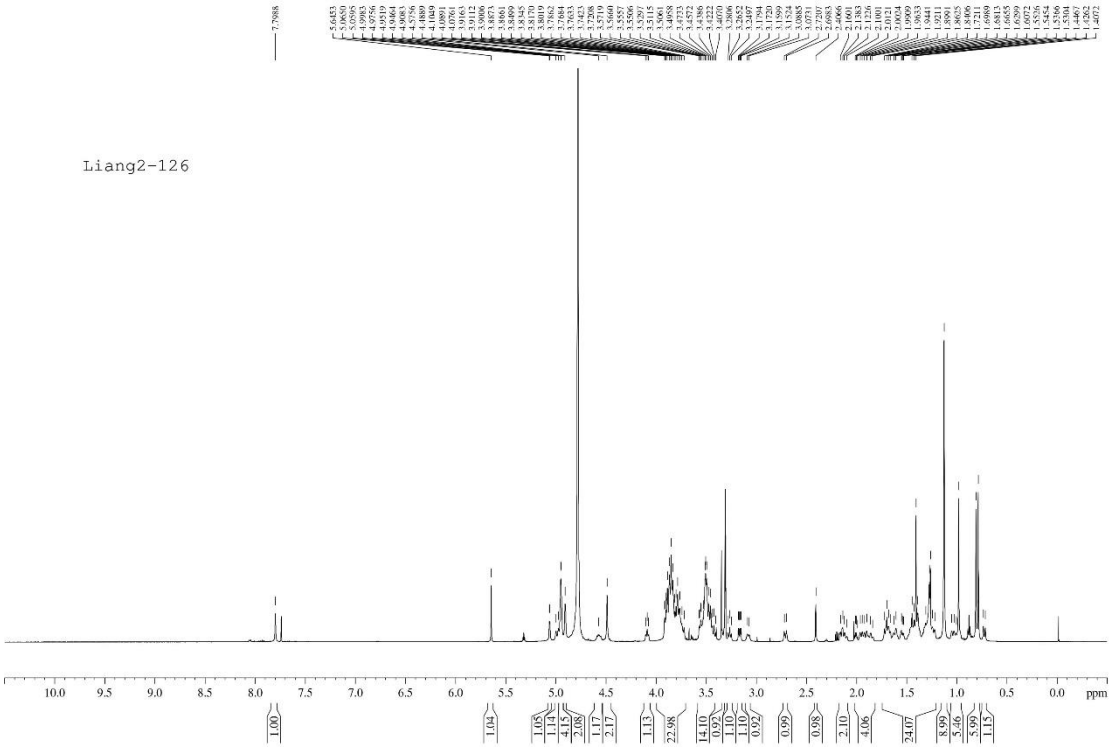


NAME	Liang2-81
EXPNO	4
PROCNO	1
Date_	20180509
Time	15.53
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	hsqcetgpsi
TD	2048
SOLVENT	CDCl3
NS	4
DS	16
SWH	7462.687
FIDRES	3.643890
AQ	0.1372660
RG	203
DW	67.000
DE	10.00
TE	300.4

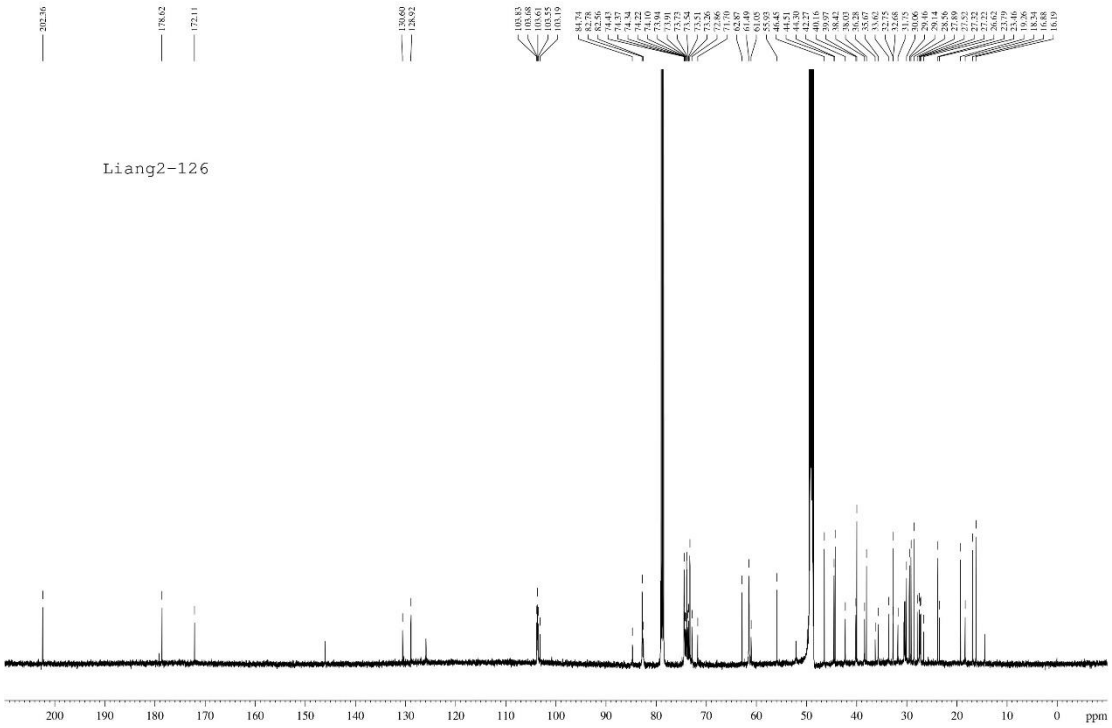
HRMS of compound **22**



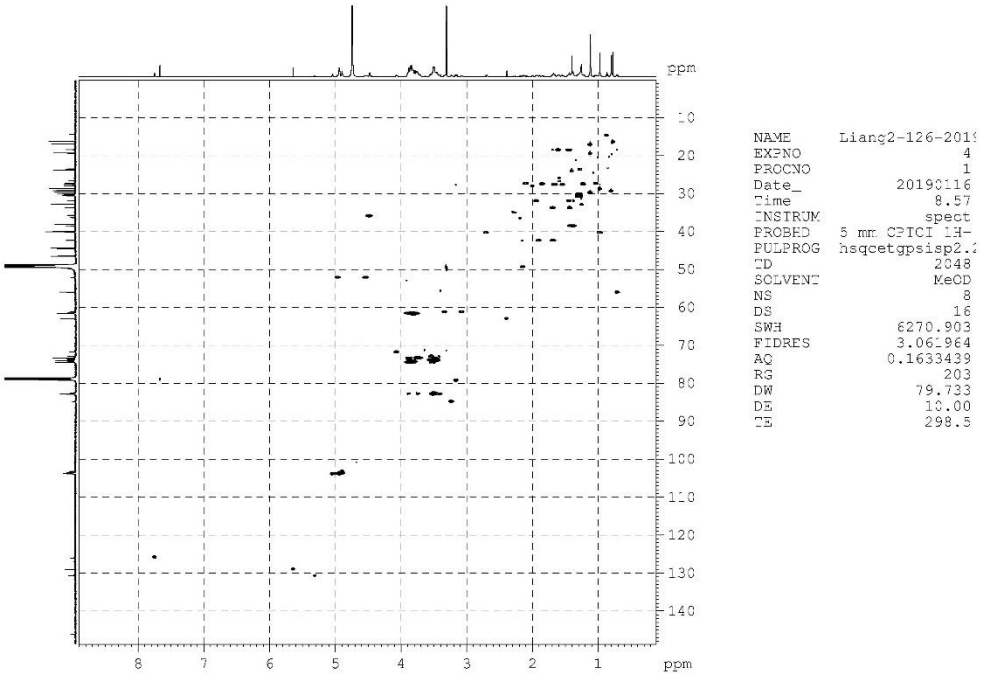
^{1}H NMR of compound **23**



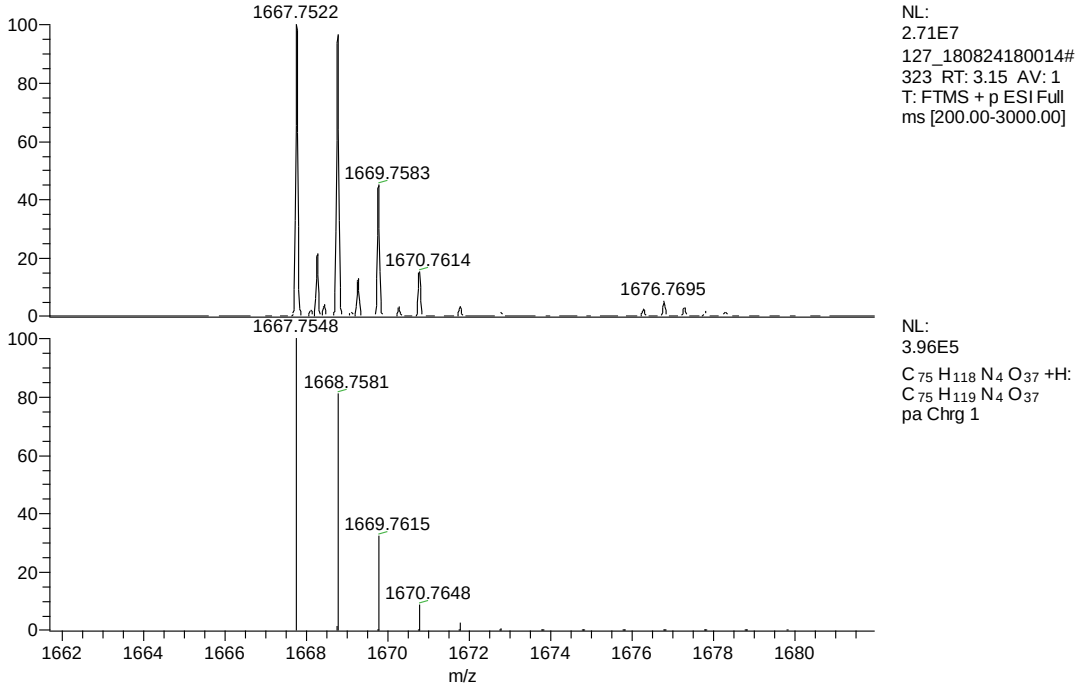
^{13}C NMR of compound **23**



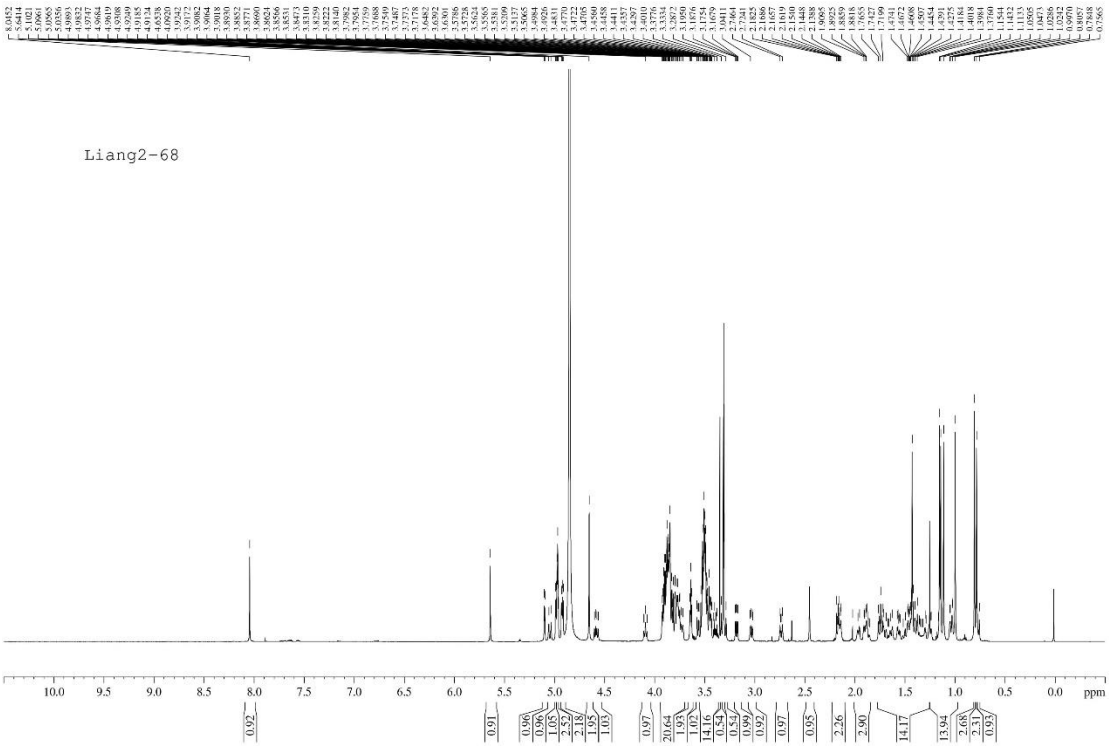
HSQC of compound **23**



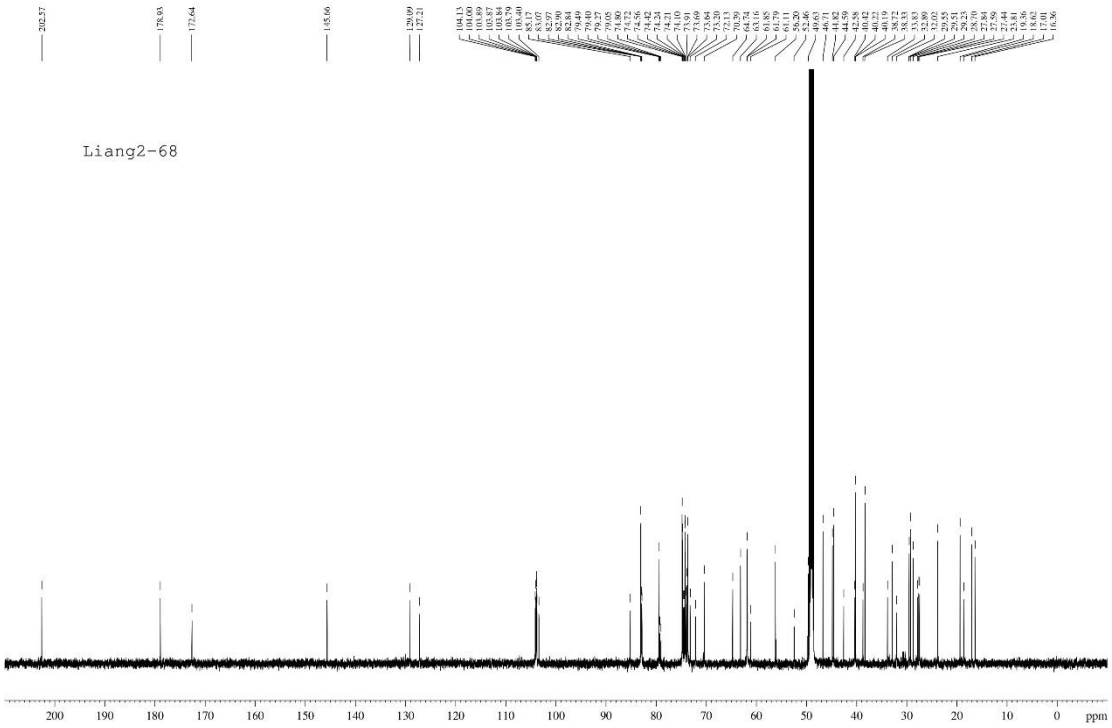
HRMS of compound **23**



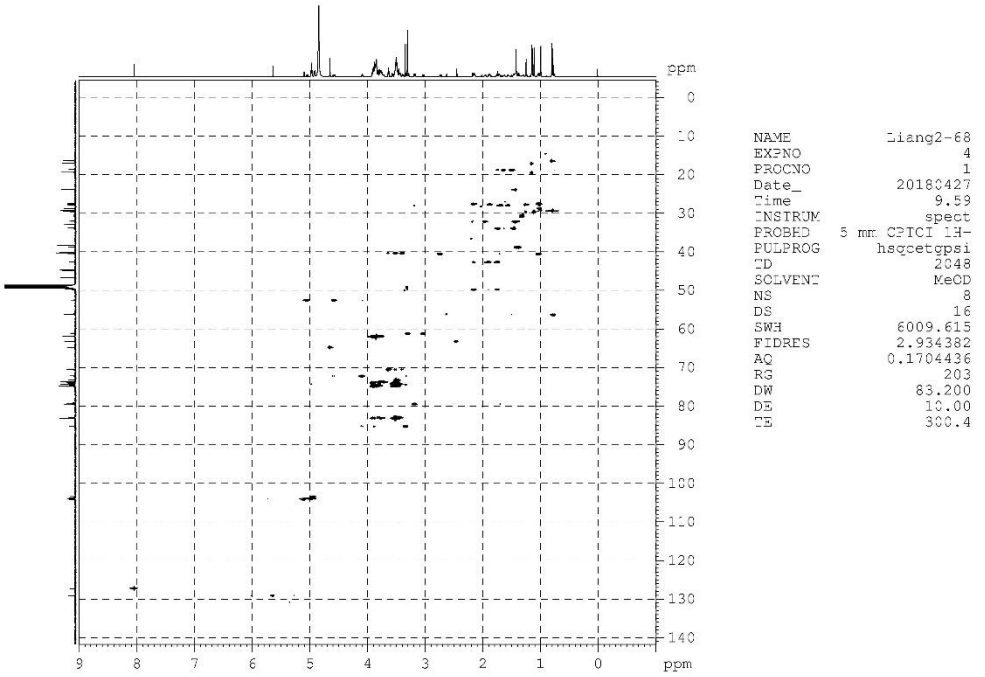
^{1}H NMR of compound **24**



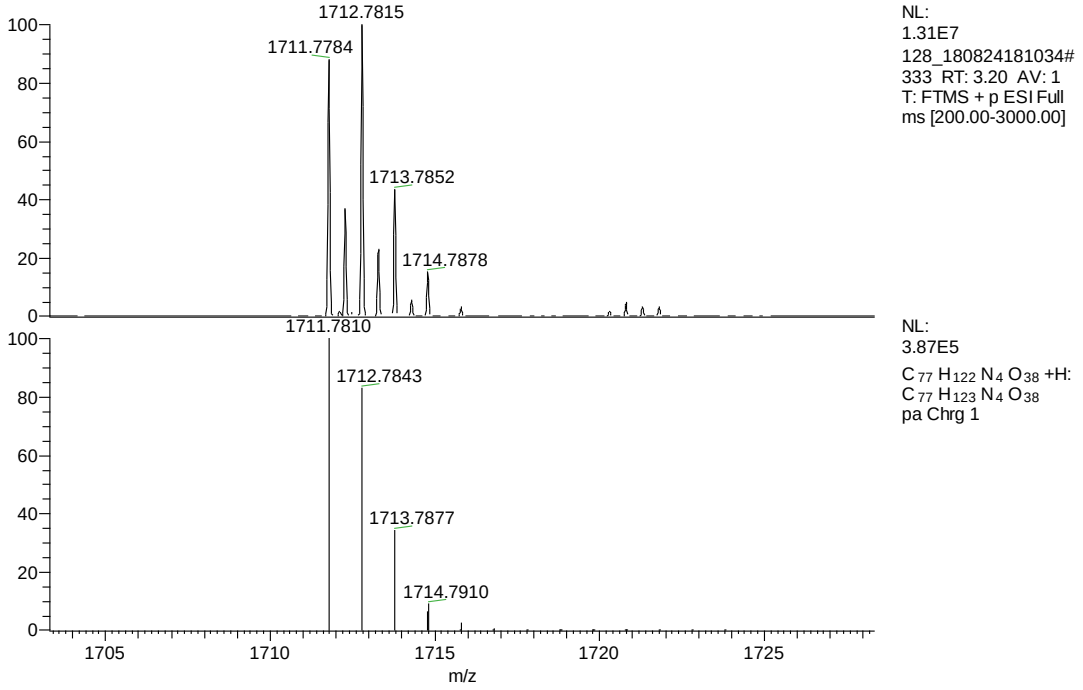
^{13}C NMR of compound **24**



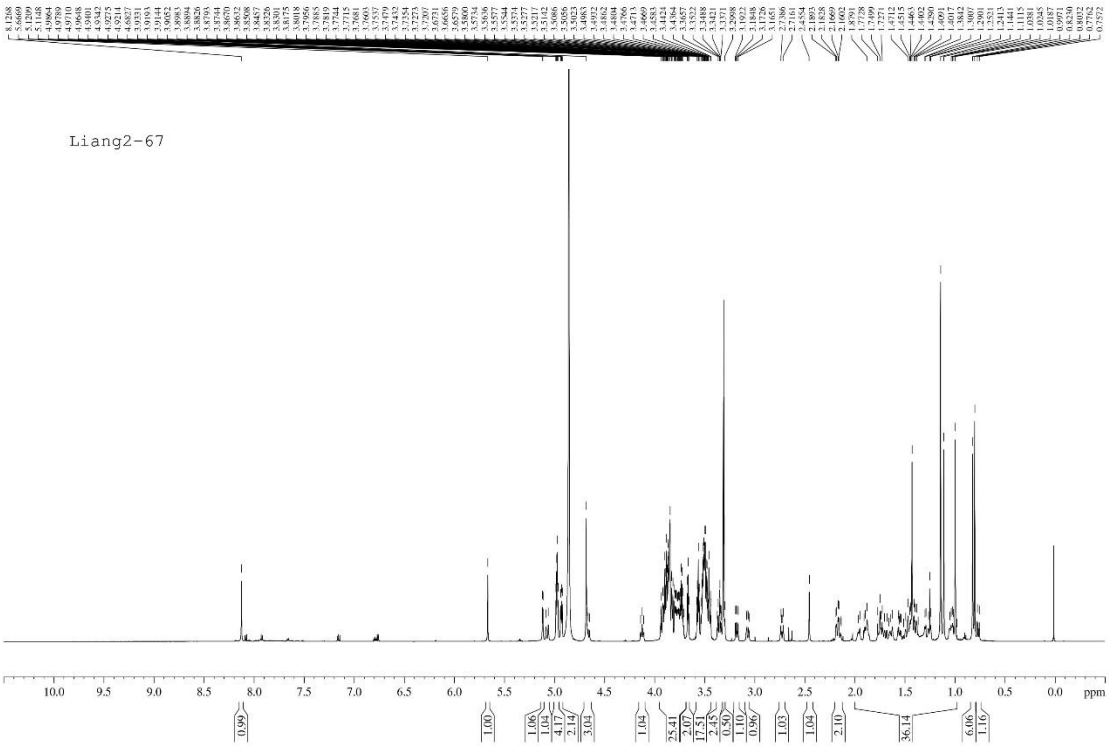
HSQC of compound **24**



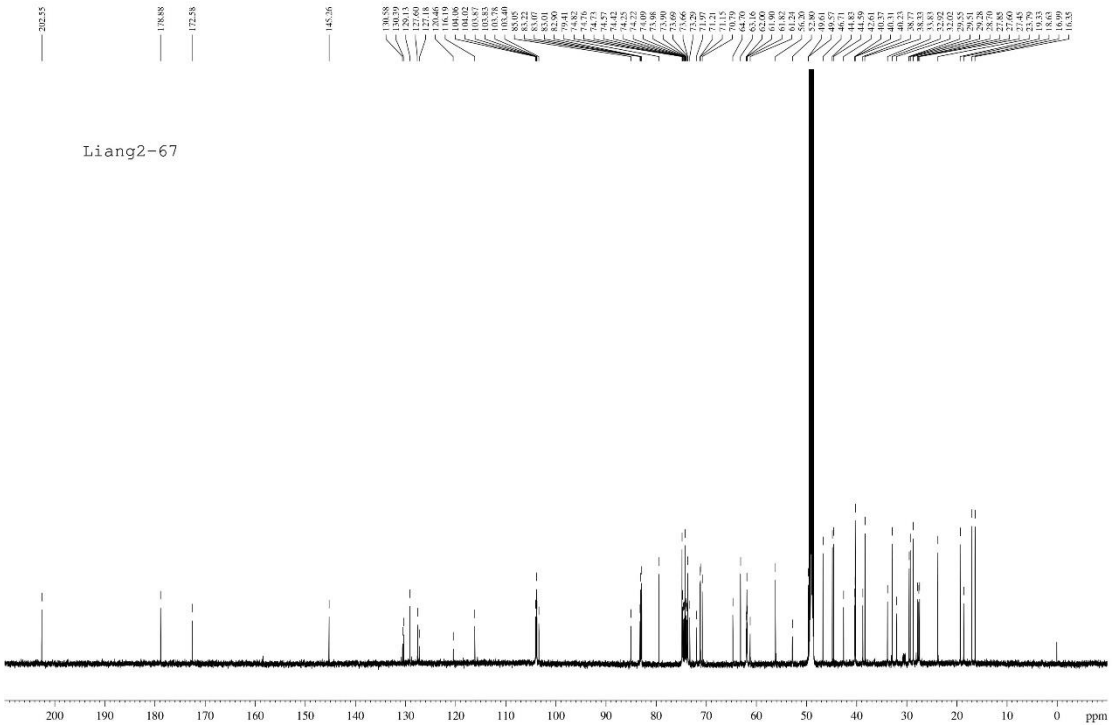
HRMS of compound **24**



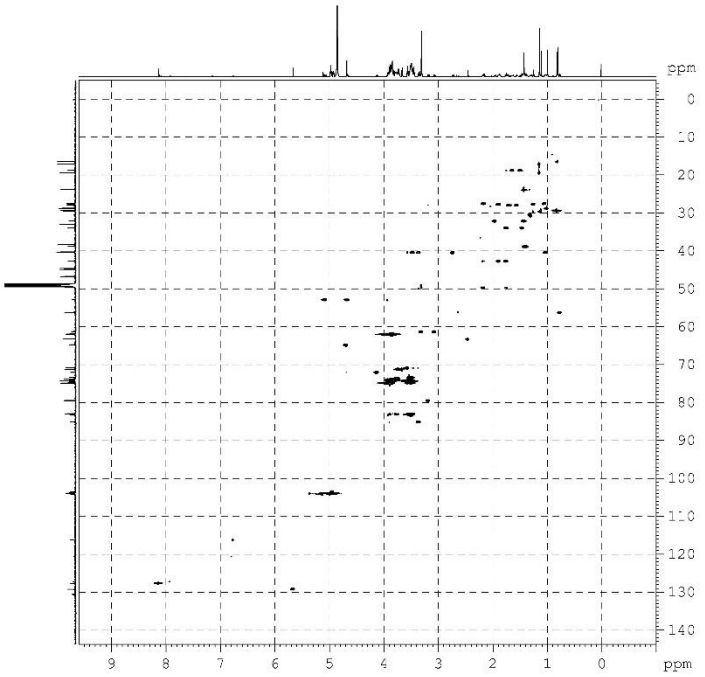
^{1}H NMR of compound **25**



^{13}C NMR of compound **25**

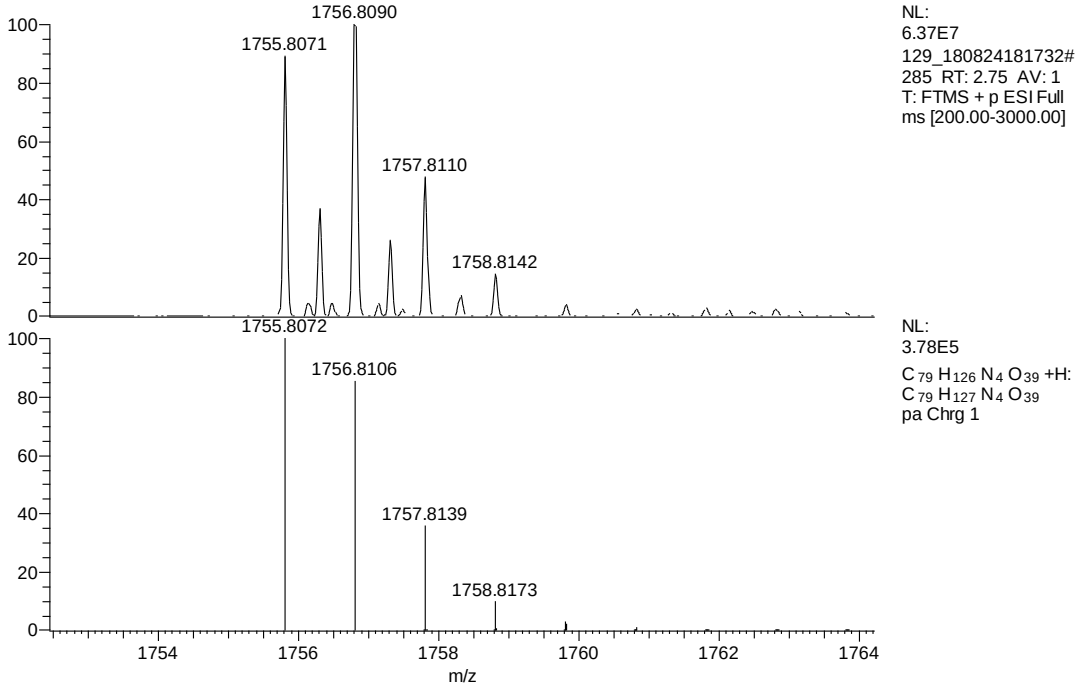


HSQC of compound **25**

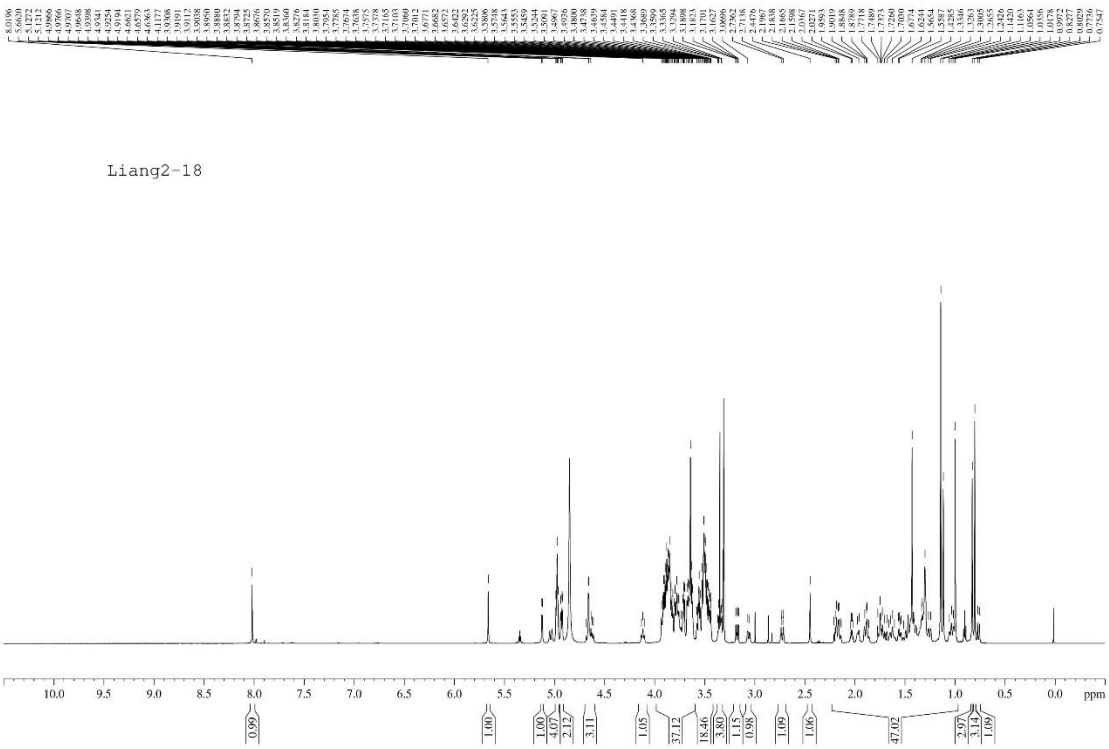


NAME	Liang2-67
EXPNO	4
PROCNO	1
Date_	20180425
Time	16.35
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	hsqcetgpsi
TD	2048
SOLVENT	MeOD
NS	8
DS	16
SWH	6421.233
FIDRES	3.135368
AQ	0.1595209
RG	203
DW	77.867
DE	10.00
TE	300.4

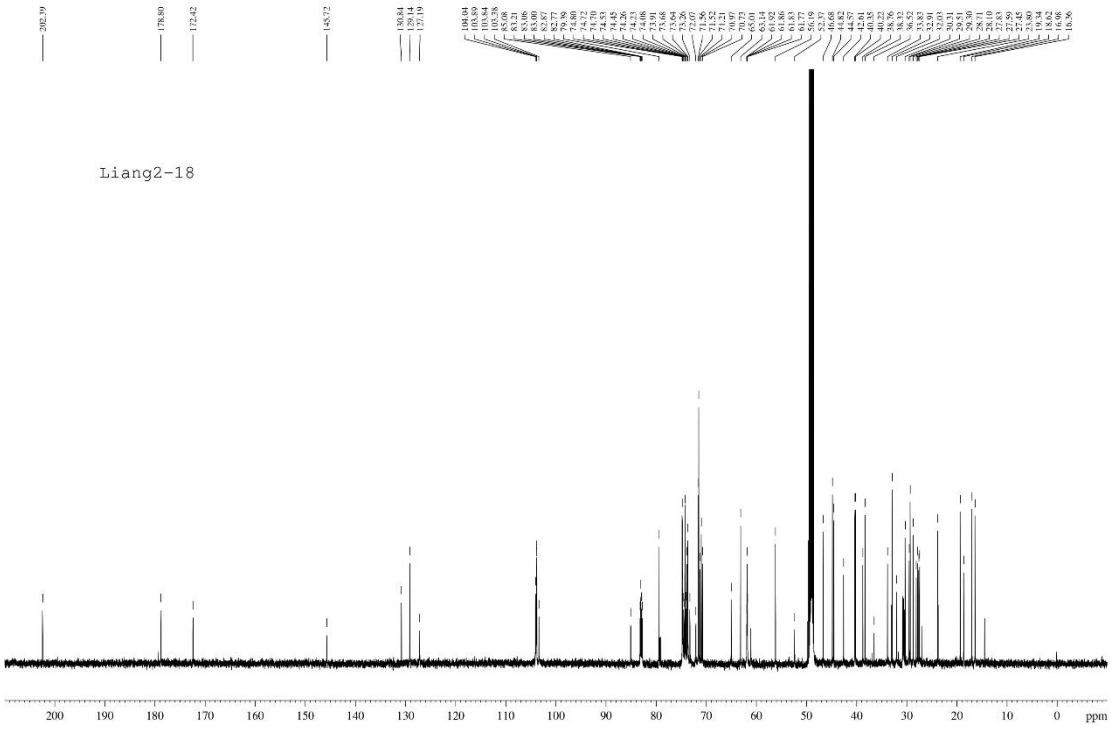
HRMS of compound **25**



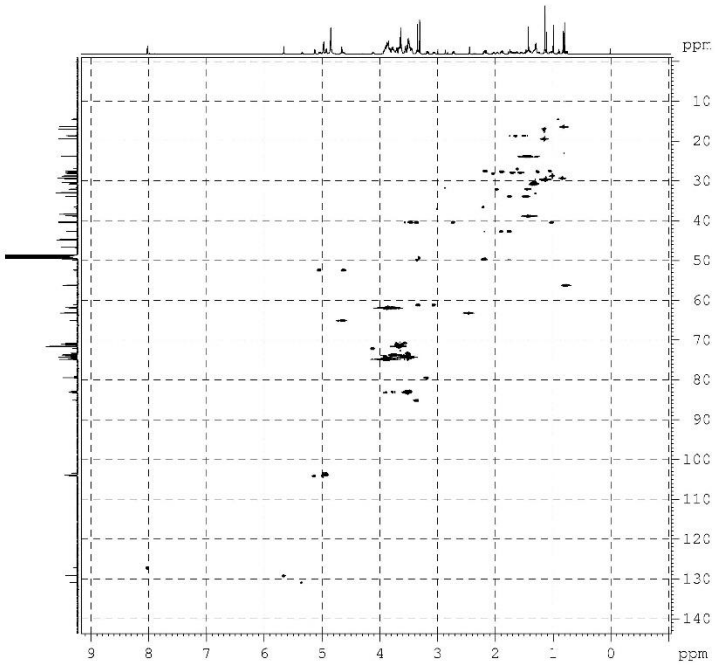
^{1}H NMR of compound **26**



^{13}C NMR of compound **26**

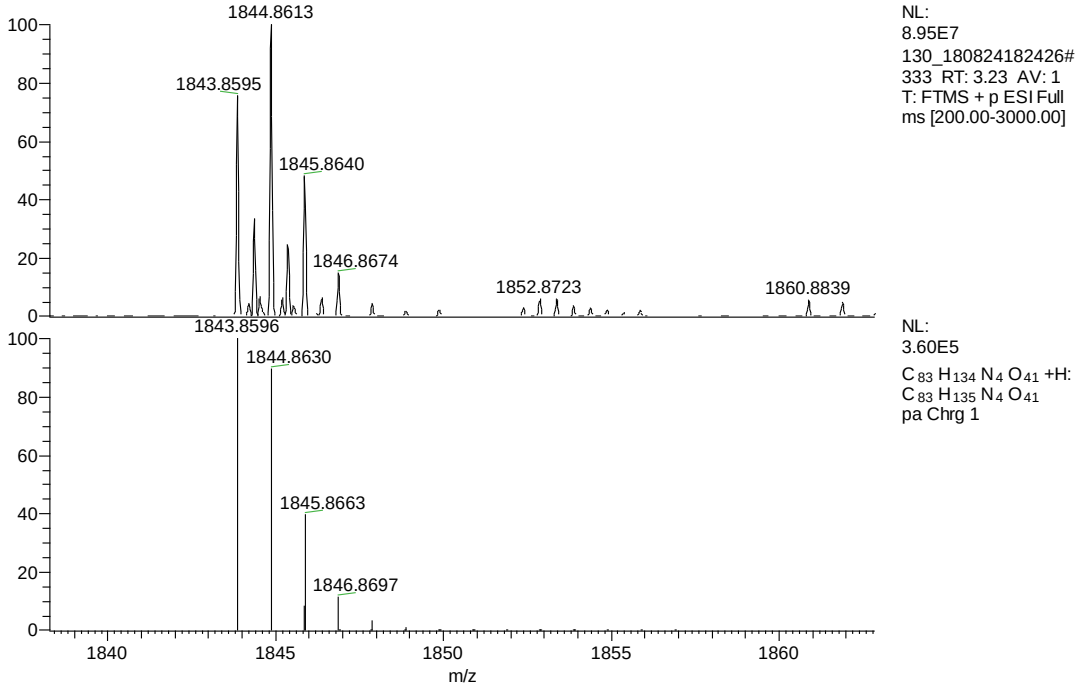


HSQC of compound **26**

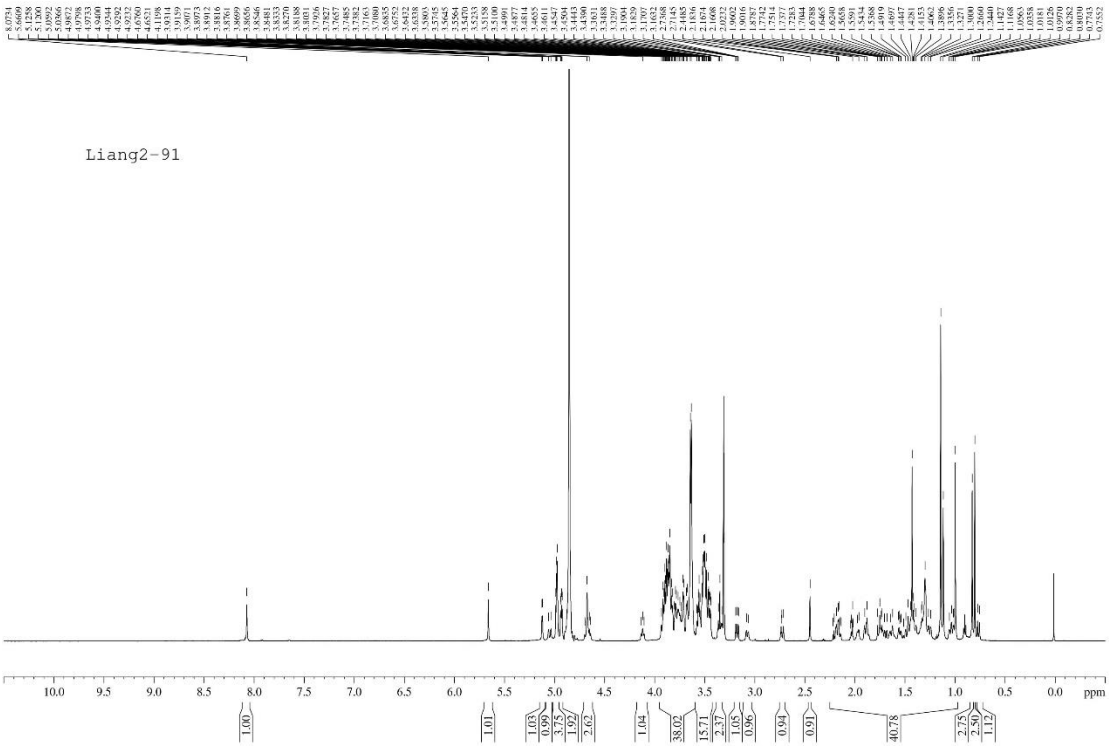


NAME	Liang2-18
EXPNO	4
PROCNO	1
Date_	20180129
Time	16.56
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	hsqcetgpsi
TD	2048
SOLVENT	MeOD
NS	4
DS	16
SWH	6127.451
FIDRES	2.991920
AQ	0.1671668
RG	203
DW	81.600
DE	10.00
TE	300.4

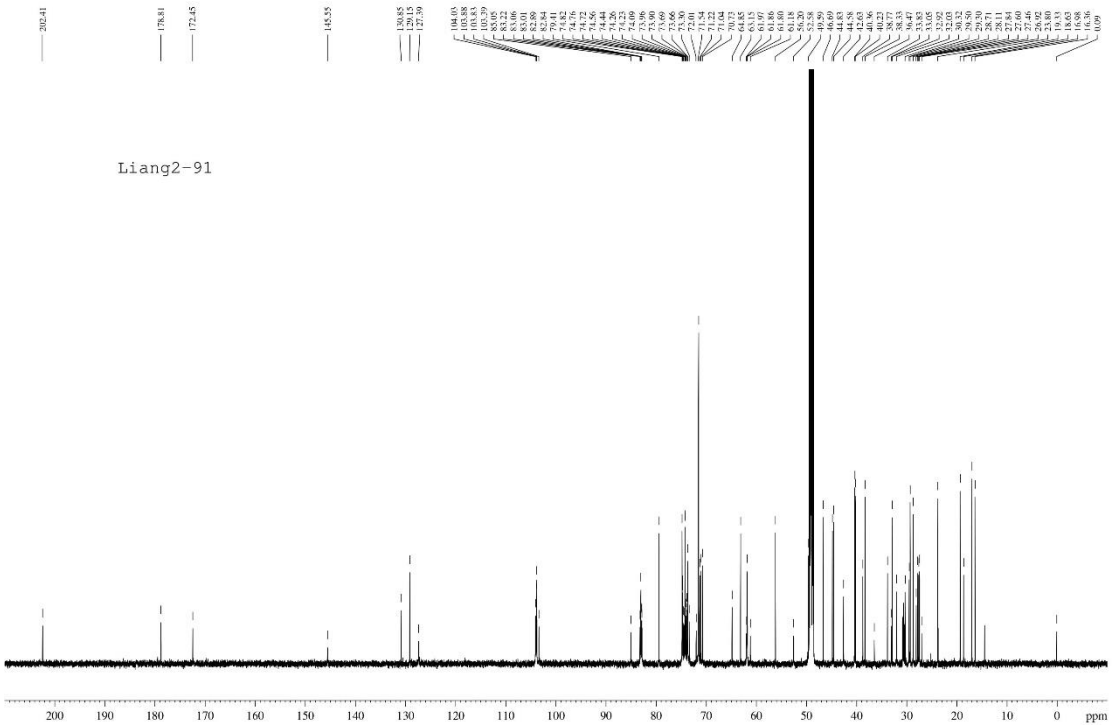
HRMS of compound **26**



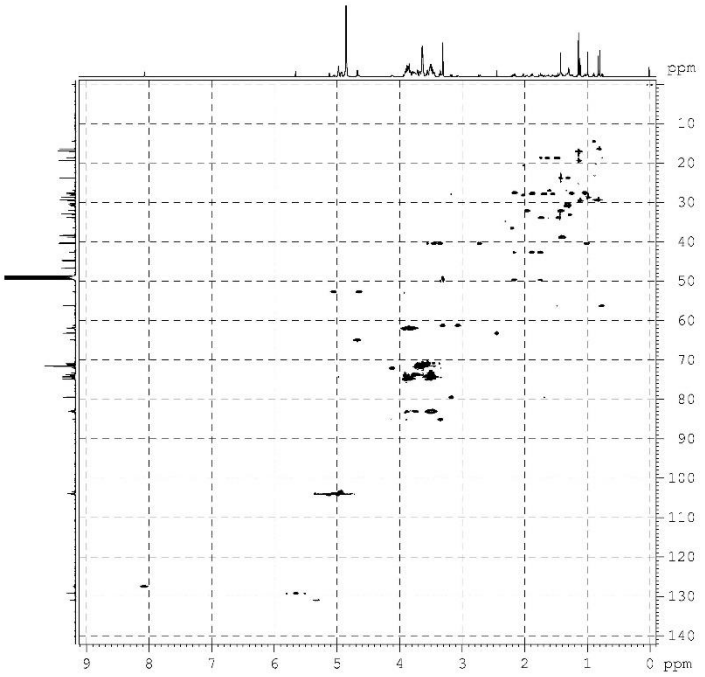
^{1}H NMR of compound **27**



^{13}C NMR of compound **27**

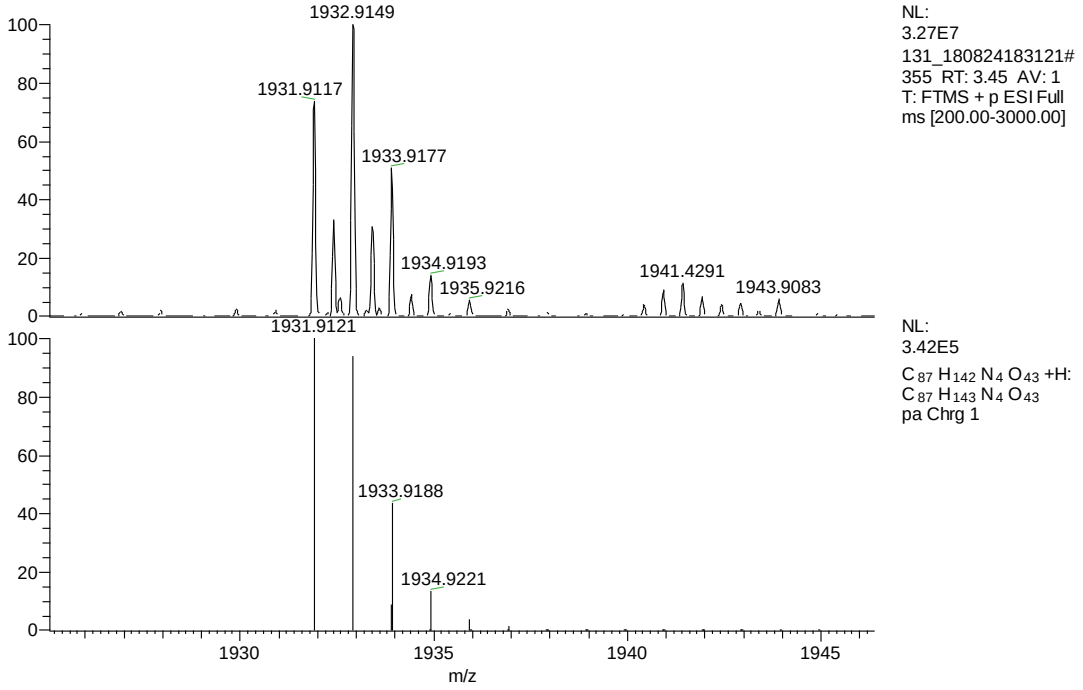


HSQC of compound **27**

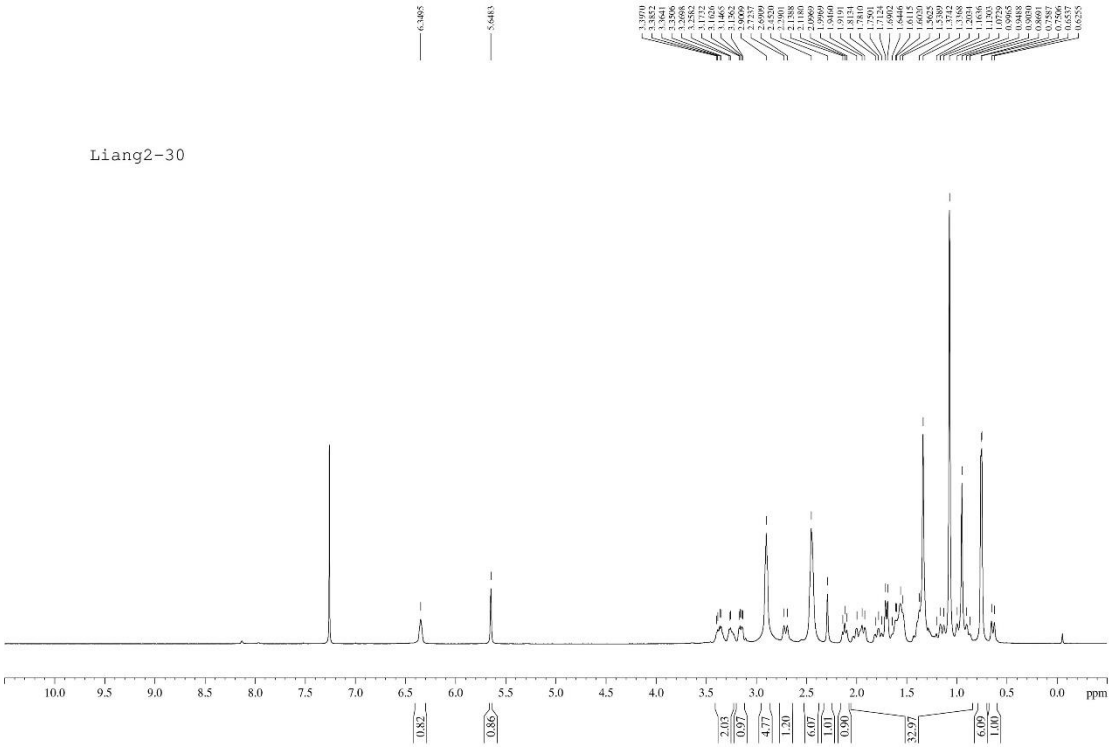


NAME	Liang2-91
EXPNO	4
PROCNO	1
Date_	20180521
Time	10.39
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	hsqcetgpsi
TD	2048
SOLVENT	MeOD
NS	8
DS	16
SWH	6097.561
FIDRES	2.977325
AQ	0.1679860
RG	203
DW	82.000
DE	10.00
TE	300.4

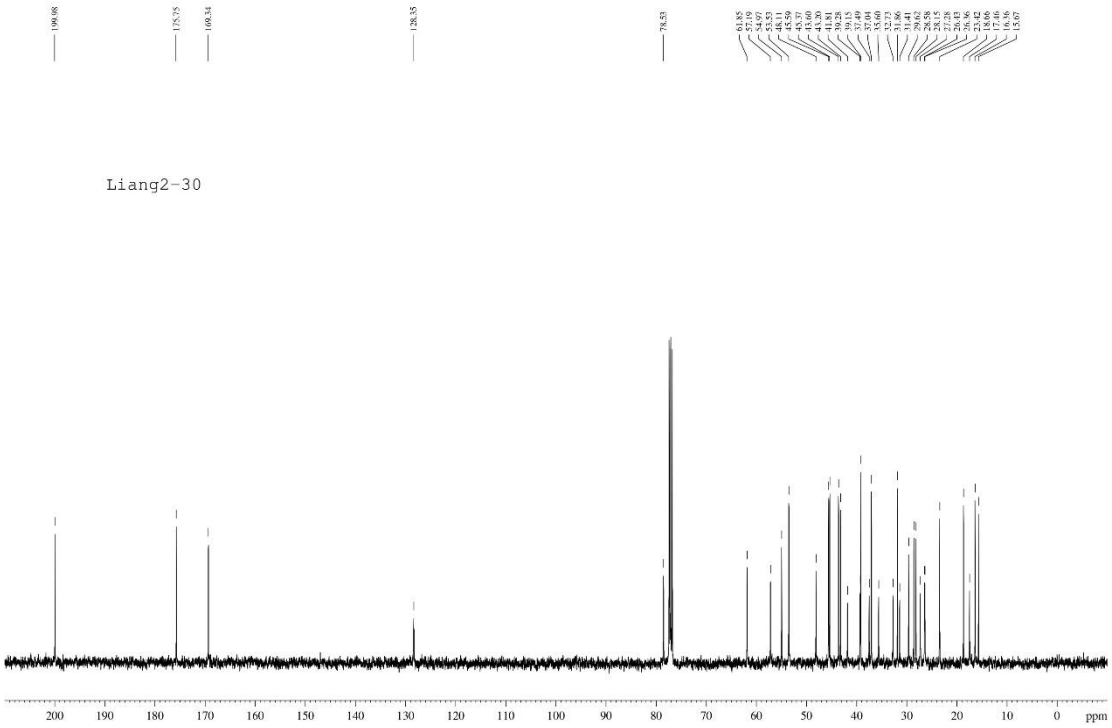
HRMS of compound **27**



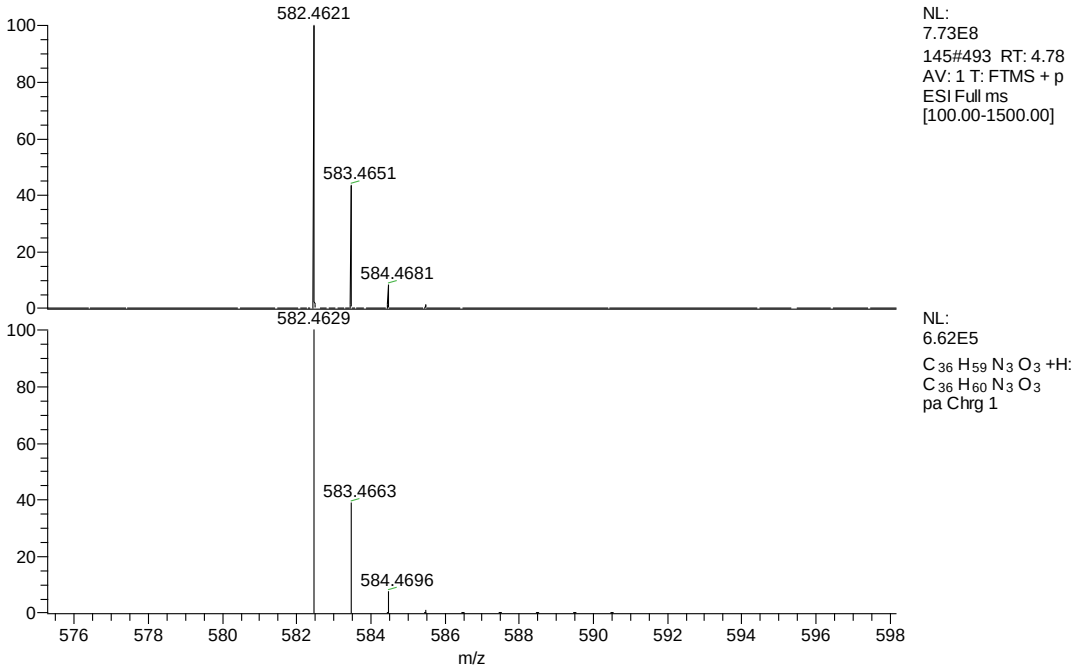
^{1}H NMR of compound **28**



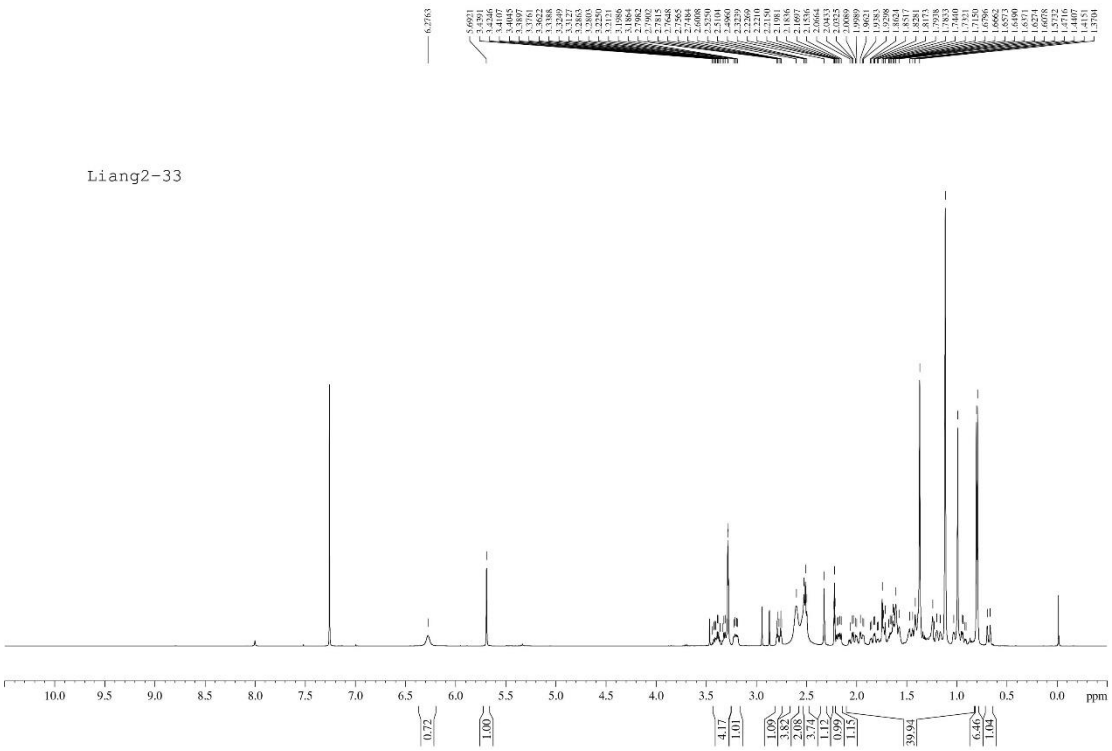
^{13}C NMR of compound **28**



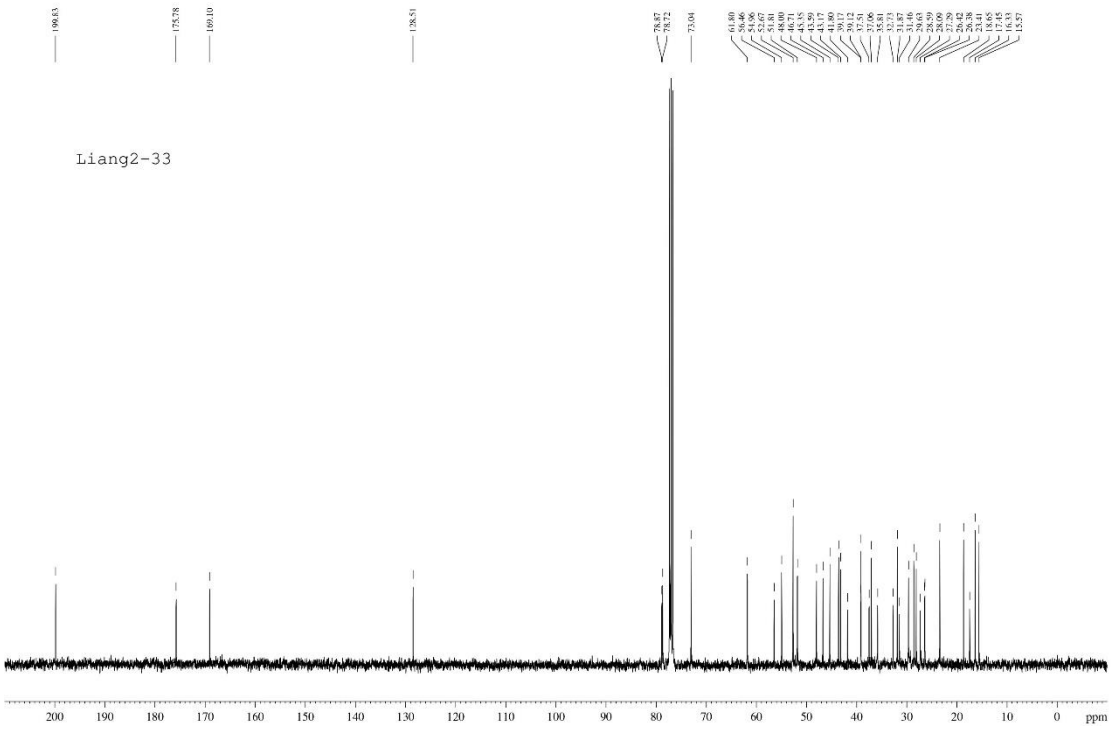
HRMS of compound **28**



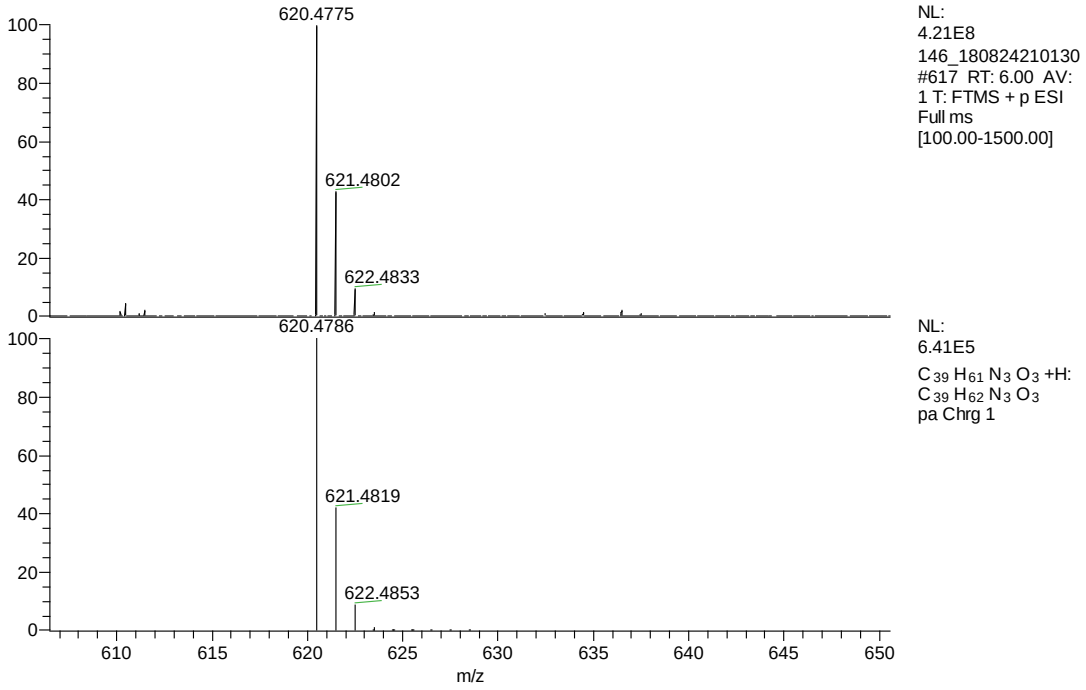
^{1}H NMR of compound **29**



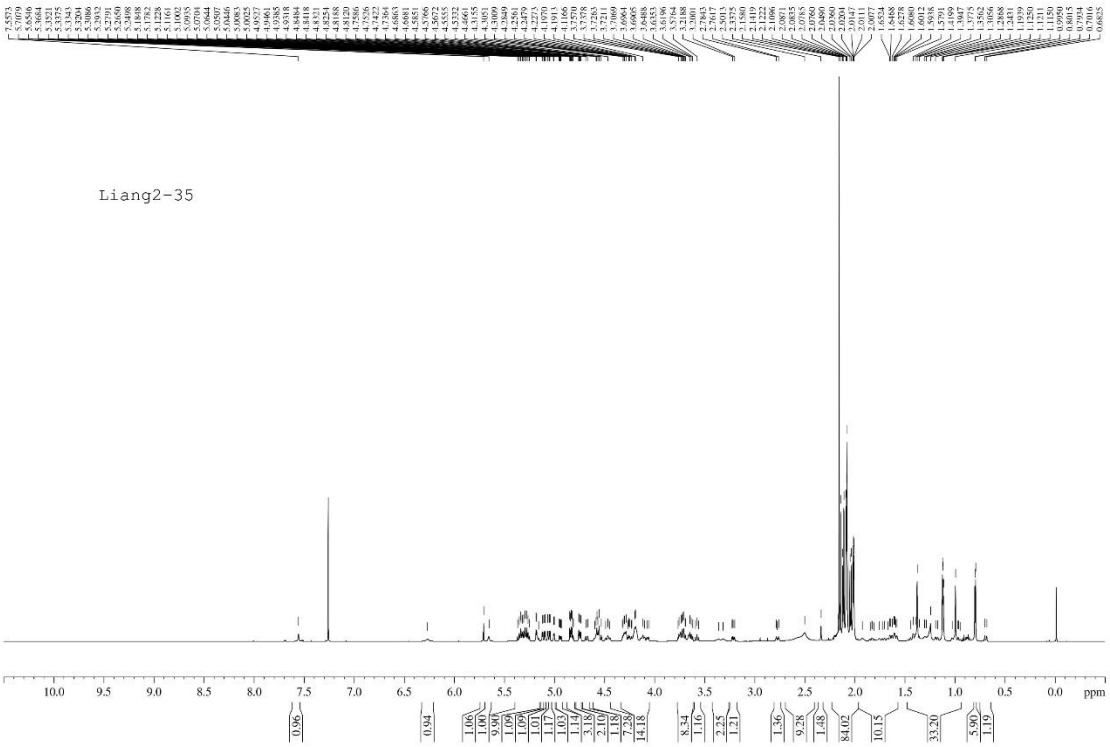
^{13}C NMR of compound **29**



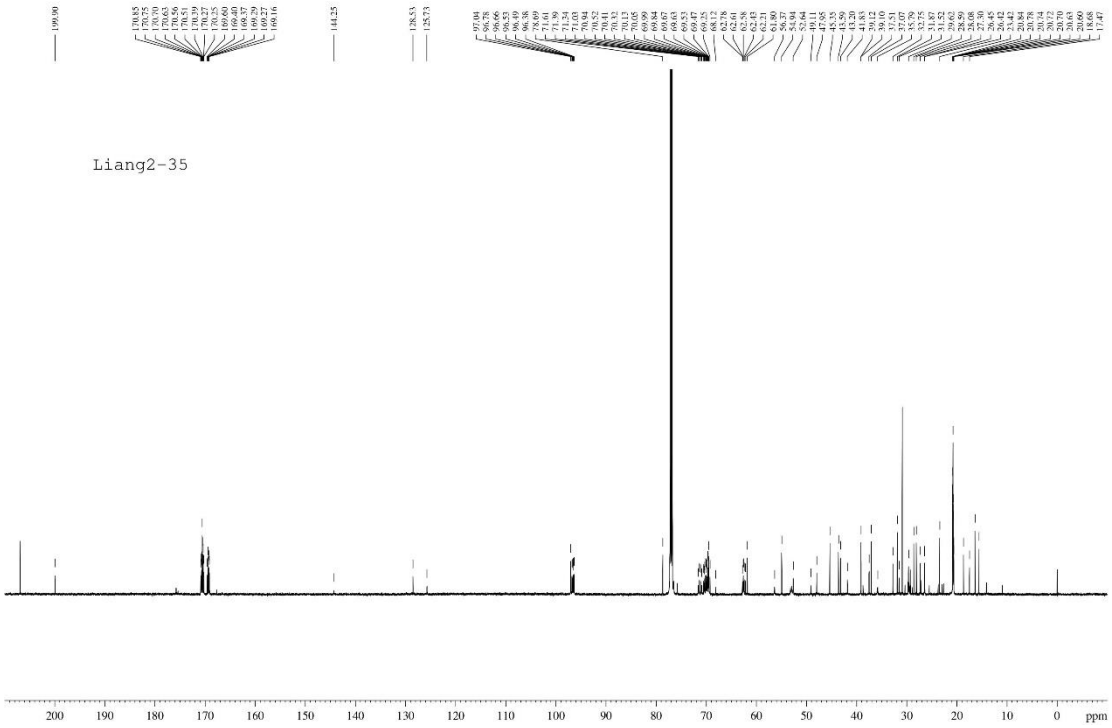
HRMS of compound **29**



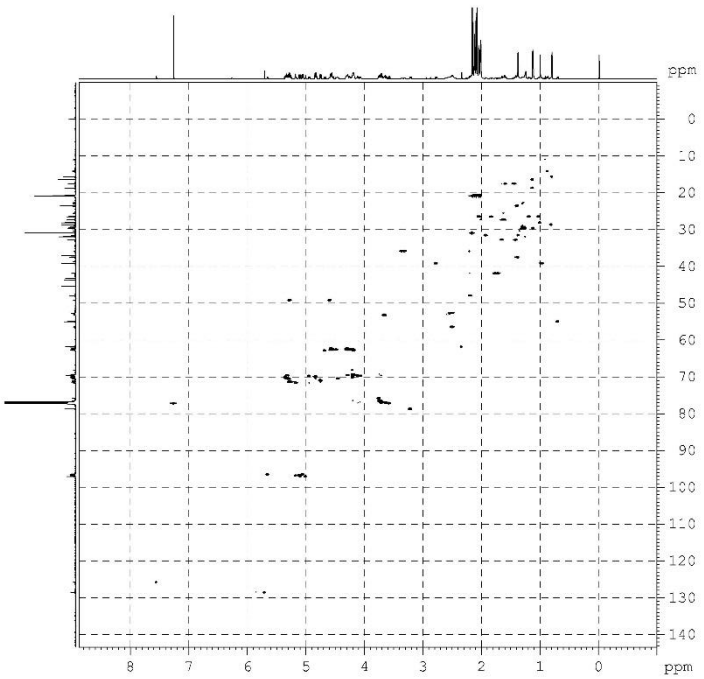
^{1}H NMR of compound **30**



^{13}C NMR of compound **30**

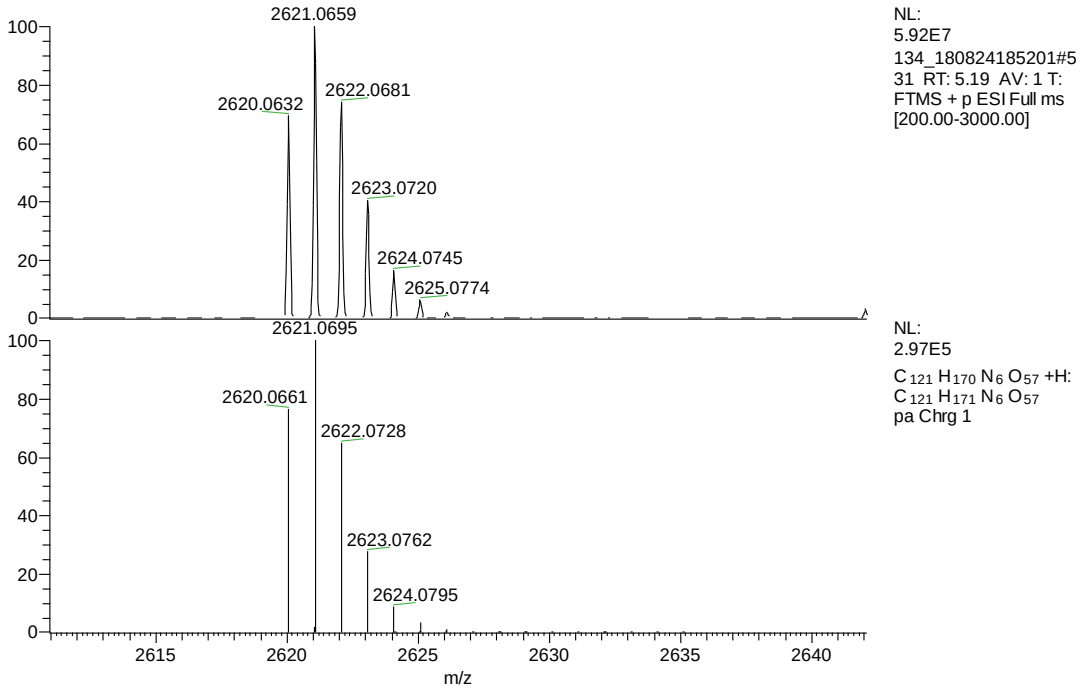


HSQC of compound **30**

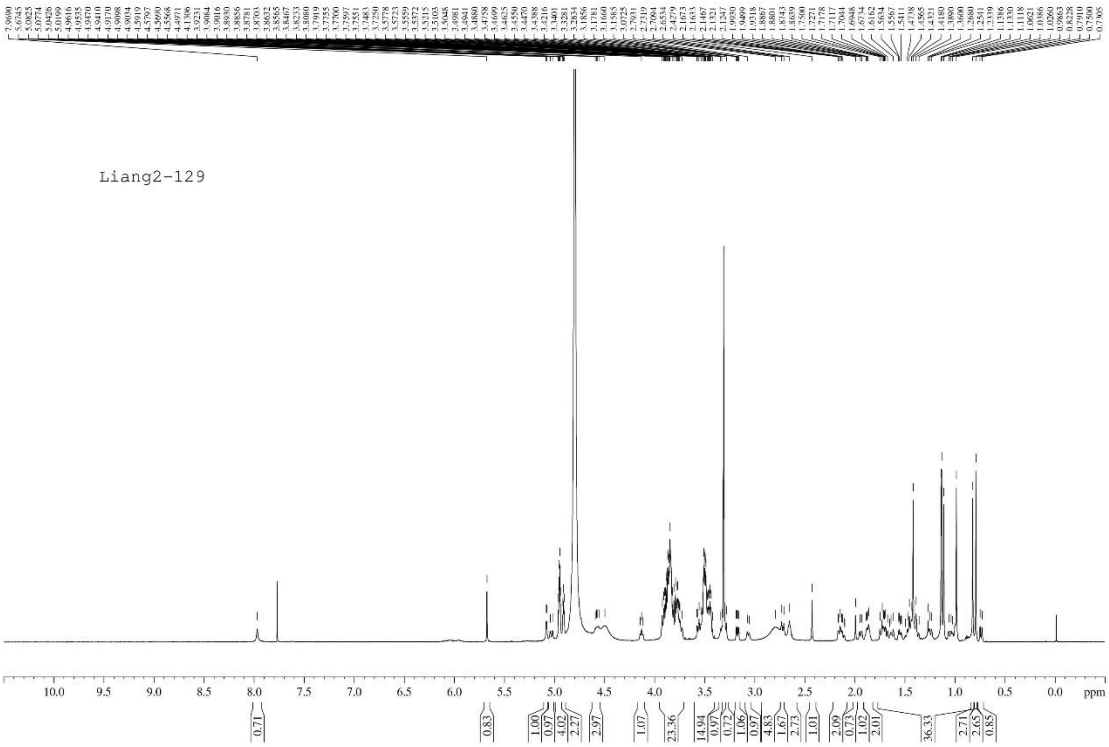


NAME	Liang2-35
EXPNO	4
PROCNO	1
Date_	20180307
Time	9.51
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	hsqcetgpsi
TD	2048
SOLVENT	CDCl3
NS	4
DS	16
SWH	6024.096
FIDRES	2.941453
AQ	0.1700340
RG	203
DW	83.000
DE	10.00
TE	300.4

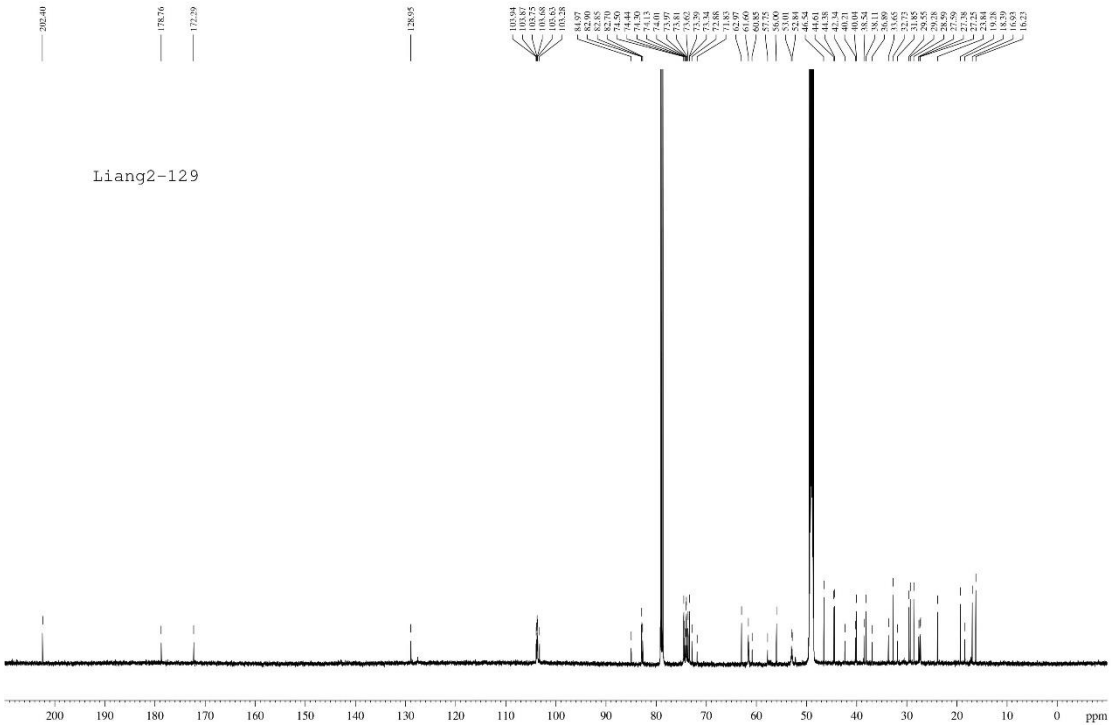
HRMS of compound **30**



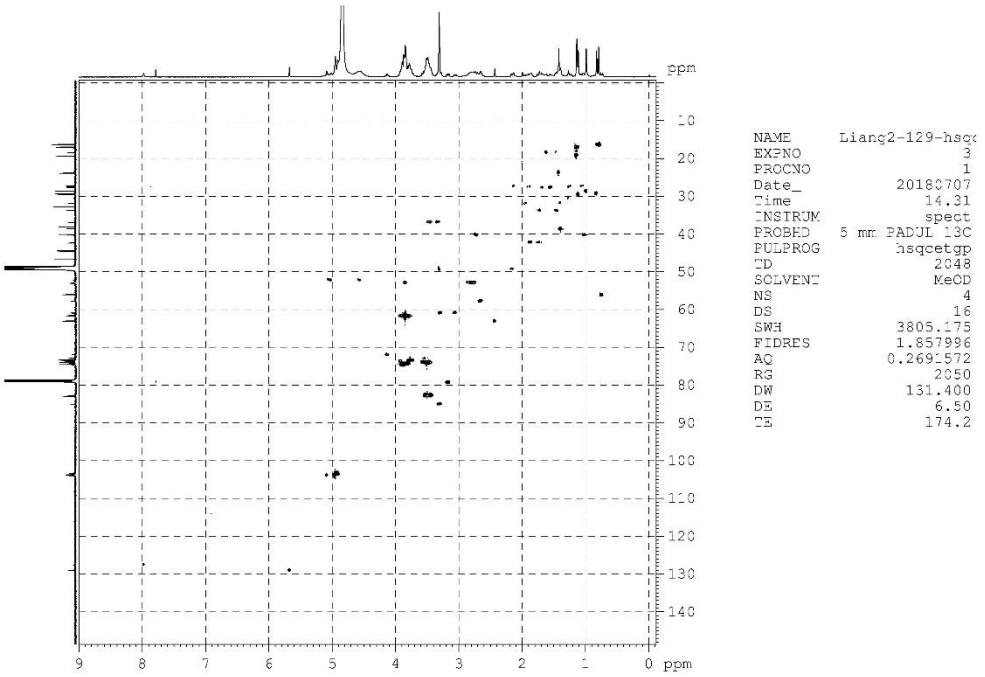
^{1}H NMR of compound **31**



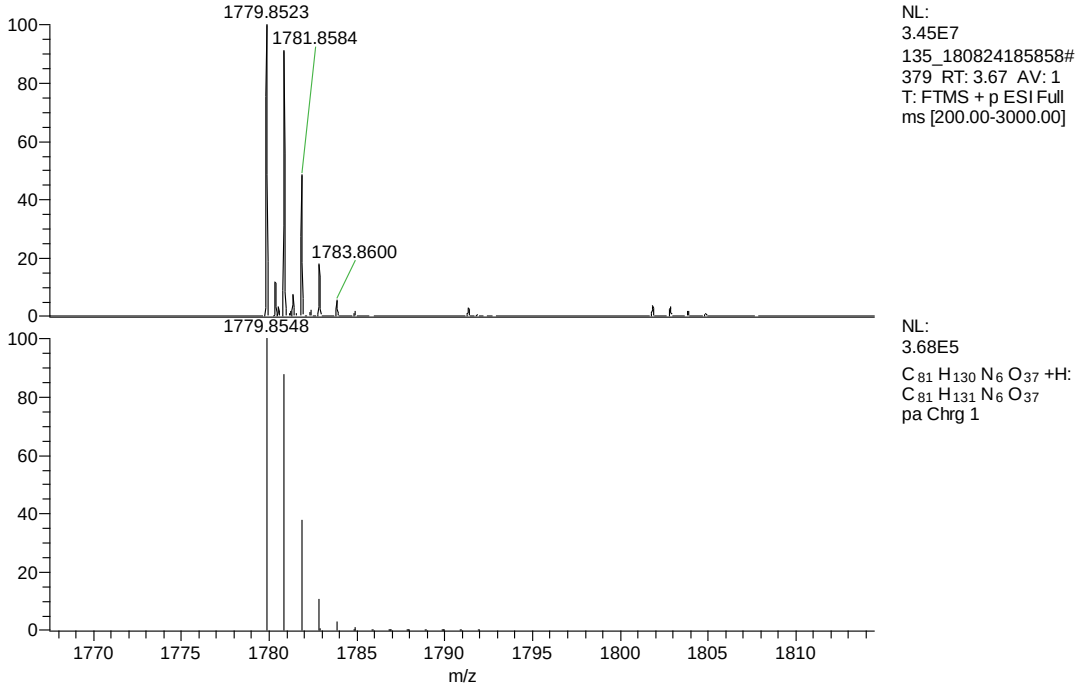
^{13}C NMR of compound **31**



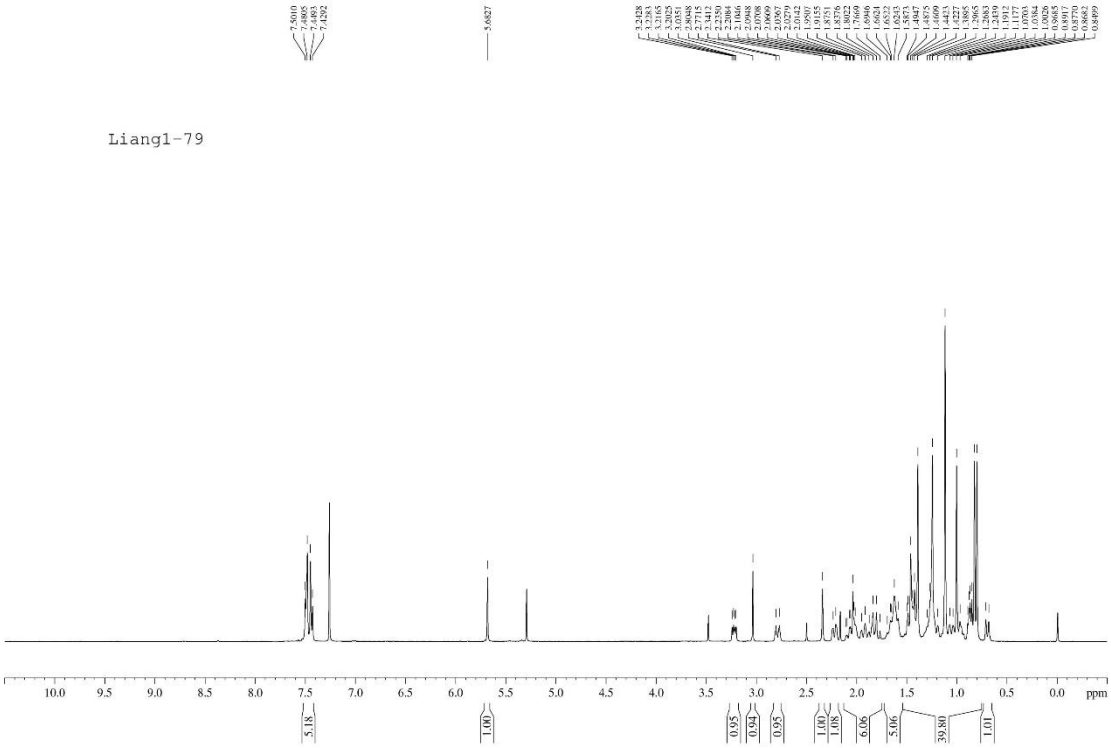
HSQC of compound **31**



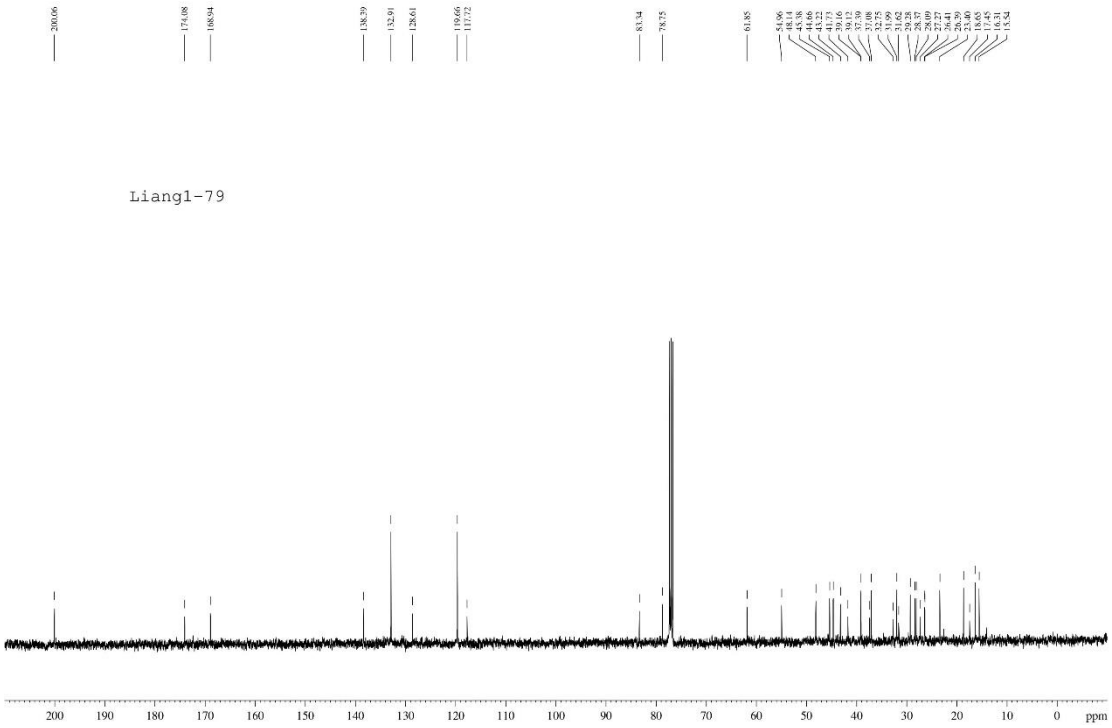
HRMS of compound **31**



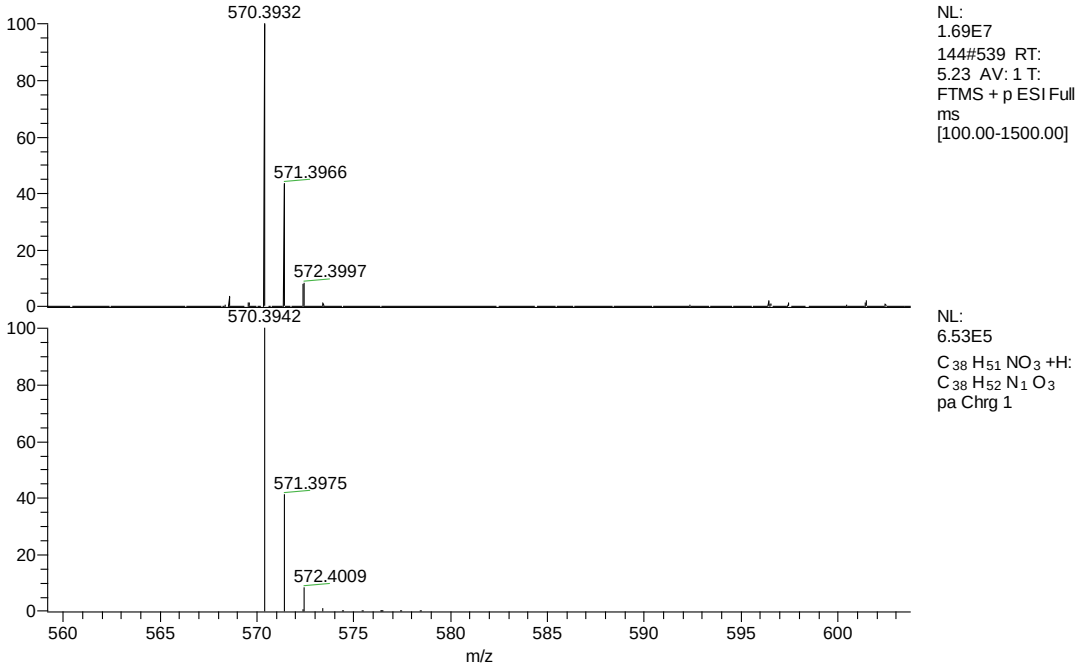
^{1}H NMR of compound **32**



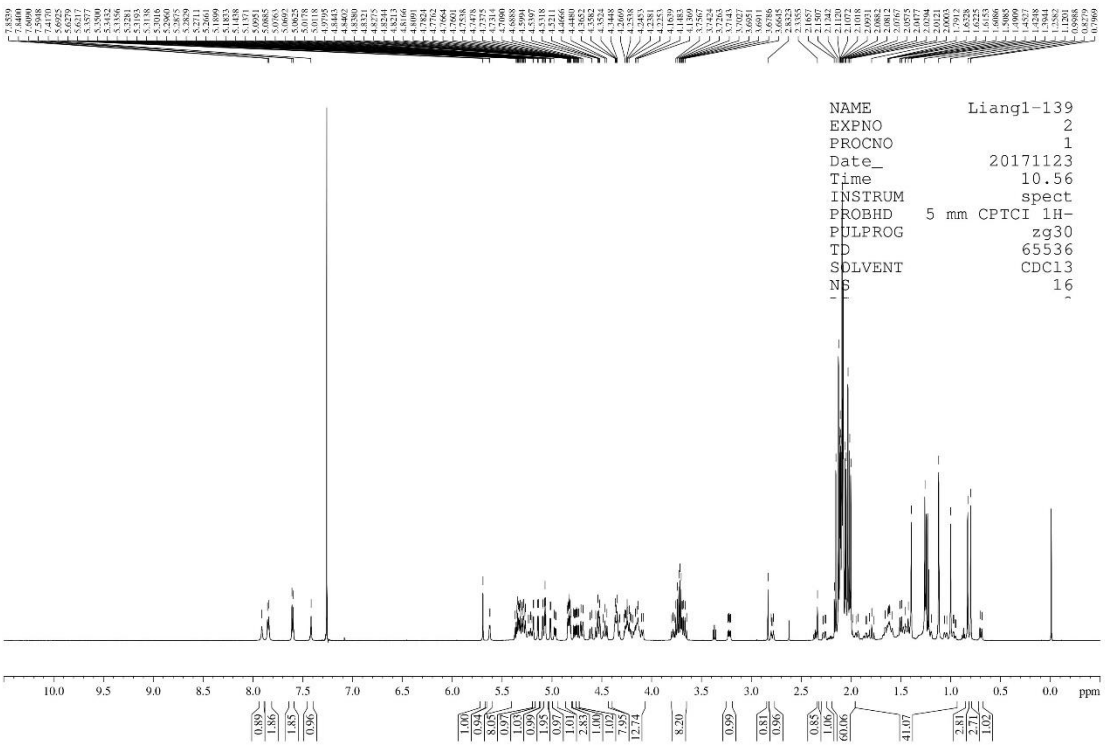
^{13}C NMR of compound **32**



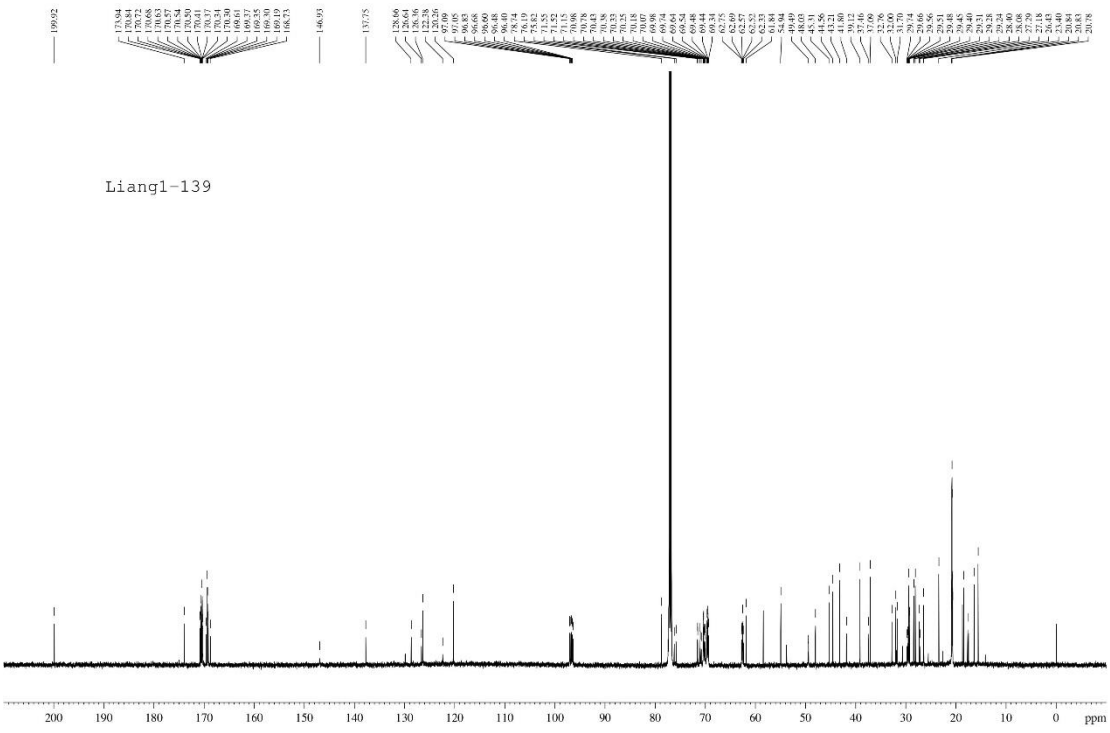
HRMS of compound **32**



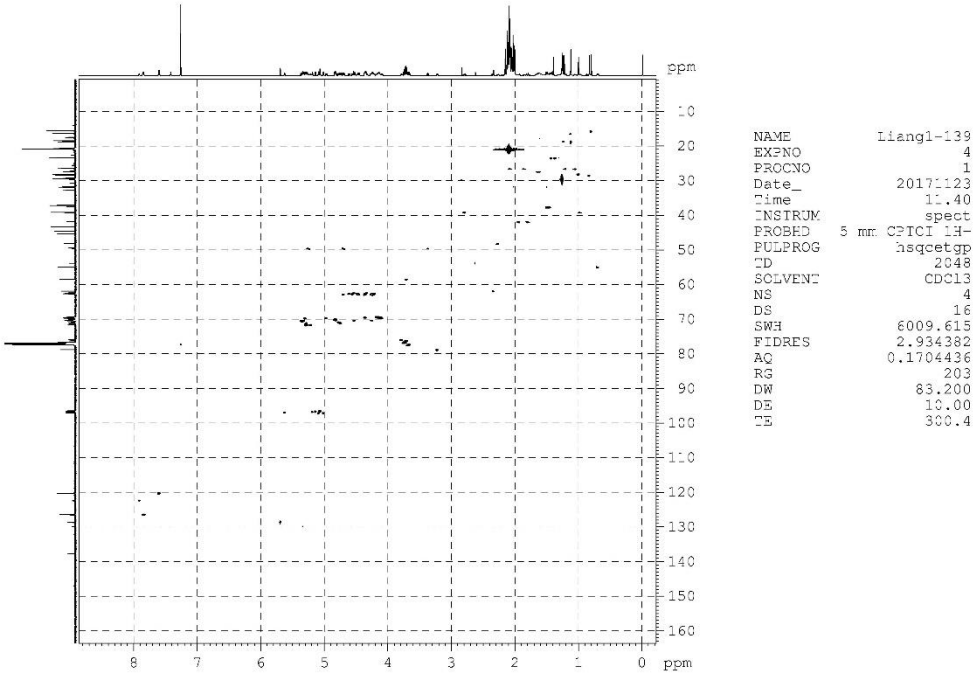
^{1}H NMR of compound **33**



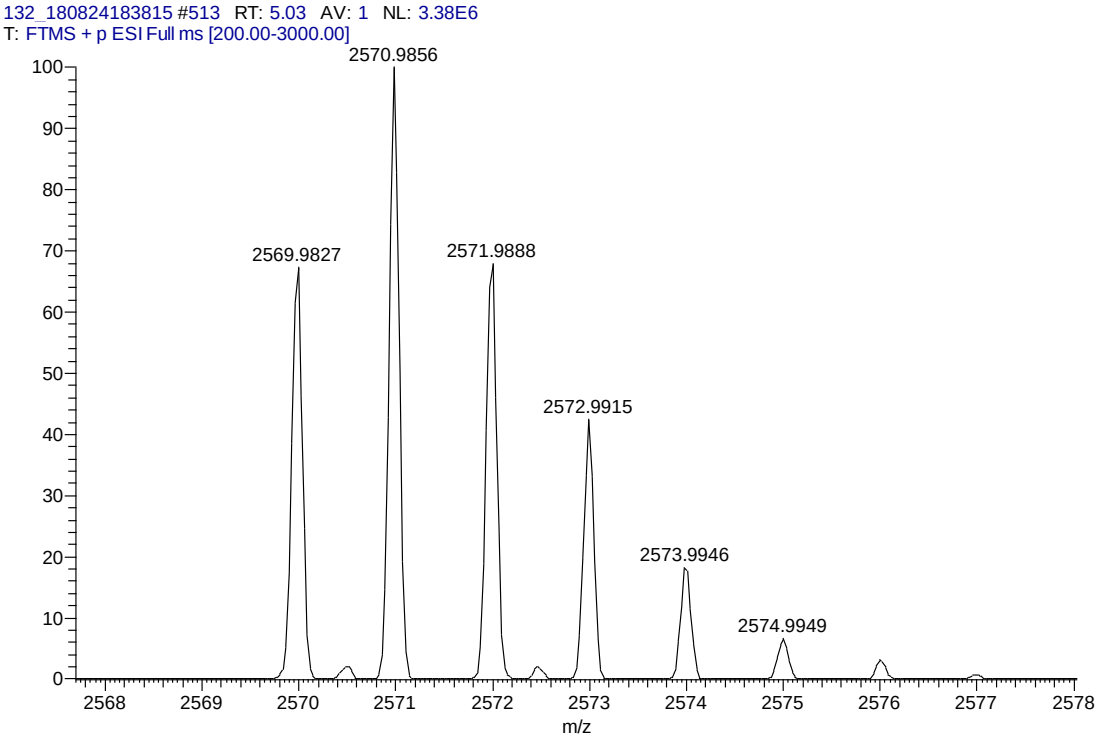
^{13}C NMR of compound **33**



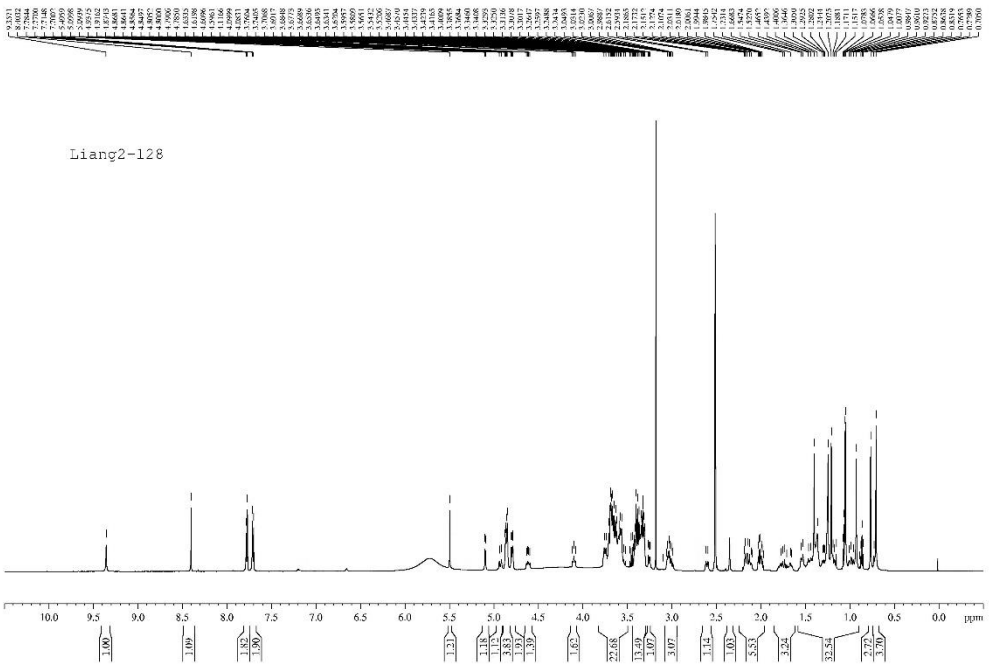
HSQC of compound **33**



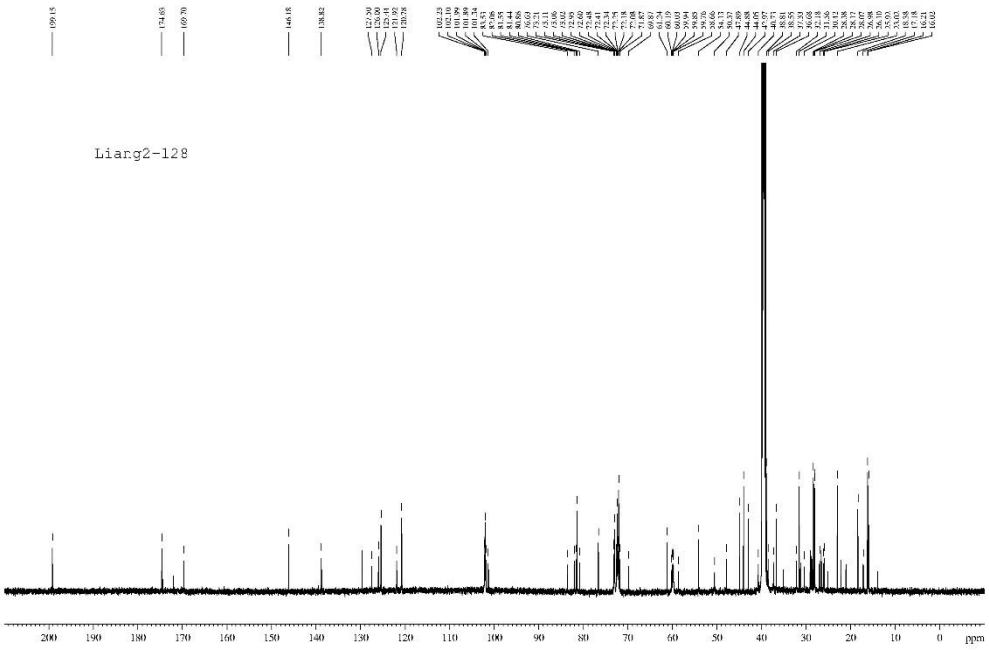
HRMS of compound **33**



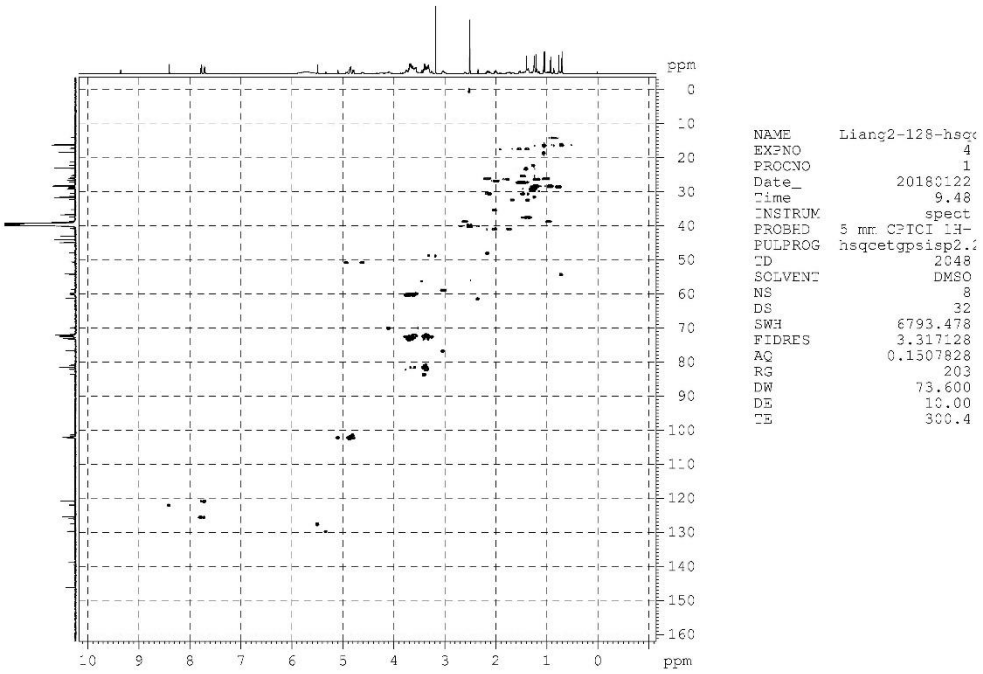
^{1}H NMR of compound **34**



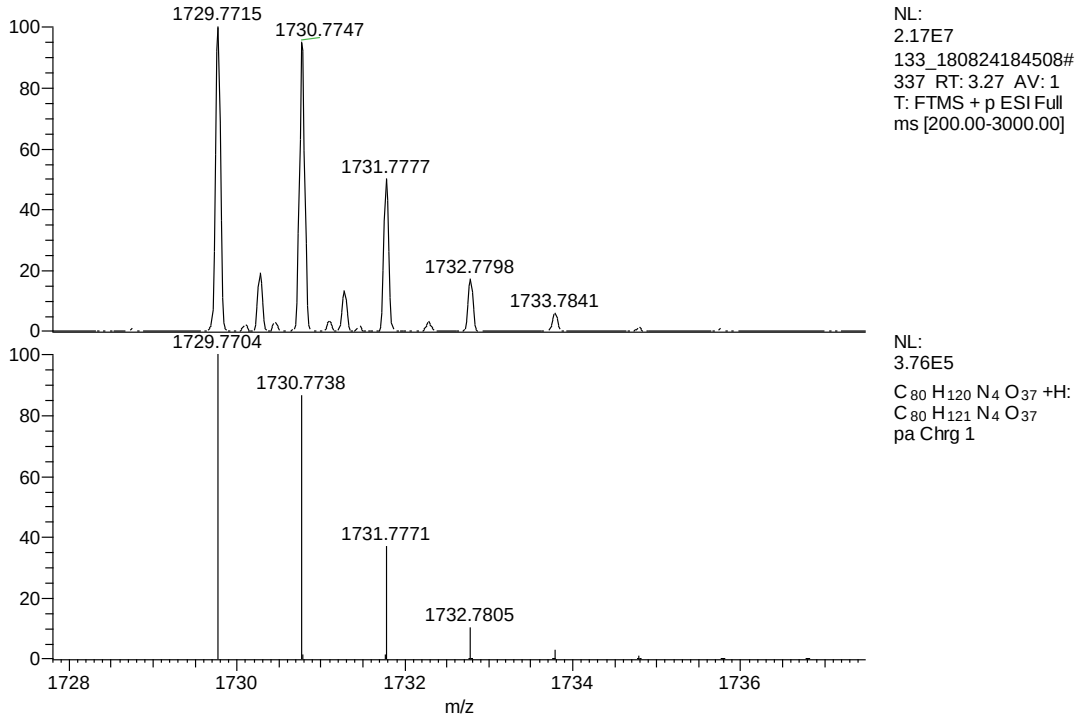
^{13}C NMR of compound **34**



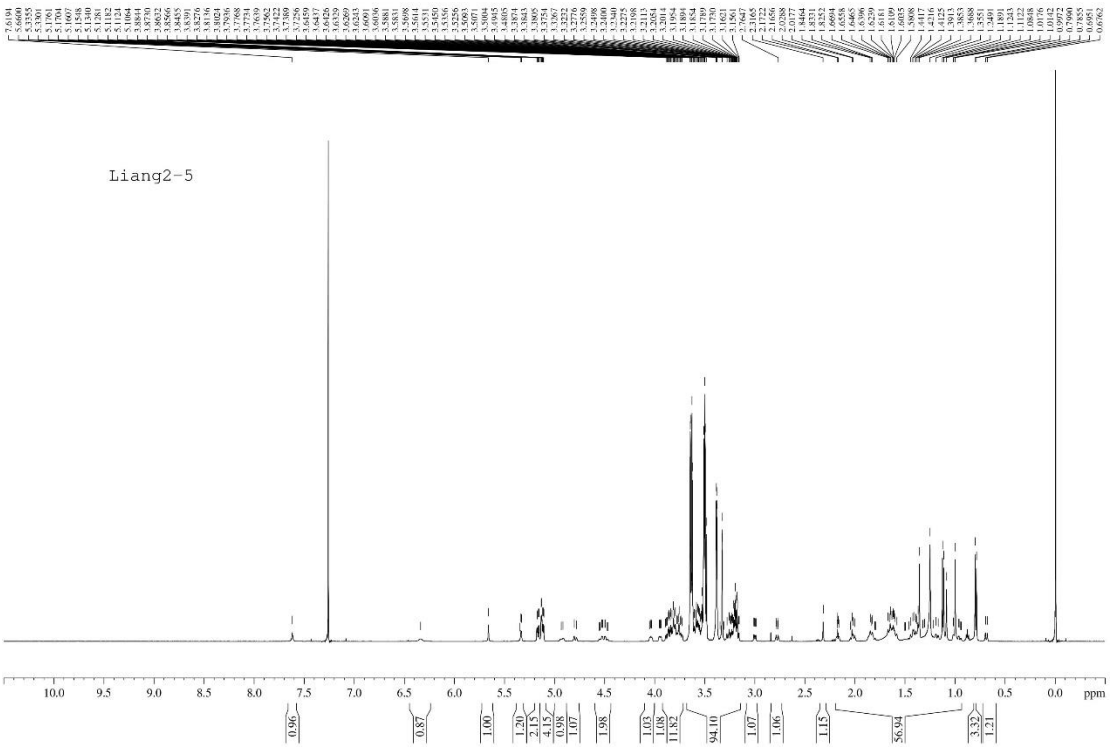
HSQC of compound **34**



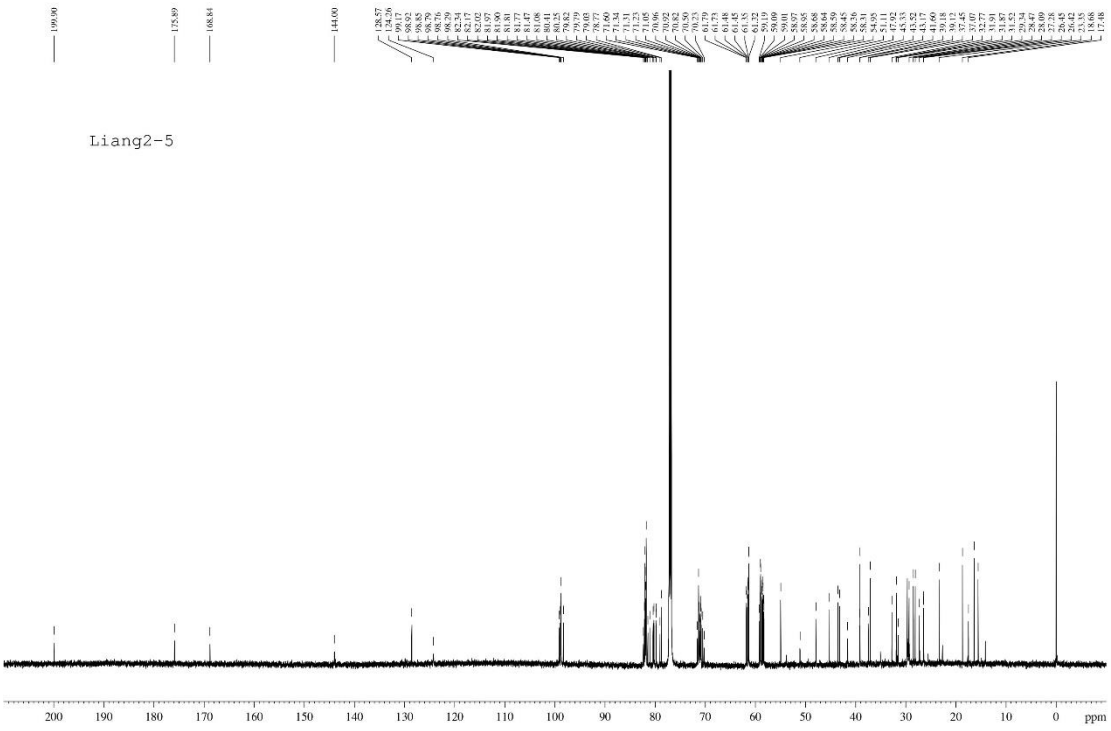
HRMS of compound **34**



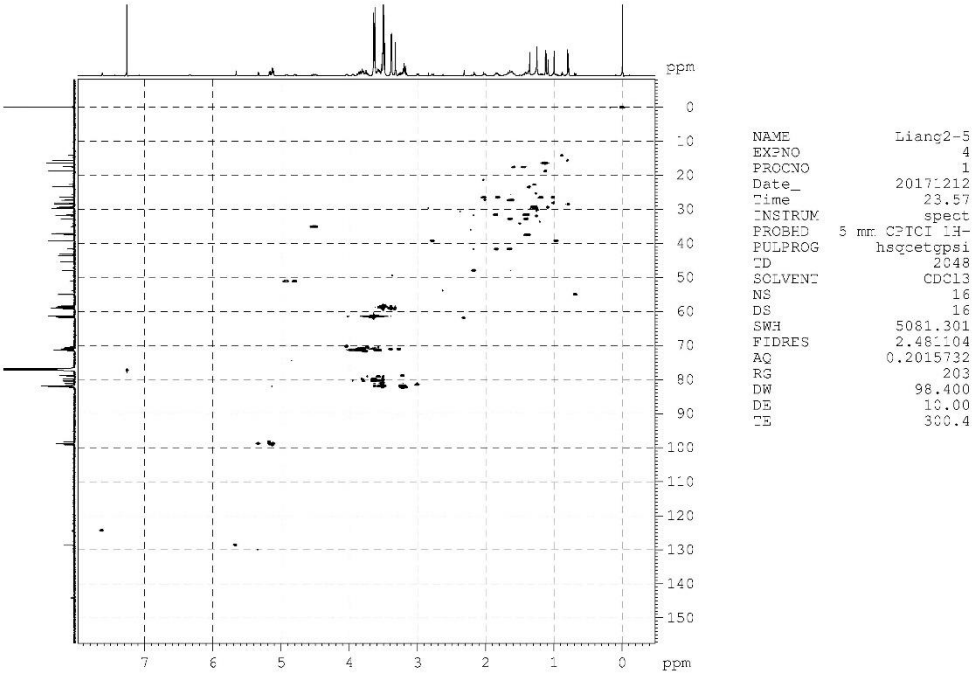
^{1}H NMR of compound **35**



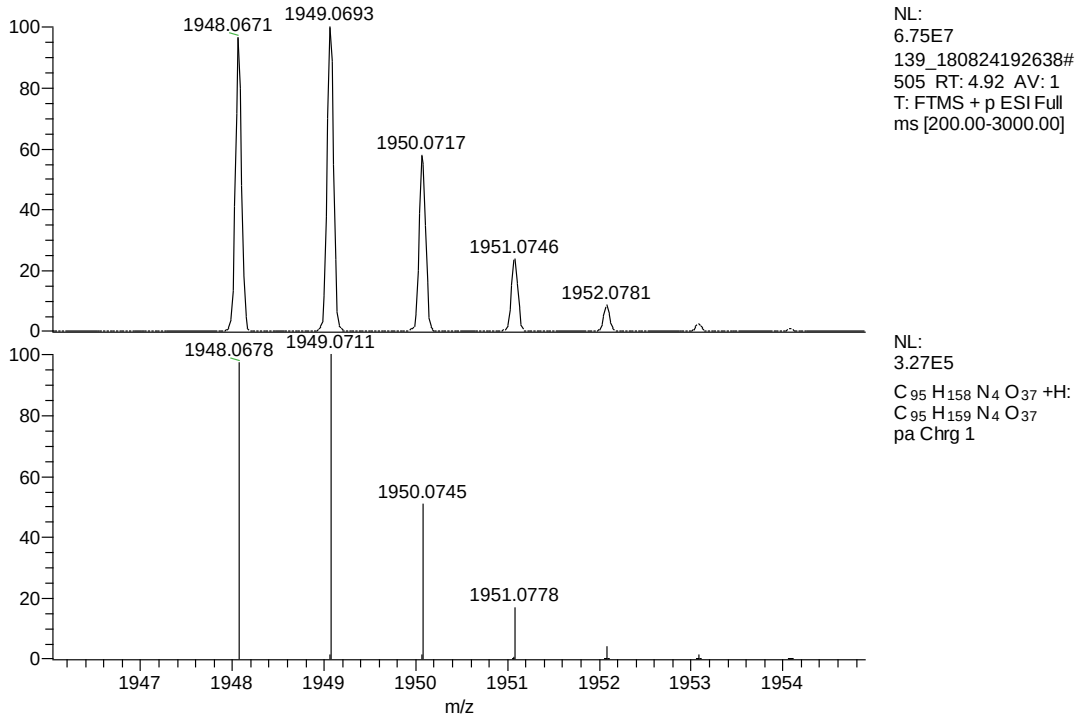
^{13}C NMR of compound **35**



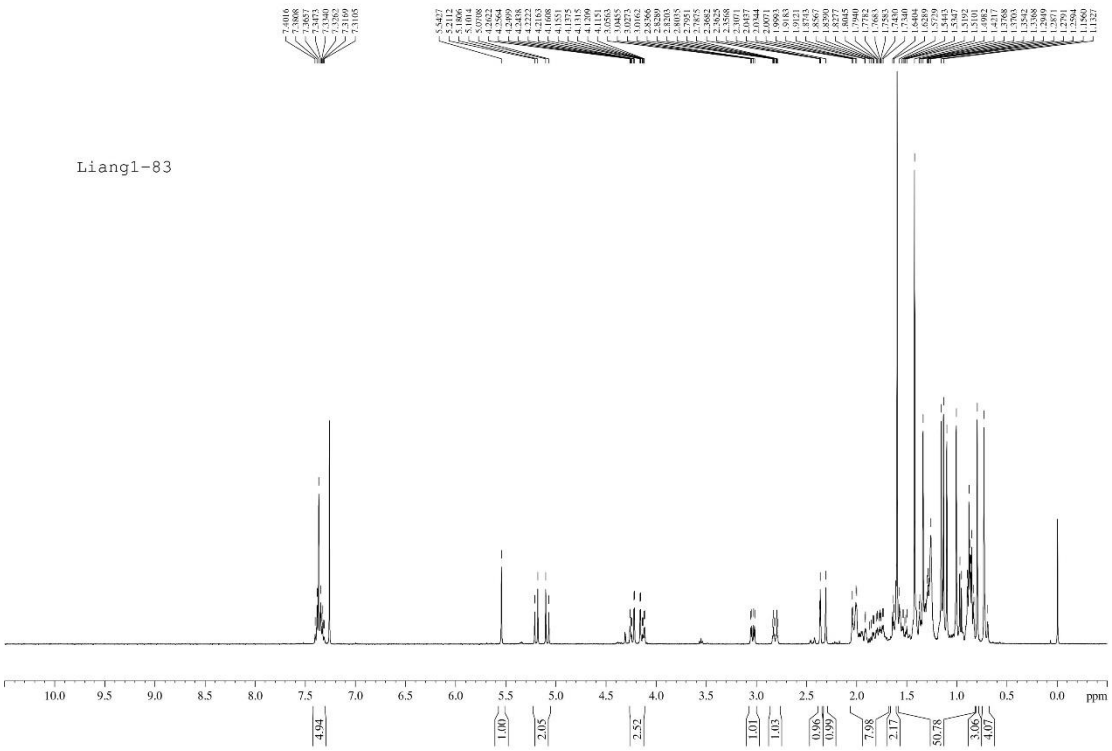
HSQC of compound **35**



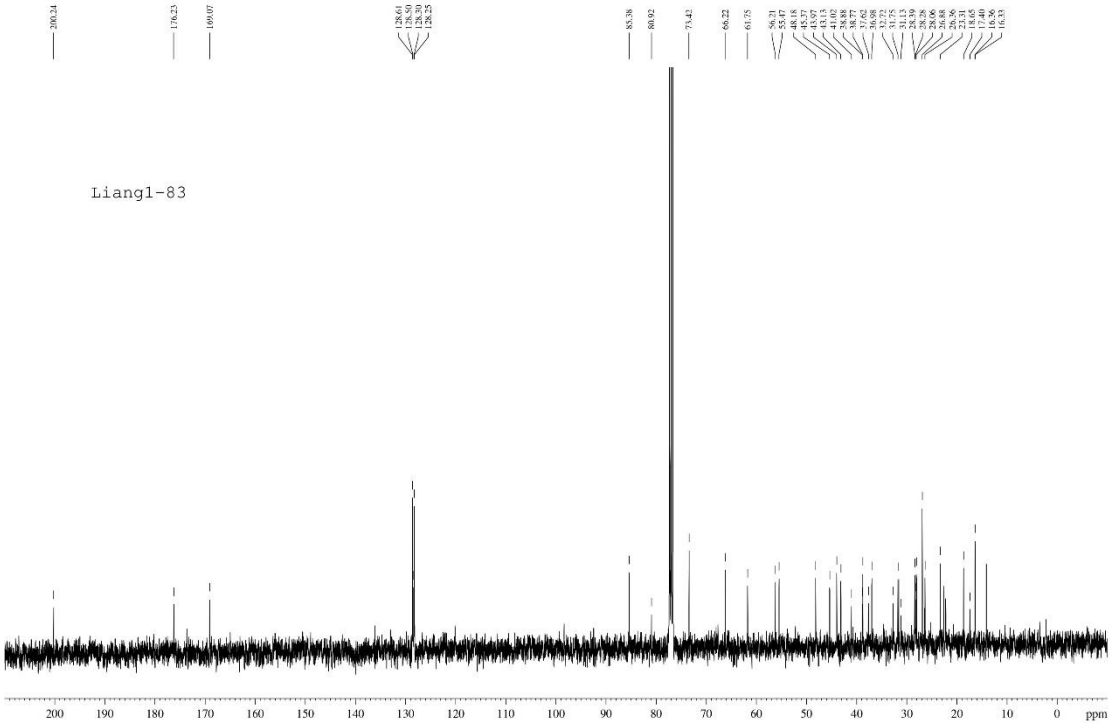
HRMS of compound **35**



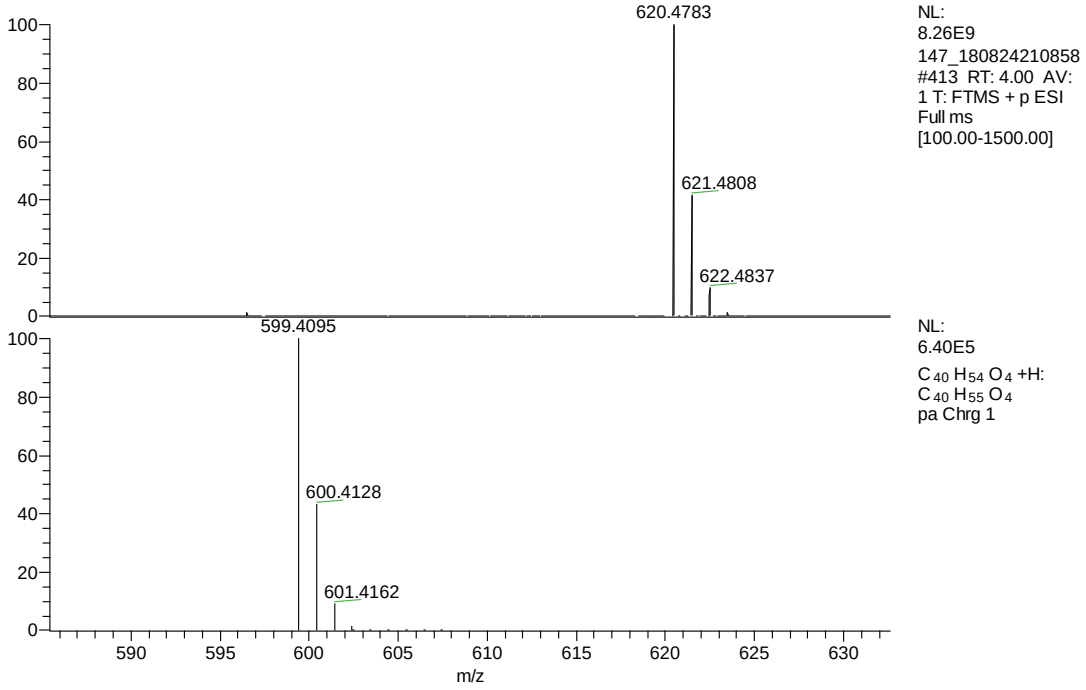
^{1}H NMR of compound **37**



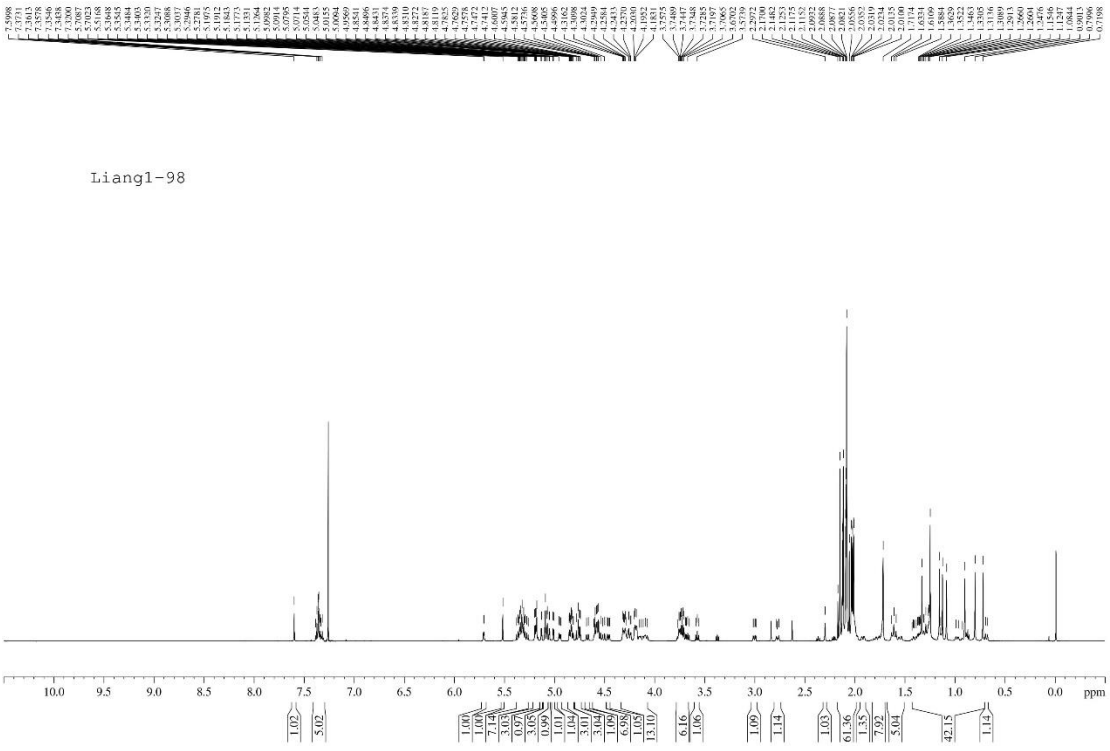
^{13}C NMR of compound **37**



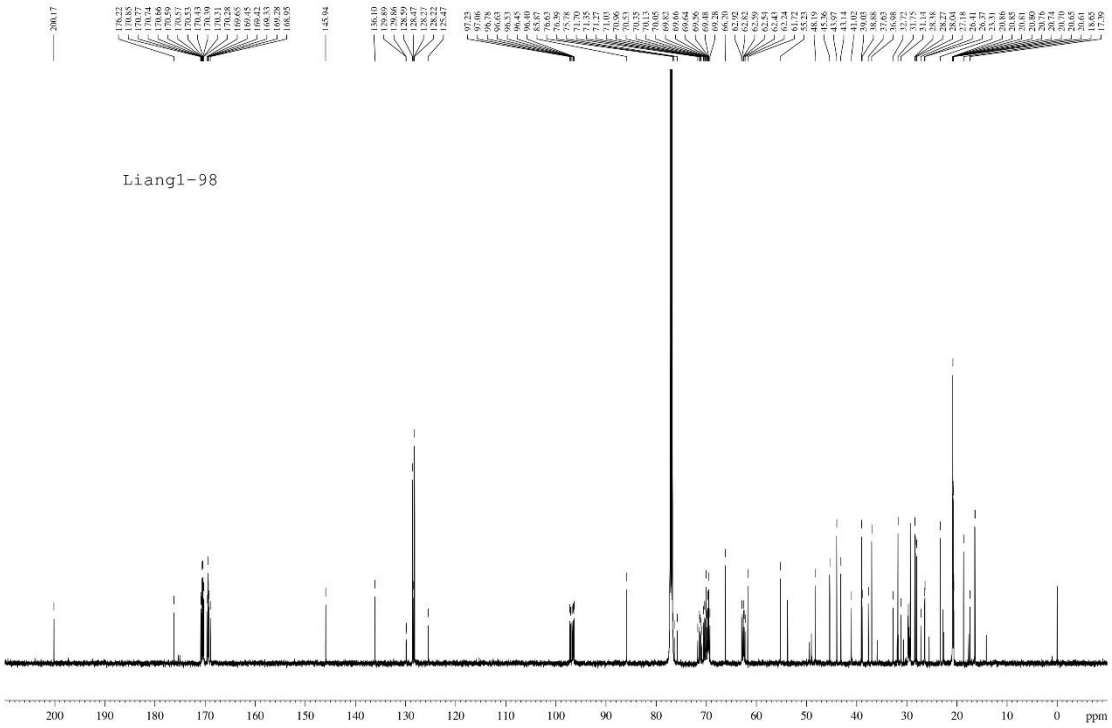
HRMS of compound **37**



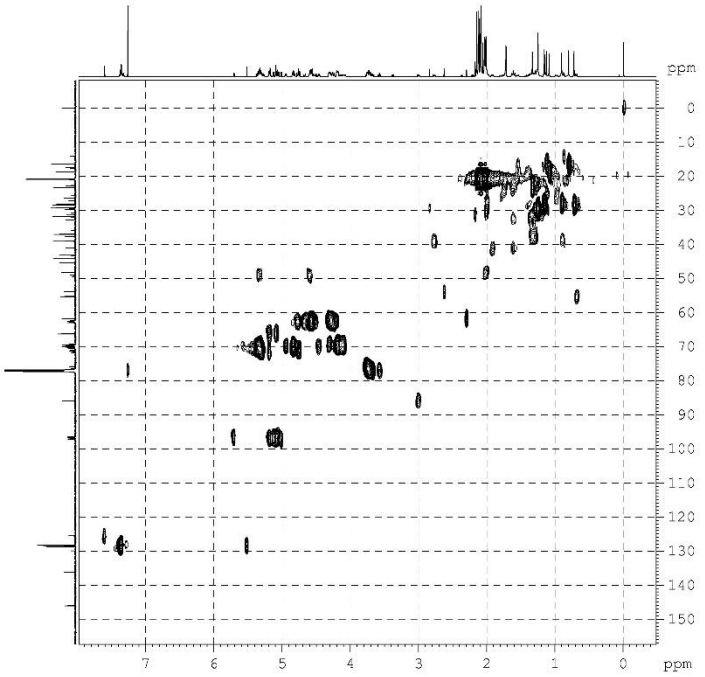
^{1}H NMR of compound **38**



^{13}C NMR of compound **38**

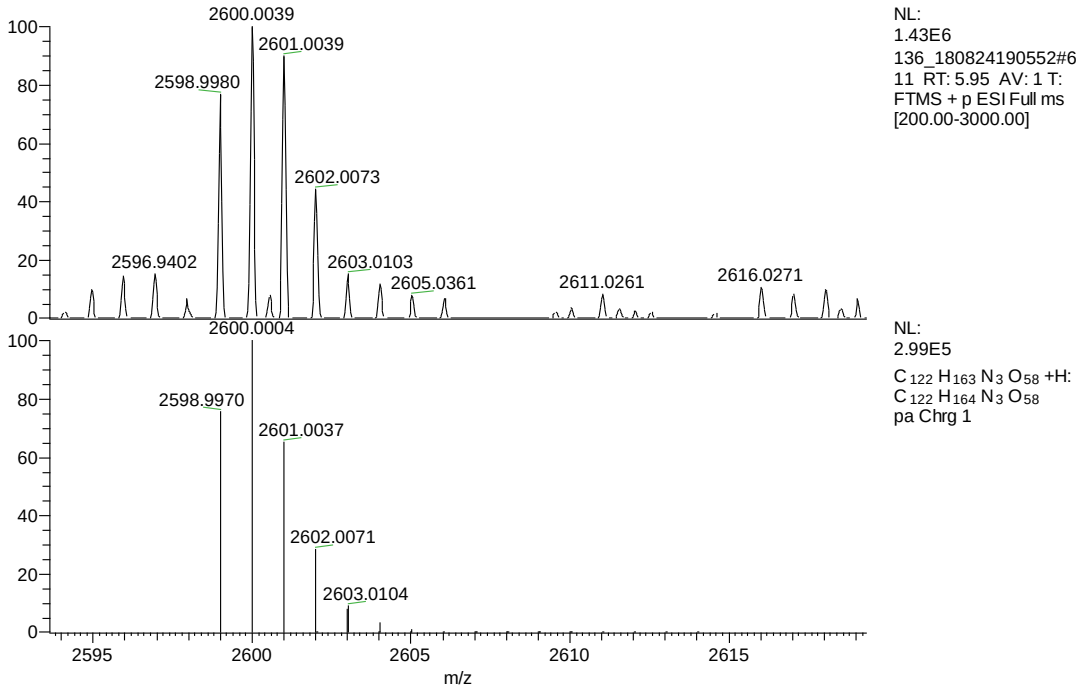


HSQC of compound **38**

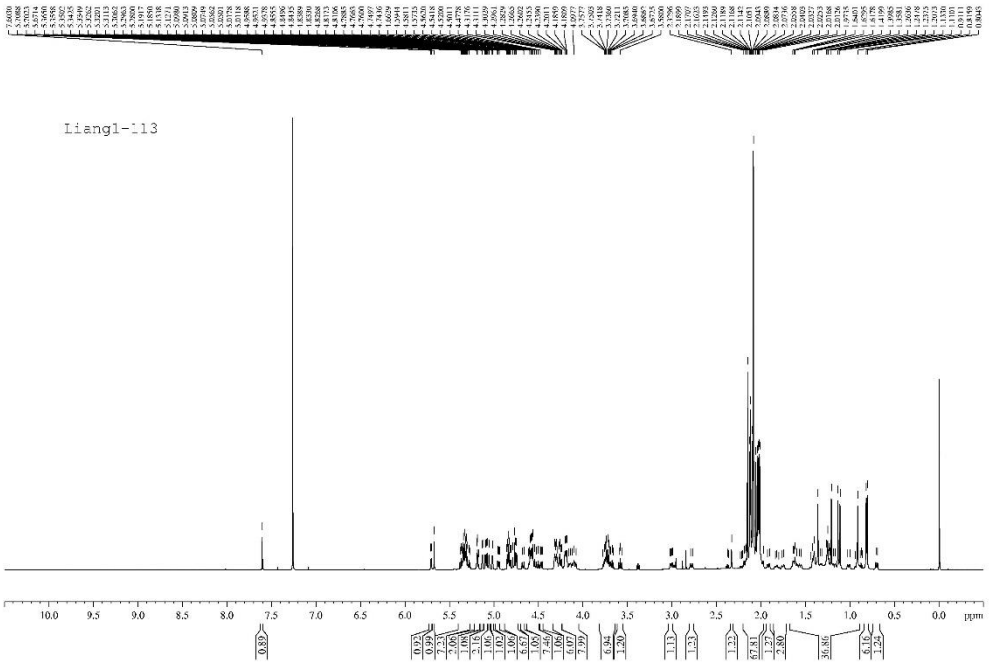


NAME	Liang1-98-hsqc
EXPNO	4
PROCNO	1
Date_	20170910
Time	11.38
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	hsqcetgp
TD	1024
SOLVENT	CDCl3
NS	16
DS	16
SWH	5341.880
FIDRES	5.216680
AQ	0.0958964
RG	183.47
DW	93.600
DE	6.50
TE	298.2

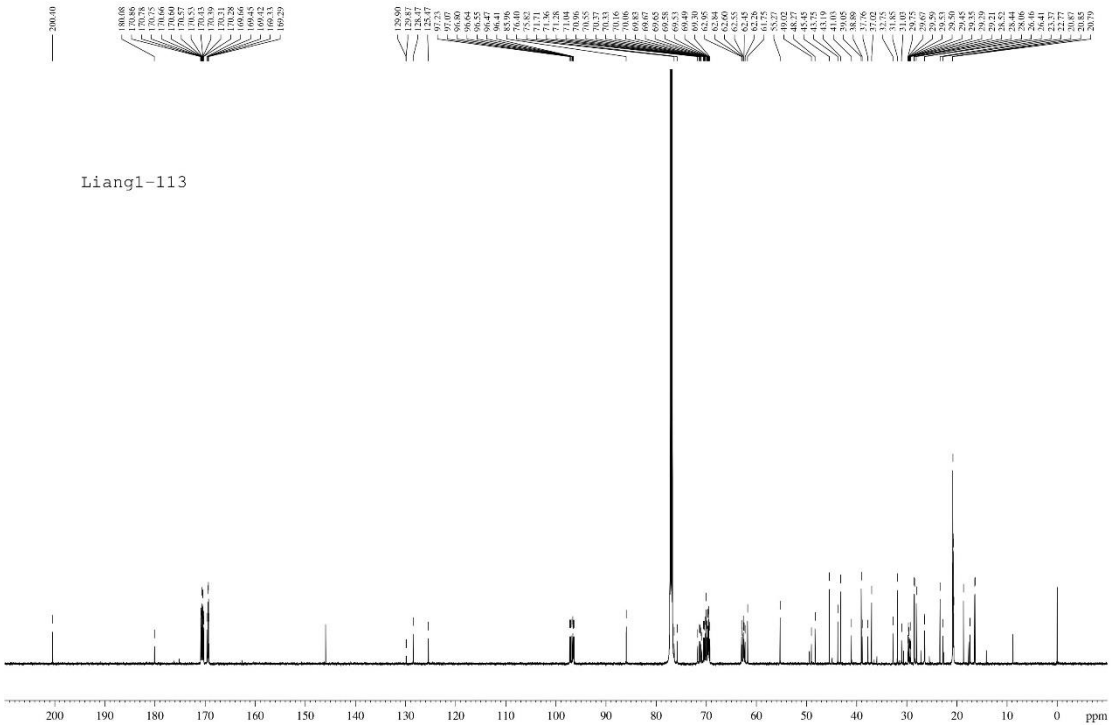
HRMS of compound **38**



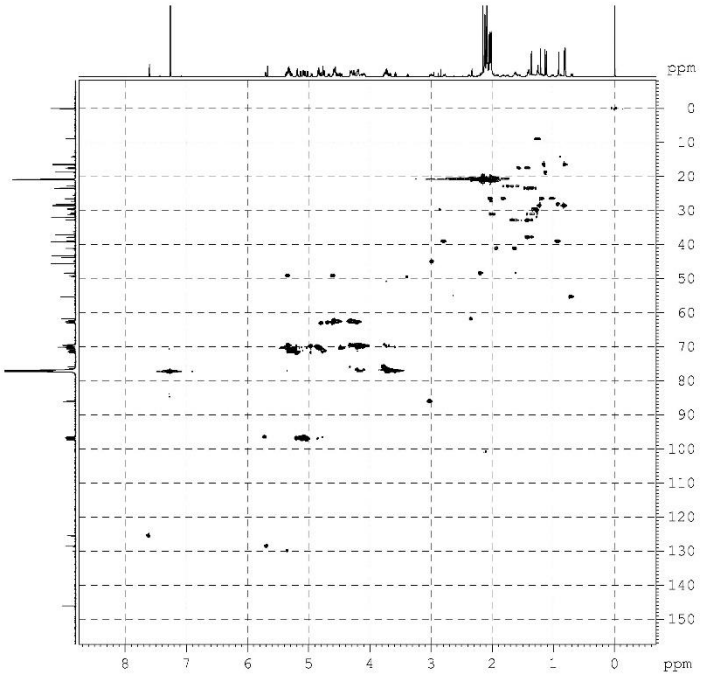
^{1}H NMR of compound **39**



^{13}C NMR of compound **39**

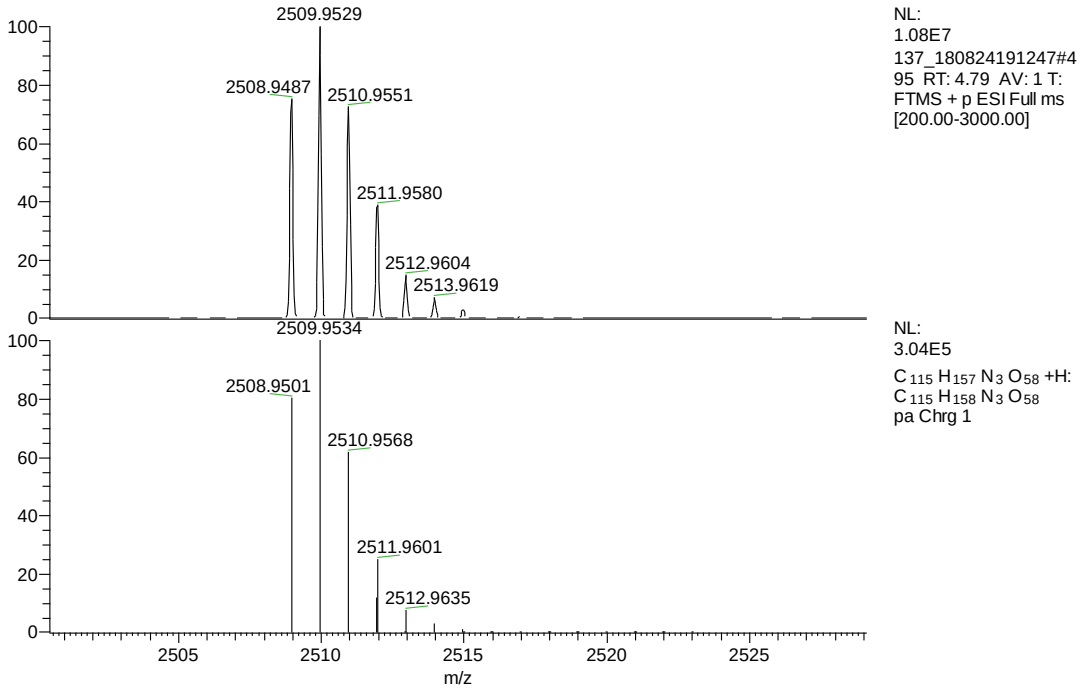


HSQC of compound **39**

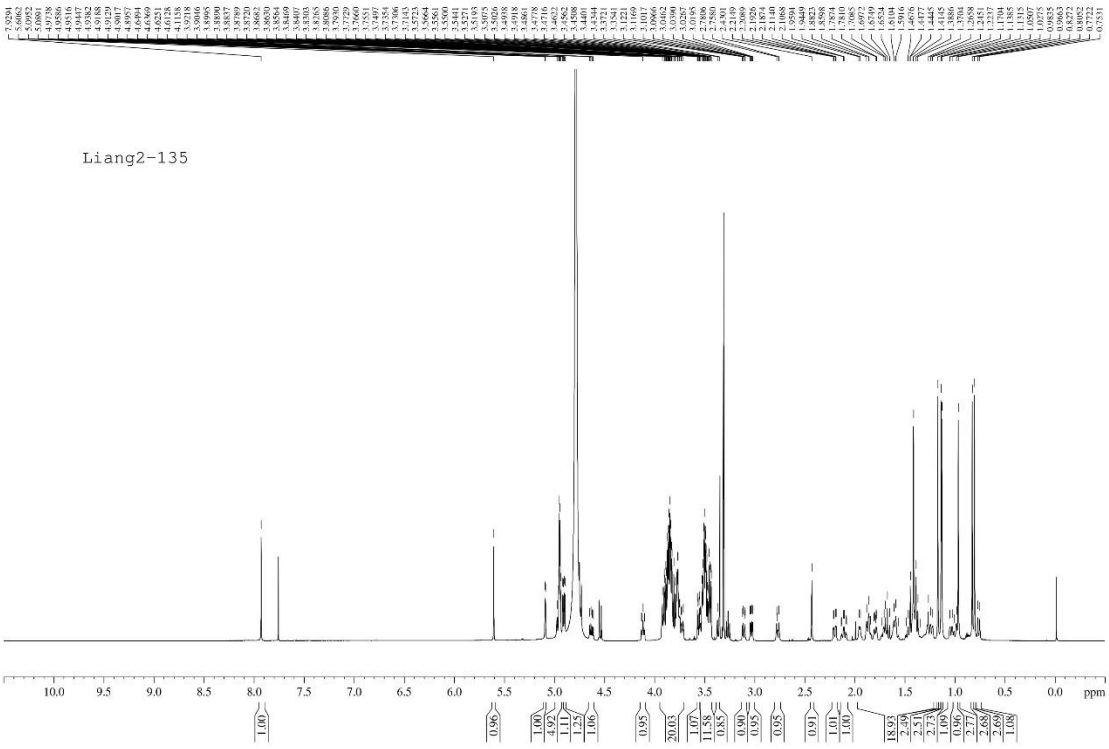


NAME	Liang1-113
EXPNO	4
PROCNO	1
Date_	20171014
Time	9.45
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	hsqcetgpsi
TD	2048
SOLVENT	CDCl3
NS	16
DS	16
SWH	5882.353
FIDRES	2.872243
AQ	0.1741300
RG	203
DW	85.000
DE	10.00
TE	300.4

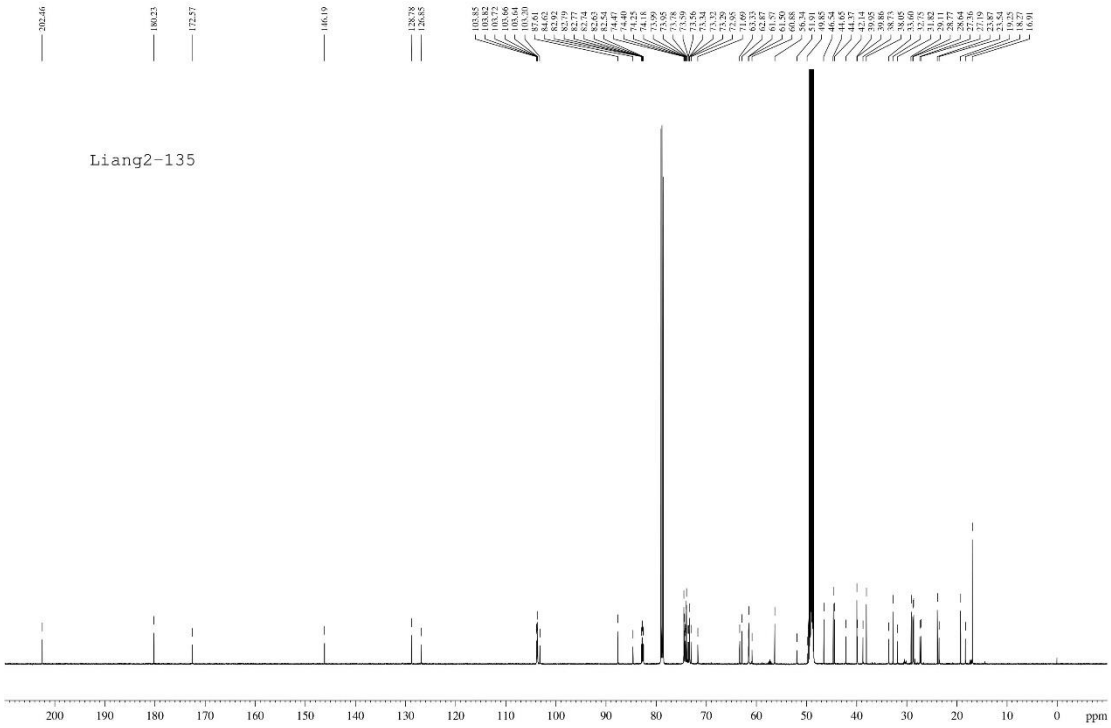
HRMS of compound **39**



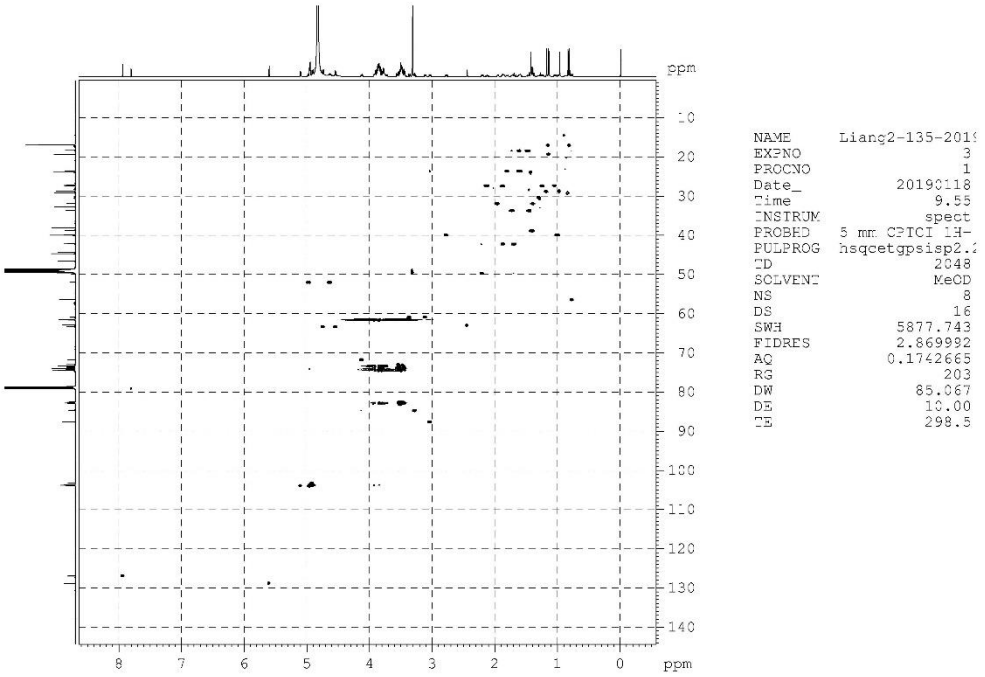
^{1}H NMR of compound **40**



^{13}C NMR of compound **40**



HSQC of compound **40**



HRMS of compound **40**