Isolation, semi-synthesis, docking-based prediction, and bioassay-based activity of *Dolichandrone spathacea* new catalpol derivatives as glucosidase inhibitors

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SUPPORTING INFORMATION

1. EXPERIMENTAL CHARACTERISATIONS
1.1. Compound 1

IR spectrum of compound **1**

(+)-ESI-MS spectrum of compound **1**

Analysis Name: QNL3-1.d
Method: Quang_Method_2014.m
Sample Name: QNL3-1
Analysis Info:

Instrument: LC-MSD-Trap-SL
Operator: Quang NV

Intens.
×10⁷

-MS, 0.3min #18

521.0

396.3

360.3

163.9 180.9
199.1
240.1
339.1
137.1
490.9 542.9

150   200   250   300   350   400   450   500   m/z

(-)-ESI-MS spectrum of compound **1**

¹H-NMR spectrum (500 MHz, CDCl₃ + CD₃OD) of compound **1**

¹H-NMR spectrum (expansion) of compound **1**
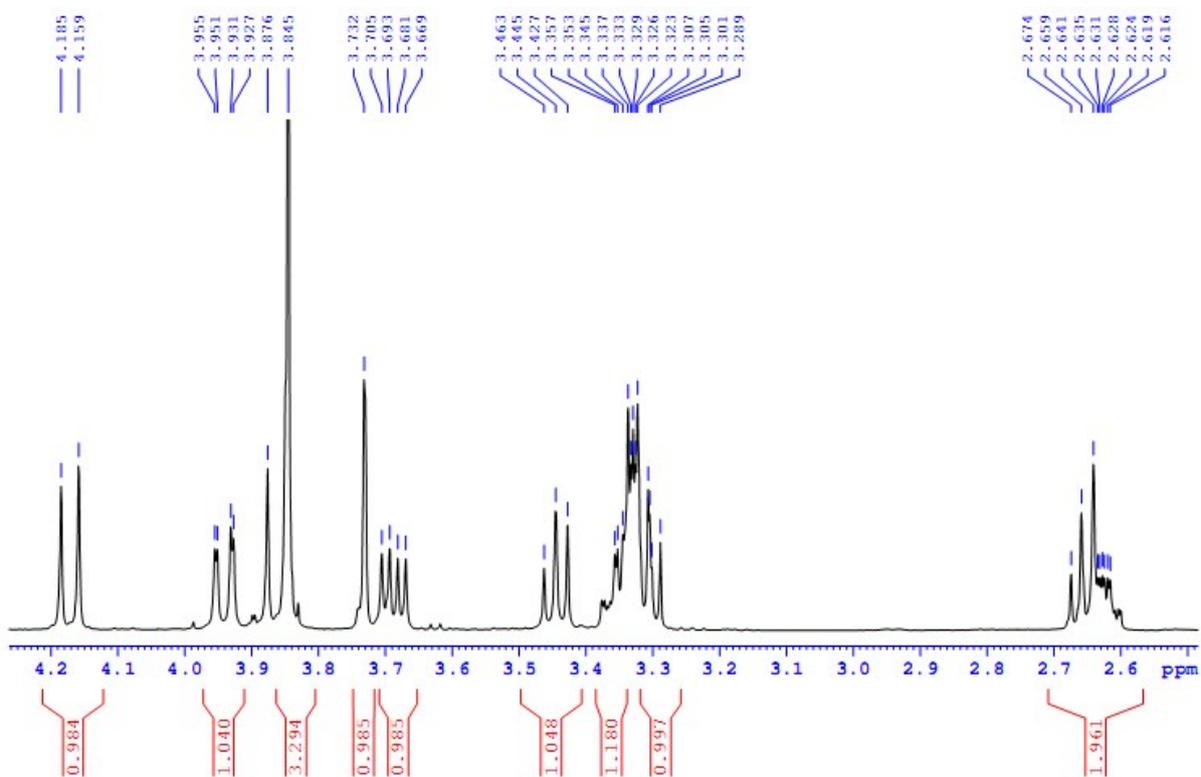
¹H-NMR spectrum (expansion) of compound **1**
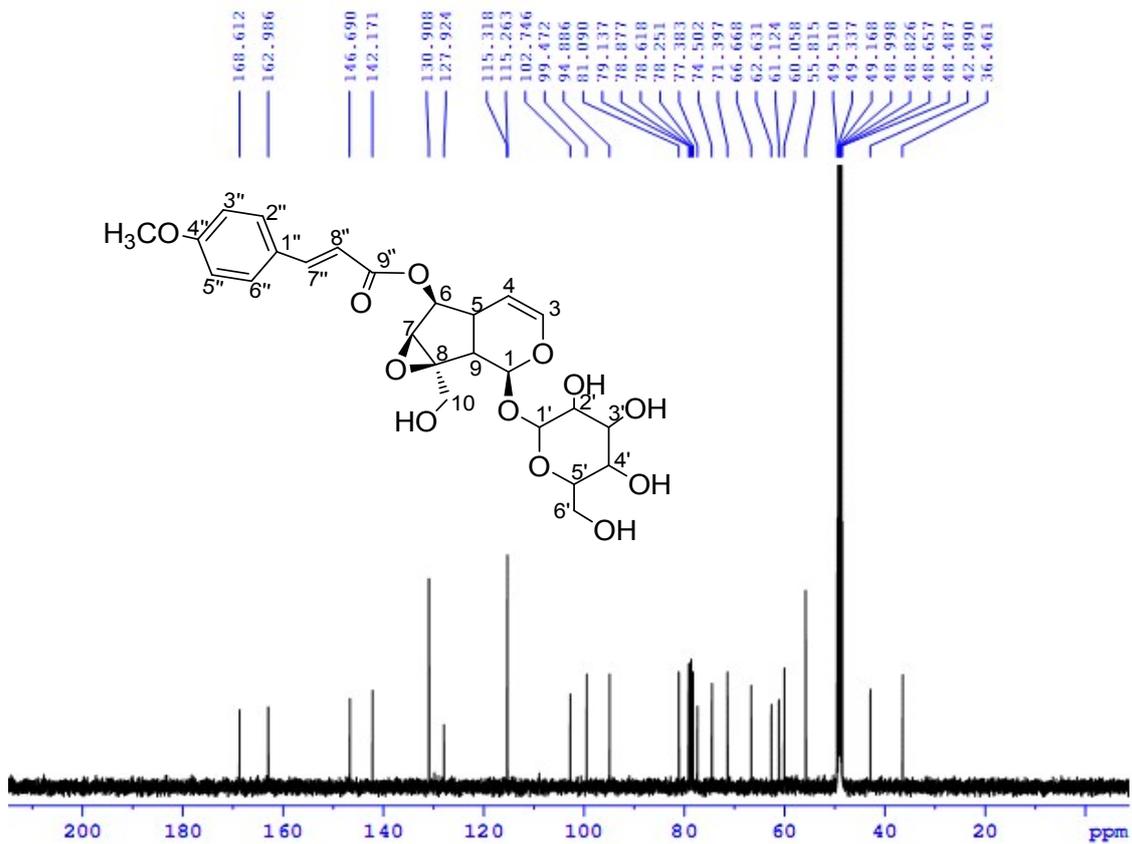
^{13}C-NMR spectrum of compound **1**
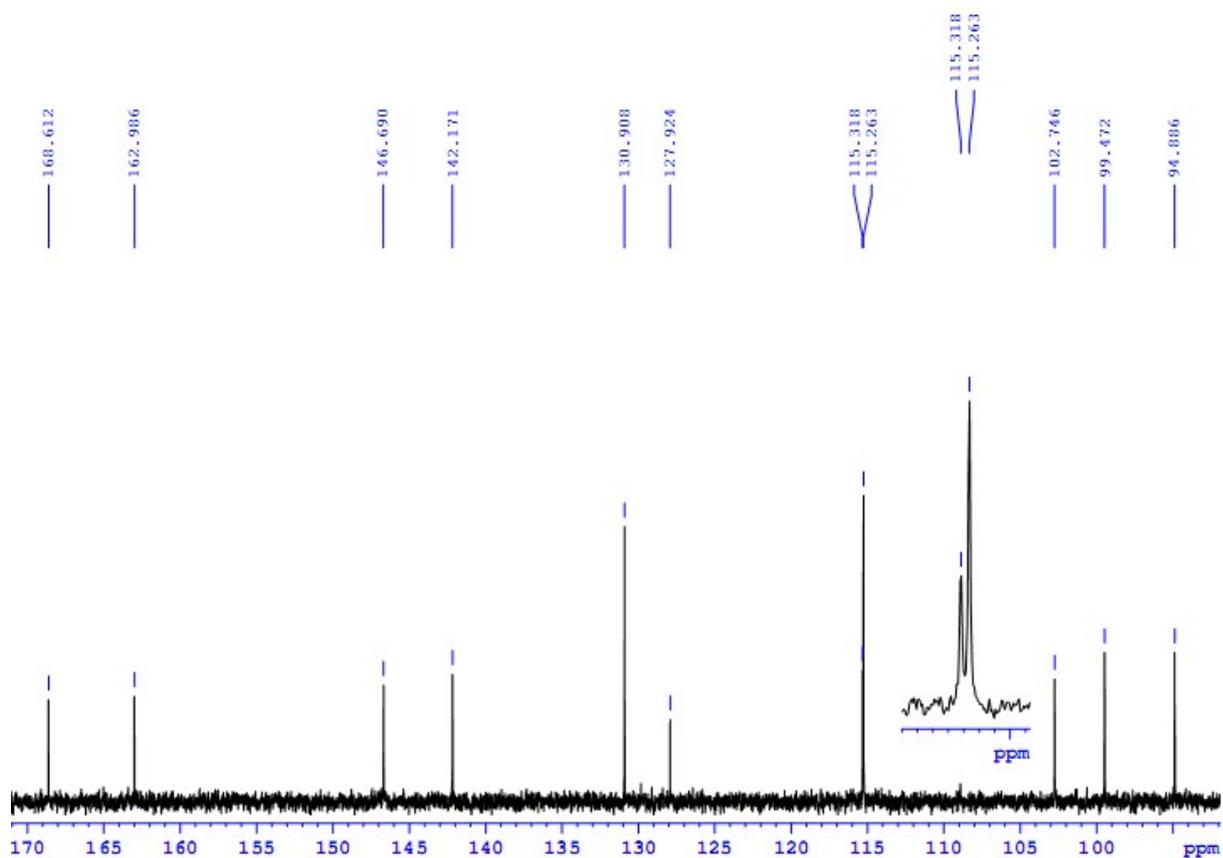
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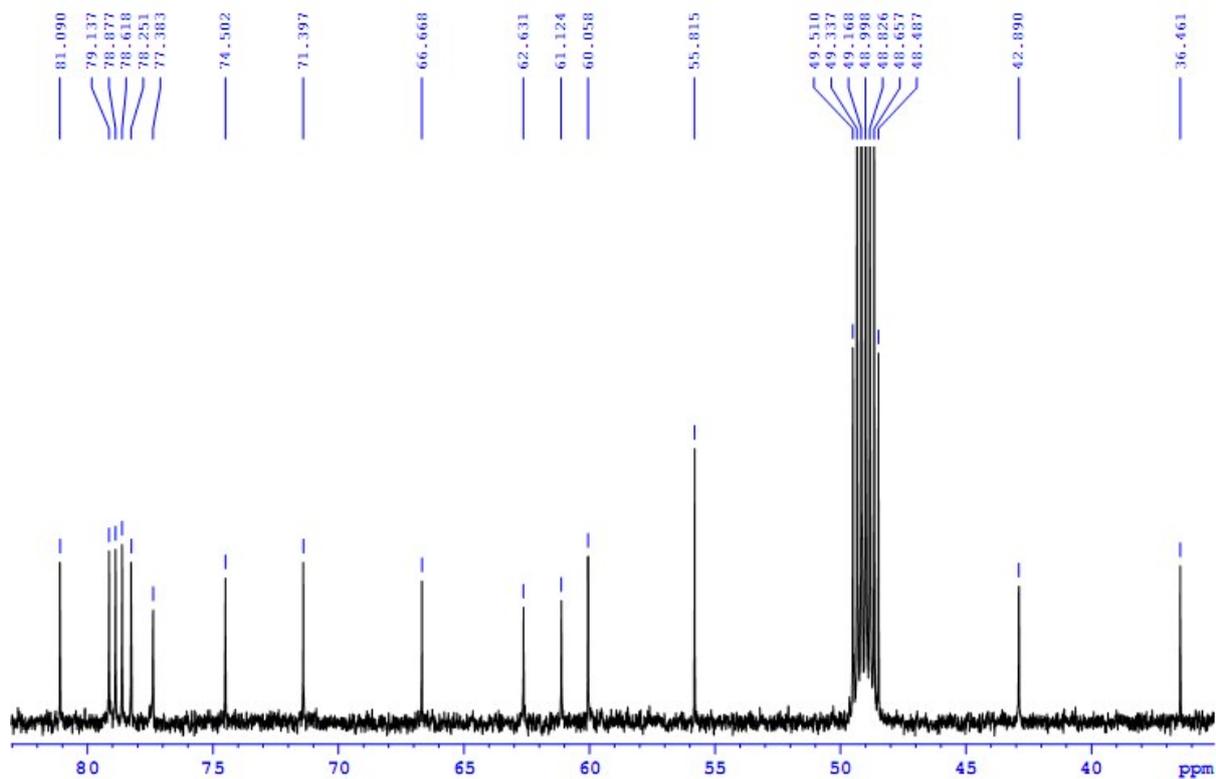
^{13}C-NMR spectrum (expansion) of compound **1**

DEPT spectrum of compound **1**

6
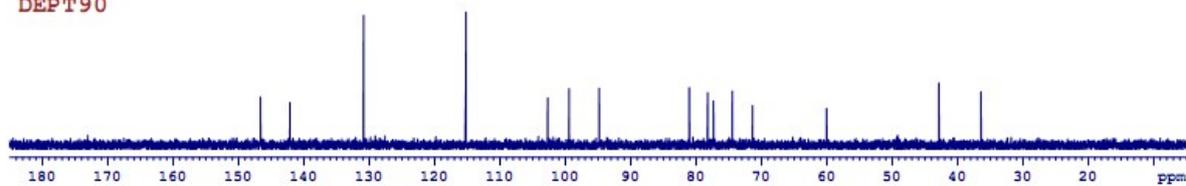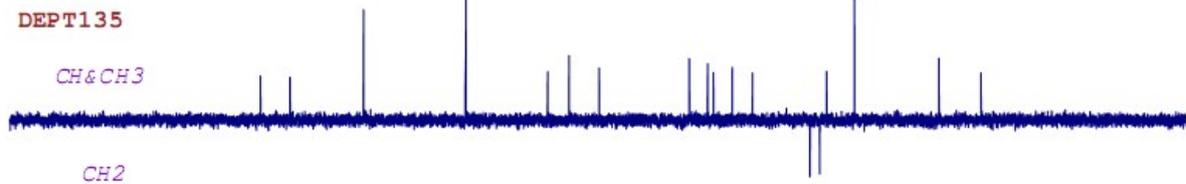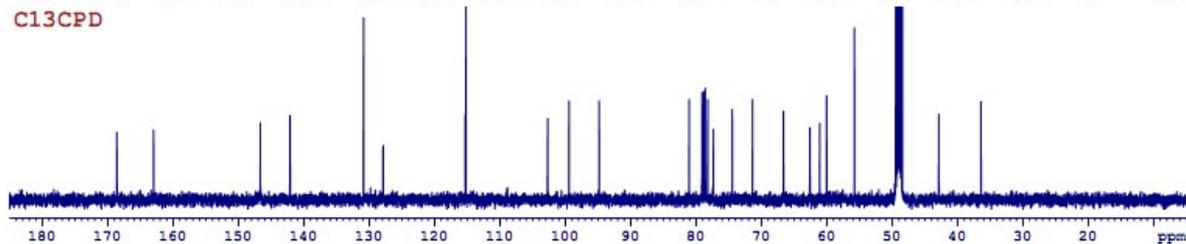
HSQC spectrum of compound **1**

HMBC spectrum of compound **1**
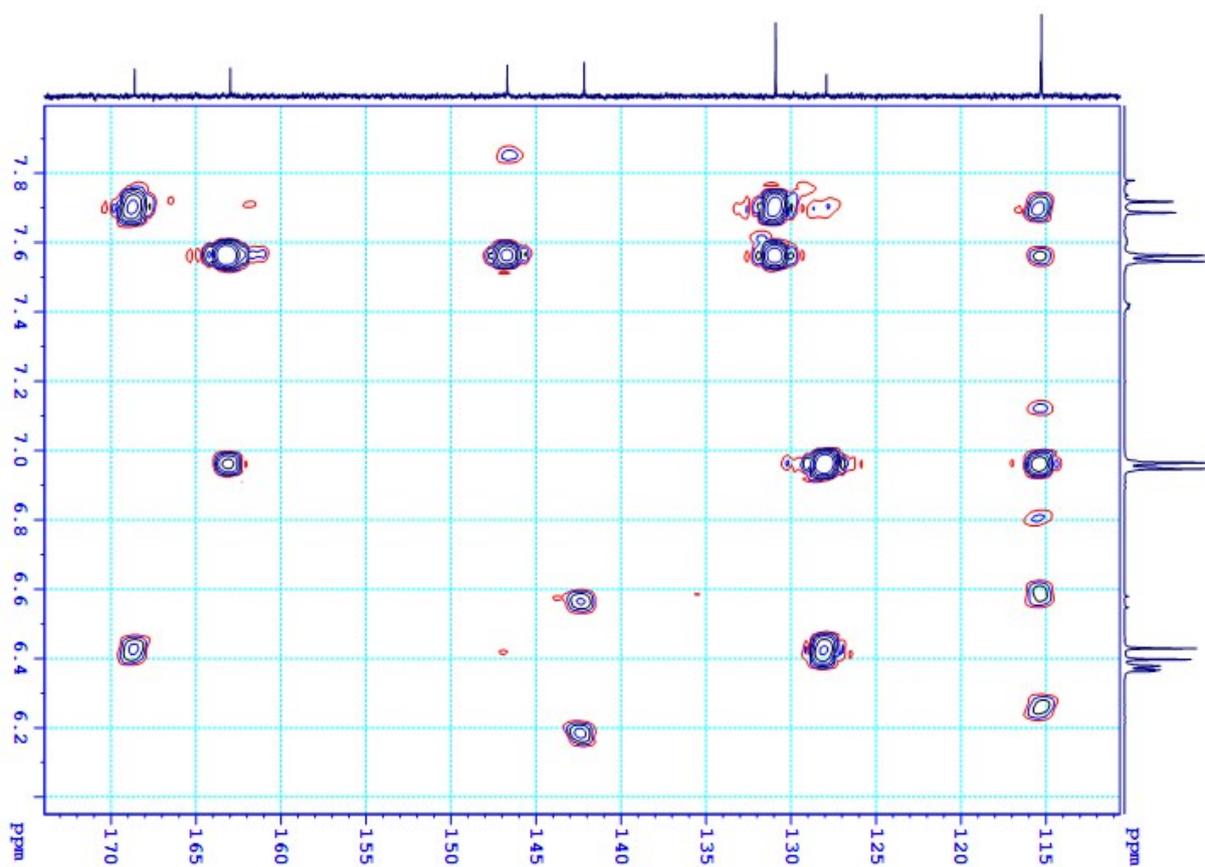
HMBC spectrum (expansion) of compound **1**
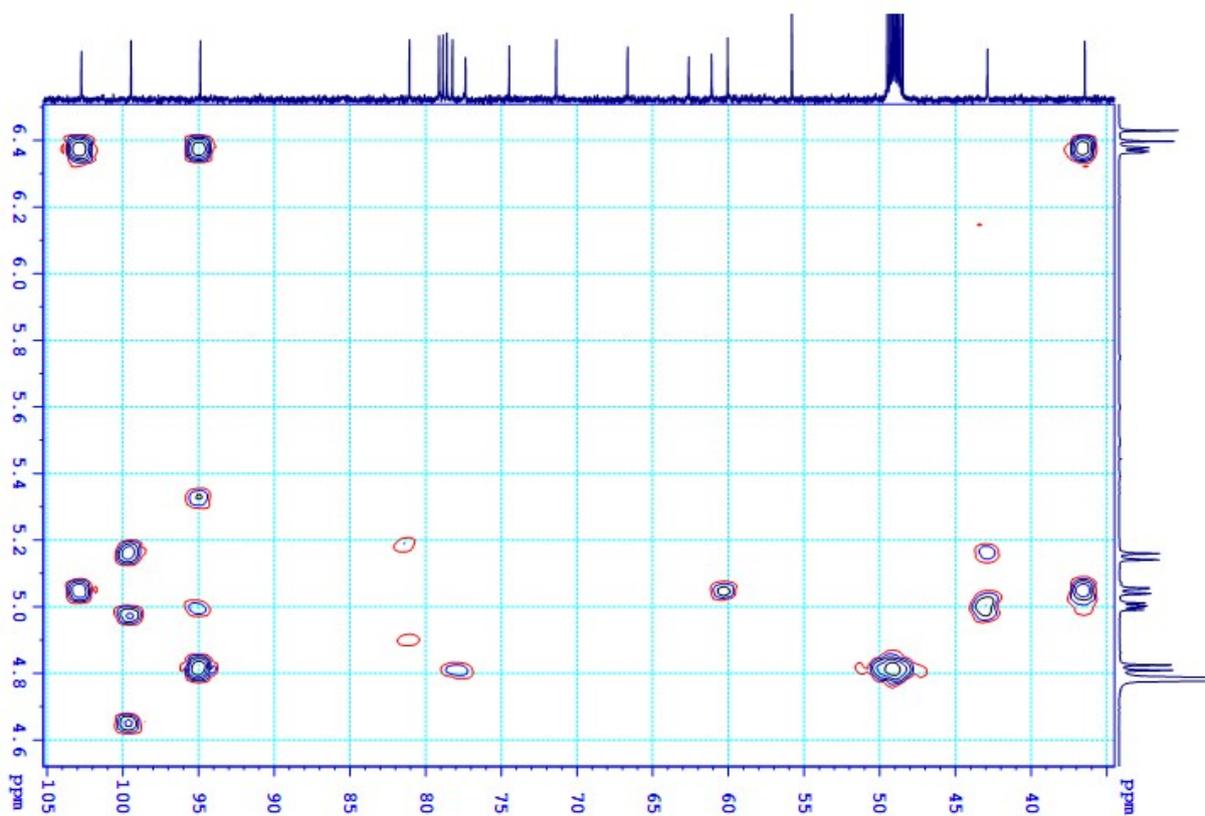
HMBC spectrum (expansion) of compound **1**
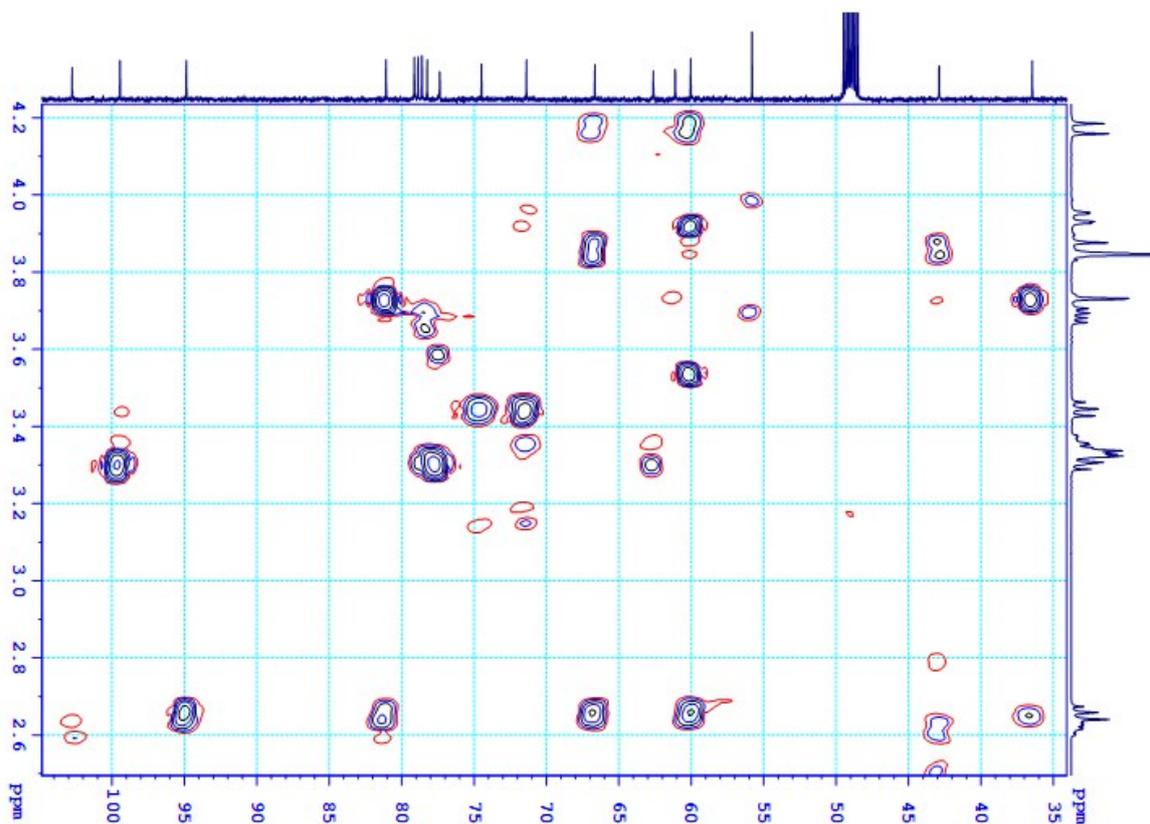
HMBC spectrum (expansion) of compound **1**
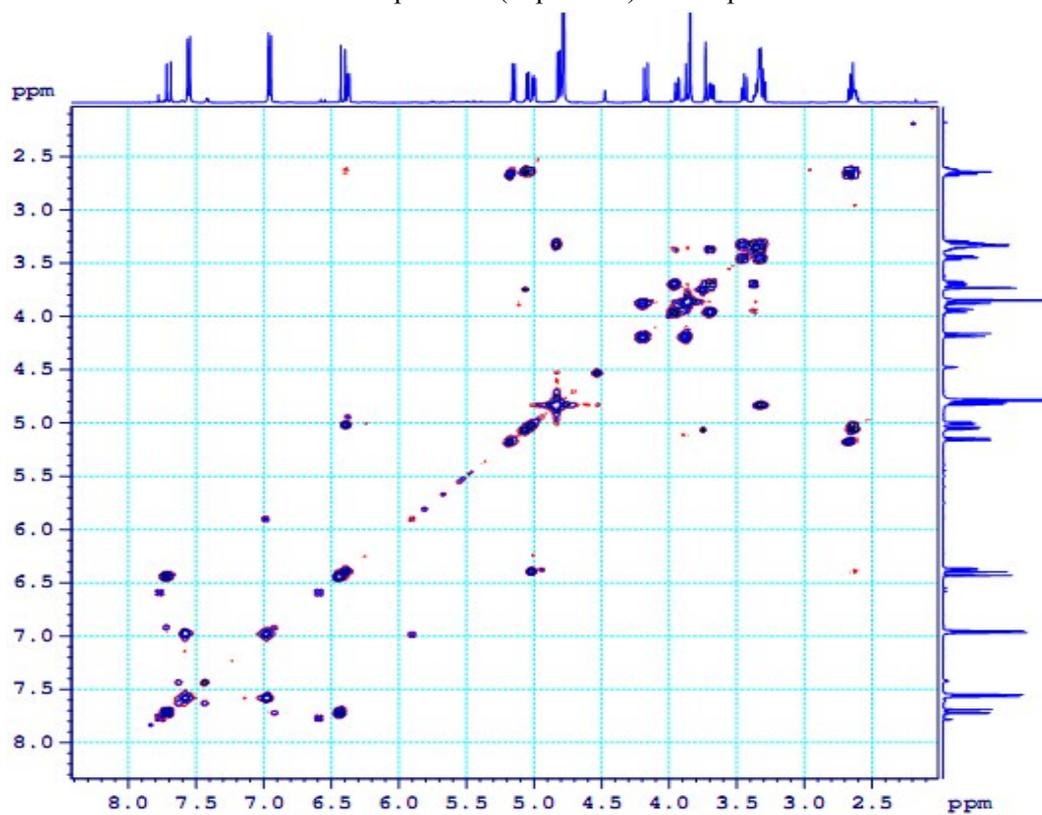
COSY spectrum of compound **1**
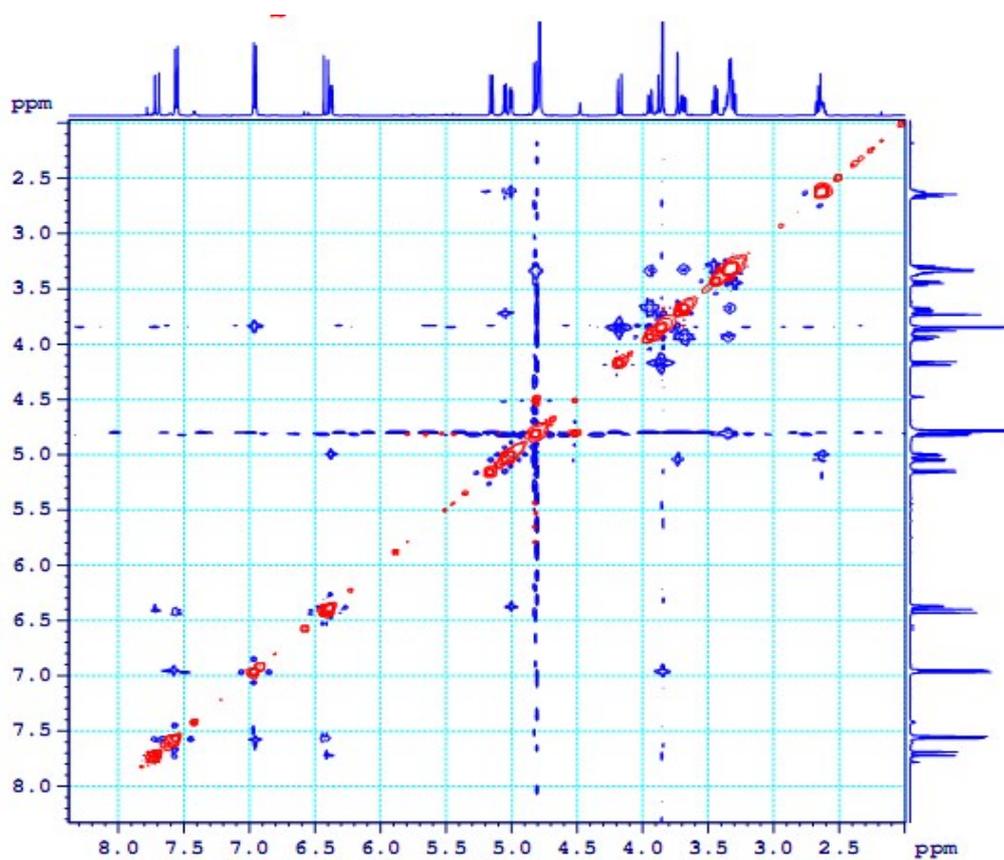
NOESY spectrum of compound **1**

1.2. Compound 2
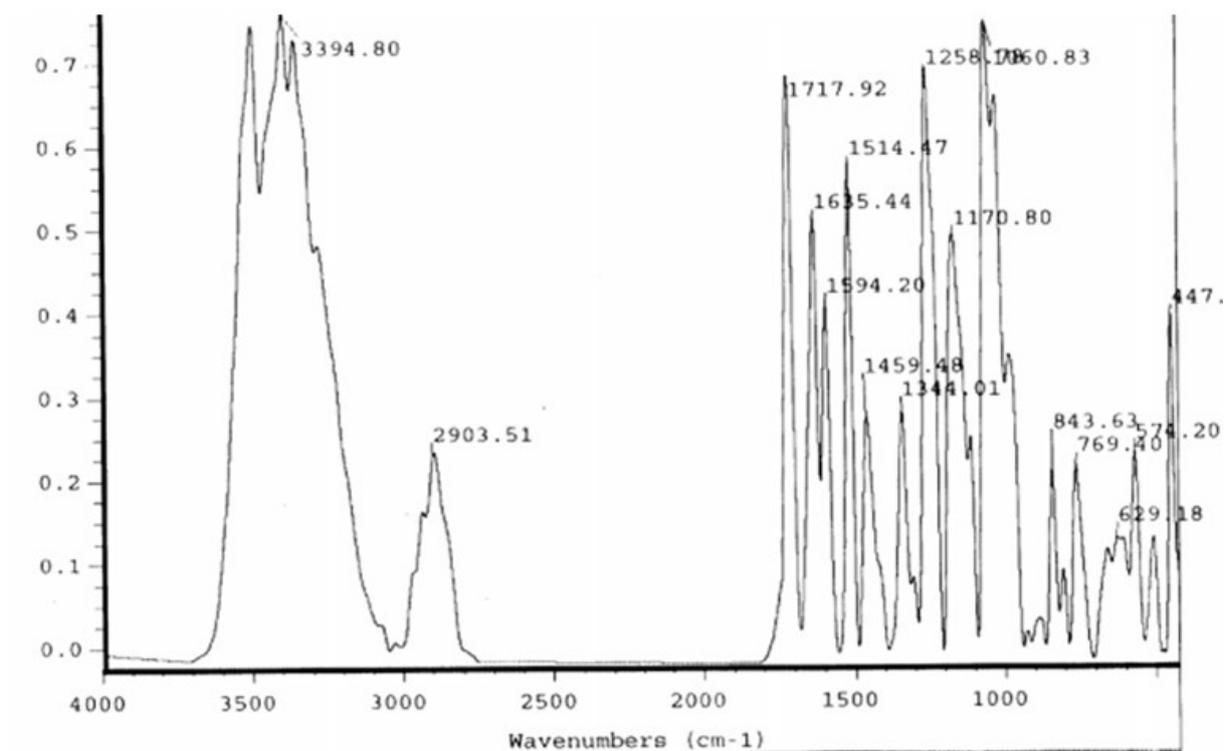
IR spectrum of compound **2**
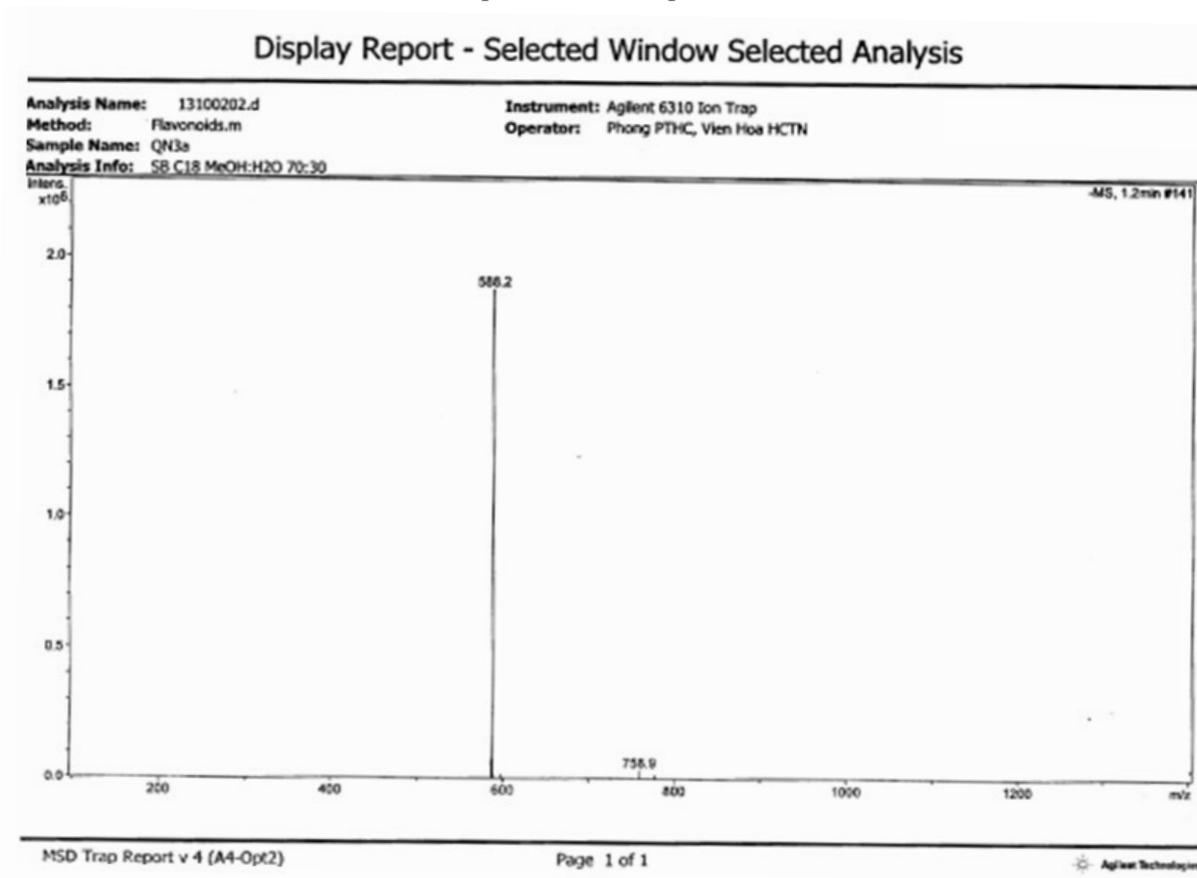
(-)-ESI-MS spectrum of compound **2**
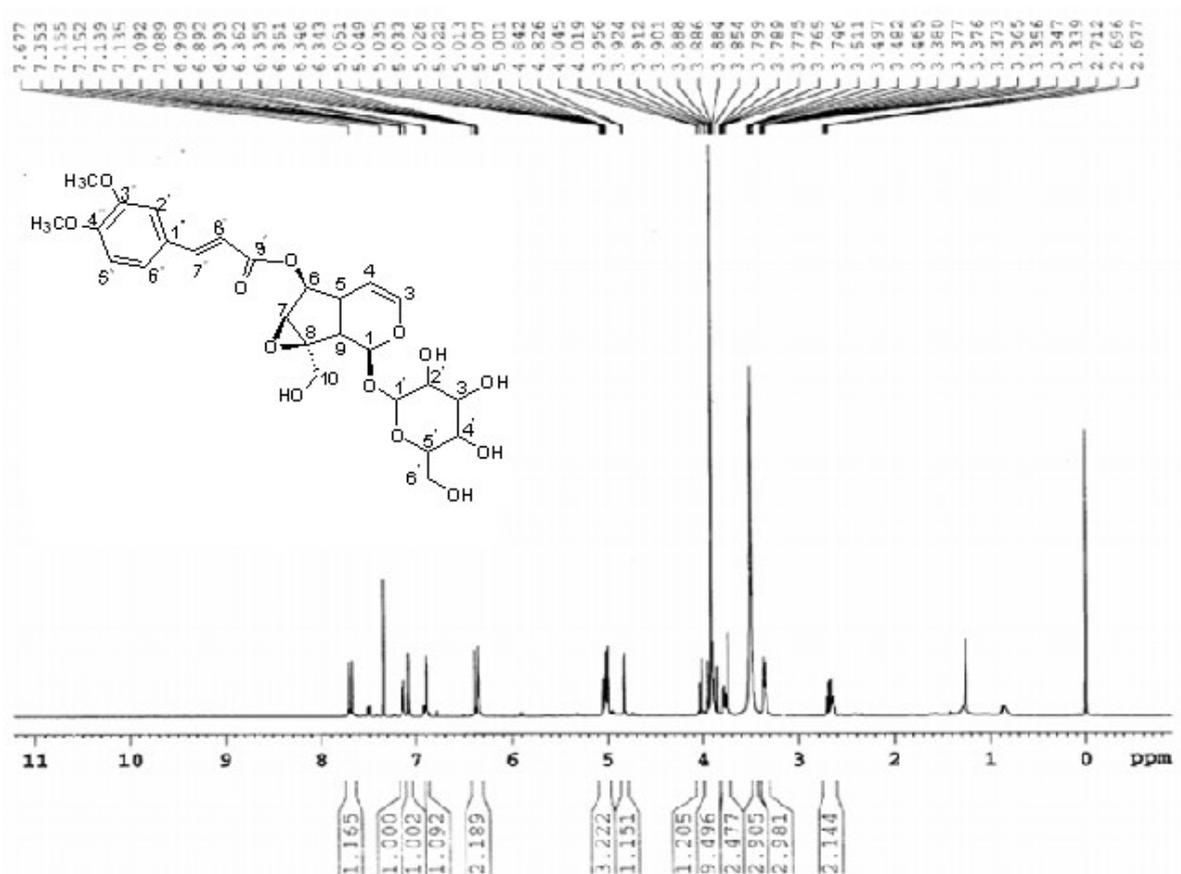
^{1}H-NMR spectrum (CDCl$_3$ + CD$_3$OD) of compound **2**
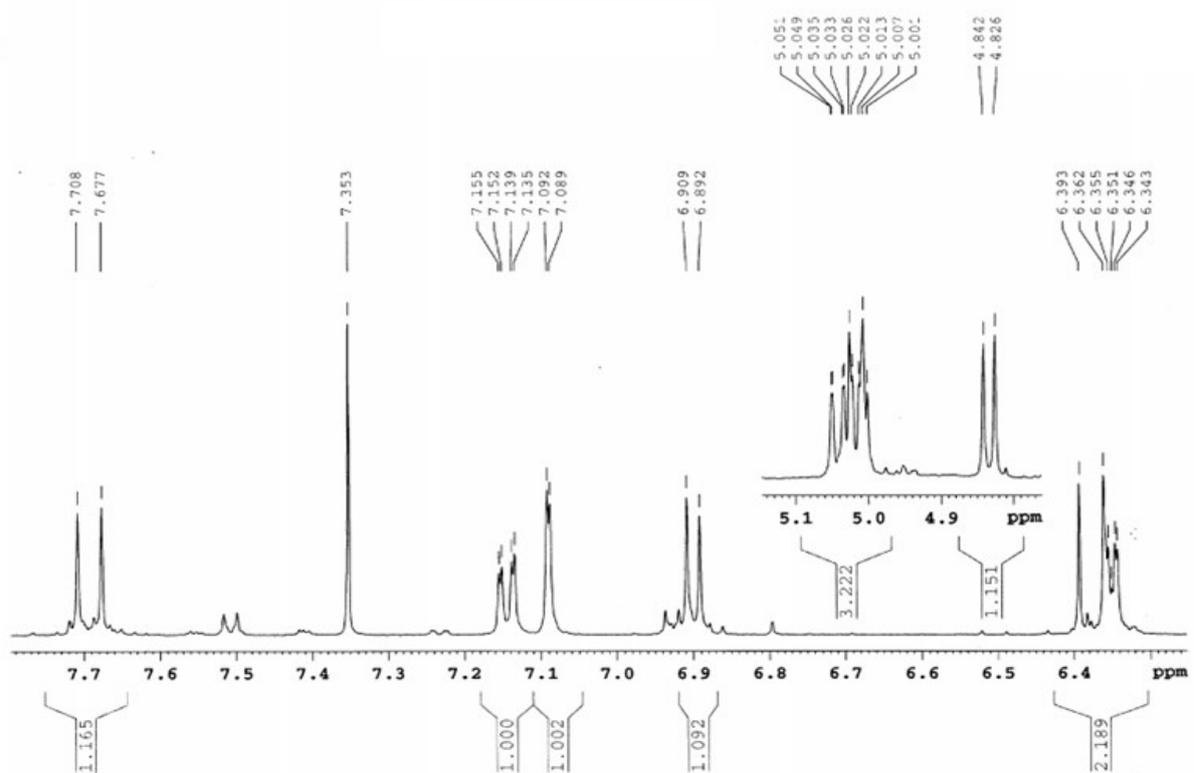
^{1}H-NMR spectrum (expansion) of compound **2**
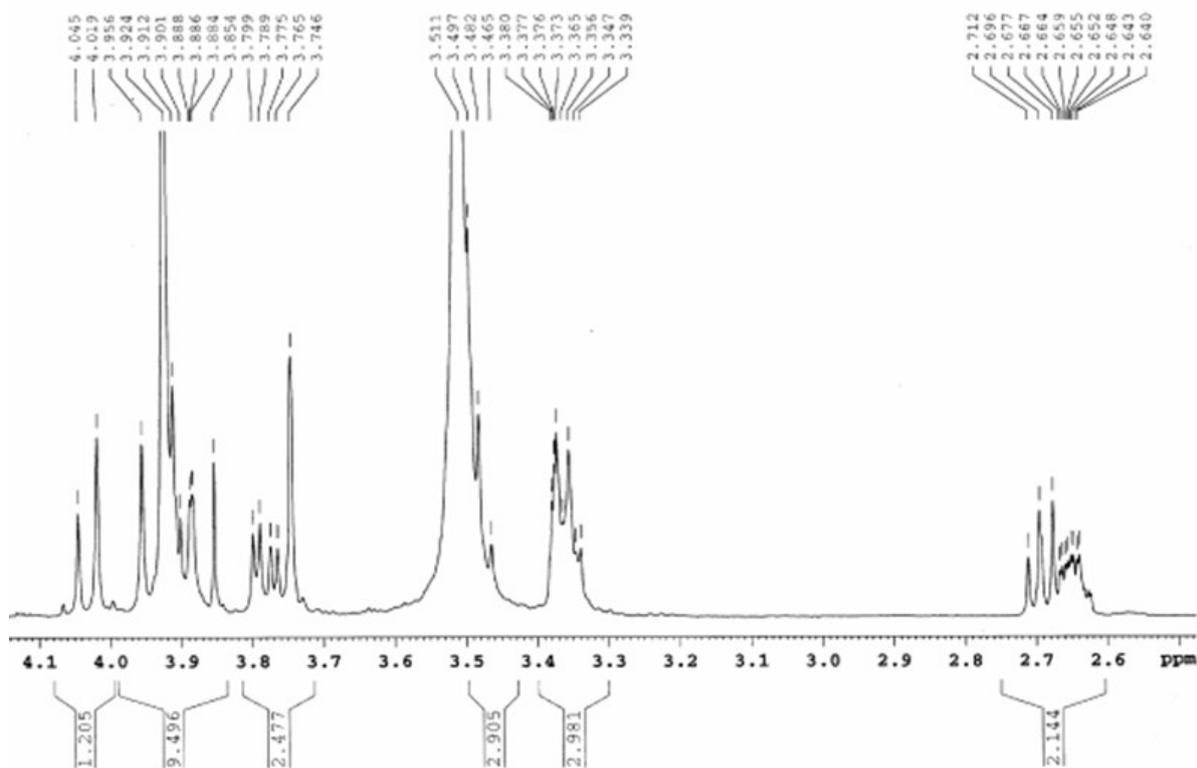
^{1}H-NMR spectrum (expansion) of compound **2**
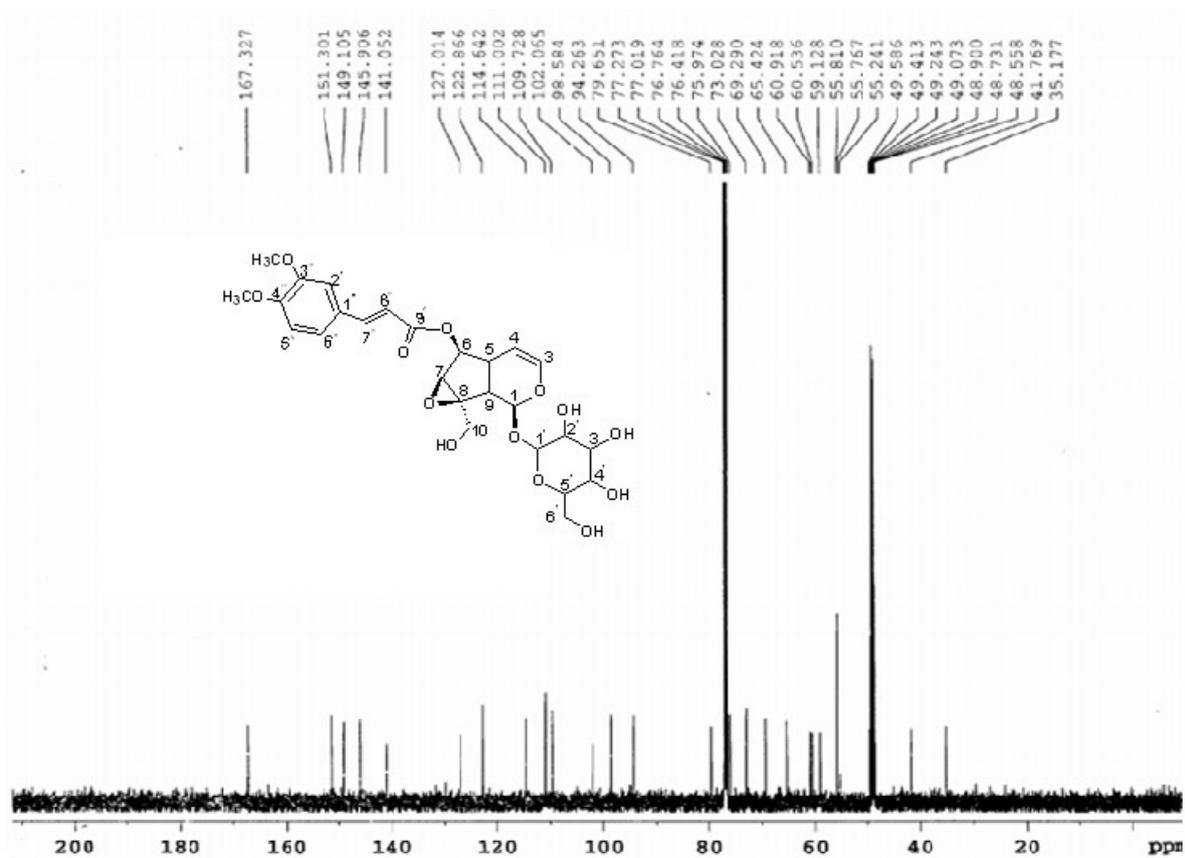
^{13}C-NMR spectrum of compound **2**
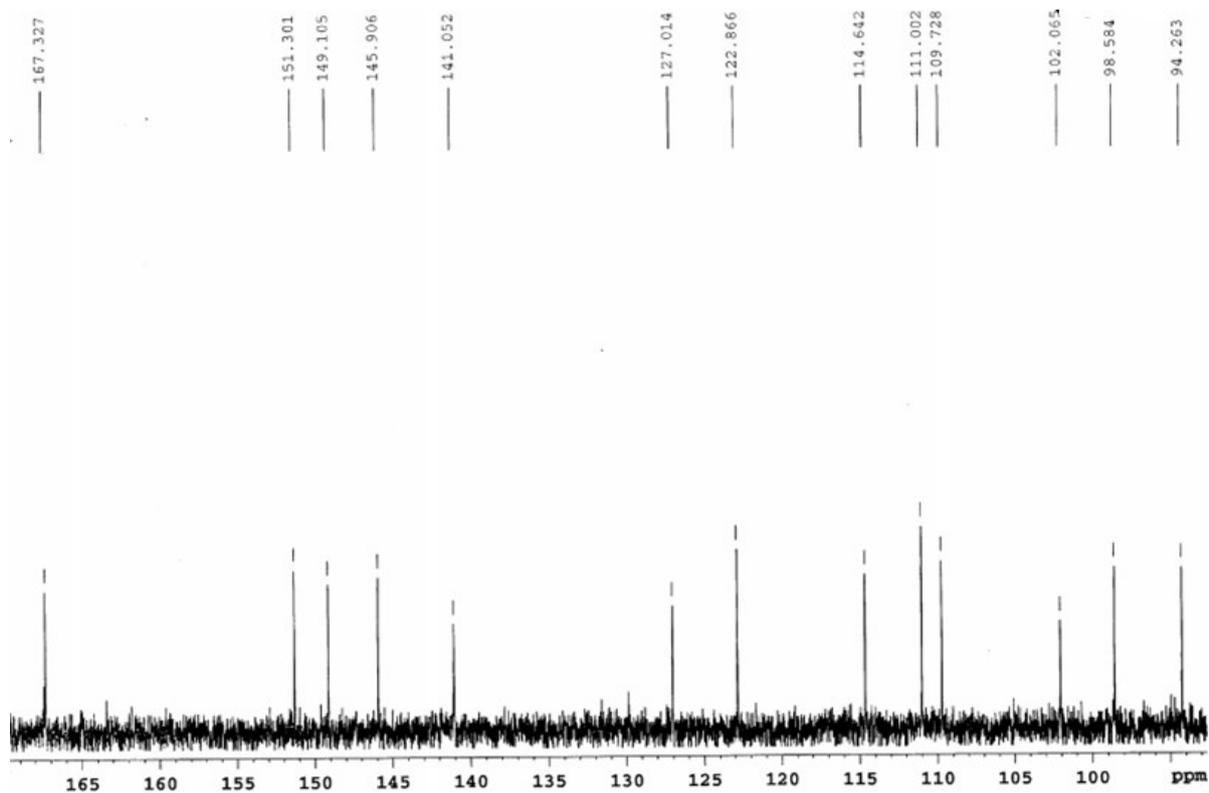
^{13}C-NMR spectrum (expansion) of compound **2**

^{13}C-NMR spectrum (expansion) of compound **2**

14
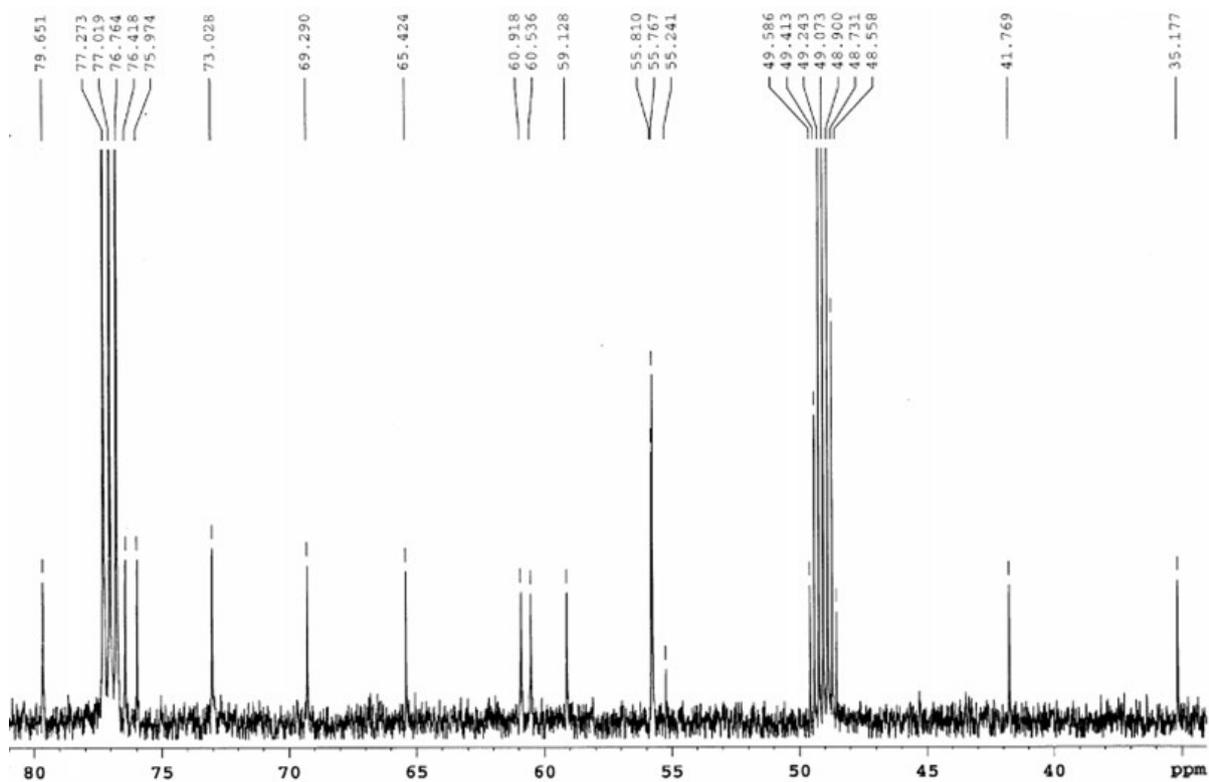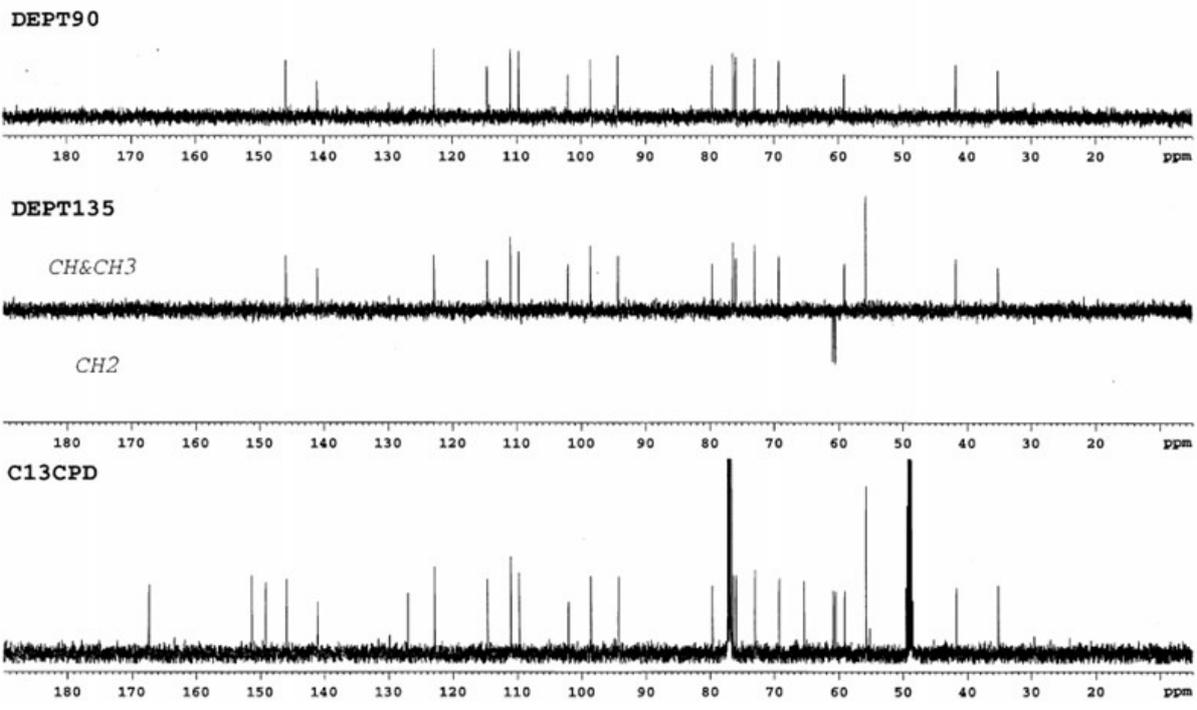
DEPT spectrum of compound **2**
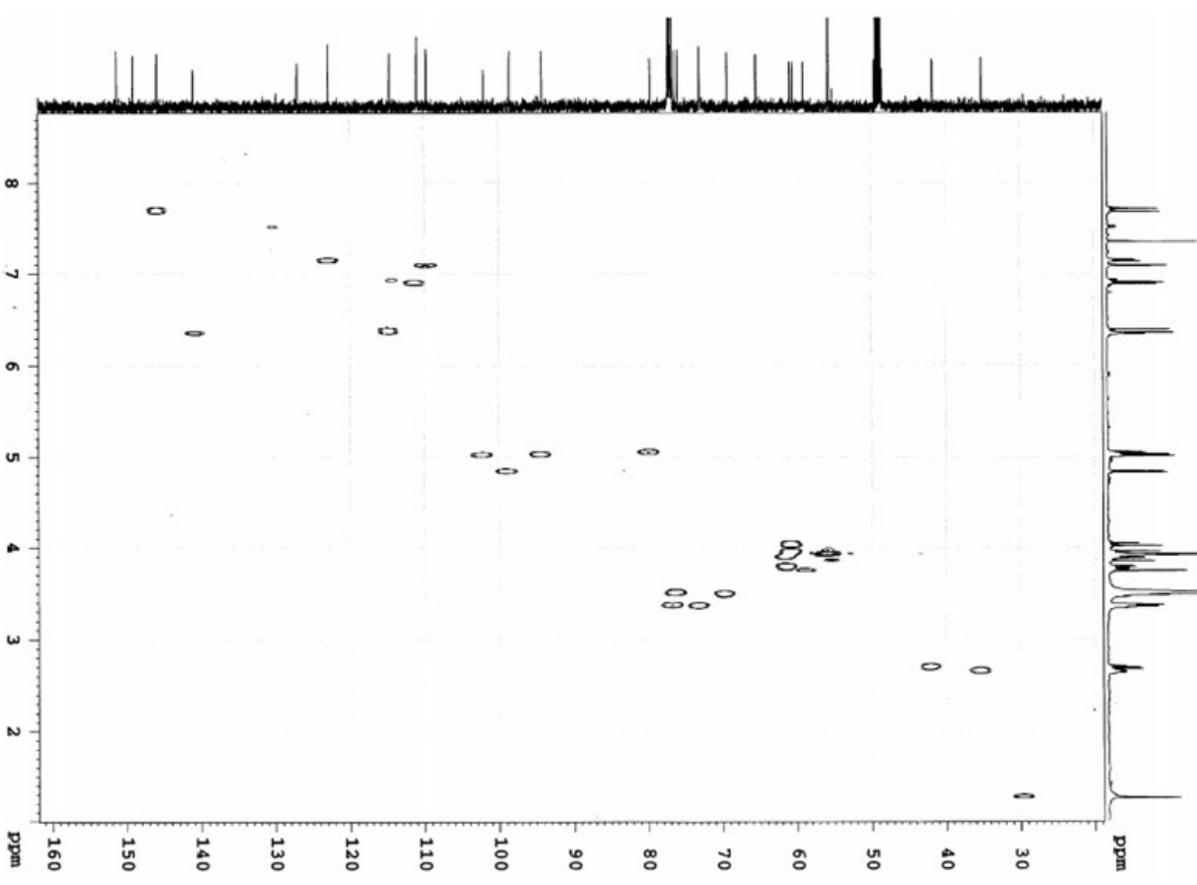
HSQC spectrum of compound **2**
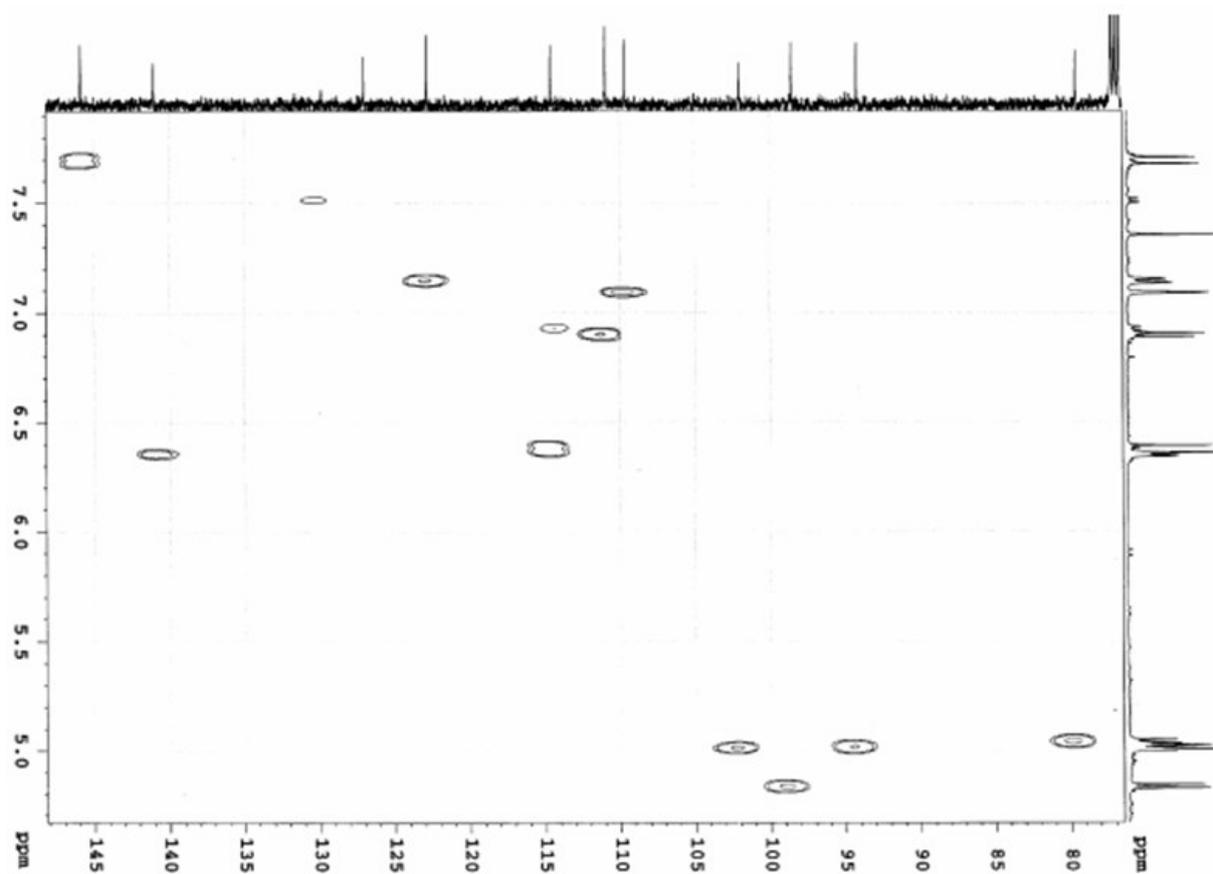
HSQC spectrum (expansion) of compound **2**

HSQC spectrum (expansion) of compound **2**

16
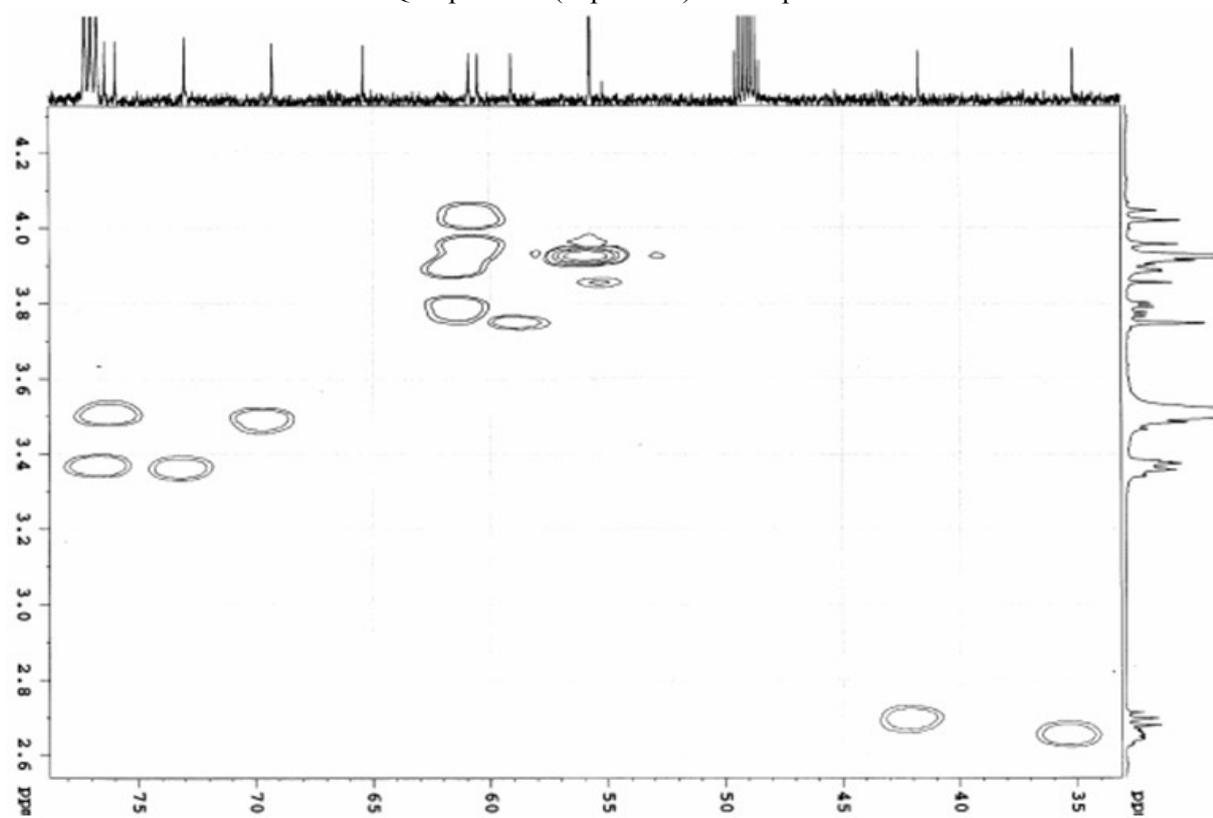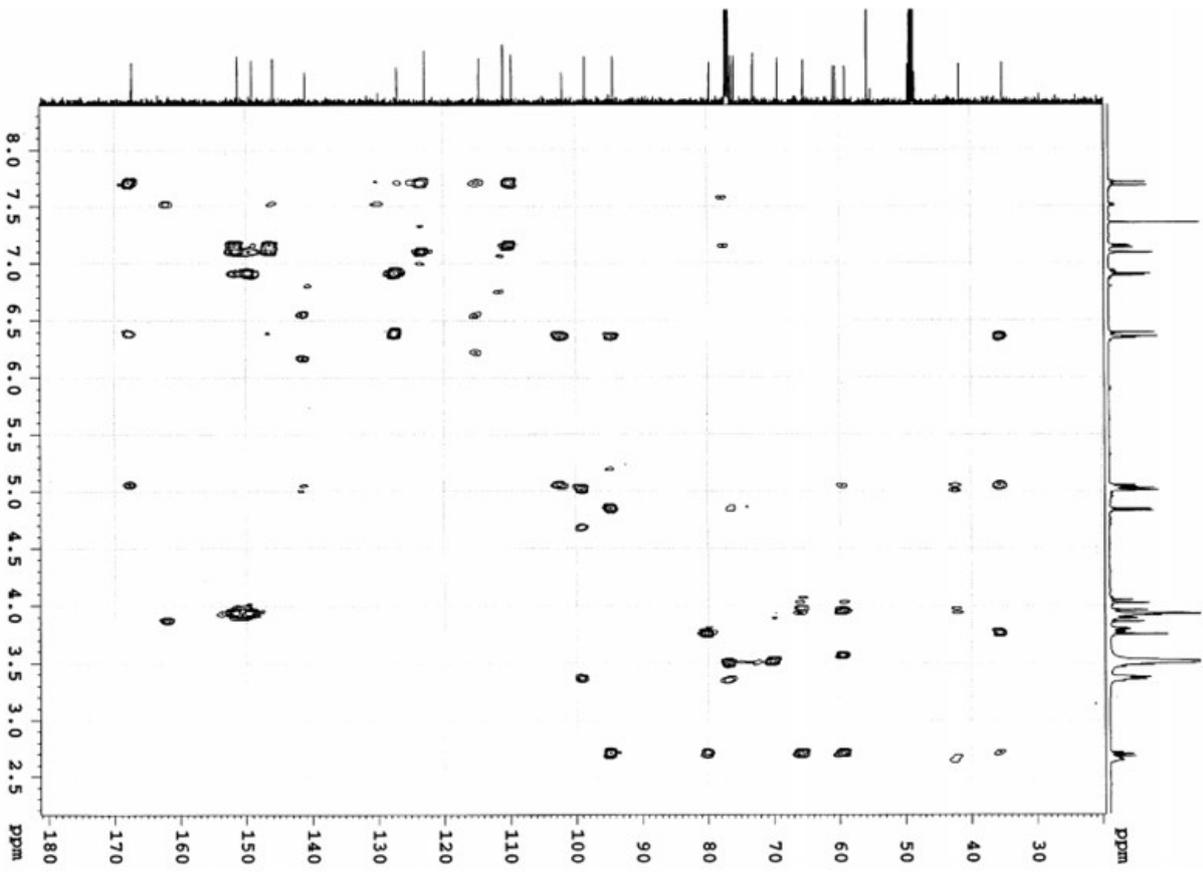
HMBC spectrum of compound **2**

HMBC spectrum (expansion) of compound **2**
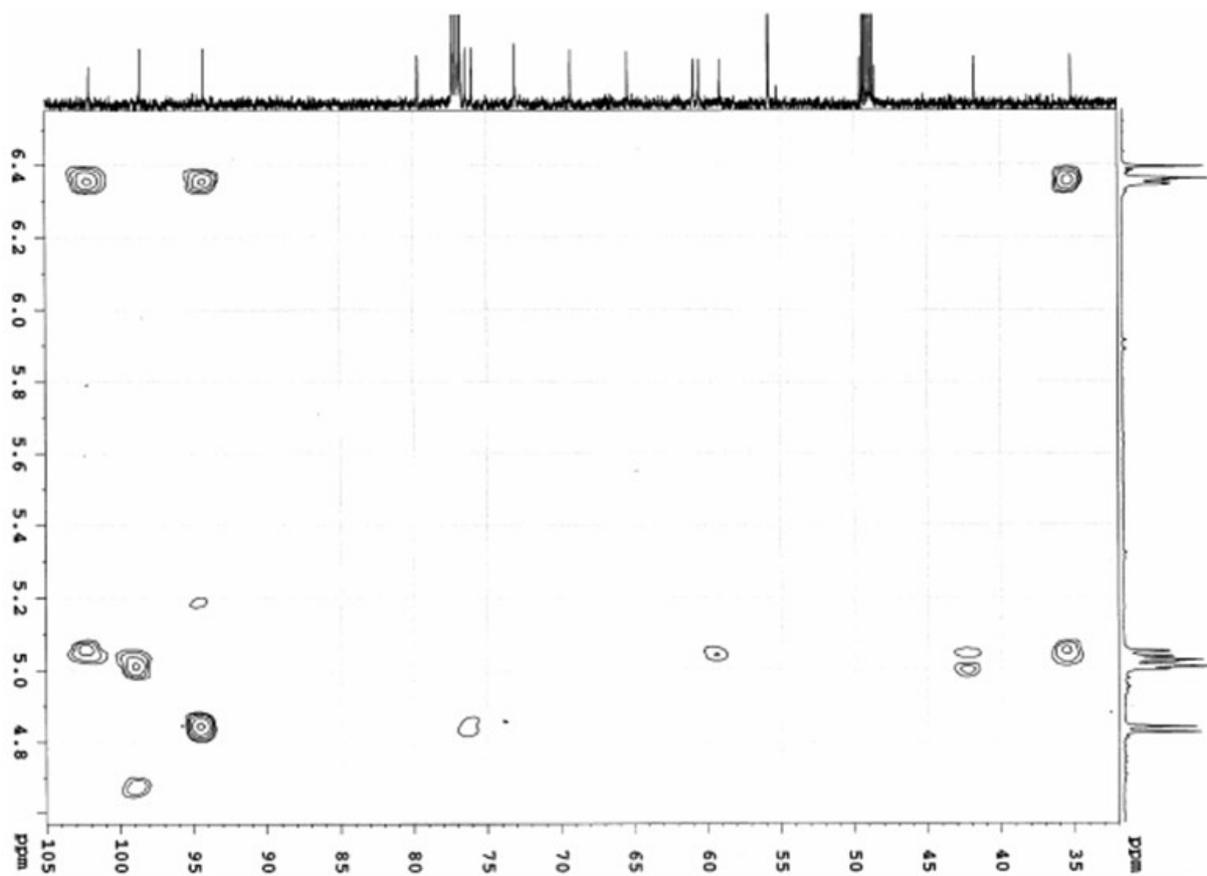
HMBC spectrum (expansion) of compound **2**


HMBC spectrum (expansion) of compound **2**

18
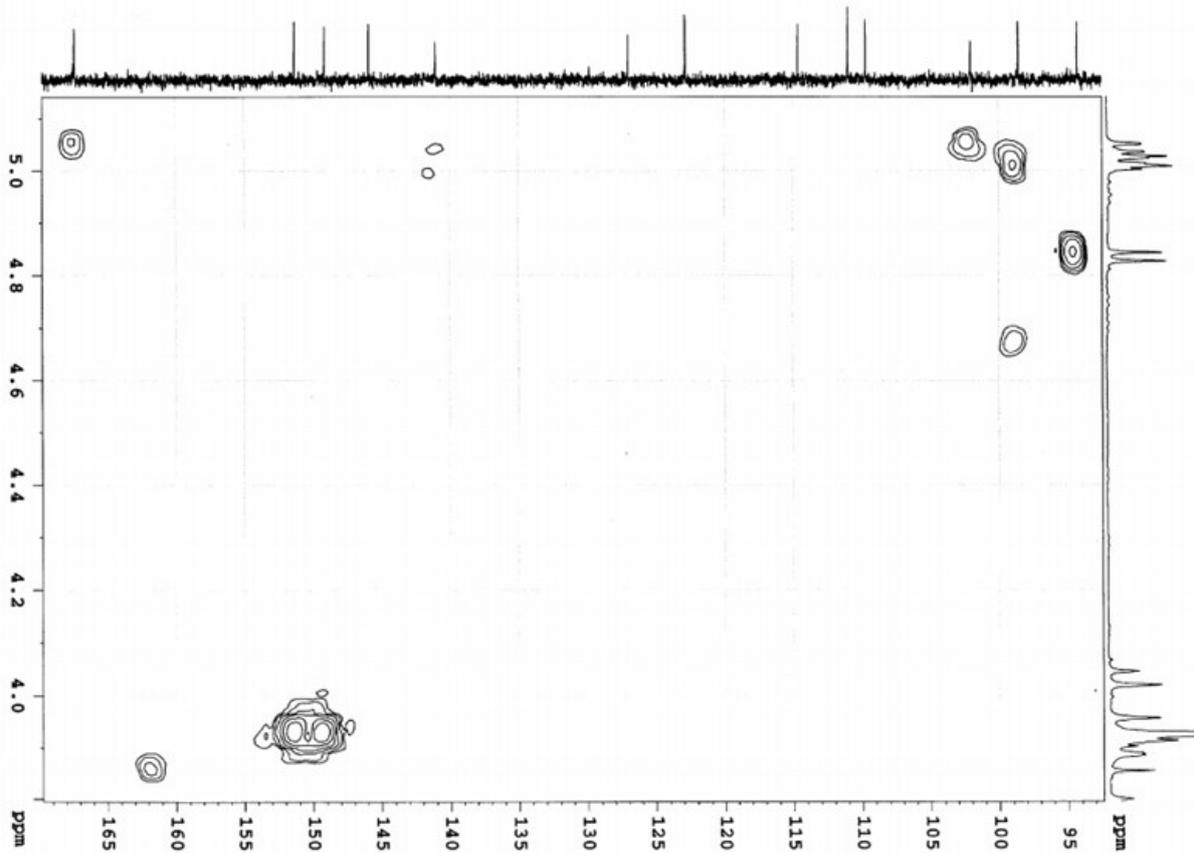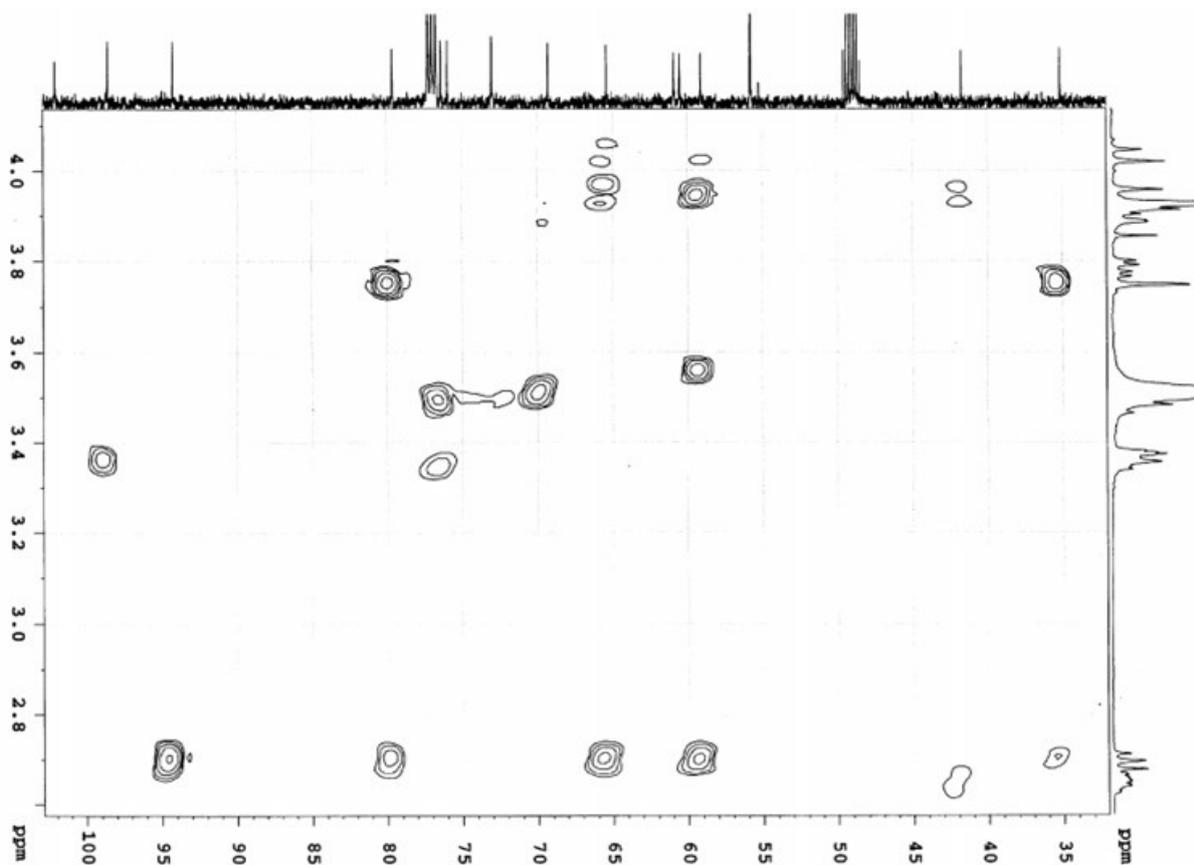
HMBC spectrum (expansion) of compound **2**
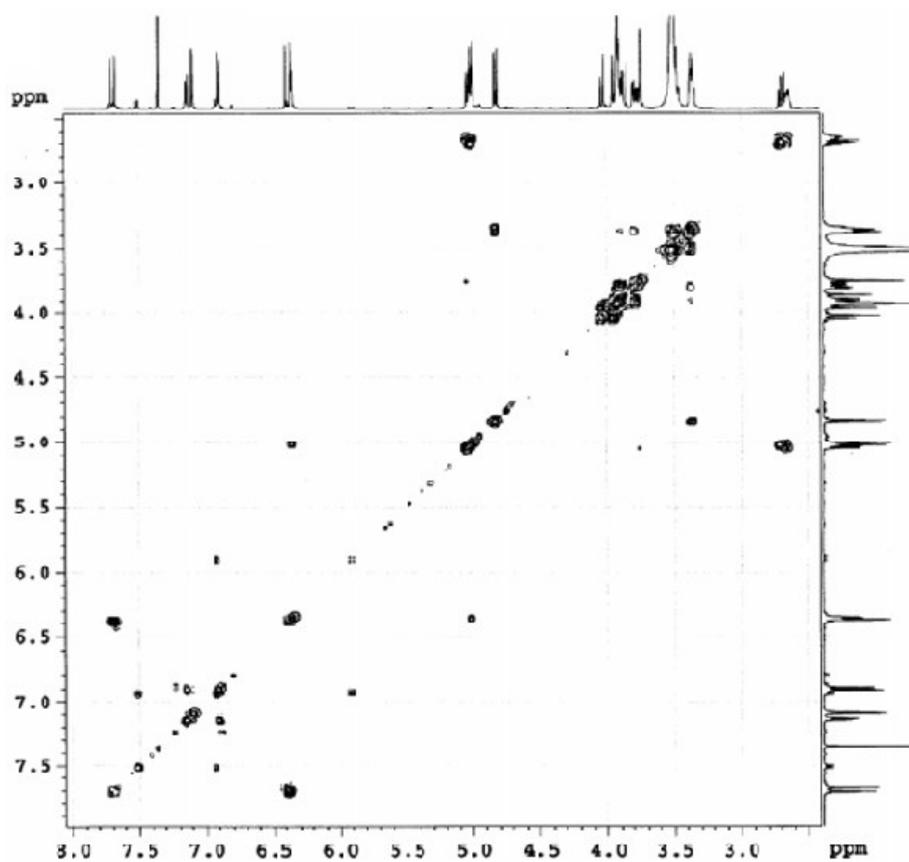

COSY spectrum of compound **2**

1.3. Compound 3

Sample name: QNLK
Operator: Le Anh VHH
Method: +IDA TOF MS/MS
Date: 2021.02.26

Spectrum from 20210226uy.wiff2 (sample 2) - QNLK, Experiment 1, +IDA TOF MS (20 - 2000) from 0.972 min
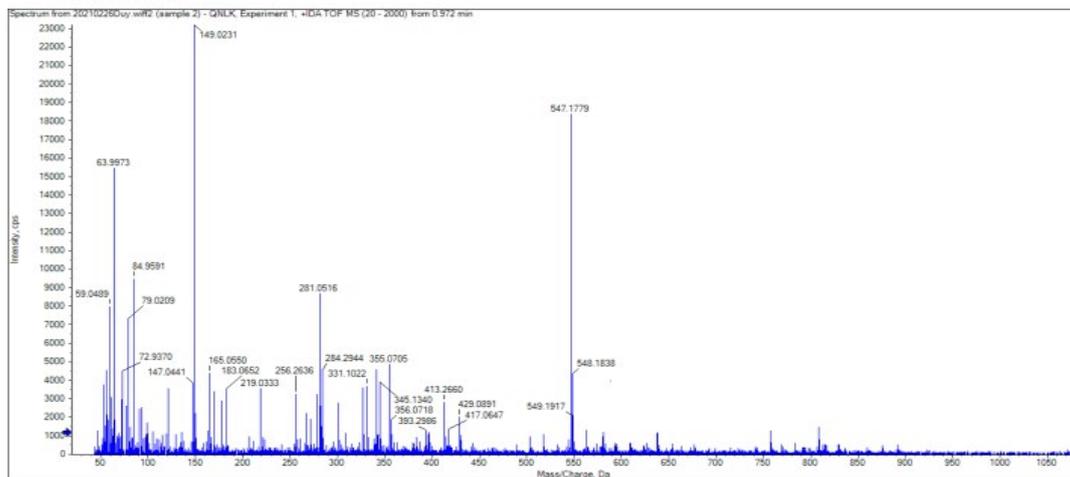
Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C25H32O12	547.17860	10.0	-0.8	1			NA/NA

Device Model: SCIEX X500 QTOF

HR-ESI-MS spectrum of compound **3**

(+)-ESI-MS spectrum of compound **3**

20
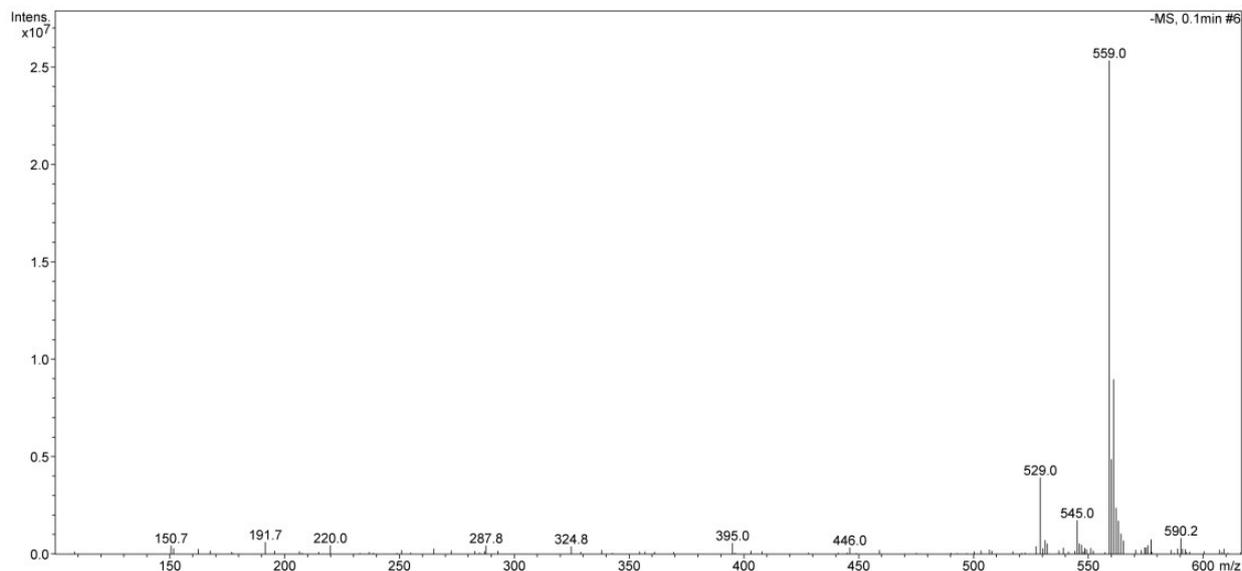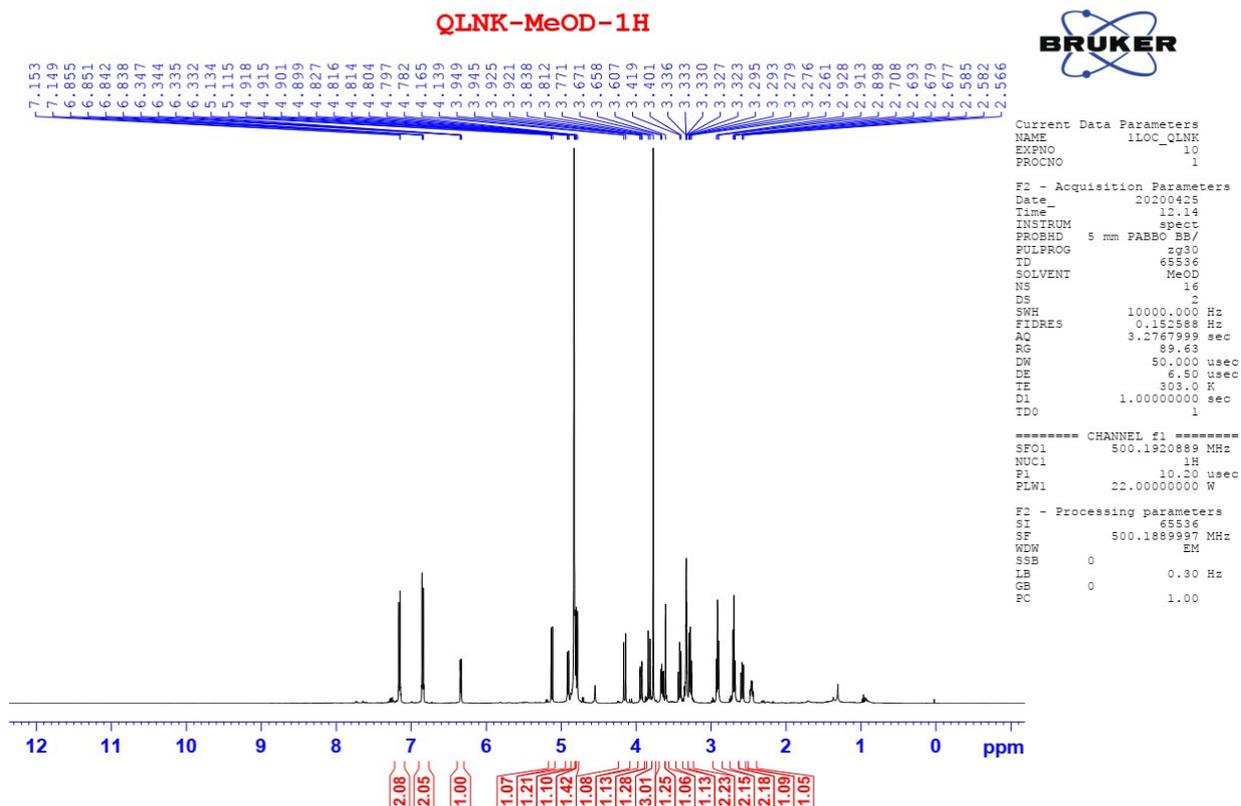
¹H-NMR spectrum of compound **3**
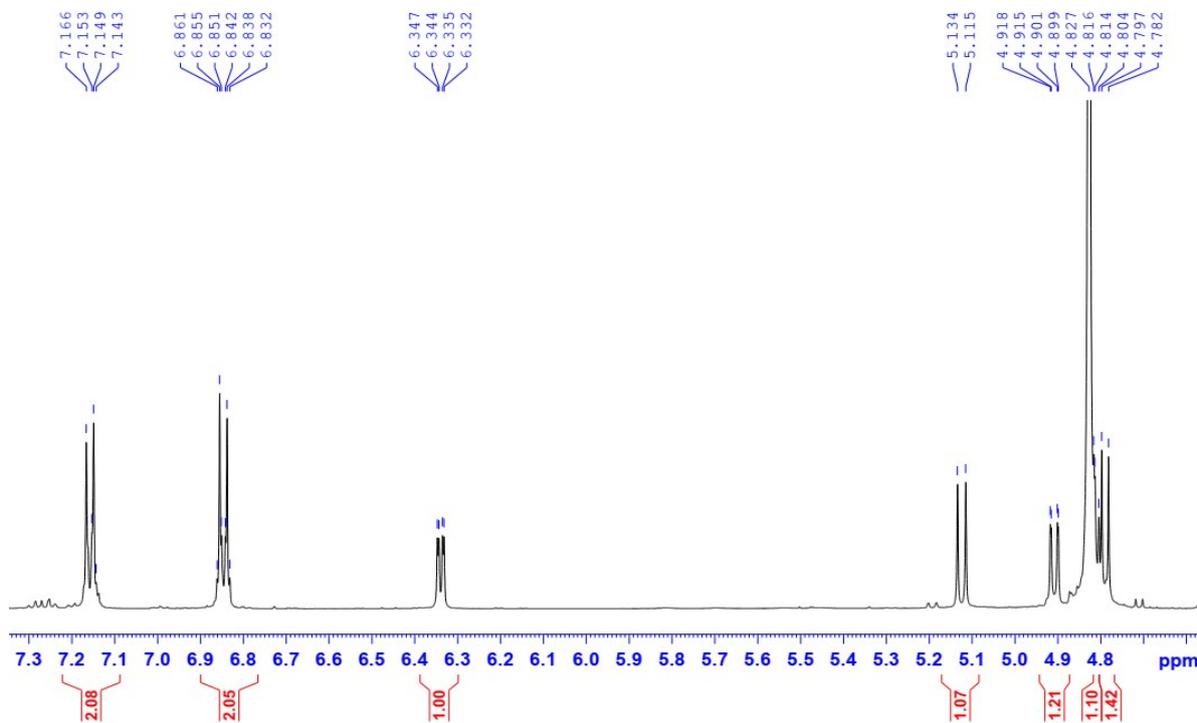
¹H-NMR spectrum (expansion) of compound **3**
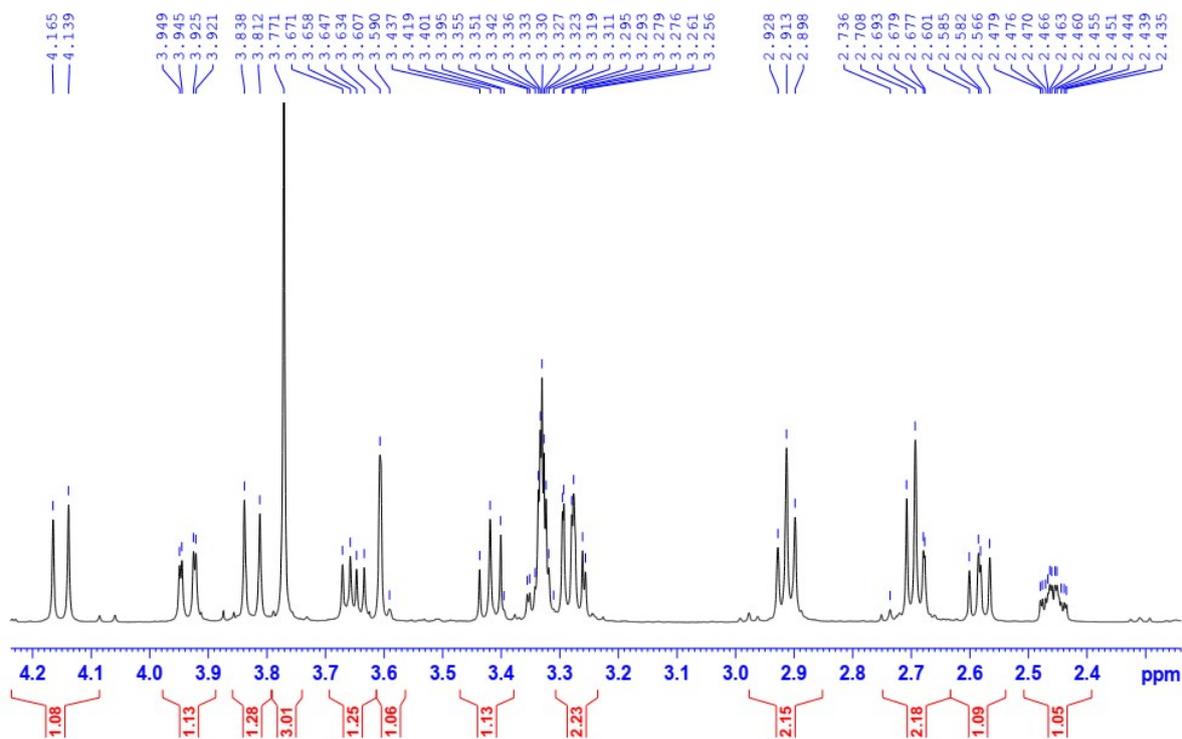
^{1}H-NMR spectrum (expansion) of compound **3**

QLNK-MeOD-C13CPD

^{13}C-NMR spectrum of compound **3**

^{13}C-NMR spectrum (expansion) of compound **3**

^{13}C-NMR spectrum (expansion) of compound **3**

DEPT90

DEPT135

CH&CH3

CH2

C13CPD

DEPT spectrum of compound **3**

DEPT90

DEPT135

CH&CH3

CH2

C13CPD

DEPT spectrum (expansion) of compound **3**

1.4. Compound 4

Sample name: QN3K
Operator: Le Anh VHH
Method: +IDA TOF MS/MS
Date: 2021.02.26

Spectrum from 20210226Duy.wiff2 (sample 5) - QN3K, Experiment 1, +IDA TOF MS (20 - 2000) from 1.725 min

577.1867

578.1909

579.2008

301.1394   381.2953   413.2640
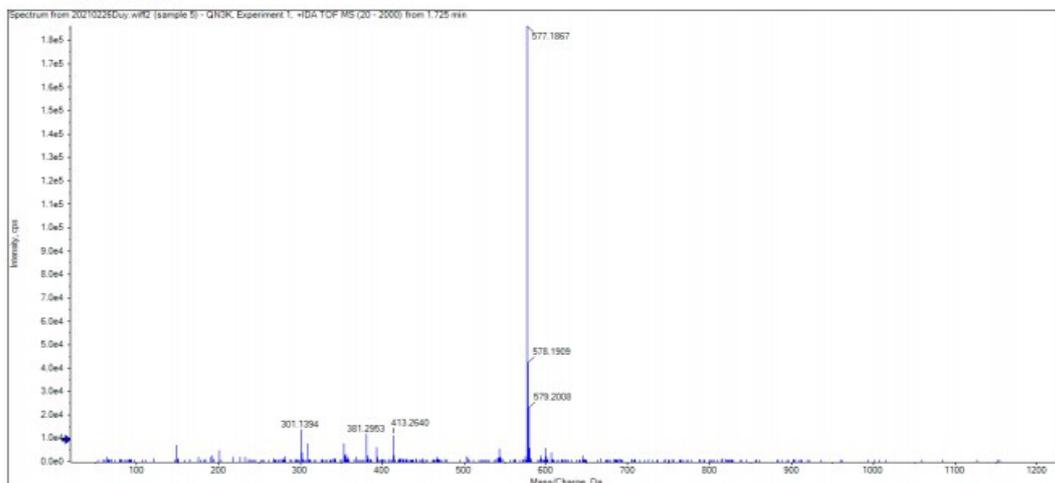
Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C26H34O13	577.18916	10.0	-4.3	1			NA/NA

Device Model: SCIEX X500 QTOF

HR-ESI-MS spectrum of compound **4**

-MS, 0.1min #8

589.1

229.7   300.8   559.2
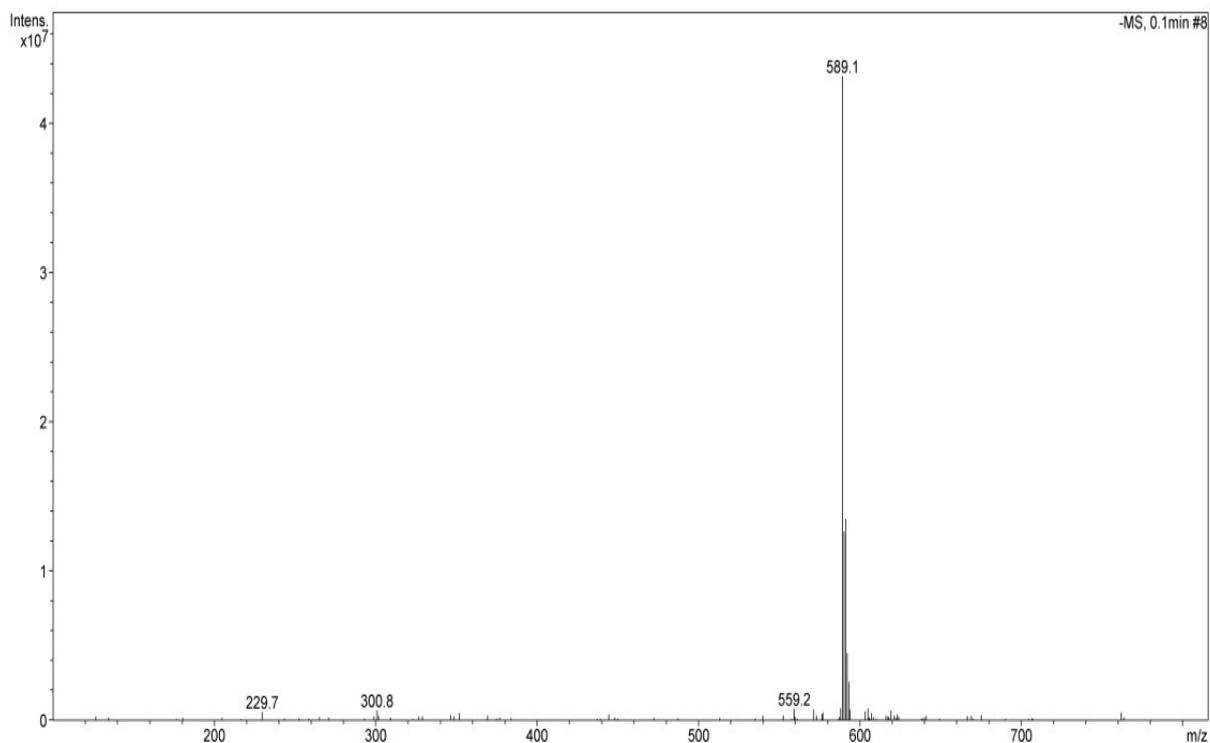
(-)-ESI-MS spectrum of compound **4**
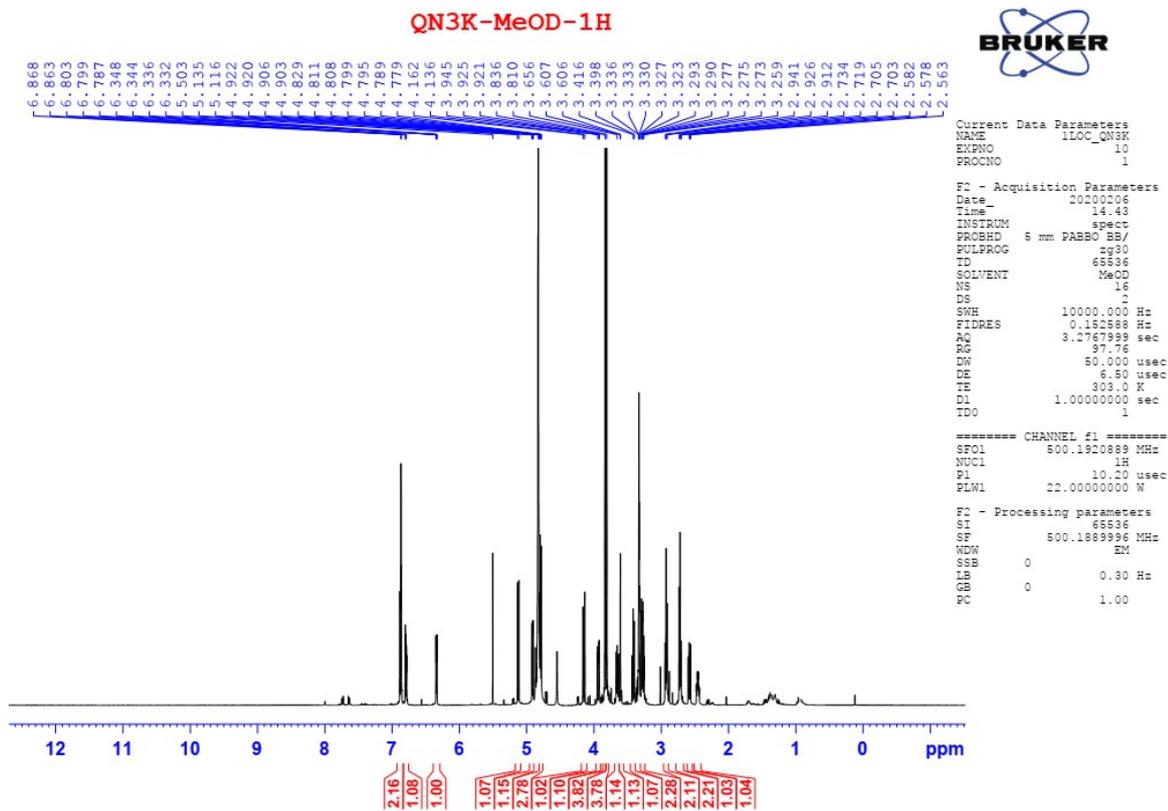
^{1}H-NMR spectrum of compound **4**
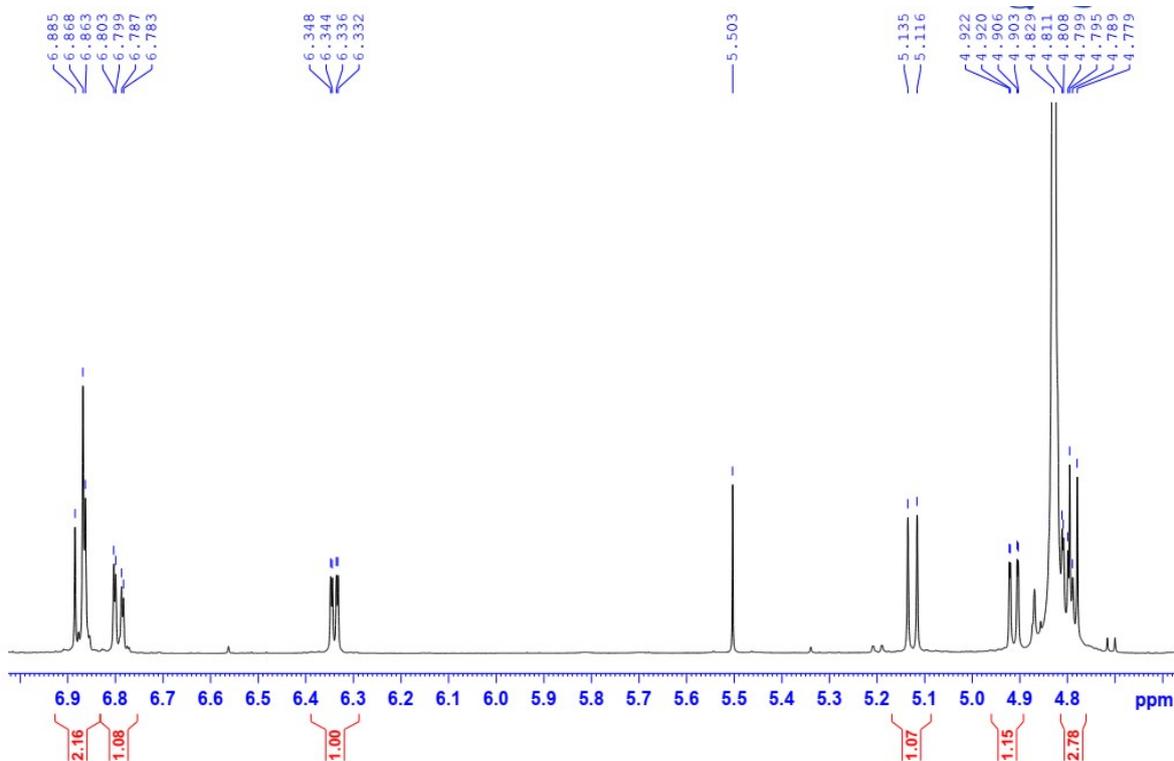
^{1}H-NMR spectrum (expansion) of compound **4**
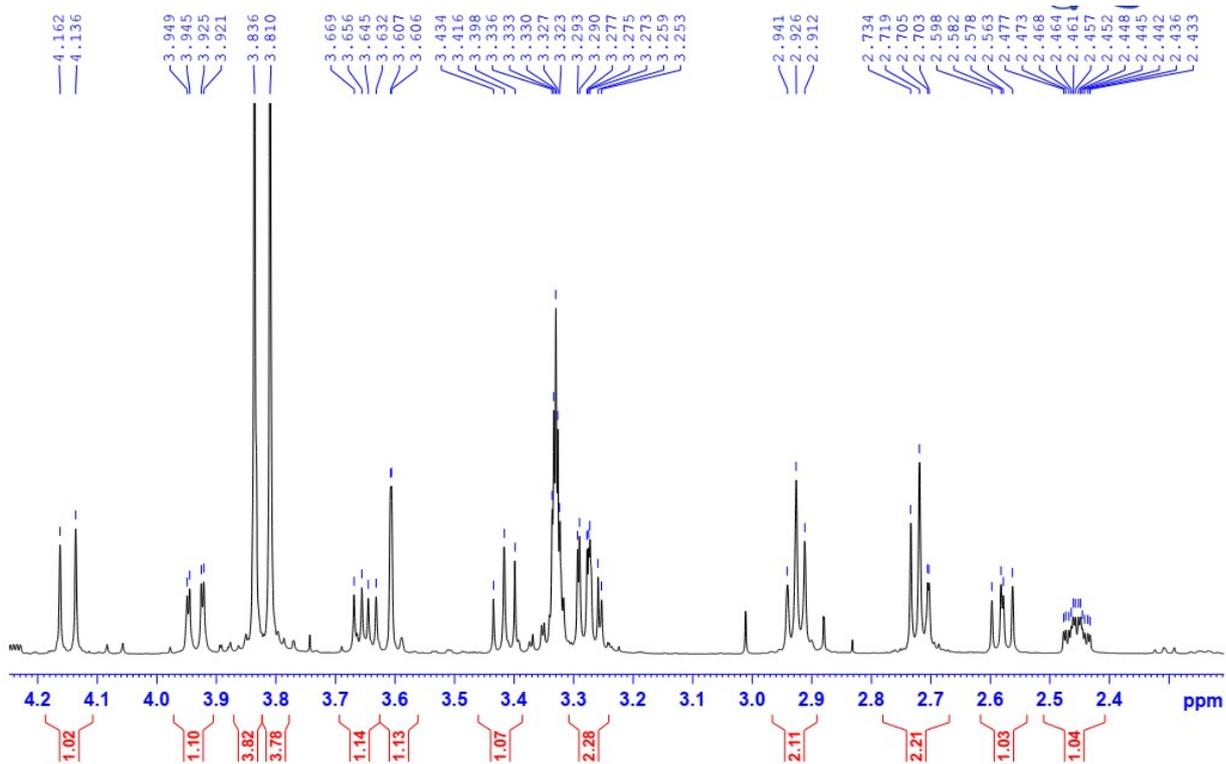
¹H-NMR spectrum (expansion) of compound **4**
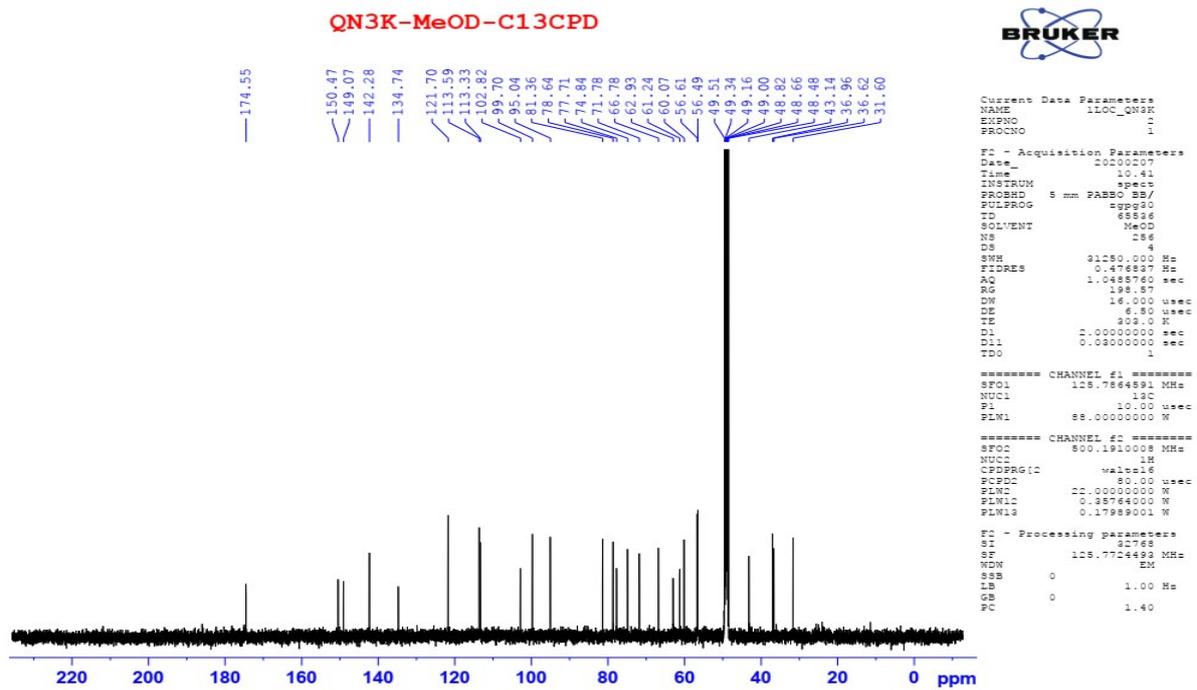
¹³C-NMR spectrum of compound **4**
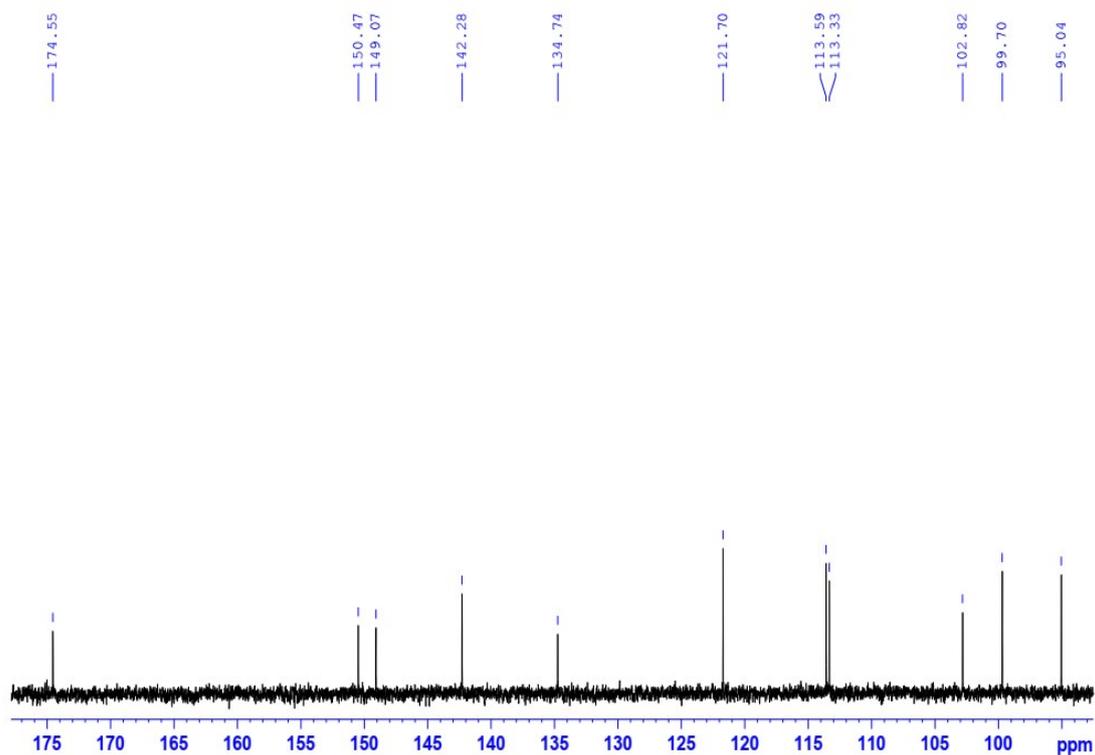
^{13}C-NMR spectrum (epansion) of compound **4**
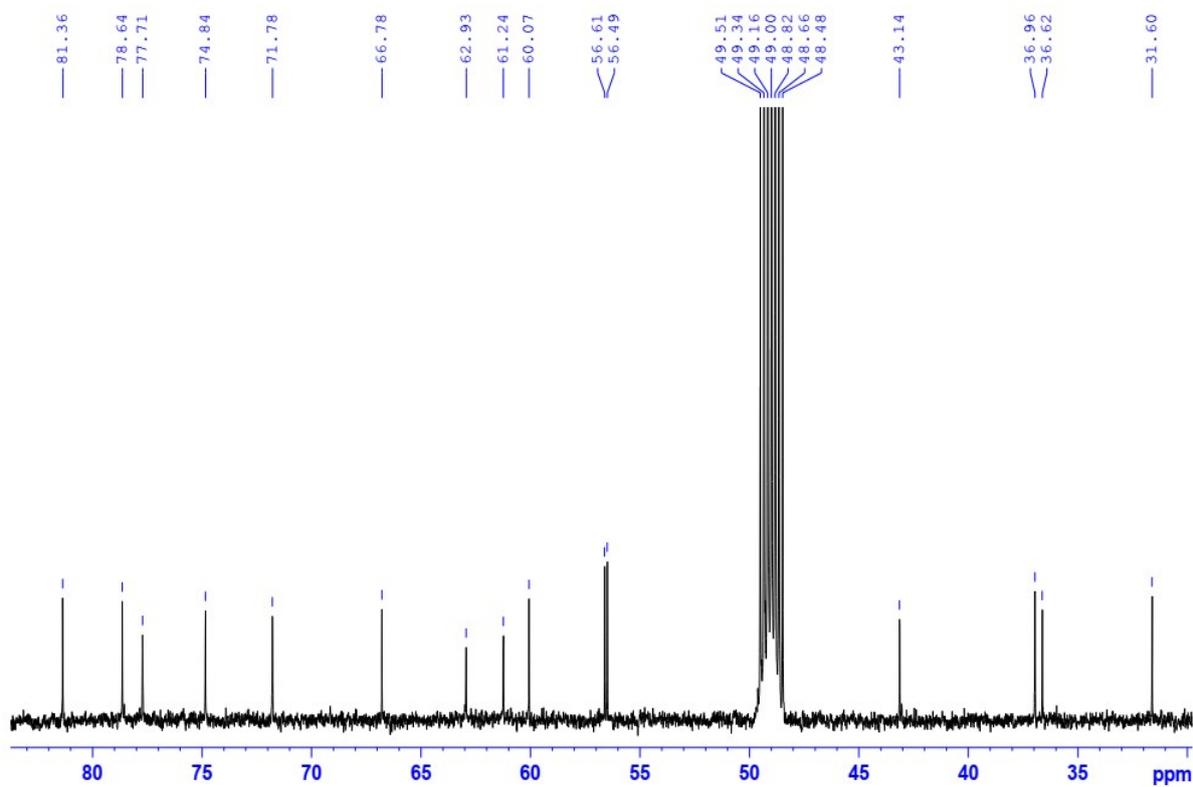
^{13}C-NMR spectrum (epansion) of compound **4**
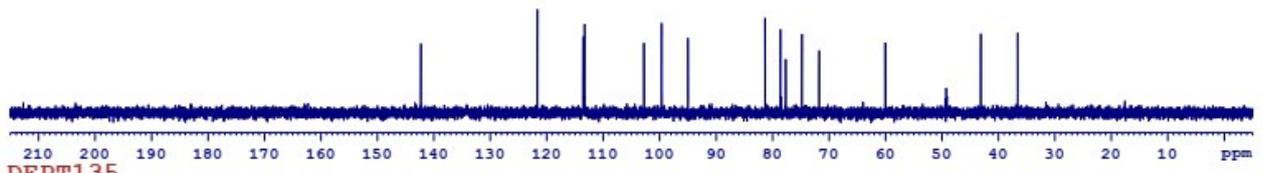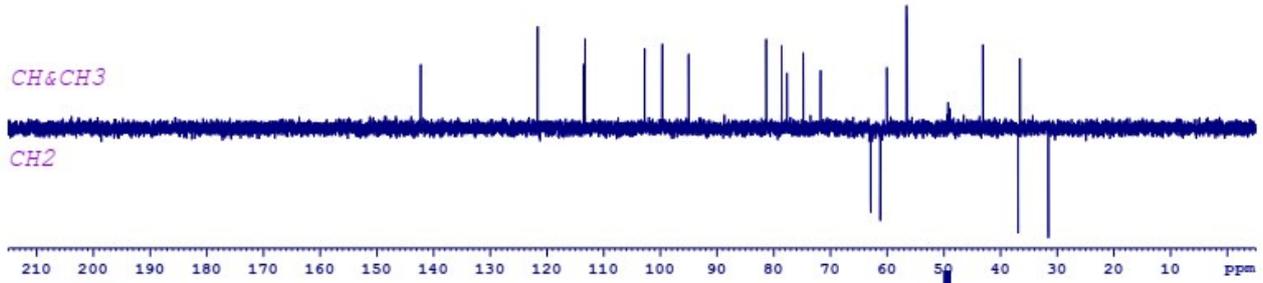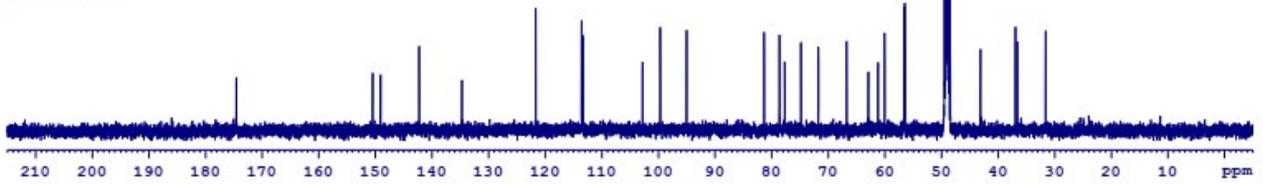
DEPT spectrum of compound **4**

1.5. Compound 5
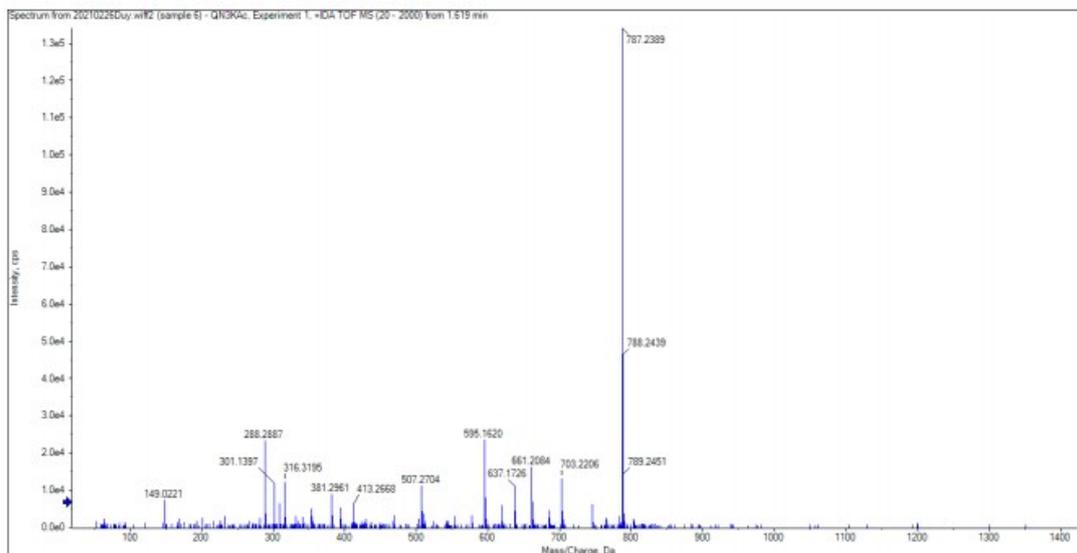
HR-ESI-MS spectrum of compound **5**

(+)-ESI-MS spectrum of compound **5**

^{1}H-NMR spectrum of compound **5**

^{1}H-NMR spectrum (expansion) of compound **5**

^{1}H-NMR spectrum (expansion) of compound **5**

^{1}H-NMR spectrum (expansion) of compound **5**
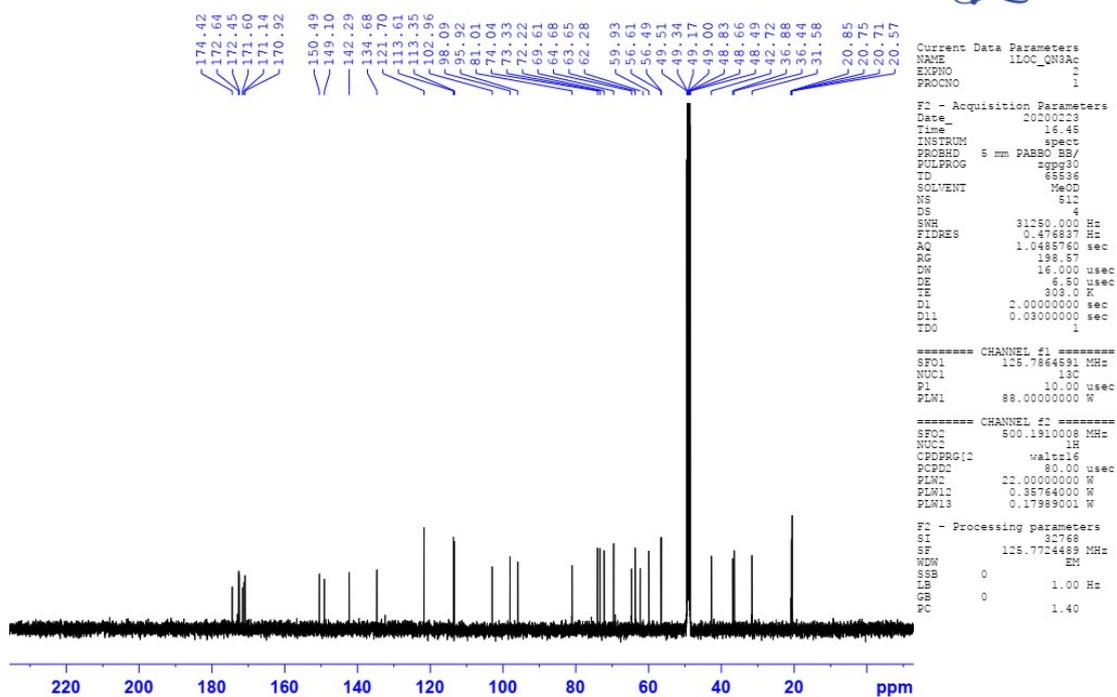
^{13}C-NMR spectrum of compound **5**

^{13}C-NMR spectrum (expansion) of compound **5**

^{13}C-NMR spectrum (expansion) of compound **5**

DEPT90

DEPT135

CH&CH3

CH2
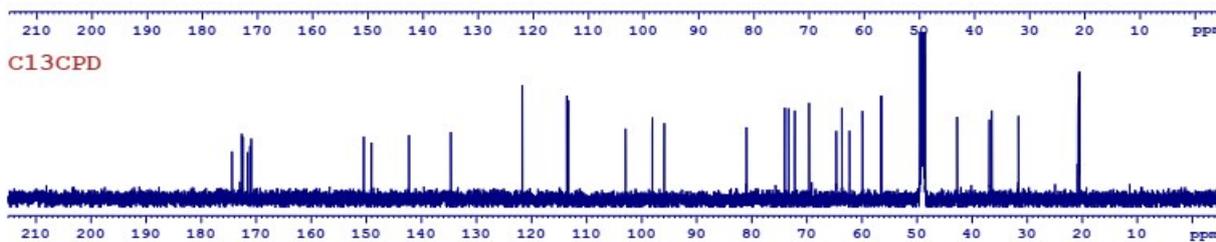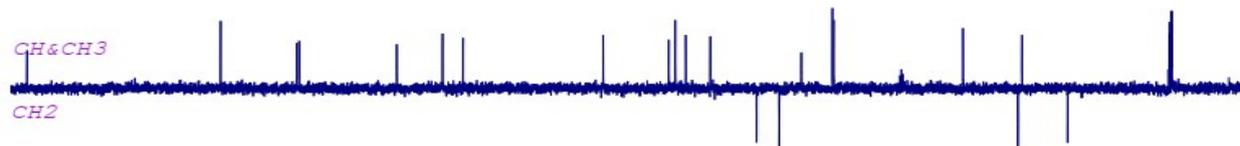
C13CPD
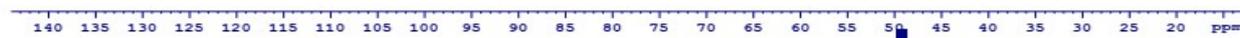
DEPT spectrum of compound **5**
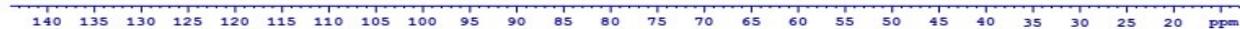
DEPT spectrum (epansion) of compound **5**

1.6. Compound 6

Sample name: QN3Ph
Operator: Le Anh VHH
Method: +IDA TOF MS/MS
Date: 2021.02.26
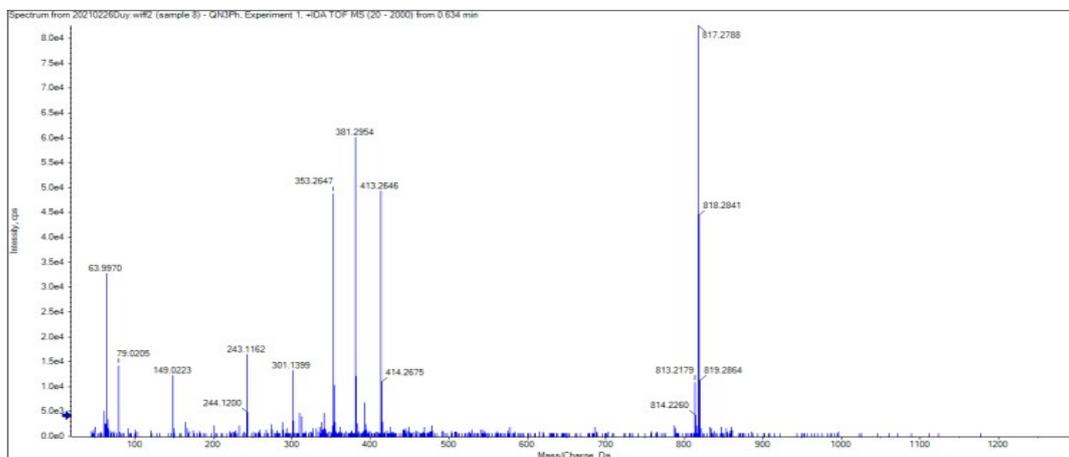
Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C45H46O13	817.28306	23.0	-5.2	1			NA/NA

Device Model: SCIEX X500 QTOF

HR-ESI-MS spectrum of compound **6**

QN3PH-CDC13-1H
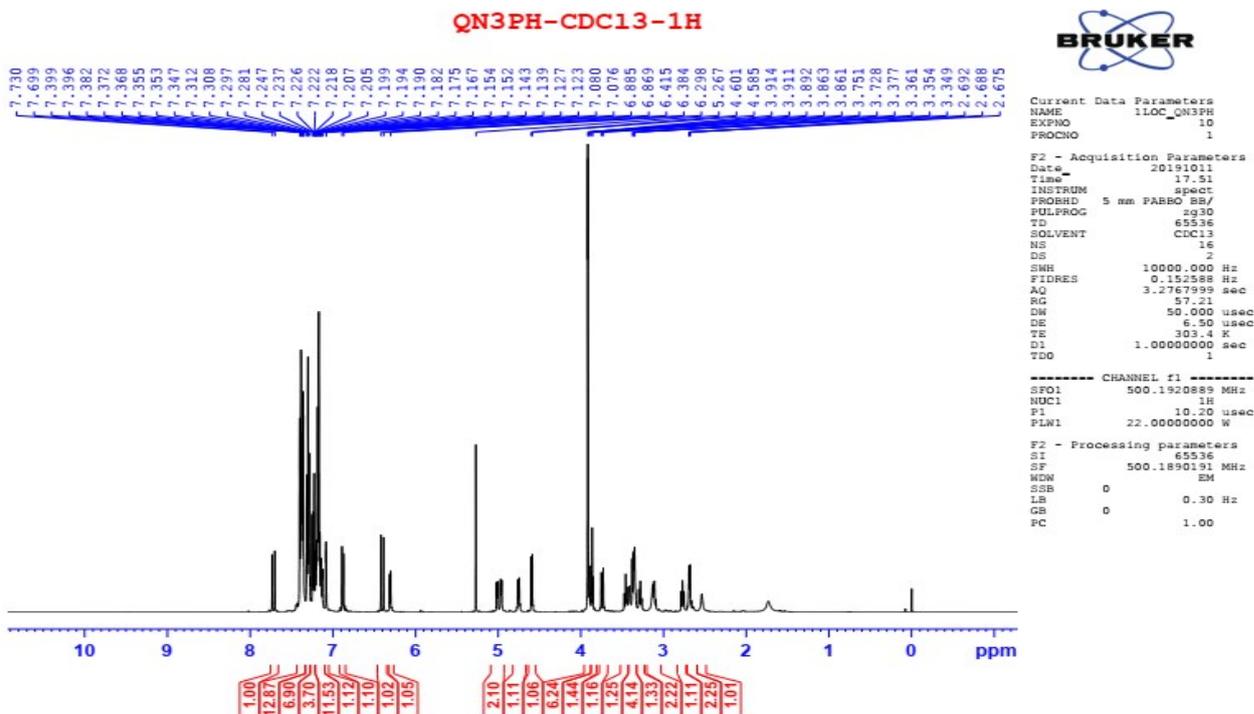
^{1}H-NMR spectrum of compound **6**

¹H-NMR spectrum (expansion) of compound **6**
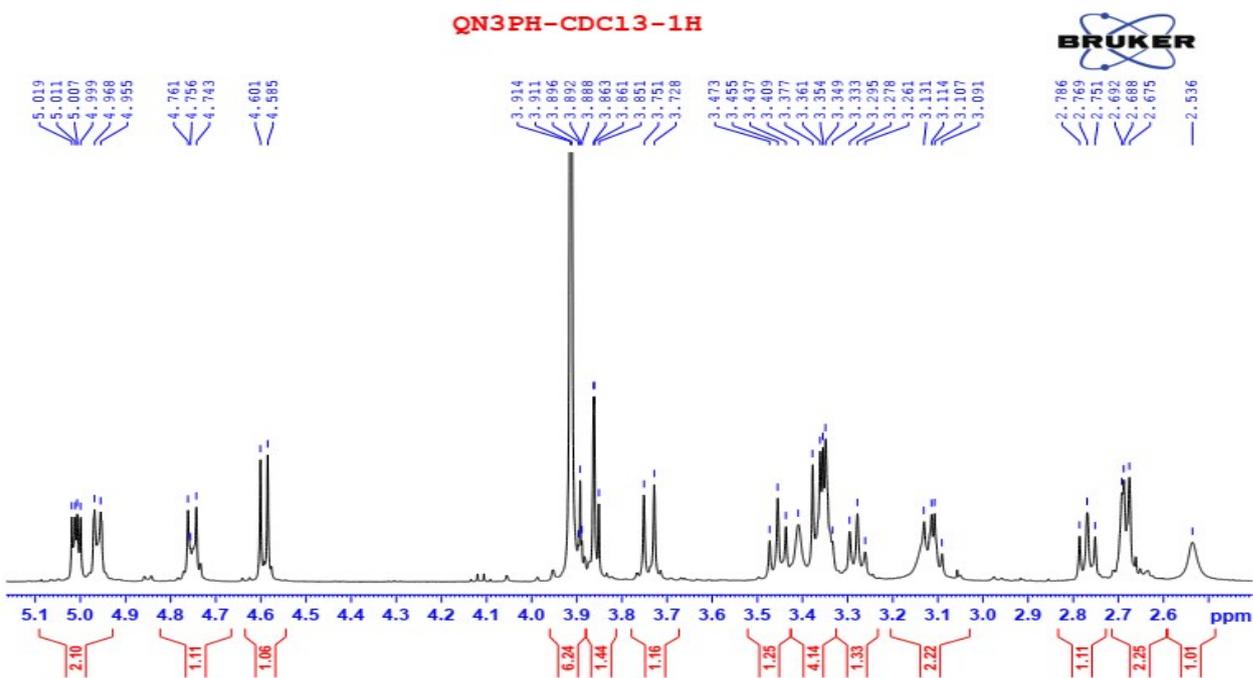
¹H-NMR spectrum (expansion) of compound **6**

BRUKER

Current Data Parameters
NAME   1LOC_QN3PH
EXPNO   2
PROCNO   1

F2 - Acquisition Parameters
Date_   20191012
Time   16.23
INSTRUM   spect
PROBHD   5 mm PABBO BB/
PULPROG   zgpg30
TD   65536
SOLVENT   CDC13
NS   256
DS   4
SWH   31250.000 Hz
FIDRES   0.476837 Hz
AQ   1.0485760 sec
RG   198.57
DW   16.000 usec
DE   6.50 usec
TE   304.8 K
D1   2.00000000 sec
D11   0.03000000 sec
TD0   1

-------- CHANNEL f1 --------
SFO1   125.7864591 MHz
NUC1   13C
P1   10.00 usec
PLW1   88.00000000 W

-------- CHANNEL f2 --------
SFO2   500.1910008 MHz
NUC2   1H
CPDPRG[2   waltz16
PCPD2   80.00 usec
PLW2   22.00000000 W
PLW12   0.35764000 W
PLW13   0.17989001 W

F2 - Processing parameters
SI   32768
SF   125.7726241 MHz
WDW   EM
SSB   0
LB   1.00 Hz
GB   0
PC   1.40

¹³C-NMR spectrum of compound **6**

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¹³C-NMR spectrum (expansion) of compound **6**

^{13}C-NMR spectrum (expansion) of compound **6**

^{13}C-NMR spectrum (expansion) of compound **6**

^{13}C-NMR spectrum (expansion) of compound **6**

DEPT spectrum of compound **6**
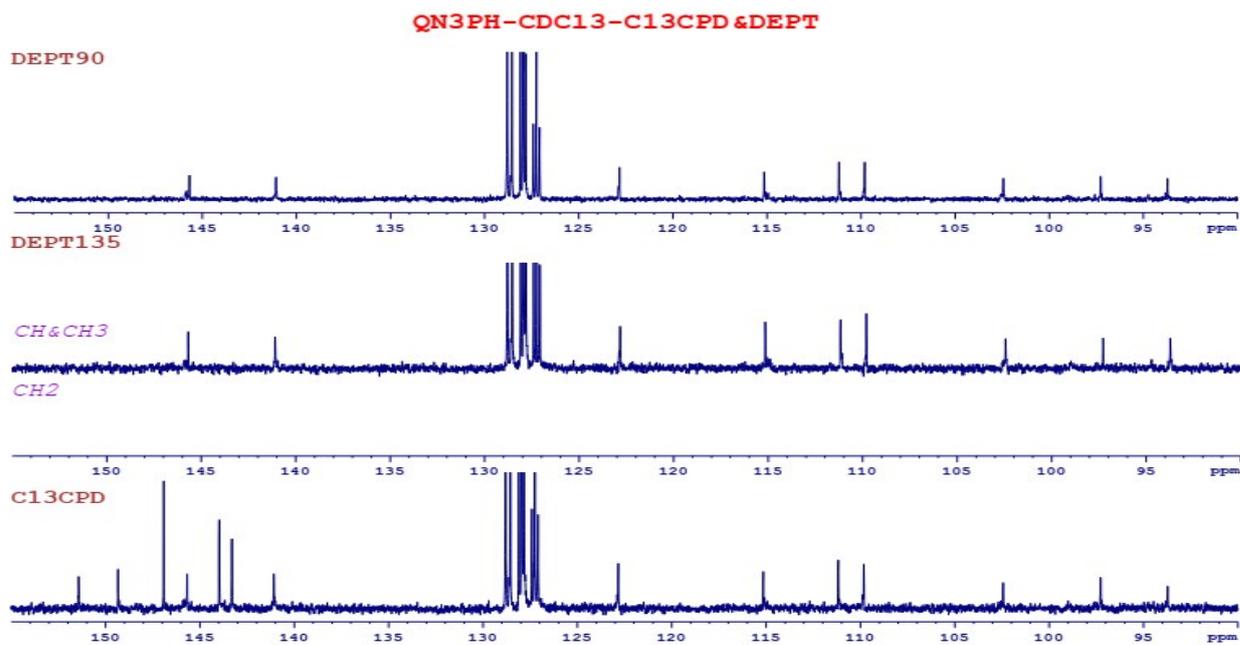
DEPT spectrum (epansion) of compound **6**
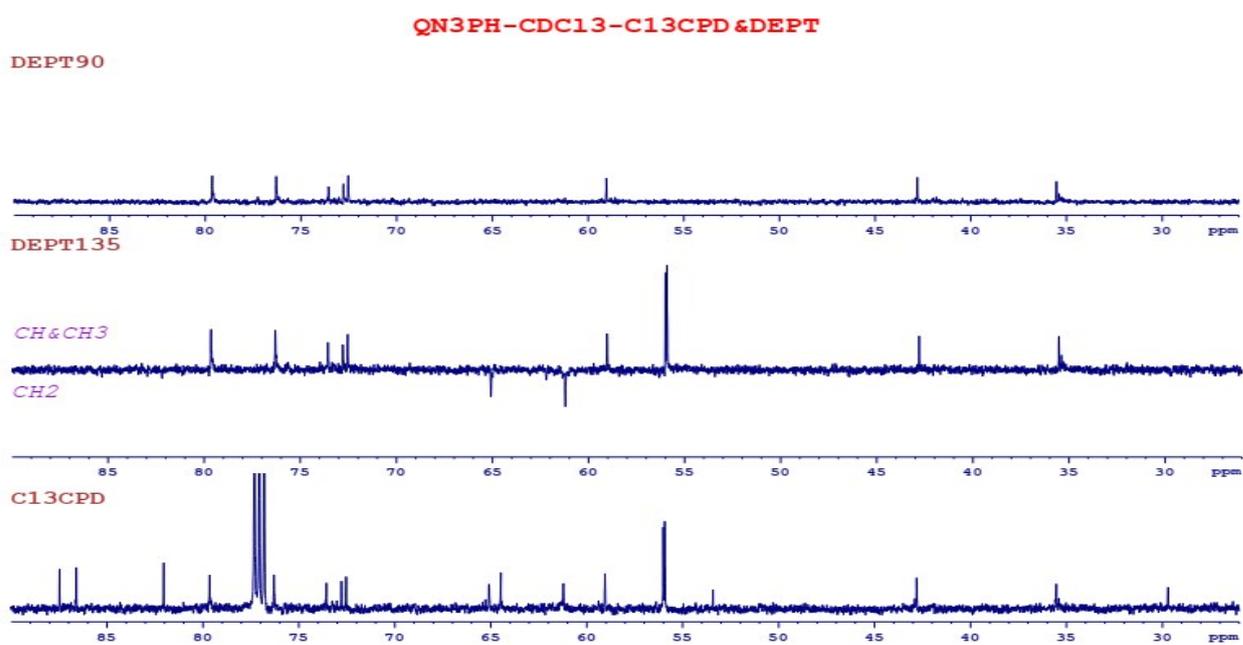
DEPT spectrum (epansion) of compound **6**

1.7. Compound 7
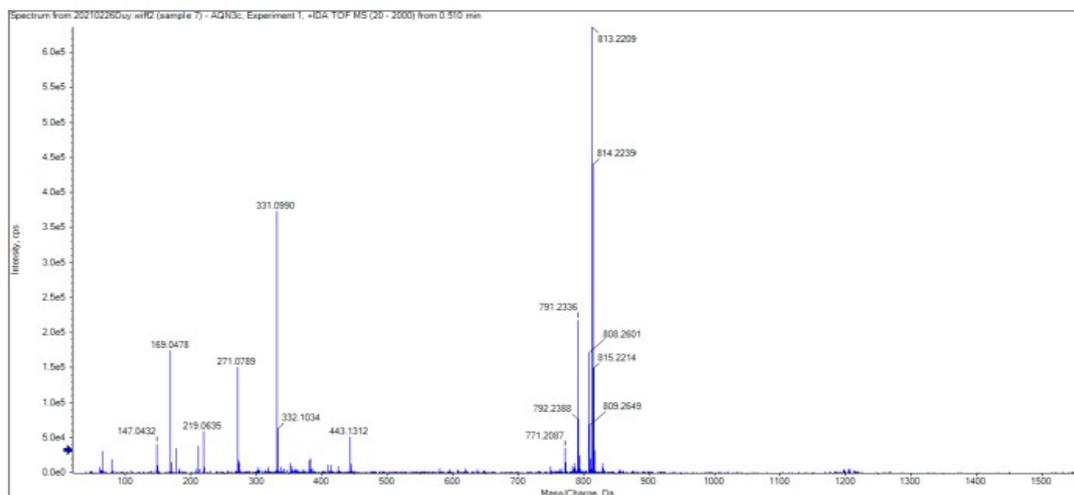
Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C37H42O19	813.22125	17.0	-1.7	1			NA/NA

Device Model: SCIEX X500 QTOF

HR-ESI-MS spectrum of compound **7**
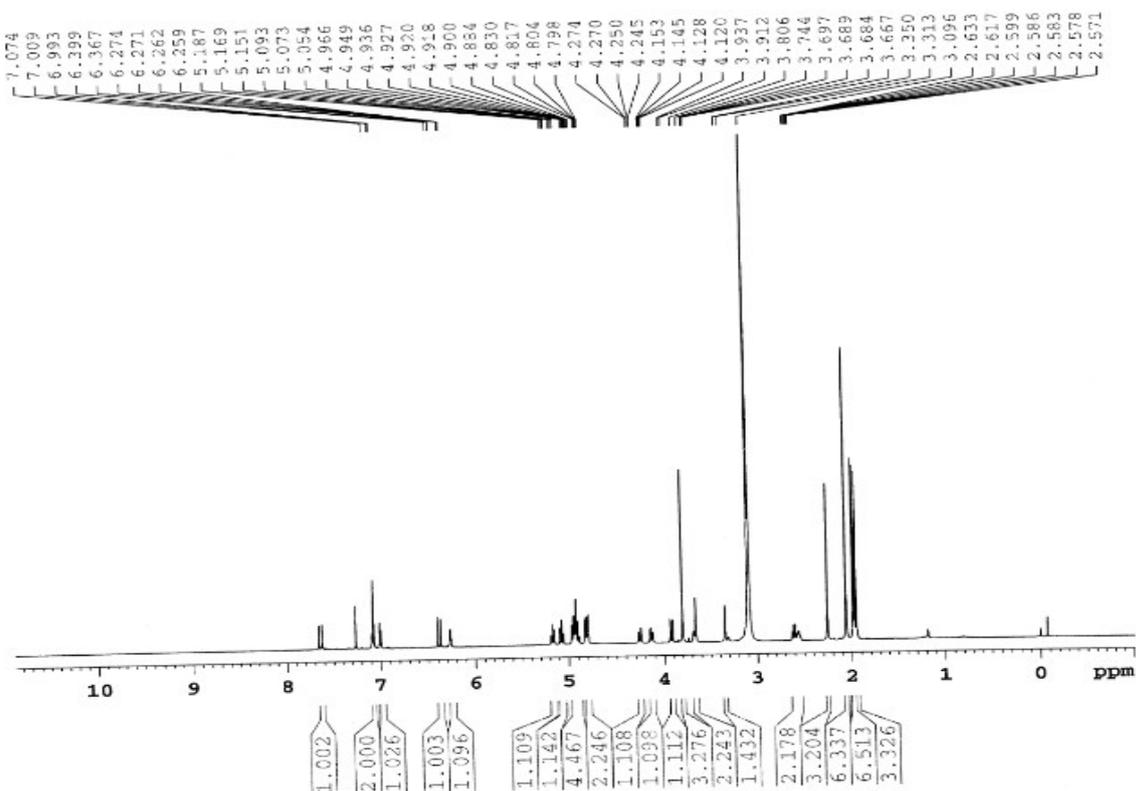
^{1}H-NMR spectrum (500 MHz, CDCl$_3$) of compound **7**
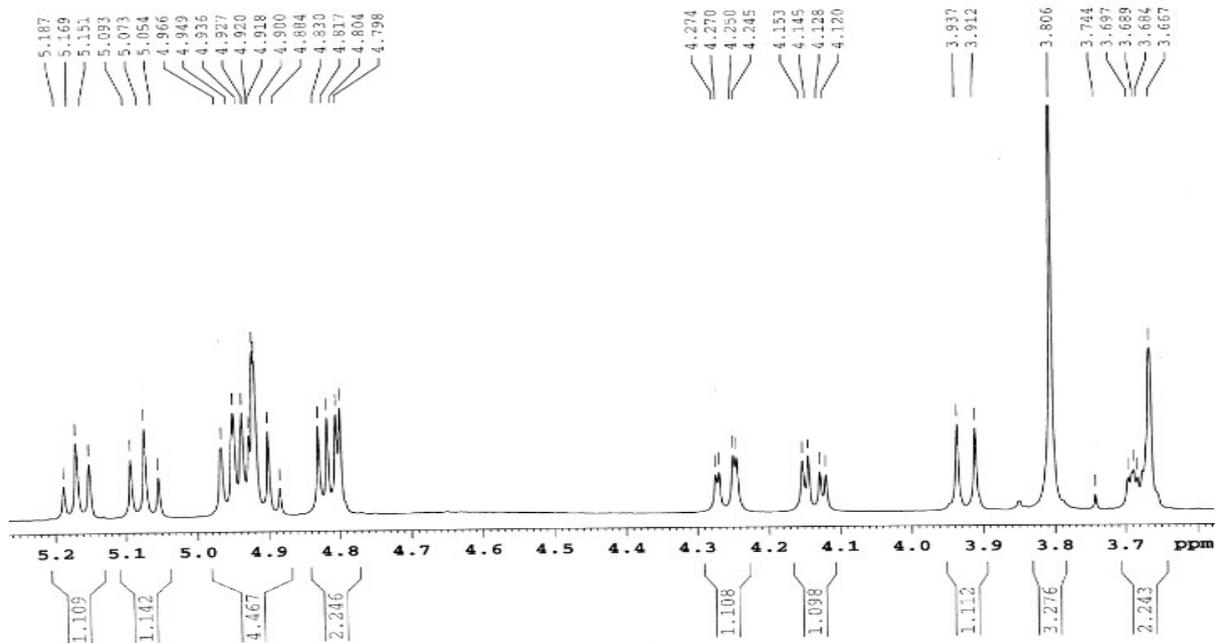
^{1}H-NMR spectrum (expansion) of compound **7**
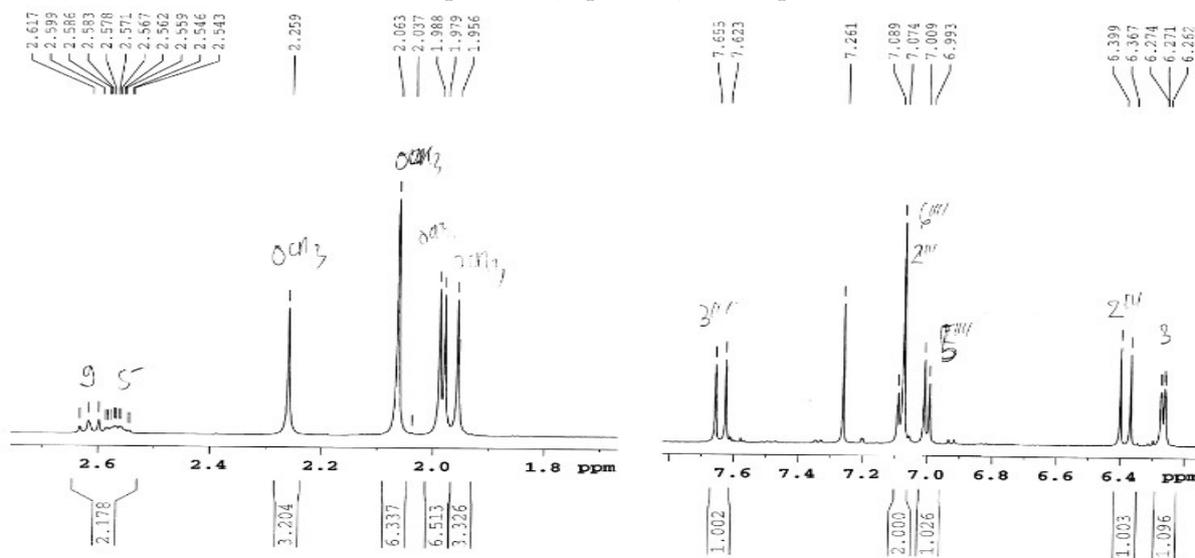
^{1}H-NMR spectrum (expansion) of compound **7**
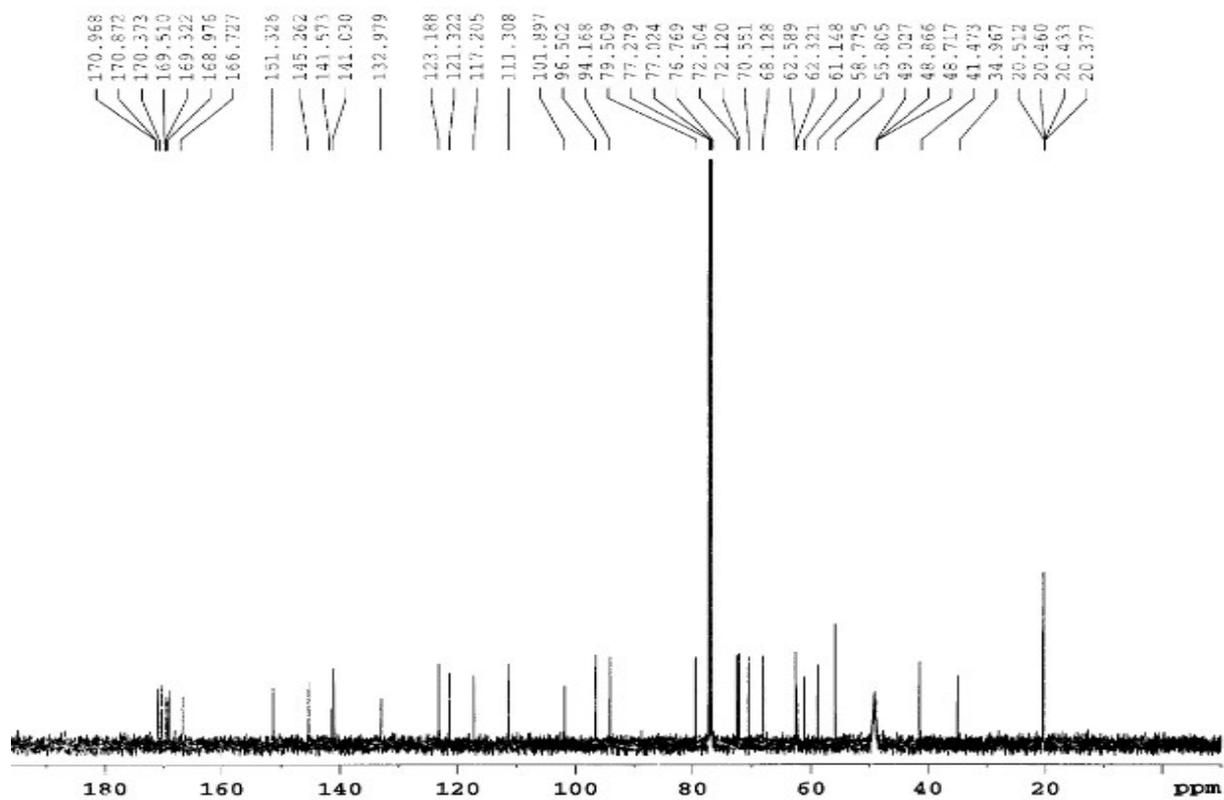
^{13}C-NMR spectrum of compound **7**
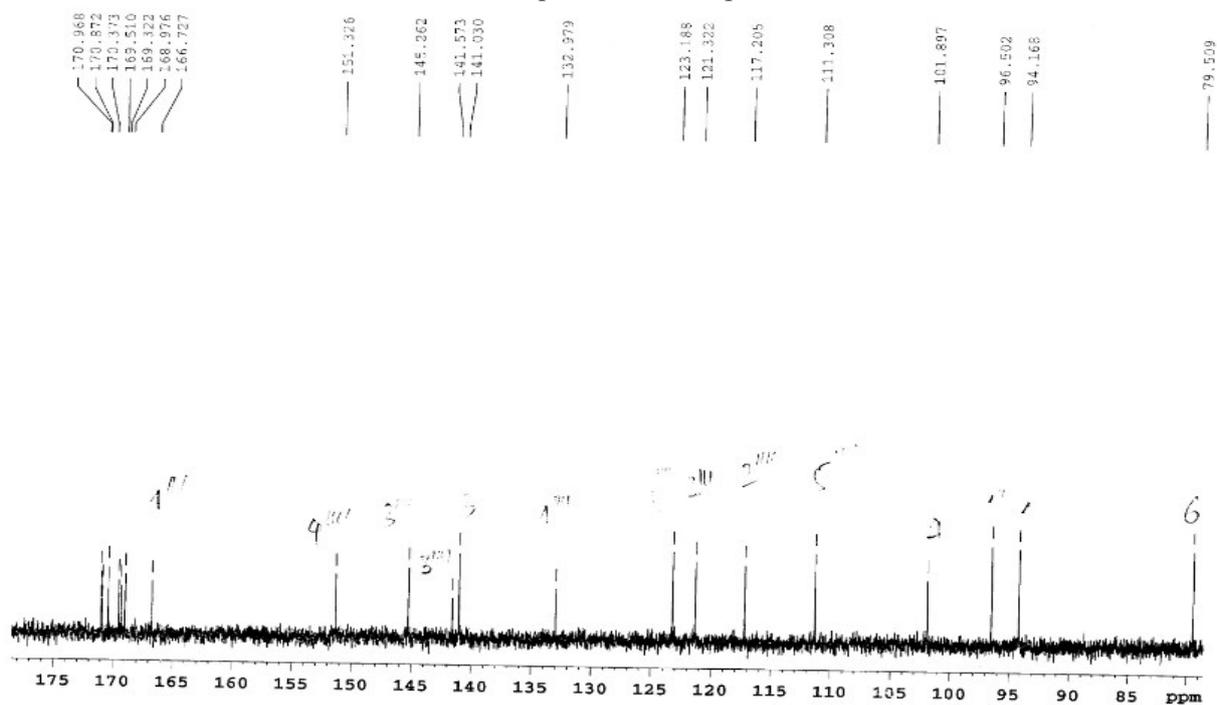

^{13}C-NMR spectrum (expansion) of compound **7**
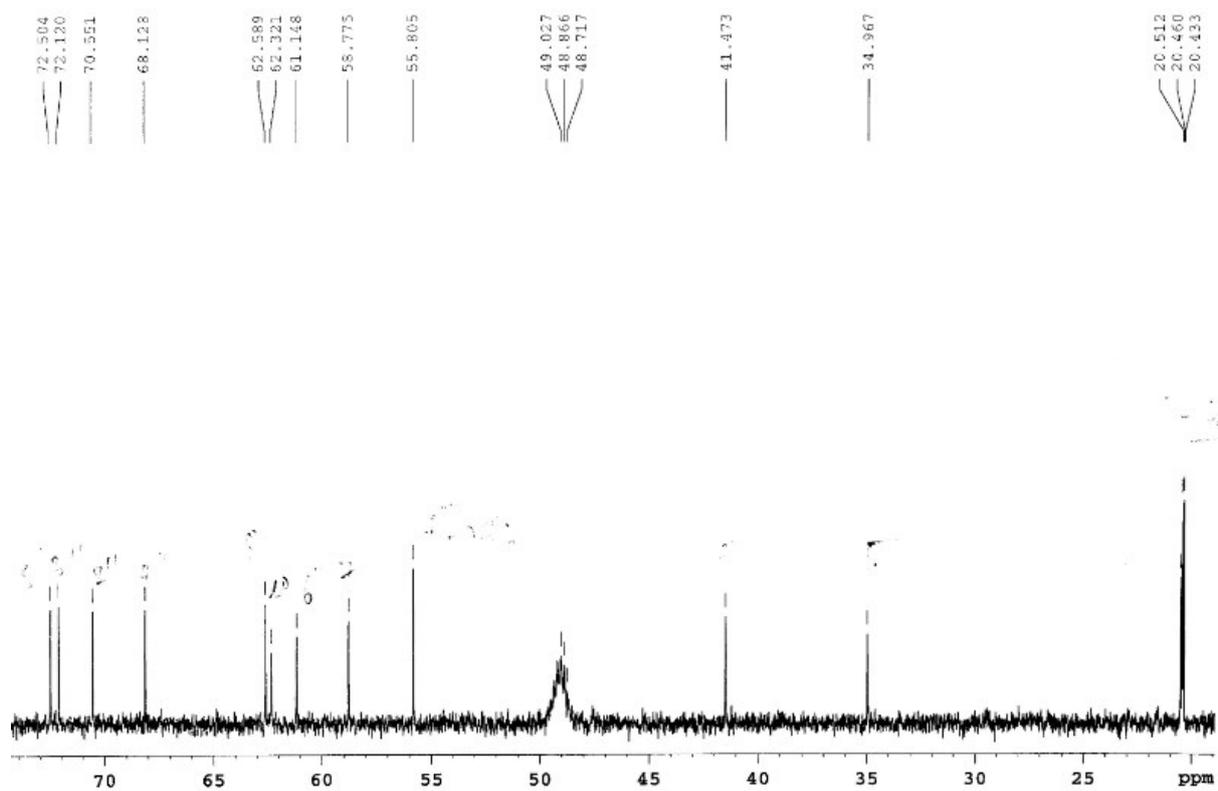
^{13}C-NMR spectrum (expansion) of compound **7**

DEPT90

DEPT135

CH&CH3

CH2

C13CPD
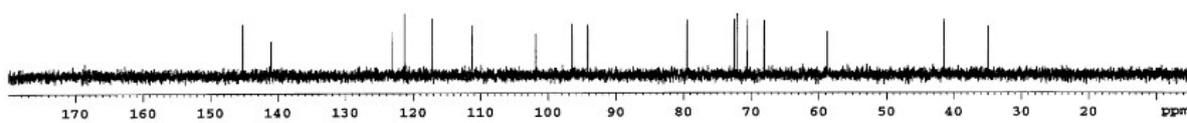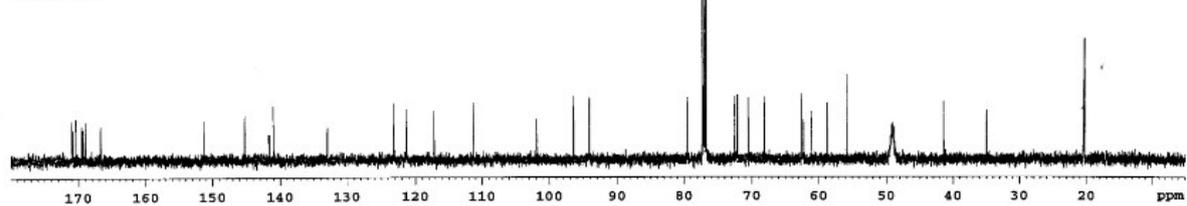
DEPT spectrum of compound **7**

1.8. Compound 8
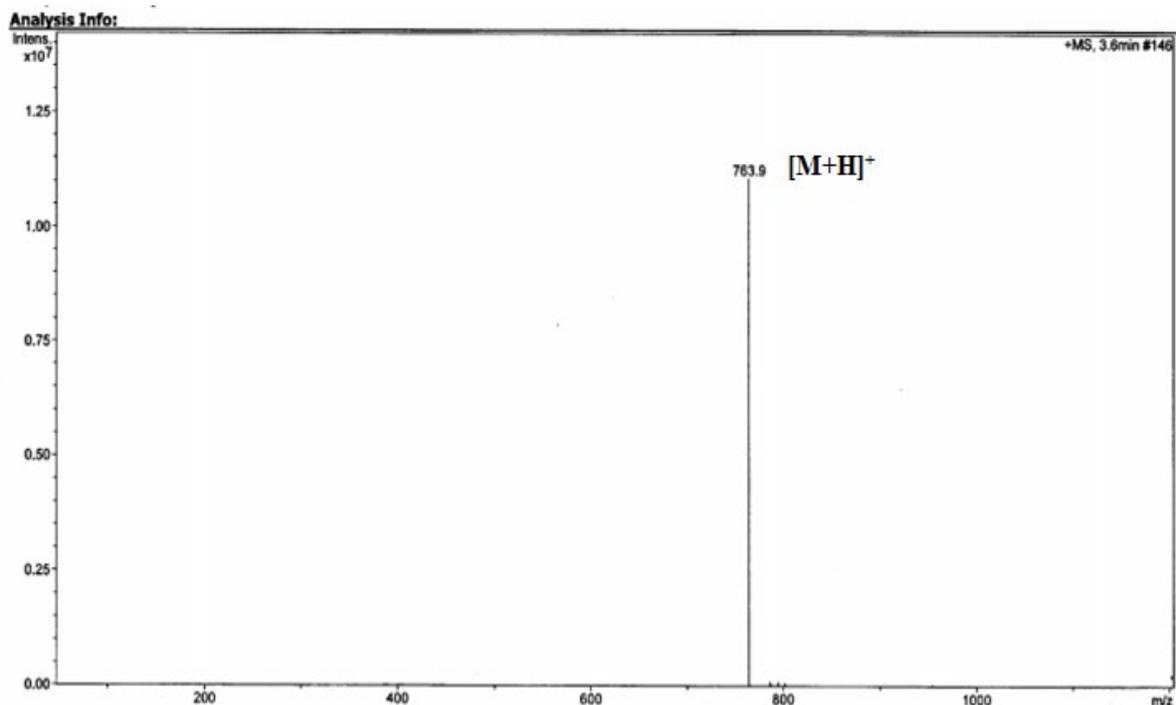
(+)-ESI-MS spectrum of compound **8**
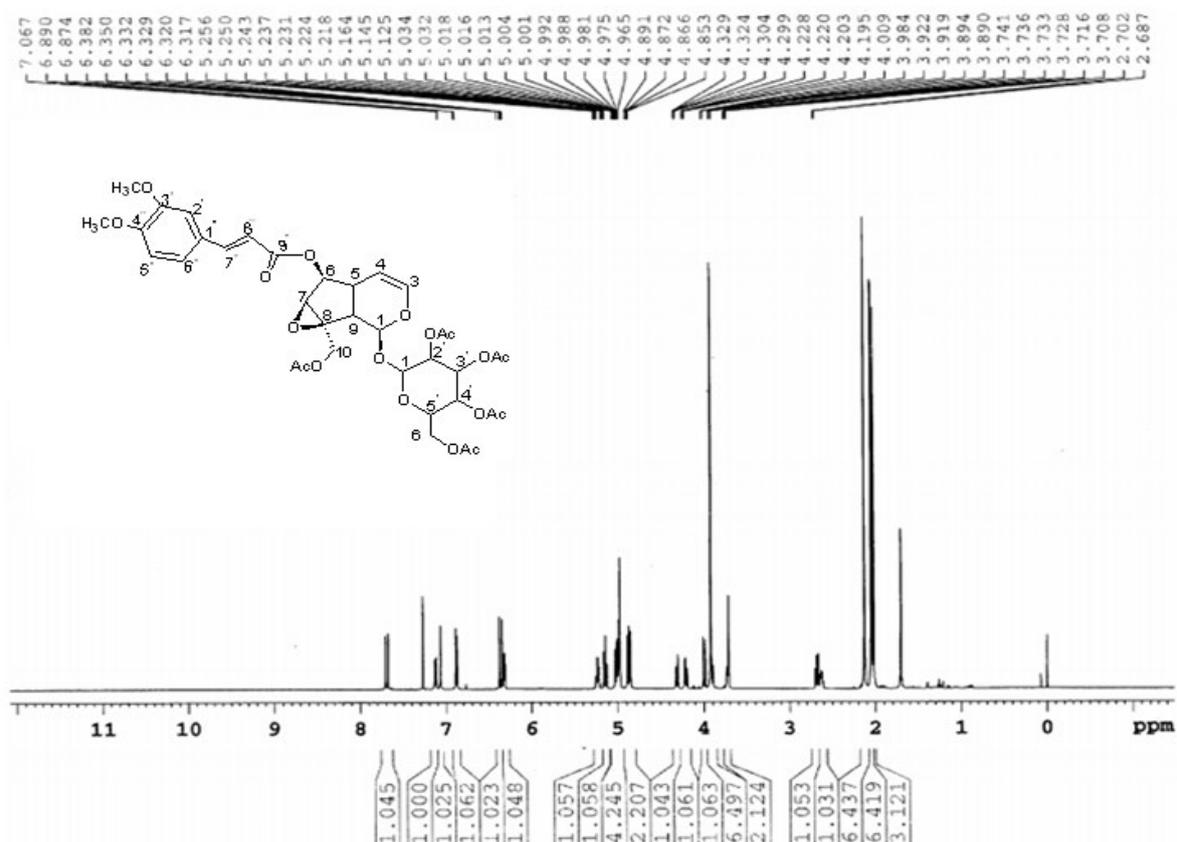
^{1}H-NMR spectrum (500 MHz, CDCl$_3$) of compound **8**
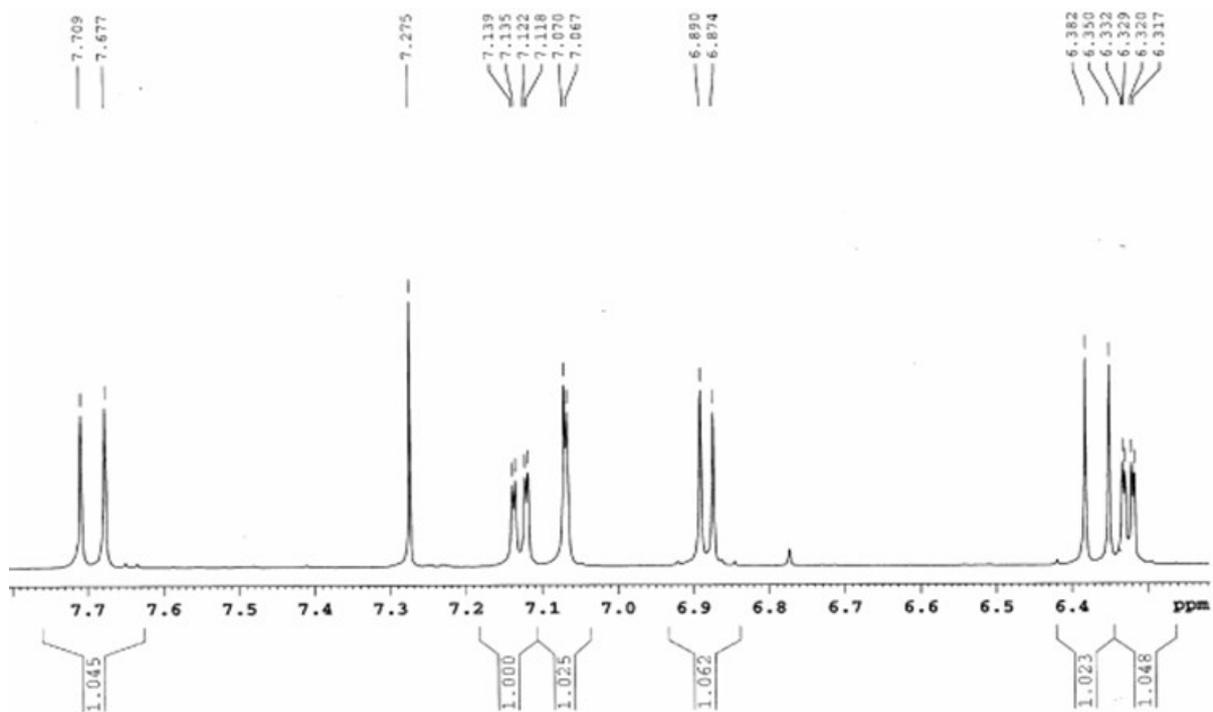
¹H-NMR spectrum (expansion) of compound **8**
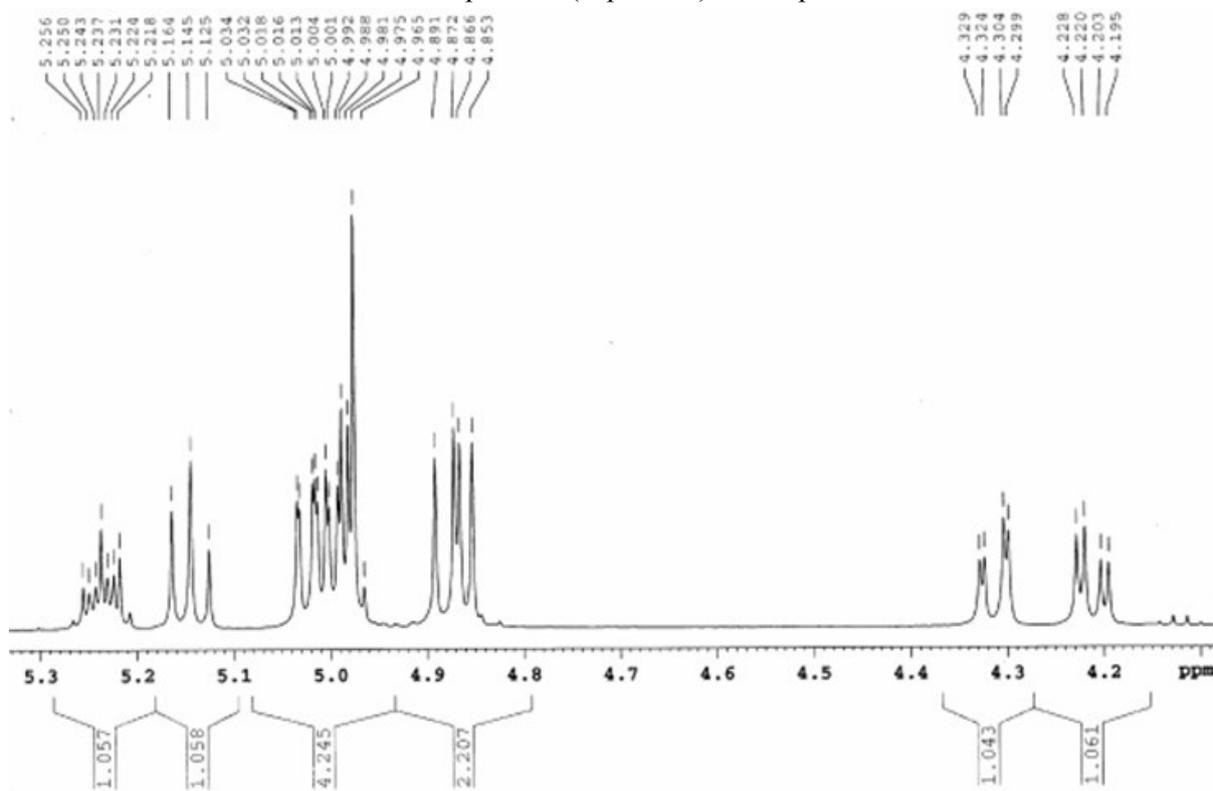
¹H-NMR spectrum (expansion) of compound **8**
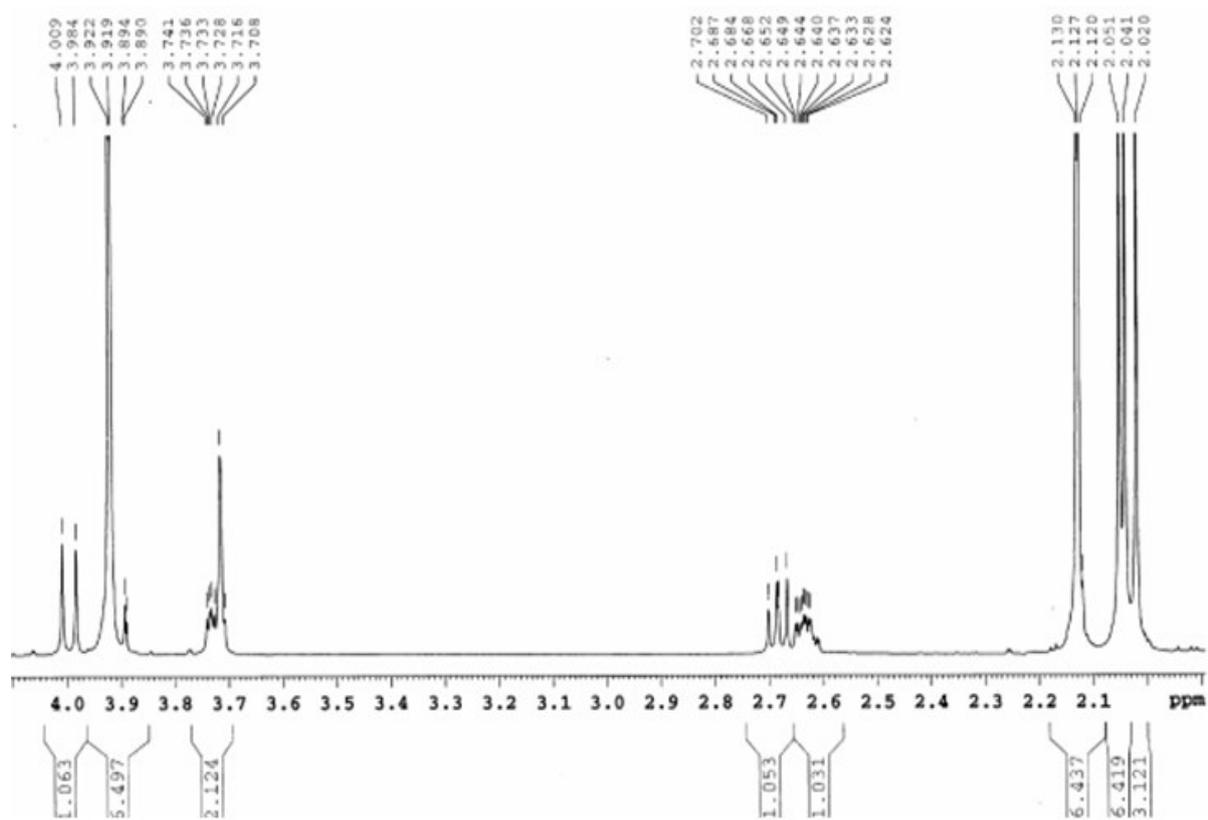
^{1}H-NMR spectrum (expansion) of compound **8**
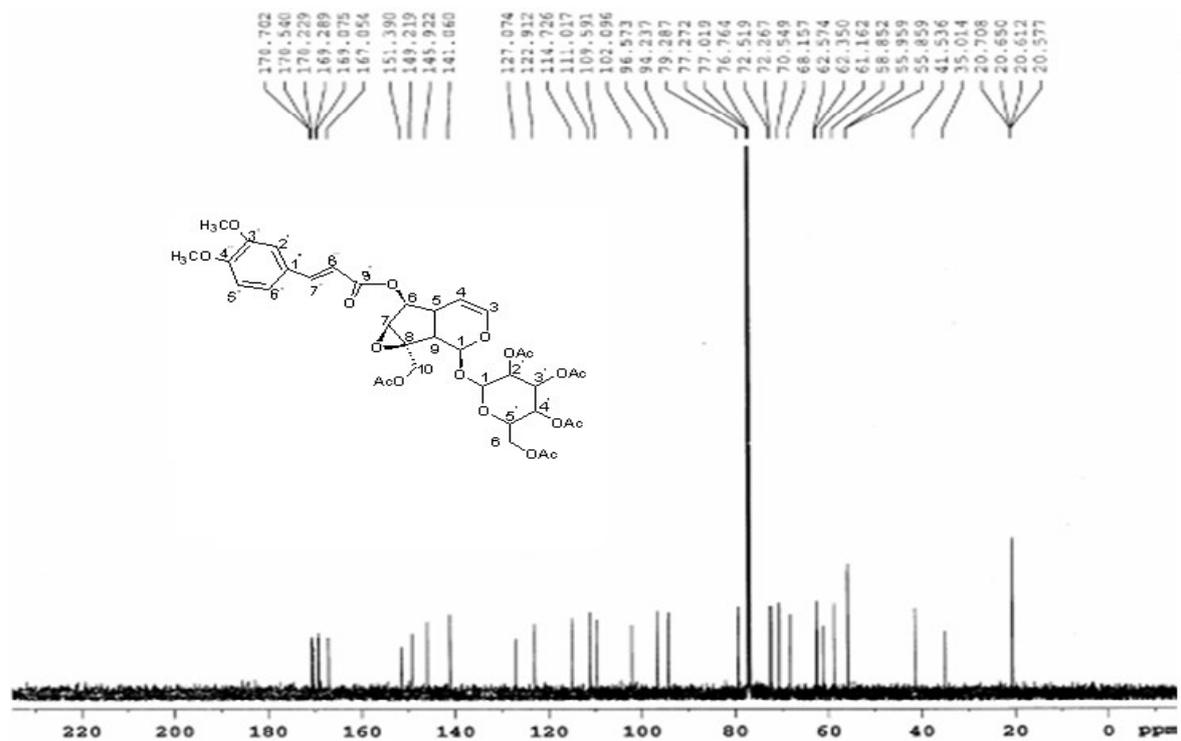
^{13}C-NMR spectrum of compound **8**
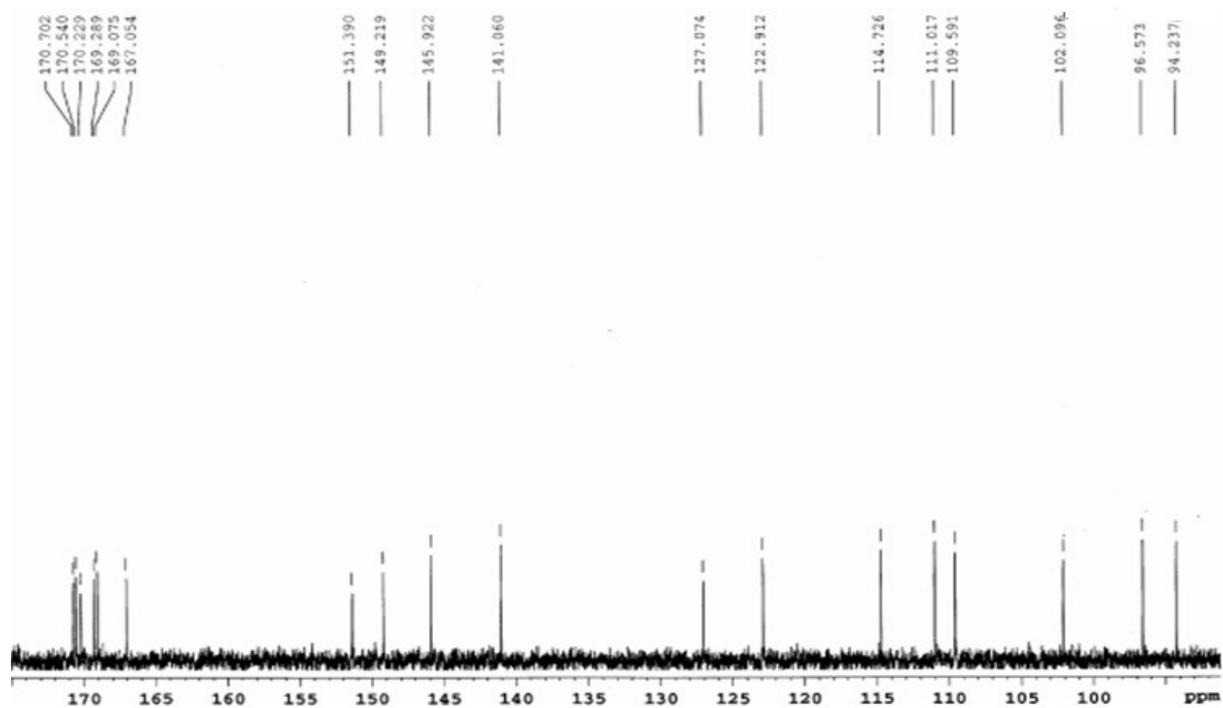
^{13}C-NMR spectrum (expansion) of compound **8**
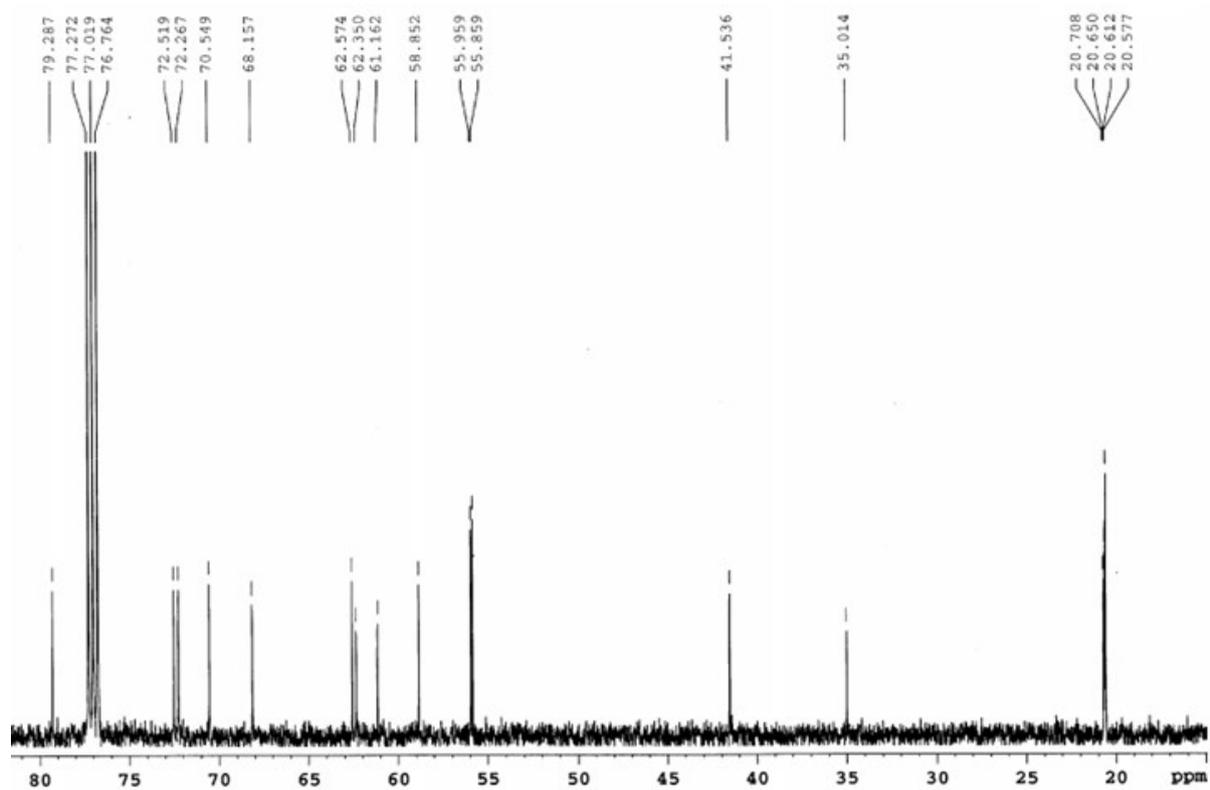
^{13}C-NMR spectrum (expansion) of compound **8**

DEPT spectrum of compound **8**
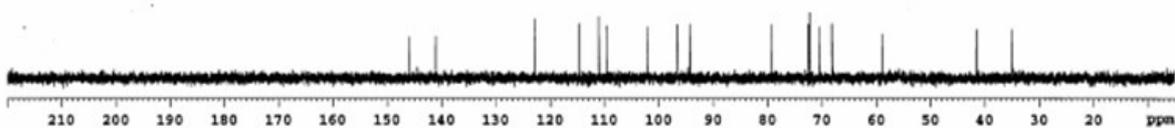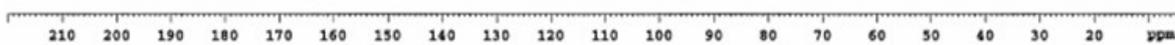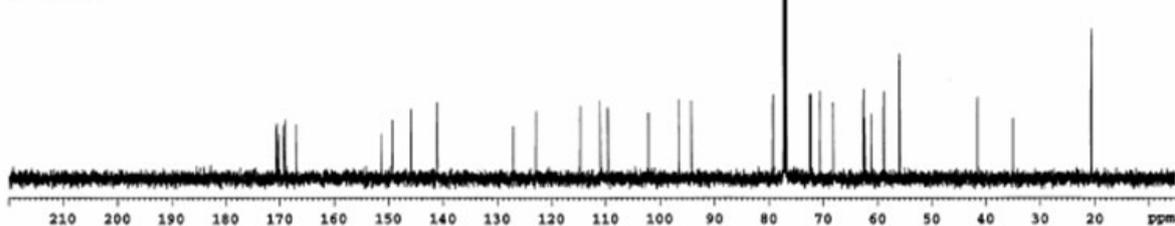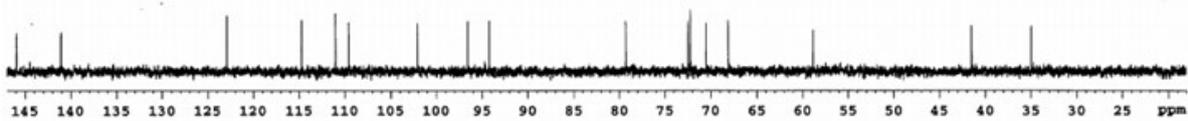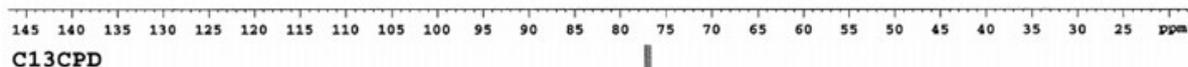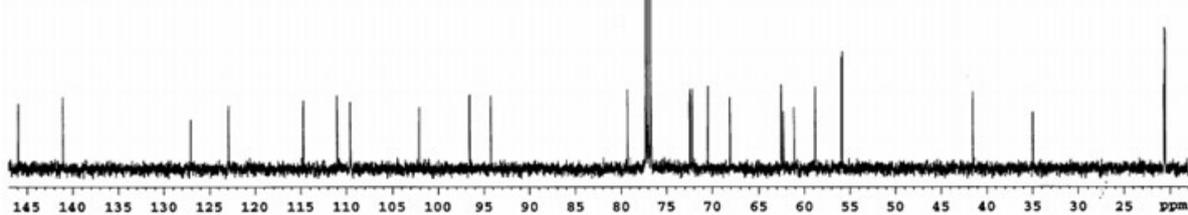
DEPT spectrum (expansion) of compound **8**

1.9. Compound 9

Sample name: QN1aceto2
**Operator: Le Anh VHH**
Method: +IDA TOF MS/MS
Date: 2021.02.26
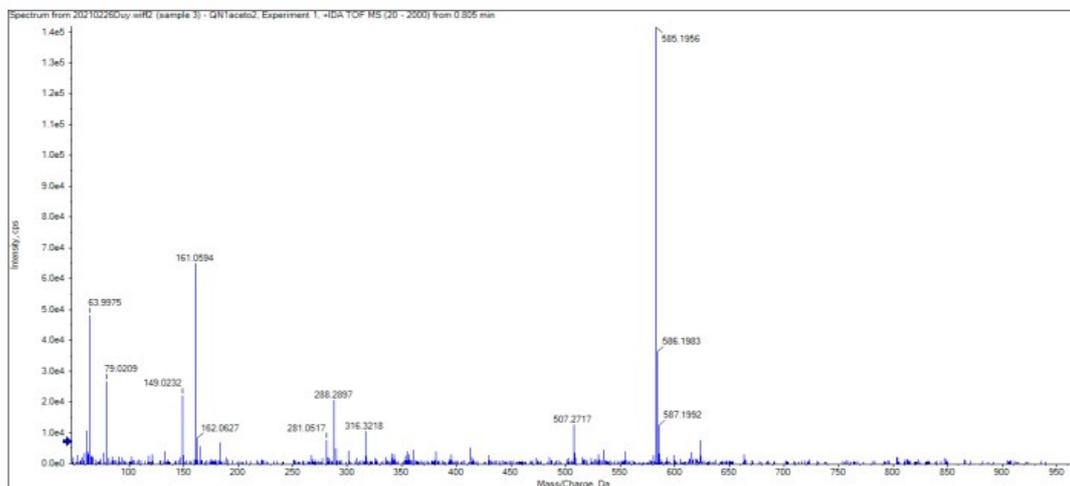
Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C28H34O12	585.19425	12.0	2.3	1			NA/NA

Device Model: SCIEX X500 QTOF

HR-ESI-MS spectrum of compound **9**
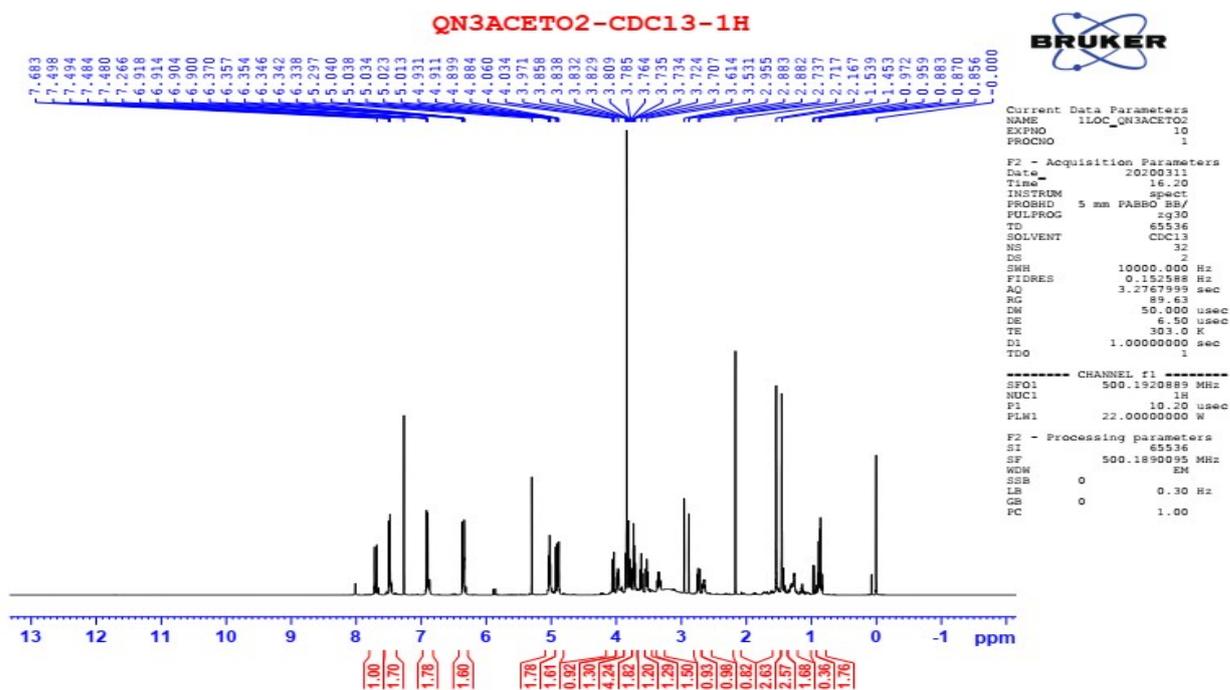
^{1}H-NMR spectrum of compound **9**
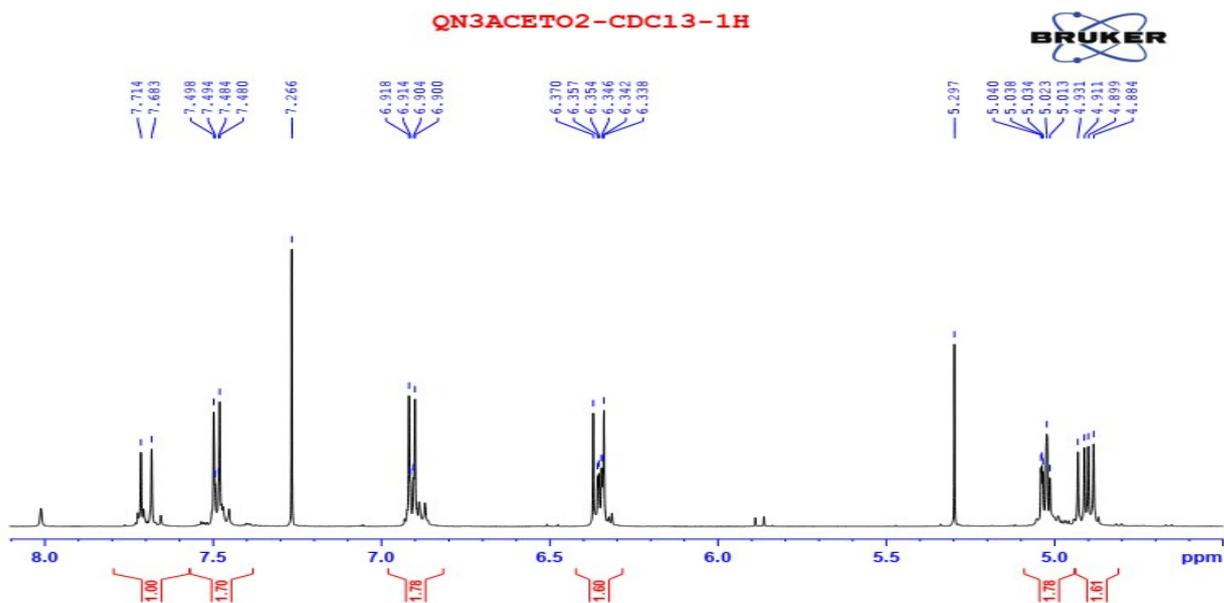
¹H-NMR spectrum (expansion) of compound **9**
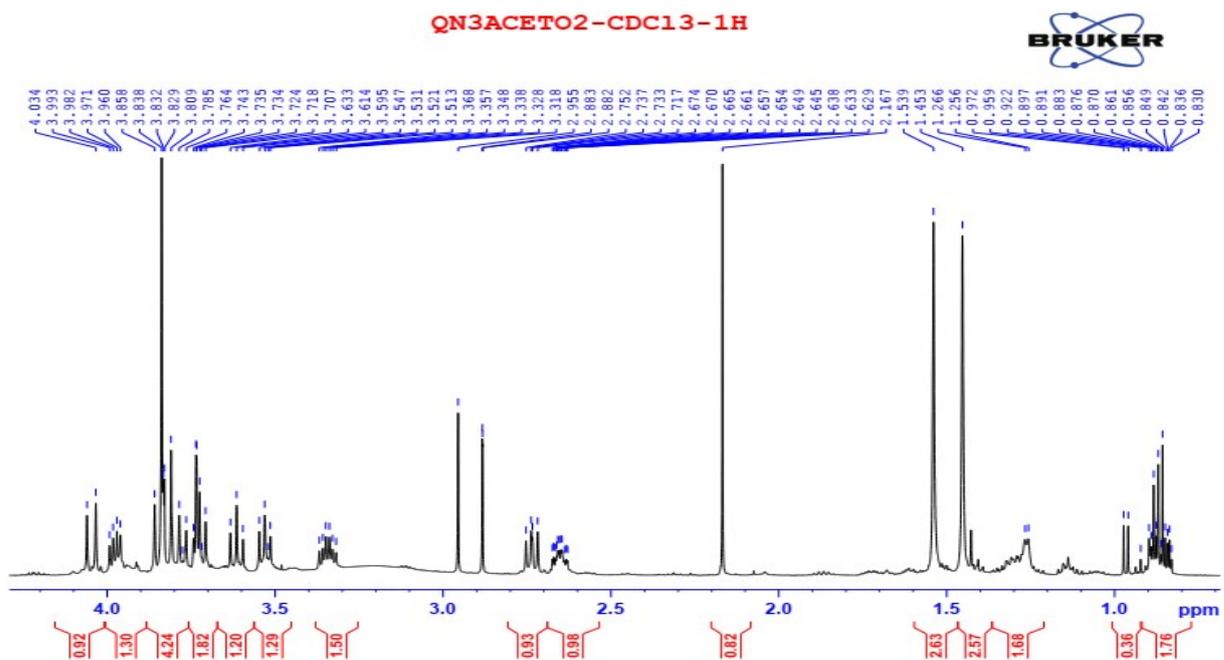
¹H-NMR spectrum (expansion) of compound **9**
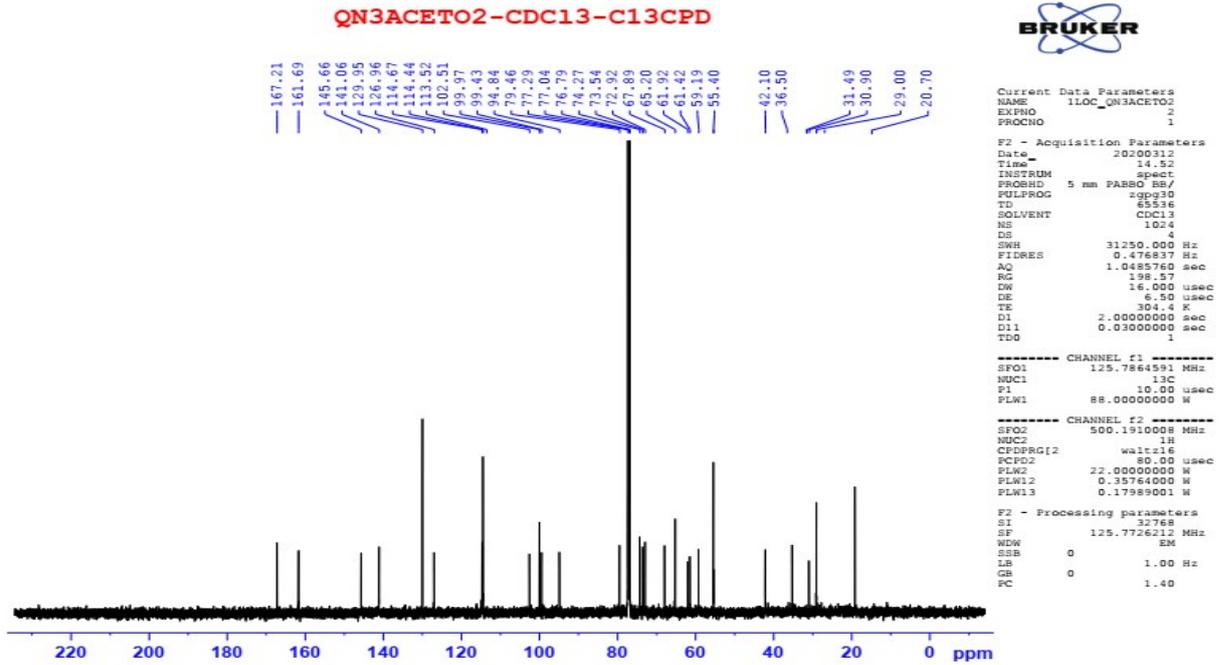
13C-NMR spectrum of compound **9**
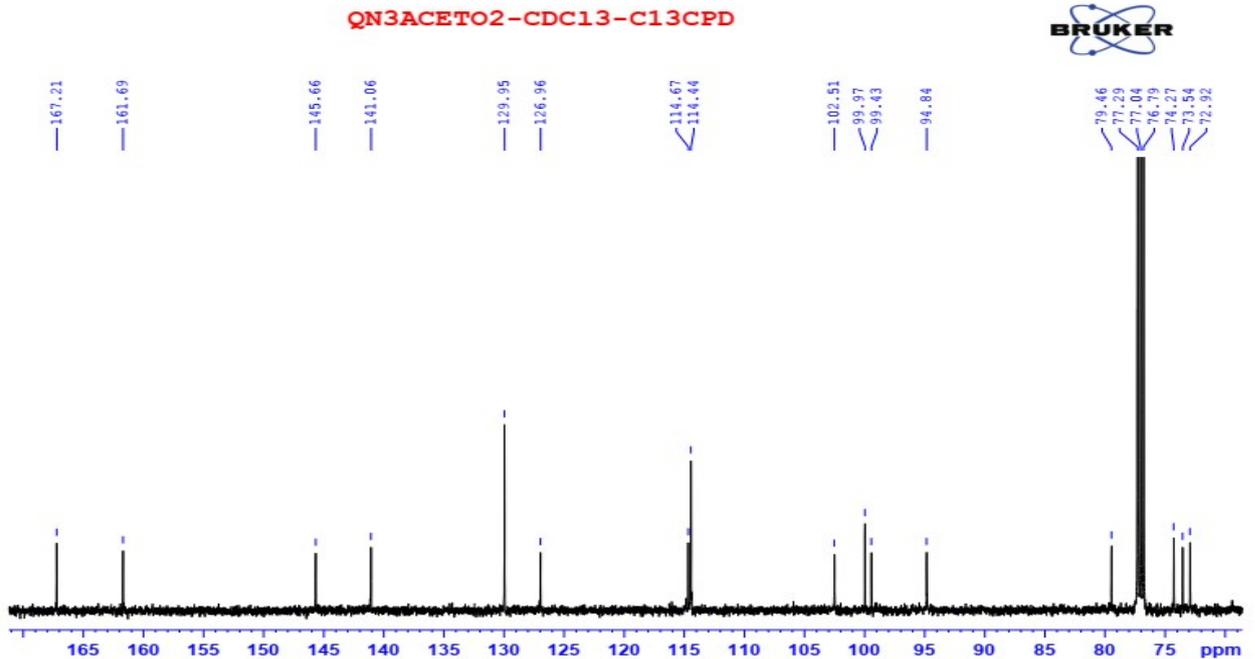
13C-NMR spectrum (expansion) of compound **9**

QN3ACETO2-CDC13-C13CPD

BRUKER

^{13}C-NMR spectrum (expansion) of compound **9**

QN3ACETO2-CDC13-C13CPD&DEPT

DEPT90

DEPT135

CH&CH3

CH2

C13CPD

DEPT spectrum of compound **9**

QN3ACETO2-CDC13-C13CPD&DEPT

DEPT spectrum (epansion) of compound **9**

QN3ACETO2-CDC13-C13CPD&DEPT
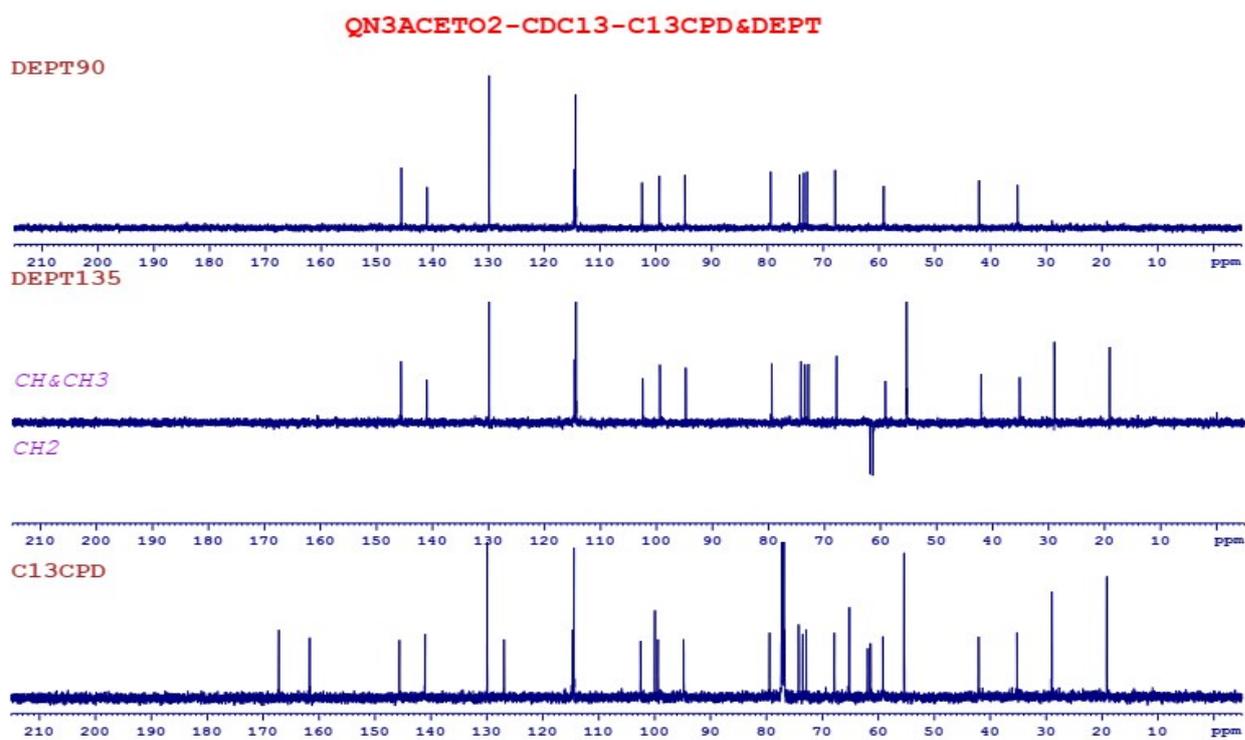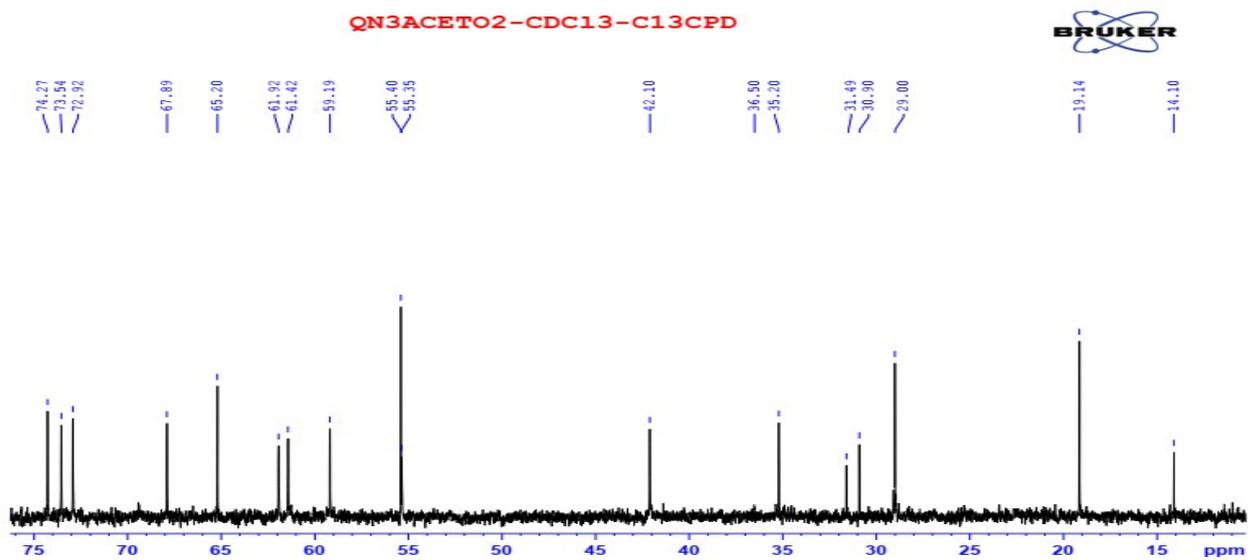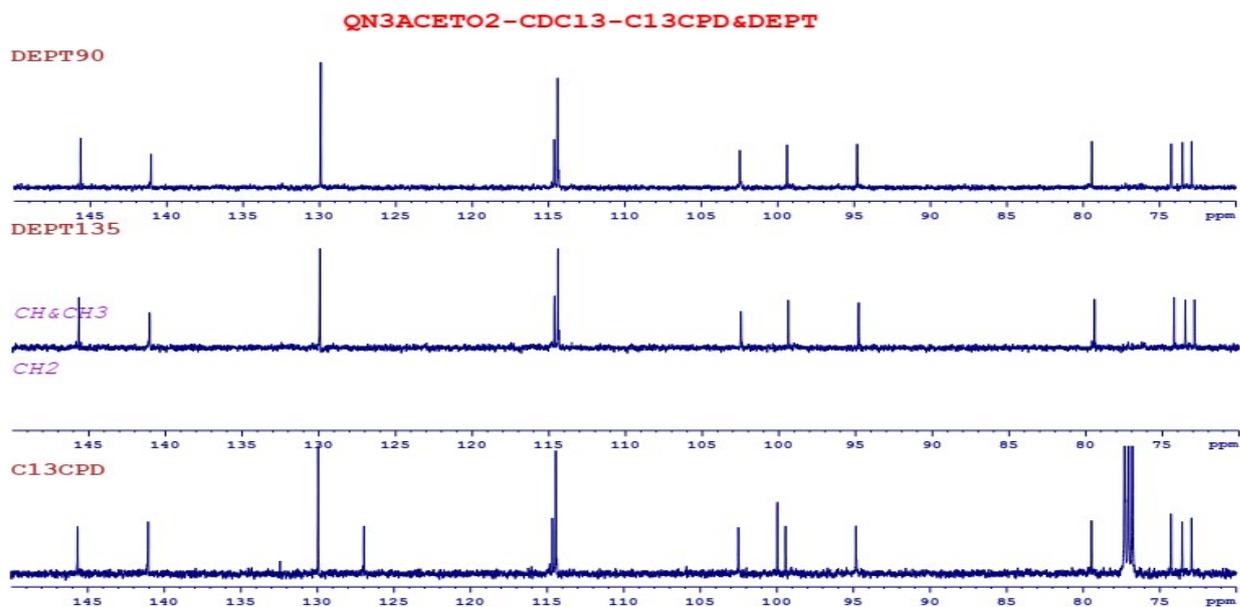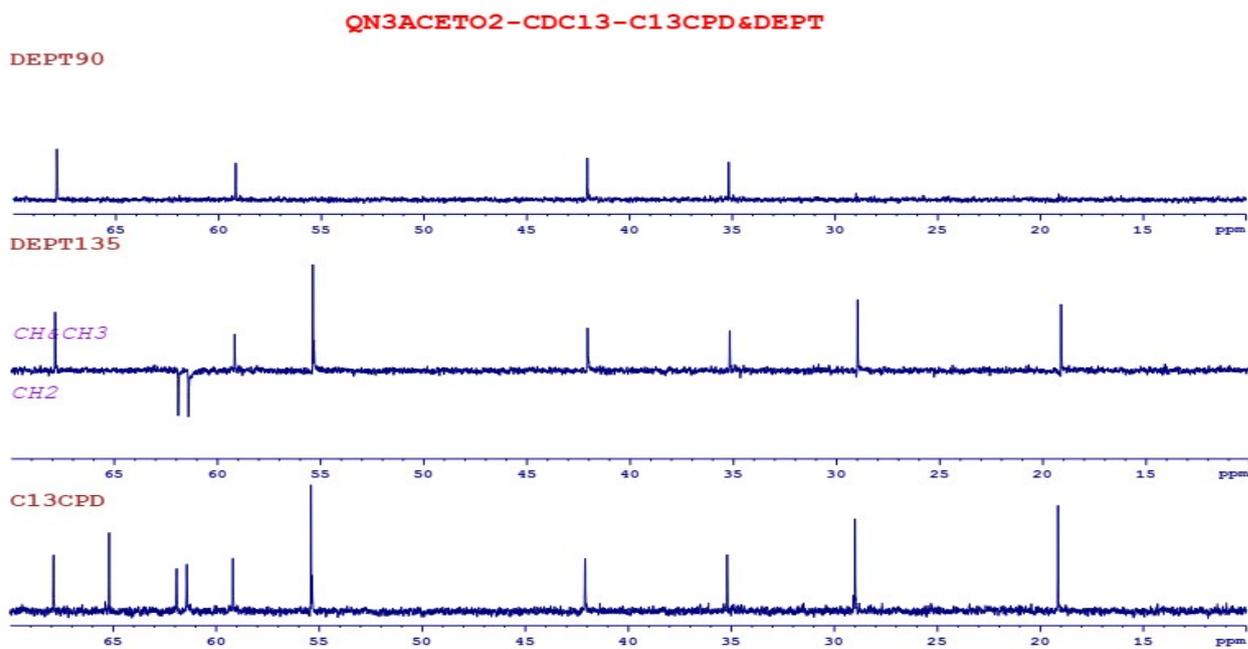
DEPT spectrum (epansion) of compound **9**

1.10. Compound 10

(+)-ESI-MS spectrum of compound **10**

(-)-ESI-MS spectrum of compound **10**

¹H-NMR spectrum of compound **10**

¹H-NMR spectrum (expansion) of compound **10**

^{1}H-NMR spectrum (expansion) of compound **10**

^{1}H-NMR spectrum (expansion) of compound **10**

COSY spectrum of compound **10**

COSY spectrum (expansion) of compound **10**
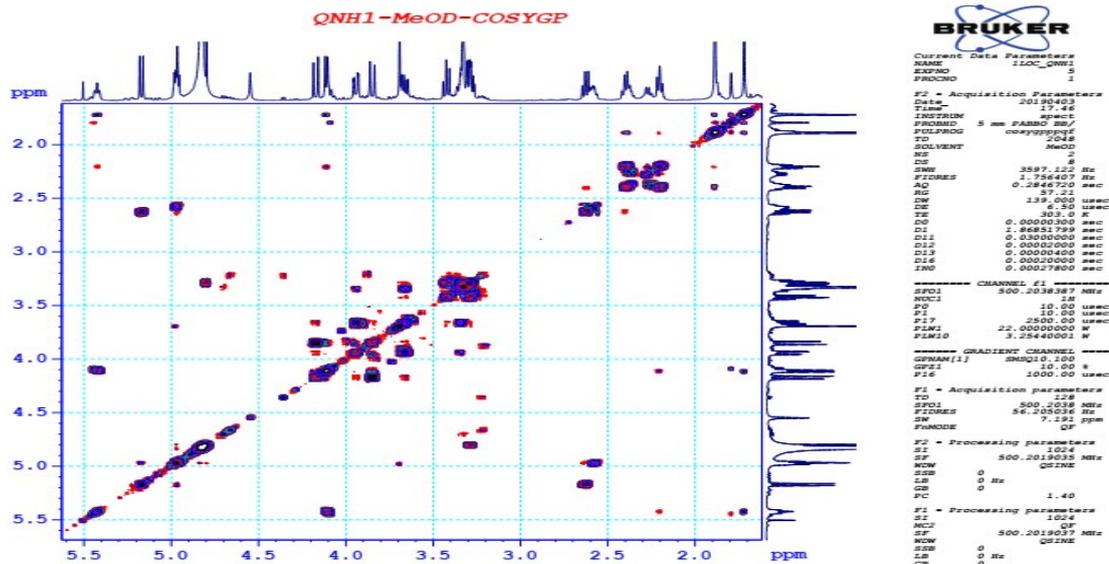
COSY spectrum (expansion) of compound **10**
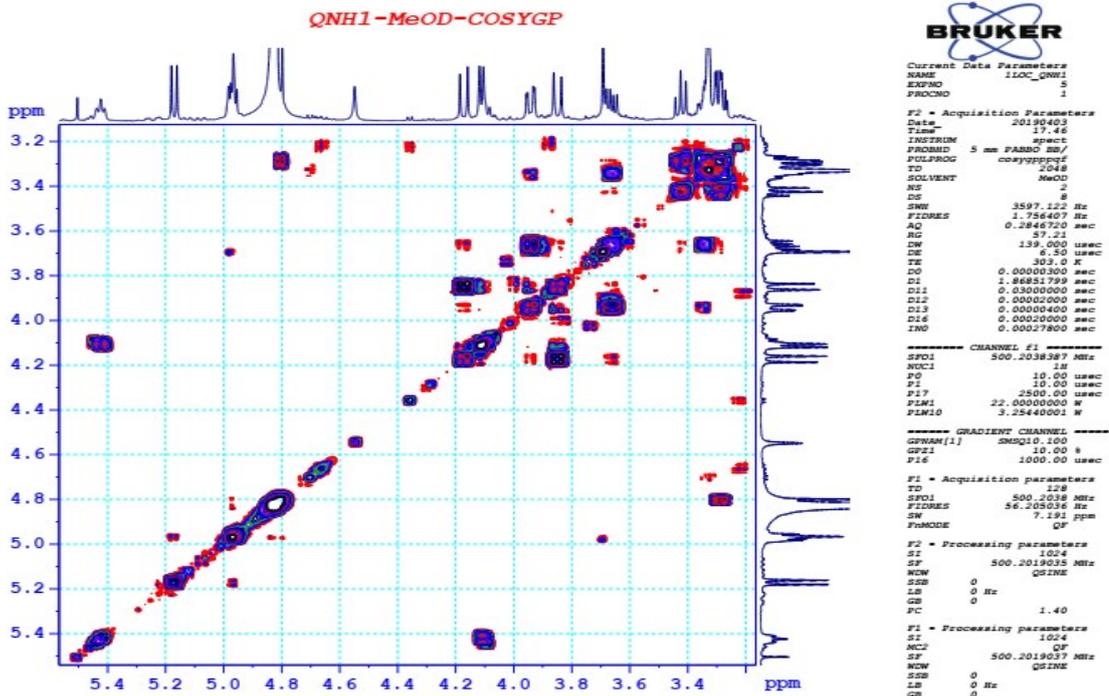
COSY spectrum (expansion) of compound **10**
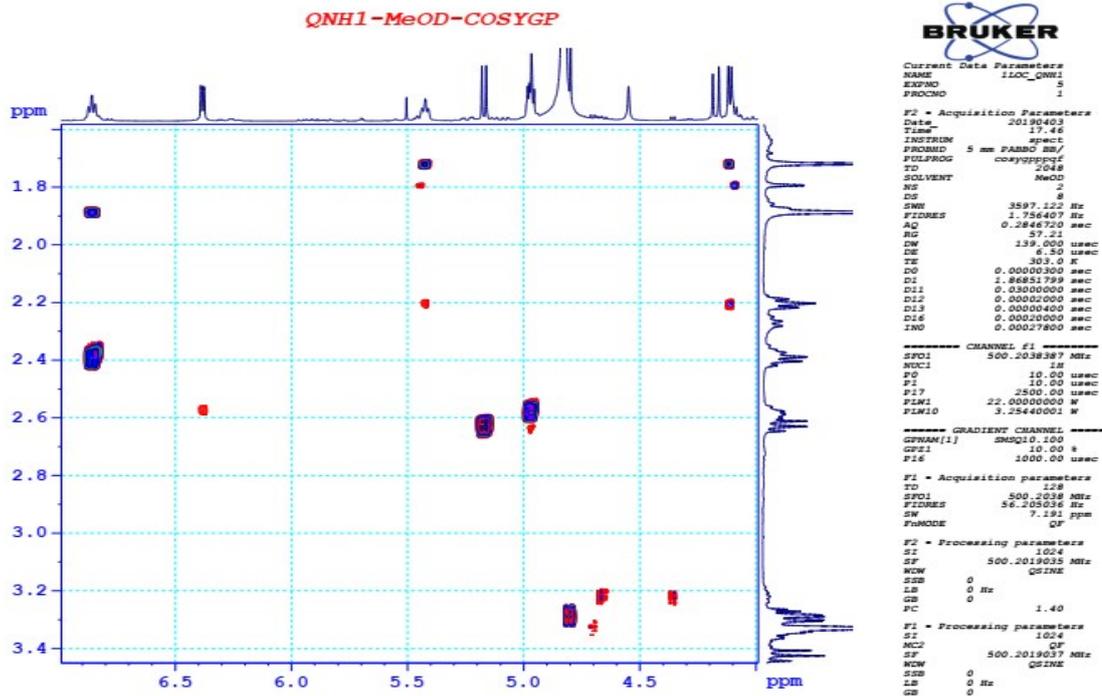
COSY spectrum (expansion) of compound **10**
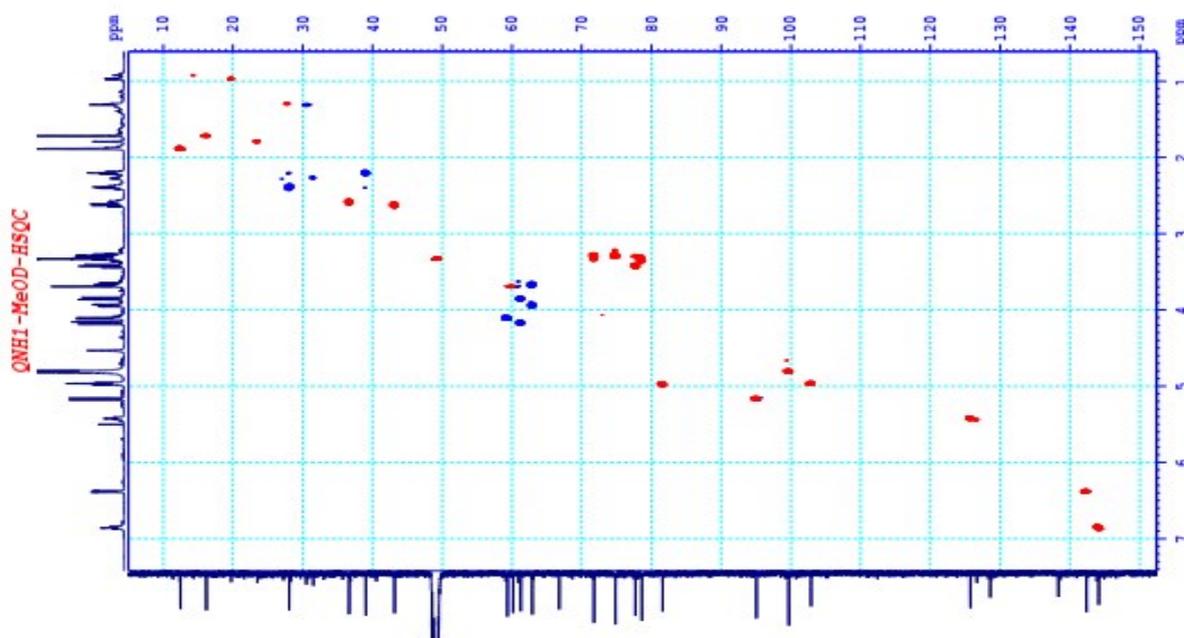
HSQC spectrum of compound **10**
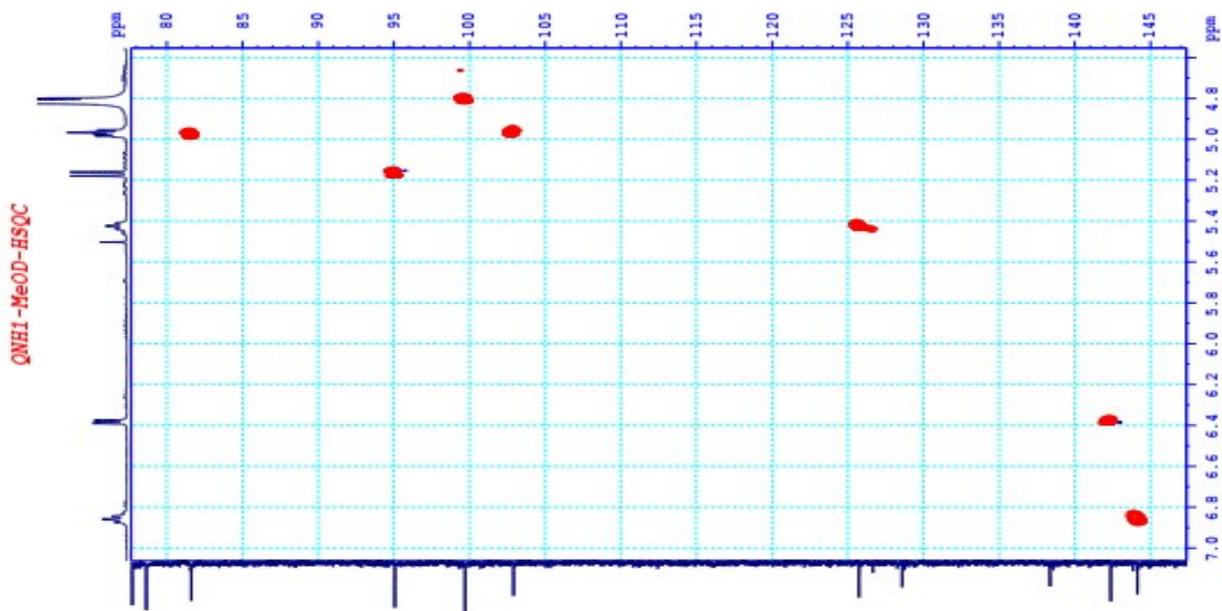
HSQC spectrum (epansion) of compound **10**
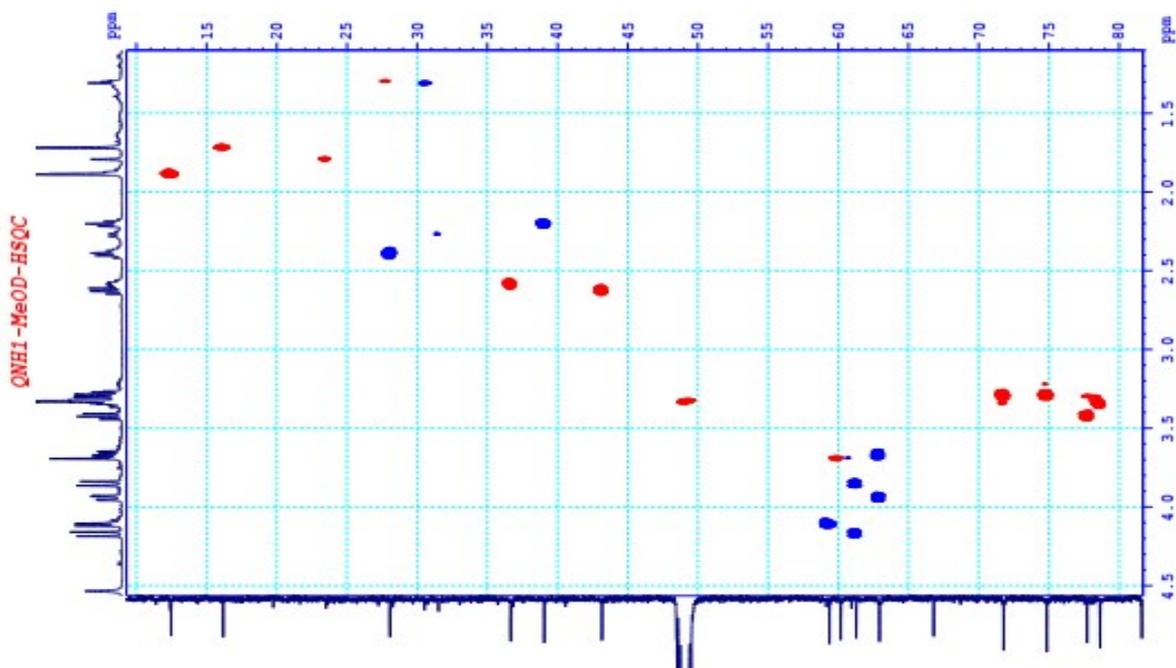
HSQC spectrum (epansion) of compound **10**
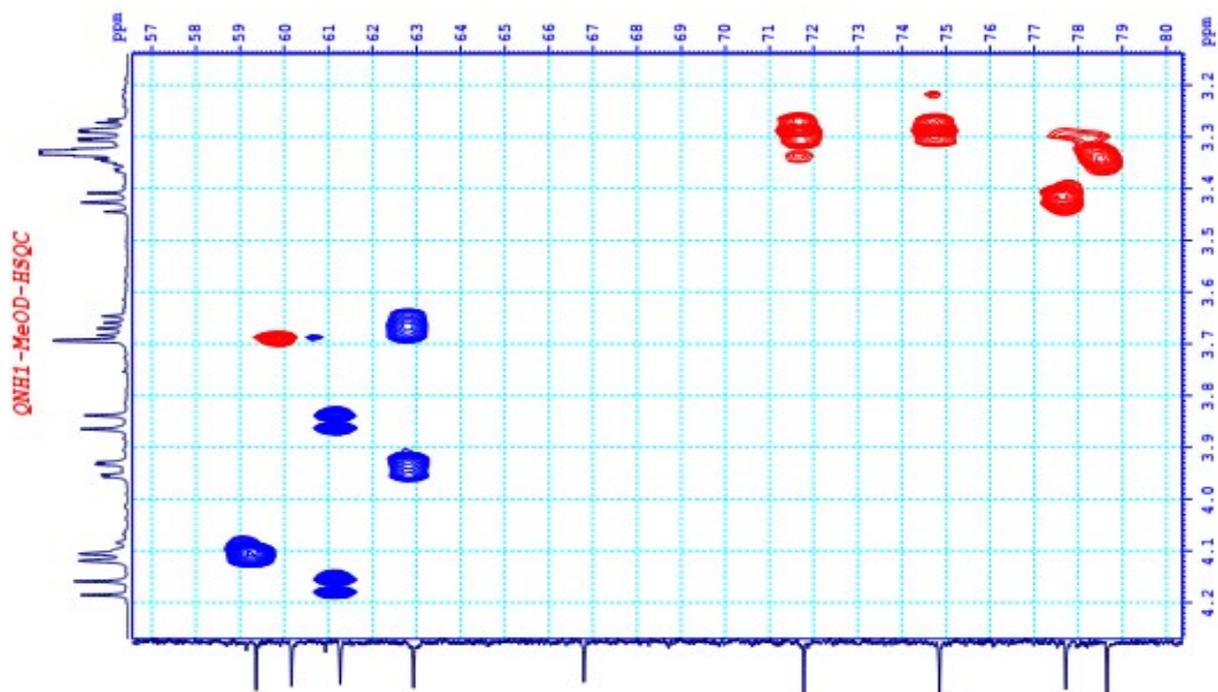
HSQC spectrum (epansion) of compound **10**
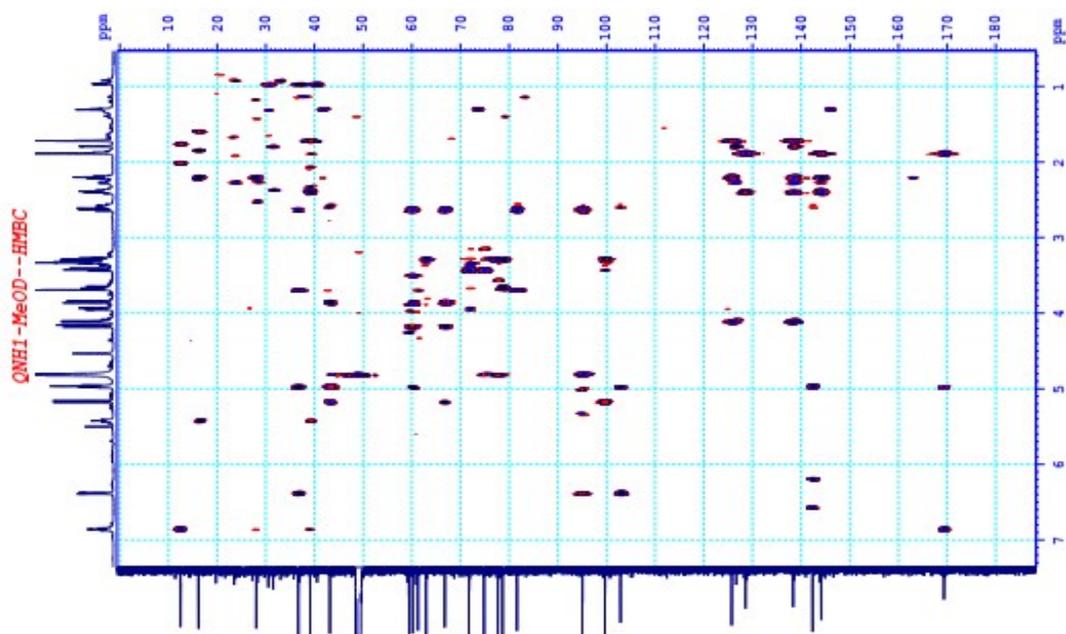
HMBC spectrum of compound **10**
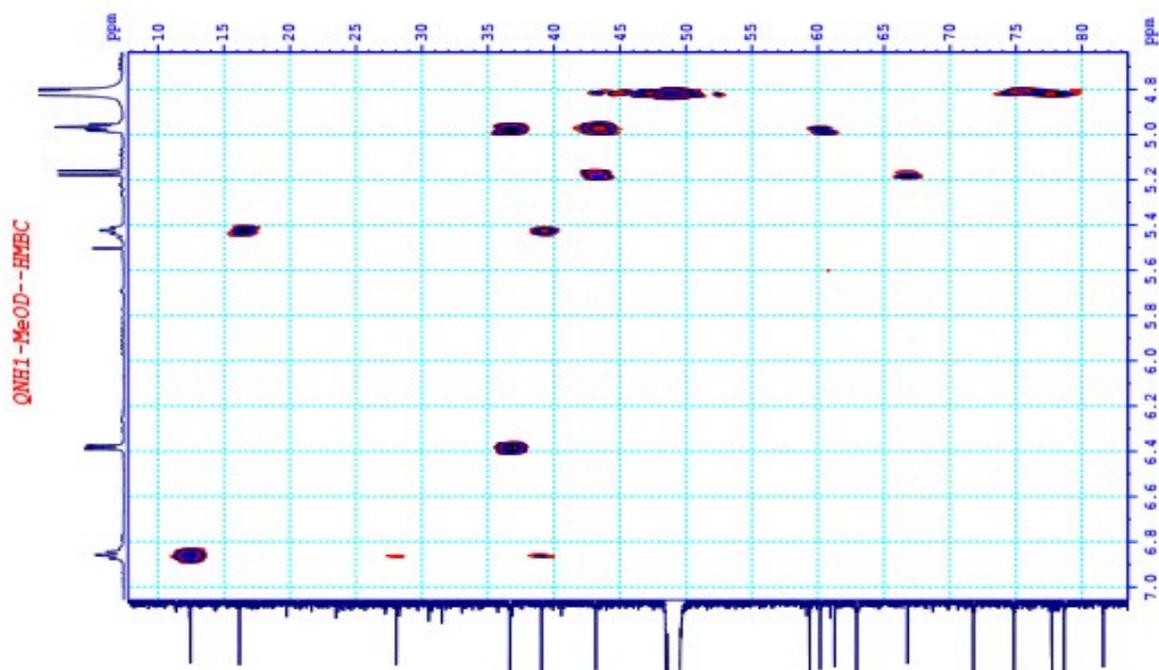
HMBC spectrum (epansion) of compound **10**
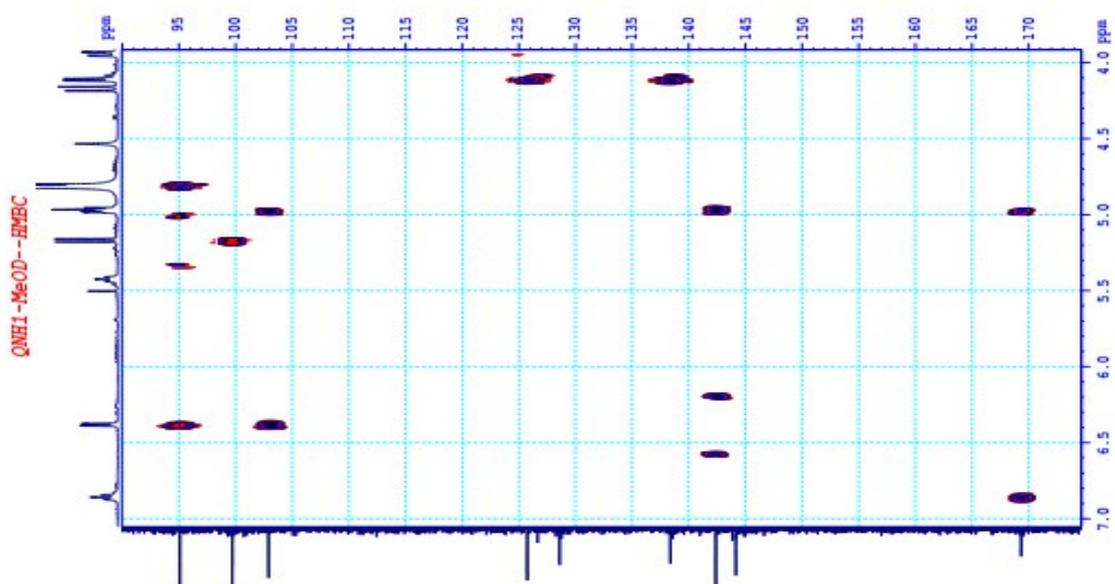
HMBC spectrum (epansion) of compound **10**
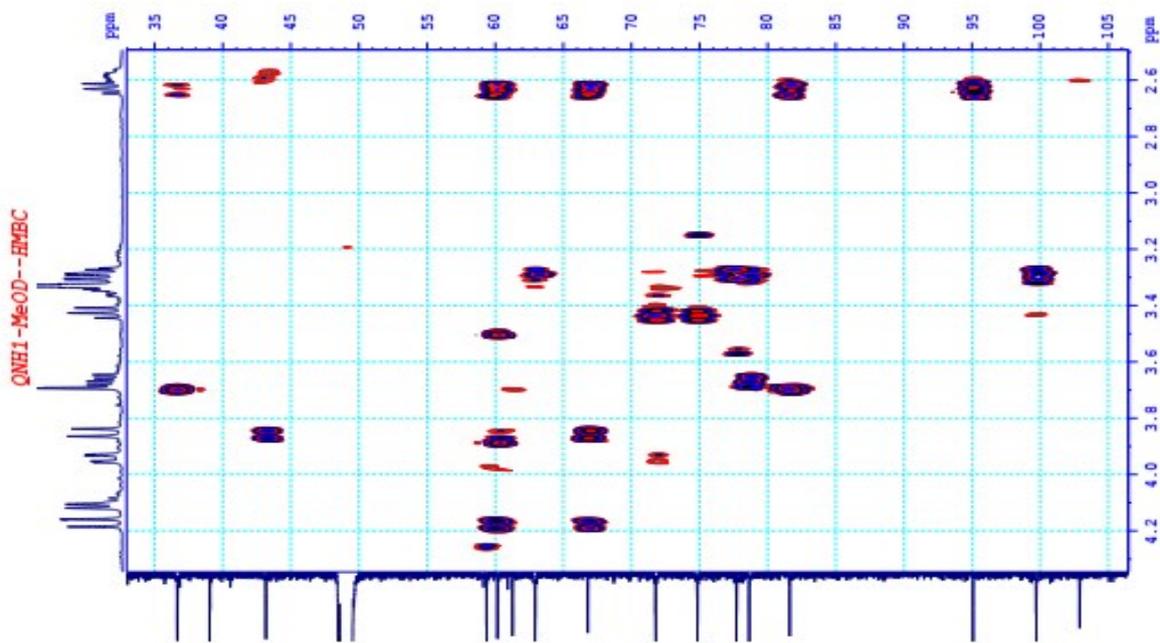
HMBC spectrum (epansion) of compound **10**
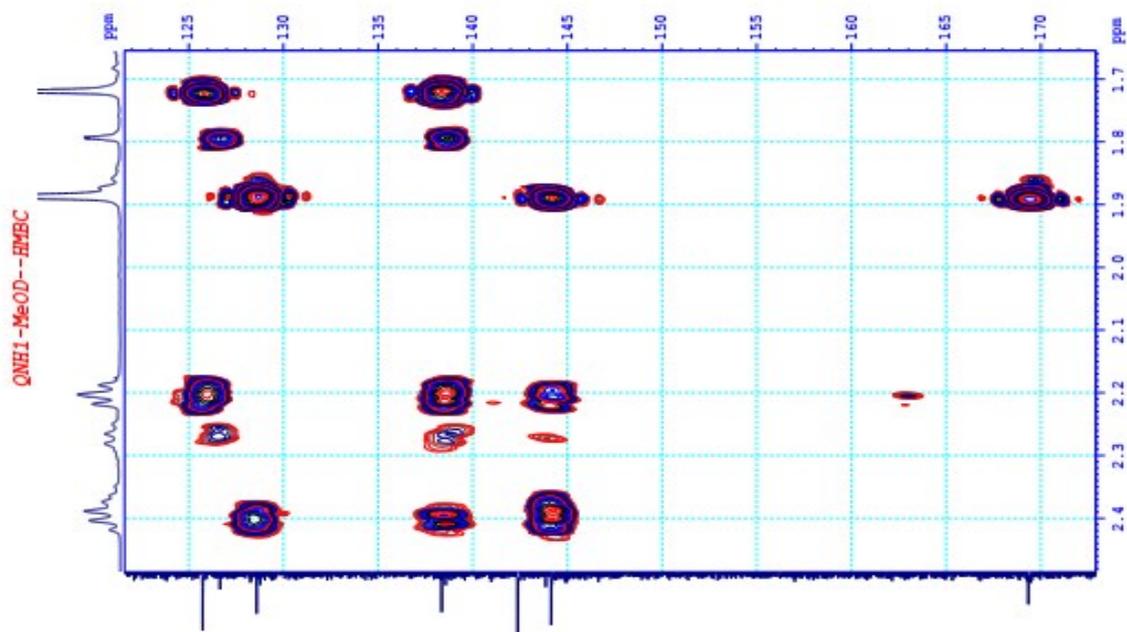
HMBC spectrum (epansion) of compound **10**
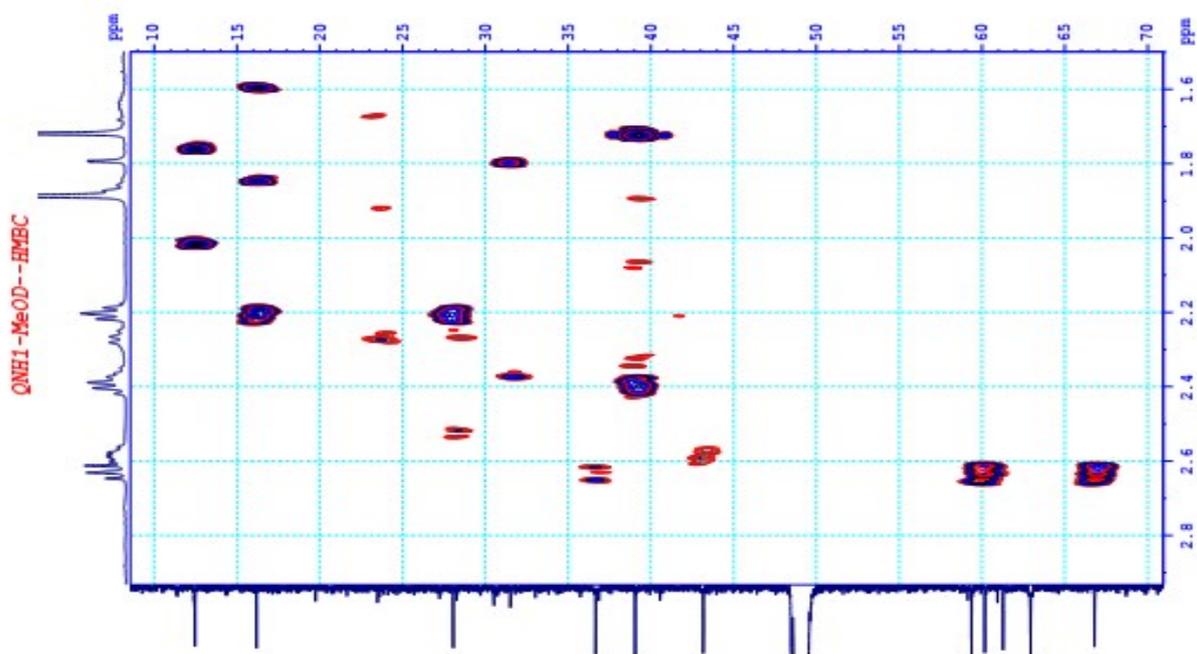
HMBC spectrum (epansion) of compound **10**

1.11. Compound 11
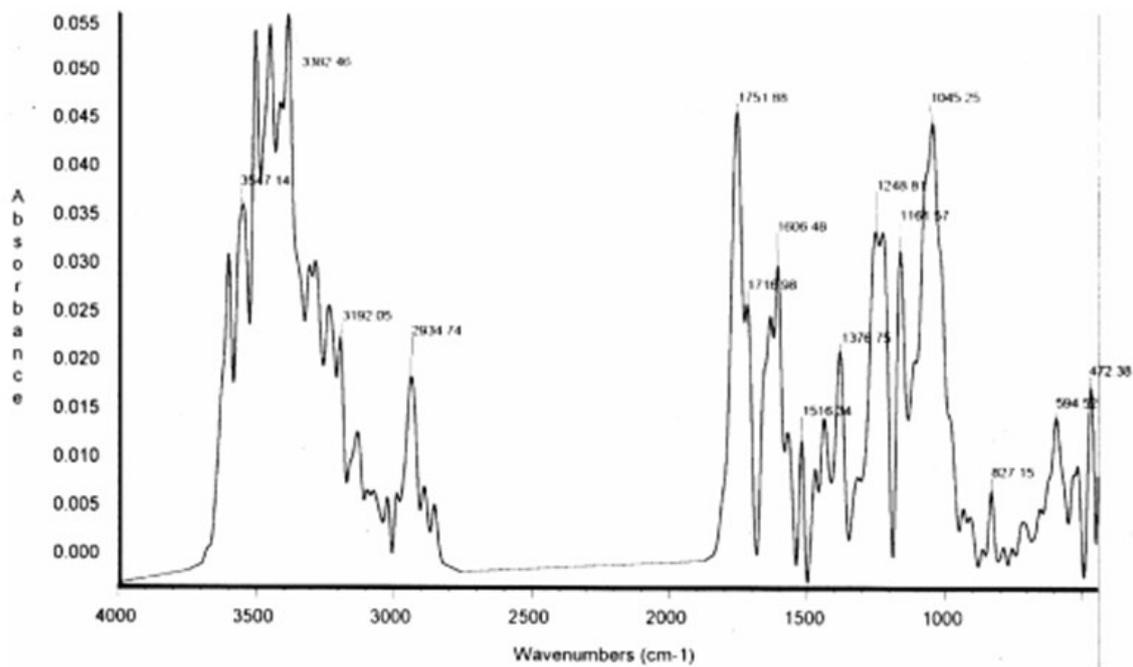
IR spectrum of compound **11**

Display Report - Selected Window Selected

Analysis Name: Thanh-AcQn316.d **Instrume** LC-MSD-Trap-SL **Print Da** 5/22/20 2:30:59
Method: Quang_2015.m **Operator:** 2195410AE0000514 **Acq. Dat** 5/22/2015 PM
Sample Na Thanh-AcQn316 2:28:53 PM
Analysis Inf
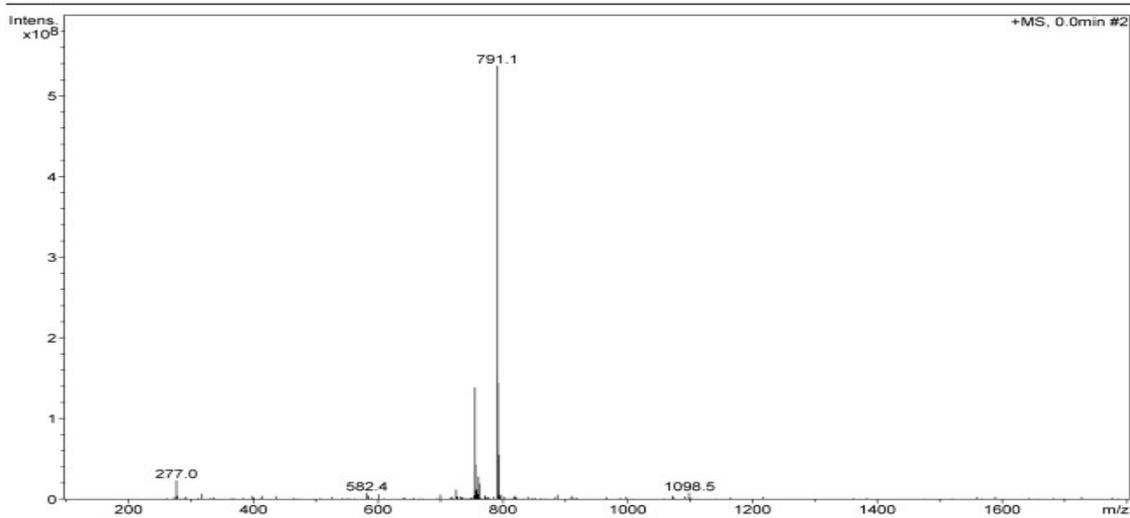
(+)-ESI-MS spectrum of compound **11**
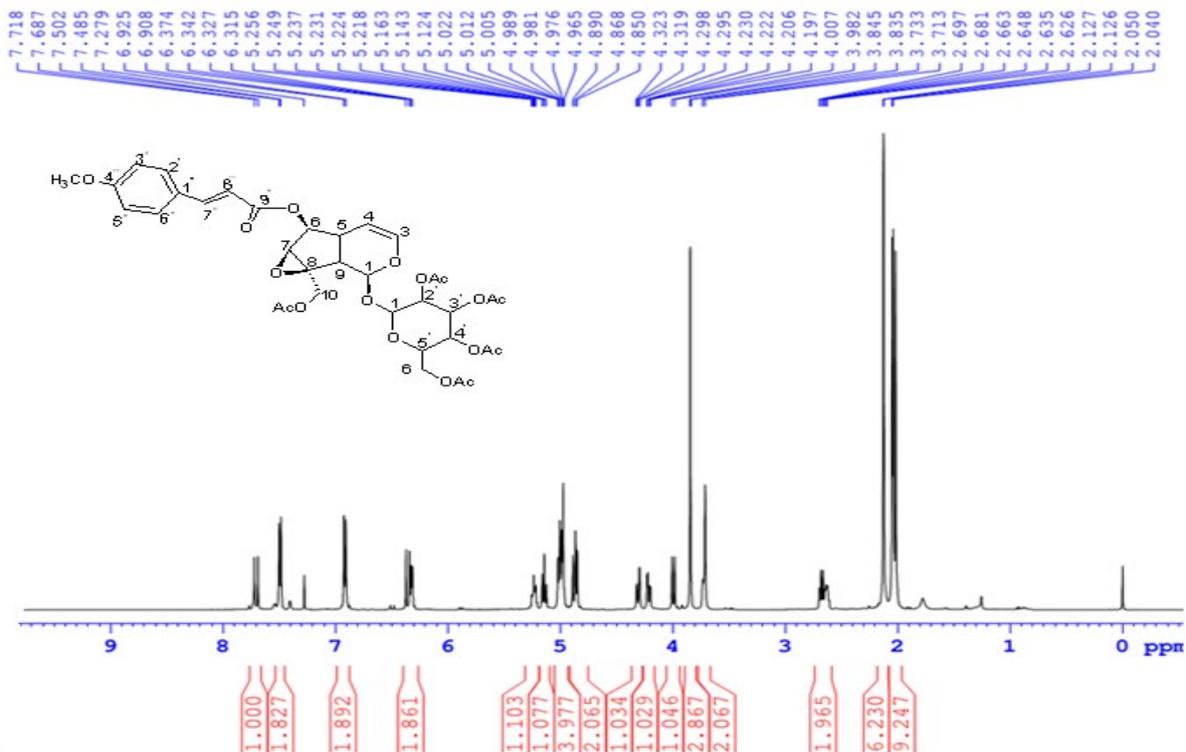
^{1}H-NMR spectrum (500 MHz, CDCl$_3$) of compound **11**
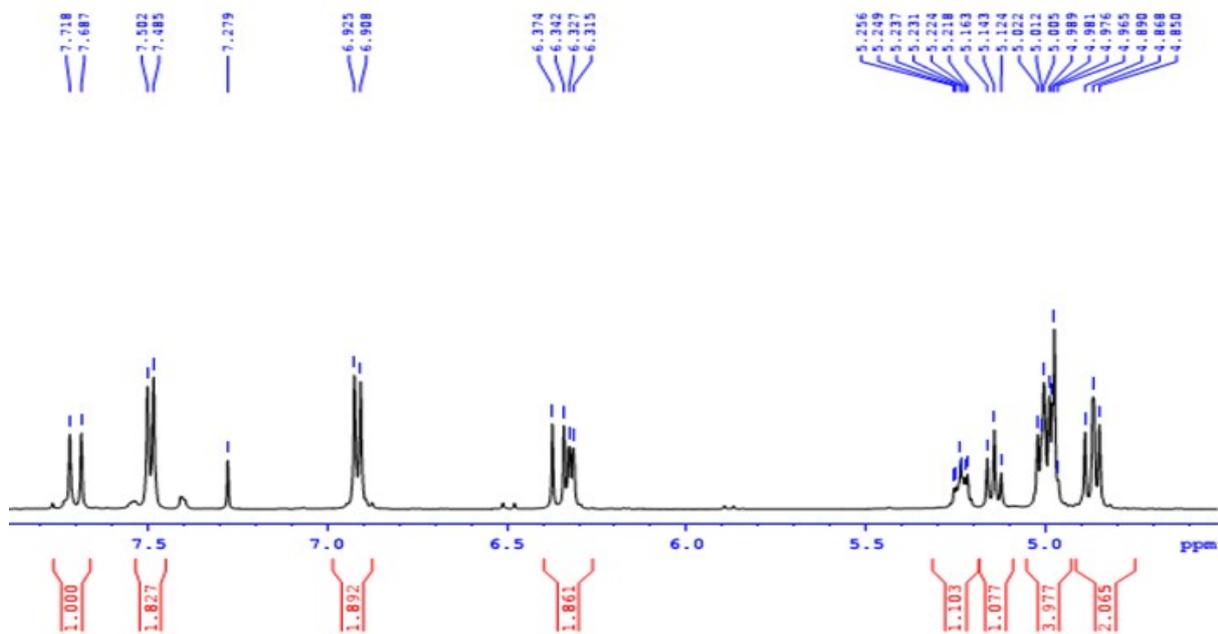
^{1}H-NMR spectrum (expansion) of compound **11**
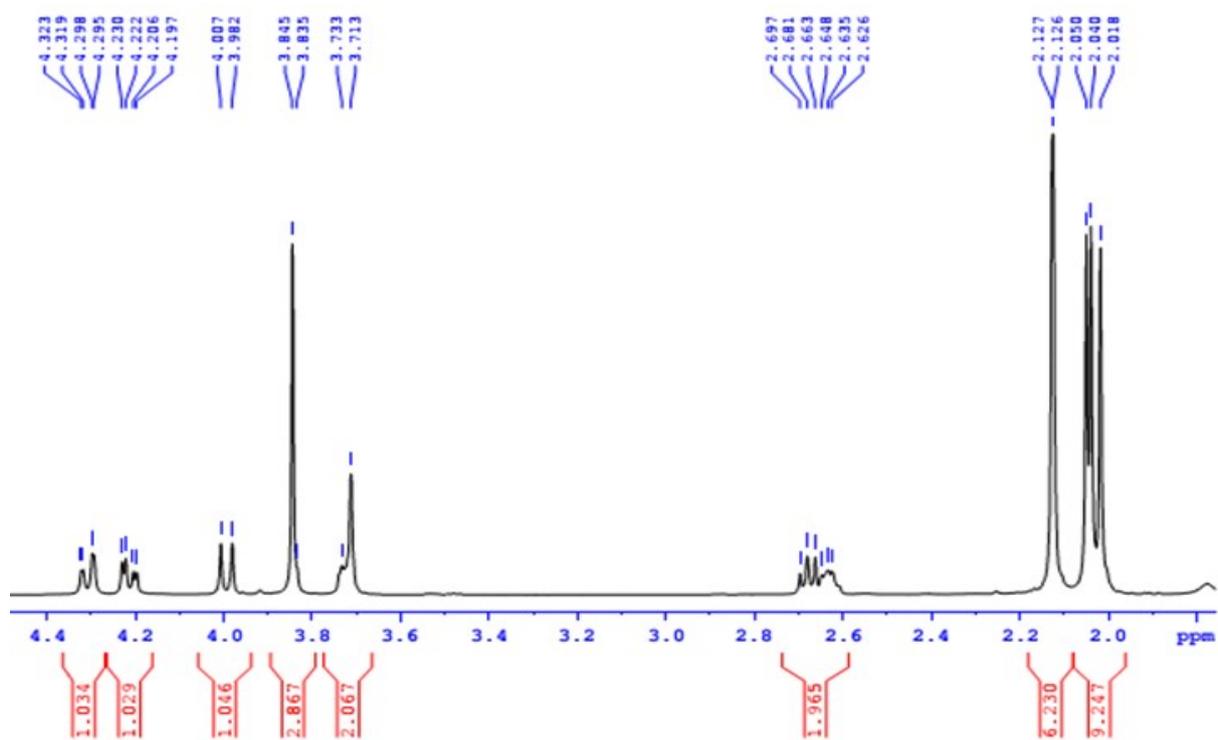
^{1}H-NMR spectrum (expansion) of compound **11**
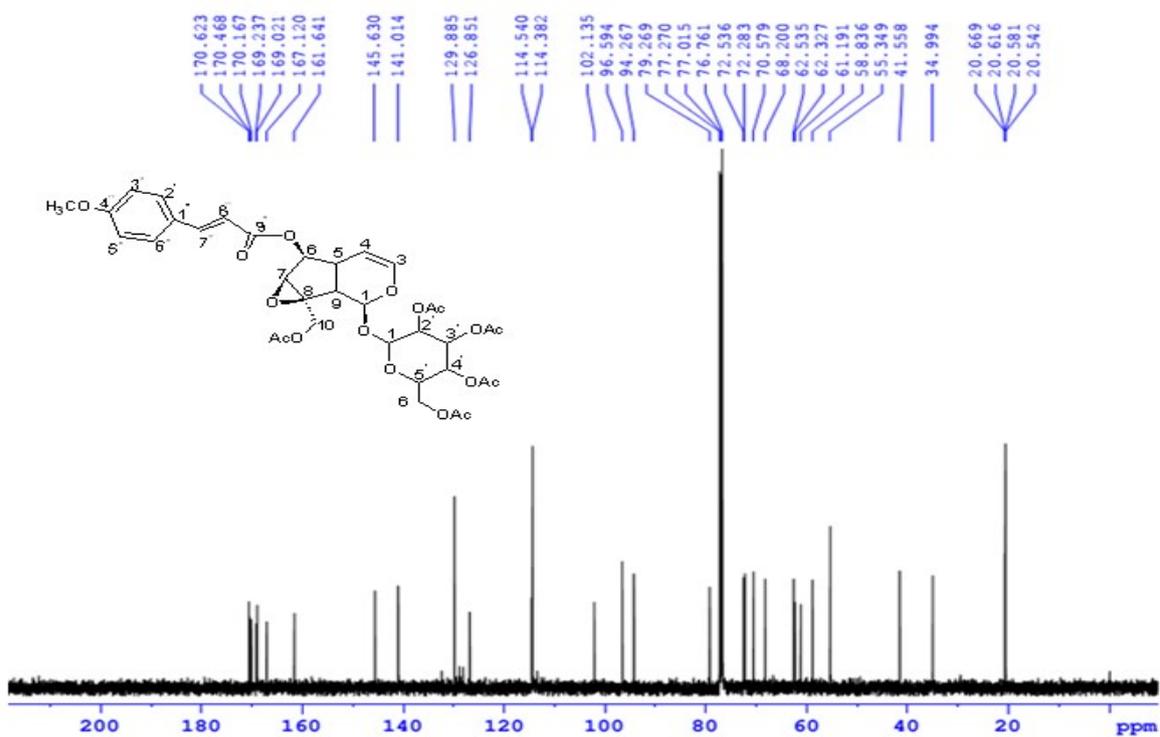
^{13}C-NMR (125 MHz, CDCl$_3$) spectrum of compound **11**
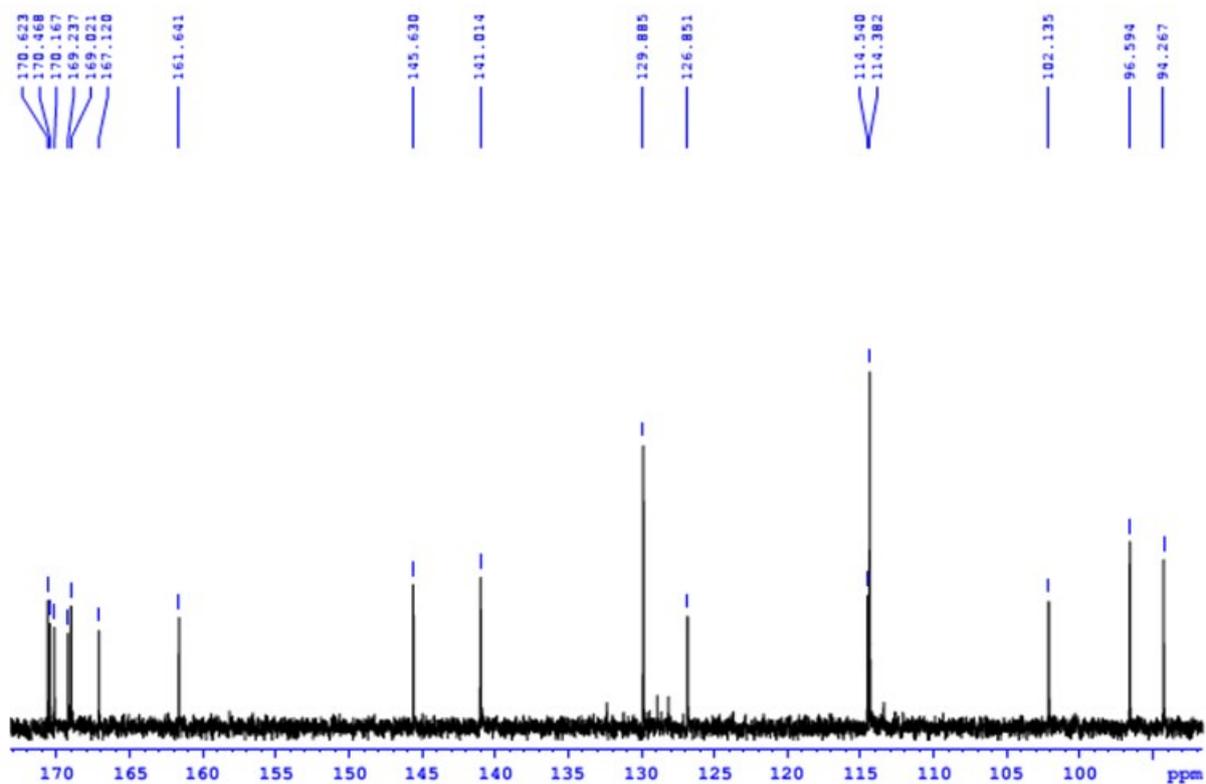
^{13}C-NMR spectrum (expansion) of compound **11**
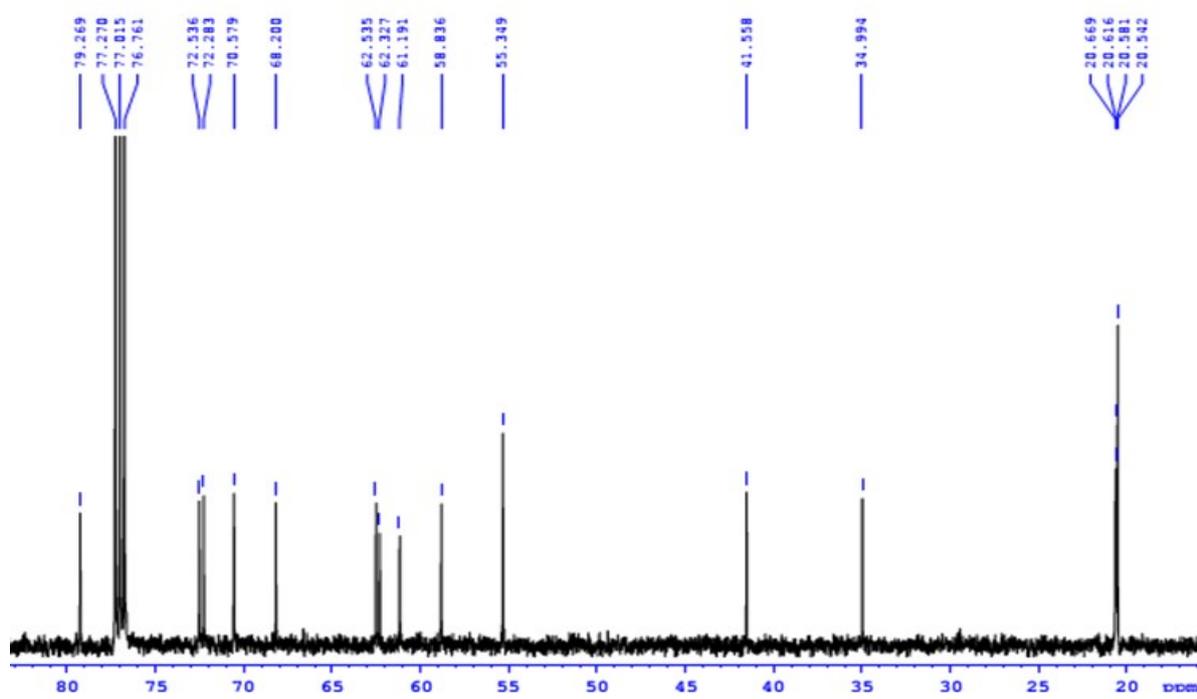

^{13}C-NMR spectrum (expansion) of compound **11**
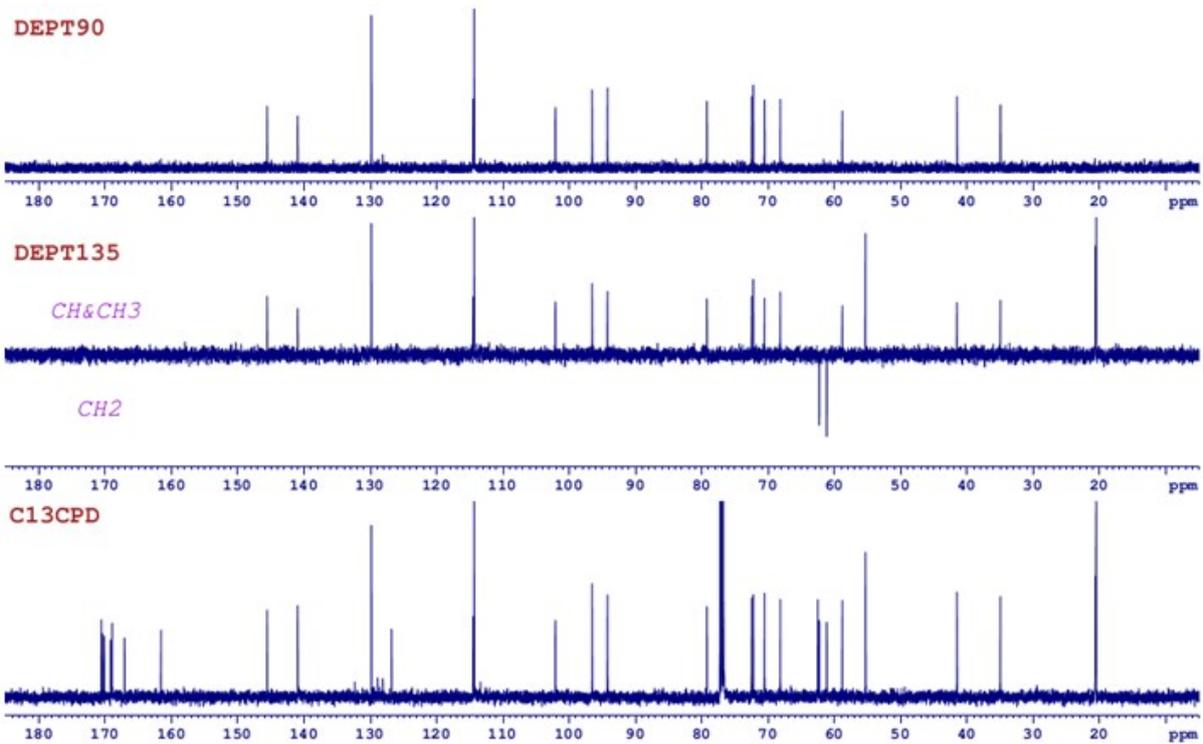
DEPT spectrum of compound **11**

1.12. Compound 12

Display Report - Selected Window Selected Analysis

Analysis Name:	AcQNL3-19.d	**Instrument:**	LC-MSD-Trap-SL	**Print Date:**	2/25/2016 2:47:40 PM
Method:	QUANG_2015.M	**Operator:**	2195410AE0000514	**Acq. Date:**	2/25/2016 2:44:49 PM
Sample Name:	AcQNL3-19				
Analysis Info:	D1				
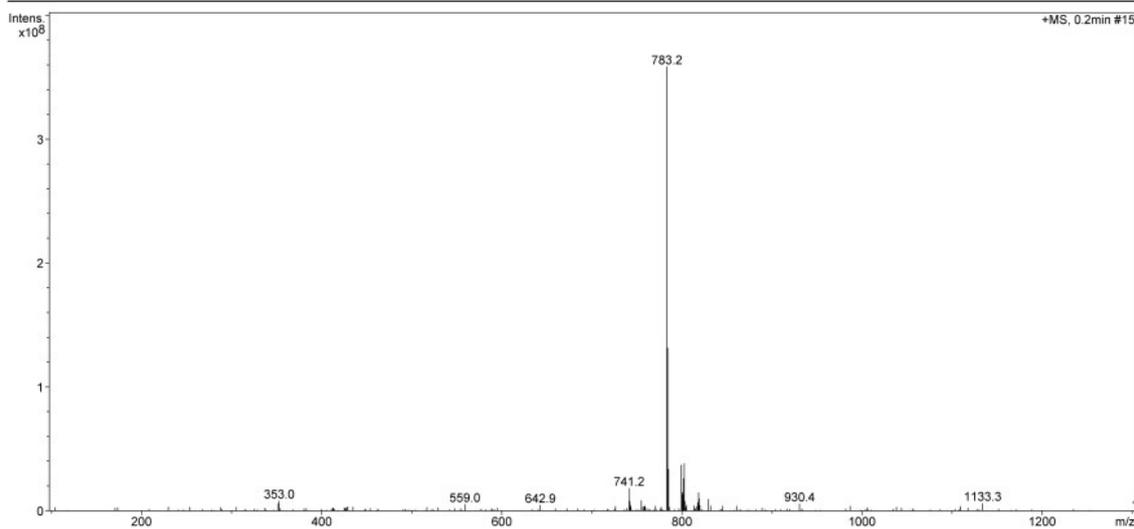
(+)-ESI-MS spectrum of compound **12**
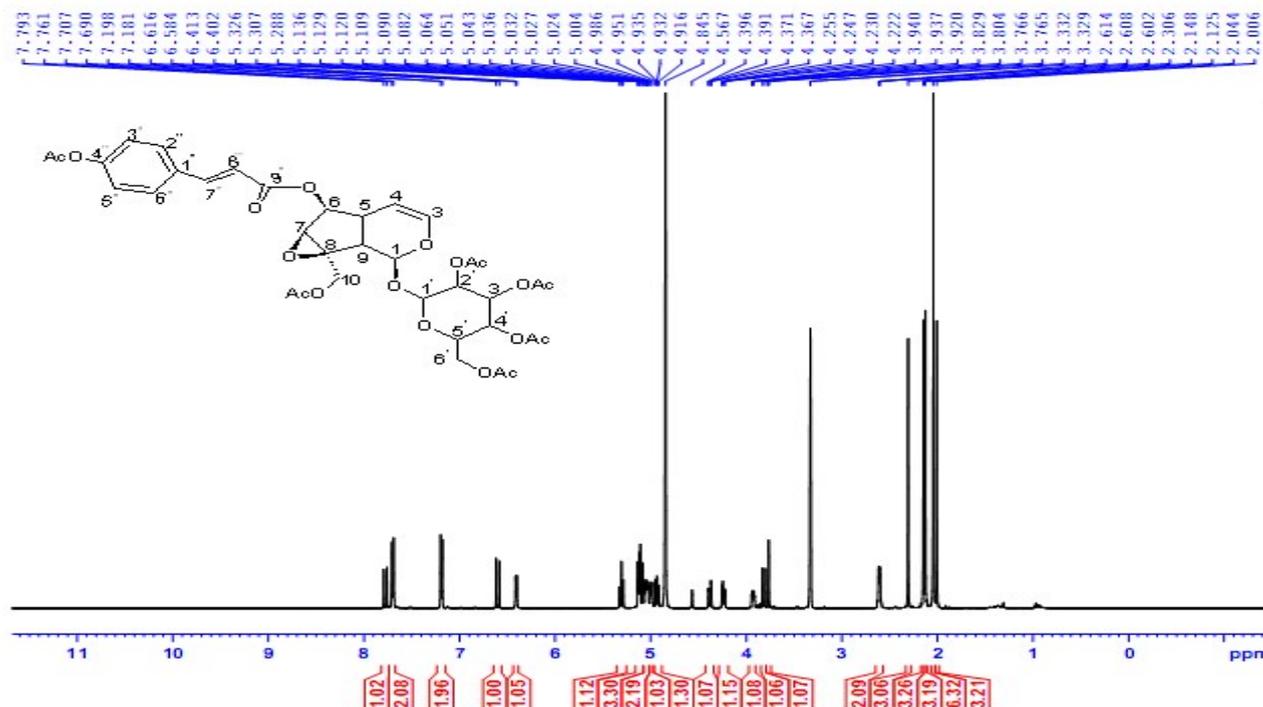
^{1}H-NMR spectrum (500 MHz, CDCl$_3$) of compound **12**
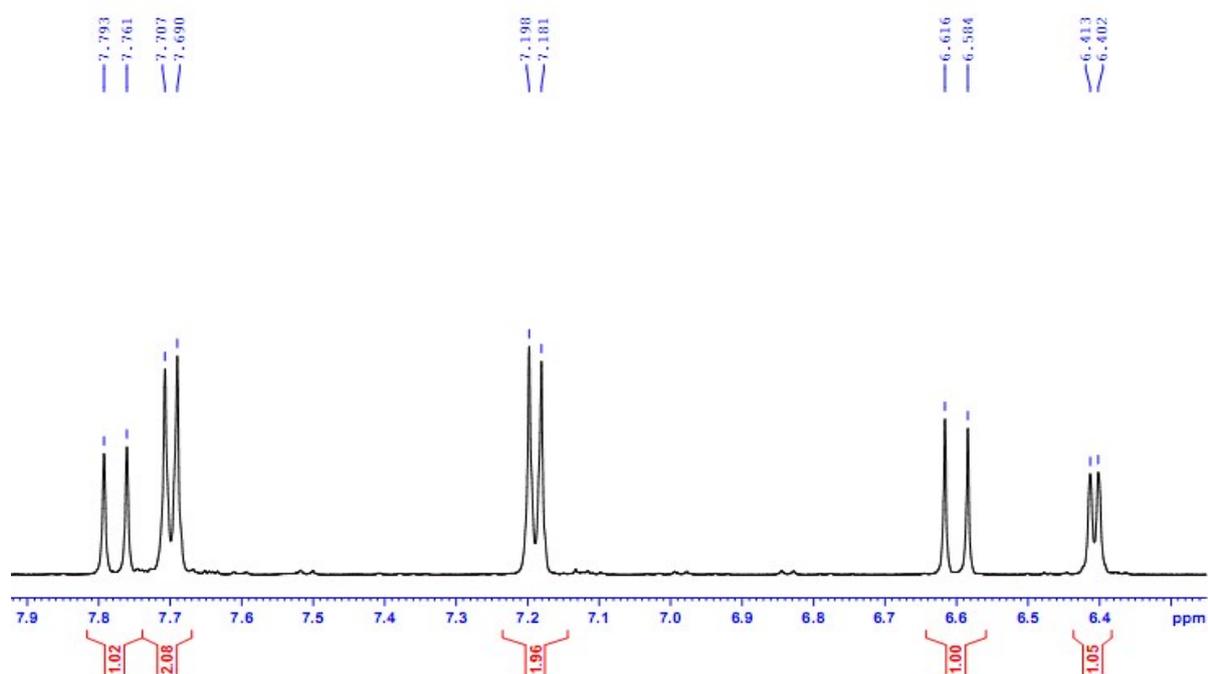
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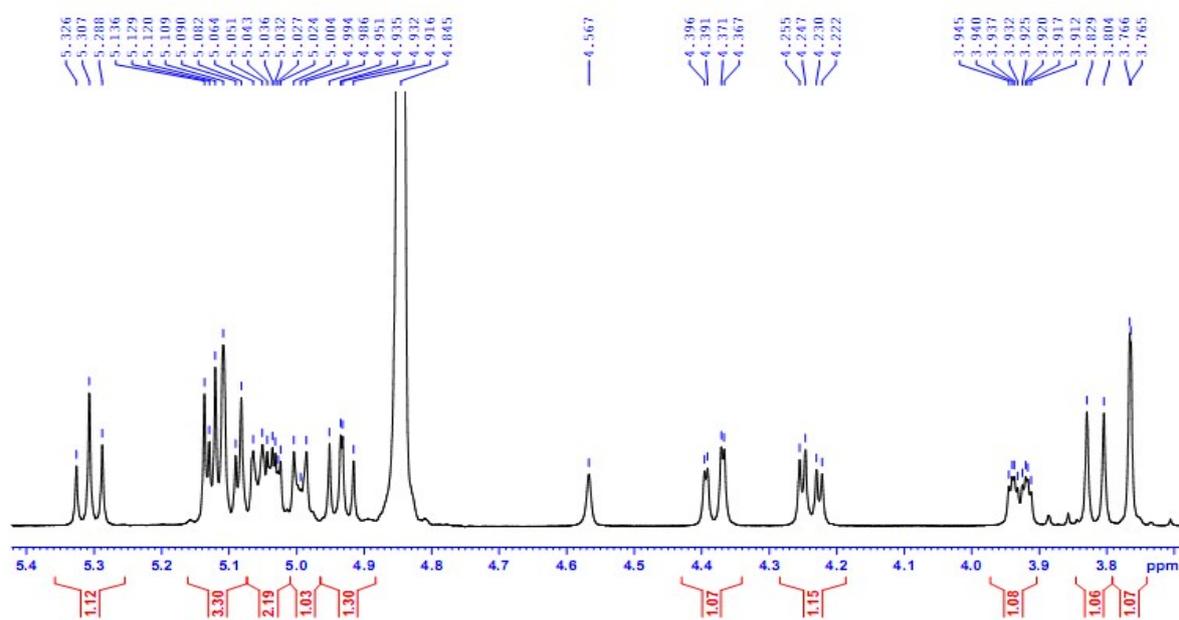
^{1}H-NMR spectrum (expansion) of compound **12**
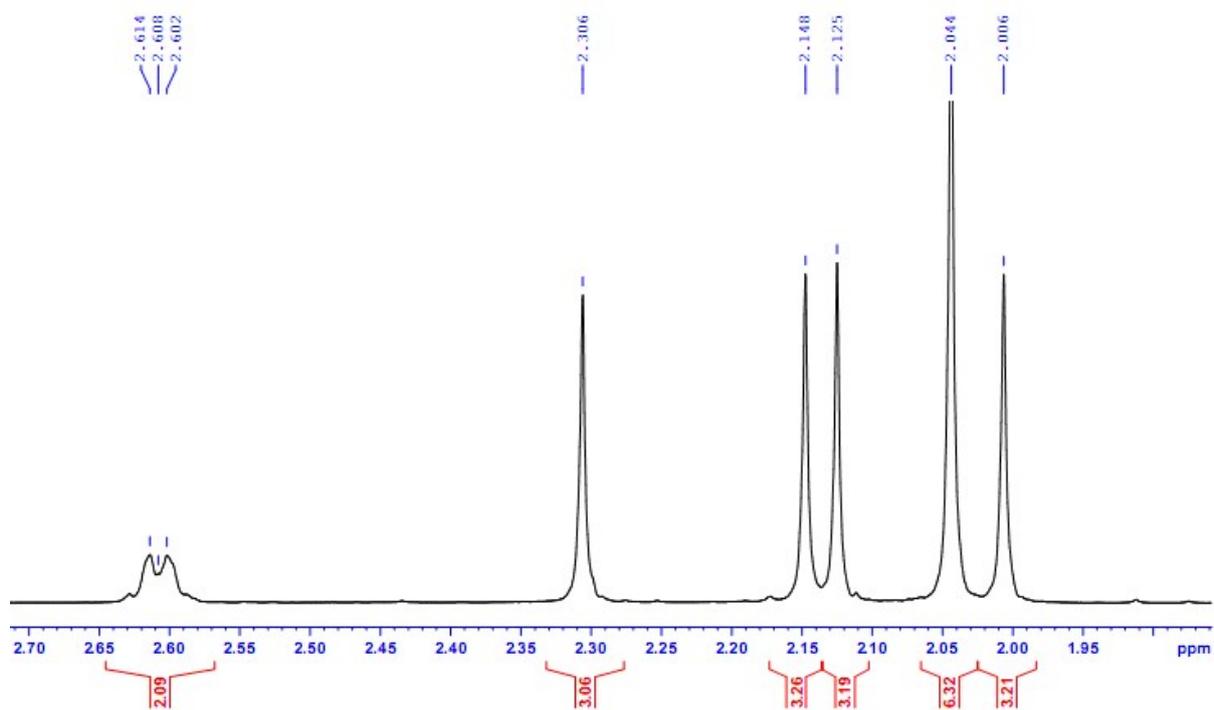
^{1}H-NMR spectrum (expansion) of compound **12**
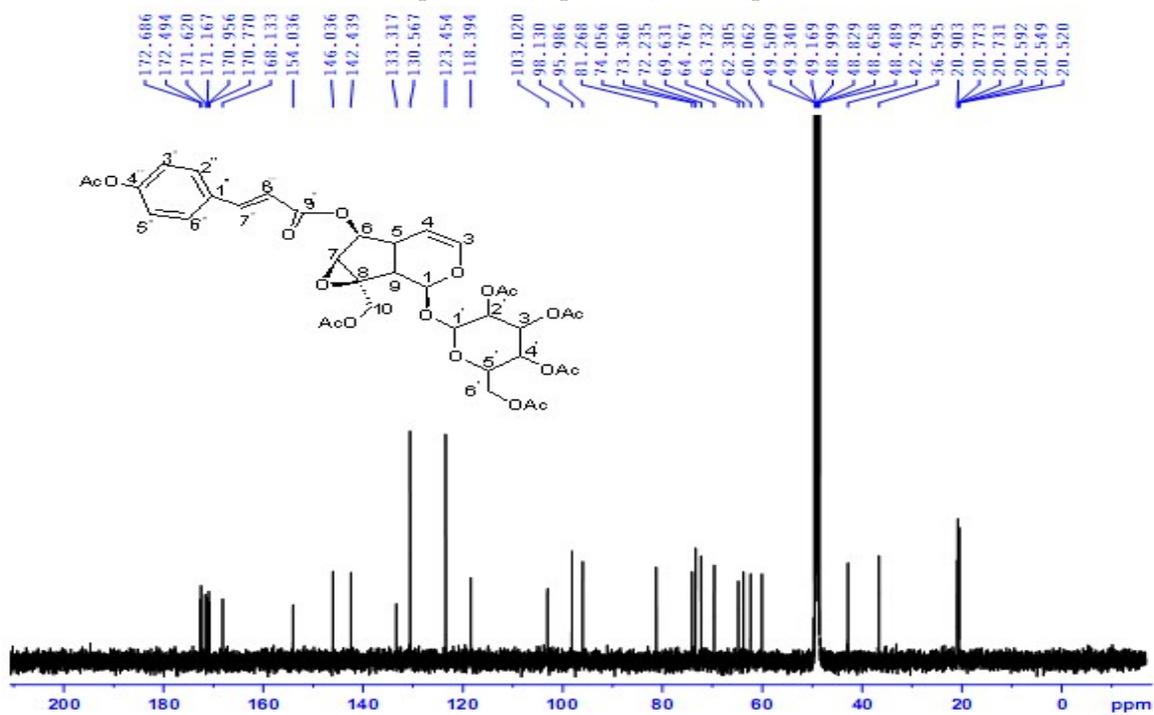
^{13}C-NMR spectrum (125 MHz, CDCl$_3$) of compound **12**

74
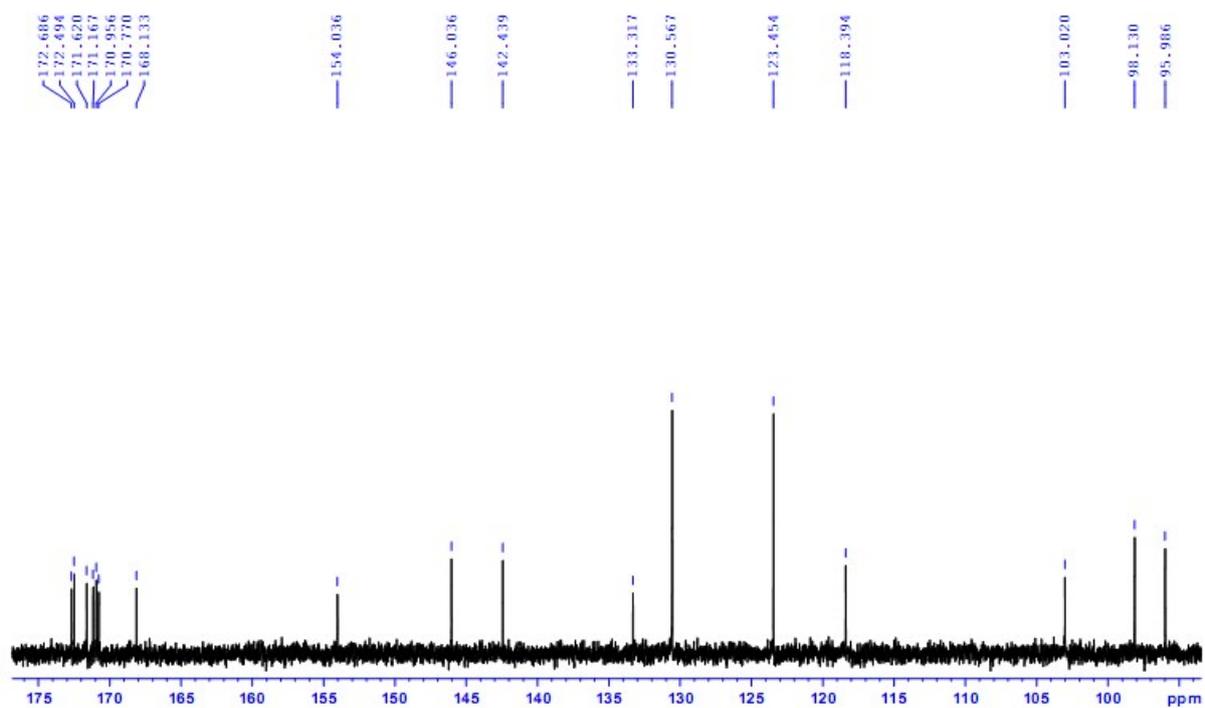
^{13}C-NMR spectrum (expansion) of compound **12**
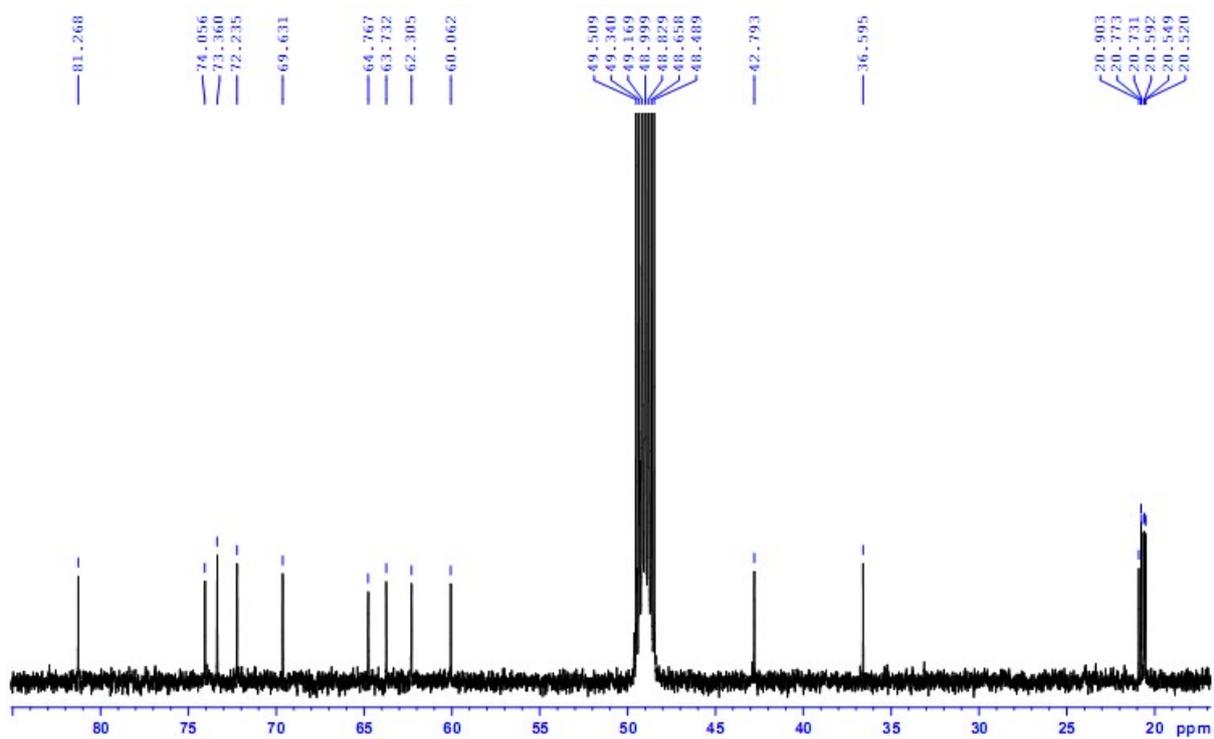
^{13}C-NMR spectrum (expansion) of compound **12**

DEPT90

DEPT135

CH&CH3

CH2

C13CPD

DEPT spectrum of compound **12**

76
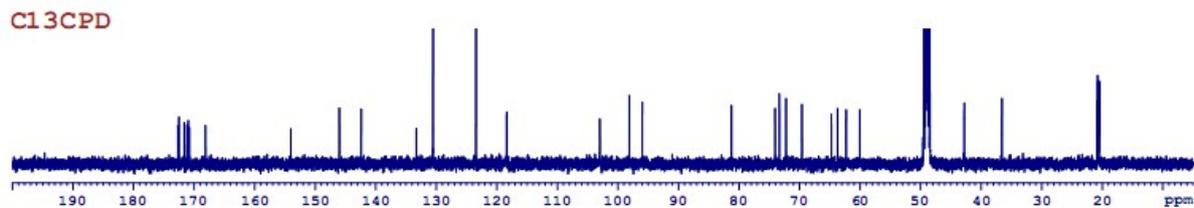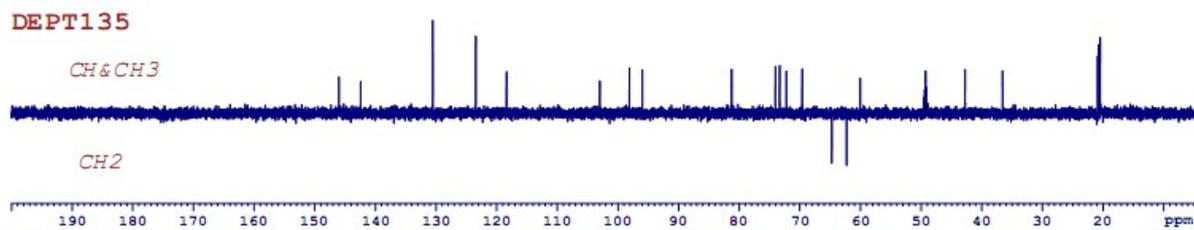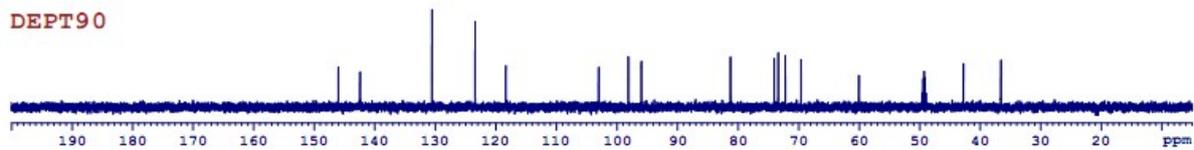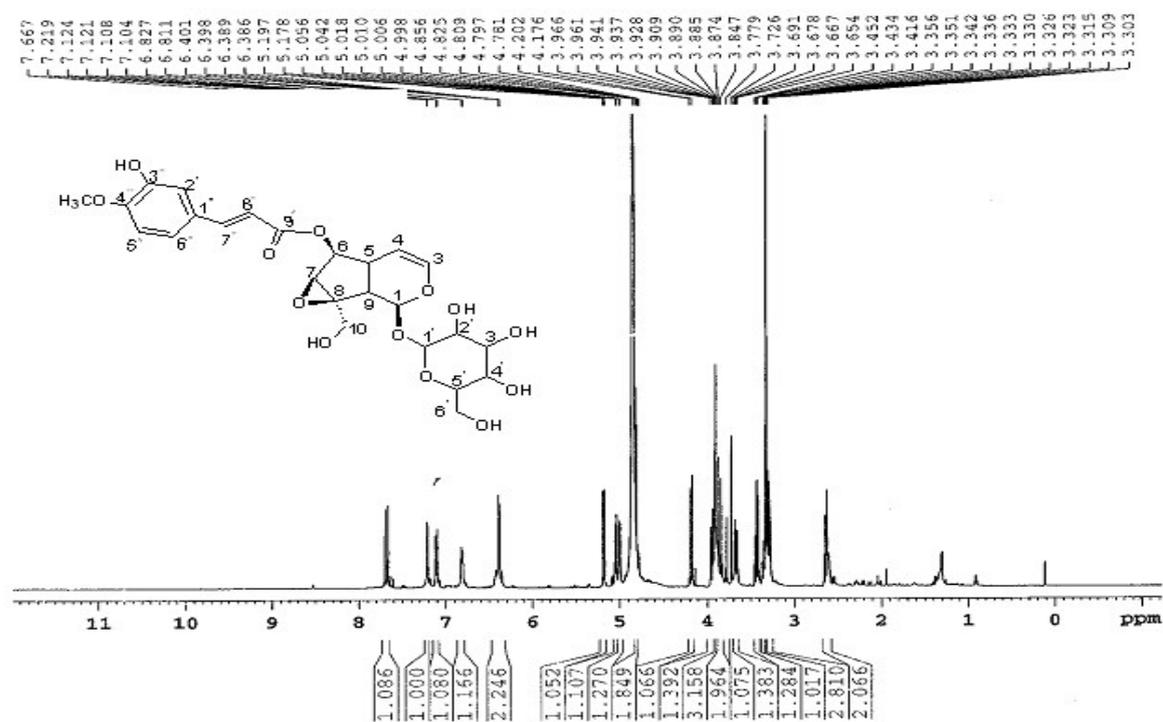
1.13. Compound 13

^{1}H-NMR spectrum (500 MHz, CD$_3$OD) of compound **13**
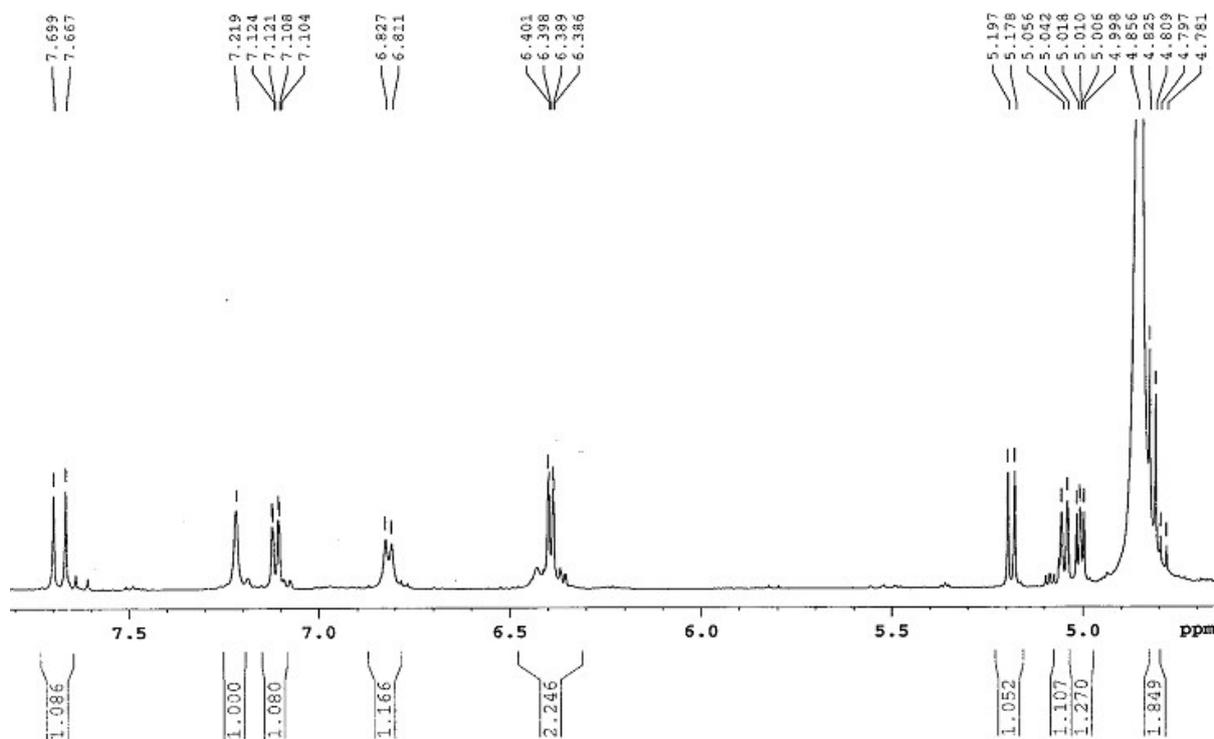
^{1}H-NMR spectrum (expansion) of compound **13**
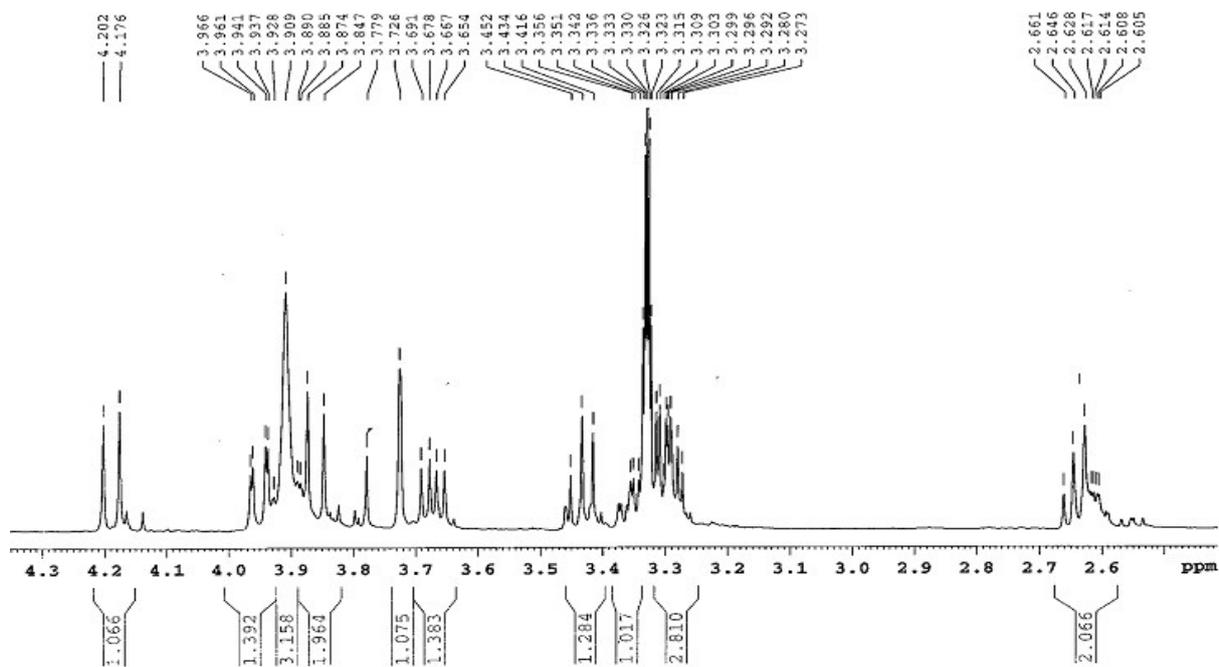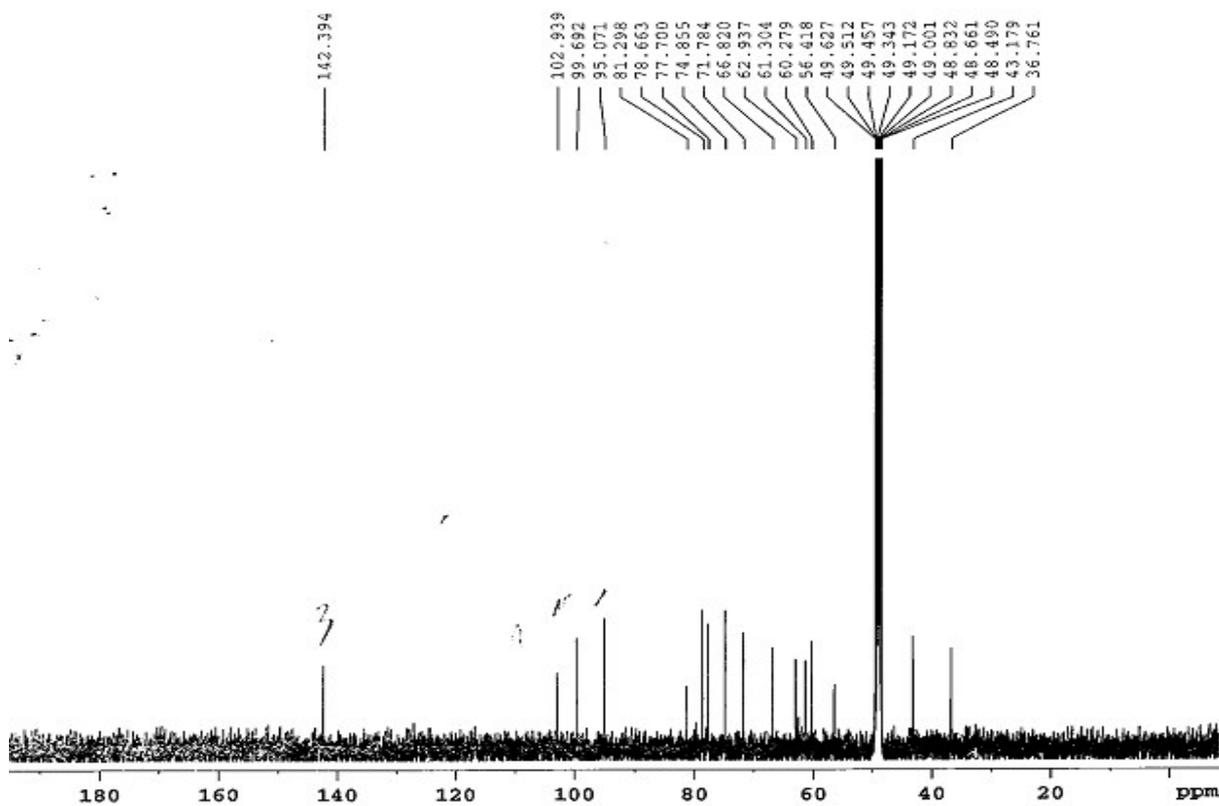
^{1}H-NMR spectrum (expansion) of compound **13**

^{13}C-NMR spectrum (125 MHz, CD$_3$OD) of compound **13**

78
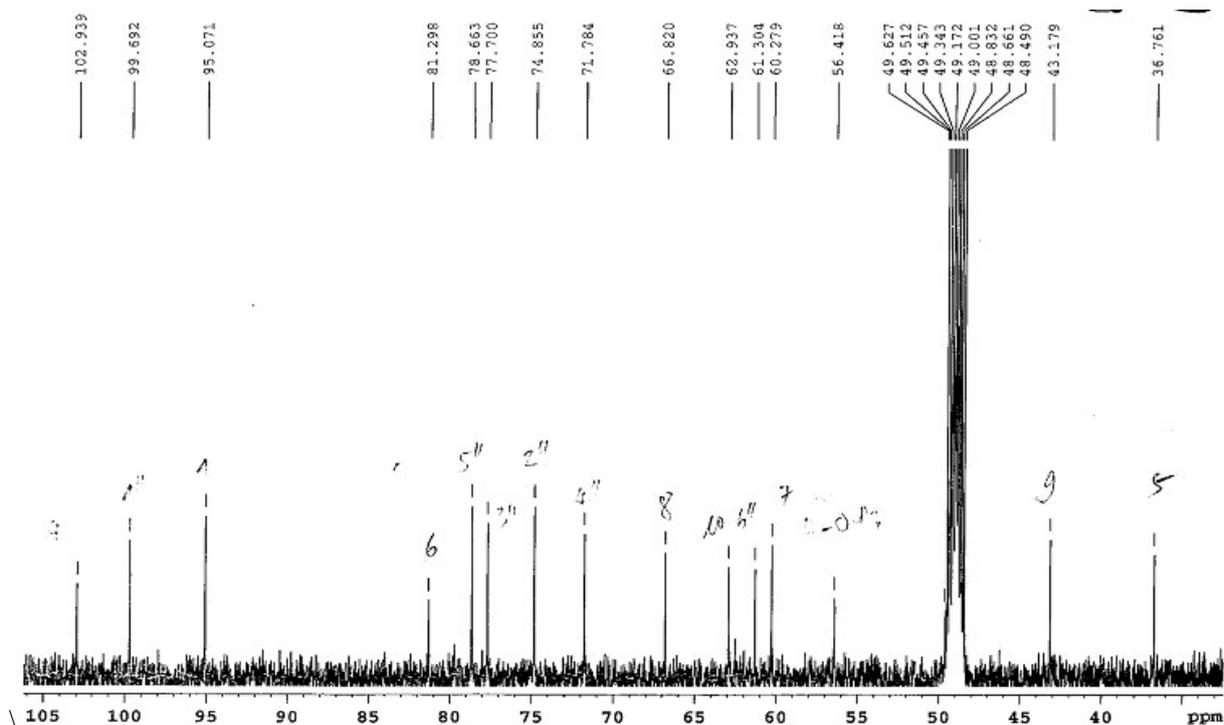
^{13}C-NMR spectrum (expansion) of compound **13**

DEPT90

DEPT135

CH&CH3

CH2
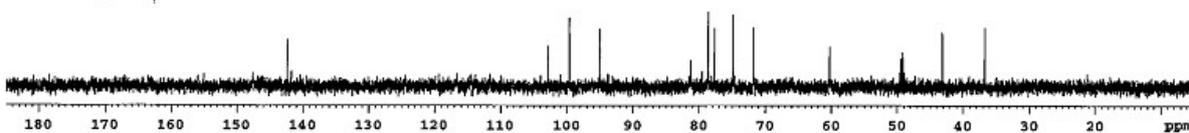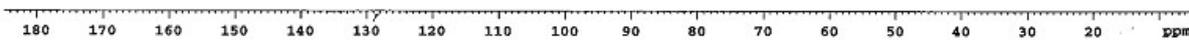
C13CPD

DEPT spectrum of compound **13**
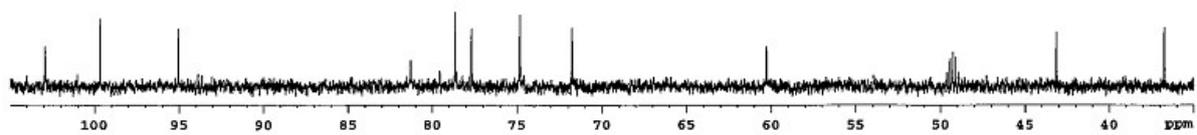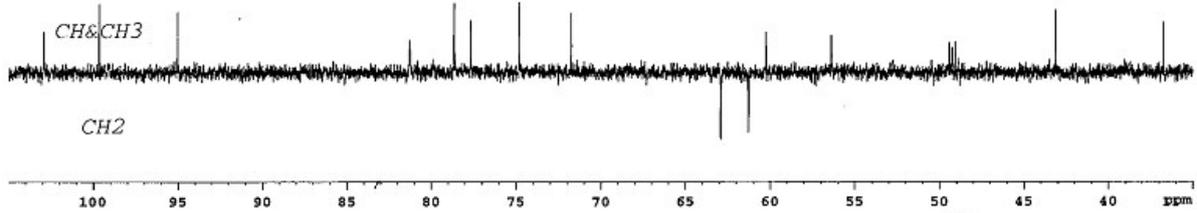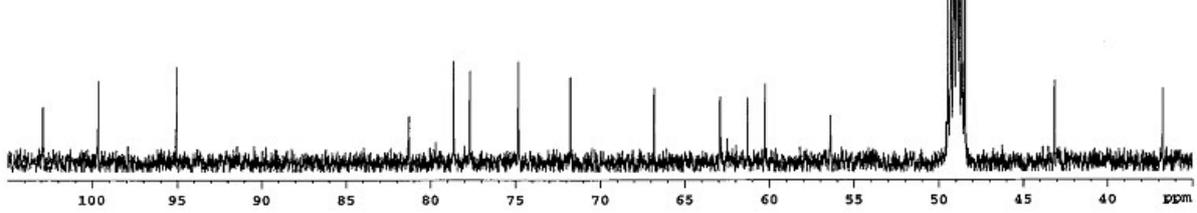
DEPT spectrum (expansion) of compound **13**

1.14. Compound 14
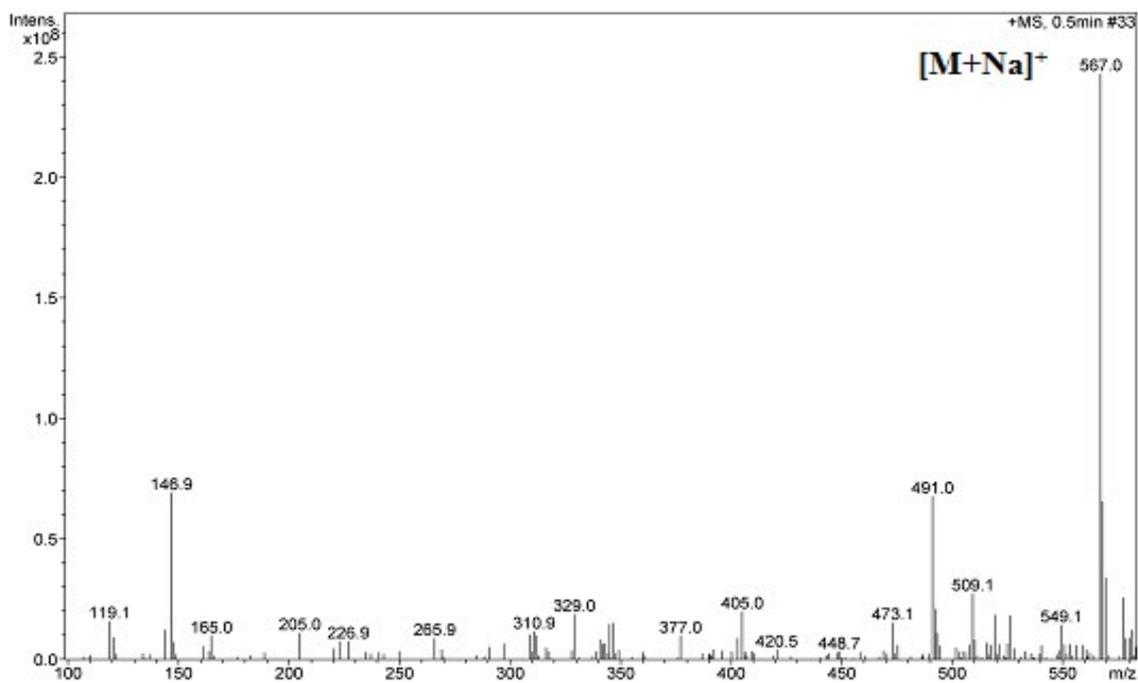
(+)-ESI-MS spectrum of compound **14**
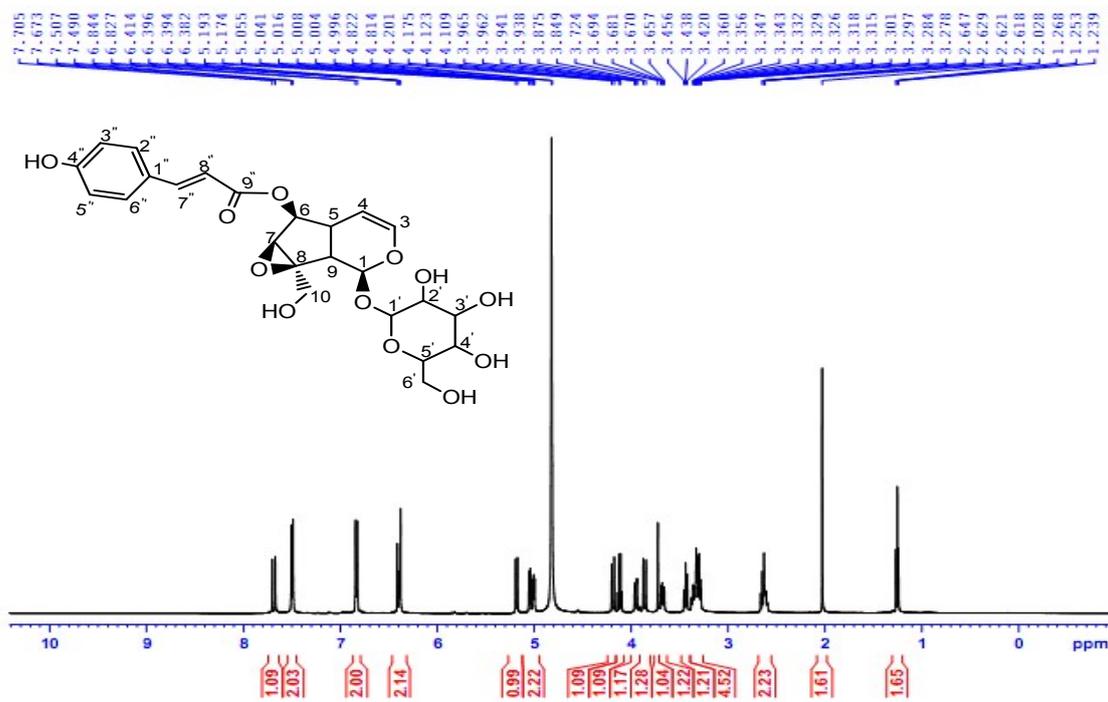
^{1}H-NMR spectrum (500 MHz, CD$_3$OD) of compound **14**
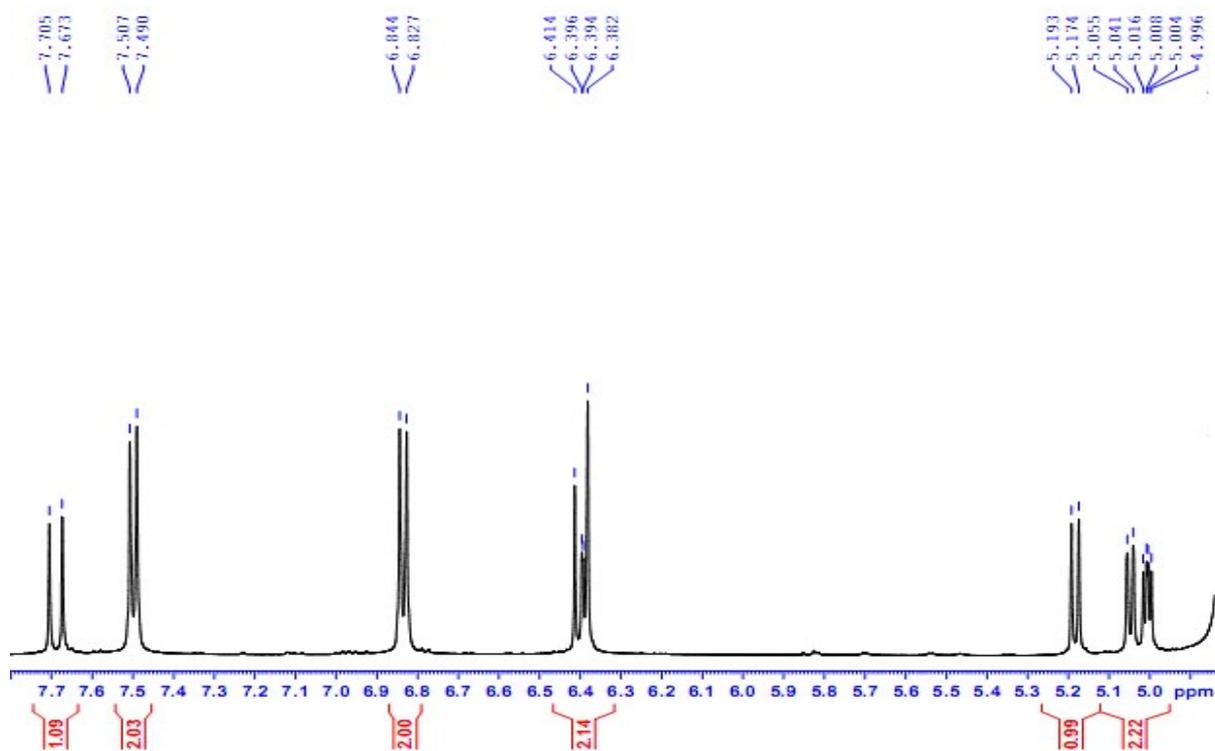
¹H-NMR spectrum (expansion) of compound **14**
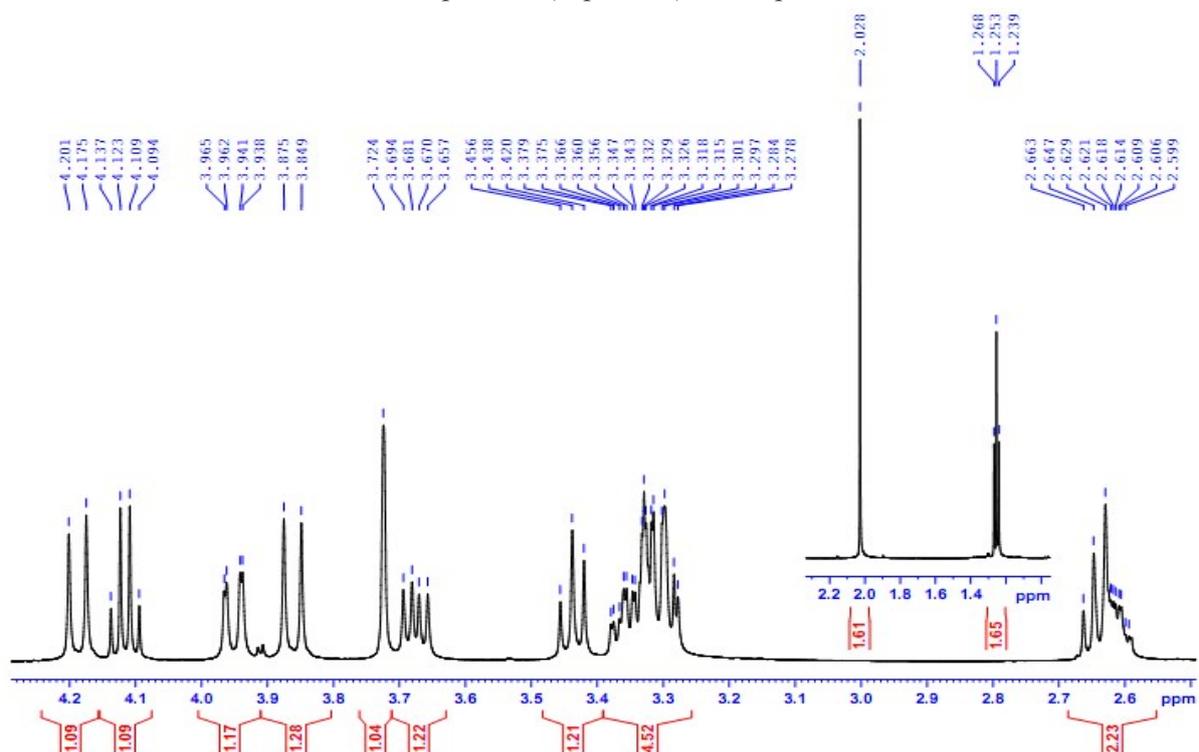

¹H-NMR spectrum (expansion) of compound **14**
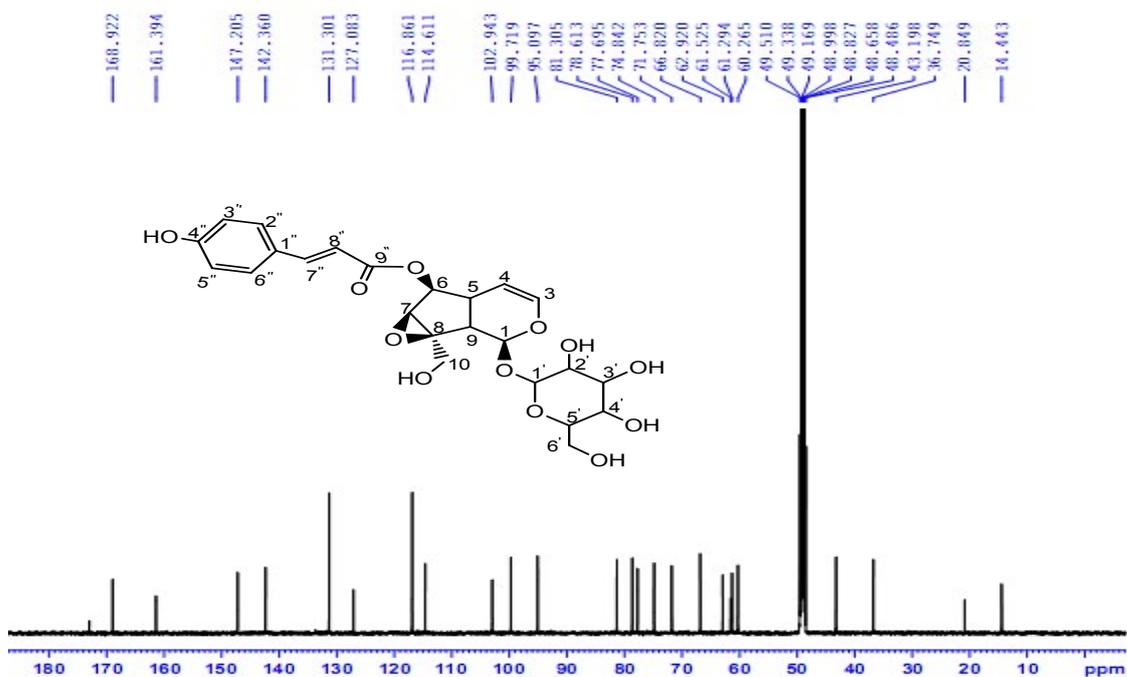
^{13}C-NMR spectrum (125 MHz, CD$_3$OD) of compound **14**
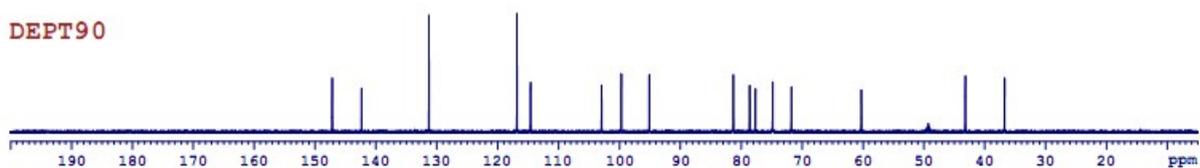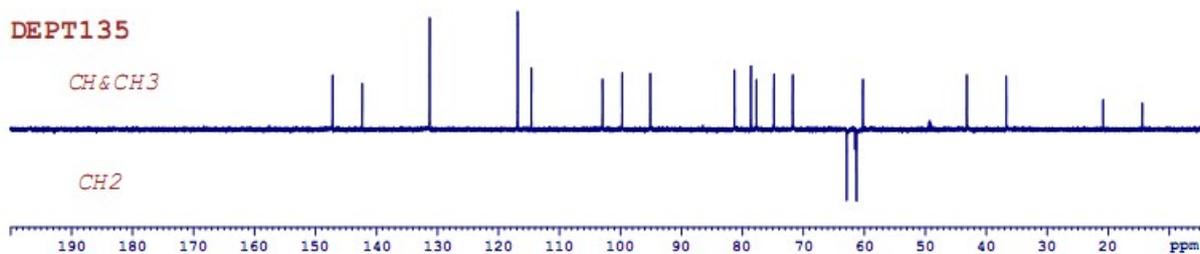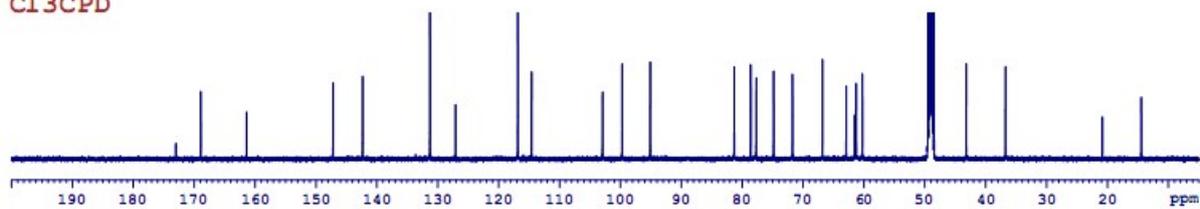
DEPT spectrum of compound **14**

1.15. Compound 15
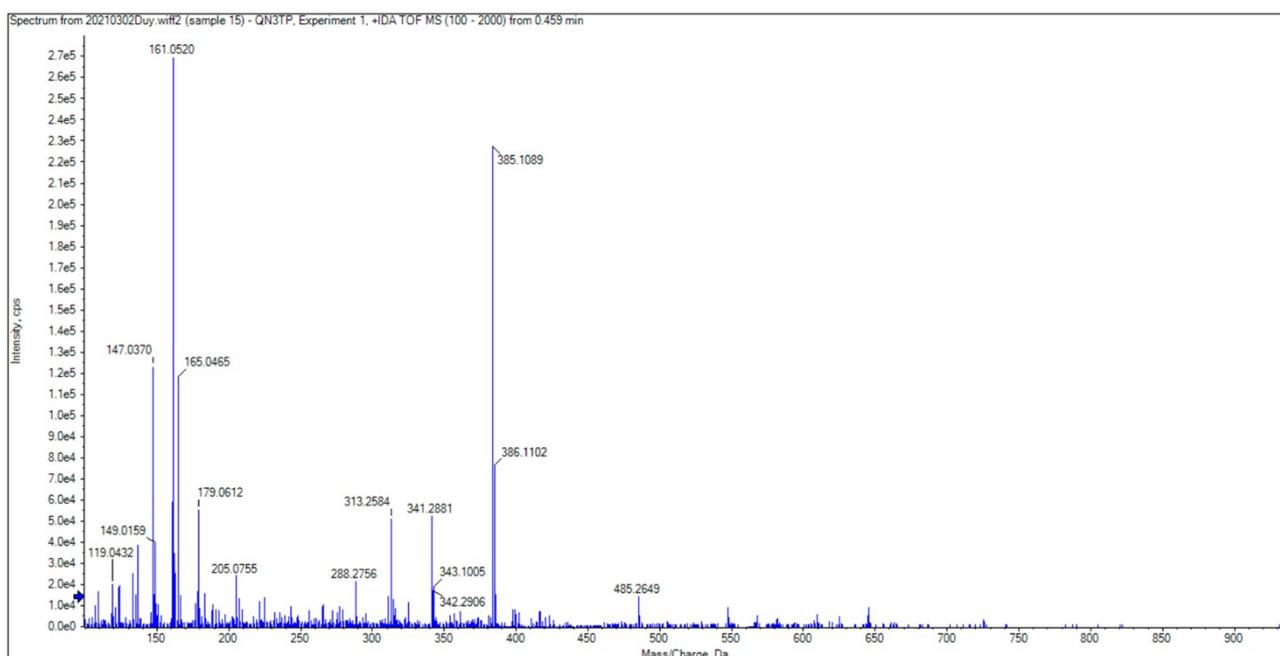
HR-ESI-MS spectrum of compound **15**
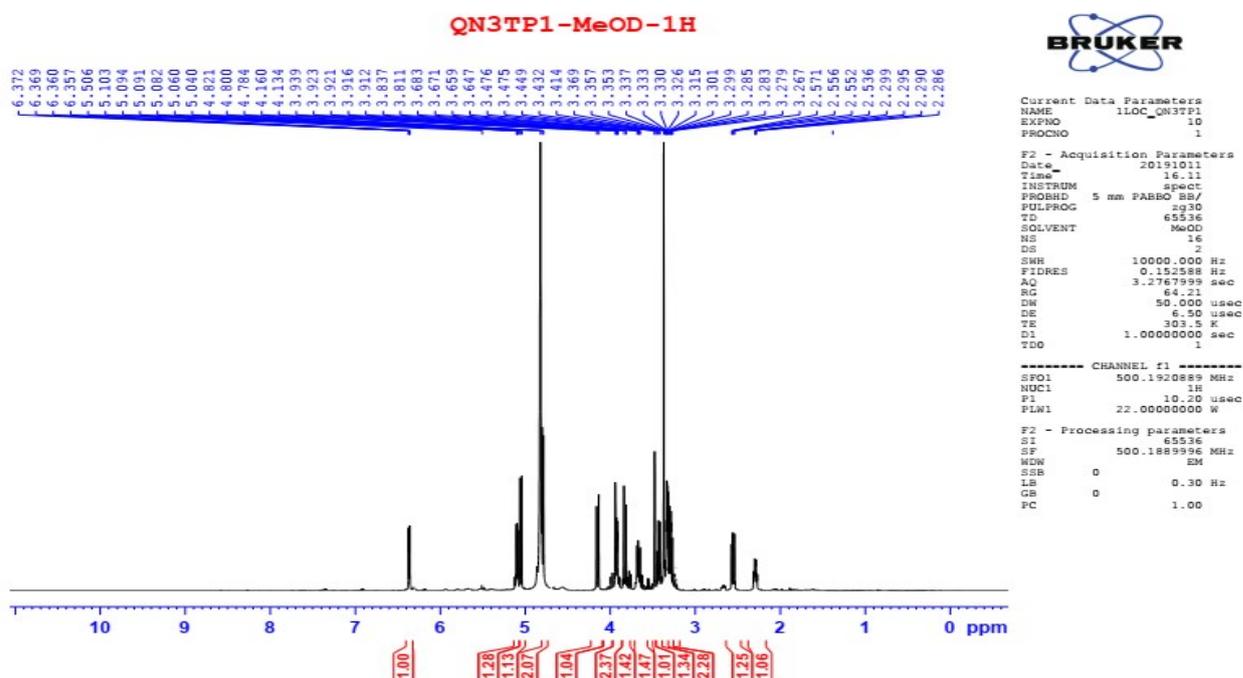
^{1}H-NMR spectrum of compound **15**
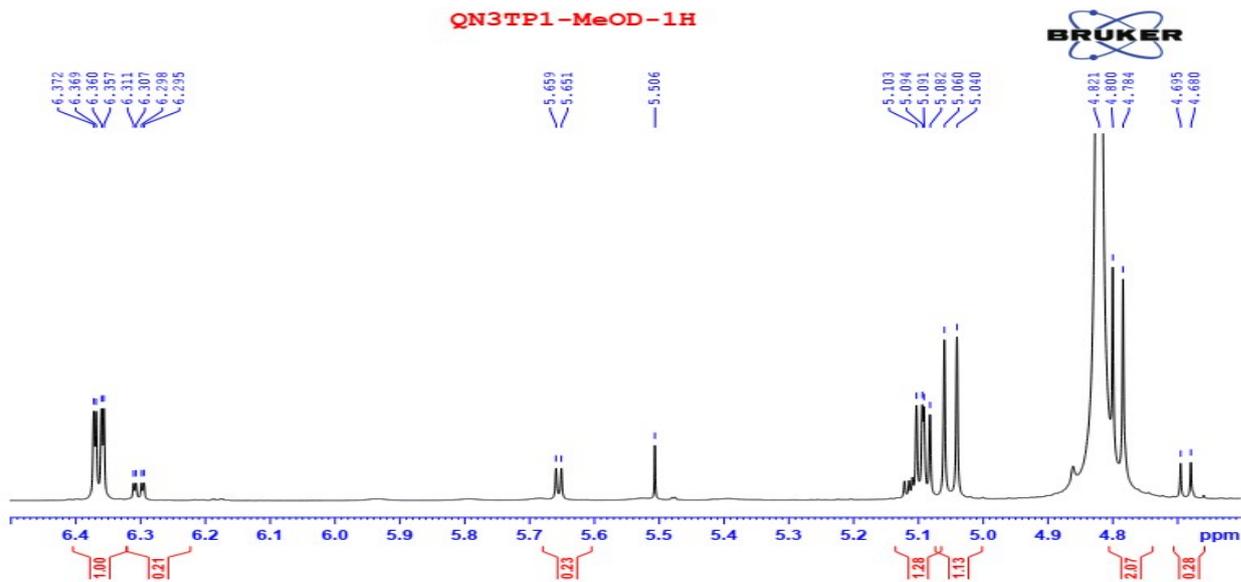
^{1}H-NMR spectrum (epansion) of compound **15**
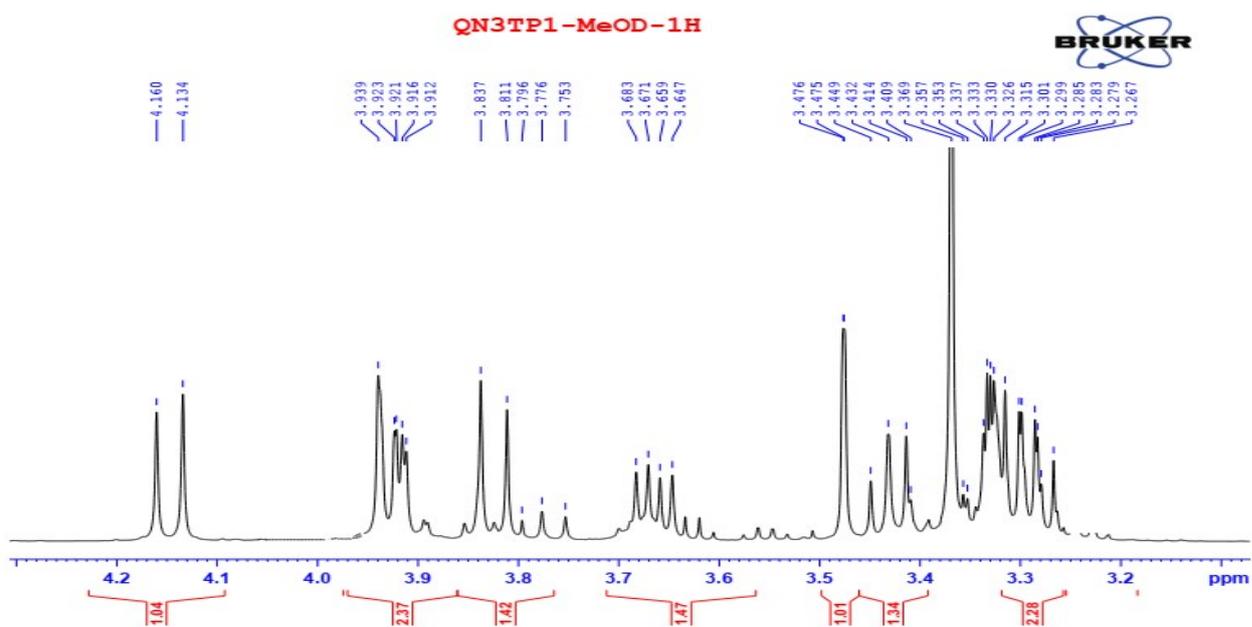
^{1}H-NMR spectrum (expansion) of compound **15**

QN3TP1-MeOD-1H

2.571
2.556
2.552
2.536

2.314
2.311
2.305
2.301
2.299
2.295
2.290
2.286
2.283
2.279
2.274
2.270

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2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 ppm

1.25 1.06
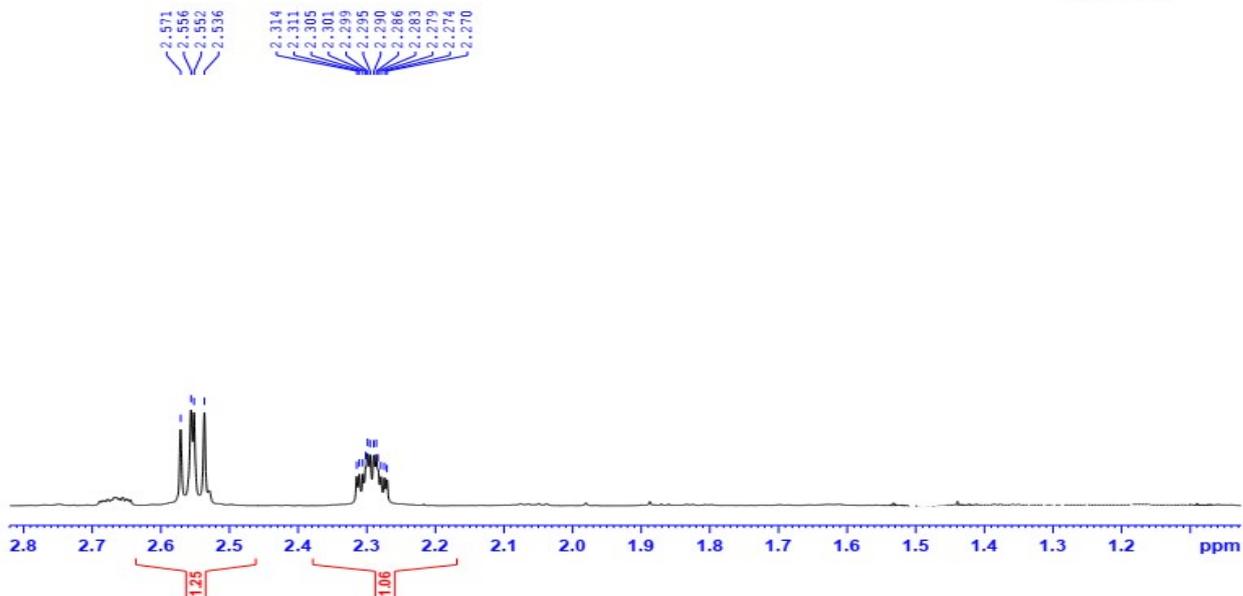
^{1}H-NMR spectrum (epansion) of compound **15**

QN3TP1-MeOD-C13CPD

141.73

104.01
99.70
95.30
79.51
78.53
77.65
74.79
71.70
66.24
62.84
62.57
61.51
49.85
49.51
49.34
49.17
49.00
48.83
48.66
48.49
43.57
39.05

BRUKER

Current Data Parameters
NAME   1LOC_QN3TP1
EXPNO   2
PROCNO   1

F2 - Acquisition Parameters
Date_   20191012
Time   17.01
INSTRUM   spect
PROBHD   5 mm PABBO BB/
PULPROG   zgpg30
TD   65536
SOLVENT   MeOD
NS   256
DS   4
SWH   31250.000 Hz
FIDRES   0.476837 Hz
AQ   1.0485760 sec
RG   198.57
DW   16.000 usec
DE   6.50 usec
TE   304.7 K
D1   2.00000000 sec
D11   0.03000000 sec
TD0   1

-------- CHANNEL f1 ========
SFO1   125.7864591 MHz
NUC1   13C
P1   10.00 usec
PLW1   88.00000000 W

-------- CHANNEL f2 ========
SFO2   500.1910008 MHz
NUC2   1H
CPDPRG[2   waltz16
PCPD2   80.00 usec
PLW2   22.00000000 W
PLW12   0.35764000 W
PLW13   0.17989001 W

F2 - Processing parameters
SI   32768
SF   125.7724540 MHz
WDW   EM
SSB   0
LB   1.00 Hz
GB   0
PC   1.40

220 200 180 160 140 120 100 80 60 40 20 0 ppm

^{13}C-NMR spectrum of compound **15**

86

^{13}C-NMR spectrum (expansion) of compound **15**

DEPT spectrum of compound **15**

DEPT spectrum (epansion) of compound **15**

2. COMPUTATIONAL VIRTUAL RENDERINGS

2.1. Visual presentation and in-pose interaction map of ligand-3W37 inhibitory complexes

Docking simulation between compounds and protein 3W37 of alpha-glucosidase enzyme
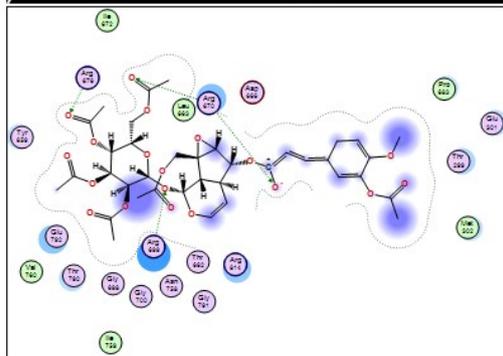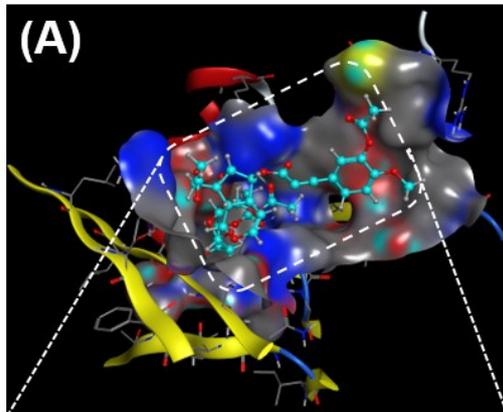
7-3W37
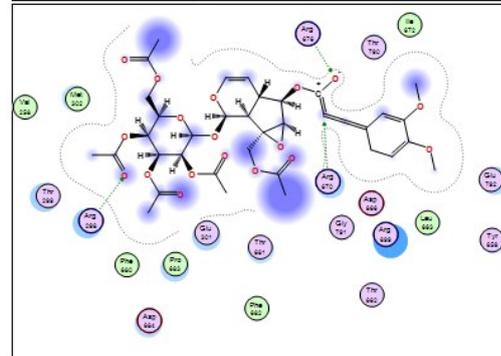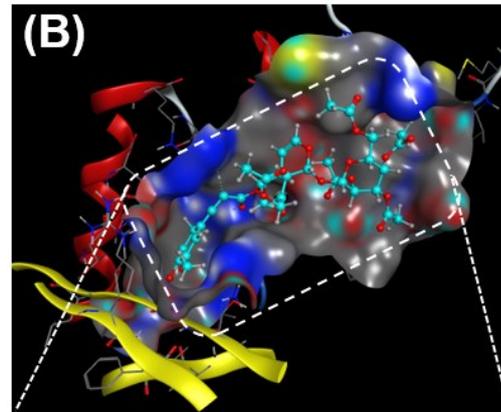
8-3W37
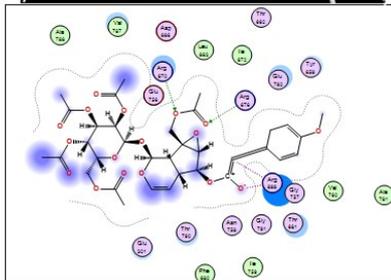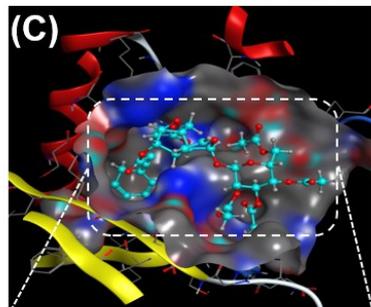
11-3W37
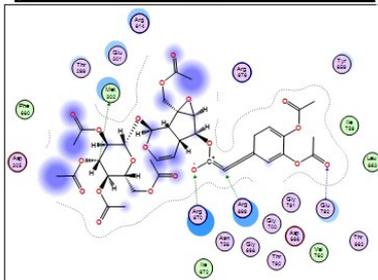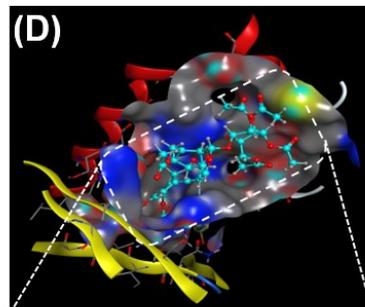
12-3W37
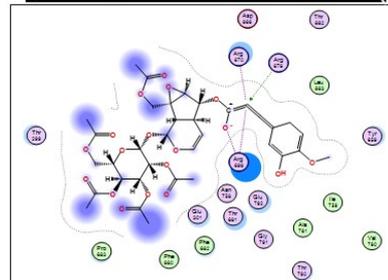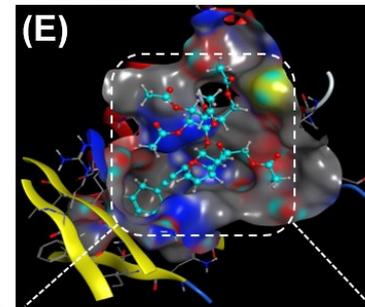
13-3W37

2.2. Visual presentation and in-pose interaction map of ligand-3AJ7 inhibitory complexes

Docking simulation between compounds and protein 3AJ7 of oligo-1,6-glucosidase enzyme
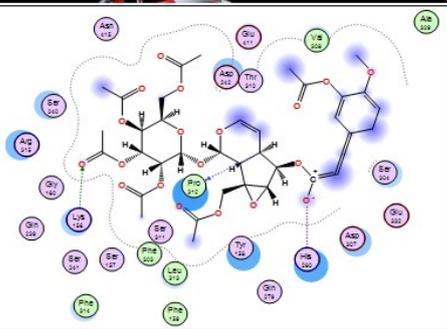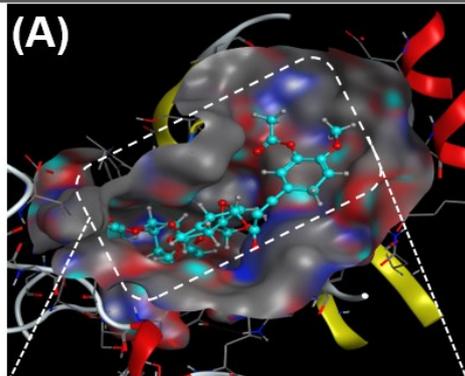
(A) 7-3AJ7
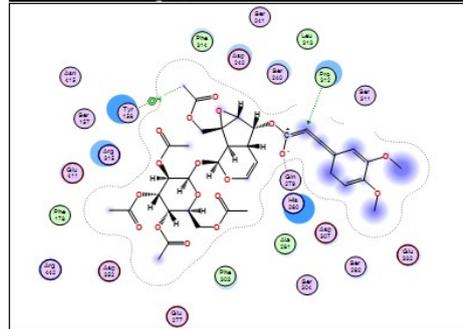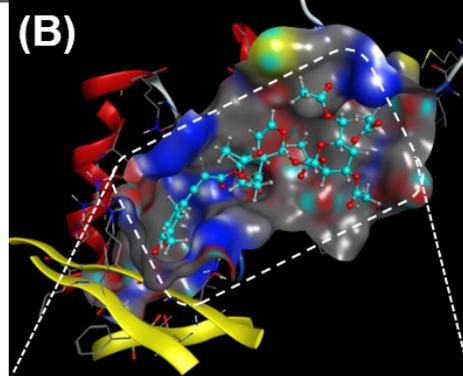
(B) 8-3AJ7
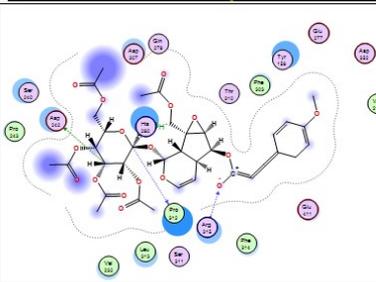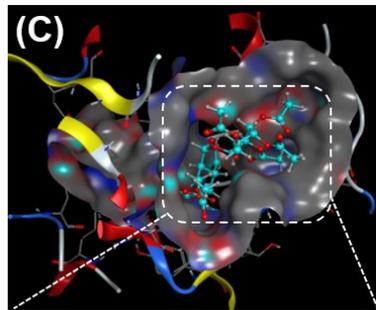
(C) 11-3AJ7
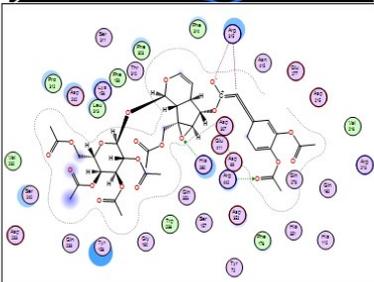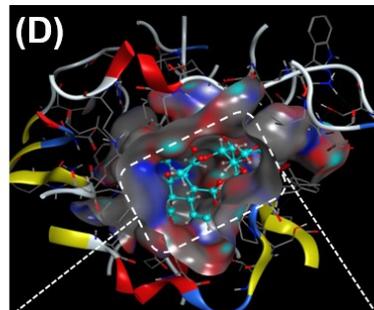
(D) 12-3AJ7
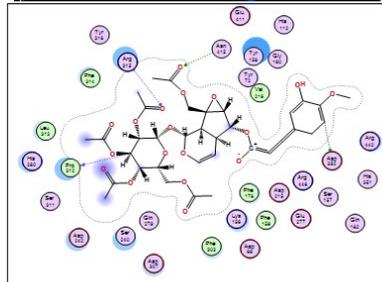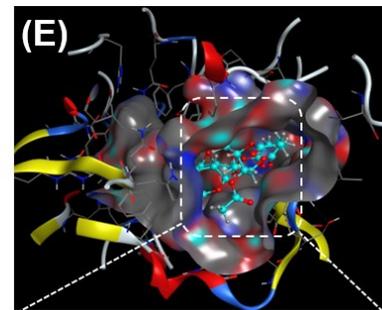
(E) 13-3AJ7

2.3. Descriptive denotation for in-pose interactions projected by MOE 2015.10 molecular docking simulation

⬤ polar	⋯➤ sidechain acceptor	◯ solvent residue	⬡⬡ arene-arene
◯ acidic	◀⋯ sidechain donor	◯ metal complex	⬡H arene-H
◯ basic	⋯➤ backbone acceptor	⋯ solvent contact	⬡+ arene-cation
◯ greasy	◀⋯ backbone donor	⋯ metal/ion contact	
⬤ proximity contour	⬤ ligand exposure	◯ receptor exposure	

2.4. Molecular docking simulation results for inhibitory complexes

Table 1. Molecular docking simulation results for inhibitory complexes with docking score energy (DS), root-mean-square deviation (RMSD); critical interactions between the complexes and the protein 3W37 with amino acids: **1-3W37**, **2-3W37**, **3-3W37**, **4-3W37**, **5-3W37**, **6-3W37**, **7-3W37**, **8-3W37**, **9-3W37**, **10-3W37**, **11-3W37**, **12-3W37**, **13-3W37**, **14-3W37**, and **15-3W37**

Ligand-protein complex			Hydrogen bond						van de Waals interaction
Name	DS	RMSD	L		P	T	D	E	
1-3W37	-14.1	1.47	O	O	Ile 759	H-donor	3.23	-1.4	Thr 299, Glu 301, Ile 672, Tyr 659, Val 760, Thr 790, Leu 663, Gly 791, Thr 662, Asn 758, Asp 666, Gly 698, Gly 700, Arg 676
			C	S	Met 302	H-donor	3.79	-1.0	
			O	N	Arg 699	H-acceptor	2.75	-2.7	
			O	N	Arg 699	H-acceptor	3.39	-0.9	
			O	N	Glu 792	H-acceptor	2.95	-1.6	
			C	N	Arg 670	H-acceptor	3.80	-8.7	
			C	N	Arg 670	ionic	3.80	-0.9	
2-3W37	-15.1	1.96	O	N	Arg 814	H-acceptor	3.13	-2.0	Leu 663, Thr 662, Tyr 659, Glu 792, Phe 680, Val 760, Thr 790, Gly 791, Ile 759, Thr 681, Gly 698, Asn 758, Ile 672, Glu 301
			C	N	Arg 670	H-acceptor	2.87	-8.1	
			O	N	Arg 670	H-acceptor	2.90	-1.7	
			O	N	Arg 676	H-acceptor	3.11	-3.2	
			C	N	Arg 699	ionic	3.17	-3.4	
			C	N	Arg 699	ionic	3.95	-0.6	
			C	O	Asp 666	ionic	3.51	-1.9	
			C	N	Arg 670	ionic	2.87	-5.4	
			C	N	Arg 670	ionic	3.55	-1.7	
			O	N	Arg 670	ionic	2.90	-5.2	
			O	N	Arg 676	ionic	3.43	-2.2	
			O	N	Arg 676	ionic	3.11	-3.8	
3-3W37	-12.9	1.33	C	O	Asp 666	H-donor	3.34	-0.7	Leu 663, Tyr 659, Ile 759, Thr 681, Gly 700, Gly 698, Gly 791, Glu 792, Thr 790, Arg 670, Phe 680, Pro 683, Glu 301, Thr 299
			O	N	Arg 814	H-acceptor	3.02	-2.8	
			O	N	Arg 699	H-acceptor	3.12	-1.7	
			O	N	Arg 676	H-acceptor	3.20	-0.9	
4-3W37	-12.3	1.72	O	O	Asp 666	H-donor	3.22	-1.2	Thr 790, Gly 791, Arg 670, Glu 792, Tyr 659, Leu 663, Arg 676, Thr 681, Glu 301, Ile 672, Phe 680
			O	O	Asp 666	H-donor	2.79	-1.9	
			O	N	Arg 814	H-acceptor	3.22	-0.9	
			O	N	Arg 814	H-acceptor	2.93	-3.4	
			O	N	Arg 699	H-acceptor	2.93	-1.2	
			6-ring	N	Arg 699	H-acceptor	4.65	-1.2	
5-3W37	-11.6	1.40	O	N	Arg 699	H-acceptor	2.92	-3.3	Phe 680, Asn 758, Arg 814, Phe 816, Thr 681, Ile 759, Phe 815, Leu 663, Gly 791, Thr 662, Asp 666, Tyr 659, Arg 670, Ile 672, Thr 790,
			O	N	Glu 792	H-acceptor	2.90	-1.4	

			O	N	Arg 676	H-acceptor	2.90	-5.1	
6-3W37	-	-	-	-	-	-	-	-	-
7-3W37	-8.1	1.84	O	N	Arg 699	H-acceptor	2.64	-2.8	Ile 659, Arg 814, Gly 791, Asn 758, Gly 700, Gly 698, Thr 790, Val 760, Glu 792, Tyr 659, Leu 663, Asp 666, Pro 683, Glu 301, Thr 299, Met 302
			O	N	Arg 670	H-acceptor	2.93	-1.0	
			O	N	Arg 676	H-acceptor	2.67	-0.8	
			O	N	Arg 670	H-acceptor	2.74	-5.6	
			O	N	Arg 670	ionic	3.94	-0.6	
			O	N	Arg 670	ionic	2.93	-4.9	
8-3W37	-10.5	1.76	C	N	Arg 670	H-acceptor	3.48	-1.0	Glu 792, Tyr 659, Leu 663, Arg 699, Asp 666, Gly 791, Thr 662, Thr 681, Phe 682. Glu 301, Pro 683, Asp 684, Phe 680, Thr 299, Val 258, Met 302, Thr 790, Ile 672
			O	N	Arg 676	H-acceptor	2.90	-0.9	
			O	N	Arg 298	H-acceptor	3.18	-1.5	
			C	N	Arg 670	ionic	3.24	-3.0	
			C	N	Arg 670	ionic	3.48	-2.0	
			O	N	Arg 676	ionic	2.90	-5.2	
9-3W37	-13.3	1.69	O	O	Glu 792	H-donor	2.88	-1.3	Tyr 659, Ile 759, Gly 791, Leu 663, Thr 662, Asp 666, Glu 301, Met 302, Thr 299
			O	N	Arg 699	H-acceptor	3.10	-2.0	
			O	N	Arg 670	H-acceptor	3.25	-0.8	
			C	N	Arg 670	ionic	3.46	-2.0	
			O	N	Arg 670	ionic	3.91	-0.7	
			O	N	Arg 670	ionic	2.81	-5.9	
10-3W37	-14.7	1.52	O	O	Asp 666	H-donor	3.21	-0.8	Glu 301, Phe 680, Met 302, Leu 663, Gly 791, Thr 662, Thr 790, Glu 792, Arg 699, Ile 672, Arg 676, Tyr 659, Gly 698, Arg 814
			O	O	Asp 666	H-donor	2.71	-1.1	
			O	N	Arg 670	H-acceptor	3.18	-0.3	
			O	O	Thr 299	H-acceptor	2.95	-1.2	
			C	N	Arg 670	ionic	3.24	-3.1	
			O	N	Arg 670	ionic	3.30	-2.8	
			O	N	Arg 670	ionic	3.30	-2.6	
11-3W37	-10.1	1.46	O	N	Arg 670	H-acceptor	2.92	-1.5	Ala 788, Val 787, Asp 666, Leu 663, Ile 672, Thr 662, Glu 792, Tyr 659, Gly 757, Val 760, Ala 761, Thr 681, Gly 791, Asn 758, Thr 790, Glu 301, Phe 680, Ile 759, Glu 765
			O	N	Arg 676	H-acceptor	2.96	-2.3	
			C	N	Arg 699	ionic	3.15	-3.6	
			O	N	Arg 699	ionic	3.92	-0.7	
12-3W37	-7.8	1.41	C	S	Met 302	H-donor	4.12	-1.0	Asp 305, Phe 680, Thr 299, Glu 301, Arg 814, Arg 676, Tyr 659, Ile 759, Leu 663, Thr 662, Val 760, Asp 666, Gly 791, Gly 700, Thr 790, Gly 698, Asn 758, Ile 672
			C	N	Arg 699	H-acceptor	3.35	-7.9	
			O	N	Arg 670	H-acceptor	2.78	-4.8	
			O	N	Glu 792	H-acceptor	3.05	-1.3	
			C	N	Arg 699	ionic	3.35	-2.5	
			O	N	Arg 670	ionic	3.12	-3.7	
			O	N	Arg 670	ionic	2.78	-6.1	
13-3W37	-8.8	1.47	O	N	Arg 670	H-acceptor	3.16	-1.1	Glu 301, Tyr 659, Val 760, Asn 758, Thr 662, Glu 792, Ala 761, Leu 663, Ile 759, Gly 791, Thr 681, Asp 666, Ile 672, Phe 680, Thr 299, Asp 305, Met 302, Pro 683
			O	N	Arg 676	H-acceptor	2.98	-4.8	
			C	N	Arg 670	ionic	3.84	-0.8	
			C	N	Arg 699	ionic	3.42	-2.2	
			O	N	Arg 670	ionic	3.58	-1.6	
			O	N	Arg 676	ionic	2.98	-4.6	
			O	N	Arg 676	ionic	3.70	-1.2	

	DS	RMSD	L	P		Type	D	E	
14-3W37	-13.0	1.01	C	N	Arg 676	H-acceptor	3.74	-6.0	Glu 301, Ile 672, Leu 663, Arg 670, Tyr 659, Glu 792, Thr 662, Gly 791, Thr 790, Phe 815, Phe 816, Arg 814, Thr 299
			C	O	Asp 666	ionic	2.94	-4.9	
			C	N	Arg 676	ionic	3.74	-1.1	
			C	N	Arg 699	ionic	3.90	-0.7	
15-3W37	-12.3	0.67	O	O	Asp 666	H-donor	3.26	-1.0	Gly 698, Tyr 659, Leu 663. Gly 791, Thr 790, Ile 759, Arg 670, Glu 792, Ile 672
			O	N	Arg 699	H-acceptor	3.22	-2.0	
			O	N	Arg 814	H-acceptor	3.17	-0.6	
			O	N	Arg 699	H-acceptor	2.99	-2.5	
			O	N	Arg 676	H-acceptor	2.97	-3.4	
DS: Docking score energy (kcal.mol^{-1}); **RMSD**: Root-mean-square deviation (Å)									
L: Ligand; **P**: Protein; **T**: Type; **D**: Distance (Å); **E**: Energy (kcal.mol^{-1});									

Table 2. Molecular docking simulation results for inhibitory complexes with docking score energy (DS), root-mean-square deviation (RMSD); critical interactions between the complexes and the protein 3AJ7 with amino acids: **1-3AJ7**, **2-3AJ7**, **3-3AJ7**, **4-3AJ7**, **5-3AJ7**, **6-3AJ7**, **7-3AJ7**, **8-3AJ7**, **9-3AJ7**, **10-3AJ7**, **11-3AJ7**, **12-3AJ7**, **13-3AJ7**, **14-3AJ7**, and **15-3AJ7**

Ligand-protein complex			Hydrogen bond						van der Waals interaction
Name	DS	RMSD	L		P	T	D	E	
1-3AJ7	-11.4	1.14	C	O	Glu 277	H-donor	2.99	-0.8	Val 216, His 112, Gln 182, Tyr 72, Arg 442, Phe 176, His 351, Phe 303, Phe 159, Gln 353, Glu 411, Gln 279, Tyr 158, Phe 314, Ser 240, Arg 315, Pro 312, Leu 313, Asp 242, Val 232
			C	O	Glu 277	H-donor	3.36	-0.7	
			O	O	Asp 215	H-donor	2.67	-3.1	
			O	O	Asp 352	H-donor	2.58	-3.7	
			O	O	Asp 352	H-donor	2.91	-0.8	
			O	O	Asp 69	H-donor	2.83	-3.1	
			O	N	Arg 213	H-acceptor	3.20	-1.7	
2-3AJ7	-13.5	1.64	O	O	Glu 411	H-donor	2.63	-2.4	Val 216, Asp 215, Arg 442, Phe 178, Phe 159, Phe 303, Tyr 316, Pro 312, Phe 314, Asp 307, Ser 240, Ser 241, Asp 242, Lys 156, Leu 313
			C	O	Asp 353	H-donor	3.24	-0.7	
			O	O	Glu 277	H-donor	2.61	-3.5	
			O	O	Glu 277	H-donor	3.11	-1.8	
			O	O	Glu 277	H-donor	2.88	-1.7	
			O	O	Glu 279	H-donor	2.58	-14.8	
			C	C	Tyr 158	H-aceptor	4.00	-1.0	
			O	C	Arg 315	H-aceptor	3.22	-0.8	
			C	N	His 280	Ionic	3.45	-2.1	
3-3AJ7	-10.6	1.71	O	O	Glu 411	H-donor	2.74	-2.9	Gln 182, Val 216, Phe 303, Arg 442, His 112, His 351. Arg 446, Tyr 158, Phe 178, Phe 159, Arg 315, Gln 279, Asp 307, Pro 312, Asp 242, His 280
			C	O	Asp 69	H-donor	3.35	-0.7	
			O	O	Asp 352	H-donor	2.99	-2.3	
			O	O	Asp 215	H-donor	2.71	-4.4	
			O	O	Glu 277	H-donor	2.57	-2.7	
			O	O	Asp 69	H-donor	2.80	-4.8	
			O	N	Arg 213	H-acceptor	3.24	-1.4	
			C	6-ring	Tyr 72	H-π	4.10	-0.6	
4-3AJ7	-10.2	1.79	O	O	Pro 312	H-donor	2.99	-1.1	Lys 156, Glu 411, Phe 159, Gln 279, Ser 157, Gly 160, His 280, Ser 311, Phe 314, Tyr 316, Ser 240, Thr 310, Asp 242, Asp 307, Ser 304
			O	O	Asn 415	H-donor	2.79	-2.1	
			O	O	Leu 313	H-donor	2.88	-1.3	
			O	O	Tyr 158	H-donor	2.96	-2.0	
			O	N	Arg 315	H-acceptor	3.09	-2.3	
			O	B	Asn 415	H-acceptor	2.89	-1.1	
5-3AJ7	-11.7	1.80	O	C	His 280	H-acceptor	3.32	-0.7	Gln 239, Ser 157, Phe 314, Glu 160, Tyr 158, Phe 159, Glu 411, Phe 303, Arg 315, Leu 313, Pro 312, Ser 240, Asp 242, Thr 245, Ser 311, Gln 279, Tyr 316, Asp 307, Ser 304, Thr 310, Val 308, Gly 309
			O	N	Lys 156	H-acceptor	2.56	-0.2	
			O	N	Asn 415	H-acceptor	3.11	-2.1	
			O	N	Ser 241	H-acceptor	3.00	-2.8	

6-3AJ7	-	-	-	-	-	-	-	-	-
7-3AJ7	-9.3	1.98	C	O	Pro 312	H-donor	3.31	-0.7	Asn 415, Ser 240, Arg 315, Gly 160, Gln 239, Ser 241, Phe 314, Ser 157, Ser 311, Phe 303, Leu 313, Phe 159, Tyr 158, Gln 279, Asp 242, Thr 310, Glu 411, Val 308, Asp 307, Glu 332, Ser 304, Ala 329
			O	N	Lys 156	H-acceptor	3.27	-2.6	
			O	N	His 280	ionic	3.53	-1.8	
8-3AJ7	-8.8	1.90	C	C	Pro 312	H-acceptor	4.19	-0.8	Arg 442, Phe 178, Glu 411, Arg 315, Ser 157, Asn 415, Asp 352, Glu 277, Phe 303, Ala 281, Ser 304, Asp 307, Ser 282, Glu 332, Phe 314, Asp 242, Ser 240, Ser 241, Leu 313, Ser 311
			O	N	His 280	ionic	3.19	-3.3	
			O	N	His 280	ionic	3.19	-3.3	
			C	6-ring	Tyr 158	H-π	4.03	-1.2	
9-3AJ7	-11.5	1.74	O	O	Glu 411	H-donor	2.77	-5.1	Val 216, Phe 178, Asp 362, Glu 277, Arg 442, Phe 314, Tyr 158, Leu 313, Asp 242, Pro 312, Thr 310, Ser 304, Asp 307, Gln 279, Phe 303, Phe 159, Asp 215
			O	N	Arg 315	H-acceptor	2.95	-2.6	
			C	N	His 280	ionic	3.68	-1.3	
			O	N	His 280	ionic	3.06	-4.1	
10-3AJ7	-12.4	1.33	O	O	Asp 242	H-donor	3.07	-1.2	Arg 446, Gln 353, Glu 411, His 351, Arg 442, Asp 352, Asp 69, Val 216, Asp 215, Glu 277, Phe 178, Phe 159, Lys 156, Tyr 158, Pro 312, Ser 311, Phe 303, Ser 240, Phe 314, Gln 279, Asp 307
			O	O	Ser 157	H-donor	2.79	-1.2	
			O	O	Leu 313	H-donor	2.77	-1.1	
			O	C	His 280	H-acceptor	3.05	-0.8	
			O	N	Ser 241	H-acceptor	3.04	-0.6	
			O	N	Arg 315	ionic	3.52	-1.8	
			O	6-ring	Tyr 72	H-π	4.08	-0.8	
11-3AJ7	-6.3	1.99	C	O	Pro 312	H-donor	3.02	-0.9	Pro 243, Ser 240, Val 232, Leu 313, Ser 311, Phe 314, Glu 411, Val 216, Asp 252, Glu 277, Tyr 158, Phe 303, Thr 310, Gln 279, Asp 307
			C	O	Asp 242	H-donor	3.14	-1.0	
			O	N	Arg 315	H-acceptor	3.05	-1.7	
			C	5-ring	His 280	H-π	4.60	-0.6	
12-3AJ7	-6.4	1.06	O	C	His 280	H-acceptor	3.18	-1.8	Val 232, Ser 240, Asp 233, Gln 239, Tyr 158, Gly 160, Trp 238, Ser 157, Tyr 72, Asp 352, Phe 178, His 351, Gln 353, His 112, Gln 182, Arg 213, Val 216, Asp 215, Glu 277, Asn 415, Asp 69, Glu 411, Phe 314, Phe 303, Thr 310, Phe 159, Ser 311, Lys 156, Leu 313, Asp 242, Pro 312, Gln 279
			O	N	Arg 442	H-acceptor	2.99	-4.3	
			C	N	Arg 315	ionic	3.56	-1.7	
			O	N	Arg 315	ionic	3.25	-3.0	
			O	N	Arg 315	ionic	3.42	-2.2	
			O	N	Arg 315	ionic	3.86	-0.8	
13-3AJ7	-7.5	1.99	C	O	Pro 312	H-donor	3.18	-1.6	Tyr 316, Phe 314, Leu 313, His 380, Ser 311, Asp 242, Ser 240, Gln 279, Asp 307, Phe 303, Lys 156, Asp 69, Phe 178, Phe 159, Asp 215, Glu 277, Arg 446, Ser 157, Gln 182, His 315, Arg 442, Val 216, Tyr 72, Tyr 158, Gly 160, His 112, Glu 411
			C	O	Asp 352	H-donor	3.30	-0.7	
			O	N	Asn 415	H-acceptor	2.94	-1.0	
			O	N	Arg 315	H-acceptor	3.29	-1.5	
14-3AJ7	-14.5	1.71	C	O	Asp 242	H-donor	3.54	-0.7	Glu 411, Asp 215, Val 216, Phe 159, Tyr 158, Arg 315, Phe 178, Phe 303, Thr 310, Ser 240, Arg
			C	O	Glu 277	ionic	3.82	-0.9	

L	DS	RMSD	L	P	Residue	Type	D	E	Interactions
			C	O	Glu 277	ionic	2.93	-5.0	213, Val 232, Leu 246, Leu 313, Asp 307, Pro 312, Gln 279, Ser 311, Phe 314, His 280
			C	O	Asp 352	ionic	3.39	-2.3	
			C	O	Glu 277	ionic	3.77	-1.0	
15-3AJ7	-11.0	1.12	O	O	Asp 242	H-donor	2.69	-4.9	Arg 315, Leu 313, Tyr 158, Lys 156, Ser 157, Gln 279, Ser 240, Ser 241, Phe 314, Pro 312
			O	O	Asp 242	H-donor	2.77	-2.6	
			O	C	His 280	H-acceptor	3.18	-1.0	

DS: Docking score energy (kcal.mol^{-1}); **RMSD**: Root-mean-square deviation (Å)

L: Ligand; **P**: Protein; **T**: Type; **D**: Distance (Å); **E**: Energy (kcal.mol^{-1})

Table 3. Molecular docking simulation results for controlled drugs as inhibitory complexes with docking score energy (DS), root-mean-square deviation (RMSD); critical interactions between the complexes and the two protein 3W37, 3AJ7 with amino acids: **D1-3W37**, **D2-3W37**, **D3-3W37**; **D1-3AJ7**, **D2-3AJ7**, and **D3-3AJ7**

Ligand-protein complex			Hydrogen bond						van der Waals interaction
Name	DS	RMSD	L		P	T	D	E	
D1-3W37	-14.2	1.58	O	O	Asp 666	H-donor	2.70	-2.1	Phe 861, Gly 791, Phe 815, Leu 663, Tyr 659, Pro 300, Thr 681, Gly 698, Phe 680, Pro 683, Thr 299, Ile 672, Arg 670, Thr 790
			O	O	Glu 792	H-donor	2.77	-1.9	
			O	O	Glu 301	H-donor	2.89	-1.4	
			O	N	Arg 699	H-acceptor	2.94	-1.5	
			O	N	Arg 699	H-acceptor	3.54	-0.6	
			O	N	Arg 676	H-acceptor	3.52	-0.6	
			O	N	Arg 814	H-acceptor	2.99	-1.6	
			O	N	Arg 699	H-acceptor	2.94	-2.2	
D2-3W37	-11.1	0.68	O	O	Asp 666	H-donor	2.77	-3.6	Gly 791, Glu 792, Thr 662, Thr 790, Leu 663, Ile 759, Tyr 659, Ile 672
			O	O	Asp 666	H-donor	2.76	-3.3	
			O	N	Arg 676	H-acceptor	2.84	-4.2	
			O	N	Arg 670	H-acceptor	2.92	-2.0	
			O	N	Arg 699	H-acceptor	3.23	-2.2	
D3-3W37	-12.7	1.52	O	O	Asp 666	H-donor	2.83	-2.3	Val 760, Leu 663, Thr 790, Asn 758, Gly 791, Arg 670, Ile 672, Tyr 659, Gly 698, Ile 701
			O	O	Glu 792	H-donor	2.91	-1.5	
			O	O	Ile 759	H-donor	2.68	-2.2	
			O	N	Arg 699	H-acceptor	2.80	-0.9	
			O	N	Arg 676	H-acceptor	3.30	-1.7	
			O	N	Gly 700	H-acceptor	2.76	-0.8	
D1-3AJ7	-15.3	1.79	O	O	Glu 411	H-donor	2.88	-1.5	Lys 156, Ser 157, Phe 159, Gln 279, Leu 313, Arg 442, Gln 353, Asp 215, Asp 352, Phe 178, Arg 213, Val 216, Arg 315, Phe 303, Thr 310, Phe 314, Ser 311, Pro 312, Ser 241, Ser 240
			O	O	Asp 307	H-donor	3.27	-1.0	
			O	O	Glu 277	H-donor	2.61	-1.3	
			O	O	Glu 277	H-donor	3.12	-1.2	
			O	O	Glu 277	H-donor	2.63	-3.4	
			O	O	Asp 242	H-donor	2.96	-1.9	
			O	O	Asp 69	H-donor	2.96	-2.9	
			C	6-ring	Tyr 158	H-π	3.95	-0.7	
			O	5-ring	His 280	H-π	3.71	-0.9	
D2-3AJ7	-10.7	1.03	O	O	Asp 233	H-donor	2.70	-3.7	Leu 313, Asn 317, Asn 235, Ile 419, Ser 236, Ala 418, His 423, Phe 433
			O	O	Glu 422	H-donor	2.97	-1.5	
			O	O	Glu 429	H-donor	3.00	-1.4	
			O	N	Lys 156	H-acceptor	3.01	-0.7	
			C	6-ring	Phe 314	H-π	3.68	-1.0	
D3-3AJ7	-13.6	0.94	O	O	Glu 277	H-donor	2.82	-1.7	Glu 411, Tyr 158, Gln 353, His 351, Asp 69, Tyr 72, Val 216, Phe 303, Gln 279, Phe 159, Phe 178, Arg 315
			O	O	Asp 352	H-donor	2.84	-1.4	
			O	O	Asp 215	H-donor	2.81	-3.2	

			N	O	Glu 277	H-donor	3.27	-3.2	
			N	O	Asp 352	H-donor	3.09	-1.8	
			C	O	Asp 352	H-donor	3.44	-0.8	
			O	N	Arg 442	H-acceptor	2.96	-2.1	
			O	N	Arg 213	H-acceptor	3.02	0.5	
			N	O	Asp 215	ionic	3.93	-0.6	
			N	O	Glu 277	ionic	3.82	-0.9	
			N	O	Glu 277	ionic	3.27	-2.9	
			N	O	Asp 352	ionic	3.09	-3.9	
DS: Docking score energy (kcal.mol^{-1}); **RMSD**: Root-mean-square deviation (Å)									
L: Ligand; **P**: Protein; **T**: Type; **D**: Distance (Å); **E**: Energy (kcal.mol^{-1})									