Supplementary

Triterpenic Acid Amides as a Promising Agent for Treatment of Metabolic Syndrome

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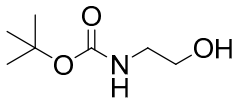
INDEX

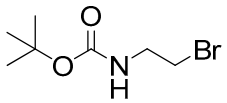
Synthesis of tert-butyl 2-bromoethylcarbamate

Tert-butyl 2-hydroxyethylcarbamate (17)



14 mmol of Boc_2O was dissolved in 60 ml of CH_2Cl_2 and cooled to 0 °C, then solution of 13 mmol of aminoethanol in 20 ml of CH_2Cl_2 was added dropwise in an argon atmosphere. After, the cooling was removed, reaction left stirring for 3 hours. Reaction was monitored by TLC in the hexane:EtOAc - 10:1 system. The reaction mixture was washed with water. The organic layer was dried over $MgSO_4$. Purification was carried out by column chromatography on silica gel in the hexane:EtOAc – 8:1 system. Colorless oil, 2.01 g. Yield 94%. The spectral data coincide with the literature data. [1].

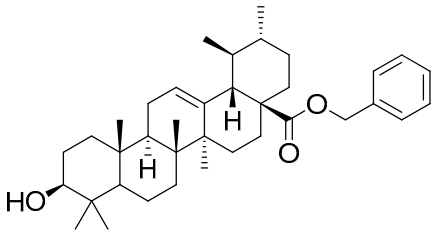
Tert-butyl 2-bromoethylcarbamate (10)



10.8 mmol of CBr_4, 9.9 mmol of tert-butyl 2-hydroxyethylcarbamate **17** were dissolved in 40 ml CH_2Cl_2, cooled in an ice bath to 0 °C. Then 9.9 mmol of PPh_3 was added in portions. After addition, reaction was stirred for 4 hours. The solvent was evaporated, and product was then purified by column chromatography in the hexane:EtOAc – 8:1 system. Yellow oil, 2.15 g. Yield 89%. The spectral data coincide with the literature data. [2]

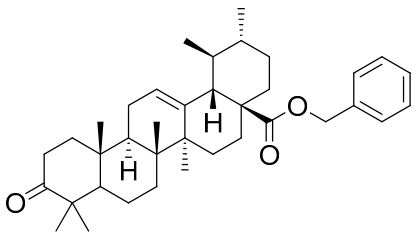
Synthesis of corosolic acid

3-hydroxyurs-12-en-28-oic acid benzyl ester (18a)



In a 100 ml round-bottom flask, 8.2 mmol of ursolic acid **8a** and 10.7 mmol of benzyl bromide were dissolved in 40 ml DMF. 3 g of K_2CO_3 were added, and the mixture was stirred for 24 hours. Reaction was monitored by TLC in chloroform. The reaction mixture was poured into 500 ml of water, and the precipitated white flakes were filtered off on a Schott filter and washed with 2x25 ml of cold CH_3CN. White powder, 4.35 g. Yield 97%. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.54 (s, 3H), 0.66 (s, 3H), 0.82 (s, 3H), 0.90 (m, 6H), 1.0 (s, 3H), 0.99-1.07 (m, 3H), 1.42-2.15 (m, 23H), 2.98 (br.s, 1H), 4.31 (bs, 1H), 4.94 (m, 1H), 5.04 (d, 1H), 5.13 (s, 1H), 7.32 (bs, 5H).

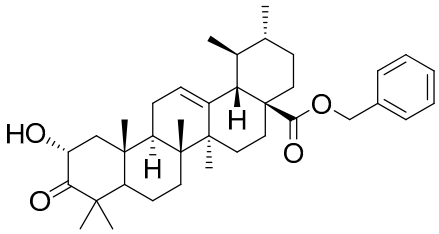
3-oxours-12-en-28-oic acid benzyl ester (18b)



To a cooled solution of 1.6 mmol of 3-hydroxyurs-12-ene-28-acid benzyl ester **18a** in 15 ml of methylene chloride 2.4 mmol of PCC (pyridinium chlorochromate) was added in

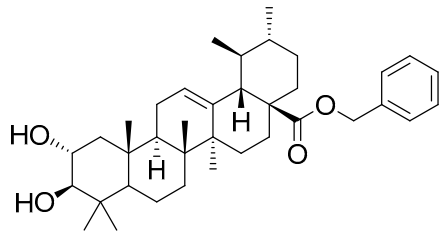
portions. After addition, the reaction was left for 4 hours under argon atmosphere. Reaction was monitored by TLC in $CHCl_3$:MeOH - 50:1 system. Then, 30 ml of Et_2O was added and stirred for 30 minutes. Ether layer was decanted, the methylene layer was evaporated on a rotary evaporator to give the crude product **18b** as light-blue powder. Yield 90%, 0.78 g. ^{1}H NMR (400 MHz, $CDCl_3$): 0.68 (s, 3H), 0.86 (d, *J*=6.3, 3H), 0.91 - 0.97 (m, 3H), 1.03 (d, *J*=7.0, 5H), 1.08 (s, 6H), 1.22 - 1.40 (m, 5H), 1.89 - 1.96 (m, 2H), 2.28 (d, *J*=11.3, 1H), 2.33 - 2.43 (m, 1H), 2.48 - 2.61 (m, 1H), 4.95 - 5.02 (m, 1H), 5.08 - 5.15 (m, 1H), 5.26 (br. s., 1H), 7.29 - 7.42 (m, 5H).

2α-hydroxy-3-oxours-12-en-28-oic acid benzyl ester (18c)



In a 100 ml round-bottomed flask, 2.3 mmol of 3-oxours-12-en-28-oic acid benzyl ester **18b** was dissolved in 15 ml of methylene chloride, cooled to 0 °C. 12 µl of H_2SO_4 were dissolved in 20 ml of MeOH, the MeOH solution was cooled to 0 °C and added in portions to the reaction mixture. Then 3.5 mmol of mCPBA (meta-Chloroperoxybenzoic acid) was added in portions, the reaction mixture was left in the dark under argon atmosphere for 72 hours. After completion of the reaction, 10 ml of 2% Na_2SO_3 solution was added and stirred for another 30 minutes. Reaction mixture was evaporated to 30 ml and then extracted three times with EtOAc. The combined organic extracts were washed with saturated solution of $NaHCO_3$ and then dried over $MgSO_4$. The solvent was stripped off, and the substance was purified by column chromatography in hexane:EtOAc - 5:1 to obtain **18c** as a white powder, 0.86 g. Yield 67%. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.59 - 0.76 (m, 3H), 0.66 (d, *J*=12.9, 3H), 0.77 - 0.97 (m, 9H), 2.22 - 2.31 (m, 2H), 2.43 (dd, *J*=12.5, 6.6, 1H), 4.56 (dd, *J*=12.5, 6.6, 1H), 4.95 - 5.04 (m, 1H), 5.07 - 5.15 (m, 2H), 5.25 (br. s., 1H), 7.30 - 7.38 (m, 5H).

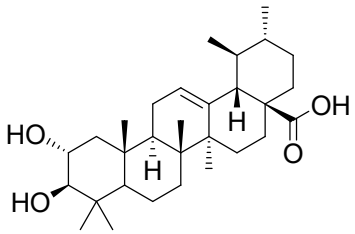
2α,3β-dihydroxyurs-12-ene-28-acid benzyl ester (18d)



In a 25 ml round bottom flask, 1 mmol of **18c** was dissolved in 6 ml THF:CH_3OH – 6:1 solution. The reaction mixture was cooled to 0 °C, then 1.2 mmol of $NaBH_4$ was added in portions with vigorous stirring. After addition, the reaction mixture was left stirring at room temperature for 4 hours. Upon completion of the reaction, the solution was acidified with 2M HCl to pH ~2-3 and then extracted with EtOAc. The organic extracts were dried over $MgSO_4$. The solvent was stripped off, and the residue was purified by column chromatography in hexane:EtOAc - 4:1 to obtain a white-yellow powder, 0.39 g. Yield 70%. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.65 (s, 3H), 0.78 - 0.88

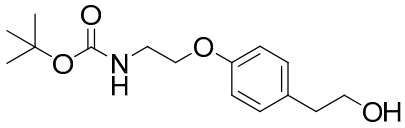
(m, 6H), 0.90 - 1.12 (m, 15H), 1.23 - 1.40 (m, 6H), 1.70 (d, *J*=12.9, 2H), 2.28 (d, *J*=11.0, 1H), 3.02 (d, *J*=9.5, 1H), 3.71 (td, *J*=10.2, 4.1, 1H), 4.99 (d, *J*=12.6, 1H), 5.05 - 5.14 (m, 1H), 5.25 (br. s., 1H), 7.29 - 7.38 (m, 5H).

Corosolic acid (8b)



In a 15 ml flask, 0.5 mmol of **18d** was dissolved in 3 ml of THF and cooled in an ice bath. The solution was degassed, then 60 mg of 10% Pd/C was added. After addition, the reaction mixture was degassed again and purged with H_2 three times and left stirring under H_2 atmosphere. Reaction was monitored by TLC in the $CHCl_3$:MeOH:AcOH - 12:4:1 system. Upon completion of the reaction, the catalyst was filtered off, THF was evaporated. Purification was carried out by recrystallization from EtOH and then isolated as a white powder, 0.16 g. Yield 71%. ^{1}H-NMR (DMSO-d_6, 400MHz): 0.70 - 1.0 (m, 21H), 2.74 (m, 1H), 2.11 (m, 1H), 3.42 (t, J=9.8, 1H), 4.24 (d, J=8.7, 1H), 4.33 (dd, J=9.0, 11.5, 1H), 5.17 (br. s., 1H).

Tert-butyl 2-(4-(2-hydroxyethyl)-phenoxy)-ethylcarbamate (11)



White powder, 2.75 g. Yield 89%. *^{1}H-NMR* (400 MHz, $CDCl_3$): 1.42 (s, 9H), 2.78 (t, *J*=6.6, 2H), 3.49 (d, *J*=4.9, 2H), 3.78 (t, *J*=6.5, 2H), 3.96 (t, *J*=5.0, 2H), 5.03 (br.s., 1H), 6.81 (d, *J*=8.6, 2H), 7.11 (d, *J*=8.4, 2H). ^{13}C NMR (101 MHz): 28.34 (3C), 66.24, 67.01, 68.67, 79.35, 80.21, 129.85 (2C), 130.47 (2C), 130.8 155.85, 157.21. Found: m/z 281.1627 $[M]^+$. $C_{15}H_{23}NO_4$. Calc.: M 281.1625.

Spectral data

(*S*)-ethyl3-(4-(4-(2-(tert-butoxycarbonylamino)-ethoxy)-phenoxy)-phenyl)-2-ethoxypropanoate (13)

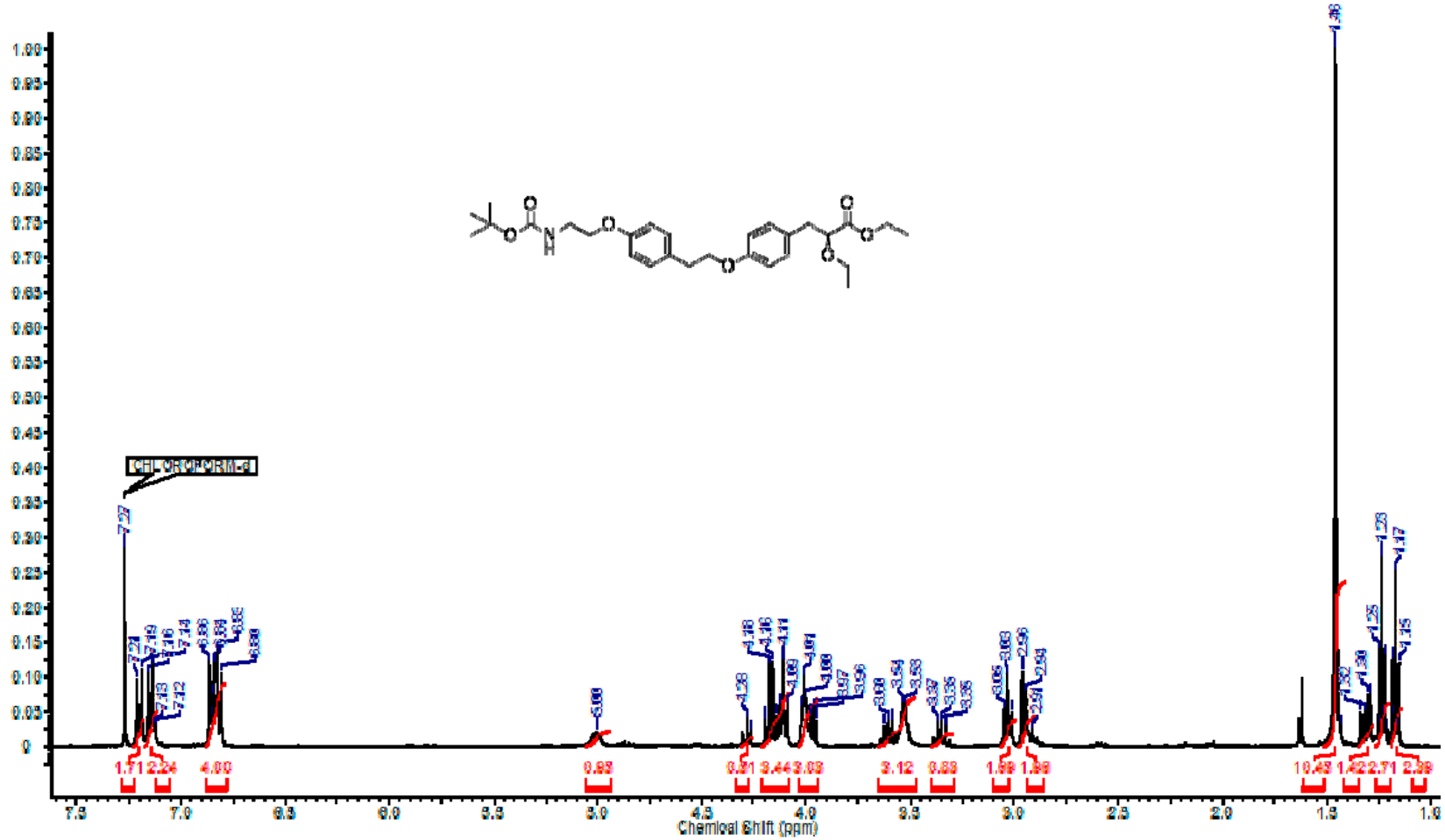


Figure S1

2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamine (14)

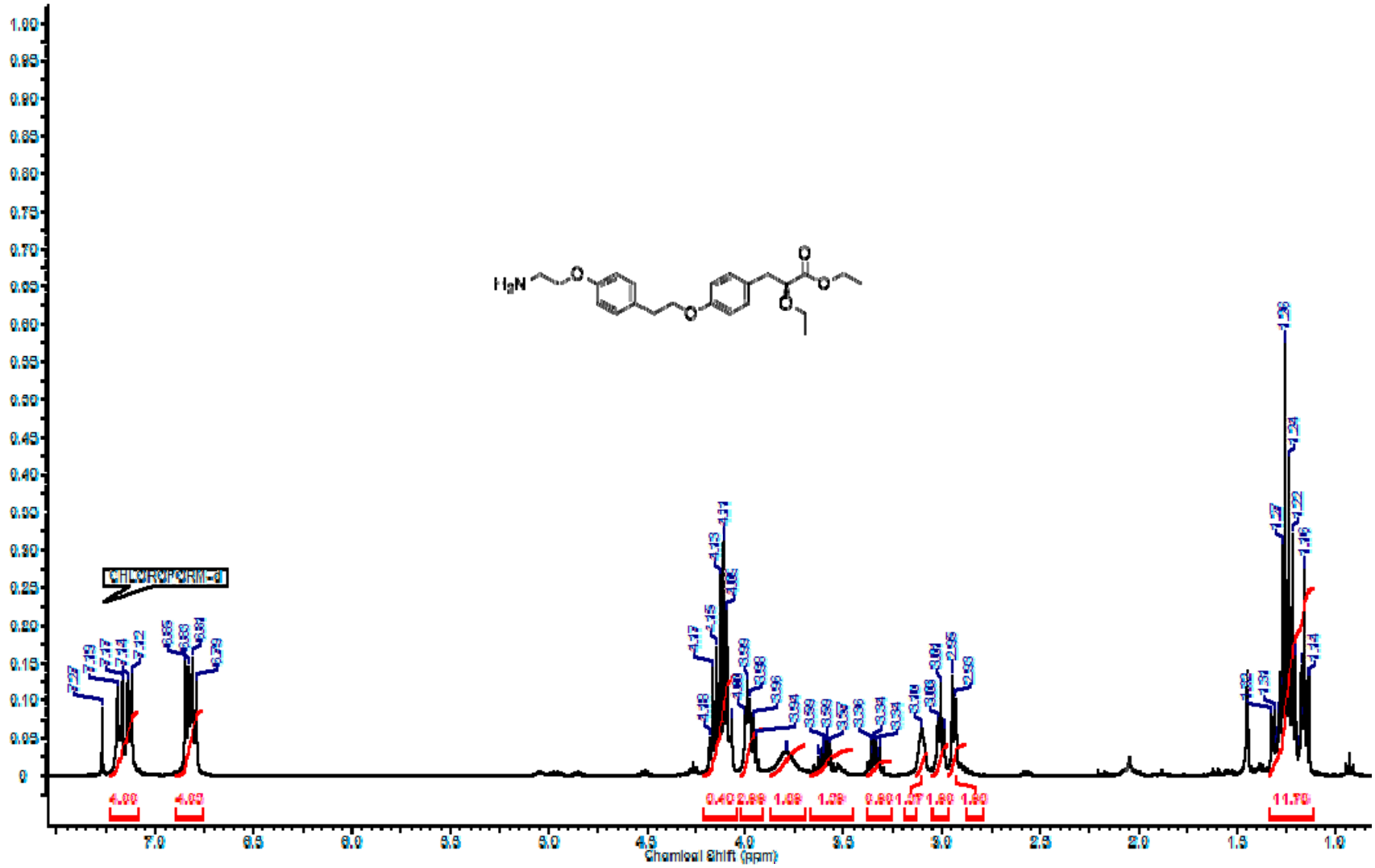


Figure S2

N-[3-Oxolup-20(29)-en-28-oyl]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (15a)

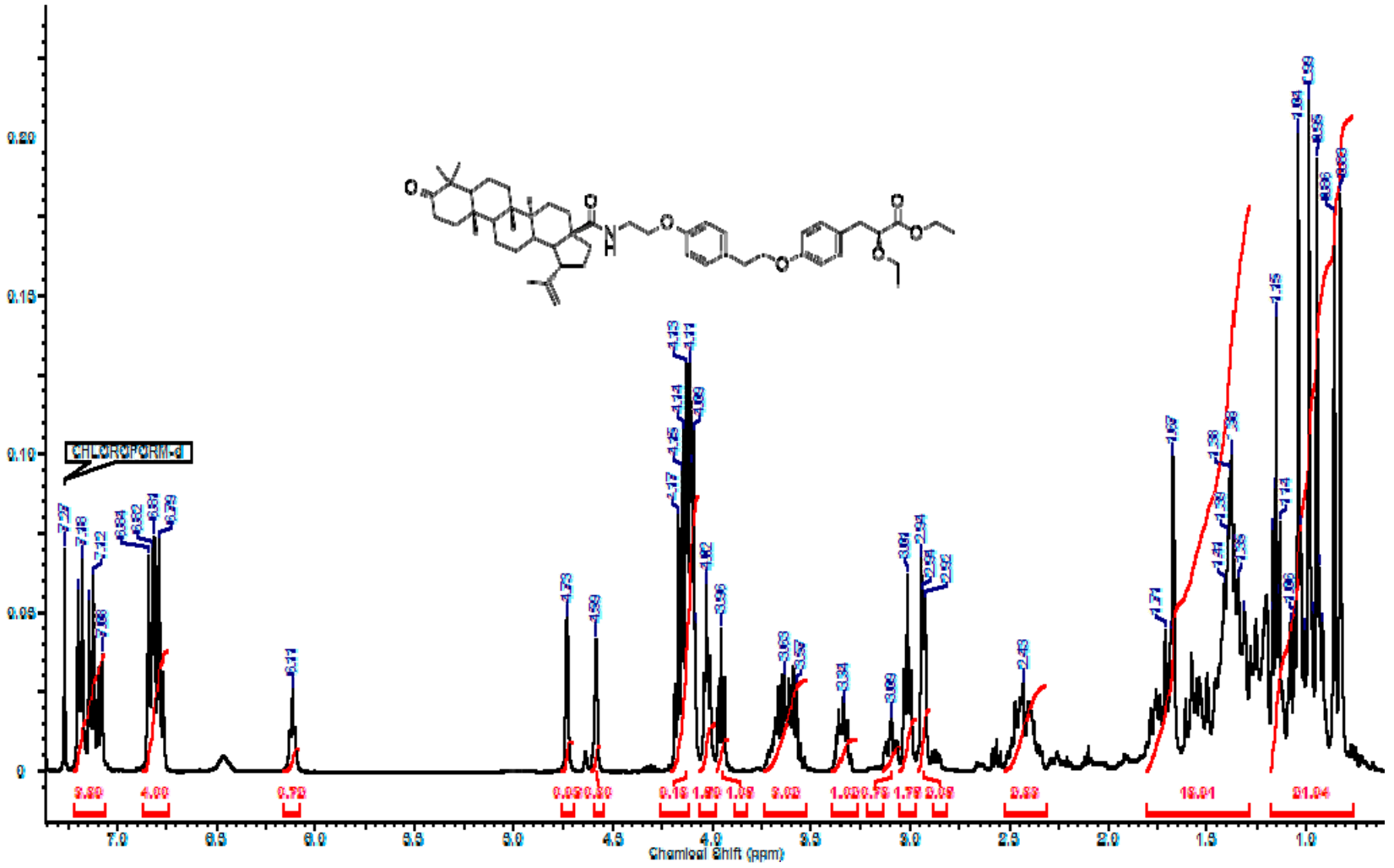
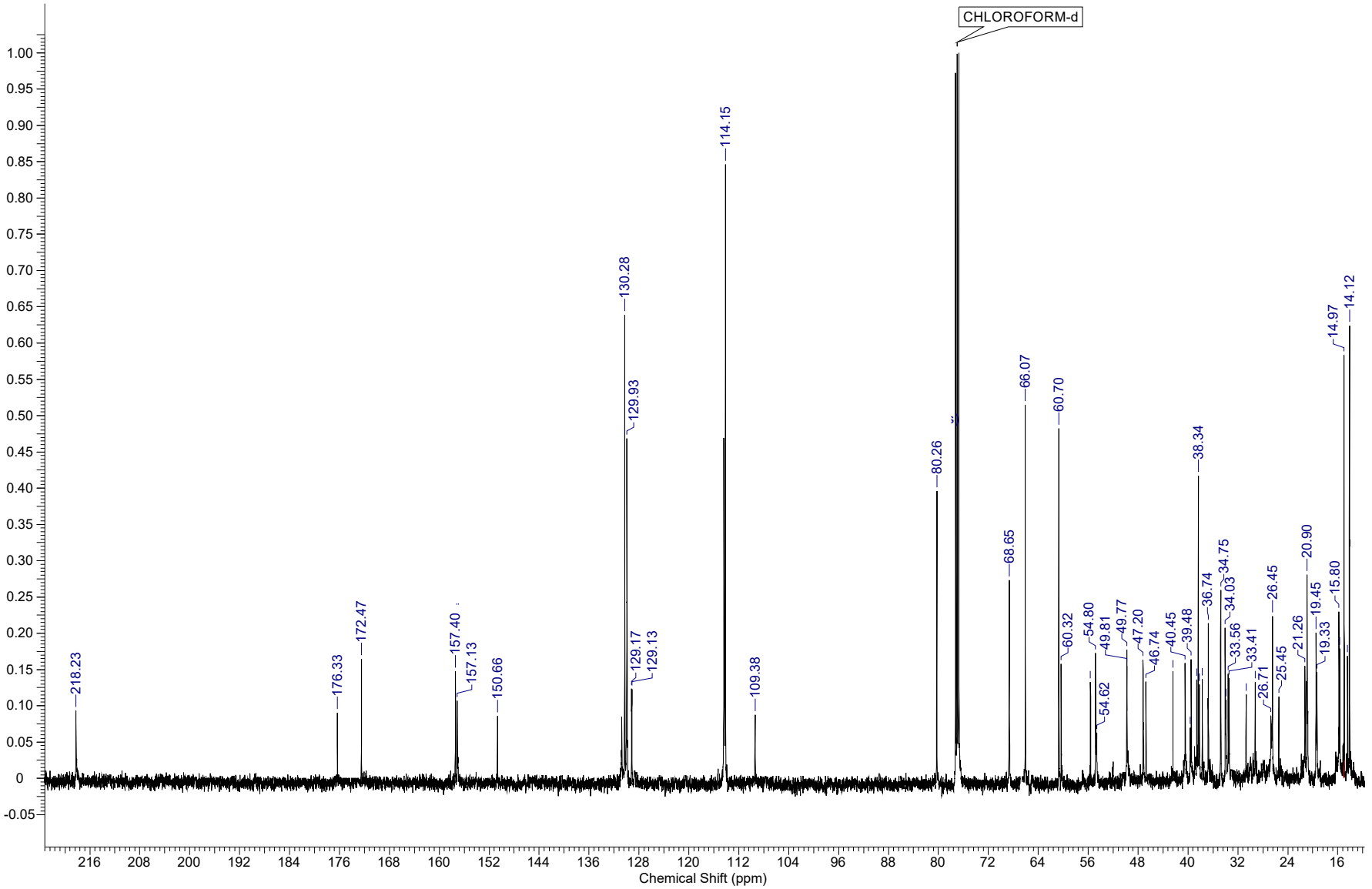


Figure S3


CHLOROFORM-d
218.23
176.33
172.47
157.40
157.13
150.66
130.28
129.93
129.17
129.13
114.15
109.38
80.26
68.65
66.07
60.70
60.32
54.80
54.62
49.81
49.77
47.20
46.74
40.45
39.48
38.34
36.74
34.75
34.03
33.56
33.41
26.71
26.45
25.45
21.26
20.90
19.45
19.33
15.80
14.97
14.12
Chemical Shift (ppm)

N-[3-Oxolup-28-oyl]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (15b)

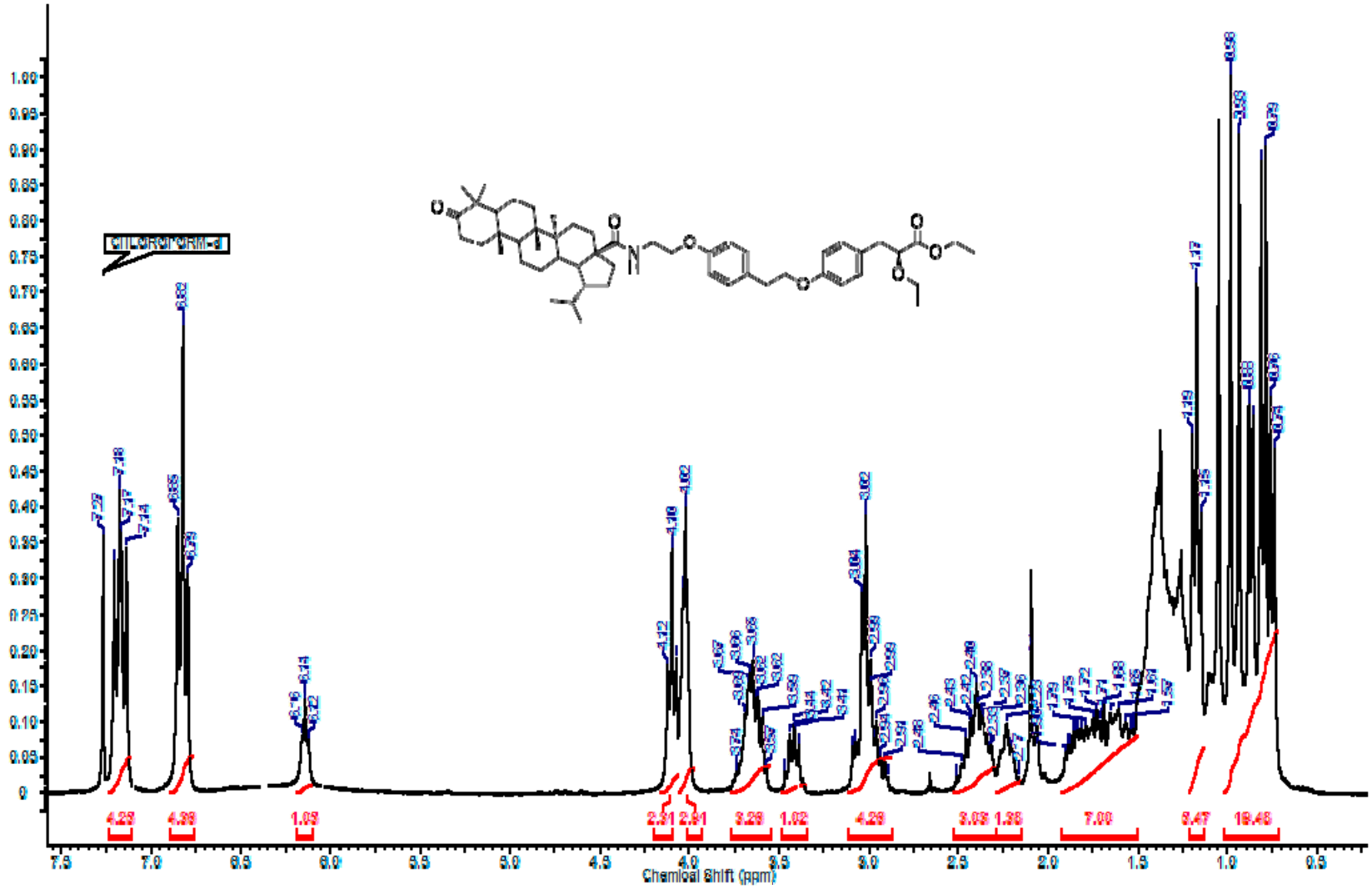
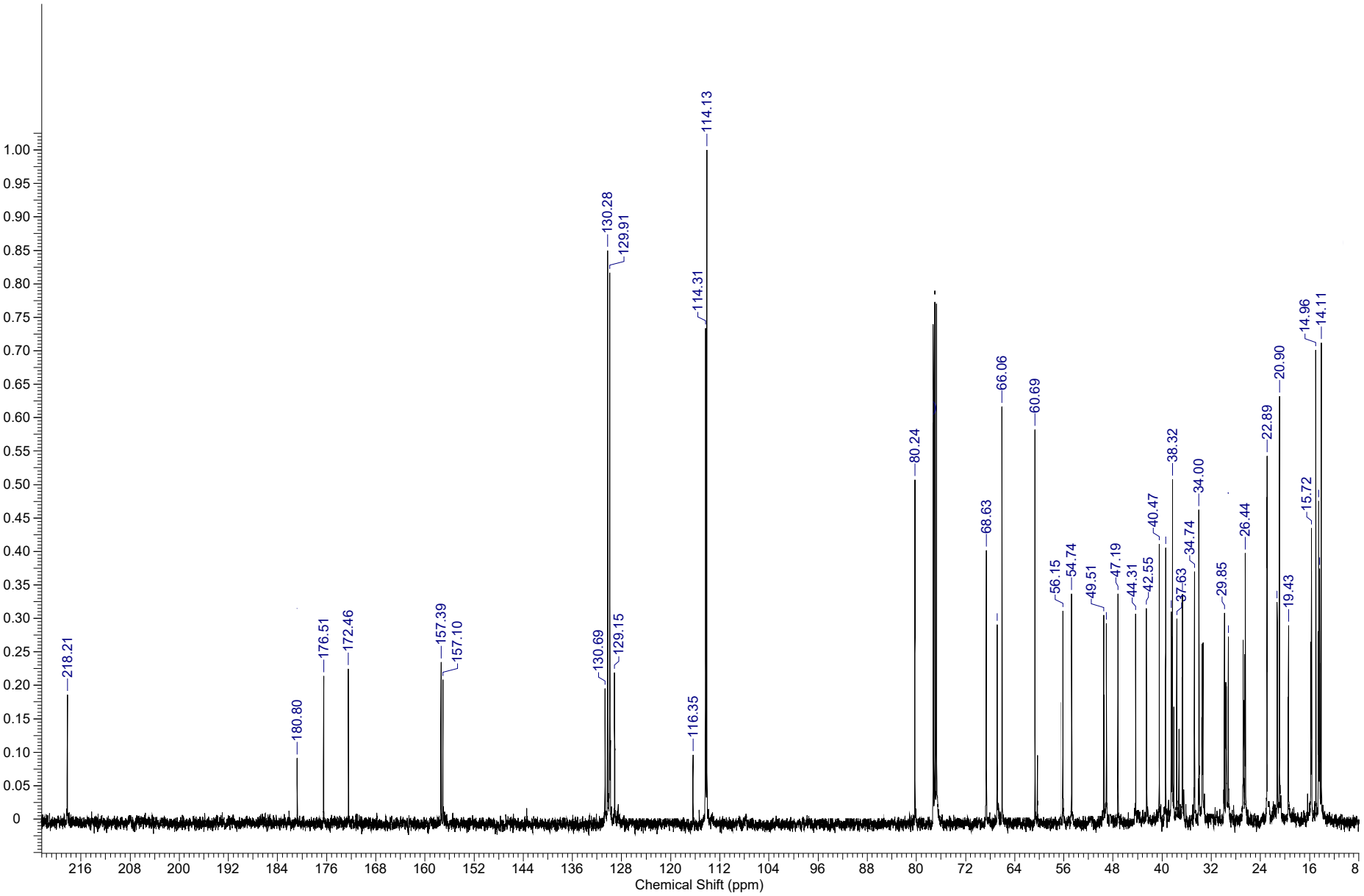


Figure S4


218.21
180.80
176.51
172.46
157.39
157.10
130.69
130.28
129.91
129.15
116.35
114.31
114.13
80.24
68.63
66.06
60.69
56.15
54.74
49.51
47.19
44.31
42.55
40.47
38.32
37.63
34.74
34.00
29.85
26.44
22.89
20.90
19.43
15.72
14.96
14.11
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
216
208
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)

[3β-acetoxy-11-oxo-18β-H-olean-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (15c)

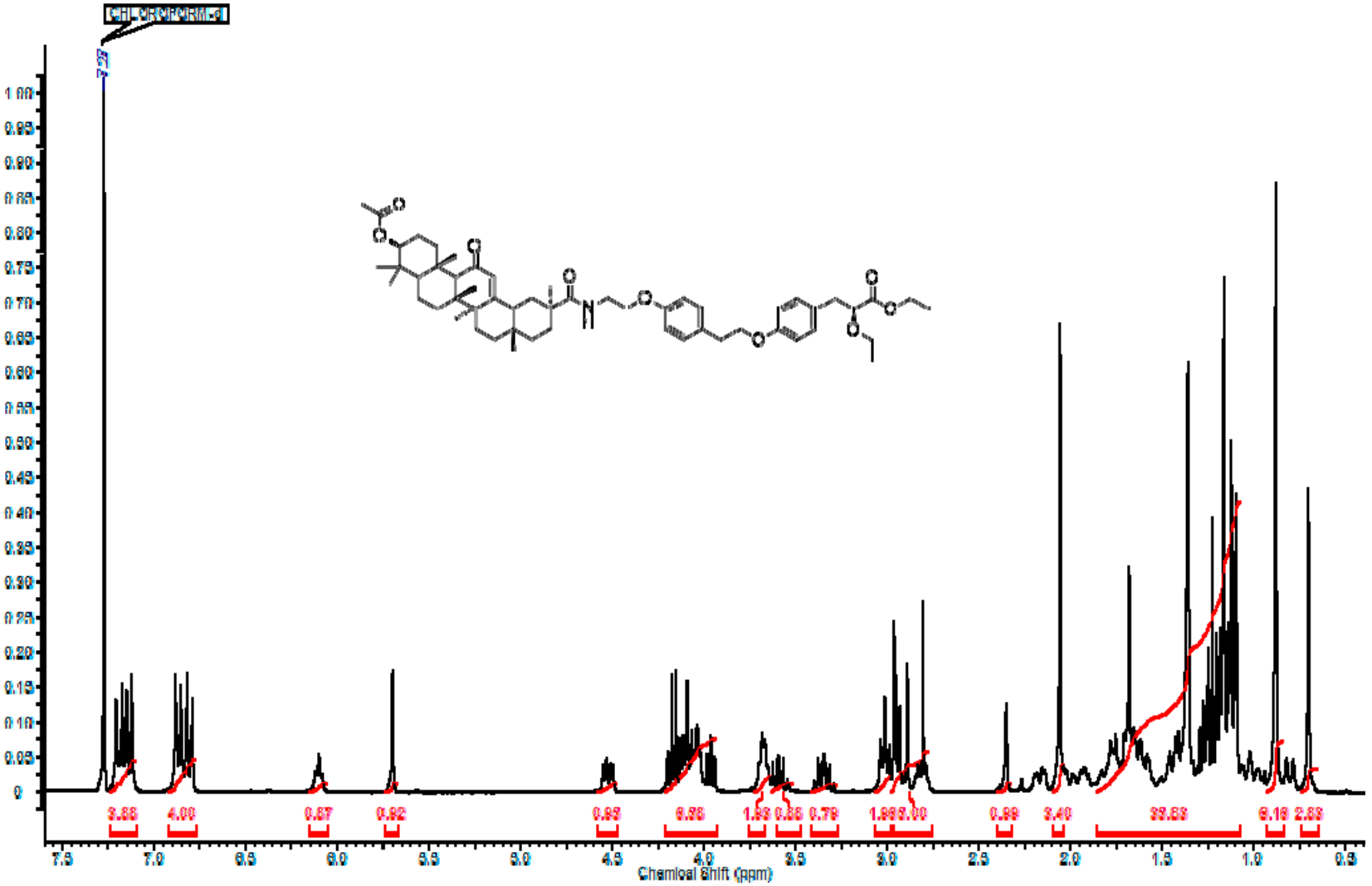
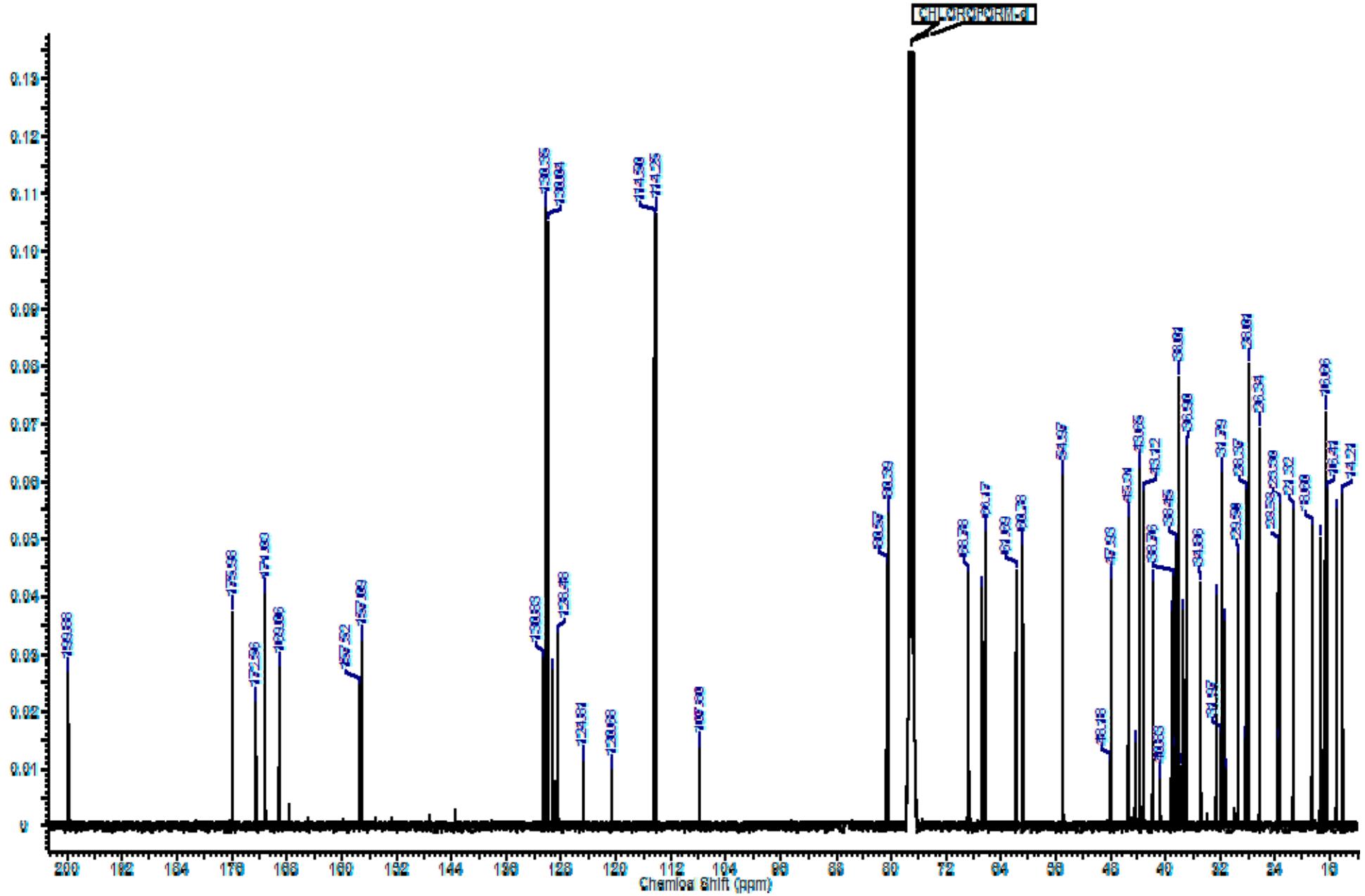


Figure S5


CHLOROFORM-D1
Chemical Shift (ppm)

[3ß-hydroxy-urs-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (15e)

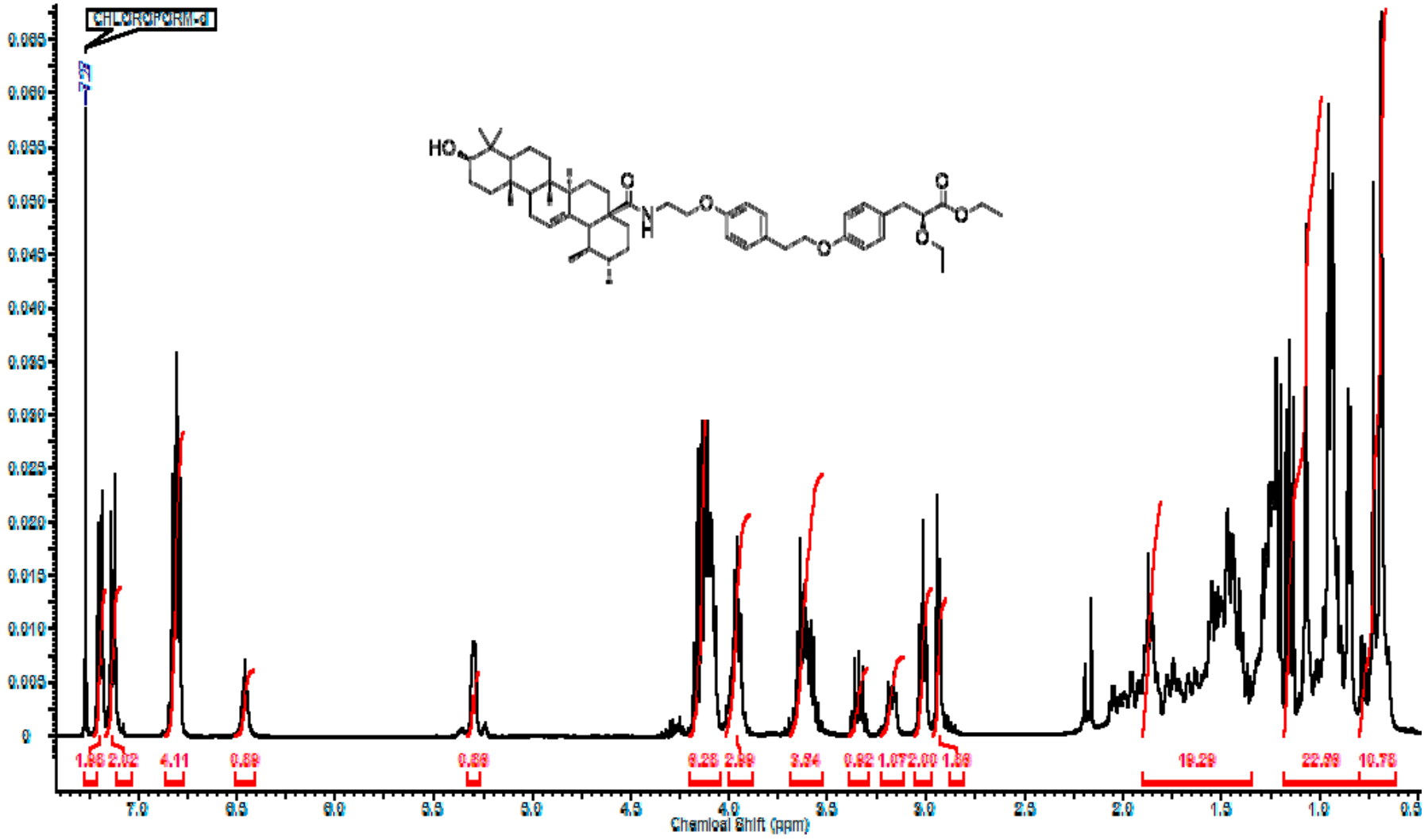
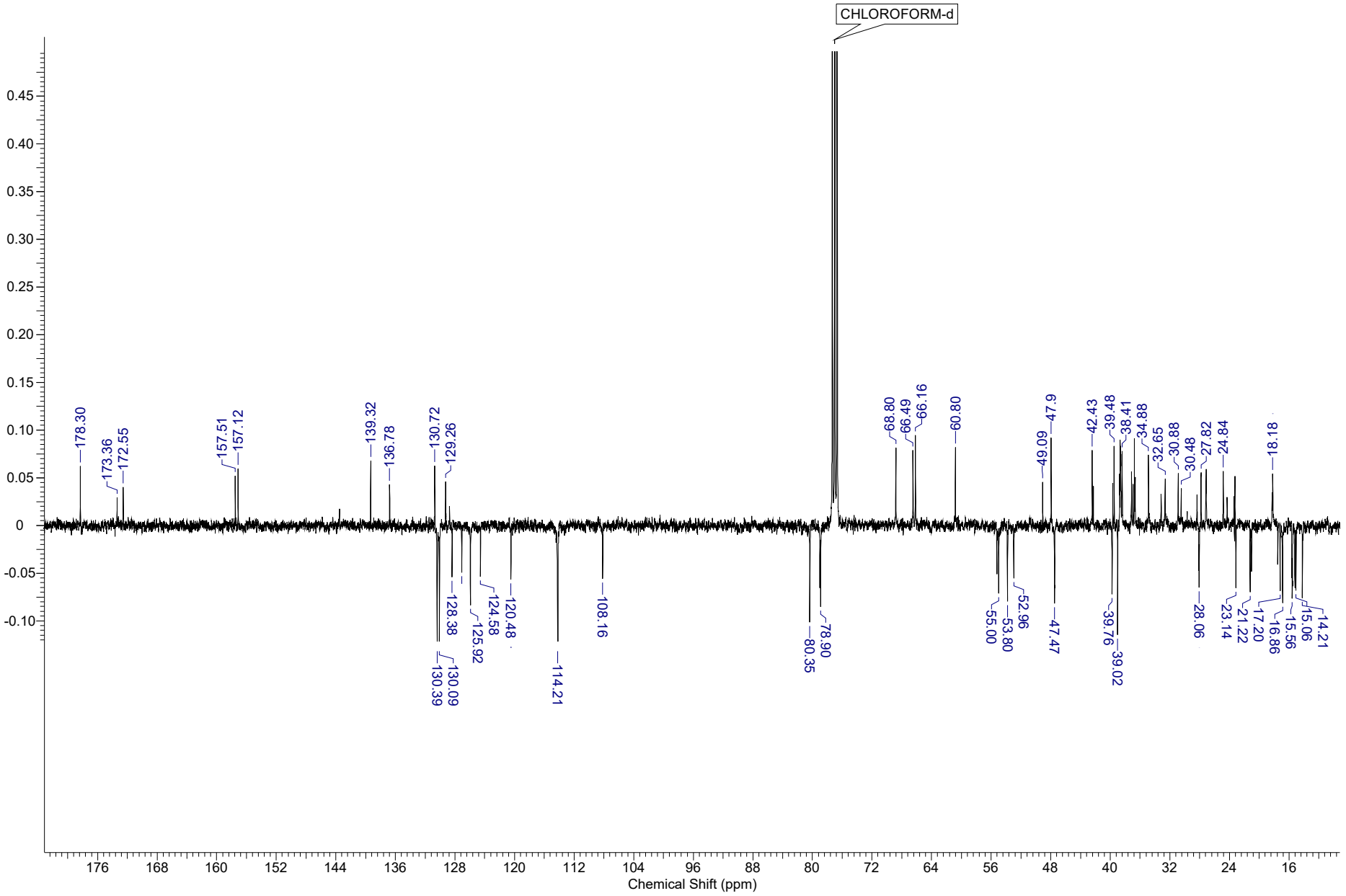


Figure S6


CHLOROFORM-d
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172.55
157.51
157.12
139.32
136.78
130.72
129.26
128.38
130.39
130.09
125.92
124.58
120.48
114.21
108.16
80.35
78.90
68.80
66.49
66.16
60.80
55.00
53.80
52.96
49.09
47.9
47.47
42.43
39.48
39.76
39.02
38.41
34.88
32.65
30.88
30.48
28.06
27.82
24.84
23.14
21.22
18.18
17.20
16.86
15.56
15.06
14.21
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
-0.05
-0.10
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

[2α,3ß-dihydroxy-urs-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (15f)

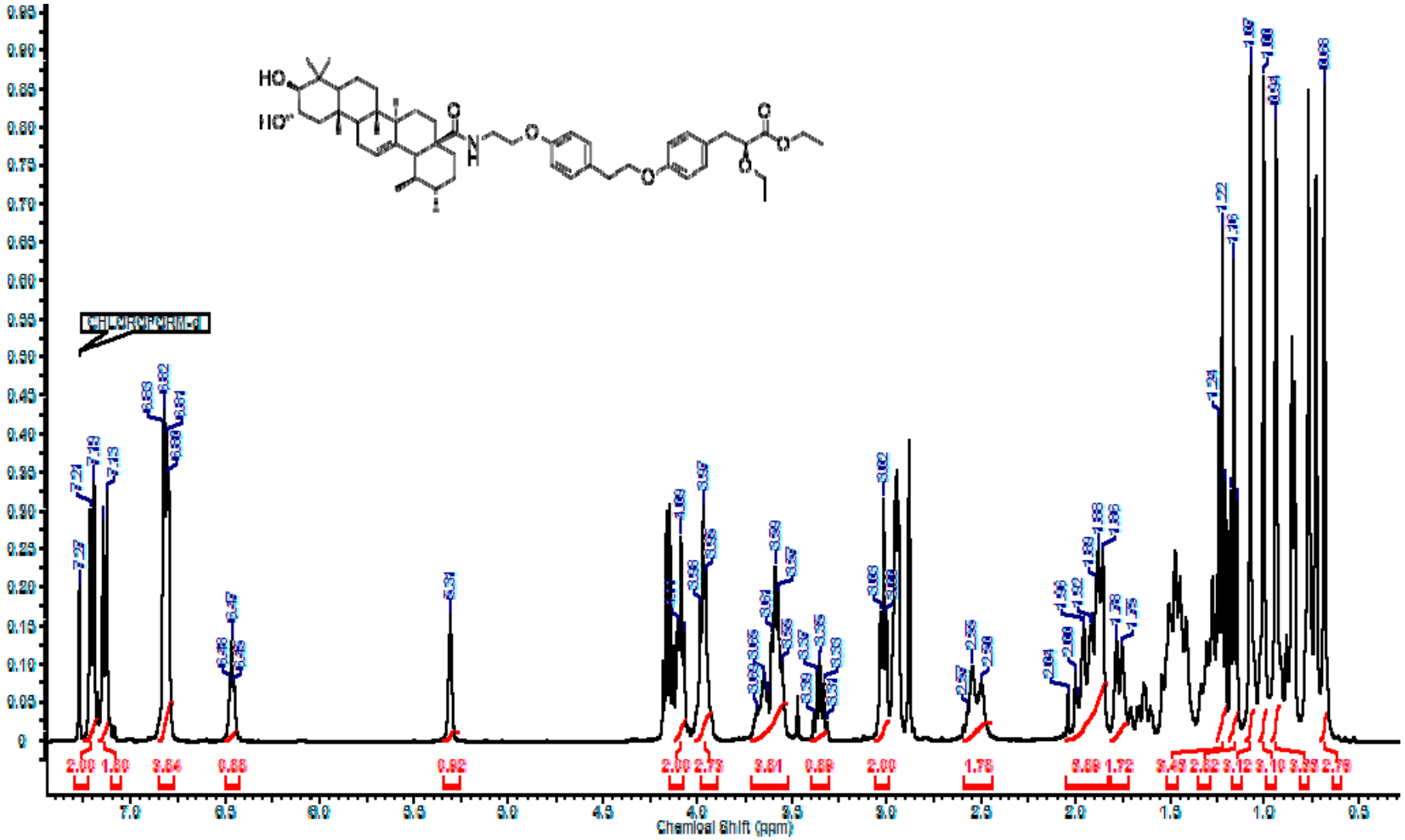
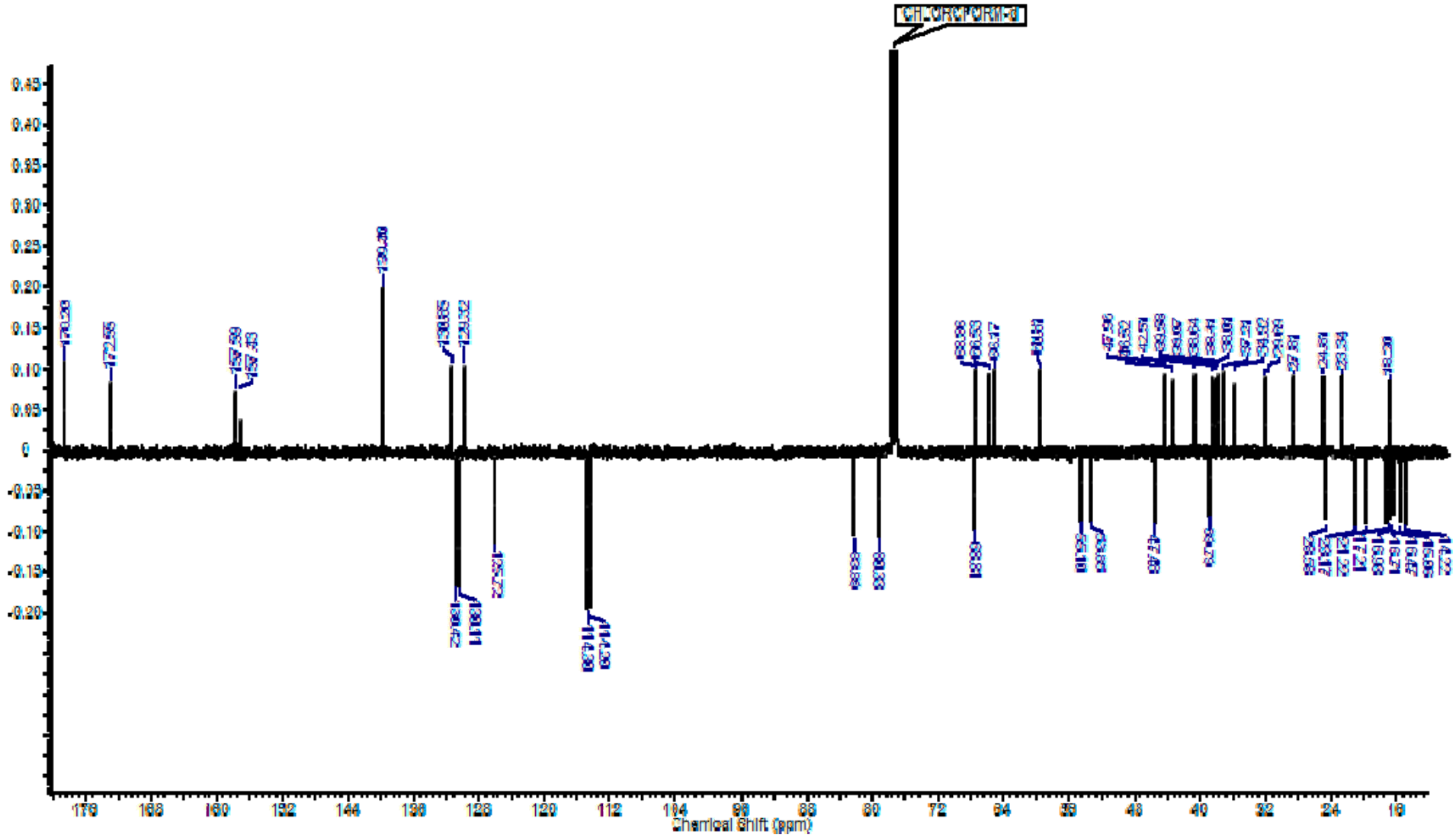


Figure S7


CHLOROFORM-d
Chemical Shift (ppm)

N-[3-Oxolup-20(29)-en-28-oyl]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (16a)

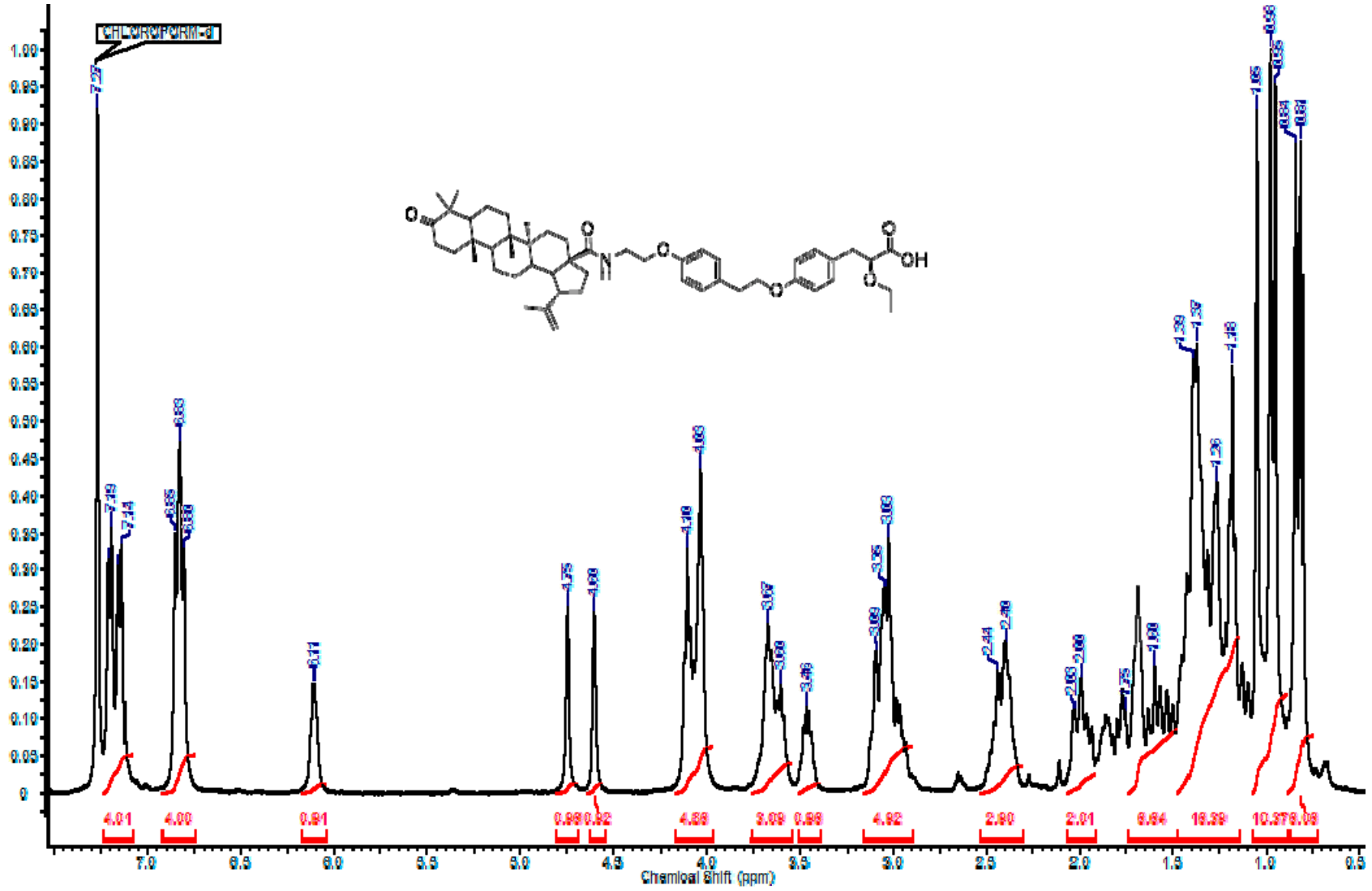
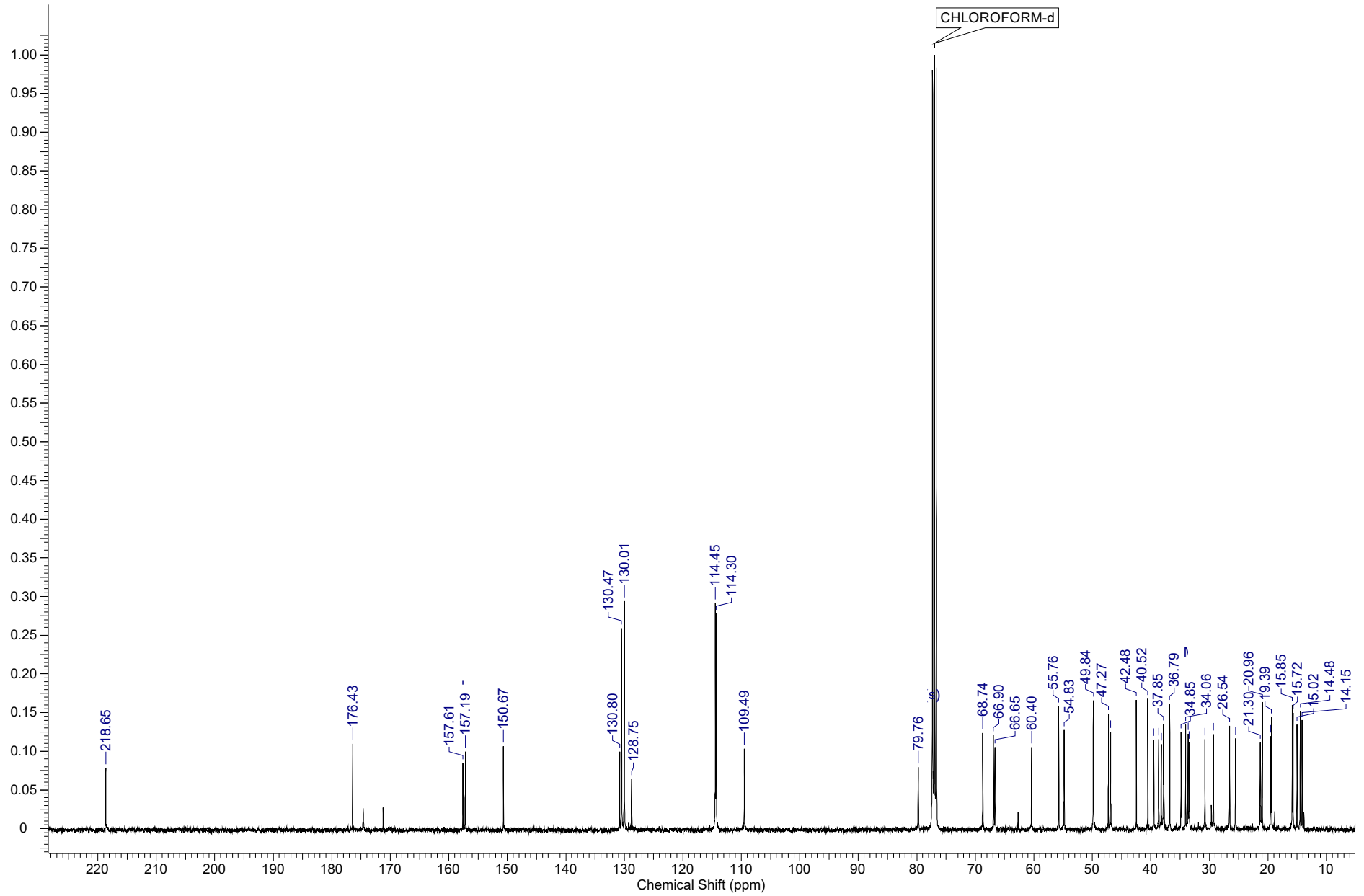


Figure S8


CHLOROFORM-d
218.65
176.43
157.61
157.19
150.67
130.47
130.80
130.01
128.75
114.45
114.30
109.49
79.76
68.74
66.90
66.65
60.40
55.76
54.83
49.84
47.27
42.48
40.52
37.85
36.79
34.85
34.06
26.54
21.30
20.96
19.39
15.85
15.72
15.02
14.48
14.15
Chemical Shift (ppm)

N-[3-Oxolup-28-oyl]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (16b)

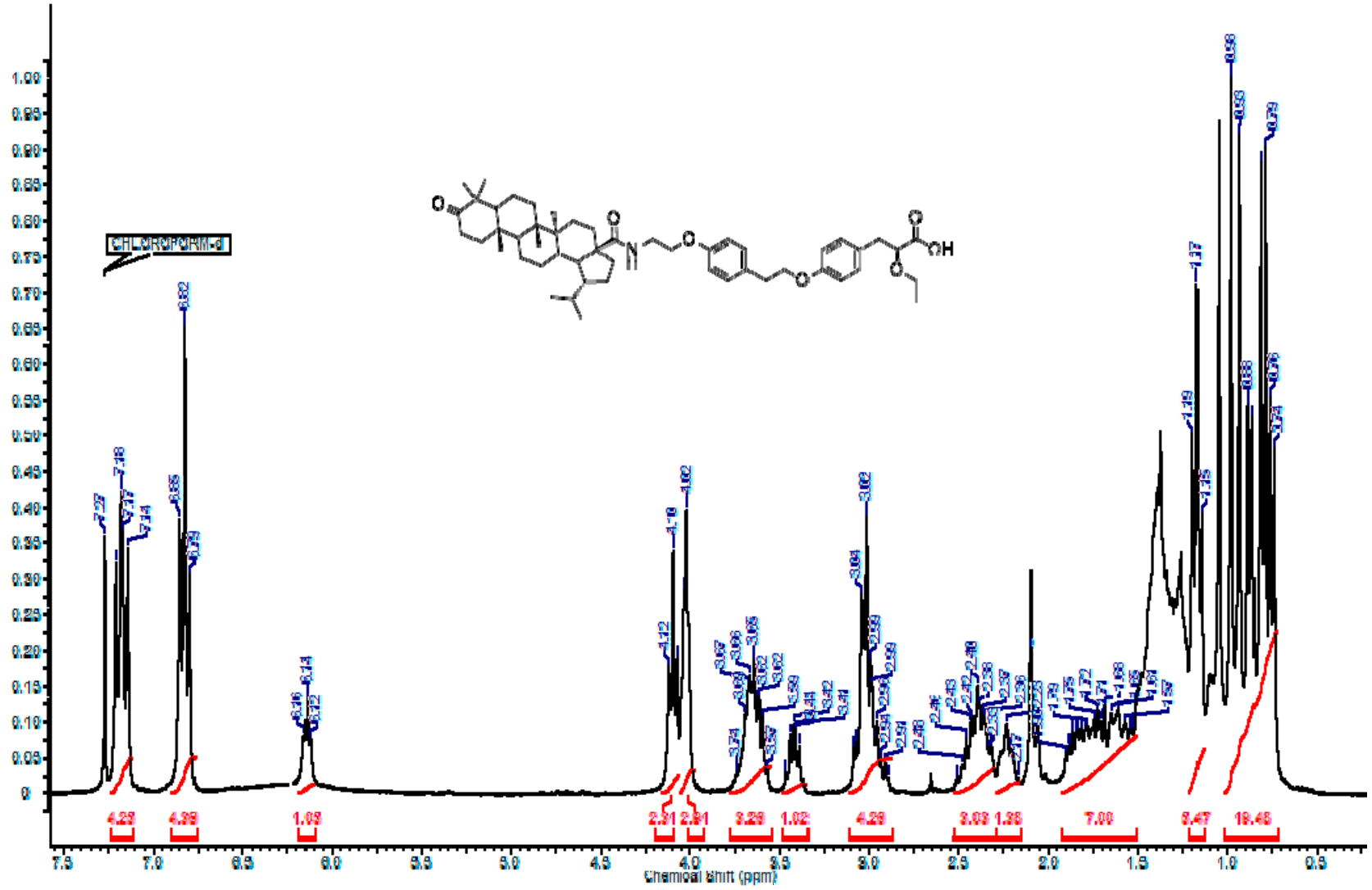
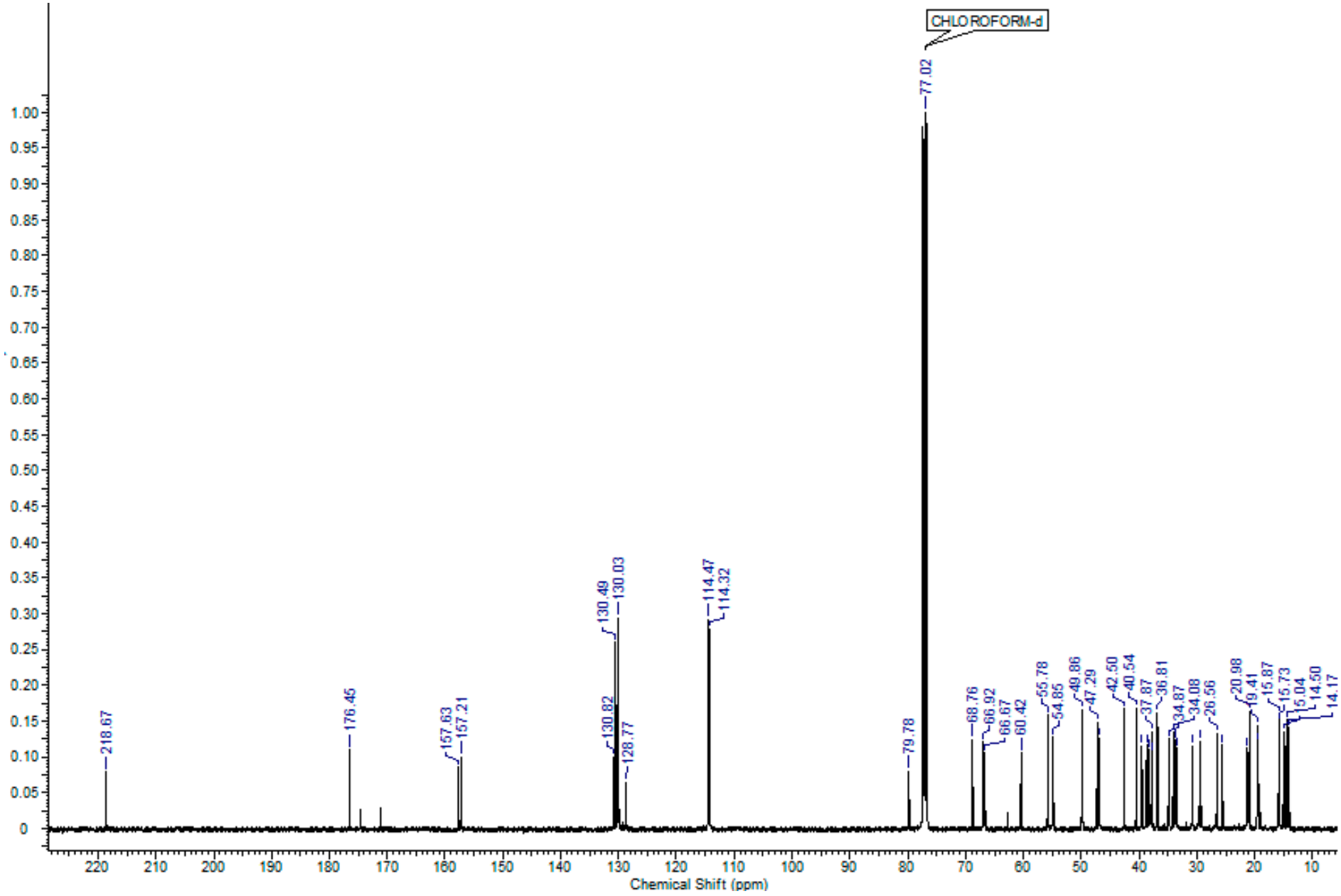


Figure S9


CHLOROFORM-d
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176.45
157.63
157.21
130.82
130.49
130.03
128.77
114.47
114.32
79.78
68.76
66.92
66.67
60.42
55.78
54.85
49.86
47.29
42.50
40.54
37.87
36.81
34.87
34.08
26.56
20.98
19.41
15.87
15.73
15.04
14.50
14.17
Chemical Shift (ppm)

[3β-acetoxy-11-oxo-18β-H-olean-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (16c)

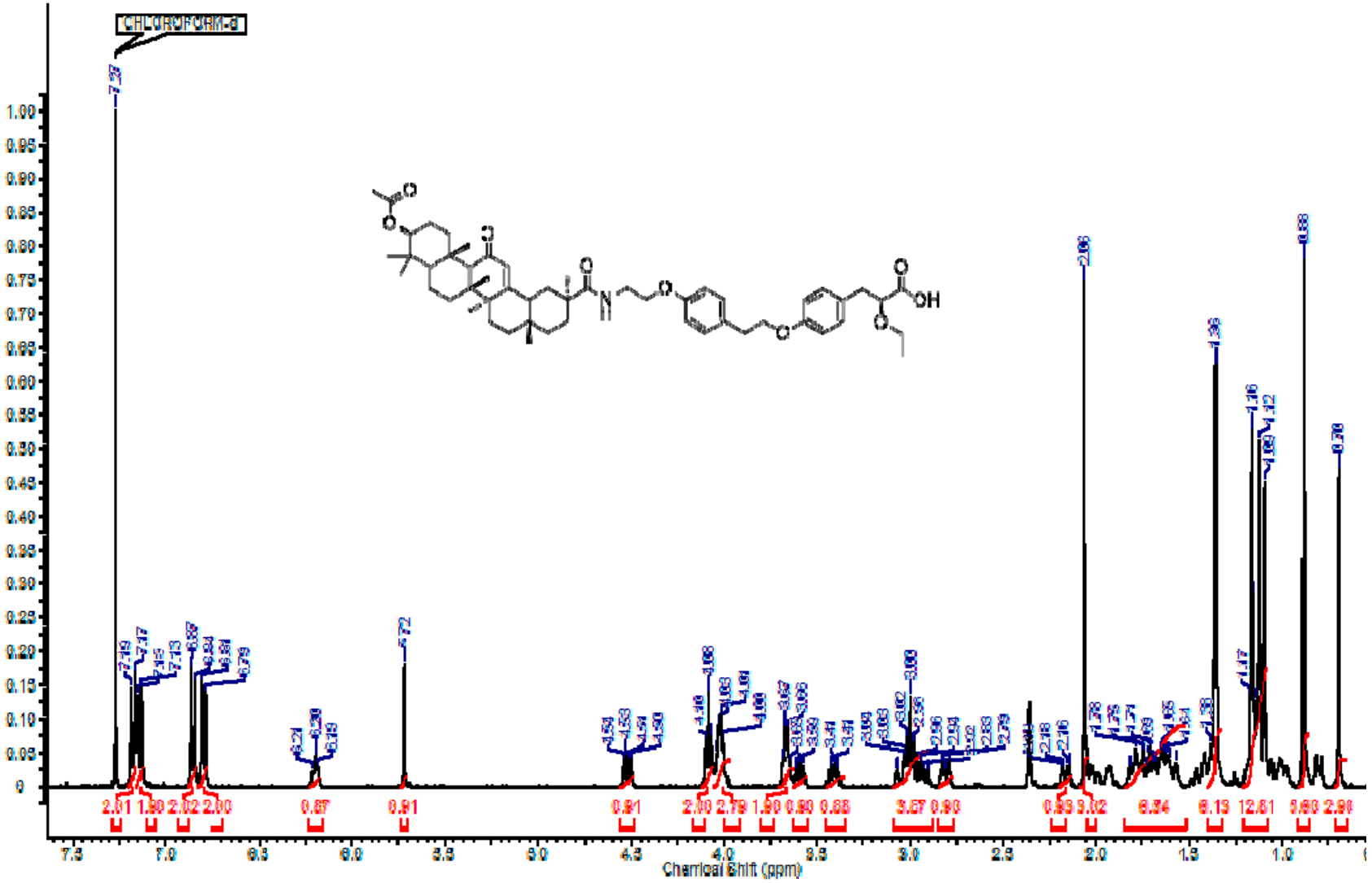
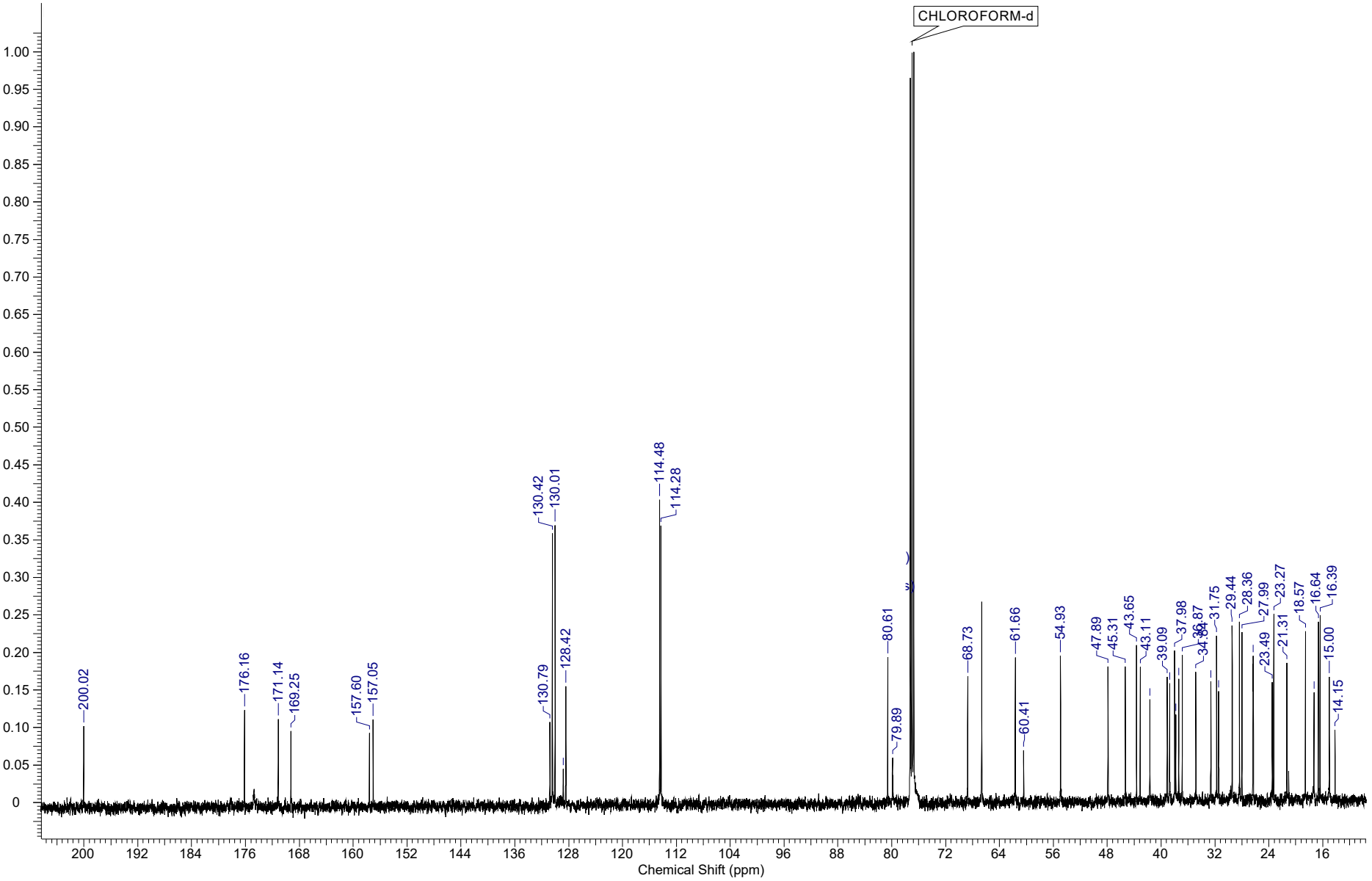


Figure S10


CHLOROFORM-d
200.02
176.16
171.14
169.25
157.60
157.05
130.79
130.42
130.01
128.42
114.48
114.28
80.61
79.89
68.73
61.66
60.41
54.93
47.89
45.31
43.65
43.11
39.09
37.98
34.87
31.75
29.44
28.36
27.99
23.49
23.27
21.31
18.57
16.64
16.39
15.00
14.15
Chemical Shift (ppm)

[3ß-hydroxy-urs-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (16e)

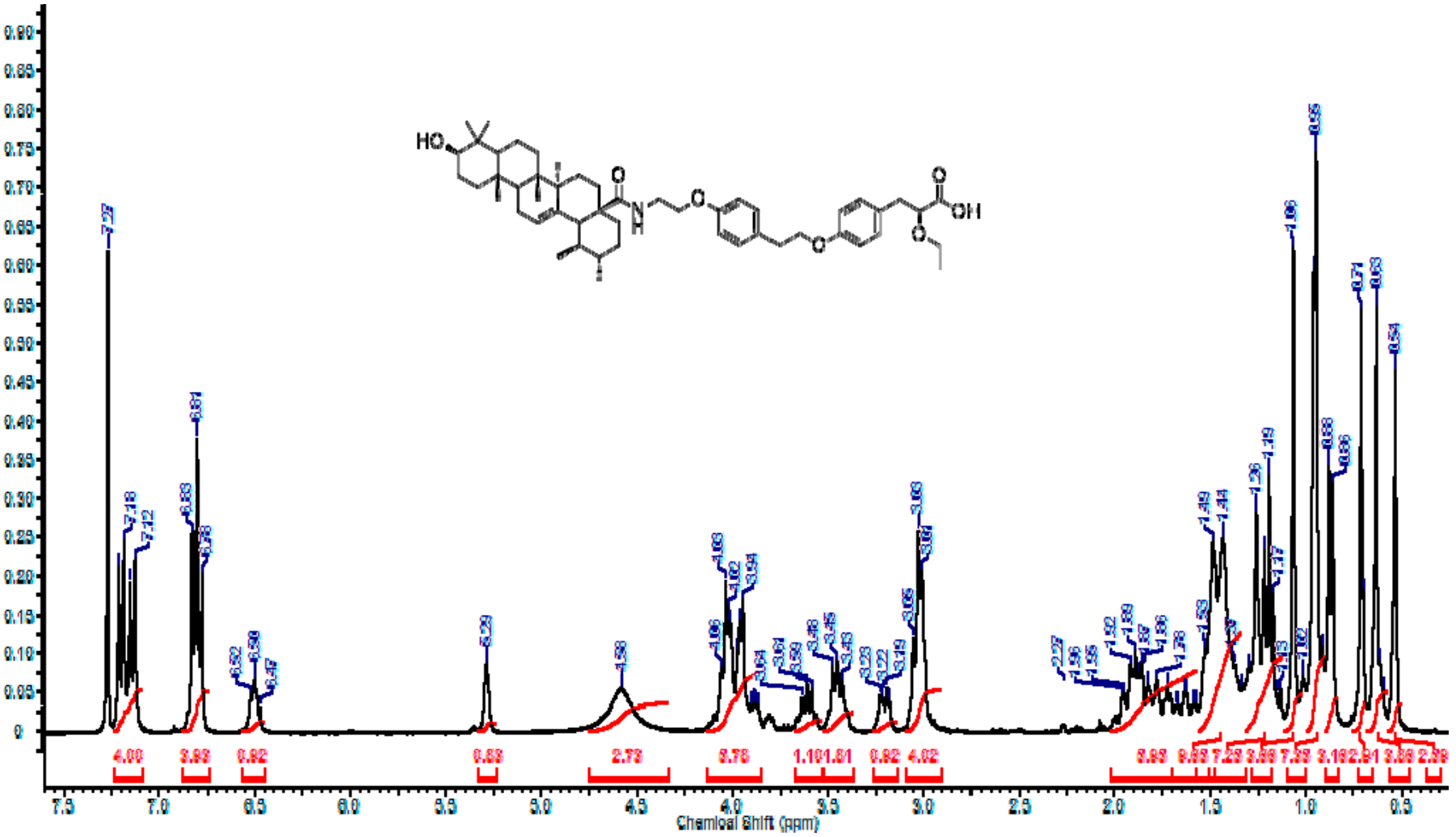
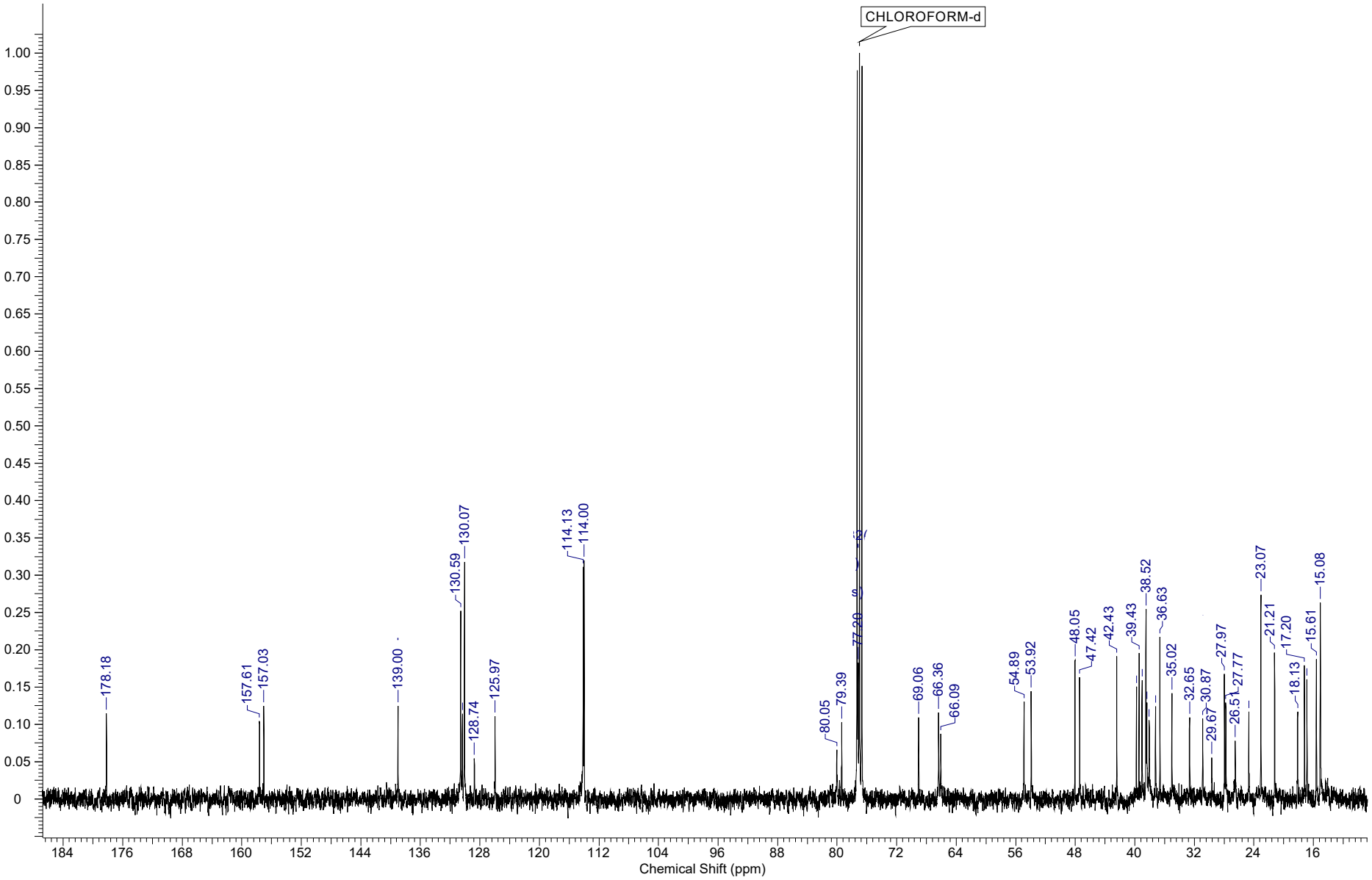


Figure S11


CHLOROFORM-d
178.18
157.61
157.03
139.00
130.59
130.07
128.74
125.97
114.13
114.00
80.05
79.39
77.00
69.06
66.36
66.09
54.89
53.92
48.05
47.42
42.43
39.43
38.52
36.63
35.02
32.65
30.87
29.67
27.97
26.51
27.77
23.07
21.21
18.13
17.20
15.61
15.08
Chemical Shift (ppm)

[2α,3ß-dihydroxy-urs-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (16f)

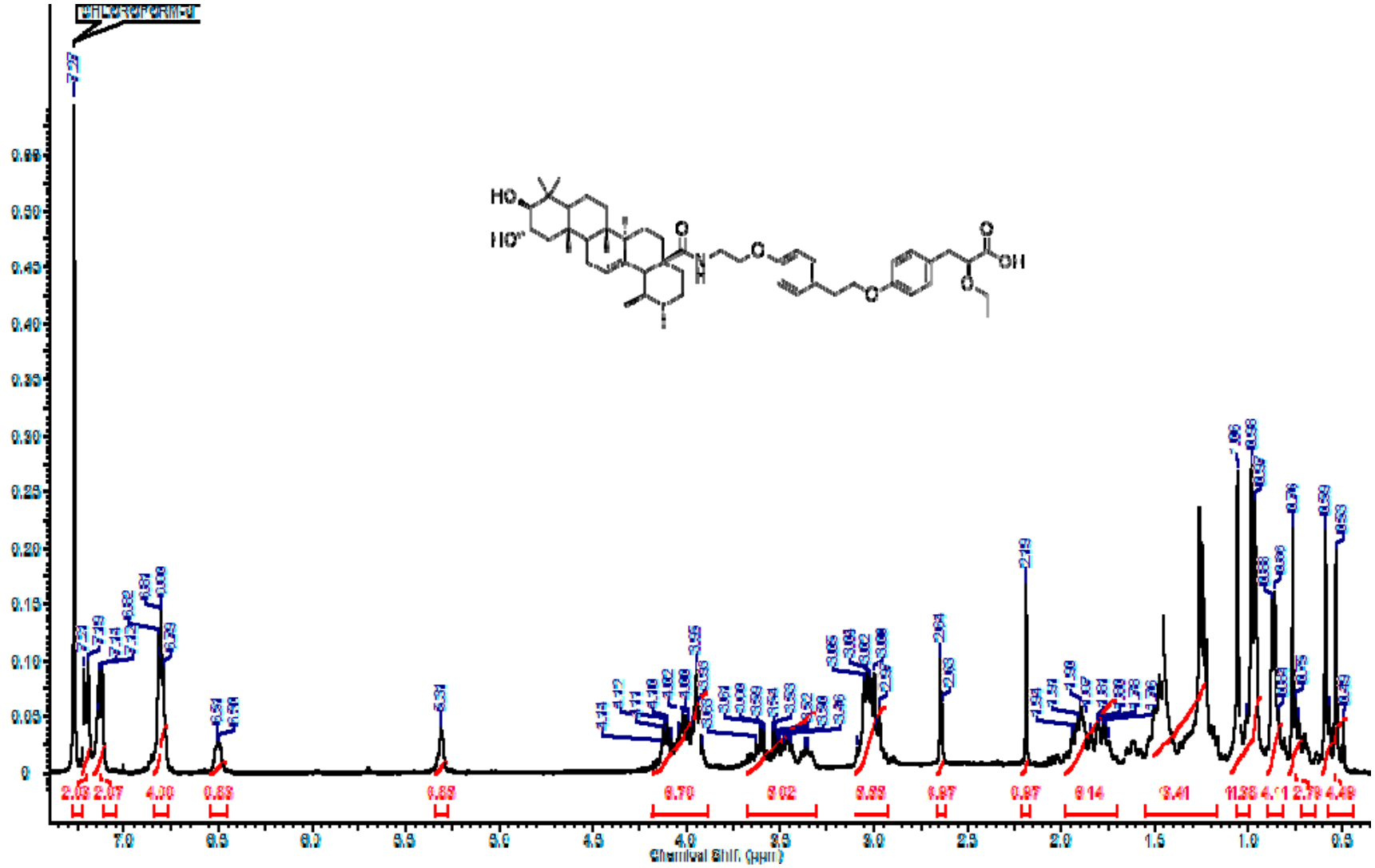
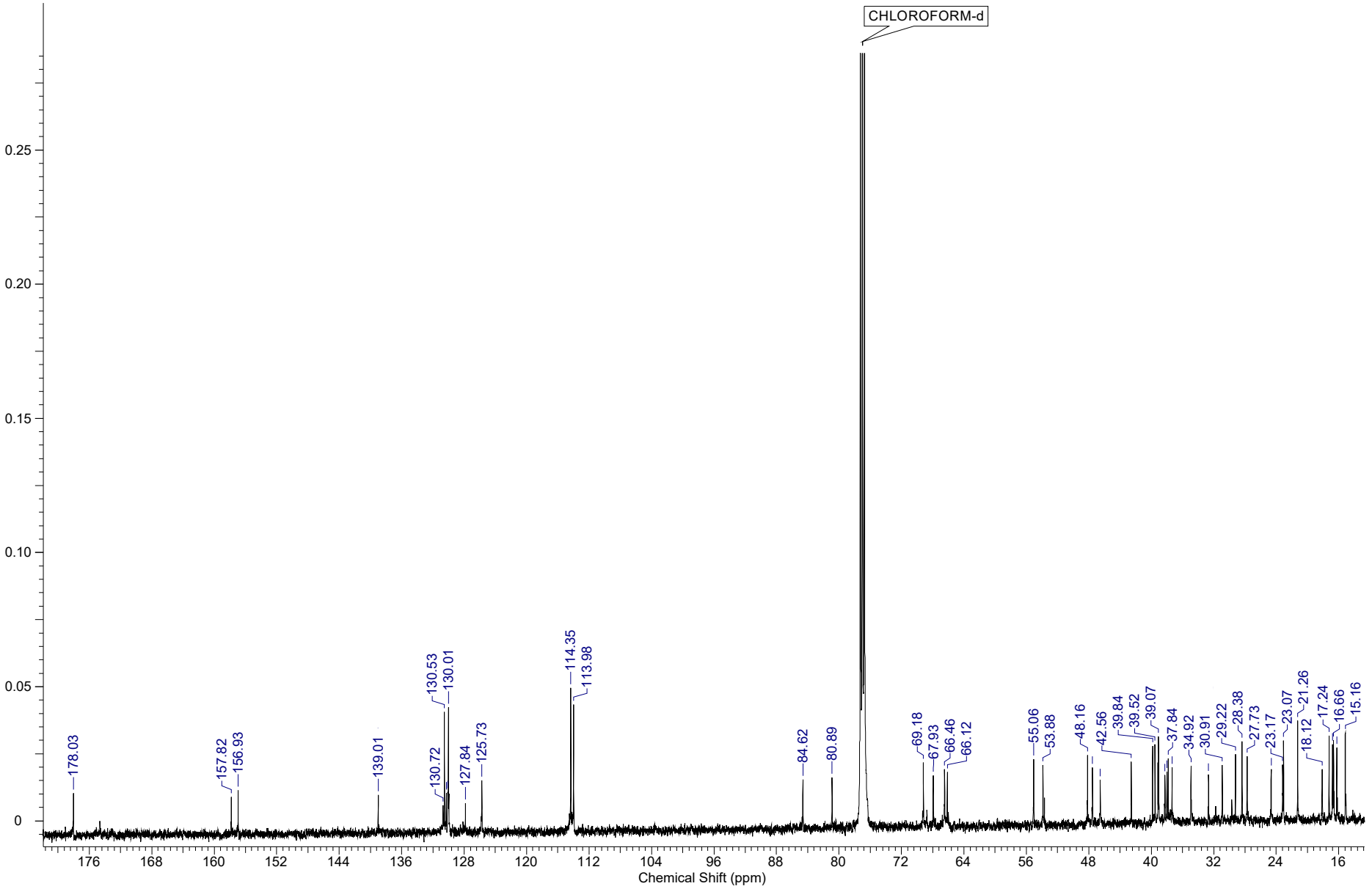


Figure S12


CHLOROFORM-d
178.03
157.82
156.93
139.01
130.72
130.53
130.01
127.84
125.73
114.35
113.98
84.62
80.89
69.18
67.93
66.46
66.12
55.06
53.88
48.16
42.56
39.84
39.52
39.07
37.84
34.92
30.91
29.22
28.38
27.73
23.17
23.07
21.26
18.12
17.24
16.66
15.16
0.25
0.20
0.15
0.10
0.05
0
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

1. W.Zhang, W. Fan, Z. Zhou, J. Garrison. ACS Medicinal Chemistry Letters, 2017, 8, 1269-1274.
2. N. Narayanaswamy, M. B. Avinash, T. Govindaraju. New Journal of Chemistry, 2013, 37, 1302.