Supplementary Materials for

Identification of new compounds with anticonvulsant and antinociceptive properties in a group of 3-substituted (2,5-dioxopyrrolidin-1-yl)(phenyl)-acetamides

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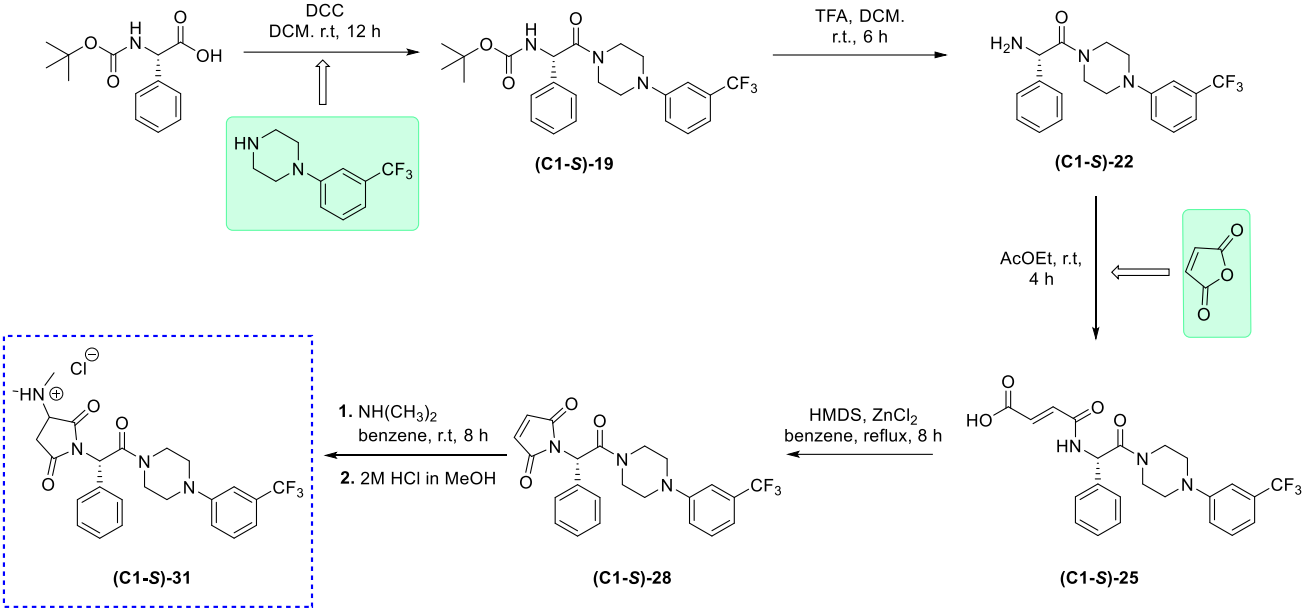
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Scheme S1. Synthetic pathway of compound **(C1-*S*)-31**.

Table S1. Anticonvulsant activity screening data in the MES, 6 Hz (32 mA) and *sc*PTZ seizure models in mice *i.p.* (dose of 100 mg/kg) at 0.5 h post compound administration.

Compd	A	R	MES	6 Hz (32 mA)	*sc*PTZ
13	-$NHCH_3$	3-CF_3	1/4	**2/4**	**2/4**
14	-$N(CH_3)_2$	3-CF_3	**4/4**	**3/4**	**2/4**
15	-$N(C_2H_5)_2$	3-CF_3	**4/4**	**3/4**	1/4
16	morpholine	3-CF_3	0/4	0/4	1/4
17	-$N(CH_3)_2$	3-OCF_3	**3/4**	**2/4**	**3/4**
18	-$N(CH_3)_2$	3-SCF_3	1/4	1/4	1/4
(C1-*R*)-31	-$N(CH_3)_2$	3-CF_3	**4/4**	**3/4**	**3/4**
(C1-*S*)-31	-$N(CH_3)_2$	3-CF_3	1/4	**2/4**	1/4
(C1-*R*)-32	-$N(CH_3)_2$	3-OCF_3	**4/4**	**3/4**	**3/4**
(C1-*R*)-33	-$N(CH_3)_2$	3-SCF_3	1/4	1/4	1/4

Data for the most potent compounds have been highlighted in bold for easier interpretation.
[a] Data indicate: number of mice protected / number of mice tested. The animals were examined at one pretreatment time – 0.5 h.
MES – the maximal electroshock seizure test.
6 Hz – the psychomotor 6 Hz seizure test (current intensity of 32 mA).
*sc*PTZ – the subcutaneous pentylenetetrazole seizure test.

Table S2. Radioligand binding and functional assays for **14** .and **(C1-*R*)-32**.

Assays were performed commercially in Eurofins Cerep SA (Celle l'Evescault, France) or Eurofins Panlabs Discovery Services Taiwan, Ltd. (New Taipei City, Taiwan), using procedures describe elsewhere:

Binding studies	Ref.
Na^+ channel (site 2)	[1]
L-type Ca^{2+}(diltiazem site, antagonist radioligand)	[2]
Functional studies	
TRPV1 (VR1) *(h)* (antagonist effect)	[3]
$Cav_{1.2}$ (L-type) *(h)* calcium ion channel cell based antagonist calcium flux assay	[4,5]

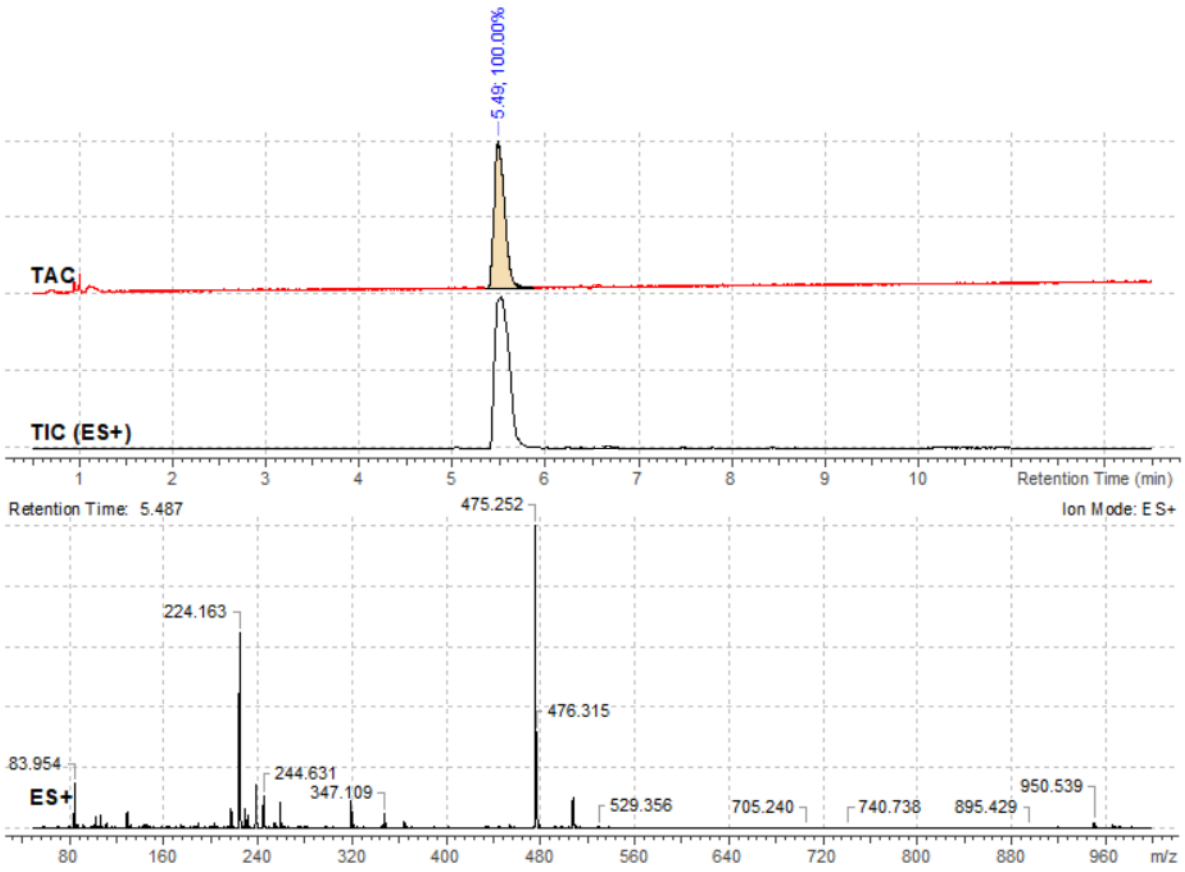
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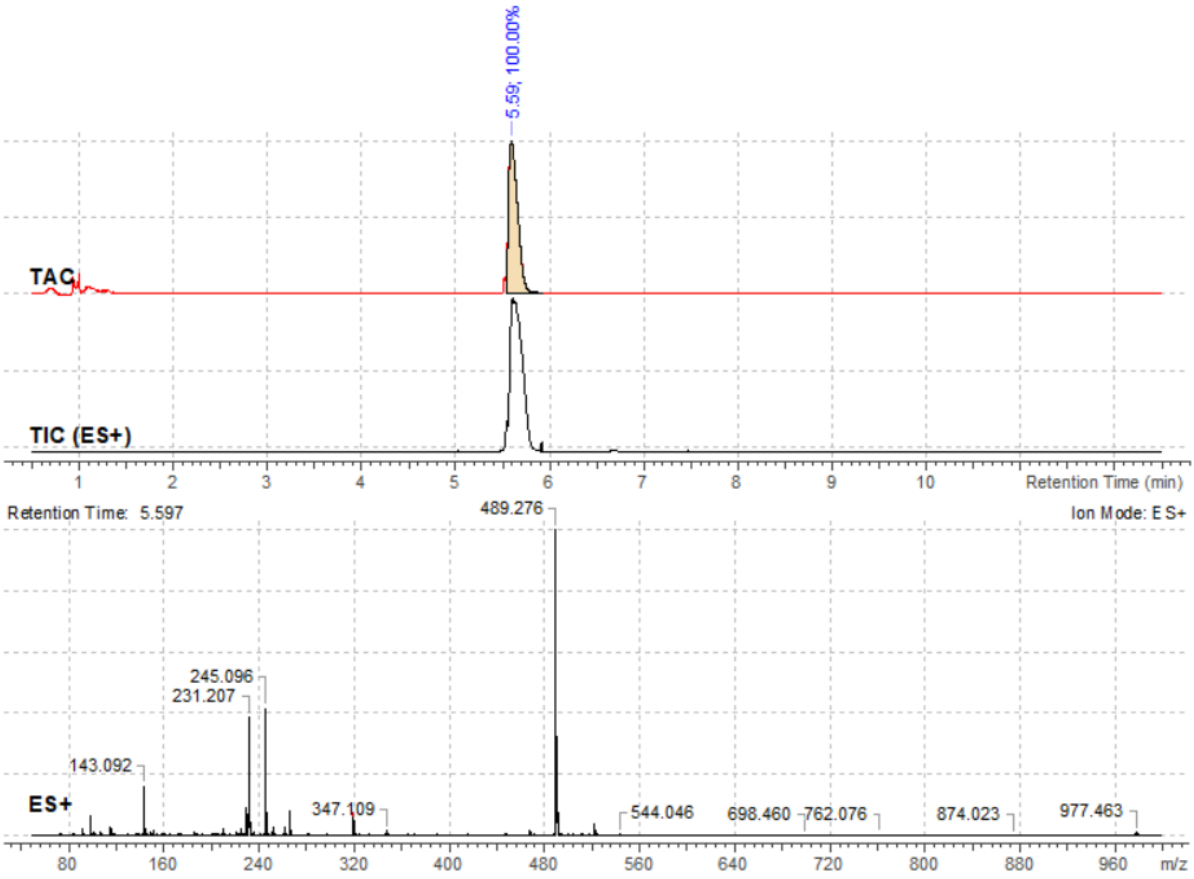
UPLC/MS traces for target final compounds

The purity of target final compounds determined by use of chromatographic UPLC method was ≥99%.

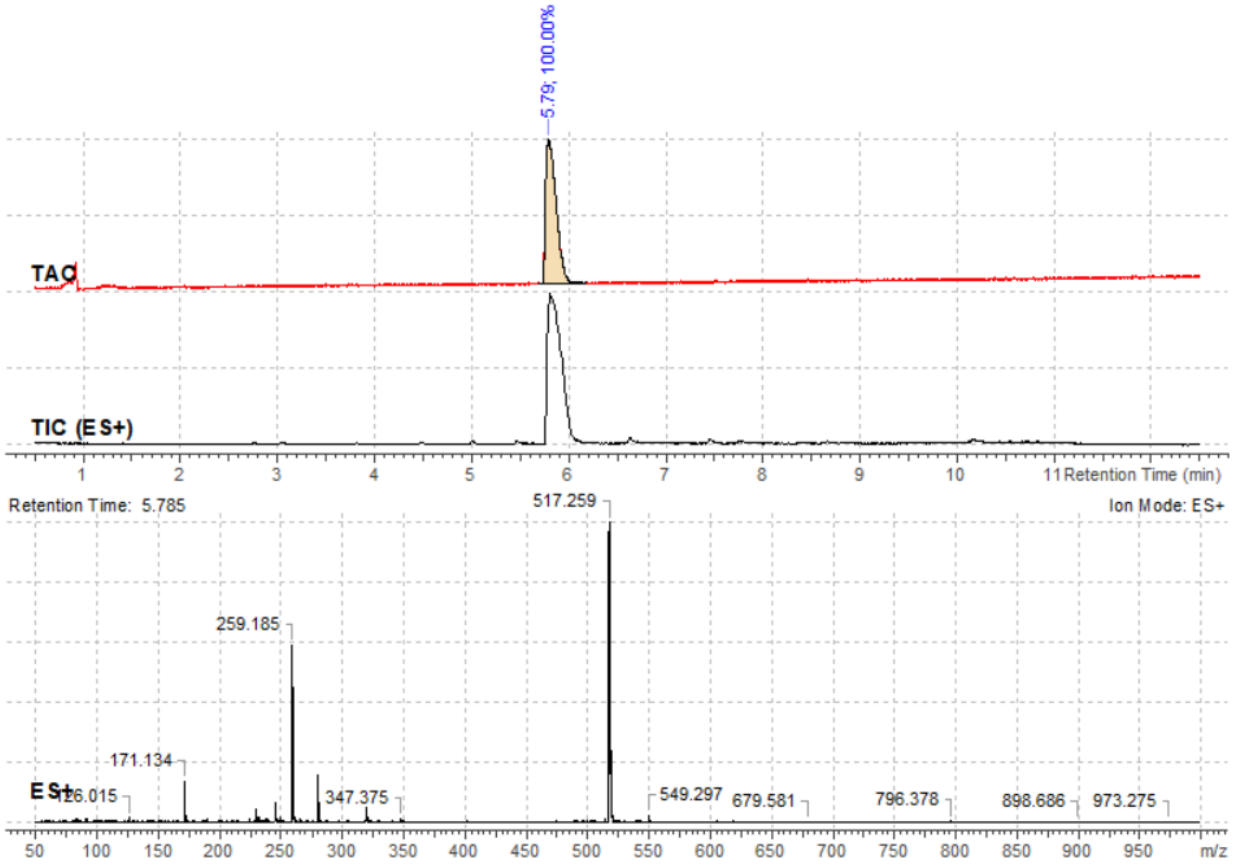
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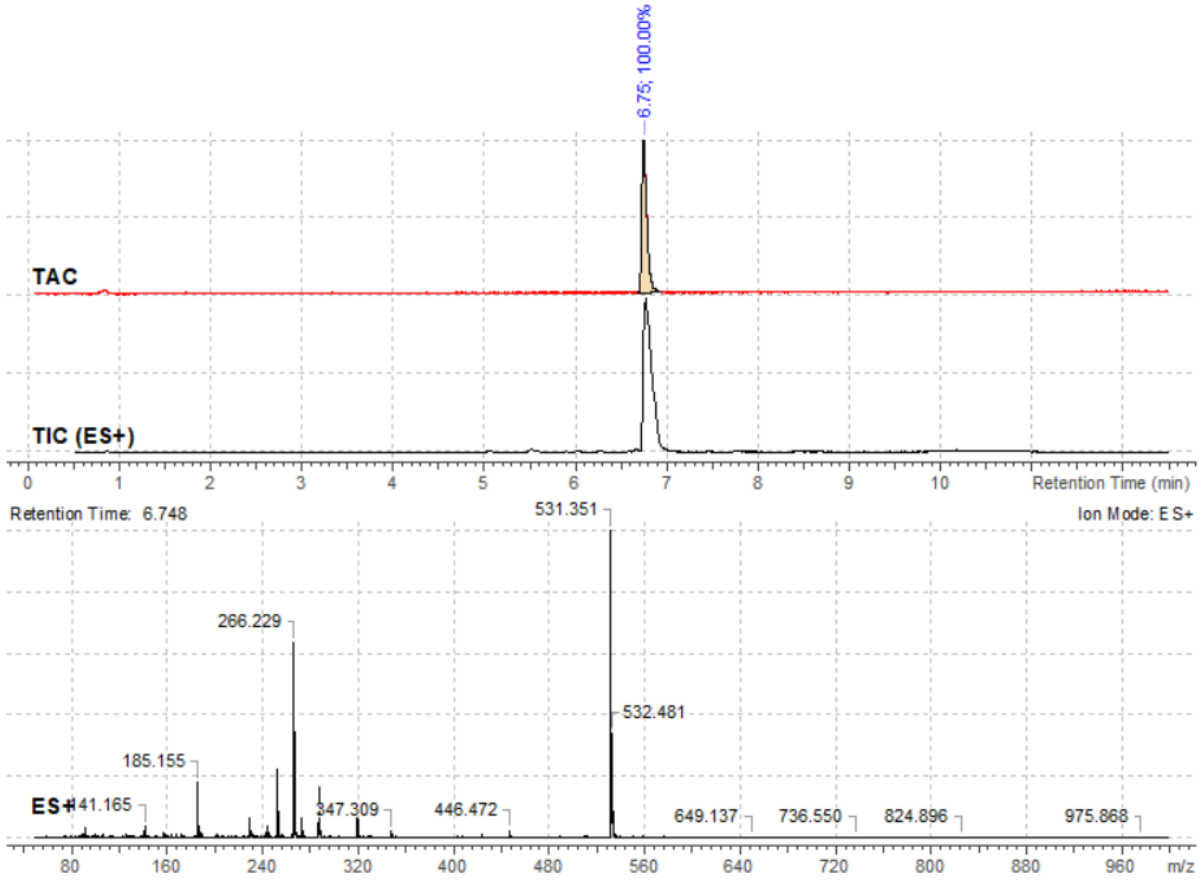
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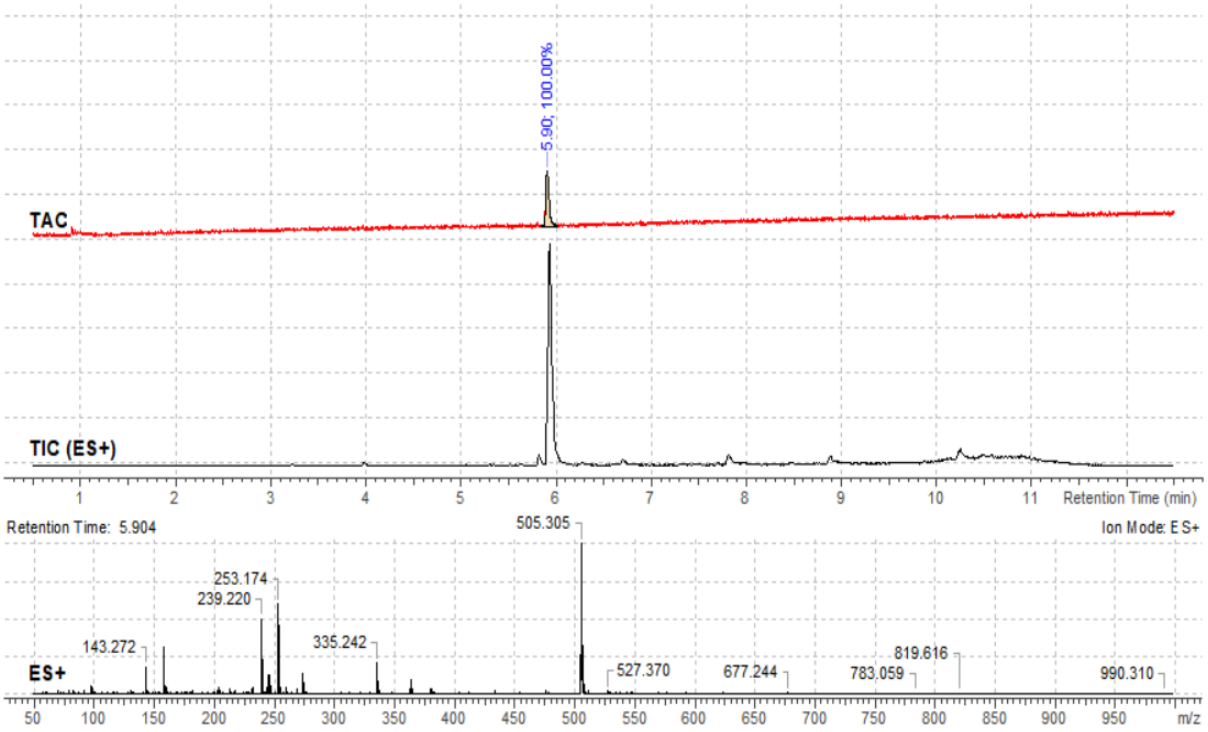
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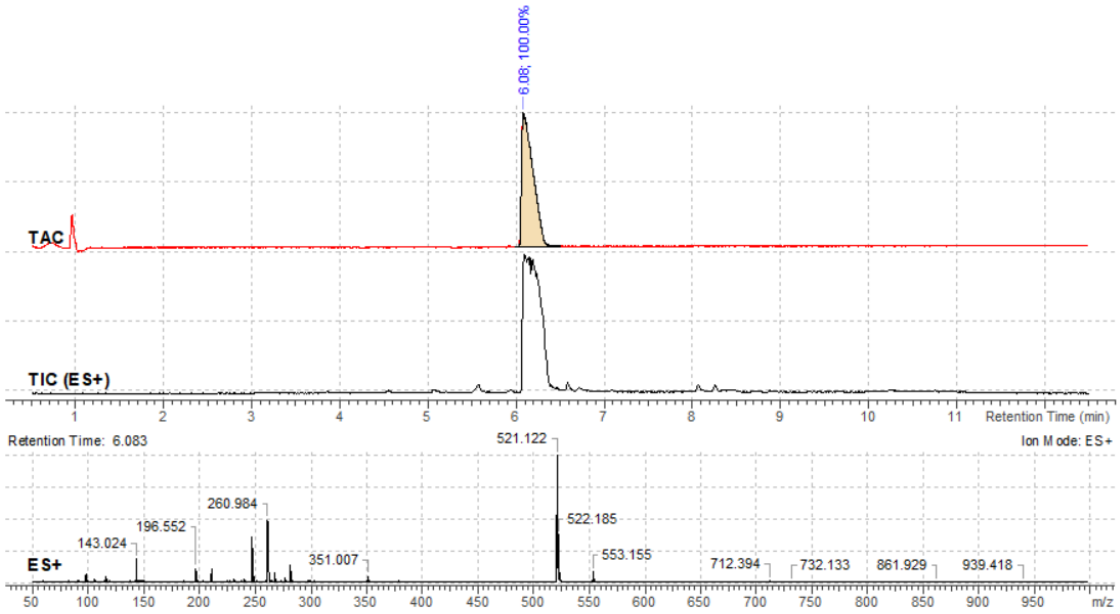
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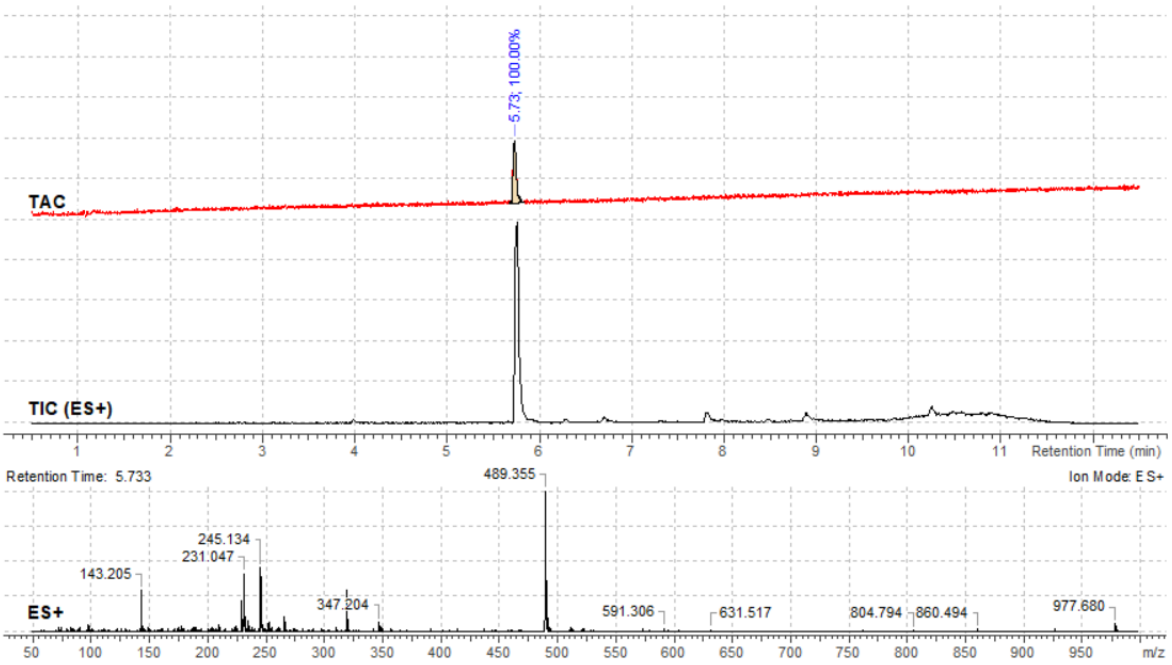
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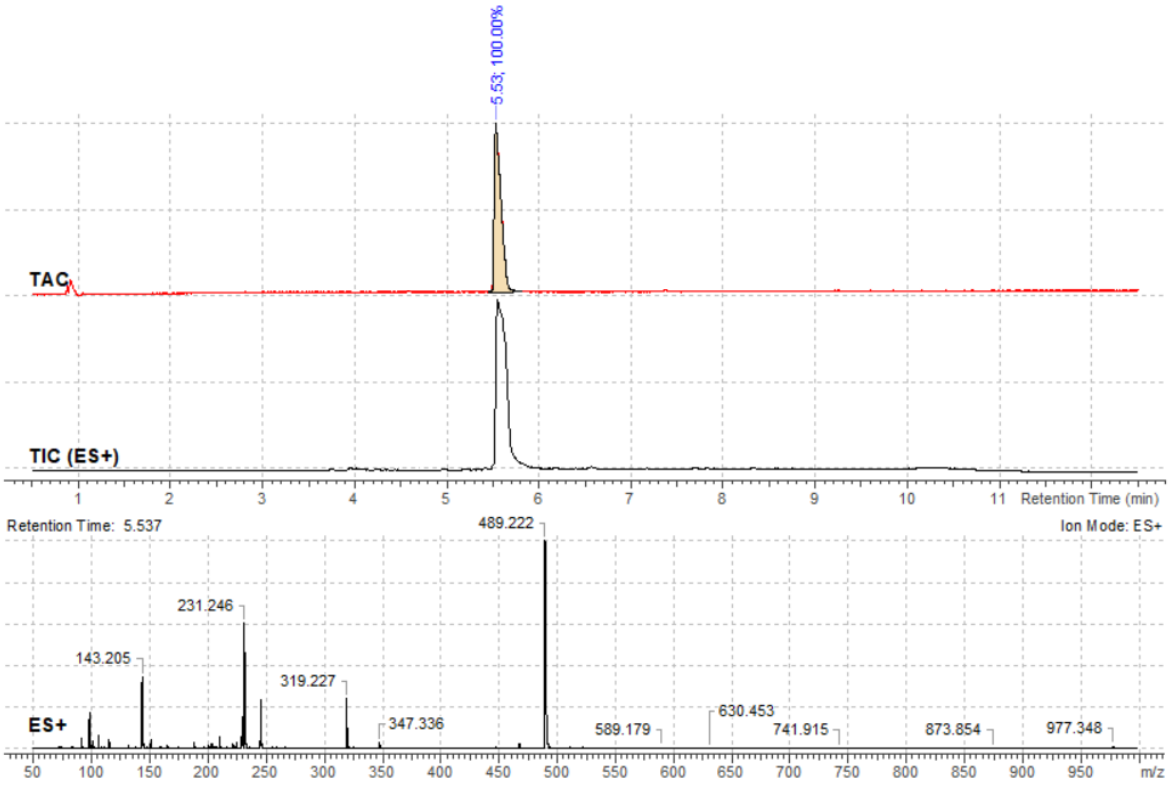
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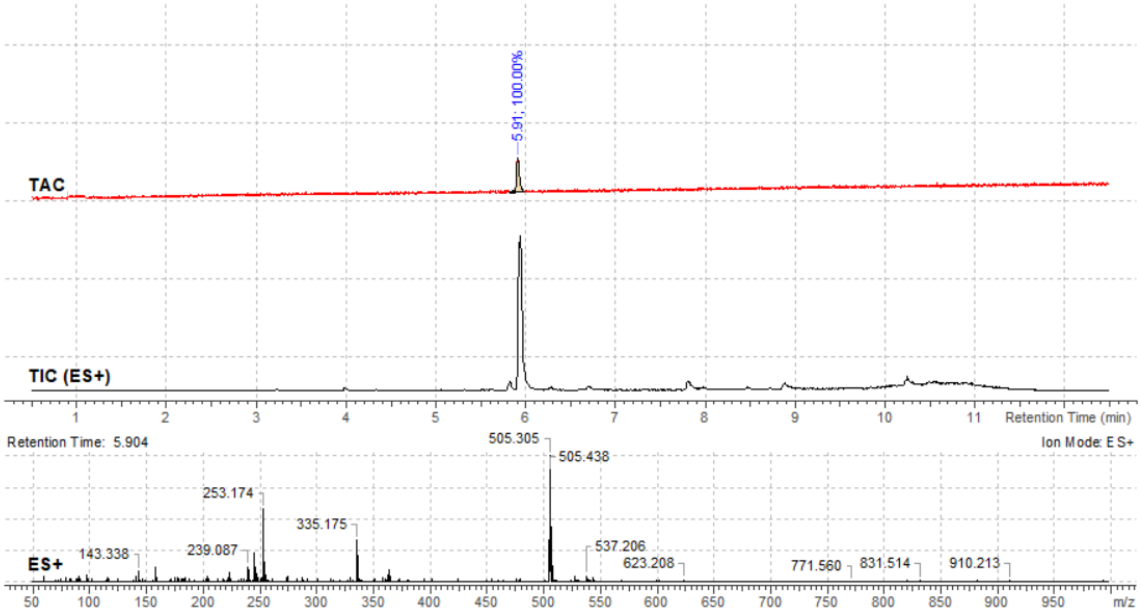
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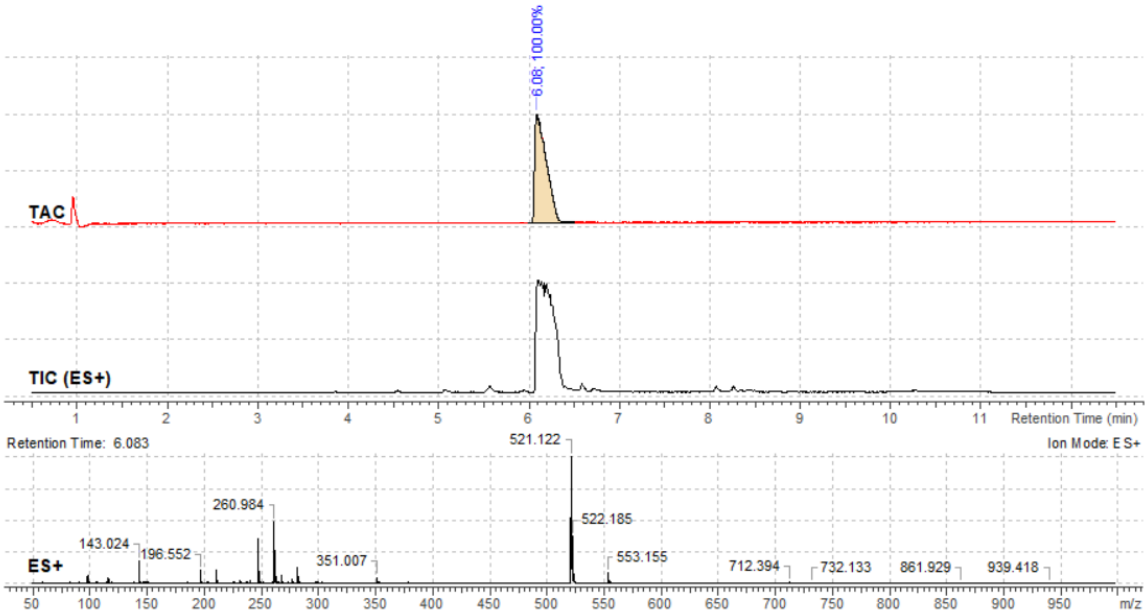
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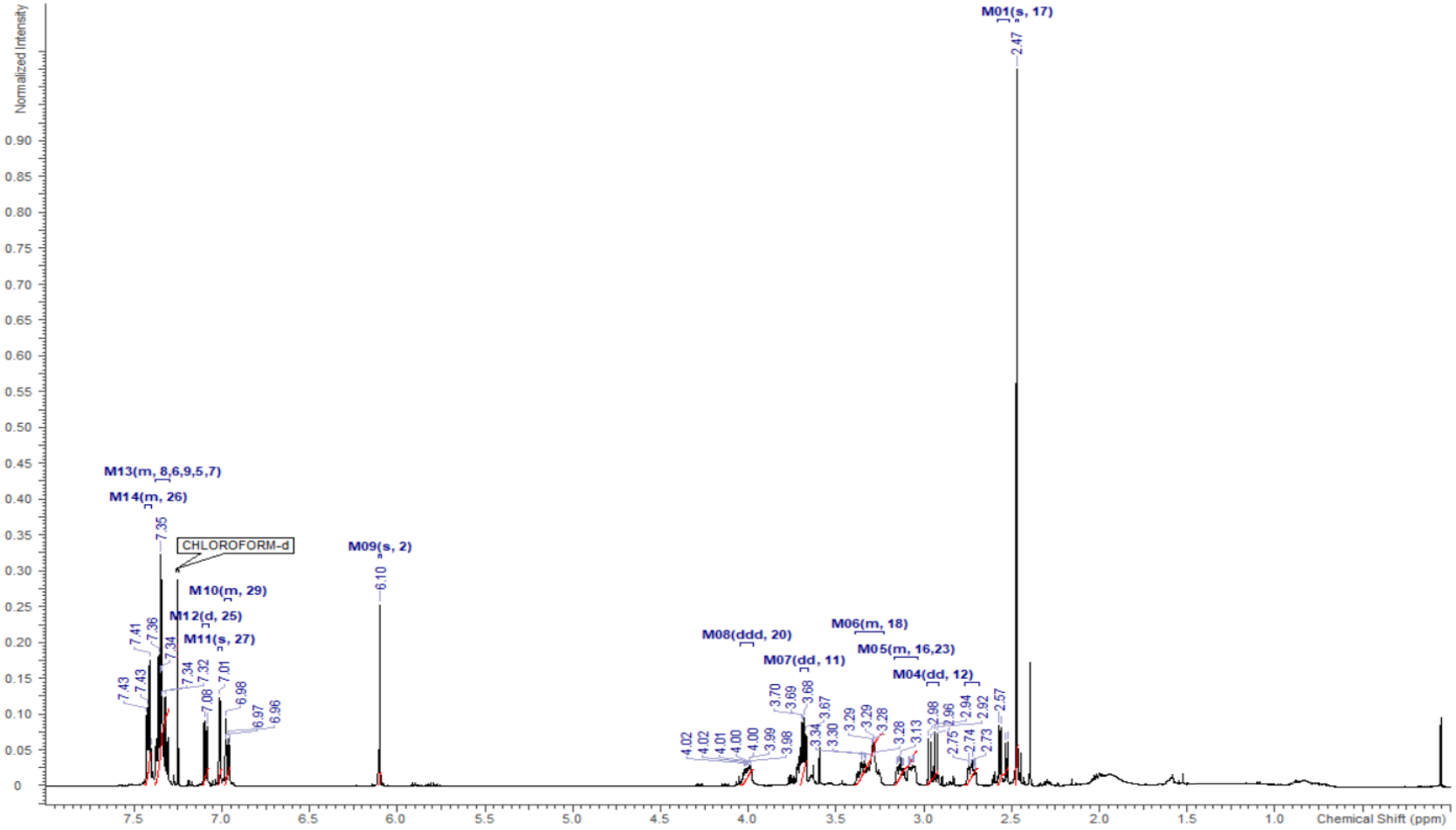
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^{1}H NMR, ^{13}C NMR spectra for final compounds

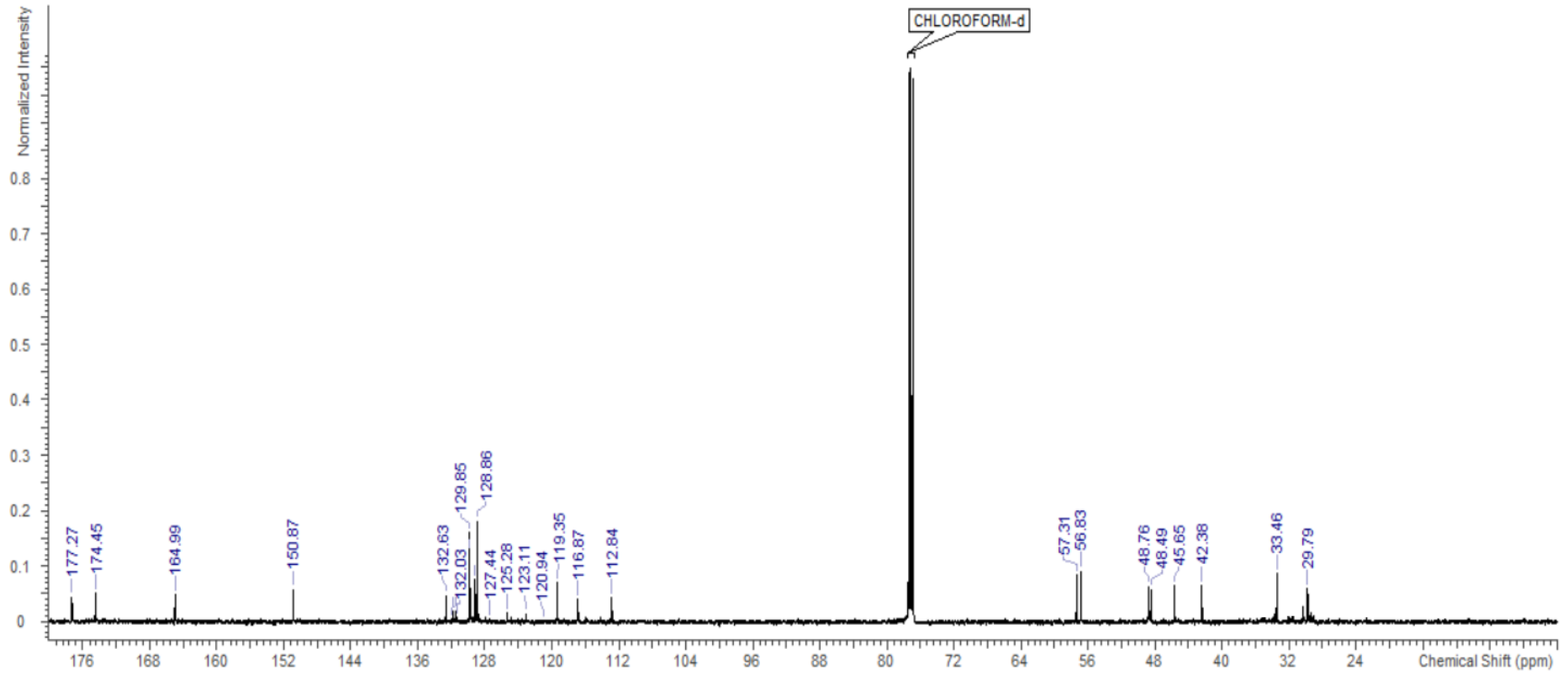
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^{1}H NMR



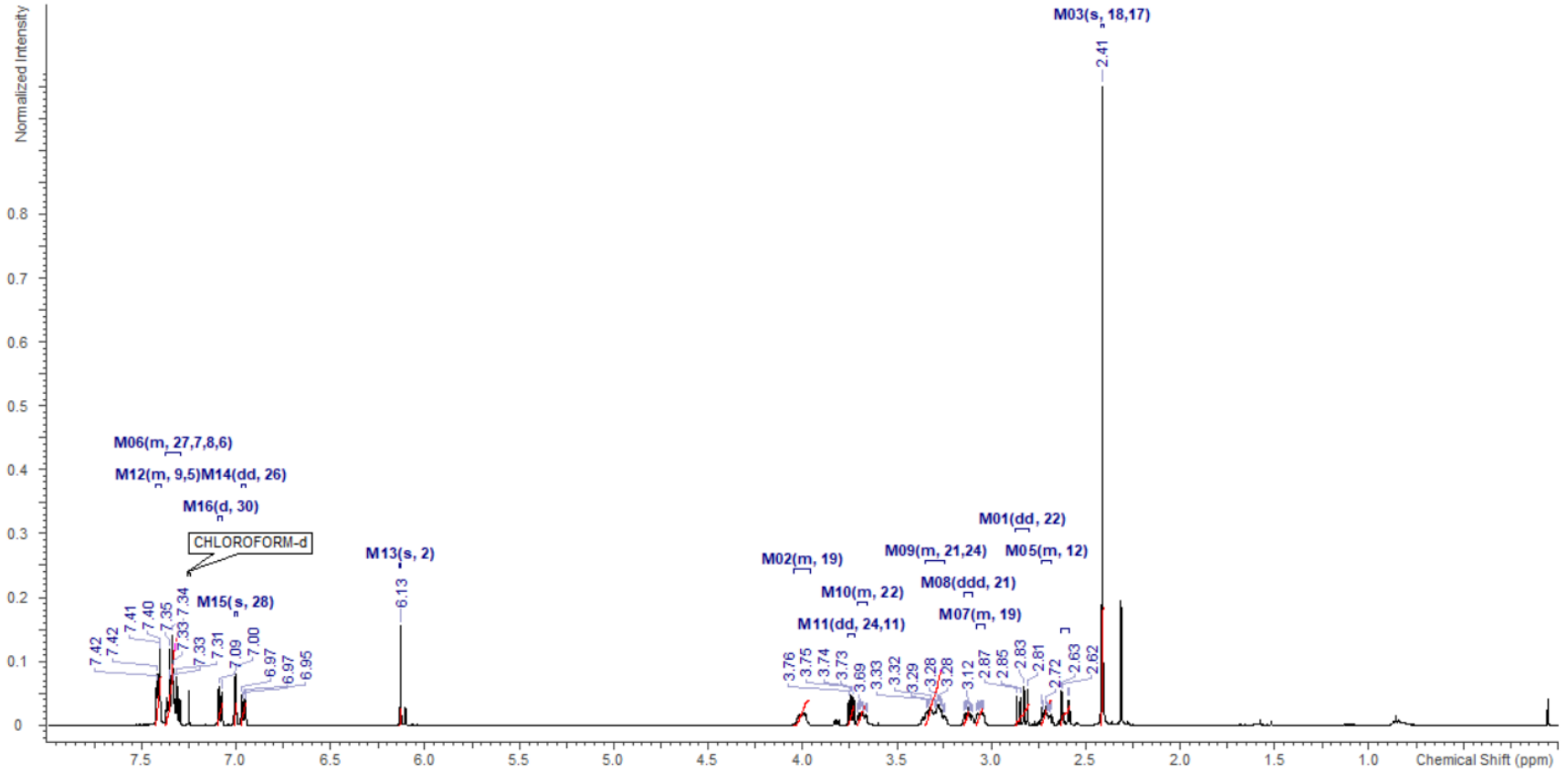
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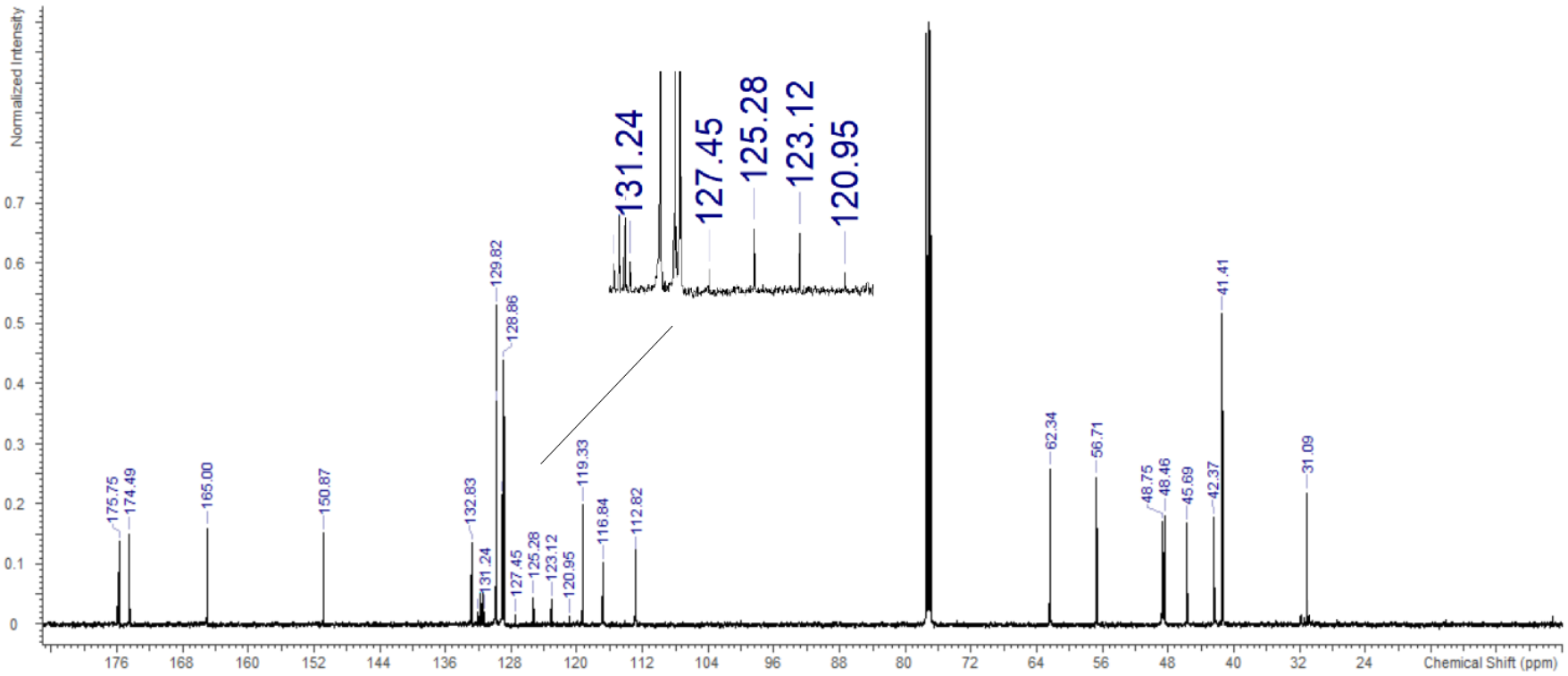
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^{1}H NMR



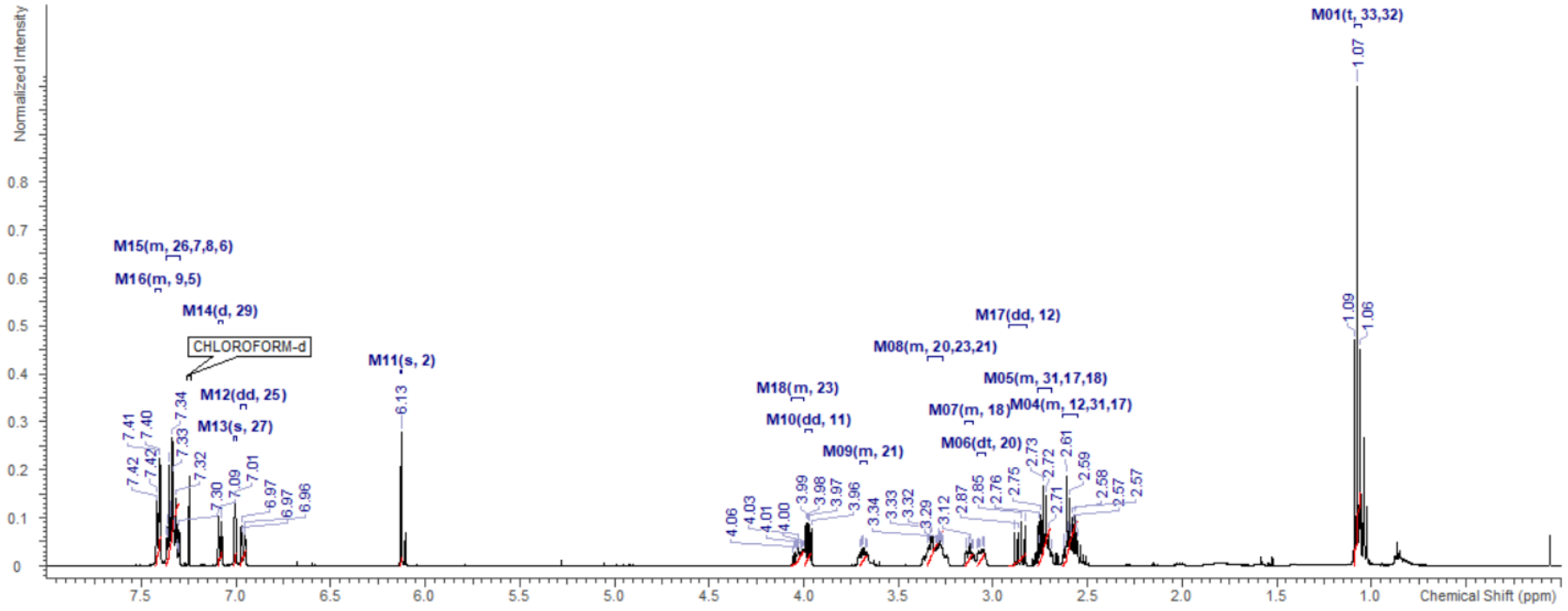
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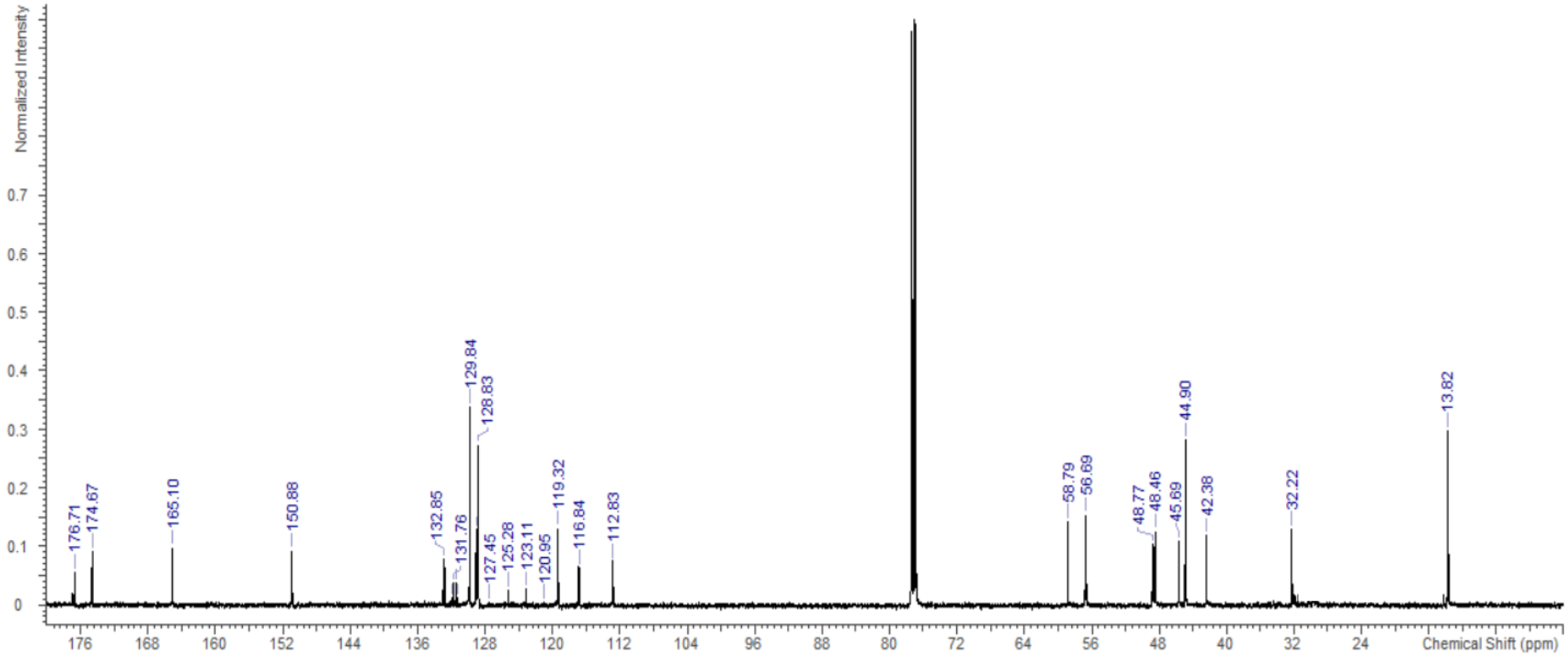
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^{1}H NMR



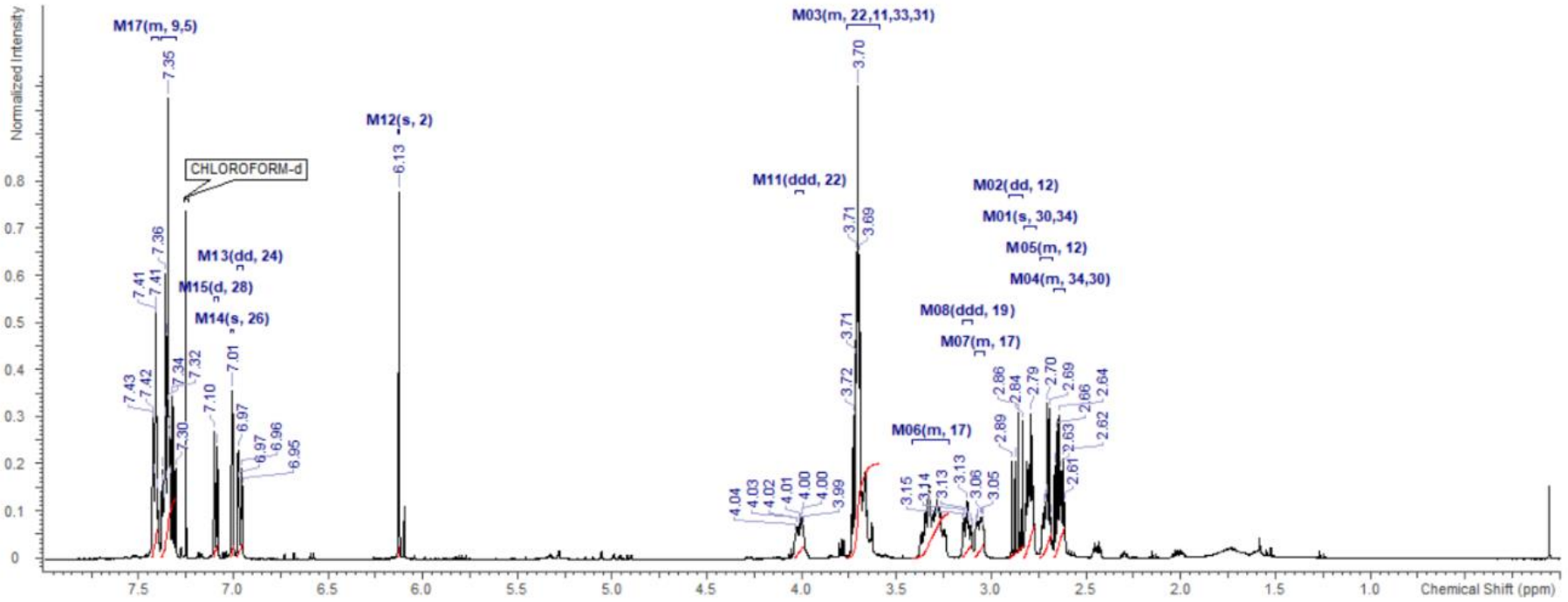
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^{13}C NMR



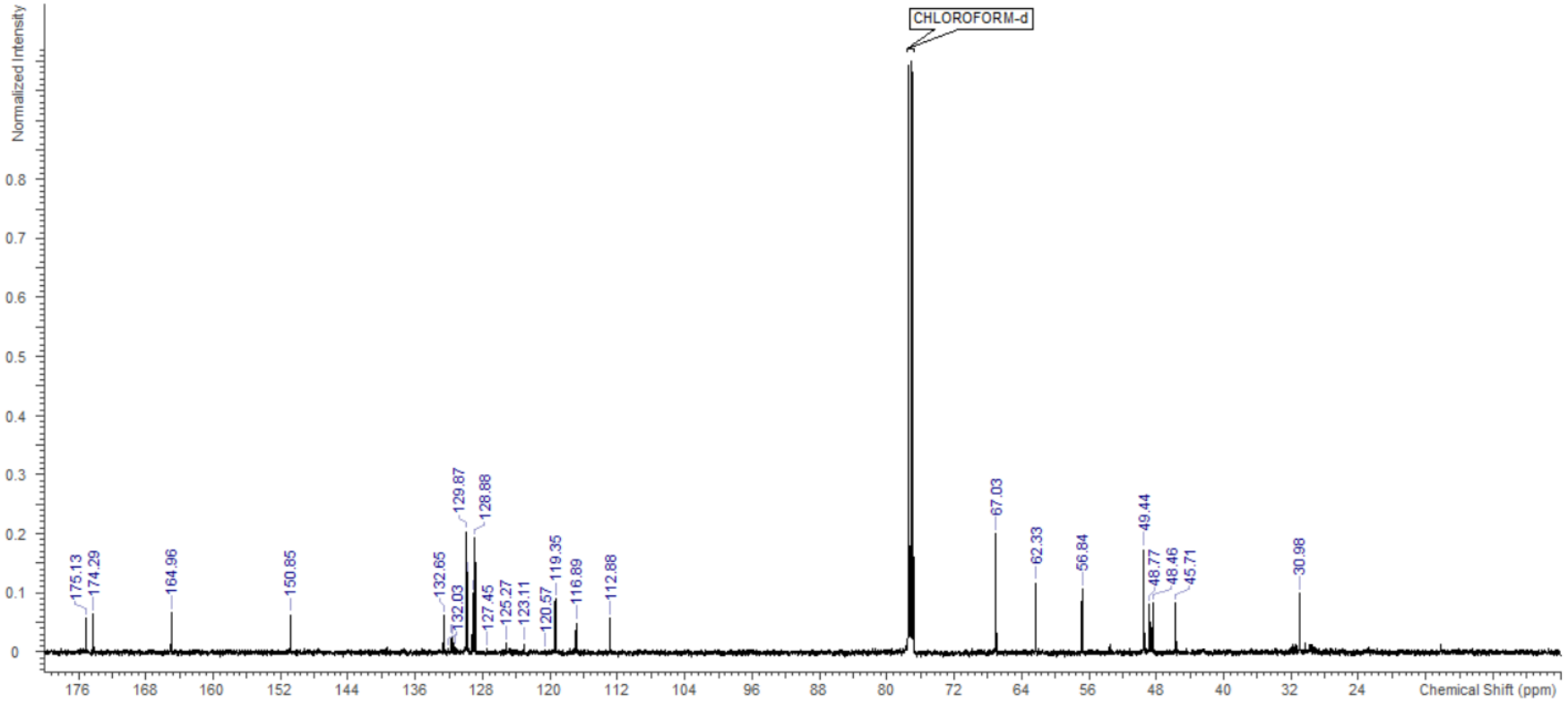
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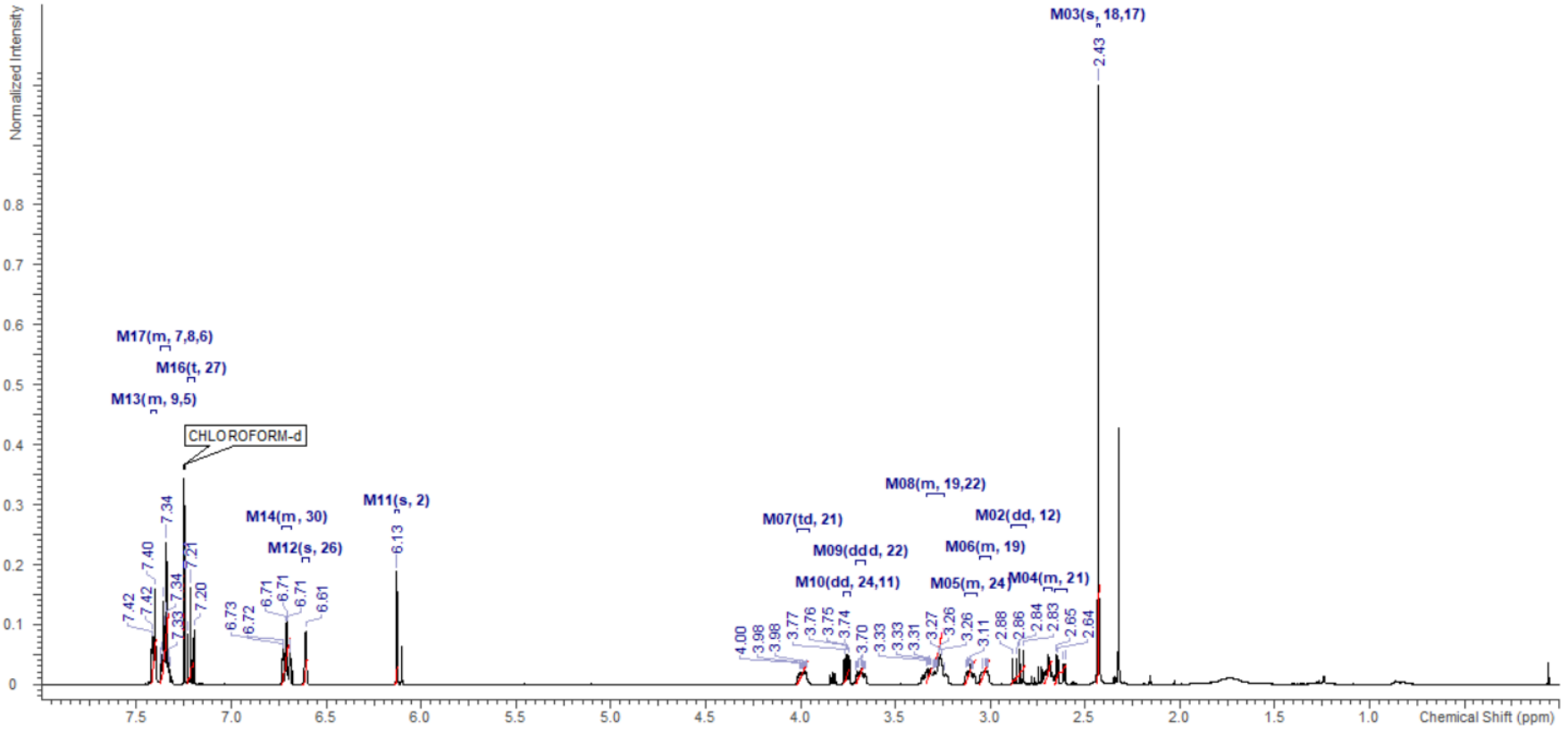
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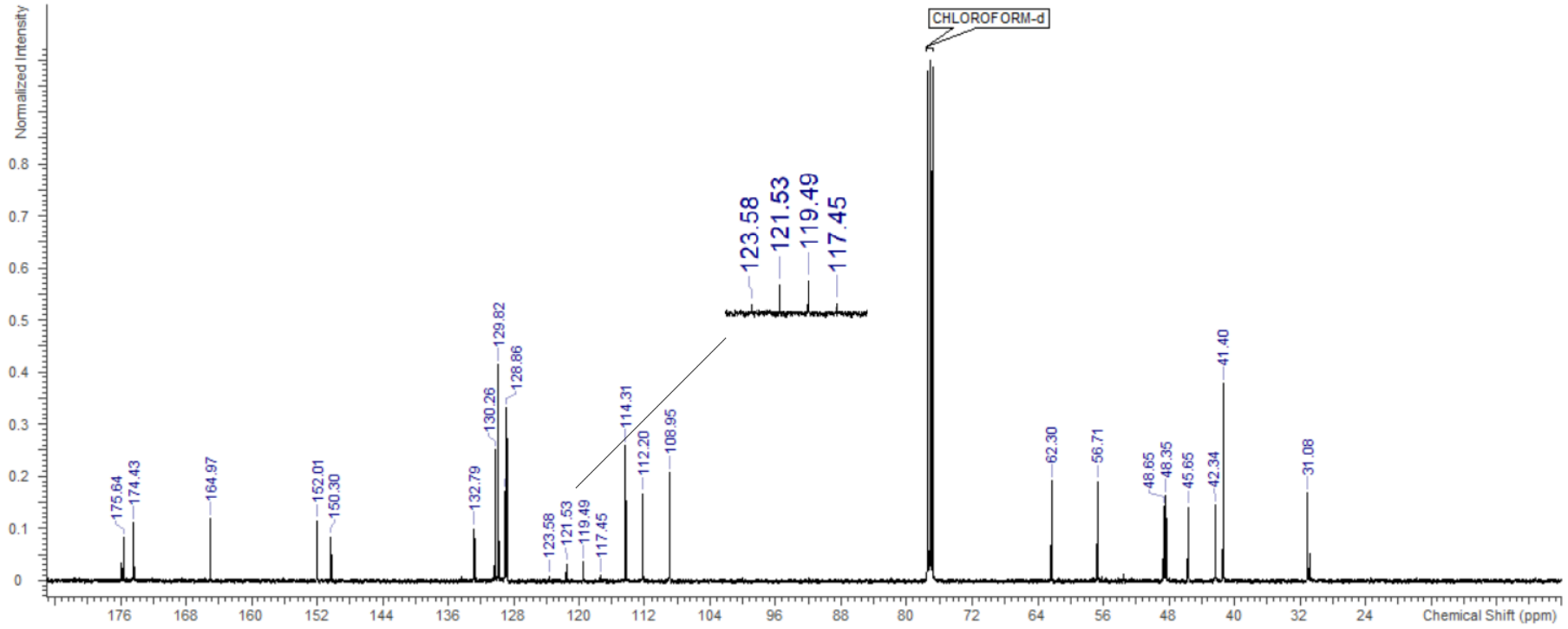
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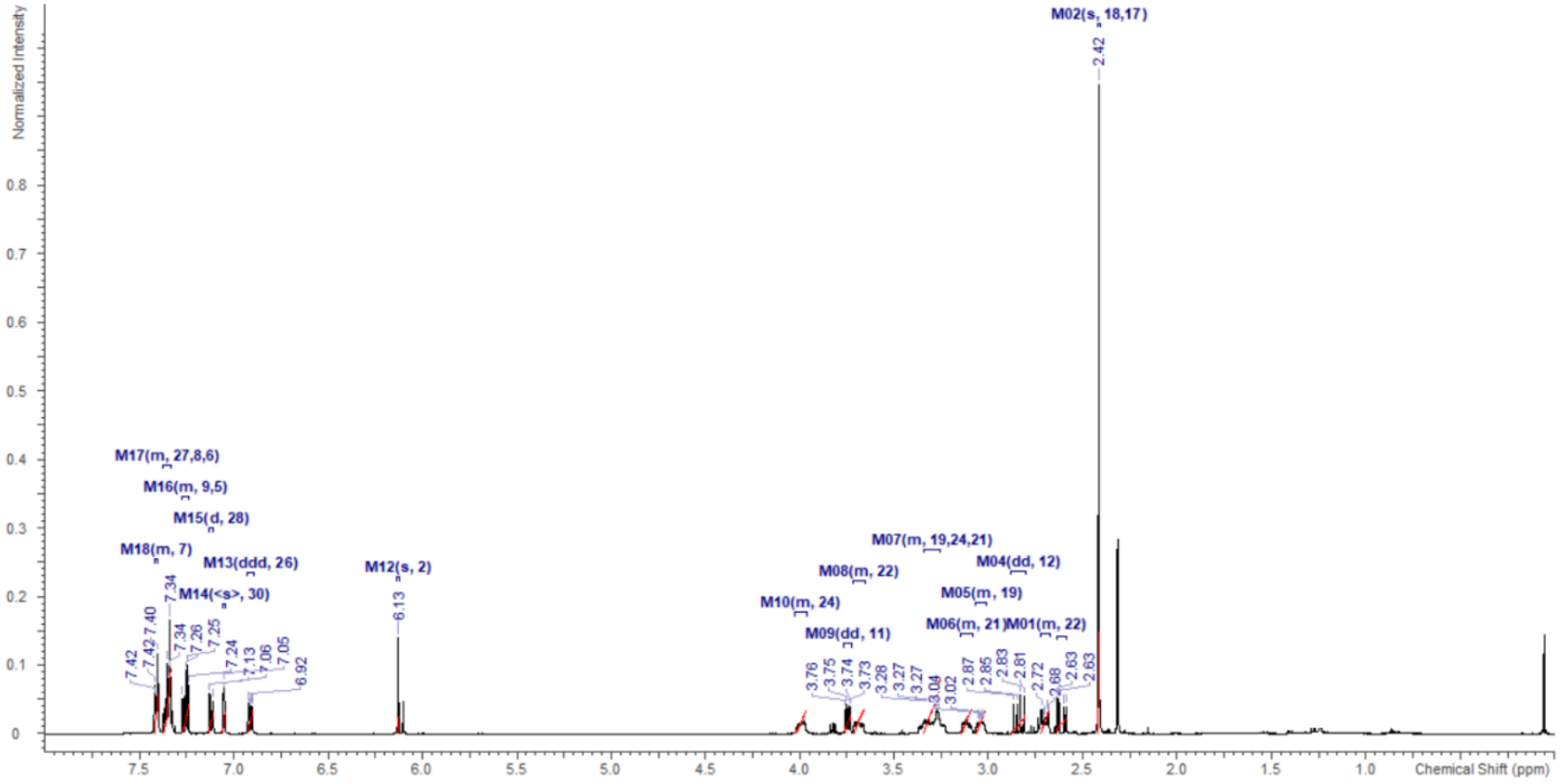
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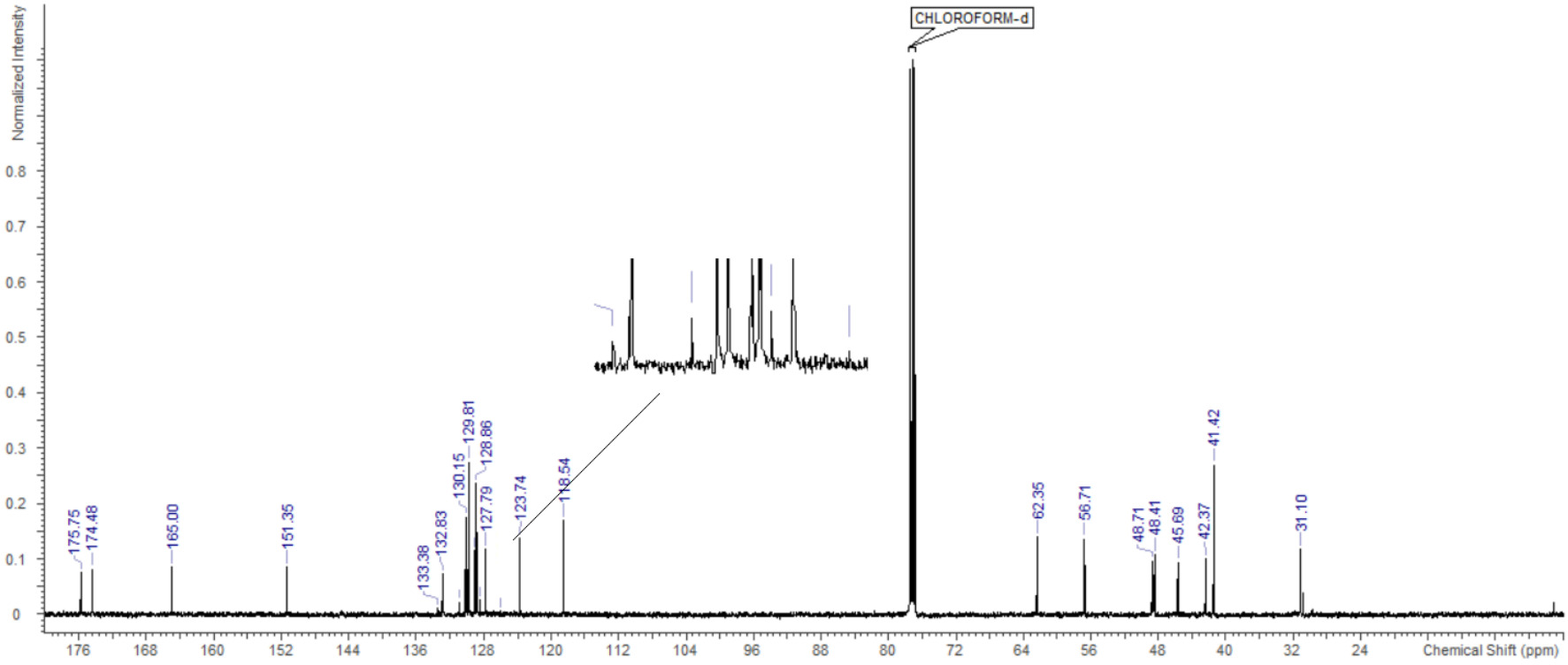
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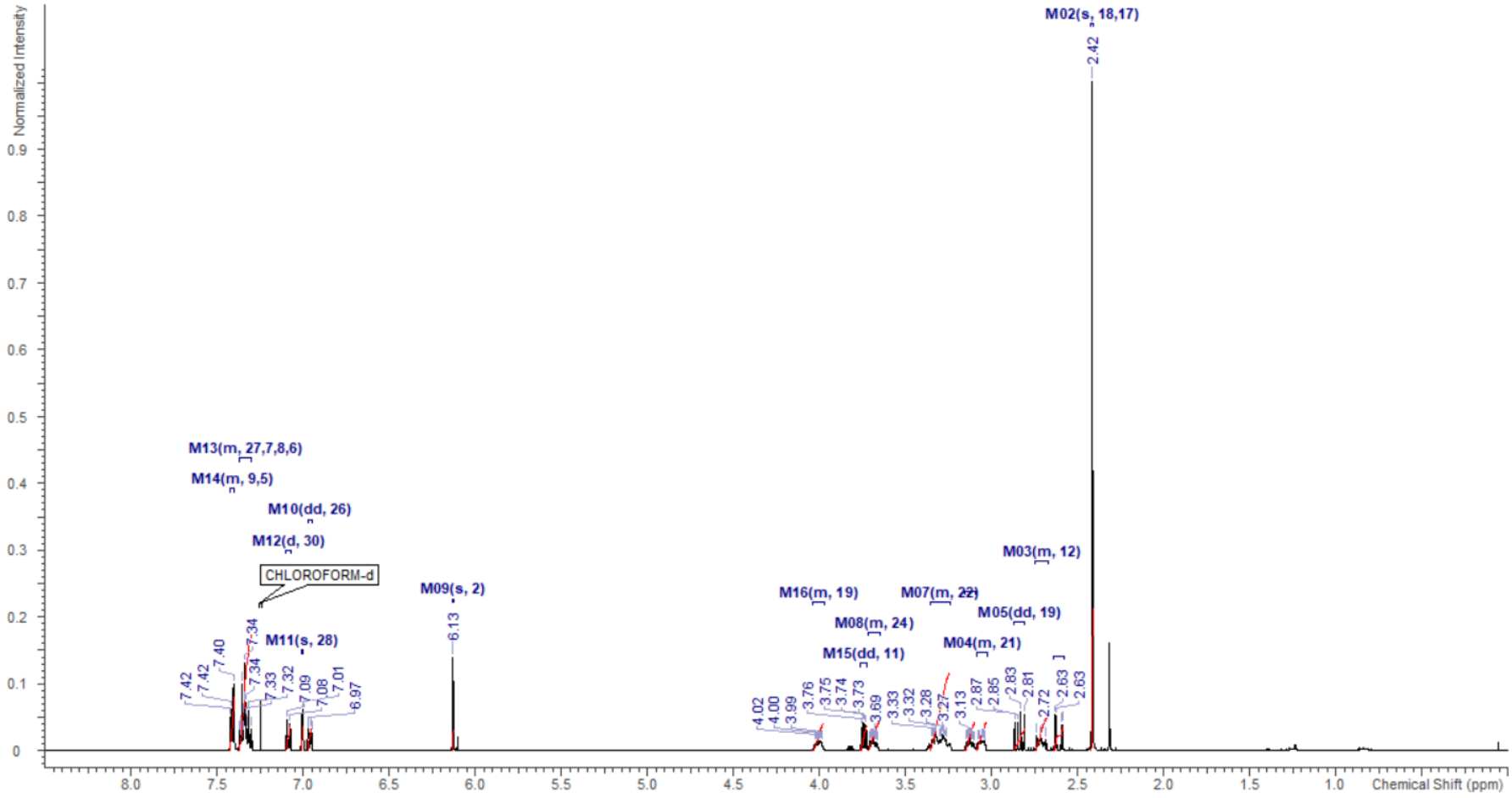
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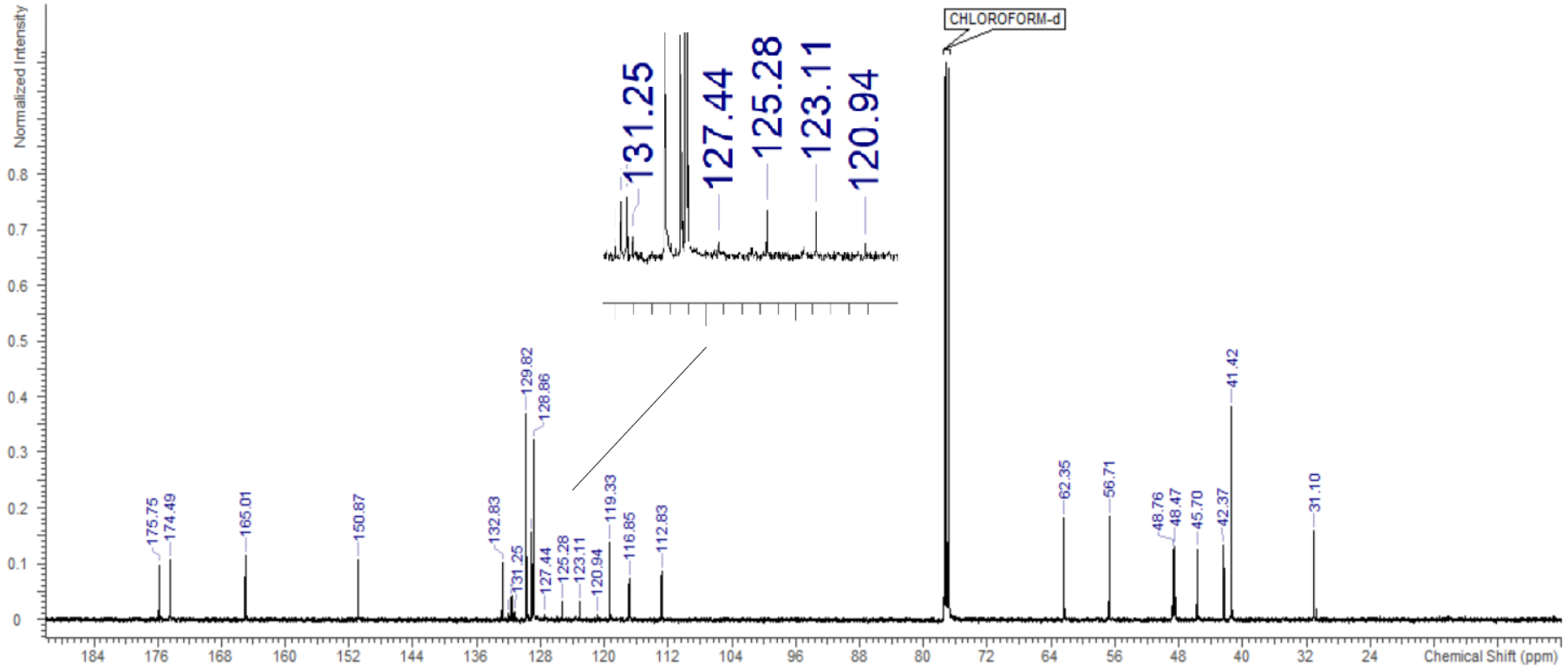
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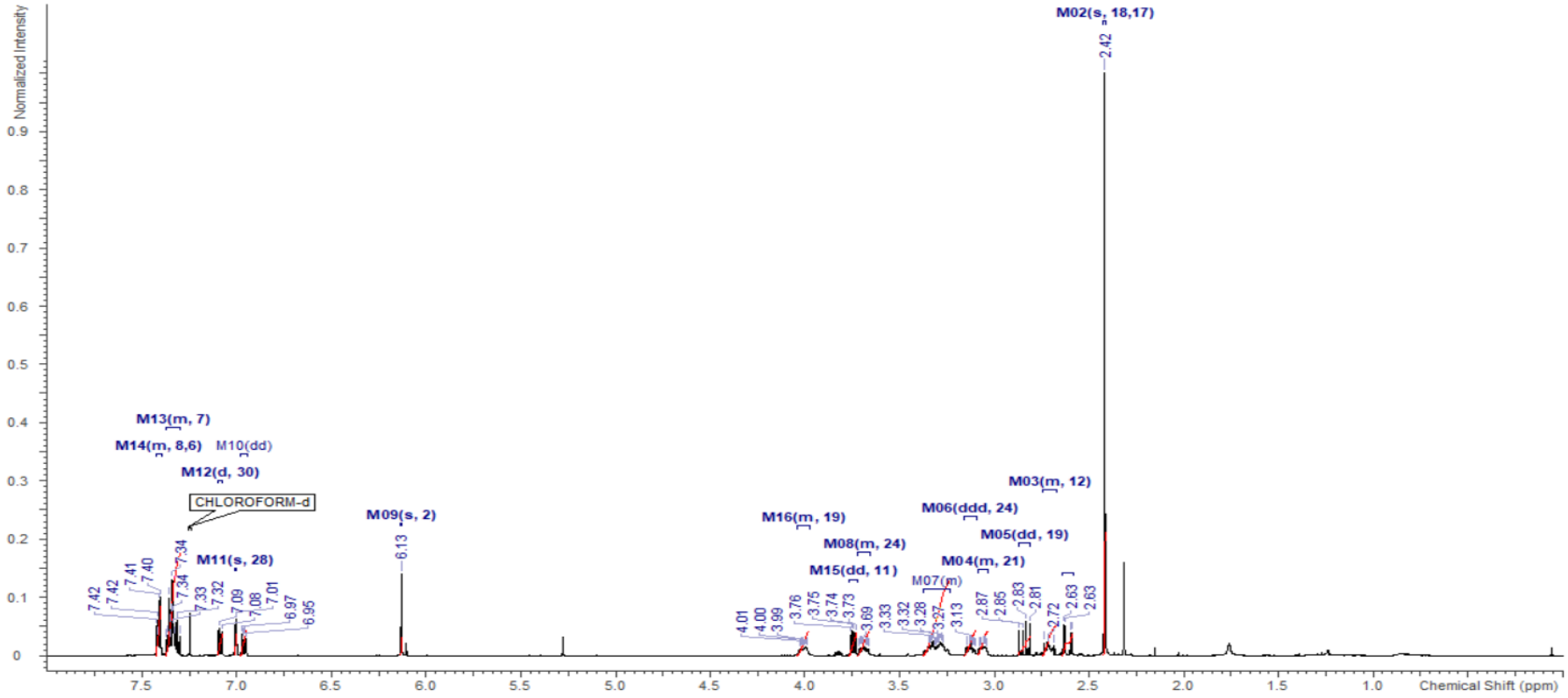
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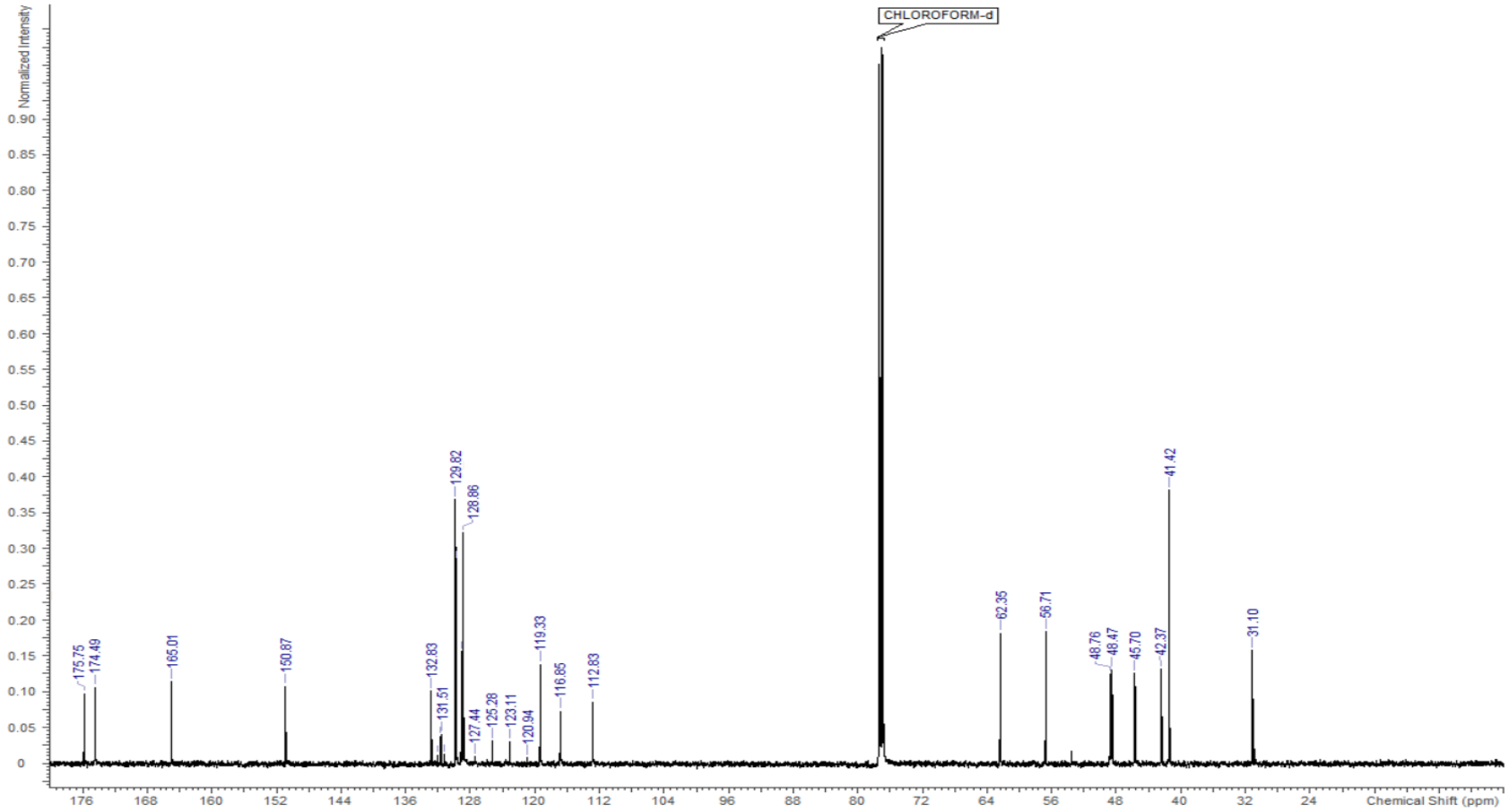
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^{1}H NMR



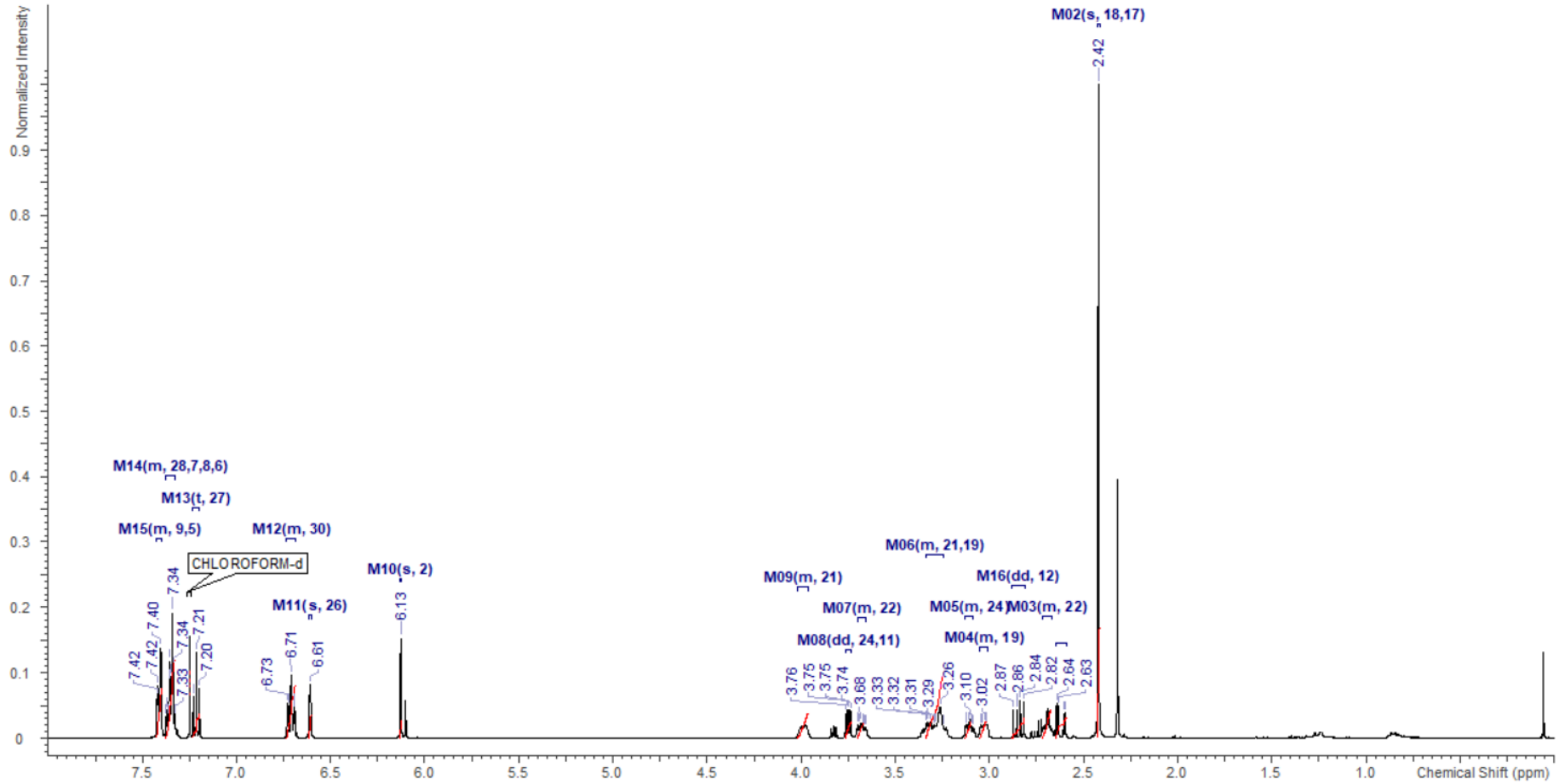
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^{13}C NMR



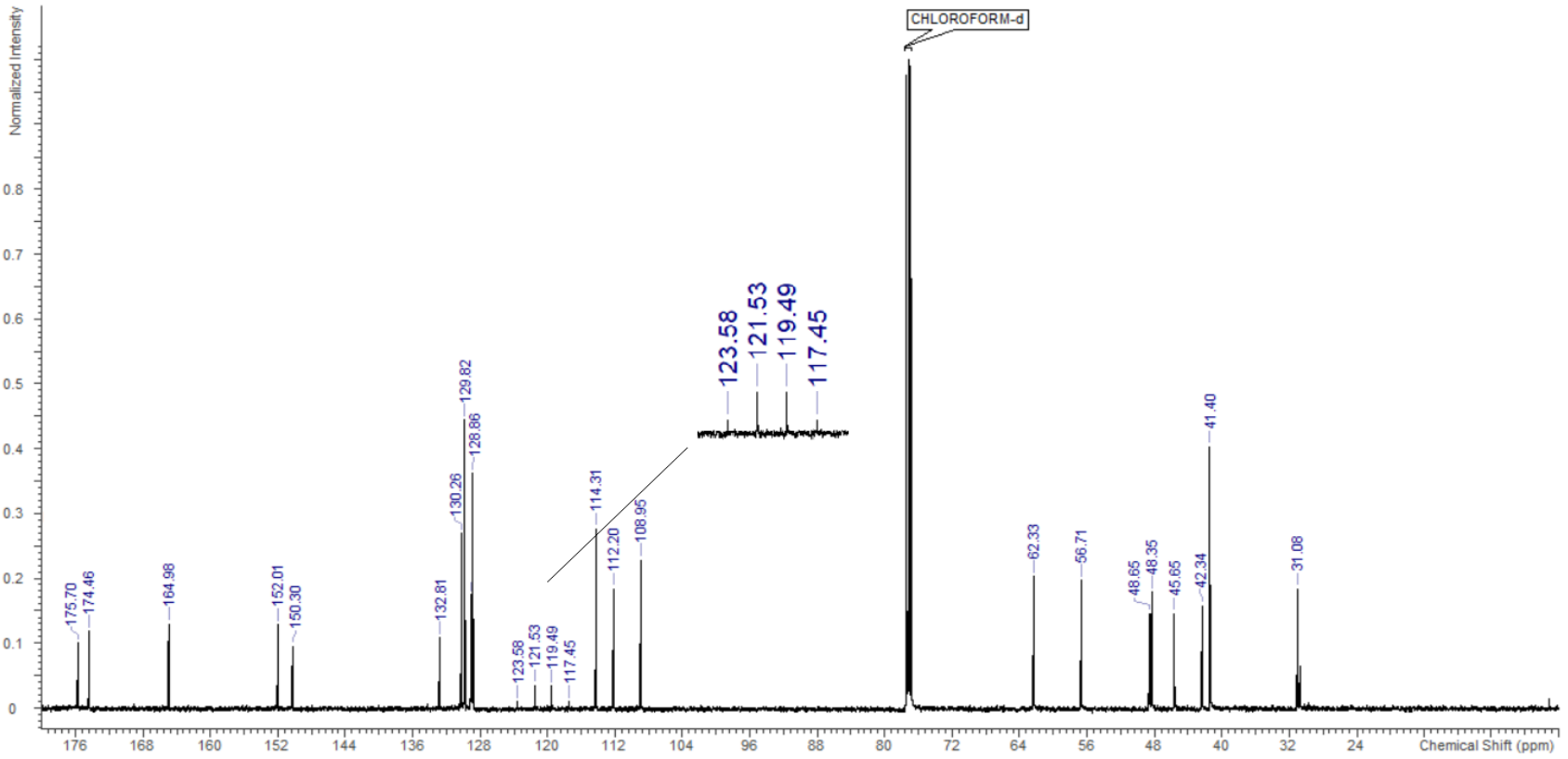
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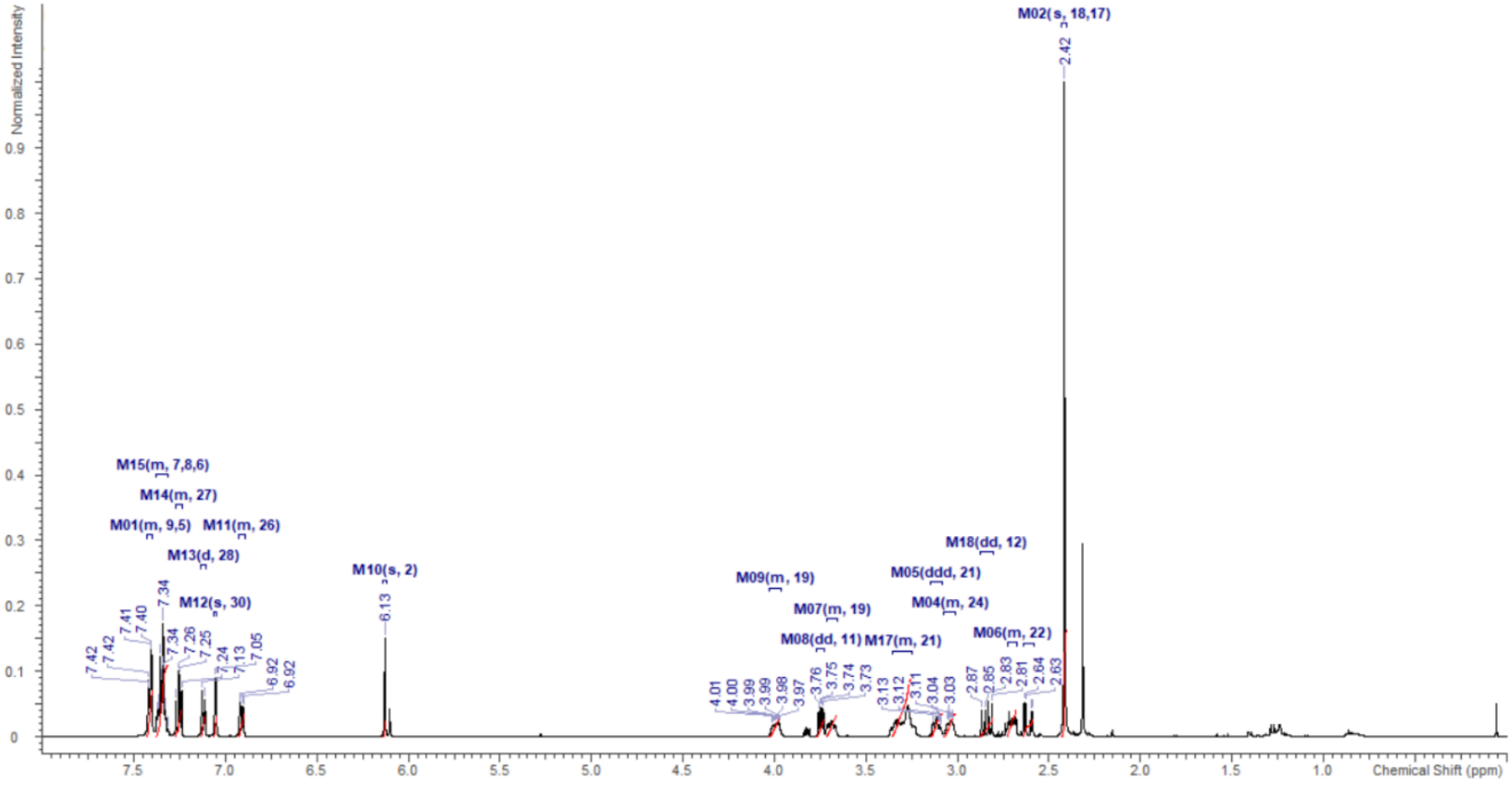
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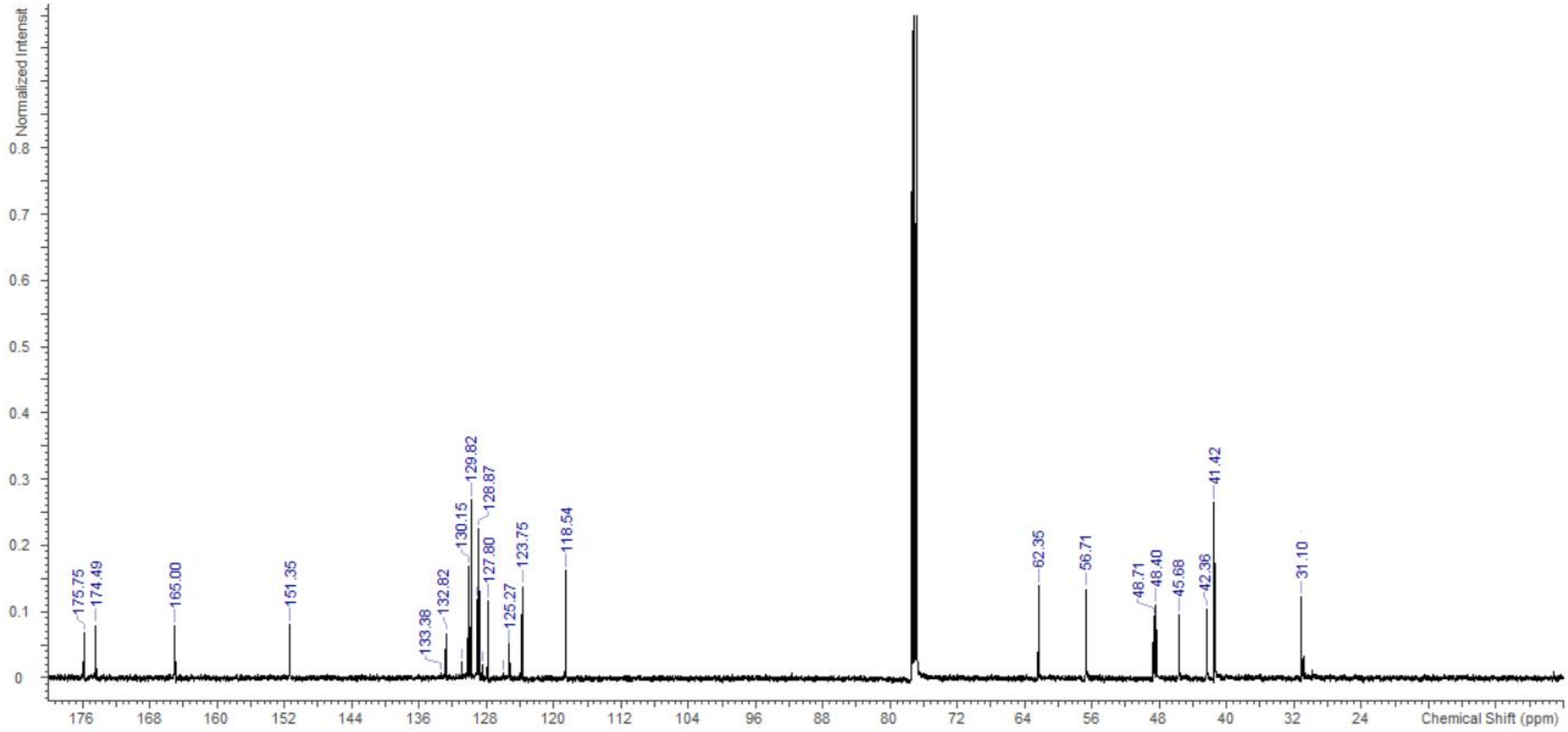
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^{1}H NMR



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^{13}C NMR



Chiral HPLC chromatograms

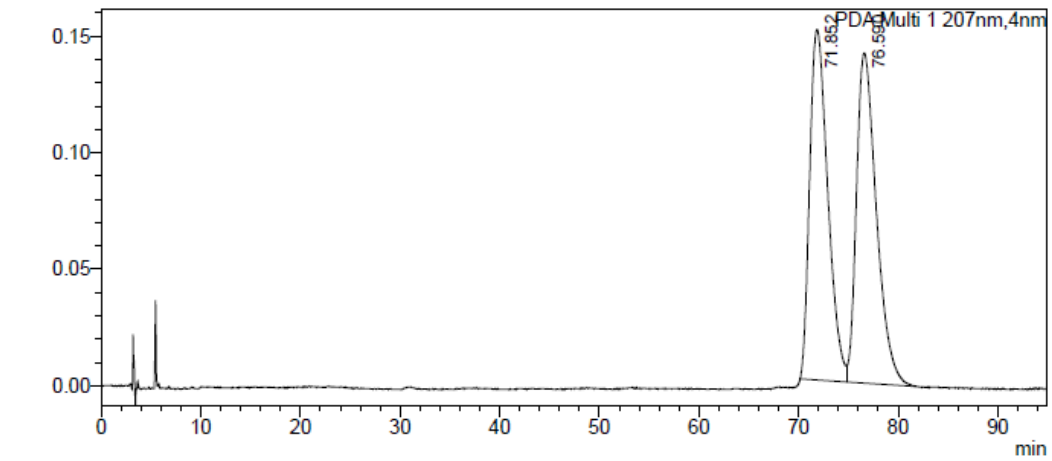
(*R,S*)-1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)-1*H*-pyrrole-2,5-dione (10)

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R,S-KA-214		
Sample ID	:		
Data Filename	: R,S-KA-214.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-26	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 04.10.2021 15:55:28	Acquired by	: Chemia leków1
Date Processed	: 08.10.2021 15:22:45	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	71.852	49.001
2	76.590	50.999
Total		100.000

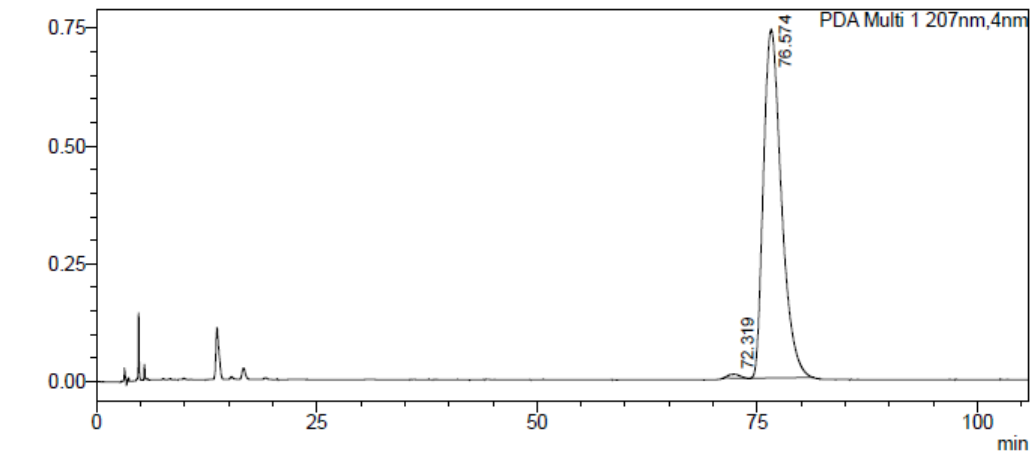
(*R*)-1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)-1*H*-pyrrole-2,5-dione (C1-*R*)-28

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R-KA-214		
Sample ID	:		
Data Filename	: R-KA-214.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-4	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 08.10.2021 09:18:37	Acquired by	: Chemia leków1
Date Processed	: 15.10.2021 16:32:07	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	72.319	0.706
2	76.574	99.294
Total		100.000

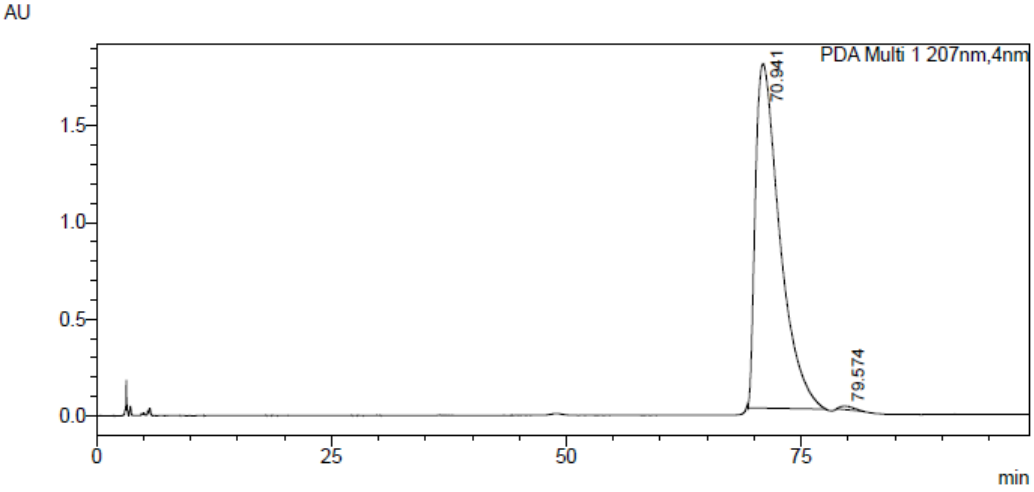
(*S*)-1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)-1*H*-pyrrole-2,5-dione (C1-*S*)-28

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: S-KA-214		
Sample ID	:		
Data Filename	: S-KA-214.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-6	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 08.10.2021 17:15:24	Acquired by	: Chemia leków1
Date Processed	: 11.10.2021 10:17:25	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	70.941	99.454
2	79.574	0.546
Total		100.000

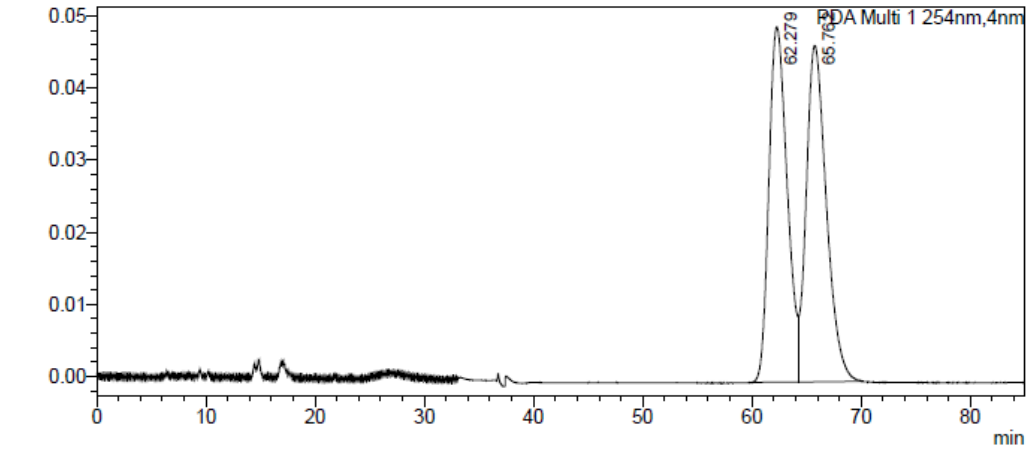
(*R,S*)-1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)ethyl)-1*H*-pyrrole-2,5-dione (11)

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R,S-KA-236		
Sample ID	:		
Data Filename	: R,S-KA-236.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-25	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 04.10.2021 14:28:47	Acquired by	: Chemia leków1
Date Processed	: 04.10.2021 15:53:46	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	62.279	48.835
2	65.762	51.165
Total		100.000

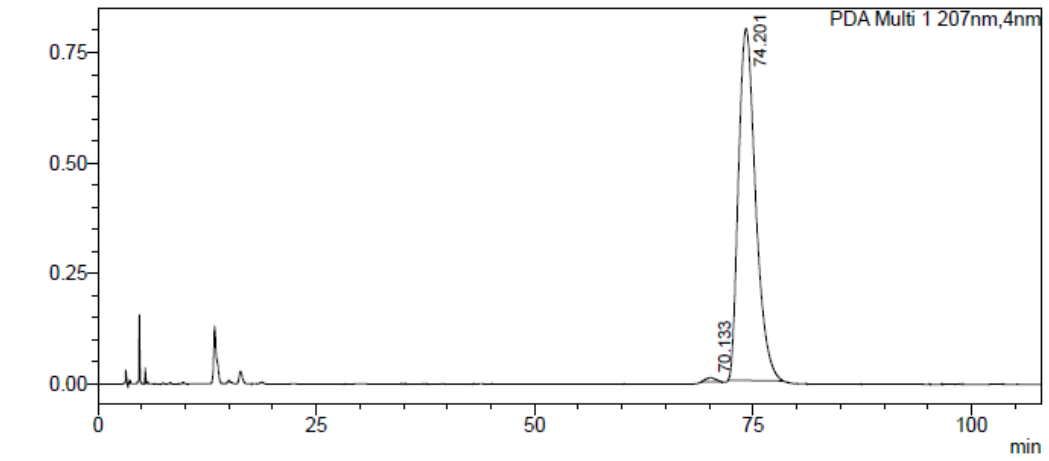
(*R*)-1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)ethyl)-1*H*-pyrrole-2,5-dione (C1-*R*)-29

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R-KA-236		
Sample ID	:		
Data Filename	: R-KA-236.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-5	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 08.10.2021 11:23:18	Acquired by	: Chemia leków1
Date Processed	: 08.10.2021 15:26:40	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	70.133	0.663
2	74.201	99.337
Total		100.000

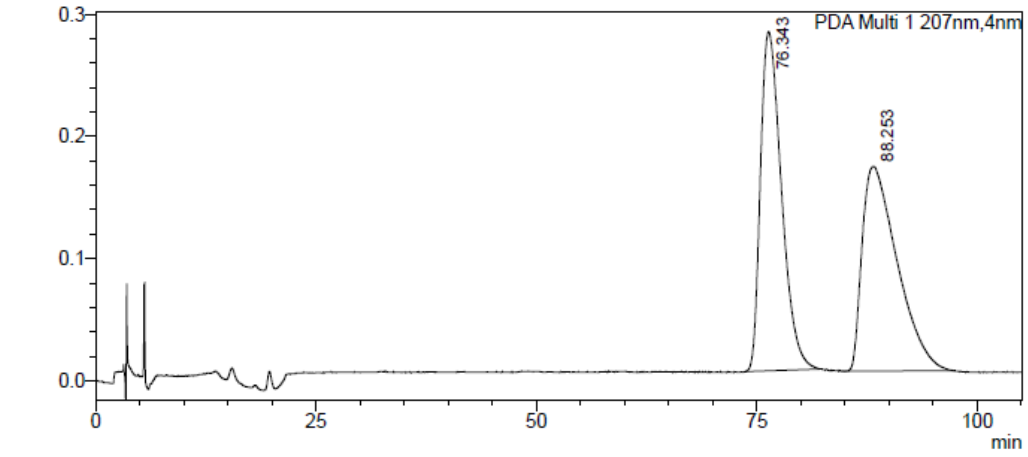
(*R,S*)-1-(2-Oxo-1-phenyl-2-(4-(3-((trifluoromethyl)thio)phenyl)piperazin-1-yl)ethyl)-1*H*-pyrrole-2,5-dione (12)

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R,S-KA-235		
Sample ID	:		
Data Filename	: R,S-KA-235.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-2	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 07.10.2021 11:26:15	Acquired by	: Chemia leków1
Date Processed	: 08.10.2021 15:29:24	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	76.343	49.847
2	88.253	50.153
Total		100.000

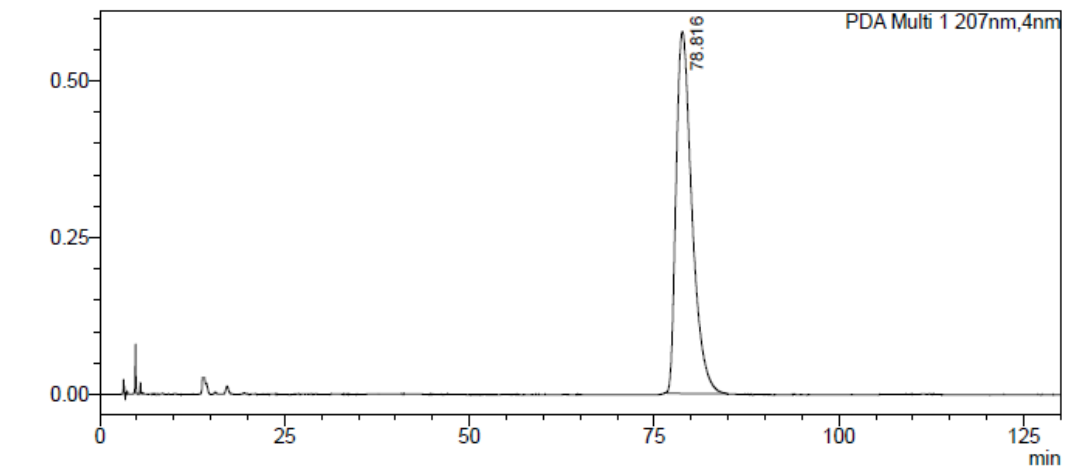
(*R*)-1-(2-Oxo-1-phenyl-2-(4-(3-((trifluoromethyl)thio)phenyl)piperazin-1-yl)ethyl)-1*H*-pyrrole-2,5-dione (C1-*R*)-30

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R-KA-235		
Sample ID	:		
Data Filename	: R-KA-235.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-3	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 07.10.2021 13:12:21	Acquired by	: Chemia leków1
Date Processed	: 15.10.2021 16:28:20	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	78.816	100.000
Total		100.000

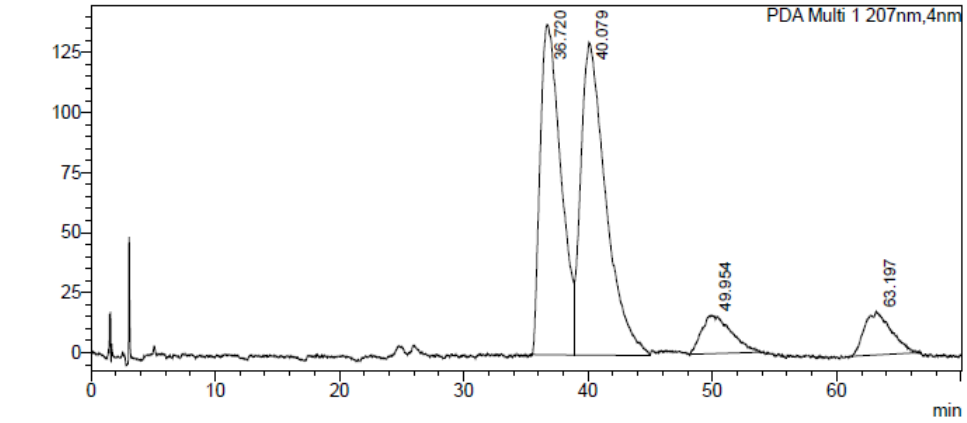
3-(Dimethylamino)-1-(2-oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)-piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (14)

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R,S-KA-223		
Sample ID	:		
Data Filename	: R,S-KA-223.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-16	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 15.10.2021 12:59:22	Acquired by	: Chemia leków1
Date Processed	: 15.10.2021 14:09:28	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	36.720	40.179
2	40.079	46.243
3	49.954	6.694
4	63.197	6.884
Total		100.000

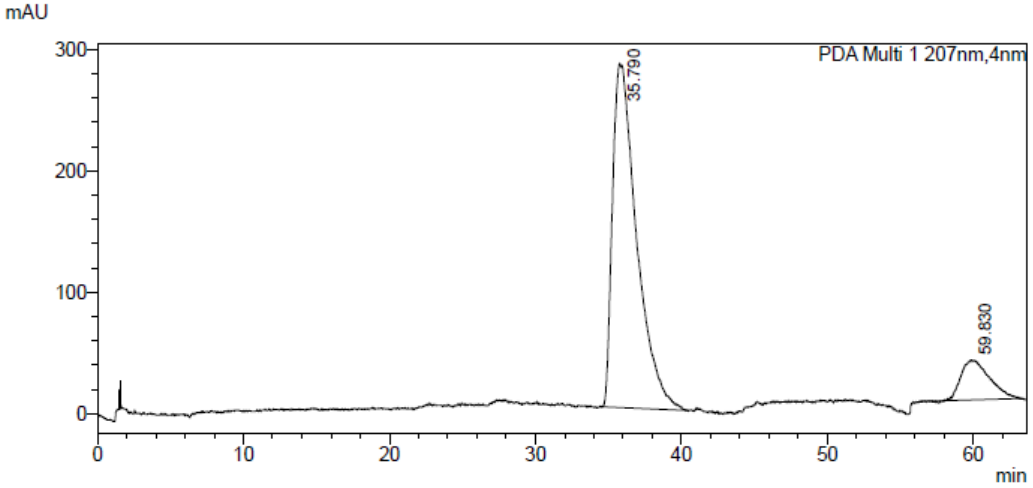
3-Dimethylamino-1-((*R*)-oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)-piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (C1-*R*)-31

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R-KA-223		
Sample ID	:		
Data Filename	: R-KA-223.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-10	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 14.10.2021 09:14:45	Acquired by	: Chemia leków1
Date Processed	: 14.10.2021 10:26:06	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	35.790	87.957
2	59.830	12.043
Total		100.000

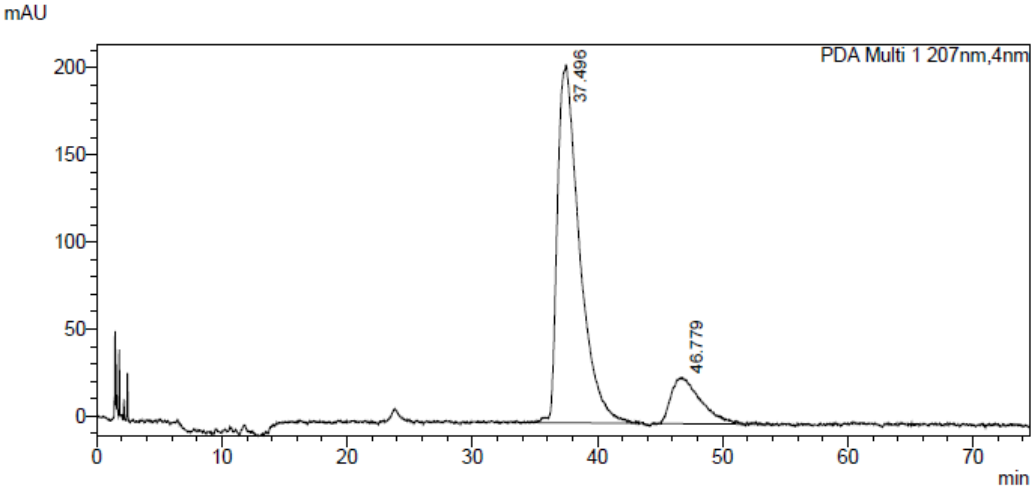
3-Dimethylamino-1-((*S*)-oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)-piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (C1-*S*)-31

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: S-KA-223		
Sample ID	:		
Data Filename	: S-KA-223.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-11	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 14.10.2021 10:19:12	Acquired by	: Chemia leków1
Date Processed	: 14.10.2021 11:33:45	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	37.496	85.241
2	46.779	14.759
Total		100.000

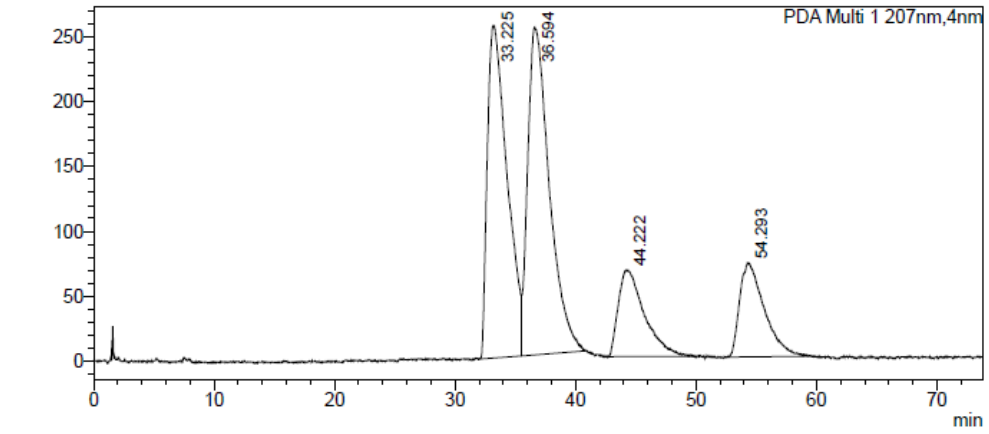
3-Dimethylamino-1-(2-oxo-1-phenyl-2-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (17)

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R,S-KA-238		
Sample ID	:		
Data Filename	: R,S-KA-238.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-7	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 13.10.2021 14:07:11	Acquired by	: Chemia leków1
Date Processed	: 13.10.2021 15:21:00	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	33.225	35.932
2	36.594	38.884
3	44.222	12.433
4	54.293	12.750
Total		100.000

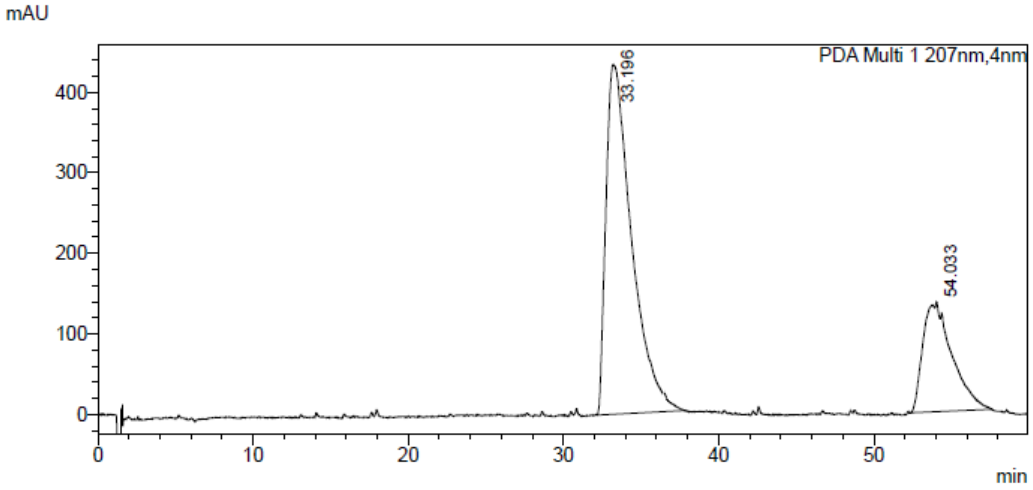
3-Dimethylamino-1-((*R*)-2-oxo-1-phenyl-2-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (C1-*R*)-32

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R-KA-238		
Sample ID	:		
Data Filename	: R-KA-238.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-8	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 13.10.2021 15:22:24	Acquired by	: Chemia leków1
Date Processed	: 13.10.2021 16:22:17	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	33.196	73.741
2	54.033	26.259
Total		100.000

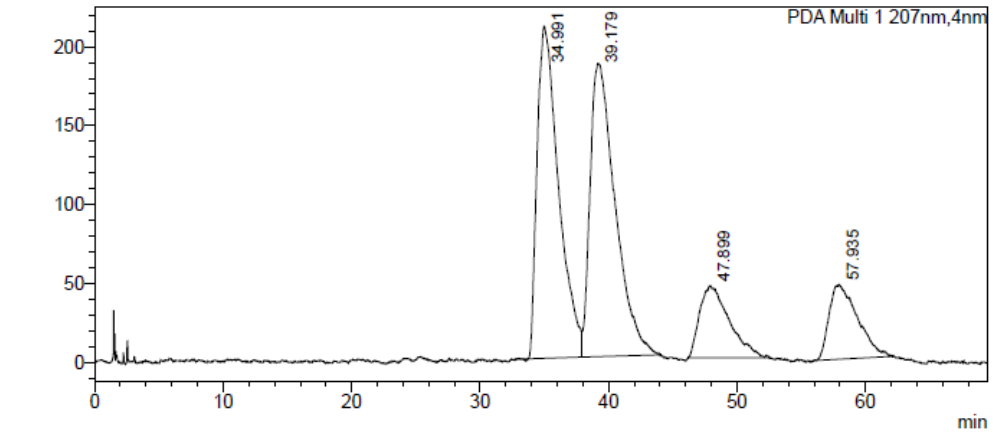
3-Dimethylamino-1-(2-oxo-1-phenyl-2-(4-(3-((trifluoromethyl)thio)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (18)

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R,S-KA-237		
Sample ID	:		
Data Filename	: R,S-KA-237.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-14	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 15.10.2021 09:47:52	Acquired by	: Chemia leków1
Date Processed	: 15.10.2021 10:57:21	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	34.991	38.066
2	39.179	39.301
3	47.899	11.345
4	57.935	11.288
Total		100.000

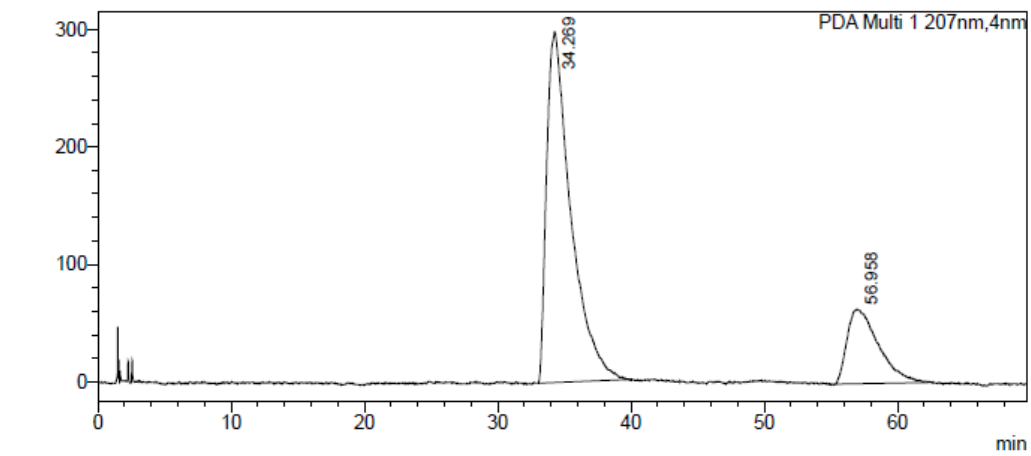
3-Dimethylamino-1-((*R*)-2-oxo-1-phenyl-2-(4-(3-((trifluoromethyl)thio)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (C1-*R*)-33

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: R-KA-237		
Sample ID	:		
Data Filename	: R-KA-237.lcd		
Method Filename	: chiralneKA.lcm		
Batch Filename	:		
Vial #	: 1-15	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 15.10.2021 11:07:19	Acquired by	: Chemia leków1
Date Processed	: 15.10.2021 12:17:01	Processed by	: Chemia leków1

<Chromatogram>



<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%
1	34.269	78.432
2	56.958	21.568
Total		100.000