

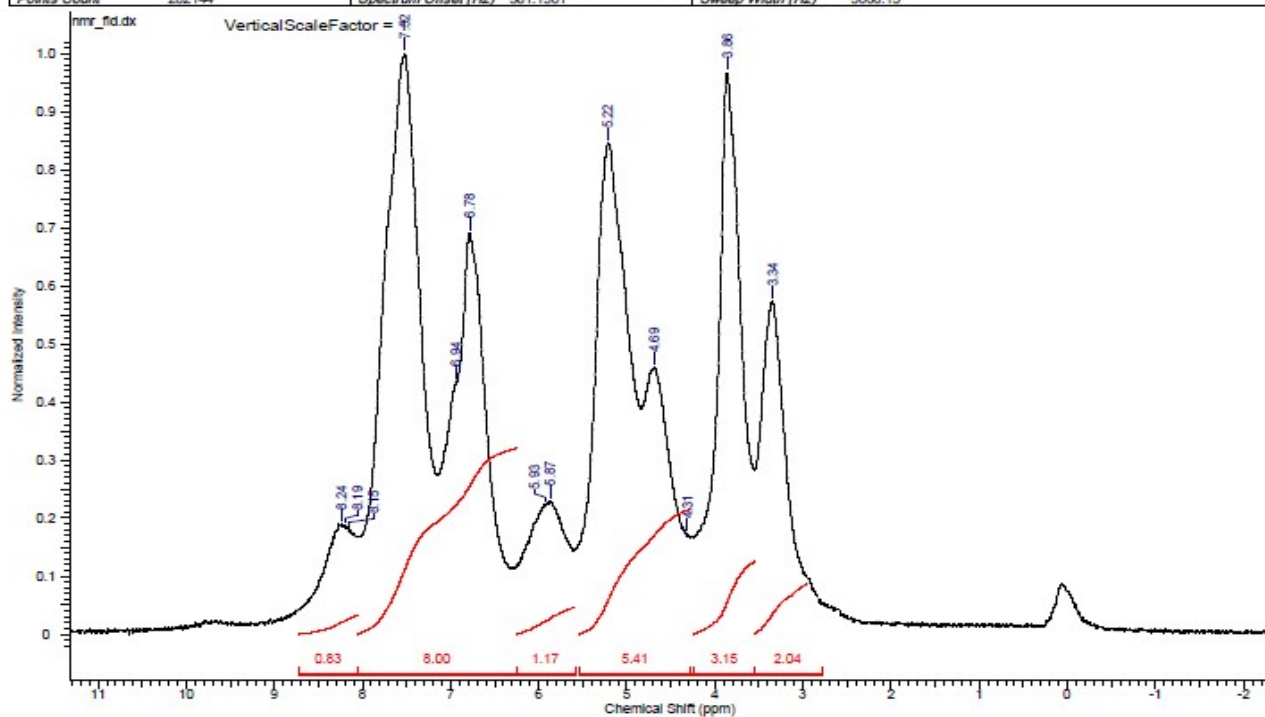
## SUPPLEMENTARY MATERIAL

### Design, Synthesis and Biological Evaluation of new Eugenol derivatives containing 1,3,4-oxadiazole as novel inhibitors of Thymidylate Synthase

#### <sup>1</sup>H NMR spectra of compounds 6-19

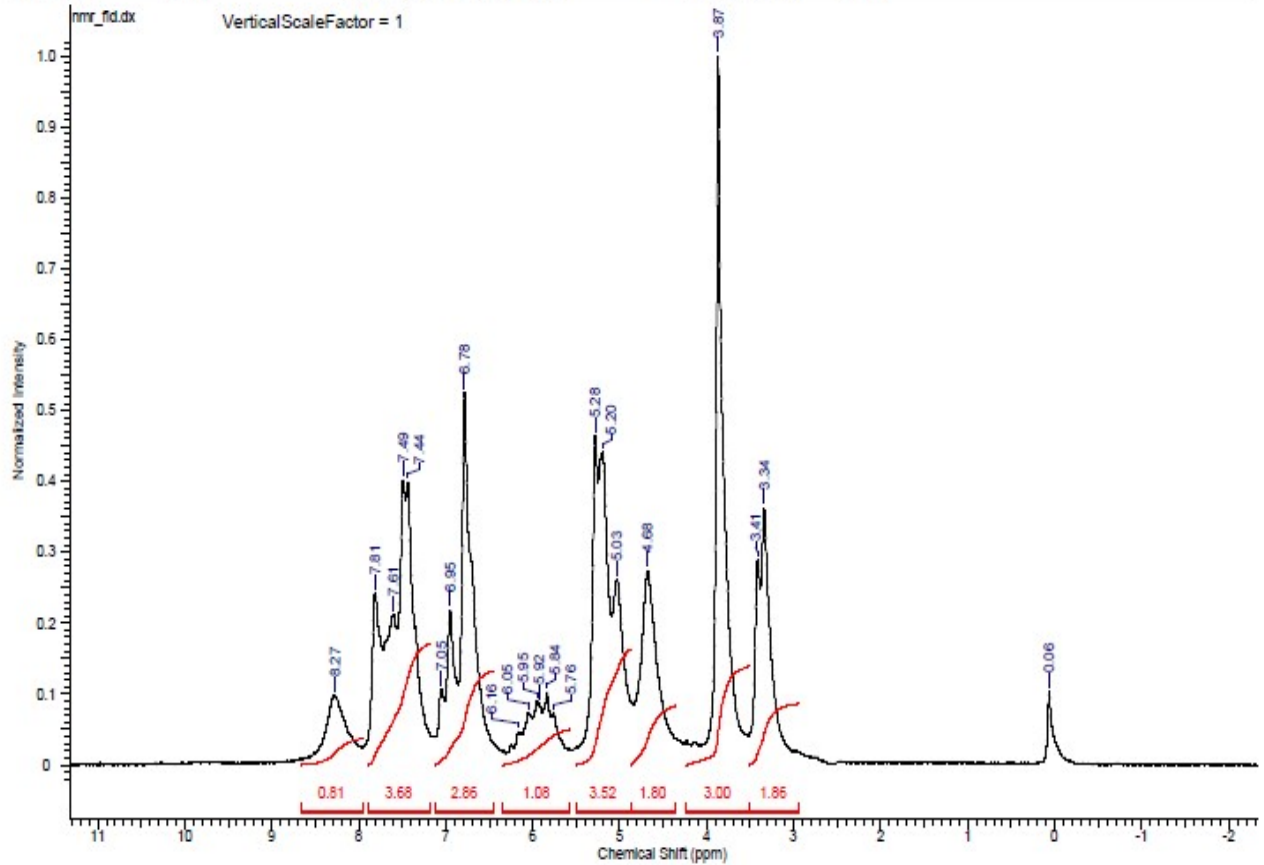
This report was created by ACD/NMR Processor Academic Edition. For more information go to [www.acdlabs.com/nmrproc/](http://www.acdlabs.com/nmrproc/)

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Frequency (MHz)	80.32	Nucleus	<sup>1</sup> H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
Points Count	262144	Spectrum Offset (Hz)	381.1301	Sweep Width (Hz)	5000.15



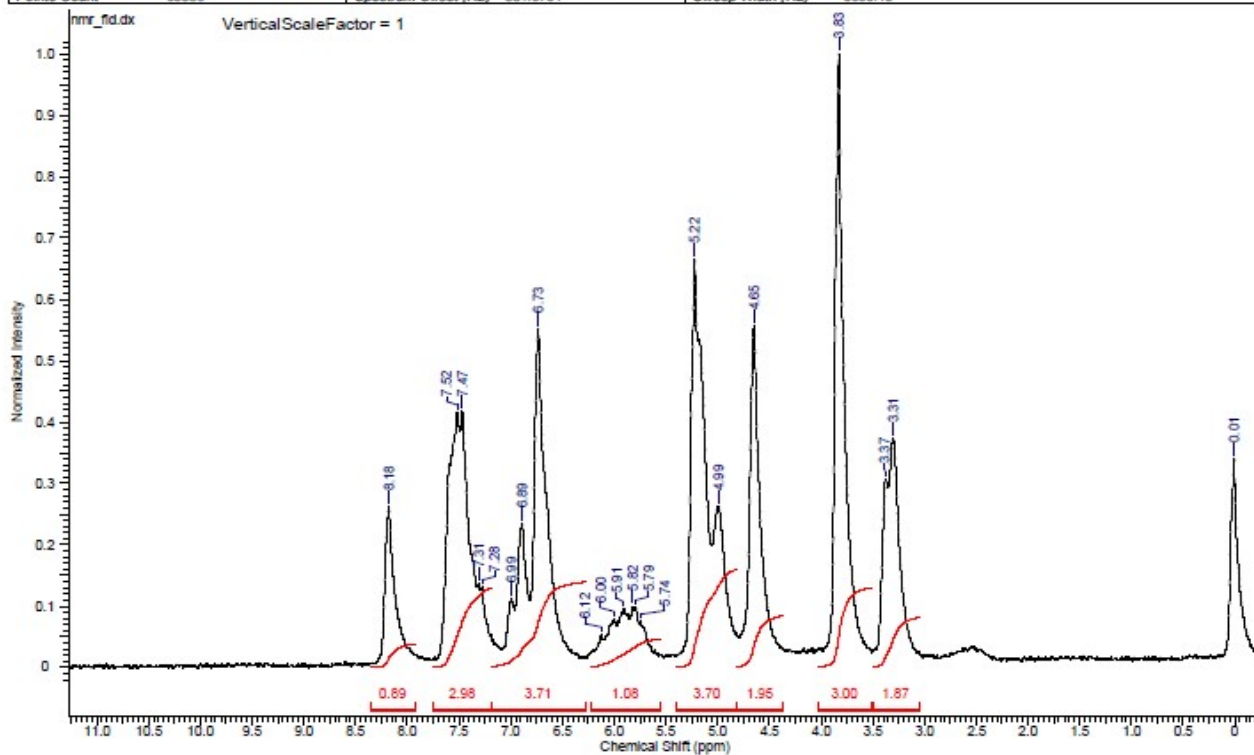
<sup>1</sup>H NMR spectrum of compound 6

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
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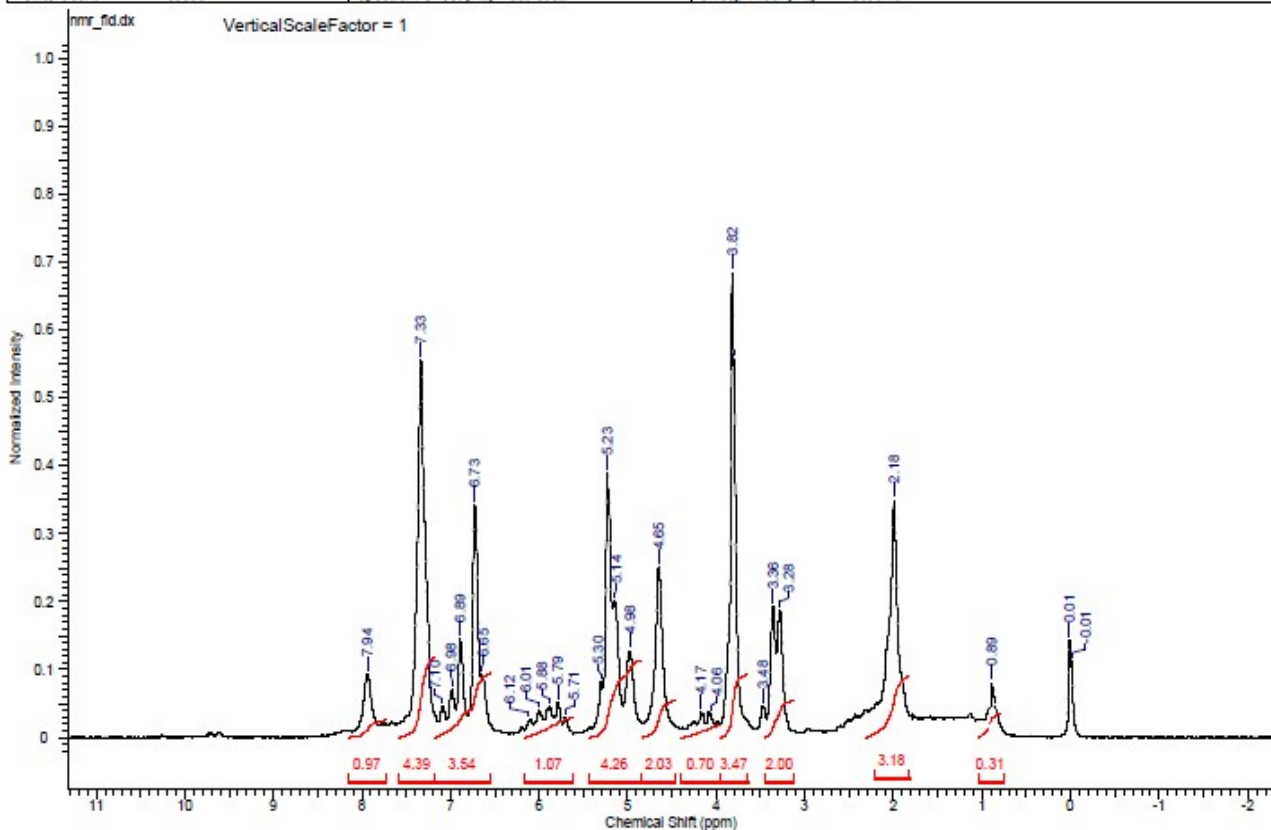
$^1\text{H}$  NMR spectrum of compound **7**

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
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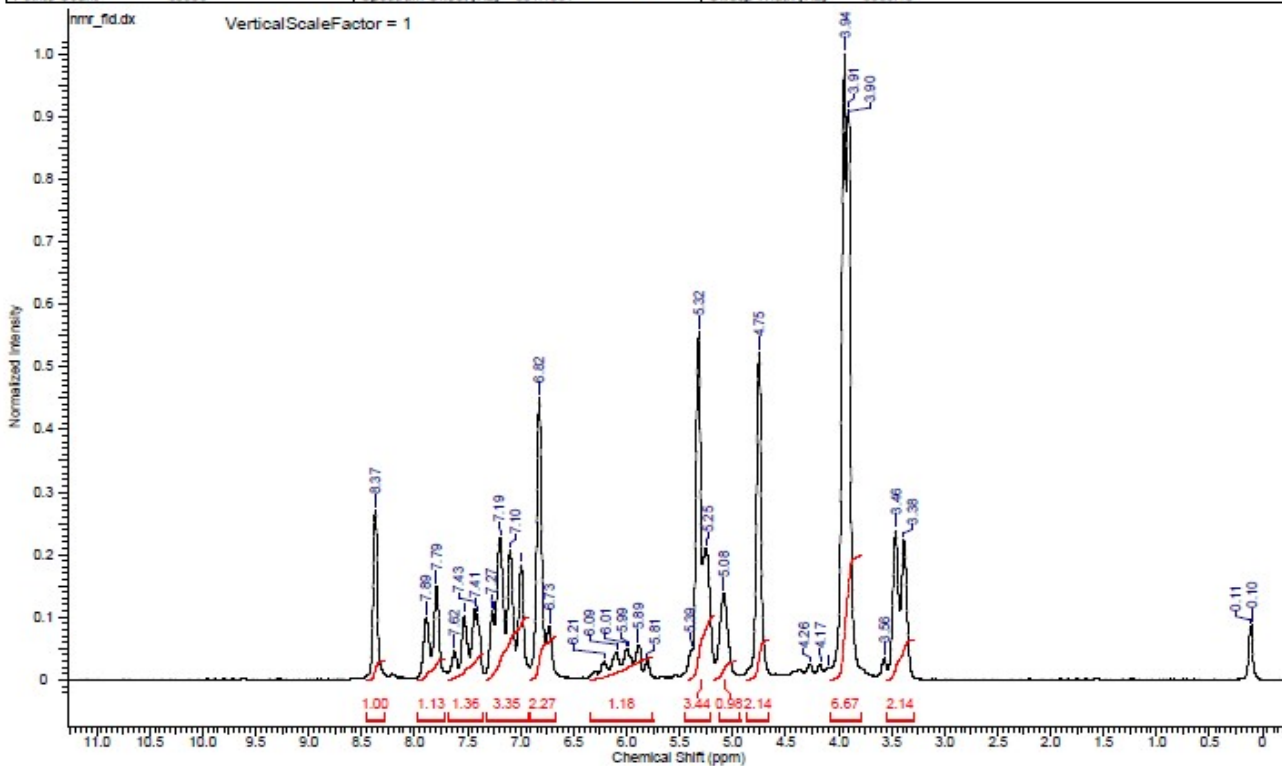
<sup>1</sup>H NMR spectrum of compound **8**

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
Points Count	65536	Spectrum Offset (Hz)	380.6982	Sweep Width (Hz)	5000.15



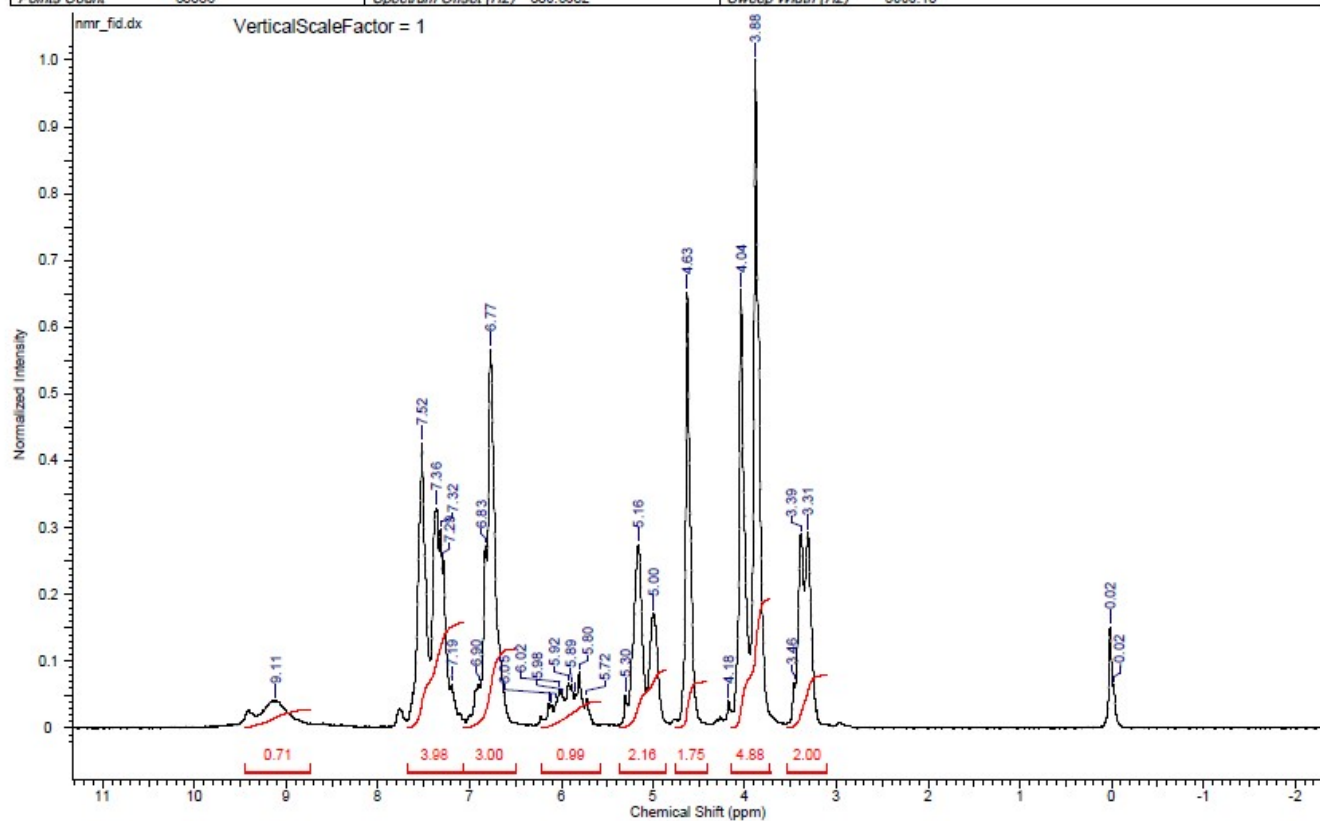
<sup>1</sup>H NMR spectrum of compound **9**

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
Points Count	65536	Spectrum Offset (Hz)	381.1301	Sweep Width (Hz)	5000.15



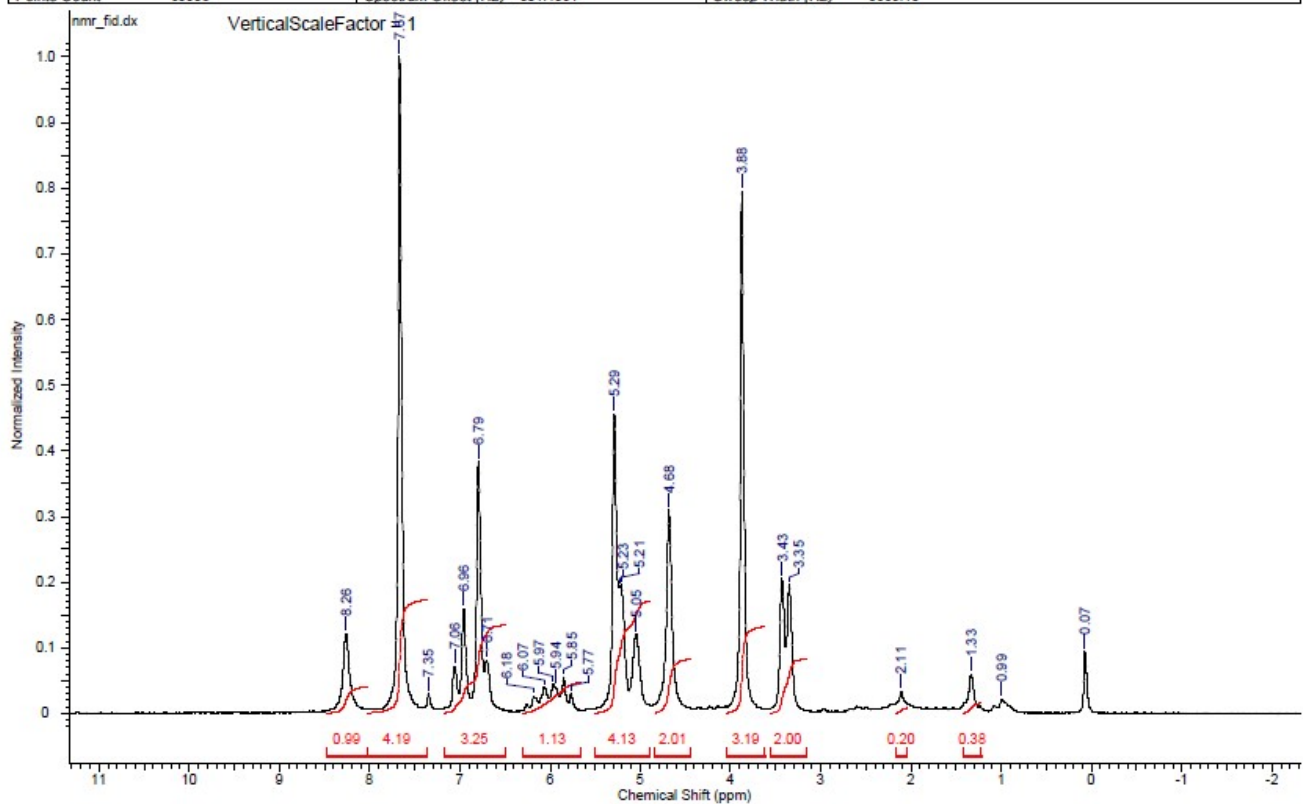
<sup>1</sup>H NMR spectrum of compound 10

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
Points Count	65536	Spectrum Offset (Hz)	380.6982	Sweep Width (Hz)	5000.15



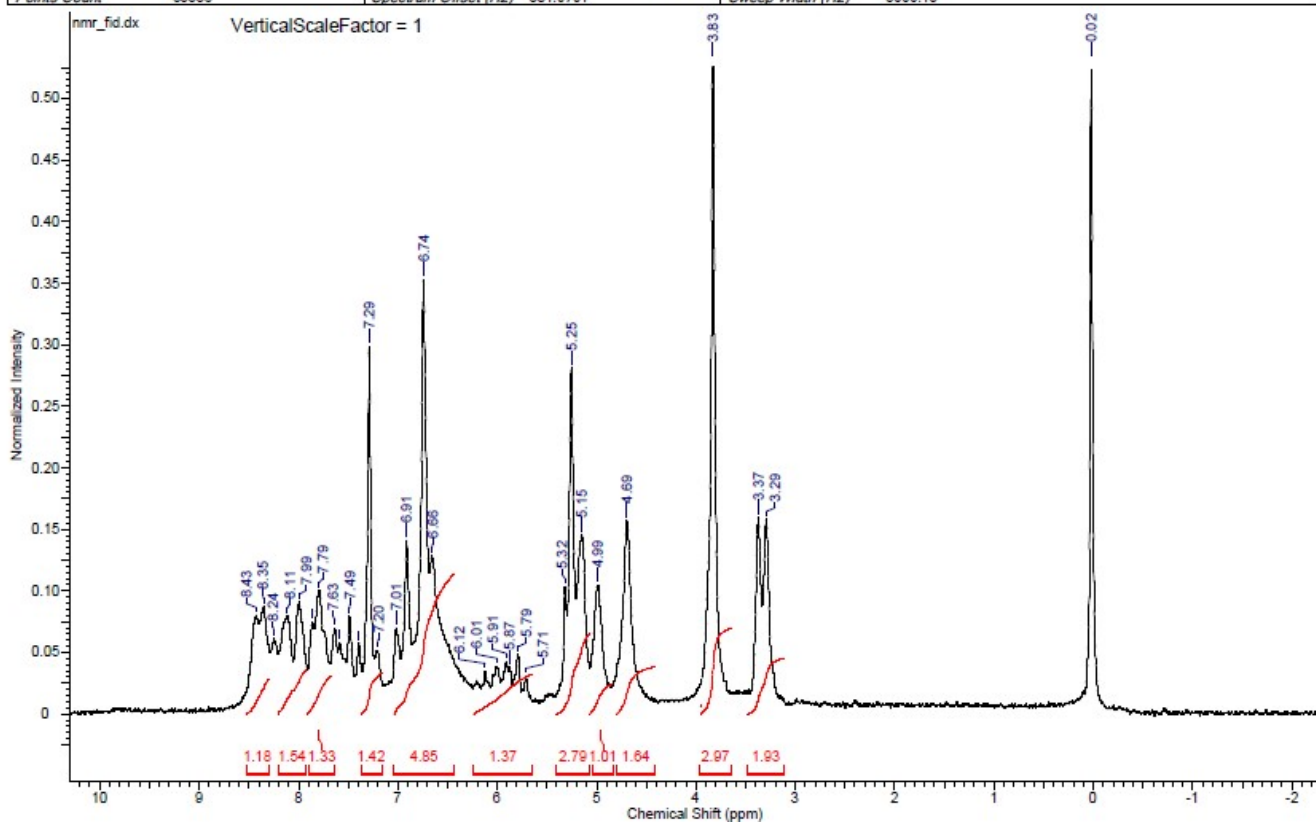
<sup>1</sup>H NMR spectrum of compound **11**

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
Points Count	65536	Spectrum Offset (Hz)	381.1301	Sweep Width (Hz)	5000.15



$^1\text{H}$  NMR spectrum of compound **12**

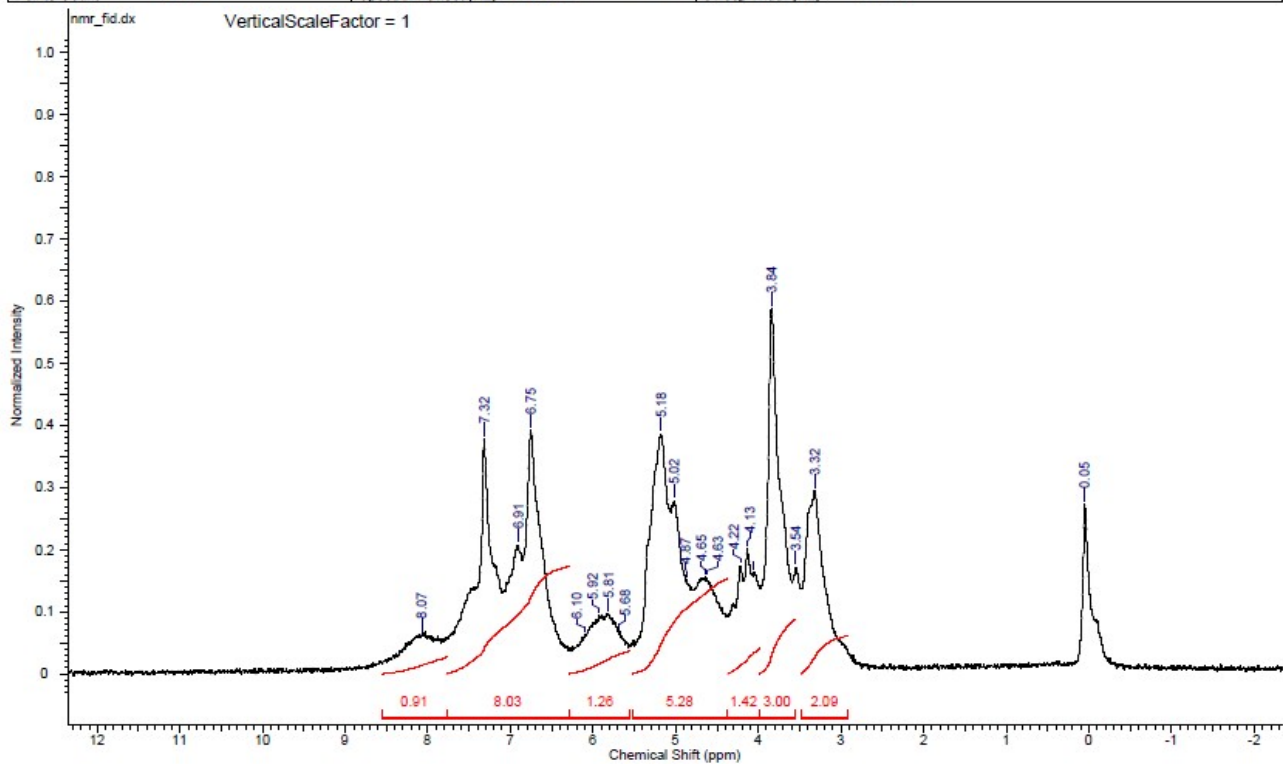
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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
Points Count	65536	Spectrum Offset (Hz)	381.0701	Sweep Width (Hz)	5000.15



<sup>1</sup>H NMR spectrum of compound **13**

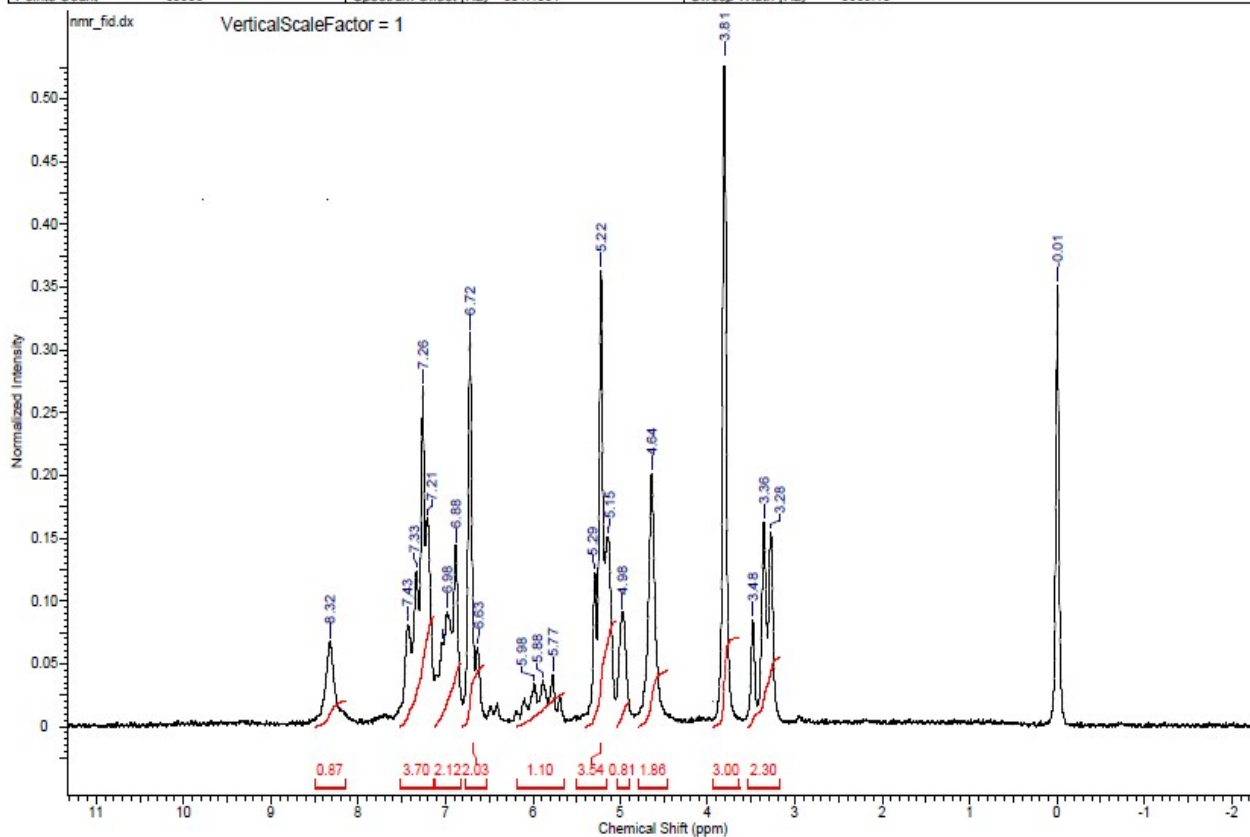


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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
Points Count	65536	Spectrum Offset (Hz)	380.6982	Sweep Width (Hz)	5000.15



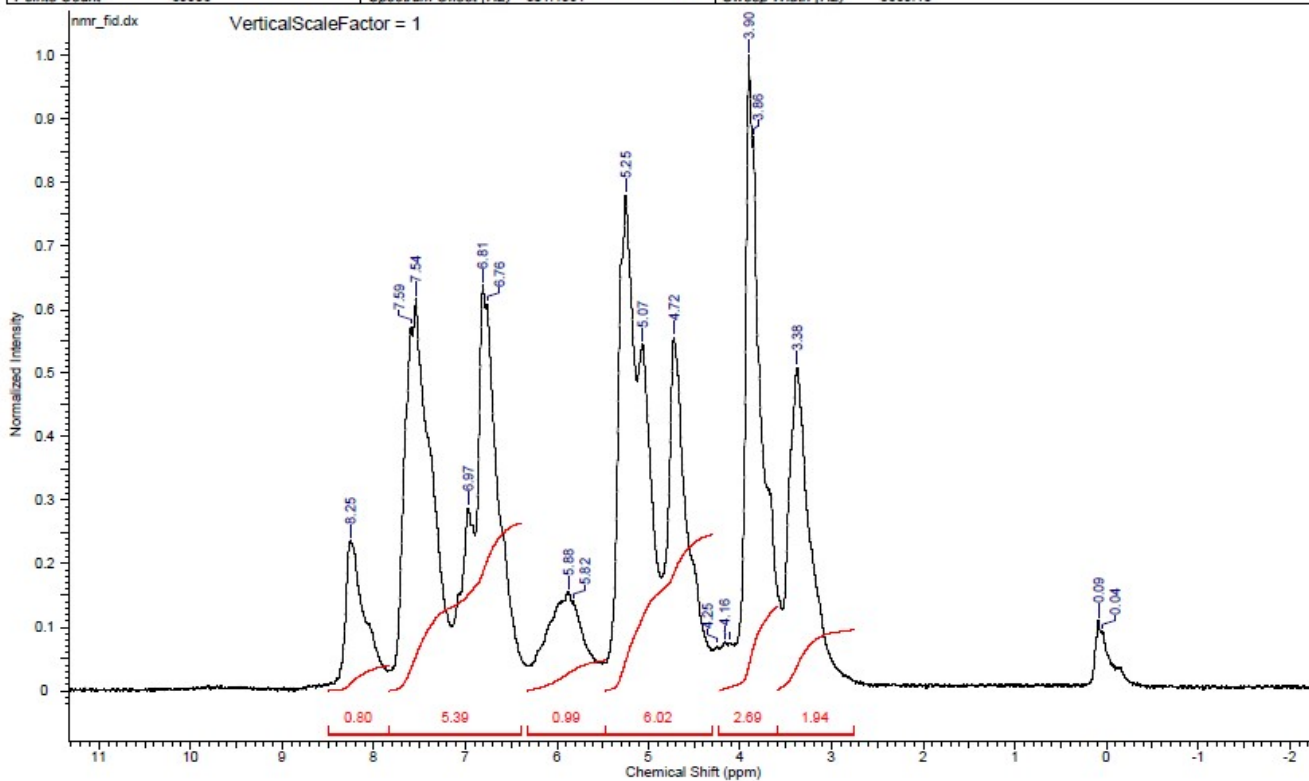
$^1\text{H}$  NMR spectrum of compound **14**

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
Points Count	65536	Spectrum Offset (Hz)	381.1301	Sweep Width (Hz)	5000.15



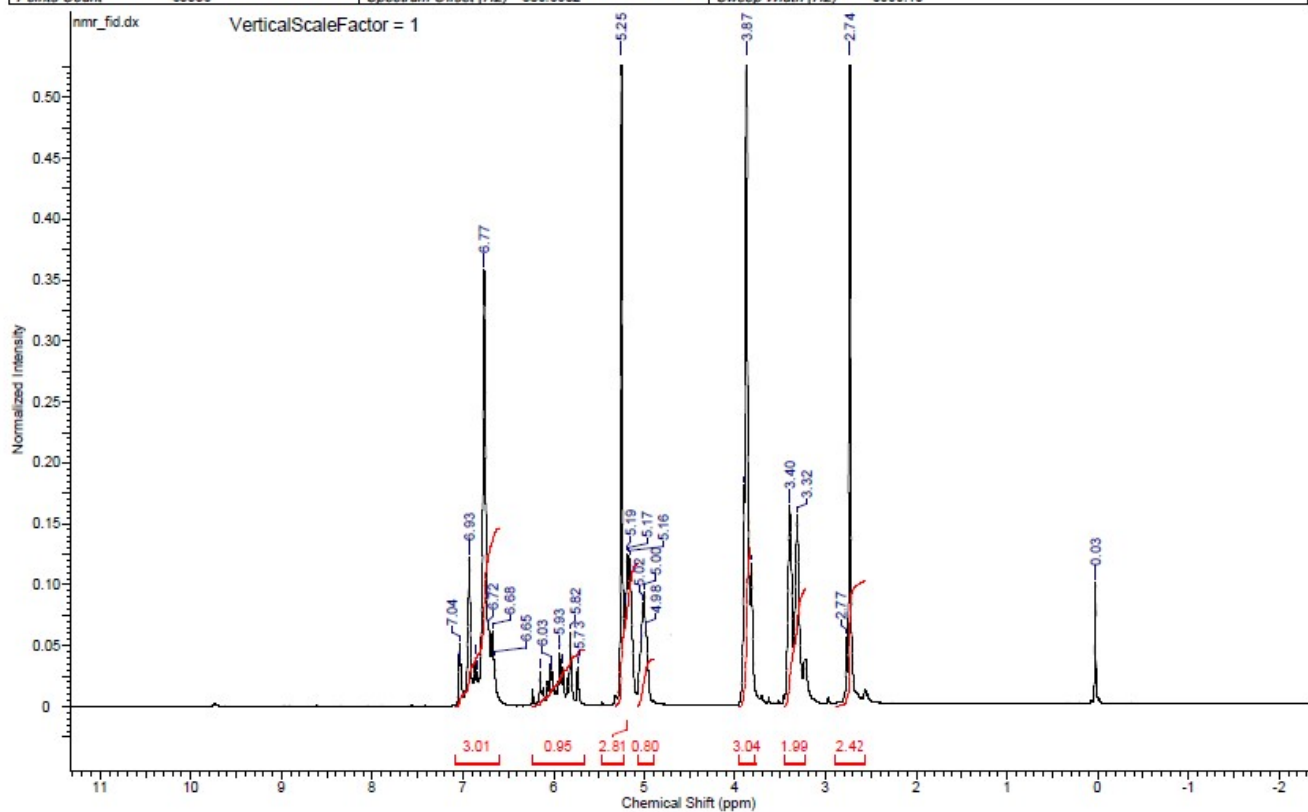
<sup>1</sup>H NMR spectrum of compound **15**

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
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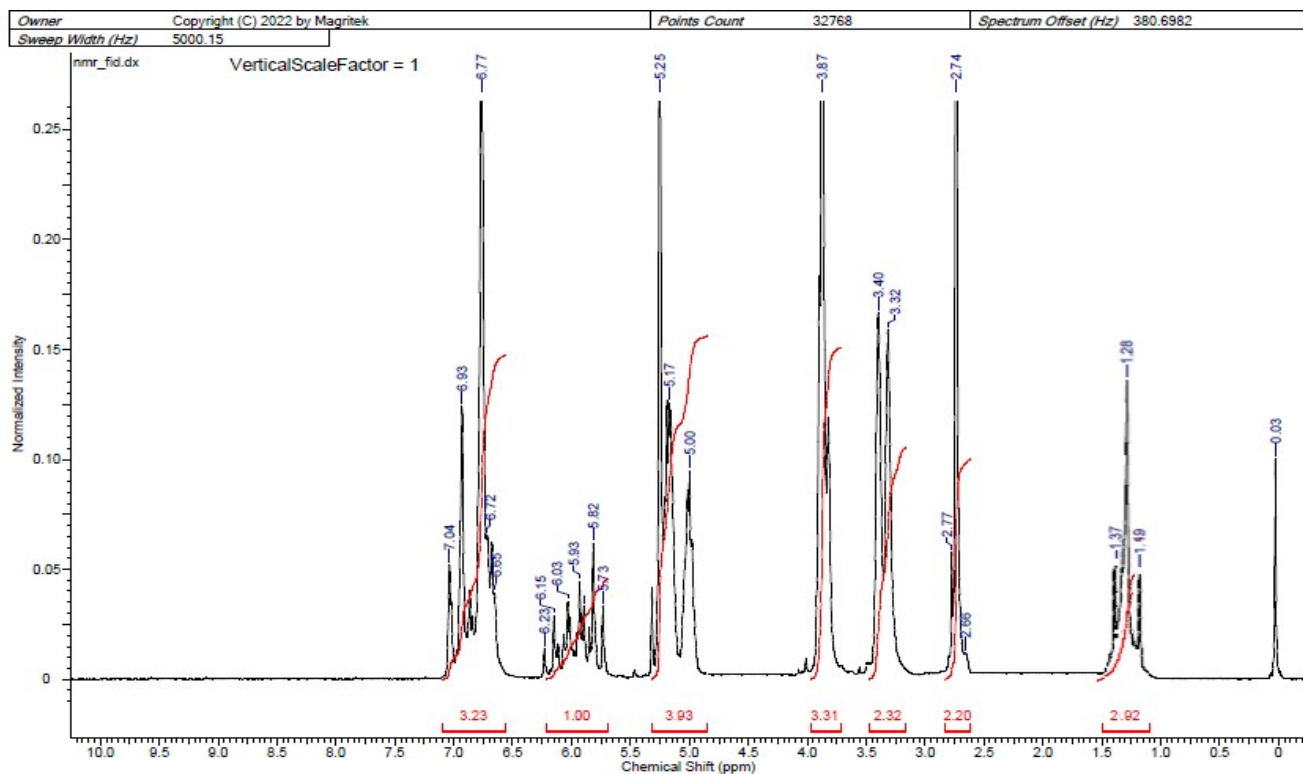


<sup>1</sup>H NMR spectrum of compound **16**

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Frequency (MHz)	80.32	Nucleus	1H	Origin	SPA3310 at Magritek
Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
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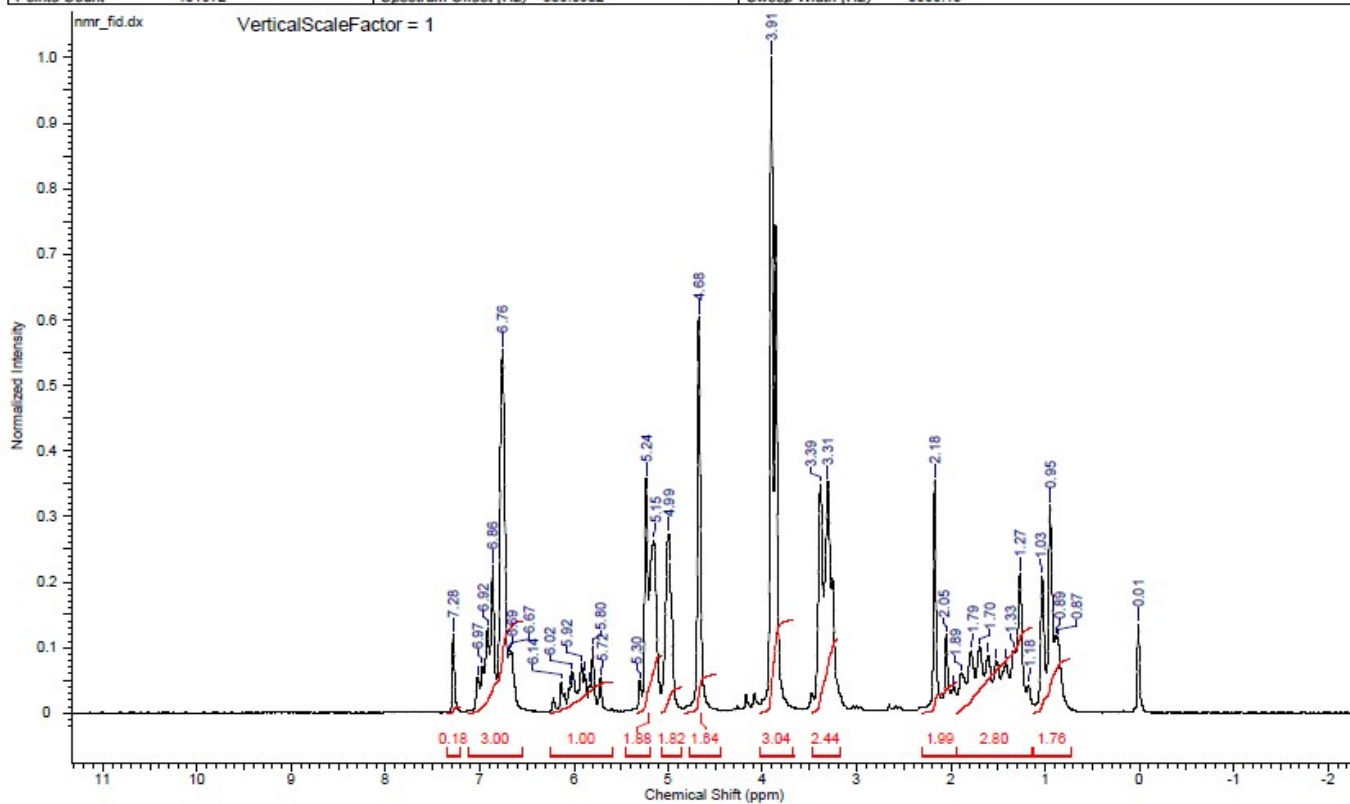


<sup>1</sup>H NMR spectrum of compound **17**



<sup>1</sup>H NMR spectrum of compound **18**

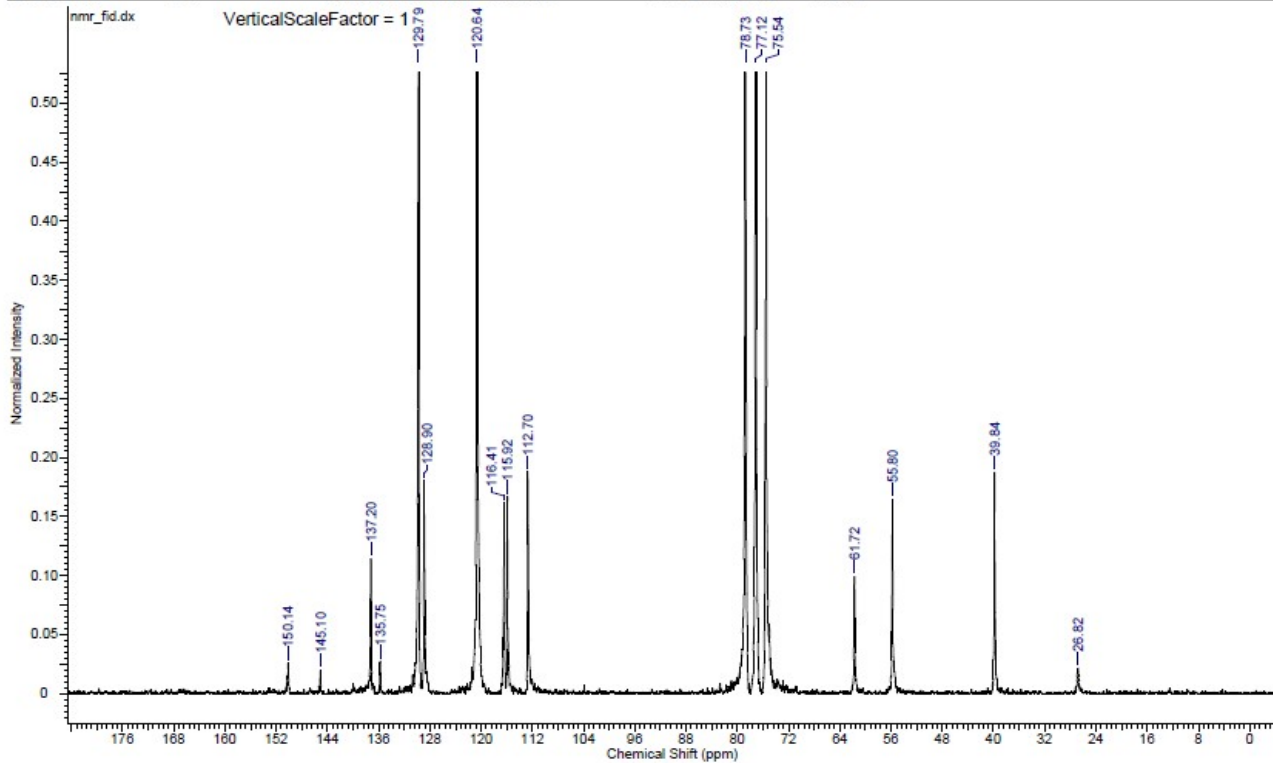
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Original Points Count	32768	Owner	Copyright (C) 2022 by Magritek		
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<sup>1</sup>H NMR spectrum of compound **19**

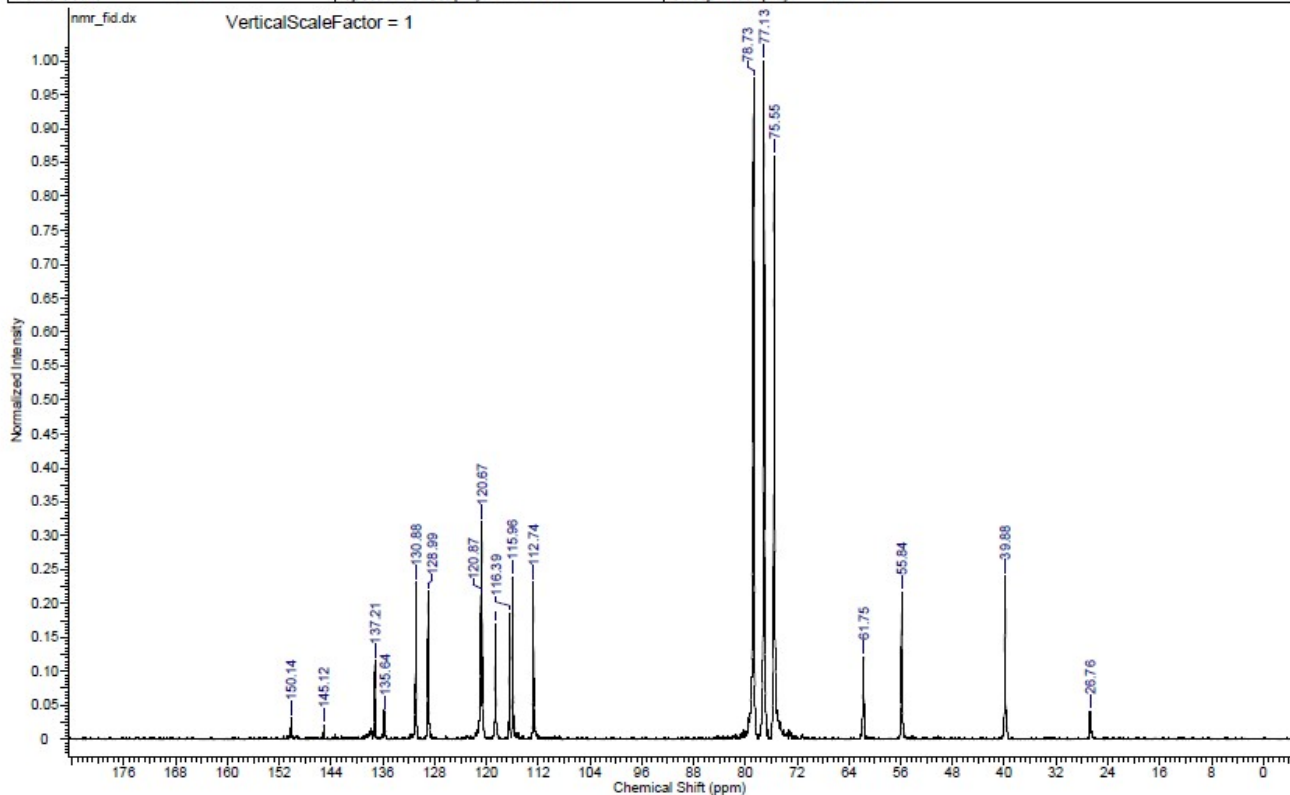
## <sup>13</sup>C NMR spectra of compounds 6-19

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Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek		
Points Count	8192	Spectrum Offset (Hz)	2222.3068	Sweep Width (Hz)	6667.49



<sup>13</sup>C NMR spectrum of compound 6

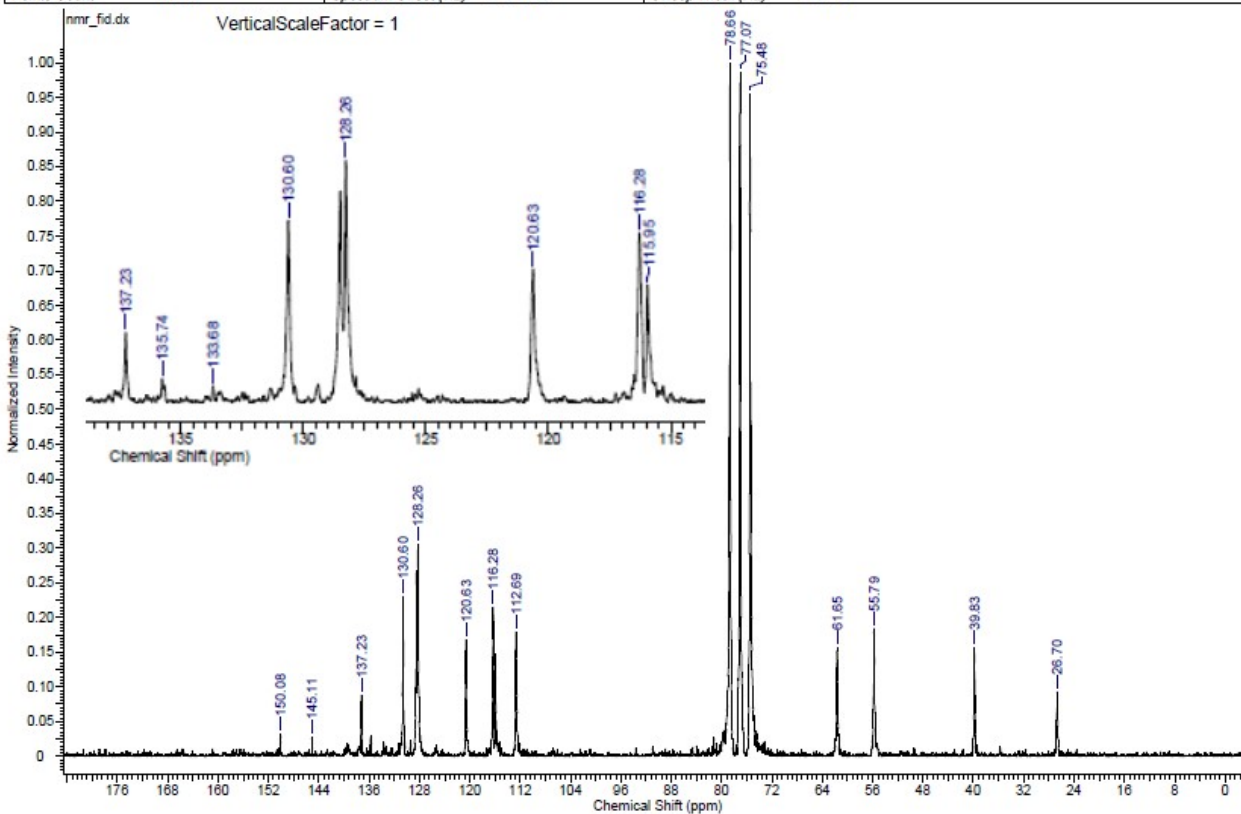
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Frequency (MHz)	20.20	Nucleus	13C	Origin	SPA3310 at Magritek
Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek		
Points Count	32768	Spectrum Offset (Hz)	2222.3120	Sweep Width (Hz)	6667.49



<sup>13</sup>C NMR spectrum of compound 7

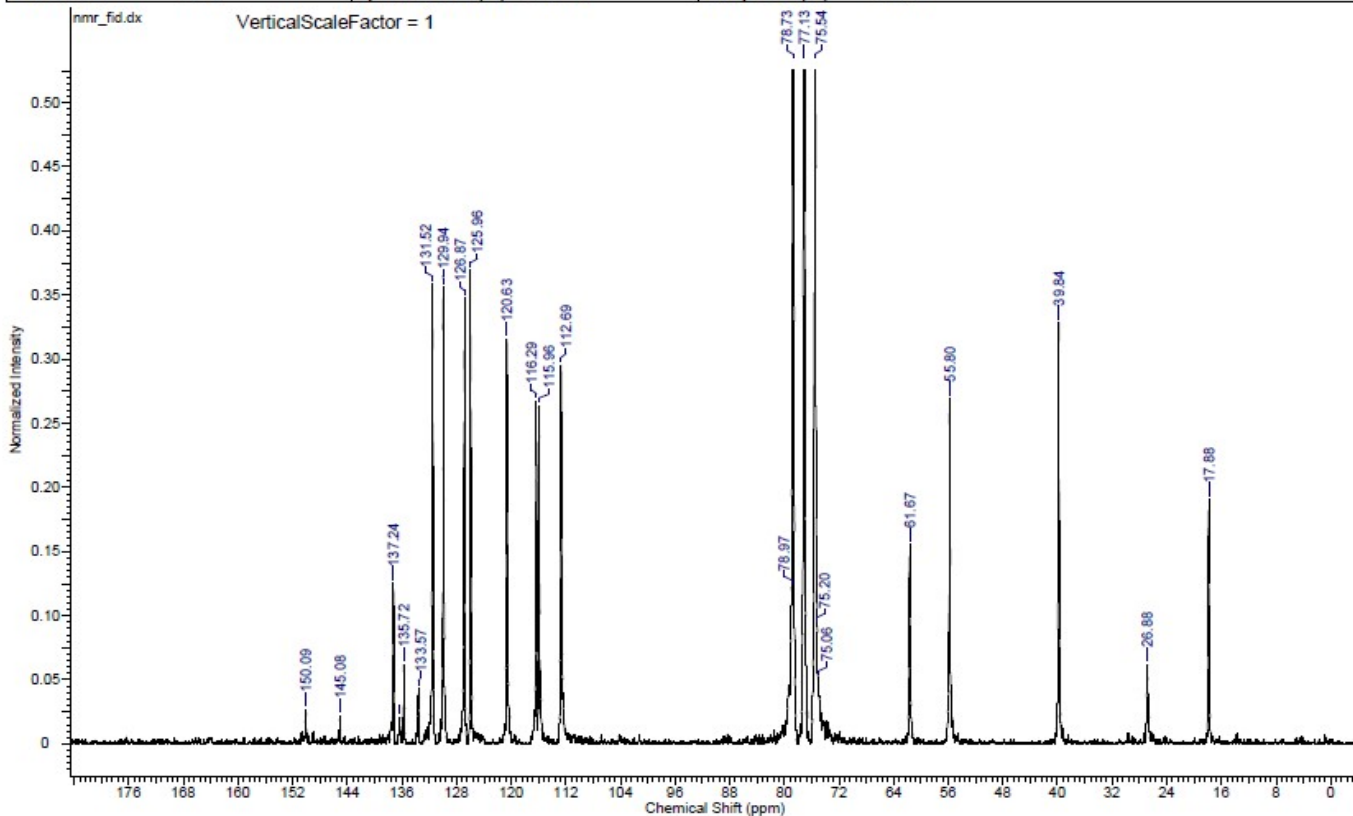


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Frequency (MHz)	20.20	Nucleus	13C	Origin	SPA3310 at Magritek
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Points Count	16384	Spectrum Offset (Hz)	2222.3130	Sweep Width (Hz)	6667.49



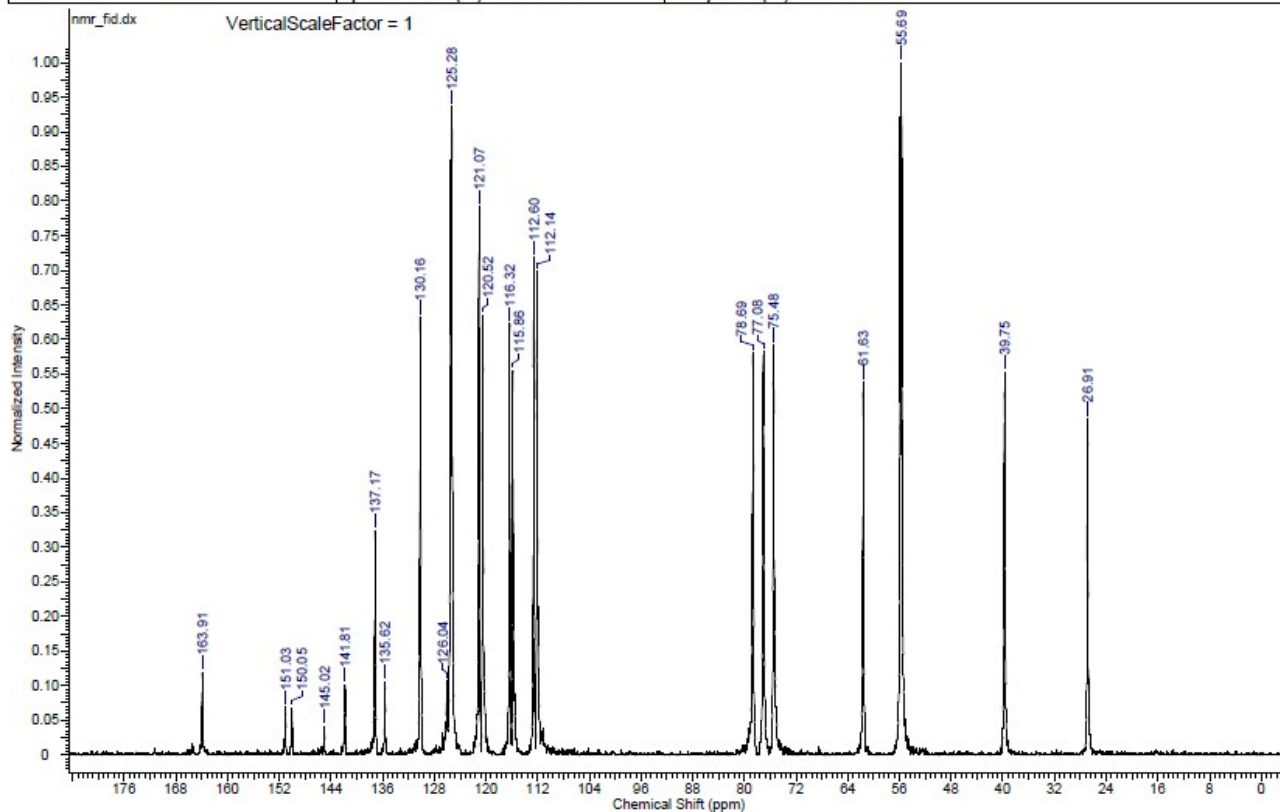
<sup>13</sup>C NMR spectrum of compound **8**

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Frequency (MHz)	20.20	Nucleus	13C	Origin	SPA3310 at Magritek
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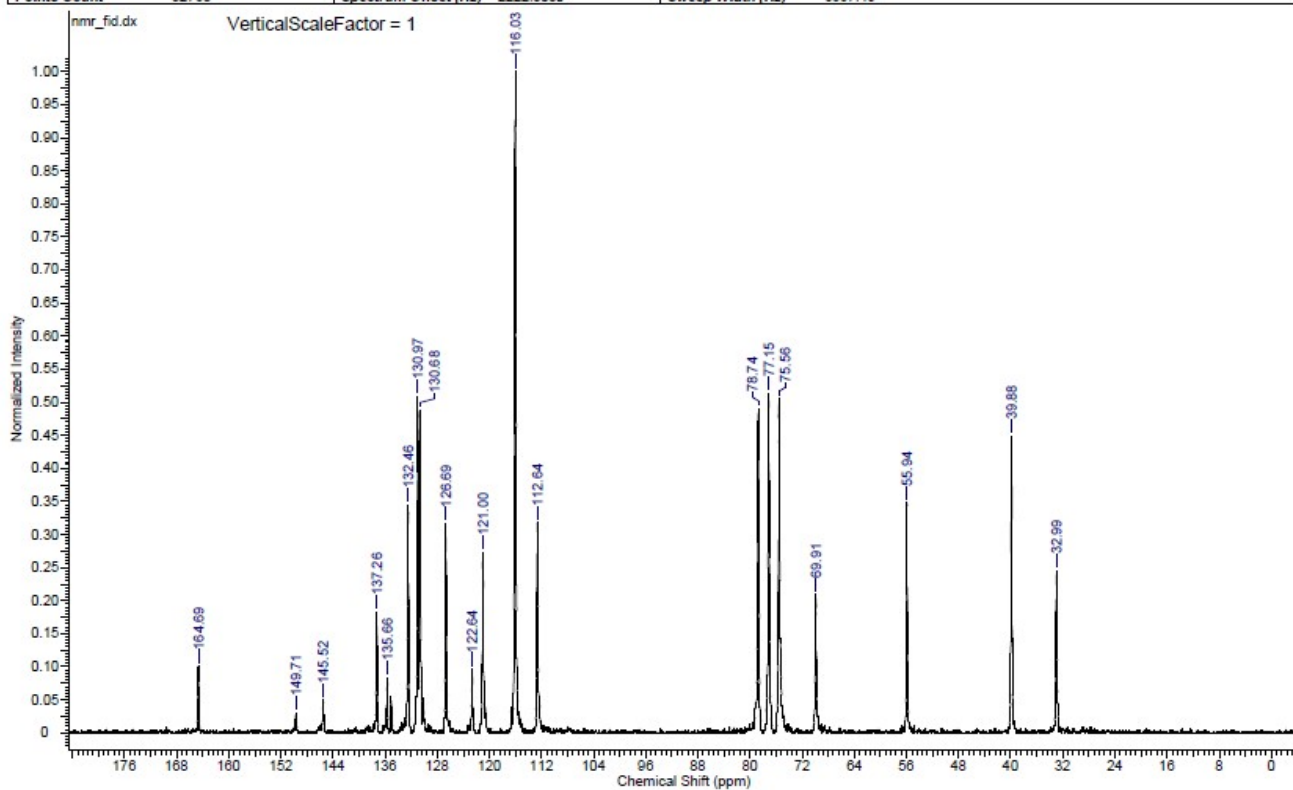
<sup>13</sup>C NMR spectrum of compound 9

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Frequency (MHz)	20.20	Nucleus	13C	Origin	SPA3310 at Magritek
Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek		
Points Count	32768	Spectrum Offset (Hz)	2222.3120	Sweep Width (Hz)	6667.49



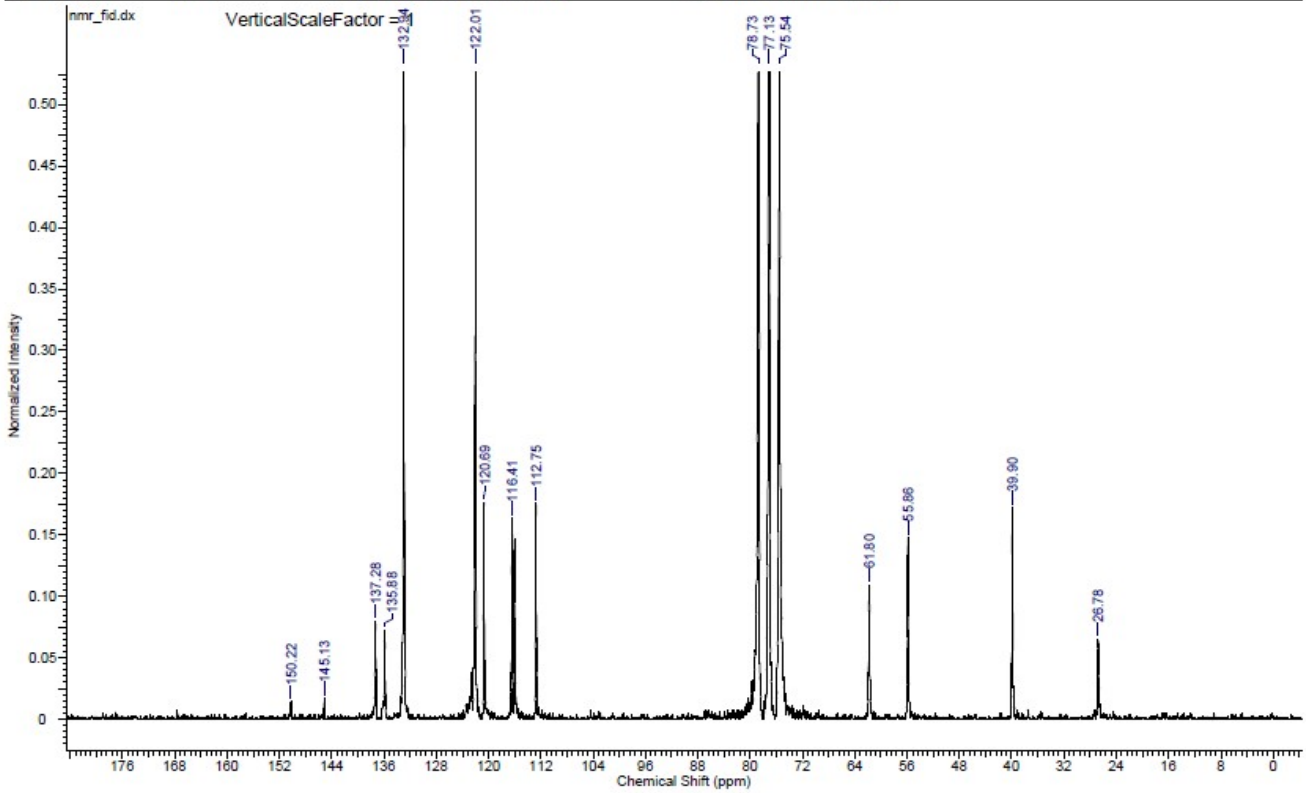
<sup>13</sup>C NMR spectrum of compound **10**

File Name	M:\EU NMR Azizah\EUA and EUTEUT carbon\144328-1D CARBON WALTZ-EUT-4 CDCl3\nmr_fid.dx		
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Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek
Points Count	32768	Spectrum Offset (Hz)	2222.3030
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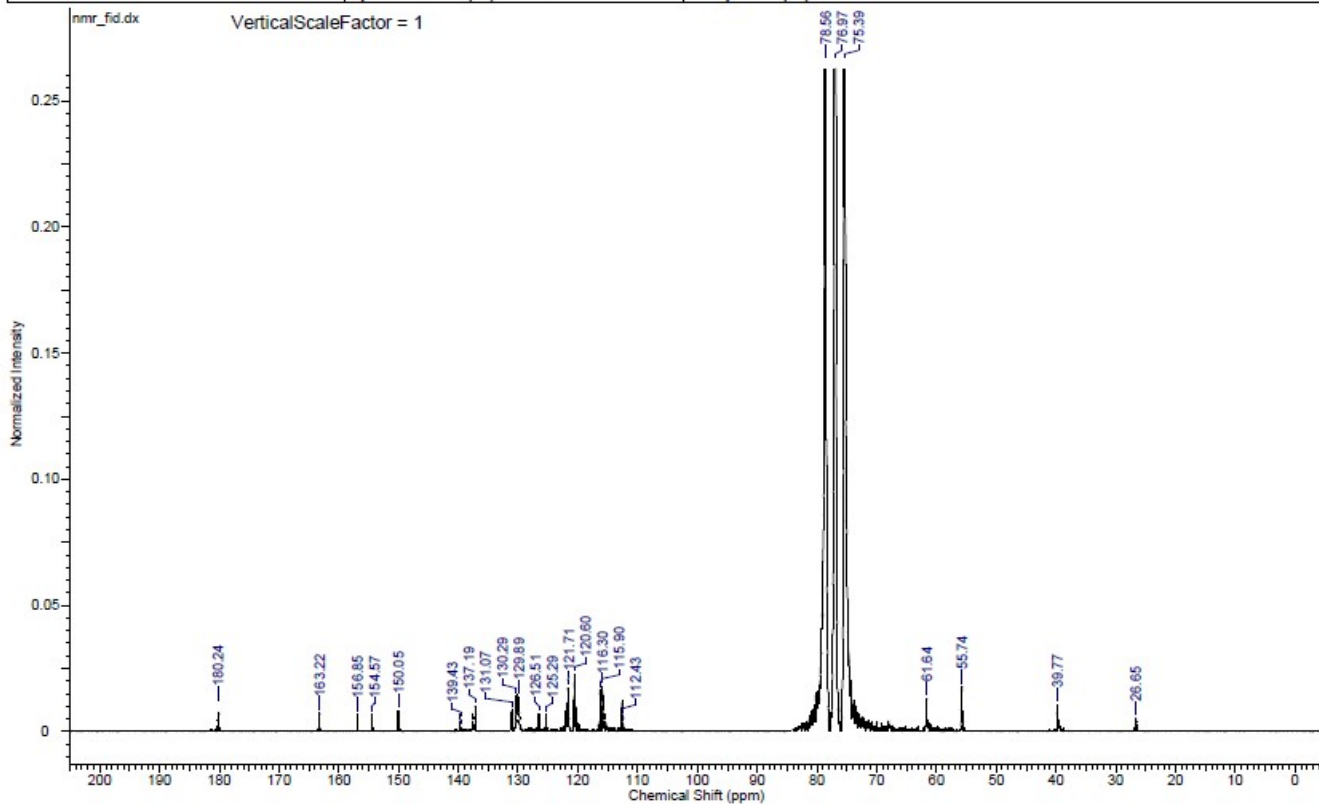
<sup>13</sup>C NMR spectrum of compound **11**

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Frequency (MHz)	20.20	Nucleus	13C	Origin	SPA3310 at Magritek
Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek		
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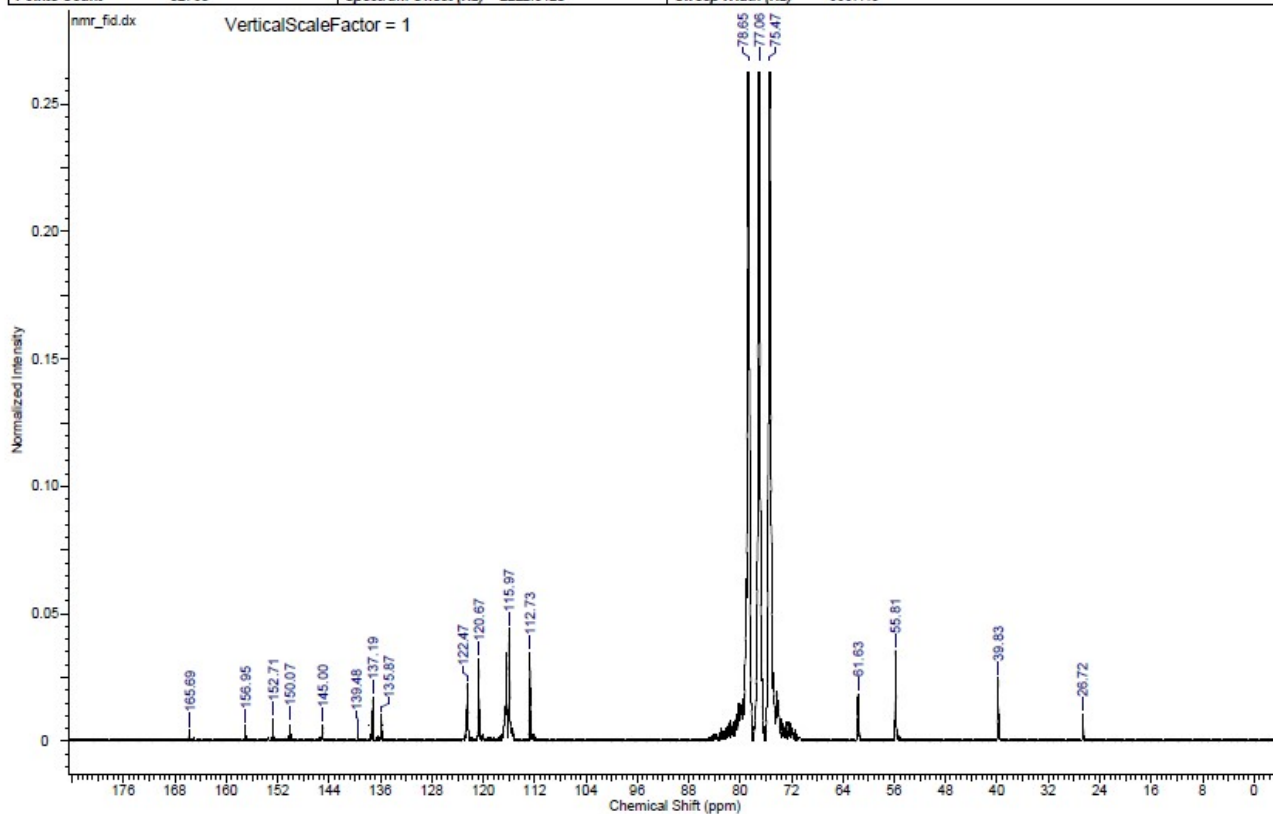
<sup>13</sup>C NMR spectrum of compound **12**

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Date Stamp	2022/05/12 14:24:43.148	File Name	M\1E\NMR Azizah\1EUA and EUT\1EUT carbon\142442-1D CARBON WALTZ-EUT-6 AZIZAH CDCL3\nmr_fid.dx		
Frequency (MHz)	20.20	Nucleus	13C	Origin	SPA3310 at Magritek
Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek		
Points Count	32768	Spectrum Offset (Hz)	2222.3169	Sweep Width (Hz)	6667.49



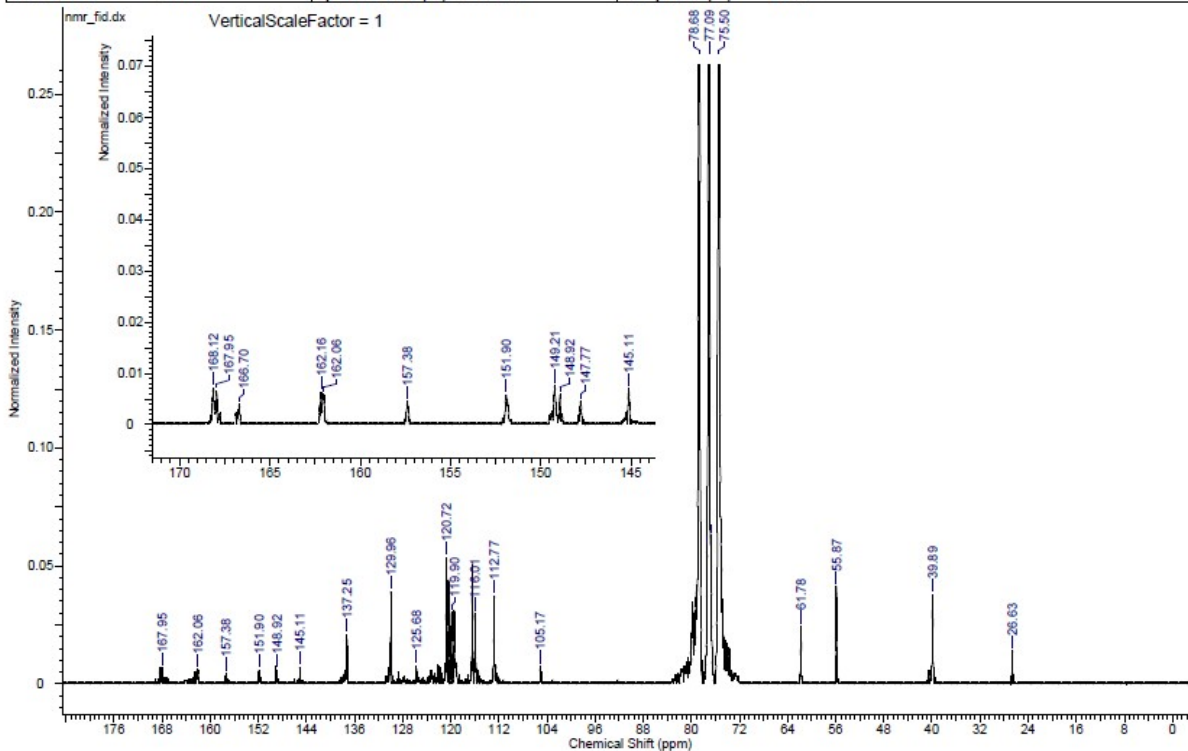
<sup>13</sup>C NMR spectrum of compound **13**

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Frequency (MHz)	20.20	Nucleus	<sup>13</sup> C	Origin	SPA3310 at Magritek
Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek		
Points Count	32768	Spectrum Offset (Hz)	2222.3120	Sweep Width (Hz)	6667.49



<sup>13</sup>C NMR spectrum of compound **14**

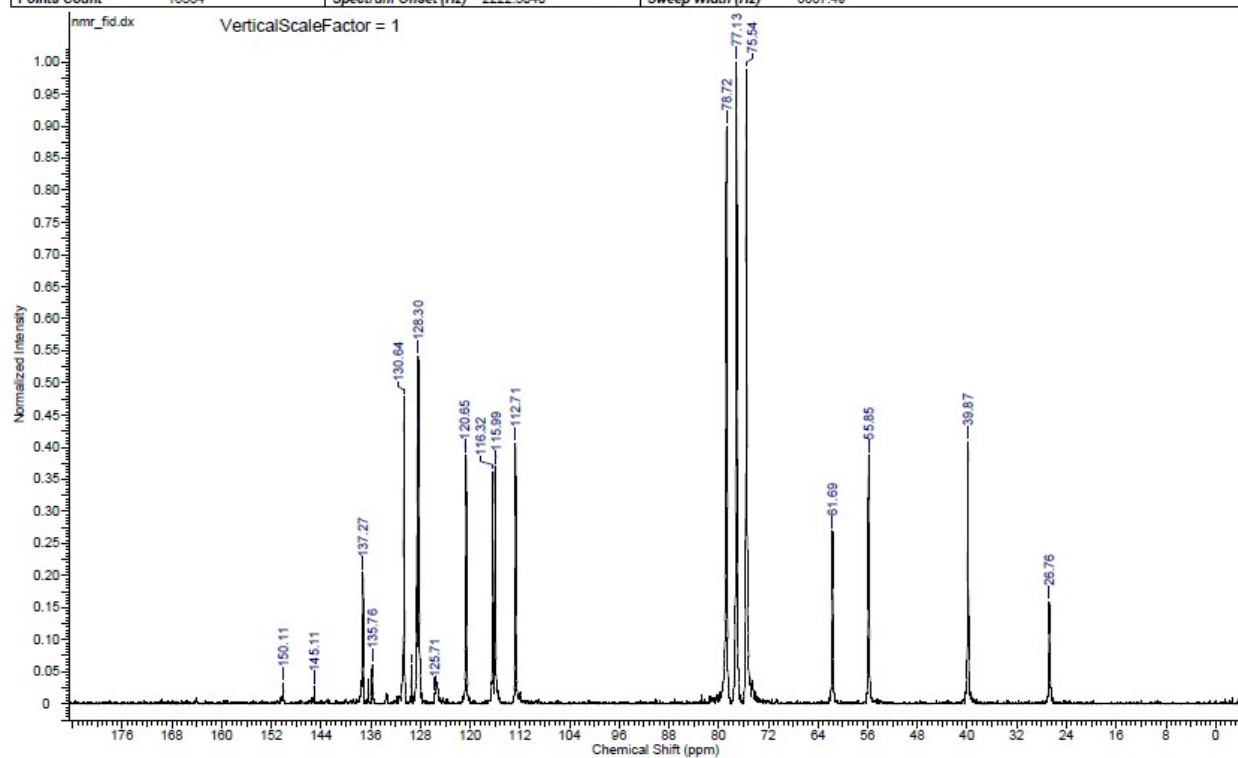
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Frequency (MHz)	20.20	Nucleus	13C	Origin	SPA3310 at Magritek
Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek		
Points Count	32768	Spectrum Offset (Hz)	2222.3179	Sweep Width (Hz)	6667.49



<sup>13</sup>C NMR spectrum of compound **15**

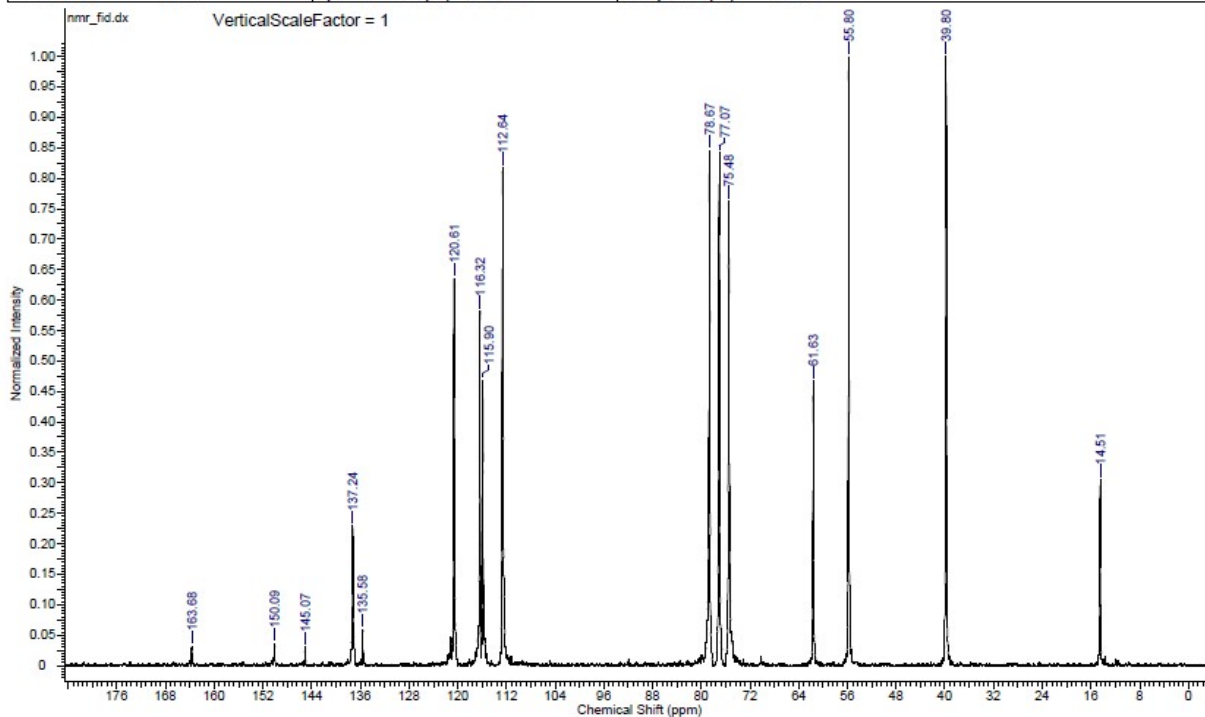


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Original Points Count	4096	Owner	Copyright (C) 2022 by Magritek		
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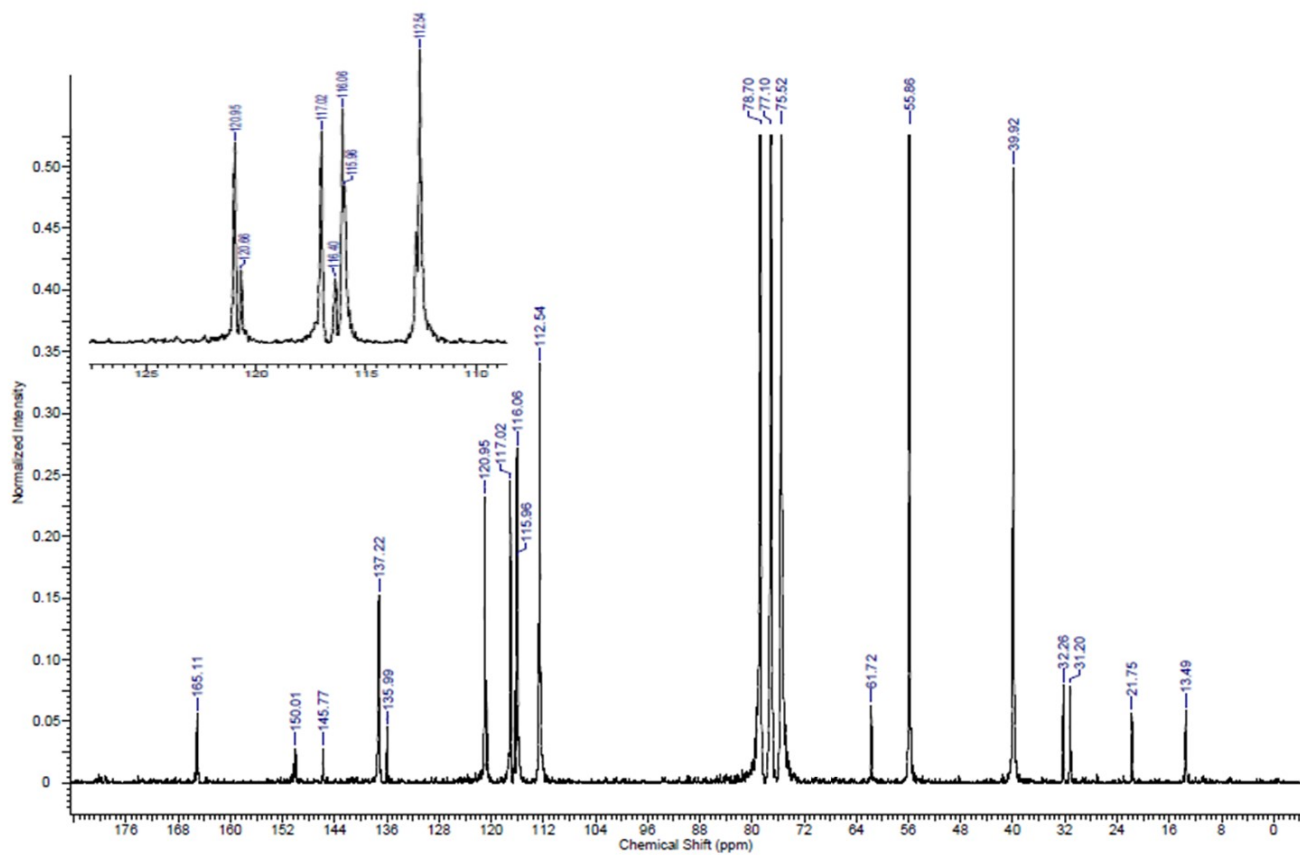


<sup>13</sup>C NMR spectrum of compound **16**

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Original Points Count	8192	Owner	Copyright (C) 2022 by Magritek		
Points Count	32768	Spectrum Offset (Hz)	2222.3030	Sweep Width (Hz)	6667.49



<sup>13</sup>C NMR spectrum of compound **17**



$^{13}\text{C}$  NMR spectrum of compound 19

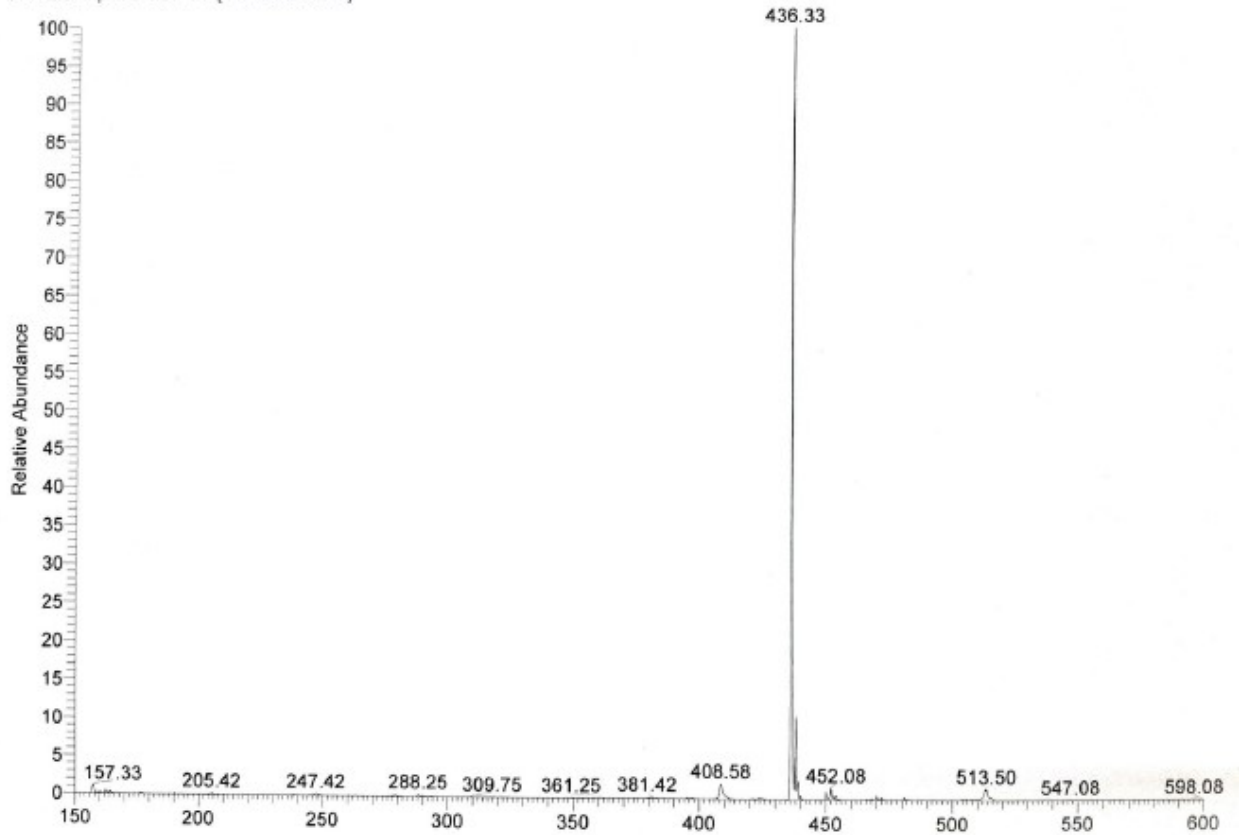
## Mass spectra of compounds 6-19

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LCF10605

9/20/2021 5:23:29 PM

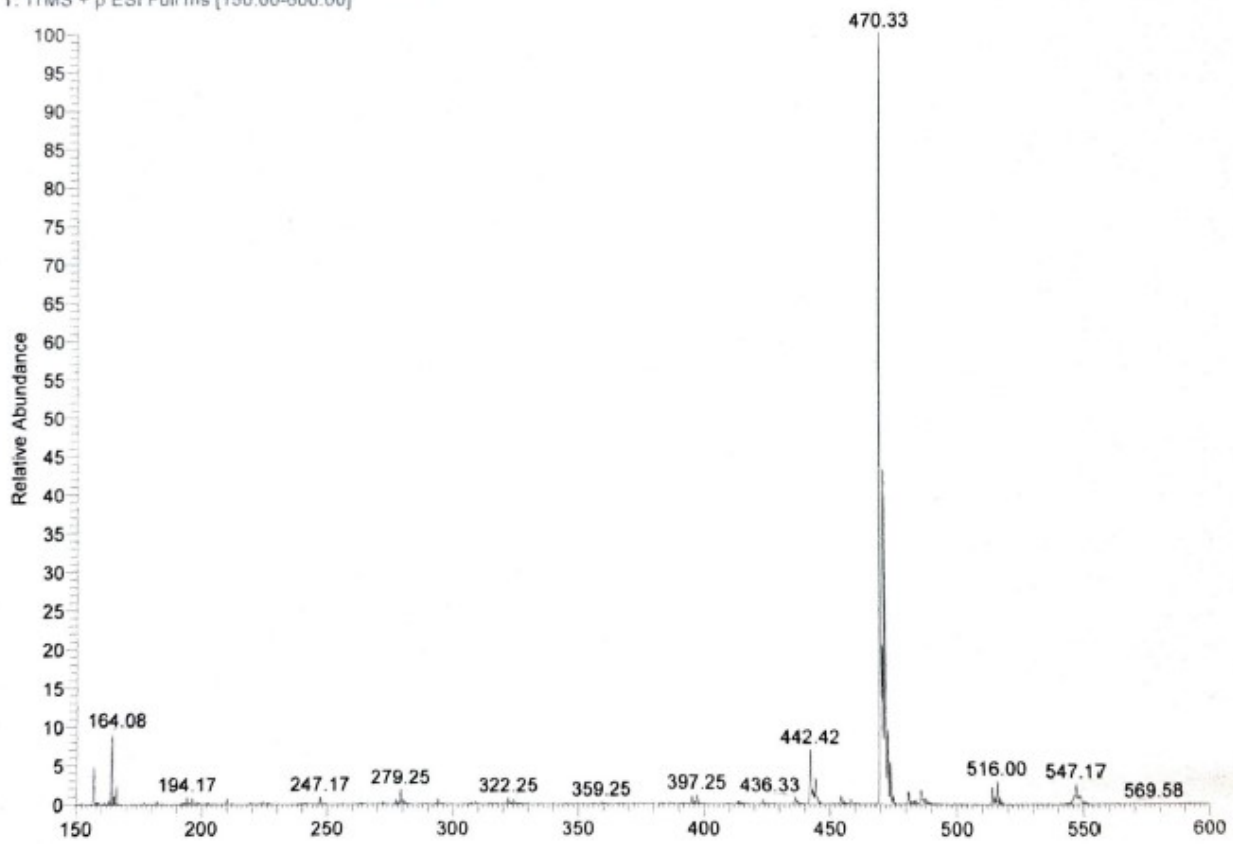
Eu-ox-tri-ph

Eu-Ox-Tri-Ph #1 RT: 0.00 AV: 1 NL: 1.39E3  
T: ITMS + p ESI Full ms [150.00-600.00]



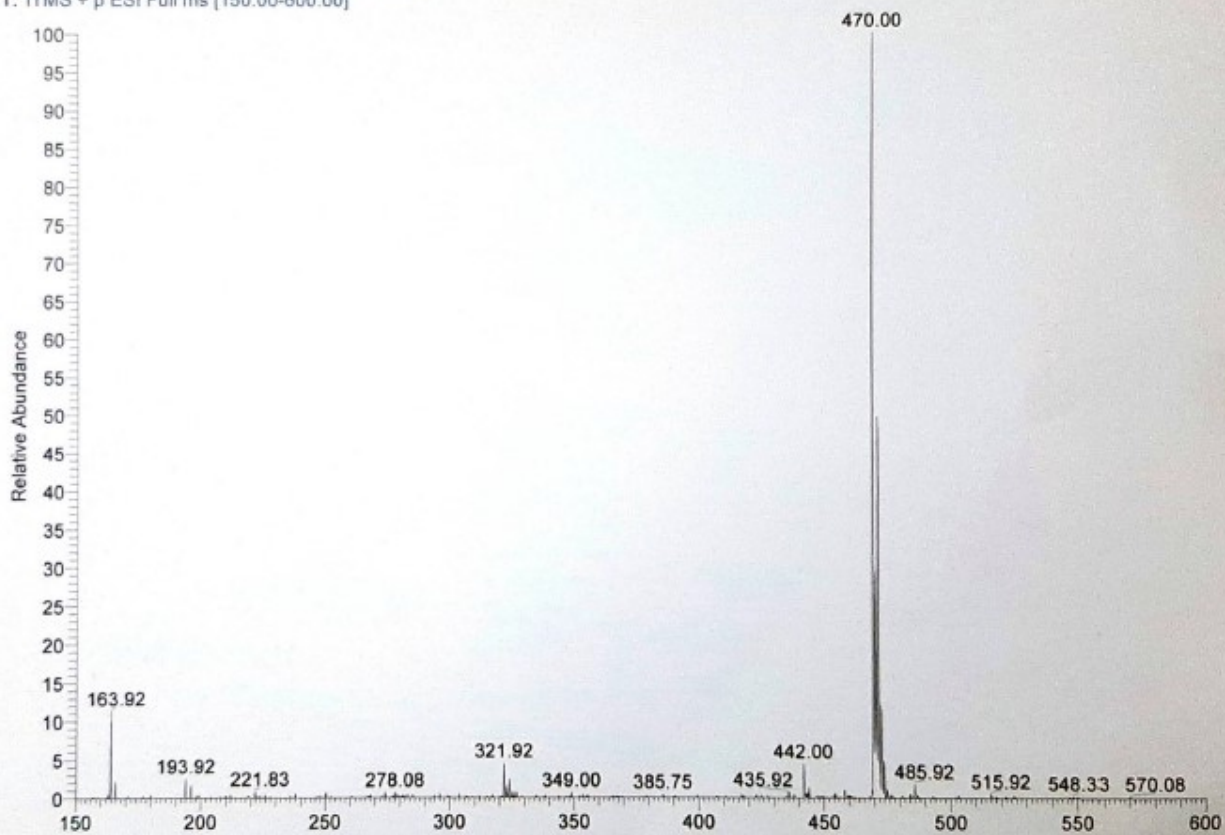
Compound 6

Eu-Ox-Tri-2-Cl#1 RT: 0.00 AV: 1 NL: 4.92E2  
T: ITMS + p ESI Full ms [150.00-600.00]



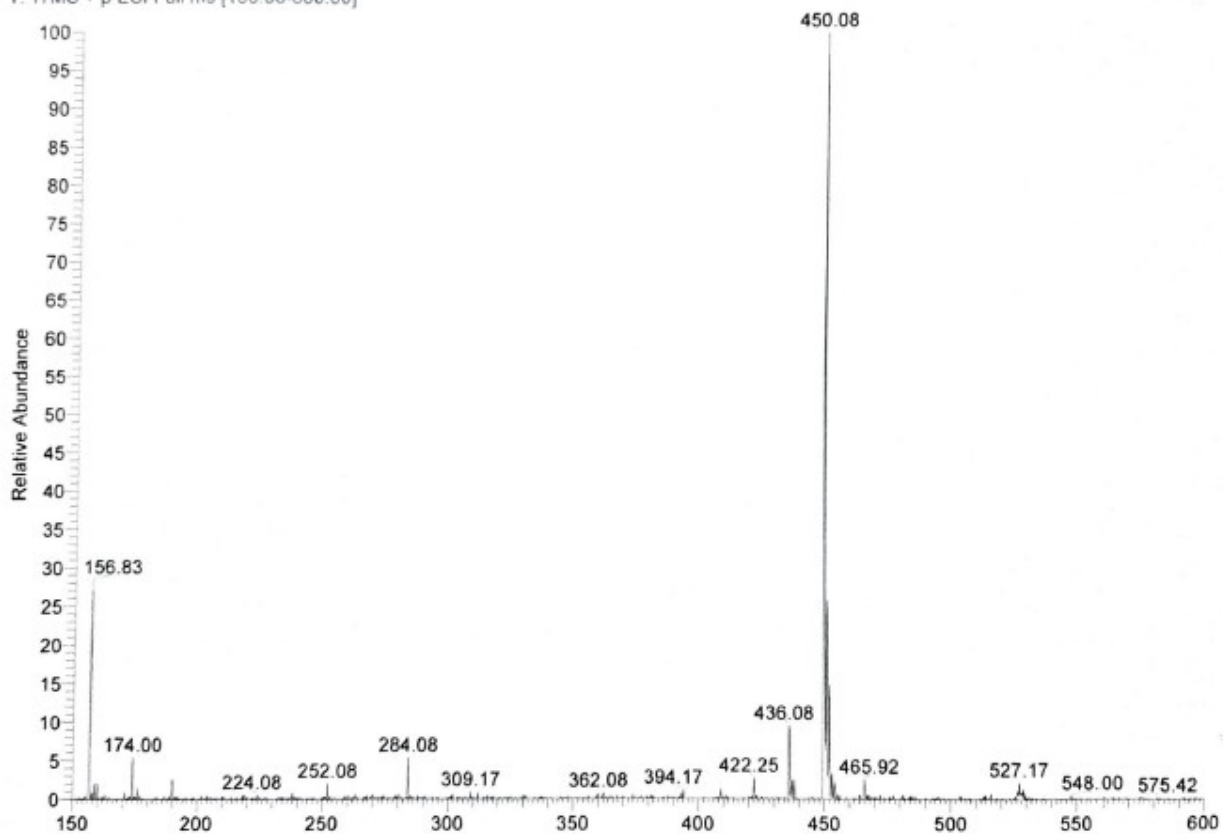
Compound 7

EU-OX-Tri-3-Cl #1 RT: 0.00 AV: 1 NL: 6.39E2  
T: ITMS + p ESI Full ms (150.00-600.00)



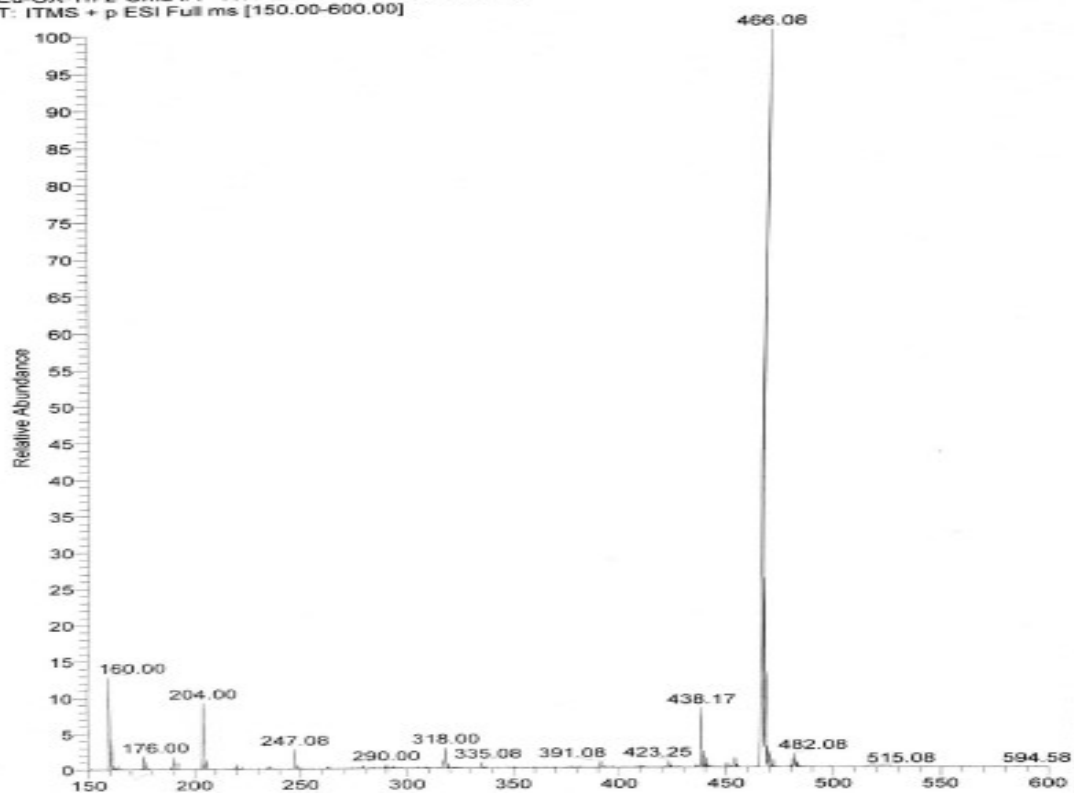
Compound 8

Eu-Ox-tri-2-Me #1 RT: 0.00 AV: 1 NL: 1.06E2  
T: ITMS + p ESI Full ms [150.00-600.00]



Compound 9

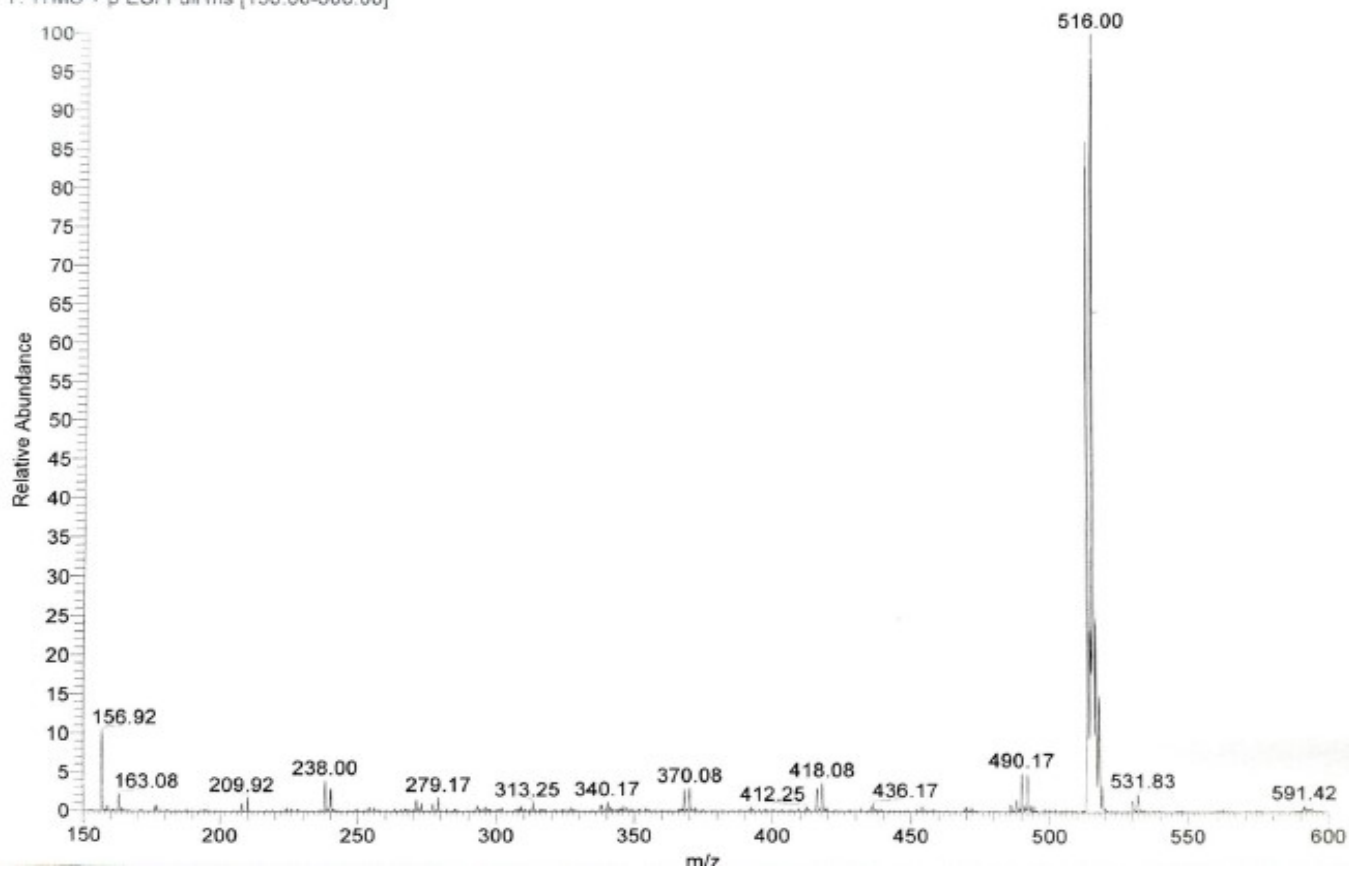
D:\Dr. Mahboob\...-OX-Tri-2-Ome LCP10623 12/9/2021 11:15:44 AM Eu-OX-Triazole-2-O-Me 464  
Eu-OX-Tri-2-Ome #1 RT: 0.00 AV: 1 NL: 2.67E3  
T: ITMS + p ESI Full ms [150.00-600.00]



Compound 10



Eu-Ox-Tri-3Br 350 #1 RT: 0.00 AV: 1 NL: 1.16E2  
T: ITMS + p ESI Full ms [150.00-600.00]



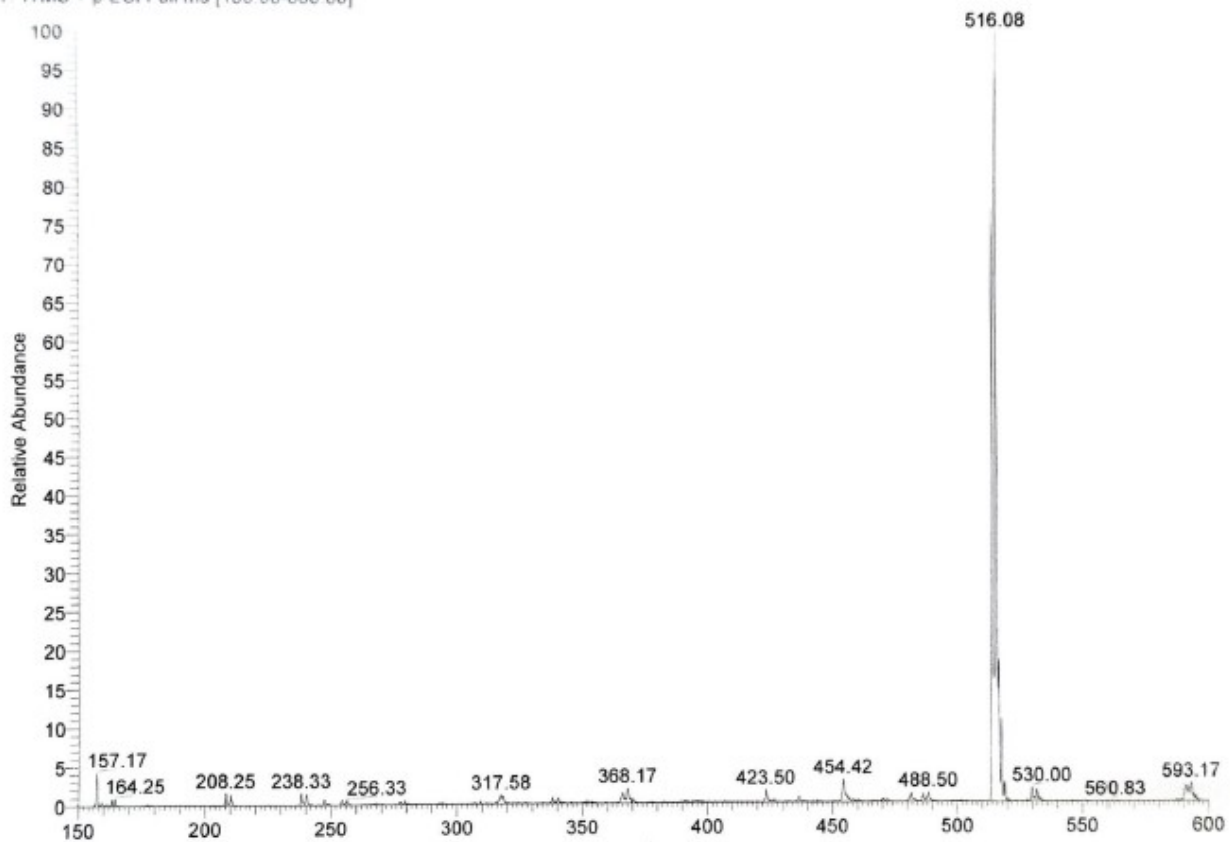
Compound 11

D:\Dr Mahboob\ 1Eu-OX-Tri-4-Br  
LCF10605

9/20/2021 5:00:42 PM

Eu-ox-tri-4-Br

Eu-OX-Tri-4-Br #1 RT: 0.00 AV: 1 NL: 6.11E2  
T: ITMS + p ESI Full ms [150.00-600.00]



Compound 12

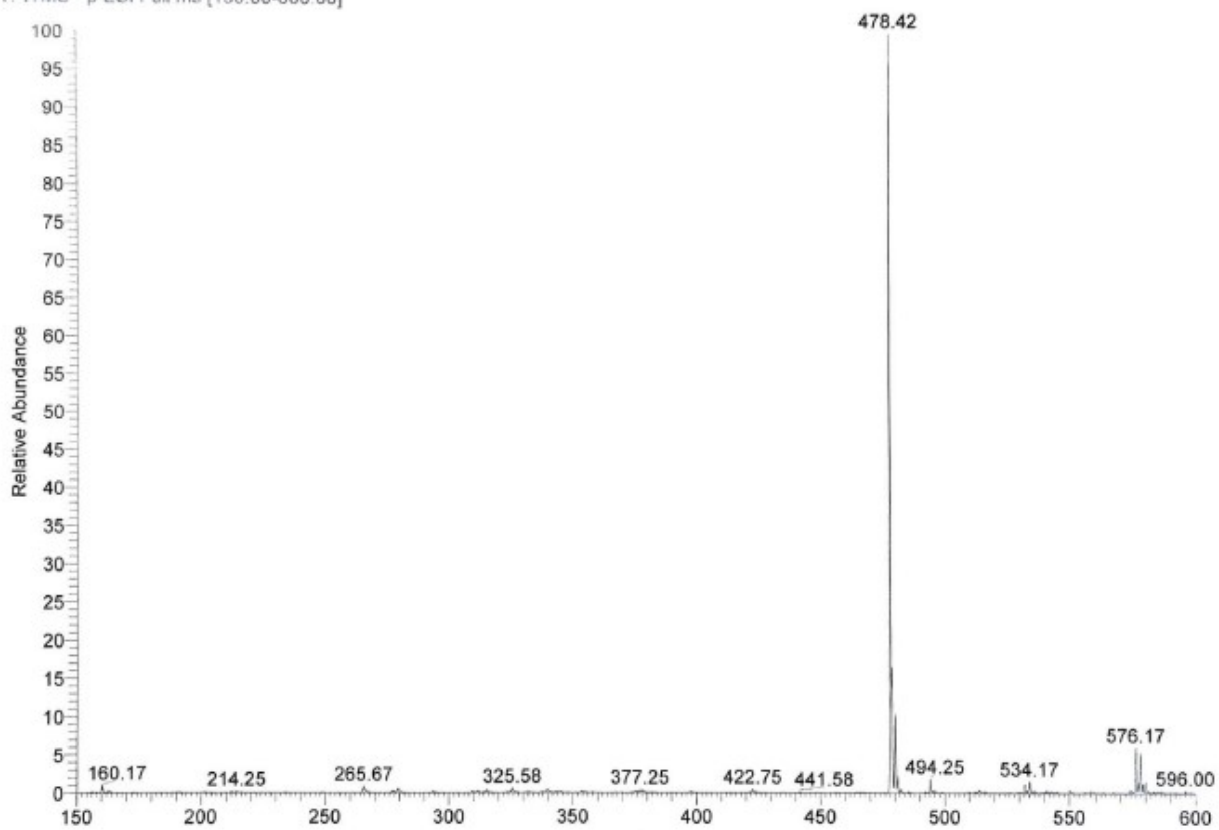
D:\Dr Mahboob\1Eu-OX-3-COOH  
LCF10805

9/20/2021 5:38:35 PM

Eu-ox-tri-Ph-3-COOH

Eu-OX-3-COOH #1 RT: 0.00 AV: 1 NL: 7.99E2

T: ITMS - p ESI Full ms [150.00-600.00]



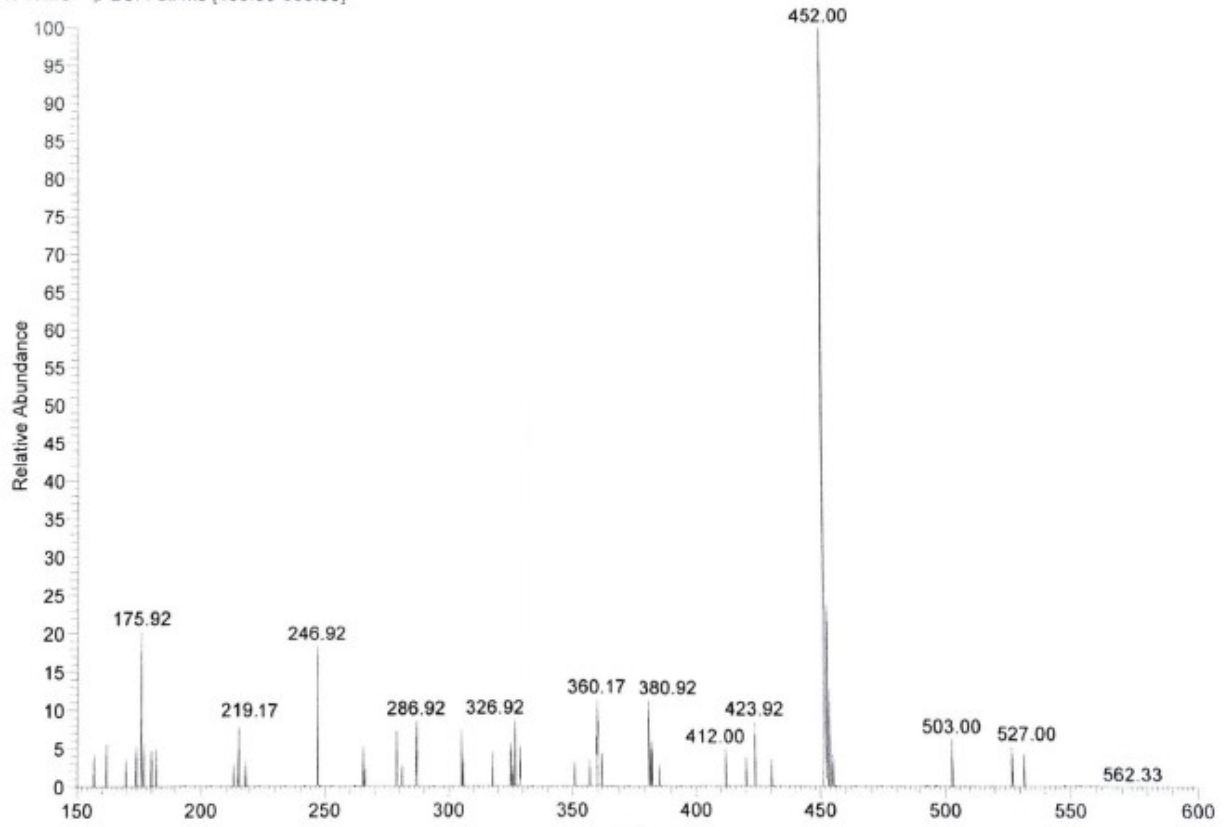
Compound 13

D:\Dr Mahboob\ Eu-OX-Tri-4-OH  
LCF10605

12/9/2021 11:38:51 AM

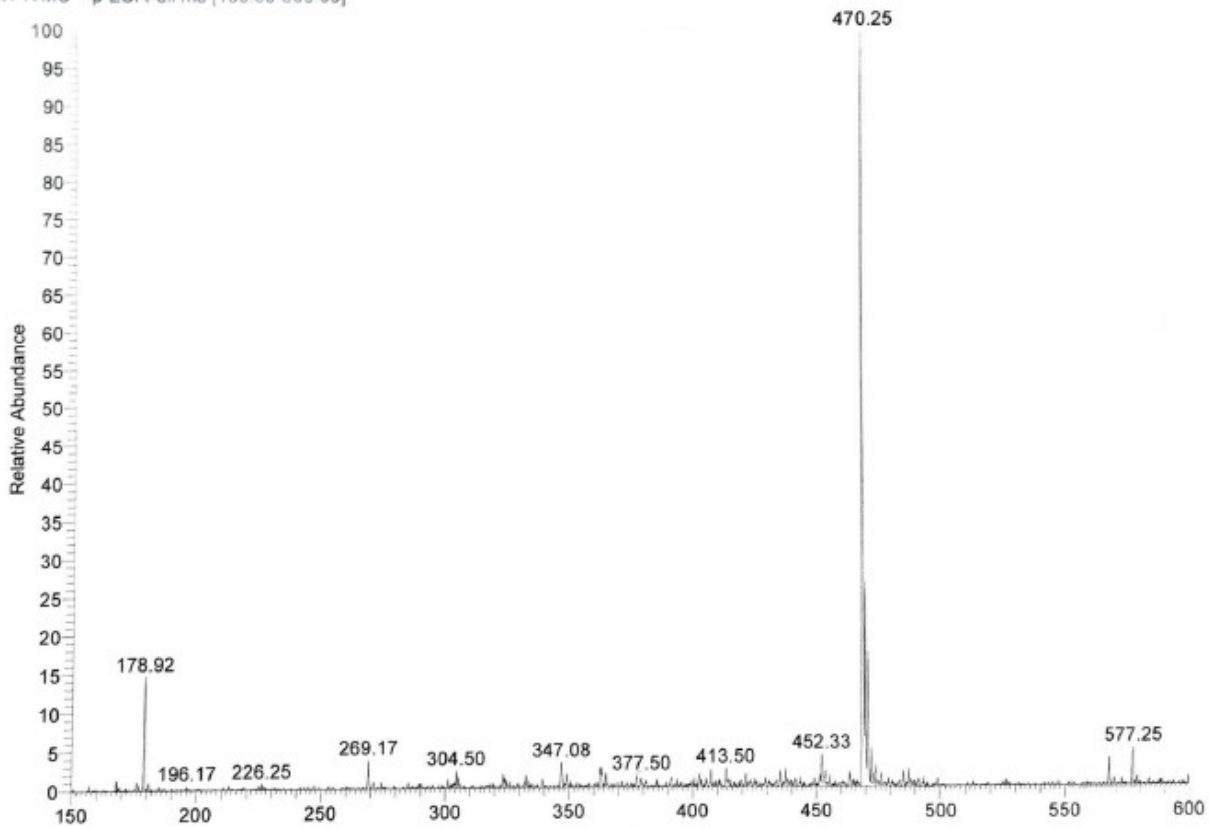
Eu-OX-Triazole-4-OH

Eu-OX-Tri-4-OH #1 RT: 0.00 AV: 1 NL: 3.78E1  
T: ITMS + p ESI Full ms [150.00-600.00]



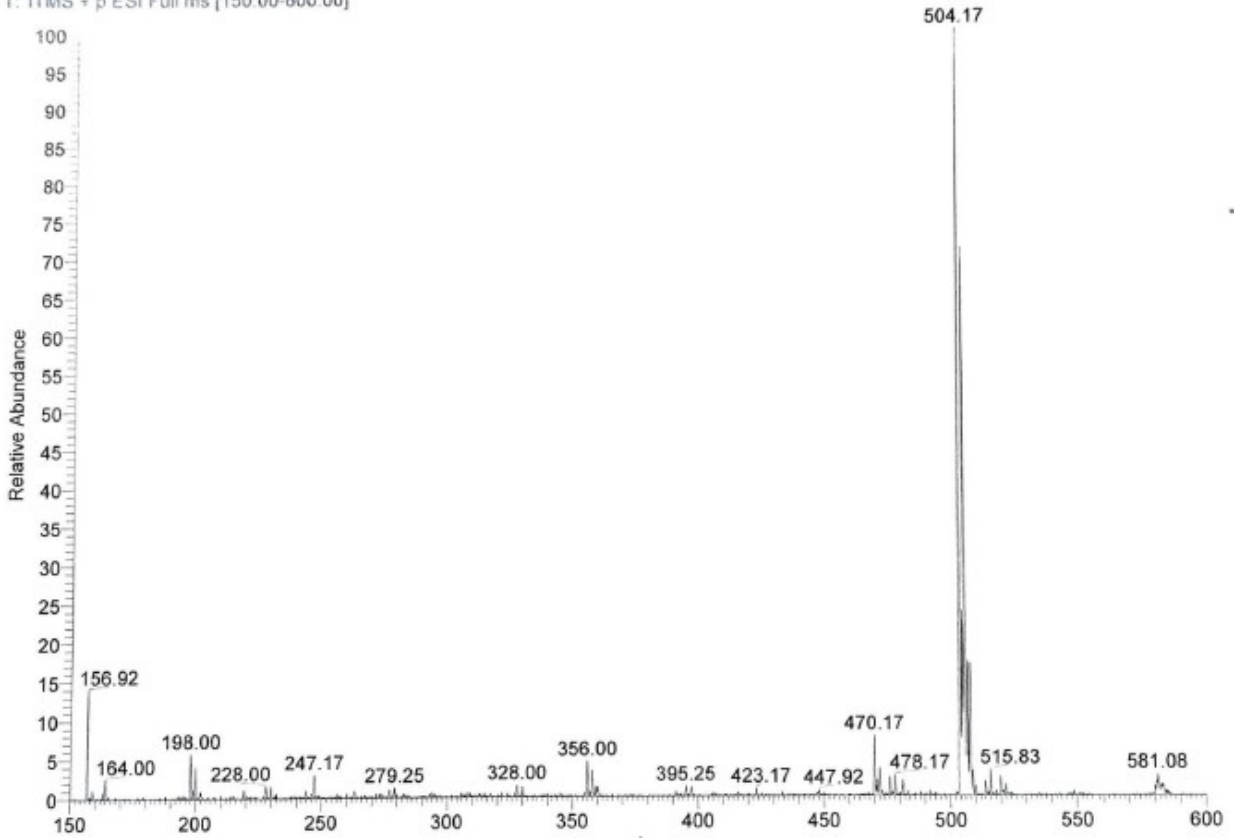
Compound 14

Eu-OX-Tri-2,4-Di-F, #1 RT: 0.00 AV: 1 NL: 9.42E2  
T: ITMS + p ESI Full ms [150.00-600.00]



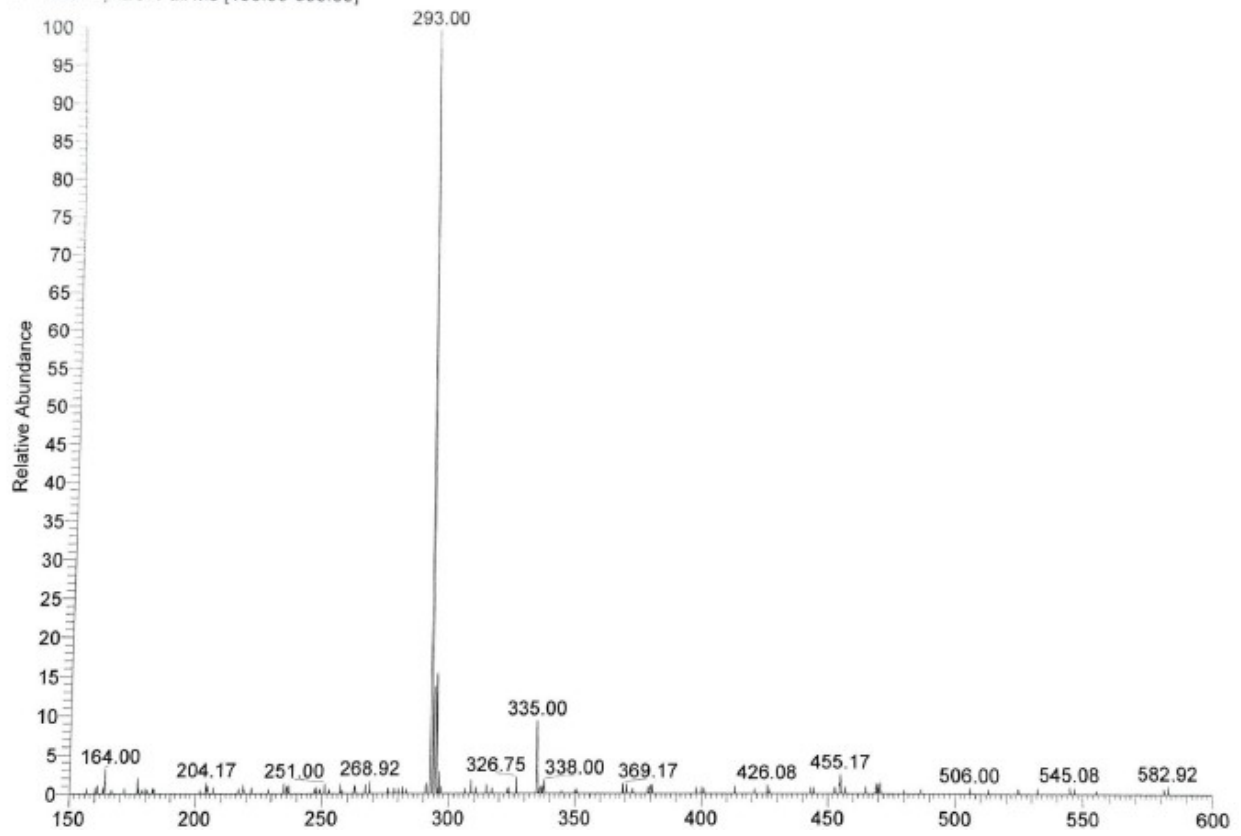
Compound 15

Eu-OX-Tri-2,4-di-Cl#1 RT: 0.00 AV: 1 NL: 1.85E2  
T: ITMS + p ESI Full ms [150.00-600.00]



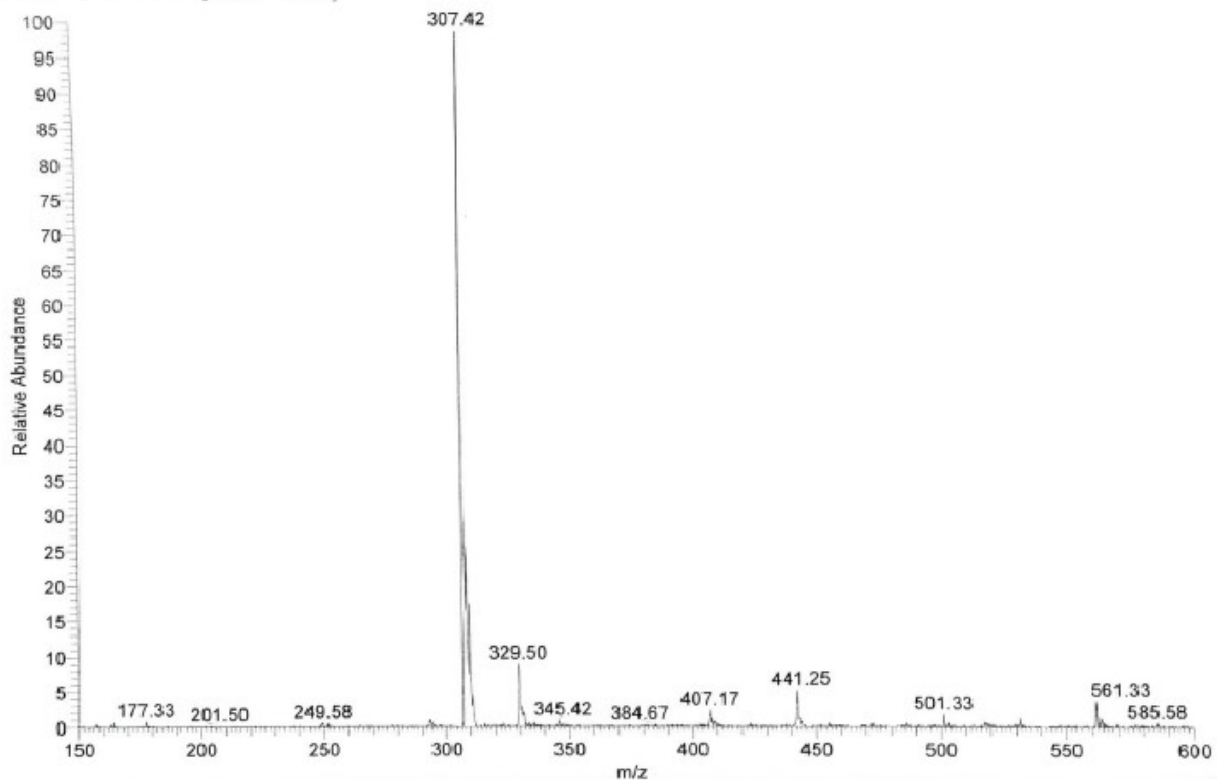
Compound 16

Eu-OX-S-Me' #1 RT: 0.00 AV: 1 NL: 2.16E2  
T: ITMS + p ESI Full ms [150.00-600.00]



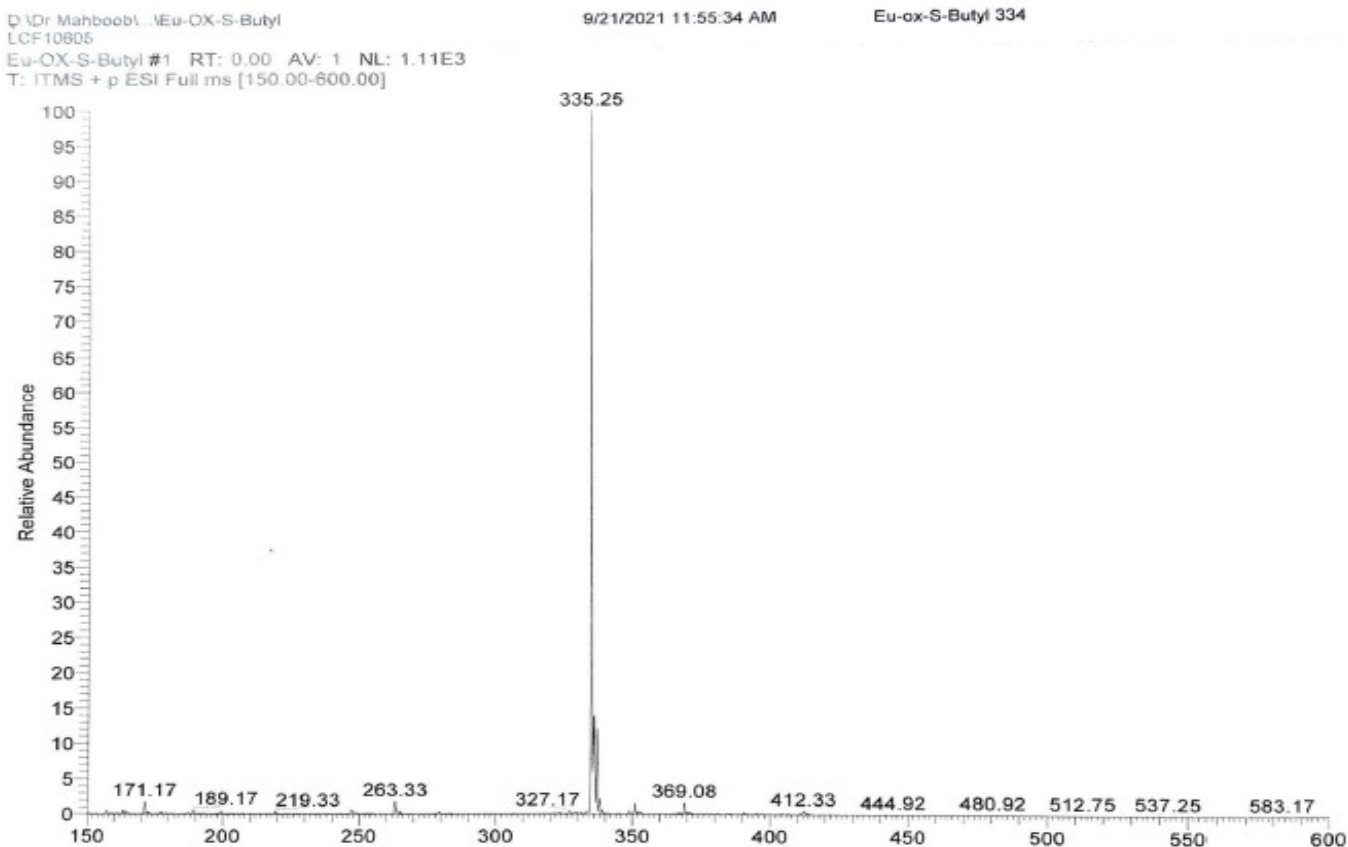
Compound 17

Eu-OX-S-Ethyl #1 RT: 0.00 AV: 1 NL: 1.60E3  
T: ITMS + p ESI Full ms [150.00-600.00]



Compound 18





**Compound 19**

## Experimental

### Ligand preparation:

The DFT Calculations have been performed foremostly using the Jaguar<sup>[1]</sup>. DFT simulations have been utilized for geometrical optimizations of studied structures, employing the B3LYP/ 6-311G\*\*(d,p) exchange-correlation functional<sup>[2]</sup>with TD-DFT measurements used for the simulations frontier molecular orbital and molecular electrostatic maps.

### Protein formulation and active site prediction:

<sup>1</sup>Schrödinger Maestro | Schrödinger. *Schrödinger Release 2018-1* 2018.

<sup>2</sup>Ha, N. Van; Dat, D.T.; Nguyet, T.T. Stereoelectronic Properties of 1,2,4-Triazole-Derived N-heterocyclic Carbenes - A Theoretical Study. *VNU J. Sci. Nat. Sci. Technol.* **2019**, *35*, doi:10.25073/2588-1140/vnunst.4935.

3D crystal structure of TM protein was obtained from the Protein Data Bank. Charges with bond orders were assigned, H atoms were added to heavy atoms. Then, selenomethionines and selenocysteines transferred to methionines and cysteines. All water molecules were removed. The OPLS force field used for protein minimization to set a maximum heavy atom 0.30 Å RMSD. The binding pockets of protein have been identified using the CASTp package. That applies the modern algorithmic and geometrical analysis for analyzing and validation the binding pockets.

### **Receptor Grid Generation and Molecular Docking**

The Glide software<sup>3</sup> was utilized for generation of Receptor grid and Docking simulation process. The created grid was parameterized using default software parameter( 1.00 van der Waals, 0.25 cut-off of charge), and submitted to OPLS force field. Then produced and centroid the definite cubic box(12 Å × 12 Å × 12 Å) into active site. This box was used for docking study which were carried out using extra precision and write XP descriptor information. This generates favourable ligand poses which are further screened through filters to examine spatial fit of the ligand in the active site. Ligand poses which pass through initial screening are subjected to evaluation and minimization of grid approximation”. Scoring was then carried on energy minimized poses to generate Glide score

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<sup>3</sup>Murphy, R.B.; Repasky, M.P.; Greenwood, J.R.; Tubert-Brohman, I.; Jerome, S.; Annabhimoju, R.; Boyles, N.A.; Schmitz, C.D.; Abel, R.; Farid, R.; et al. WScore: A Flexible and Accurate Treatment of Explicit Water Molecules in Ligand-Receptor Docking. *J. Med. Chem.* **2016**, doi:10.1021/acs.jmedchem.6b00131.