

## **Manipulating Estrogenic/Anti-Estrogenic Activity Of Triphenylethylenes Towards Development Of Novel Anti-Neoplastic SERMs**

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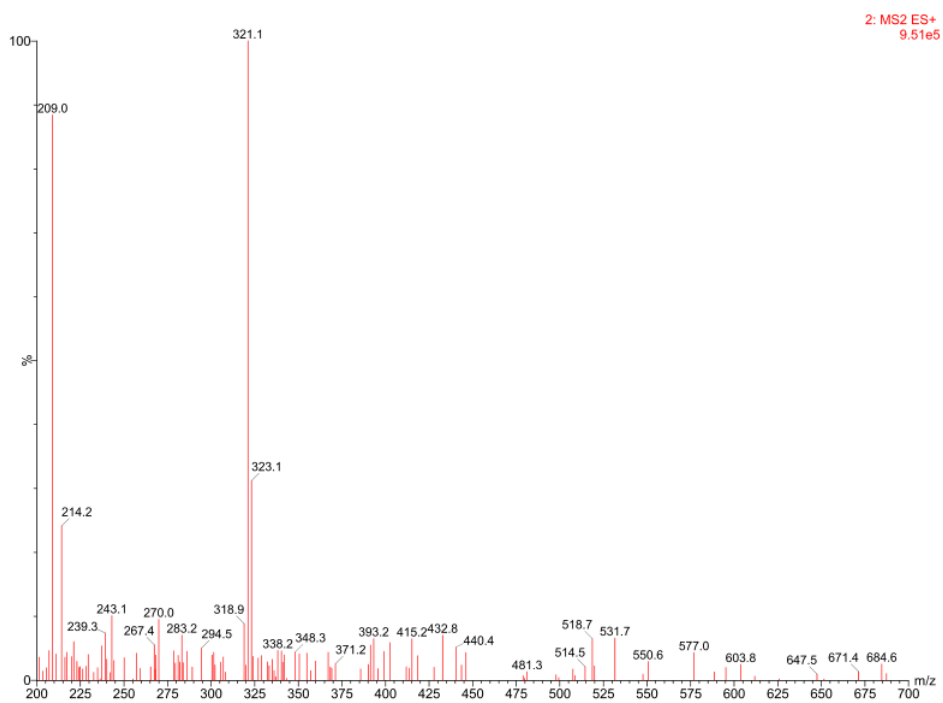
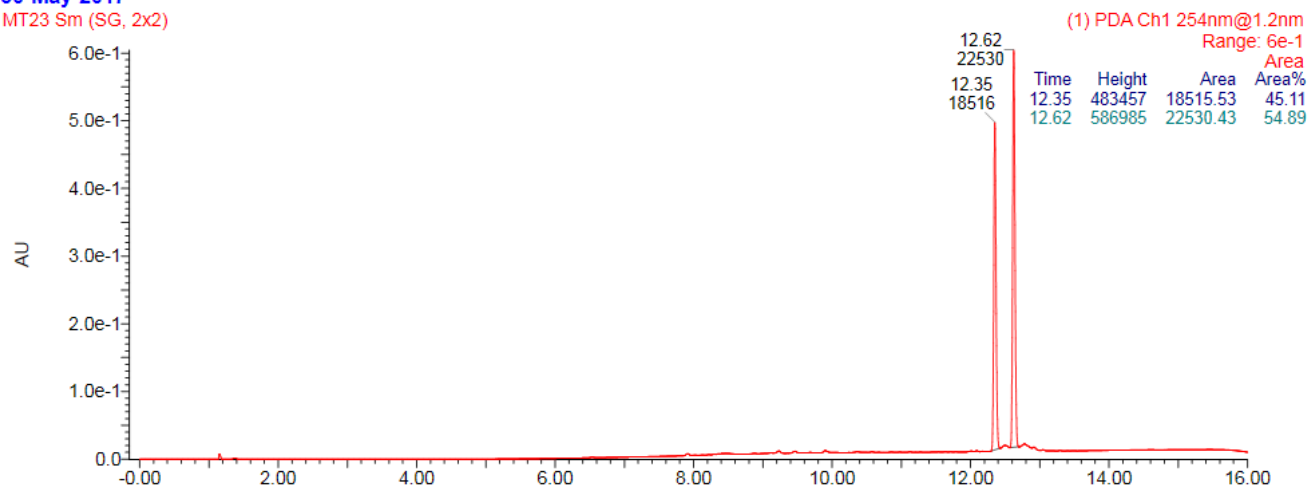
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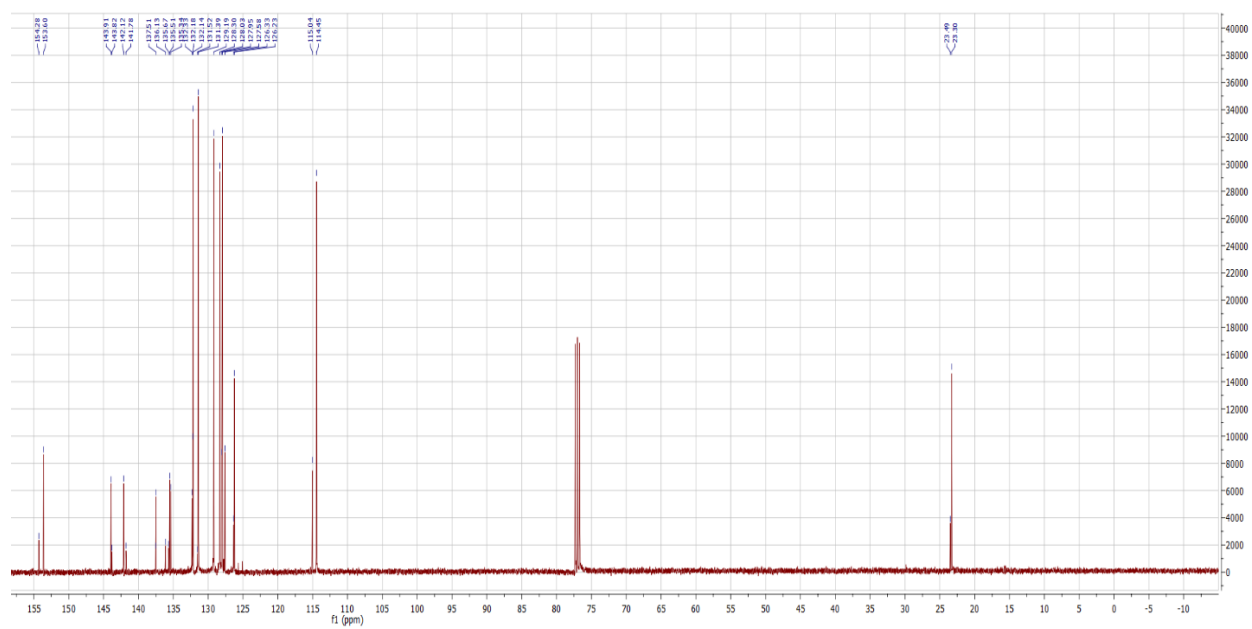
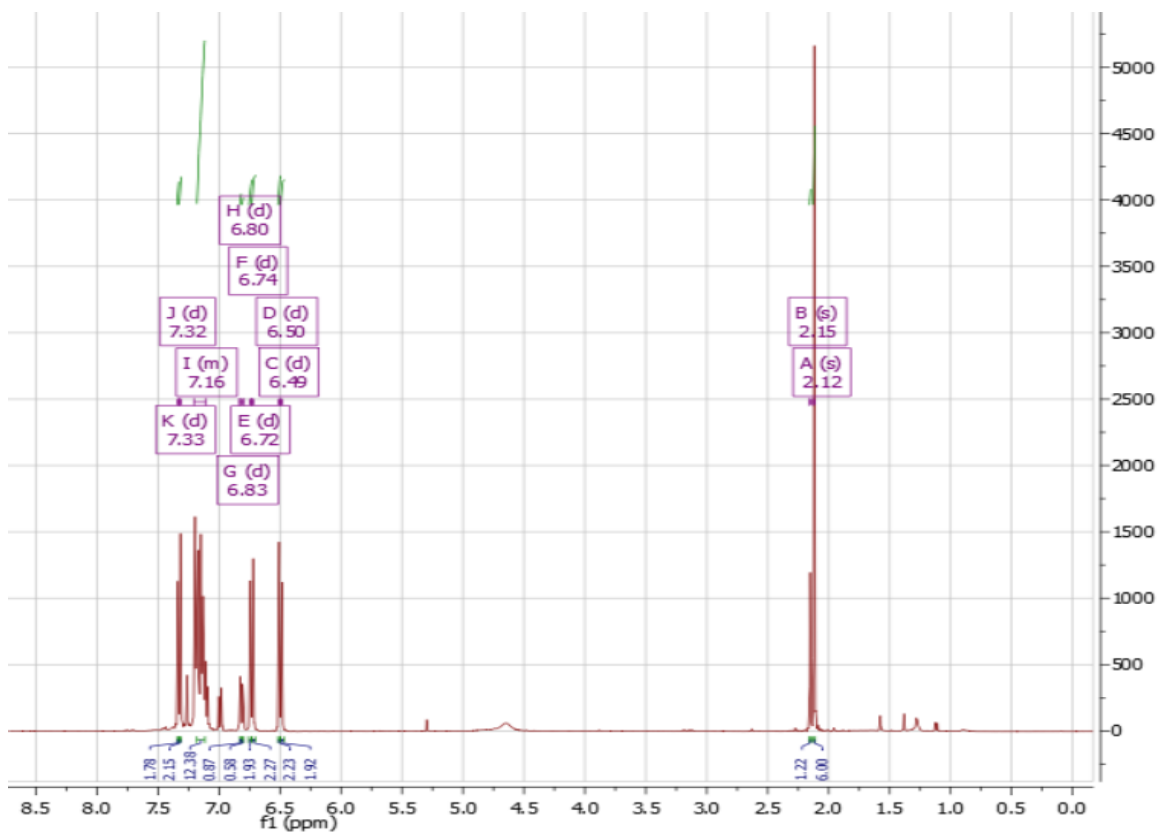
1. Compounds characterization  
LC-MS /  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR

*E/Z*-4-[1-(4-Chloro-phenyl)-2-phenylpropenyl]-phenol (1)

30-May-2017

MT23 Sm (SG, 2x2)

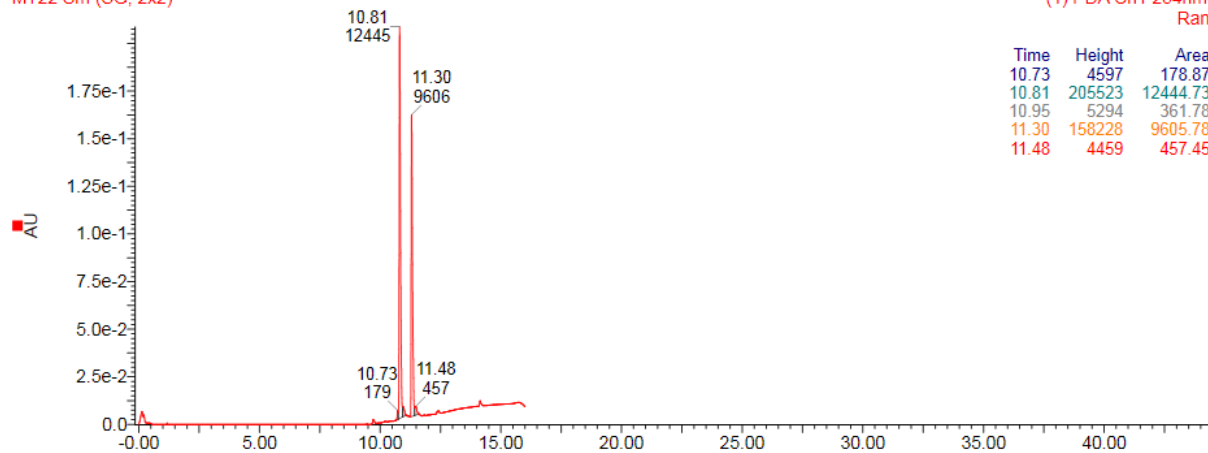




*E/Z*-4-[1-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-propenyl]-phenol (2)

04-Mar-2017

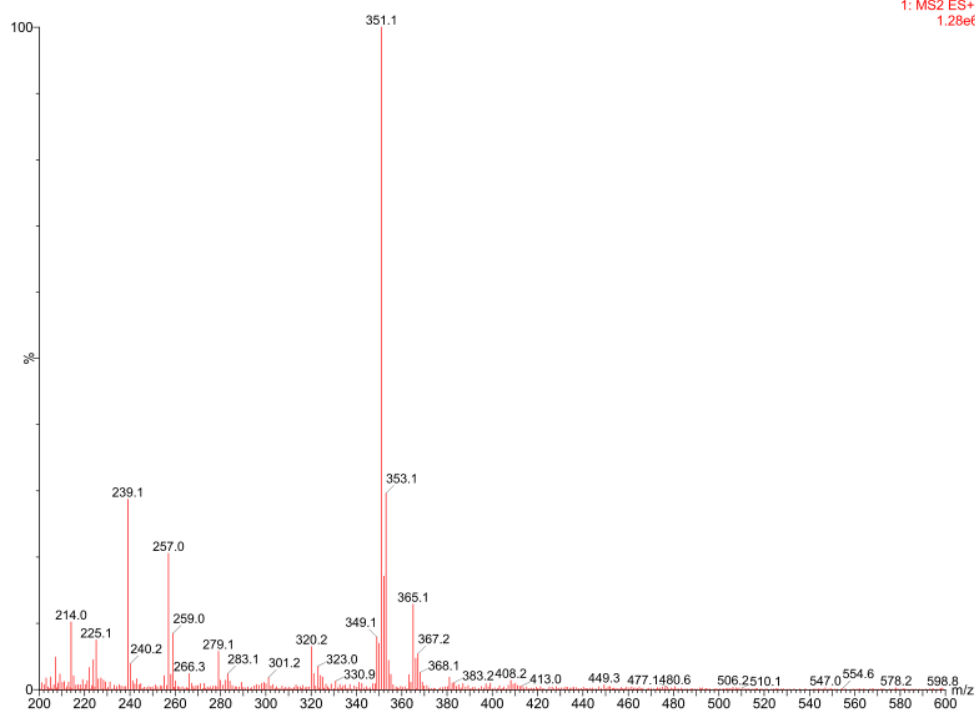
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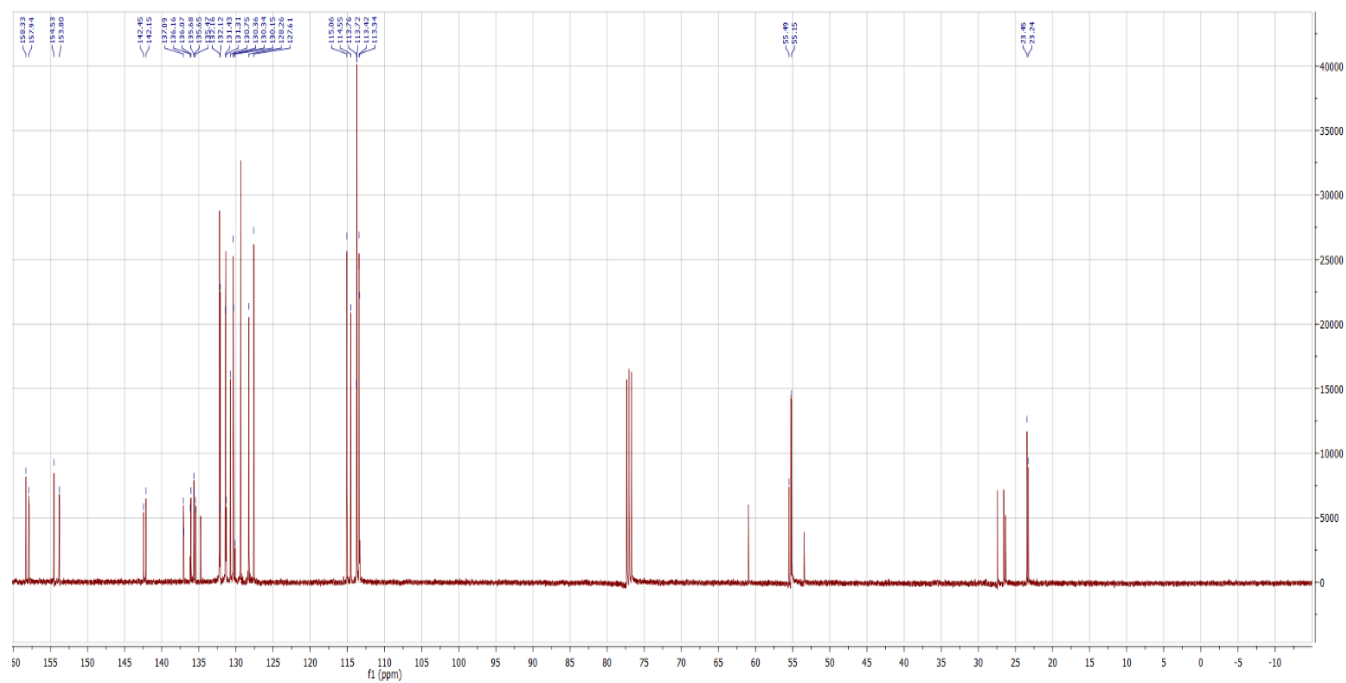
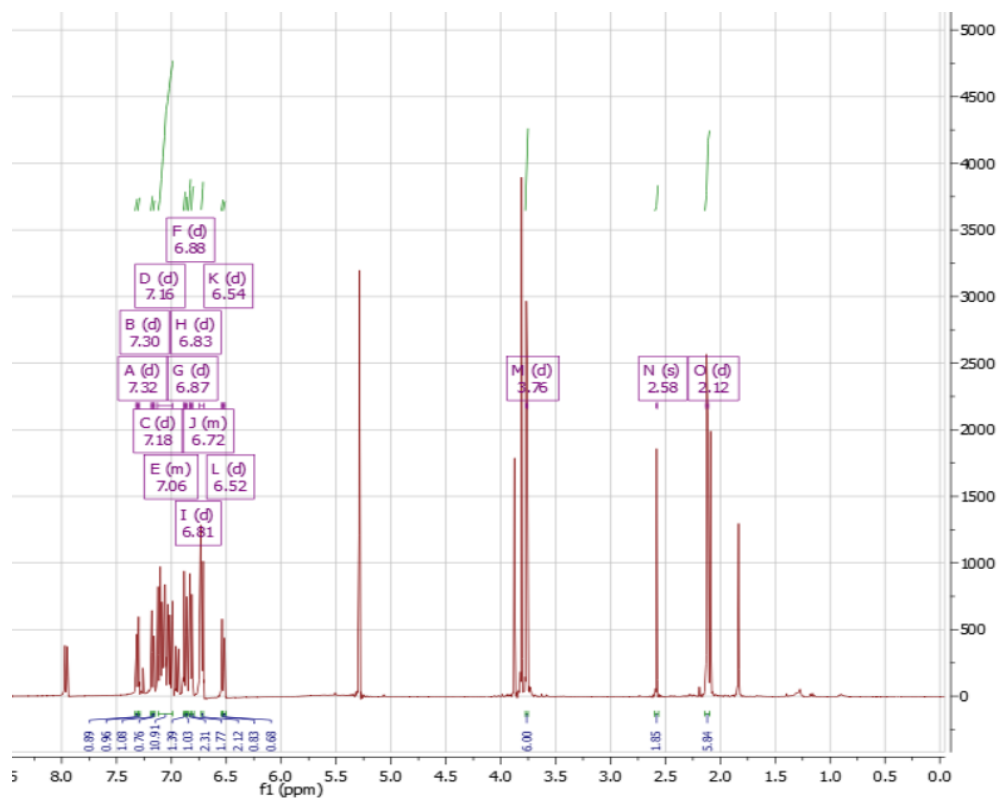
(1) PDA Ch1 254nm@1.2nm

Range: 2e-1

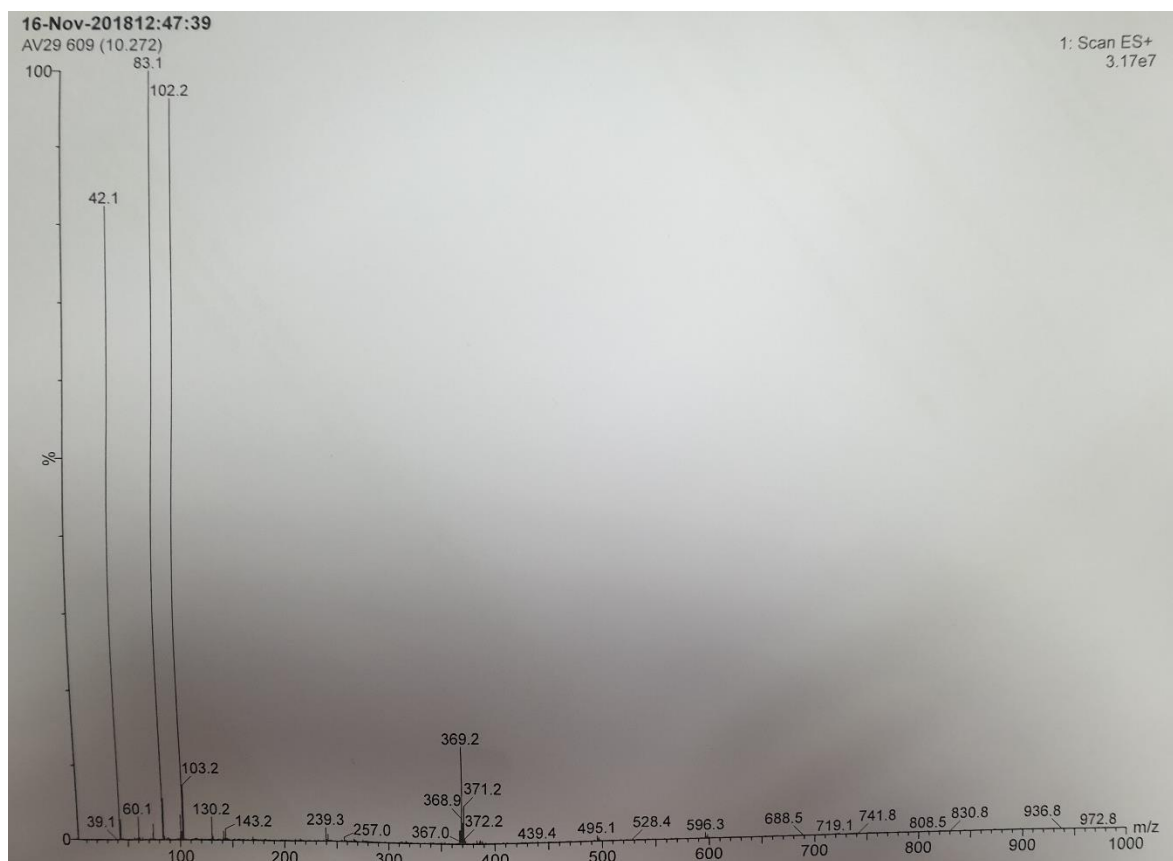
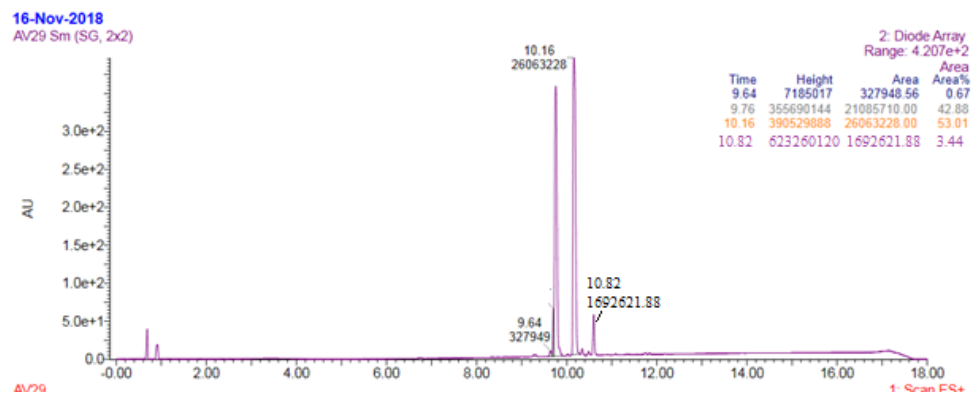
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10.81	205523	12444.73	53.99
10.95	5294	361.78	1.57
11.30	158228	9605.78	41.68
11.48	4459	457.45	1.98

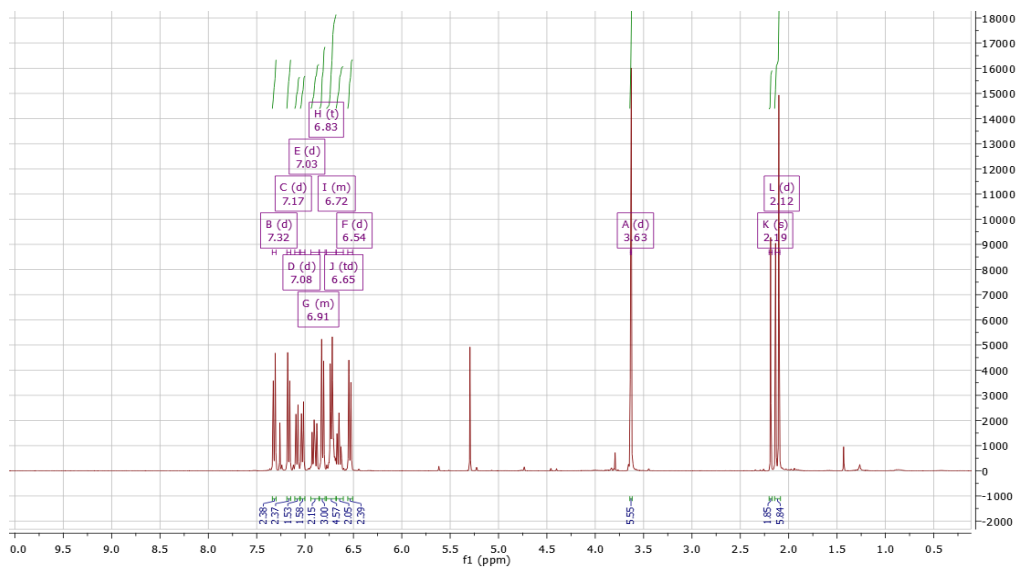
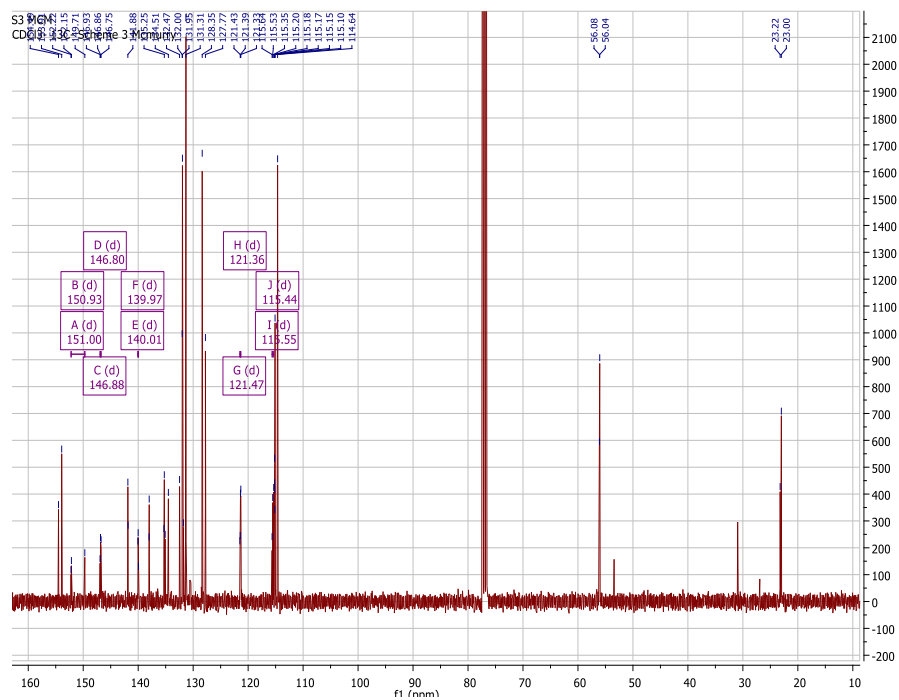


1: MS2 ES+  
1.28e6



***E/Z*-4-[1-(4-Chlorophenyl)-2-(4-fluoro-3-methoxyphenyl) propenyl]-phenol (4)**



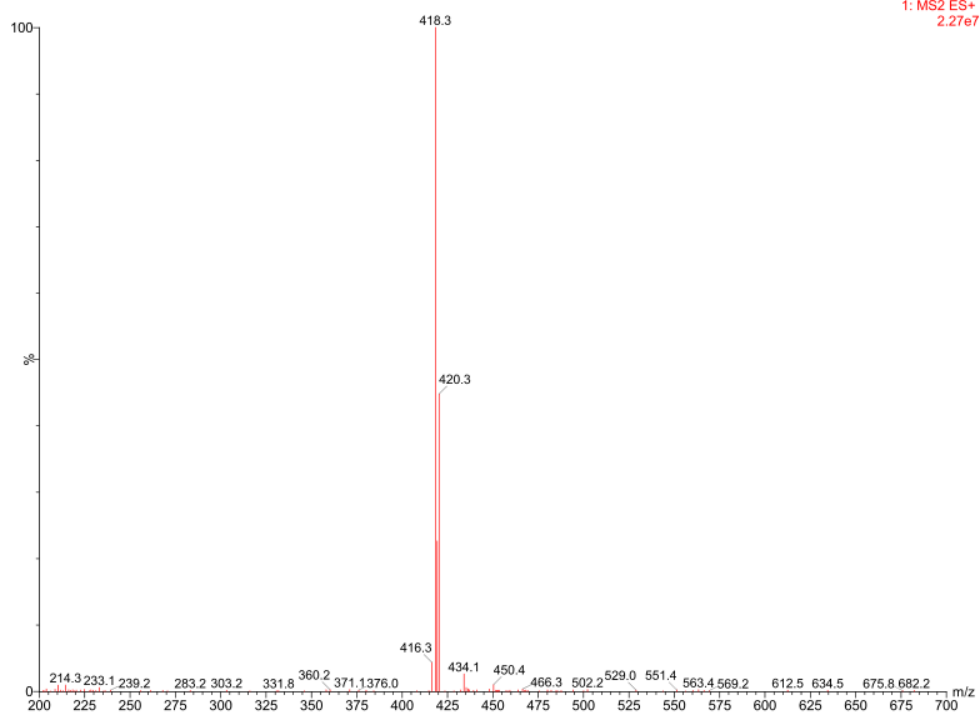
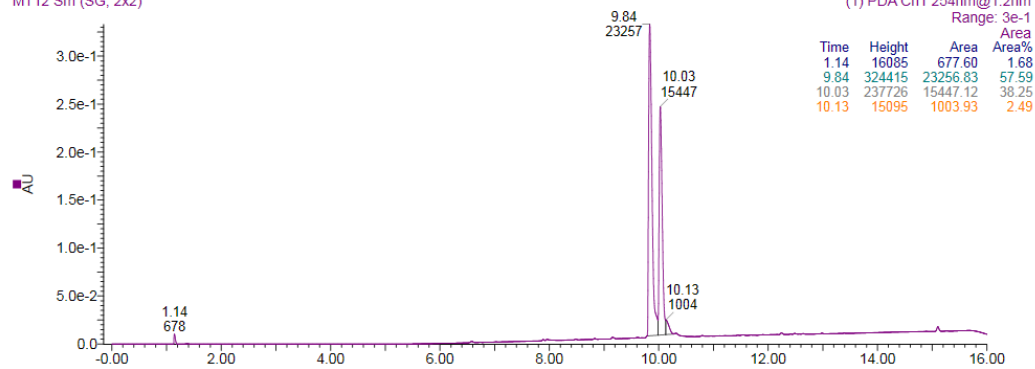


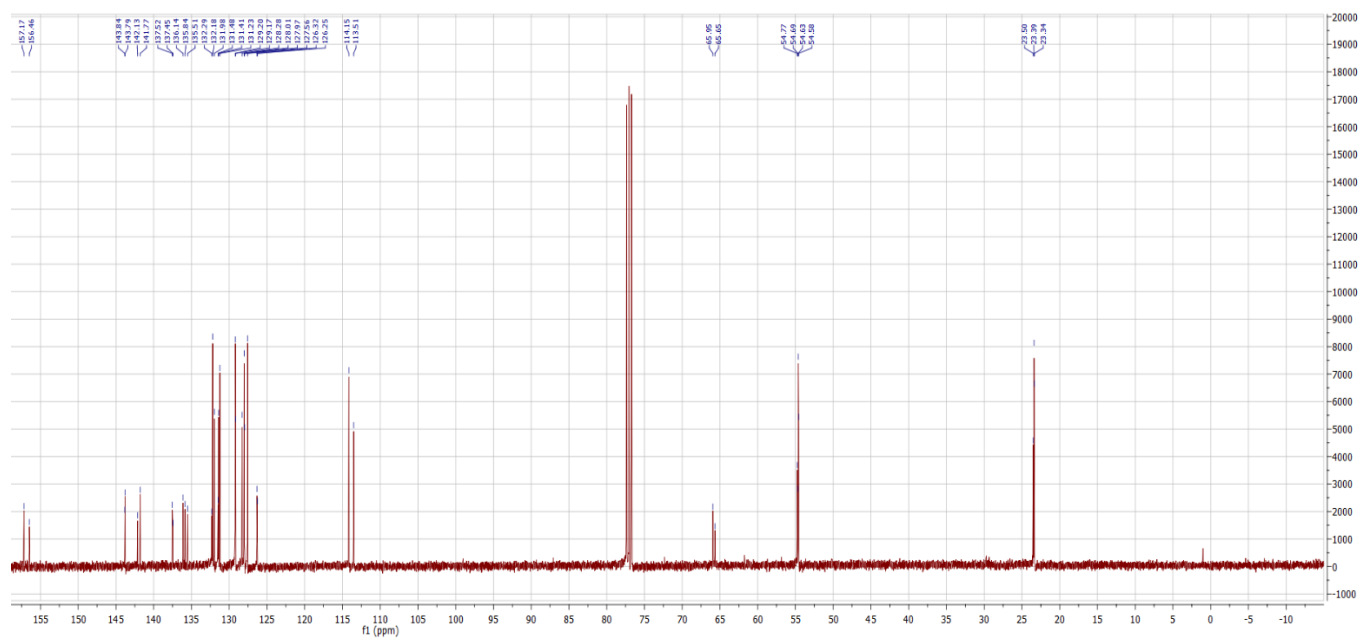
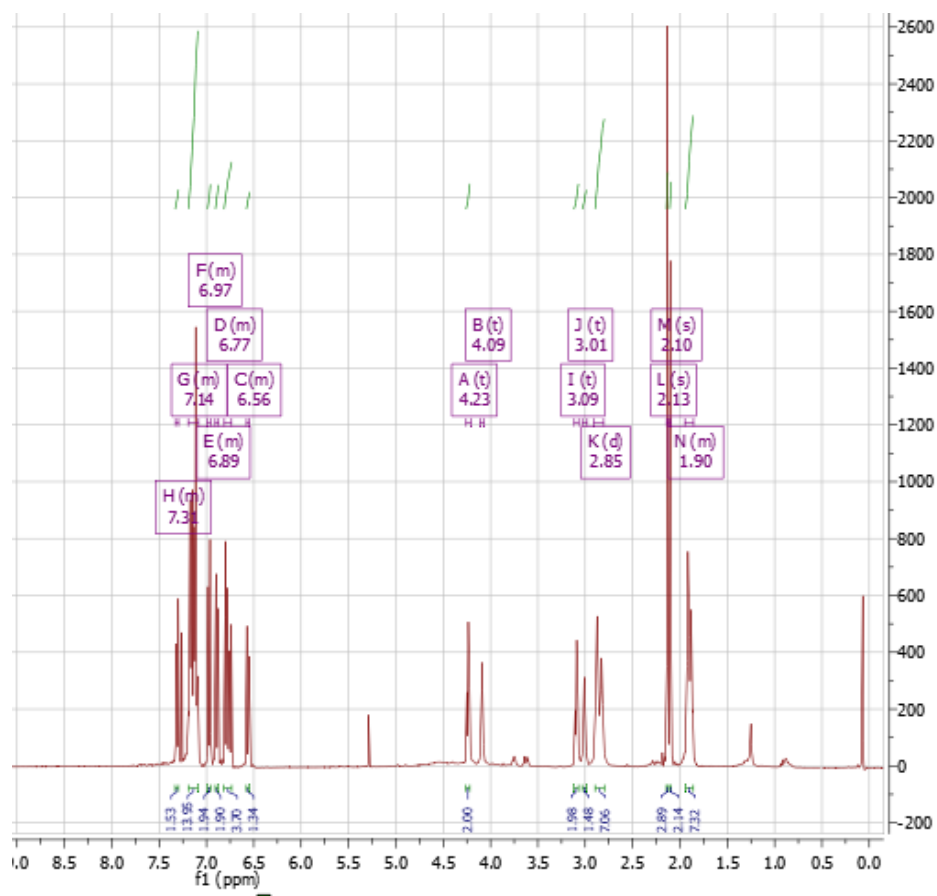
*E/Z*-1-(2-{4-[1-(4-Chloro-phenyl)-2-phenyl-propenyl]-phenoxy}-ethyl)-pyrrolidine (6).



21-Jun-2017

MT12 Sm (SG, 2x2)

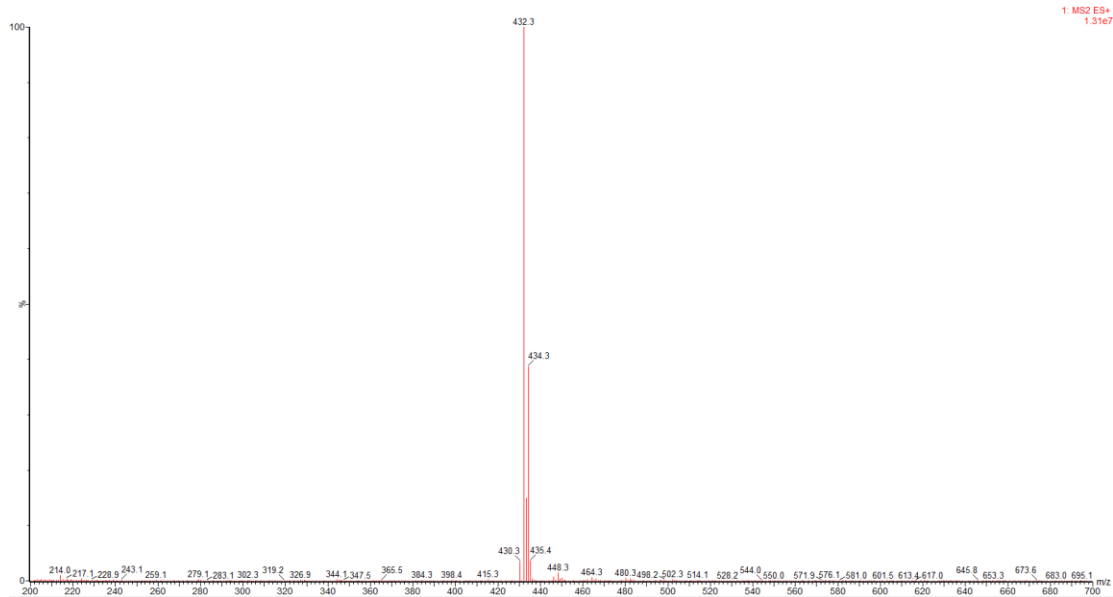
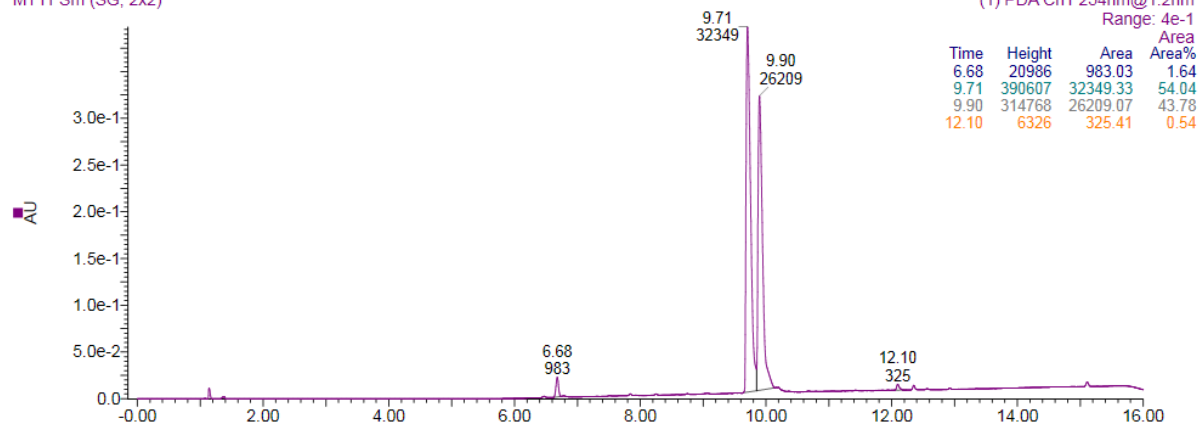


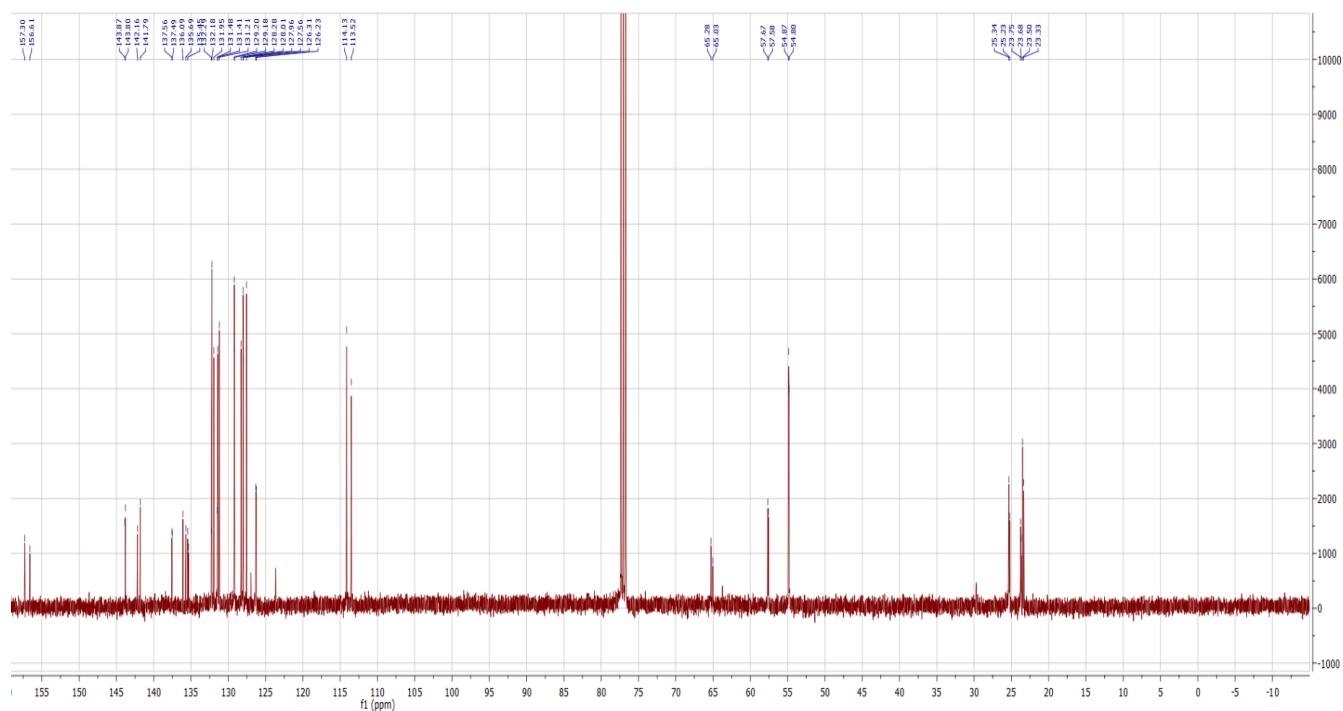
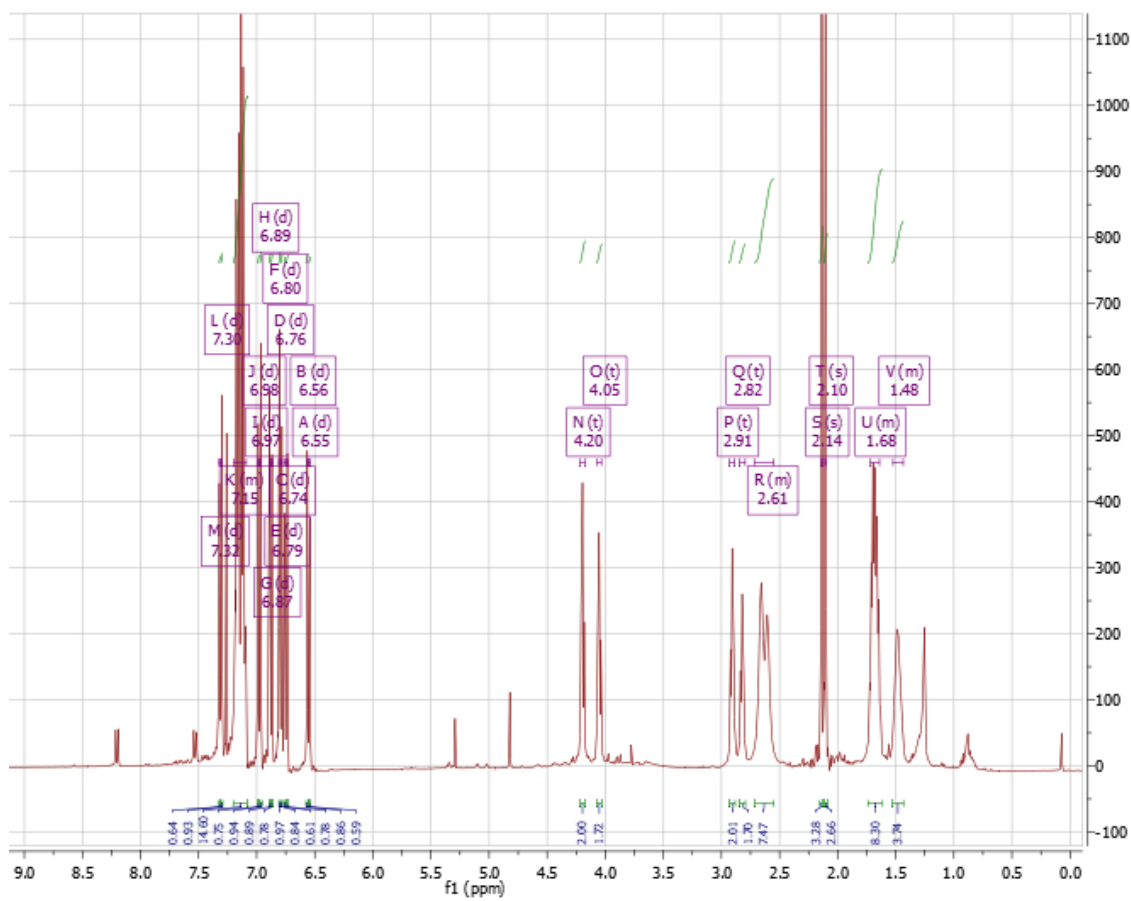


***E/Z*-1-(2-{4-[1-(4-Chloro-phenyl)-2-phenyl-propenyl]-phenoxy}-ethyl)-piperidine (7)**

21-Jun-2017

MT11 Sm (SG, 2x2)

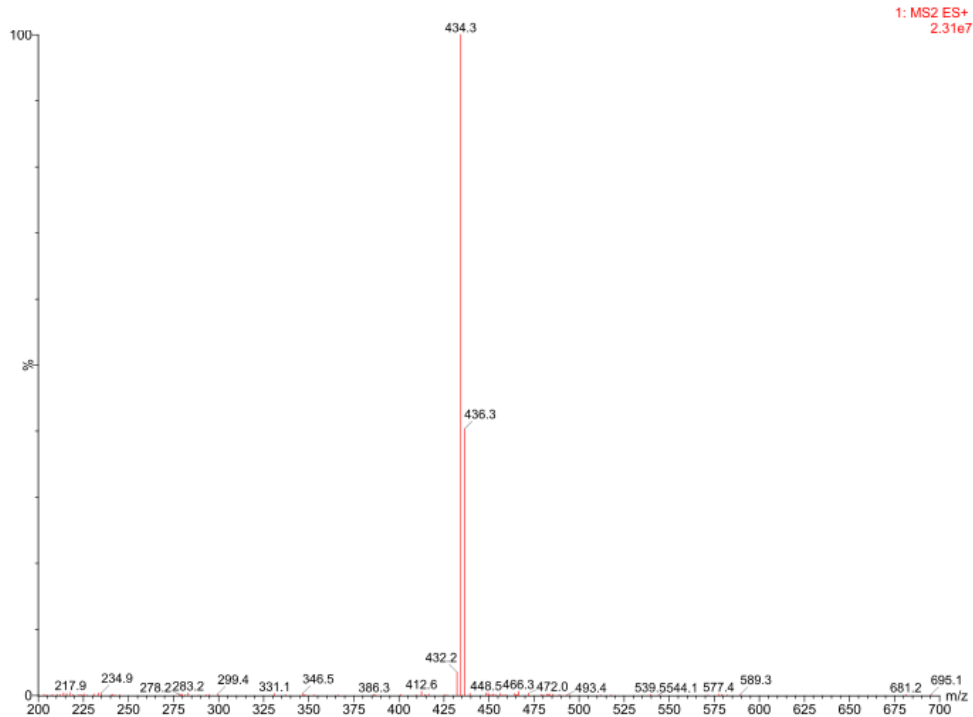
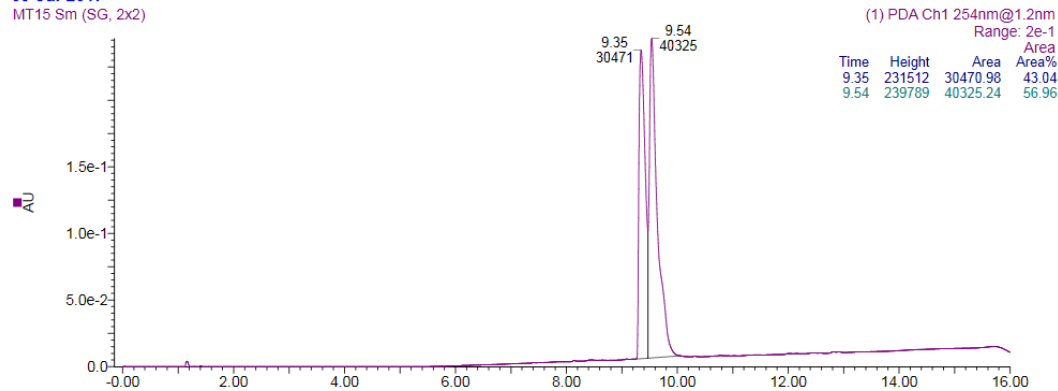


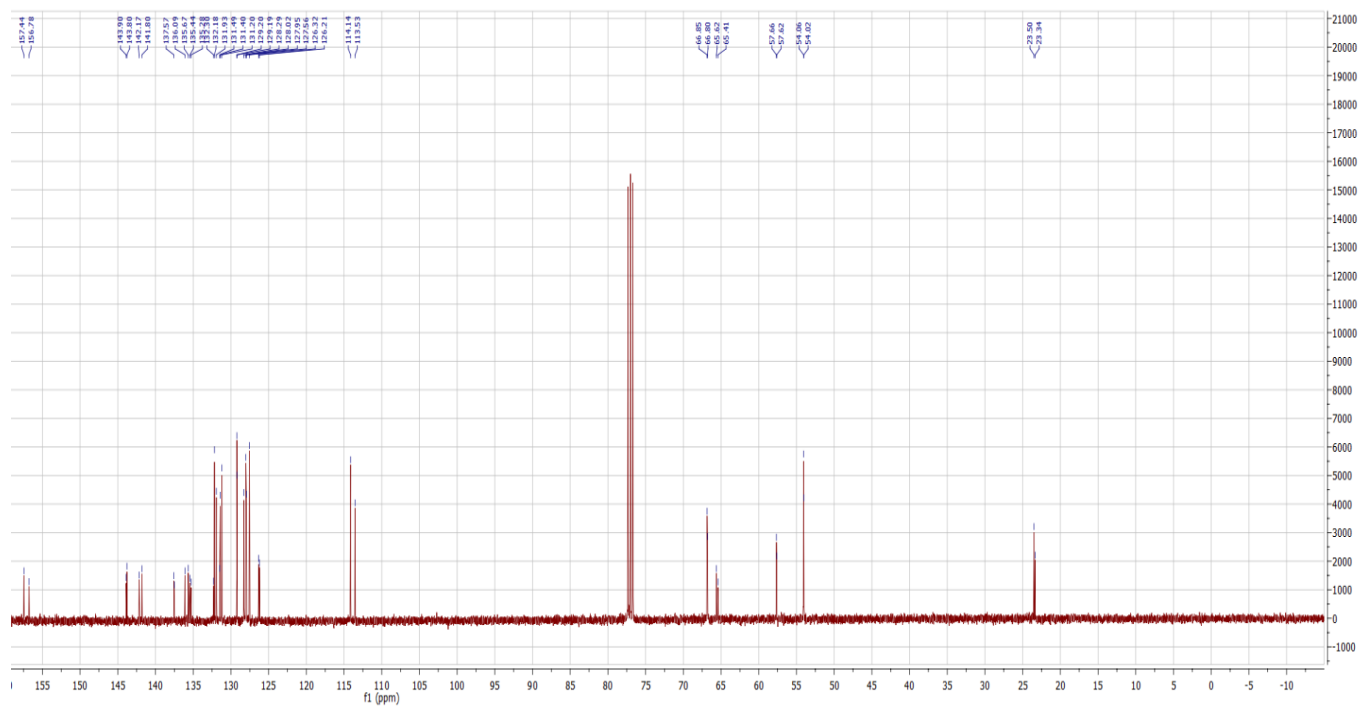
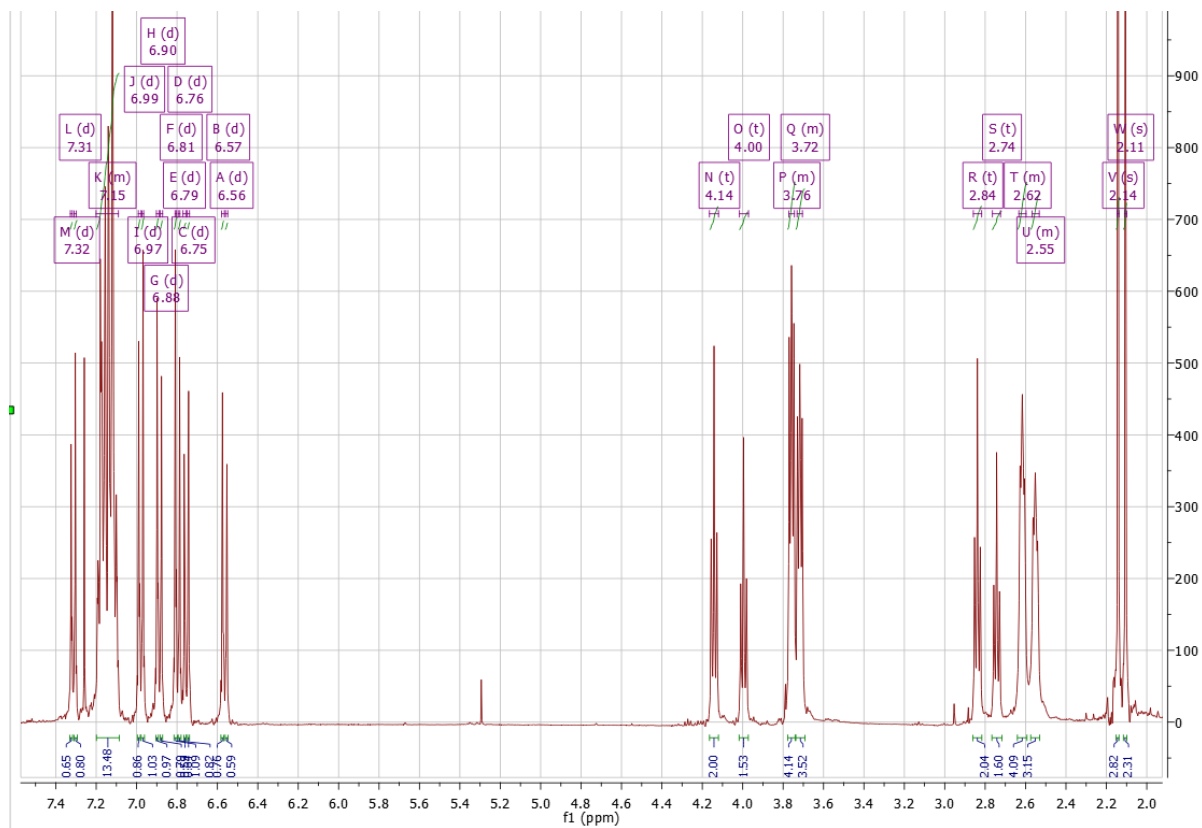


***E/Z*-4-(2-{4-[1-(4-Chloro-phenyl)-2-phenyl-propenyl]-phenoxy}-ethyl)-morpholine (8).**

09-Jul-2017

MT15 Sm (SG, 2x2)

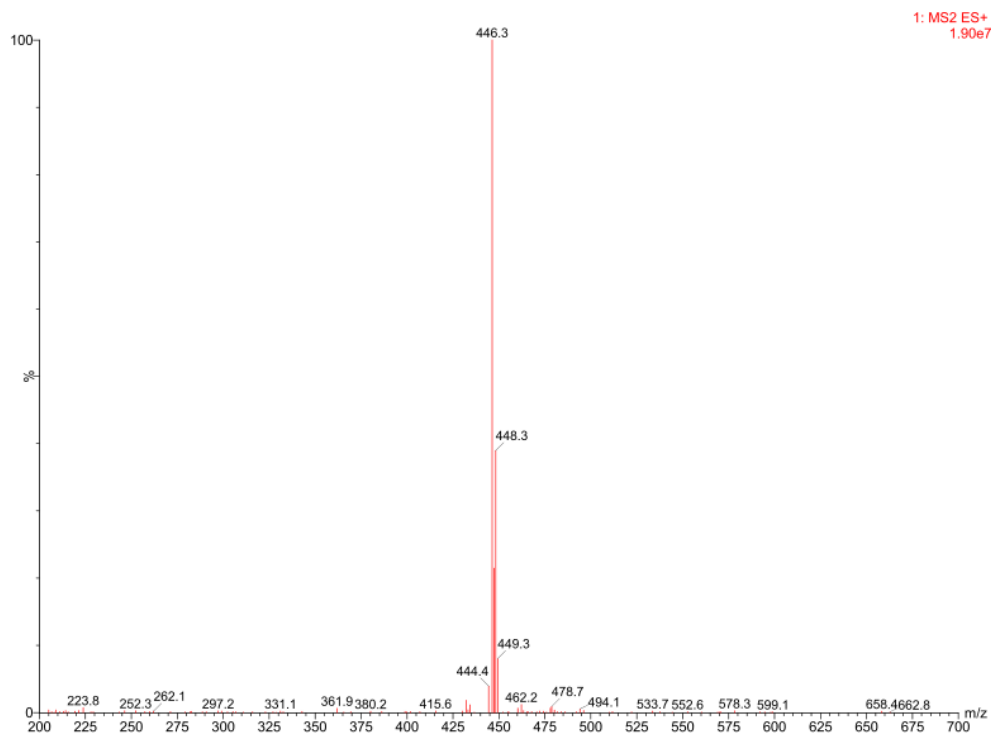
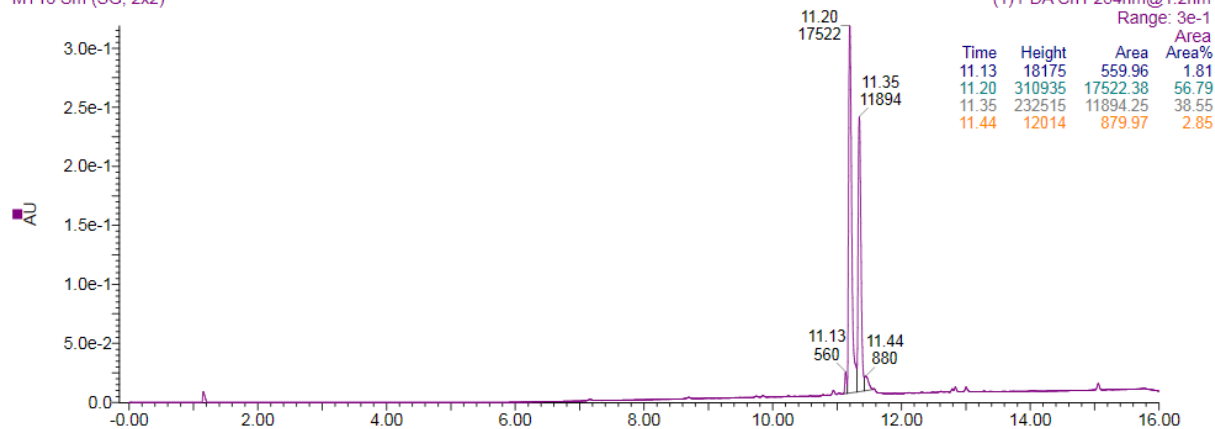


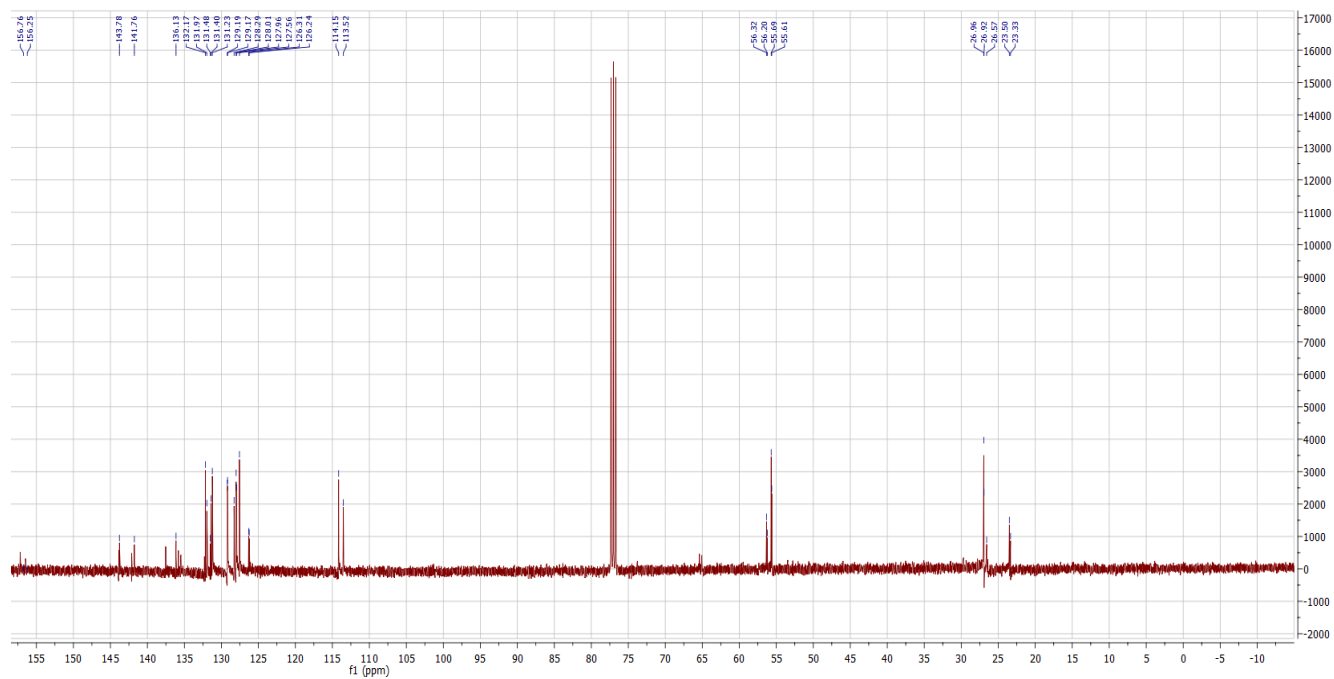
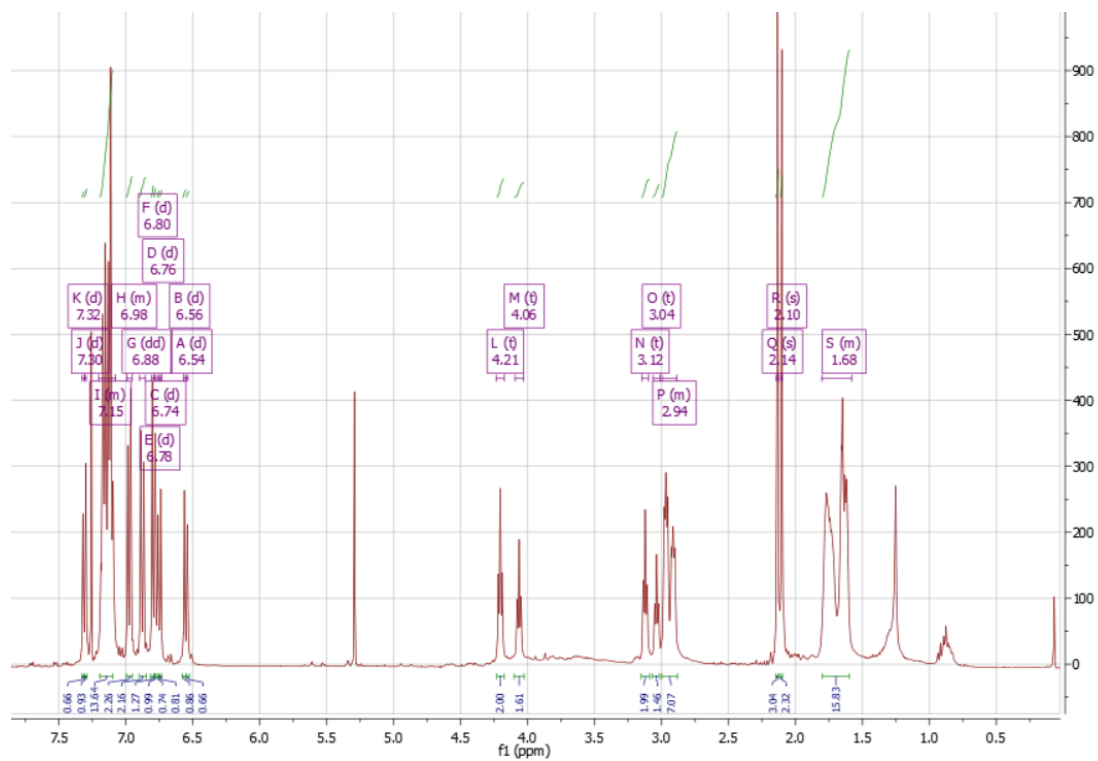


***E/Z*-1-(2-{4-[1-(4-Chloro-phenyl)-2-phenyl-propenyl]-phenoxy}-ethyl)-azepane (9).**

21-Jun-2017

MT13 Sm (SG, 2x2)



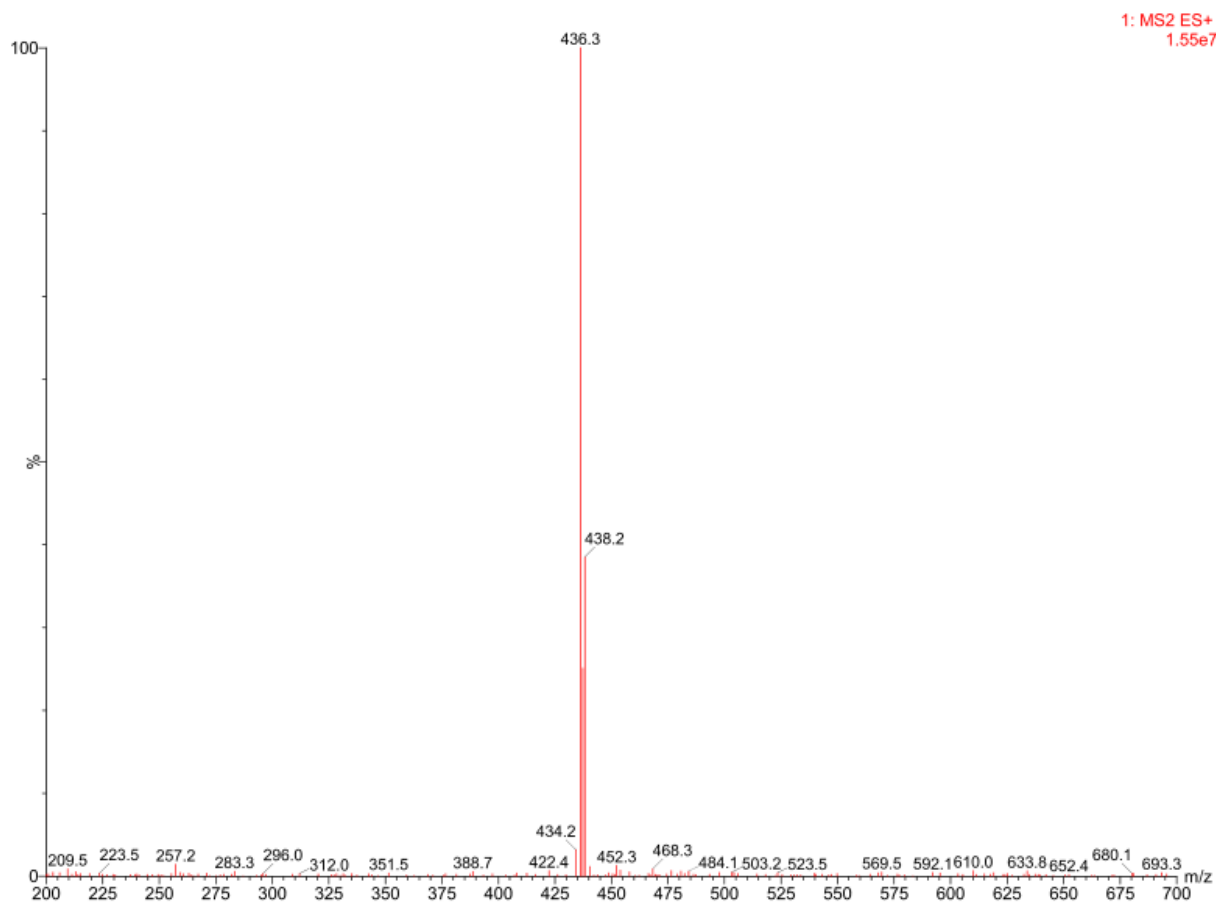
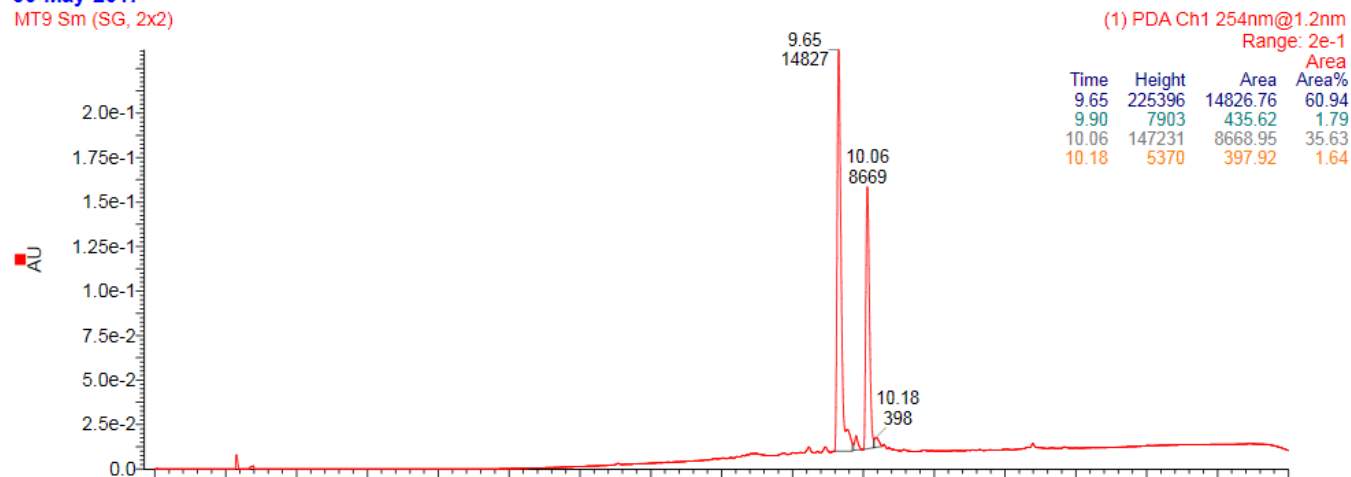


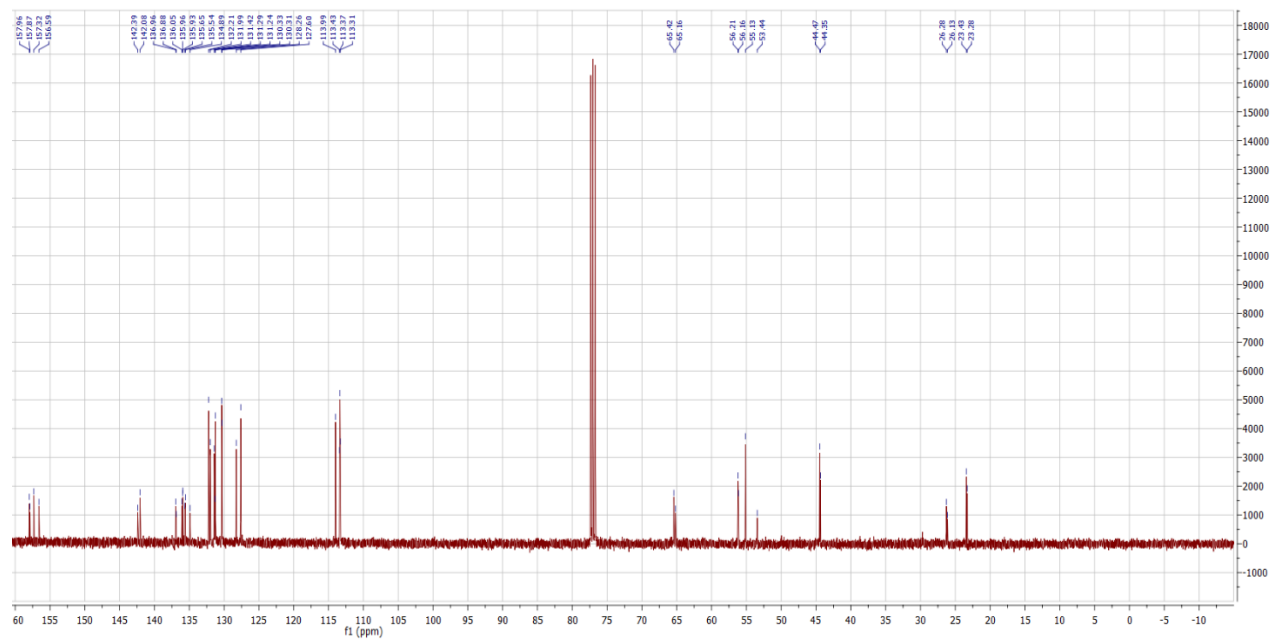
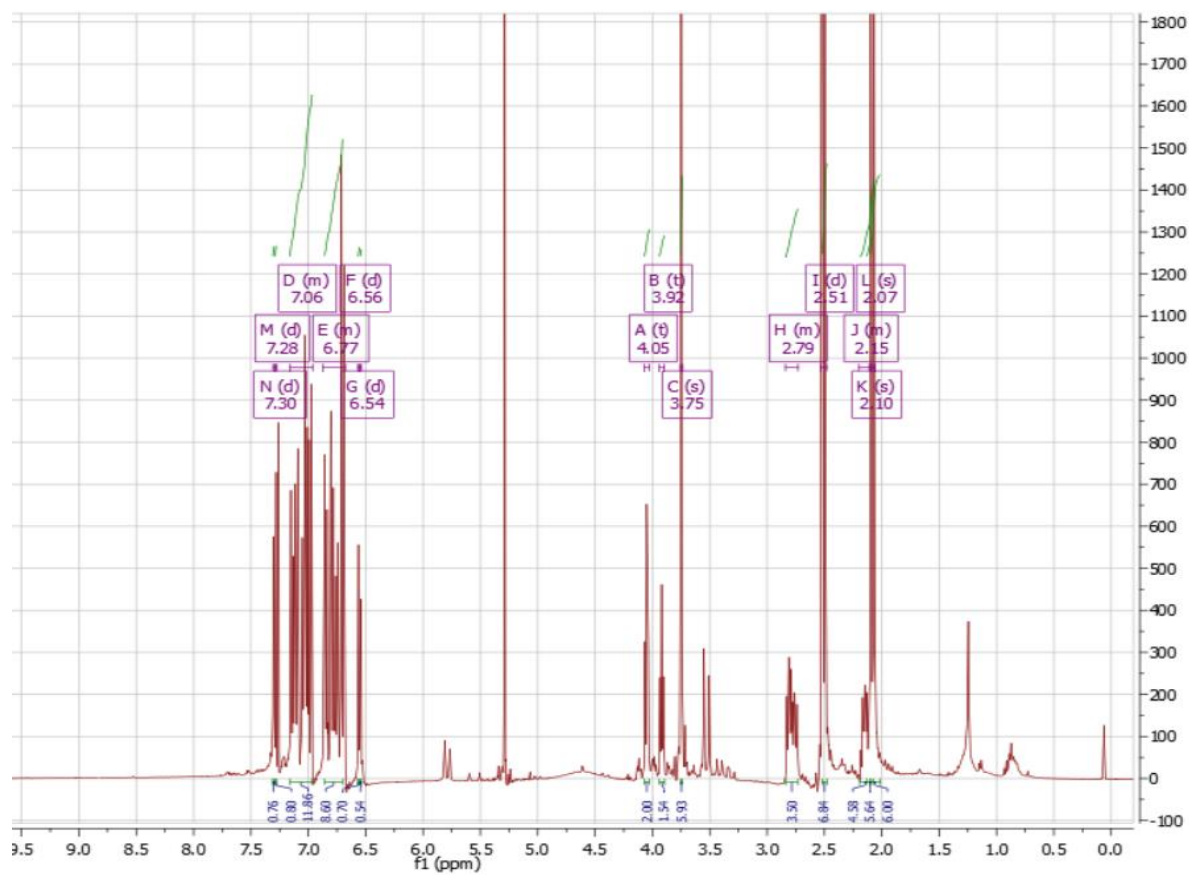


*E/Z*-(3-{4-[1-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-propenyl]-phenoxy}-propyl)-dimethyl-amine (10).

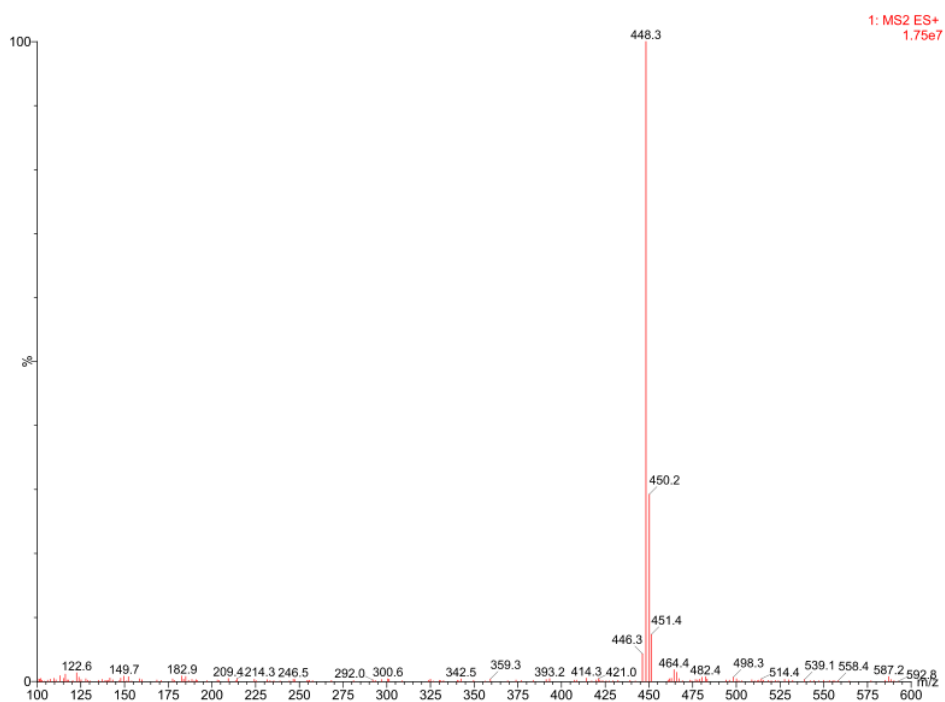
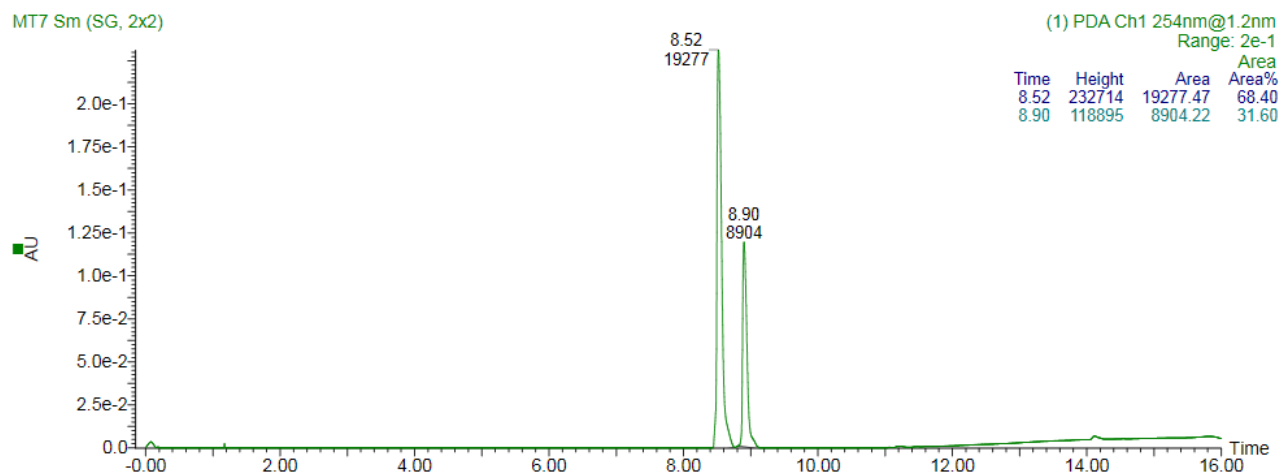
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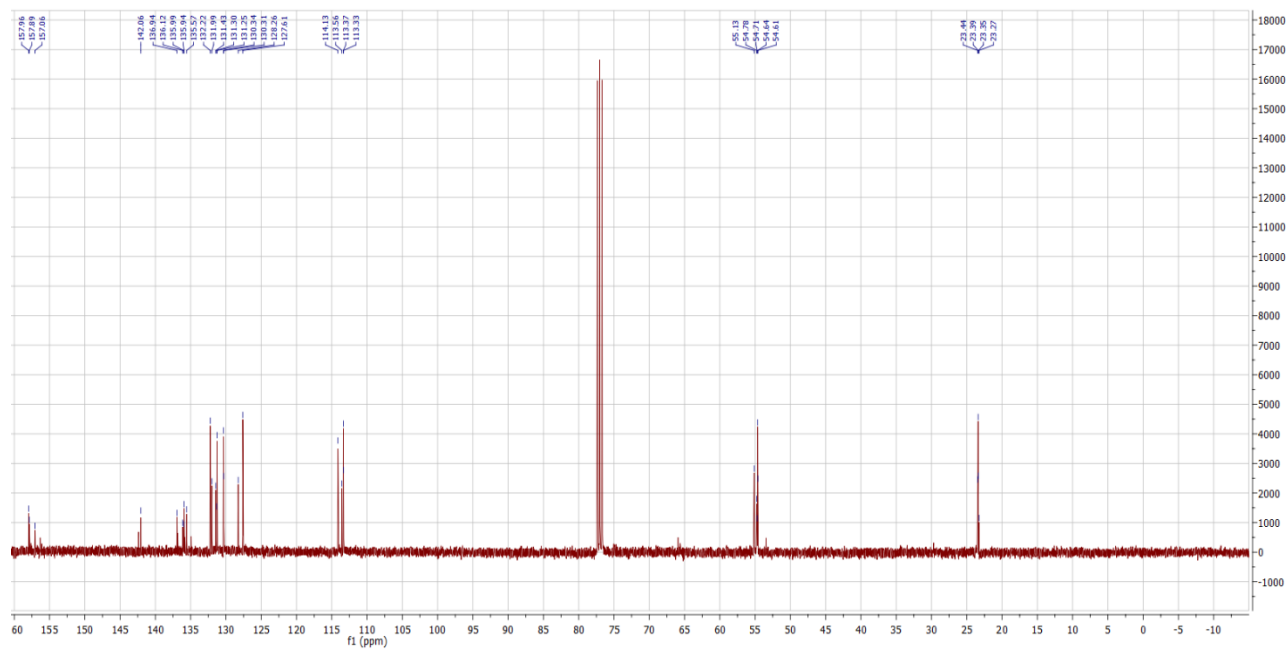
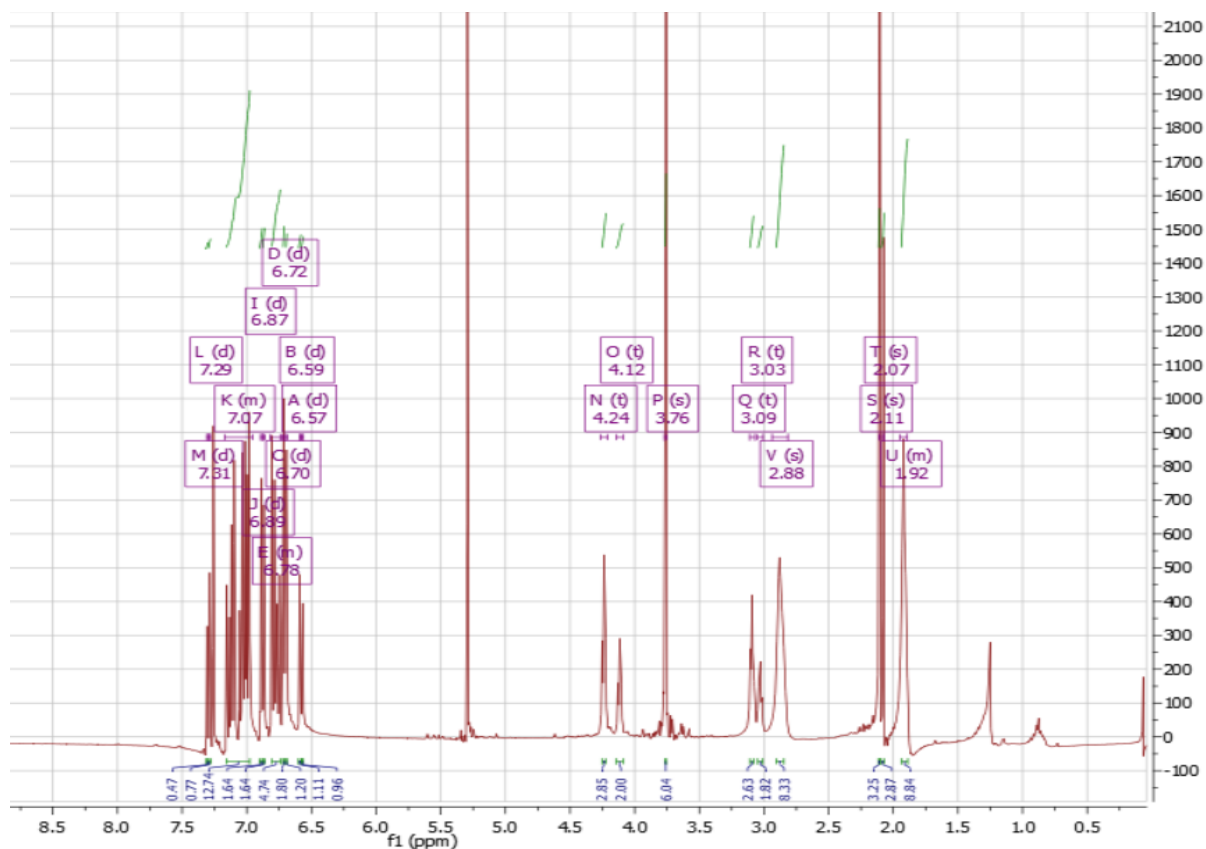
MT9 Sm (SG, 2x2)





***E/Z*-1-(2-{4-[1-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-propenyl]-phenoxy}-ethyl)-pyrrolidine (11).**

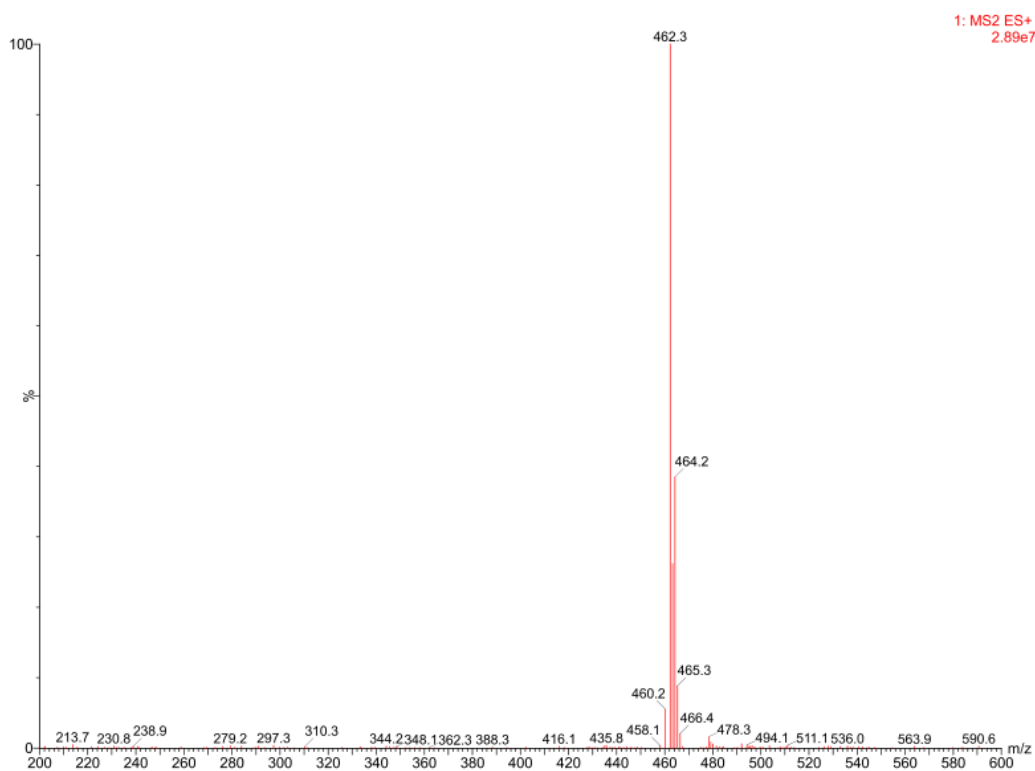
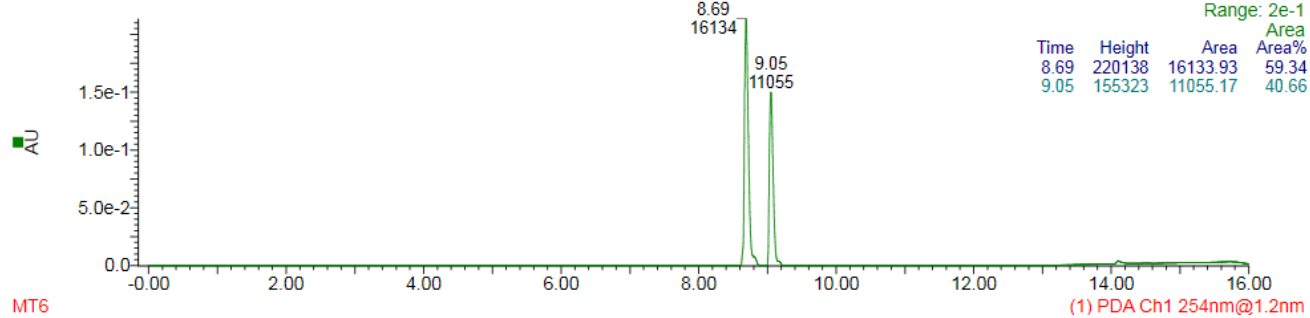


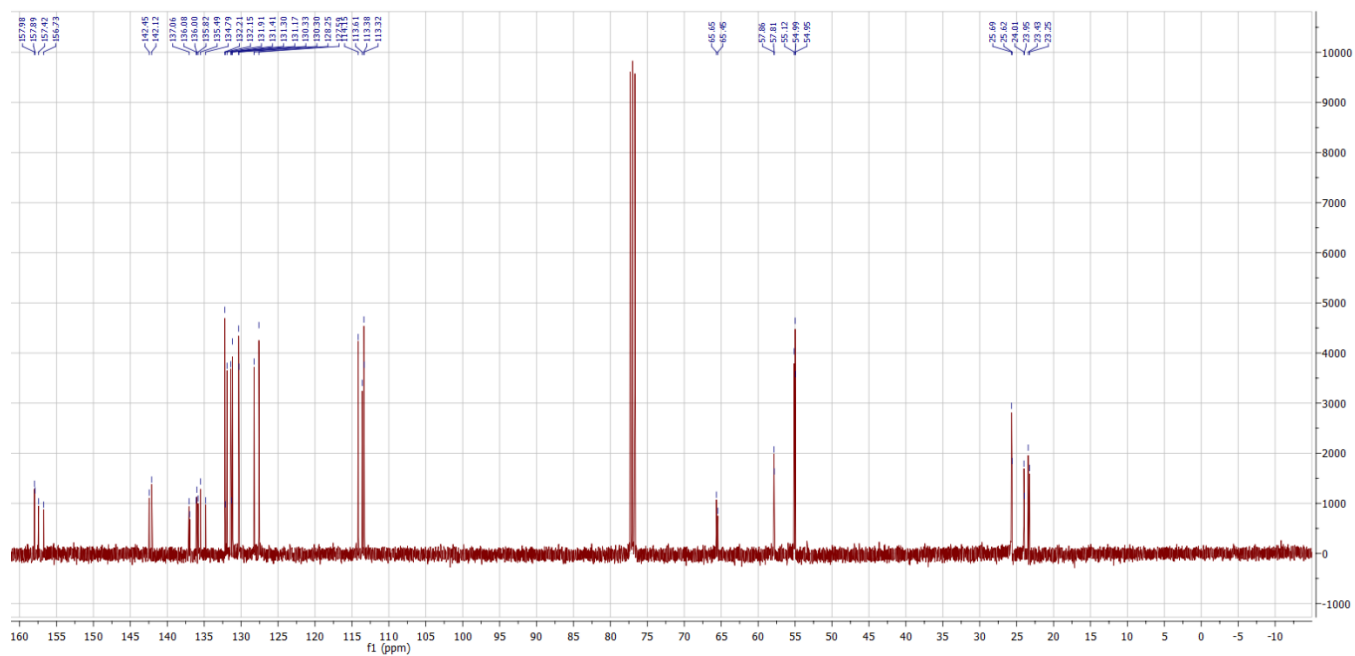


***E/Z*-1-(2-{4-[1-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-propenyl]-phenoxy}-ethyl)-piperidine (12).**

20-Mar-2017

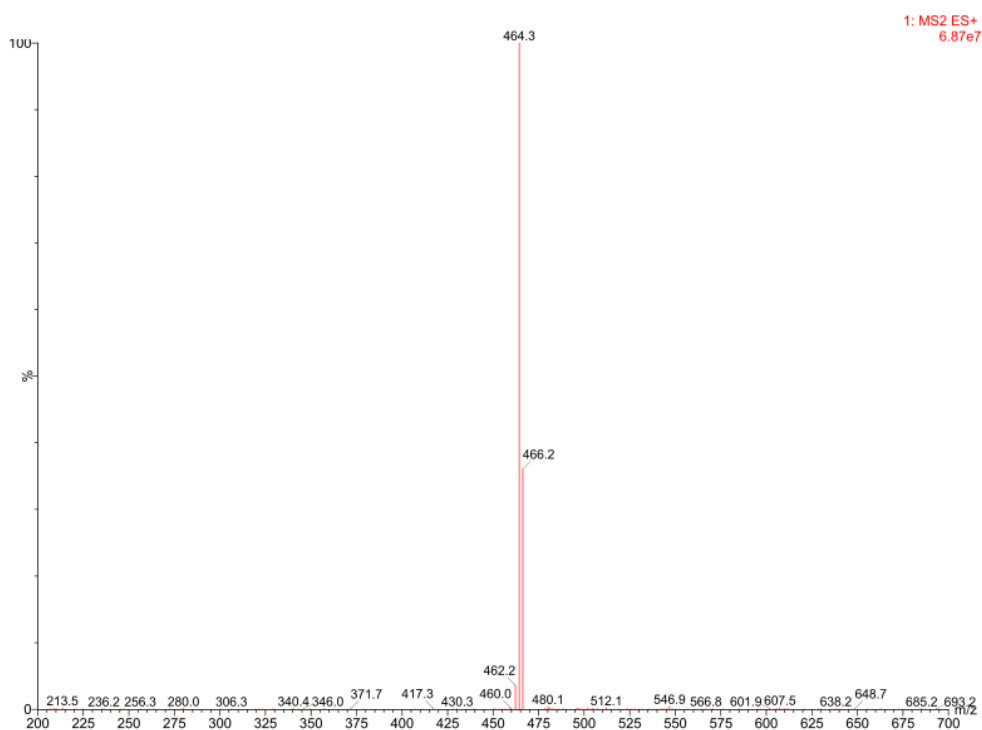
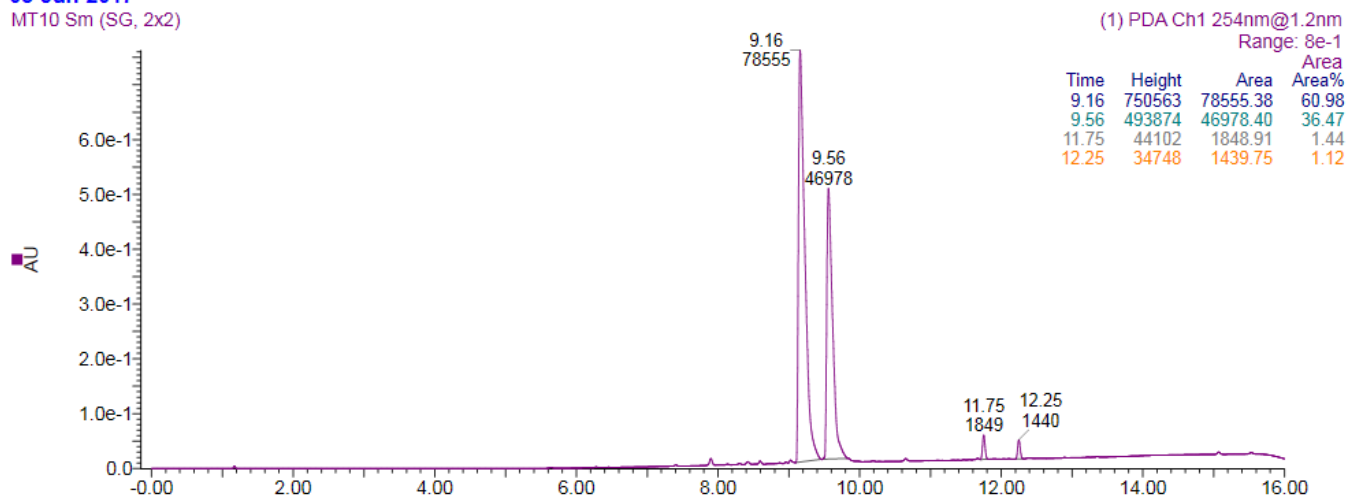
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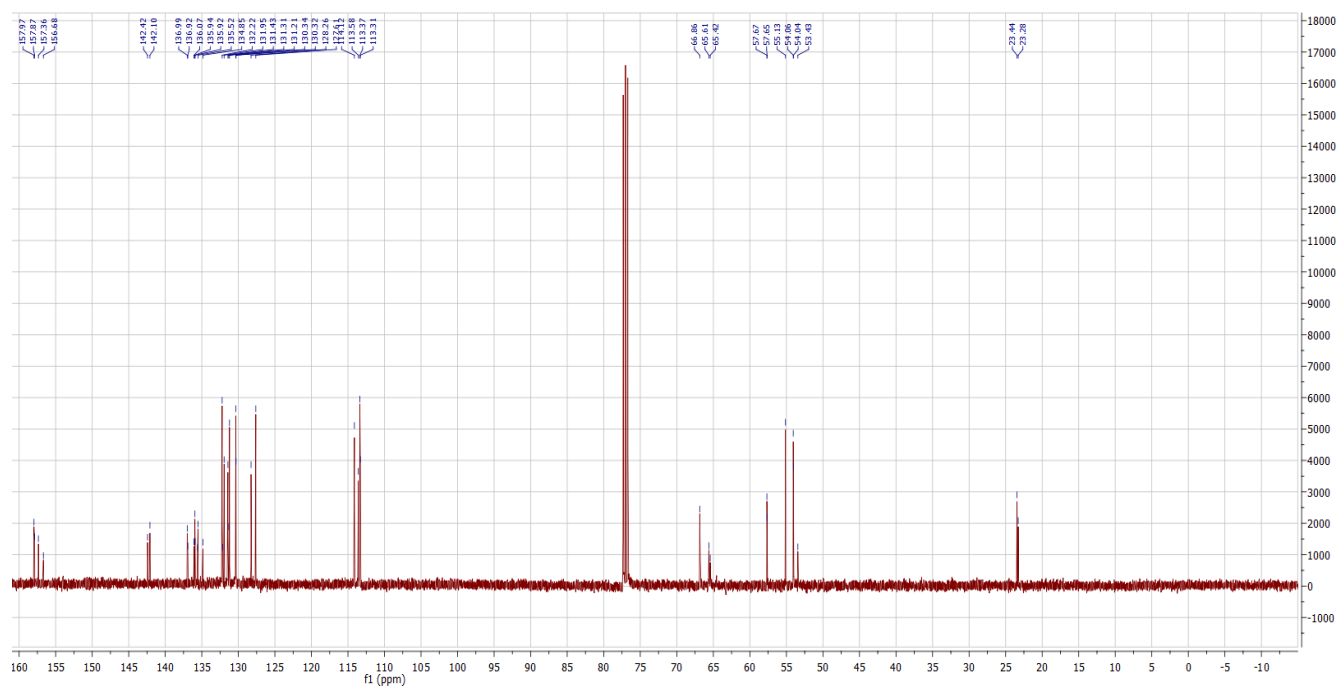
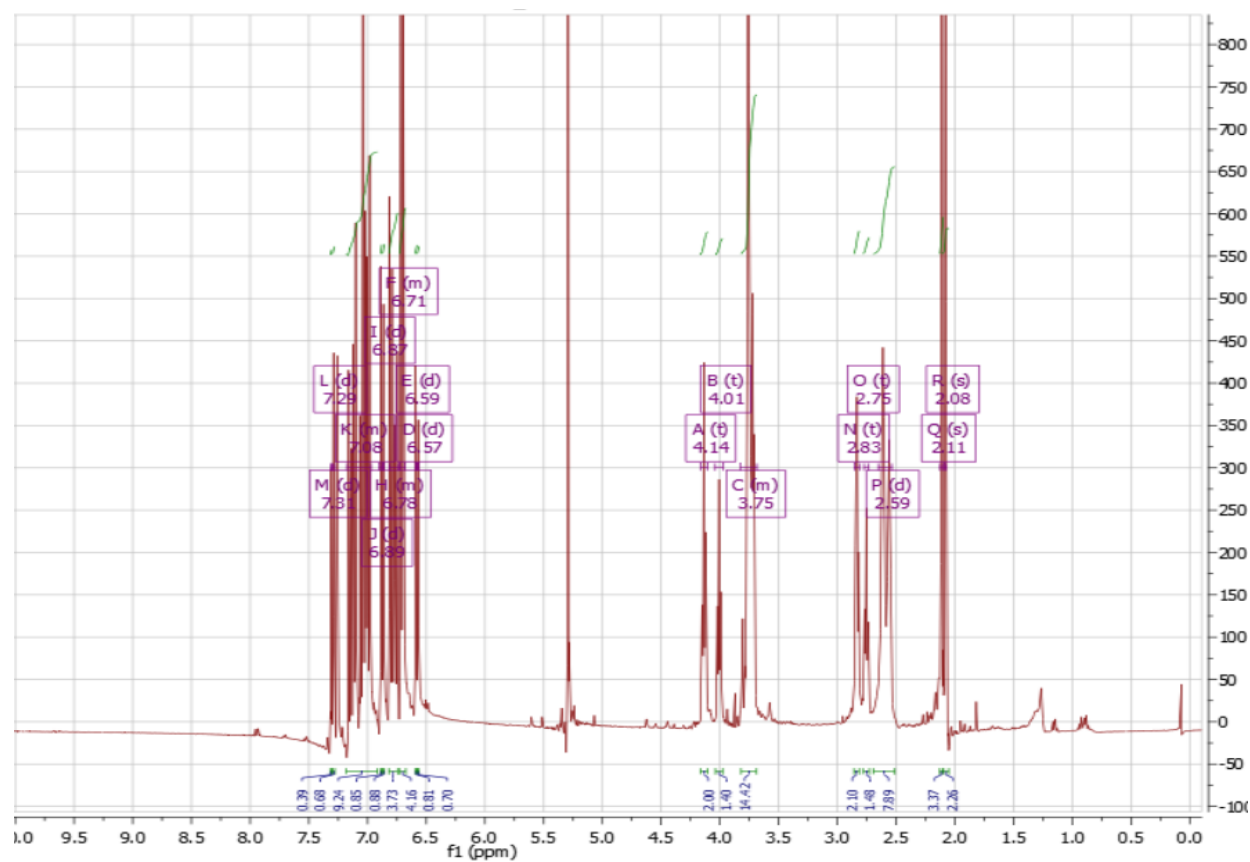




*E/Z*-4-(2-{4-[1-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-propenyl]-phenoxy}-ethyl)-morpholine (13).

08-Jun-2017  
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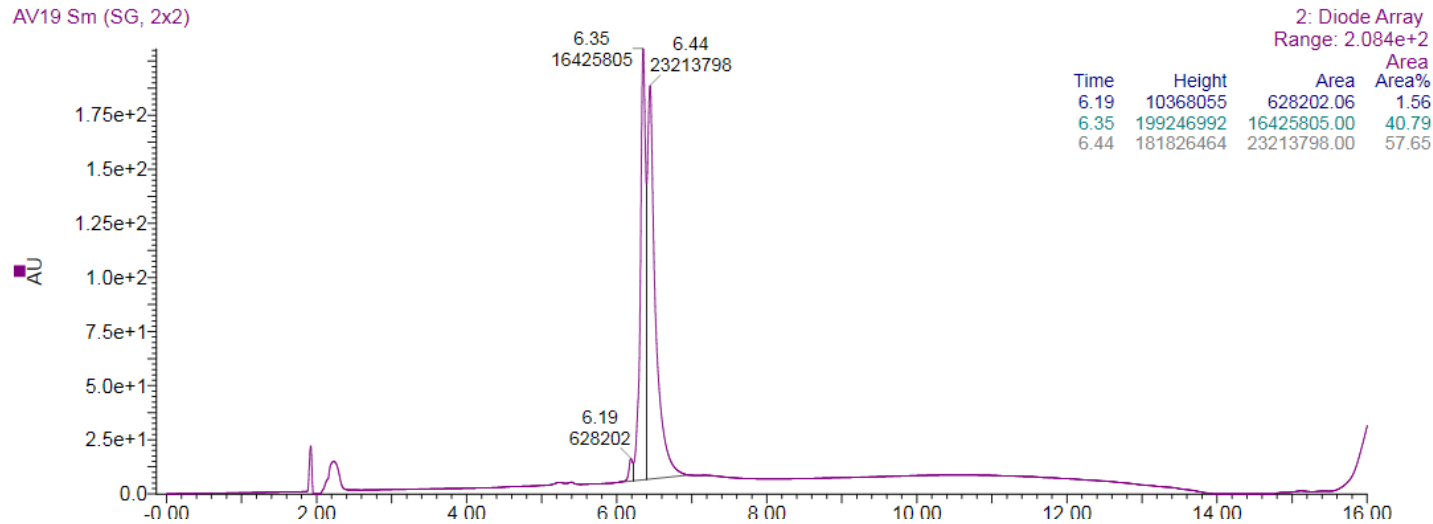




***E/Z*-(3-[4-[1-(4-Chlorophenyl)-2-(3-fluoro-4-methoxyphenyl)-propenyl]-phenoxy}-propyl)-dimethyl-amine (15)**

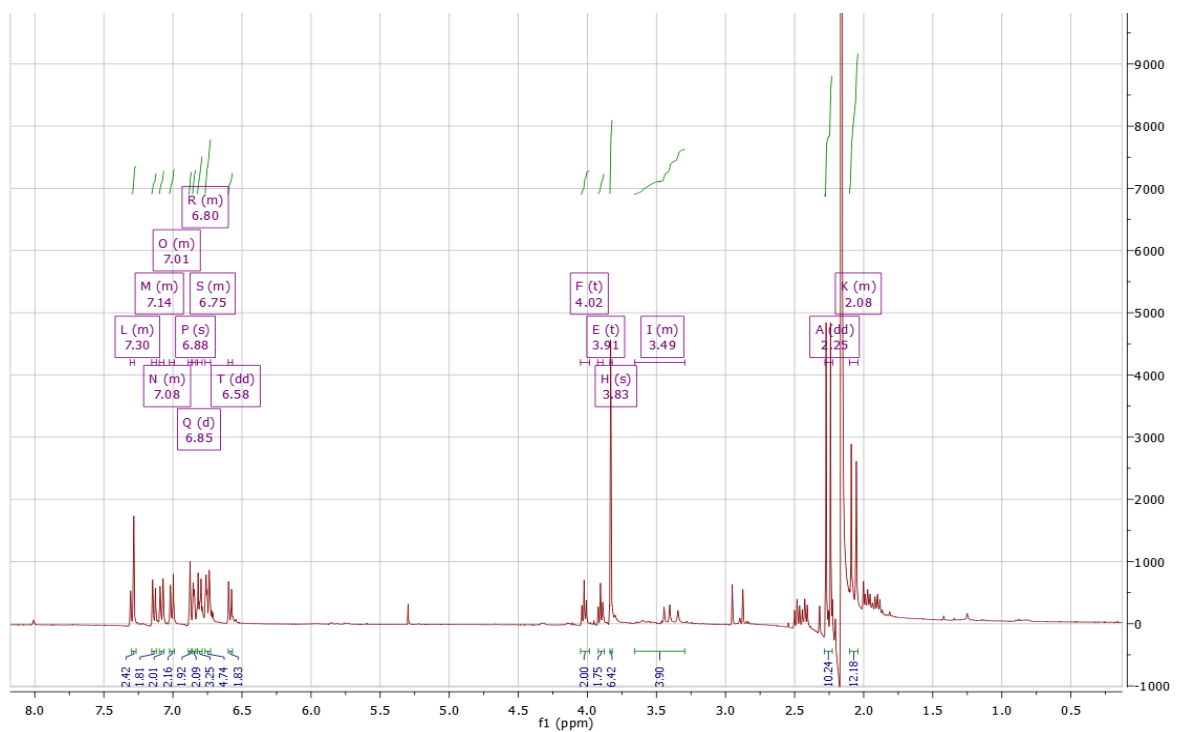
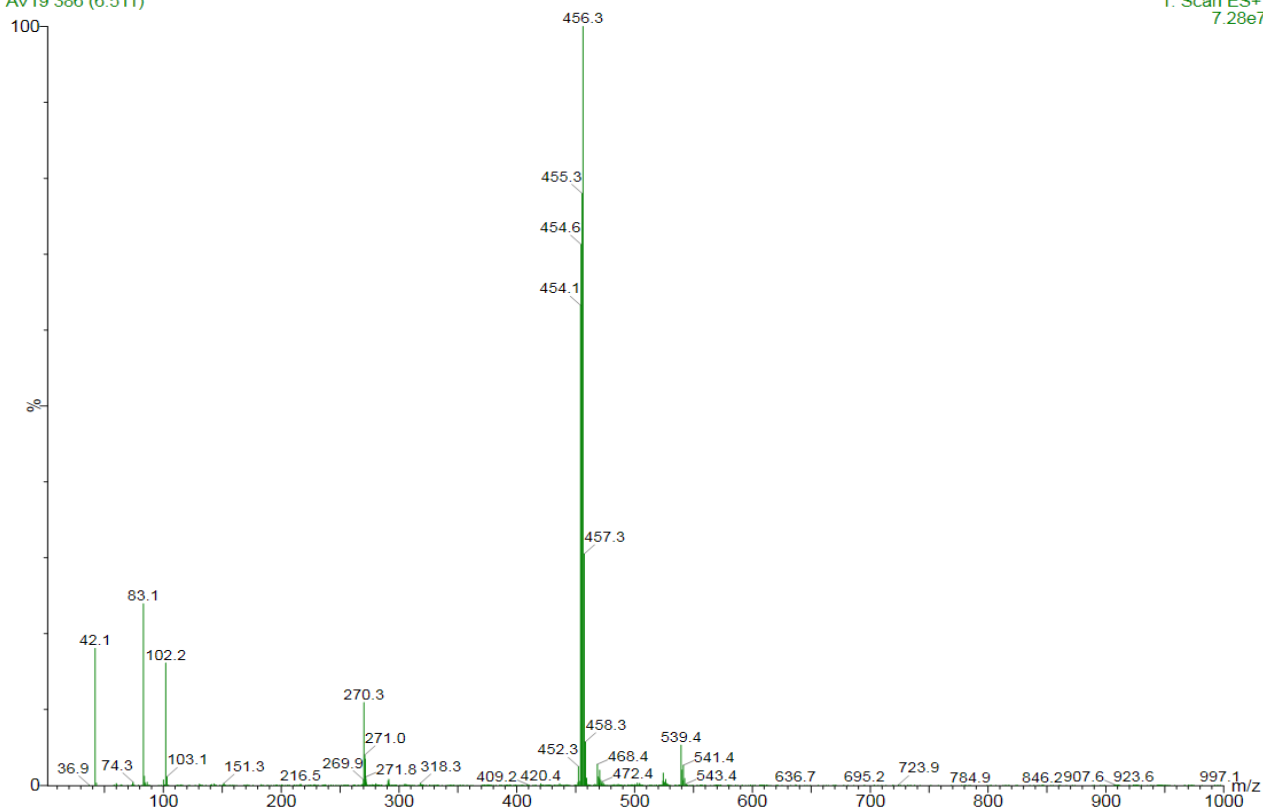
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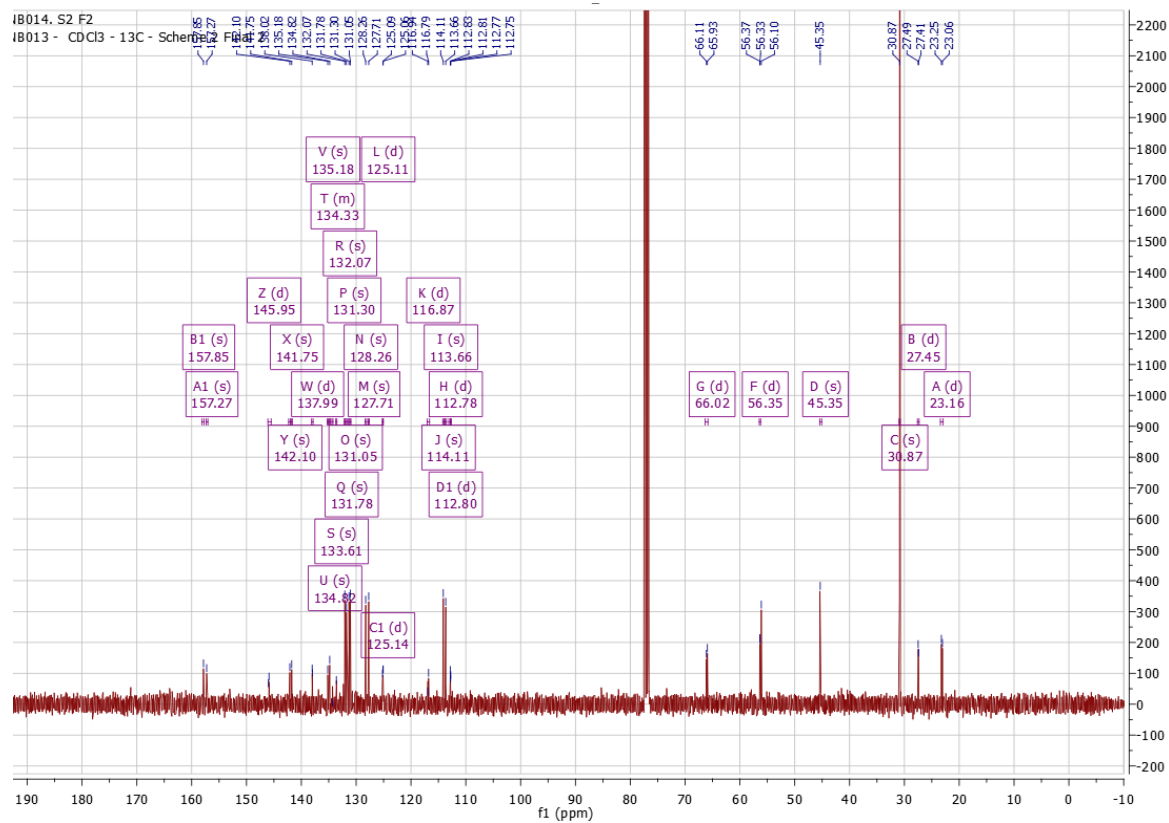
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25-Oct-2018 13:52:15  
AV19 386 (6.511)

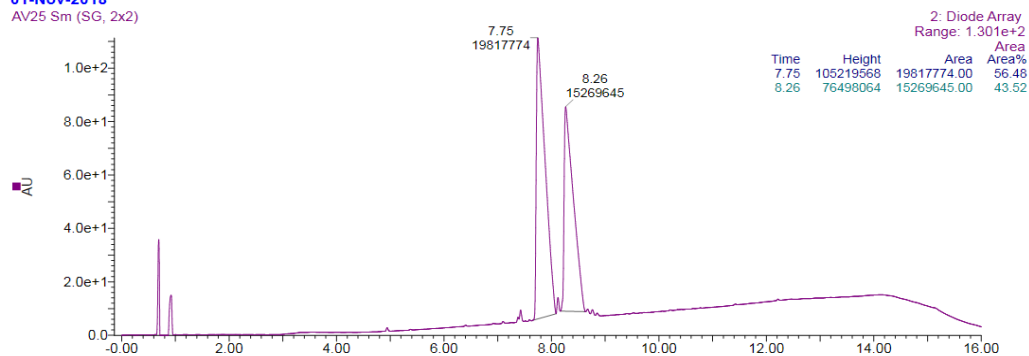
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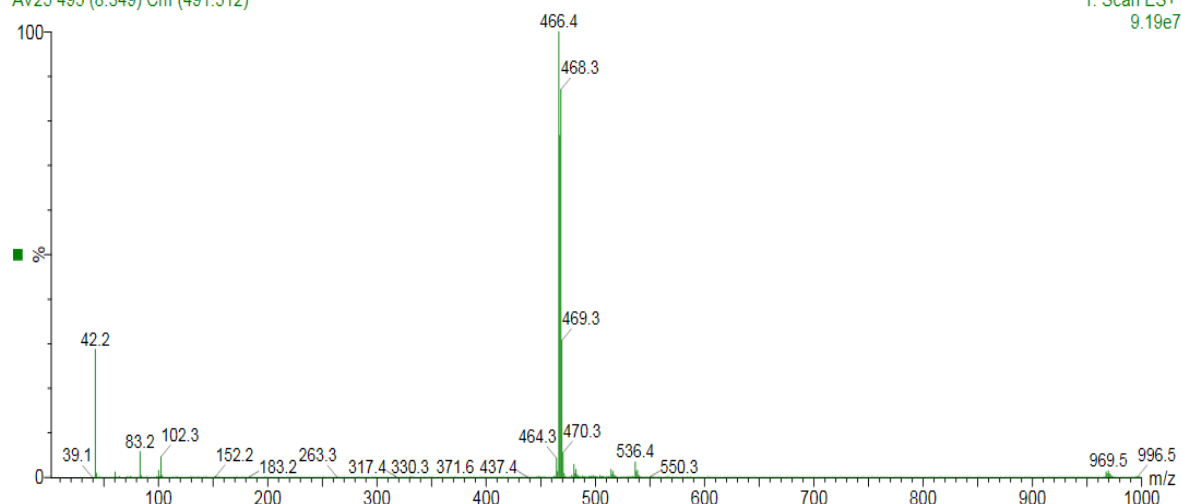
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(16)**

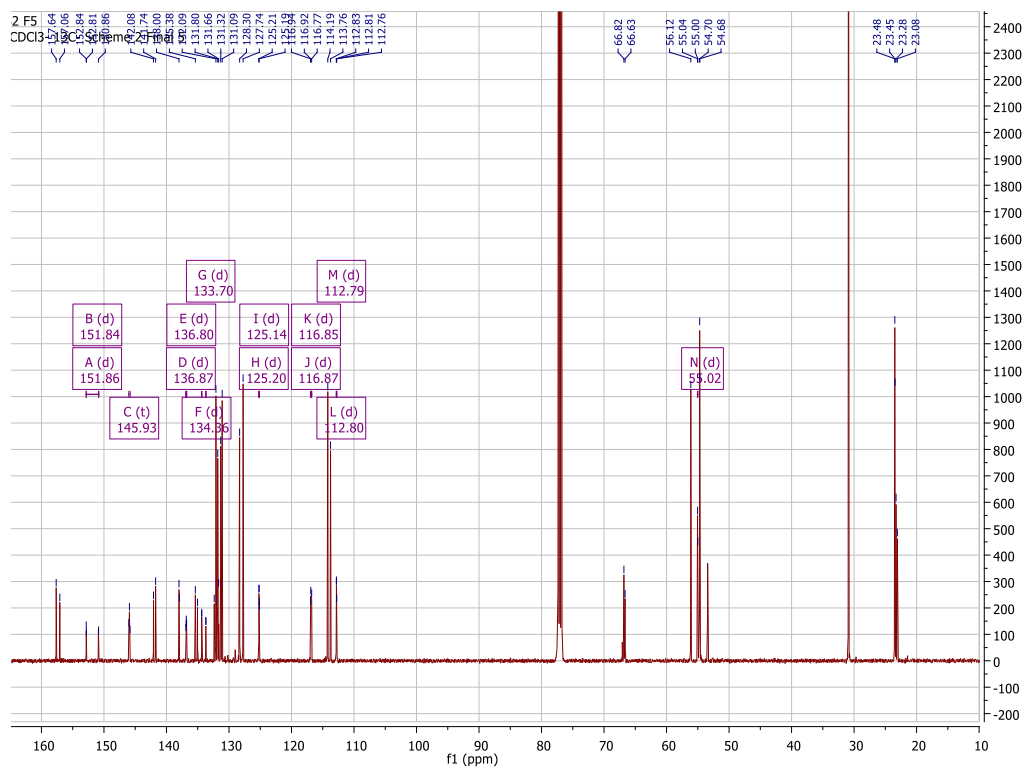
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01-Nov-2018 17:51:49

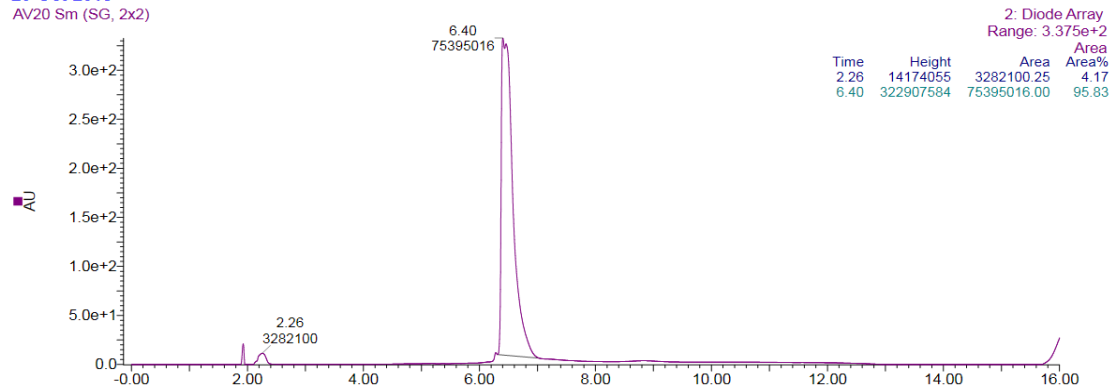
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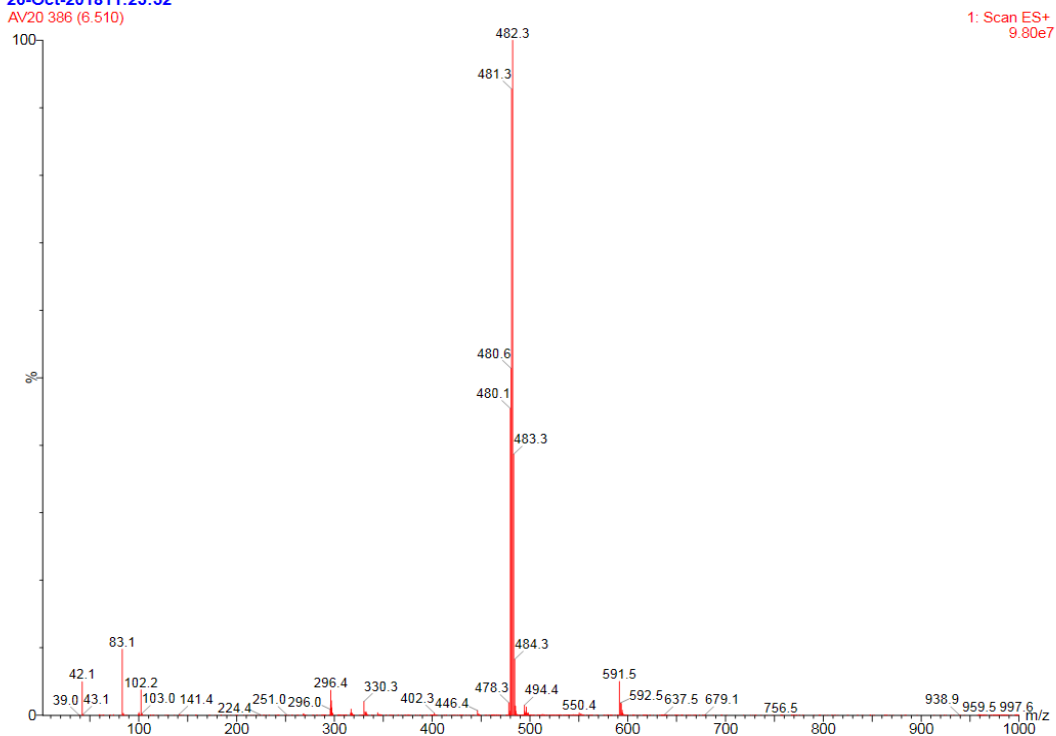


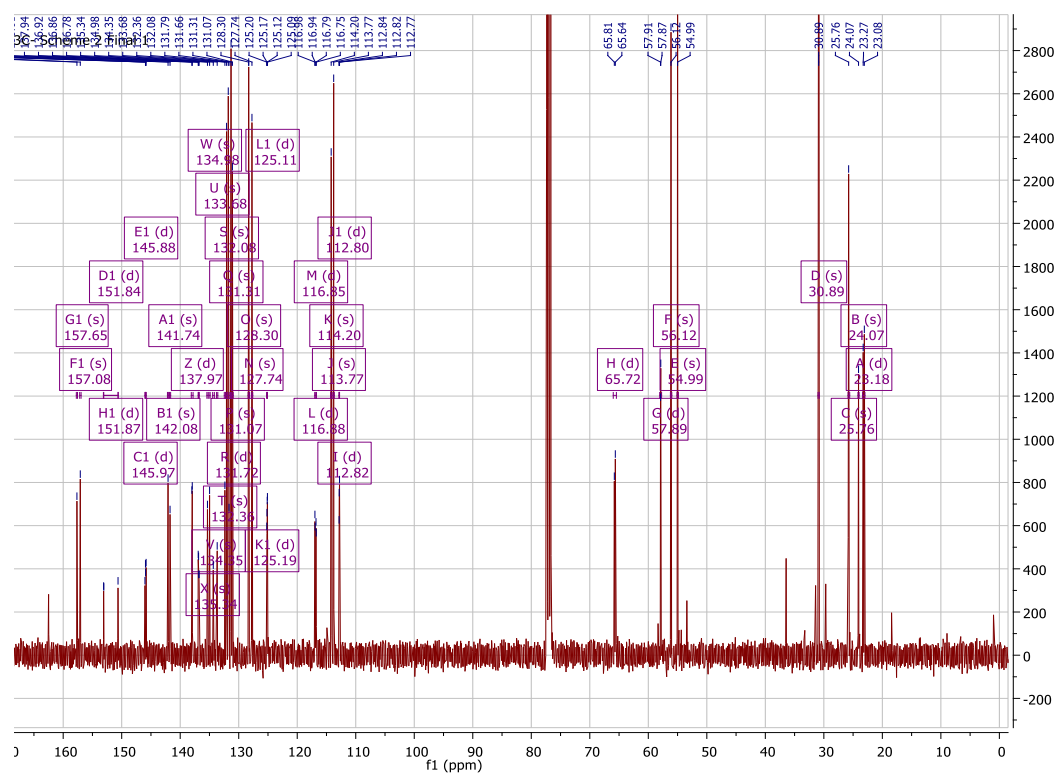
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(17)**

26-Oct-2018  
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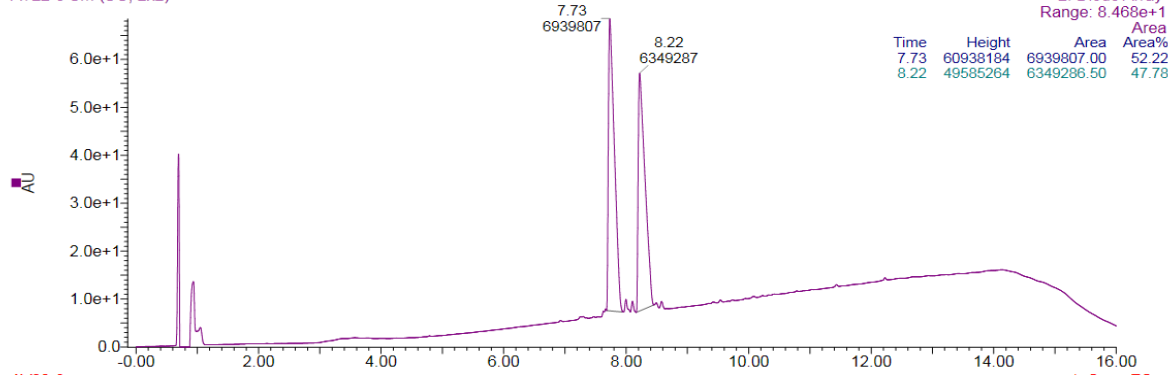
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AV20 386 (6.510)



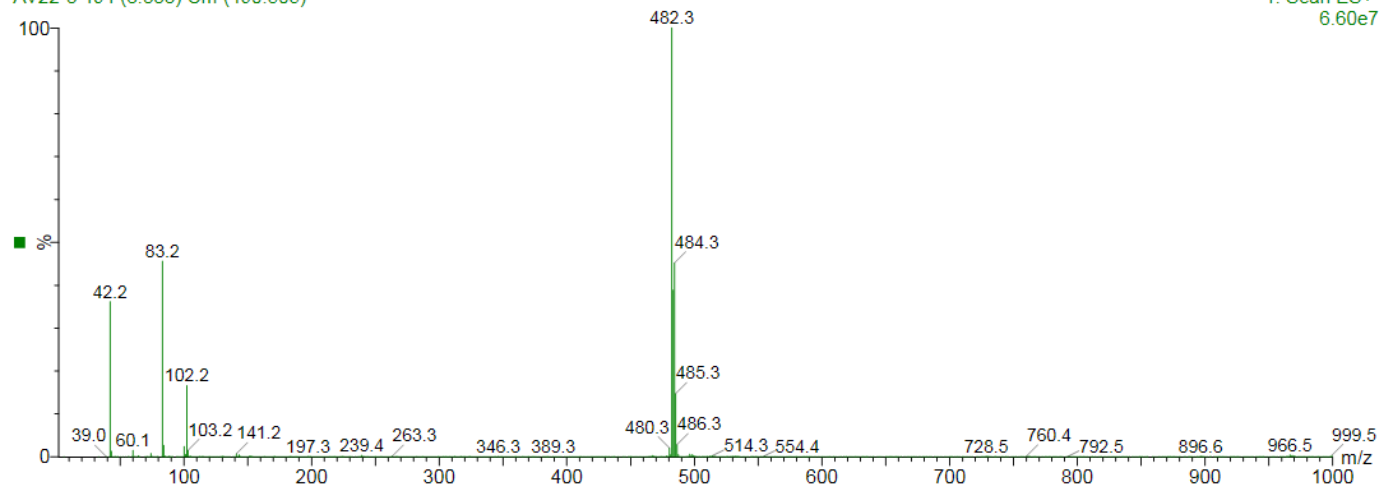


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(18)**

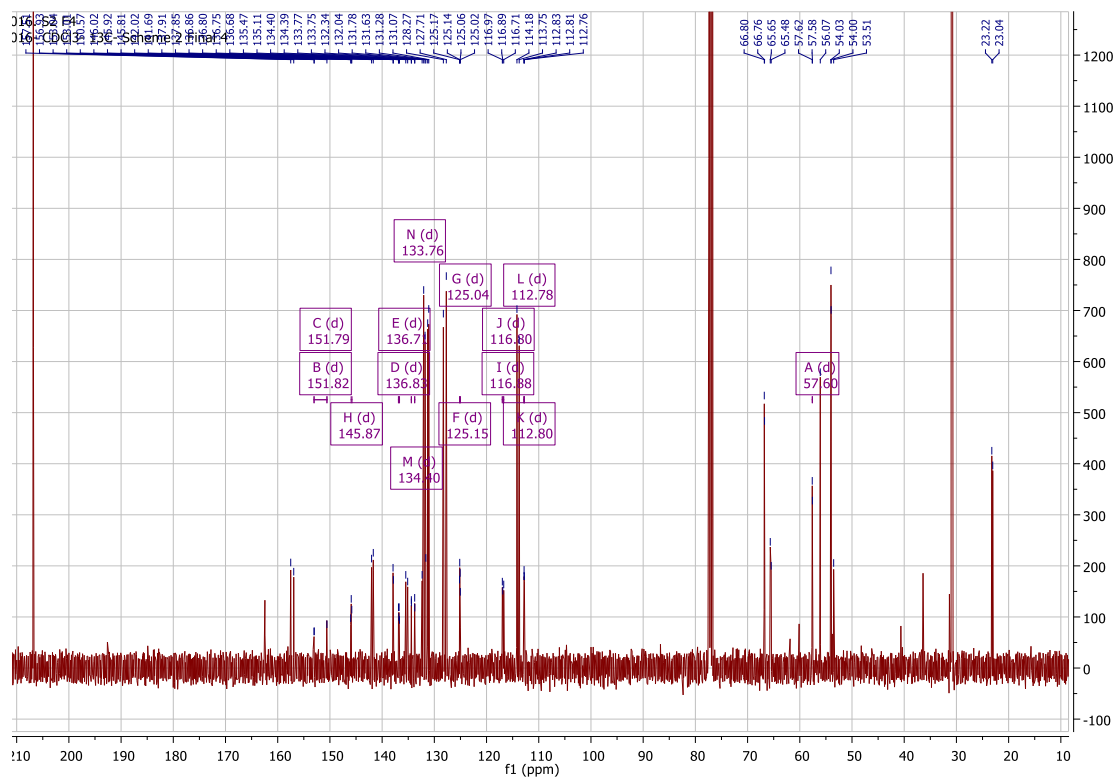
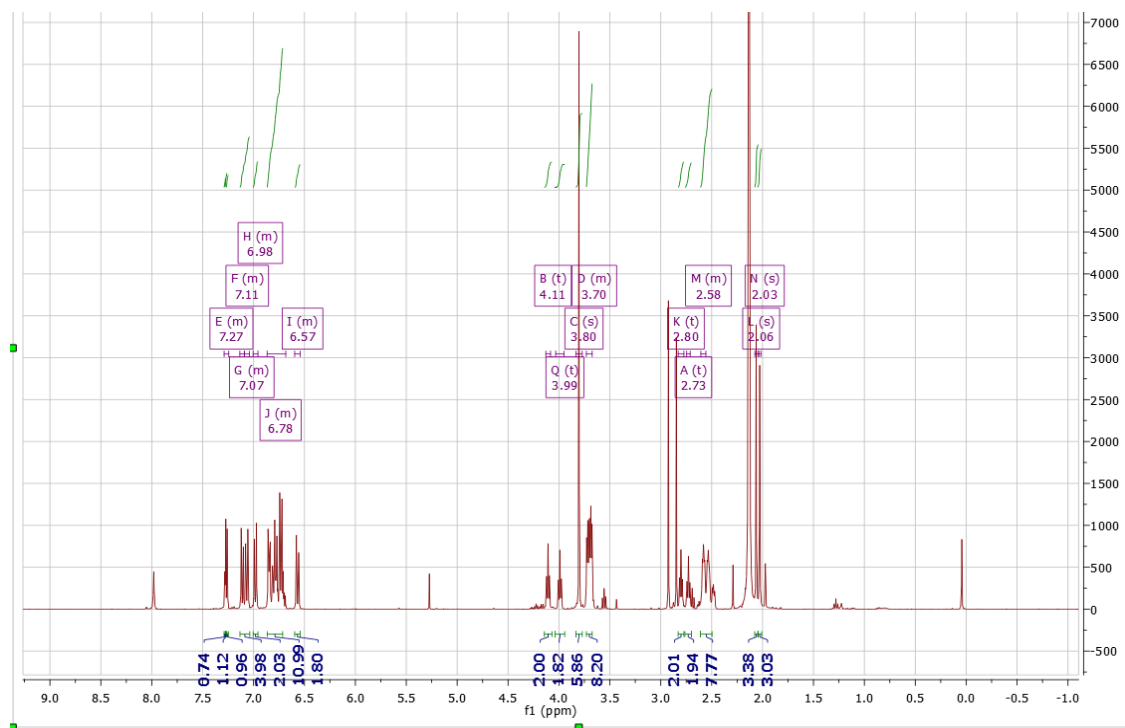
01-Nov-2018  
AV22-3 Sm (SG, 2x2)



01-Nov-2018 13:49:58  
AV22-3 494 (8.333) Cm (490:505)

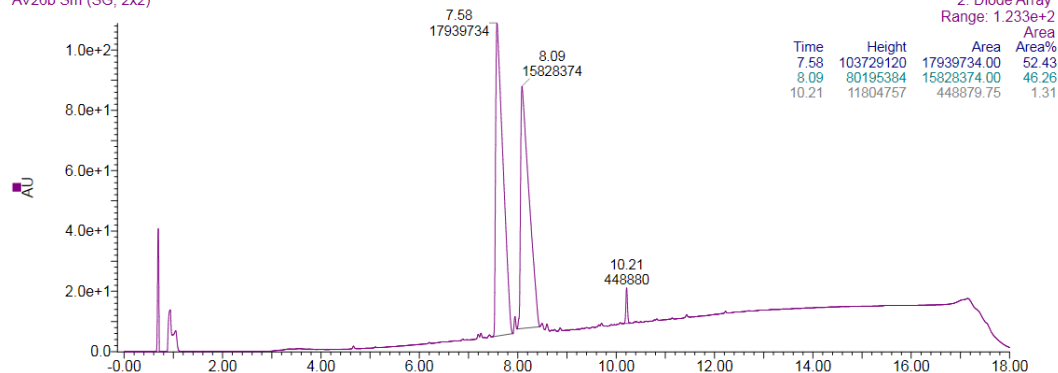






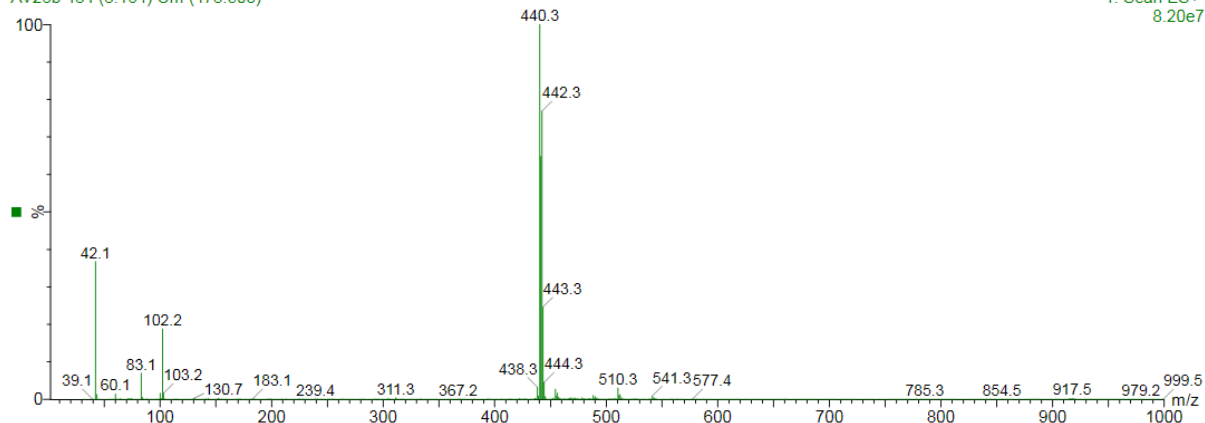
***E/Z*-(2-{4-[1-(4-Chlorophenyl)-2-(3-fluoro-4-methoxyphenyl)-propenyl]-phenoxy}-ethyl)-dimethyl-**

02-Nov-2018  
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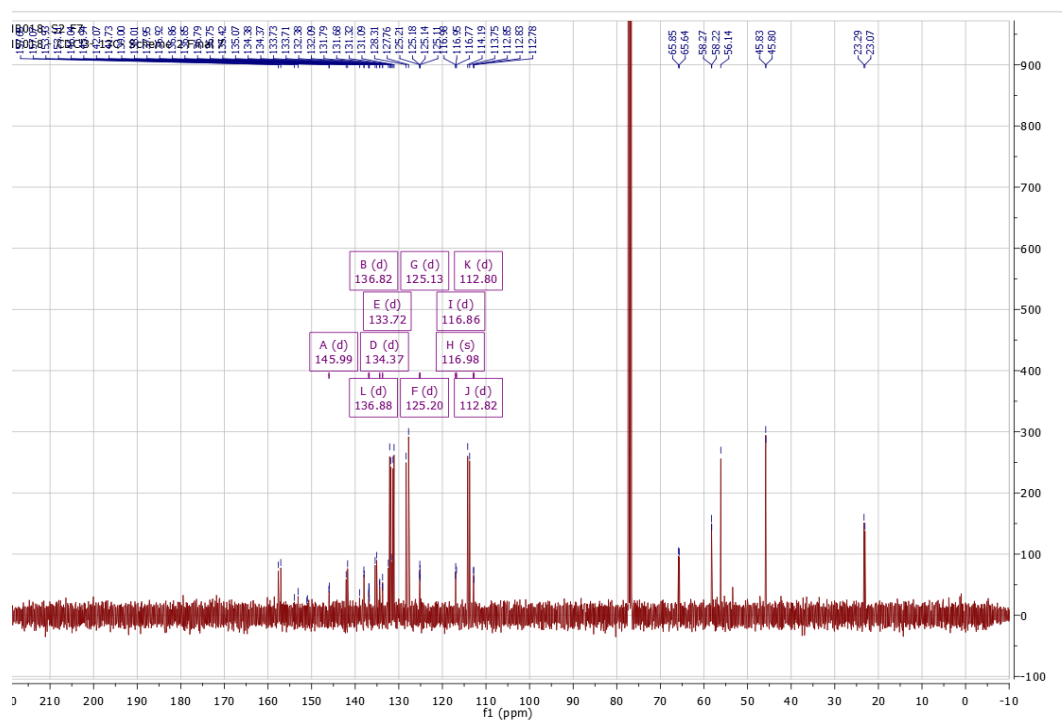


amine (20)

02-Nov-2018 16:37:47  
AV26b 484 (8.164) Cm (478:503)



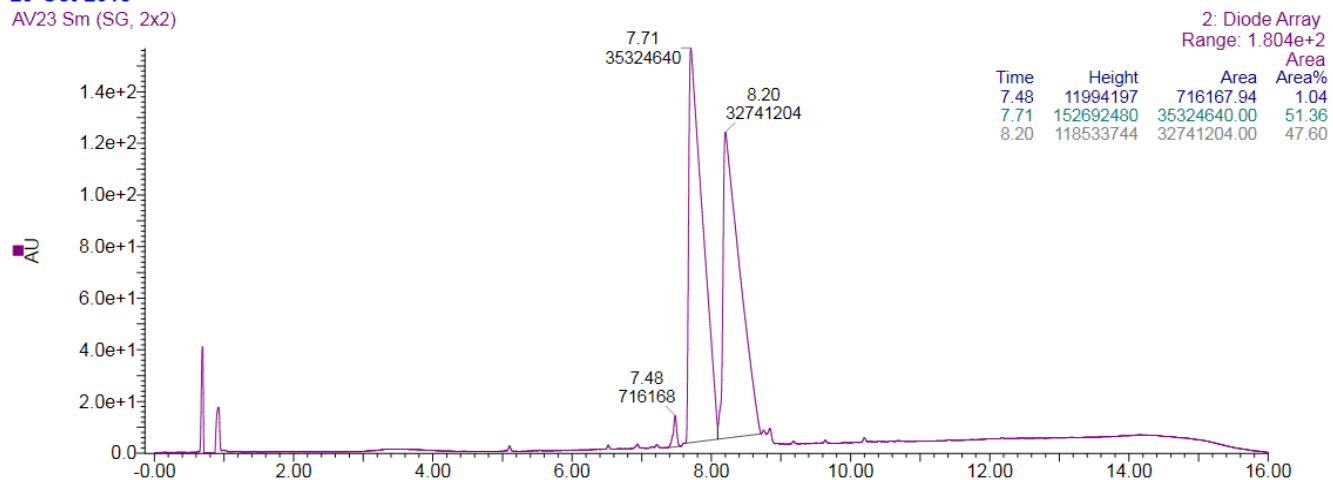
1: Scan ES+  
8.20e7



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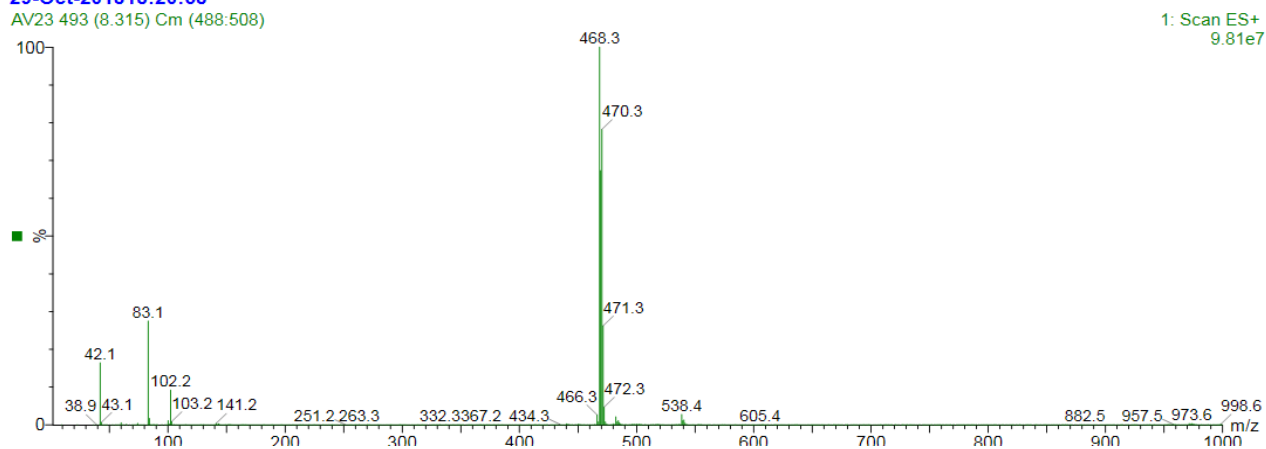
29-Oct-2018

AV23 Sm (SG, 2x2)



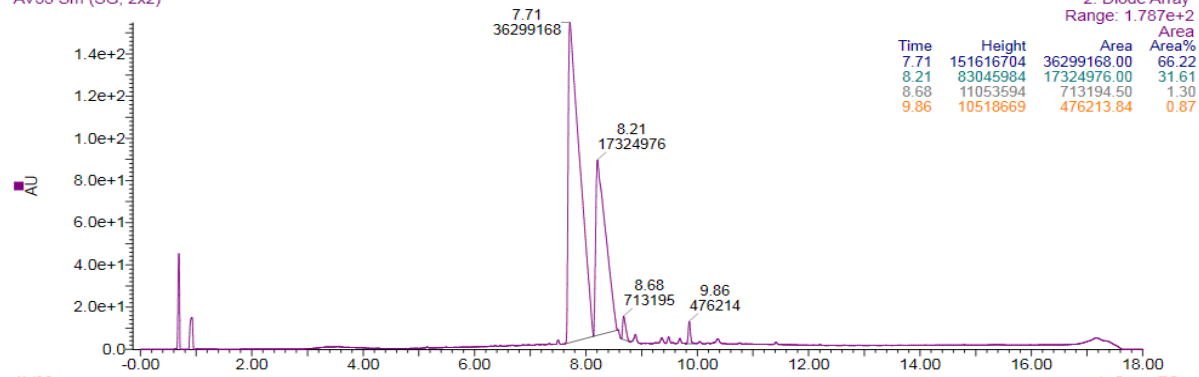
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AV23 493 (8.315) Cm (488:508)

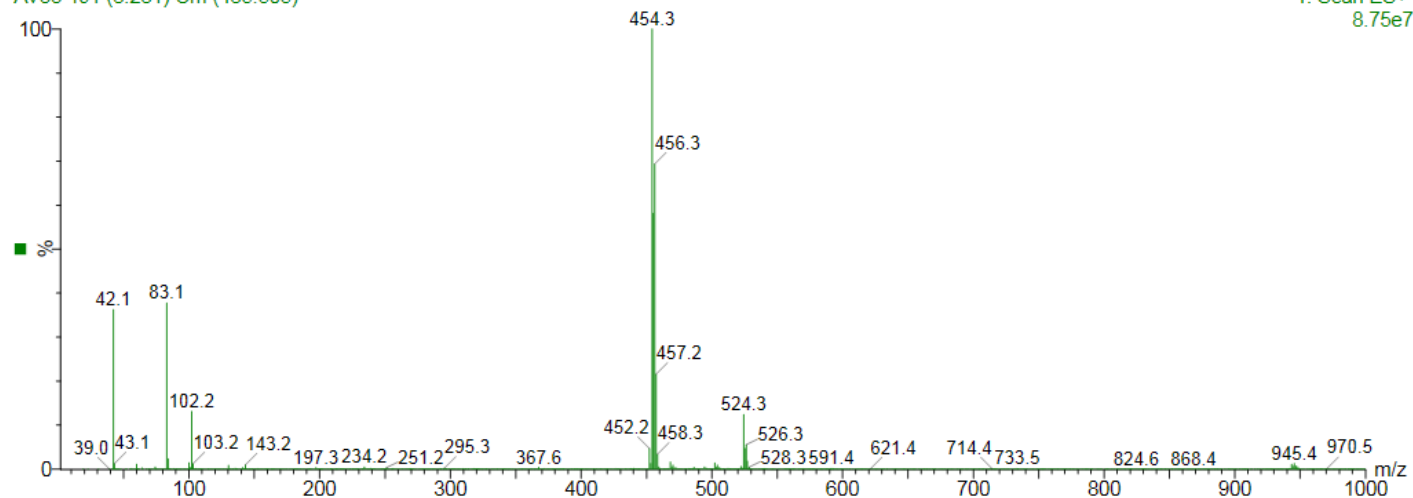


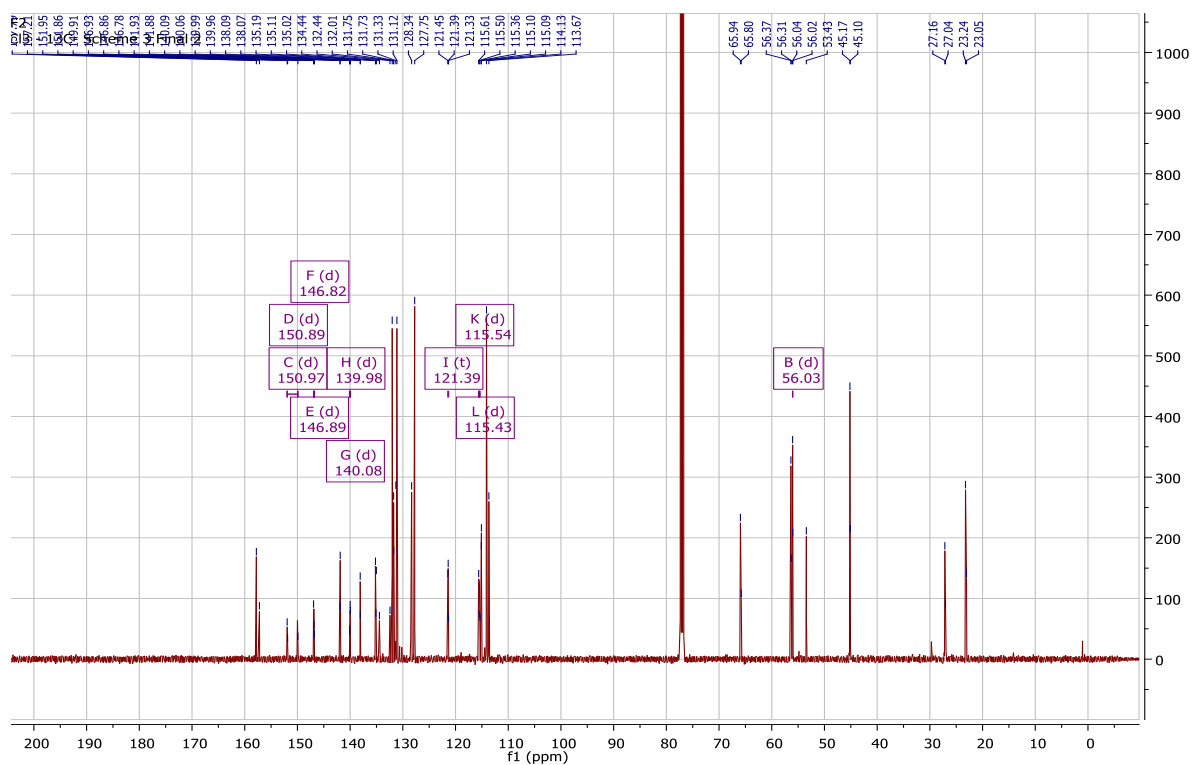
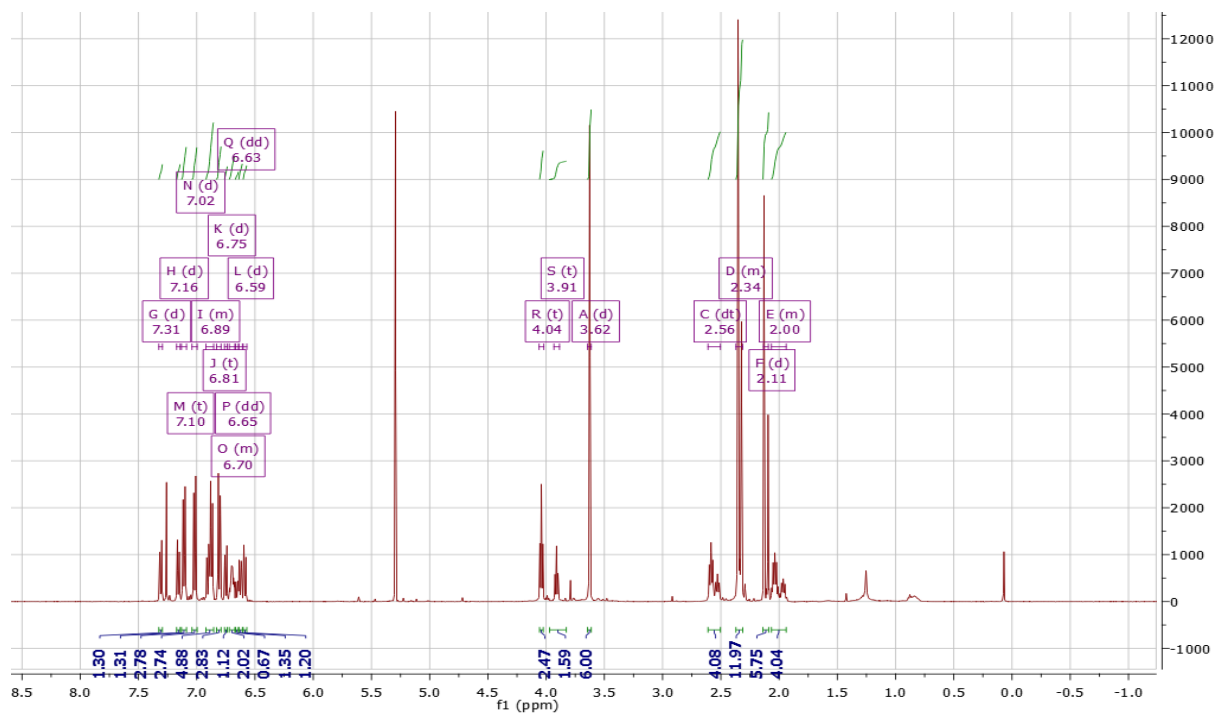


20-Nov-2018  
AV33 Sm (SG, 2x2)



20-Nov-2018 16:38:07  
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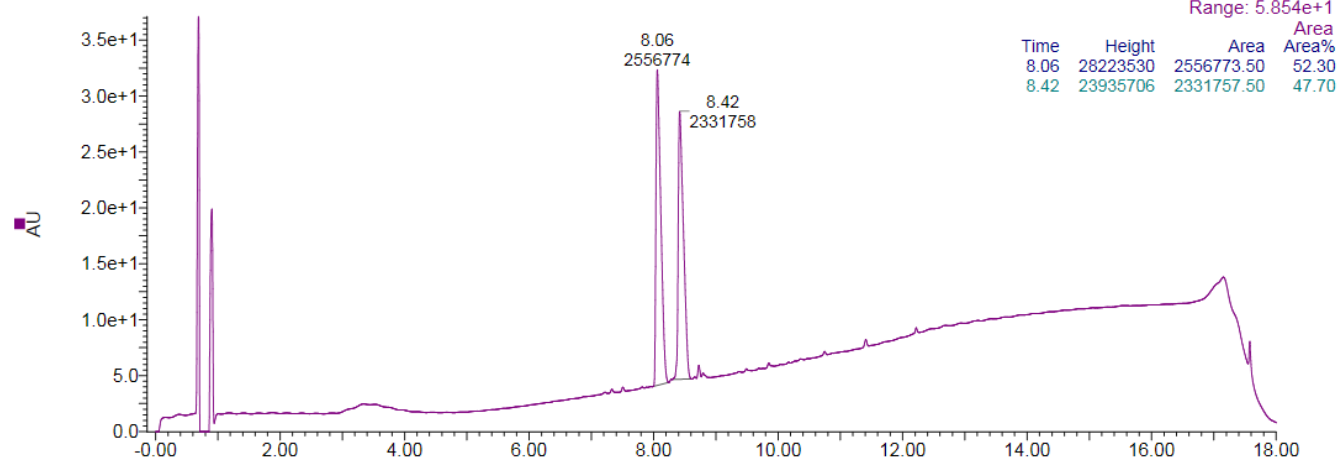




**E/Z -1-(2-{4-[1-(4-Chlorophenyl)-2-(4-fluoro-3-methoxyphenyl)-propenyl]-phenoxy}-ethyl)-pyrrolidine  
(23)**

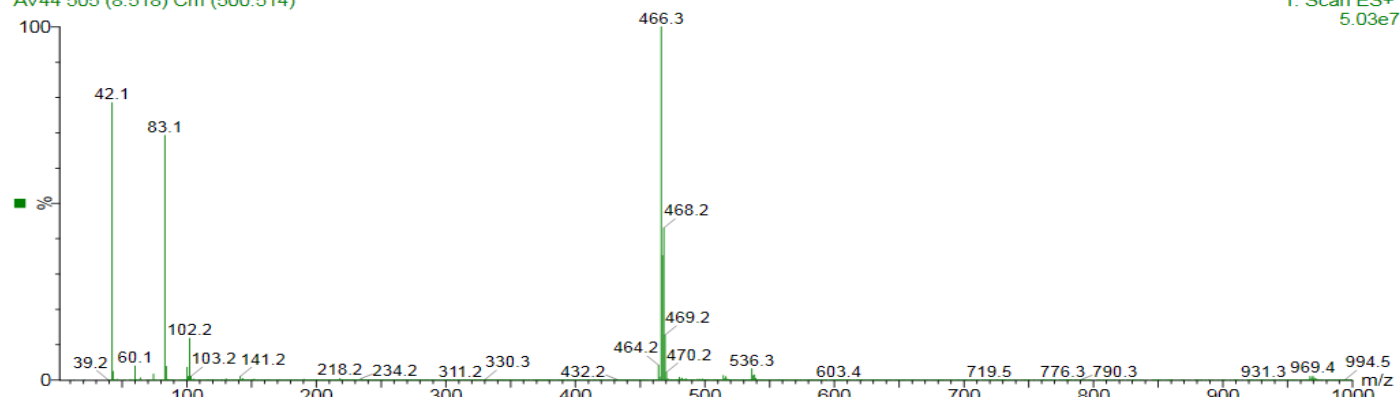
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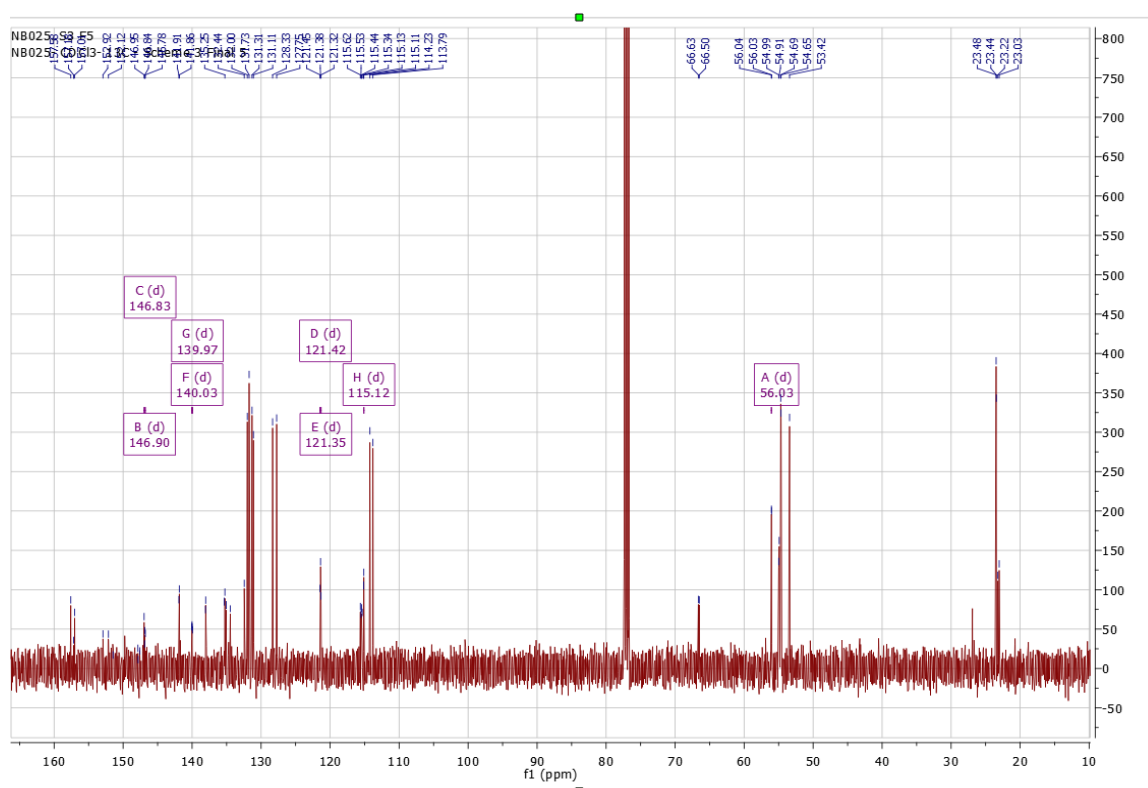


30-Nov-2018 13:28:27

AV44 505 (8.518) Cm (500:514)



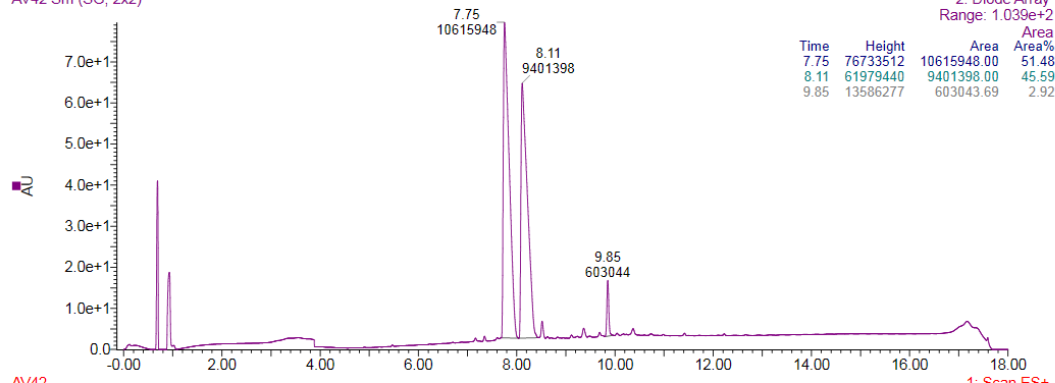




***E/Z*-4-(2-{4-[1-(4-Chlorophenyl)-2-(4-fluoro-3-methoxyphenyl)-propenyl]-phenoxy}ethyl)-morpholine  
(25)**

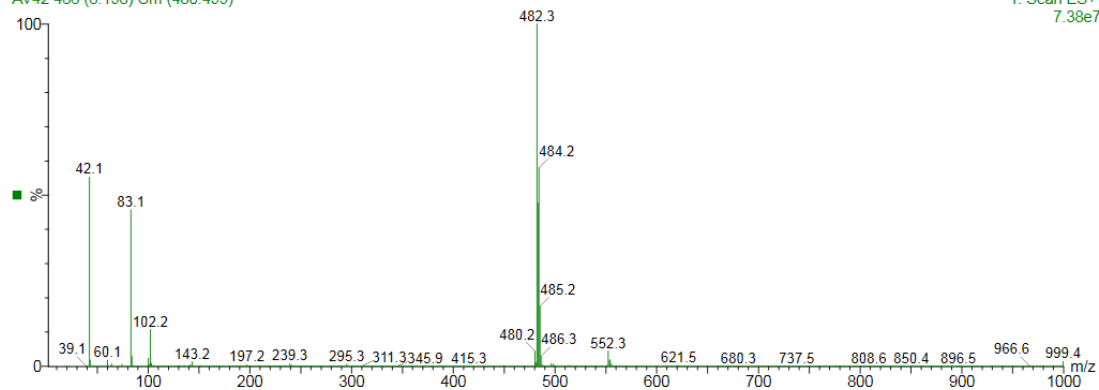
27-Nov-2018

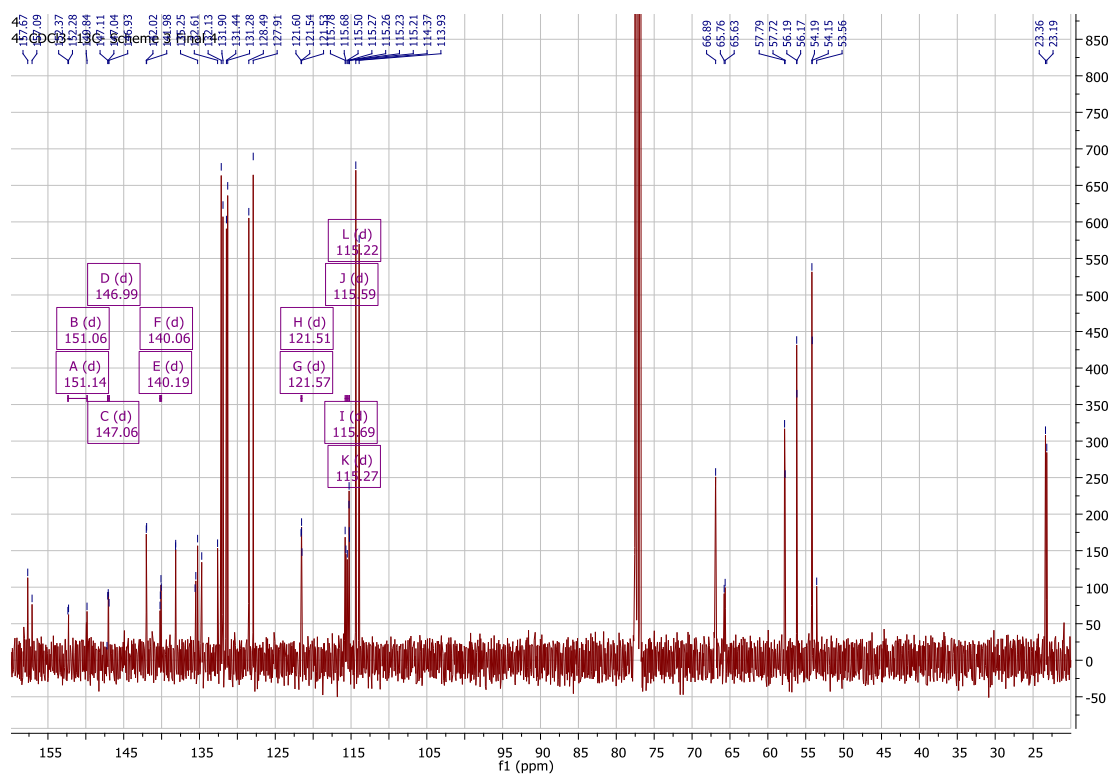
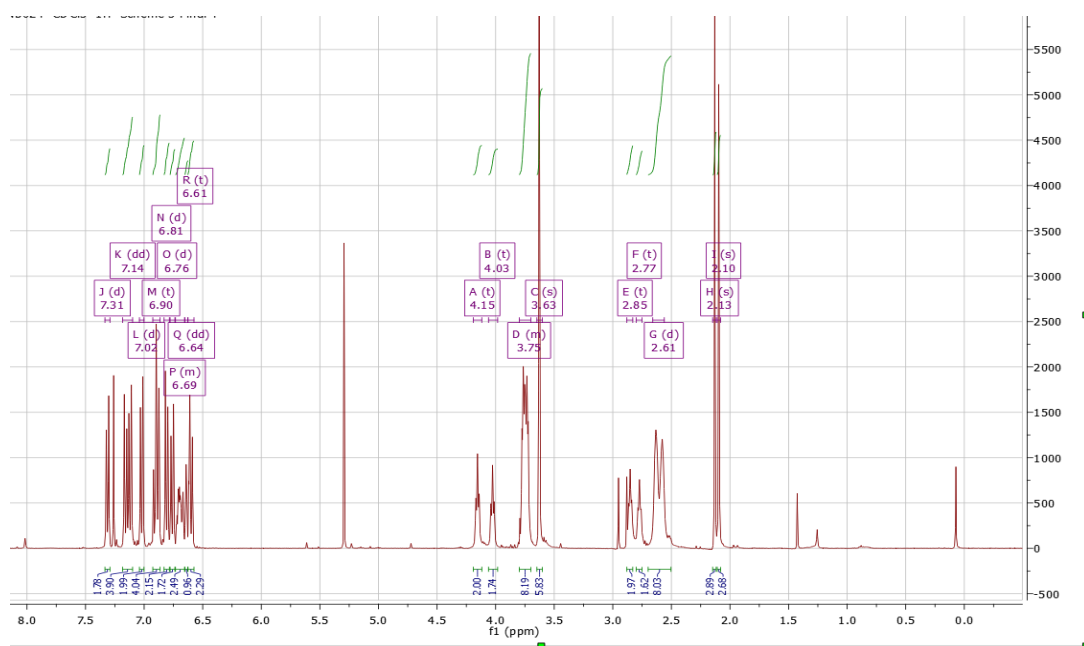
AV42 Sm (SG, 2x2)



27-Nov-2018 16:48:10

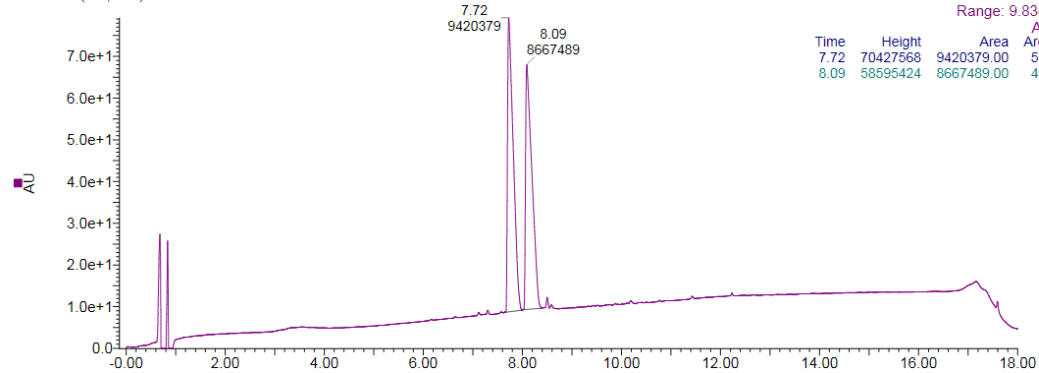
AV42 486 (8.198) Cm (480:499)



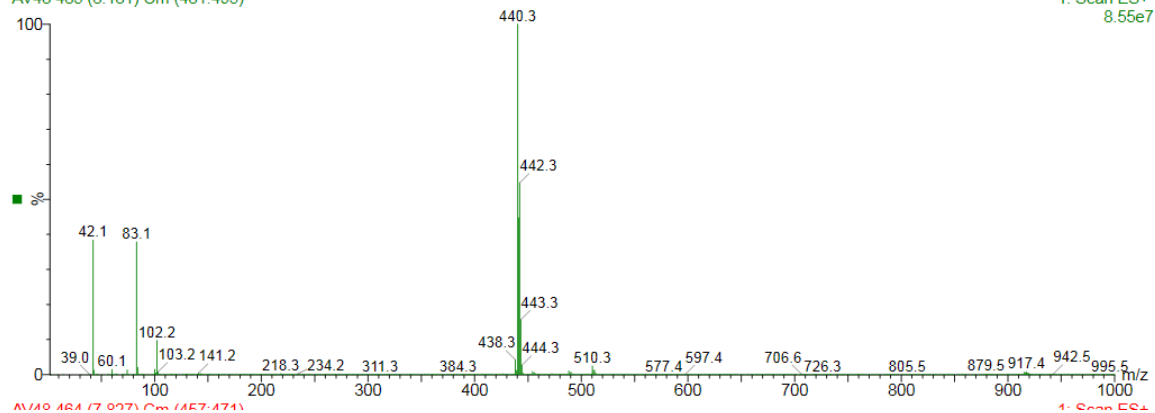


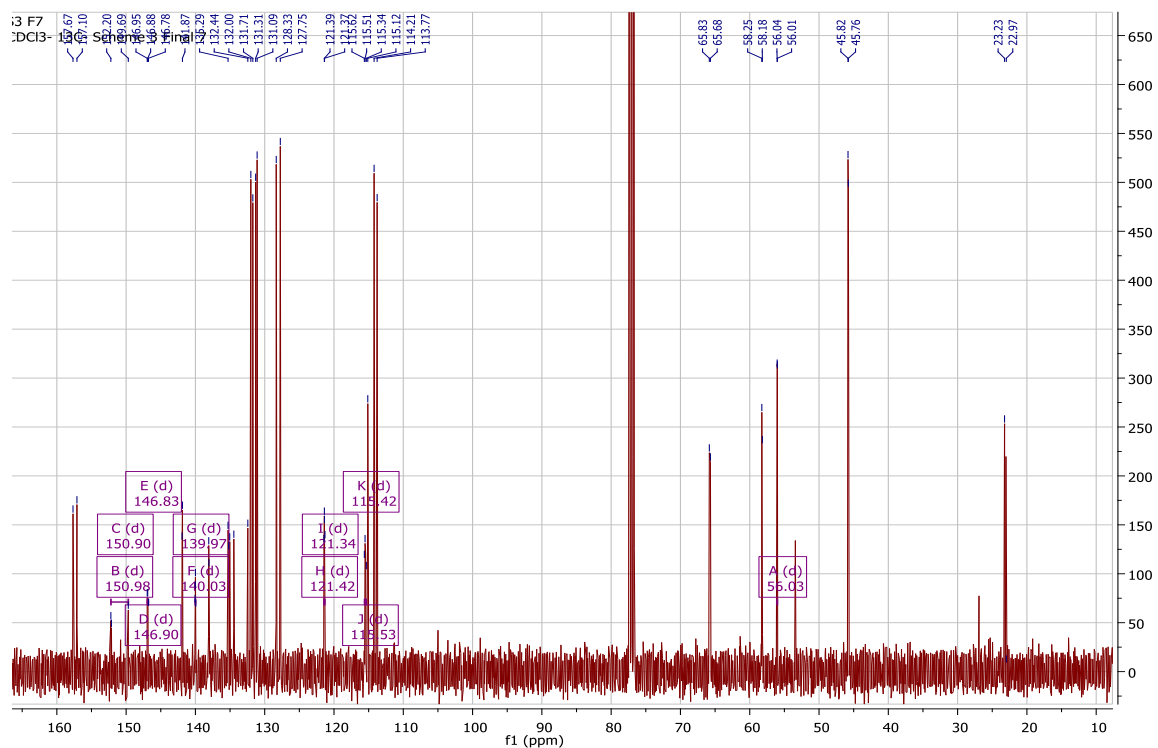
*E/Z*-2-{4-[1-(4-Chlorophenyl)-2-(4-fluoro-3-methoxyphenyl)-propenyl]-phenoxy}ethyl)-dimethyl-amine (27)

03-Dec-2018  
AV48 Sm (SG, 2x2)



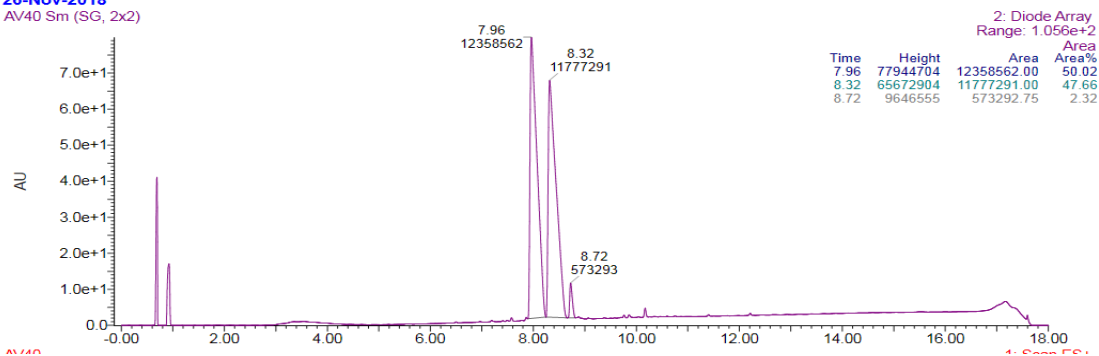
03-Dec-2018 09:36:41  
AV48 485 (8.181) Cm (481:495)



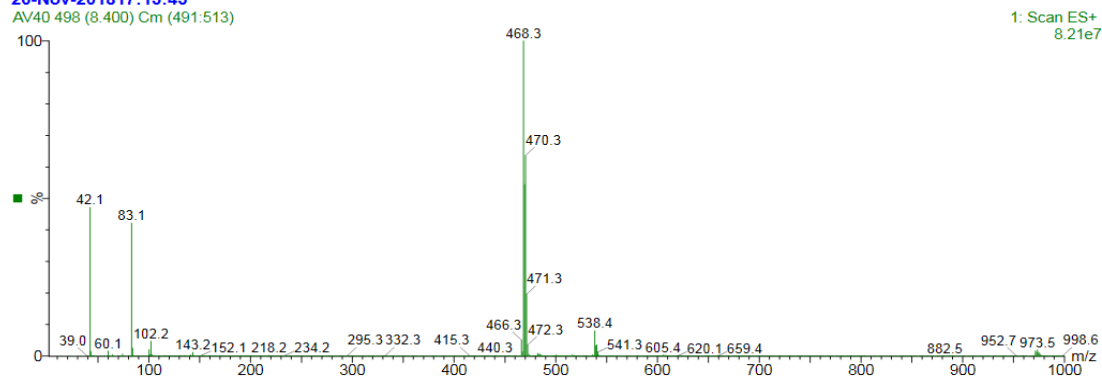


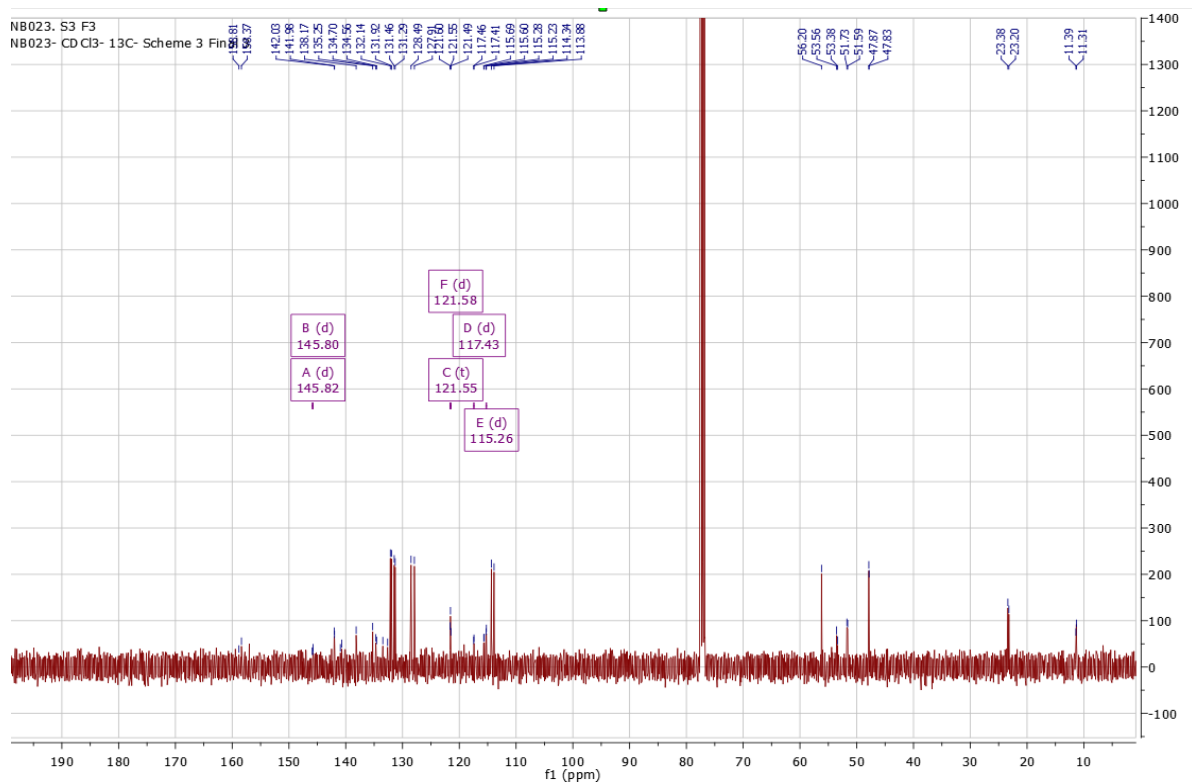
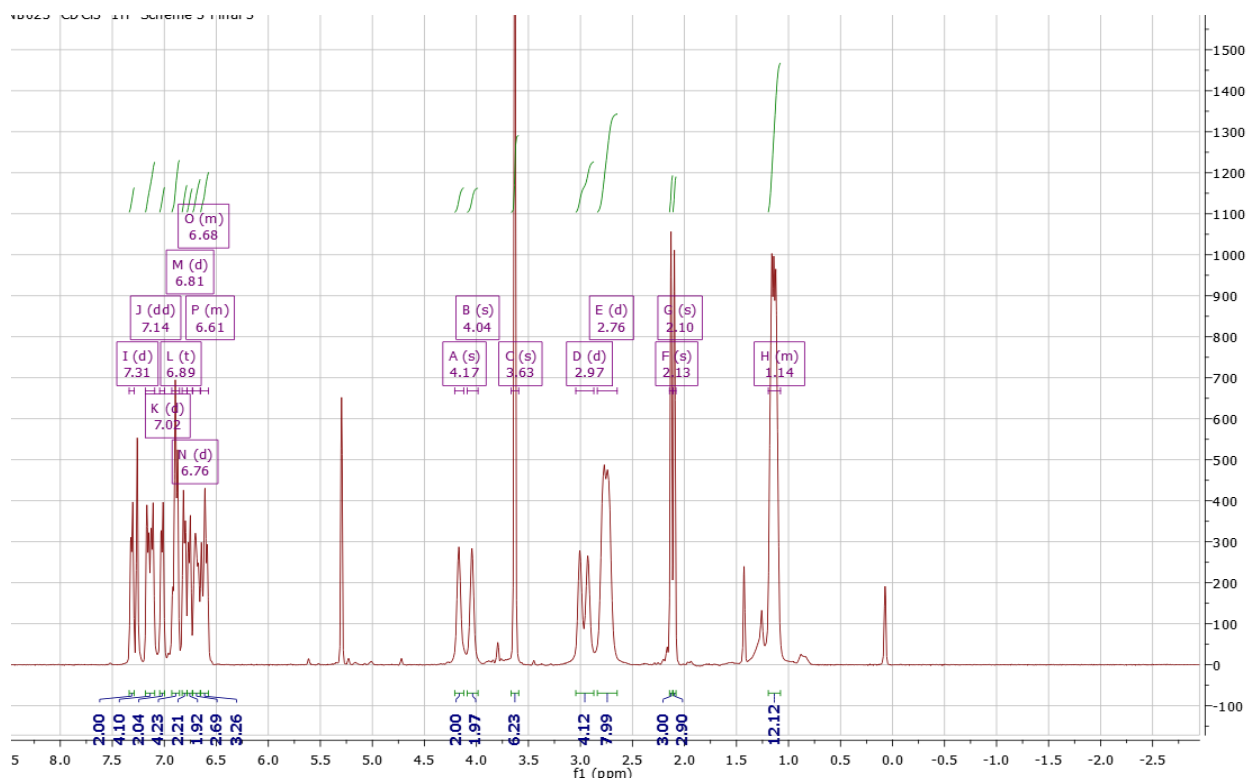
*E/Z*-(2-{4-[1-(4-Chlorophenyl)-2-(4-fluoro-3-methoxyphenyl)-propenyl]-phenoxy}-ethyl)-diethyl-amine (28).

26-Nov-2018  
AV40 Sm (SG, 2x2)

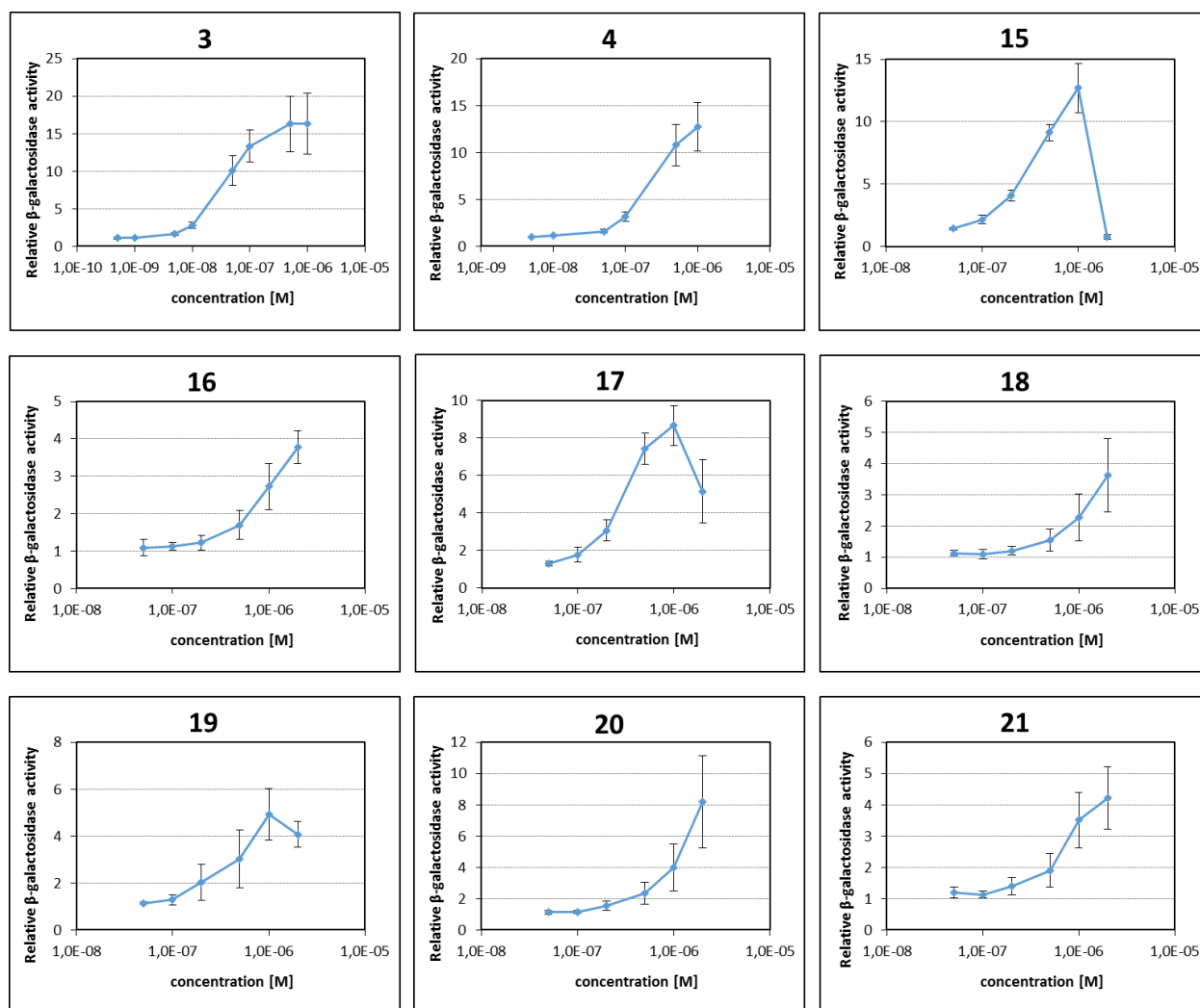


26-Nov-2018 17:13:43  
AV40 498 (8.400) Cm (491:513)





2. Dose response curves for to determine EC<sub>50</sub> values (agonistic activity) of selected compounds in YES assay, results of AlkP and uterotrophic assays

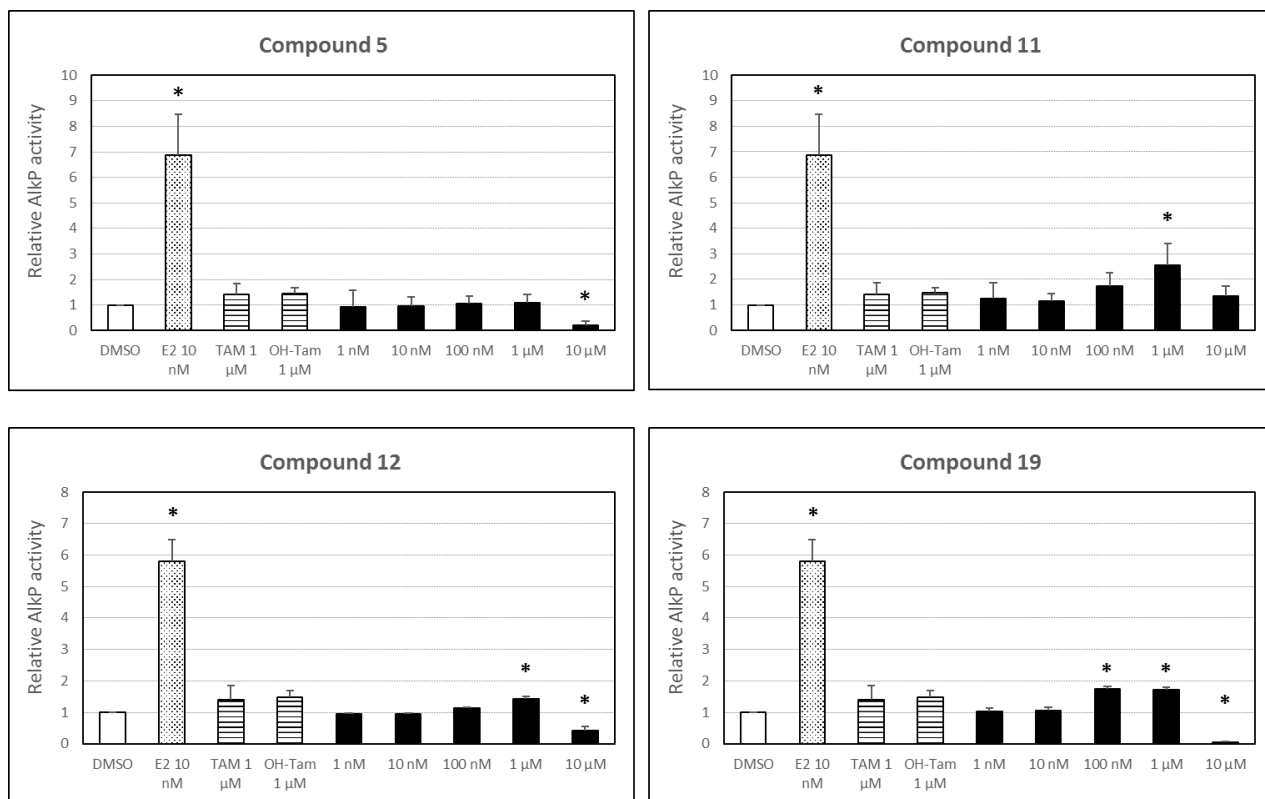


**Figure S1:** Relative  $\beta$ -galactosidase activity of selected compounds after two days treatment in YES assay. DMSO was used as solvent control and set to 1, mean  $\pm$  SD were calculated by three independent experiments.

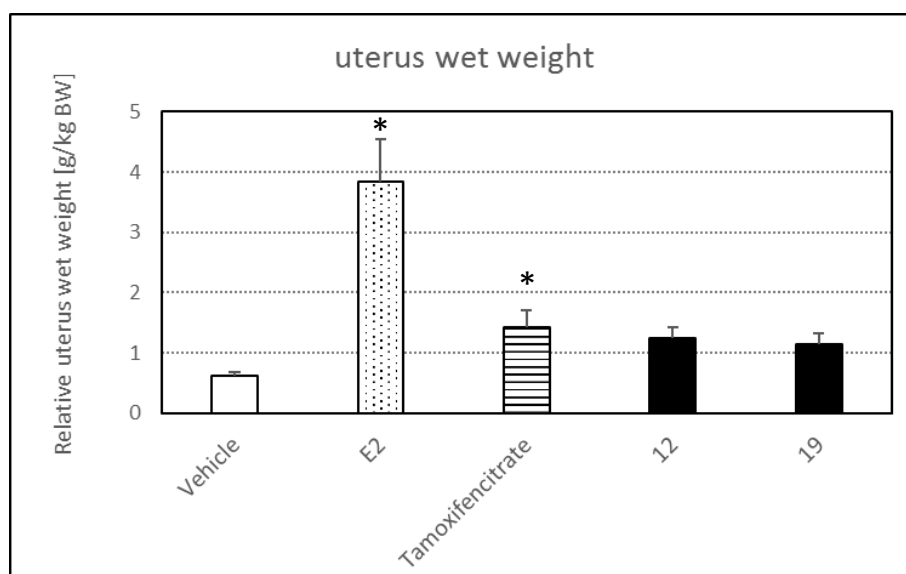


**Table S1:** Relative Alkaline phosphatase activity (AlkP) after an incubation of 72 h in Ishikawa cells, compounds are tested at a concentration of 1  $\mu$ M. DMSO was used as solvent control and set to 1, mean  $\pm$  SD were calculated by three independent experiments.

Code	Relative AlkP activity
	Mean $\pm$ SD
3	1.13 $\pm$ 0.43
4	1.10 $\pm$ 0.39
5	1.08 $\pm$ 0.33
6	2.55 $\pm$ 1.35
7	2.55 $\pm$ 1.80
8	1.16 $\pm$ 0.15
9	2.94 $\pm$ 1.29
10	2.55 $\pm$ 1.80
11	2.56 $\pm$ 0.83
12	1.43 $\pm$ 0.07
13	3.74 $\pm$ 2.05
14	6.58 $\pm$ 2.24
15	0.86 $\pm$ 0.12
16	0.98 $\pm$ 0.53
17	1.31 $\pm$ 0.41
18	1.01 $\pm$ 0.24
19	1.71 $\pm$ 0.08
20	1.12 $\pm$ 0.46
21	0.90 $\pm$ 0.13
22-28	Compounds were not selected for AlkP assay because of their low estrogenic effects in YES assay



**Figure S2:** Relative Alkaline phosphatase activity (AlkP) for compounds **5**, **11**, **12**, **19** after three days treatment in human endometrial adenocarcinoma Ishikawa cells. DMSO was used as solvent control and set to 1, mean  $\pm$  SD were calculated by three independent experiments. Tam and 4-OH-Tam (1  $\mu$ M) were tested for comparison. \*  $p < 0.05$  versus DMSO control (Tukey test)



**Figure S3:** Relative uterus wet weight following a three days treatment of ovariectomized rats (vehicle = control) with E2 (10  $\mu$ g/kg BW/ day), TAM (10 mg/kg BW/ day), compound **12** (10 mg/kg BW/ day), and compound **19** (10 mg/kg BW/ day). \*  $p < 0.05$  versus control (Tukey test)

**Figure S4:** DTP log (GI<sub>50</sub>, TGI, LC<sub>50</sub>)  $\mu$ M TAM (NSC 180973)

### GI<sub>50</sub> Mean Graph for Compound 180973

NCI Cancer Screen Current Data

Average GI<sub>50</sub> over all cell lines is 3.94E-6 M

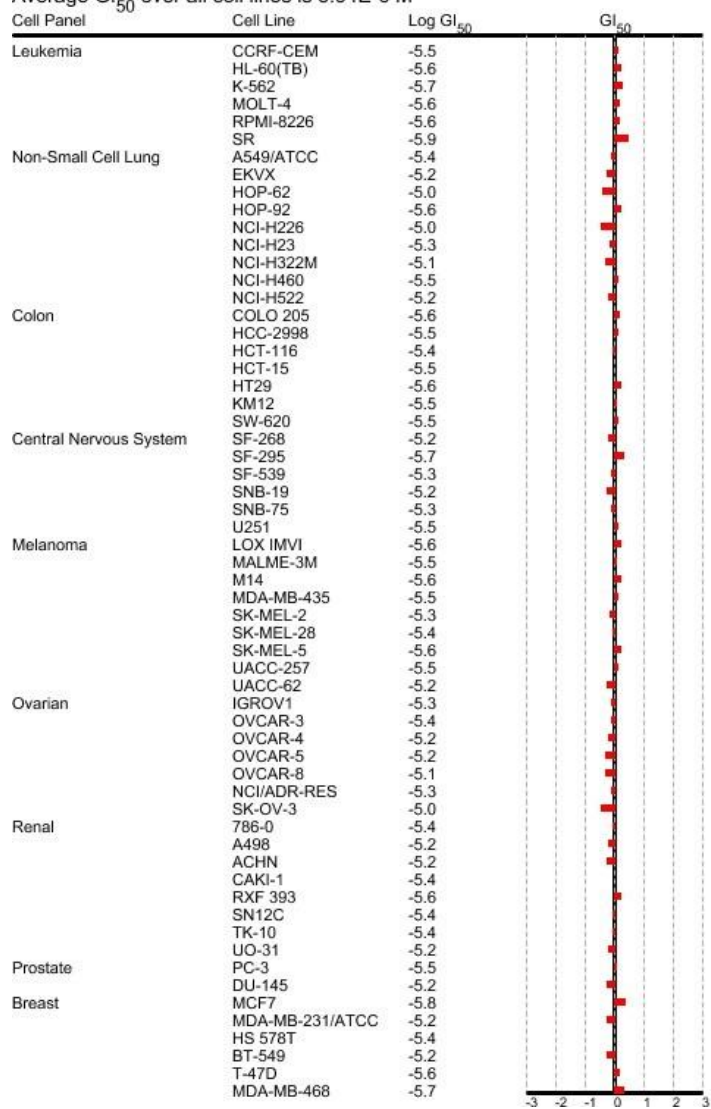


Figure S5: Dose response curves compound 11 on different subpanels ( $\mu\text{M}$ )

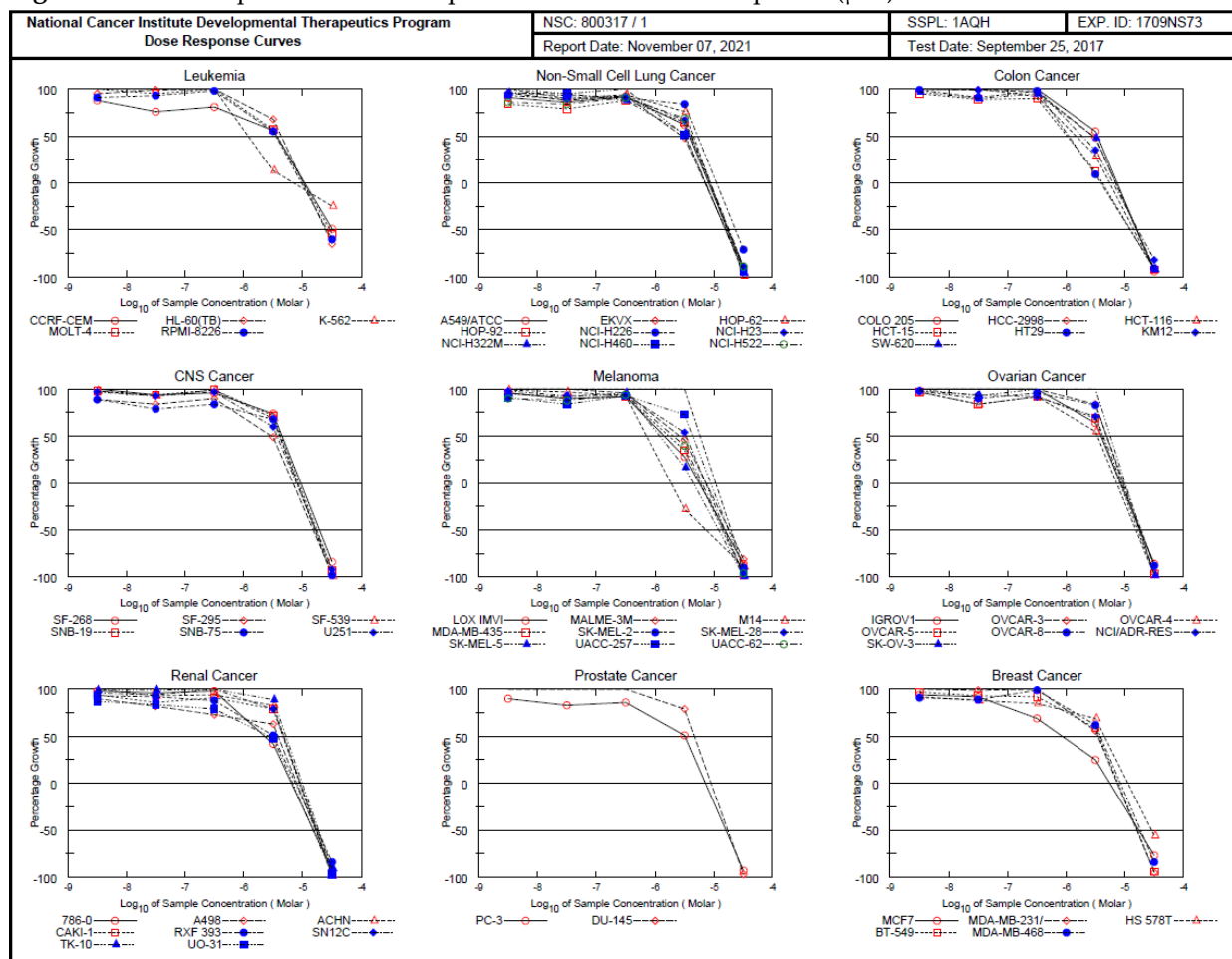


Figure S6: Dose response curves compound 12 on different subpanels ( $\mu\text{M}$ )

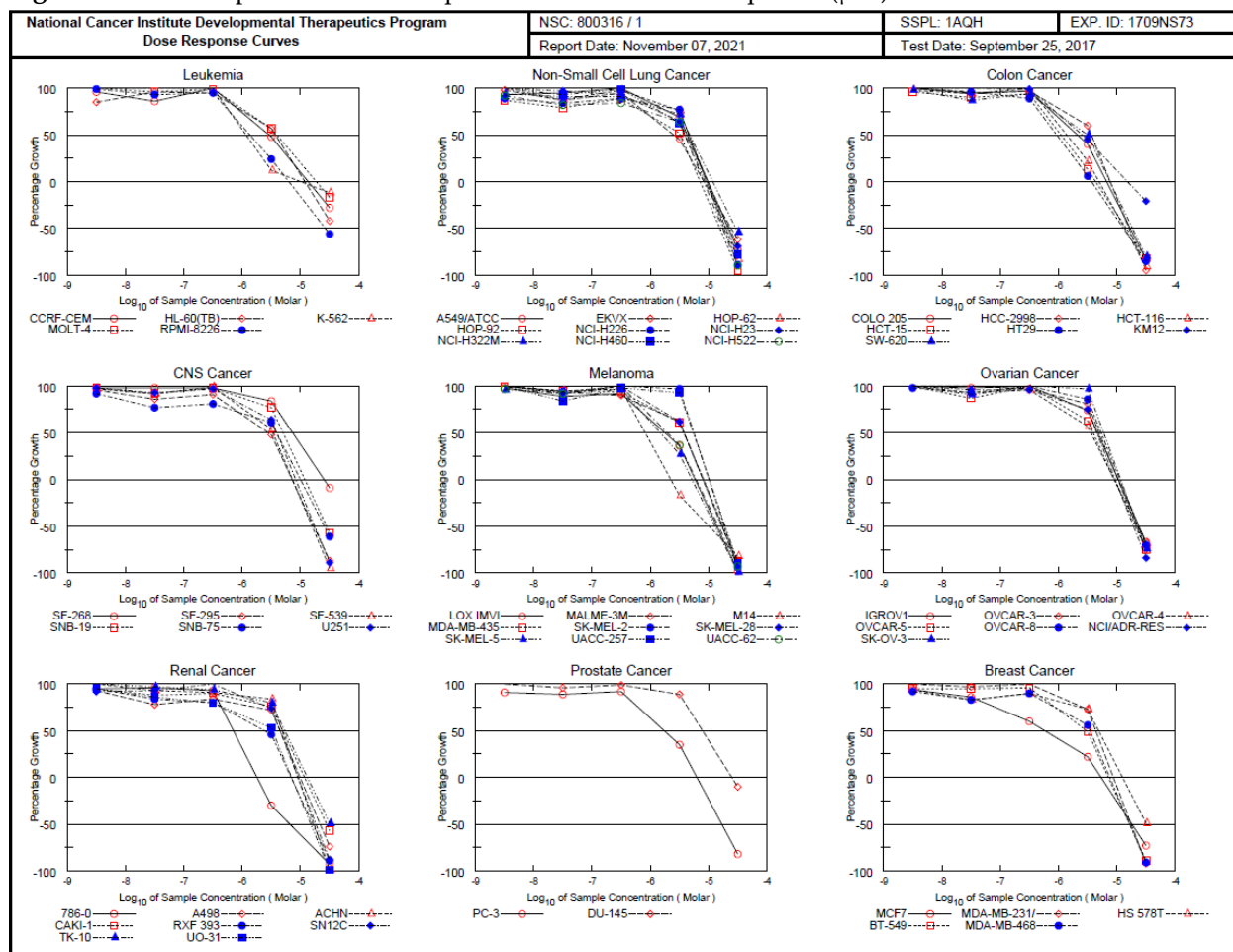


Figure S7: Dose response curves compound 16 on different subpanels ( $\mu\text{M}$ )

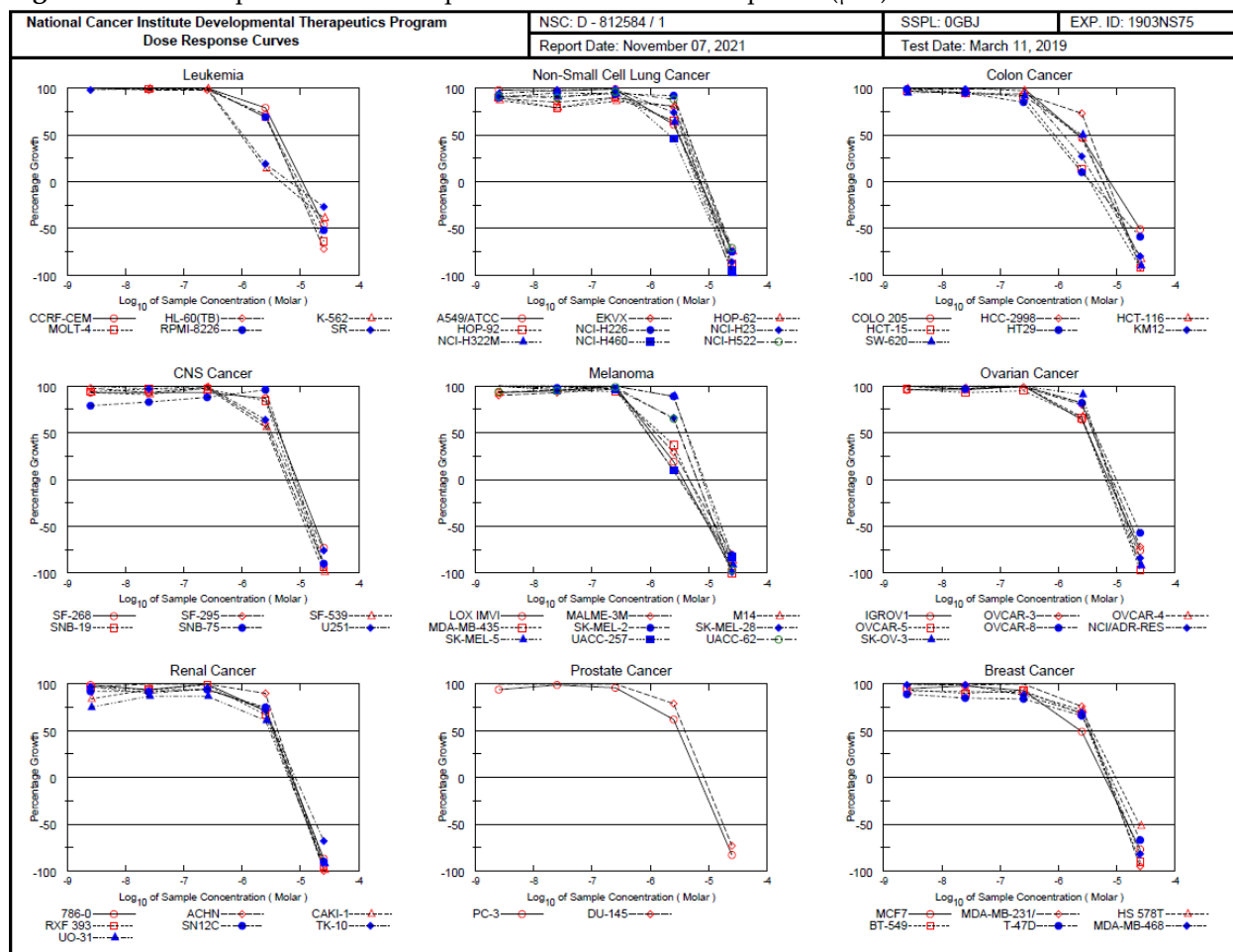
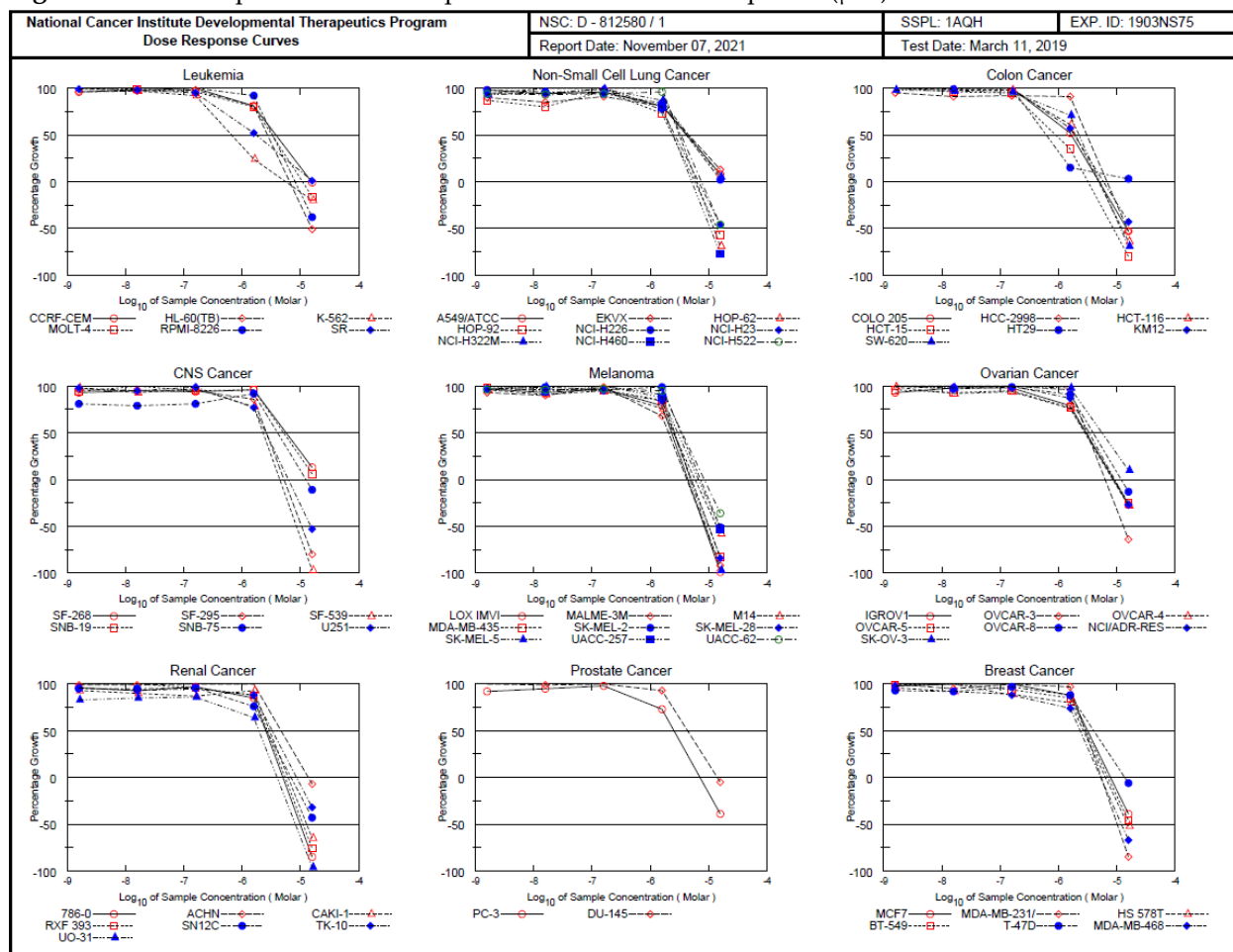
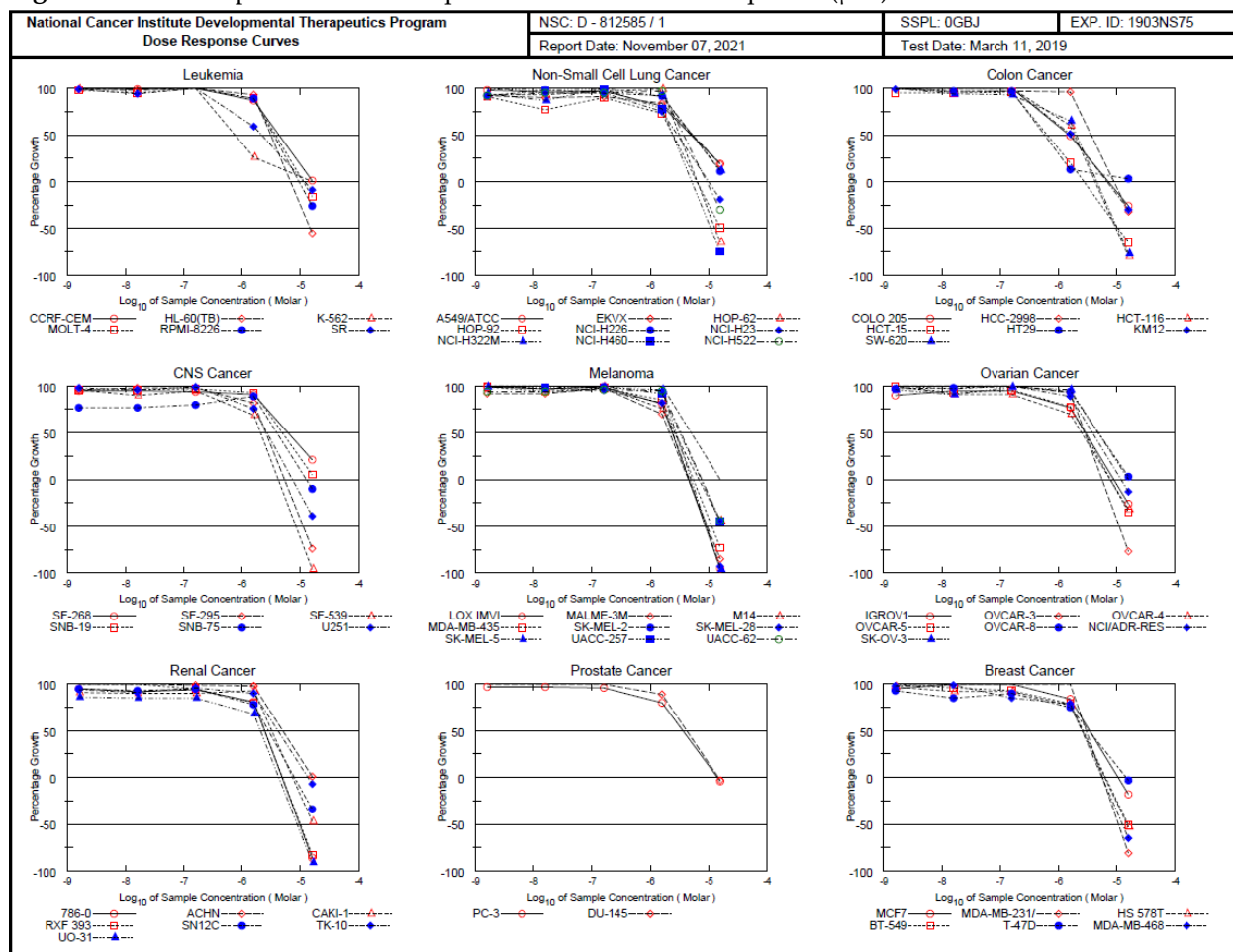


Figure S8: Dose response curves compound 17 on different subpanels ( $\mu\text{M}$ )





**Figure S9:** Dose response curves compound 19 on different subpanels ( $\mu\text{M}$ )



**Figure S10:** Dose response curves compound 19 on different subpanels ( $\mu\text{M}$ )

