

Electronic Supplementary Information (ESI)

Molecular formula, purity, calculated mass, m/3z and m/2z measured of macrocyclic apelin analogs.

Structure-activity relationship of novel macrocyclic biased apelin receptor agonists

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[§] These authors contributed equally to directing this study.

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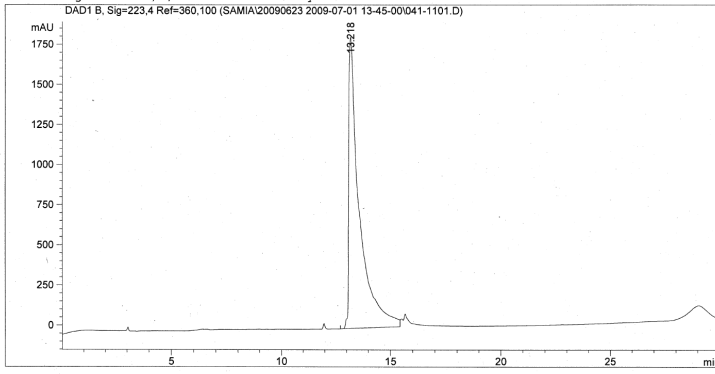
Email: eric.marsault@usherbrooke.ca

N°	Sequence ^a	Mol. formula	Purity %	Calculated mass	m/2z measured ^b	m/3z or m/z measured ^b
Ape13	Pyr-R-P-R-L-S-H-K-G-P-M-P-F	C ₆₉ H ₁₀₈ N ₂₂ O ₁₆ S	100	1532.8035	767.6	512.0
1	R-P-R-L-S- AllylGly -K-G-P- AllylGly -F	C ₅₆ H ₉₀ N ₁₈ O ₁₃	100	1223.4490	613.2	409.5
2	R-P-R-L-S- AllylGly -K-G-P- AllylGly -Tyr(OBn)	C ₆₃ H ₉₆ N ₁₈ O ₁₄	95.0	1329.5730	666.4	444.9
3	R-P-R-L-S- AllylGly -K-G-P- AllylGly -A	C ₅₀ H ₈₆ N ₁₈ O ₁₃	100	1147.3510	575.2	384.0
4	R-P-R-L-S- AllylGly -K-G-P- AllylGly	C ₄₇ H ₈₁ N ₁₇ O ₁₂	100	1076.2720	539.7	360.3
5	R-P-R-L-S- AllylGly -K-G-Tyr(OBn)-P- AllylGly	C ₆₃ H ₉₆ N ₁₈ O ₁₄	99.6	1329.5730	665.8	444.2
6	R-P-R-L-S- AllylGly -K-Tyr(OBn)-G-P- AllylGly	C ₆₃ H ₉₆ N ₁₈ O ₁₄	100	1329.5730	665.7	444.2
7	R-P-R-L-S- AllylGly -K-G-P- AllylGly -P-Tyr(OBn)	C ₆₈ H ₁₀₃ N ₁₉ O ₁₅	100	1426.6900	714.1	476.5
8	R-P-R-L-S- AllylGly -K-G-P- AllylGly -βAla-Tyr(OBn)	C ₆₆ H ₁₀₁ N ₁₉ O ₁₅	100	1400.6520	701.1	467.8
9	R-P-R-L-S- AllylGly -K-G-P- AllylGly -γAbu-Tyr(OBn)	C ₆₇ H ₁₀₃ N ₁₉ O ₁₅	100	1414.6790	708.8	473.1
10	R-P-R-L-S- AllylGly -K-G-P- AllylGly -A-Tyr(OBn)	C ₆₆ H ₁₀₁ N ₁₉ O ₁₅	100	1400.6520	701.2	467.8
11	R-P-R-L-S- AllylGly -[8-aminocaprylic]- AllylGly -P-Tyr(OBn)	C ₆₃ H ₉₆ N ₁₆ O ₁₃	99.3	1285.5600	643.8	459.6
12	R-P-R-L-S- AllylGly -βAla-βAla- AllylGly -Tyr(OBn)	C ₅₆ H ₈₄ N ₁₆ O ₁₃	97.5	1189.3870	596.2	460.0
13	R-P-R-L-S- AllylGly -βAla-βAla- AllylGly -P-Tyr(OBn)	C ₆₁ H ₉₁ N ₁₇ O ₁₄	100	1286.5040	644.7	430.3
14	R-P-R-L-S- AllylGly -Nle-G-P- AllylGly -Tyr(OBn)	C ₆₃ H ₉₅ N ₁₇ O ₁₄	99.5	1314.5580	658.7	439.7
15	K-P-K-L-S- AllylGly -K-G-P- AllylGly -Tyr(OBn)	C ₆₃ H ₉₆ N ₁₄ O ₁₄	100	1273.5450	638.1	425.9
16	Orn-P-Orn-L-S- AllylGly -K-G-P- AllylGly -Tyr(OBn)	C ₆₁ H ₉₂ N ₁₄ O ₁₄	99.5	1245.4910	623.7	1245.7 (m/z)
17	R-L-S- AllylGly -K-G-P- AllylGly -Tyr(OBn)	C ₅₂ H ₇₇ N ₁₃ O ₁₂	100	1076.2670	539.2	1076.8 (m/z)
18	AllylGly -K-G-P- AllylGly -Tyr(OBn)	C ₃₇ H ₄₉ N ₇ O ₈	100	719.8400	361.0	720.6 (m/z)
19	Pyr-R-P-R-L-S- AllylGly -K-G-P- AllylGly -Tyr(OBn)	C ₆₈ H ₁₀₁ N ₁₉ O ₁₆	100	1440.6730	721.8	481.8
20	Ac-R-P-R-L-S- AllylGly -K-G-P- AllylGly -Tyr(OBn)	C ₆₅ H ₉₈ N ₁₈ O ₁₅	98.3	1371.6100	687.2	458.7
21	Des-amino-R-P-R-L-S- AllylGly -K-G-P- AllylGly -Tyr(OBn)	C ₆₃ H ₉₅ N ₁₇ O ₁₄	95.7	1314.5580	658.6	439.8

^a AllylGly residues in bold are cyclized via the olefin metathesis reaction, also called Ring Closing Metathesis (RCM) reaction.

^b Sometimes, the m/z signal of the macrocyclic analogues was not observed, consistently with the presence of several positively charged residues.

Ape13: Pyr-R-P-R-L-S-H-K-G-P-M-P-F



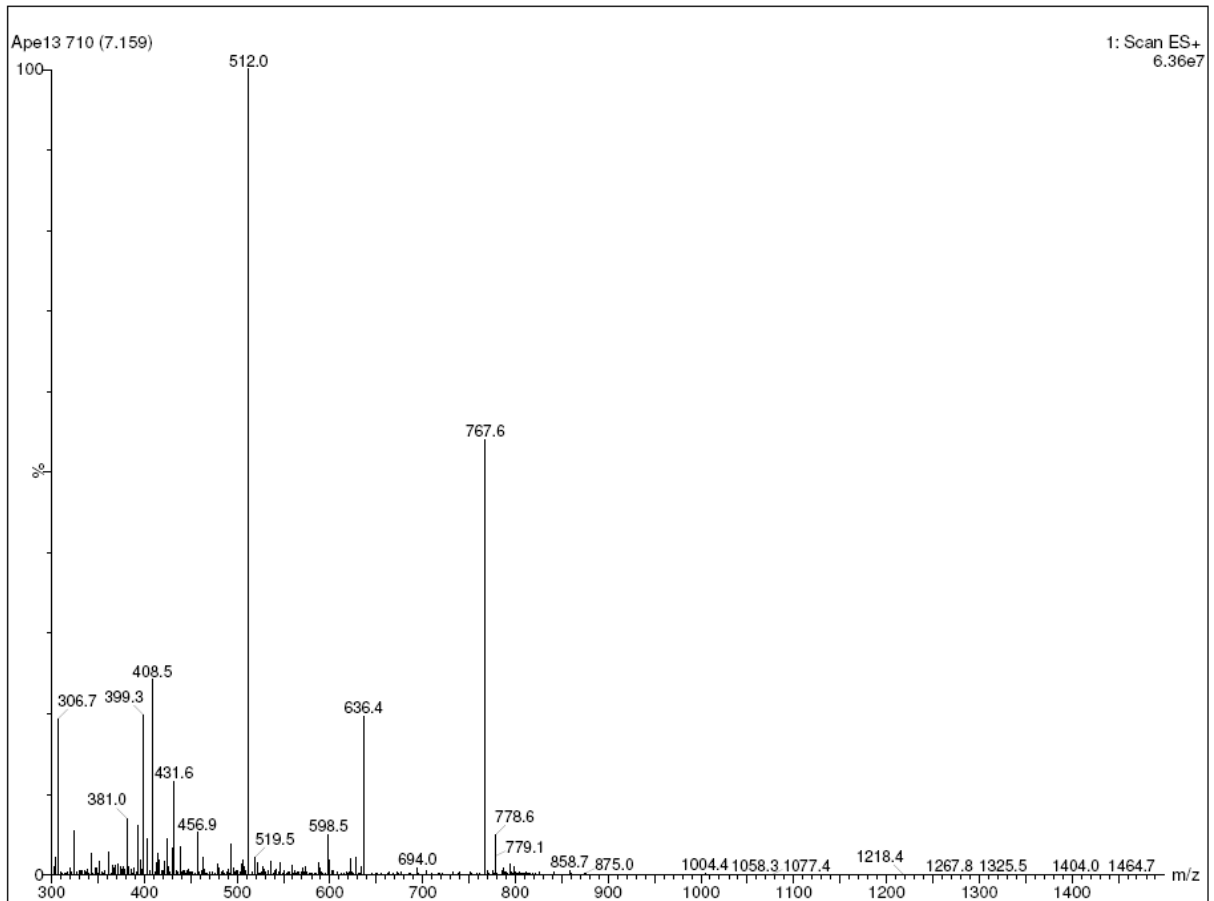
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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

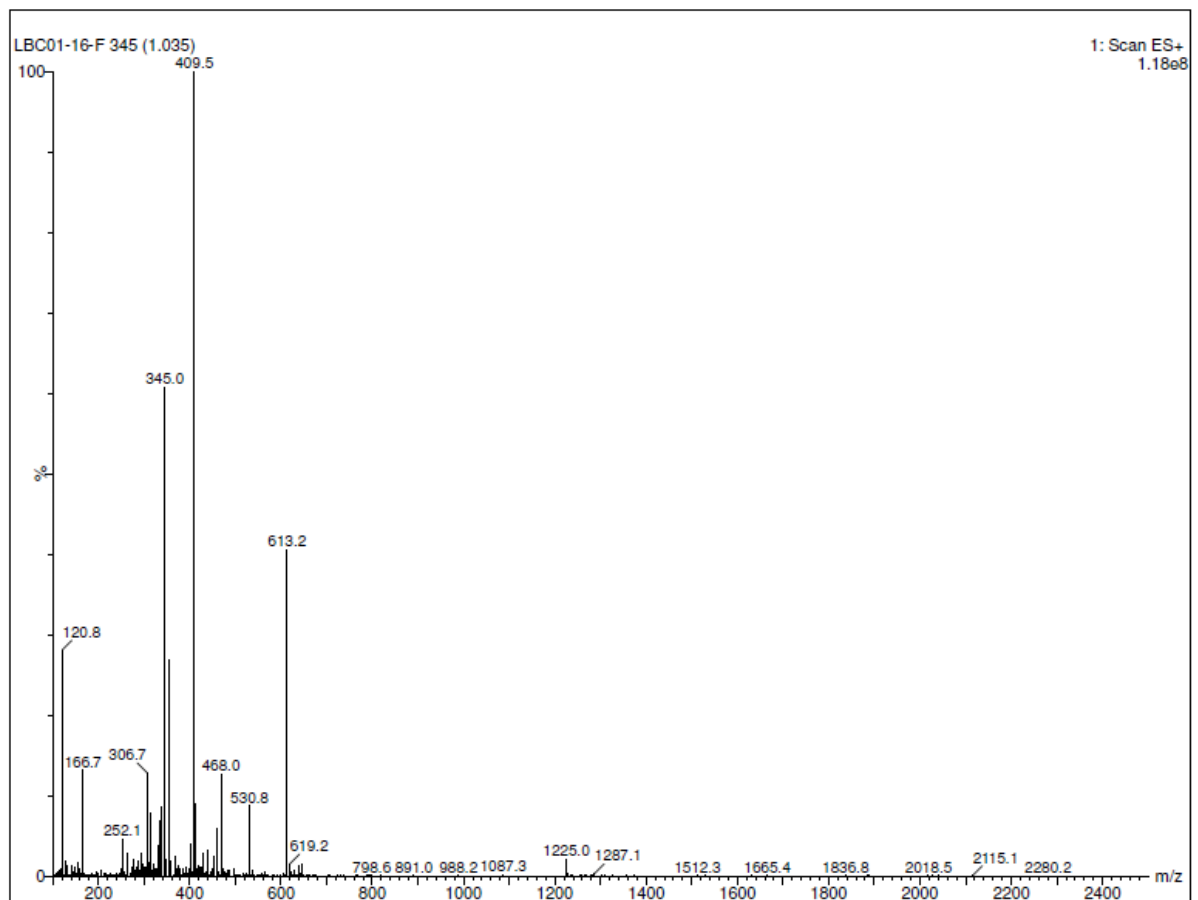
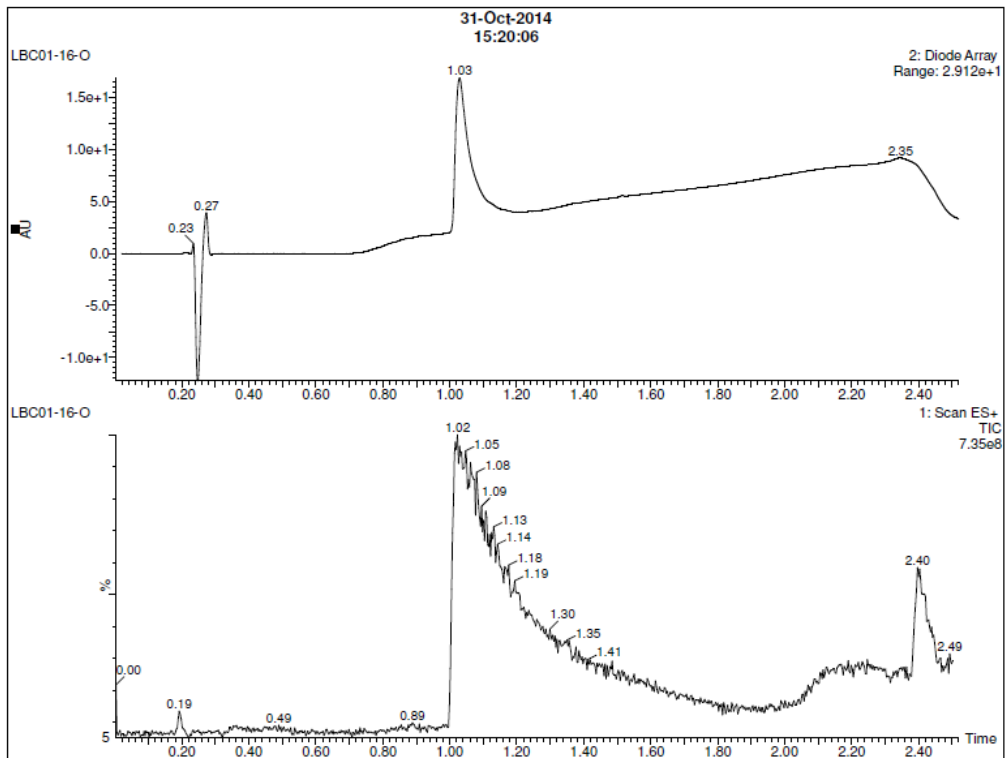
Signal 1: DAD1 B, Sig=223,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.218	BV	0.4536	6.06405e4	1816.00732	100.0000

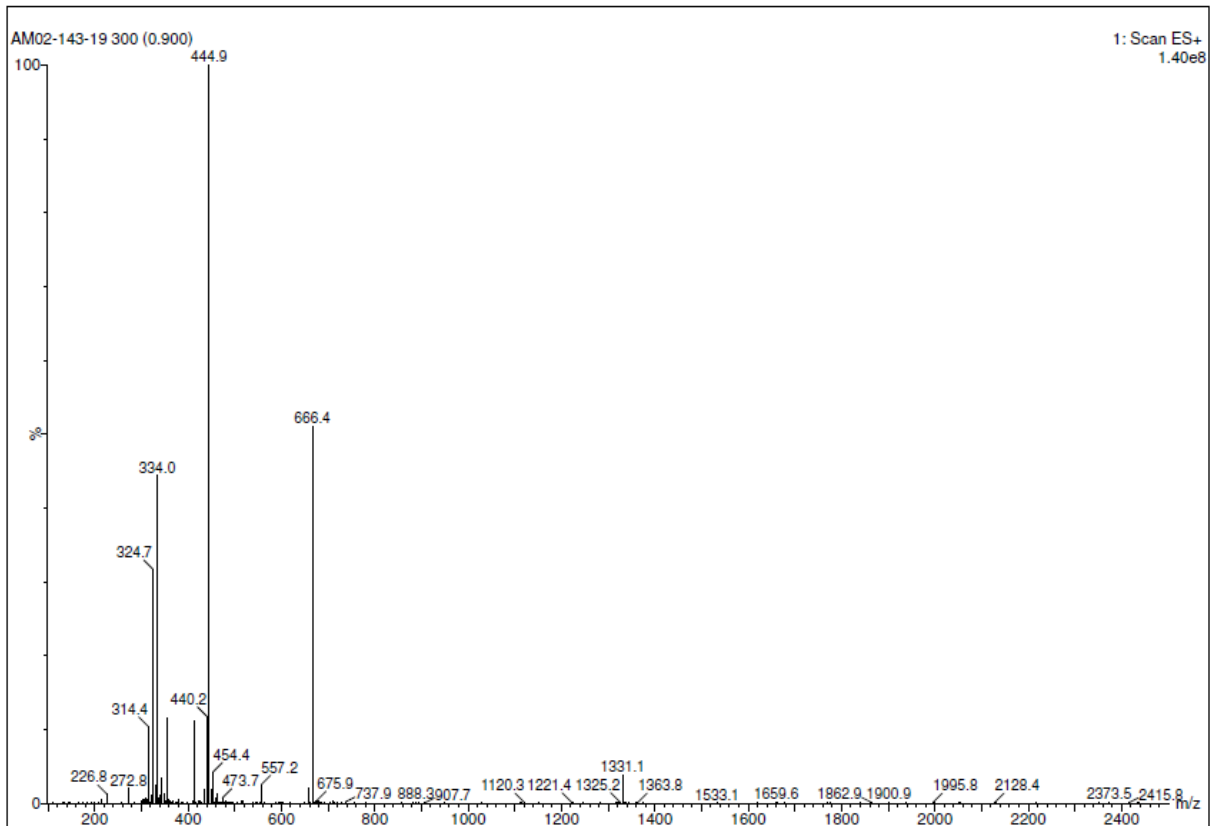
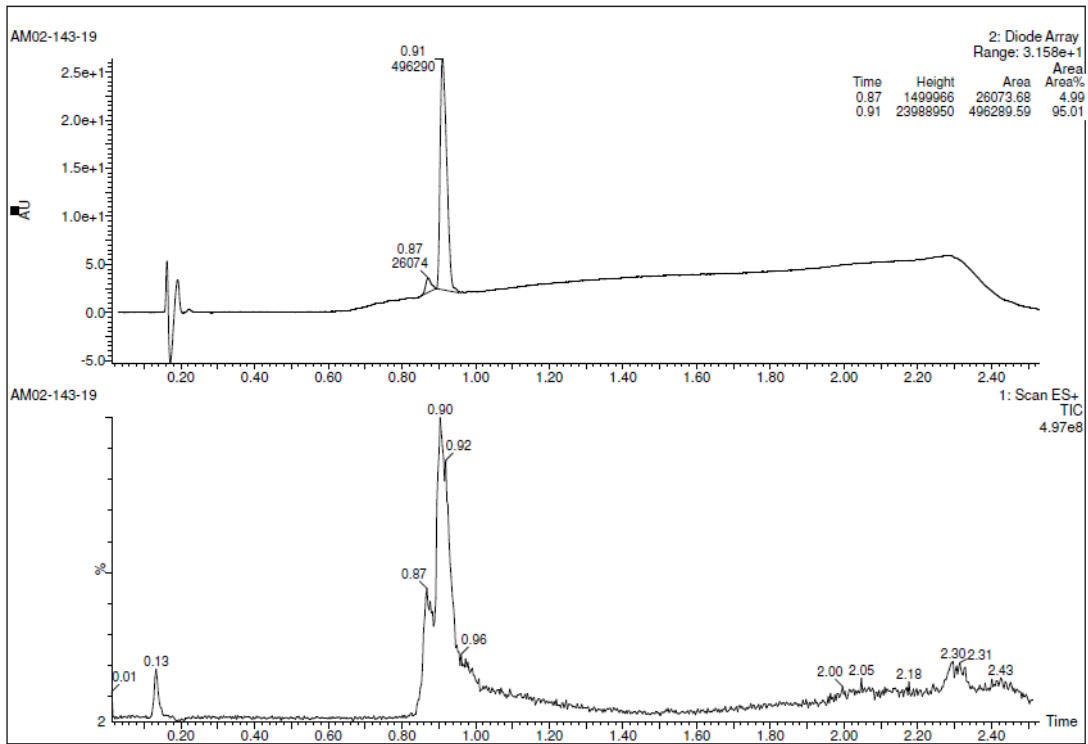
Totals : 6.06405e4 1816.00732



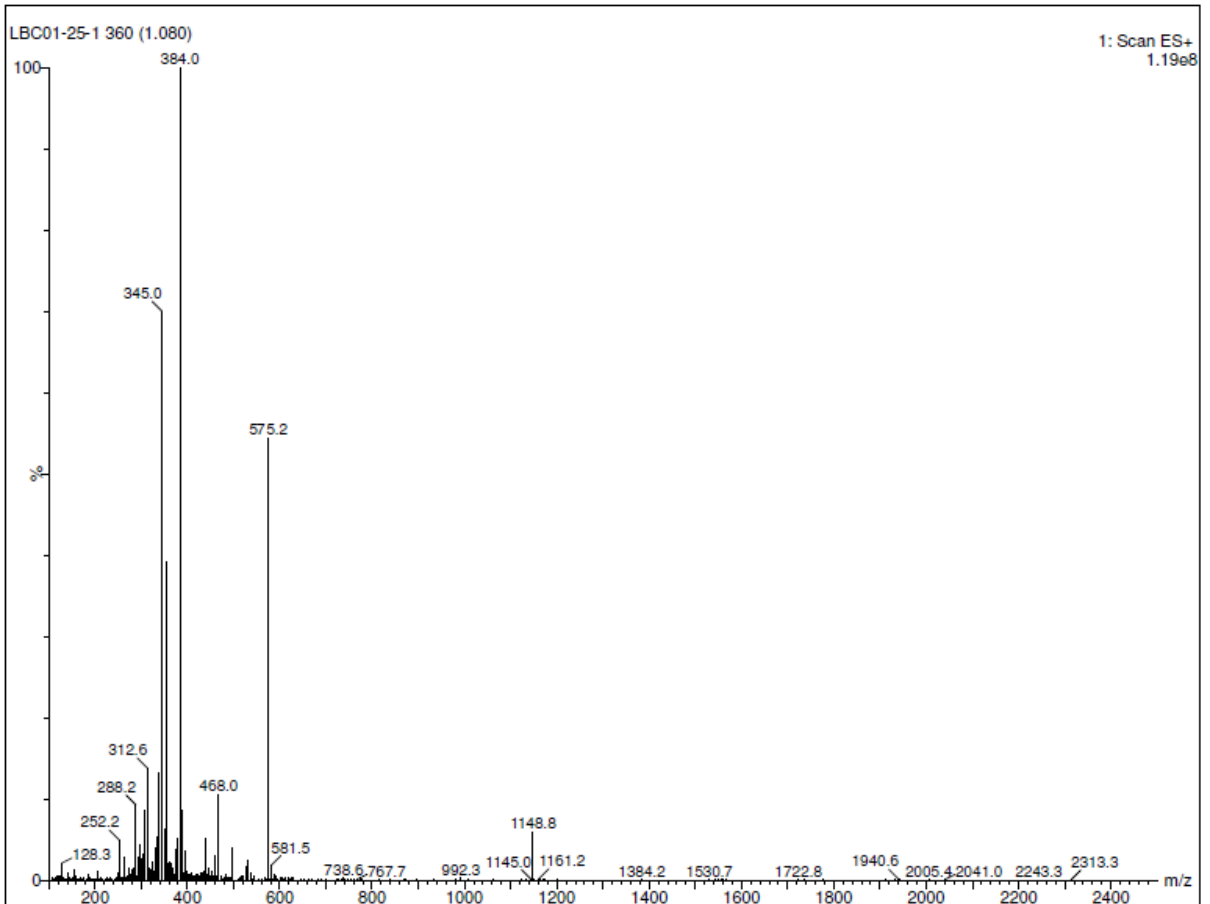
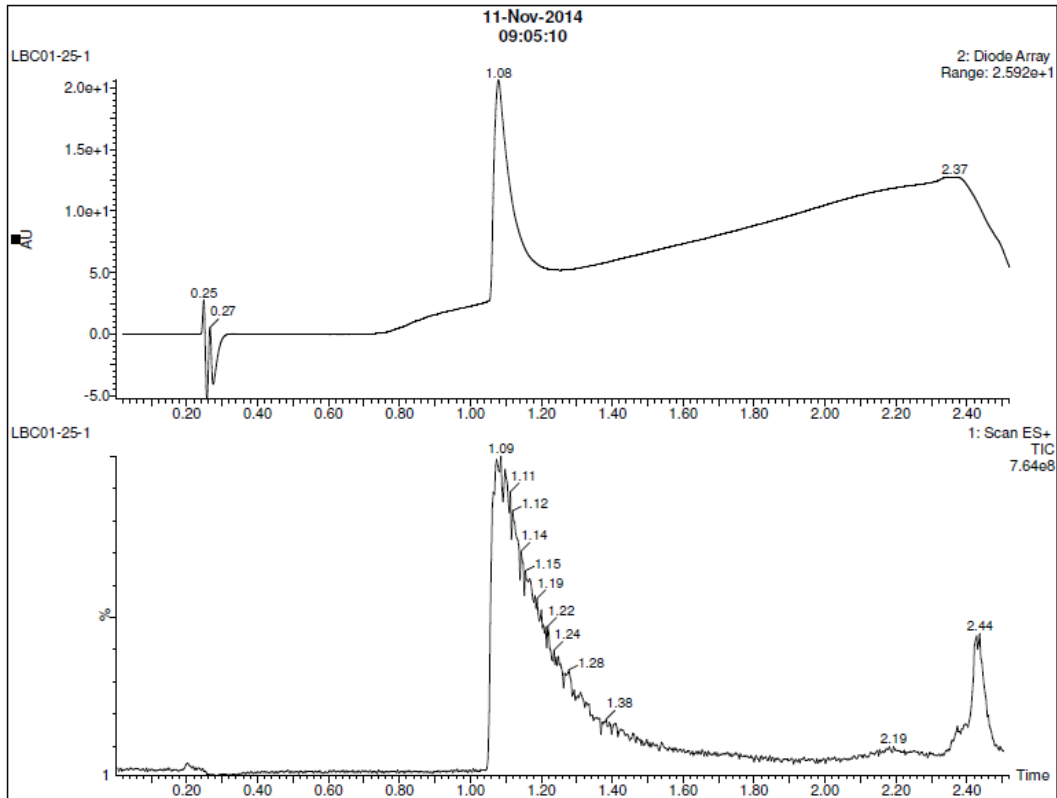
1: R-P-R-L-S-AllyGly-K-G-P-AllyGly-F



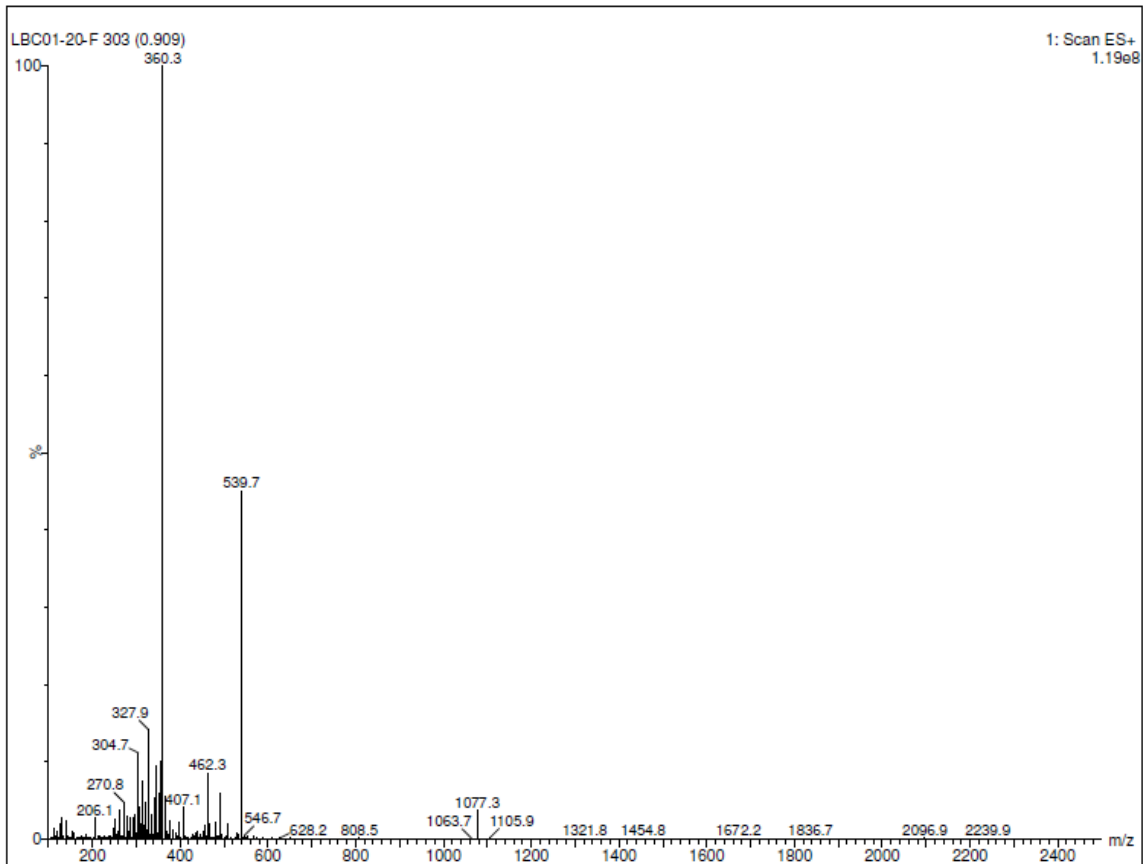
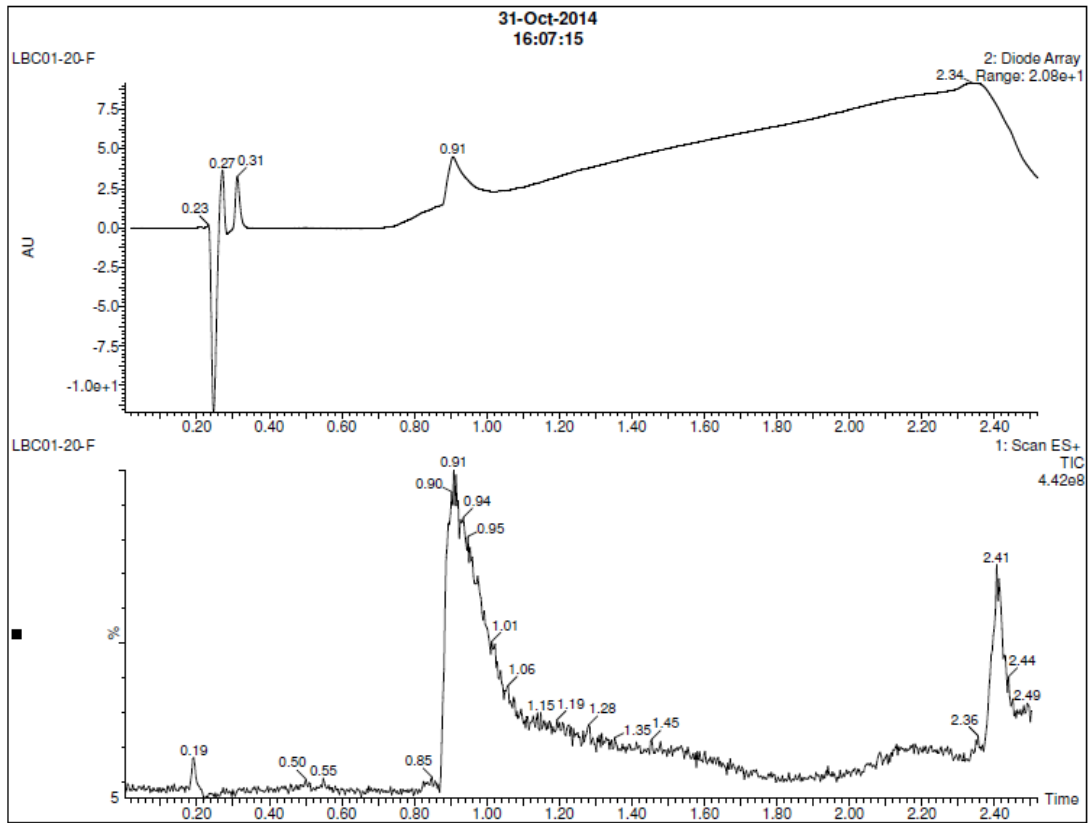
2: R-P-R-L-S-AllylGly-K-G-P-AllylGly-Tyr(OBn)



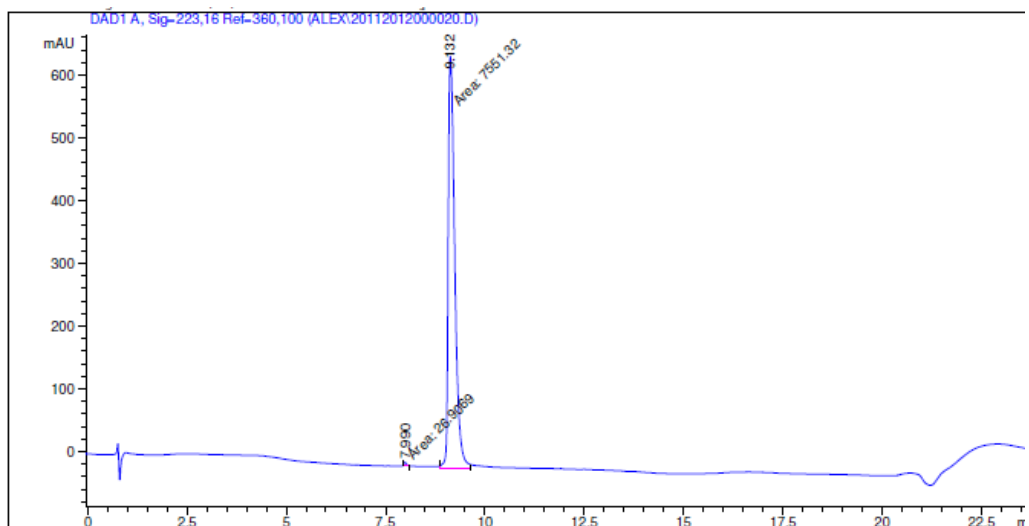
3: R-P-R-L-S-AllylGly-K-G-P-AllylGly-A



4: R-P-R-L-S-AllylGly-K-G-P-AllylGly



5: R-P-R-L-S-AllylGly-K-G-Tyr(OBn)-P-AllylGly

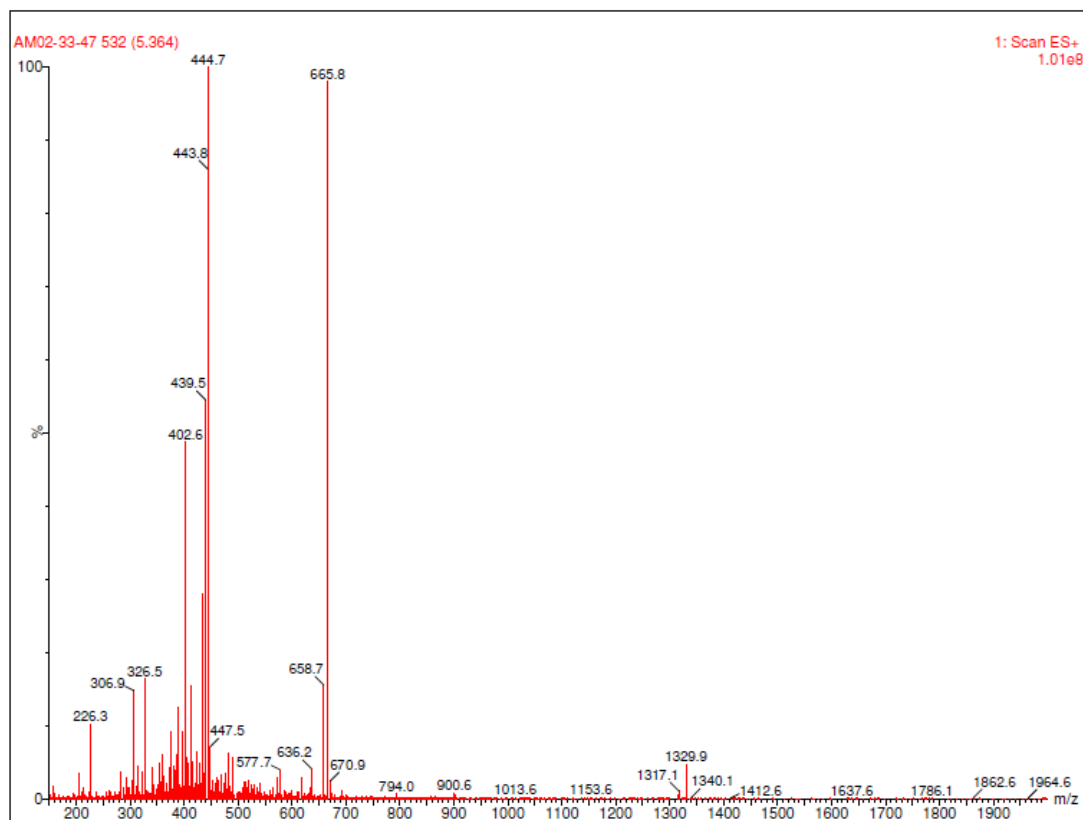


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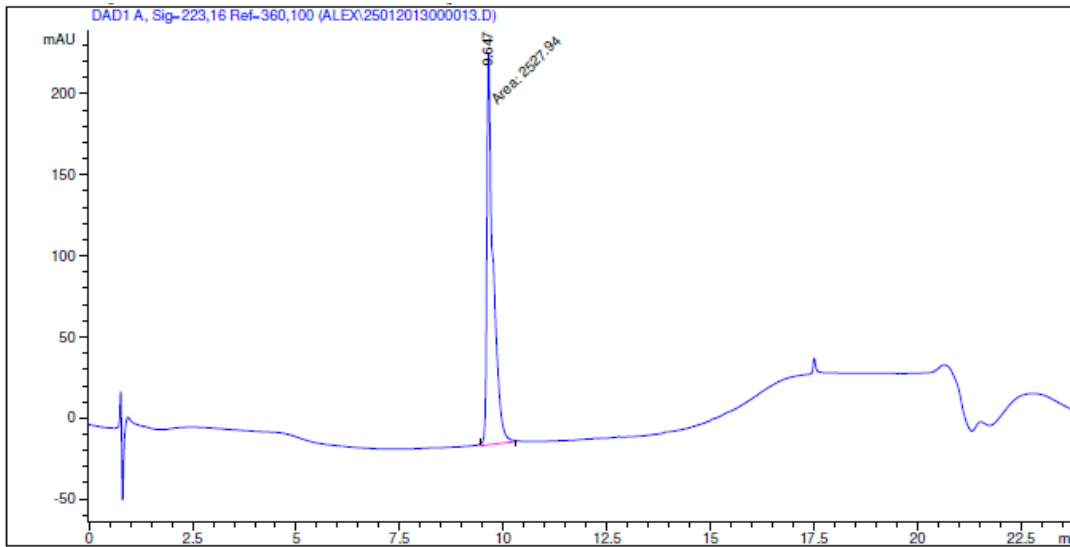
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 Dilution : 1.0000
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig-223,16 Ref-360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.990	MM	0.0808	26.90690	5.55239	0.3551
2	9.132	MM	0.1918	7551.32227	656.20282	99.6449



6: R-P-R-L-S-AllylGly-K-Tyr(OBn)-G-P-AllylGly

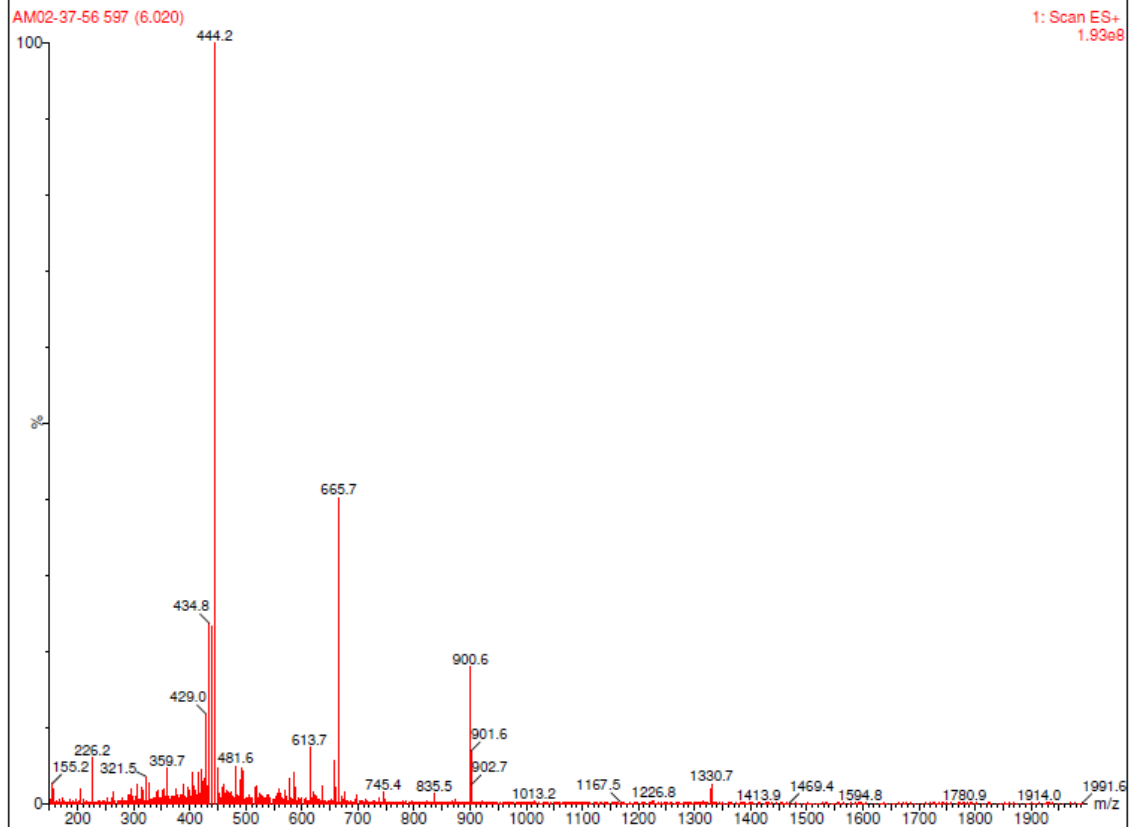


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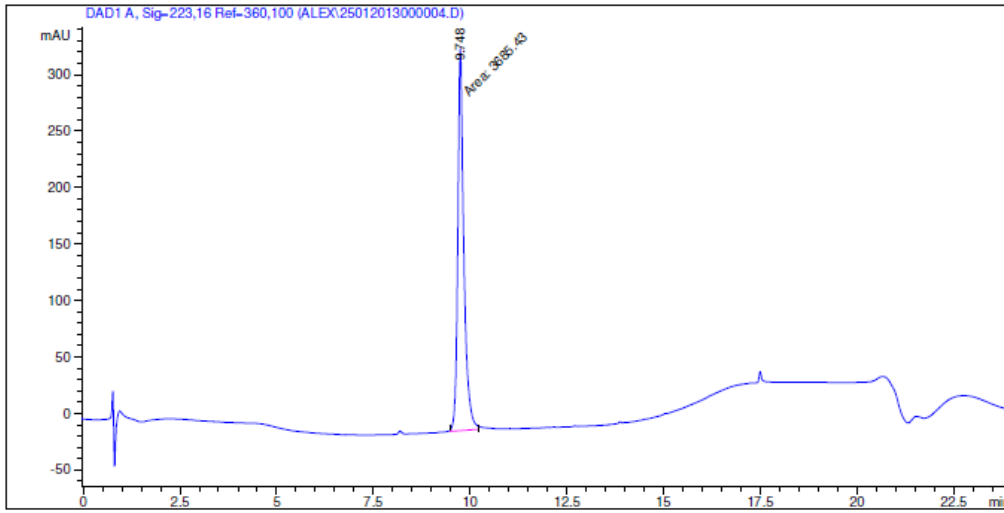
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 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig-223,16 Ref-360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.647	MM	0.1743	2527.93799	241.76709	100.0000



7: R-P-R-L-S-AllyIGly-K-G-P-AllyIGly-P-Tyr(OBn)

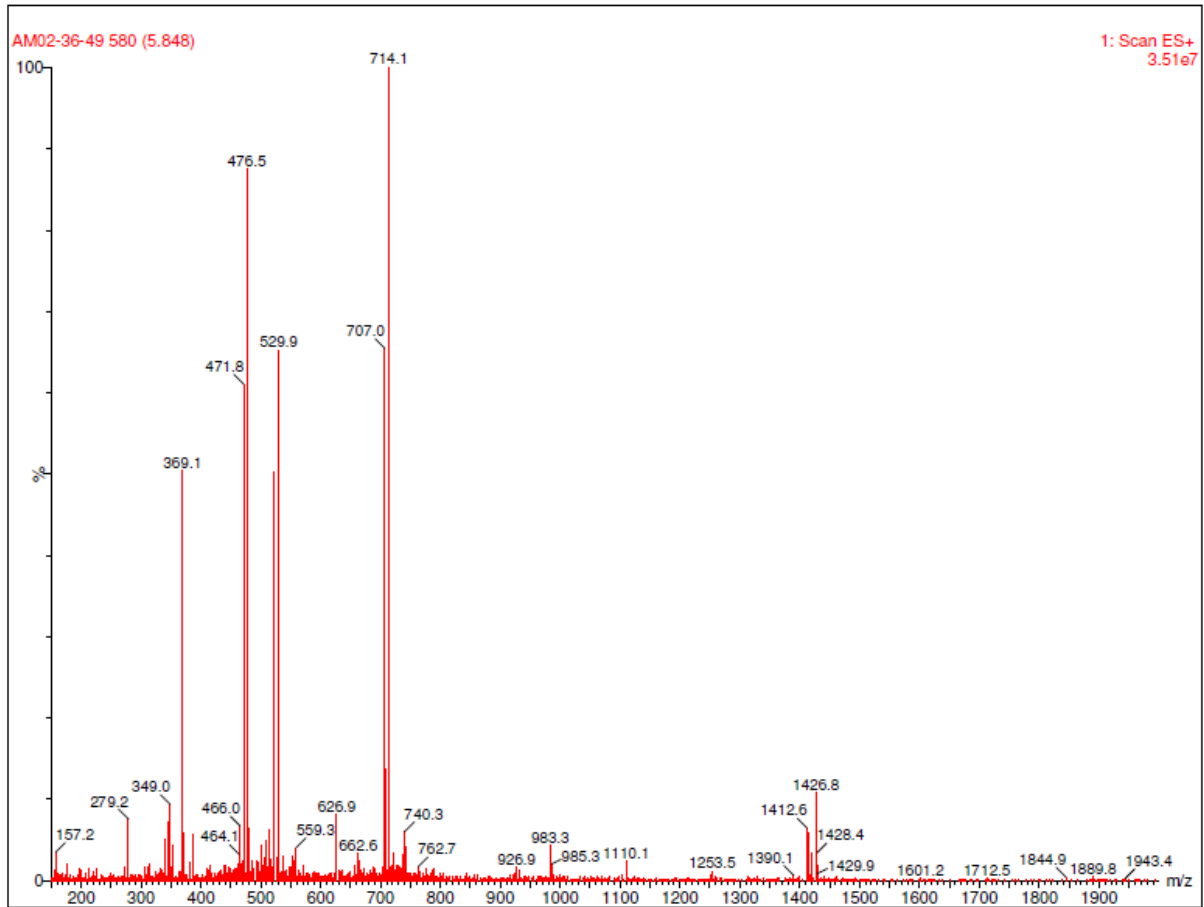


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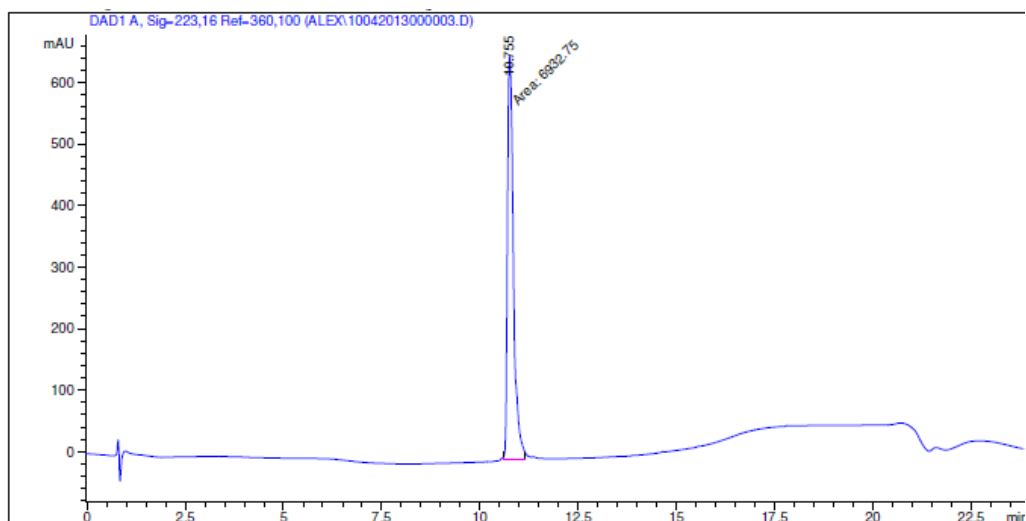
Sorted By : Signal
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 Dilution : 1.0000
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig-223,16 Ref-360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.748	MM	0.1815	3685.42554	338.50626	100.0000



8: R-P-R-L-S-AllylGly-K-G-P-AllylGly-βAla-Tyr(OBn)

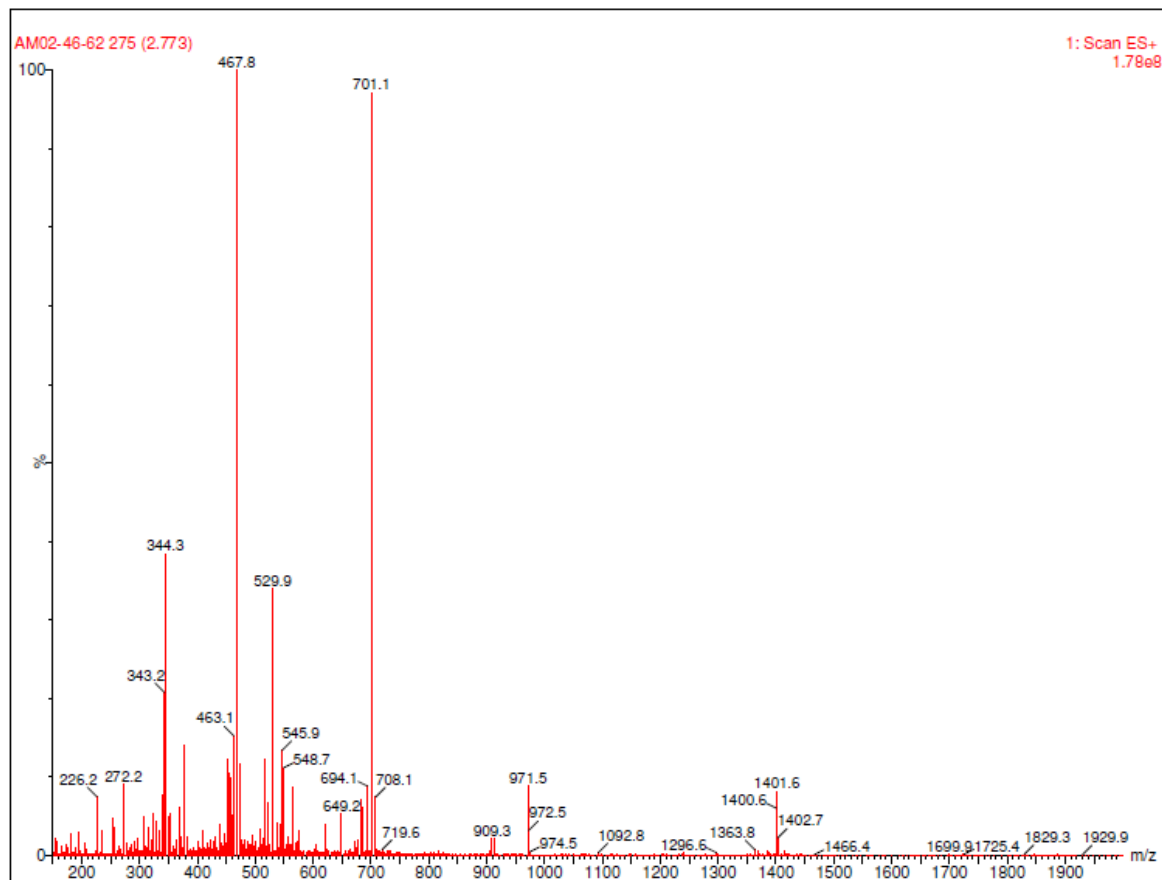


Area Percent Report

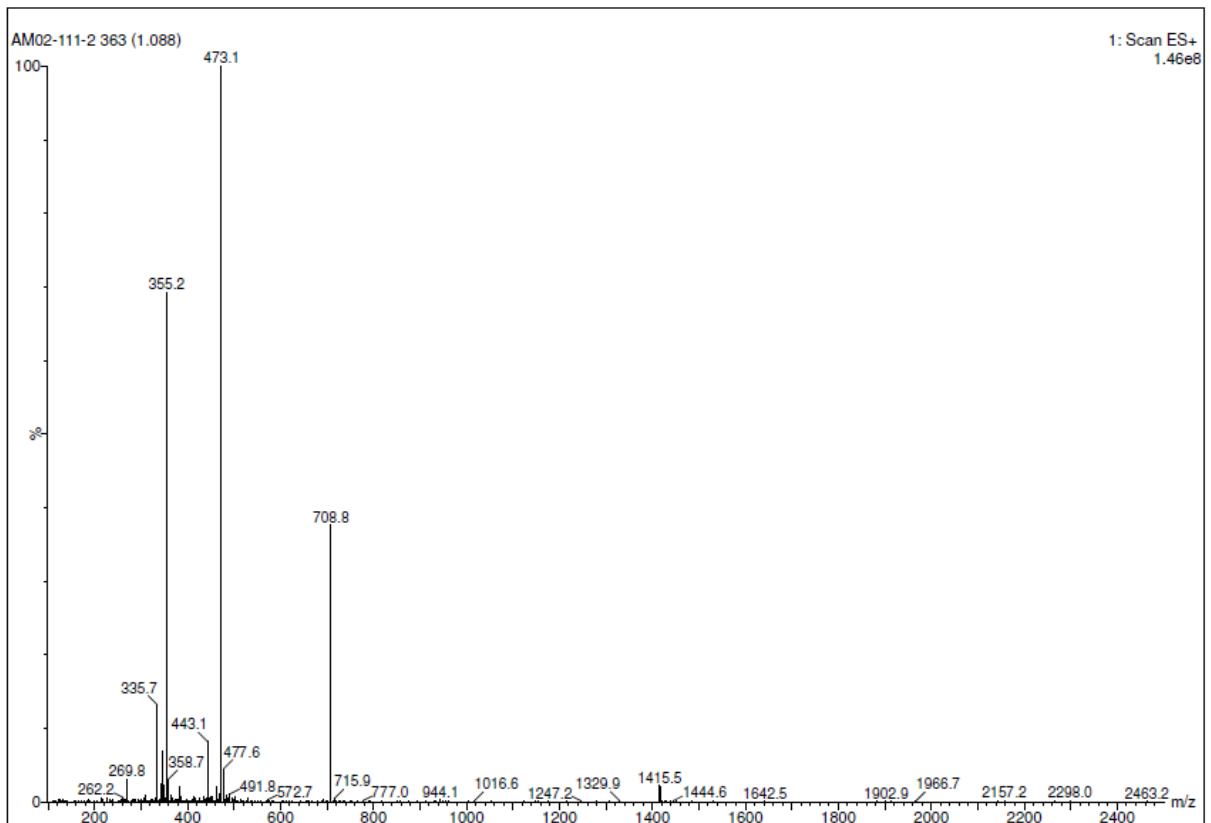
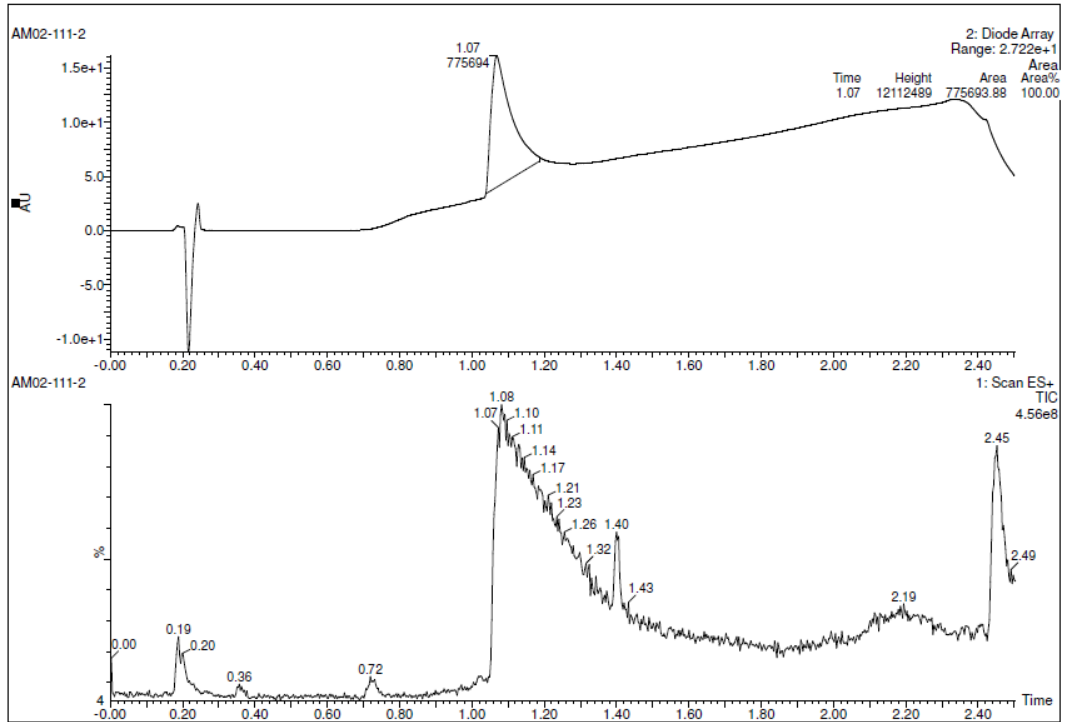
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Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig-223,16 Ref-360,100

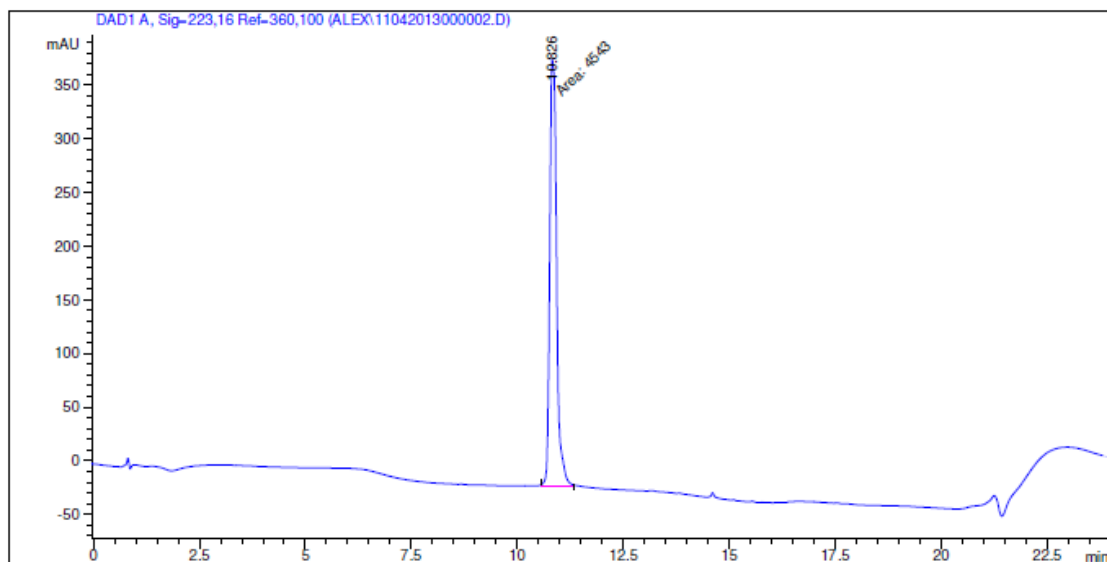
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.755	MM	0.1767	6932.75244	654.08435	100.0000



9: R-P-R-L-S-AllyGly-K-G-P-AllyGly-γAbu-Tyr(OBn)



10: R-P-R-L-S-AllylGly-K-G-P-AllylGly-A-Tyr(OBn)

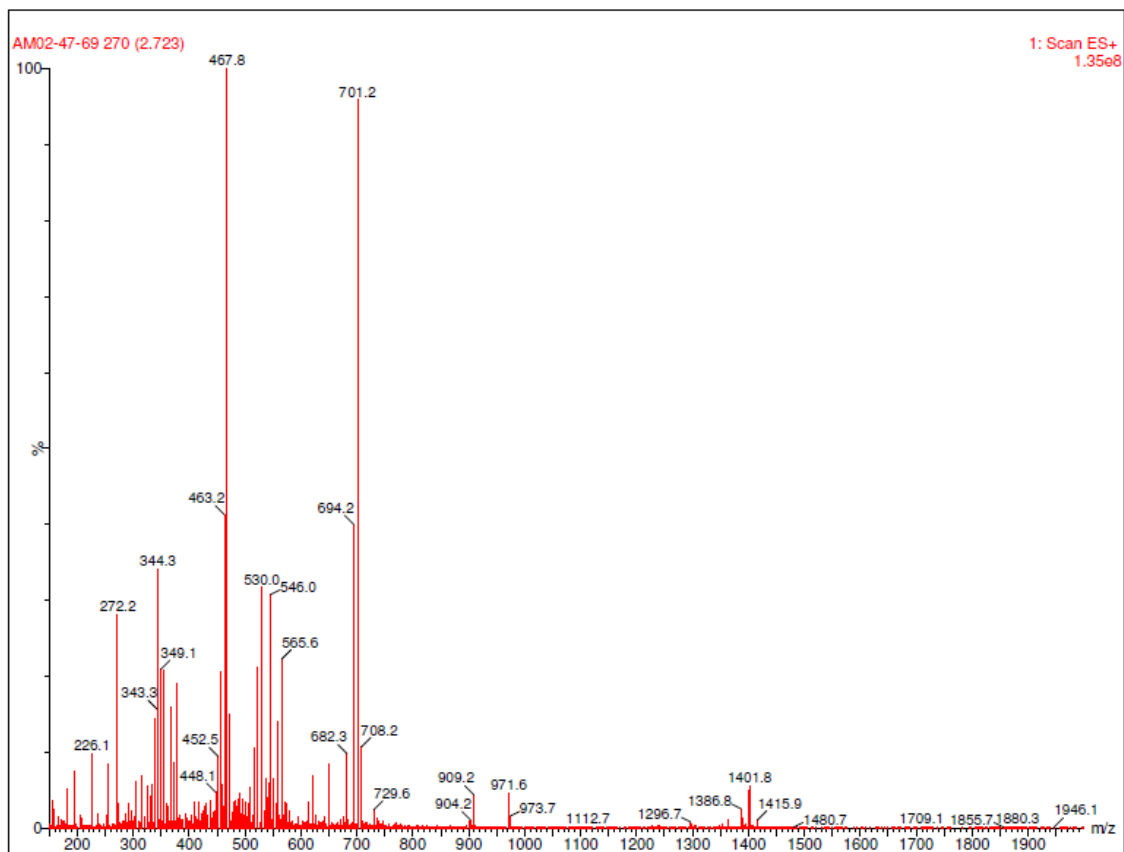


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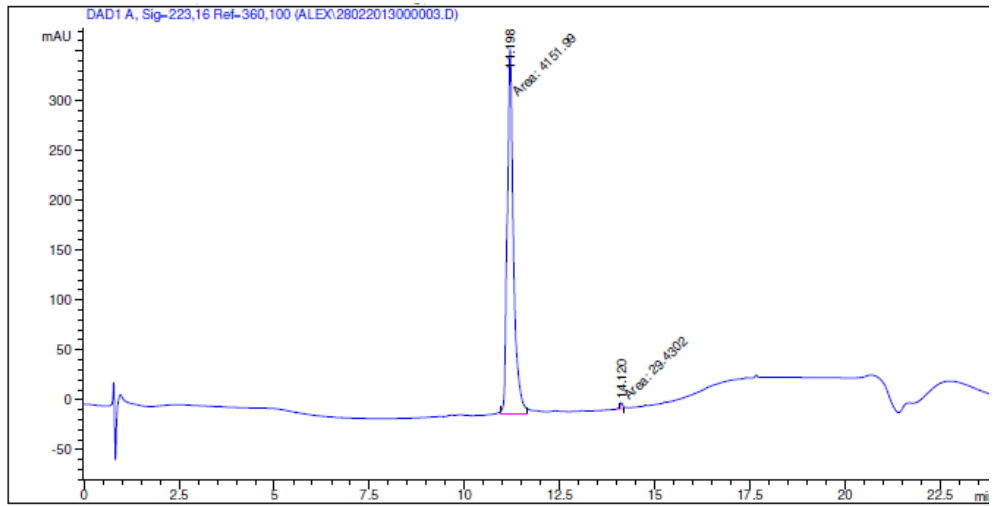
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 Dilution : 1.0000
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=223,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.826	MM	0.1897	4543.00195	399.17548	100.0000



11: R-P-R-L-S-AllyIGly-[8-aminocaprylic]-AllyIGly-P-Tyr(OBn)

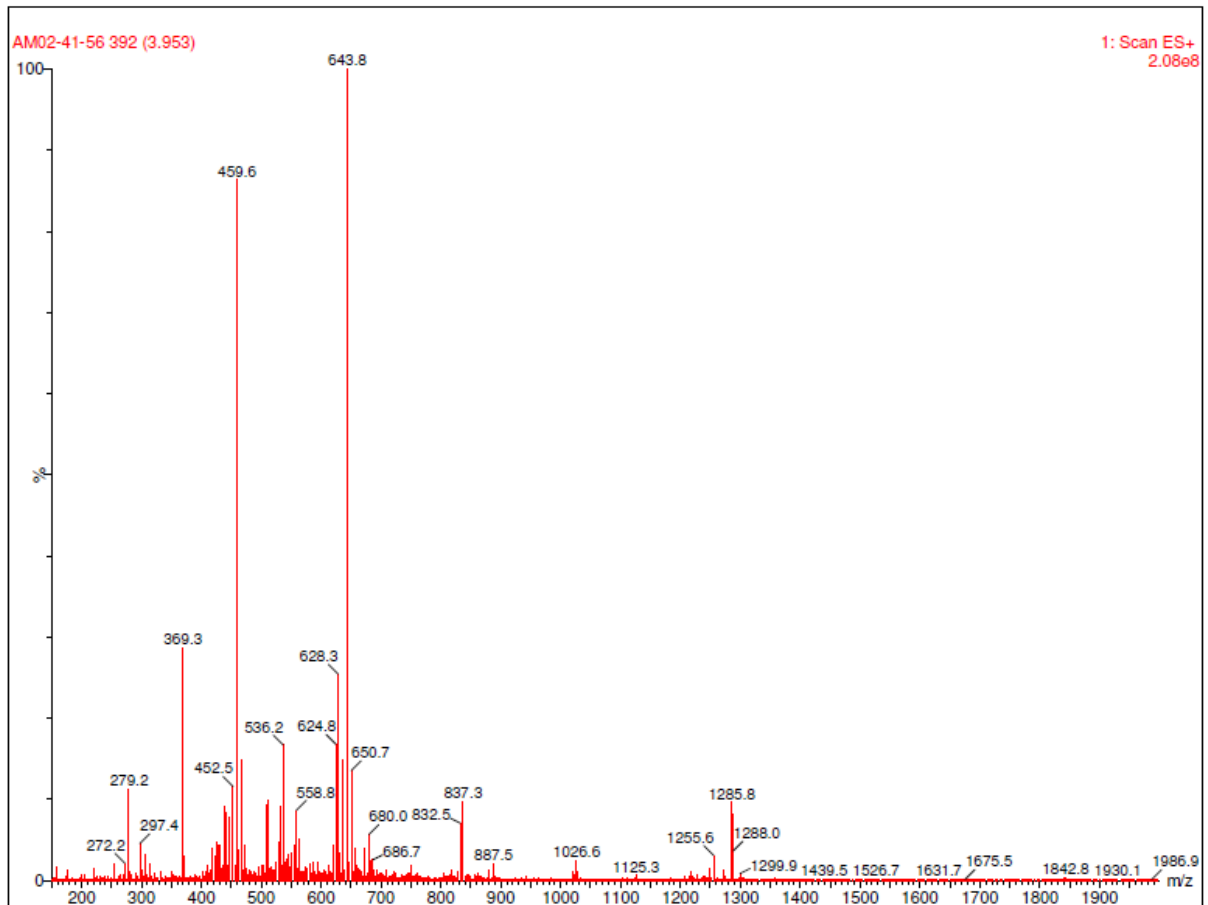


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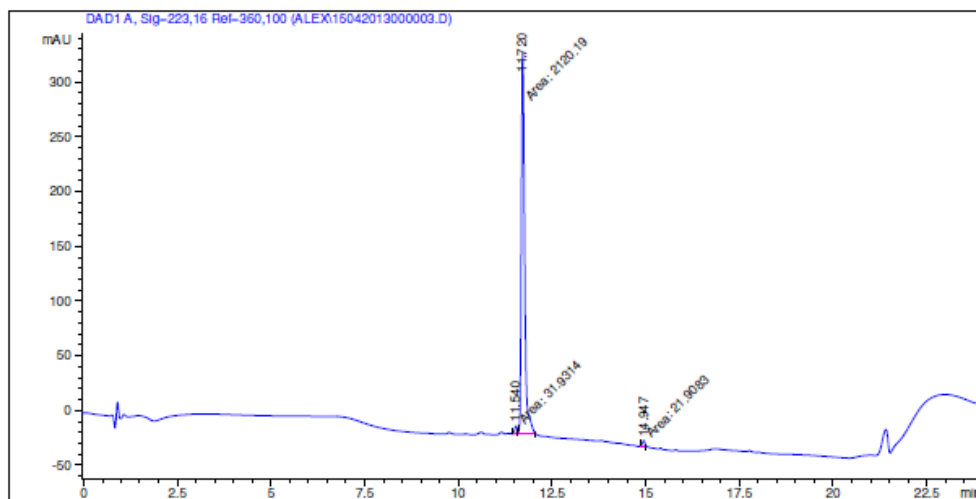
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Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig-223,16 Ref-360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.198	MM	0.1894	4151.98779	365.37491	99.2962
2	14.120	MM	0.0802	29.43024	6.11297	0.7038



12: R-P-R-L-S-AllylGly-βAla-βAla-AllylGly-Tyr(OBn)

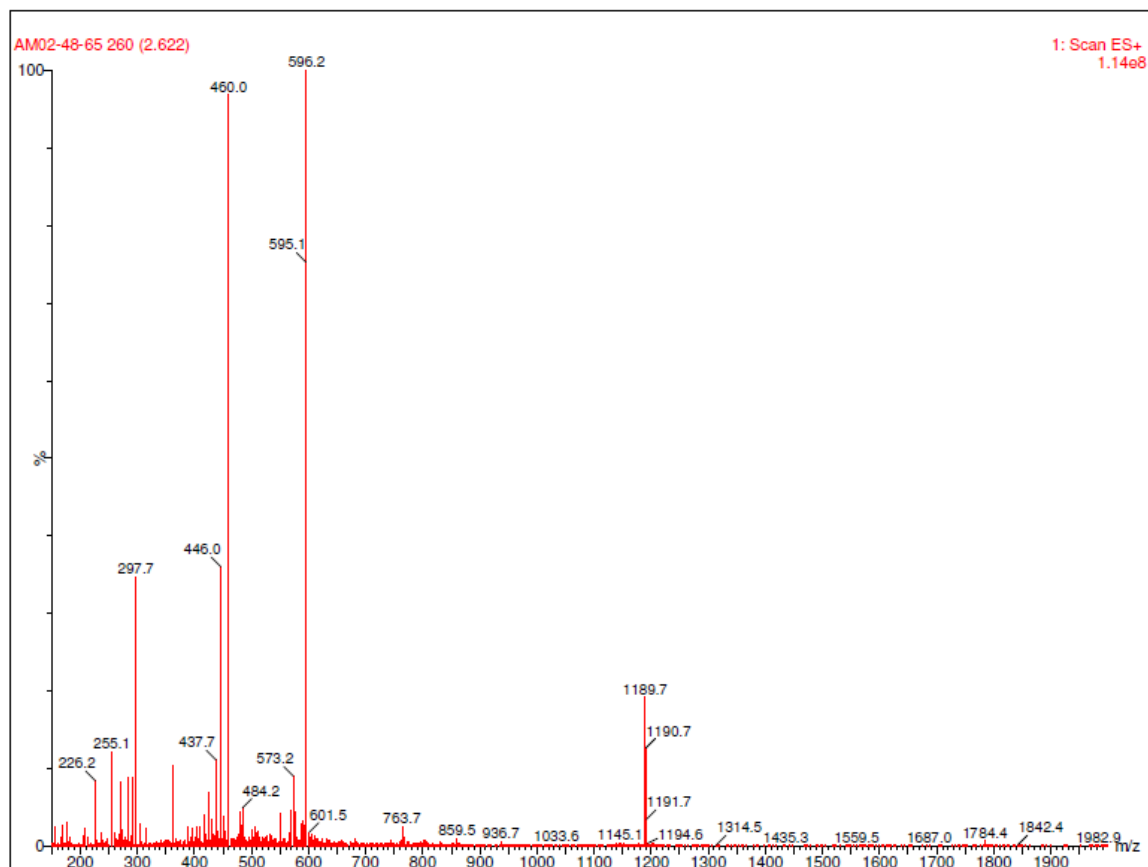


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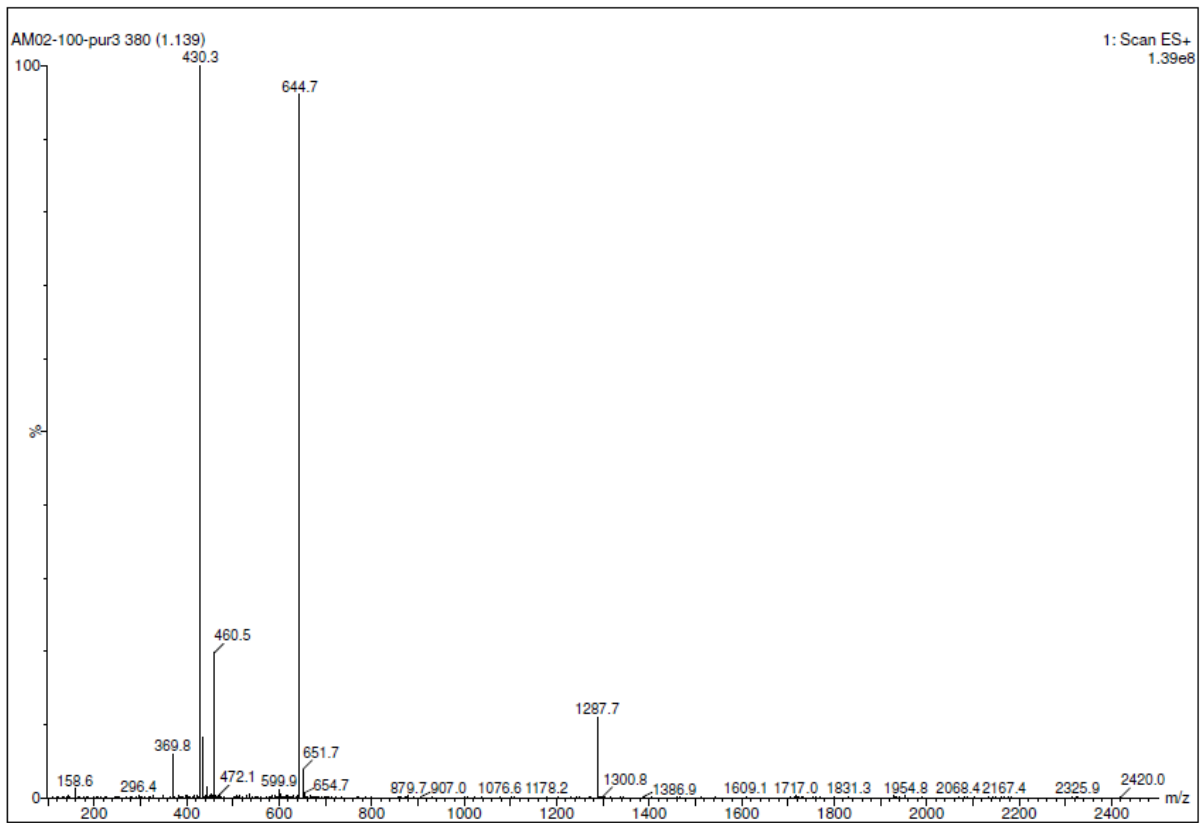
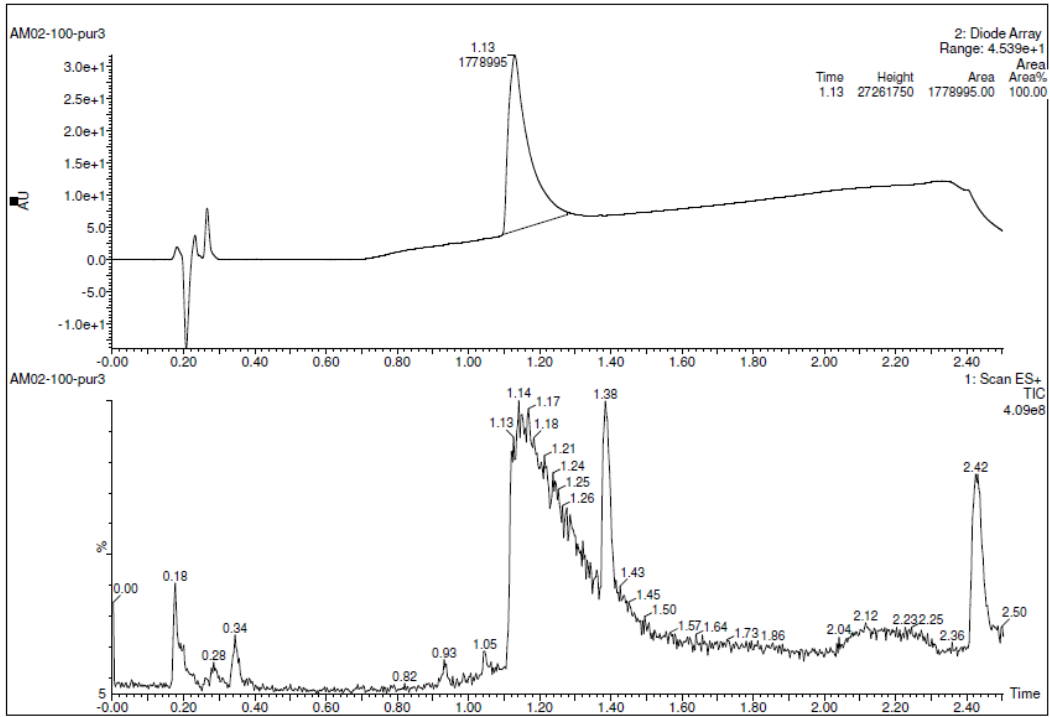
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Signal 1: DAD1 A, Sig=223,16 Ref=360,100

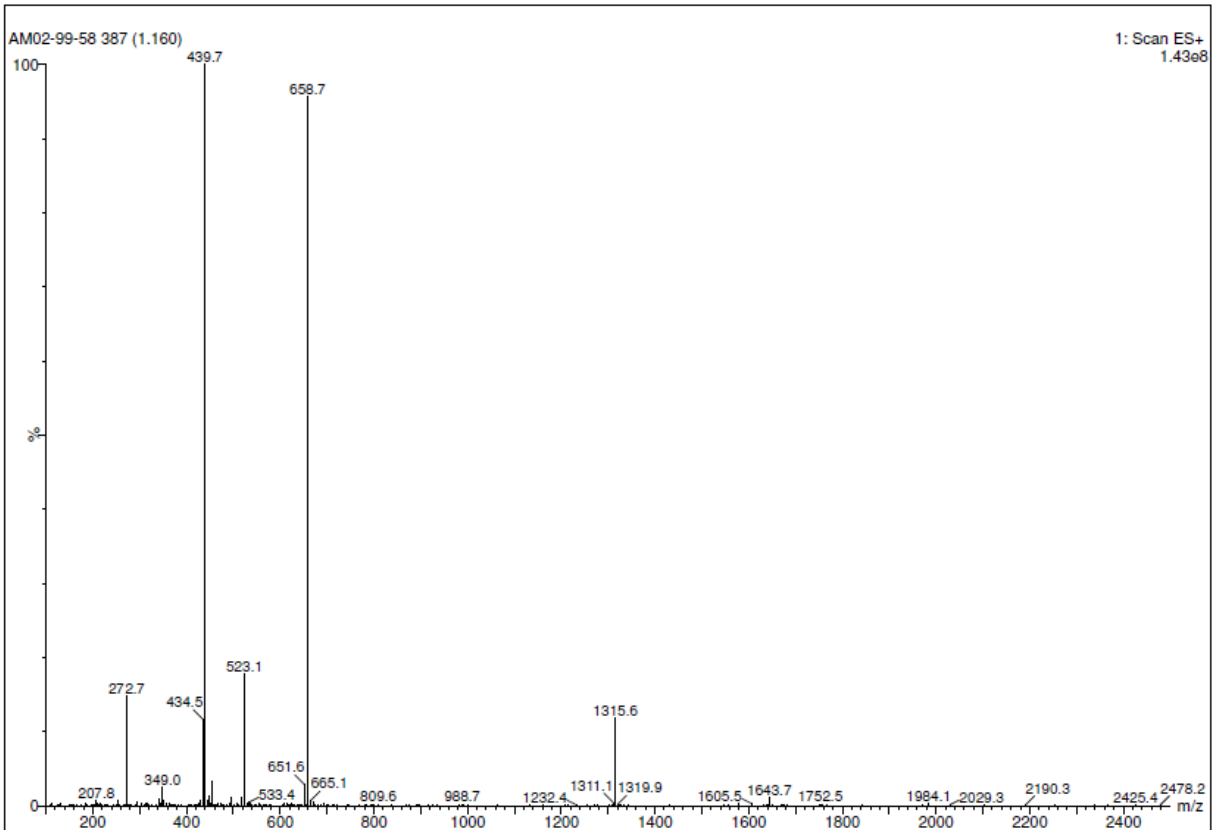
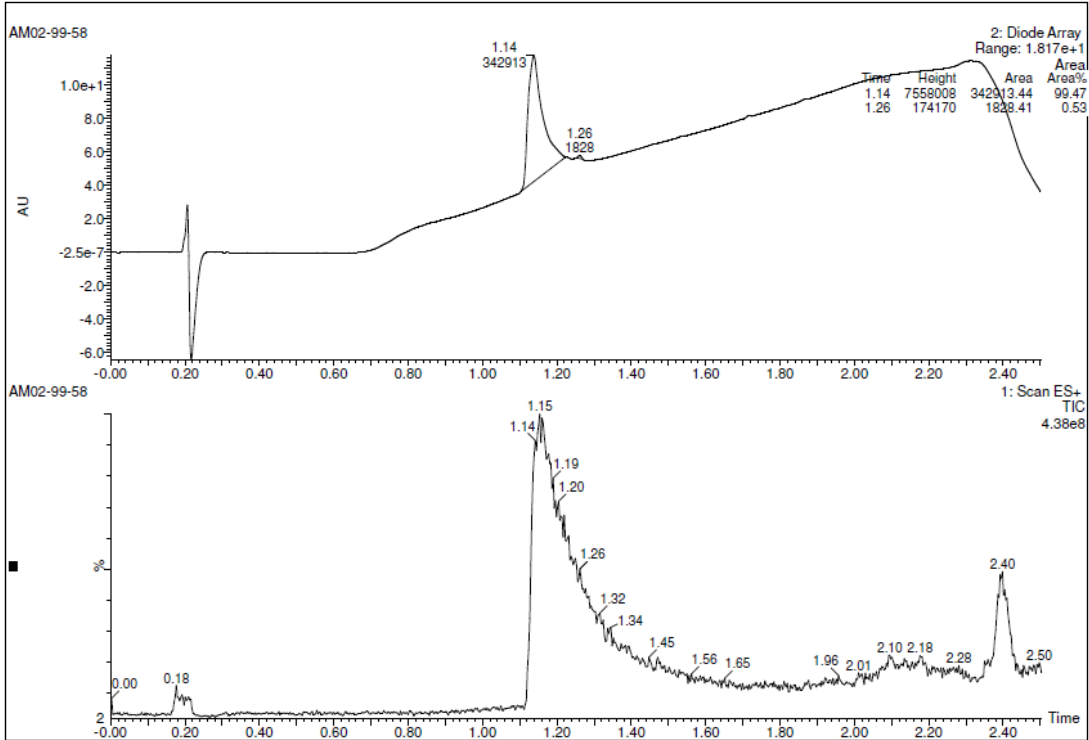
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.540	MM	0.0787	31.93145	6.76066	1.4688
2	11.720	MM	0.1018	2120.18774	346.96326	97.5235
3	14.947	MM	0.0689	21.90834	5.30213	1.0077



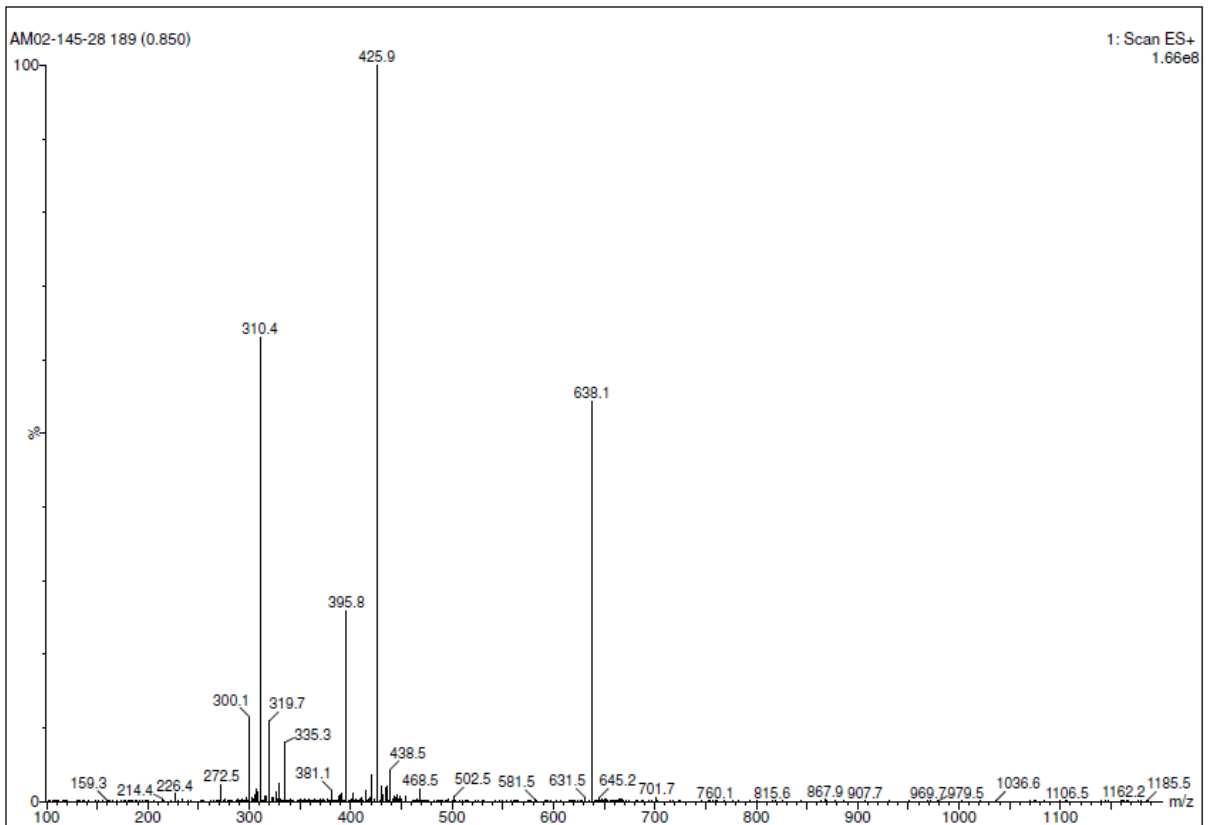
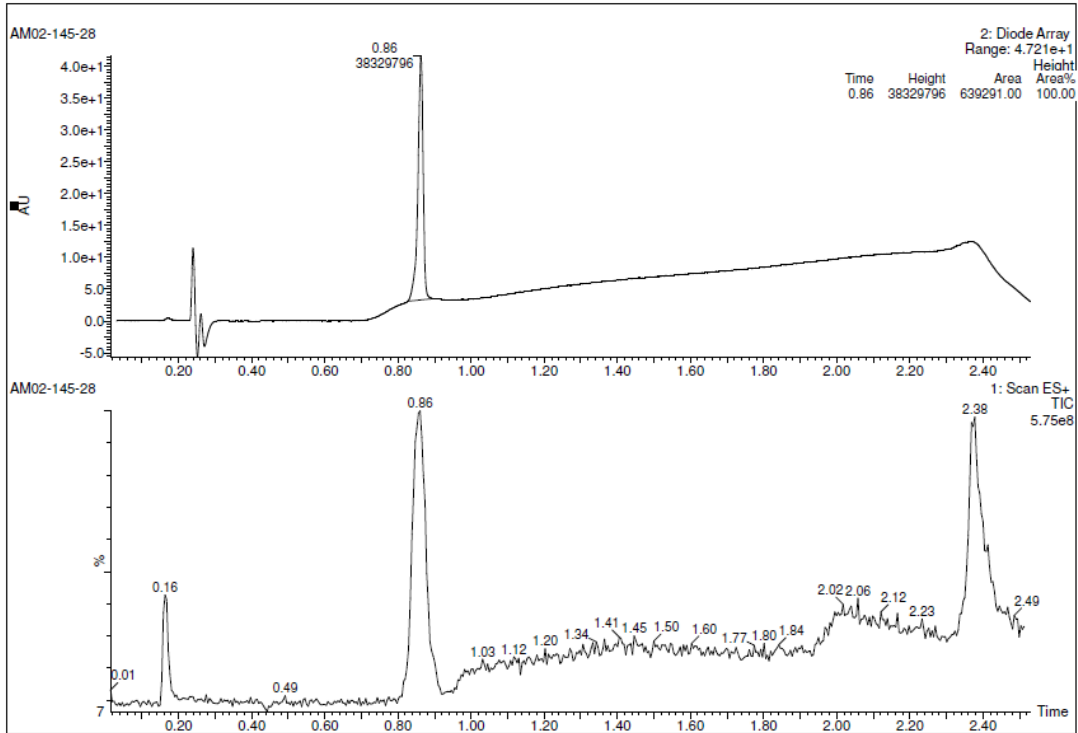
13: R-P-R-L-S-AllylGly-βAla-βAla-AllylGly-P-Tyr(OBn)



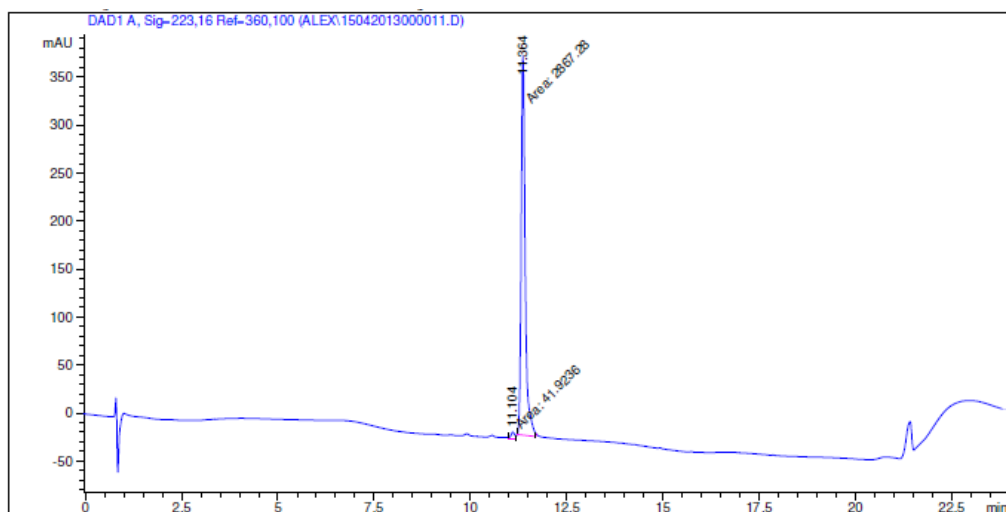
14: R-P-R-L-S-AllyIGly-Nle-G-P-AllyIGly-Tyr(OBn)



15: K-P-K-L-S-AllylGly-K-G-P-AllylGly-Tyr(OBn)



16: Orn-P-Orn-L-S-AllylGly-K-G-P-AllylGly-Tyr(OBn)

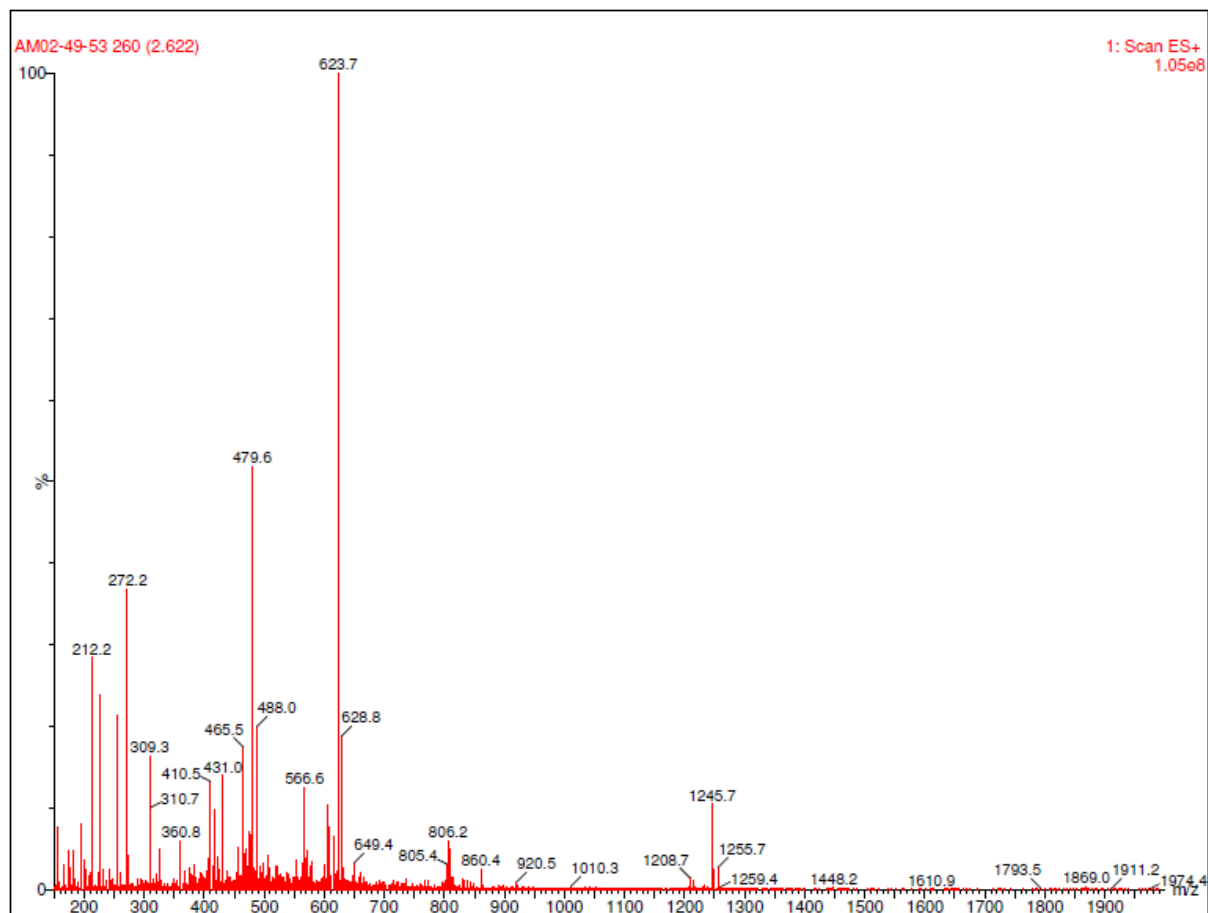


 Area Percent Report

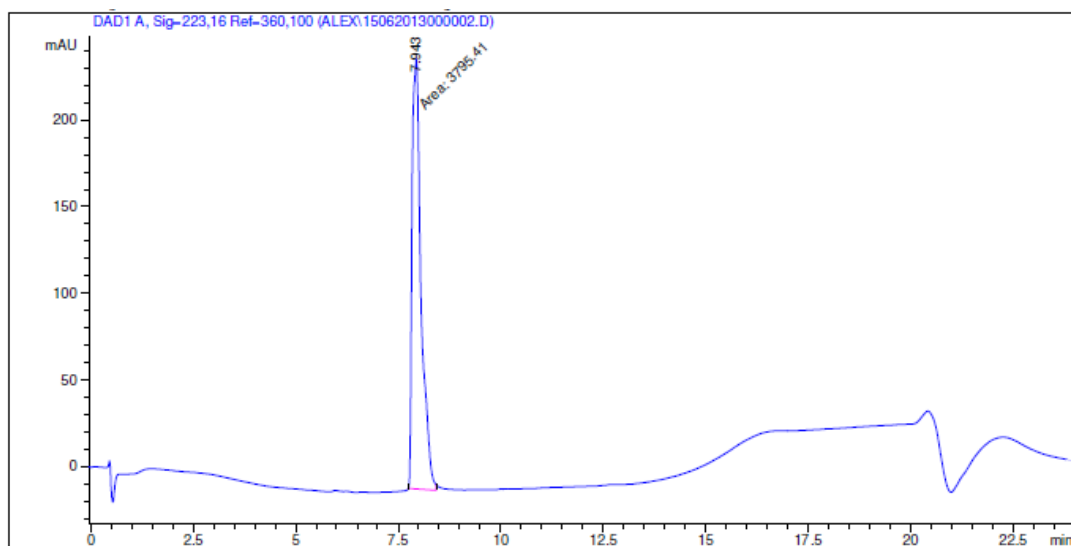
Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig-223,16 Ref-360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.104	MM	0.1044	41.92359	6.69498	1.4411
2	11.364	MM	0.1208	2867.28271	395.73755	98.5589



17: R-L-S-AllylGly-K-G-P-AllylGly-Tyr(OBn)

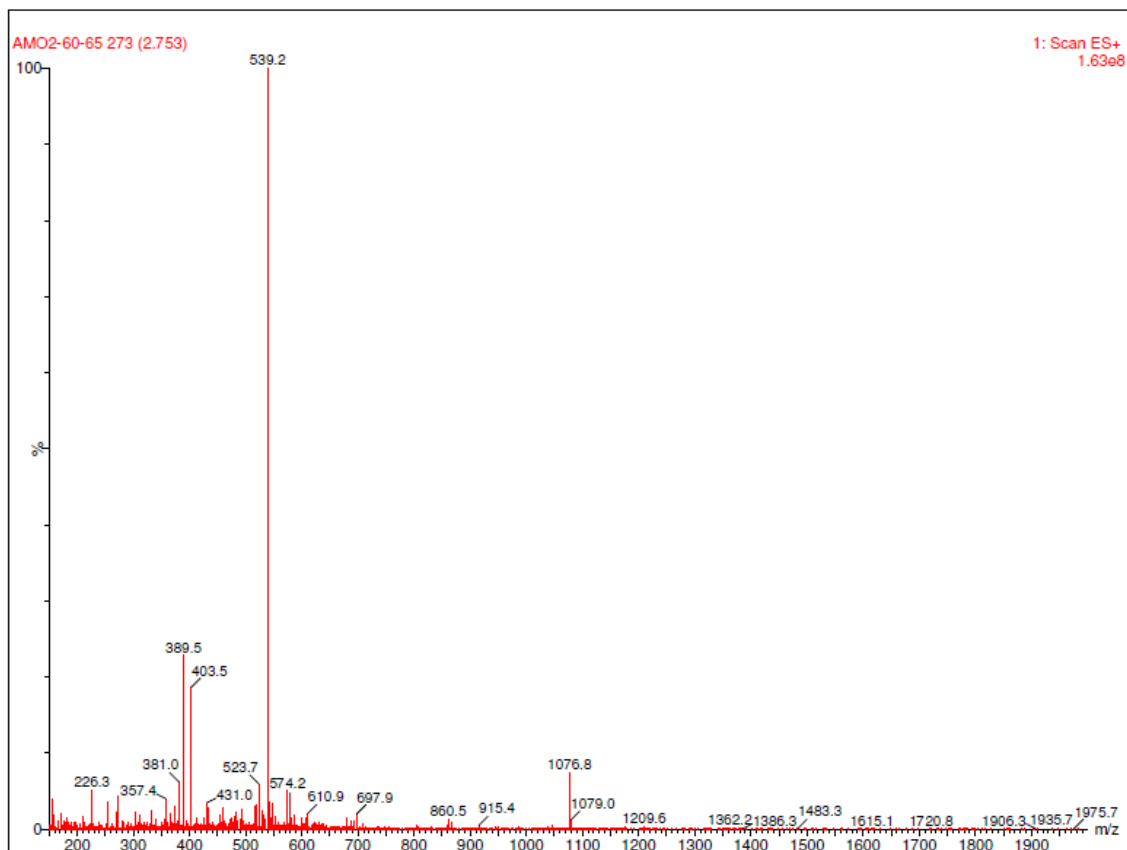


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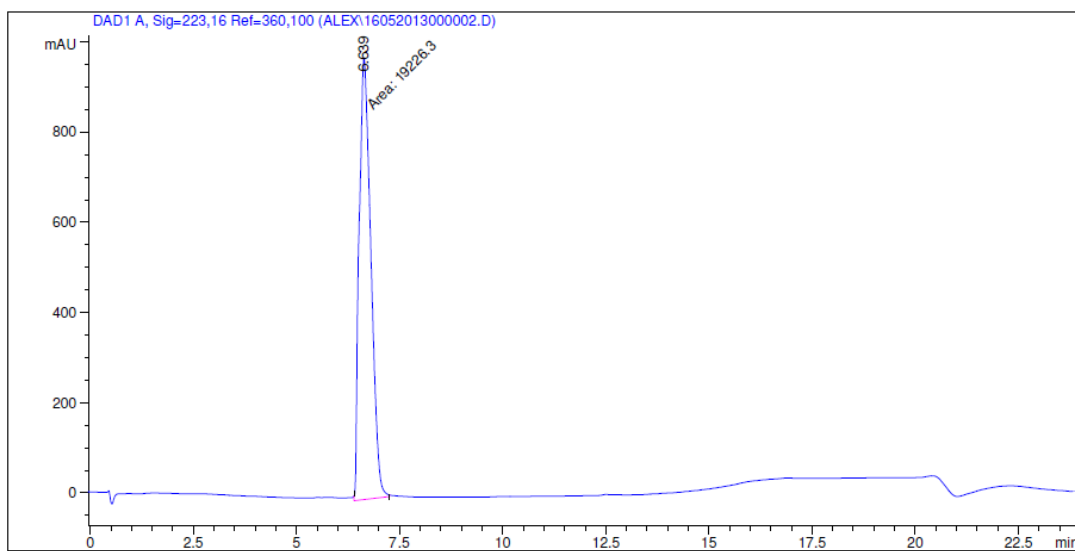
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 Dilution : 1.0000
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig-223,16 Ref-360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.943	MM	0.2547	3795.40942	248.39760	100.0000



18: AllylGly-K-G-P-AllylGly-Tyr(OBn)

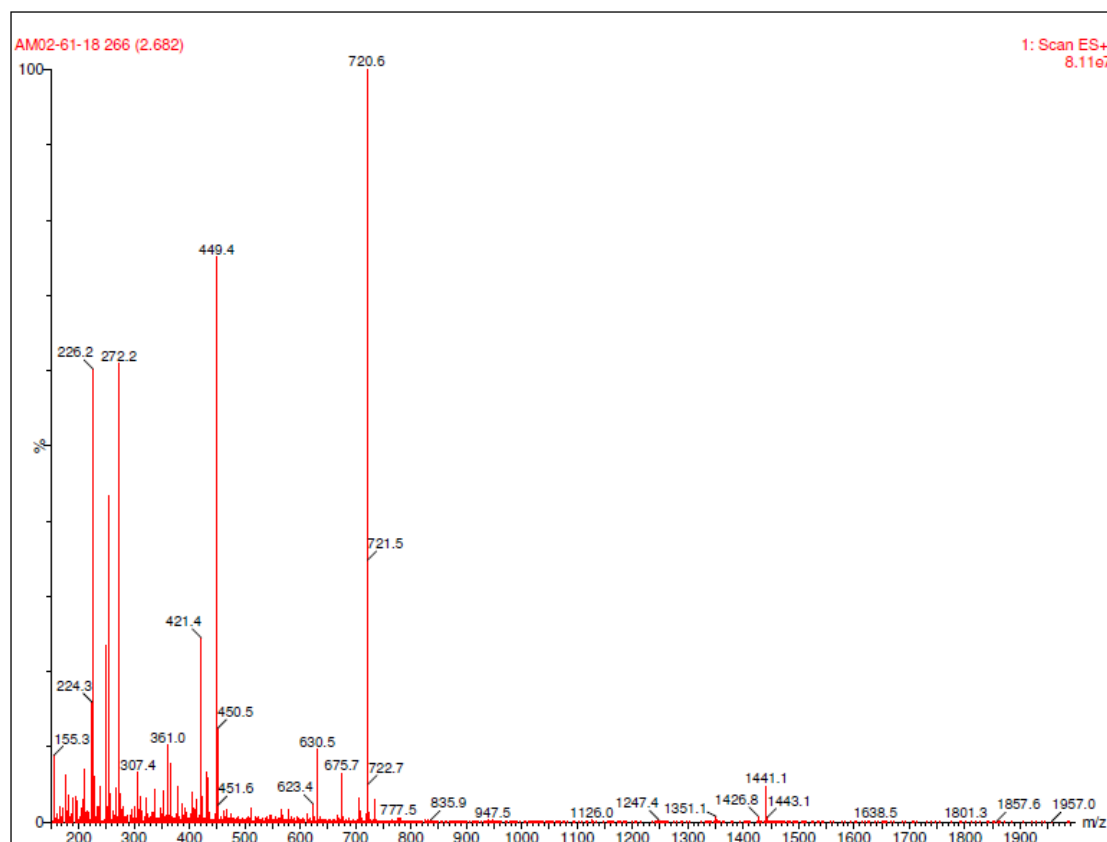


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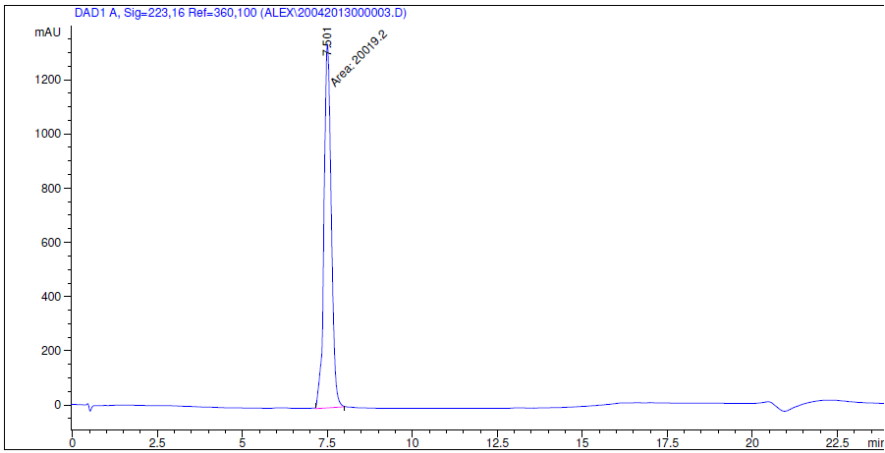
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 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=223,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.639	MM	0.3276	1.92263e4	977.99957	100.0000



19: Pyr-R-P-R-L-S-AllylGly-K-G-P-AllylGly-Tyr(OBn)

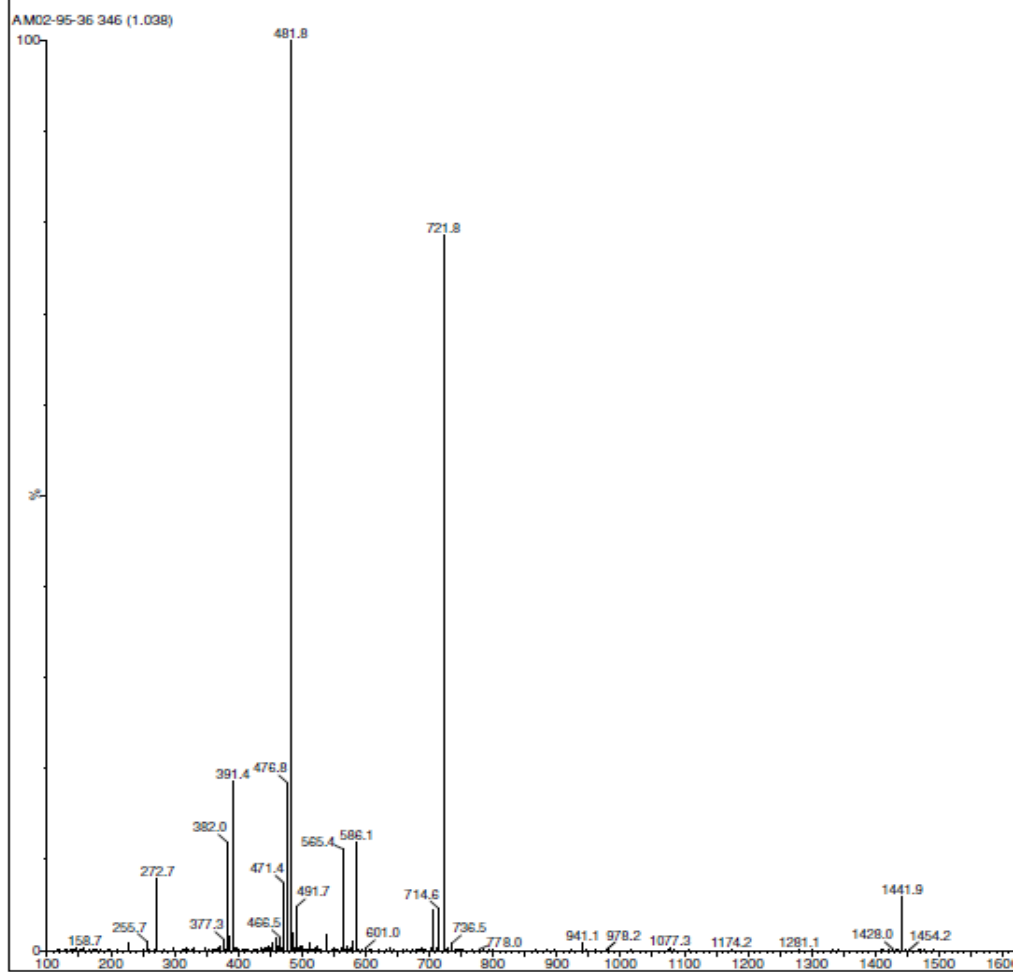


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Area Percent Report
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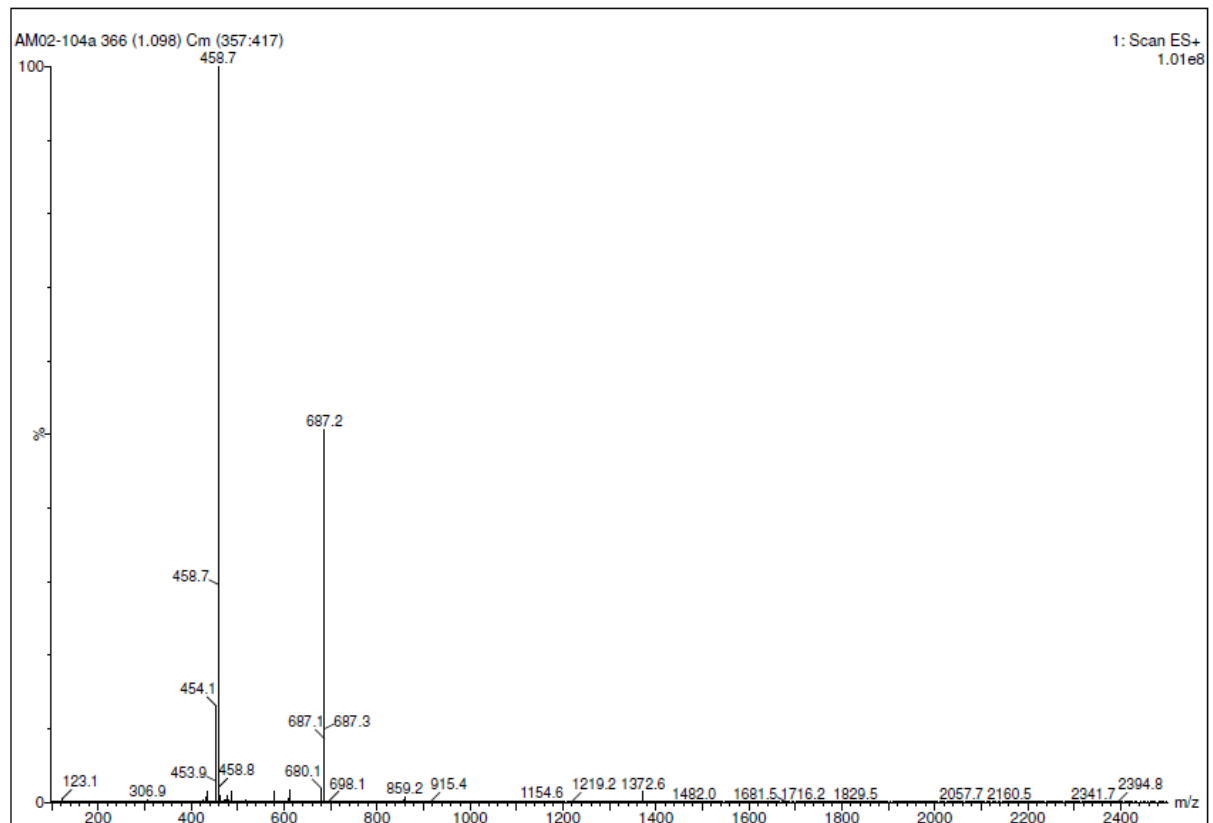
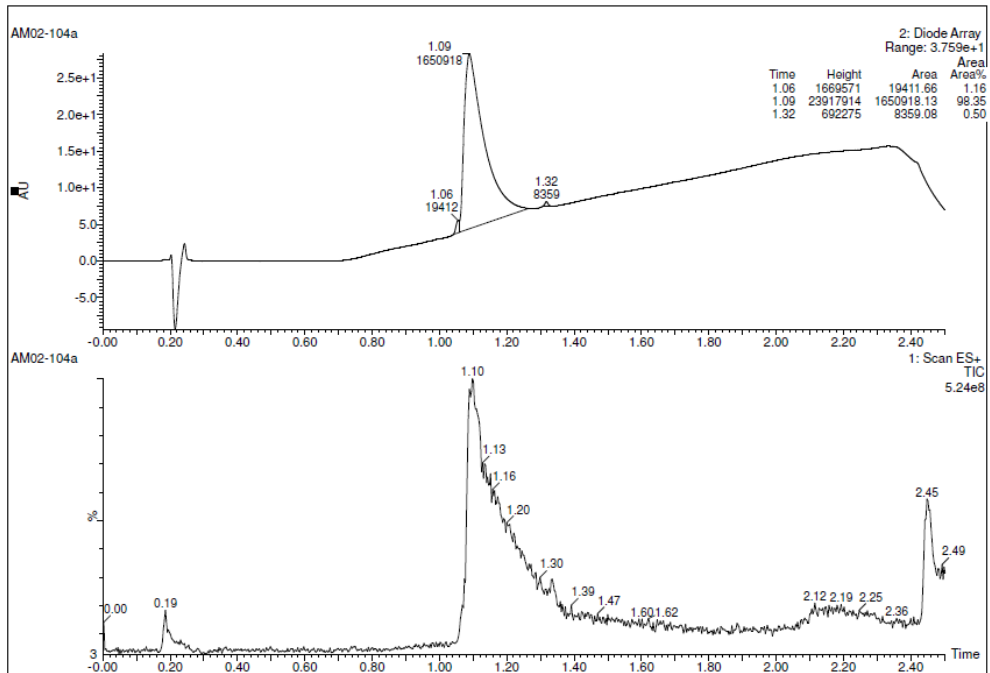
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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=223,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.501	MM	0.2485	2.00192e4	1342.45593	100.0000



20: Ac-R-P-R-L-S-AllylGly-K-G-P-AllylGly-Tyr(OBn)



21: Des-amino-R-P-R-L-S-AllyIGly-K-G-P-AllyIGly-Tyr(OBn)

