

## Supporting Information

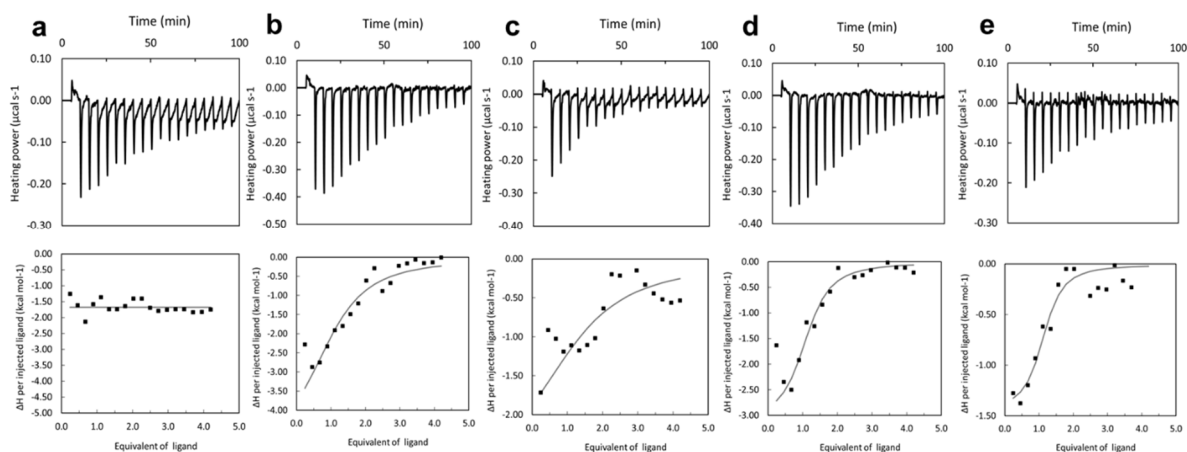
# $\alpha/\beta$ -Peptides as nanomolar triggers of lipid raft-mediated endocytosis through GM1 ganglioside recognition

Anasztázia Hetényi <sup>1,5</sup>, Enikő Szabó <sup>2,5</sup>, Norbert Imre <sup>1</sup>, Kaushik Nath Bhaumik <sup>1</sup>, Attila Tököli <sup>1</sup>, Tamás Füzesi <sup>1</sup>, Réka Hollandi <sup>3</sup>, Peter Horvath <sup>3</sup>, Ágnes Czibula <sup>2,\*</sup>, Éva Monostori <sup>2</sup>, Mária A. Deli <sup>4</sup> and Tamás A. Martinek <sup>1,\*</sup>

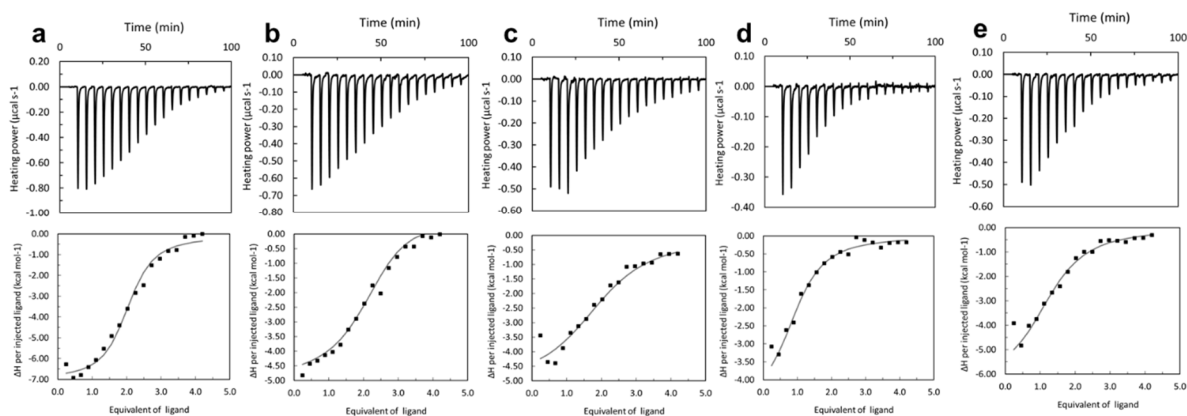
- <sup>1</sup> Department of Medical Chemistry, University of Szeged, Dóm tér 8., 6720 Szeged, Hungary
- <sup>2</sup> Institute of Genetics, Biological Research Centre, Temesvári krt. 62., 6726 Szeged, Hungary
- <sup>3</sup> Institute of Biophysics, Biological Research Centre, Temesvári krt. 62., 6726 Szeged, Hungary
- <sup>4</sup> Synthetic and Systems Biology Unit, Biological Research Centre, Temesvári krt. 62., 6726 Szeged, Hungary
- <sup>5</sup> These authors contributed equally to this work
- \* Correspondence: martinek.tamas@med.u-szeged.hu, czibula.agnes@brc.hu

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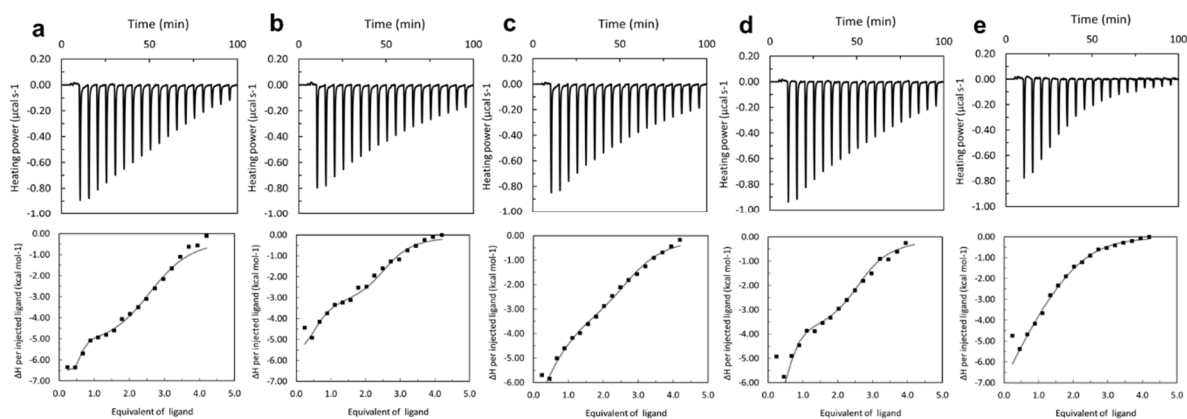
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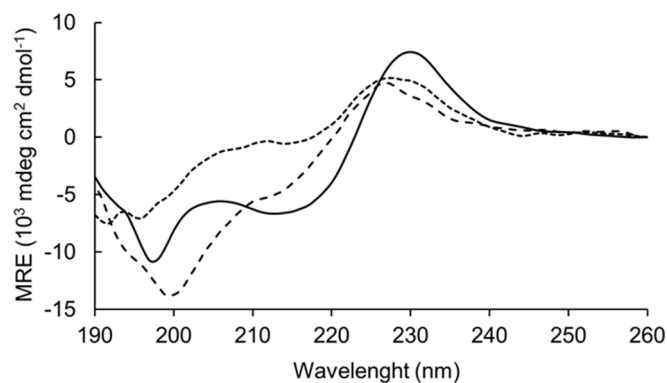
**Figure S1.** ITC detection of interactions of GM1 with *A/a* derivatives (a) AYKYW, (b) WAKYW, (c) WYAYW, (d) WYKAW and (e) WYKYA. Titrations were carried out with GM1:DPC 1:5 bicelles.



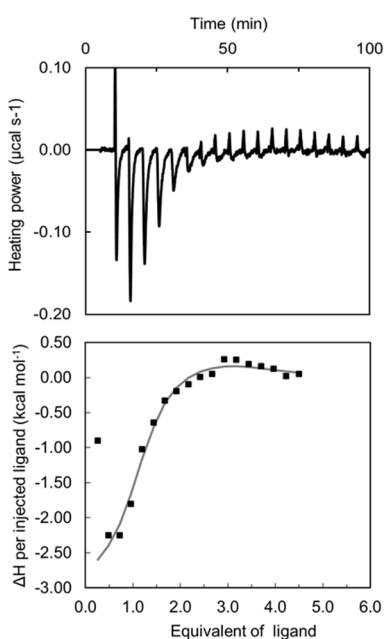
**Figure S2.** ITC detection of interactions of GM1 with *d* derivatives (a) wYKYW, (b) WyKYW, (c) WYKYW, (d) WYKYw and (e) WYKYw. Titrations were carried out with GM1:DPC 1:5 bicelles.



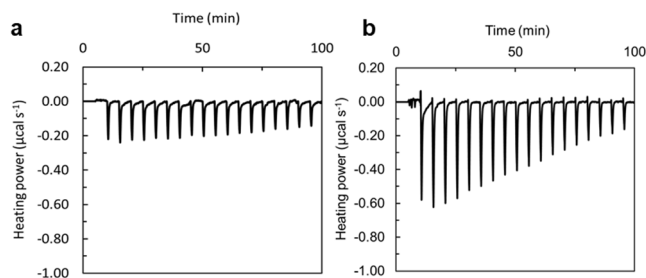
**Figure S3.** ITC detection of interactions of GM1 with  $\beta$ -derivatives (a) W $\beta$ YKYW, (b) WY $\beta$ KYW, (c) WYK $\beta$ YW, (d) WYKY $\beta$ W and (e) WYKYW $\beta$ . Titrations were carried out with GM1:DPC 1:5 bicelles.



**Figure S4.** CD spectrum of peptides WYKYW (black), WAKAW (long dashed), and AYKYA (short dashed) (200  $\mu$ M) at 303 K.



**Figure S5.** ITC detection of interactions of GM1 with carrier-NA conjugates. Enthalpograms of NA(biotinyl-Penetratin-WYK $^{\beta}$ YW)<sub>4</sub> ( $n=1$ ,  $K_D=79$  nM). Titrations were carried out with GM1:DPC 1:5 bicelles.



**Figure S6.** ITC enthalpogram obtained for WYKYW with pure GM1 micelles (a) and with GM1:DPC 1:5 bicelles (b).

**Table S1.** Half-lives of compounds in protease assay with chymotrypsin. In most cases, the peak belonging to the sequence was not detected at the first sampling (2 minutes), hence the half-life is < 24s with a 3% detection limit. \* No degradation was detected during the experiment.

Sequence	Half-life (s)	
	Chymotrypsin	Trypsin
WYKYW	< 24	< 24
W <sup>β</sup> YKYW	< 24	110
WY <sup>β</sup> KYW	75	900
WYK <sup>β</sup> YW	650	>> 24 h*
WYKY <sup>β</sup> W	< 24	410
WYKYW <sup>β</sup>	< 24	< 24

*Statistical Analysis:* Statistical analysis included one-way analysis of variance (ANOVA) with post hoc Tukey honestly significant difference test (\* $p < 0.1$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ; \*\*\*\* $p < 0.0001$ ). The results of the statistical test are included in Table S2.

**Table S2**

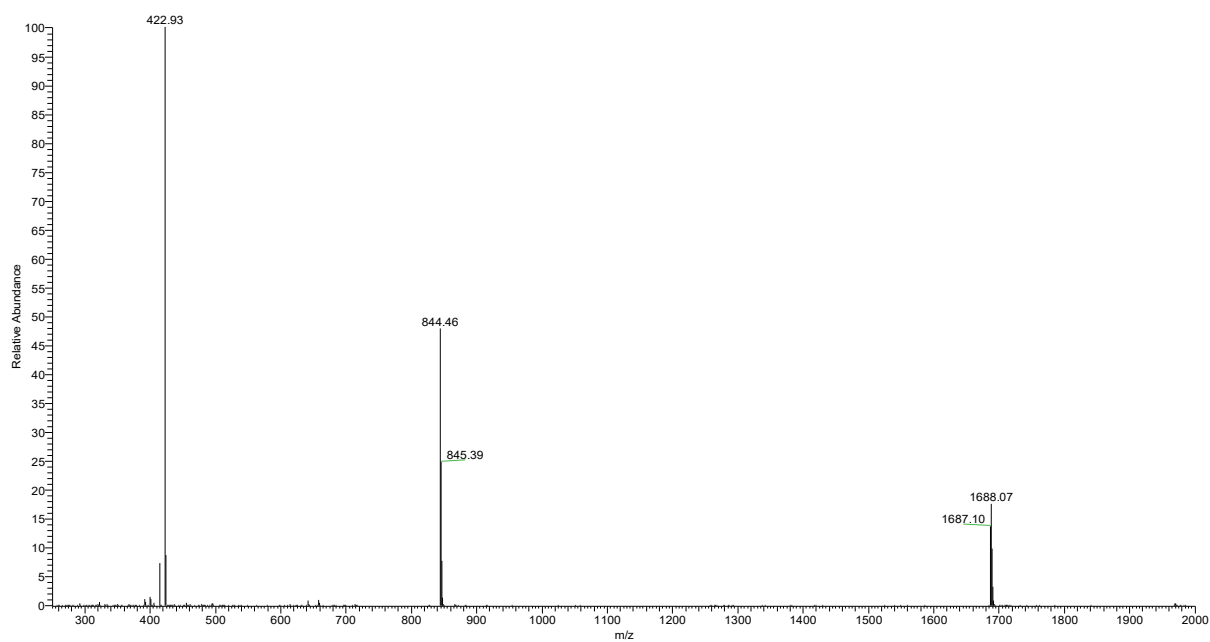
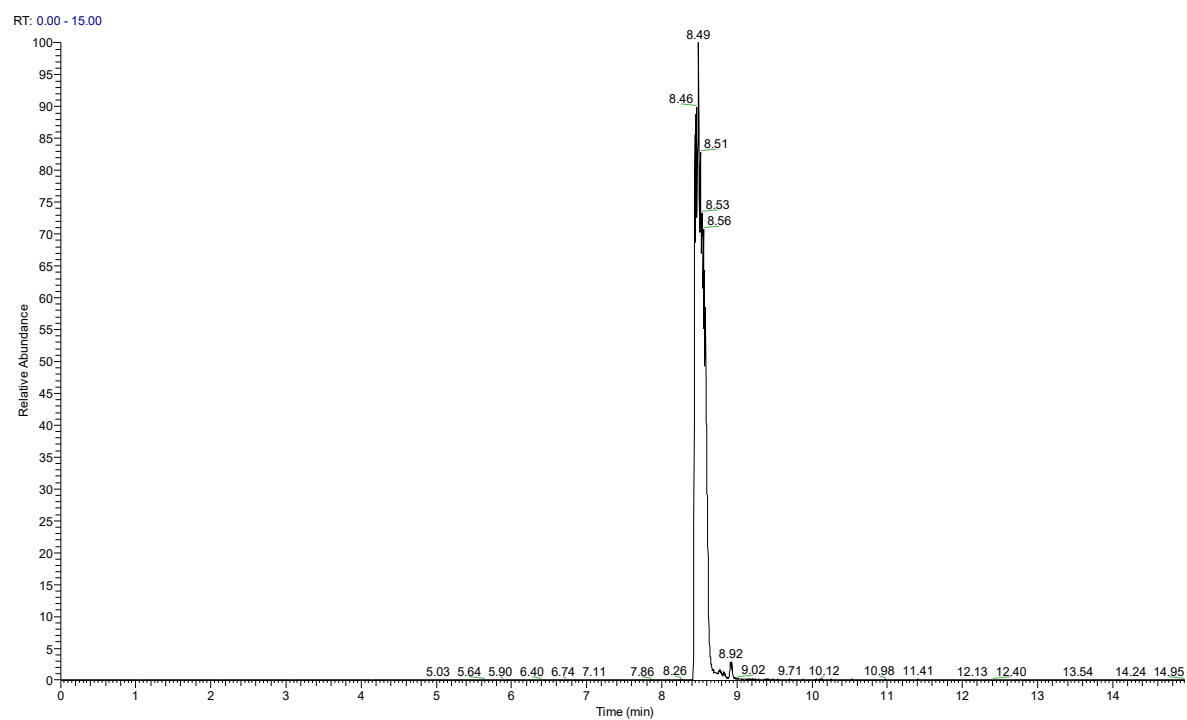
1 hour	Summary	Adjusted P Value
WYKYW vs. W <sup>β</sup> YKYW	****	<0,0001
WYKYW vs. WY <sup>β</sup> KYW	****	<0,0001
WYKYW vs. WYK <sup>β</sup> YW	*	0,0448
WYKYW vs. WYKY <sup>β</sup> W	****	<0,0001
WYKYW vs. WYKYW <sup>β</sup>	**	0,0099
W <sup>β</sup> YKYW vs. WY <sup>β</sup> KYW	ns	0,1567
W <sup>β</sup> YKYW vs. WYK <sup>β</sup> YW	***	0,0001
W <sup>β</sup> YKYW vs. WYKY <sup>β</sup> W	ns	>0,9999
W <sup>β</sup> YKYW vs. WYKYW <sup>β</sup>	***	0,0008
WY <sup>β</sup> KYW vs. WYK <sup>β</sup> YW	ns	0,5618
WY <sup>β</sup> KYW vs. WYKY <sup>β</sup> W	*	0,0141
WY <sup>β</sup> KYW vs. WYKYW <sup>β</sup>	ns	0,8793
WYK <sup>β</sup> YW vs. WYKY <sup>β</sup> W	****	<0,0001
WYK <sup>β</sup> YW vs. WYKYW <sup>β</sup>	ns	>0,9999
WYKY <sup>β</sup> W vs. WYKYW <sup>β</sup>	****	<0,0001

4 hours	Summary	Adjusted P Value
WYKYW vs. W <sup>β</sup> YKYW	****	<0,0001
WYKYW vs. WY <sup>β</sup> KYW	ns	0,1364
WYKYW vs. WYK <sup>β</sup> YW	****	<0,0001
WYKYW vs. WYKY <sup>β</sup> W	****	<0,0001
WYKYW vs. WYKYW <sup>β</sup>	****	<0,0001
W <sup>β</sup> YKYW vs. WY <sup>β</sup> KYW	****	<0,0001
W <sup>β</sup> YKYW vs. WYK <sup>β</sup> YW	ns	0,0734
W <sup>β</sup> YKYW vs. WYKY <sup>β</sup> W	ns	>0,9999
W <sup>β</sup> YKYW vs. WYKYW <sup>β</sup>	**	0,0082
WY <sup>β</sup> KYW vs. WYK <sup>β</sup> YW	ns	0,1742
WY <sup>β</sup> KYW vs. WYKY <sup>β</sup> W	****	<0,0001
WY <sup>β</sup> KYW vs. WYKYW <sup>β</sup>	****	<0,0001
WYK <sup>β</sup> YW vs. WYKY <sup>β</sup> W	*	0,0248
WYK <sup>β</sup> YW vs. WYKYW <sup>β</sup>	****	<0,0001
WYKY <sup>β</sup> W vs. WYKYW <sup>β</sup>	ns	0,0891

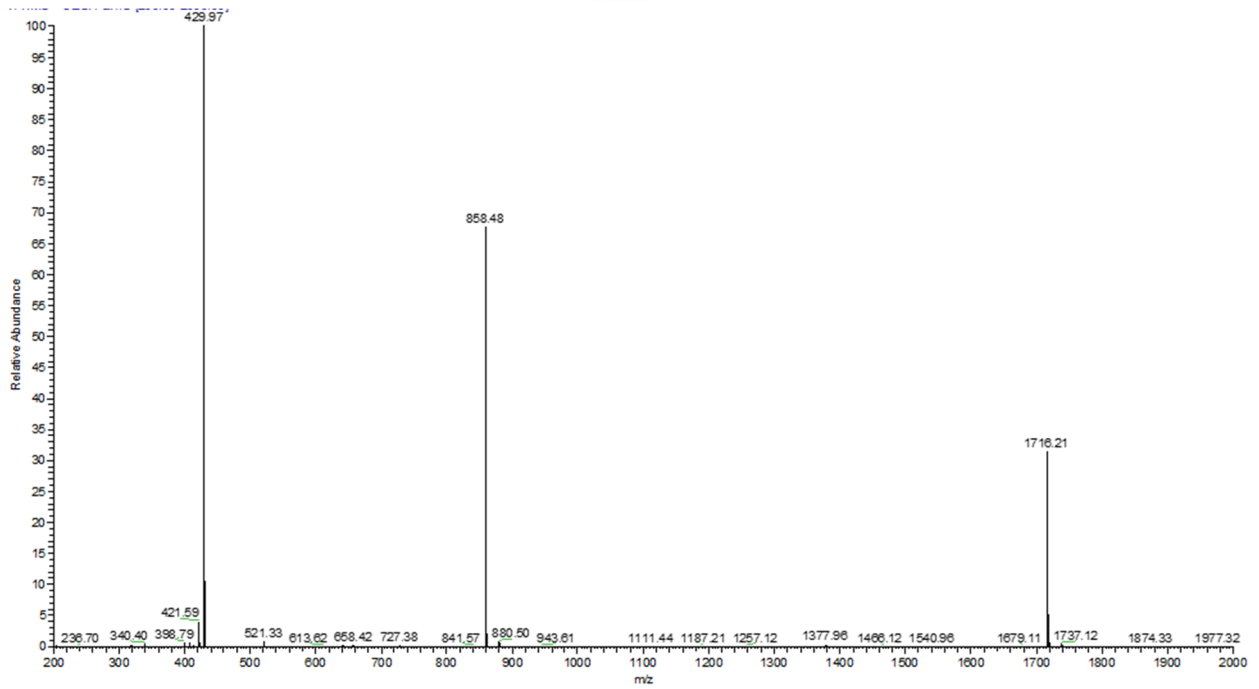
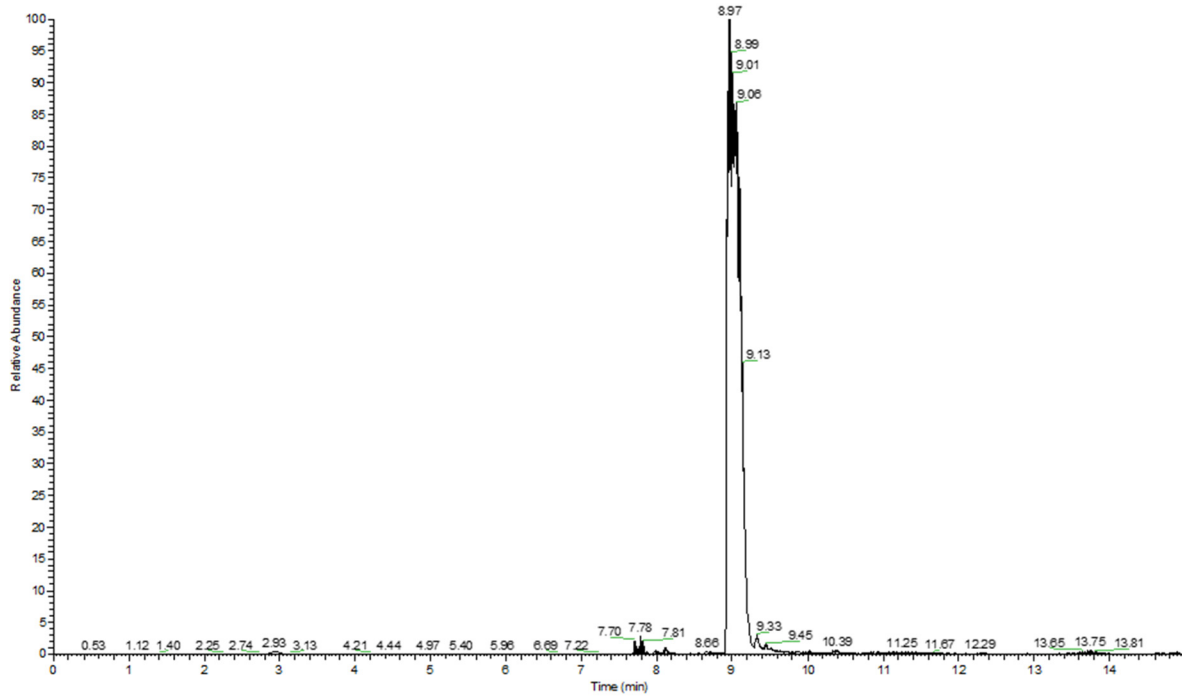
## Peptide characterization data

HPLC chromatograms and MS spectra for each sequence are shown below.

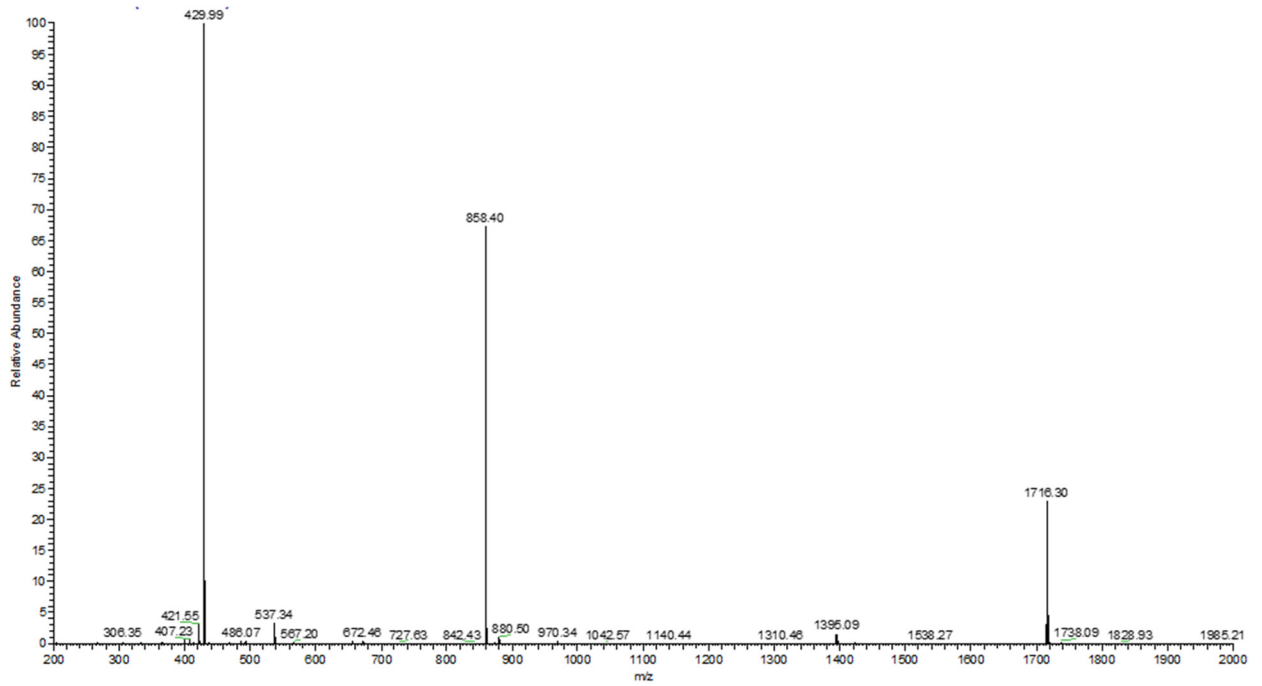
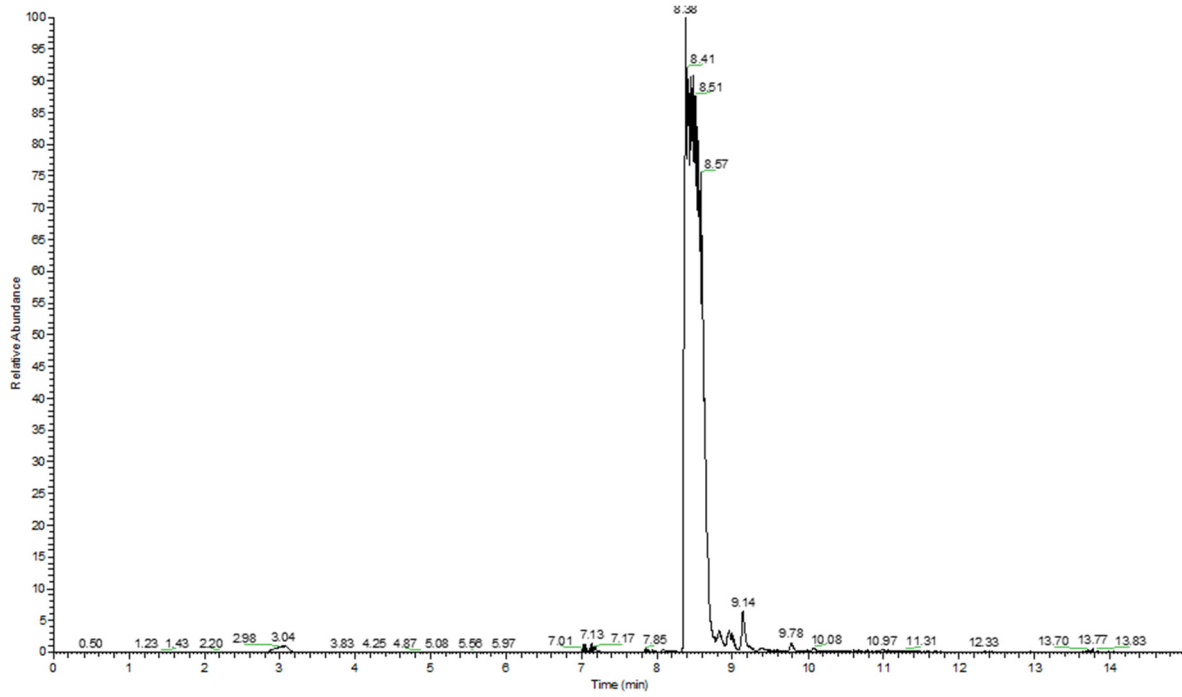
### WYKYW (WYKYW-NH<sub>2</sub>)



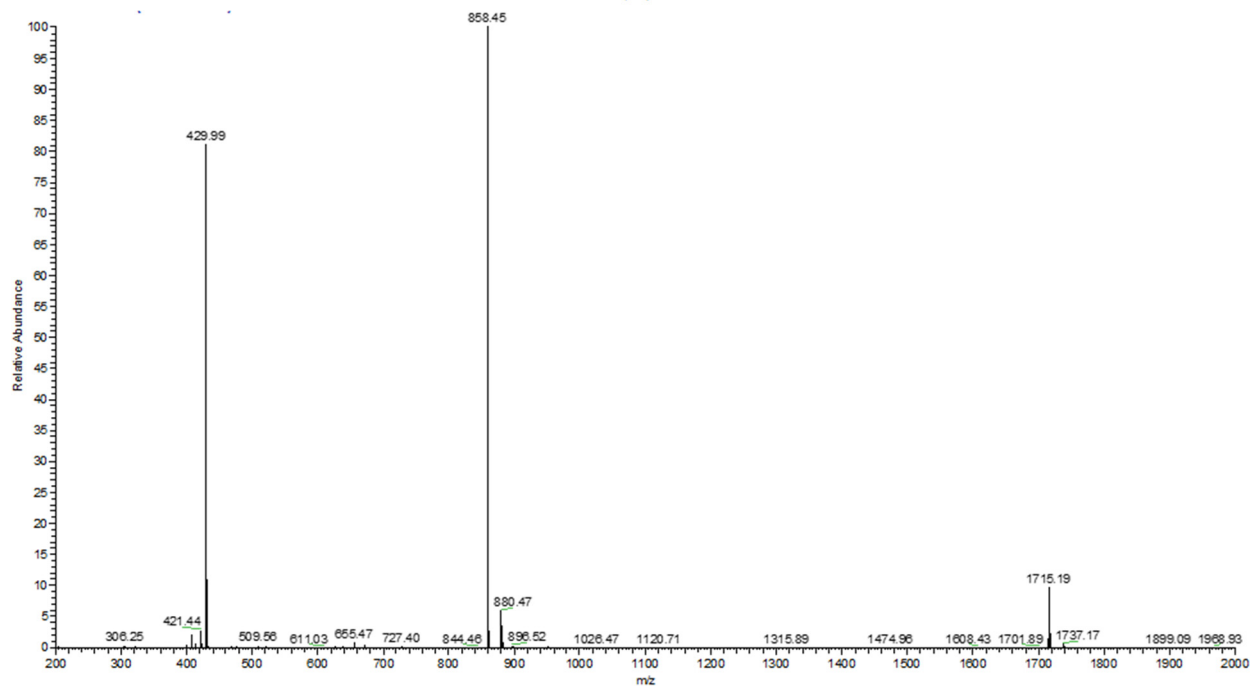
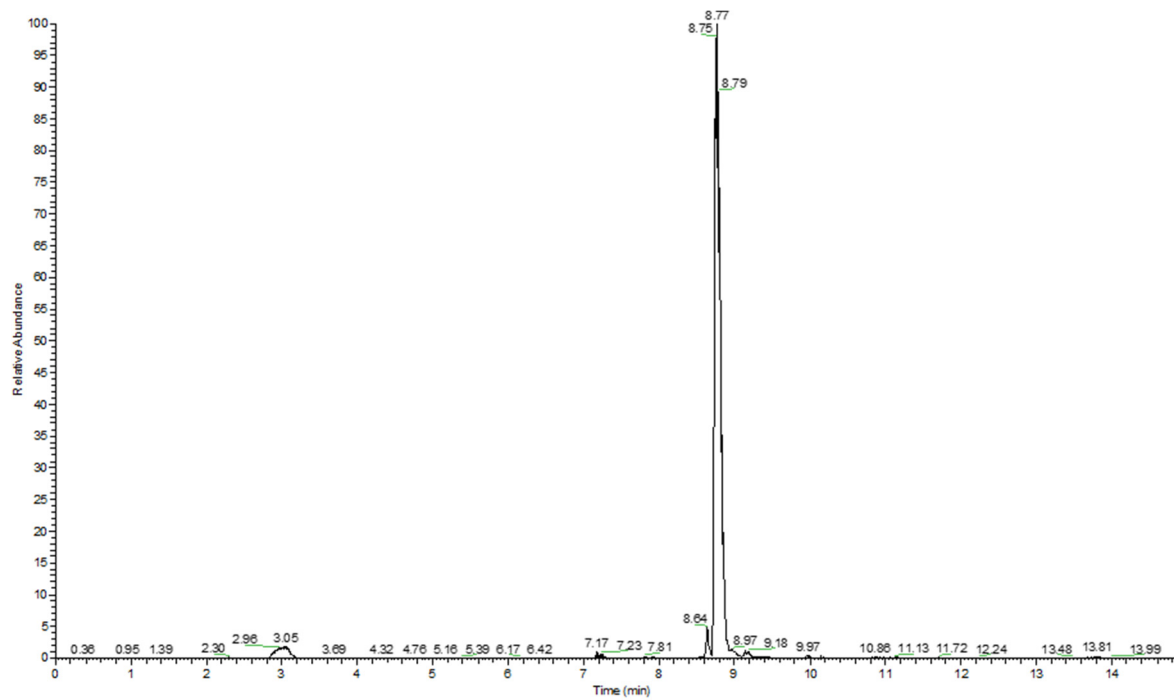
W $\beta$ YKYW



WY<sup>β</sup>KYW

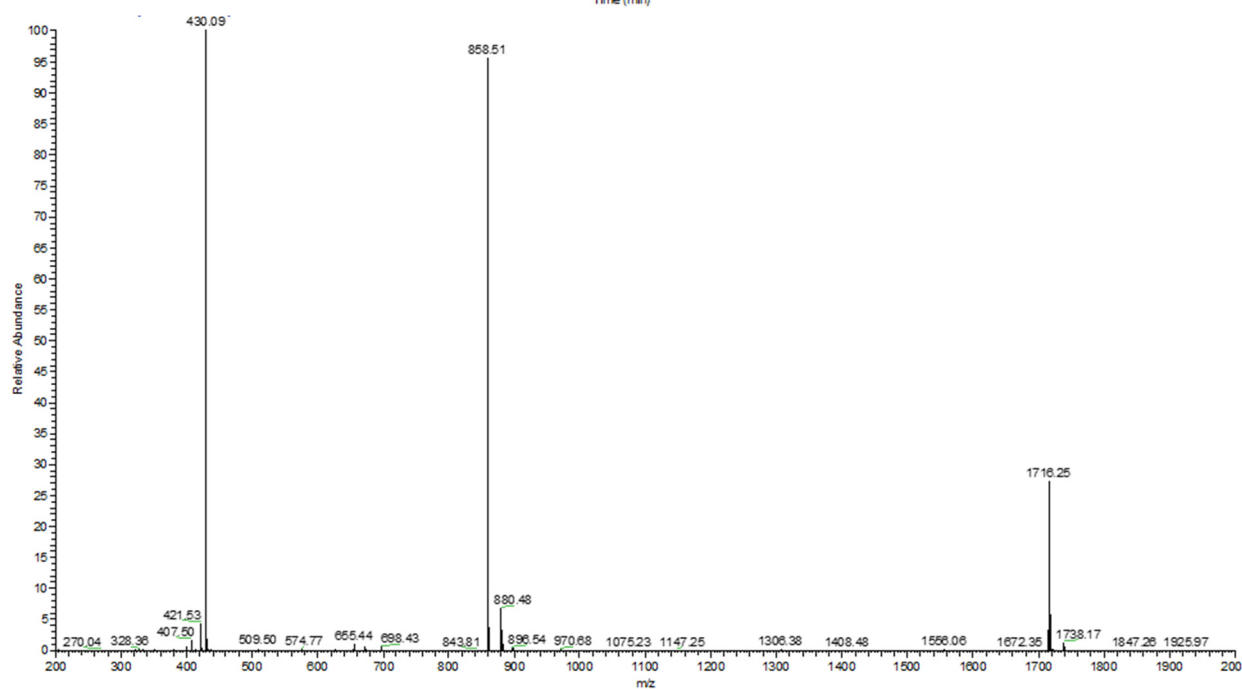
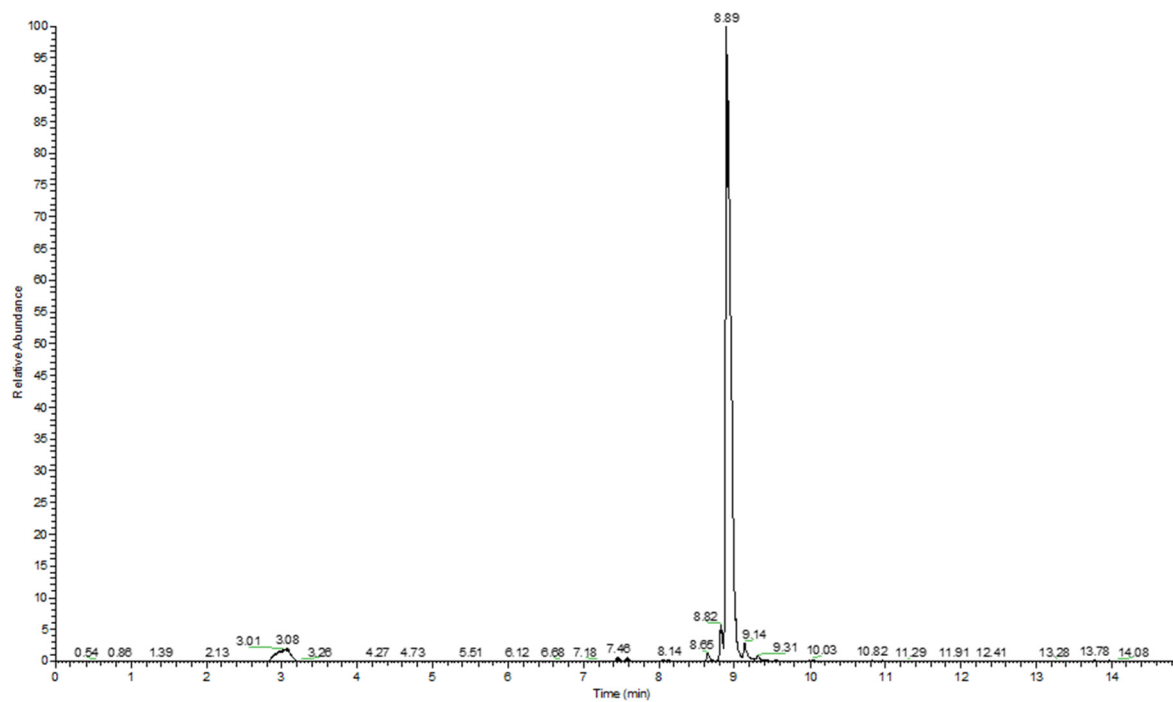


WYK $\beta$ YW

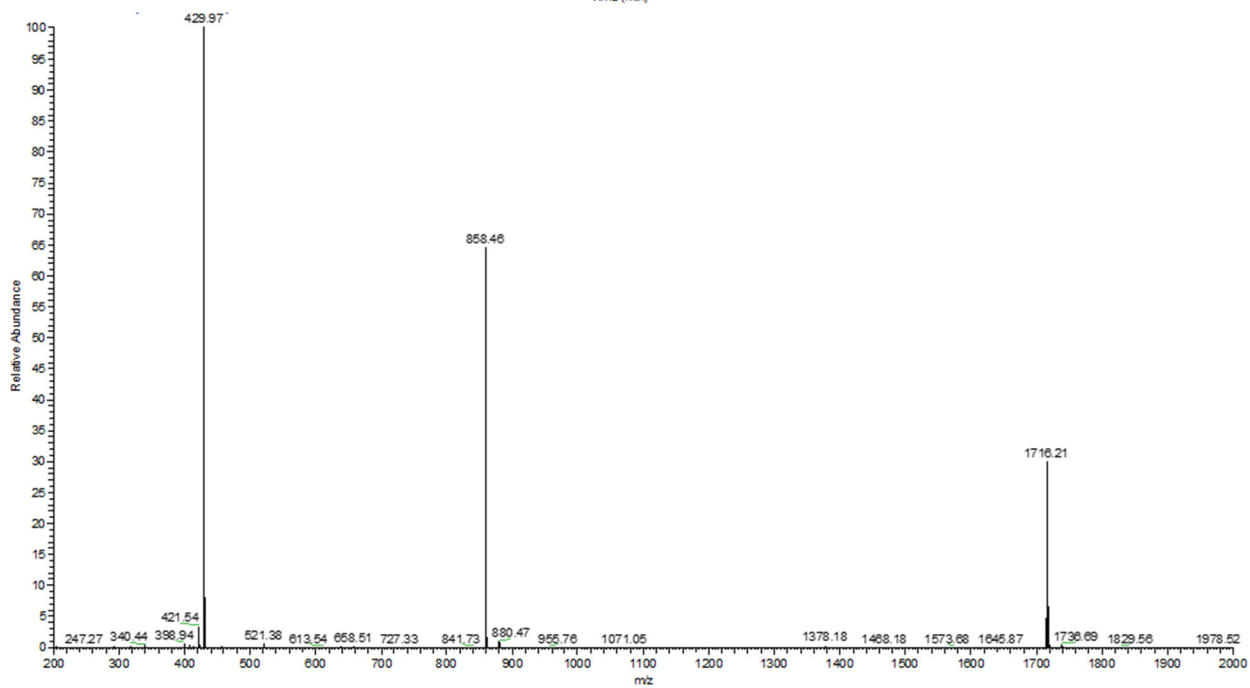
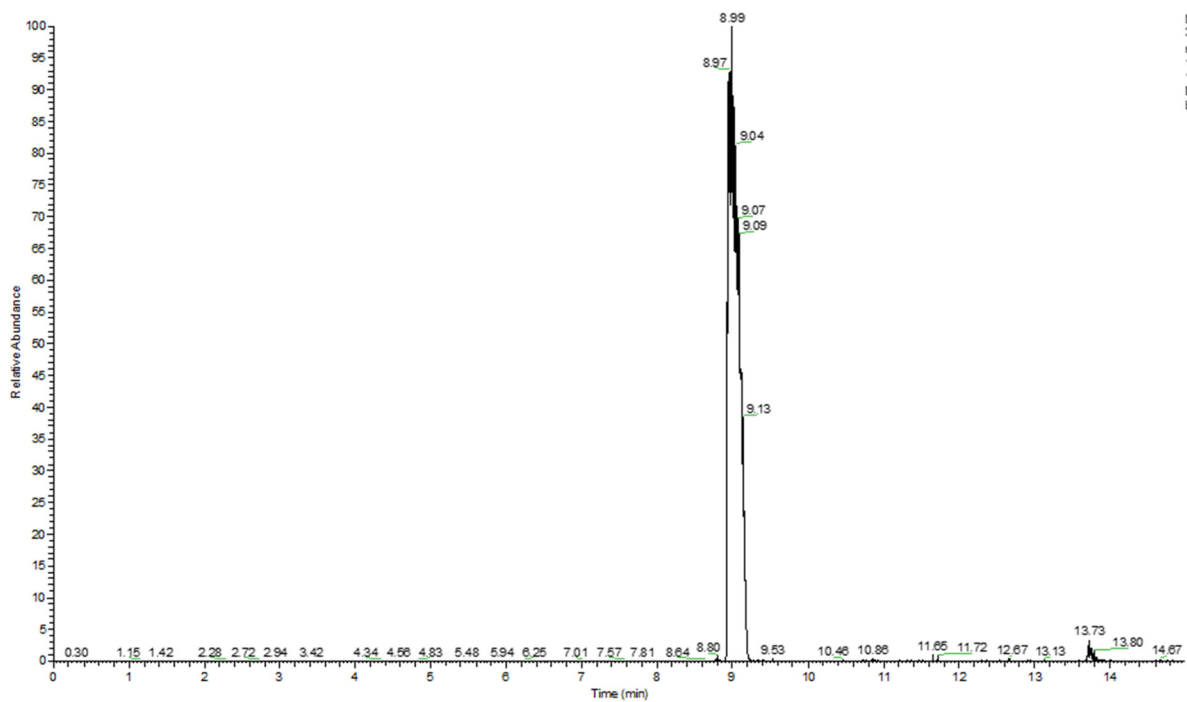




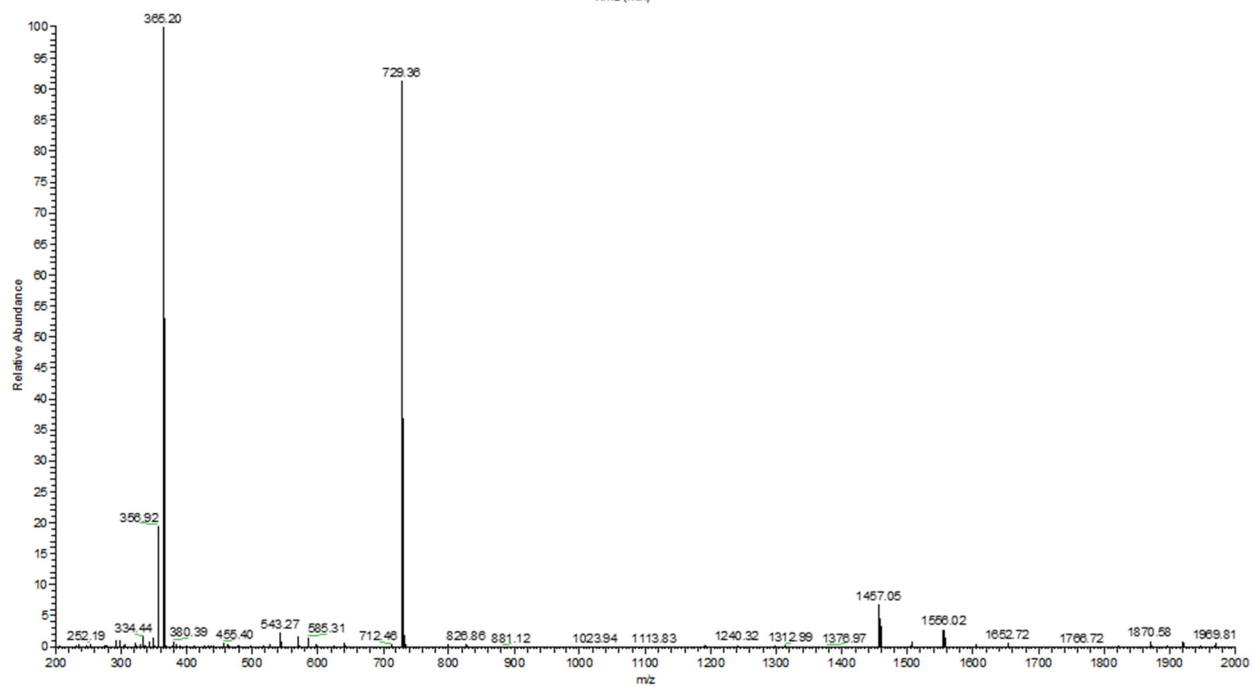
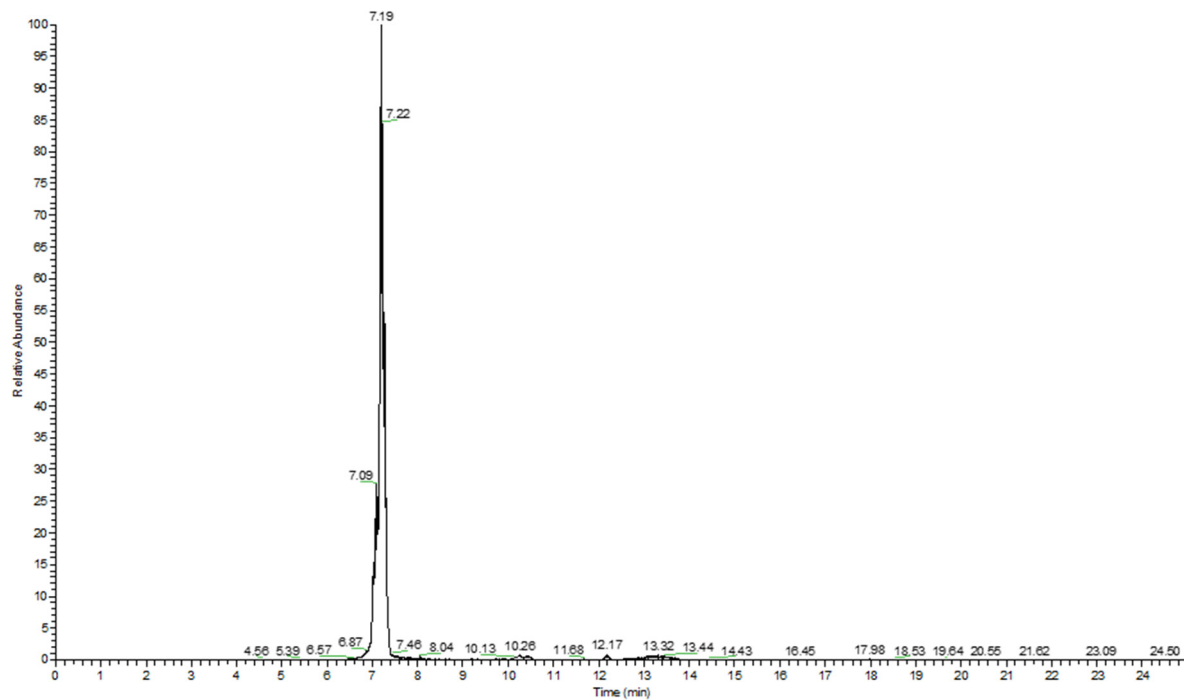
WYKY $\beta$ W



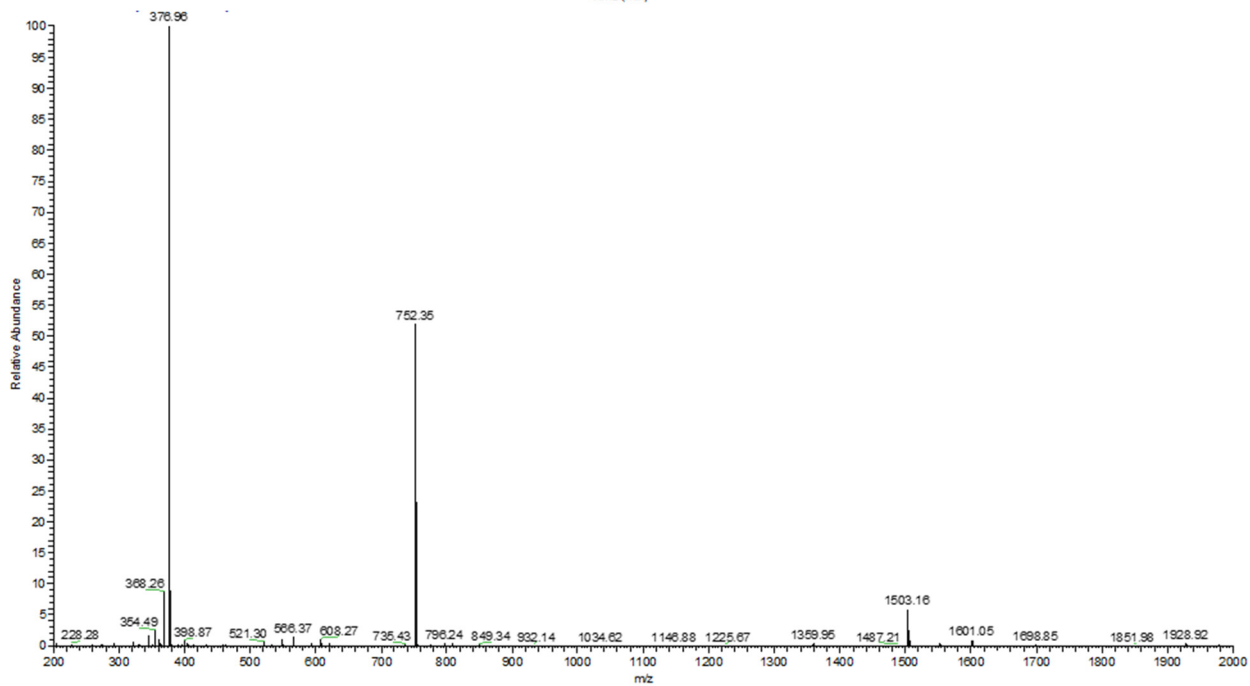
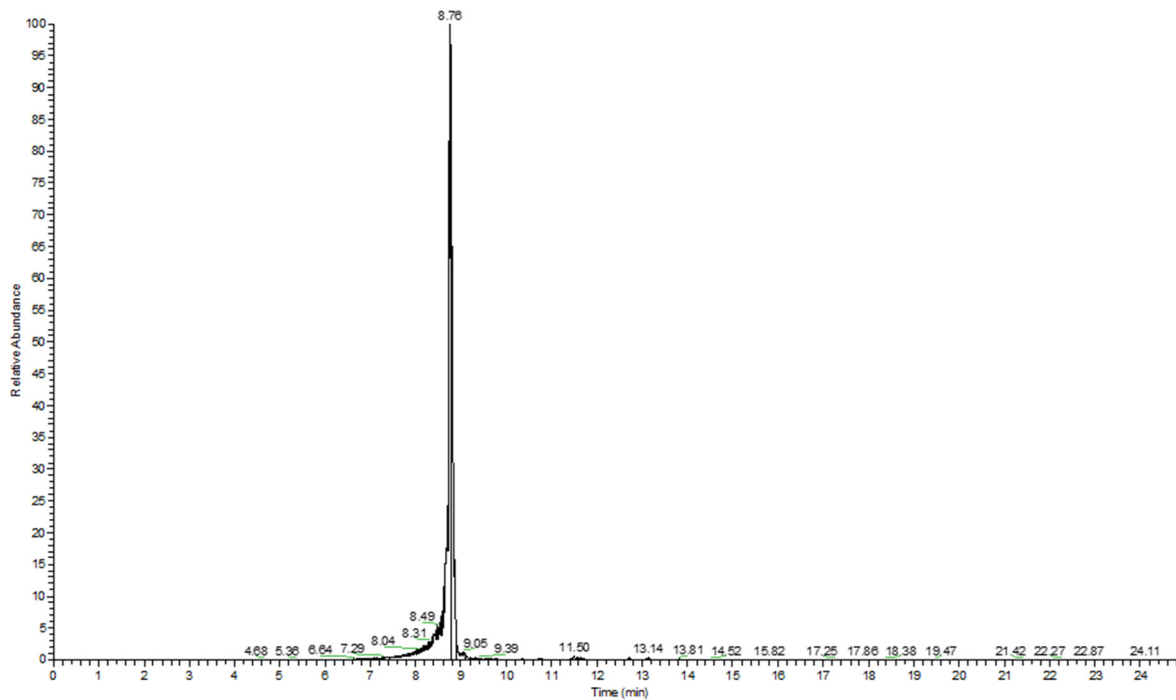
WYKYW $\beta$



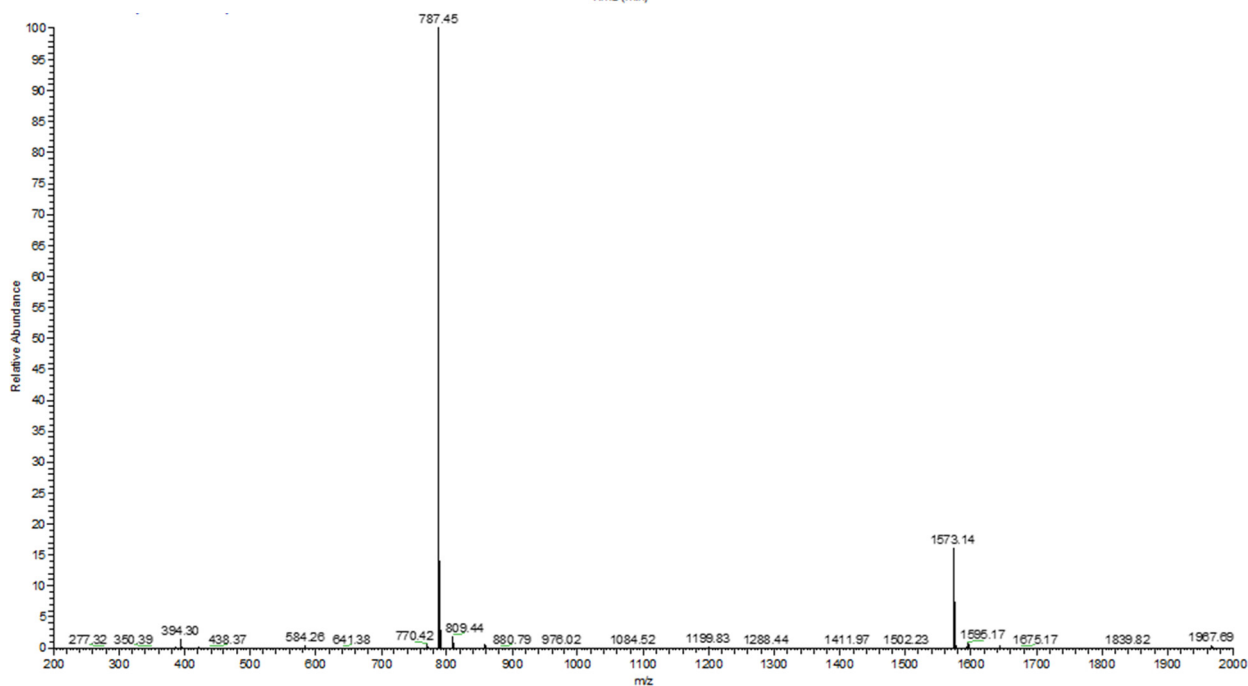
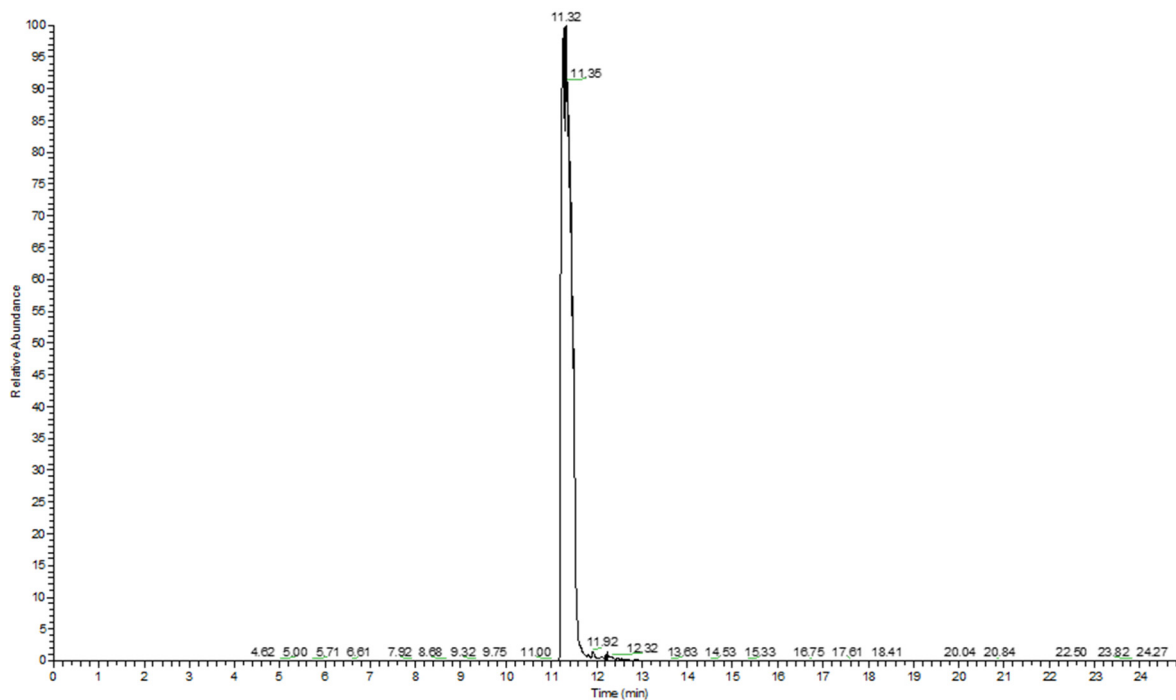
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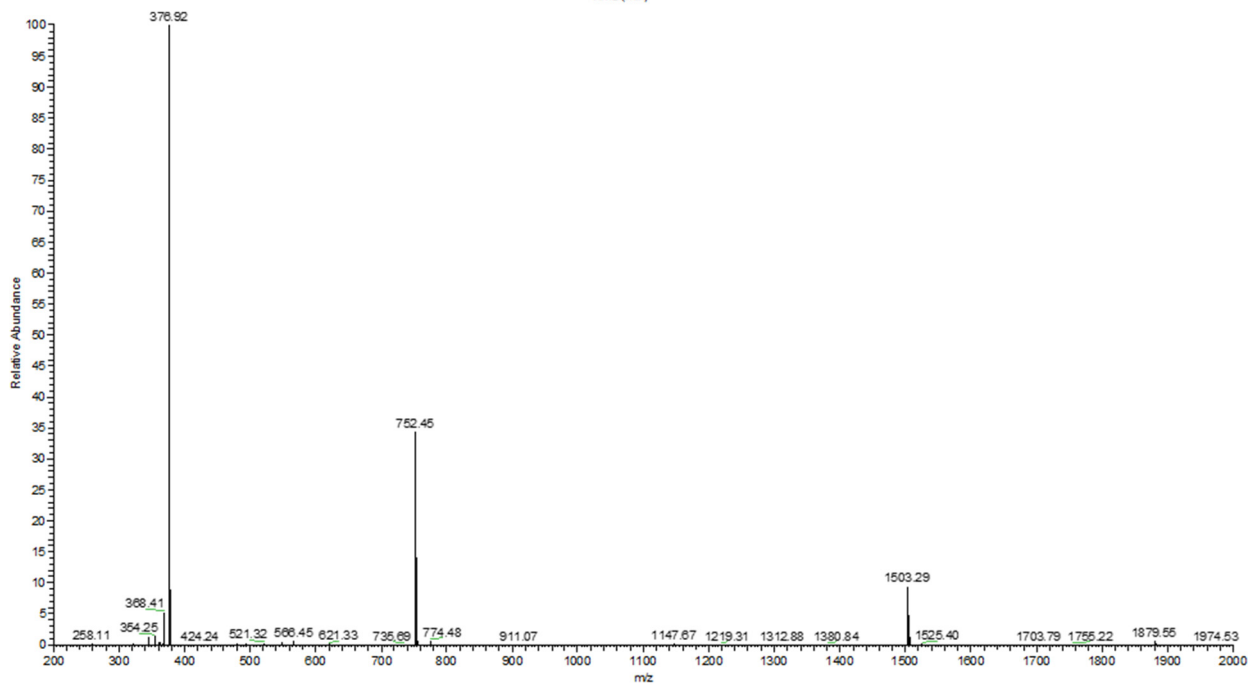
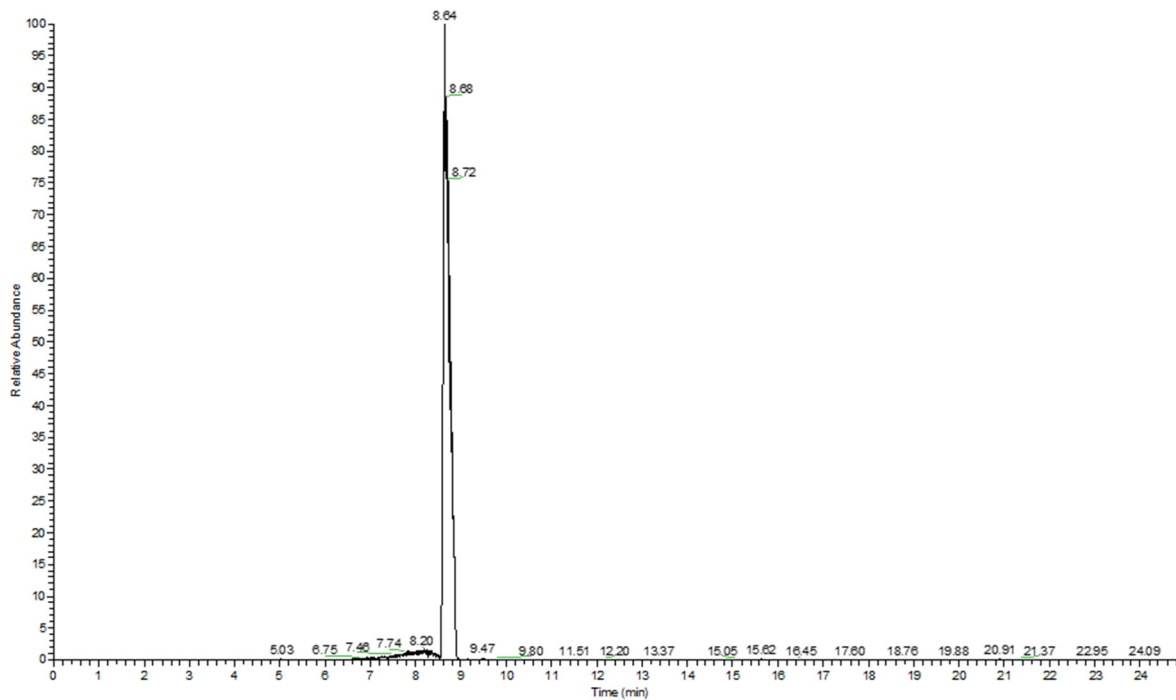
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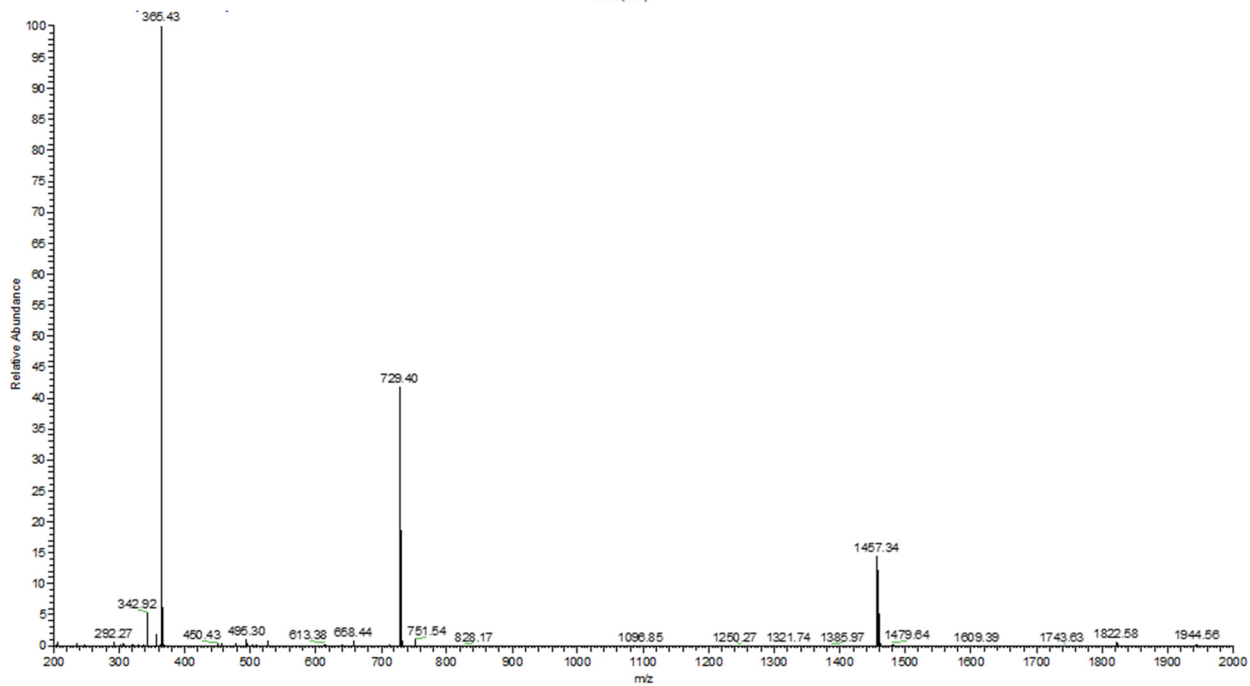
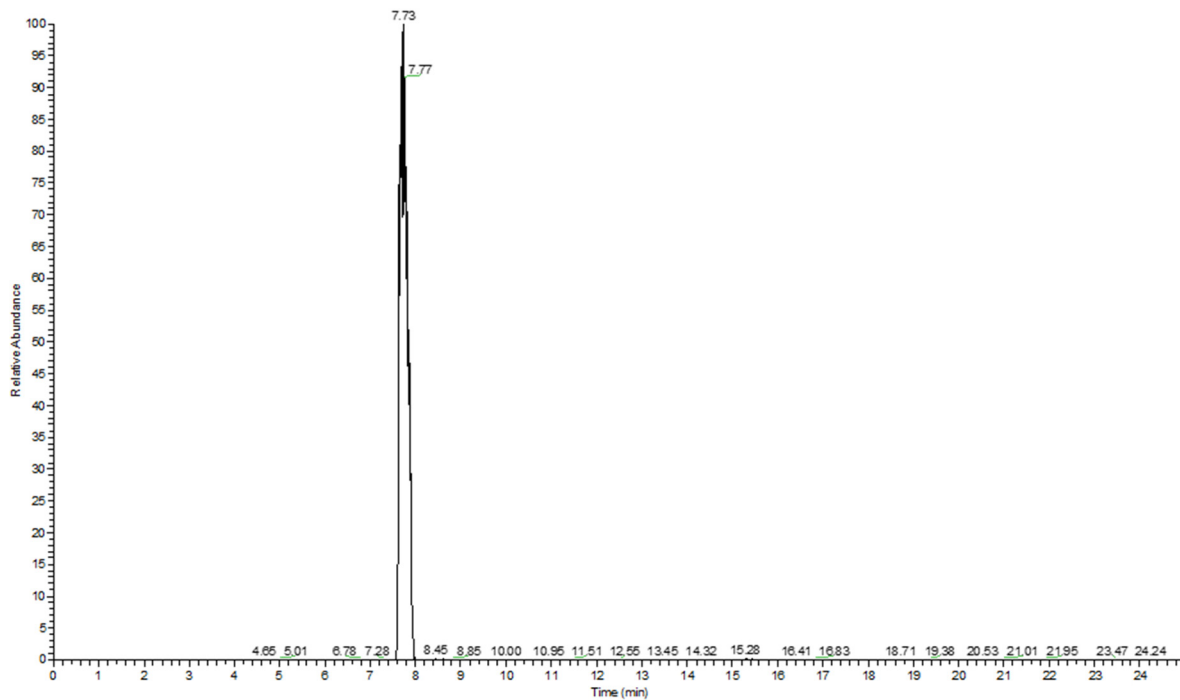
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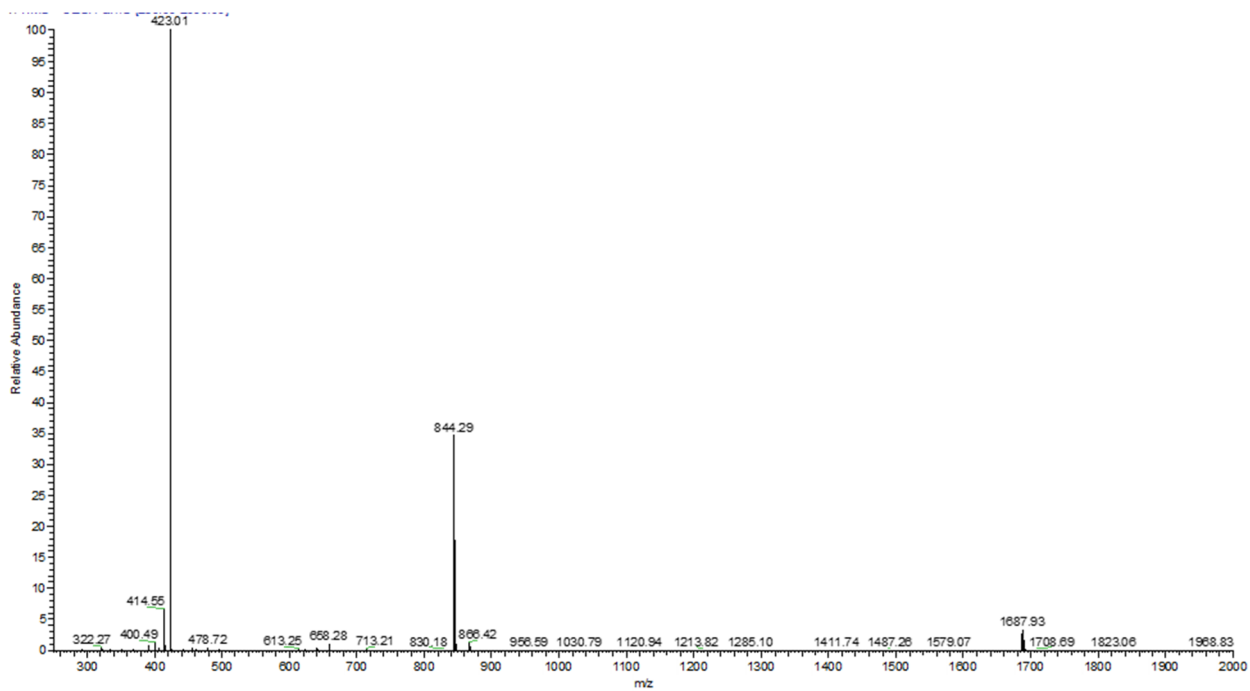
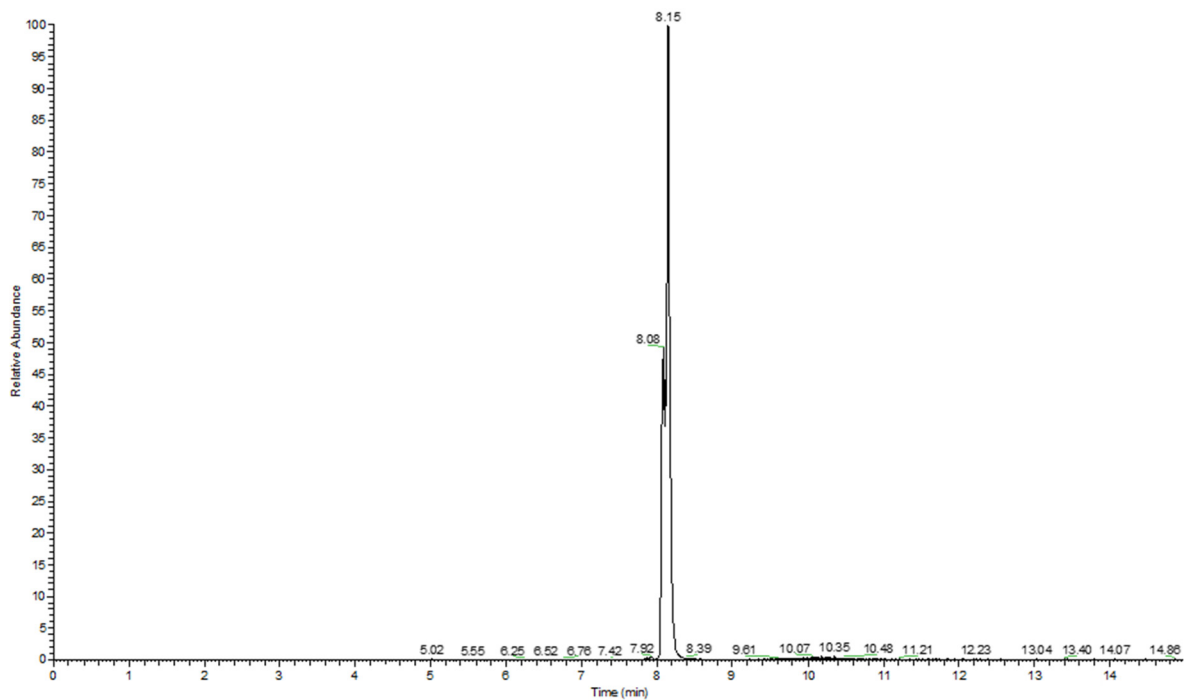
# WYKAW



# WYKYA

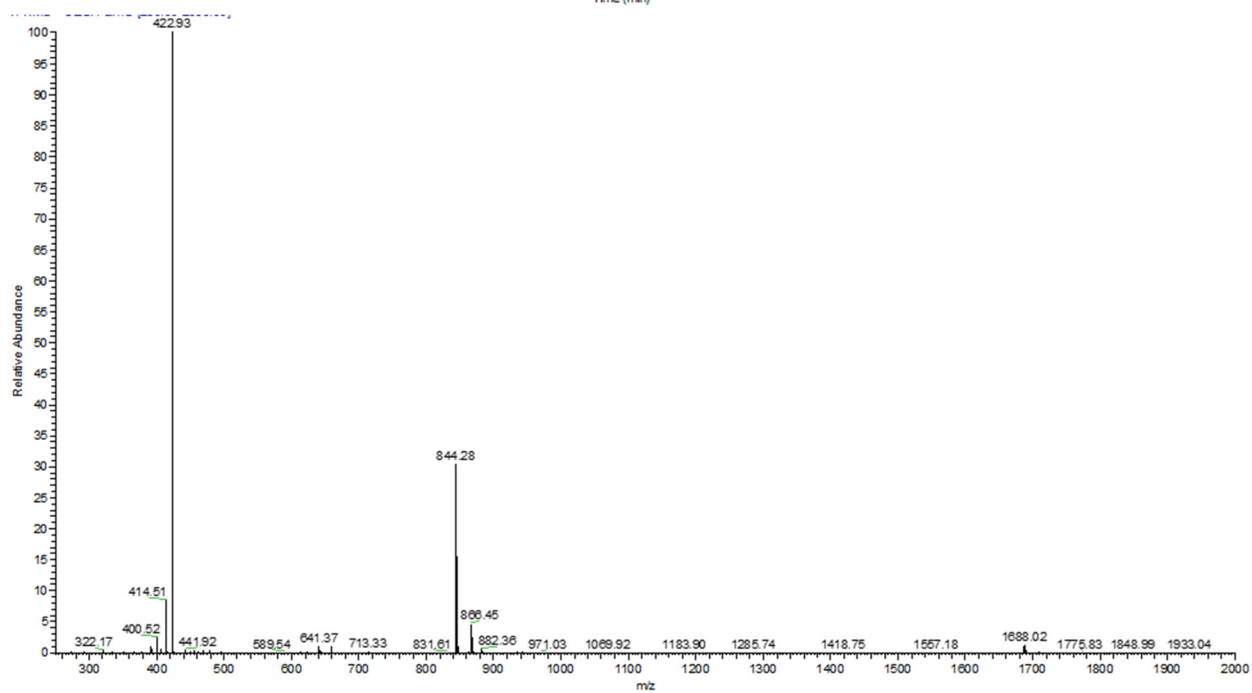
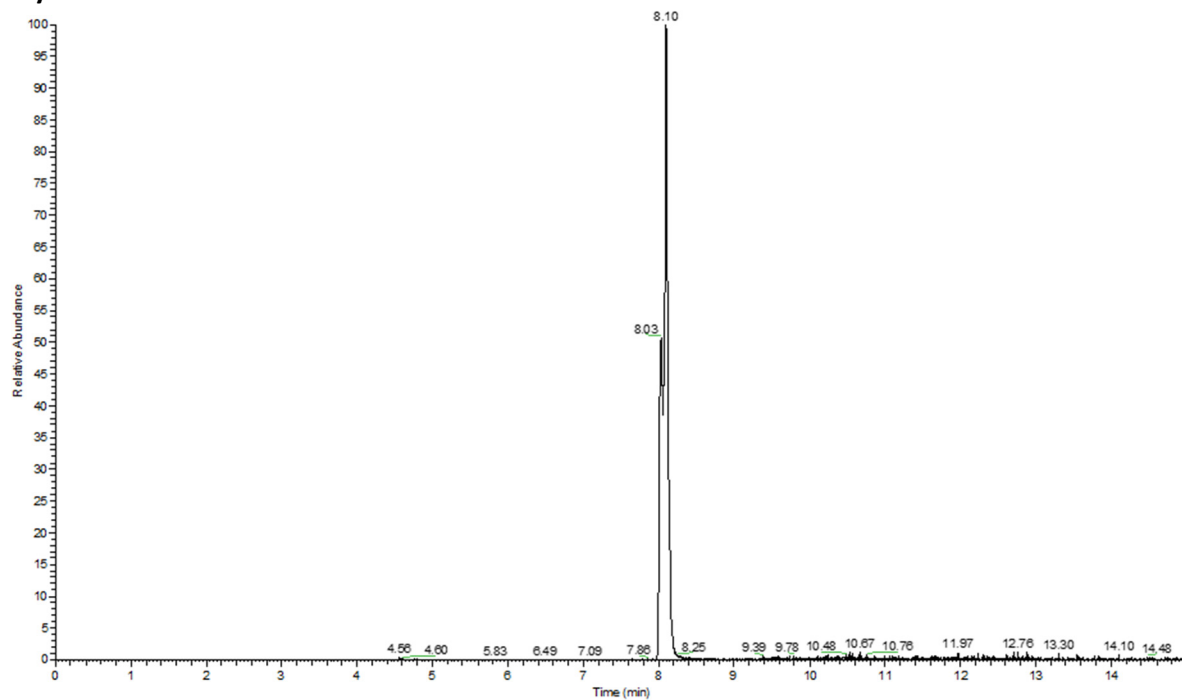


wYKYW

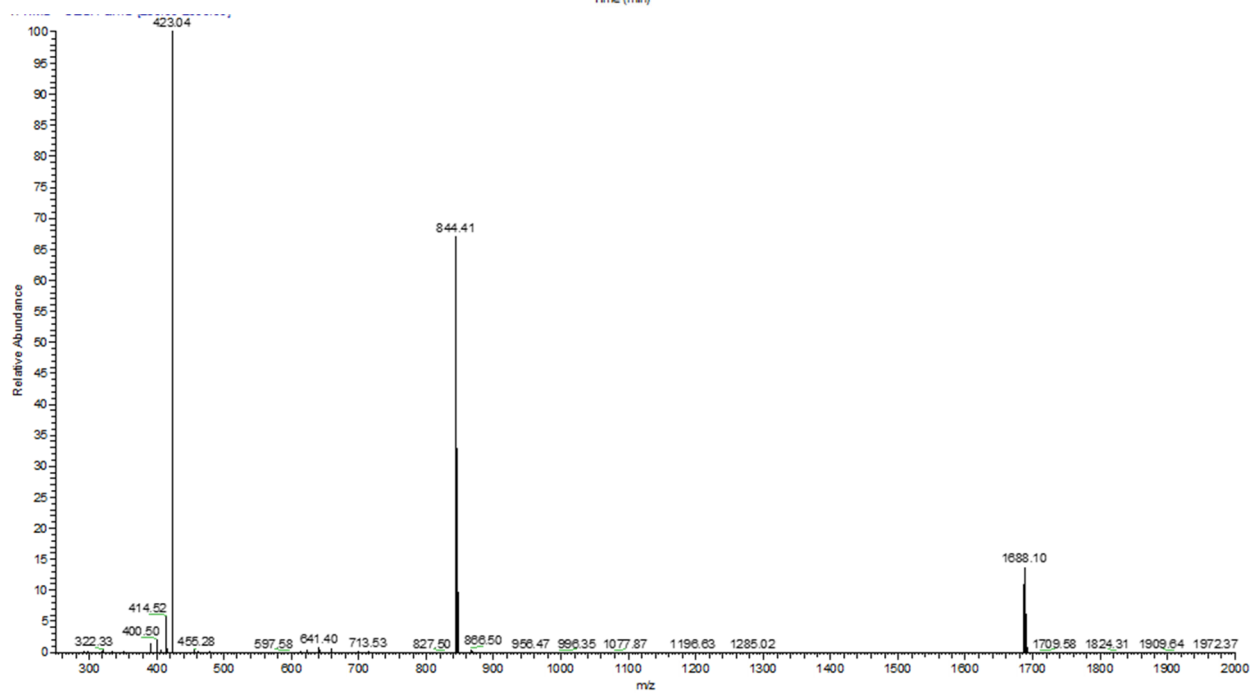
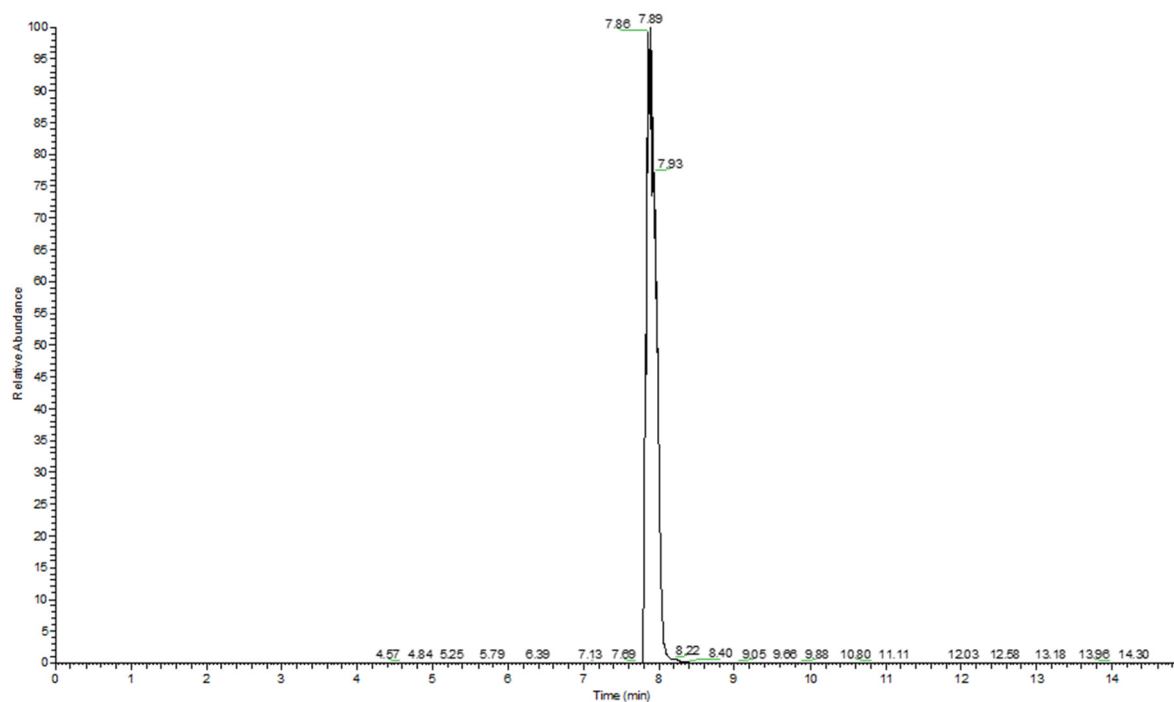




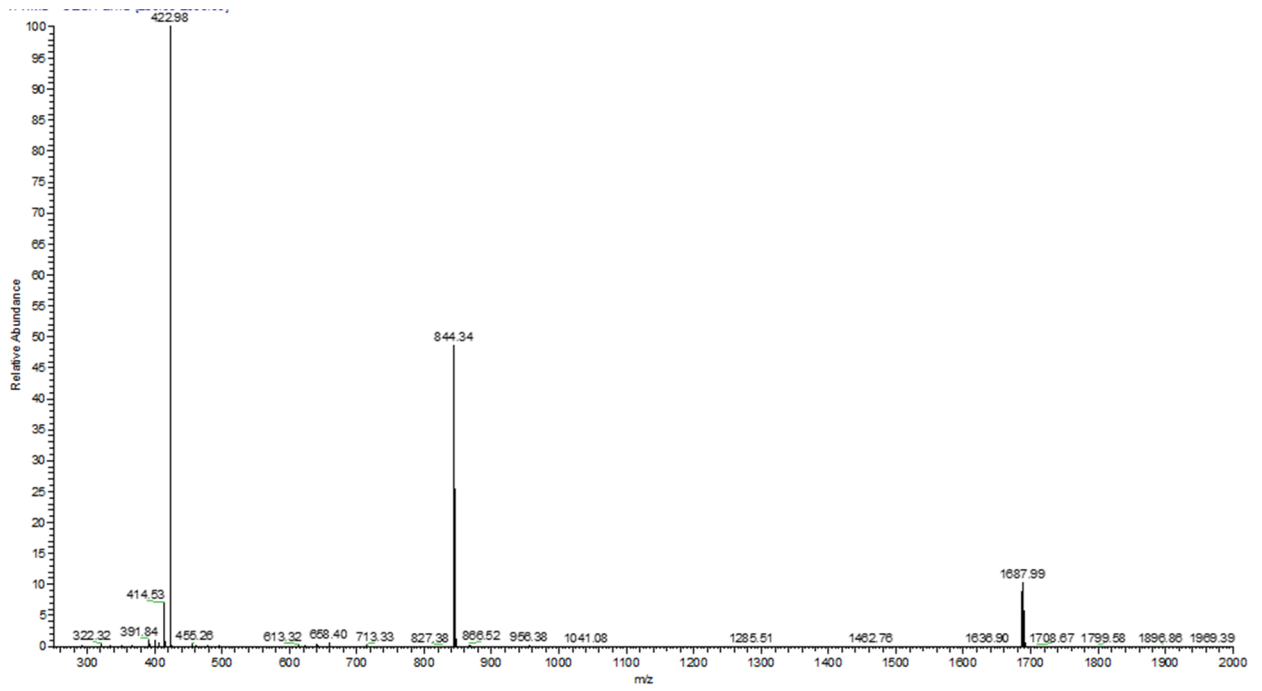
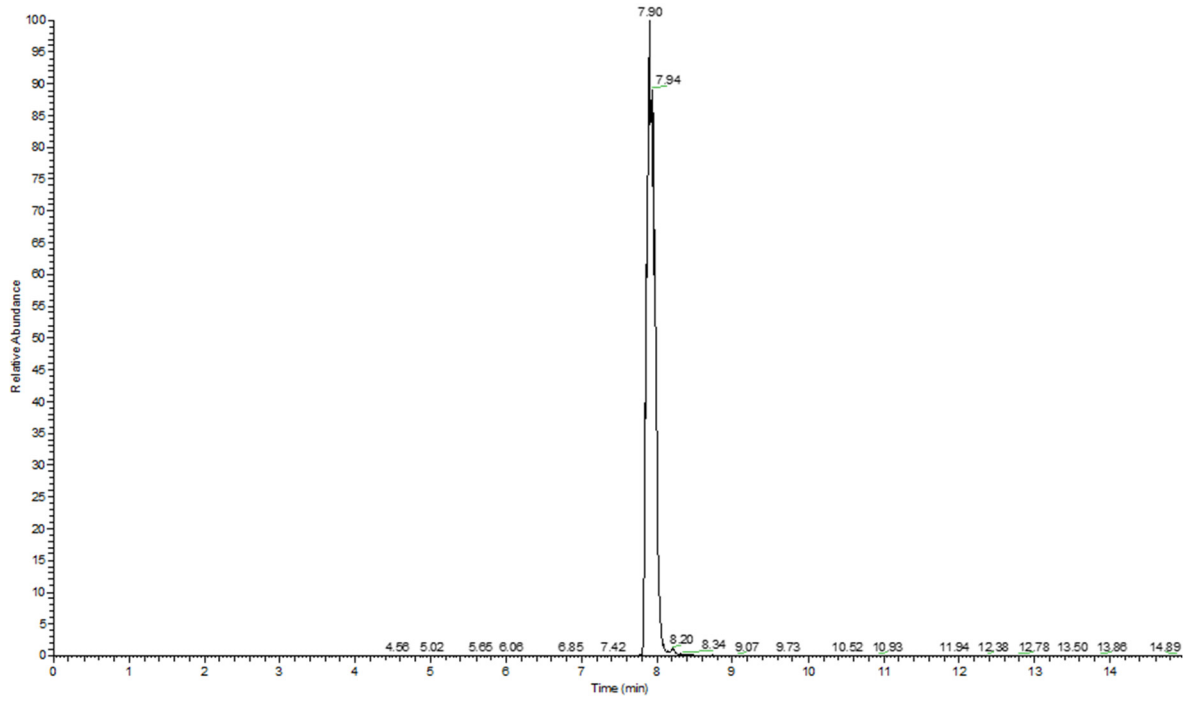
WyKYW



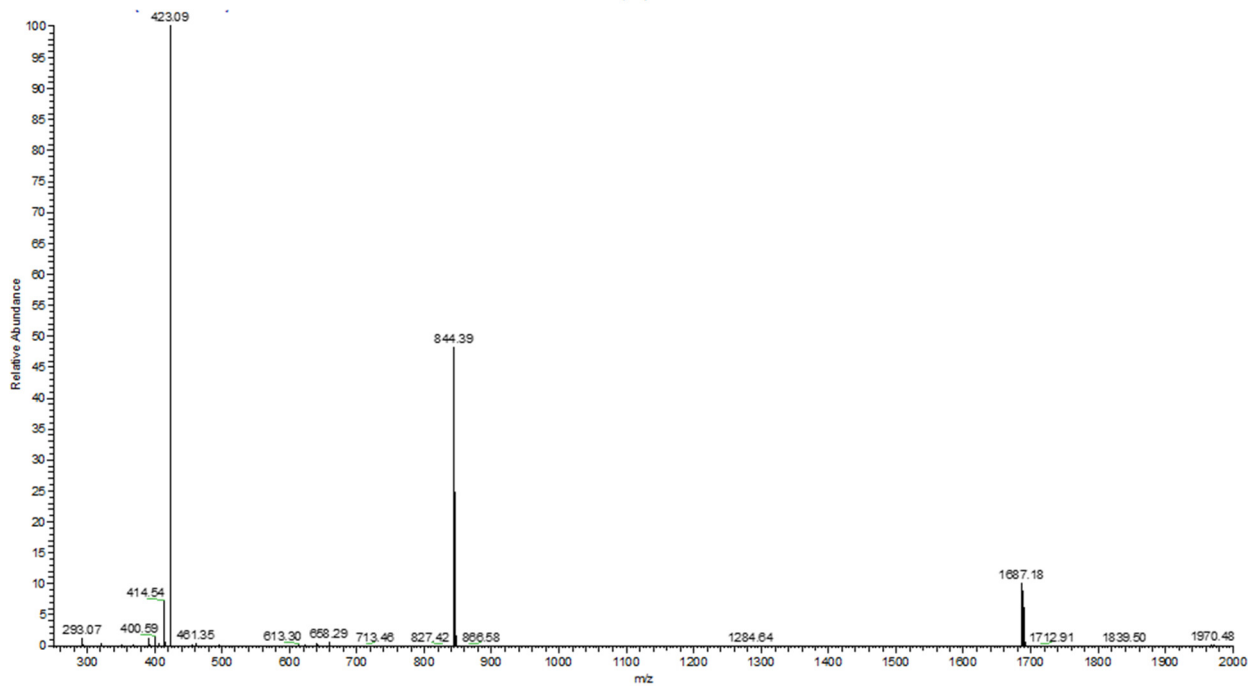
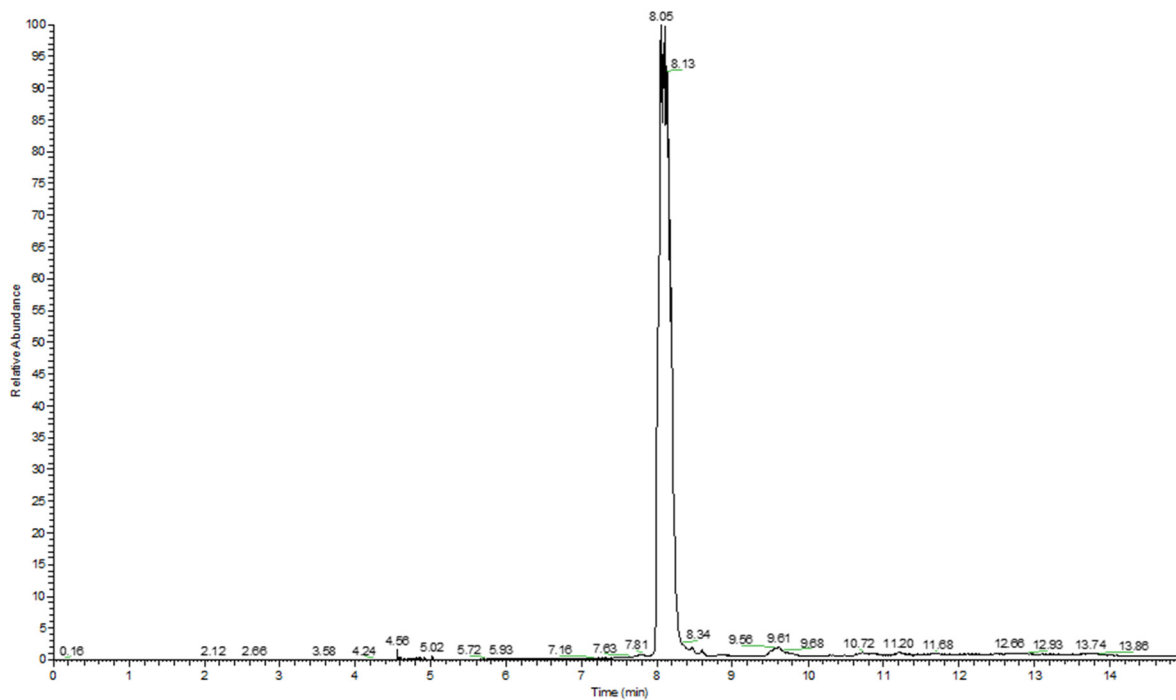
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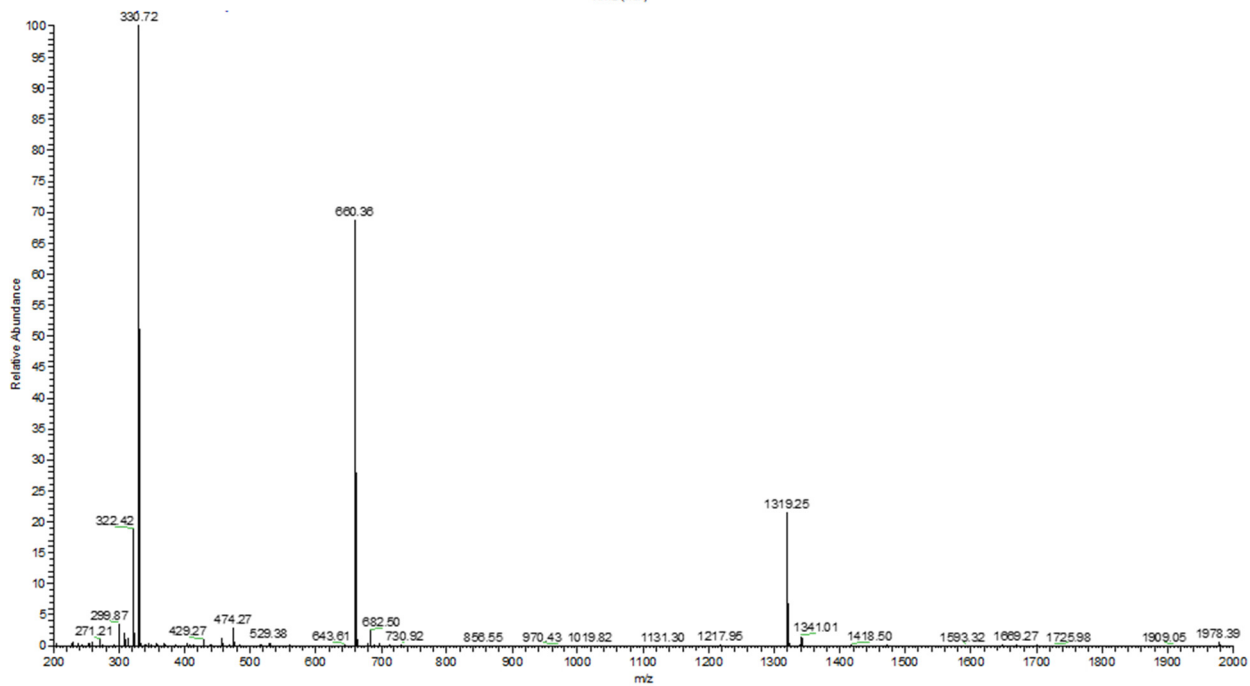
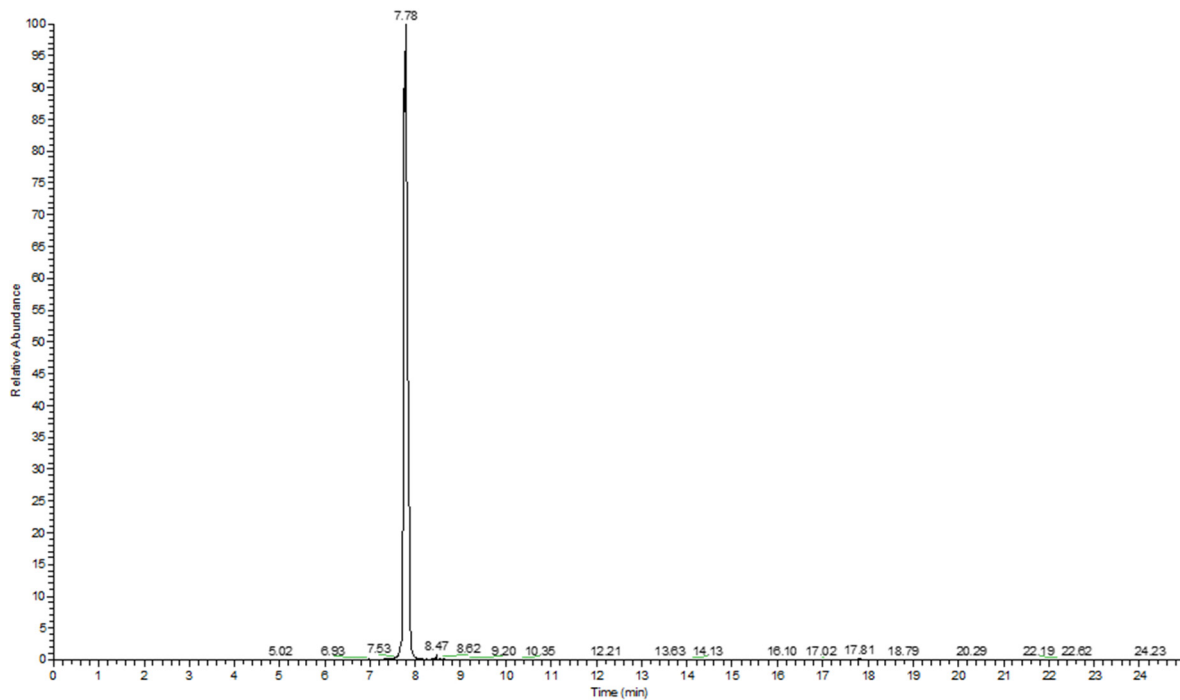
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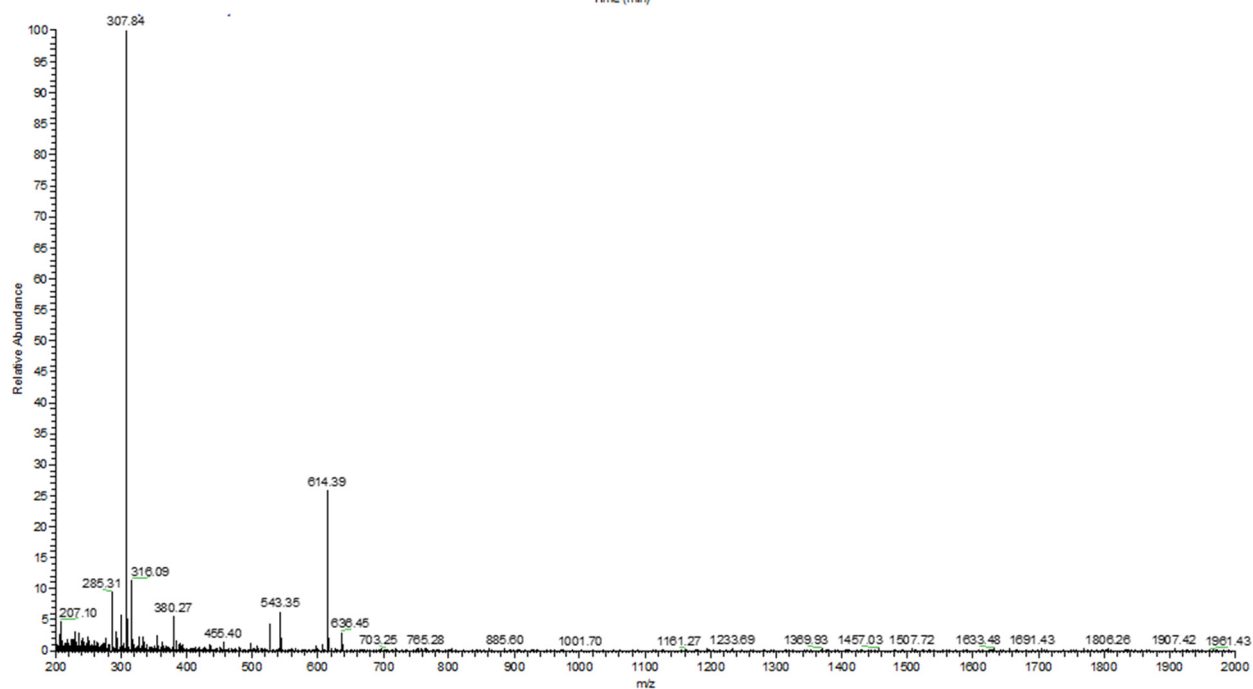
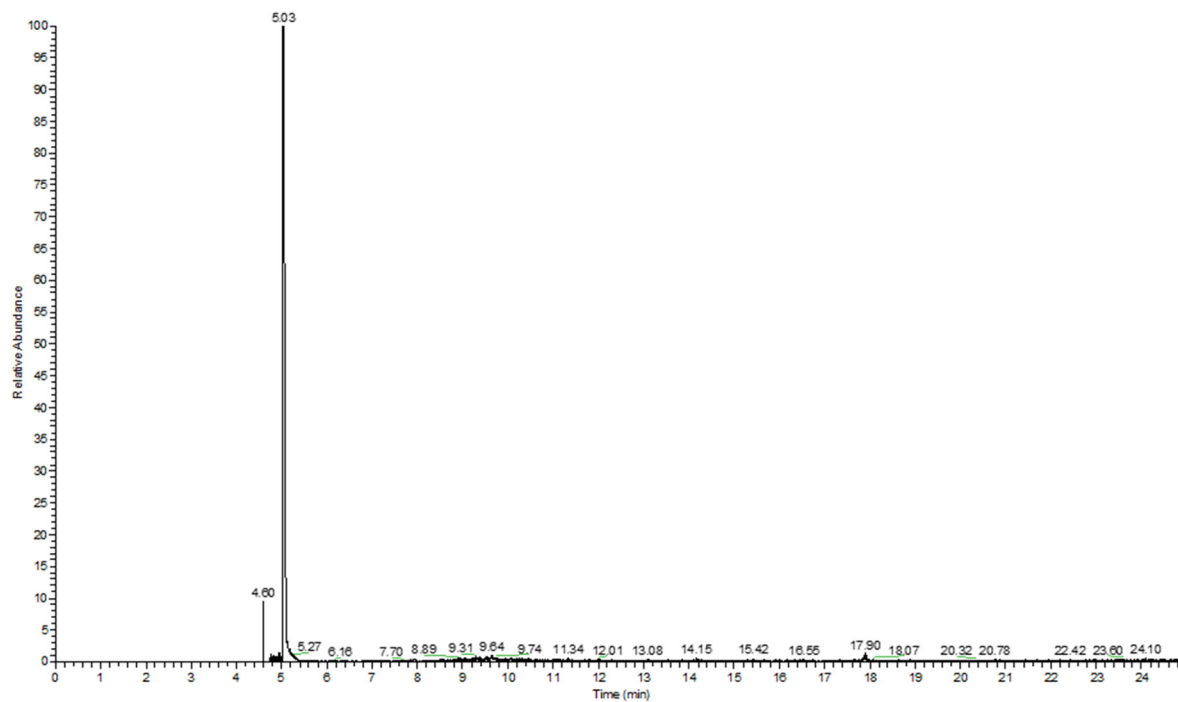
WYKYw



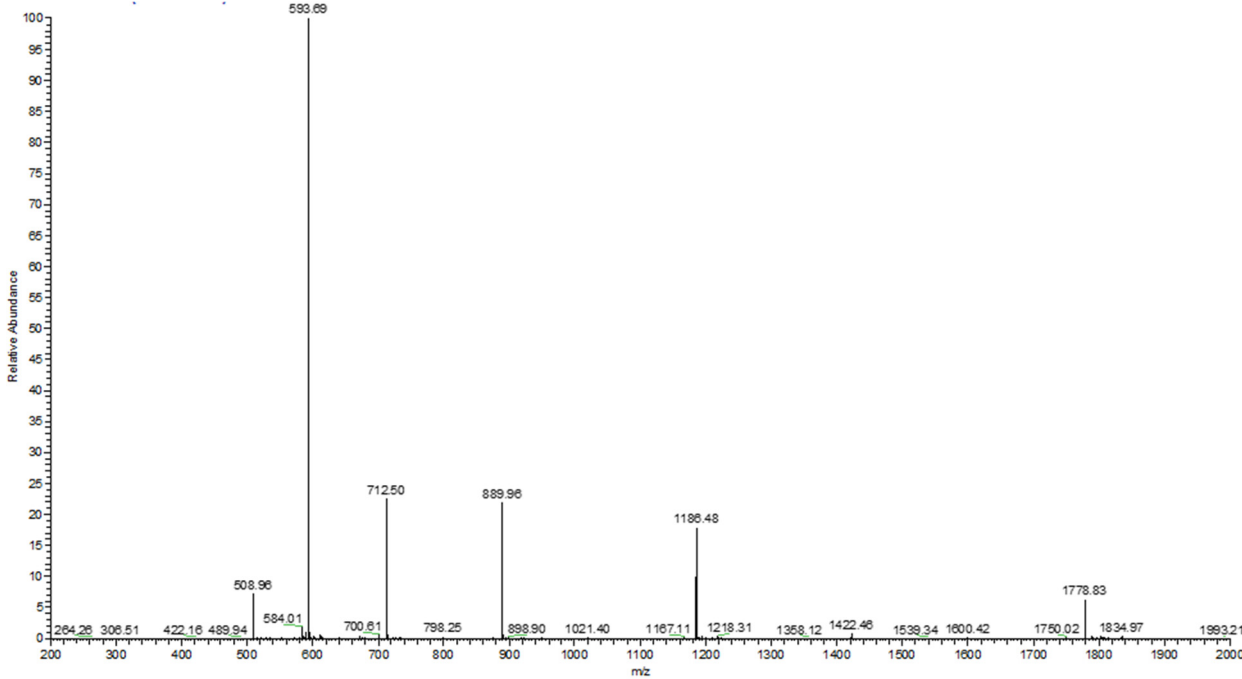
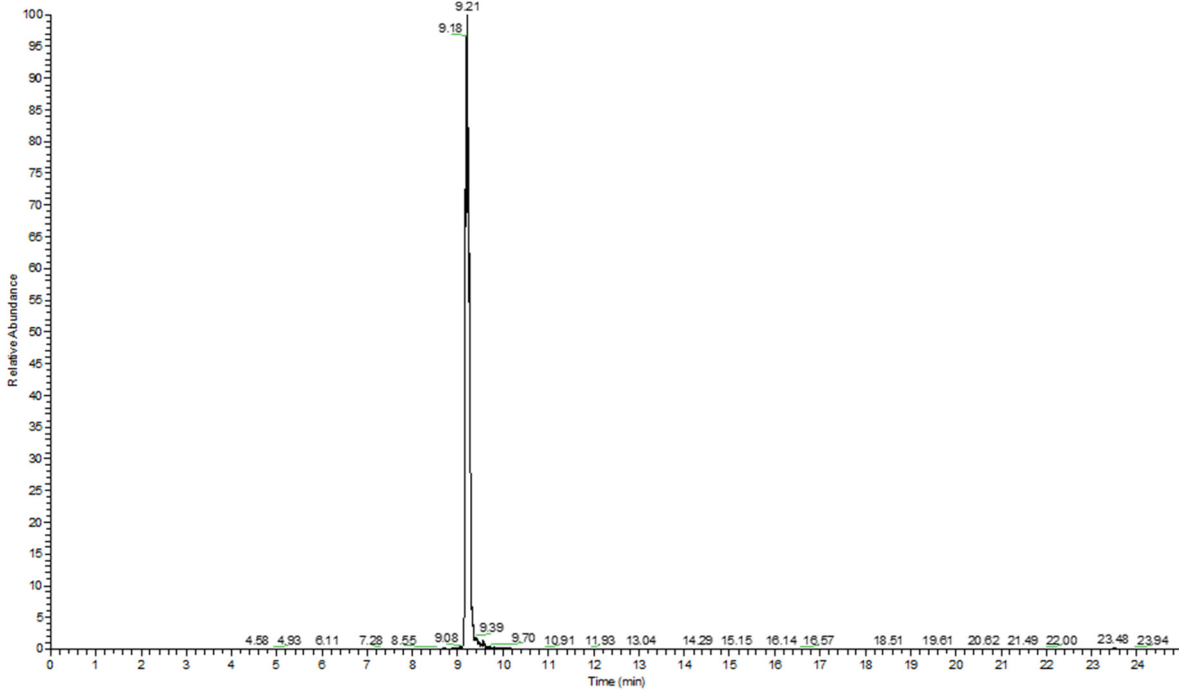
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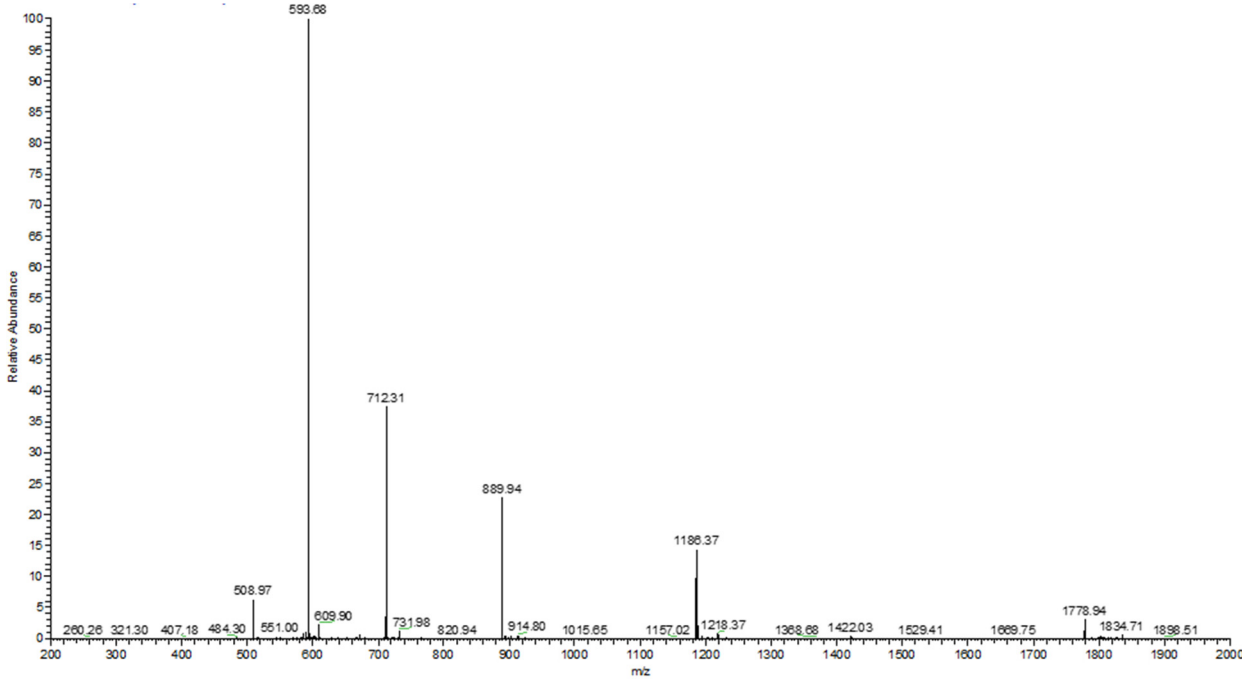
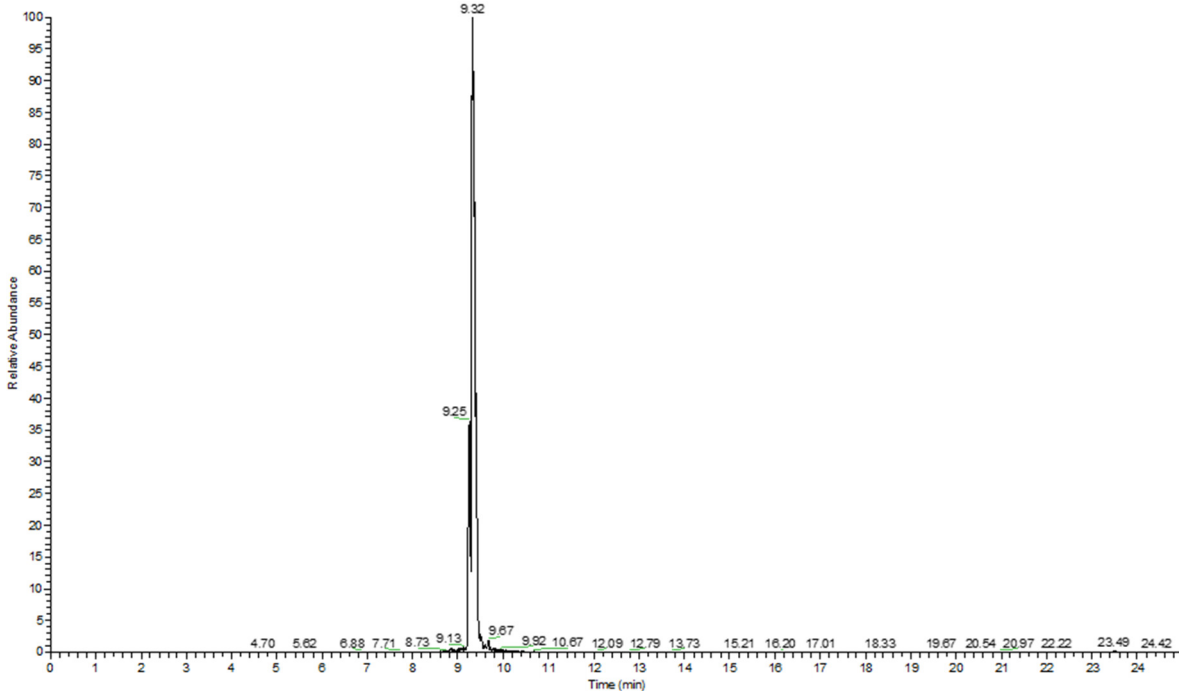
# AYKYA



**Biotin-Penetratin-GG-W<sup>β</sup>YKYW (K(Biotin)-RQIKIWFQNRRMKWKKGGW<sup>β</sup>YKYW-NH<sub>2</sub>)**

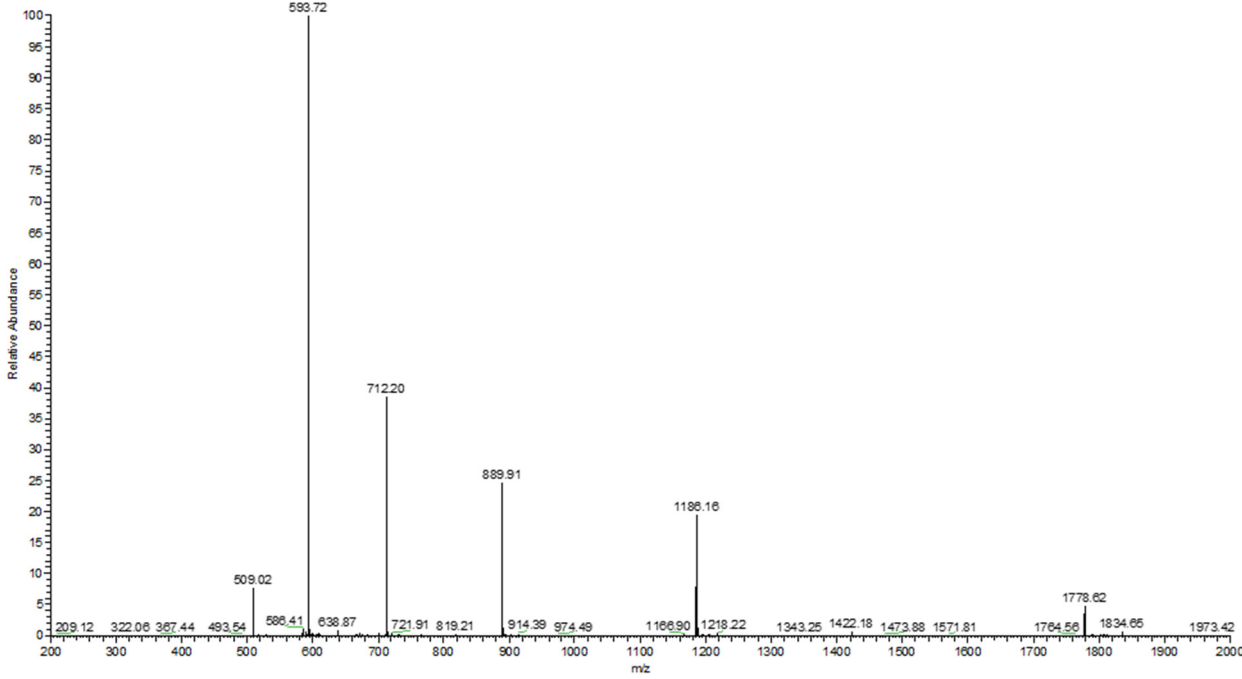
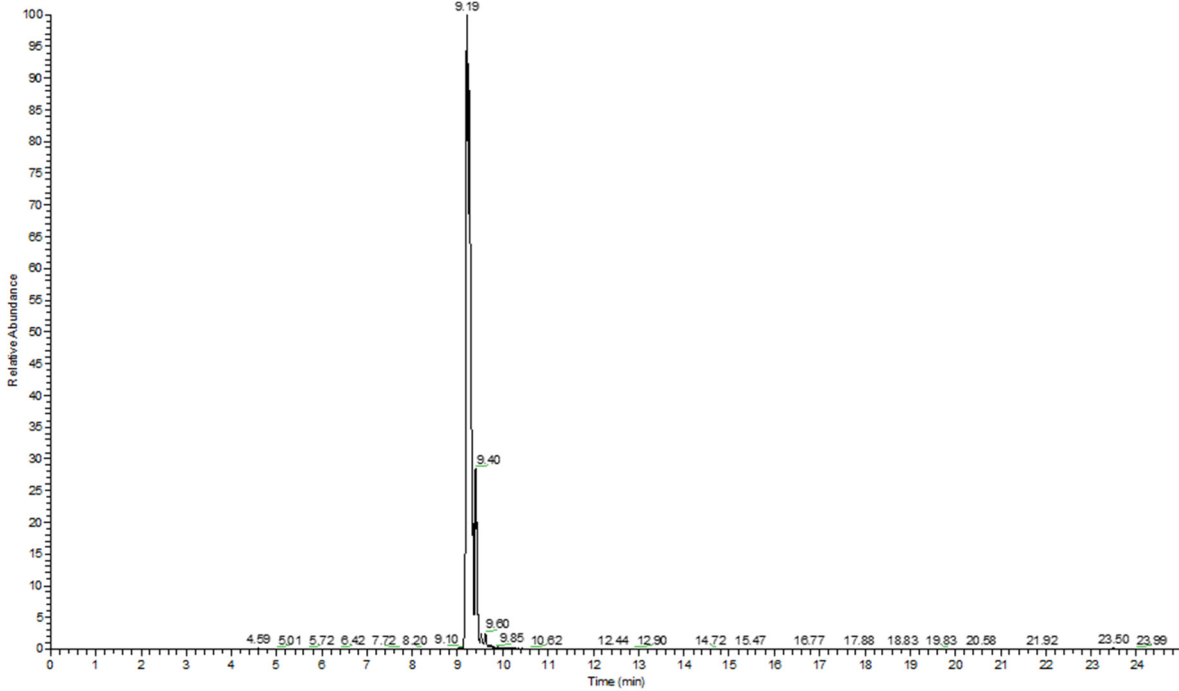


Biotin-Penetratin-GG-WY<sup>β</sup>KYW (K(Biotin)-RQIKIWFQNRRMKWKKGGWY<sup>β</sup>KYW-NH<sub>2</sub>)

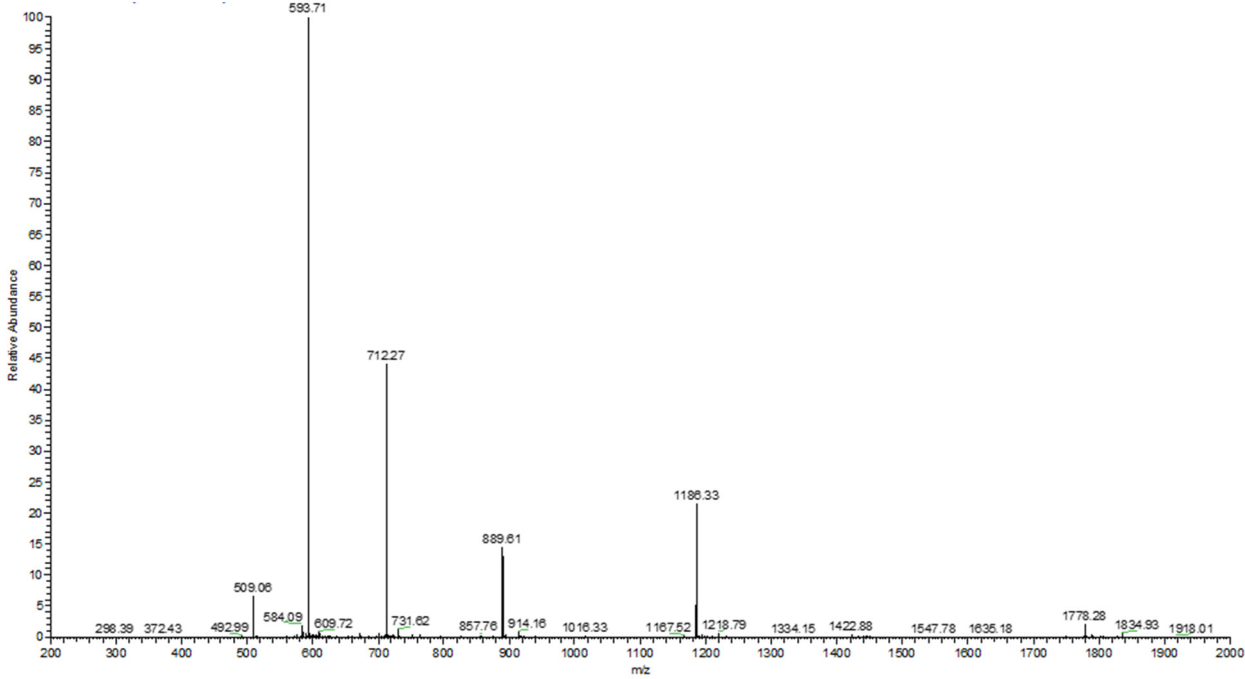
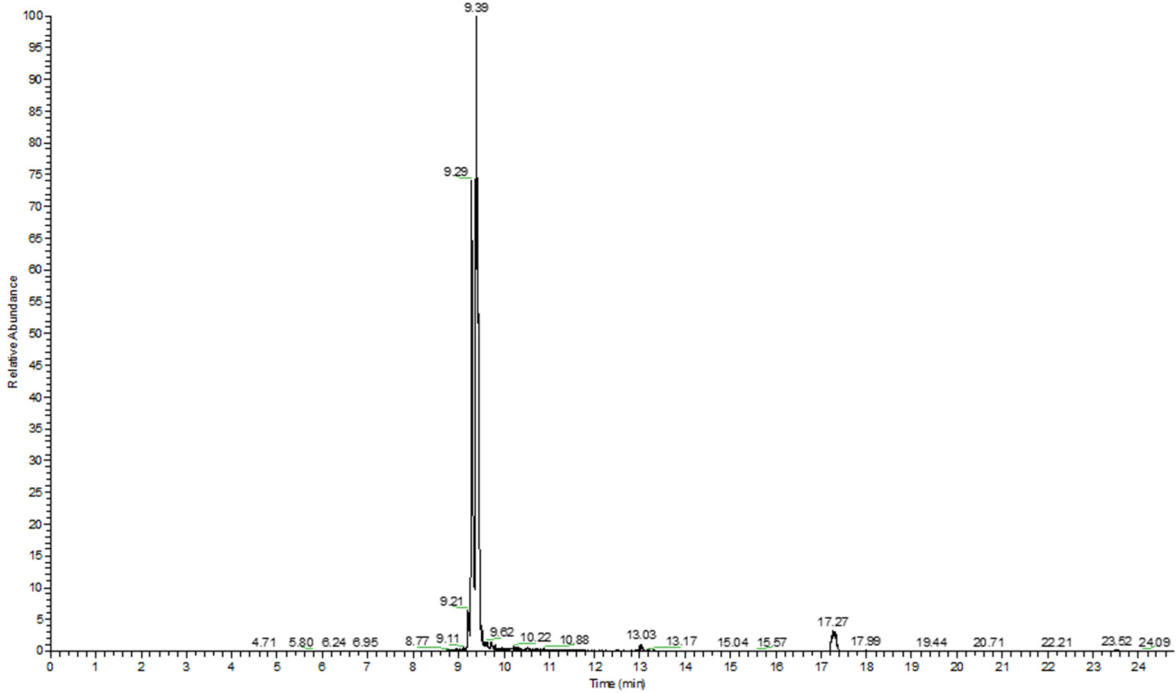




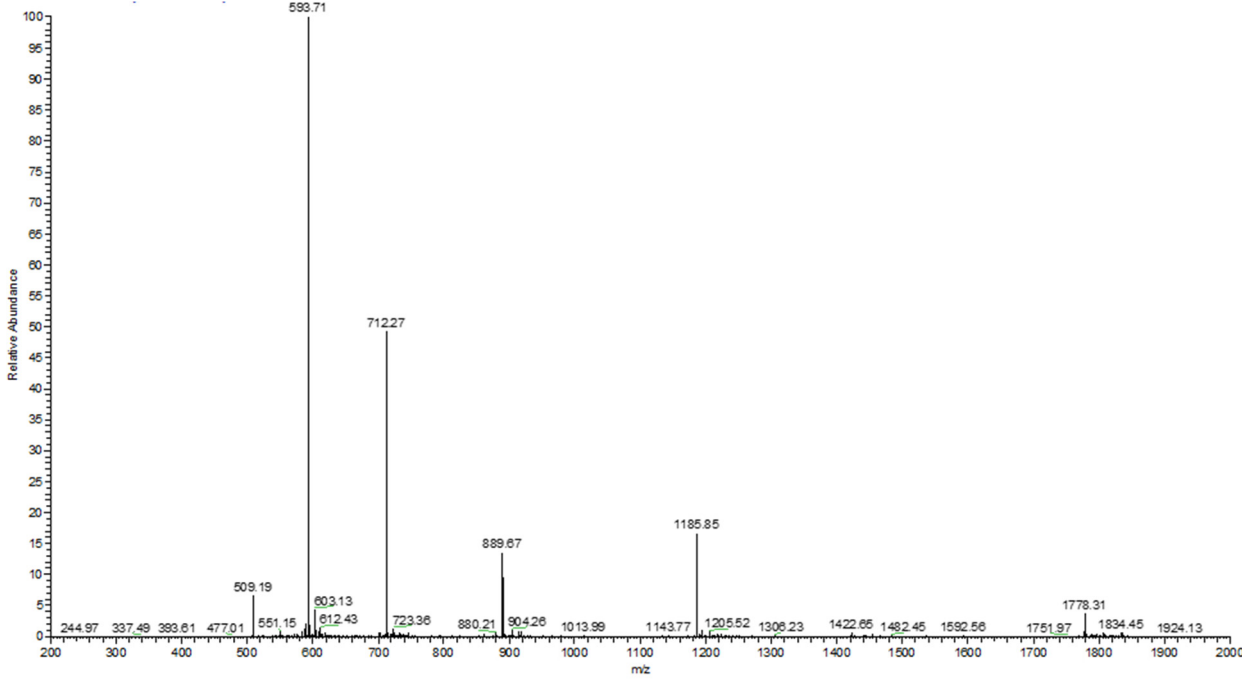
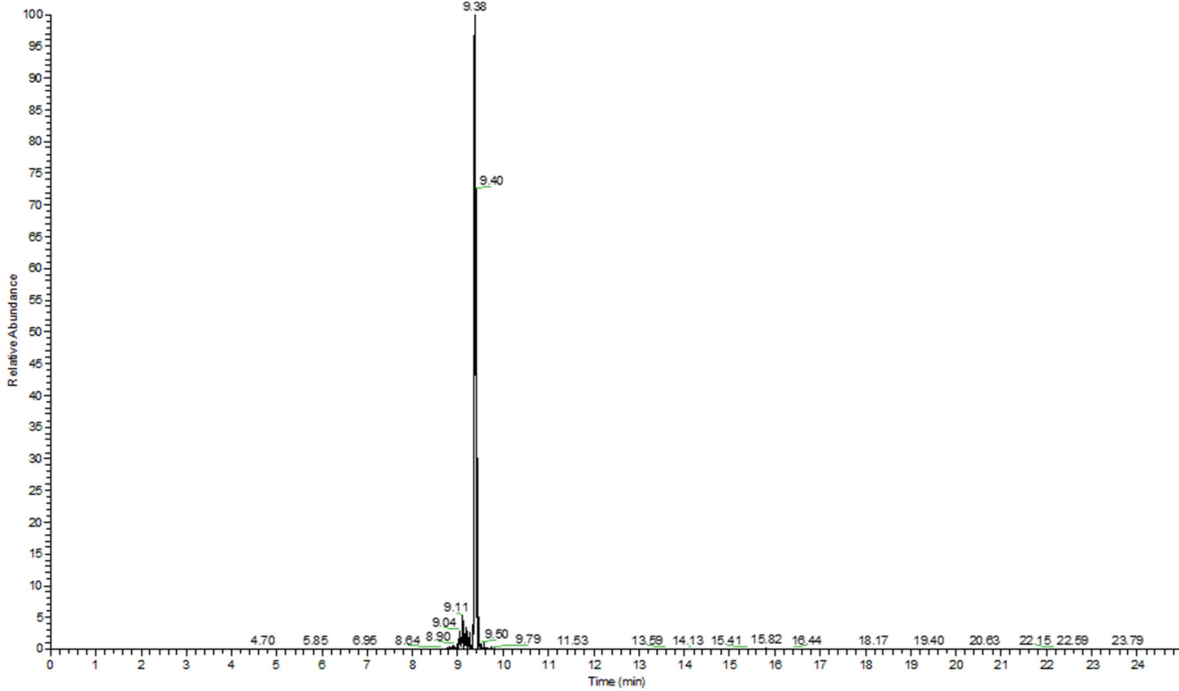
Biotin-Penetratin-GG-WYK<sup>β</sup>YW (K(Biotin)-RQIKIWFQNRRMKWKKGGWYK<sup>β</sup>YW-NH<sub>2</sub>)



**Biotin-Penetratin-GG-WYKY<sup>β</sup>W (K(Biotin)-RQIKIWFQNRRMKWKKGGWYKY<sup>β</sup>W-NH<sub>2</sub>)**



**Biotin-Penetratin-GG-WYKYW<sup>β</sup> (K(Biotin)-RQIKIWFQNRRMKWKKGGWYKYW<sup>β</sup>-NH<sub>2</sub>)**



# Biotin-Penetratin-GG-WYKYW (K(Biotin)-RQIKIWFQNRRMKWKKGGWYKYW-NH<sub>2</sub>)

RT: 0.00 - 25.00

