Chapter 10

References

10 References

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Appendix

Tables

Table A.1. Binding energy and ligand efficiency of the rest of the compounds with cluster size less than Lenvatinib.

COCONUT database ID	Binding Energy (kcal/mol)	Ligand Efficiency (kcal/mol)	Cluster size	Total poses
CNP0270128	-11.49	-0.311	12	100
CNP0110050	-11.41	-0.317	20	100
CNP0165710	-12.15	-0.312	12	100
CNP0440820	-12.26	-0.423	31	100
CNP0345049	-11.94	-0.351	31	100
CNP0226239	-11.85	-0.212	3	100
CNP0447716	-13.16	-0.183	9	100
CNP0425642	-13.56	-0.202	5	100
CNP0226338	-13.99	-0.359	26	100

Table A.2. Predicted ADMET properties of the rest of the compounds.

COCONUT database ID	BBB	Water Solubility	HIA (%)	hERG Inhibition	PPB (%)	Rodent Carcinogenicity	CYP2D6 Inhibitor	Lipinski's Ro5 Violations
CNP0270128	0.085	Poorly Soluble	97.61	Medium Risk	93.14	Non-Carcinogen	Non-Inhibitor	One
CNP0110050	0.357	Poorly Soluble	96.56	Medium Risk	90.95	Carcinogen	Non-Inhibitor	One
CNP0165710	0.395	Moderately Soluble	90.61	Medium Risk	87.48	Carcinogen	Non-Inhibitor	Two
CNP0440820	2.51	Moderately Soluble	94.22	Medium Risk	95.21	Non-Carcinogen	Non-Inhibitor	Zero
CNP0345049	0.064	Poorly Soluble	97.47	Medium Risk	91.03	Non-Carcinogen	Non-Inhibitor	One
CNP0226239	0.028	Moderately Soluble	0.34	Ambiguous	100	Non-Carcinogen	Non-Inhibitor	Three
CNP0447716	0.533	Poorly Soluble	24.89	Ambiguous	67.36	Non-Carcinogen	Non-Inhibitor	Three
CNP0425642	0.027	Poorly Soluble	0	Ambiguous	100	Carcinogen	Non-Inhibitor	Three
CNP0226338	0.031	Poorly Soluble	97.64	Low risk	96.50	Non-Carcinogen	Non-Inhibitor	Two

Table A.3. Summary of interaction of coumestans with EGFR protein.

Ligands	Binding Energy (kcal/mol)	Ligand Efficiency (kcal/mol)	Ligand-Protein Interactions (PDB Id. 6DUK)
Gefitinib	-9.49	-0.306	Met 766 (Pi-Sulfur), Leu 777 (Pi-Alkyl), Leu 788 (Pi-Sigma, Pi-Alkyl), Met 790 (Pi-Sulfur), Arg 841 (Halogen), Asp 855 (H-Bond)
Erlotinib	-8.71	-0.3	Val 726 (Pi-Sigma, Pi-Alkyl), Lys 745 (H-Bond), Met 766 (Pi-Sulfur, Pi-Alkyl), Met 793 (H-Bond), Met 790 (Pi-Sulfur), Asp 855 (H-Bond)
6	-9.76	-0.361	Leu 747 (Pi-Alkyl), Leu 788 (Pi-Sigma, Pi-Alkyl), Asp 855 (H-Bond), Leu 858 (Pi-Sigma, Pi-Alkyl)
8	-9.67	-0.372	Leu 747 (Pi-Sigma, Pi-Alkyl), Leu 788 (Pi-Sigma, Pi-Alkyl), Asp 855 (H-Bond), Leu 858 (Pi-Sigma, Pi-Alkyl)
12	-9.5	-0.339	Leu 788 (Pi-Sigma, Pi-Alkyl), Asp 855 (H-Bond), Leu 858 (Pi-Alkyl), Leu 861 (H-Bond, Pi-Sigma)
4	-9.41	-0.376	Met 766 (Pi-Sulfur), Leu 788 (Pi-Sigma, Pi-Alkyl), Asp 855 (H-Bond), Leu 858 (Pi-Sigma, Pi-Alkyl)
14	-9.35	-0.374	Lys 745 (H-Bond), Met 766 (Pi-Sulfur), Cys 775 (H-Bond), Leu 858 (Pi-Sigma, Pi-Alkyl)
2	-9.34	-0.359	Lys 745 (Pi-cation), Asp 837 (h-bond), Asp 855 (H-Bond), Leu 858 (Pi-Sigma)
10	-9.33	-0.373	Lys 745 (H-Bond, Pi-Alkyl), Asp 855 (H-Bond), Leu 858 (Pi-Sigma, Pi-Alkyl), Leu 861 (H-Bond, Pi-Sigma)
11	-9.19	-0.353	Lys 745 (H-Bond, Pi-Alkyl), Leu 747 (Pi-Sigma, Pi-Alkyl), Asp 855 (H-Bond), Leu 858 (Pi-Sigma, Pi-Alkyl)
13	-9.18	-0.367	Lys 745 (H-Bond), Met 766 (Pi-Sulfur), Met 790 (Pi-Sulfur), Leu 858 (Pi-Sigma, Pi-Alkyl)
3	-9.07	-0.363	Lys 745 (H-Bond), Thr 854 (H-Bond), Asp 855 (H-Bond), Leu 858 (Pi-Sigma, Pi-Alkyl)
15	-8.86	-0.403	Lys 745 (H-Bond), Leu 777 (H-Bond), Leu 788 (Pi-Sigma, Pi-Alkyl), Leu 858 (Pi-Sigma)
7	-8.79	-0.338	Lys 745 (H-Bond, Pi-Alkyl), Leu 788 (Pi-Sigma, Pi-Alkyl), Asp 855 (H-Bond), Leu 858 (Pi-Sigma, Pi-Alkyl)
9	-8.76	-0.324	Met 766 (Pi-Sulfur, Pi-Alkyl), Leu 788 (Pi-Sigma, Pi-Alkyl), Asp 855 (H-Bond), Leu 861 (H-Bond, Pi-Sigma)

Table A.4. Predicted ADMET properties of the rest of the compounds.

Ligands	BBB	Aqueous solubility (mg/ml)	HIA(%)	hERG inhibition	Rodent carcinogenicity	CYP2D6 inhibition
2	0.06	30.57	94.42	Medium risk	Non-carcinogen	Non-inhibitor
3	0.047	4.06	96.13	Medium risk	Non-carcinogen	Non-inhibitor
4	0.047	10.18	96.13	Medium risk	Carcinogen	Non-inhibitor
6	0.056	17.25	91.41	Medium risk	Non-carcinogen	Non-inhibitor
7	0.054	9.75	94.48	Medium risk	Non-carcinogen	Non-inhibitor
8	0.054	7.55	94.47	Medium risk	Non-carcinogen	Non-inhibitor
9	0.052	13.36	91.41	Medium risk	Non-carcinogen	Non-inhibitor
10	1.286	4.54	94.29	Medium risk	Non-carcinogen	Non-inhibitor
11	0.215	1.78	96.15	Medium risk	Carcinogen	Non-inhibitor
12	0.019	16.39	94.88	Medium risk	Non-carcinogen	Non-inhibitor
13	0.077	0.377	96.13	Medium risk	Non-carcinogen	Non-inhibitor
14	0.055	4.06	96.13	Medium risk	Non-carcinogen	Non-inhibitor
15	0.057	52.32	96.25	Medium risk	Non-carcinogen	Non-inhibitor

Table A.5. The binding energy, ligand efficiency, and interactions of isolated phytoconstituents of *P. corylifolia* with EGFR protein (PDB: 6DUK).

Ligands	Binding Energy (kcal/mol)	Ligand Efficiency (kcal/mol)	Interactions with EGFR (PDB Id: 6DUK)
Apterin	-9.03	-0.301	A:Lys 745 (H-Bond), A:Arg 776 (H-Bond), A:Thr 854 (H-Bond, Charged-positive), A:Asp 855 (H-Bond, Charged-negative), A:Phe 856 (H-Bond, Hydrophobic)
Isoimperatorin	-8.95	-0.447	A:Lys 745 (H-Bond, Pi-Cation), A:Met 790 (Hydrophobic), A:Phe 856 (Pi-Pi Stacking, Hydrophobic), A:Thr 854 (Charged-positive), A:Asp 855 (Charged-negative)
Heratomin	-8.47	-0.423	A:LYS 745 (H-Bond), A:CYS 775 (Hydrophobic), A:ARG 776 (H-Bond), A:THR 854 (Charged-positive), A:ASP 855 (Charged-negative)
Oxypeucedanin	-8.43	-0.401	A:LYS 745 (H-Bond), A:LEU 777 (Hydrophobic), A:THR 854 (Charged-positive), A:PHE 856 (Pi-Pi Stacking, Hydrophobic), A:LEU 858 (Hydrophobic)
Psoralidin	-8.36	-0.334	A:LYS 745 (H-Bond), A:ARG 776 (H-Bond), A:CYS 775 (H-Bond, Hydrophobic), A:ILE 780 (Hydrophobic)
Marmesin	-8.25	-0.458	A:LYS 745 (H-Bond), A:ARG 776 (H-Bond), A:THR 854 (Charged-positive), A:ASP 855 (Charged-negative), A:LEU 858 (Hydrophobic)
Heratomol benzoate	-7.36	-0.32	A:LYS 745 (H-Bond), A:ILE 789 (Hydrophobic), A:ASP 855 (Charged-negative), A:PHE 856 (Pi-Pi Stacking, Hydrophobic), A:LEU 858 (Hydrophobic)
Isobergapten	-7.24	-0.453	A:LYS 745 (H-Bond), A:ARG 776 (H-Bond), A:ILE 789 (Hydrophobic), A:THR 854 (Charged-positive), A:ASP 855 (Charged-negative)
Isopsoralen	-7.11	-0.508	A:LYS 745 (H-Bond), A:ARG 776 (H-Bond), A:MET 790 (Hydrophobic), A:THR 854 (Charged-positive), A:LEU 858 (Hydrophobic)
Bergapten	-7.06	-0.441	A:LYS 745 (H-Bond), A:ARG 776 (H-Bond), A:ILE 789 (Hydrophobic), A: ASP 855 (Charged-negative), A:LEU 858 (Hydrophobic)
Psoralen	-6.96	-0.497	A:LYS 745 (H-Bond), A:ARG 776 (H-Bond), A:MET 790 (Hydrophobic), A:PHE 856 (H-Bond, Pi-Pi Stacking, Hydrophobic)

Table A.6. Melting point of phytoconstituents isolated from *V. negundo*.

Compound	Reported melting point	Observed melting point
Lupeol	216 °C	217 °C
Ursolic Acid	284 °C	283 °C
Betulinic Acid	303 °C	301 °C
Gardenin B	176-177 ºC	178 °C
Butine	224-226 °C	223 °C
Luteolin	329.5 °C	331 °C
2,3 dehydrosilychristin	254-256 °C	252 °C
Apigenin	347.5 °C	347 °C
Gallic Acid	210 °C	211 °C
Ferulic Acid	169 °C	168 °C
Isoorientin	236-237 °C	238 °C
Agnuside	146 °C	148 °C
Negundoside	188-192 °C	191 °C
Butrin	194-195 °C	195 °C
Silychristin	174-176 °C	179 °C

Figures

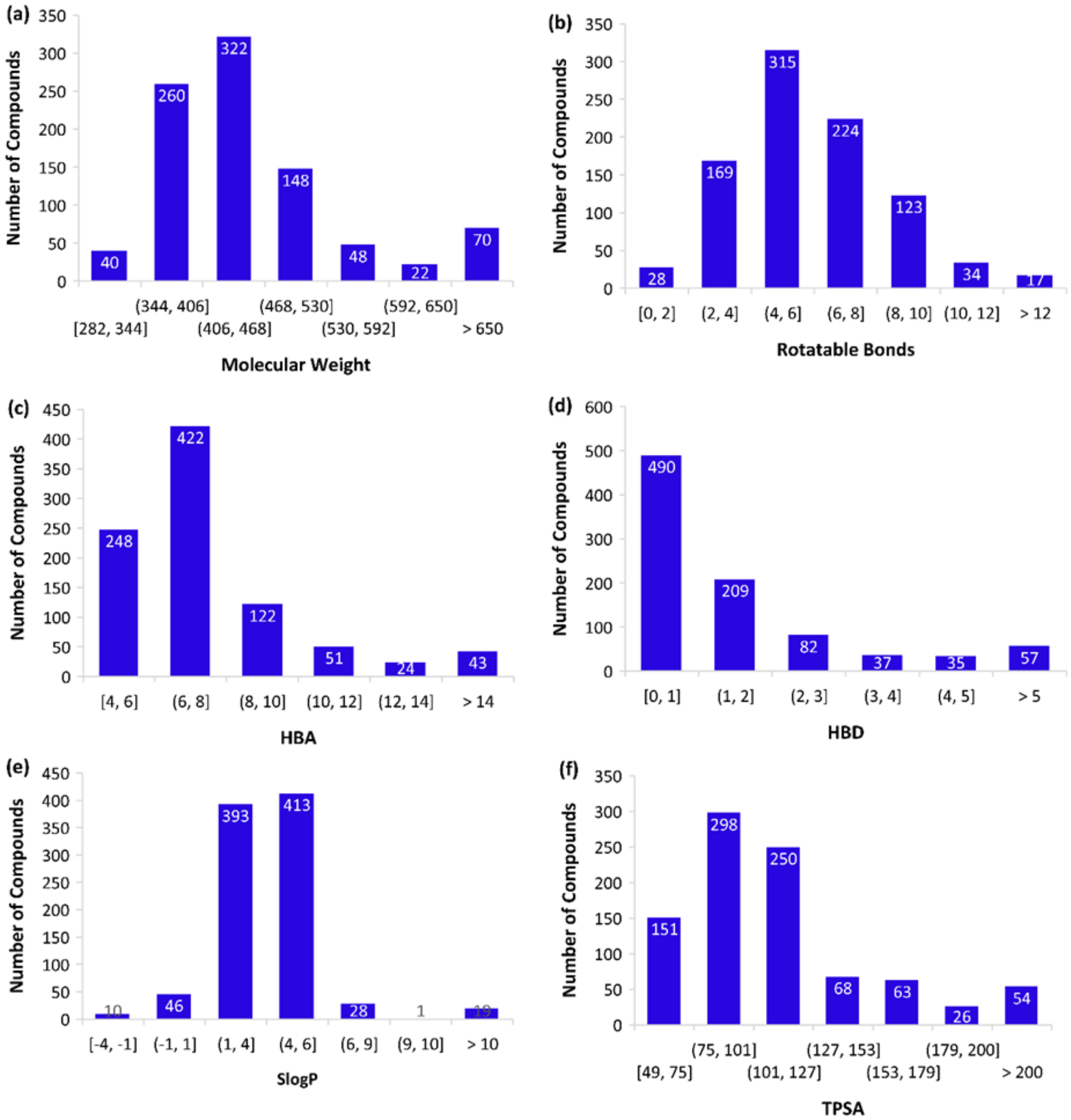

Figure A.1. Distribution of molecular properties of the compounds used in HTVS.

```
Structural alignment:

                     ..........+.........+.........+.........
model   SSA 1   820 CCCCHHHHHCCCCEEEEEECCCCCCCCEEEEEEEEECCCC
3wzd    SSA 2   846 --------------------------CEEEEEEEEECCCC
model       1   820 LPYDASKWEFPRDRLKLGKPLGRGAFGQVIEADAFGIDKT
3wzd        2   846 --------------------------GQVIEADAFGIDKT

                     ..........+.........+.........+.........
model   SSA 1   860 CEEEEEEEEEECCCCCHHHHHHHHHHHHHHHHHCCCCCCC
3wzd    SSA 2   860 CEEEEEEEEEECCCCCHHHHHHHHHHHHHHHHHCCCCCCC
model       1   860 ATCRTVAVKMLKEGATHSEHRALMSELKILIHIGHHLNVV
3wzd        2   860 ATCRTVAVKMLKEGATHSEHRALMSELKILIHIGHHLNVV

                     ..........+.........+.........+.........
model   SSA 1   900 CCCEEECCCCCEEEEEECCCCCCCHHHHHHHHCCEEECCC
3wzd    SSA 2   900 CCCEEECCCCCEEEEEECCCCCCCHHHHHHHHCCEEECCC
model       1   900 NLLGACTKPGGPLMVIVEFCKFGNLSTYLRSKRNEFVPYK
3wzd        2   900 NLLGACTKPGGPLMVIVEFCKFGNLSTYLRSKRNEFVPYK

                     ..........+.........+.........+.........
model   SSA 1   940 CCCCCCCCCCCCCCCCCCCCCCCECCCCCCCCCCCCCCCC
3wzd    SSA 2   940 -C--------------------------------------
model       1   940 TKGARFRQGKDYVGAIPVDLKRRLDSITSSQSSASSGFVE
3wzd        2   940 -V--------------------------------------

                     ..........+.........+.........+.........
model   SSA 1   980 CCCCCCCCCCCCCCCCCCCCEHHHHHHHHHHHHHHHHHHH
3wzd    SSA 2   991 -----------CCCCCCCCCEHHHHHHHHHHHHHHHHHHH
model       1   980 EKSLSDVEEEEAPEDLYKDFLTLEHLICYSFQVAKGMEFL
3wzd        2   991 -----------APEDLYKDFLTLEHLICYSFQVAKGMEFL

                     ..........+.........+.........+.........
model   SSA 1   102 HHHCCCCCCCCCCCCCCCCCEEECCCCCCCCCCCCCCCCC
3wzd    SSA 2   102 HHHCCCCCCCCCCCCCCCCCEEECCCC-C-----------
model       1   102 ASRKCIHRDLARNILSEKNVKICDFGLARDIYKDPDYVRK
3wzd        2   102 ASRKCIHRDLARNILSEKNVKICDFGL-A-----------

                     ..........+.........+.........+.........
model   SSA 1   106 CCCHHHHHHHCHHHHHHCCCHHHHHHHHHHHHHCCCCCCC
3wzd    SSA 2   106 ----HHHHHHCHHHHHHCCCHHHHHHHHHHHHHCCCCCCC
model       1   106 GDARLPLKWMAPETIFDRVYTIQSDVWSFGVLWEIFSLGA
3wzd        2   106 ----LPLKWMAPETIFDRVYTIQSDVWSFGVLWEIFSLGA

                     ..........+.........+.........+.........
model   SSA 1   110 CCCCCCCCCCCCCCCCCCCCCCCCCCHHHHHHHHHHHCCC
3wzd    SSA 2   110 CCCCCCCCCCCCCCCCCCCCCCCCCCHHHHHHHHHHHCCC
model       1   110 SPYPGVKIDEFCRLKEGTRMRAPDYTPEMYQTMLDCWHGE
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                     ..........+.........+.........+.........
model   SSA 1   114 CCCCCCHHHHHHHHHHHCCC--------------------
3wzd    SSA 2   114 CCCCCCHHHHHHHHHHHCCCCCCCHHHHHCCCCEEEEECC
model       1   114 PSQRPTFSELVEHLGNLQAN--------------------
3wzd        2   114 PSQRPTFSELVEHLGNLQANLPYDASKWEFPRDRLKLGKP

                     ..........+.........+.........+.........
model   SSA 1       --
3wzd    SSA 2   840 CC
model       1       --
3wzd        2   840 LG


Alignment Score:  0.008 (smaller is better)
           RMSD:  0.437 Angstrom
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Figure A.2. Sequence alignment of the template and modeled protein.

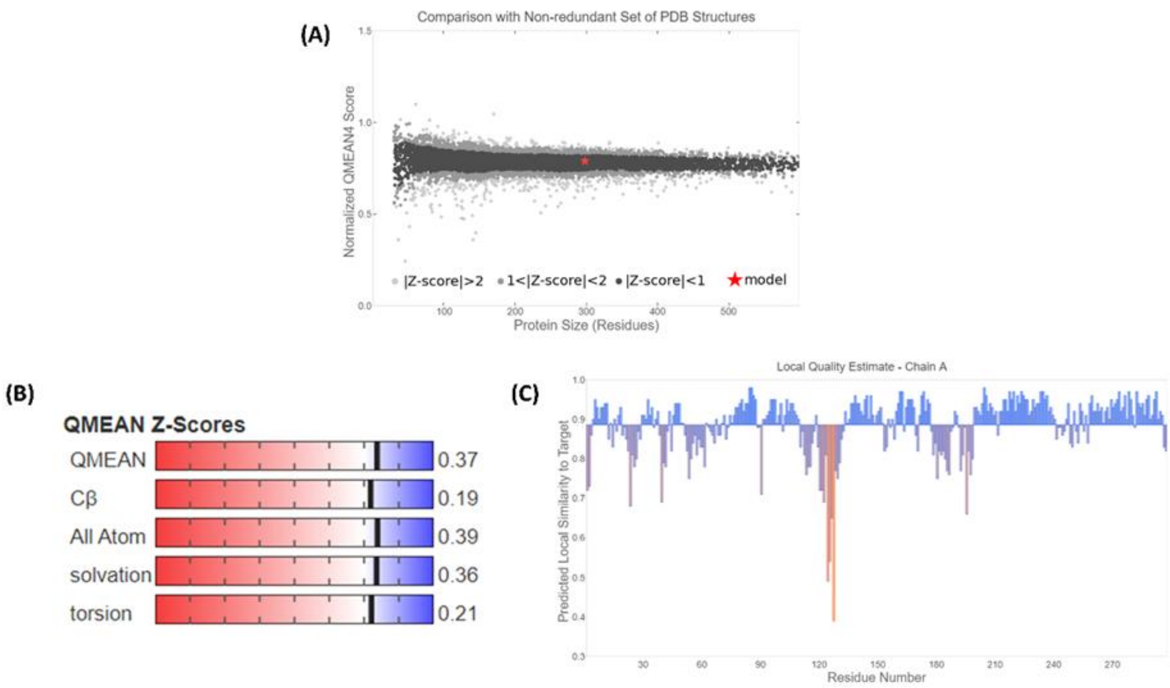


Figure A.3. Evaluation of protein obtained from homology modeling. (**A**) Model comparison with set of PDB structures, (**B**) QMEAN and the related elements of the prepared model, and (**C**) Estimation of local quality of the prepared model.

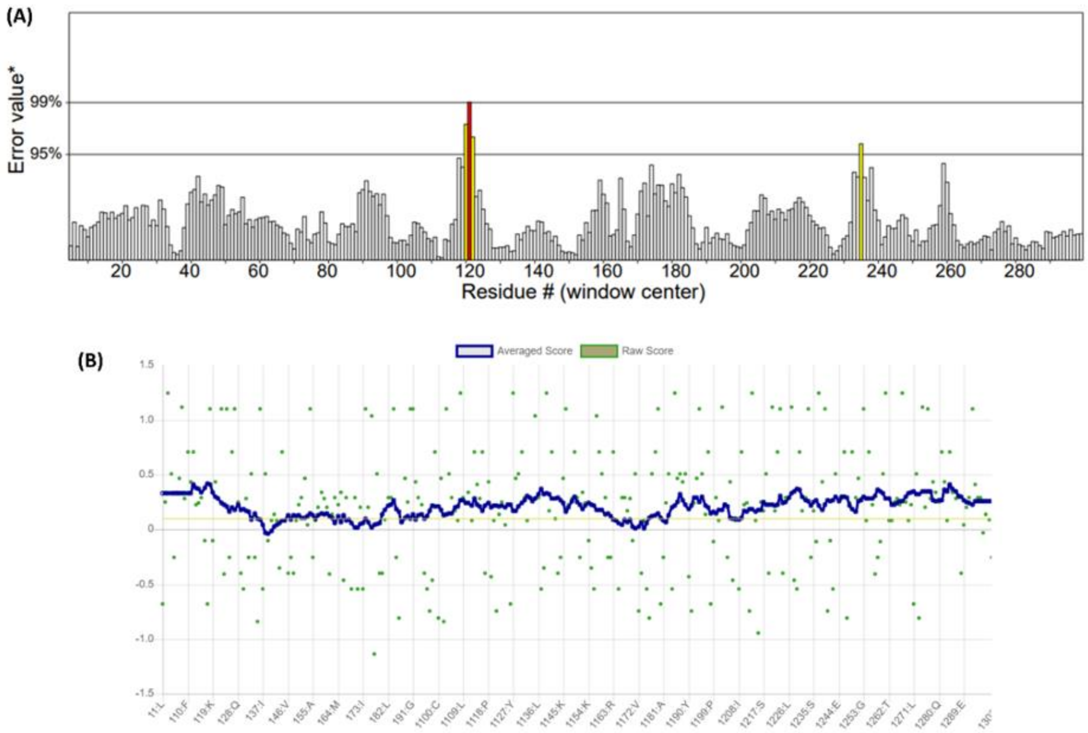


Figure A.4. Evaluation of protein obtained from homology modeling. (**A**) ERRAT plot and (**B**) VERIFY3D plot of modelled VEGFR-2 protein.

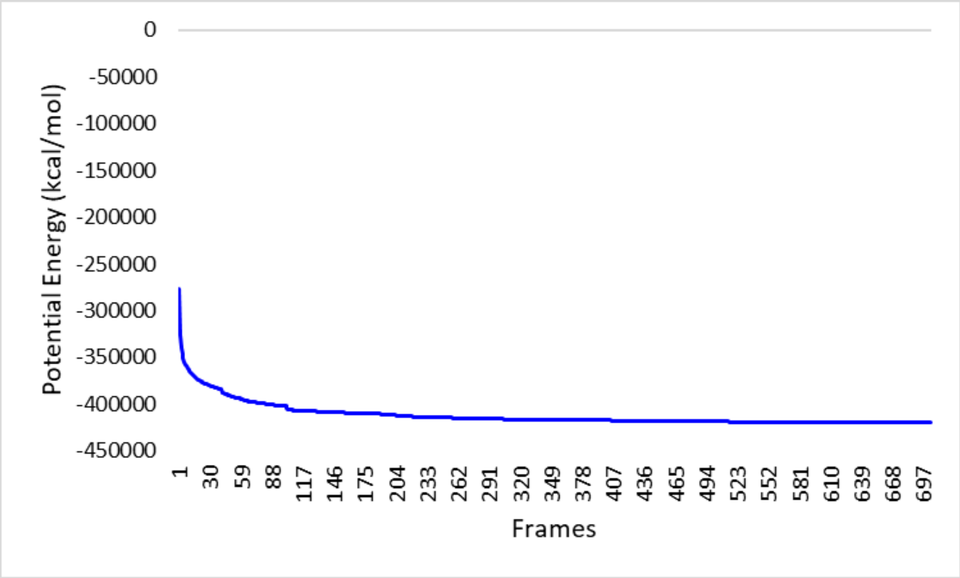


Figure A.5. Energy minimization plot of protein (gas phase).

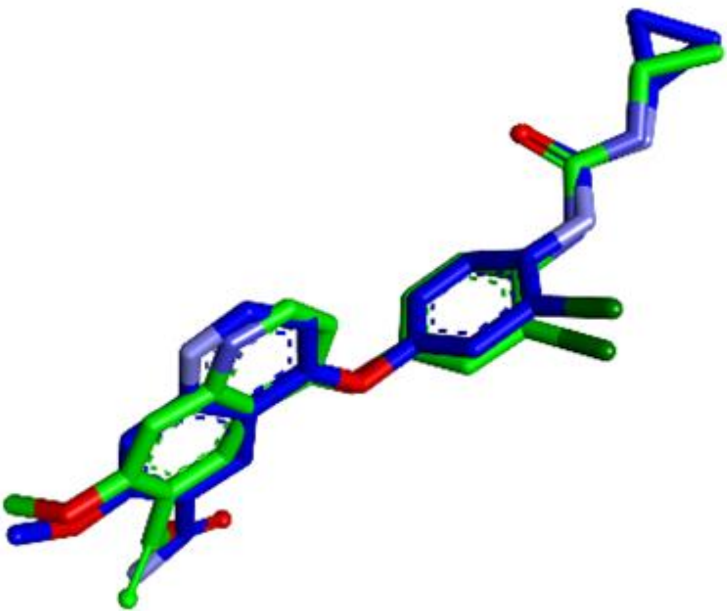


Figure A.6. Superimposition of docked structure (blue) with co-crystallized ligand (green).

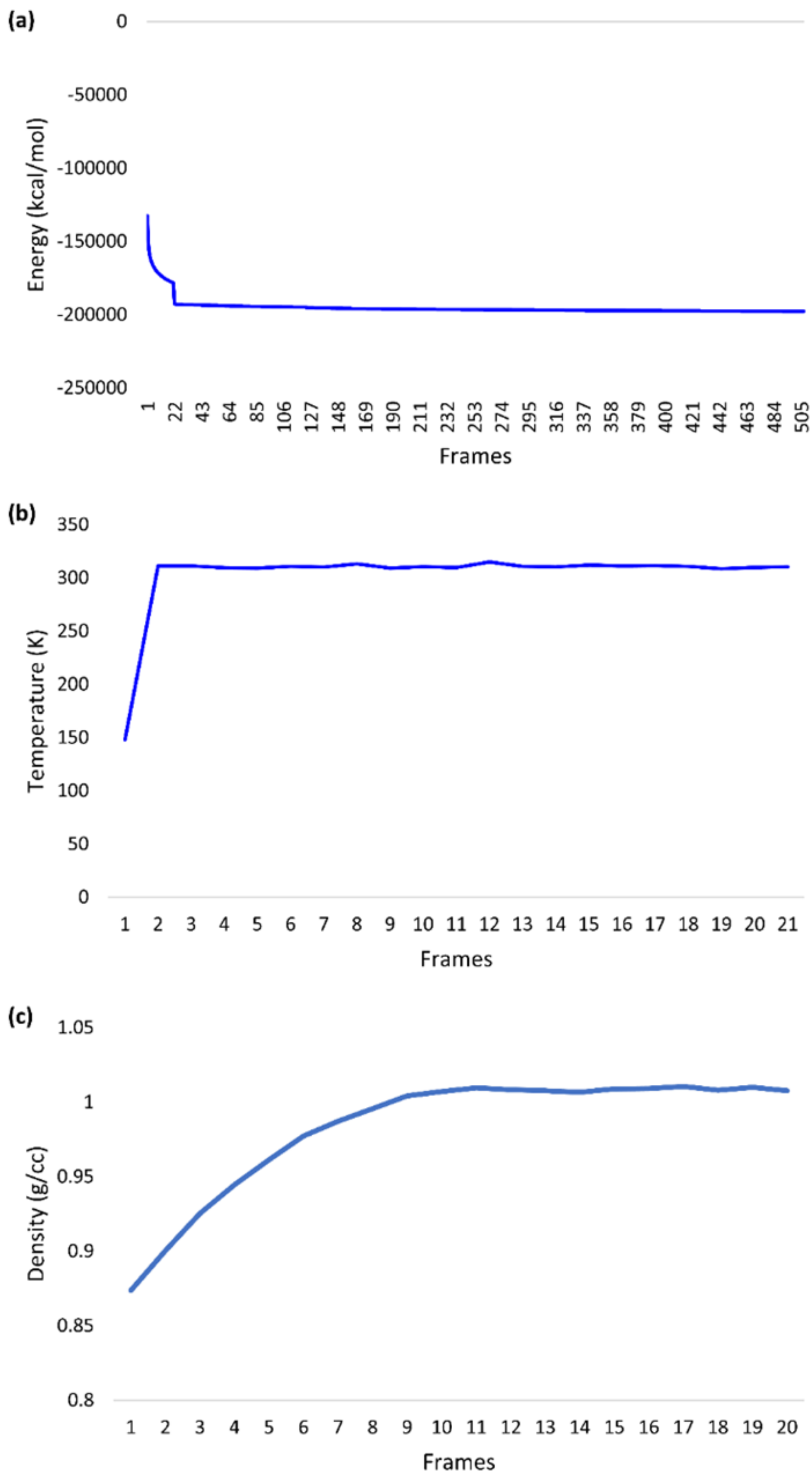


Figure A.7. (a) Energy minimization plot of CNP0056360-VEGFR-2 complex, (b) Temperature plot of CNP0056360-VEGFR-2 complex system, and (c) Density plot of CNP0056360-VEGFR-2 complex system.

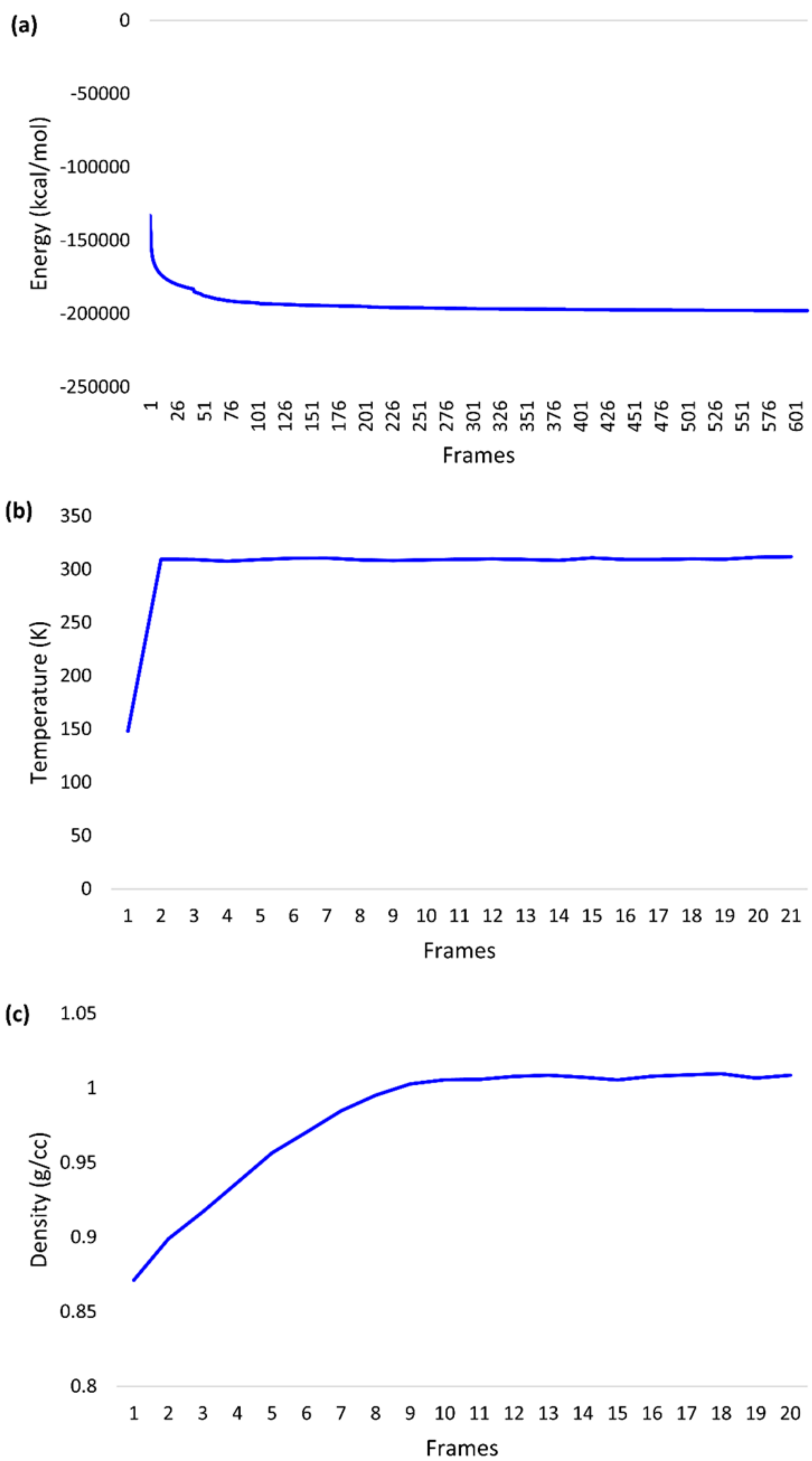


Figure A.8. (a) Energy minimization plot of CNP0340213-VEGFR-2 complex, (b) Temperature plot of the CNP0340213-VEGFR-2 complex system, and (c) Density plot of the CNP0340213-VEGFR-2 complex system.

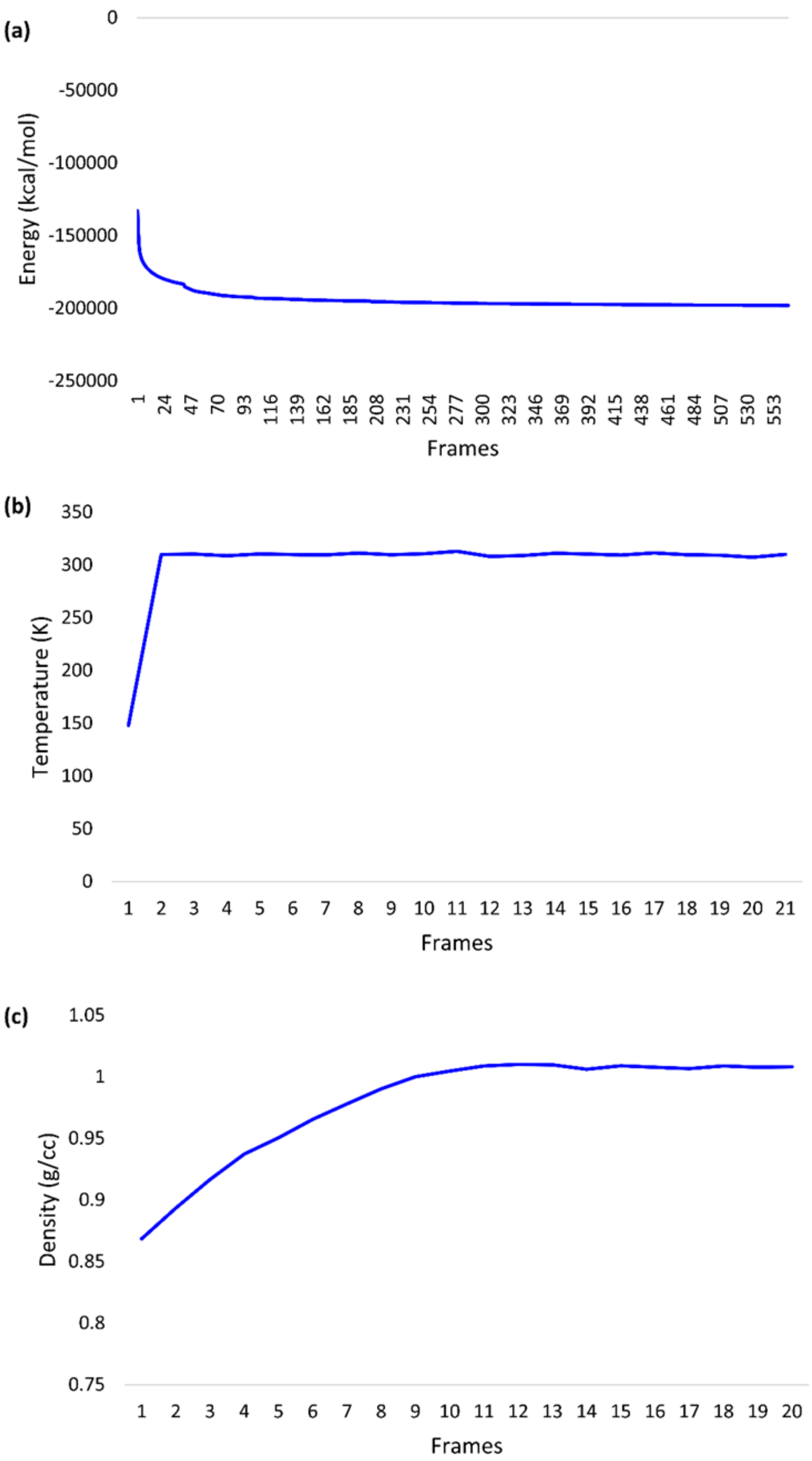


Figure A.9. (a) Energy minimization plot of CNP0366287-VEGFR-2 complex, (b) Temperature plot of CNP0366287-VEGFR-2 complex system, and (c) Density plot of CNP0366287-VEGFR-2 complex system.

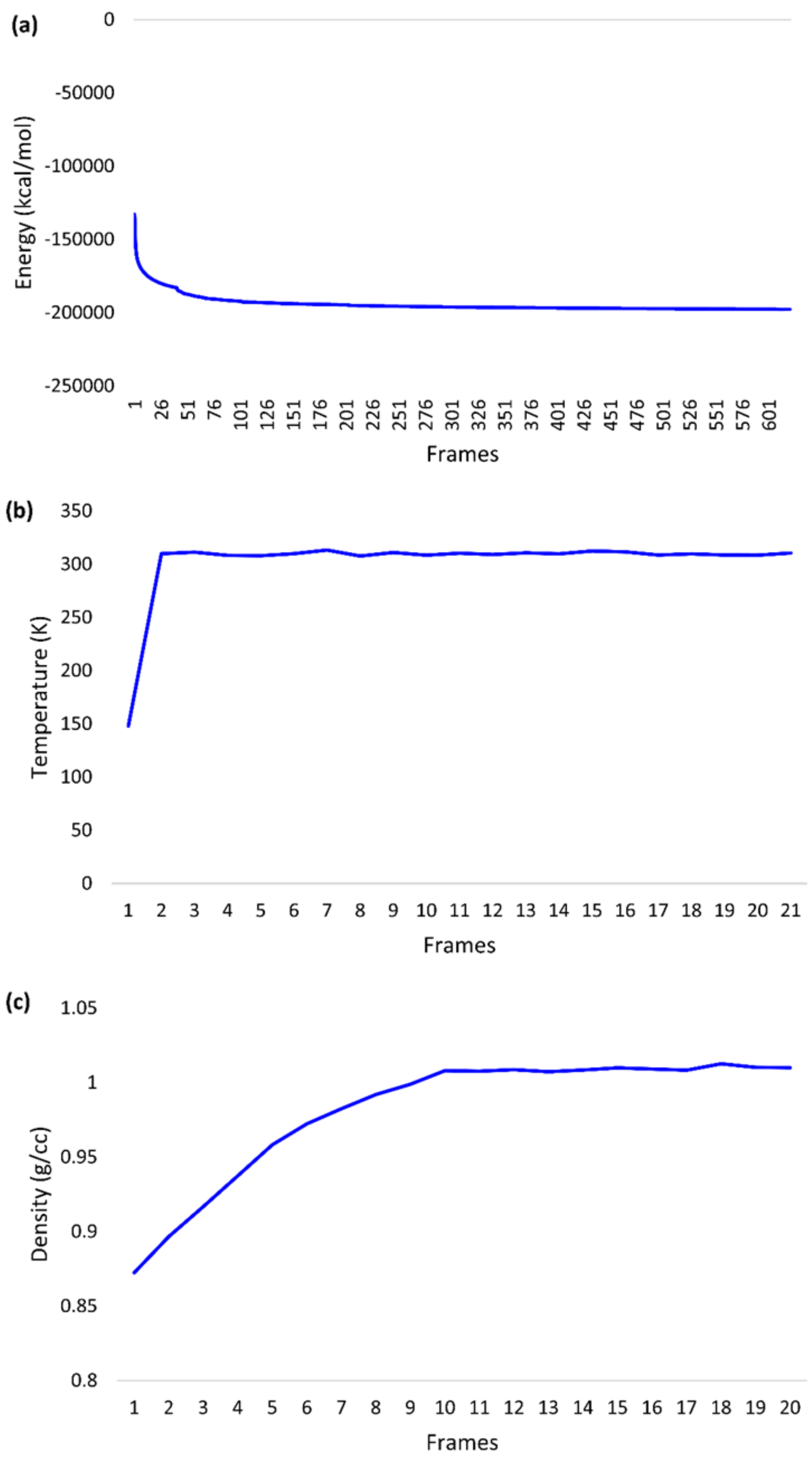


Figure A.10. (a) Energy minimization plot of lenvatinib-VEGFR-2 complex, (b) Temperature plot of lenvatinib-VEGFR-2 complex system, and (c) Density plot of lenvatinib-VEGFR-2 complex system.

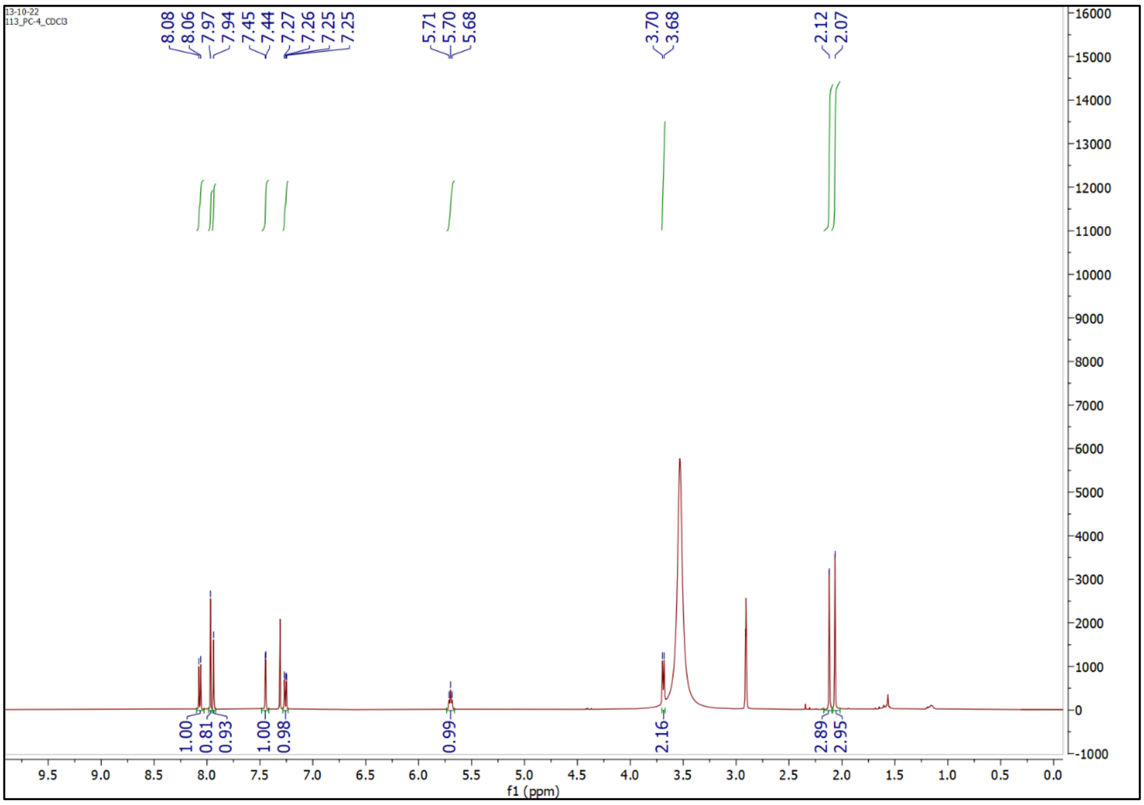


Figure A.11. 1H NMR spectra of Psoralidin.

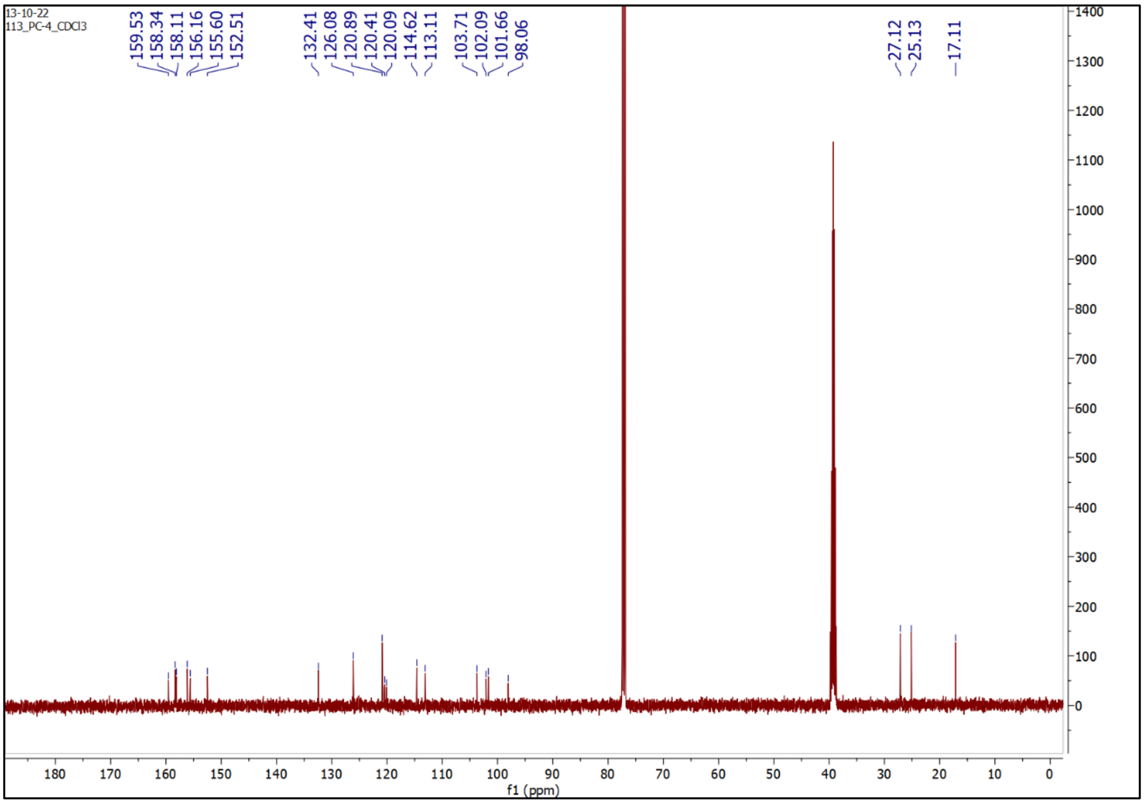


Figure A.12. 13C NMR spectra of Psoralidin.

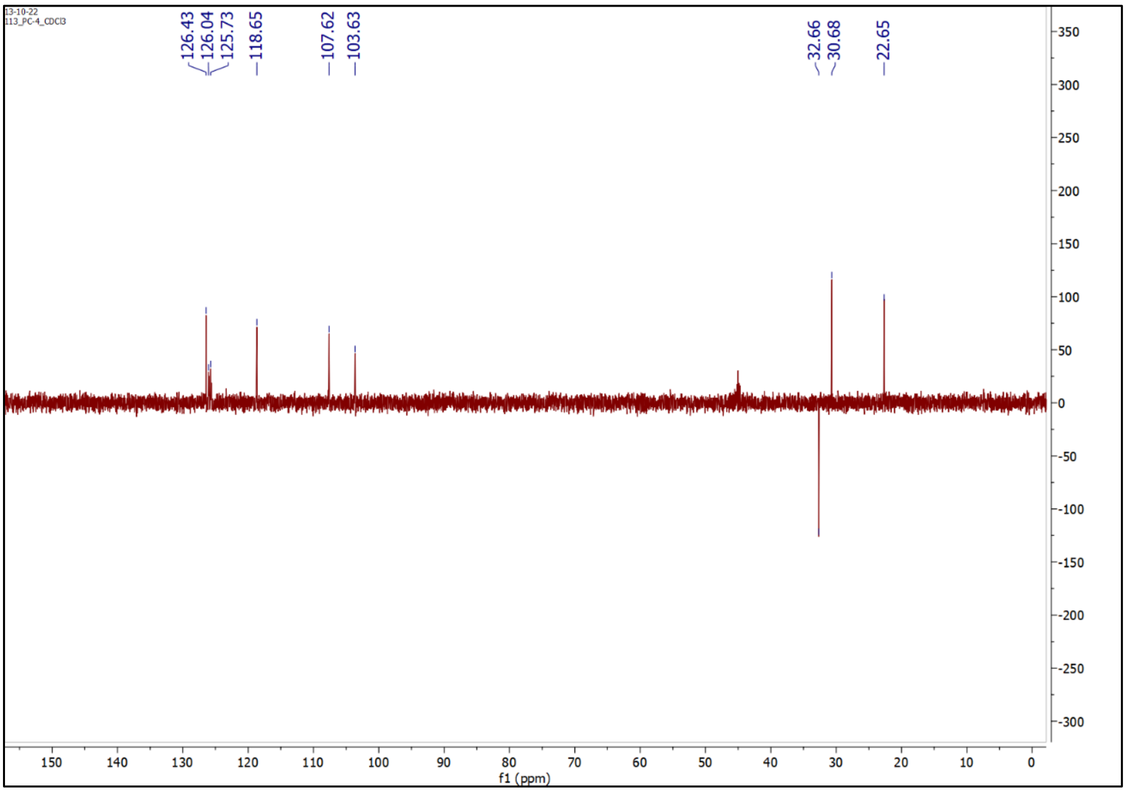


Figure A.13. DEPT-135 spectra of Psoralidin.

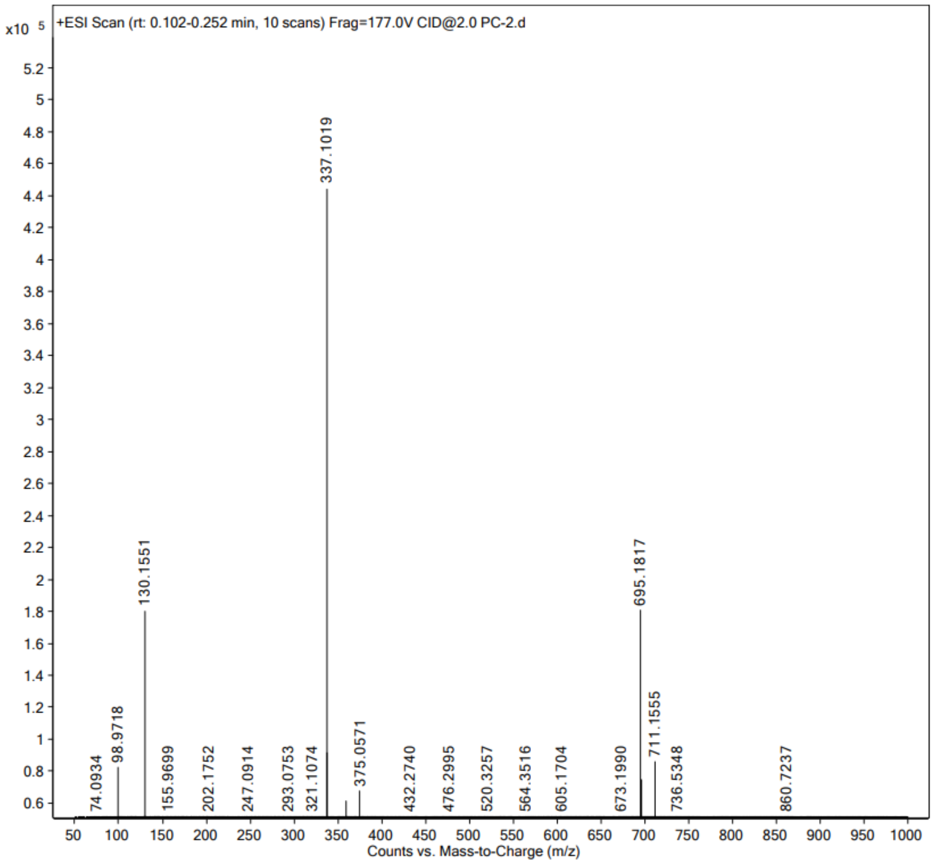


Figure A.14. HRMS spectra of Psoralidin (**1**).

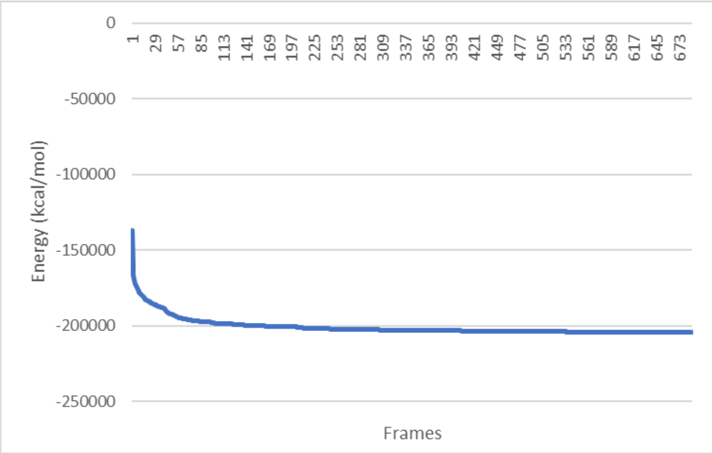


Figure A.15. A plot of the potential energy of EGFR protein during energy minimization.

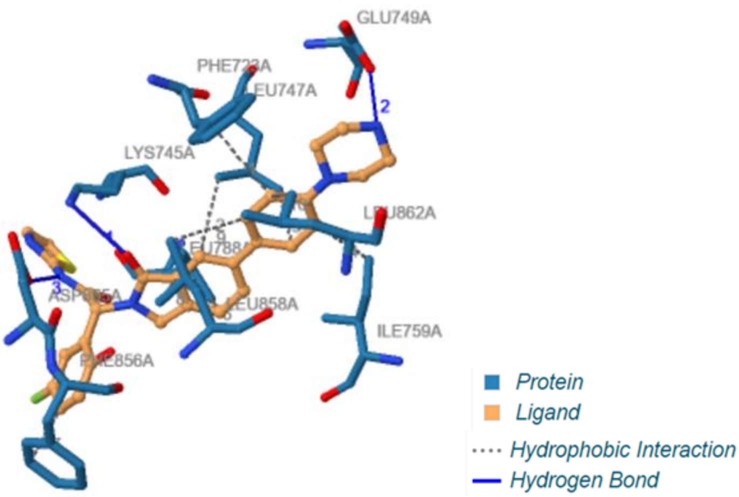


Figure A.16. The active site residues of EGFR.

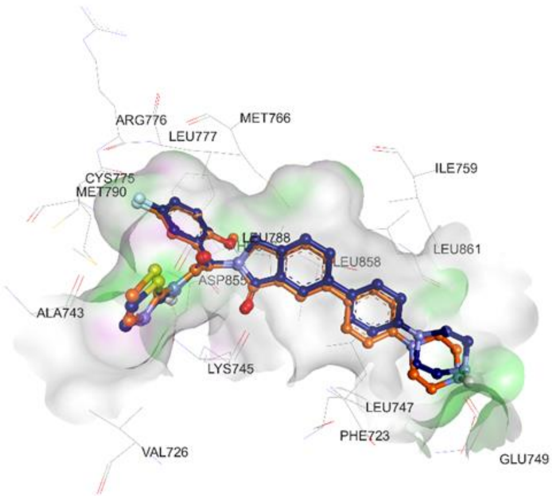


Figure A.17. Superimposition of docked structure (orange) with co-crystallized ligand (blue).

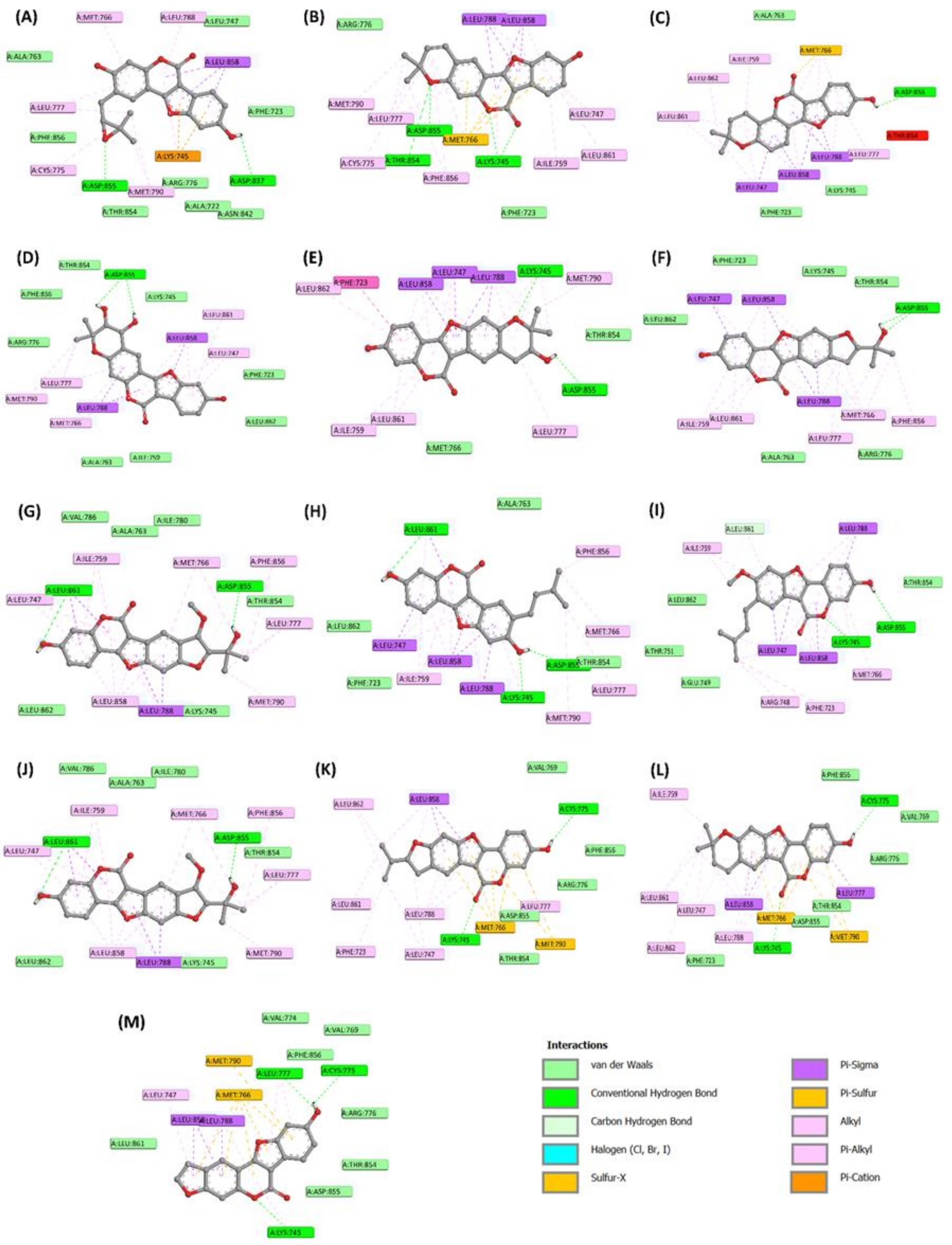


Figure A.18. 2D interaction diagram of (A) Compound 2, (B) Compound 3, (C) Compound 4, (D) Compound 6, (E) Compound 7, (F) Compound 8, (G) Compound 9, (H) Compound 10, (I) Compound 11, (J) Compound 12, (K) Compound 13, (L) Compound 14, and (M) Compound 15 with EGFR protein.

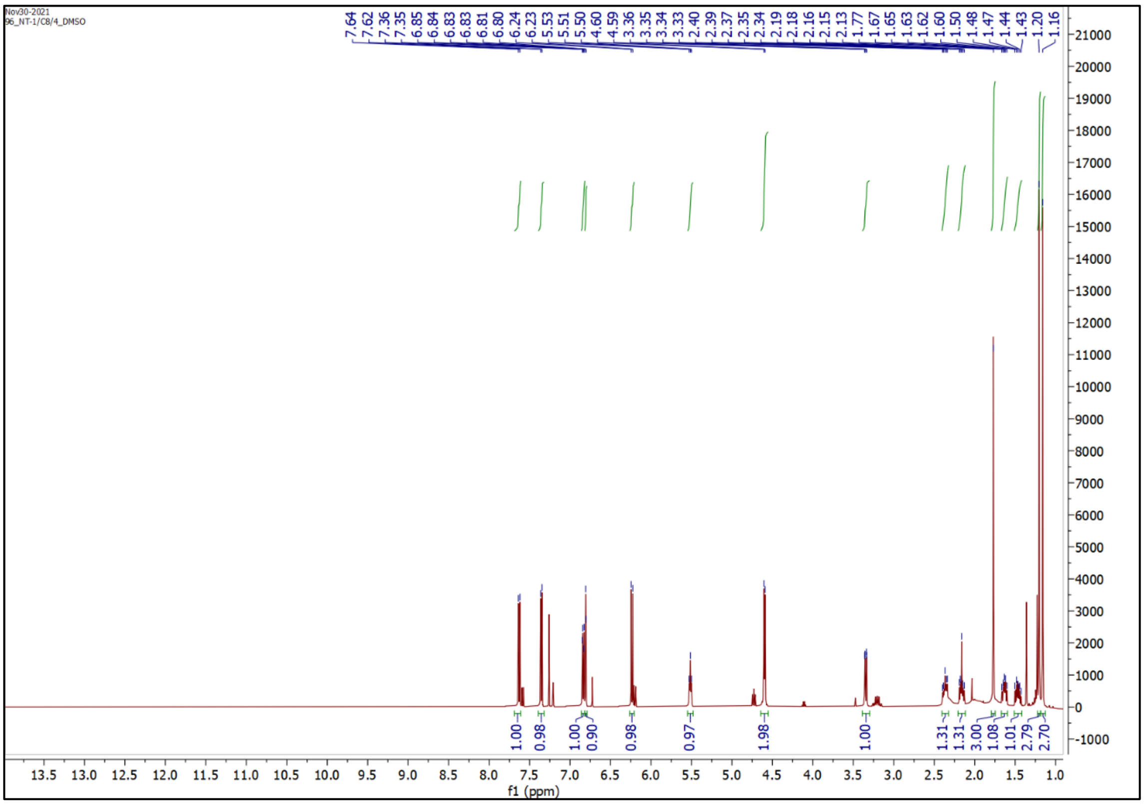


Figure A.19. 1H NMR spectra of Marmin.

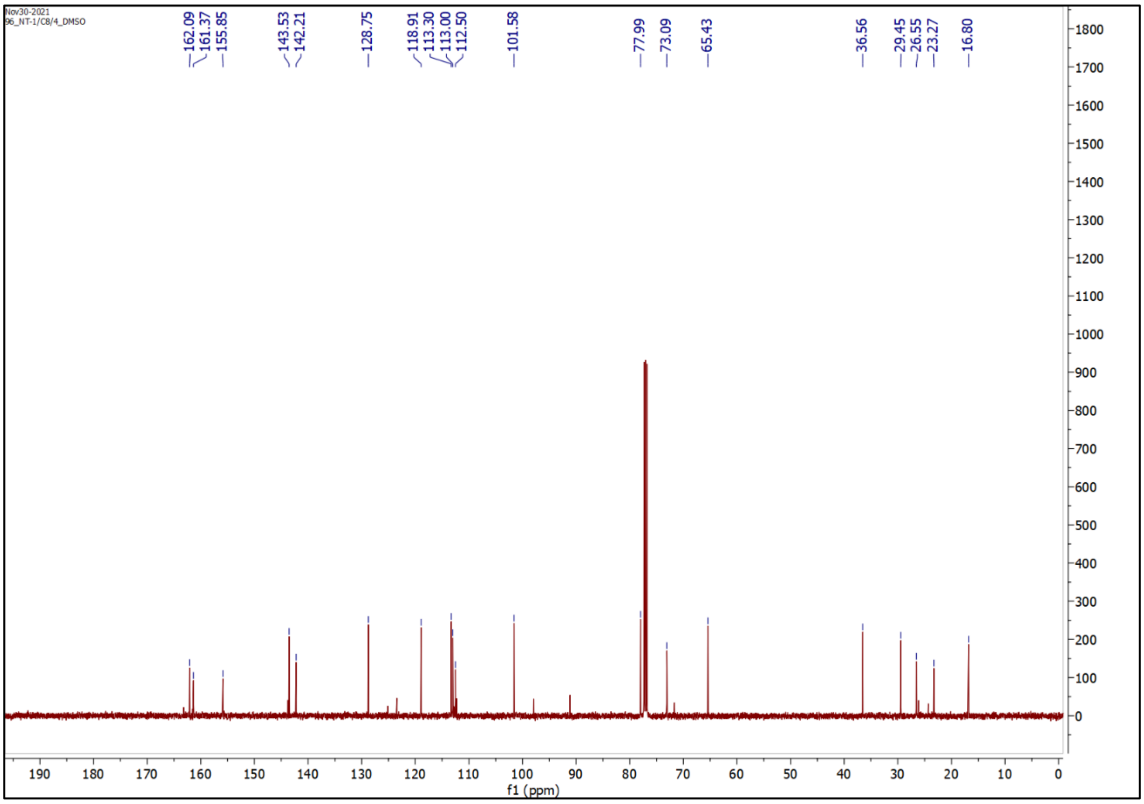


Figure A.20. 13C NMR spectra of Marmin.

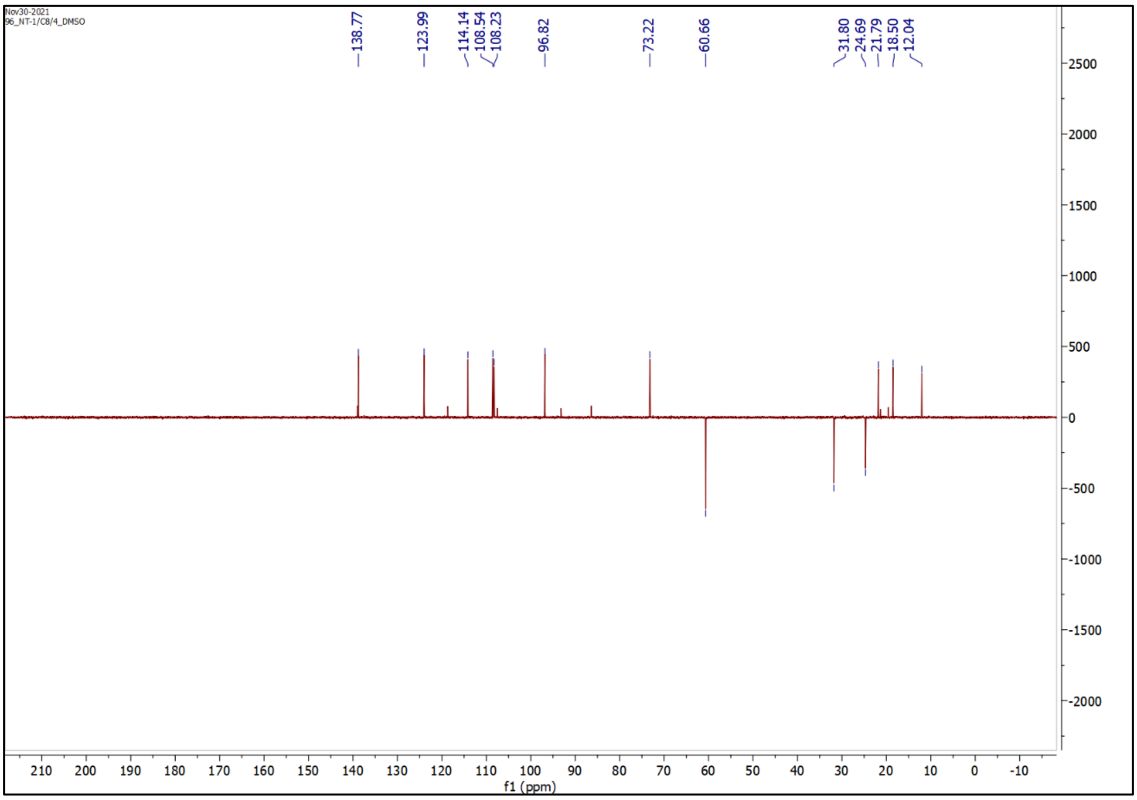


Figure A.21. DEPT-135 spectra of Marmin.

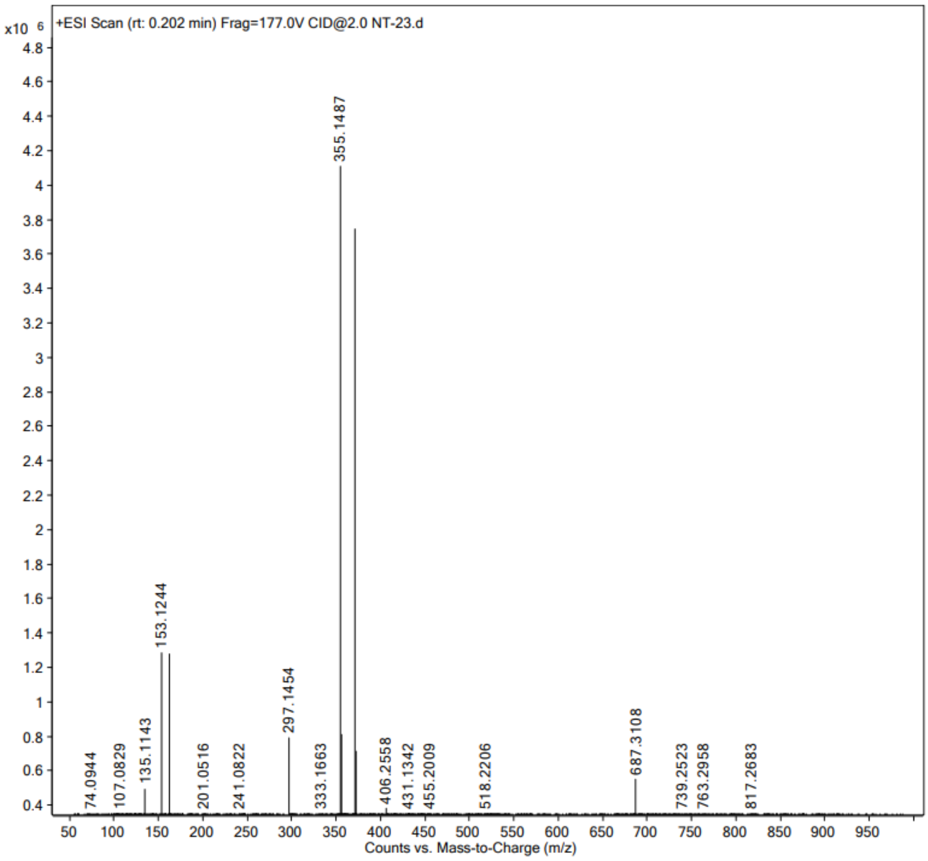


Figure A.22. HRMS spectra of Marmin.

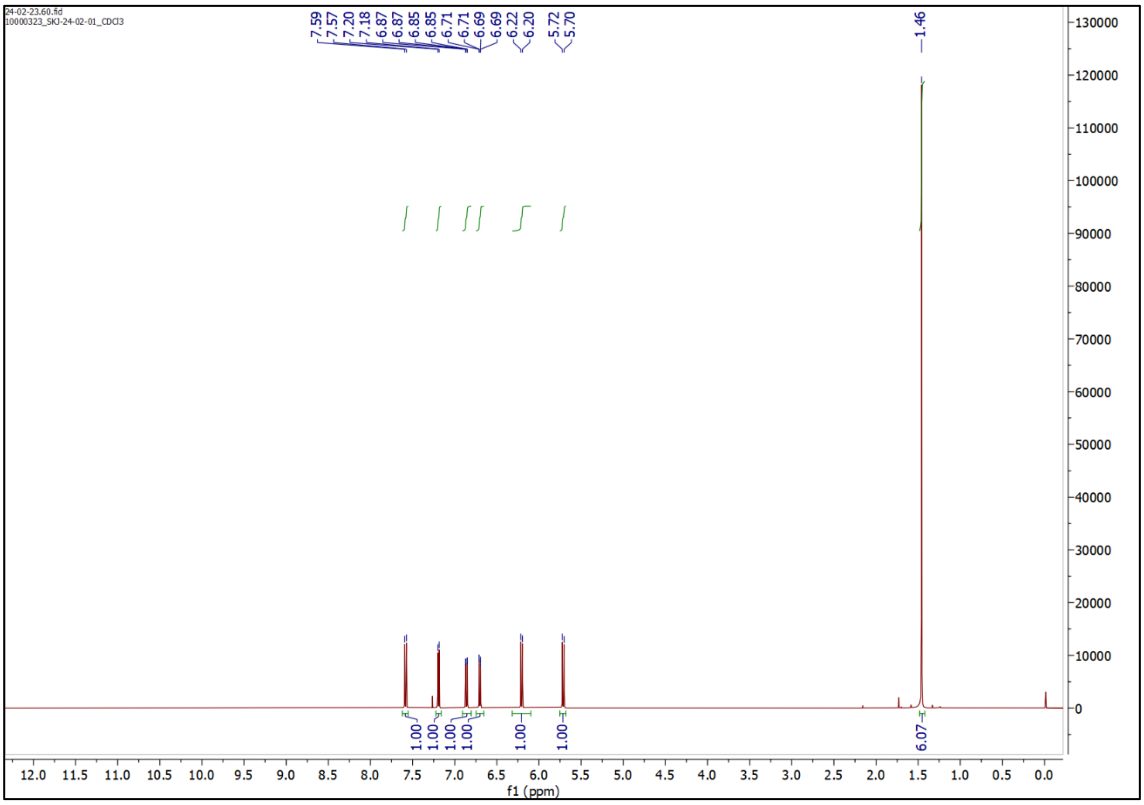


Figure A.23. 1H NMR spectra of Seselin.

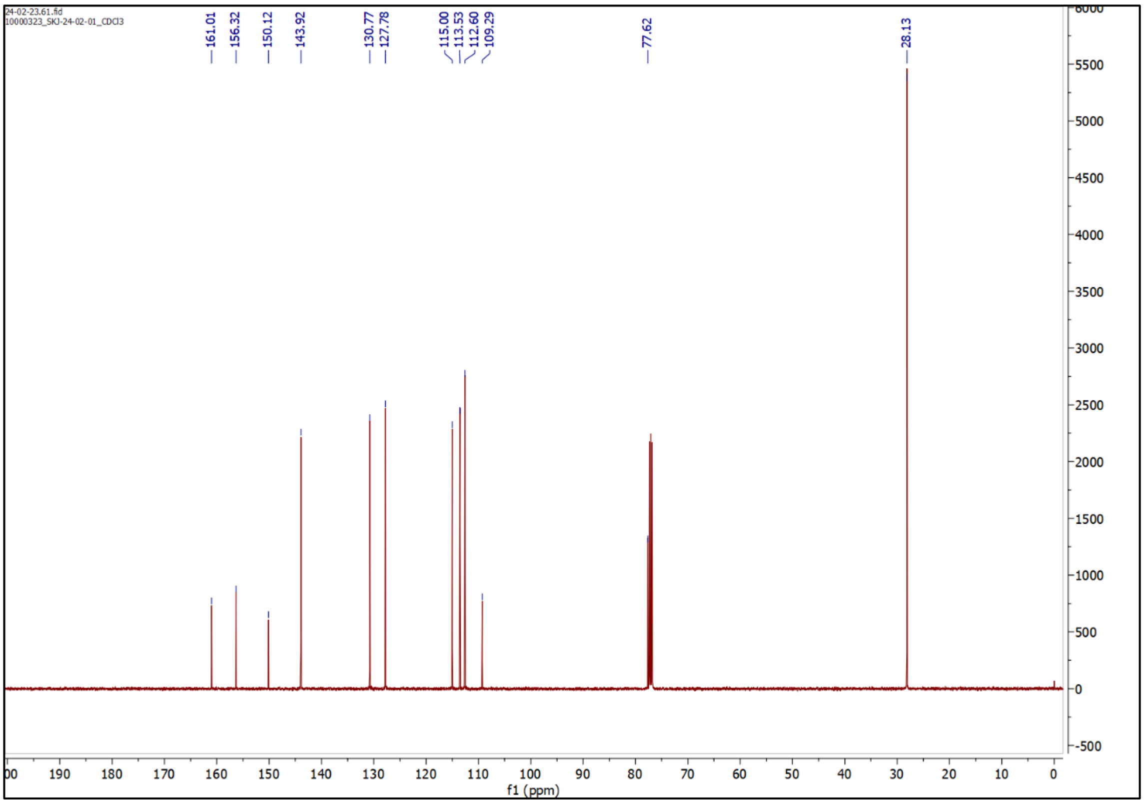


Figure A.24. 13C NMR spectra of Seselin.

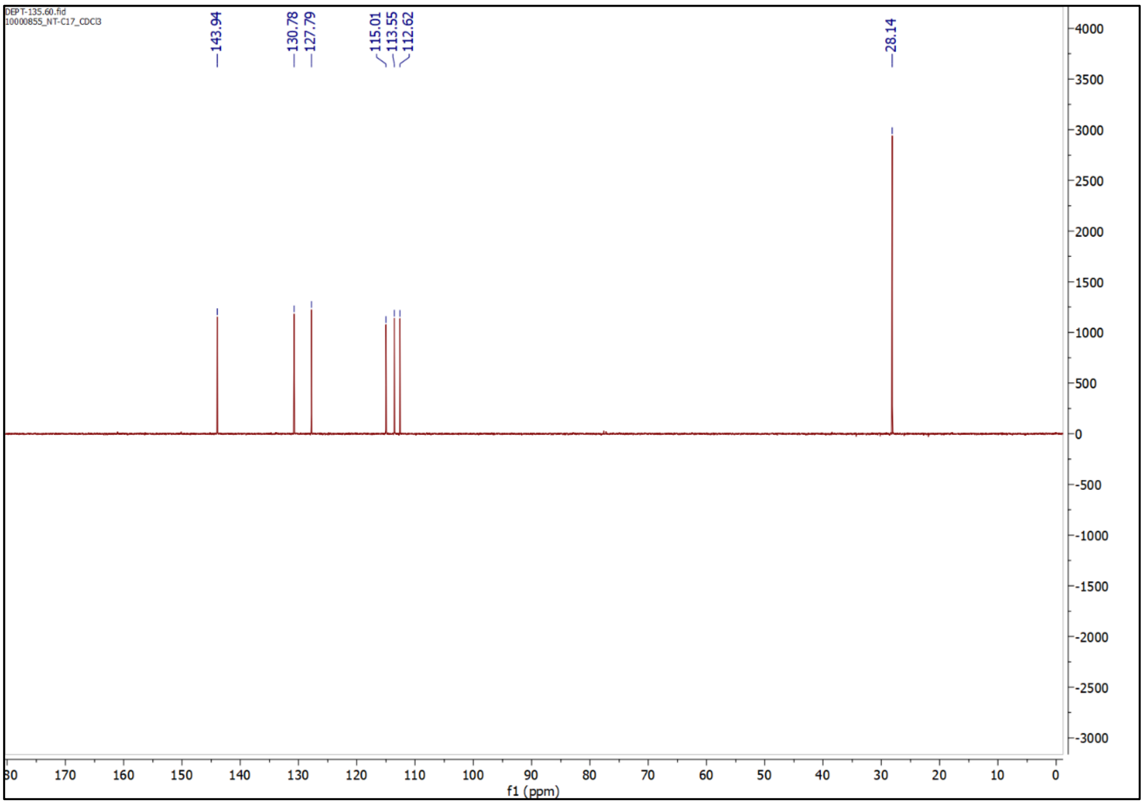


Figure A.25. DEPT-135 spectra of Seselin.

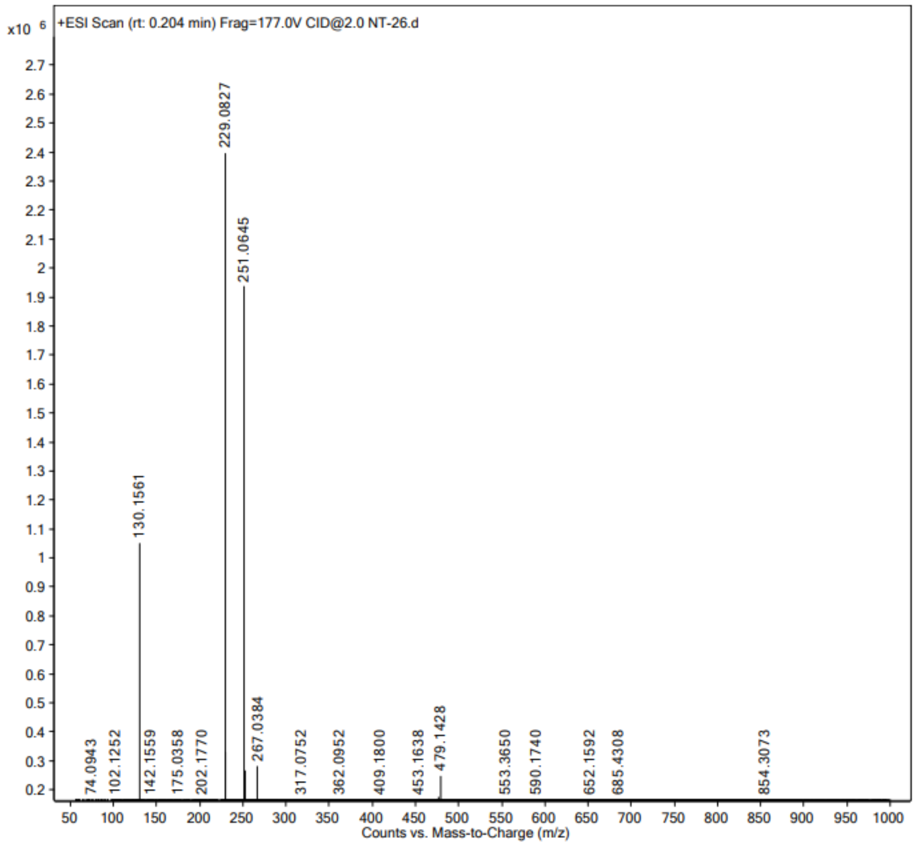


Figure A.26. HRMS spectra of Seselin.

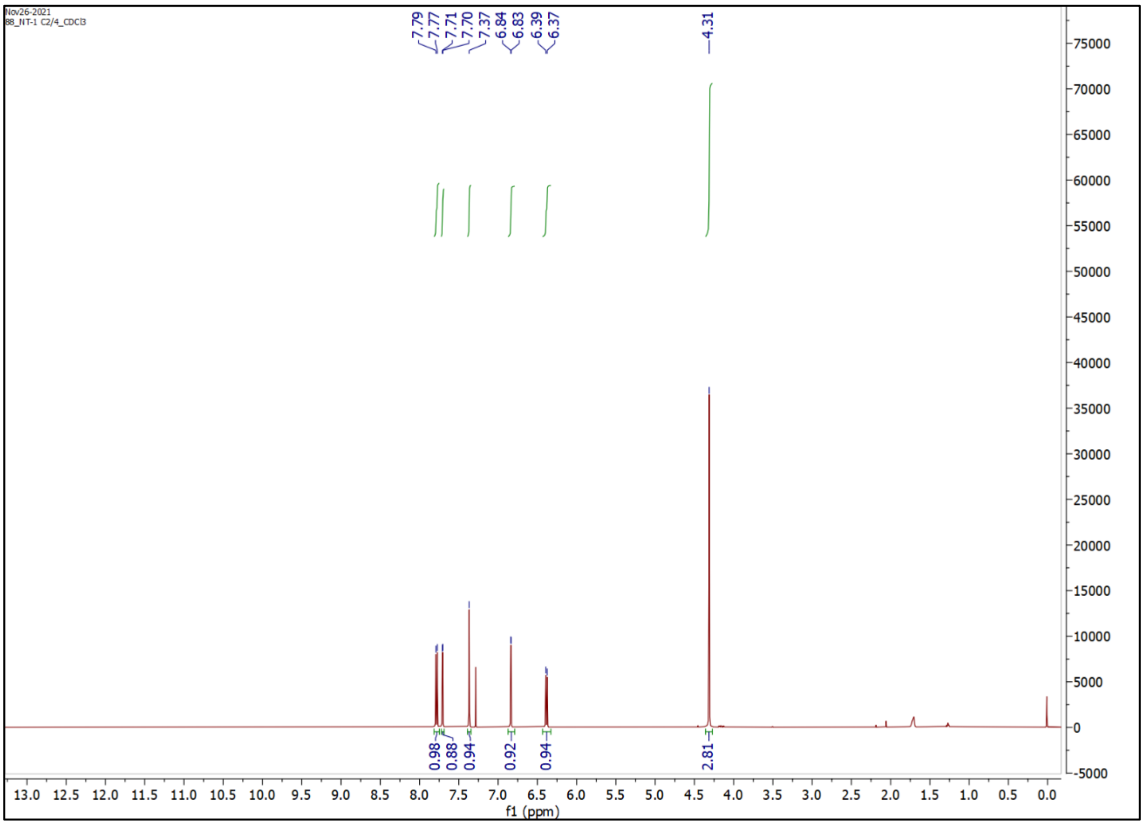


Figure A.27. 1H NMR spectra of Xanthotoxin.

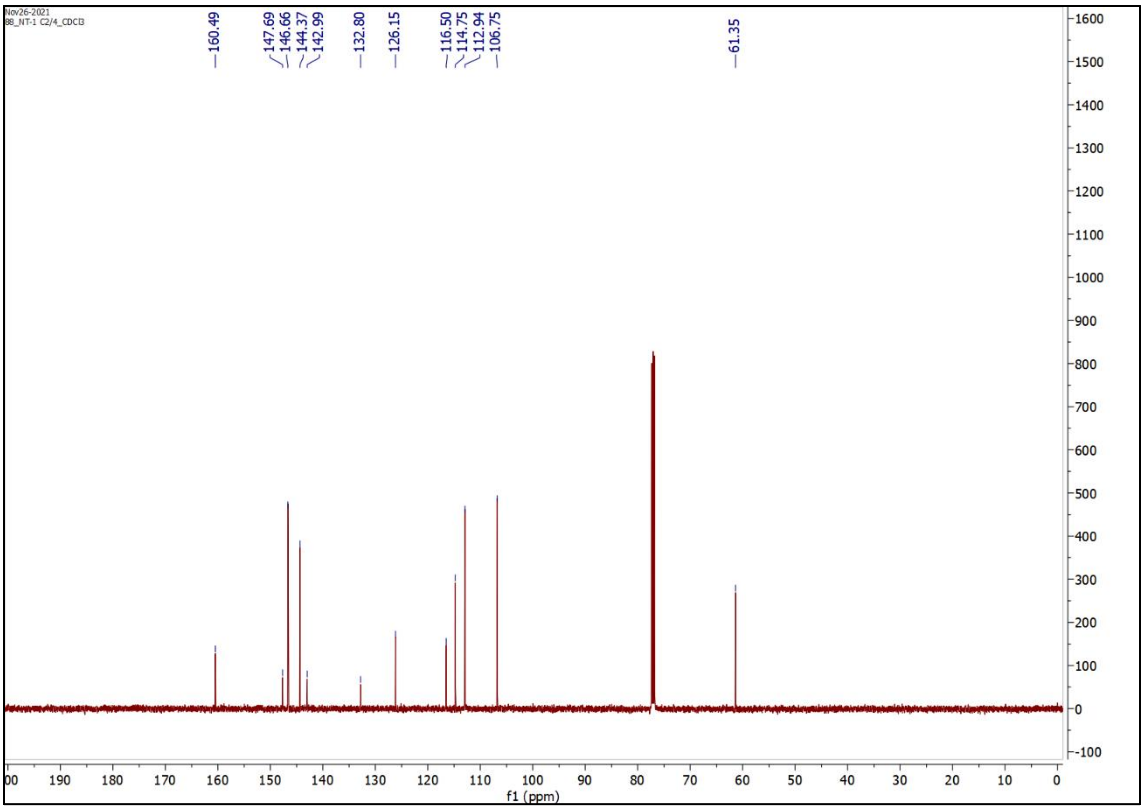


Figure A.28. 13C NMR spectra of Xanthotoxin.

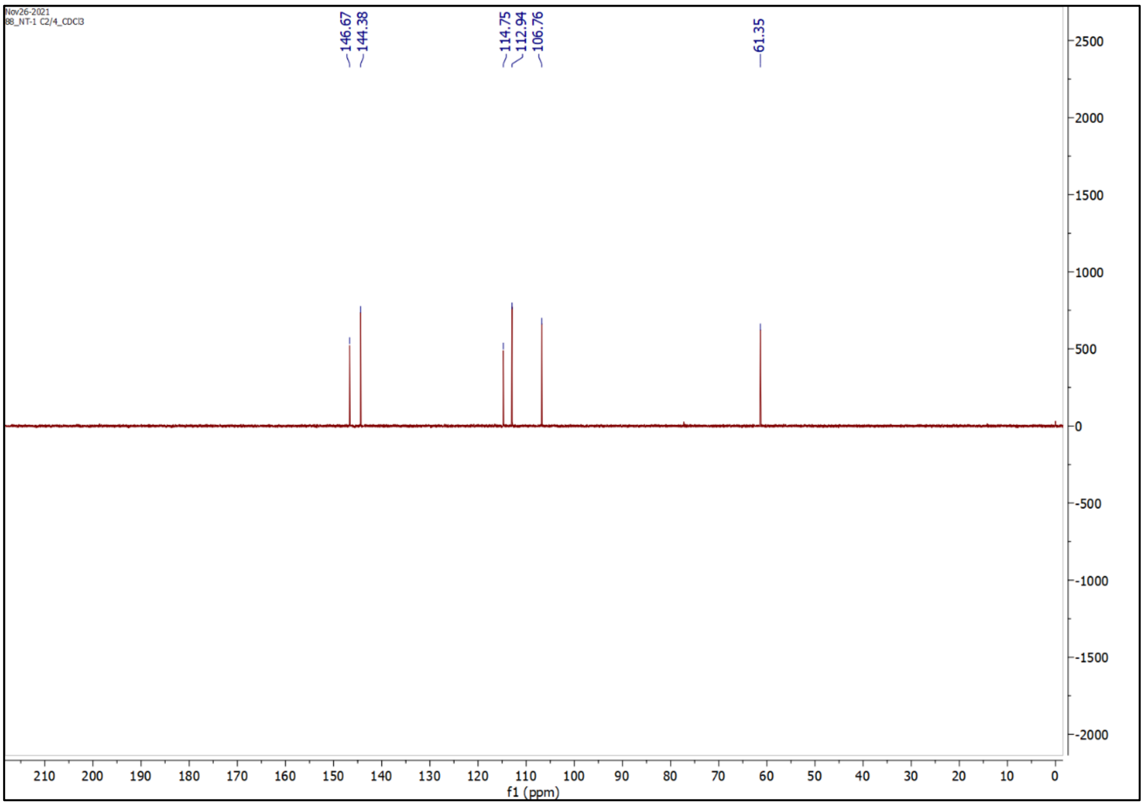


Figure A.29. DEPT-135 spectra of Xanthotoxin.

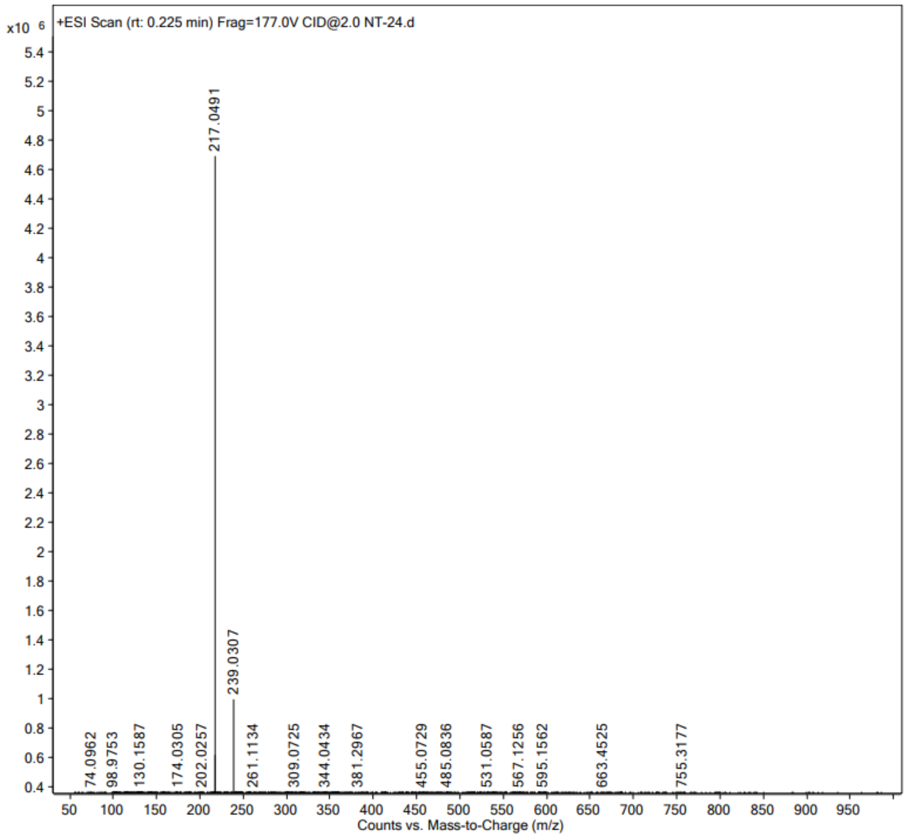


Figure A.30. HRMS spectra of Xanthotoxin.

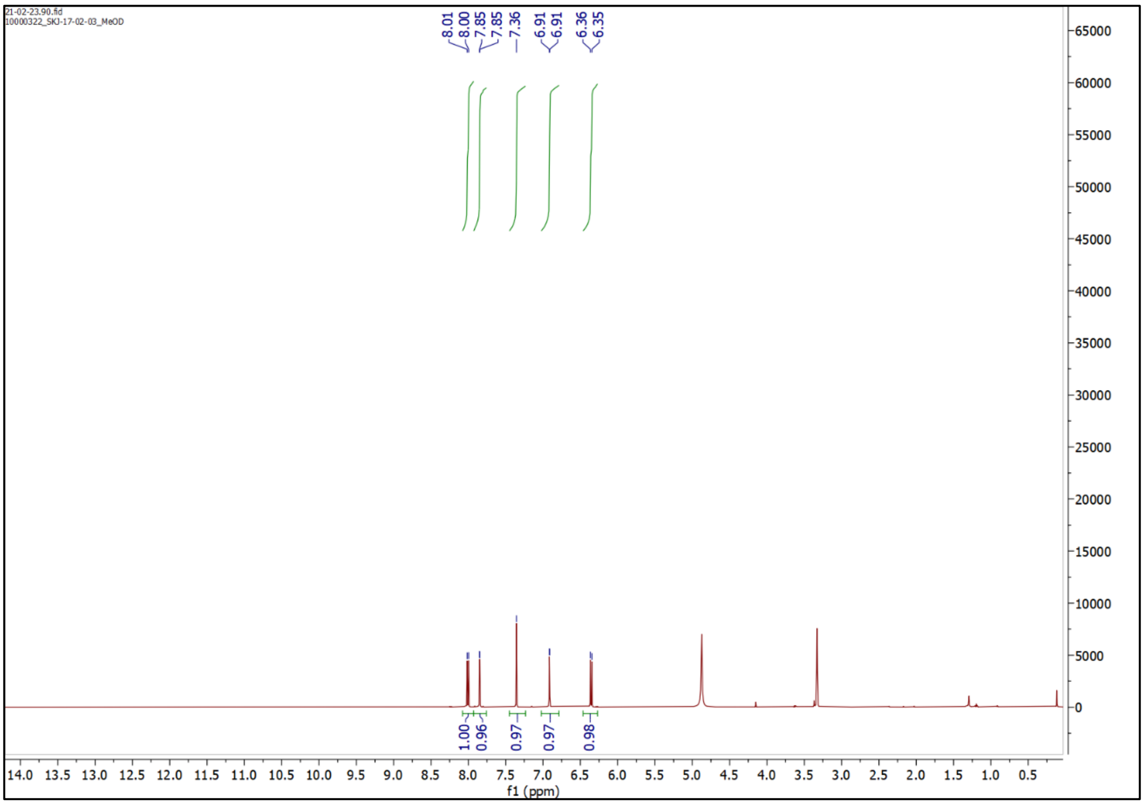


Figure A.31. 1H NMR spectra of Xanthotoxol.

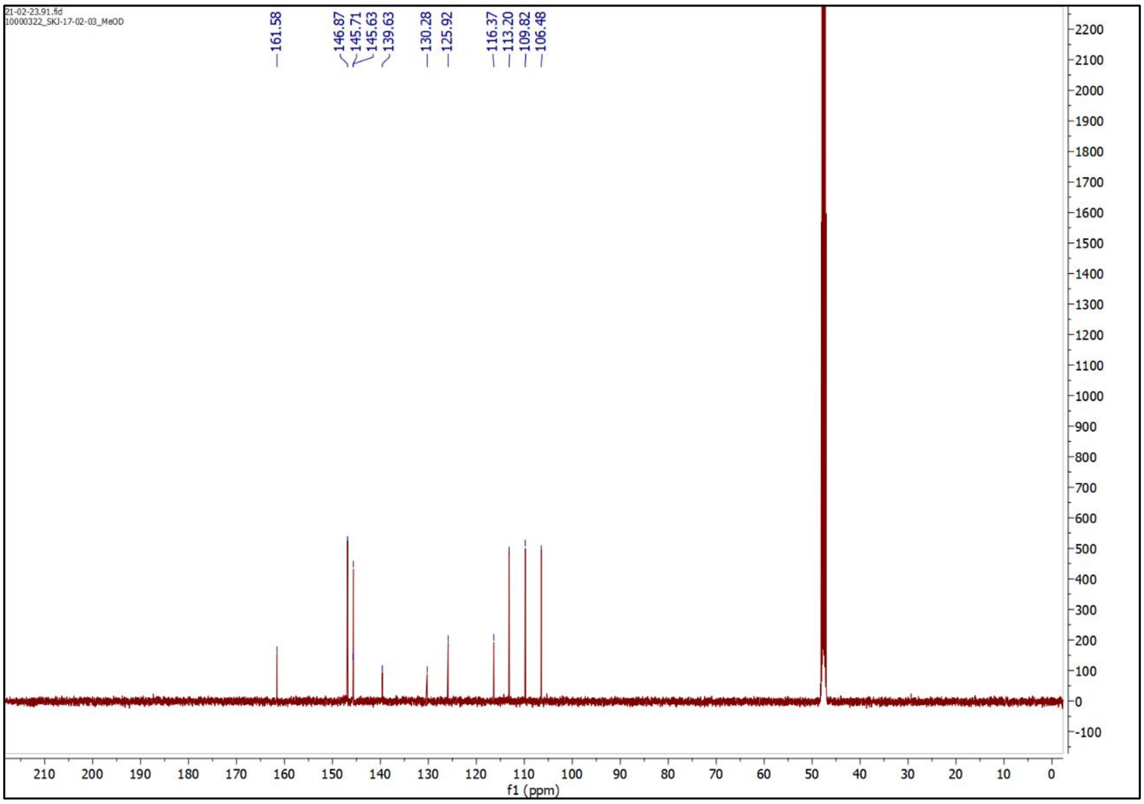


Figure A.32. 13C NMR spectra of Xanthotoxol.

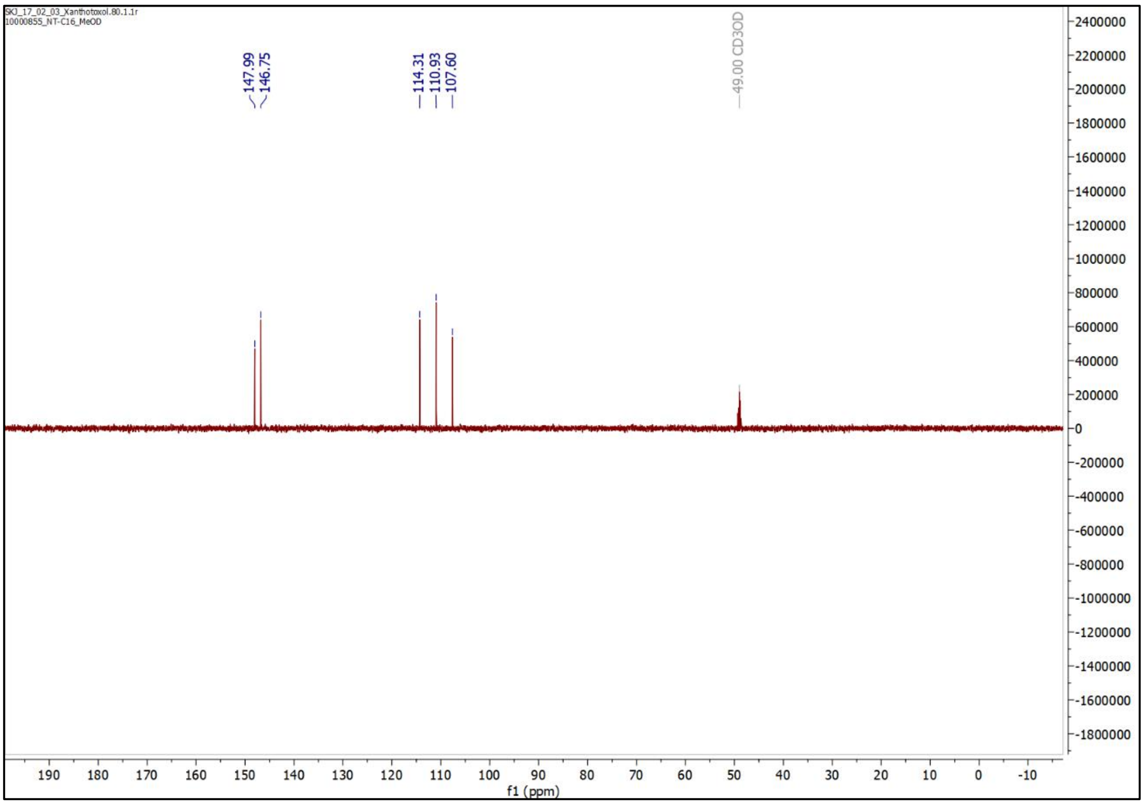


Figure A.33. DEPT-135 spectra of Xanthotoxol.

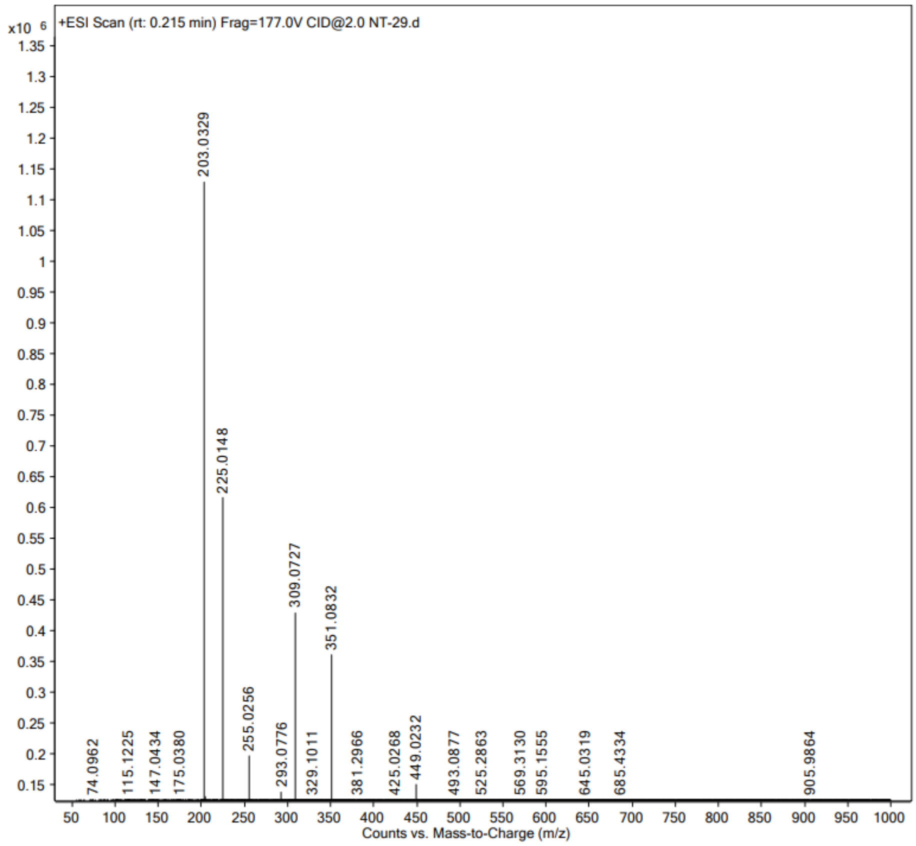
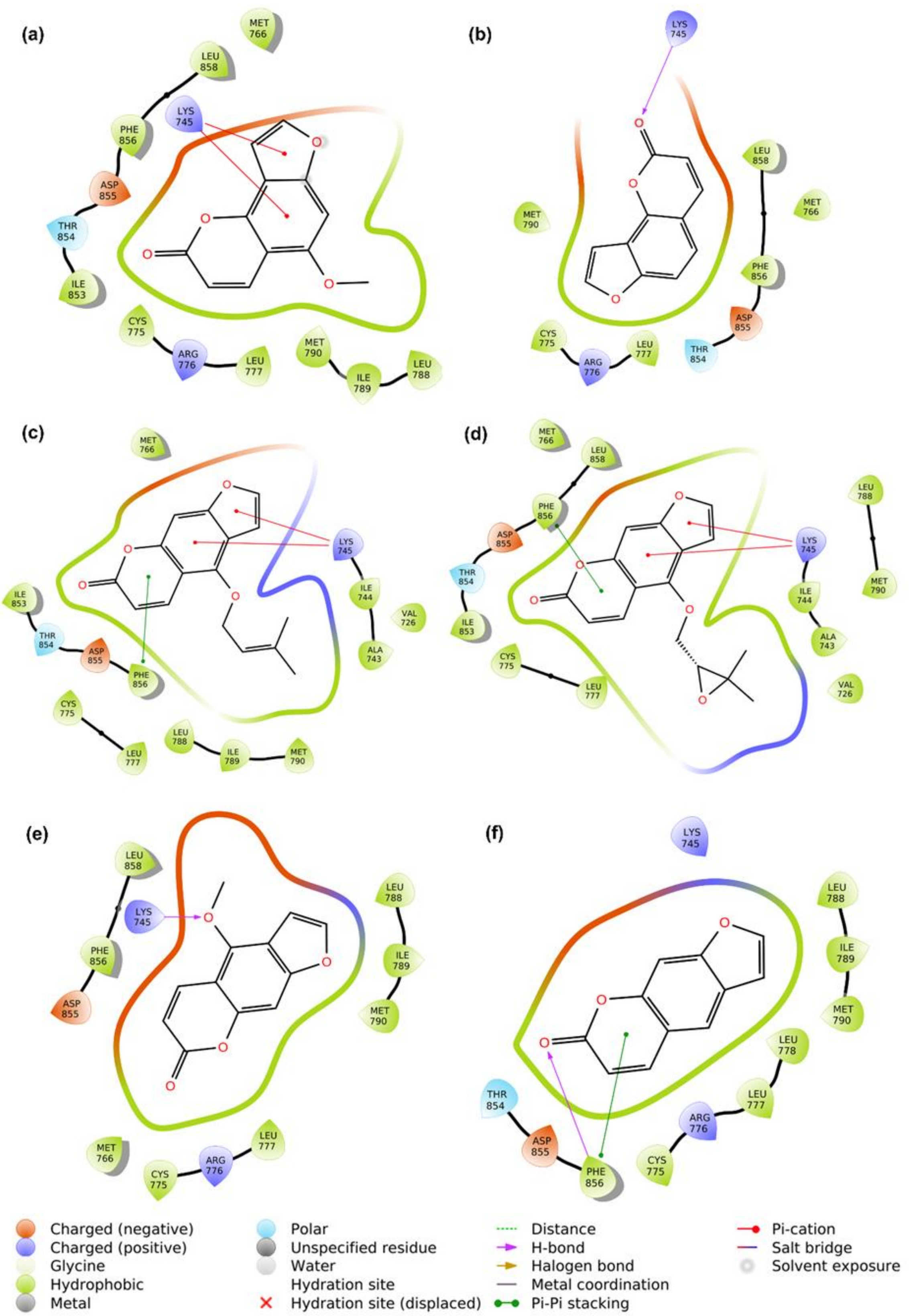


Figure A.34. HRMS spectra of Xanthotoxol.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ILE 789
LEU 788
(b)
LYS 745
LEU 858
MET 766
MET 790
PHE 856
ASP 855
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CYS 775
ARG 776
LEU 777
(c)
MET 766
LYS 745
ILE 744
VAL 726
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MET 790
(d)
MET 766
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Charged (positive)
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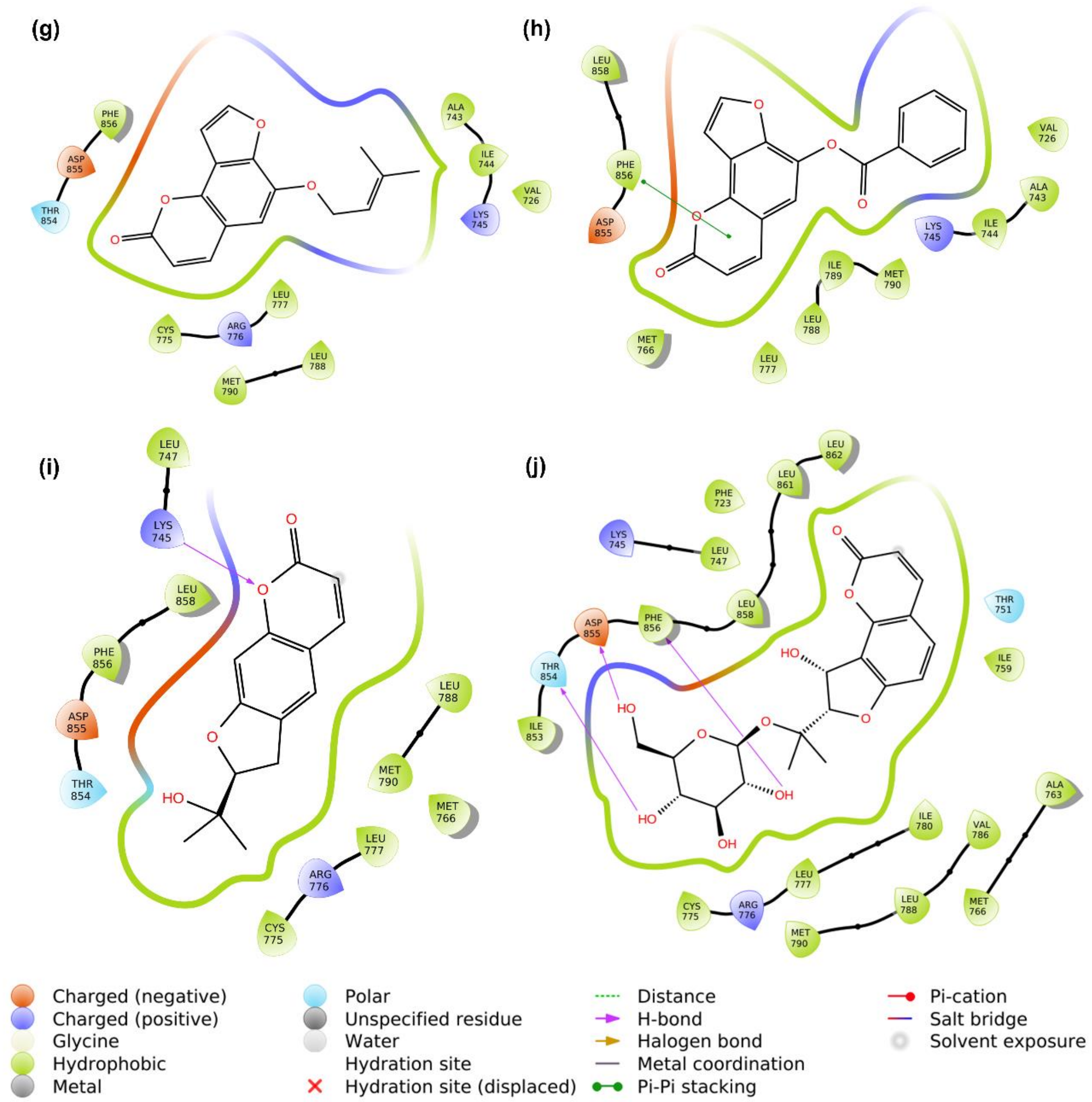

Figure A.35. Ligand-interaction diagrams of coumarins isolated from *P. corylifolia*. (a) Isobergapten, (b) Isopsoralen, (c) Isoimperatorin, (d) Oxypeucedanin, (e) Bergapten, (f) Psoralen, (g) Heratomine, (h) Heratomol benzoate, (i) Marmesin, and (j) Apterin.

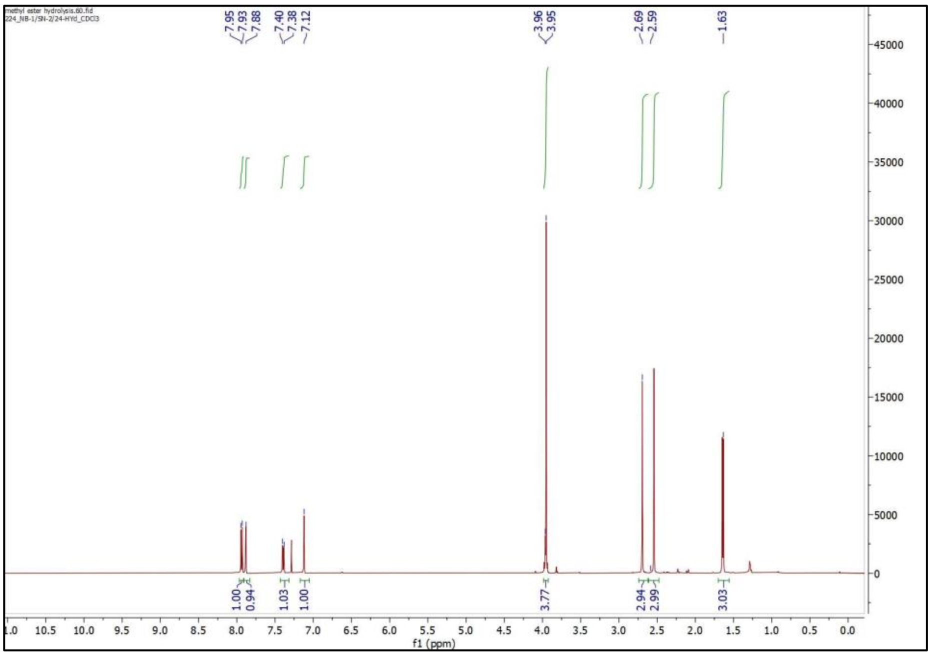

Figure A.36. 1H NMR spectrum of compound **12** in $CDCl_3$.

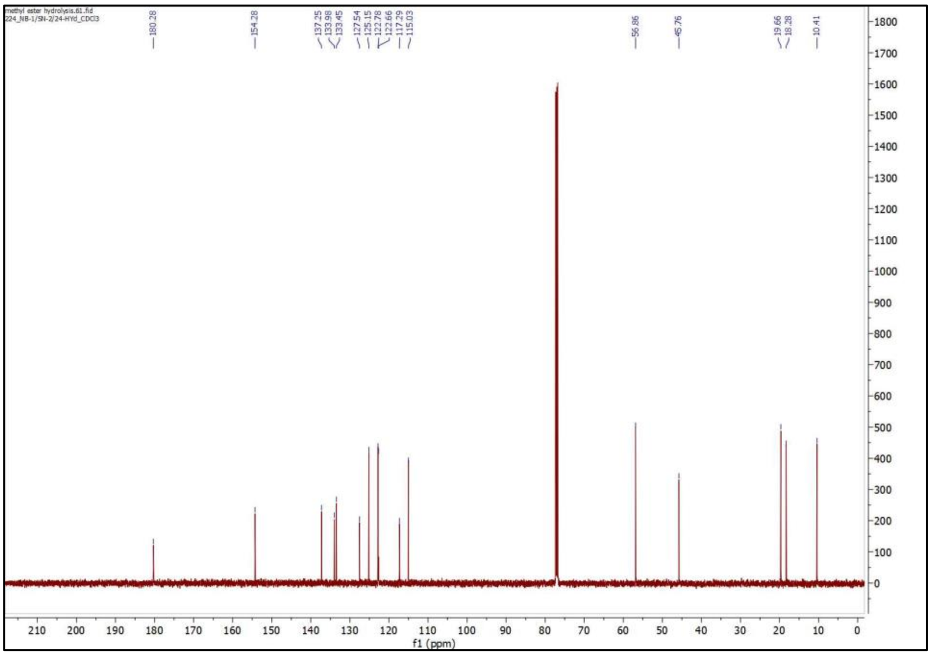

Figure A.37. 13C NMR spectrum of compound **12** in $CDCl_3$.

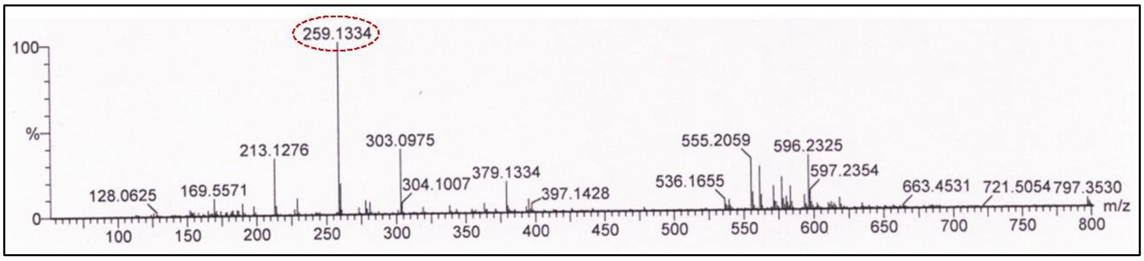

Figure A.38. HRMS spectra of compound **12**.

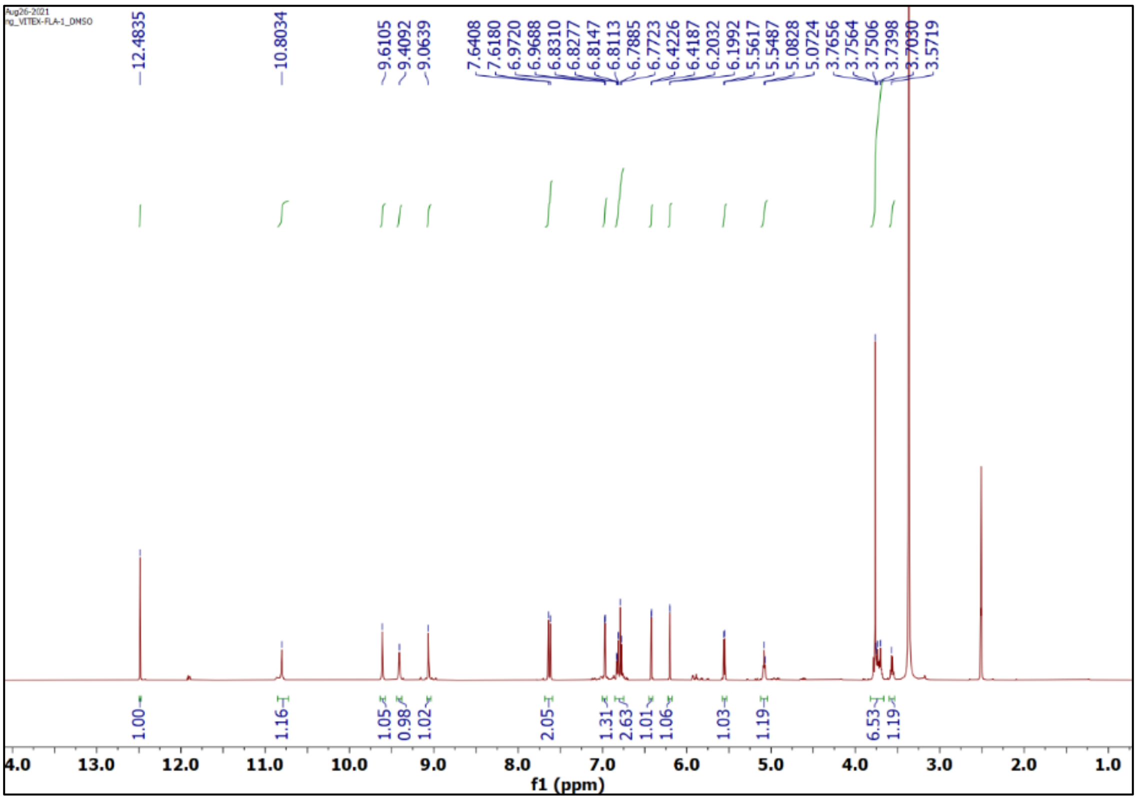

Figure A.39. 1H NMR spectrum of 2,3-Dehydrosilychristin (**7**) in DMSO.

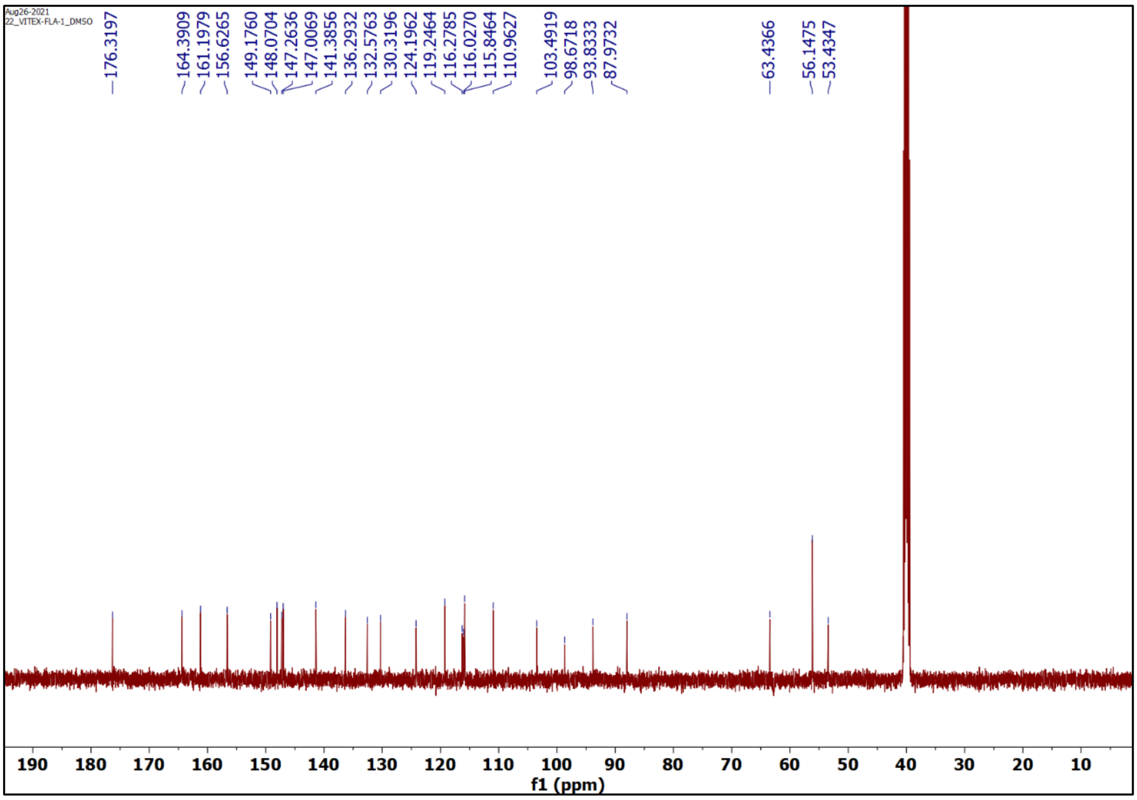

Figure A.40. 13C NMR spectrum of 2,3-Dehydrosilychristin (**7**) in DMSO.

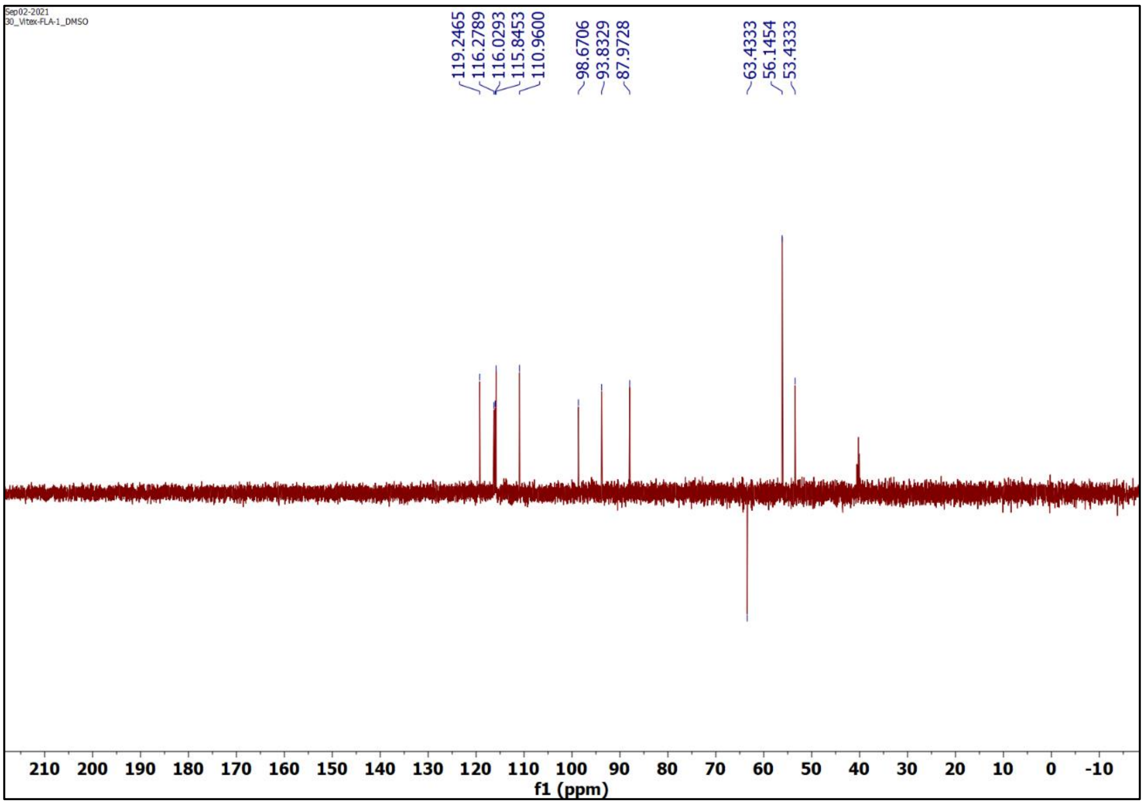

Figure A.41. DEPT-135 NMR spectrum of 2,3-Dehydrosilychristin (**7**) in DMSO.

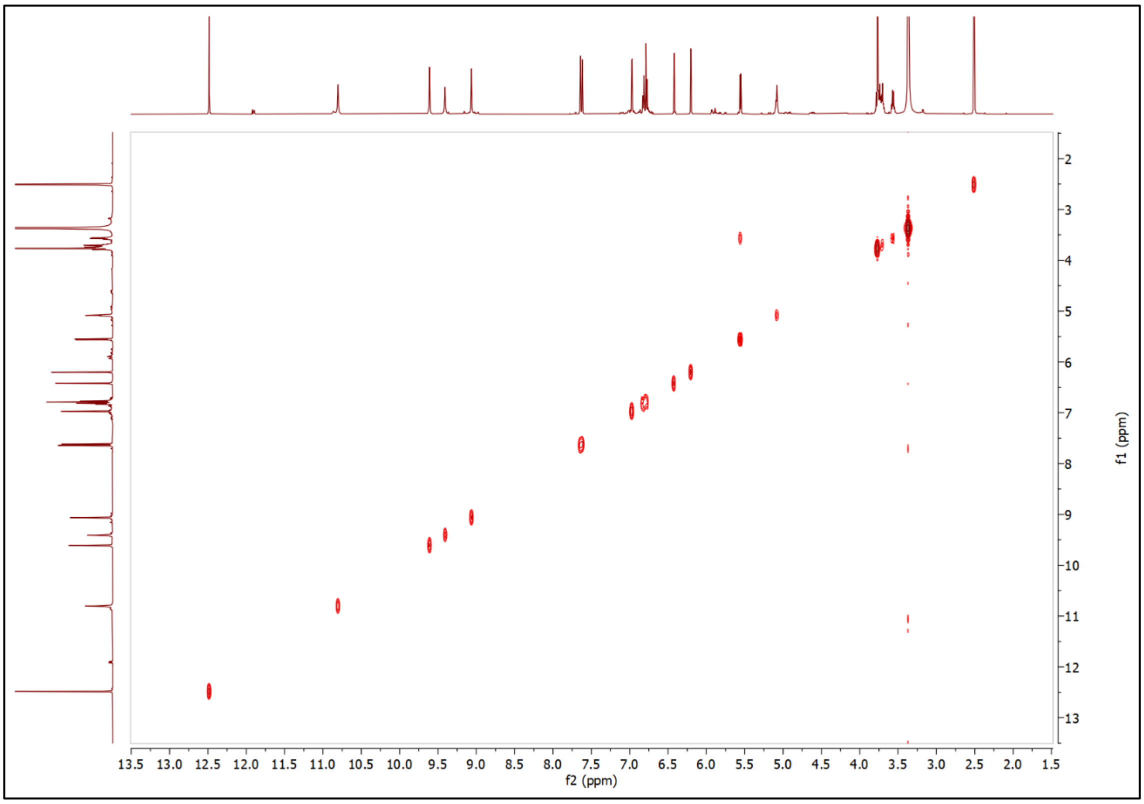

Figure A.42. COSY NMR spectrum of 2,3-Dehydrosilychristin (**7**) in DMSO.

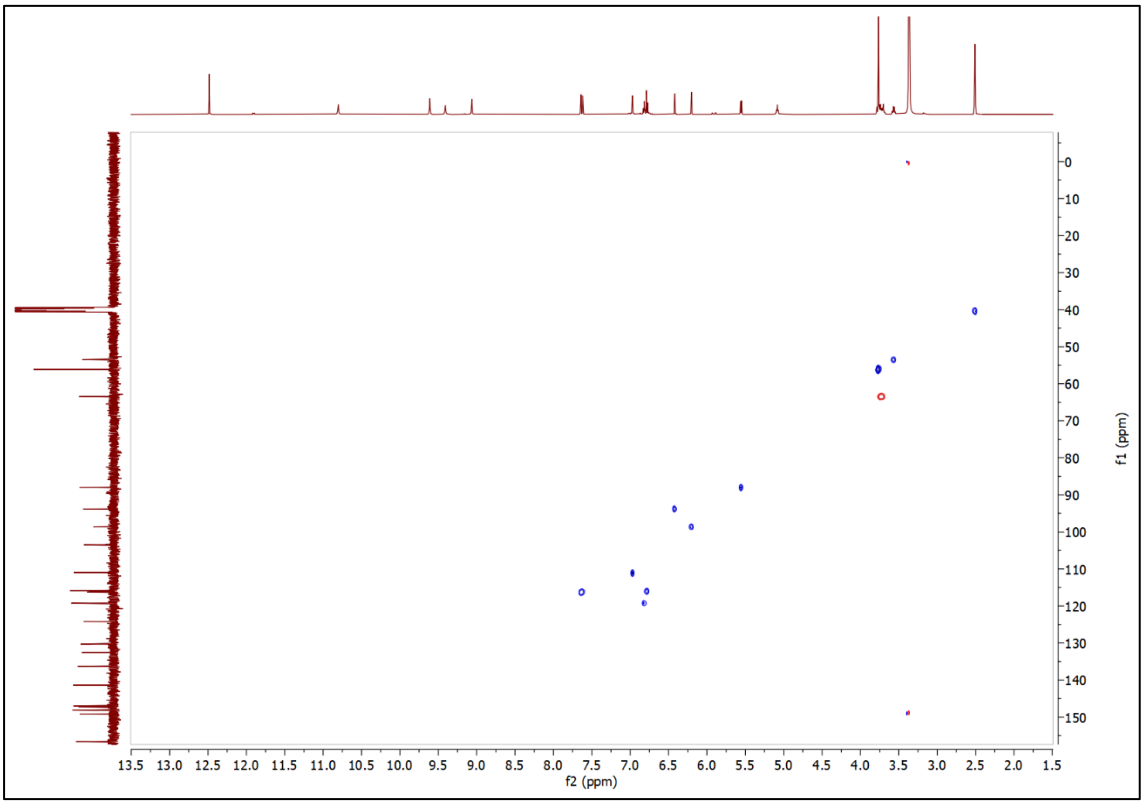

Figure A.43. HSQC NMR spectrum of 2,3-Dehydrosilychristin (**7**) in DMSO.

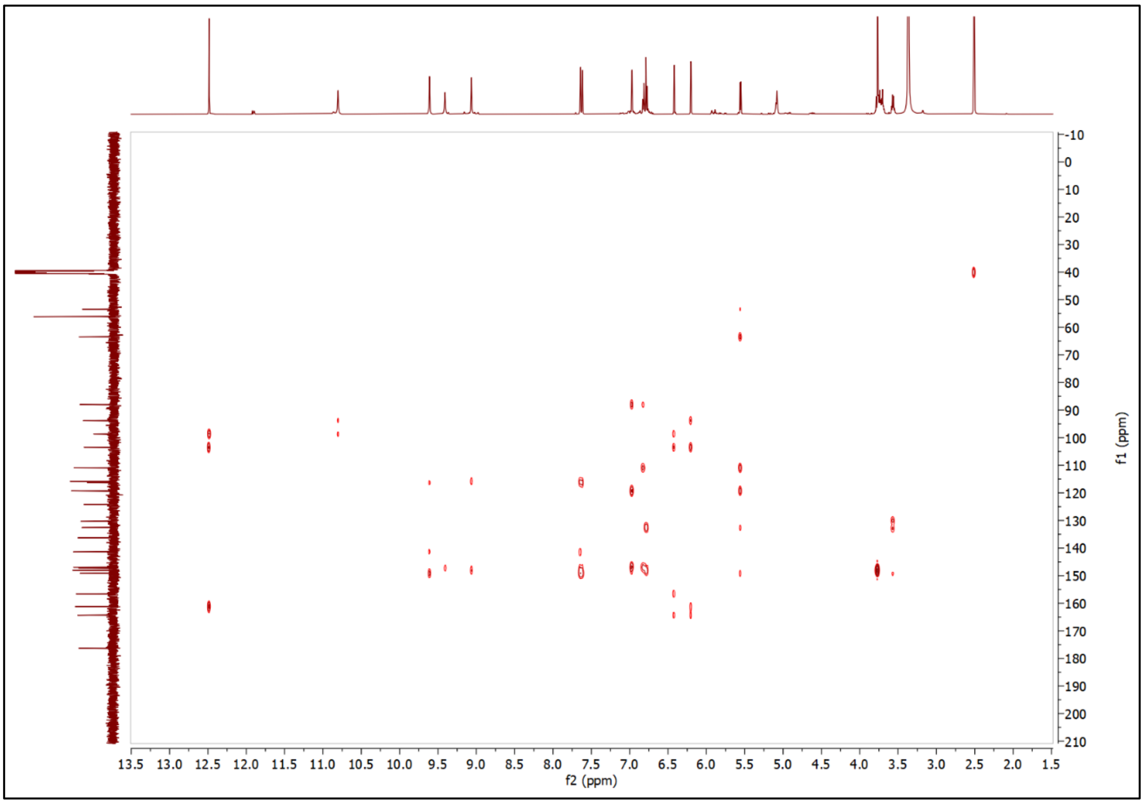

Figure A.44. HMBC NMR spectrum of 2,3-Dehydrosilychristin (**7**) in DMSO.

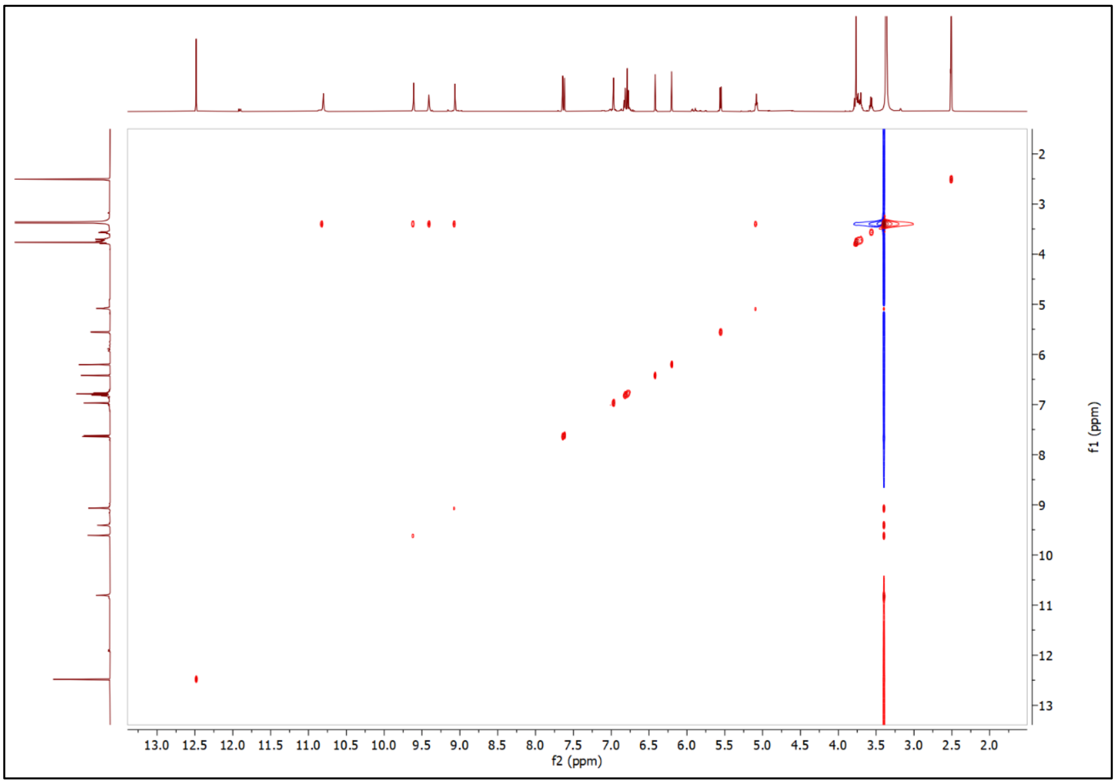

Figure A.45. NOESY NMR spectrum of 2,3-dehydrosilychristin (**7**) in DMSO.

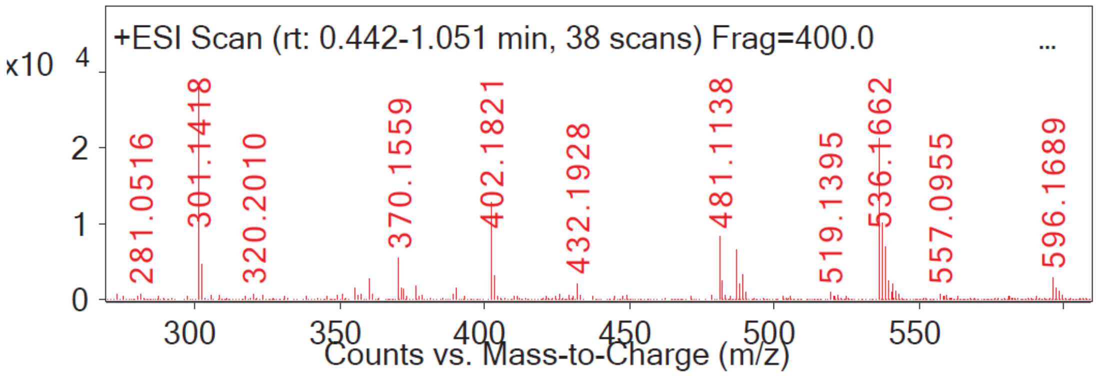

Figure A.46. Mass spectrum of 2,3-Dehydrosilychristin (**7**).

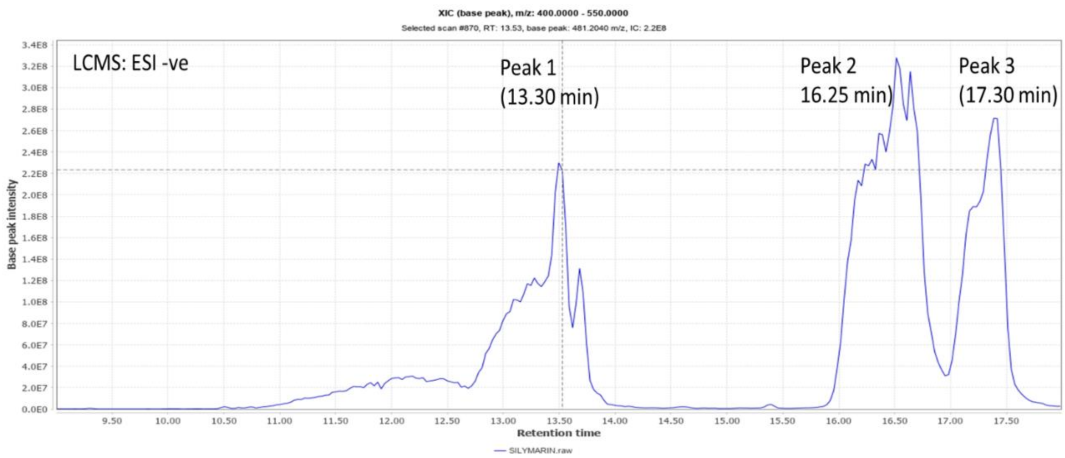

Figure A.47. LC-MS chromatogram of Silymarin.

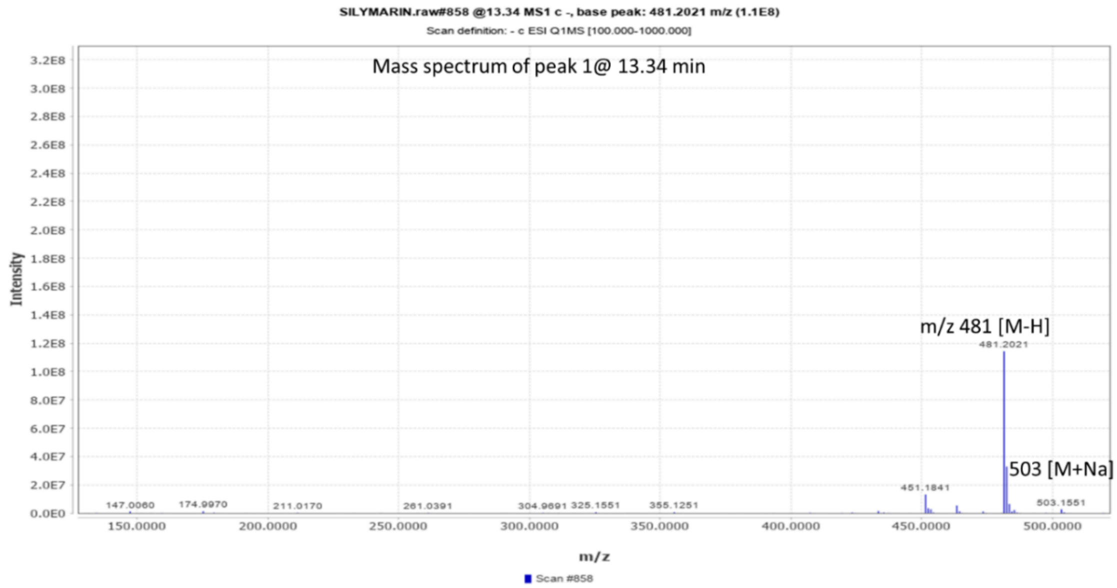

Figure A.48. Mass spectrum of peak 1.

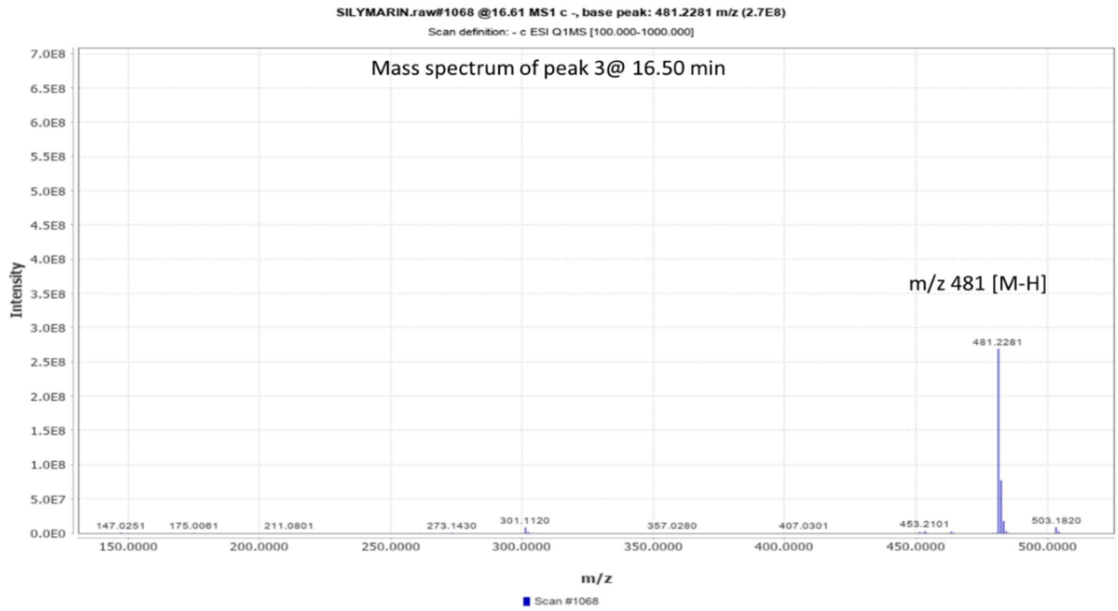

Figure A.49. Mass spectrum of peak 2.

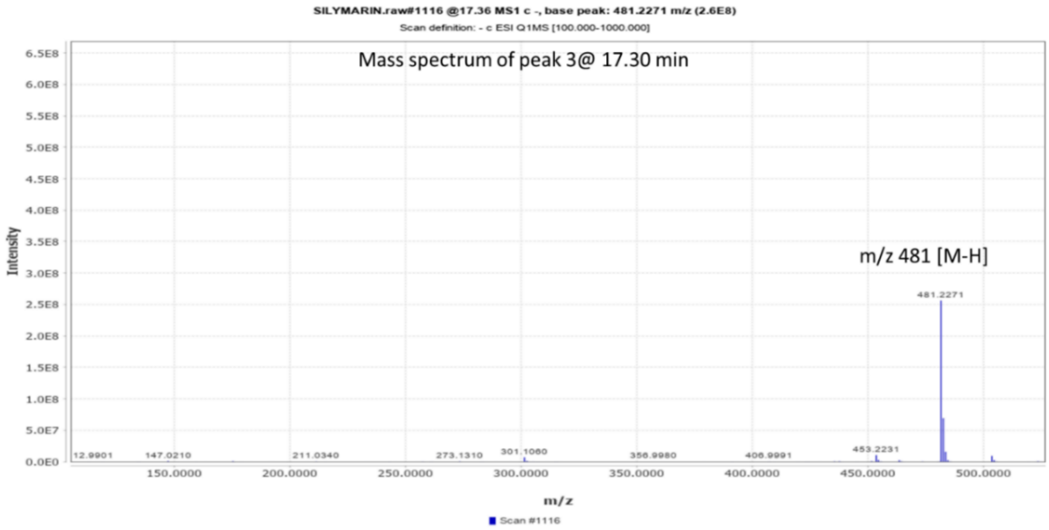

Figure A.50. Mass spectrum of peak 3.

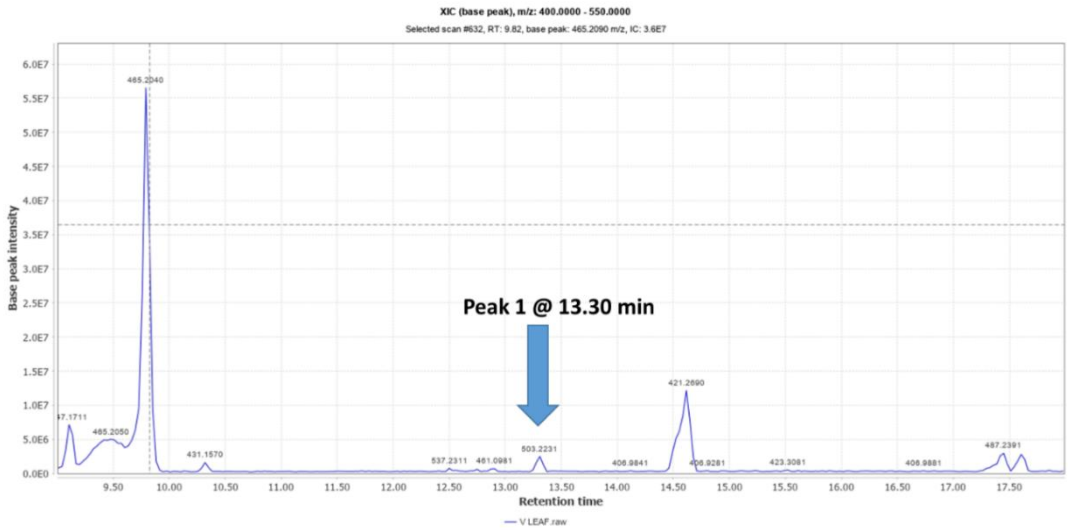

Figure A.51. LC-MS chromatogram of leaf extract of *Vitex negundo*.

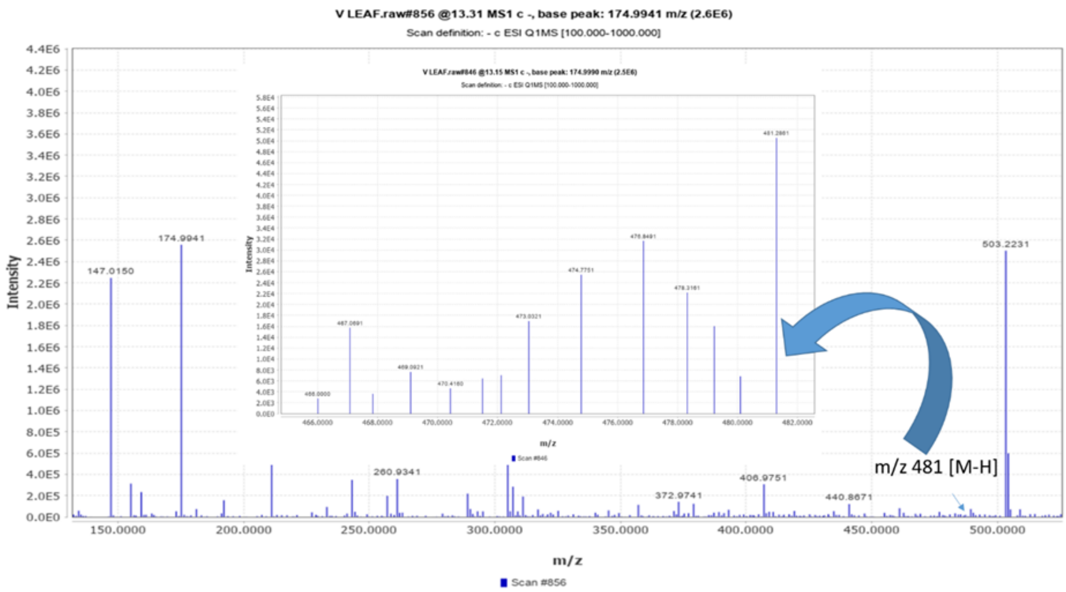

Figure A.52. Mass spectrum of peak 1 at 13.30 min of leaf extract.

List of Publications

List of publications from thesis work

1. **Tripathi, N.**, Bhardwaj, N., Kumar, S., Jain, S. K. *Phytochemical and Pharmacological Aspects of Psoralen – A Bioactive Furanocoumarin from Psoralea corylifolia Linn.* Chemistry & Biodiversity, 2023. 20(11): p. e202300867.
2. **Tripathi, N.**, Shah, H., Bhardwaj, N., Sarkar, R., Jain, S. K. *In silico analysis, isolation, and cytotoxicity evaluation of the coumestans from Cullen corylifolium (L.) Medik.* Natural Product Research, 2023: p. 1-8.
3. **Tripathi, N.**, Parmar, A., Pandey, N., Bhardwaj, N., Chakrabarty, S., Sarkar, R., Kumar, H., Jain, S. K. *Isolation, Cytotoxicity, and In-silico Screening of Coumarins from Psoralea corylifolia Linn.* Chemistry & Biodiversity, 2024. 21(2): p. e202301841.
4. **Tripathi, N.**, Saraf, P., Bhardwaj, N., Shrivastava, S. K., Jain, S. K. *Identifying inflammation-related targets of natural lactones using network pharmacology, molecular modeling and in vitro approaches.* Journal of Biomolecular Structure and Dynamics, 2024: p. 1-16.
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