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A. Pharmacophore-based virtual screening

Table A1. Evaluation of the quality of MAO-B protein sequence (PDB ID: 2V5Z) by PROCHECK

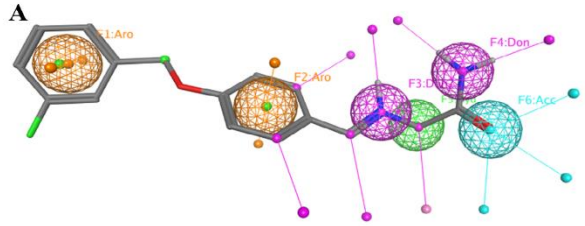
Parameters for evaluation	No. of residues	Score
Residues in most favored regions	415	92.84%
Residues in additional allowed regions	29	6.48%
Residues in generously allowed regions	1	0.22%
Residues in disallowed regions	2	0.45%
Number of non-glycine and non-proline residues	447	100.00%
Number of end-residues (excl. Gly and Pro)	2	-
Number of glycine residues (shown as triangles)*	42	-
Number of proline residues	29	-
Total number of residues	520	-

*****Refer to Figure A2 for details.

A brief protocol followed for the evaluation of protein structure through SAVES server

The protein structure of monoamine oxidase B (PDB ID: 2V5Z) was uploaded to the SAVES v6.0 web server (https://saves.mbi.ucla.edu/). Then protein was analyzed for different parameters namely, ERRAT, Verify 3D, PROVE, WHATCHEK, PROCHECK and CRYST. The Ramachandran plot from the results of PROCHECK was then downloaded.

A



B

F1: Aro	0					
F2: Aro	4.6	0				
F3: Don	2.6	7.2	0			
F4: Don	9.8	5.3	2.6	0		
F5: Hyd	8.5	4.0	1.7	2.0	0	
F6: Acc	8.7	4.4	2.0	1.7	2.6	0
	F1: Aro	**F2: Aro**	**F3: Don**	**F4: Don**	**F5: Hyd**	**F6: Acc**

Figure A1. (a) Pharmacophore model of co-crystallized safinamide developed by MOE. (b) The distance between pharmacophoric features is presented in the distance matrix. Aro = Aromatic, Don = Donor, Hyd = Hydrophobic, Acc = Acceptor.

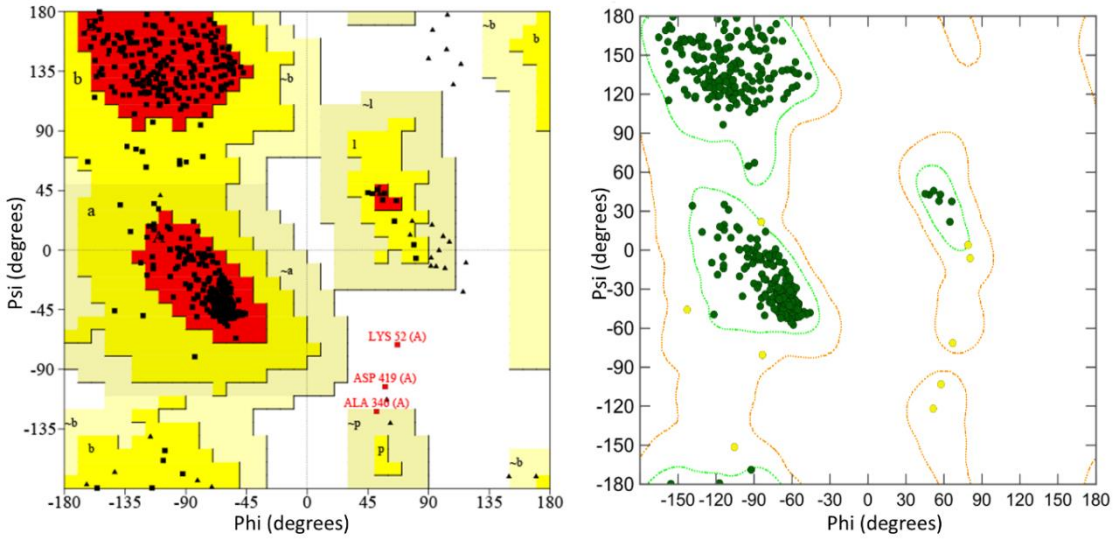


Figure A2. Ramachandran plot of MAO-B (PDB ID: 2V5Z) obtained from PROCHECK (yellow) and MOE (green), respectively.

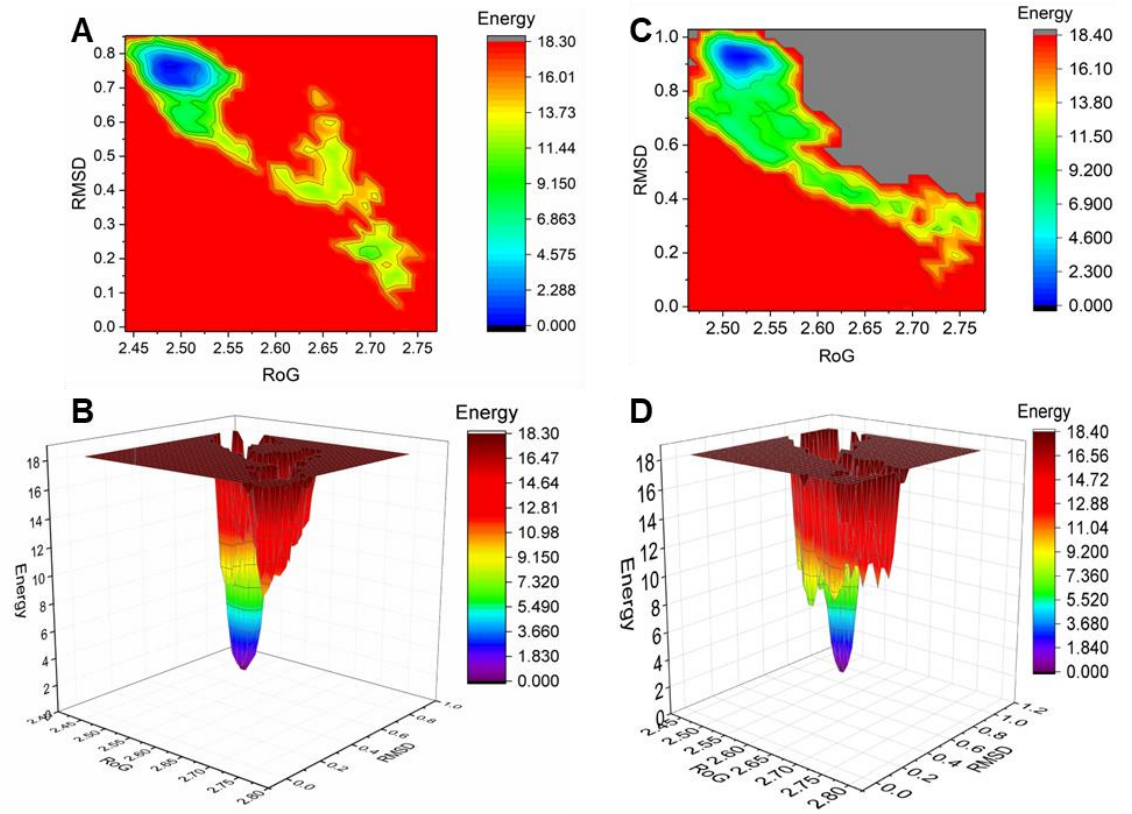


Figure A3. MD simulation results of MAO-B apoprotein and its complex with **ZINC02181408**; A) 2D contour map of MAO-B apoprotein; B) funnel like 3D energy projection diagram of MAO-B apoprotein 2V5Z; C) 2D contour map of MAO-B and **ZINC02181408** complex; D) funnel like 3D energy projection diagram of MAO-B complexed with **ZINC02181408**.

B. Spectral data of selected compounds

B1. Benzothiazole-derived Thioacetamides (ZBTI series)

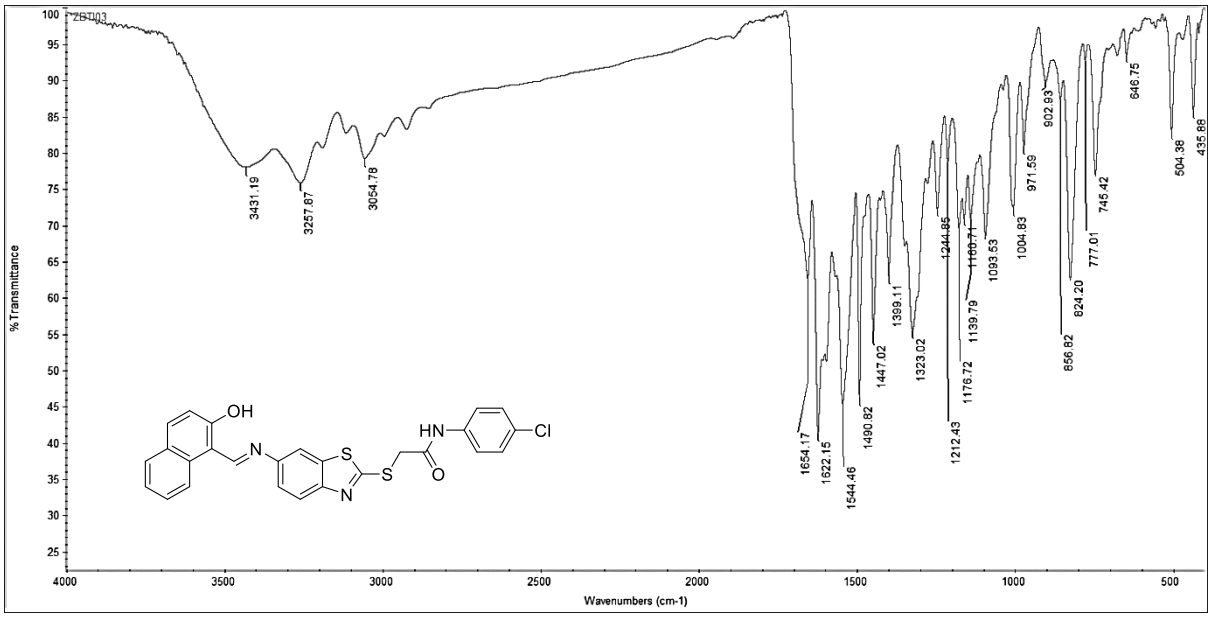


Figure A4. FTIR spectrum of compound **ZBTI03**

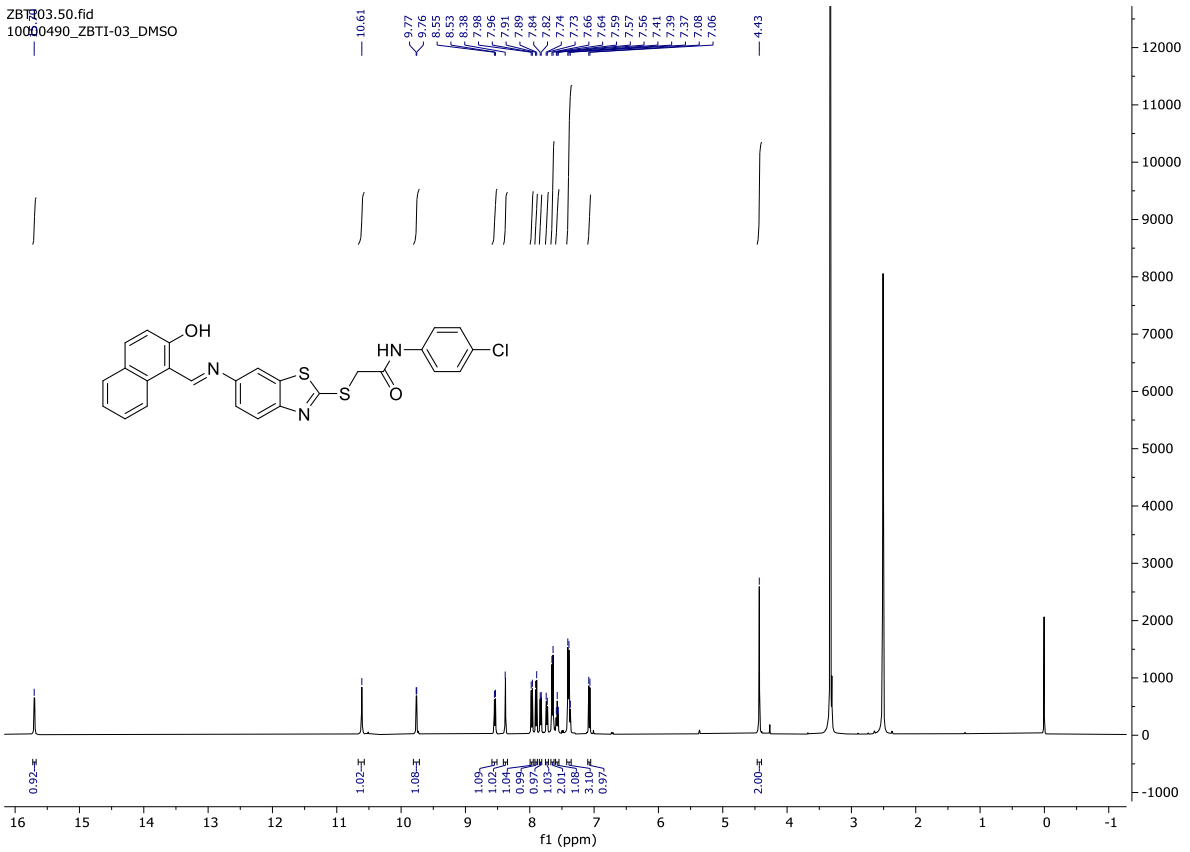


Figure A5. ^{1}H NMR spectrum of compound **ZBTI03**

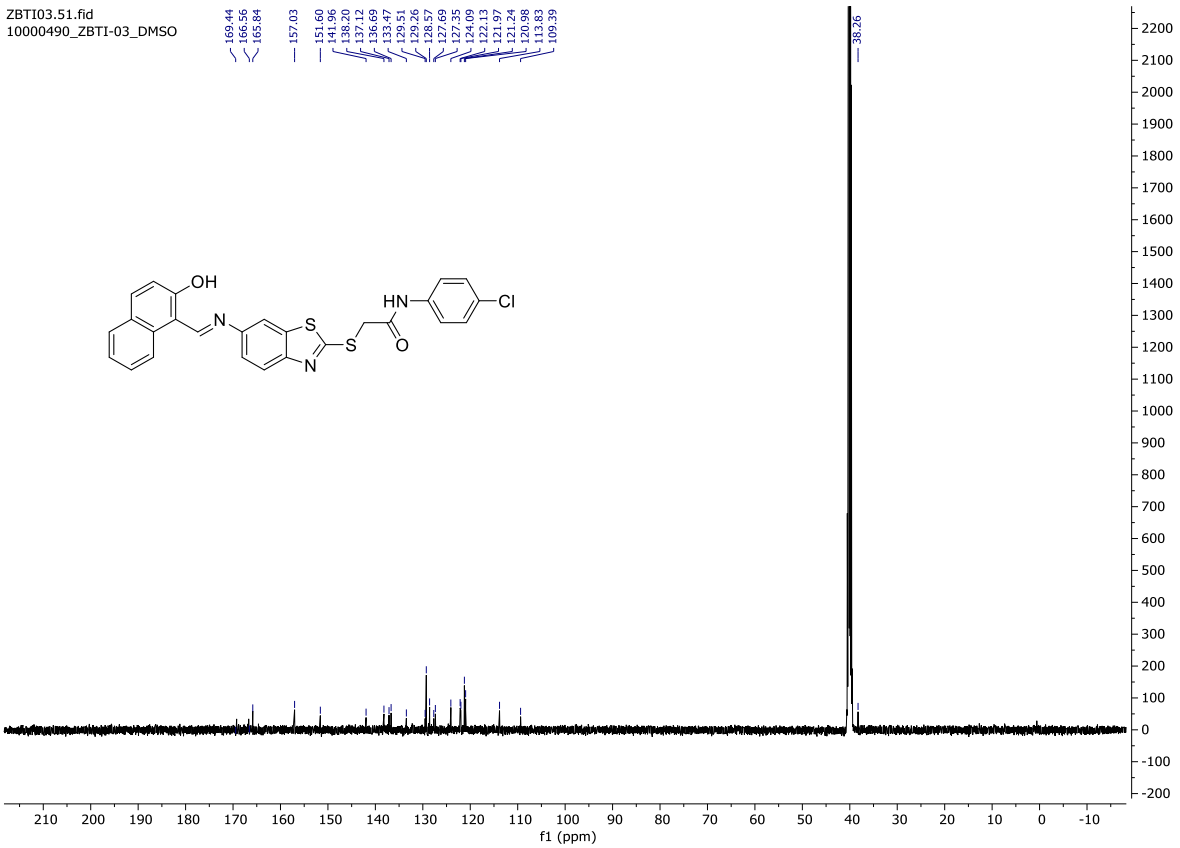


Figure 6. ^{13}C NMR spectrum of compound **ZBTI03**

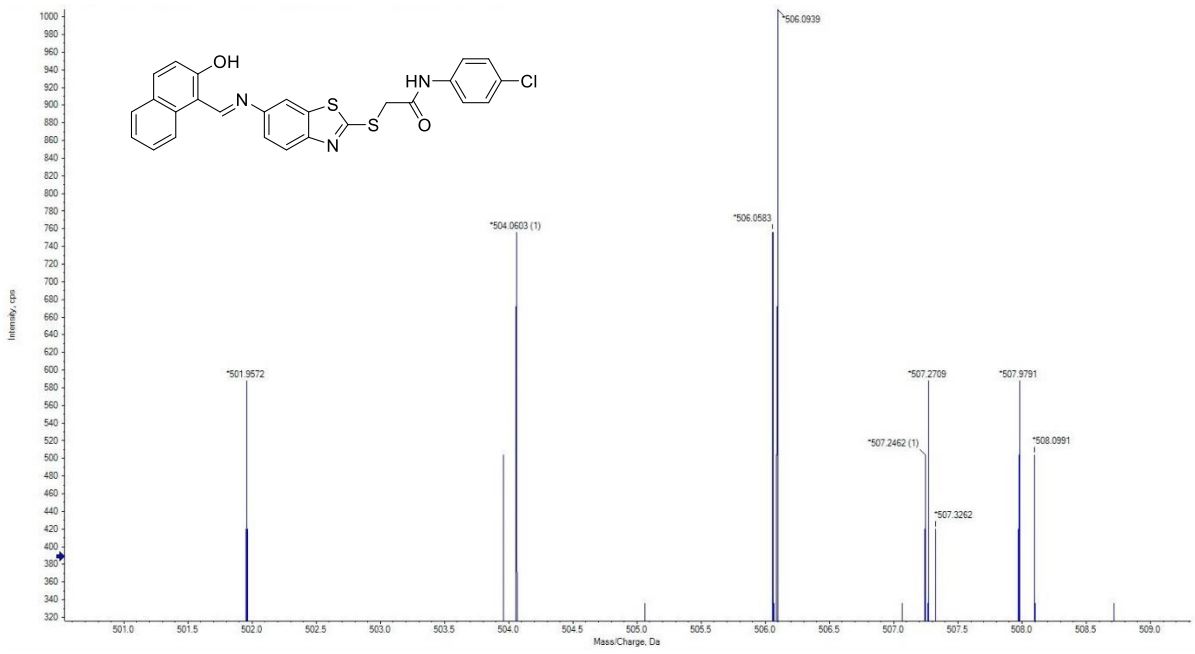


Figure 7. HRMS spectrum of compound **ZBTI03**

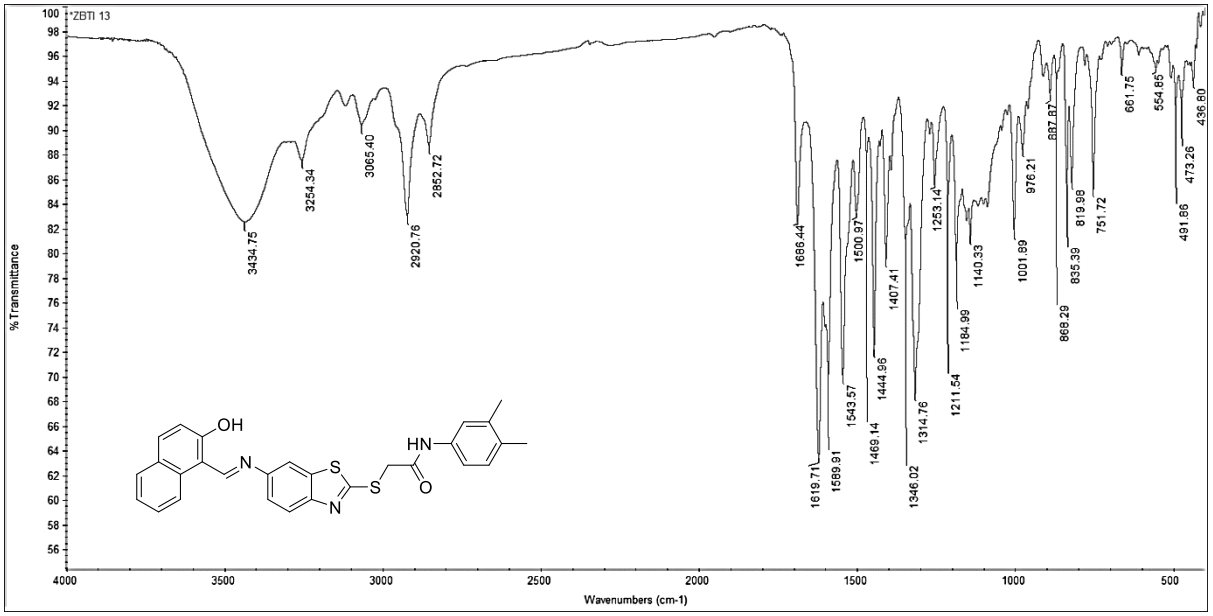


Figure 8. FTIR spectrum of compound **ZBTI13**

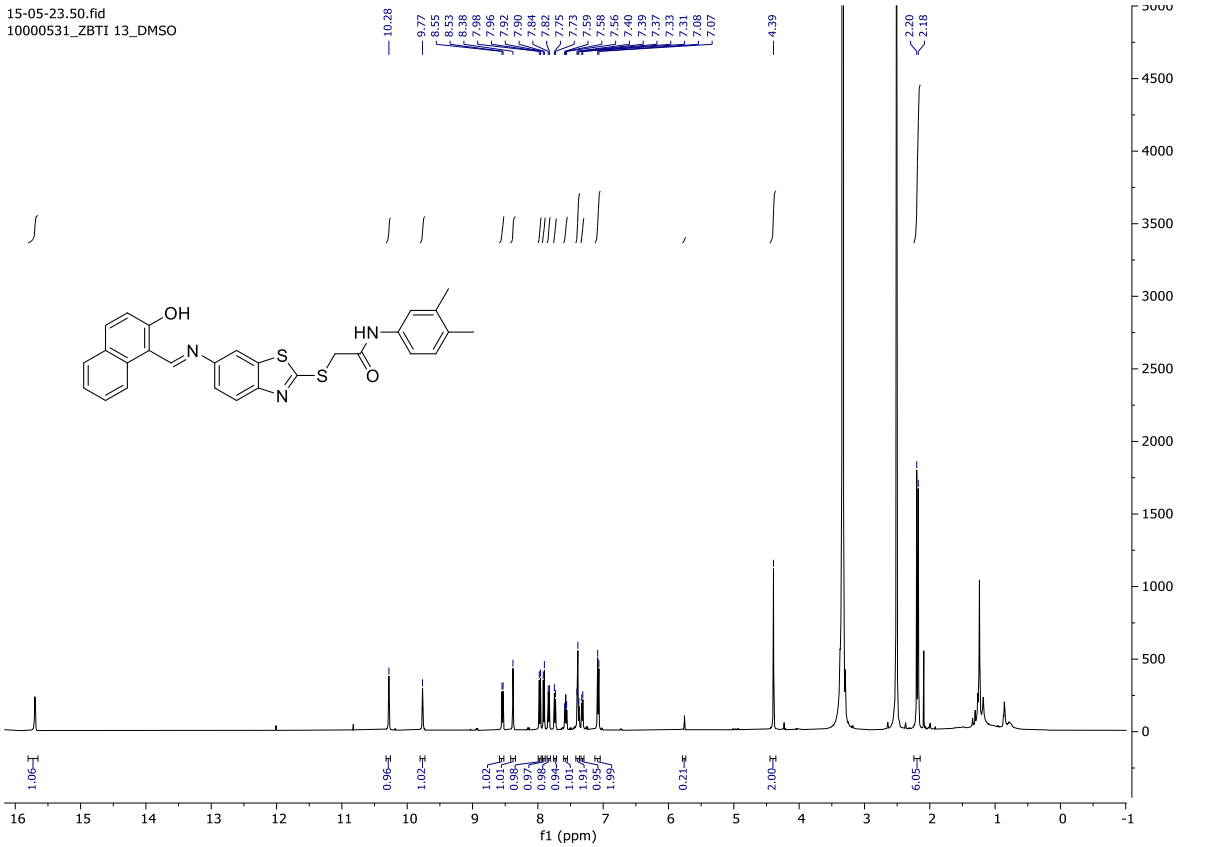


Figure A9. ^{1}H NMR spectrum of compound **ZBTI13**

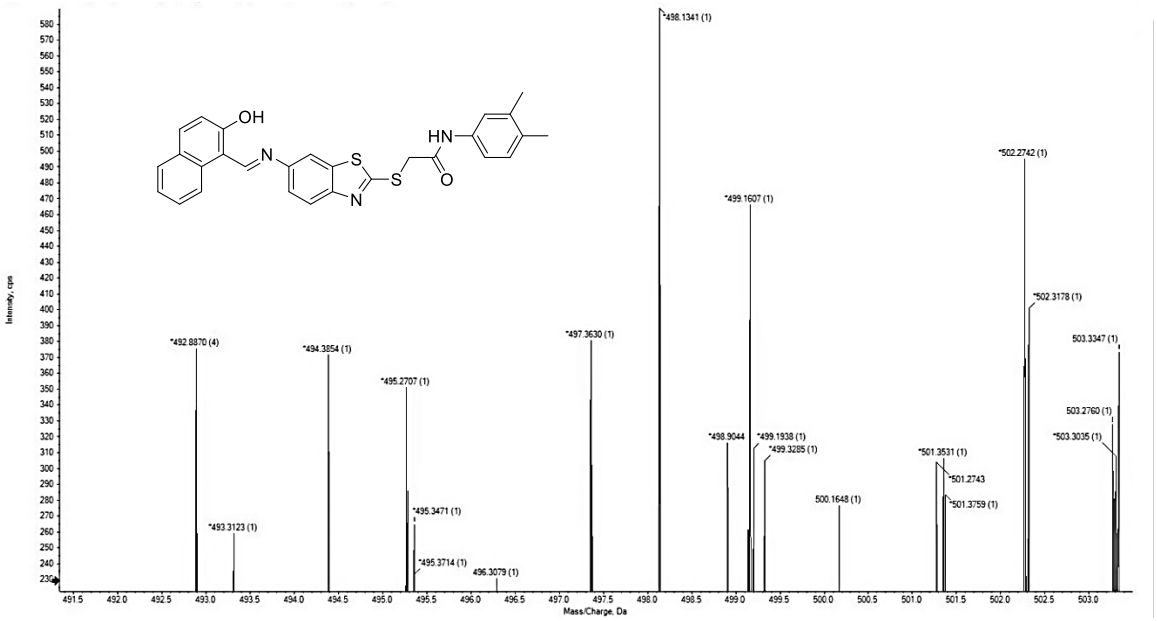


Figure A10. HRMS spectrum of compound **ZBTI13**

B2. Sesamol-derived O-acetamides (SMA series)

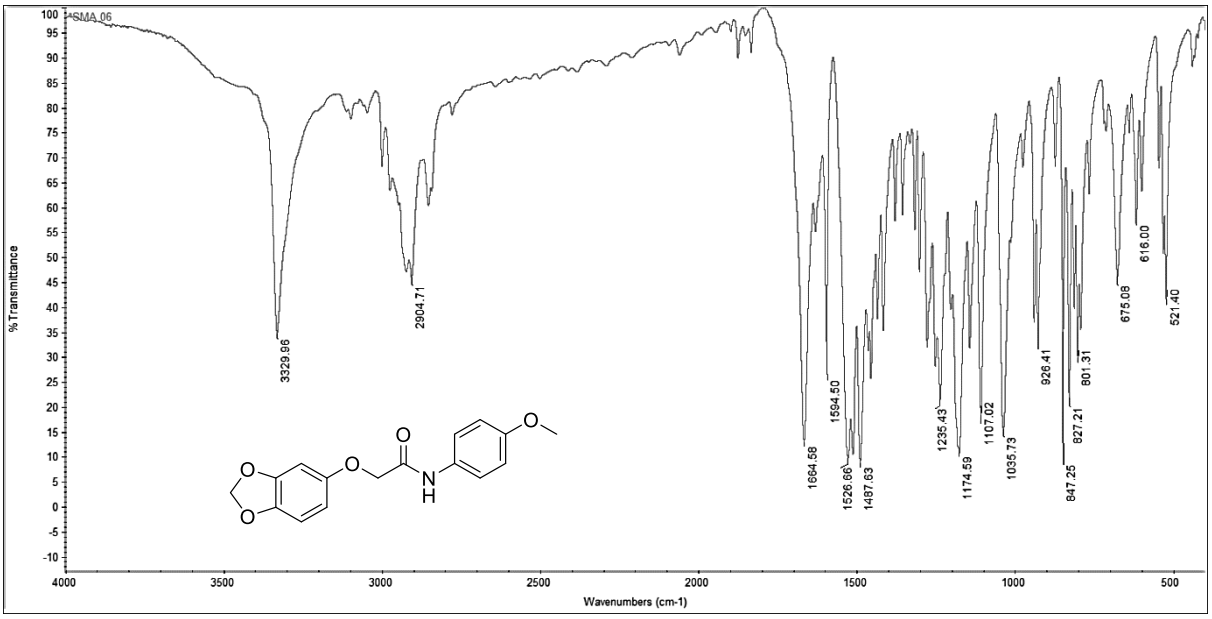


Figure A11. FTIR spectrum of compound **SMA06**

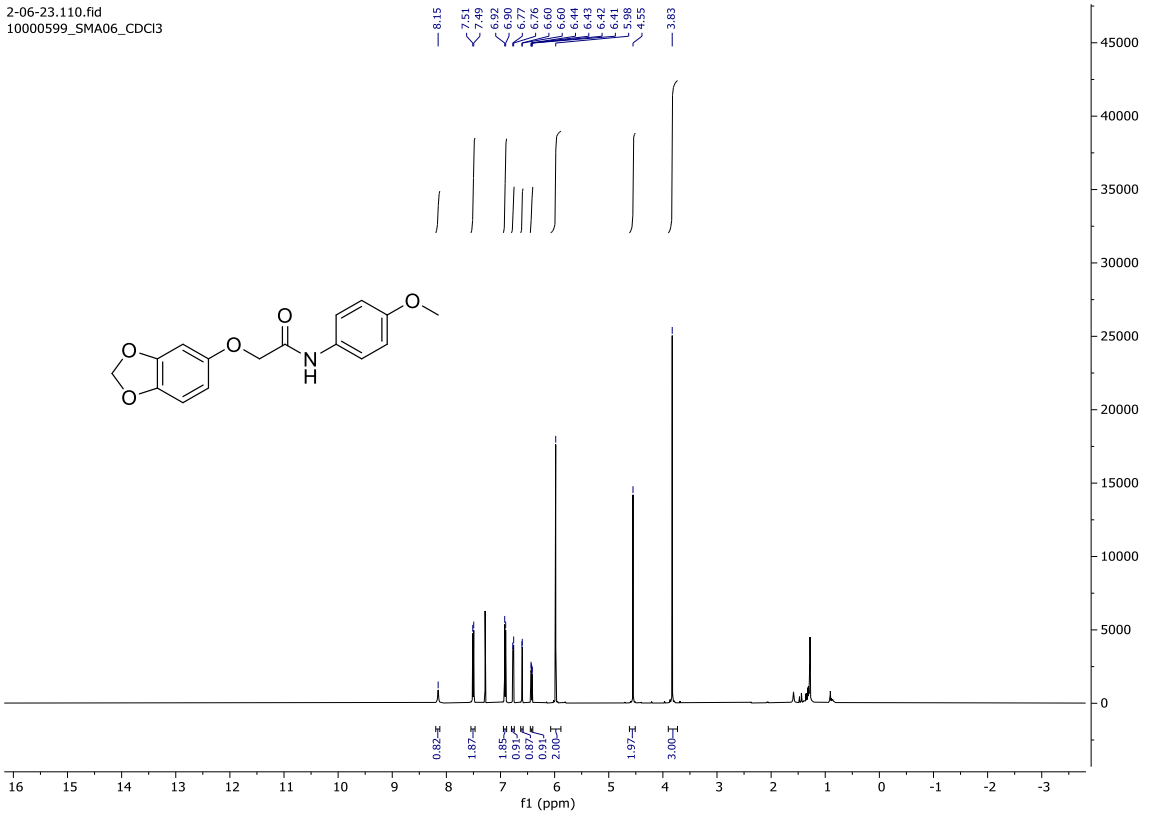


Figure A12. ^{1}H NMR spectrum of compound **SMA06**

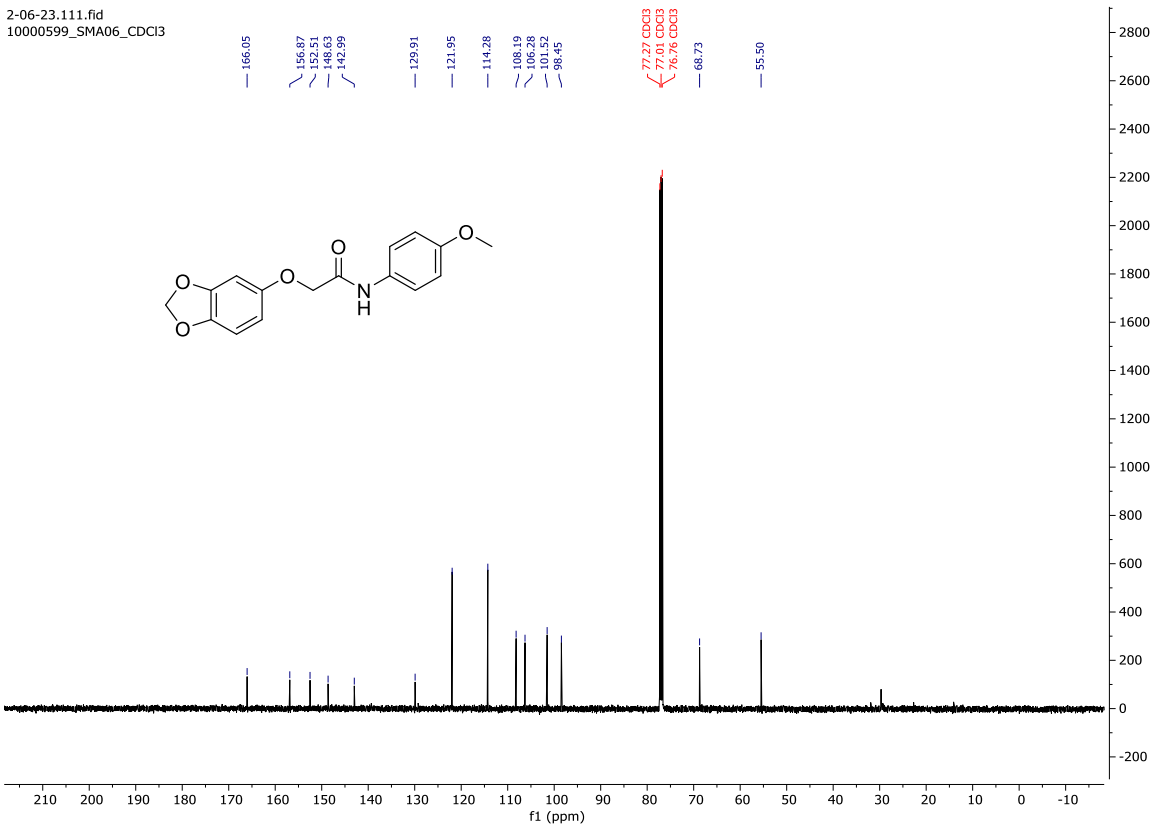


Figure A13. ^{13}C NMR spectrum of compound **SMA06**

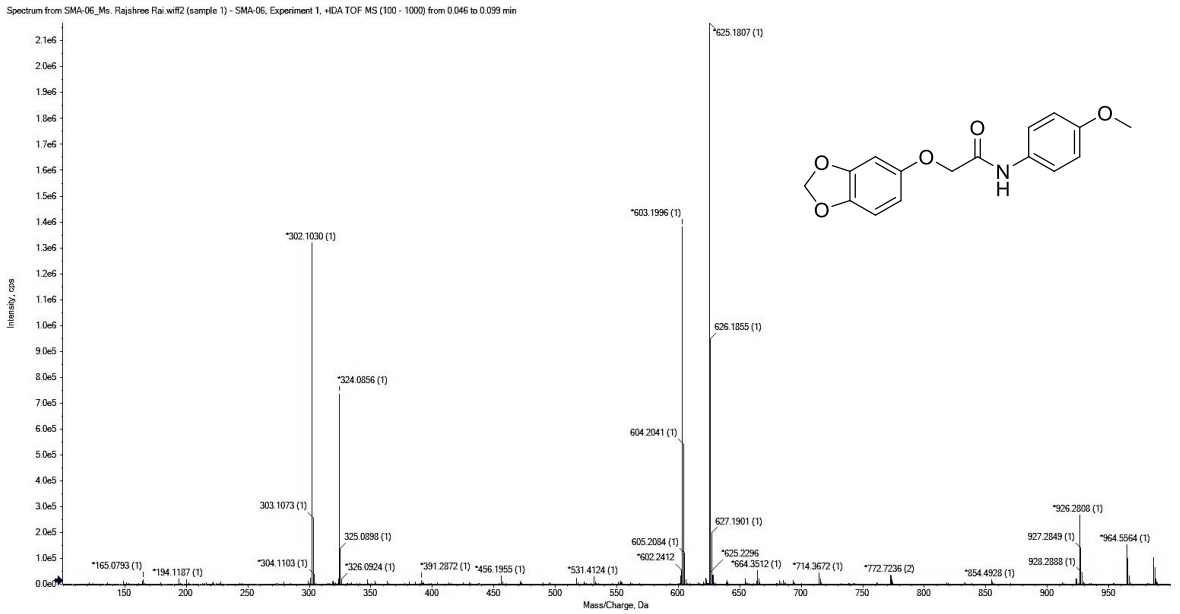


Figure A14. HRMS spectrum of compound **SMA06**

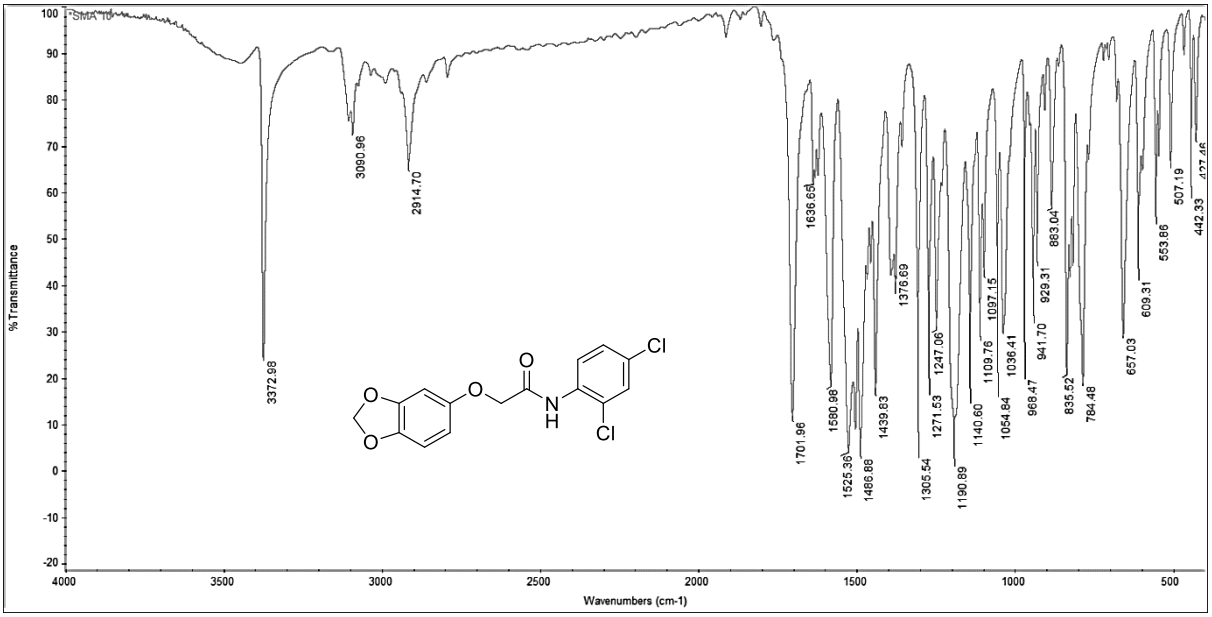


Figure A15. FTIR spectrum of compound **SMA09**

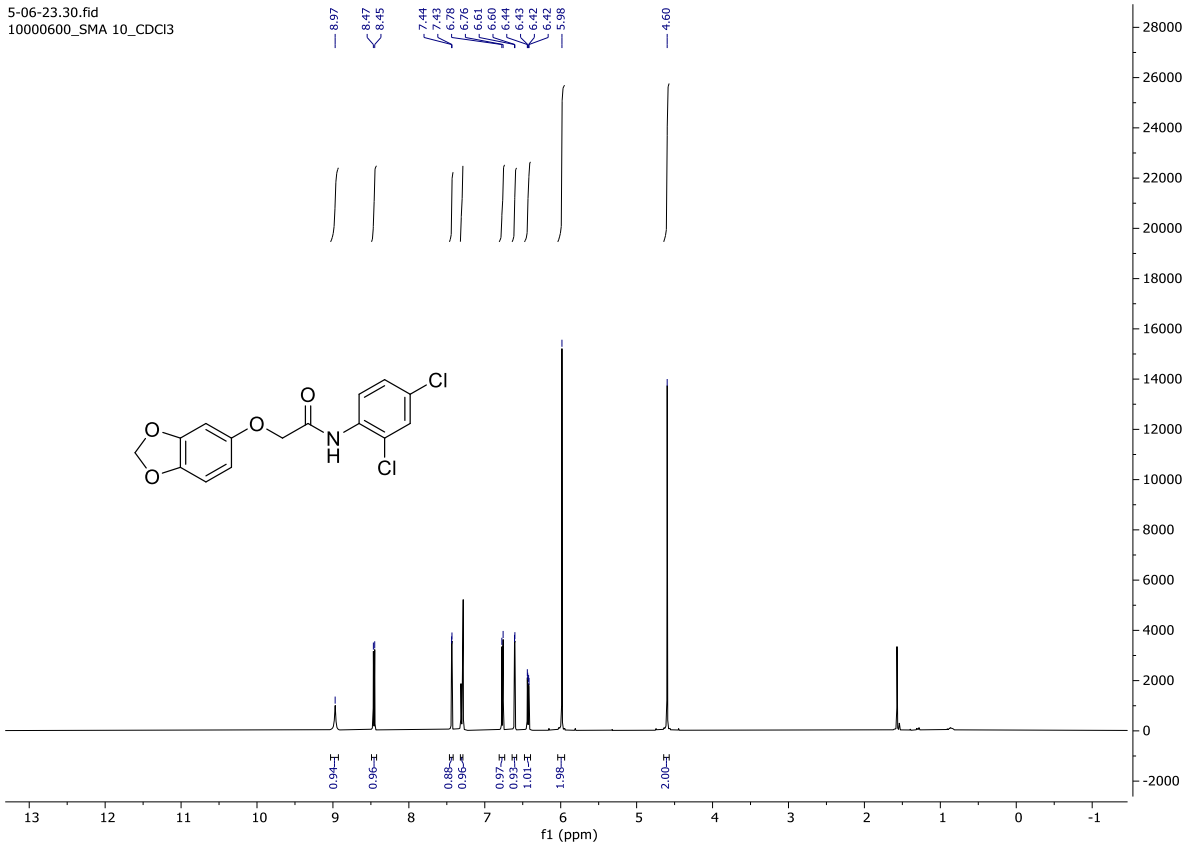


Figure A16. ^{1}H NMR spectrum of compound **SMA09**

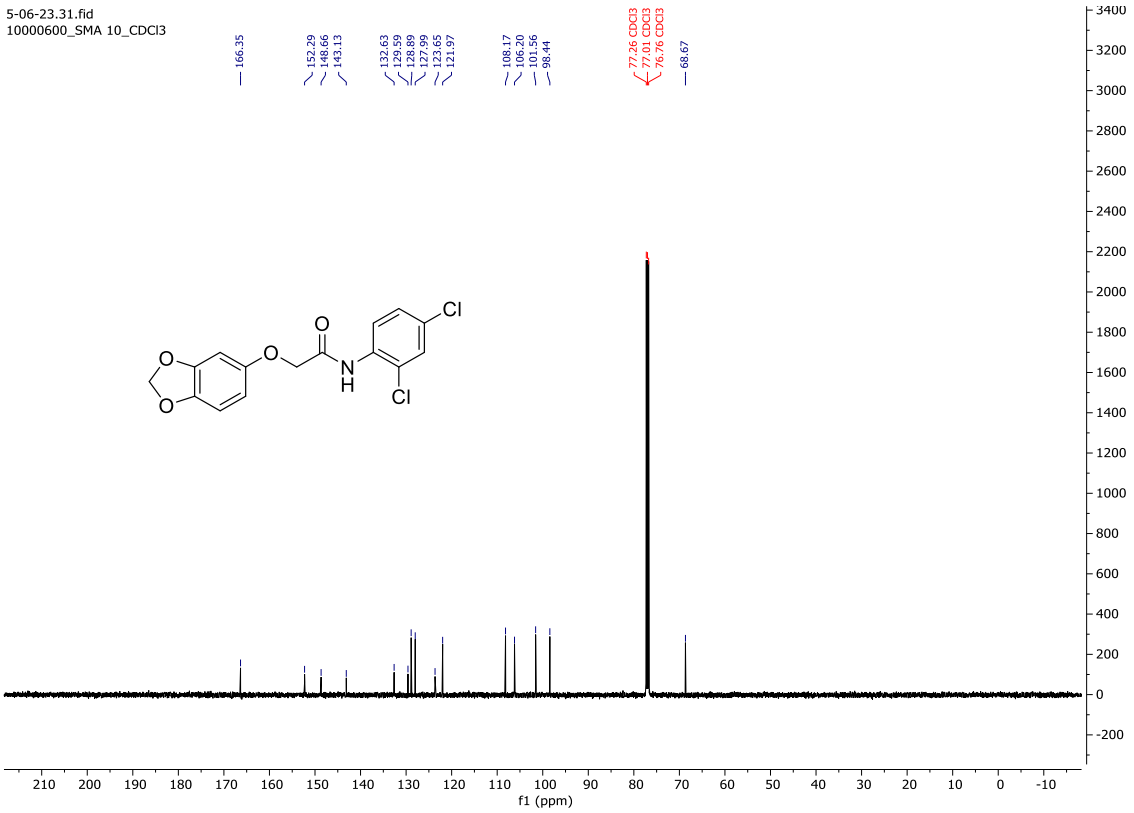


Figure A17. ^{13}C NMR spectrum of compound **SMA09**

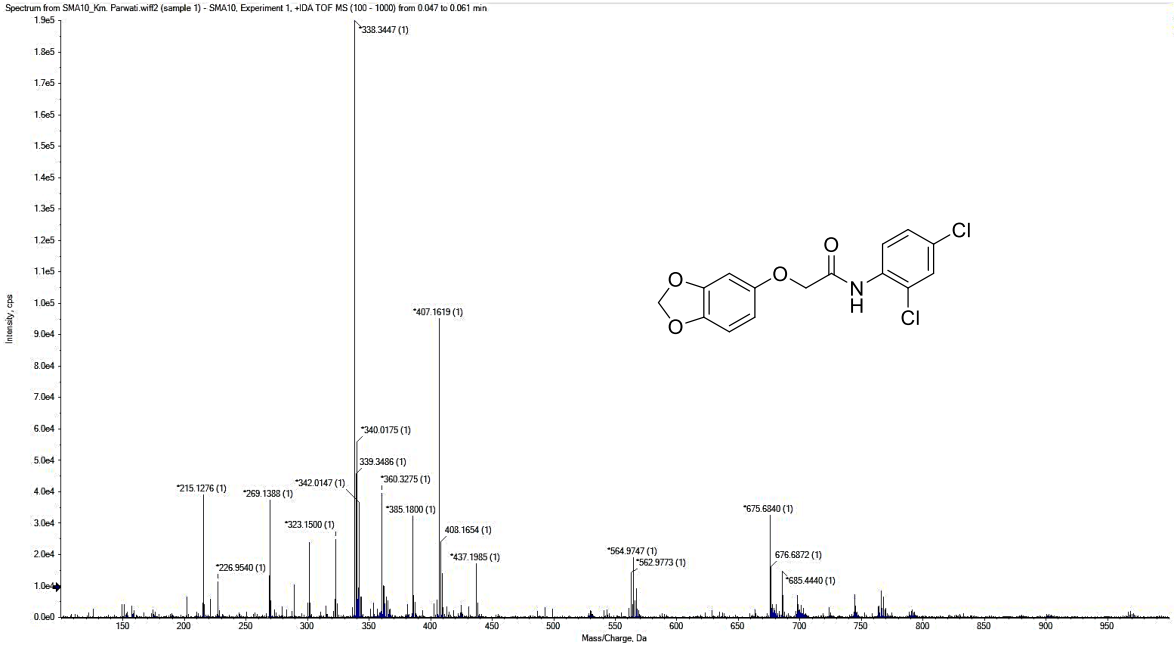


Figure A18. HRMS spectrum of compound **SMA09**

B3. Sesamol-derived O-alkyl carbohydrazones (SMH series)

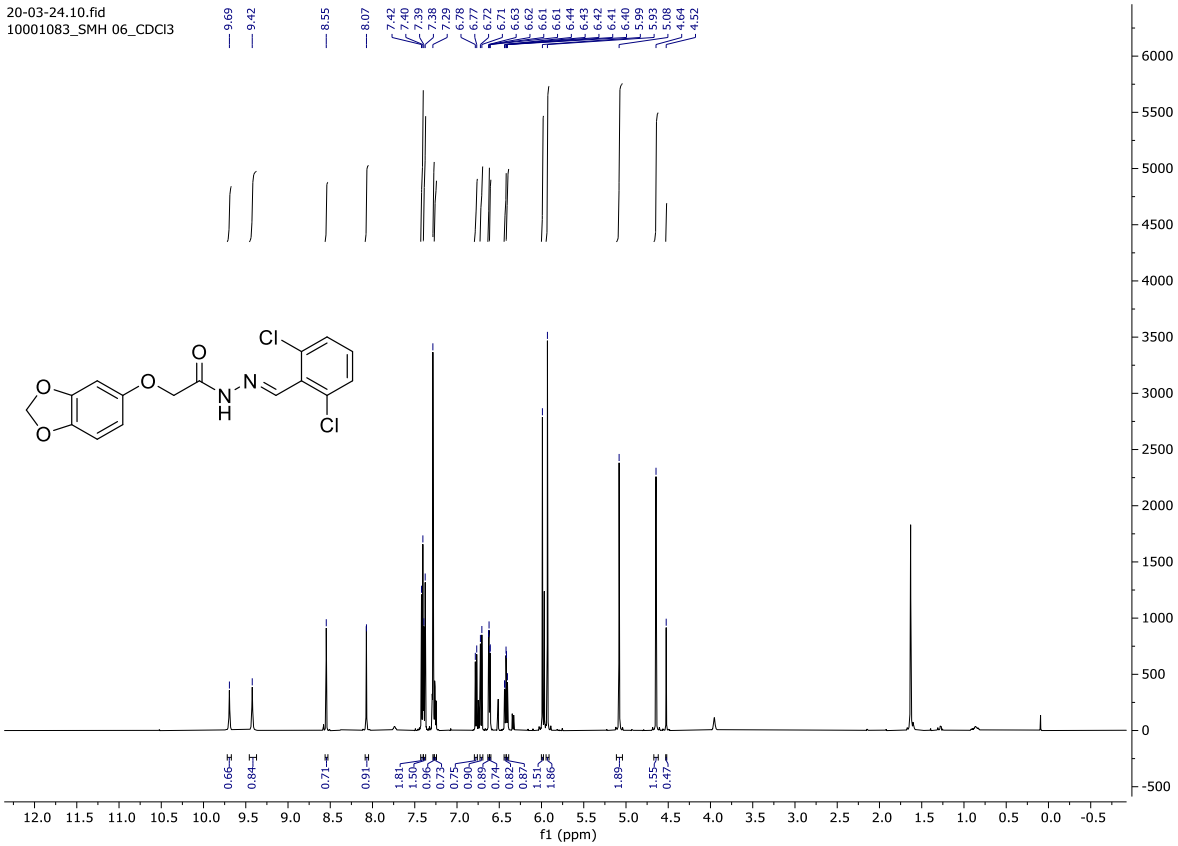


Figure A19. ^{1}H NMR spectrum of compound **SMH06**

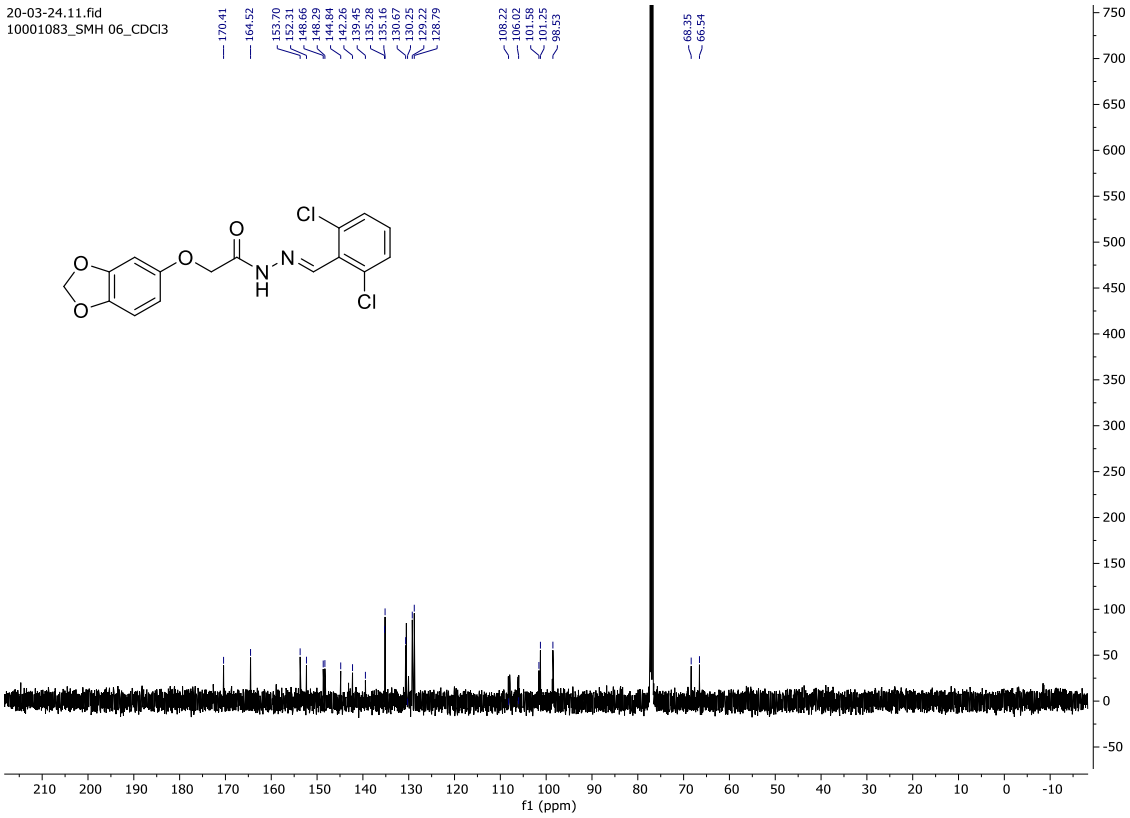


Figure A20. ^{13}C NMR spectrum of compound **SMH06**

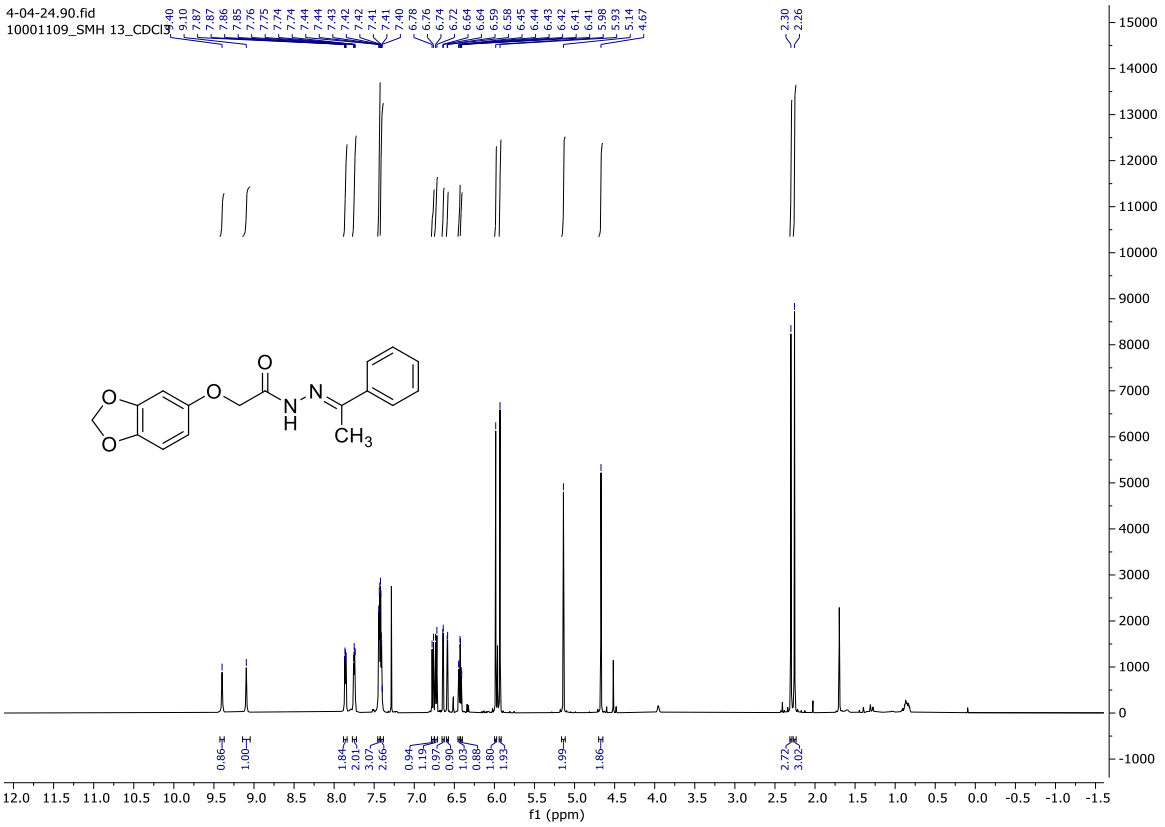


Figure A21. ^{1}H NMR spectrum of compound **SMH13**

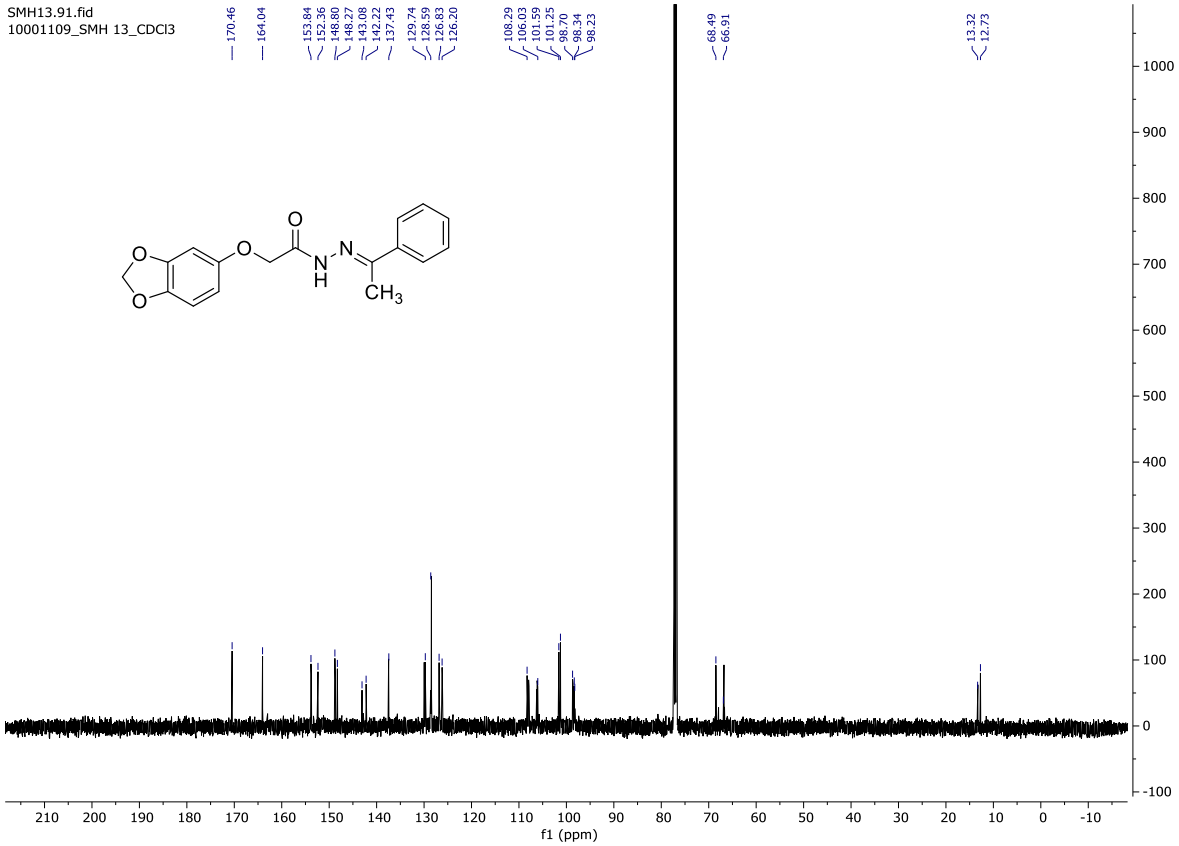


Figure A22. ^{13}C NMR spectrum of compound **SMH13**

B4. Eugenol/Isoeugenol-derived Carbohydrazones (SEH/SIEH series)

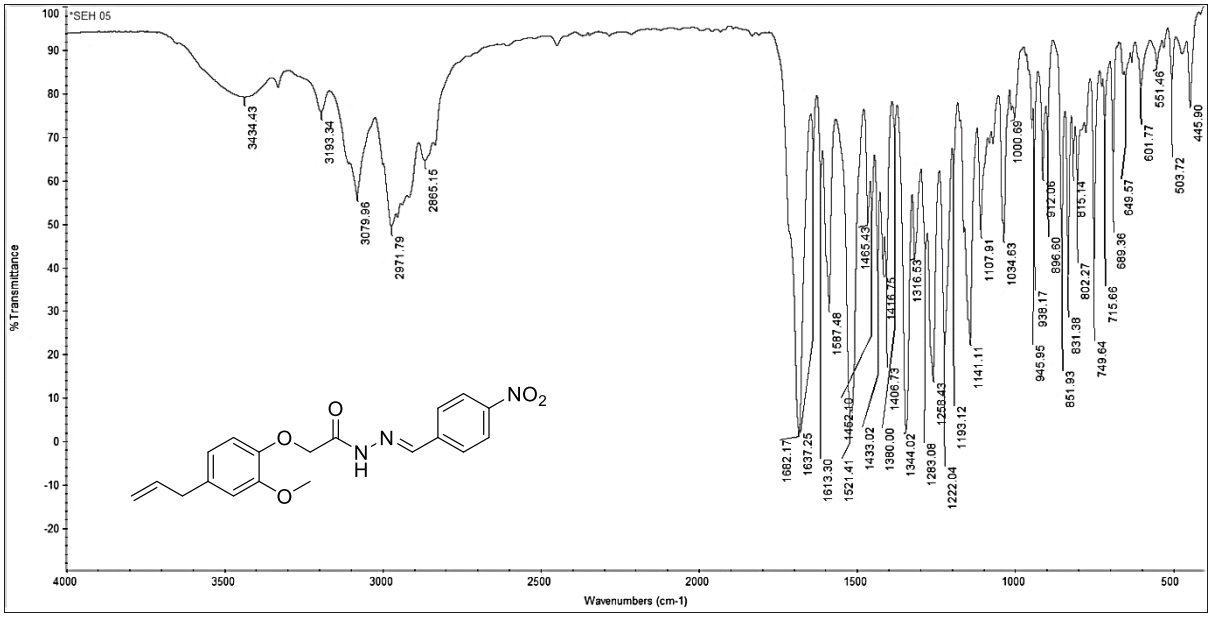


Figure A23. FTIR spectrum of compound **SEH05**

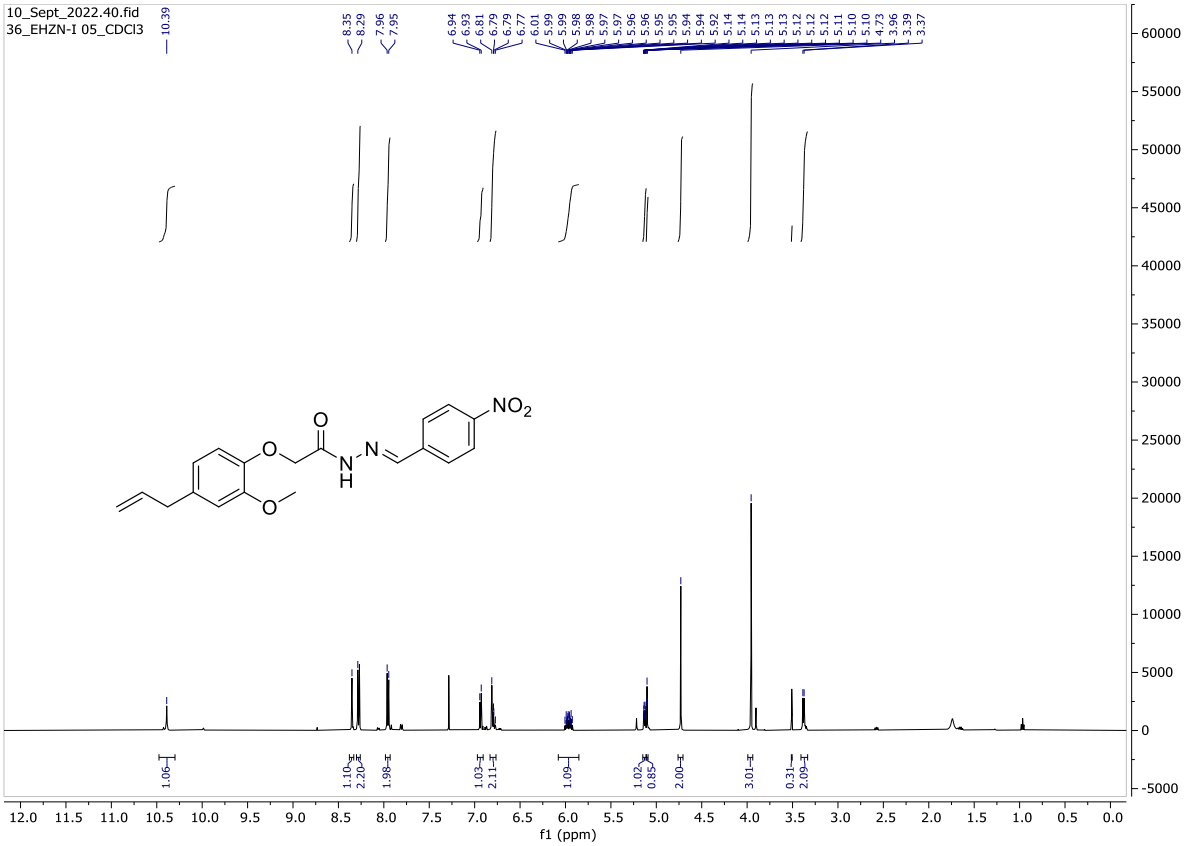


Figure A24. ^{1}H NMR spectrum of compound **SEH05**

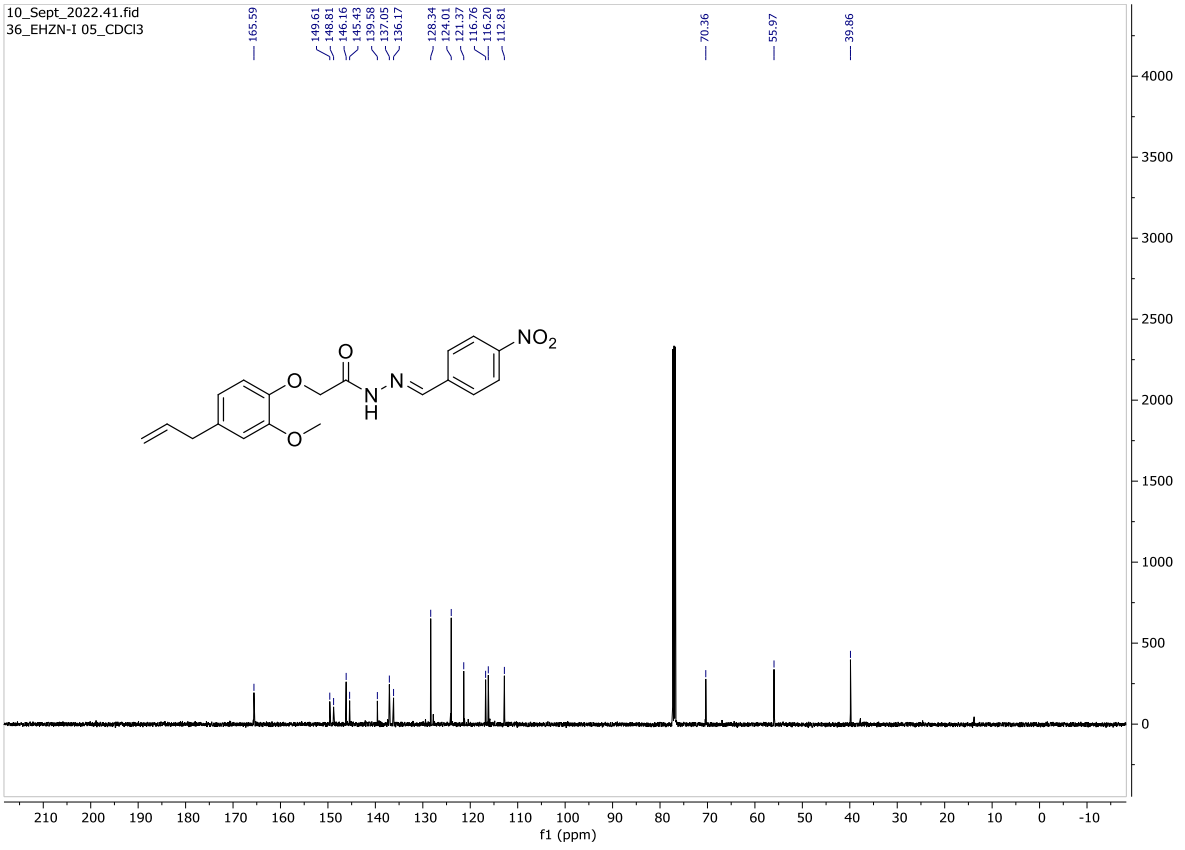


Figure A25. ^{13}C NMR spectrum of compound **SEH05**

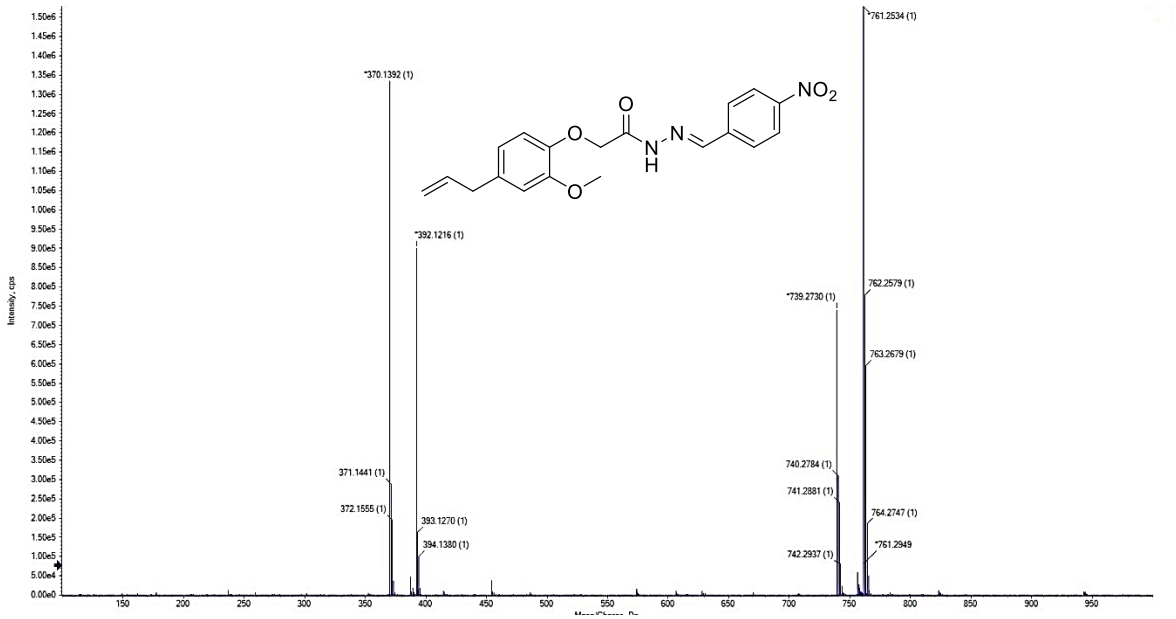


Figure A26. HRMS spectrum of compound **SEH05**

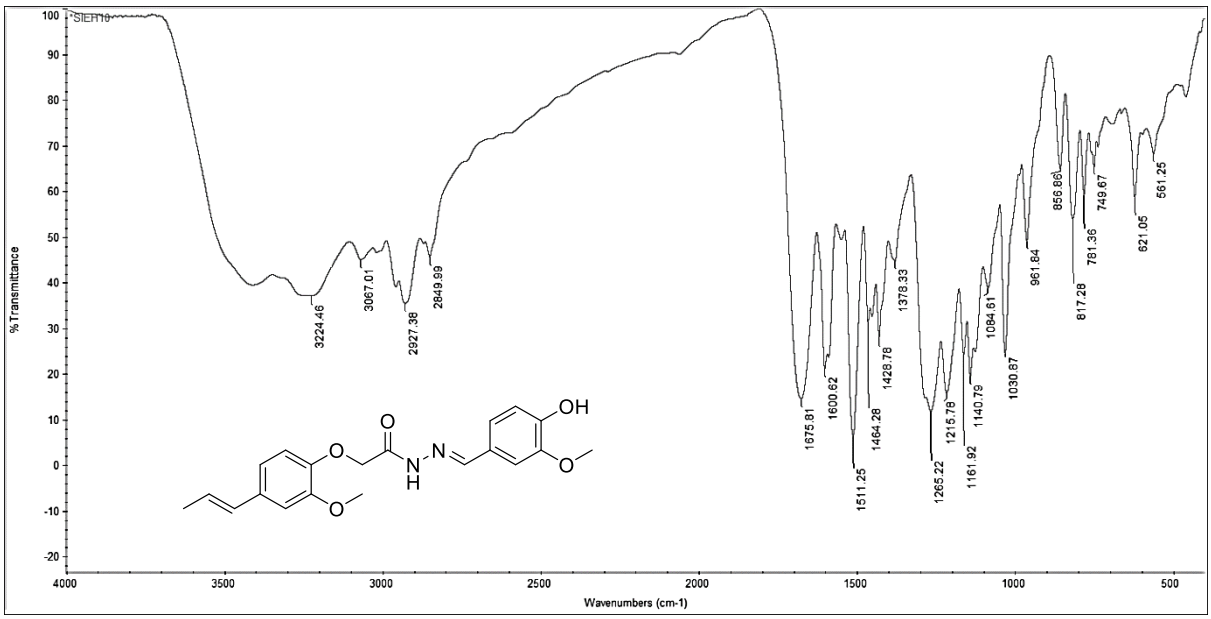


Figure A27. FTIR spectrum of compound **SIEH10**

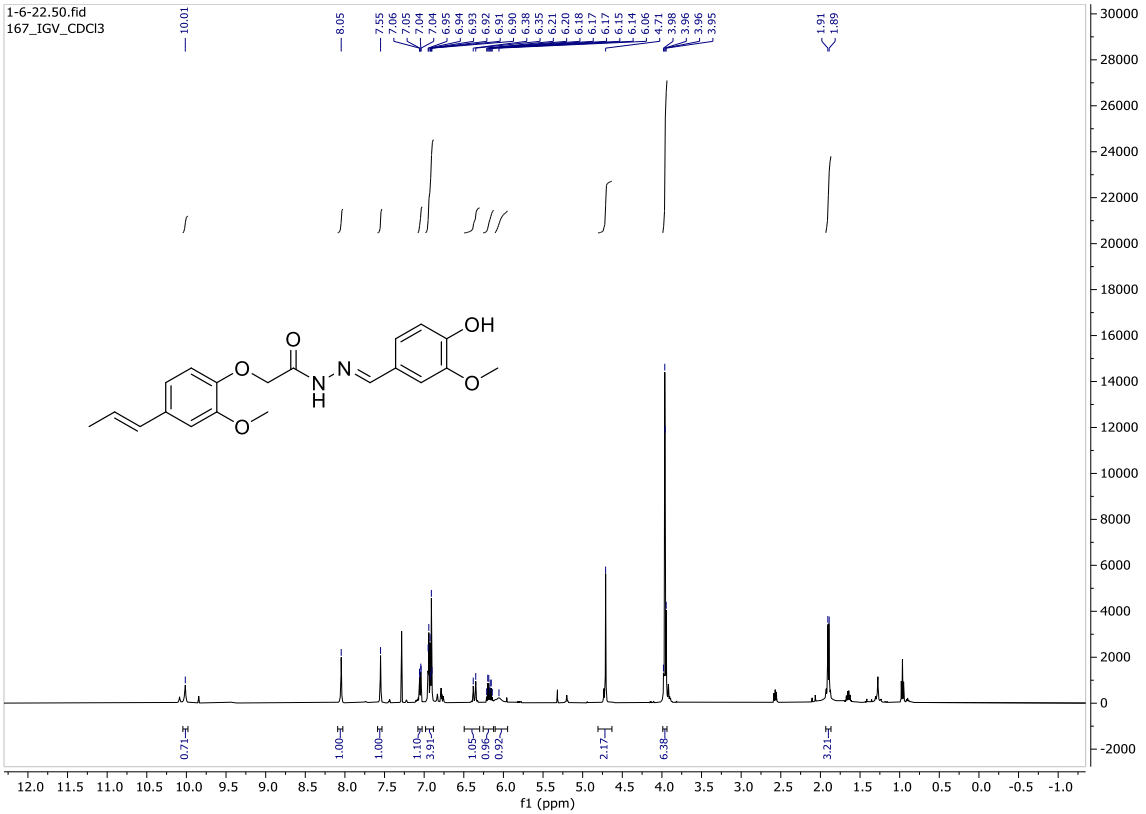


Figure A28. ^{1}H NMR spectrum of compound **SIEH10**

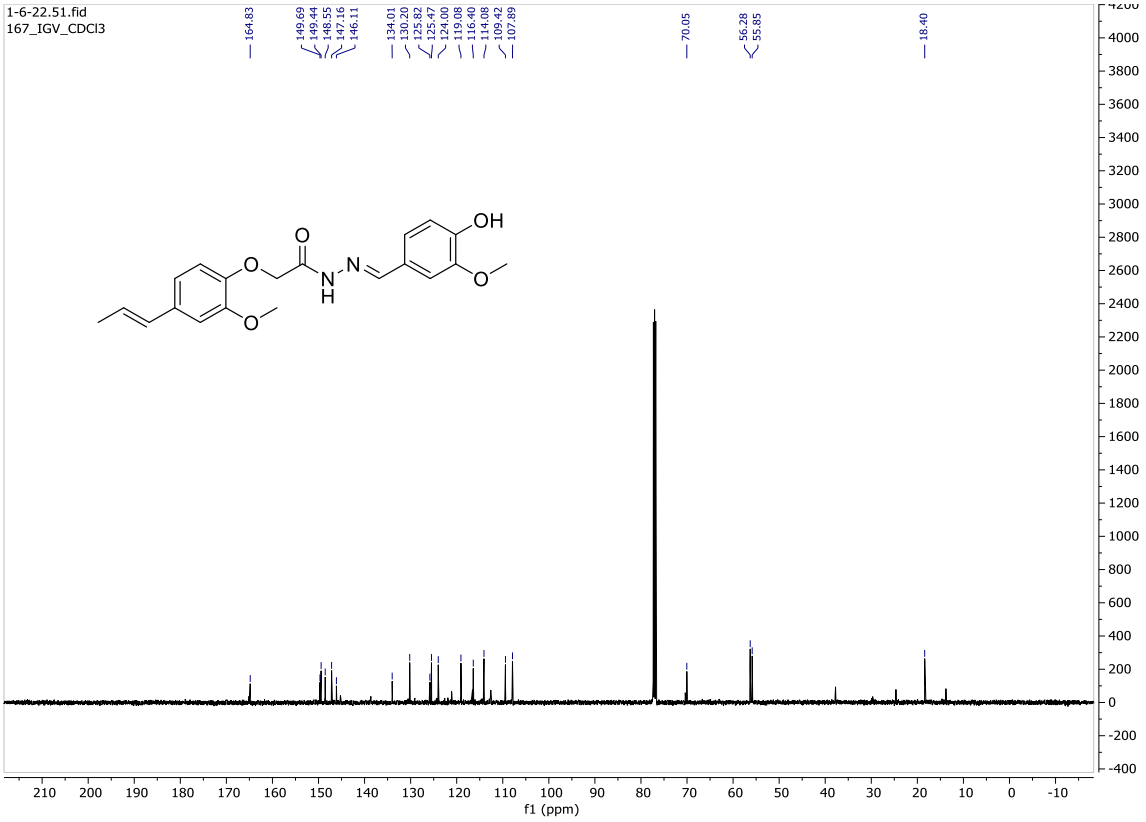


Figure A29. ^{13}C NMR spectrum of compound **SIEH10**

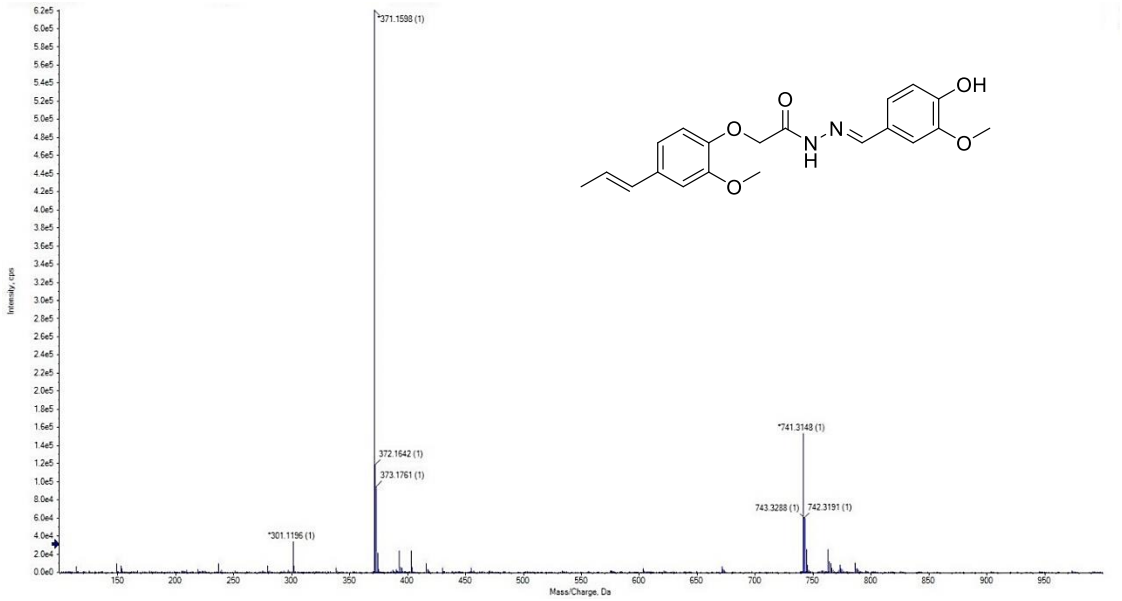


Figure A30. HRMS spectrum of compound **SIEH10**

C. UV-based logP determination

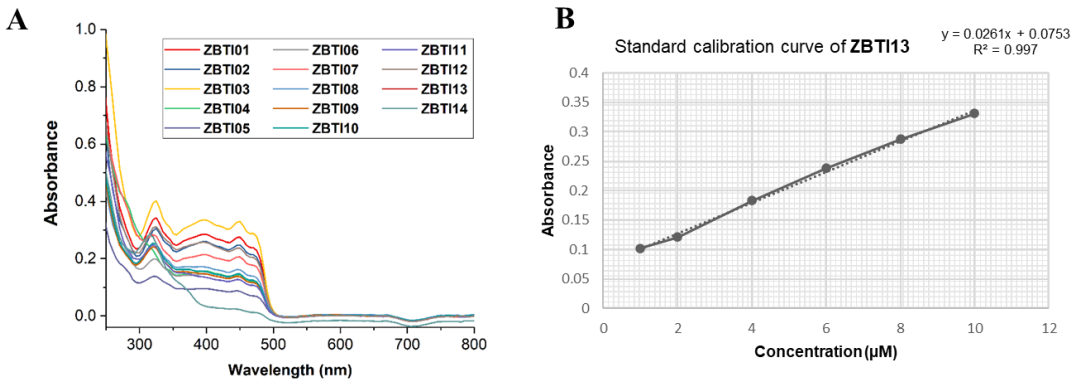
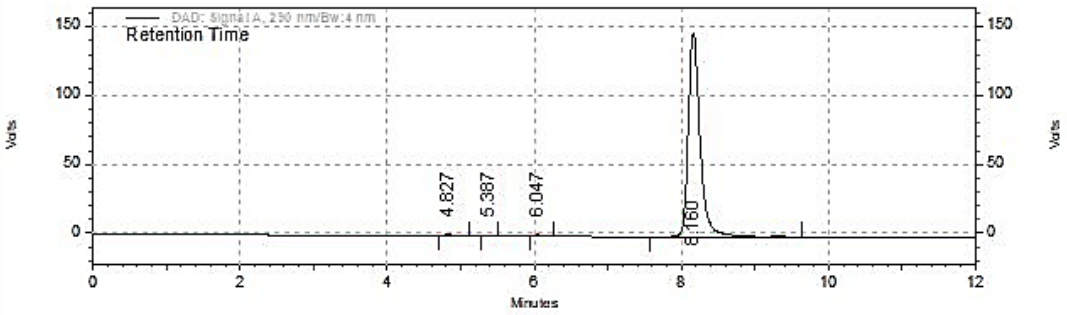


Figure A31. A) λ_{max} spectra of compounds **ZBTI01-ZBTI14**; B) Standard calibration curve (at λmax = 315 nm) of compound **ZBTI13**

D. RP-HPLC method development and validation of purity

Area % Report

Data File: C:\Users\IIT-BHU\Desktop\RM_HPLC_Data_ALL\ZBTI13R_50.rslt\ZBTI13R_50.dat
Method: C:\Enterprise\Projects\Method\ZBTI_SK_3.met
Acquired: 28-09-24 11:34:53 (GMT+05:30)
Printed: 28-09-24 11:50:01 (GMT+05:30)



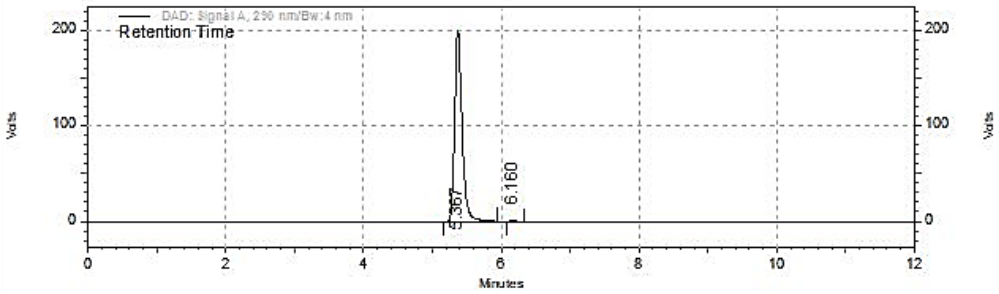
DAD: Signal A,
290 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
4.827	17393	0.50	1995	0.63
5.387	8608	0.25	1287	0.41
6.047	14324	0.41	1895	0.60
8.160	3469043	98.85	310708	98.36
Totals	3509368	100.00	315885	100.00

Figure A32. HPLC chromatogram of compound **ZBTI13** at 50 μM concentration

Area % Report

Data File: C:\Users\IIT-BHU\Desktop\RM_HPLC_Data_ALL\SMA09_50_A.rslt\SMA09_50_A.dat
Method: C:\Enterprise\Projects\Method\ZBTI_SK_3.met
Acquired: 26-09-24 17:19:26 (GMT +05:30)
Printed: 26-09-24 17:33:39 (GMT +05:30)



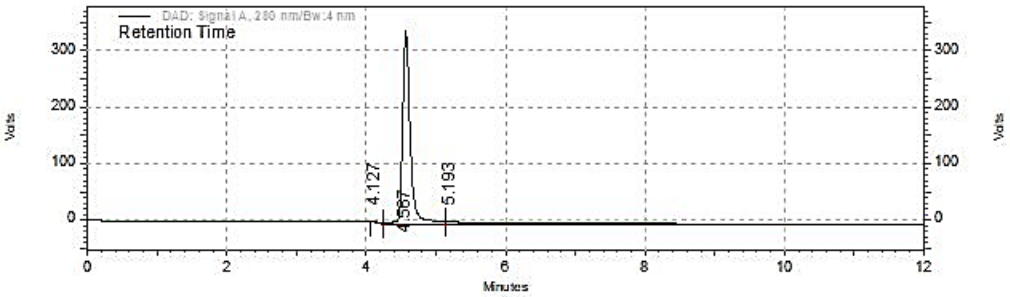
DAD: Signal A,
290 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
5.367	3193649	99.68	420804	99.66
6.160	10173	0.32	1434	0.34
Totals	3203822	100.00	422238	100.00

Figure A33. HPLC chromatogram of compound **SMA09** at 50 μM concentration

Area % Report

Data File: C:\Users\IIT-BHU\Desktop\RM_HPLC_Data_ALL\SMH06_50_1.rslt\SMH06_50_1.dat
Method: C:\Enterprise\Projects\Method\ZBTI_SK_3.met
Acquired: 25-09-24 14:14:51 (GMT +05:30)
Printed: 25-09-24 14:27:05 (GMT +05:30)



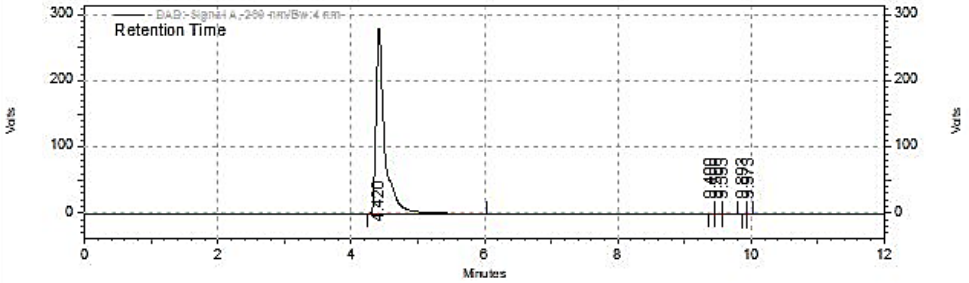
DAD: Signal A,
280 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
4.127	21719	0.32	2712	0.37
4.567	5456273	80.64	718293	98.39
5.193	1288151	19.04	9018	1.24
Totals	6766143	100.00	730023	100.00

Figure A34. HPLC chromatogram of compound **SMH06** at 50 μM concentration

Area % Report

Data File: C:\Users\IIT-BHU\Desktop\RM_HPLC_Data_ALL\SIEH11_50.rslt\SIEH11_50.dat
Method: C:\Enterprise\Projects\Method\ZBTI_SK_3.met
Acquired: 28-09-24 13:45:49 (GMT+05:30)
Printed: 28-09-24 13:59:25 (GMT+05:30)



DAD: Signal A,
290 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
4.420	5379712	99.99	587502	99.98
9.400	80	0.00	31	0.01
9.500	92	0.00	27	0.00
9.593	195	0.00	31	0.01
9.893	43	0.00	16	0.00
9.973	64	0.00	23	0.00
Totals	5380186	100.00	587630	100.00

Figure A35. HPLC chromatogram of compound **SIEH11** at 50 μM concentration

LIST OF PUBLICATIONS

1. **Kumar, S.**, and Ayyannan, S. R. (**2022**). Identification of new small molecule monoamine oxidase-B inhibitors through pharmacophore-based virtual screening, molecular docking and molecular dynamics simulation studies. *J. Biomol. Struct. Dyn.*, 6789-6810. doi: 10.1080/07391102.2022.2112082.
2. **Kumar, S.**, Mitra, R., and Ayyannan, S. R. (**2024**). Design, synthesis and evaluation of sesamol-derived acetamides as dual inhibitors of monoamine oxidases and cholinesterases. *Med. Chem. Res. 33, 1974–1991* doi: 10.1007/s00044-024-03304-1.
3. **Kumar, S.**, Mitra, R., and Ayyannan, S. R. (**2024**). Design, Synthesis and Evaluation of Benzothiazole-derived Phenyl Thioacetamides as Dual Inhibitors of Monoamine Oxidases and Cholinesterases. *Mol. Divers.* (accepted, in press).
4. **Kumar, S.**; Jagannadhula, H.; Ayyannan, S. R. (**2022**). Design, Synthesis and Evaluation of Dual MAO AChE Inhibitory Capabilities of Some Novel Substituted Aryl Hydrazones. J Pharm Chem 8 (Supplement). 186. Retrieved from https://pubs.vensel.org/index.php/jphchem/article/view/272.
5. **Kumar, S.**, Mitra, R., and Ayyannan, S. R. Exploration of a library of Eugenol and Isoeugenol-derived Carbohydrazones as Dual Inhibitors of Monoamine Oxidases and Cholinesterases. (Under communication).
6. **Kumar, S.**, Mitra, R., and Ayyannan, S. R. Sesamol-derived Carbohydrazones as dual Monoamine Oxidase and Acetylcholinesterase Inhibitors: Design, Synthesis and Neuroprotective Evaluation (Under communication).