Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Data

Tail-approach based design, synthesis, and cytotoxic evaluation of novel disubstituted and trisubstituted 1,3-thiazole benzenesulfonamide derivatives with suggested carbonic anhydrase IX inhibition mechanism

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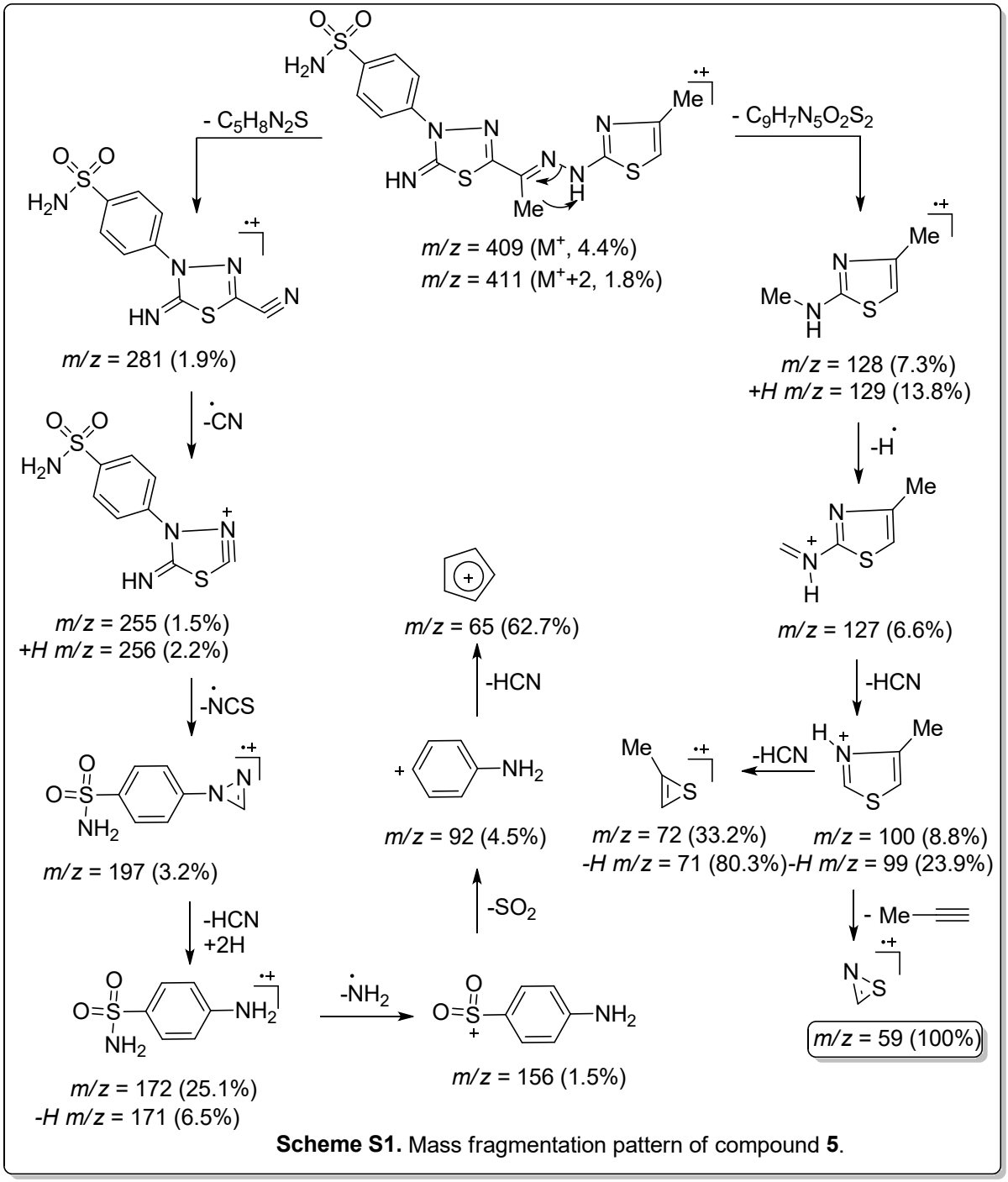
1. Materials and instrumentation

1) All melting points were determined on the Stuart SMP11 apparatus and were uncorrected.
2) The IR spectra were recorded in KBr discs on a Jasco FT/IR-460 plus spectrophotometer at the College of Science, King Khalid University.
3) The ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 at 850 MHZ on a BrukerAvanceAV-850 NMRUltrshield^{TM} spectrometer at King Abdulaziz University, Jeddah, Saudi Arabia.
4) Mass spectra were measured using the Shimadzu GC/MS-QP 1000 EX mass spectrometer at 70 eV at the Micro Analytical Center, Cairo University, Giza, Egypt.
5) Elemental analyses were conducted at the Micro Analytical Center, Cairo University, Giza, Egypt.
6) Biological activities were tested at the Holding Company for Biological Products and Vaccines, VACSERA, Giza, Egypt.

2. Computational Calculations

Gaussian 09 package software[1], was used to carry out all quantum chemical calculations using the method of DFT-B3LYP[2,3]combined with a standard 6-31G(d) basis set. The suggested geometries for the synthesized compounds were initially optimized using Pulay's gradient approach.[4] Frequency calculations were performed to verify that the optimized geometries are actual minimums with real wavenumbers.[5]



Scheme S1. Mass fragmentation pattern of compound **5**.

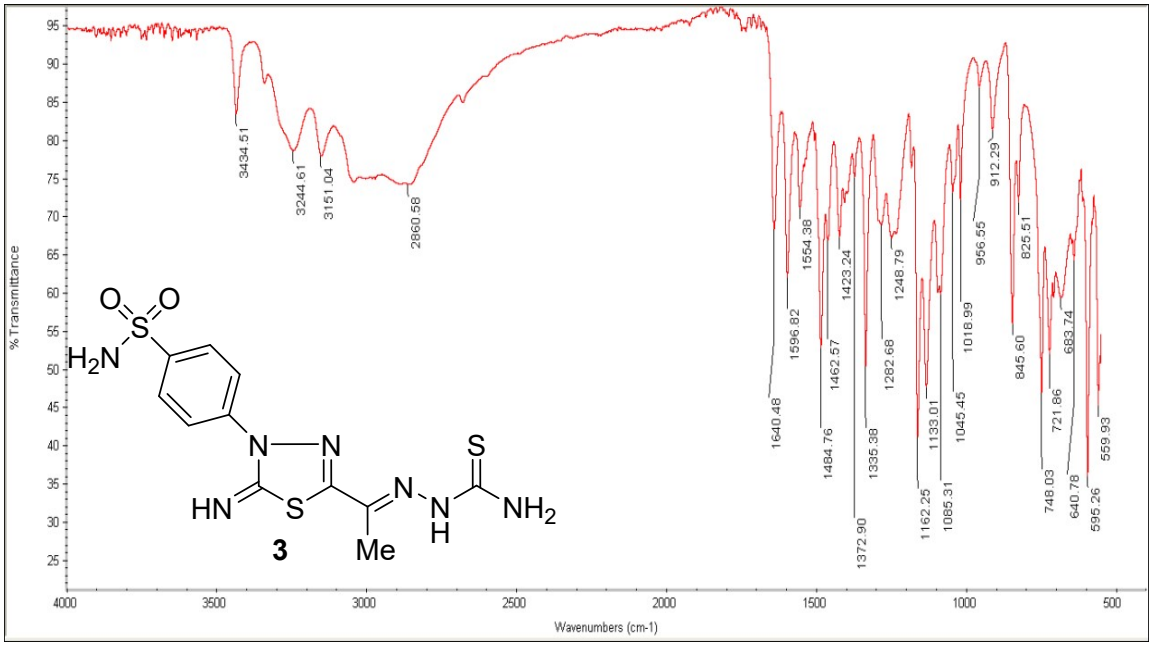


Figure S1. IR spectrum of compound **3.**

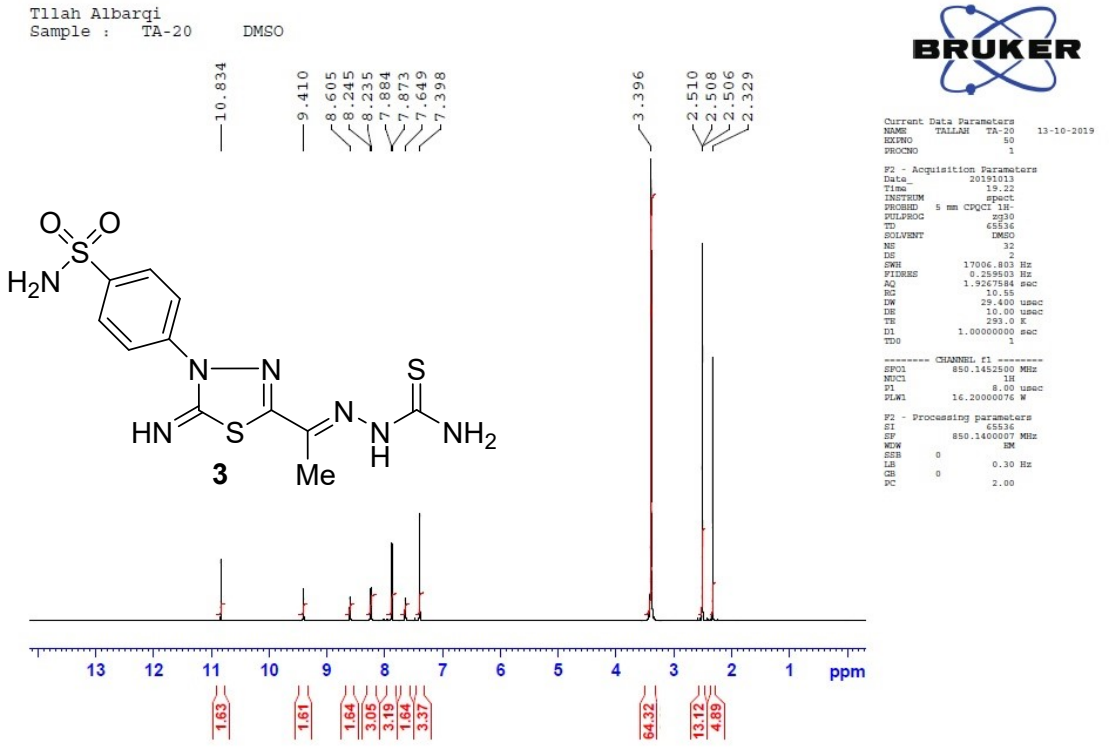


Figure S2. ^{1}H-NMR spectrum of compound **3**.

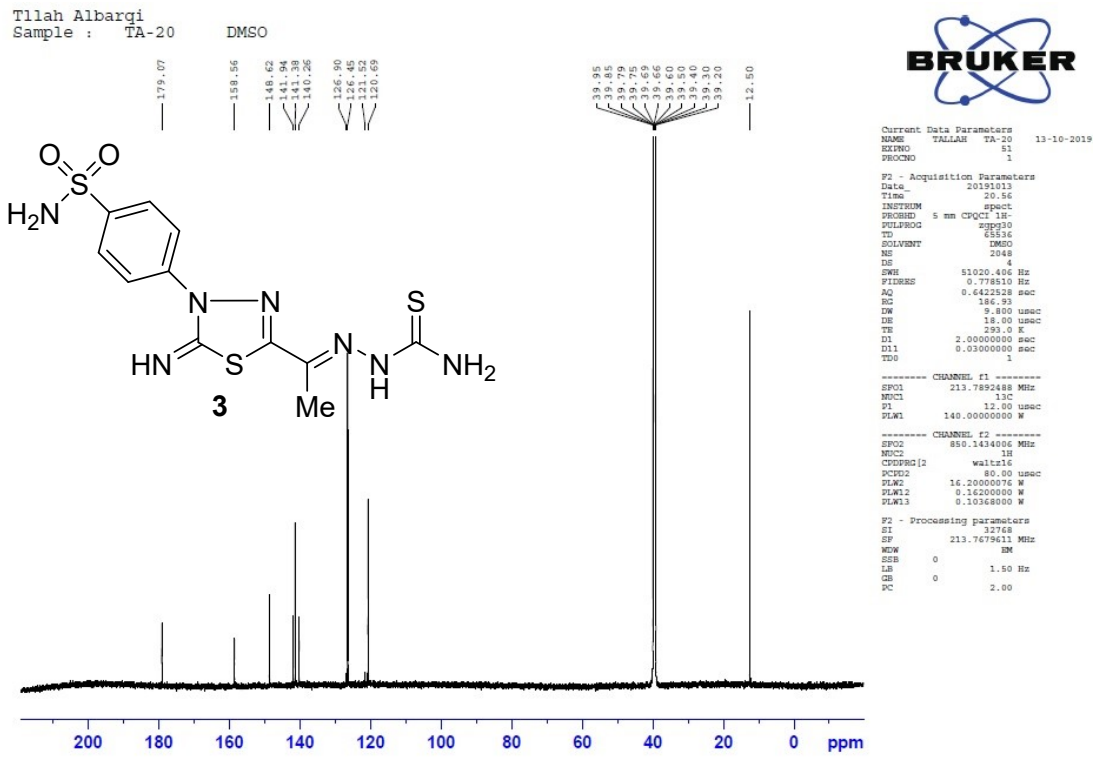


Figure S3. ^{13}C-NMR spectrum of compound **3**.

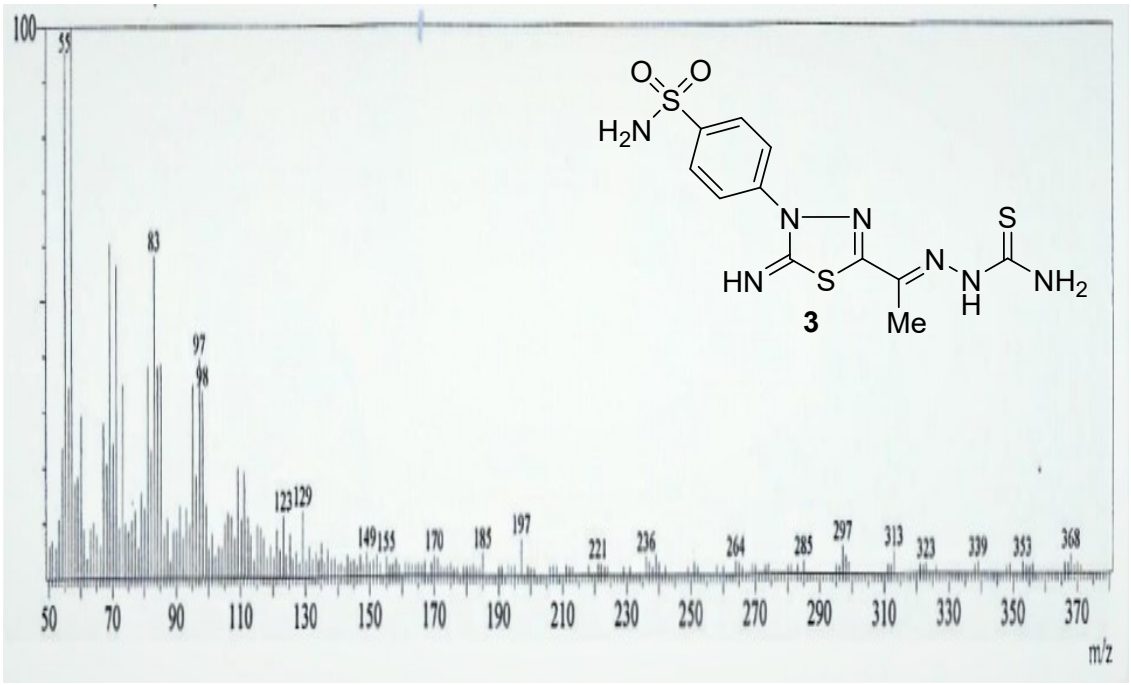


Figure S4. Mass spectrum of compound **3.**

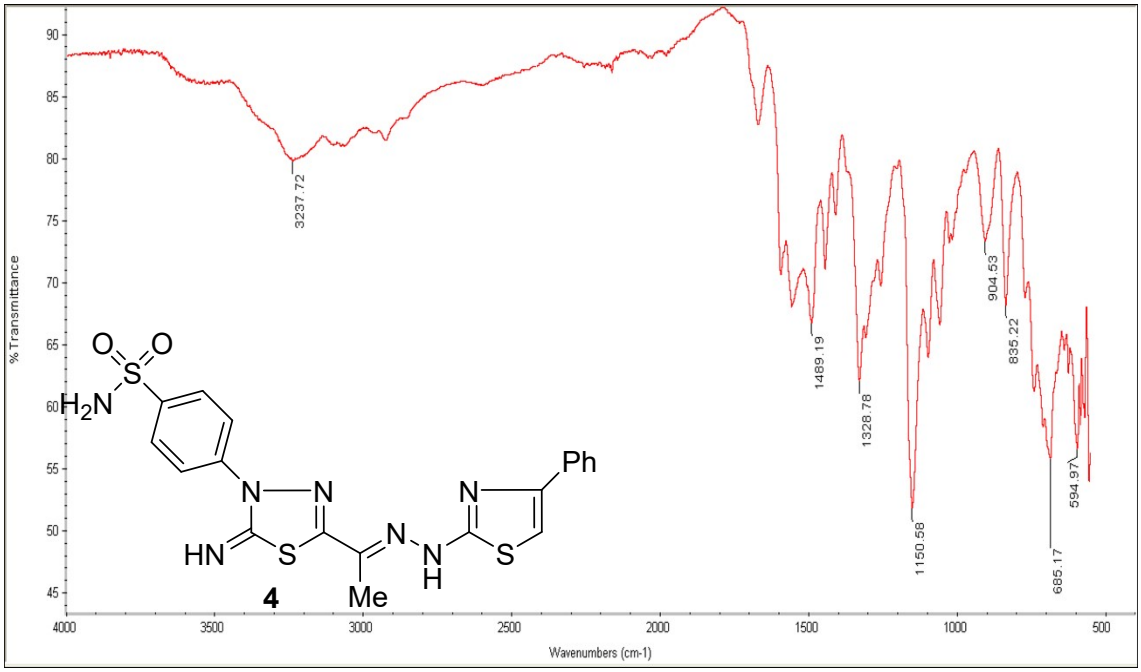


Figure S5. IR spectrum of compound **4.**

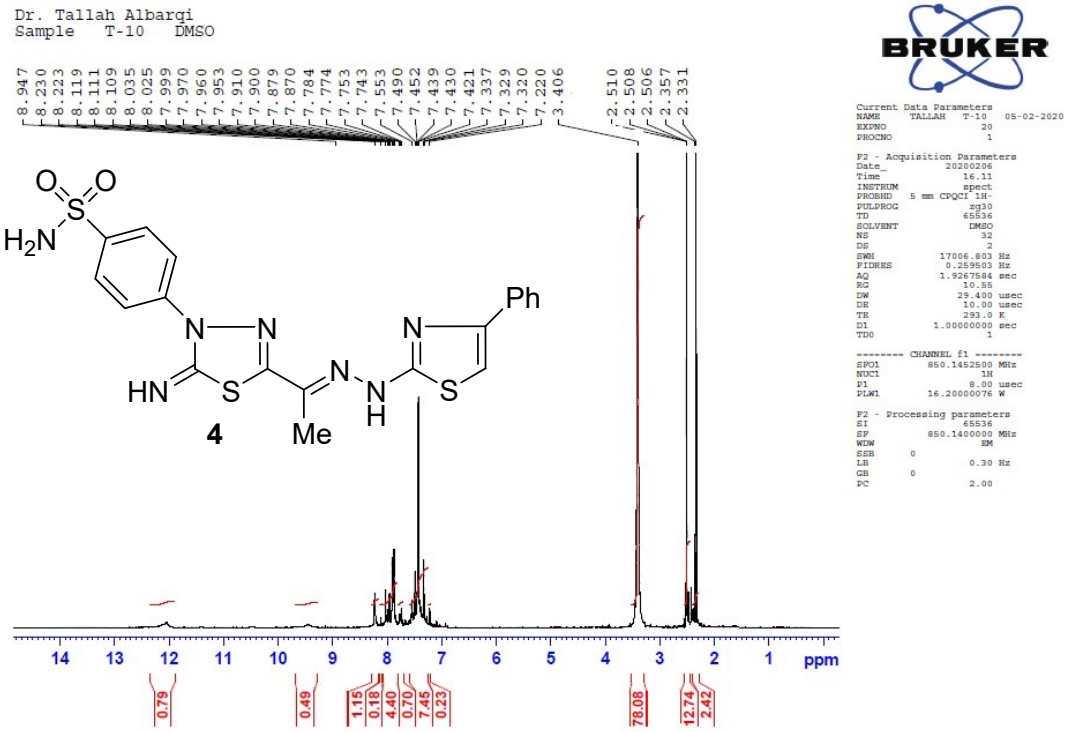


Figure S6. ^{1}H-NMR spectrum of compound **4**.

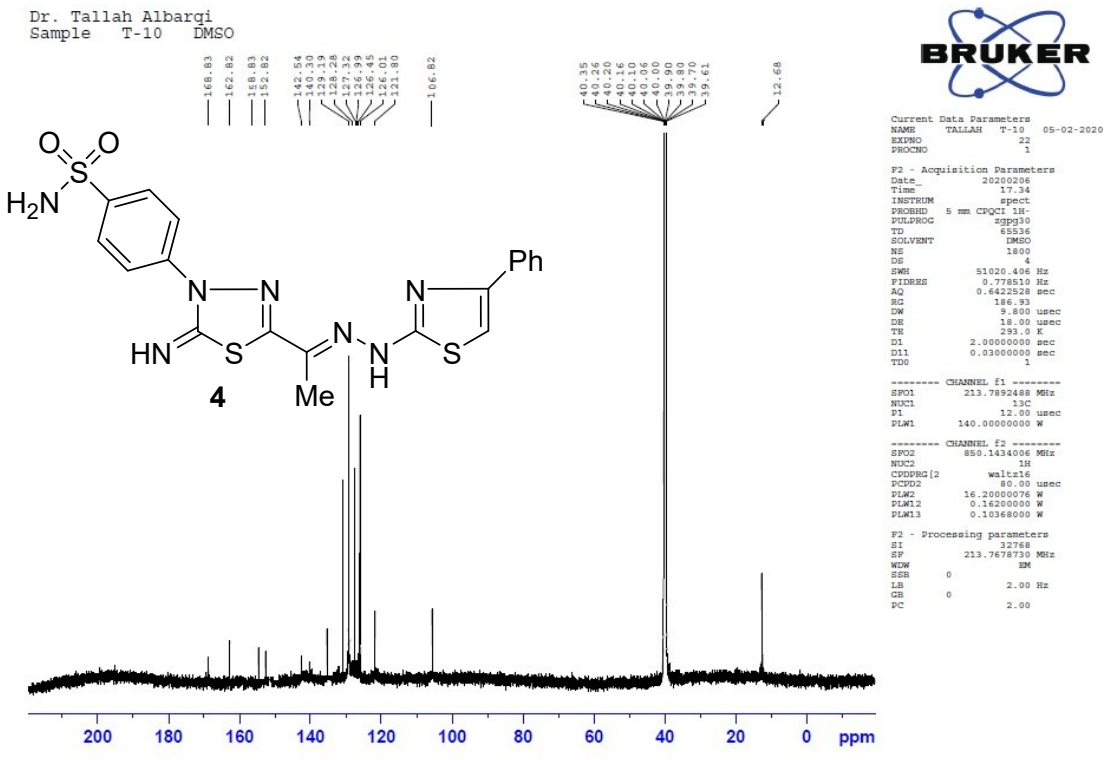


Figure S7. ^{13}C-NMR spectrum of compound **4**.

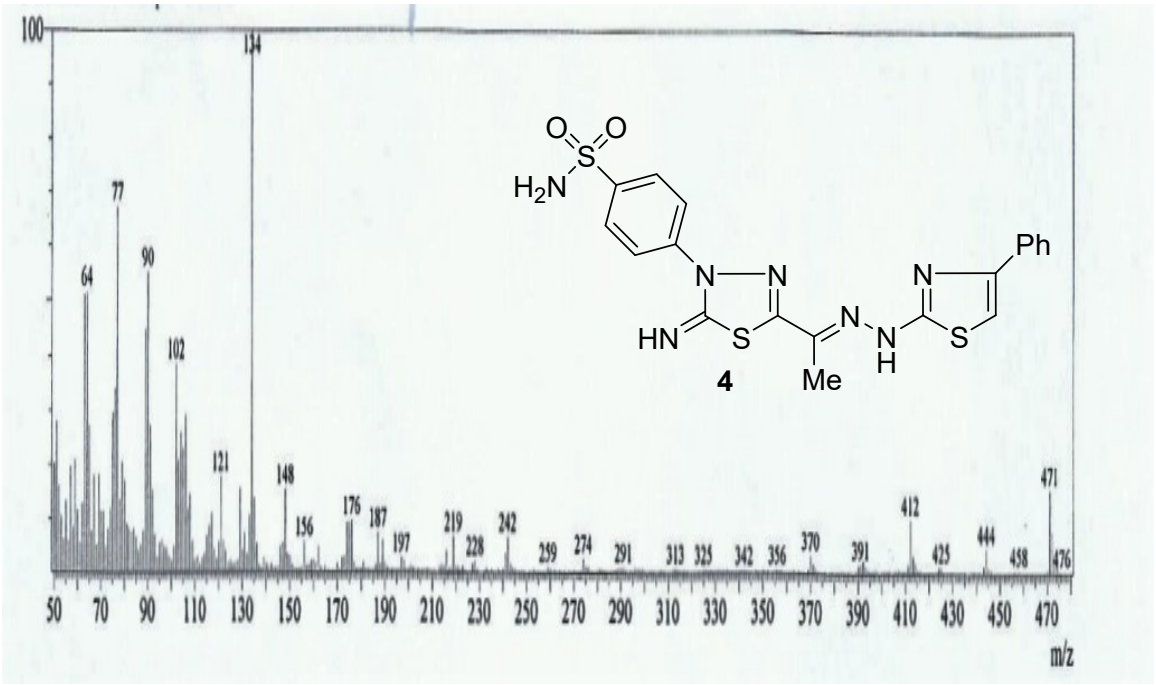


Figure S8. Mass spectrum of compound **4**.

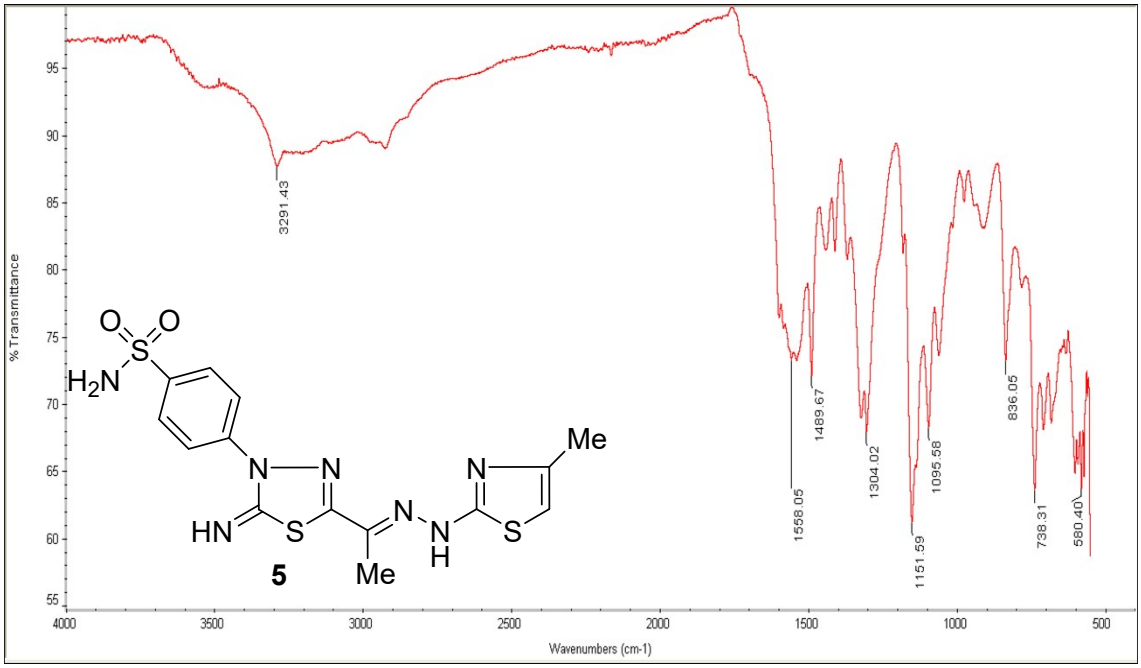


Figure S9. IR spectrum of compound **5**.

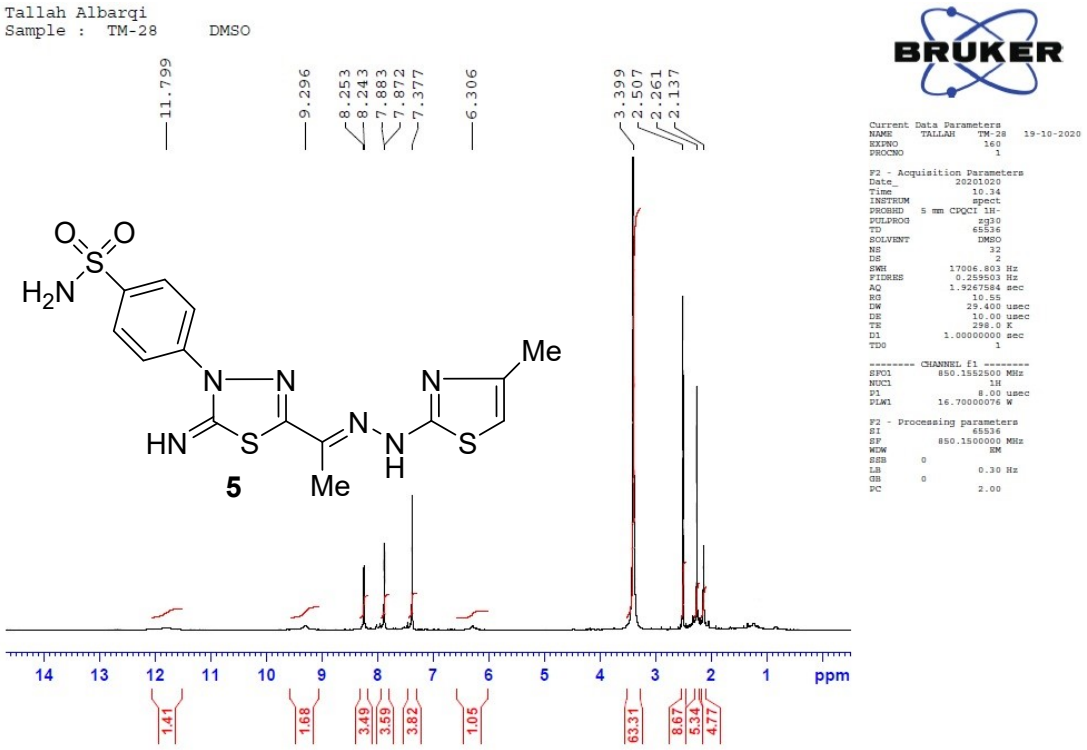


Figure S10. ^{1}H-NMR spectrum of compound **5**.

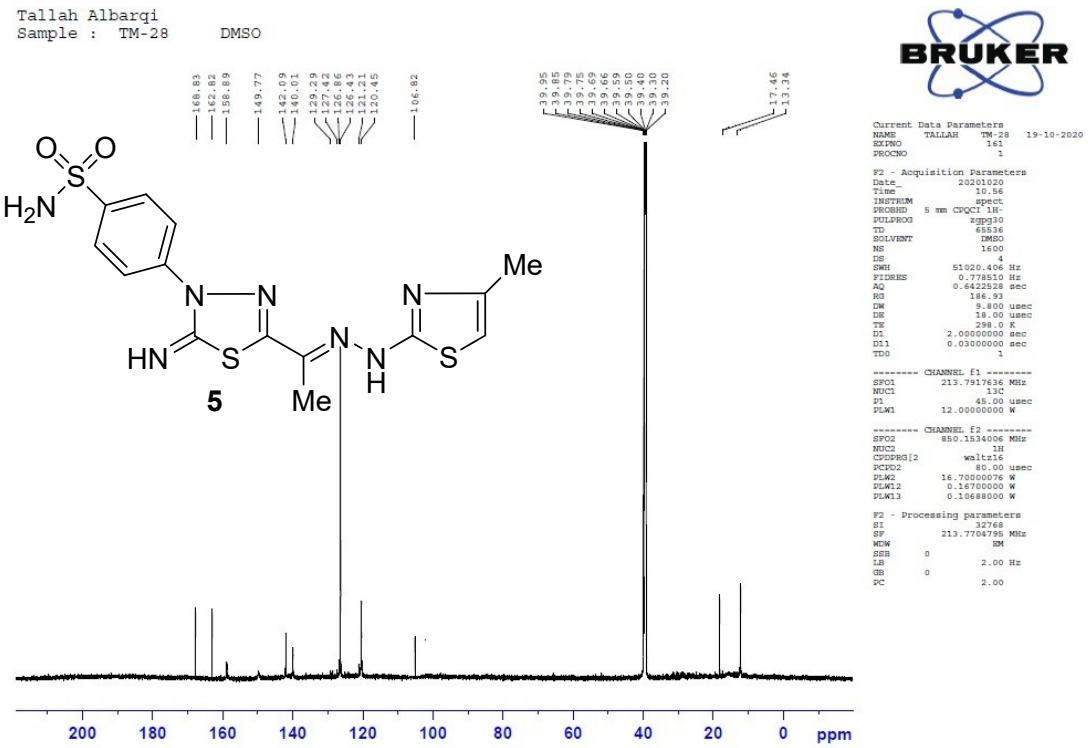


Figure S11. ^{13}C-NMR spectrum of compound **5**.

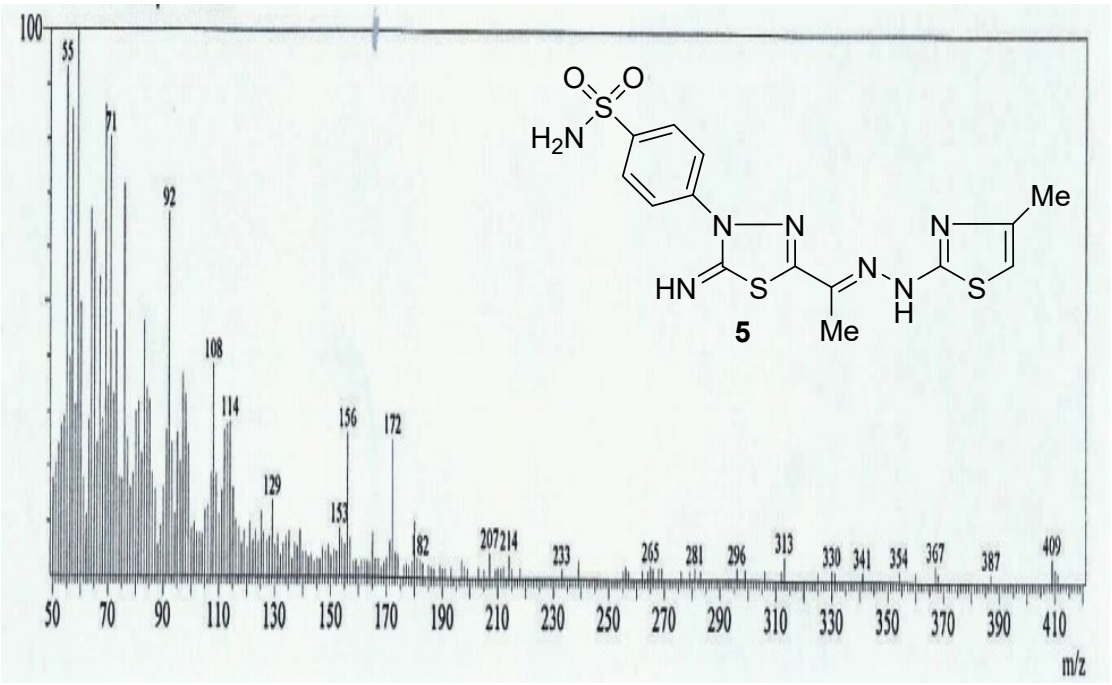


Figure S12. Mass spectrum of compound **5.**

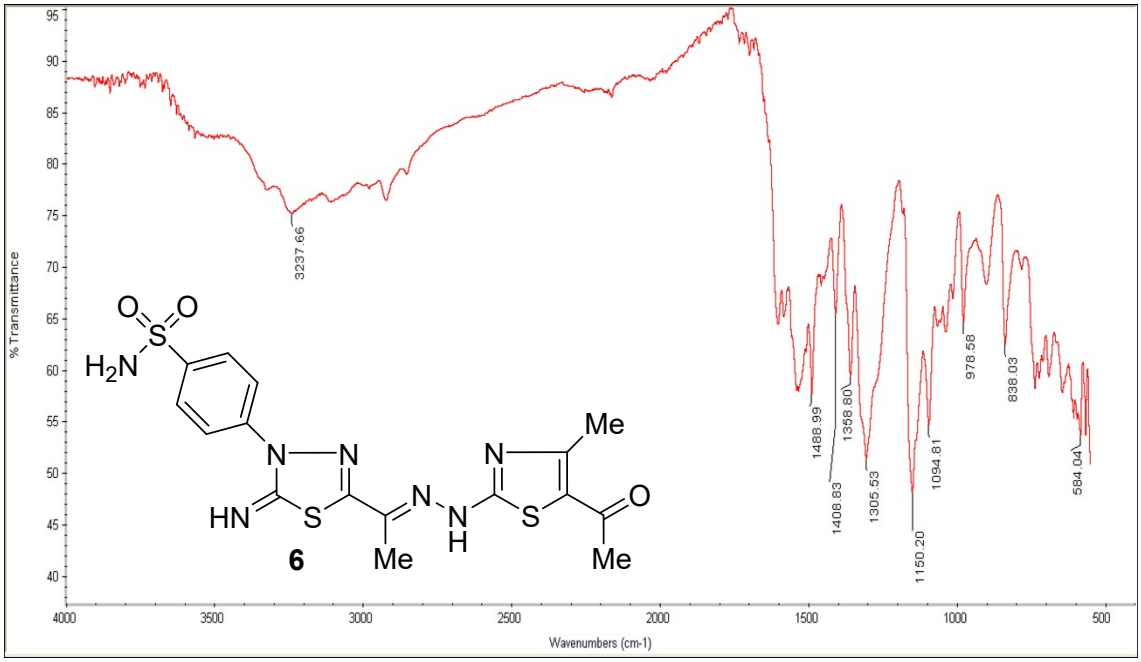


Figure S13. IR spectrum of compound **6**

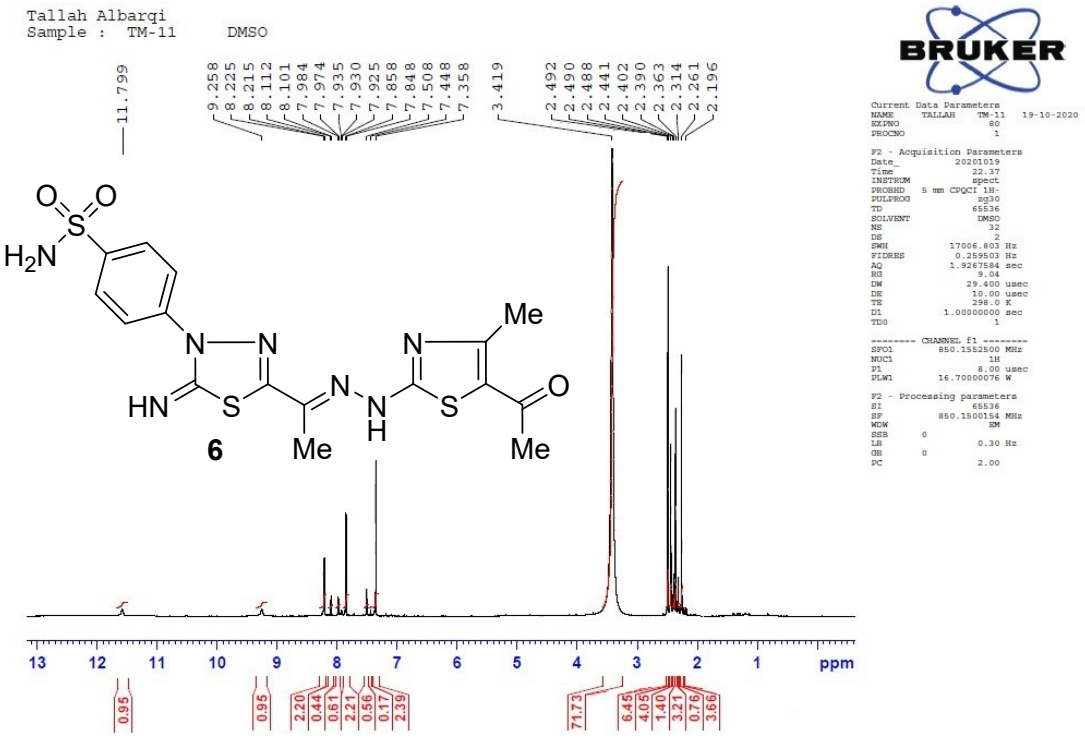


Figure S14. ^{1}H-NMR spectrum of compound **6**.

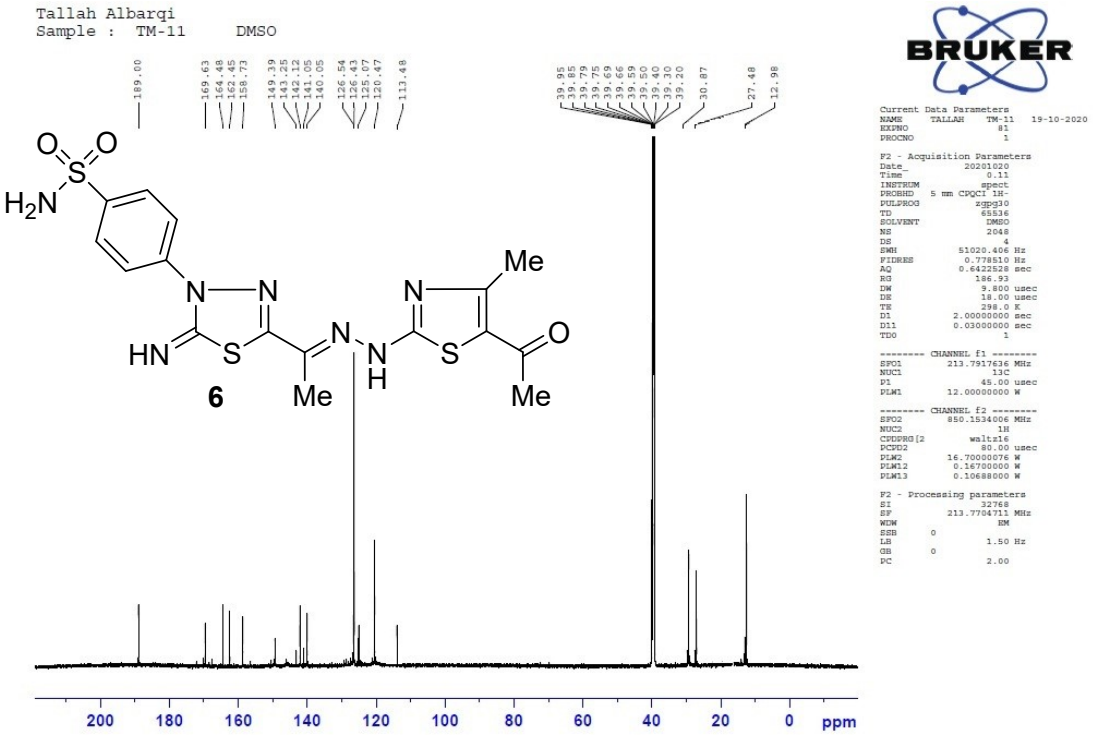


Figure S15. ^{13}C-NMR spectrum of compound **6**.

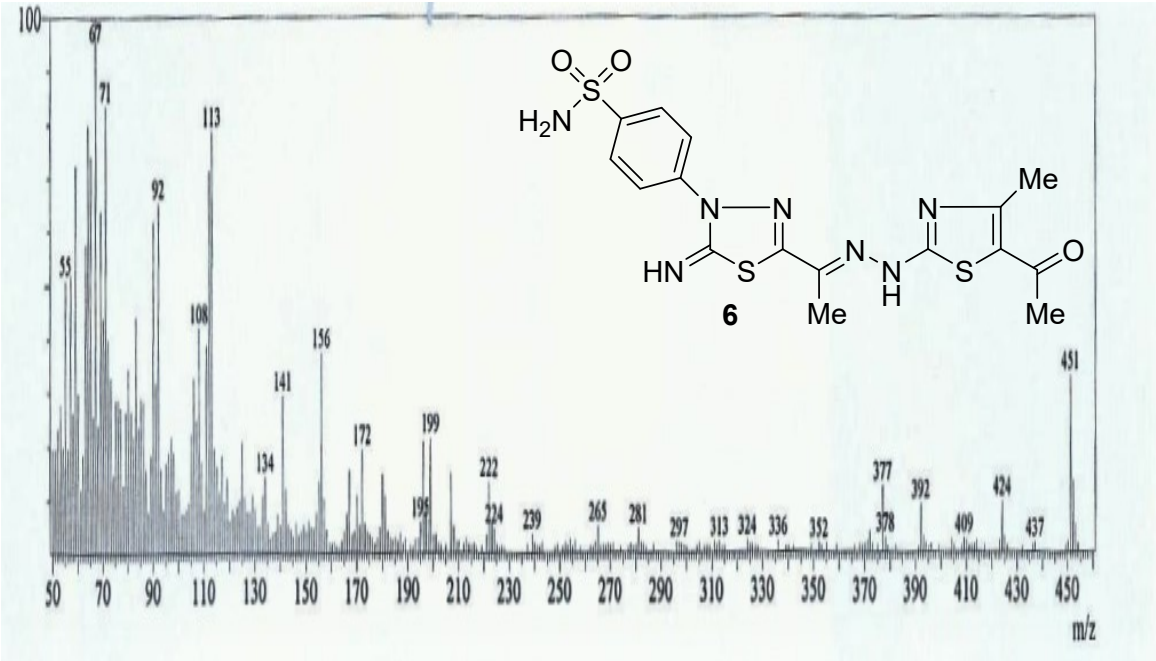


Figure S16. Mass spectrum of compound **6.**

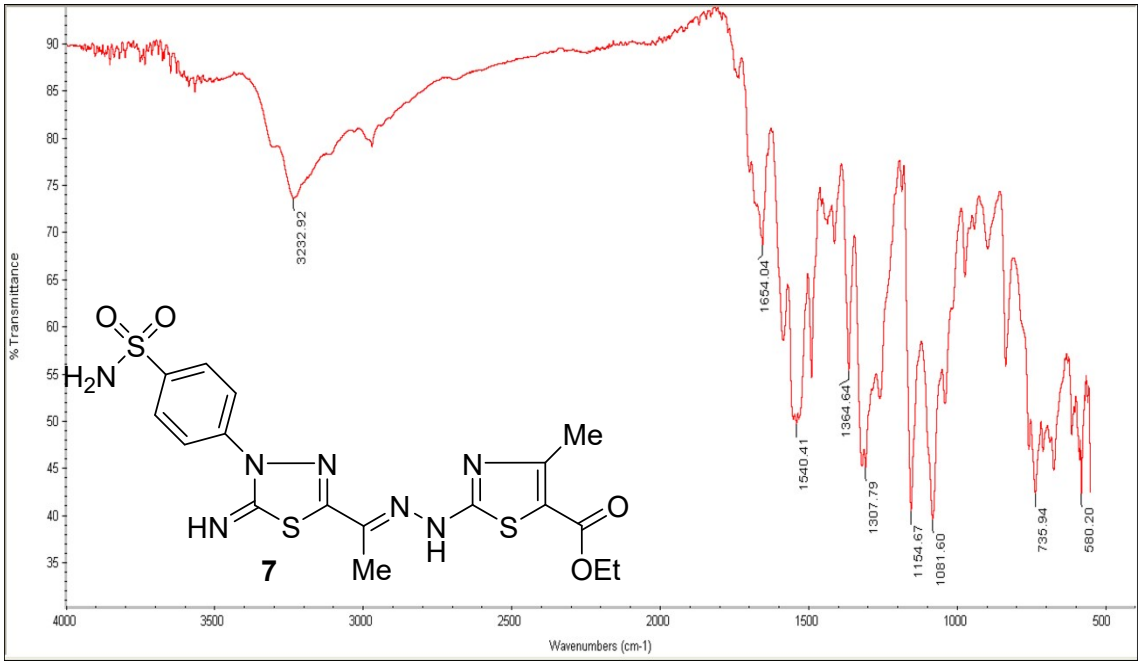


Figure S17. IR spectrum of compound **7**.

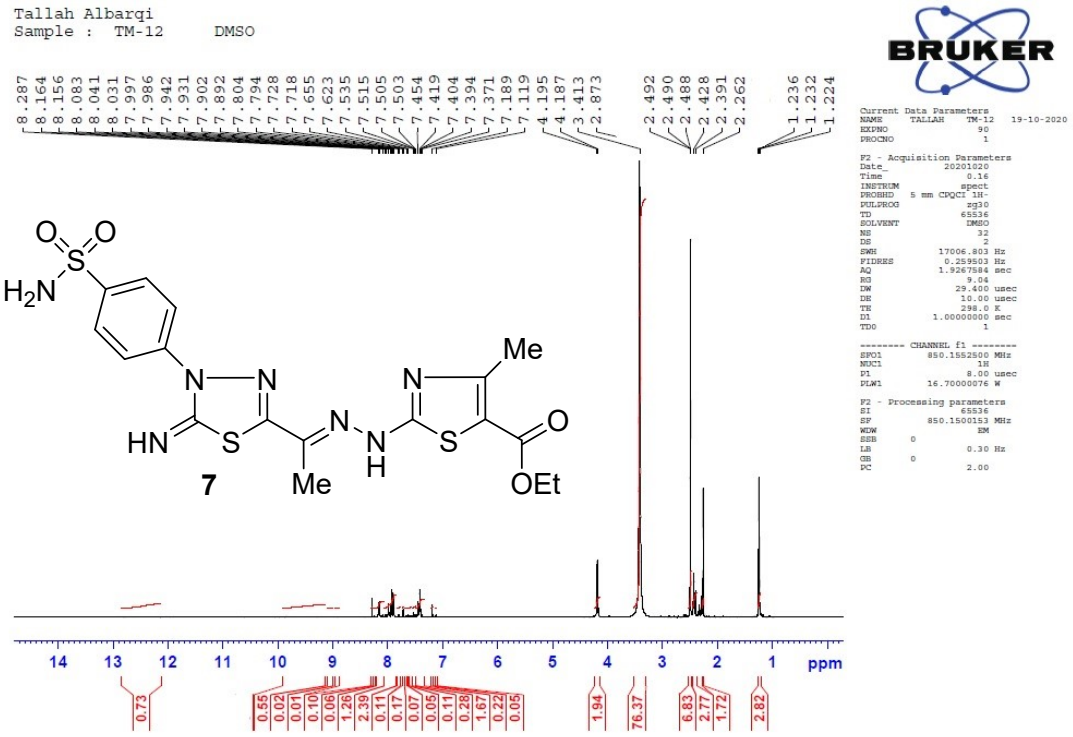


Figure S18. ^{1}H-NMR spectrum of compound **7**.

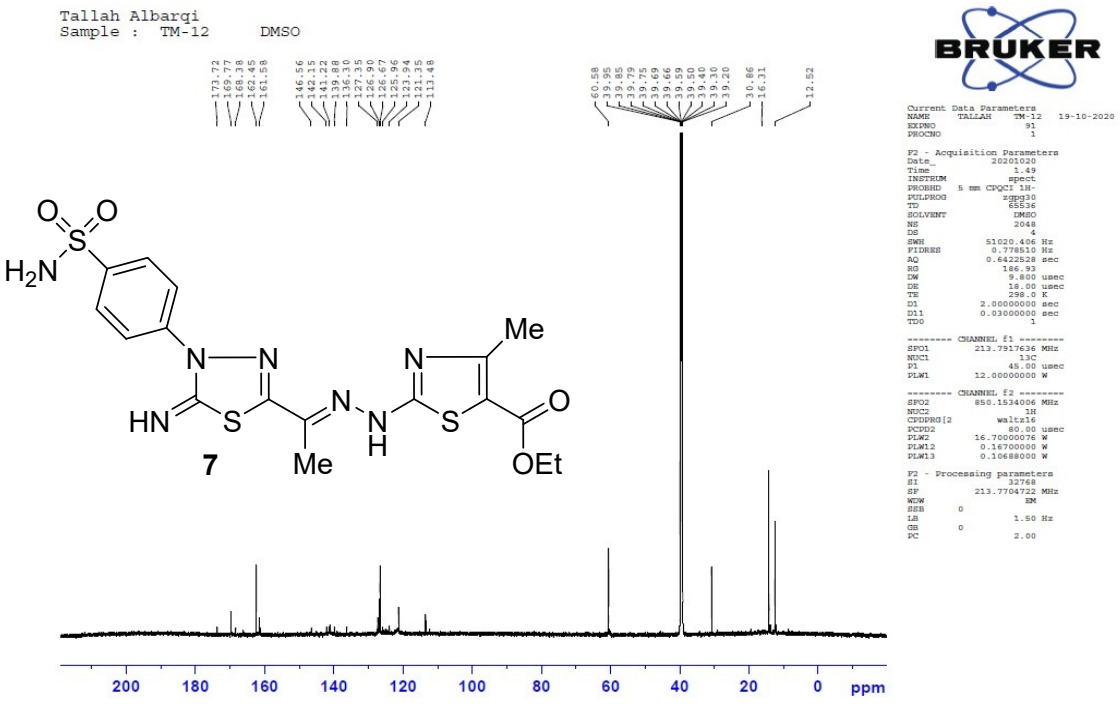


Figure S19. ^{13}C-NMR spectrum of compound **7**.

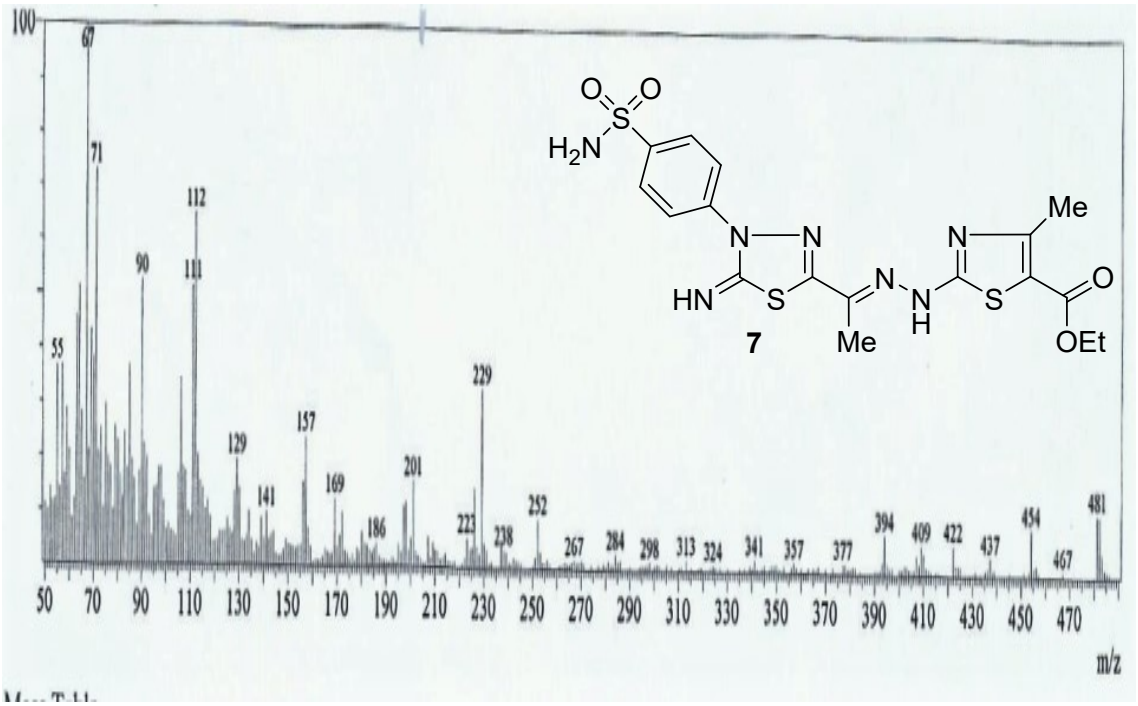


Figure S20. Mass spectrum of compound **7**.

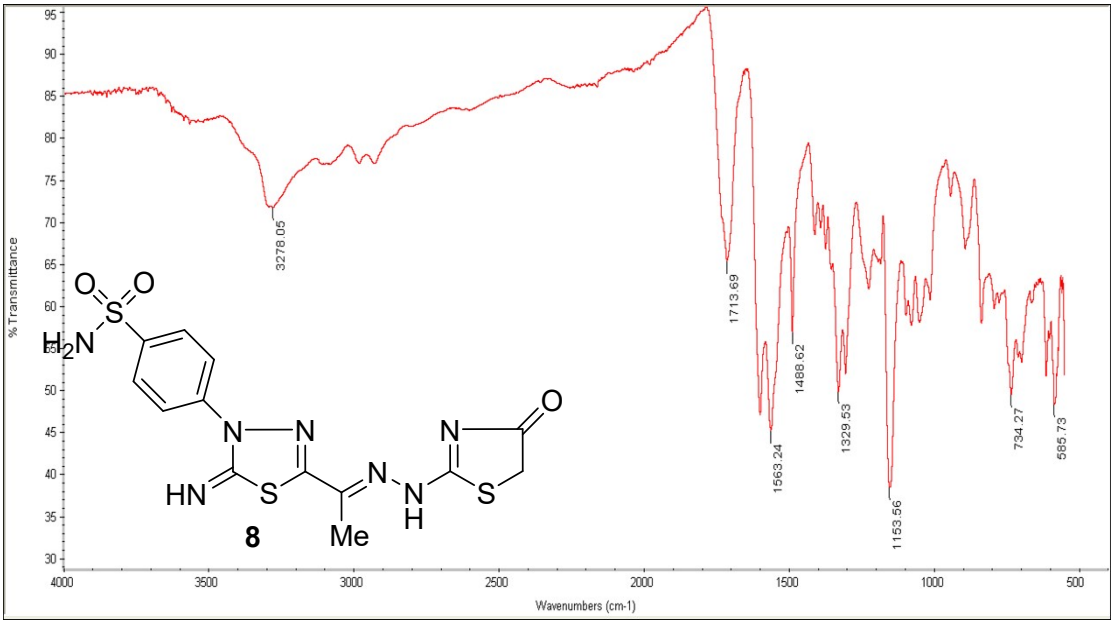


Figure S21. IR spectrum of compound **8**.

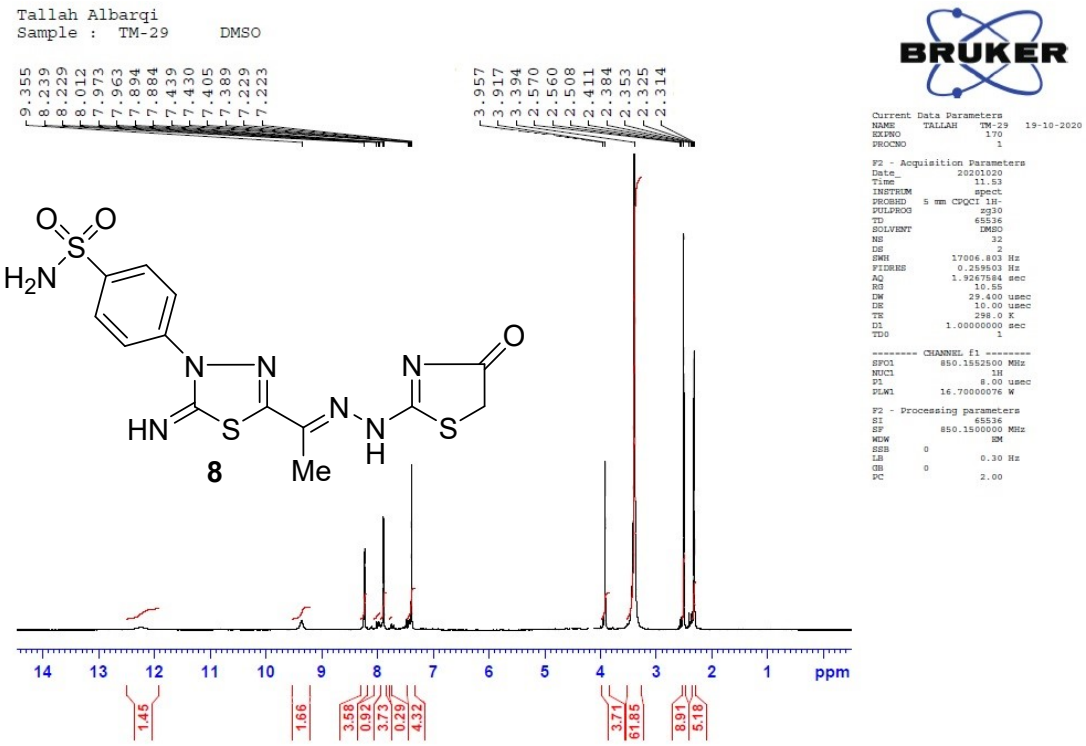


Figure S22. ^{1}H-NMR spectrum of compound **8**.

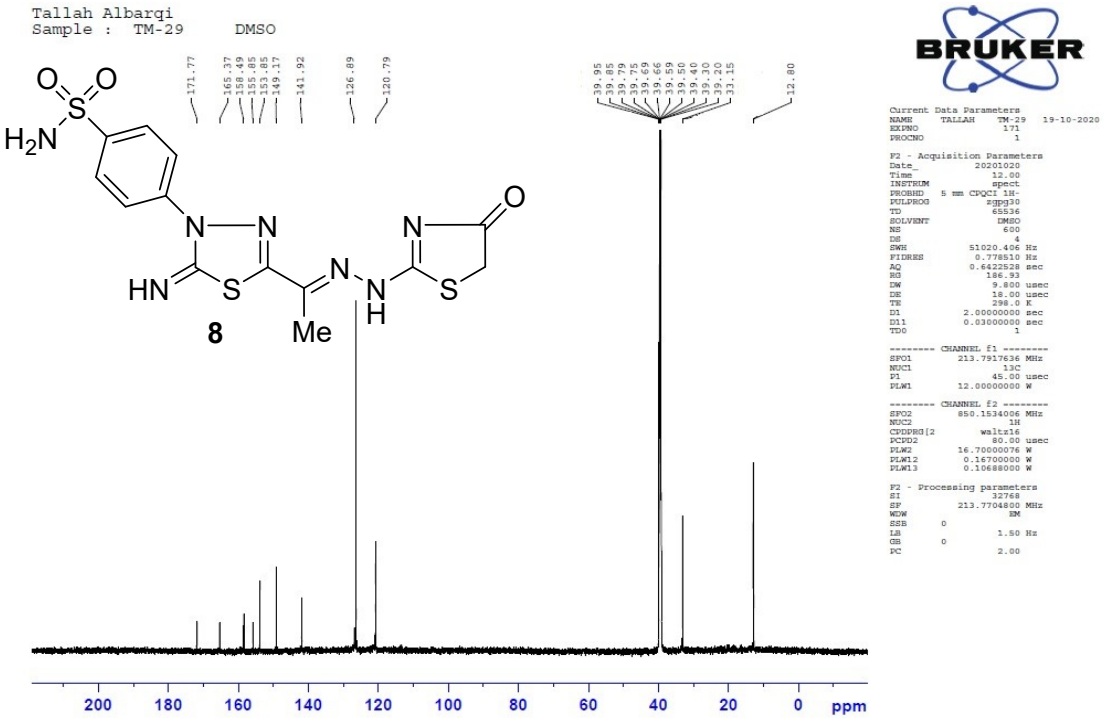


Figure S23. ^{13}C-NMR spectrum of compound **8**.

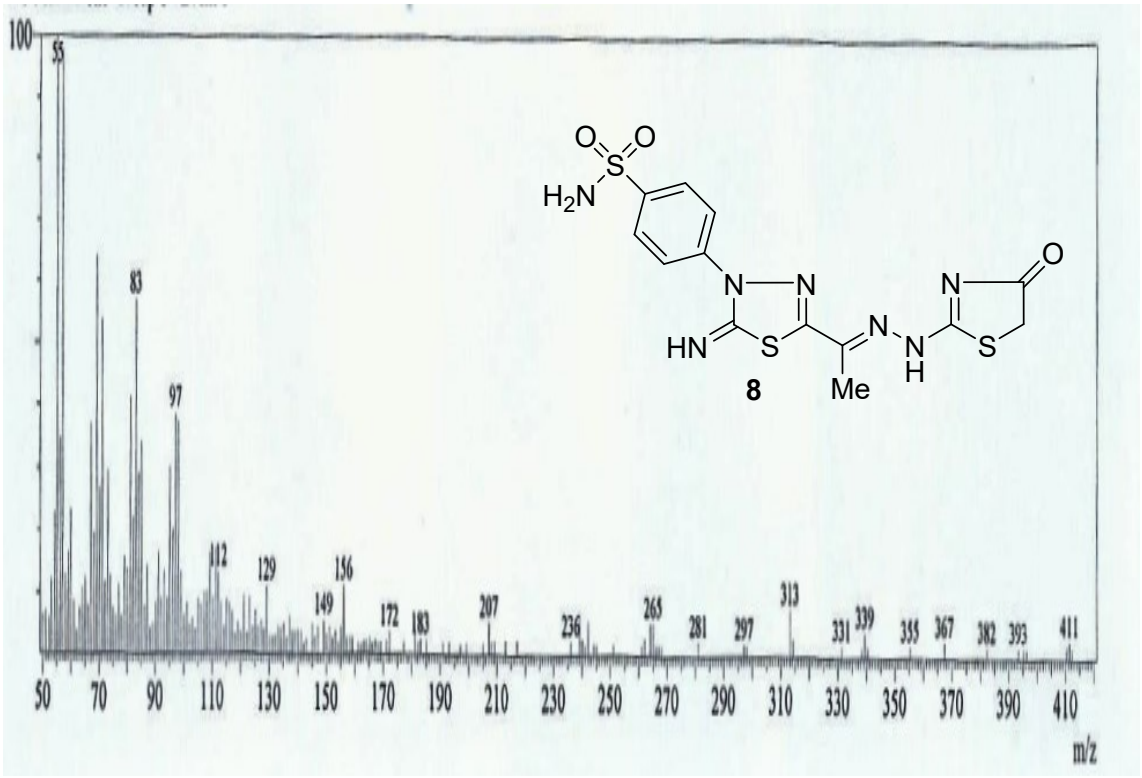


Figure S24. Mass spectrum of compound **8.**

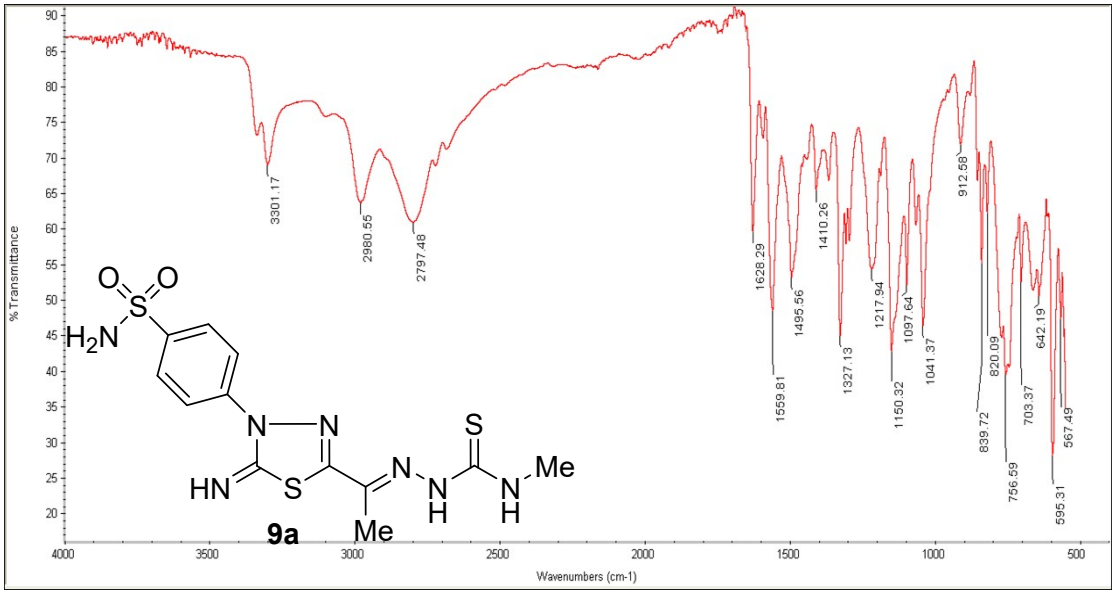


Figure S25. IR spectrum of compound **9a**.

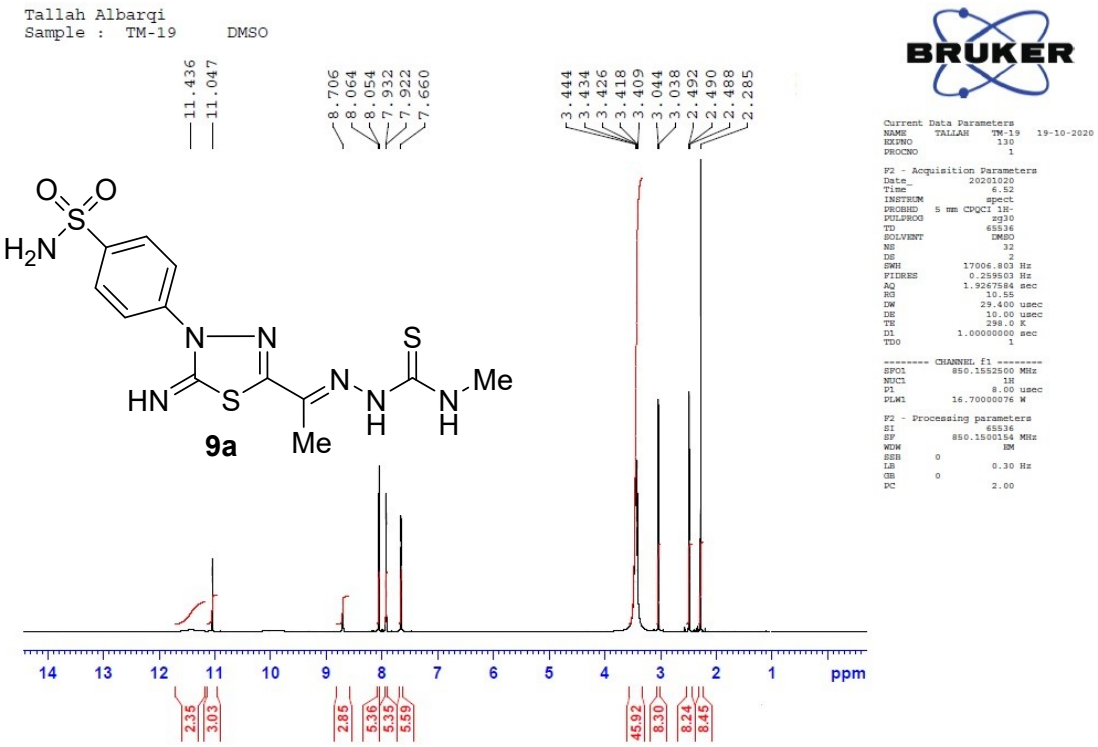


Figure S26. ^{1}H-NMR spectrum of compound **9a**.

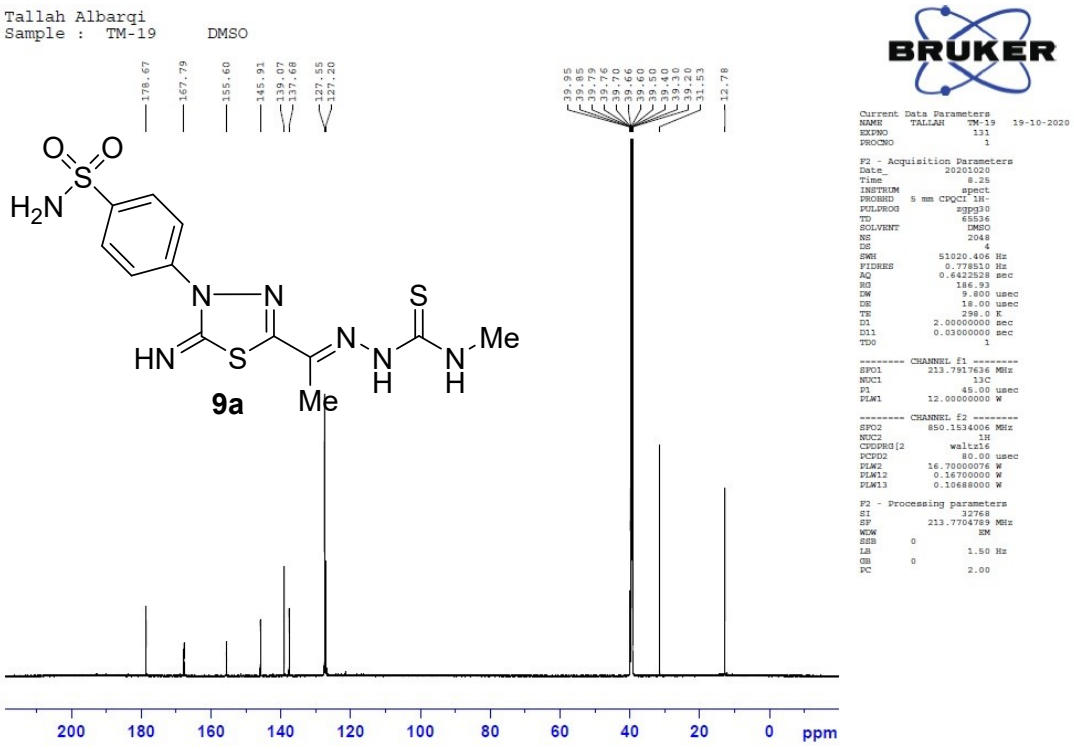


Figure S27. ^{13}C-NMR spectrum of compound **9a**.

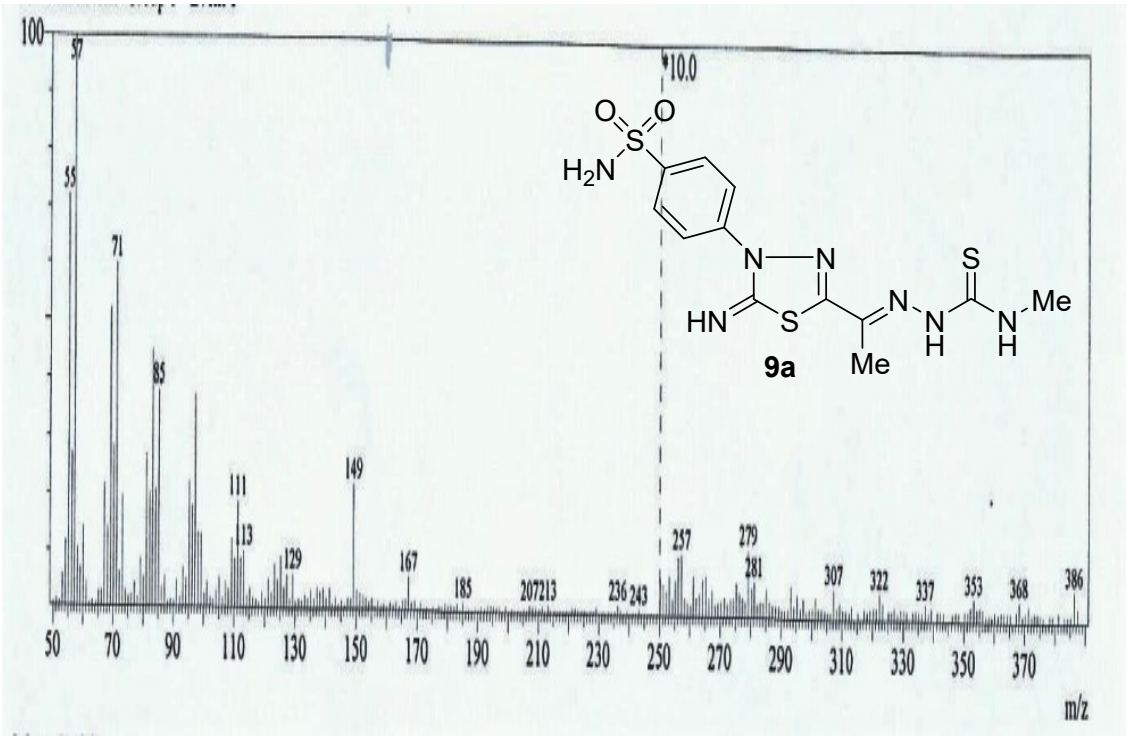


Figure S28. Mass spectrum of compound **9a.**

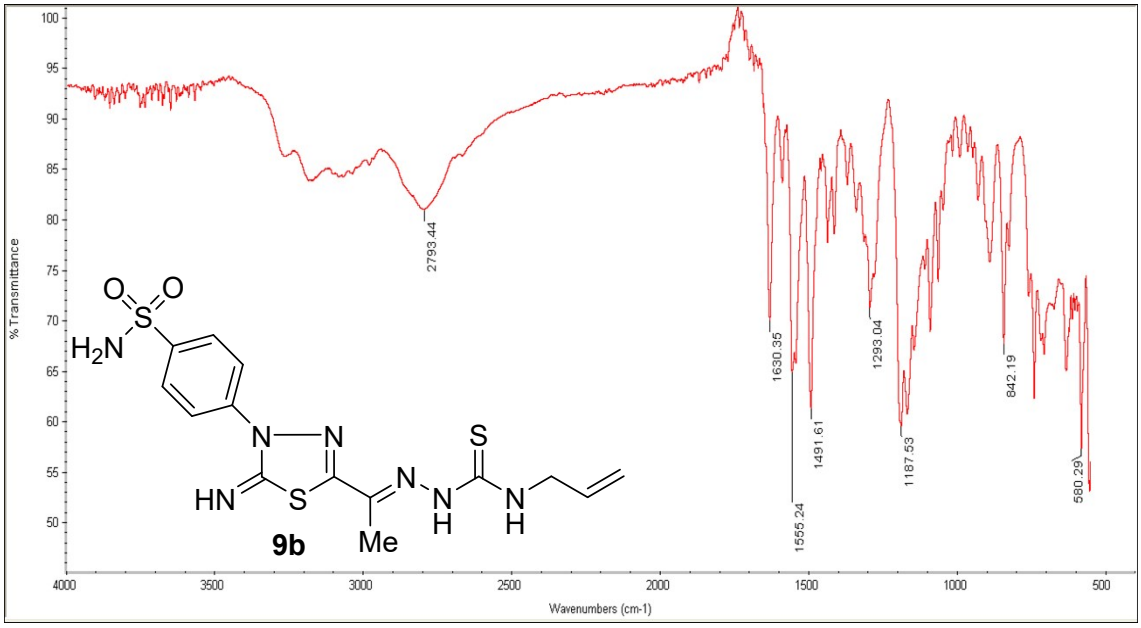


Figure S29. IR spectrum of compound **9b**.

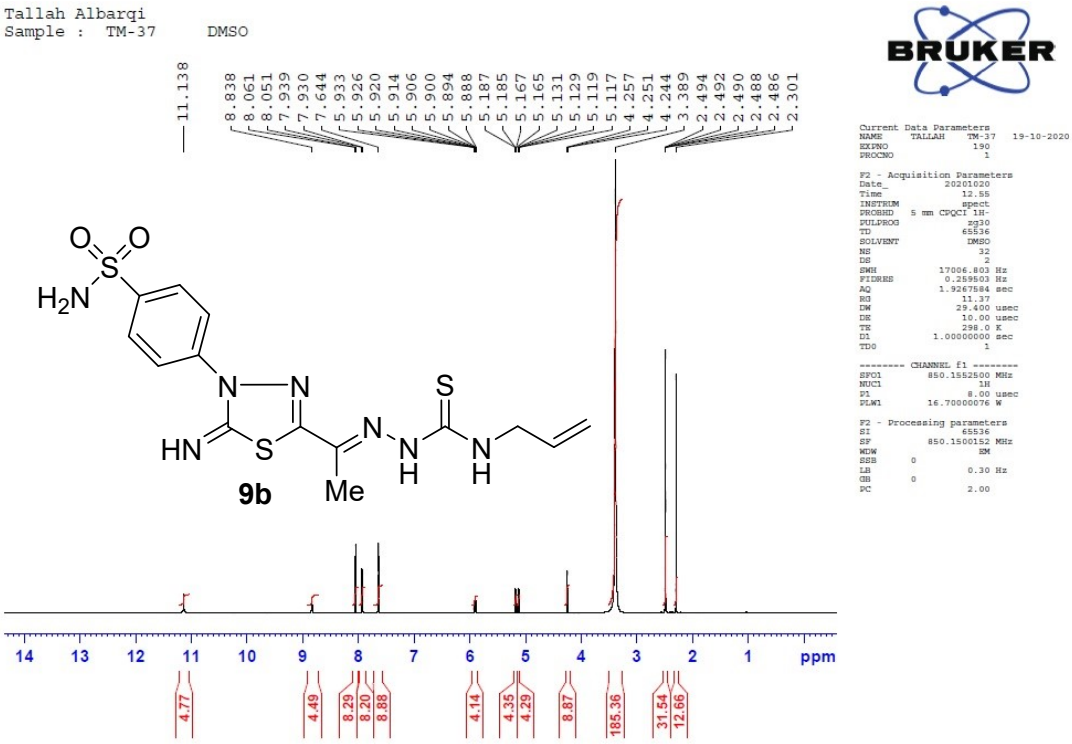


Figure S30. ^{1}H-NMR spectrum of compound **9b**.

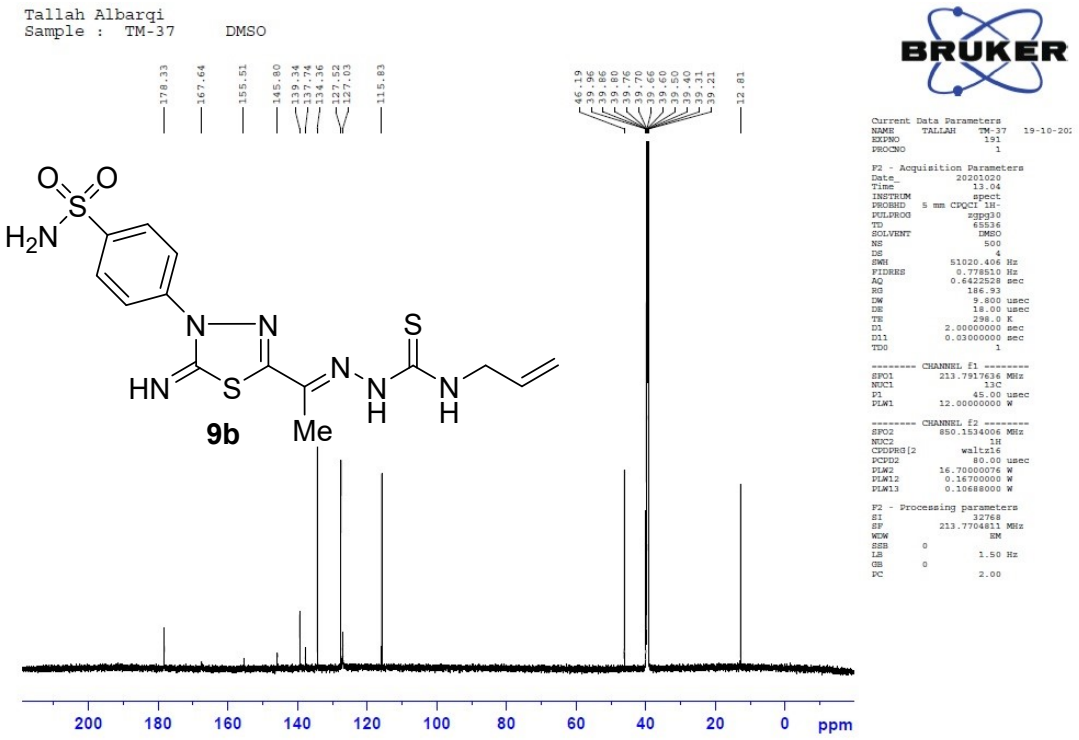


Figure S31. ^{13}C-NMR spectrum of compound **9b**.

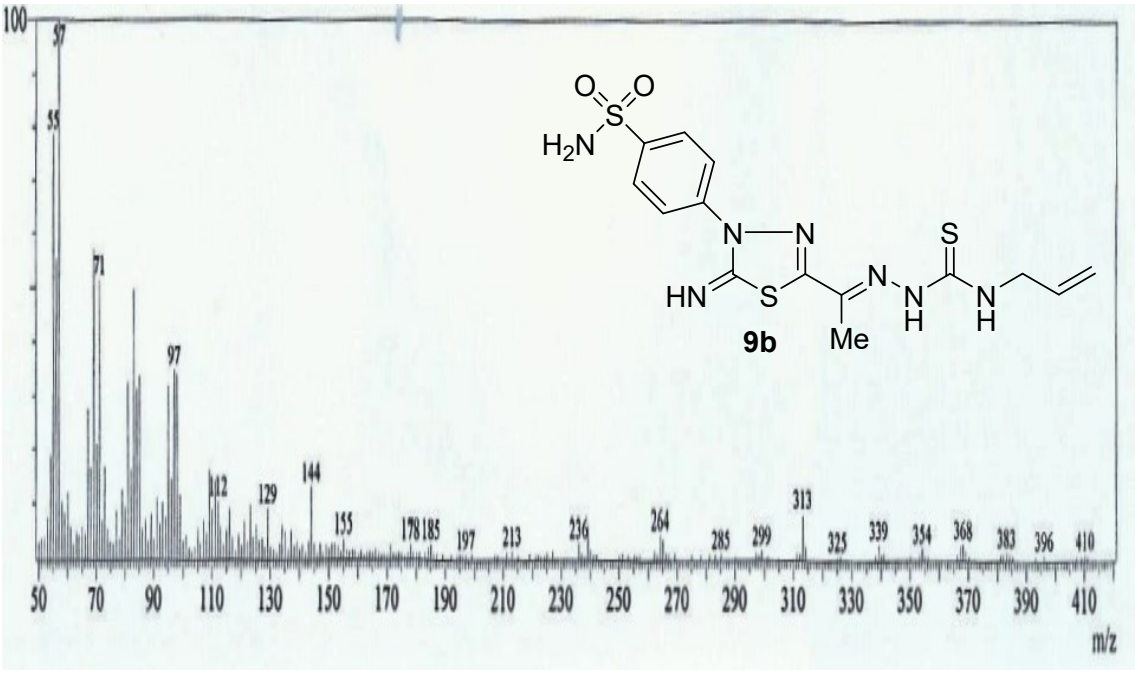


Figure S32. Mass spectrum of compound **9b.**

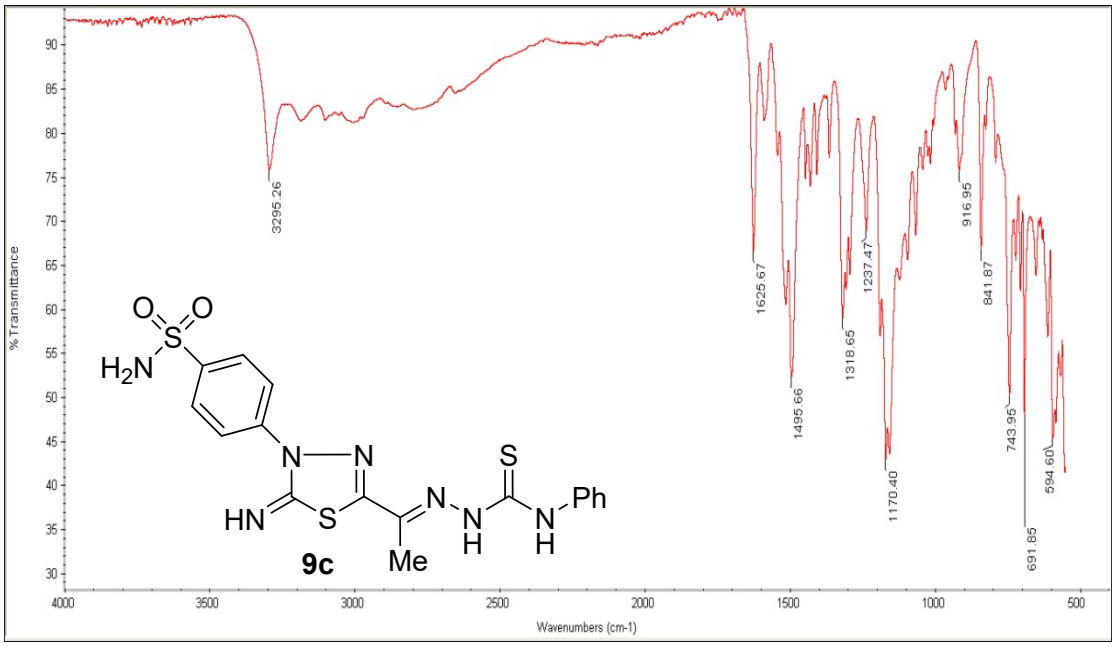


Figure S33. IR spectrum of compound **9c**.

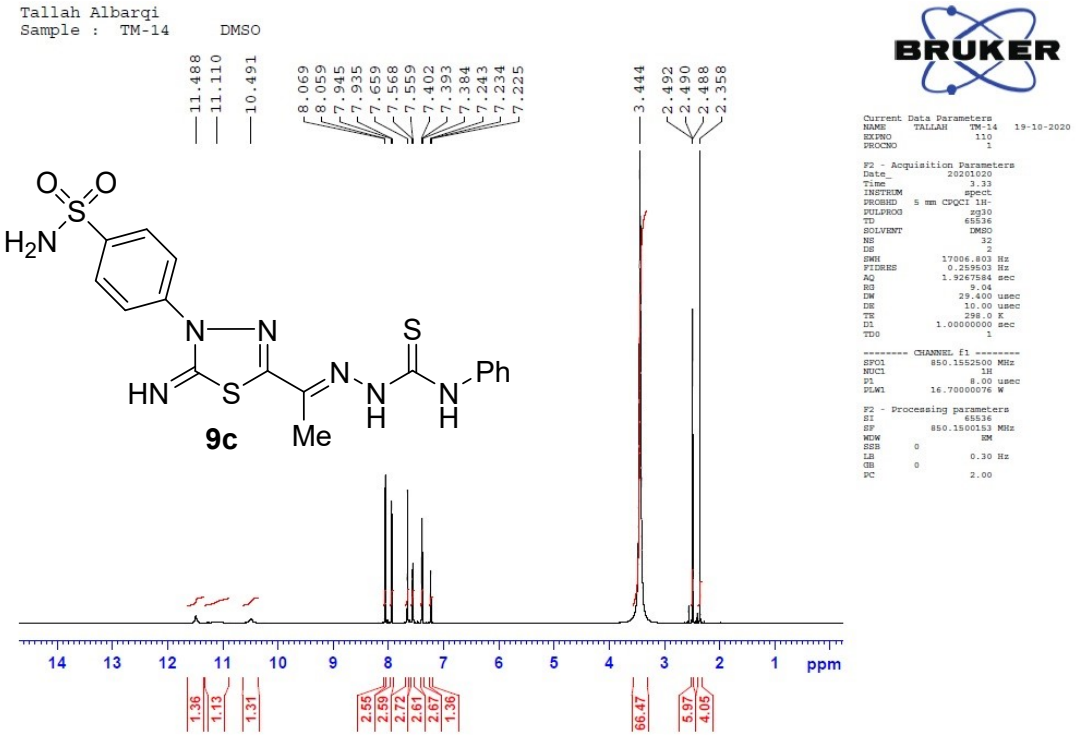


Figure S34. ^{1}H-NMR spectrum of compound **9c**.

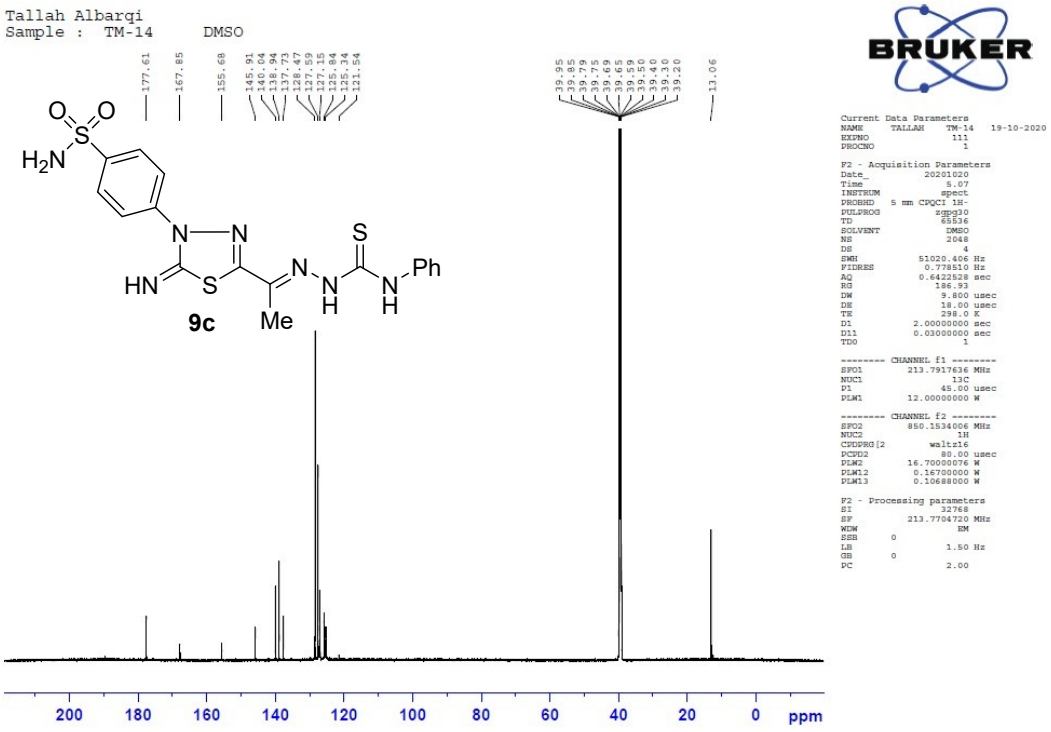


Figure S35. ^{13}C-NMR spectrum of compound **9c**.

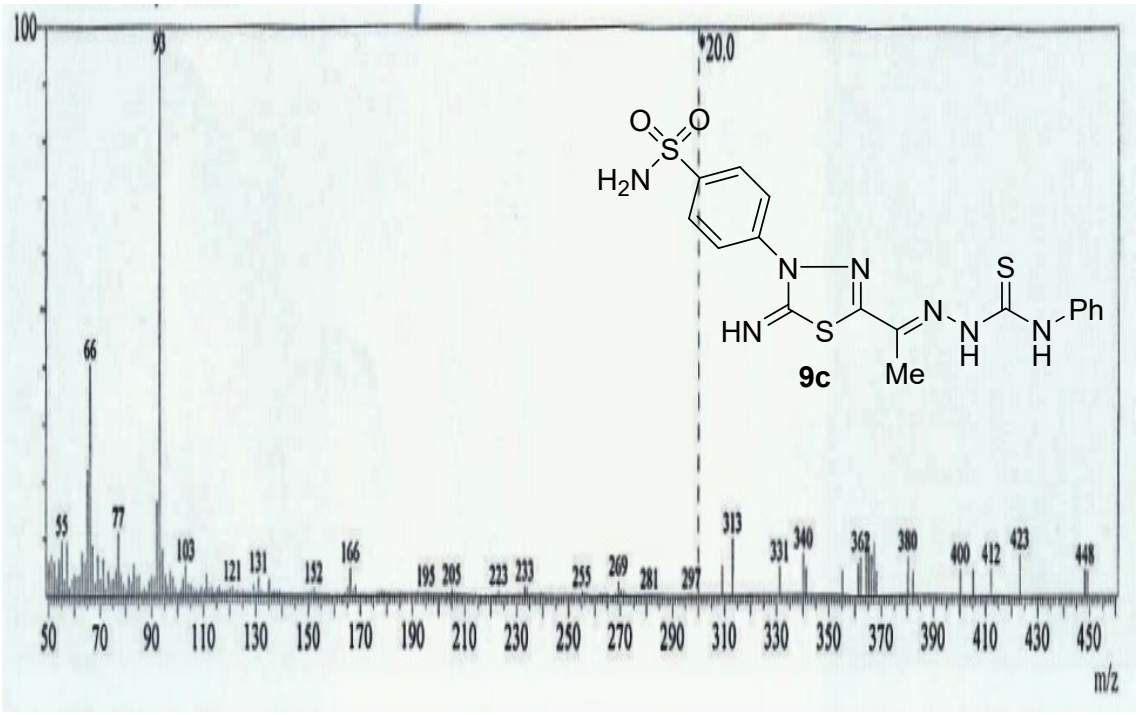


Figure S36. Mass spectrum of compound **9c.**

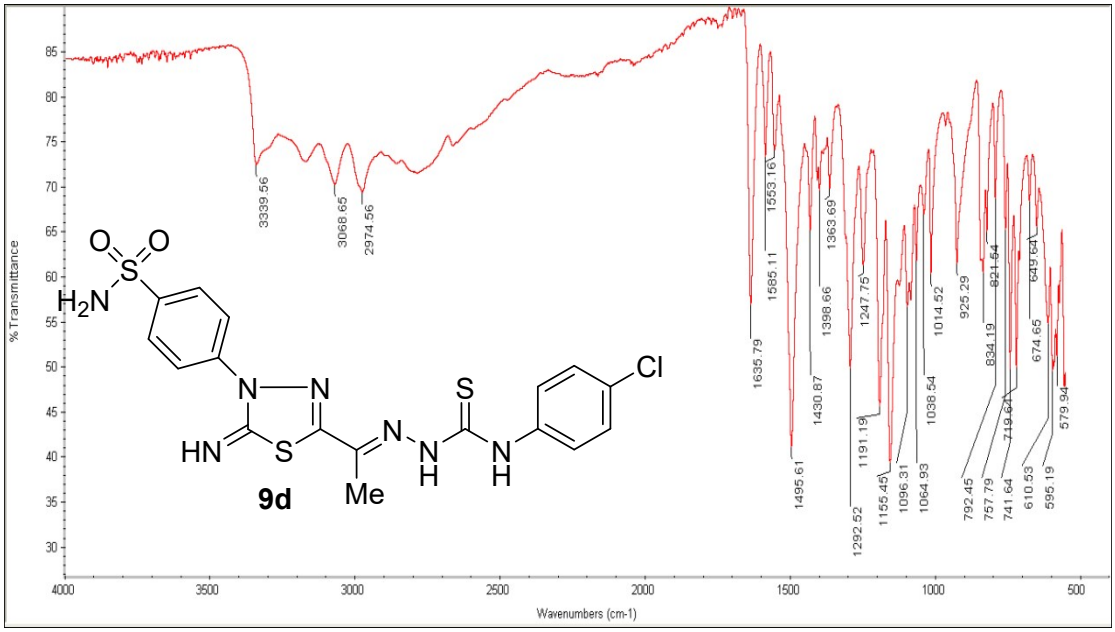


Figure S37. IR spectrum of compound **9d**.

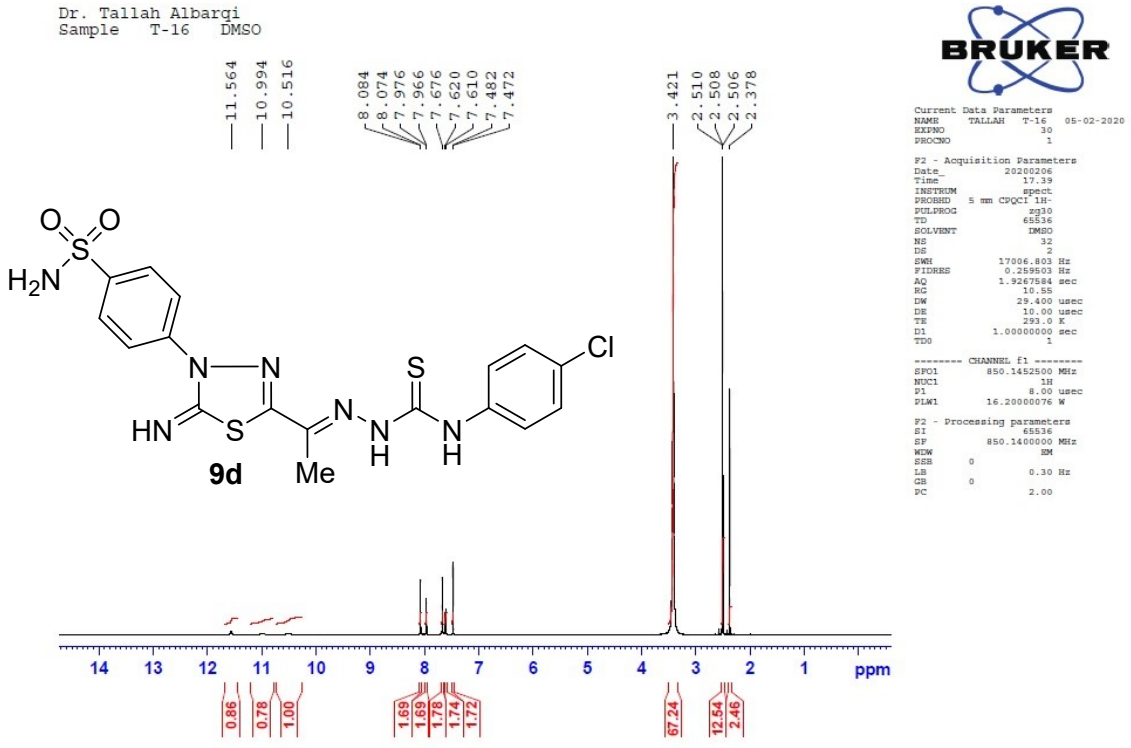


Figure S38. ^{1}H-NMR spectrum of compound **9d**.

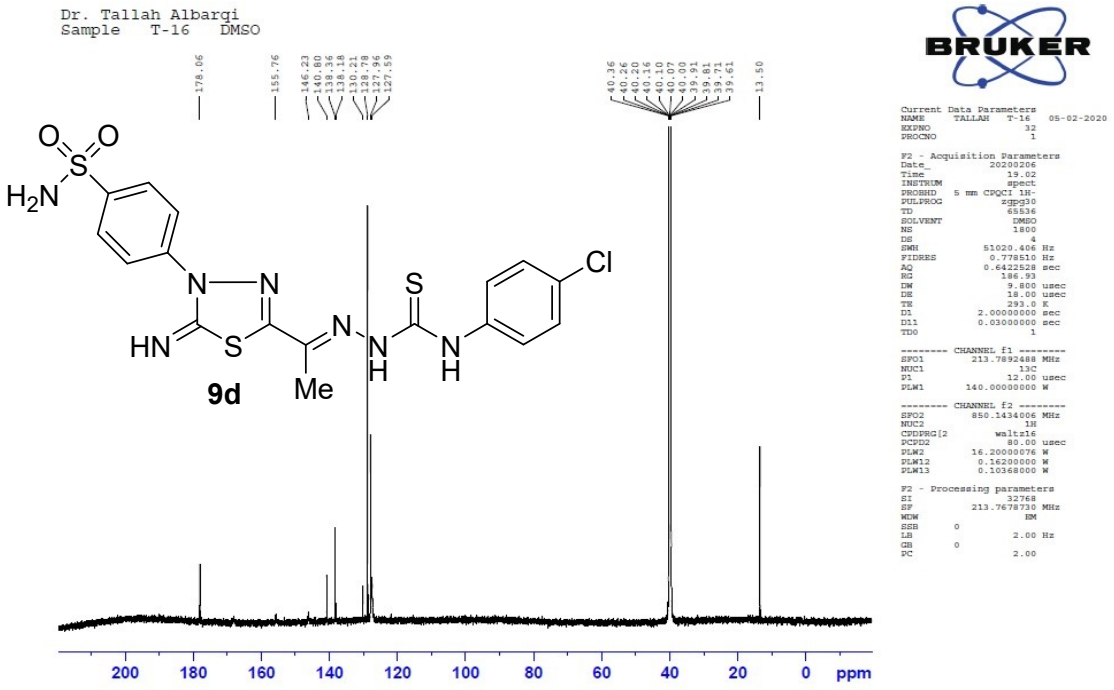


Figure S39. ^{13}C-NMR spectrum of compound **9d**.

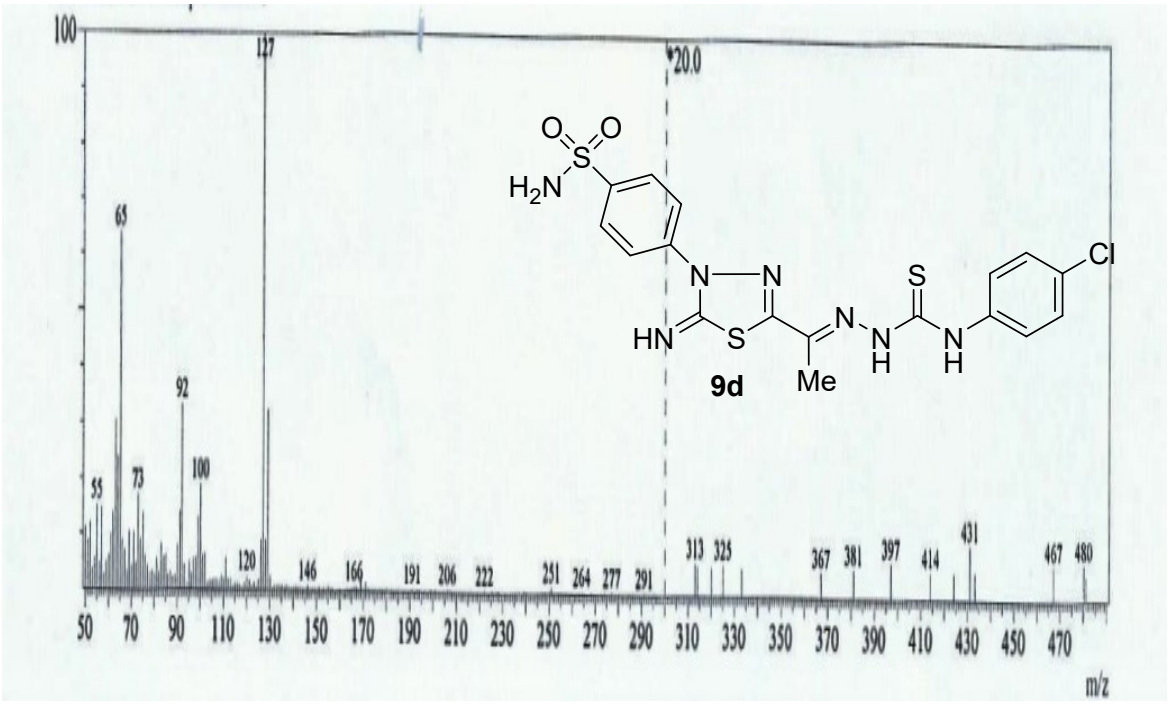


Figure S40. Mass spectrum of compound **9d.**

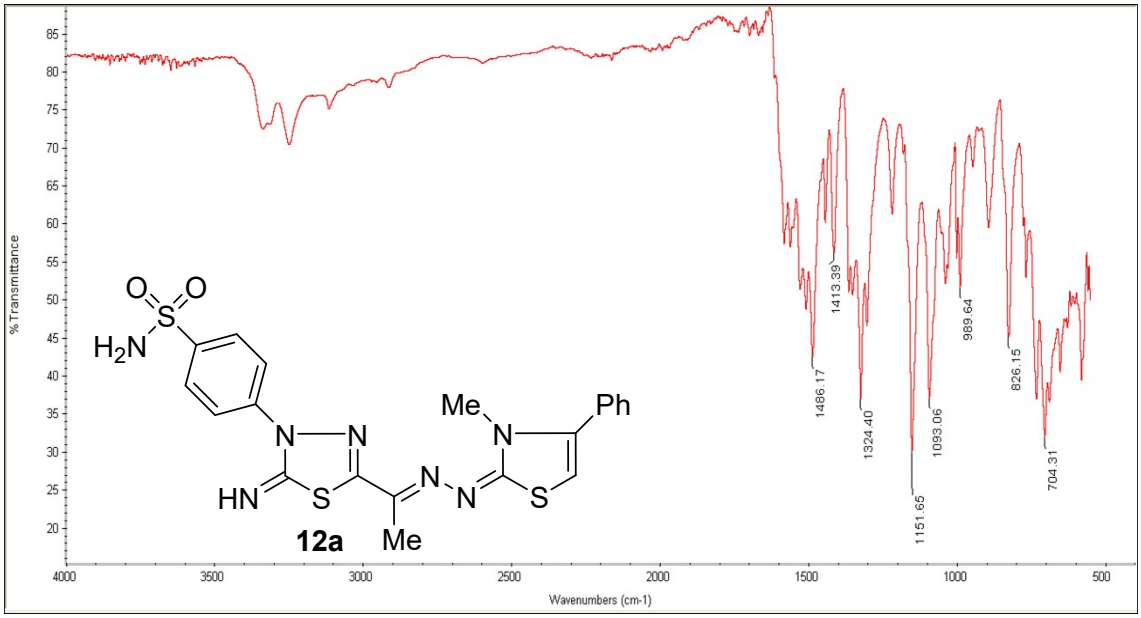


Figure S41. IR spectrum of compound **12a.**

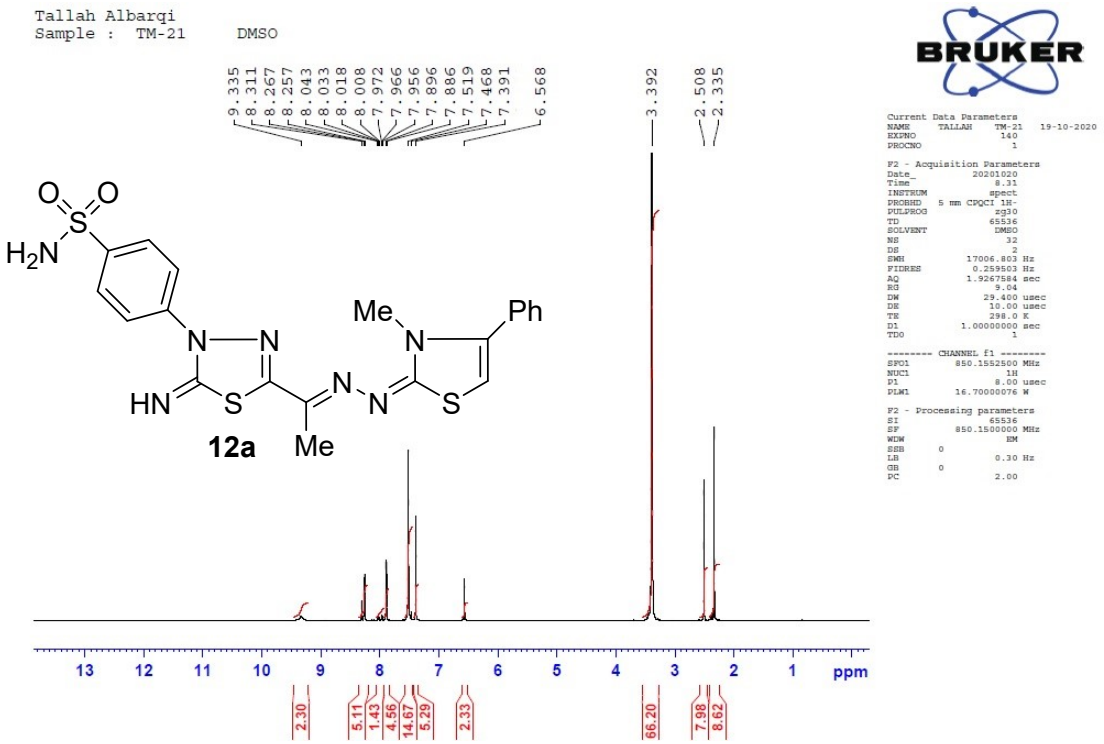


Figure S42. ^{1}H-NMR spectrum of compound **12a**.

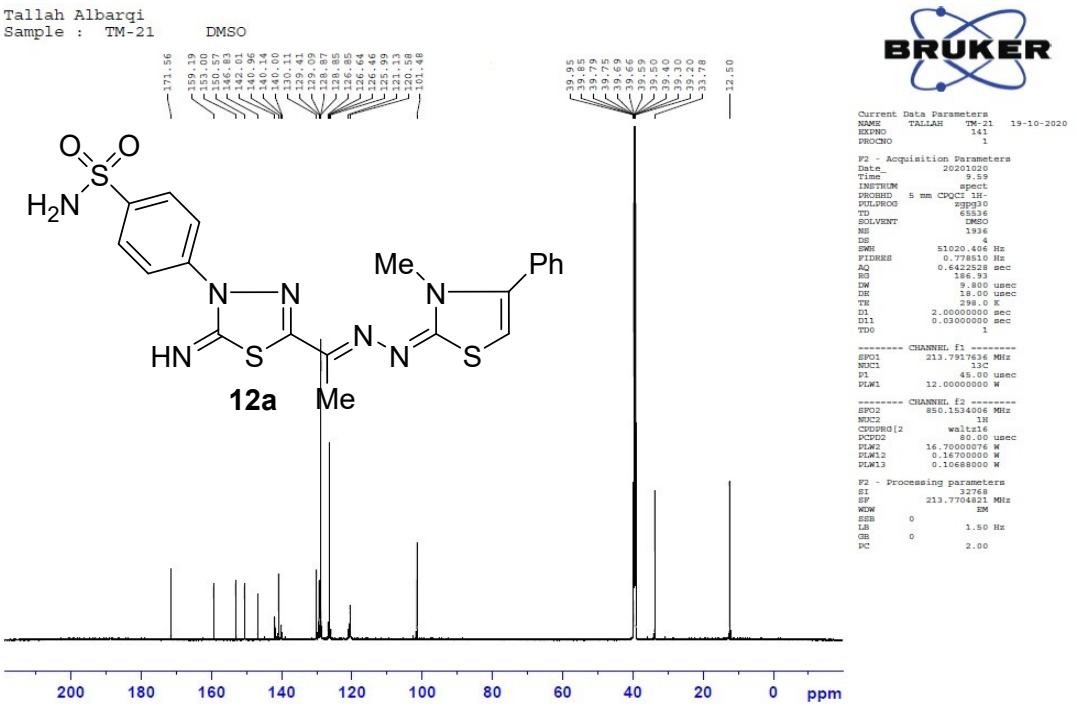


Figure S43. ^{13}C-NMR spectrum of compound **12a**.

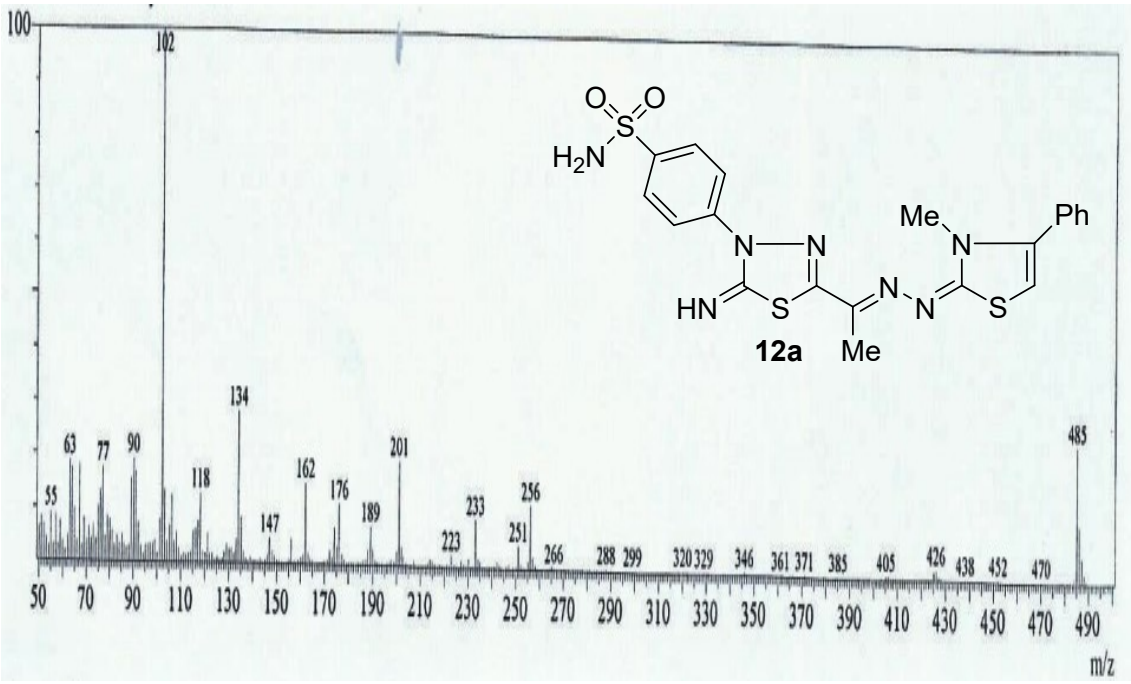


Figure S44. Mass spectrum of compound **12a.**

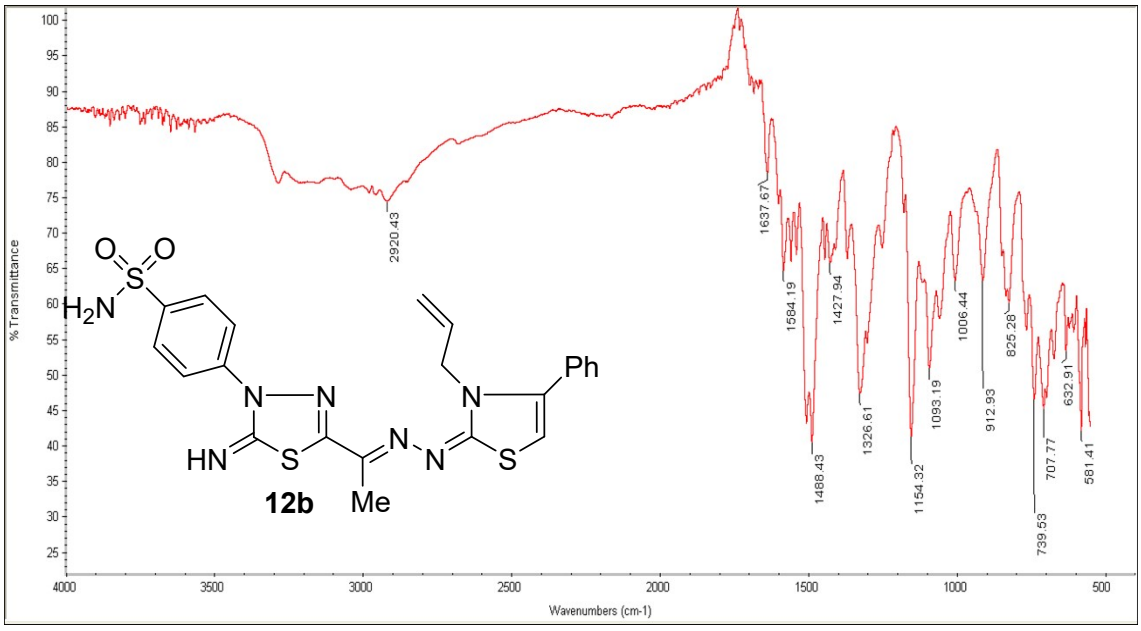


Figure S45. IR spectrum of compound **12b**.

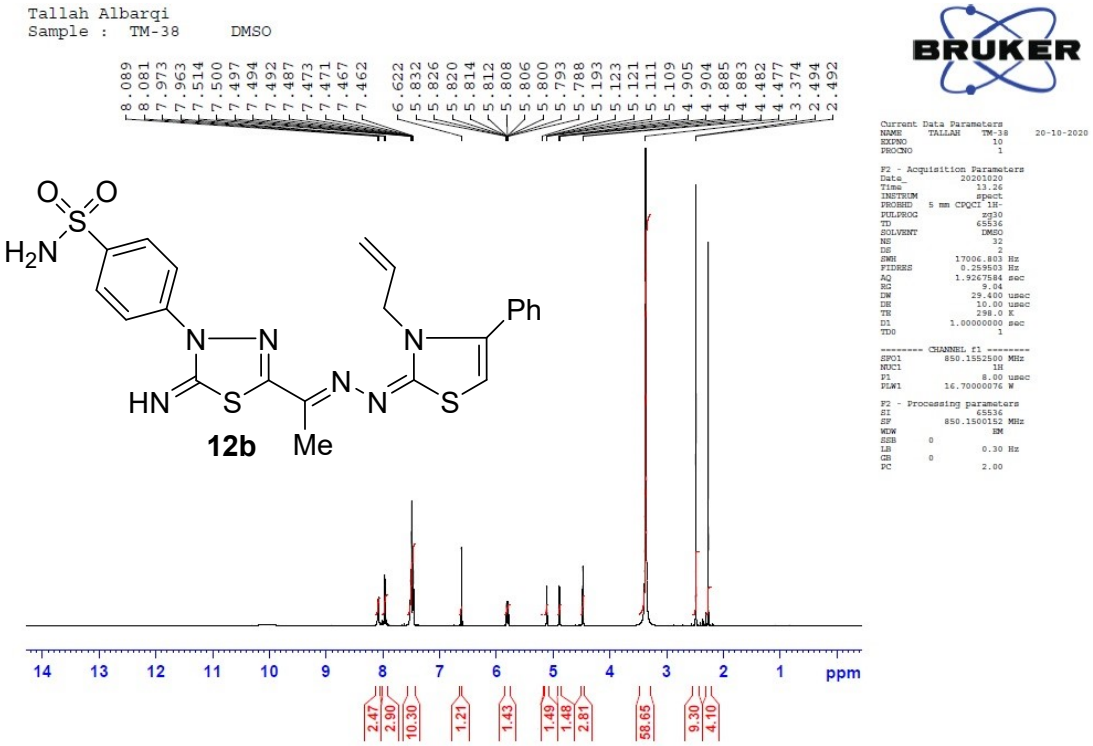


Figure S46. ^{1}H-NMR spectrum of compound **12b**.

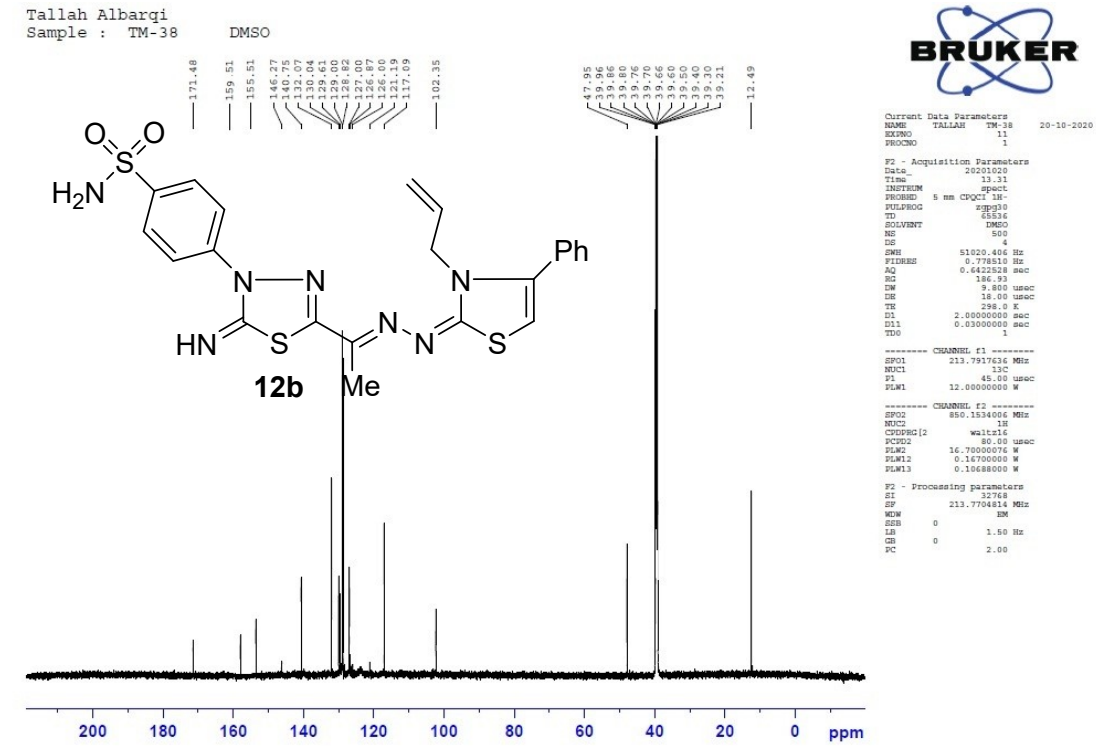


Figure S47. ^{13}C-NMR spectrum of compound **12b**.

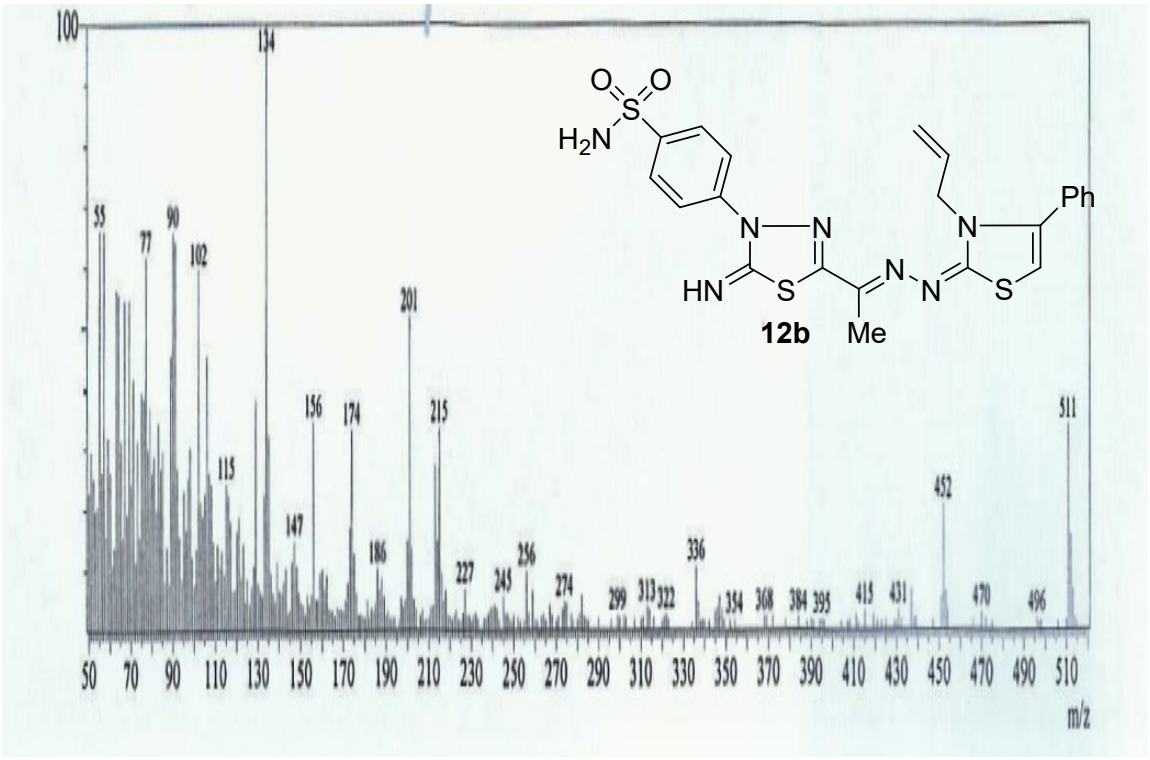


Figure S48. Mass spectrum of compound **12b.**

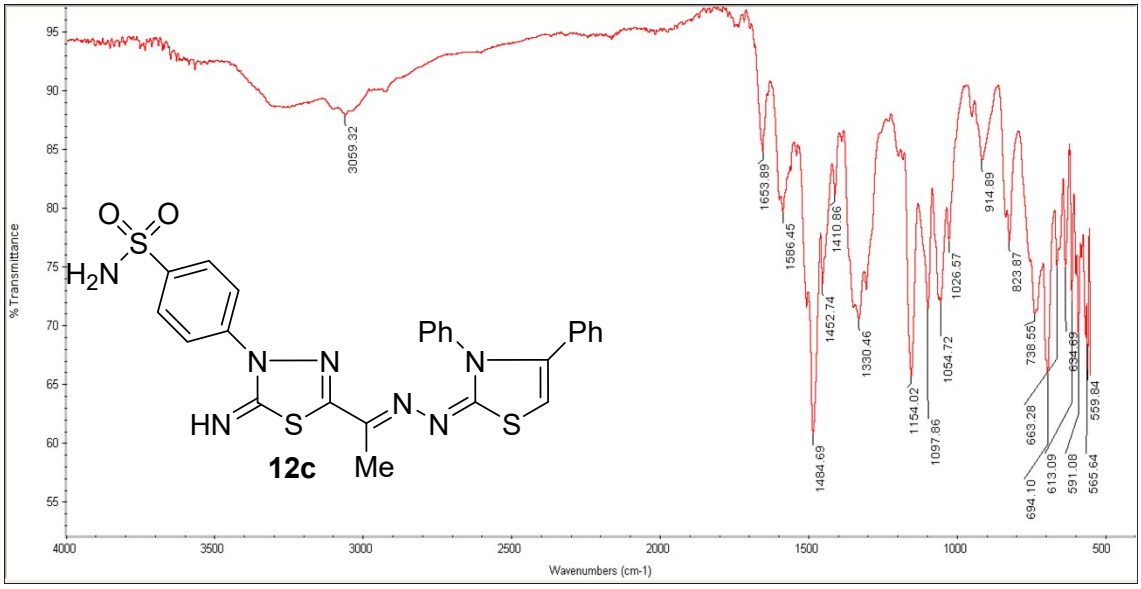


Figure S49. IR spectrum of compound **12c**.

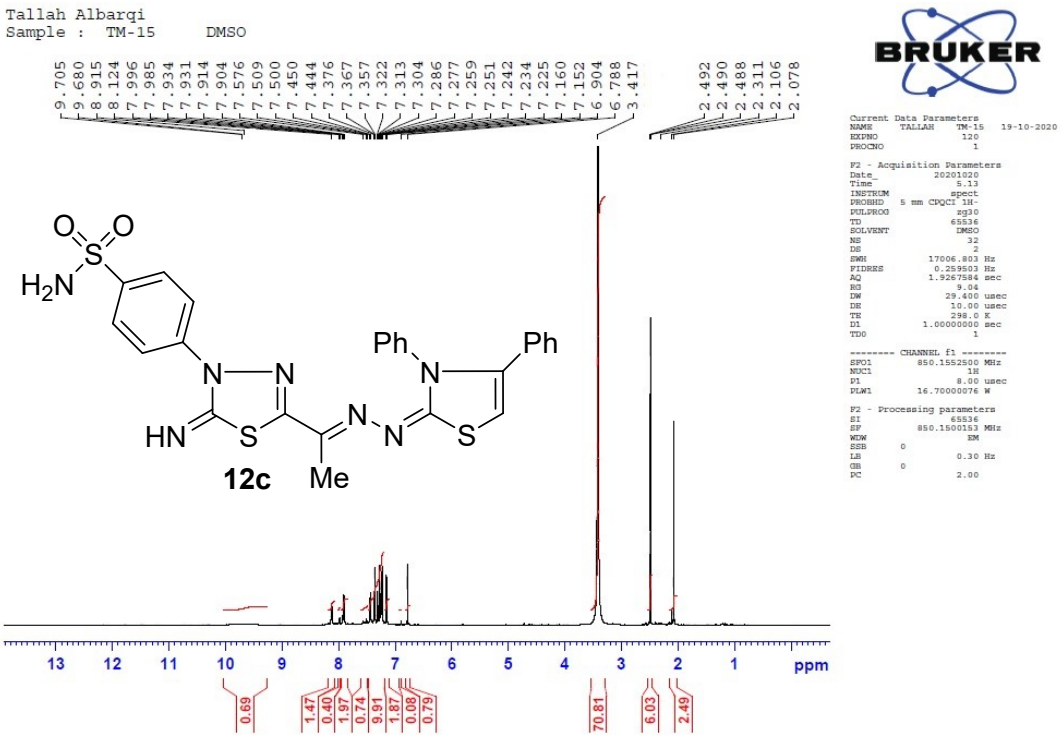


Figure S50. ^{1}H-NMR spectrum of compound **12c**.

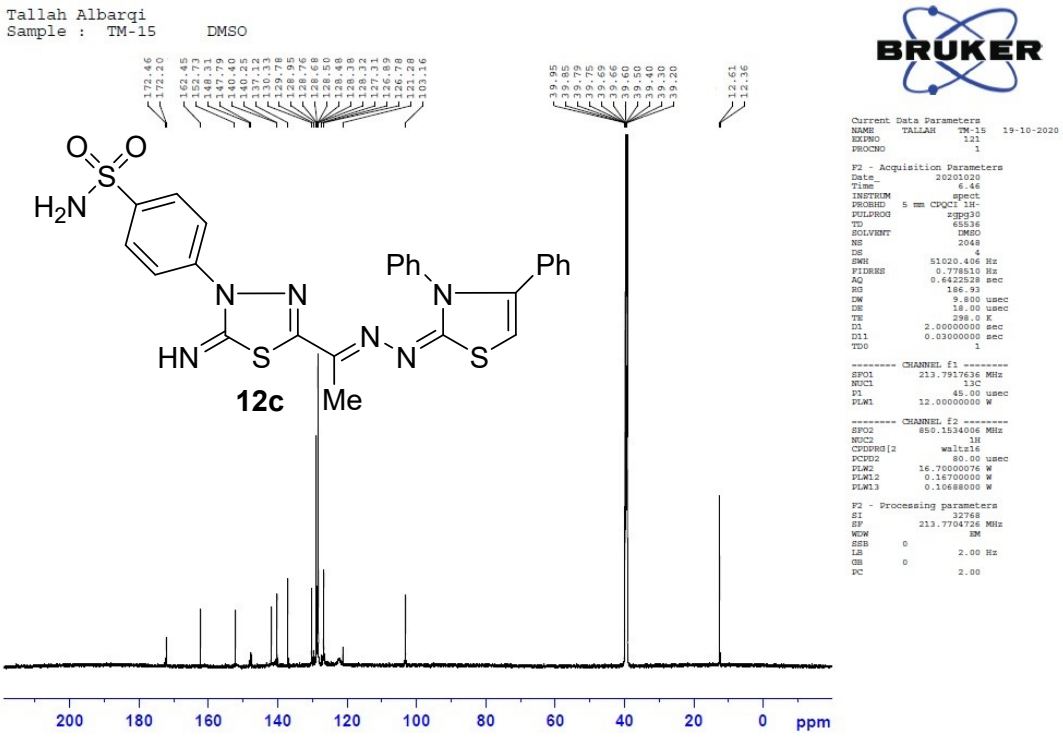


Figure S51. ^{13}C-NMR spectrum of compound **12c**.

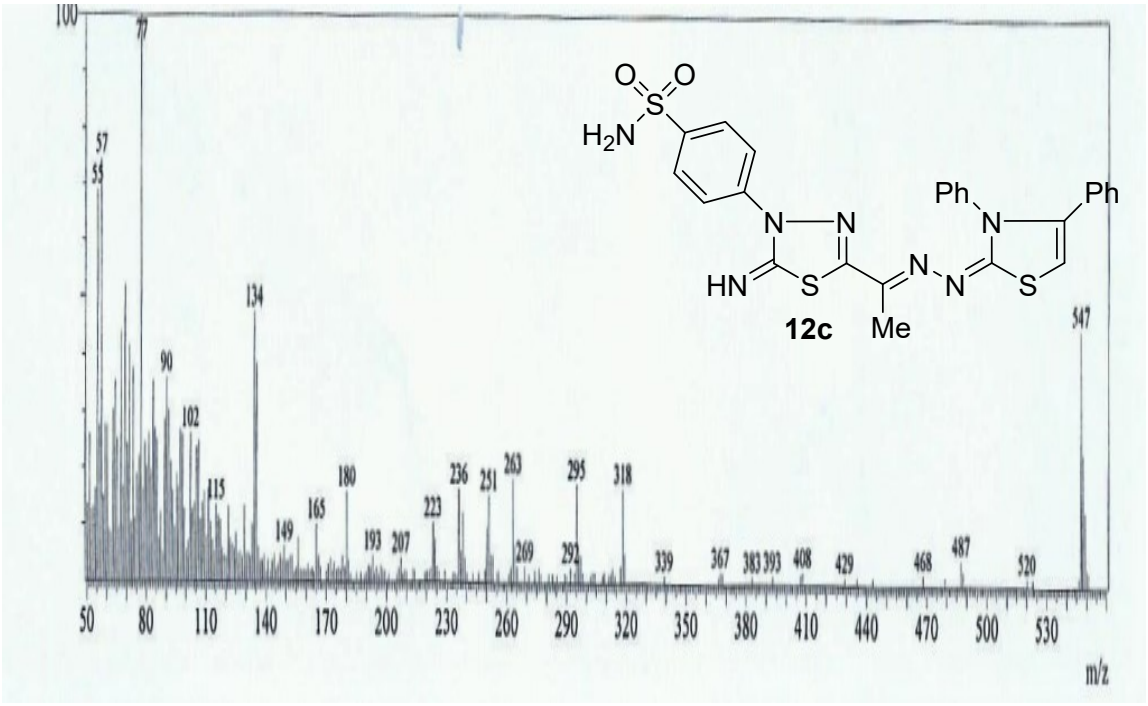


Figure S52. Mass spectrum of compound **12c.**

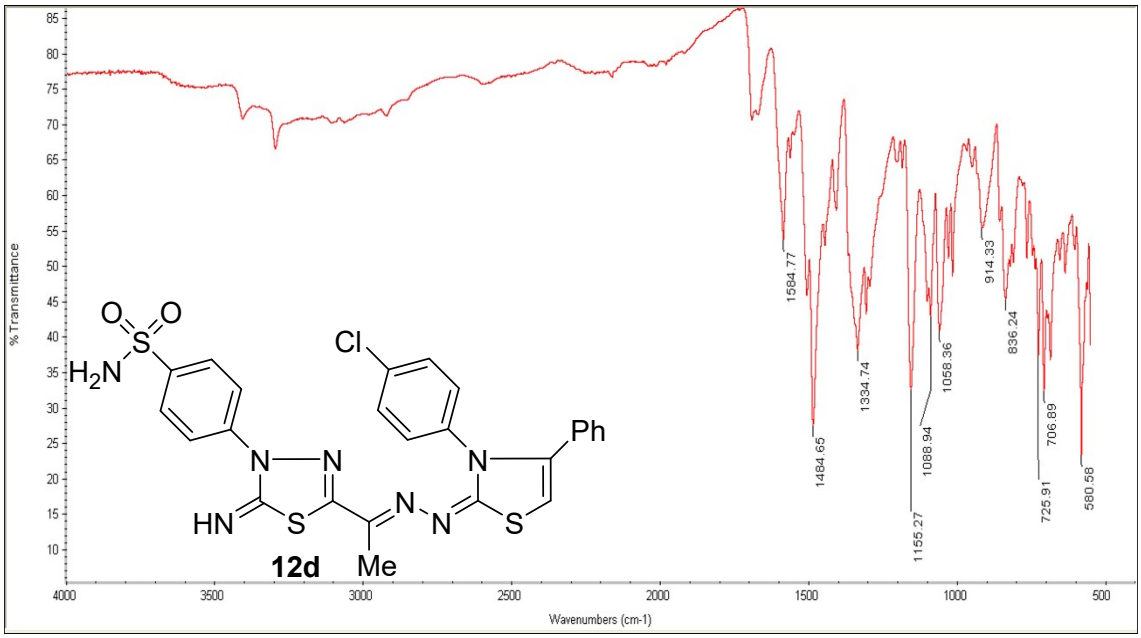


Figure S53. IR spectrum of compound **12d**.

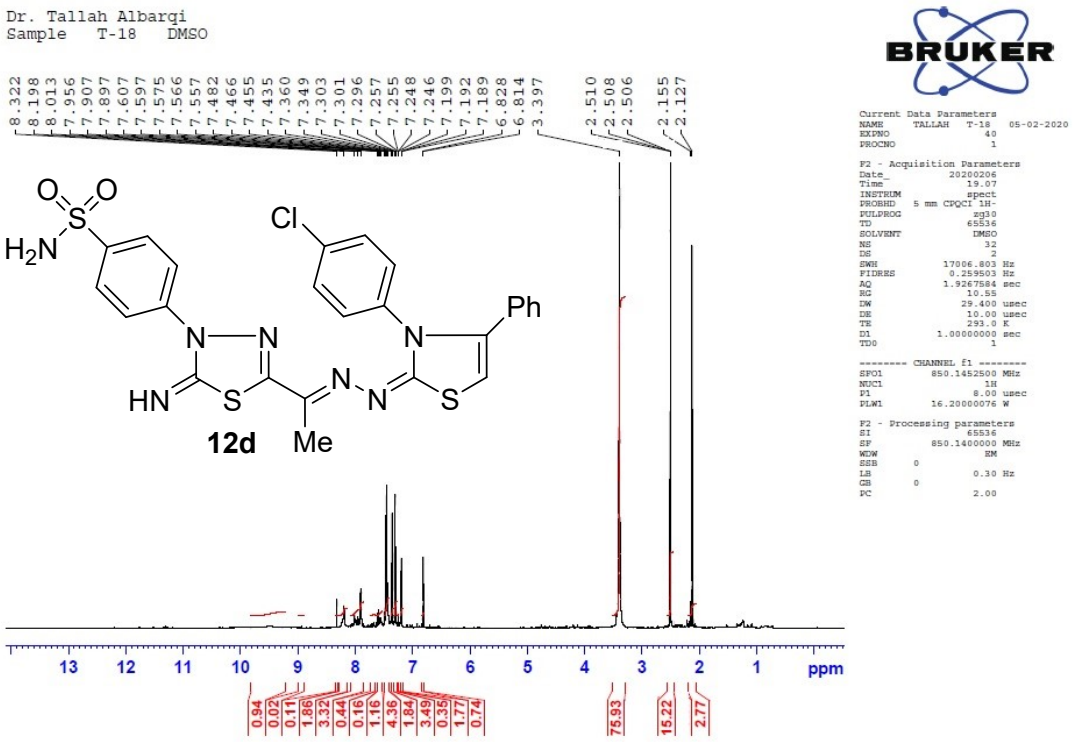


Figure S54. [1]H-NMR spectrum of compound **12d**.

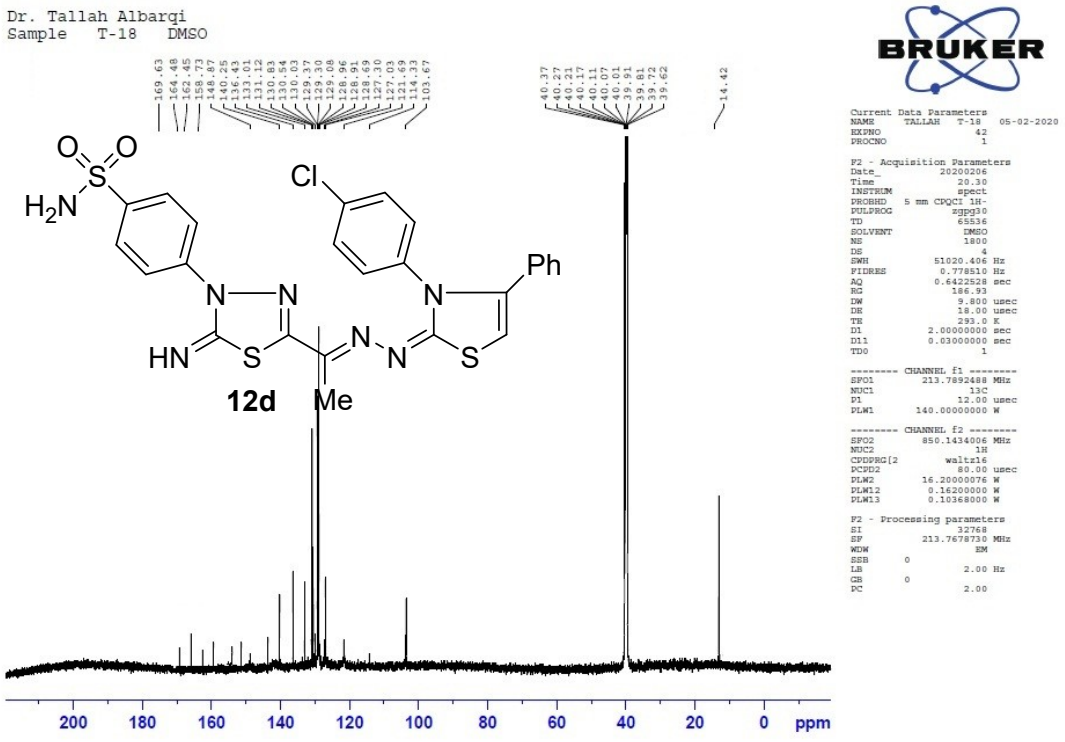


Figure S55. [13]C-NMR spectrum of compound **12d**.

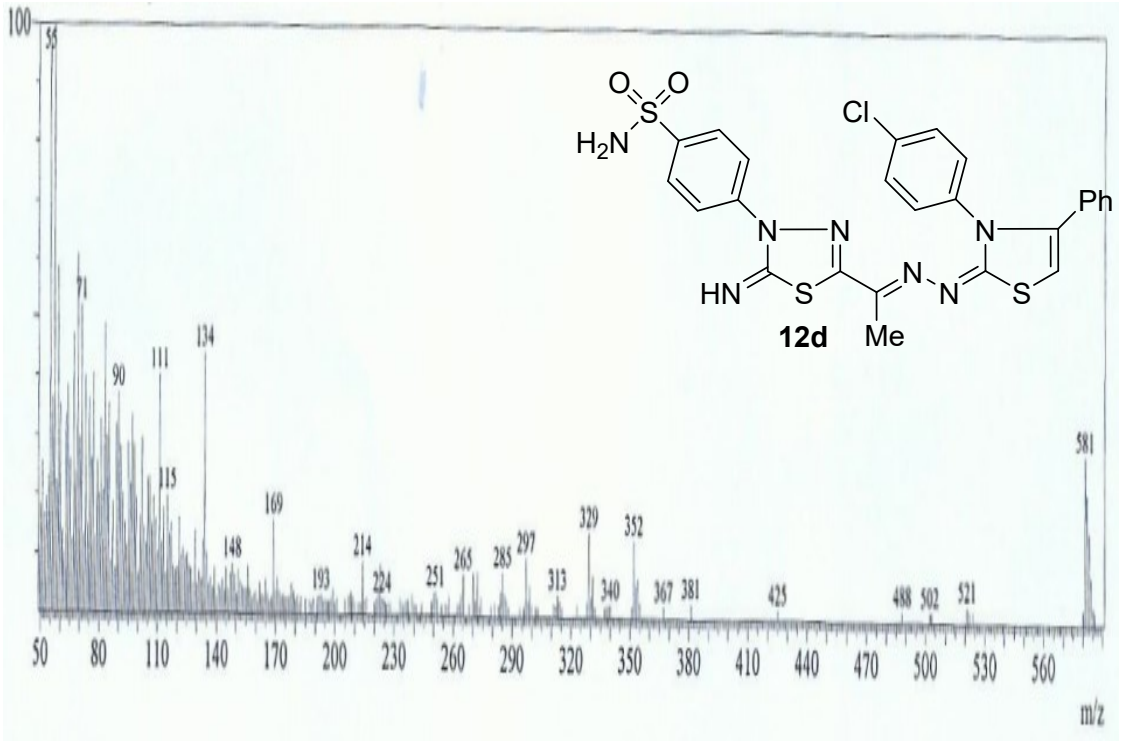
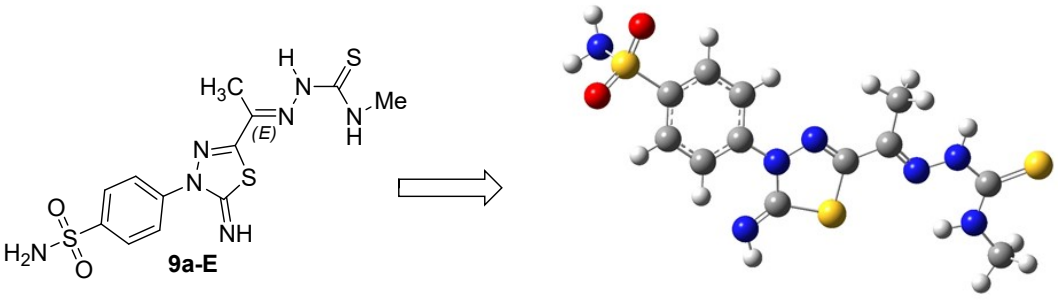
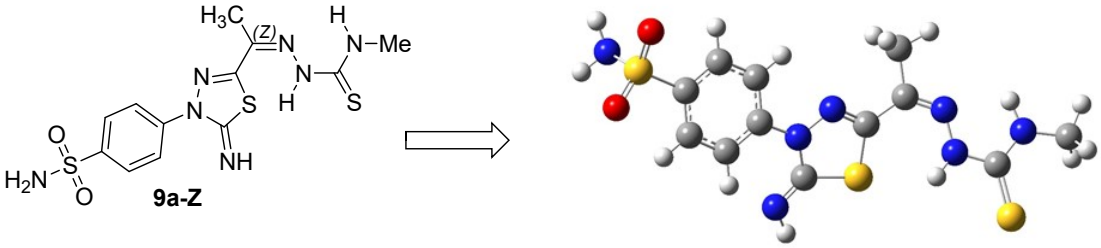


Figure S56. Mass spectrum of compound **12d.**



9a-E
HF= - 2194.475905 Hartree



9a-Z
HF= -2194.465113 Hartree

Figure S57. Optimized geometries for the proposed configurations of compound **9a** obtained from B3LYP/6-31G(d) calculations.

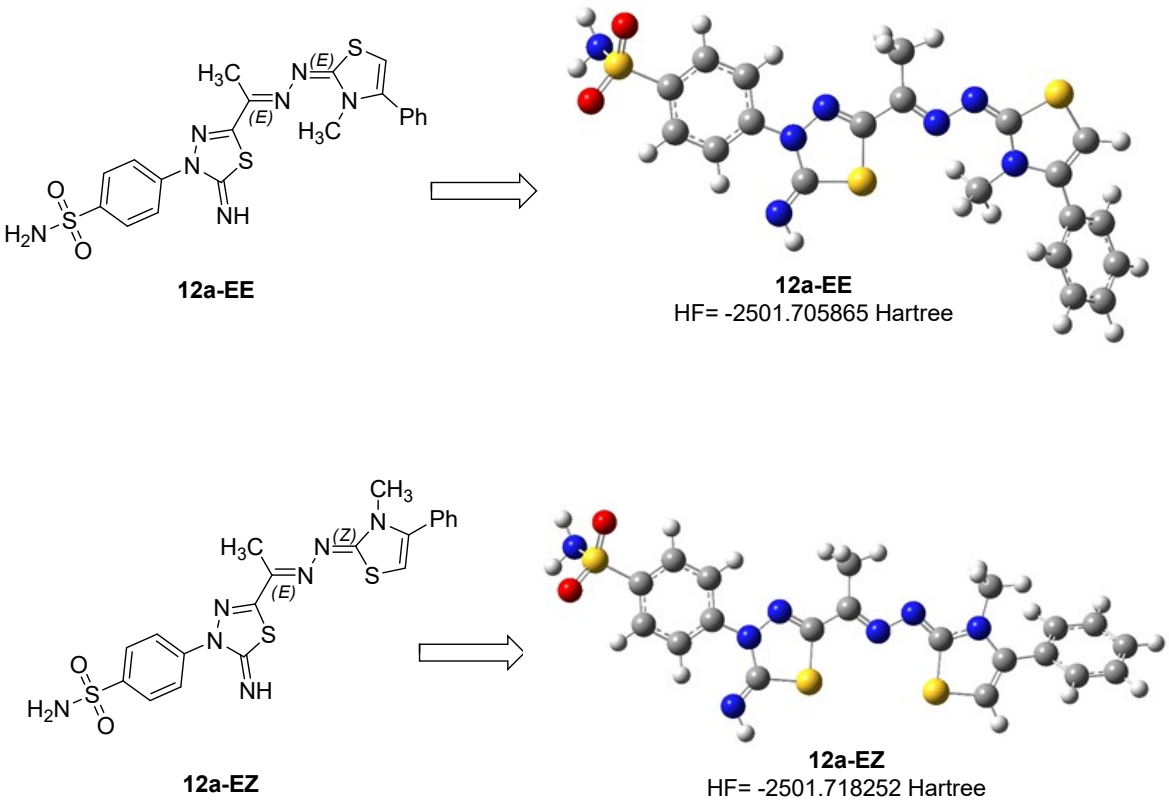


Figure S58. Optimized geometries for the proposed configurations of compound **12a** obtained from B3LYP/6-31G(d) calculations.

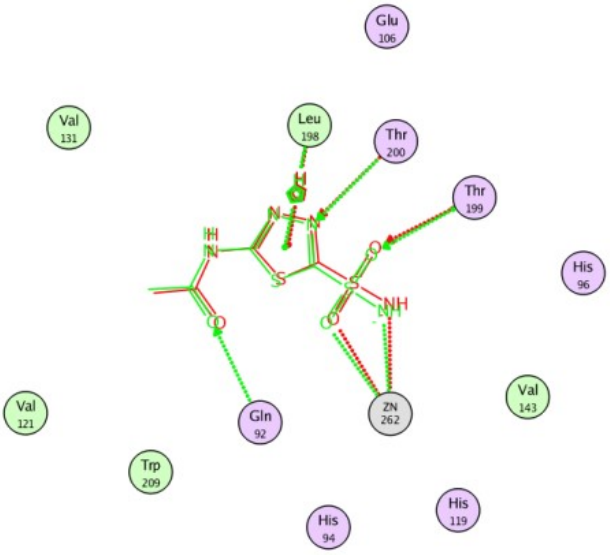


Figure S59. The superimposed orientations of the re-docked **AAZ** during validation protocol of molecular docking of hCAIX using PDB: 3IAI, RMSD =0.374 Å.

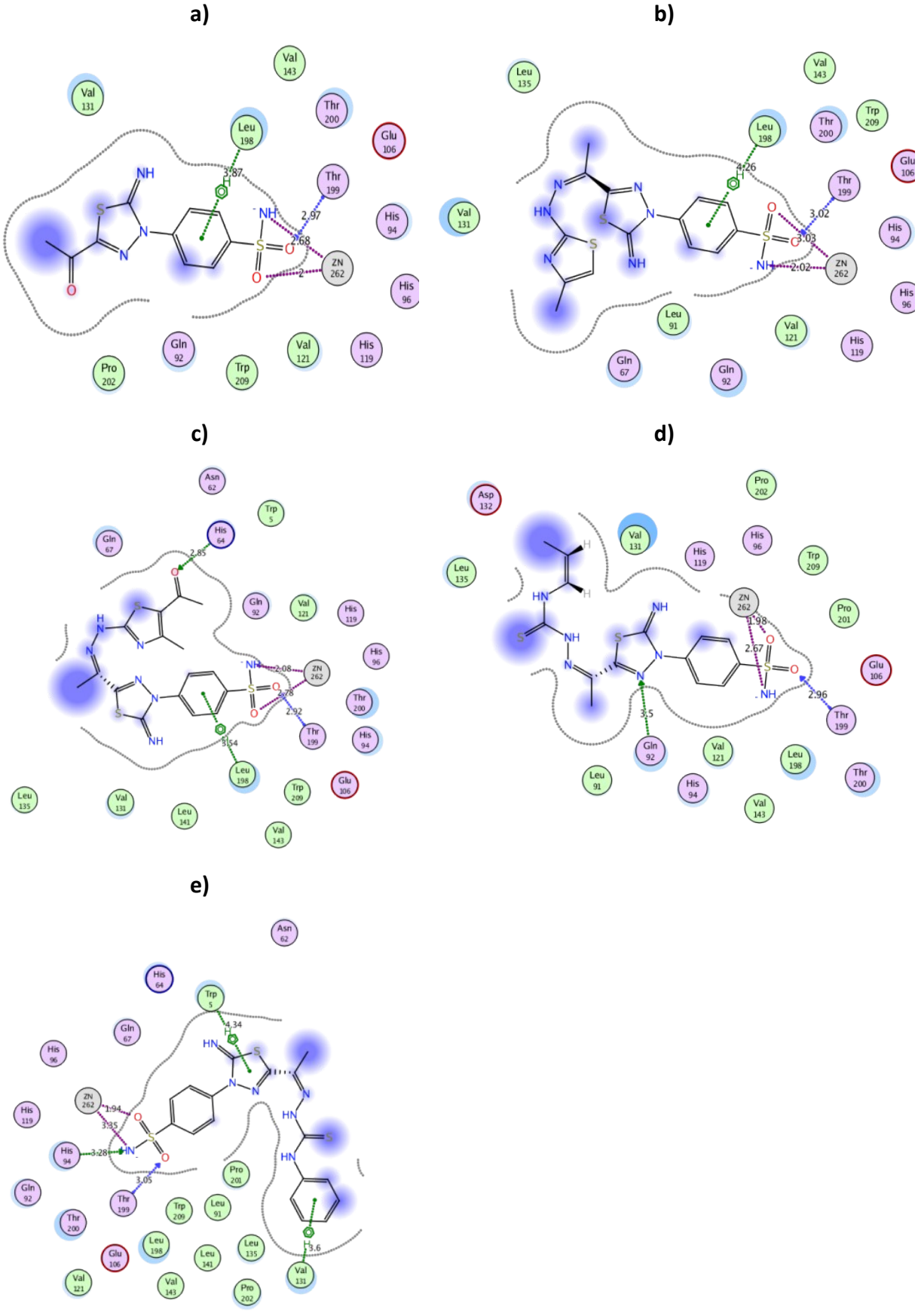


Figure S60. The 2D interaction of derivatives **1** (a), **5** (b), **6** (c), **9b** (d), and **9c** (e) using hCAIX (PDB 3IAI, 2.20 Å with their corresponding bond length in Å.

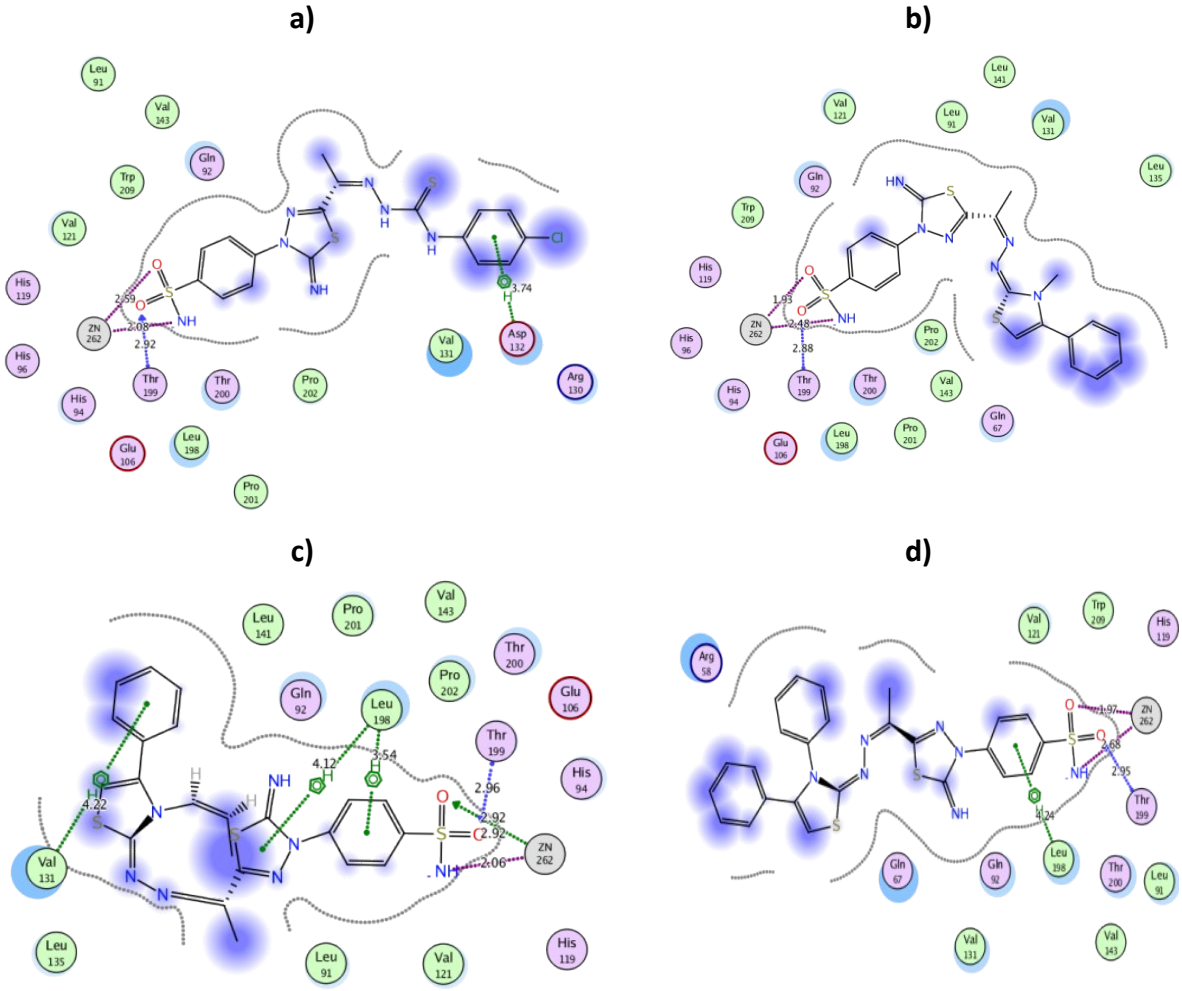


Figure S61. The 2D interaction of derivatives **9d** (a), **12a** (b), **12b** (c), and **12c** (d) using hCAIX (PDB 3IAI, 2.20 Å with their corresponding bond length in Å.

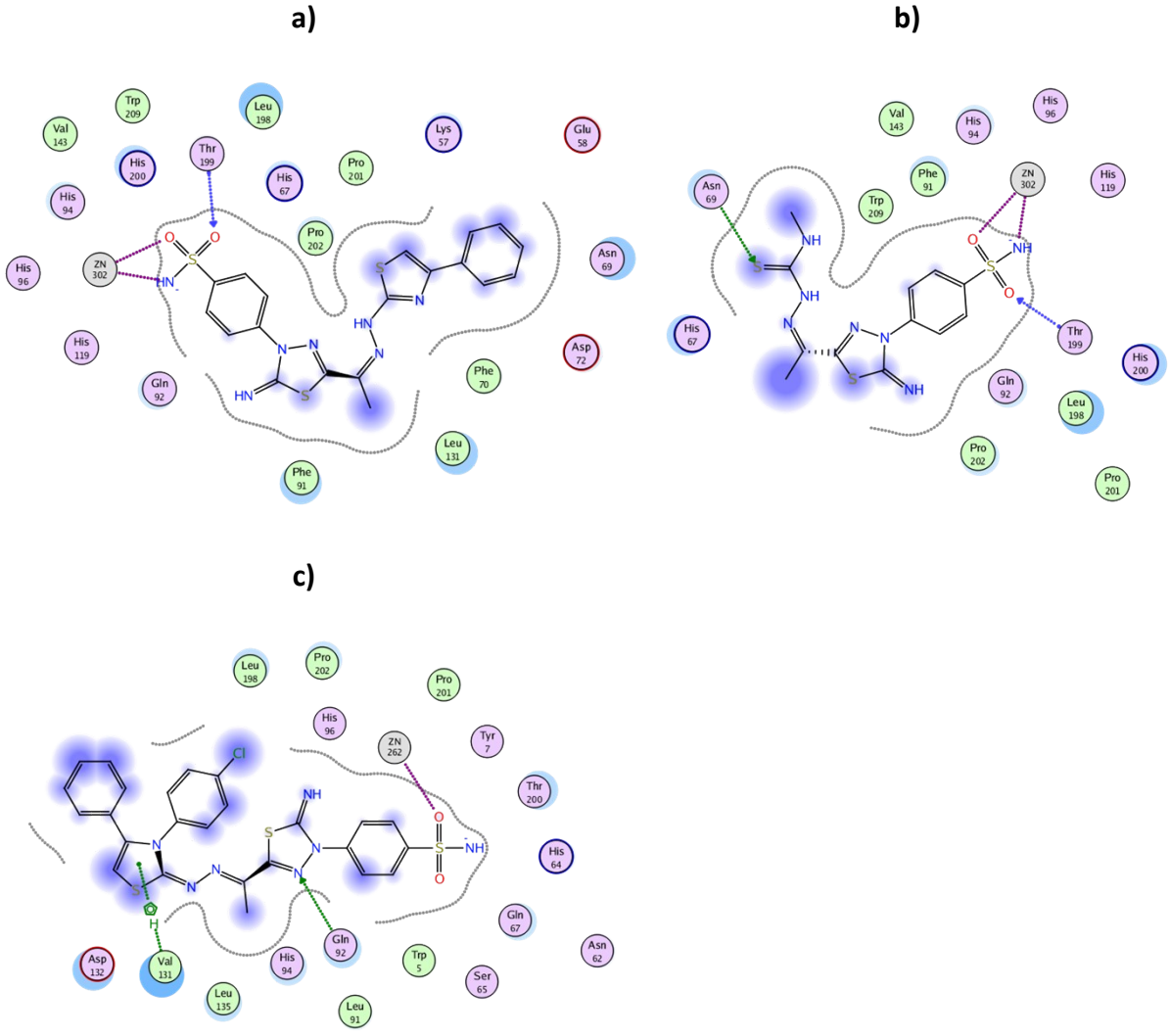


Figure S62. The 2D interaction of **4, 9a** and **12d** using hCAI (PDB:3W6H, 2.96 Å).

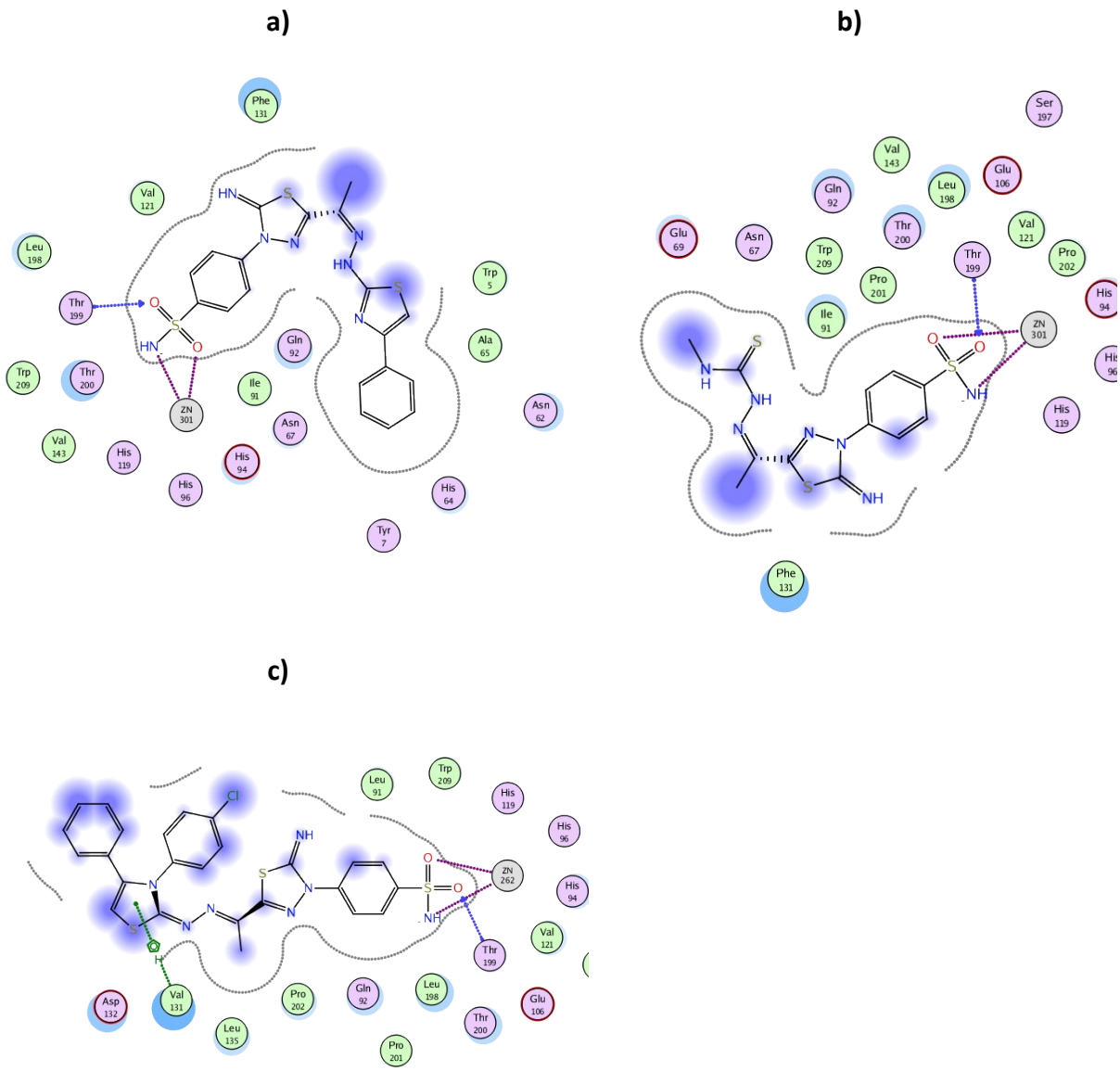


Figure S61. The 2D interaction of **4, 9a** and **12d** using hCAII (PDB:3SH4, 1.10 Å).

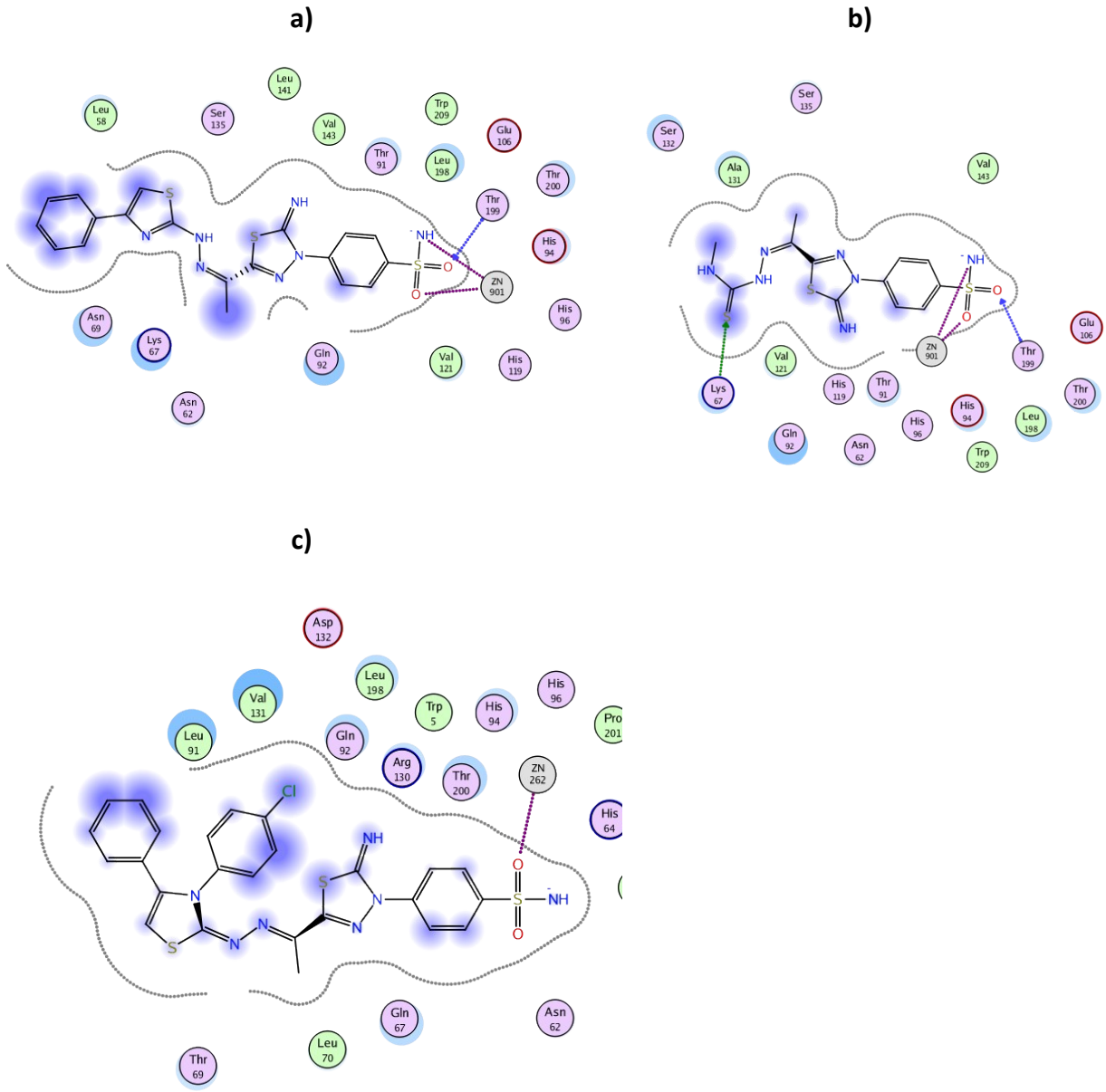


Figure S62. The 2D interaction of **4, 9a** and **12d** using hCAXII (PDB:1JD0, 1.50 Å).

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