

## Supplementary Data

### **Novel asymmetrical azines appending 1,3,4-thiadiazole sulfonamide: Synthesis, molecular structure analyses, *in silico* ADME, and cytotoxic effect**

Samir Bondock\*<sup>a,b</sup>, Tallah Albarqi<sup>a</sup>, Ibrahim A. Shaaban<sup>a,c</sup>, Moaz M. Abdou<sup>d</sup>

<sup>a</sup>Chemistry Department, Faculty of Science, King Khalid University, 9004 Abha, Saudi Arabia

<sup>b</sup>Chemistry Department, Faculty of Science, Mansoura University, 35516 Mansoura, Egypt

<sup>c</sup>Department of Chemistry, Faculty of Science (Men's Campus), Al-Azhar University, Nasr City  
11884, Cairo, Egypt

<sup>d</sup>Egyptian Petroleum Research Institute, Nasr City, 11727, Cairo, Egypt

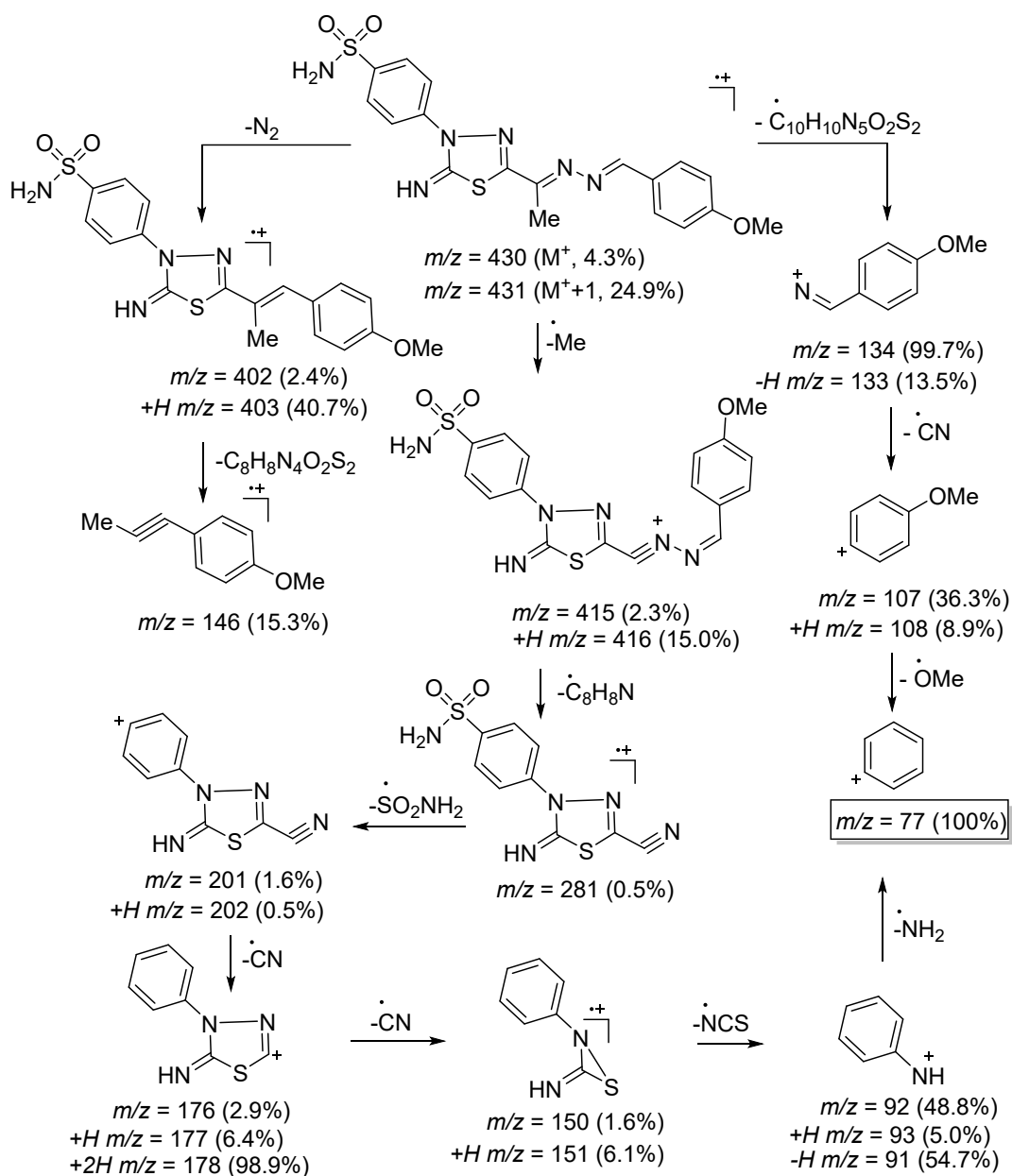
#### **Correspondence**

Samir Bondock, Chemistry Department, Faculty of Science, Mansoura University, 35516 Mansoura,  
Egypt.

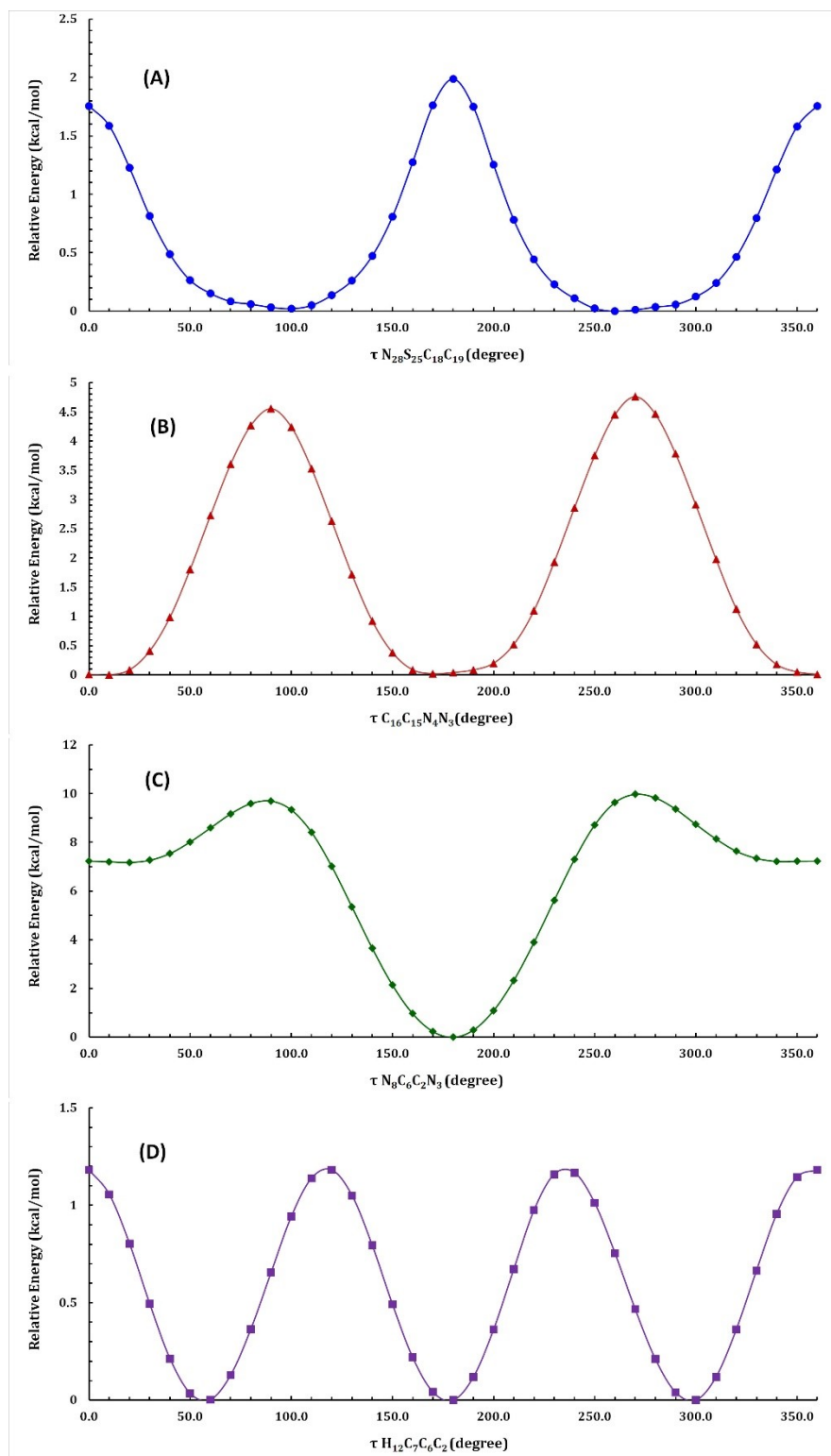
Email: [bondock@mans.edu.eg](mailto:bondock@mans.edu.eg)

## **1. Materials and instrumentation**

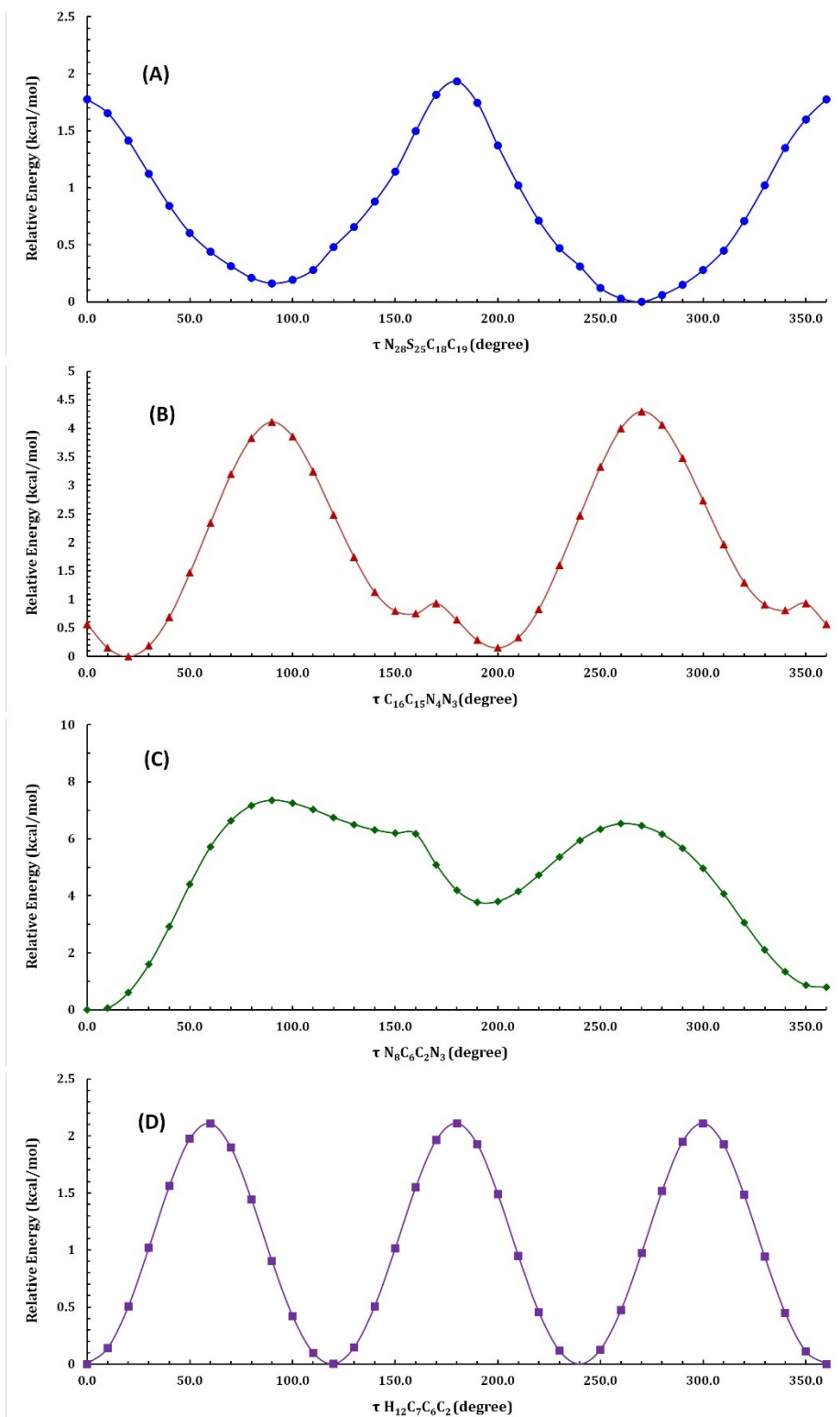
- 1) All melting points were determined on Stuart SMP11 apparatus and were uncorrected.
- 2) The IR spectra were recorded in KBr discs, on a Jasco FT/IR-460 plus spectrophotometer at College of Science, King Khalid University.
- 3) The  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were recorded in  $\text{DMSO-d}_6$  at 850 MHz on a BrukerAvanceAV-850 NMRUltrshield™ 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 carried out at the Micro Analytical Center, Cairo University, Giza, Egypt.
- 6) Screening of the synthesized compounds in vitro against three human cancer cell lines: hepatocellular carcinoma (HepG-2), colon cancer (Caco-2), breast cancer (MCF-7) and one normal lung fibroblast (WI-38). The cell lines were obtained from American Type Culture Collection (ATCC) by the Holding company for biological products and vaccines (VACSERA), Giza, Egypt.



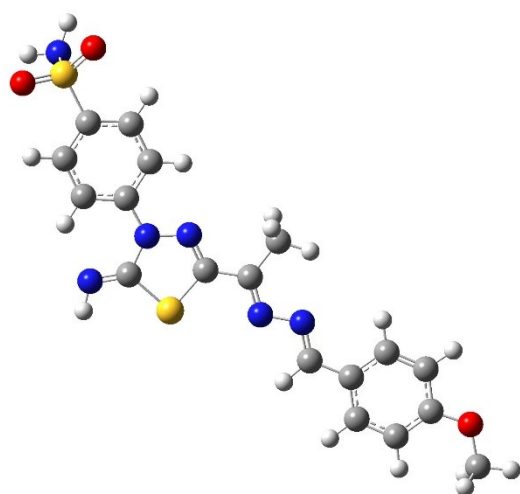
**Scheme 1.** Mass fragmentation pattern of compound **7a**.



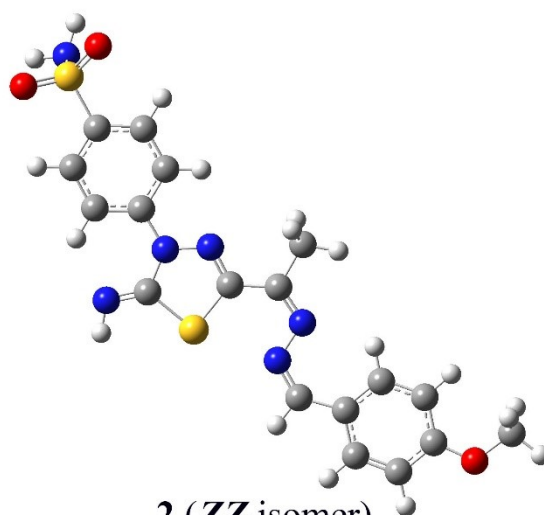
**Figure S1.** The computed PES for internal rotations in the E isomers of **5**; **(A)** sulfonamide moiety, **(B)** phenyl sulfonamide moiety, **(C)** C(CH<sub>3</sub>)NNH<sub>2</sub> moiety and **(D)** methyl moiety.



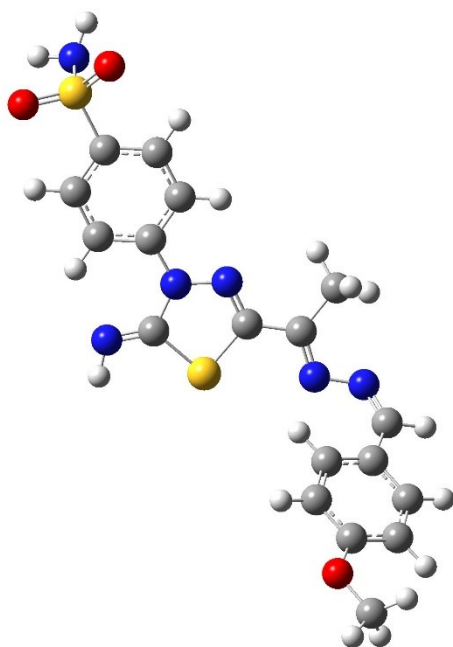
**Figure S2.** The computed PES for internal rotations in the Z isomers of **5**; **(A)** sulfonamide moiety, **(B)** phenyl sulfonamide moiety, **(C)**  $C(CH_3)NNH_2$  moiety and **(D)** methyl moiety.



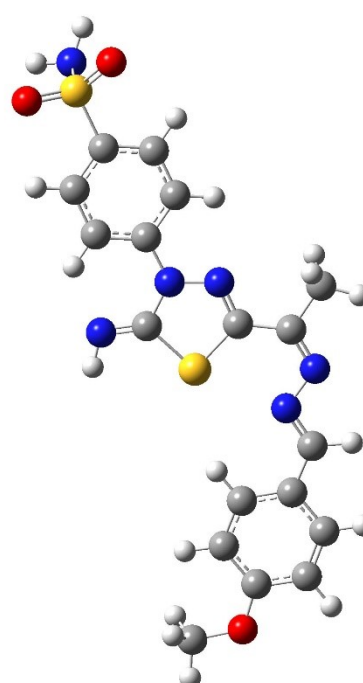
**1 (*EE* isomer)**  
HF= -2047.174609



**2 (*ZZ* isomer)**  
HF= -2047.166237

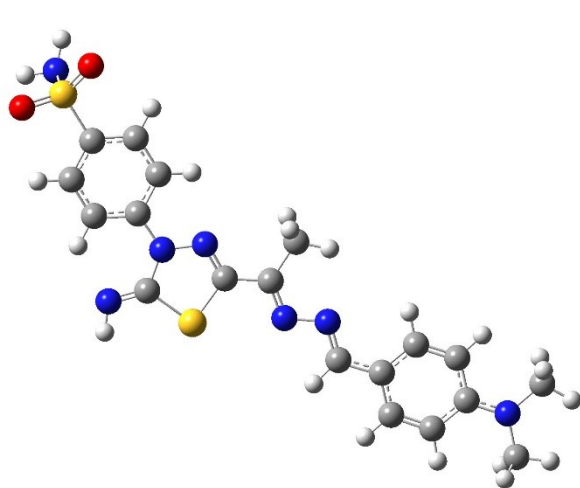


**3 (*EZ* isomer)**  
HF= -2047.168535

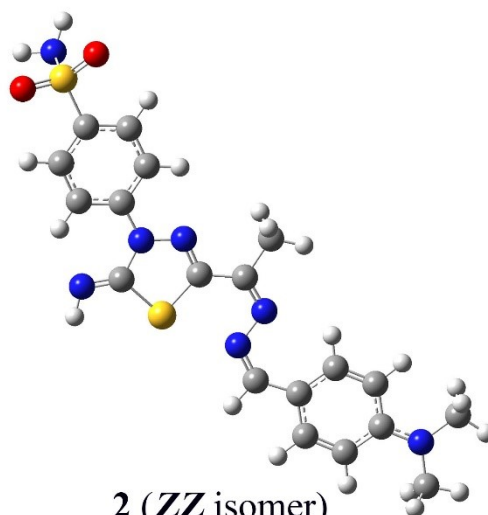


**4 (*ZE* isomer)**  
HF= -2047.171529

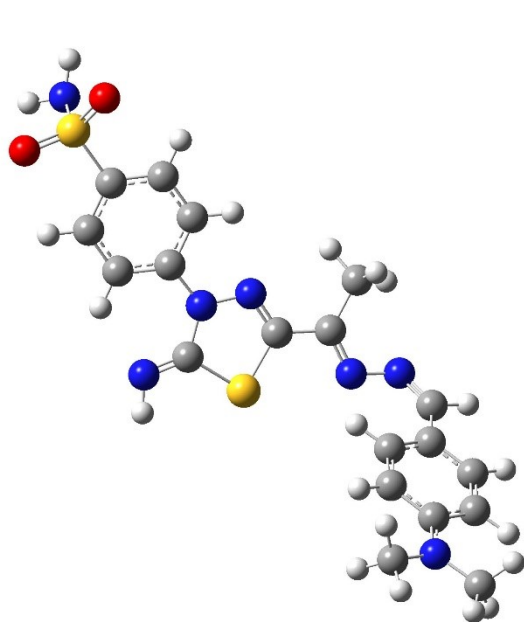
**Figure S3.** Optimized geometries for the proposed configurations of compound **7a** obtained from B3LYP/6-31G(d) calculations.



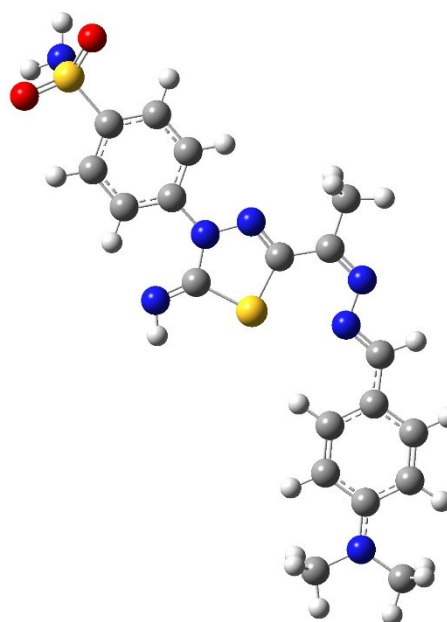
**1** (*EE* isomer)  
HF= -2066.621509



**2** (*ZZ* isomer)  
HF= -2066.613383

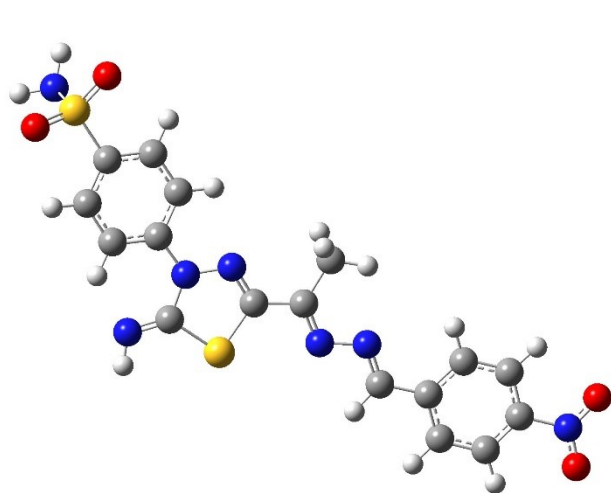


**3** (*EZ* isomer)  
HF= -2066.615461

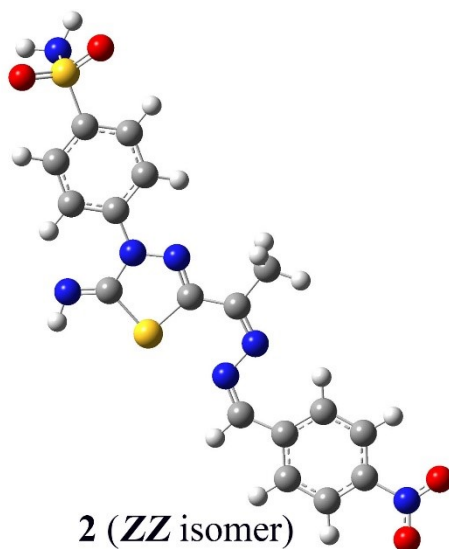


**4** (*ZE* isomer)  
HF= -2066.618754

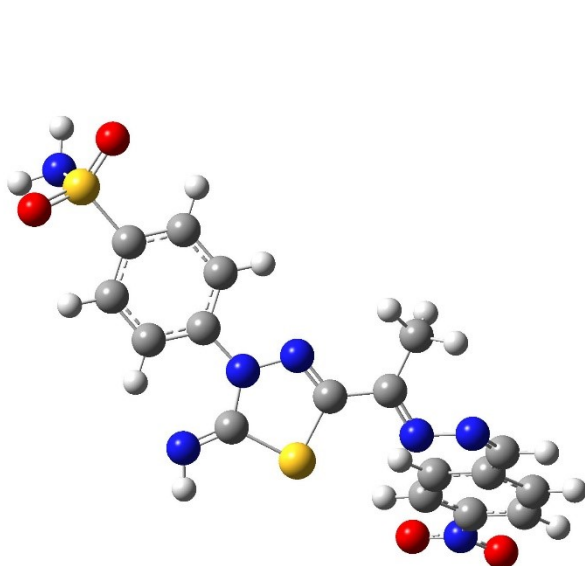
**Figure S4.** Optimized geometries for the proposed configurations of compound **7b** obtained from B3LYP/6-31G(d) calculations.



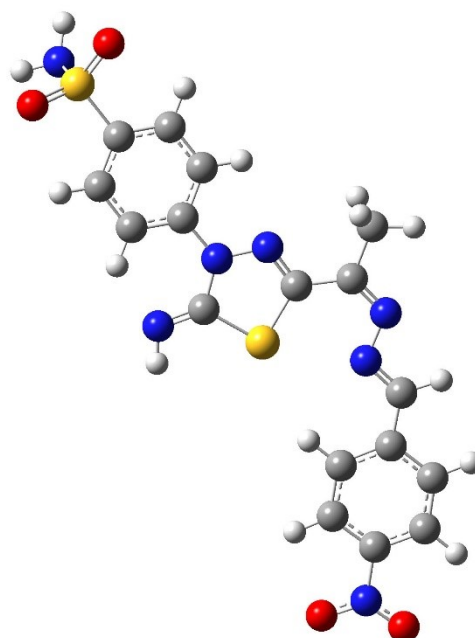
**1 (*EE* isomer)**  
HF= -2137.148645



**2 (*ZZ* isomer)**  
HF= -2137.139759



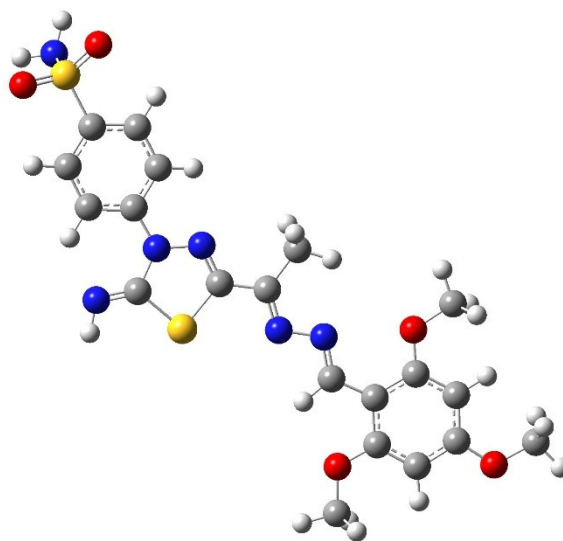
**3 (*EZ* isomer)**  
HF= -2137.142714



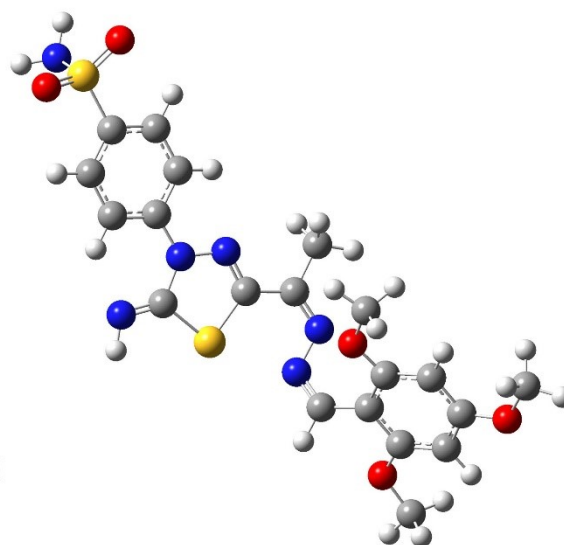
**4 (*ZE* isomer)**  
HF= -2137.145381

**Figure S5.** Optimized geometries for the proposed configurations of compound **7c** obtained from B3LYP/6-31G(d) calculations.

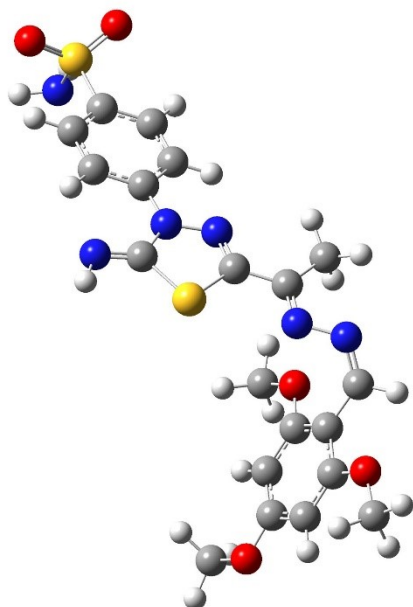




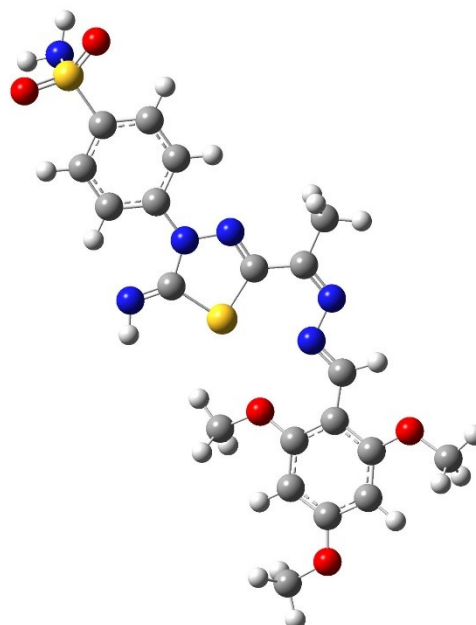
**1 (*EE* isomer)**  
HF= -2276.213429



**2 (*ZZ* isomer)**  
HF= -2276.204309

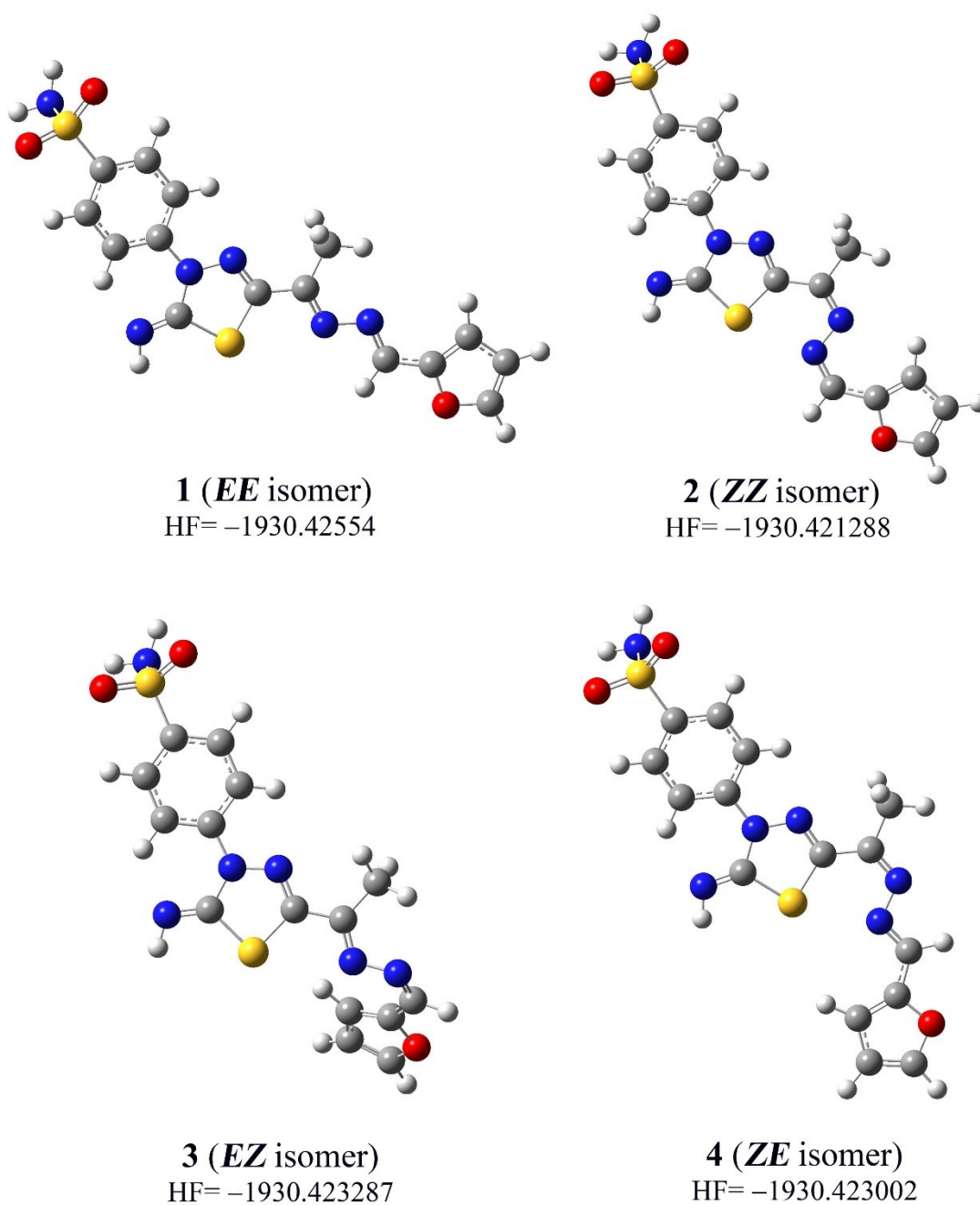


**3 (*EZ* isomer)**  
HF= -2276.207865

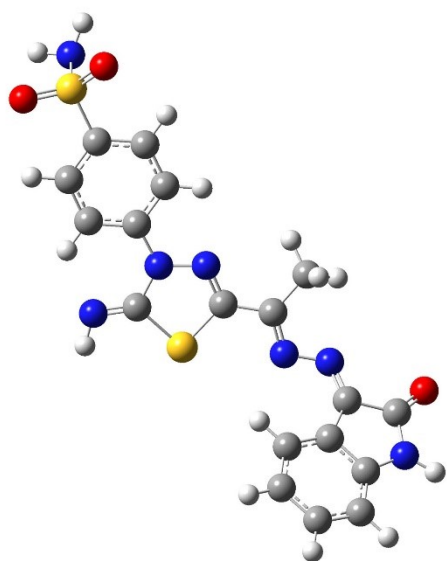


**4 (*ZE* isomer)**  
HF= -2276.210618

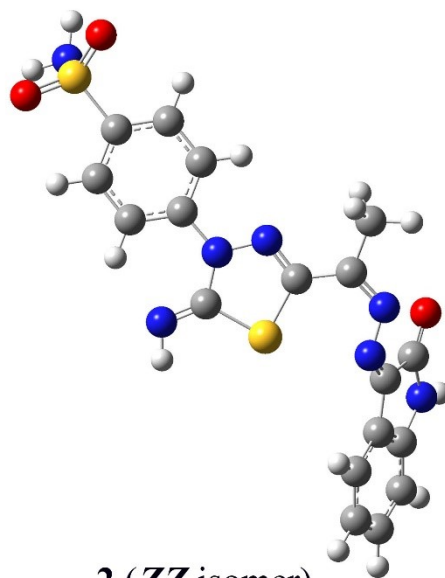
**Figure S6.** Optimized geometries for the proposed configurations of compound **9** obtained from B3LYP/6-31G(d) calculations.



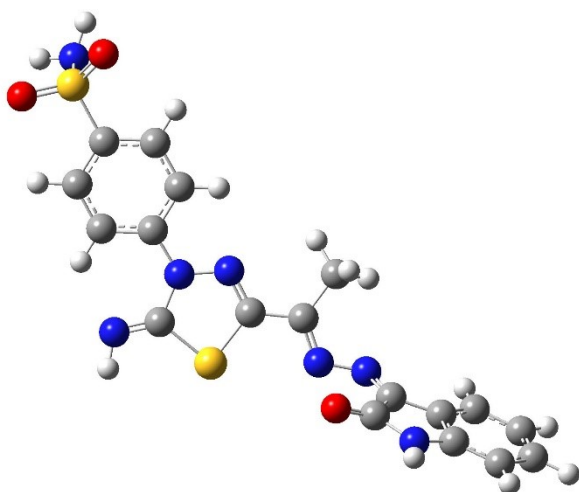
**Figure S7.** Optimized geometries for the proposed configurations of compound **11** obtained from B3LYP/6-31G(d) calculations.



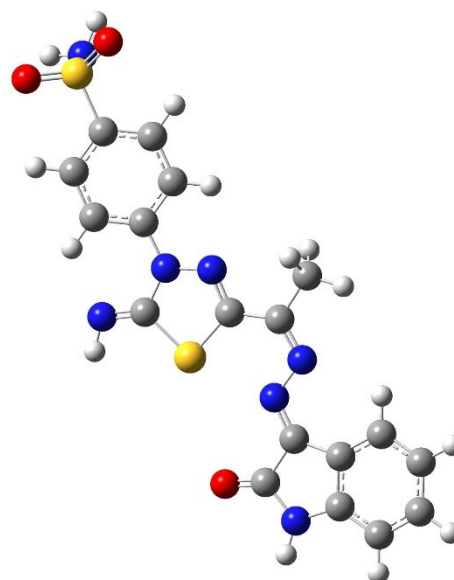
**1 (*EE* isomer)**  
HF= -2100.141412



**2 (*ZZ* isomer)**  
HF= -2100.136203

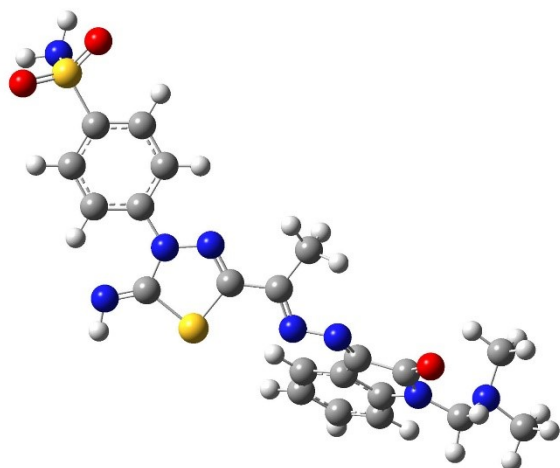


**3 (*EZ* isomer)**  
HF= -2100.140941

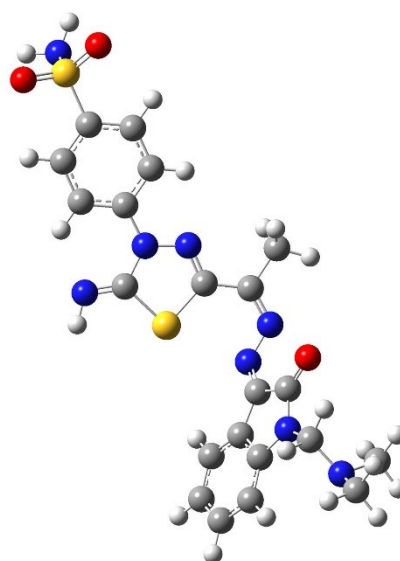


**4 (*ZE* isomer)**  
HF= -2100.140155

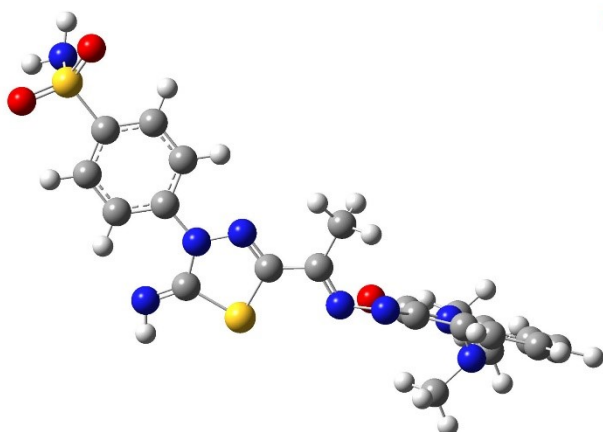
**Figure S8.** Optimized geometries for the proposed configurations of compound **13** obtained from B3LYP/6-31G(d) calculations.



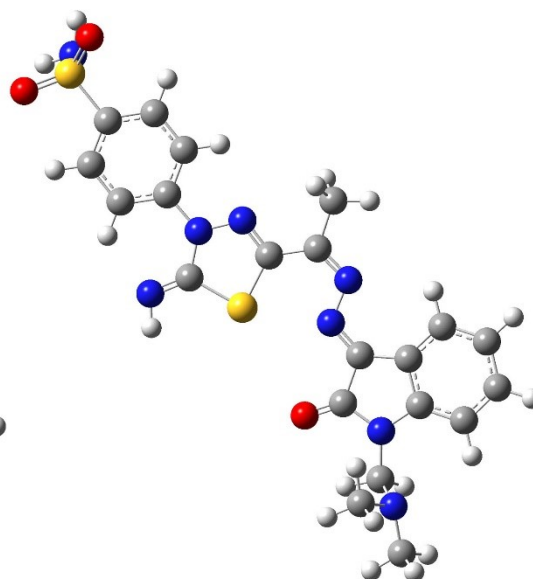
**1 (*EE* isomer)**  
HF= -2273.419471



**2 (*ZZ* isomer)**  
HF= -2273.414291

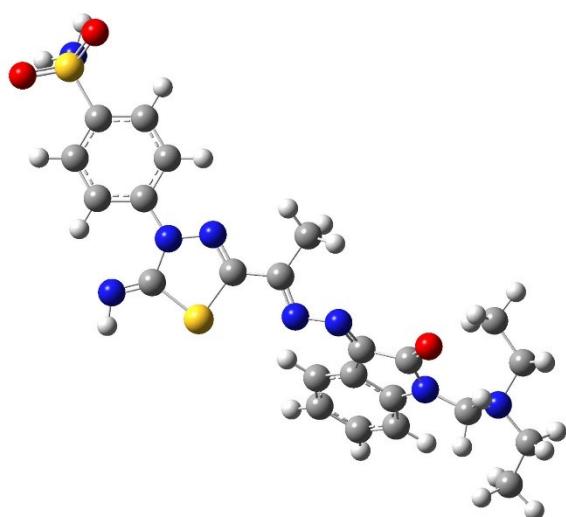


**3 (*EZ* isomer)**  
HF= -2273.419083

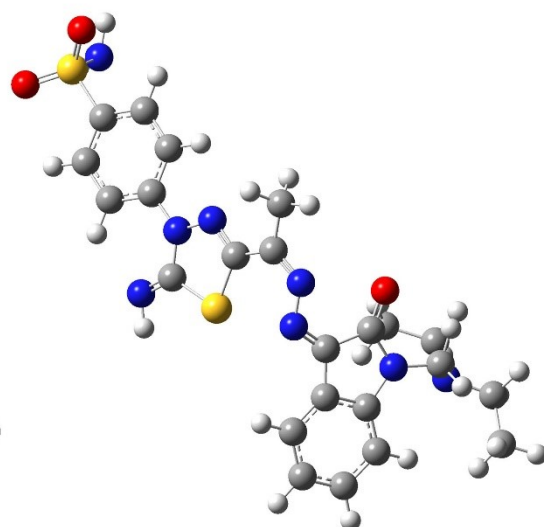


**4 (*ZE* isomer)**  
HF= -2273.41831

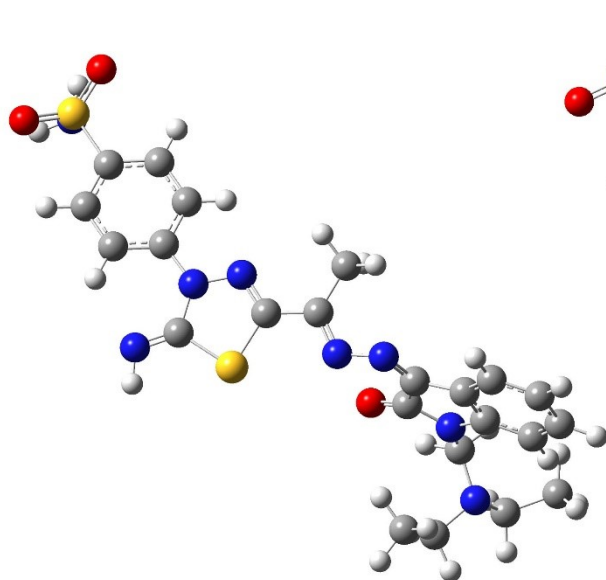
**Figure S9.** Optimized geometries for the proposed configurations of compound **15a** obtained from B3LYP/6-31G(d) calculations.



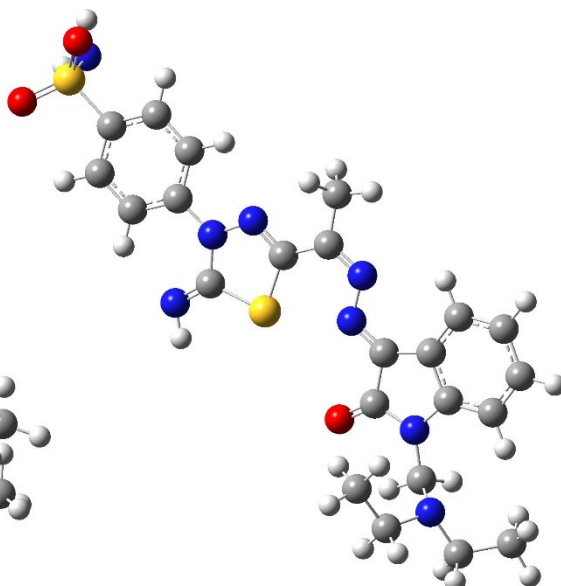
**1 (*EE* isomer)**  
HF= -2352.04409



**2 (*ZZ* isomer)**  
HF= -2352.038863

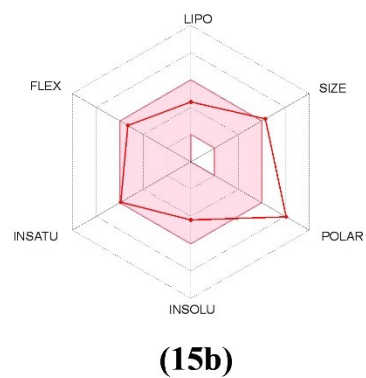
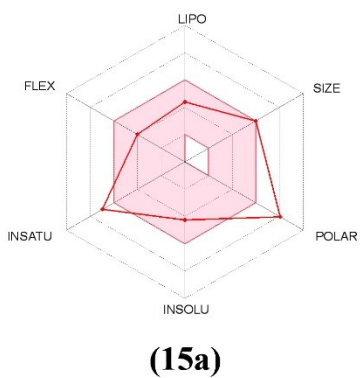
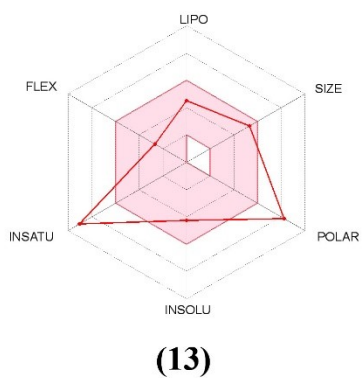
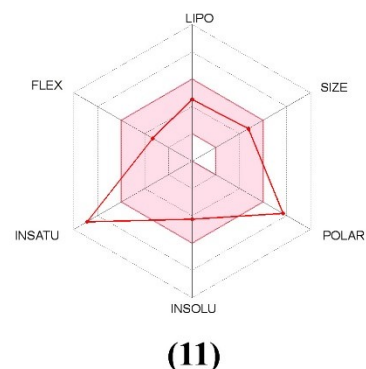
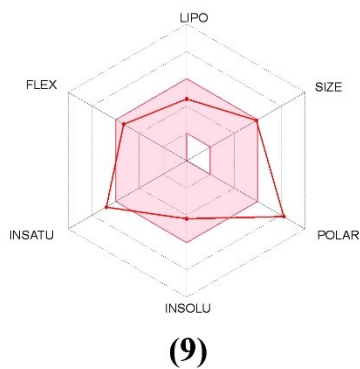
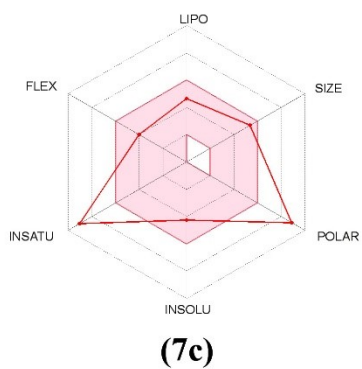
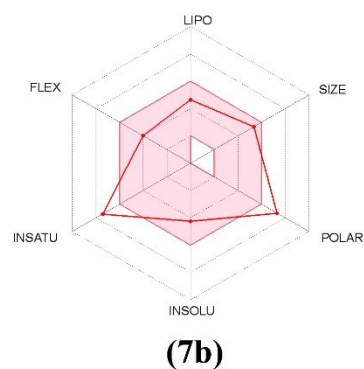
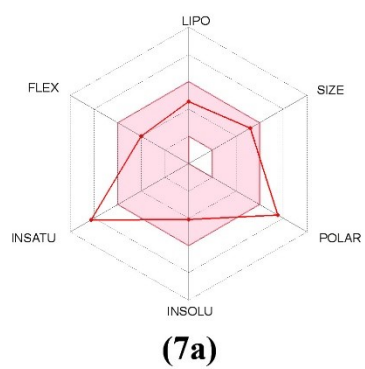


**3 (*EZ* isomer)**  
HF= -2352.043659



**4 (*ZE* isomer)**  
HF= -2352.042893

**Figure S10.** Optimized geometries for the proposed configurations of compound **15b** obtained from B3LYP/6-31G(d) calculations.



**Figure S11.** Swiss ADME's bioavailability radar of the synthesized compounds.

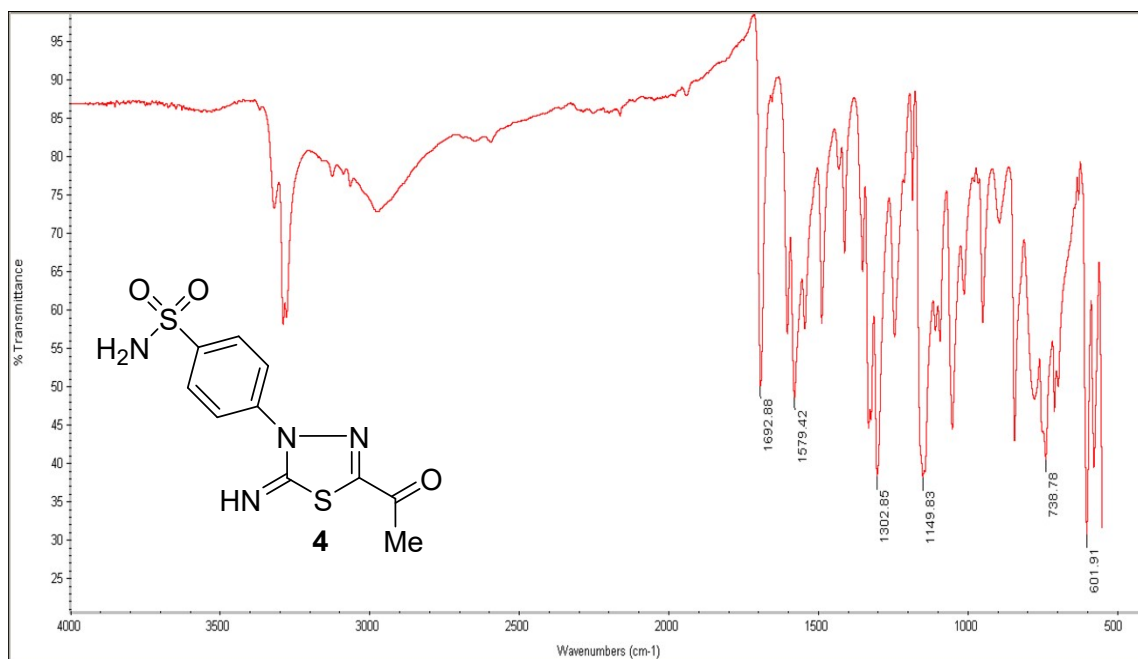


Figure S12. IR spectrum of compound 4

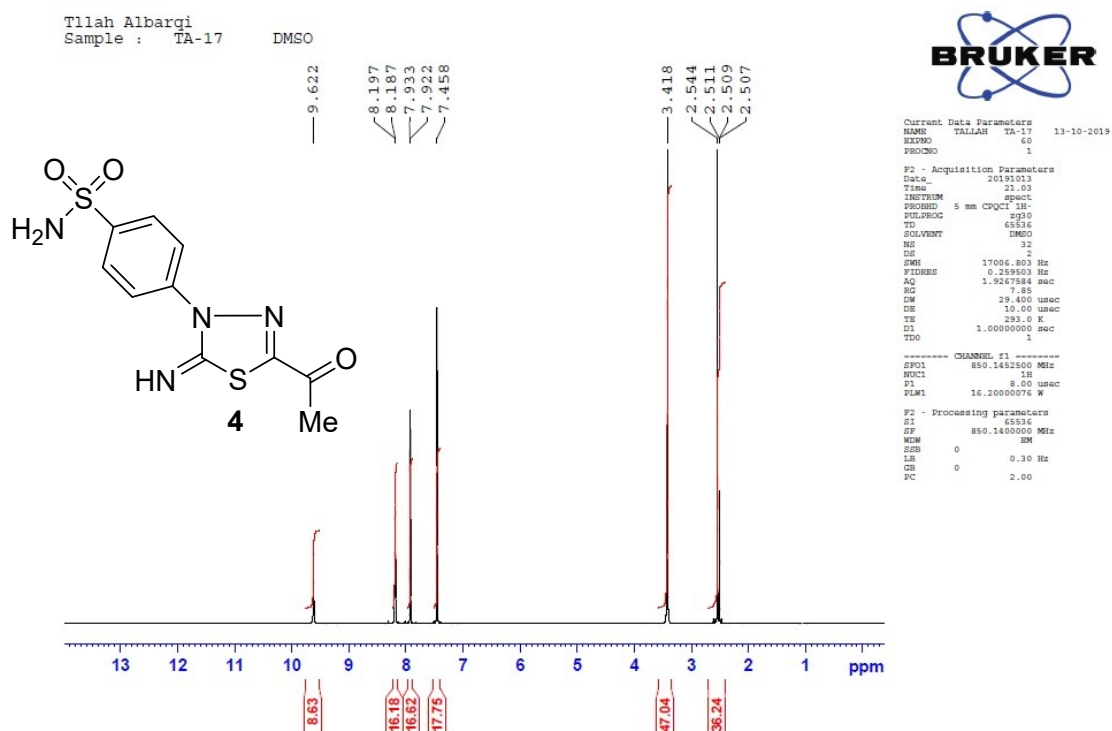


Figure S13. <sup>1</sup>H-NMR spectrum of compound 4.

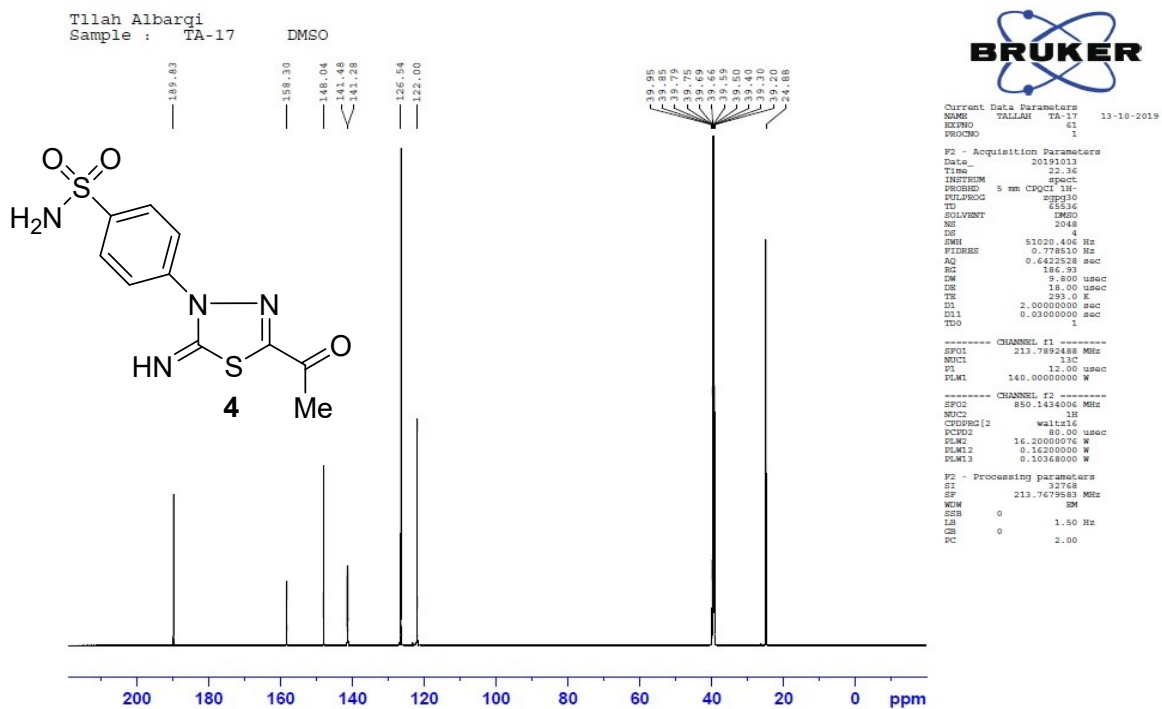


Figure S14.  $^{13}\text{C}$ -NMR spectrum of compound 4.

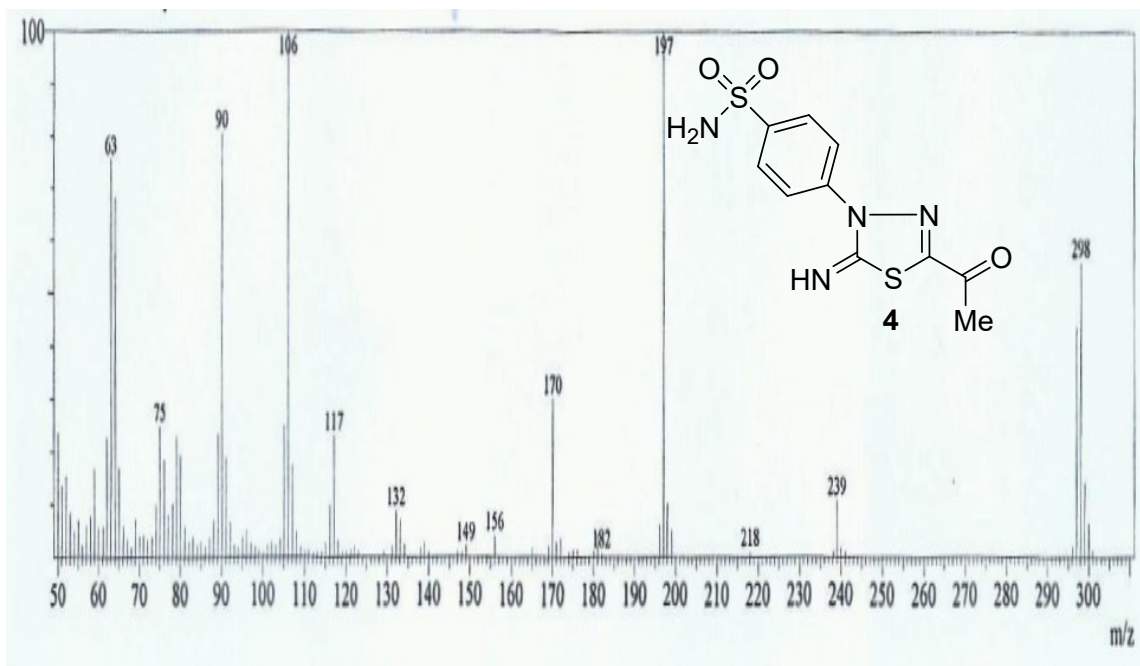


Figure S15. Mass spectrum of compound 4.



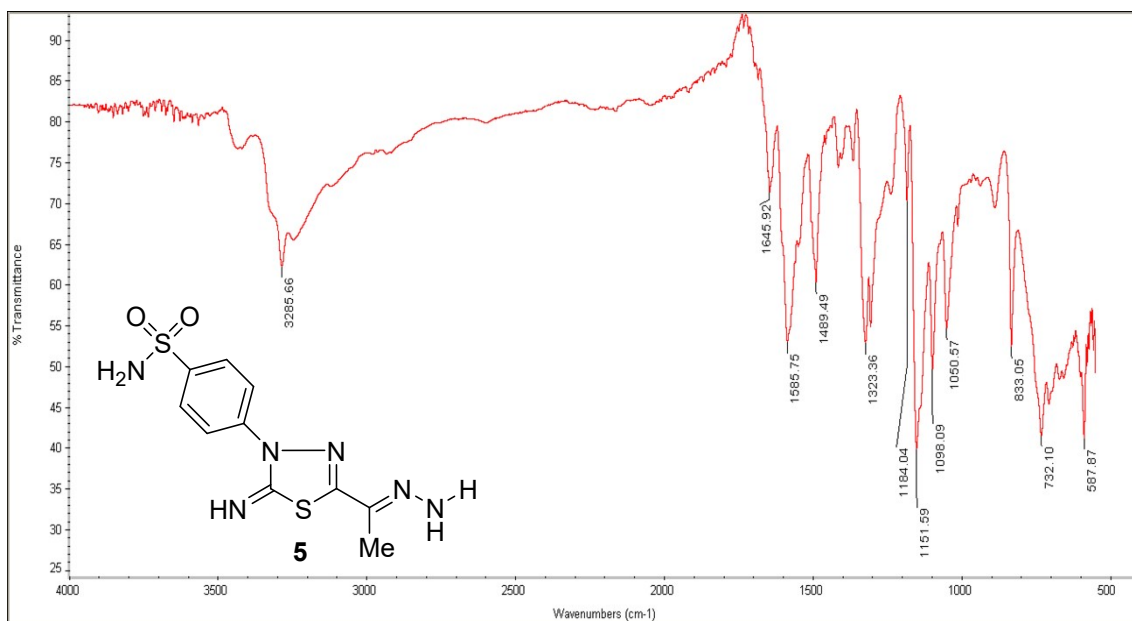


Figure S16. IR spectrum of compound 5.

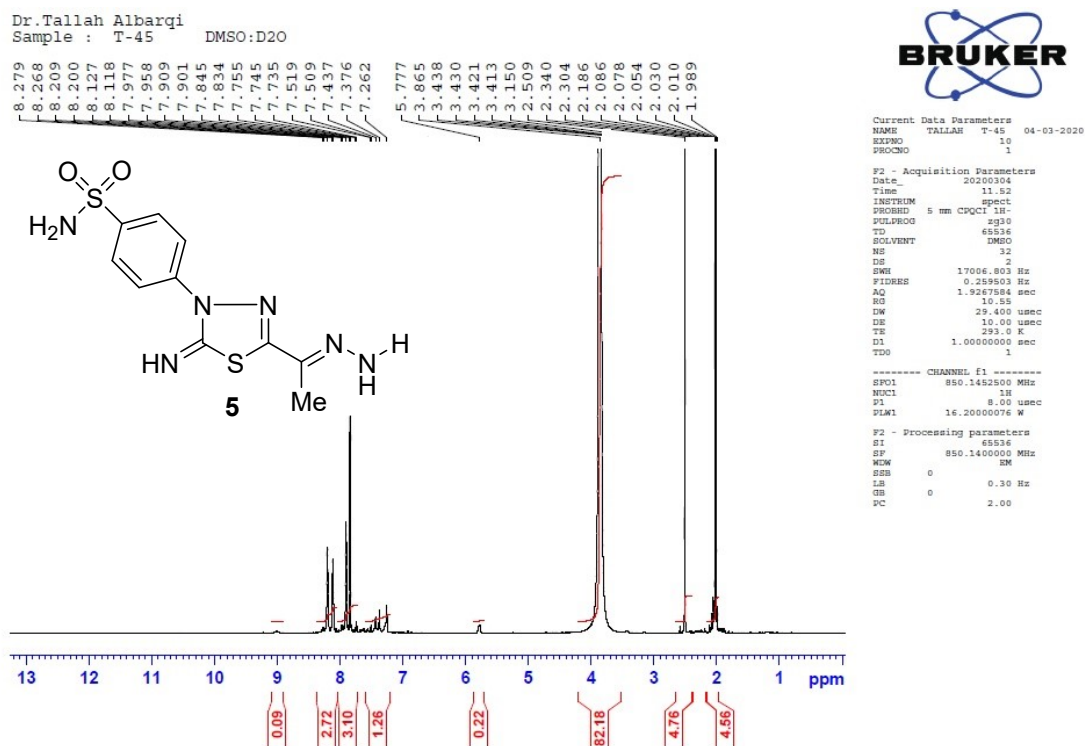


Figure S17. <sup>1</sup>H-NM spectrum of compound 5.

Dr. Tallah Albarqi  
Sample T-45 DMSO

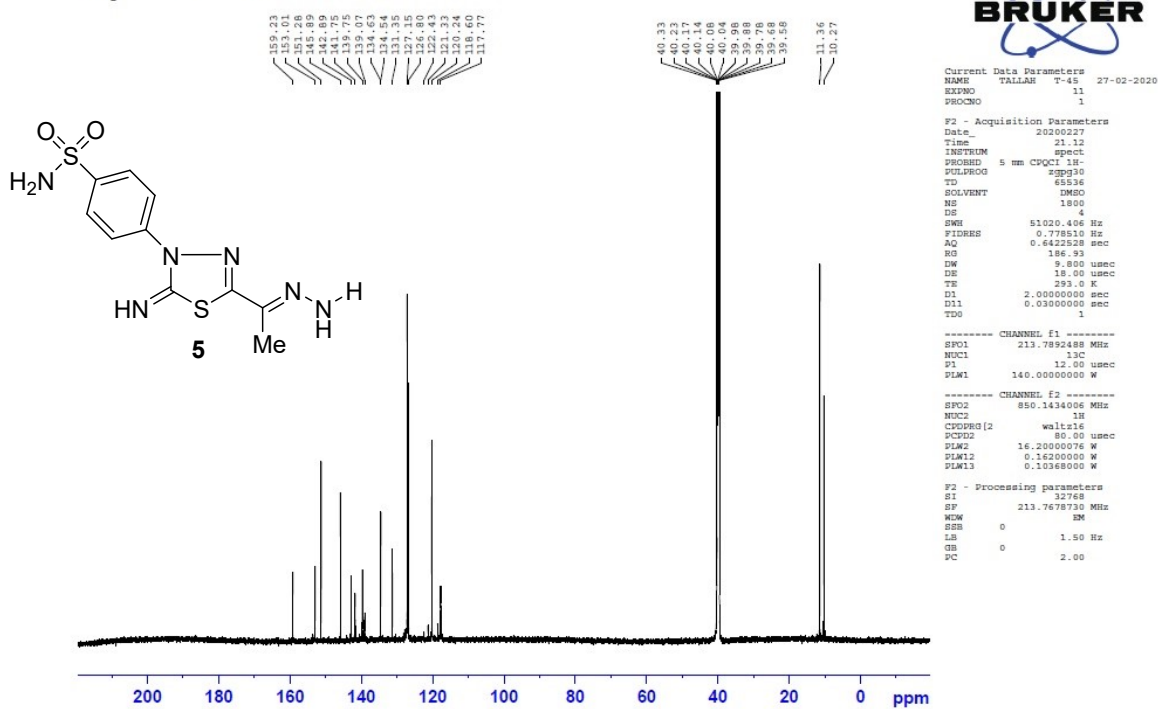


Figure S18. <sup>13</sup>C-NMR spectrum of compound 5.

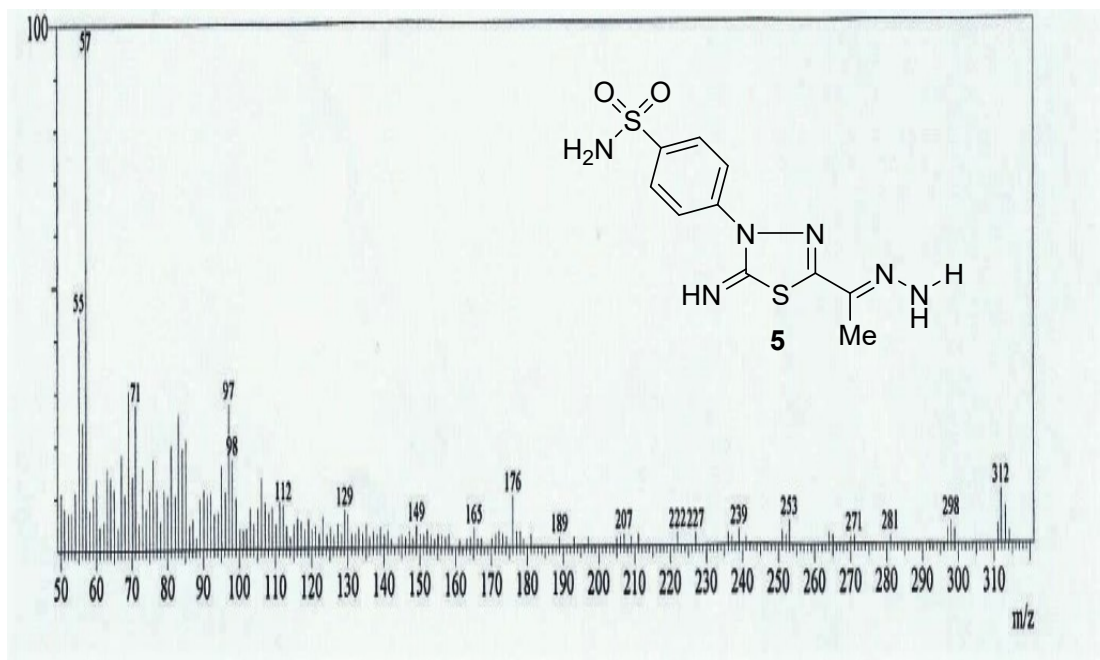
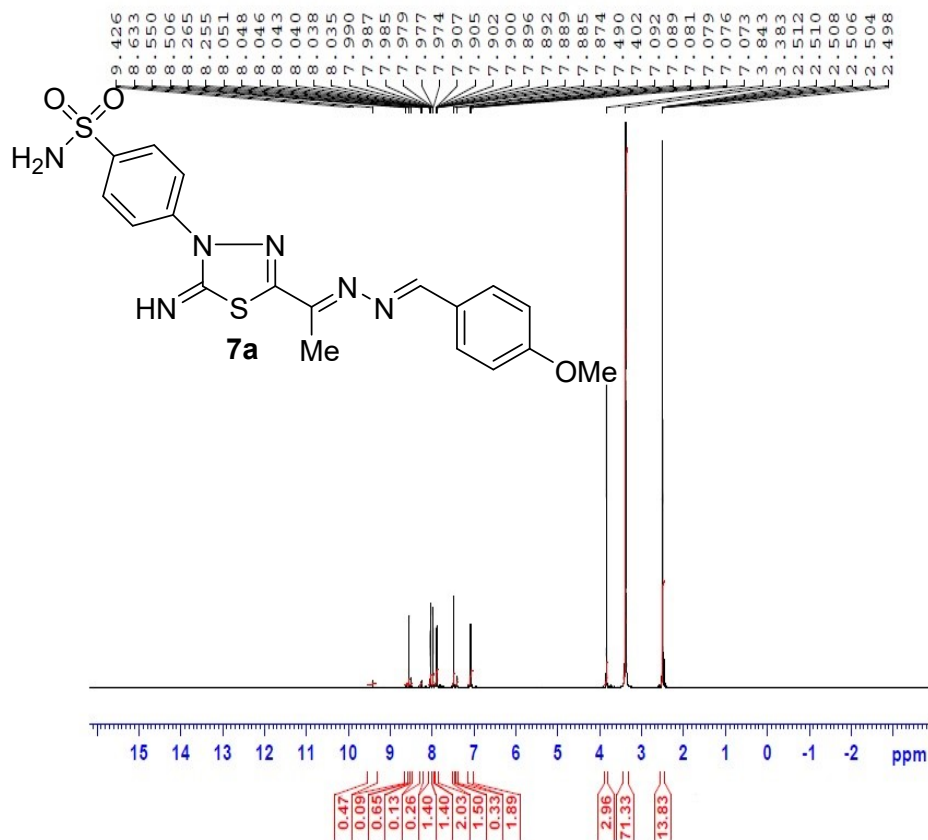


Figure S19. Mass spectrum of compound 5.

Tallah Albarqi  
Sample TM-34 DMSO



Current Data Parameters  
NAME TALLAH TM-34 20-12-2020  
EXPNO 80  
PROCNO 1

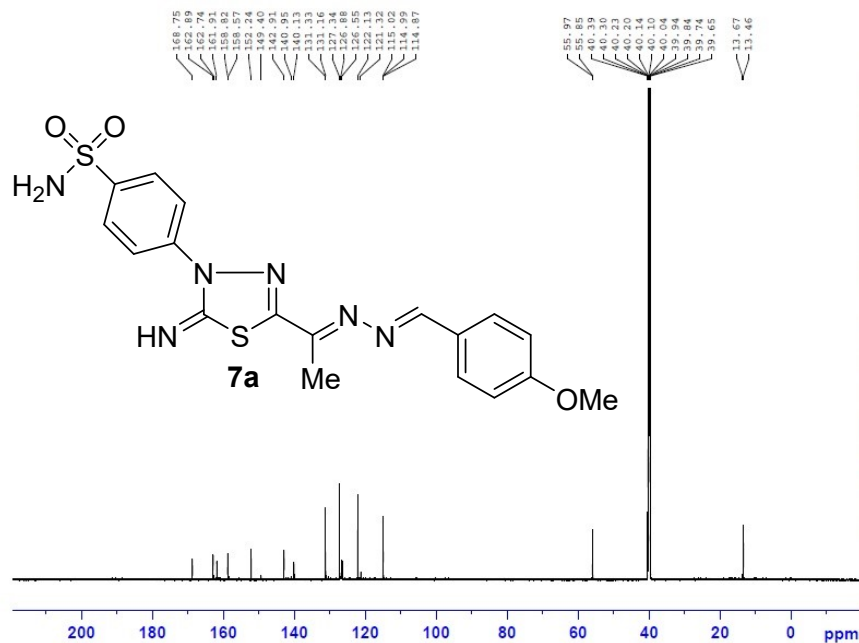
F2 - Acquisition Parameters  
Date\_ 20201221  
Time 8.13  
INSTRUM spect  
PROBHD 5 mm CPQCI 1H-  
PULPROG zg30  
TD 65536  
SOLVENT DMSO  
NS 32  
DS 2  
SWH 17006.803 Hz  
FIDRES 0.259503 Hz  
AQ 1.9267584 sec  
RG 11.37  
DW 29.400 usec  
DE 10.00 usec  
TE 298.0 K  
D1 1.00000000 sec  
TDO 1

----- CHANNEL f1 -----  
SFO1 850.1552500 MHz  
NUC1 1H  
P1 8.00 usec  
PLW1 16.70000076 W

F2 - Processing parameters  
SI 65536  
SF 850.1500000 MHz  
WDW EM  
SFB 0  
LB 0.30 Hz  
GB 0  
PC 2.00

Figure S20. <sup>1</sup>H-NMR spectrum of compound 7a.

Tallah Albarqi  
Sample TM-34 DMSO



Current Data Parameters  
NAME TALLAH TM-34 20-12-2020  
EXPNO 82  
PROCNO 1

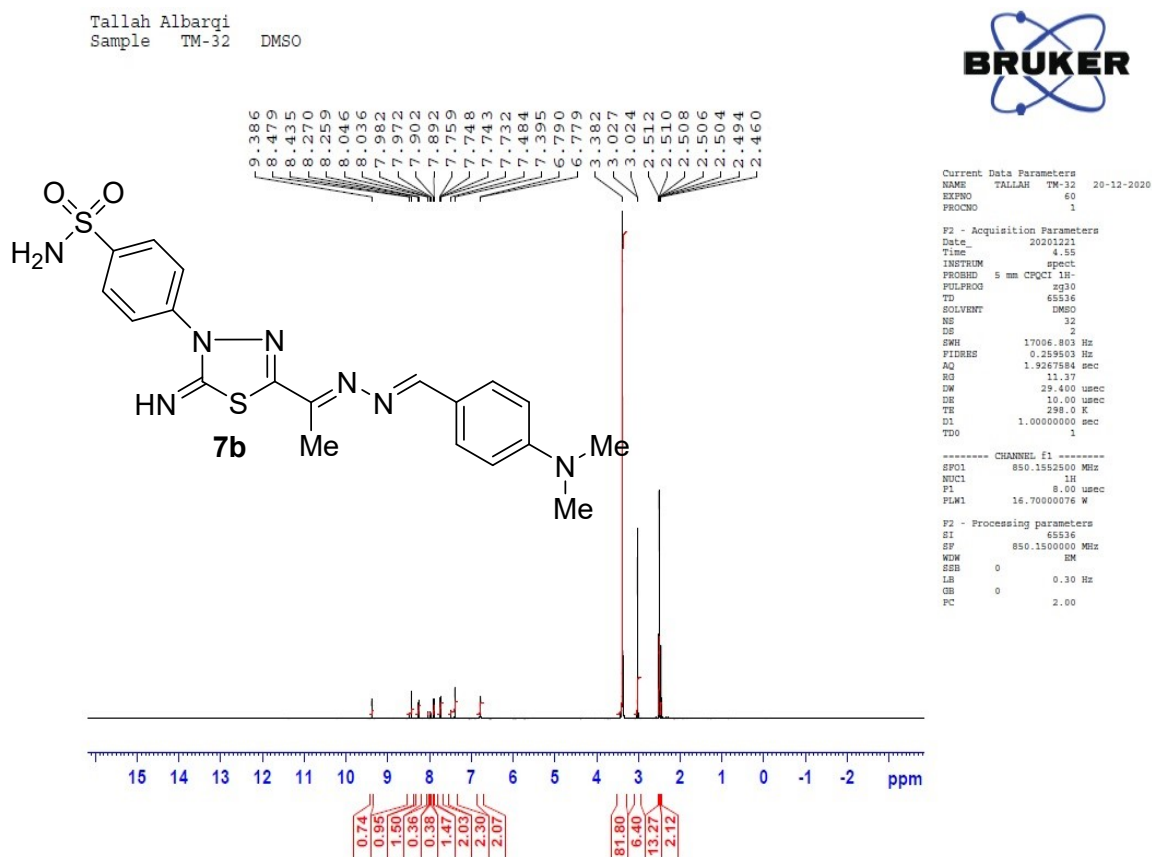
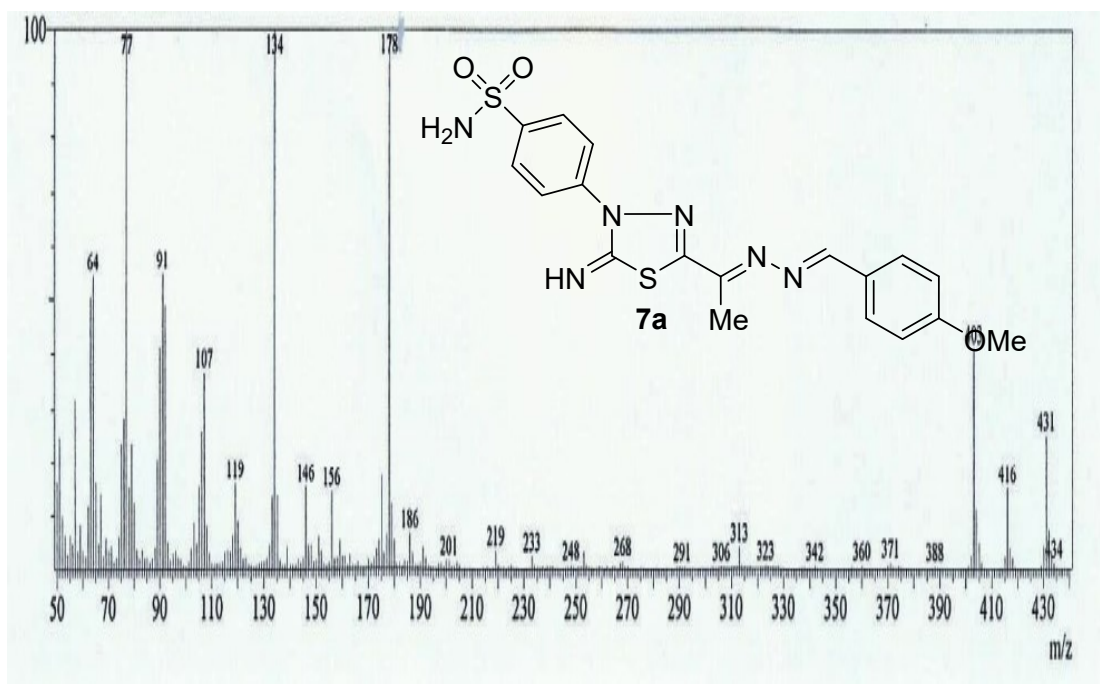
F2 - Acquisition Parameters  
Date\_ 20201221  
Time 9.47  
INSTRUM spect  
PROBHD 5 mm CPQCI 1H-  
PULPROG zgpg30  
TD 65536  
SOLVENT DMSO  
NS 2048  
DS 4  
SWH 51030.406 Hz  
FIDRES 0.778510 Hz  
AQ 0.6422528 sec  
RG 186.93  
DW 9.800 usec  
DE 18.00 usec  
TE 298.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TDO 1

----- CHANNEL f1 -----  
SFO1 213.7917636 MHz  
NUC1 13C  
P1 45.00 usec  
PLW1 12.00000000 W

----- CHANNEL f2 -----  
SFO2 850.1334006 MHz  
NUC2 1H  
CFORH2[2] waltz16  
PCPD2 80.00 usec  
PLW2 16.70000076 W  
PLW12 0.16700000 W  
PLW13 0.10688000 W

F2 - Processing parameters  
SI 32768  
SF 213.7763878 MHz  
WDW EM  
SFB 0  
LB 1.00 Hz  
GB 0  
PC 2.00

Figure S21. <sup>13</sup>C-NMR spectrum of compound 7a.



Tallah Albarqi  
Sample TM-32 DMSO

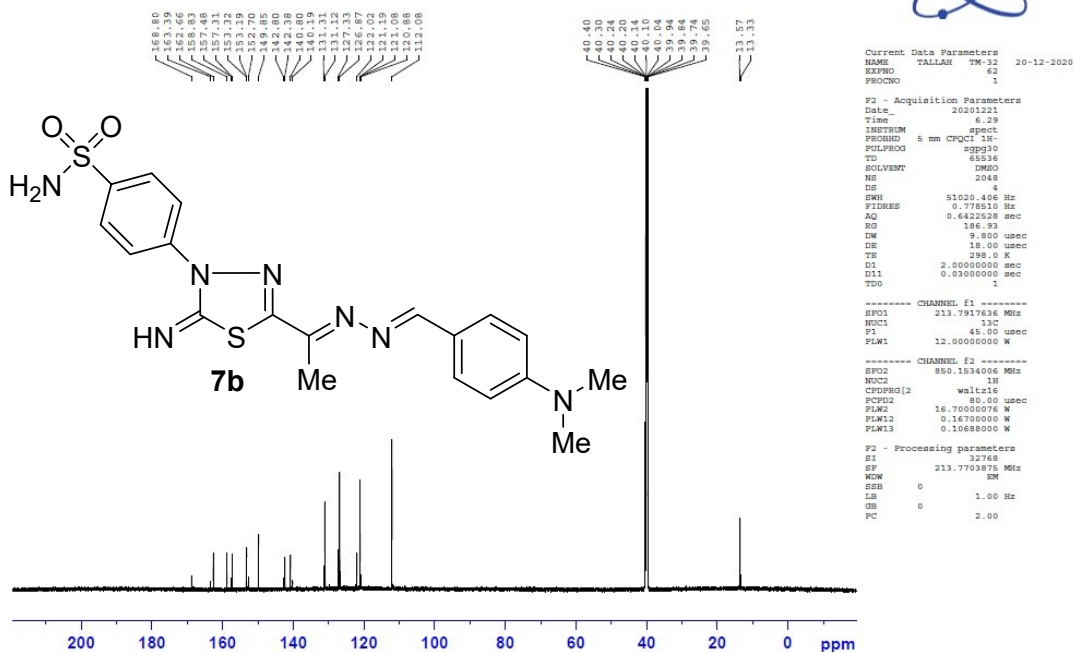


Figure S24. <sup>13</sup>C-NMR spectrum of compound 7b.

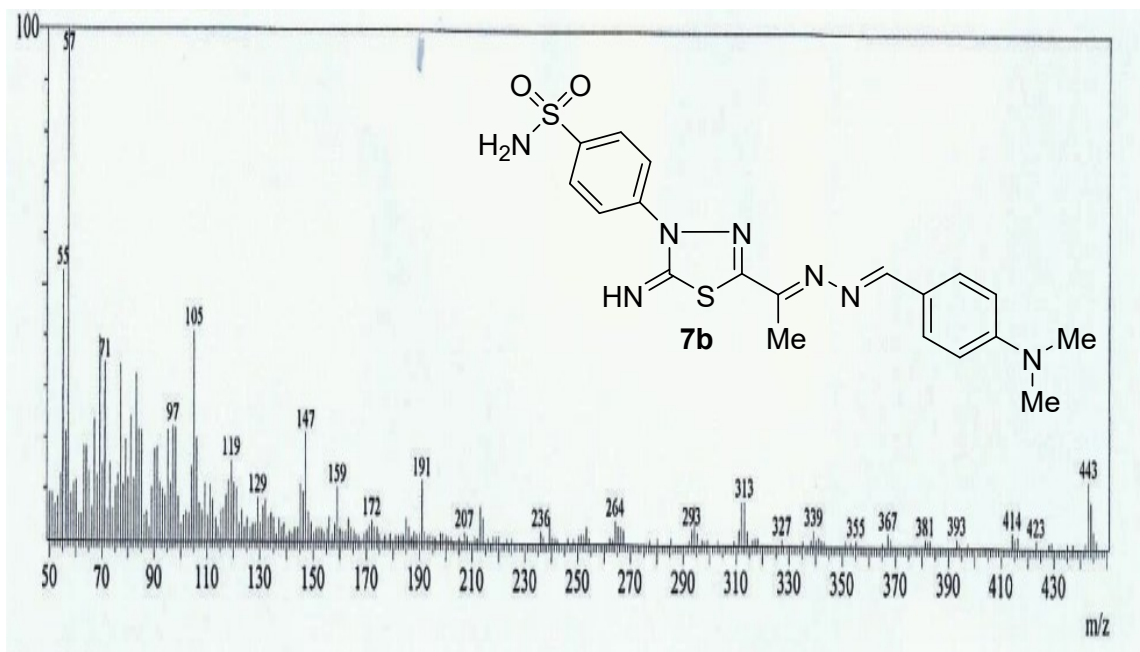
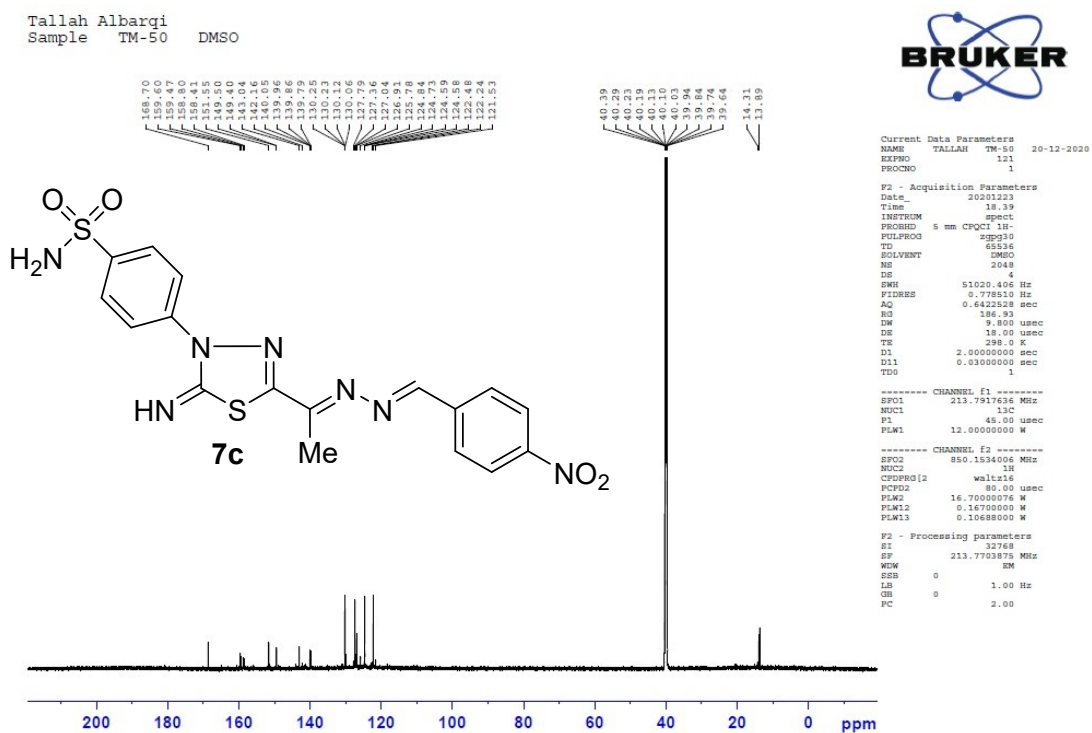
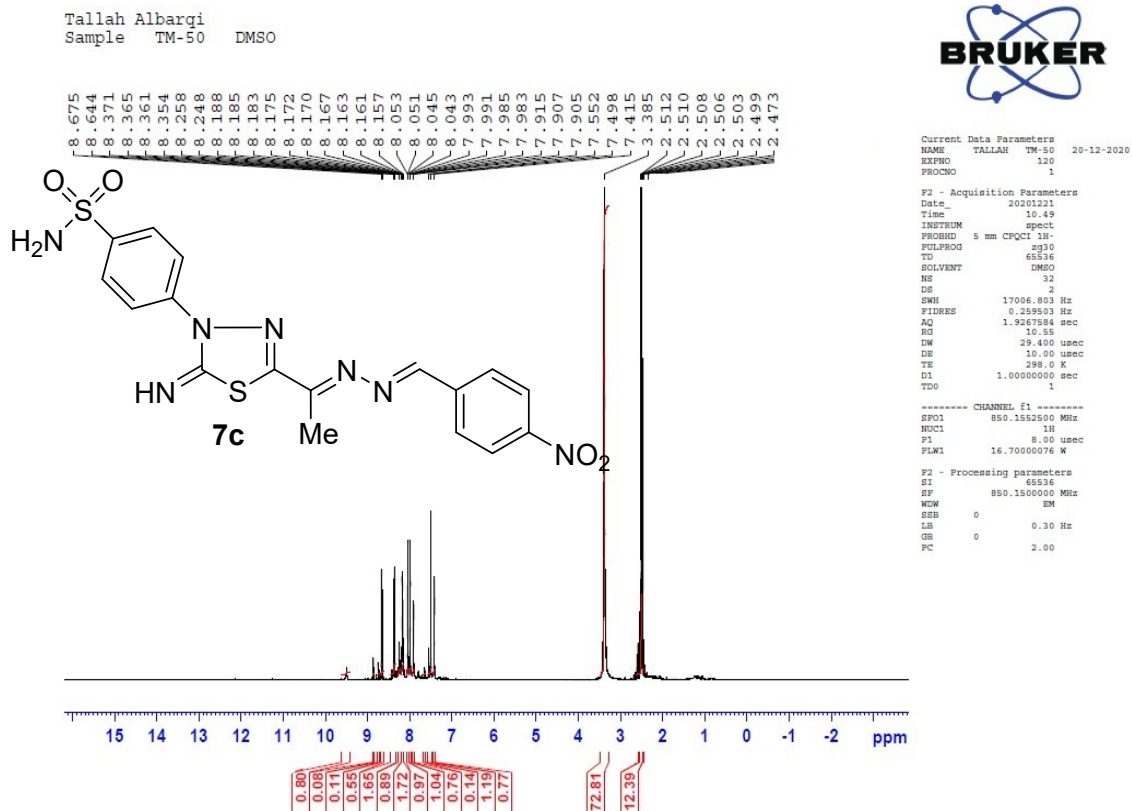
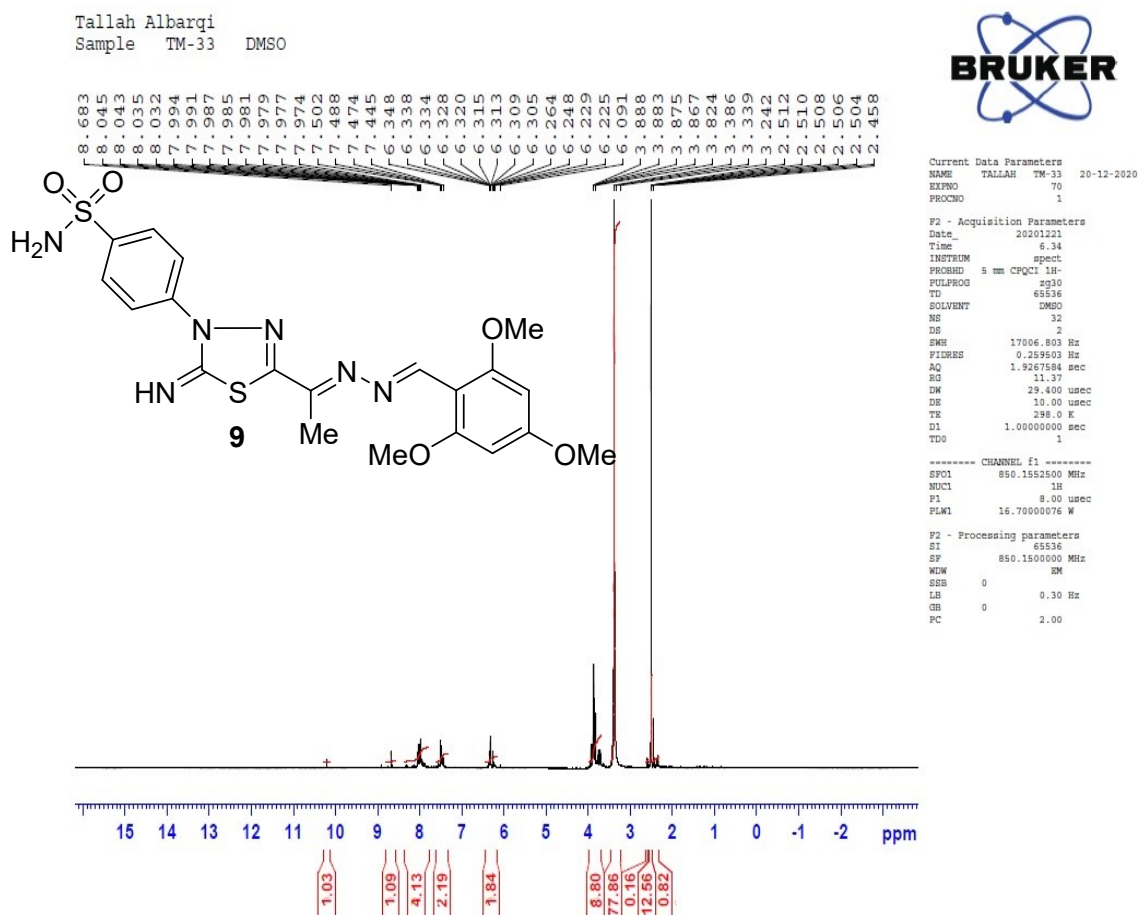
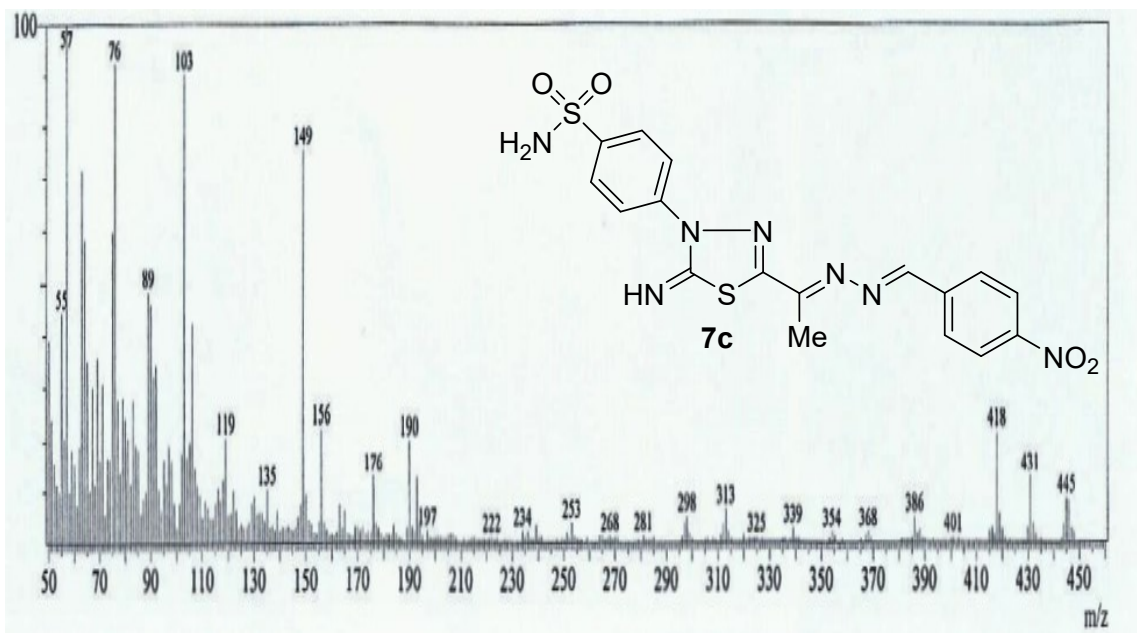


Figure S25. Mass spectrum of compound 7b.





Current Data Parameters  
NAME TALLAH TM-33 20-12-2020  
EXPTNO 70  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20201221  
Time 6.34  
INSTRUM spect  
PROBHD 5 mm CPQCI 1H-  
PULPROG zgpg  
TD 65536  
SOLVENT DMSO  
NS 32  
DS 2  
SWH 17006.803 Hz  
FIDRES 0.259503 Hz  
AQ 1.9267584 sec  
RG 11.37  
DM 29.400 usec  
DE 10.00 usec  
TE 298.0 K  
D1 1.00000000 sec  
TDO 1

----- CHANNEL f1 -----  
SP01 850.1552500 MHz  
NUC1 1H  
P1 8.00 usec  
PLM1 16.70000076 W

F2 - Processing parameters  
SI 65536  
SF 850.1500000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 2.00

Tallah Albarqi  
Sample TM-33 DMSO

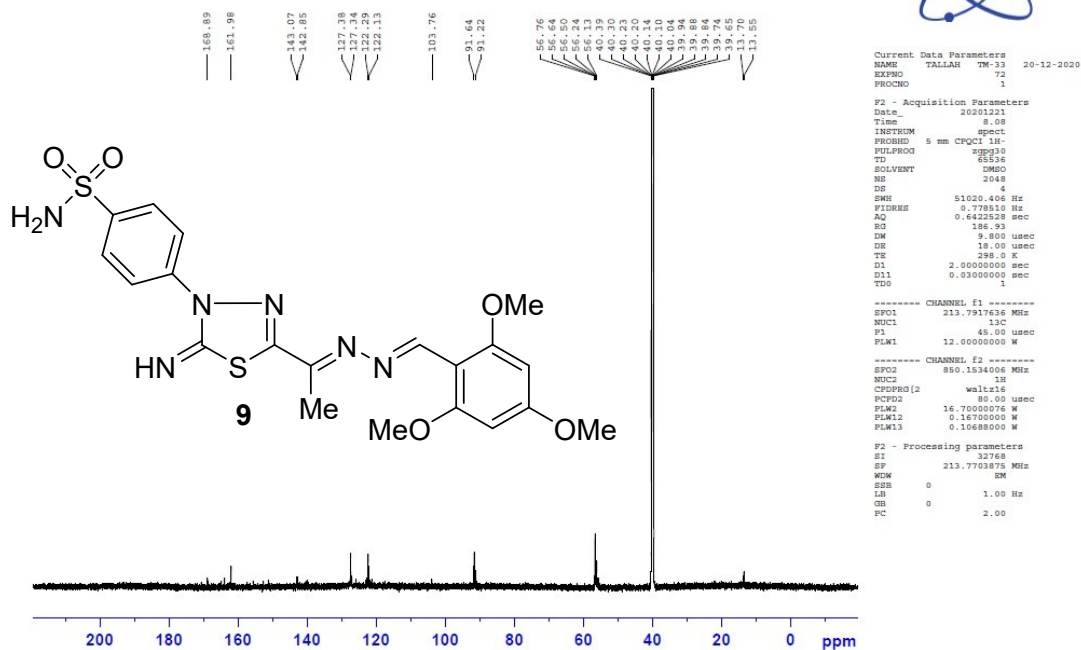


Figure S30. <sup>13</sup>C-NMR spectrum of compound 9.

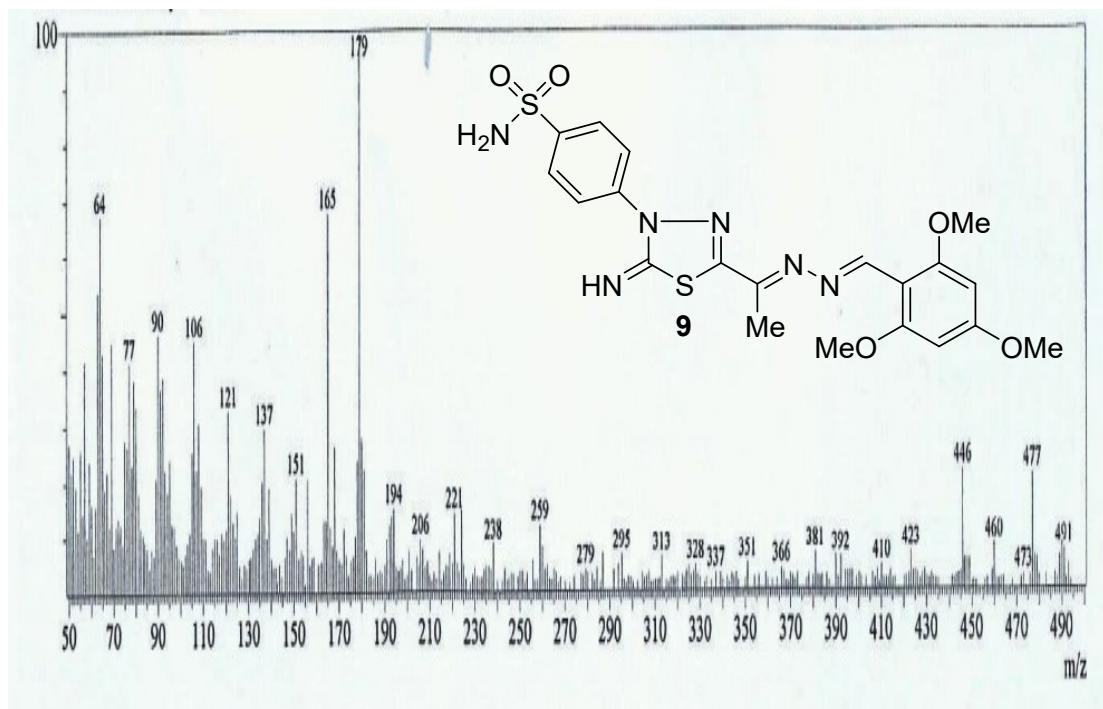


Figure S31. Mass spectrum of compound 9.



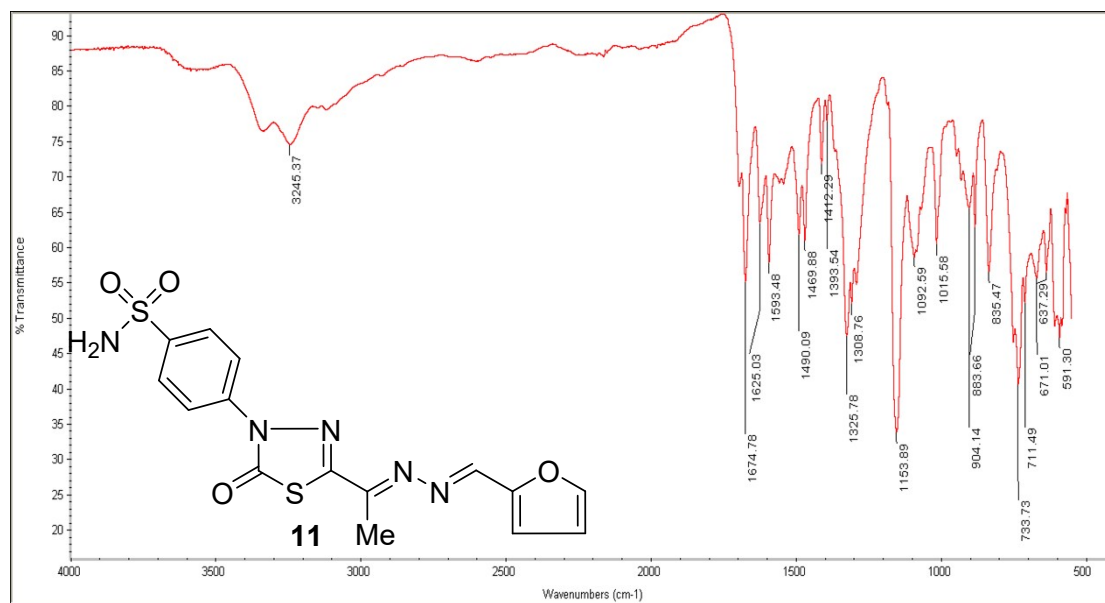


Figure S32. IR spectrum of compound **11**.

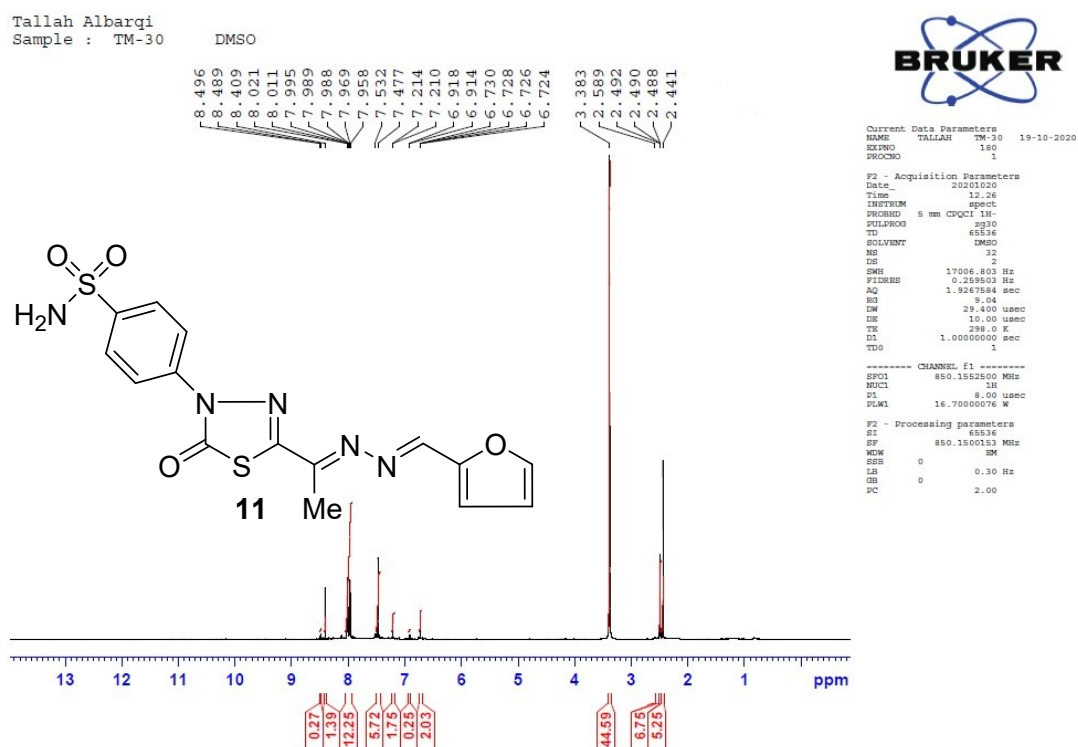


Figure S33. <sup>1</sup>H-NMR spectrum of compound **11**.

Tallah Albarqi  
Sample : TM-30

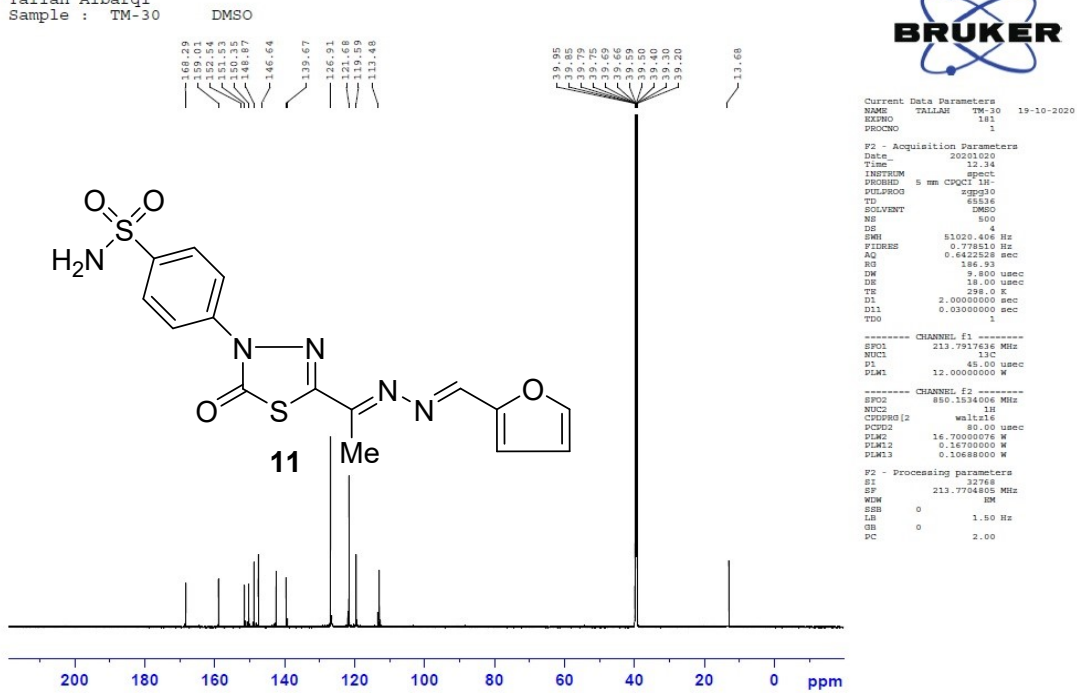


Figure S34. <sup>13</sup>C-NMR spectrum of compound 11.

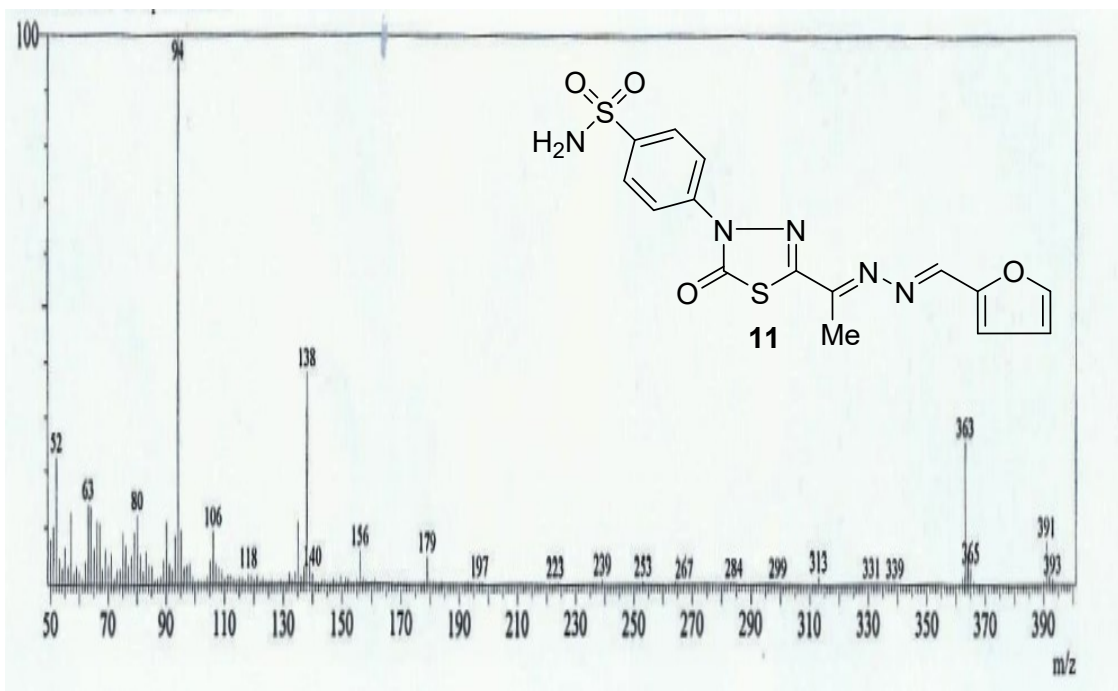


Figure S35. Mass spectrum of compound 11.

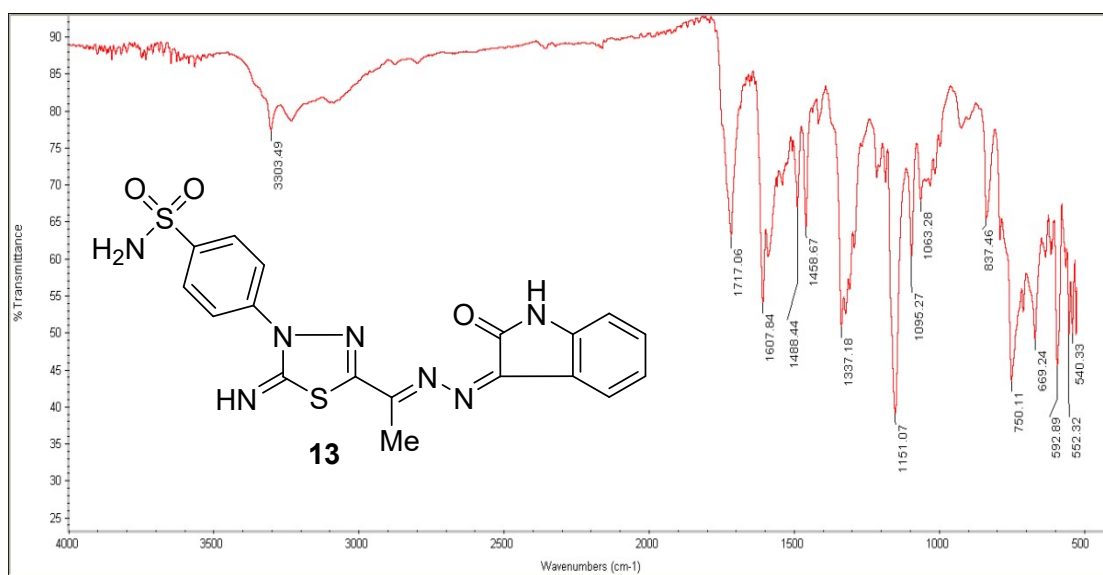


Figure S36. IR spectrum of compound 13.

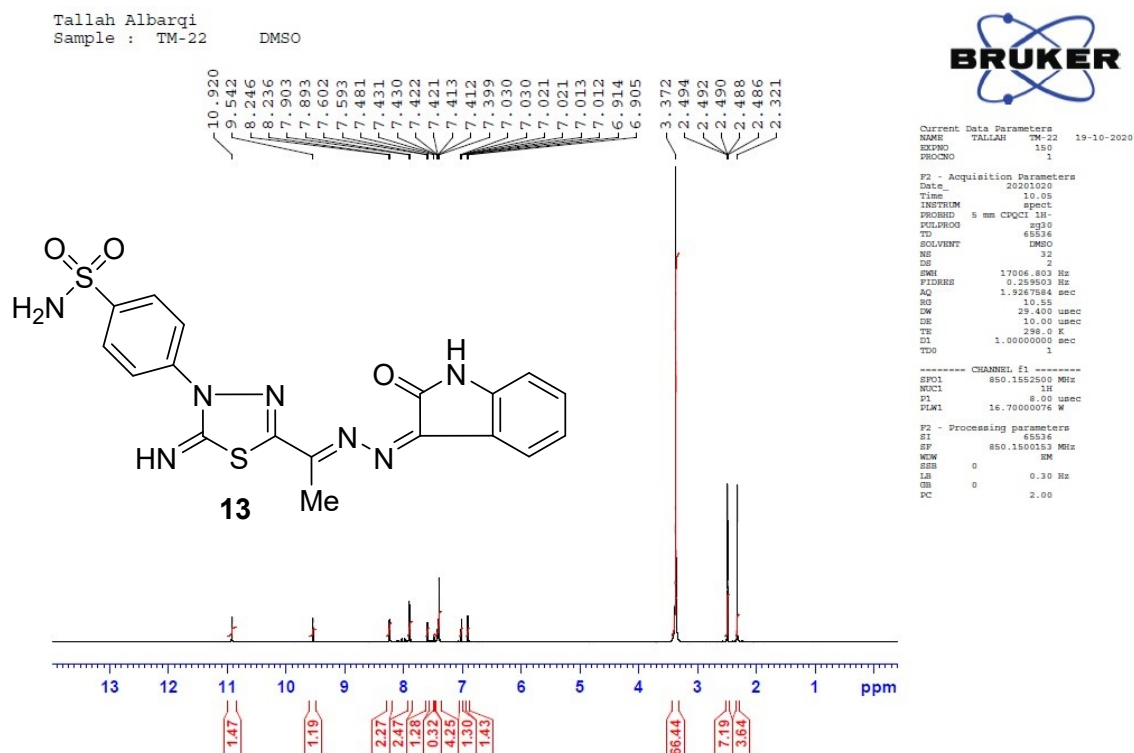


Figure S37. <sup>1</sup>H-NMR spectrum of compound 13.

Tallah Albarqi  
Sample : TM-22

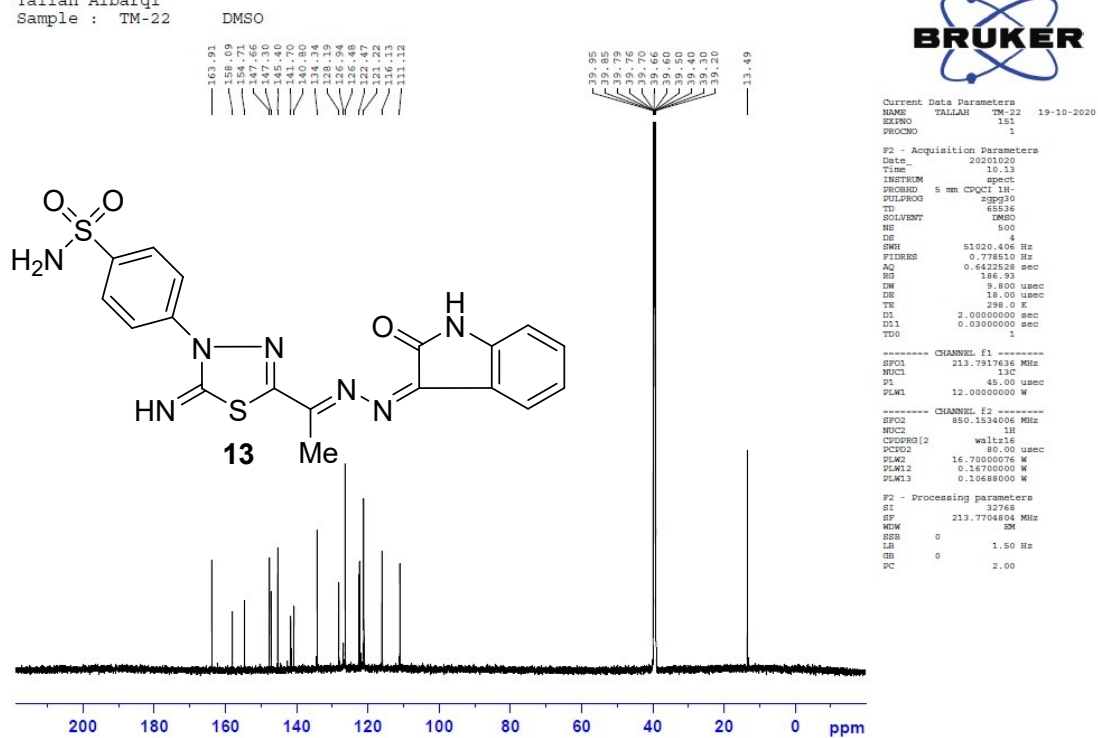


Figure S38. <sup>13</sup>C-NMR spectrum of compound **13**.

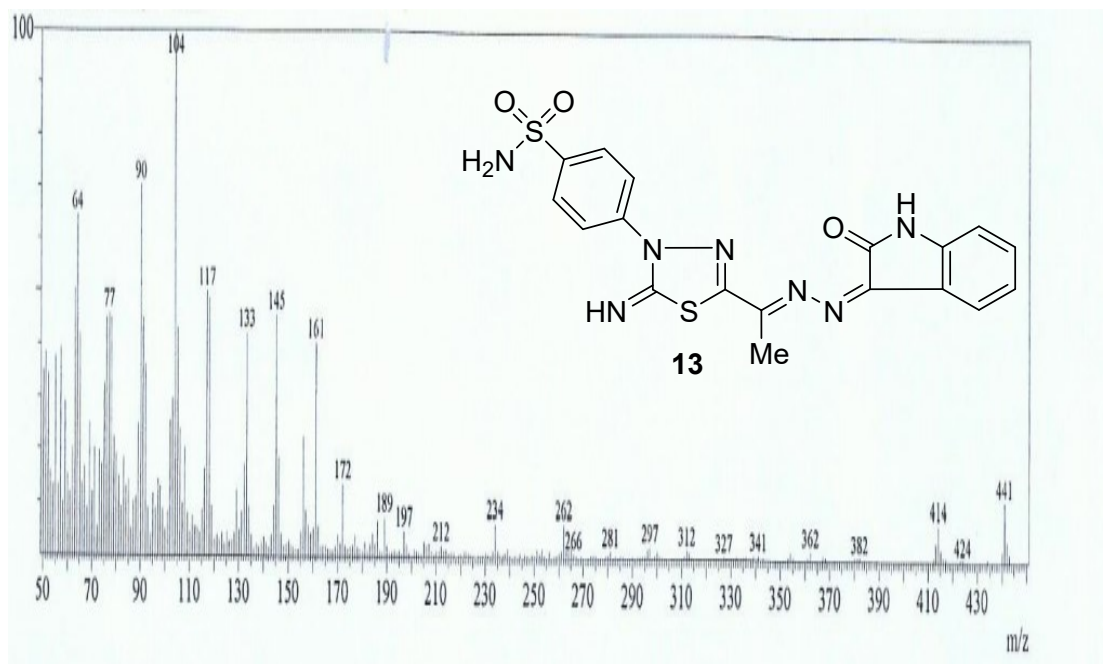


Figure S39. Mass spectrum of compound **13**.

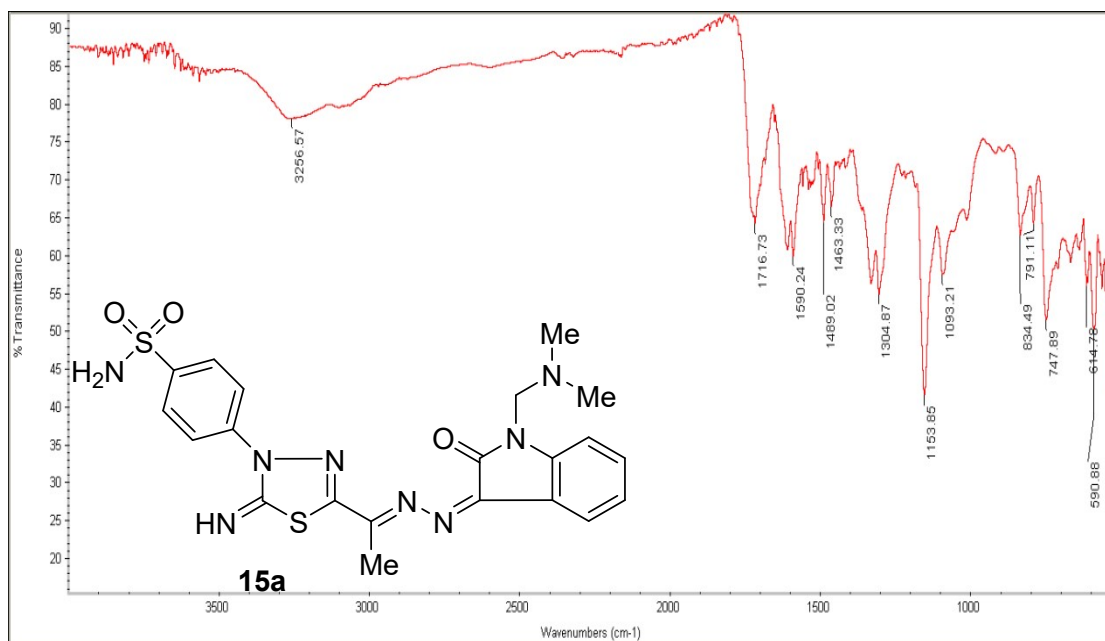


Figure S40. IR spectrum of compound 15a.

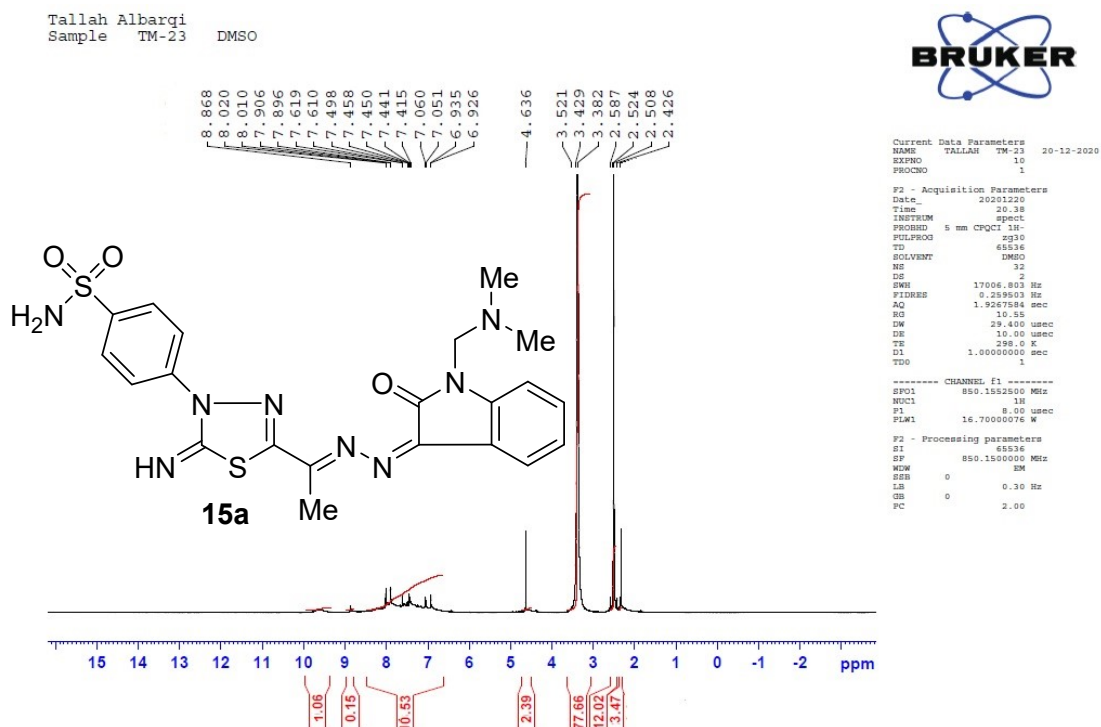


Figure S41. <sup>1</sup>H-NMR spectrum of compound 15a.

Tallah Albarqi  
Sample TM-23 DMSO

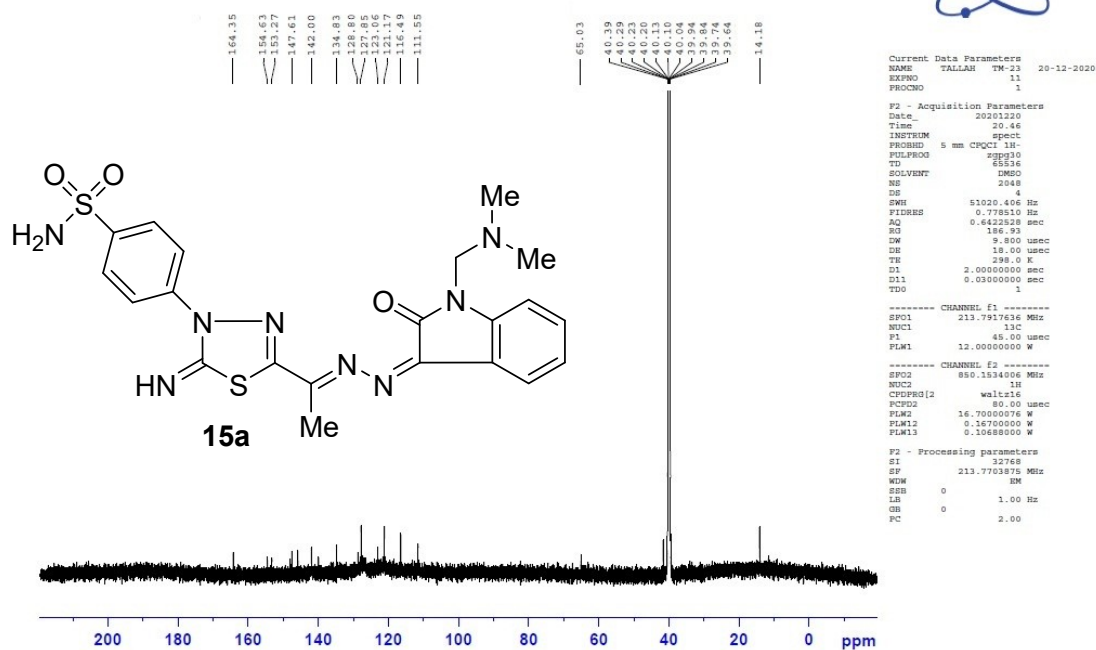


Figure S42. <sup>13</sup>C-NMR spectrum of compound 15a.

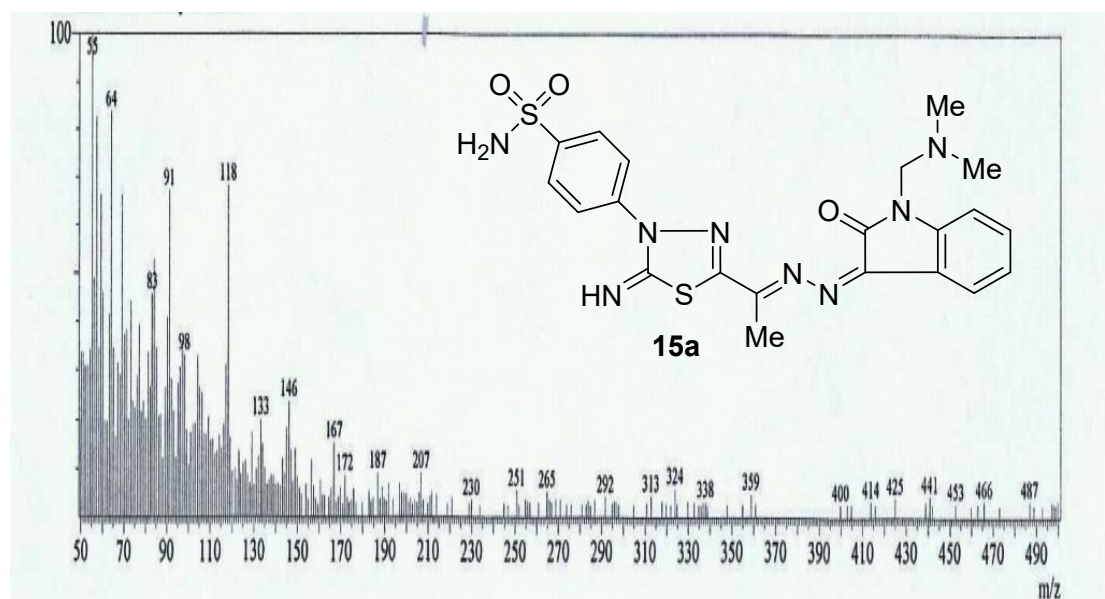


Figure S43. Mass spectrum of compound 15a.

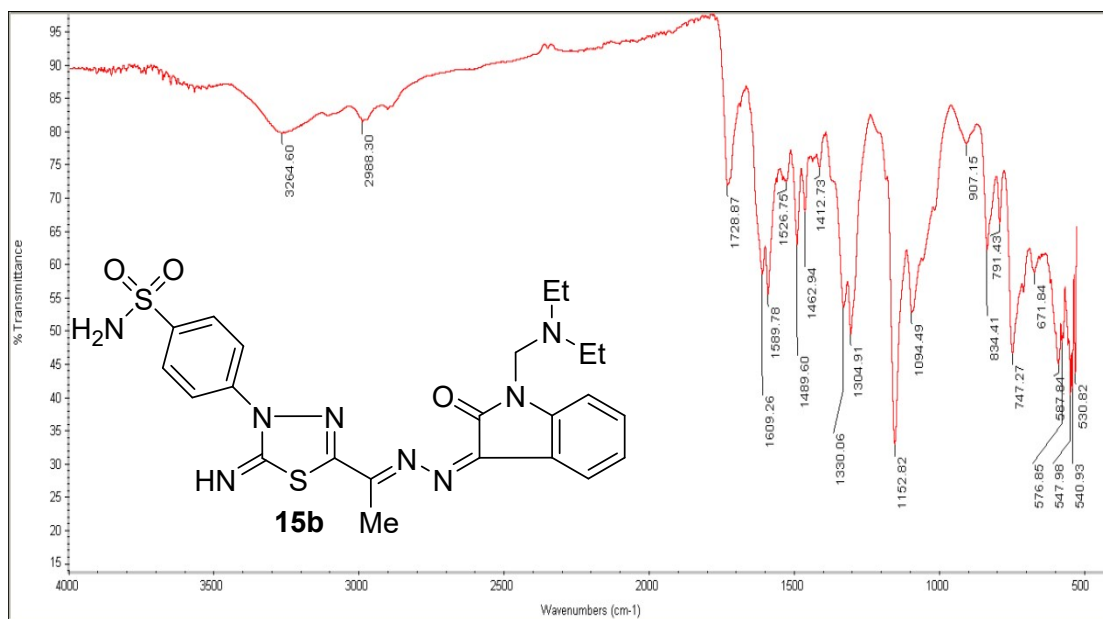


Figure S44. IR spectrum of compound **15b**.

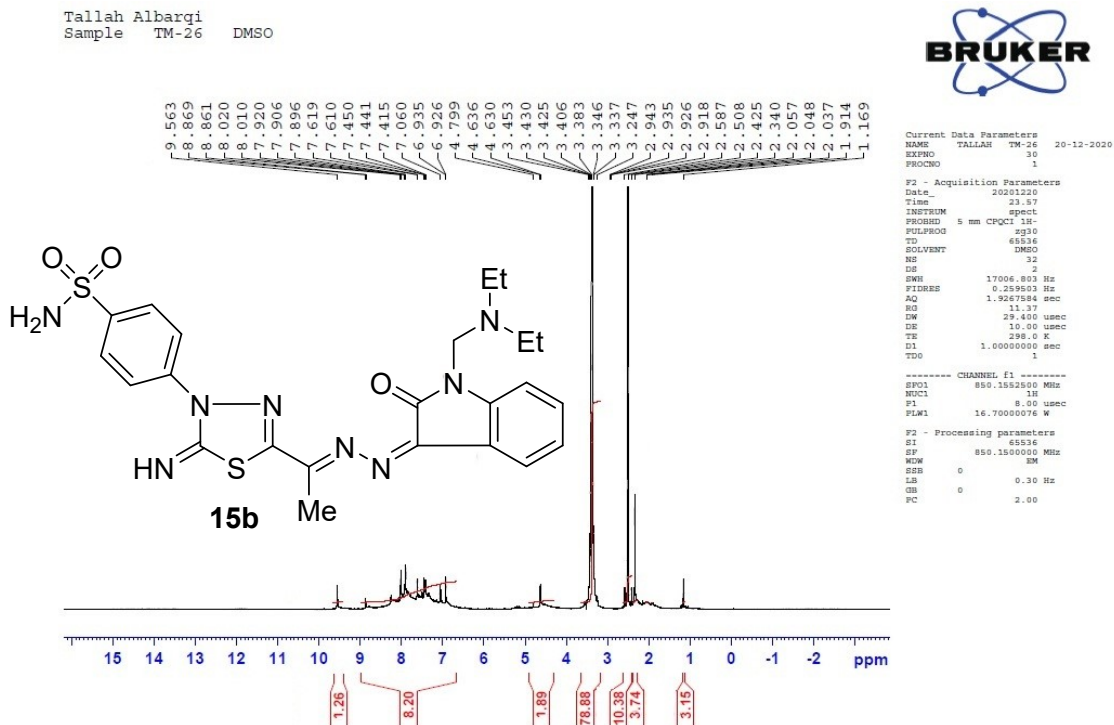


Figure S45.  $^1\text{H-NMR}$  spectrum of compound **15b**.

Tallah Albarqi  
Sample TM-26 DMSO

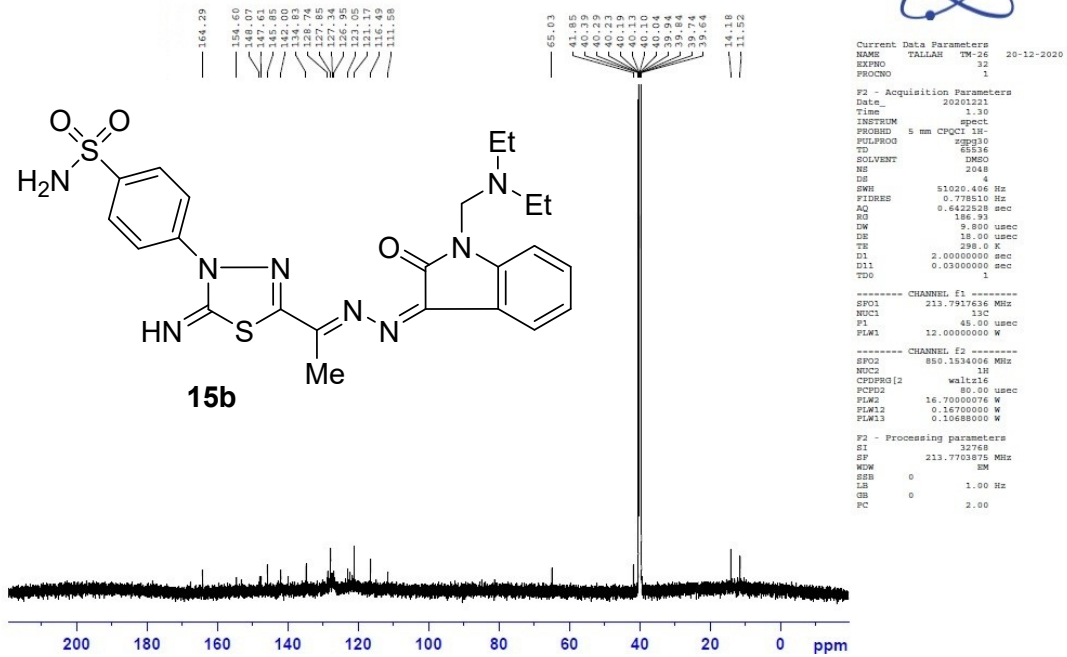


Figure S46. <sup>13</sup>C-NMR spectrum of compound 15b.

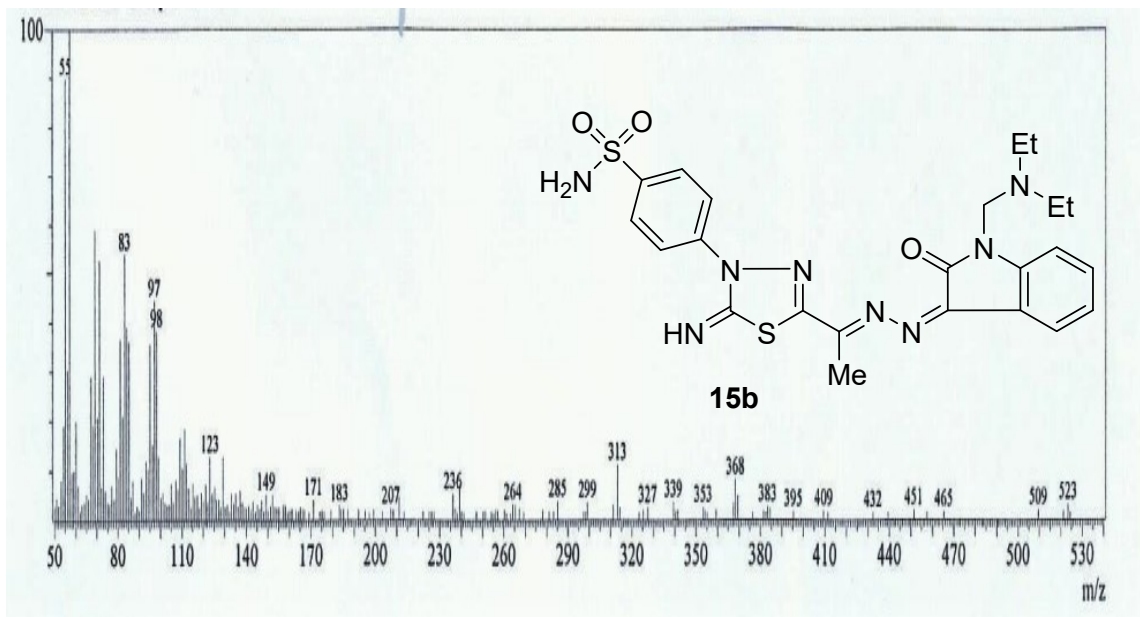


Figure S47. Mass spectrum of compound 15b.



**Table S1** Calculated<sup>a</sup> energies (E) and energy differences ( $\Delta E$ ) for possible configurations of the synthesized products.

Cpd	E (Hartree)	$\Delta E$ (kcal/mol) <sup>b</sup>		
	<b>1 (EE)</b> <sup>c</sup>	<b>2 (ZZ)</b> <sup>c</sup>	<b>3 (EZ)</b> <sup>c</sup>	<b>4 (ZE)</b> <sup>c</sup>
<b>7a</b>	-2047.174609	5.27	3.83	3.81
<b>7b</b>	-2066.621509	5.12	3.81	1.74
<b>7c</b>	-2137.148645	5.60	3.74	2.06
<b>9</b>	-2276.213429	5.75	3.51	1.77
<b>11</b>	-1930.42554	2.68	1.42	1.60
<b>13</b>	-2100.141412	3.28	0.30	0.79
<b>15a</b>	-2273.419471	3.26	0.24	0.73
<b>15b</b>	-2352.04409	3.29	0.27	0.75

<sup>a</sup> The DFT-B3LYP functional combined with 6-31G(d) basis set were applied in these calculations.

<sup>b</sup> Energy differences ( $\Delta E$ ) are relative to the most stable configuration (**1**, EE),

<sup>c</sup> The optimized geometries of the proposed configurations for all synthesized compounds **7a-c**, **9**, **11**, **13**, **15a** and **15b** (Figures S3-S10 at supplementary material).