Supplementary Materials

Discovery of 2-(furan-2-ylmethylene)hydrazine-1-carbothioamide derivatives as novel inhibitors of SARS-CoV-2 main protease

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Figure Legends

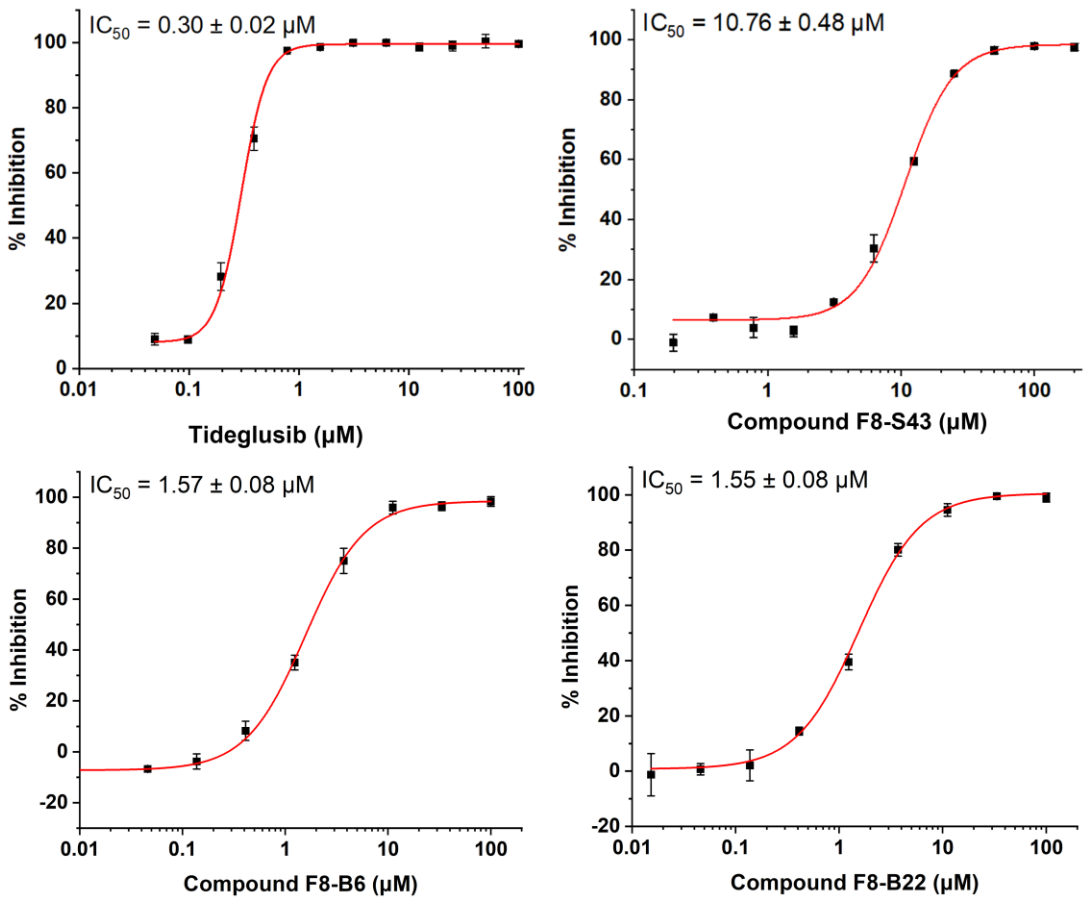


Figure S1. The concentration-activity relationship for identified SARS-CoV-2 M^{pro} inhibitors.

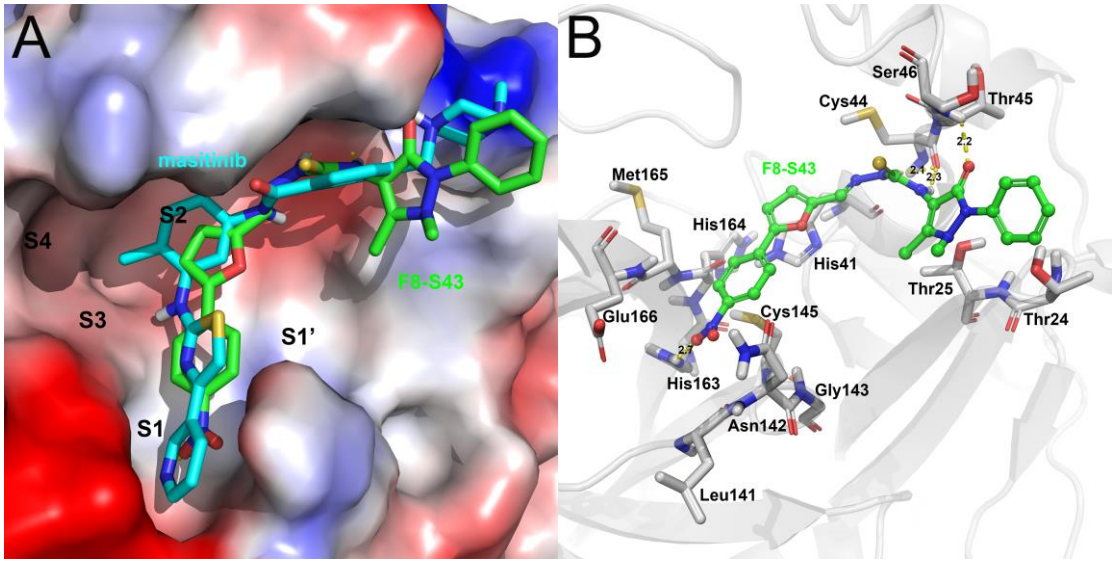


Figure S2. Predicted binding mode of compound **F8-S43**. (A) Superimposition of the crystal structure of SARS-CoV-2 M^{pro} (PDB ID: 7JU7) with compound **F8-S43**. (B) The binding modes of compound **F8-S43** with SARS-CoV-2 M^{pro} in the cartoon. Hydrogen bonds are represented by yellow lines. Images depicting the proposed binding modes were generated using PyMOL software.

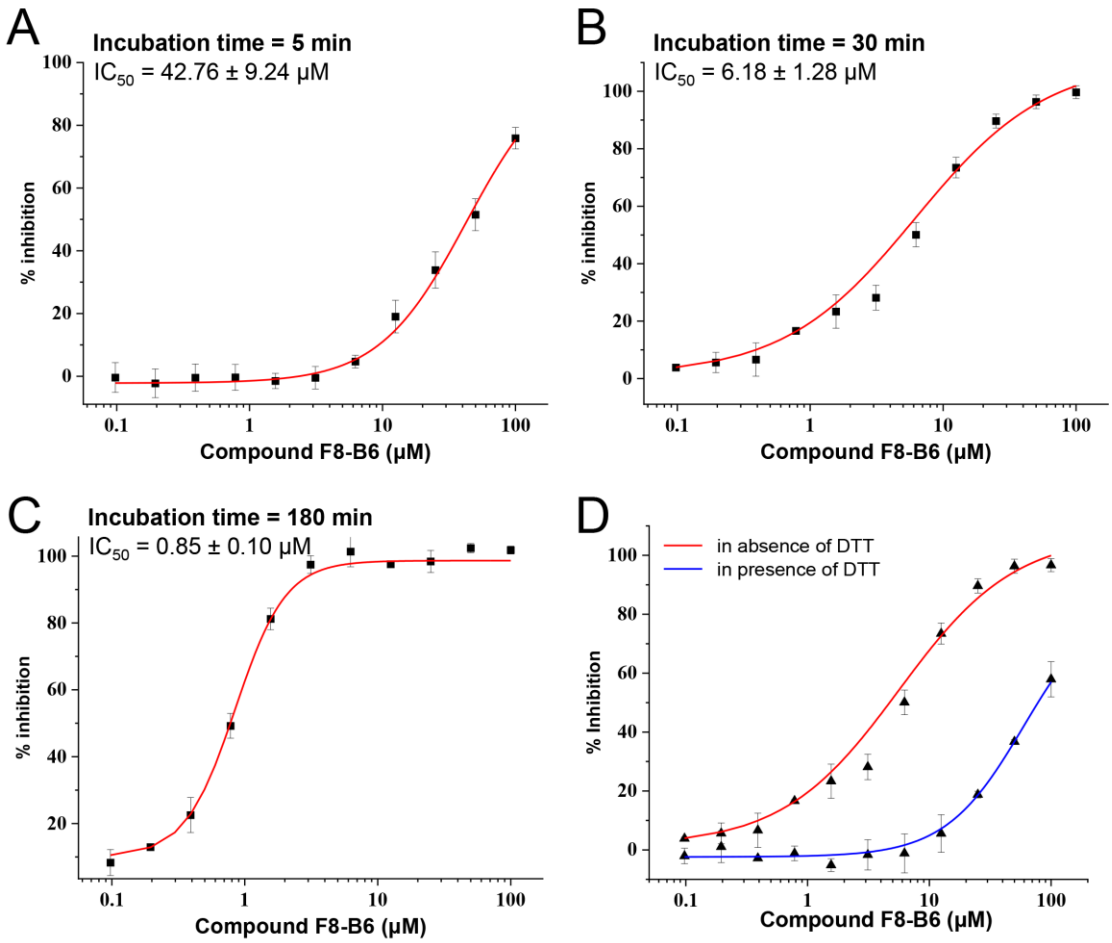


Figure S3. Dose-response curves of the inhibition activity of **F8-B6** under different incubation times 5 min (A), 30 min (B), 180 min (C). (D) Dose-response curves of the inhibition activity of **F8-B6** in the presence or absence of DTT.

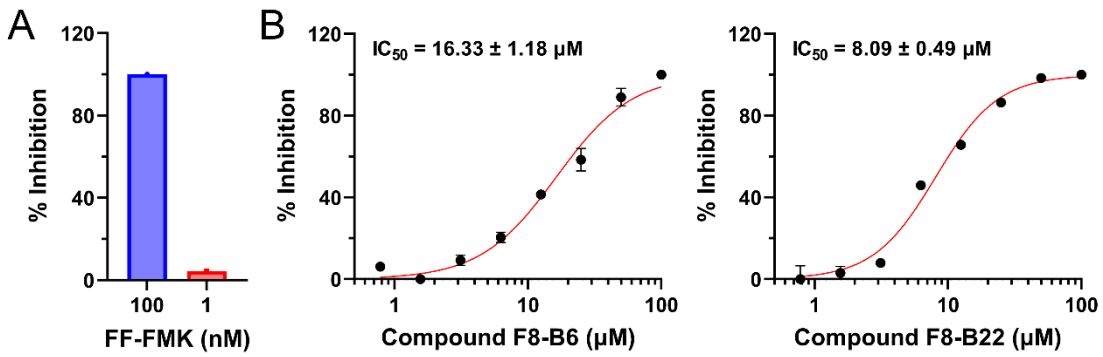
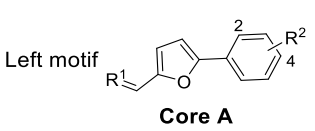


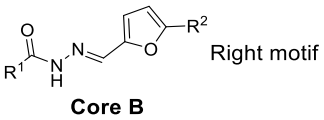
Figure S4. (A) The inhibition of Cathepsin L inhibitor **FF-FMK**. (B) The concentration-activity relationship for compounds **F8-B6** and **F8-B22** against Cathepsin L. Data are presented as geometric mean values of at least two independent runs.

Table S1. The chemical structures and enzymatic activities of the 27 analogs of **F8**.



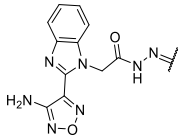
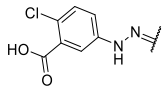
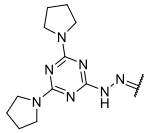
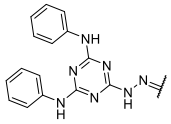
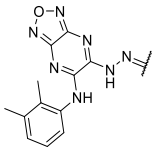
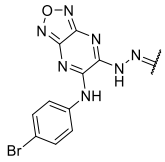
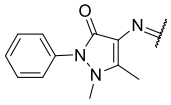
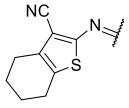
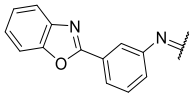
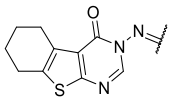
Core A

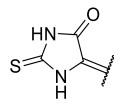
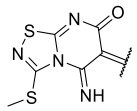
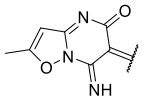
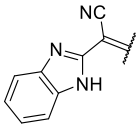
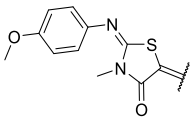
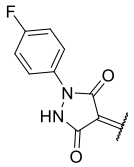
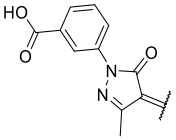
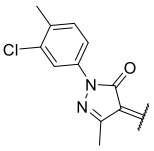
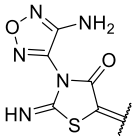
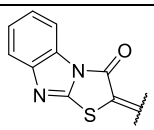
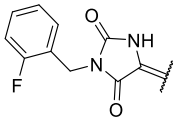
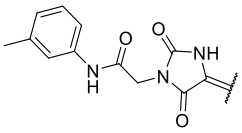
F8, **F8-S44** to **F8-S65**

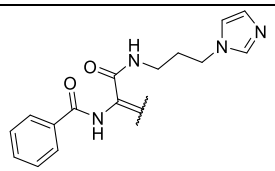
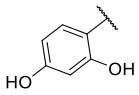
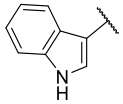
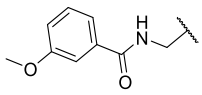
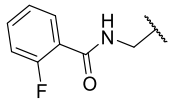
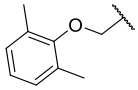


Core B

F8-S66 to **F8-S70**

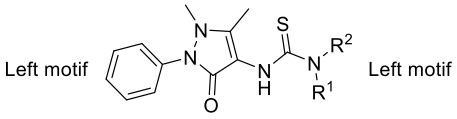
Compounds	Core	R^1	R^2	Inhibition% (50 μM) [a]	IC_{50} ± SD (μM) [a]
Tideglusib	—	——	——	98.6	0.30 ± 0.02
F8	A		3-COOH	65.0	21.28 ± 0.89
F8-S44	A		3-COOH, 4-Cl	< 20.0	N.T. [b]
F8-S45	A		3-COOH	28.2	N.T.
F8-S46	A		3-COOH, 4-OH	< 20.0	N.T.
F8-S47	A		3-COOH	34.6	N.T.
F8-S48	A		3-COOH, 4-OH	45.9	N.T.
F8-S49	A		$3\text{-}NO_2$	< 20.0	N.T.
F8-S50	A		3-COOH, 4-Cl	< 20.0	N.T.
F8-S51	A		$4\text{-}NO_2$	21.3	N.T.
F8-S52	A		3-COOH	30.0	N.T.

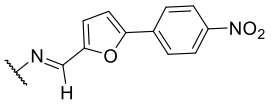
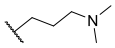
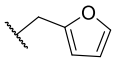
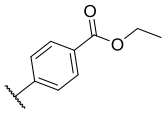
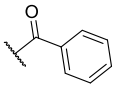
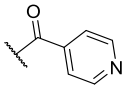
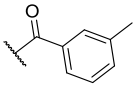
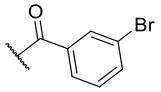
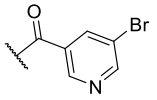
F8-S53	A		2-COOH	< 20.0	N.T.
F8-S54	A		3-COOH	< 20.0	N.T.
F8-S55	A		3-COOH	< 20.0	N.T.
F8-S56	A		3-COOH	< 20.0	N.T.
F8-S57	A		3-COOH, 4-Cl	27.1	N.T.
F8-S58	A		3-COOH	33.8	N.T.
F8-S59	A		3-COOH	28.5	N.T.
F8-S60	A		4-COOH	< 20.0	N.T.
F8-S61	A		3-COOH	30.3	N.T.
F8-S62	A		3-COOH	< 20.0	N.T.
F8-S63	A		3-COOH, 4-Cl	53.4	N.T.
F8-S64	A		3-COOH	24.2	N.T.

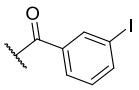
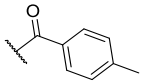
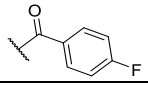
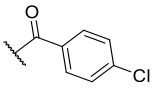
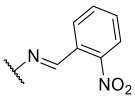
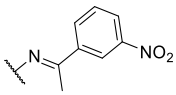
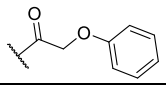
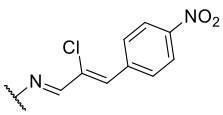
F8-S65	A		3-NO_2	28.8	N.T.
F8-S66	B		NO_2	< 20.0	N.T.
F8-S67	B		NO_2	< 20.0	N.T.
F8-S68	B		NO_2	< 20.0	N.T.
F8-S69	B		NO_2	< 20.0	N.T.
F8-S70	B		NO_2	< 20.0	N.T.

[a] Data are presented as geometric mean values of at least two independent runs. [b] Not tested.

Table S2. Enzymatic activity and chemical structures of the 22 analogs of **F8-S43**.

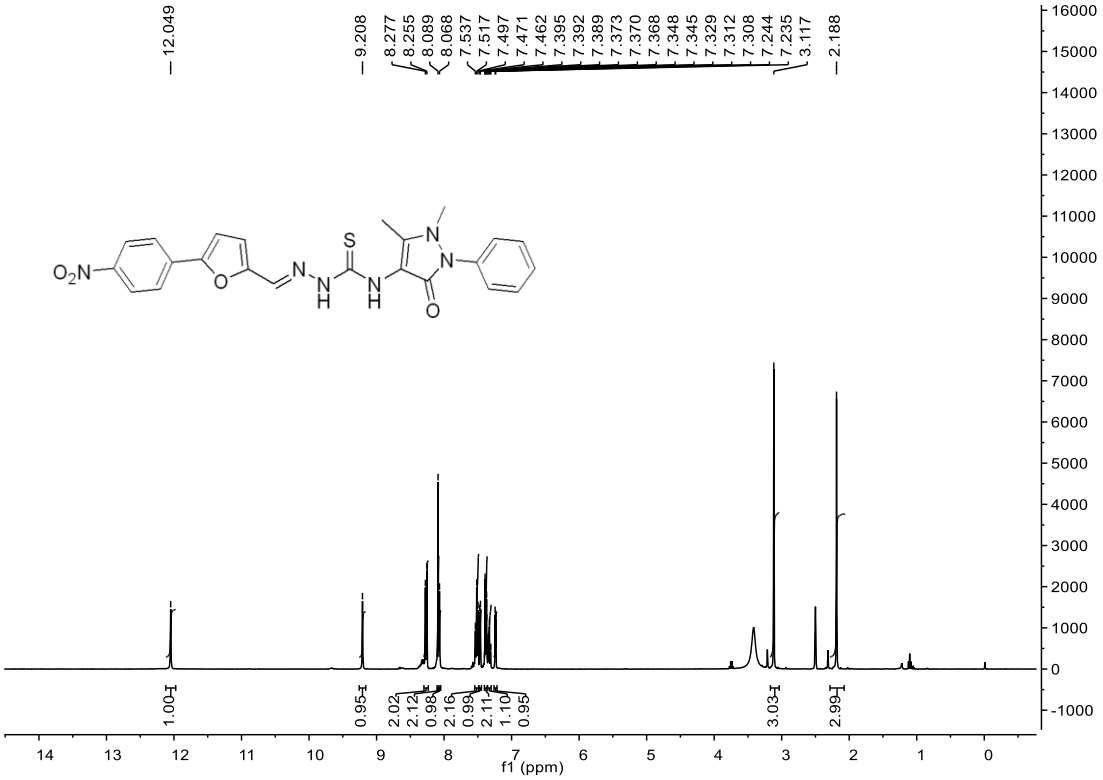


Compounds	R^1	R^2	Inhibition% (50 μM) [a]	IC_{50} ± SD (μM) [a]
Tideglusib	-----	-----	98.6	0.30 ± 0.02
F8-S43	H		95.0	10.76 ± 0.48
F8-S43-S11	H	H	< 20.0	N.T. [b]
F8-S43-S12	H		< 20.0	N.T.
F8-S43-S13	H		< 20.0	N.T.
F8-S43-S14	Me		< 20.0	N.T.
F8-S43-S15	H		< 20.0	N.T.
F8-S43-S16	H		< 20.0	N.T.
F8-S43-S17	H		< 20.0	N.T.
F8-S43-S18	H		< 20.0	N.T.
F8-S43-S19	H		< 20.0	N.T.
F8-S43-S20	H		< 20.0	N.T.
F8-S43-S21	H		< 20.0	N.T.
F8-S43-S22	H		< 20.0	N.T.
F8-S43-S23	H		< 20.0	N.T.
F8-S43-S24	H		< 20.0	N.T.

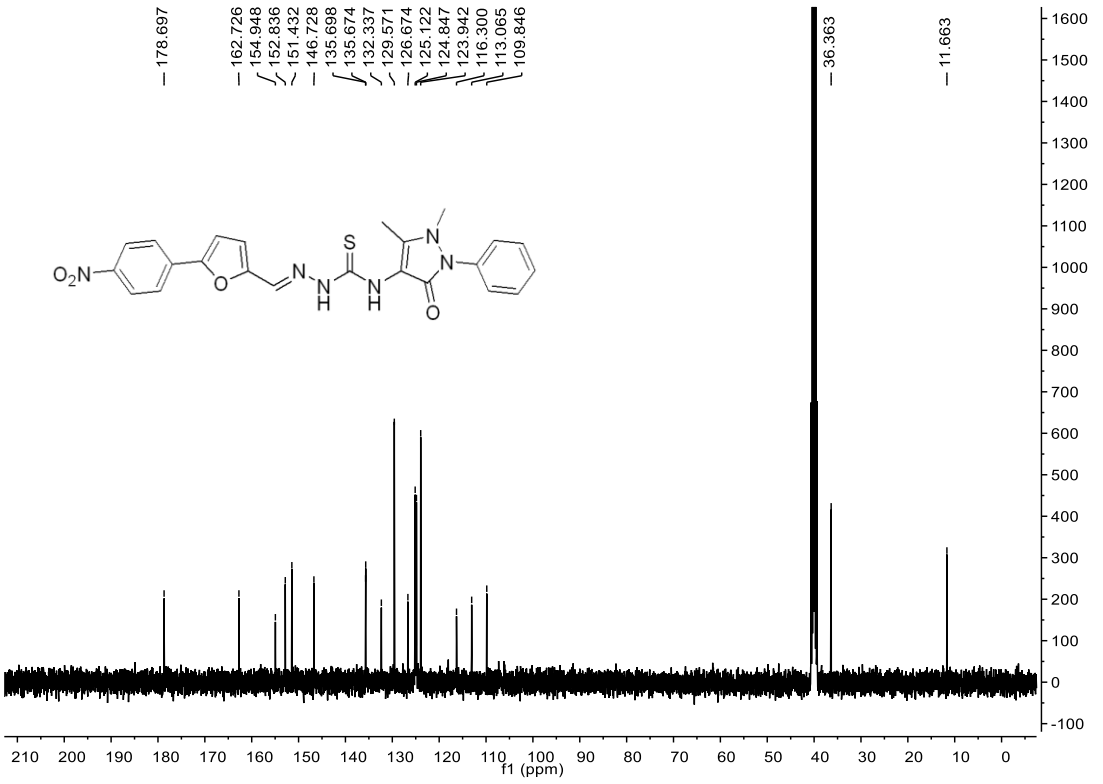
F8-S43-S25	H		< 20.0	N.T.
F8-S43-S26	H		< 20.0	N.T.
F8-S43-S27	H		< 20.0	N.T.
F8-S43-S28	H		< 20.0	N.T.
F8-S43-S29	H		< 20.0	N.T.
F8-S43-S30	H		< 20.0	N.T.
F8-S43-S31	H		< 20.0	N.T.
F8-S43-S32	H		21.2	N.T.

[a] Data are presented as geometric mean values of at least two independent runs. [b] Not tested.

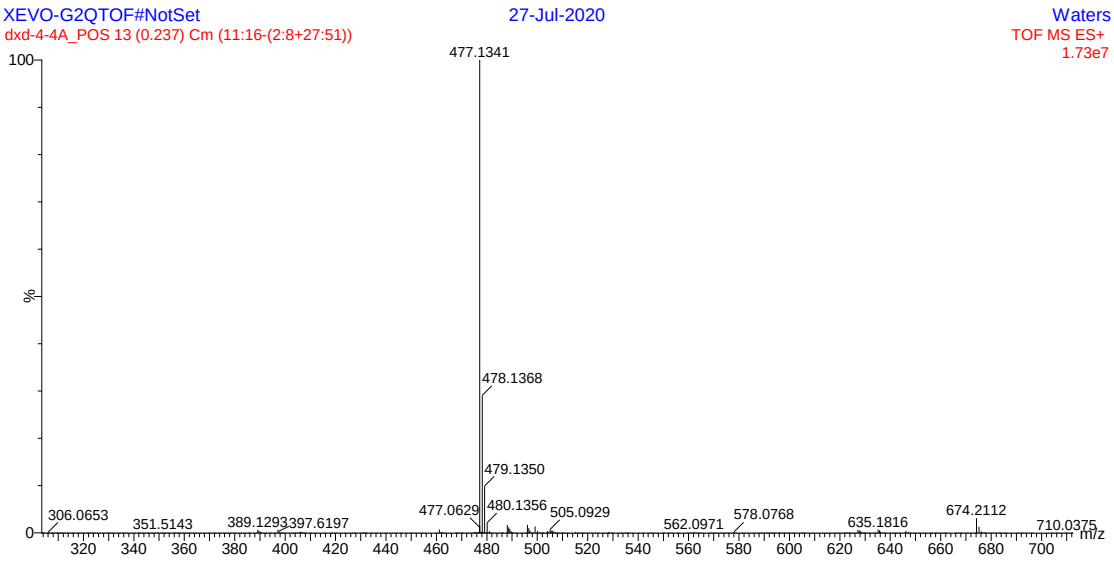
NMR Spectra



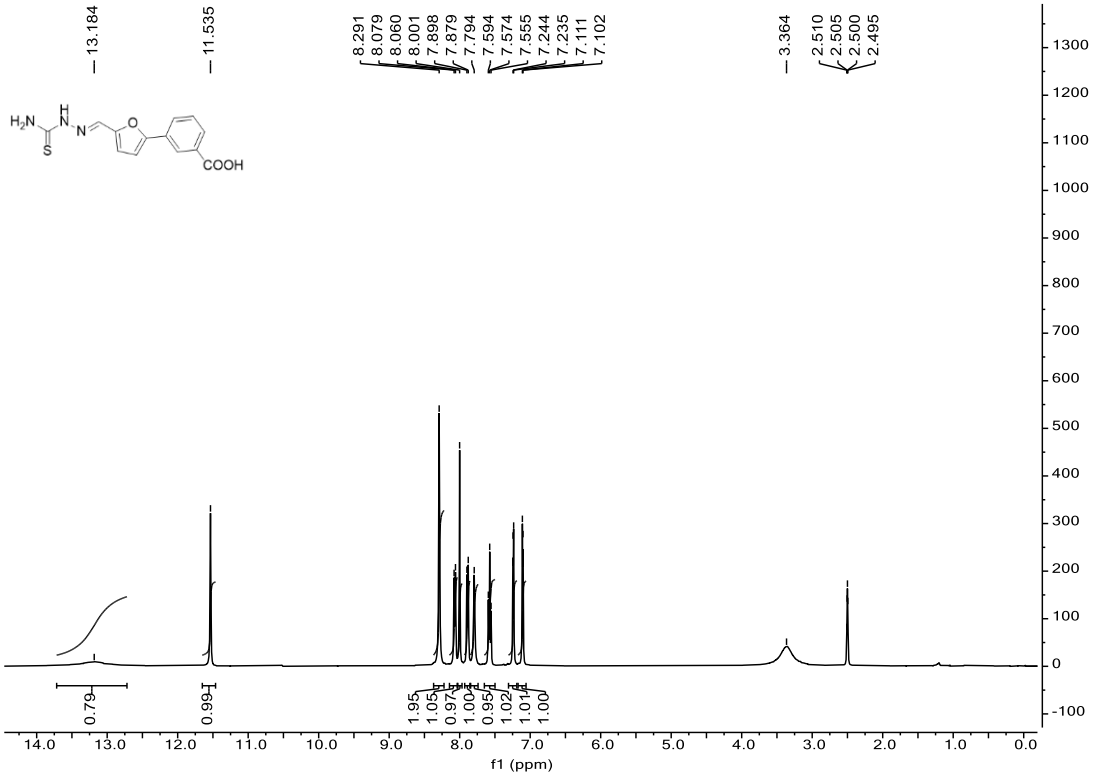
^{1}H NMR of compound **F8-S43** (400 MHz, DMSO-d_6)



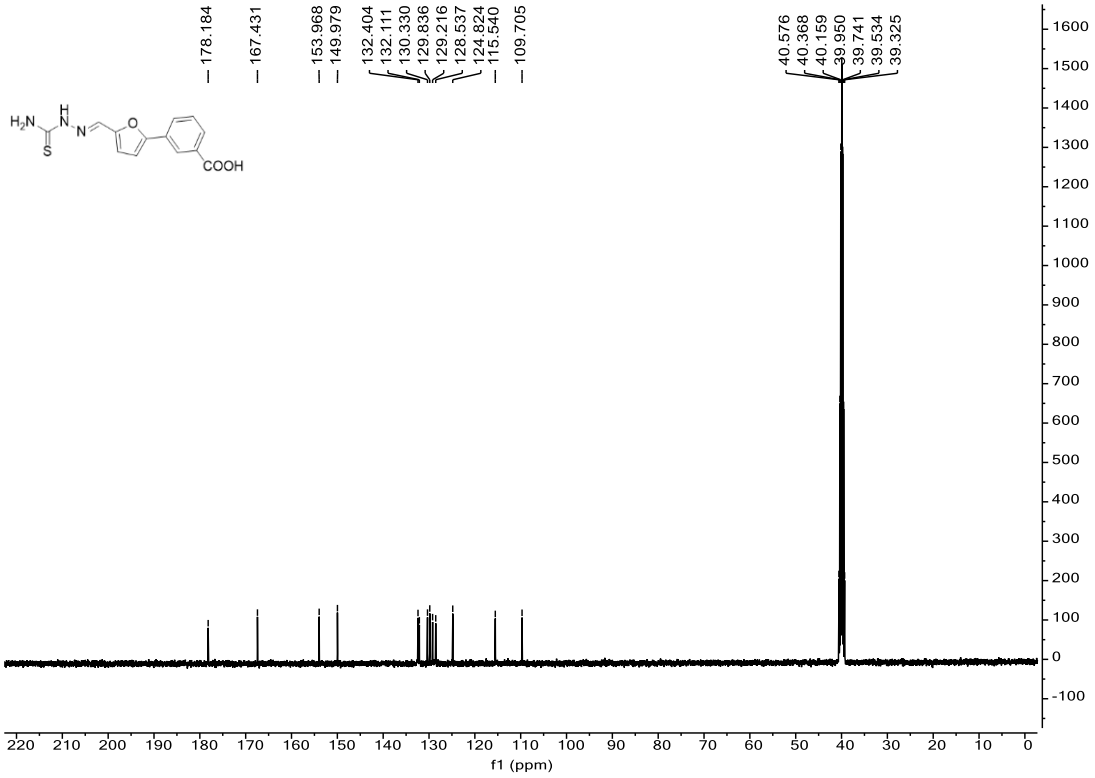
^{13}C NMR of compound **F8-S43** (100 MHz, DMSO-d_6)



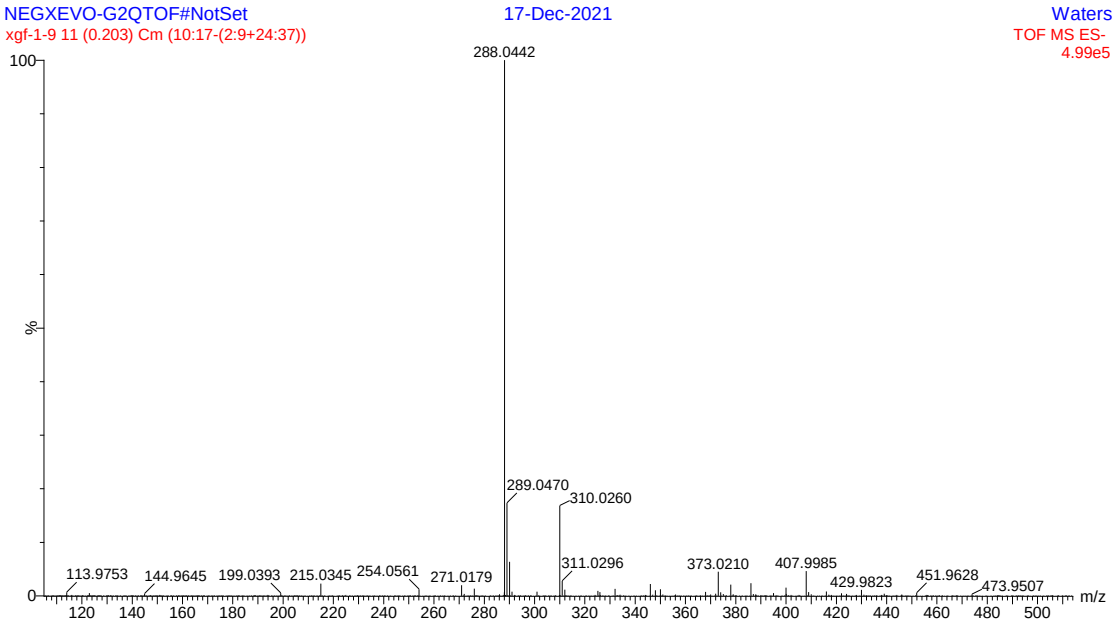
HRMS of compound **F8-S43** (ESI)



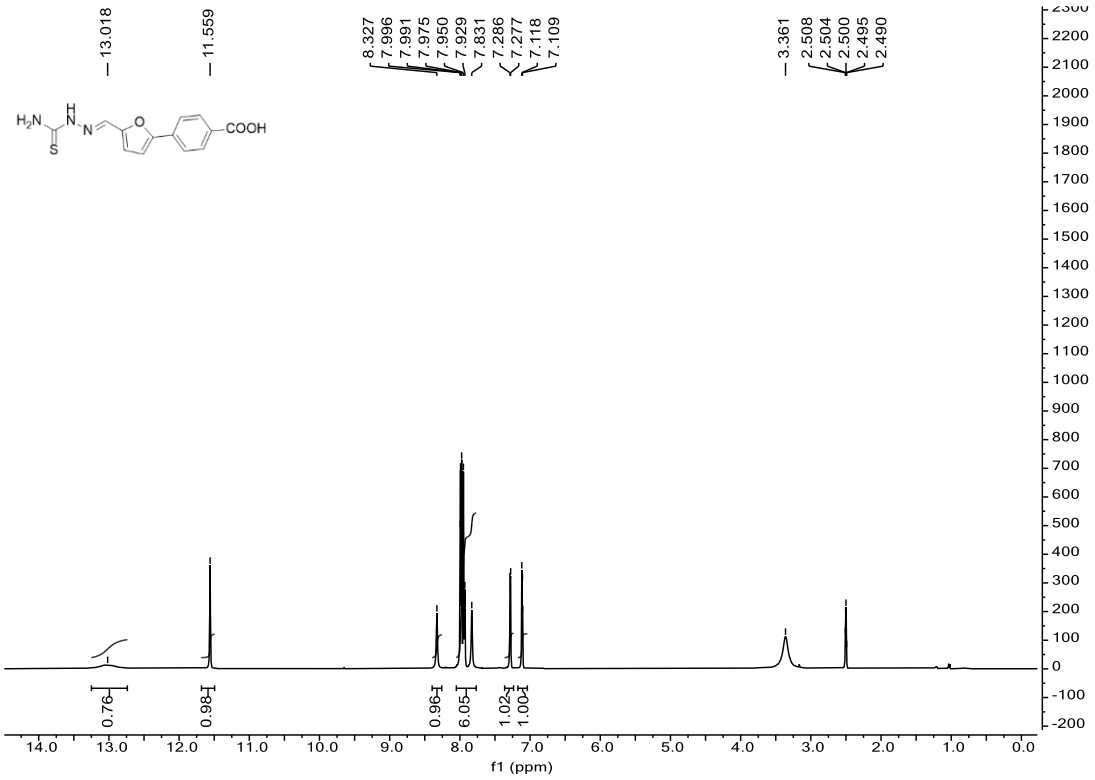
^{1}H NMR of compound **F8-A1** (400 MHz, DMSO-d_6)



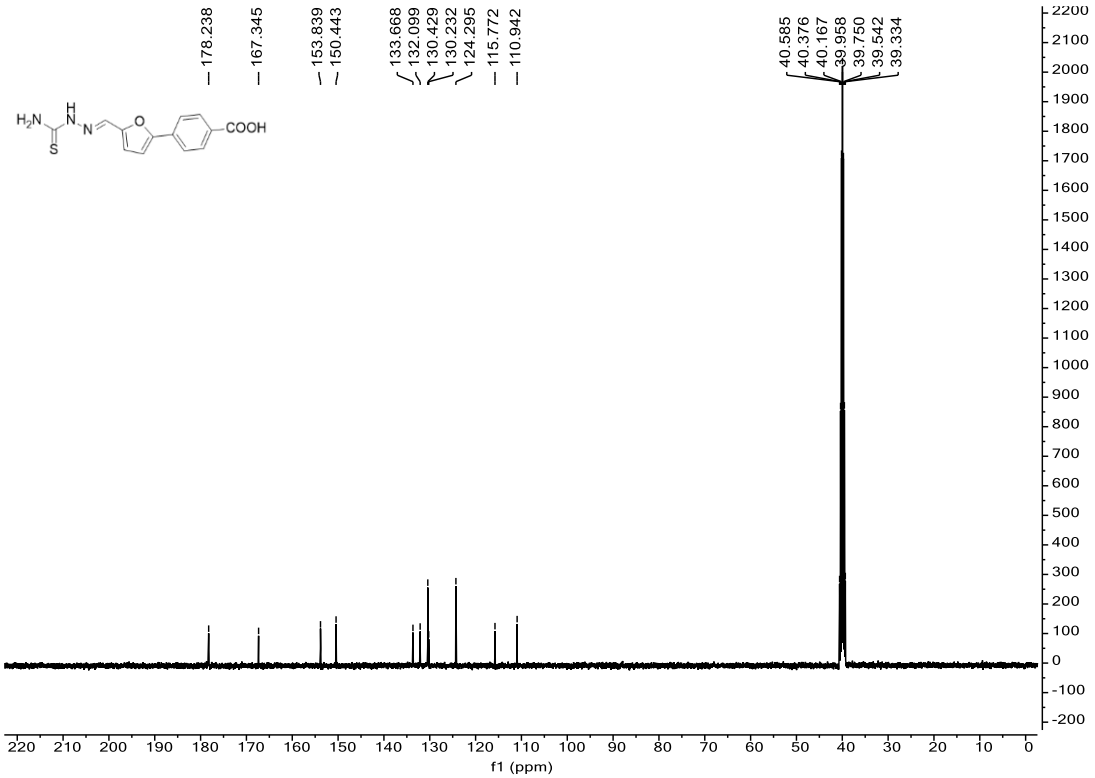
^{13}C NMR of compound **F8-A1** (100 MHz, DMSO-d_6)



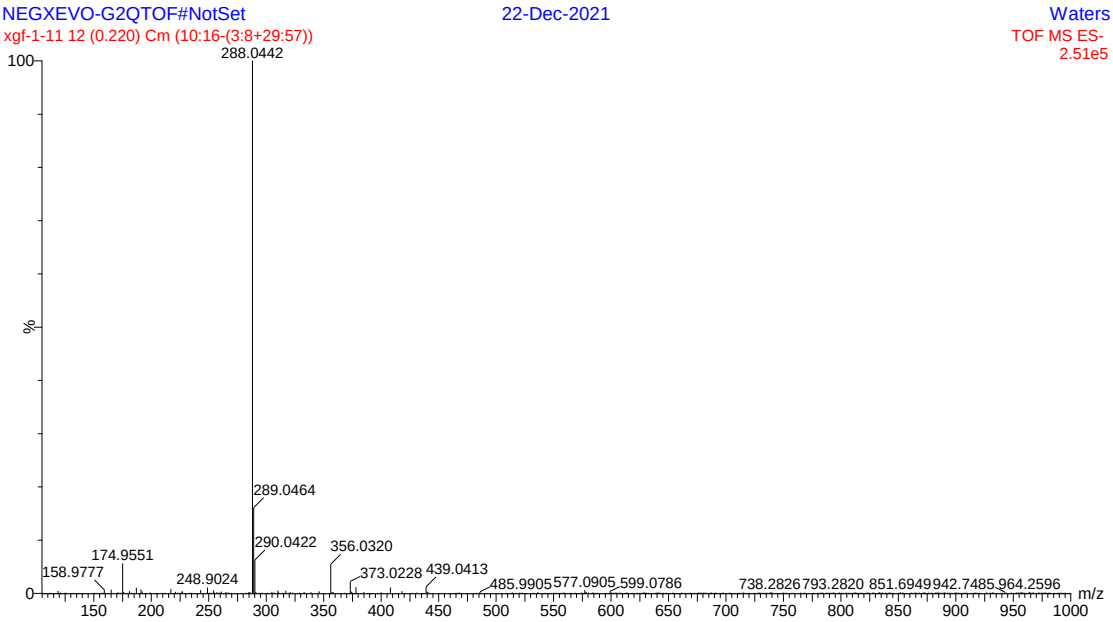
HRMS of compound **F8-A1** (ESI)



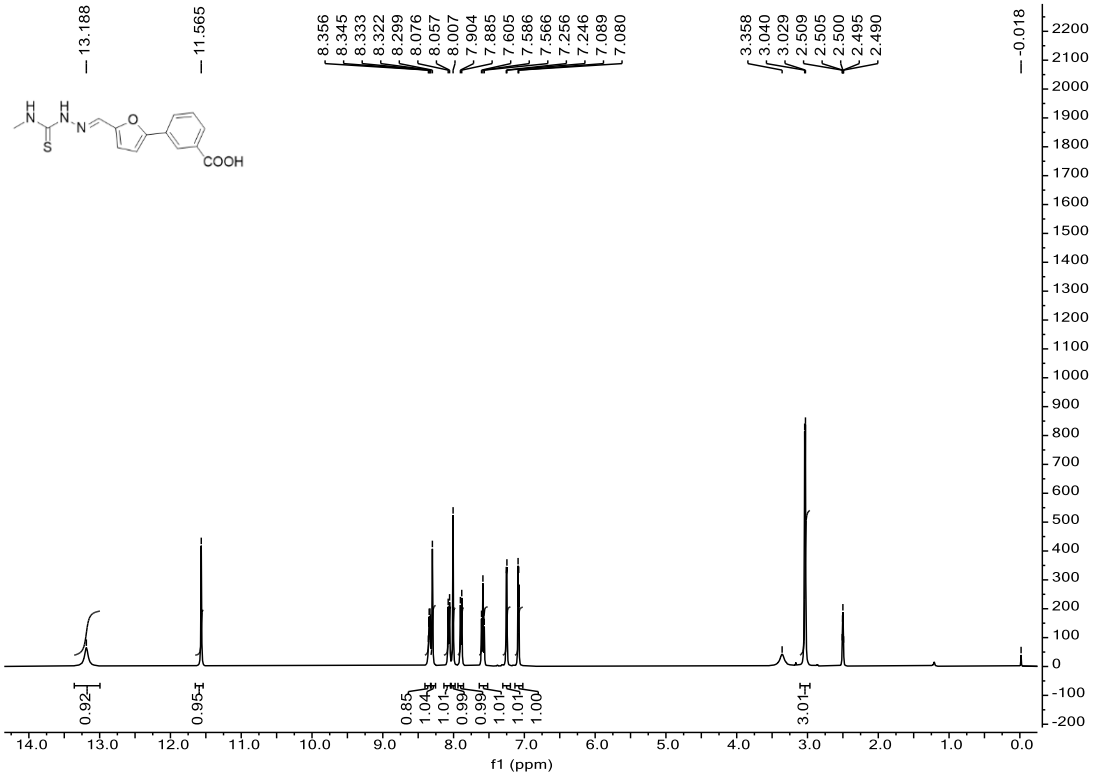
^{1}H NMR of compound **F8-A2** (400 MHz, DMSO-d_6)



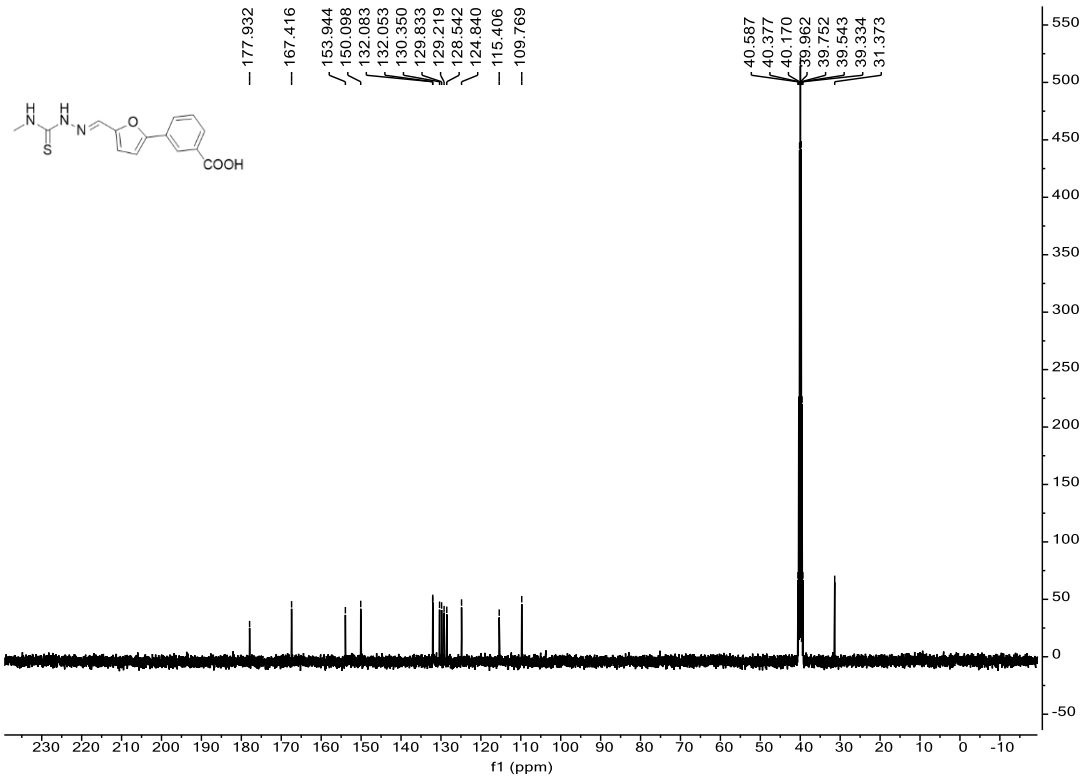
^{13}C NMR of compound **F8-A2** (100 MHz, DMSO- d_6)



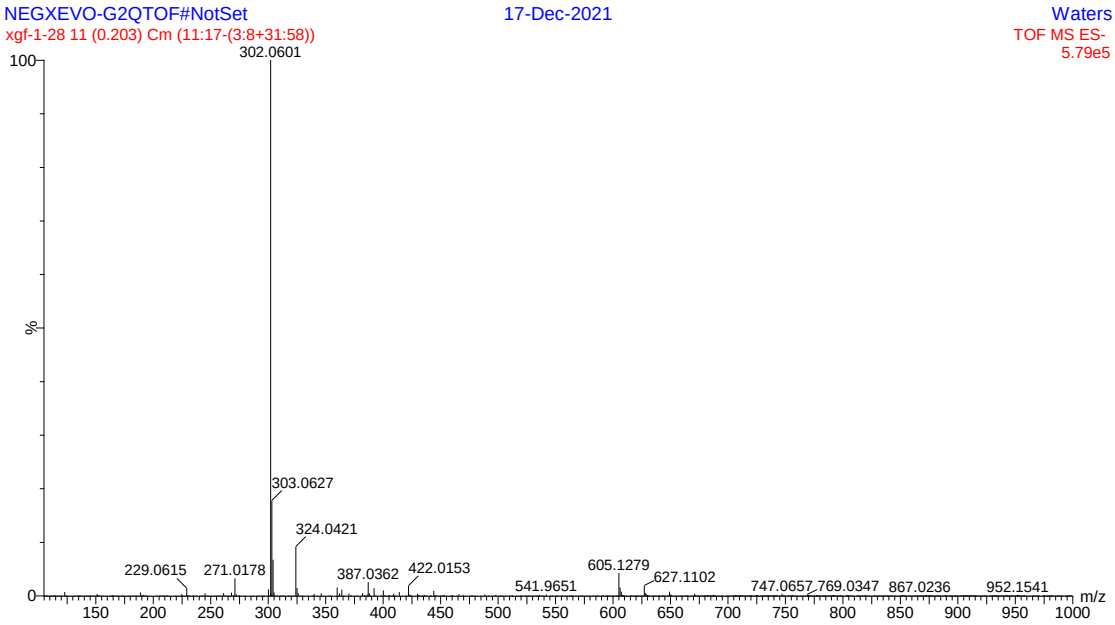
HRMS of compound **F8-A2** (ESI)



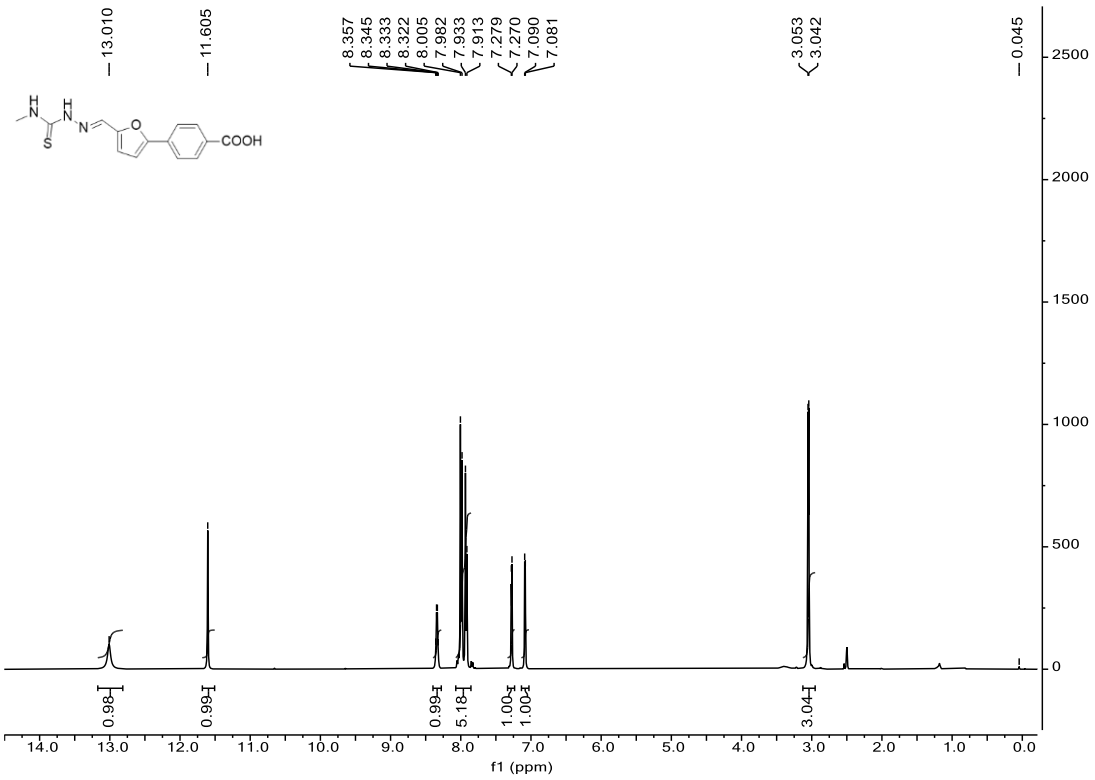
^{1}H NMR of compound **F8-A3** (400 MHz, DMSO-d_6)



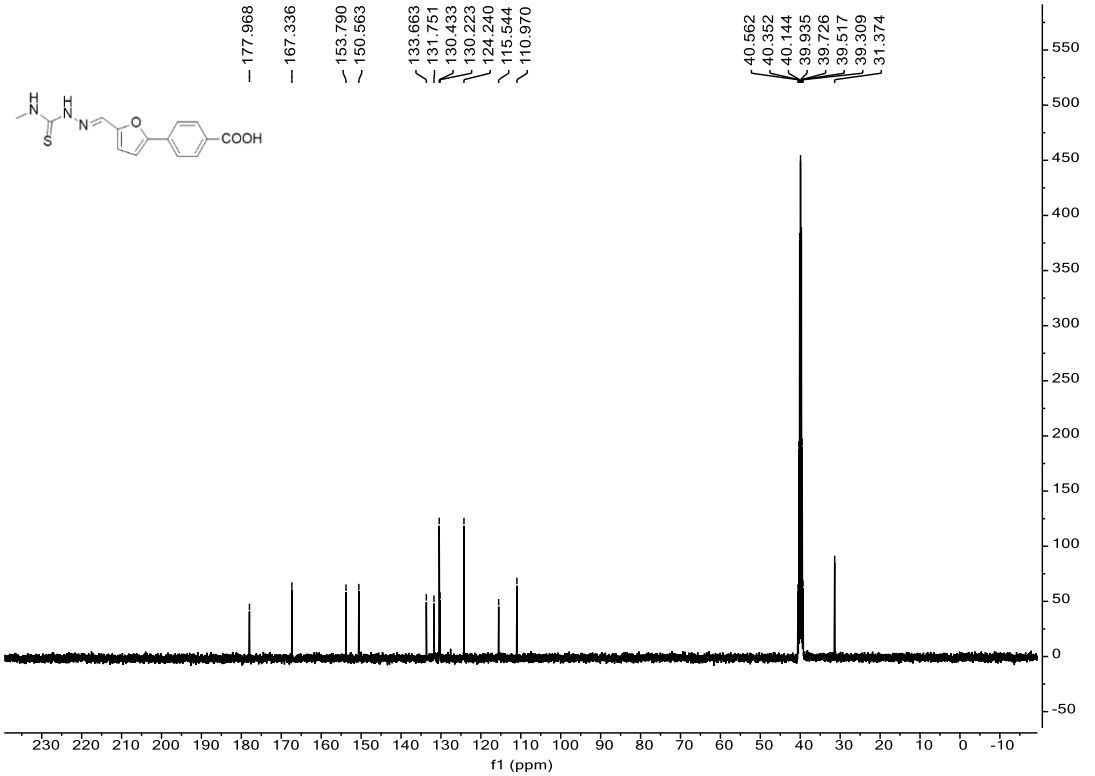
^{13}C NMR of compound **F8-A3** (100 MHz, DMSO- d_6)



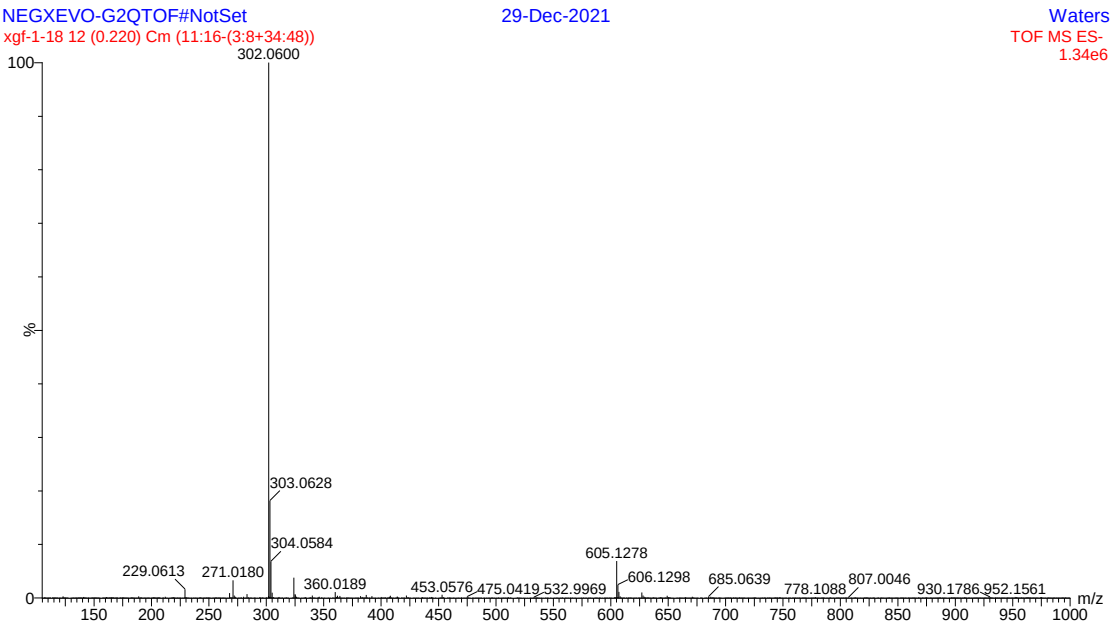
HRMS of compound **F8-A3** (ESI)



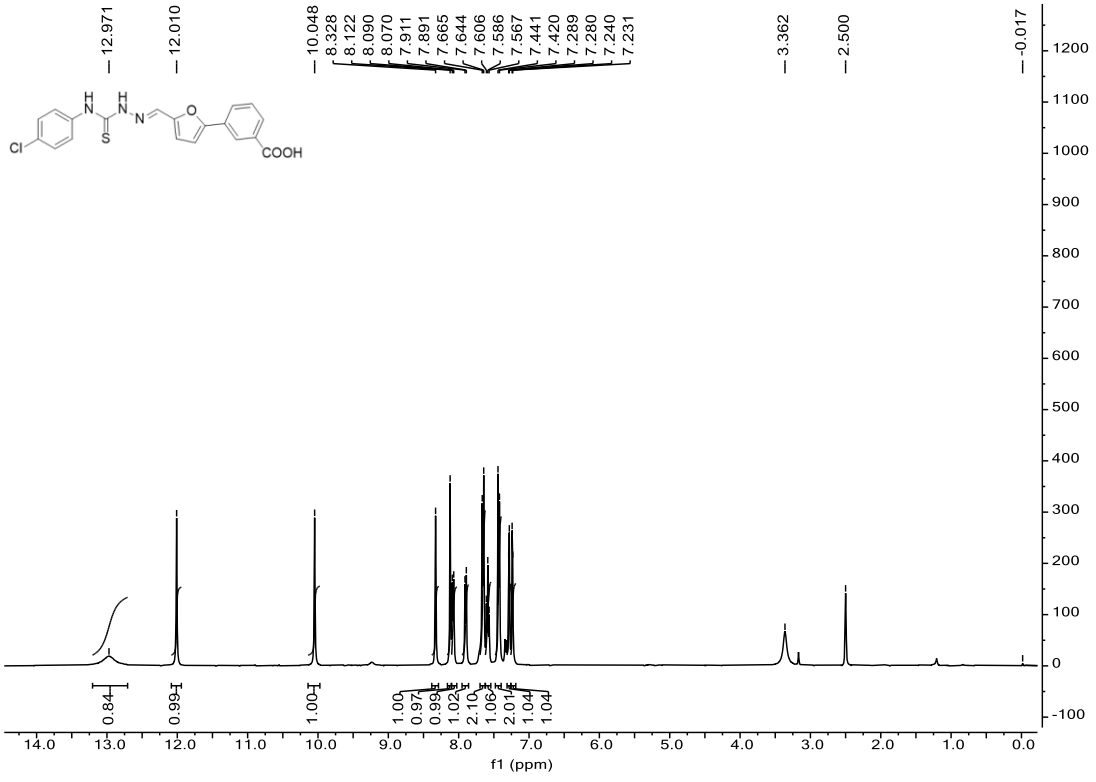
^{1}H NMR of compound **F8-A4** (400 MHz, DMSO-d_6)



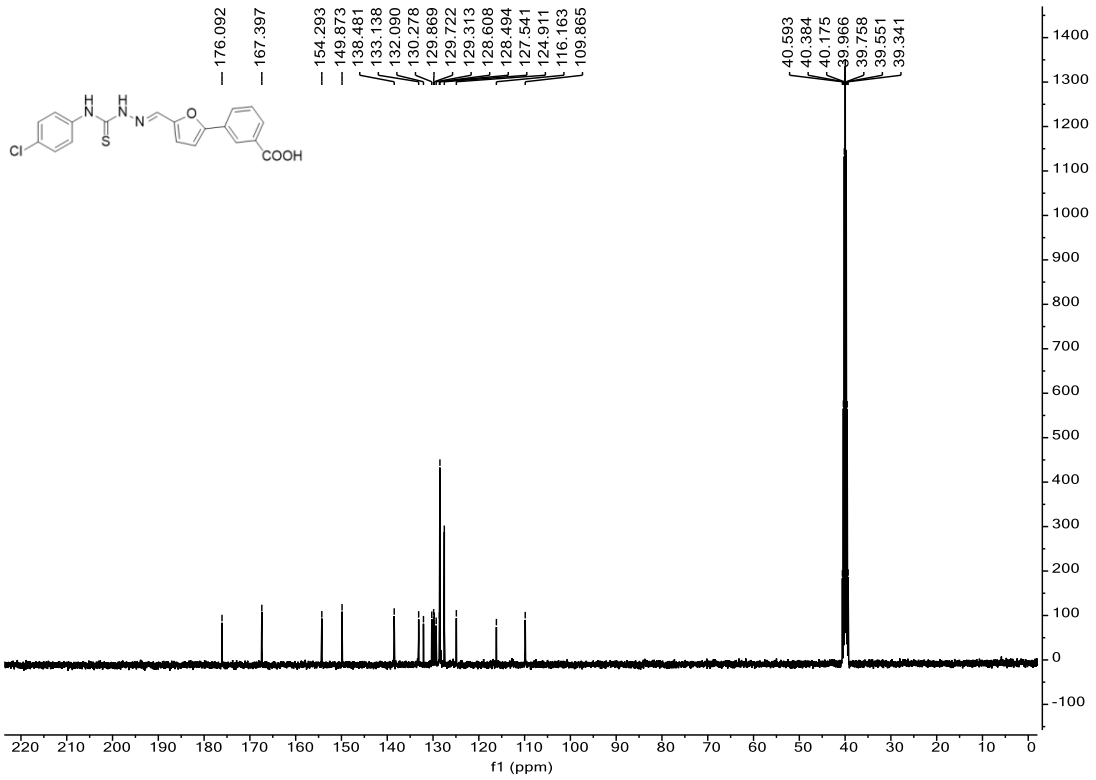
^{13}C NMR of compound **F8-A4** (100 MHz, DMSO- d_6)



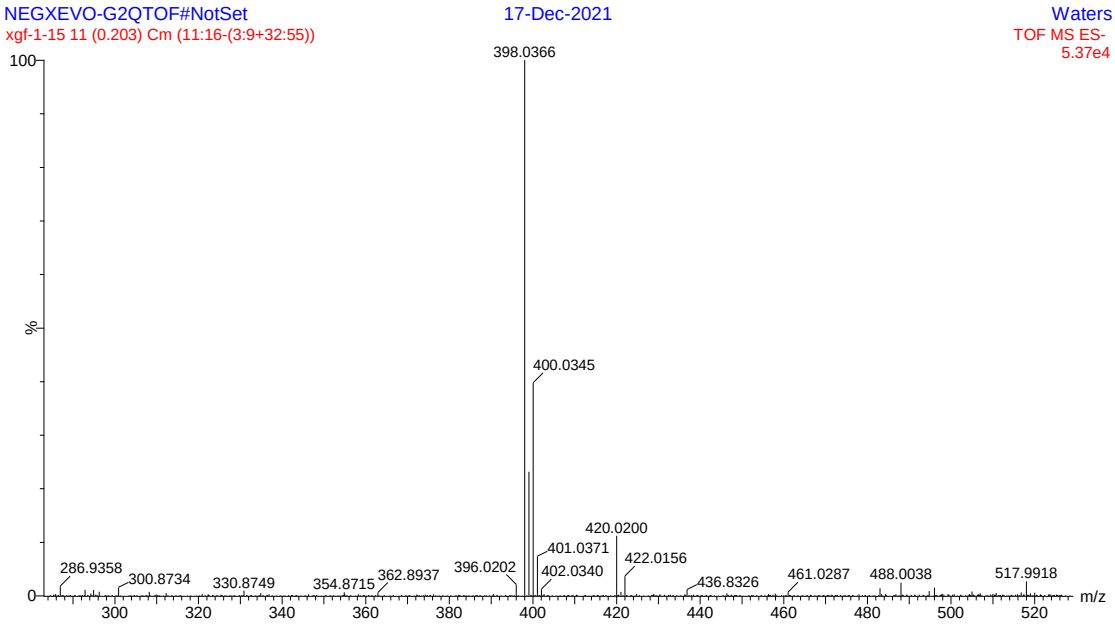
HRMS of compound **F8-A4** (ESI)



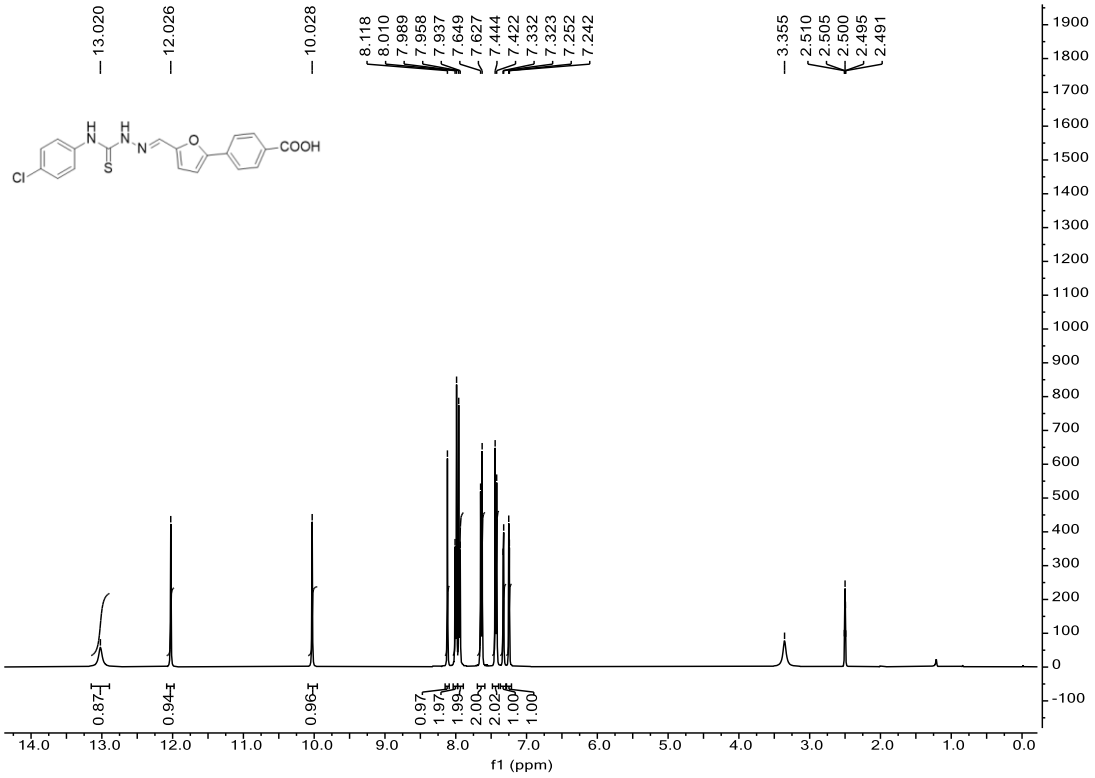
^{1}H NMR of compound **F8-A5** (400 MHz, DMSO-*d*$_6$)



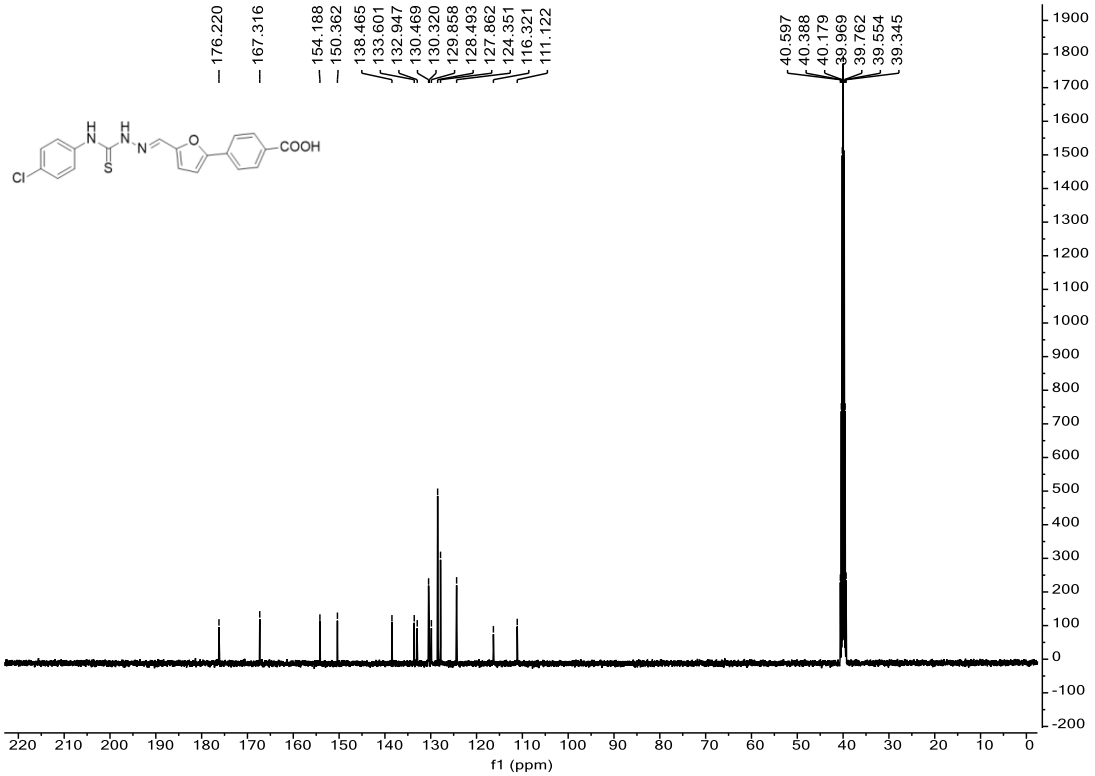
^{13}C NMR of compound **F8-A5** (100 MHz, DMSO-d_6)



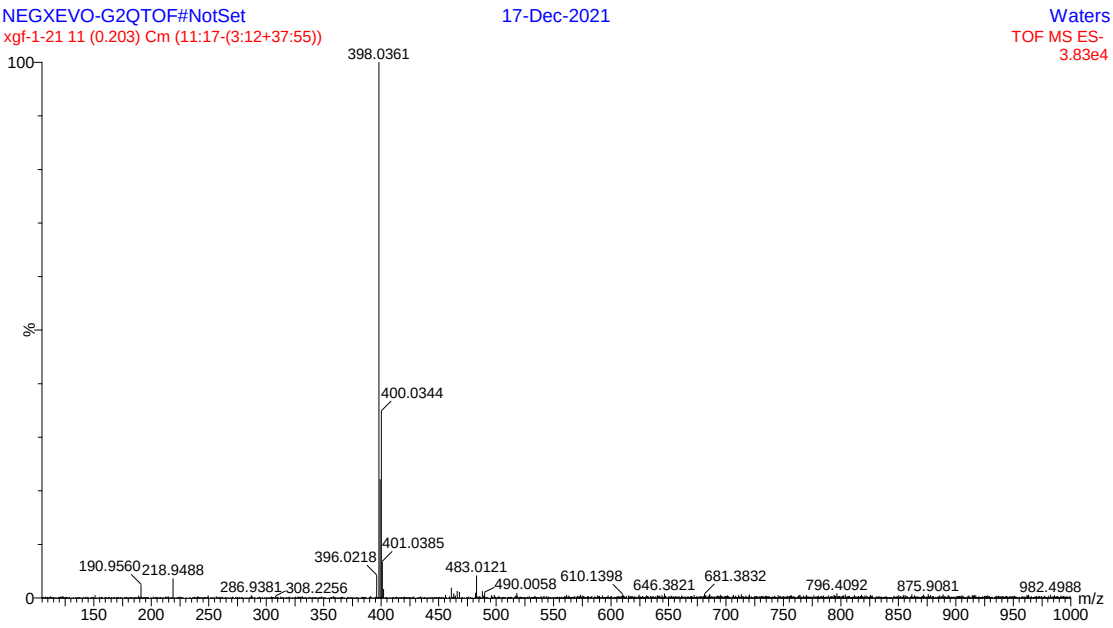
HRMS of compound **F8-A5** (ESI)



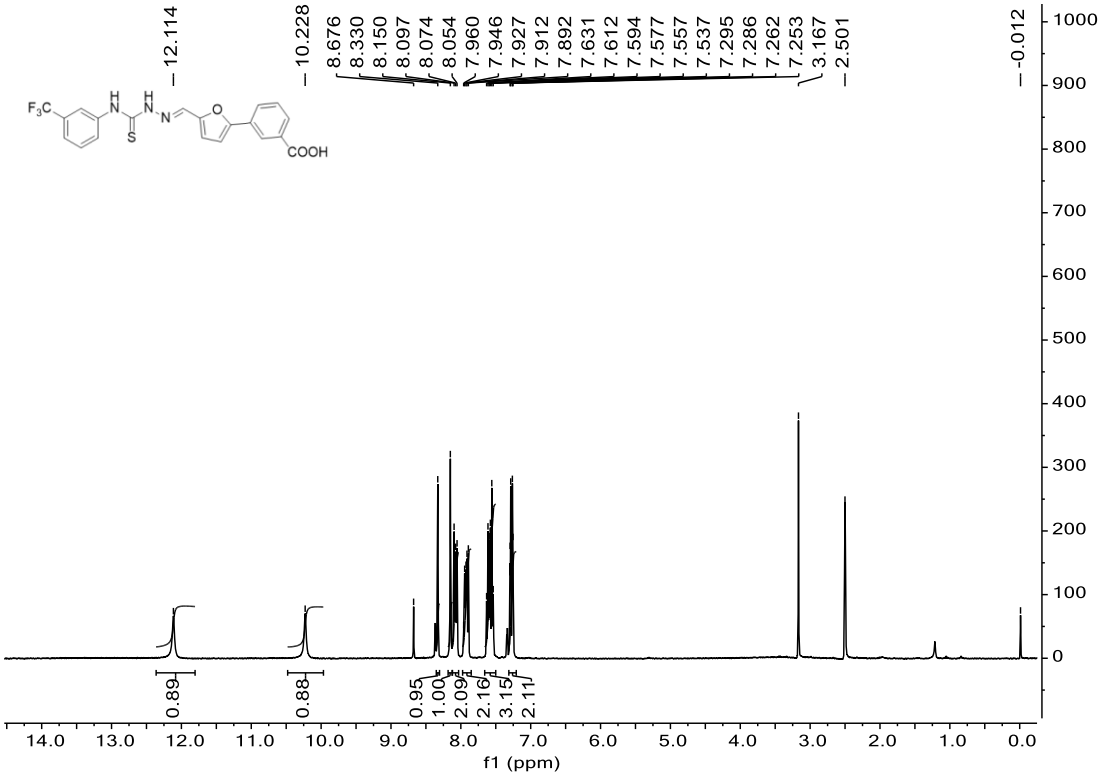
^{1}H NMR of compound **F8-A6** (400 MHz, DMSO-d_6)



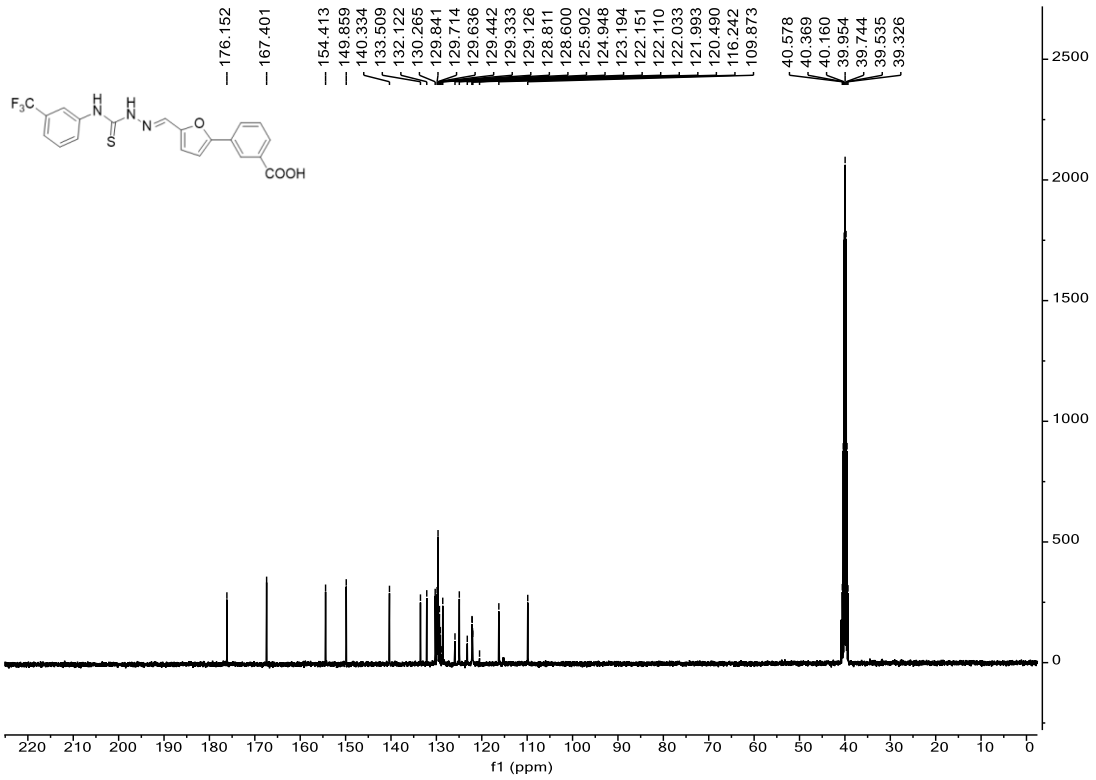
^{13}C NMR of compound **F8-A6** (100 MHz, DMSO-d_6)



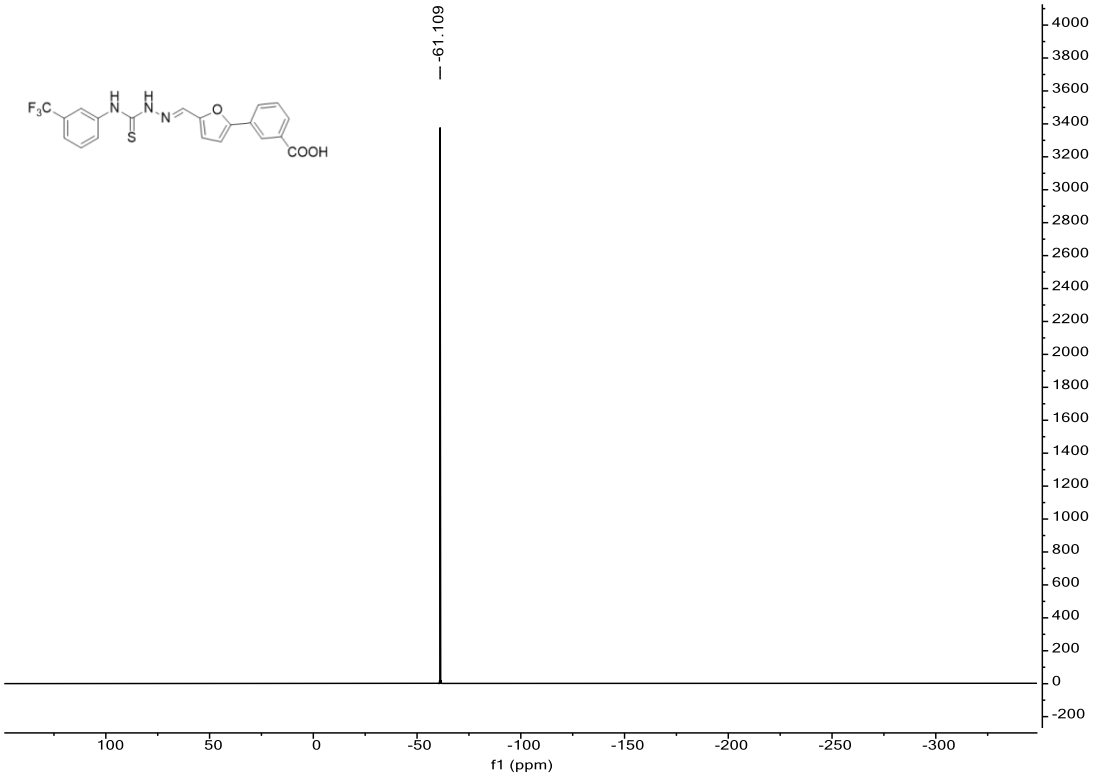
HRMS of compound **F8-A6** (ESI)



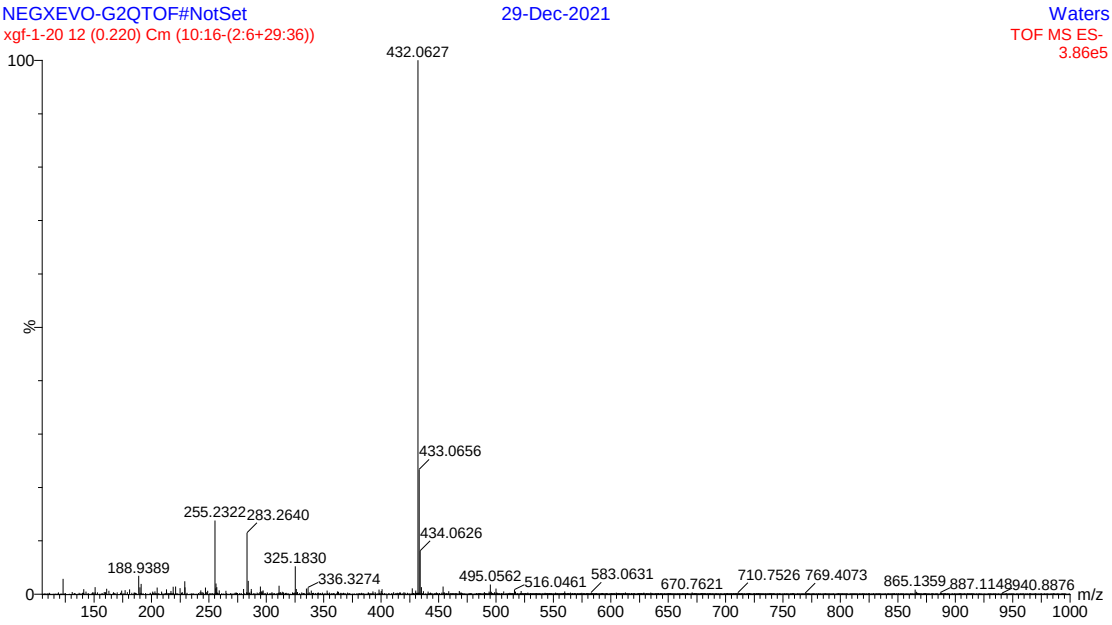
^{1}H NMR of compound **F8-A7** (400 MHz, DMSO-*d*$_6$)



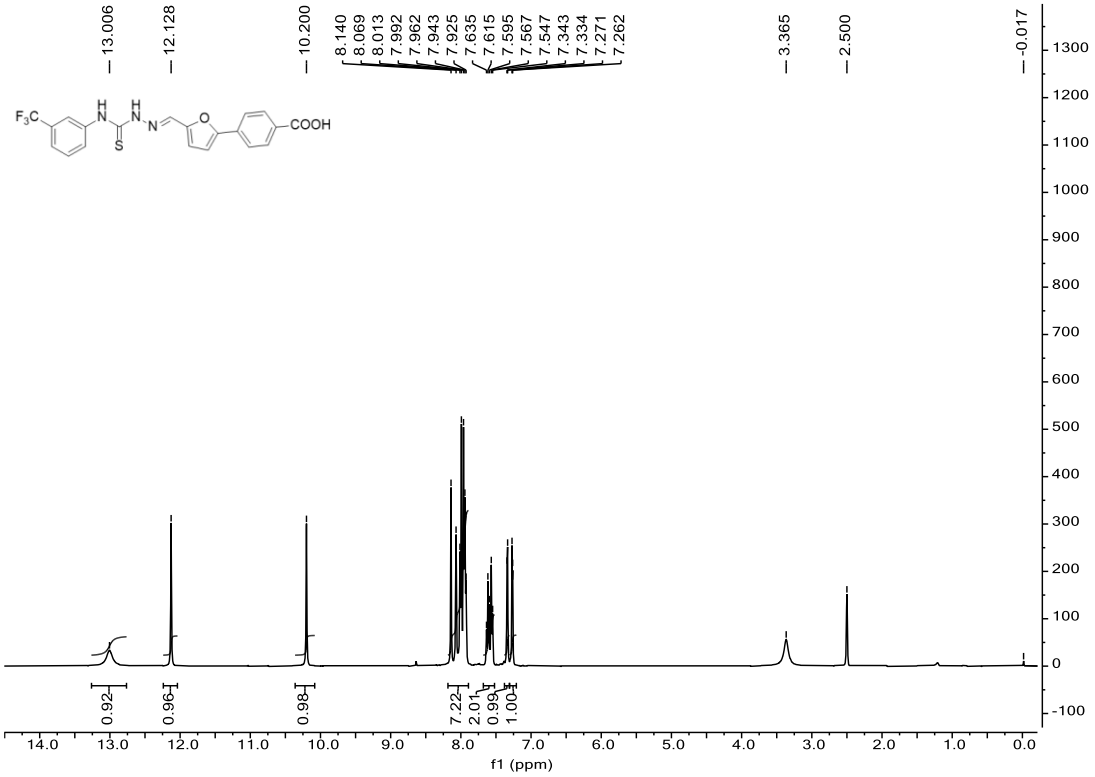
^{13}C NMR of compound **F8-A7** (100 MHz, DMSO-d_6)



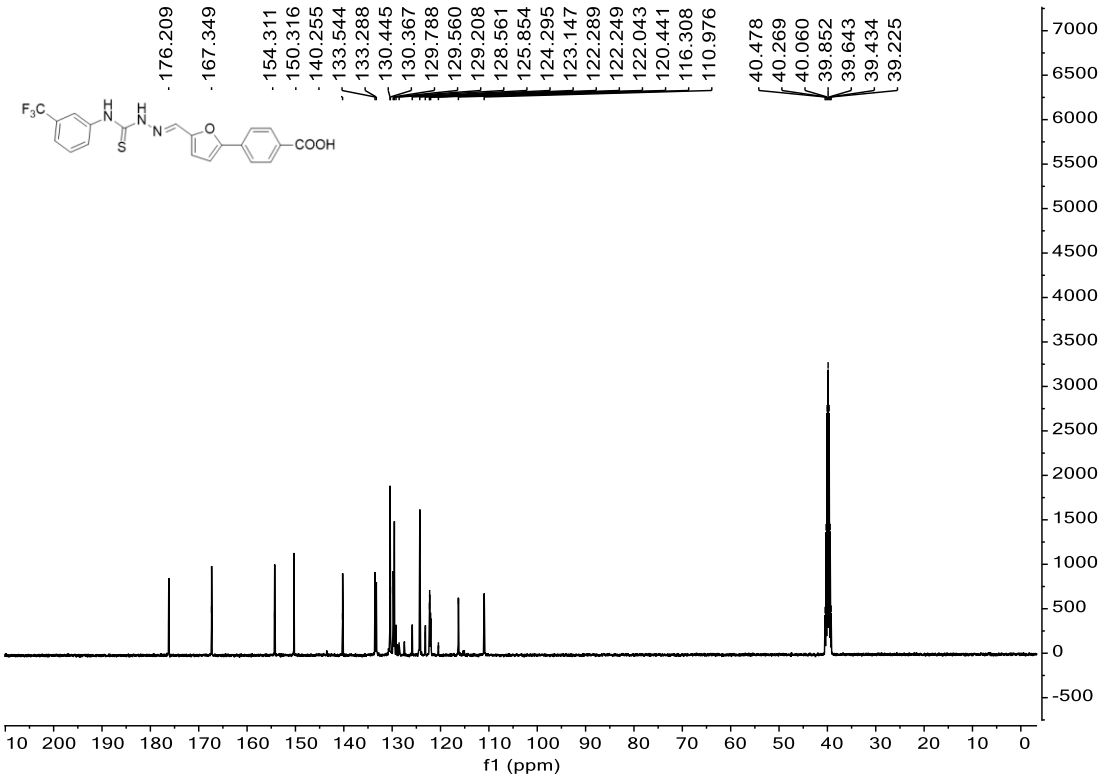
^{19}F NMR of compound **F8-A7** (376 MHz, DMSO-d_6)



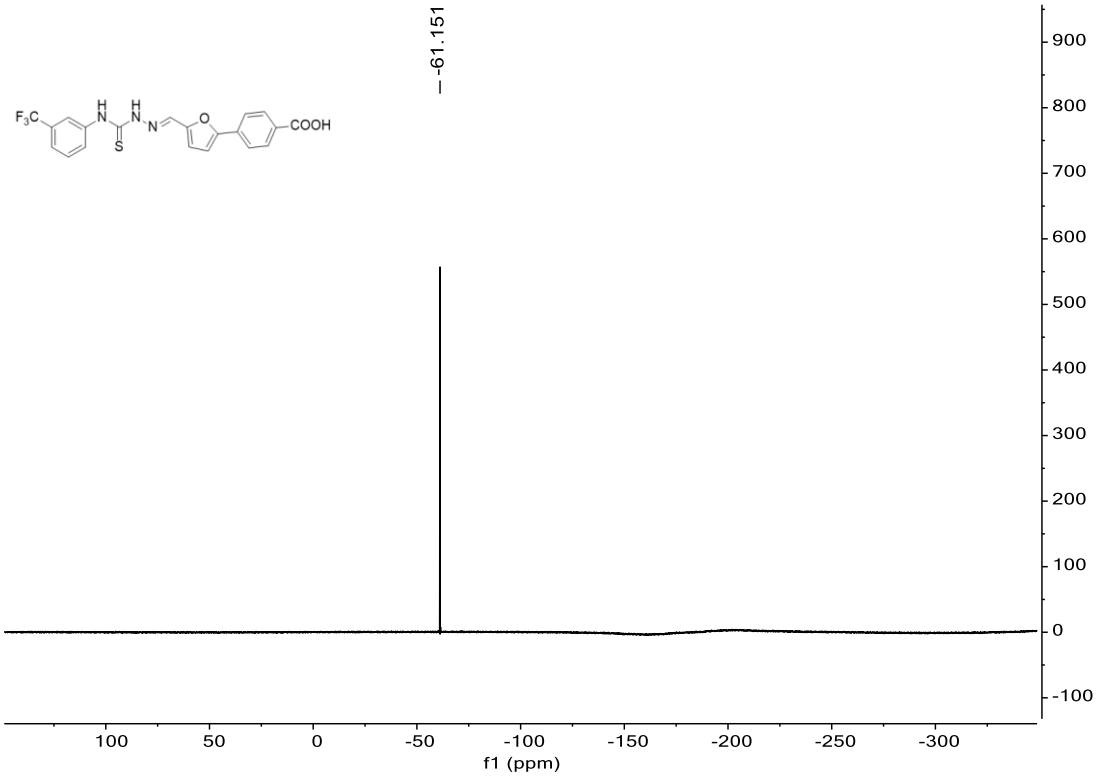
HRMS of compound **F8-A7** (ESI)



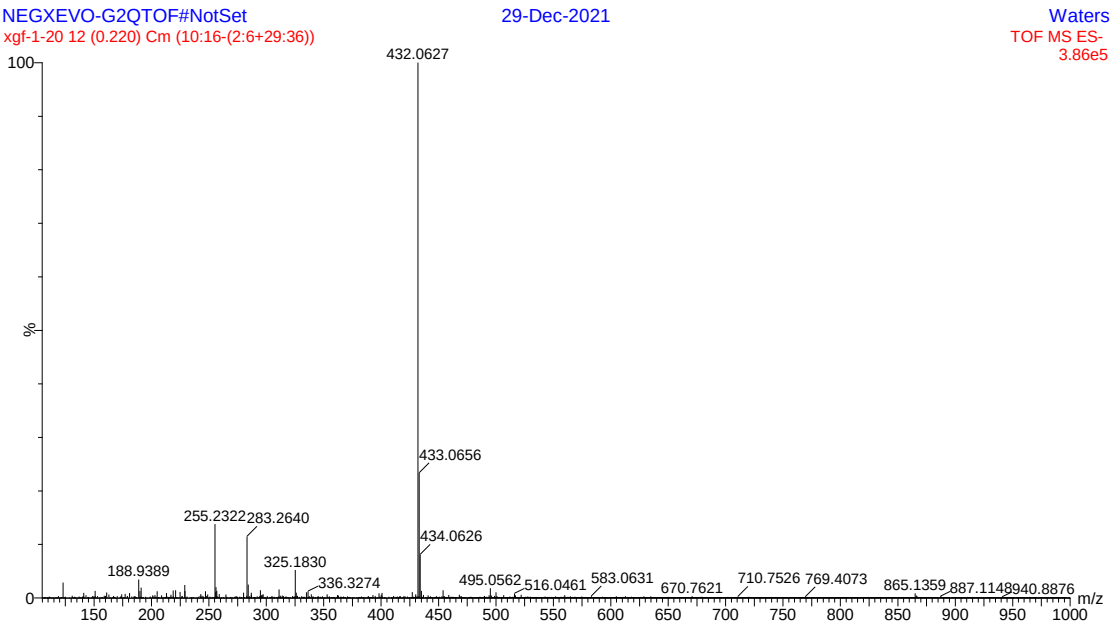
^{1}H NMR of compound **F8-A8** (400 MHz, DMSO-d_6)



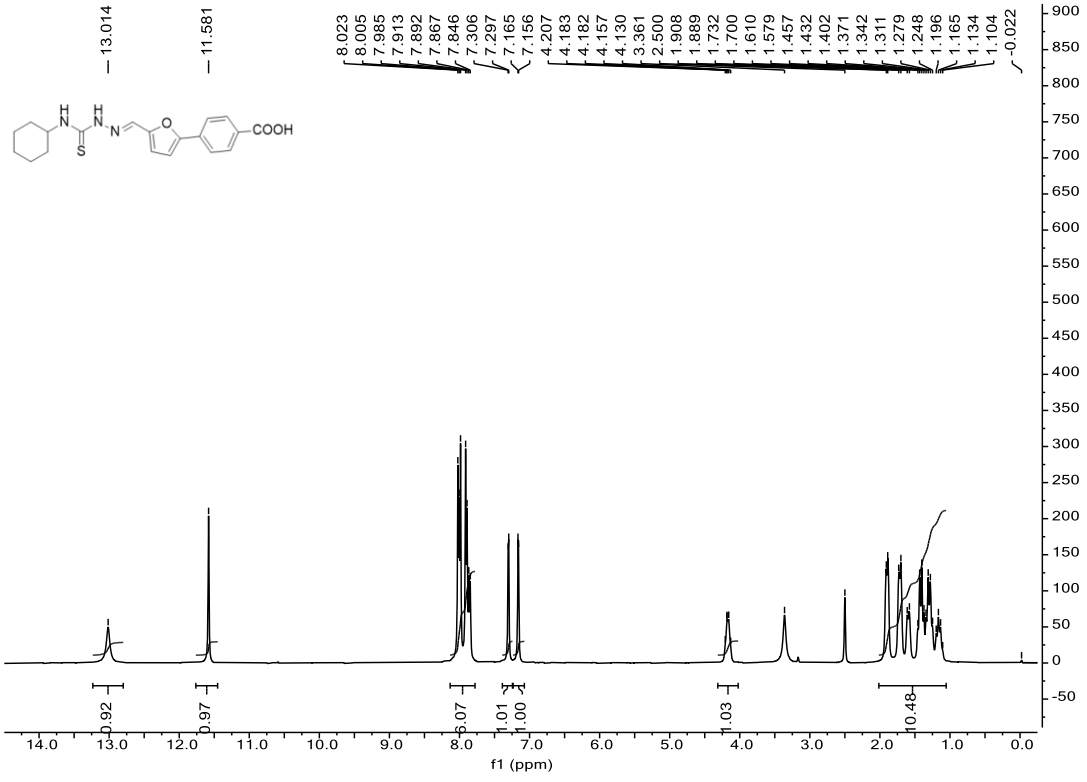
^{13}C NMR of compound **F8-A8** (400 MHz, DMSO-d_6)



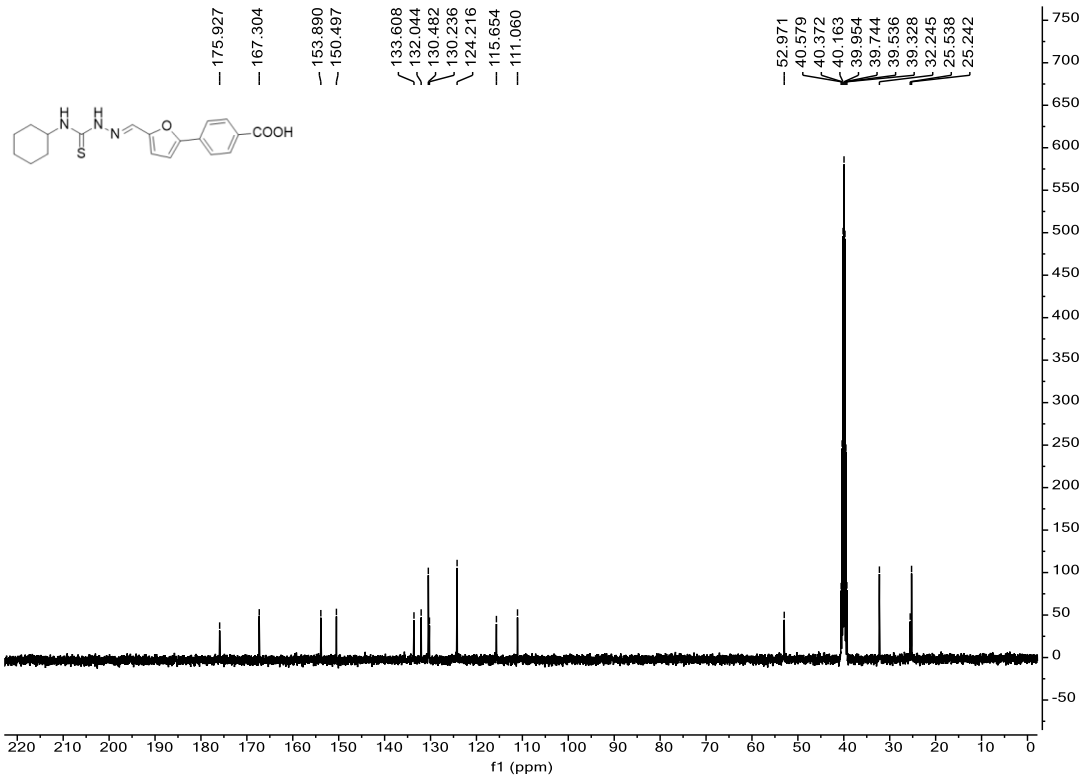
^{19}F NMR of compound **F8-A8** (376 MHz, DMSO-d_6)



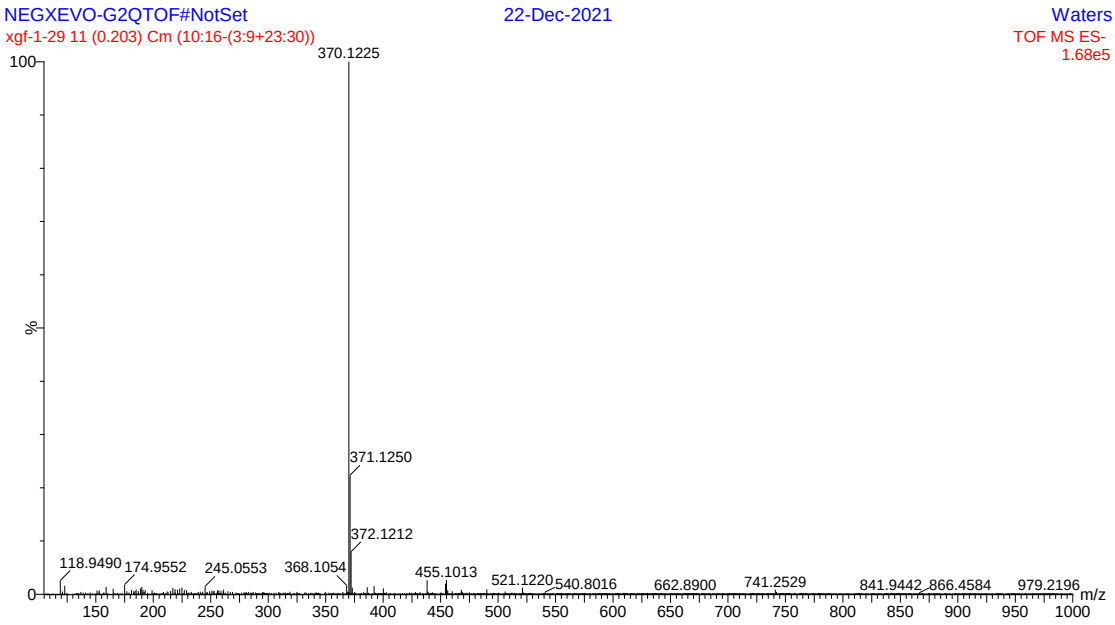
HRMS of compound **F8-A8** (ESI)



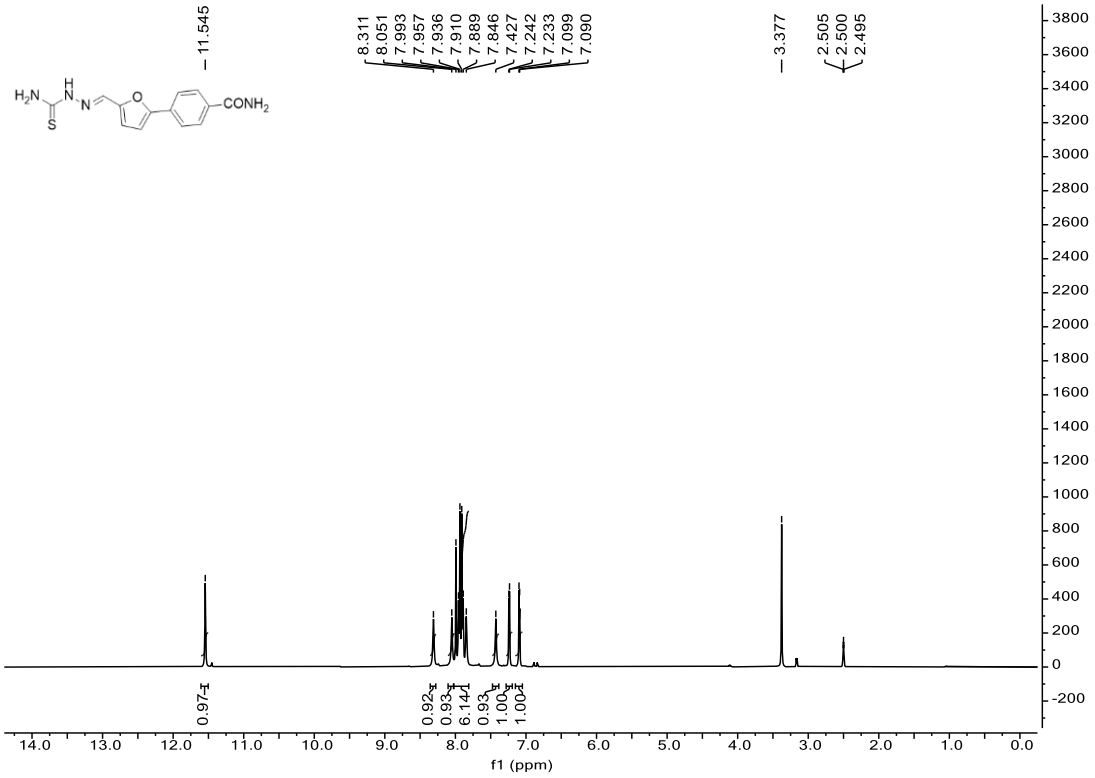
^{1}H NMR of compound **F8-A9** (400 MHz, DMSO-d_6)



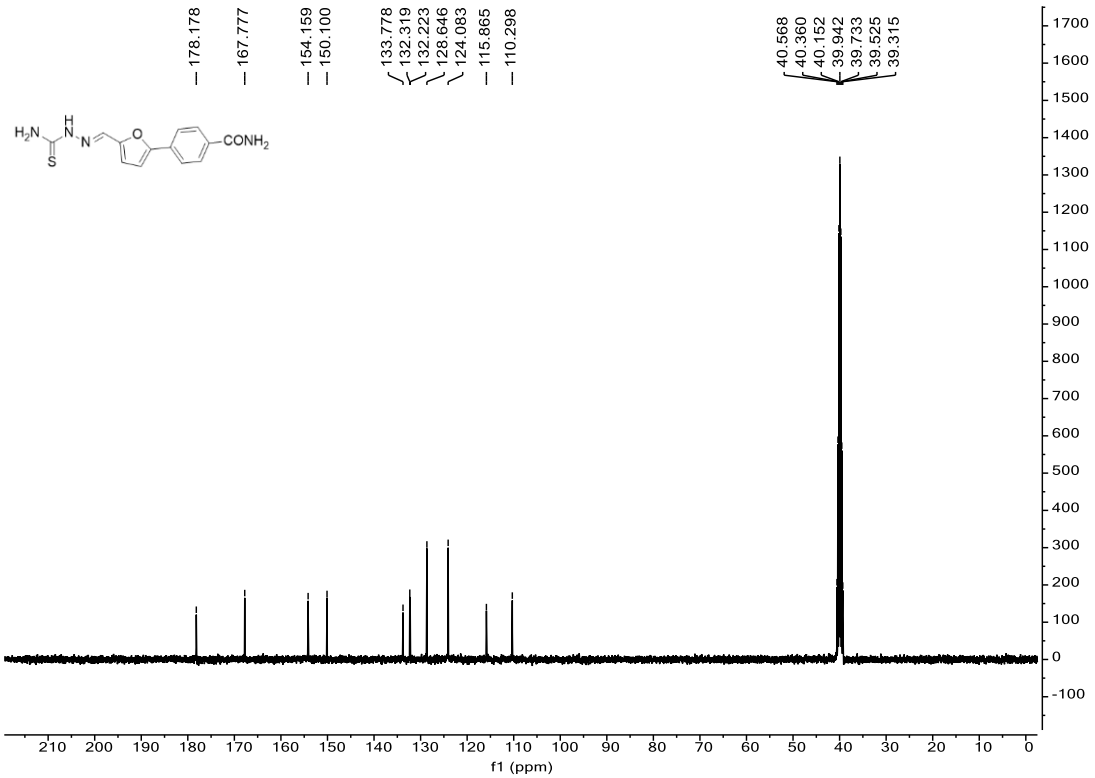
^{13}C NMR of compound **F8-A9** (100 MHz, DMSO-d_6)



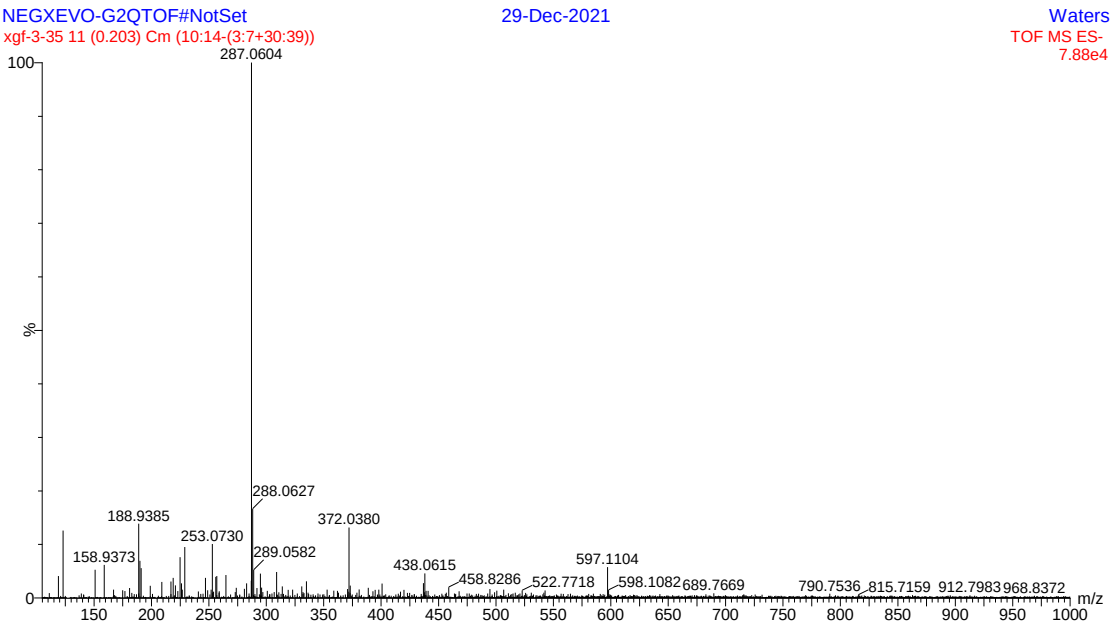
HRMS of compound **F8-A9** (ESI)



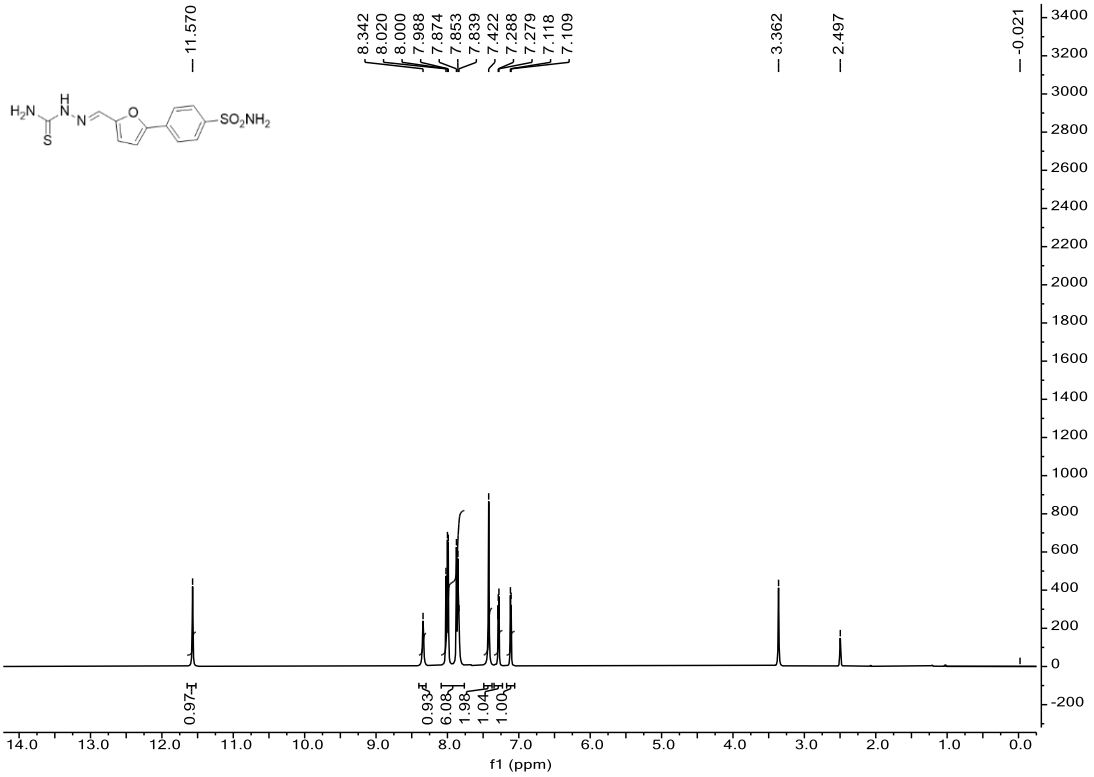
^{1}H NMR of compound **F8-B1** (400 MHz, DMSO-d_6)



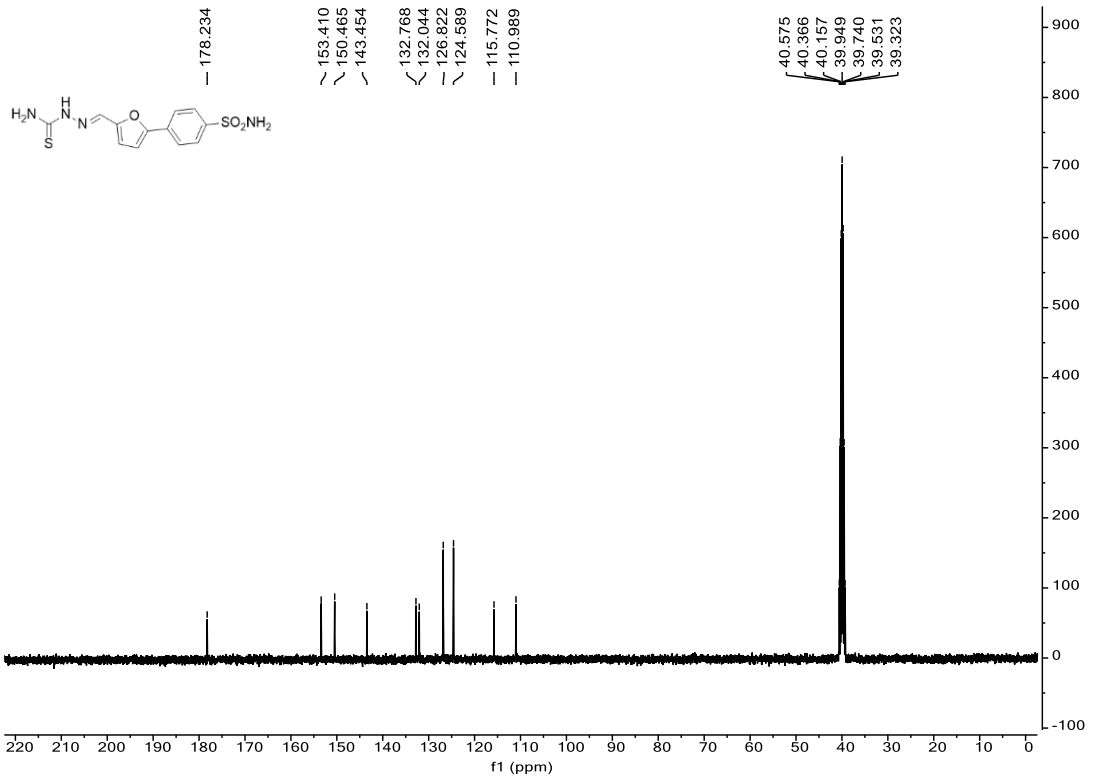
^{13}C NMR of compound **F8-B1** (100 MHz, DMSO-d_6)



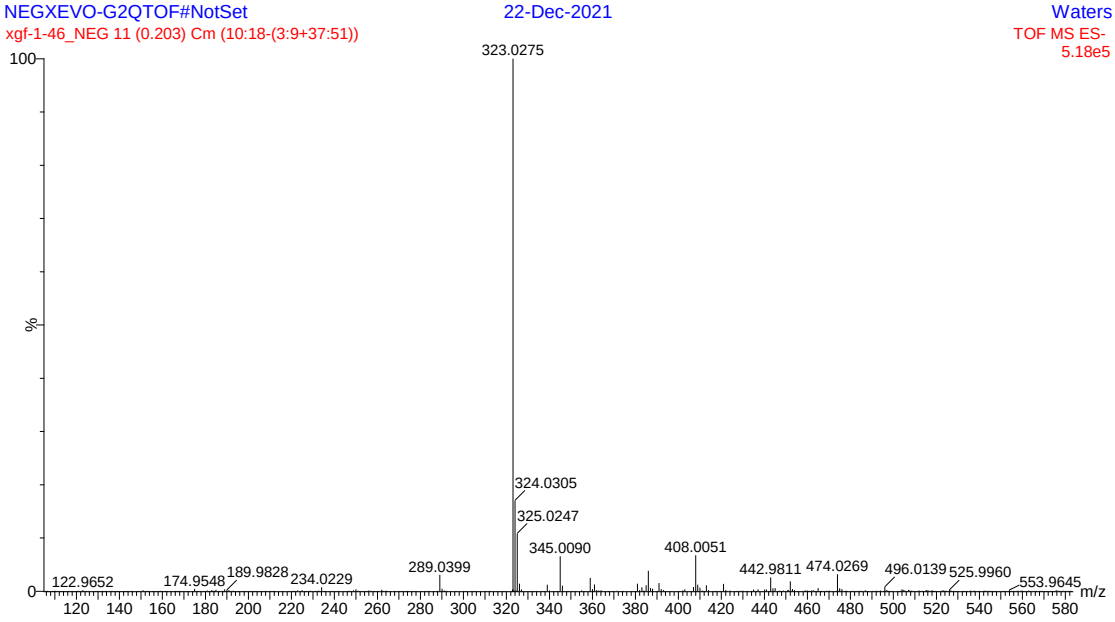
HRMS of compound **F8-B1** (ESI)



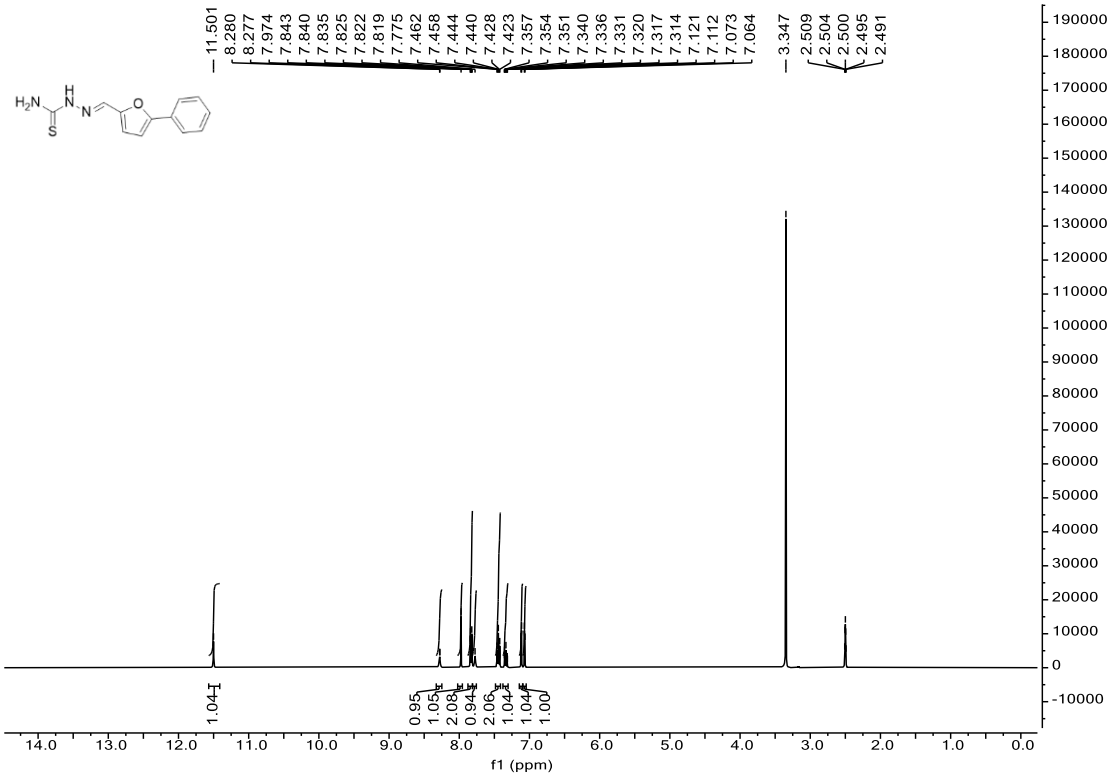
^{1}H NMR of compound **F8-B2** (400 MHz, DMSO-d_6)



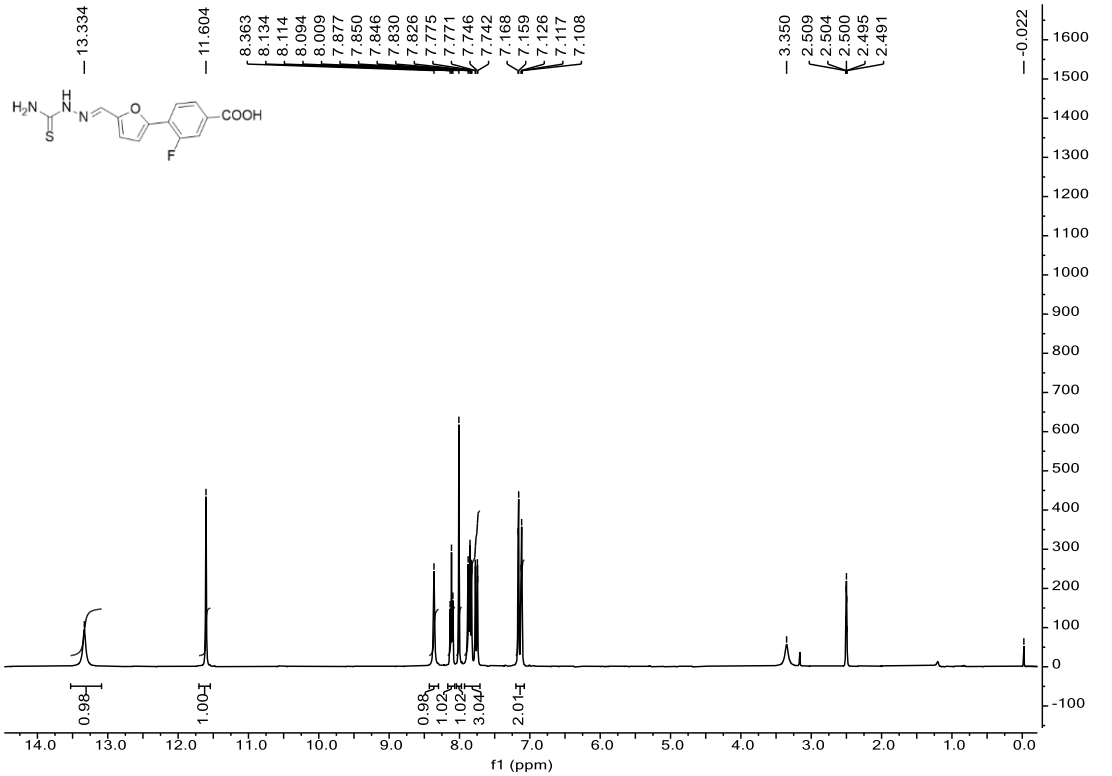
^{13}C NMR of compound **F8-B2** (100 MHz, DMSO-d_6)



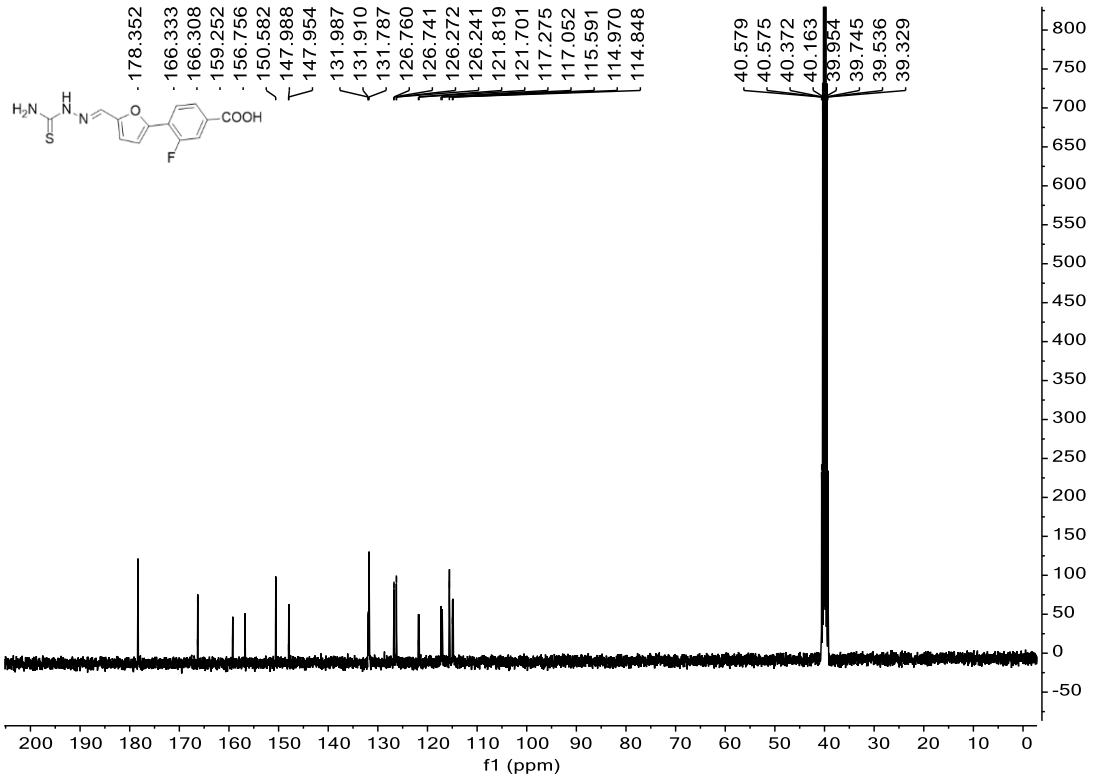
HRMS of compound **F8-B2** (ESI)



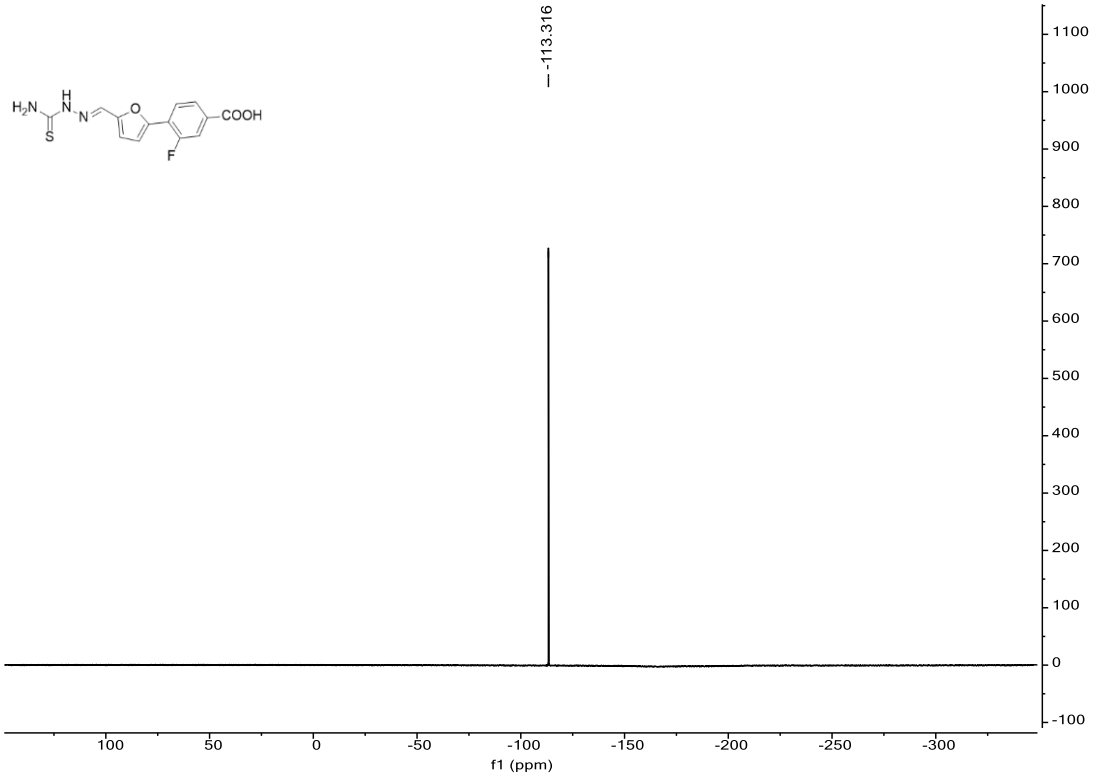
^{1}H NMR of compound **F8-B3** (400 MHz, DMSO-d_6)



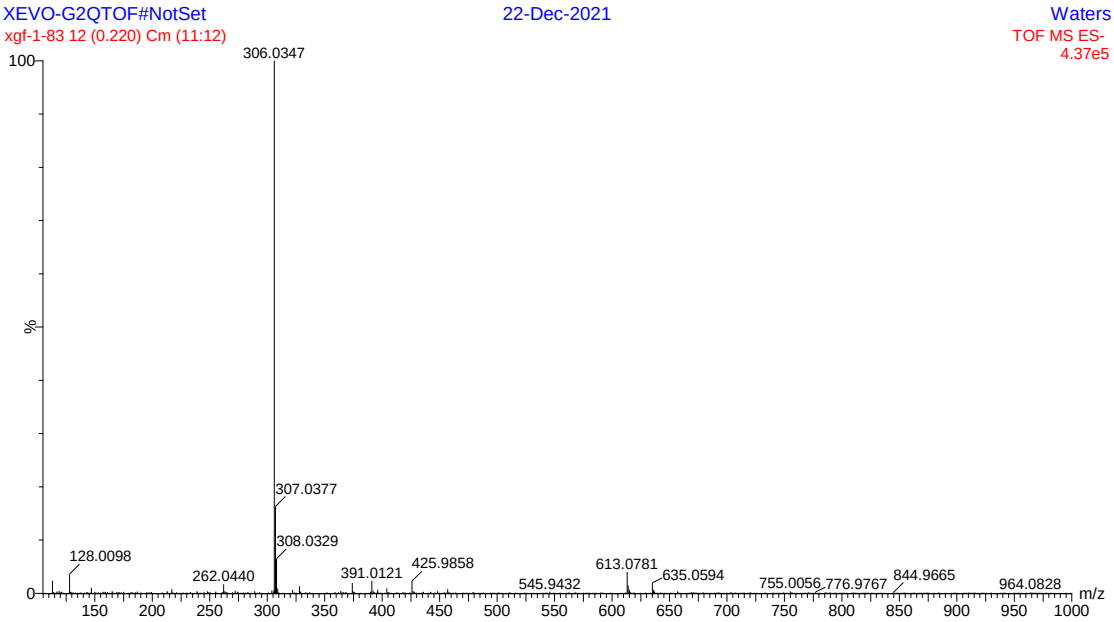
^{1}H NMR of compound **F8-B4** (400 MHz, DMSO-d_6)



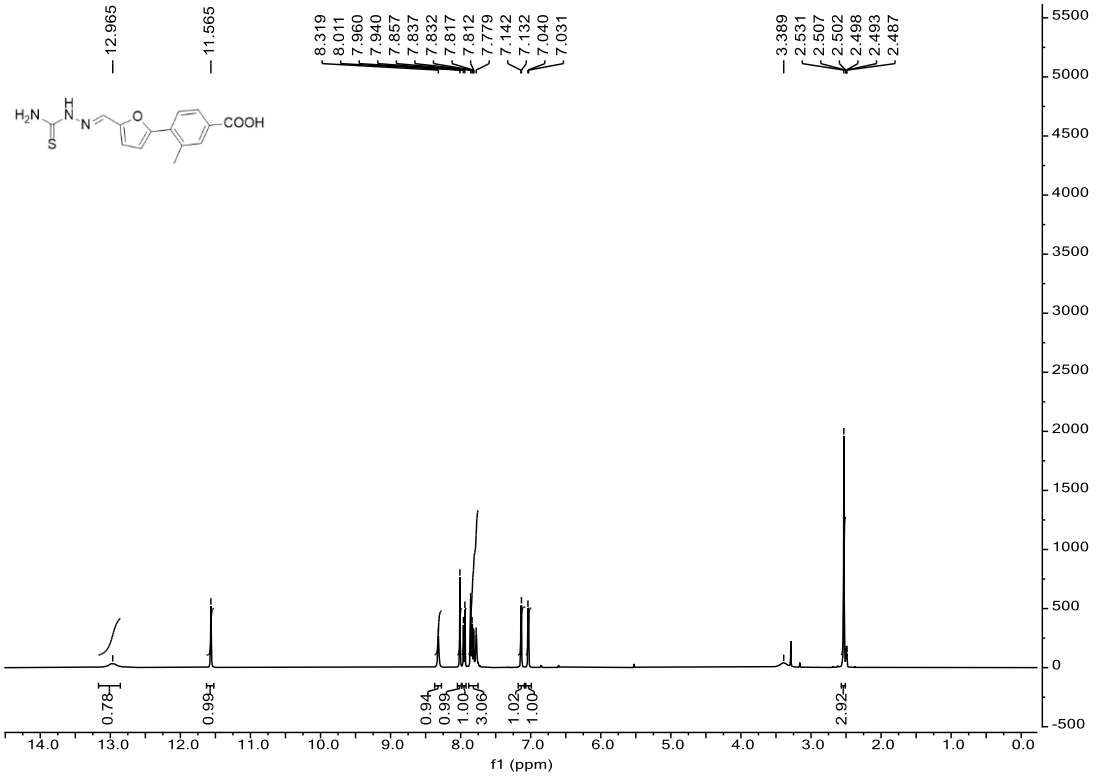
^{13}C NMR of compound **F8-B4** ((100 MHz, DMSO-d_6)



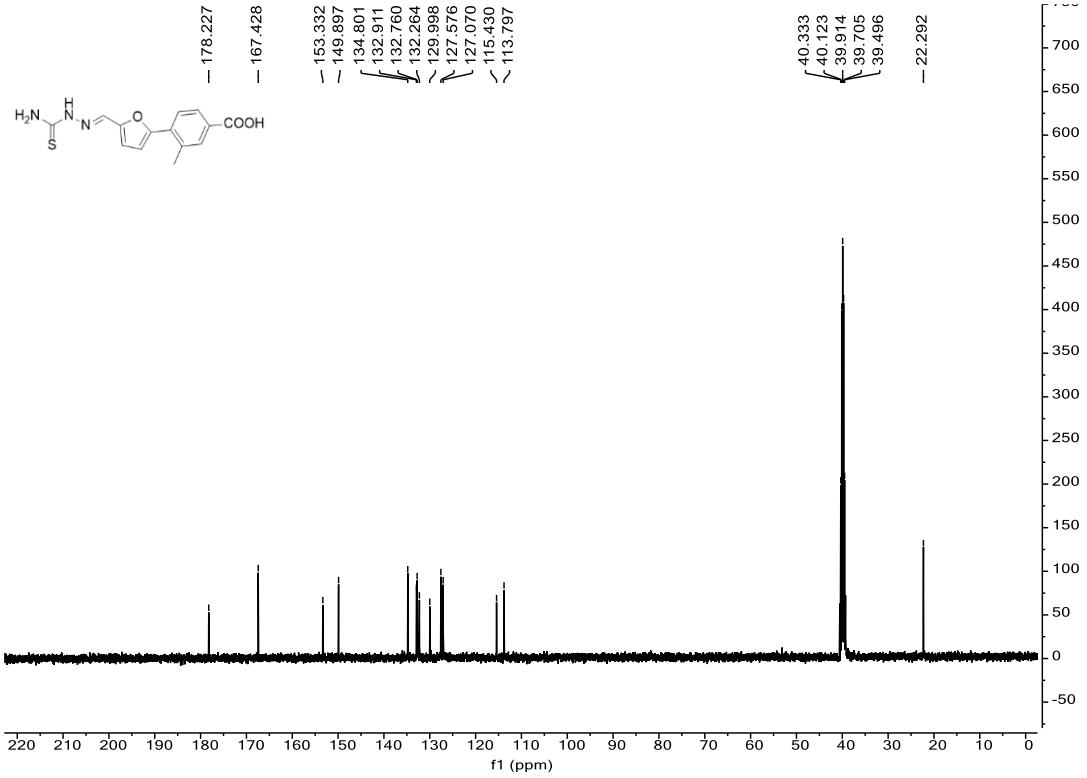
^{19}F NMR of compound **F8-B4** (376 MHz, DMSO-d_6)



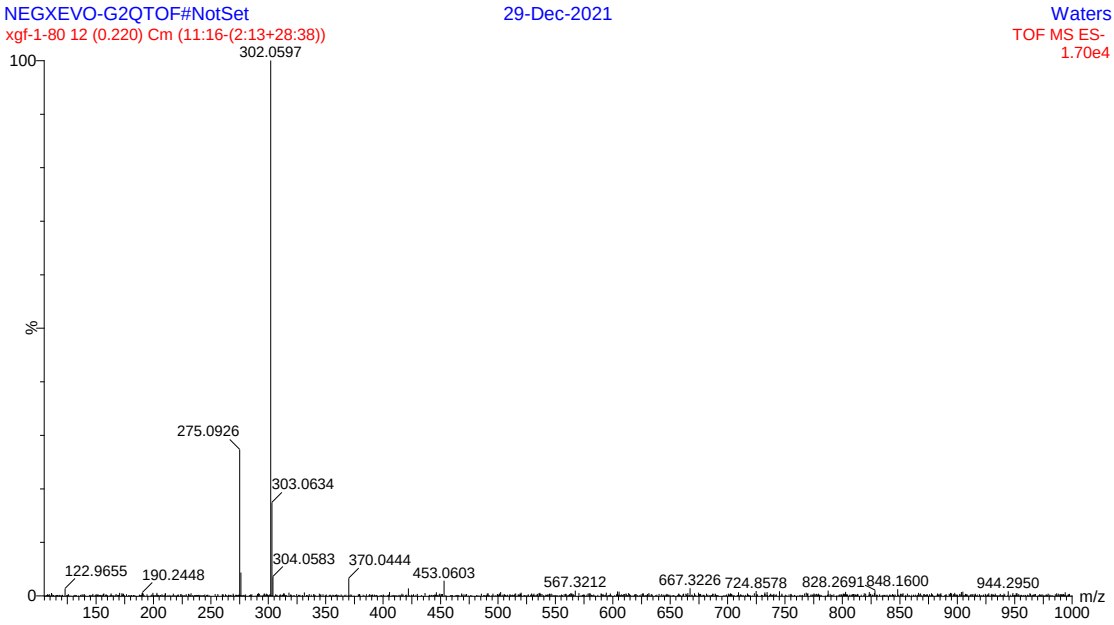
HRMS of compound **F8-B4** (ESI)



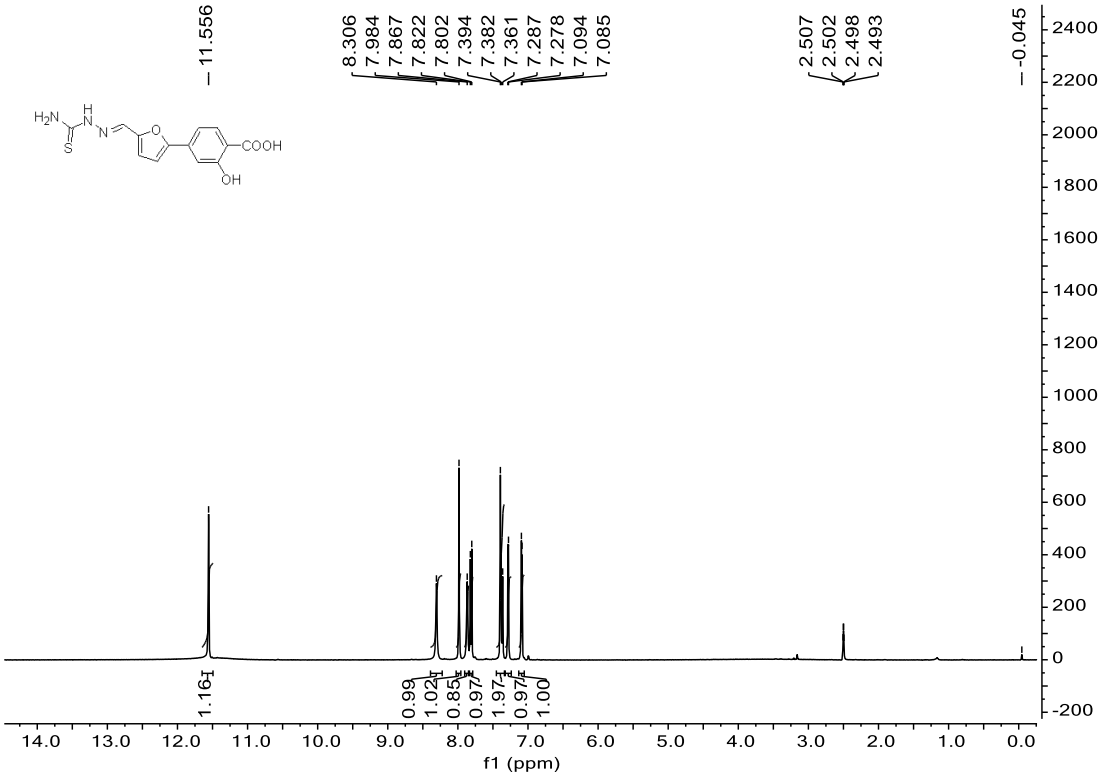
^{1}H NMR of compound **F8-B5** (400 MHz, DMSO-*d*$_6$)



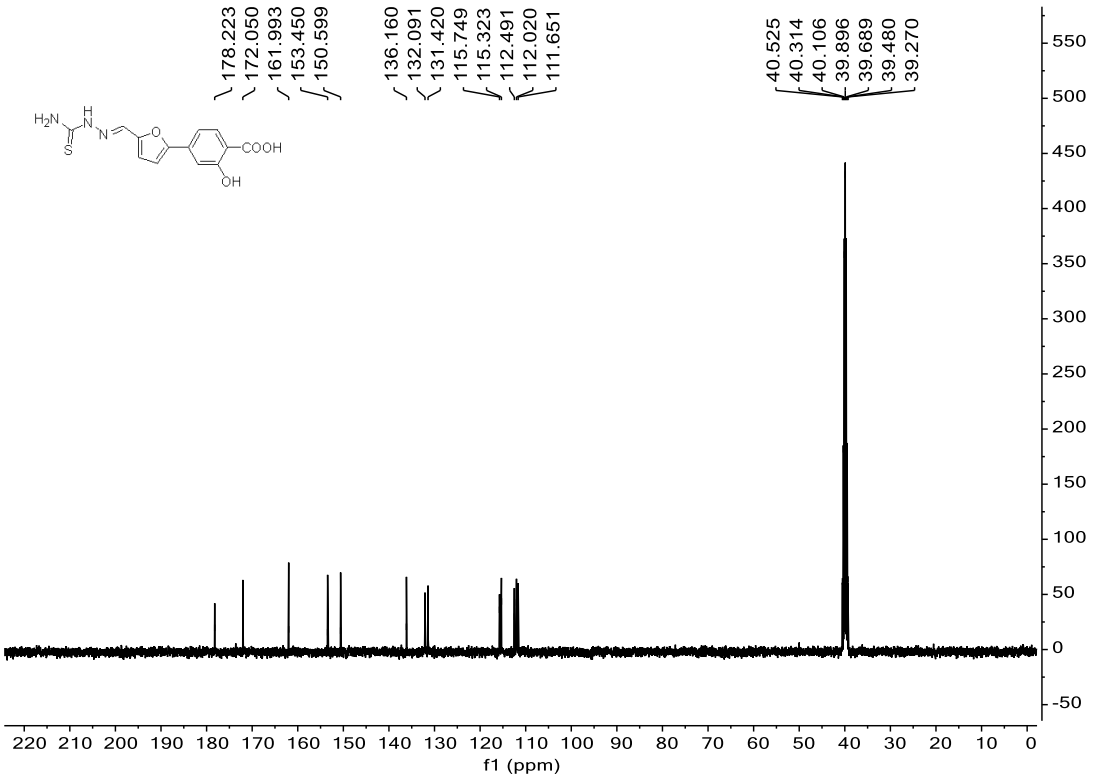
^{13}C NMR of compound **F8-B5** ((100 MHz, DMSO-d_6)



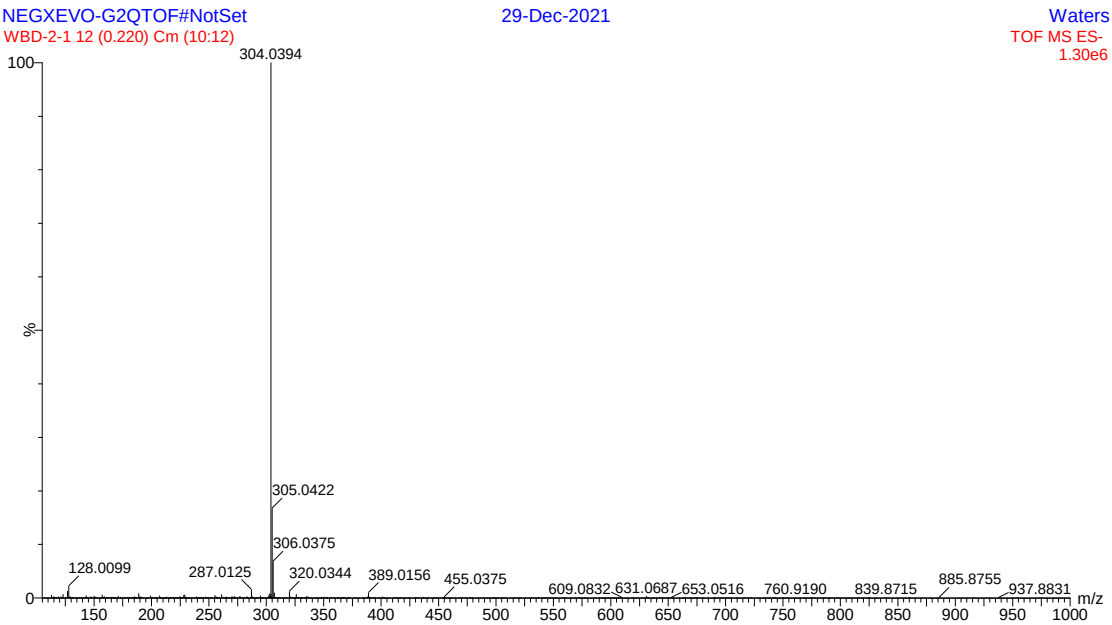
HRMS of compound **F8-B5** (ESI)



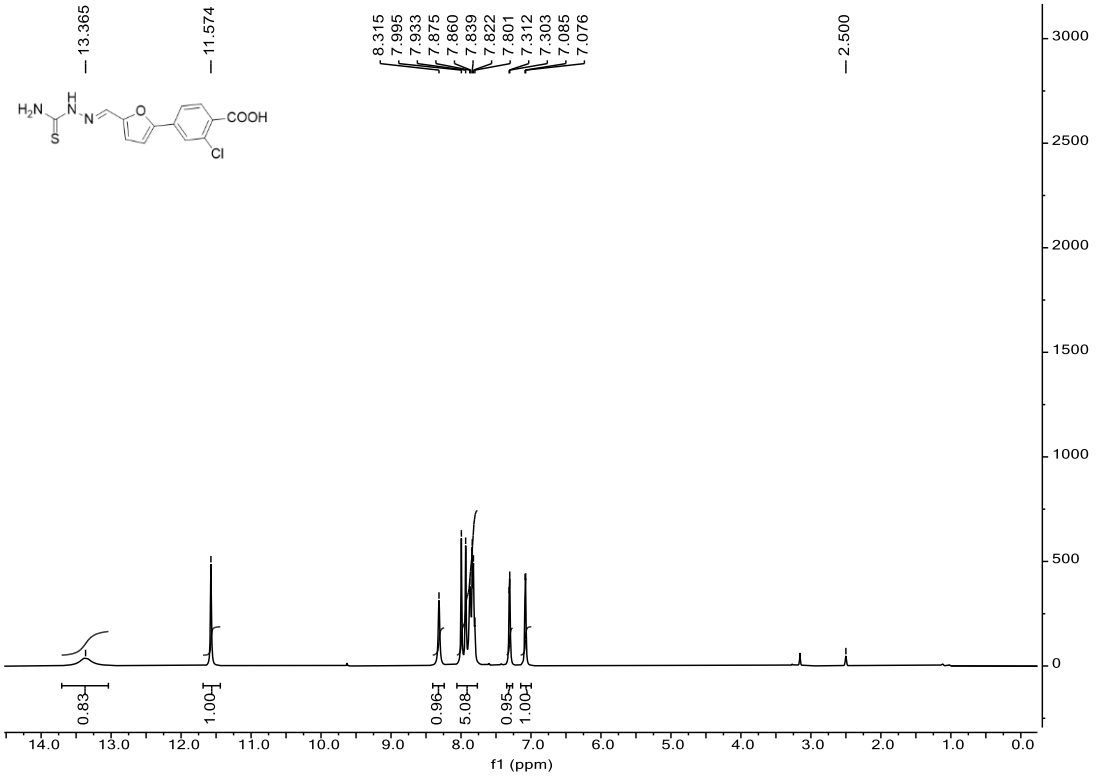
^{1}H NMR of compound **F8-B6** (400 MHz, DMSO-d_6)



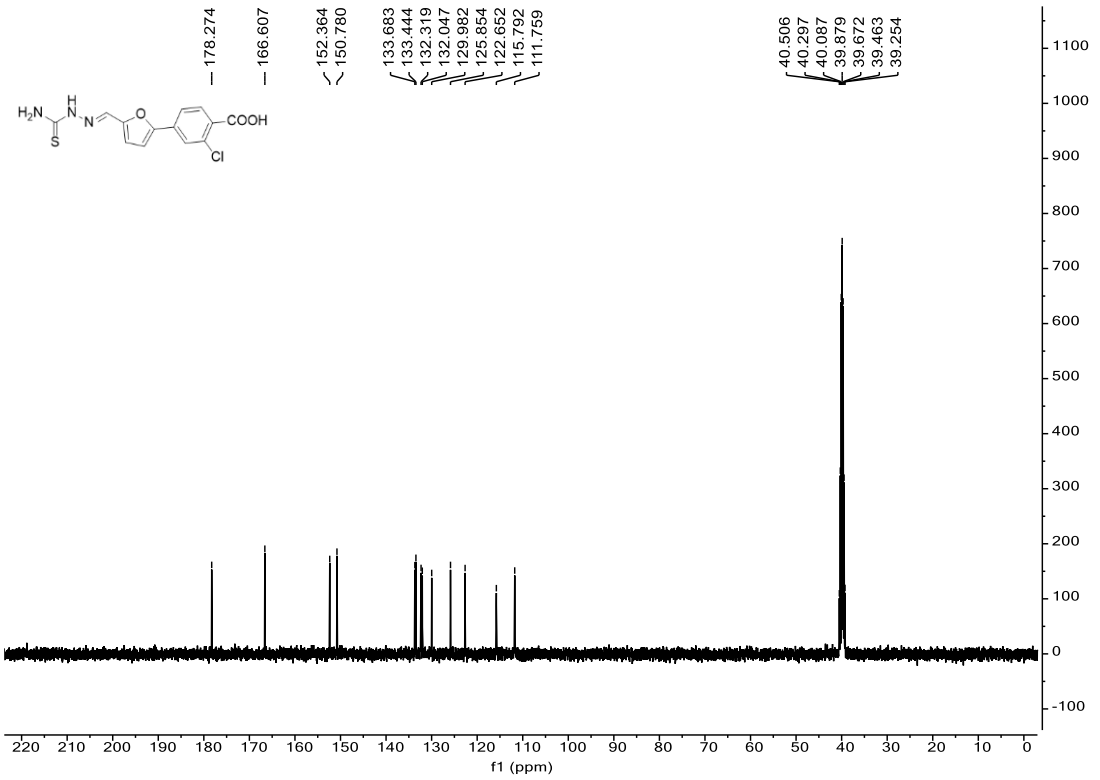
^{13}C NMR of compound **F8-B6** ((100 MHz, DMSO-d_6)



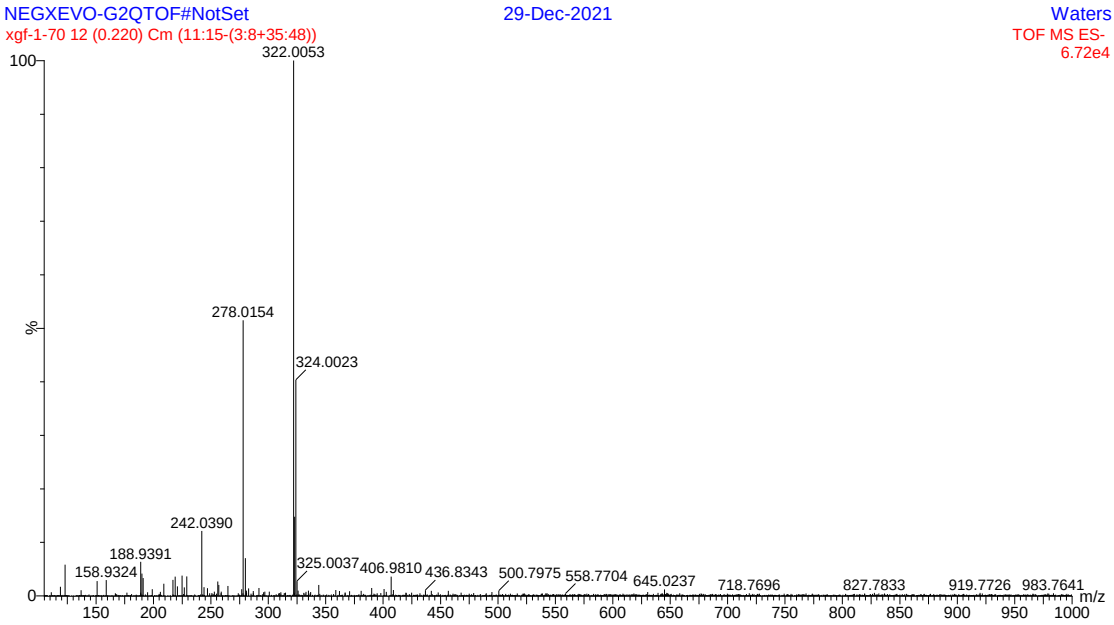
HRMS of compound **F8-B6** (ESI)



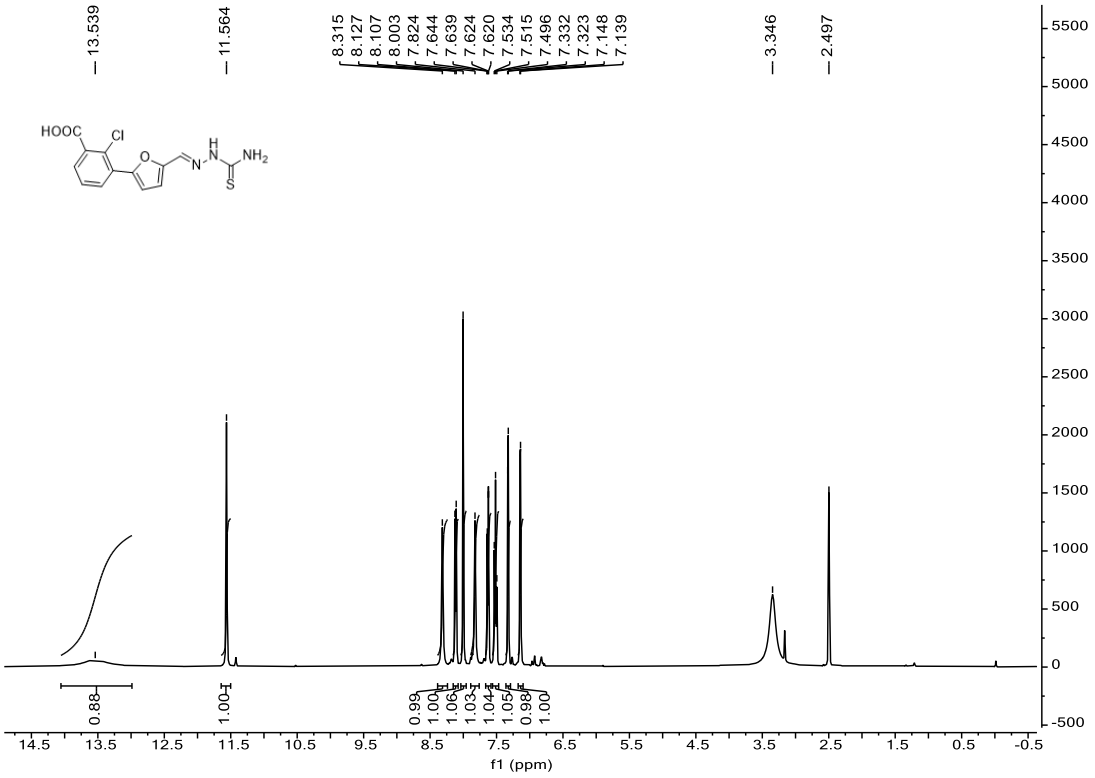
^{1}H NMR of compound **F8-B7** (400 MHz, DMSO-*d*$_6$)



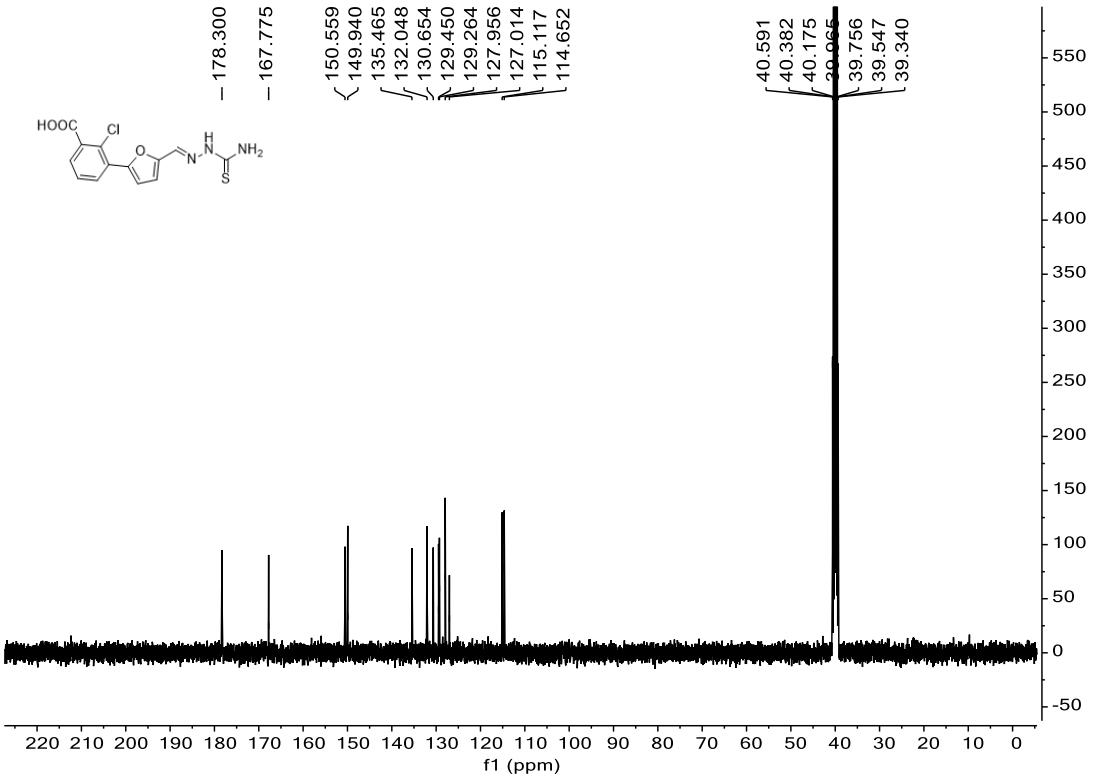
^{13}C NMR of compound **F8-B7** ((100 MHz, DMSO-d_6)



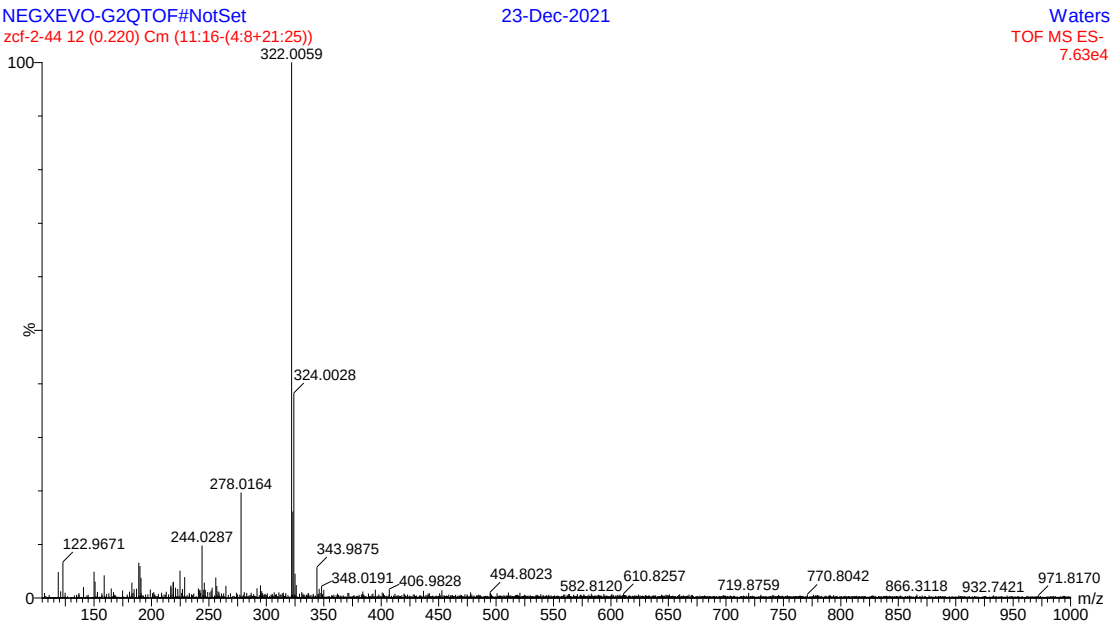
HRMS of compound **F8-B7** (ESI)



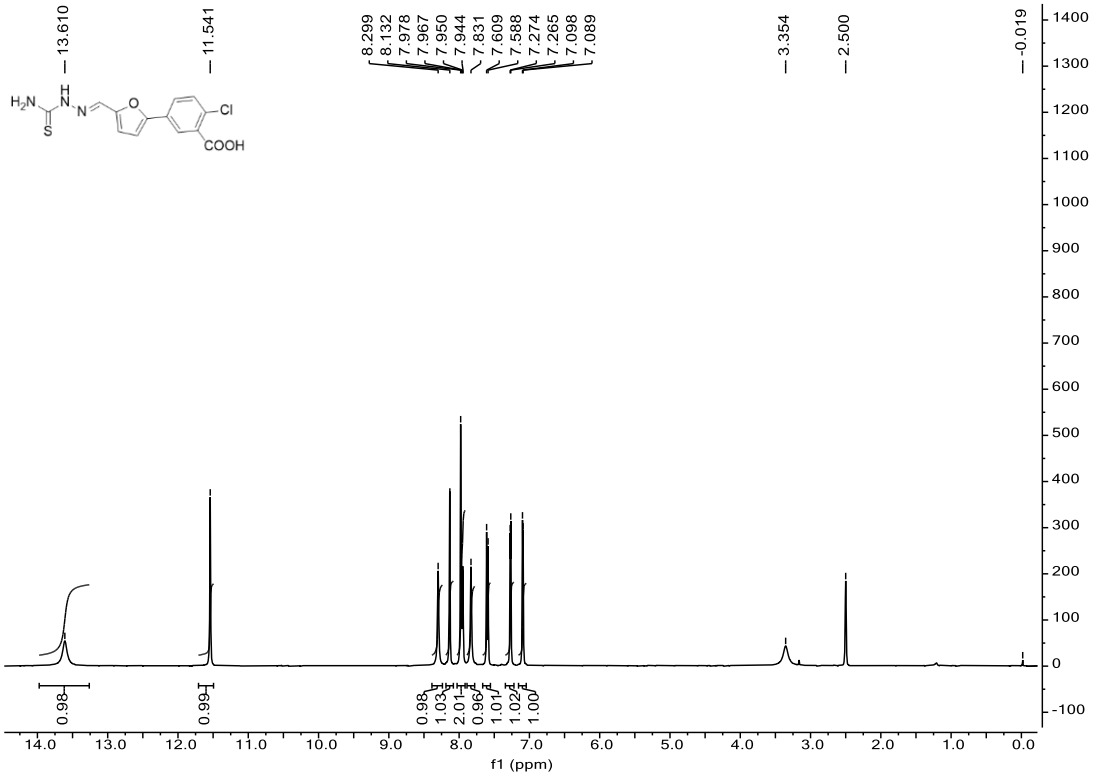
^{1}H NMR of compound **F8-B8** (400 MHz, DMSO-d_6)



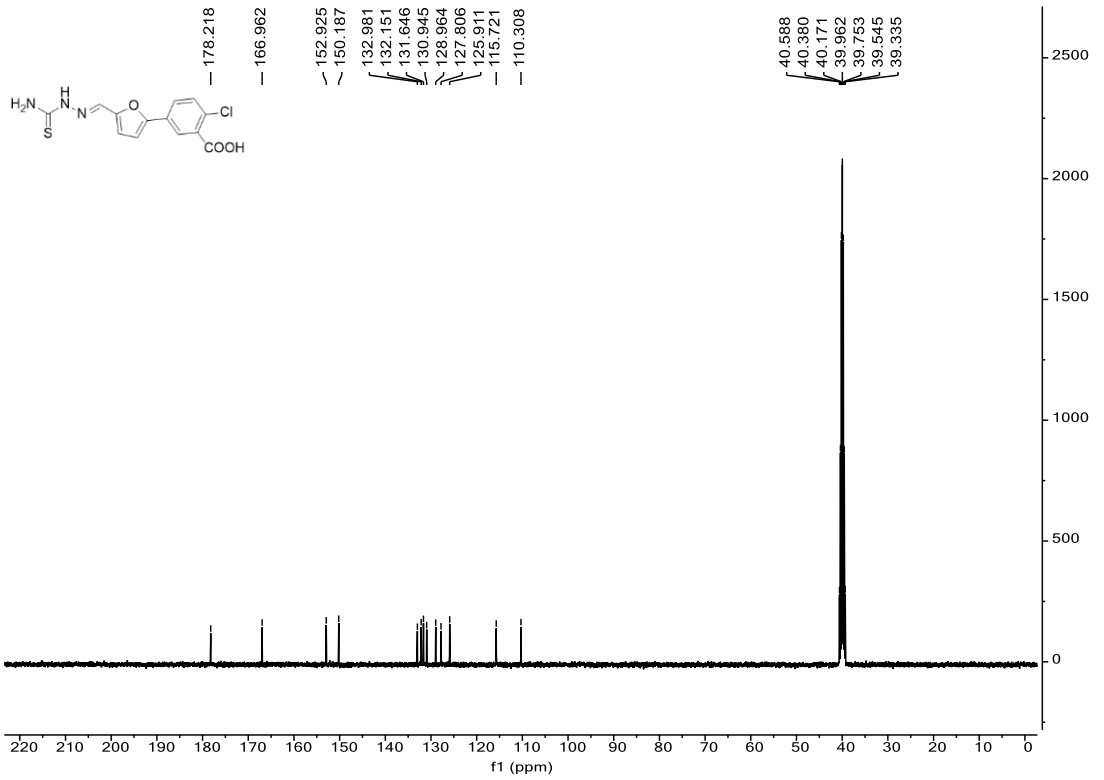
^{13}C NMR of compound **F8-B8** ((100 MHz, DMSO-d_6)



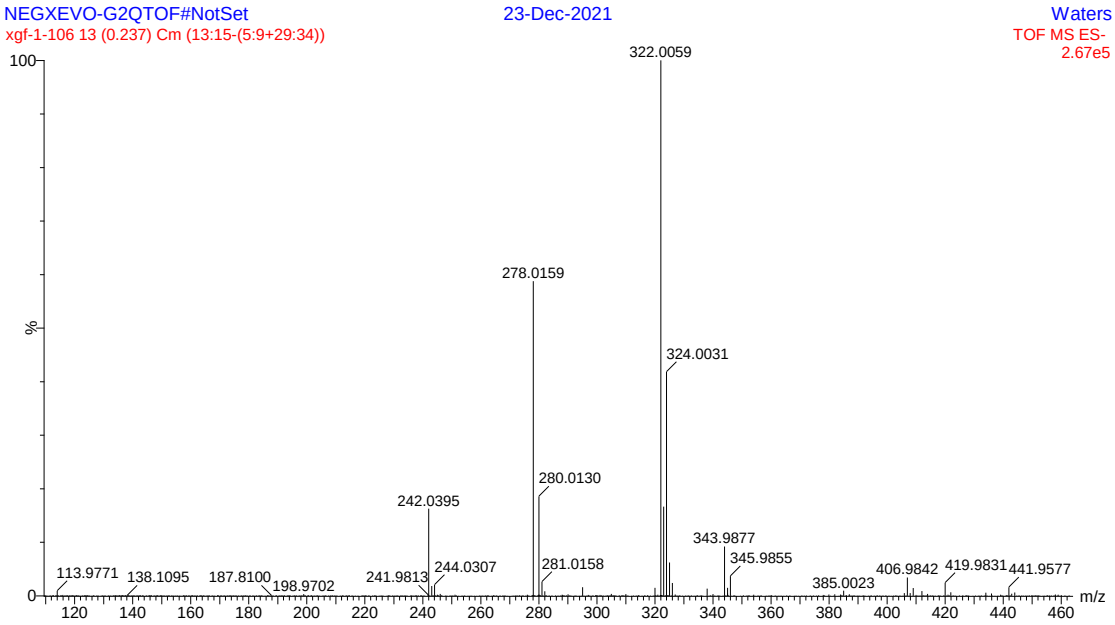
HRMS of compound **F8-B8** (ESI)



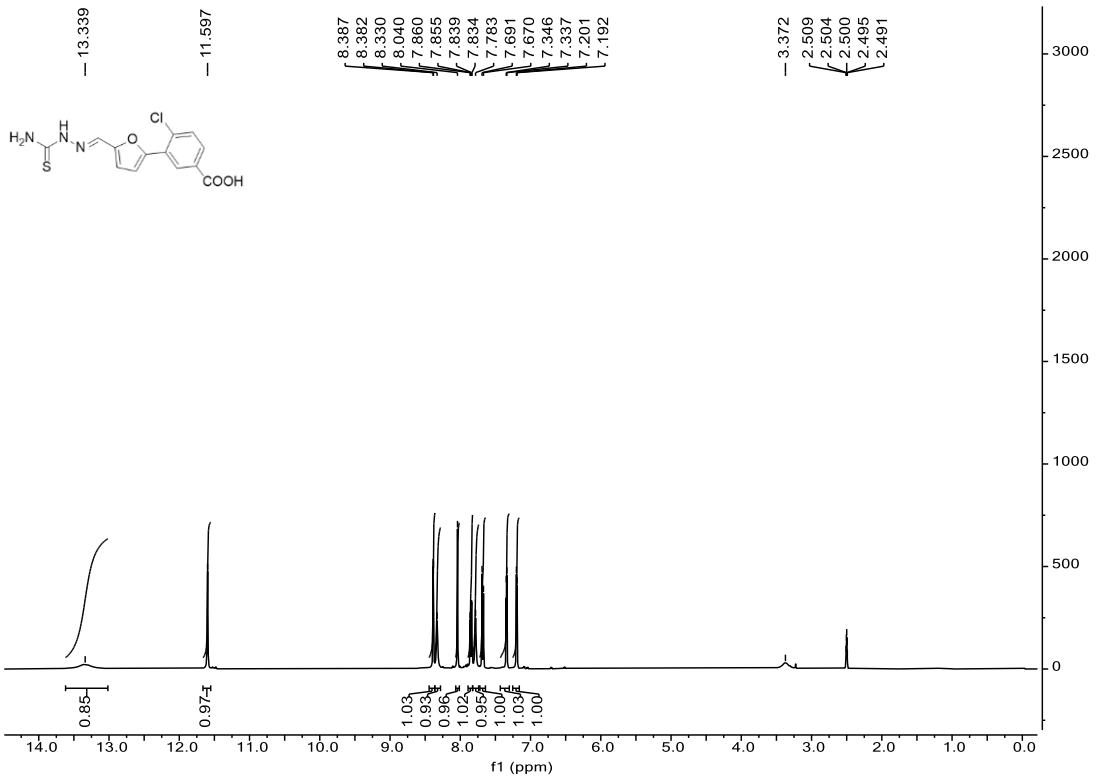
^{1}H NMR of compound **F8-B9** (400 MHz, DMSO-d_6)



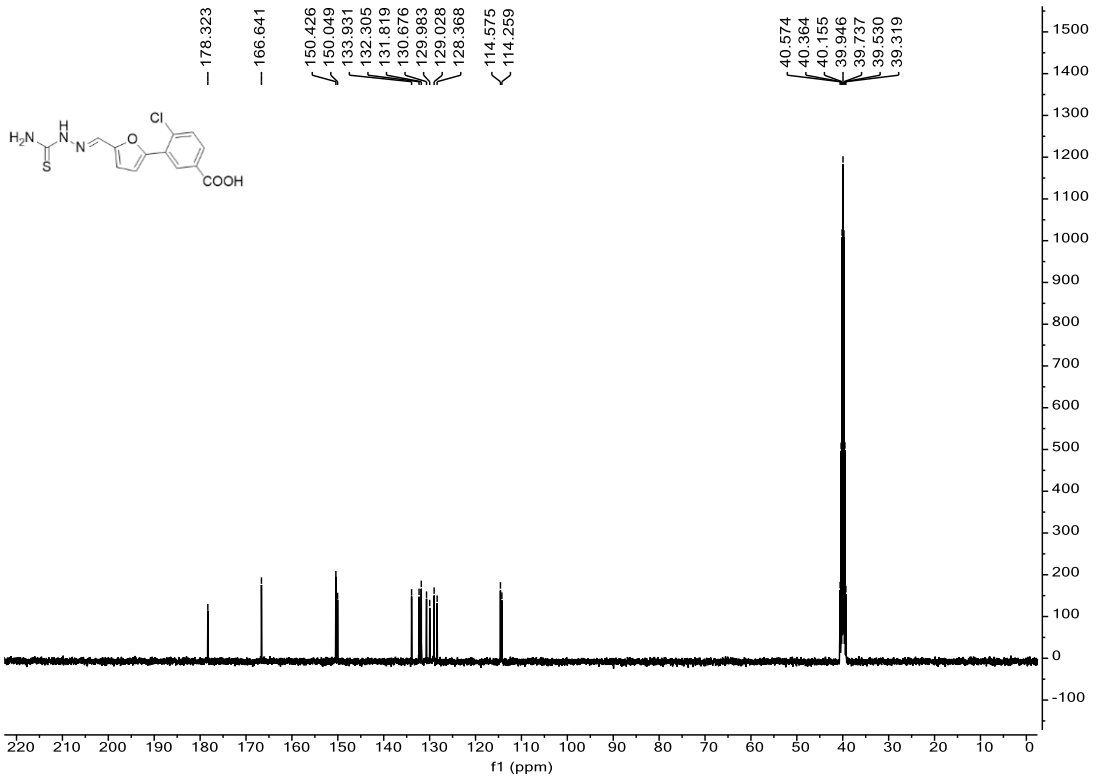
^{13}C NMR of compound **F8-B9** ((100 MHz, DMSO-d_6)



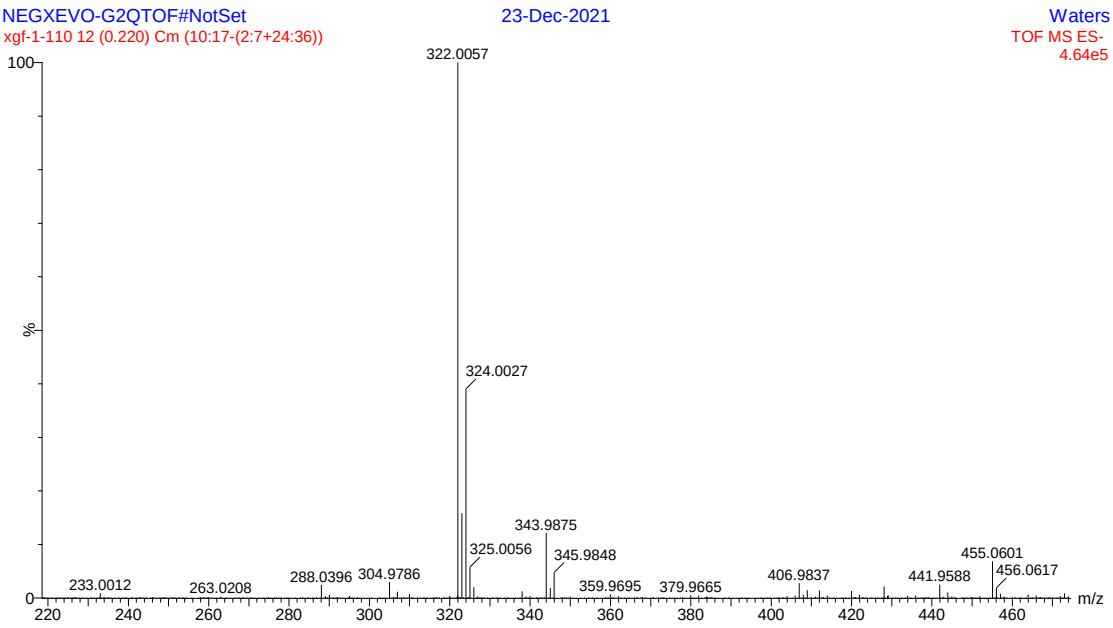
HRMS of compound **F8-B9** (ESI)



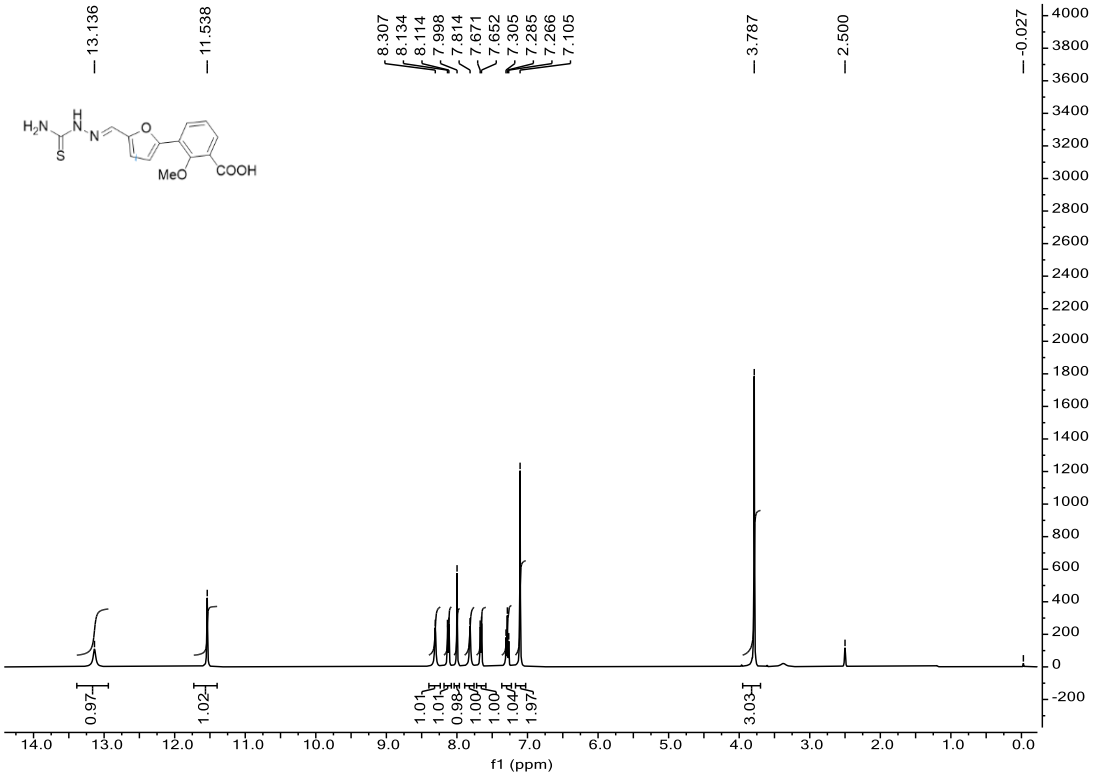
^{1}H NMR of compound **F8-B10** (400 MHz, DMSO-d_6)



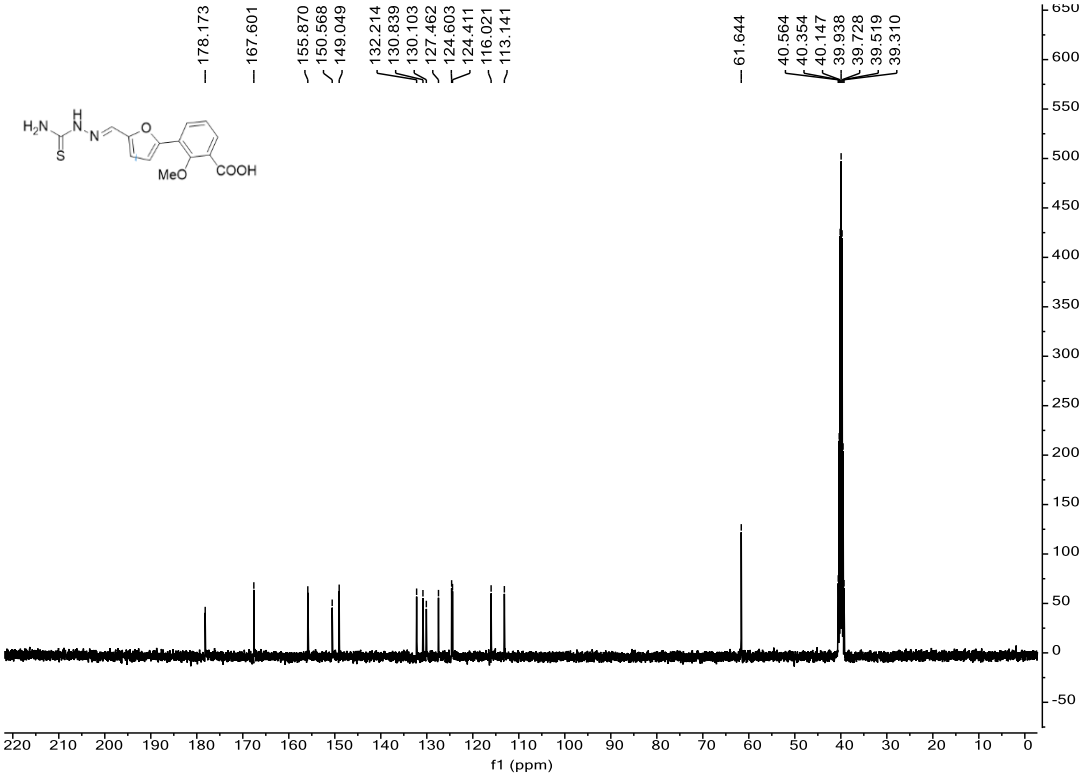
^{13}C NMR of compound **F8-B10** ((100 MHz, DMSO-d_6)



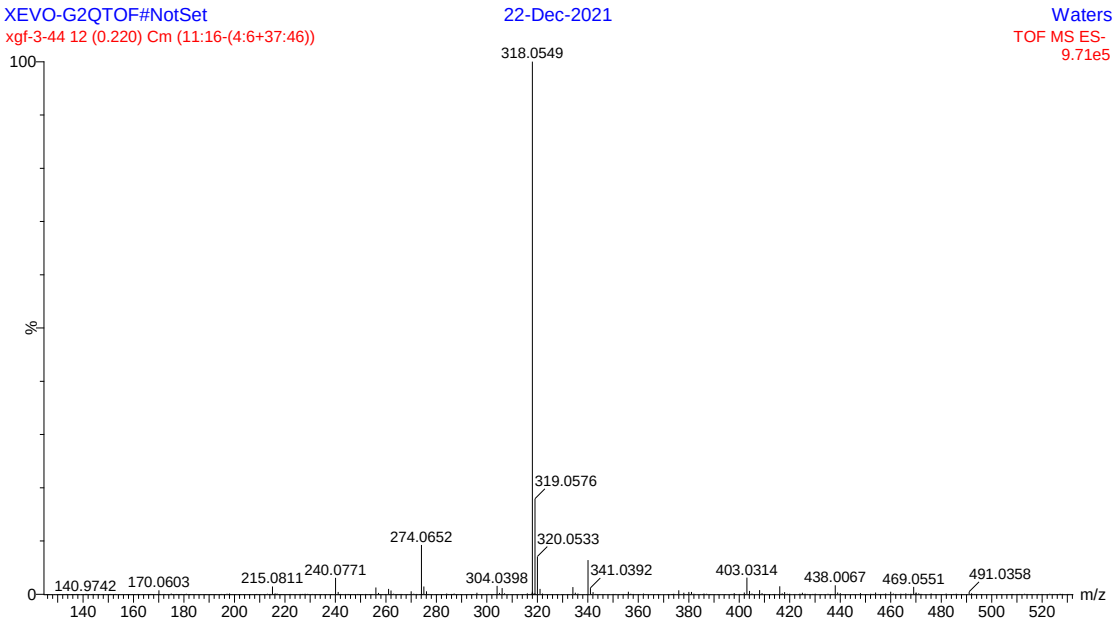
HRMS of compound **F8-B10** (ESI)



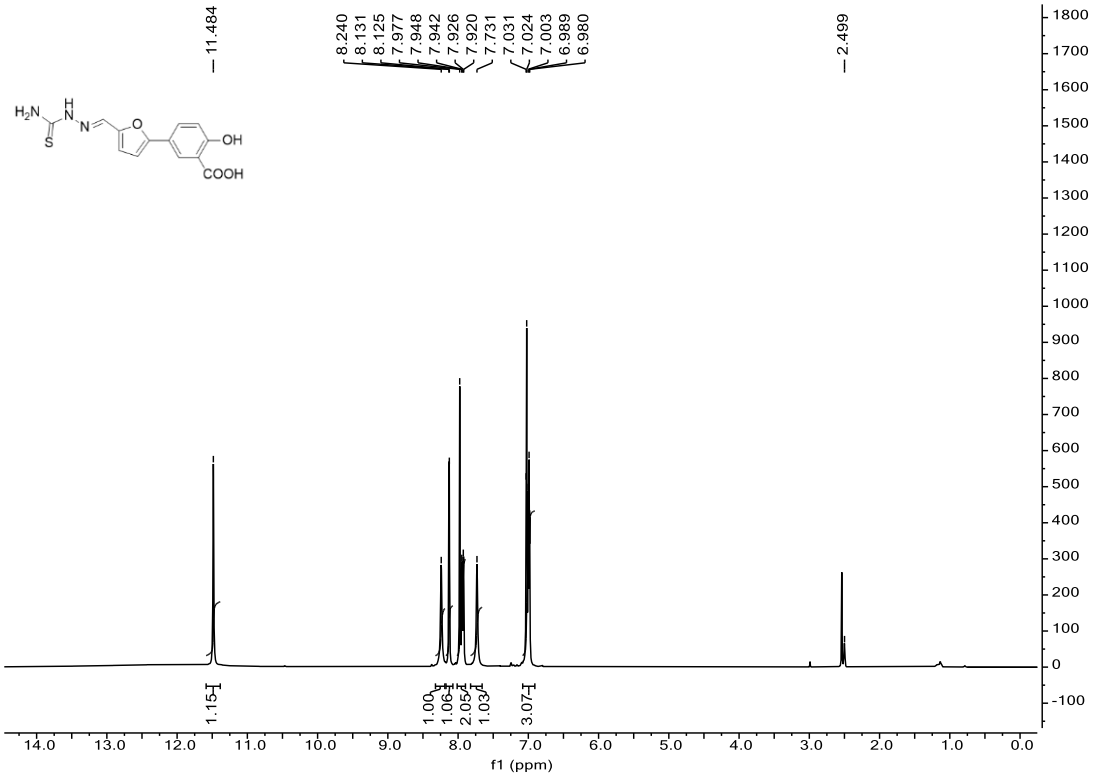
^{1}H NMR of compound **F8-B11** (400 MHz, DMSO-d_6)



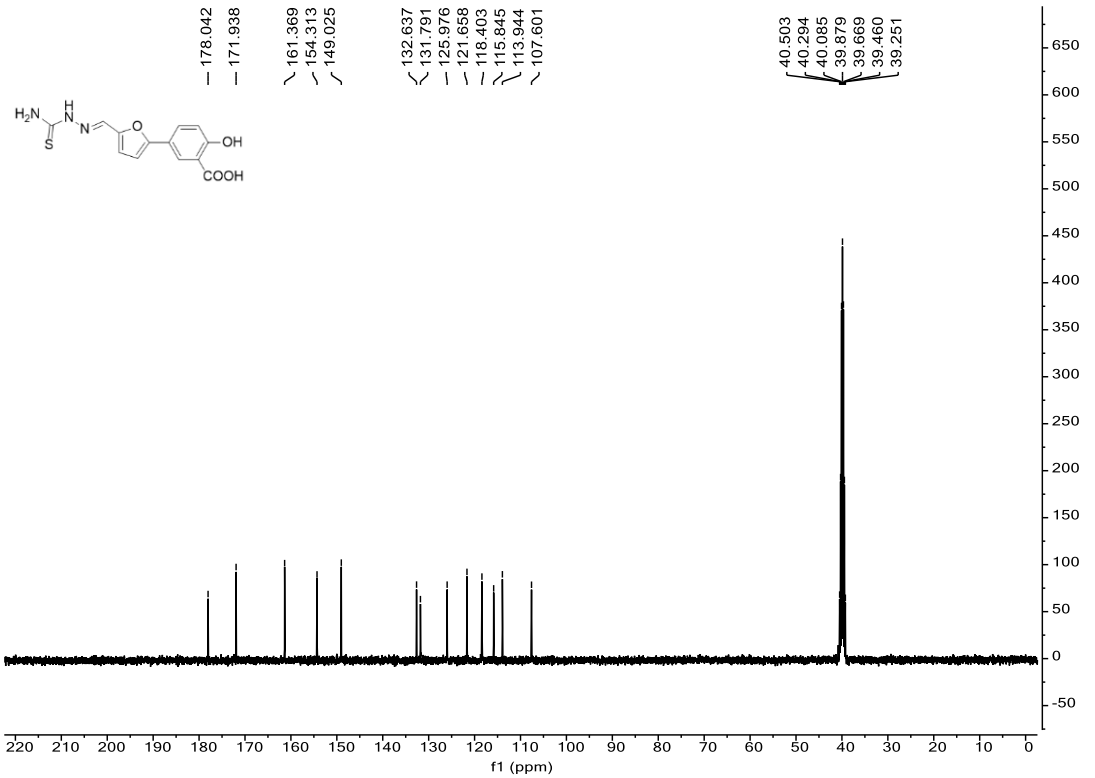
^{13}C NMR of compound **F8-B11** (100 MHz, DMSO-d_6)



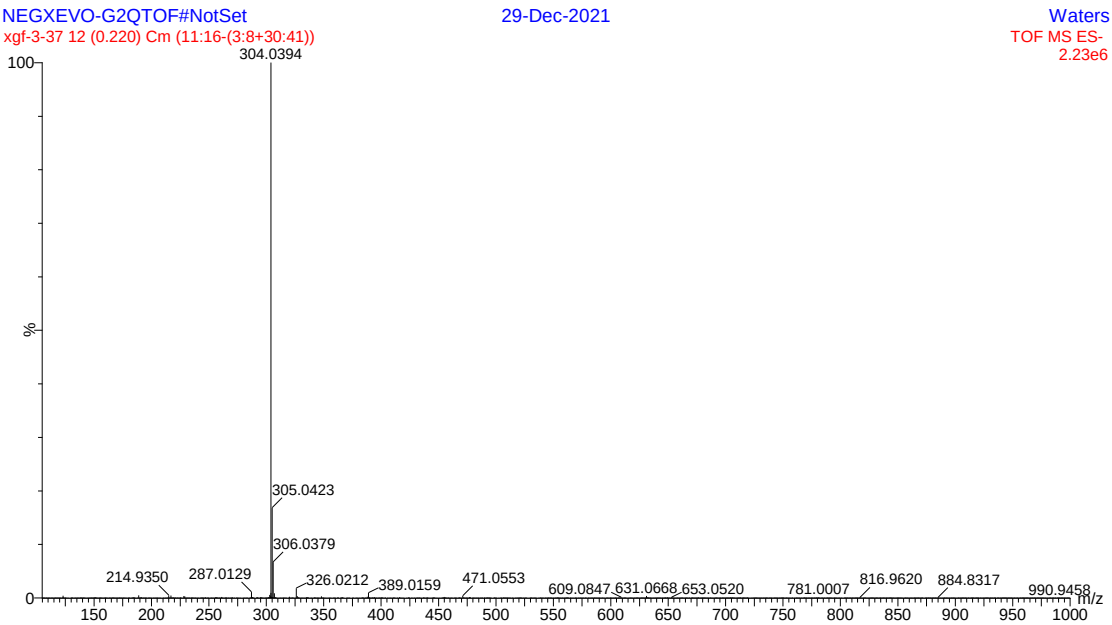
HRMS of compound **F8-B11** (ESI)



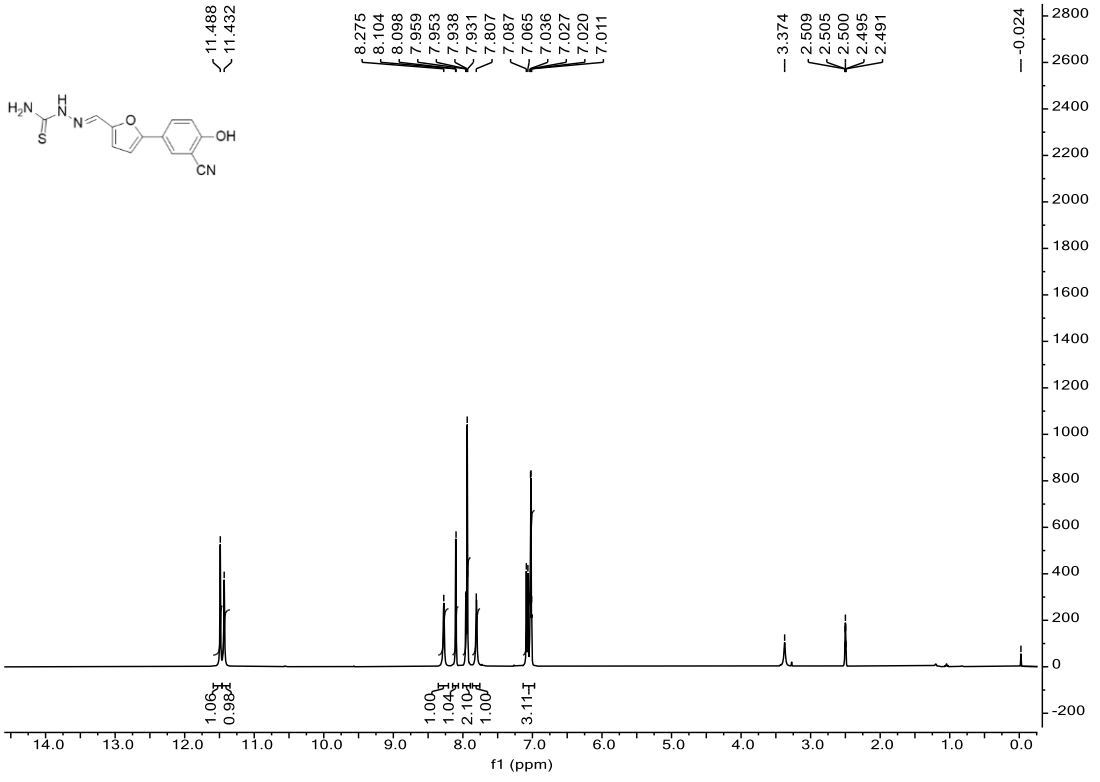
^{1}H NMR of compound **F8-B12** (400 MHz, DMSO-d_6)



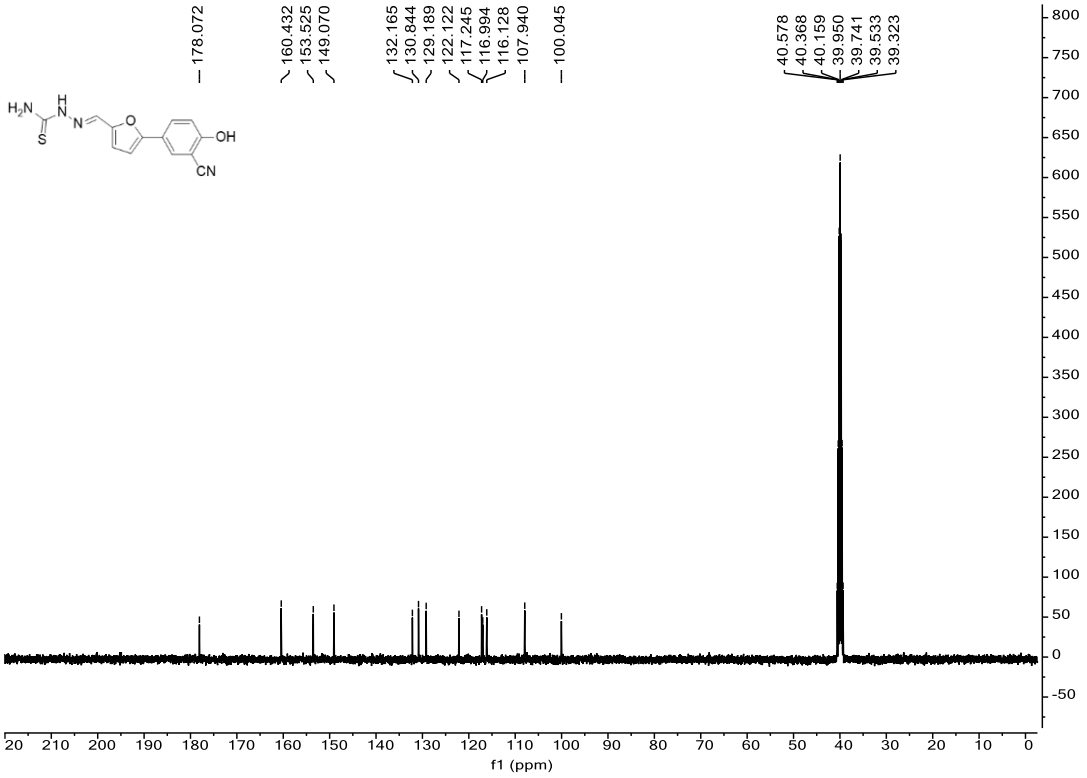
^{13}C NMR of compound **F8-B12** (100 MHz, DMSO-d_6)



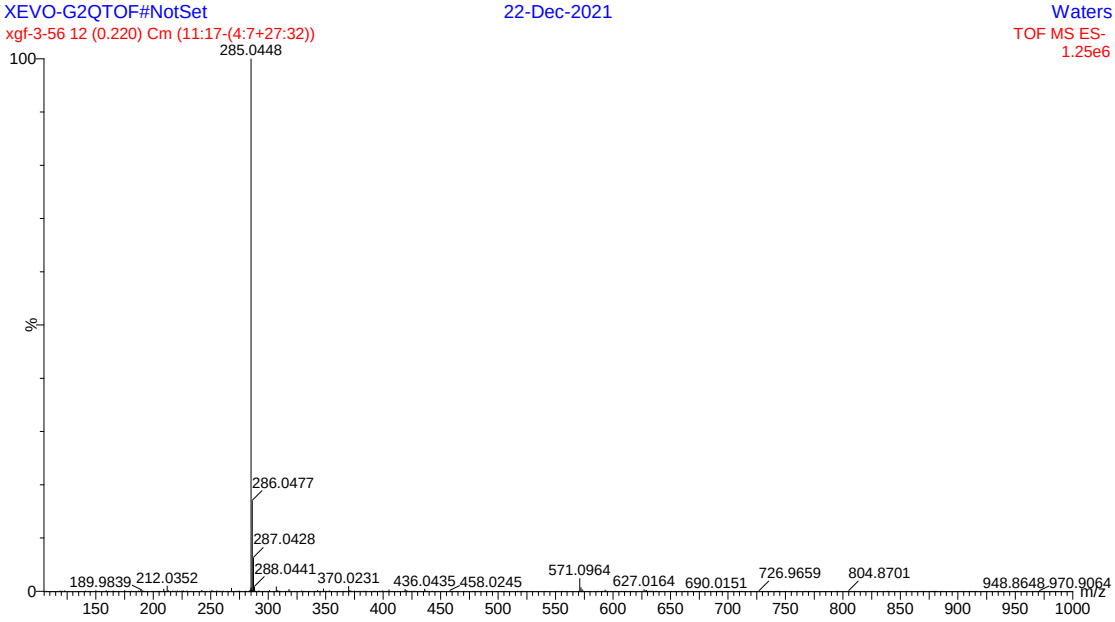
HRMS of compound **F8-B12** (ESI)



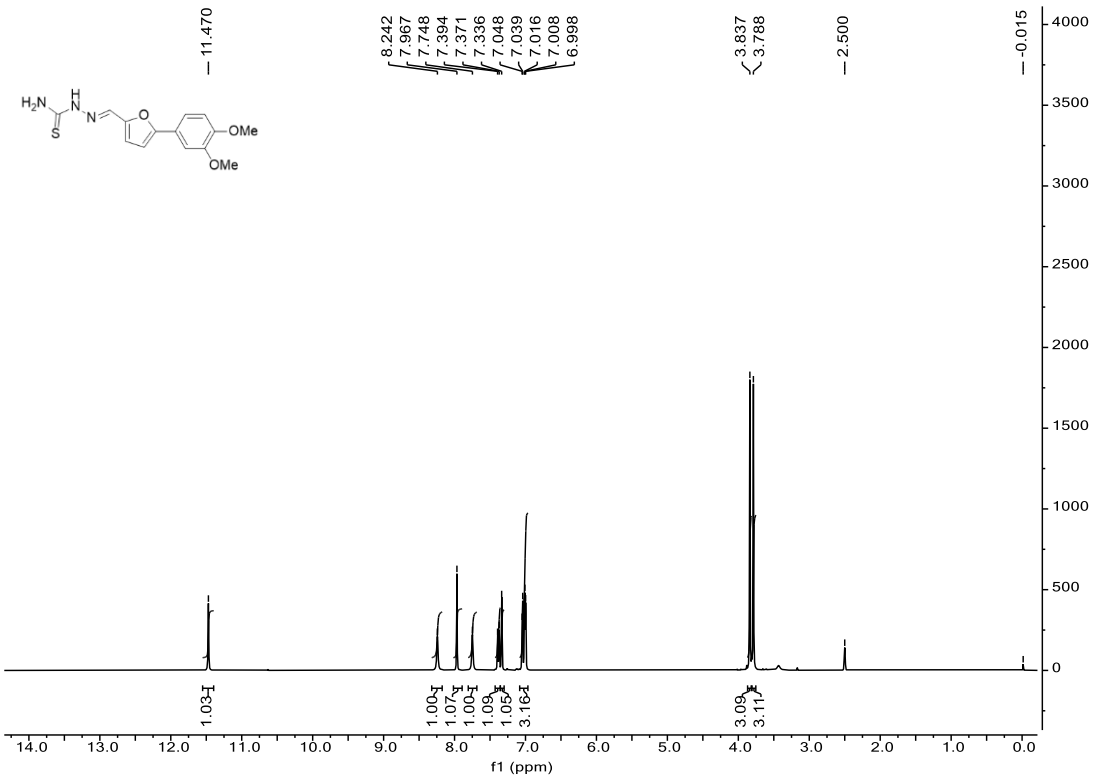
^{1}H NMR of compound **F8-B13** (400 MHz, DMSO-d_6)



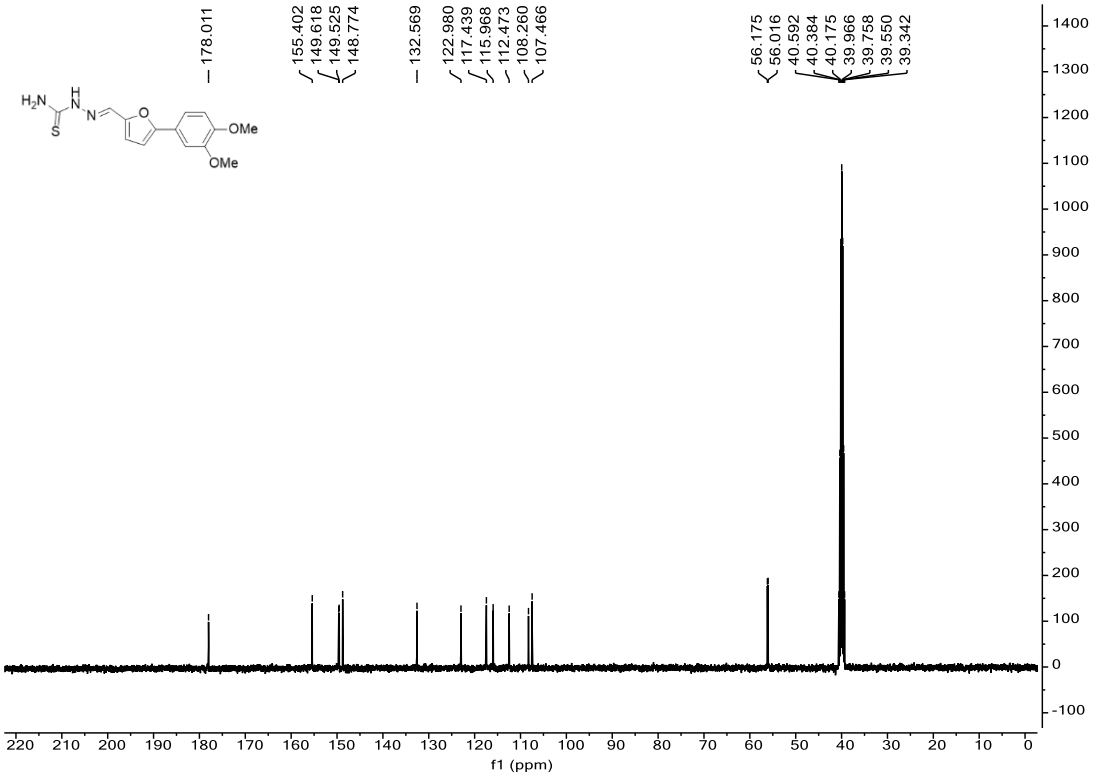
^{13}C NMR of compound **F8-B13** (100 MHz, DMSO-d_6)



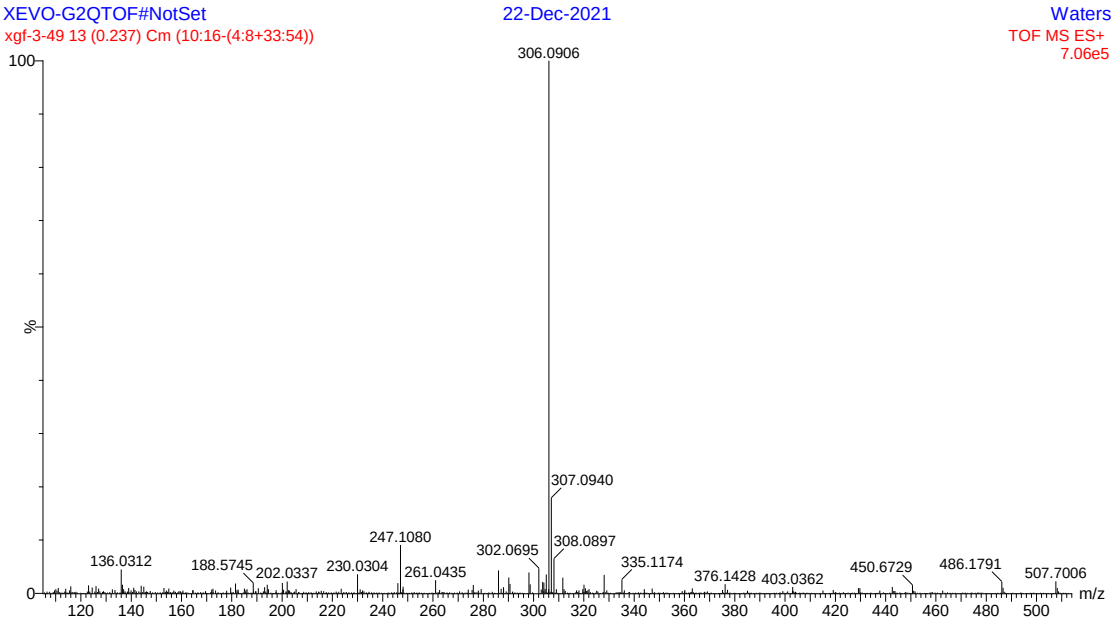
HRMS of compound **F8-B13** (ESI)



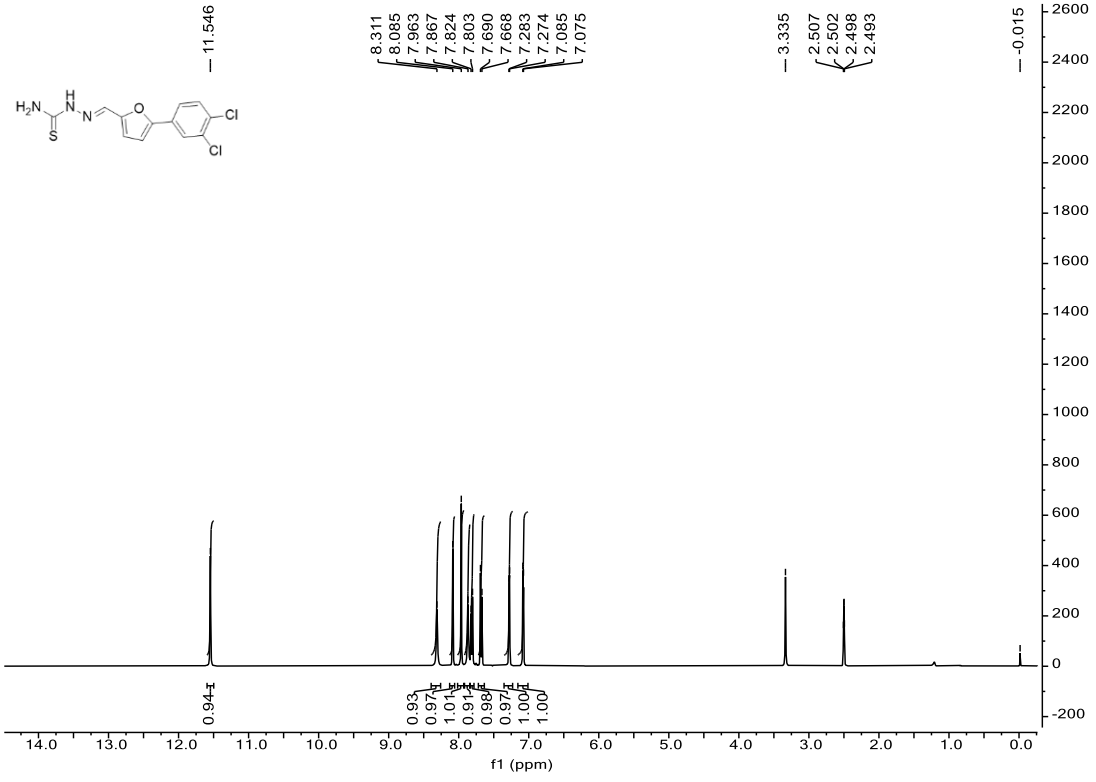
^{1}H NMR of compound **F8-B14** (400 MHz, DMSO-d_6)



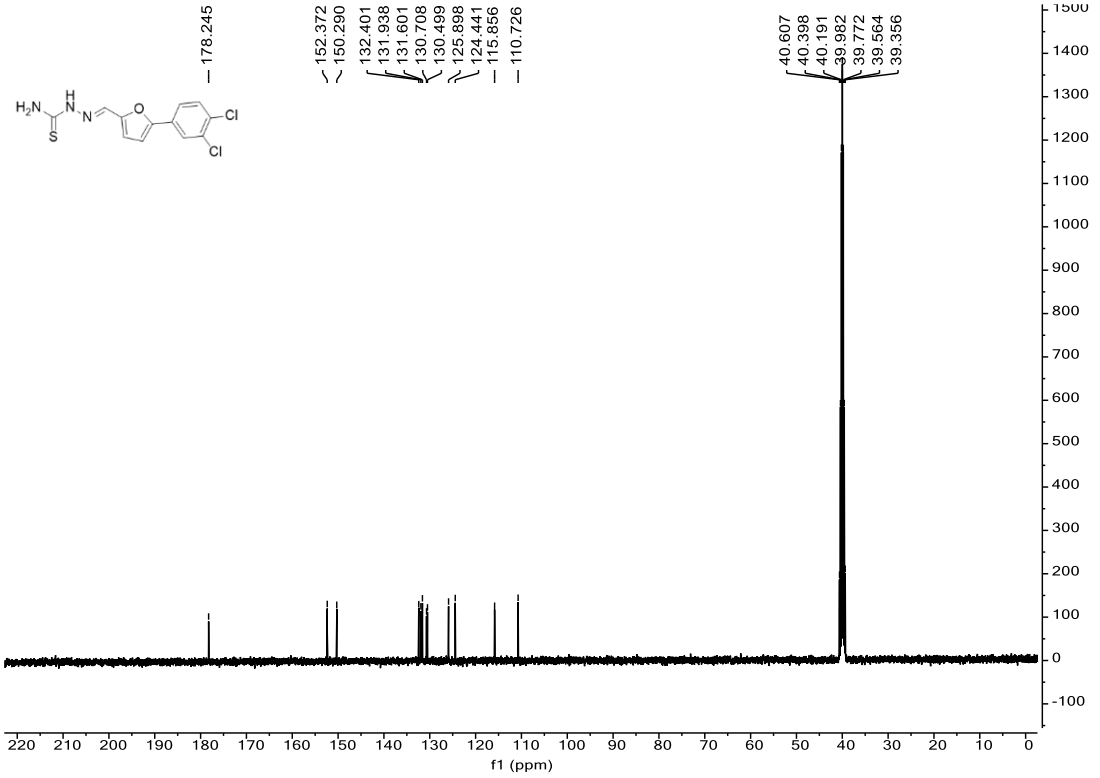
^{13}C NMR of compound **F8-B14** ((100 MHz, DMSO-d_6)



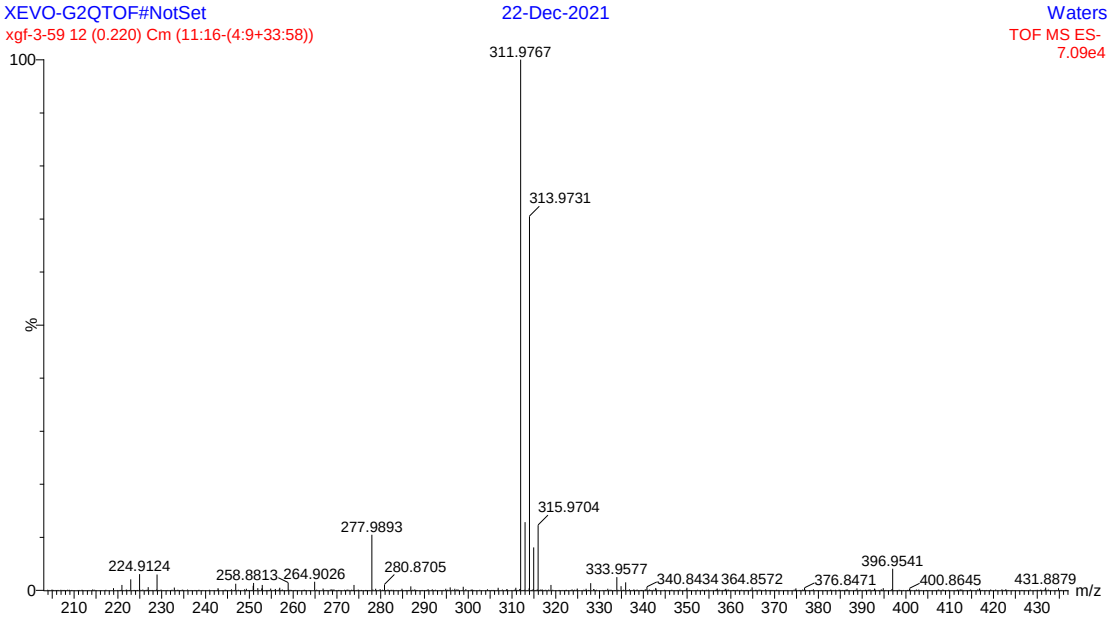
HRMS of compound **F8-B14** (ESI)



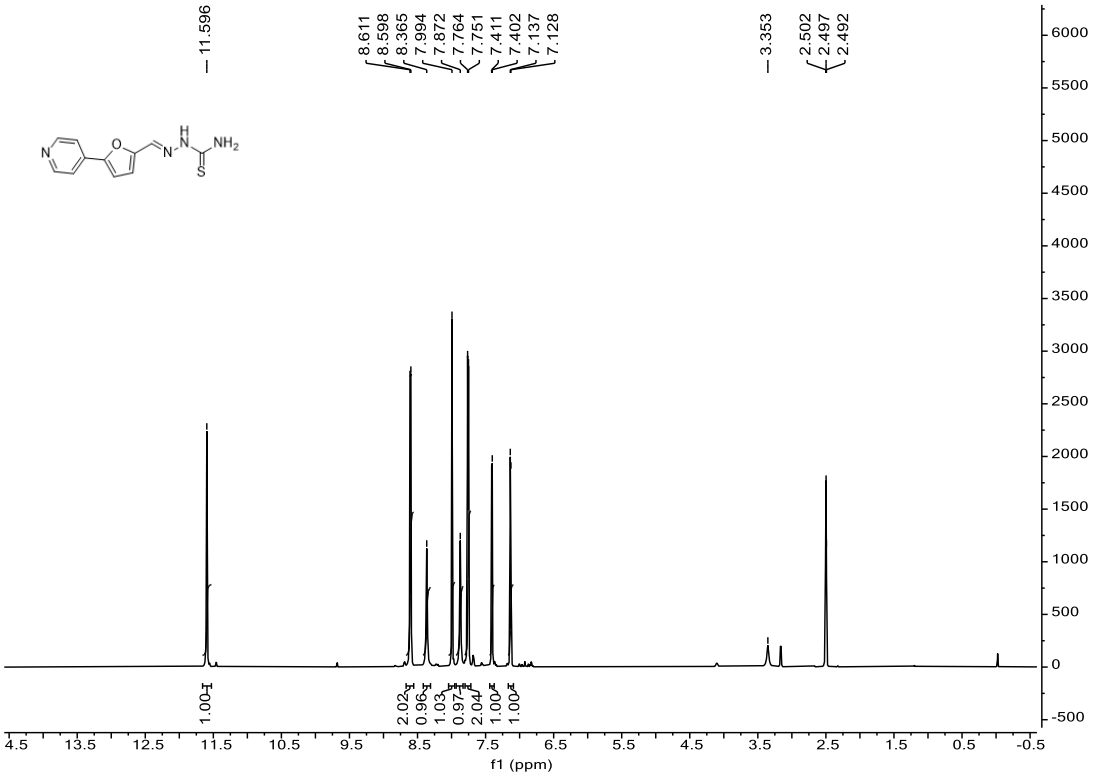
^{1}H NMR of compound **F8-B15** (400 MHz, DMSO-d_6)



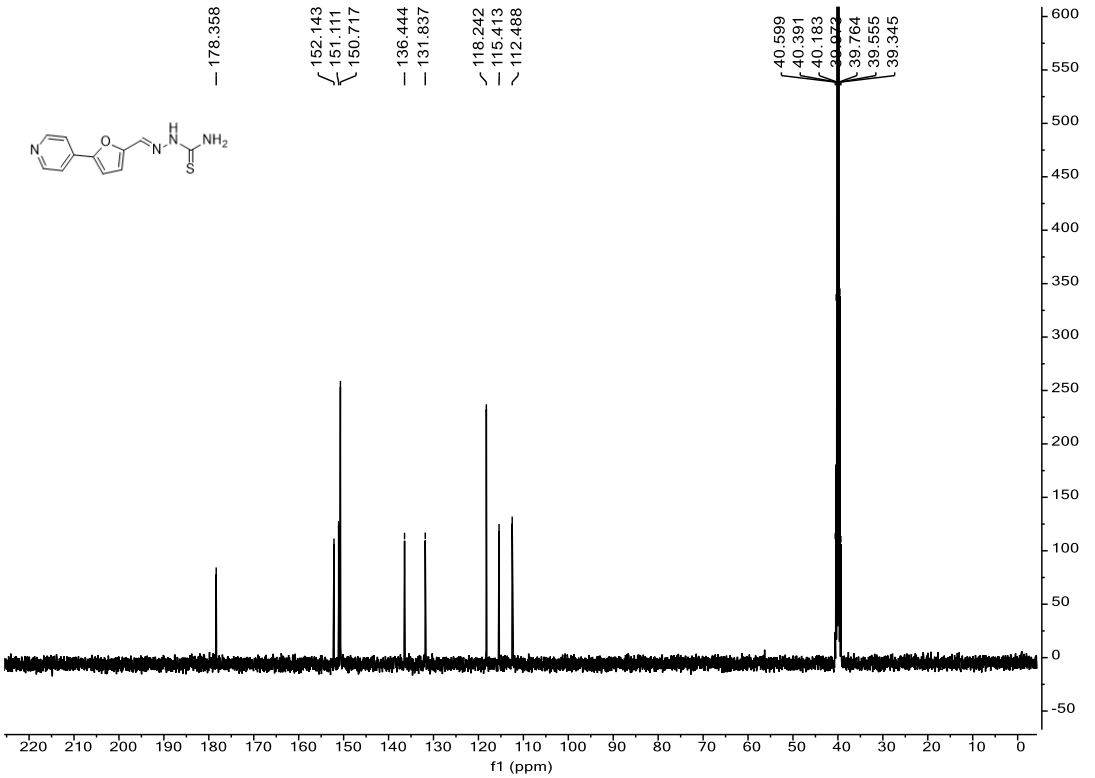
^{13}C NMR of compound **F8-B15** (100 MHz, DMSO-d_6)



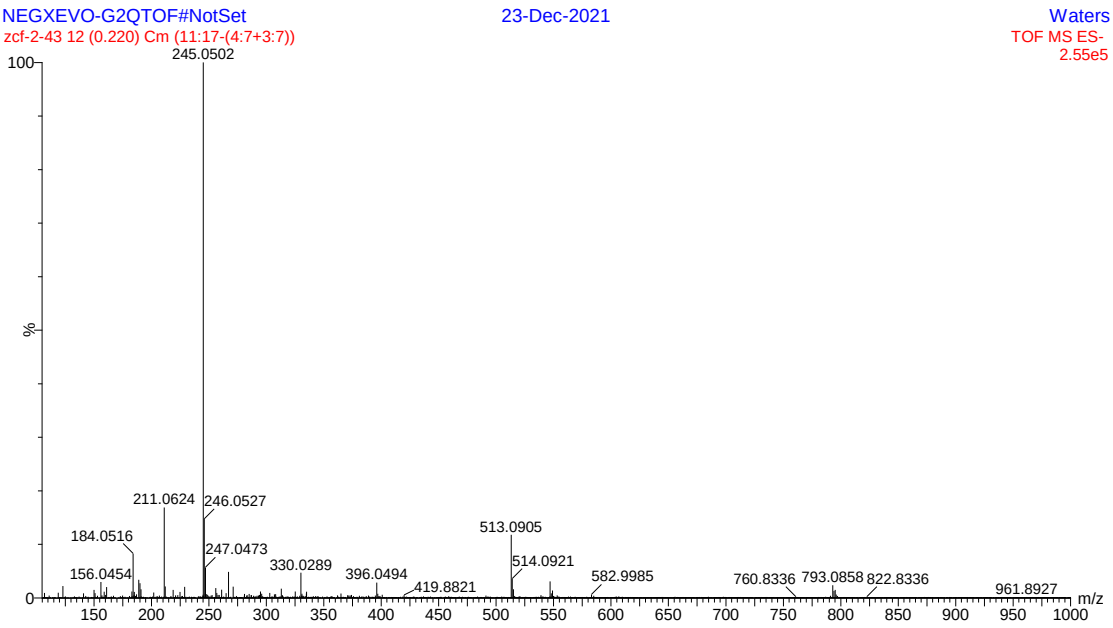
HRMS of compound **F8-B15** (ESI)



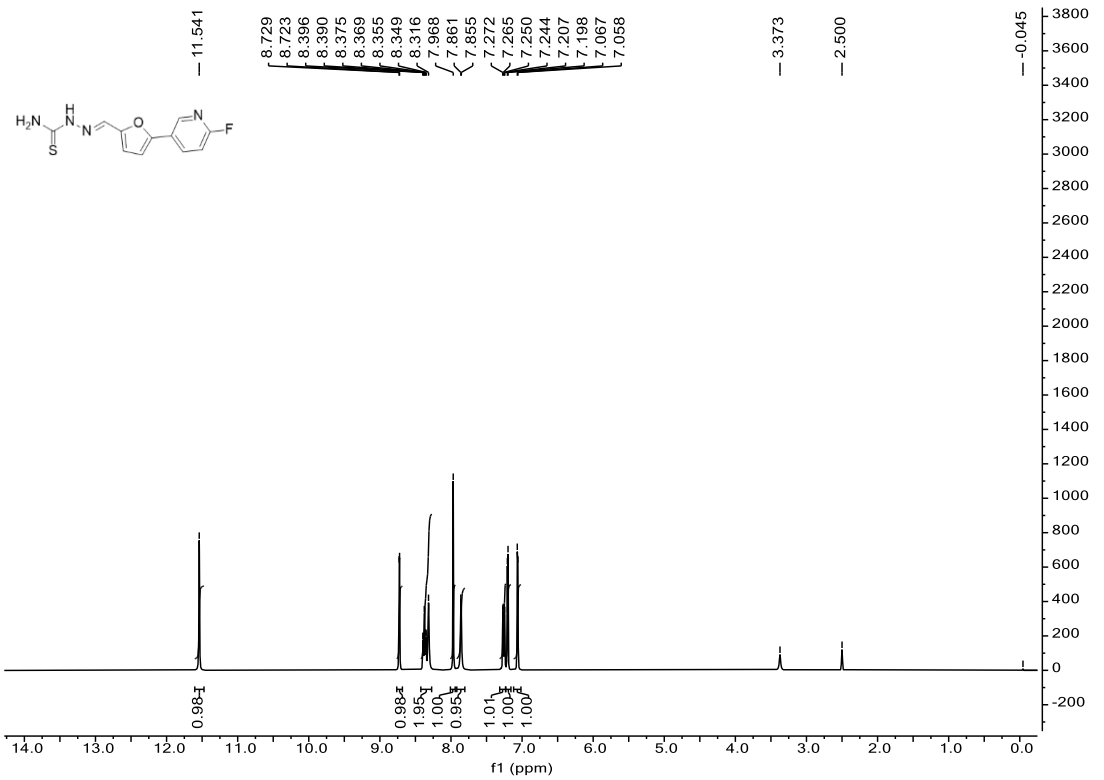
^{1}H NMR of compound **F8-B16** (400 MHz, DMSO-d_6)



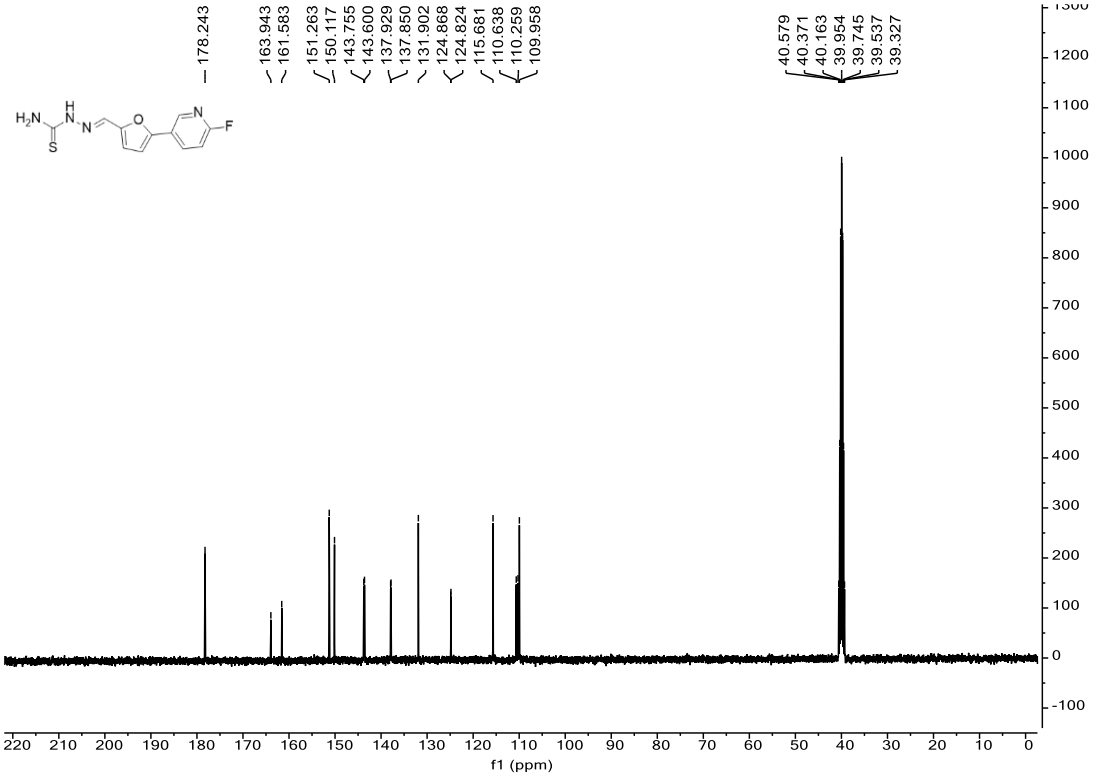
^{13}C NMR of compound **F8-B16** (100 MHz, DMSO-d_6)



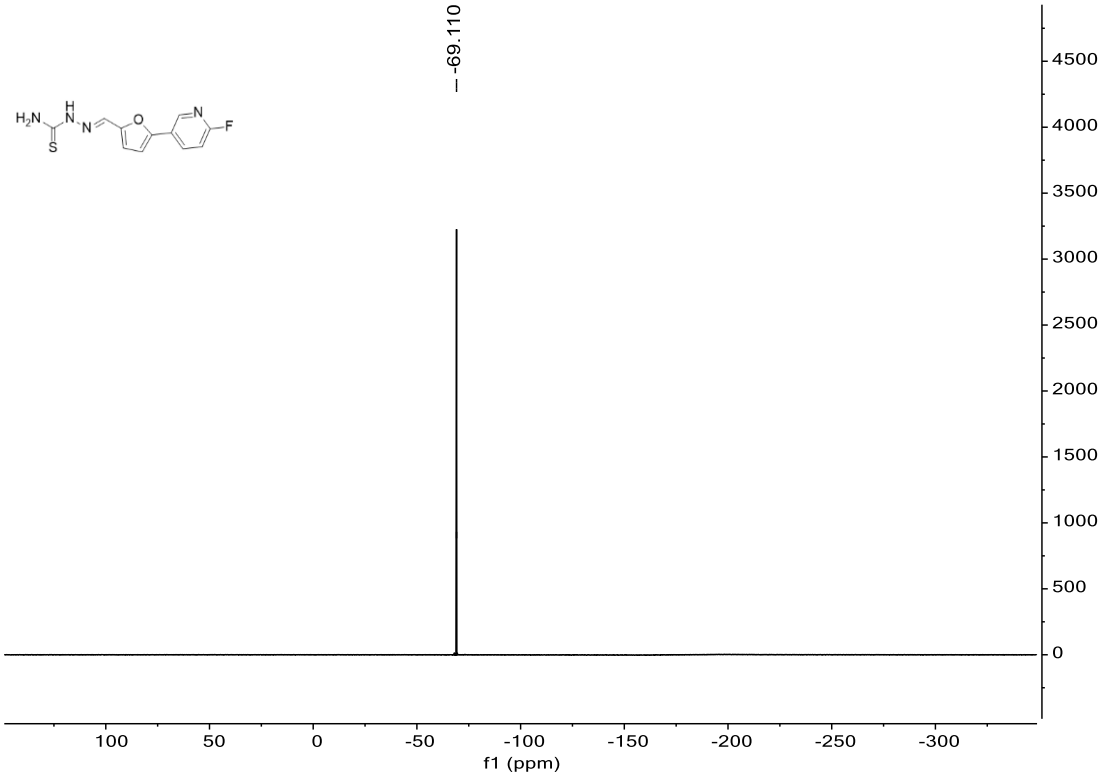
HRMS of compound **F8-B16** (ESI)



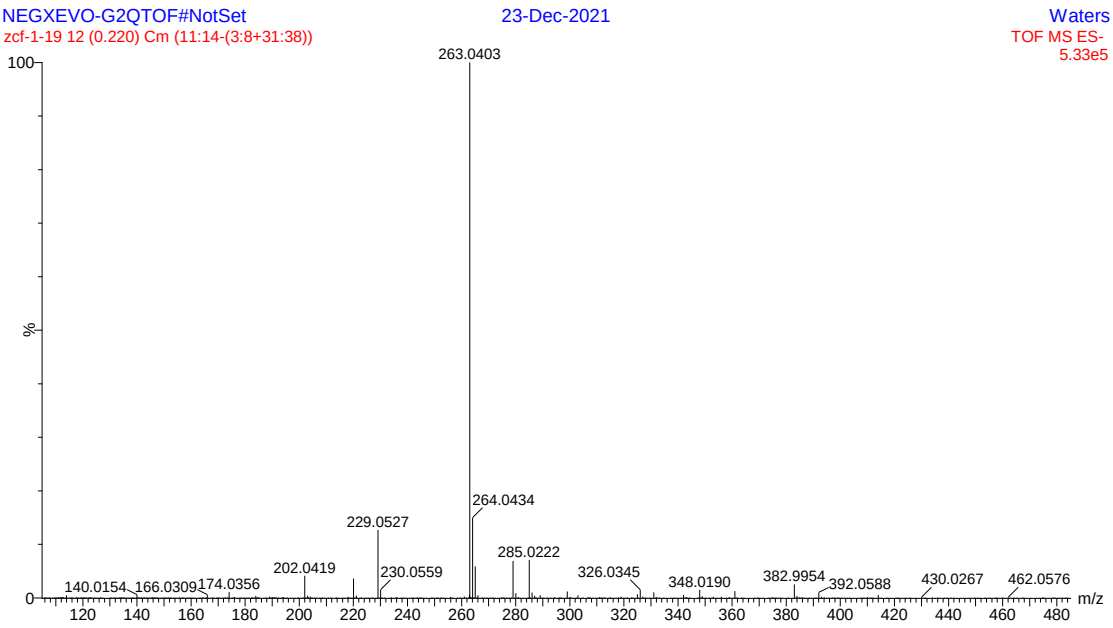
^{1}H NMR of compound **F8-B17** (400 MHz, DMSO-d_6)



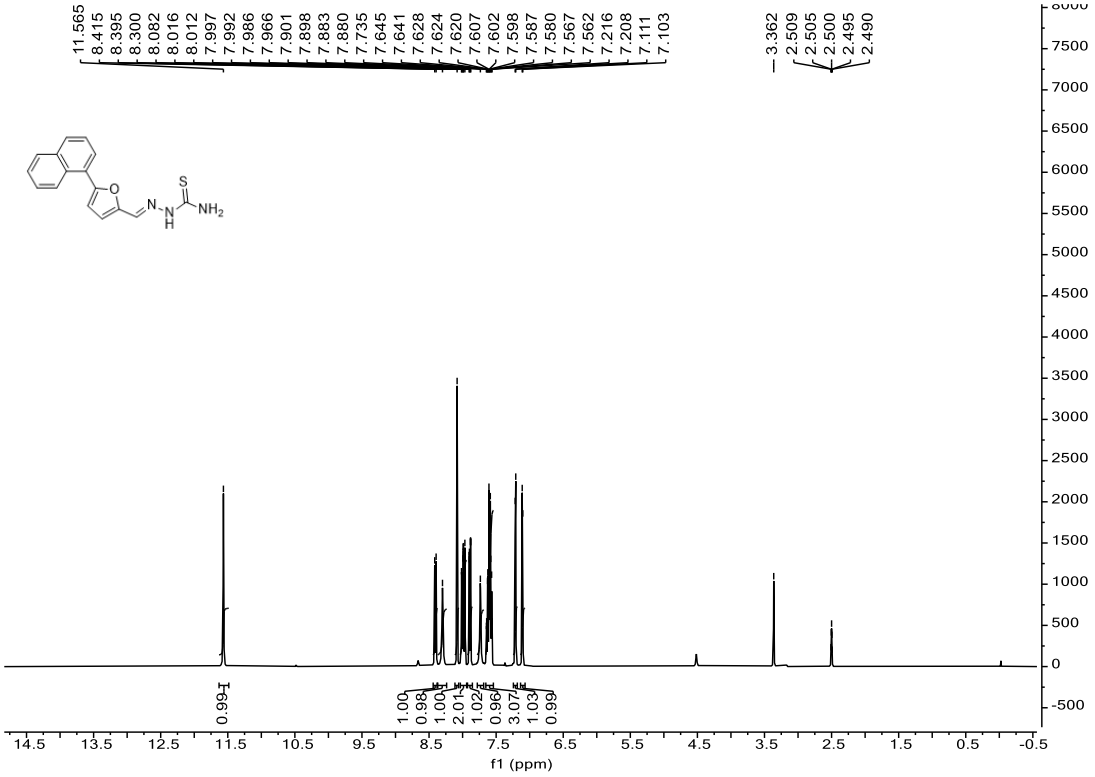
^{13}C NMR of compound **F8-B17** ((100 MHz, DMSO-d_6)



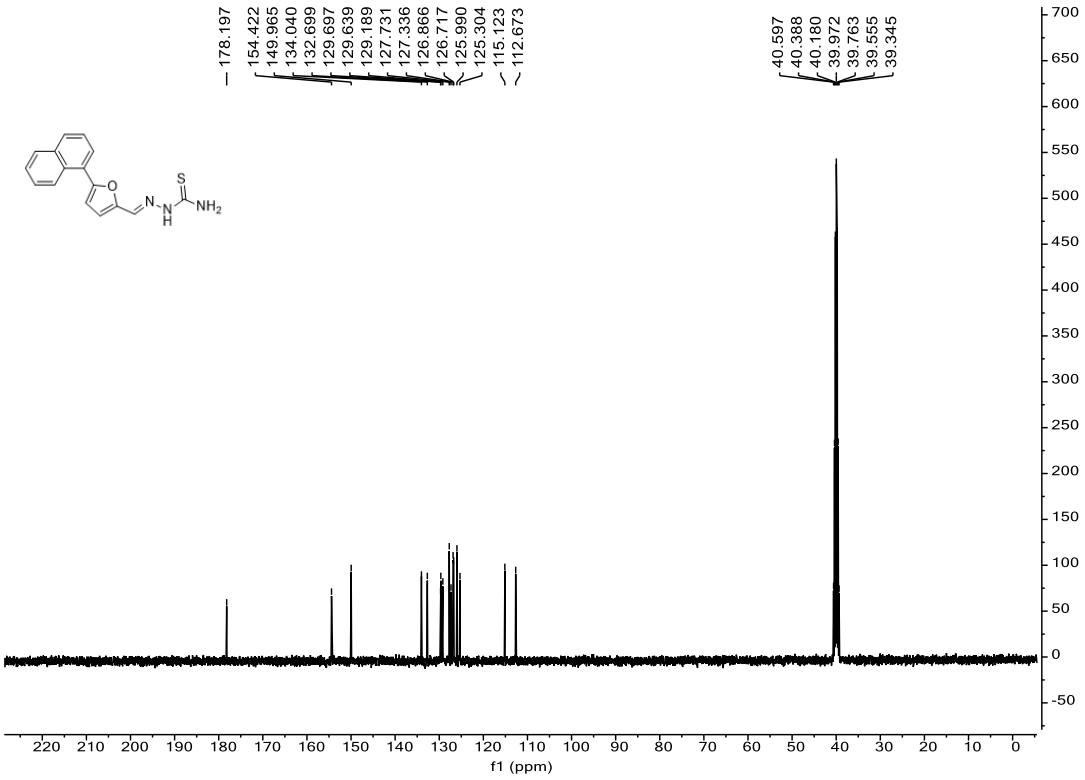
^{19}F NMR of compound **F8-B17** (376 MHz, DMSO-d_6)



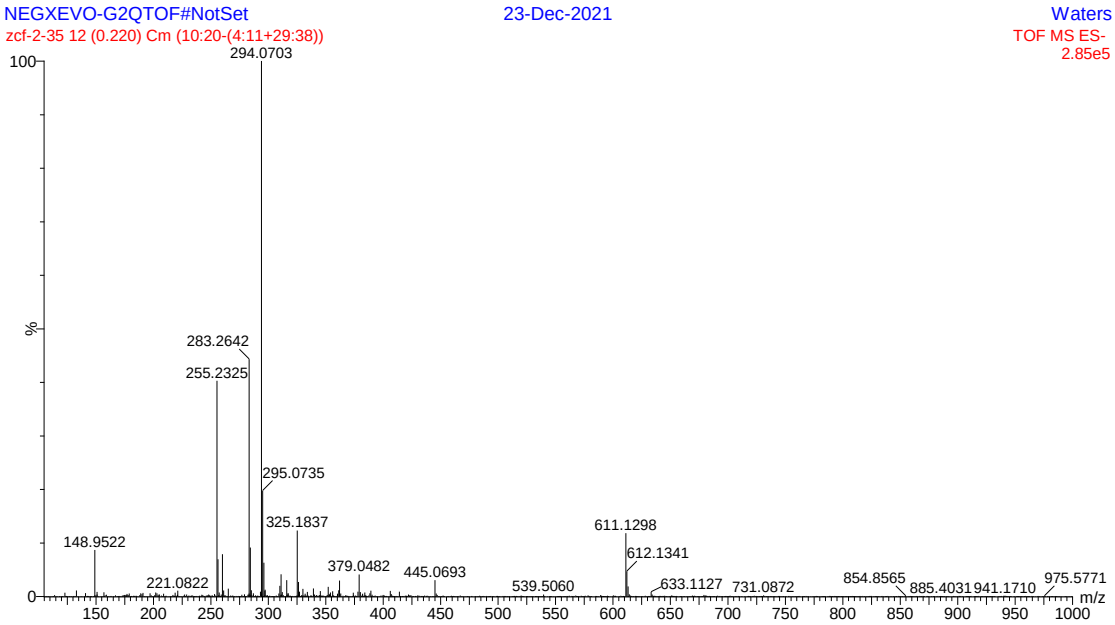
HRMS of compound **F8-B17** (ESI)



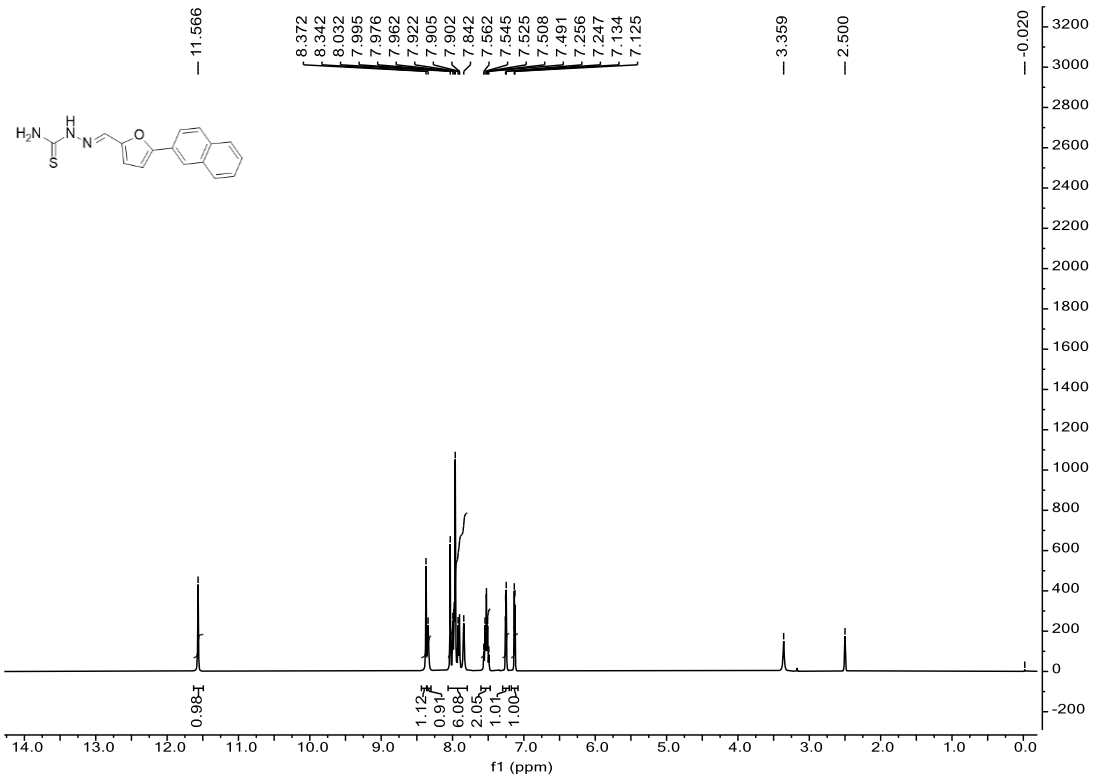
^{1}H NMR of compound **F8-B18** (400 MHz, DMSO-d_6)



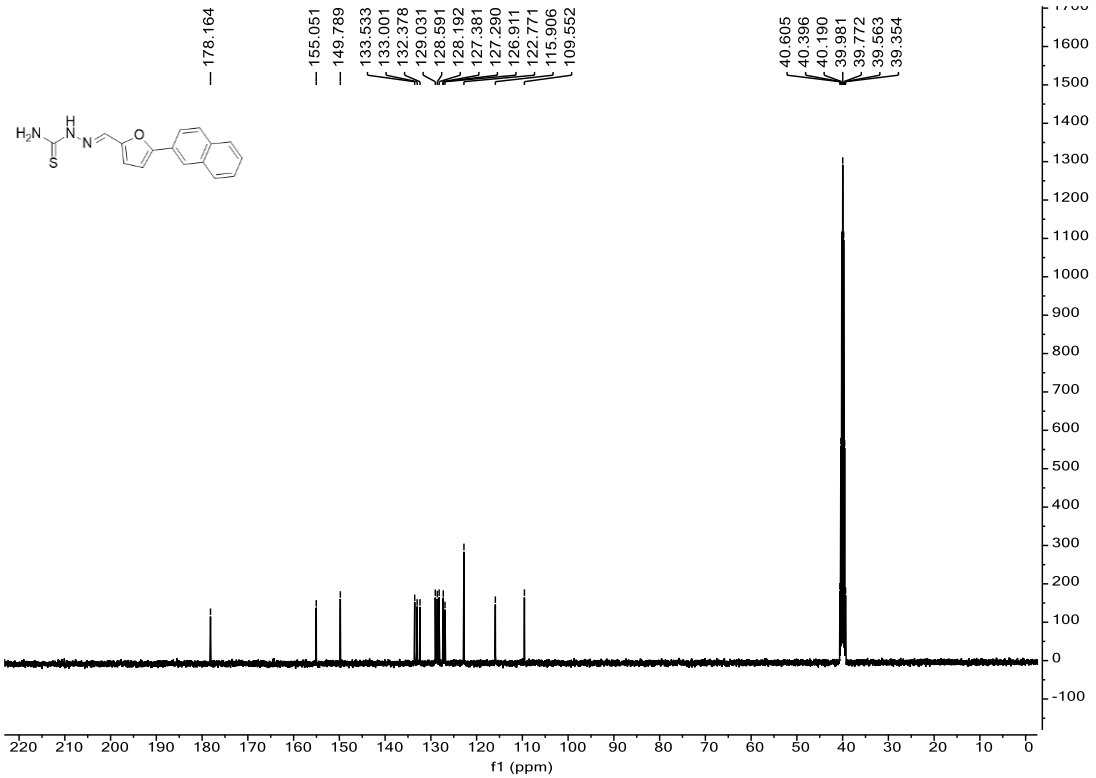
^{13}C NMR of compound **F8-B18** (100 MHz, DMSO-d_6)



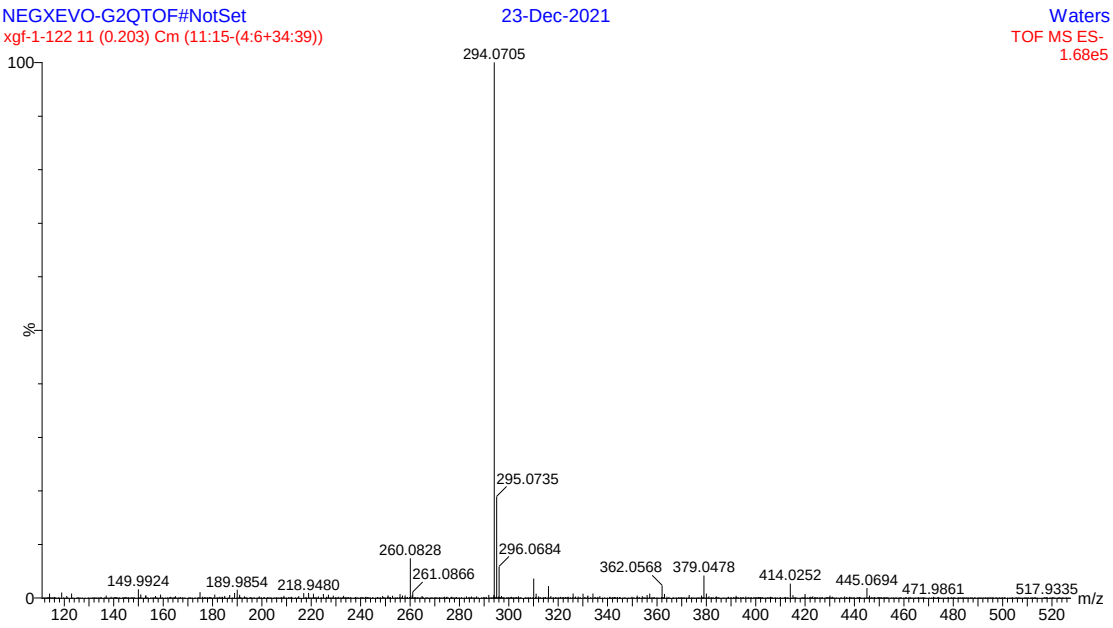
HRMS of compound **F8-B18** (ESI)



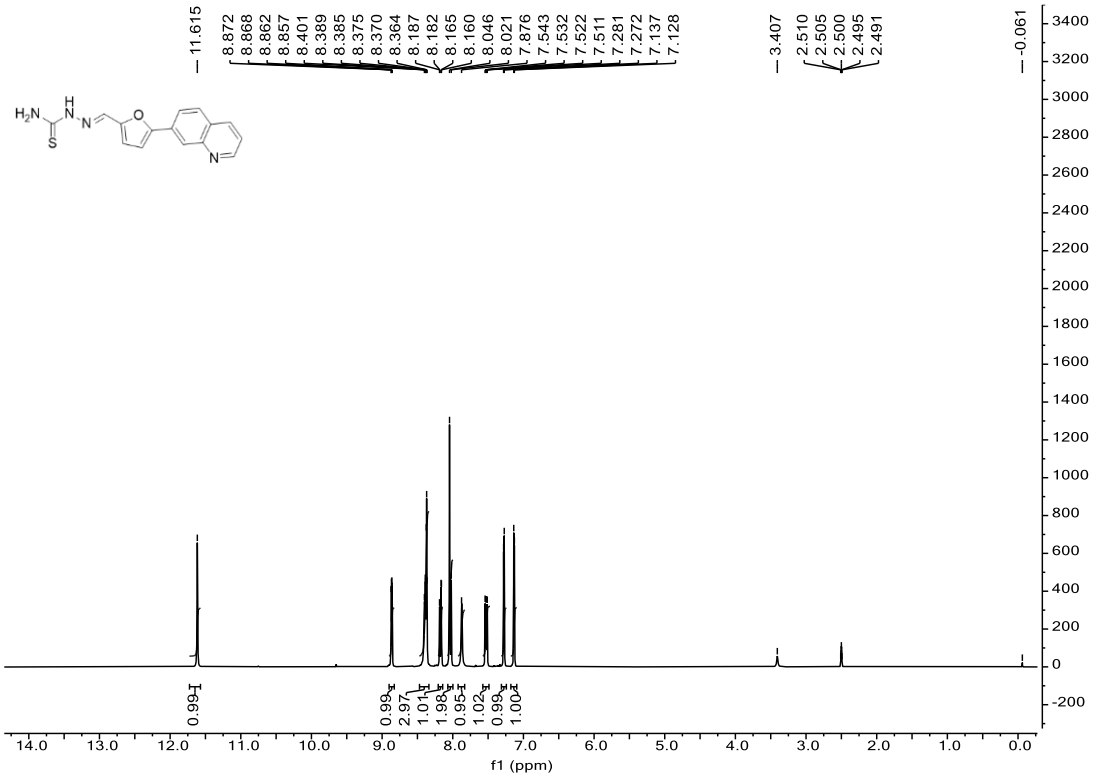
^{1}H NMR of compound **F8-B19** (400 MHz, DMSO-d_6)



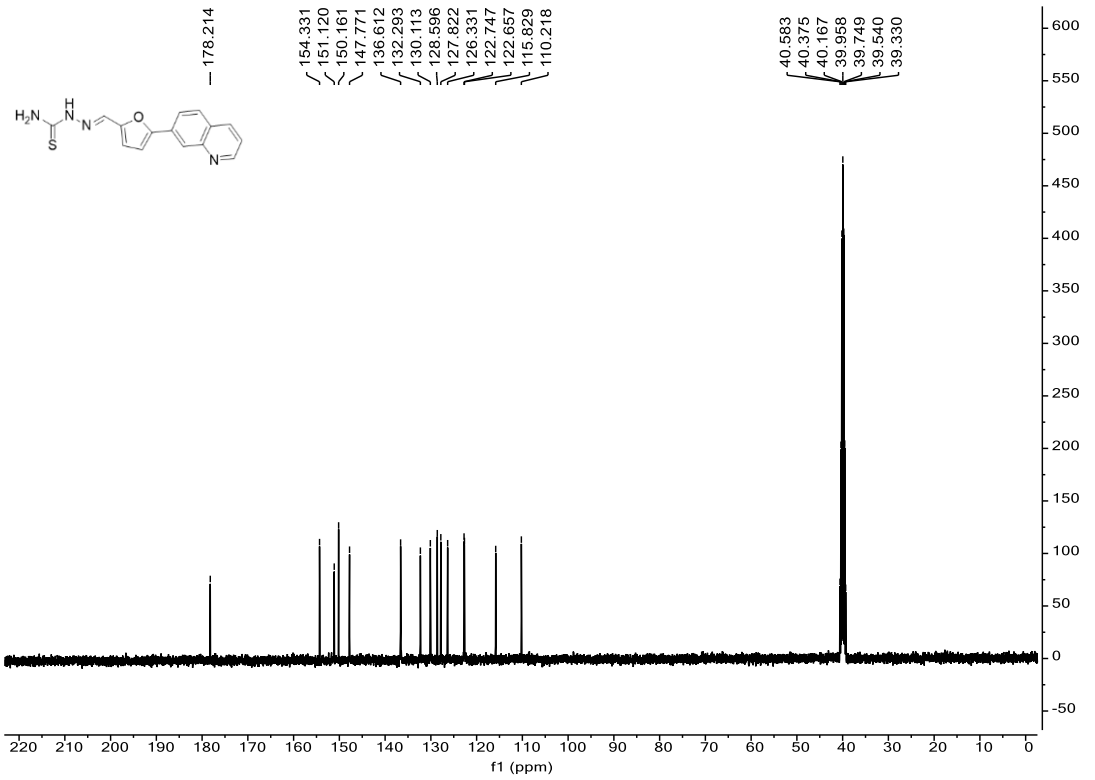
^{13}C NMR of compound **F8-B19** ((100 MHz, DMSO-d_6)



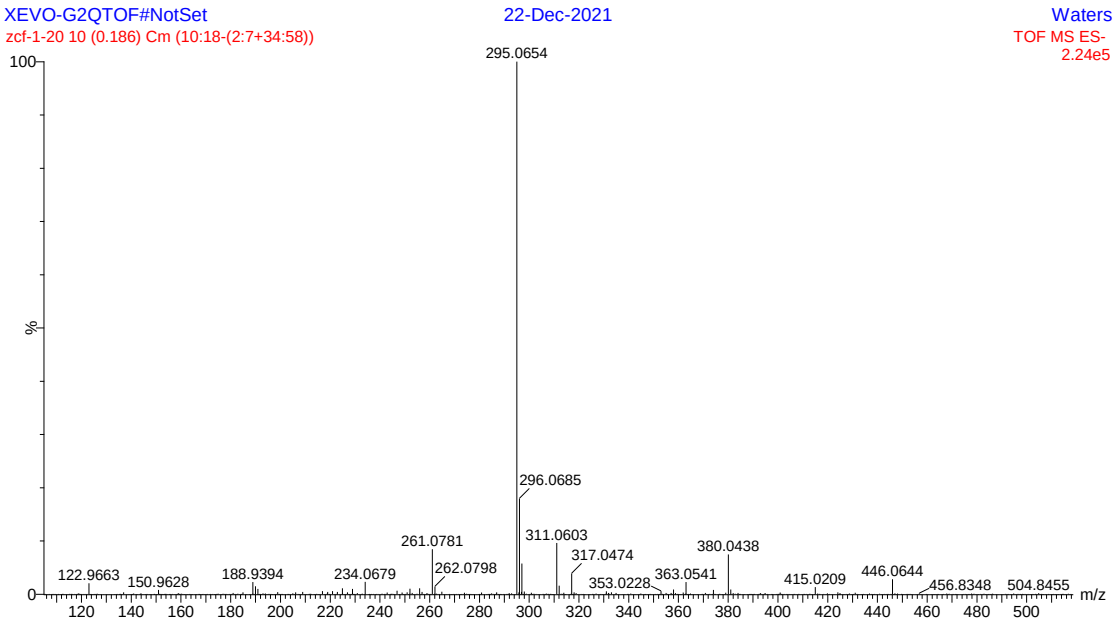
HRMS of compound **F8-B19** (ESI)



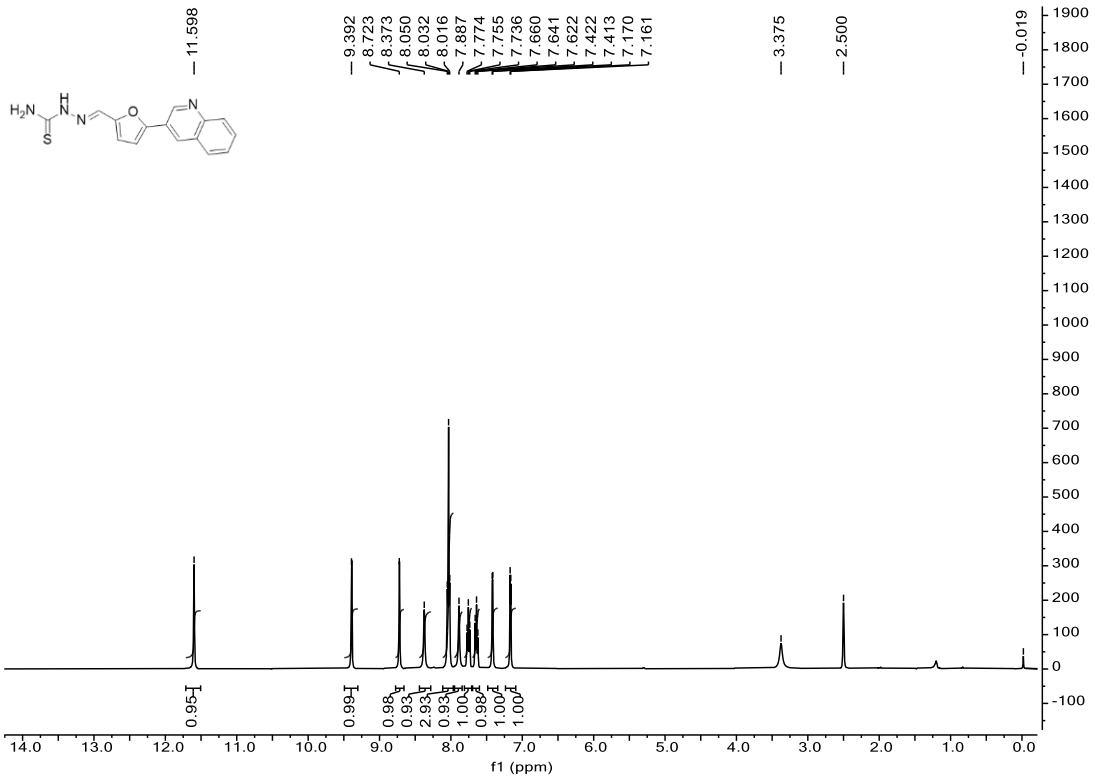
^{1}H NMR of compound **F8-B20** (400 MHz, DMSO-d_6)



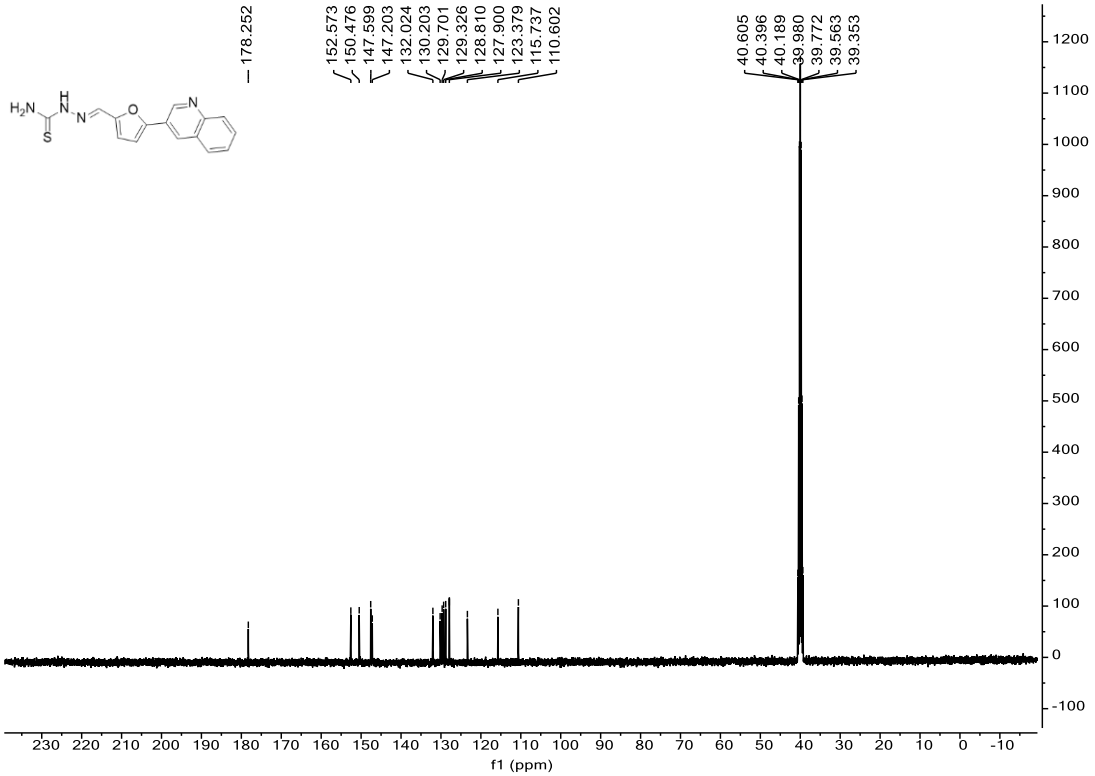
^{13}C NMR of compound **F8-B20** (100 MHz, DMSO-d_6)



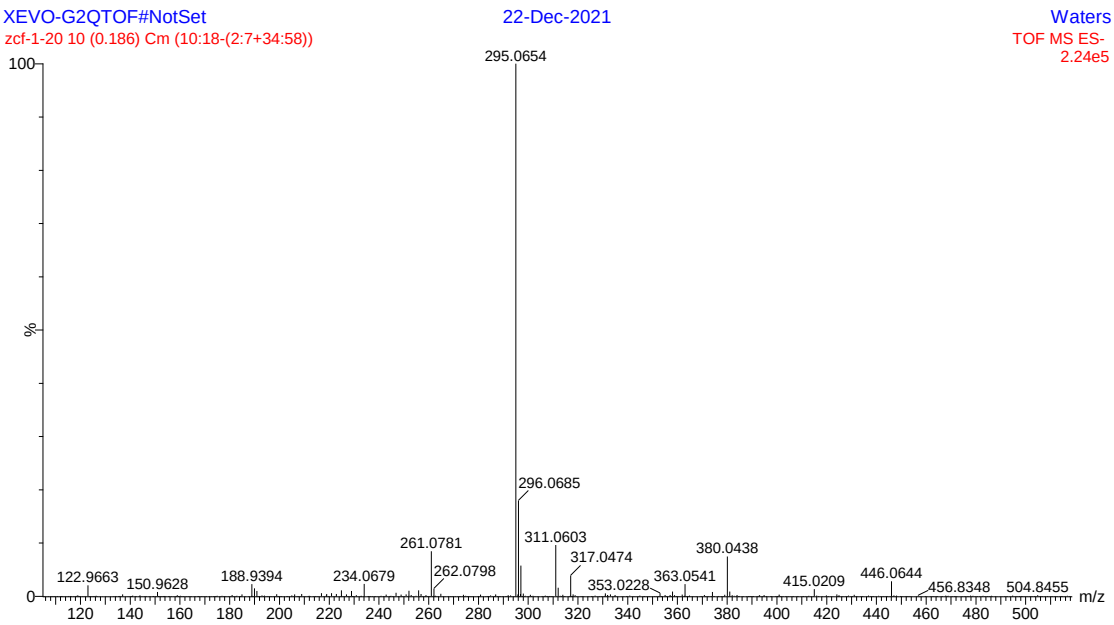
HRMS of compound **F8-B20** (ESI)



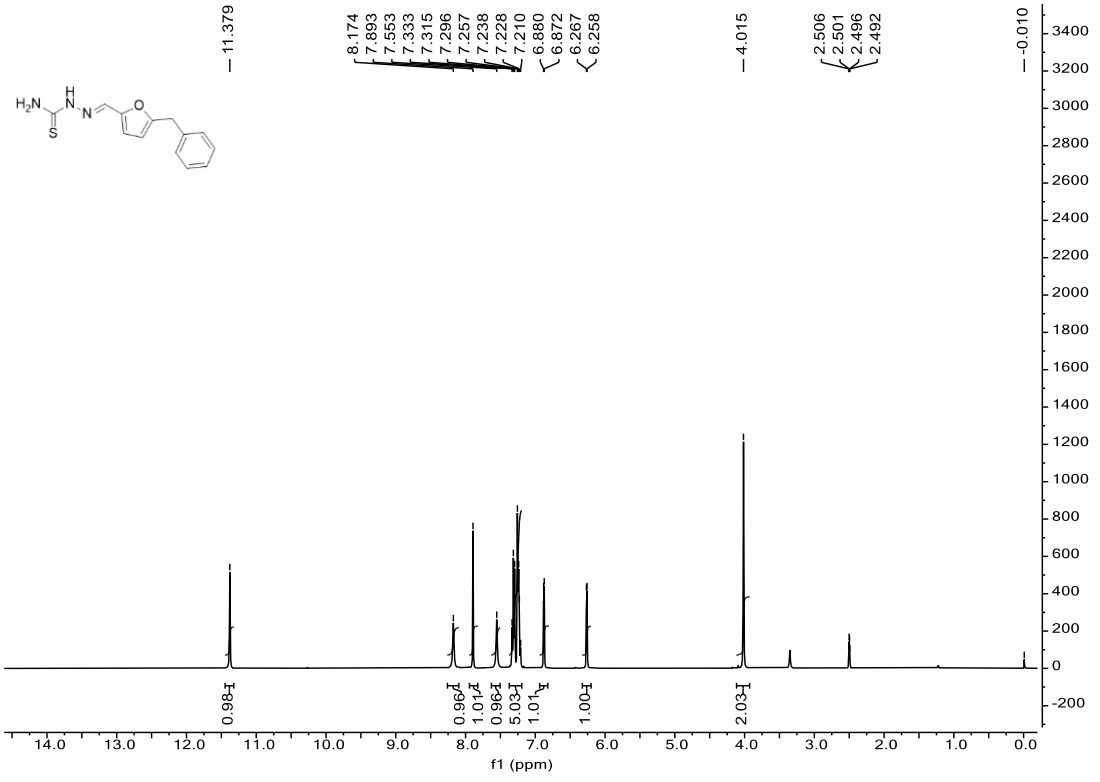
^{1}H NMR of compound **F8-B21** (400 MHz, DMSO-d_6)



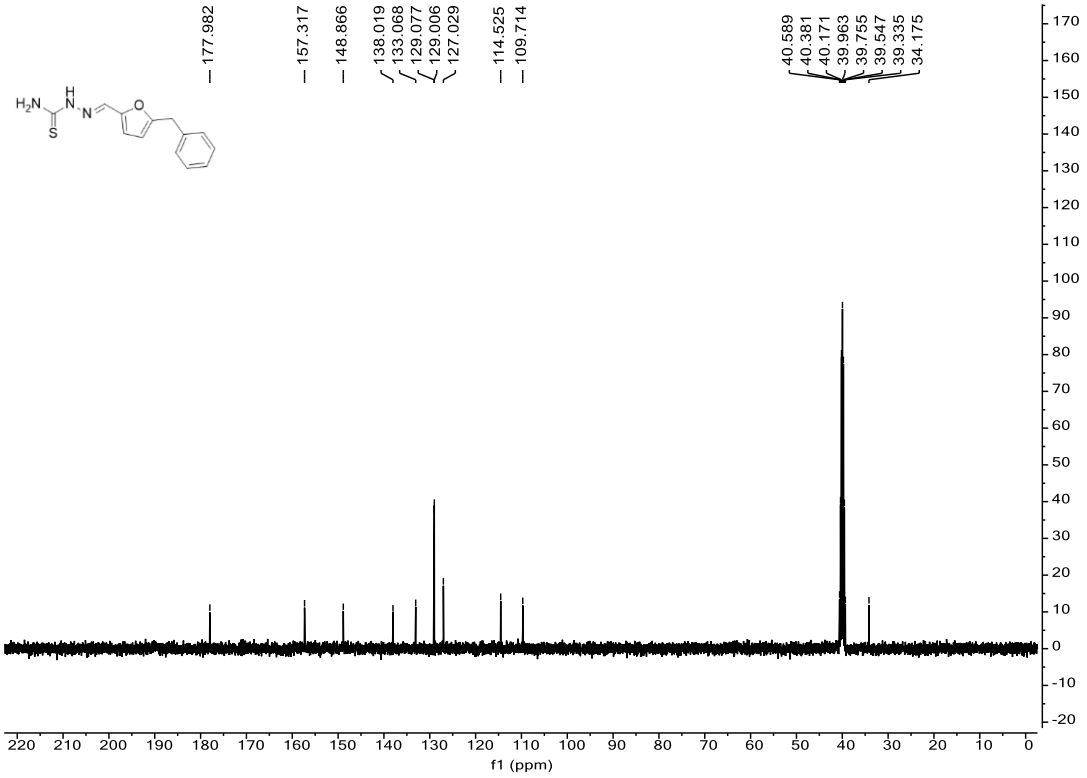
^{13}C NMR of compound **F8-B21** ((100 MHz, DMSO-d_6)



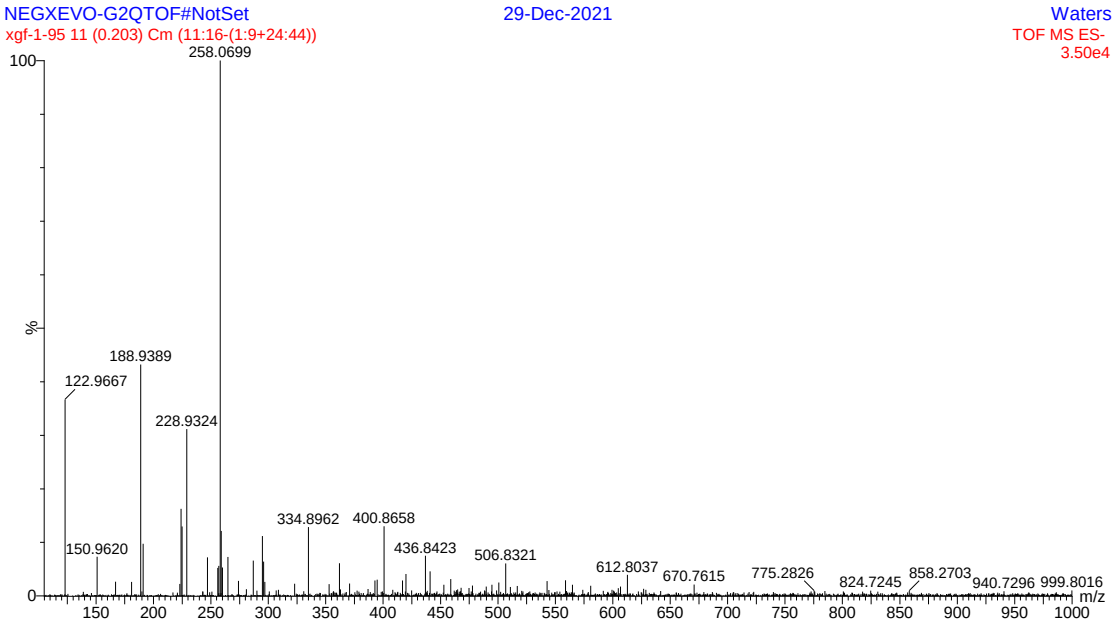
HRMS of compound **F8-B21** (ESI)



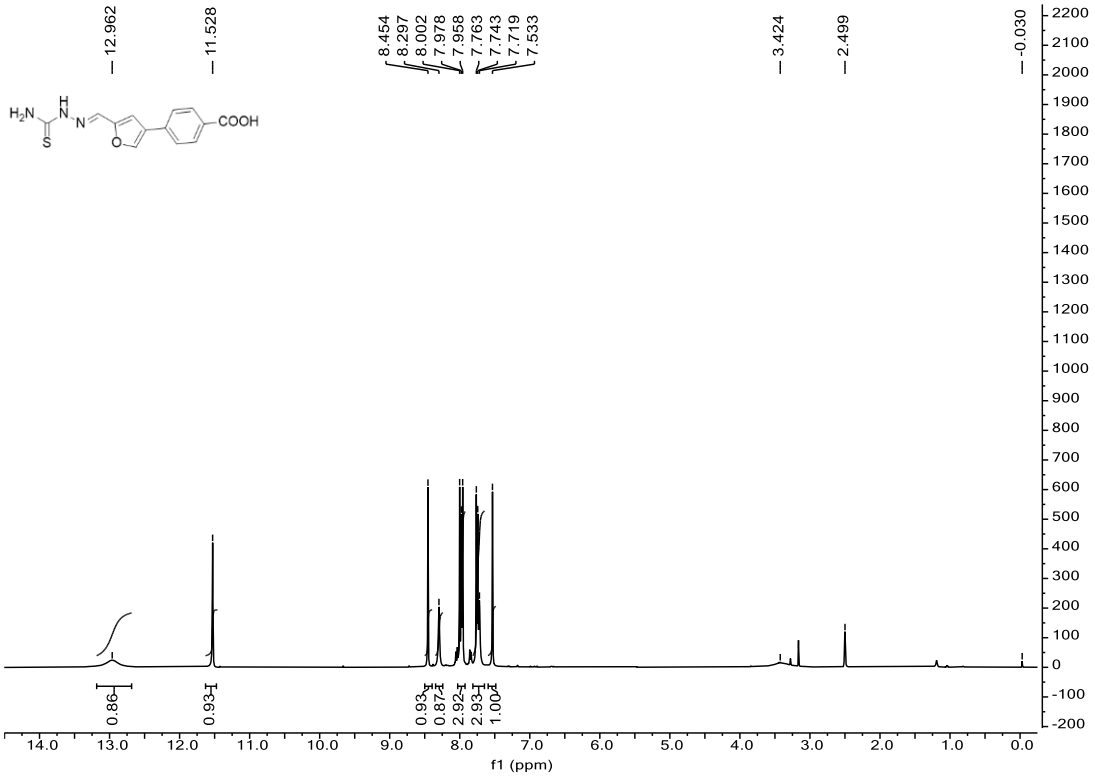
^{1}H NMR of compound **F8-B22** (400 MHz, DMSO-d_6)



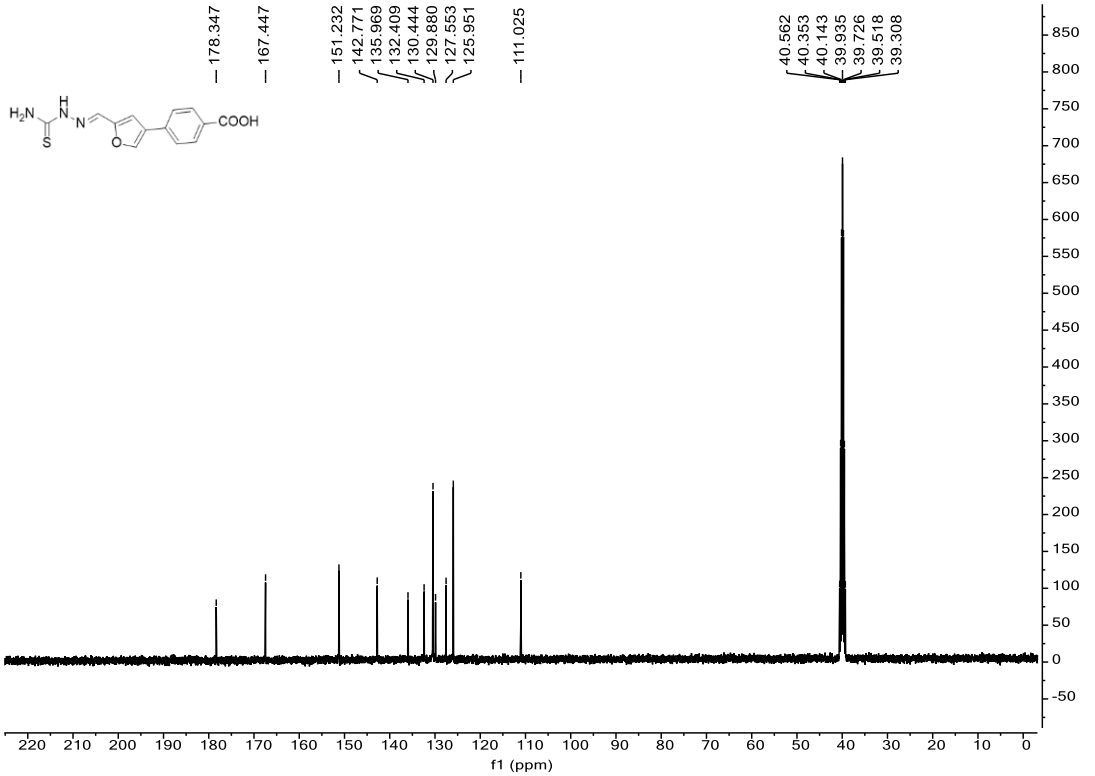
^{13}C NMR of compound **F8-B22** (100 MHz, DMSO-d_6)



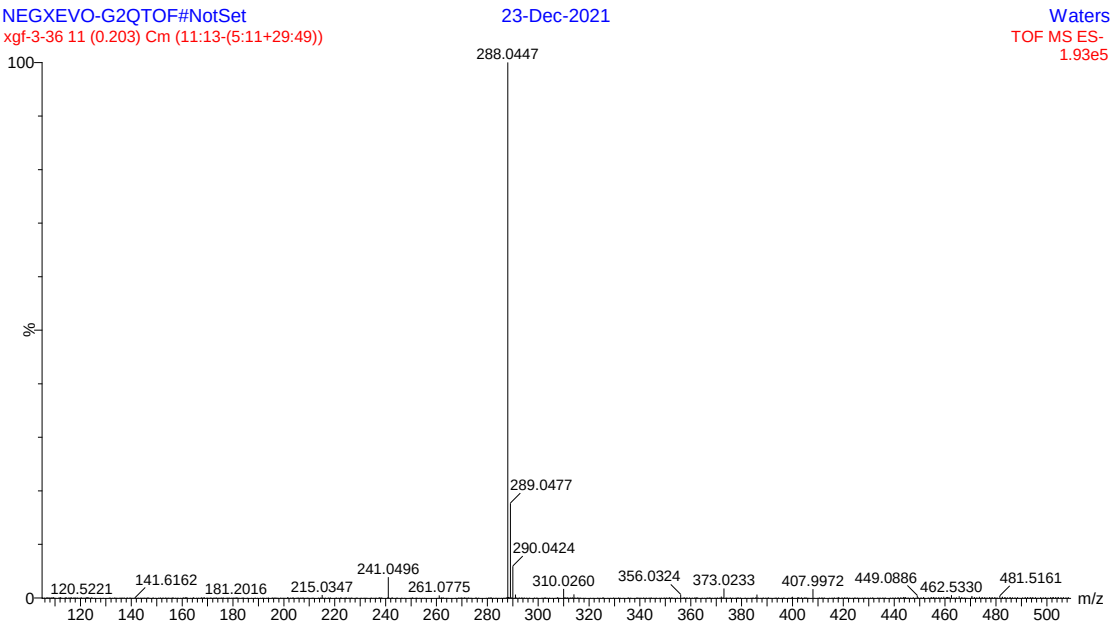
HRMS of compound **F8-B22** (ESI)



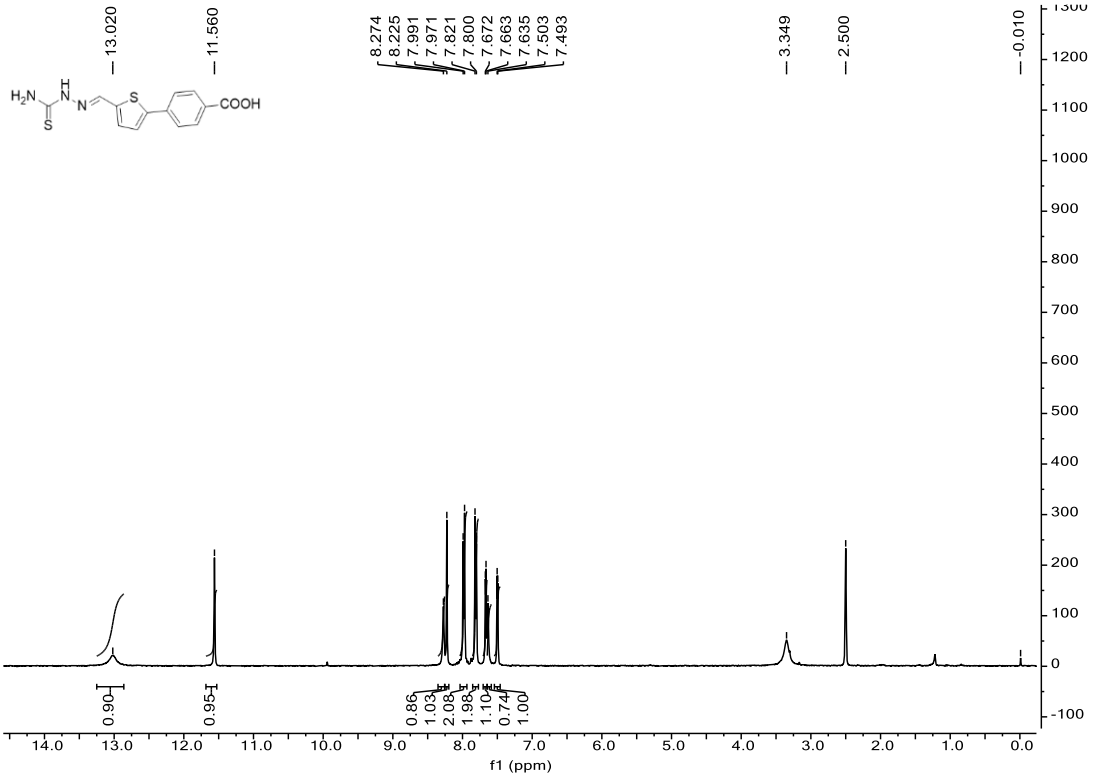
^{1}H NMR of compound **F8-C1** (400 MHz, DMSO-d_6)



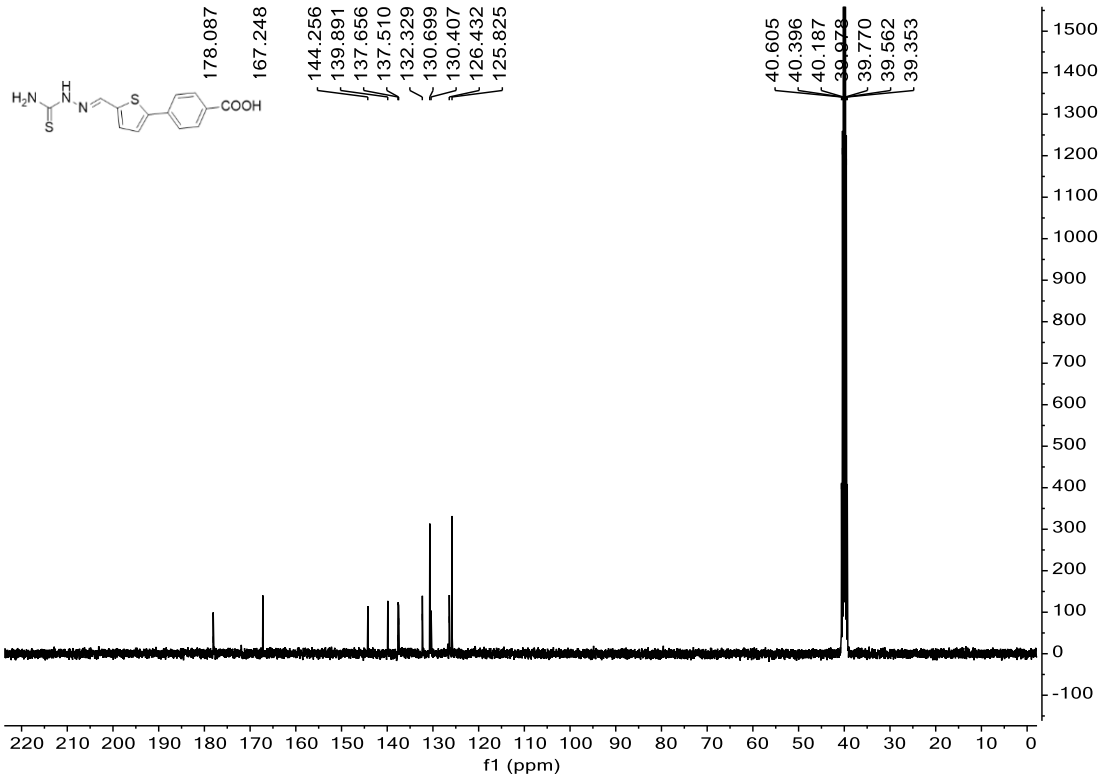
^{13}C NMR of compound **F8-C1** (100 MHz, DMSO-d_6)



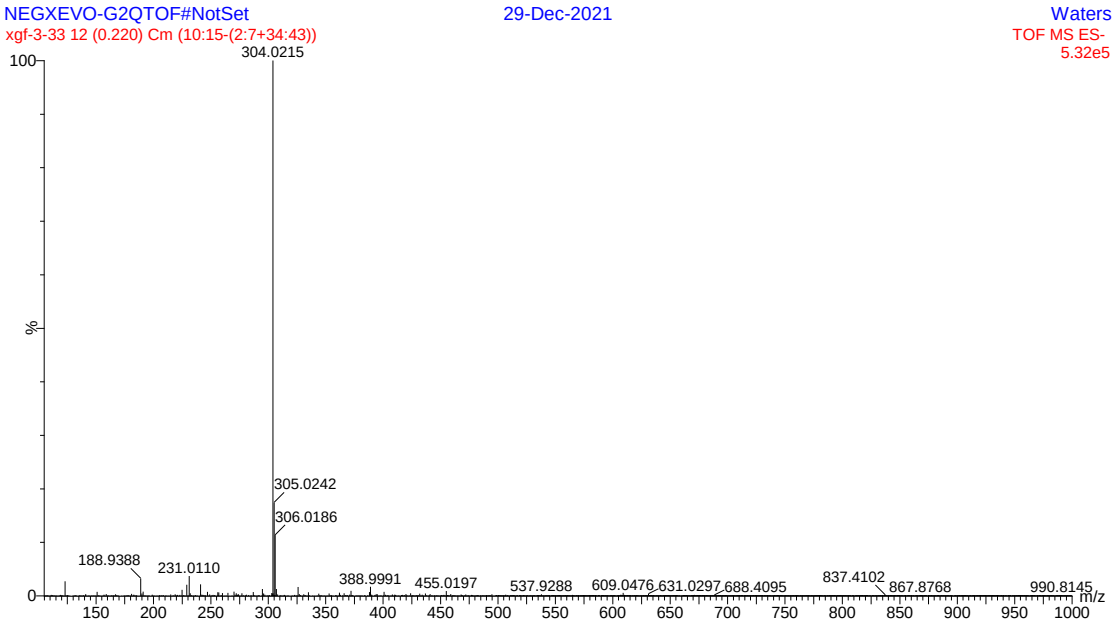
HRMS of compound **F8-C1** (ESI)



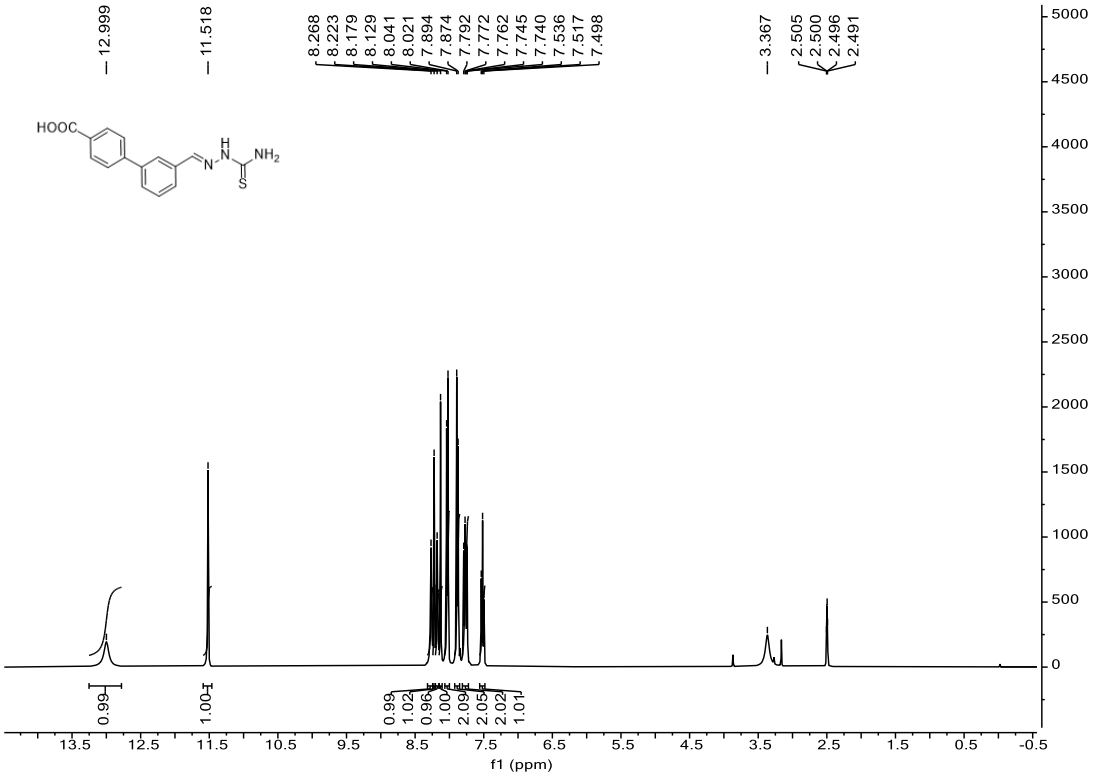
^{1}H NMR of compound **F8-C2** (400 MHz, DMSO-d_6)



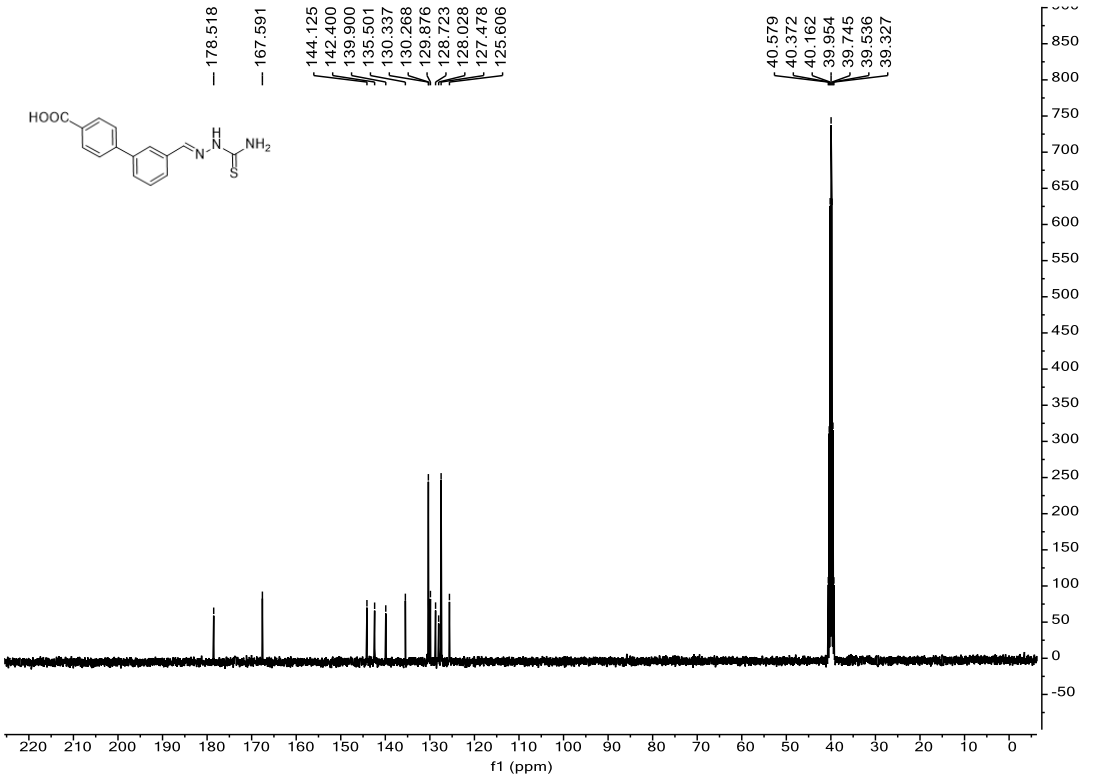
^{13}C NMR of compound **F8-C2** (100 MHz, DMSO-d_6)



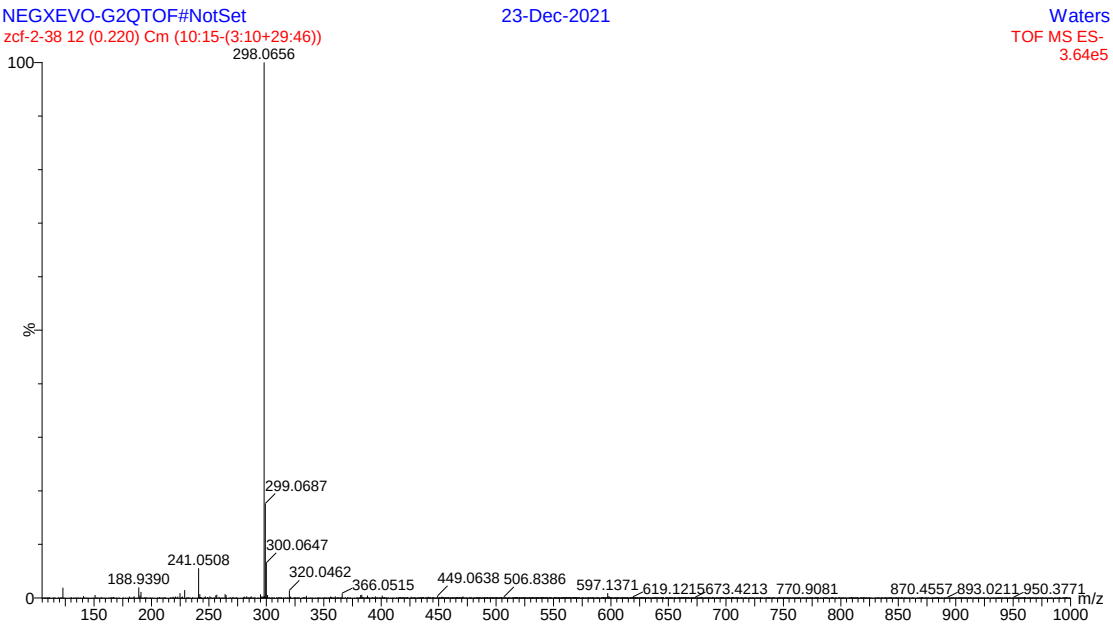
HRMS of compound **F8-C2** (ESI)



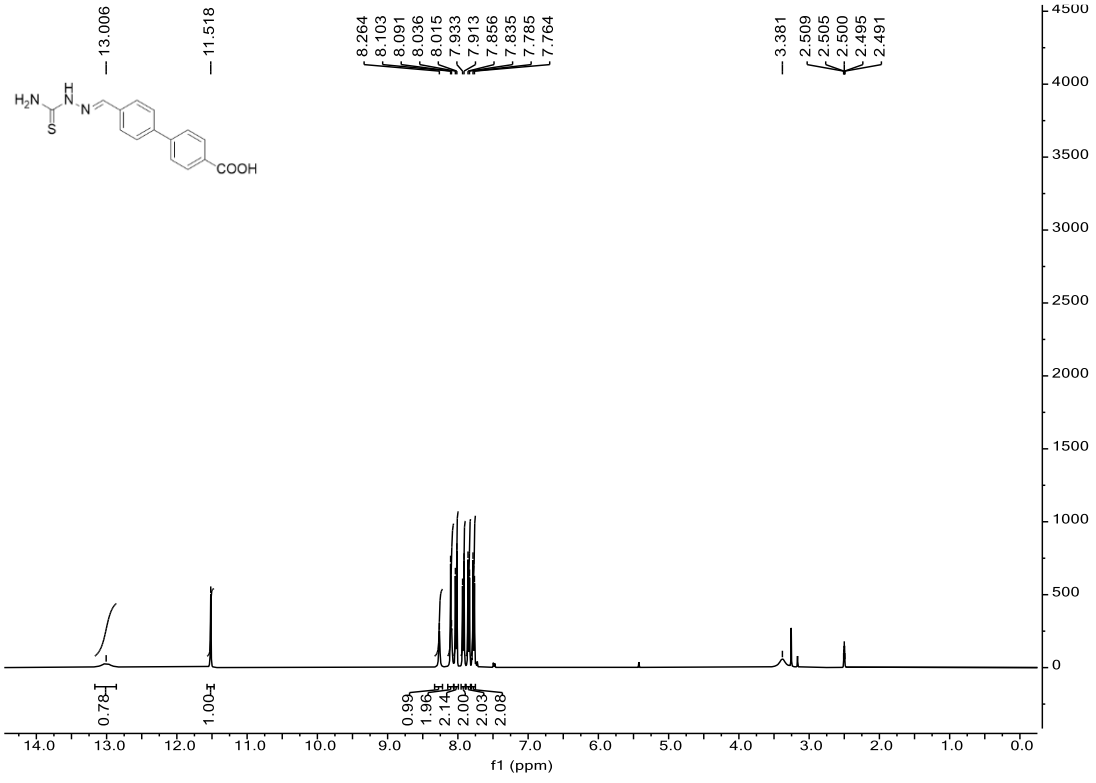
^{1}H NMR of compound **F8-C3** (400 MHz, DMSO-d_6)



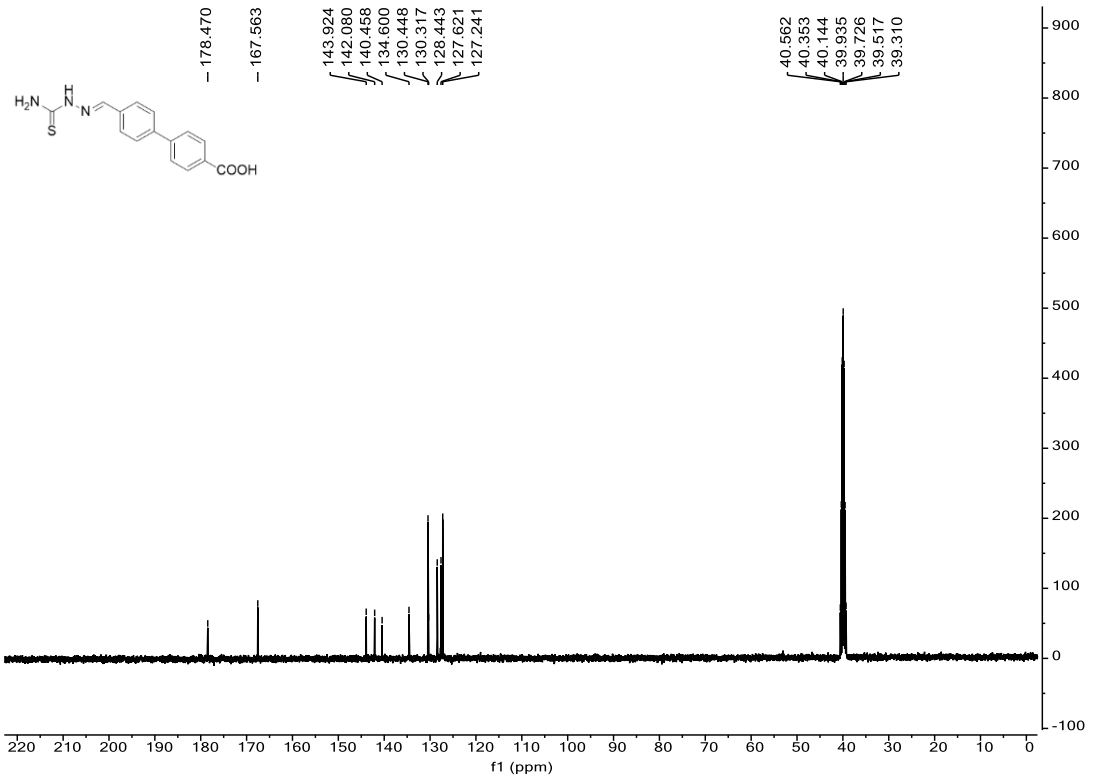
^{13}C NMR of compound **F8-C3** (100 MHz, DMSO-d_6)



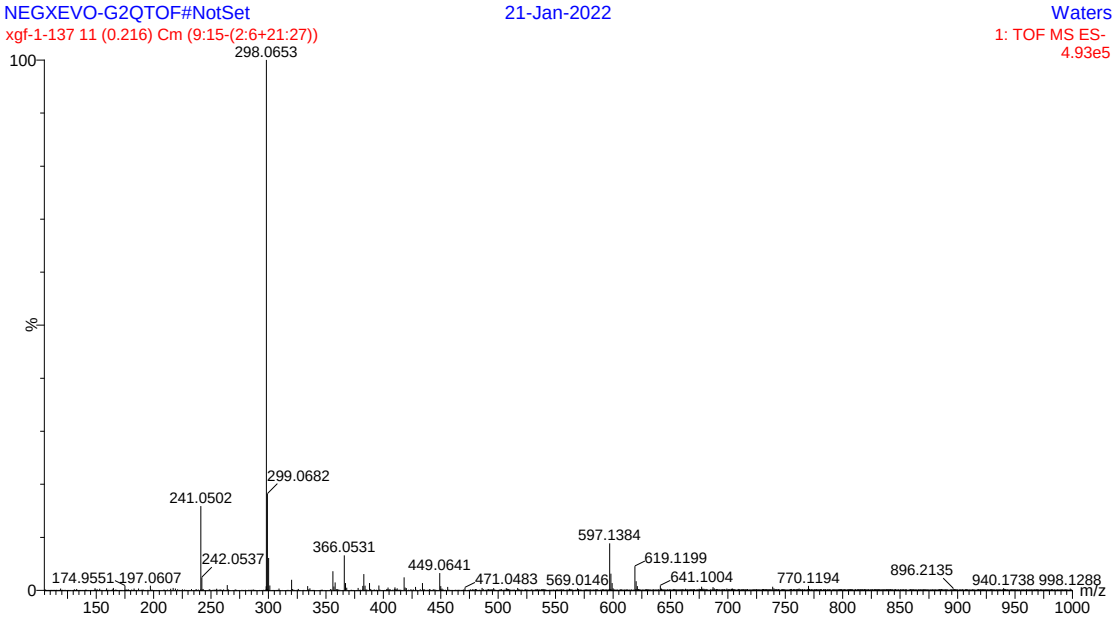
HRMS of compound **F8-C3** (ESI)



^{1}H NMR of compound **F8-C4** (400 MHz, DMSO-*d*$_6$)



^{13}C NMR of compound **F8-C4** (100 MHz, DMSO-d_6)



HRMS of compound **F8-C4** (ESI)