Electronic Supplementary Material (ESI) for MedChemComm.

Supporting Information

Novel Tetrazoloquinoline-Thiazolidinone Conjugates as Possible Antitubercular Agents: Synthesis and Molecular docking

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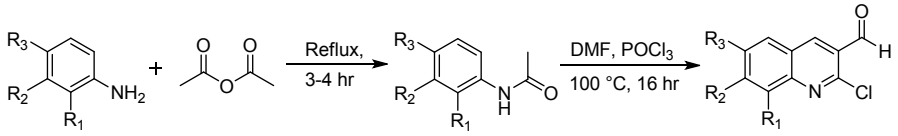


a-f

a, R_1 = H, R_2 = H, R_3 = H
b, R_1 = Me, R_2 = H, R_3 = H
c, R_1 = H, R_2 = Me, R_3 = H
d, R_1 = H, R_2 = H, R_3 = Me
e, R_1 = H, R_2 = OMe, R_3 = H
f, R_1 = H, R_2 = H, R_3 = OMe

Scheme S1: Synthesis of 2-chloro-3-formylquinolines **(1a-i).**[1]

1 R. M. Singh and A. Srivastava, *Indian J. Chem*., 2005, **44**, 1868.

a-f **1a-f**

1a, R_1 = H, R_2 = H, R_3 = H
1b, R_1 = Me, R_2 = H, R_3 = H
1c, R_1 = H, R_2 = Me, R_3 = H
1d, R_1 = H, R_2 = H, R_3 = Me
1e, R_1 = H, R_2 = OMe, R_3 = H
1f, R_1 = H, R_2 = H, R_3 = OMe

2 N. K. Ladani, M. P. Patel and R. G. Patel, *Arkivoc*, 2009, **7**, 292.

Table S1

Effect of temperature on the synthesis of **4a** under solvent-free condition[a]

Entry	Temp (°C)	Time (h)[b]	Yield[c] (%)
1	RT	24	-
2	50	4.2	42
3	60	3.5	65
4	70	2	80
5	80	1	90
6	90	1	90

[a]**Reaction conditions**: **1a** (1 mmol), **2a** (1 mmol) and 3 (2 mmol) at 80 °C for 1h. [b]Reaction progress monitored by TLC. [c]Isolated yield.

Table S2

Optimization of catalyst concentration.[a]

Entry	Mol %	Solvent	Time (h)[b]	Temp (°C)	Yield[c] (%)
1	5	solvent free	5	80	48
2	10	solvent free	3.2	80	66
3	15	solvent free	1.5	80	80
4	20	solvent free	1	80	90
5	25	solvent free	1	80	90

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol) and 3 (2 mmol) at 80 °C for 1h. [b]Reaction progress monitored by TLC (entry 1-5, h). [c]Isolated yield.

Table S3

Recycling of the IL in the synthesis of *N*-(4-oxo-2-(tetrazolo[1,5-*a*]quinolin-4-yl)thiazolidin-3-yl)isonicotinamide.[a]

Entry	Reaction cycle	Isolated yield (%)[b]
1	1st fresh	90
2	2nd cycle	88
3	3rd cycle	83
4	4th cycle	80

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3** (2 mmol) and 20% [DBUH][OAc] at 80 °C. [b]Isolated yield.

Table S4

Antitubercular activity of compounds against avirulent strain of dormant MTB H37Ra

Entry	% Inhibition of MTB H37Ra growth in presence of compounds			Entry	% Inhibition of MTB H37Ra growth in presence of compounds		
	30 µg/mL	10 µg/mL	3 µg/mL		30 µg/mL	10 µg/mL	3 µg/mL
4a	96.5	95.8	87.3	**4j**	93.5	91.8	93.6
4b	-32.0	-5.7	-9.5	**4k**	-4.5	-3.9	-2.3
4c	-6.7	-1.6	-8.8	**4l**	4.3	-8.8	13.8
4d	98.3	93.9	90.9	**4m**	94.1	95.1	92.6
4e	-2.7	-8.2	-2.9	**4n**	-56.4	-88.2	-82.4
4f	-2.9	-7.9	-4.7	**4o**	5.7	8.5	1.5
4g	94.0	93.6	91.3	**4p**	92.0	92.0	66.8
4h	-4.8	-3.5	-1.7	**4q**	78.7	81.1	9.0
4i	-2.5	-2.1	-3.0	**4r**	12.5	-6.4	13.8

The % Inhibition in the presence of test material is calculated by following formula.% inhibition = (Average of Control-Average of Compound)/ (Average of Control-Average of Blank) X 100), where control is culture medium with cells and DMSO and blank is culture medium without cells. Compounds were considered inactive if %I <90 at 30 µg/mL. For all samples, each compound concentration was tested in triplicates in a single experiment.

Table S5

Antitubercular activity of compounds against avirulent strain of dormant *M. Bovis* BCG

Entry	% Inhibition of *M. bovis* BCG growth in presence of compounds			Entry	% Inhibition of *M. bovis* BCG growth in presence of compounds		
	30 µg/mL	10 µg/mL	3 µg/mL		30 µg/mL	10 µg/mL	3 µg/mL
4a	98.2	93.9	94.5	**4j**	94.9	94.7	93.3
4b	28.1	16.4	-26.4	**4k**	77.3	14.7	7.1
4c	-8.0	23.6	12.8	**4l**	-23.0	33.1	21.2
4d	94.0	94.3	94.2	**4m**	98.3	94.1	94.2
4e	19.0	-12.1	17.3	**4n**	97.8	37.8	-15.8
4f	15.2	17.8	11.5	**4o**	30.8	-1.3	9.6
4g	99.4	98.9	97.2	**4p**	98.5	92.1	91.3
4h	7.4	4.7	12.4	**4q**	93.1	30.1	-21.8
4i	45.5	20.1	7.4	**4r**	18.0	7.0	19.4

The % Inhibition in the presence of test material is calculated by following formula.% inhibition = (Average of Control-Average of Compound)/ (Average of Control-Average of Blank) X 100), where control is culture medium with cells and DMSO and blank is culture medium without cells. Compounds were considered inactive if %I <90 at 30 µg/mL. For all samples, each compound concentration was tested in triplicates in a single experiment.

Table S6

Primary screening of compounds against MCF-7

Entry	MCF-7			Entry	MCF-7		
	100 µg/mL	30 µg/mL	10 µg/mL		100 µg/mL	30 µg/mL	10 µg/mL
4a	39.8	29.5	0.0	**4j**	47.5	30.3	13.0
4b	25.1	12.4	2.0	**4k**	35.7	7.9	0.0
4c	42.3	-0.7	0.0	**4l**	30.3	28.6	8.0
4d	-3.6	-17.4	0.0	**4m**	27.6	8.9	0.0
4e	23.5	24.5	23.7	**4n**	31.0	20.7	10.0
4f	47.8	7.2	-1.8	**4o**	16.7	10.4	19.4
4g	21.4	22.9	0.0	**4p**	30.6	25.7	9.7
4h	36.3	32.1	0.0	**4q**	27.5	35.7	0.0
4i	45.1	8.2	5.4	**4r**	1.7	-1.1	12.5

The % Inhibition in the presence of test material is calculated by following formula.% inhibition = (Average of Control-Average of Compound)/ (Average of Control-Average of Blank) X 100), where control is culture medium with cells and DMSO and blank is culture medium without cells. Compounds were considered inactive if %I <90 at 100 µg/mL. For all samples, each compound concentration was tested in triplicates in a single experiment.

Table S7

Primary Cytotoxic study of compounds against A549.

Entry	A549			Entry	A549		
	100 µg/mL	30 µg/mL	10 µg/mL		100 µg/mL	30 µg/mL	10 µg/mL
4a	9.0	-13.2	-8.2	**4j**	0.0	0.0	1.8
4b	0.0	0.0	-15.9	**4k**	18.3	0.0	1.2
4c	17.6	0.2	30.8	**4l**	37.3	14.9	9.7
4d	21.5	-1.4	7.0	**4m**	-19.5	-10.5	-14.1
4e	33.2	35.6	19.3	**4n**	8.0	-12.1	-7.5
4f	22.8	5.9	1.0	**4o**	18.9	14.7	3.2
4g	0.0	0.0	0.0	**4p**	30.9	22.7	22.6
4h	31.7	7.8	27.4	**4q**	1.8	-11.0	9.7
4i	25.4	6.0	3.4	**4r**	14.8	-10.6	0.0

The % Inhibition in the presence of test material is calculated by following formula.% inhibition = (Average of Control-Average of Compound)/ (Average of Control-Average of Blank) X 100), where control is culture medium with cells and DMSO and blank is culture medium without cells. Compounds were considered inactive if %I <90 at 100 µg/mL. For all samples, each compound concentration was tested in triplicates in a single experiment.

Table S8

Primary Cytotoxic study of compounds against HCT 116

Entry	HCT 116			Entry	HCT 116		
	100 µg/mL	30 µg/mL	10 µg/mL		100 µg/mL	30 µg/mL	10 µg/mL
4a	27.5	16.7	13.3	**4j**	38.3	9.7	9.1
4b	30.5	26.4	26.4	**4k**	47.3	31.3	-1.0
4c	44.1	41.6	0.2	**4l**	26.3	15.7	9.3
4d	26.1	15.8	12.0	**4m**	19.2	-4.2	17.2
4e	10.3	-3.3	-1.5	**4n**	13.7	2.6	0.7
4f	48.4	46.0	4.8	**4o**	18.7	12.4	8.7
4g	31.2	30.0	24.8	**4p**	47.6	39.4	34.3
4h	33.7	21.8	12.6	**4q**	9.7	22.9	12.0
4i	30.3	24.1	16.5	**4r**	0.0	-12.7	0.0

The % Inhibition in the presence of test material is calculated by following formula.% inhibition = (Average of Control-Average of Compound)/ (Average of Control-Average of Blank) X 100), where control is culture medium with cells and DMSO and blank is culture medium without cells. Compounds were considered inactive if %I <90 at 100 µg/mL. For all samples, each compound concentration was tested in triplicates in a single experiment.

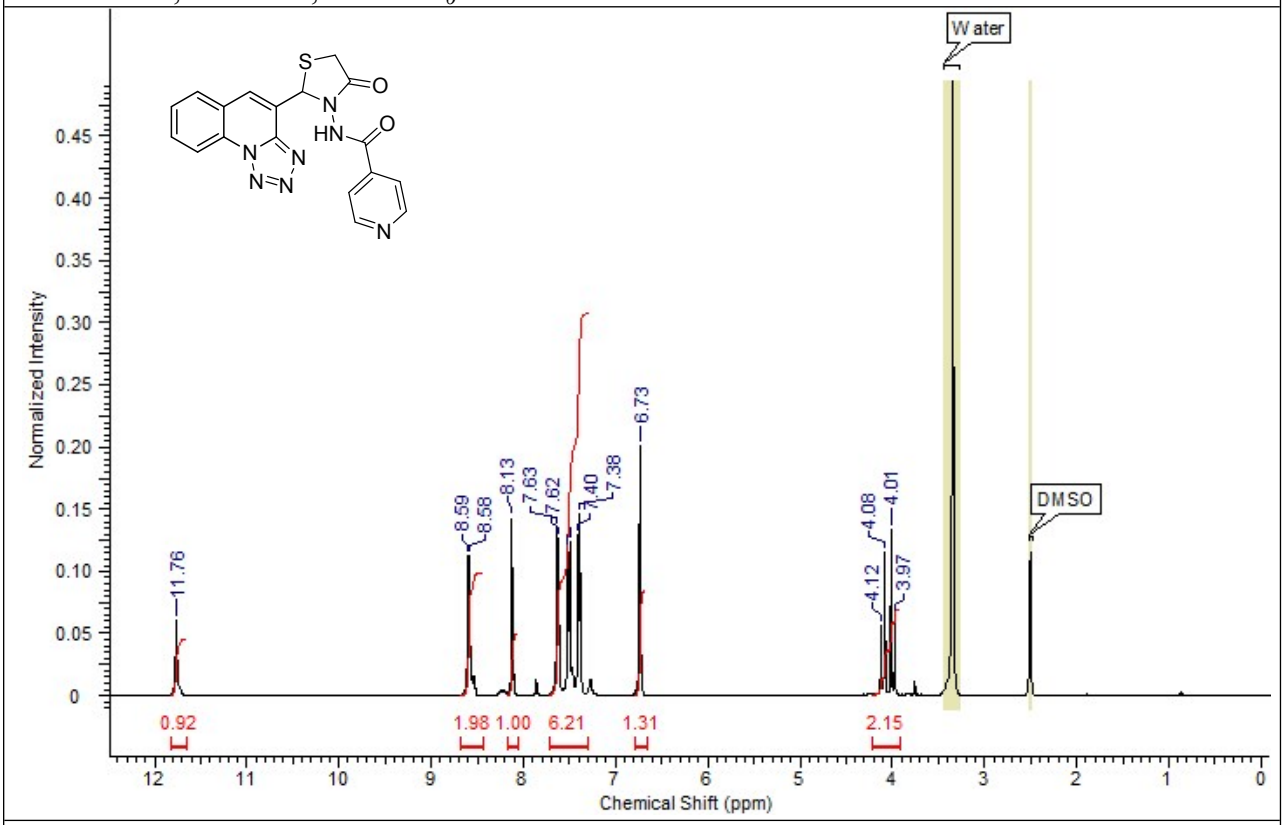
Table S9 Anti-mycobacterial activitiy of the 4-thiazolidinone incorporated tetrazoloquinolines[a]

Entry	MTB H37Ra (μmol/mL)		*M. bovis* BCG (μmol/mL)	
	IC_{50}	MIC	IC_{50}	MIC
4a	0.36	13.55	0.69	0.43
4b	> 76.69	> 76.69	> 76.69	> 76.69
4c	> 68.90	> 68.90	> 68.90	> 68.90
4d	1.23	1.77	0.07	0.51
4e	> 73.99	> 73.99	> 73.99	> 73.99
4f	> 66.75	> 66.75	> 66.75	> 66.75
4g	0.25	2.61	0.03	0.30
4h	> 73.99	> 73.99	> 73.99	> 73.99
4i	> 66.75	> 66.75	> 66.75	> 66.75
4j	0.15	2.14	3.77	8.43
4k	> 73.99	> 73.99	> 73.99	> 73.99
4l	> 66.75	> 66.75	> 66.75	> 66.75
4m	0.26	1.66	0.06	0.36
4n	2.92	> 71.23	6.74	20.11
4o	> 64.45	> 64.45	> 64.45	> 64.45
4p	0.14	0.99	0.03	0.14
4q	3.92	> 71.23	39.68	> 71.23
4r	> 64.45	> 64.45	> 64.45	> 64.45
[a]RP	0.0023 ± 0.00022	0.024 ± 0.0021	0.005 ± 0.00028	0.021 ± 0.039

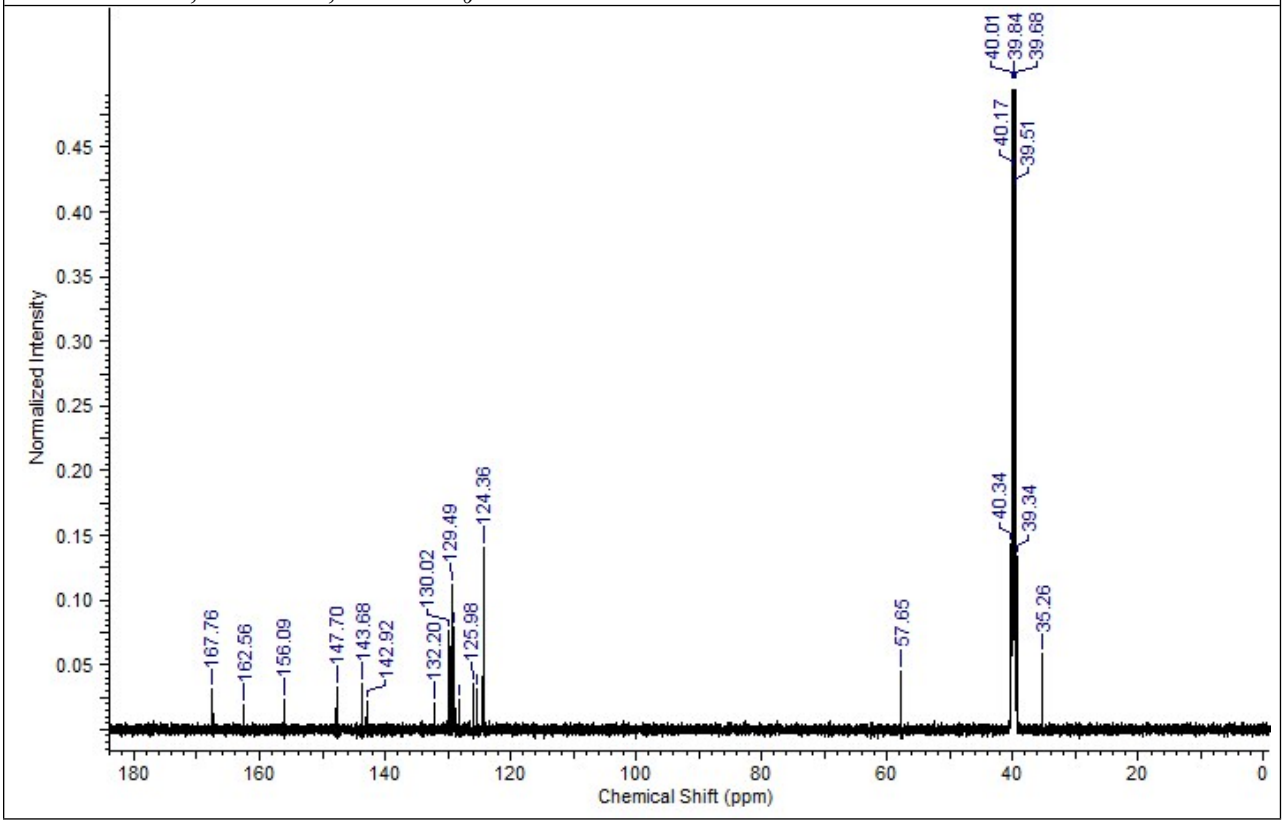
Table S10 *In vitro* cytotoxicity of selected 4-thiazolidinone incorporated tetrazoloquinoline derivatives

Entry	MCF-7 (Breast) Cell line		A549 (Lung) Cell line		HCT 116 (Colorectal) Cell line	
	GI_{50} (µmol/mL)	GI_{90} (µmol/mL)	GI_{50} (µmol/mL)	GI_{90} (µmol/mL)	GI_{50} (µmol/mL)	GI_{90} (µmol/mL)
4a	> 255.48	> 255.48	> 255.48	> 255.48	> 255.48	> 255.48
4d	> 246.65	> 246.65	> 246.65	> 246.65	> 246.65	> 246.65
4g	> 246.65	> 246.65	> 246.65	> 246.65	> 246.65	> 246.65
4j	> 246.65	> 246.65	> 246.65	> 246.65	> 246.65	> 246.65
4m	> 237.45	> 237.45	> 237.45	> 237.45	> 237.45	> 237.45
4p	> 237.45	> 237.45	> 237.45	> 237.45	> 237.45	> 237.45
Rifampicin	>121.51	>121.51	>121.51	>121.51	>121.51	>121.51
Paclitaxel	0.0056	0.087	0.0041	0.08	0.15	6.69

4a. ^{1}H NMR, 400 MHz, DMSO-d_6



4a. ^{13}C NMR, 100 MHz, DMSO-d_6



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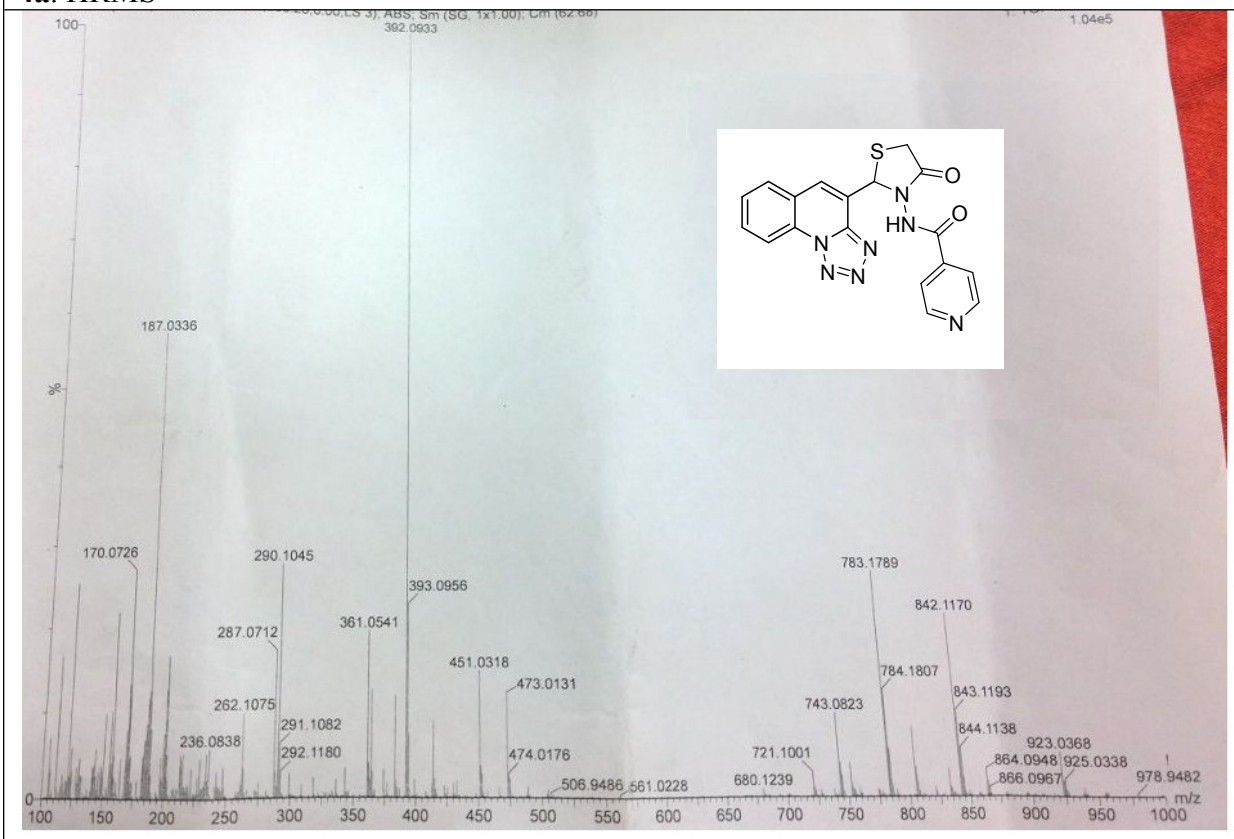
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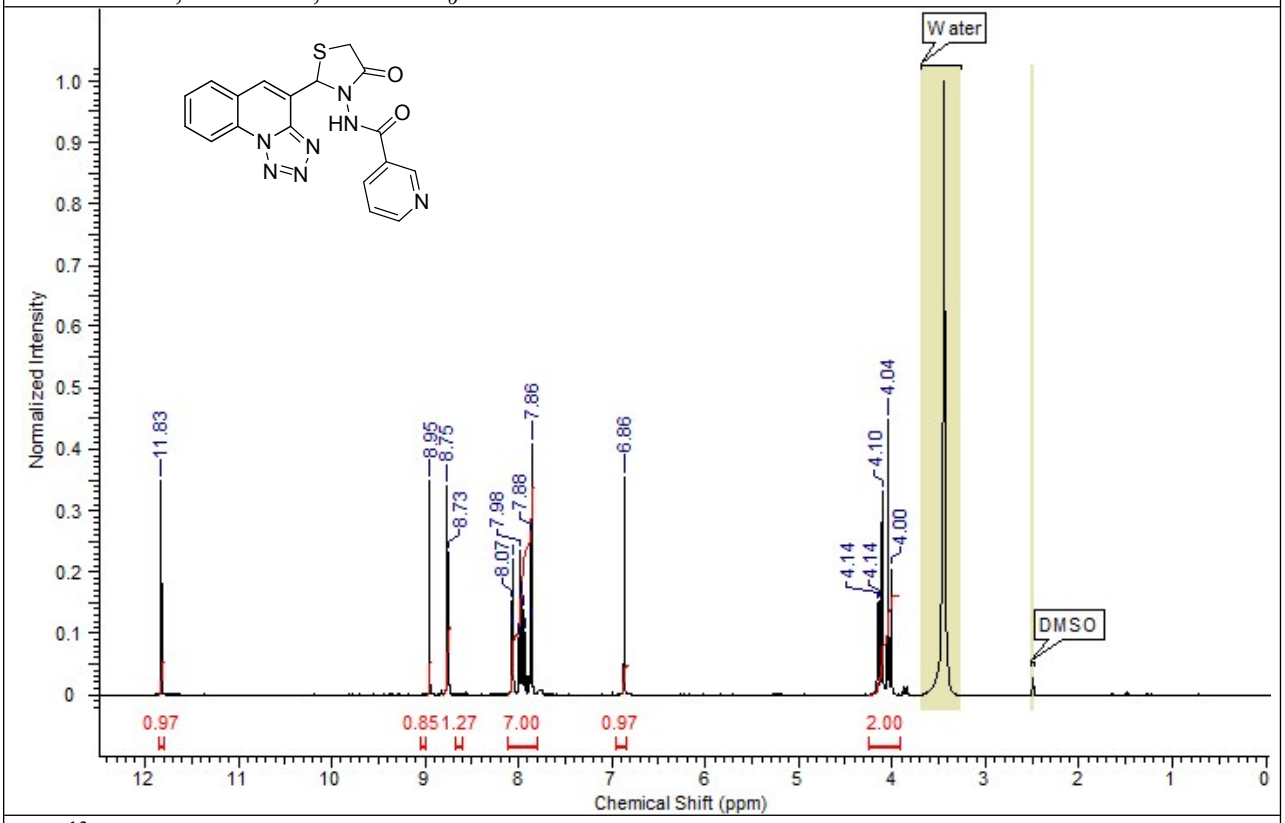
978.9482
m/z
100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000
S
O
N
HN
O
N
N
N
N

4b. ^{1}H NMR, 400 MHz, DMSO-d_6



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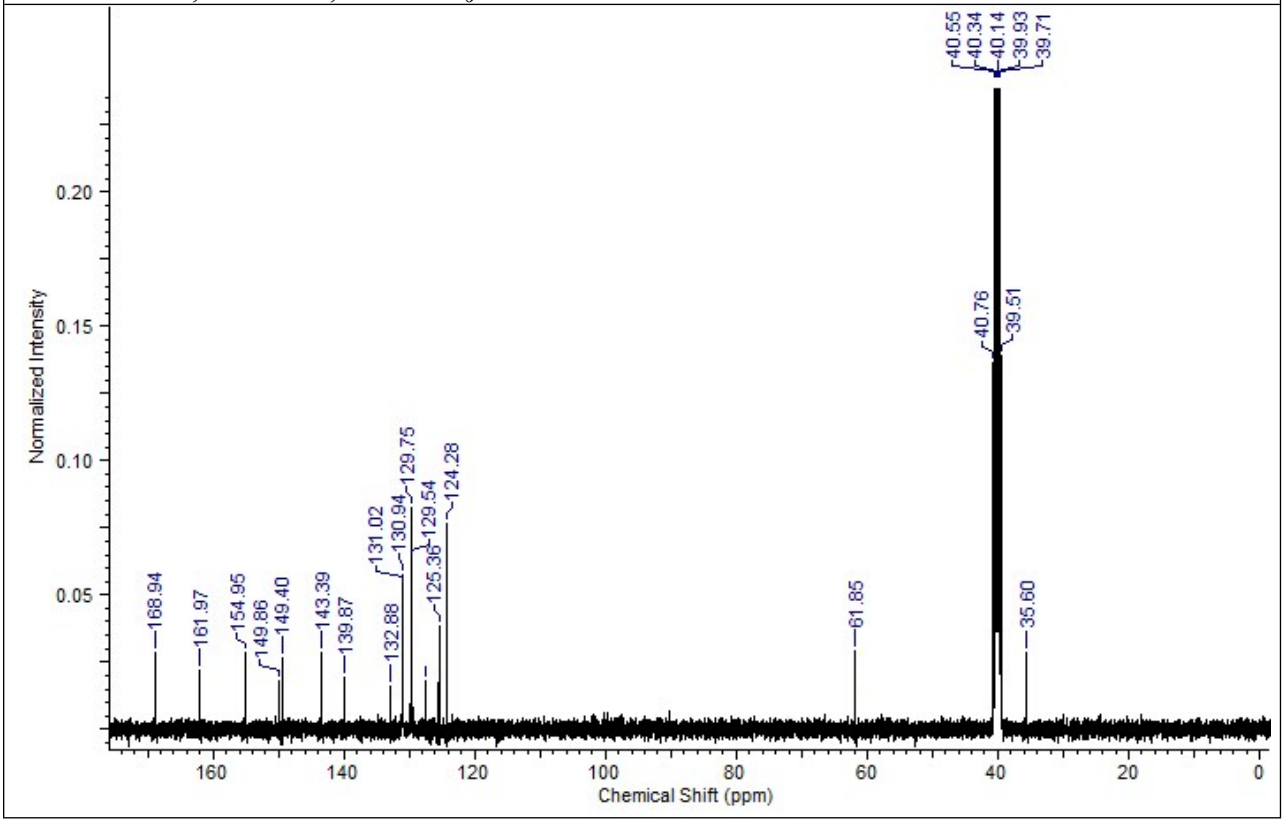

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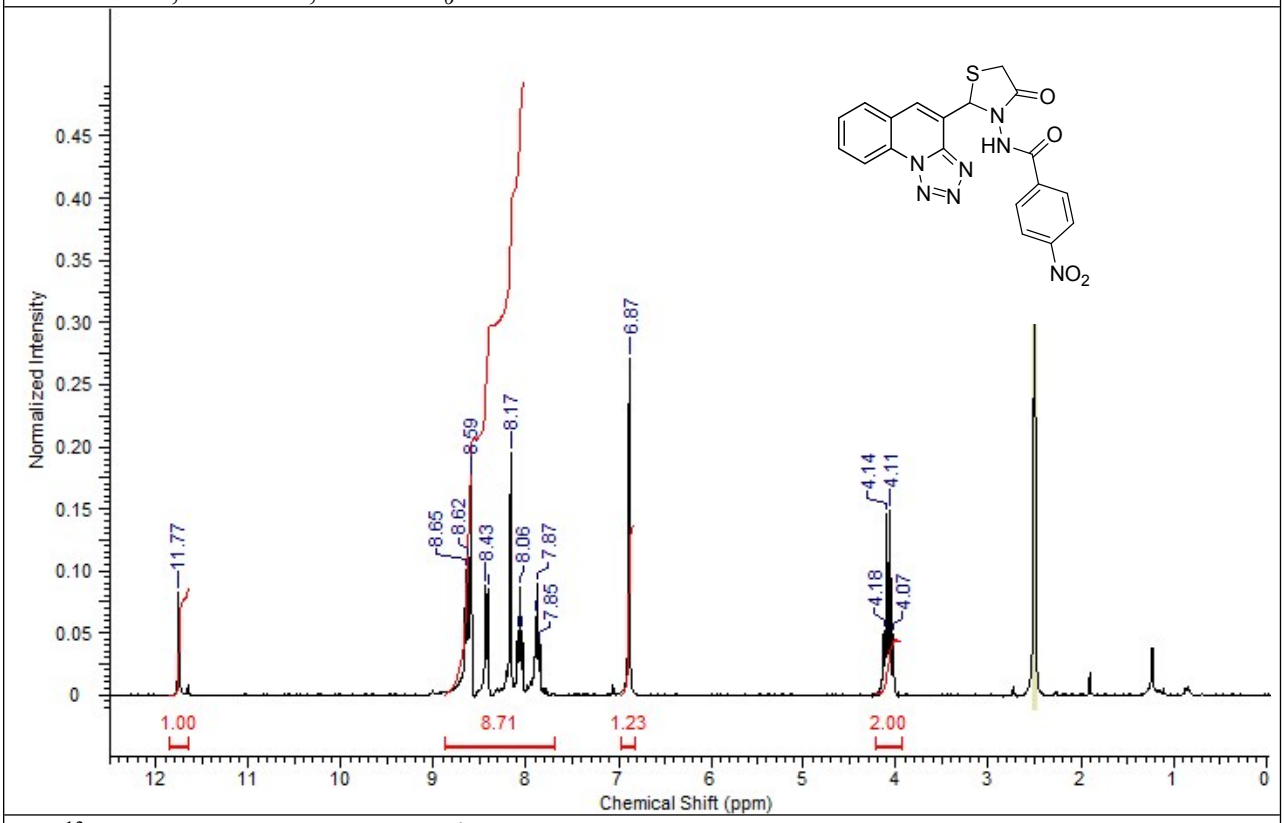

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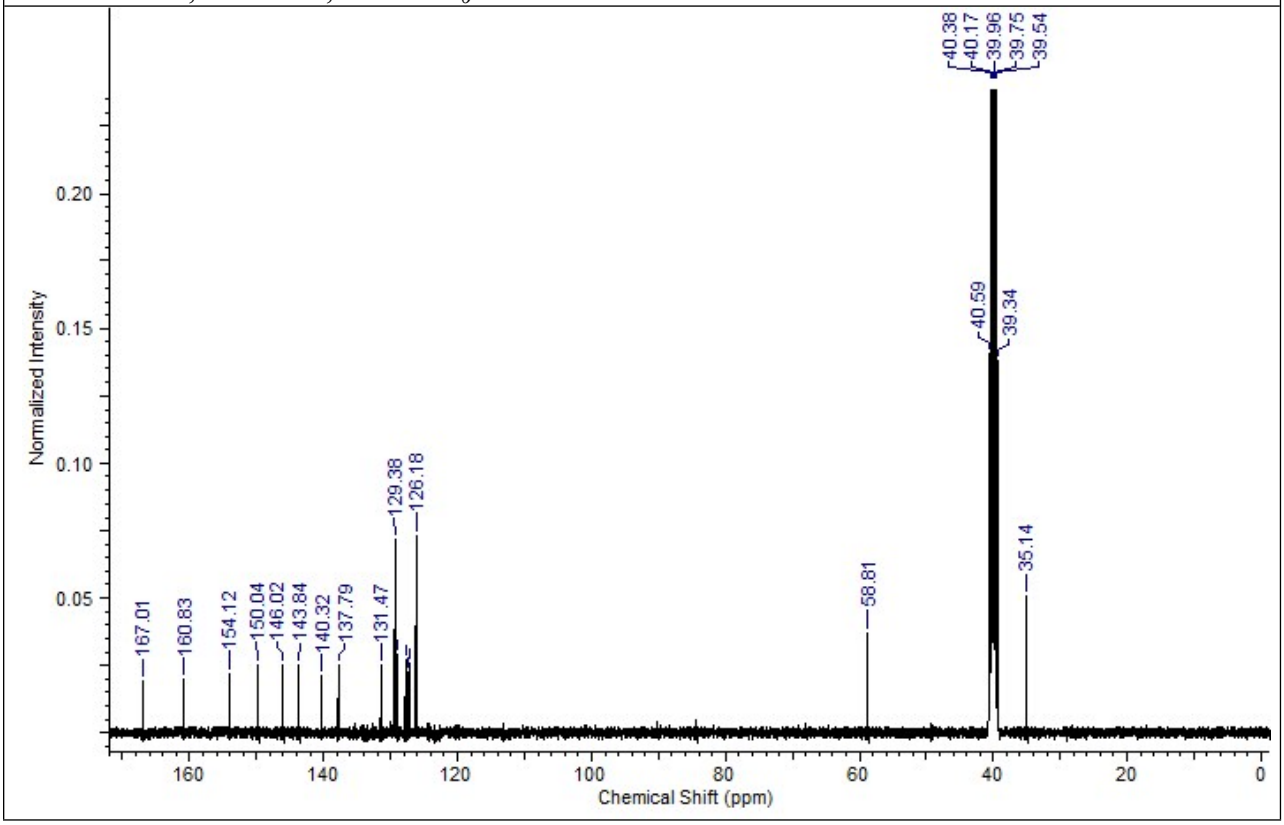

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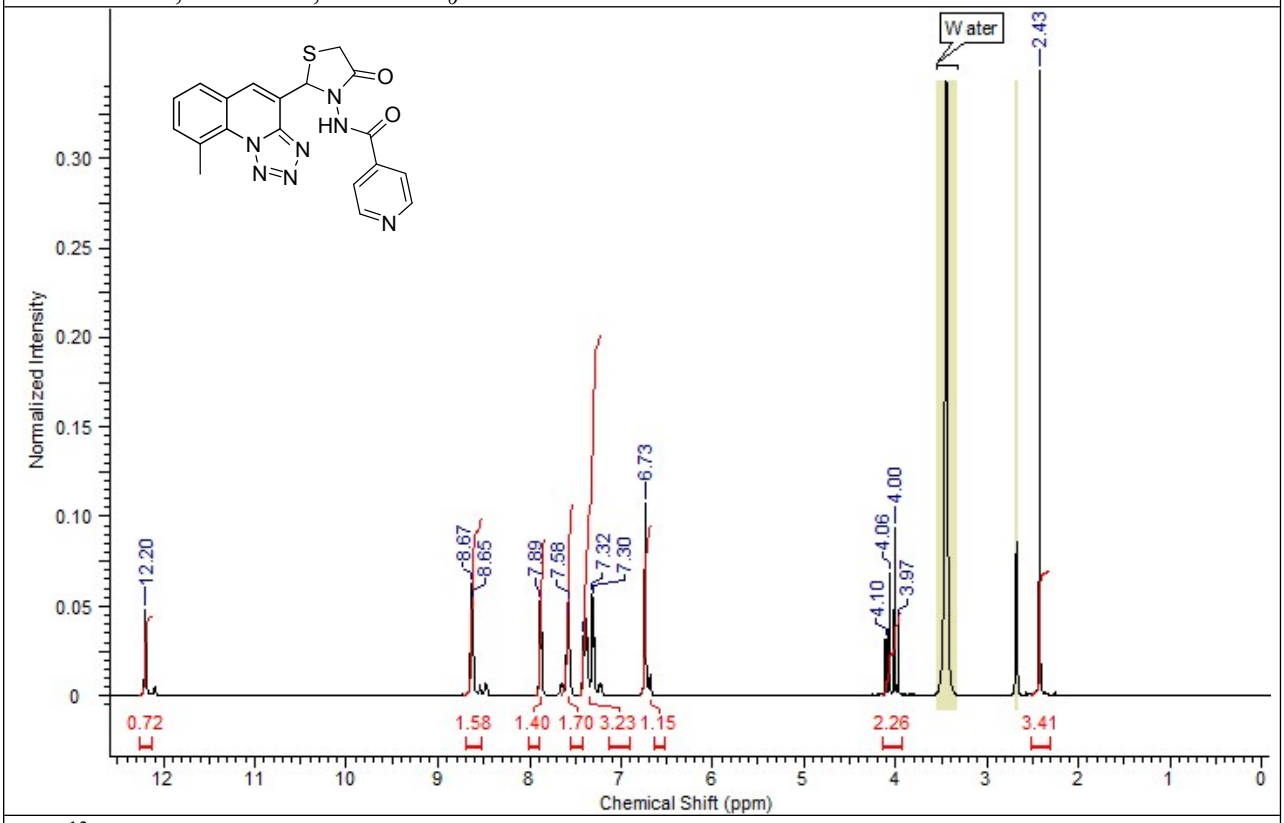

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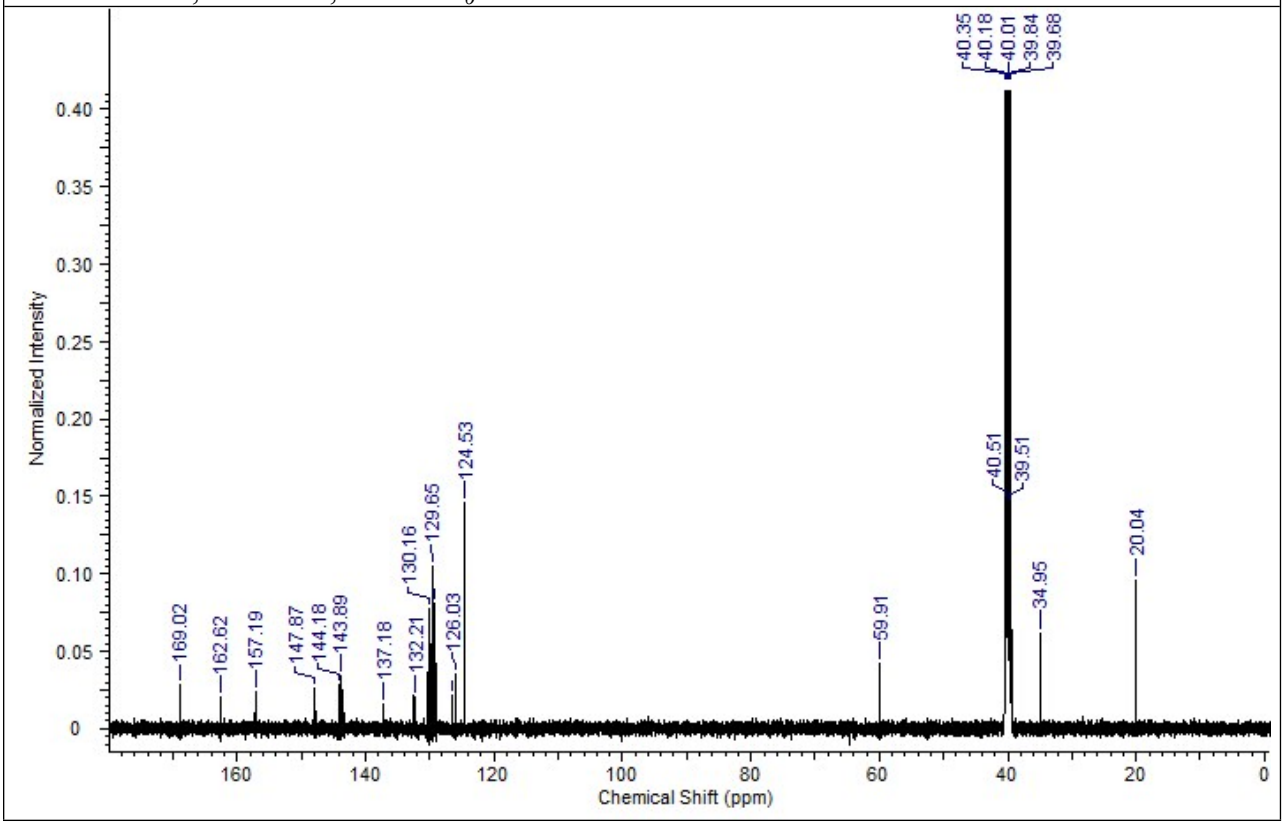

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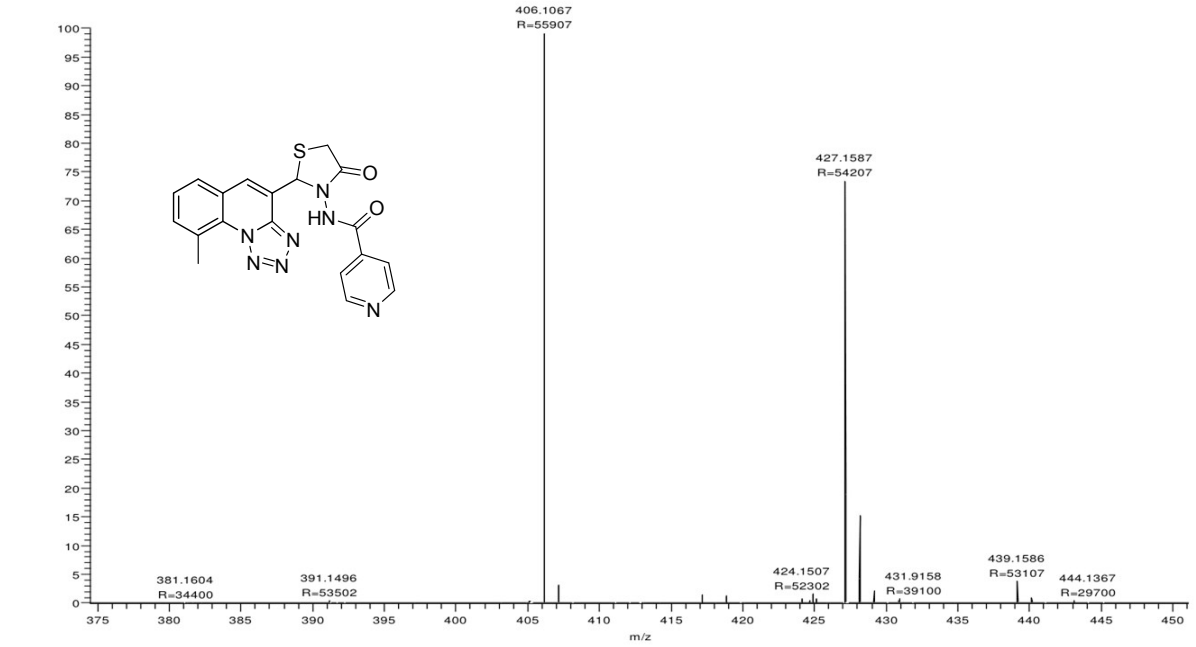

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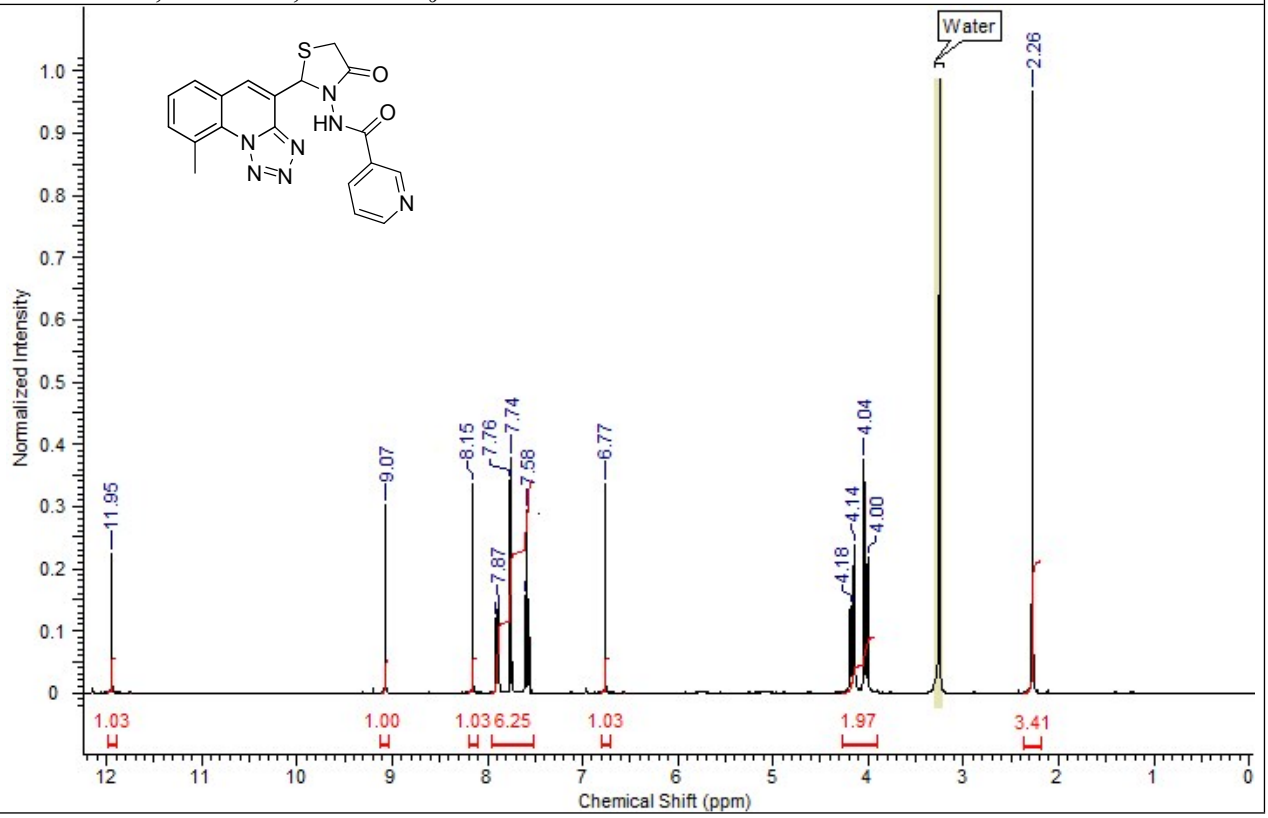

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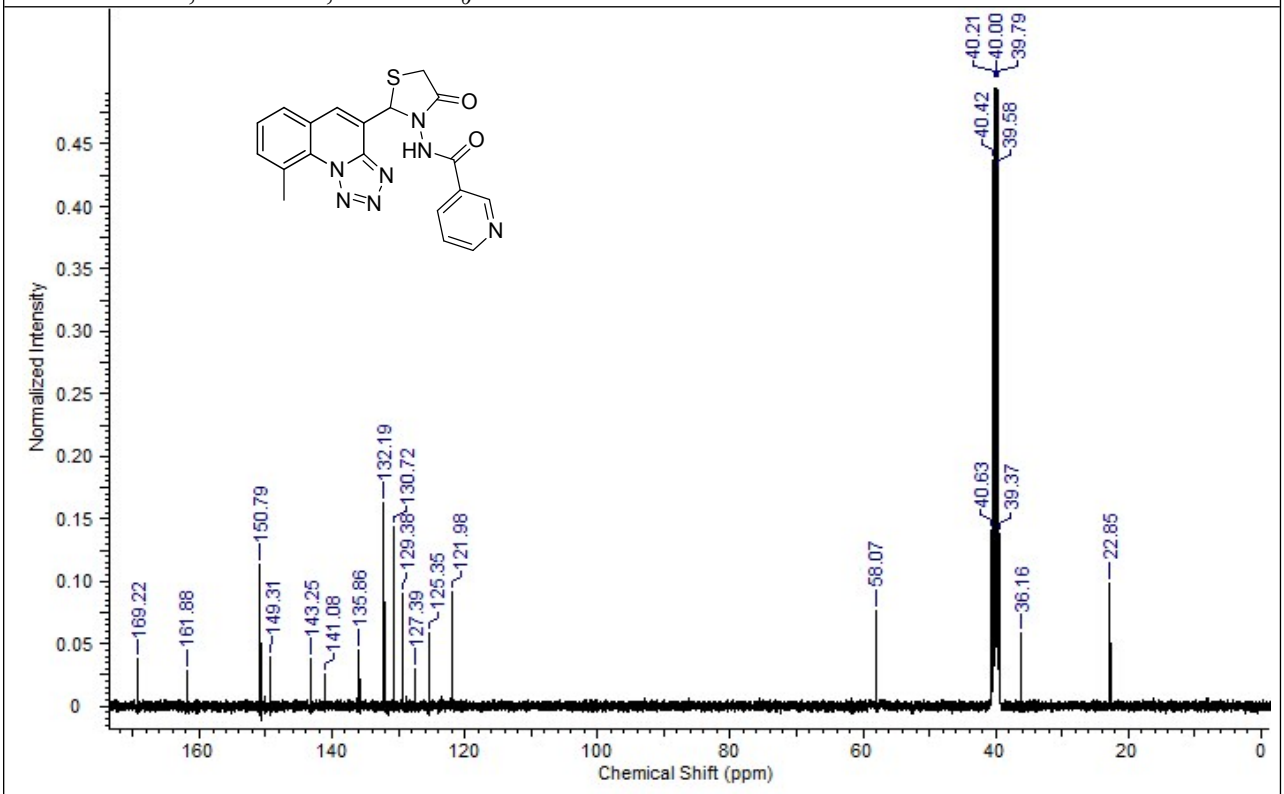

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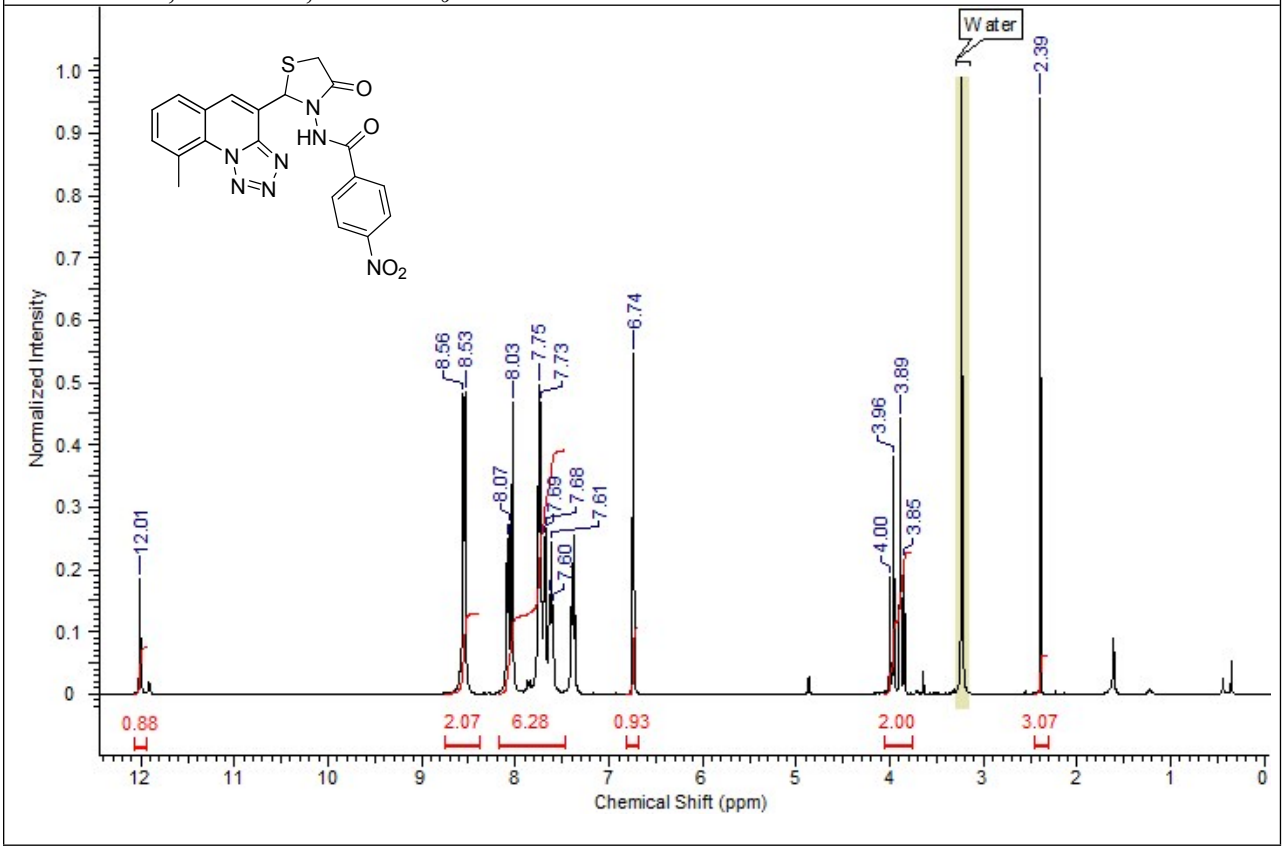

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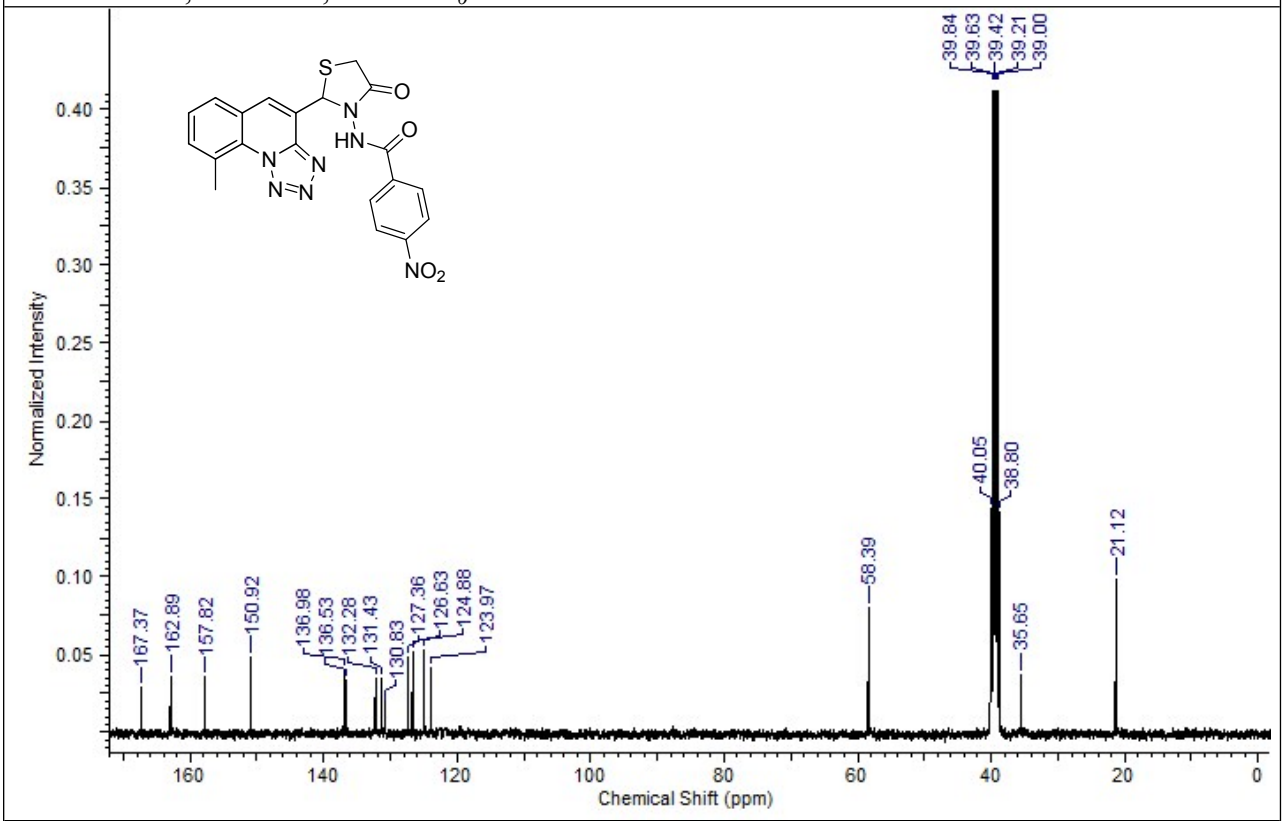

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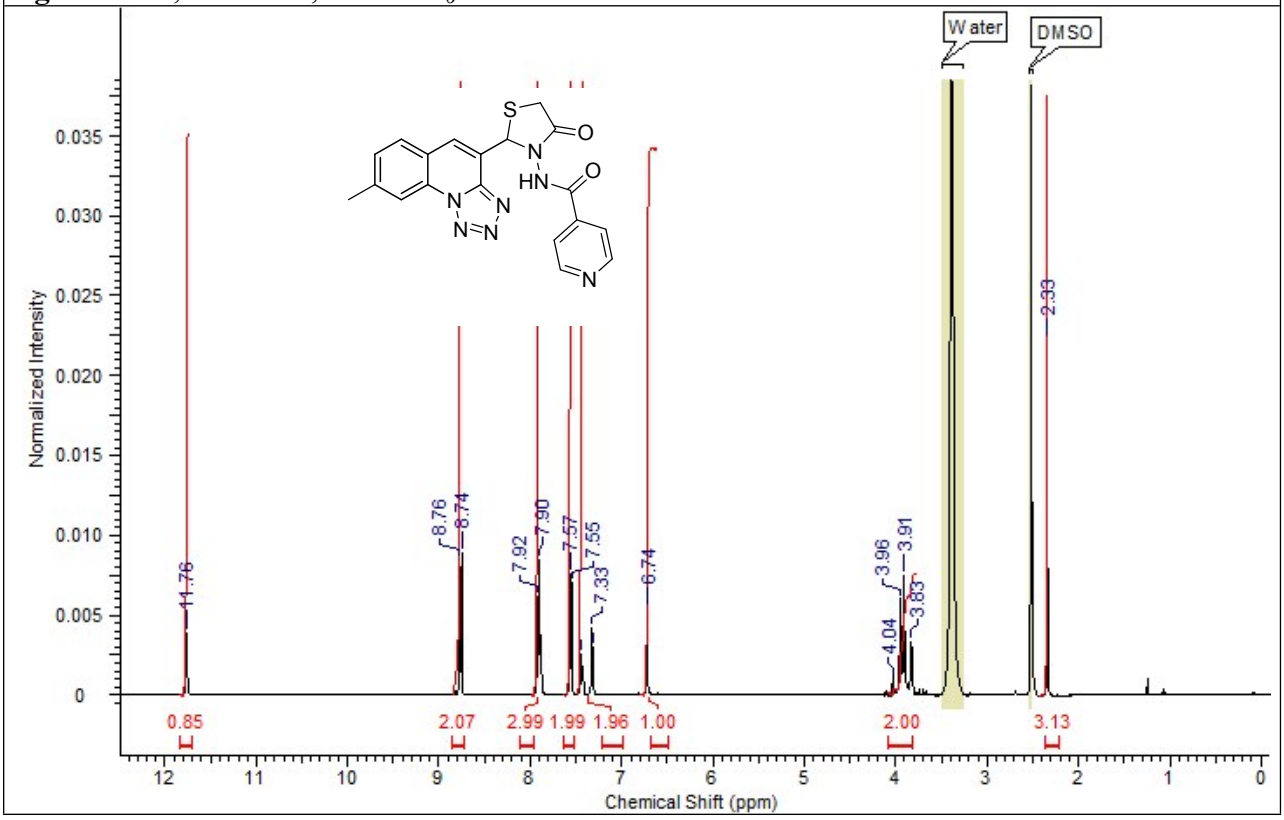

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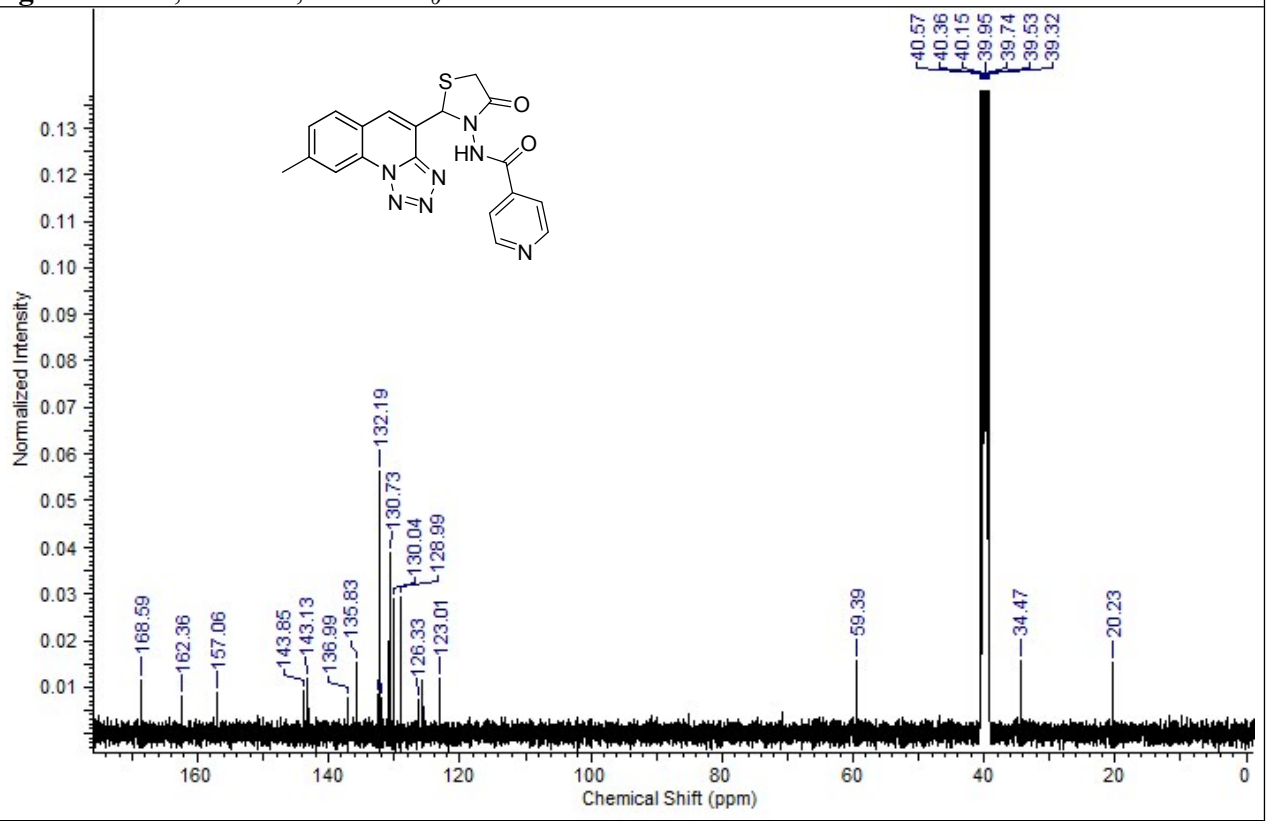

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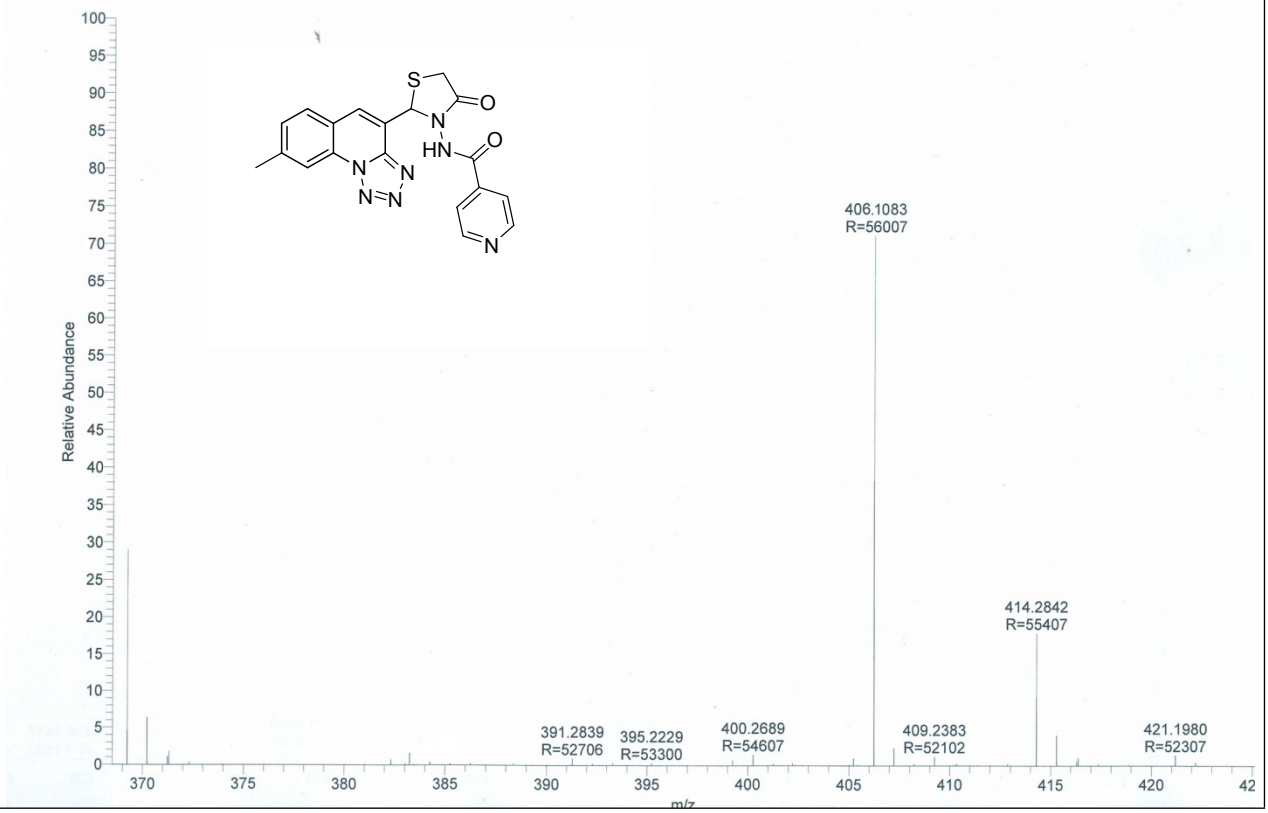

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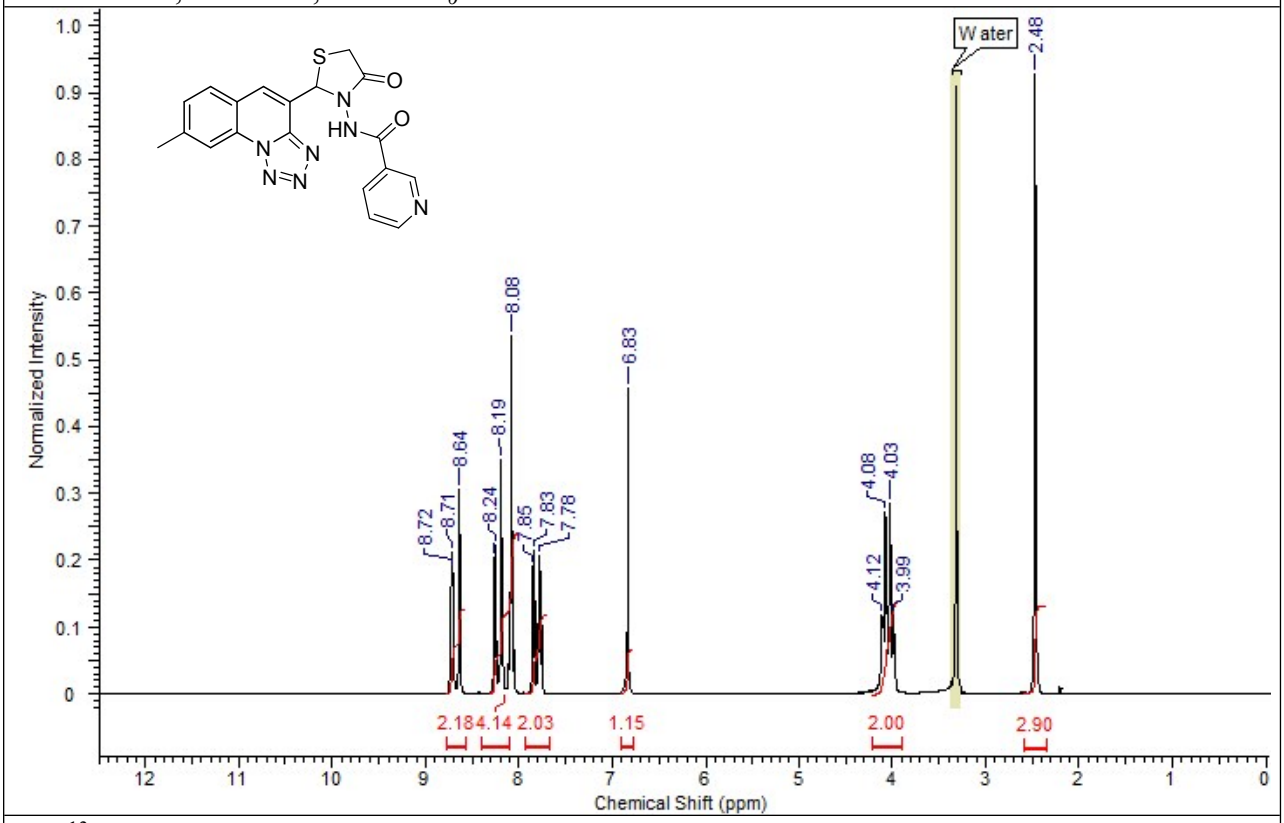

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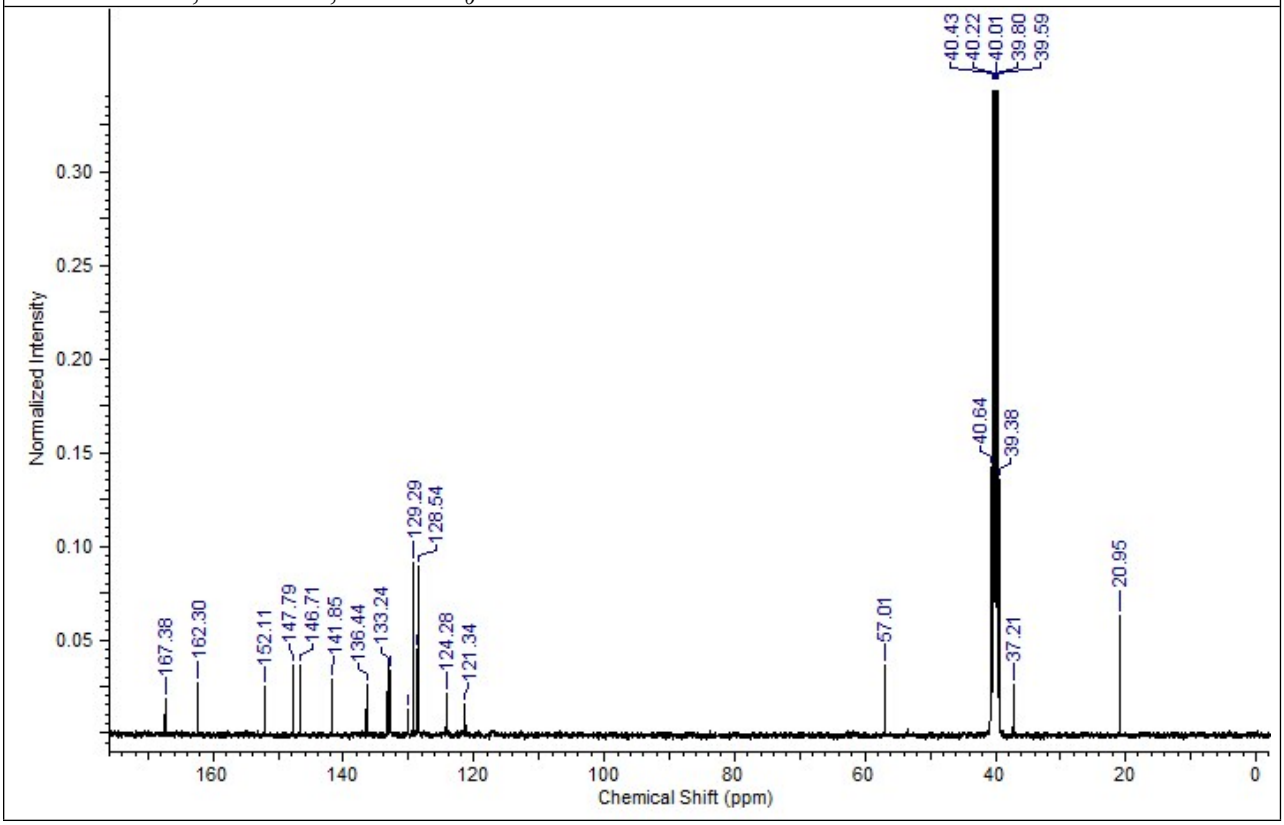

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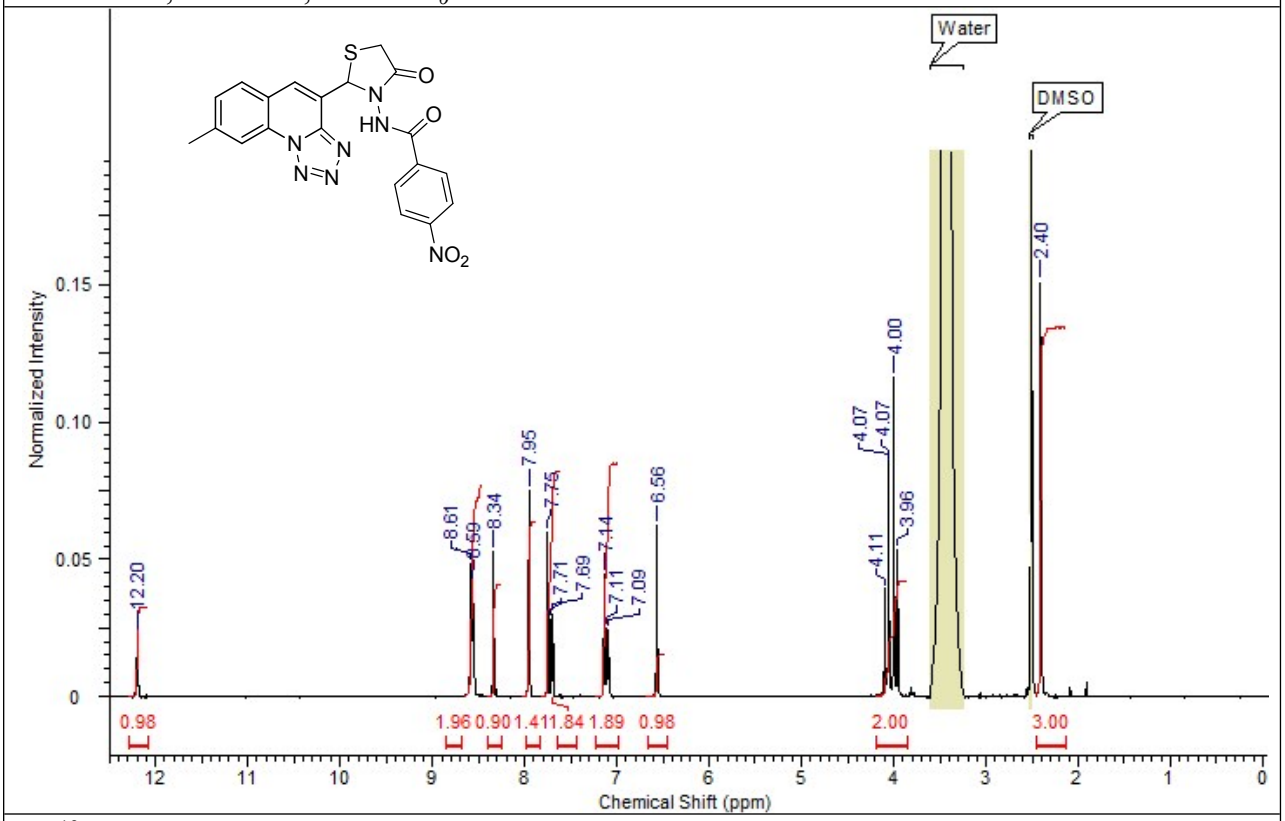

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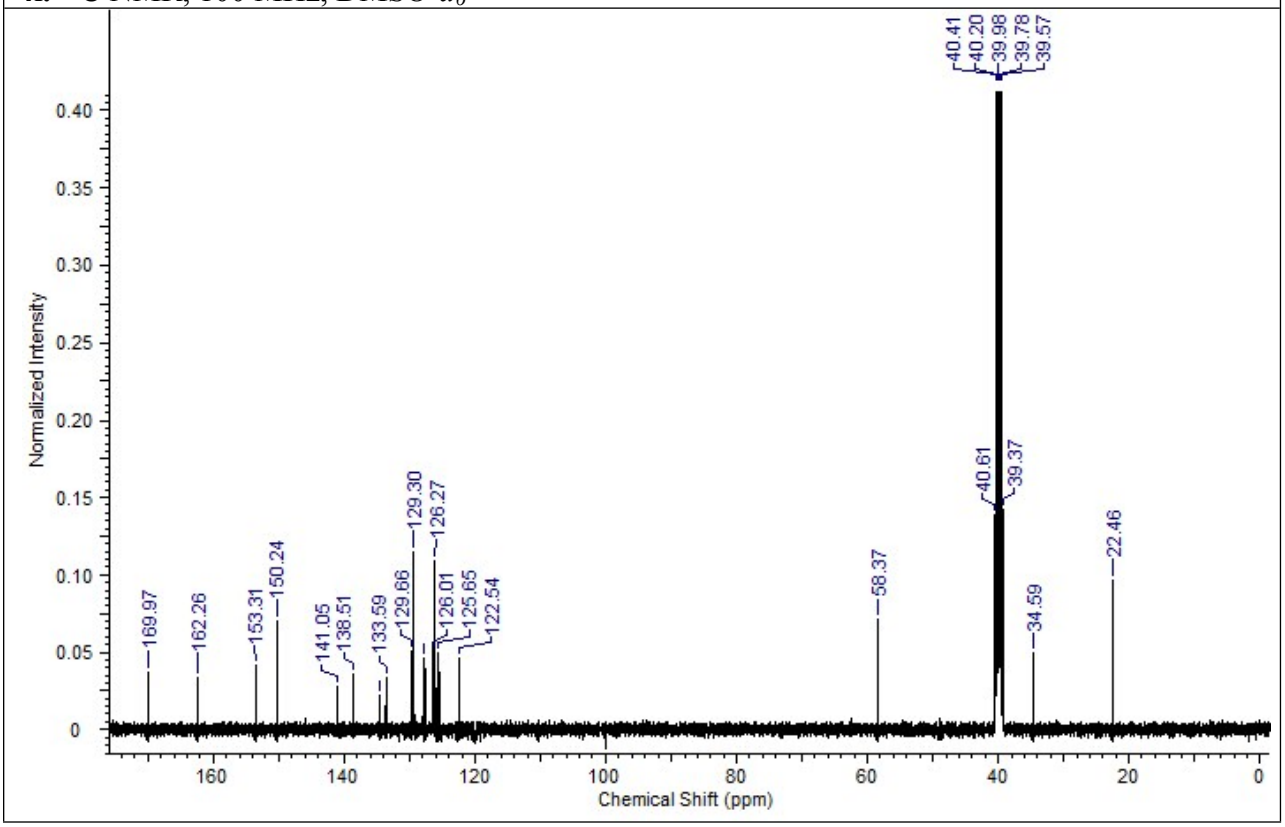

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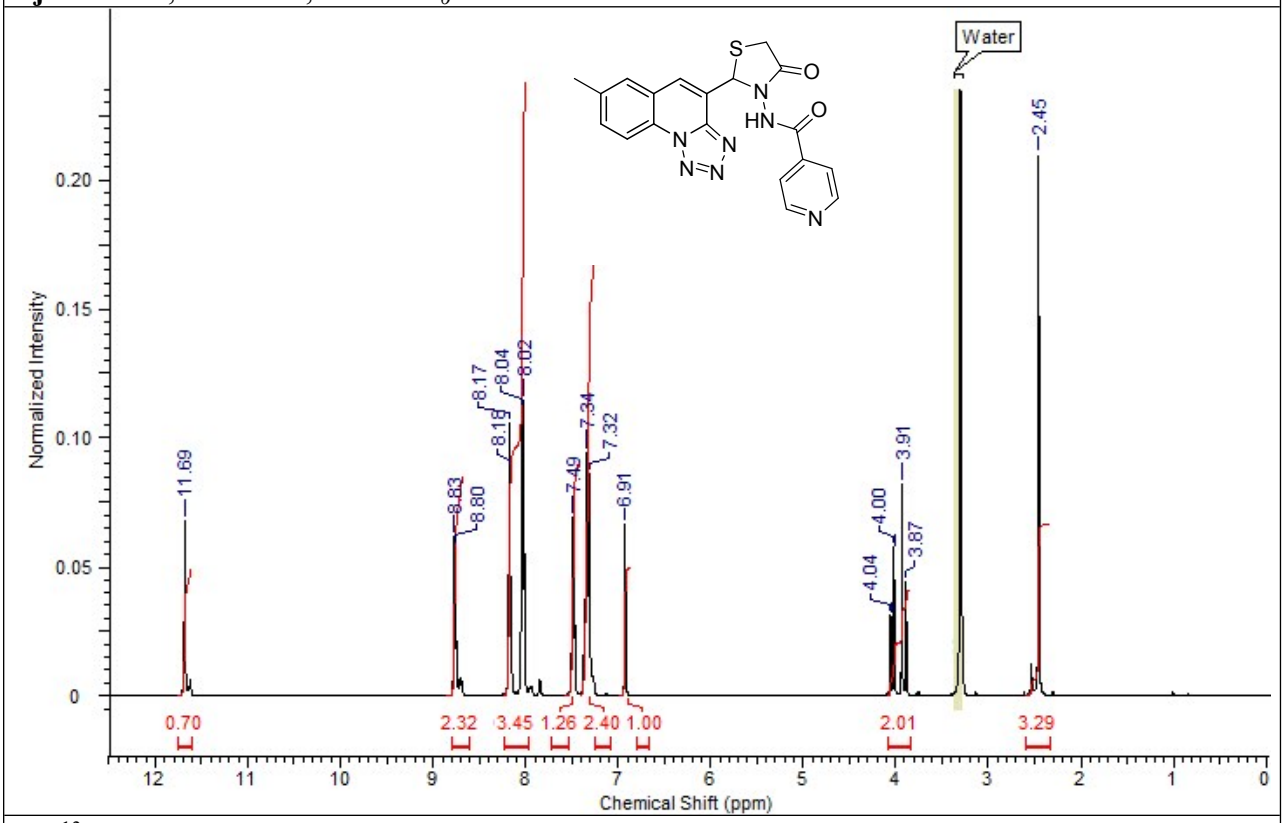
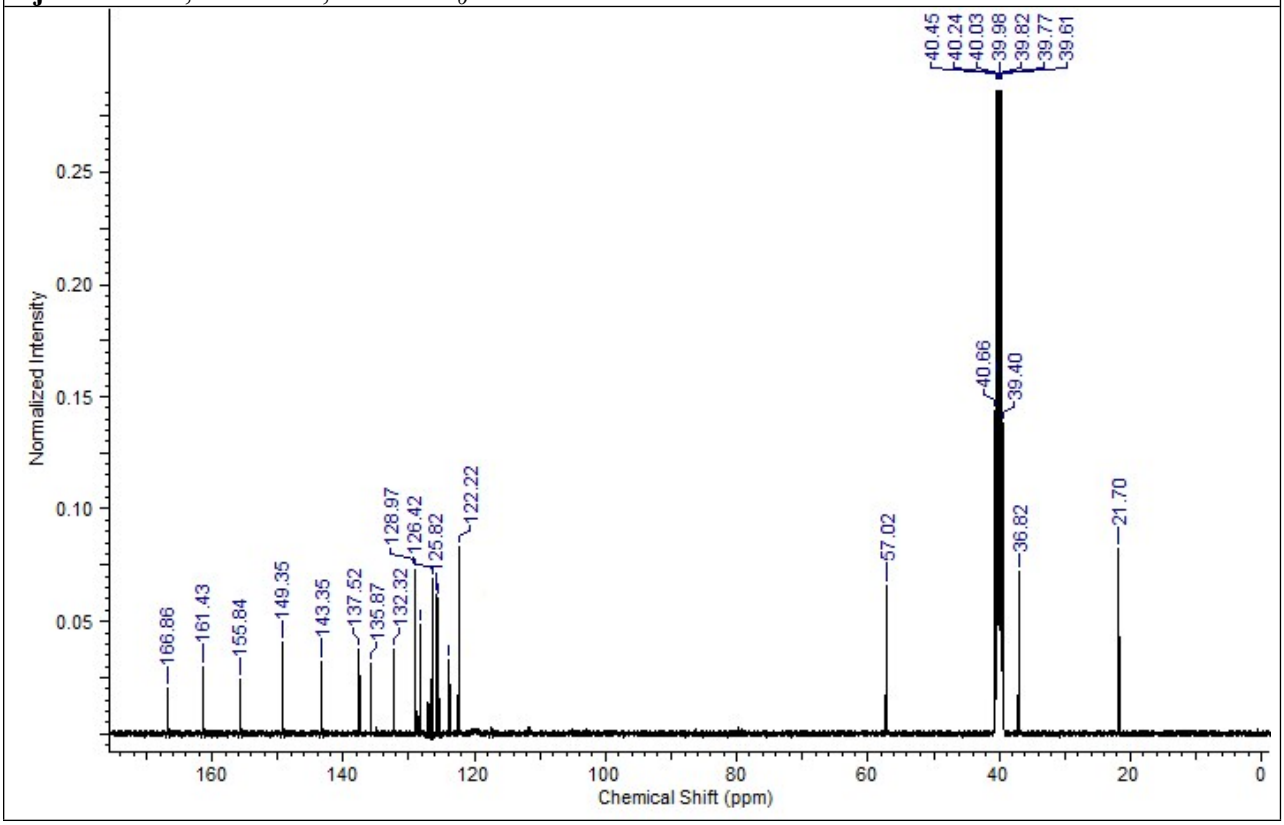
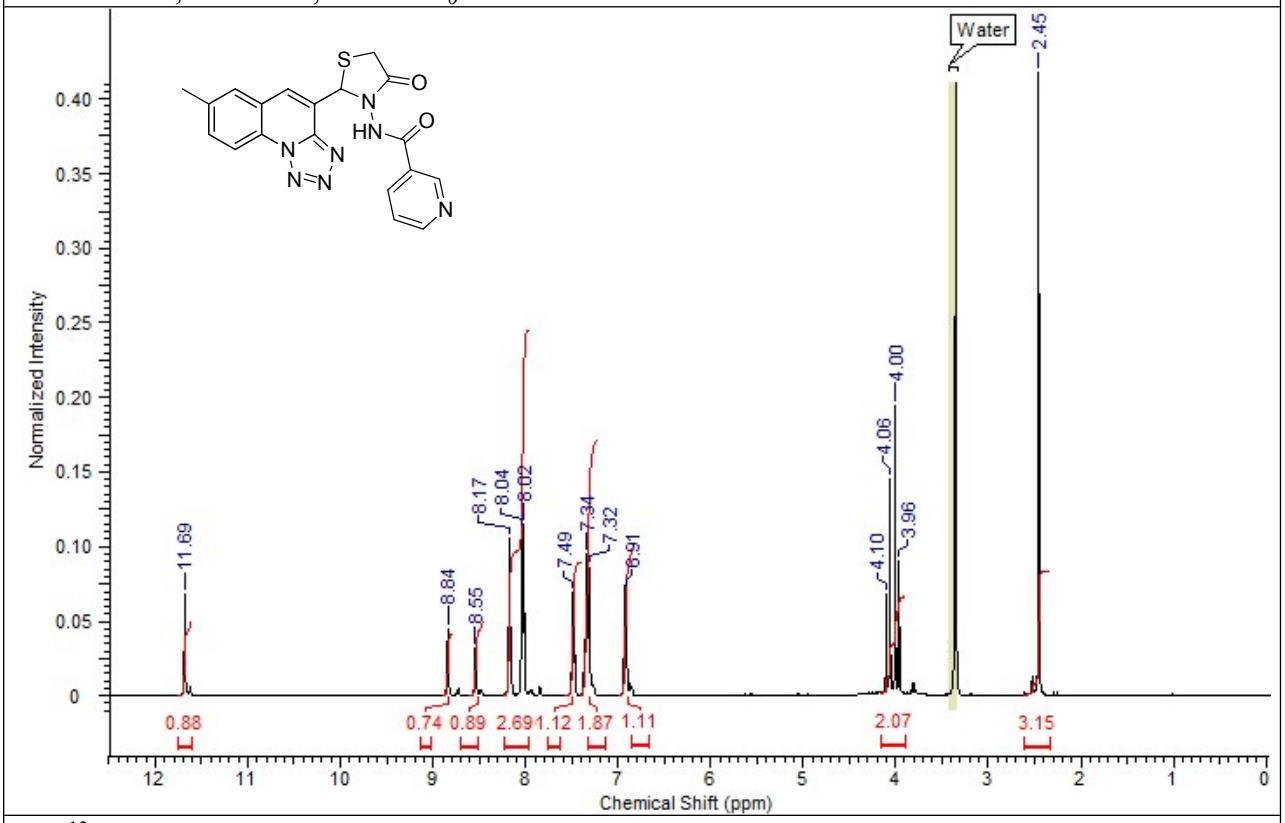


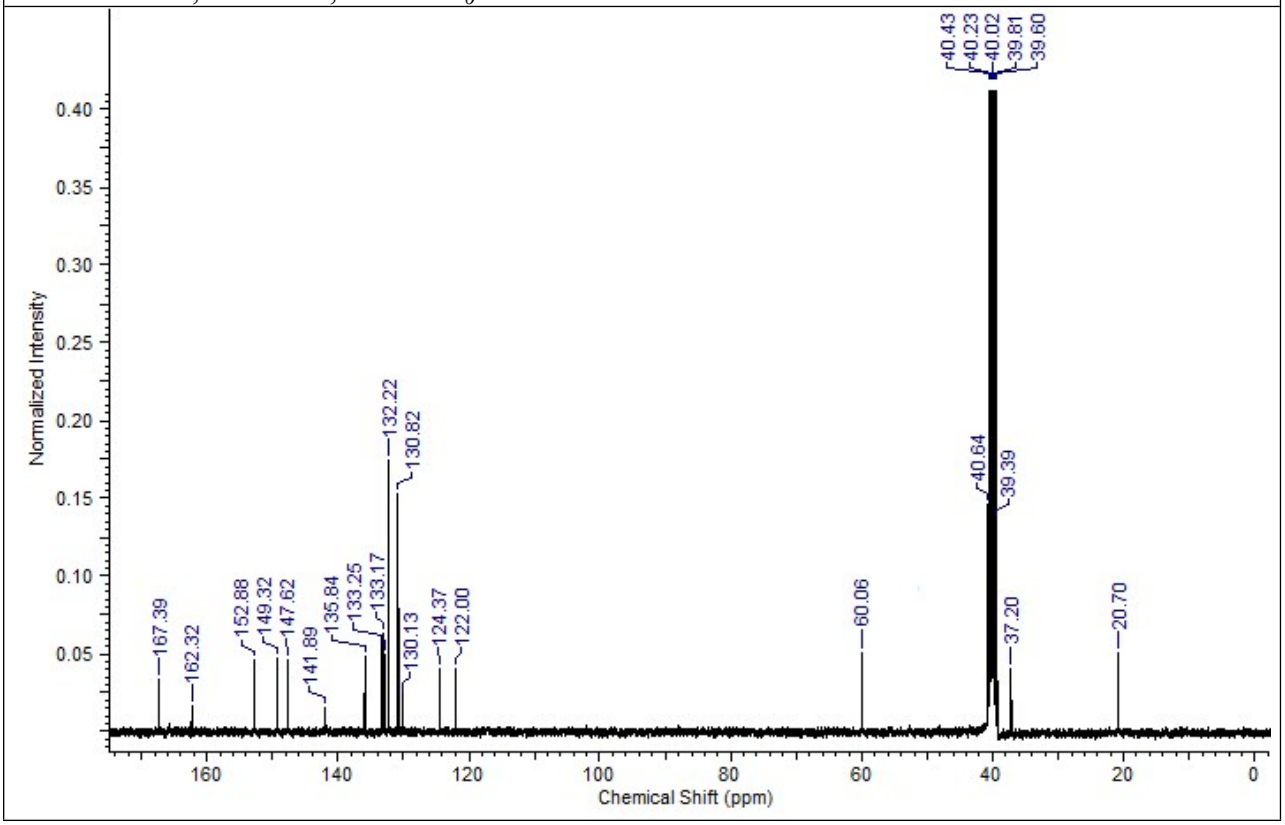
4j. ^{13}C NMR, 100 MHz, DMSO-d_6



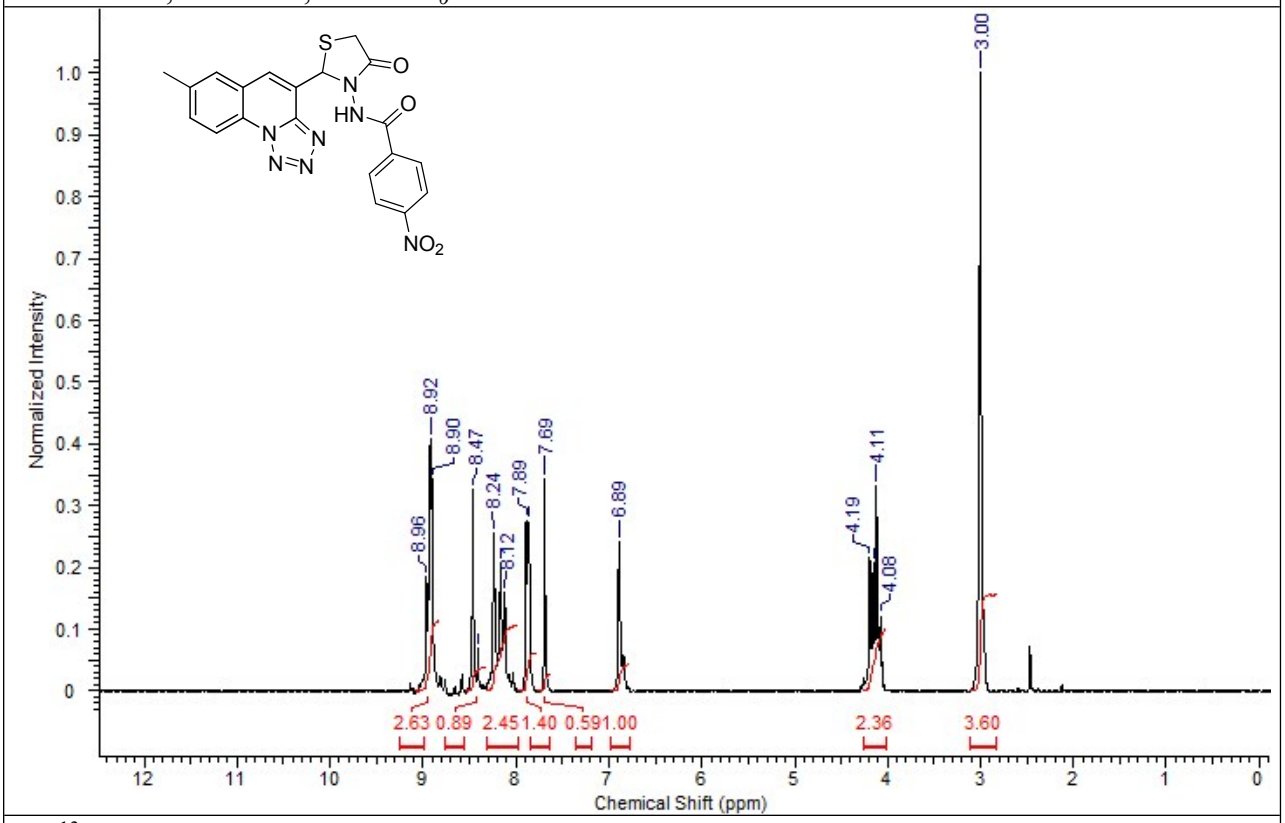
4k. ^{1}H NMR, 400 MHz, DMSO-d_6



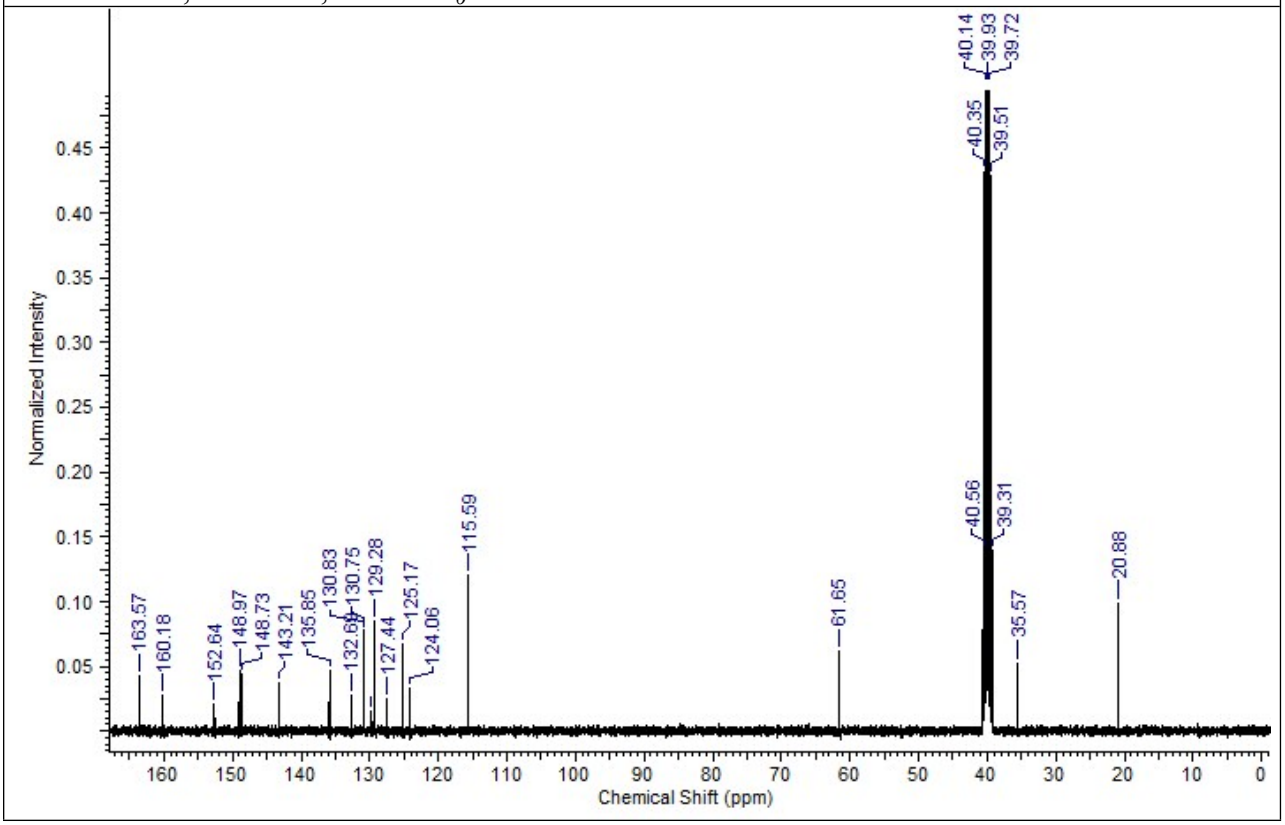
4k. ^{13}C NMR, 100 MHz, DMSO-d_6



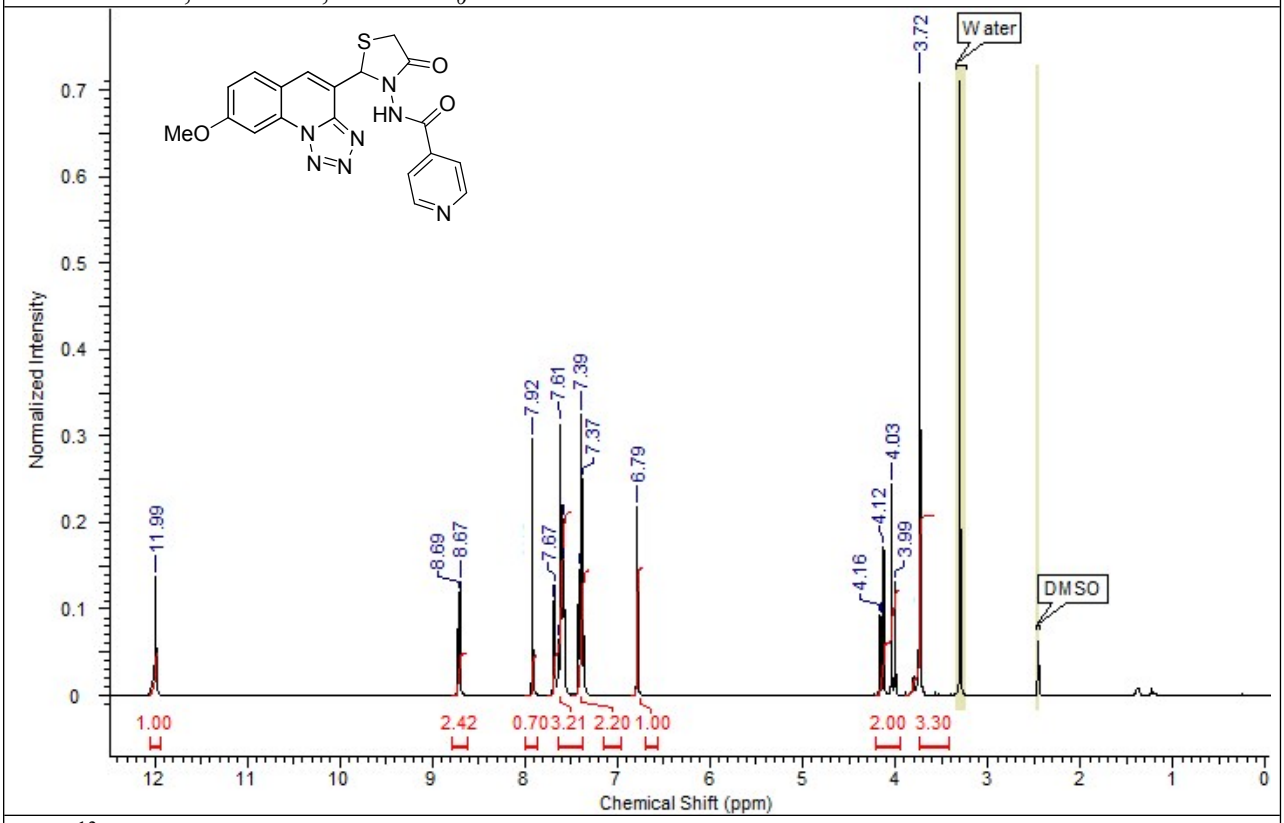
4l. ^{1}H NMR, 400 MHz, DMSO-d_6



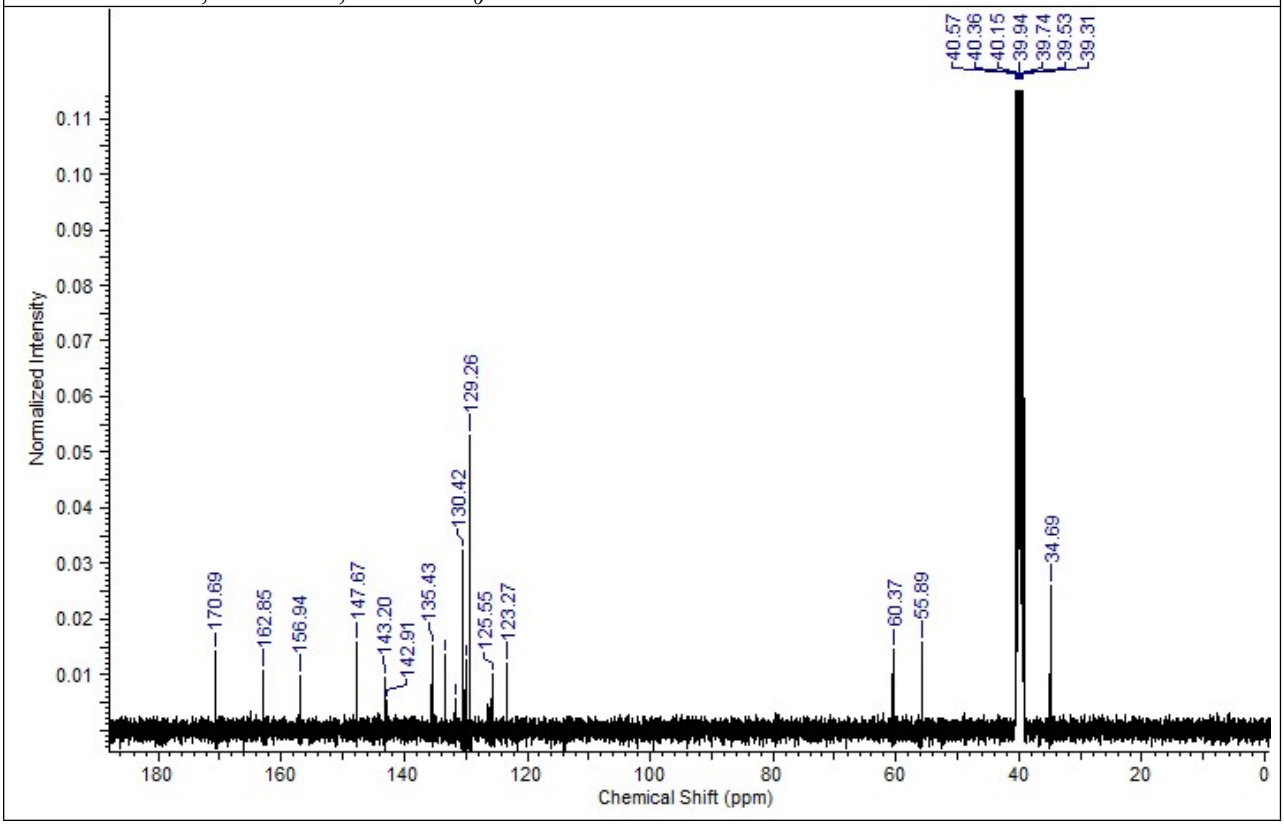
4l. ^{13}C NMR, 100 MHz, DMSO-d_6



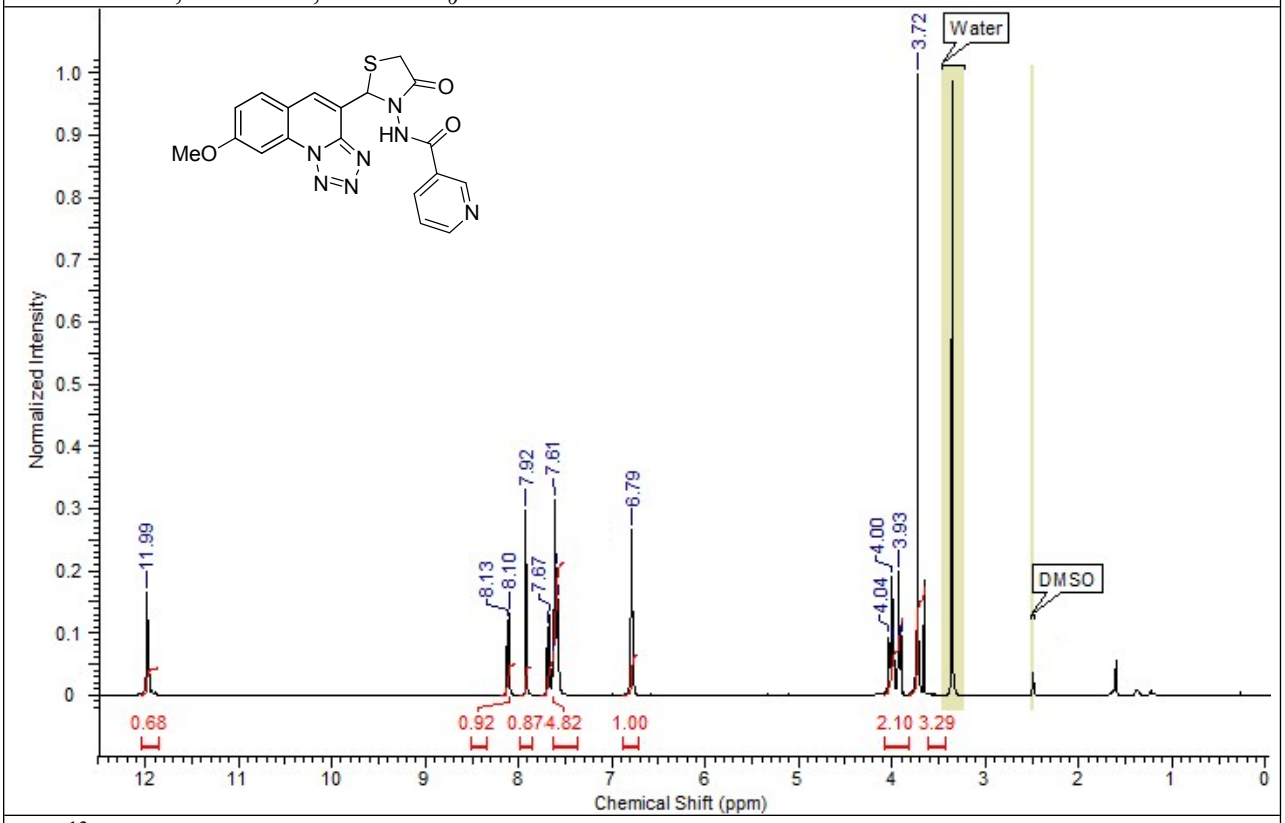
4m. ^{1}H NMR, 400 MHz, DMSO-d_6



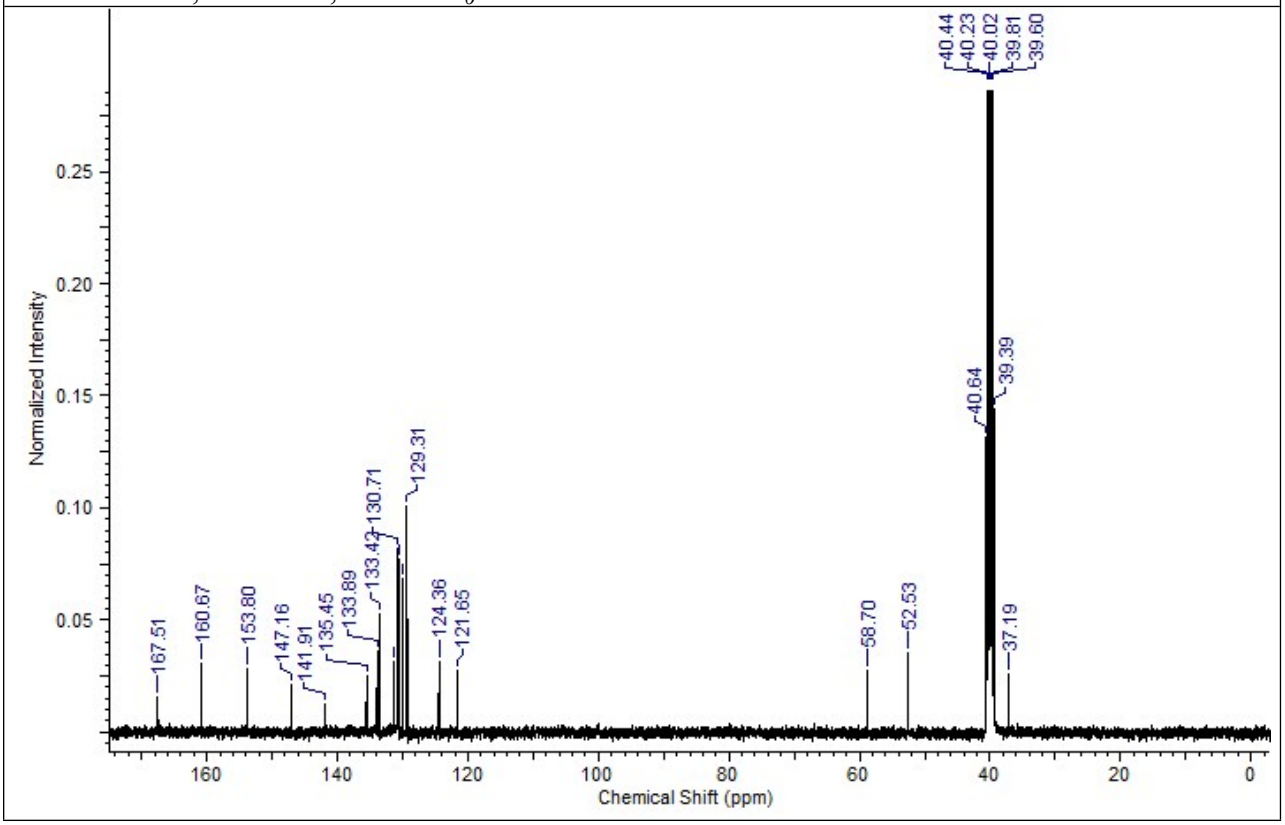
4m. ^{13}C NMR, 100 MHz, DMSO-d_6



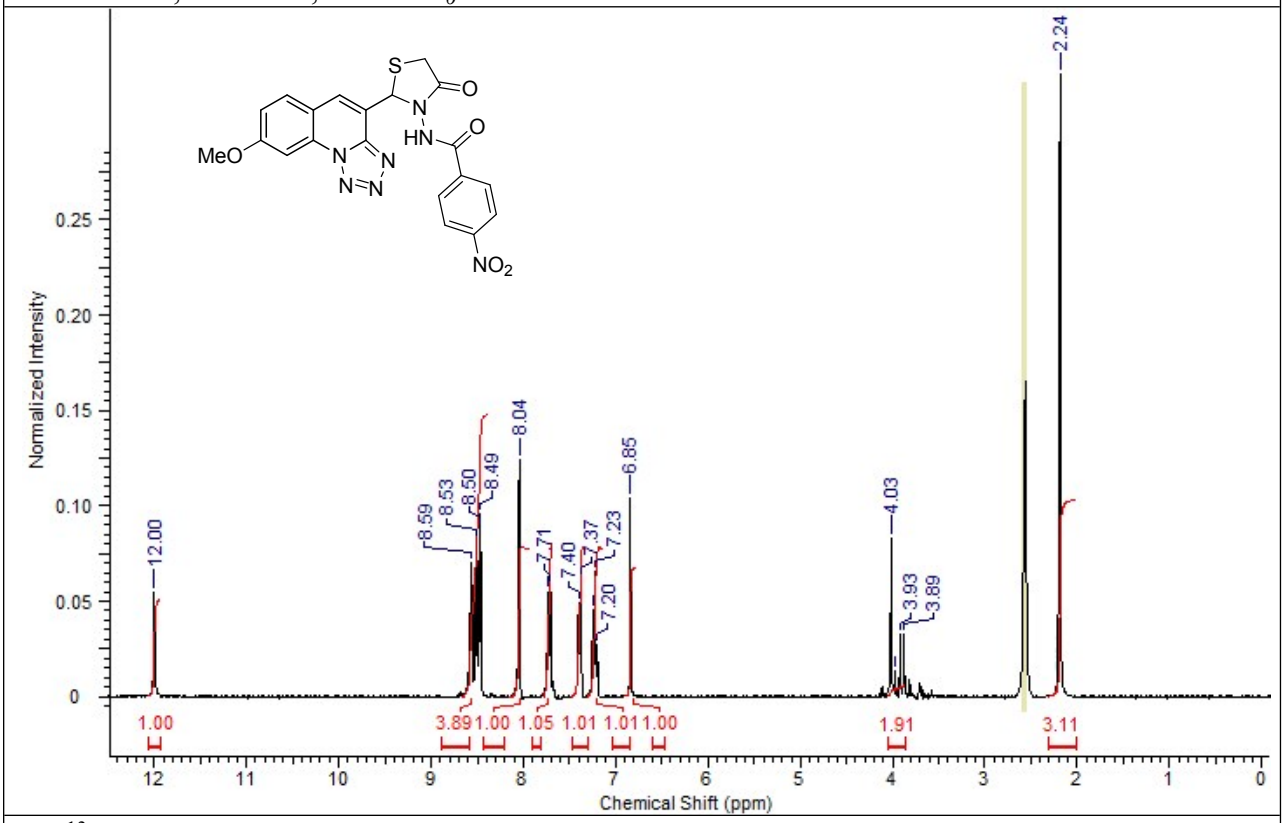
4n. ^{1}H NMR, 400 MHz, DMSO-d_6



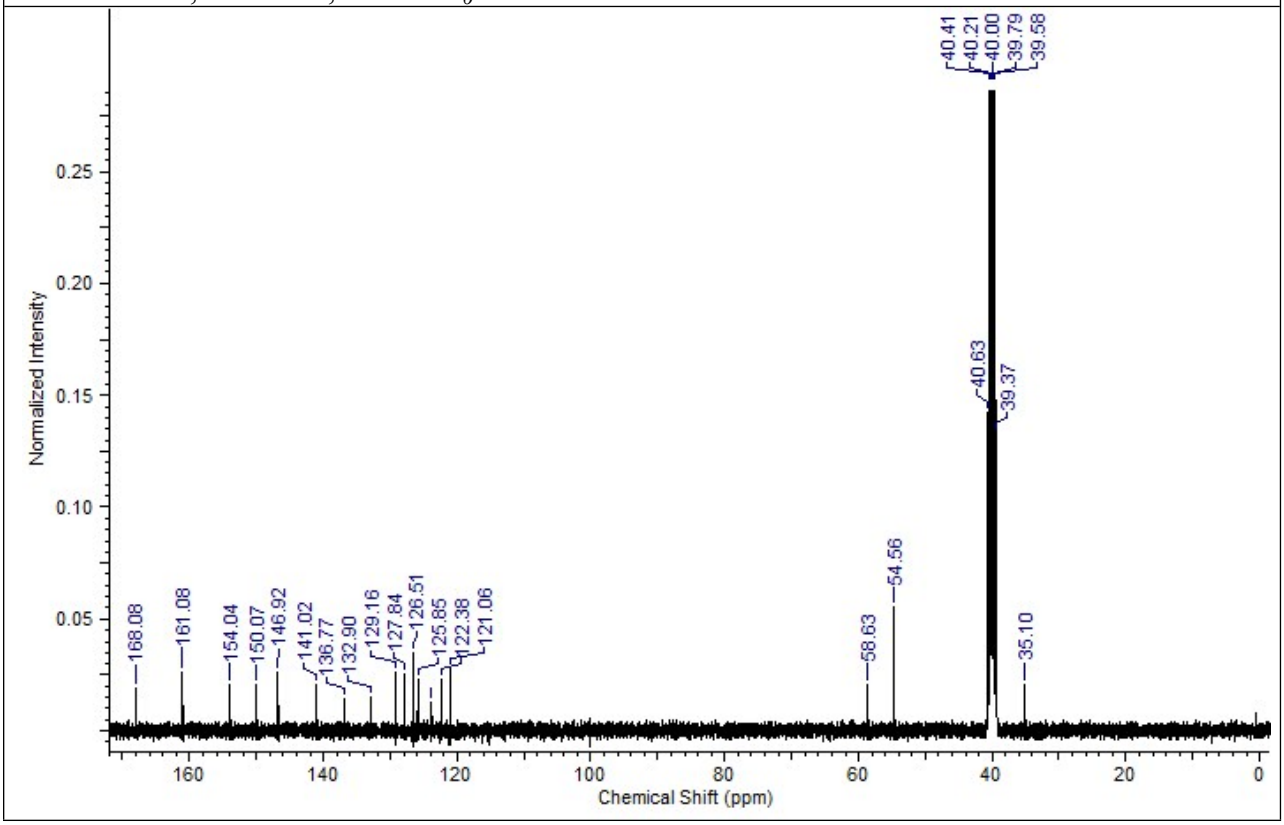
4n. ^{13}C NMR, 100 MHz, DMSO-d_6



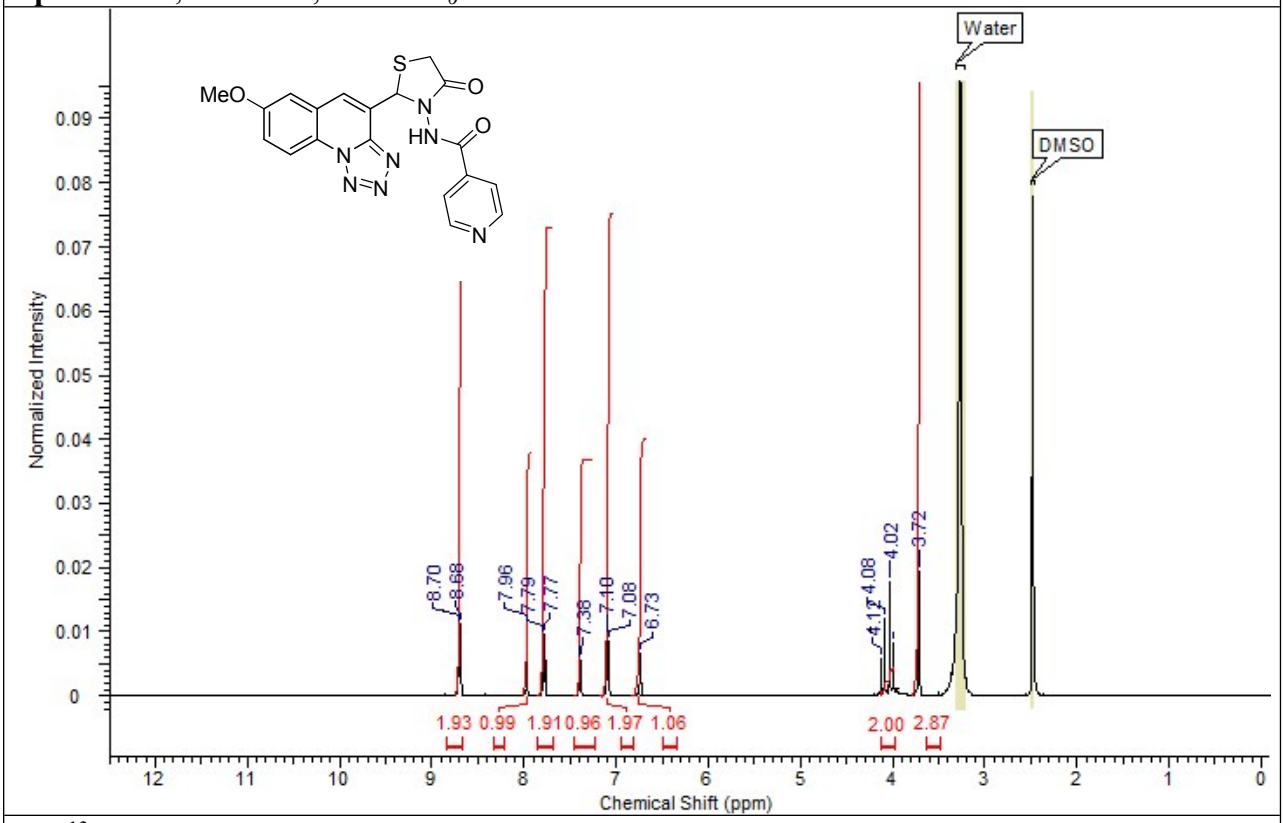
4o.[1]H NMR, 400 MHz, DMSO-d_6



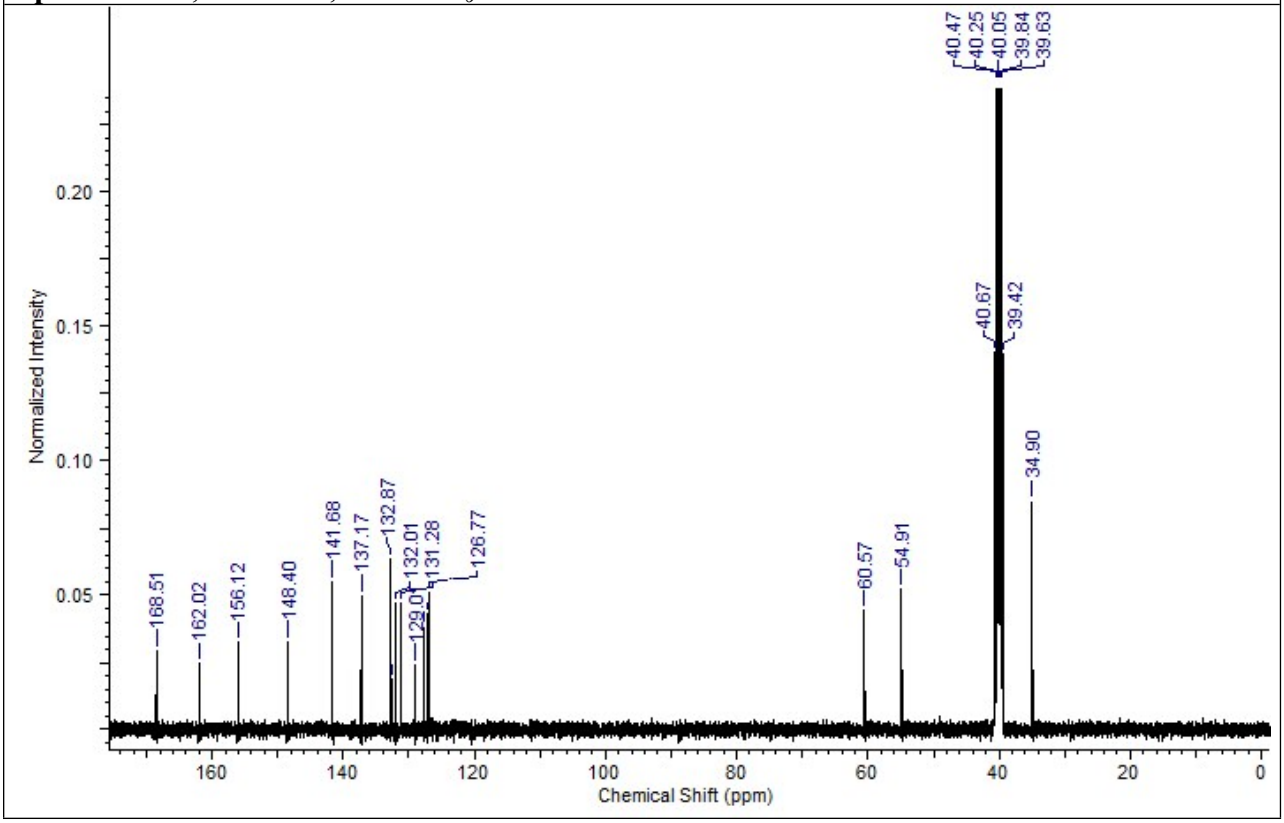
4o. [13]C NMR, 100 MHz, DMSO-d_6



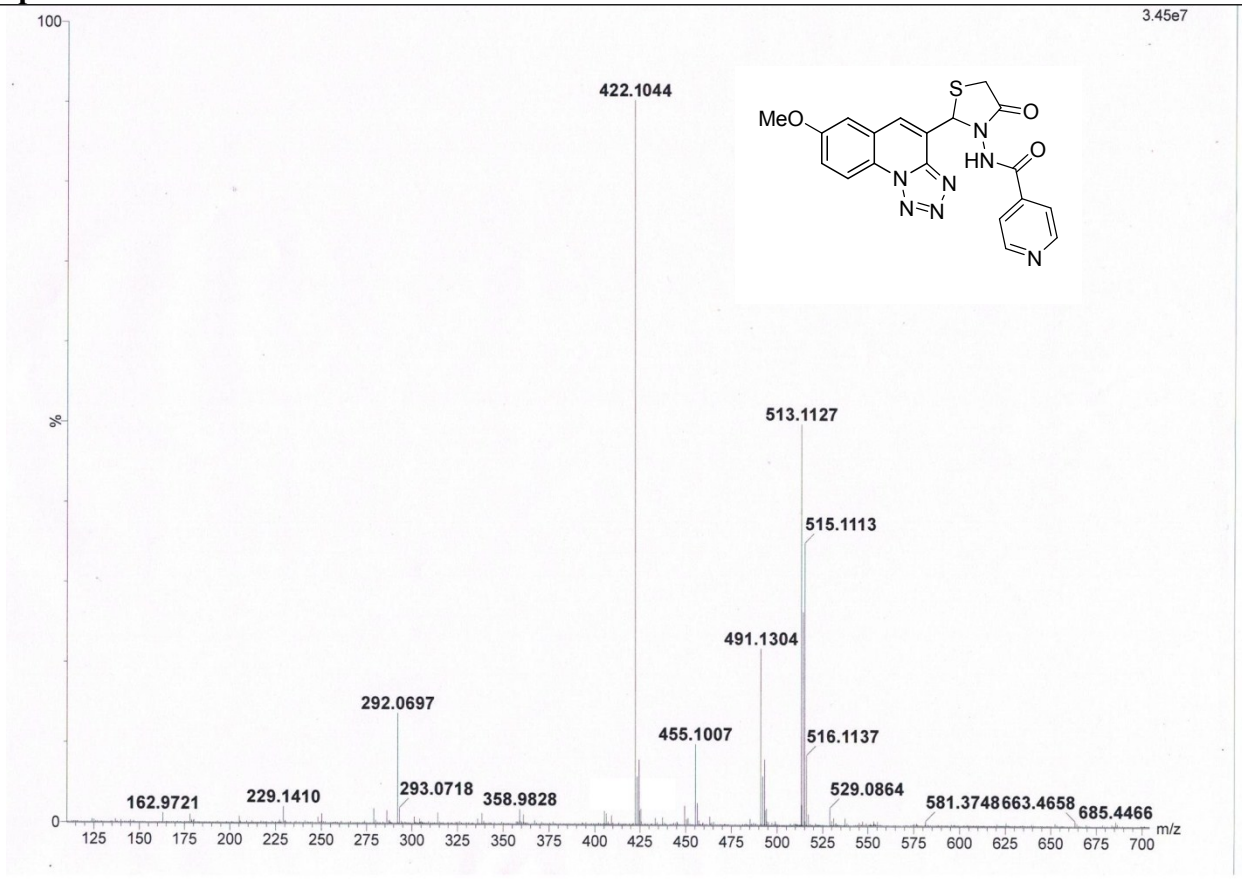
4p.[1]H NMR, 400 MHz, DMSO-d_6



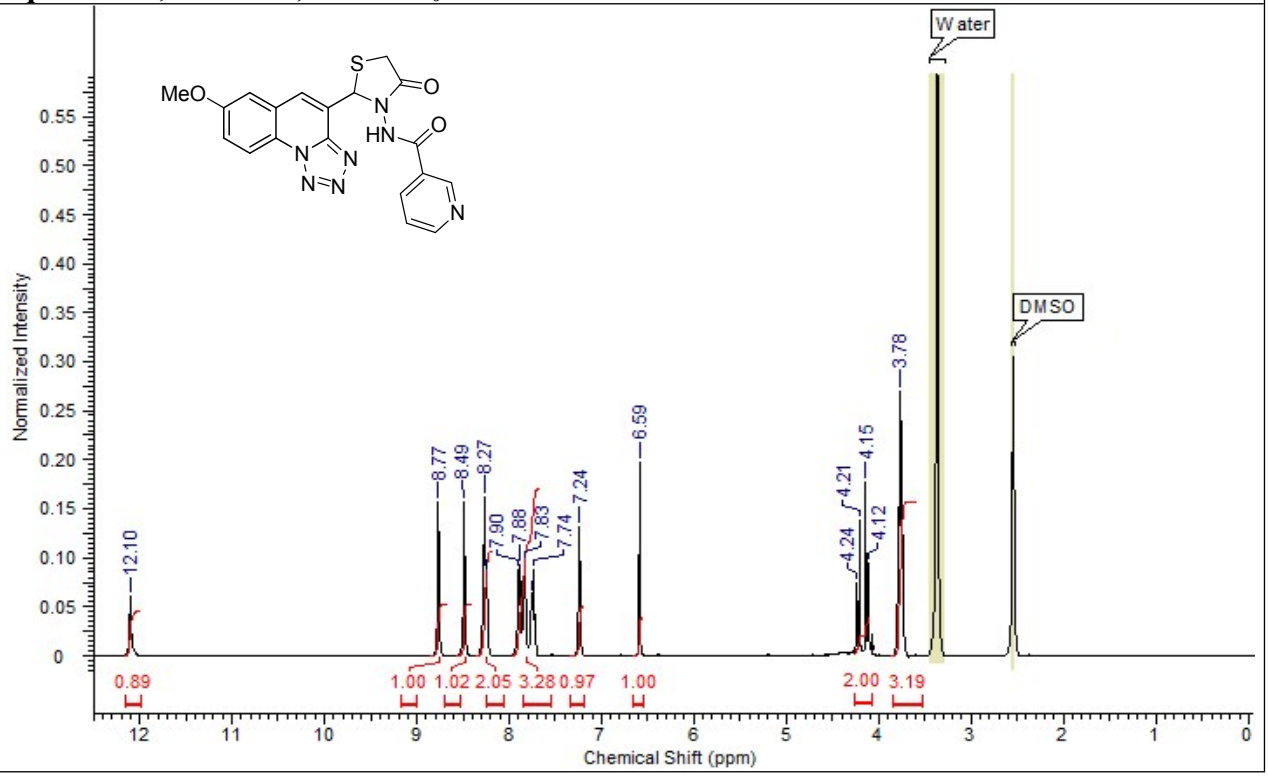
4p. [13]C NMR, 100 MHz, DMSO-d_6



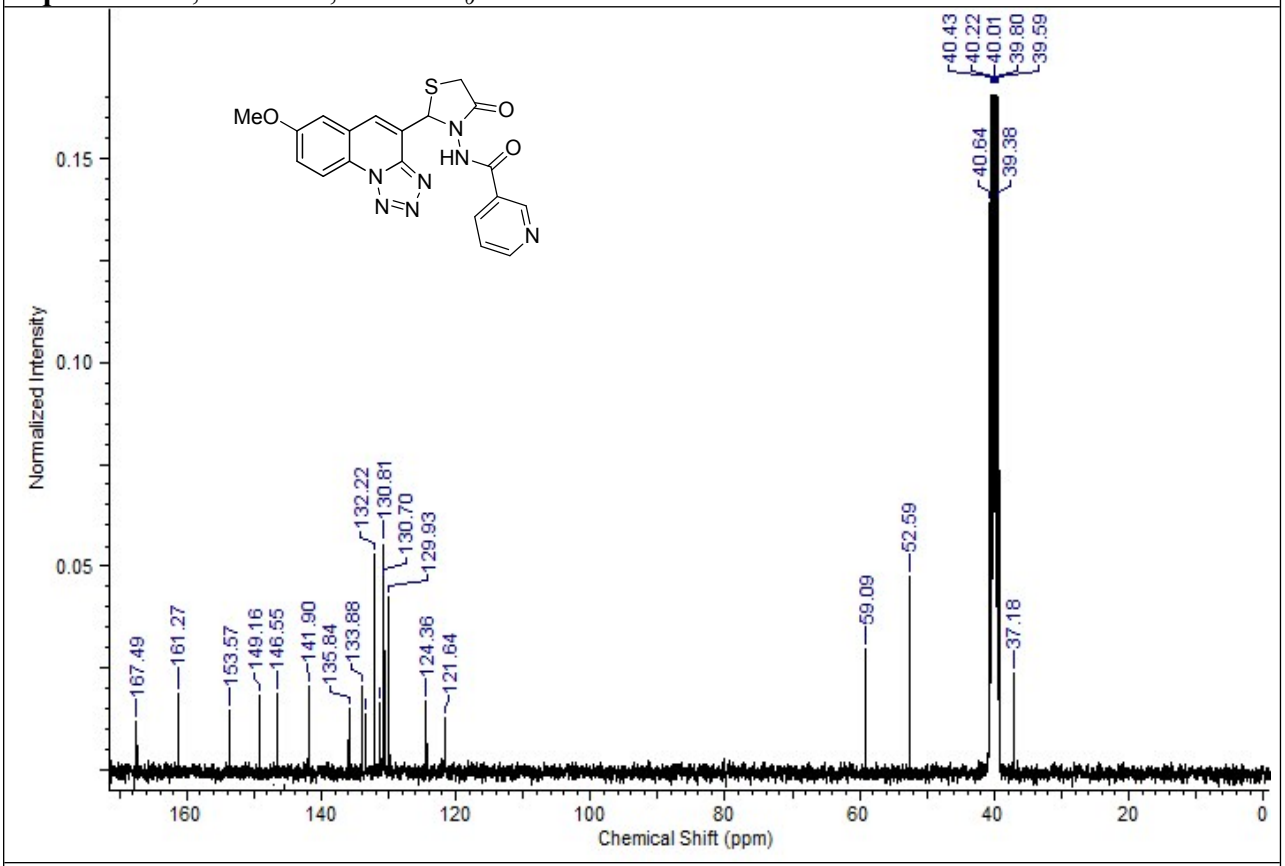
4p. HRMS



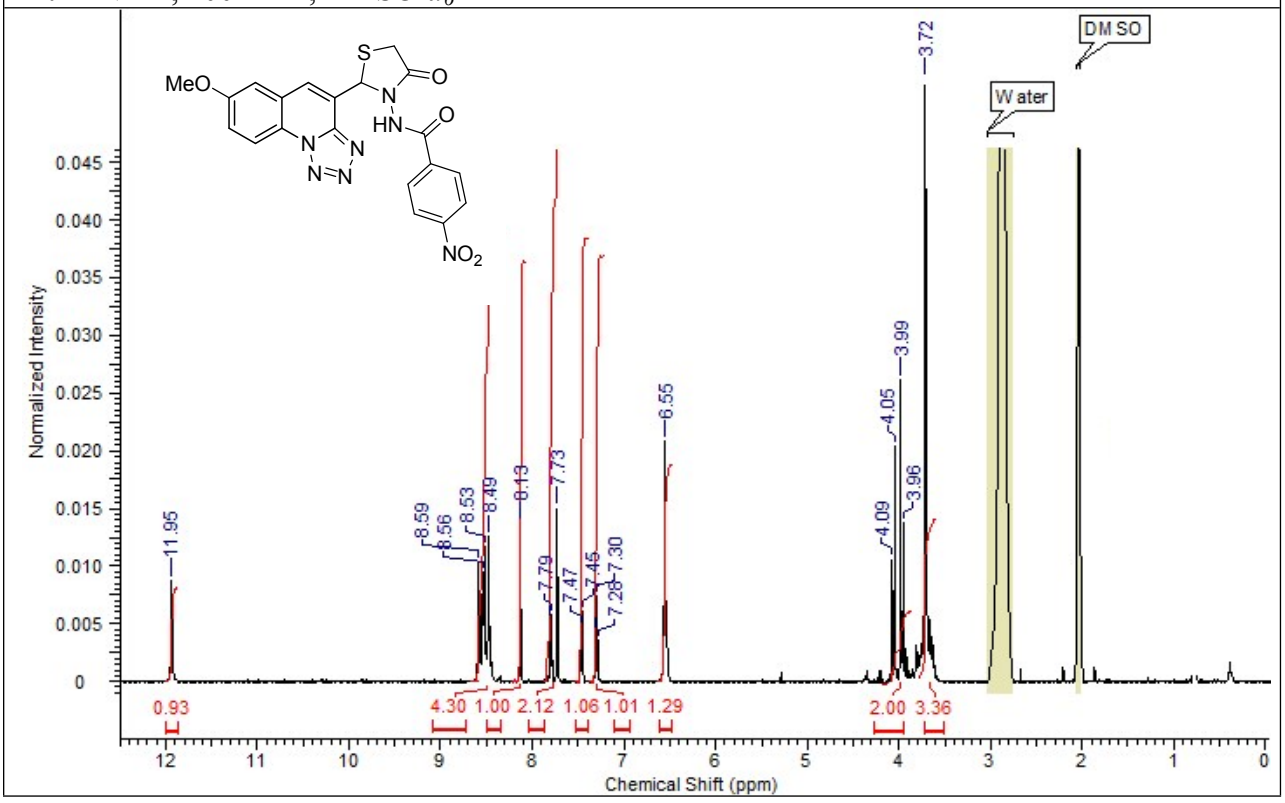
4q.[1]H NMR, 400 MHz, DMSO-d_6



4q. ^{13}C NMR, 100 MHz, DMSO-d_6



4r.^{1}H NMR, 400 MHz, DMSO-d_6



4r. ^{13}C NMR, 100 MHz, DMSO-d_6