

Rational Design, Synthesis and Biological Evaluation of Novel Pyrazoline-Based Antiproliferative Agents in MCF-7 Cancer Cells

Ismail Salama ^{1,*}, Safaa M. Kishk ^{1,*}, Mariam M. Fakhry ², Kazem Mahmoud ², Mohamed S. Nafie ³, Ahmad O. Noor ⁴ and Rawan H. Hareeri ⁵

¹ Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt

² Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Egyptian Russian University, Badr 11829, Egypt

³ Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia 41522, Egypt

⁴ Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah 21589, Saudi Arabia

⁵ Department of Pharmacology and Toxicology, Faculty of Pharmacy, King Abdulaziz University, Jeddah 21589, Saudi Arabia

* Correspondence: ismail_mohamed@pharm.suez.edu.eg (I.S.); safaa_keshk@pharm.suez.edu.eg (S.M.K.)

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Docking validation

1. Validation for 1xkk

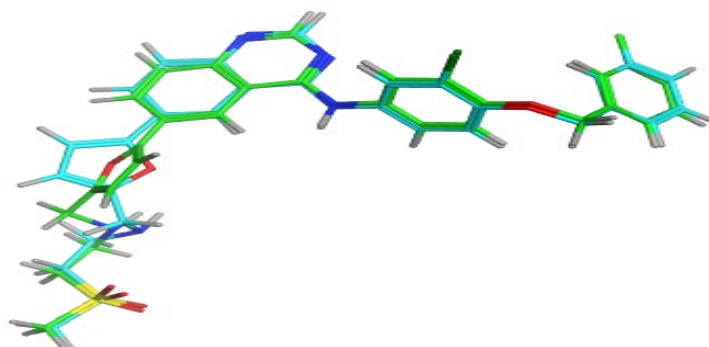


Figure S1: Redocking validation for EGFR; RMSD = 0.6 and S-score = -11. 83

2. Validation for 3rcd

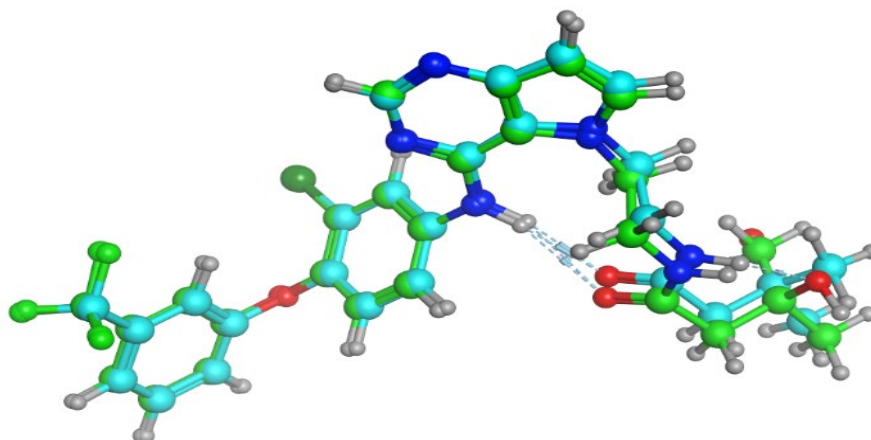


Figure S2: Redocking validation for HER2; RMSD= 0.6 and S-score = -10.11

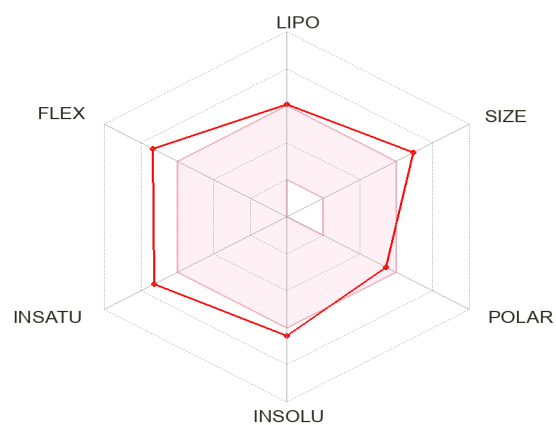


Figure S3: bioavailability radar for Lapatinib

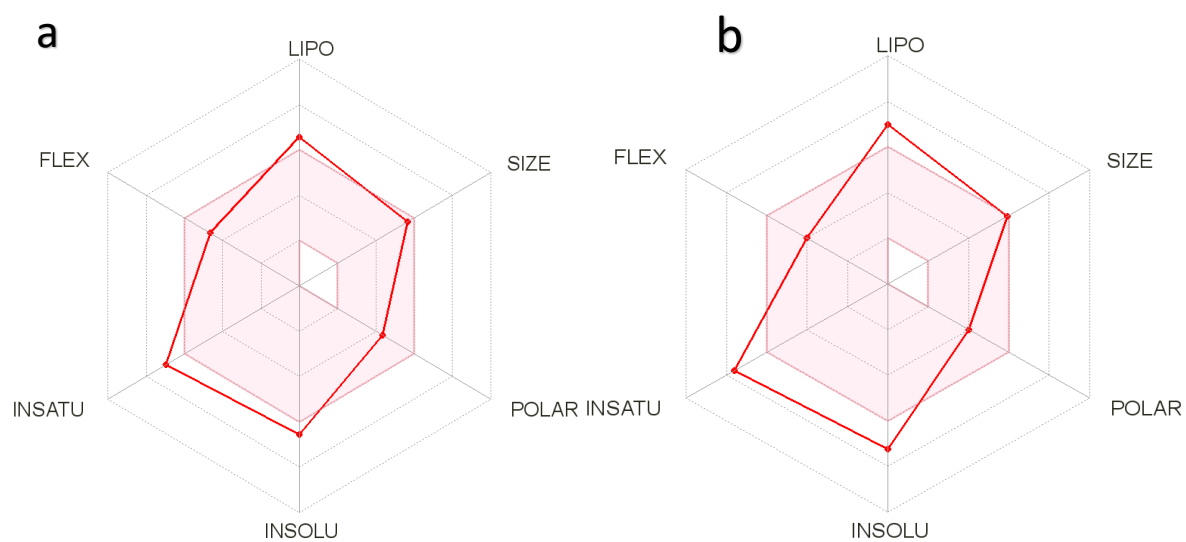


Figure S4: A) bioavailability radar for 6e; B) bioavailability radar for 6k

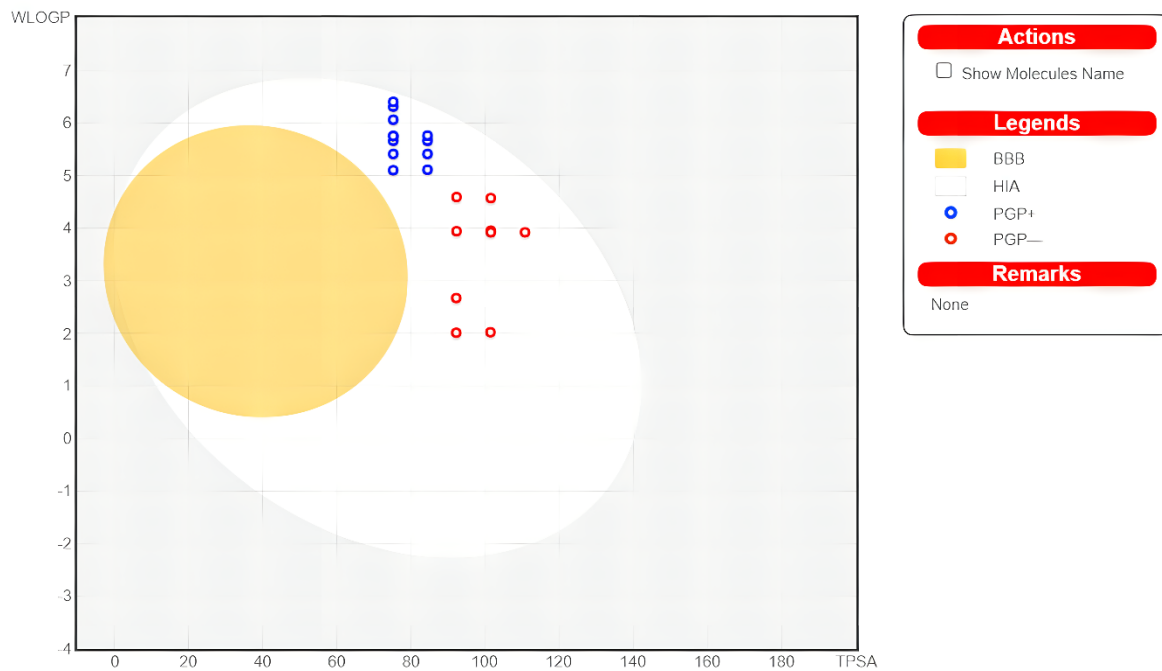


Figure S5: Boiled egg model as indication of bioavailability

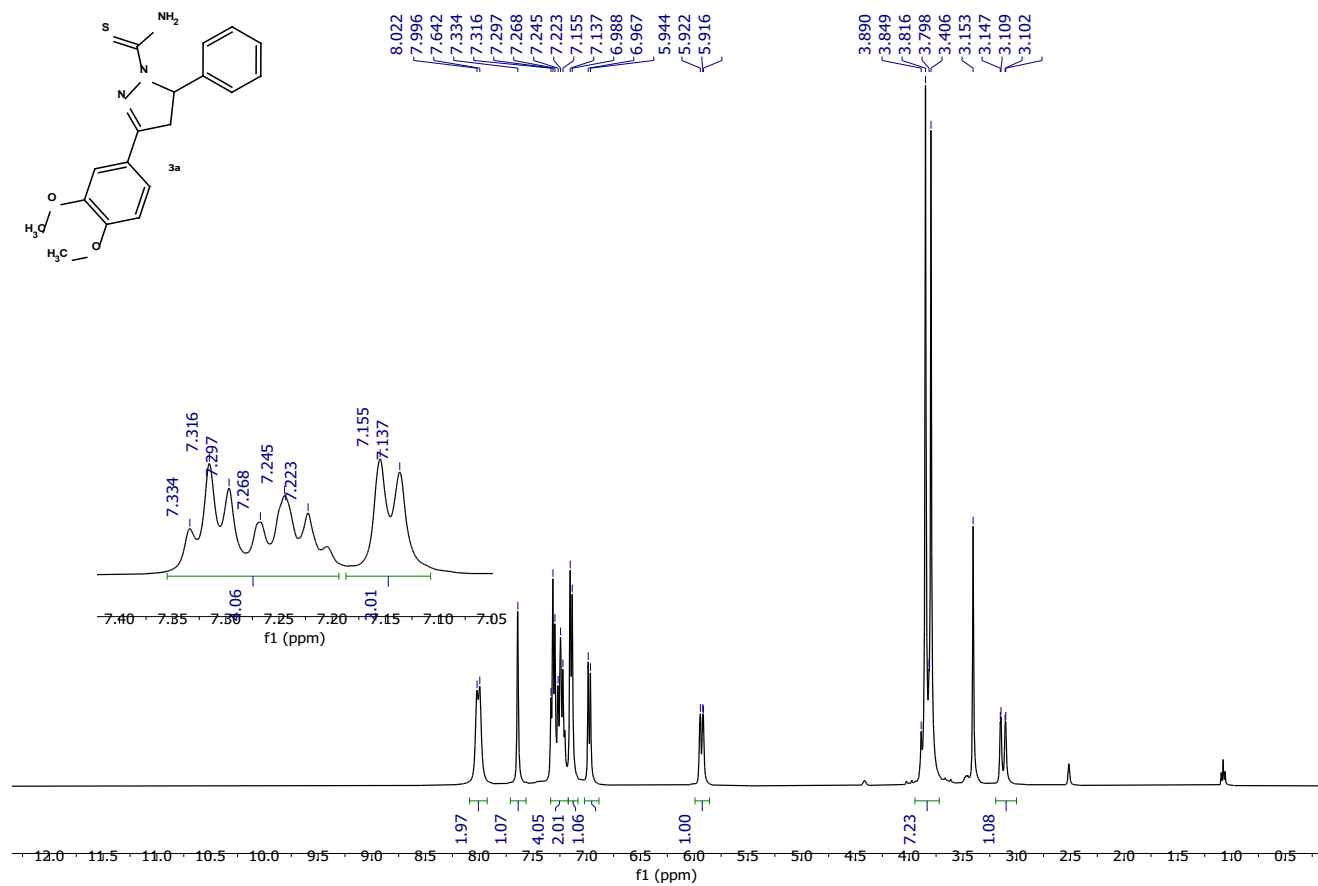


Figure S6: ^1H NMR of compound 3a

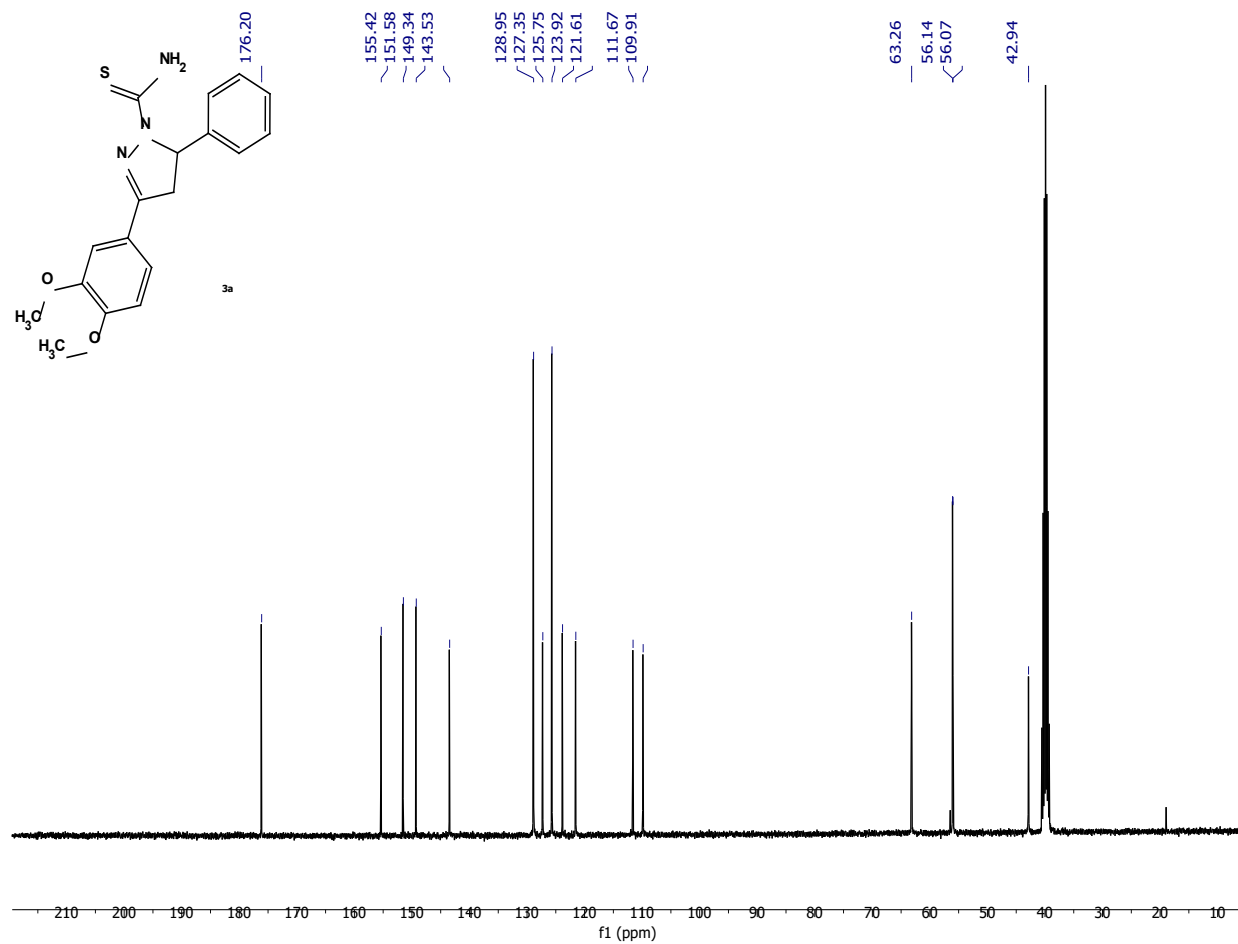


Figure S7: ^{13}C NMR of compound 3a

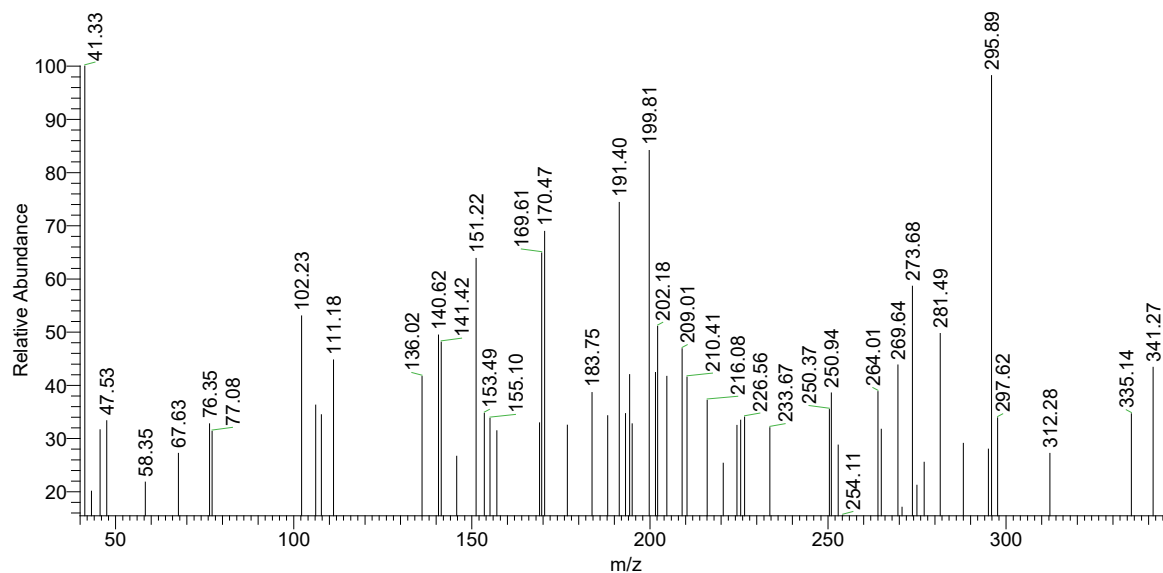
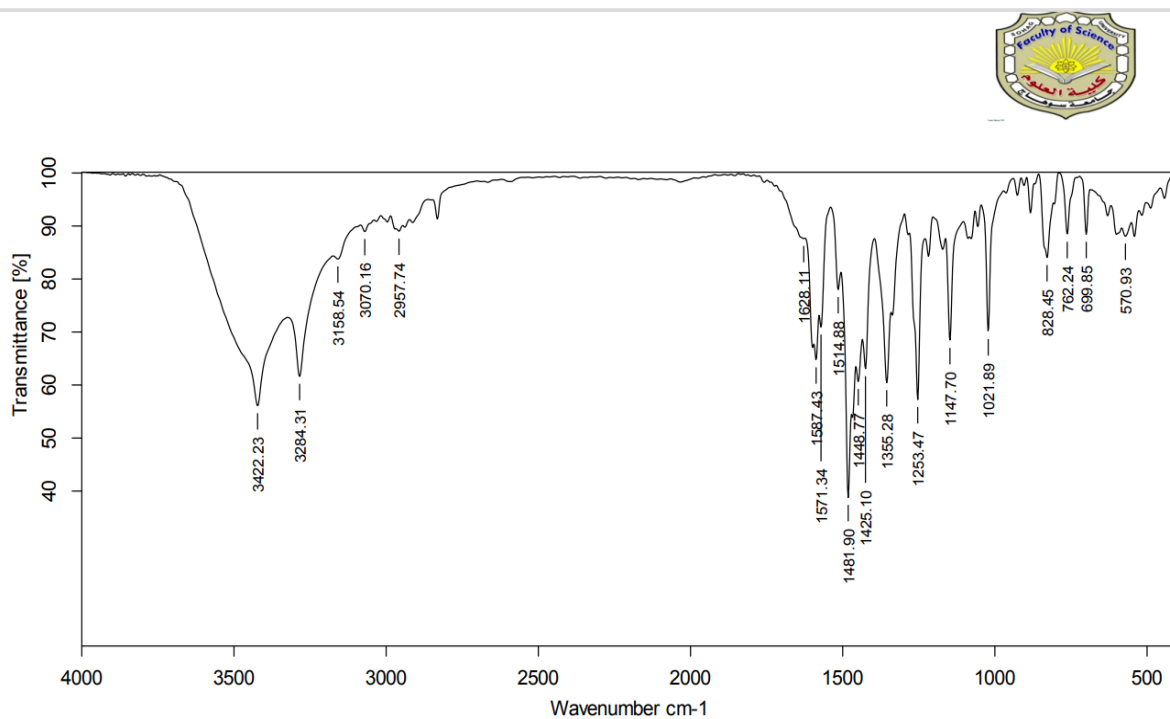


Figure S8: Mass of compound 3a



3a _TRANS.0

11:37:47 0

25/07/2021

Figure S9: IR of compound 3a

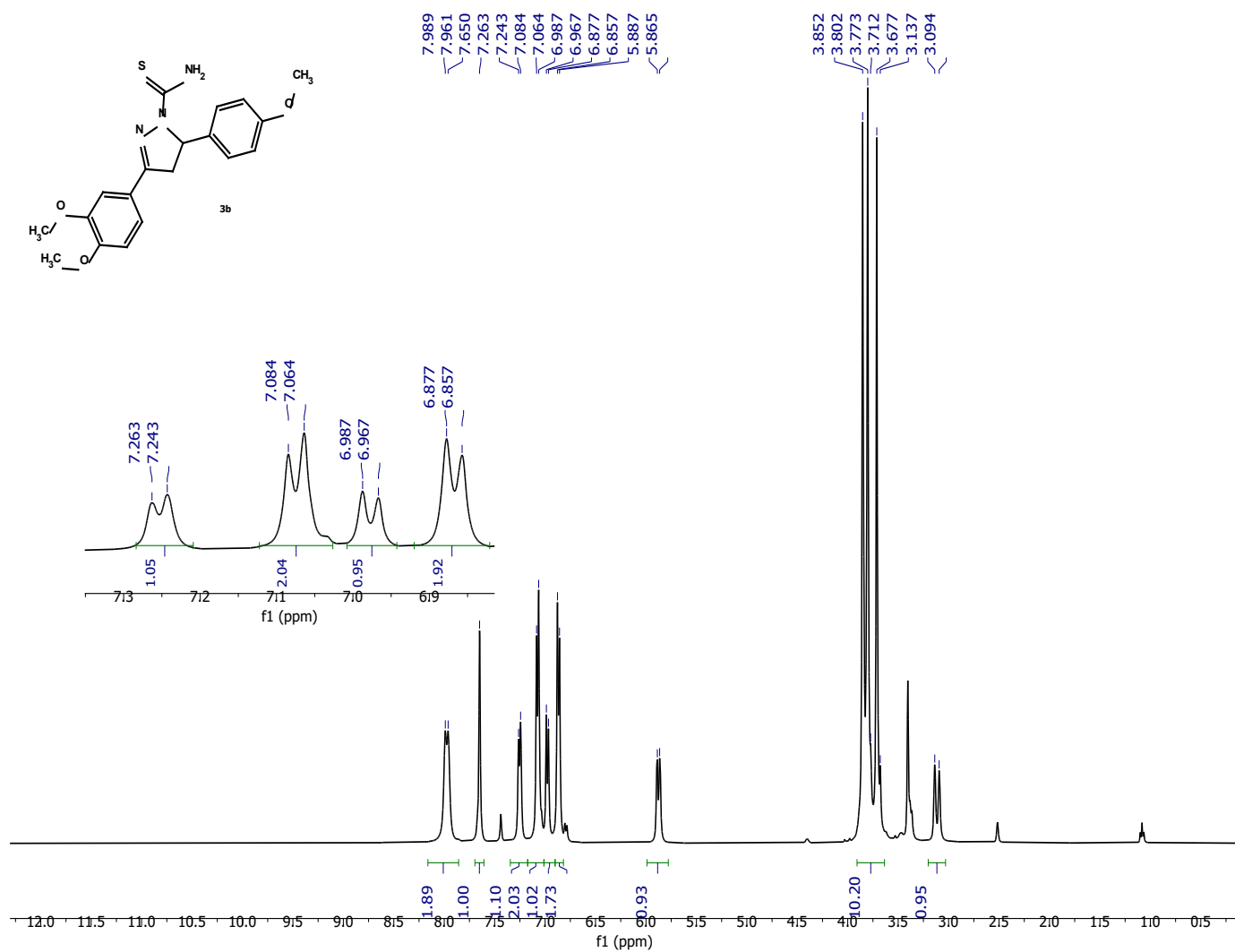


Figure S10: ¹H NMR of compound 3b

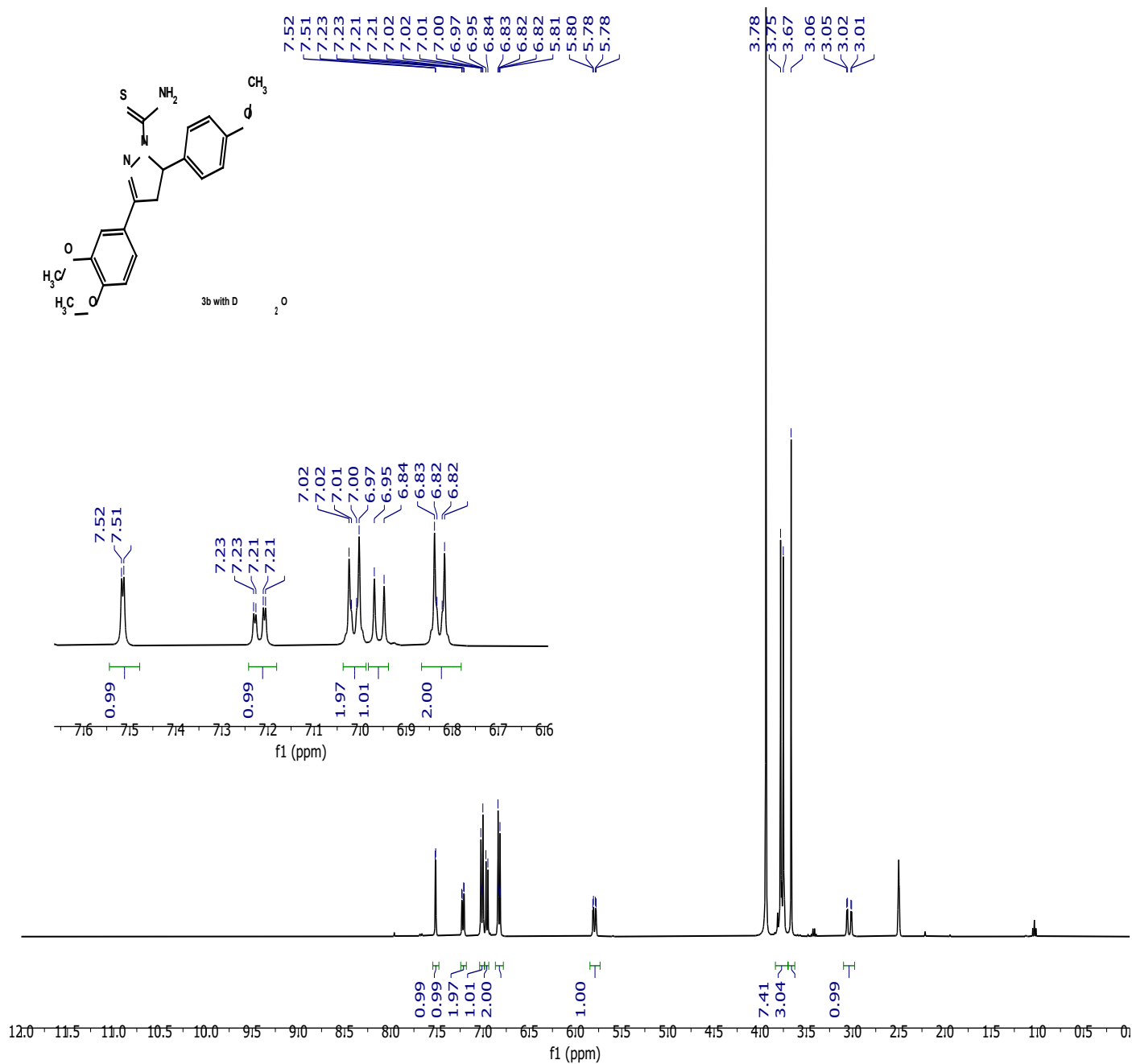


Figure S11: ^1H NMR (D_2O) of compound 3b

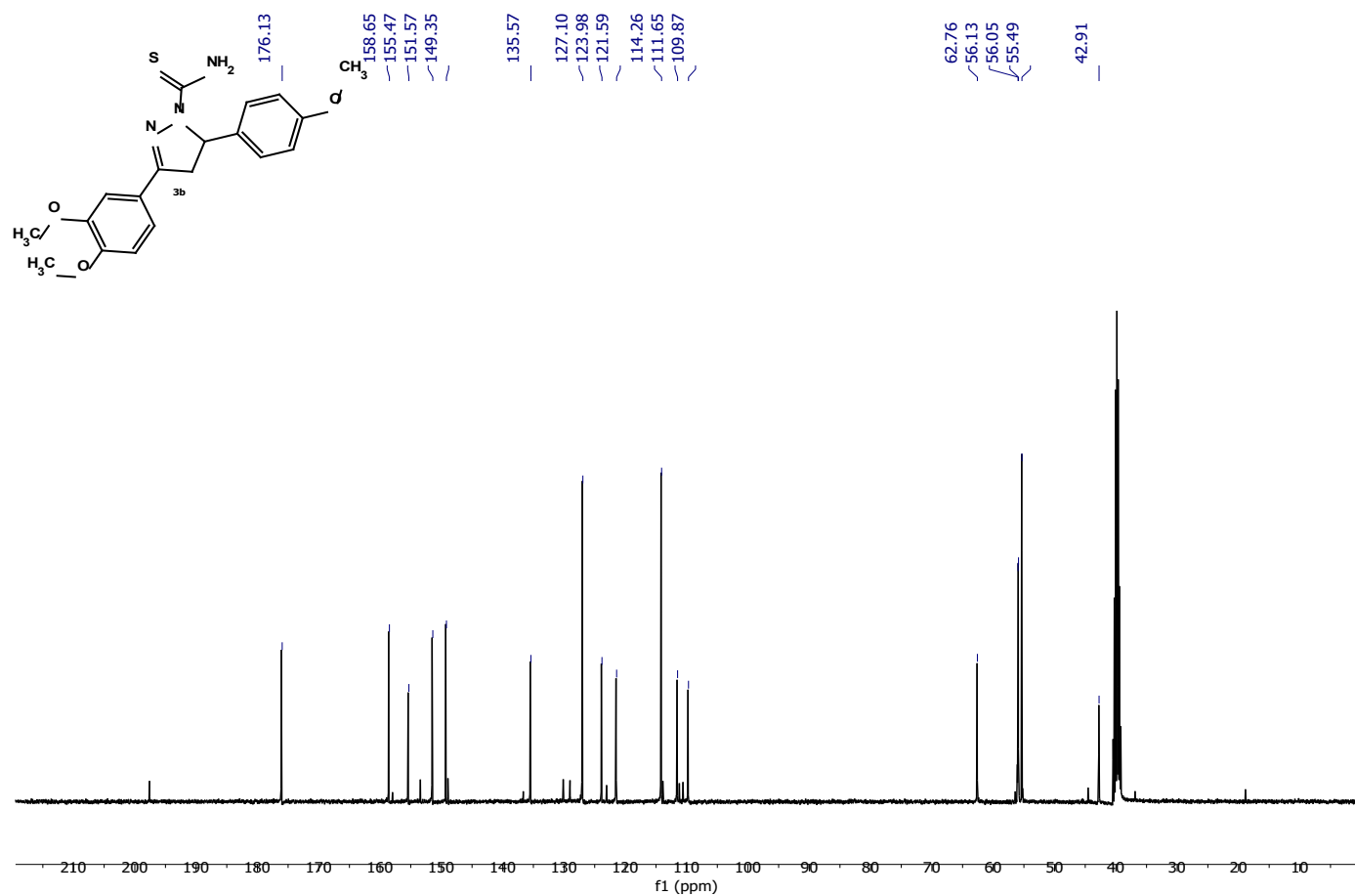


Figure S12: ¹³C NMR of compound 3b

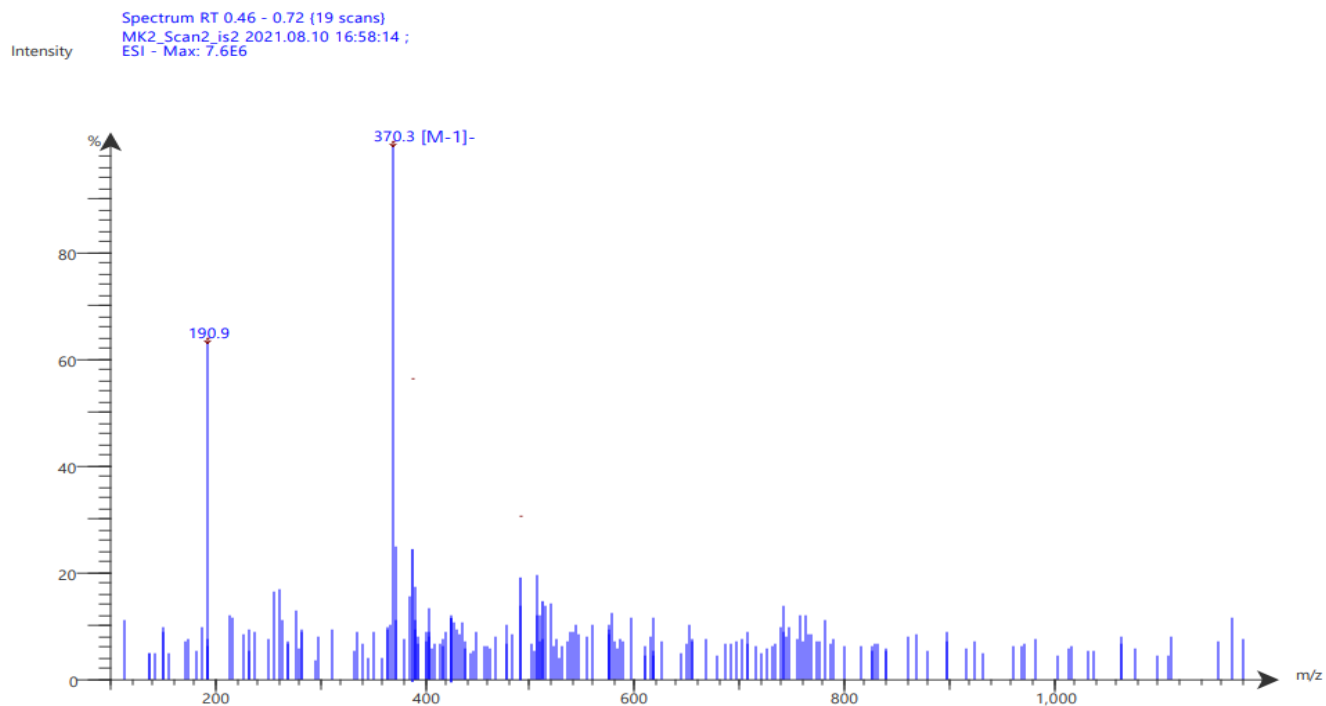
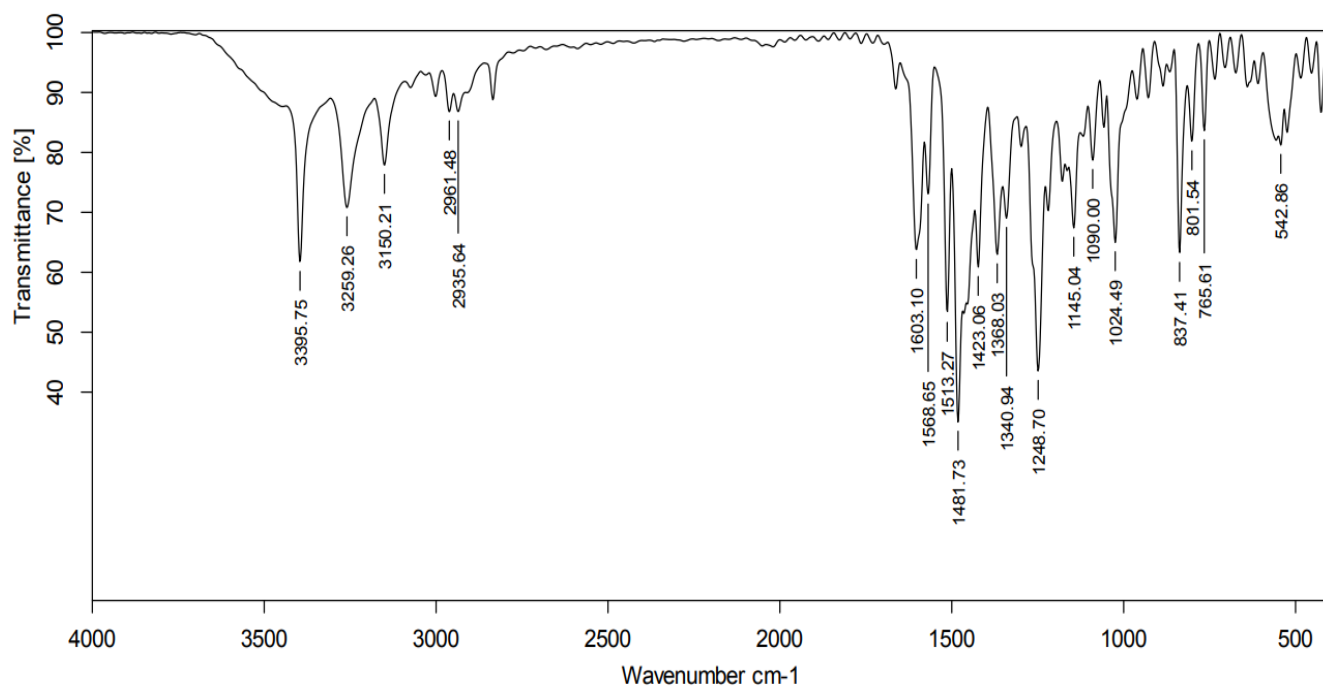


Figure S13: Mass of compound 3b



3b_TRANS.0

11:34:40 Ö

25/07/2021

Figure S14: IR of compound 3b

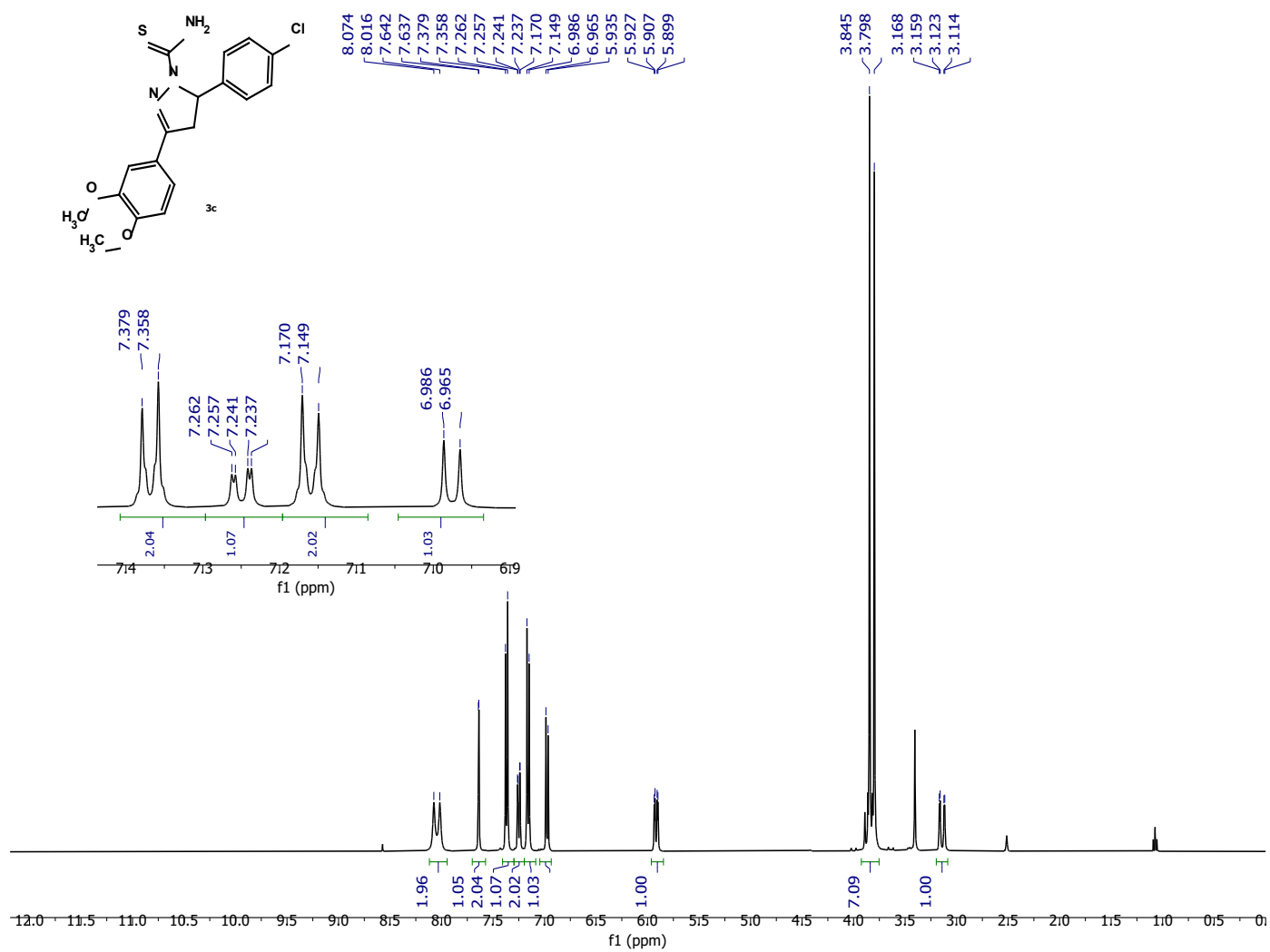


Figure S15: ^1H NMR of compound 3c

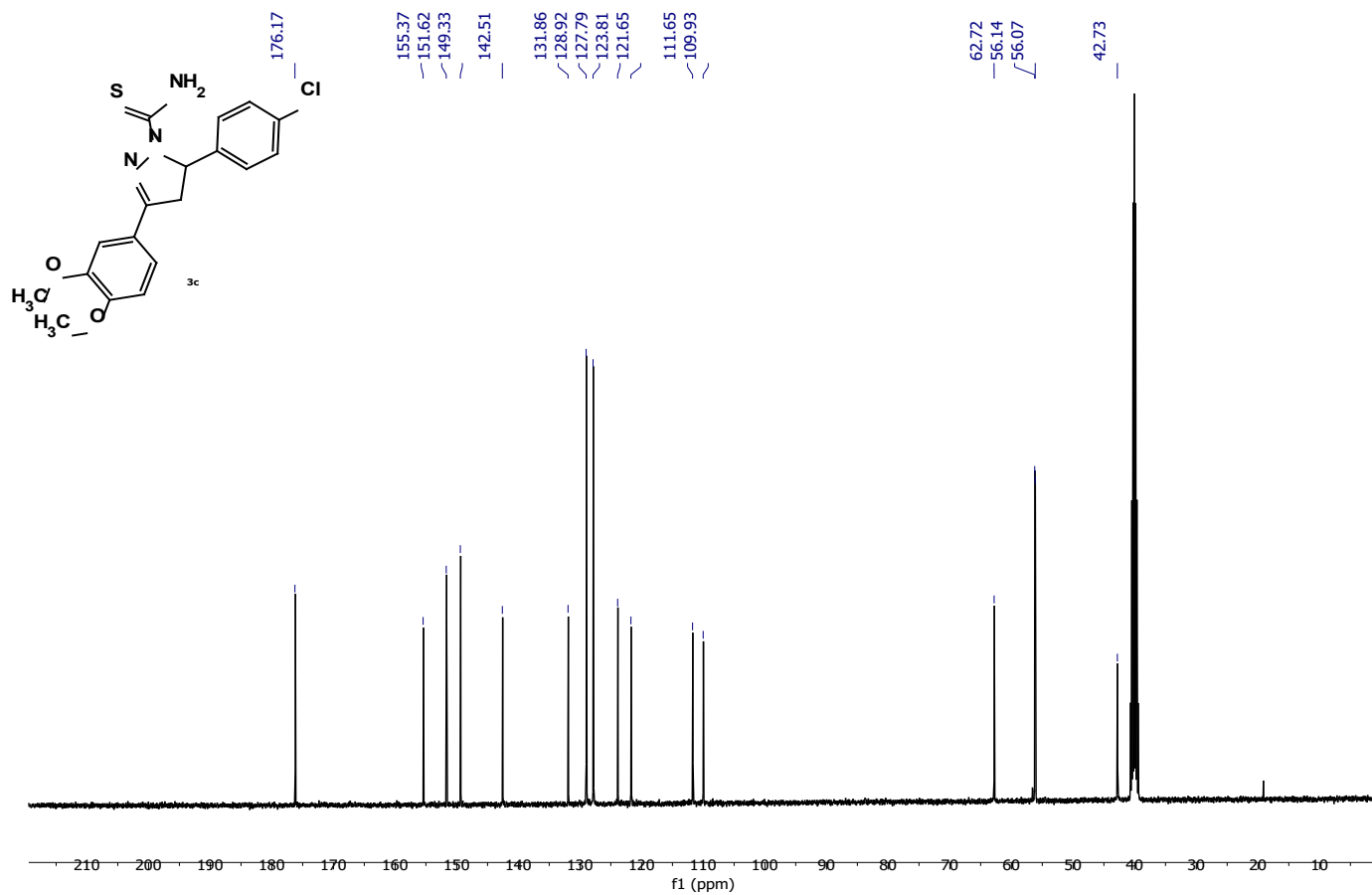


Figure S16: ^{13}C NMR of compound 3C

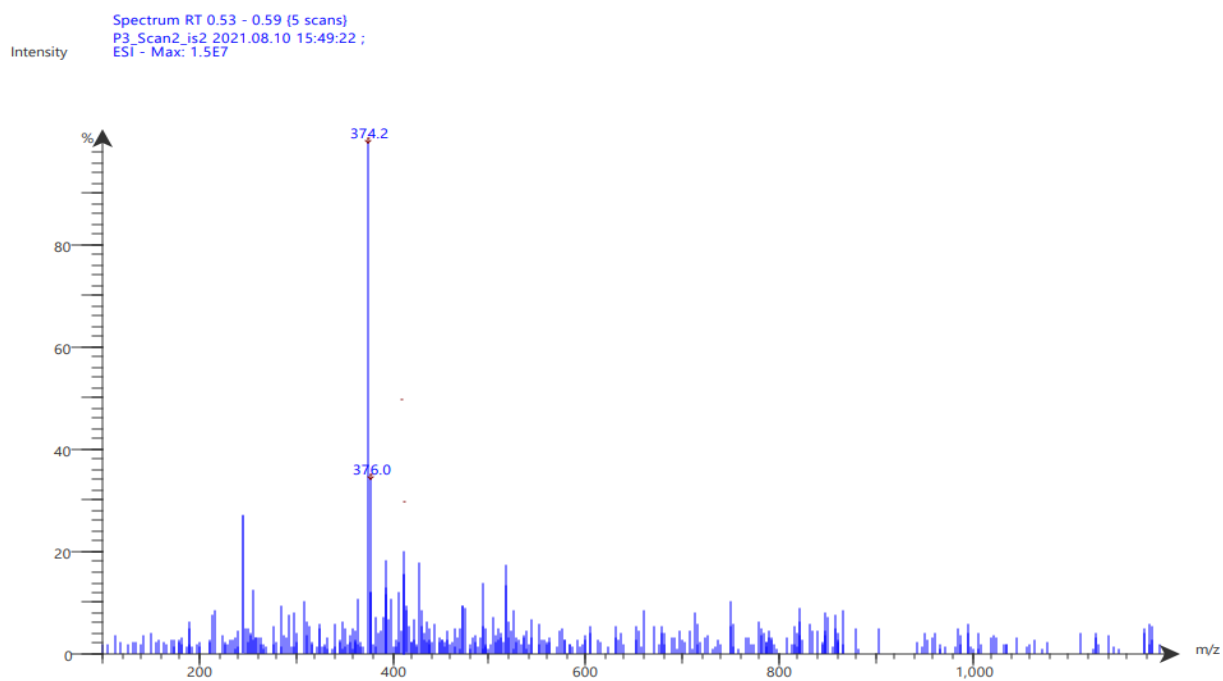
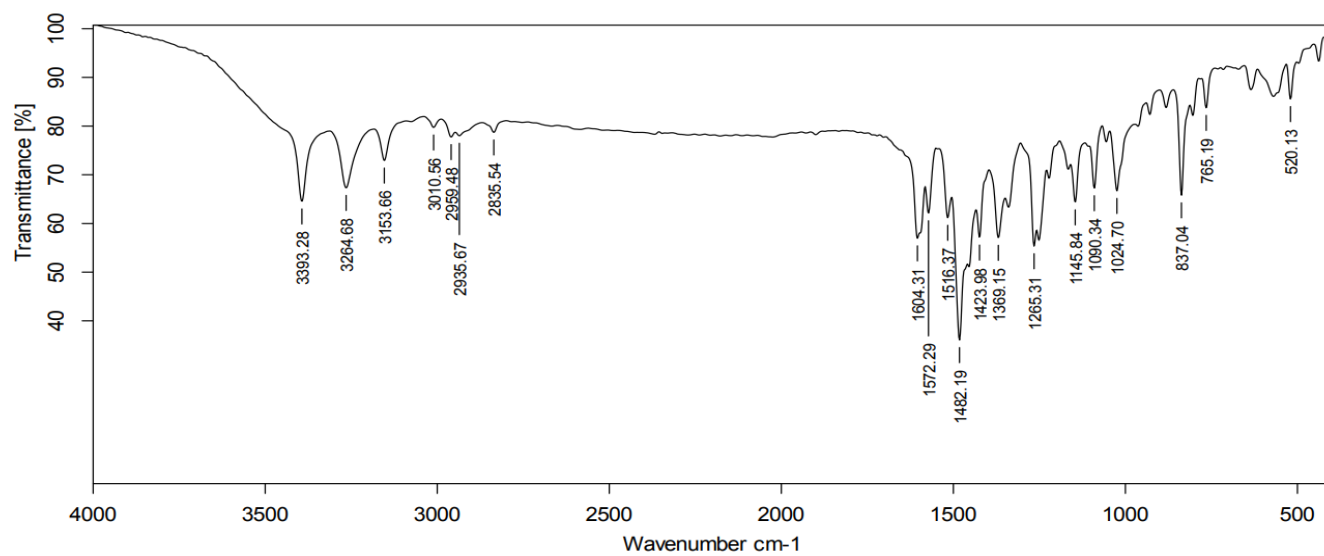


Figure S17: Mass of compound 3C



3c_TRANS.0

11:36:18 O

25/07/2021

Figure S18: IR of compound 3C

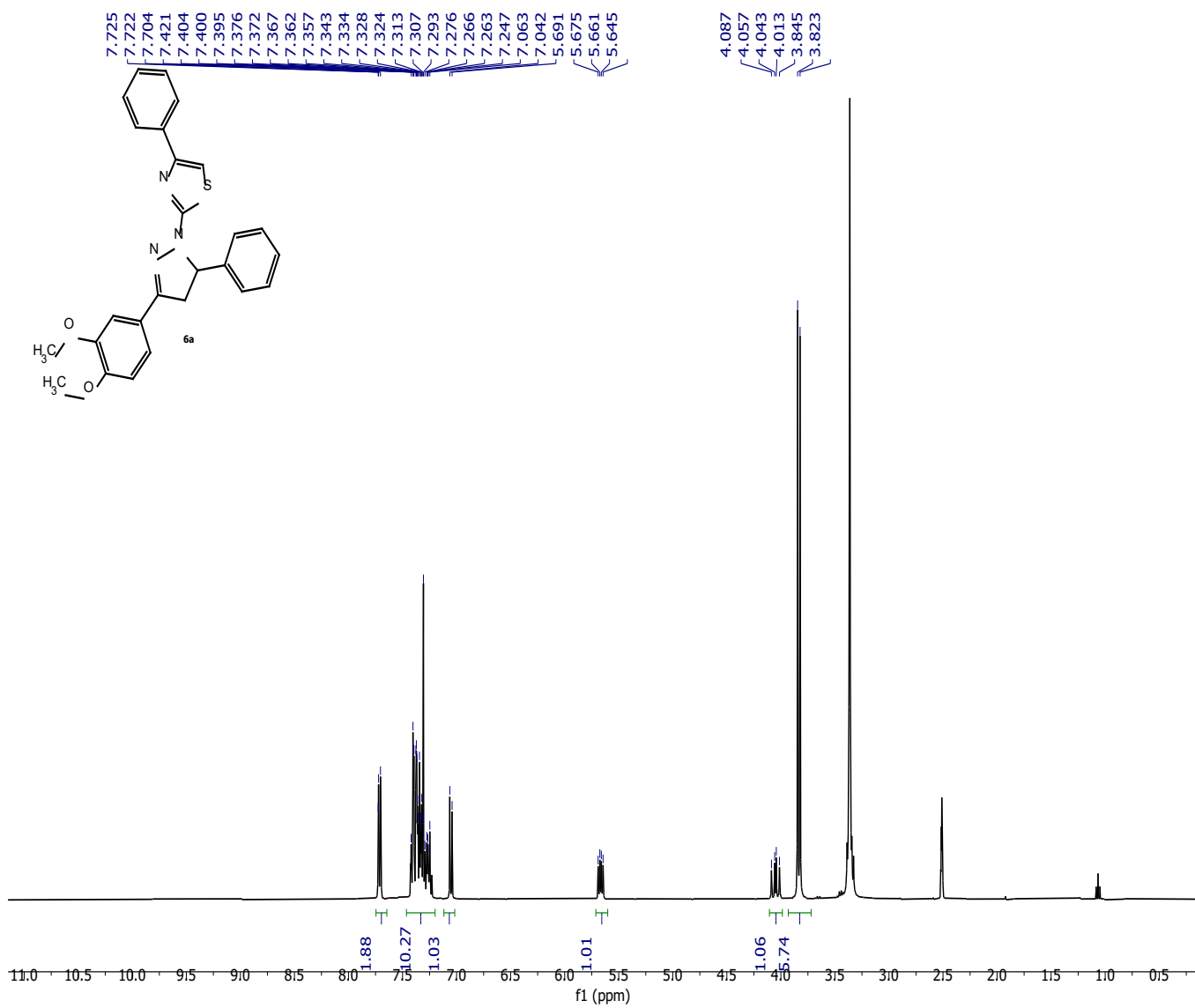


Figure S19: ¹H NMR of compound 6a

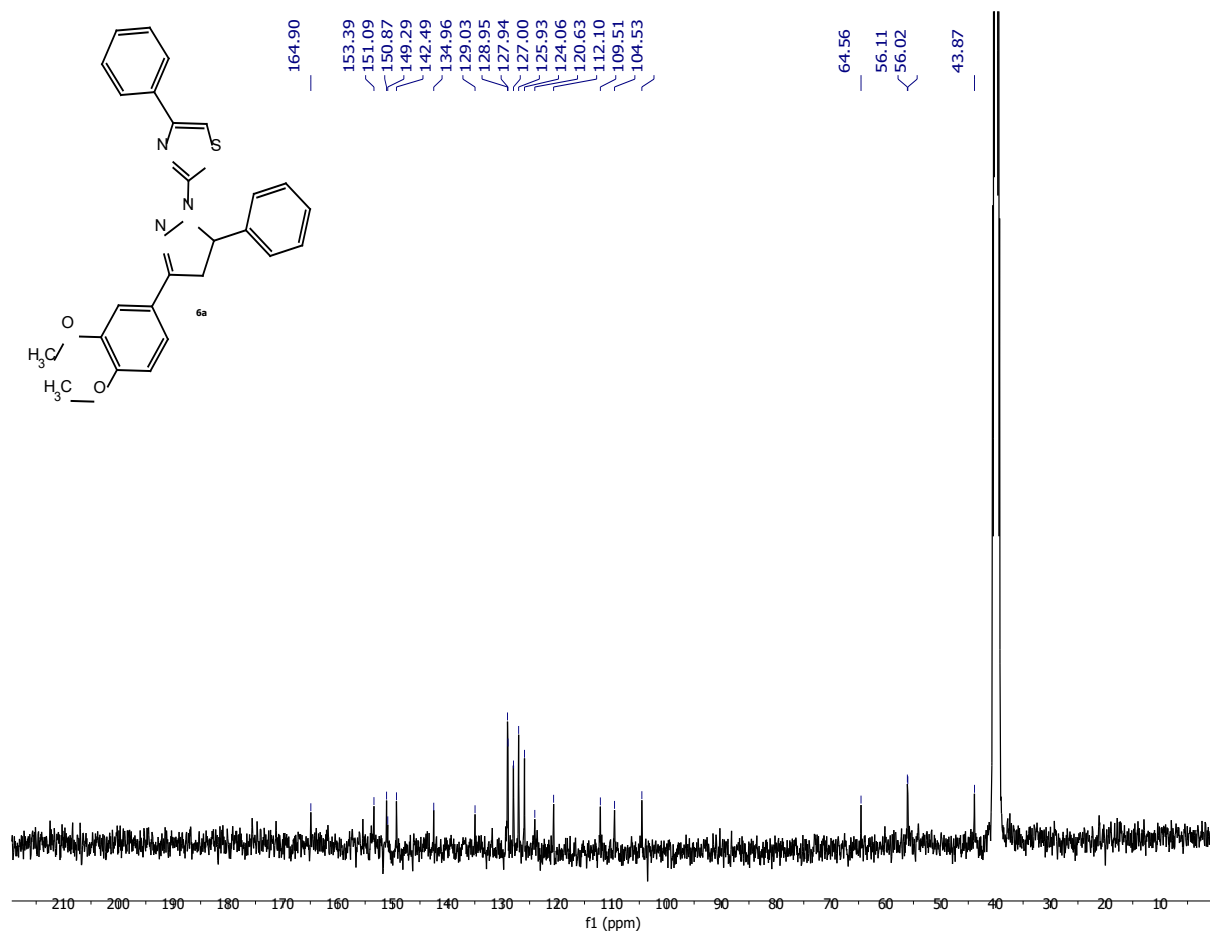


Figure S20: ¹³C NMR of compound 6a

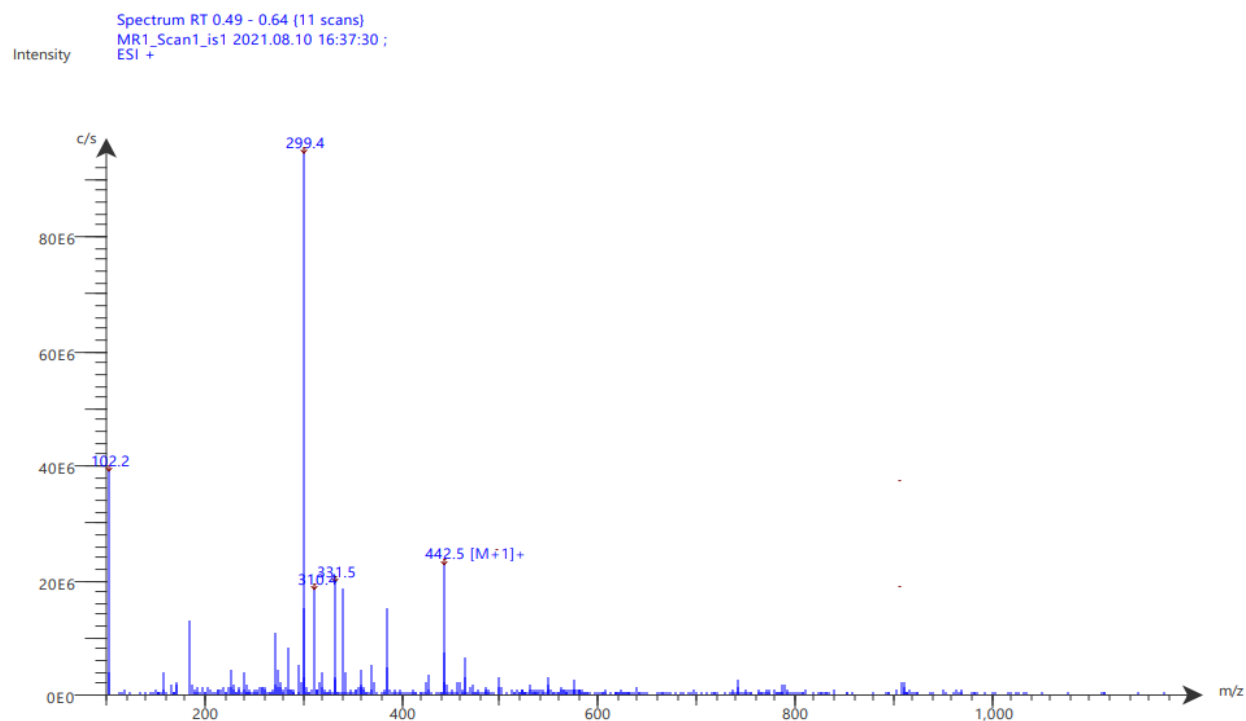
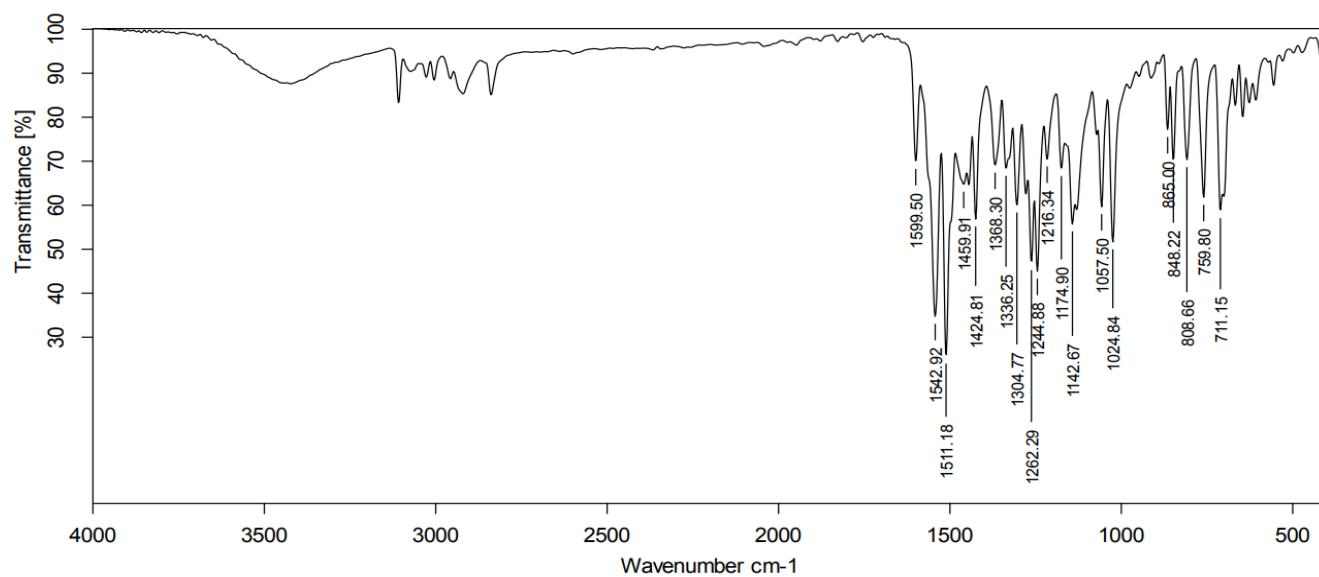


Figure S21: Mass of compound 6a



6a_TRANS.0

10:42:03 0

26/07/2021

Figure S22: IR of compound 6a

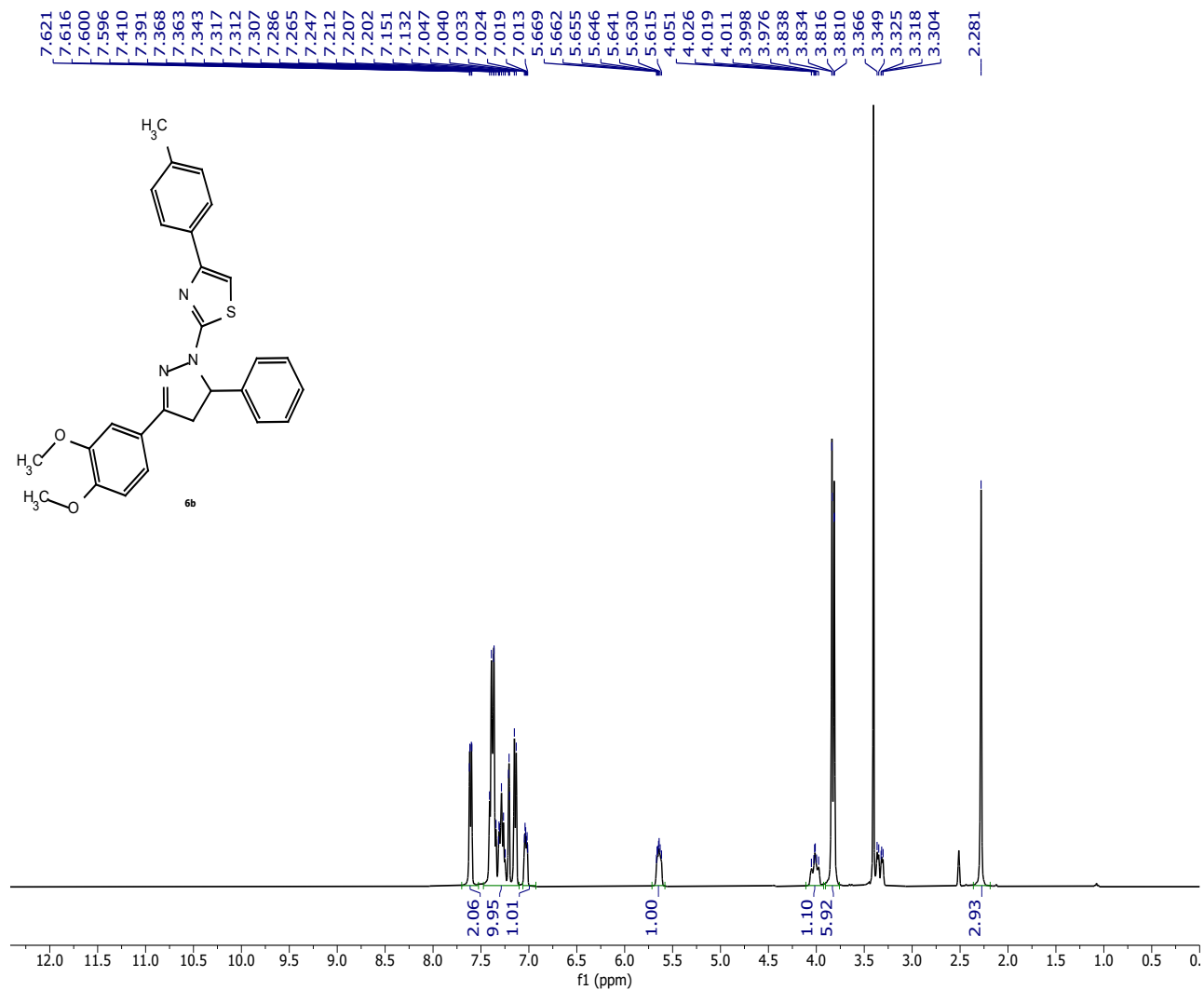


Figure S23: ¹H NMR of compound 6b

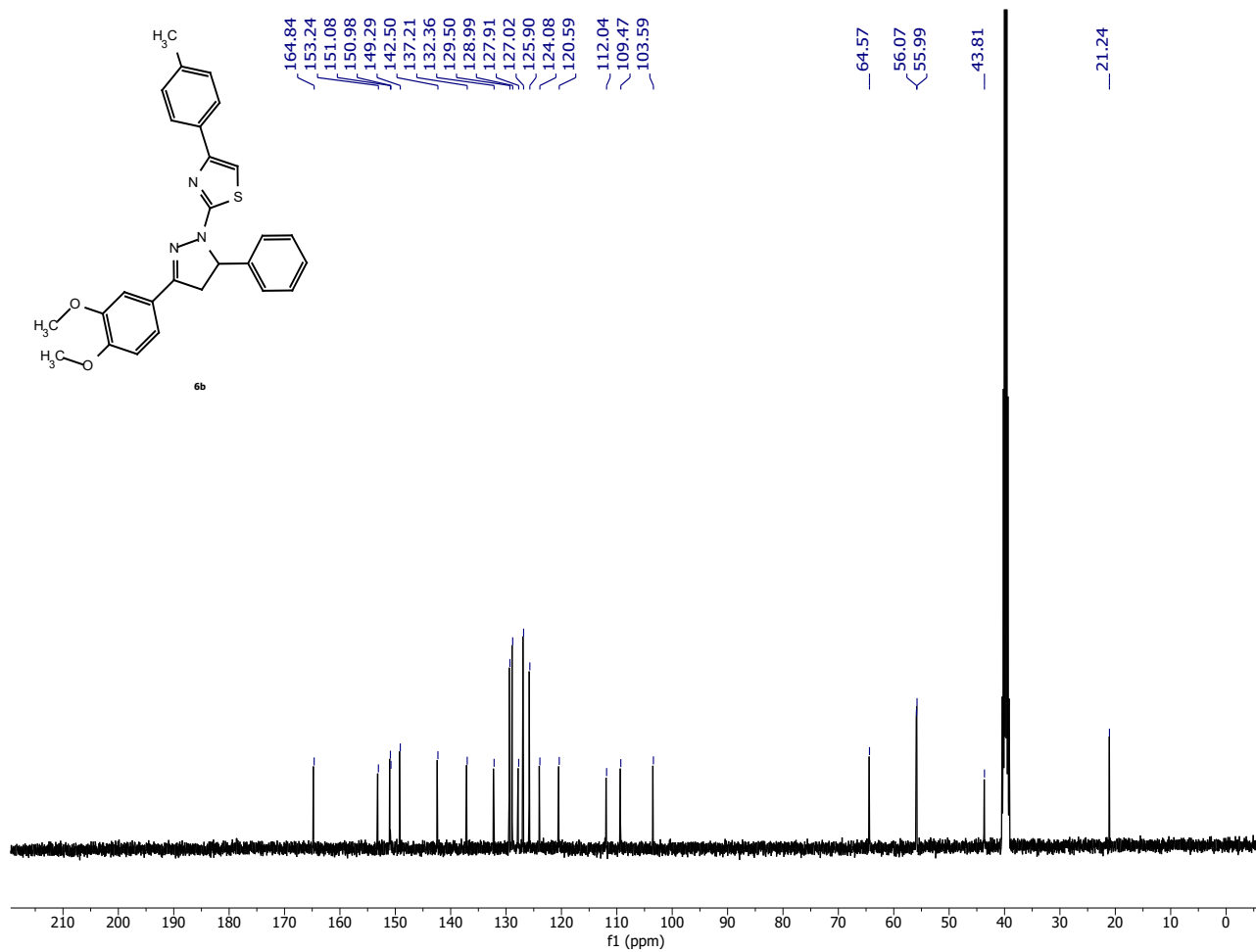


Figure S24: ^{13}C NMR of compound 6b

mariam-medhat-mq1 #158-161 RT: 2.66-2.71 AV: 4 NL: 1.70E2
T: + c EI Full ms [40.00-1000.00]

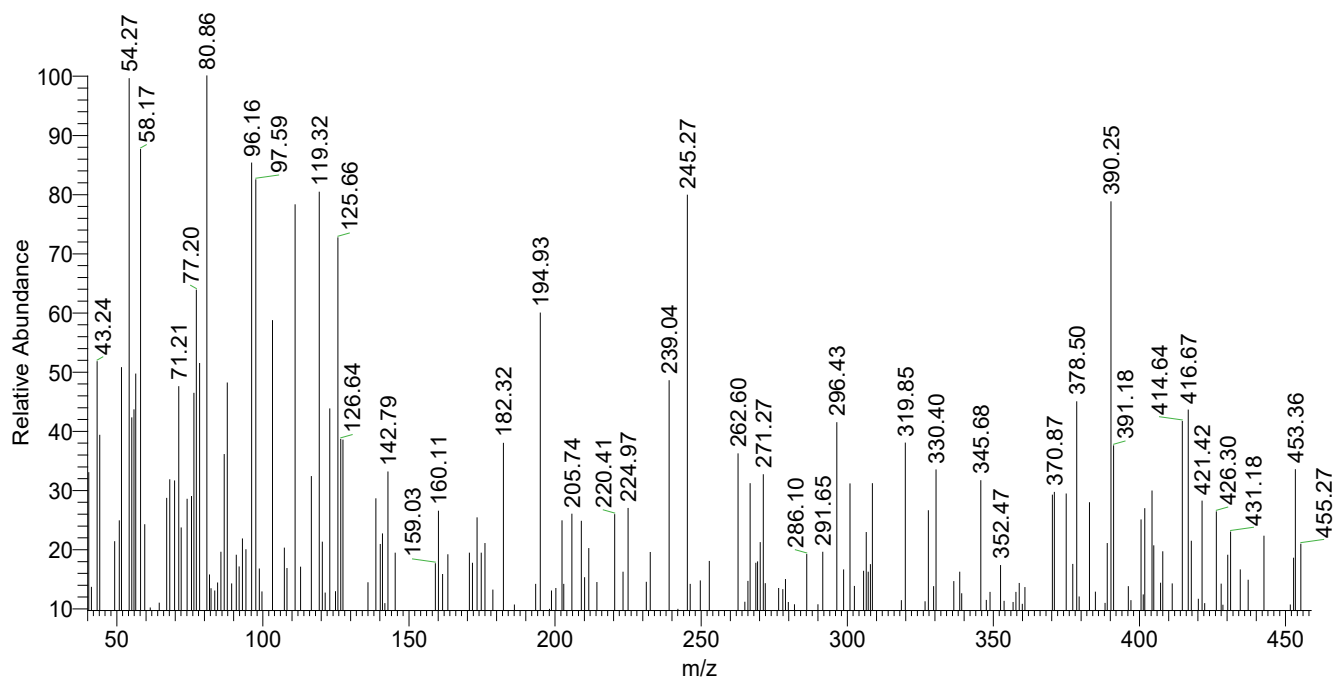
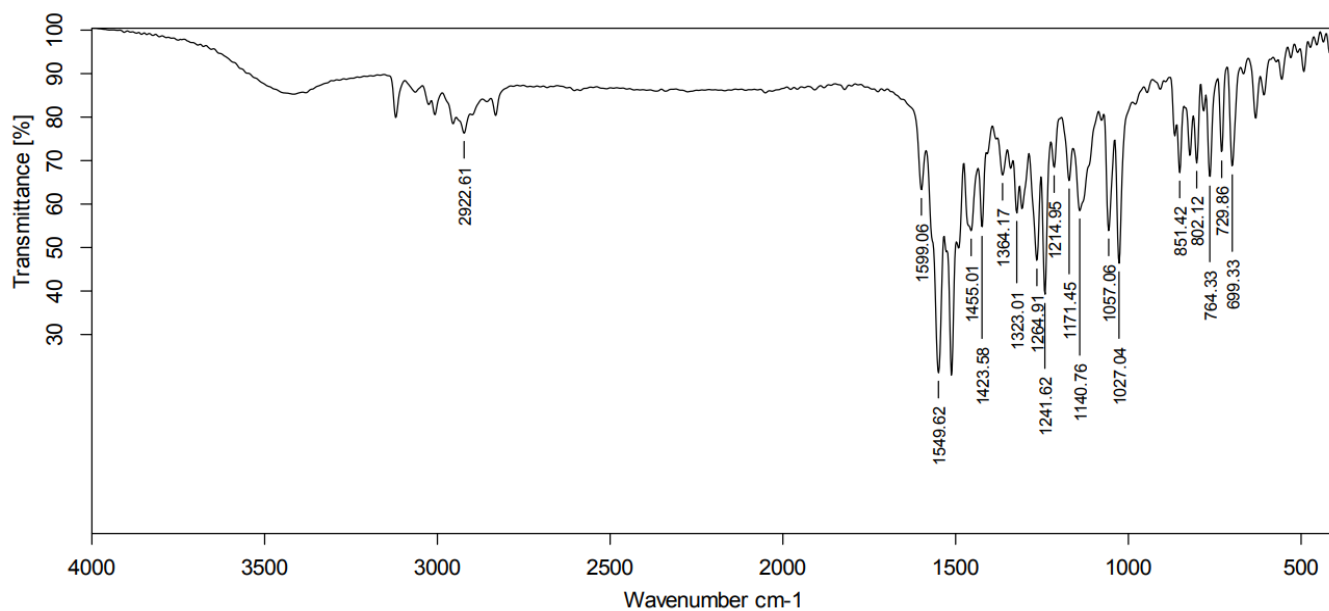


Figure S25: Mass of compound 6b



6b_TRANS.0

11:18:56 Ö

26/07/2021

Figure S26: IR of compound 6b

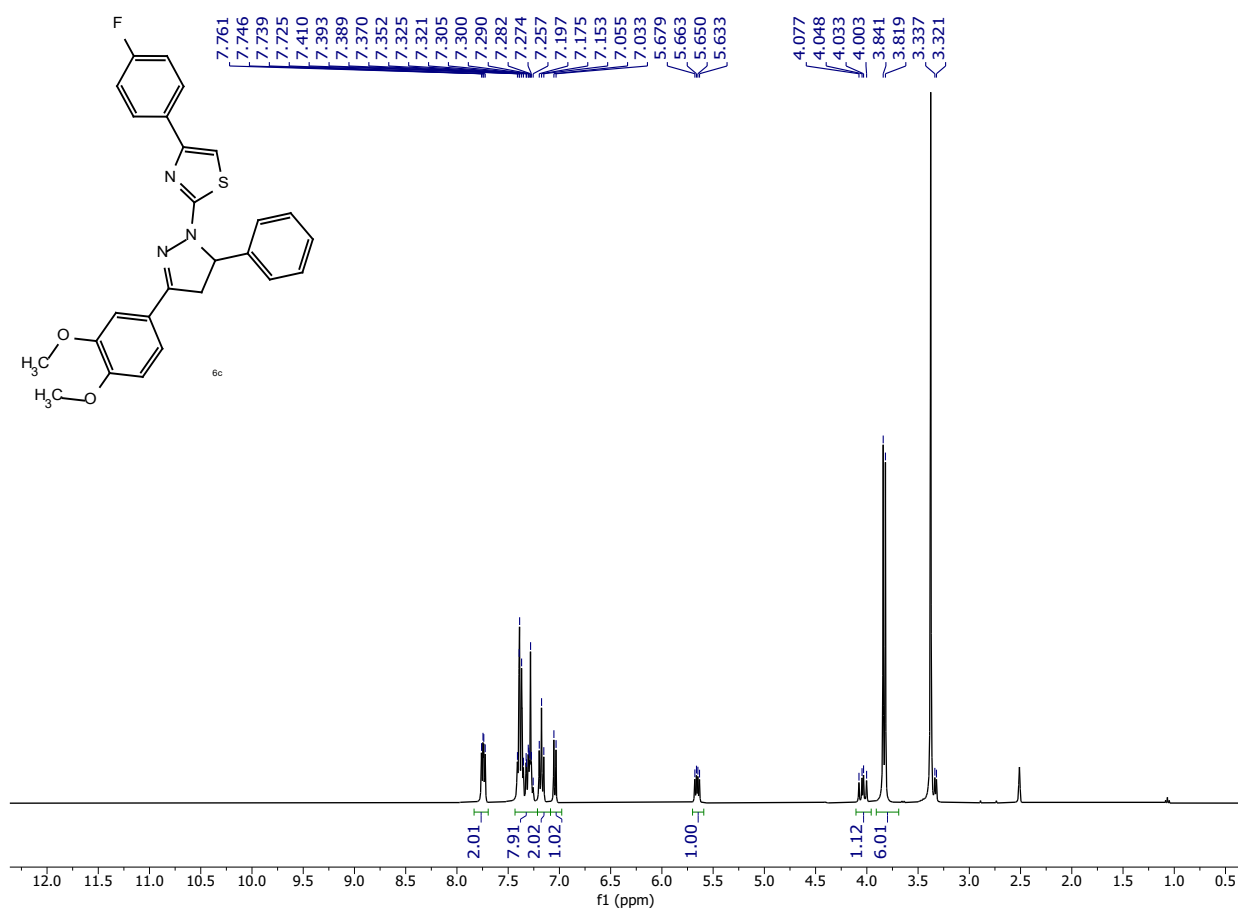


Figure S27: ¹H NMR of compound 6C

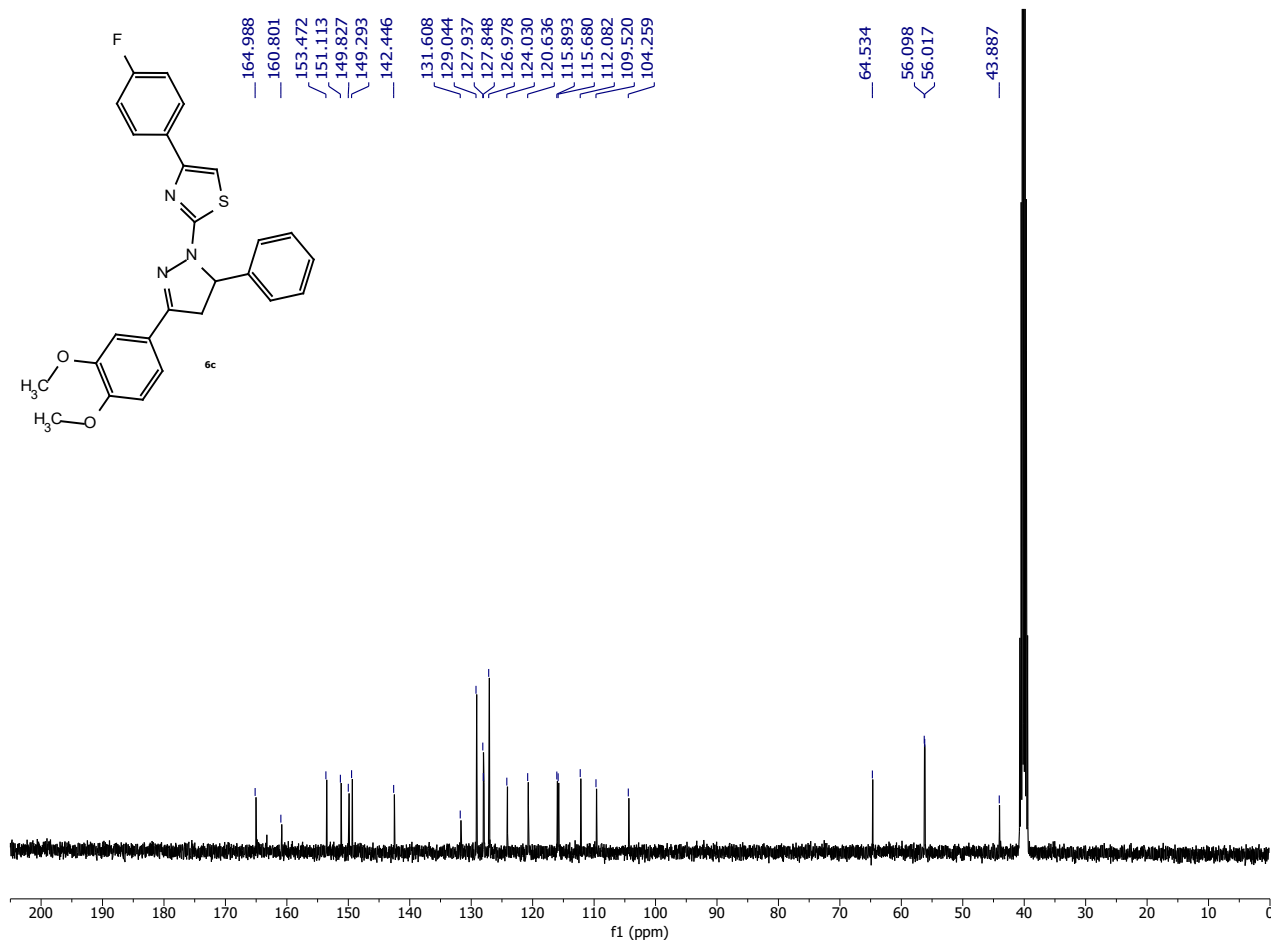


Figure S28: ¹³C NMR of compound 6C

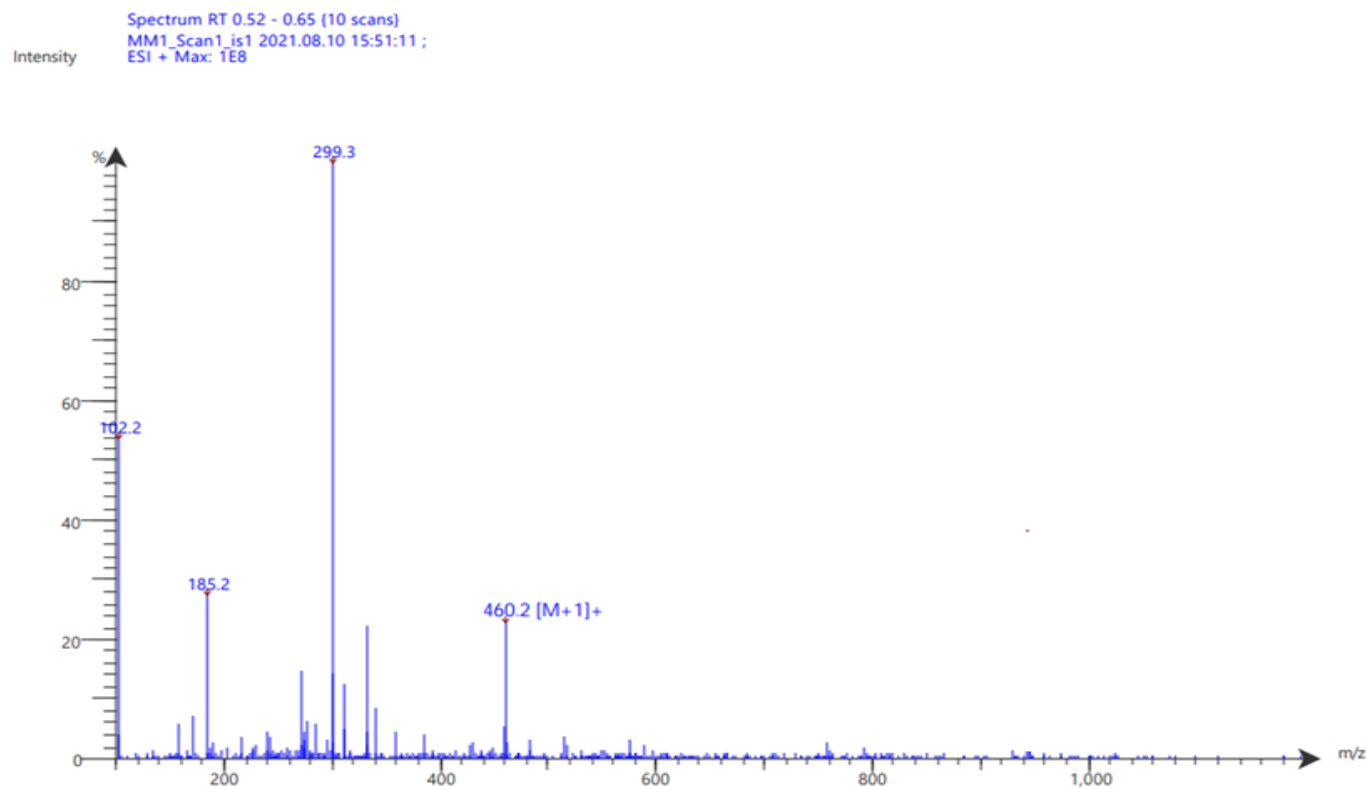


Figure S29: Mass of compound 6C

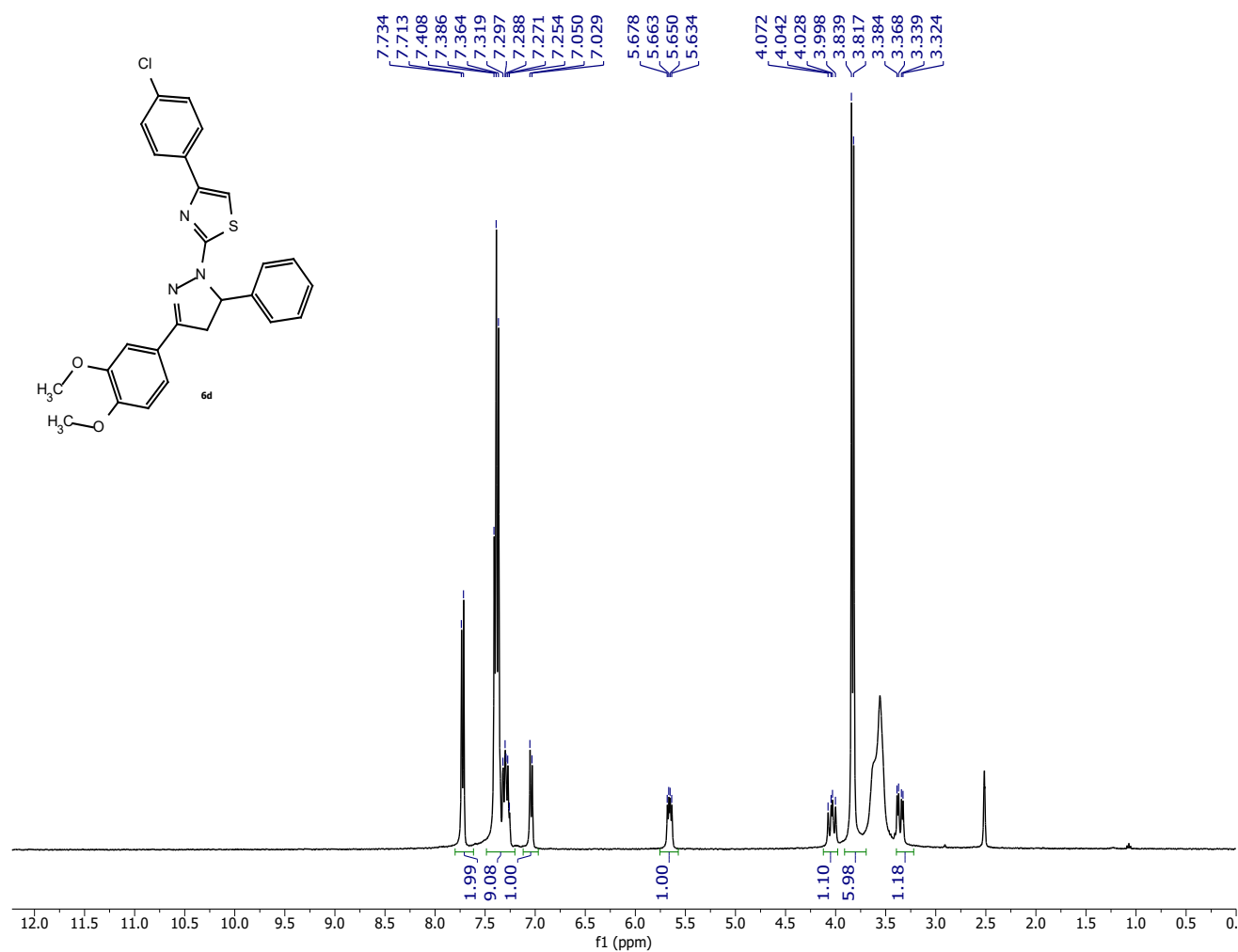


Figure S30: ¹H NMR of compound 6d

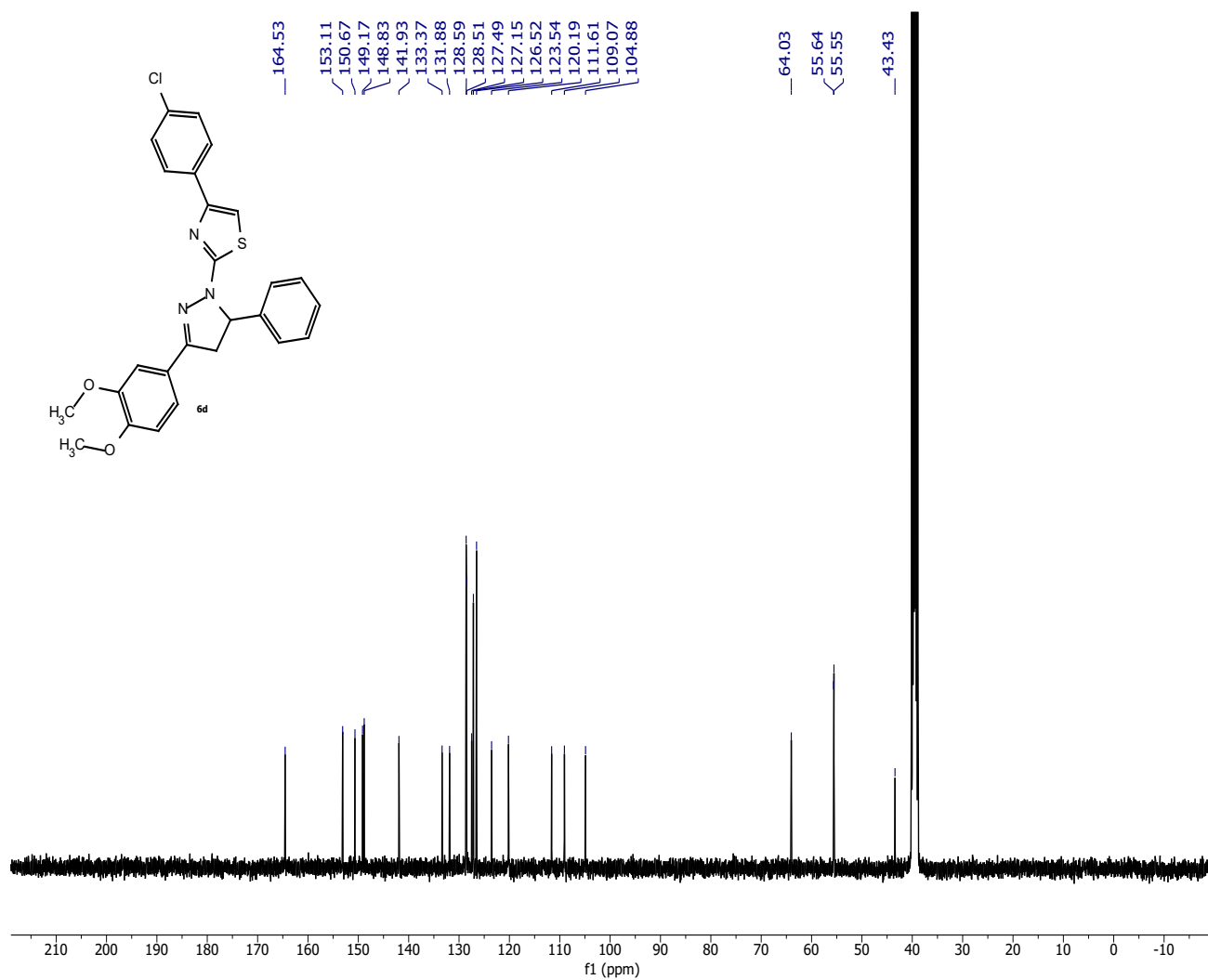


Figure S31: ¹³C NMR of compound 6d

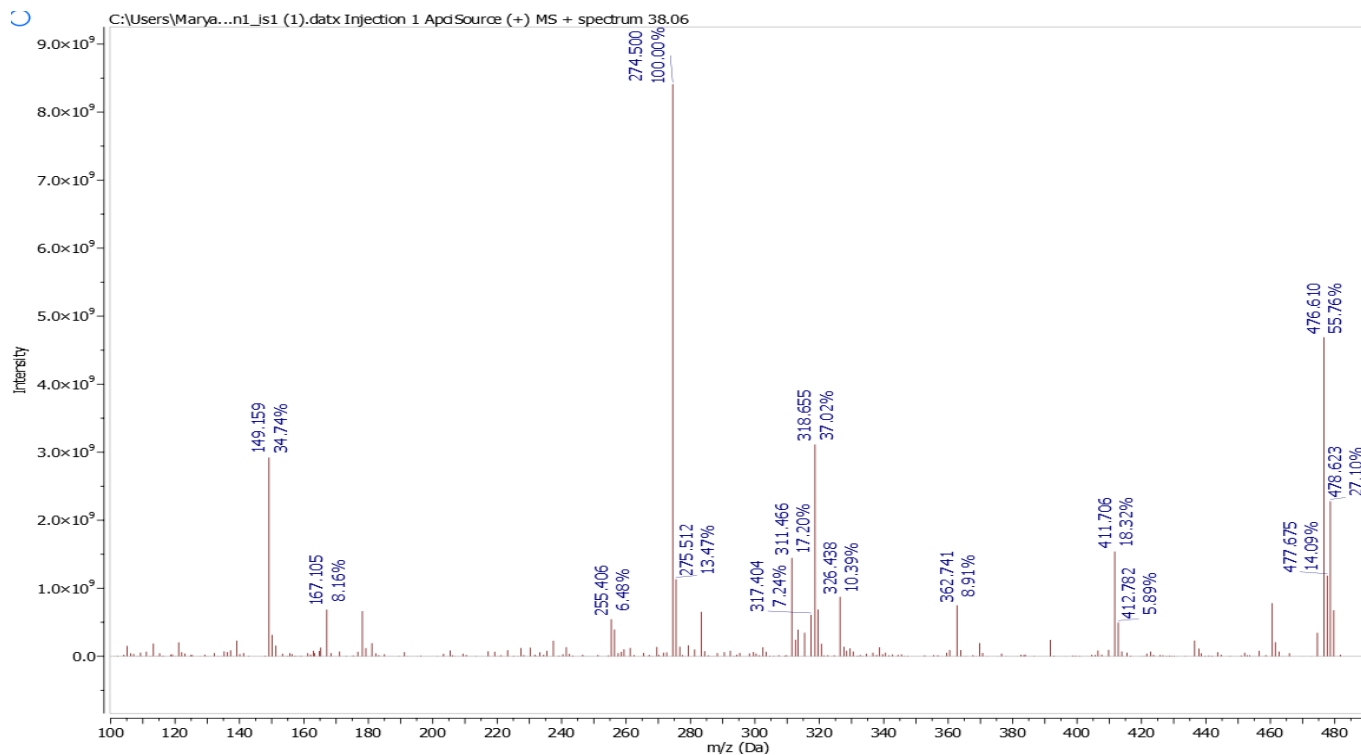
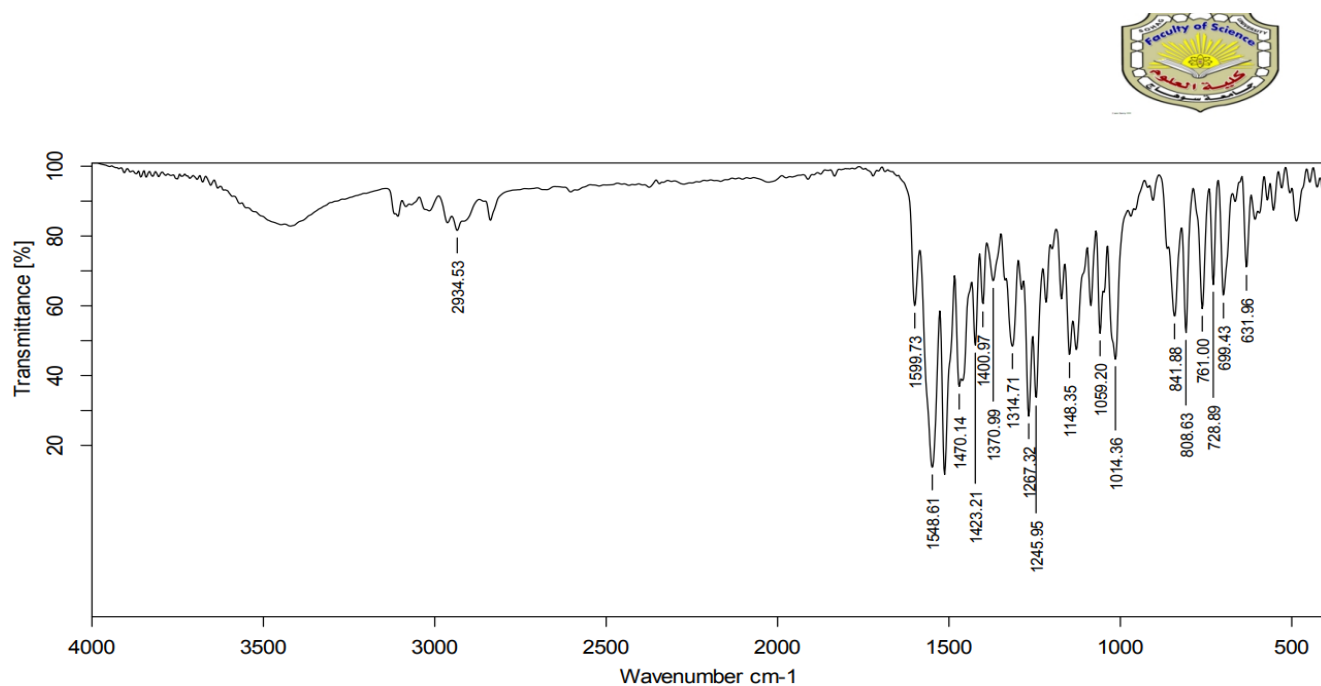


Figure S32: Mass of compound 6d



6d_TRANS.0

10:25:06 Ö

14/07/2021

Figure S33: IR of compound 6d

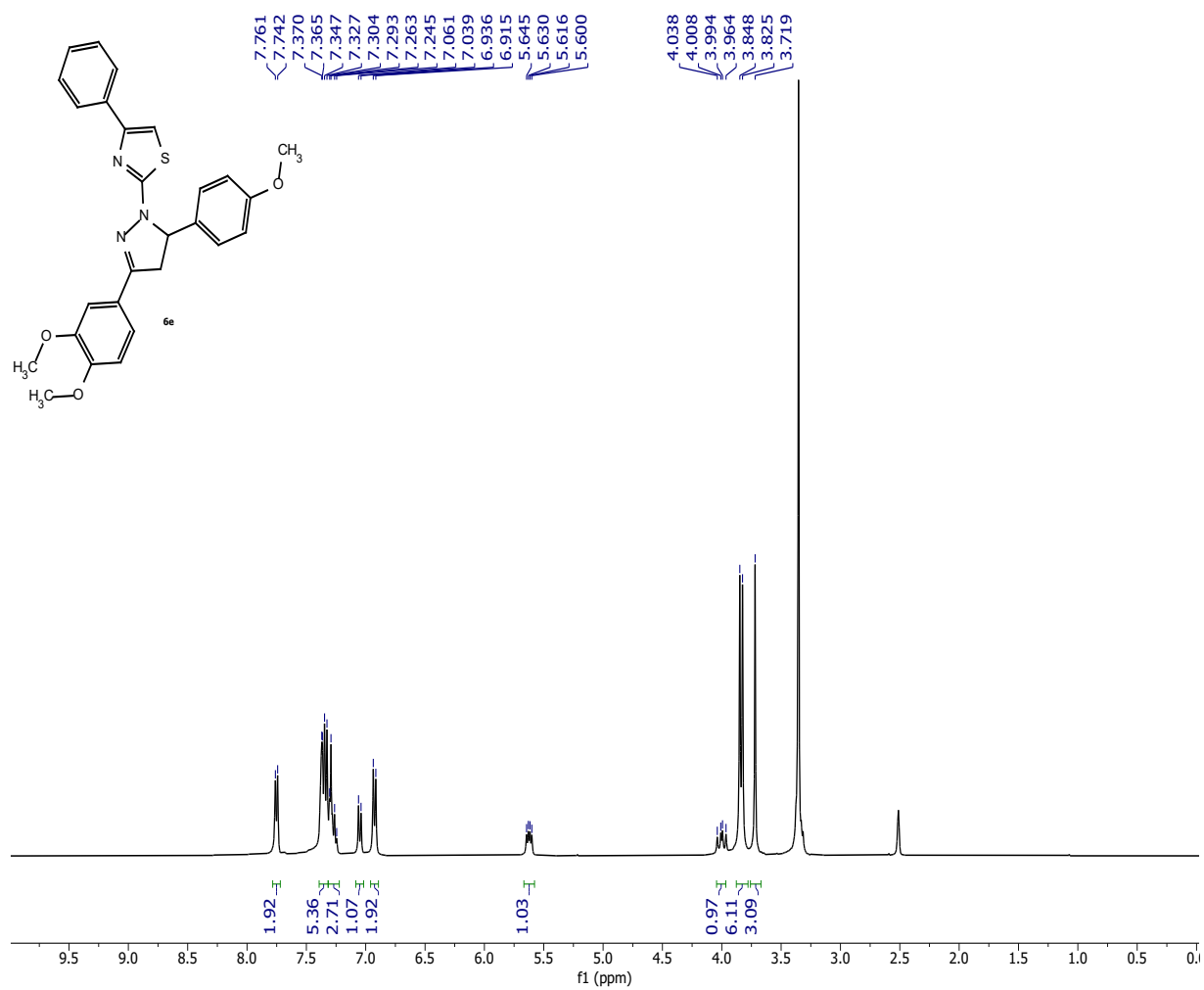


Figure S34: ^1H NMR of compound **6e**

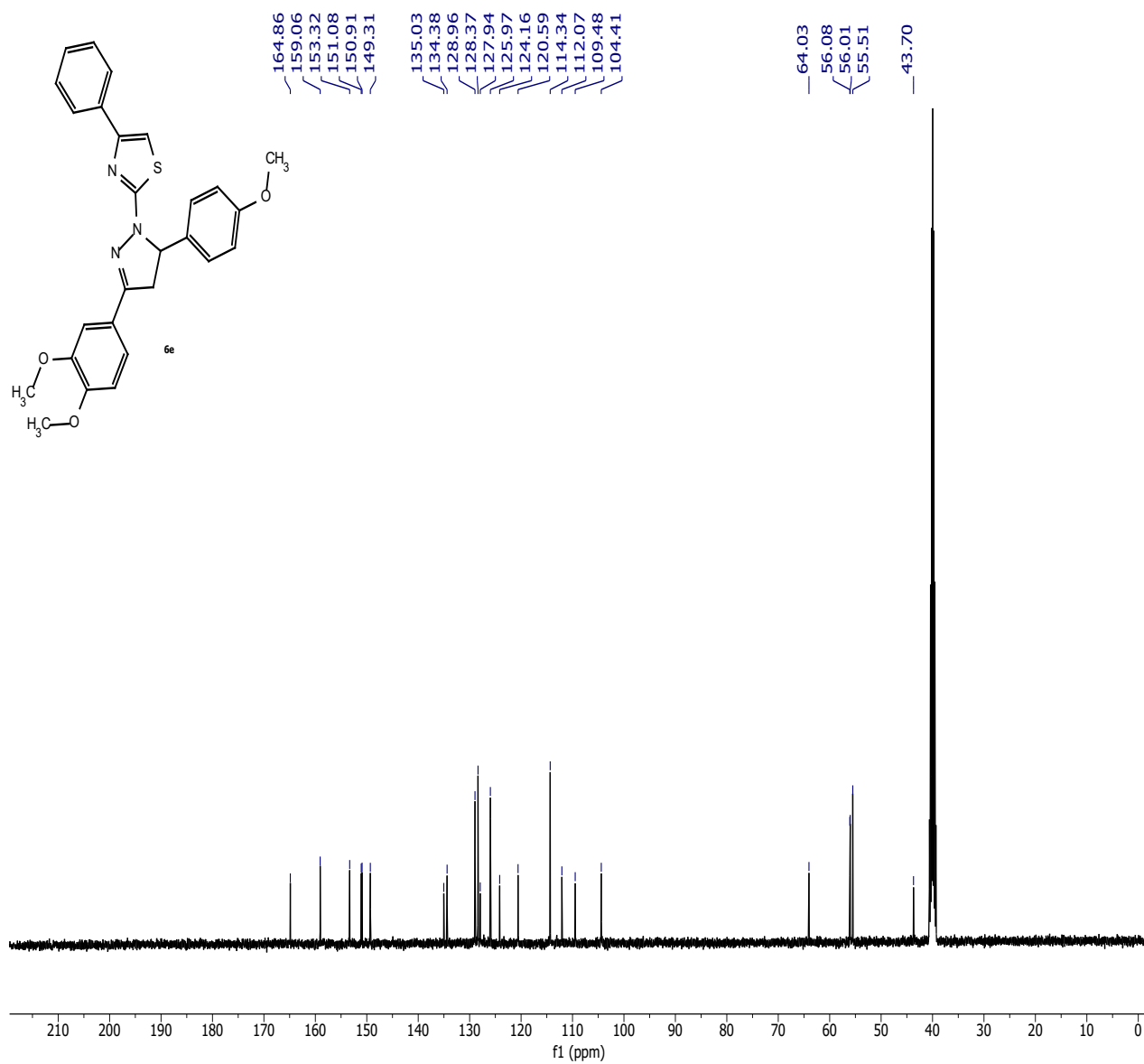


Figure S35: ^{13}C NMR of compound 6e

mariam-medhat-x1 #96 RT: 1.62 AV: 1 NL: 5.92E2
T: + c EI Full ms [40.00-1000.00]

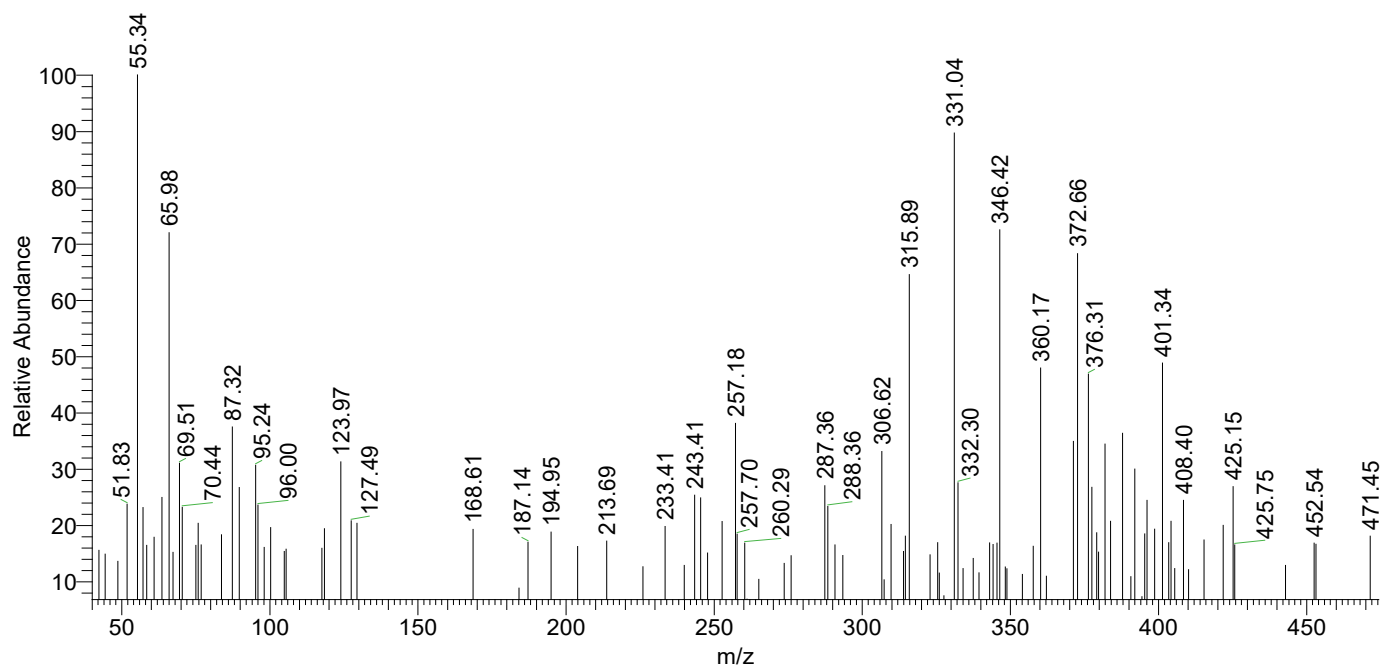
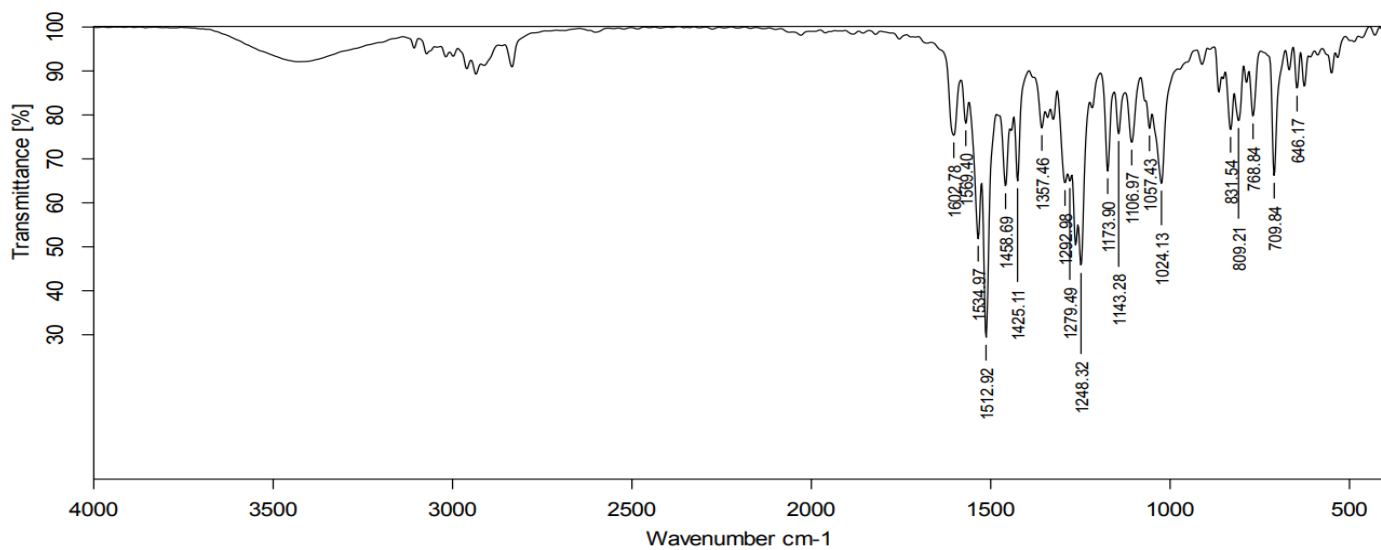


Figure S36: Mass of compound 6e



6e_TRANS.0

10:37:36 Ö

26/07/202

Figure S37: IR of compound 6e

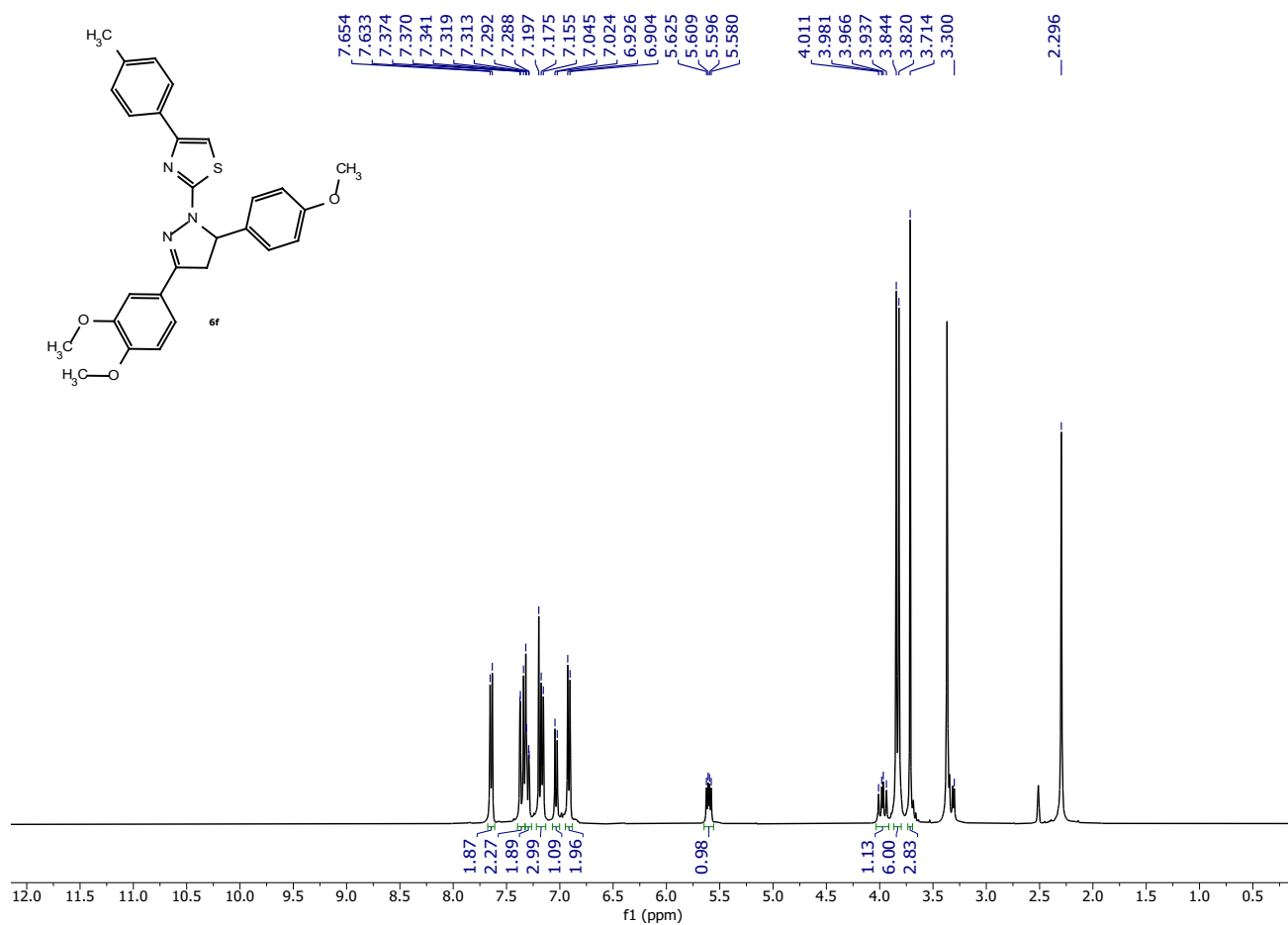


Figure S38: ¹H NMR of compound 6f

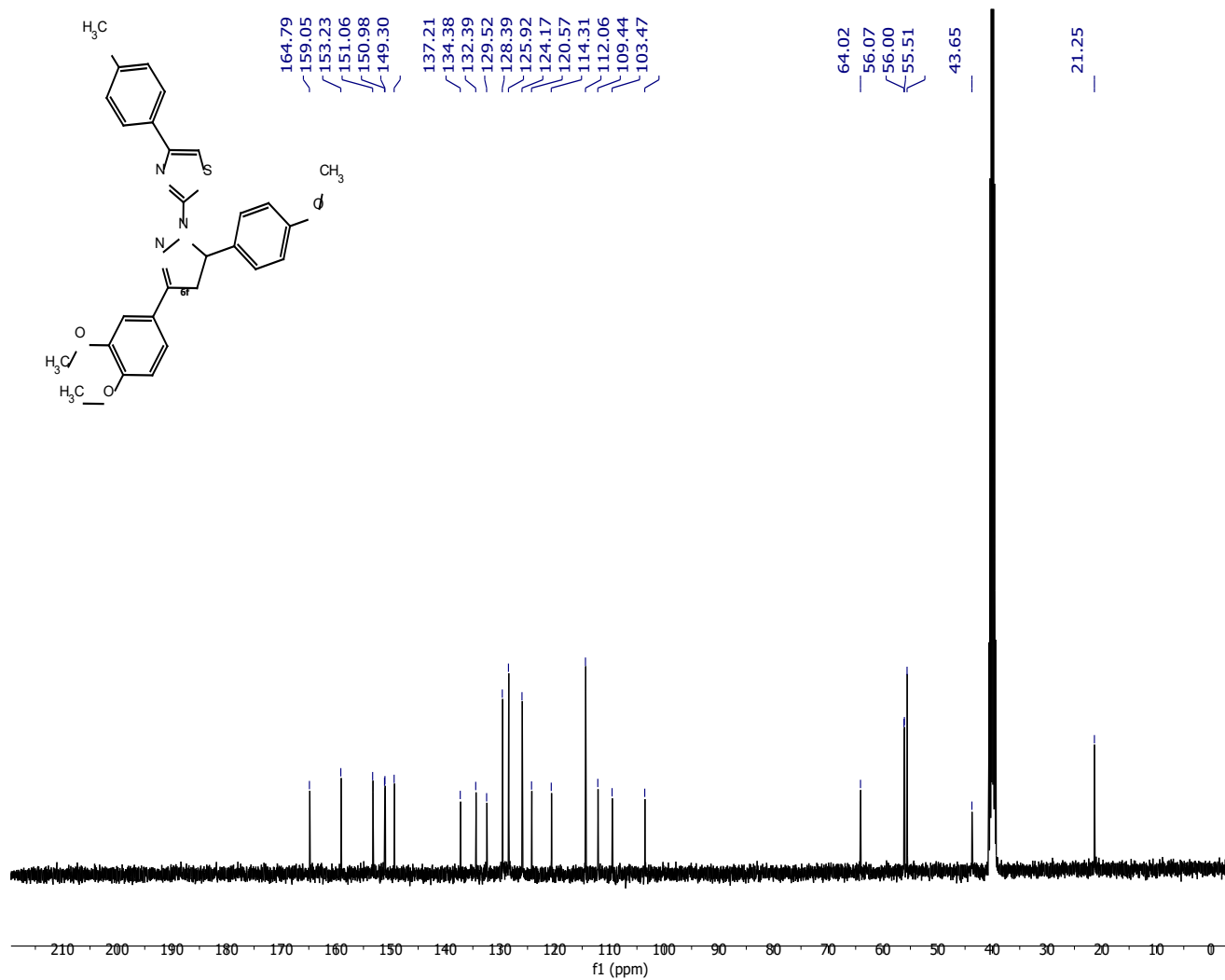


Figure S39: ^{13}C NMR of compound 6f

Spectrum RT 0.45 - 0.56 (9 scans)
X2_Scan1_is1 2021.08.10 16:35:42 ;
ESI +

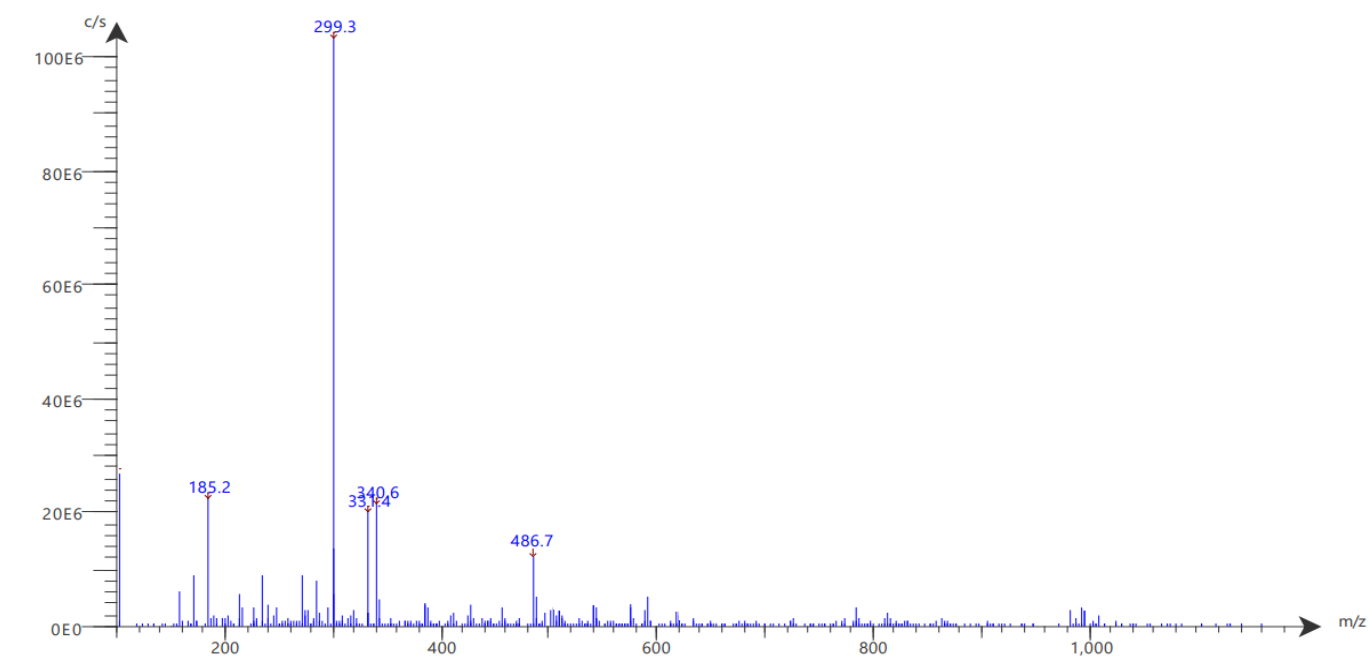


Figure S40: Mass of compound 6f

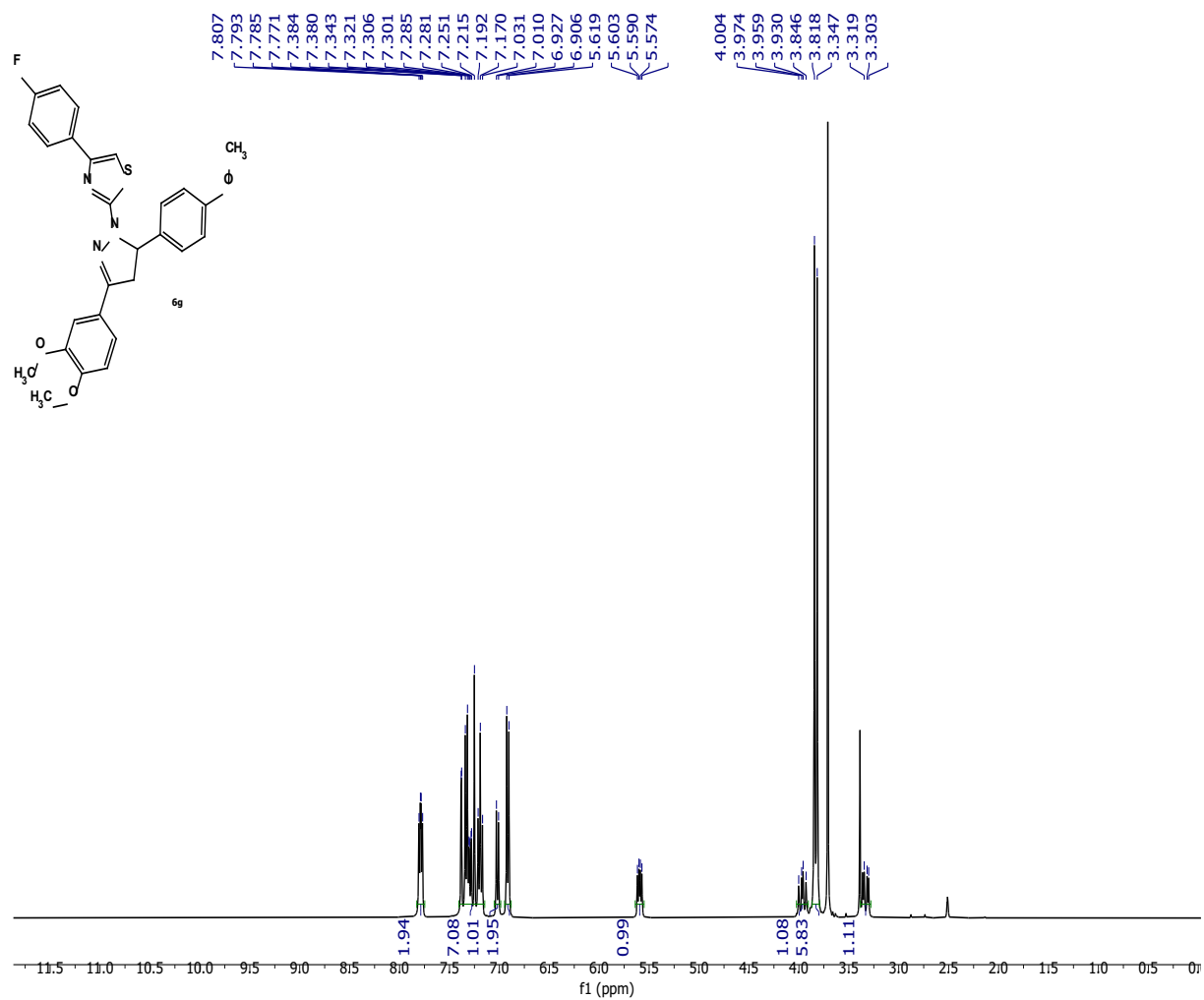


Figure S41: ¹H NMR of compound 6g

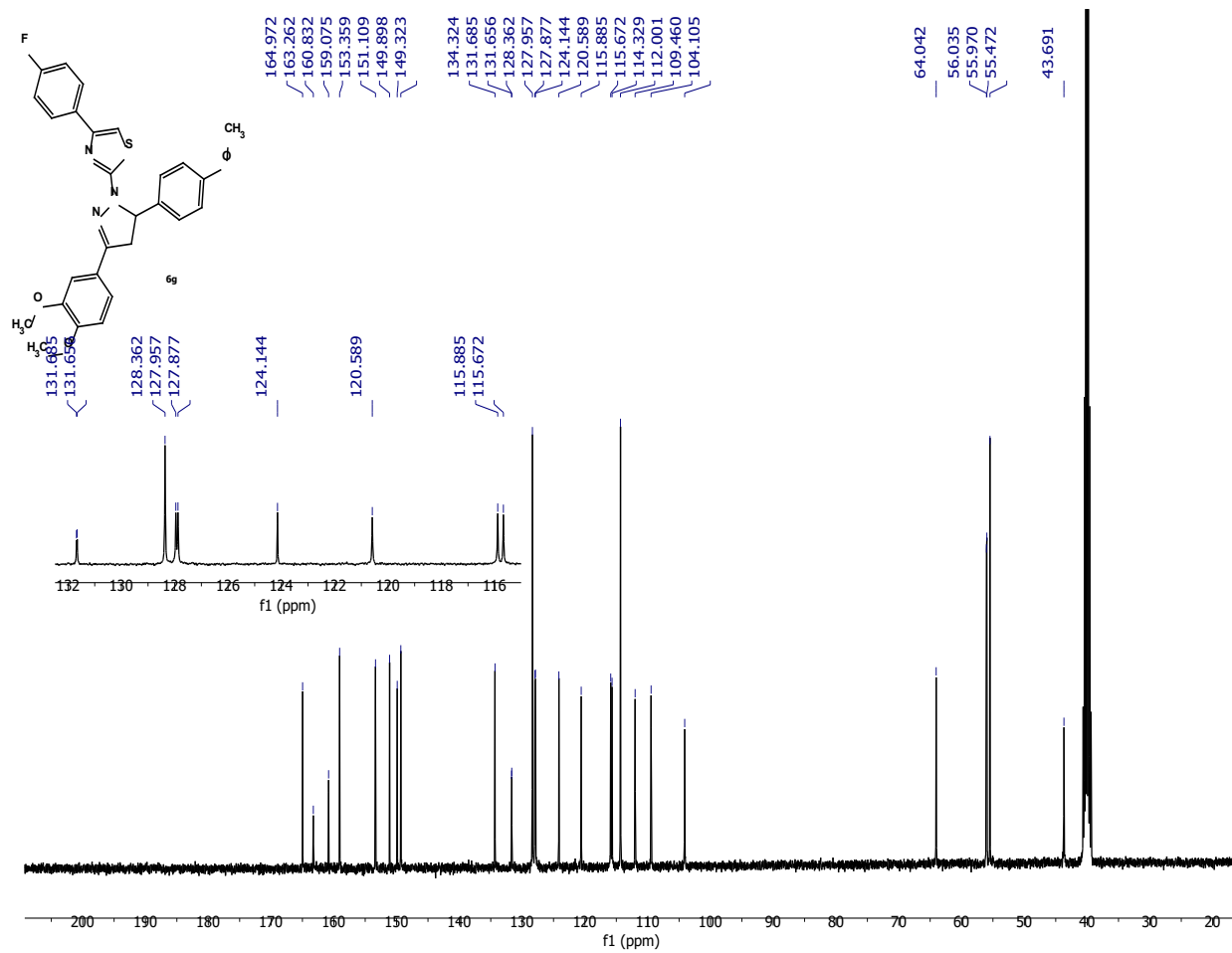


Figure S42: ¹³CNMR of compound 6g

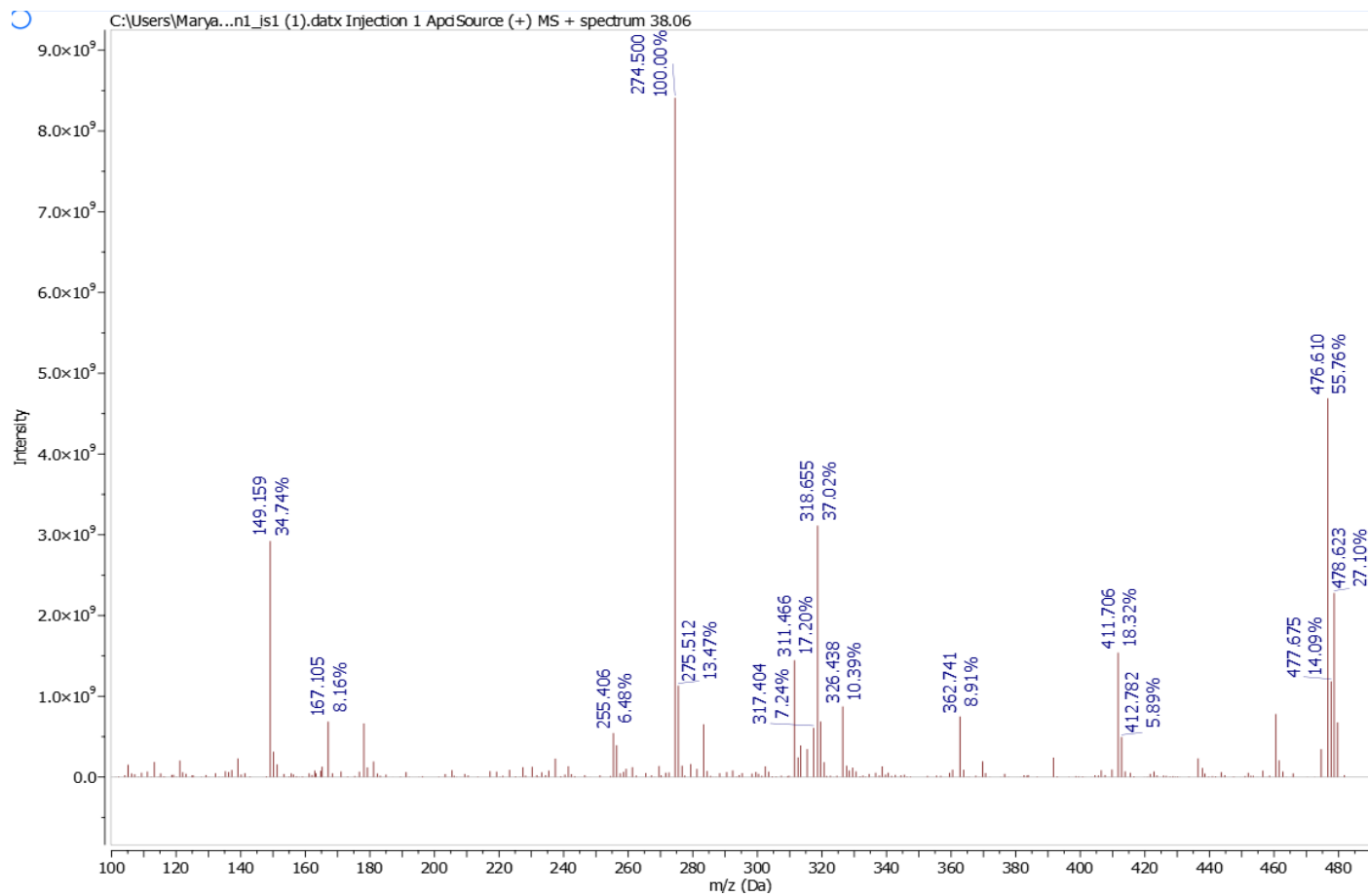


Figure S43: Mass of compound 6g

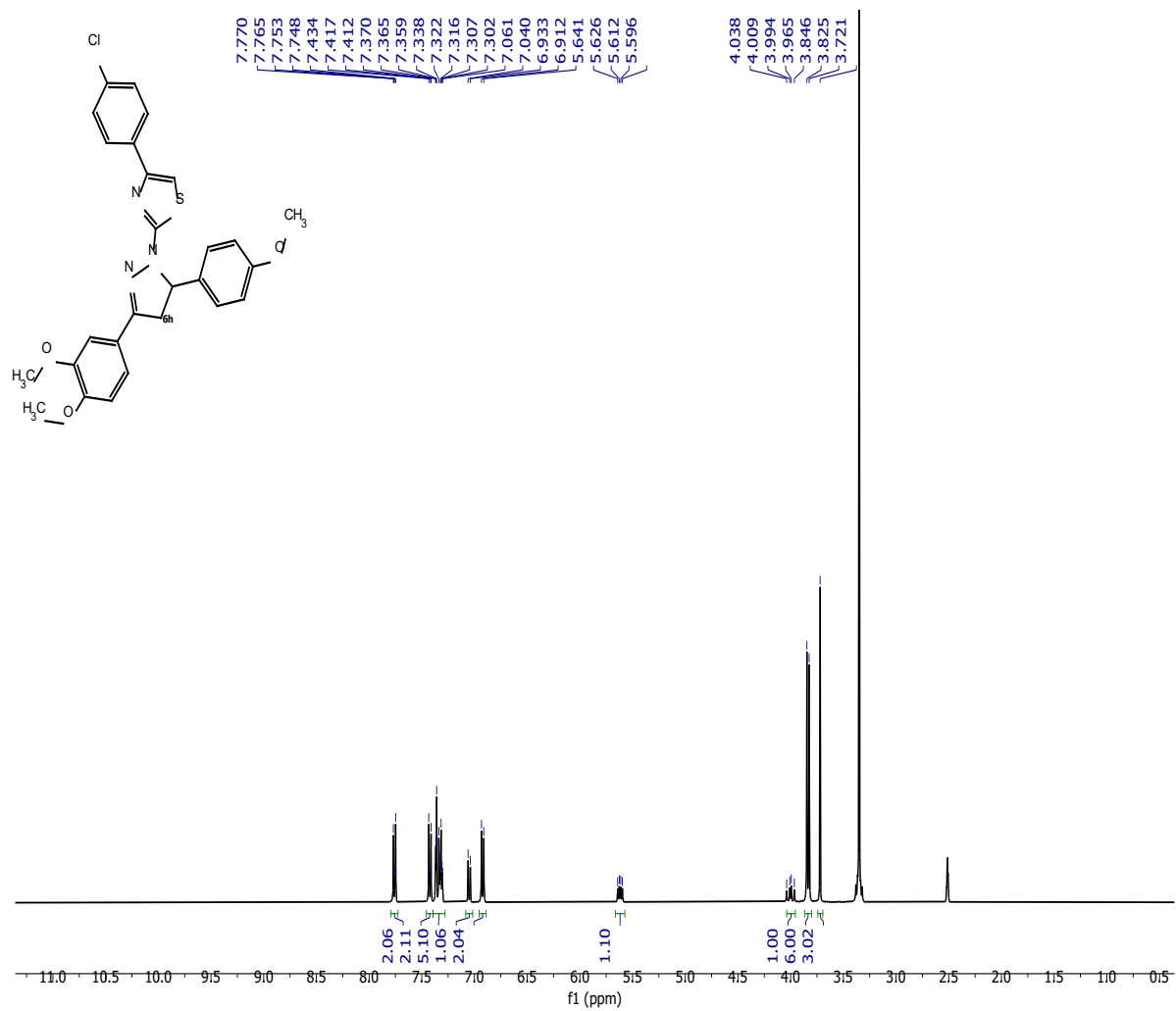


Figure S44: ¹H NMR of compound 6h

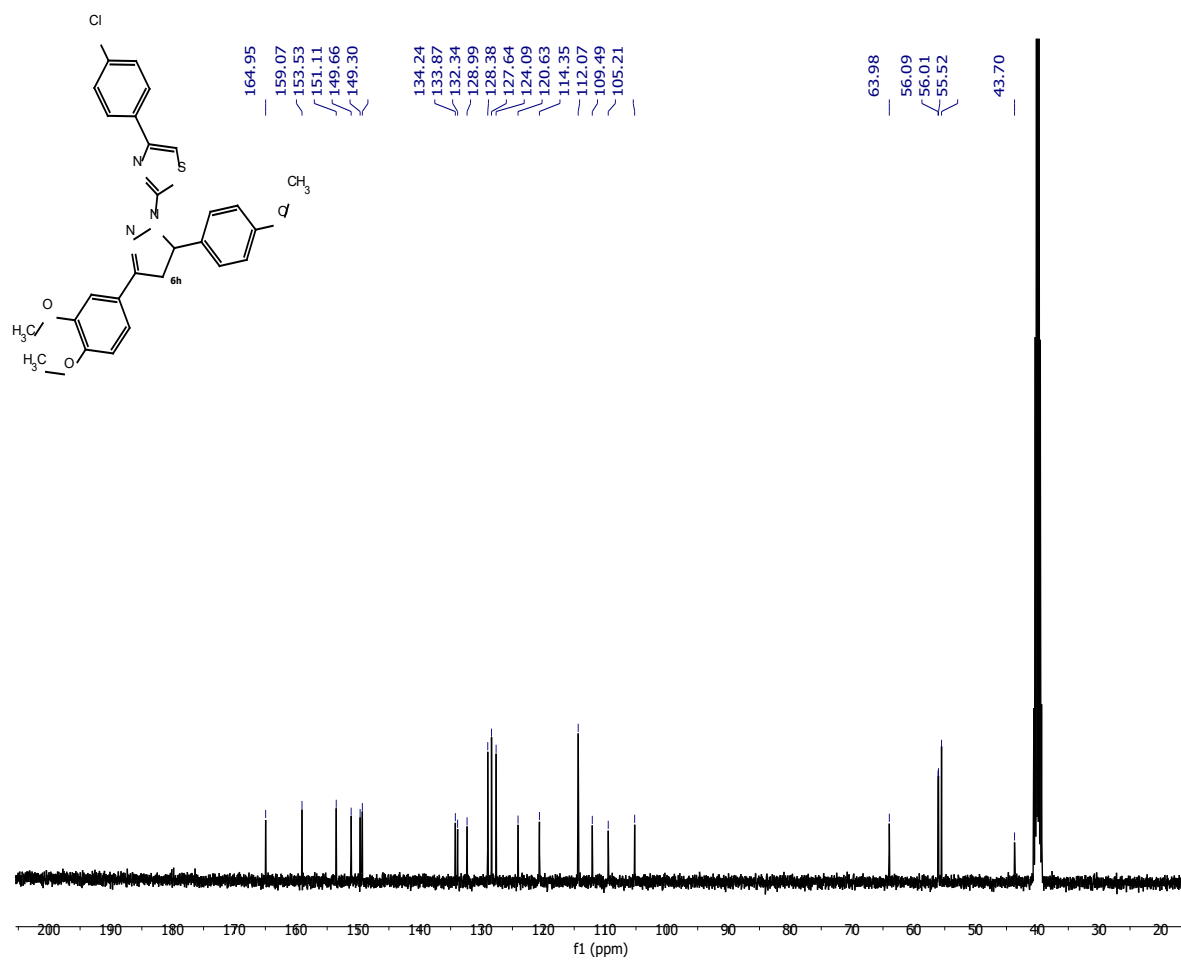


Figure S45: ^{13}C NMR of compound 6h

Spectrum RT 0.51 - 0.66 (11 scans)
MM4_Scan2.is2 2021.08.10 15:59:09 ;
ESI - Max: 4.1E6

Intensity

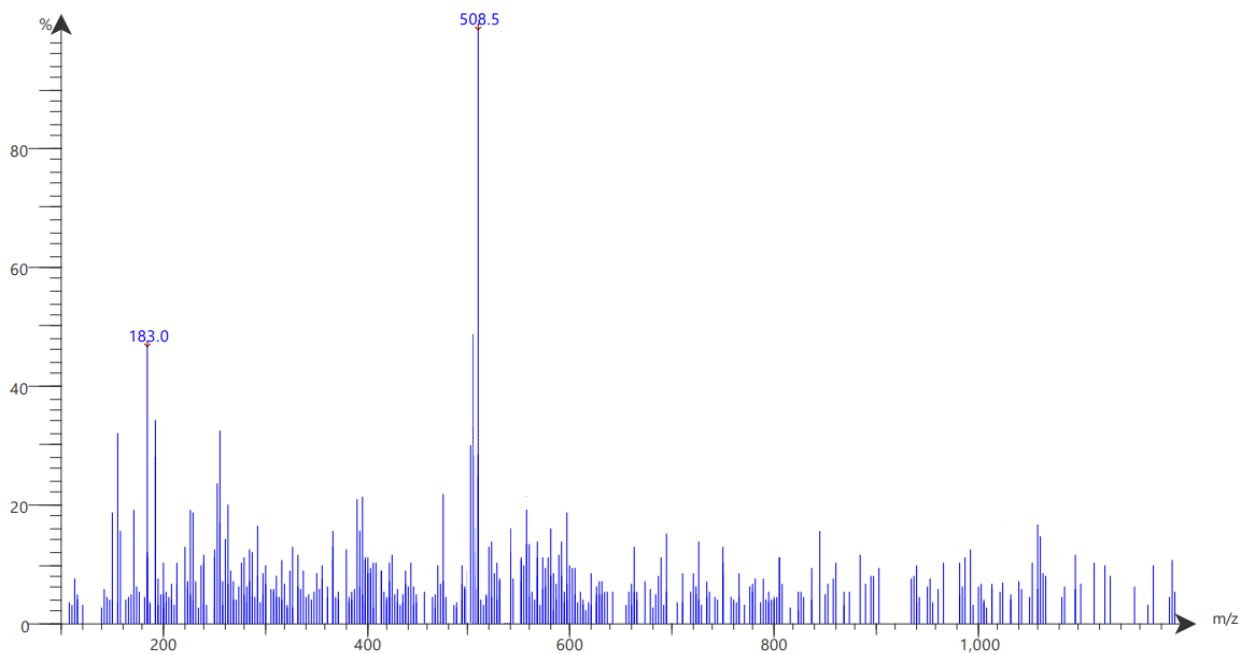
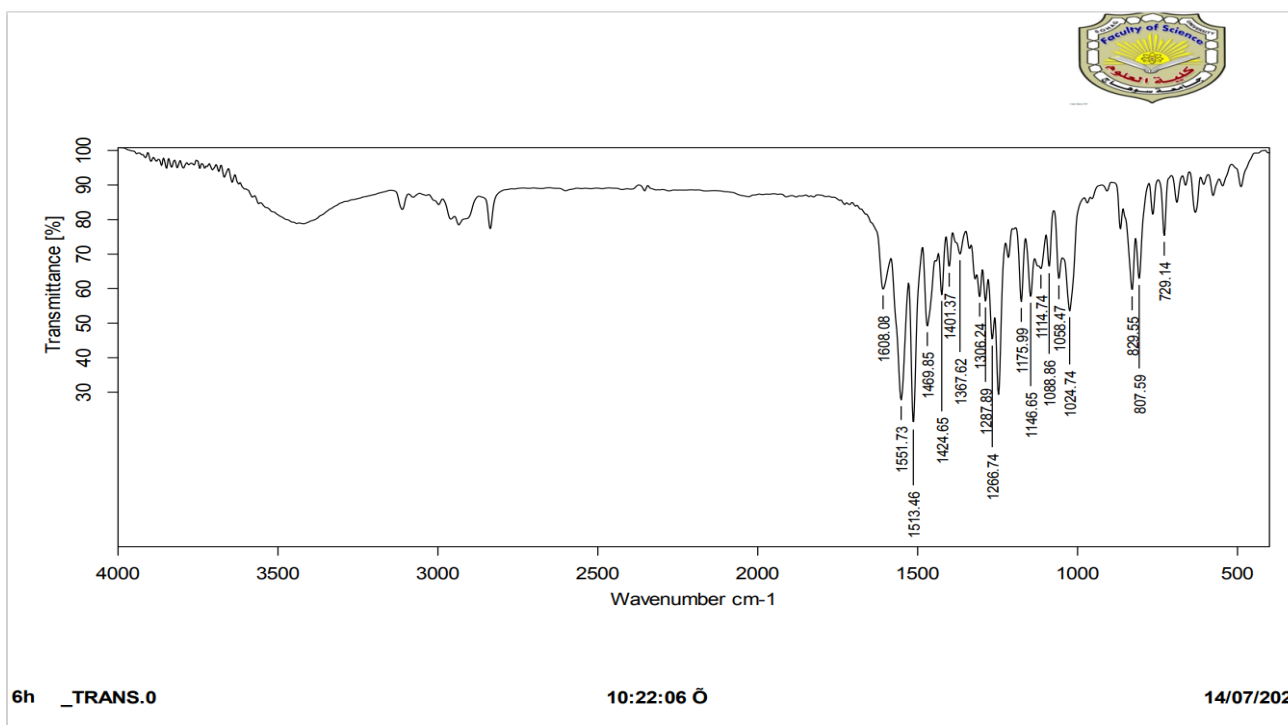


Figure S46: Mass of compound 6h



6h _TRANS.0

10:22:06 O

14/07/2021

Figure S47: IR of compound 6h

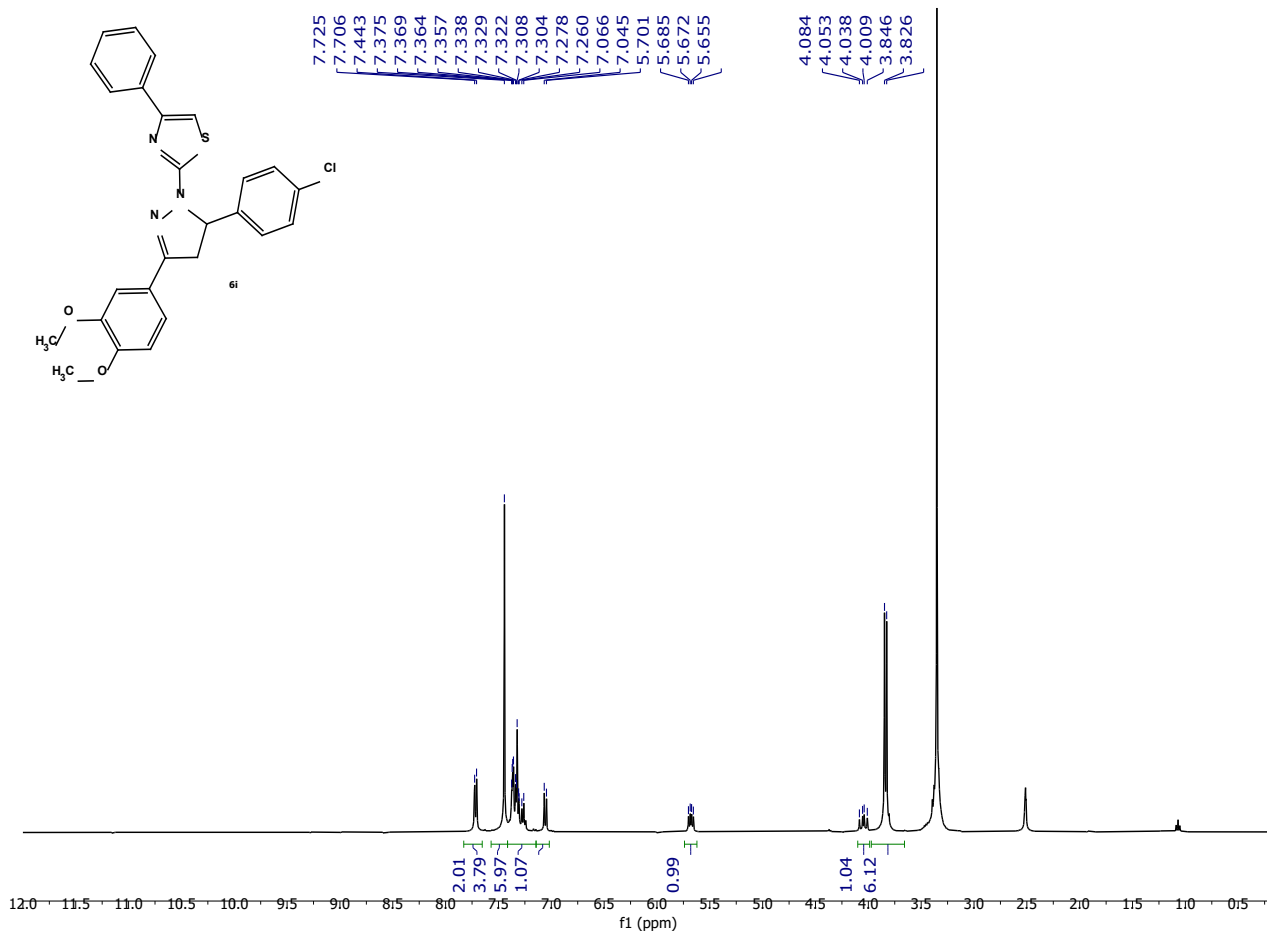


Figure S48: ¹H NMR of compound 6i

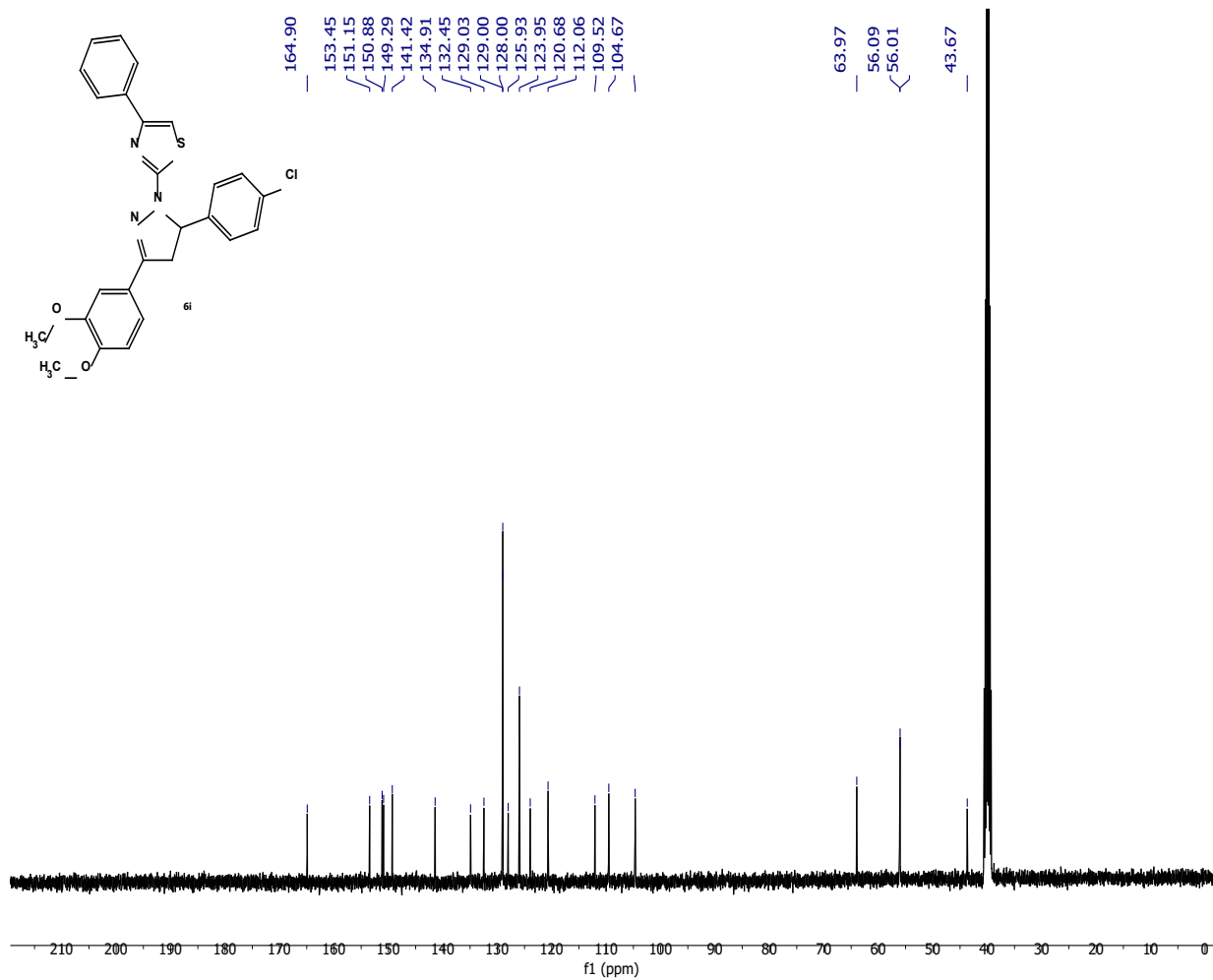


Figure S49: ¹³C NMR of compound 6i

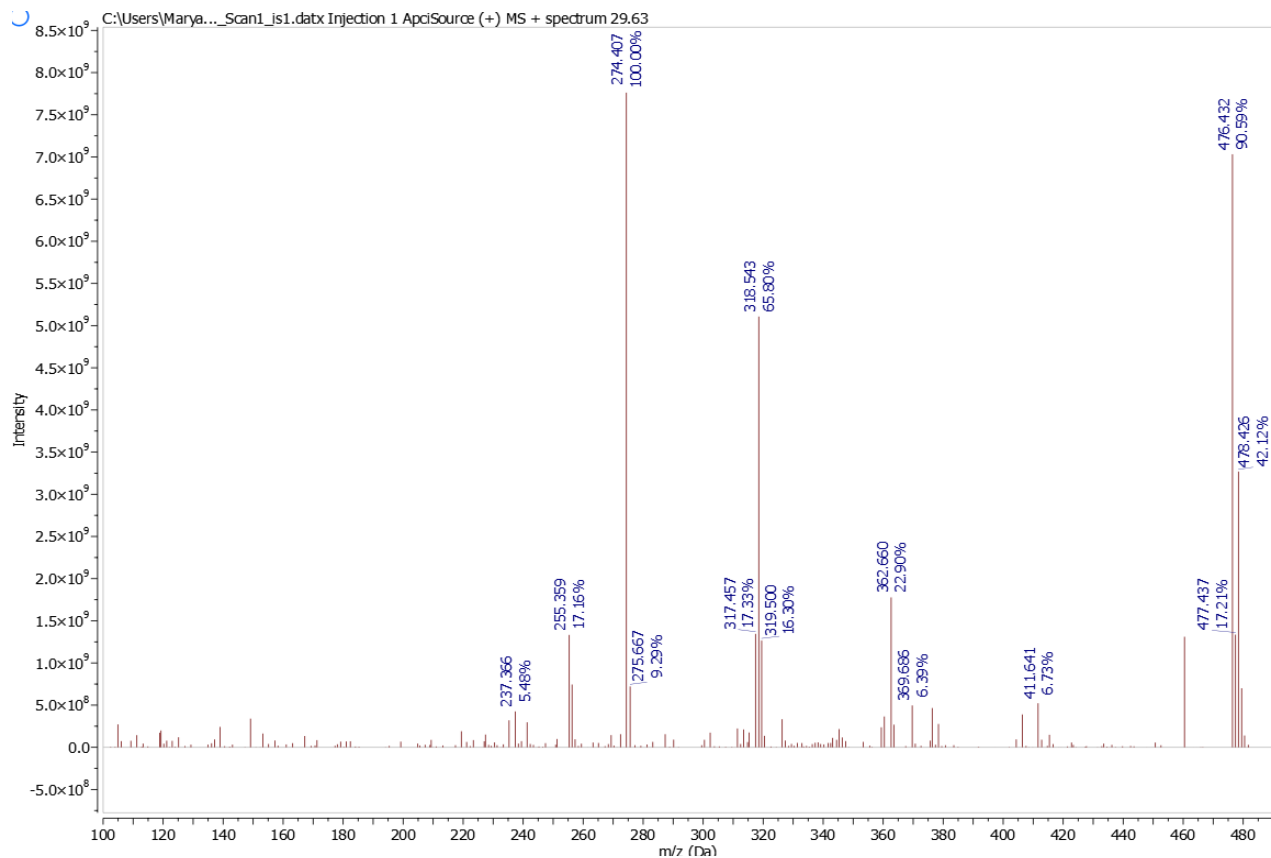


Figure S50: Mass of compound 6i

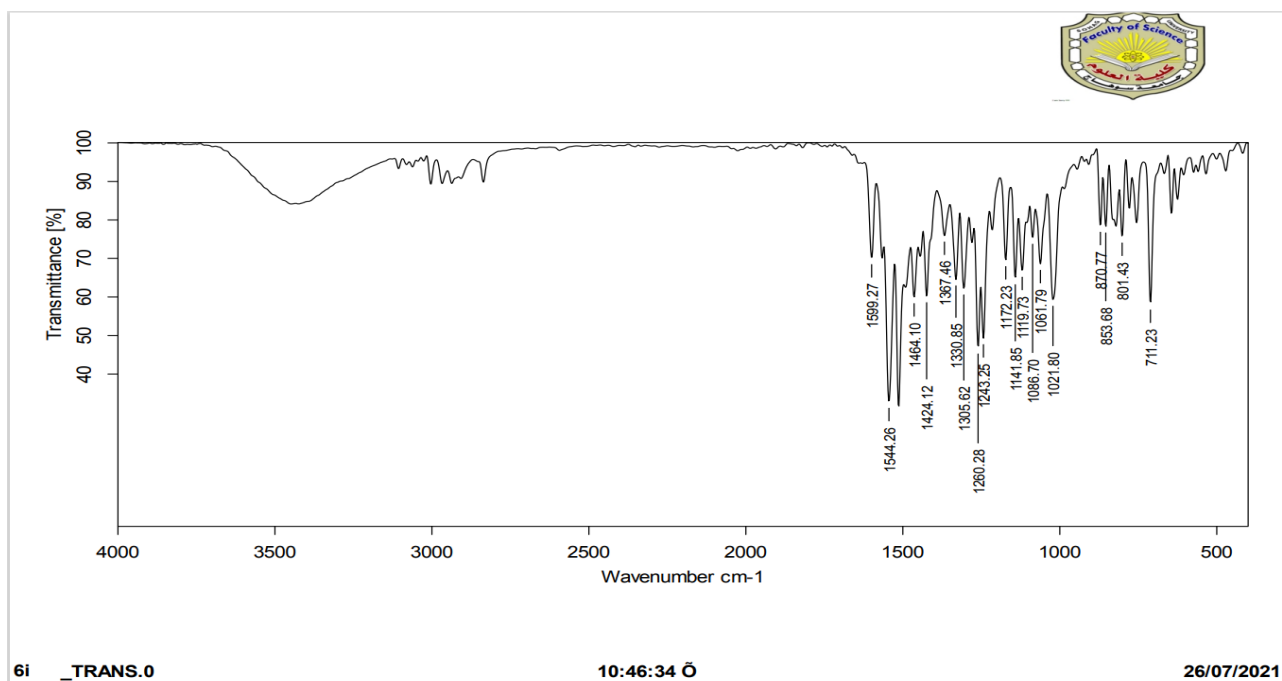


Figure S51: IR of compound 6i

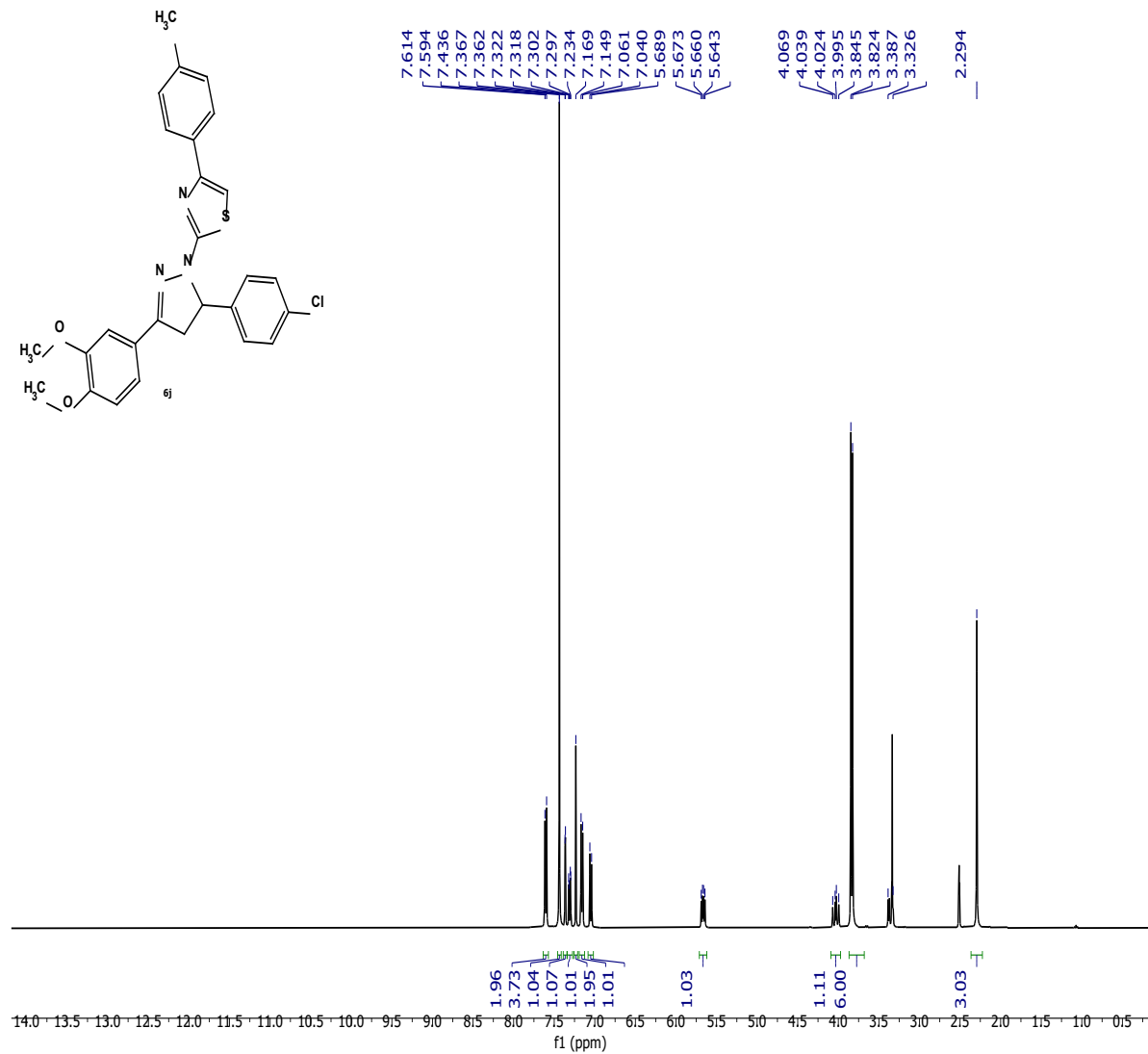


Figure S52: ¹H NMR of compound 6j

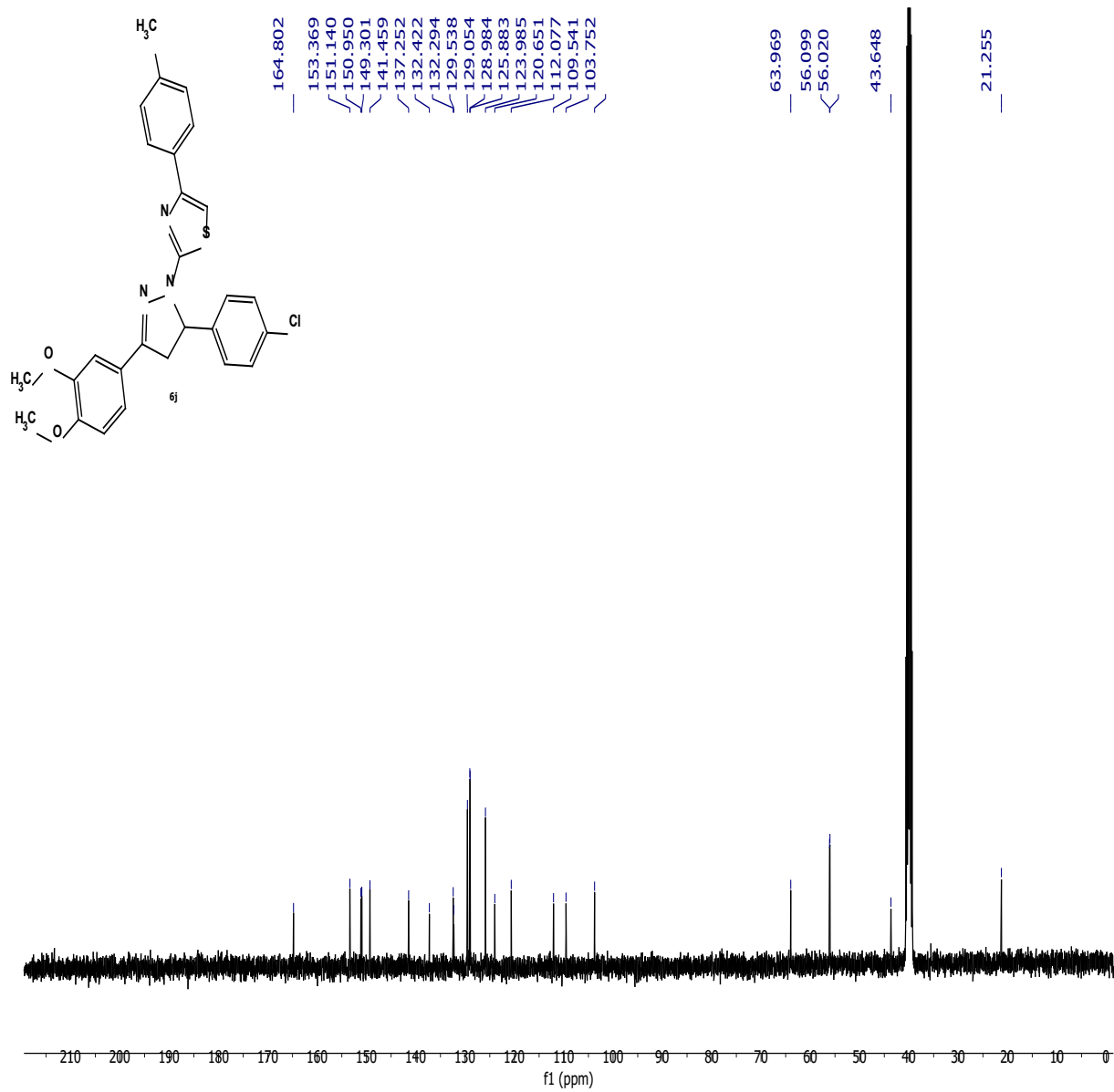


Figure S53: ¹³C NMR of compound 6j

Spectrum RT 0.51 - 0.68 (13 scans)
MQ32_Scan1.js1 2021.08.10 16:49:31 ;
ESI + Max: 9.5E7

Intensity

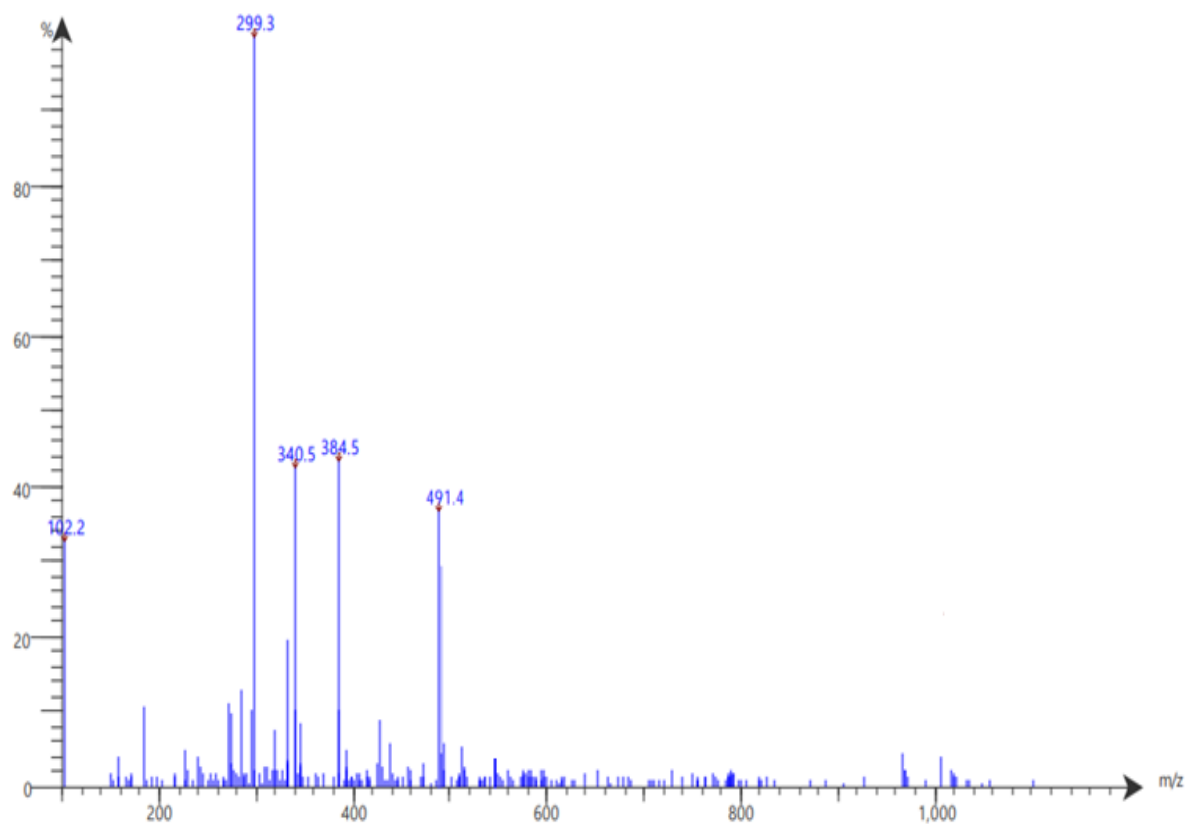


Figure S54: Mass of compound 6j

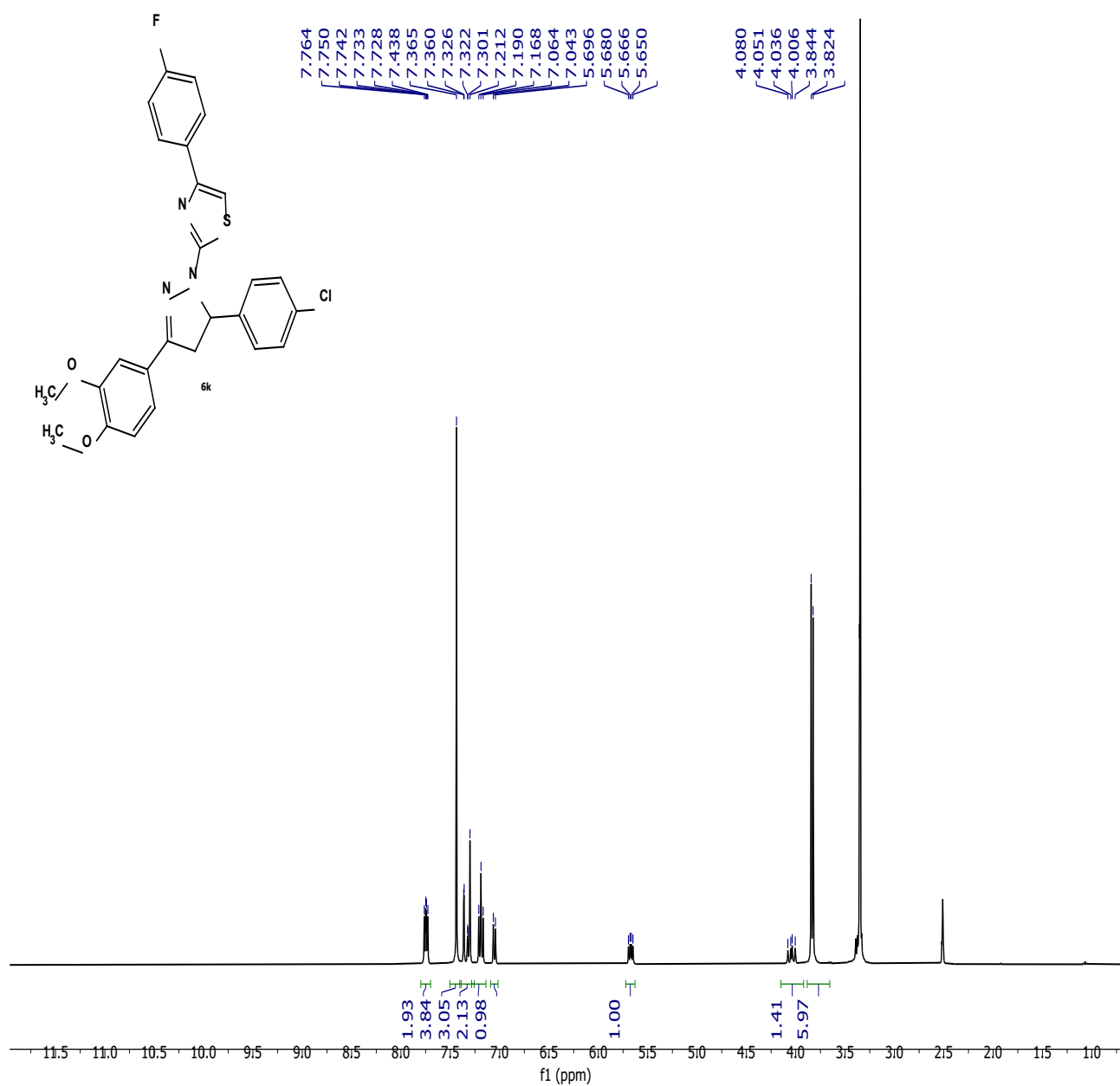


Figure S55: ¹H NMR of compound 6k

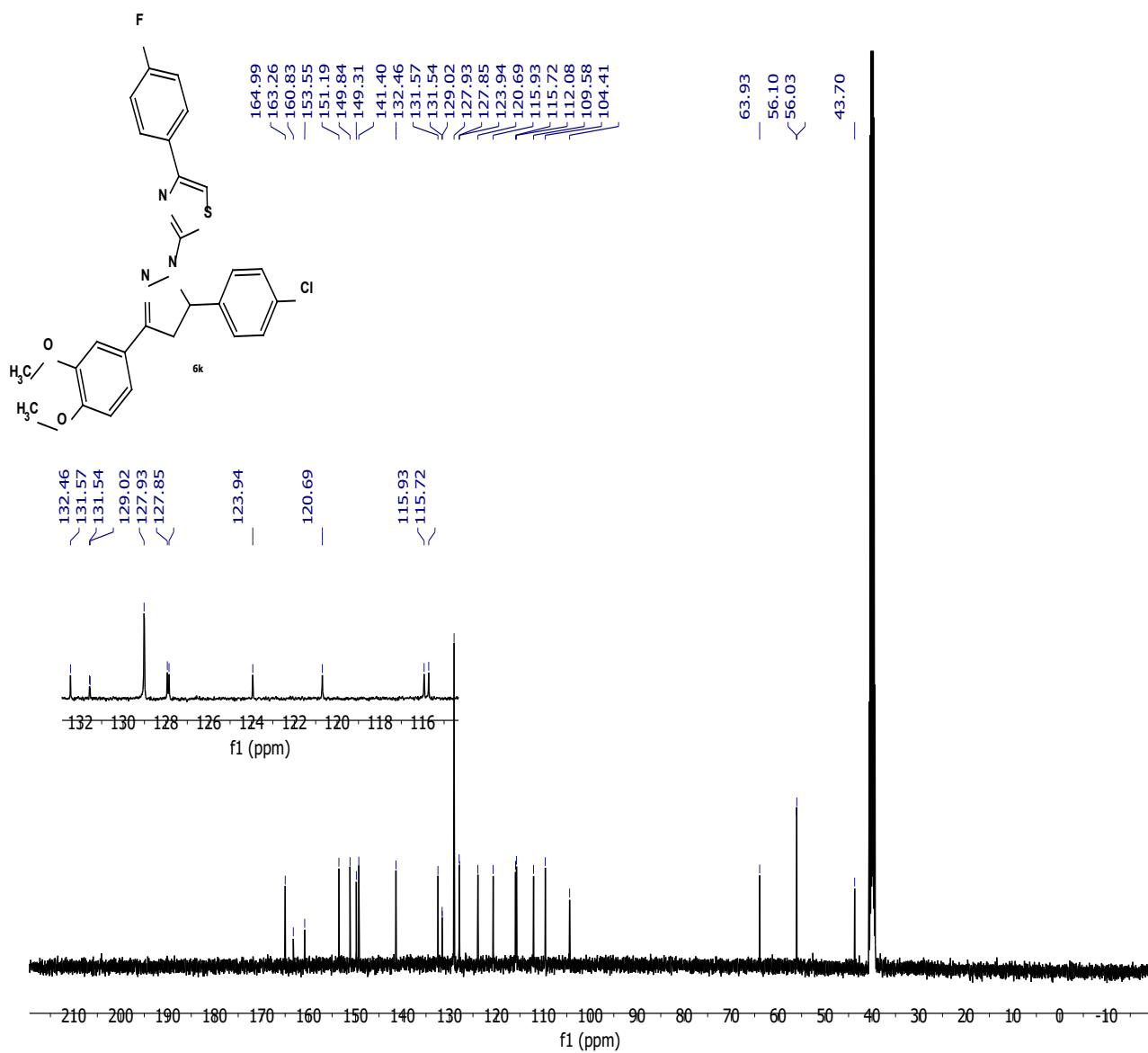


Figure S56: ^{13}C NMR of compound 6k

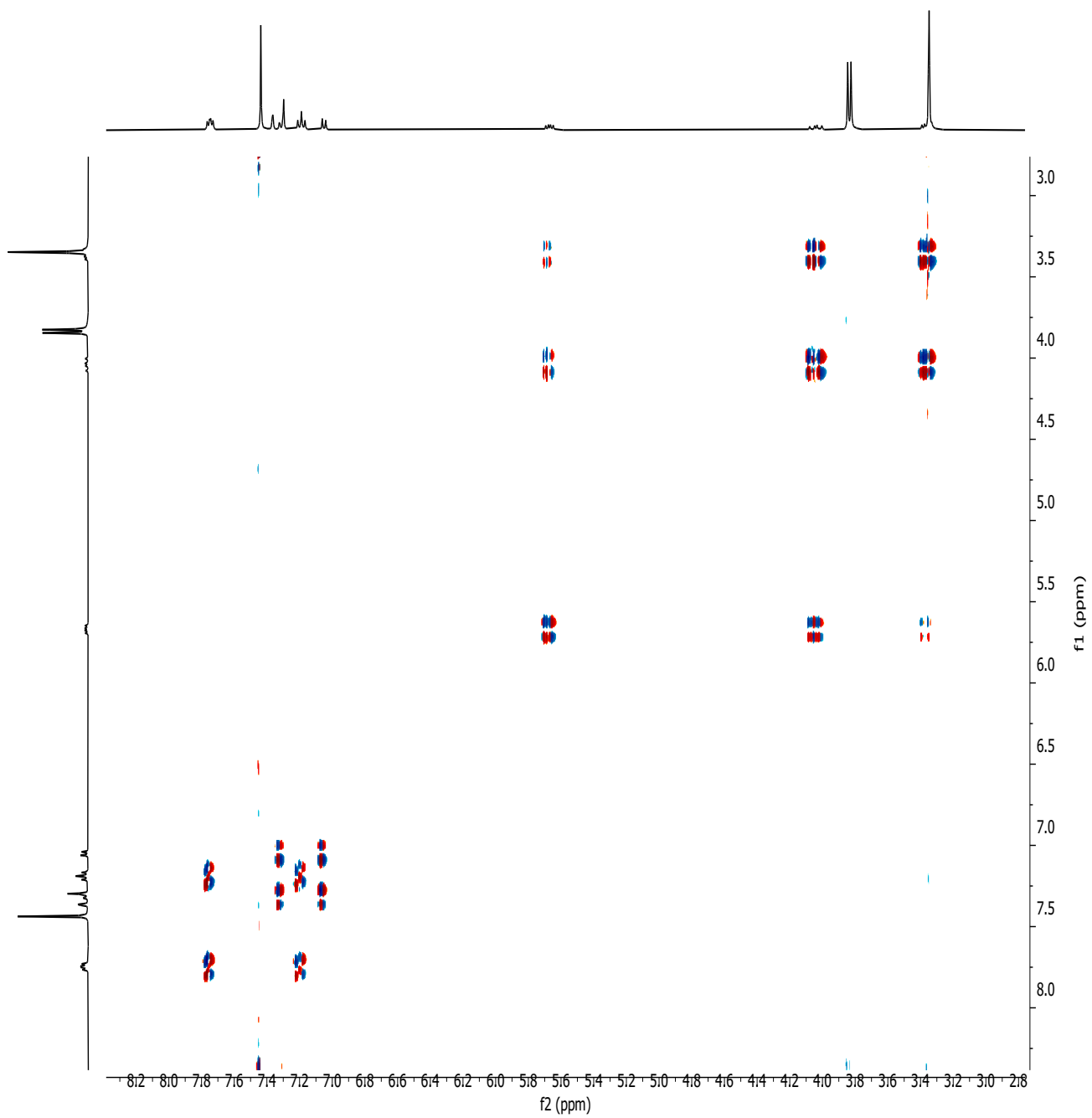


Figure S57: ^1H - ^1H Cosy of compound 6k

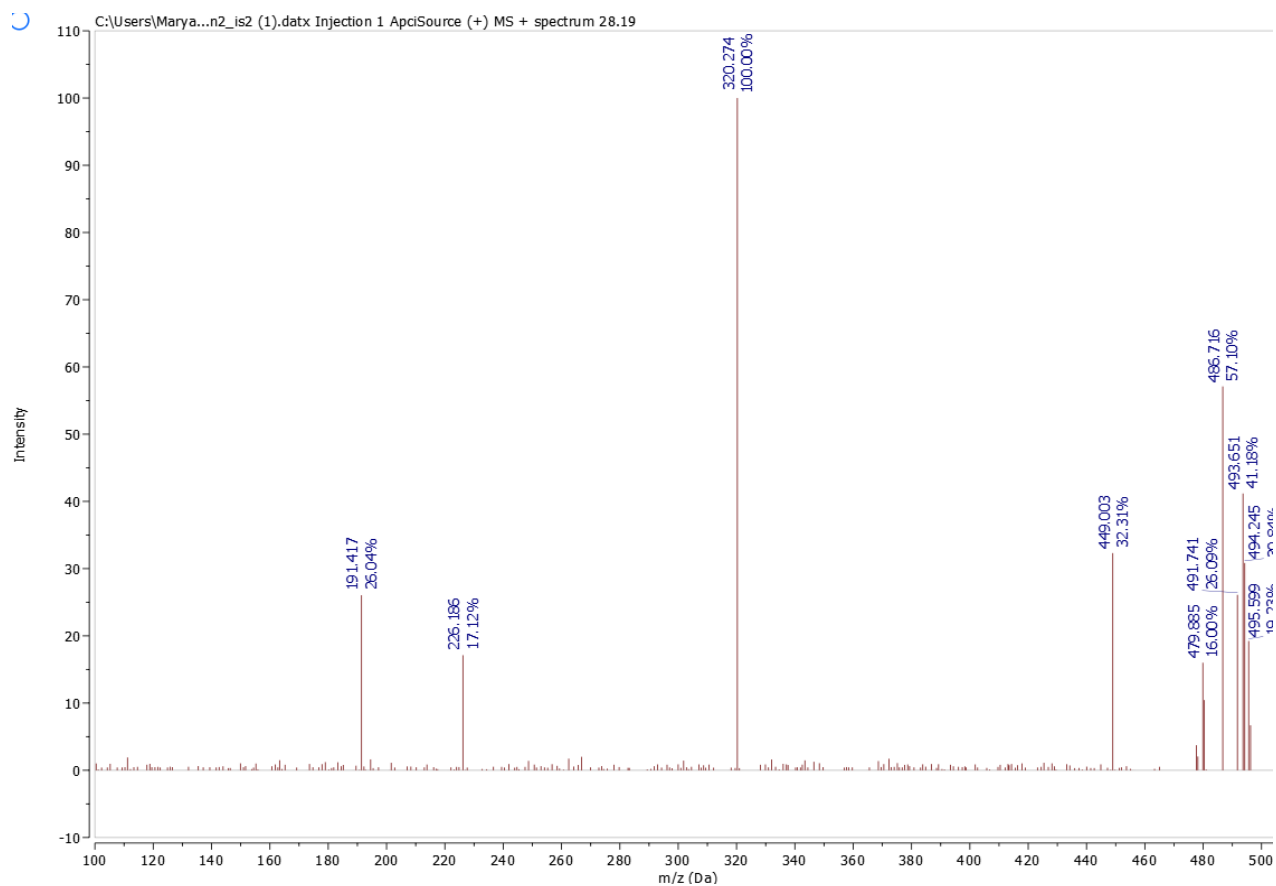


Figure S58: Mass of compound 6K

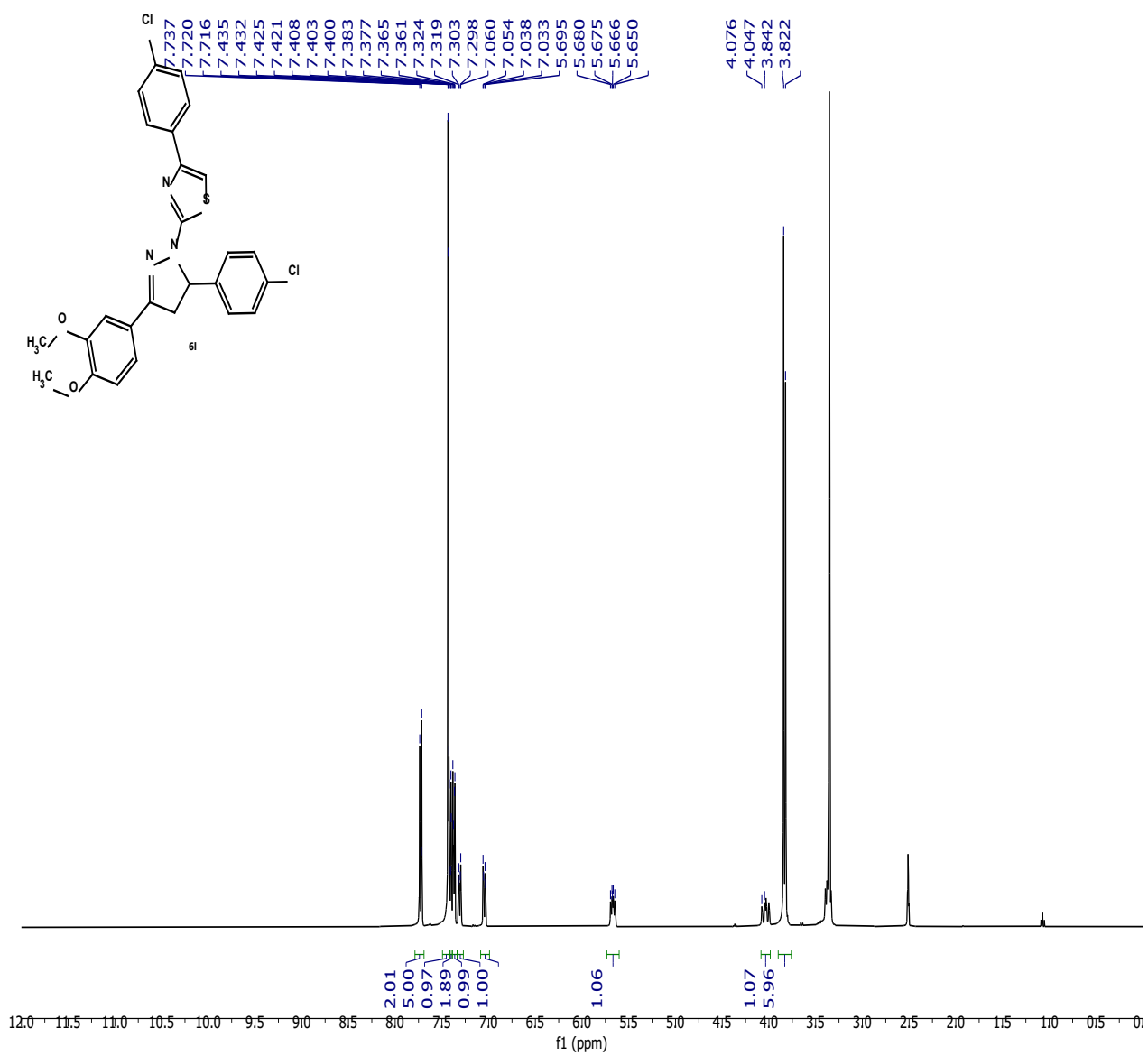


Figure S59: ¹H NMR of compound 6l

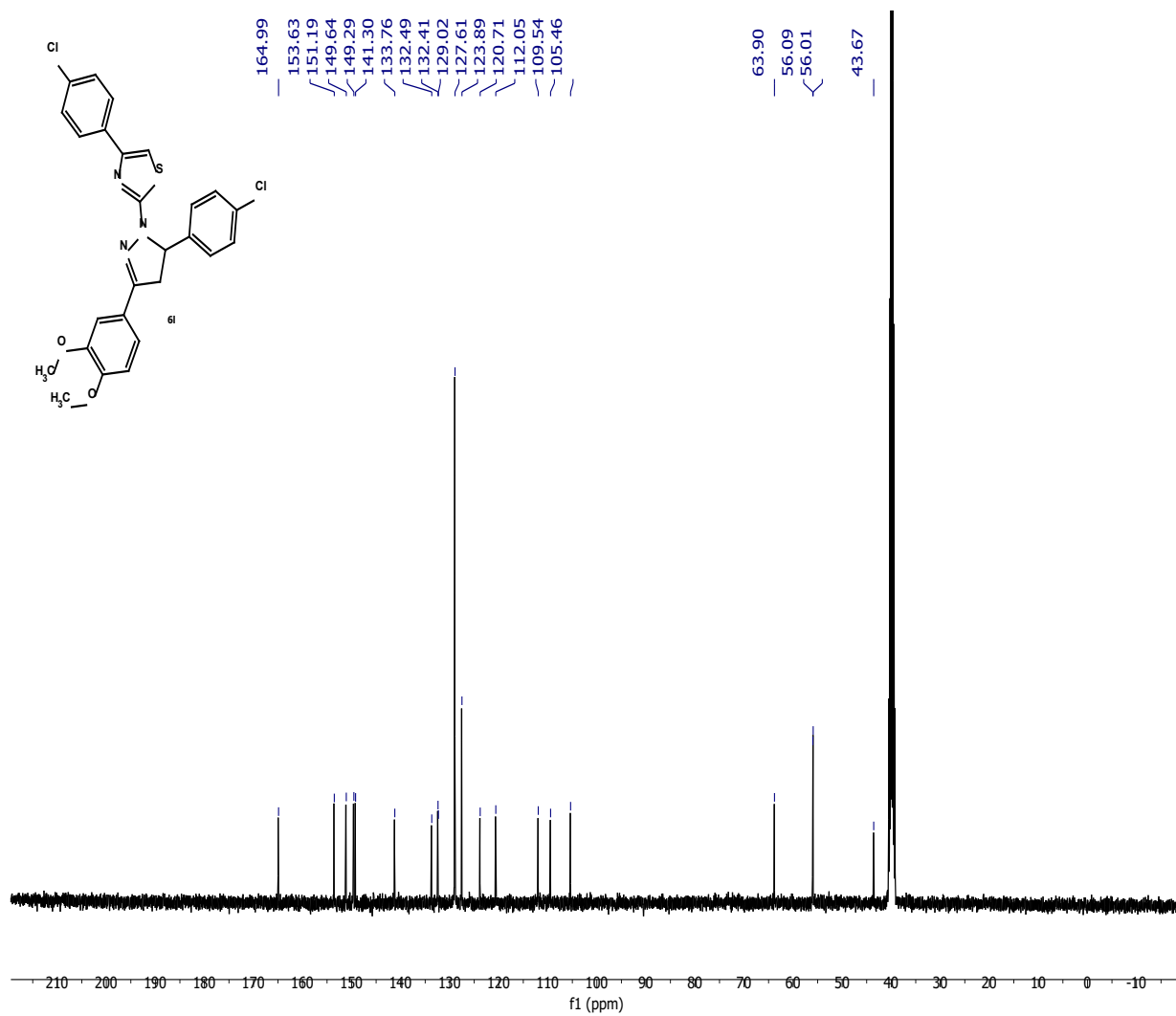


Figure S60: ¹³C NMR of compound 6l

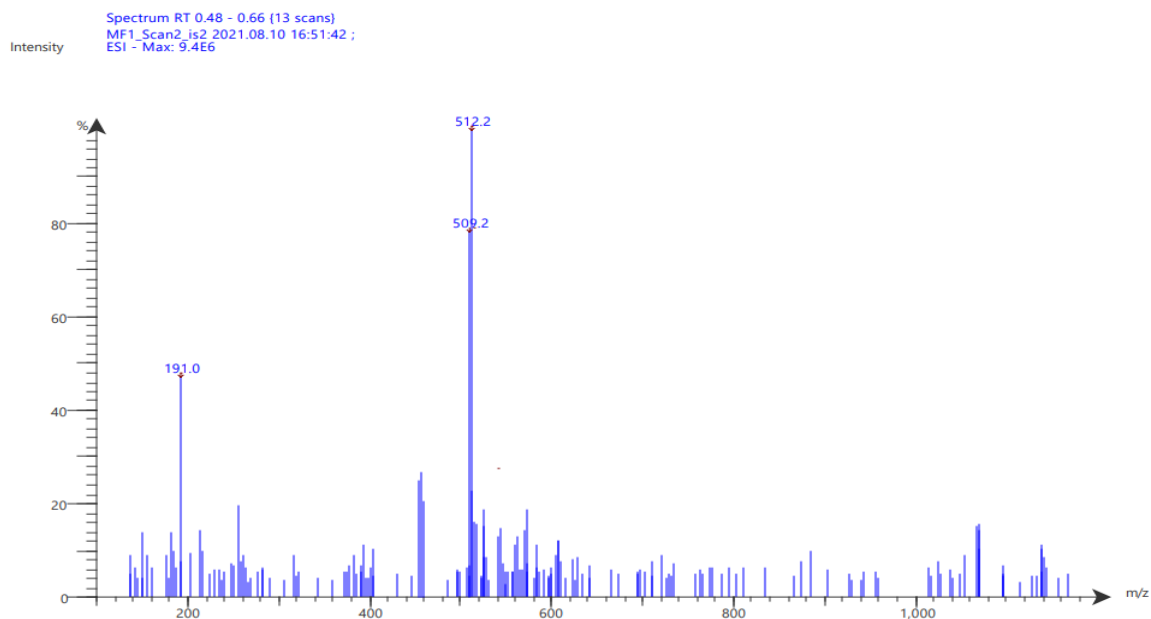
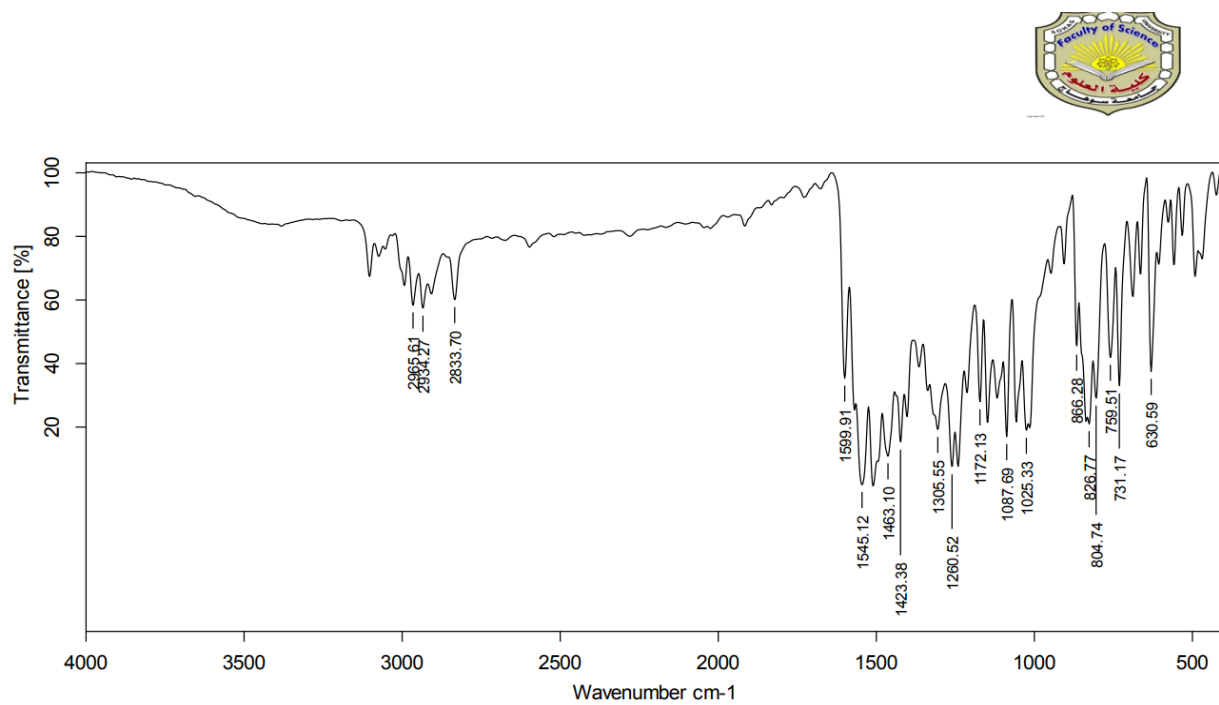


Figure S61: Mass of compound 6l



6l_TRANS.0

10:31:47 O

14/07/2021

Figure S62: IR of compound 6l

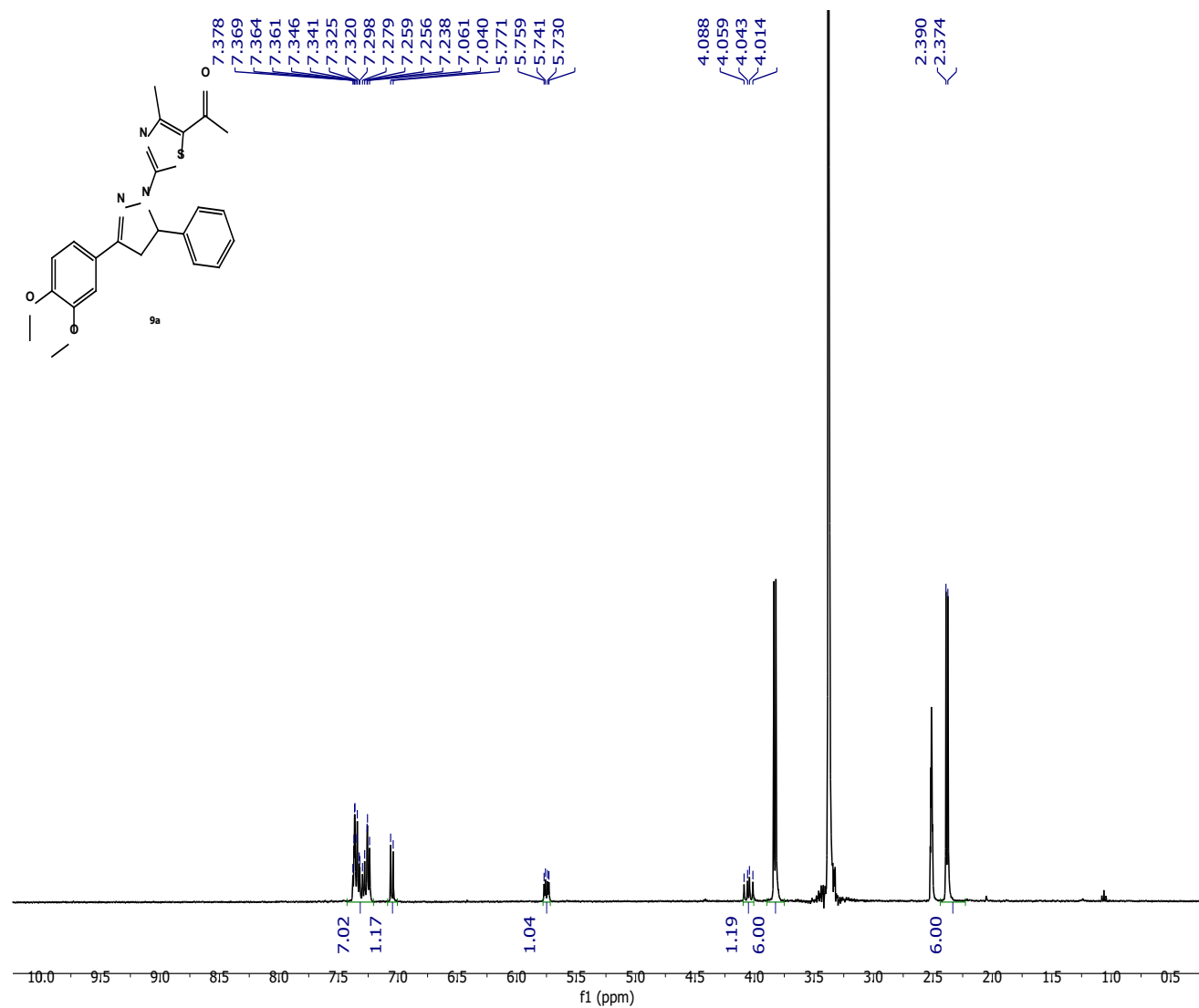


Figure S63: ¹H NMR of compound 9a

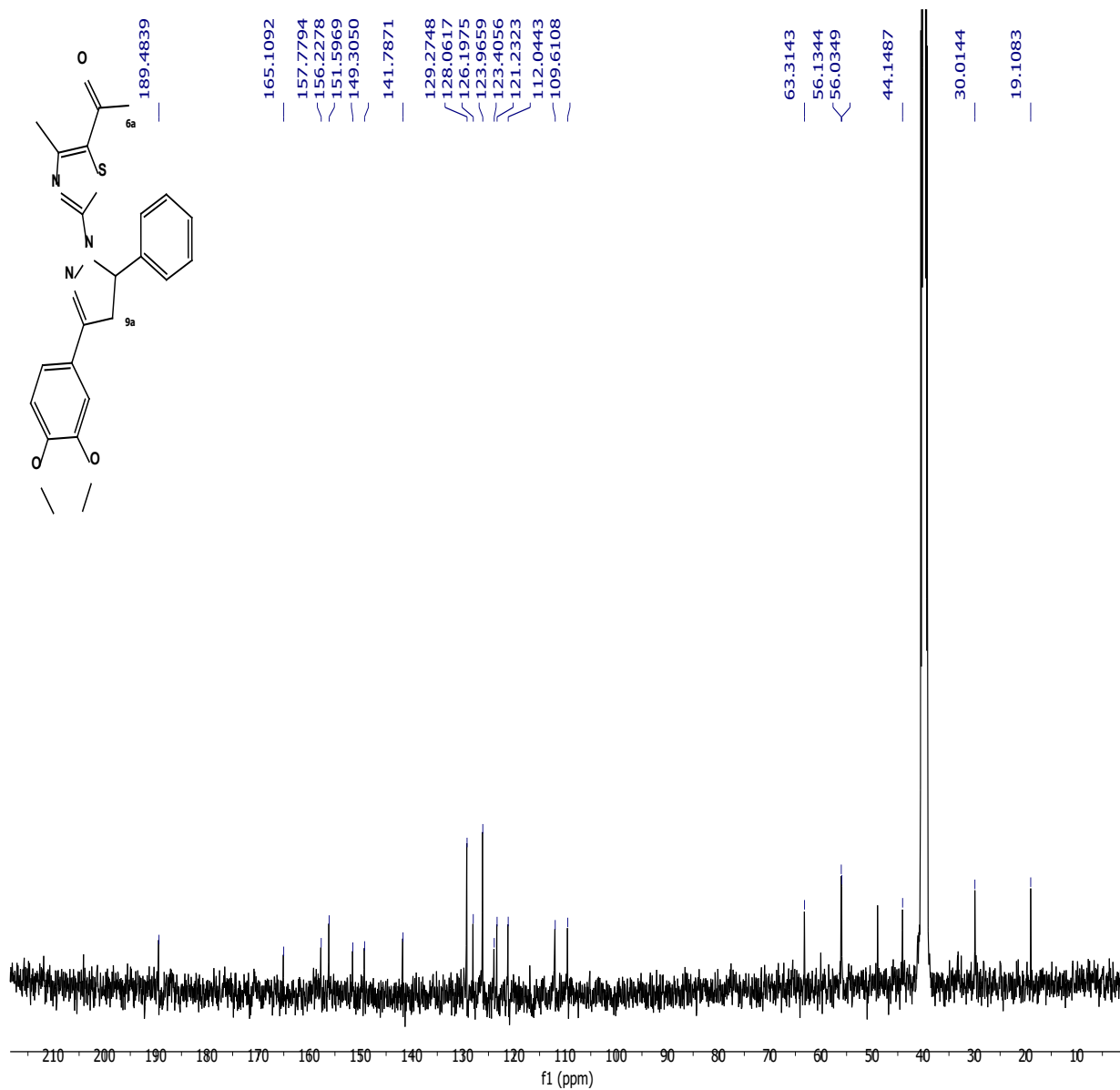


Figure S64: ^{13}C NMR of compound 9a

Spectrum RT 1.07 - 1.31 (15 scans)
sample_Scan2_is2 2022.04.17 13:03:34 ;
ESI - Max: 6.2E6

Intensity

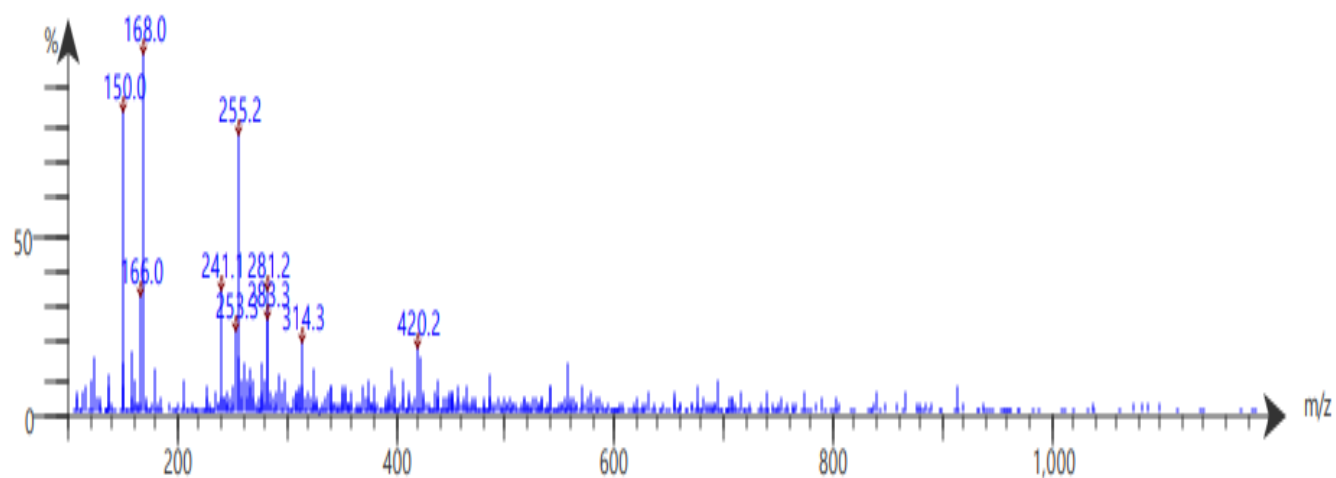


Figure S65: Mass of compound 9a

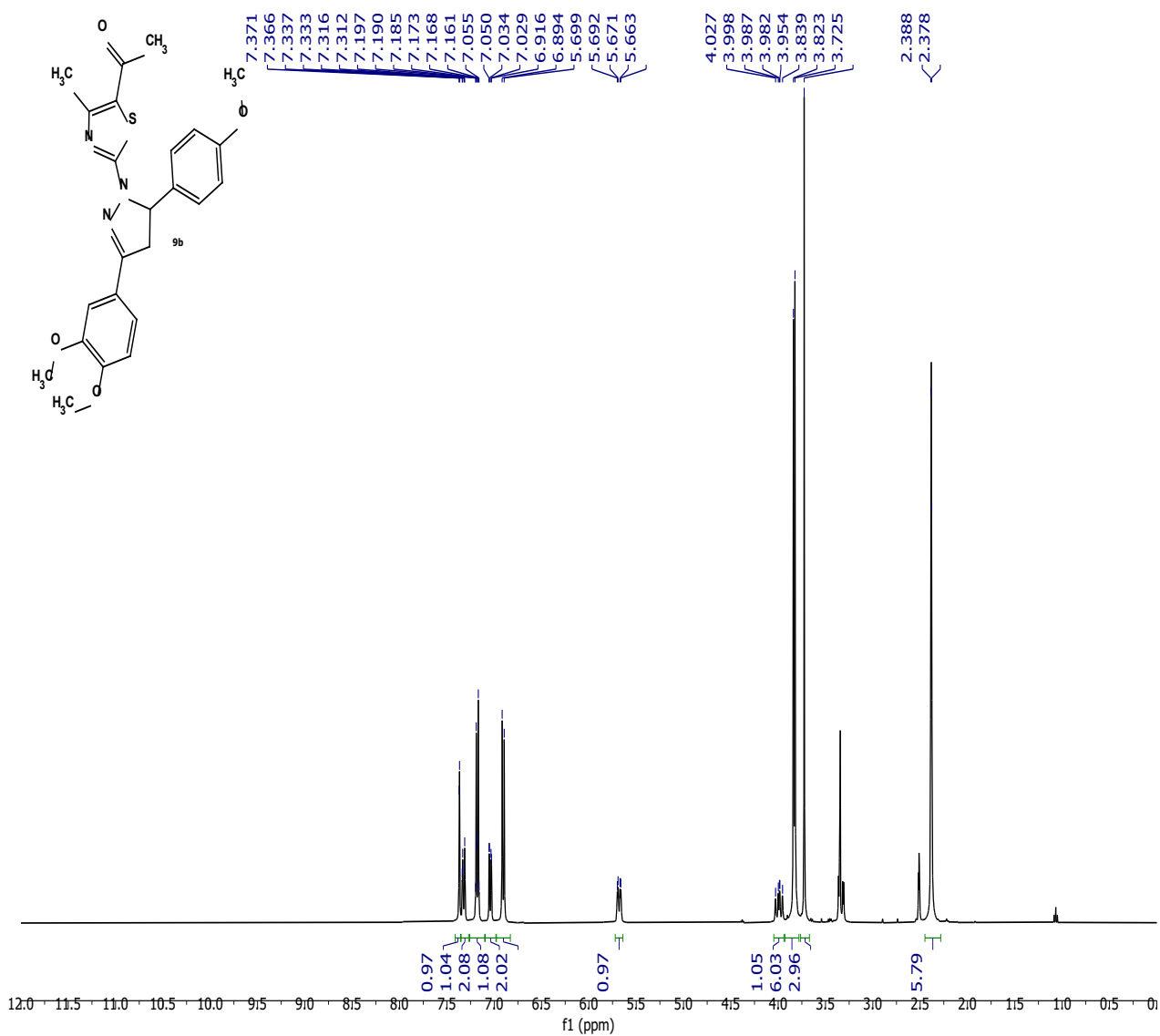


Figure S66: ¹H NMR of compound 9b

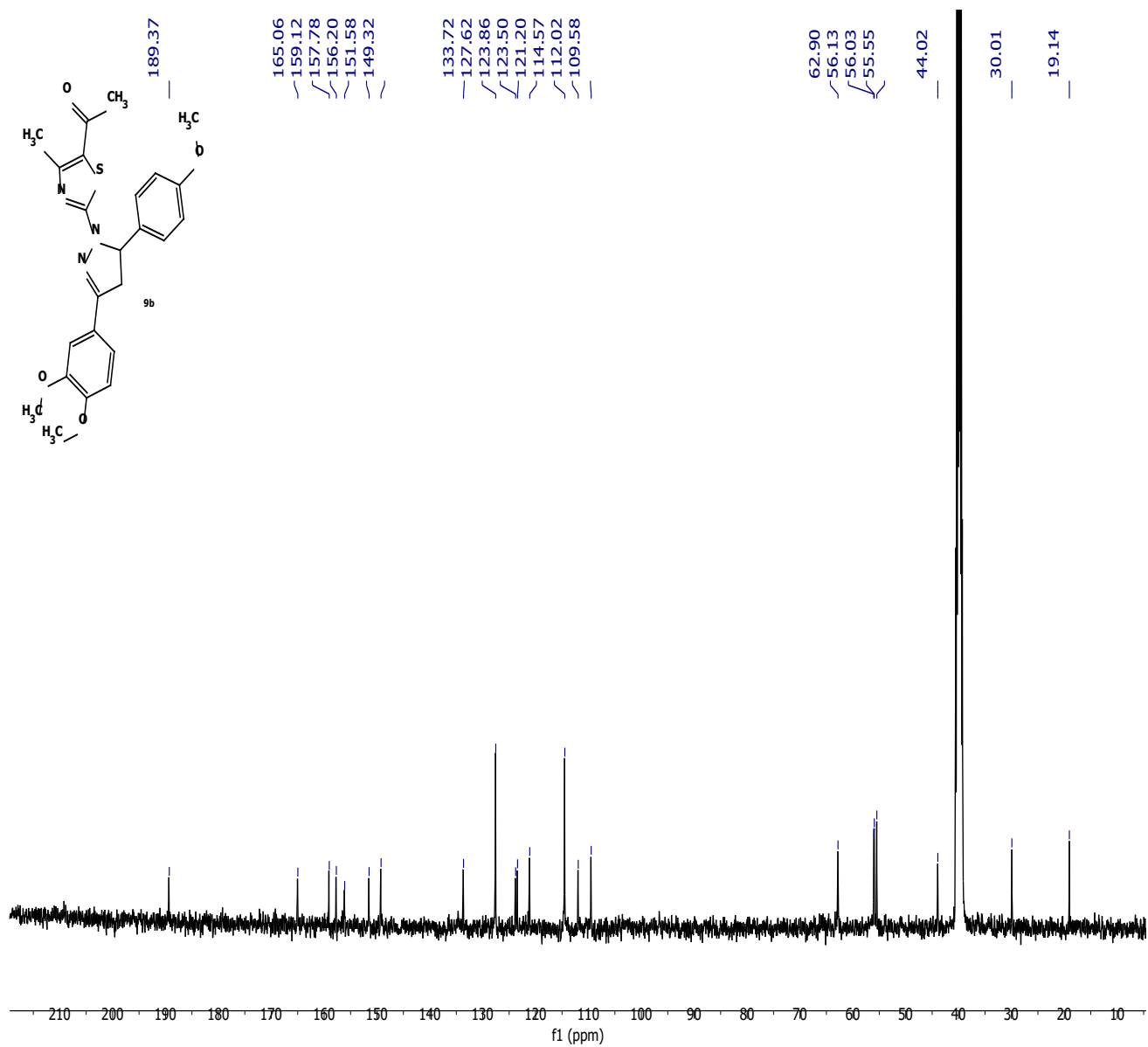


Figure S67: ¹³C NMR of compound 9b

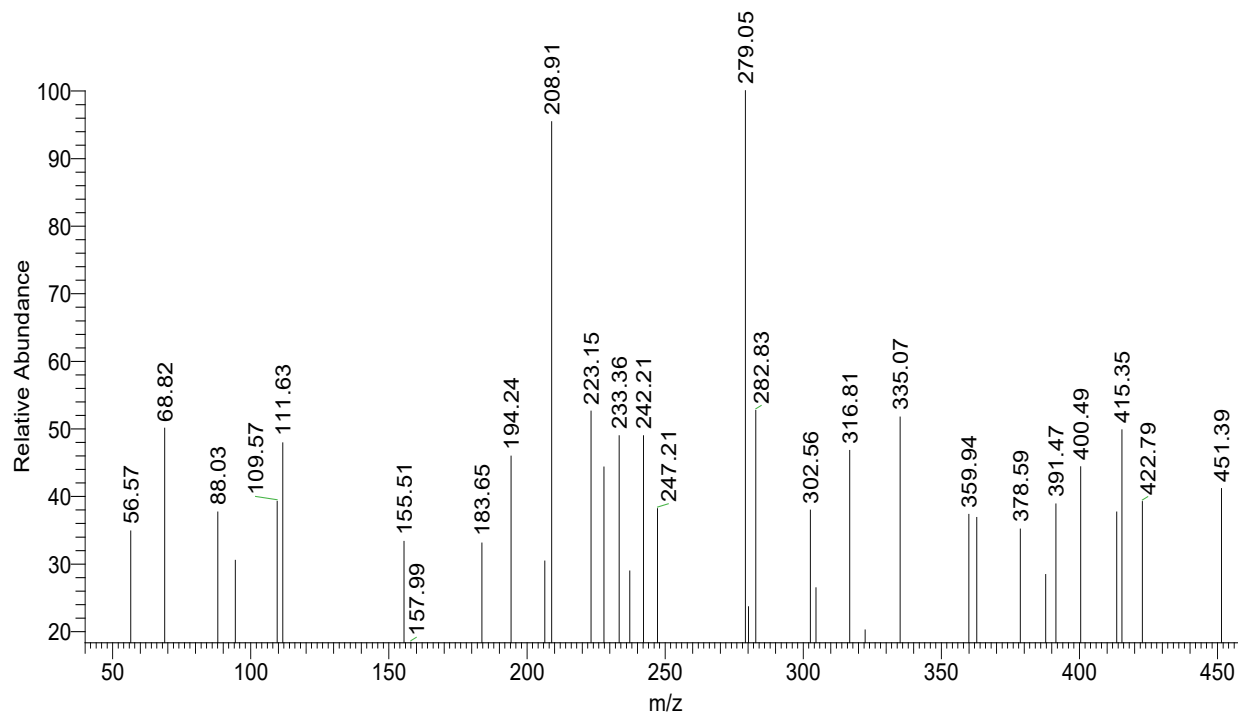


Figure S68: Mass of compound 9b

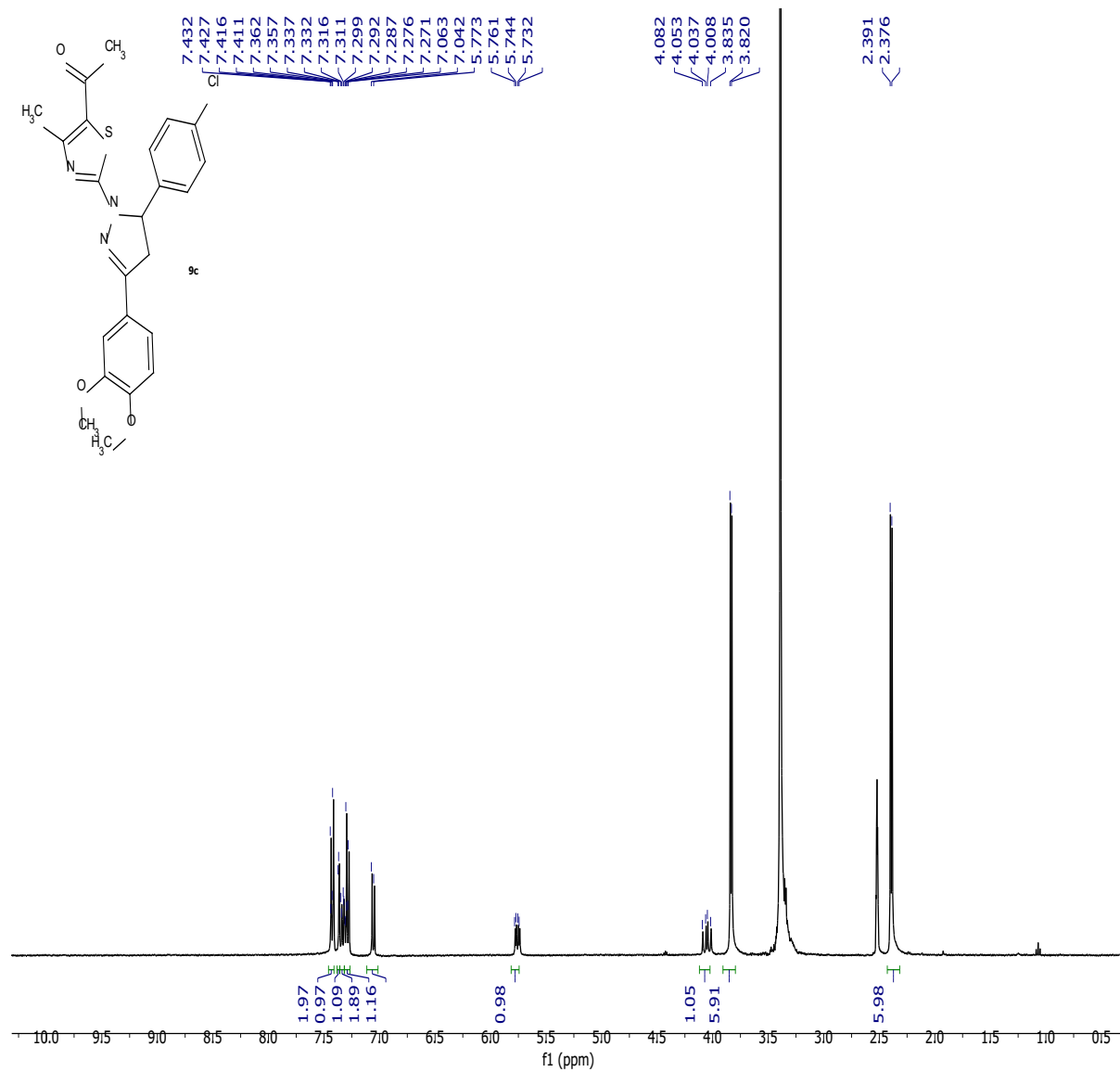


Figure S69: ^1H NMR of compound 9c

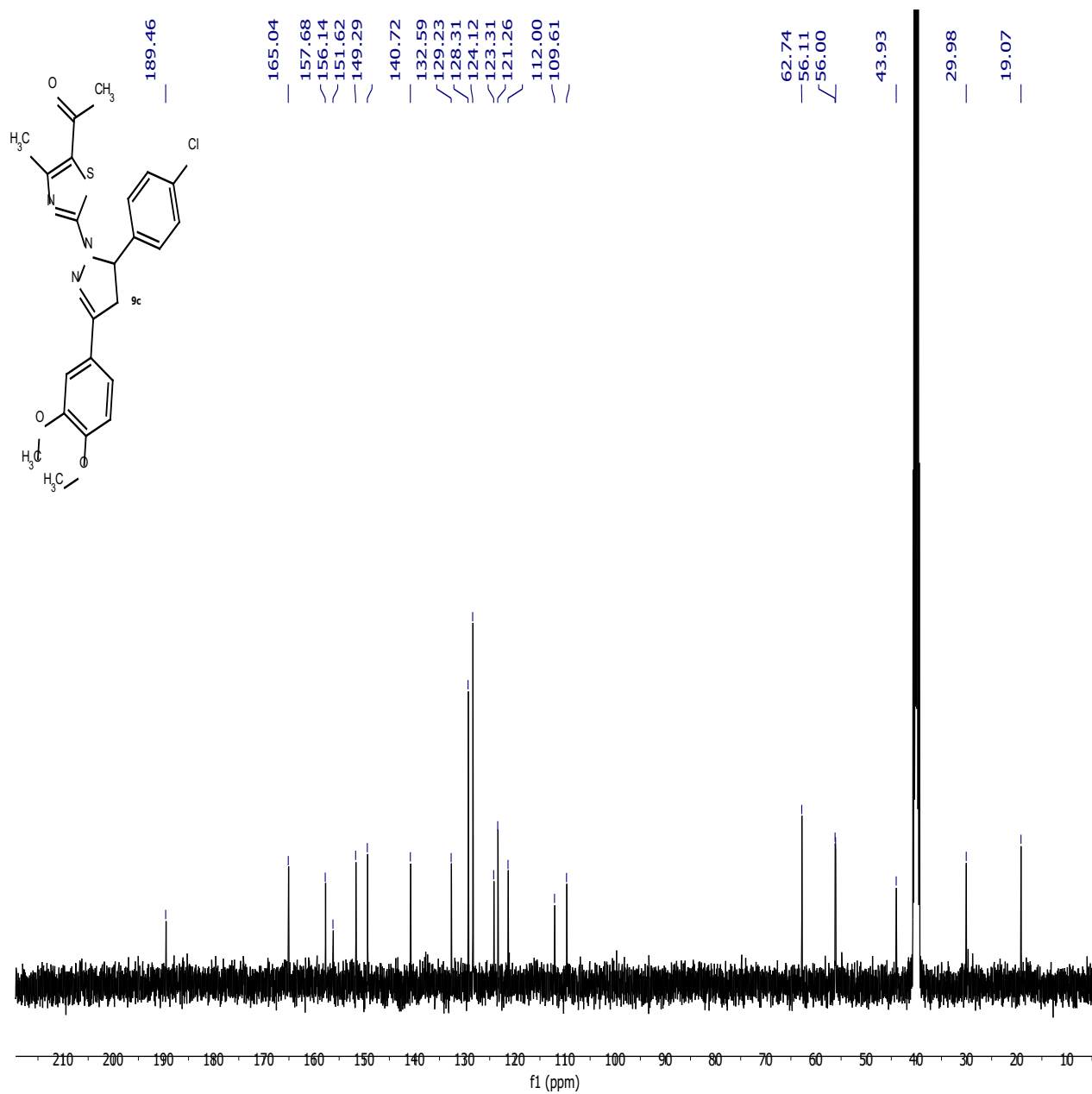


Figure S70: ¹³C NMR of compound 9c

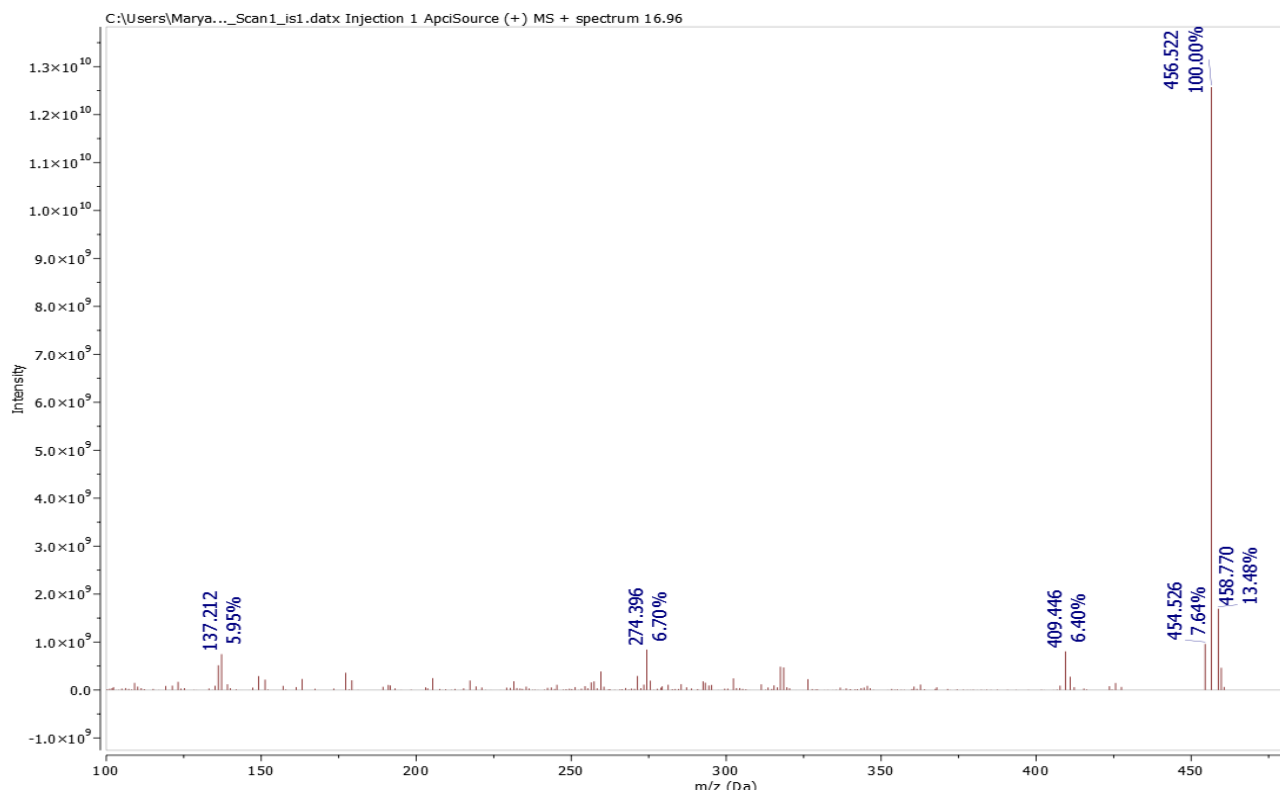
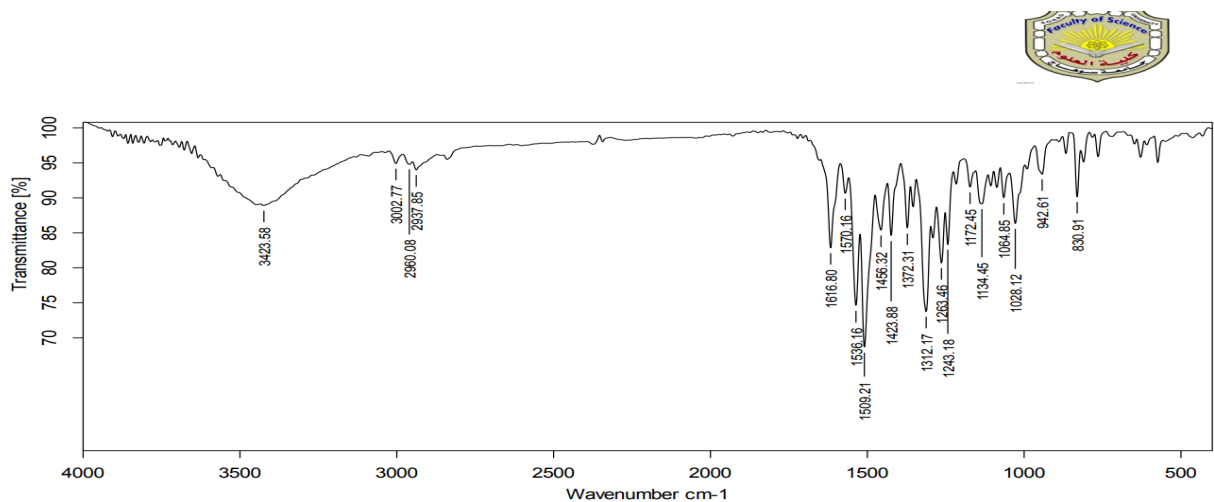


Figure S71: Mass of compound 9c



9c_TRANS.0

11:03:12 O

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Figure S72: IR of compound 9c

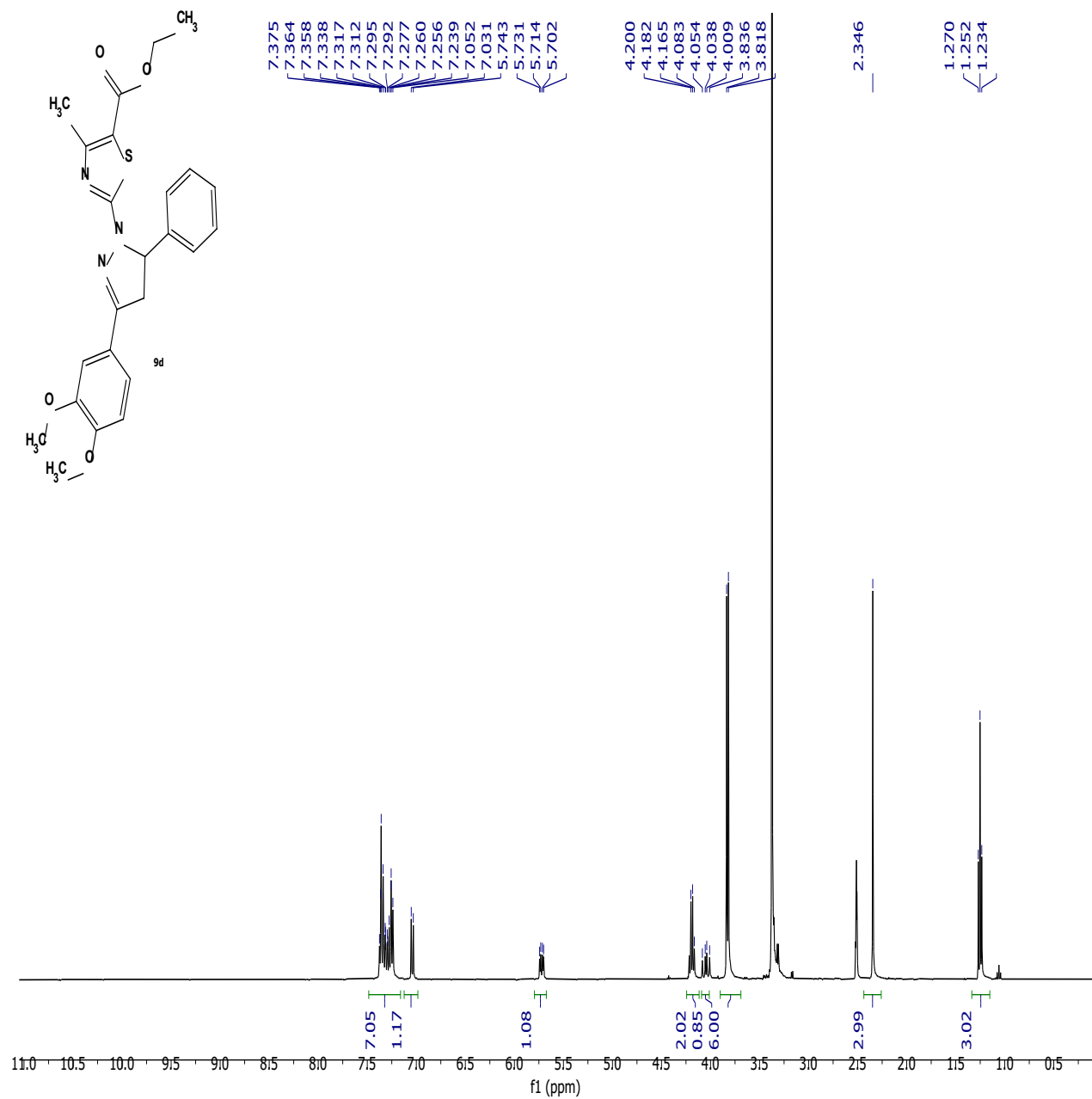


Figure S73: ¹H NMR of compound 9d

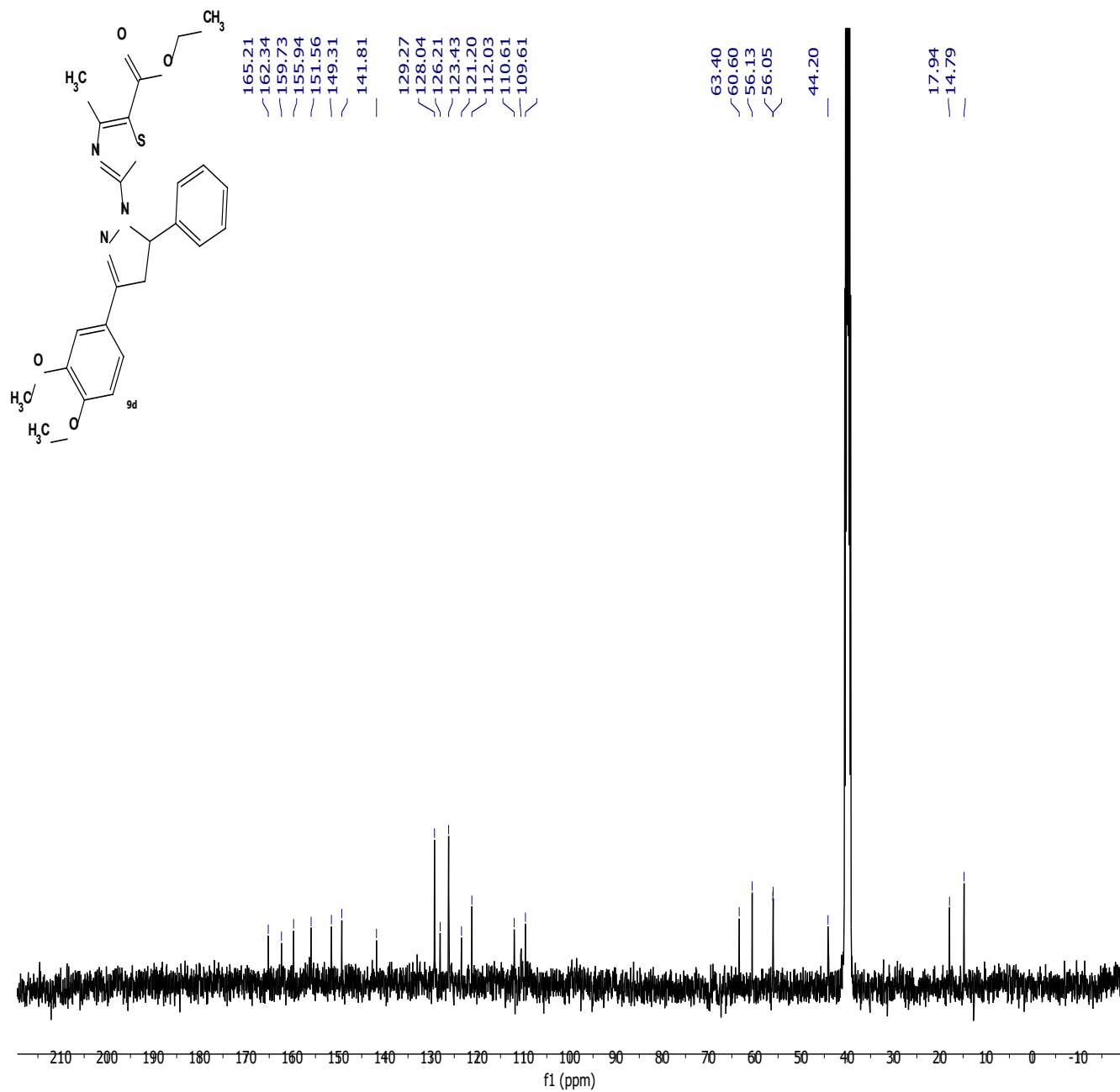


Figure S74: ^{13}C NMR of compound 9d

Spectrum RT 0.53 - 0.60 (6 scans)
Mu1_Scan2_is2 2021.08.10 16:00:48 ;
ESI -

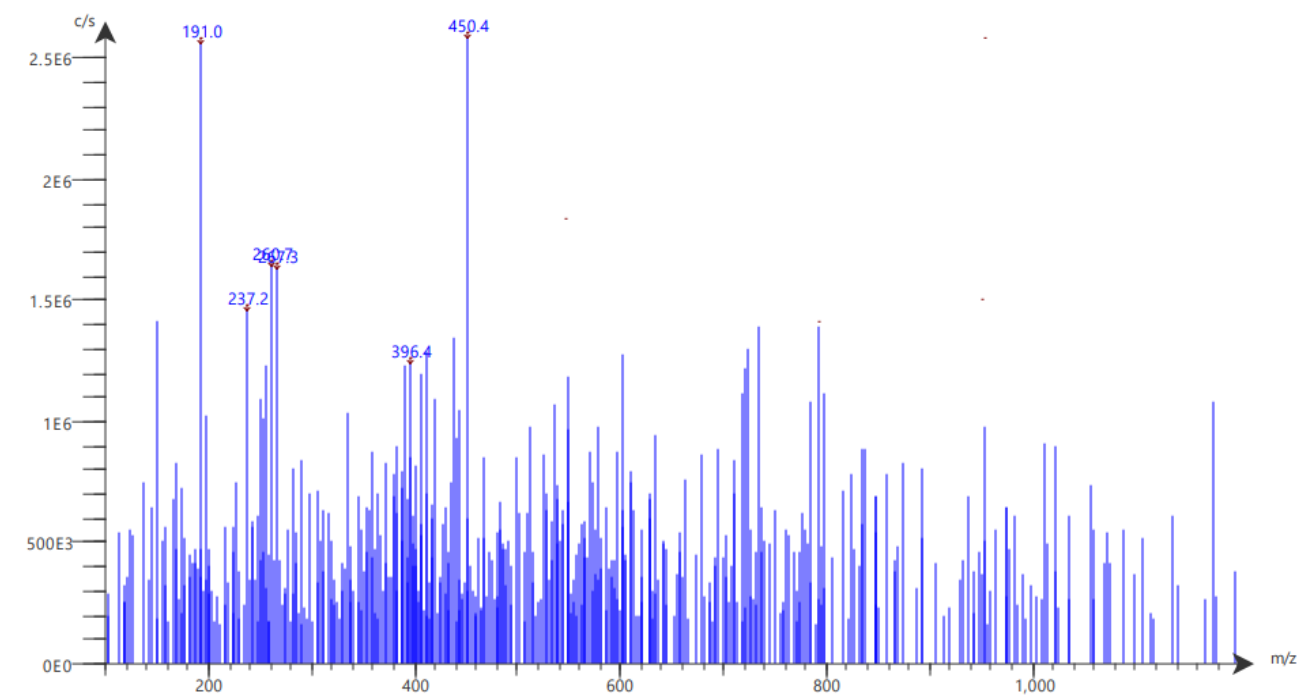


Figure S75: Mass of compound 9d

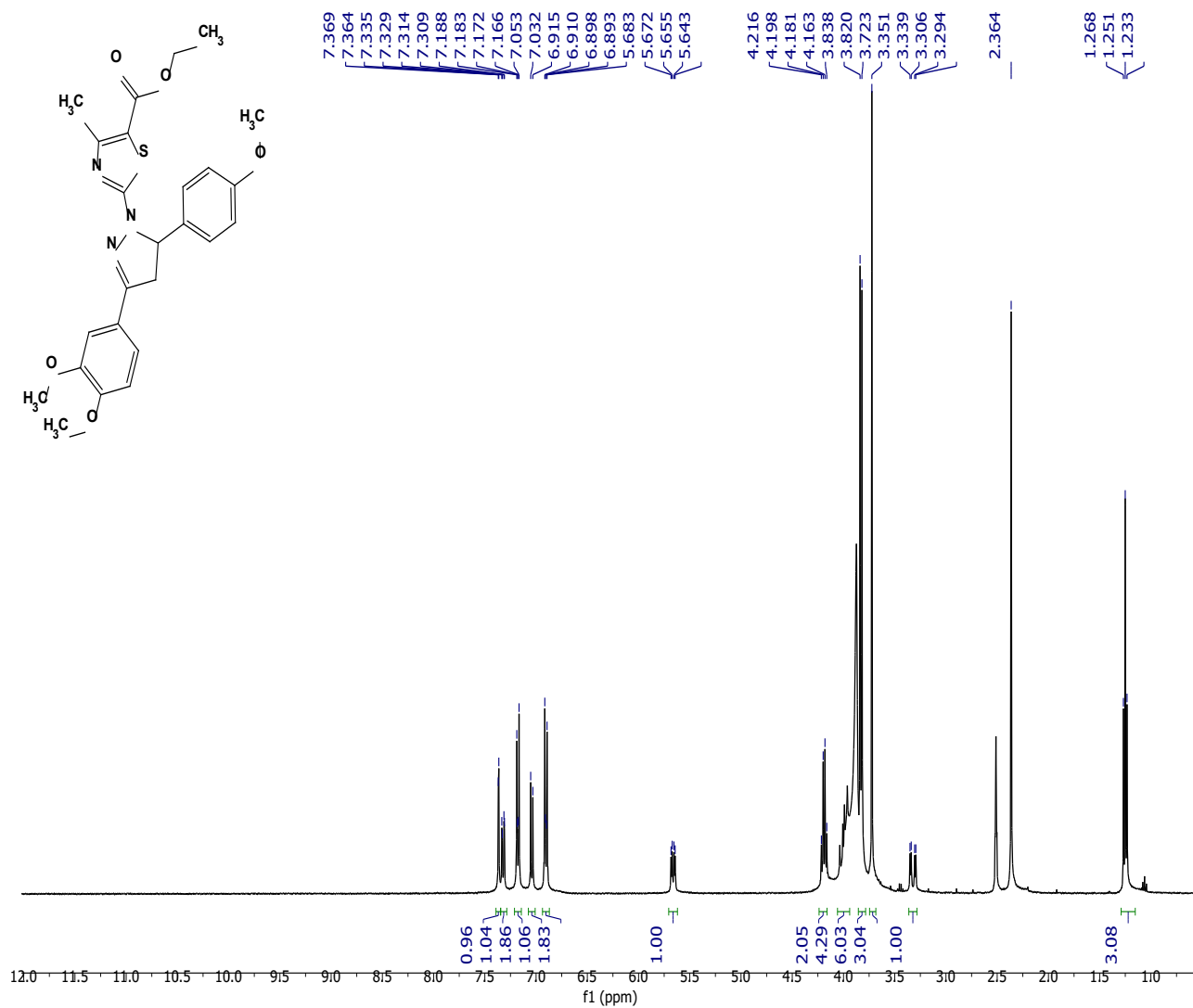


Figure S76: ¹H NMR of compound 9e

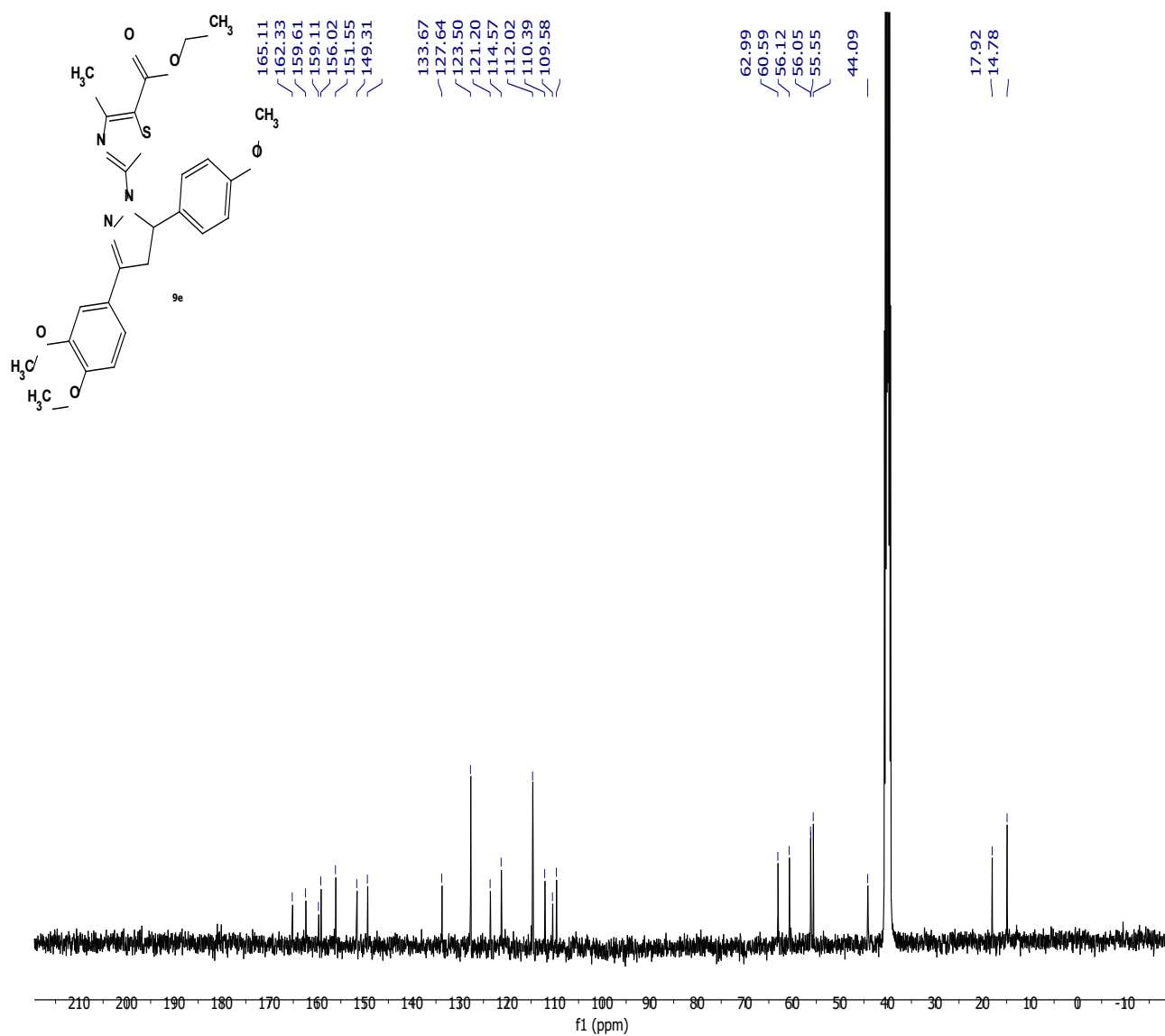


Figure S77: ^{13}C NMR of compound 9e

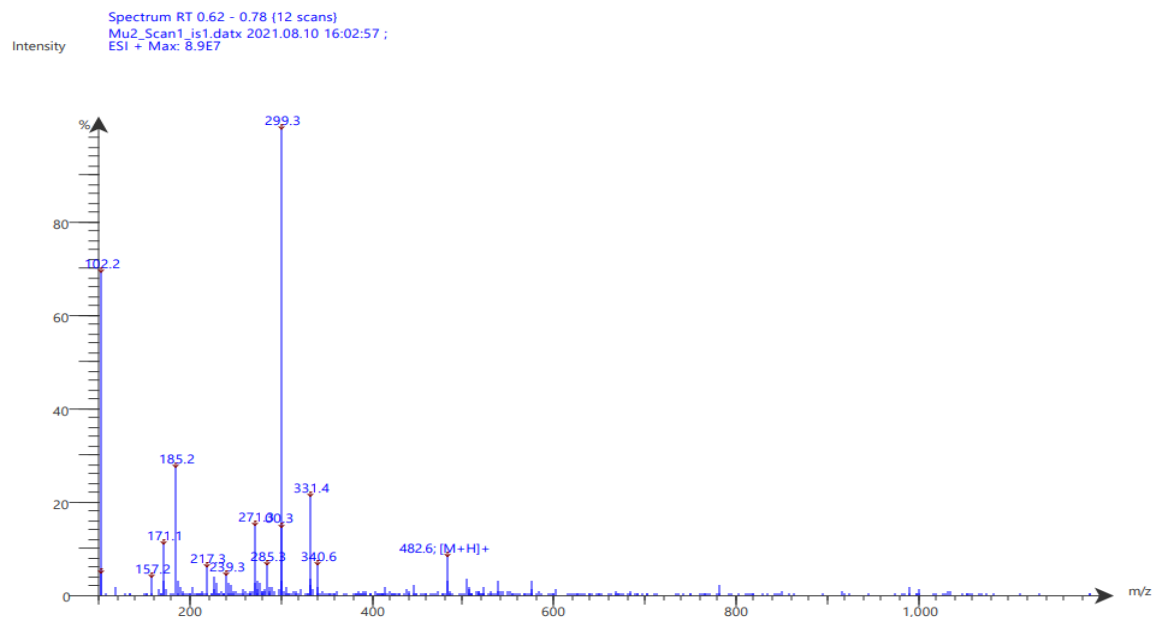
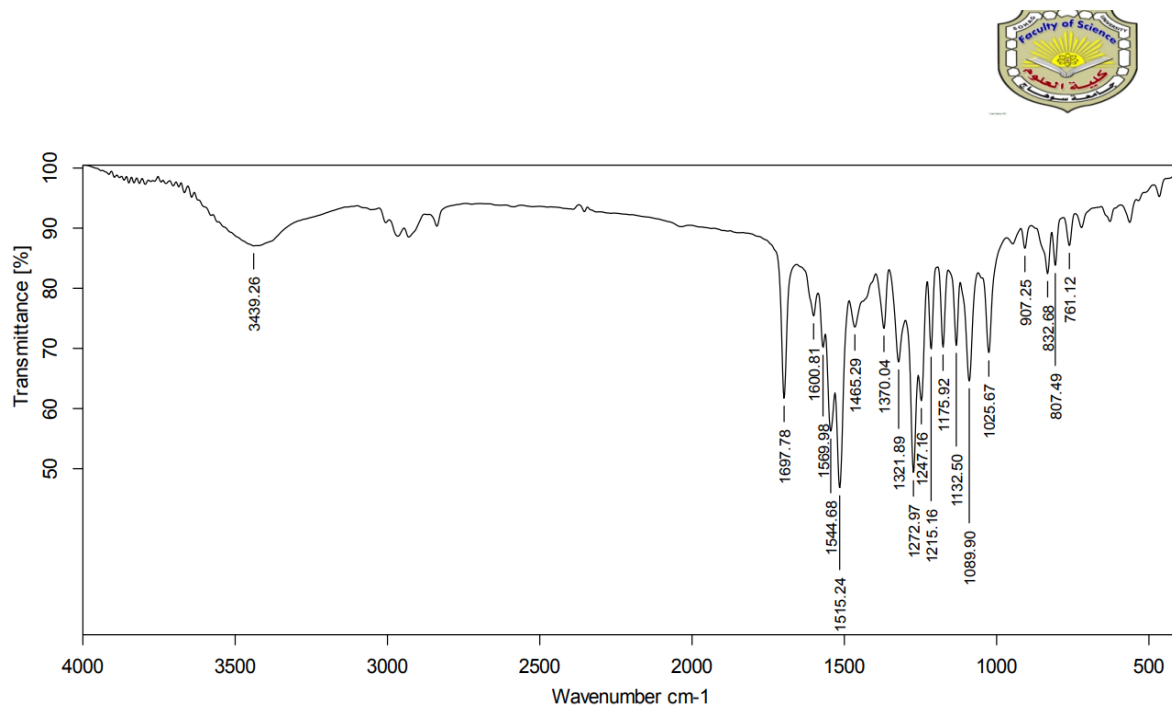


Figure S78: Mass of compound 9e



9e_TRANS.0

10:47:30 O

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Figure S79: IR of compound 9e

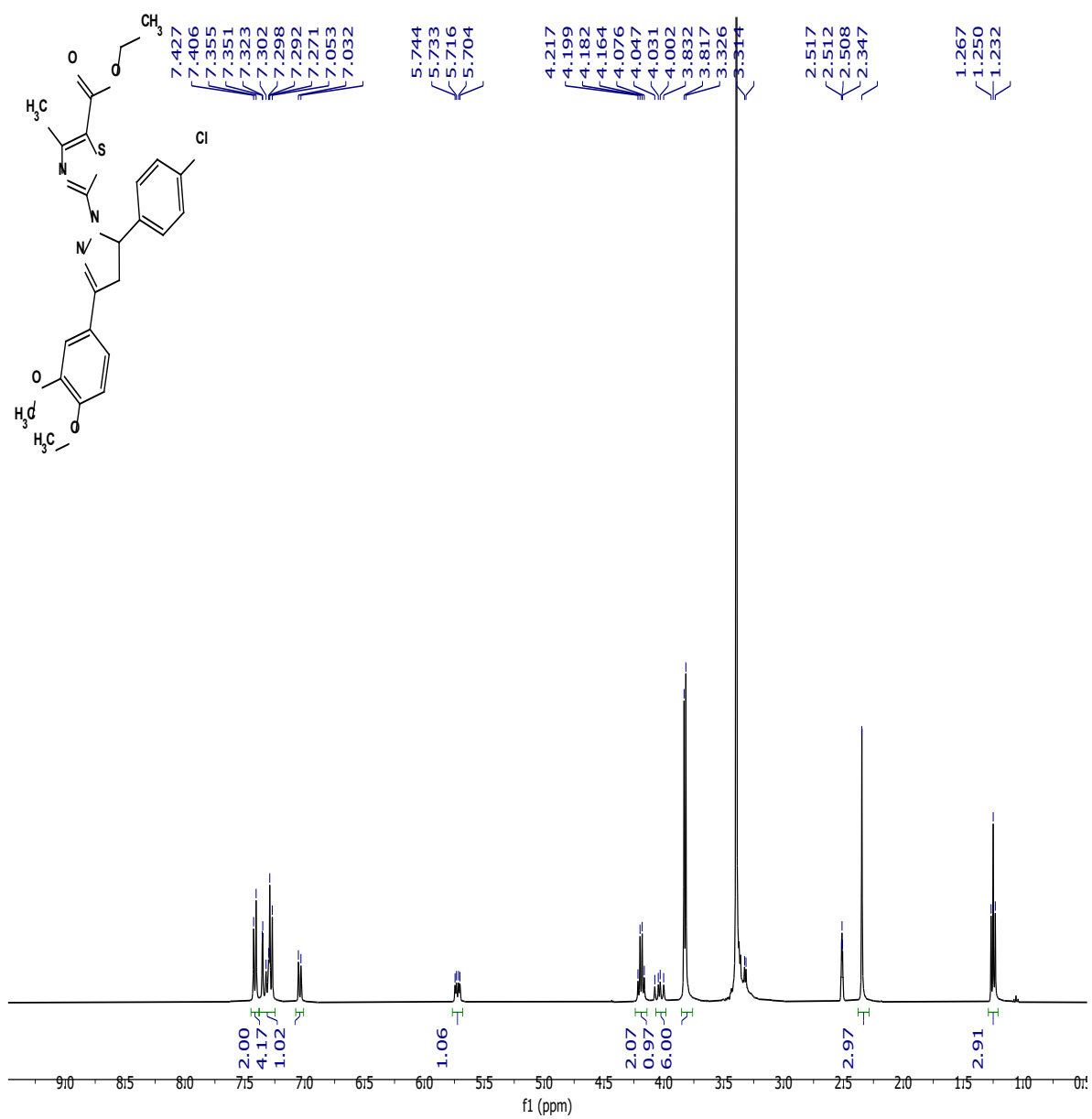


Figure S80: ^1H NMR of compound 9f

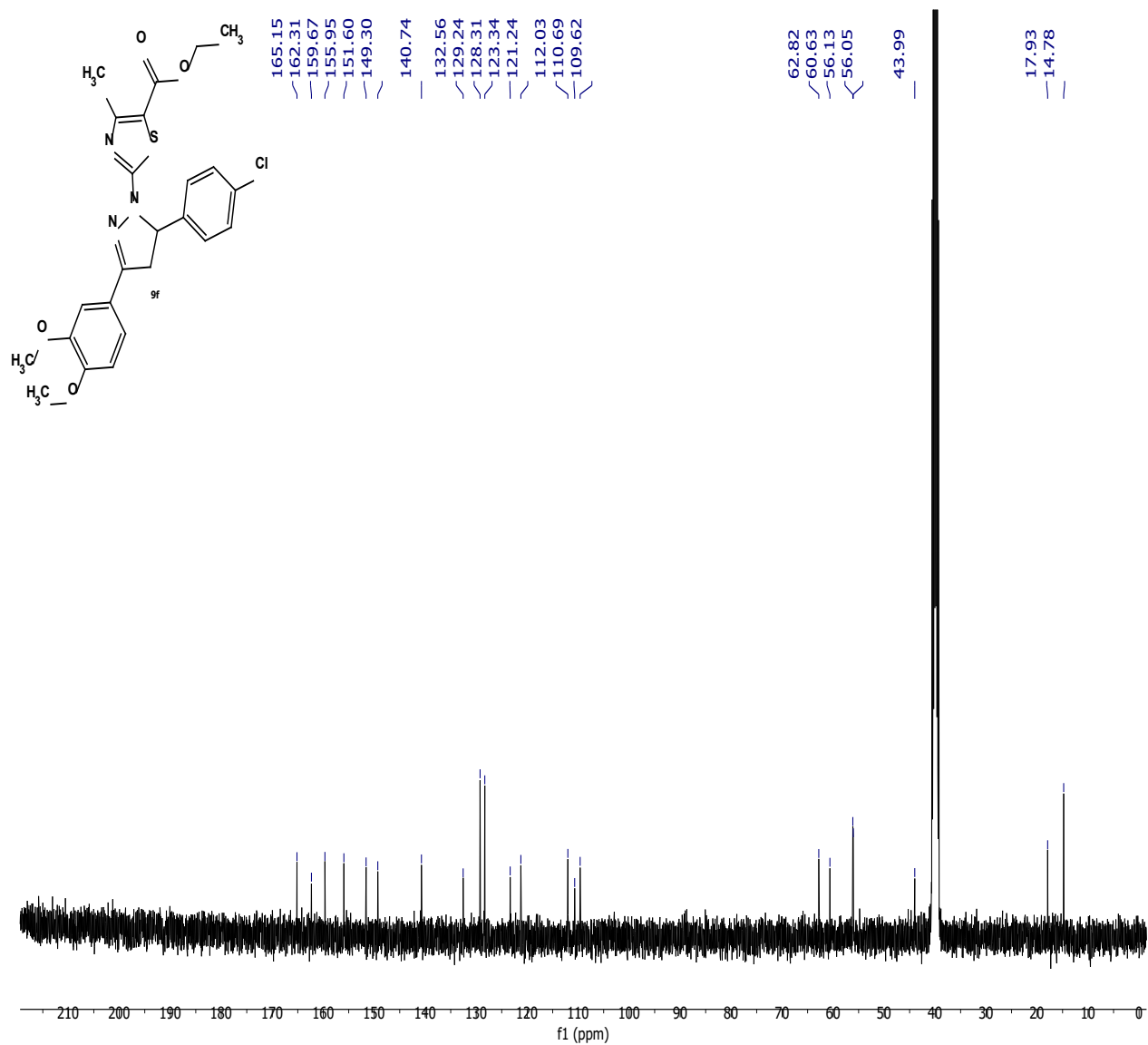


Figure S81: ¹³C NMR of compound 9f

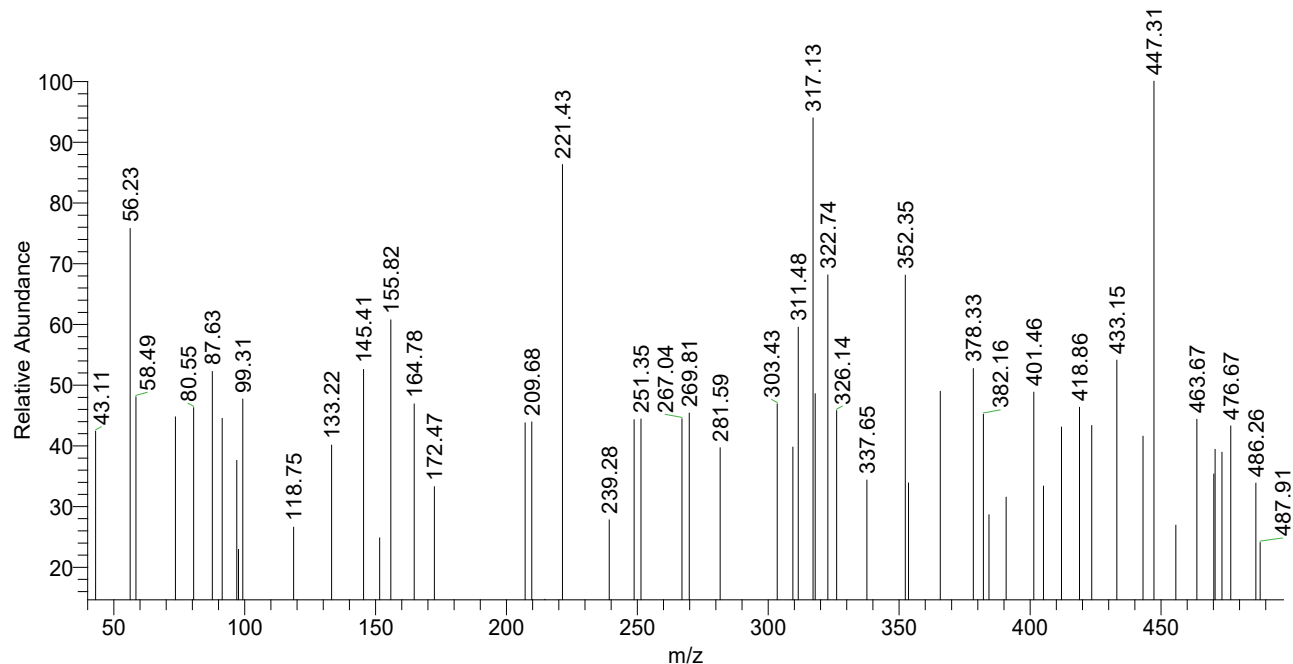
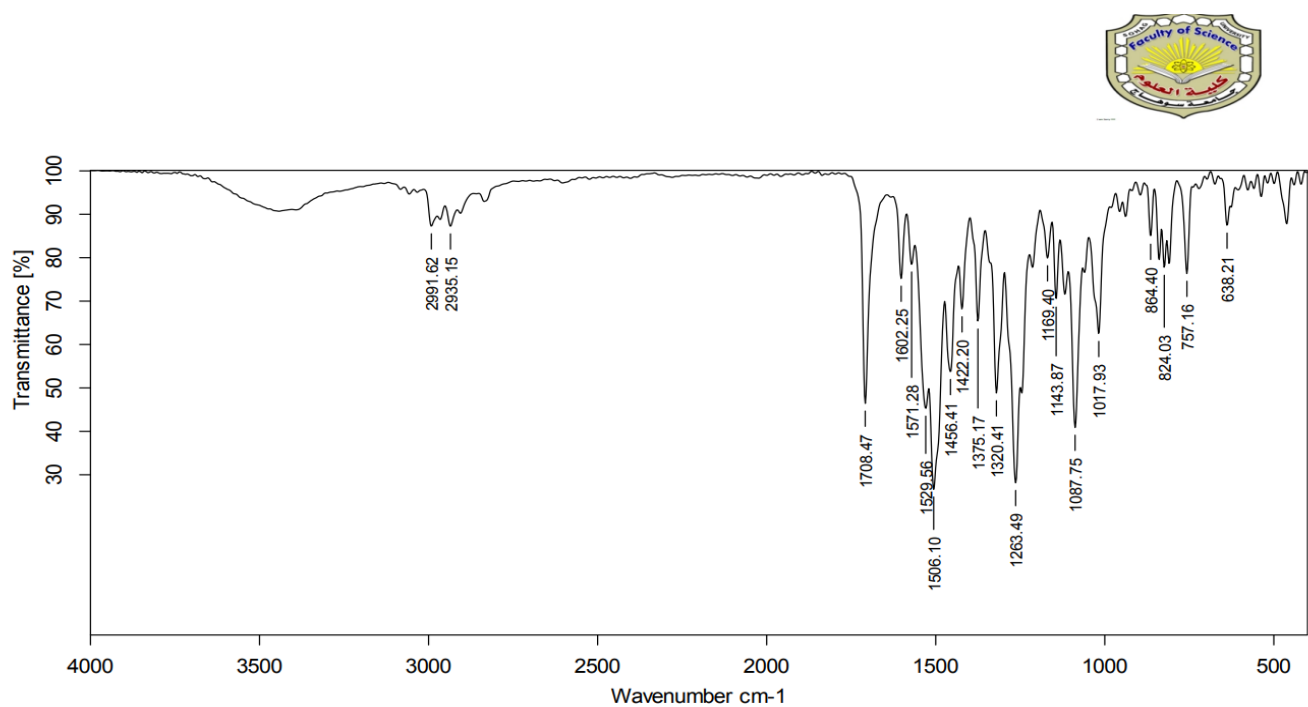


Figure S82: Mass of compound 9f



9f_TRANS.0

11:06:34 0

14/07/2021

Figure S83: IR of compound 9f

Al-Azhar University The Regional Center for Mycology and Biotechnology



Requester Data:

Name: Dr. Mariem Medhat Fakhry
Authority: Faculty of Pharmacy, Egyptian Russian University

Sample Data:

Eleven samples had been submitted for elemental analysis.

Analysis Report:

Sample Code	C%	H%	N%	S%
6a	70.95	5.41	9.80	7.43
6i	65.43	4.85	9.12	6.78
6d	64.07	5.69	9.53	7.23
9e	62.51	5.83	8.97	6.81
9f	59.58	5.06	8.89	6.72
9b	64.09	5.67	9.48	7.28
9c	60.81	5.08	9.41	7.14
9a	65.78	5.63	10.15	7.68
3c	57.65	4.97	11.45	8.70
6e	69.04	5.60	9.17	6.93
6f	69.47	5.78	8.81	6.72

INVESTIGATOR

M. Elmassry




DIRECTOR

H. Sheikh

Al-Azhar University Campus - Nasr City, Cairo, Egypt.
Tel: 0202 22620373 Fax : 0202 22620373
E.mail:rcmb@azhar.edu.eg
Website: <http://www.azhar.edu.eg.htm> * http://www.azhar.edu.eg/pages/fungi_center.htm
Facebook : RCMB AZHAR P.O. box mail : 11751 Nasr City Cairo, Egypt.

Al-Azhar University
The Regional Center for Mycology and Biotechnology



Requester Data:

Name: Dr. Mariem Medhat Fakhry
Authority: Faculty of Pharmacy, Egyptian Russian University


Sample Data:

Ten samples had been submitted for elemental analysis.

Analysis Report:

Sample Code	C%	H%	N%	S%
6L	61.40	4.29	8.51	6.37
6K	63.51	4.45	8.75	6.42
3a	63.59	5.78	12.52	9.48
3b	61.72	5.86	11.58	8.75
6c	67.78	5.01	9.42	6.85
6g	66.51	5.11	8.75	6.68
6d	65.87	4.80	9.09	6.85
6h	64.23	4.93	8.47	6.50
6b	71.42	5.67	9.49	7.18
6j	66.46	5.11	8.79	6.61

INVESTIGATOR *M. Elasser*



DIRECTOR *H. Shikhl*

Al-Azhar University Campus – Nasr City, Cairo, Egypt.
 Tel: 0202 22620373 Fax : 0202 22620373
 E.mail:rcmb@azhar.edu.eg
 Website: <http://www.azhar.edu.eg.htm> * http://www.azhar.edu.eg/pages/fungi_center.htm
 Facebook : RCMB AZHAR P.O. box mail : 11751 Nasr City Cairo, Egypt.

Figure S84: Elemental analysis (CHN) for 3a-c, 6a-l, 9a-f

Table S1: Predicted properties and Lipinski's parameters for target compounds and lapatinib as a reference.

Compound No.	RB	HBA	HBD	MR	TPSA	CLogP	Log S	Lipinski's violations	Veber's violations
3a	5	3	1	105.51	92.17	2.66	-3.68	0	0
3b	6	4	1	112	101.4	2.74	-3.75	0	0
3c	5	3	1	110.52	92.17	3.2	-4.27	0	0
6a	6	4	0	136.35	75.19	5.04	-6.49	0	0
6b	6	4	0	141.32	75.19	5.36	-6.79	0	0
6c	6	5	0	136.31	75.19	5.35	-6.65	0	0
6d	6	4	0	141.36	75.19	5.57	-7.08	1	0
6e	7	5	0	142.85	84.42	5.06	-6.56	0	0
6f	7	5	0	147.81	84.42	5.42	-6.86	0	0
6g	7	6	0	142.8	84.42	5.39	-6.72	0	0
6h	7	5	0	147.86	84.42	5.61	-7.15	1	0
6i	6	4	0	141.36	75.19	5.57	-7.08	1	0
6j	6	4	0	146.33	75.19	5.96	-7.38	1	0
6k	6	5	0	141.32	75.19	5.94	-7.24	1	0
6l	6	4	0	146.37	75.19	6.16	-7.68	2	0
9a	6	5	0	126.08	92.26	4.1	-5.47	0	0
9b	7	6	0	132.57	101.49	4.18	-5.54	0	0
9c	6	5	0	131.09	92.26	4.64	-6.07	0	0
9d	8	6	0	131.97	101.49	4.43	-5.83	0	0
9e	9	7	0	138.46	110.72	4.44	-5.91	0	0
9f	8	6	0	136.98	101.49	4.99	-6.43	0	0
lapatinib	11	8	2	153.88	114.73	5.19	-7.27	1	0

Table S2: Predicted *in silico* ADME properties for target compounds.

Compound No.	HIA	BPB	BBB	Skin P
3a	97.284	88.037	0.0429	-3.0845
3b	97.856	87.451	0.08	-3.2976
3c	96.954	89.75	0.0593	-3.1369
6a	97.567	93.43	2.7355	-2.3729
6b	97.598	92.803	2.3387	-2.3461
6c	97.569	91.82	1.4974	-2.6339
6d	97.767	91.79	1.2769	-2.402
6e	97.623	92.213	2.8912	-2.5218
6f	97.616	91.775	2.8309	-2.507
6g	97.621	91.299	2.057	-2.8202
6h	97.7	90.979	1.9193	-2.5594
6i	97.767	91.954	1.7181	-2.402
6j	97.819	91.629	1.2075	-2.3803
6k	97.771	91.83	0.7849	-2.6709

6l	98.012	93.086	0.6125	-2.3609
9a	99.011	90.105	1.023	-3.2079
9b	99.547	89.727	0.8536	-3.4273
9c	98.186	91.34	1.3662	-3.2681
9d	99.547	90.086	1.118	-3.1375
9e	99.845	89.995	0.88	-3.3557
9f	98.786	90.223	1.2438	-3.2
Lapatinib	96.867	97.564	0.03139	-2.324

Table S3: Toxicity prediction using Osiris server.

Compound no.	Mutagenic	Irritant	Reproductive effect	Drug-score
3a	no	no	yes	0.46
3b	no	no	yes	0.45
3c	no	no	yes	0.39
6a	no	no	no	0.19
6b	no	no	no	0.17
6c	no	no	no	0.17
6d	no	no	no	0.15
6e	no	no	no	0.18
6f	no	no	no	0.16
6g	no	no	no	0.16
6h	no	no	no	0.14
6i	no	no	no	0.15
6j	no	no	no	0.14
6k	no	no	no	0.14
6l	no	no	no	0.13
9a	no	no	no	0.27
9b	no	no	no	0.26
9c	no	no	no	0.2
9d	no	no	no	0.25
9e	no	no	no	0.24
9f	no	no	no	0.19
lapatinib	no	no	no	0.13