Supporting information File

Unravelling the potency of triazole analogues for inhibiting α-Synuclein fibrillogenesis and *in vitro* disaggregation

Mudasir Maqbool[1], Joshna Gadhavi[2], Anju Singh[1], Pravin Hivare[2], Sharad Gupta[2*], Nasimul Hoda[1*]

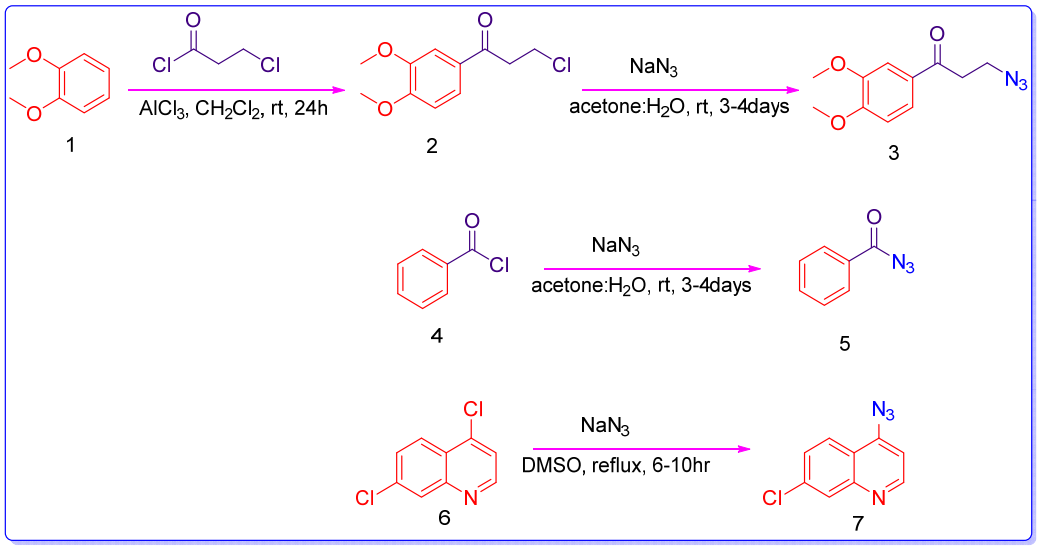
[1]Drug Design and Synthesis Lab., Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi-110025, India.
[2]Biological Engineering, Indian Institute of Technology Gandhinagar, Palaj, Gandhinagar, Gujarat, India.

Corresponding authors:

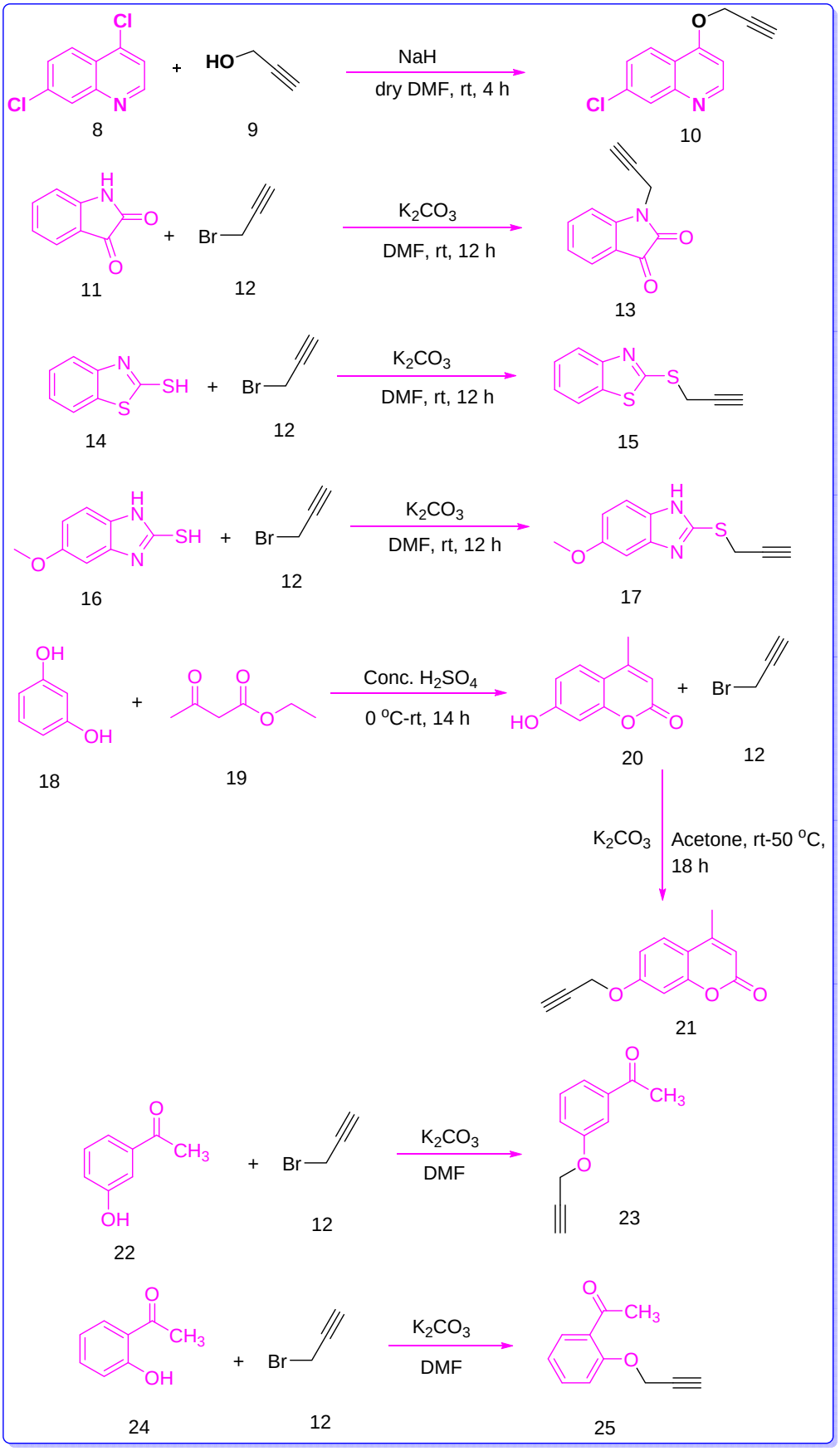
Nasimul Hoda**,** PhD
Professor
Department of Chemistry,
Jamia Millia Islamia,
Jamia Nagar, New Delhi-110025, India.
Email: nhoda@jmi.ac.in

Sharad Gupta, PhD
Associate Professor
Biological Engineering,
Indian Institute of Technology Gandhinagar,
Palaj, Gandhinagar, Gujarat, India
E-mail: sharad@iitgn.ac.in

Scheme S1: Scheme for the synthesis of different azides



Scheme S2: Synthetic scheme for the synthesis of different alkynes


Cl
Cl
N
HO
NaH
dry DMF, rt, 4 h
O
Cl
N
8
9
10
H
N
O
O
Br
K_2CO_3
DMF, rt, 12 h
N
O
O
11
12
13
N
SH
S
Br
K_2CO_3
DMF, rt, 12 h
N
S
S
14
12
15
H
N
SH
N
O
Br
K_2CO_3
DMF, rt, 12 h
H
N
S
N
O
16
12
17
OH
OH
O
O
O
Conc. H_2SO_4
0 ^oC-rt, 14 h
HO
O
O
Br
18
19
20
12
K_2CO_3
Acetone, rt-50 ^oC, 18 h
O
O
O
21
O
CH_3
OH
Br
K_2CO_3
DMF
O
CH_3
22
12
23
O
CH_3
OH
Br
K_2CO_3
DMF
O
CH_3
O
24
12
25

Chemistry

Procedure for the synthesis of compound 2

A mixture of aluminium chloride (5.3 g, 39.7 mol) and 25 mL DCM was allowed for stirring at room temperature. 3-chloropropionylchloride (5.5 g, 43.3 mol) dissolved in 20 mL DCM was added dropwise to the stirring solution of $AlCl_3$. After half an hour, 1,2-dimethoxybenzene (5.0 g, 36.1 mol) was added to the reaction mixture and the mixture was allowed for stirring for 24 h at room temperature. On the completion of the reaction, the reaction mixture was poured into ice-cold water and the organic part was derived with DCM (50 mL x 3). The organic layer was washed with sodium bicarbonate and brine solution and was dried over Na_2SO_4. The crude product **(2)** obtained was purified by column chromatography using ethylacetate/hexanes (25:75) in 65.5% yield.

Procedure adopted for the synthesis of compounds 3 and 5

10.6 mol of chloro-compound (**2** or **4**) was dissolved in 30 mL acetone. An aqueous solution of sodium azide (63.0 mol) was added dropwise to the stirring solution at room temperature. The reaction took 3–4 days for completion. The reaction mixture was poured into ice-cold water and the organic part was extracted with diethyl ether (30 mL x 3). The organic layer was dried over Na_2SO_4. The compounds obtained (**3** and **5**) in 65–75% yield were used for onward reaction steps without purification.

Procedure followed for the synthesis of compound 7

To a solution of 4,7-dichloroquinoline (1.0 g, 5.0 mol) in 30 mL DMSO, NaN_3 (0.39 g, 6.0 mol) was added. The reaction vessel was wrapped with aluminium foil to avoid light and the mixture was allowed for stirring at room temperature for 6-10 h duration. After the disappearance of the starting materials, the reaction mixture was poured into 50 mL water and the desired product was extracted with DCM (20 mL x 3). The DCM layer was washed with brine solution and dried over Na_2SO_4. The crude product **7** was purified with column chromatography using ethylacetate/hexanes (40:60), in 49% yield.

Procedure for the synthesis of compound 10

Propargyl alcohol (0.5 g, 8.9 mol) was dissolved in dry DMF at 0 °C. NaH (0.6 g, 25.0 mol) was added in small instalments and the mixture was allowed for stirring at 0 °C for half an hour. A solution of 4,7-dichloroquinoline (1.7 g, 8.5 mol) was added dropwise to the reaction mixture. The reaction was allowed for string for 4 h at room temperature. After the completion, the reaction was quenched with ice-cold water and the organic compound was obtained by ethylacetate. The organic layer was washed with brine solution and dried over

Na_2SO_4. The crude product **10** was purified by column chromatography using ethylacetate/hexanes (15:85) in 63% yield. The pure compound obtained was white coloured powder.

General procedure for the synthesis of terminal alkyl compounds 13,15,17, 23 and **25.**

In general, precursor compounds: **11,14,16,22** and **24** (3.32 mol) were dissolved in 30 mL dry DMF at room temperature. Potassium carbonate (4.98 mol) was added to the stirring reaction mixtures. After 1 h, 3.98 mol of propargyl bromide dissolved in 20 mL dry DMF was added dropwise. The reaction mixtures were allowed for string at room temperature till the disappearance of the starting materials (12–24 h). The reaction mixtures were poured into ice-cold water and the organic compound were obtained by ethylacetate. The organic layers were washed with brine solution and dried over Na_2SO_4. The crude products (**13, 15, 17, 23** and **25**) were purified by column chromatography using ethylacetate/hexanes (usually 5:95). The pure compounds obtained in 60–70% yield were proceeded for further reactions.

Procedure for the synthesis compound 21[1]

A solution of resorcinol (2.0 g, 18.16 mol) in Ethyl acetoacetate (2.4 mL, 19 mol) was added dropwise to concentrated H_2SO_4 (20 mL) in a round bottom flask at 0 °C. The reaction was allowed for stirring overnight at room temperature. In the next morning, the reaction mixture was carefully poured into crushed ice with continuous stirring. A solid precipitate obtained was filtered, the residue was washed with cold water and dried to obtain pale yellow powder **(20)** in 49% yield. In the next step, K_2CO_3 (1.16 g, 8.3 mol) was added to a solution of 7-hydroxy-4-methylchroman-2-one **(20)** (1 g, 5.6 mol) and acetone. The reaction mixture was allowed for stirring at room temperature for 1 h. 8.3 mol of propargyl bromide dissolved in 20 mL acetone was added dropwise to the reaction mixture. It took 18 h to complete the reaction at 50 °C. After the completion of the reaction, the acetone was removed using vacuum rota evaporator and the organic layer was extracted with ethylacetate (30 mL x 3). The organic layer was washed with brine solution and dried over Na_2SO_4. The crude product **21** was purified by column chromatography using ethylacetate/hexanes (15:85) in 72% yield.

Prediction of solubility and lipophilicity

A web-based platform ADMETlab, designed on Django framework in Python for calculating chemical ADMET properties was used to predict drug likeliness of the compounds and whether these compounds can cross the BBB etc.[2]

Table S1*: Predicted values of the compounds that support their ability to pass through Blood-brain barrier (BBB).*

Compounds	Molecular Weight	Volume distribution	Water solubility (LogS)	cLogD (distribution coefficient at pH 7.4)	clogP	Plasma protein binding (PPB)	Blood Brain Barrier probability	Clearance (Extraction)	H-Bond Acceptor	H-Bond Donor	Lipinski`s rule
Tr1	452.13	-0.489	-5.323	1.788	4.349	90.077	0.862	1.022	8	0	✓
Tr3	418.16	-0.115	-4.825	1.55	3.384	91.848	0.86	1.741	8	0	✓
Tr5	291.31	-0.399	-2.318	0.021	1.061	69.557	0.912	1.54	7	1	✓
Tr6	364.04	-0.462	-5.266	1.238	3.747	92.652	0.932	0.796	6	0	✓
Tr7	442.11	-0.574	-4.942	1.734	3.768	92.1	0.735	0.739	7	1	✓
Tr8	455.16	-0.659	-3.967	1.62	2.598	87.153	0.684	1.05	6	0	✓
Tr9	449.16	-0.325	-4.923	1.305	3.562	91.85	0.667	1.307	7	0	✓
Tr10	418.08	-0.425	-5.152	1.387	4.463	92.109	0.831	1.237	7	0	✓
Tr11	387.09	-0.002	-4.916	2.84	4.284	84.548	0.947	1.189	9	0	✓
Tr12	409.02	-0.03	-5.735	2.886	5.371	84.673	0.93	0.806	7	1	✓
Tr13	422.07	-0.154	-4.905	1.603	4.646	89.554	0.881	1.248	6	0	✓
Tr14	409.16	-0.312	-4.723	1.529	3.35	89.116	0.882	1.379	6	0	✓
Tr15	420.14	-0.753	-4.228	0.712	2.298	91.483	0.913	0.959	6	0	✓
Tr16	409.16	-0.384	-4.702	1.521	3.35	88.732	0.867	1.403	8	0	✓
Tr17	378.09	-0.298	-5.409	1.532	4.251	93.711	0.918	0.986	8	0	✓
Tr18	378.09	-0.272	-5.437	1.545	4.251	93.414	0.929	0.991	8	0	✓

Spectral data

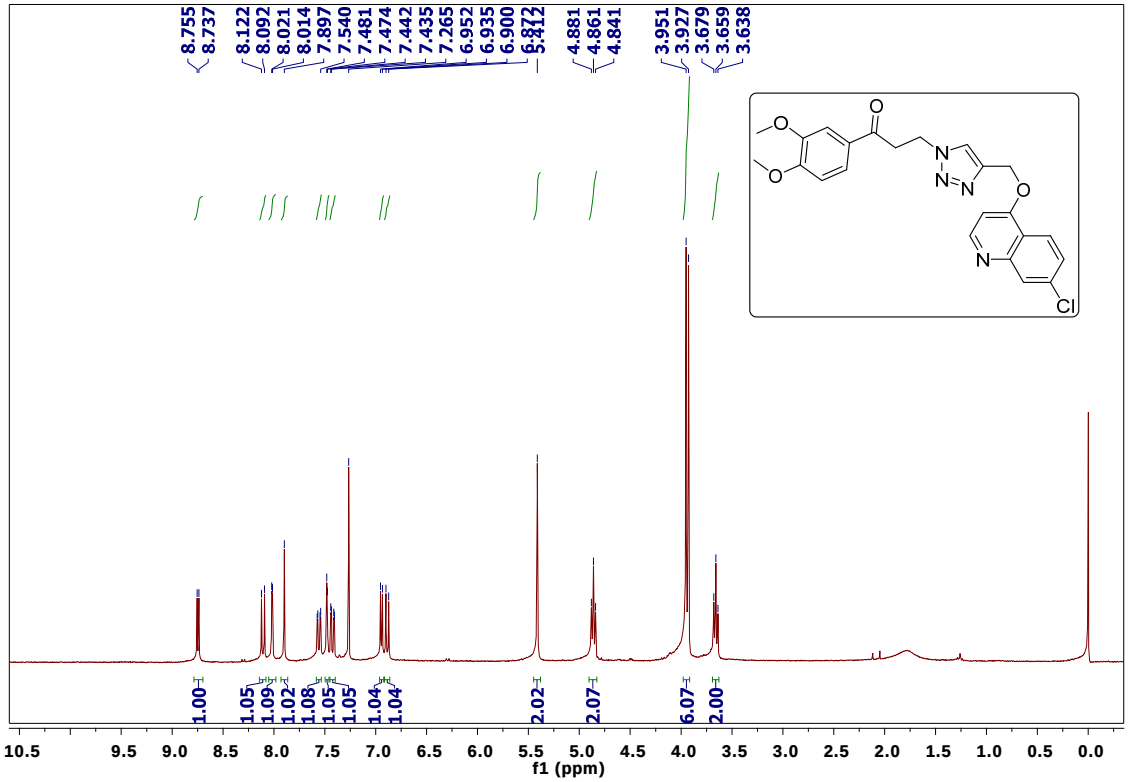


Figure S1:^{1}H NMR of Tr1

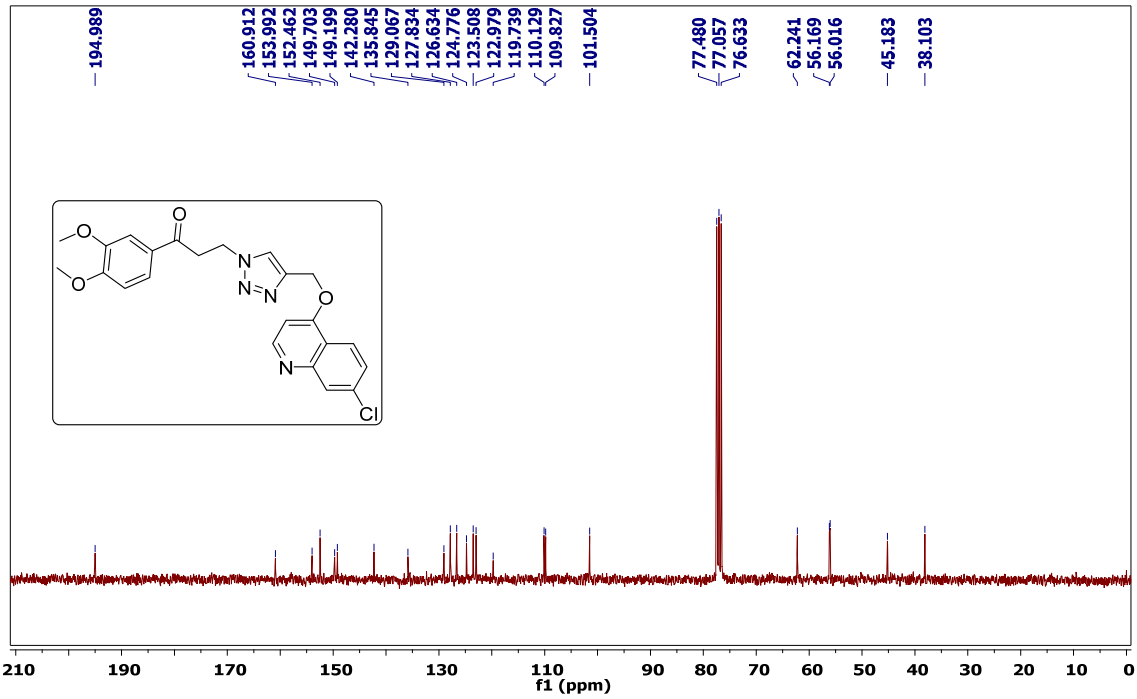


Figure S2:^{13}C NMR of Tr1

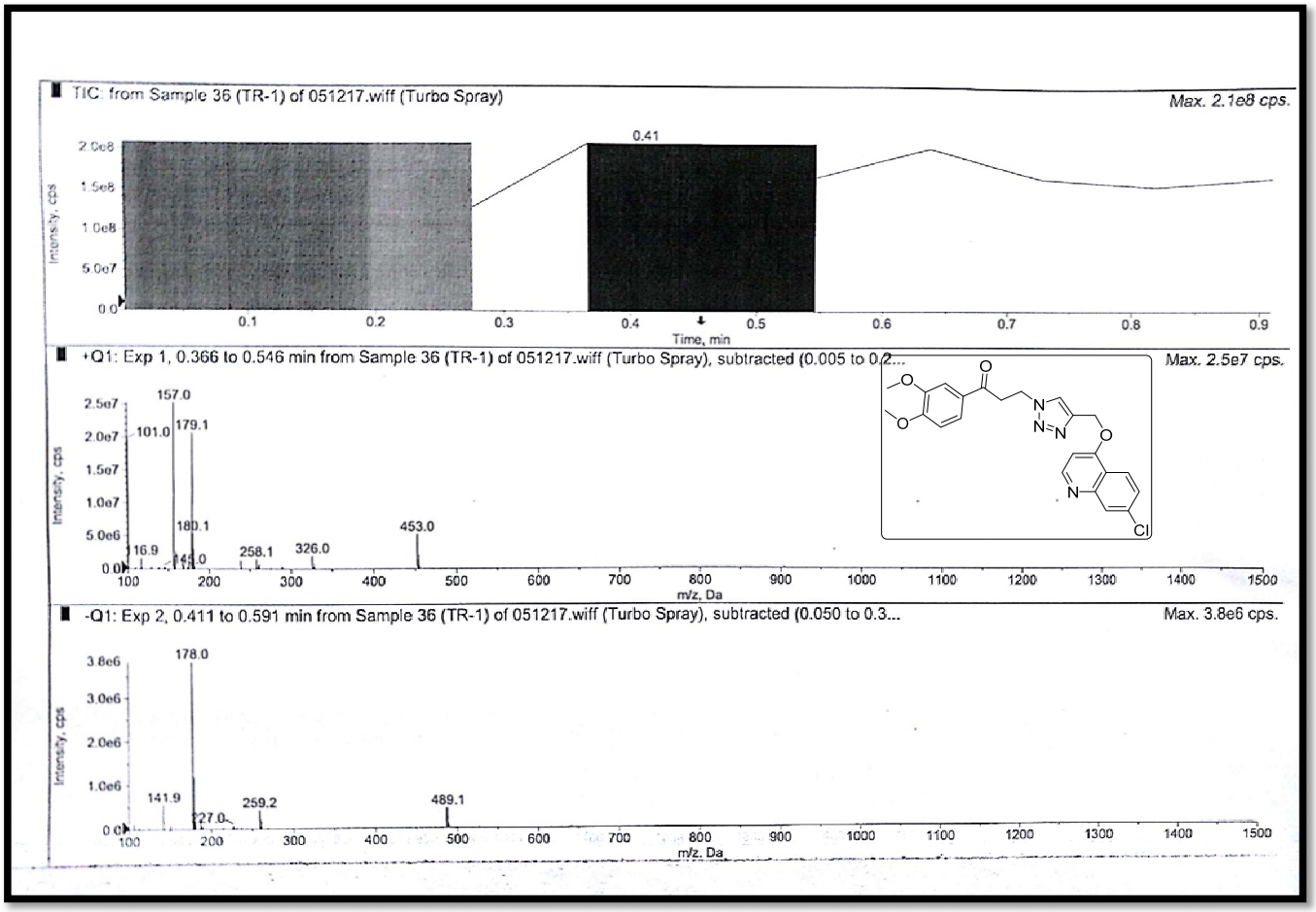


Figure S3: Mass spectrum of Tr1

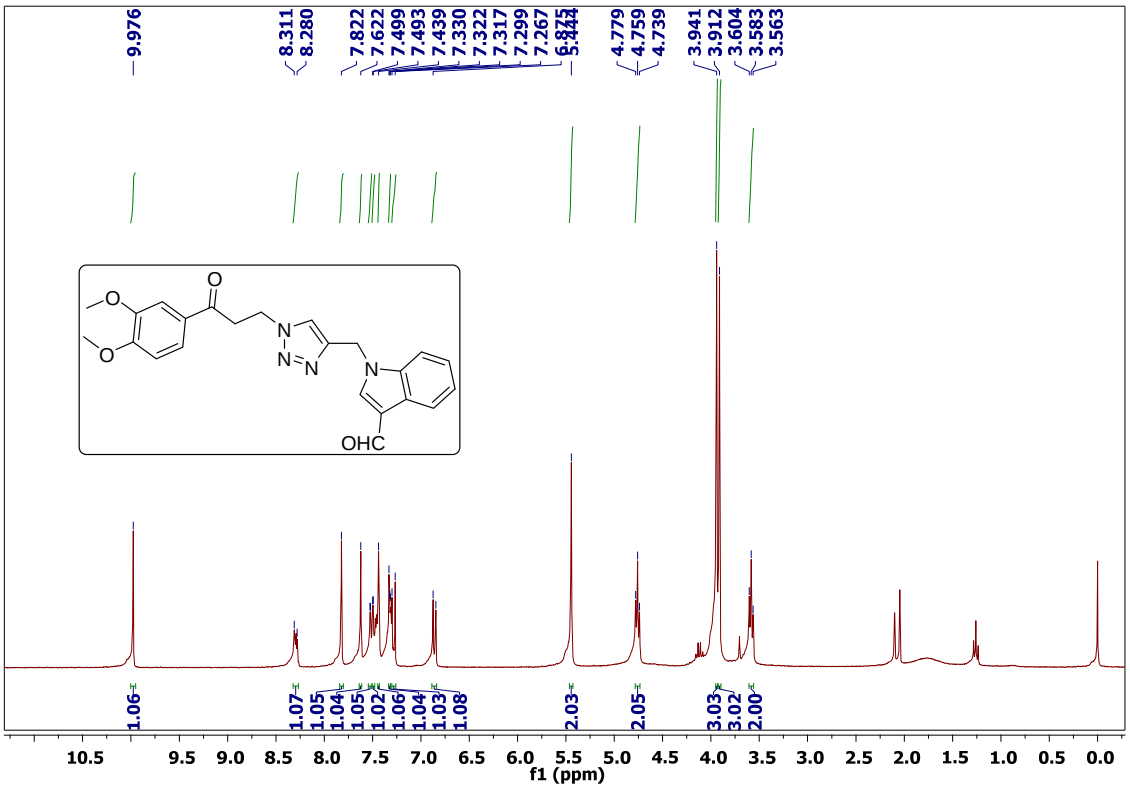


Figure S4: ^{1}H NMR of Tr3

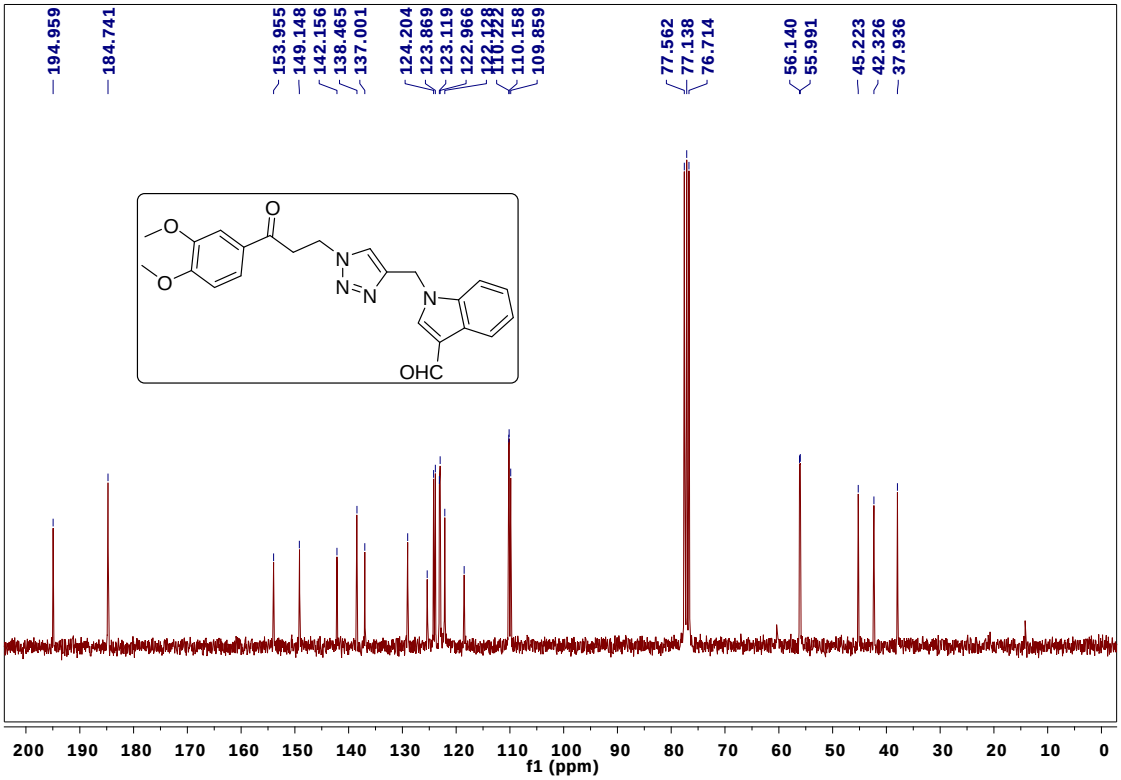


Figure S5: ^{13}C NMR of Tr3

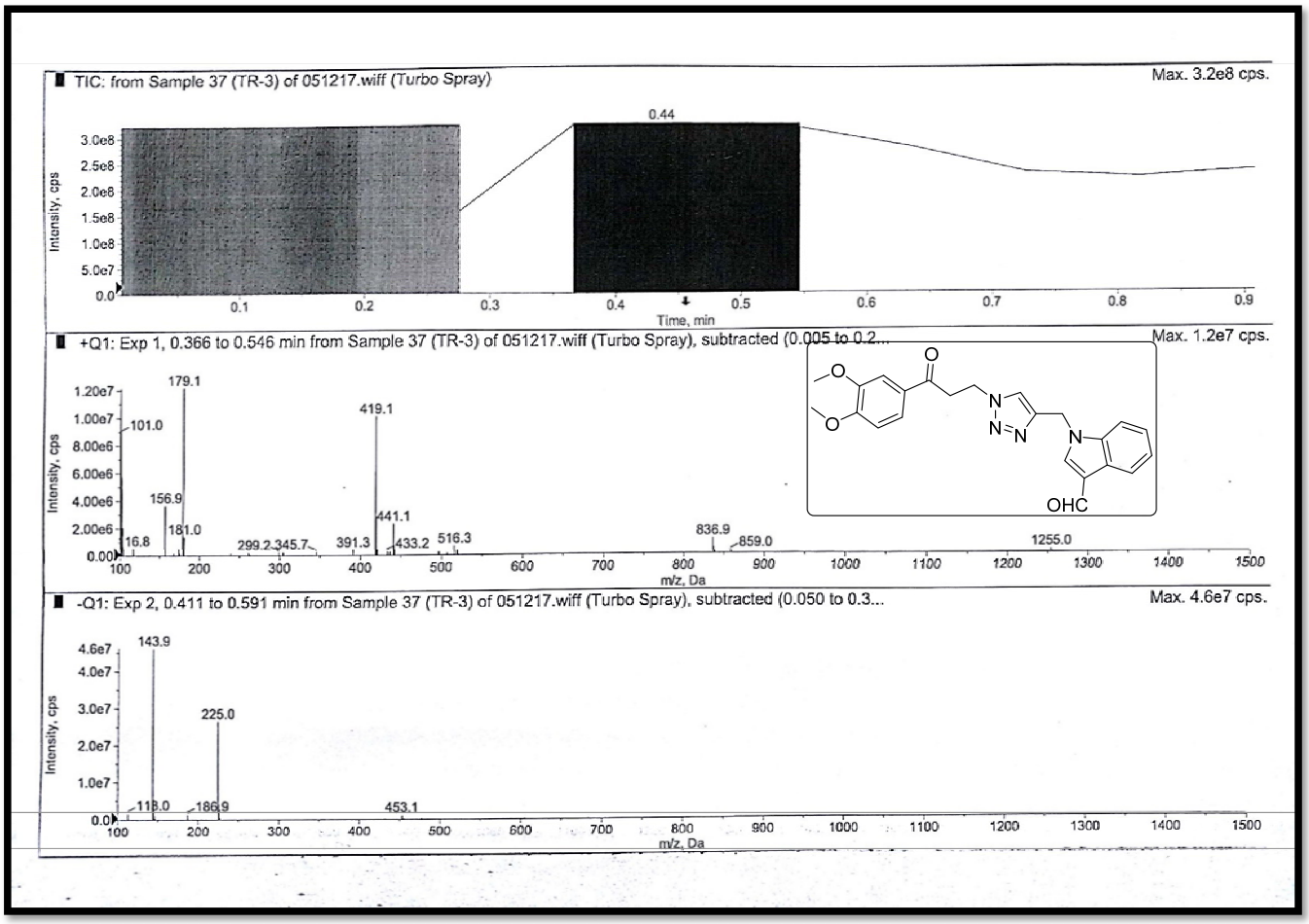


Figure S6: Mass spectrum of Tr3

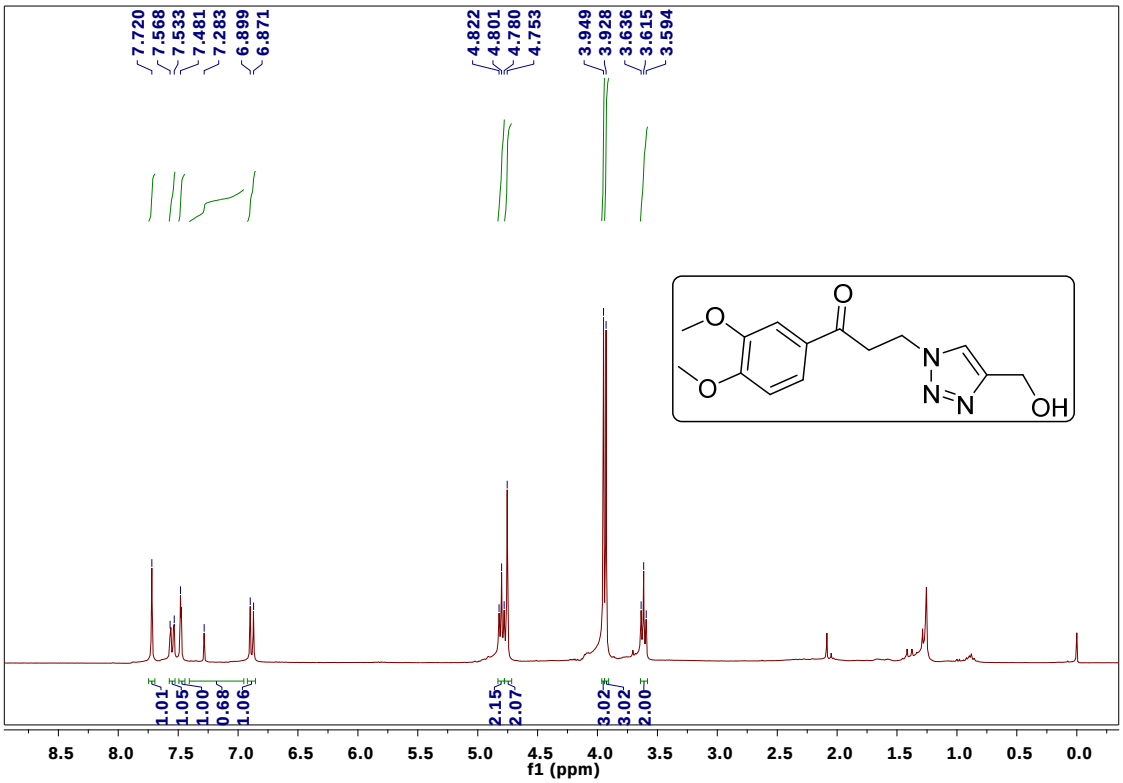


Figure S7: ^{1}H NMR of Tr5

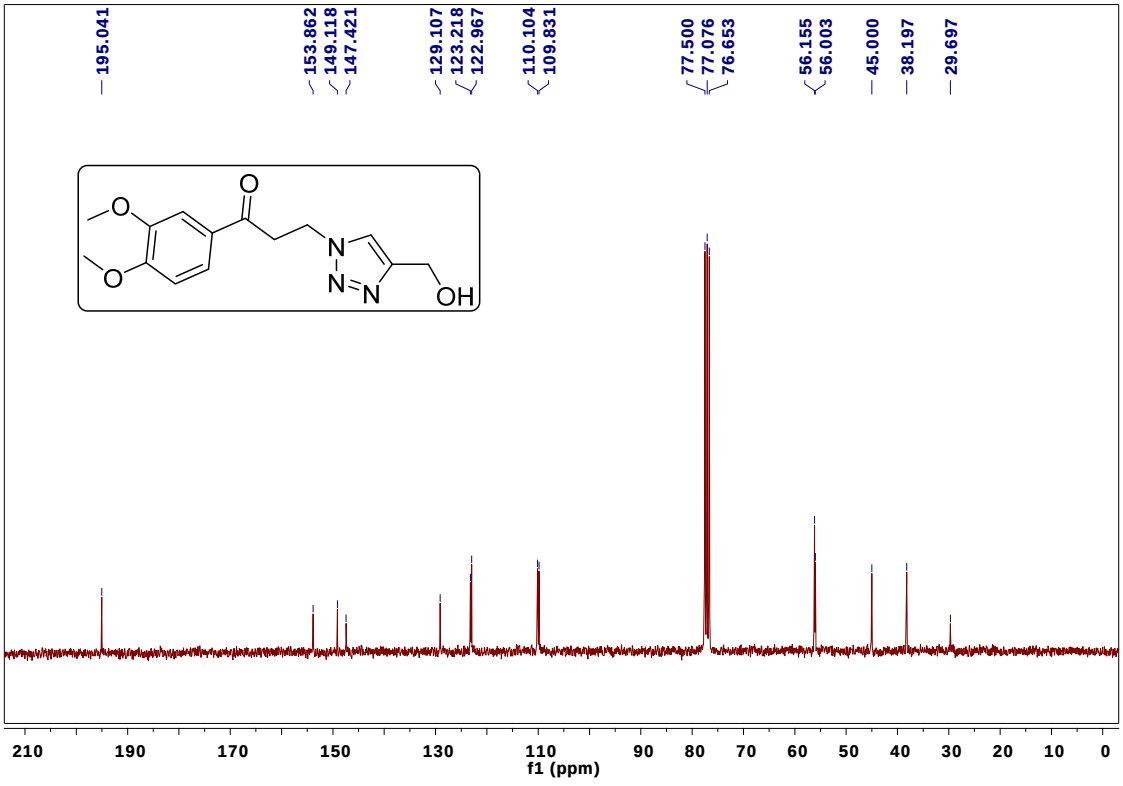


Figure S8: ^{13}C NMR of Tr5

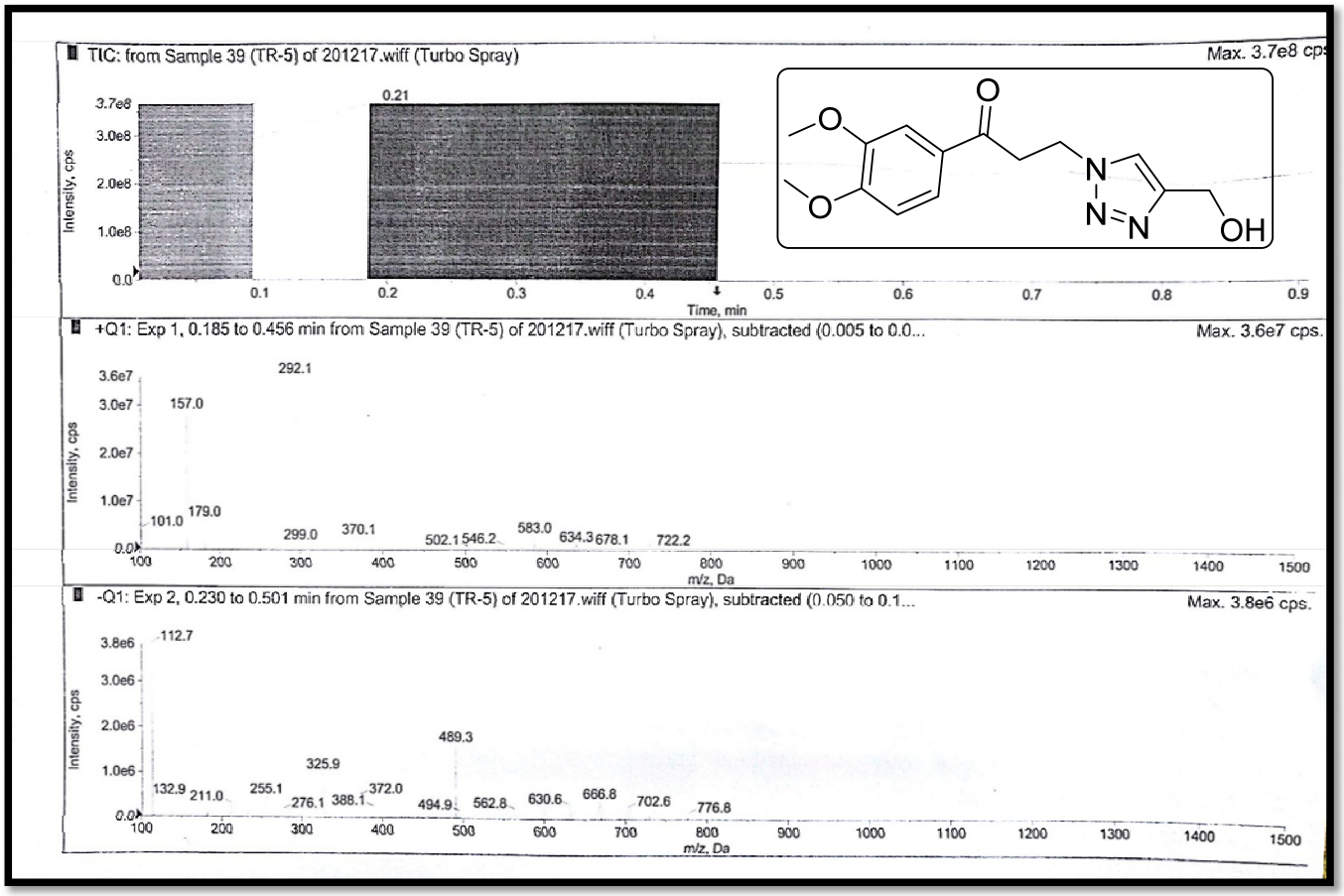


Figure S9: Mass spectrum of Tr5

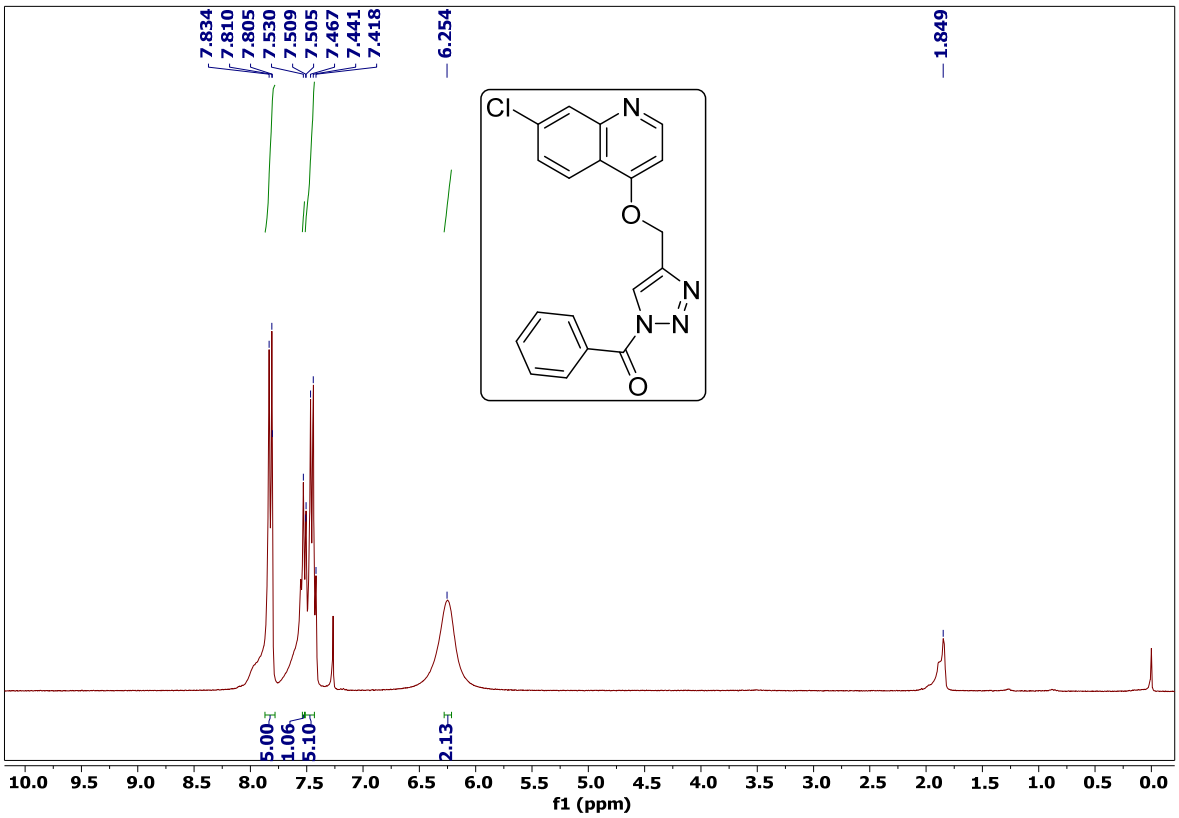


Figure S10: ^{1}H NMR of Tr6

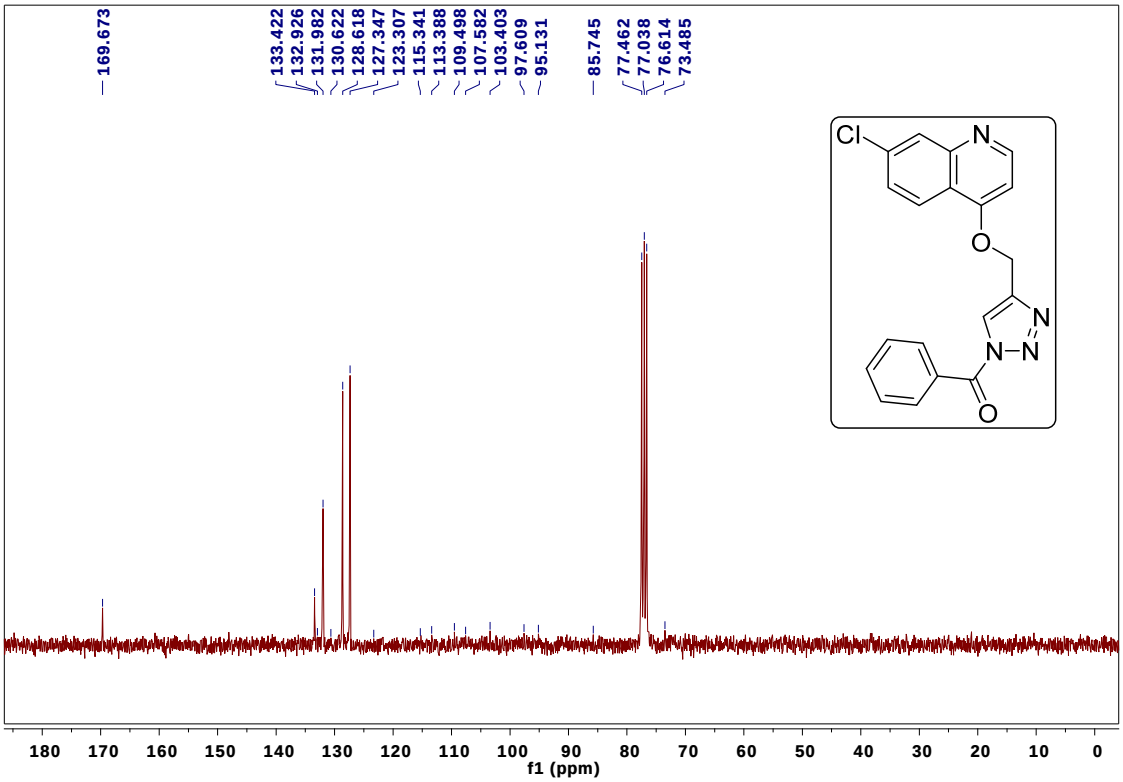


Figure S11: ^{13}C NMR of Tr6

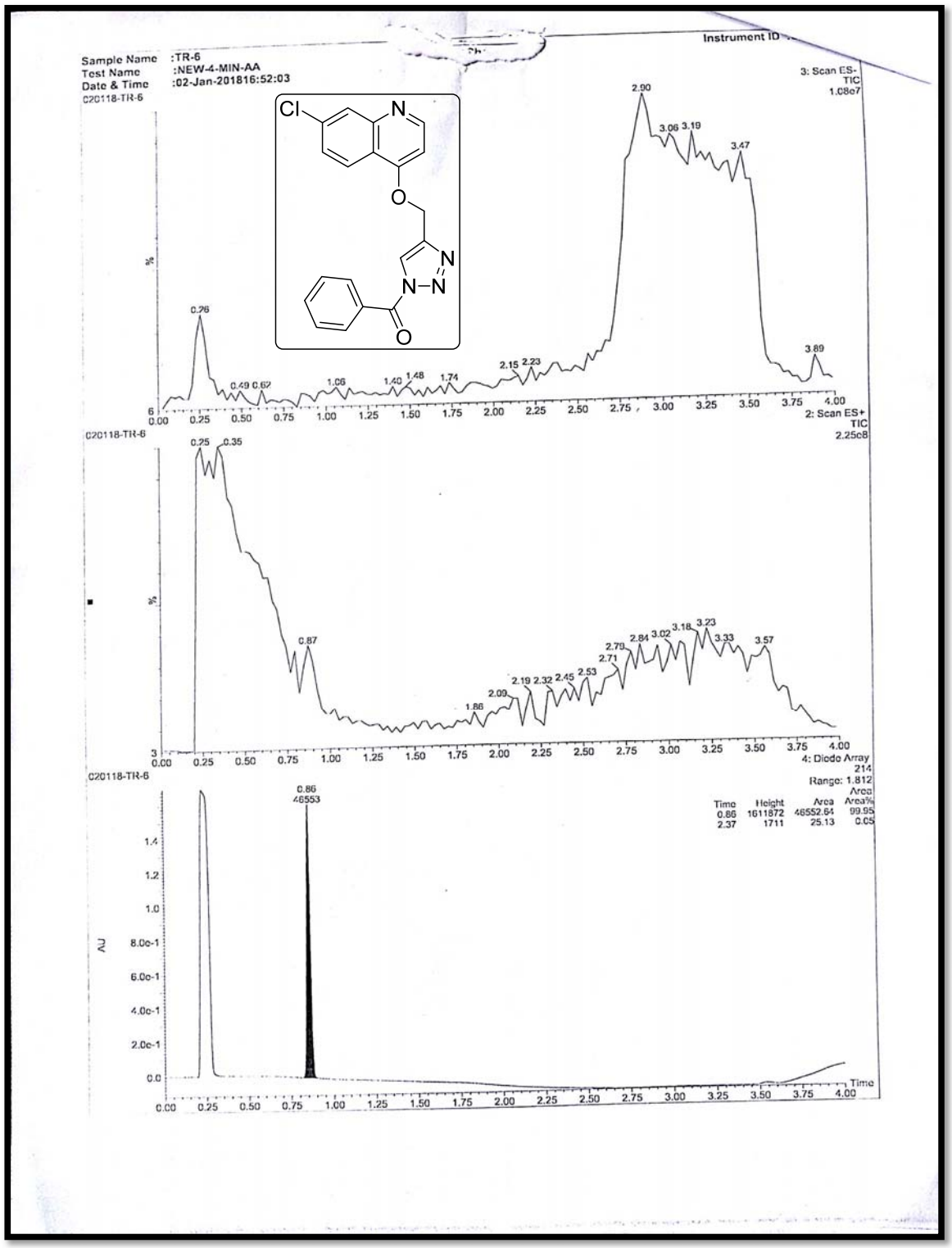


Figure S12a: Mass spectrum of Tr6

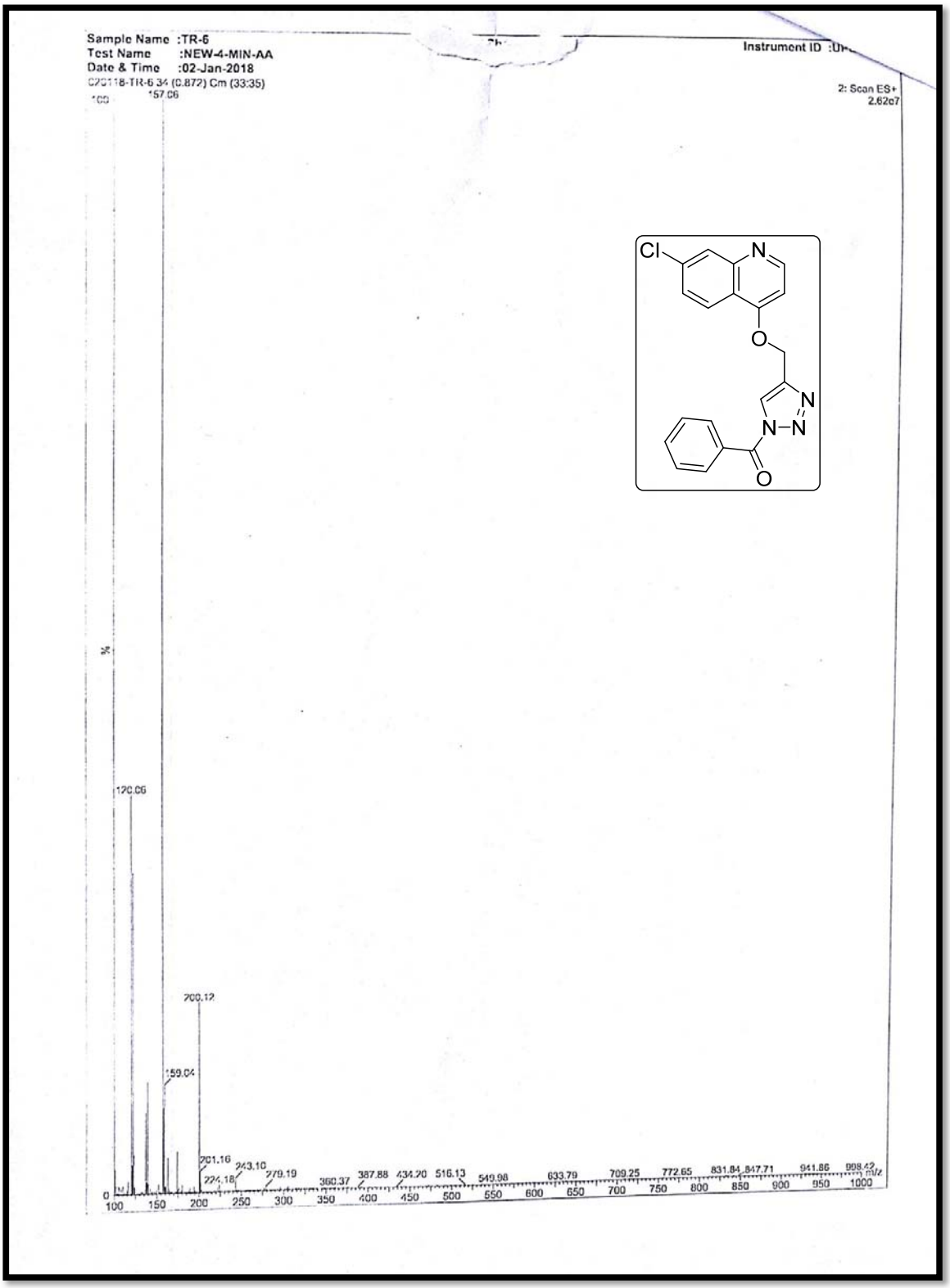


Figure S12b: Mass spectrum of Tr6

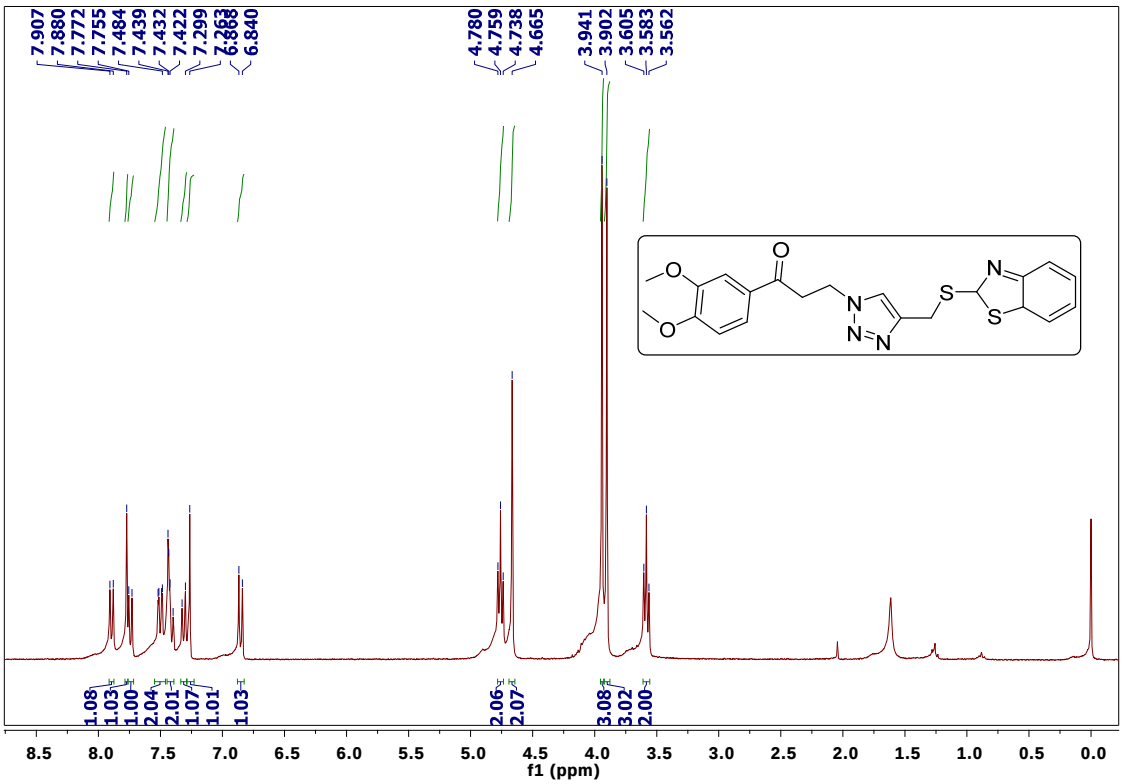


Figure S13: ^{1}H NMR of Tr7

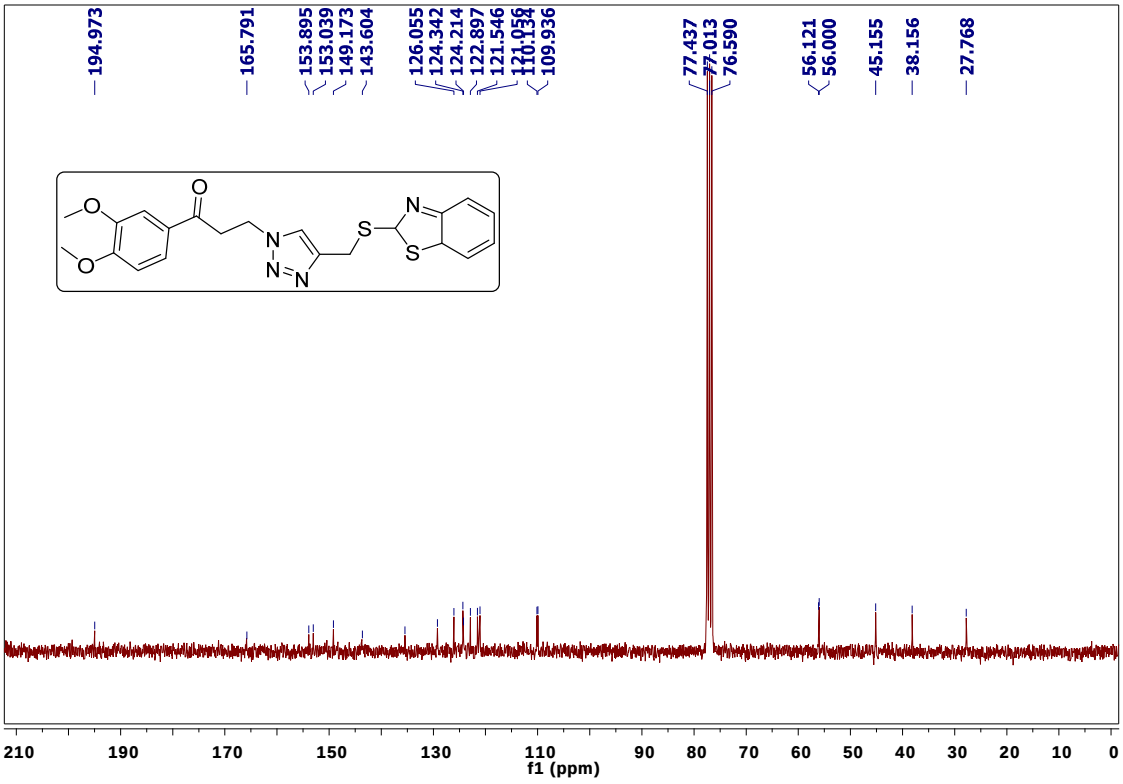


Figure S14: ^{13}C NMR of Tr7

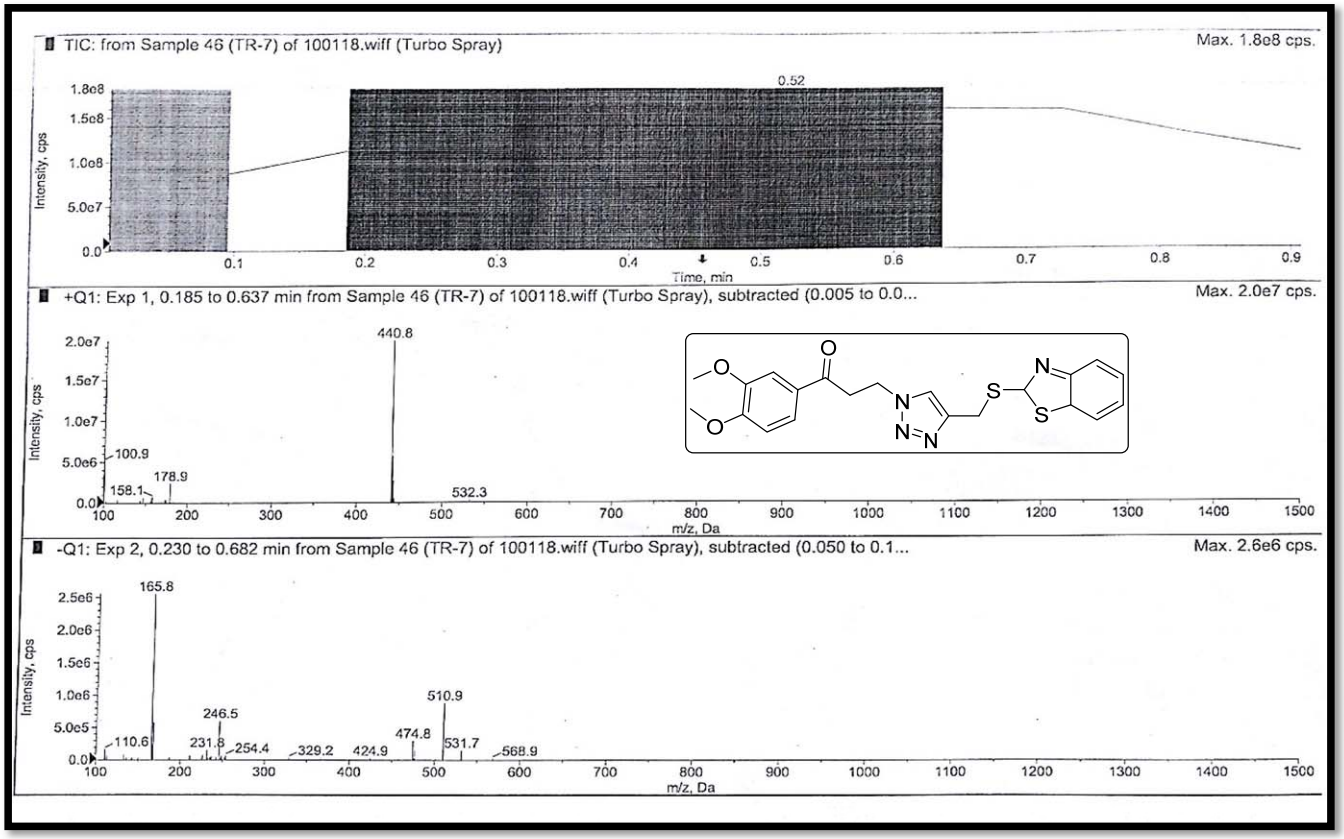


Figure S15: Mass spectrum of Tr7

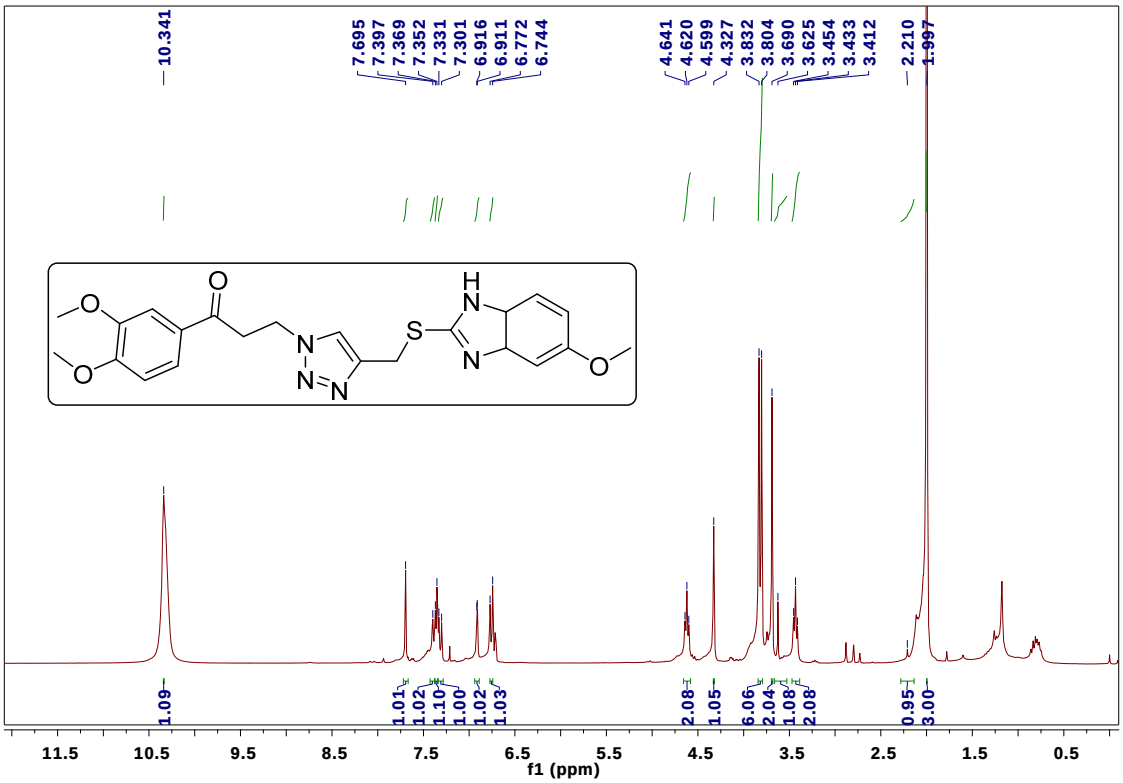


Figure S16: ^{1}H NMR of Tr8

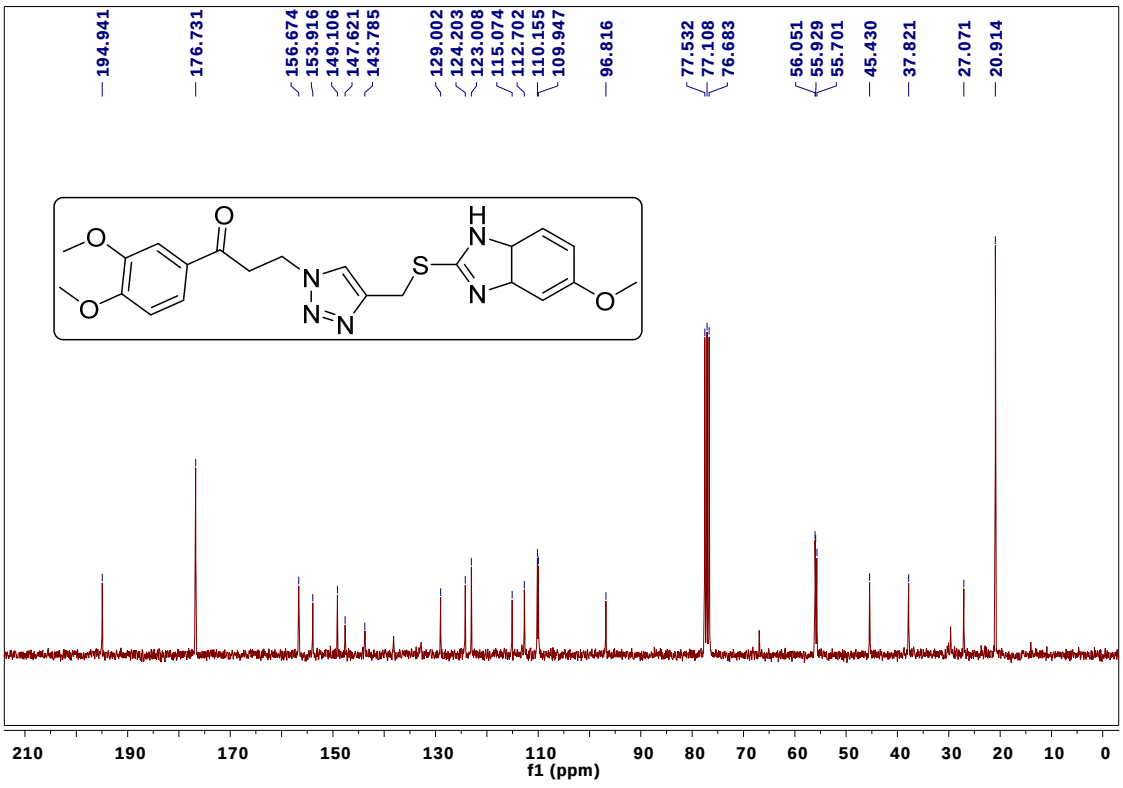


Figure S17: ^{13}C NMR of Tr8

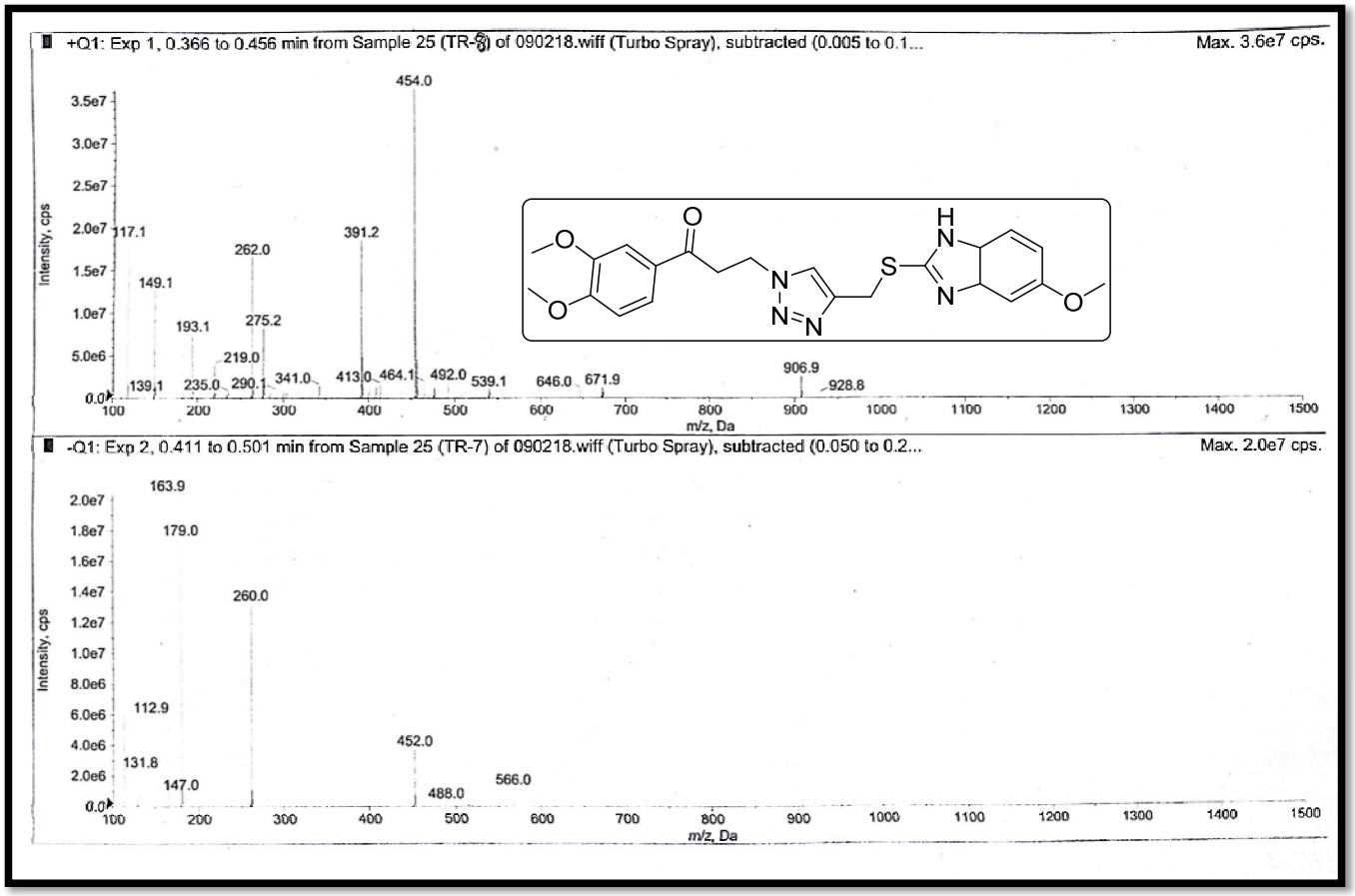


Figure S18: Mass spectrum of Tr8

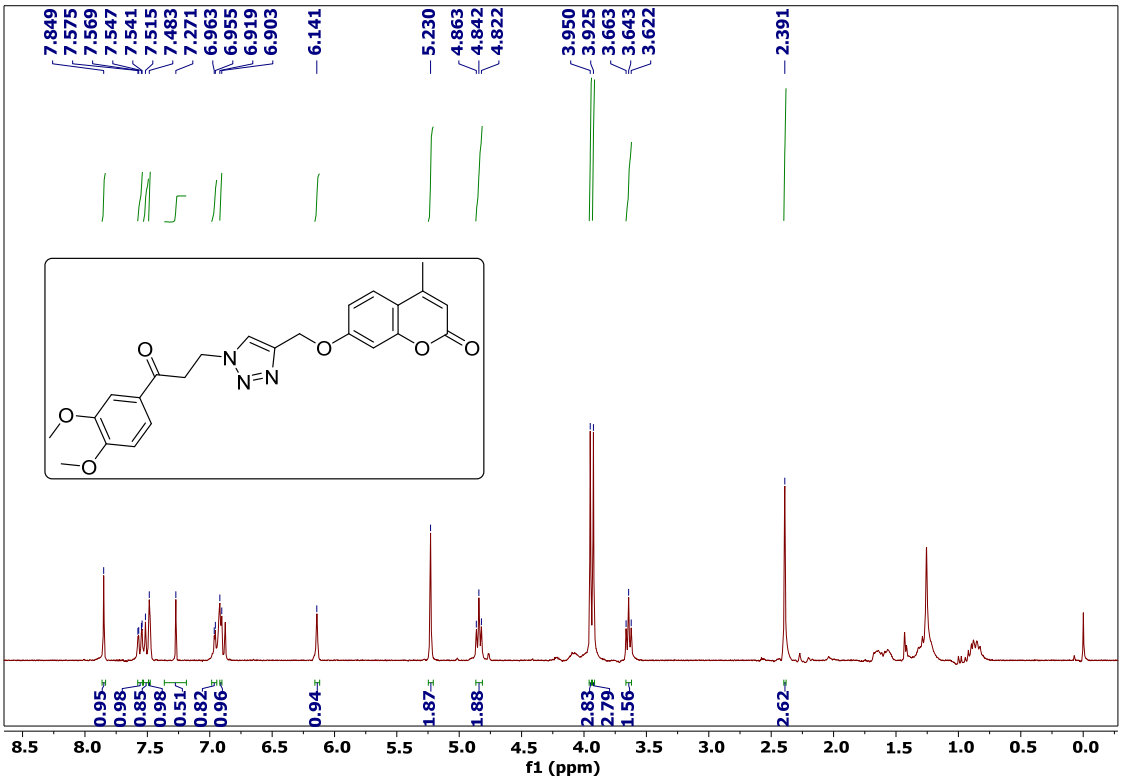


Figure S19: ^{1}H NMR of Tr9

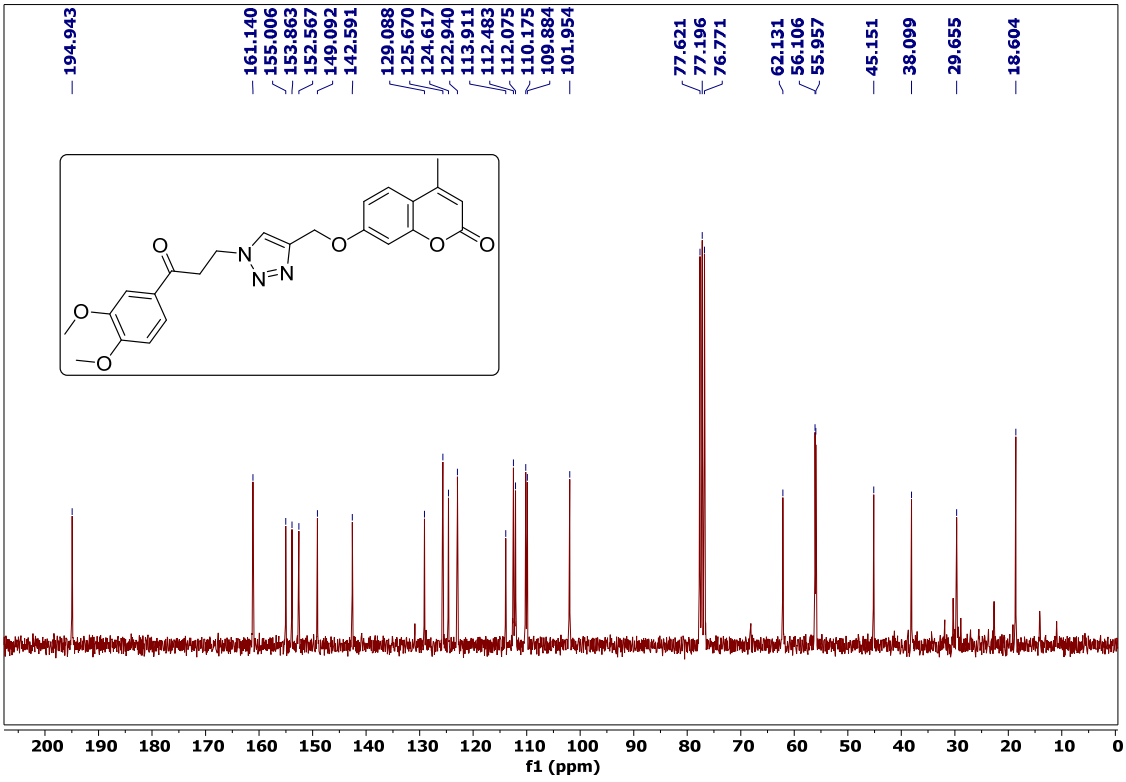


Figure S20: ^{13}C NMR of Tr9

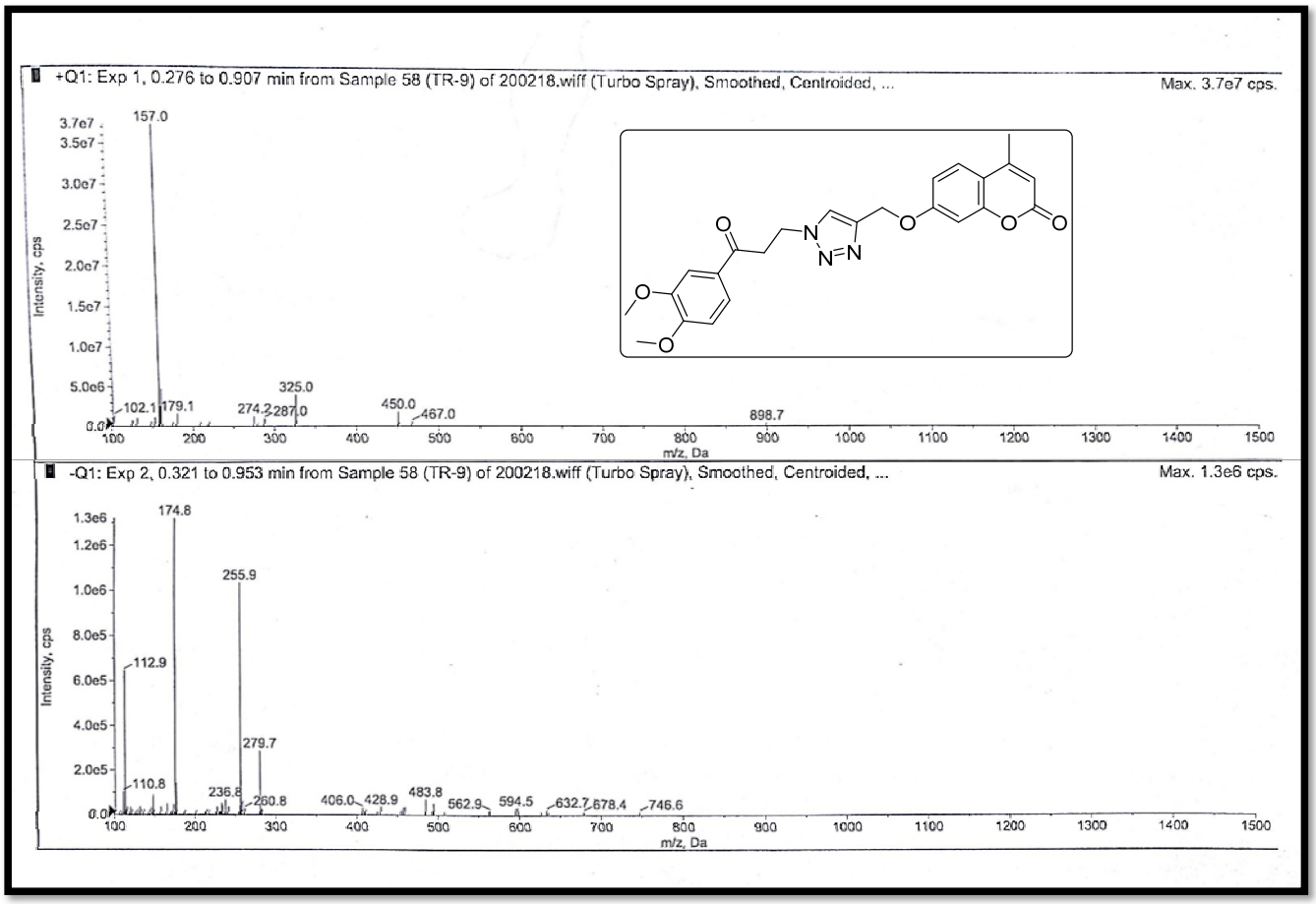


Figure S21: Mass spectrum of Tr9

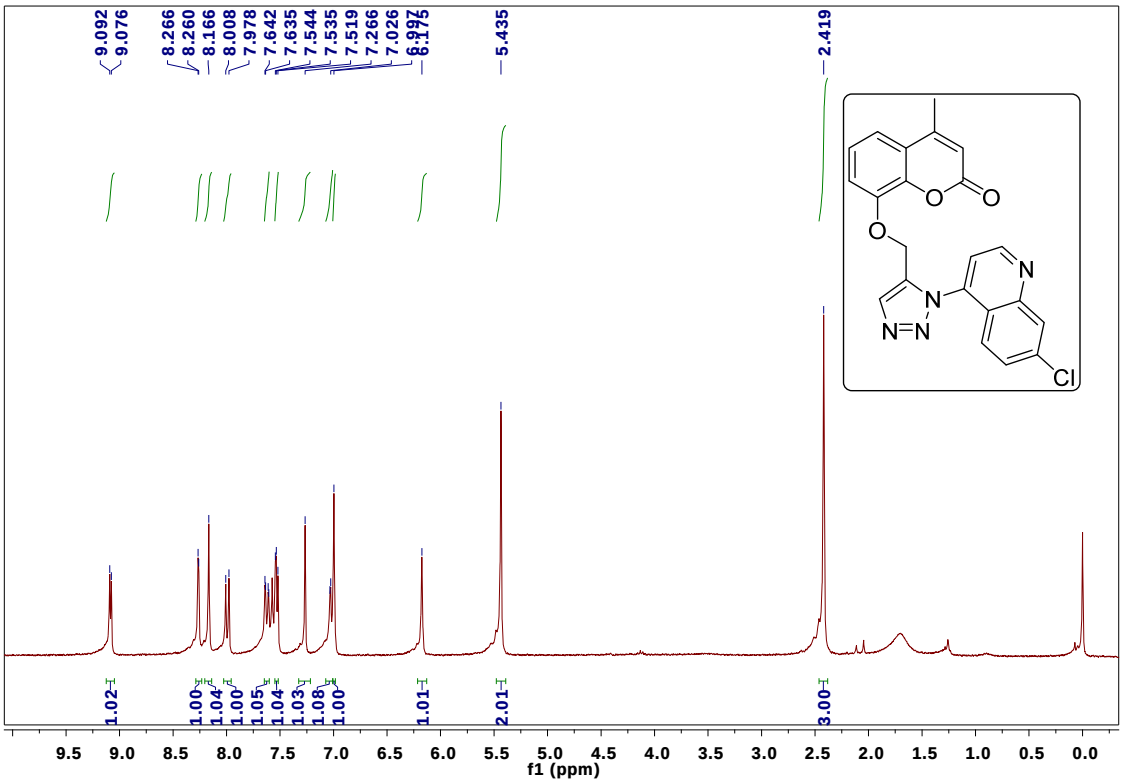


Figure S22: ^{1}H NMR of Tr10

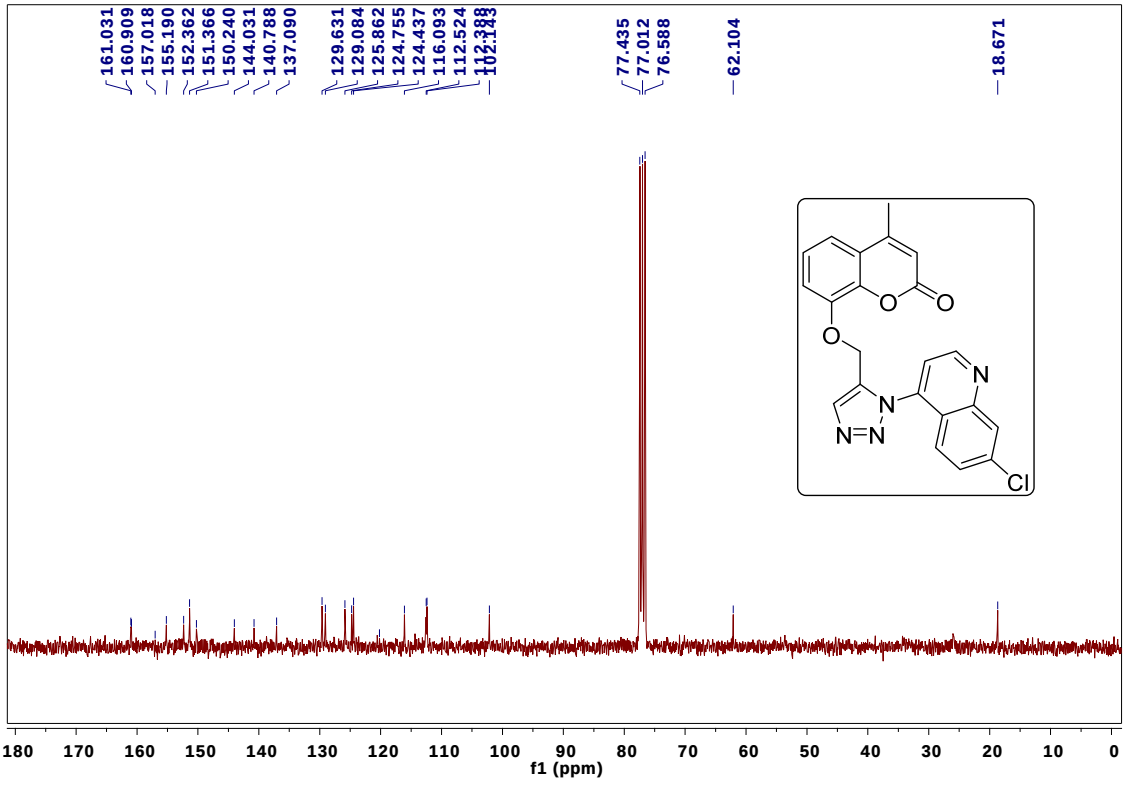


Figure S23: ^{13}C NMR of Tr10

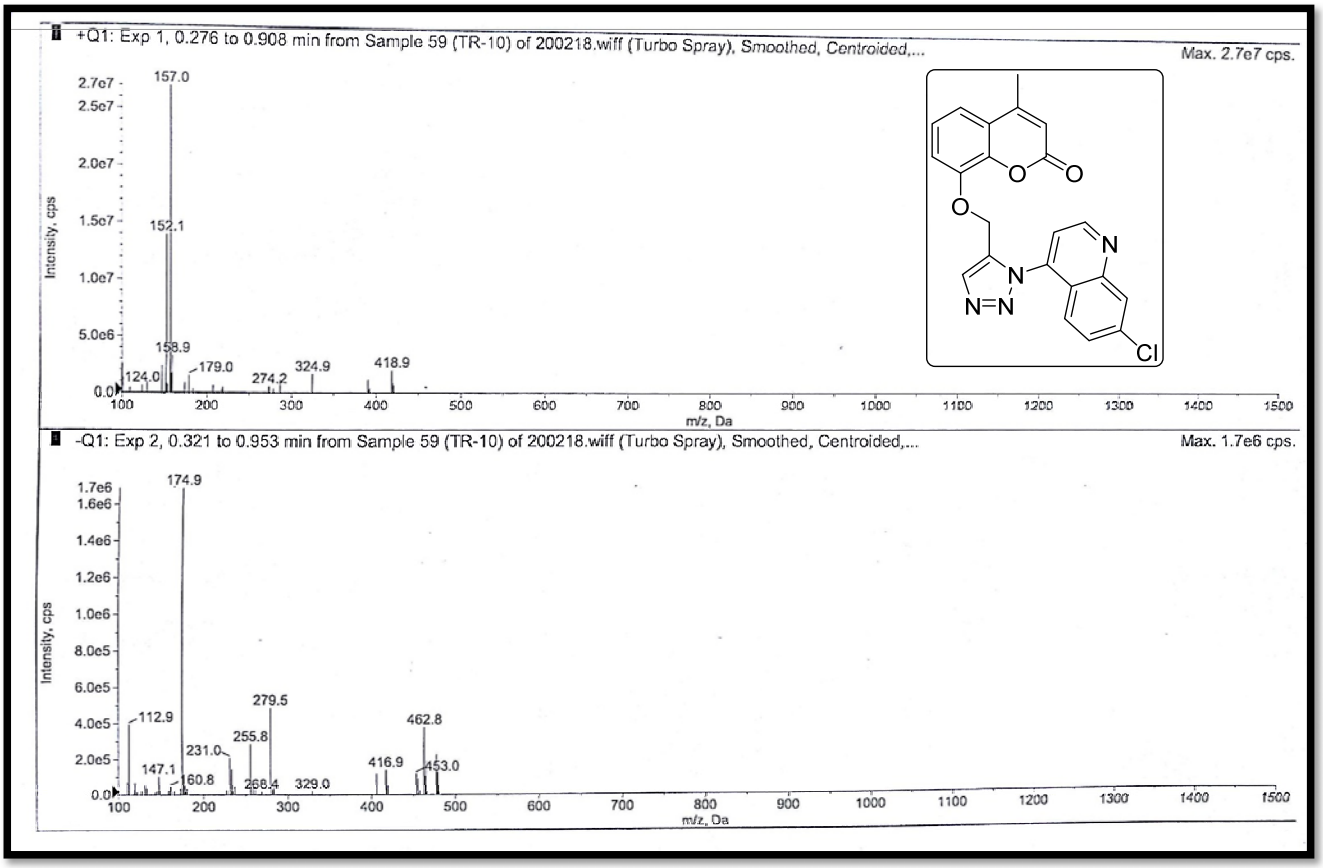


Figure S24: Mass spectrum of Tr10

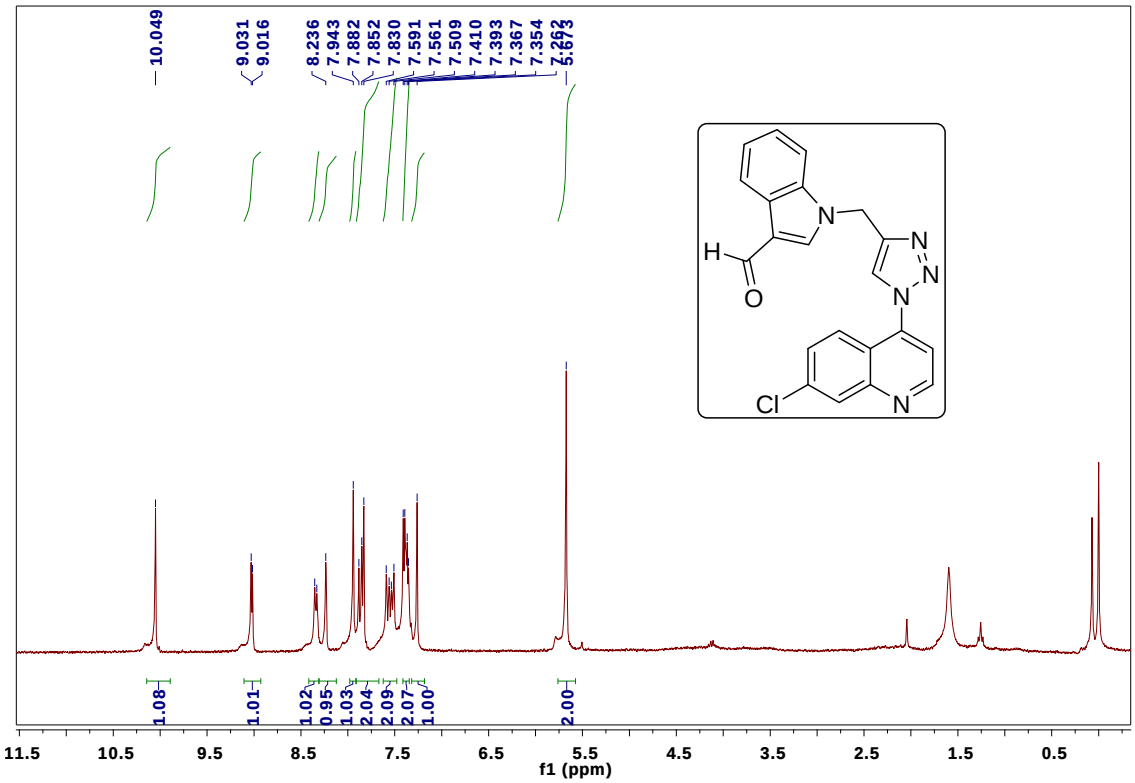


Figure S25: ^{1}H NMR of Tr11

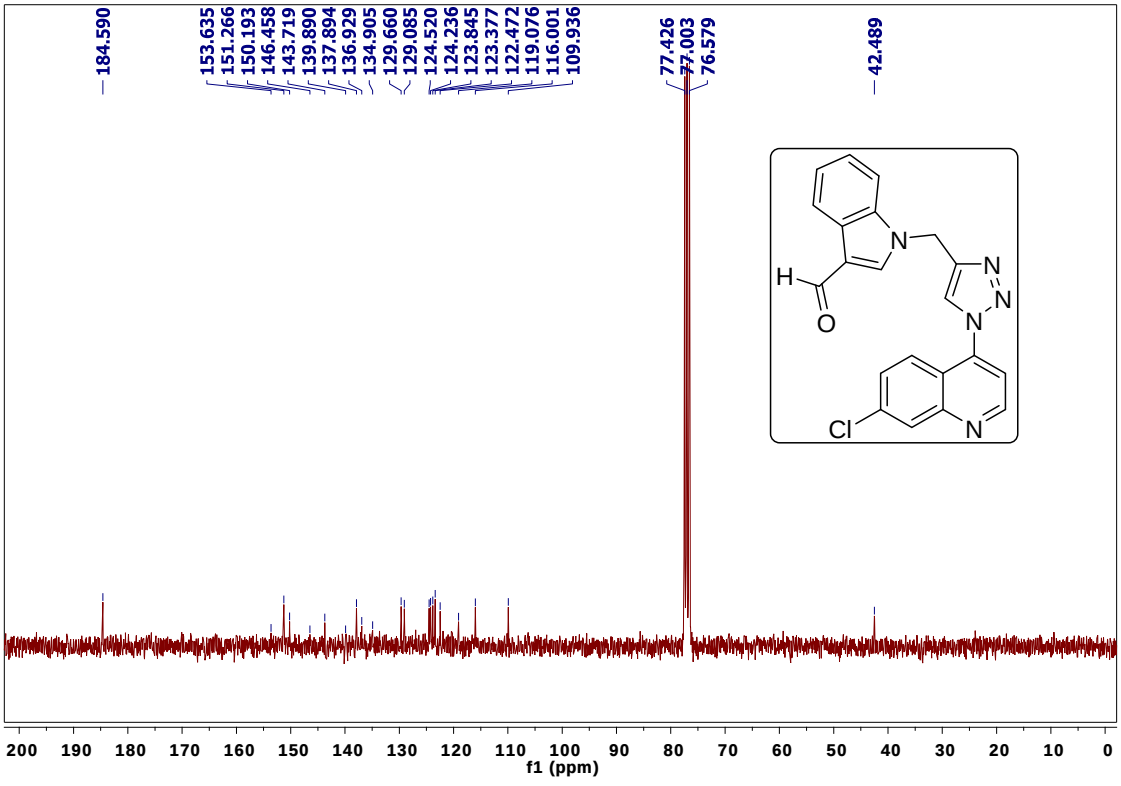


Figure S26: ^{13}C NMR of Tr11

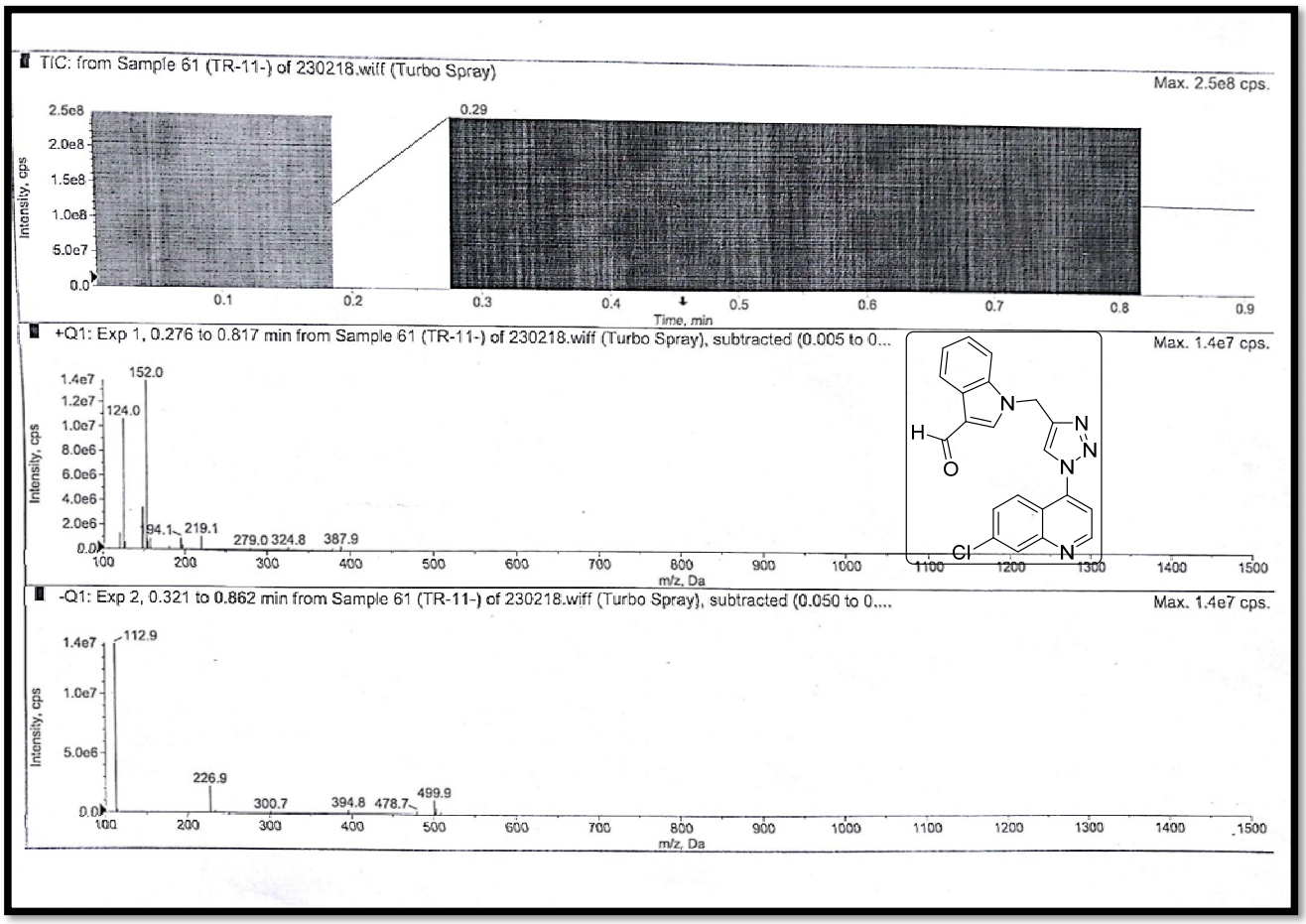


Figure S27: Mass spectrum of Tr11

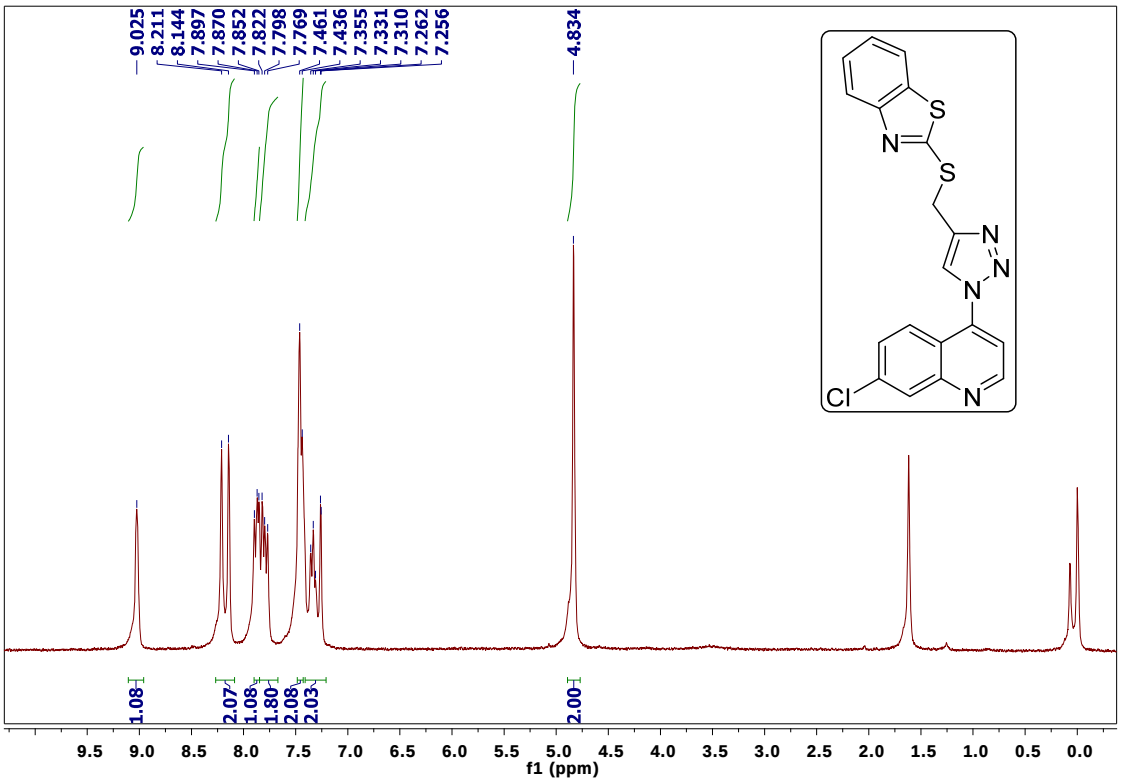


Figure S28: ^{1}H NMR of Tr12

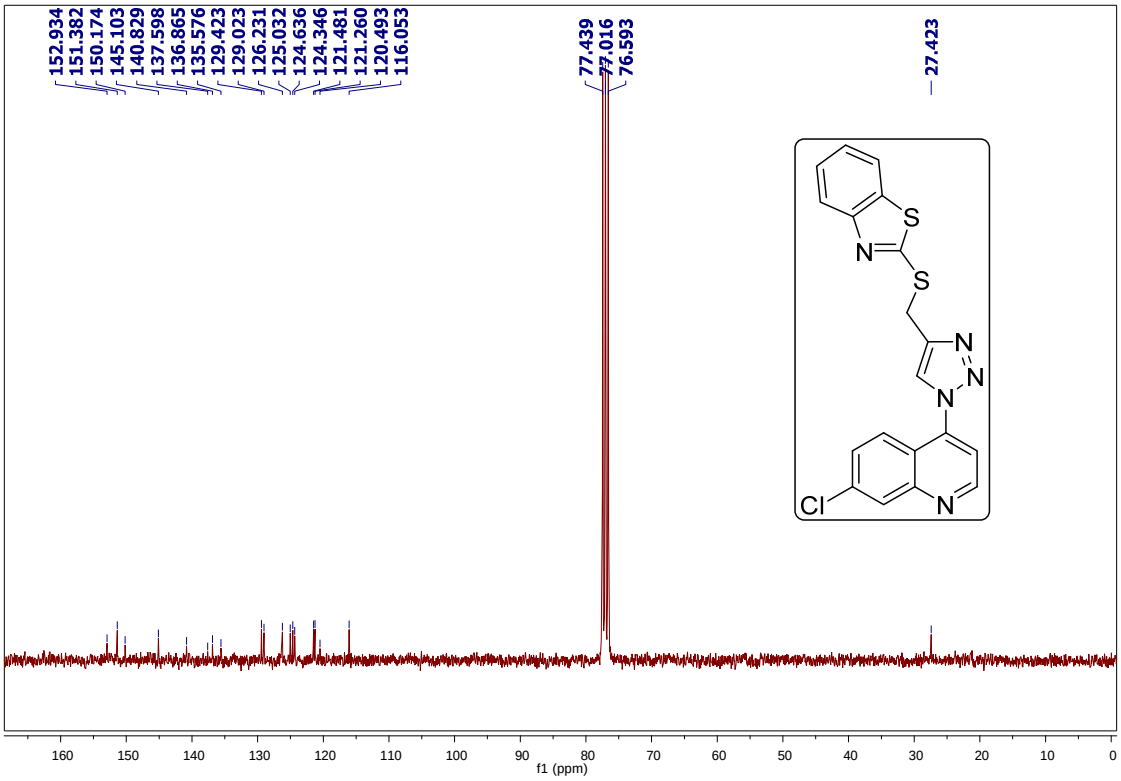


Figure S29: ^{13}C NMR of Tr12

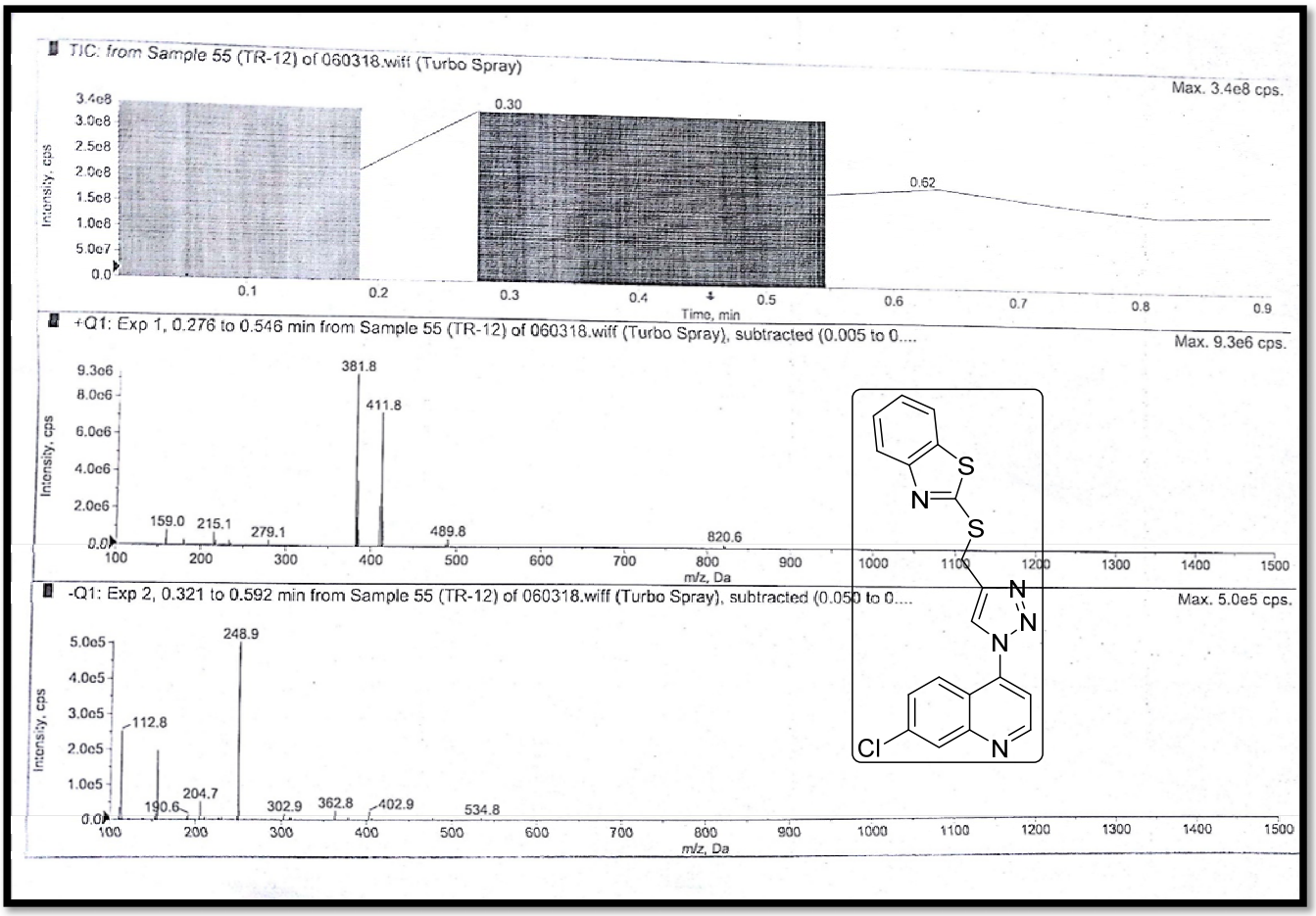


Figure S30: Mass spectrum of Tr12

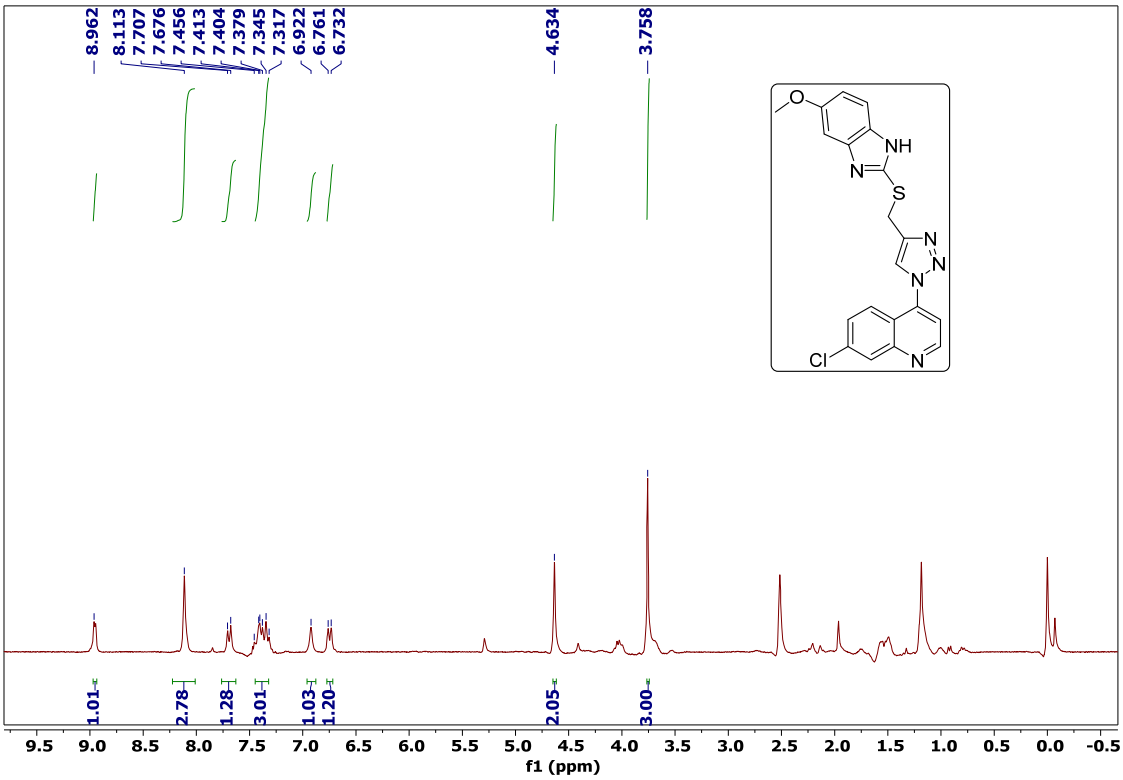


Figure S31: ^{1}H NMR of Tr13

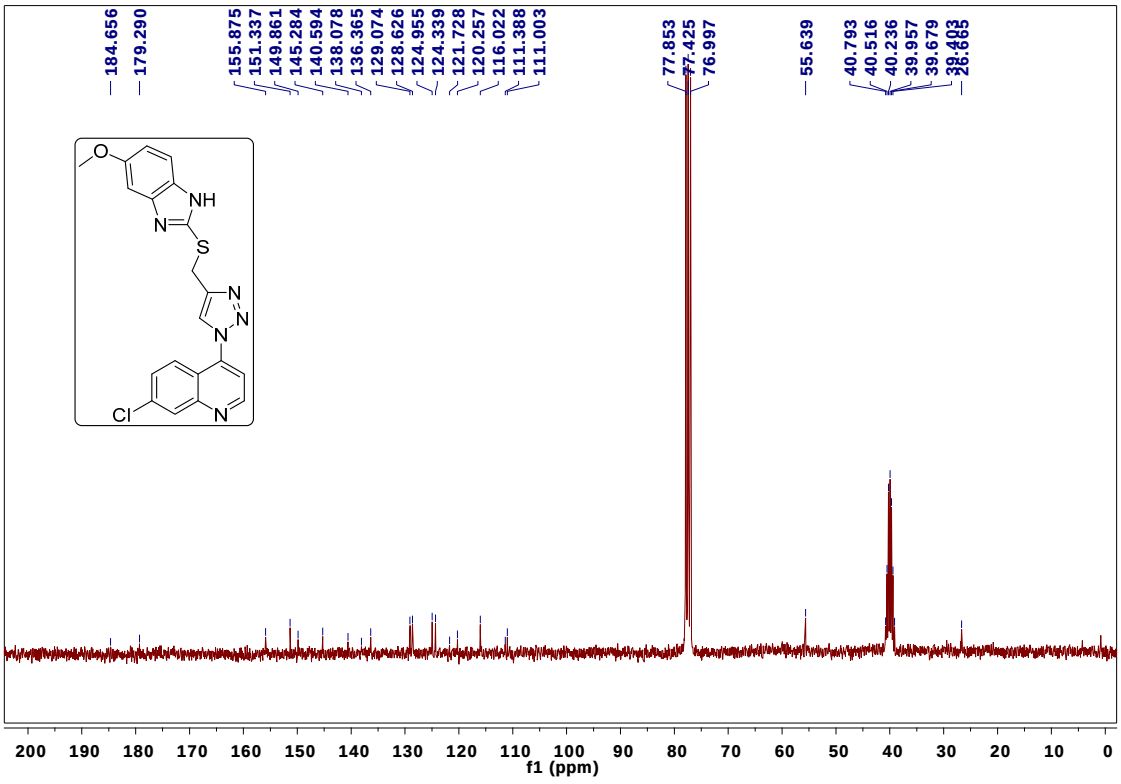


Figure S32: ^{13}C NMR of Tr13

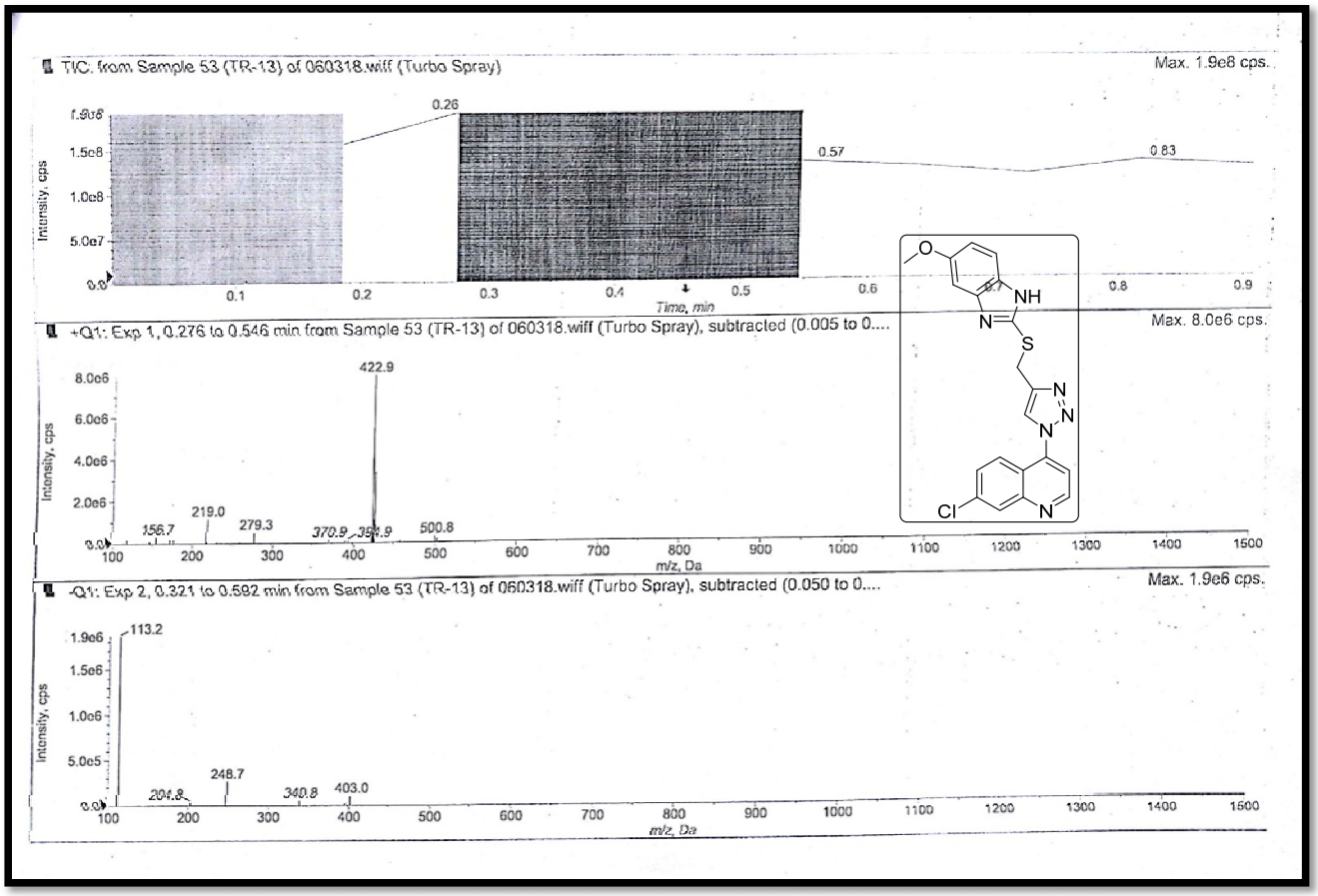


Figure S33: Mass spectrum of Tr13

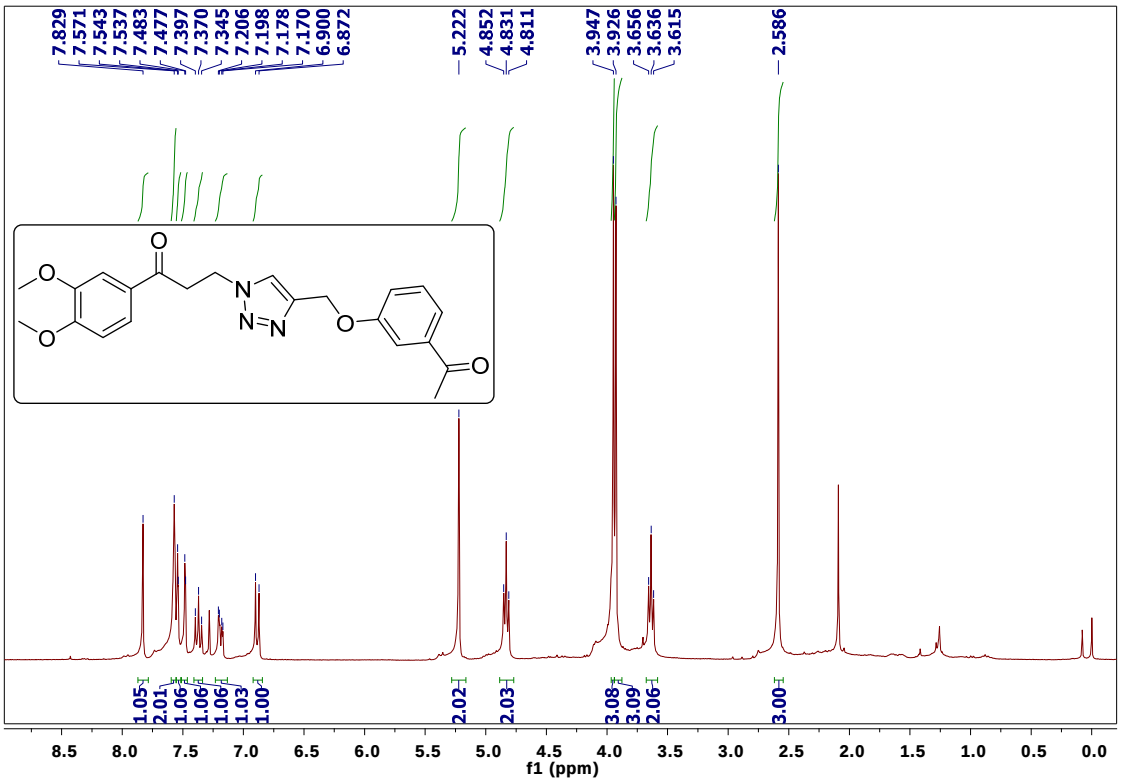


Figure S34: ^{1}H NMR of Tr14

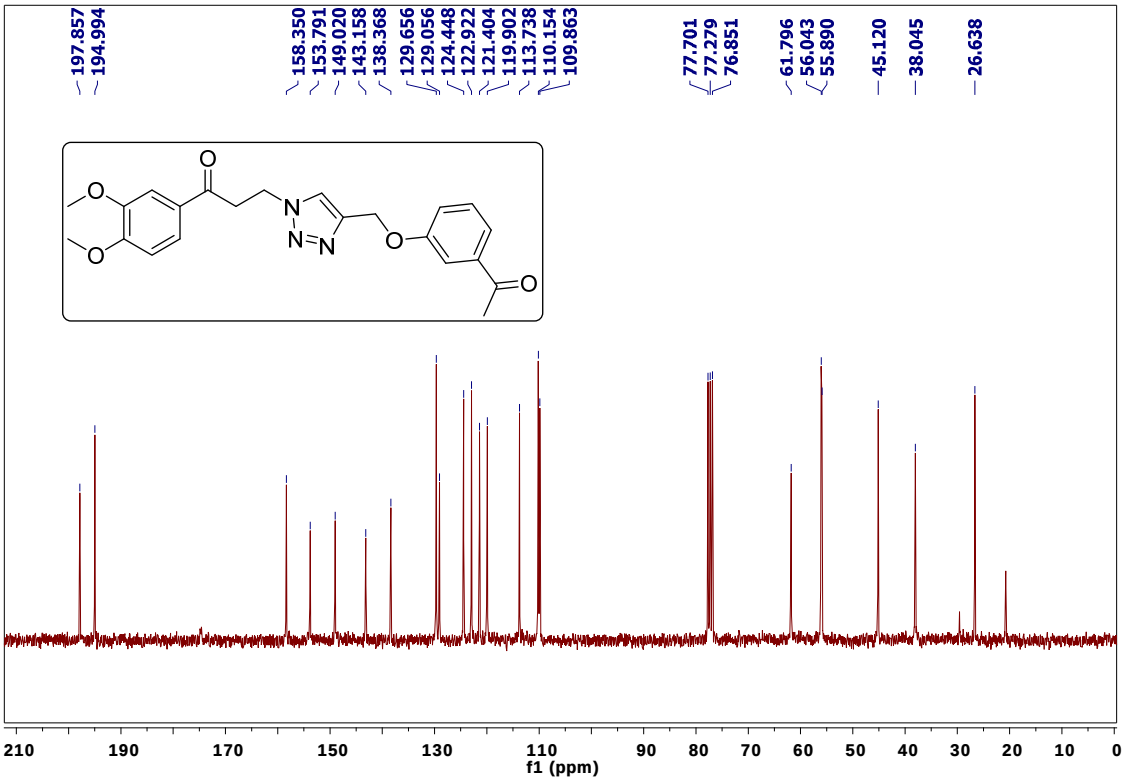


Figure S35: ^{13}C NMR of Tr14

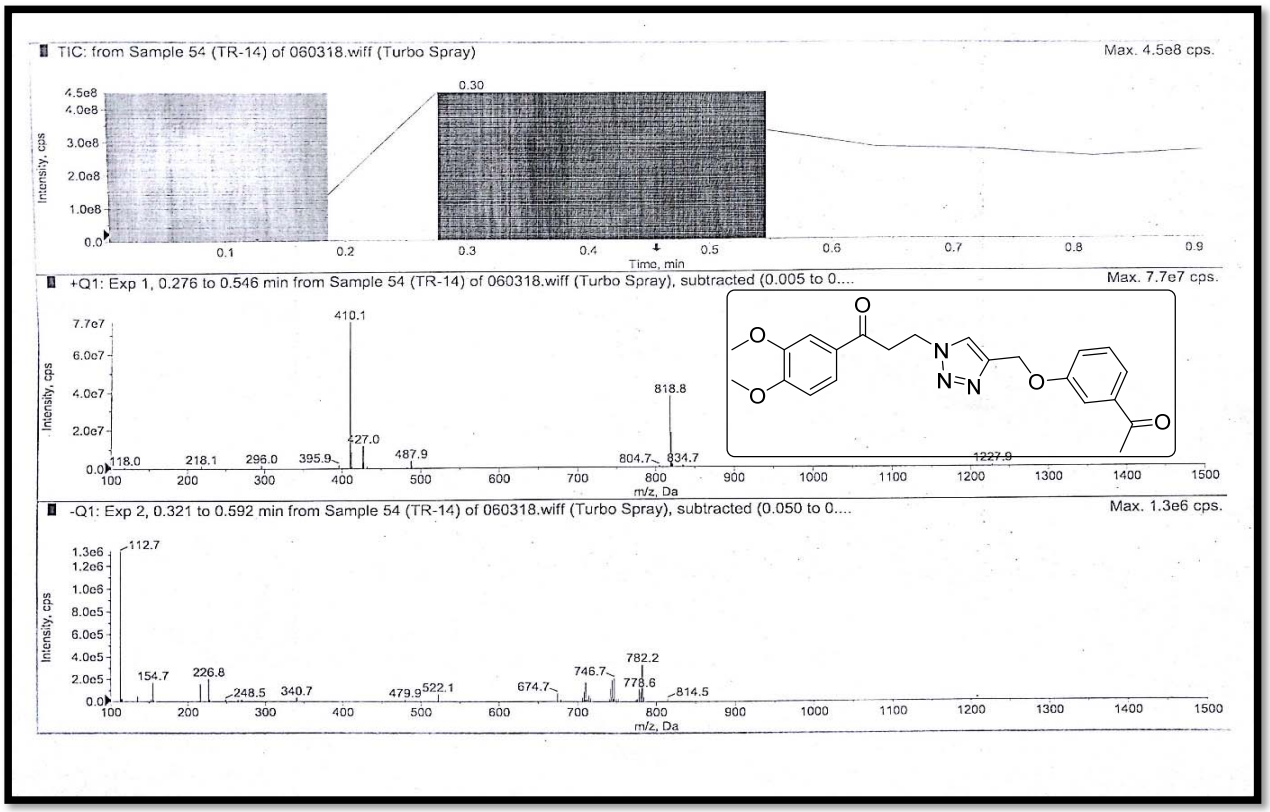


Figure S36: Mass spectrum of Tr14

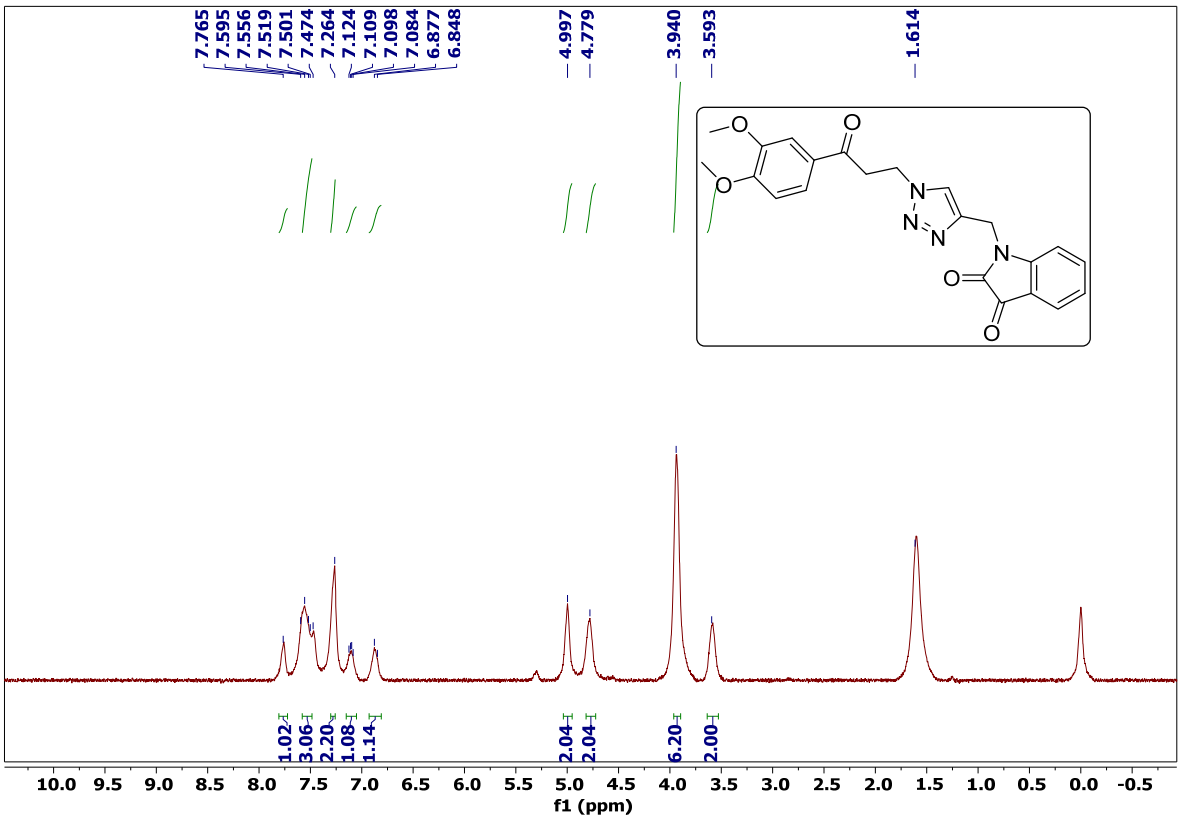


Figure S37: ^{1}H NMR of Tr15

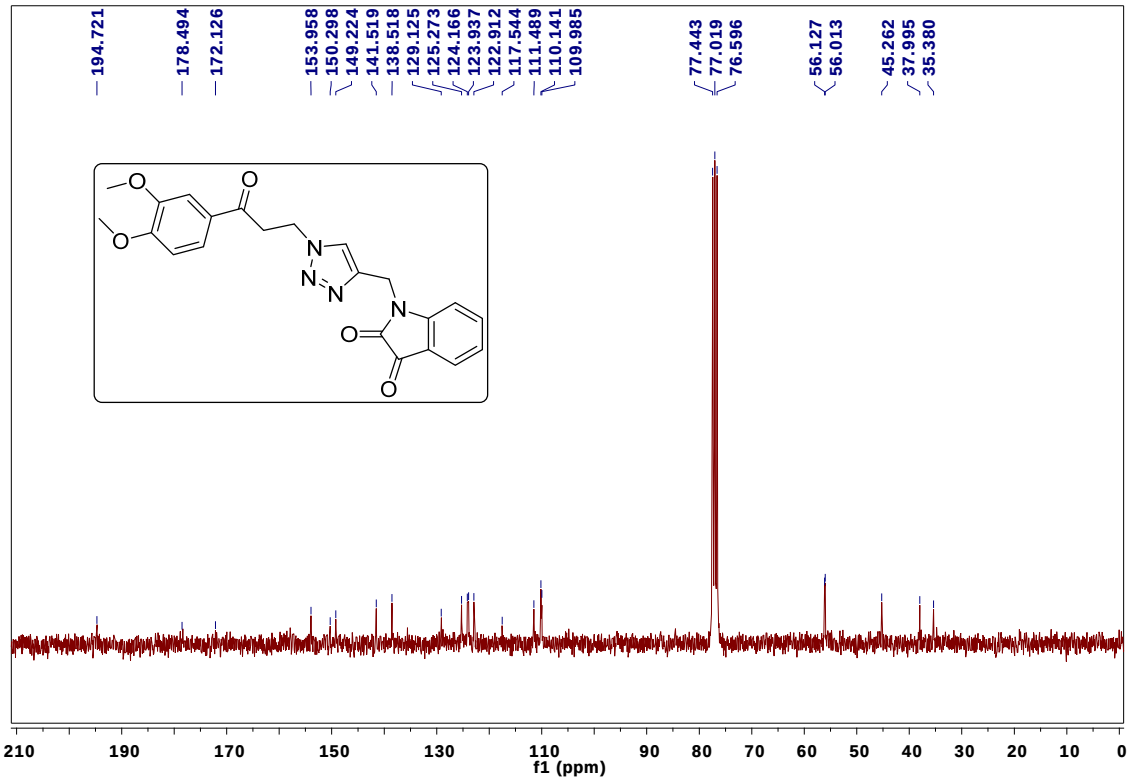


Figure S38: ^{13}C NMR of Tr15

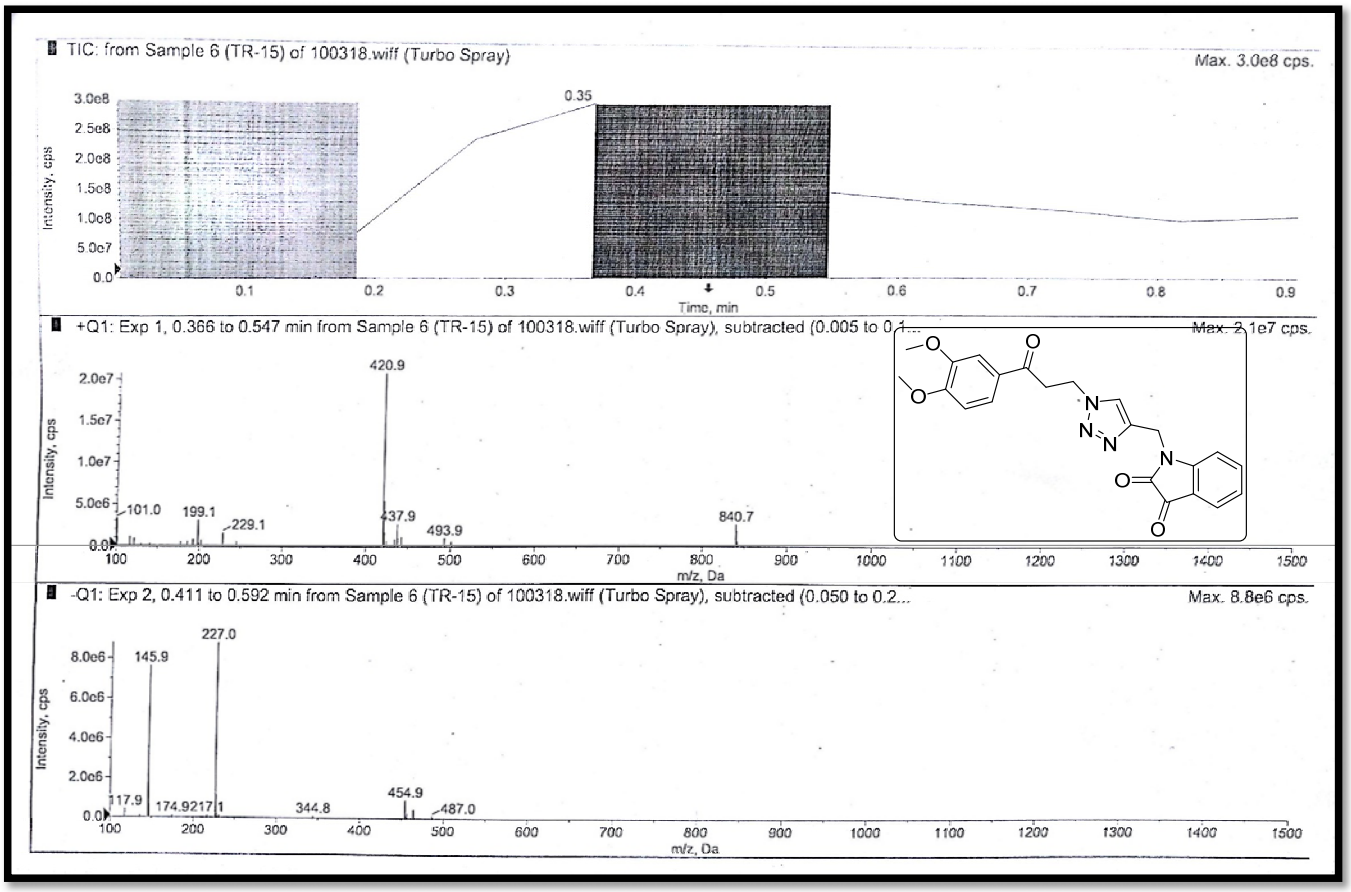


Figure S39: Mass spectrum of Tr15

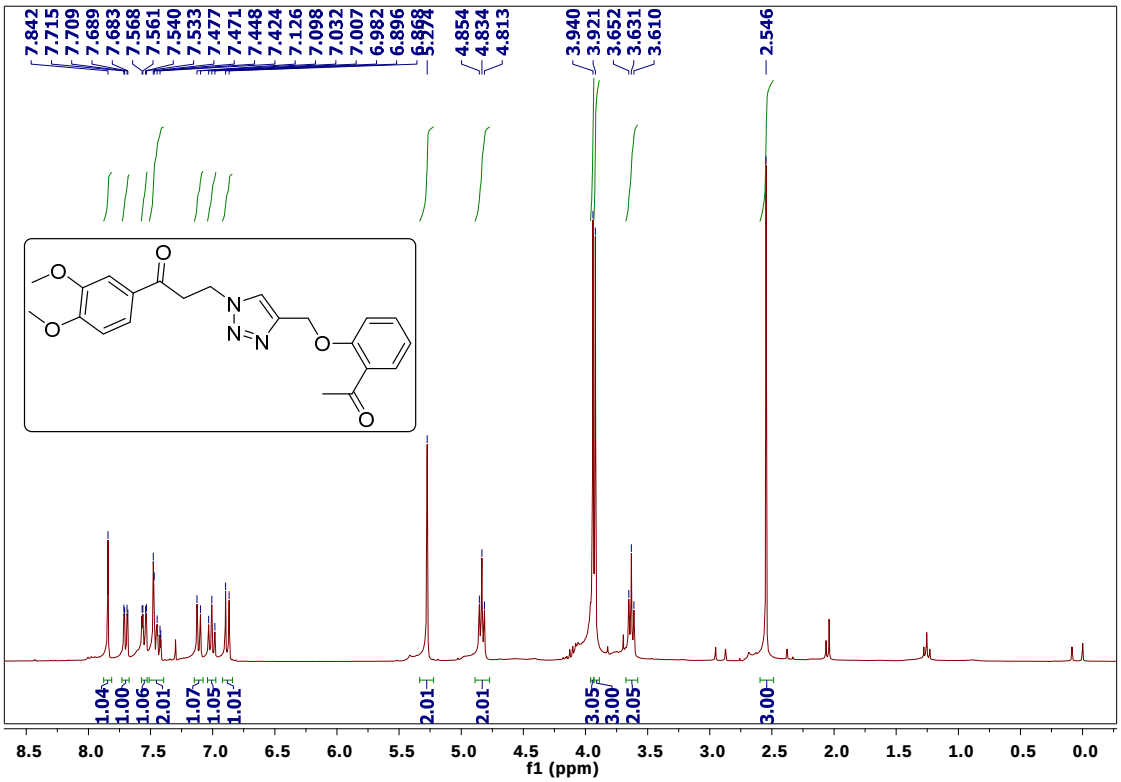


Figure S40: ^{1}H NMR of Tr16

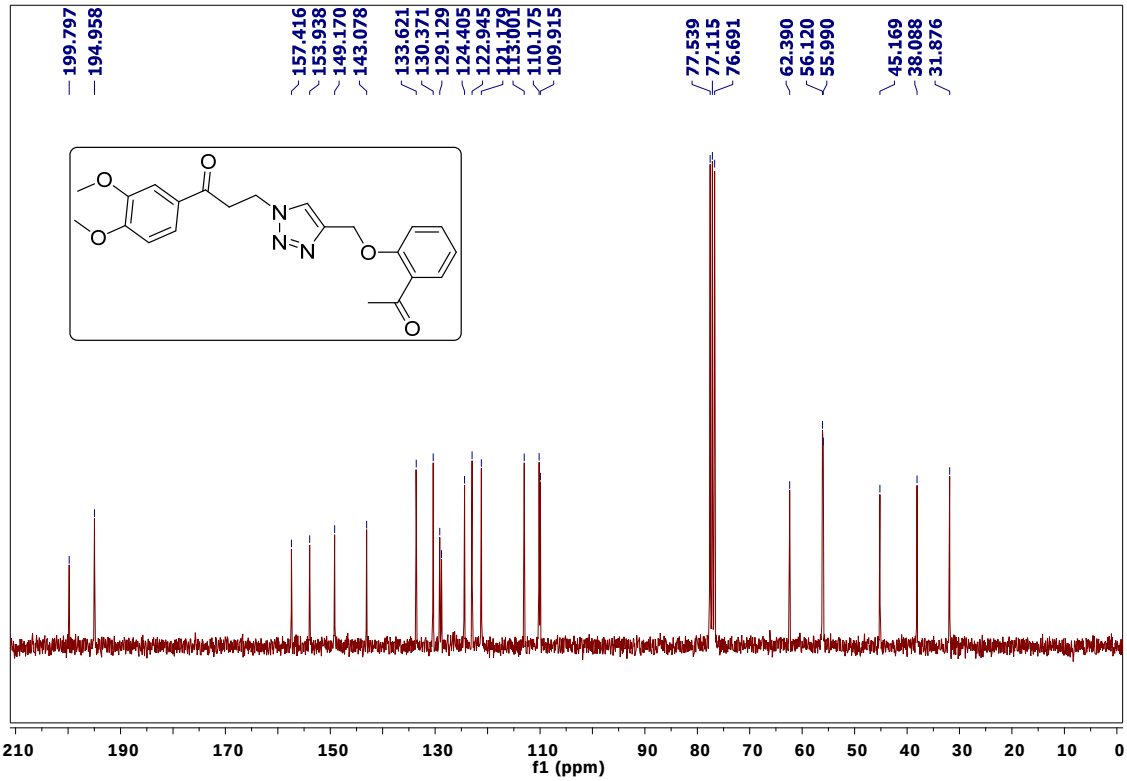


Figure S41: ^{13}C NMR of Tr16

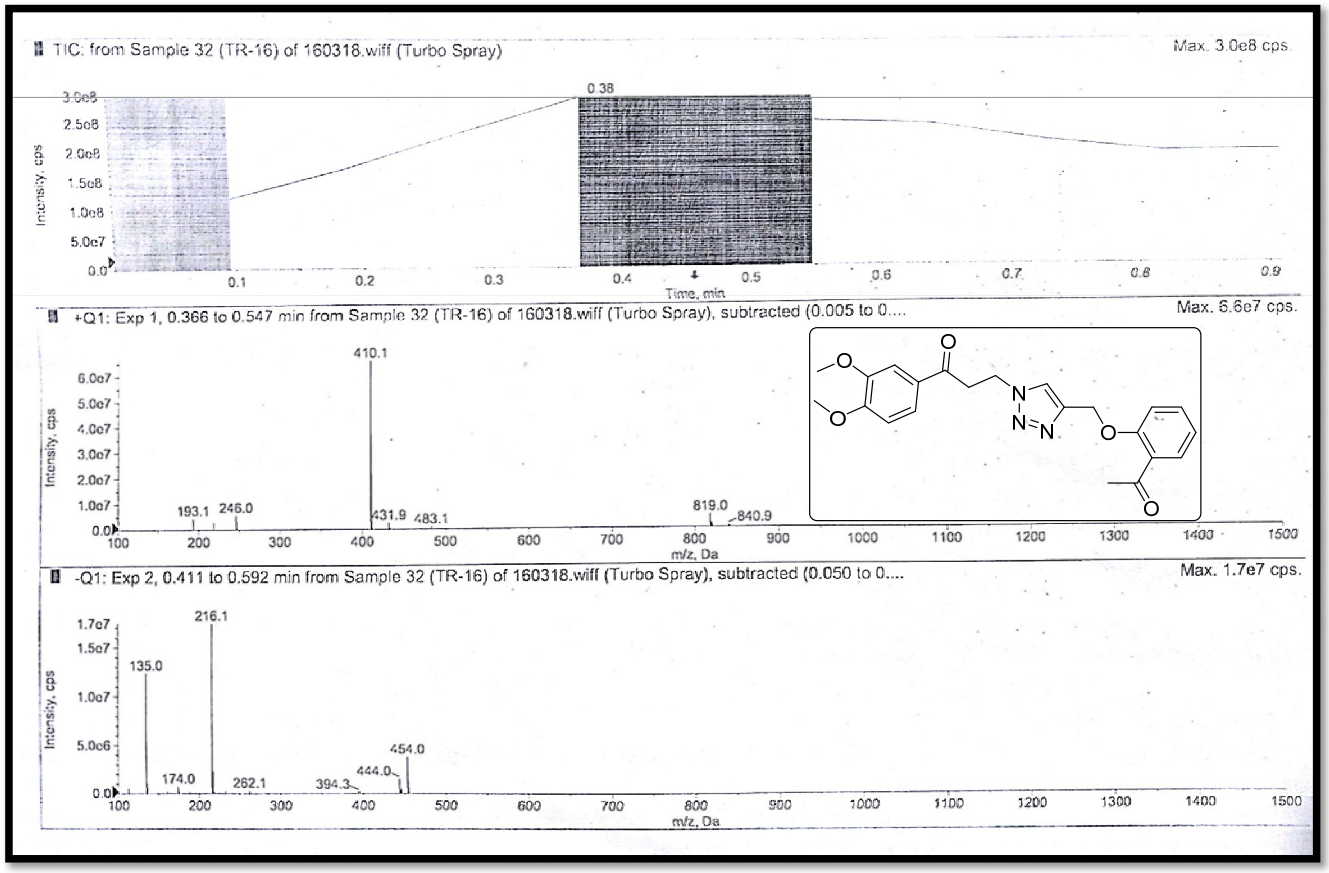


Figure S42: Mass spectrum of Tr16

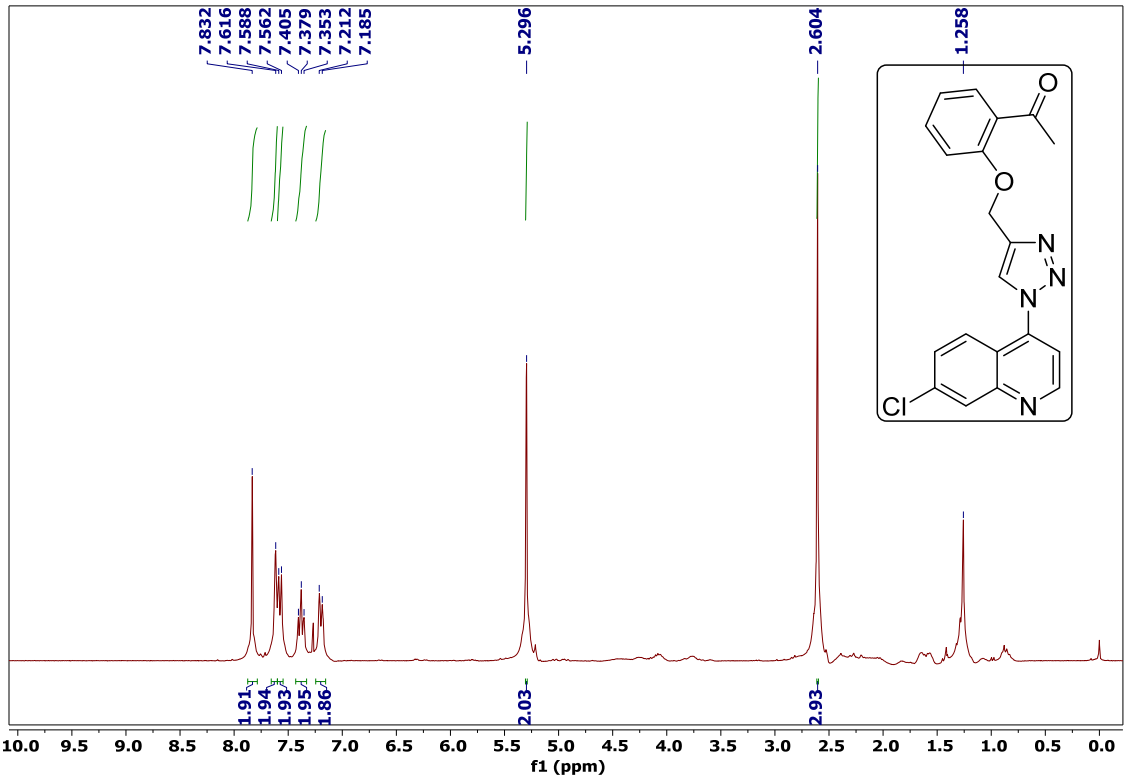


Figure S43: ^{1}H NMR of Tr17

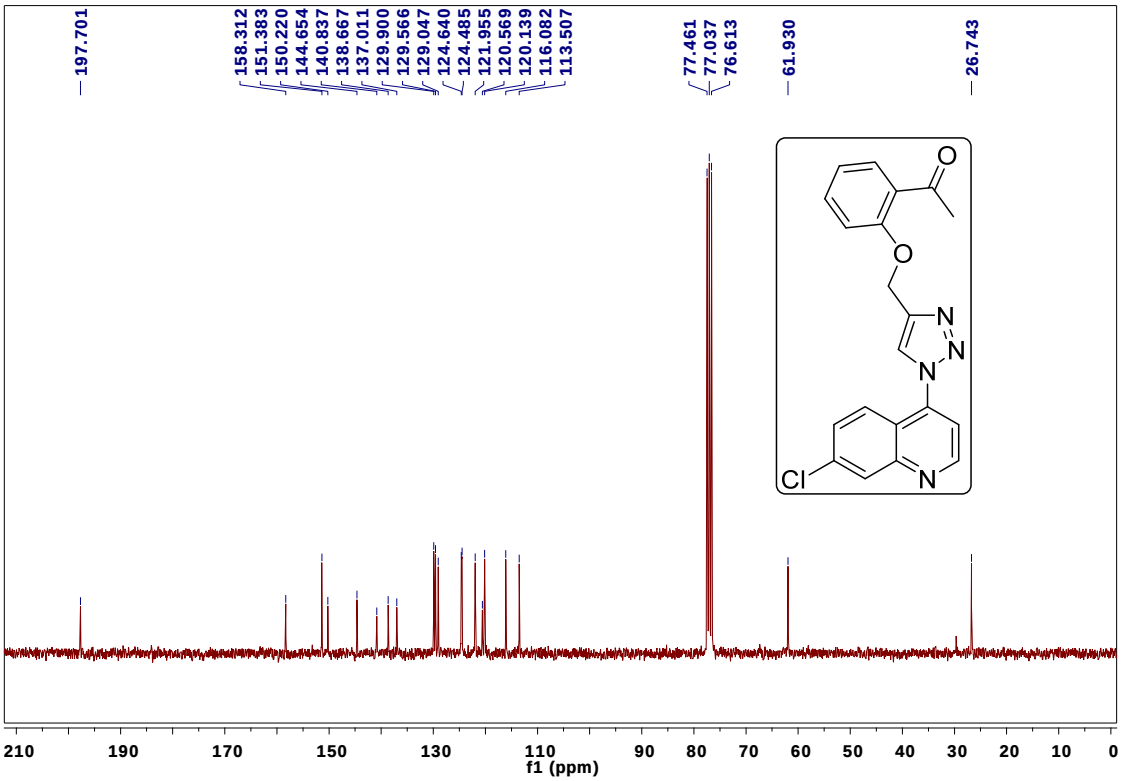


Figure S44: ^{13}C NMR of Tr17

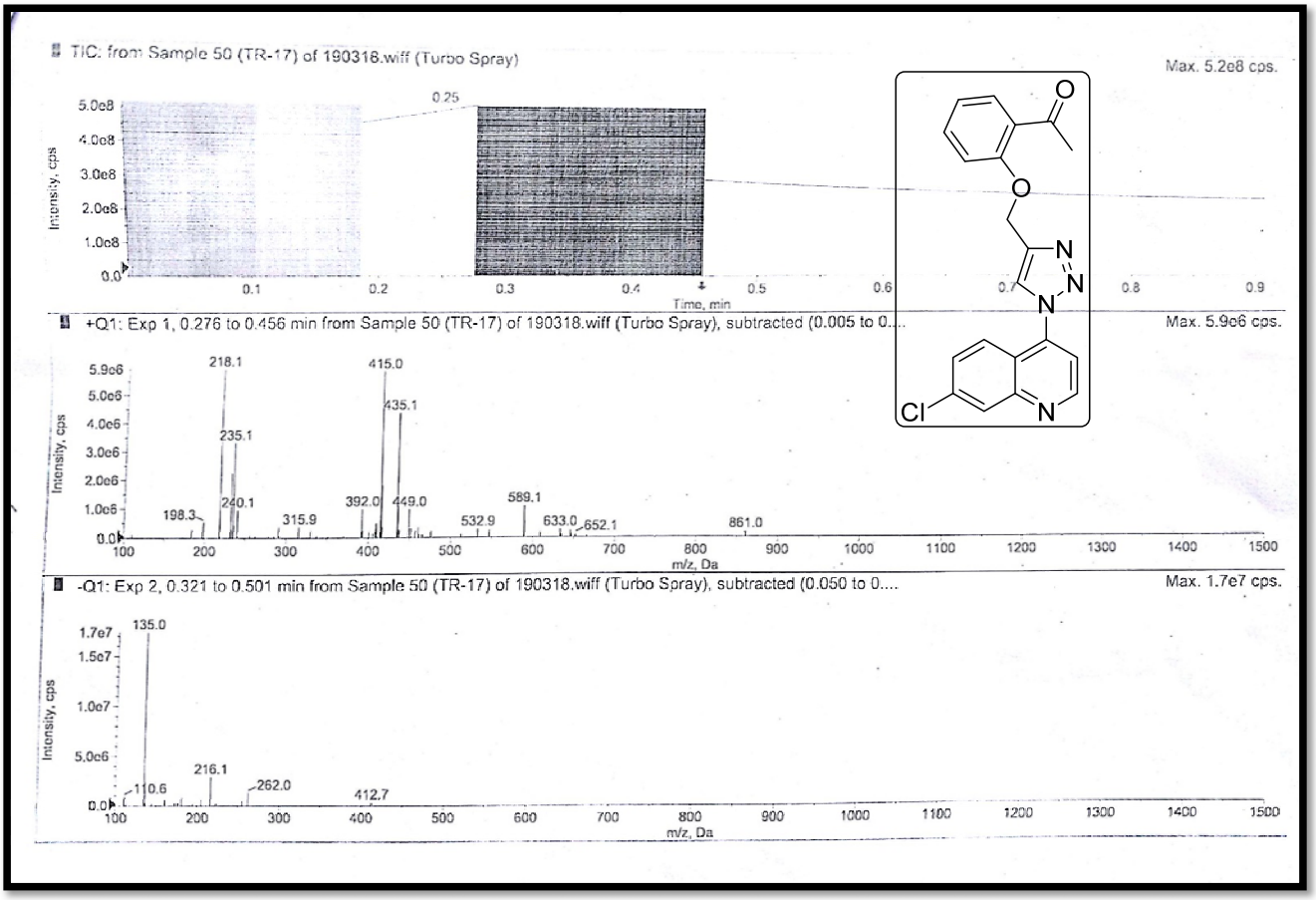


Figure S45: Mass spectrum of Tr17

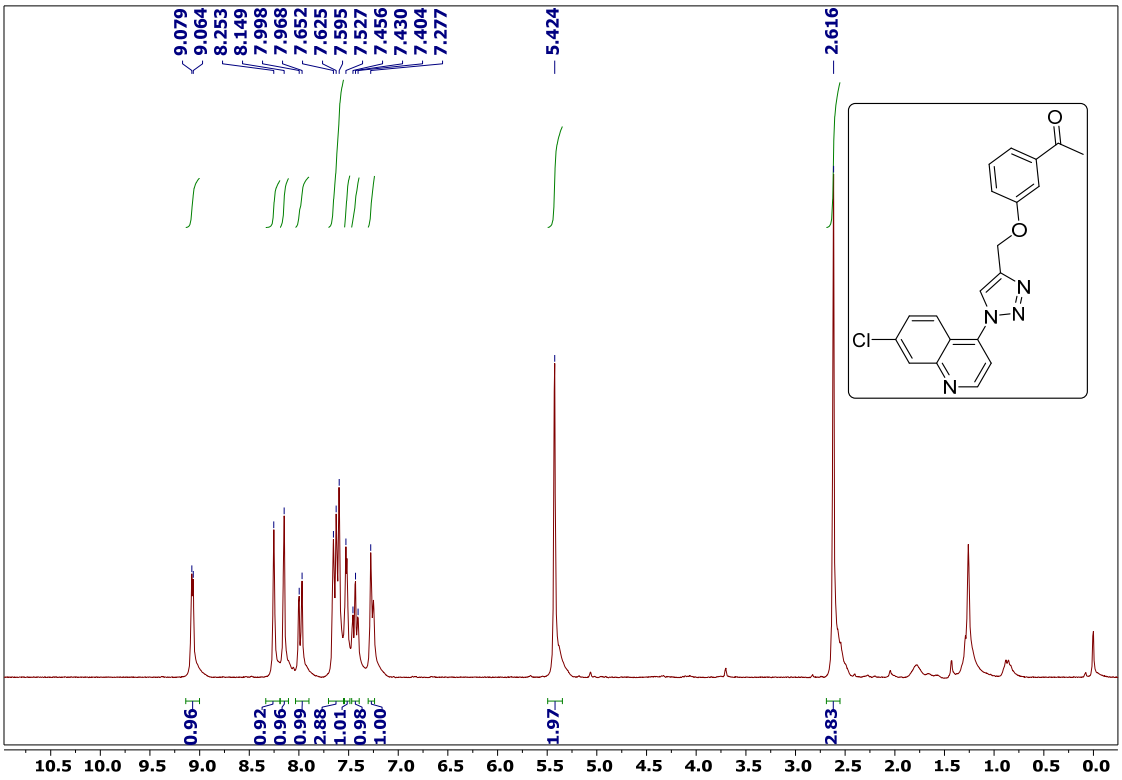


Figure S46: ^{1}H NMR of Tr18

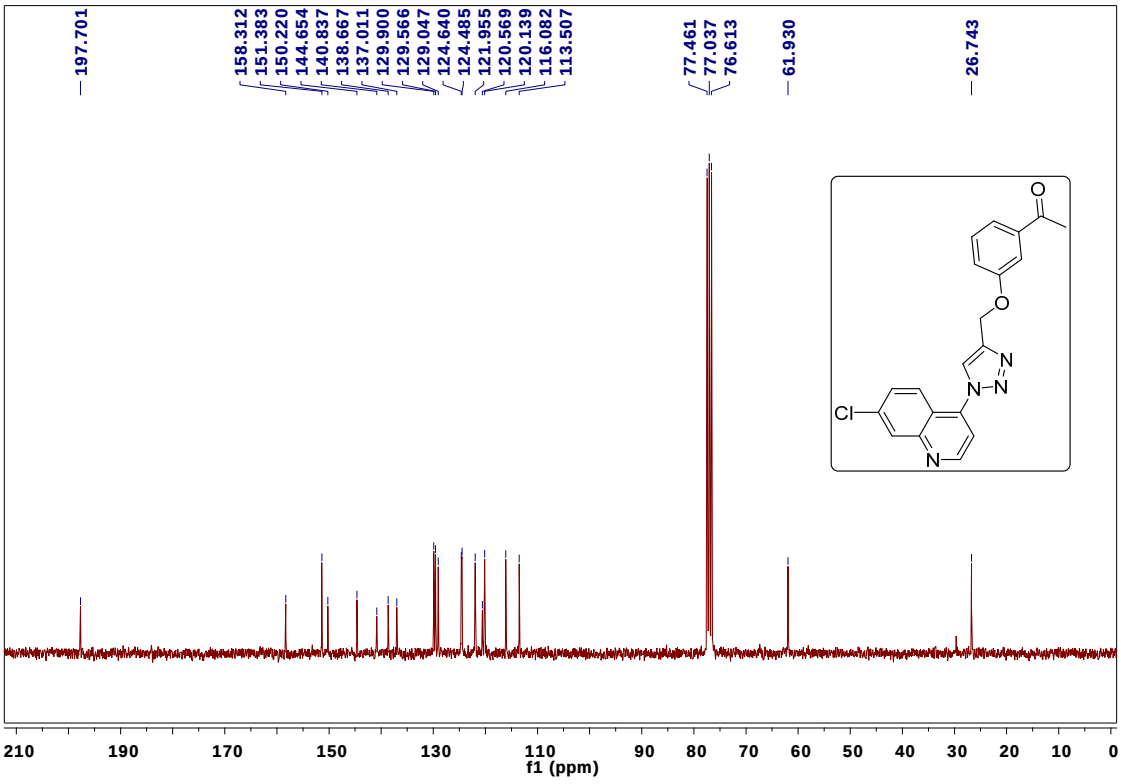


Figure S47: ^{13}C NMR of Tr18

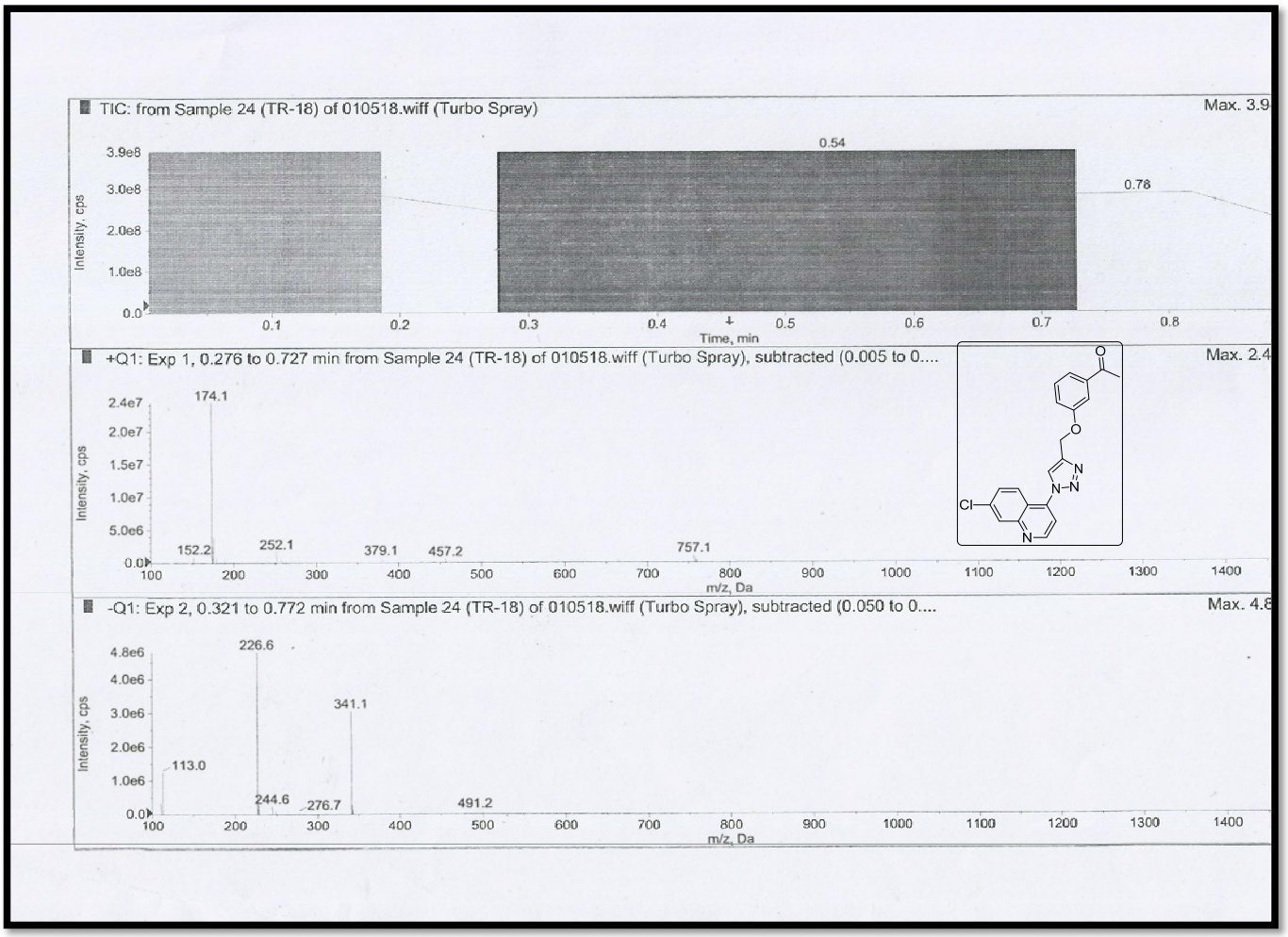


Figure S48: Mass spectrum of Tr18

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