Supporting Information

New *N*-Phenylacetamide Incorporated 1,2,3-Triazoles: [Et_3NH][OAc] Mediated Efficient Synthesis and Biological Evaluation

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1. ADMET Predication.

In Silico assessment of all synthesized triazole derivatives **6a-g**, **7a-g** and **8a-g** was performed for the prediction of ADMET properties and to analyze Pharmacokinetics and physicochemical properties of synthesized derivatives. In this study, we assessed absorption, distribution, metabolism, excretion and toxicity properties using ADMET predictor FAFDrugs2 offline program which runs on Linux platform. ADMET predictor FAFDrugs2 does ADMET assessment or filtering of compounds who have lead and druglike properties.[1] In this study, we have calculated the druglike properties of all the synthesized compounds **6a-g**, **7a-g** and **8a-g**. following to the Lipinski's rule of five evaluate druglikenes.[2] Lipinski's rule of five also known as **Pfizer's rule of five** (RO5) approach has been widely used as a filter for substances that would likely be further utilized as a lead for drug design programs. We have also analyzed parameters like a number of rotatable bonds (<10) and the number of rigid bonds, which implies that the compound may have a good oral drug bio-availability and very good intestinal absorption rate while passing through the GI track.[3] The values of polar surface area (PSA) for synthesized triazole derivatives **6a-g**, **7a-g** and **8a-g** indicated these agents have very high solubility and also have good oral bioavailability. The parameters, molecular weight, No. of Hydrogen bond donor and No. of Hydrogen bond Acceptors, LogP, Max size ring and the ratio of H/C are associated with the oral absorption rate, showed that all synthesized compounds **6a-g**, **7a-g** and **8a-g** had good absorption. The percentage of absorption (% ABS) was calculated using TPSA by using formula %ABS=109-(0.345xTPSA).[3]

All the analyzed physical, chemical descriptors and pharmaceutically relevant properties for ADMET prediction by using FAF Drugs 2 and data are summarized in **Table 1**. The ADMET prediction data obtained from all the synthesized triazole derivatives **6a-g**, **7a-g** and **8a-g** were within the range of accepted values, none of the synthesized triazole derivatives has violated the Lipinski's rule of five (RO5).

Table 1 *In silico* drug-like properties of synthesized triazole derivatives **6a-g**, **7a-g** and **8a-g**

Entry	MW	LogP	%ABS	PSA	RotatableB	RigidB	HBD	HBA	Ratio H/C	Toxicity
6a	308.335	2.5688	85.1812	69.04	6	19	1	4	0.352	NT
6b	322.361	2.8772	85.1812	69.04	6	19	1	4	0.333	NT
6c	322.361	2.8772	85.1812	69.04	6	19	1	4	0.333	NT
6d	322.361	2.8772	85.1812	69.04	6	19	1	4	0.333	NT
5e	342.78	3.2222	85.1812	69.04	6	19	1	4	0.411	NT
6f	342.78	3.2222	85.1812	69.04	6	19	1	4	0.411	NT
6g	342.78	3.2222	85.1812	69.04	6	19	1	4	0.411	NT
7a	338.361	2.5774	81.9969	78.27	7	19	1	5	0.388	NT
7b	352.387	2.8858	81.9969	78.27	7	19	1	5	0.368	NT
7c	352.387	2.8858	81.9969	78.27	7	19	1	5	0.368	NT
7d	352.387	2.8858	81.9969	78.27	7	19	1	5	0.368	NT
7e	372.806	3.2308	81.9969	78.27	7	19	1	5	0.444	NT
7f	372.806	3.2308	81.9969	78.27	7	19	1	5	0.444	NT
7g	372.806	3.2308	81.9969	78.27	7	19	1	5	0.444	NT
8a	353.332	3.0002	71.3881	109.02	7	20	1	6	0.529	NT
8b	367.359	3.3086	71.3881	109.02	7	20	1	6	0.5	NT
8c	367.359	3.3086	71.3881	109.02	7	20	1	6	0.5	NT
8d	367.359	3.3086	71.3881	109.02	7	20	1	6	0.5	NT

8e	387.777	3.6536	71.3881	109.02	7	20	1	6	0.588	NT
8f	387.777	3.6536	71.3881	109.02	7	20	1	6	0.588	NT
8g	387.777	3.6536	71.3881	109.02	7	20	1	6	0.588	NT

(Percent absorption, MW: molecular weight, LogP: logarithm of partition coefficient of compound between n-octanol and water, %ABS: Percentage of Absorption, PSA: Polar surface area, n-RotBond: number of rotatable bonds, n-RigBond: number of rigid bonds, HBA: hydrogen bond acceptors, HBD: hydrogen bond donor and (NT: Nontoxic)

2. General Experimental procedure for the synthesis of substituted 1-(prop-2-ynyloxy) benzene (2a-c):

To the stirred solution of appropriate phenols **1a-c** (20 mmol) in *N,N*-dimethylformamide (DMF) (20 mL), K_2CO_3 (24 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes, which results into the corresponding oxyanion. To this mixture, propargyl bromide (20 mmol) was added and stirred for 2 h. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction was quenched by crushed ice. In case of solid product, it was filtered and the obtained crude solid product was crystallized using ethanol. The crystallized products were taken for next step. When the products are liquid, it has been extracted in ethyl acetate (20 mL × 3). The combined organic layers were dried over $NaSO_4$. The solvent was removed under reduced pressure and used for the further reaction without purification.

2.1. General experimental procedure for the 2-chloro-*N*-phenylacetamide (4a-g)

The stirred solution of appropriate anilines **3a-g** (20 mmol) in dichloromethane (DCM) (20 mL), triethylamine (20 mmol) was added. The reaction mixture was stirred at 0 ℃ till the addition of Chloroacetyl chloride (20 mmol) and then stirred at room temperature for 3-5 hrs. This resulted into the corresponding 2-chloro-*N*-phenylacetamide. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system the reaction was quenched by crushed ice. In case of solid product, it was filtered and the obtained crude solid product and used for the further reaction without purification.

2.2 General experimental procedure for the 2-azido-*N*-phenylacetamide (5a-g)

2-chloro-*N*-phenylacetamide on nucleophilic substitution with sodium azide (NaN_3) in toluene (20 mL), refluxed for 5-7 h. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. After the completion of reaction, toluene was removed under reduced pressure and then the reaction was quenched by crushed ice. In case of solid product, it was filtered and the obtained crude solid product was crystallized using ethanol. The crystallized products were taken for next step. When the products are liquid, it has been extracted in ethyl acetate (20 mL × 3). The combined organic layers were dried over $NaSO_4$. The solvent was removed under reduced pressure and used for the further reaction without purification.

2.3 General experimental procedure for the Triethylammonium Acetate [Et_3NH][OAc]. The ionic liquid was synthesized using standard literature procedure.[4] The reaction was carried out in a 100 ml round-bottomed flask, which was immersed in a heated oil-bath and fitted with a reflux condenser. Acetic acid (6.0 g, 0.1 mol) was added drop wise into the triethylamine (10.12 g, 0.1 mol) at 60 °C in 2 hours. After the addition, the reaction mixture was stirred for 2 hours at 80 °C to ensure the reaction had proceeded to completion. The reaction mixture was dried at 80 °C in high vacuum until the weight of the residue remained constant. The yield of [Et_3NH][OAc] was 94%. **^{1}H NMR (200 MHz, $CDCl_3$, δ ppm)** 1.25 (t, 9H), 2.05 (s, 3H), 3.07 (q, 6H), 8.39 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)** δ 7.3, 28.5, 43.8, 175.4.

3. References

1 D. Lagorce, H. Sperandio and M. Miteva. *BMC Bioinformatics,* 2008**, 9**, 396.

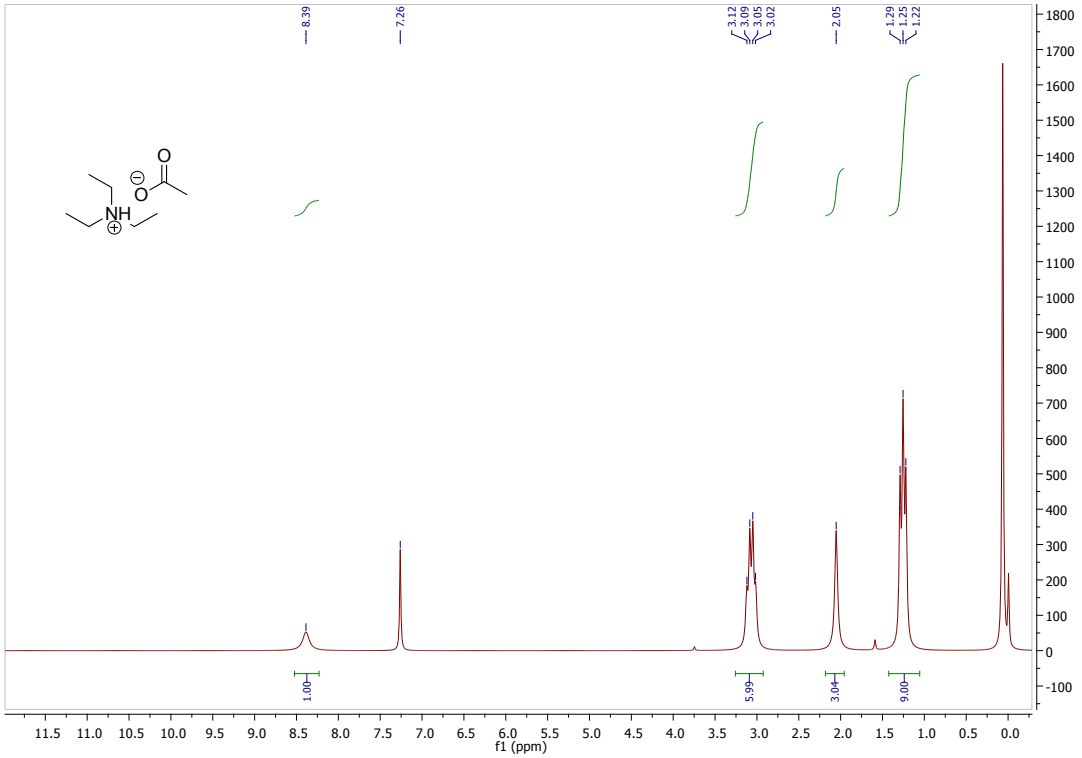
2 C. A Lipinski, F Lombardo and B.W. Dominy, *Adv. Drug Deliv. Rev.,* 2001**, 46**, 3.

3 P. Ertl, B. Rohde and P. Selzer, *J. Med. Chem.,*2000, **43**, 3714.

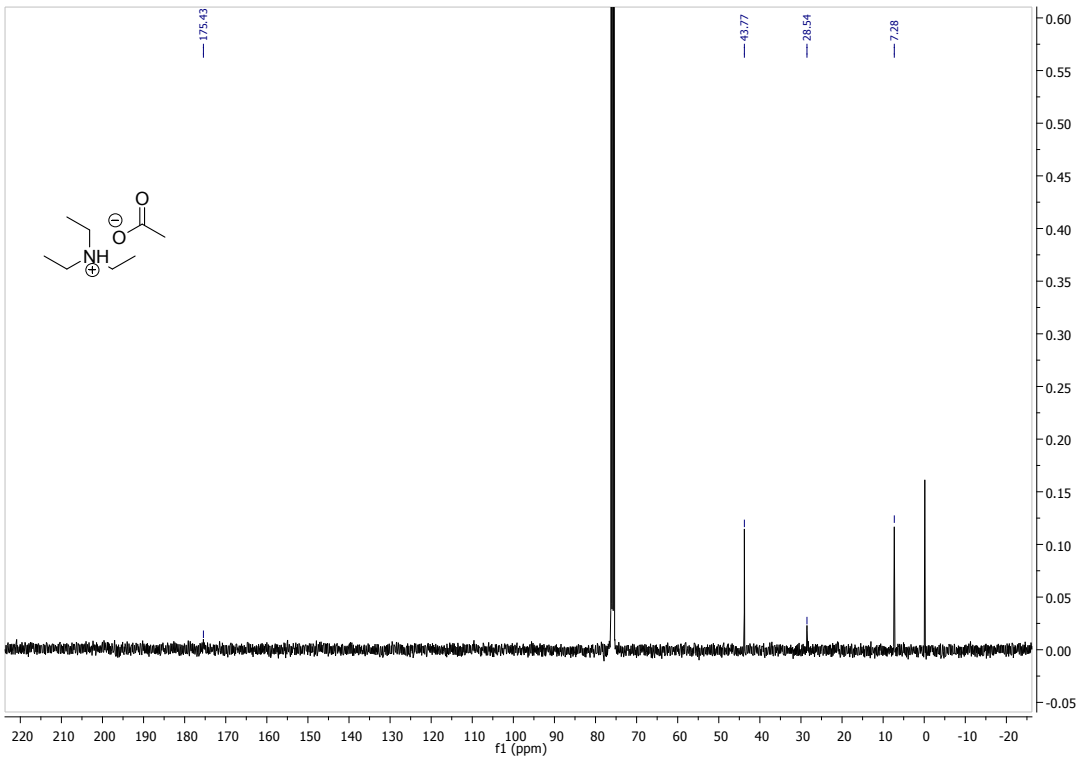
4 C. Wang, L. Guo, H. Li, Y. Wang, J. Weng and L. Wu, *Green Chem*., 2006, **8**, 603.

4. ^{1}H and ^{13}C NMR spectra

[Et_3NH][OAc] ^{1}H NMR, 200 MHz, $CDCl_3$



[Et_3NH][OAc] ^{1}H NMR, 100 MHz, $CDCl_3$



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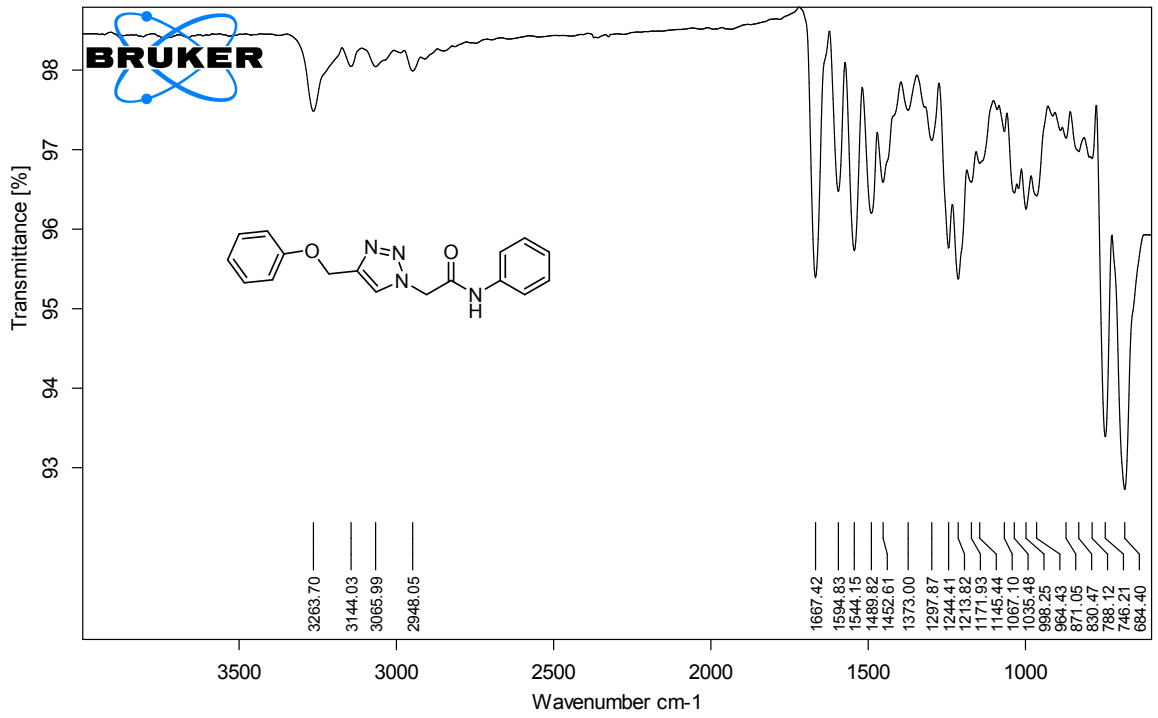

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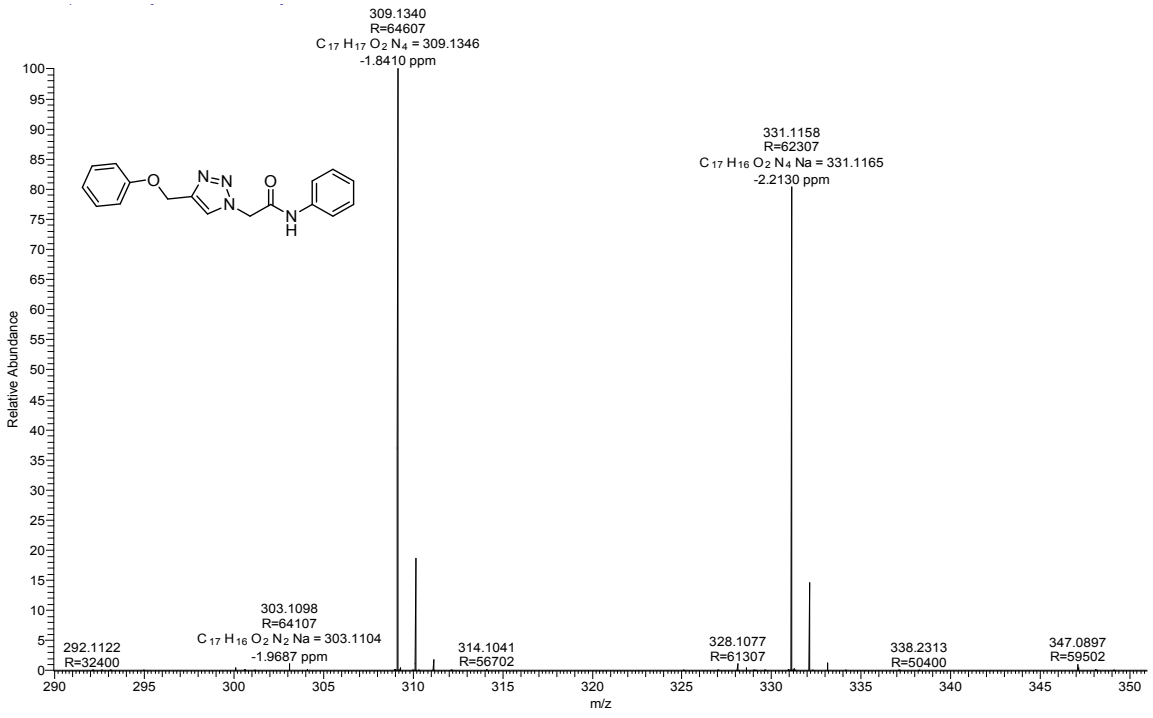
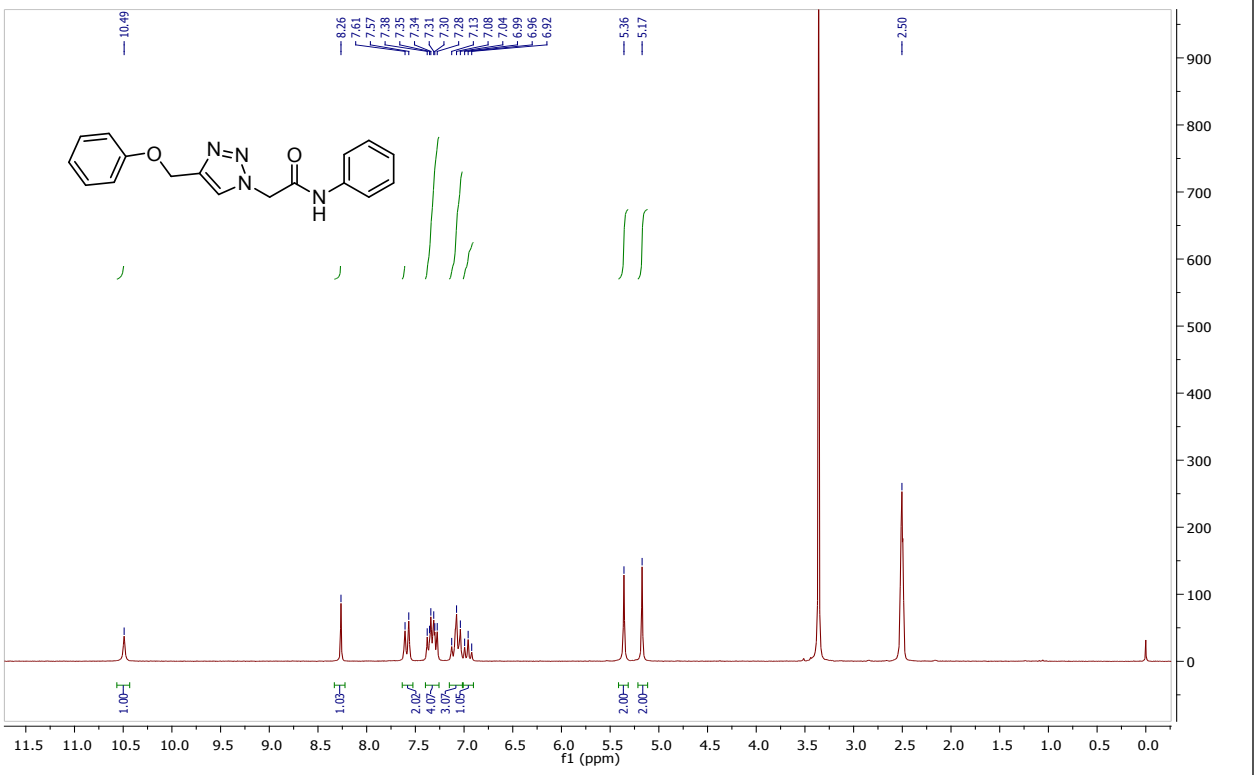


6a. ^{1}H NMR, 200 MHz, DMSO-d_6



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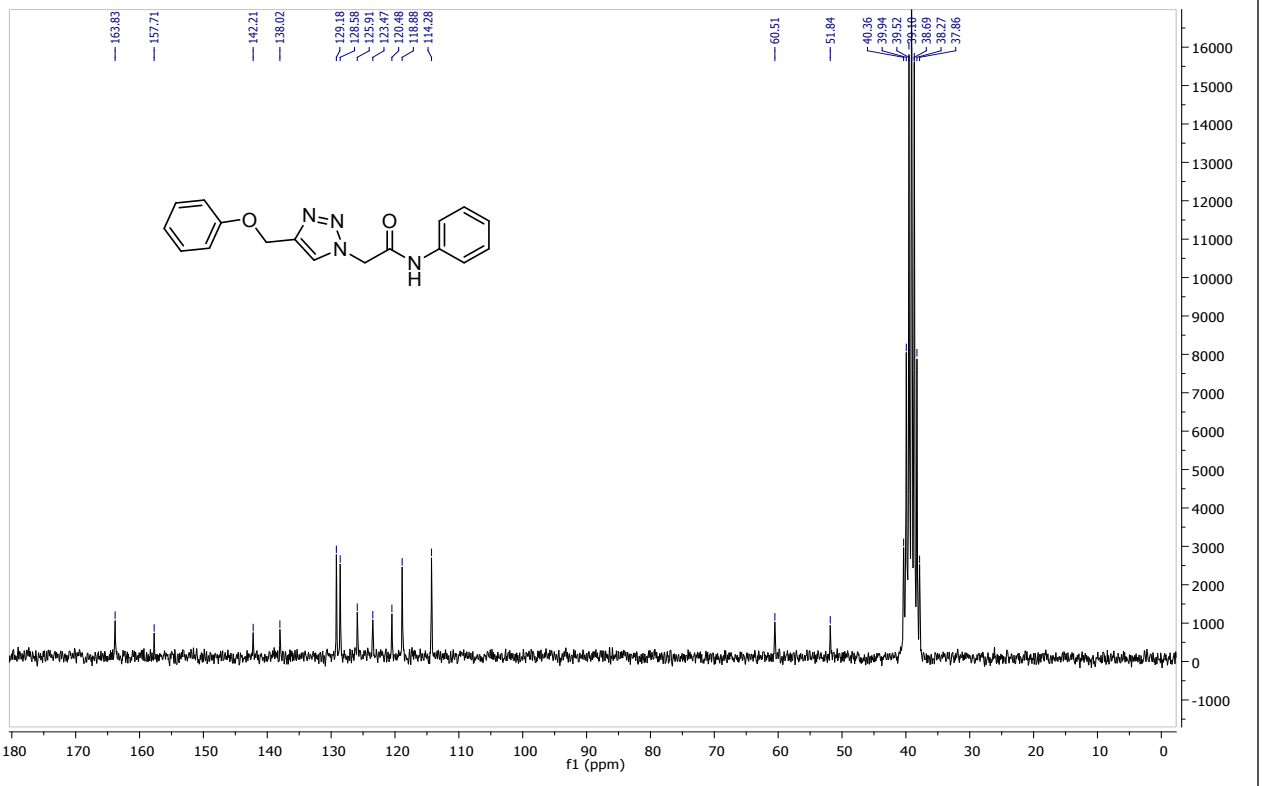

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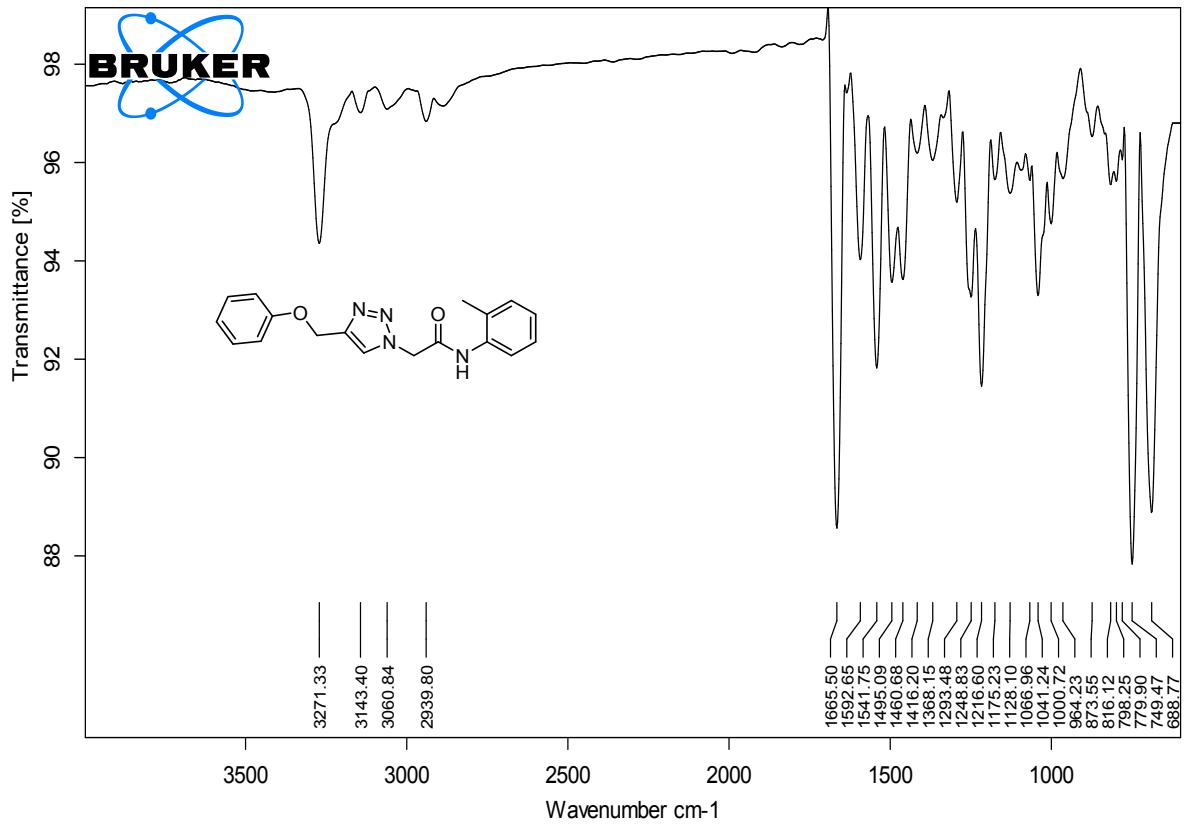

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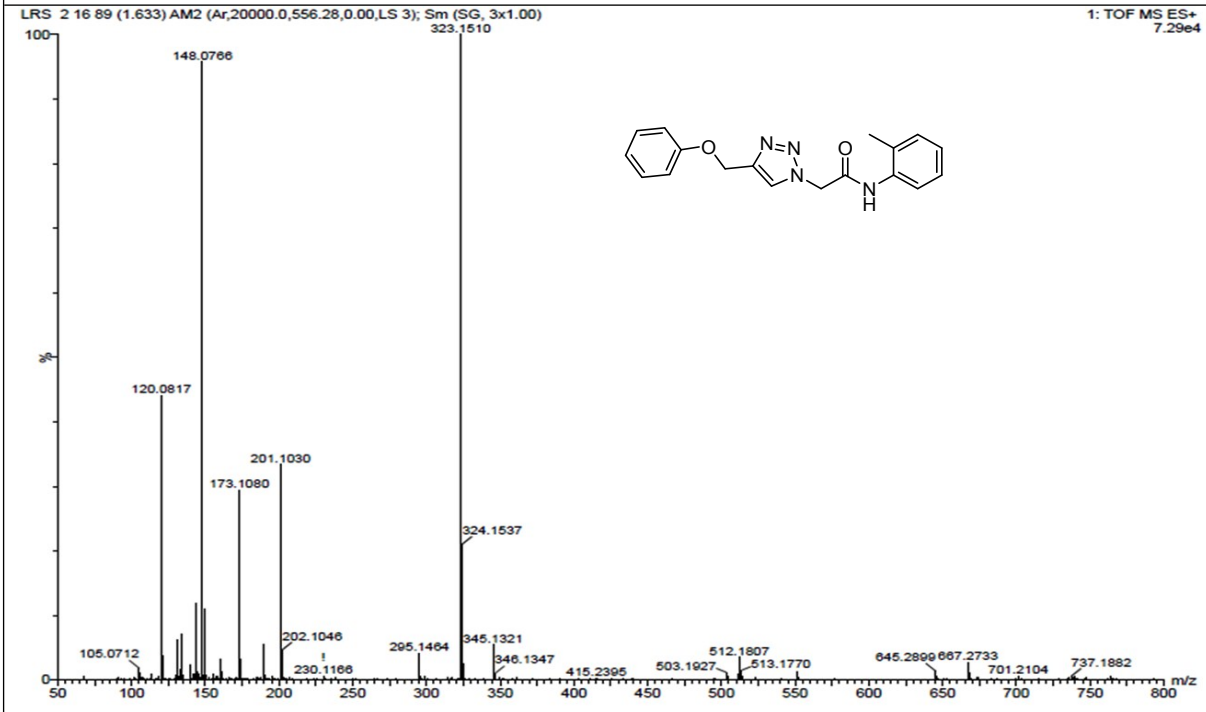

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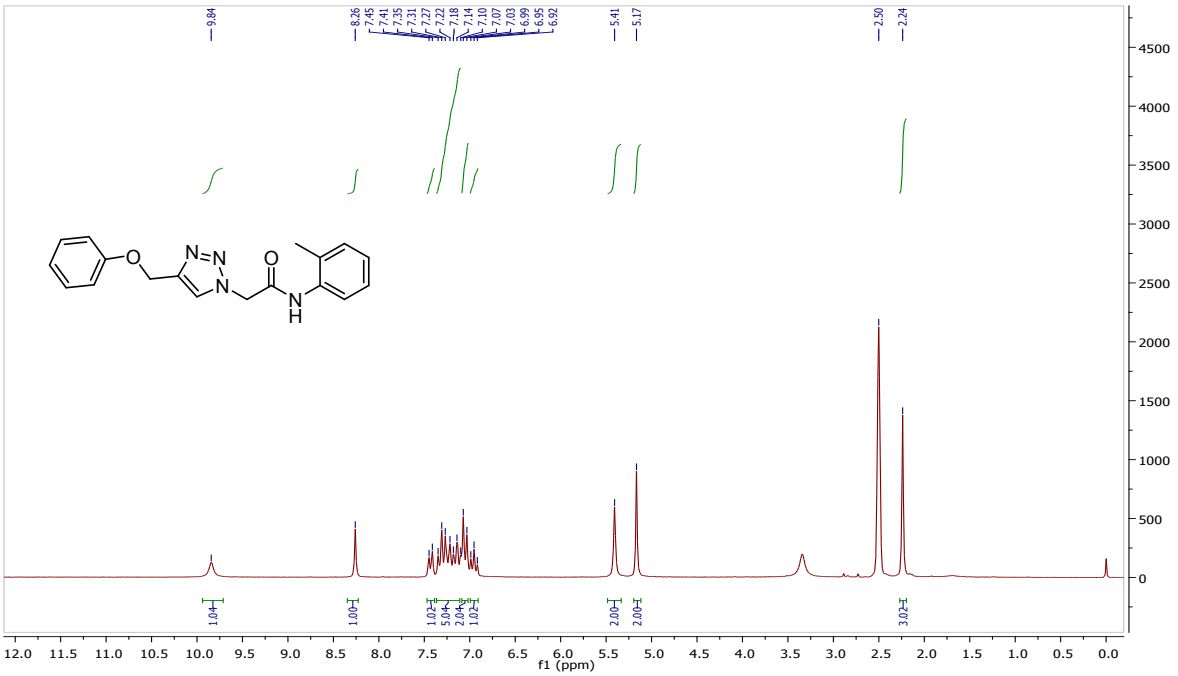

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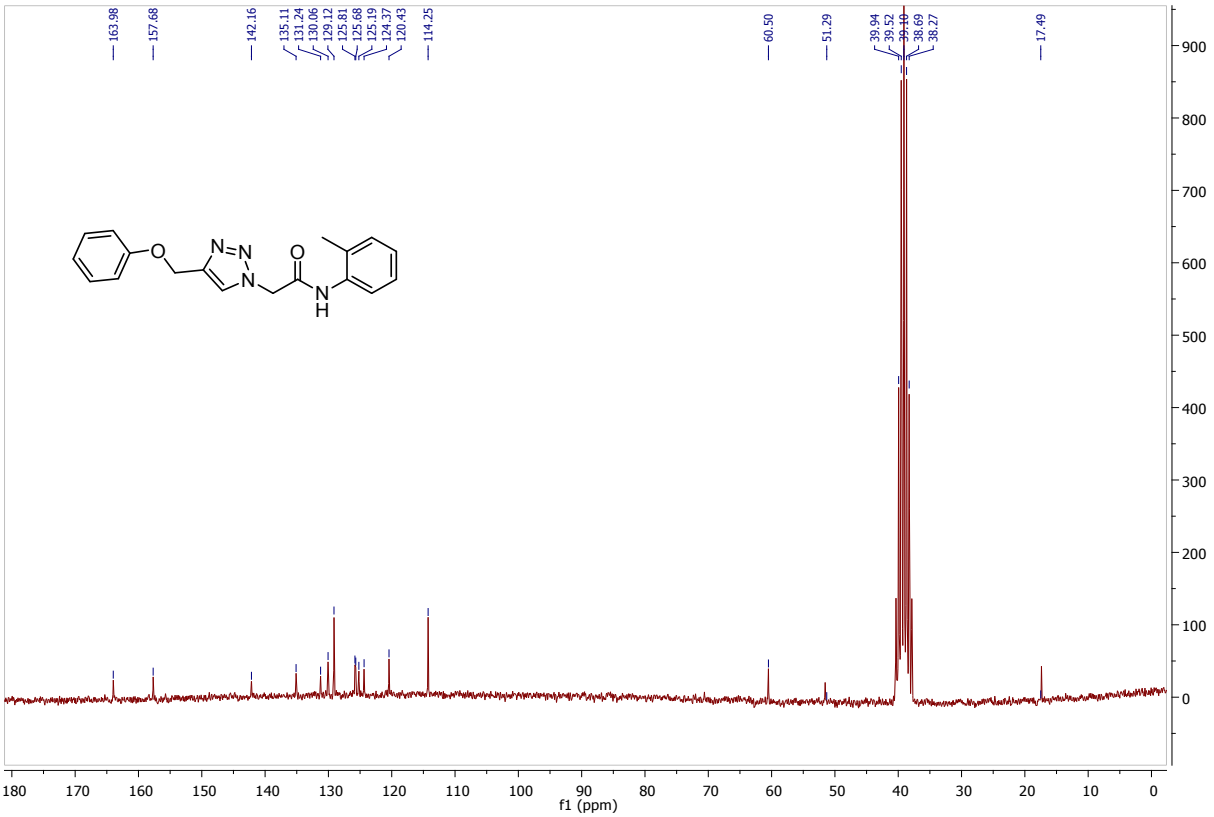

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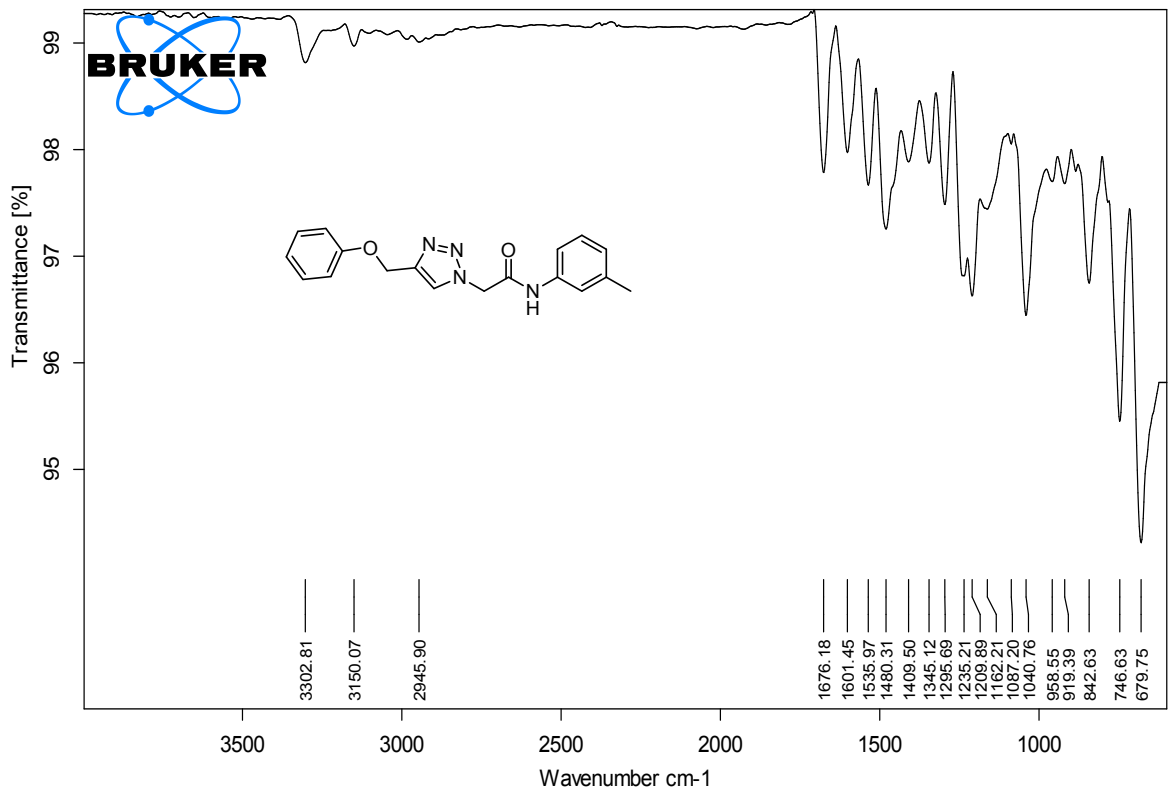

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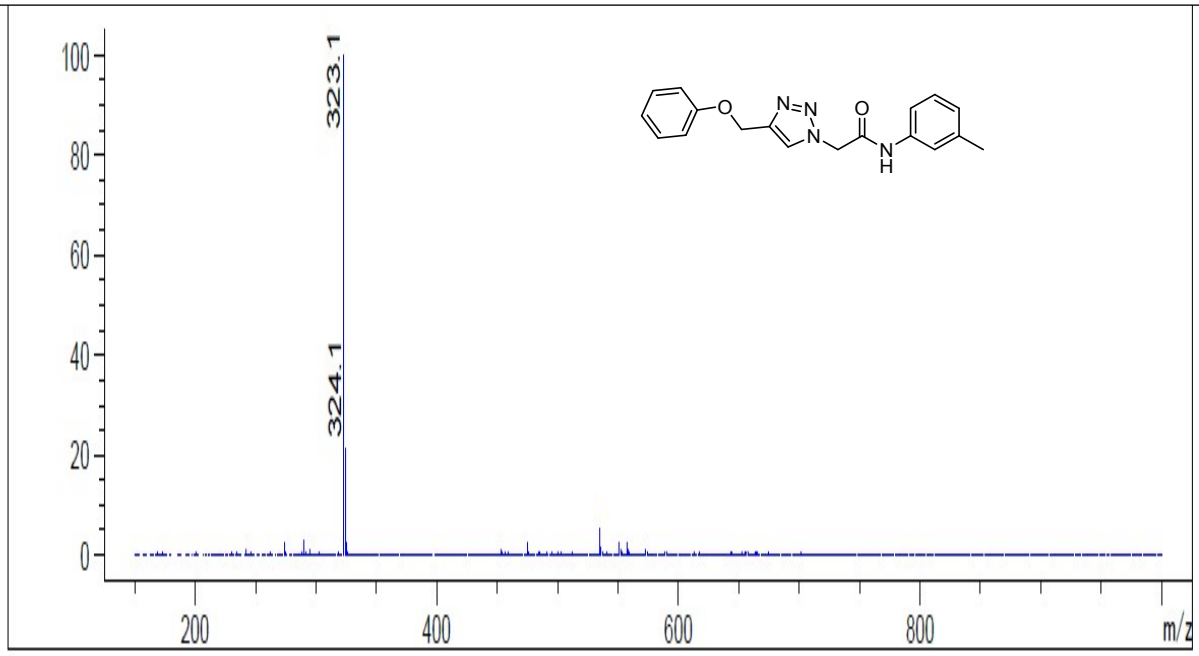
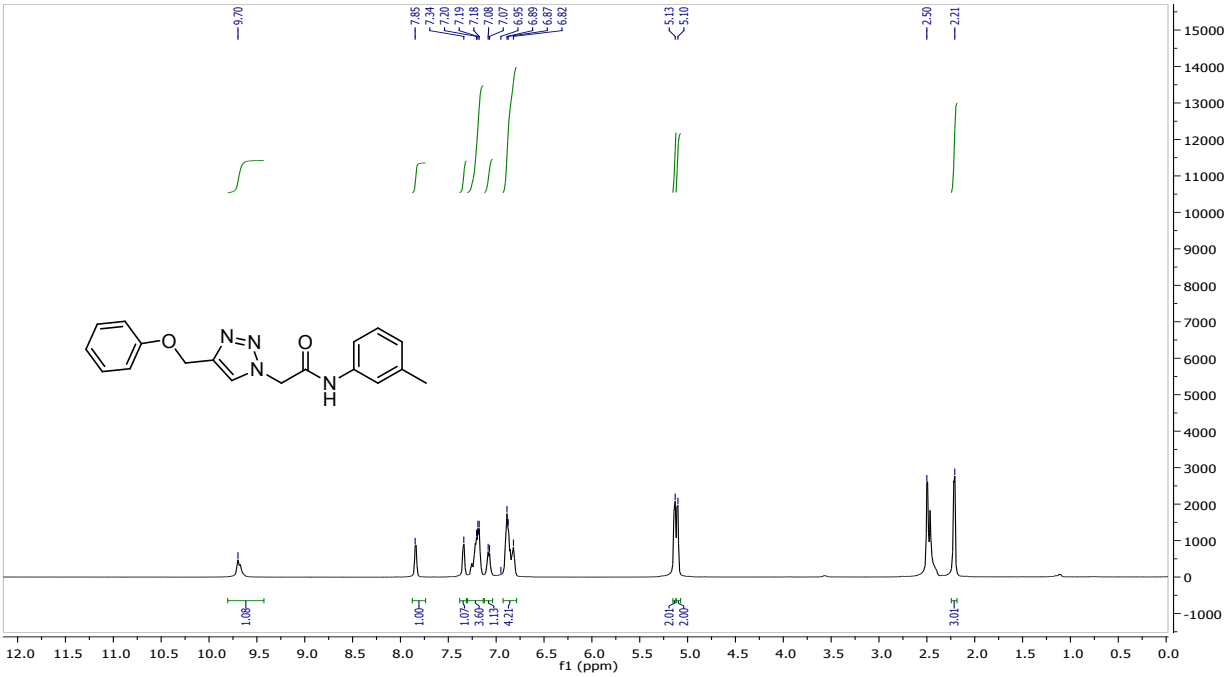


6c. ^{1}H NMR, 500 MHz, $CDCl_3$+DMSO-d_6



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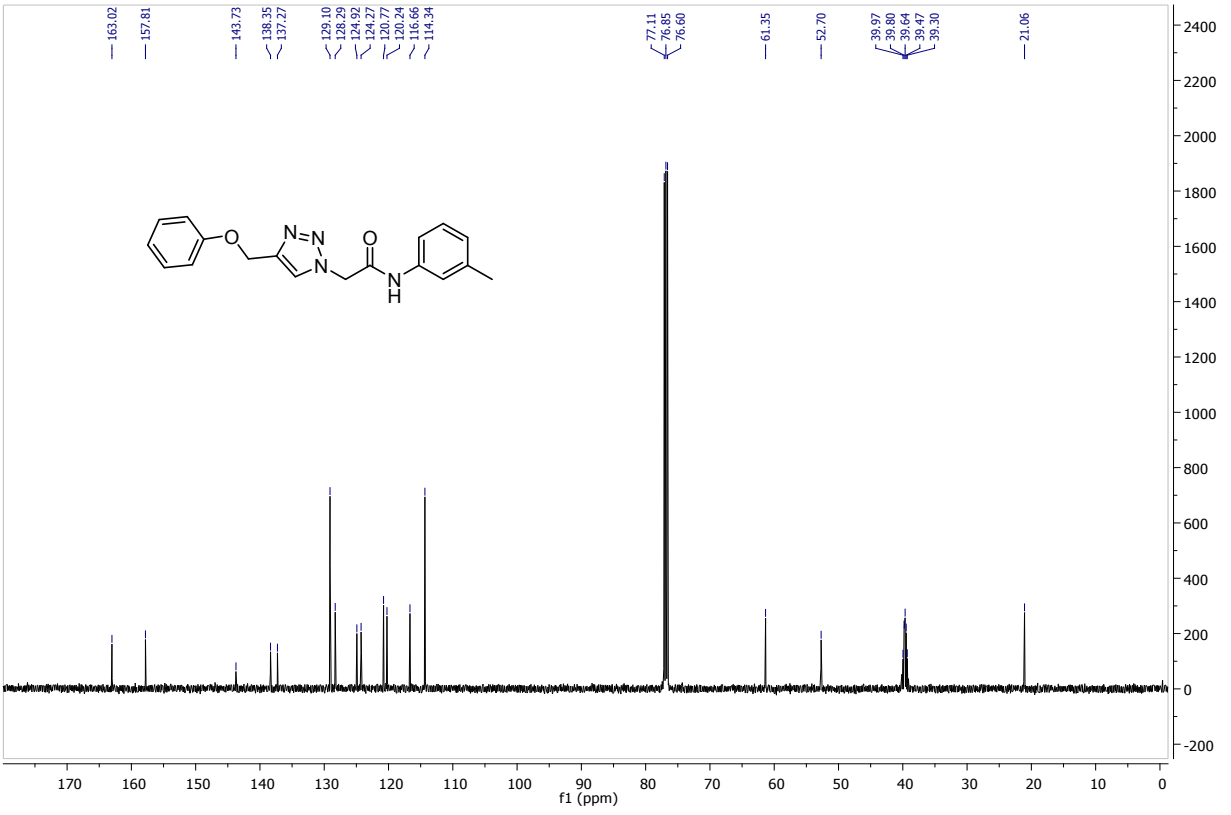
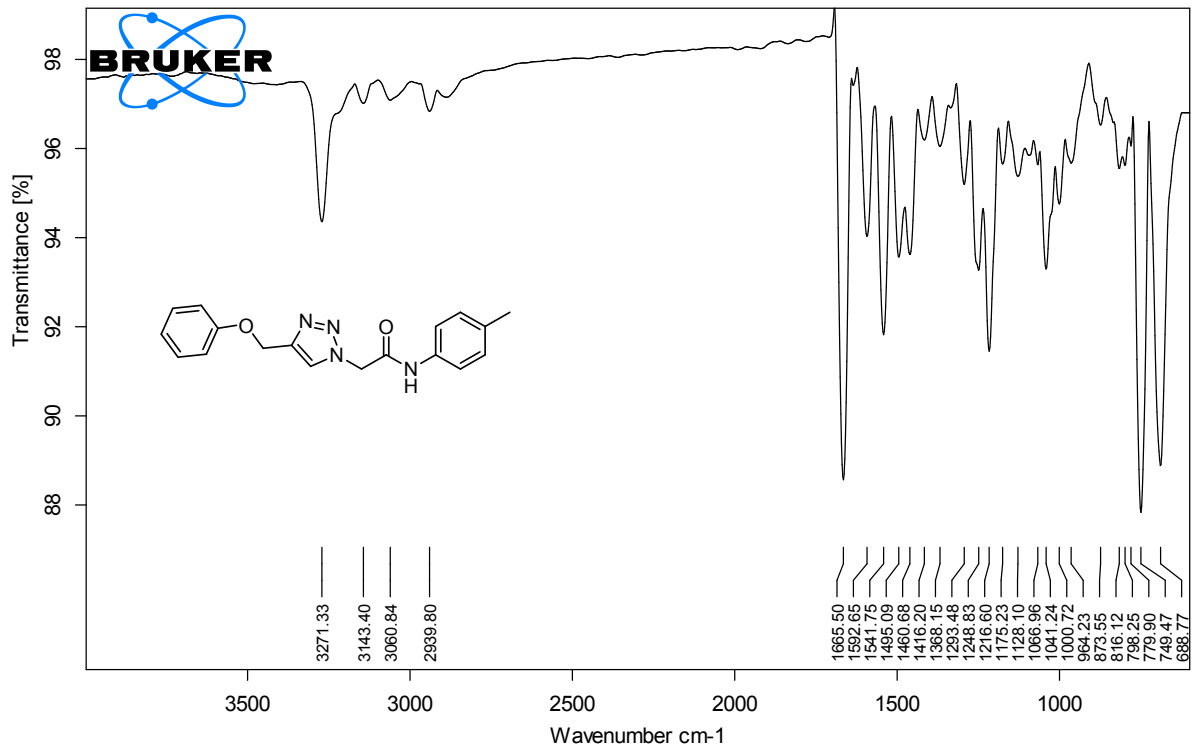


6d. FT-IR



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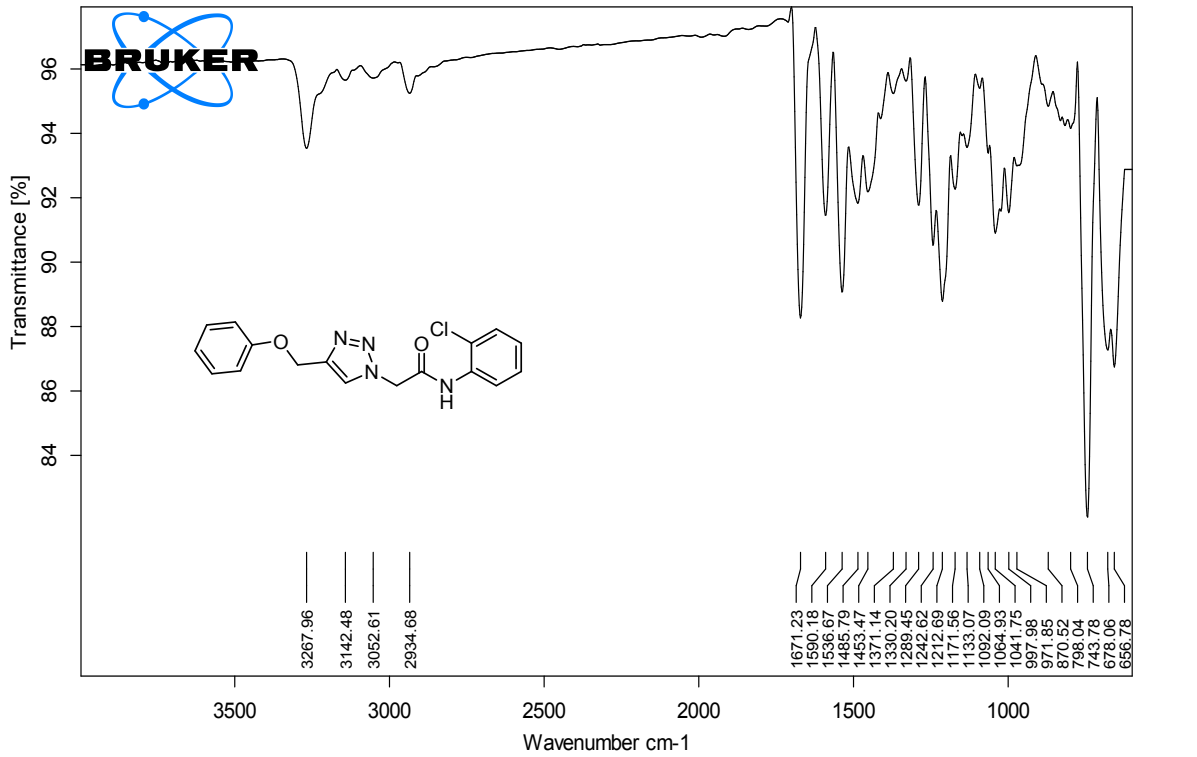

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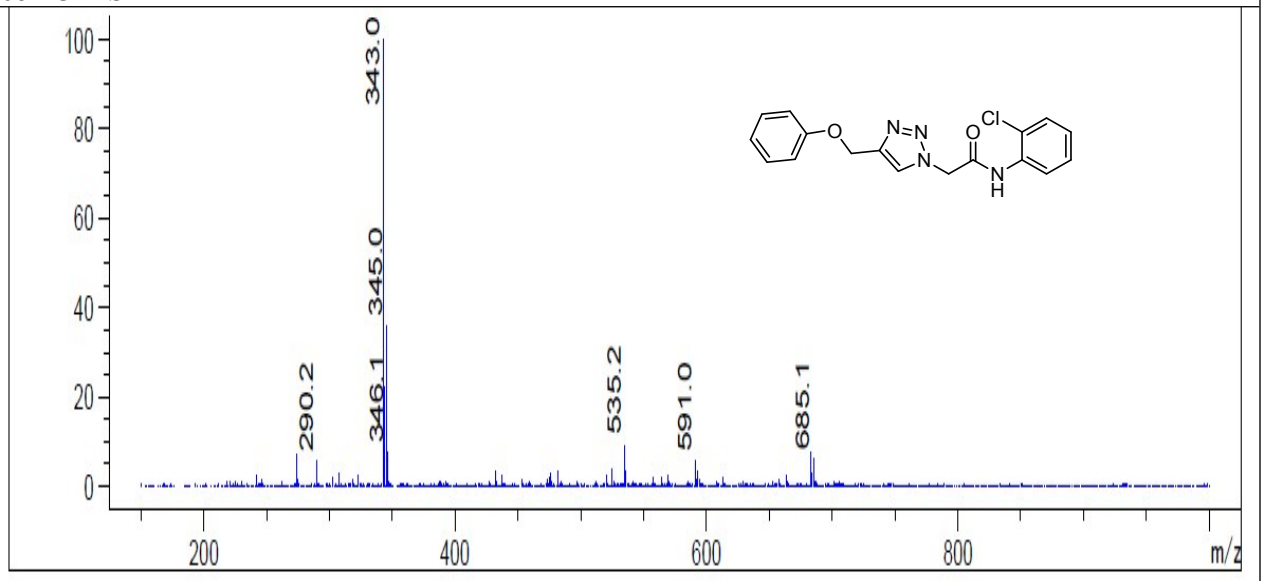
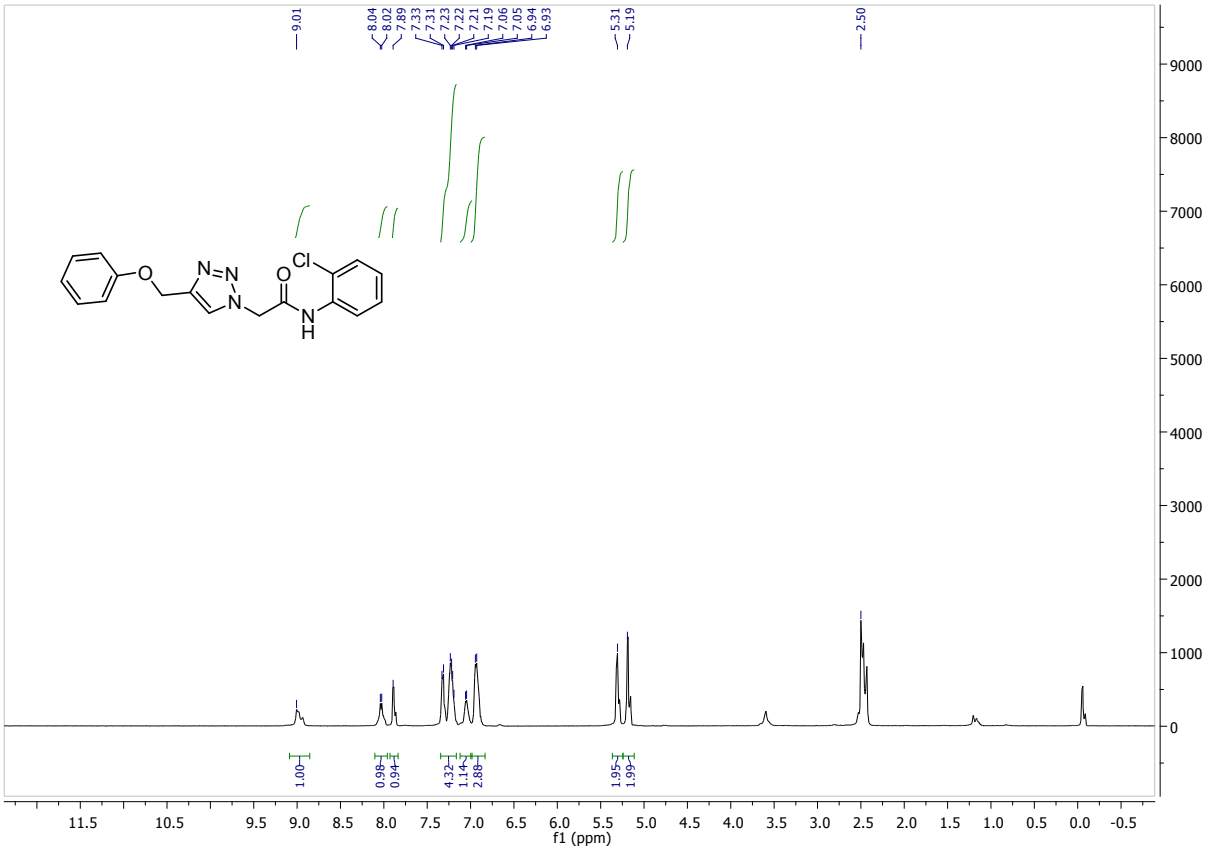
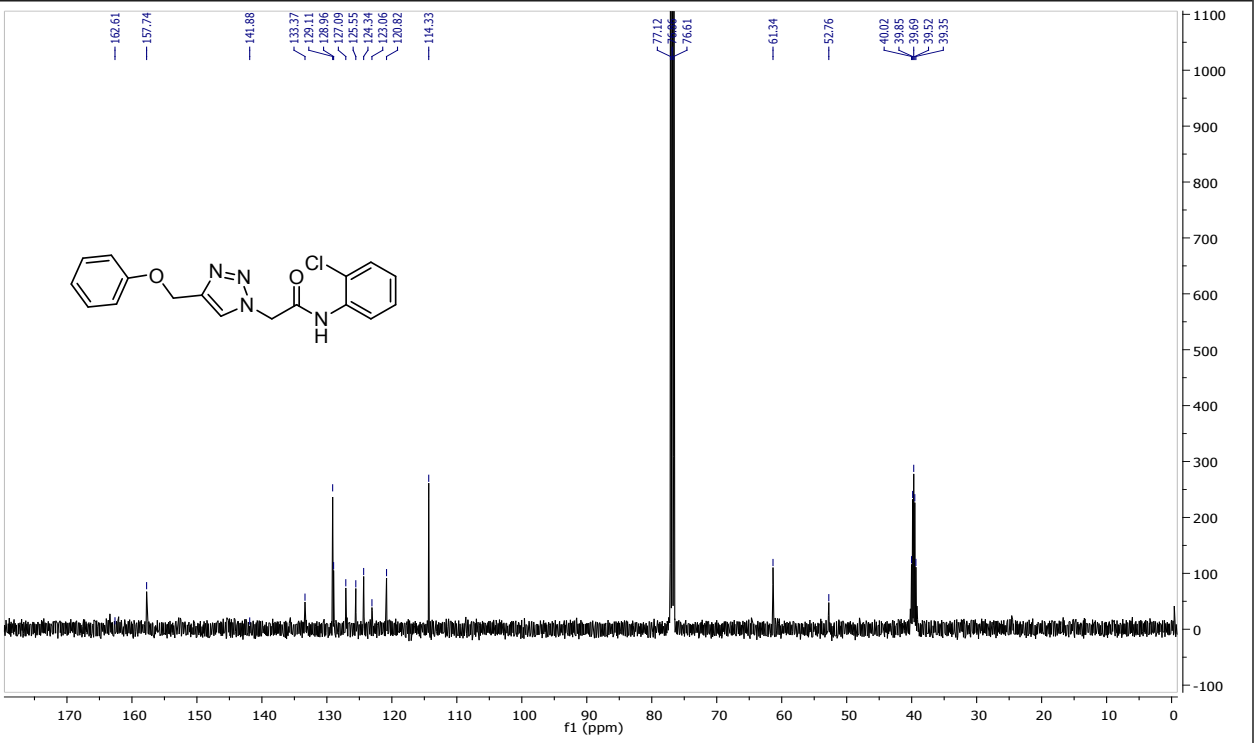


6e ^{1}H NMR, 500 MHz, $CDCl_3$+DMSO-d_6



6e. ^{13}C NMR, 125 MHz, $CDCl_3$+DMSO-d_6



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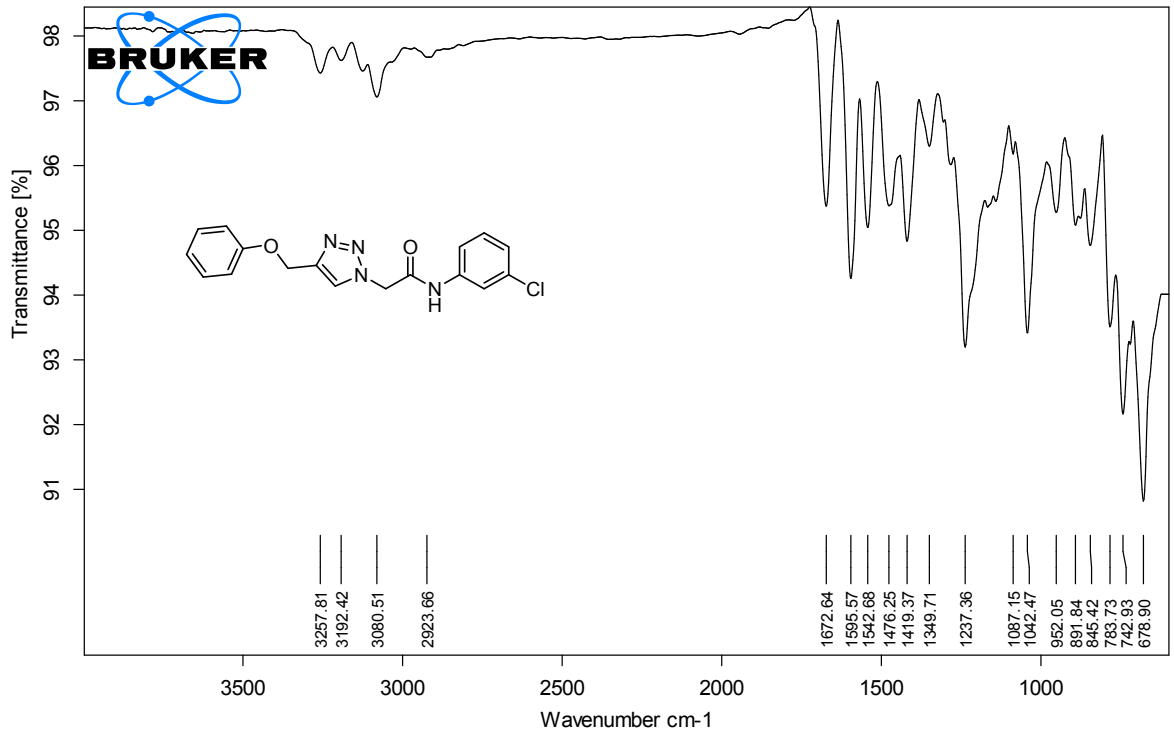

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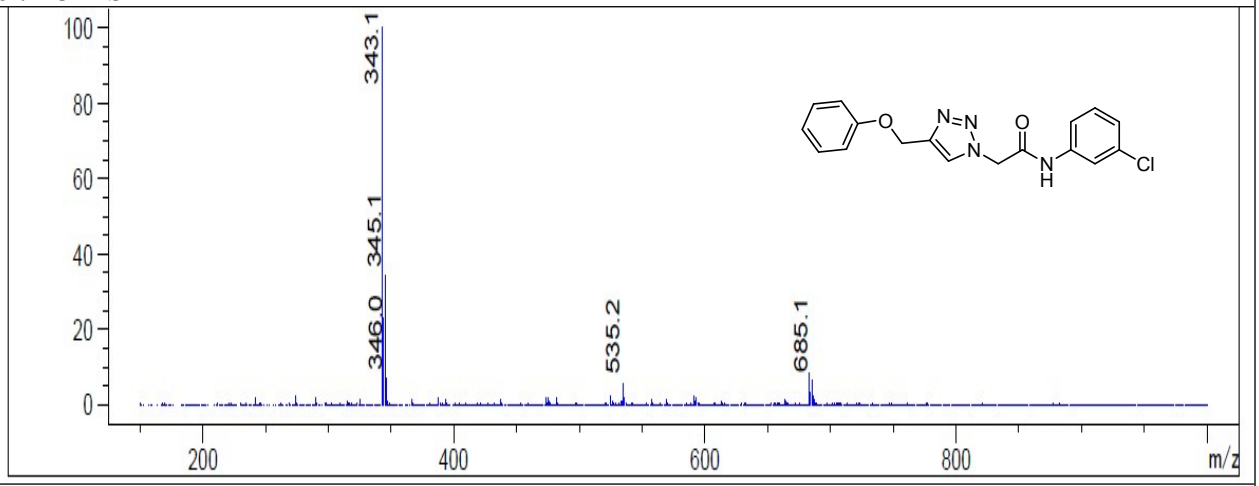
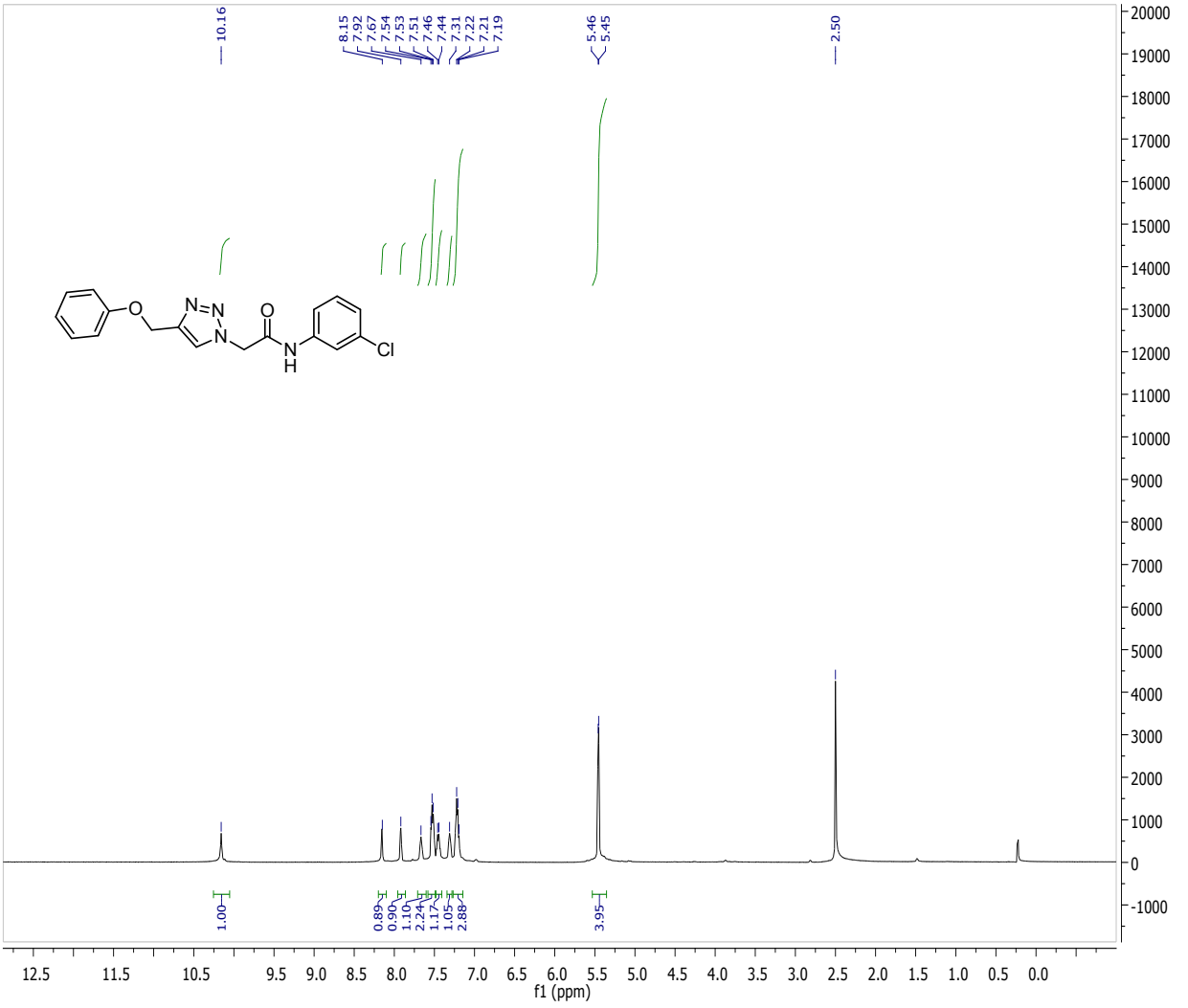
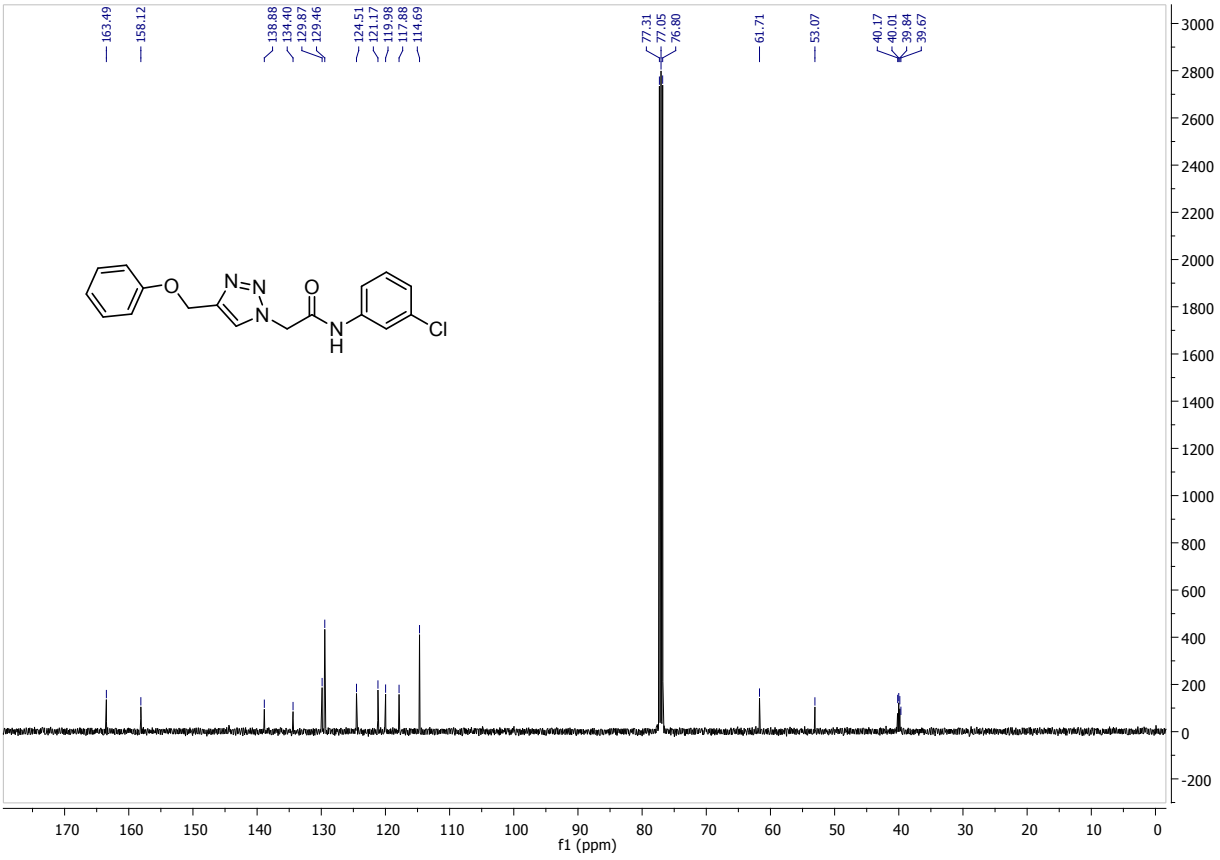


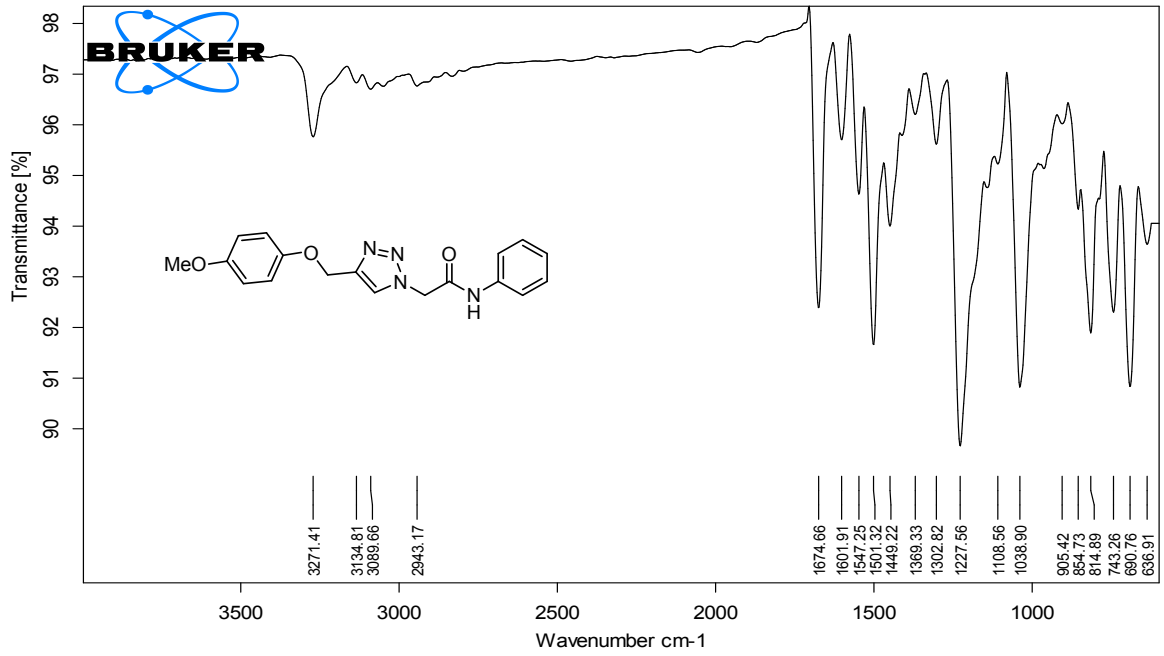
6f. ^{1}H NMR, 500 MHz, $CDCl_3$+DMSO-d_6



6f. ^{13}C NMR, 125 MHz, $CDCl_3$+DMSO-d_6



7a. FT-IR



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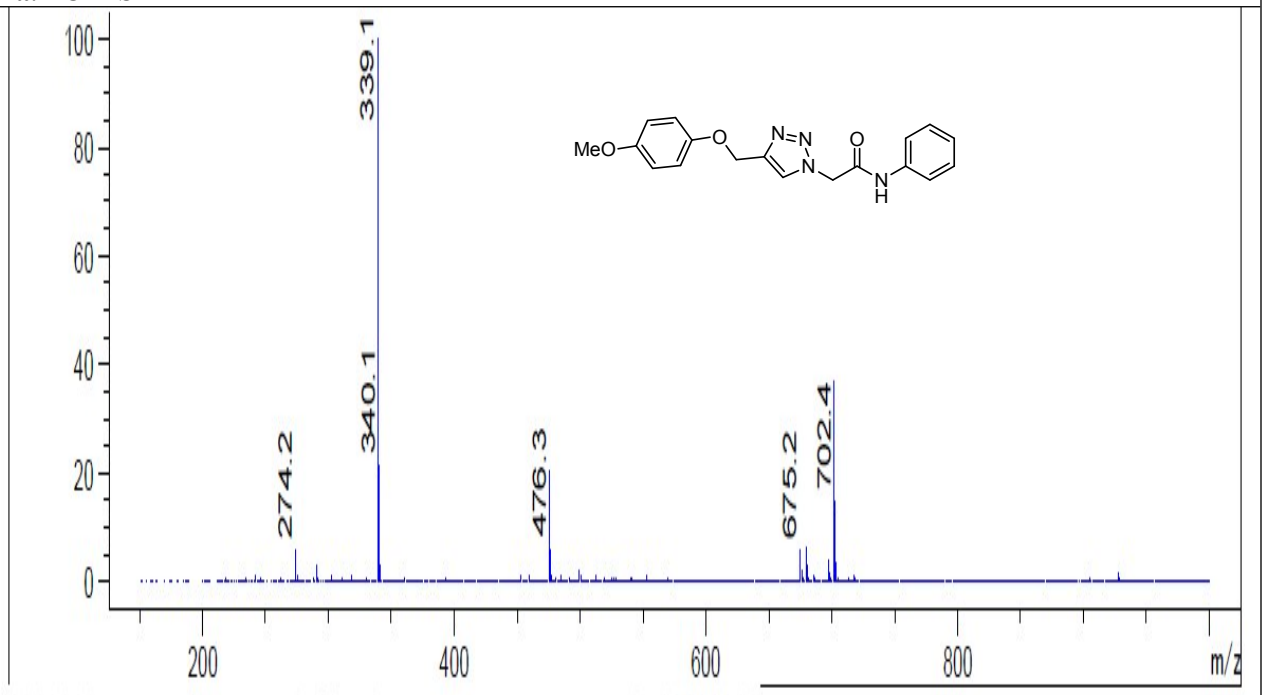
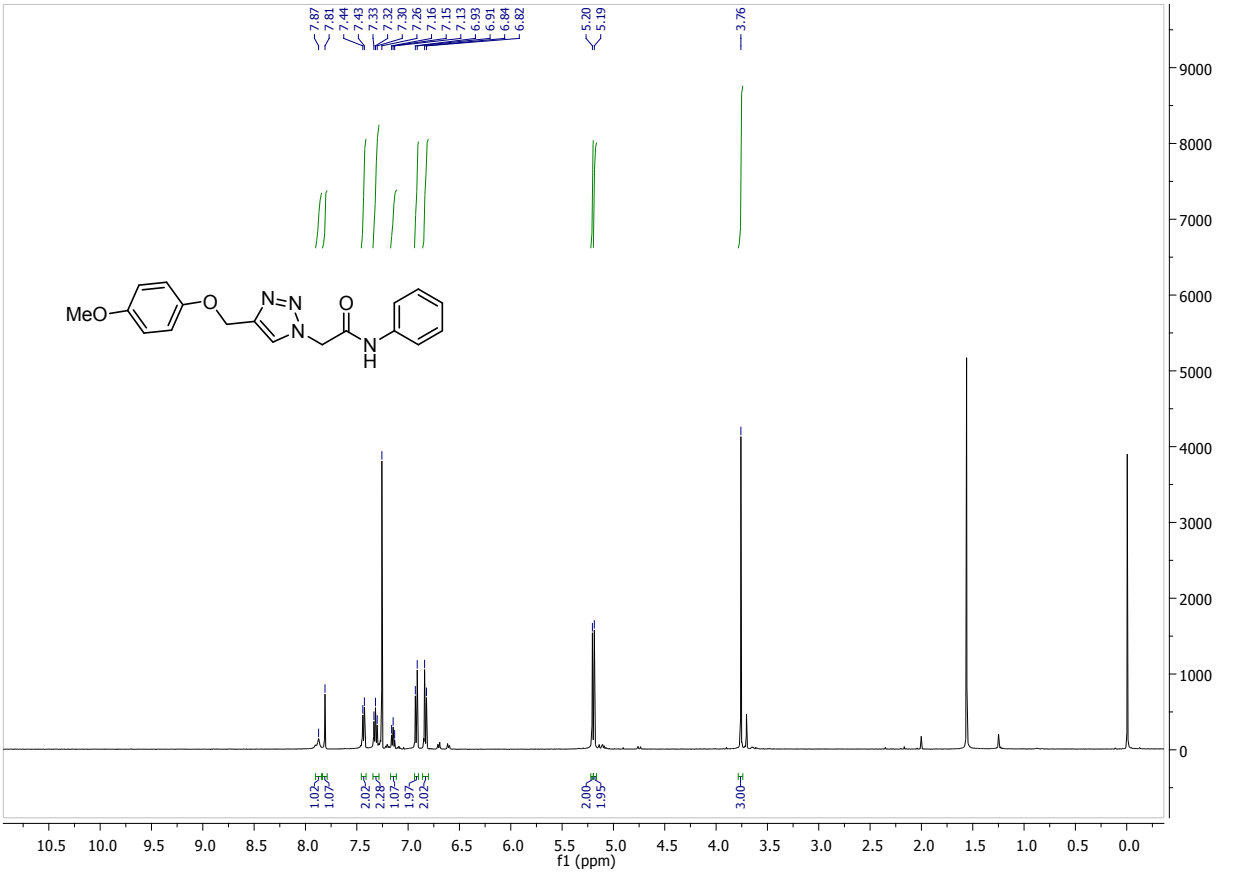


7a. ^{1}H NMR, 500 MHz, $CDCl_3$



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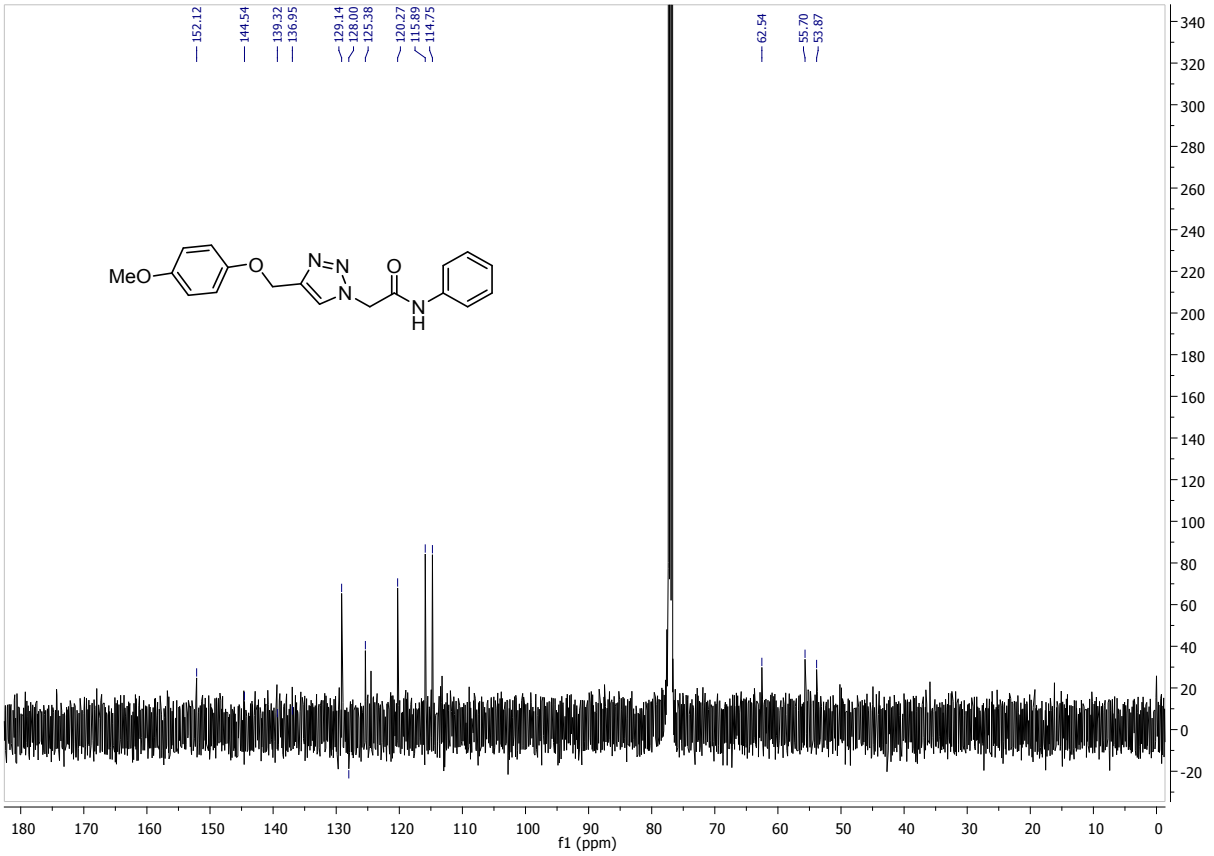

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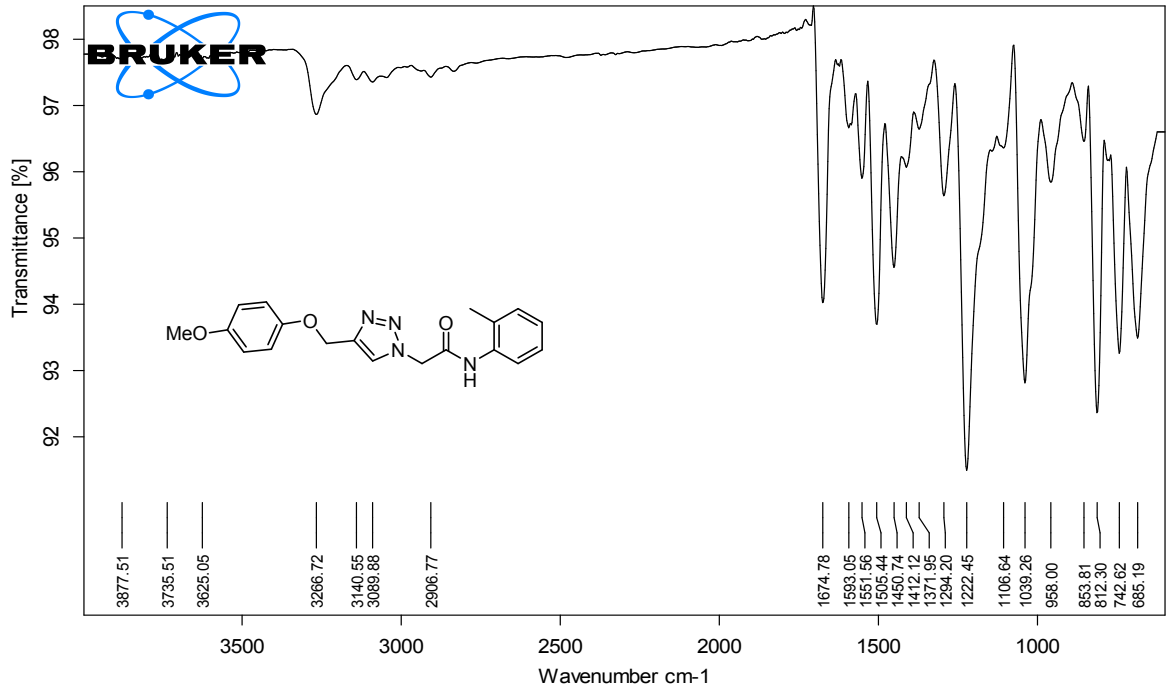

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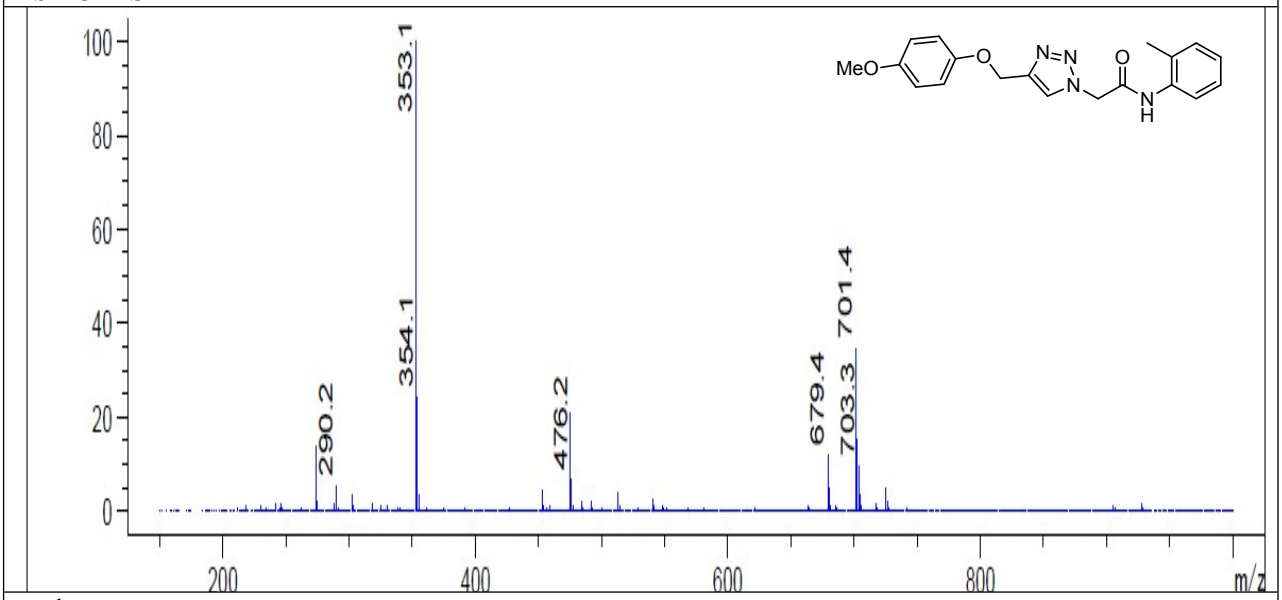

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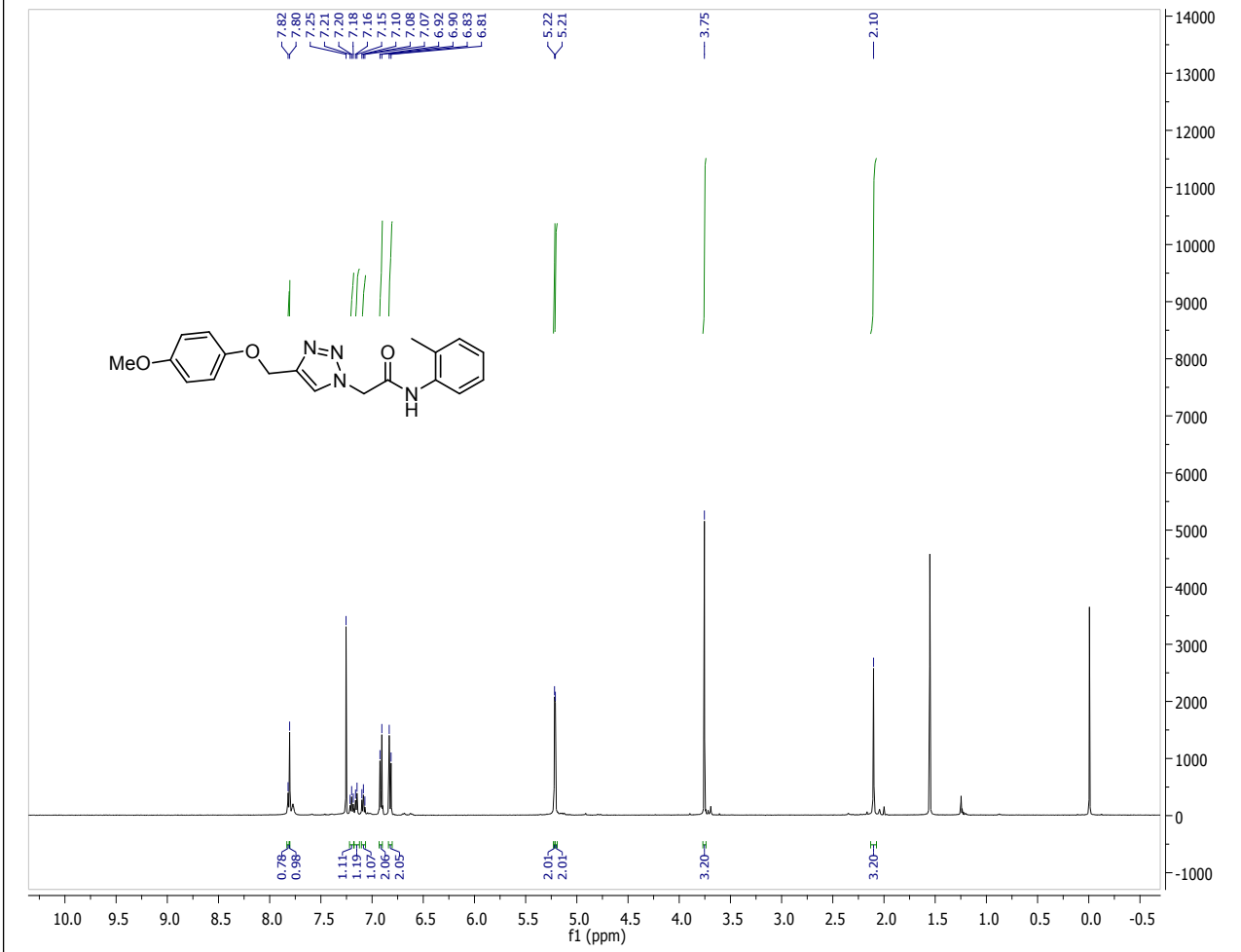

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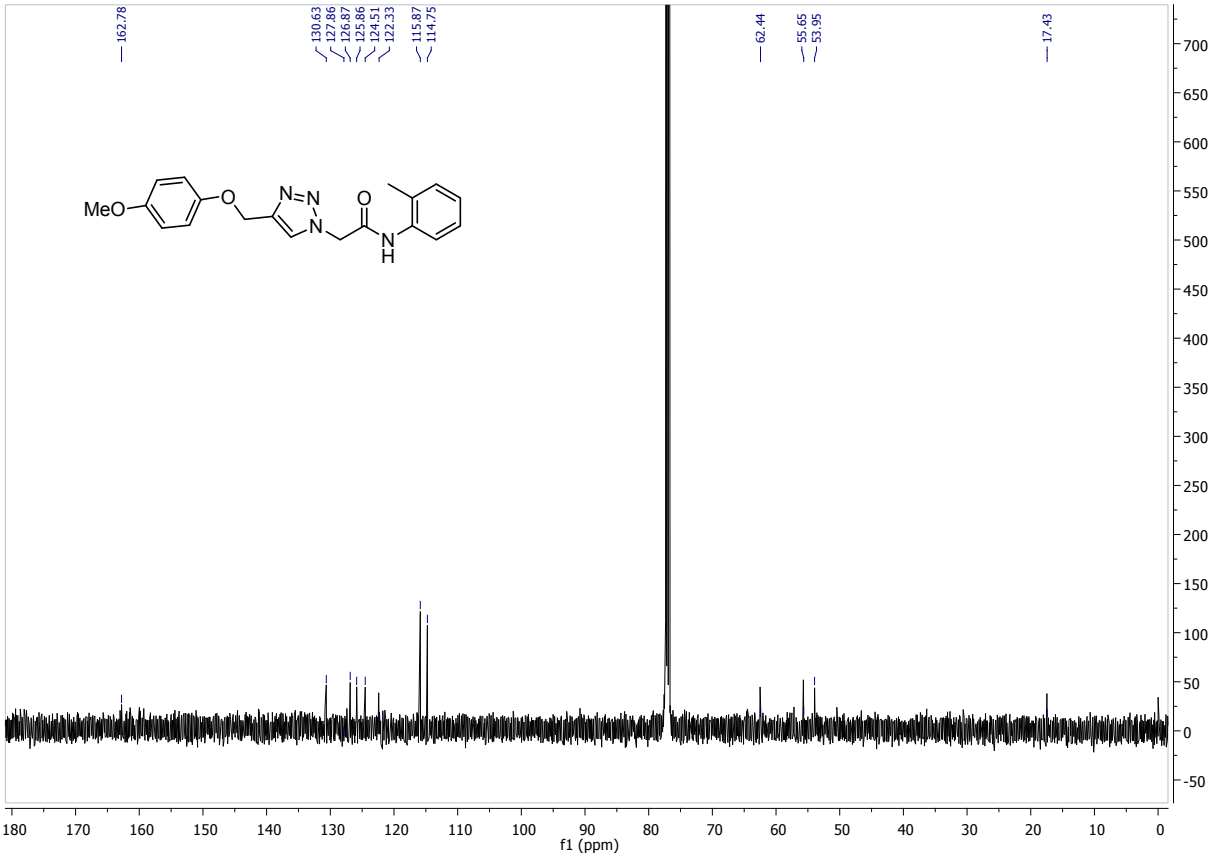

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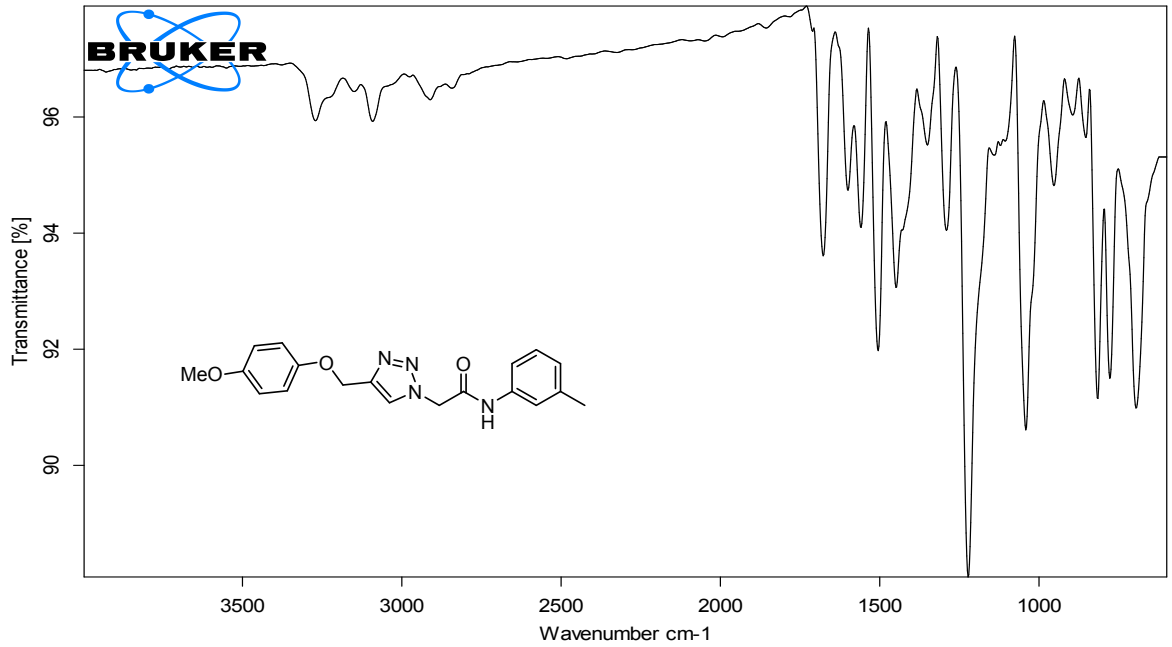

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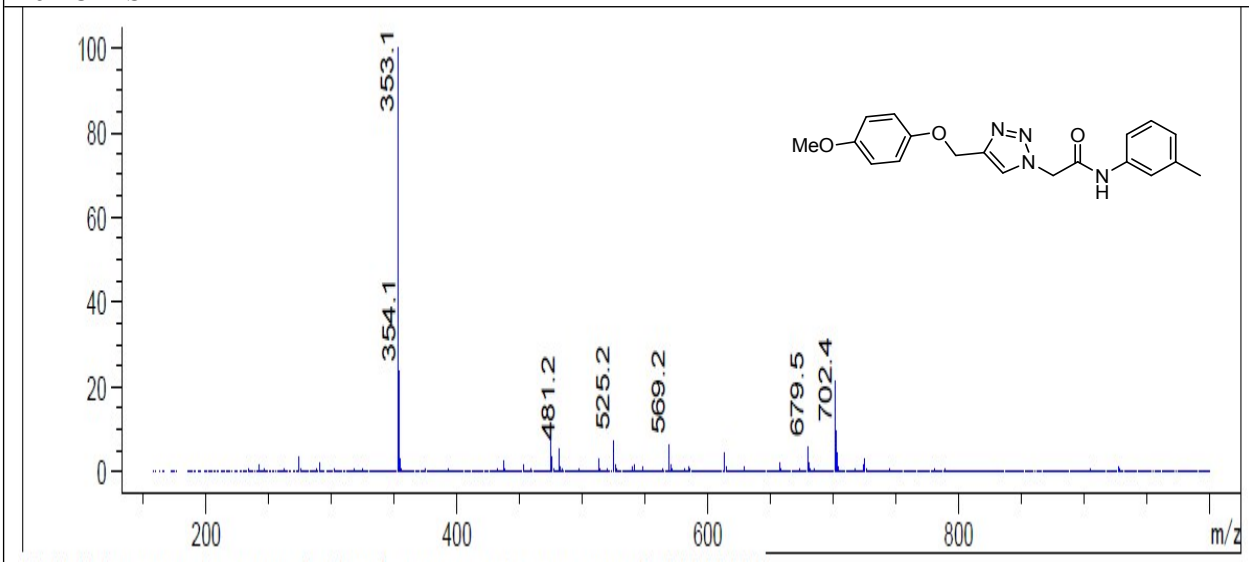
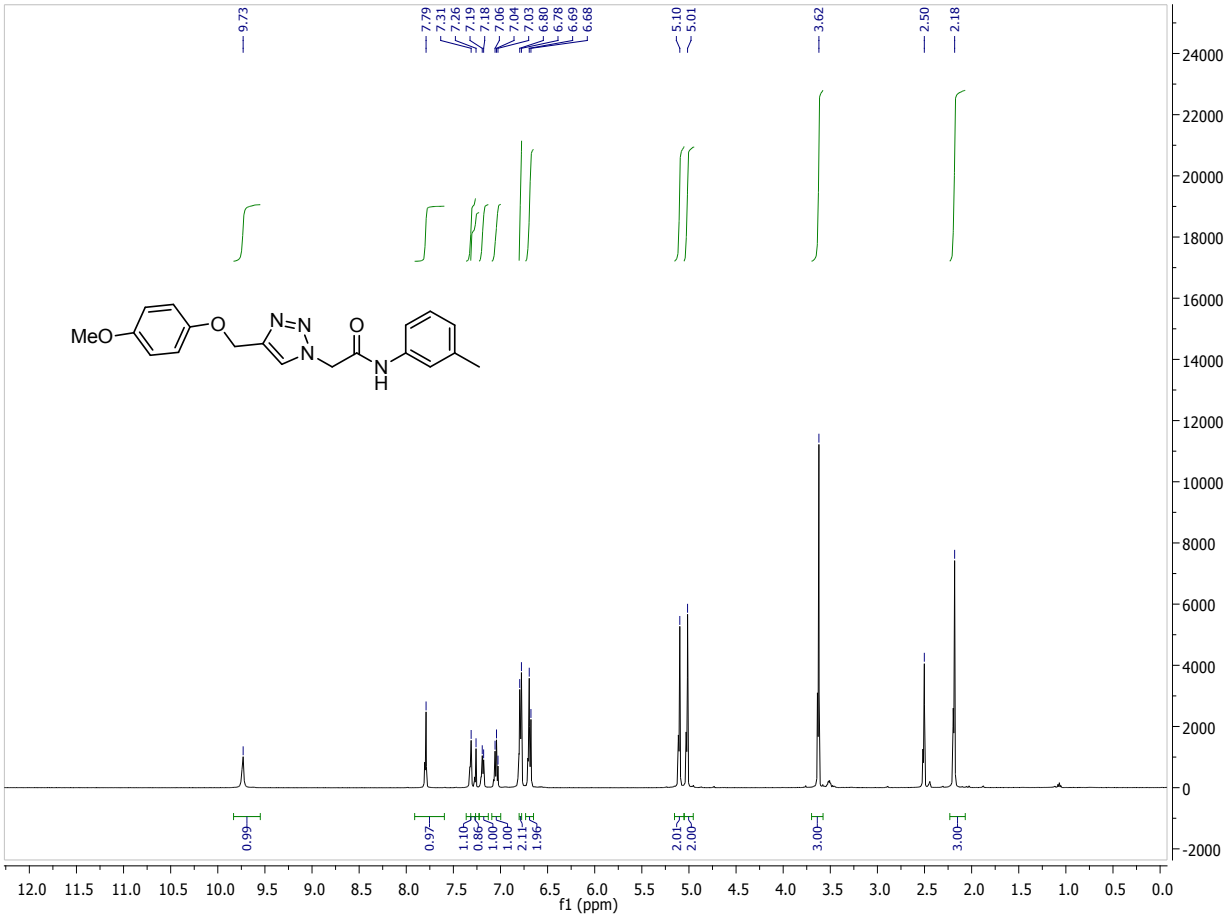


7c ^{1}H NMR, 500 MHz, $CDCl_3$+DMSO-d_6



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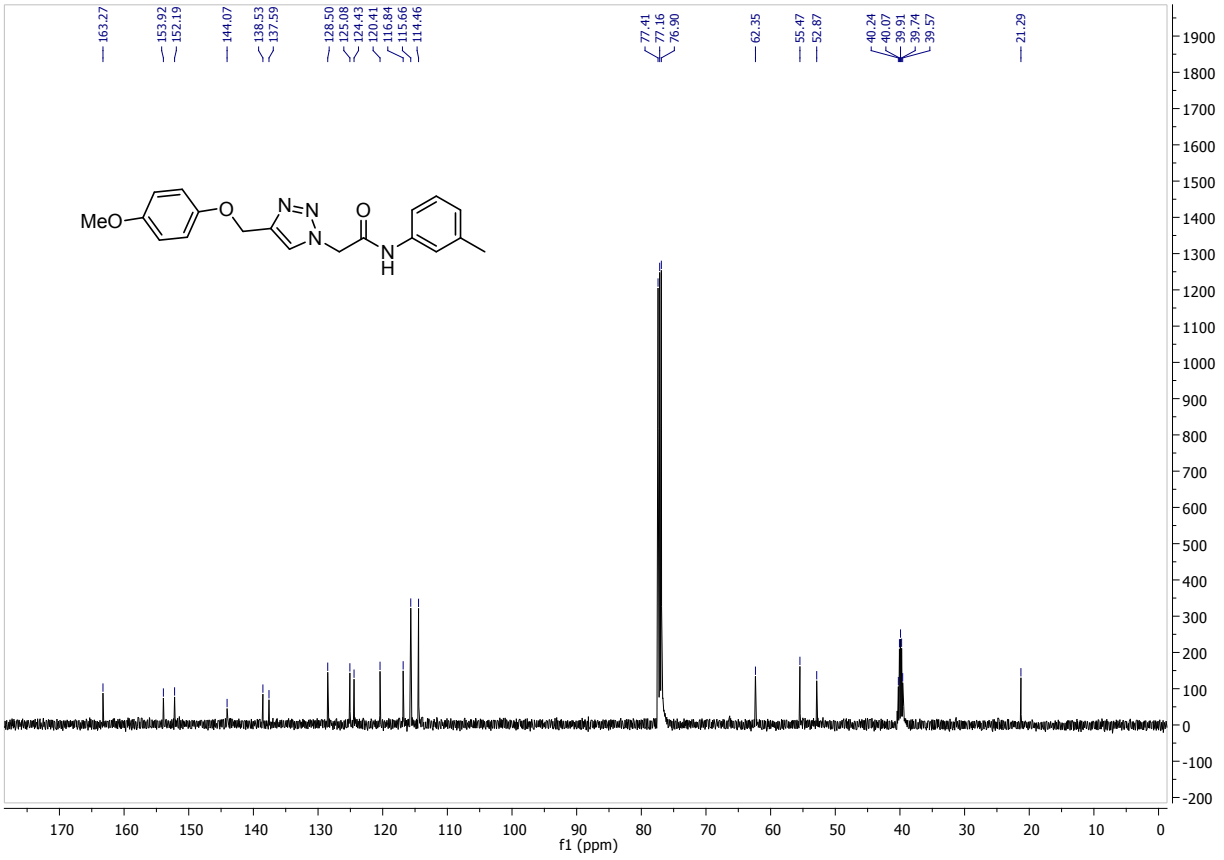
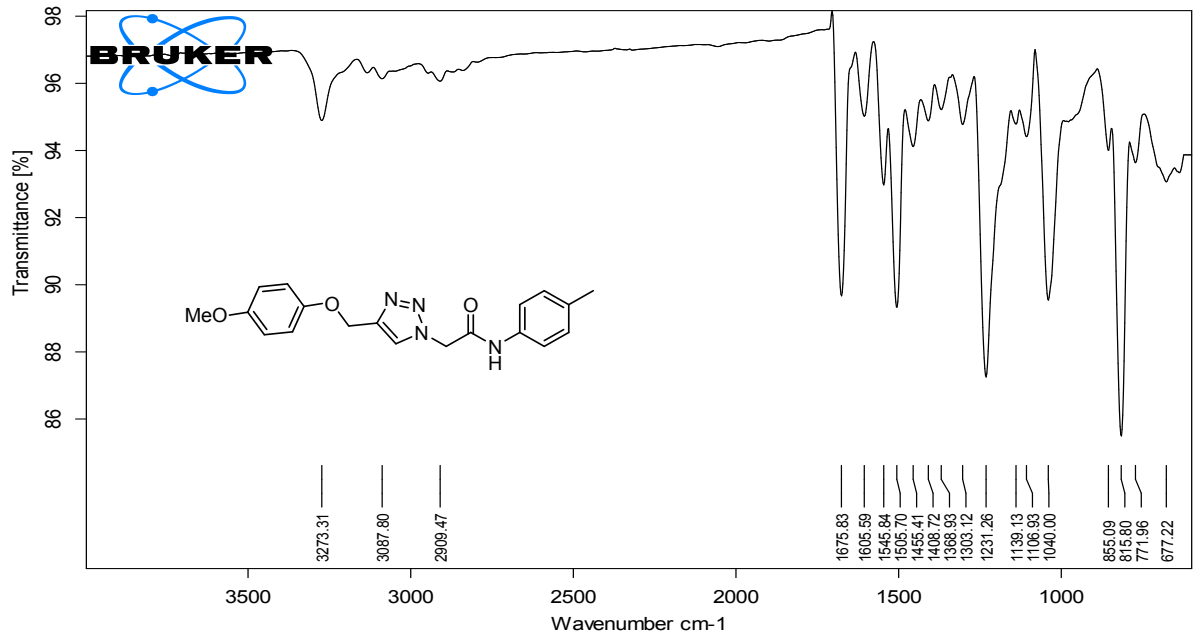


7d. FT-IR



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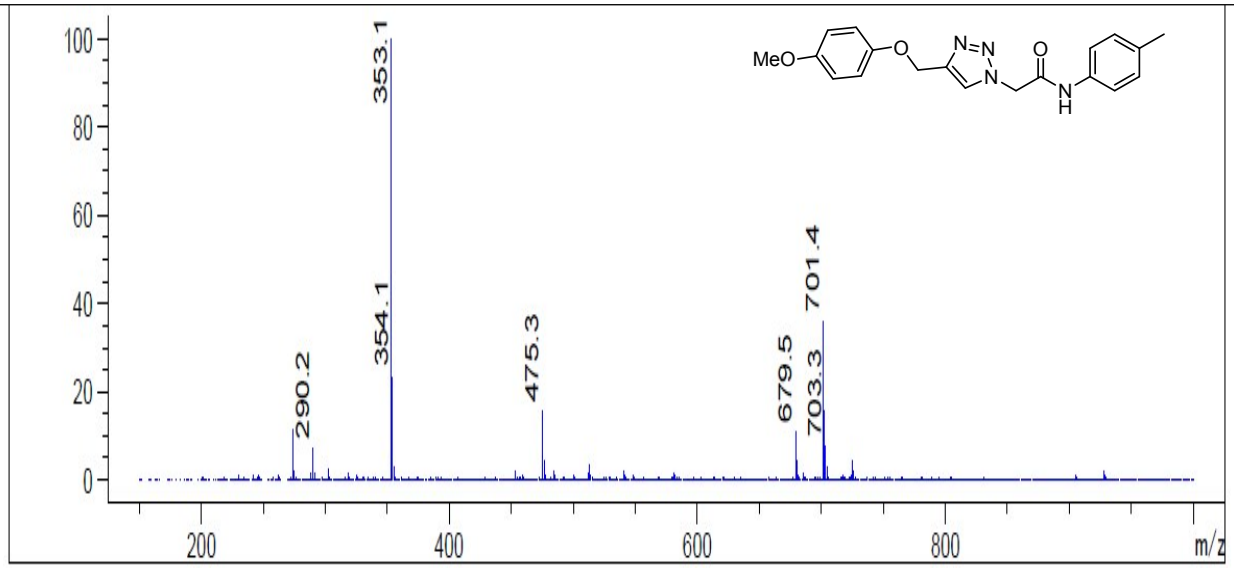
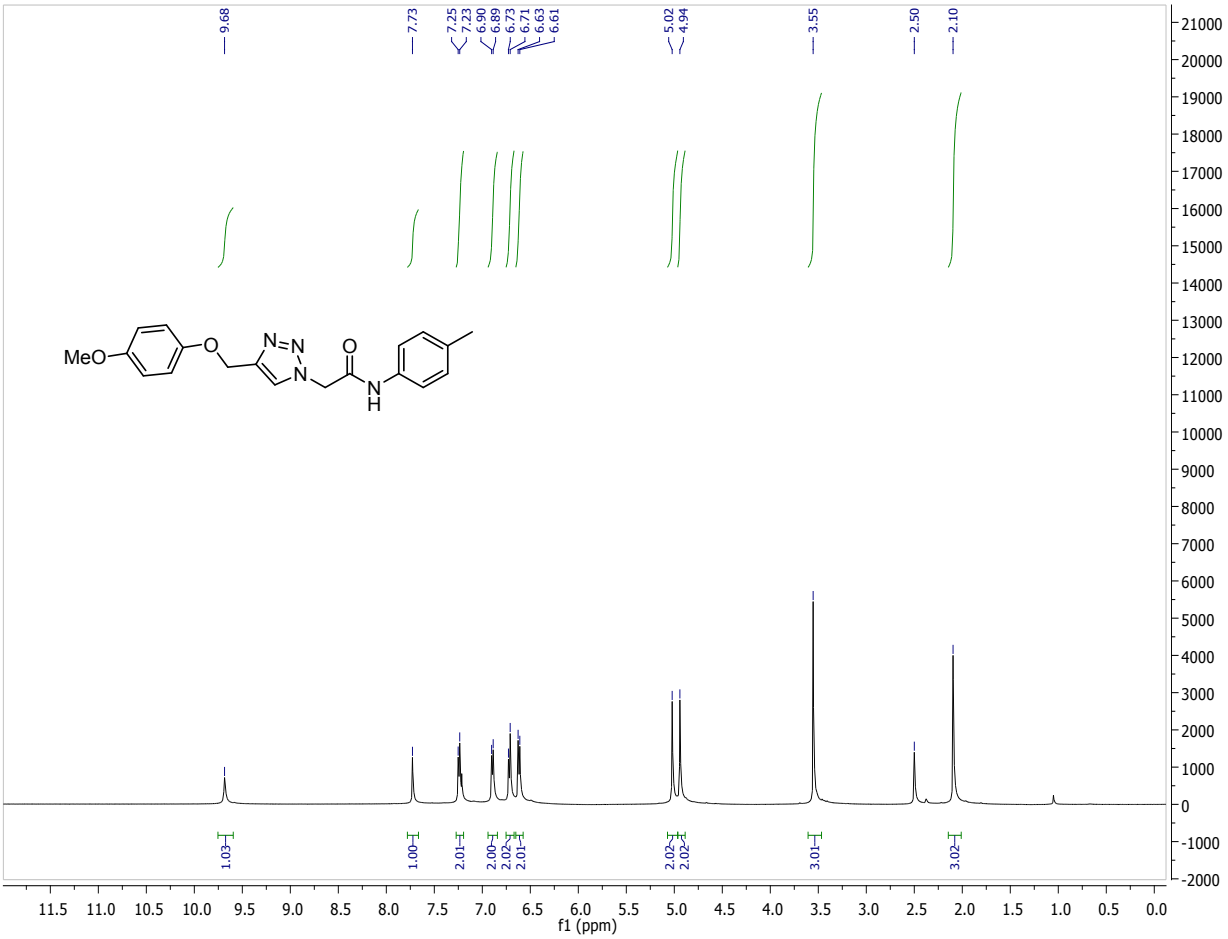
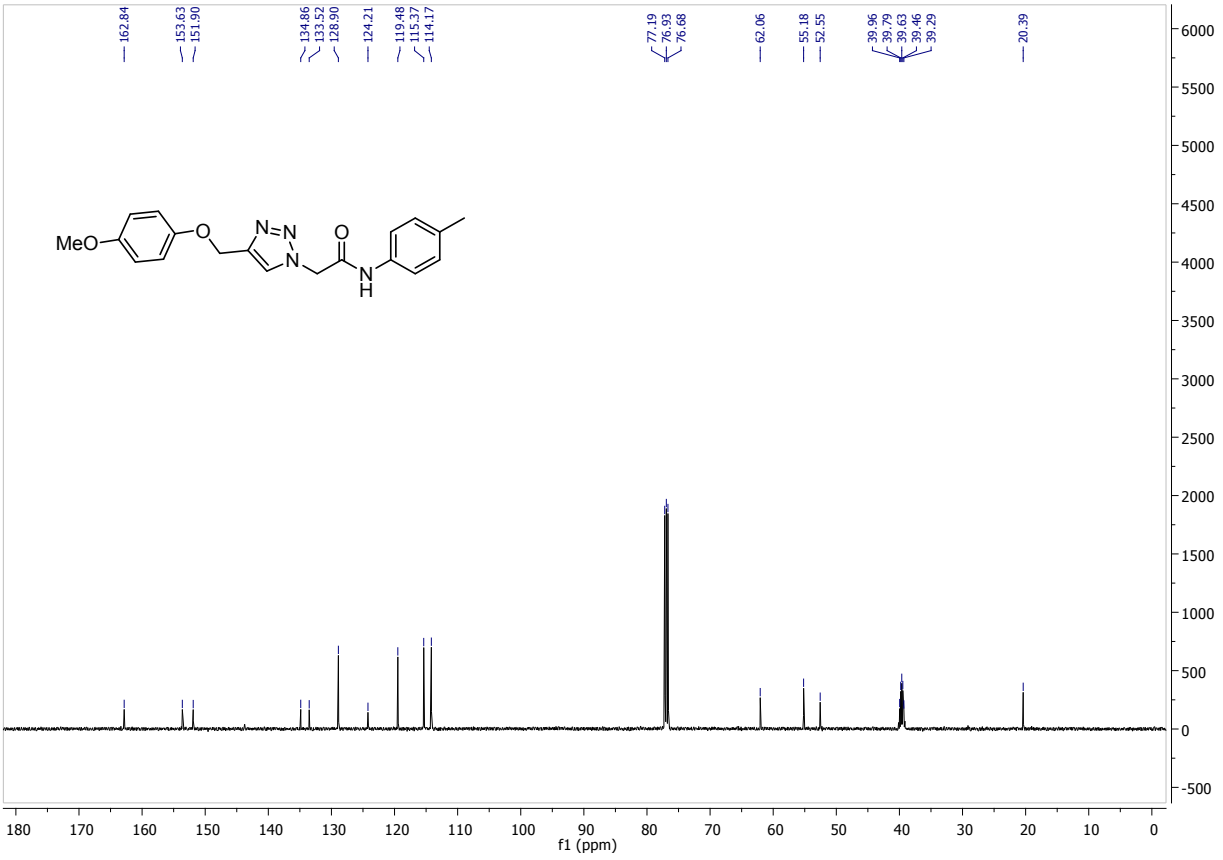


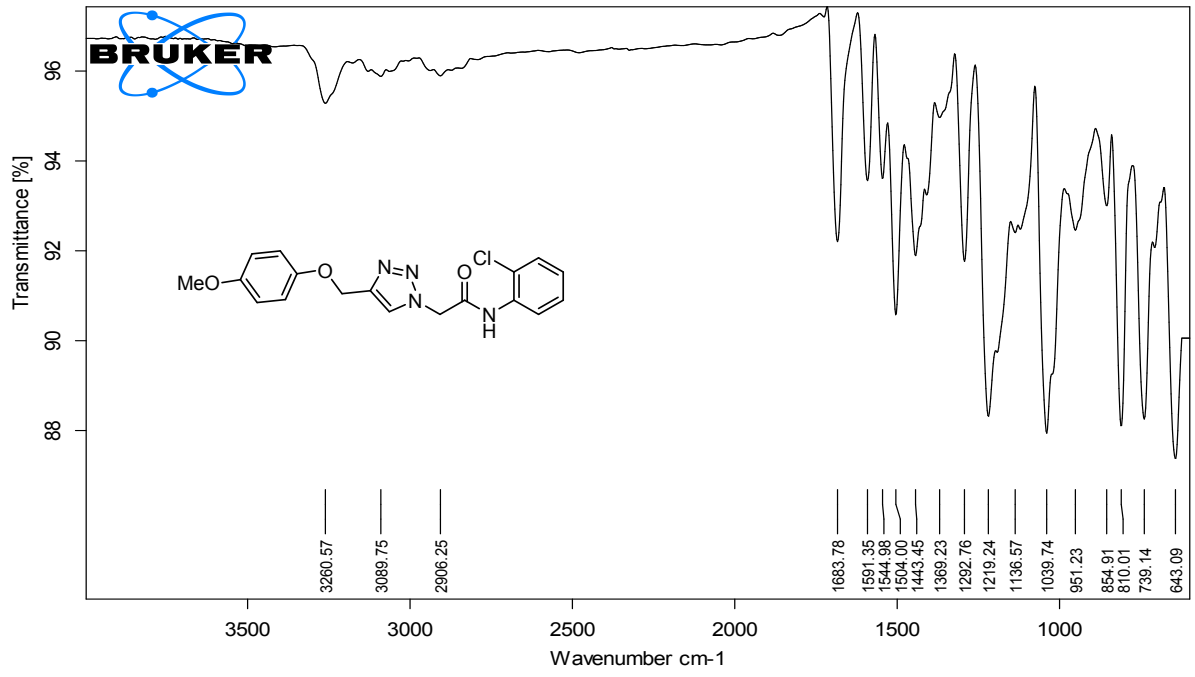
7d. ^{1}H NMR, 500 MHz, $CDCl_3$+DMSO-d_6



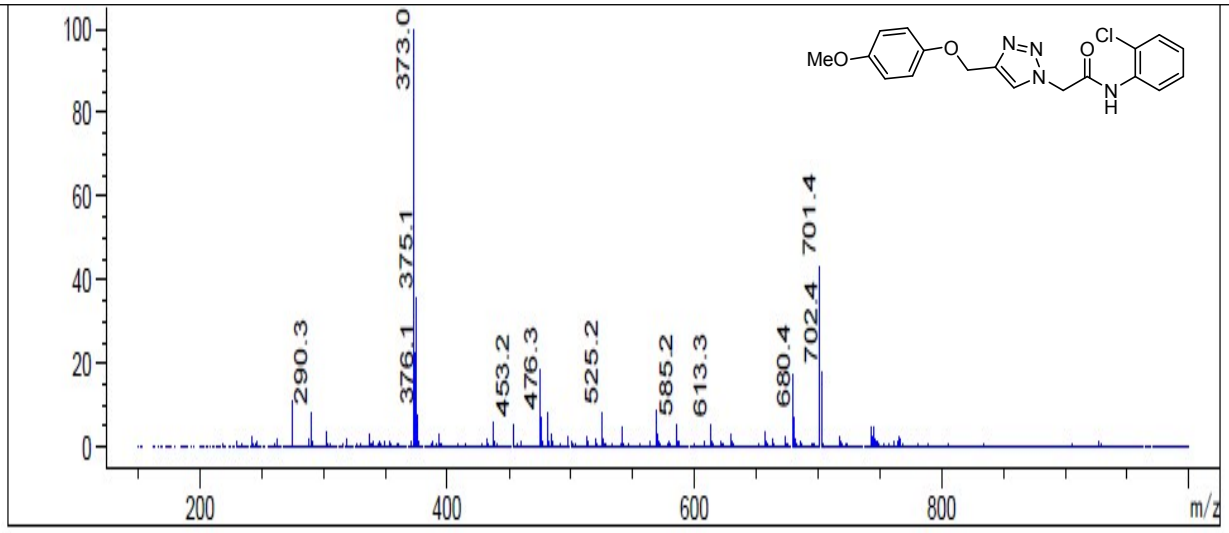
7d. ^{13}C NMR, 125 MHz, $CDCl_3$+DMSO-d_6



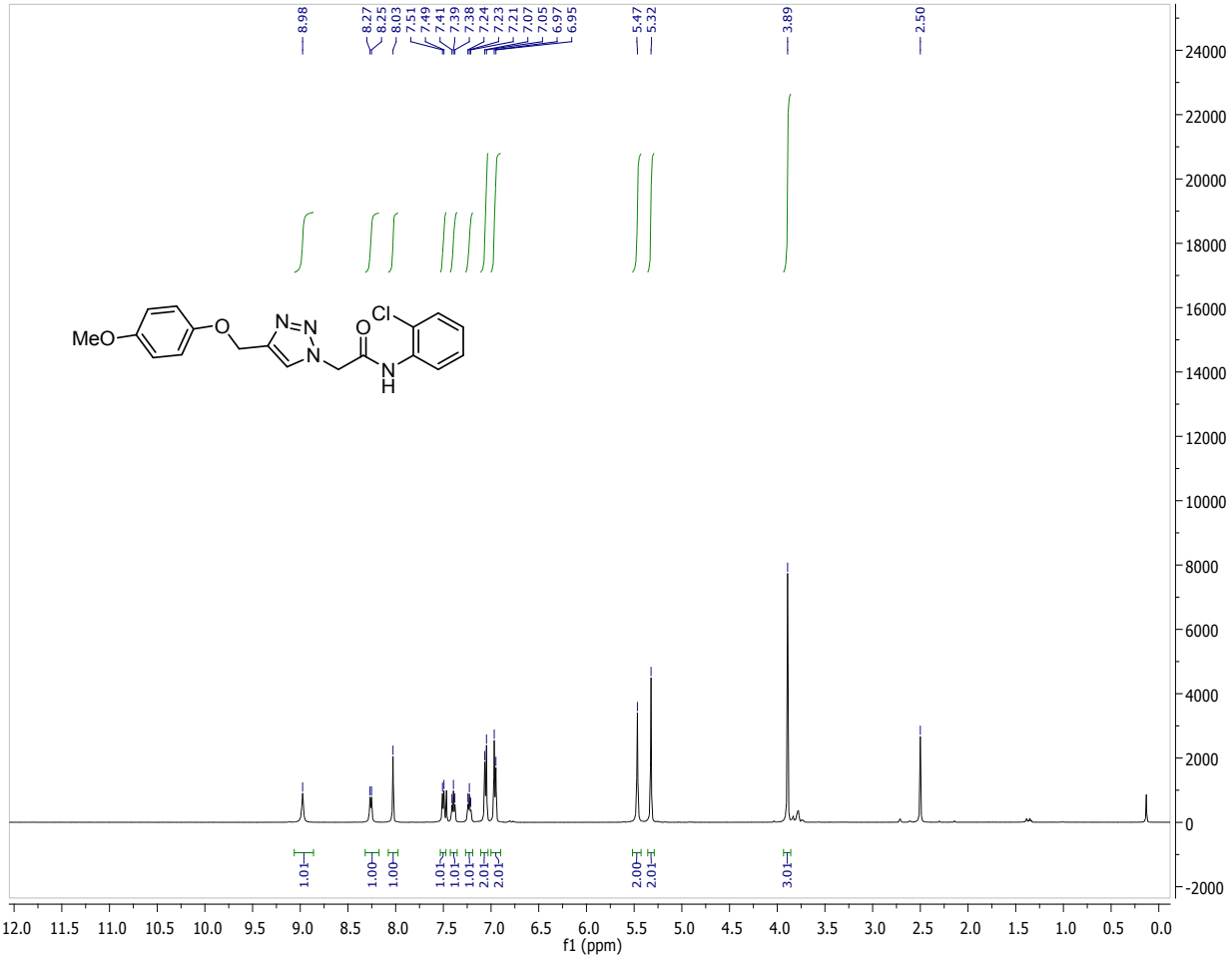
7e. FT-IR



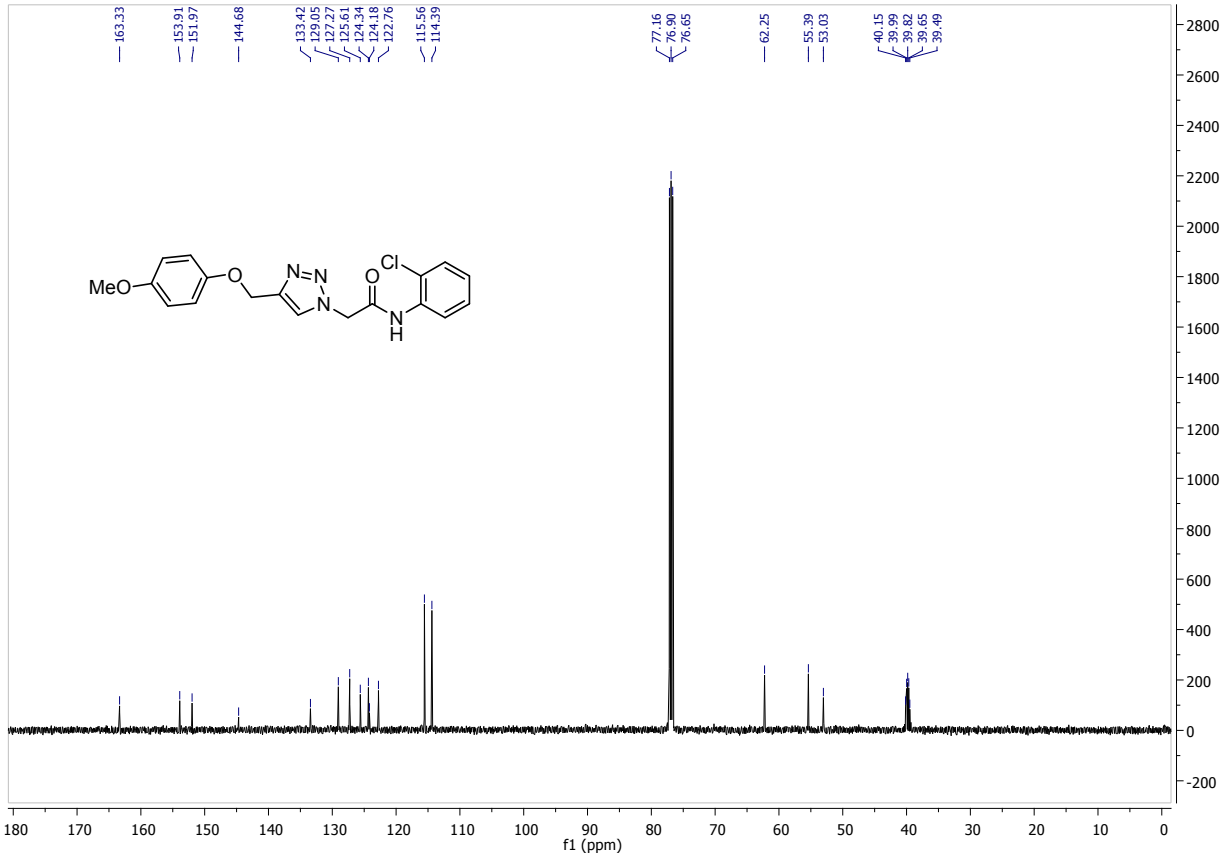
7e. LC-MS



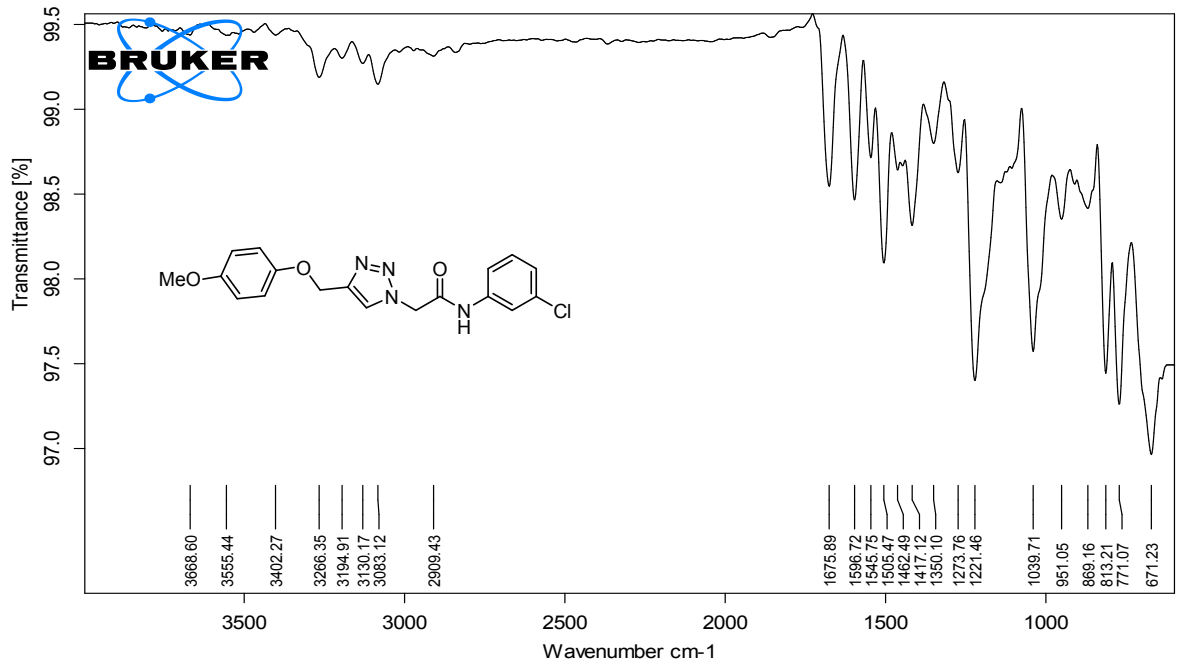
7e. ^{1}H NMR, 500 MHz, $CDCl_3$+DMSO-d_6



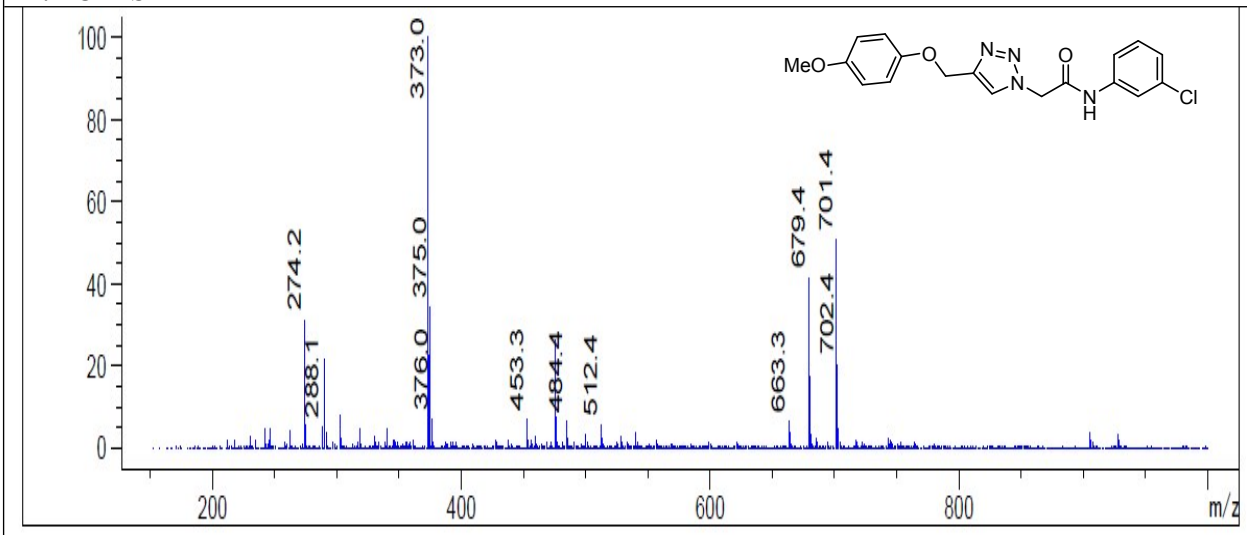
7e. ^{13}C NMR, 125 MHz, $CDCl_3$+DMSO-d_6



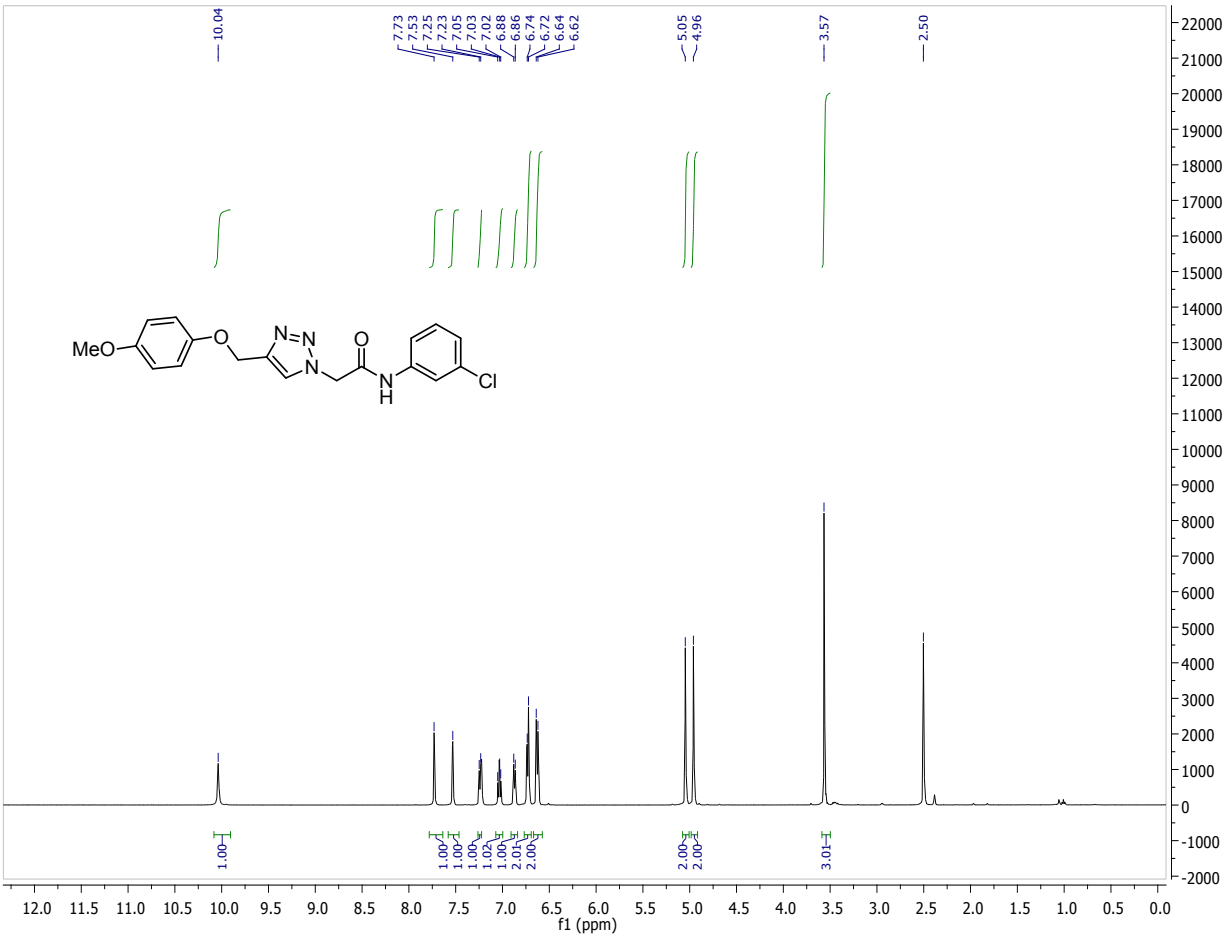
7f. FT-IR



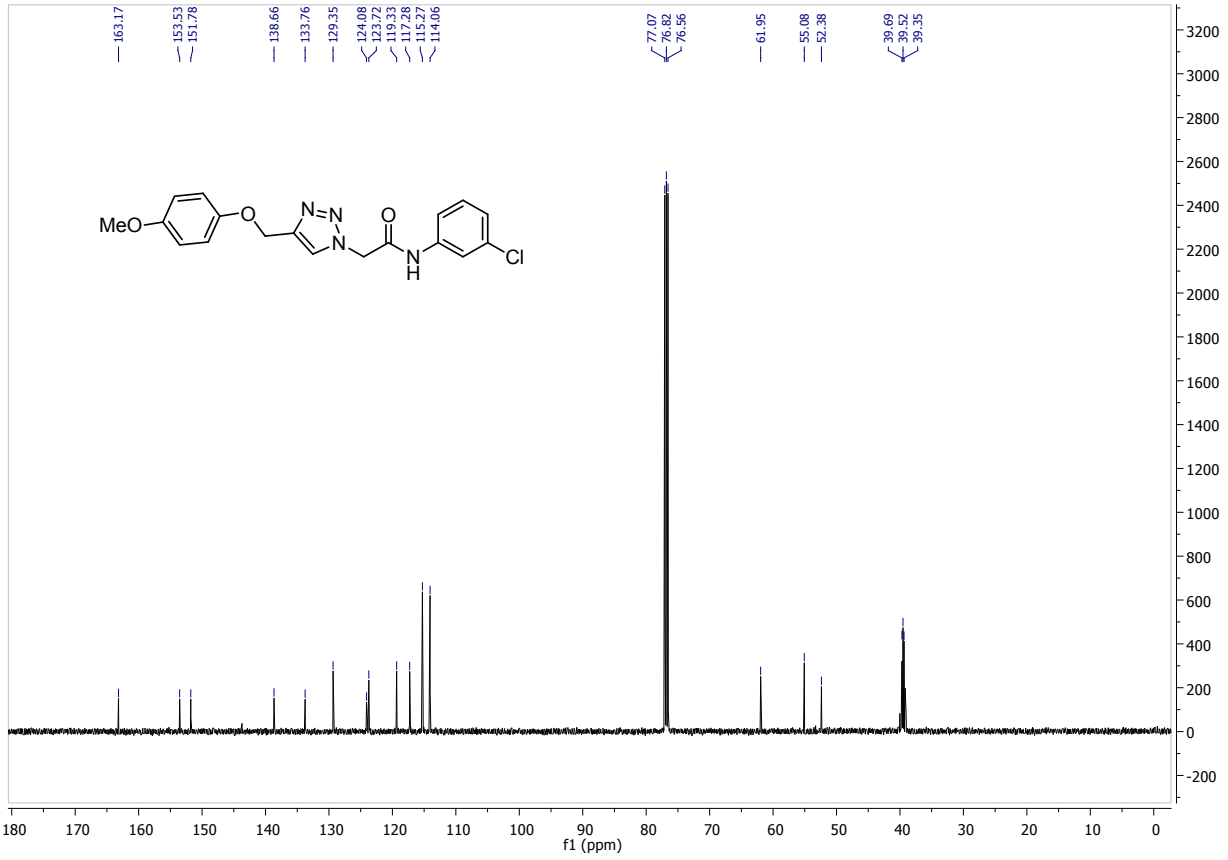
7f. LC-MS



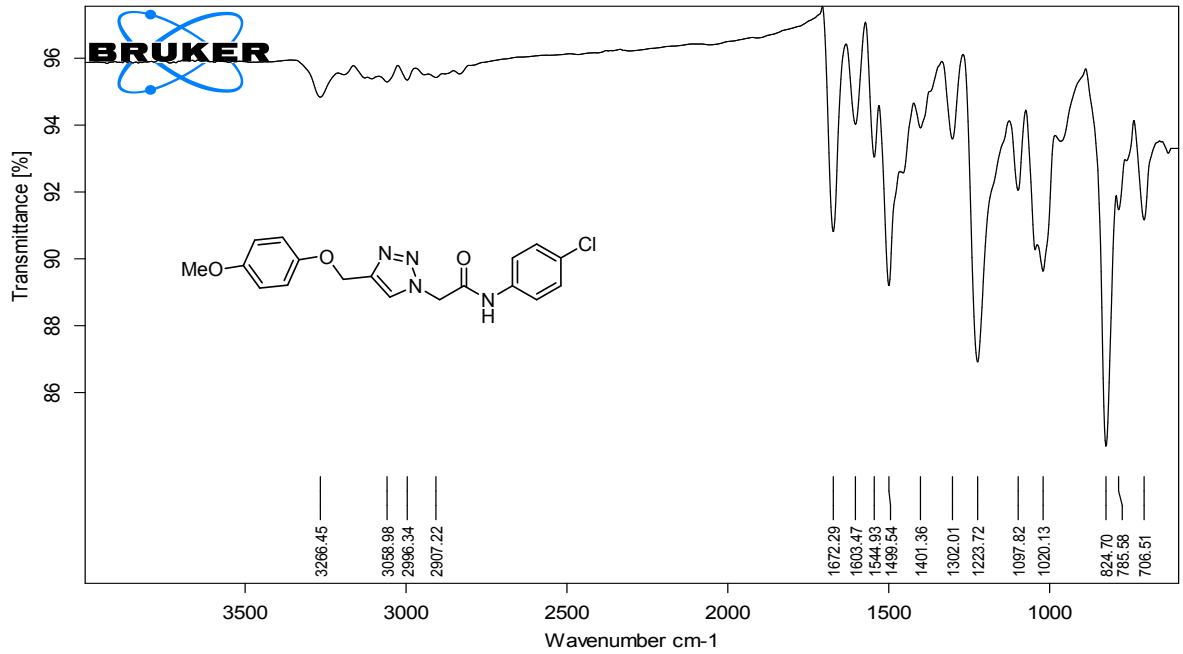
7f. ^{1}H NMR, 500 MHz, $CDCl_3$+DMSO-d_6



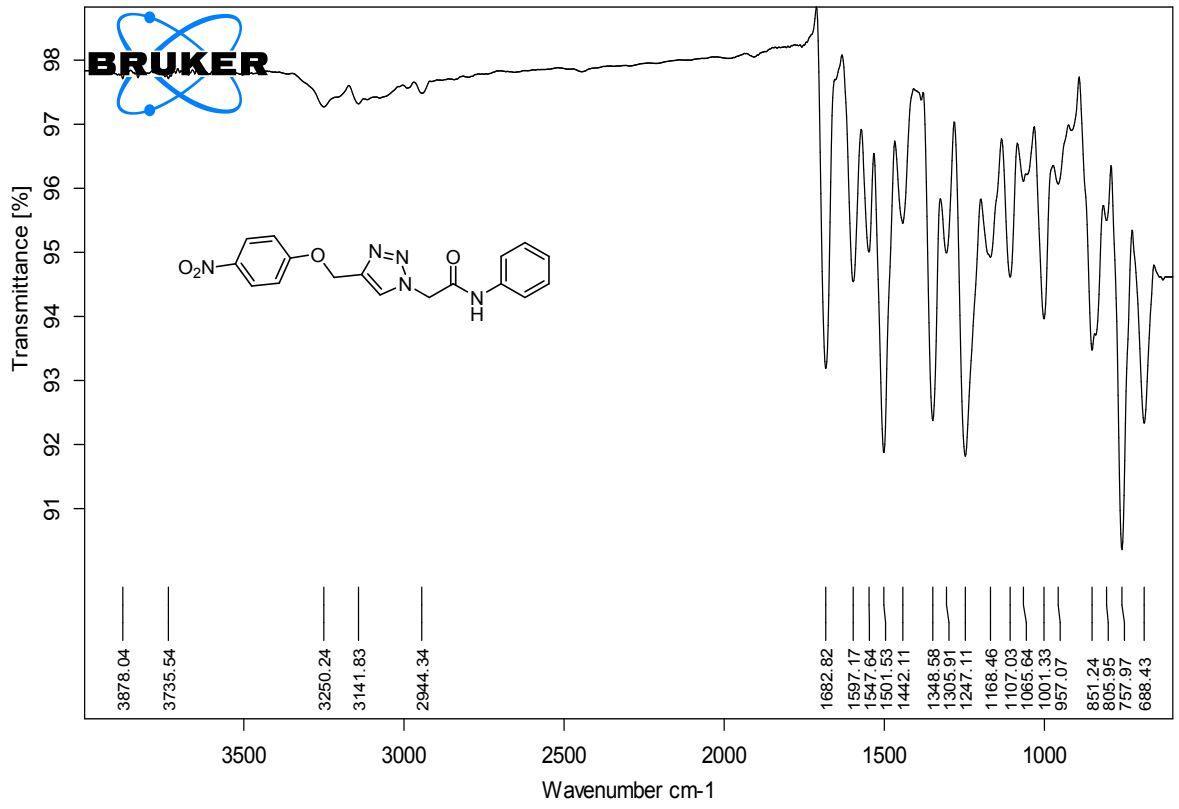
7f. ^{13}C NMR, 125 MHz, $CDCl_3$+DMSO-d_6



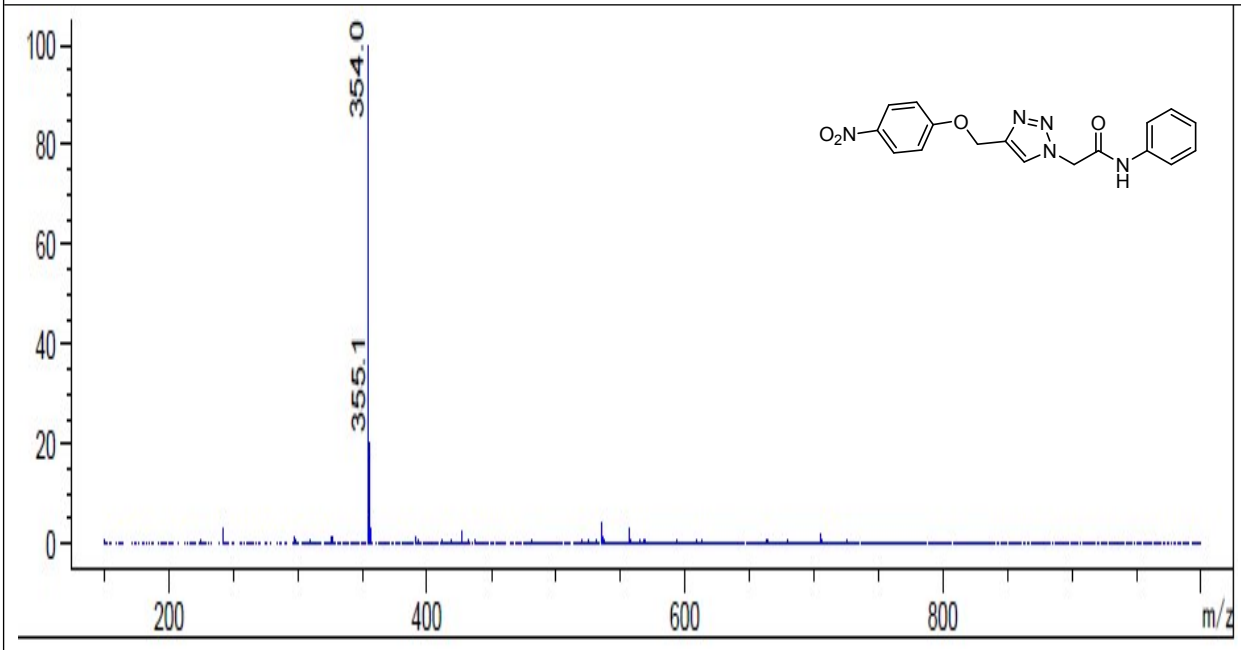
7g. FT-IR



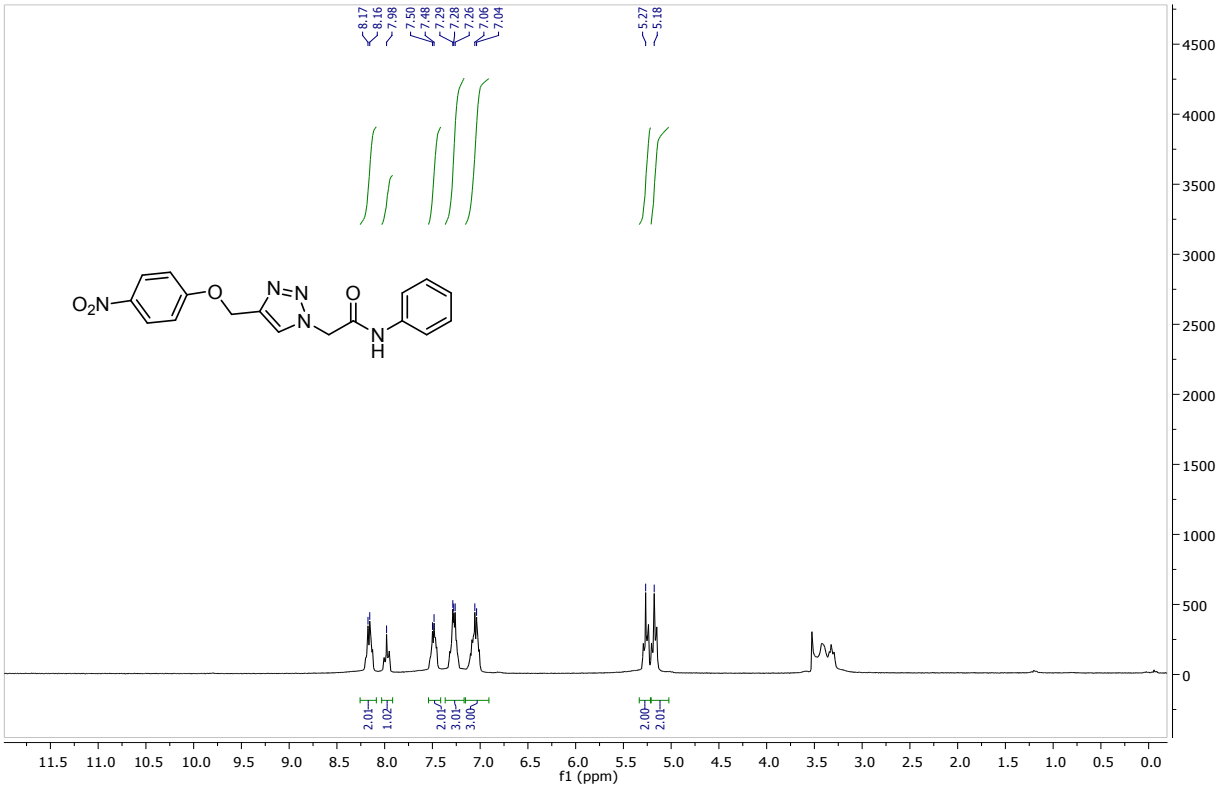
8a. FT-IR



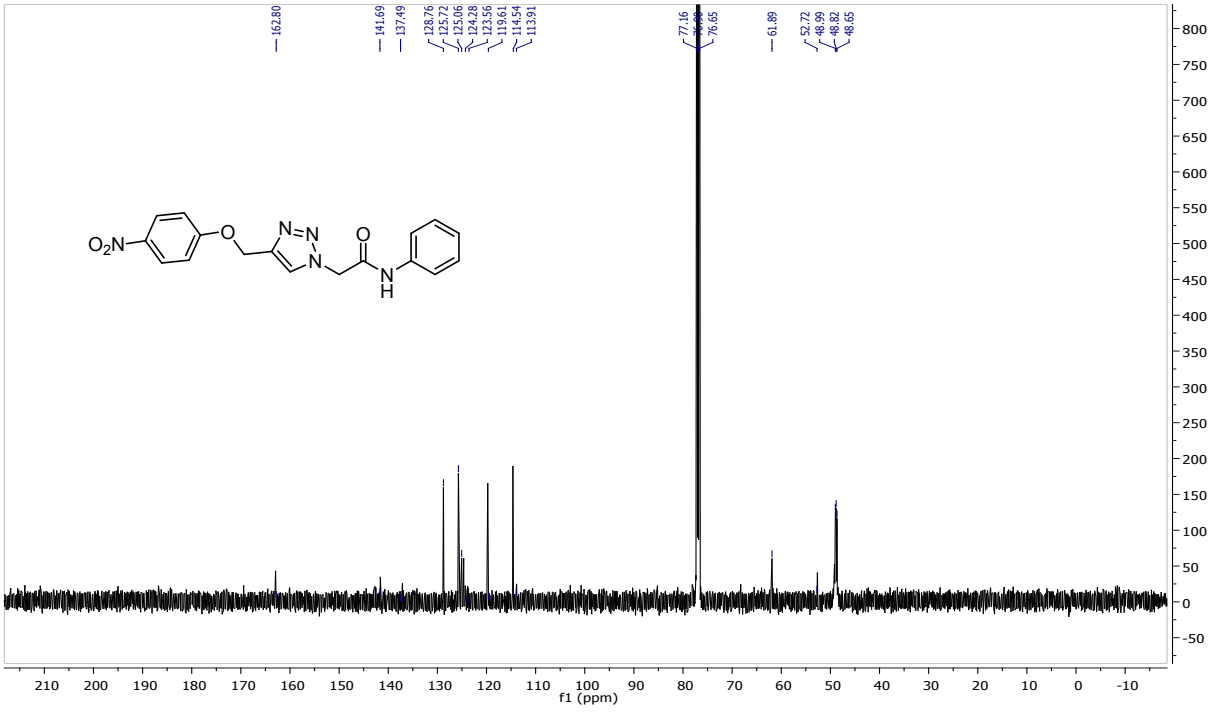
8a. LC-MS



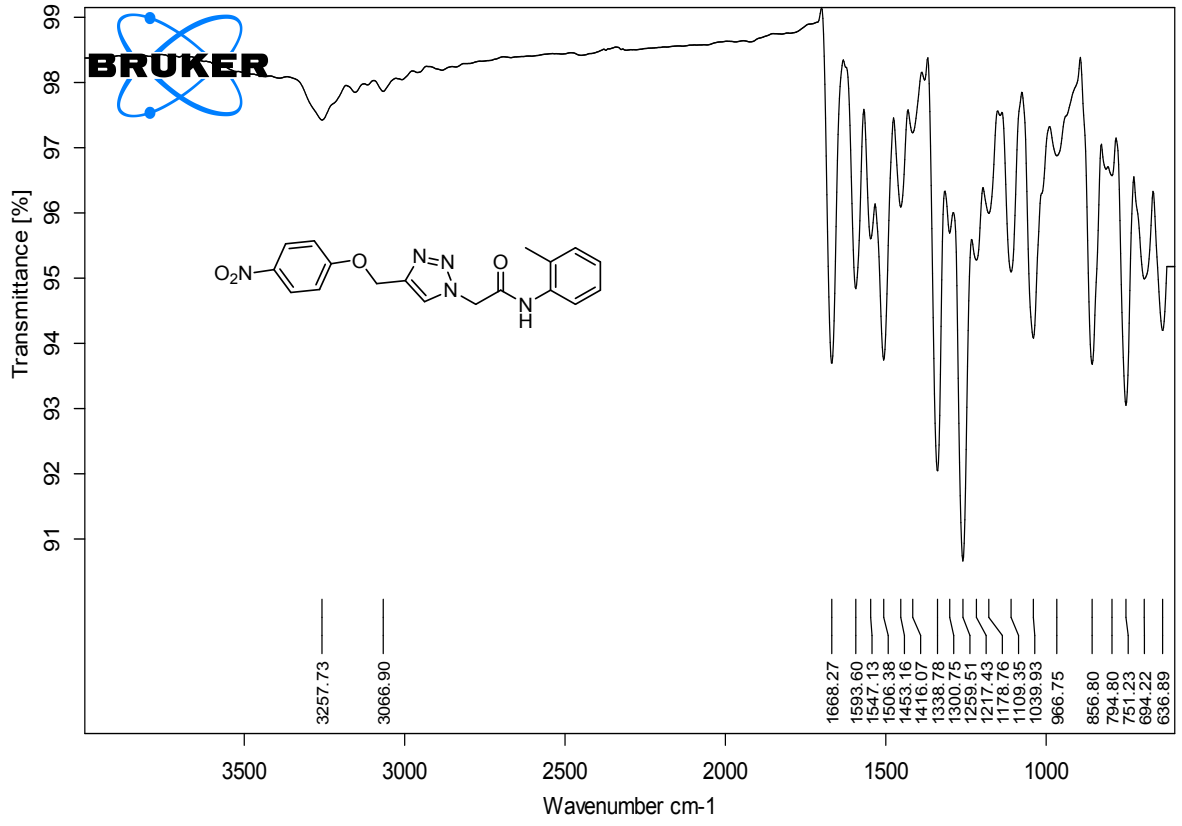
8a. ^{1}H NMR, 500 MHz, $CDCl_3$+CD_3OD



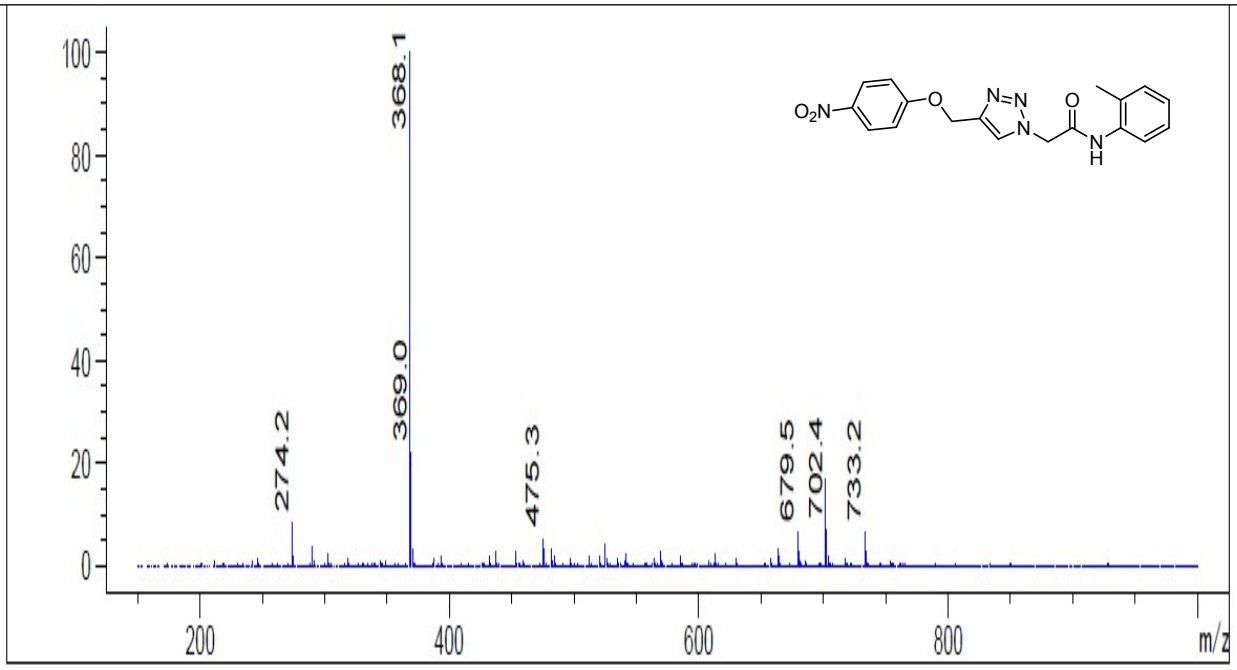
8a. ^{13}C NMR, 125 MHz, $CDCl_3$+CD_3OD



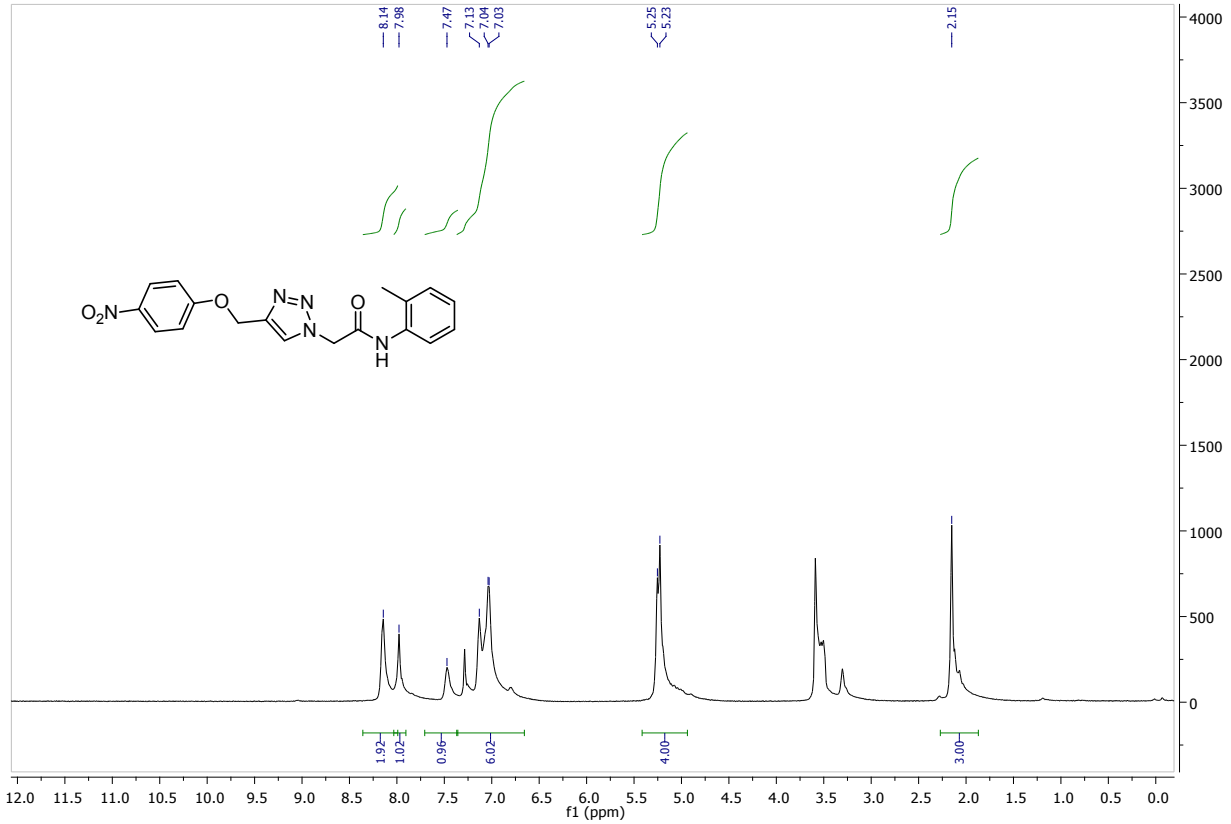
8b. FT-IR



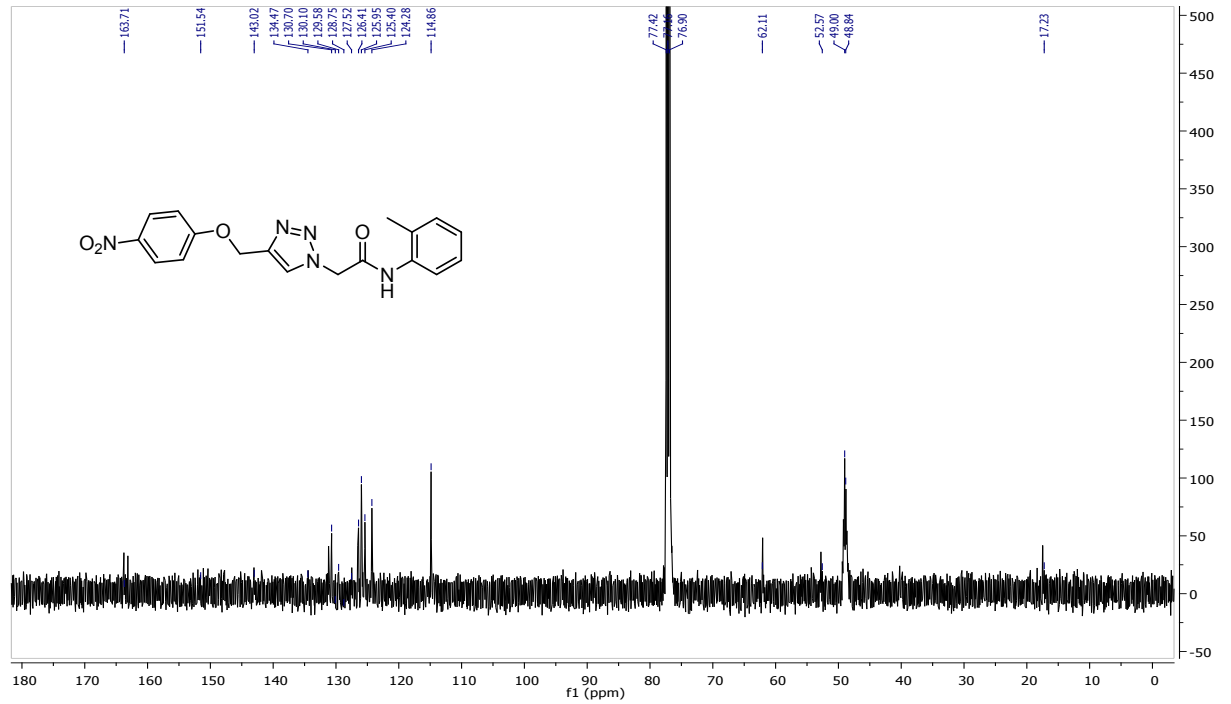
8b. LC-MS



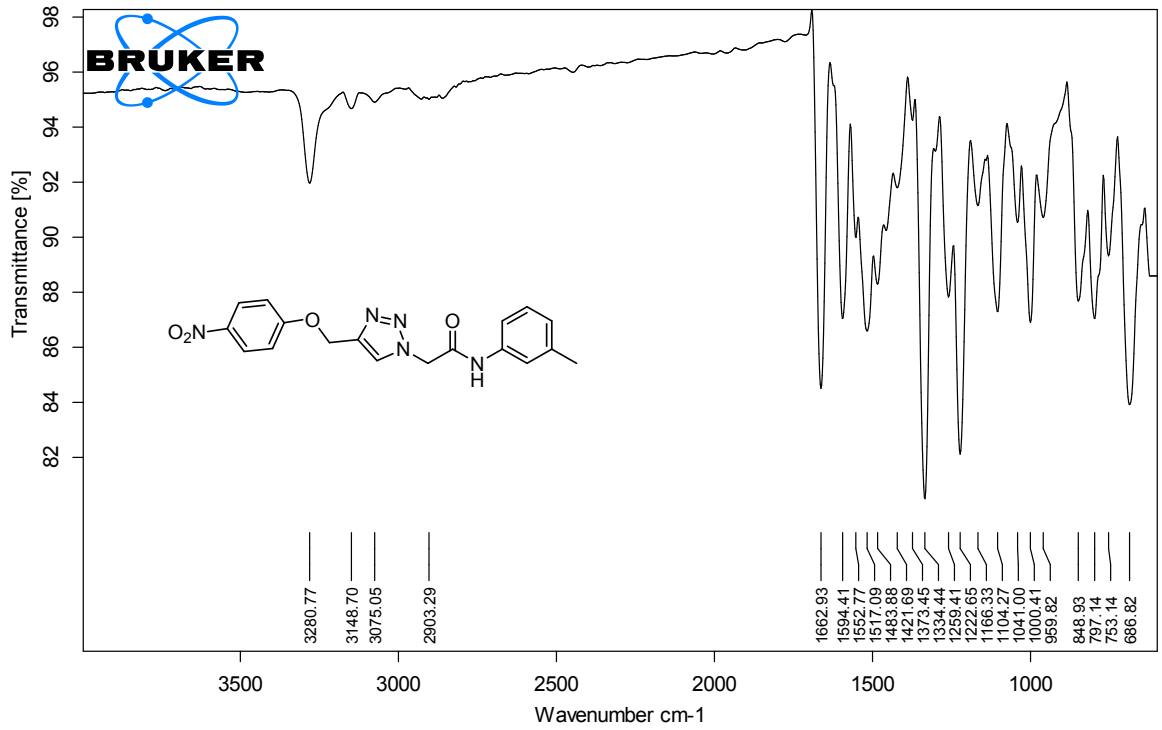
8b. ^{1}H NMR, 500 MHz, $CDCl_3$+CD_3OD



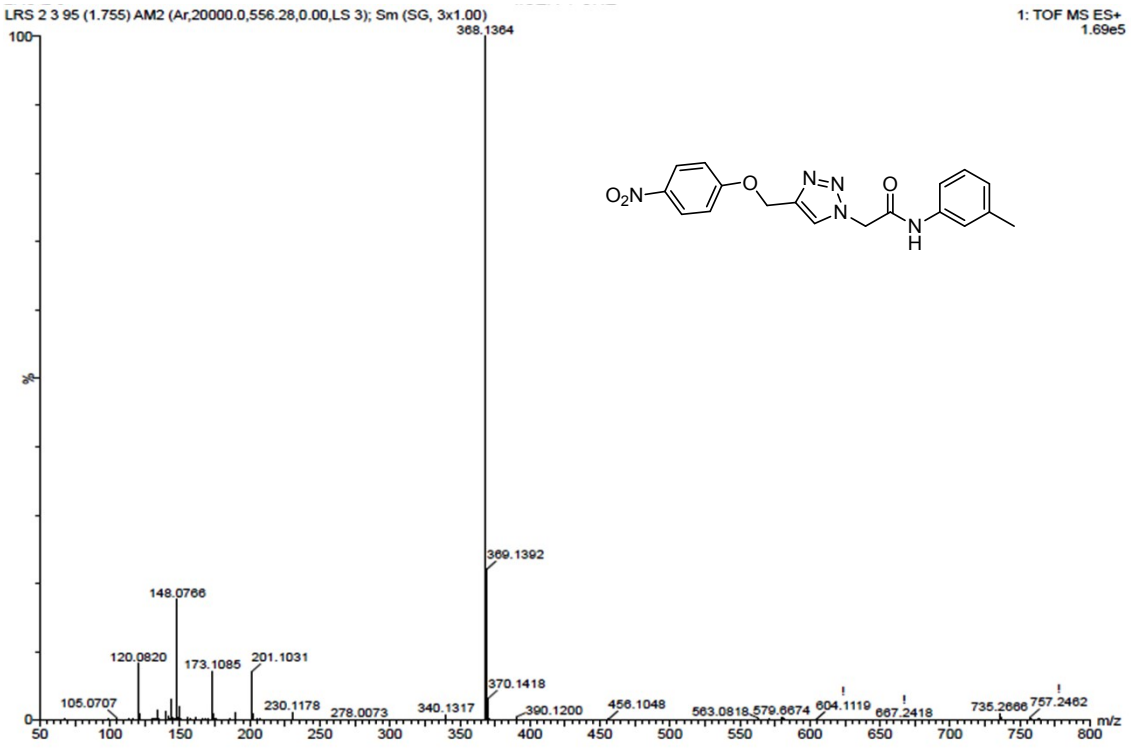
8b. ^{13}C NMR, 125 MHz, $CDCl_3$+CD_3OD



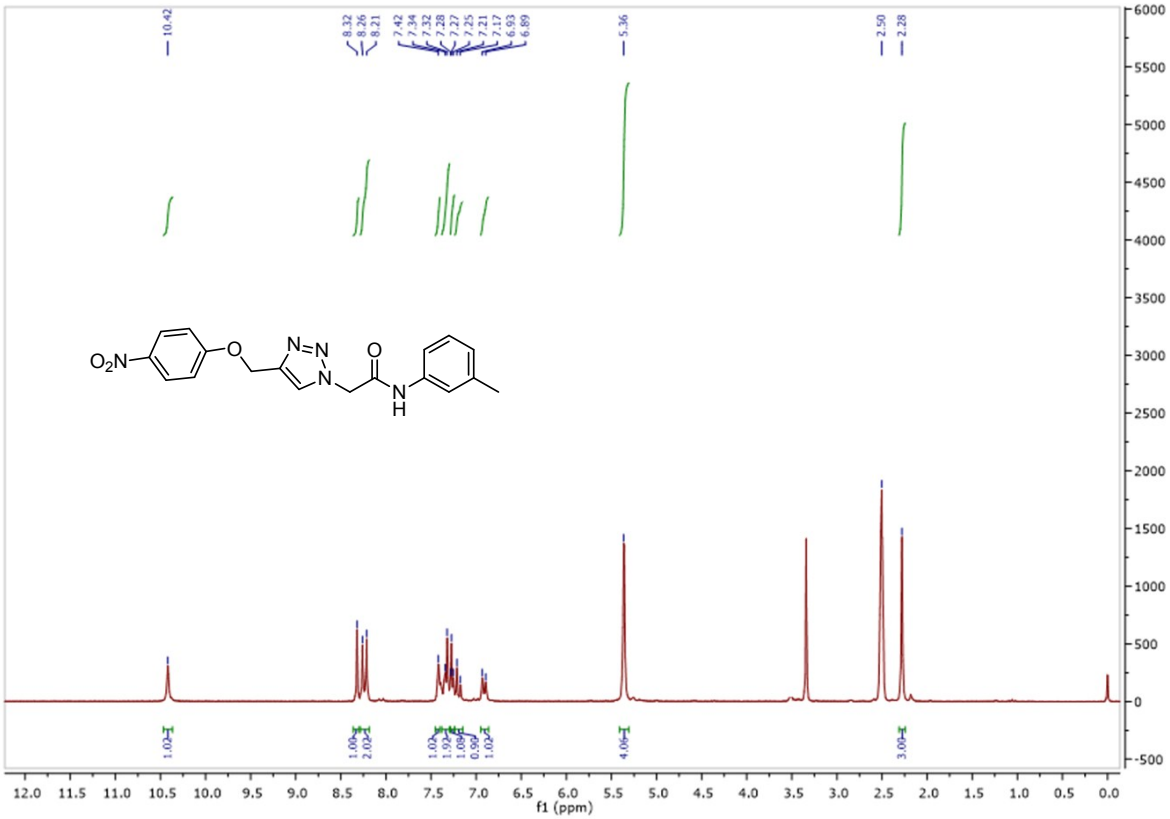
8c. FT-IR



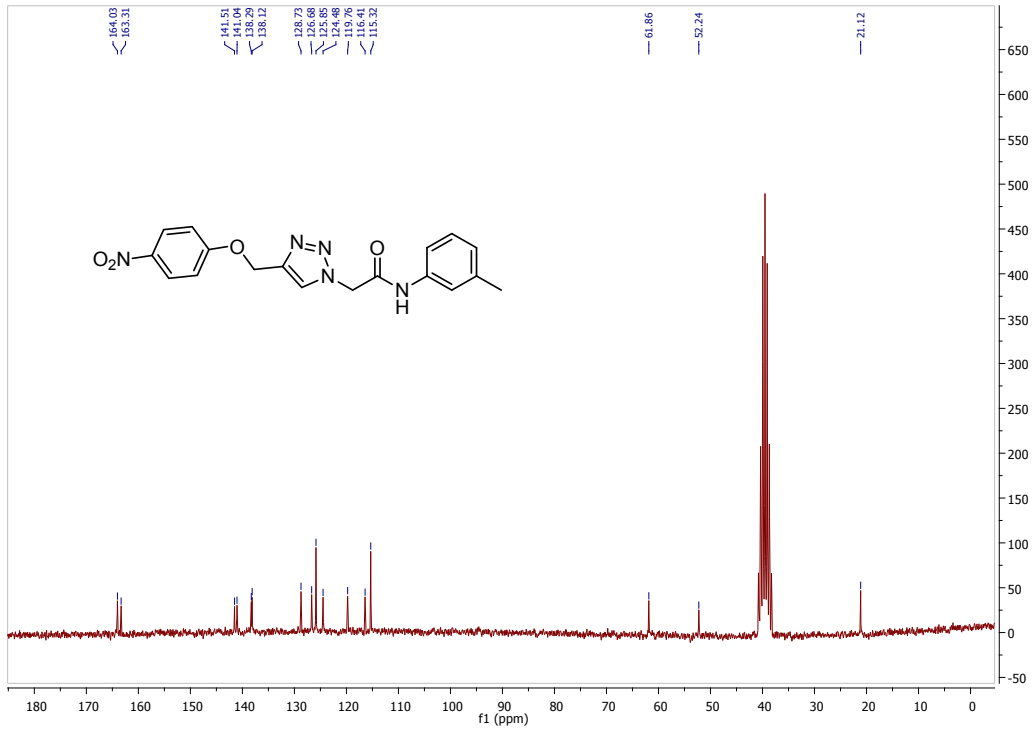
8c. HRMS



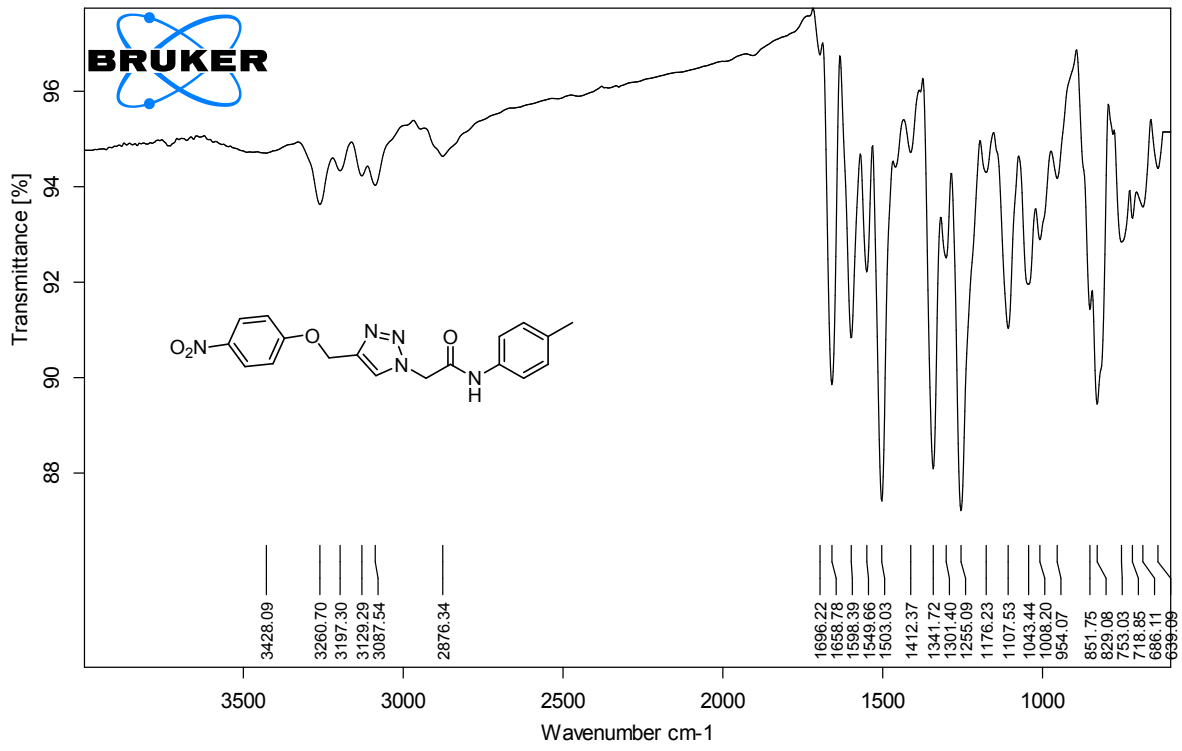
8c. ^{1}H NMR, 200 MHz, DMSO-d_6



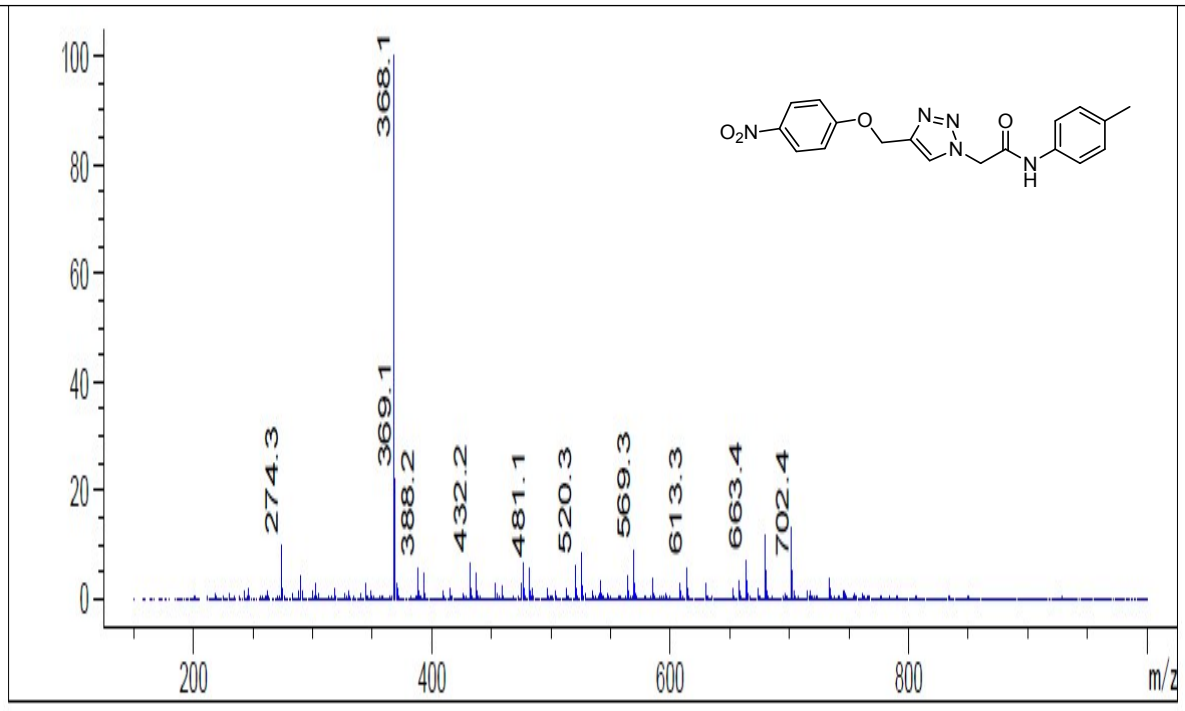
8c. ^{13}C NMR, 50 MHz, DMSO-d_6



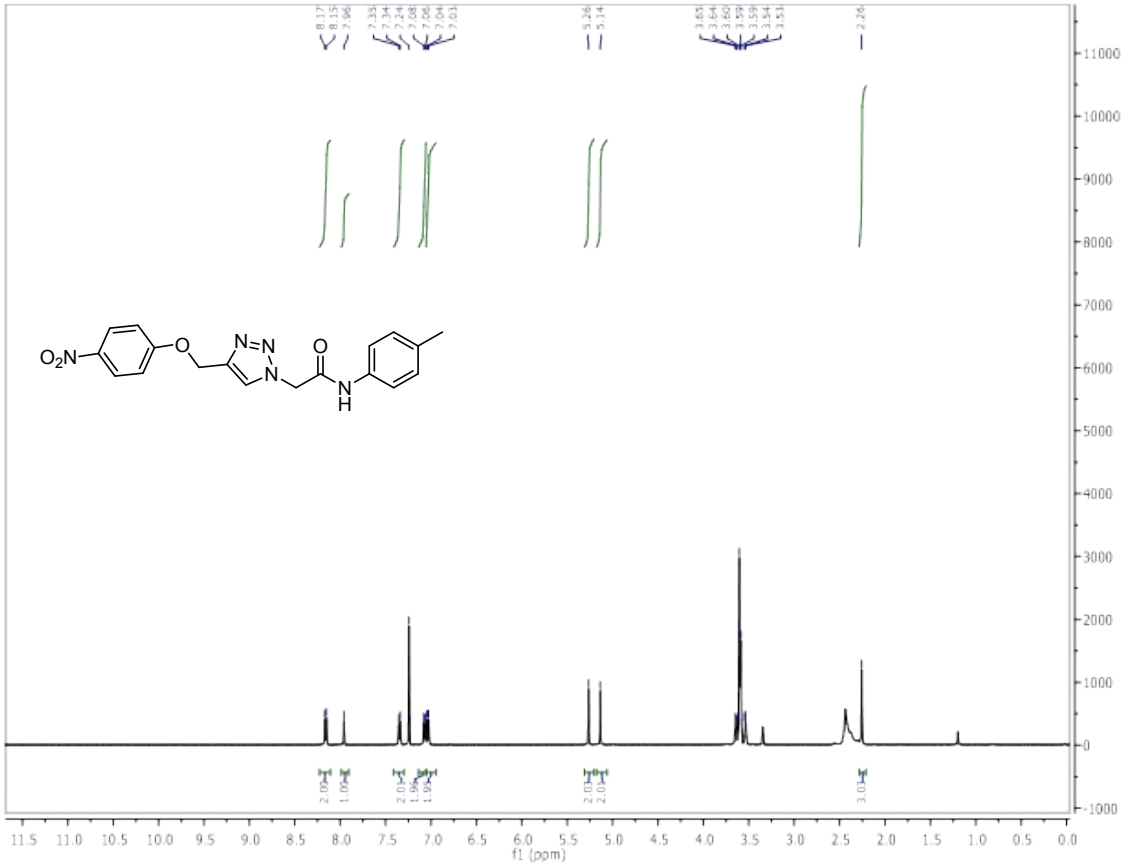
8d. FT-IR



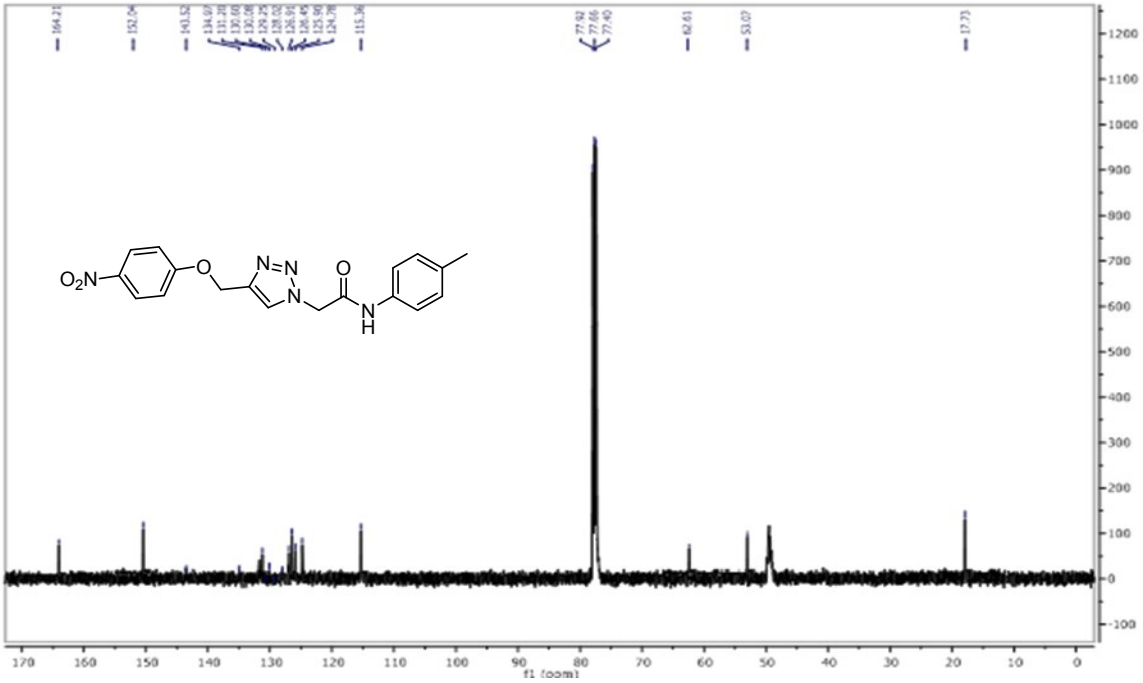
8d. LC-MS



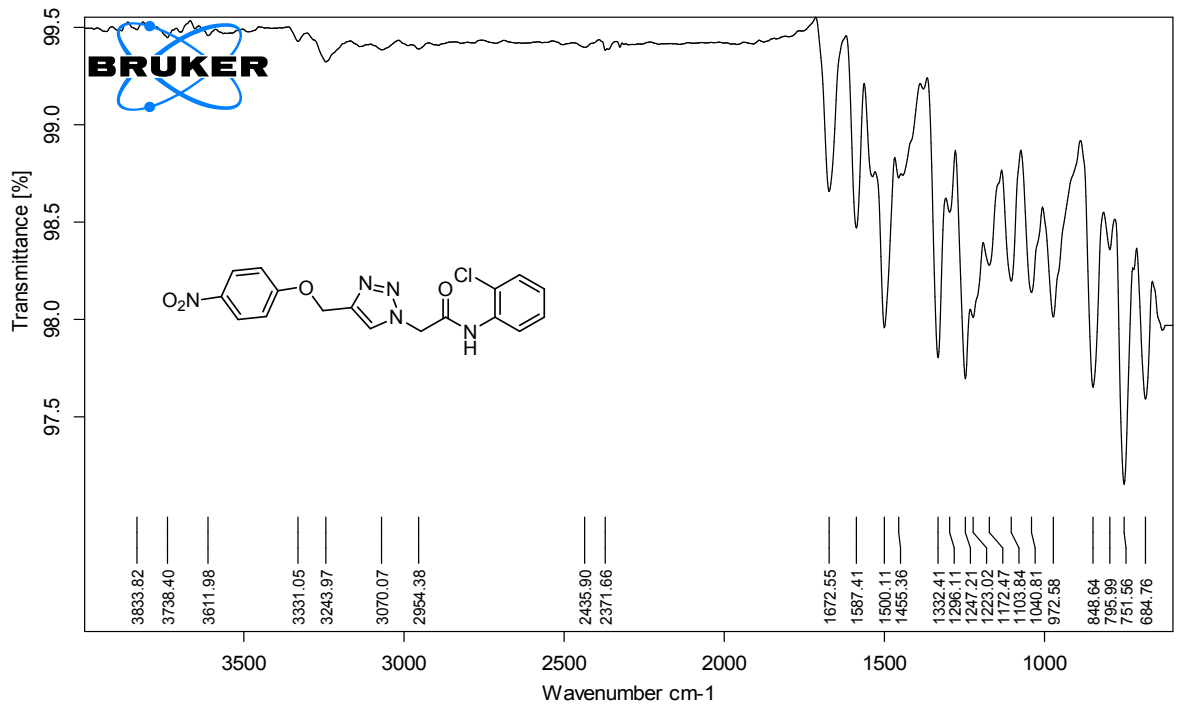
8d. ^{1}H NMR, 500 MHz, $CDCl_3$+CD_3OD



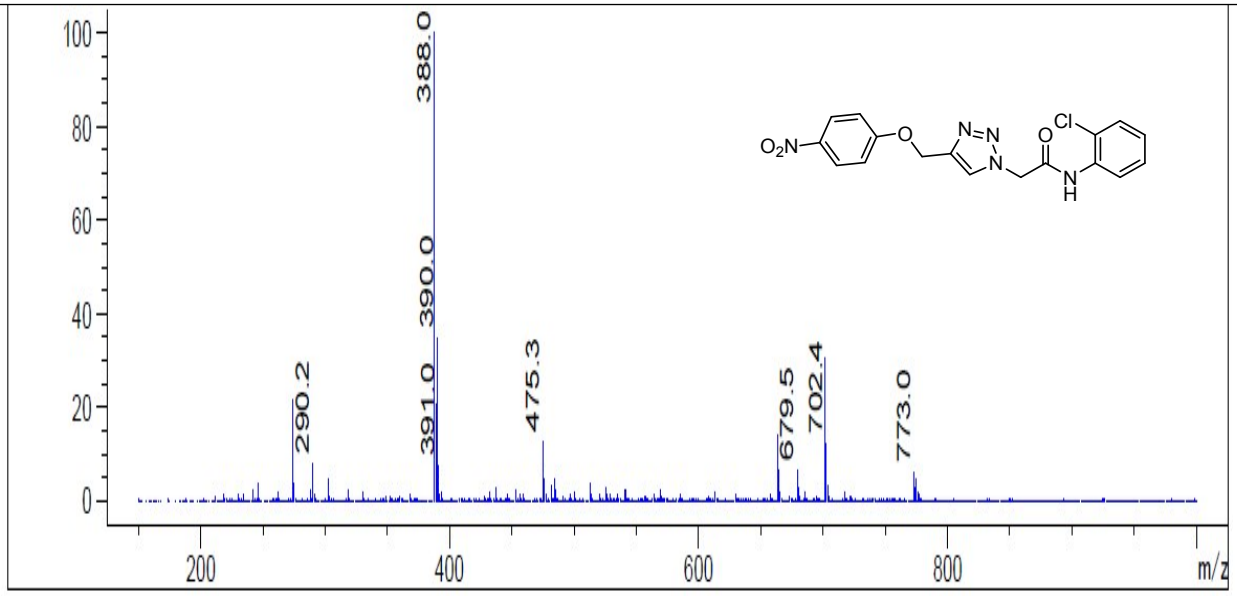
8d. ^{13}C NMR, 125 MHz, $CDCl_3$+CD_3OD



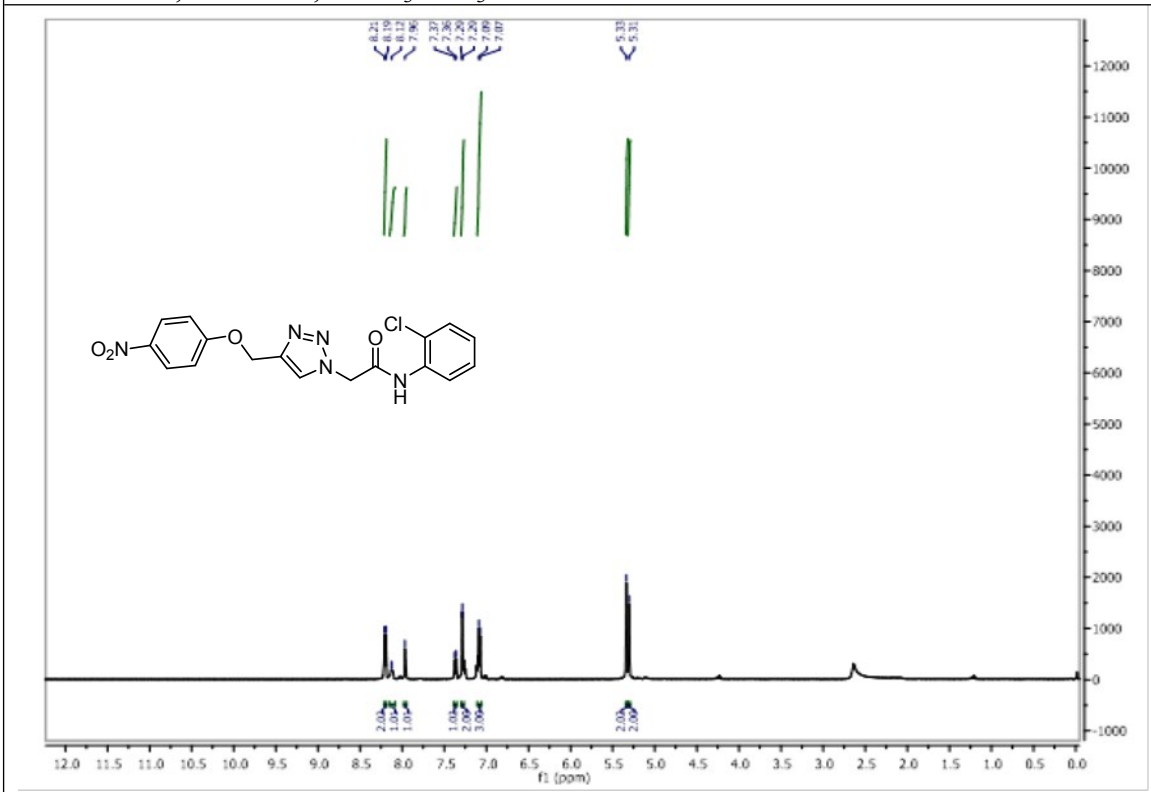
8e. FT-IR



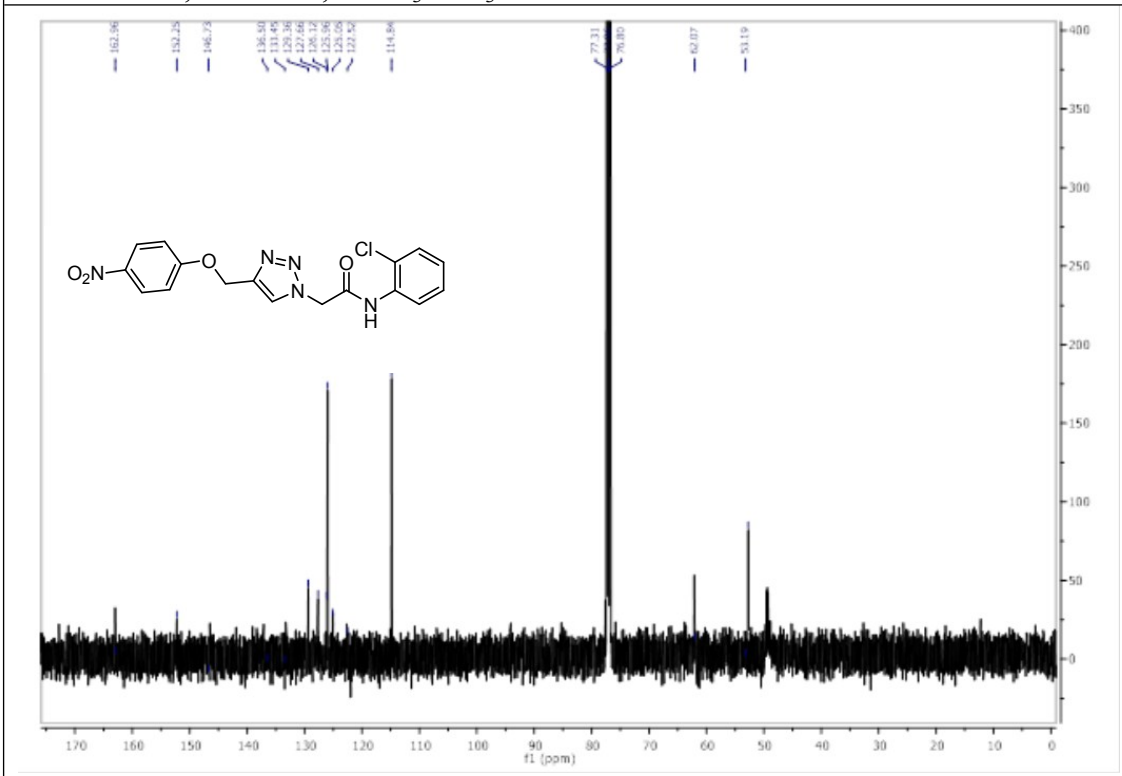
8e. LC-MS



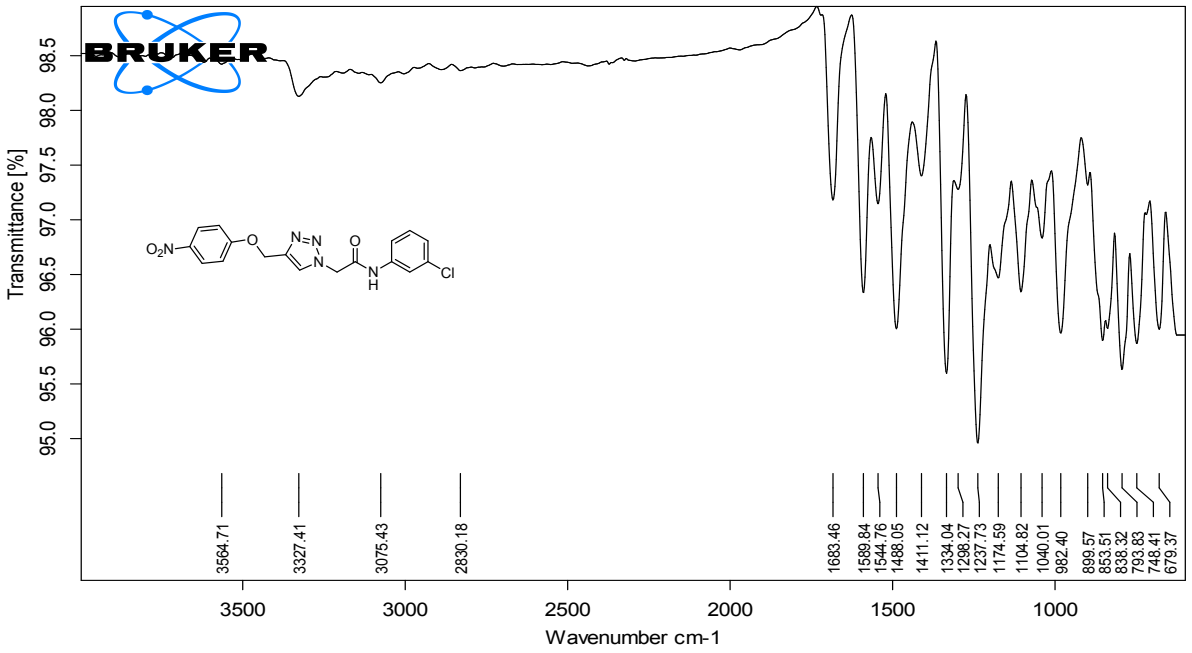
8e. ^{1}H NMR, 500 MHz, $CDCl_3$+CD_3OD



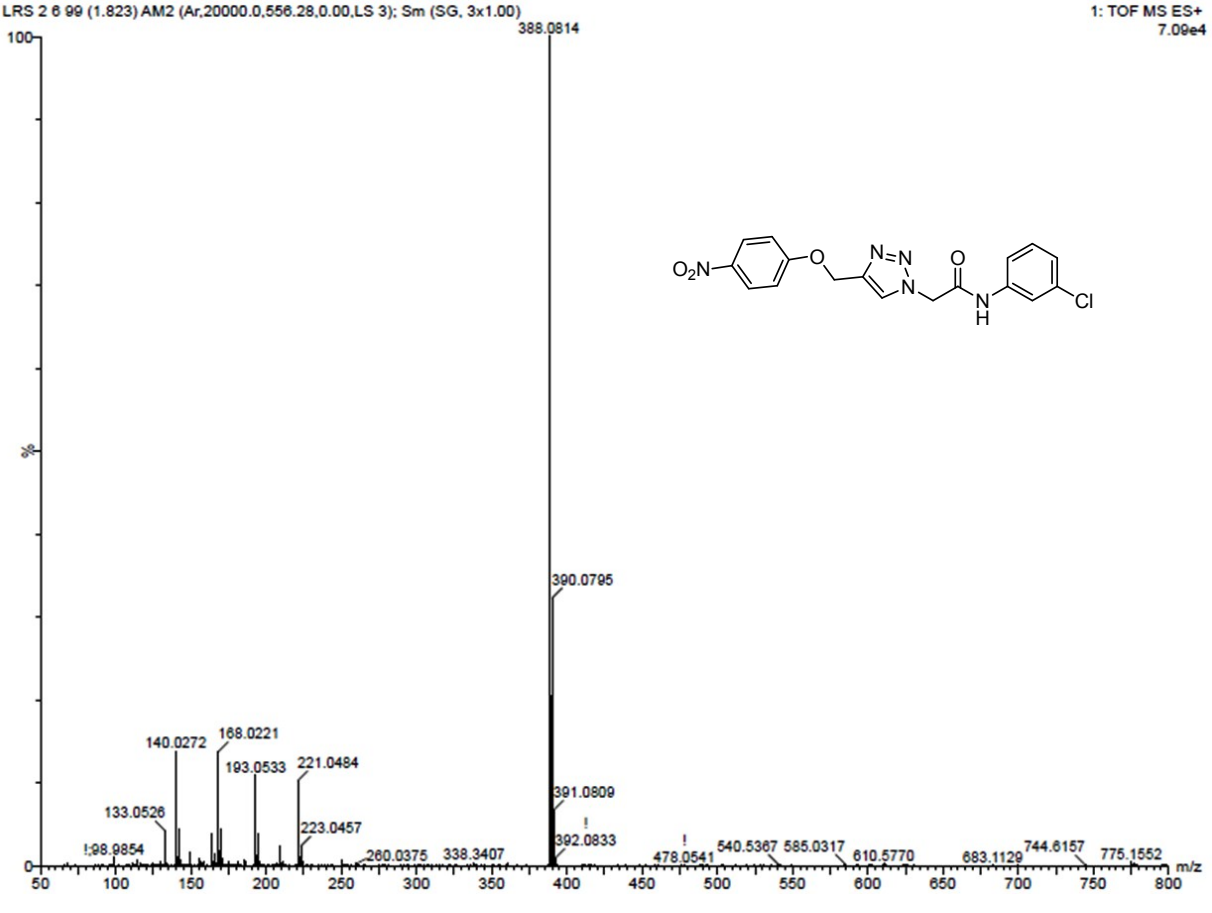
8e. ^{13}C NMR, 125 MHz, $CDCl_3$+CD_3OD



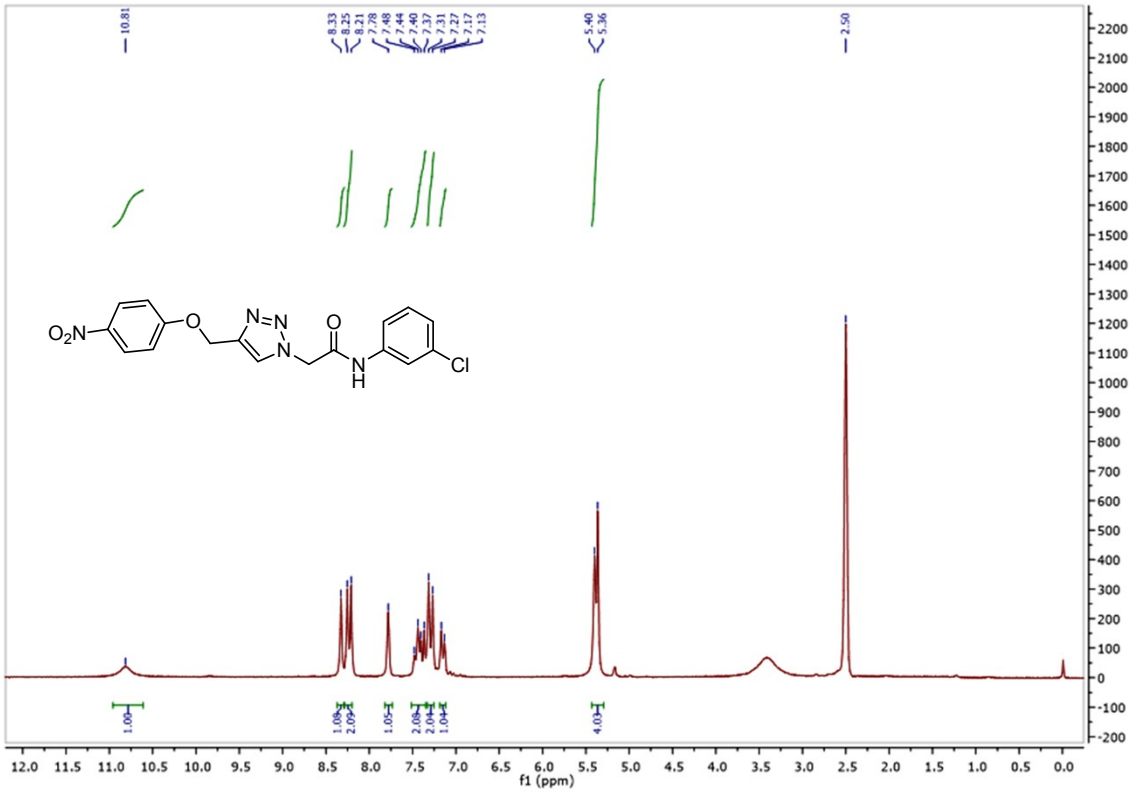
8f. FT-IR



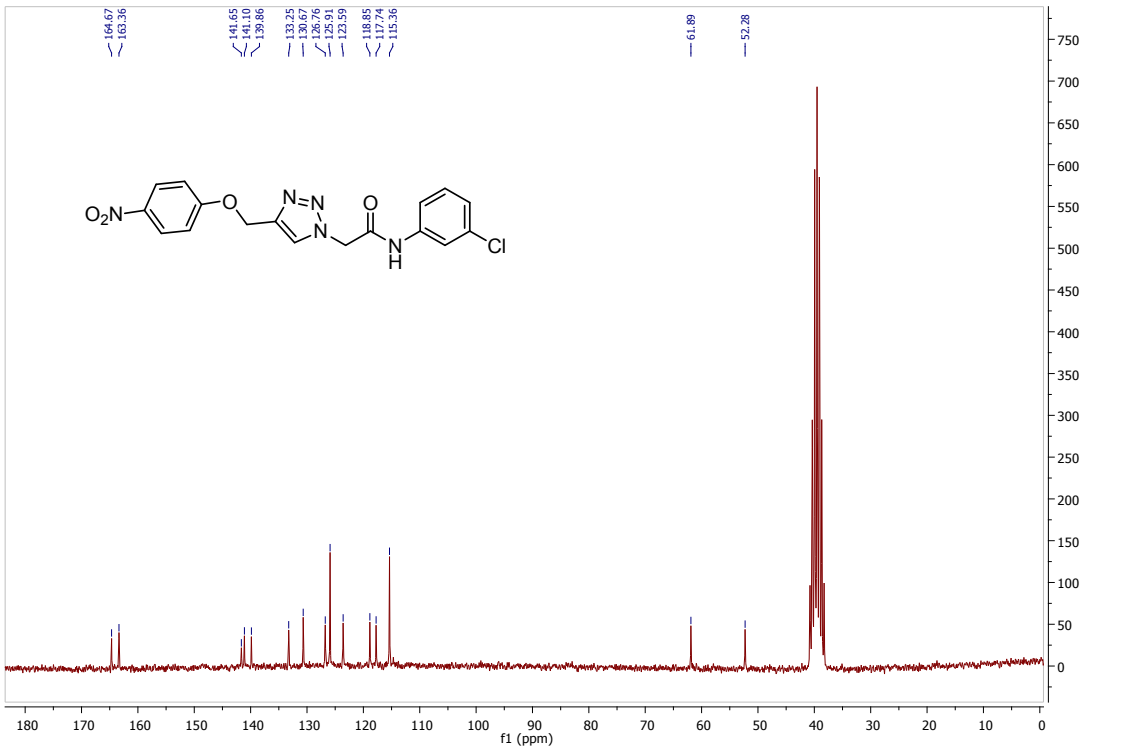
8f. HRMS



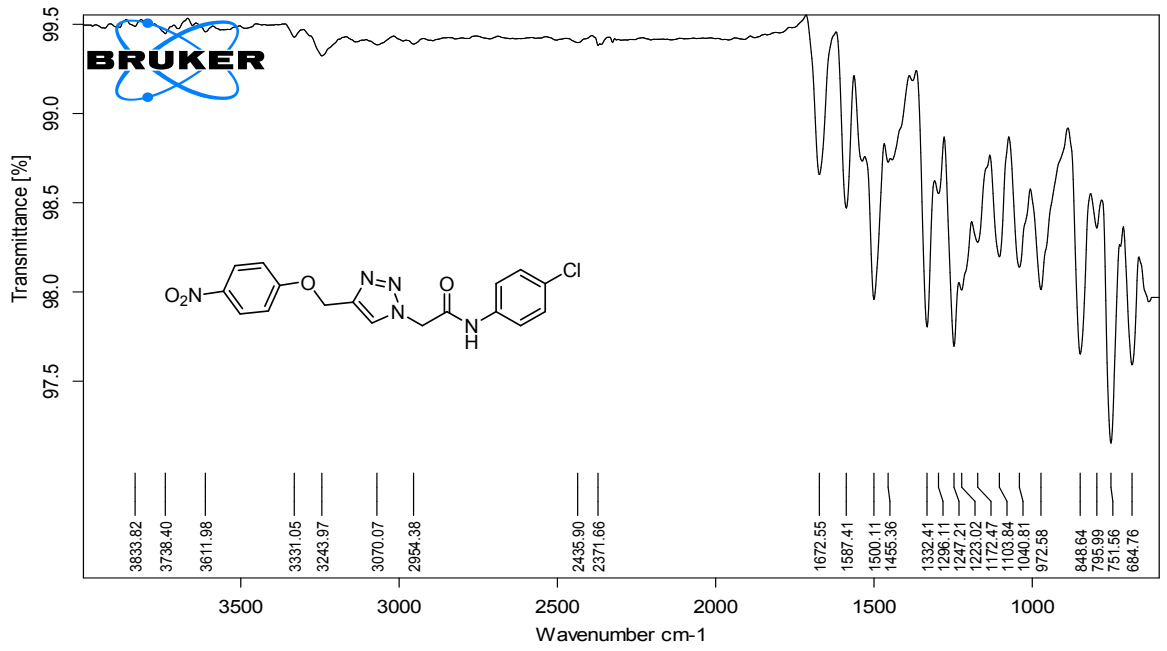
8f. ^{1}H NMR, 200 MHz, DMSO-d_6



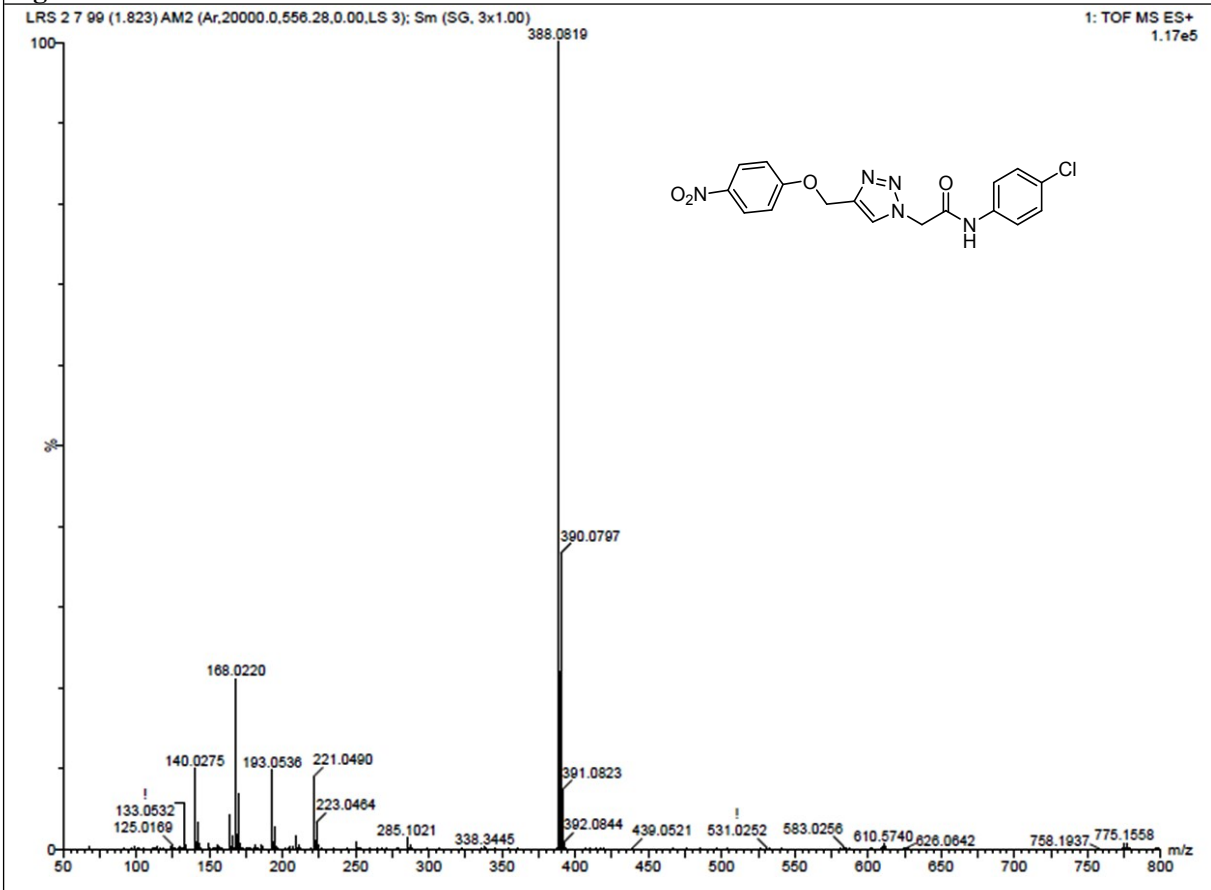
8f. ^{13}C NMR, 50 MHz, DMSO-d_6



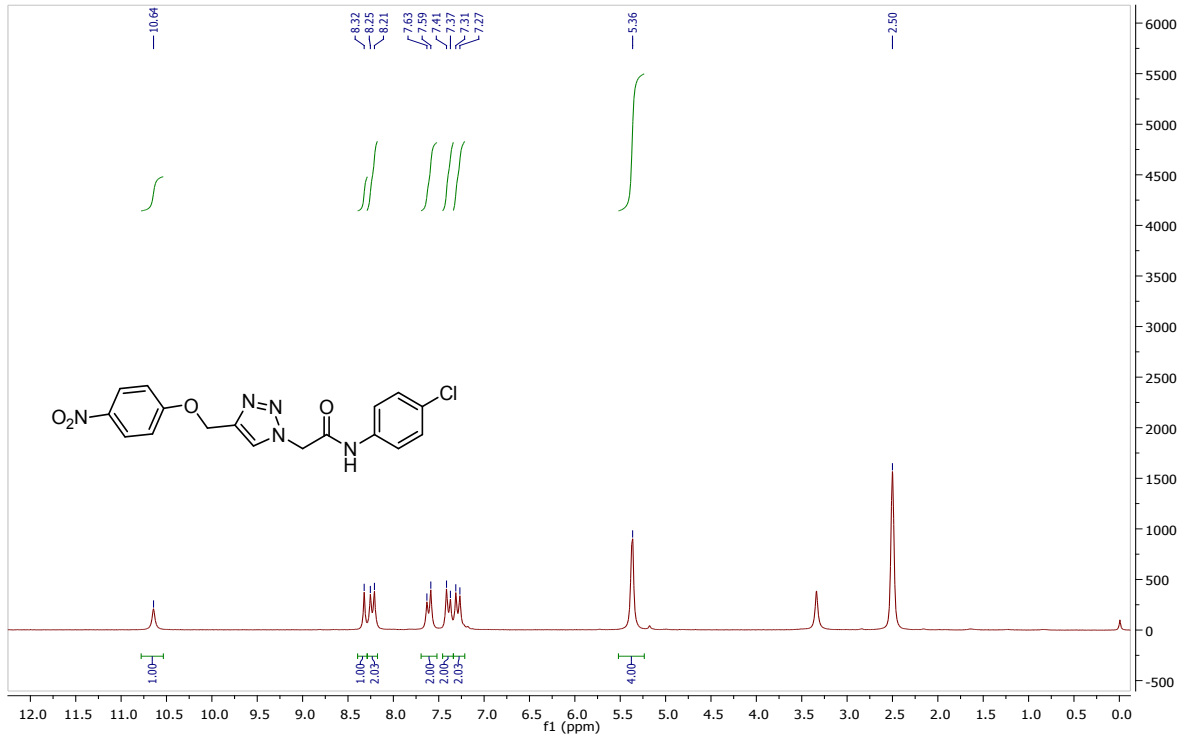
8g. FT-IR



8g. HRMS



8g. ^{1}H NMR, 200 MHz, DMSO-d_6



8g. ^{13}C NMR, 50 MHz, DMSO-d_6