Supporting Information

1,2,3-Triazole Derivatives as Antitubercular Agents: Synthesis, Biological Evaluation and Molecular Docking Study

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1. Synthesis of Benzyl azides (8-12):

1.1. Synthesis of benzyl alcohols:

Various substituted benzaldehydes (1 equiv.) were taken in round bottom flask, methanol used as a solvent and allowed reaction mixture for stirring below 0 ^{o}C. Then, $NaBH_4$ (3 equiv.) were added slowly with constant stirring and maintaining the temperature below 0 ^{o}C. The progress of the reaction was monitored by thin layer chromatography (TLC) using ethyl acetate: hexane as a solvent system. After completion of the reaction as indicated by TLC, the reaction mixture was then poured on crushed ice and extracted in ethylacetate (3 x 10 mL).The combined organic layer was dried over $MgSO_4$. Solvent was removed under reduced pressure, and the substituted benzyl alcohols were sufficiently pure to use without further work up.

1.1.2. Synthesis of benzyl bromides:

These benzyl alcohols (1 equiv) were taken in RBF and dichloromethane as a solvent. This reaction allowed to stir below 5 °C, then drop by drop added phosphorus tribromide (PBr_3) (1 equiv). The progress of the reaction was monitored by thin layer chromatography (TLC) using ethyl acetate: hexane as a solvent system. After completion of reaction as indicated by TLC, the reaction mass was then poured on crushed ice.Ethylacetate was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3 x 10 mL of ethylacetate and the combined organic layers were dried over $MgSO_4$. Solvent was removed under reduced pressure, and the substituted benzyl bromides were sufficiently pure to use without further purification.

1.1.3. Synthesis of benzyl azides:

To a stirred solution of the corresponding bromide (1.0 equiv) in a 50 mL water/acetone mixture (1:4) was added NaN_3 (1.5 equiv).The resulting suspension was stirred at room temperature for 24 hours. The progress of the reaction was monitored by thin layer chromatography (TLC) using ethyl acetate:hexane as a solvent system. After the completion of reaction as indicated by TLC, the reaction mixture was then poured on crushed ice. Ethyl acetate was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3 x 10 mL of ethylacetate and the combined organic layers were dried over $MgSO_4$. Solvent was removed under reduced pressure, and the azides were **8-12** sufficiently pure to use without further purification.

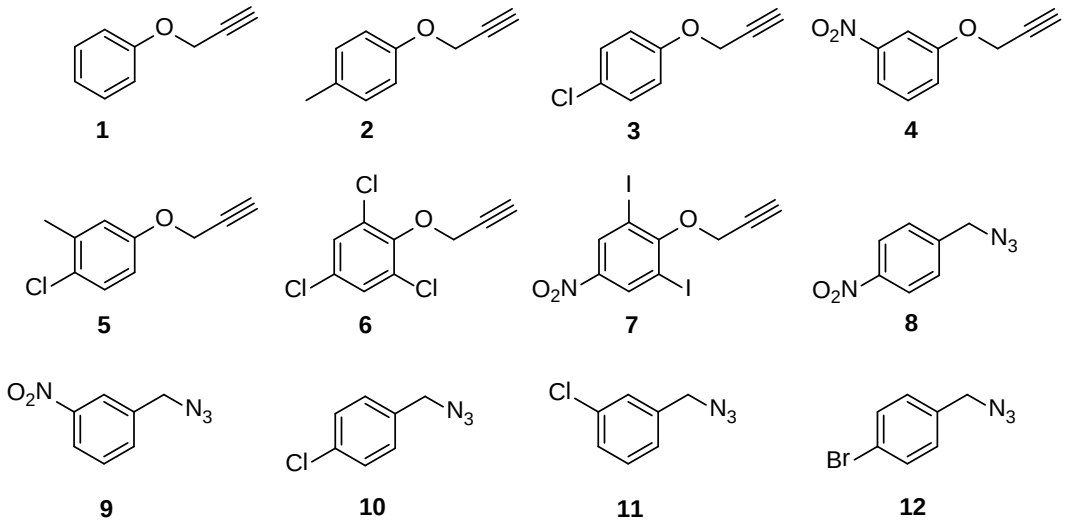
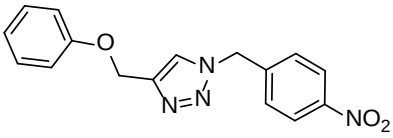


Figure S1. Synthesized alkynes and azide derivatives **1-12**.



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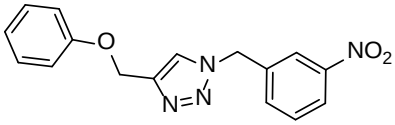

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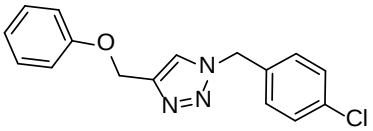

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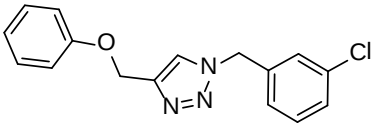

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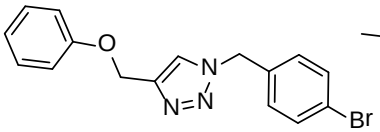

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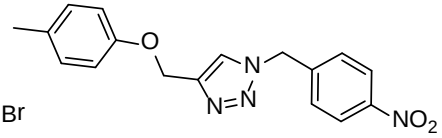

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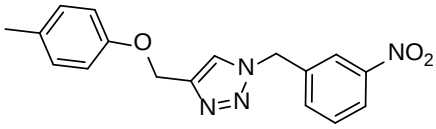

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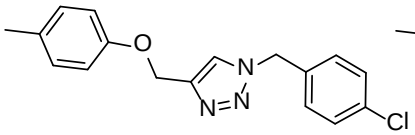

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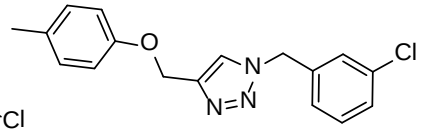

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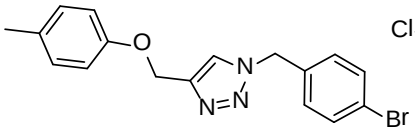

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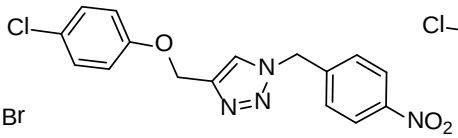

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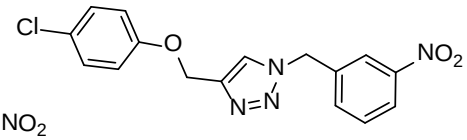

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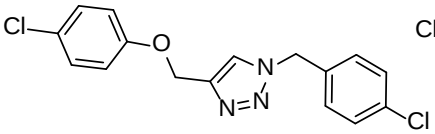

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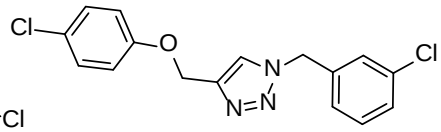

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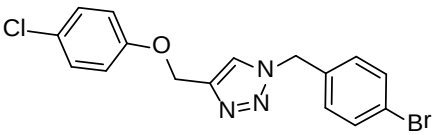

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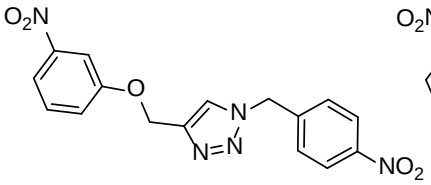

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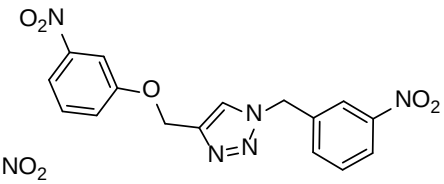

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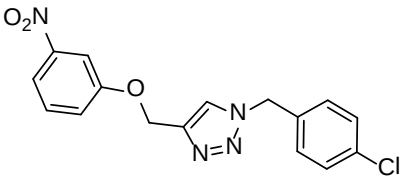

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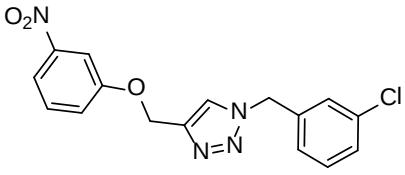

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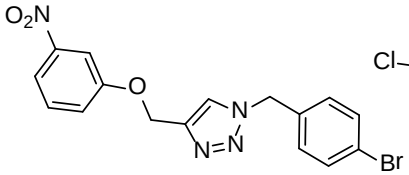

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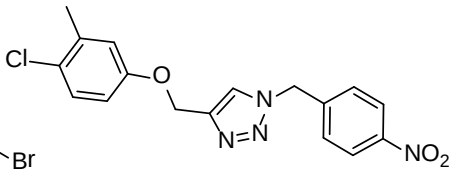

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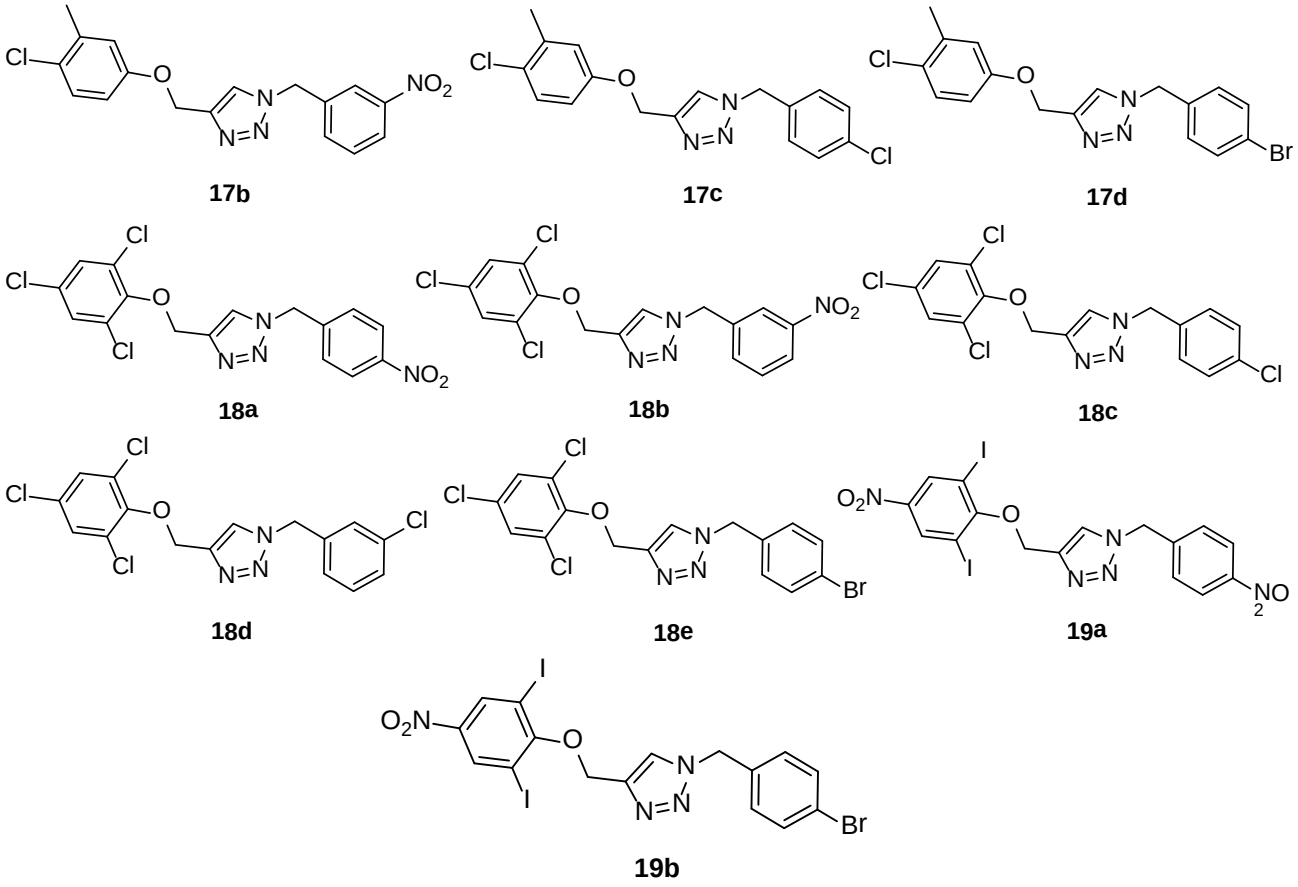


Figure S2. Synthesized 1-(substituted benzyl)-4-(substituted phenoxymethyl)-1*H*-1,2,3-triazole analogs **13-19**.

Table S1 Anti-tubercular activity of compounds against avirulent strain of dormant MTB H37Ra

Compound	% Inhibition of MTB H37Ra growth in presence of compounds			Activity	Compound	% Inhibition of MTB H37Ra growth in presence of compounds			Activity
	30 µg/ml	10 µg/ml	3 µg/ml	+/-		30 µg/ml	10 µg/ml	3 µg/ml	+/-
13a	92.16	70.29	67.58	+	**16a**	13.79	-0.21	-0.11	-
13b	67.15	66.44	65.61	-	**16b**	1.66	0.47	18.37	-
13c	90.07	62.24	55.75	+	**16c**	27.79	16.25	31.92	-
13d	91.48	71.82	70.67	+	**16d**	56.04	43.04	29.17	-
13e	91.36	77.74	66.32	+	**16e**	34.97	24.07	11.79	-
14a	90.07	73.54	70.45	+	**17a**	91.59	74.87	72.14	+
14b	74.34	71.82	60.72	-	**17b**	80.06	77.81	69.83	-
14c	95.30	76.29	67.93	+	**17c**	91.33	80.98	75.45	+
14d	91.52	70.64	71.67	+	**17d**	79.99	75.64	60.90	-
14e	66.20	63.92	48.11	-	**18a**	80.40	73.56	71.63	-
15a	91.63	73.32	25.85	+	**18b**	70.81	68.37	63.49	-
15b	91.36	56.75	50.57	+	**18c**	91.14	84.73	81.09	+
15c	95.87	94.61	73.62	+	**18d**	76.78	71.44	68.76	-
15d	92.01	80.72	71.86	+	**18e**	90.90	87.64	71.40	+
15e	94.15	95.18	77.99	+	**19a**	71.63	68.46	60.56	-
					19b	52.46	47.65	39.02	-

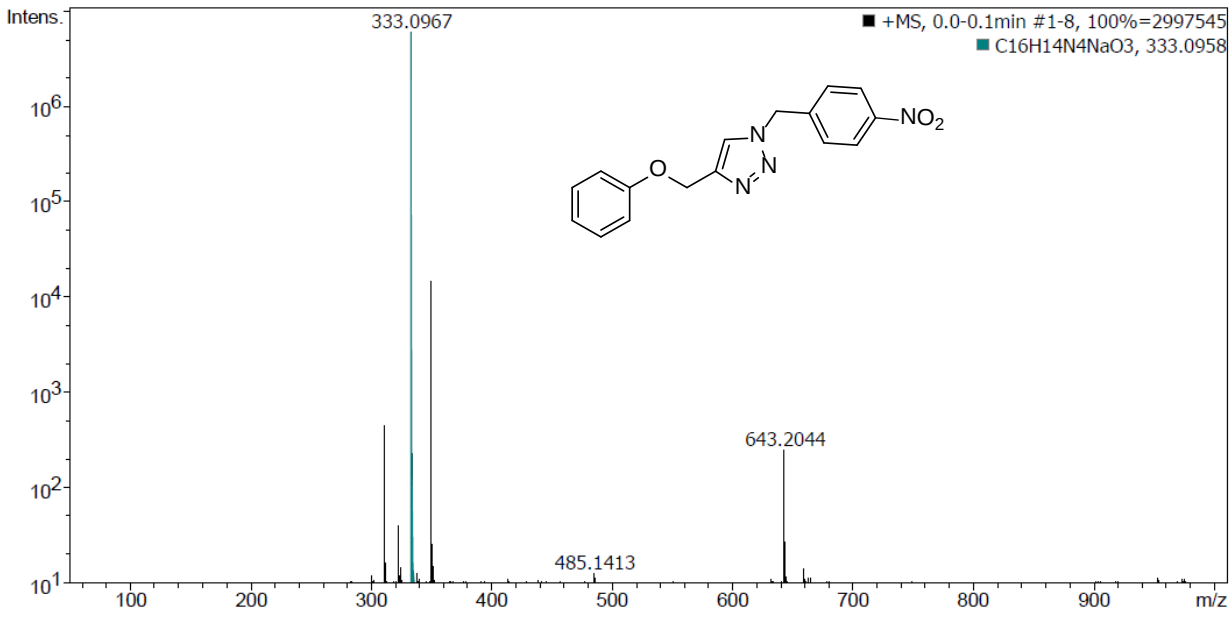
The % Inhibition in the presence of test material is calculated by following formula.
% inhibition = (Average of Control-Average of Compound)/ (Average of Control-Average of Blank) X 100), where control is culture medium with cells and DMSO and blank is culture medium without cells. Compounds were considered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

Table S2 Experimentally determined Anti-tubercular activity of the key compounds[a]

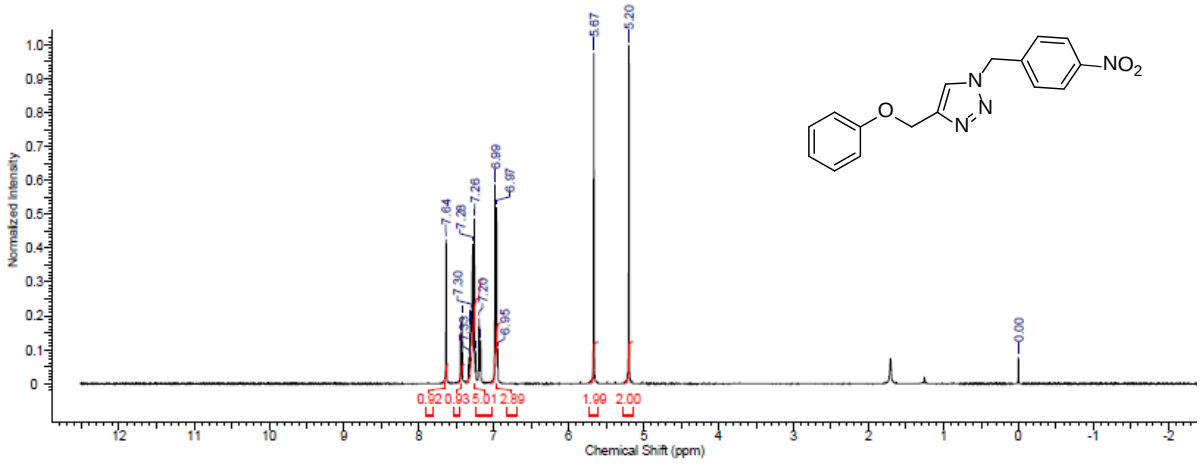
Compound	IC_{50} and IC_{90} values (µg/mL) of compounds with SD values			
	M. tuberculosis H37Ra (ATCC 25177)			
	In Vitro (Dormant)		*In Vitro* (Active)	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}
13a	1.70 ± 0. 31	28.05 ± 0. 28	>100 ± 0. 23	>100 ± 0. 19
13c	3.54 ± 0. 93	29.93 ± 0. 48	>100± 0. 52	>100± 0. 24
13d	2.28 ± 0. 81	27.66 ± 0. 59	>100± 0. 35	>100± 0. 98
13e	3.16 ± 0. 12	28.85 ± 0. 78	>100± 0. 19	>100± 0. 23
14a	1.12 ± 0. 33	29.91 ± 0. 06	>100± 0. 18	>100± 0. 07
14c	2.48 ± 0. 77	24.18 ± 0. 77	>100± 0. 47	>100± 0. 14
14d	3.06 ± 0. 59	28.92 ± 0. 04	>100± 0. 38	>100± 0. 79
15a	3.64 ± 0. 29	27.53 ± 0. 45	>100± 0. 90	>100± 0. 10
15b	2.57 ± 0. 28	29.20 ± 0. 01	>100± 0. 60	>100± 0. 18
15c	0.74 ± 0. 30	8.20 ± 0. 06	>100± 0. 39	>100± 0. 40
15d	2.87 ± 0. 85	25.82 ± 0. 15	>100± 0. 16	>100± 0. 05
15e	0.52 ± 0. 63	5.78 ± 0. 71	>100± 0. 01	>100± 0. 66
17a	0.74 ± 0. 34	28.15 ± 0. 12	>100± 0. 79	>100± 0. 17
17c	0.16 ± 0. 04	26.89 ± 0. 52	>100± 0. 28	>100± 0. 12
18c	0.83 ± 0. 10	7.73 ± 0. 60	>100± 0. 75	>100± 0. 66
18e	0.92 ± 0. 50	27.80 ± 0. 63	>100± 0. 70	>100± 0. 80
[b]**Rifampicin**	0.0014± 0.62	0.043± 0.15	0.0018± 0.13	0.048±0.44

[a]IC_{50} /IC_{90} in µg/mL. Antitubercular activity of each agent was determined by serial dose dependent dilutions. [bc]Standard antitubercular drugs and positive controls. Data were expressed as the means of triplication. SD (±): Standard Deviation.

13a.HRMS



13a.^{1}H NMR, 200 MHz, $CDCl_3$



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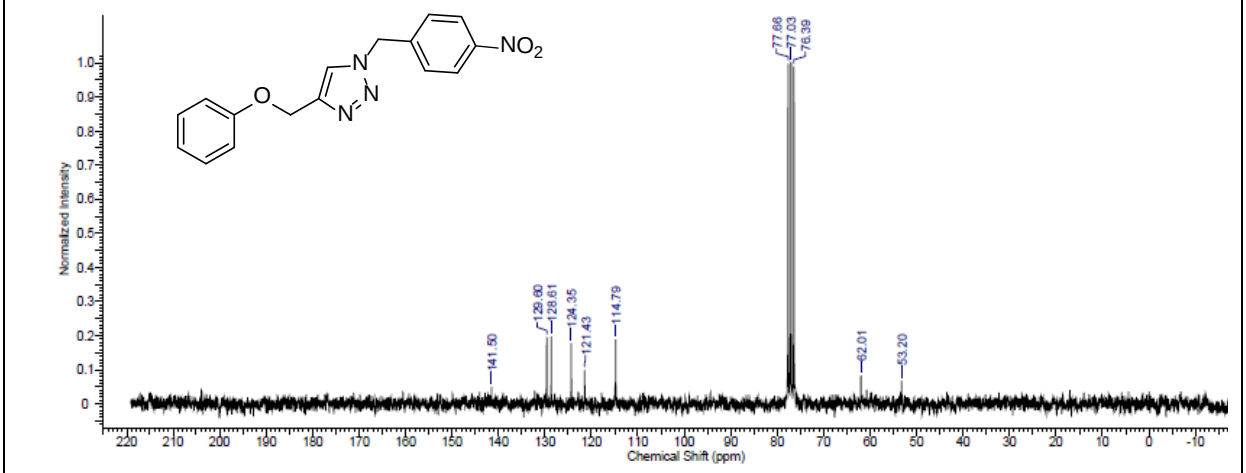

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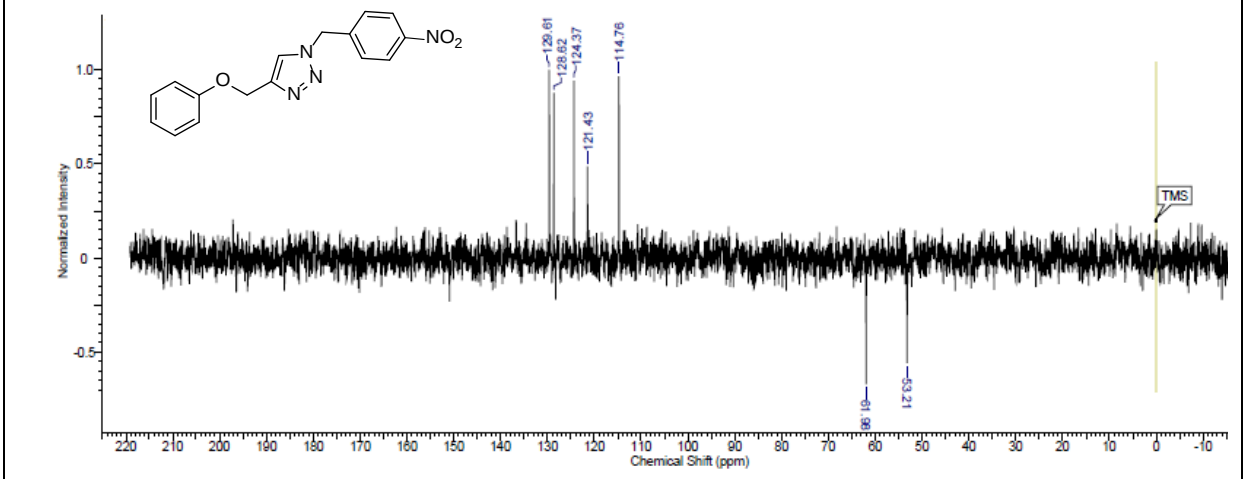

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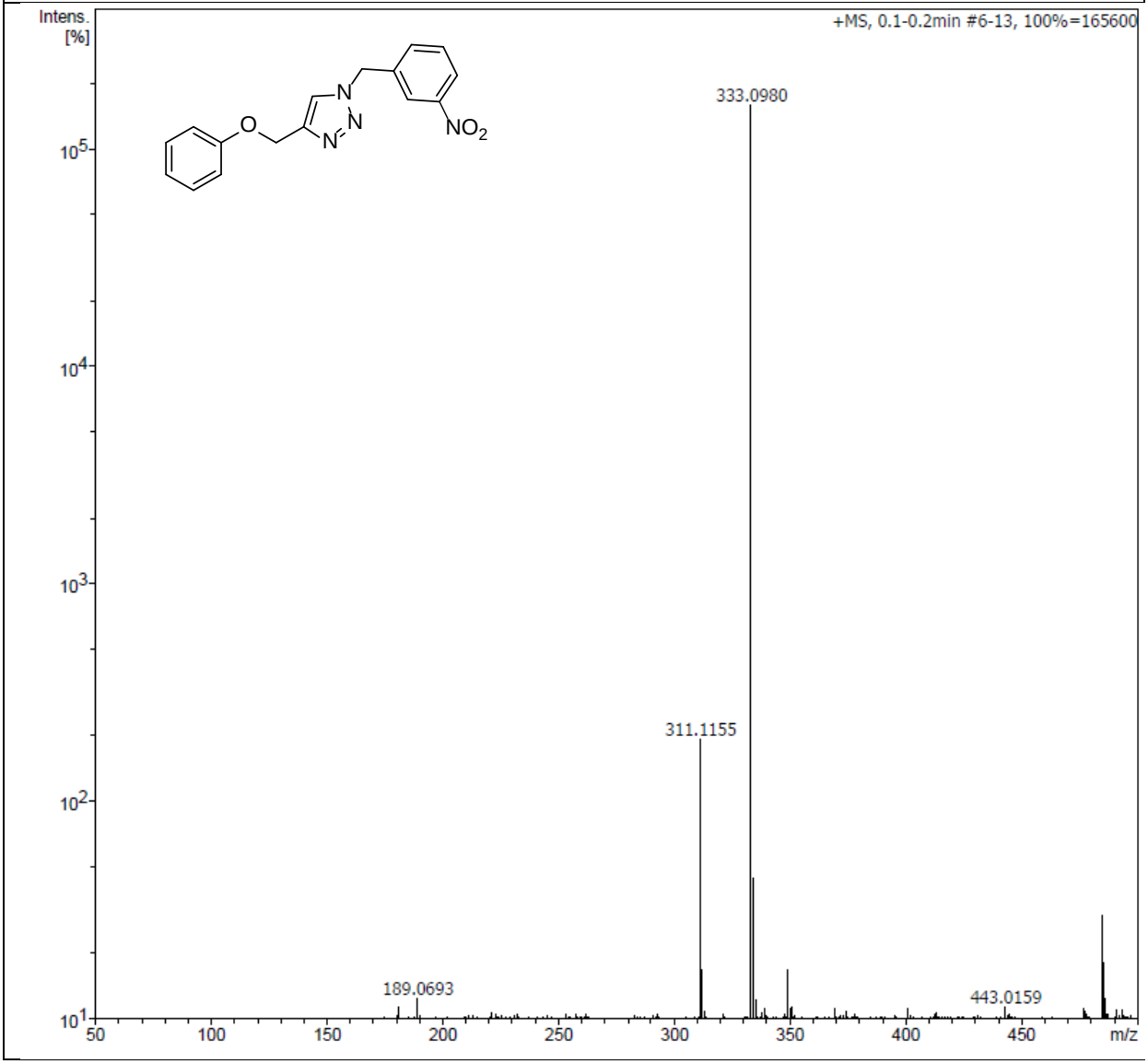
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300
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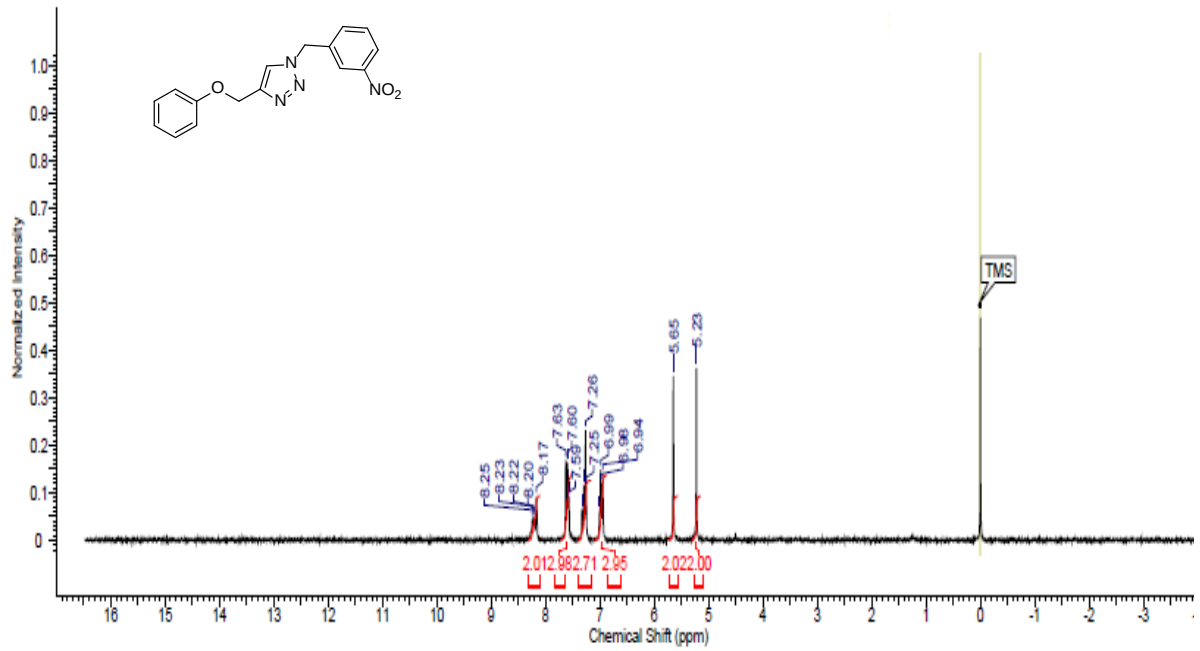
m/z

13b. ^{1}H NMR, 200 MHz, $CDCl_3$



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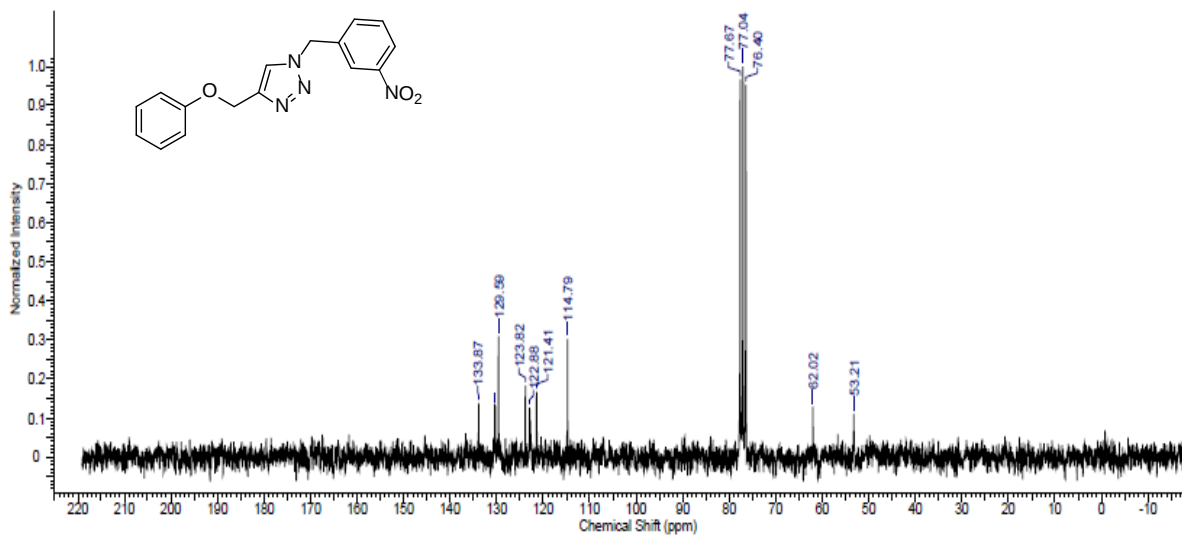

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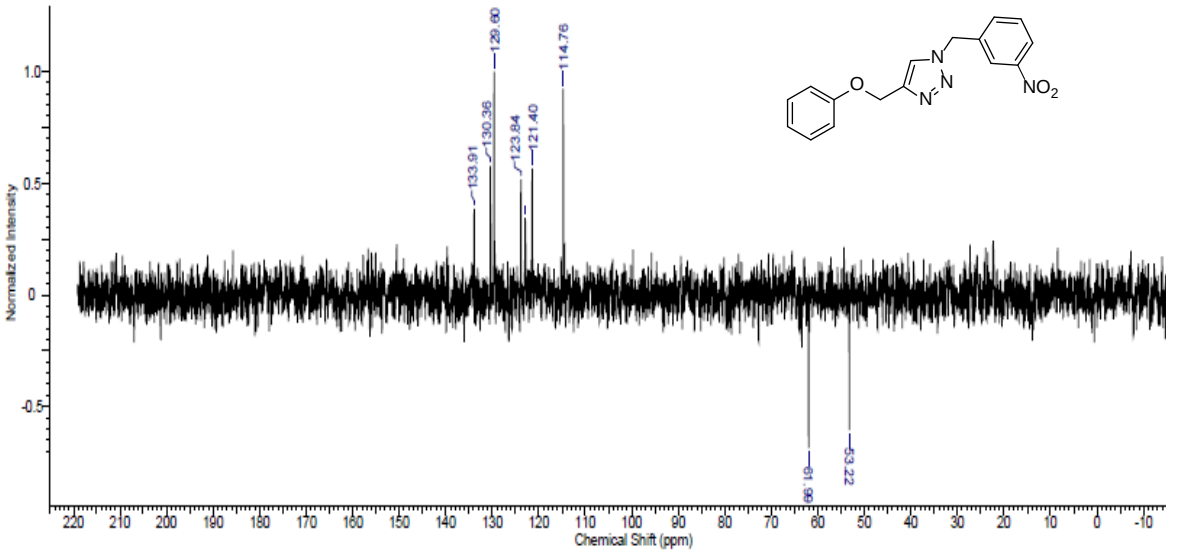

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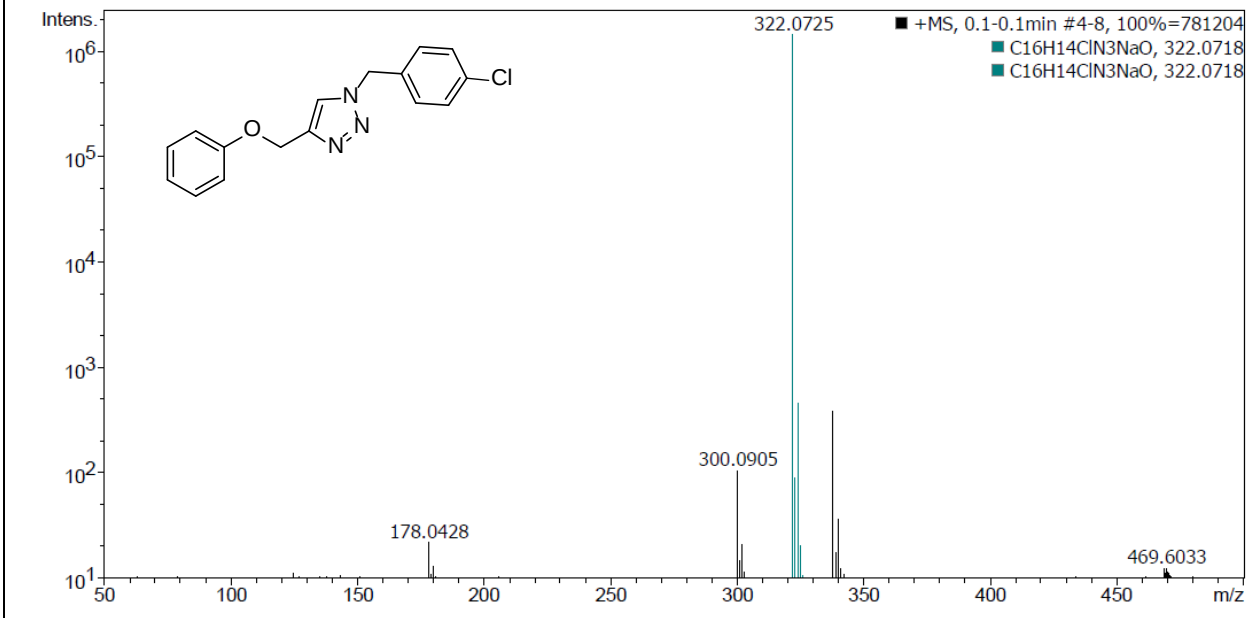

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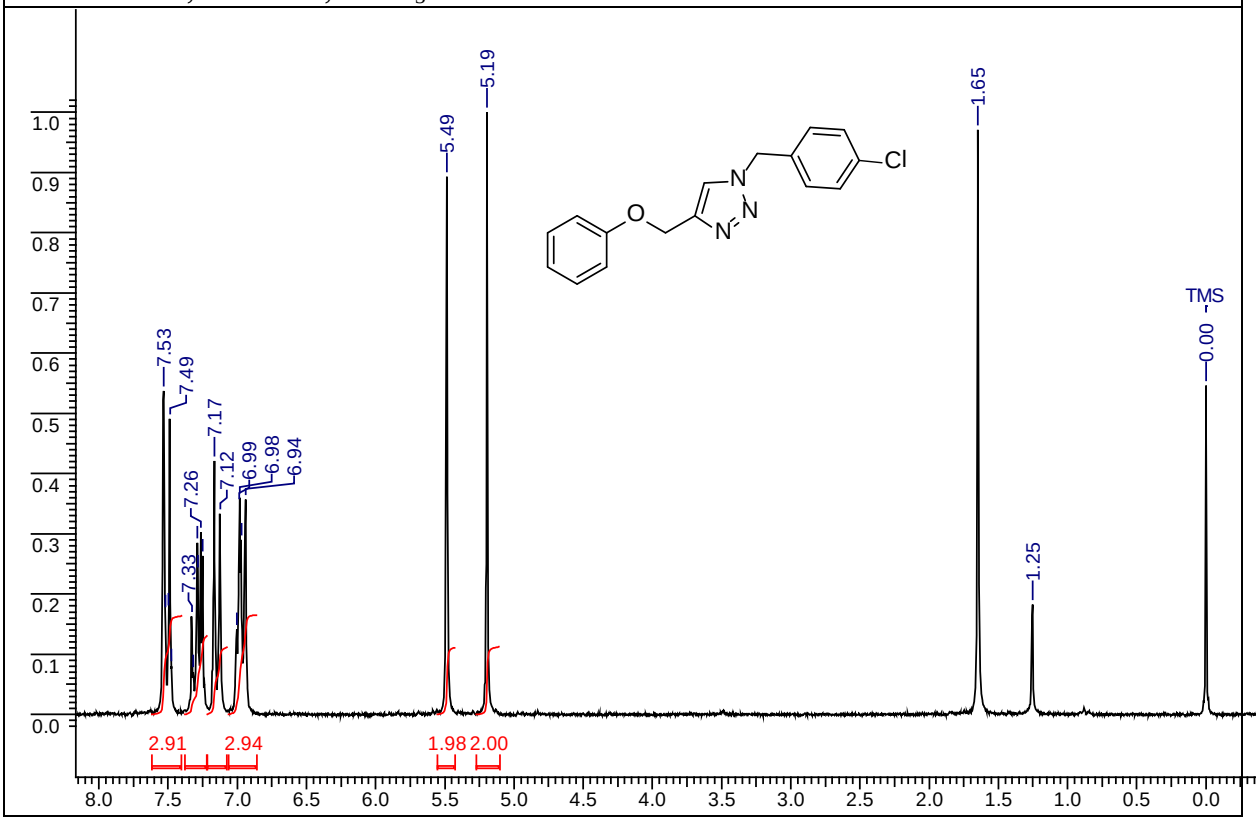

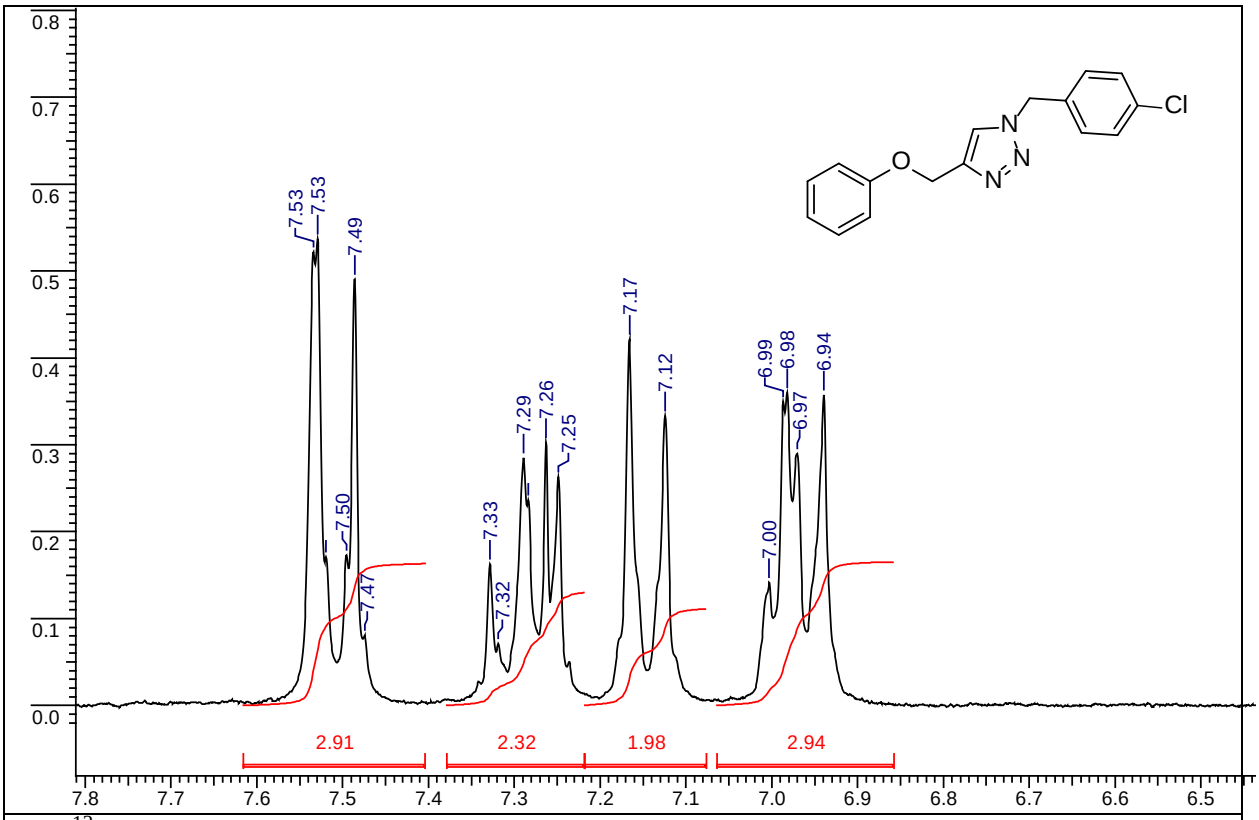

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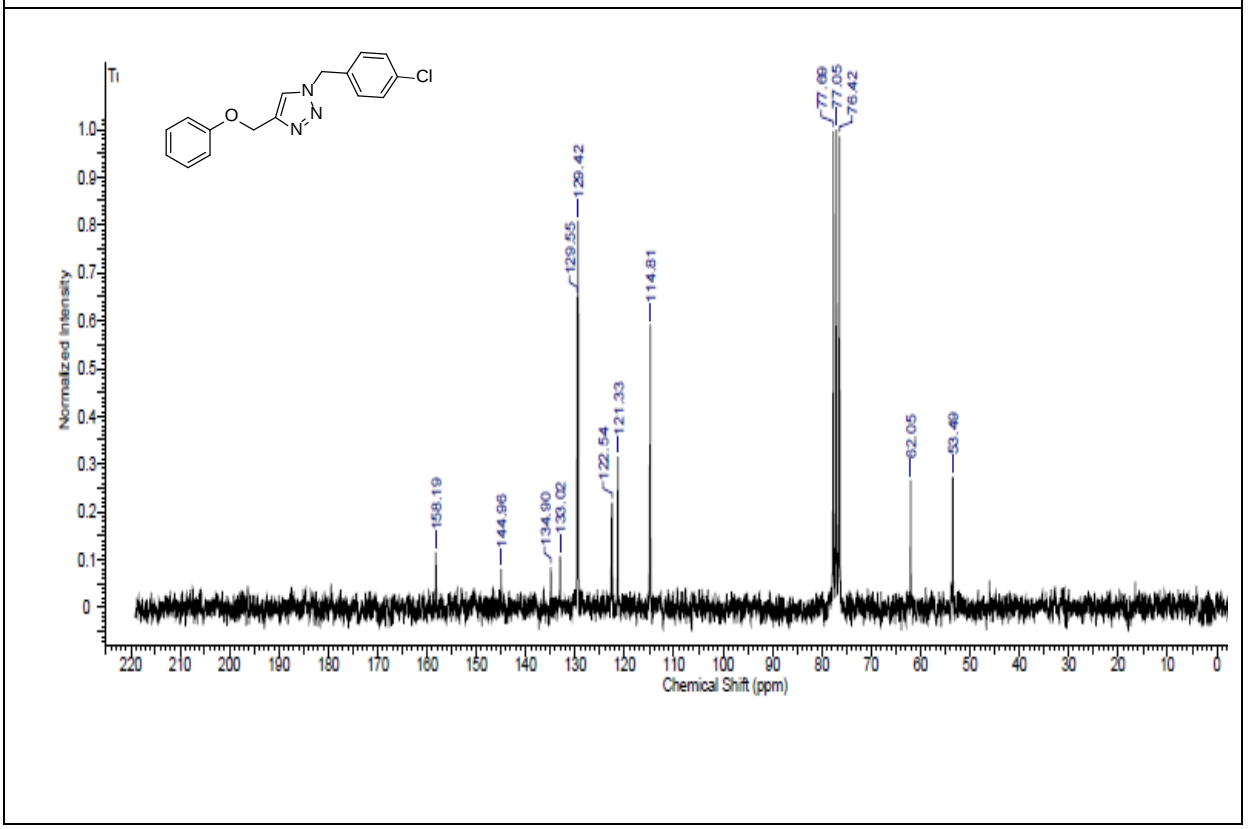

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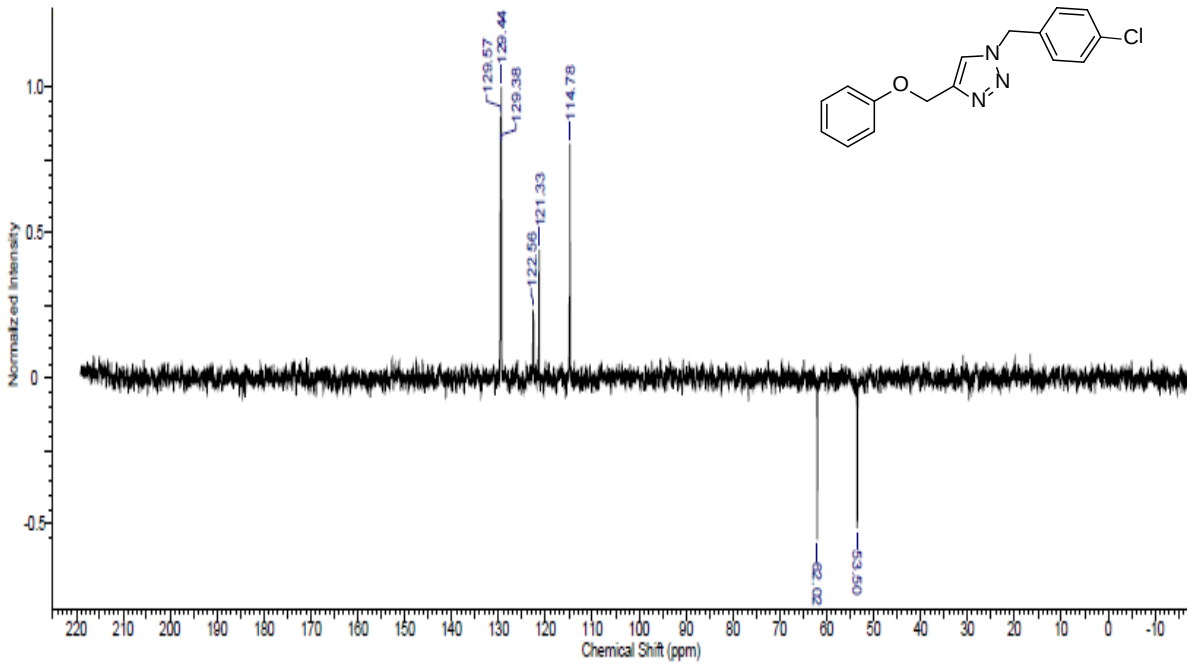

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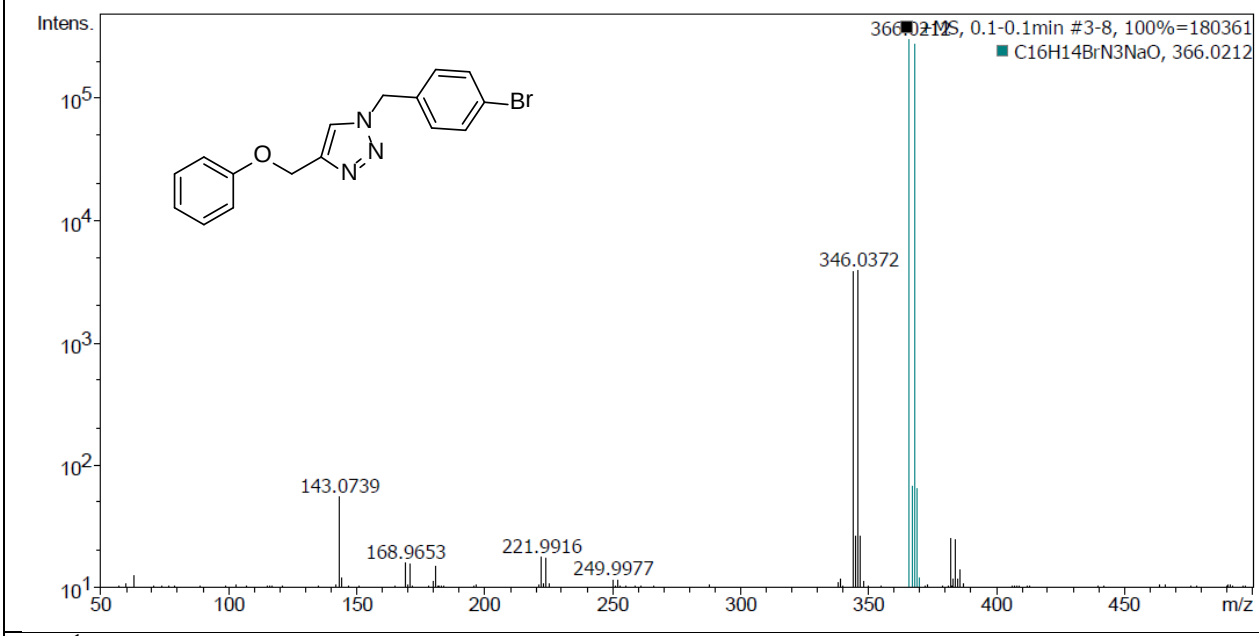

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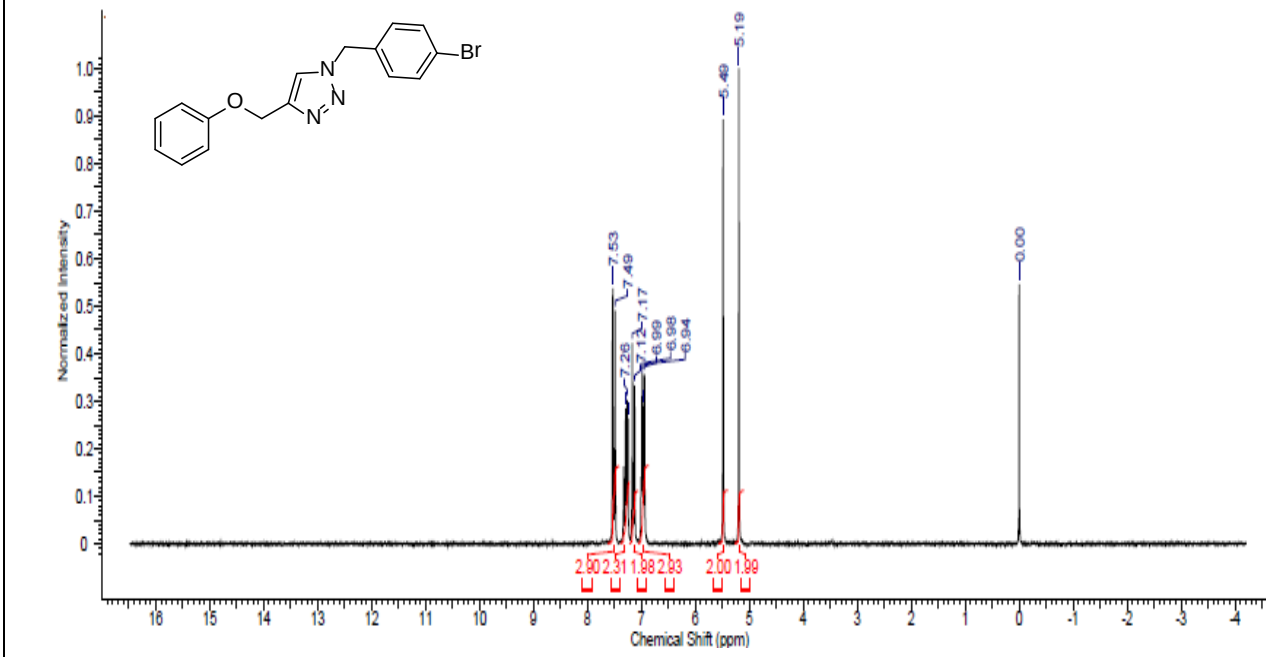

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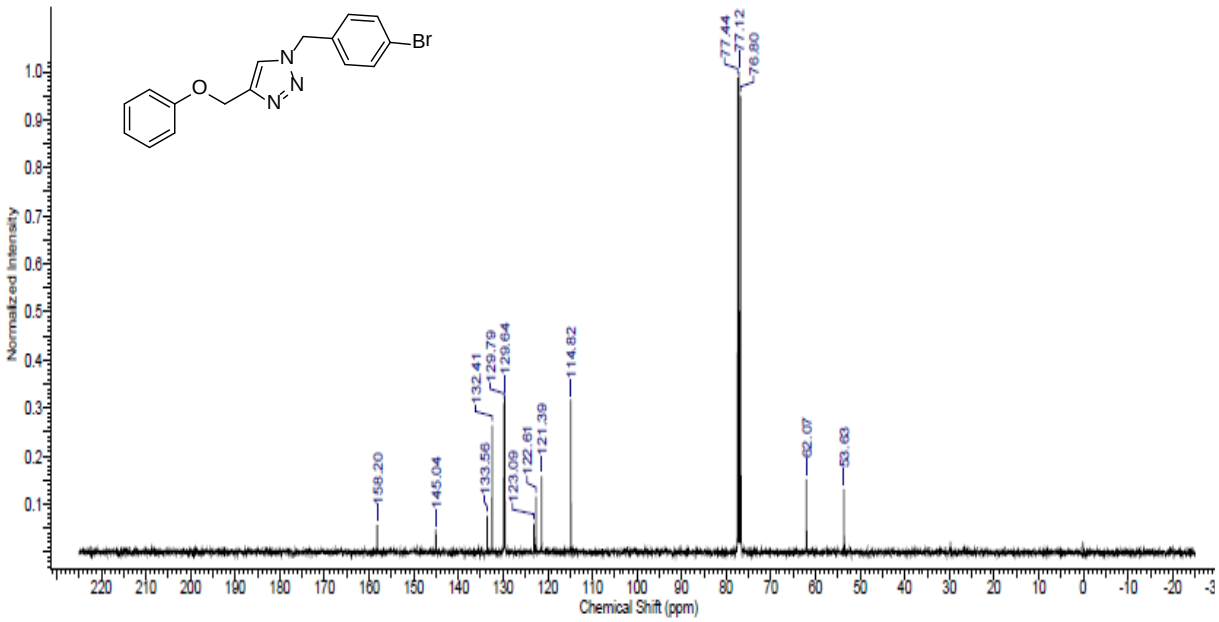

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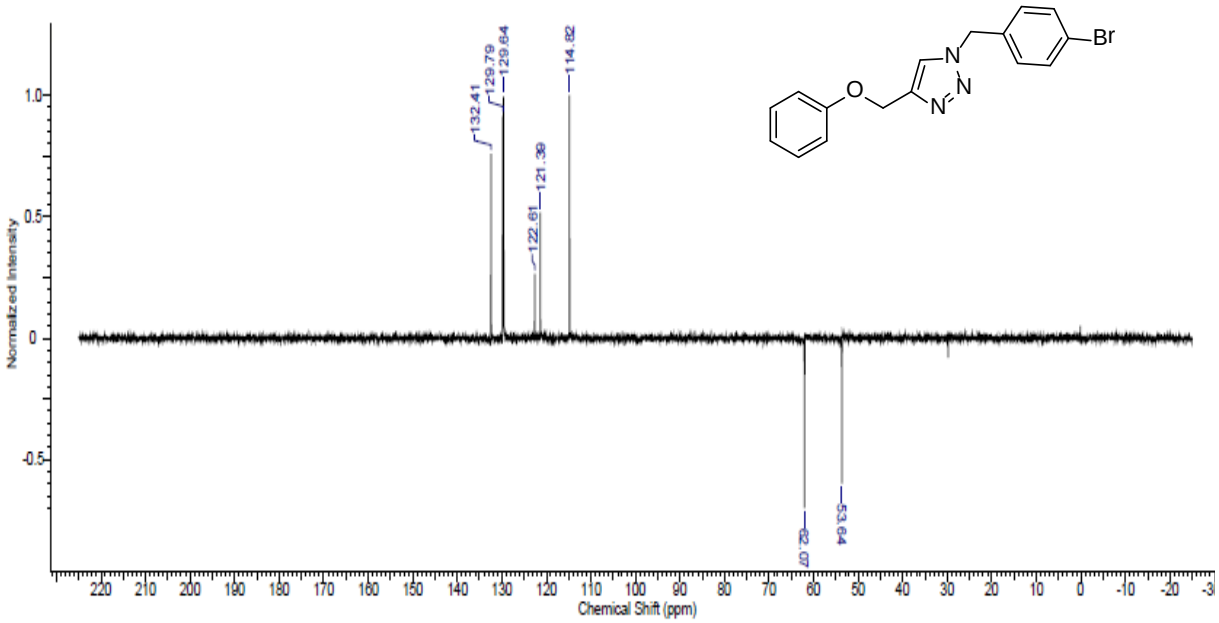
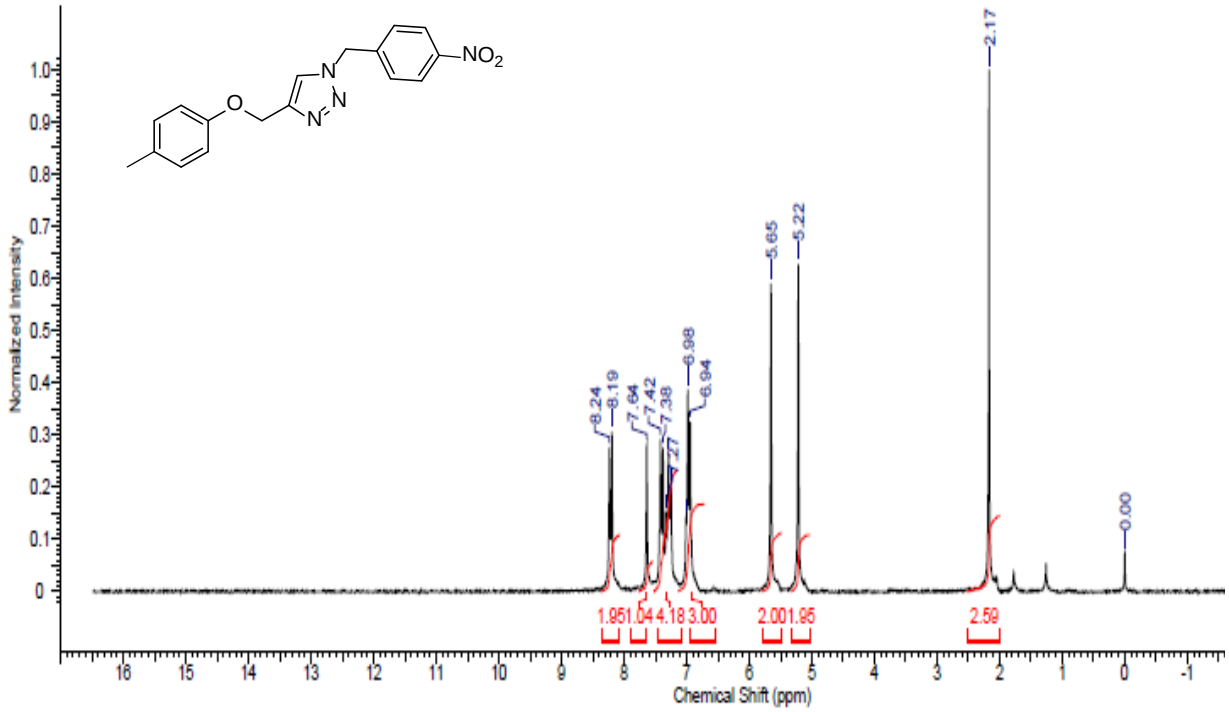
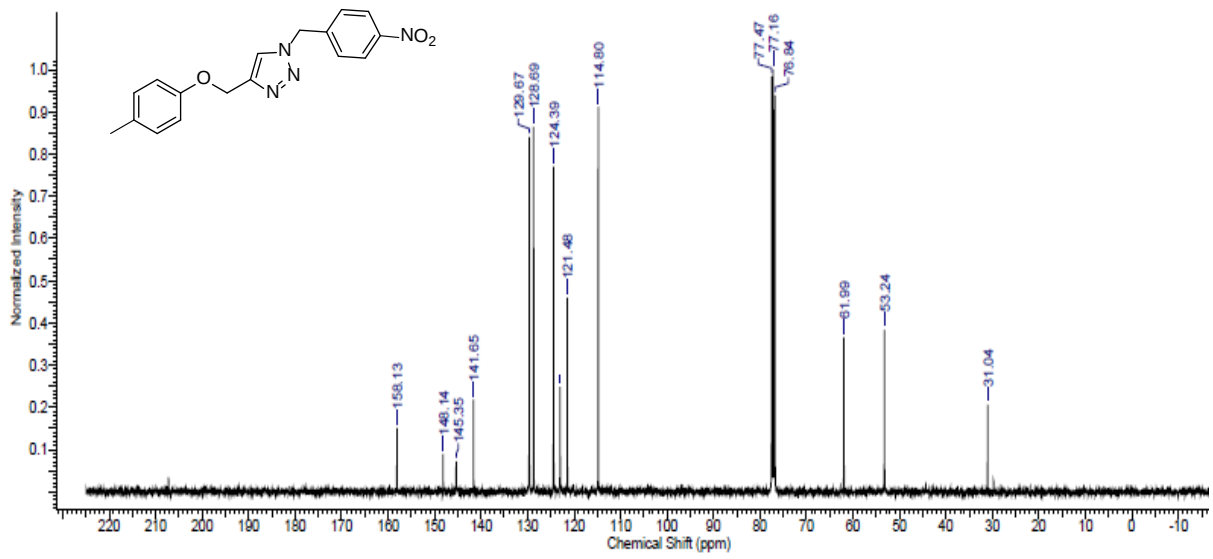


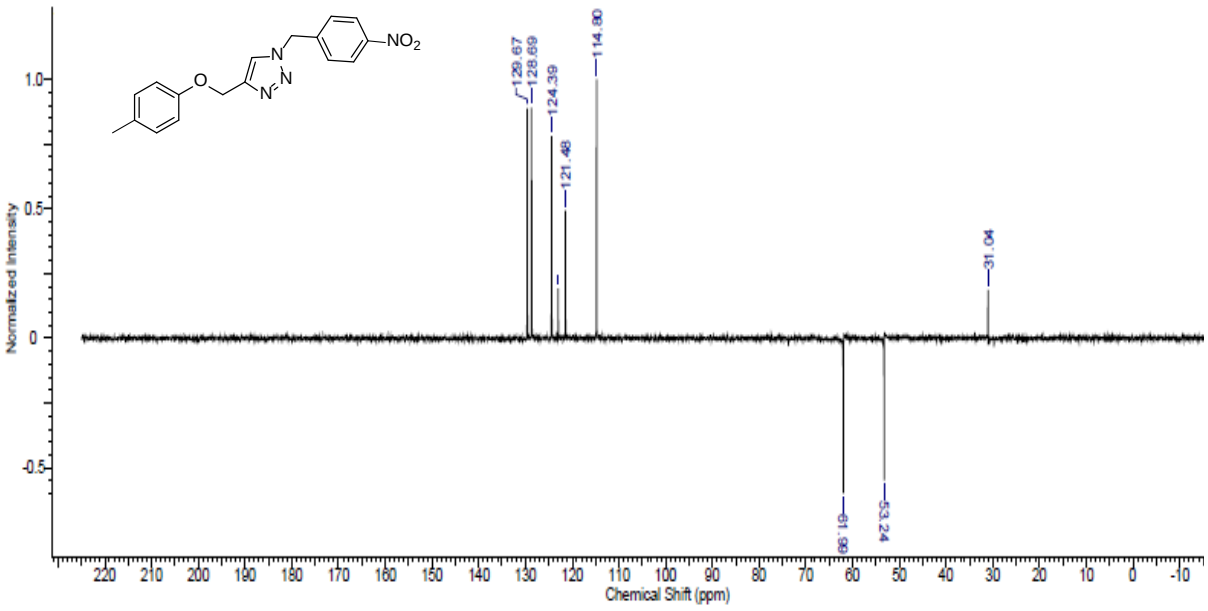
14a. ^{1}H NMR, 200 MHz, $CDCl_3$



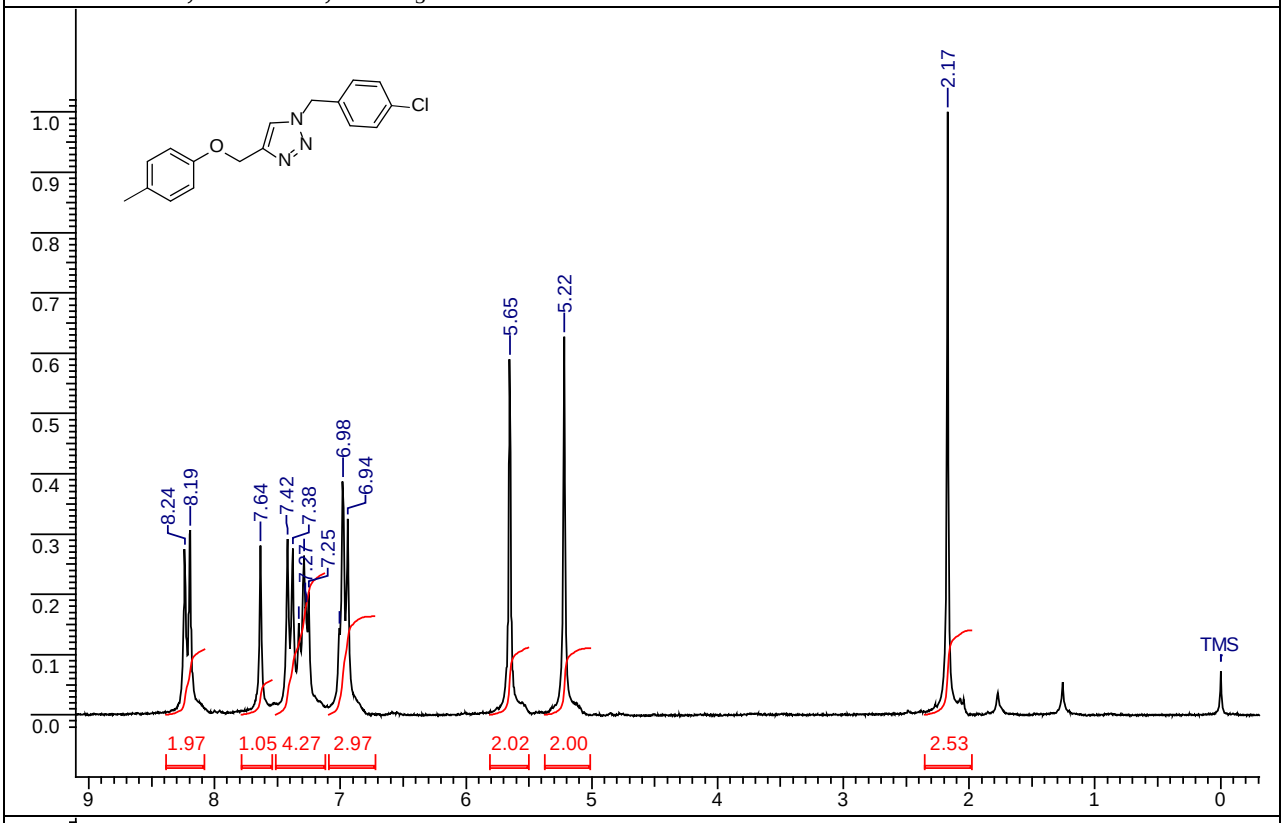
14a. ^{13}C NMR, 50 MHz, $CDCl_3$

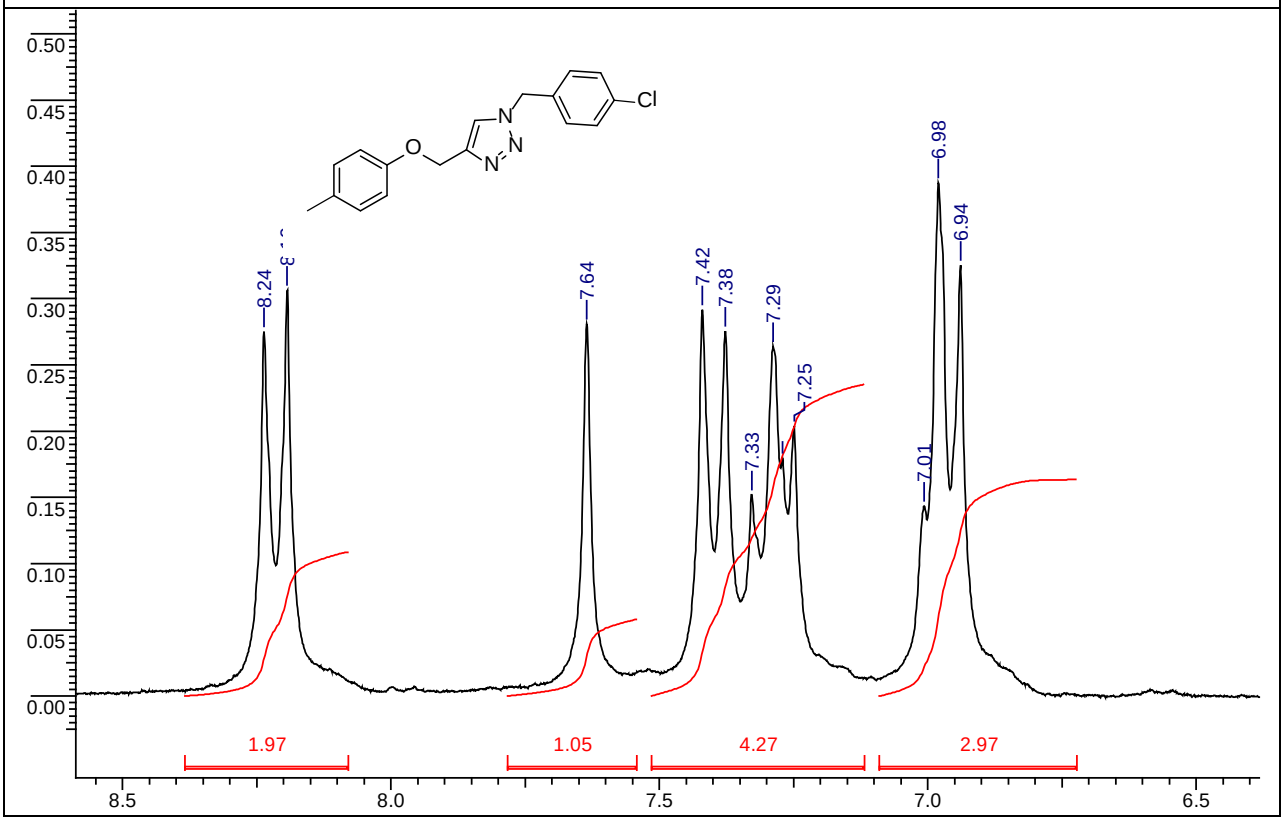


14a.DEPT, 50 MHz, $CDCl_3$

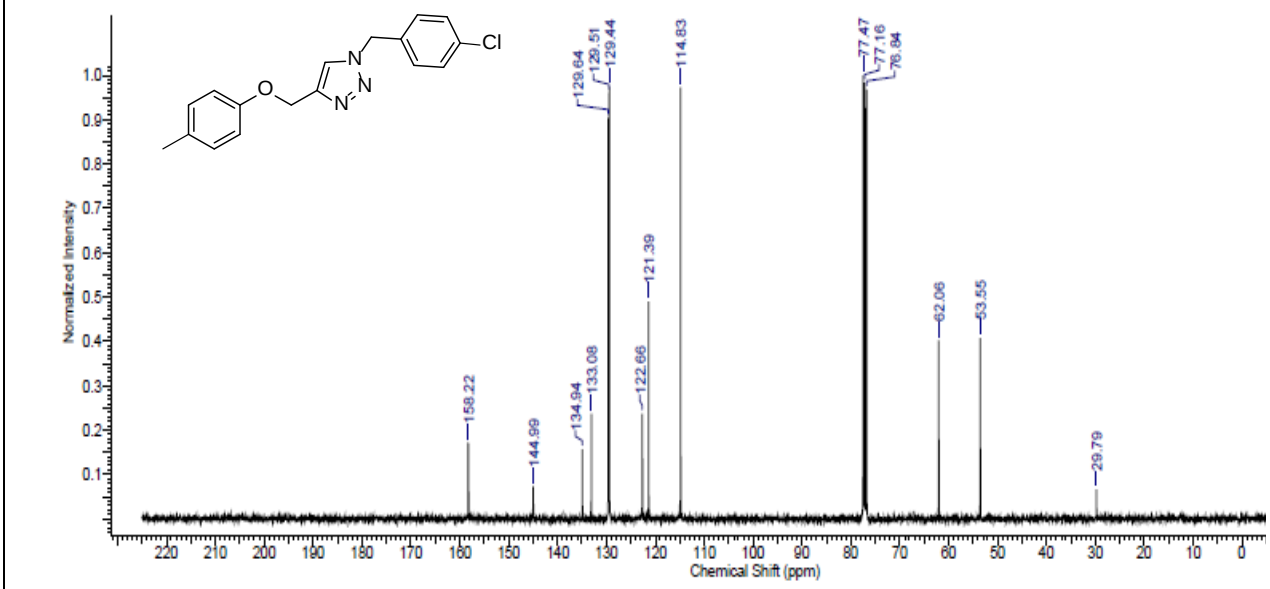


14c. ^{1}H NMR, 200 MHz, $CDCl_3$

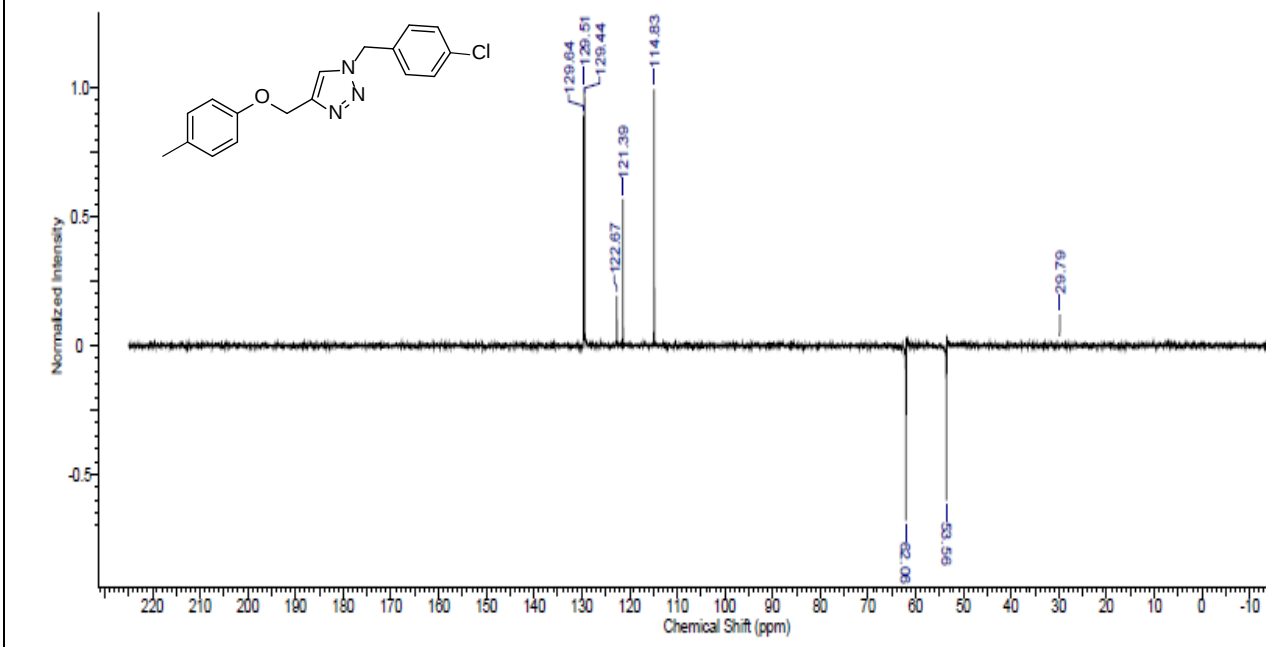




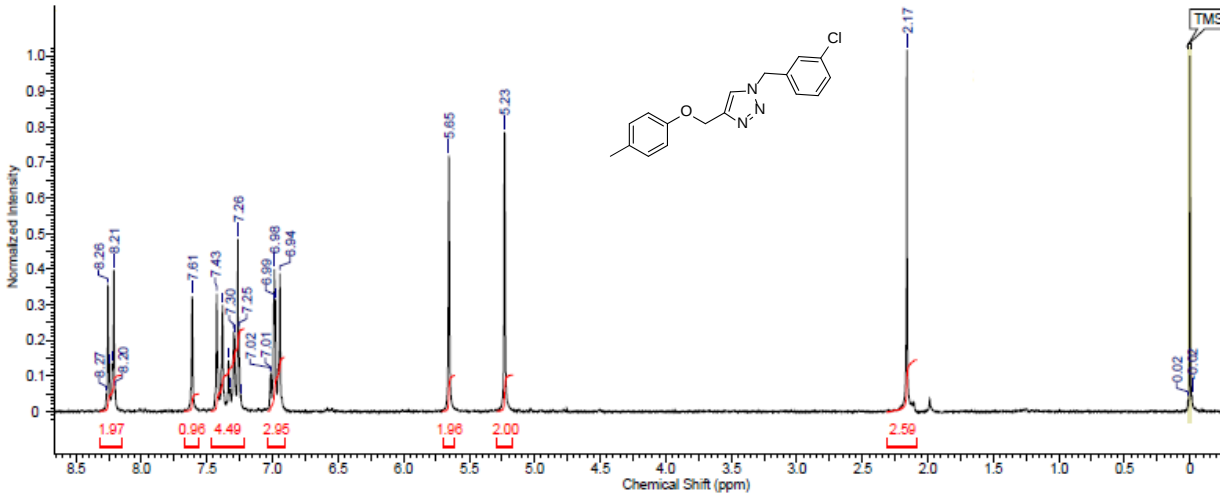
14c. ^{13}C NMR, 50 MHz, $CDCl_3$



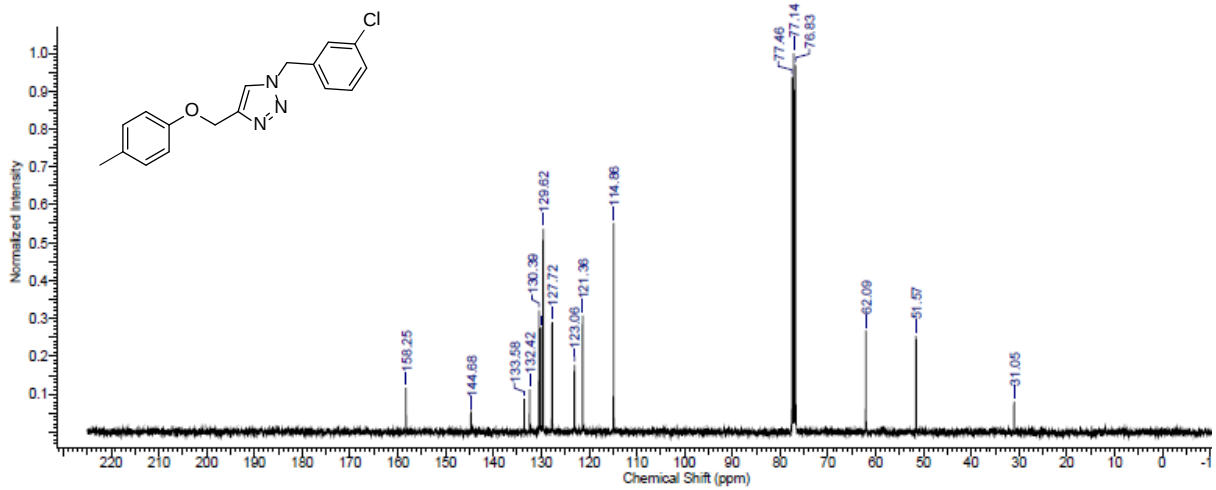
14c. DEPT, 50 MHz, $CDCl_3$



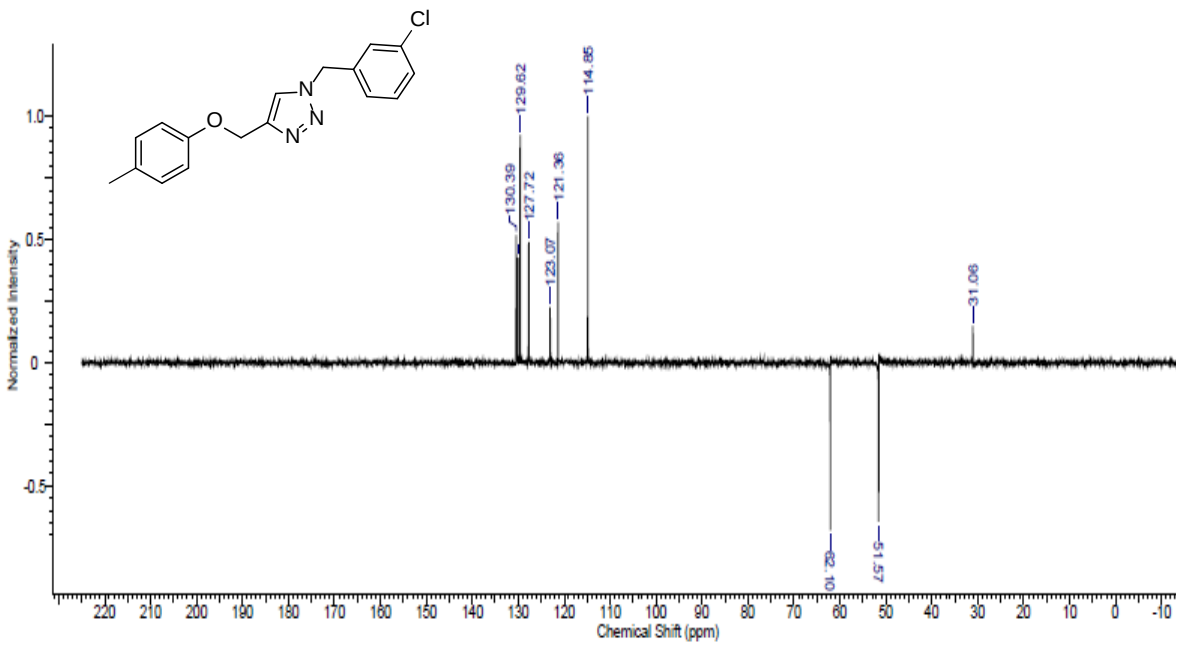
14d. ^{1}H NMR, 200 MHz, $CDCl_3$



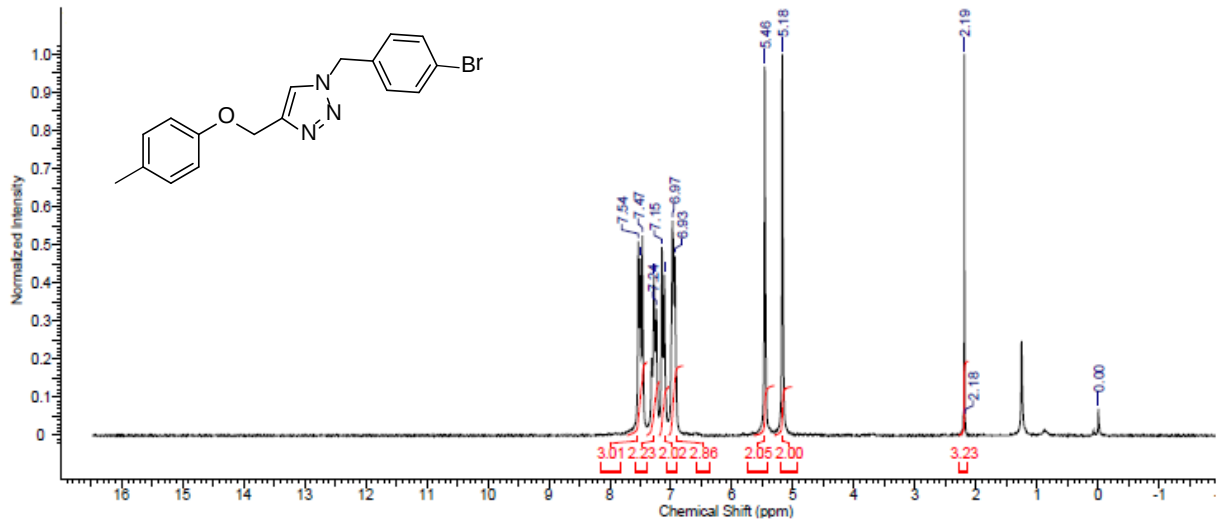
14d. ^{13}C NMR, 50 MHz, $CDCl_3$



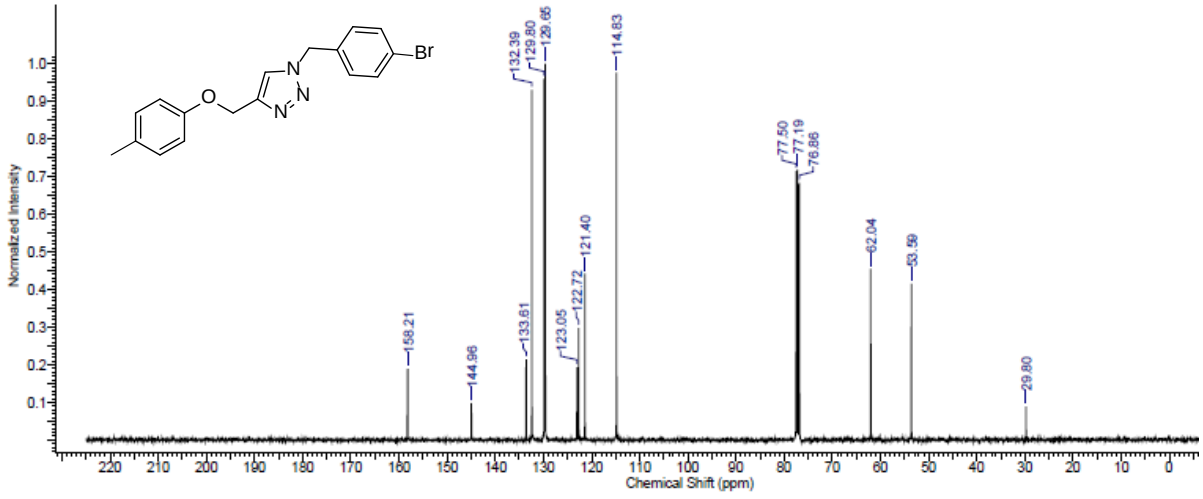
14d.DEPT, 50 MHz, $CDCl_3$



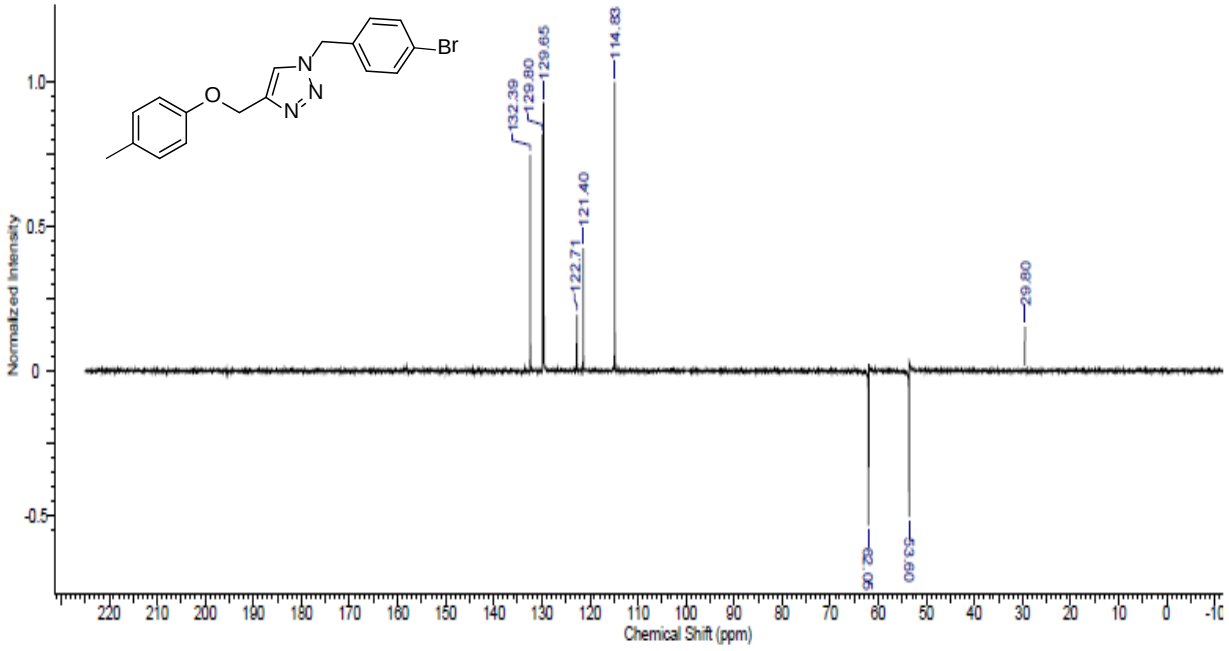
14e. ^{1}H NMR, 200 MHz, $CDCl_3$



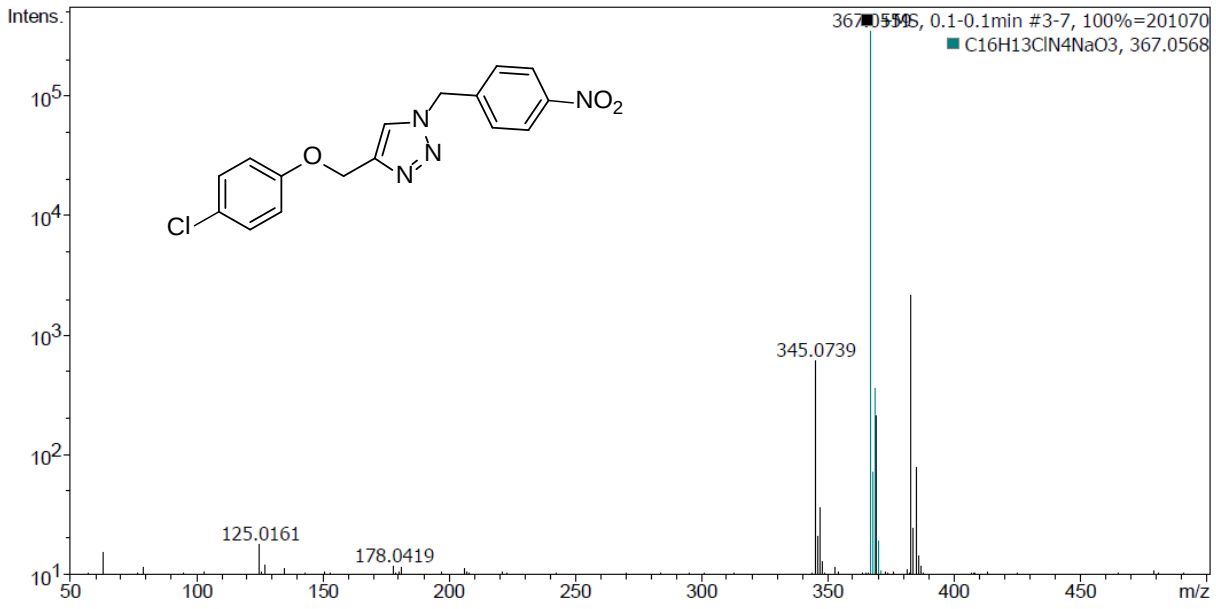
14e. ^{13}C NMR, 200 MHz, $CDCl_3$



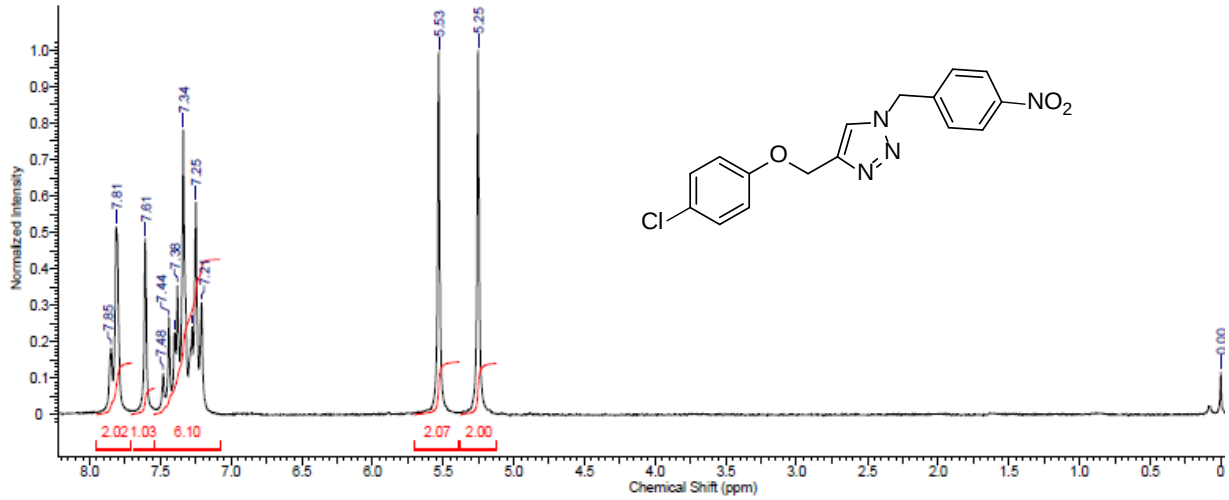
14e.DEPT, 50 MHz, $CDCl_3$



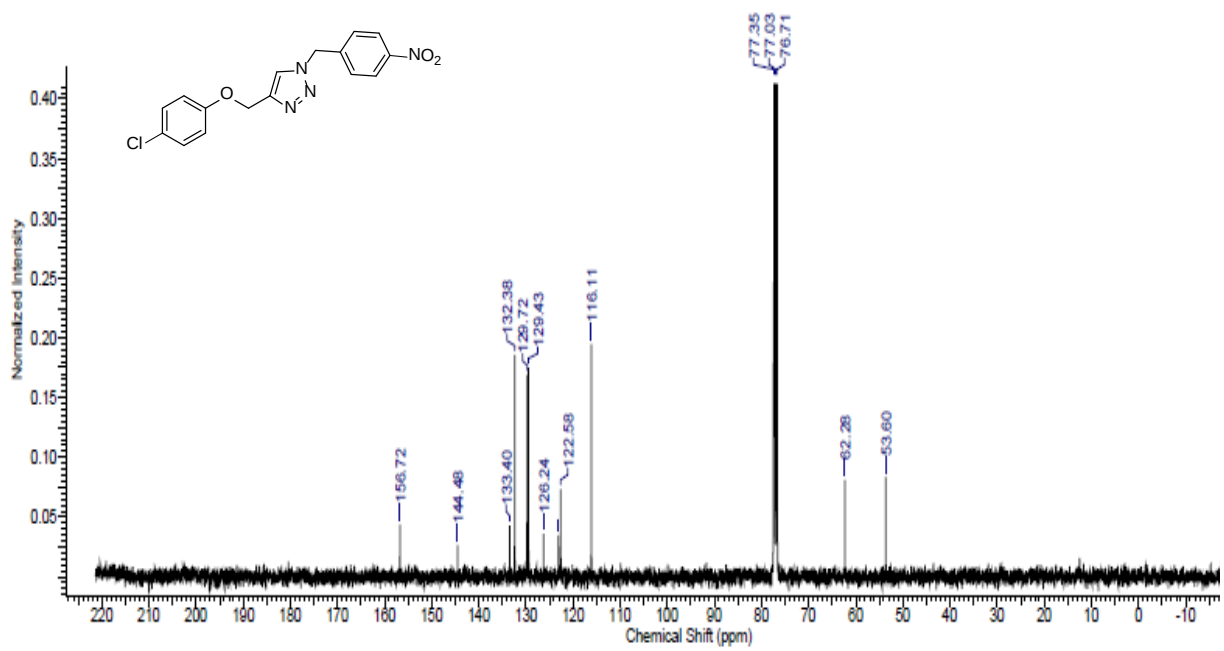
15a.HRMS



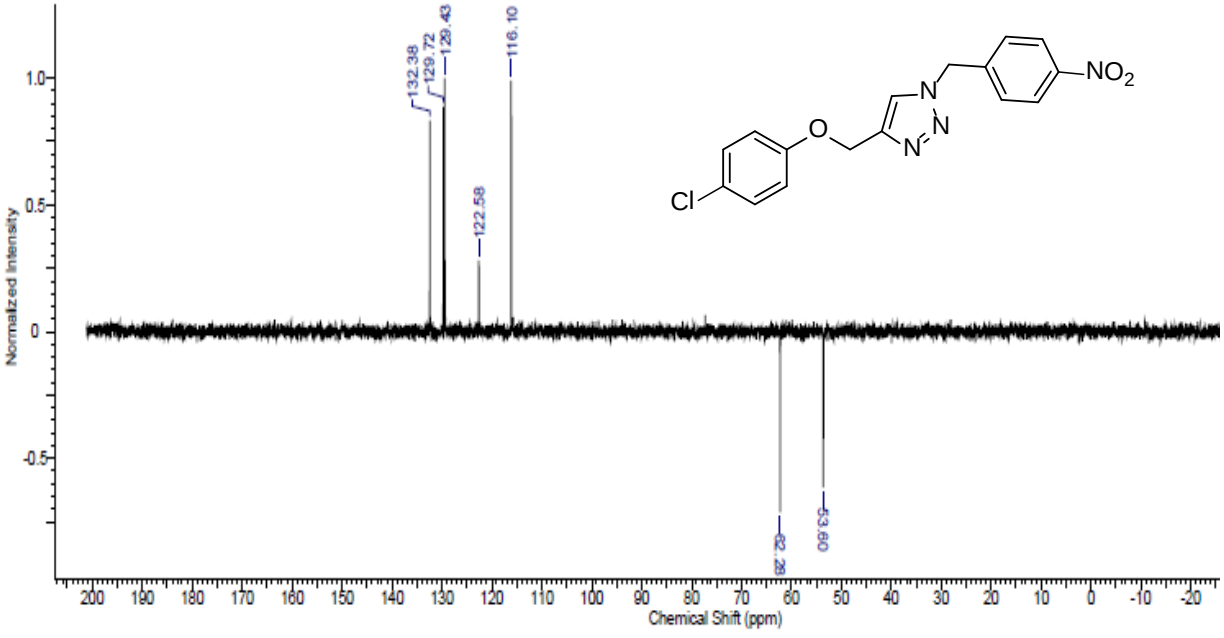
15a. ^{1}H NMR, 200 MHz, $CDCl_3$



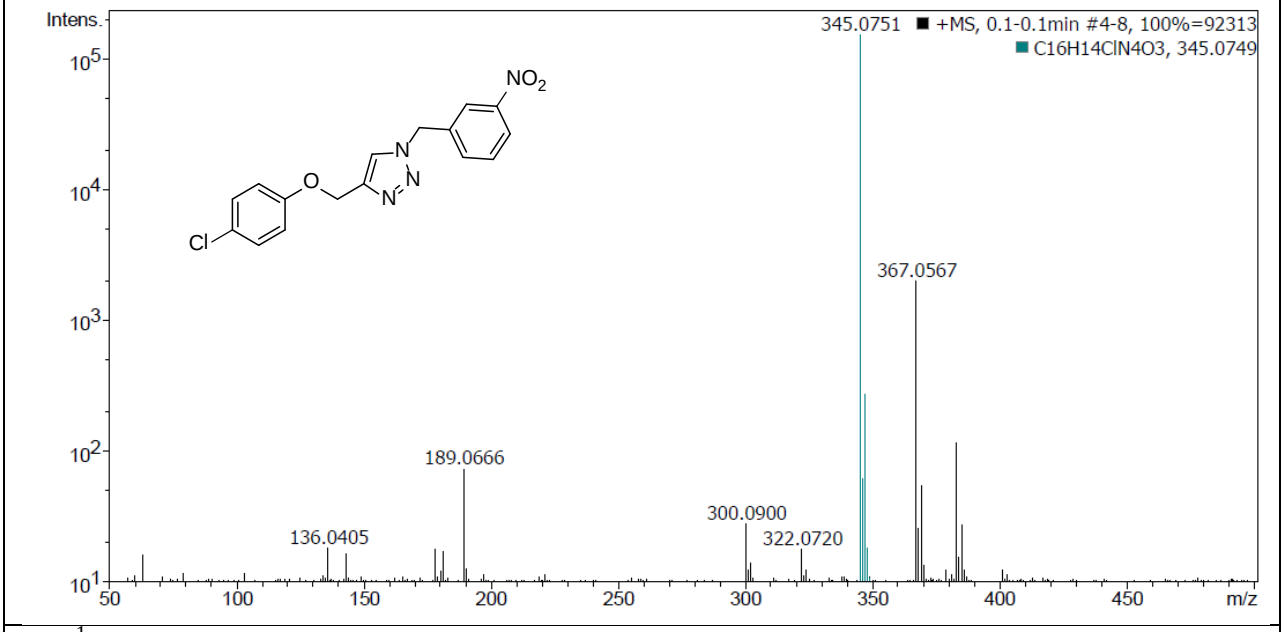
15a. ^{13}C NMR, 100 MHz, $CDCl_3$



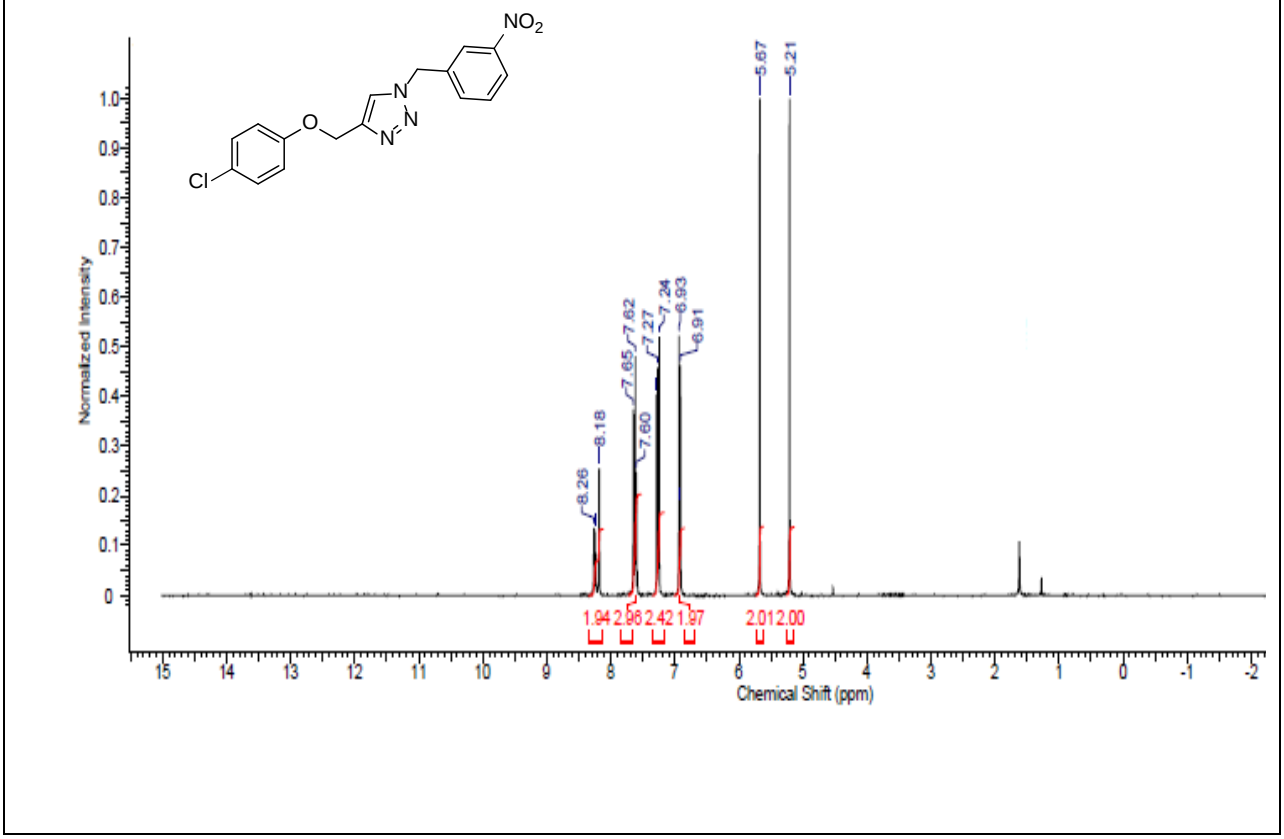
15a.DEPT, 100 MHz, $CDCl_3$



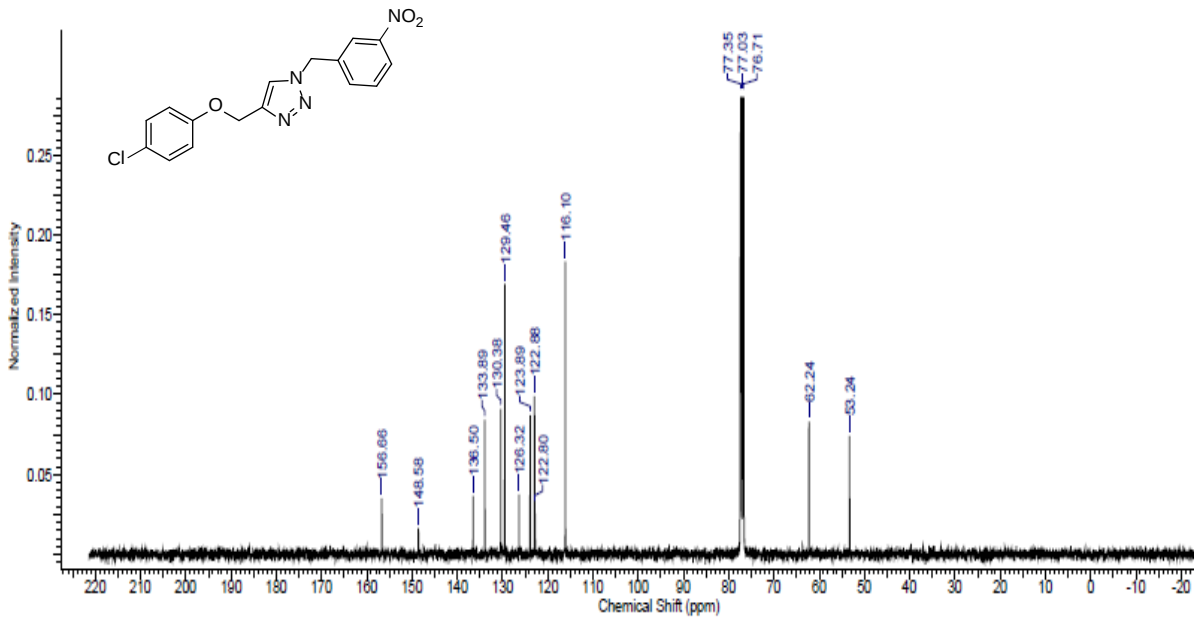
15b.HRMS



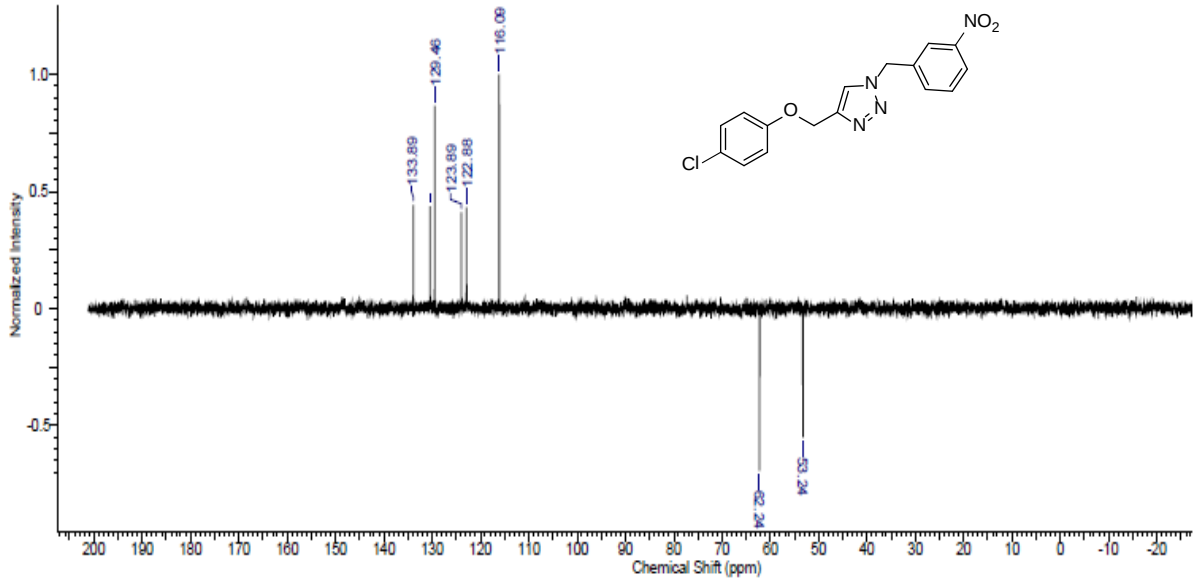
15b.^{1}H NMR, 400 MHz, $CDCl_3$



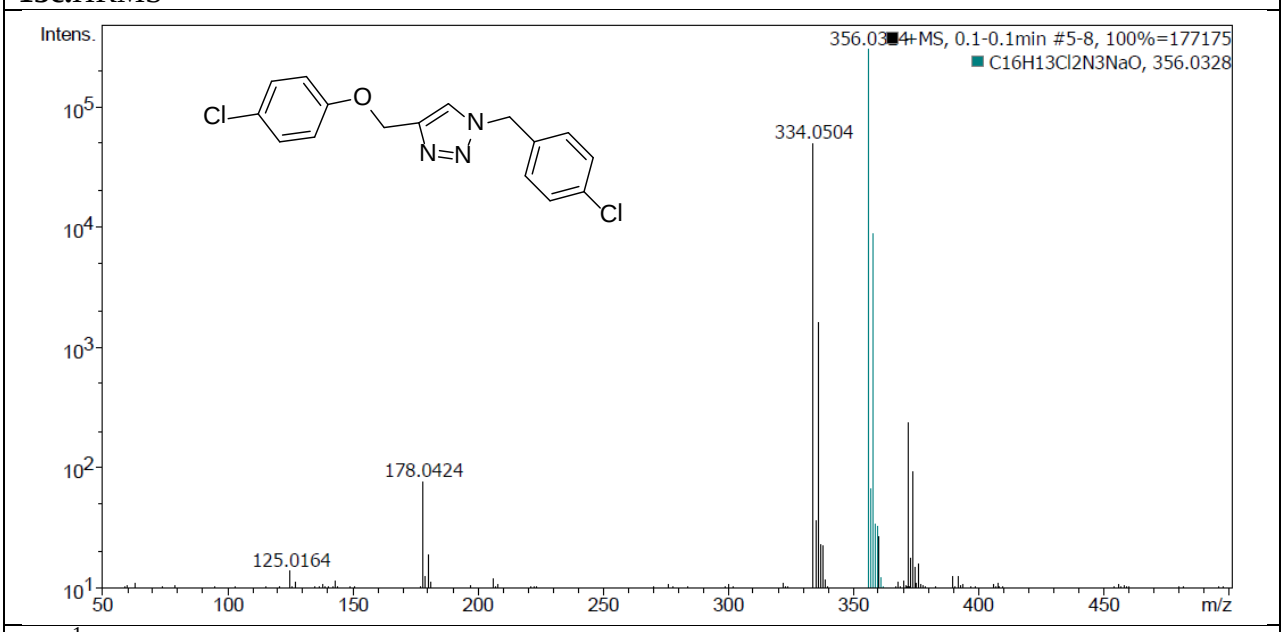
15b. ^{13}C NMR, 100 MHz, $CDCl_3$



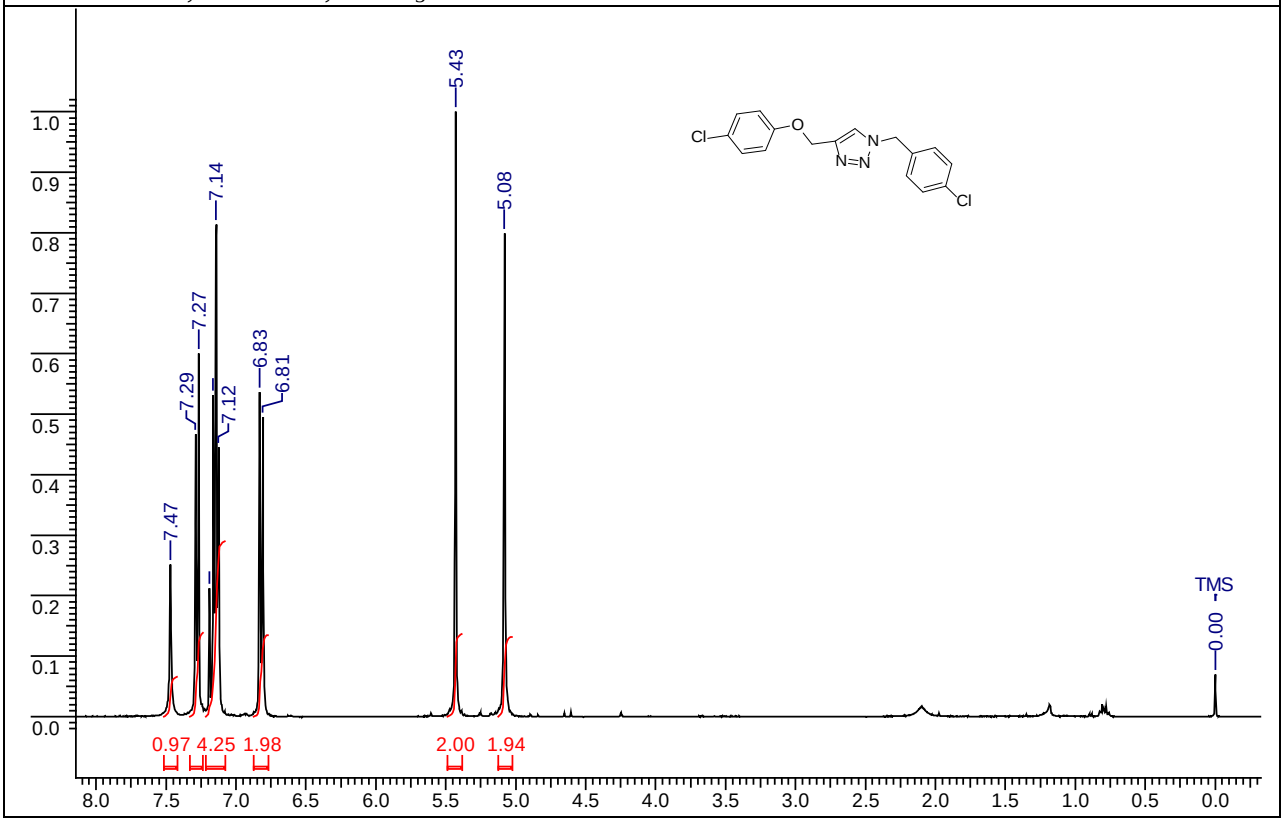
15b.DEPT, 100 MHz, $CDCl_3$



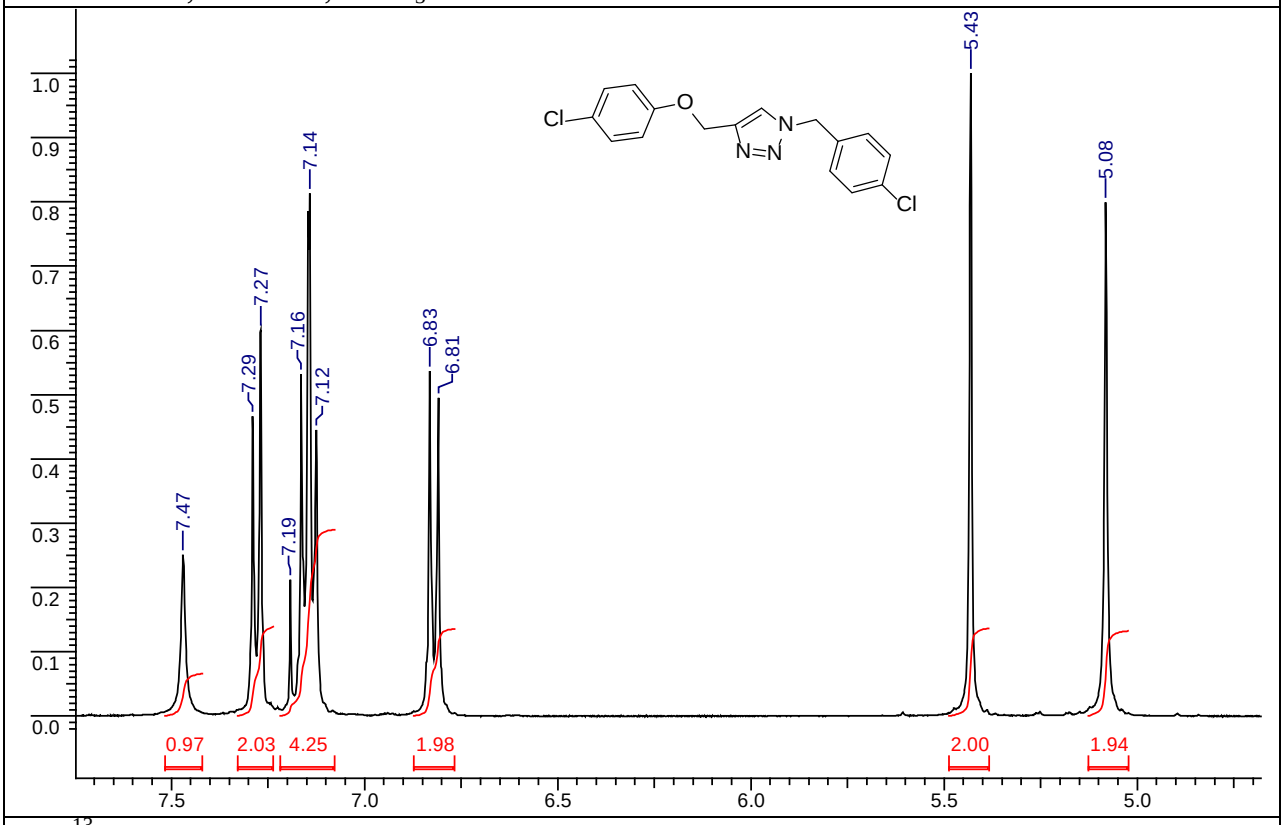
15c.HRMS



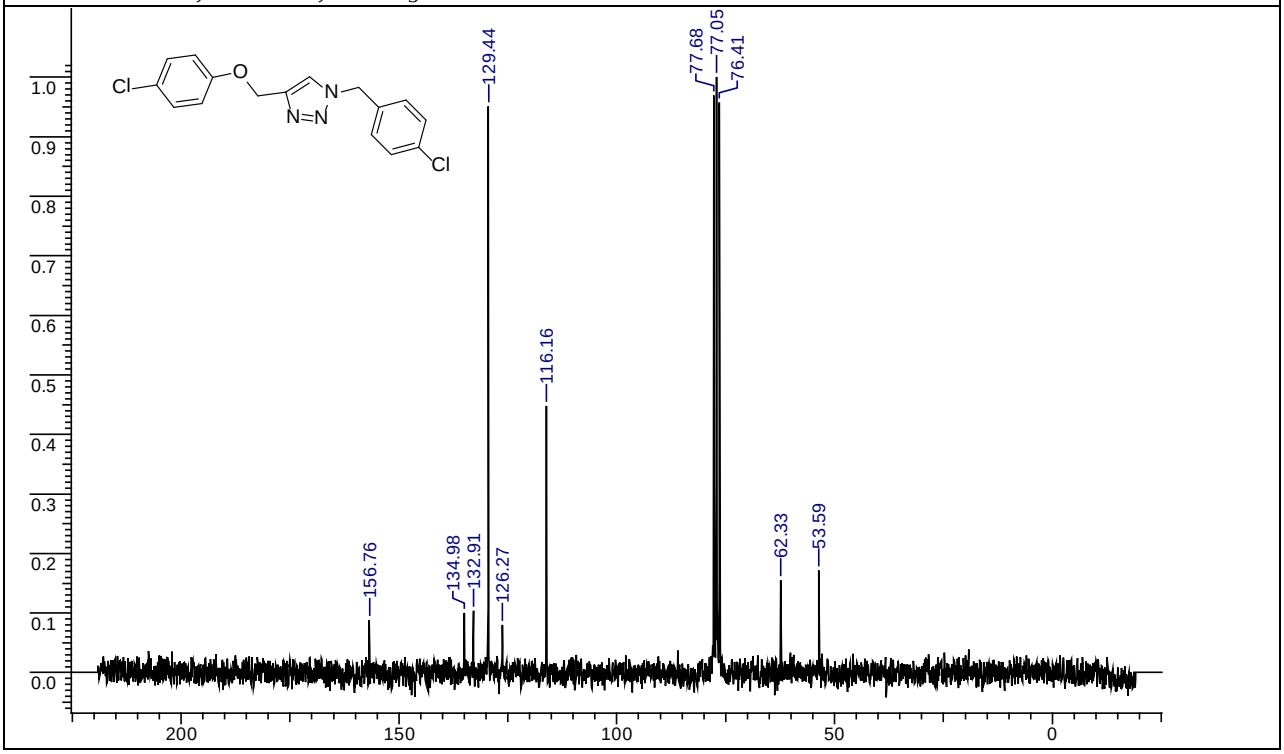
15c.^{1}H NMR, 200 MHz, $CDCl_3$



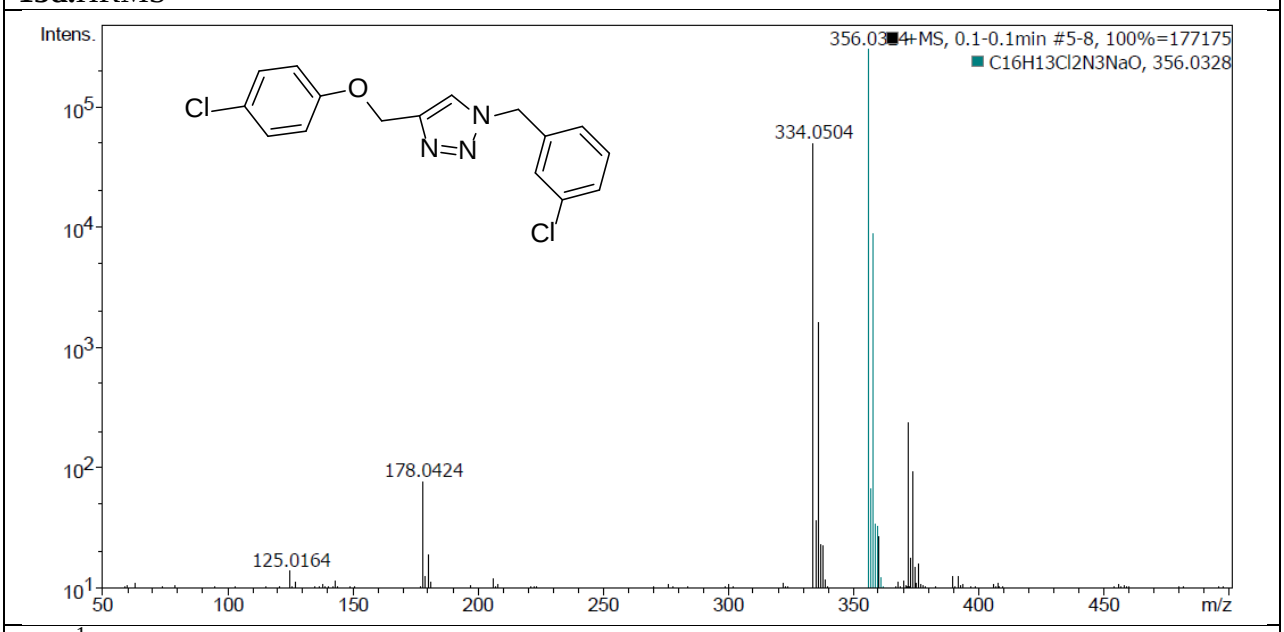
15c. ^{1}H NMR, 200 MHz, $CDCl_3$



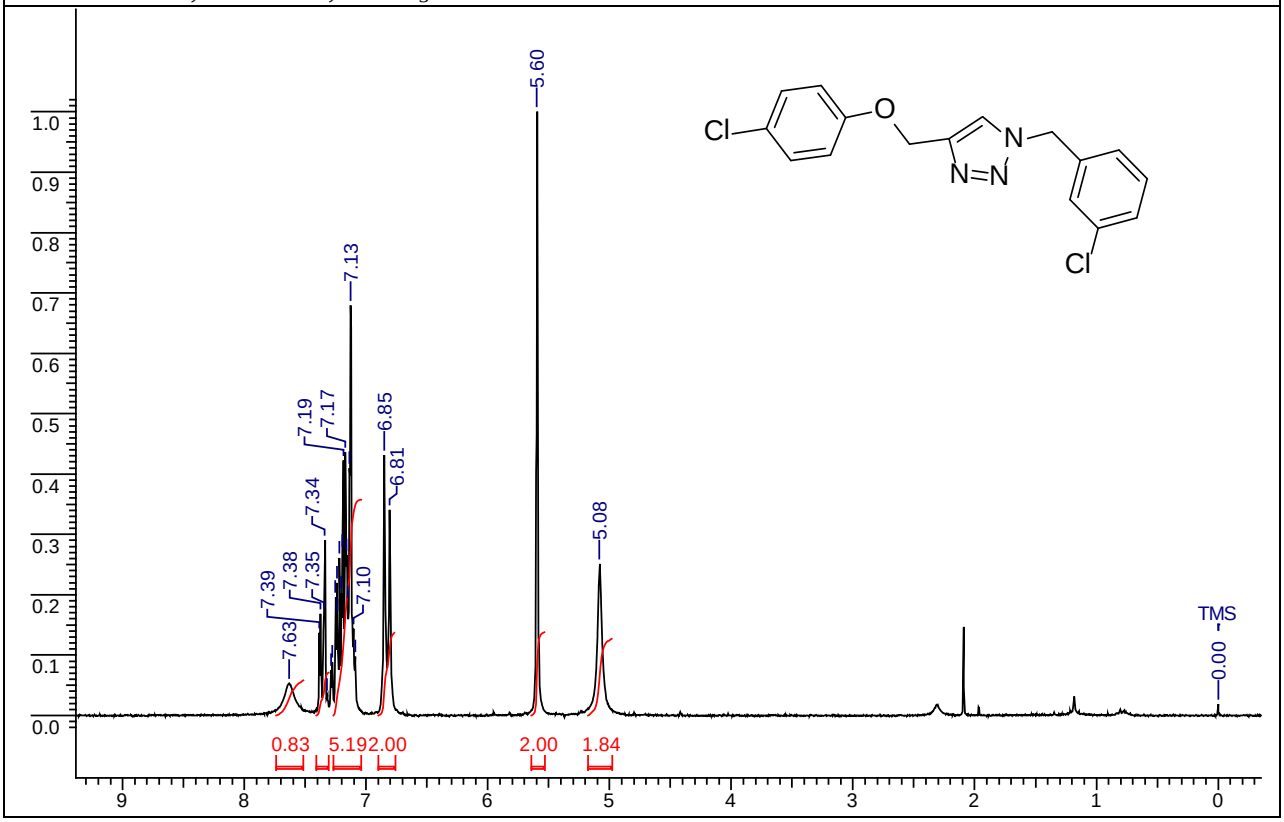
15c. ^{13}C NMR, 50 MHz, $CDCl_3$



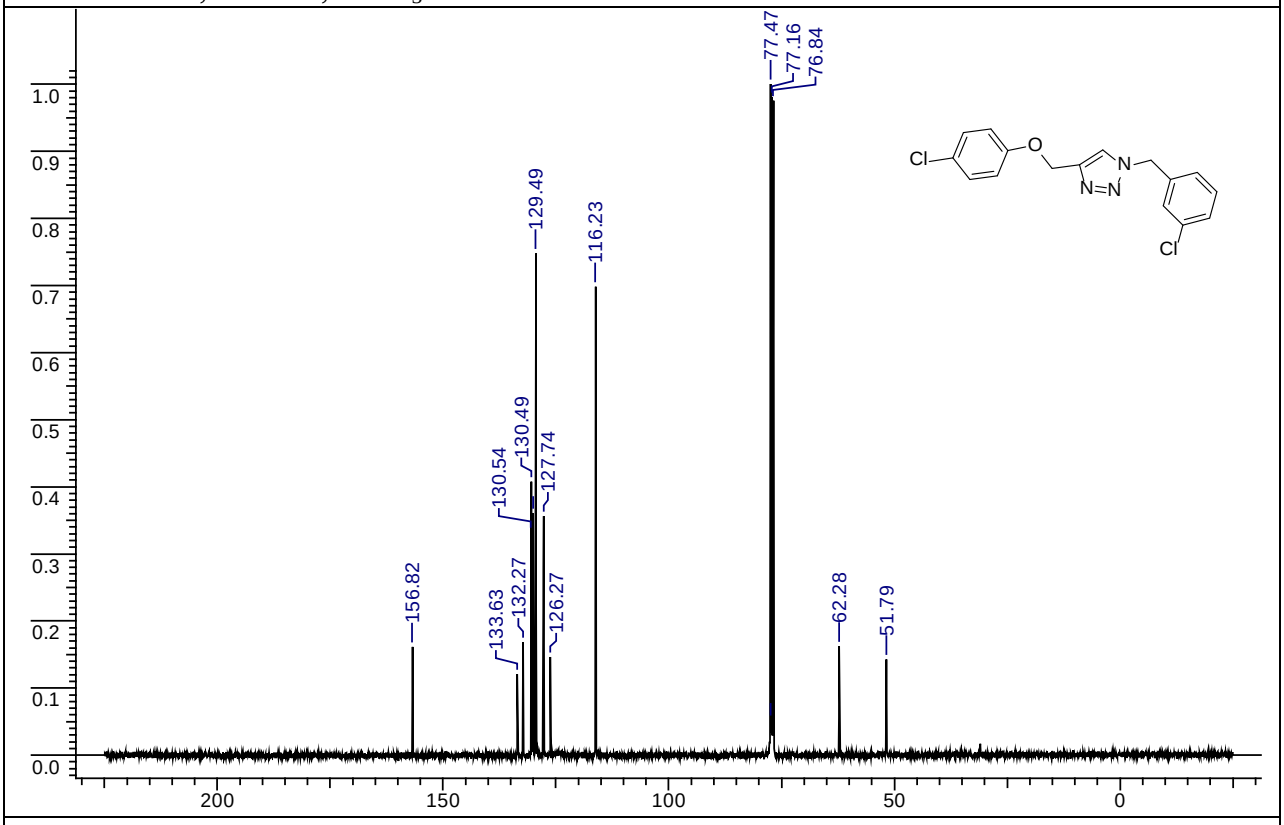
15d.HRMS



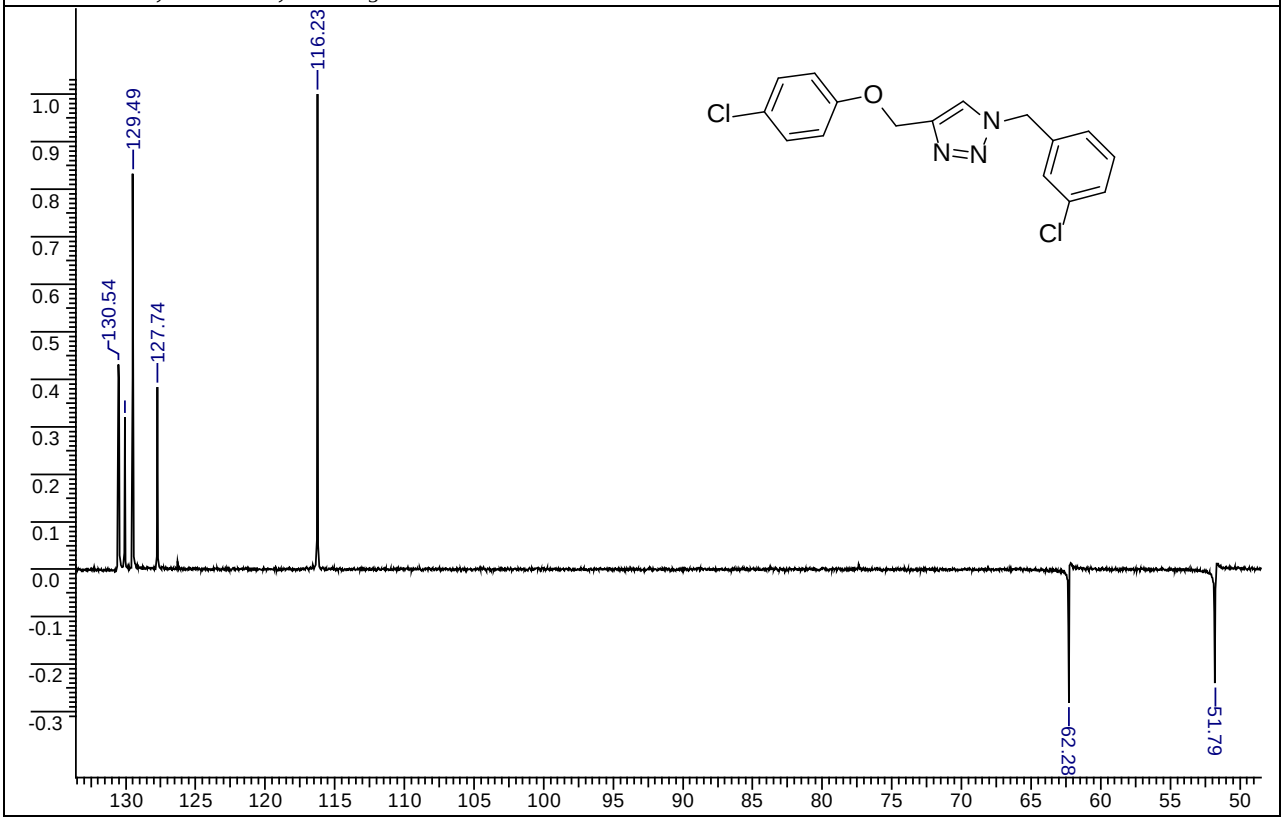
15d.^{1}H NMR, 200 MHz, $CDCl_3$



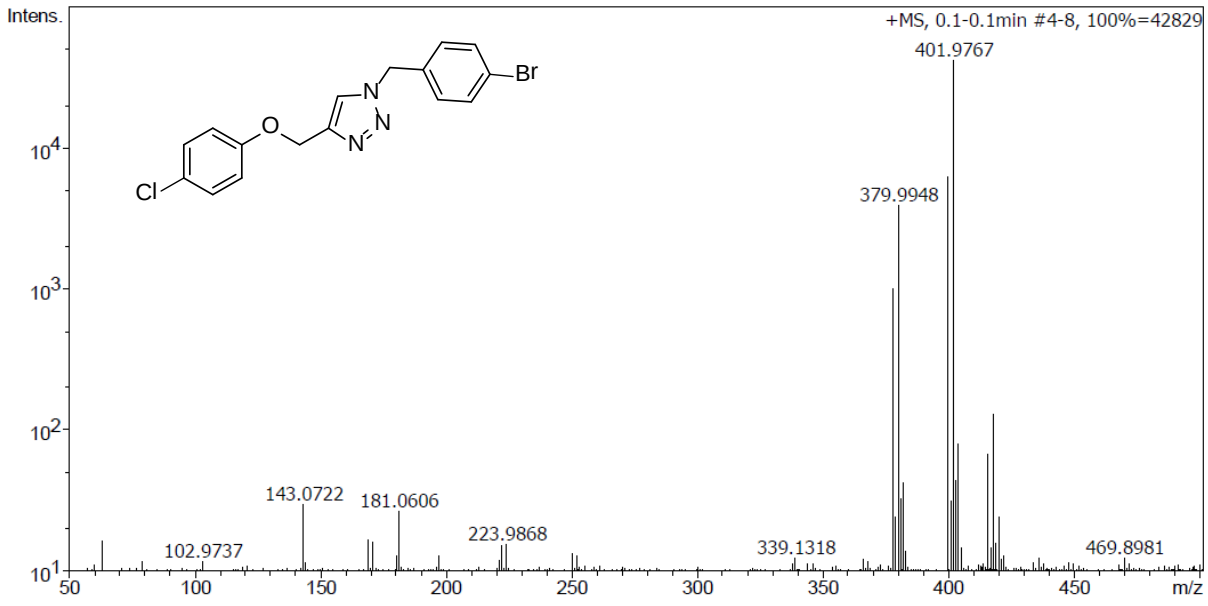
15d. ^{13}C NMR, 50 MHz, $CDCl_3$



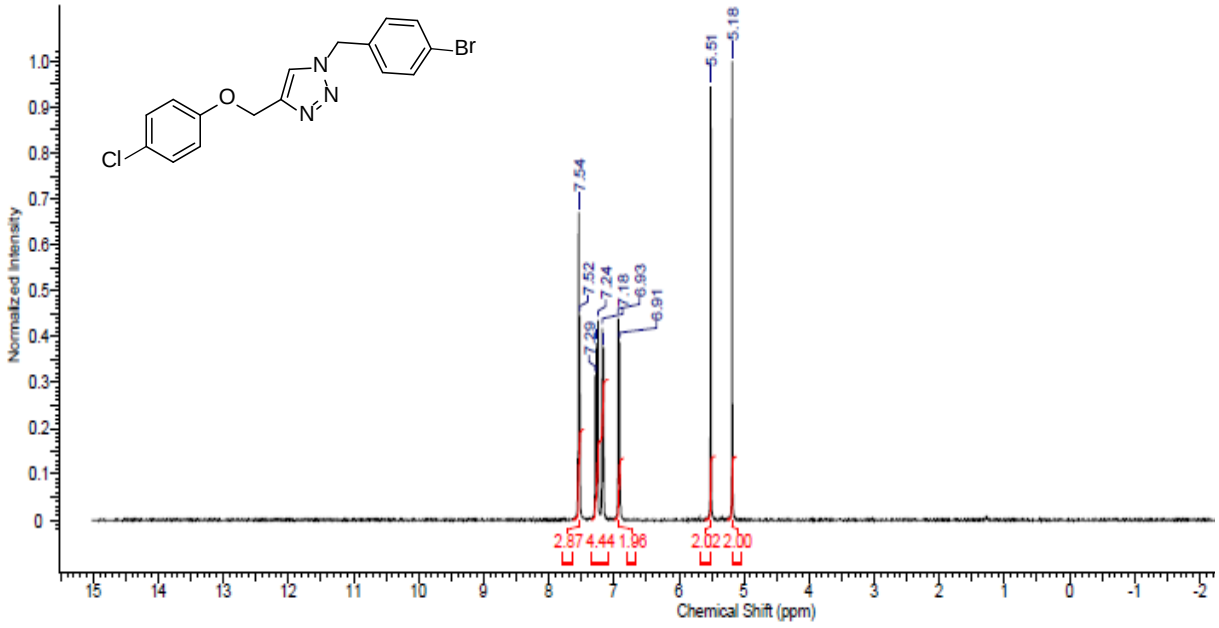
15d. DEPT, 50 MHz, $CDCl_3$



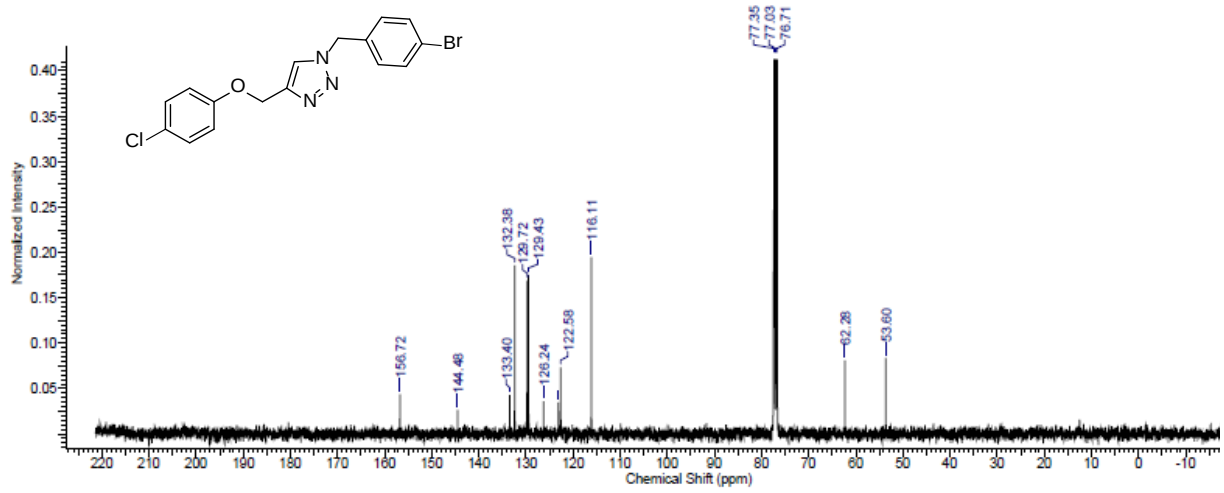
15e.HRMS



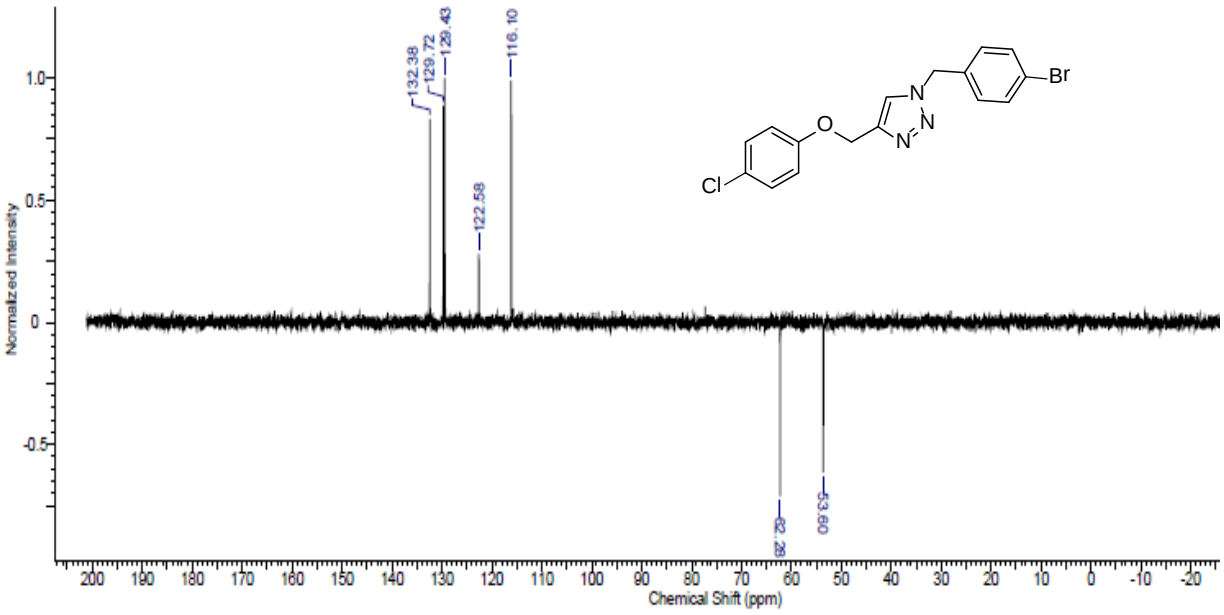
15e.^{1}H NMR, 400 MHz, $CDCl_3$



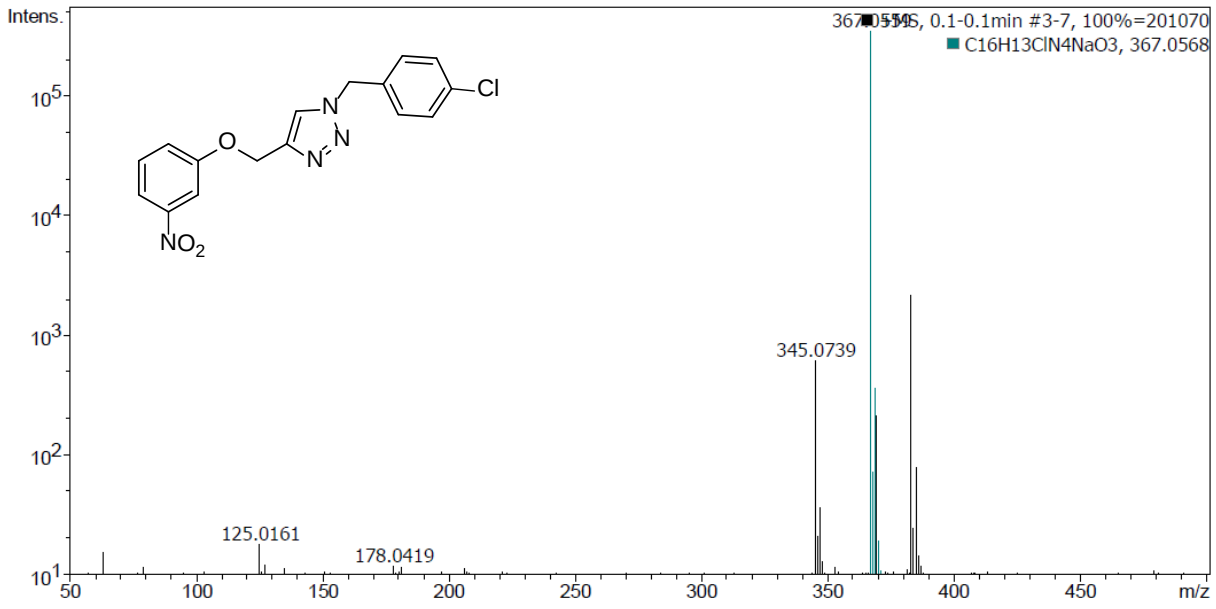
15e. ^{13}C NMR, 100 MHz, $CDCl_3$



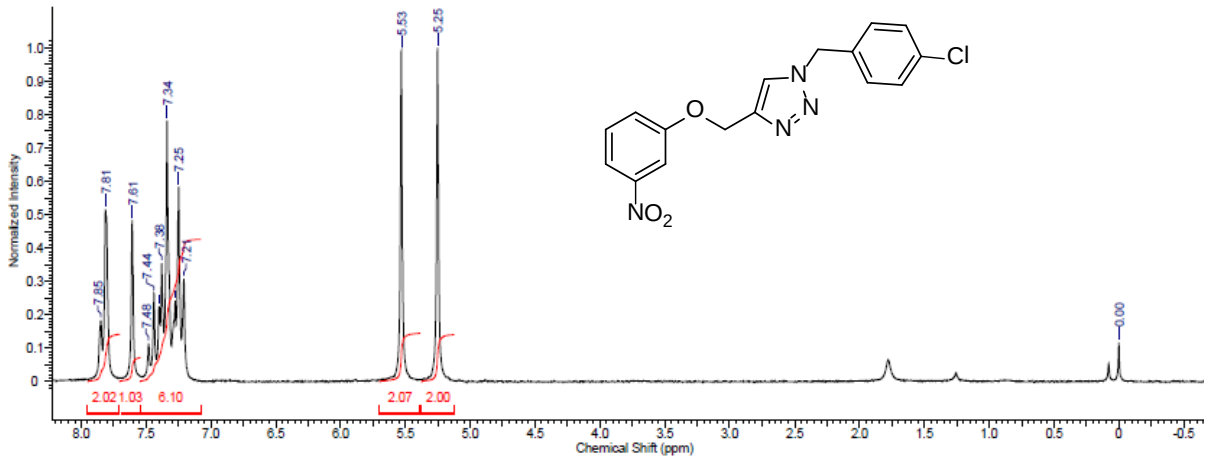
15e.DEPT, 100 MHz, $CDCl_3$



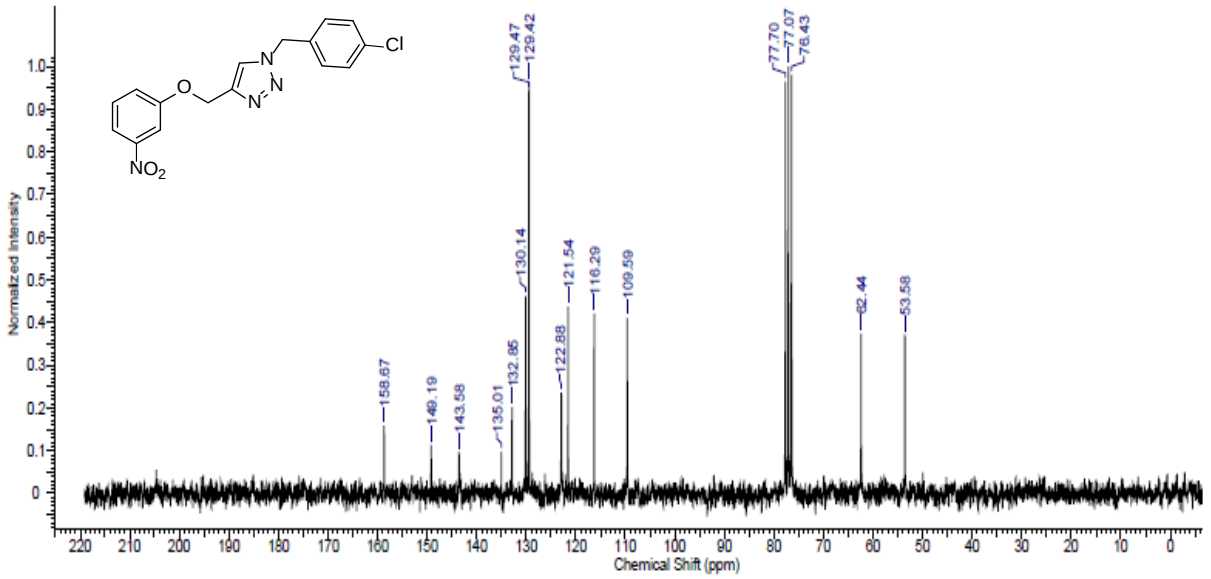
16c.HRMS



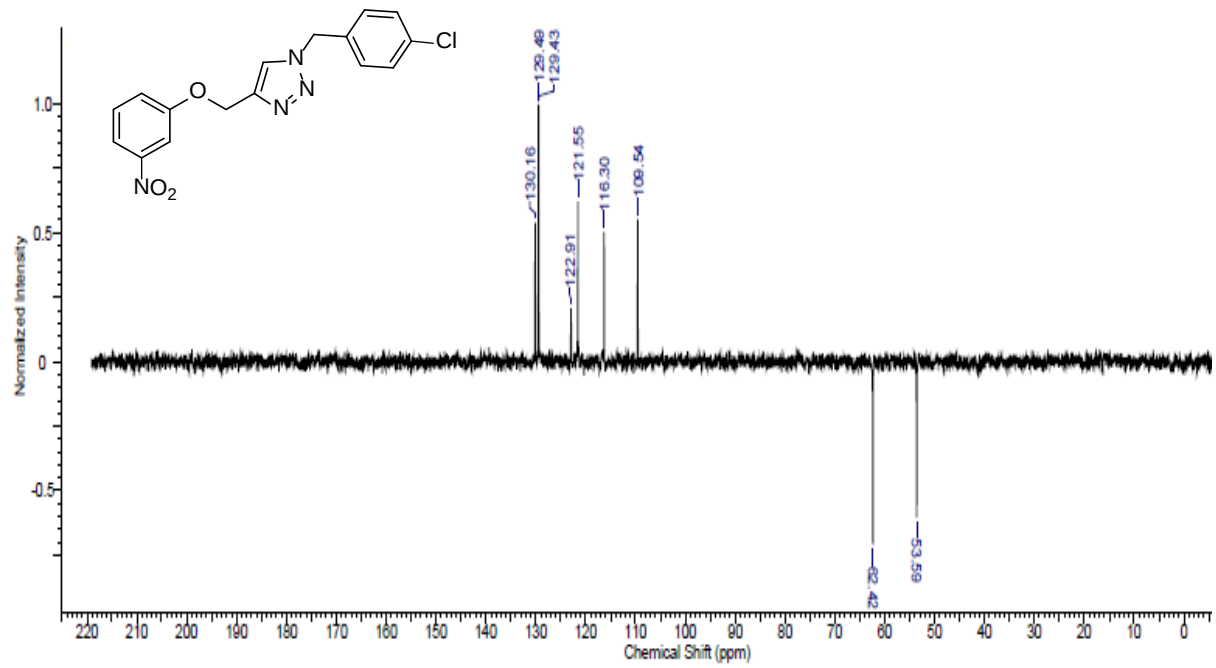
16c.^{1}H NMR, 200 MHz, $CDCl_3$



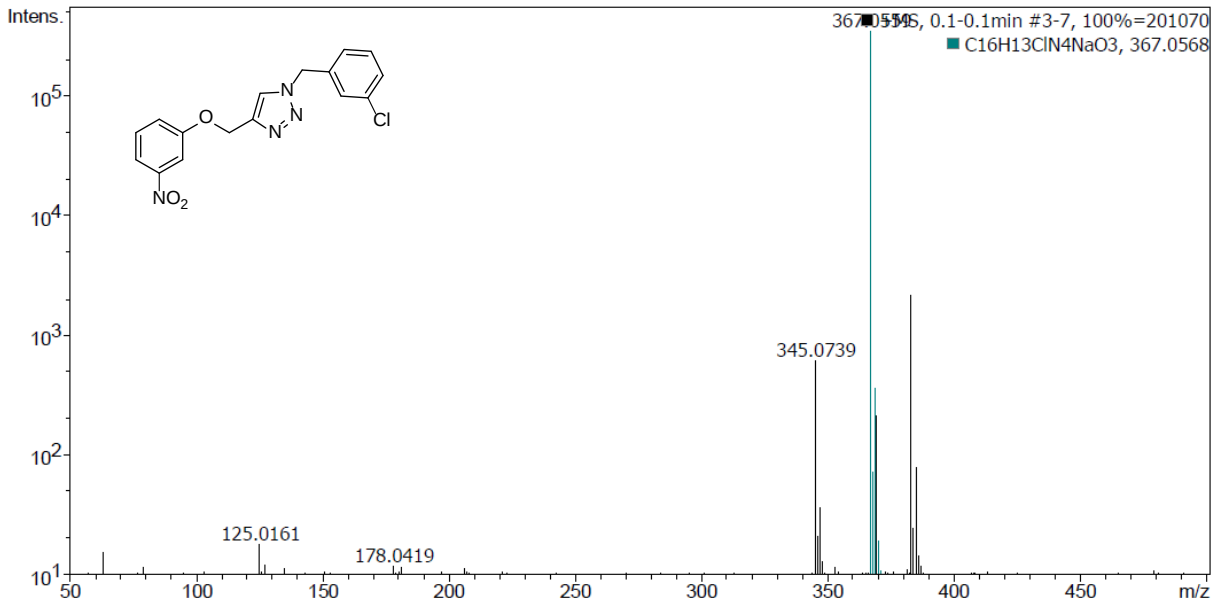
16c. ^{13}C NMR, 50 MHz, $CDCl_3$



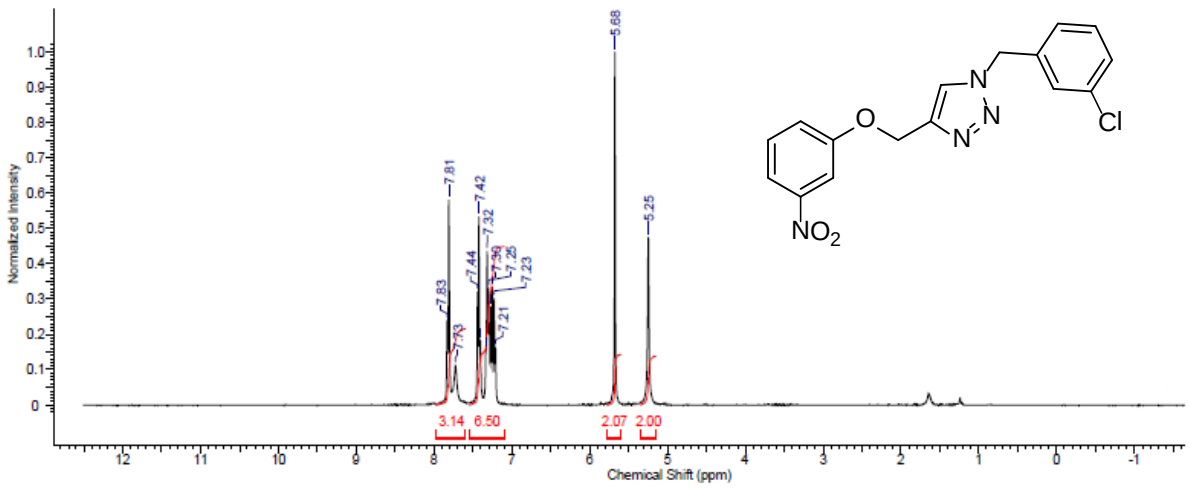
16c.DEPT, 50 MHz, $CDCl_3$



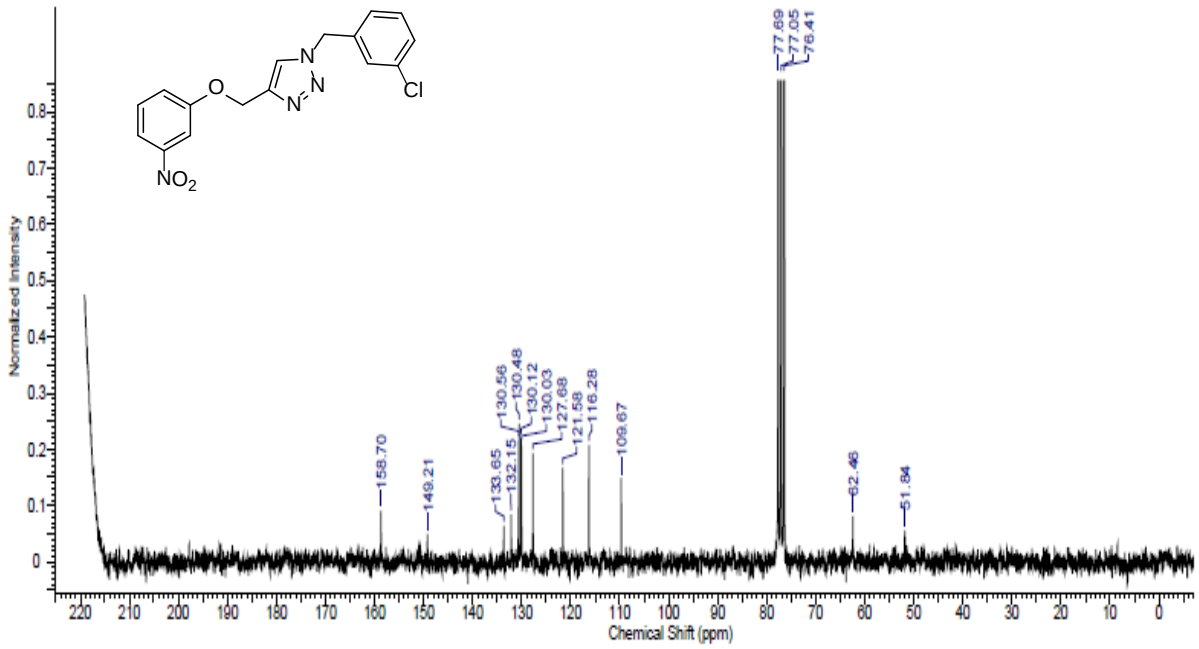
16d.HRMS



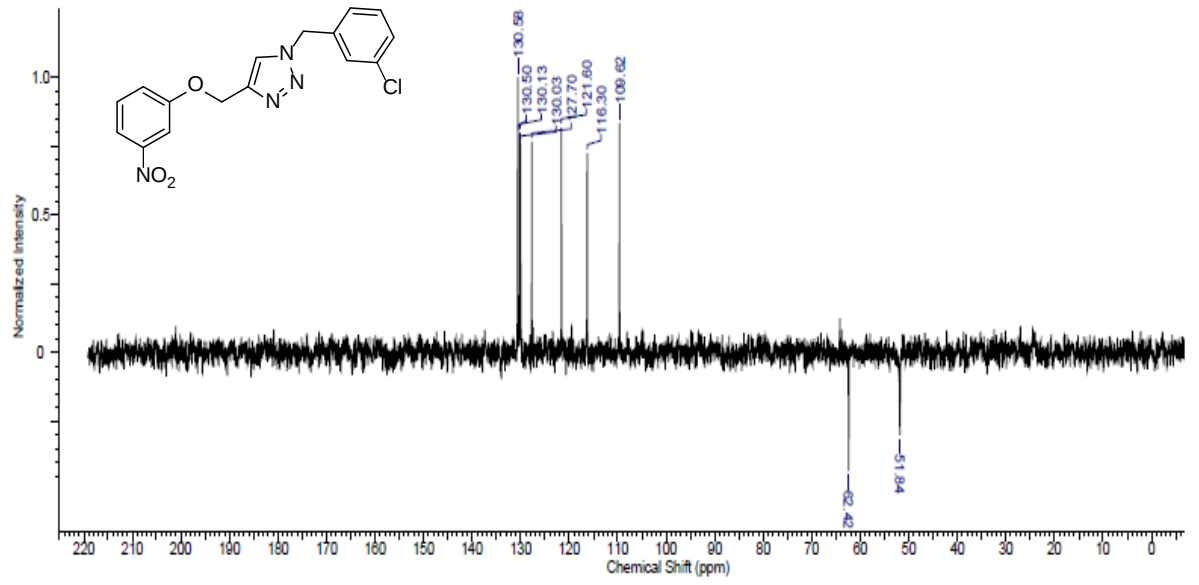
16d.^{1}H NMR, 200 MHz, $CDCl_3$



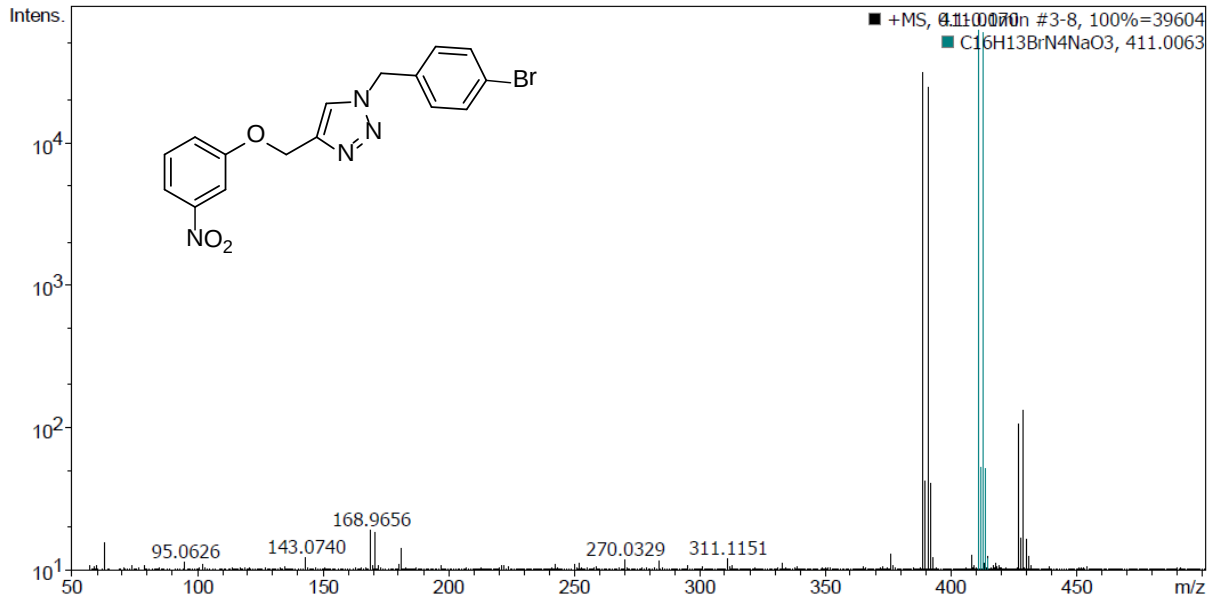
16d. ^{13}C NMR, 50 MHz, $CDCl_3$



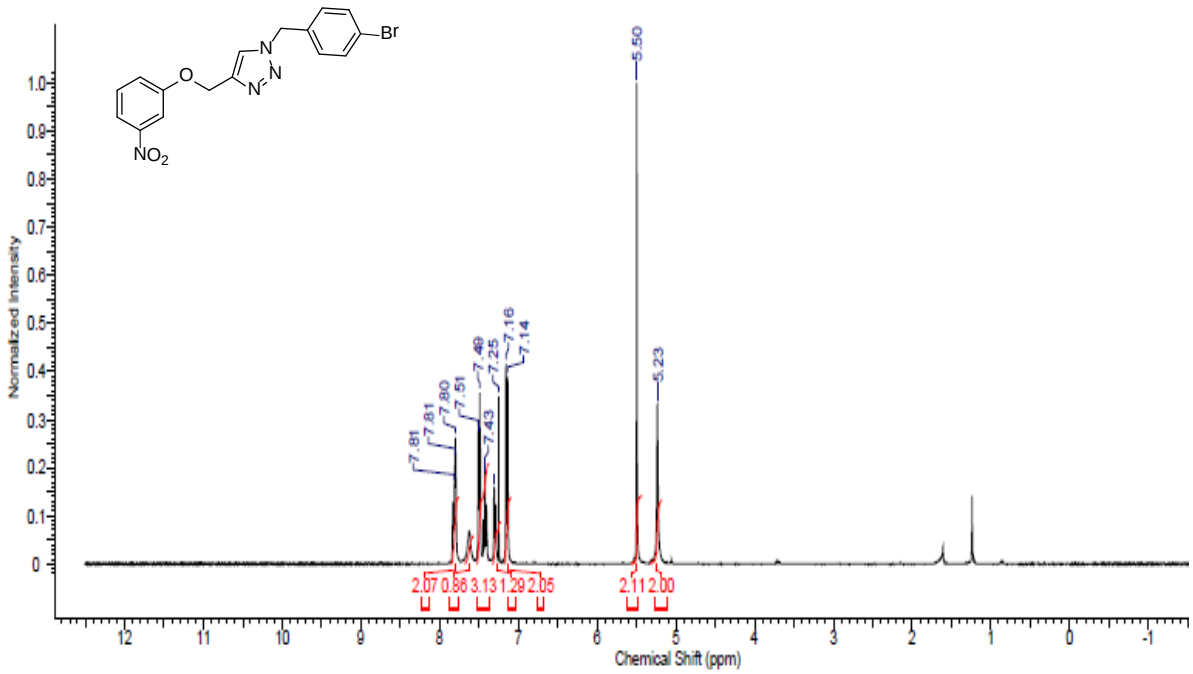
16d.DEPT, 50 MHz, $CDCl_3$



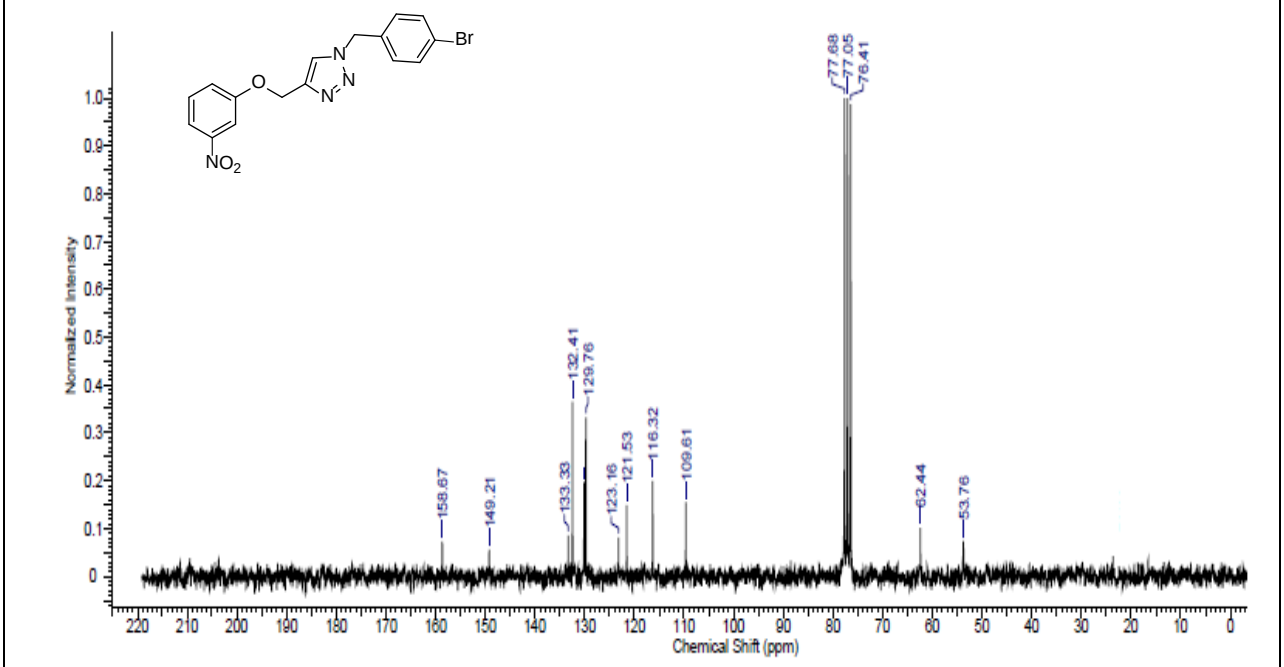
16e.HRMS



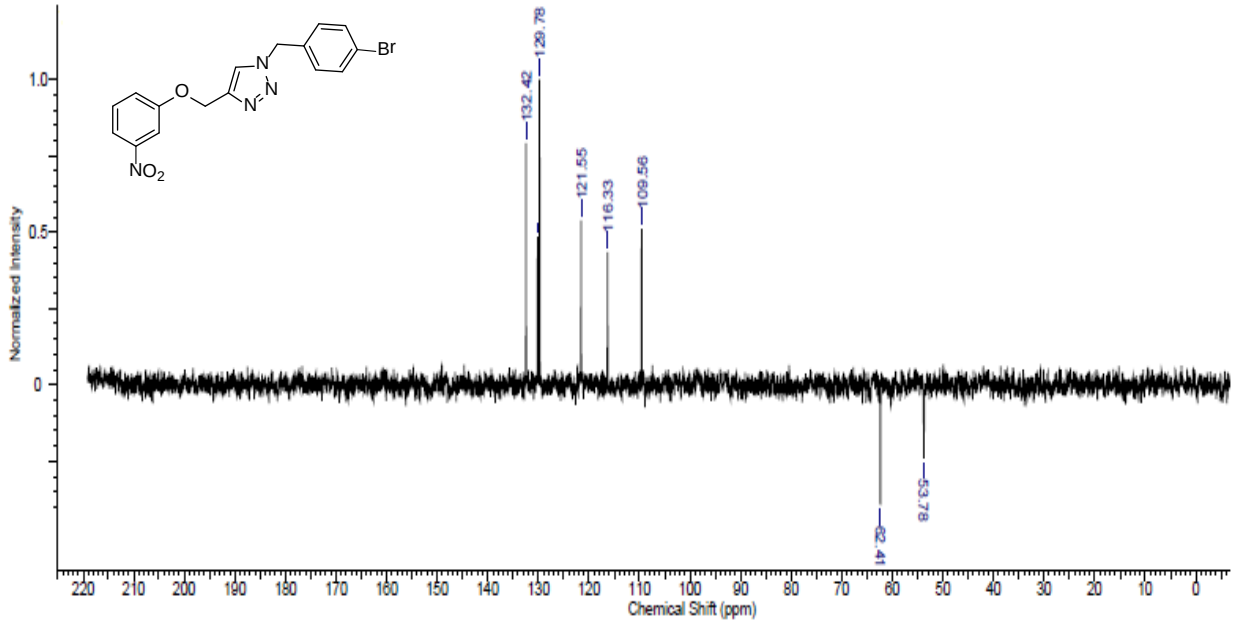
16e.^{1}H NMR, 400 MHz, $CDCl_3$



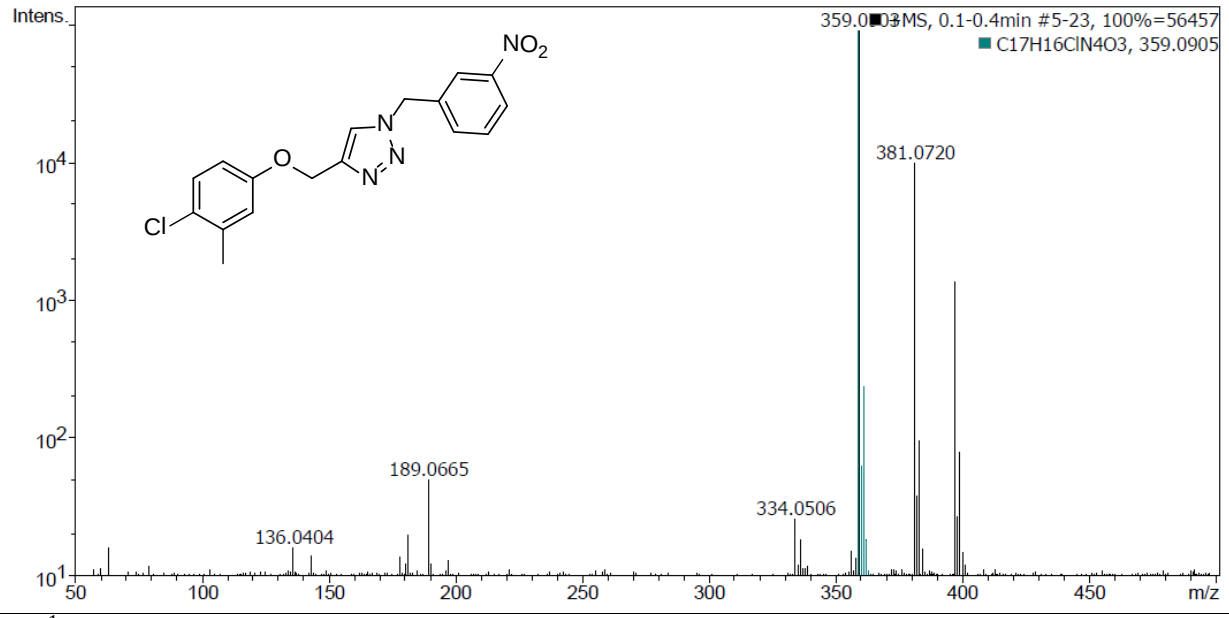
16e. ^{13}C NMR, 50 MHz, $CDCl_3$



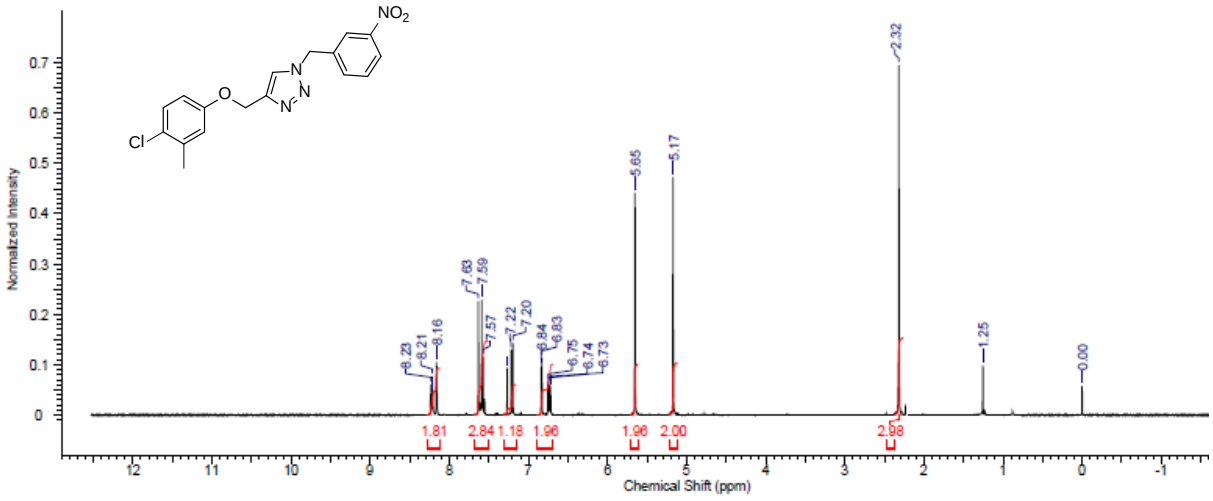
16e.DEPT, 50 MHz, $CDCl_3$



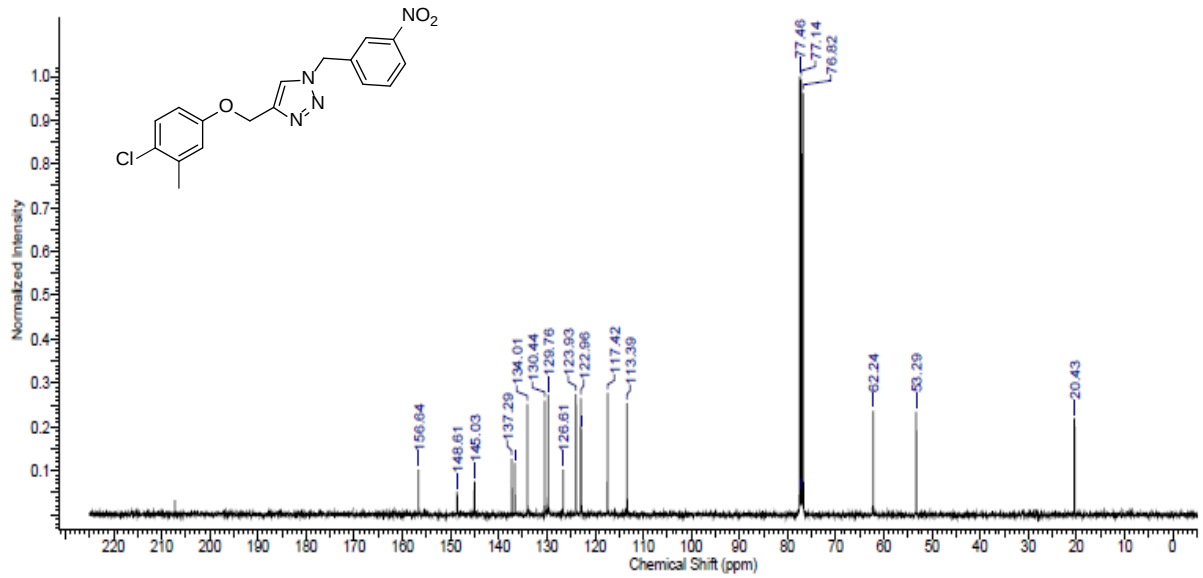
17b.HRMS



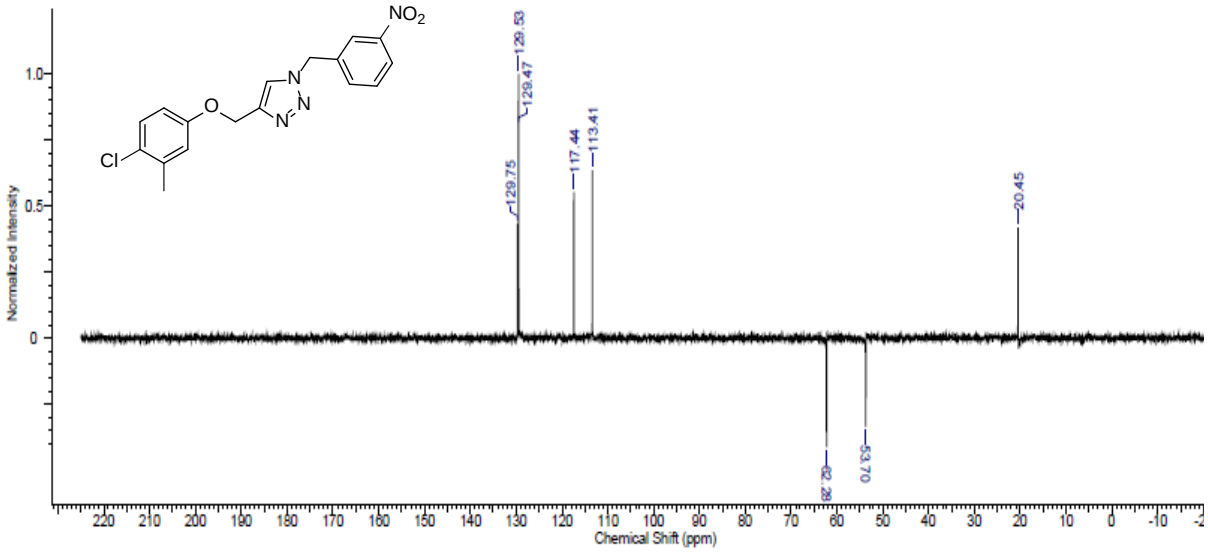
17b.^{1}H NMR, 200 MHz, $CDCl_3$



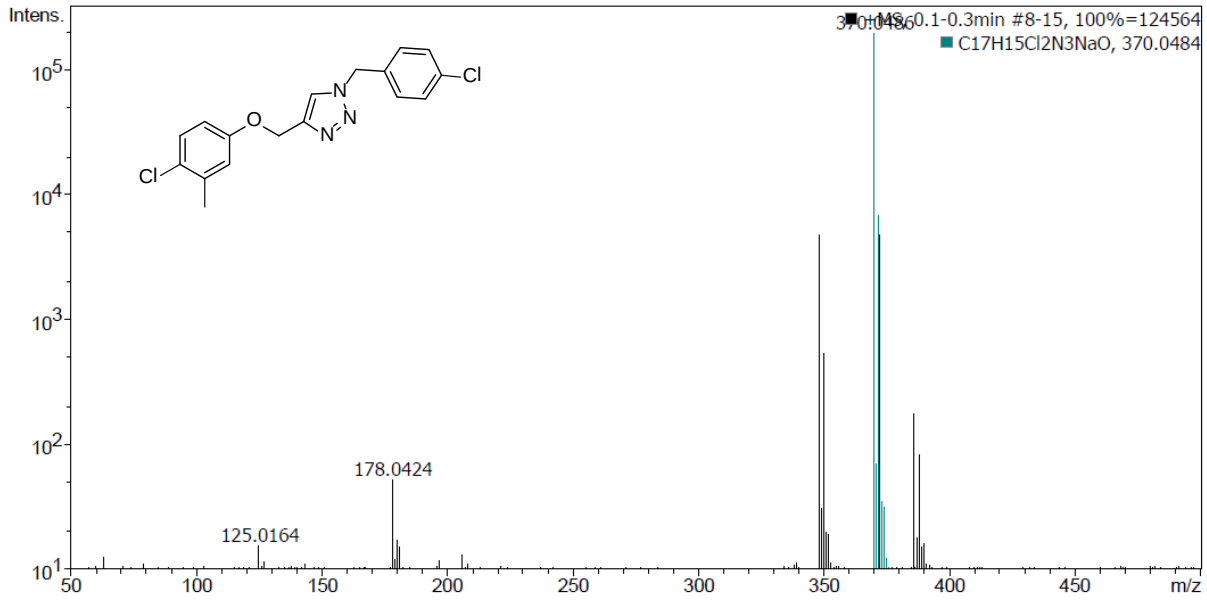
17b. ^{13}C NMR, 100 MHz, $CDCl_3$



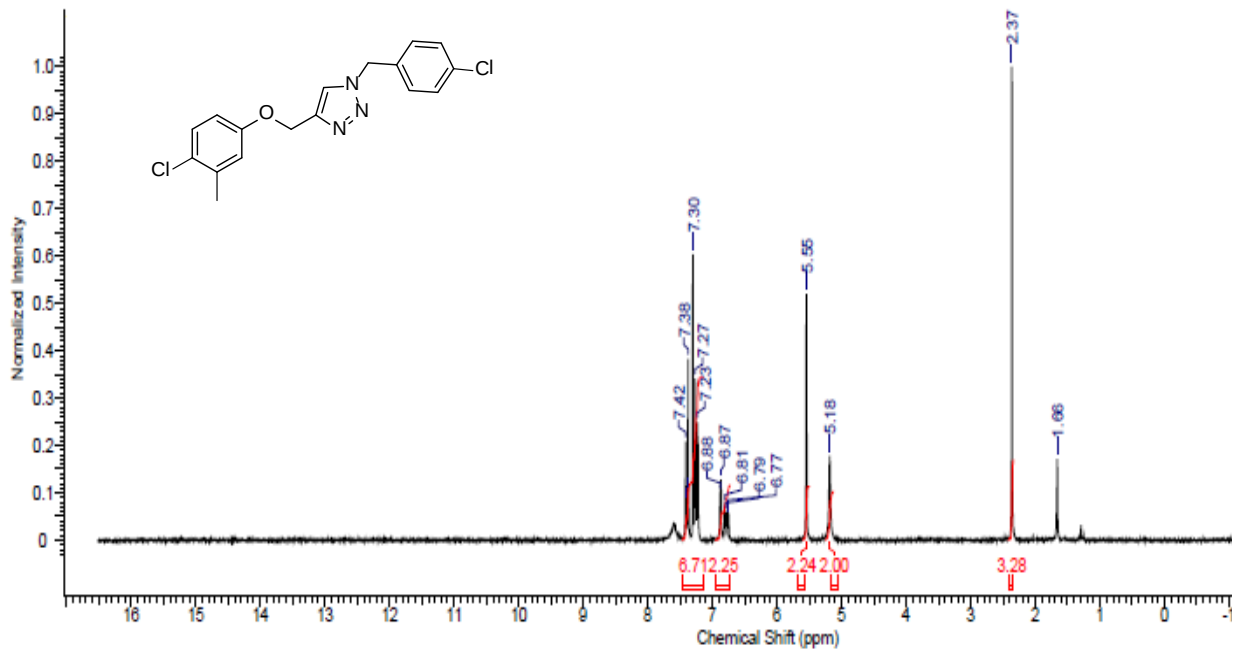
17b.DEPT, 100 MHz, $CDCl_3$



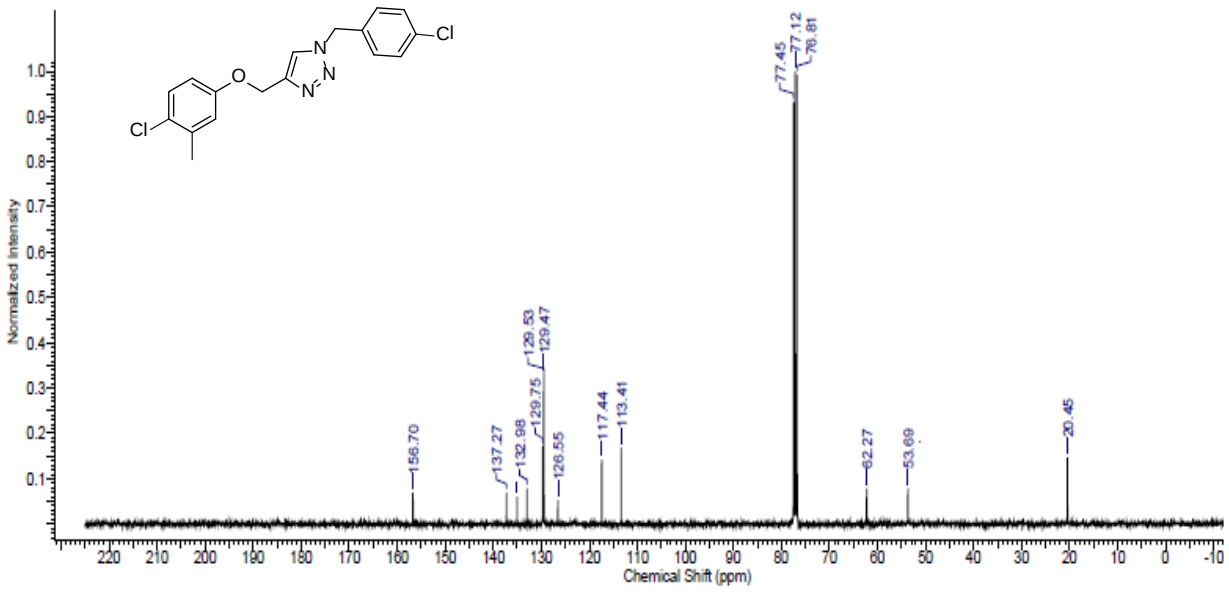
17c.HRMS



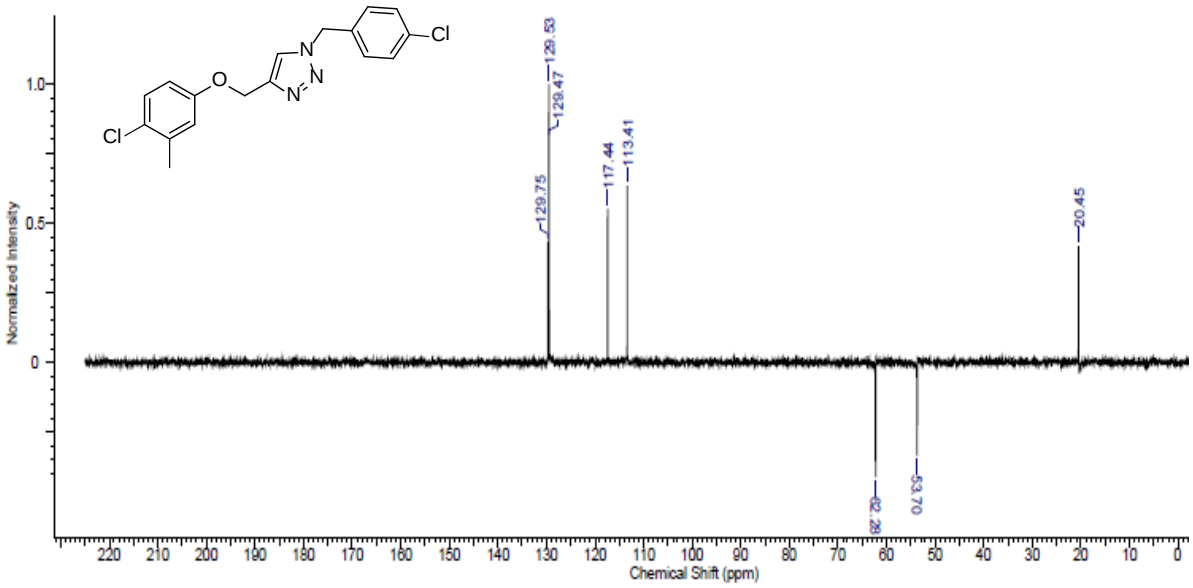
17c.^{1}H NMR, 200 MHz, $CDCl_3$



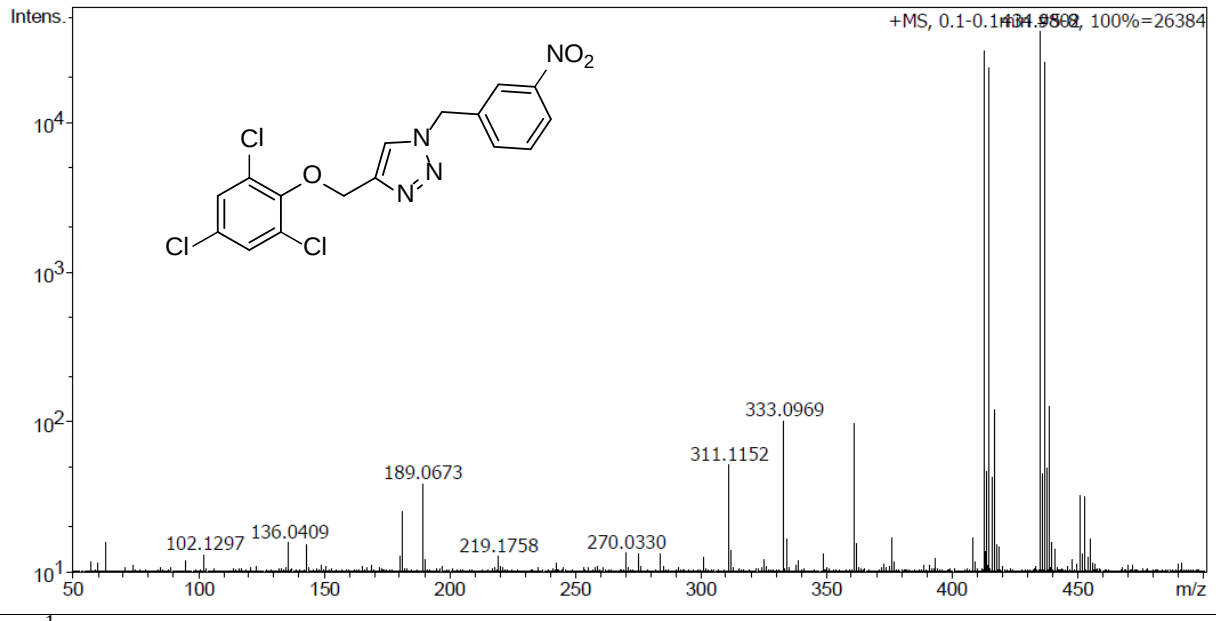
17c. ^{13}C NMR, 100 MHz, $CDCl_3$



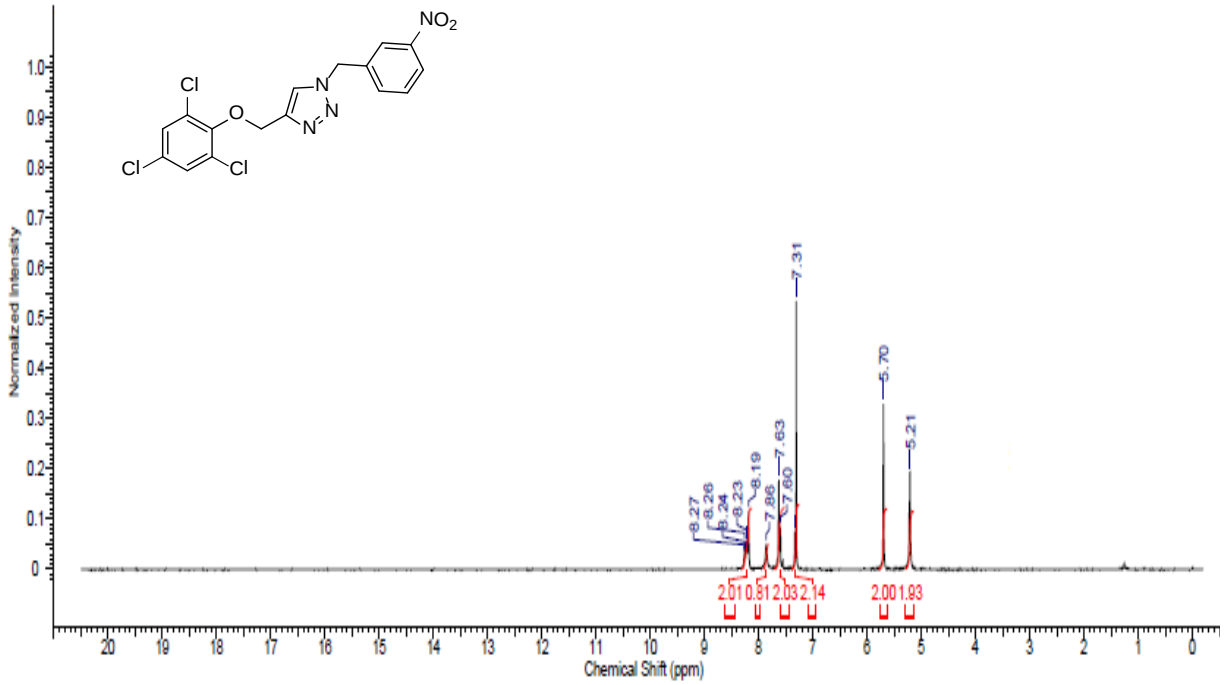
17c. DEPT, 100 MHz, $CDCl_3$



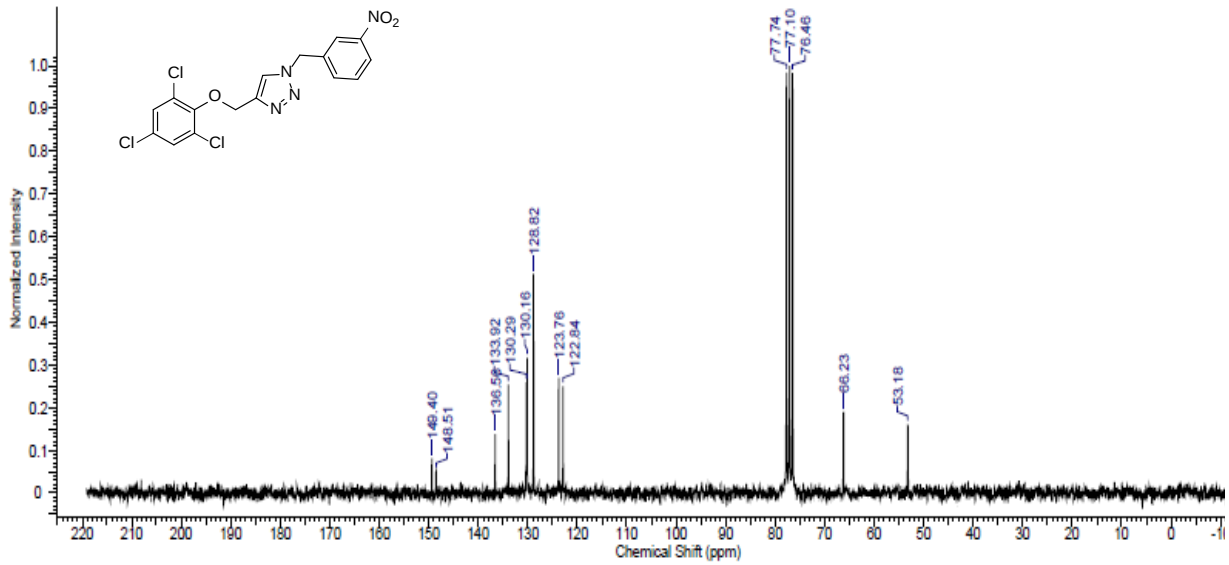
18b.HRMS



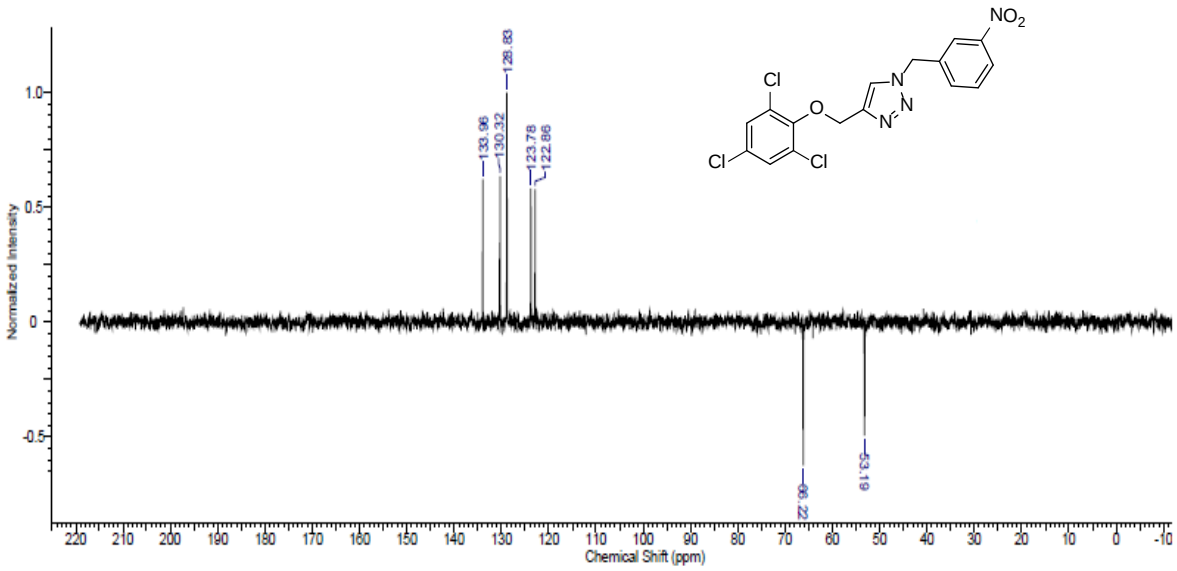
18b.^{1}H NMR, 200 MHz, $CDCl_3$



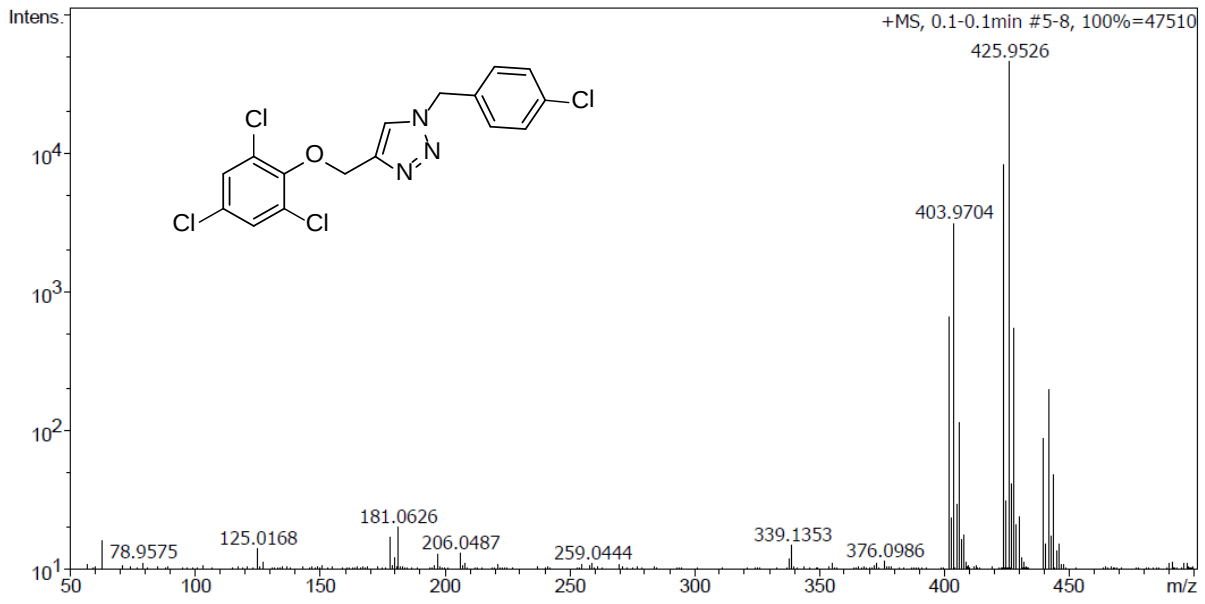
18b. ^{13}C NMR, 50 MHz, $CDCl_3$



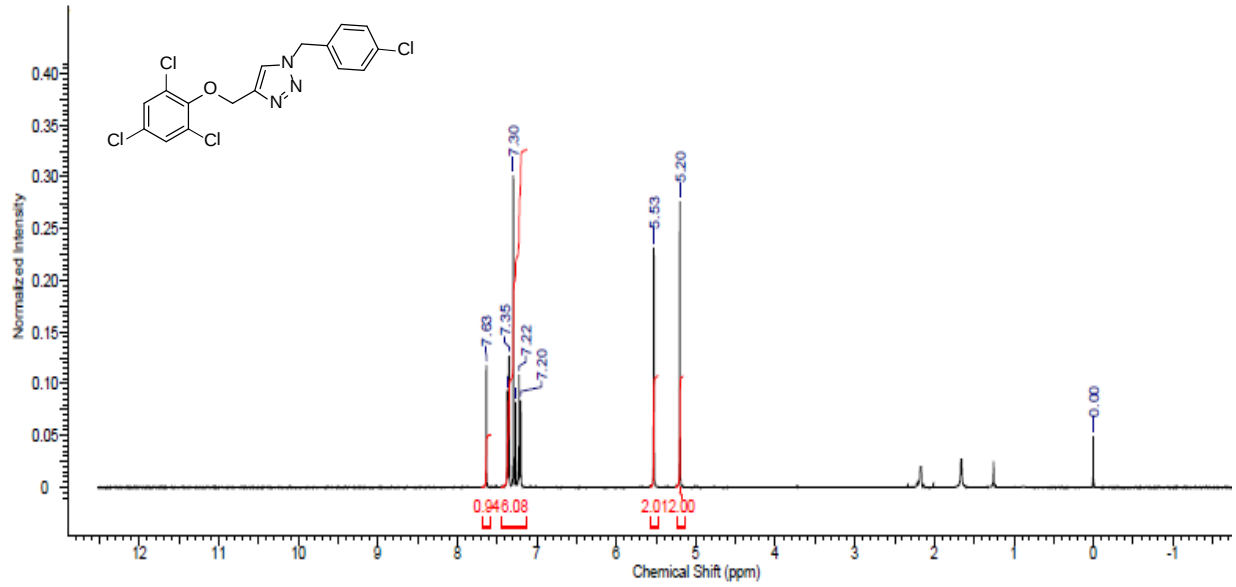
18b. DEPT, 50 MHz, $CDCl_3$



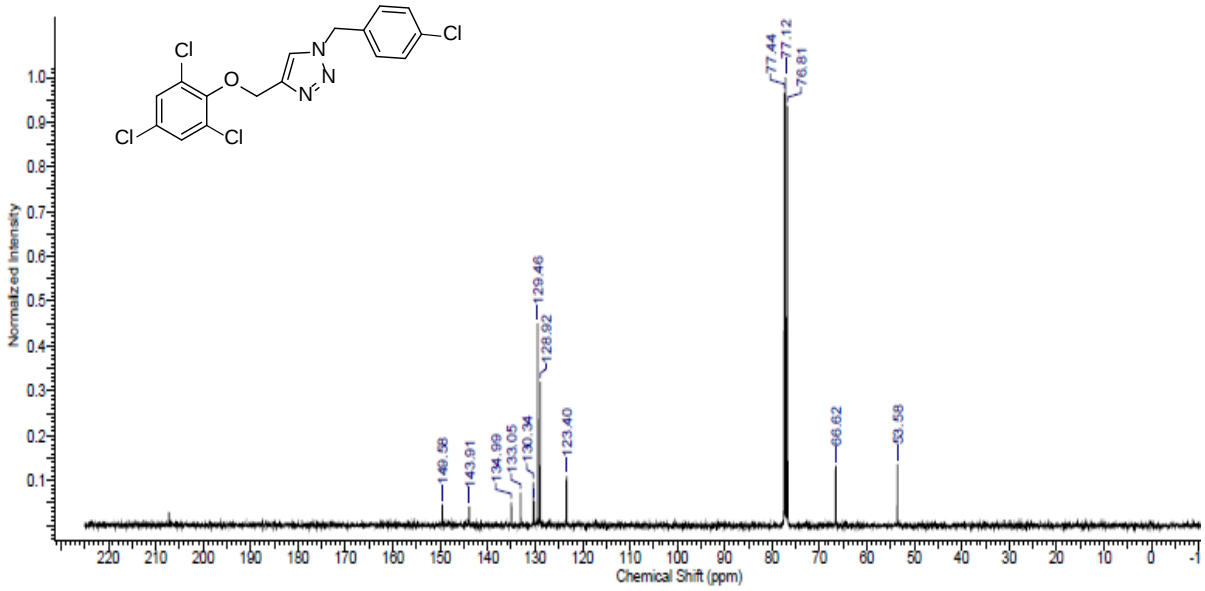
18c.HRMS



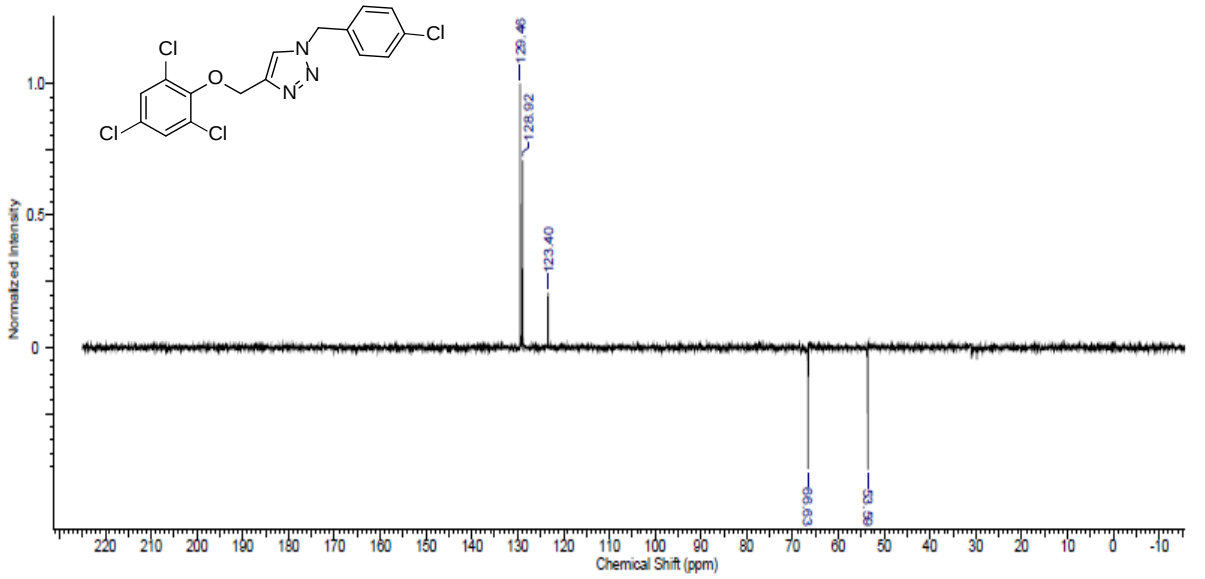
18c.^{1}H NMR, 400 MHz, $CDCl_3$



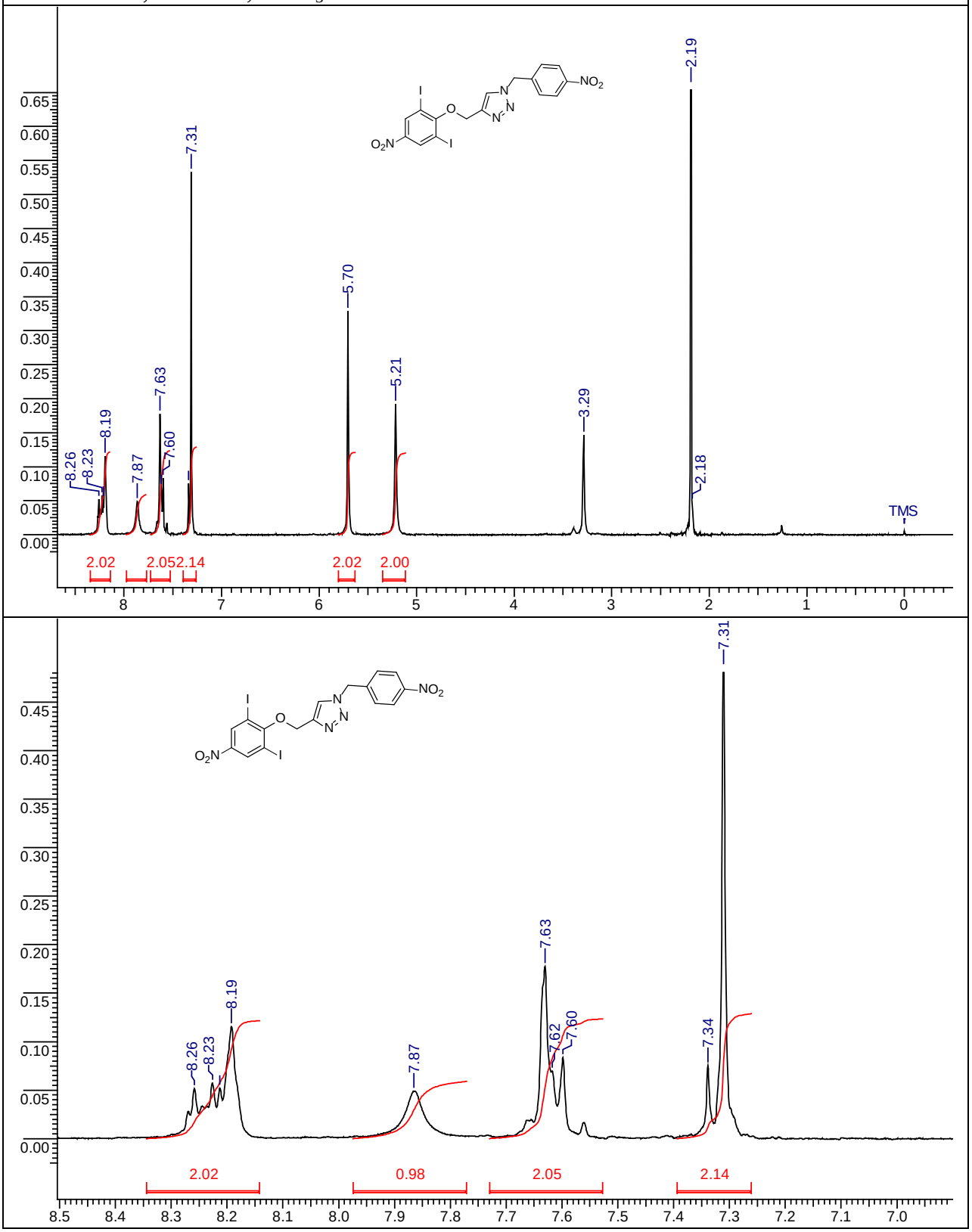
18c. ^{13}C NMR, 100 MHz, $CDCl_3$



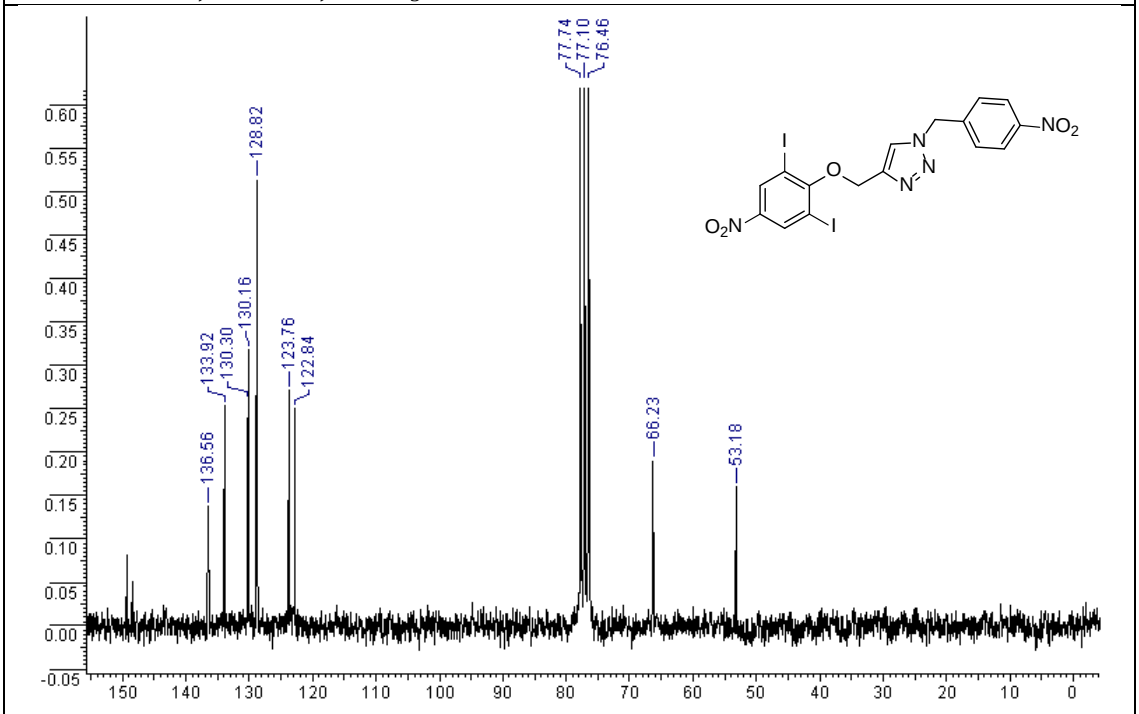
18c.DEPT, 100 MHz, $CDCl_3$



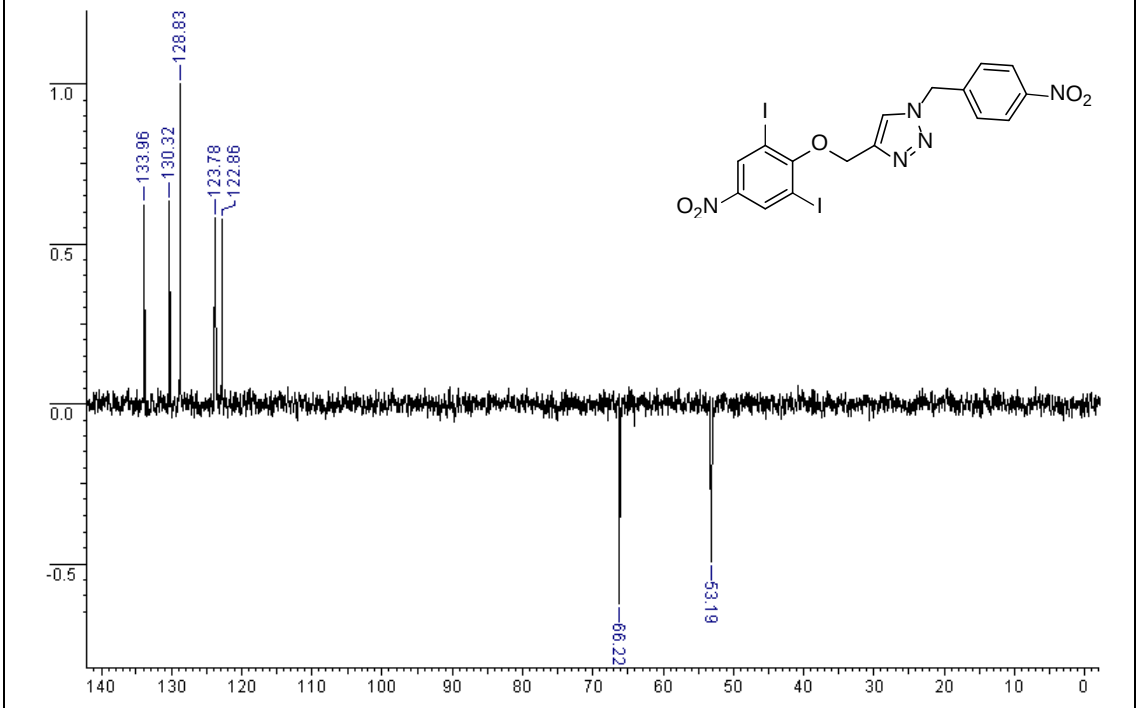
19a. ^{1}H NMR, 400 MHz, $CDCl_3$



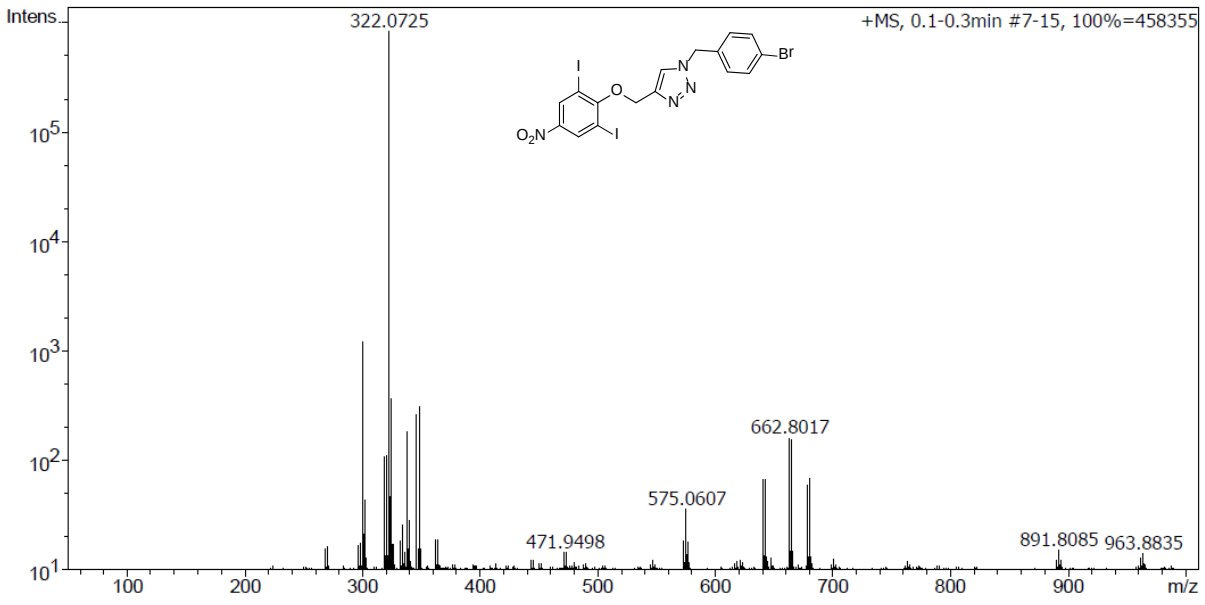
19a. ^{13}C NMR, 50 MHz, $CDCl_3$



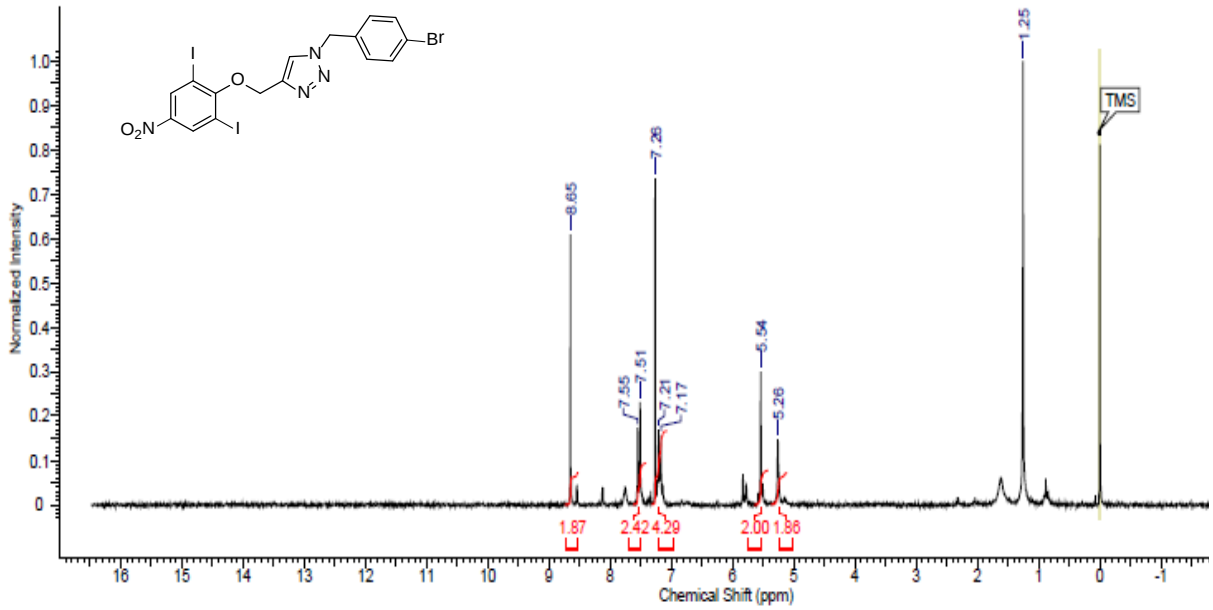
19a.DEPT, 50 MHz, $CDCl_3$



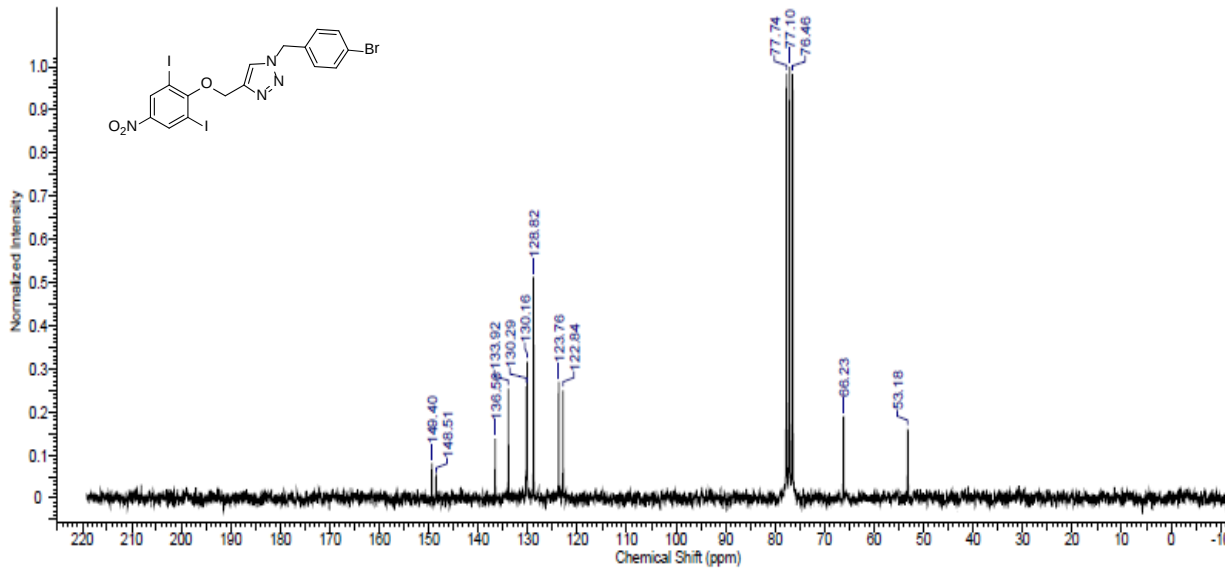
19b.HRMS



19b.^{1}H NMR, 400 MHz, $CDCl_3$



19b. ^{13}C NMR, 100 MHz, $CDCl_3$



19b. DEPT, 100 MHz, $CDCl_3$