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Novel alkoxy (1,2,3-triazole) benzaldehyde hybrids as antimicrobial agents, SAR studies

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ABSTRACT

A novel series of 2-alkoxy (1,2,3-triazole) benzaldehyde hybrids composed of Vanillin are synthesized for antimicrobial evaluation. Of antimicrobial strains tested, consisted of *Staphylococcus aureus* ATCC 43300 was treated as gram positive bacteria strain and *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Acinetobacter baumannii* ATCC 19606 *Pseudomonas aeruginosa* ATCC 27853 were evaluated as gram-positive bacteria *Candida albicans* ATCC 90028 (yeast) *Cryptococcus neoformans* var. grubii H99 ATCC 208821 yeast.

***Keywords*:** triazole, benzaldehyde hybrids, antimicrobial evaluation, *Escherichia coli*, *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Cryptococcus neoformans, Candida albicans, Vanilla planifolia*

1. INTRODUCTION

The Vanilla orchid (*Vanilla planifolia* Jacks. ex Andrews) grown primarily in southern America, is member of the Orchid family. Vanilla generally depends on the moisture available in the air to receive its nutrients, and the roots must connect with the ground for the plant to

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growth recently the search for Natural bioactive alike compounds has been increased for drug development. One such area of interest is anticancer drug development field. In the fight against cancer natural molecules have shown excellent pharmaco therapeutic potential [1-6]. Some compounds having phenolic structure have shown great antioxidant activities too [7, 8]. Considering the involvement of reactive species as a source of various types of cancer, diets and/or drug therapies involving bioactive substances with antioxidant activity may well represent a preventive treatment approach to maintain the well-being of the patient.

One of such compounds which have shown great exploitation for their cyto-toxicity is Vanilla. Vanilla is a natural occurring substance that has found use in varying field from pharmaceutical, nutritional and cosmetics. Vanilla is a plant secondary metabolite and one of the major constituent of vanilla. The structure consists of phenolic phenyl propane C6-C1 carbonic structure derivative. Vanilla finds its uses in processed foods, beverages and medicinal uses [8, 9]. Vanillin has antitumor potential [10] and the activity shown by the compounds are found to be promising by nature [11]. Vanillin is found to show radical scavengers property which leads to reduce chance of cancer promotion [12]. Herbs and plants consist of many active moieties which possess antimicrobial activities and are found to be potent against a wide range of bacteria, yeast and moulds [16]. Thus they provide a potentially rich source of novel biocides and preservatives. The antimicrobial activity of this naturally occurring compound are due to the low molecular weight phenolic compounds that forms the skeleton of the product [17]. Vanillin (4-hydroxy-3-methoxybenzaldehyde) is the major constituent of vanilla beans and is produced naturally via a multi-step curing process, it is synthetically produced (nature identical) from lignin, eugenol or guaiacol [18]. Vanillin has generally used as a flavoring / aroma compound in foods and fragrance industries. Synthetic vanillin is also used as an intermediate in the chemical and pharmaceutical industries for the synthesis of herbicides and drugs [19]. Recently, studies have shown that vanillin can act as an antioxidant [20]. Moreover, vanillin exhibits strong antimicrobial properties with activity demonstrated against a number of yeast and mould strains [21]. In order to use vanillin as commercial product there is a need to understand the mechanism behind vanillin metabolism for the improved activity. The mode of action of the antimicrobials classes are 1. (a) reaction with the cell membrane, (b) inactivation of essential enzymes, or (c) destruction or inactivation of genetic material (Davidson 1993). As Phenolic compounds are hydrophobic in nature and are therefore regarded as membrane active [22]. Recent mode of action studies using plant essential oils (oregano, thyme and tea tree) or some of their phenolic constituents (carvacrol, eugenol and thymol) against several pathogenic bacteria and yeasts have shown that their activity resides in their ability to perturb the cell membrane resulting in the loss of chemiosmotic control leading to cell death [23].

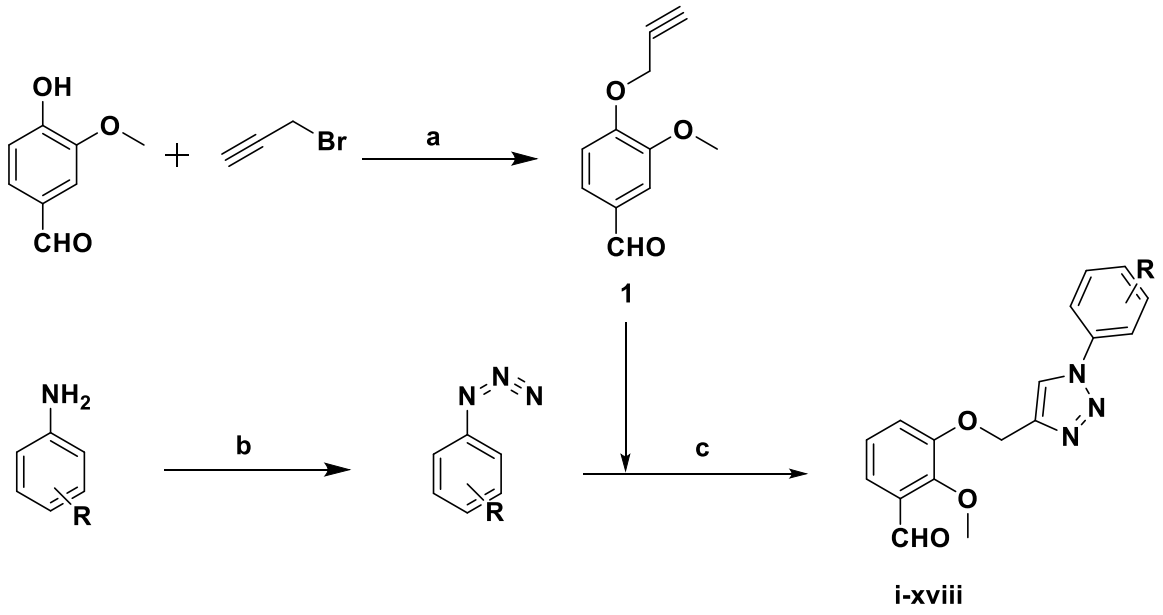
Synthesizing 1,2,3-triazoles using Cu(I) catalyst can be carried out in one pot. This adds a feather to the hat to click chemistry reaction. Fokin [24] first reported one pot synthesis of Triazole in 2004 directly from azide and terminal alkyne. He generated azide in situ from amine by using sodium azide. This method helped as isolating azide was not required. One Pot synthesis can be carried out by conventional heating or in microwave mode too. Erik Van der Eycken et al. [25] had reported microwave assisted synthesis of 1,2,3-triazole in 2004. In order to develop biologically important heterocycles, it is important to develop library of compounds of particular type. This library of compounds helps in further development of new moieties which can be subjected to biological evaluation. These library of compounds can be a part of database which helps in developing a proper SAR data. Our present work aims on this path to develop a facile protocol for the synthesis of 1,4-disubsituted triazoles from azides and alkynes.

2. RESULTS AND DISCUSSION

As previously discussed, Vanillin and 1,2,3-triazoles have significant part in medicinal chemistry. As a result fusing both the active species, we have developed two series of compounds, keeping vanillin derivatives as fixed base part. In order to synthesize the series, Vanillin was treated by propagyl bromide to produce compound 3-methoxy-4-(prop-2-ynyloxy)benzaldehyde (1) and 3-ethoxy-4-(prop-2-ynyloxy)benzaldehyde (2), the product (1) was then further subjected to react with various subsituted azide, these azides were synthesized in lab from respective anilines and were directly taken to further step by TLC confirmation.

The reaction between azide and (1) yield final compounds in high yield above 70%. The reagents that were used for the reaction were $CuSO_4 \cdot 5H_2O$ as catalyst, Sodium ascorbate as reductant.

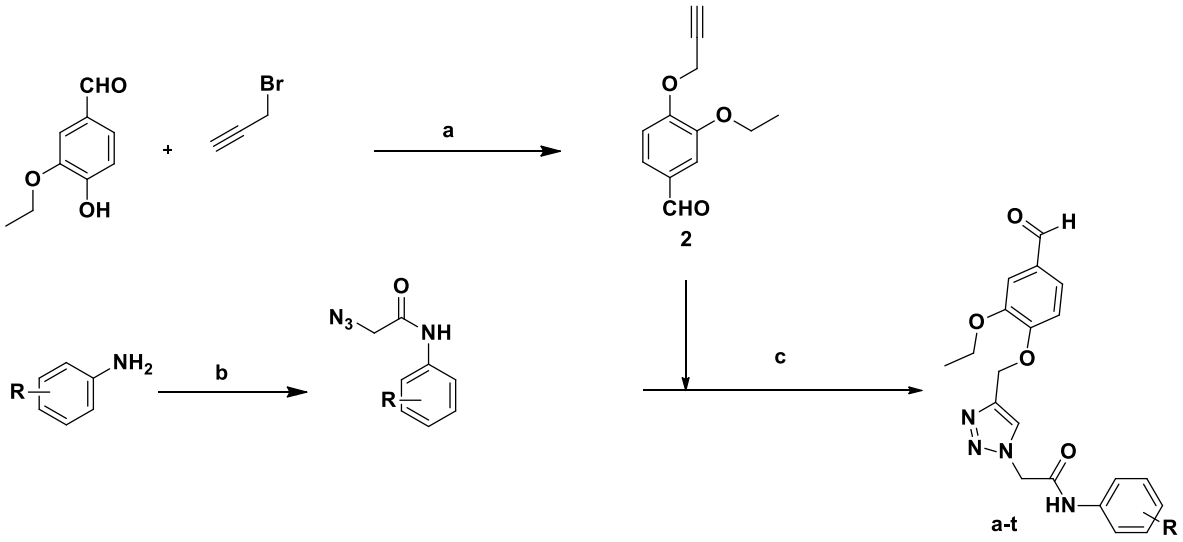
These combination of reagents was reached after thorough optimization of reagents by switching to different combination of copper source and temperature variations. The most notable change in the final reaction pathway was the time required as the reactivity of different azides were different. These compounds were further subjected for anti-microbial screening at CO-ADD Australia.



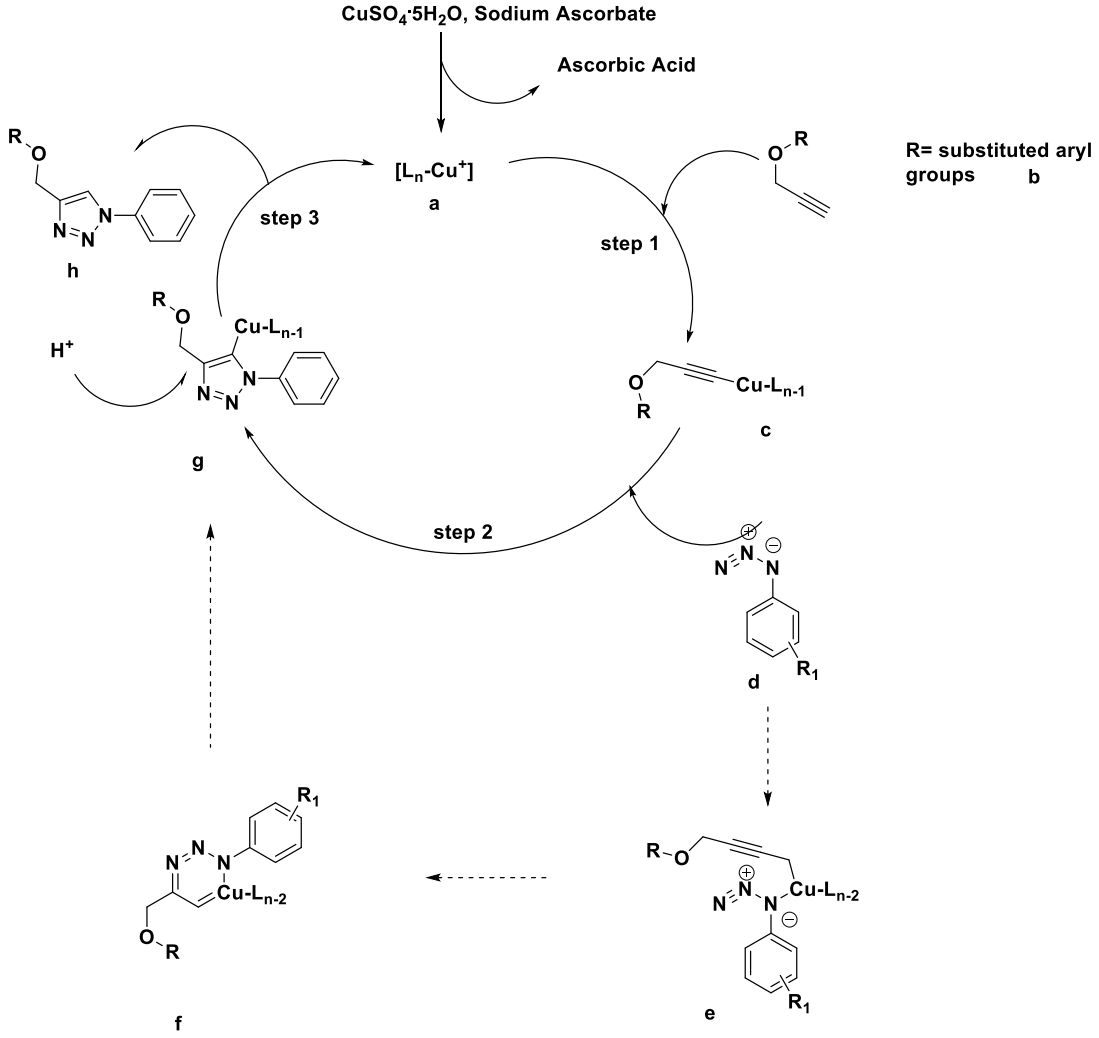
Scheme 1:- (a) $CsCO_3$,DMF, RT ; (b) $NaNO_3$,HCl, NaN_3; (c) Sodium Ascorbate, $CuSO_4$, DMF,BuOH, H_2O.

Based upon recent literature survey, the reaction mechanism of click chemistry, using sodium ascorbate and copper containing complex is shown in Scheme 11 above. The Cu(I) ion produced from $CuSO_4 \cdot 5H_2O$ by insitu reduction due to sodium ascorbate, reacts with the terminal alkynes b to form acteylide complex c.

This intermediate c immediately reacts with phenyl azides d, to form g by following the pathway shown above forming intermediate e, f. It follows [3+2] cycloaddition. The triazole ring is formed and it loses Cu(I) ion to give product h.



Scheme 2:- (a) CsCO3,DMF, RT ; (b) acetyl chloride, NaN3; (c) Sodium Ascorbate, CuSO4, DMF,BuOH, H2O.



Scheme 3: Reaction Mechanism

3. SAR AND ANTIMICROBIAL ACTIVITY

Final products were tested for their in vitro growth inhibitory activity against human pathogens. A series of microbial strain consisting of gram positive and gram negative bacteria culture was used to test the given set of compounds. Two yeast culture strains were also administered for the activity of synthesized compounds. Staphylococcus aureus ATCC 43300 was treated as gram positive bacteria strain and Escherichia coli ATCC 25922, Klebsiella pneumoniae ATCC 700603, Acinetobacter baumanii ATCC 19606 Pseudomonas aeruginosa ATCC 27853 were evaluated as gram-positive bacteria Candida albicans ATCC 90028 (yeast) Cryptococcus neoformans var. grubii H99 ATCC 208821 yeast were also tested. The observed antimicrobial data of the compounds and the reference drugs are given in Tables 1 and 2. In antibacterial studies the Inhibition of bacterial growth was determined measuring absorbance at 600 nm (OD600), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references.

Whereas while studying the yeast culture Growth inhibition of C. albicans was determined measuring absorbance at 530 nm (OD530), while the growth inhibition of C. neoformans was determined measuring the difference in absorbance between 600 and 570 nm (OD600-570), after the addition of resazurin (-0.001% final concentration) and incubation at 35 °C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references.

The inhibition is calculated on percentage growth inhibition and the individual sample that is being subjected to study is analyzed on the basis of media only and control drug injected strains. Percentage growth inhibition of an individual sample is calculated based on Negative controls (media only) and Positive Controls (bacterial/fungal media without inhibitors). Please note negative inhibition values indicate that the growth rate (or OD600) is higher compared to the Negative Control (Bacteria/fungi only, set to 0% inhibition). The growth rates for all bacteria and fungi has a variation of -/+ 10%, which is within the reported normal distribution of bacterial/fungal growth. Any significant variation (or outliers/hits) is identified by the modified Z-Score, and actives are selected by a combination of inhibition value and Z-Score.

The activity of an individual test compound was calculated on the growth inhibition rate and Z-score ratio. Some compounds showed less growth inhibition but had better Z-score ratio whereas some other compounds showed acceptable growth inhibition with less Z-score ratio. Such compounds were deemed to be inactive. For an test compound to be potent it was needed that it showed good figures in growth inhibition and Z-score criteria. Z-Score analysis is done to investigate outliers or hits among the samples. The Z-Score is calculated based on the sample population using a modified Z-Score method which accounts for possible skewed sample population. The modified method uses median and MAD (median average derviation) instead of average and sd, and a scaling factor [Iglewicz, B. & Hoaglin, D. C. Volume 16: How to Detect and Handle Outliers. The ASQC Basic Reference in Quality Control: Statistical Techniques, 1993]: $M(i) = 0.6745 * (x(i) - \text{median}(x))/MAD$. M(i) values of > |2.5| (absolute) label outliers or hits. All screening is performed as two replica (n=2), with both replicas on different assay plates, but from single plating and performed in a single screening experiment (microbial incubation). Each individual value is reported in the table (see ..1 and ..2). In

addition, two values are used as quality controls for individual plates: Z'-Factor [1 - (3 * (sd(NegCtrl) + sd(PosCtrl))/(average(PosCtrl) – average(NegCtrl)))] and Standard Antibiotic controls at different concentrations (>MIC and < MIC). The plate passes the quality control if Z'-Factor >0.4 and Standards are active and inactive at highest and lowest concentrations, respectively. Data not supplied. When the synthesized compounds were compared they were found to show less potency. But when a detailed structure activity relationship data was develop a peculiar information was constructed. The Z-score exhibited an interesting data about the compounds SAR and which can be further used for improvement of the series. The first series consisting of methoxy analogue of vanillin 2-methoxy-4-((1-subs-1H-1,2,3-triazol-4-yl)oxy)Benzaldehyde didnt showed any good result under Z-score category. But the compound xiii, xviii, viii, xvi, xix, showed decent Z-score. When these compounds were compared to the second series of ethoxy analogue counterpart it was found the Z-score improved significantly. The compounds of second series a, b, d, e, g, h, i, j, k, l, m, n, o, p, q, s, t. we're showing significant Z-score but the inhibition growth was showing non active to toxic level readings.

Table 1. Data of compound exhibiting Z-score

Acinetobacter baumannii				*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*	
A	3.77	b	3.28	a	2.16		
	2.92	e	2.81	b	2.33	b	2.88
D	2.76		2.57	l	3.25		
	2.36	g	2.7	o	2.56		
H	2.39	i	2.54	s	2.26		
	2.42	k	3.58		2.21		
J	2.71		3.23	xvii	2.38		
L	4.00	m	2.32				
	2.40	n	3.03				
O	3.28		2.44				
Q	3.11	p	2.51				
	2.55	s	3.23				
T	3.13		2.20				
	2.67	xiv	3.20				
Xviii	2.90	viii	2.48				
	2.87	xiii	3.33				

Table 2. Data of compound exhibiting inhibition growth.

Name	Sa	Ec	Kp	Pa	Ab	Ca	Cn
B	0.65	-3.37	-10.51	9.3	-21.69	2.57	-23.7
C	8.3	4.4	-17.74	13	-10.88	5.79	-7.7
D	24.26	-3.62	0.03	15.67	-34.01	26.4	-29.82
E	21.09	-6.11	14.68	18.85	-34.62	8.8	-35.2
F	22.87	0.02	16.81	21.09	-29.18	5.56	-37.21
G	19.29	-1.29	21.14	14.84	-30.87	28.32	-34.05
H	15.75	-1.16	16.02	18.6	-29.32	7.34	-34.62
I	18.91	-1.23	15.37	16.55	-30.74	5.91	-38.07
J	16.5	-3.95	5.76	17.5	-28.2	3.29	-39.79
K	7.71	0.34	-19.77	23.19	-24.51	6.07	-5.92
L	9.38	-2.1	-25.75	18.66	-16.94	5.6	-2.96
M	17.41	1.46	4.51	12.66	-28.45	2.9	-35.48
N	5.53	-5.46	-20.19	18.61	-17.24	4.85	-10.37
O	10.12	-5.49	8.34	8.34	-40.62	10.14	-33.18
P	18.11	-1.93	-9.6	17.63	-30.84	7.65	5.33
Q	20.33	-5.14	-2.69	14.53	-27.2	2.9	-15.41
R	12.68	-4.5	-2.07	18.96	-25.95	8.39	-19.1
S	4.17	-2.54	-20.98	18.3	-15.1	3.54	-5.33
T	15.36	-7.73	15.13	16.37	-38.74	10.21	-28.01
Ii	1	14.19	10.23	6.61	12.16	0.31	-114.02
Iv	10.92	2.92	7.03	18.01	1.05	5.8	-44.49
Vi	7.56	15.21	4.52	20.77	-14.34	5.17	-72.53
Vii	-1.71	3.07	-1.65	8.81	-1.96	2.95	-123.52
Viii	-2.68	-6.95	-1.71	6.07	-12.26	-2.67	-81.62
Ix	-4.23	6.66	13.41	17.37	45.51	0.1	-91.07

Xiii	11.38	6.37	-7.23	15.58	-25.74	5.45	-9.24
Xiv	1.25	13.81	-3.34	9.2	-22.5	-0.24	-57.7
Xv	6.02	-5.37	10.27	11.67	3.29	0.45	-131.84
Xvi	9.48	20.54	9.48	13.28	17.8	3.36	-72.71
Xvii	4.38	2.69	-4.66	15.34	-11.82	20.18	-73.92
Xviii	0.88	-12.37	7.25	4.47	-25.18	5.68	-83.42

4. EXPERIMENTAL SECTION

Procedure for one pot synthesis of 3-methoxy-4-(prop-2-ynyloxy)benzaldehyde (1) / 3-ethoxy-4-(prop-2-ynyloxy) benzaldehyde (2)

To a solution of Vanillin / 3-ethoxy Vanillin (3 mmol, 1 equiv.) in DMF solvent, add CsCO3 (3 mmol, 1 equiv.) and propargyl bromide (3.6 mmol, 1.2 equiv.) drop wise and stir the resulting mixture for 2 hours at room temperature. Progress of the reaction was monitored by TLC.After completion of reaction, reaction mass was poured into crushed ice.Desired solid product (1) / (2) falls out, which can be isolated by vacuum filtration and washed well with water. No any purification techniques required white solid.

Procedure for one pot synthesis of 3-methoxy-4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (i)

In a clean and dry bottom flask 1-azido-4-nitrobenzene (2 mmol, 1 equiv.) and 3-methoxy-4-(prop-2-ynyloxy)benzaldehyde (2 mmol, 1 equiv.) were charged in appropriate amount and then DMF+t-BuOH+H_2O (2:1:2, v/v, 5 ml) were added and stirred for few minutes. Followed by sequential addition of sodium ascorbate (2 mmol, 1 equiv.) and $CuSO_4 \cdot 5H_2O$ (0.2 equiv.) into it to initiate the chemical reaction. The resulting mixture was then stirred for 12 hours at room temperature. Progress of the reaction was monitored by TLC. The reaction was worked up by dilution of the contents with water and extraction with ethyl acetate (5 times). The combined ethyl acetate was washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure on a rotavapor to get desired product without chromatographic purification techniques. (Remaining final compounds i-xviii and a-t were synthesized in the same manner)

5. SUPPLEMENTARY DATA

3-methoxy-4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (i)

Yellowish white solid, Yield: 92 %, m/z: 354 M.P. 199 °C ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.87 (s, 1H) 9.22 (s, 1H) 8.26-8.47 (m, 4H) 7.43-7.59 (d, 3H) 5.40 (s, 2H) 3.83 (s, 3H,). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 190.67, 152.60, 149.28, 146.79, 143.72, 140.70, 130.07, 125.80, 125.56, 120.75, 123.81, 112.67, 109.70, 61.45, 55.47.

4-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (ii)

Yellowish white solid, Yield: 87%, m/z: 387, M.P. 152 °C ^{1}H NMR (400 MHz, DMSO- *d*$_6$) δ 9.86 (s, 1H) 9.0 (s, 1H) 7.90-7.92 (d, 2H) 7.81-7.85 (d, 2H) 7.58-7.60 (d, 1H) 7.42-7.45 (d, 2H) 5.36 (s, 2H) 3.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO- *d*$_6$) δ 191.37, 152.60, 149.20, 143.19, 135.61, 132.73, 129.96, 125.77, 123.35, 122.04, 121.43, 112.56, 109.60, 61.45, 55.40.

4-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (iii)

White solid, Yield: 87%, m/z: 343, M.P. 174○C ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.87 (s, 1 H) 9.04 (s, 1 H) 7.90 - 8.04 (m, 2 H) 7.65 - 7.74 (m, 2 H) 7.54 - 7.65 (m, 1 H) 7.38 - 7.49 (m, 2 H) 5.37 (s, 2H) 3.37 (s, 3 H).^{13}C NMR (100 MHz, DMSO- d$_6$) δ 191.42, 152.65, 149.25, 143.23, 135.27, 133.09, 130.01, 129.87, 125.8, 123.46, 121.87, 112.61, 109.64, 61.52, 55.45.

3-methoxy-4-((1-p-tolyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (iv)

White solid, Yield: 95%, m/z: 323, M.P. 90 °C ^{1}H NMR (400 MHz, DMSO- *d*$_6$) δ 9.89 (s, 1H) 8.09 (s, 1H) 7.55 – 7.35 (m, 4H) 7.15 – 6.99 (m, 3H) 5.48 – 4.97 (m, 2H) 3.95 – 3.73 (m, 3H) 2.52 – 2.16 (m, 3H).

4-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (v)

White solid, Yield: 95%, m/z: 337, M.P. 200 °C ^{1}H NMR (400 MHz, DMSO- *d*$_6$) δ 9.82 (s, 1 H) 8.60 (s, 2 H) 7.78 (s, 2 H) 7.64 (m, 2 H) 7.49 (m, 1 H) 5.37 (s, 2 H) 3.92 (s, 3 H) 2.22 - 2.47 (m, 6 H). ^{13}C NMR (100 MHz, DMSO- *d*$_6$) δ 190.42, 154.73, 149.94, 147.40, 139.64, 138.61, 133.51, 130.79, 126.53, 125.42, 123.89, 120.65, 117.05, 114.44, 111.06, 57.70, 56.53, 19.52, 15.08.

4-((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (vi)

White solid, Yield: 95%, m/z: 343, M.P. 136°C ^{1}H NMR (400 MHz, DMSO- *d*$_6$) δ 9.87 (s, 1H) 8.08 (s, 1H) 7.70 (s, 1H) 7.54 – 7.35 (m, 3H) 7.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO- *d*$_6$) δ 190.67, 154.98, 150.19, 147.86, 139.47, 133.91, 133.76, 130.46, 125.80, 125.67, 121.31, 119.90, 118.70, 114.69, 111.31, 57.96, 56.79, 7.07 (d, J = 32.6 Hz, 2H) 5.27 (s, 2H) 3.82 (s, 3H).

4-((1-(2,6-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (vii)

White solid, Yield: 84%, m/z: 337, M.P. 179 °C ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.87 (s, 1 H) 8.94 (s, 1 H) 7.50 - 7.64 (m, 4 H) 7.37 - 7.50 (m, 1 H) 7.24 (d, J = 8.28 Hz, 2.33 Hz, 1 H) 5.35 (s, 2 H) 3.83 (s, 3 H) 2.29 (s, 6 H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 191.44, 151.75, 149.35, 149.27, 139.38, 130.23, 129.98, 125.49, 123.22, 117.74, 112.83, 112.60, 109.80, 109.63, 78.91, 56.06, 55.53, 55.45, 20.81.

4-((1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (viii)

White solid, Yield: 78%, m/z: 361, M.P. 154 °C ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.87 (s, 1H) 9.04 (s, 1H) 8.25 (d, J = 3.6 Hz, 1H) 8.00 (d, J = 5.1 Hz, 1H) 7.77 – 7.49 (m, 2H) 7.44 (d, J = 7.9 Hz, 2H) 5.38 (s, 2H) 3.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 192.01, 156.29,

153.24, 149.86, 143.85, 134.08, 130.63, 126.42, 124.32, 123.13, 121.67, 121.60, 118.83, 118.61, 113.22, 110.25, 62.11, 56.05.

4-((1-(3,4-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (ix)

White solid, Yield: 78%, m/z: 337, M.P. 114 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H) 8.09 (s, 1H) 7.53 – 7.26 (m, 4H) 7.06 (d, J = 16.4 Hz, 2H) 5.34 – 5.16 (m, 2H) 4.04 – 3.66 (m, 3H) 2.38 – 2.32 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.41, 152.72, 149.28, 142.90, 138.14, 137.20, 134.41, 130.55, 129.99, 125.83, 123.15, 120.99, 117.39, 112.62, 109.68, 61.61, 55.45, 19.39, 18.94.

3-methoxy-4-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (x)

White solid, Yield: 78%, m/z: 339, M.P. 196 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H) 8.08 (s, 1H) 7.48 – 7.40 (m, 3H) 7.39 (s, 1H) 7.03 (s, 1H) 6.93 – 6.79 (m, 2H) 5.27 – 5.23 (m, 2H) 3.86 – 3.79 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.43, 152.72, 151.75, 149.35, 149.25, 130.24, 125.49, 121.85, 114.86, 112.83, 109.80, 78.89, 78.54, 56.06, 55.53, 55.44.

3-methoxy-4-((1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy) benzaldehyde (xi)

White solid, Yield: 78%, m/z: 393, M.P. 216 °C ^{1}H NMR (400 MHz, DMSO-d_6) 9.80 (s, 1H) 8.11 (s, 1H) 7.36 – 7.39 (m, 3H) 7.22 (s, 1H) 7.1 (s, 1H) 6.76 – 6.90 (m, 2H) 5.16 – 5.22 (m, 2H) 3.88 – 3.92 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6)δ 191.43, 152.72, 151.75, 149.35, 149.25, 130.24, 125.49, 121.85, 114.86, 112.83, 109.80, 78.89, 78.54, 56.06, 55.53, 55.44.

3-methoxy-4-((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (xii)

Yellowish white solid, Yield: 78% m/z: 354, MP 170 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s , 1H) 7.52 – 8.10 (m, 4H) 7.06 – 7.5 (m, 2H) 8.72 (s, 2H) 4.92 (d, J = 1.9 Hz, 2H) 3.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.42, 152.65, 149.25, 143.23, 135.27, 133.09, 130.01, 129.87, 125.8, 123.46, 121.87, 112.61, 109.64, 61.52, 55.45.

4-((1-(2-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (xiii)

Yellowish white solid, Yield: 83%, m/z: 387, MP 110 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s , 1H) 7.44 – 8.01 (m, 4H) 7.02 –7.32 (m, 2H) 8.66 (s, 2H) 4.87 (d, J = 1.8 Hz, 2H) 3.91 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.23, 152.42, 150.65, 149.35, 149.33, 130.24, 125.51, 122.73, 114.86, 112.83, 109.80, 78.89, 78.54, 56.06, 55.57, 55.45.

4-((1-(3-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (xiv)

Yellowish white solid, Yield: 87%, m/z: 387, MP 123 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H) 8.08 (s, 1H), 7.87 (s, 1H), 7.49 (s, 1H), 7.42 (d, J = 27.9 Hz, 2H), 7.27 (s, 1H), 7.15 (s, 1H), 7.04 (s, 1H), 5.27 – 5.23 (m, 2H), 3.86 – 3.82 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.67 154.98, 150.19, 147.86, 139.27, 133.76, 130.50, 128.07, 125.67, 122.91, 122.86, 119.90, 118.29, 114.69, 111.31, 57.96, 56.79.

3-methoxy-4-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (xv)

Yellowish white solid, Yield: 73%, m/z: 354, MP 176 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1 H) 7.90 - 8.04 (s, 1 H) 7.65 - 7.74 (m, 3 H) 7.54 - 7.65 (m, 2 H) 7.38 - 7.49 (m, 2 H) 5.37 (s, 2 H) 3.79 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.42, 152.65, 149.25, 143.23, 135.27, 133.09, 130.01, 129.87, 125.8, 123.46, 121.87, 112.61, 109.64, 61.52, 55.45.

3-methoxy-4-((1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (xvi)

White solid, yield: 86%, m/z: 339, MP 189 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1 H) 7.35 - 7.83 (m, 6 H) 7.13 - 7.29 (m, 2 H) 5.32 - 5.41 (d, 2 H) 3.82 - 3.87 (m, 6 H).^{13}C NMR (100 MHz, DMSO-d_6) δ 191.43, 152.72, 151.75, 149.35, 149.25, 130.24, 125.49, 121.85, 114.86, 112.83, 109.80, 78.89, 78.54, 56.06, 55.53, 55.44.

3-methoxy-4-((1-(2,4,5-trichlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (xvii)

White solid, Yield: 83%, m/z: 412, M.P. 156 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (d, J = 2.1 Hz, 1H) 8.96 (s, 1H) 8.06 – 6.98 (m, 5H) 5.36 (s, 2H) 3.84 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.42, 152.72, 149.27, 144.67, 142.93, 134.42, 129.99, 129.11, 125.85, 123.30, 120.20, 112.61, 109.66, 56.07, 55.54, 55.45.

4-((1-(4-ethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (xviii)

White solid, Yield: 96%, m/z: 337, M.P. 102 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H) 8.08 (s, 1H) 7.50 (d, J = 7.5 Hz, 2H) 7.45 (dd, J = 7.5, 1.4 Hz, 1H) 7.39 (d, J = 1.4 Hz, 1H) 7.14 (d, J = 7.5 Hz, 2H) 7.03 (d, J = 7.5 Hz, 1H) 5.25 (s, 2H) 3.84 (s, 3H) 2.61 (q, J = 6.7 Hz, 2H) 1.32 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.43, 152.72, 151.76, 149.28, 144.68, 142.93, 134.42, 130.25, 130.00, 129.11, 125.85, 123.30, 120.21, 112.86, 112.62, 109.66, 55.54, 55.46, 27.66, 15.43.

2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (a)

White solid, Yield: 93%, m/z: 323, M.P. 170 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1 H) 9.85 (s, 1 H) 8.31 (s, 1 H) 7.52 - 7.64 (m, 3 H) 7.29 - 7.48 (m, 4 H) 7.10 (t, J = 6.84 Hz, 1 H) 5.38 (s, 2 H) 5.32 (s, 2 H) 4.09 (q, J = 7.03 Hz, 2 H) 1.34 (t, J = 6.90 Hz, 3 H)

2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorophenyl) acetamide (b)

White solid, Yield: 87%, m/z: 398, M.P. 176 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H) 9.84 (s, 1H) 8.30 (s, 1H) 7.78 (d, J = 8.2 Hz, 1H) 7.70 (s, 1H) 7.55 (d, J = 7.2 Hz, 1H) 7.50 – 7.26 (m, 4H) 5.49 (s, 2H) 5.31 (s, 2H) 4.08 (d, J = 6.1 Hz, 2H) 1.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.41, 165.03, 152.92, 148.43, 141.88, 133.33, 129.87, 129.76, 129.06, 127.68, 127.06, 126.73, 125.58, 112.81, 110.76, 63.78, 61.56, 51.92, 14.52.

N-(4-chlorophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (c)

White solid, Yield: 93%, m/z: 414, M.P. 176 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H) 9.84 (s, 1H) 8.31 (s, 1H) 7.77 (s, 1H) 7.70 (s, 1H) 7.54 (s, 1H) 7.41 (d, J = 15.4 Hz, 4H)

5.49 (s, 2H) 5.31 (s, 2H) 4.08 (s, 2H) 1.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 191.42, 165.04, 152.91, 148.42, 141.87, 133.33, 129.86, 129.06, 127.68, 126.75, 125.59, 112.80, 110.73, 63.77, 61.56, 51.92, 14.52.

N-(4-bromophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (d)

Yellowish white solid, Yield: 77%, m/z: 459 M.P. 198 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (br s, 1 H) 9.85 (s, 1 H) 8.32 (s, 1 H) 7.48 - 7.62 (m, 5 H) 7.36 - 7.48 (m, 2 H) 5.40 (s, 2 H) 5.33 (s, 2 H) 4.10 (q, J = 6.94 Hz, 2 H) 1.34 (br t, J = 6.90 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.40, 164.38, 152.93, 148.44, 141.86, 137.74, 131.73, 129.87, 126.71, 125.59, 121.11, 115.40, 112.81, 110.76, 63.78, 61.58, 52.22, 14.53.

N-(2,4-dimethylphenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (e)

White solid, Yield: 72%, m/z: 408, M.P. 190 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H) 9.76 (s, 1H) 8.30 (s, 1H) 7.55 (d, J = 7.3 Hz, 1H) 7.43 (d, J = 8.3 Hz, 1H) 7.40 (s, 1H) 7.28 (d, J = 8.0 Hz, 1H) 7.03 (s, 1H) 6.97 (d, J = 7.9 Hz, 1H) 5.40 (s, 2H) 5.31 (s, 2H) 4.10 (m, 2H) 2.24 (s, 3H) 2.19 (s, 3H) 1.32 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.42, 164.26, 152.94, 148.43, 141.80, 134.68, 132.86, 131.51, 130.92, 129.86, 126.67, 126.53, 125.59, 124.75, 112.80, 110.74, 63.77, 61.58, 51.89, 48.57, 20.42, 17.69, 14.51.

N-(2-chlorophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (f)

White solid, Yield: 72%, m/z: 414 M.P. 158 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (br s, 1 H) 9.85 (s, 1 H) 8.32 (s, 1 H) 7.75 (br d, J=7.53 Hz, 1 H) 7.55 (br t, J=8.91 Hz, 2 H) 7.31 - 7.49 (m, 3 H) 7.16 - 7.29 (m, 1 H) 5.50 (br s, 2 H) 5.33 (br s, 2 H) 3.99 - 4.19 (m, 2 H) 1.33 (br t, J = 6.65 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.43, 164.86, 152.92, 148.43, 141.87, 134.10, 129.86, 129.61, 127.54, 126.75, 126.26, 125.86, 125.60, 112.80, 110.73, 63.77, 61.56, 51.92, 14.52.

N-(3,4-dichlorophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (g)

White solid, Yield: 75%, m/z: 449. M.P. 178 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (br s, 1 H) 9.86 (s, 1 H) 8.33 (s, 1 H) 7.97 (s, 1 H) 7.61 (br d, J = 8.78 Hz, 1 H) 7.57 (br d, J = 8.03 Hz, 1 H) 7.37 - 7.53 (m, 3 H) 5.43 (s, 2 H) 5.34 (s, 2 H) 4.10 (q, J = 6.53 Hz, 2 H) 1.35 (br t, J = 6.78 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.38, 164.79, 152.91, 148.42, 141.90, 138.41, 131.13, 130.84, 129.86, 126.72, 125.58, 125.27, 120.42, 119.24, 112.77, 110.71, 63.76, 61.56, 52.19, 14.51.

2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-fluorophenyl) acetamide (h)

White solid, Yield: 74%, m/z: 398, M.P. 166 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (br s, 1 H) 9.85 (s, 1 H) 8.33 (s, 1 H) 7.93 (br s, 1 H) 7.56 (br d, J = 7.78 Hz, 1 H) 7.36 - 7.49 (m, 2 H) 7.24 - 7.35 (m, 1 H) 7.13 - 7.24 (m, 2 H) 5.49 (br s, 2 H) 5.33 (br s, 2 H) 4.09 (q, J = 6.53

Hz, 2 H) 1.34 (br t, J = 6.78 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.49, 164.86, 153.00, 148.50, 129.93, 126.82, 125.67, 125.44, 124.57, 124.54, 123.77, 115.75, 115.56, 112.86, 110.80, 63.84, 61.64, 52.05, 14.58.

N-(3-bromophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (i)

Yellowish white solid, Yield: 88%, m/z: 459, M.P. 150 °C, ^{1}H NMR (400 MHz, DMSO) δ 10.69 (s, 1H) 9.83 (s, 1H) 8.31 (s, 1H) 7.92 (s, 1H) 7.54 (d, J = 7.8 Hz, 1H) 7.49 (d, J = 6.7 Hz, 1H) 7.45 – 7.36 (m, 2H) 7.28 (d, J = 7.4 Hz, 2H) 5.40 (s, 2H) 5.32 (s, 2H) 3.47 (s, 2H) 1.32 (t, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.35, 164.58, 152.92, 148.44, 139.88, 130.86, 129.87, 126.70, 126.39, 125.56, 121.63, 121.57, 117.96, 112.75, 110.71, 63.76, 61.56, 52.18, 48.55, 14.47.

2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide (j)

White solid, Yield: 91%, m/z: 425, M.P. 176 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H) 9.84 (s, 1H) 8.32 (s, 1H) 8.25 (d, J = 8.8 Hz, 2H) 7.82 (d, J = 8.9 Hz, 2H) 7.55 (d, J = 7.9 Hz, 1H) 7.45 – 7.33 (m, 2H) 5.46 (s, 2H) 5.32 (s, 2H) 4.12 – 4.06 (m, 2H) 1.33 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.56, 165.42, 153.01, 148.53, 144.55, 142.67, 129.97, 126.85, 125.69, 125.21, 119.10, 112.91, 110.86, 63.89, 61.65, 52.41, 48.67, 14.62.

N-(4-chlorophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (k)

White solid, Yield: 93%, m/z: 414, M.P. 184 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (br s, 1 H) 9.86 (s, 1 H) 8.33 (s, 1 H) 7.51 - 7.70 (m, 3 H) 7.35 - 7.48 (m, 4 H) 5.40 (s, 2 H) 5.34 (s, 2 H) 4.10 (q, J = 6.78 Hz, 2 H) 1.34 (br t, J = 6.78 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.40, 164.36, 152.92, 148.43, 141.86, 137.33, 129.86, 128.82, 127.35, 126.72, 125.59, 120.73, 112.78, 110.72, 63.76, 61.57, 52.19, 14.52.

N-(3-chlorophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (m)

White solid, Yield: 83%, m/z.414, M.P. 178 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (br s, 1 H) 9.86 (s, 1 H) 8.34 (s, 1 H) 7.80 (s, 1 H) 7.57 (br d, J = 8.28 Hz, 1 H) 7.34 - 7.52 (m, 4 H) 7.17 (br d, J = 7.53 Hz, 1 H) 5.43 (s, 2 H) 5.34 (s, 2 H) 4.10 (q, J = 6.78 Hz, 2 H) 1.35 (br t, J = 6.90 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.39, 164.63, 152.93, 148.43, 141.88, 139.78, 133.18, 130.62, 129.87, 126.72, 125.59, 123.50, 118.70, 117.59, 112.78, 110.72, 63.76, 61.57, 52.20, 14.52.

N-(2-chloro-4-nitrophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (n)

White solid, Yield: 87%, m/z: 459, M.P. 156 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H) 9.83 (s, 1H) 8.35 (d, J = 21.9 Hz, 2H) 8.22 (s, 2H) 7.54 (d, J = 8.0 Hz, 1H) 7.45 – 7.35 (m, 2H) 5.60 (s, 2H) 5.32 (s, 2H) 4.08 (dd, J = 13.7, 6.8 Hz, 2H) 1.32 (t, J = 6.9 Hz, 3H). ^{13}C NMR

(100 MHz, DMSO-d_6) δ 191.53, 165.88, 153.00, 148.52, 143.65, 140.49, 129.97, 126.89, 125.67, 125.12, 124.67, 123.86, 123.29, 112.90, 110.85, 63.88, 61.65, 52.35, 48.67, 14.61.

2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl) acetamide (o)

White solid, Yield: 71%, m/z: 410, M.P. 190 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H) 9.84 (s, 1H) 8.30 (s, 1H) 7.55 (d, J = 7.9 Hz, 1H) 7.50 (d, J = 8.7 Hz, 2H) 7.46 – 7.37 (m, 2H) 6.90 (d, J = 8.8 Hz, 2H) 5.33 (d, J = 8.4 Hz, 4H) 4.09 (q, J = 6.8 Hz, 2H) 3.72 (s, 3H) 3.72 (s, 3H) 1.33 (t, J = 6.9 Hz, 3H).

N-(3-chloro-2-methylphenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (p)

White solid, Yield: 71%, m/z: 428, M.P. 166 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (br s, 1 H) 9.85 (br s, 1 H) 8.32 (br s, 1 H) 7.56 (br d, J = 7.53 Hz, 1 H) 7.28 - 7.48 (m, 4 H) 7.23 (br d, J = 7.53 Hz, 1 H) 5.45 (br s, 2 H) 5.32 (br s, 2 H) 4.09 (br d, J = 6.52 Hz, 2 H) 2.27 (br s, 3 H) 1.33 (br t, J = 6.02 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.41, 164.65, 152.93, 148.44, 141.85, 136.97, 133.86, 130.35, 129.87, 126.94, 126.70, 126.41, 125.59, 124.28, 112.81, 110.76, 63.77, 61.58, 51.86, 15.06, 14.52.

N-(4-bromo-2-methylphenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (q)

Yellowish white solid, Yield: 83%, m/z: 473, M.P. 180 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 - 9.92 (m, 2 H) 8.30 (s, 1 H) 7.56 (br d, J = 7.78 Hz, 1 H) 7.34 - 7.51 (m, 5 H) 5.43 (s, 2 H) 5.32 (s, 2 H) 4.09 (q, J = 6.78 Hz, 2 H) 2.24 (s, 3 H) 1.33 (br t, J = 6.78 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.43, 164.52, 152.93, 148.43, 141.83, 134.96, 134.15, 132.83, 129.87, 128.85, 126.69, 126.37, 125.59, 117.56, 112.82, 110.77, 63.78, 61.58, 51.92, 17.50, 14.53.

2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2,4,5-trichlorophenyl)acetamide (r)

White solid, Yield: 90%, m/z: 483, M.P. 192 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (br s, 1 H) 9.77 - 9.93 (m, 1 H) 8.32 (s, 1 H) 8.12 (s, 1 H) 7.81 - 8.00 (m, 1 H) 7.56 (dd, J = 8.28, 1.76 Hz, 1 H) 7.44 (d, J = 8.28 Hz, 1 H) 7.40 (d, J = 1.76 Hz, 1 H) 5.52 (s, 2 H) 5.33 (s, 2 H) 4.09 (q, J = 6.94 Hz, 2 H) 1.18 - 1.39 (m, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.41, 165.44, 152.92, 148.43, 141.91, 134.36, 130.68, 129.90, 129.87, 127.63, 126.75, 125.83, 125.58, 112.81, 110.76, 63.78, 61.56, 52.00, 14.53.

2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-ethylphenyl) acetamide (s)

White solid, Yield: 89%, m/z: 425, M.P. 186 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (br s, 1 H) 9.85 (s, 1 H) 8.31 (s, 1 H) 7.37 - 7.59 (m, 5 H) 7.17 (br d, J = 8.03 Hz, 2 H) 5.35 (br d, J = 15.81 Hz, 4 H) 4.09 (q, J = 6.69 Hz, 2 H) 2.54 - 2.74 (m, 2 H) 1.34 (br t, J = 6.78 Hz, 3 H) 1.06 - 1.25 (m, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.41, 163.87, 152.95, 148.44, 141.82, 139.17, 136.05, 129.87, 128.07, 126.70, 125.59, 119.26, 112.81, 110.76, 63.78, 61.58, 52.17, 27.55, 15.59, 14.52.

2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-nitrophenyl) acetamide (t)

White solid, Yield: 74%, m/z: 408, M.P. 172 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1 H) 9.85 (s, 1 H) 8.60 (br s, 1 H) 8.34 (s, 1 H) 7.85 - 8.02 (m, 2 H) 7.66 (br t, J = 8.16 Hz, 1 H) 7.57 (br d, J = 8.03 Hz, 1 H) 7.37 - 7.49 (m, 2 H) 5.45 (s, 2 H) 5.34 (s, 2 H) 4.10 (q, J = 6.78 Hz, 2 H) 1.34 (br t, J = 6.78 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.42 165.07, 152.93, 148.44, 147.96, 141.91, 139.44, 130.43, 129.87, 126.73, 125.59, 125.18, 118.32, 113.35, 112.83, 110.78, 63.79, 61.58, 52.21, 14.53.

6. CONCLUSIONS

Recently, we have synthesized a series of Vanillin linked triazole conjugates bearing a amide or amine linker for antimicrobial evaluation. We demonstrated that these conjugates exhibited not so significant potent in vitro activity and therapeutic efficacy against antibacterial and fungal strains. To continue our research on the developing vanillin linked triazoles, we have synthesized a two series. The preliminary antimicrobial studies revealed that these agents did not exhibited significant antimicrobial activity in inhibiting various strains in vitro. We demonstrate that the newly synthesized conjugates are generally less potent.

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Reference

[1] M. V. Sobral, A. L. Xavier, T. C. Lima, D. P. de Sousa, *The Scientific World Journal* 2014; 2014: 953451

[2] A. A. Carvalho, L. N. Andrade, É. B. V. de Sousa, D. P. de Sousa, *BioMed Research International* 2015; 2015: 392674

[3] L. N. Andrade, T. C. Lima, R. G. Amaral, C. do Ó. Pessoa, B. M. Soares, L. G. do Nascimento, A. A. Carvalho, D. P. de Sousa, *Molecules* 2015, 20, 13264-13280

[4] D. P. De Sousa, Bioactive Essential Oils and Cancer, Springer, 2015.

[5] V. Georgiev, A. Ananga, V. Tsolova, *Nutrients* 2014, 6, 391-415

[6] C. Kanadaswami, L.-T. Lee, P.-P. H. Lee, J.-J. Hwang, F.-C. Ke, Y.-T. Huang, M.-T. Lee, *In vivo* 2005, 19, 895-909

[7] H. Priefert, J. Rabenhorst, A. Steinbüchel, *Applied Microbiology and Biotechnology* 2001, 56, 296-314

[8] G. S. Clark, *Perfumer and Flavourist* 1990, 15, 45-54

[9] N. A. Zamzuri, S. Abd-Aziz, *Journal of the Science of Food and Agriculture* 2013, 93, 429-438

[10] L. S. Pedroso, G. M. Fávero, L. E. A. de Camargo, R. M. Mainardes, N. M. Khalil, *Journal of enzyme inhibition and medicinal chemistry* 2013, 28, 734-740

[11] A. Tai, T. Sawano, F. Yazama, H. Ito, *Biochimica et Biophysica Acta (BBA) - General Subjects* 2011, 1810, 170-177

[12] T. Sawa, M. Nakao, T. Akaike, K. Ono, H. Maeda, *Journal of Agricultural and Food Chemistry* 1999, 47, 397-402

[13] B. Ames, M. Shigenaga, Molecular biology of free radical scavenging systems. JG Scandalios. Plainview, NY, Cold Spring Harbor Laboratory Press: ix 1992, 284.

[14] B. N. Ames, L. S. Gold, *Proceedings of the National Academy of Sciences* 1990, 87, 7772–7776

[15] S. Ahmad, Oxidative Stress and Antioxidant Defenses in Biology, Springer Science & Business Media, 2012.

[16] (a) Y. B. Kim, E. H. Choi, G. Keum, S. B. Kang, D. H. Lee, H. Y. Koh, Y. Kim, *Organic letters* 2001, 3, 4149-4152

(b) N. Aziz, S. Farag, L. Mousa, M. Abo-Zaid, *Microbios* 1998, 93, 43-54

(c) L. G. Gorris, E. J. Smid, *Journal of applied microbiology* 1998, 85, 211-218

(d) M. Friedman, P. R. Henika, R. E. Mandrell, *Journal of food protection* 2002, 65, 1545-1560

[17] G. W. Gould, *Journal of food protection* 1996, 59, 82-86

(b) P. Davidson, A. Naidu, in Natural Food Antimicrobial Systems, CRC Press, 2000, pp. 278-307

[18] (a) M. B. Hocking, Journal of chemical education 1997, 74, 1055

(b) S. Ramachandra Rao, G. A. Ravishankar, *Journal of the Science of Food and Agriculture* 2000, 80, 289-304

[19] N. J. Walton, M. J. Mayer, A. Narbad, Phytochemistry 2003, 63, 505–515.

[20] J. Burri, M. Graf, P. Lambelet, J. Löliger, *Journal of the Science of Food and Agriculture* 1989, 48, 49-56

[21] (a) A. López-Malo, S. Alzamora, A. Argaiz, *Food Microbiology* 1995, 12, 213-219

(b) P. Cerrutti, S. M. Alzamora, *International Journal of Food Microbiology* 1996, 29, 379-386

(c) D. J. Fitzgerald, M. Stratford, M. J. Gasson, A. Narbad, *Journal of food protection* 2004, 67, 391-395

[22] (a) J. Sikkema, J. A. de Bont, B. Poolman, *Journal of Biological Chemistry* 1994, 269, 8022-8028

(b) J. Sikkema, J. A. de Bont, B. Poolman, *Microbiological reviews* 1995, 59, 201-222

[23] (a) A. Ultee, E. Kets, E. Smid, *Applied and environmental microbiology* 1999, 65, 4606-4610

(b) S. Cox, C. Mann, J. Markham, H. C. Bell, J. Gustafson, J. Warmington, S. G. Wyllie, *Journal of applied microbiology* 2000, 88, 170-175

(c) R. Lambert, P. N. Skandamis, P. J. Coote, G. Nychas, *Journal of applied microbiology* 2001, 91, 453-462

(d) C. F. Carson, B. J. Mee, T. V. Riley, *Antimicrobial agents and chemotherapy* 2002, 46, 1914-1920

(e) S. A. Burt, R. D. Reinders, *Letters in applied microbiology* 2003, 36, 162–167

(f) S. E. Walsh, J. Maillard, A. Russell, C. Catrenich, D. Charbonneau, R. Bartolo, *Journal of applied microbiology* 2003, 94, 240-247

[24] A. K. Feldman, B. Colasson, V. V. Fokin, *Organic letters* 2004, 6, 3897-3899.

[25] P. Appukkuttan, W. Dehaen, V. V. Fokin, E. Van der Eycken, *Organic letters* 2004, 6, 4223-4225

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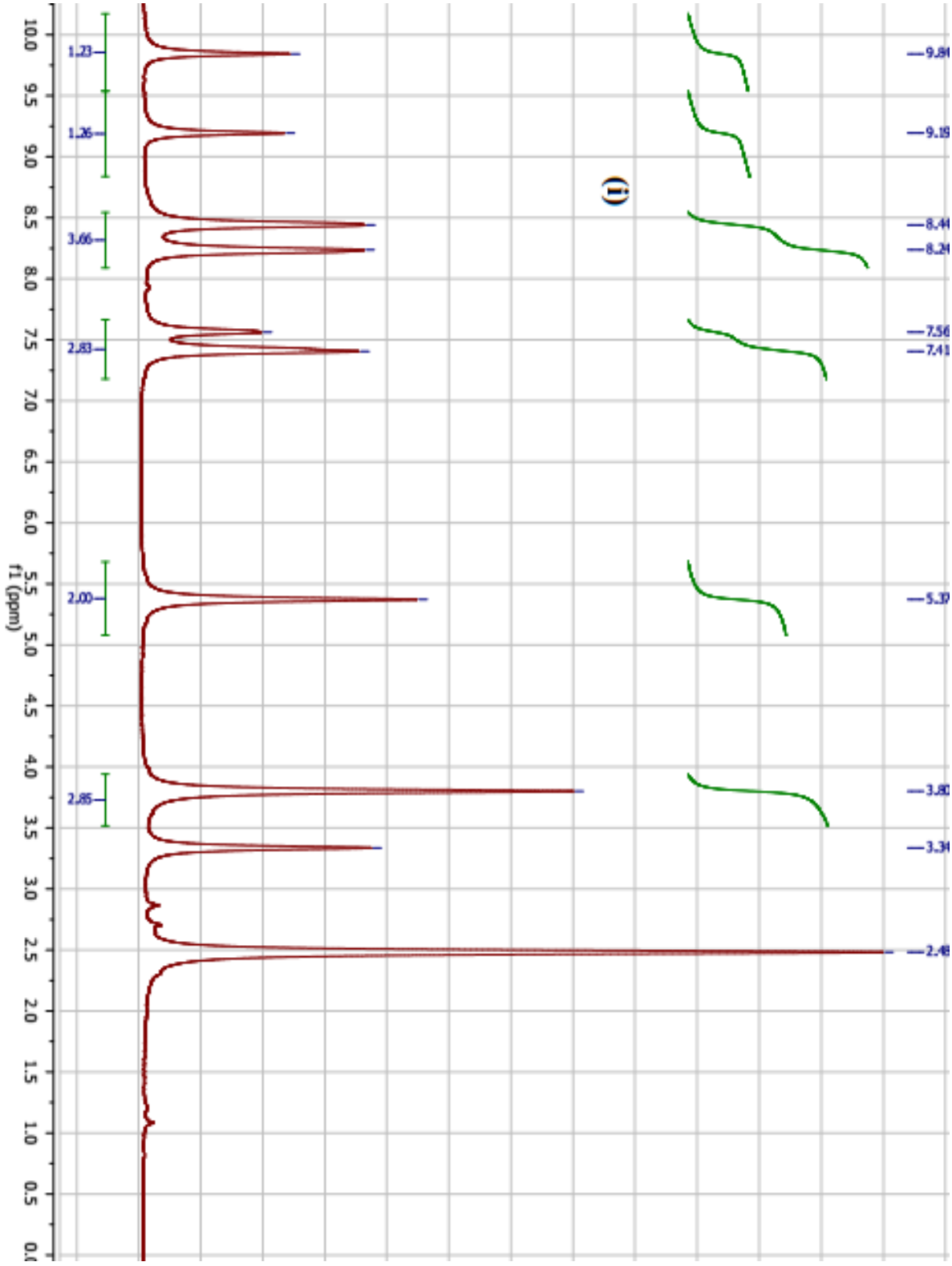

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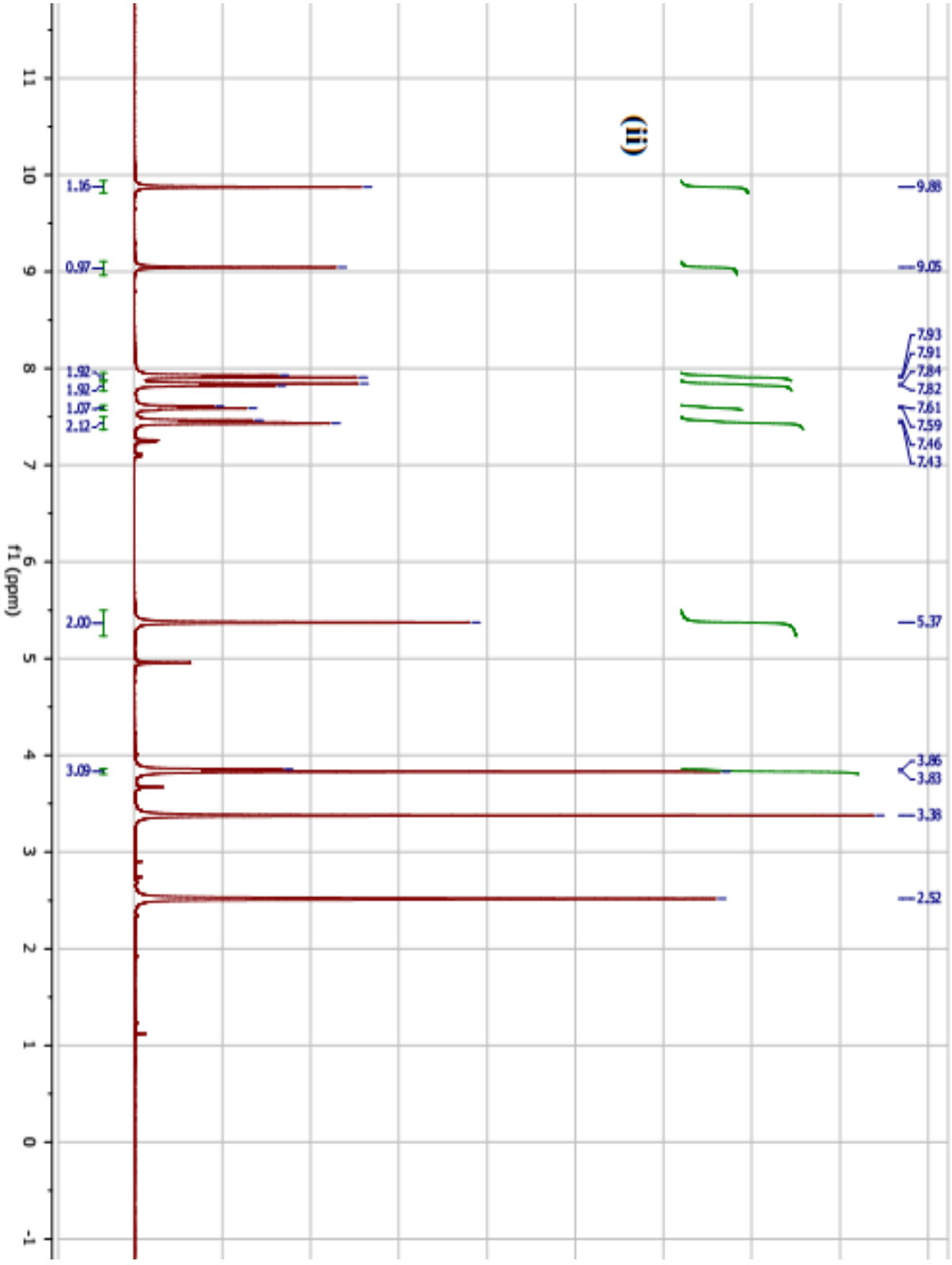

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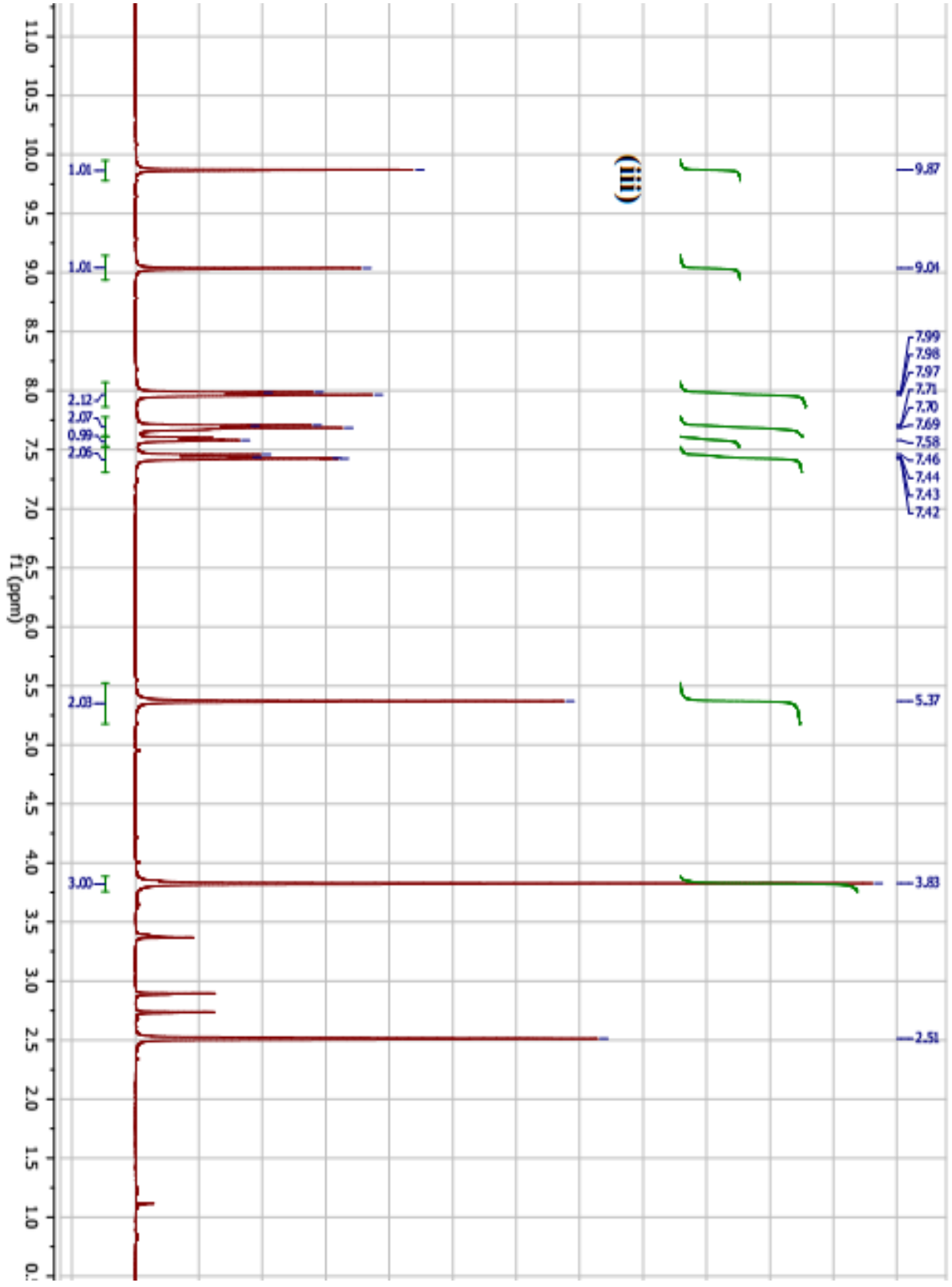

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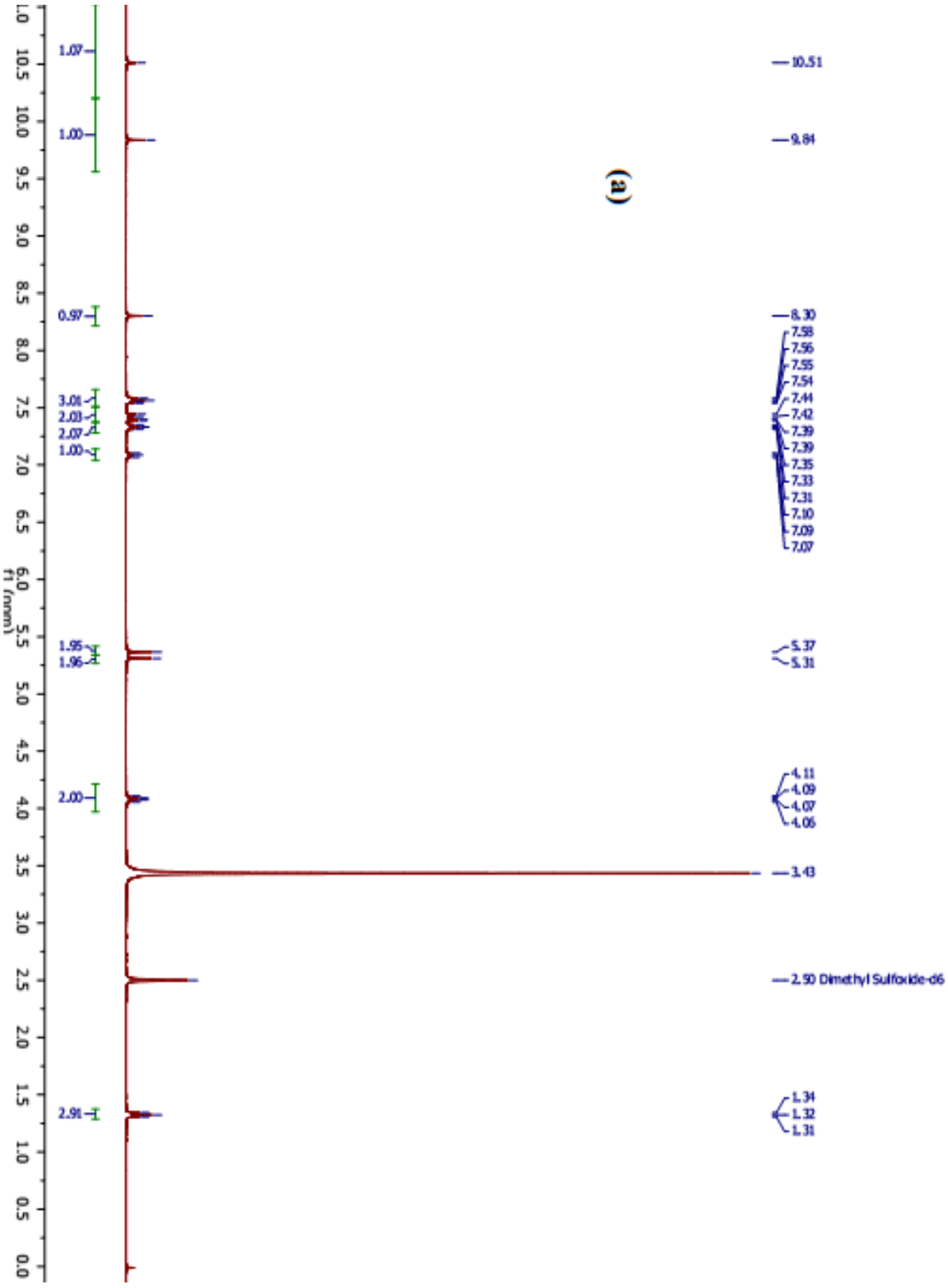

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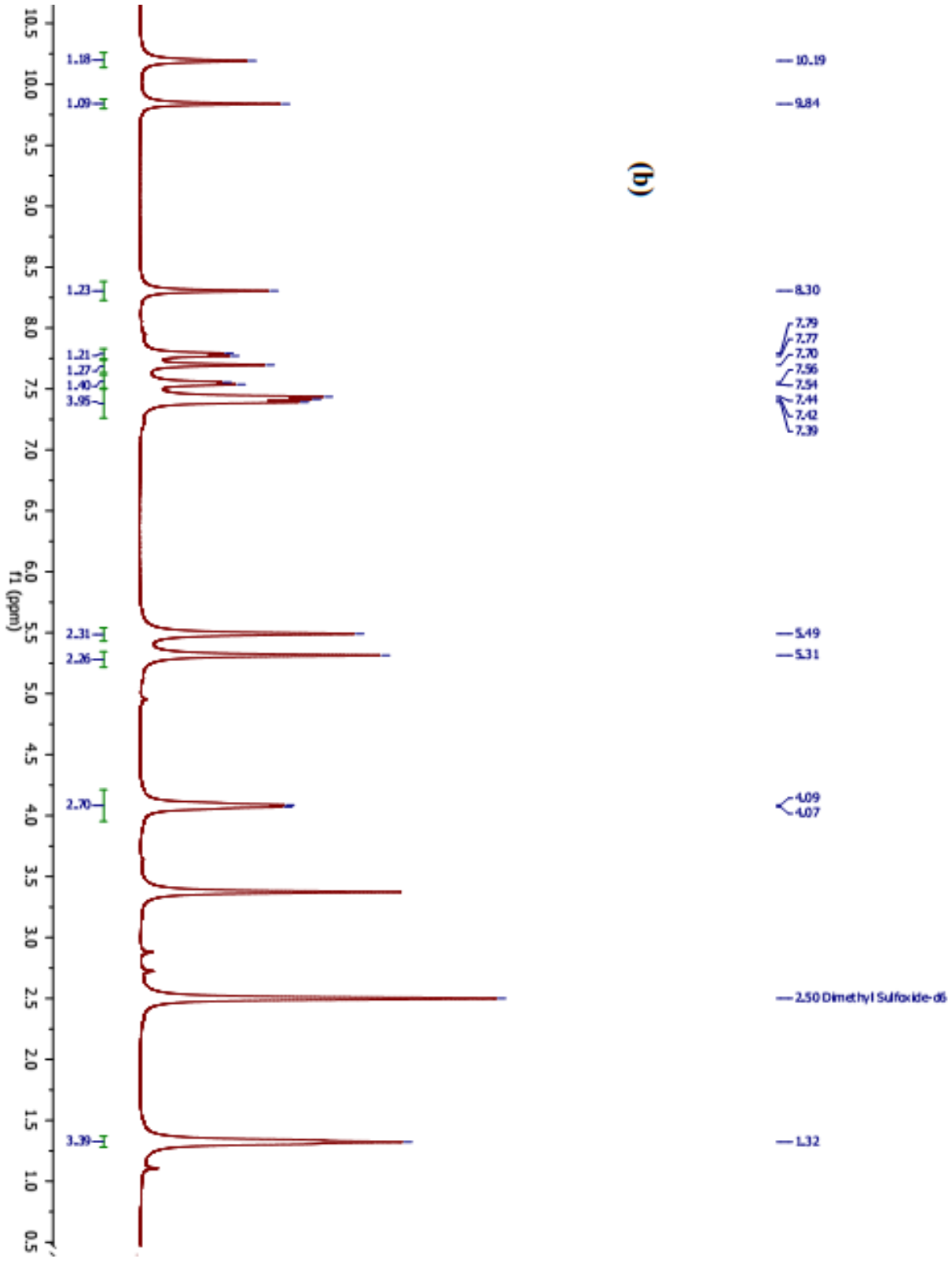

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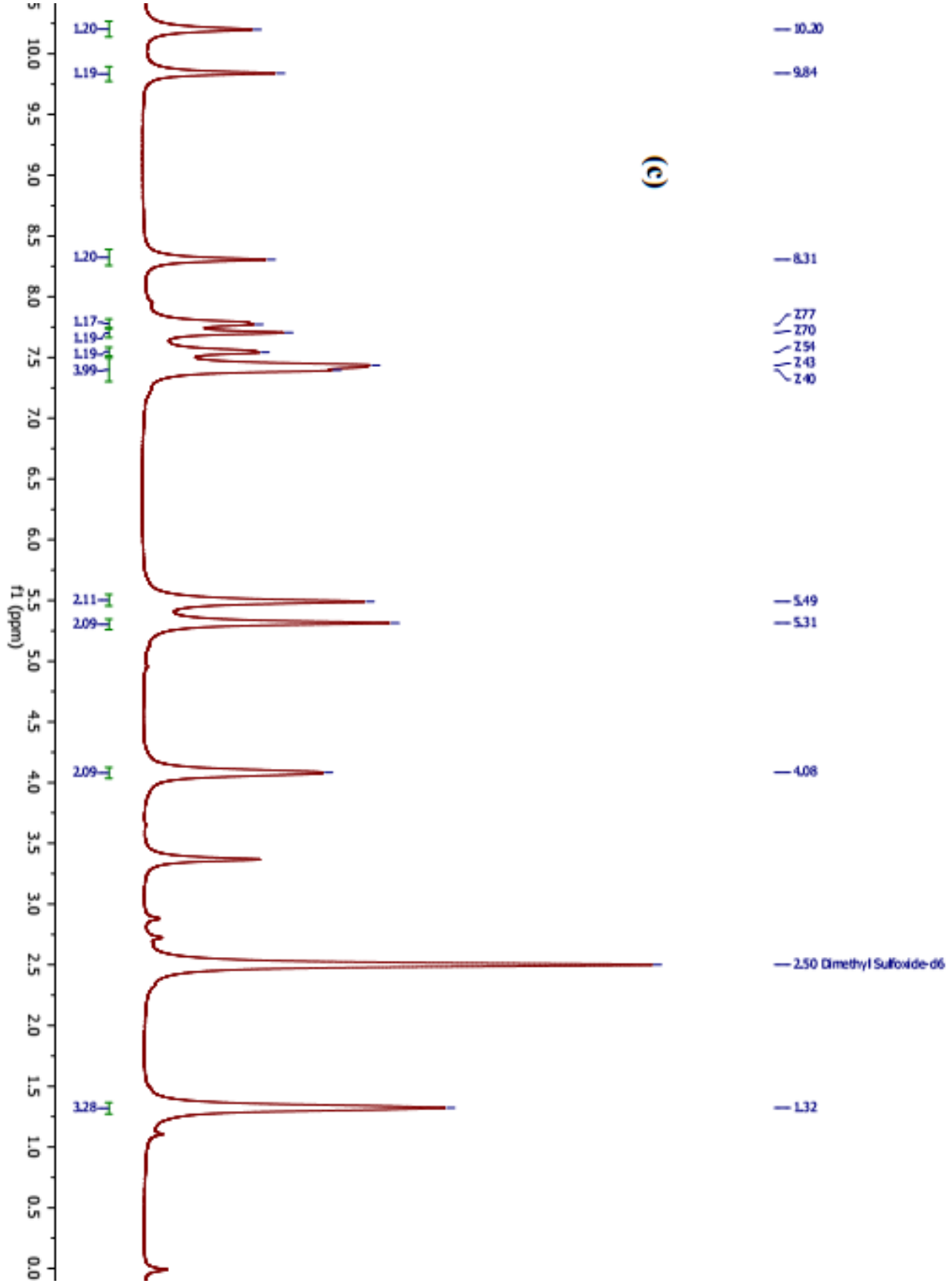

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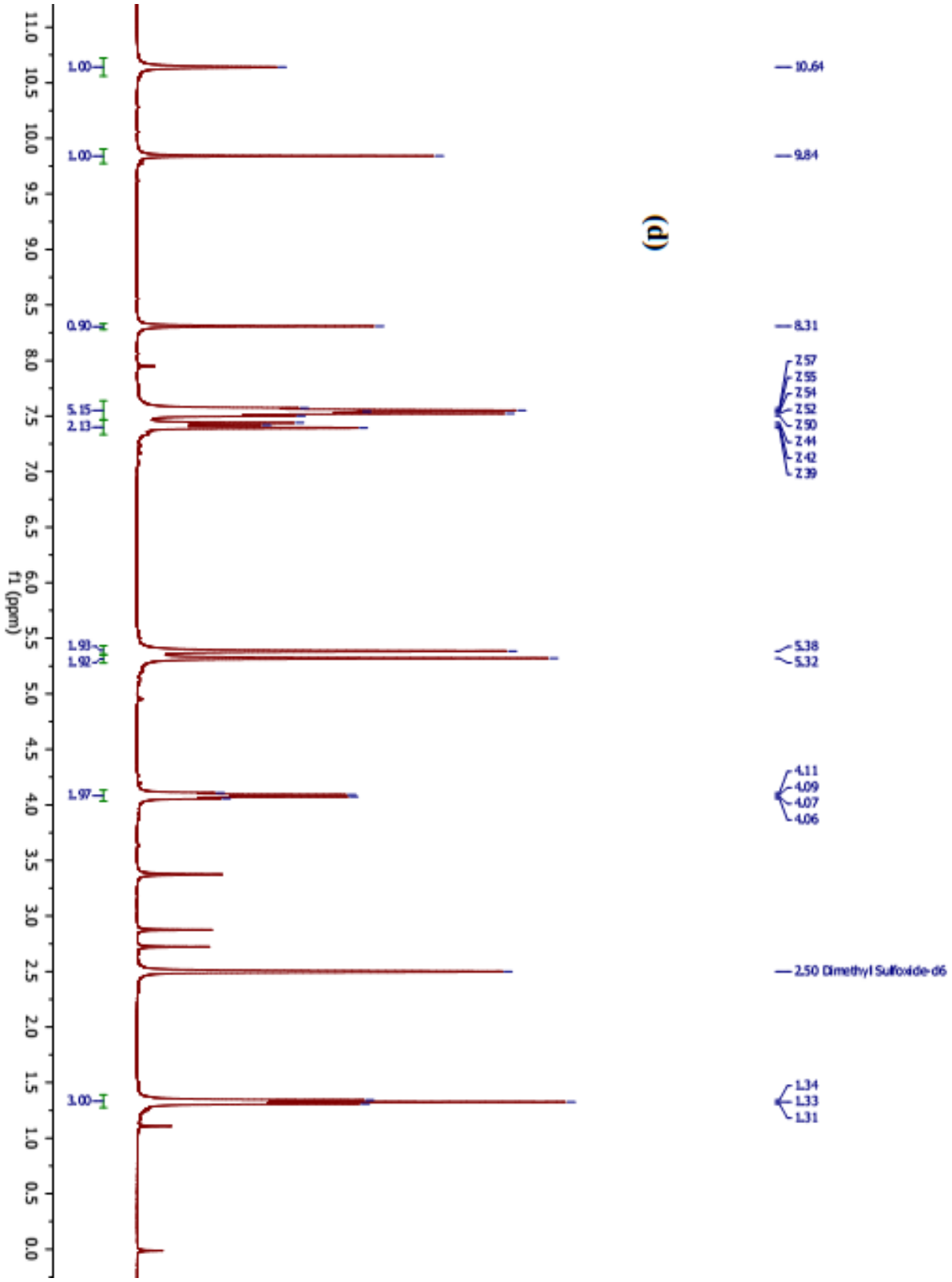

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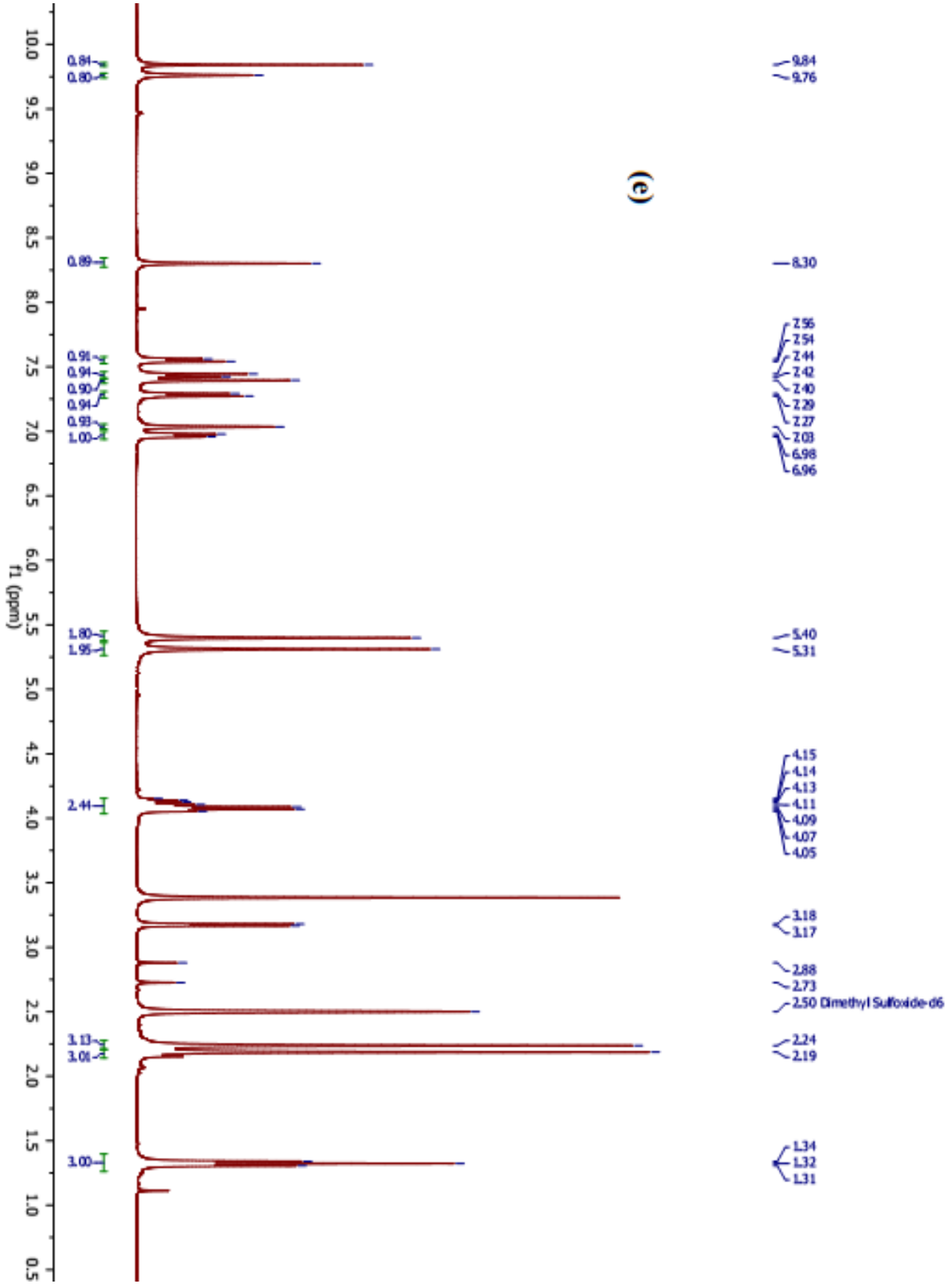

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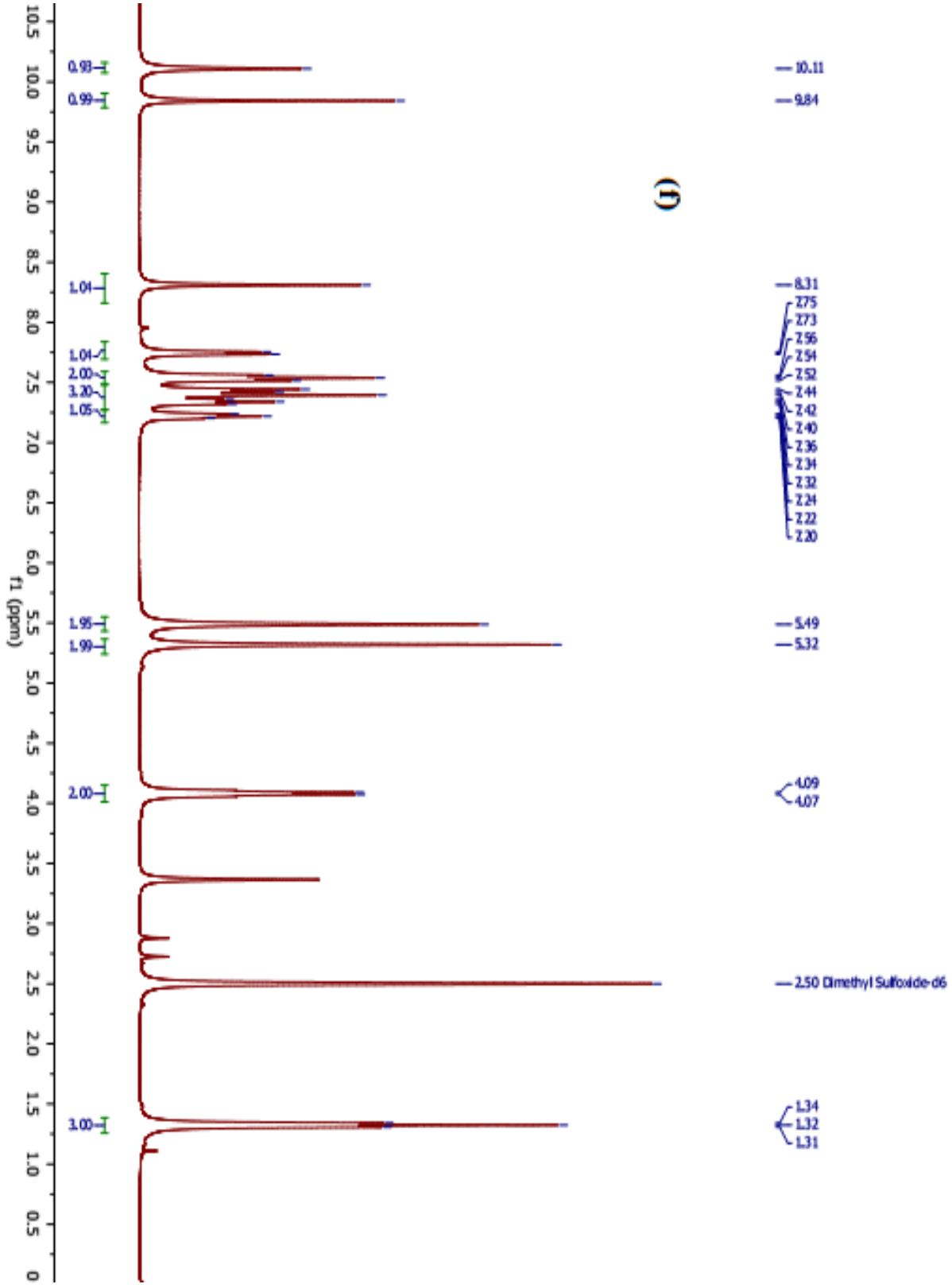

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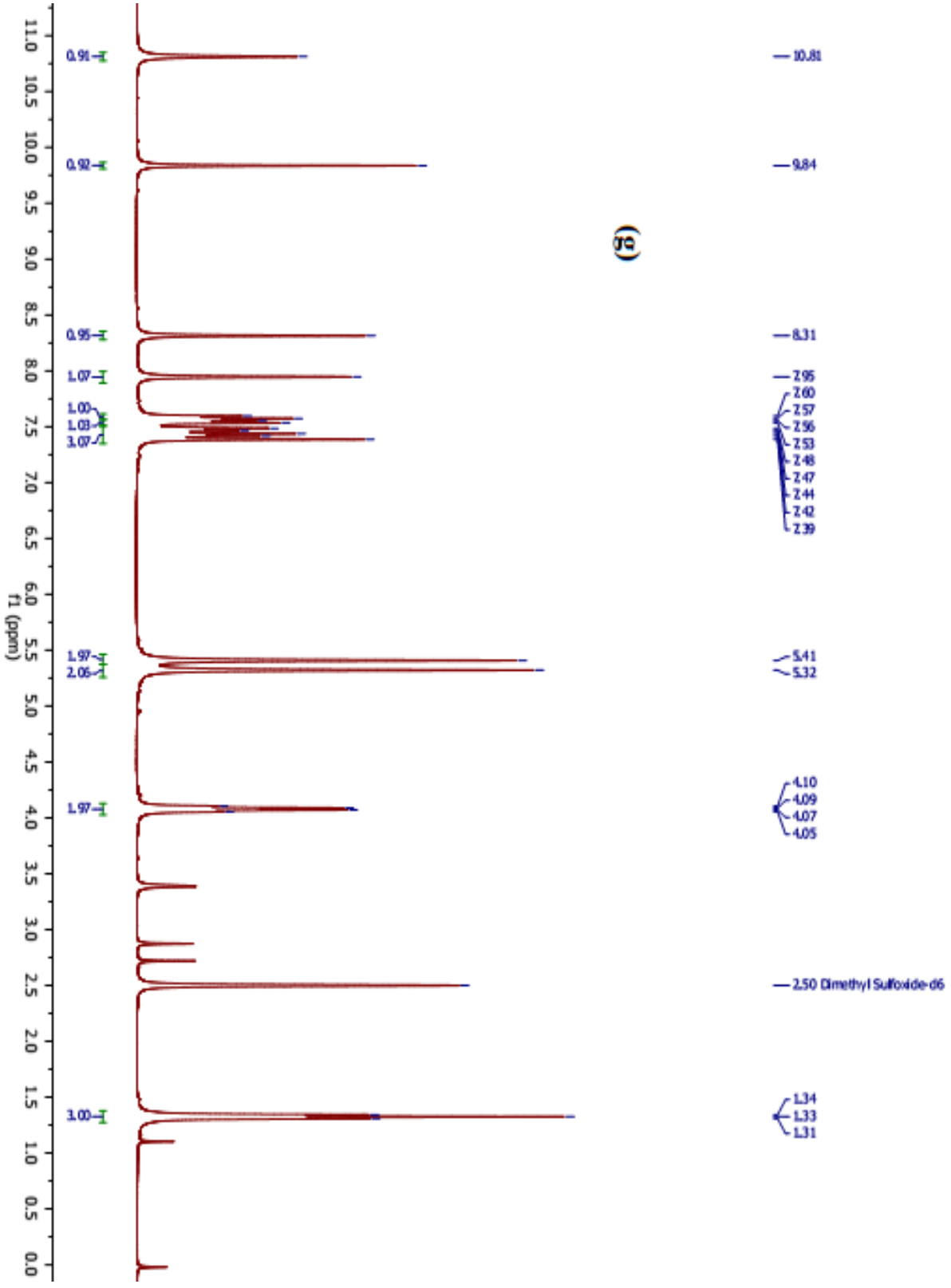

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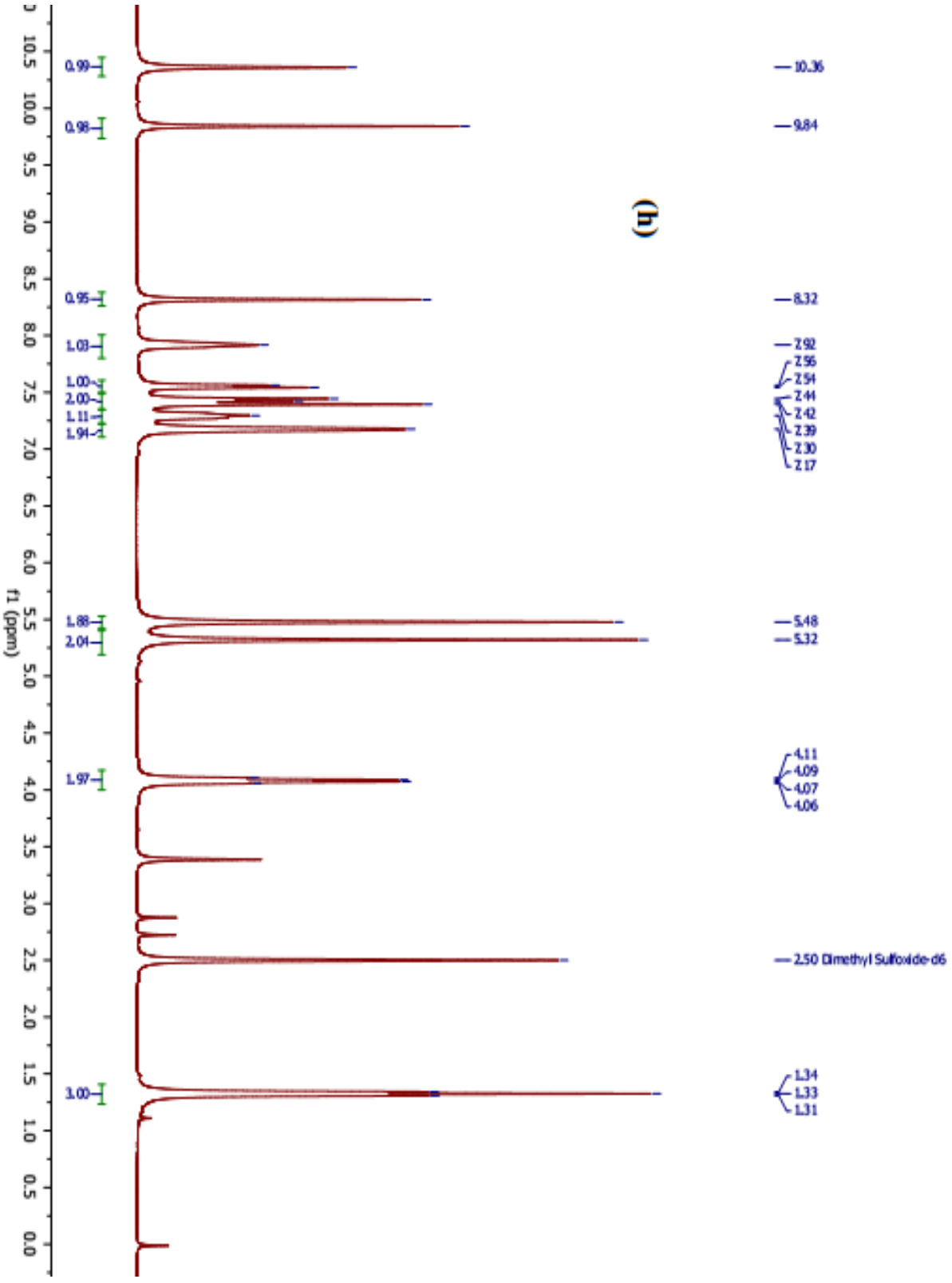

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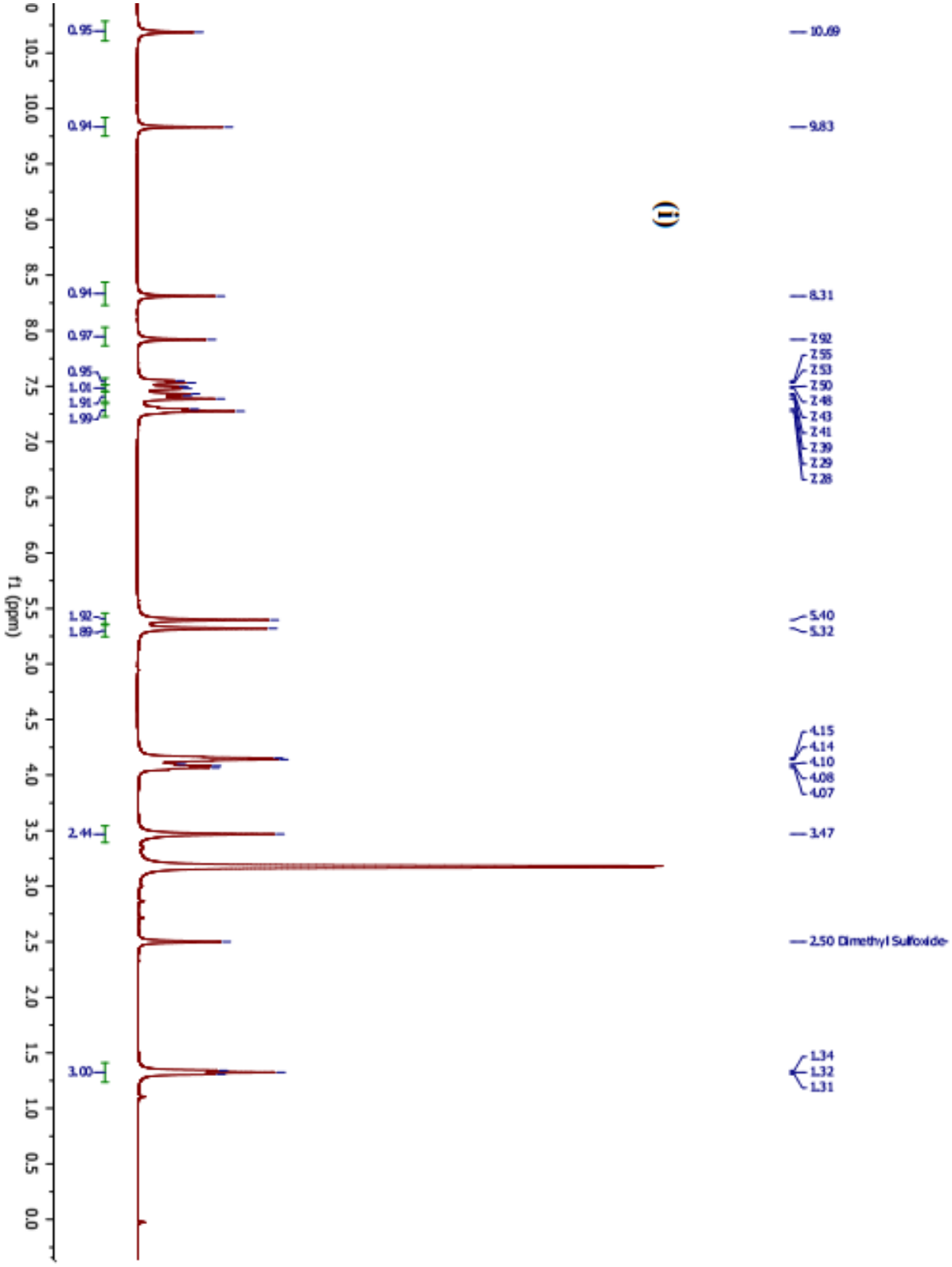

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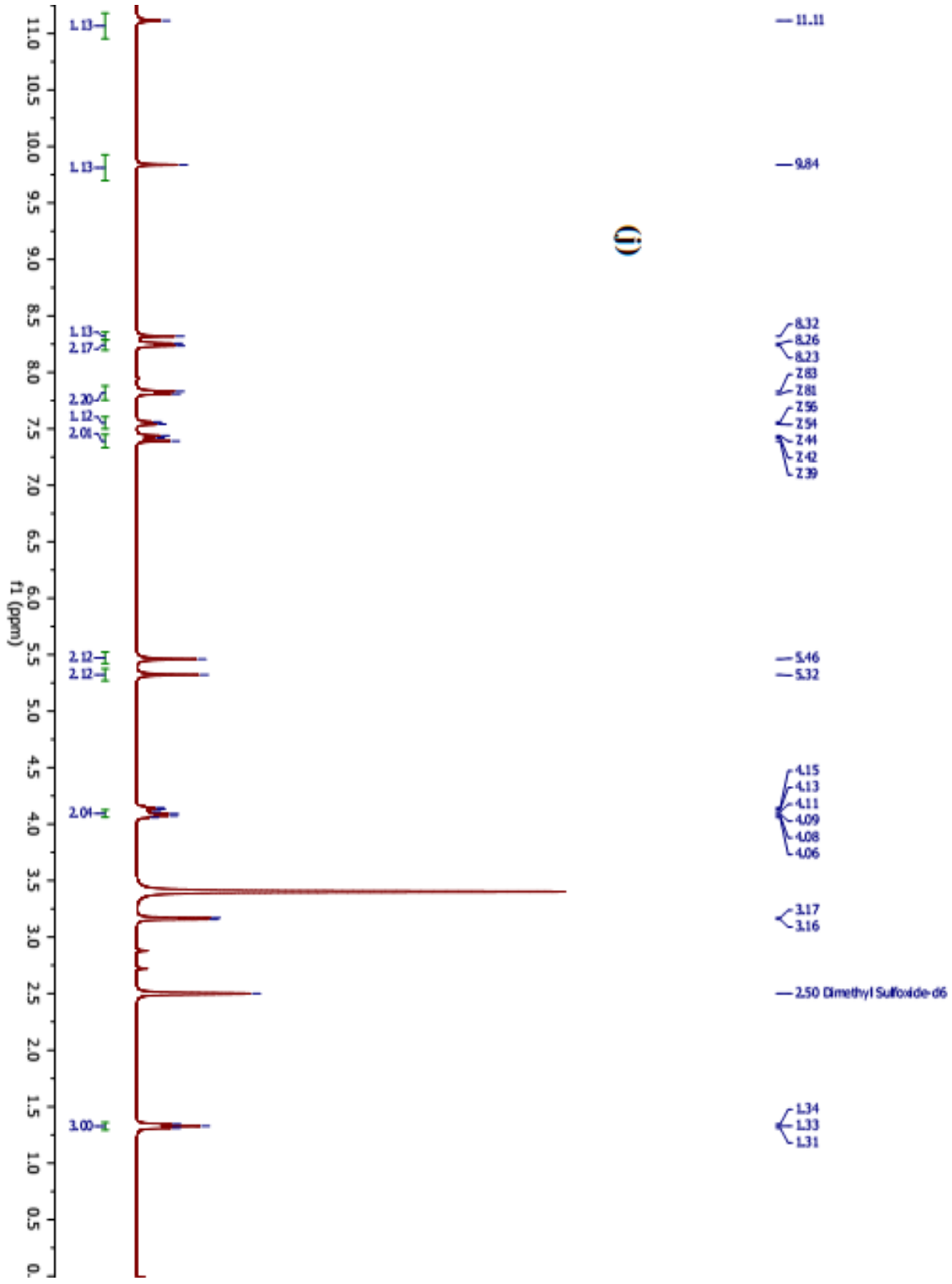

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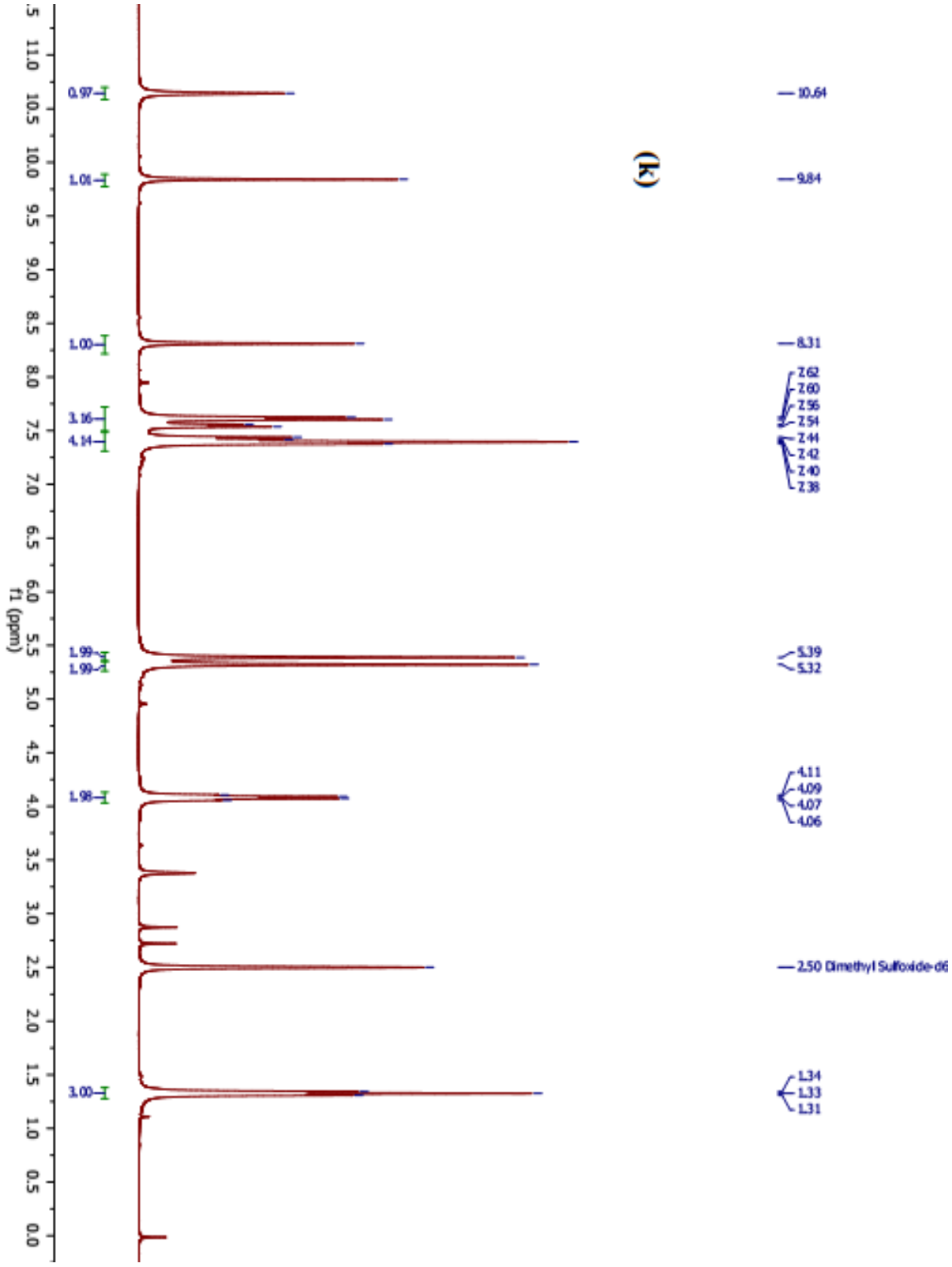

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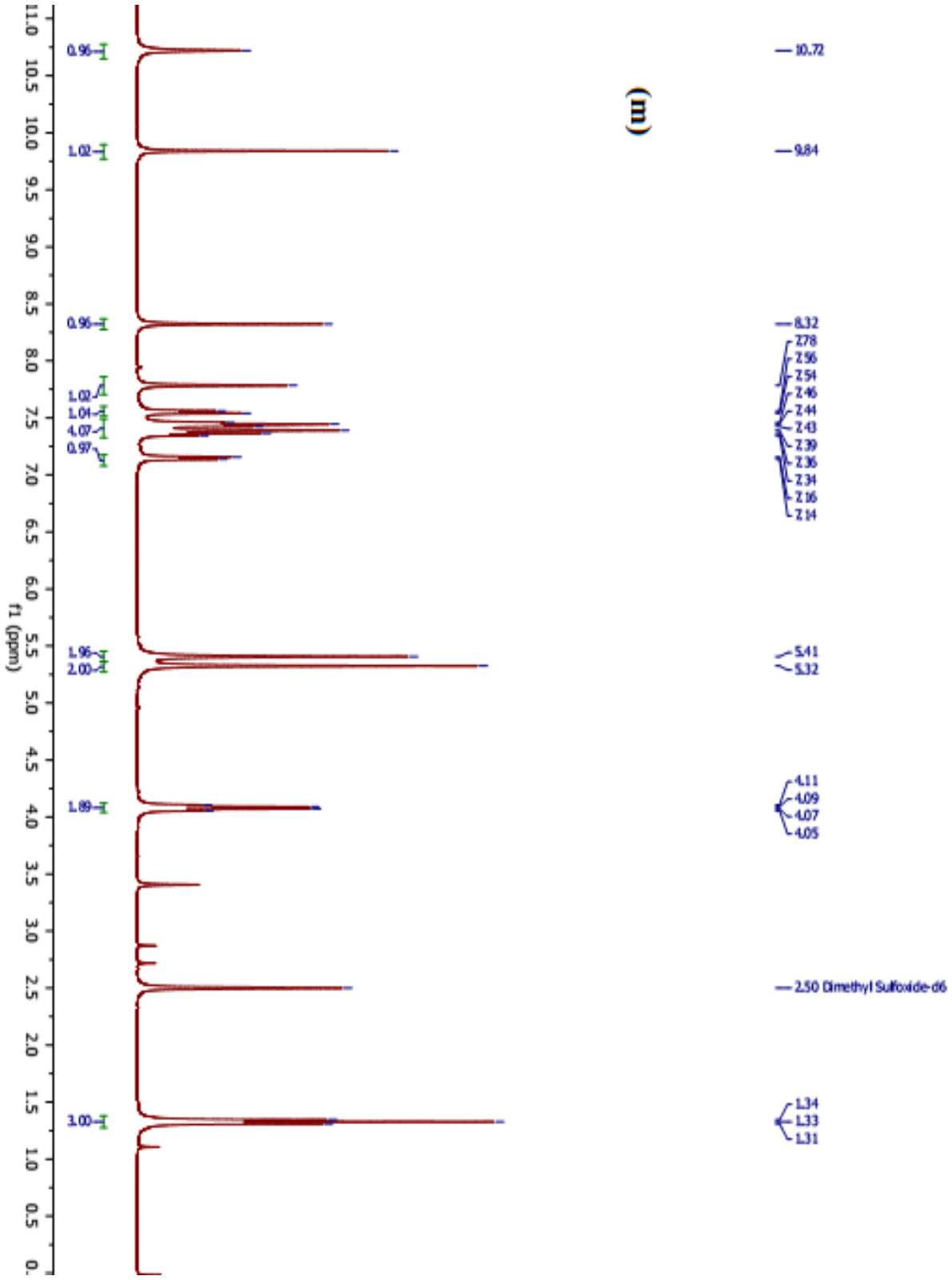

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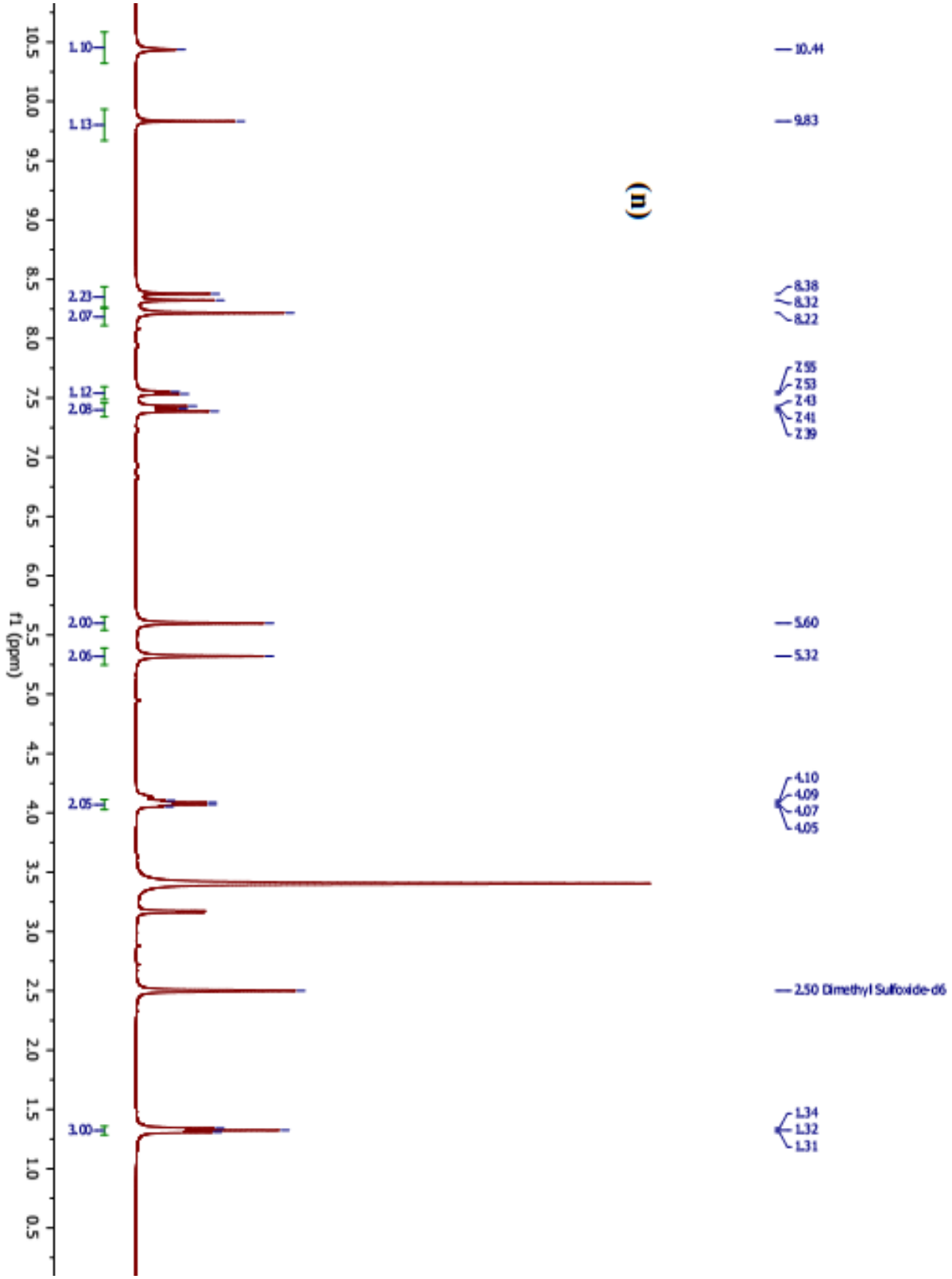

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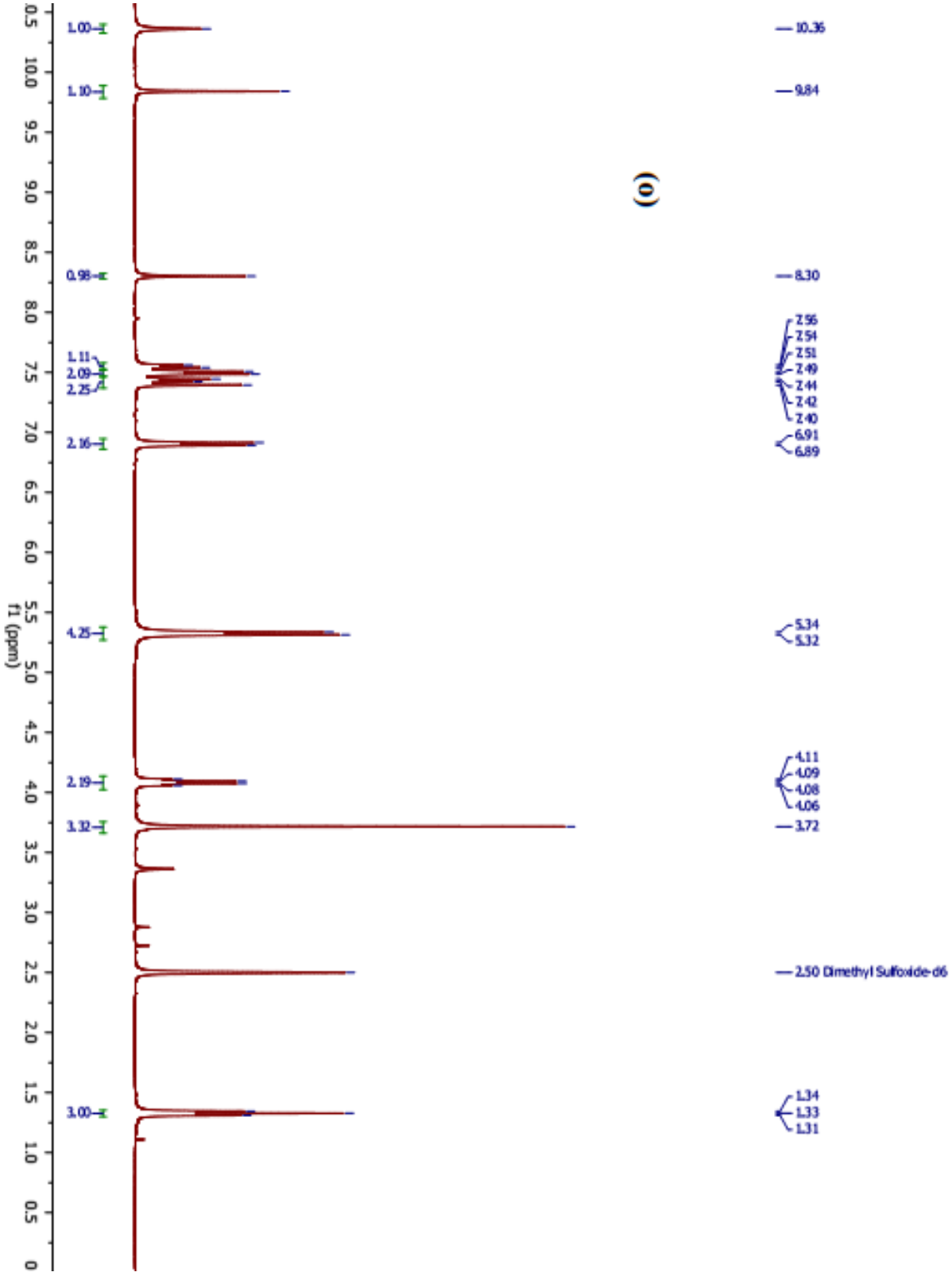

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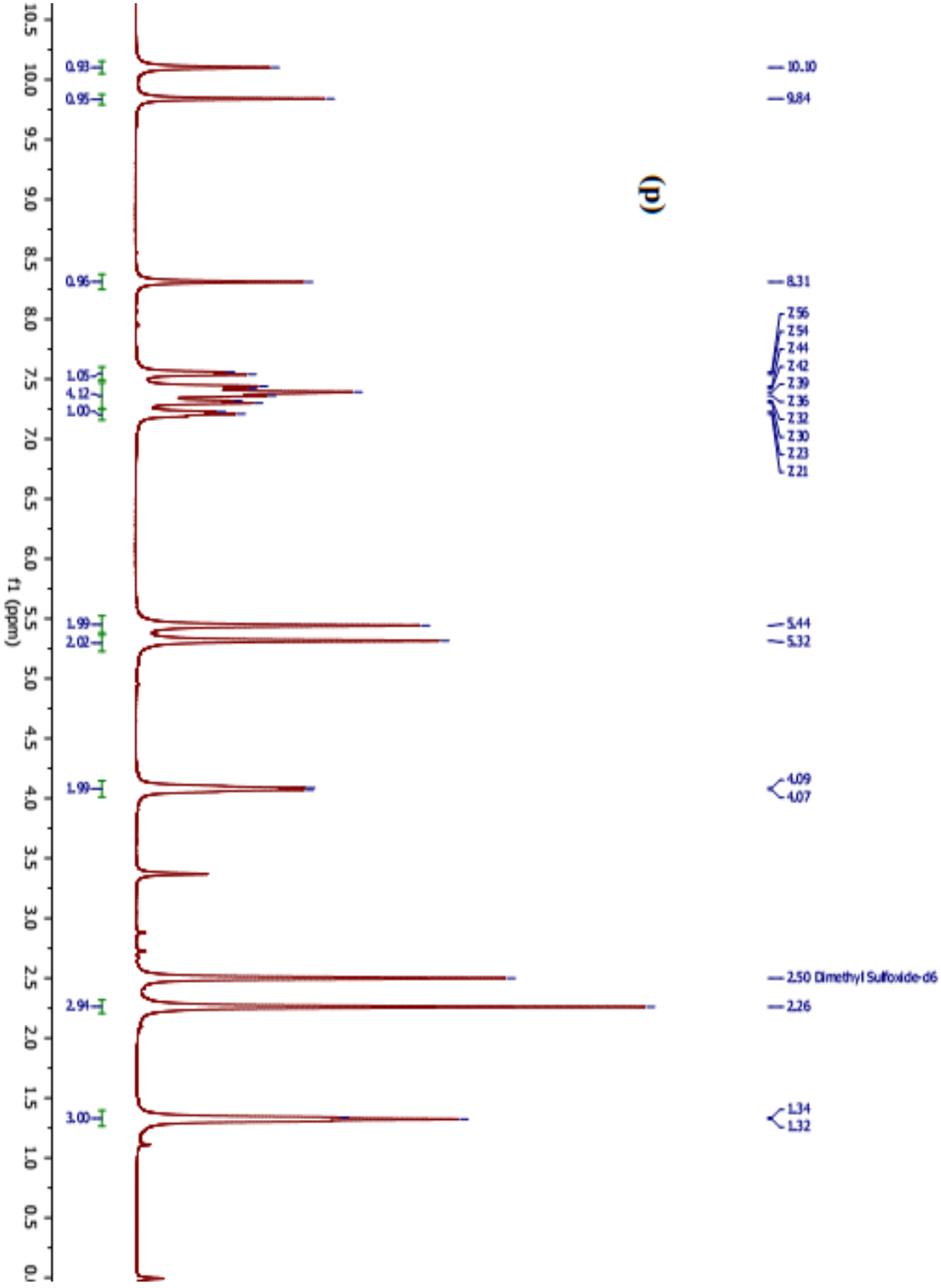

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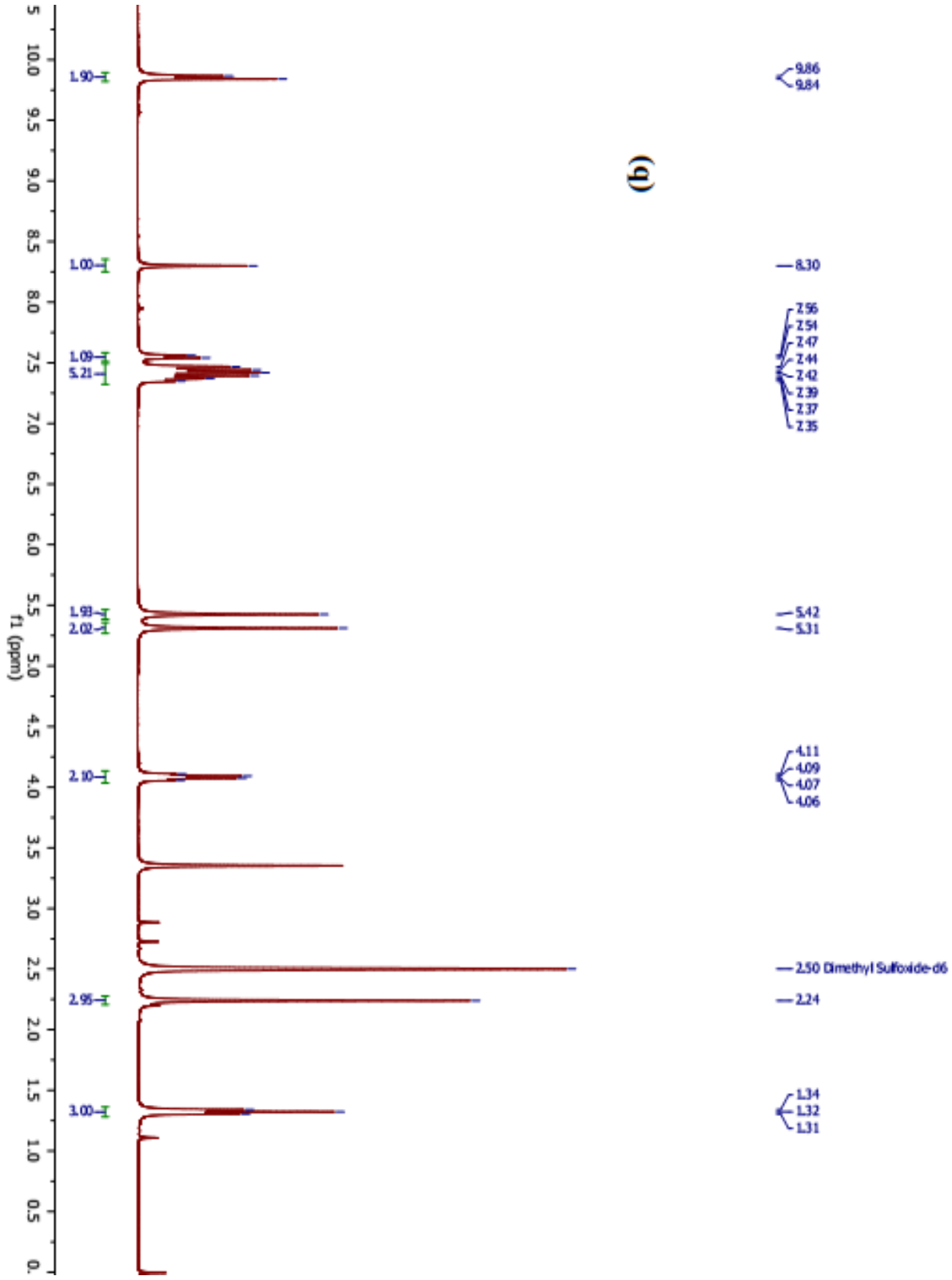

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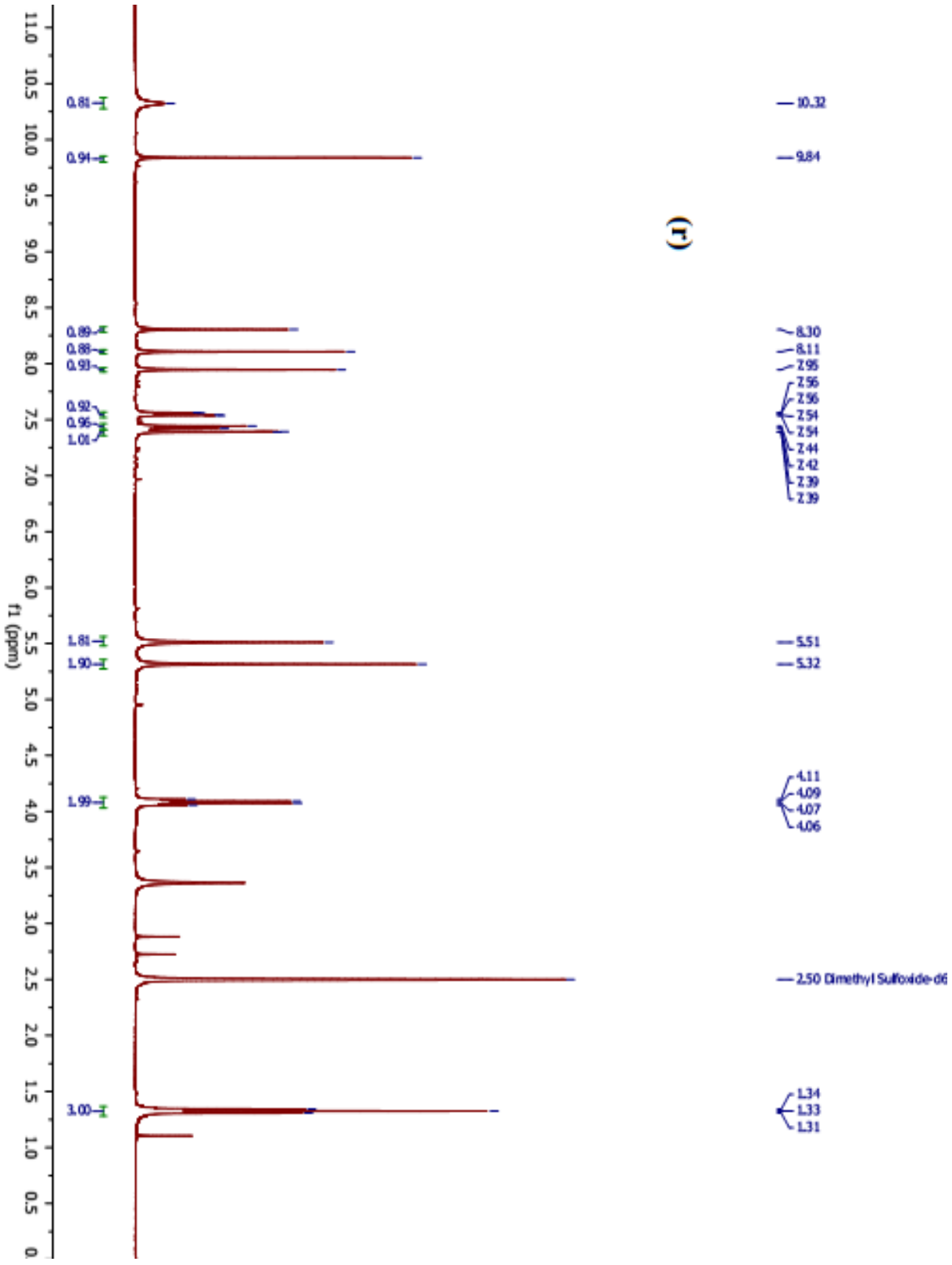

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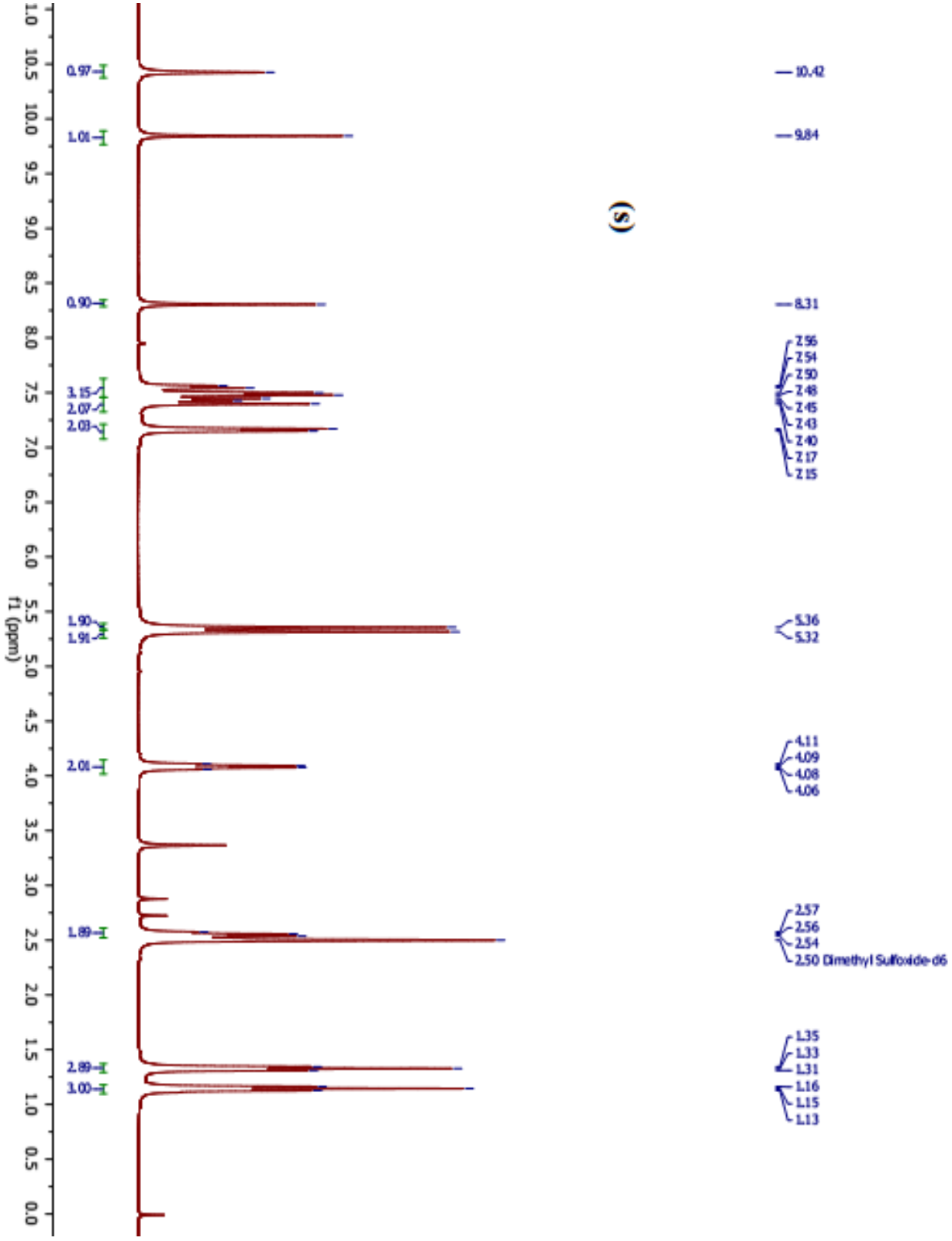

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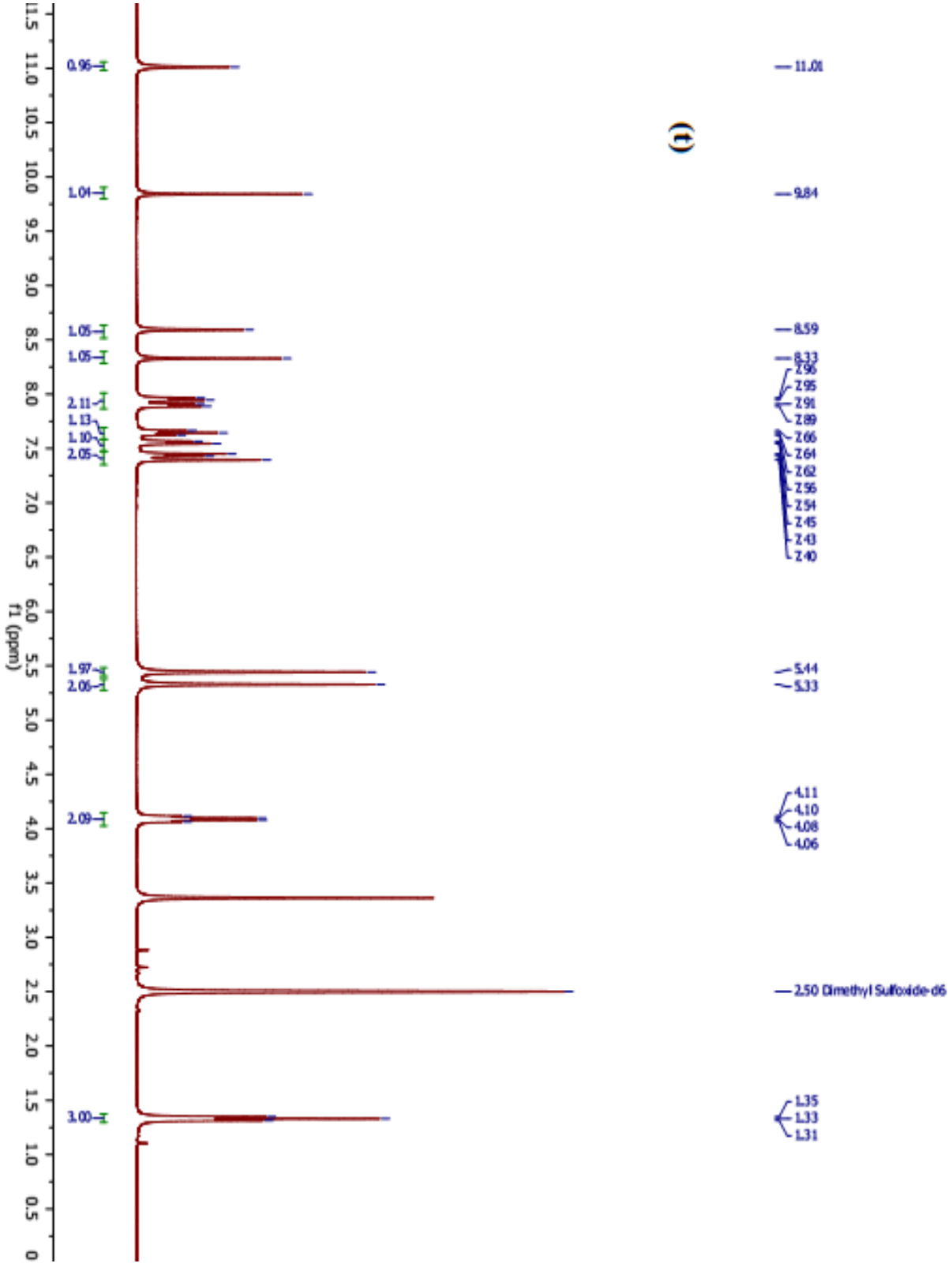

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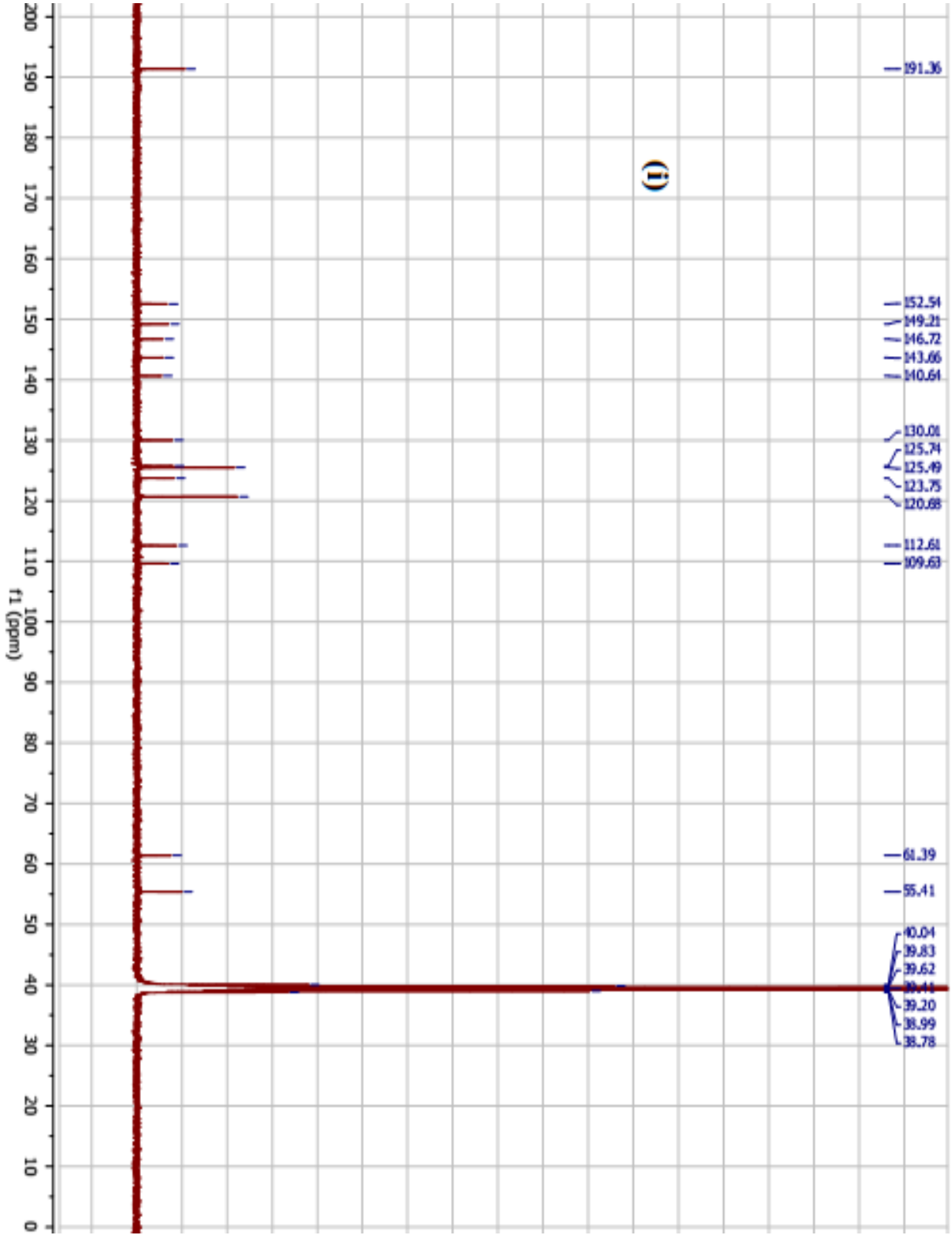
^{13}C NMR Data



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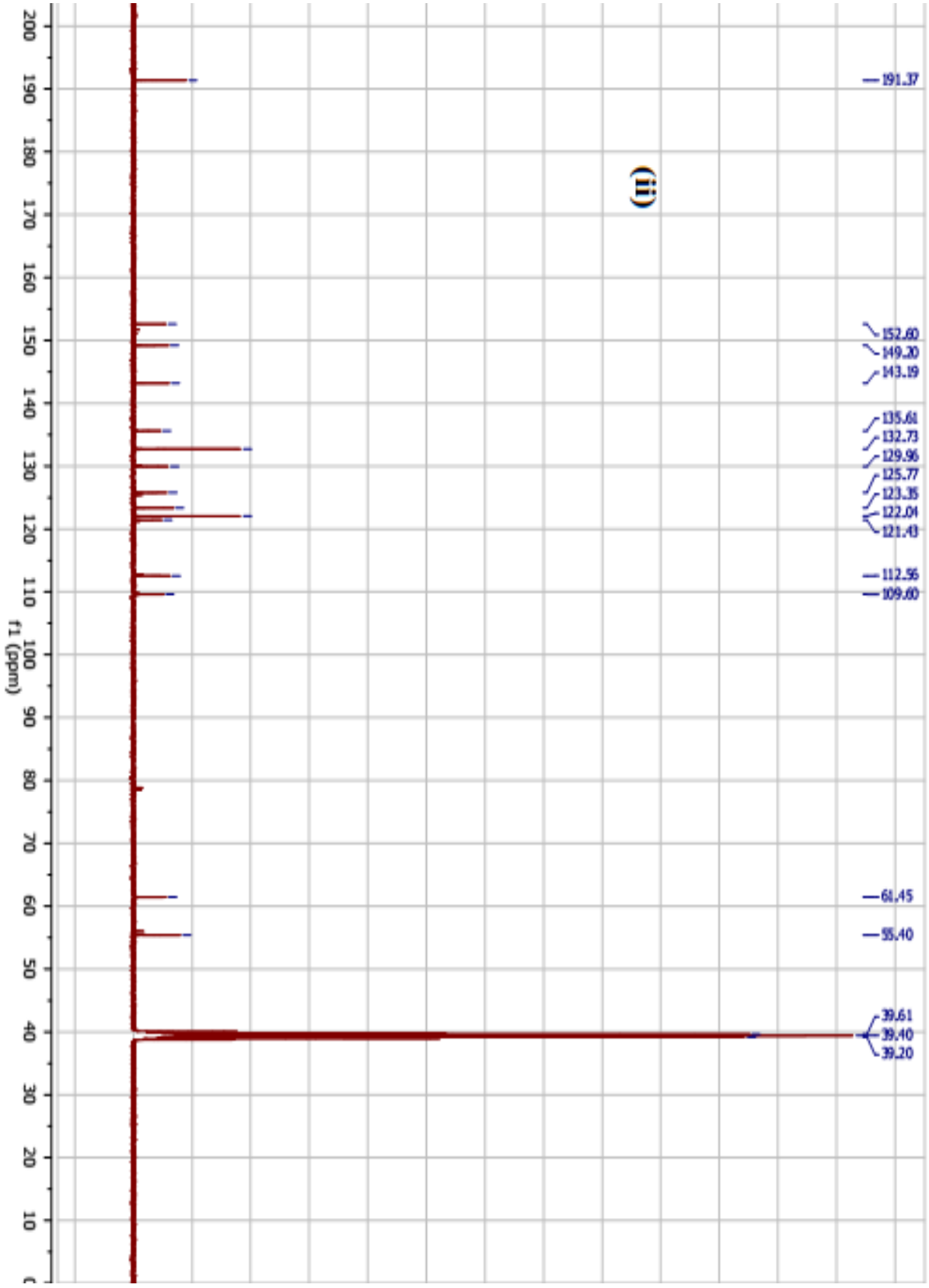

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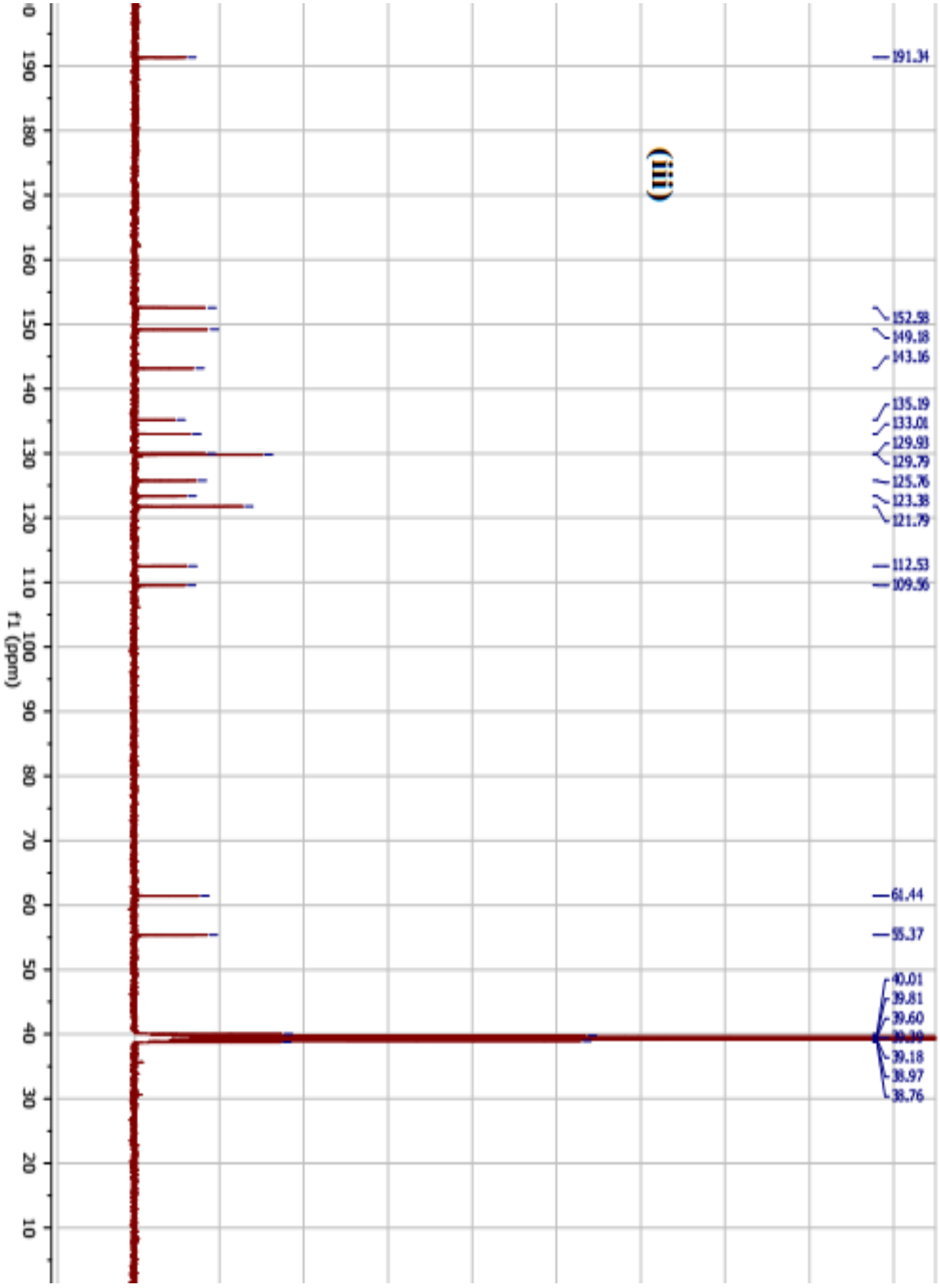

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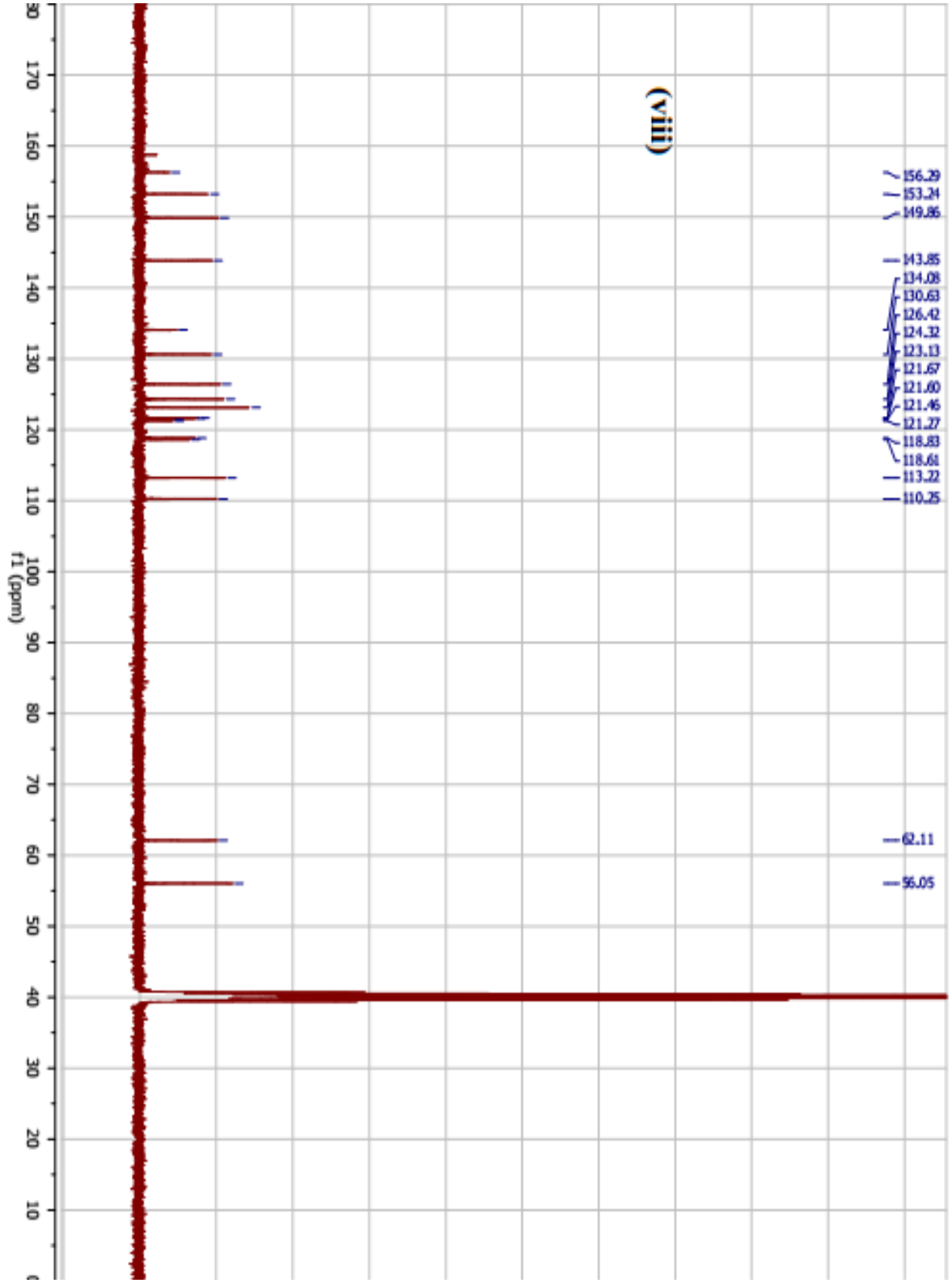

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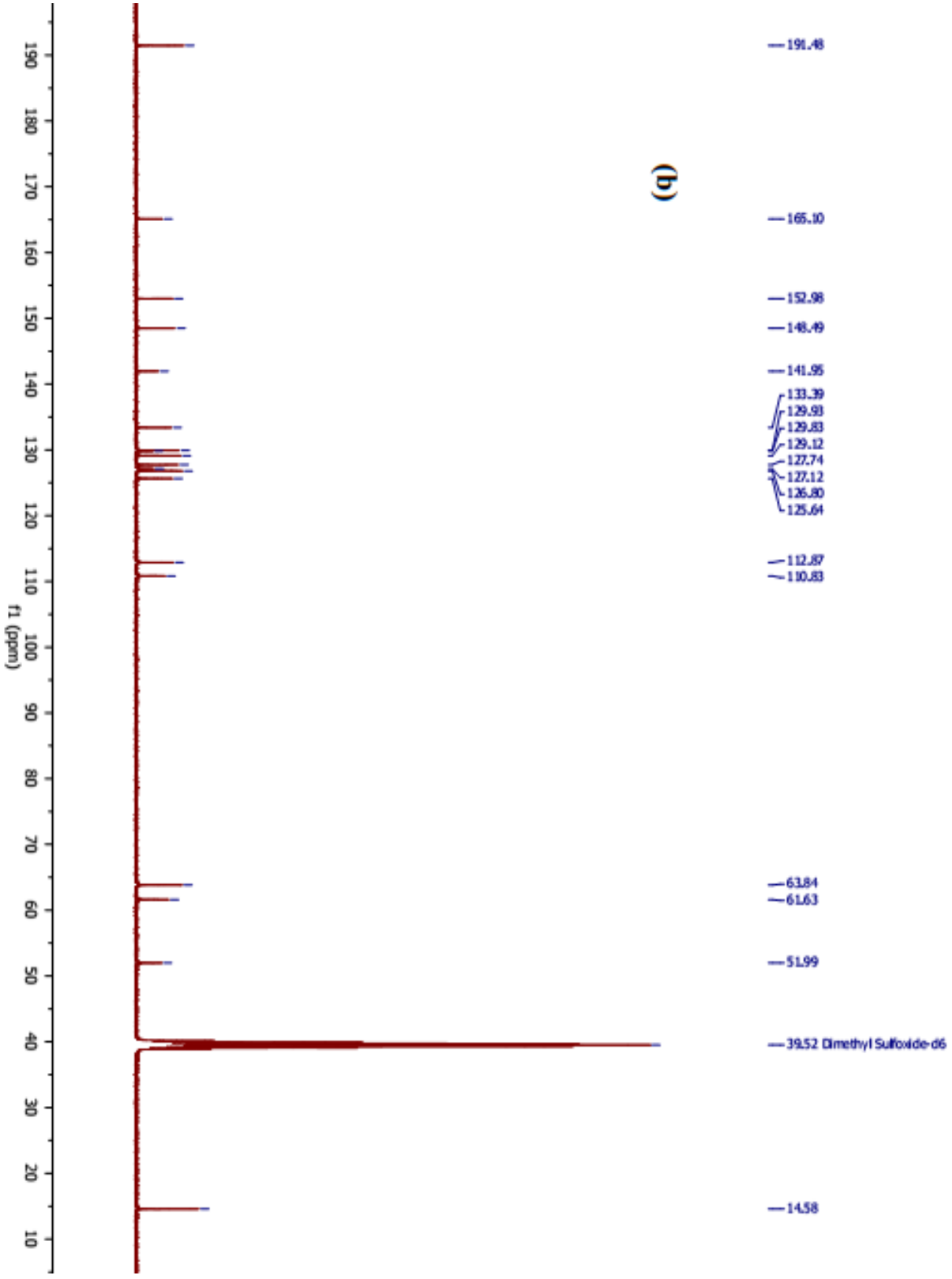

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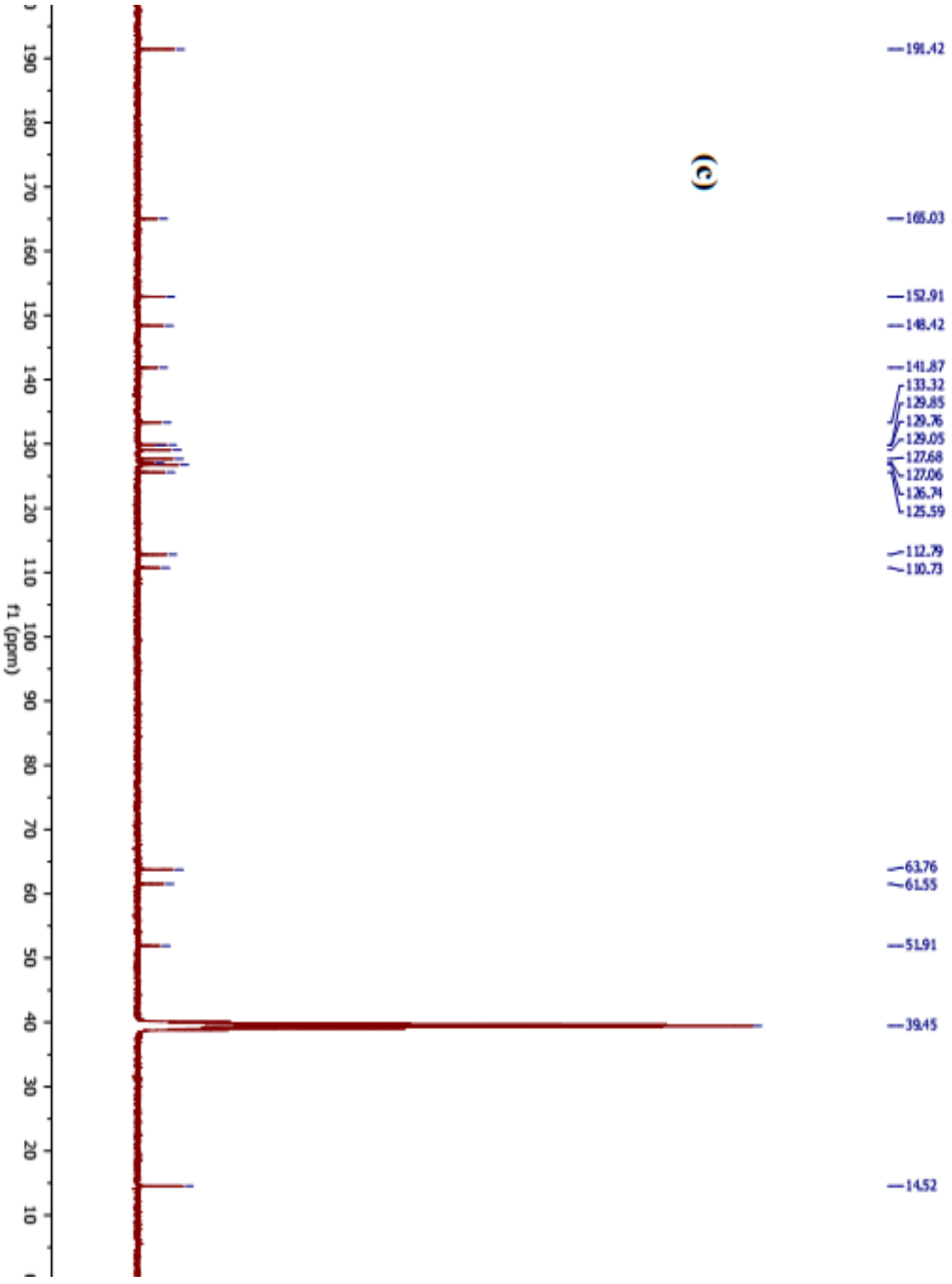

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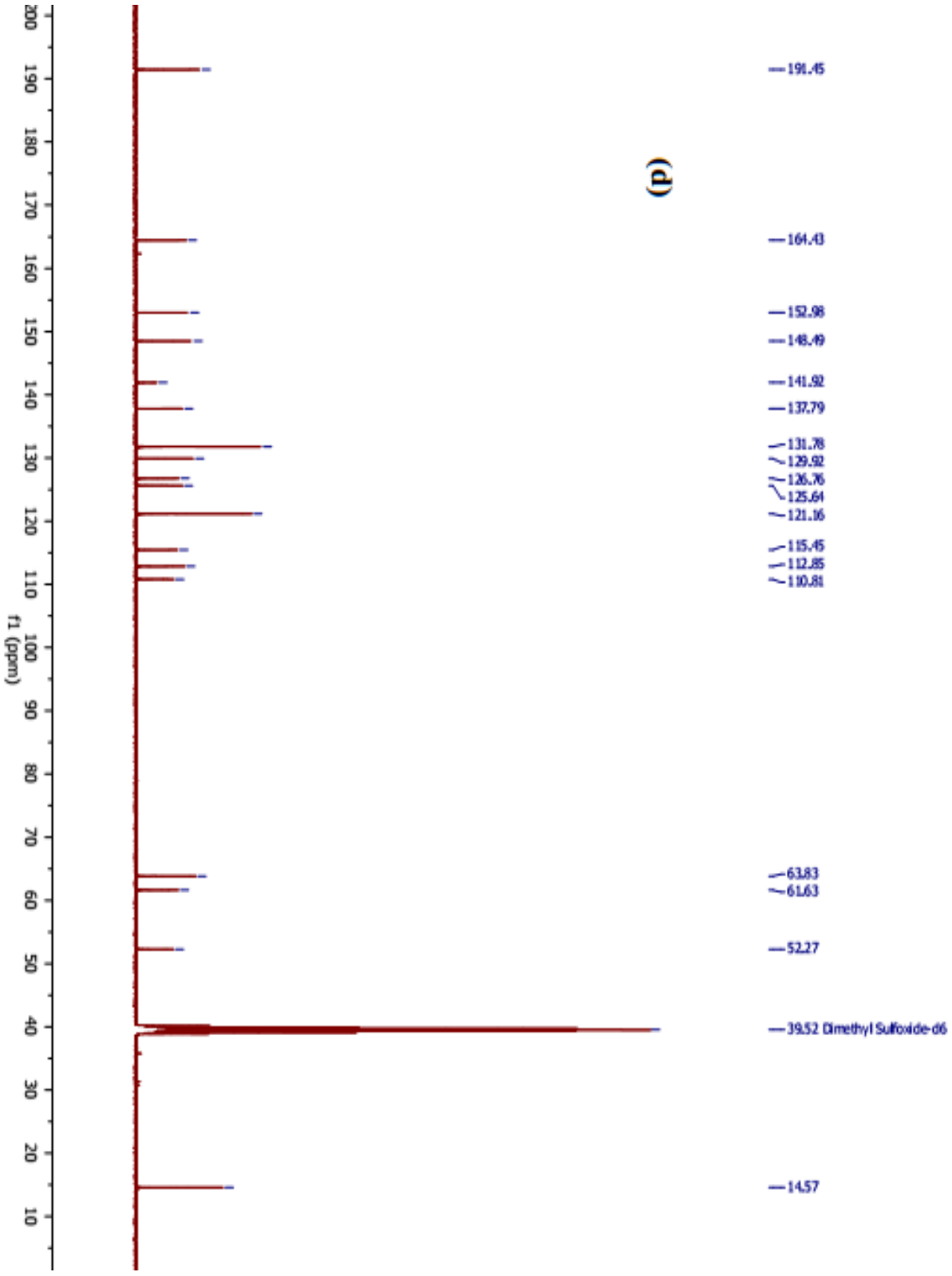

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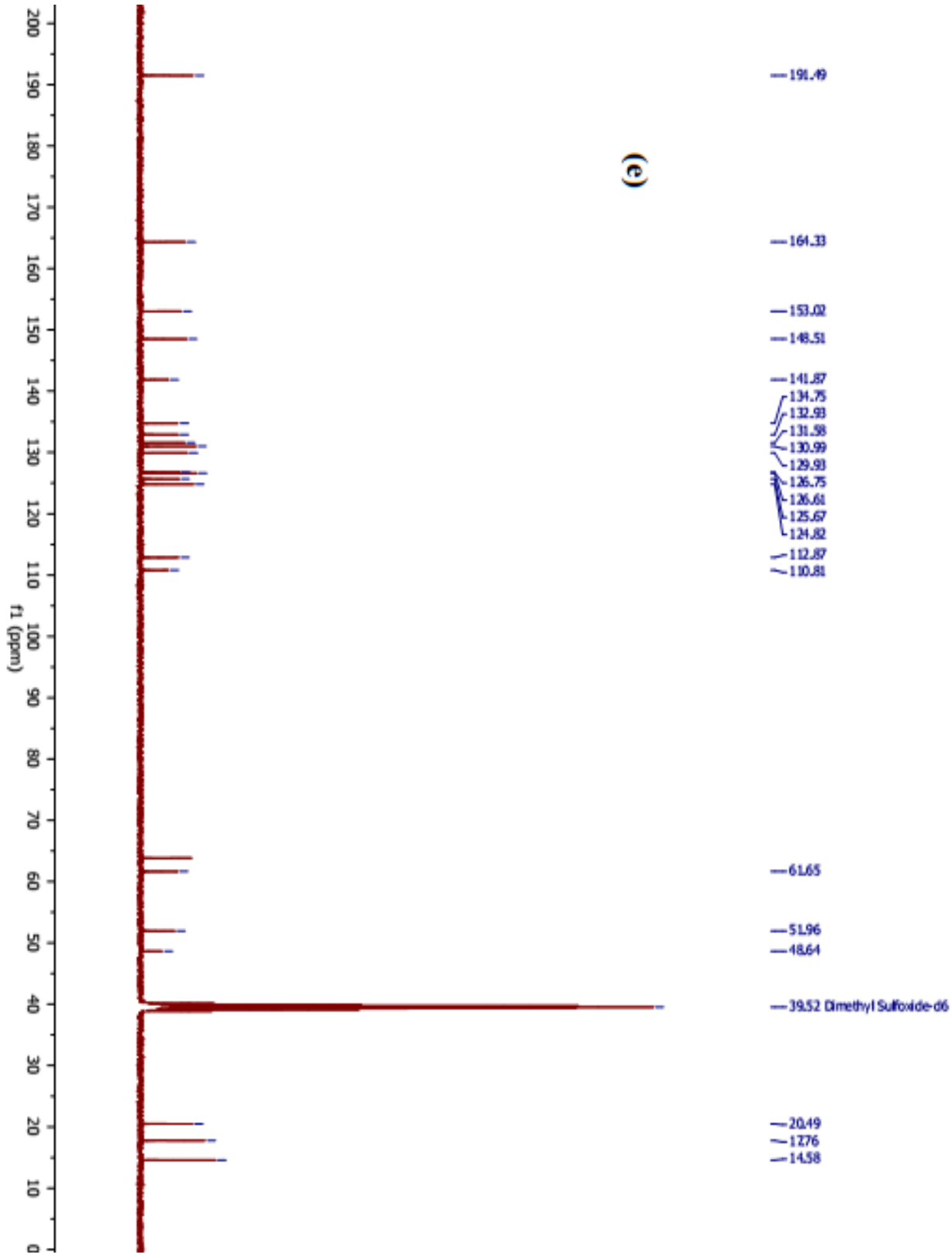

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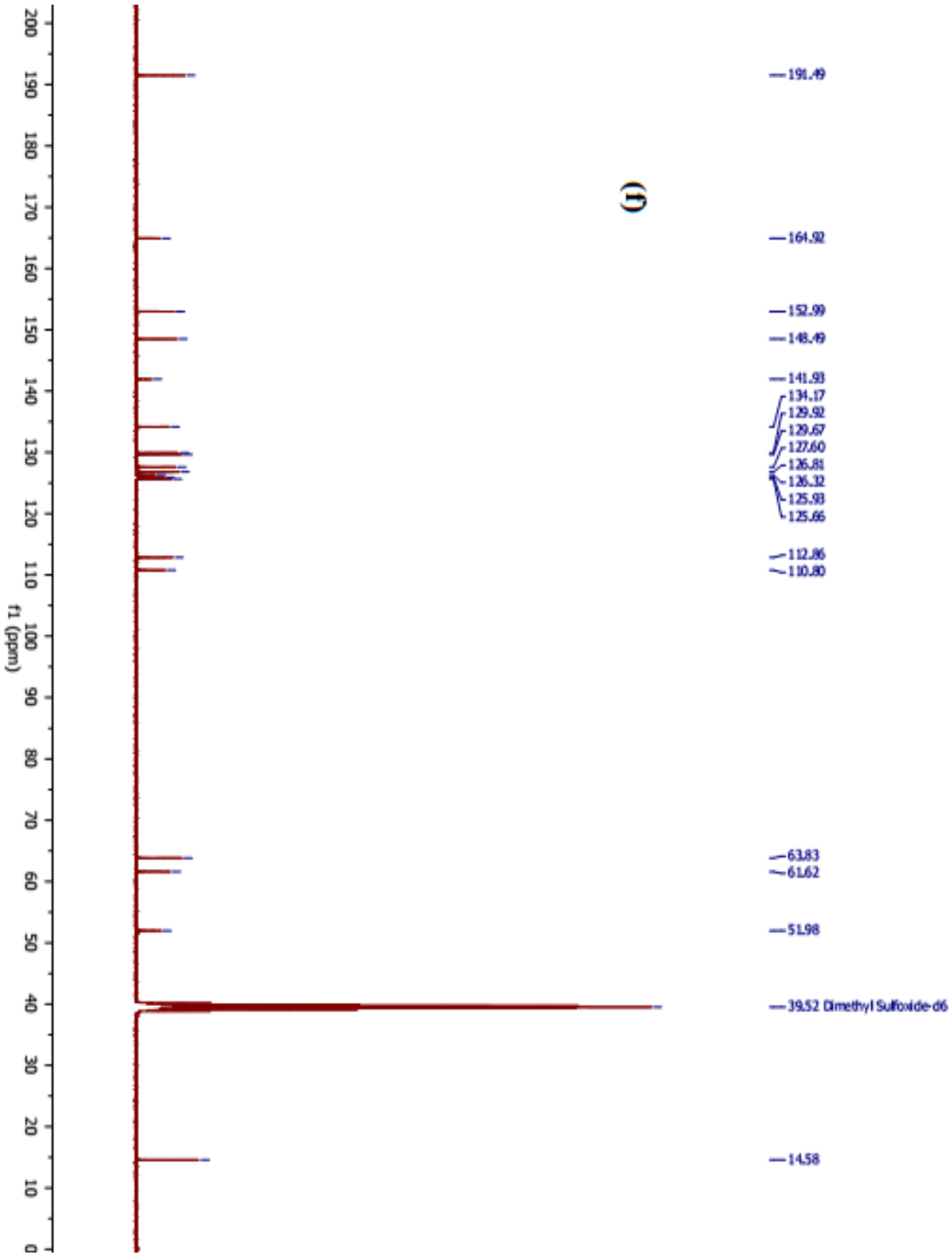

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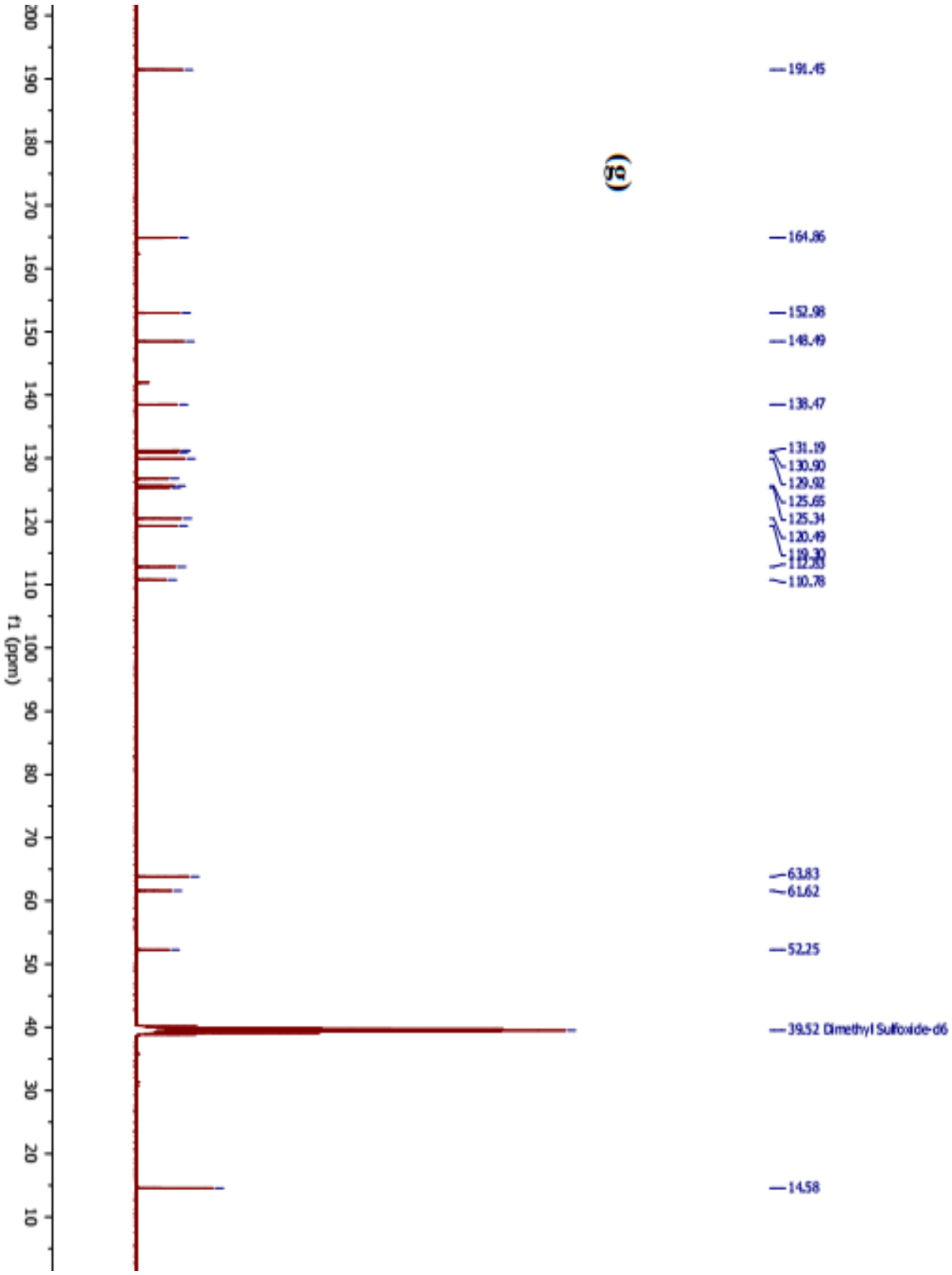

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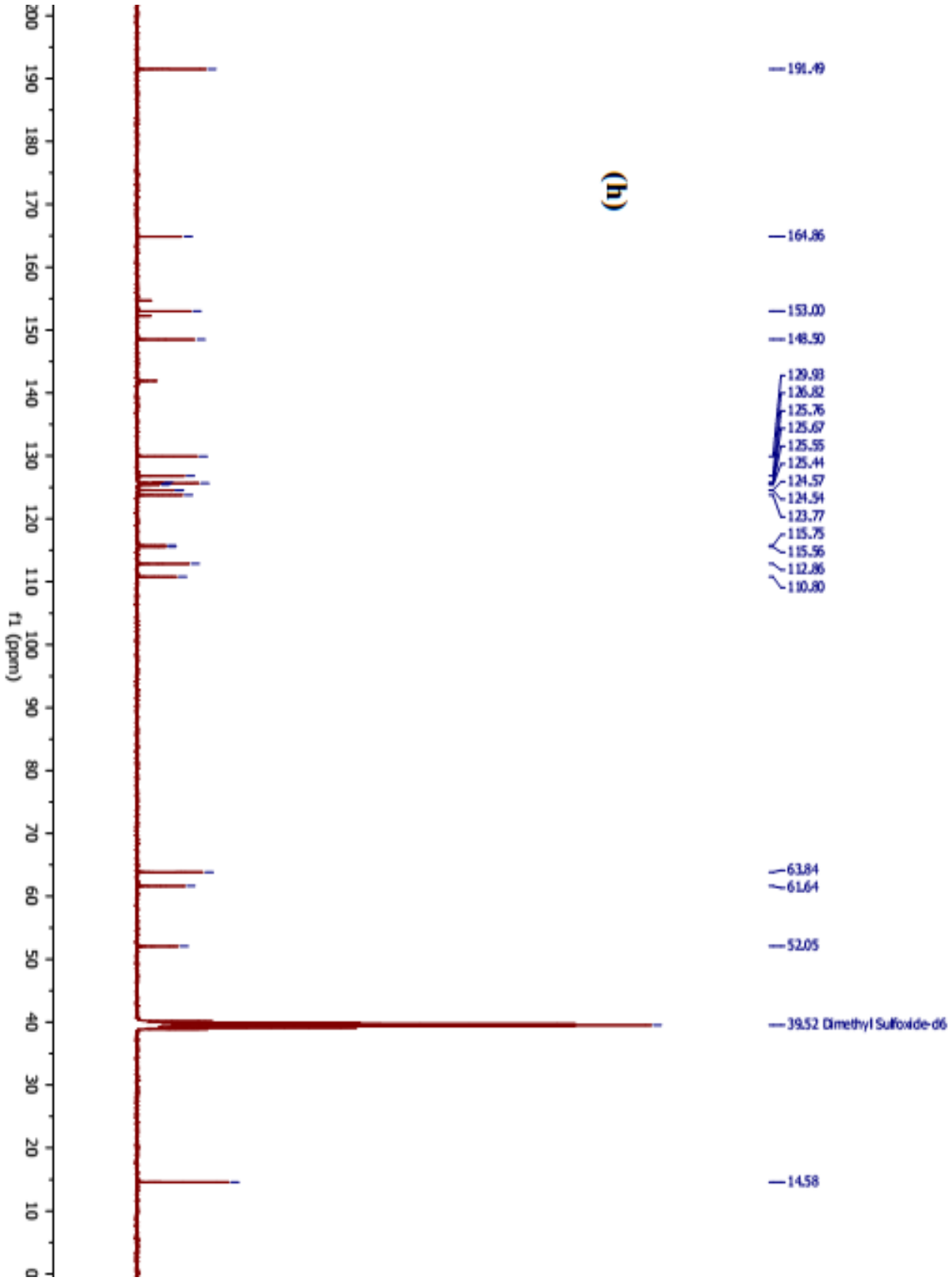

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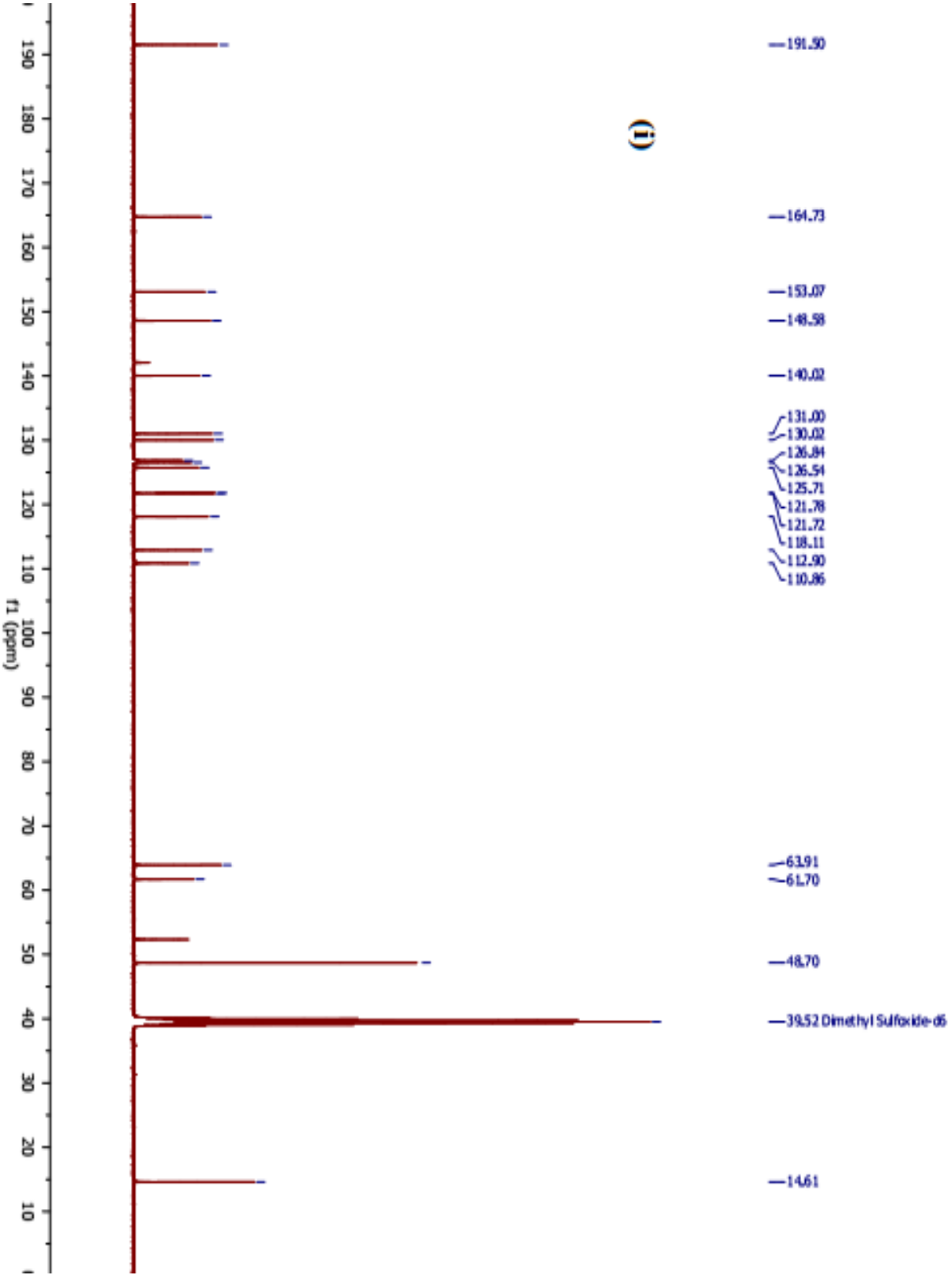

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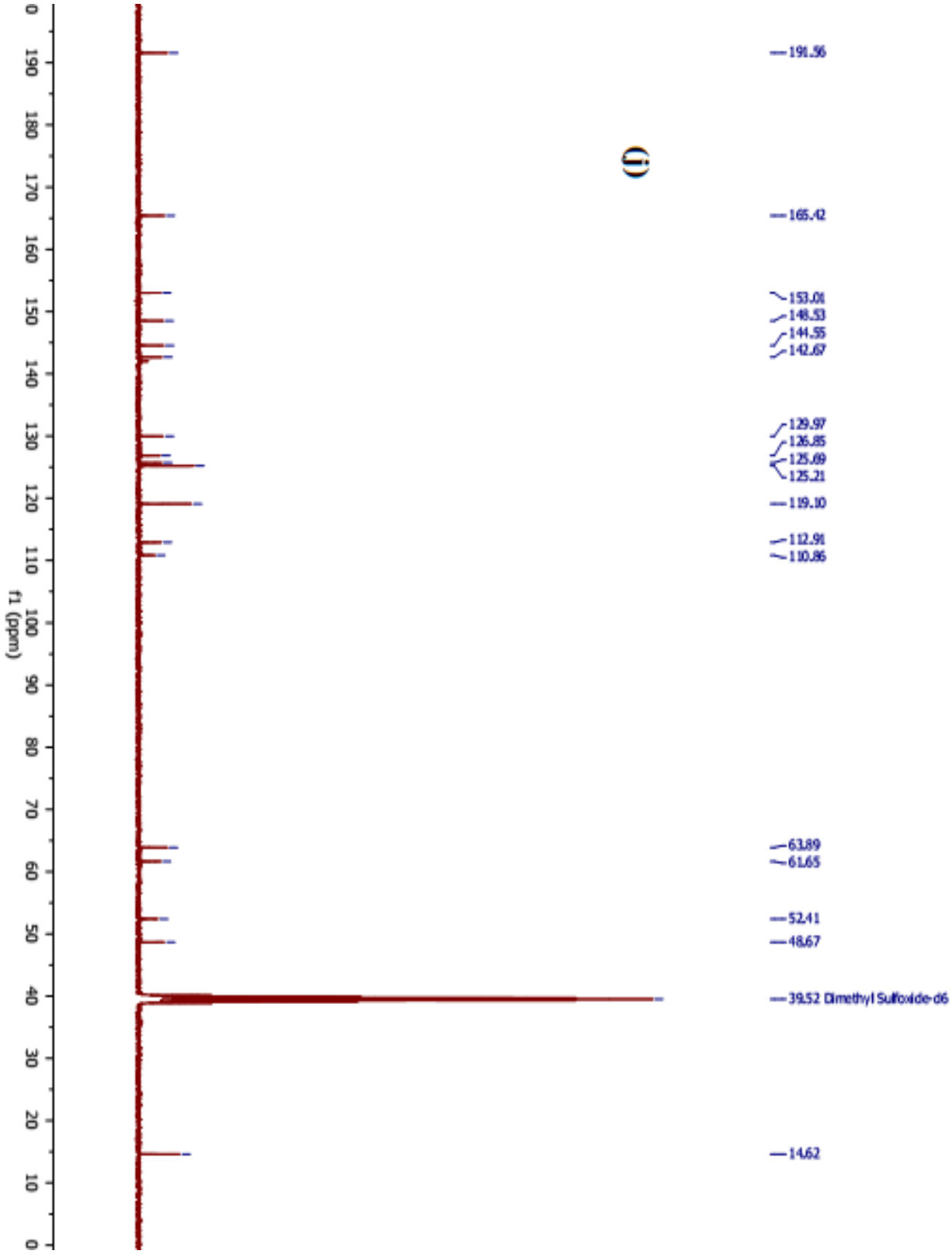

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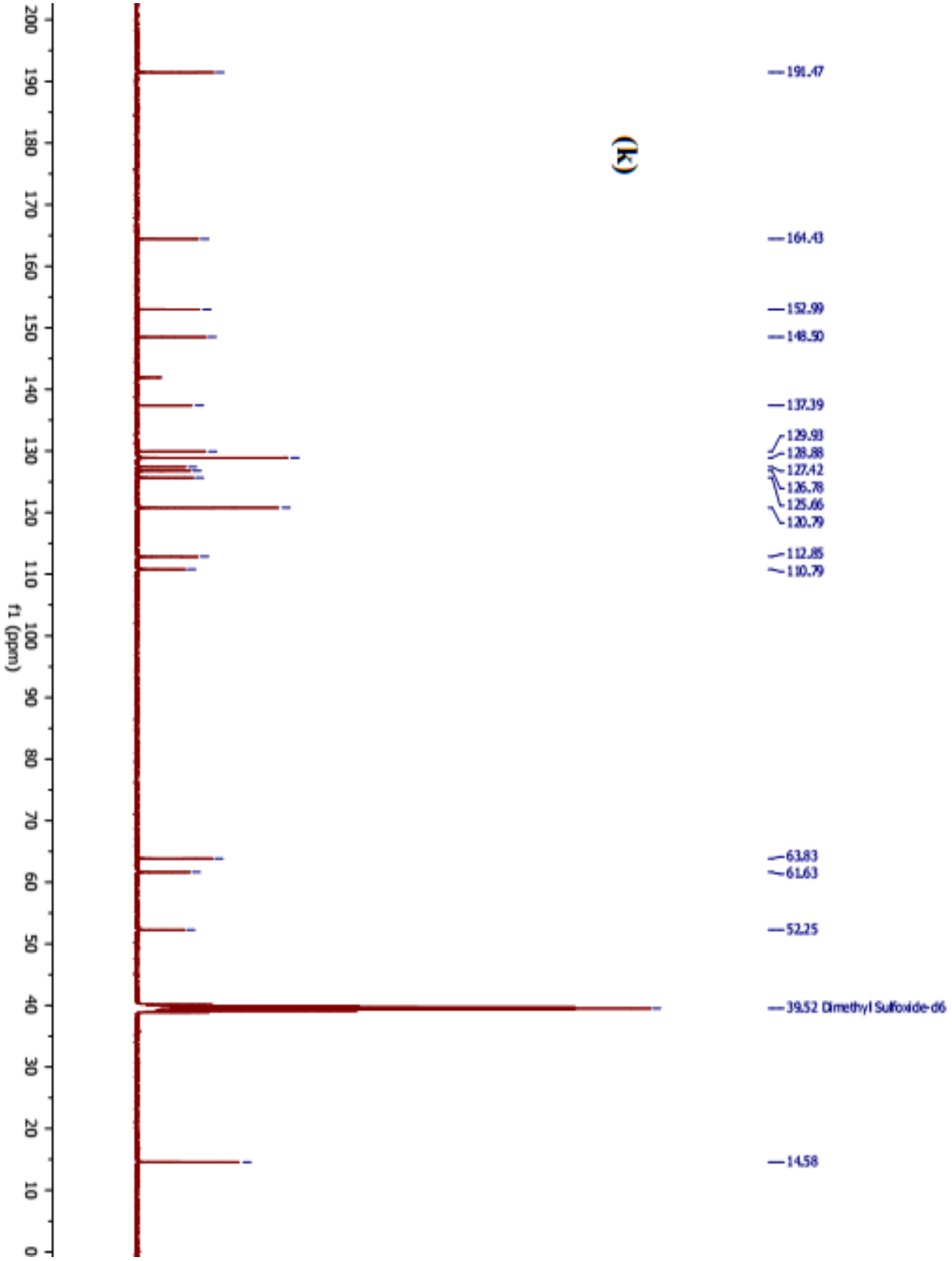
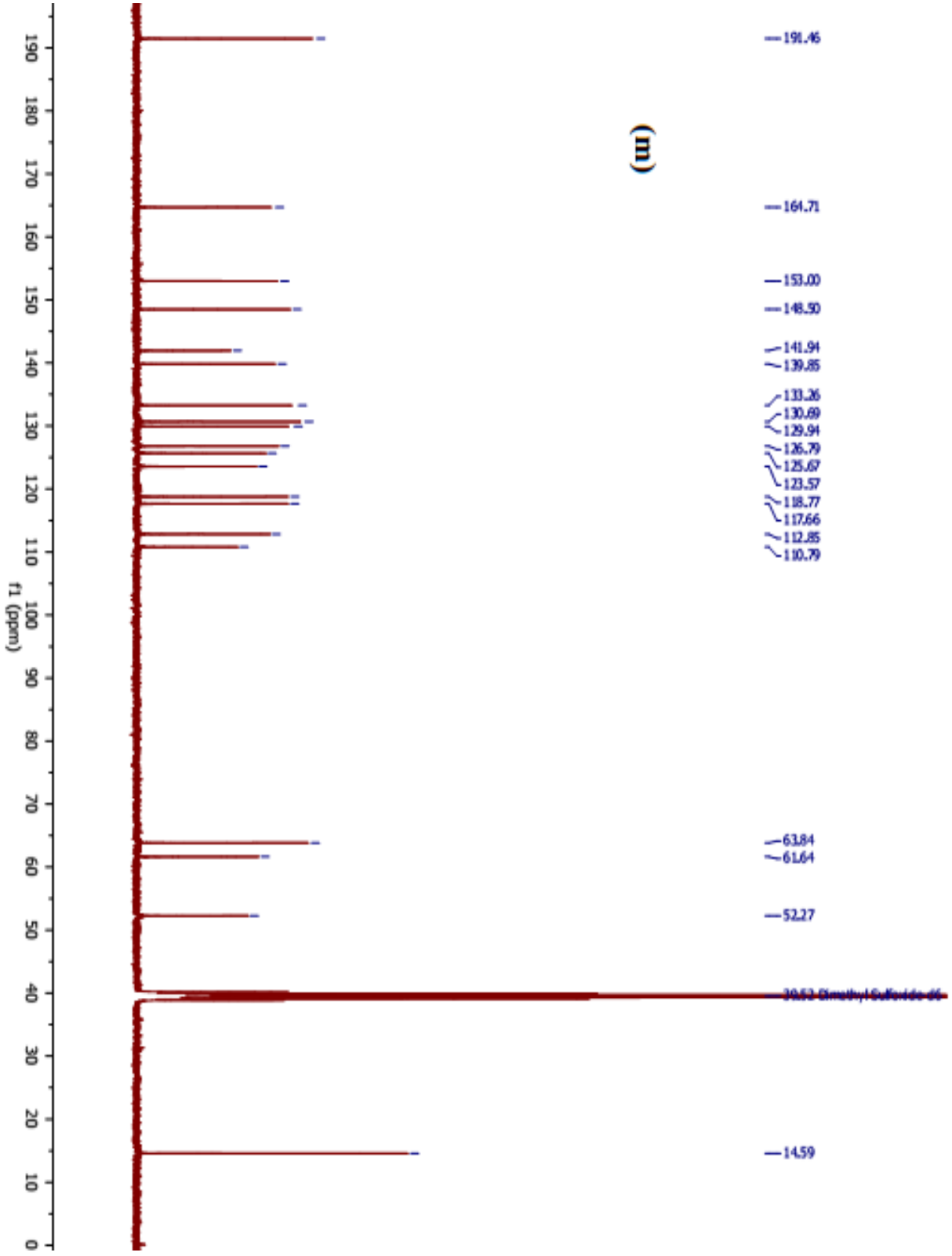
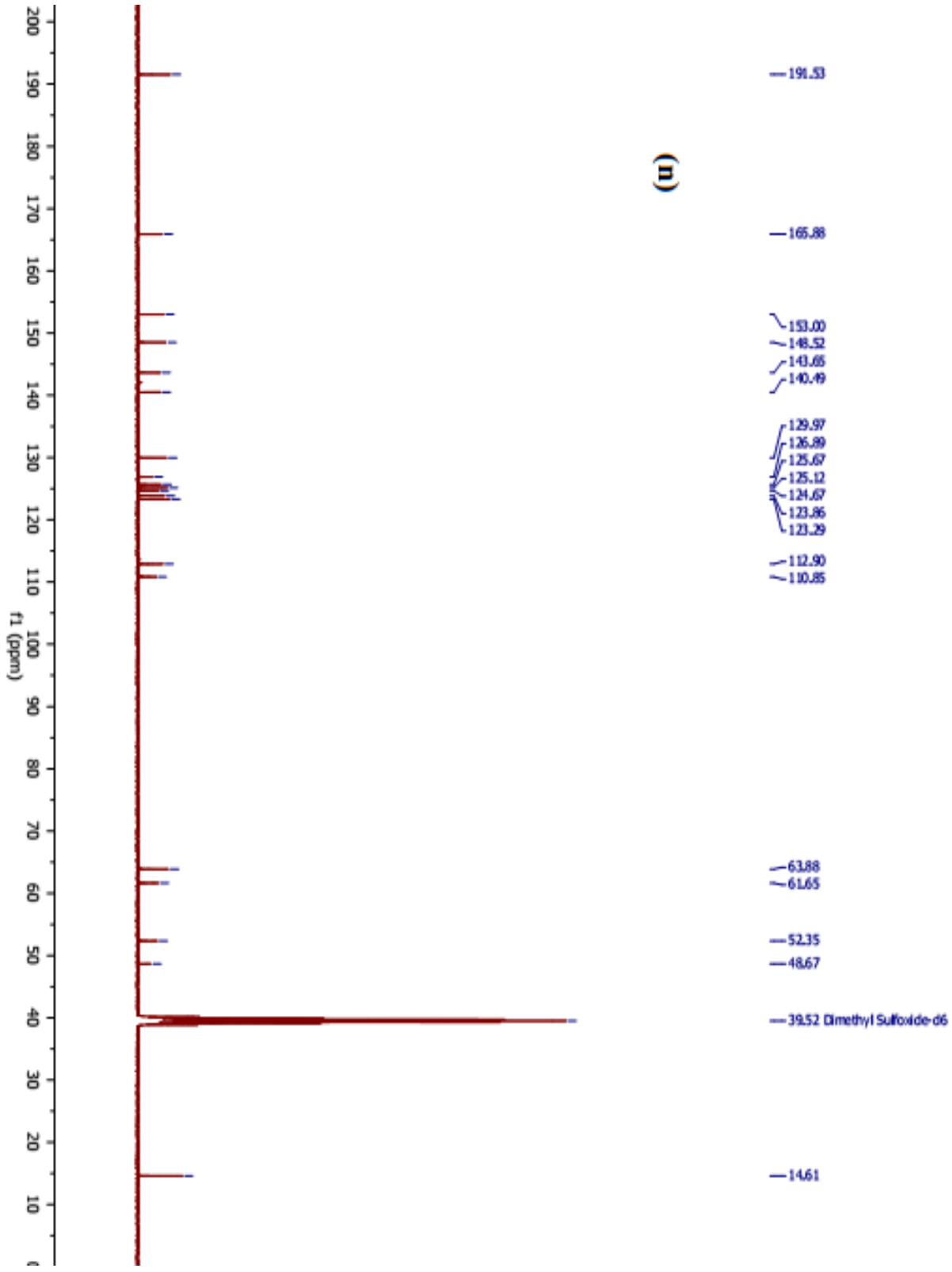


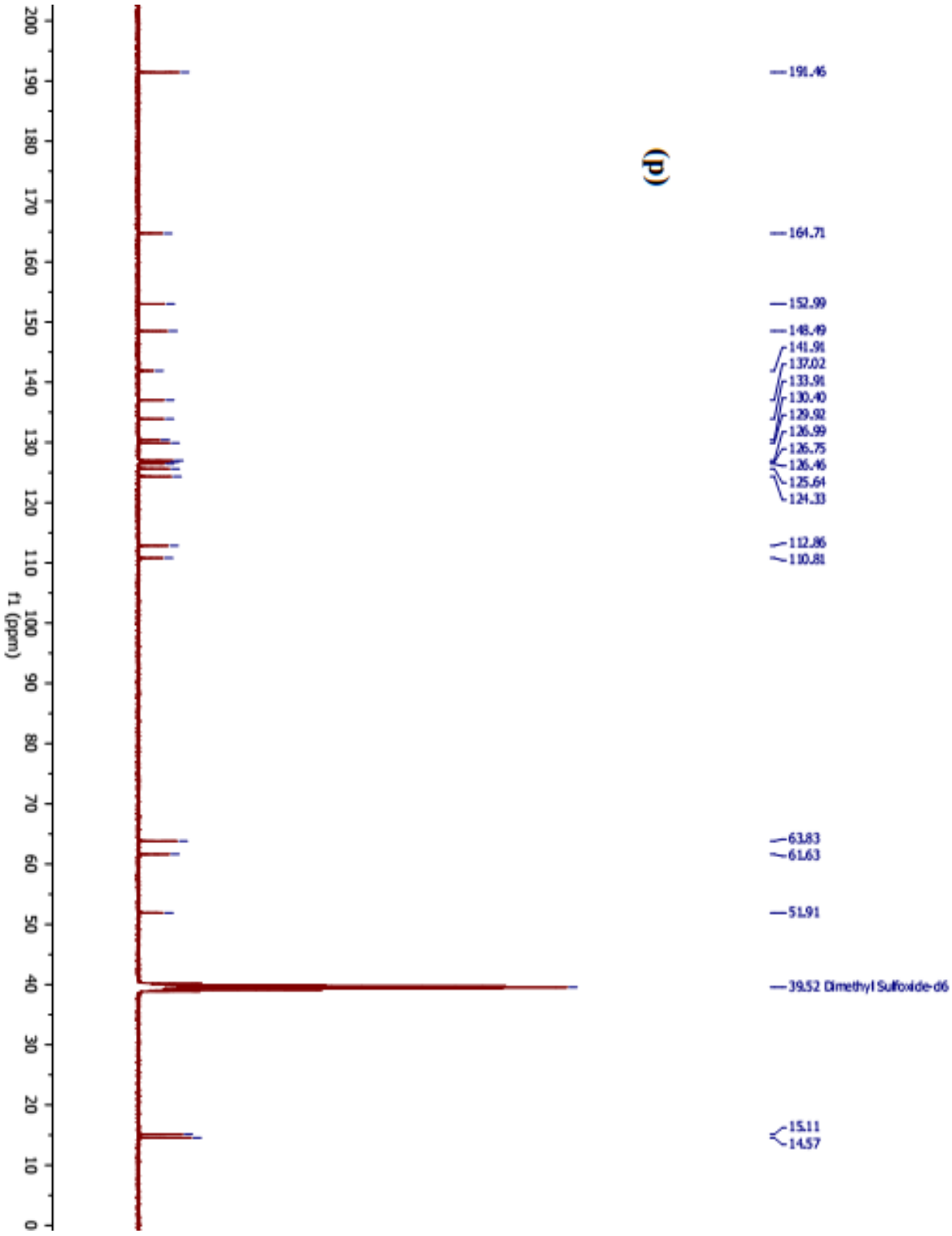
N-(4-chlorophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (k)



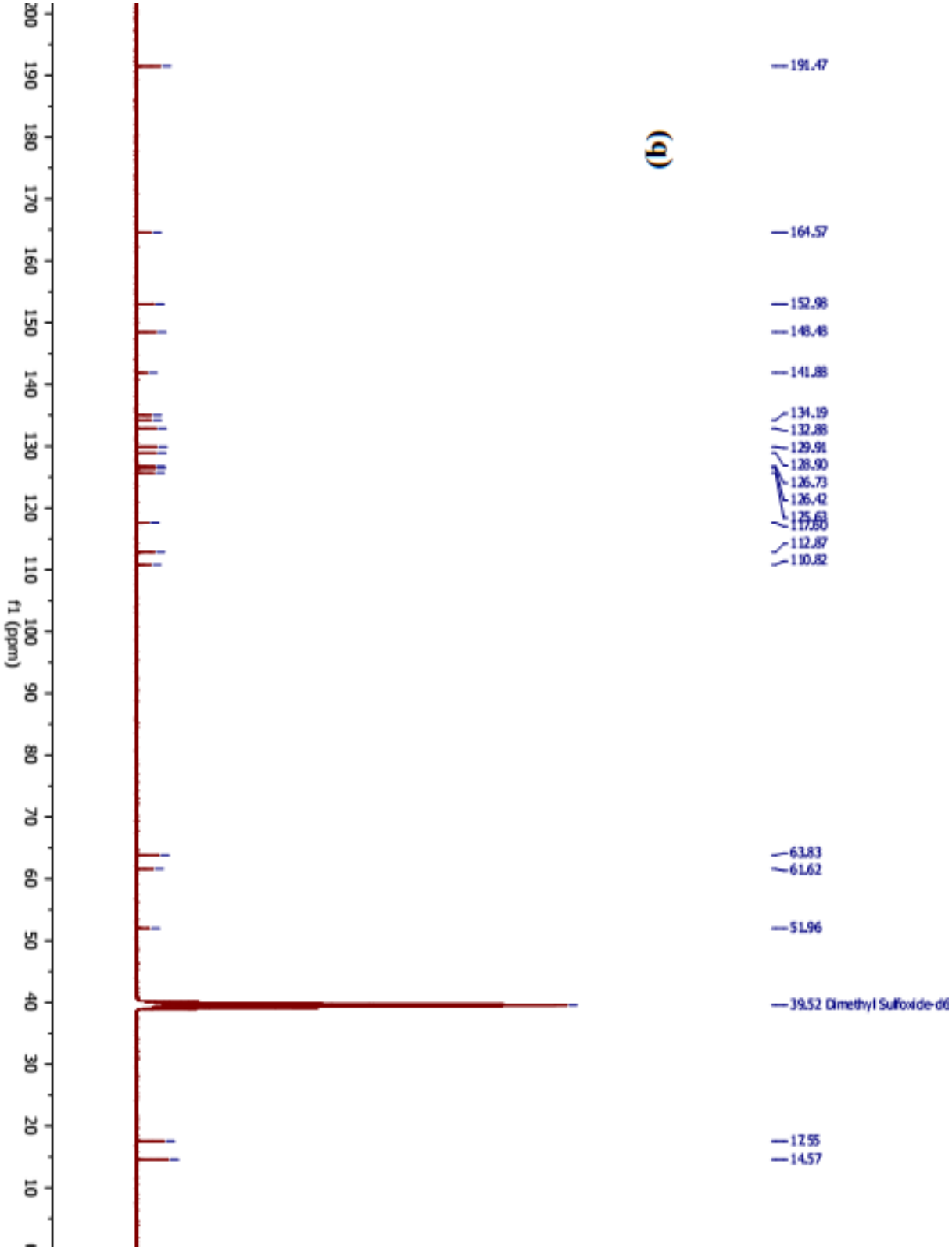
N-(3-chlorophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (m)



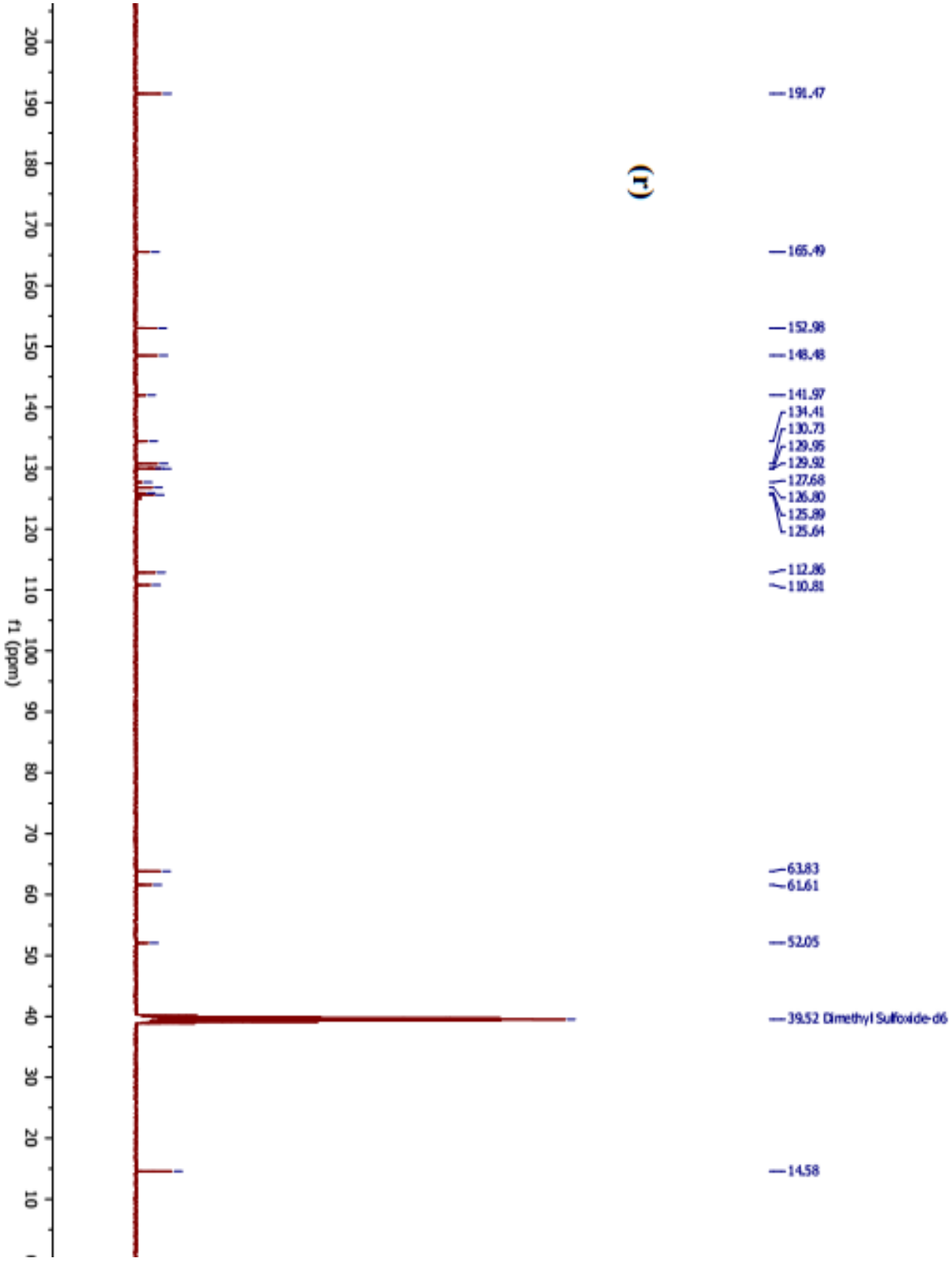
N-(2-chloro-4-nitrophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (n)



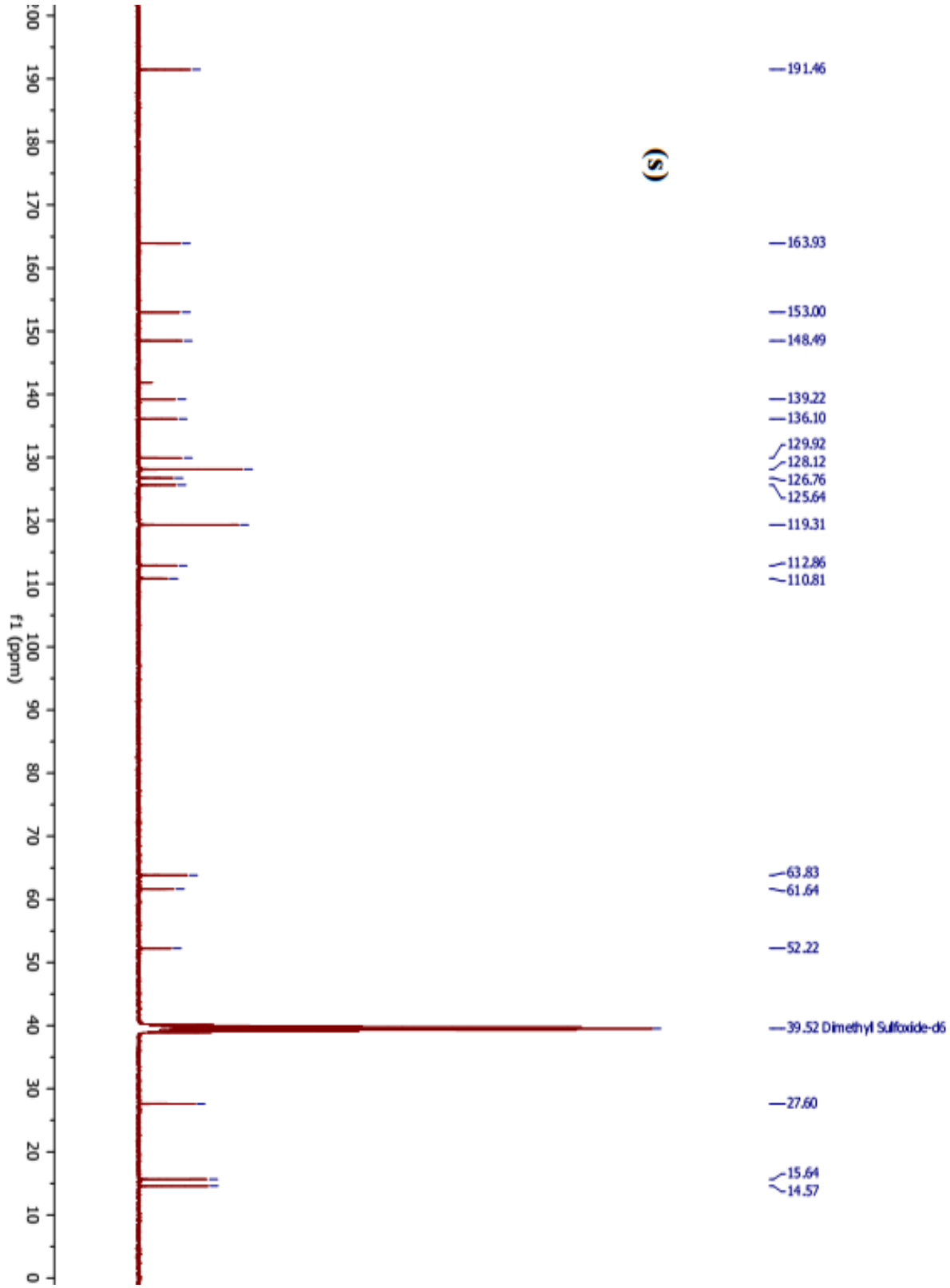
N-(3-chloro-2-methylphenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (p)



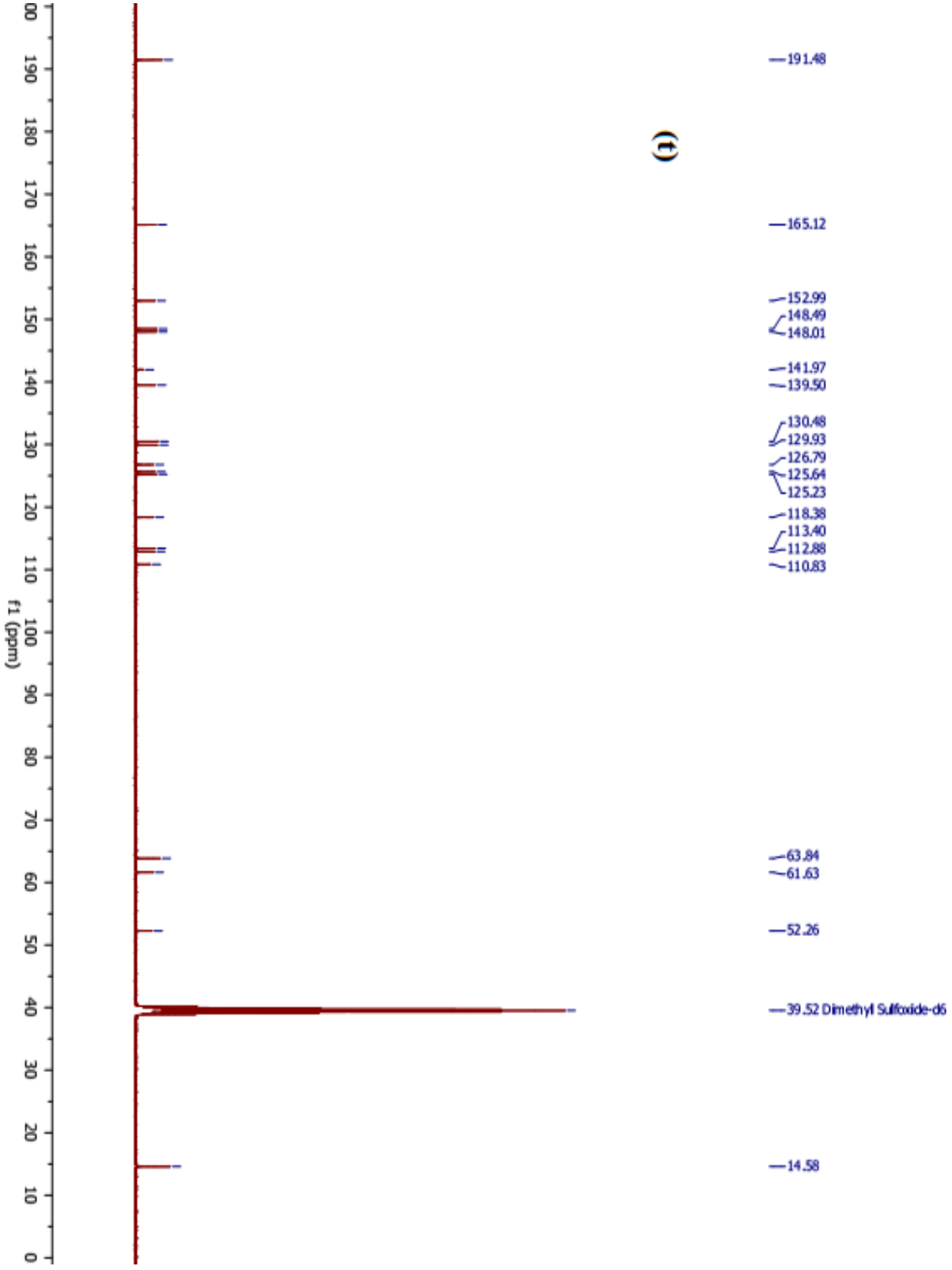
N-(4-bromo-2-methylphenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (q)



2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2,4,5-trichlorophenyl) acetamide (r)

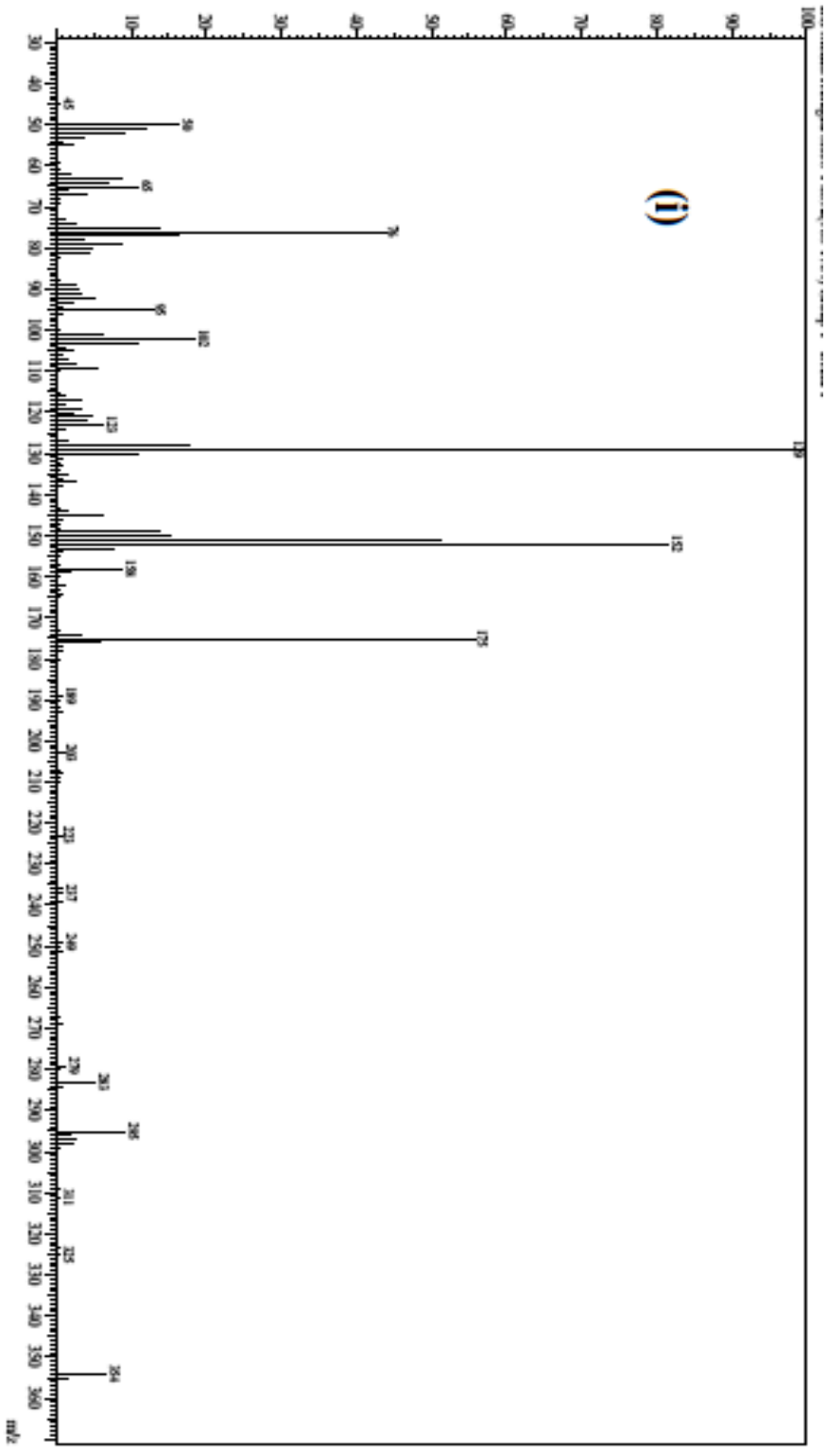


2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-ethylphenyl) acetamide (s)

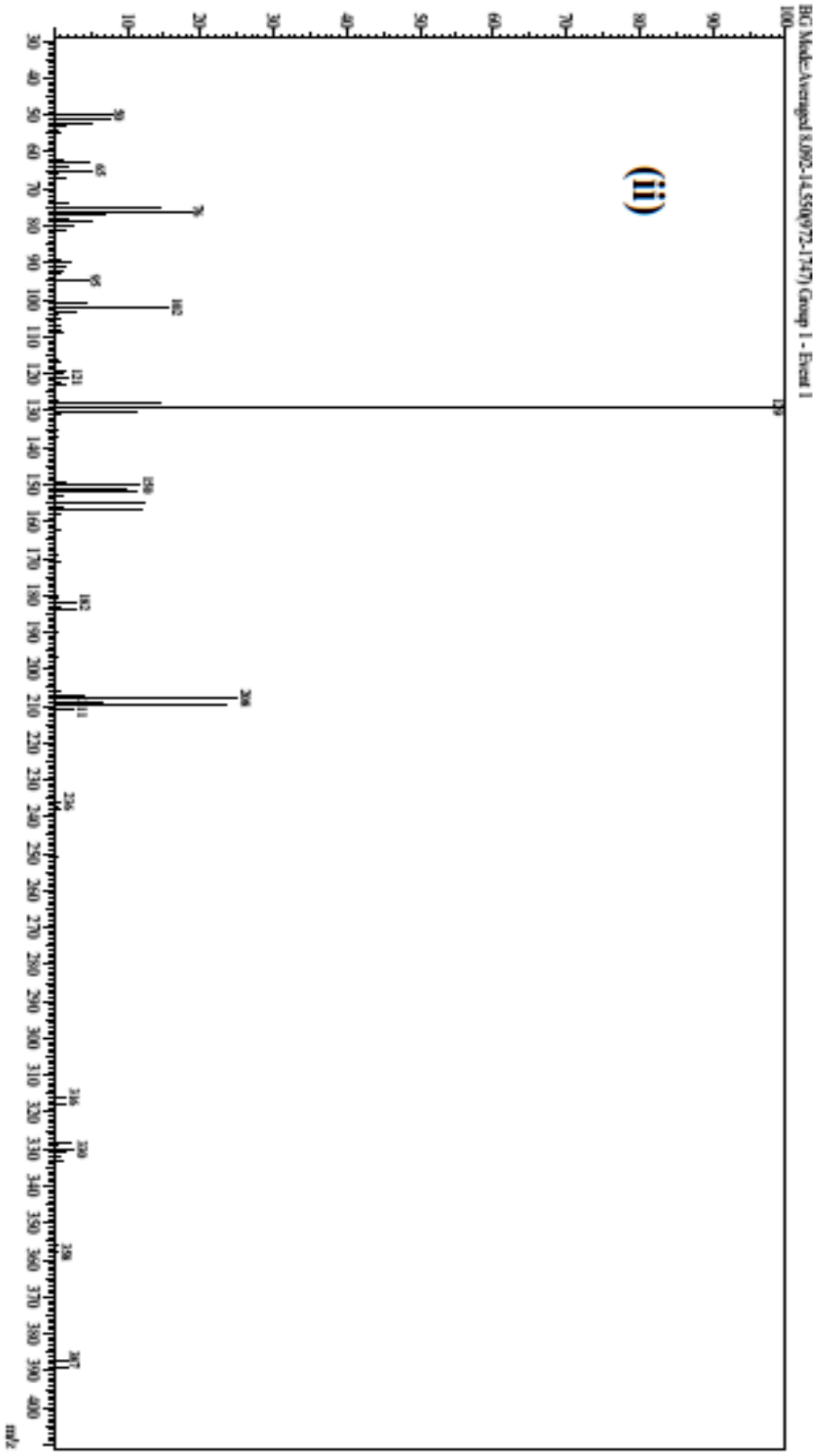


2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-nitrophenyl) acetamide (t)

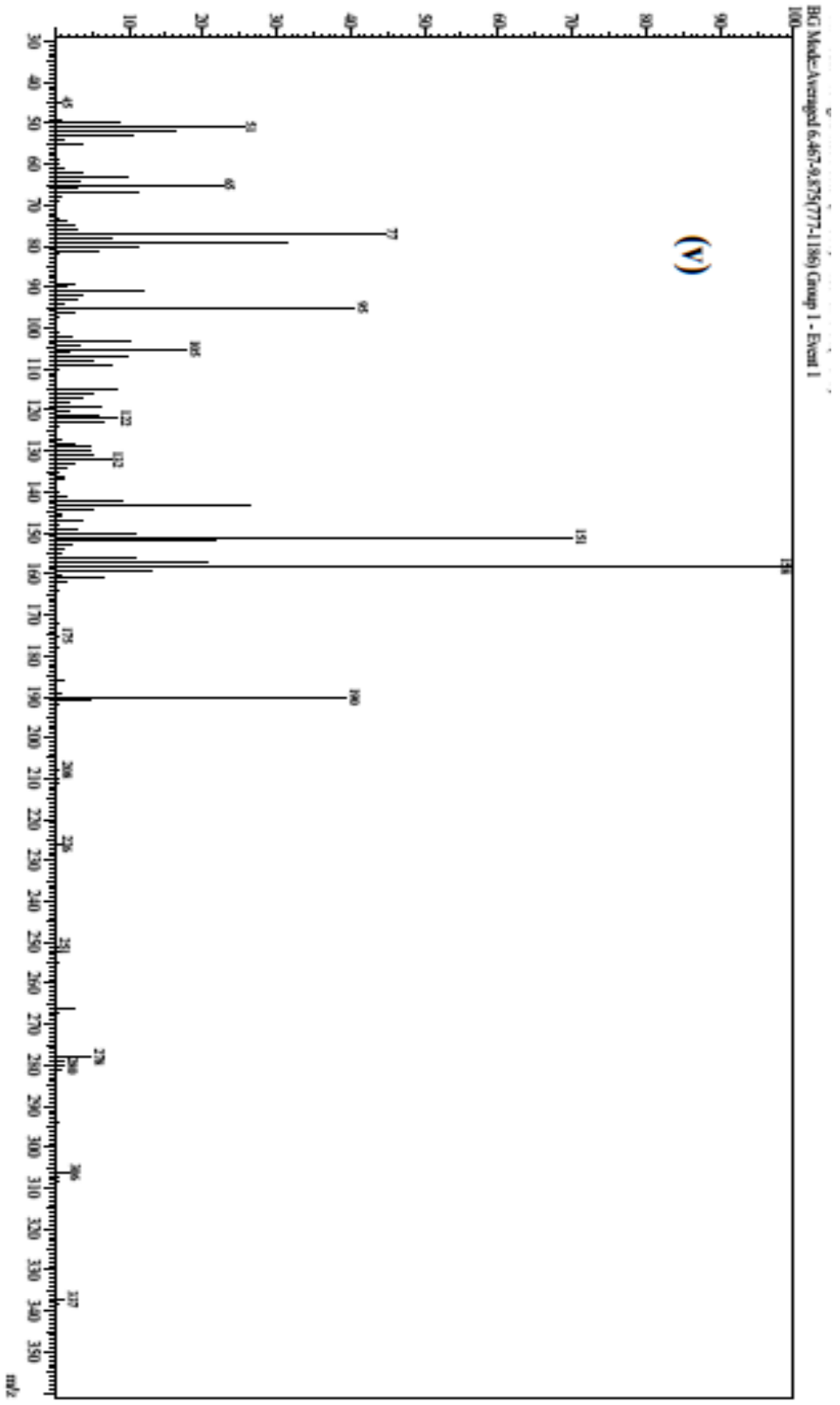
Mass data



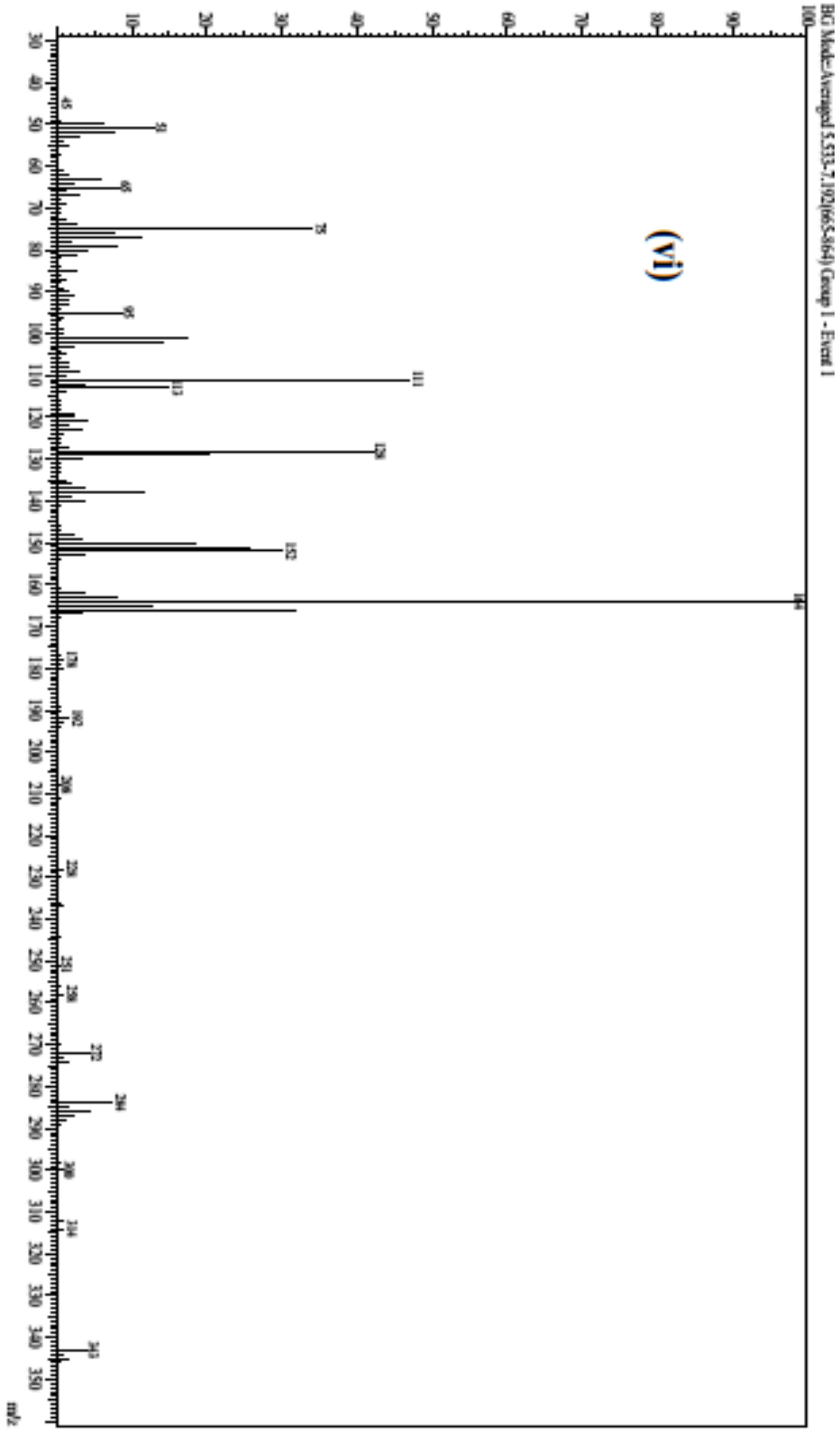
3-methoxy-4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (i)



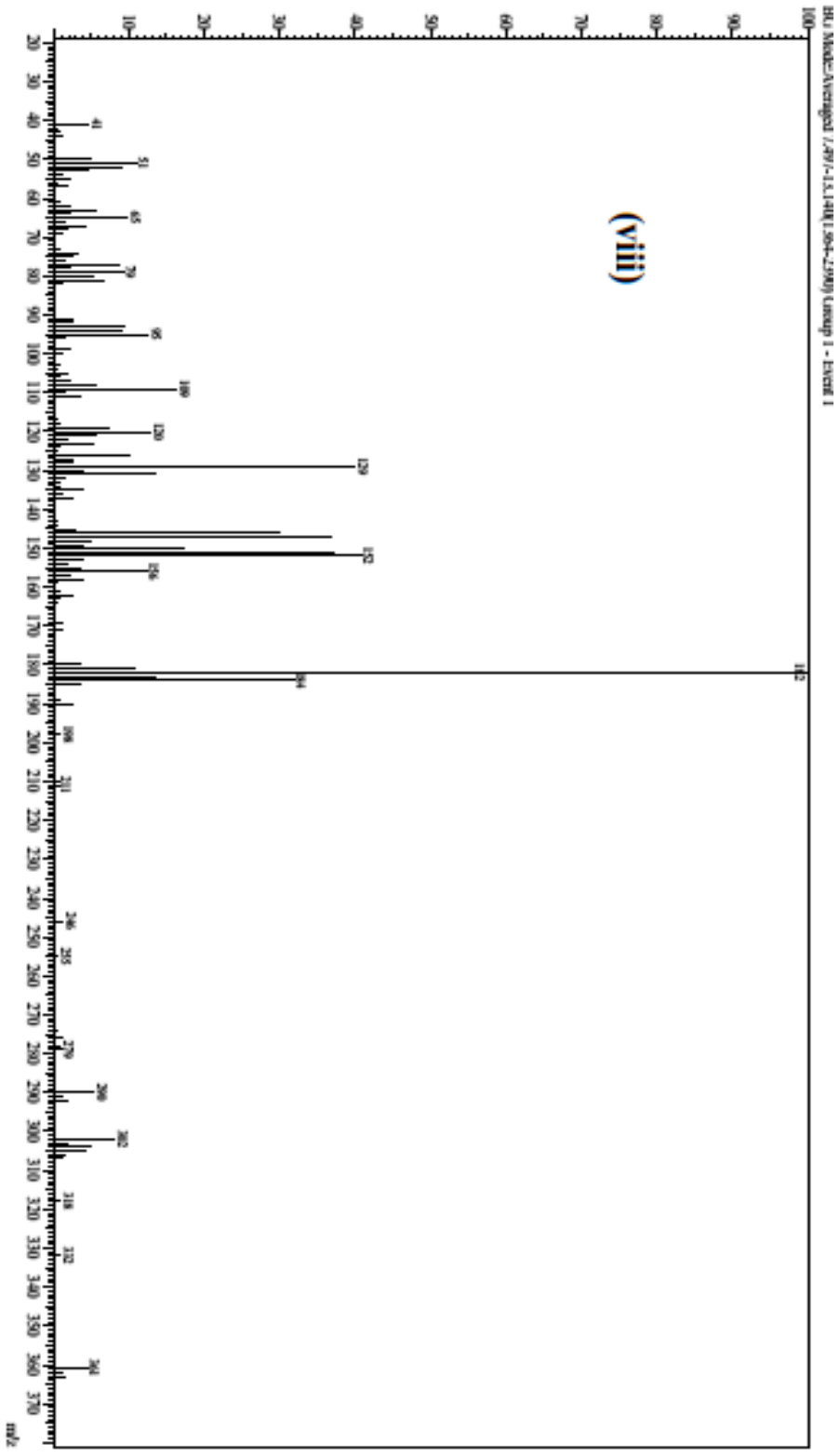
4-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (ii)



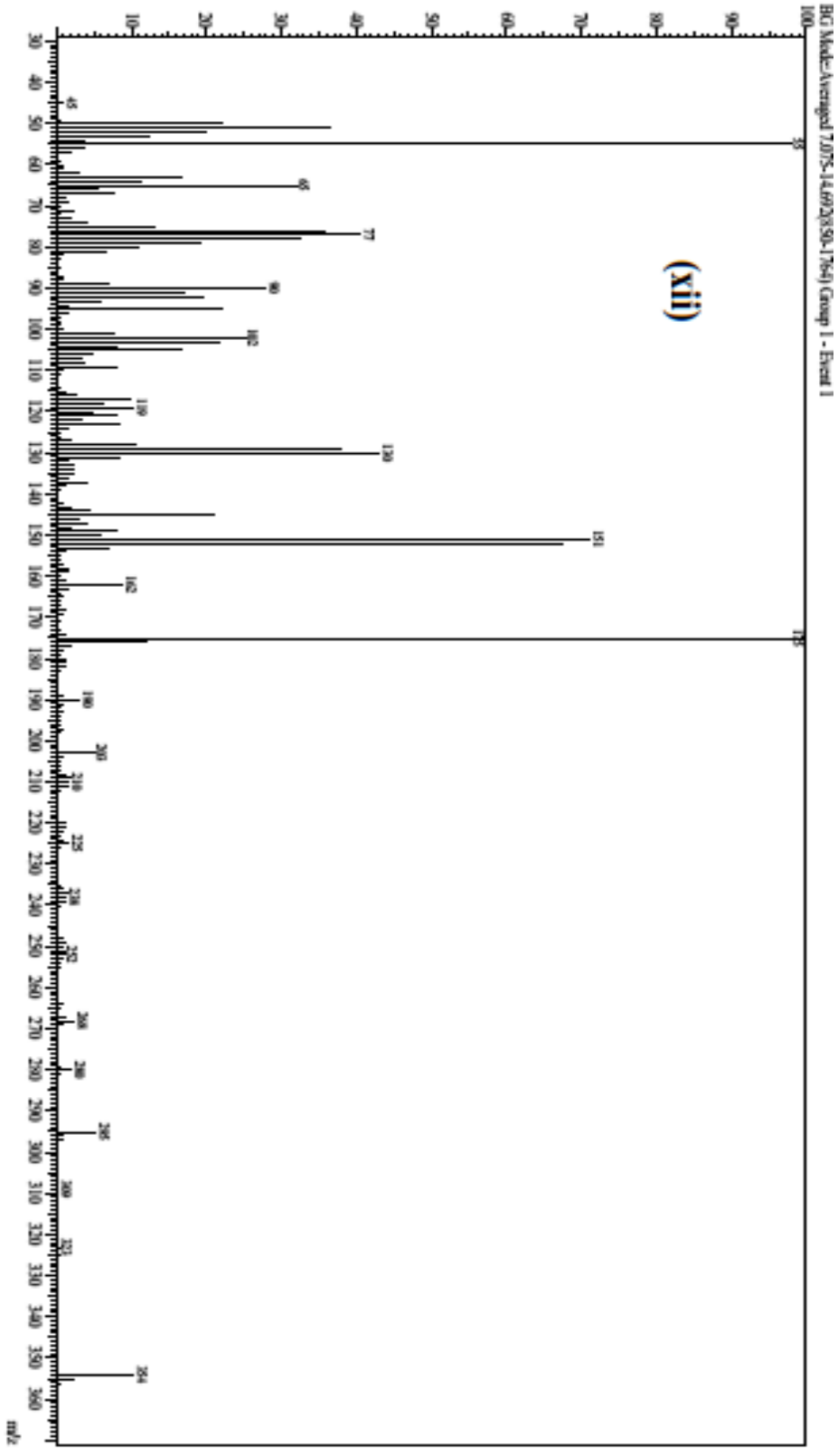
4-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (v)



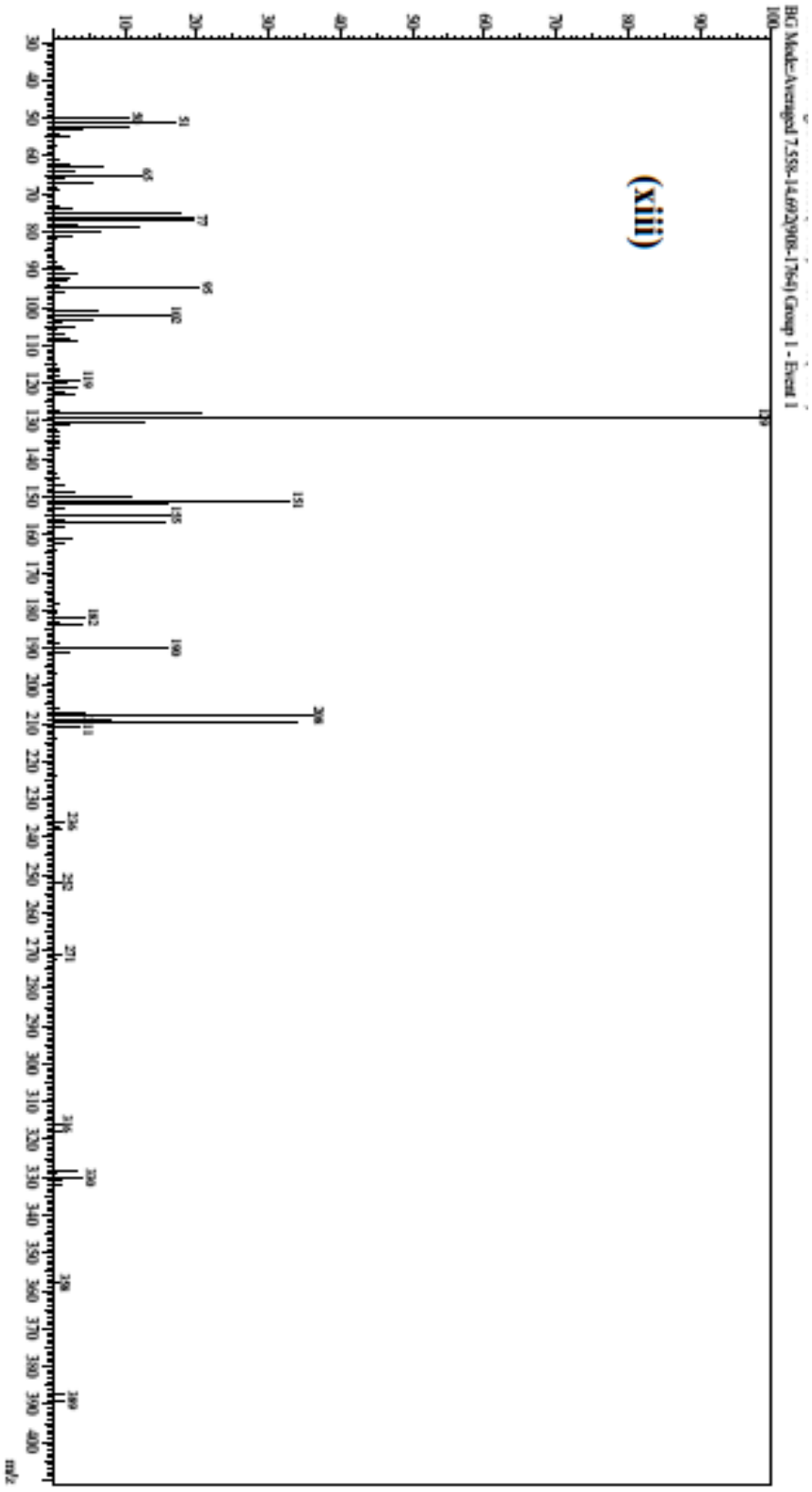
4-((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (vi)



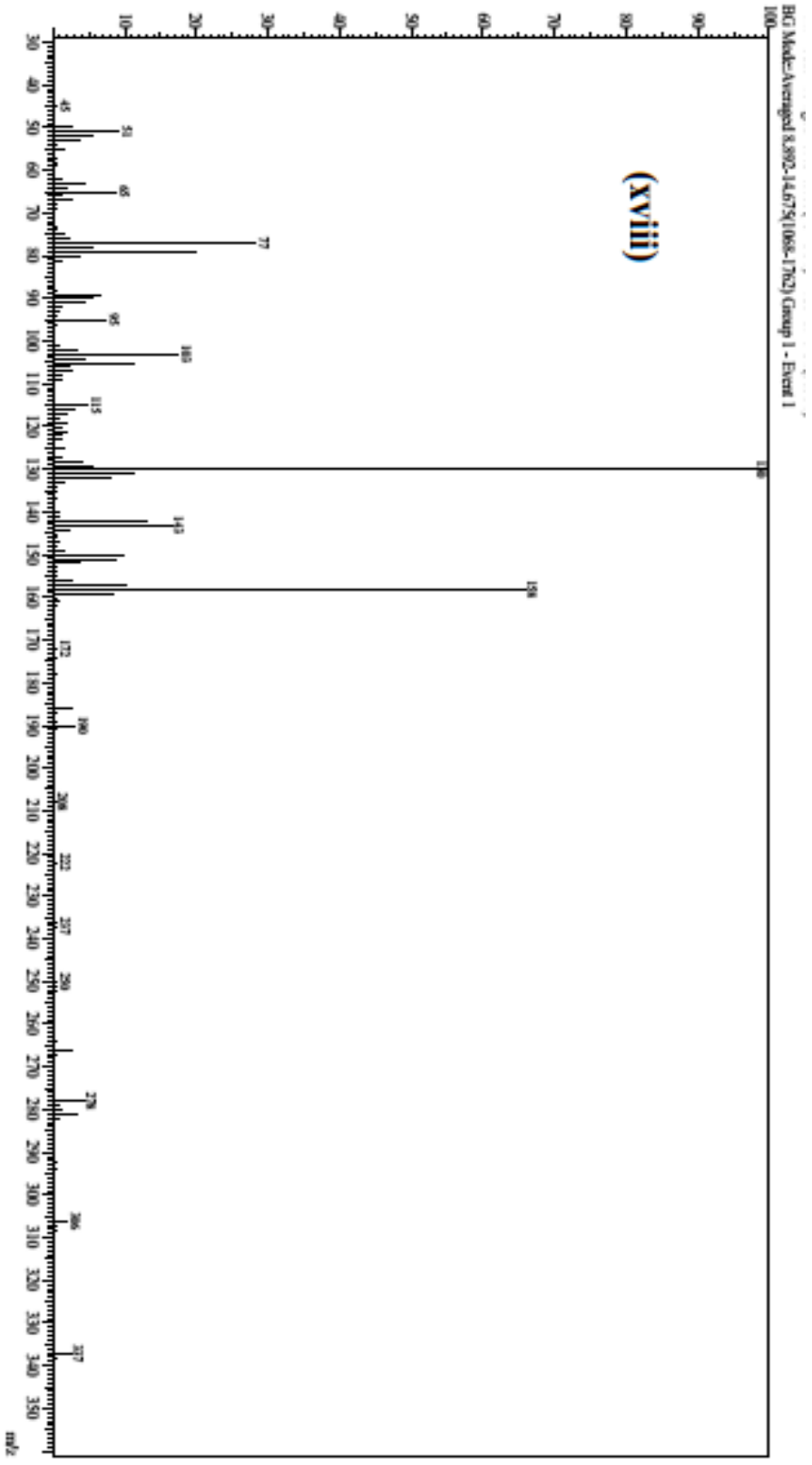
4-((1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (viii)



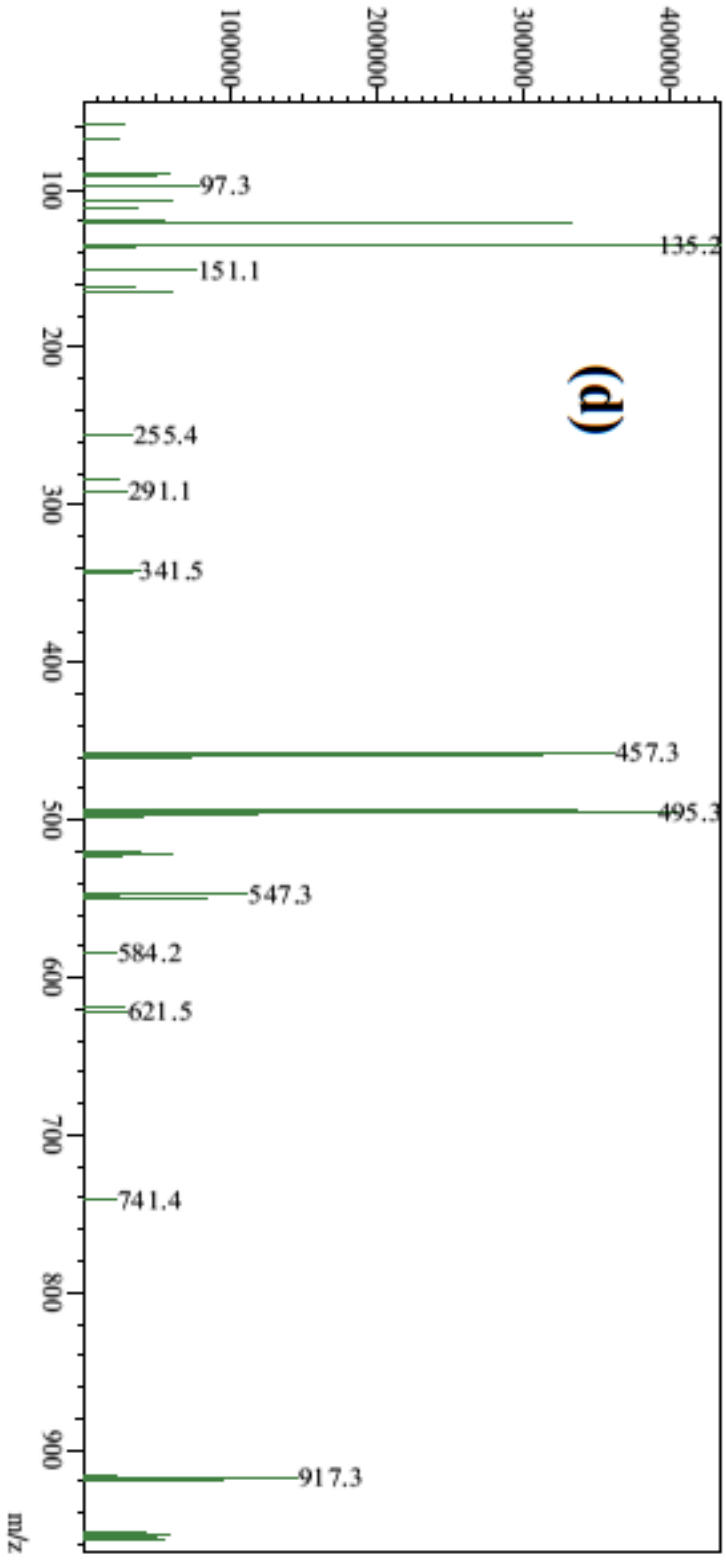
3-methoxy-4-((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (xii)



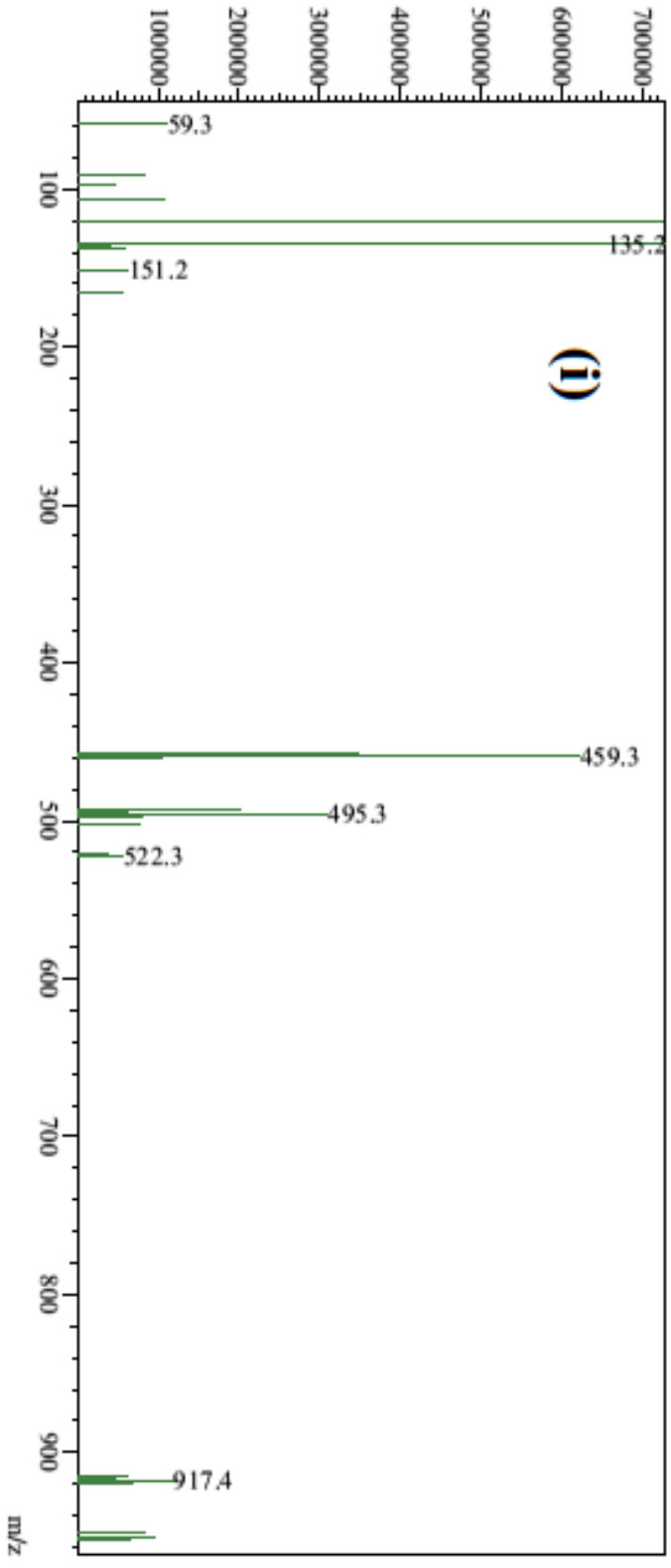
4-((1-(2-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (xiii)



4-((1-(4-ethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (xviii)



N-(4-bromophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (d)



N-(3-bromophenyl)-2-(4-((2-ethoxy-4-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetamide (i)