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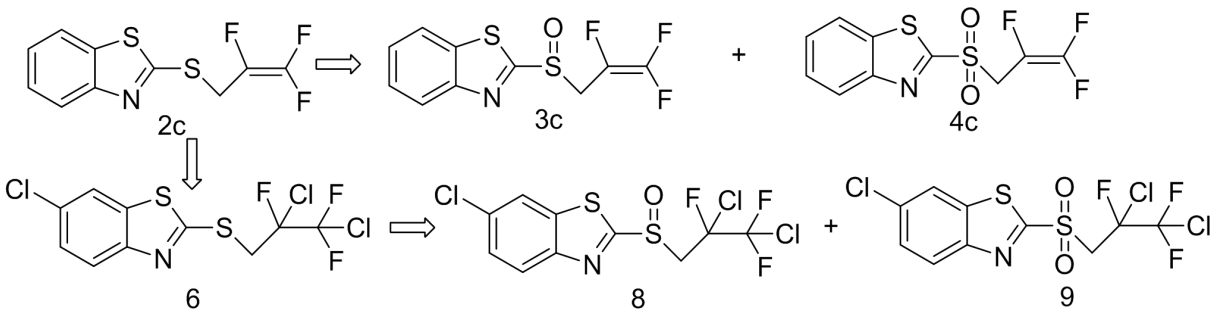

Compd.	IC50 (μM)		
	SH-SY5Y	HepG2	MCF-7
3c	7.0±0.5	4.7±0.1	8.6±0.7
4c	2.64±0.1	3.71±0.2	7.2±0.4
8	2.1±0.1	6.9±1.9	12.2±0.2
9	6.0±0.2	6.1±1.0	8.4±0.2

Highlights

- Two series of novel trifluorobutenyl derivatives of heterocyclic with convenient and efficient synthesis methods have been reported for the first time.
- The thirty-seven compounds were evaluated for the antitumor activity on three cancer cell lines (SH-SY5Y, MCF-7 and HepG2) using conventional MTT assay.
- The compounds **3c**, **3h**, **4c**, **8**, **9**, **10** and **11** showed considerablly good antitumor activity, with IC_{50} values ranging between 0.4 μM and 41.5 μM.

Fluoroalkane thioheterocyclic derivatives and their antitumor activity

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Abstract

Two series of novel trifluorobutenyl derivatives of heterocyclic with convenient and efficient synthesis methods and their antitumor activity on three cell lines have been reported for the first time. The derivatives were synthesized by the nucleophilic substitution between 4-bromo-1,1,2-trifluorobutene-1-ene and commercially available nitrogen-containing heterocycles with sulfydryl or monosubstituted malononitrile. The twenty-four new compounds were characterized by ^{1}HNMR, ^{13}CNMR and HR-MS. Totally, thirty-seven compounds were evaluated for the antitumor activity on three cancer cell lines (SH-SY5Y, MCF-7 and HepG2) using conventional MTT assay. The pharmacological results indicated that the compounds **3c**, **3h**, **4c**, **8**, **9**, **10** and **11** showed potent to moderate antitumor activity against three cancer cell lines, with IC_{50} values ranging between 0.4 μM and 41.5 μM. Even though they had less active than the reference compound taxol against MCF-7 and HepG2 lines, but they were better than the reference compound noscapine against SH-SY5Y cells, especially the compound **3h** with a IC_{50} value of 0.4 μM.

Keywords: heterocyclic, trifluorobutenyl derivatives, nucleophilic substitution, oxidation, monosubstituted malononitrile, antitumor activity

1. Introduction

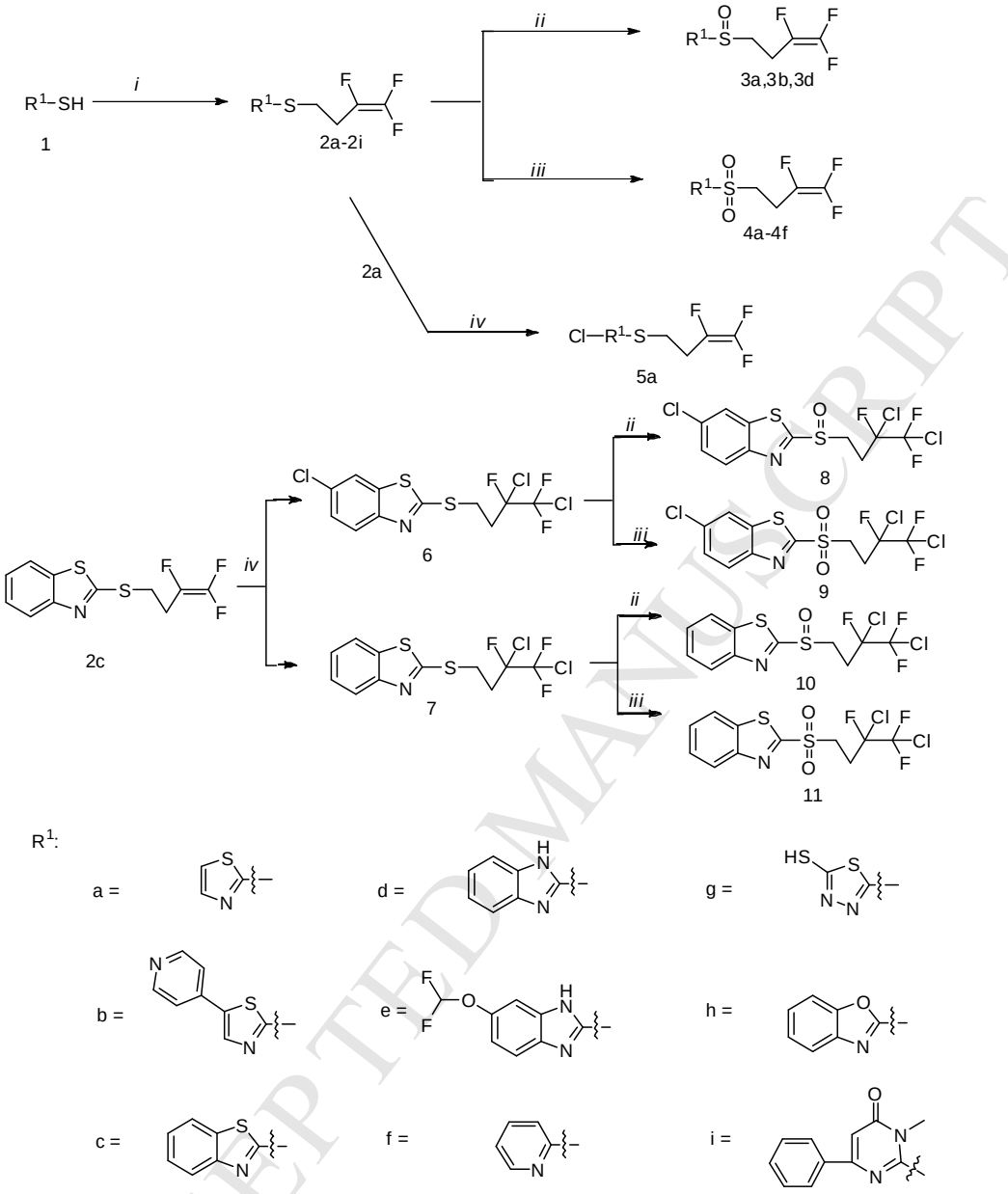
Nitrogen-containing heterocycles with sulfur atom are an important class of compounds in medicinal chemistry. Especially, thiazole and its derivatives, such as Vitamin B_1, Penicillin [1] and coenzyme cocarboxylase [2], play a significant role.

Benzothiazole derivatives are known for different biological properties, including antitubercular [3], antimalarial [4], anticonvulsant [5], antiheμmintic [6], analgesic [7], anti-inflammtory [8], antidiabetic [9] and antitumor activities [10]. Benzimidazole is structural isostere of benzothiazole, and the key building block for a variety of compounds, which has crucial role in the functions of biologically important molecules, such as anticancer [11], antimicrobial [12], proton pump inhibitor [13], antiviral [14].

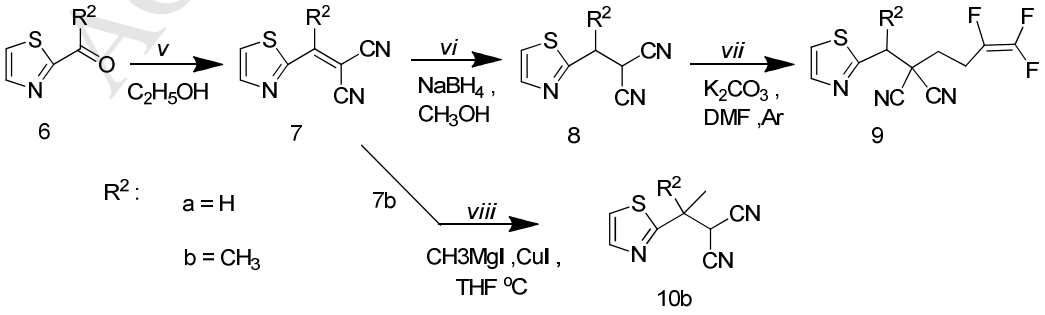
Fluorine, characterized by its small size and high electronegativity, often furnishes organic molecules with unequalled chemical and biological properties including stability, lipophilicity, and bioavailability [15]. The trifluorobutenyl derivatives are of great interest in medicinal chemistry [16]. However, the synthesis of trifluorobutenyl derivatives normally required reflux conditions, longer reaction times and other strict conditions.

On the other hand, the sulfonic acid functional group has important application in synthetic molecules with important biological and pharmacological activities [17]. The formation of carbon-sulfur bonds need various catalysis which is limited by their use of a strong base and high temperature [18]. In addition, some traditional oxidants such as trifluoroperacetic acid [19], an $MeNO_2$ solution in dilute HNO_3/H_2SO_4 [20], iodic acid [21], and other hypervalentiodine reagents [22] are applied frequently to the oxidation of the sulfides. However, most of these reagents perform the disadvantages of low effective oxygen content, environmentally unfavorable byproducts and high cost. Therefore it is highly desirable to develop a simple, less-expensive, safer, and highly efficient method.

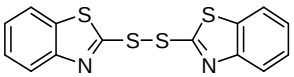
Herein we report two convenient and eco-friendly methods for the synthesis of trifluorobutenyl derivatives (Scheme I and Scheme II). The compounds of **17**, **18** and **19** were synthesized according to the literature procedures [23,24]. The antitumor activity of all the compounds was evaluated in vitro using the MTT assay against the cancer cell lines (SH-SY5Y, MCF-7 and HepG2).



Scheme 1. Synthesis of compounds **2-11**. Reagents and conditions: *i*: K_2CO_3,CH_3CN; *ii*: H_2O_2 (1equiv), CH_3COOH, 0□; *iii*: H_2O_2 (3equiv), CH_3COOH, 20-30□; *iv*: NCS,CCl_4



Scheme 2. Synthesis of compounds **13-16**. Reagents and conditions: *v*: $CH_2(CN)_2$, C_2H_5OH; *vi*: $NaBH_4$, CH_3OH; *vii*: K_2CO_3, DMF, Ar; *viii*: CH_3MgI, CuI, THF 0□.



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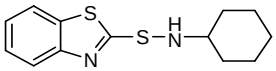

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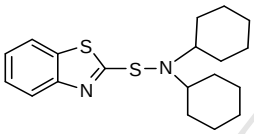

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Scheme 3. The compounds of **17**, **18** and **19**

2. Results and Discussion

2.1 Chemistry

In the scheme I, the commercially available nitrogen-containing heterocycles with sulfydryl **1** served as convenient starting materials that were alkylated with 4-bromo-1,1,2-trifluorobutene-1-ene. Thiol **1** was converted to the corresponding potassium salt in the presence of K_2CO_3, and the resulting salt was subjected to a nucleophilic substitution upon 4-bromo-1,1,2-trifluorobutene-1-ene to obtain thioether compounds **2**. It has been reported that use of strong bases and reaction temperatures over 55-60° C led to concurrent formation of small amounts of N-alkylated products [25]. Therefore the S-alkylation reaction of hetaryl thiols was carried out with good yield of 60-80% at room temperature in the present of K_2CO_3. The bonds of heterocycle were not easily broken because K_2CO_3 was slightly soluble in organic solvent.

The compounds **2** were selective oxidized by hydrogen peroxide in CH_3COOH or introduced chlorine atom by NCS. Although water was also used as the oxidation reaction solvent, but further oxidation of the product sulfoxide **3** is difficult under the conditions [26]. The oxidation reaction (***ii*** and ***iii***) illustrate that hydrogen peroxide, without the help of a catalyst, could slowly oxidize thioanisole to the sulfoxide **3** at 0°C and to sulfones **4** at room temperature with an excellent selectivity in CH_3COOH. Hydrogen peroxide is the best fit oxidant due to its effective oxygen content, low cost, safety in storage and operation and, mainly, the environmentally friendly character. It gave the expected result with good yield of 50-70%.

In the scheme II, the first step was a Knoevenagel condensation between malononitrile and an aromatic aldehyde or ketone **12** at room temperature in the

absence of catalysts to afford the arylmethylene malononitriles **13**, which was isolated in a practically pure form without further purification. The reaction is usually catalyzed by various amines or their corresponding ammonium salts [27]. But the method (***v***) we adopted was achieved at room temperature without catalysts. The reaction was effective in less ethanol and had a good yield of 70-80%. The intermediates **13** were reduced in a second step to afford the desired monosubstituted malononitrile **14**. The reaction (***vi***) was carried in ice bath which was mild enough to tolerate a sensitive thiazole ring. The monosubstituted malononitrile **14** reacted with 4-bromo-1,1,2-trifluorobutene-1-ene in the present of KCO_3 in DMF to furnish the corresponding compounds **15**. The ice bath and argon atmosphere were applied to protect the sensitive thiazole ring

2.2 In vitro antitumor activity

The antitumor activity of synthesized trifluorobutenyl derivatives was assessed in vitro by the MTT assay against three human cancer cell lines, human breastcancer cell（MCF-7）, human hepatoma cell（HepG2） and human neuroblastoma cell （SH-SY5Y）. It has been reported that noscapine, an current clinically used antitussive drug which is used for brain tumor in drug development could cross the blood-brain barrier and inhibit glioblastoma growth [28]. We used noscapine as the positive control medicine in inducing SH-SY5Y cells apoptosis. Besides, the proverbial anticancer drug taxol has been reported to induce HepG2 cells apoptosis and was used to treat breast cancer, thus taxol serves as the positive control medicine [29,30]. The antitumor activities were expressed in terms of IC_{50} (μM) and summarized in Table 1.

As shown in Table 1, among the 37 synthesized compounds，most of them showed no obvious antitumor activity against three cancer cell lines, while compounds **3c**, **3h**, **4c**, **8**, **9**, **10**, **11** showed excellent antitumor activity with IC_{50} values ranging from 0.4 μM to 41.5 μM. Compound **13b** exhibited moderate antitumor activity against these three cell lines. Compound 18 showed some activity on HepG2 and MCF-7 cells, while compound **19** had certain potent antitumor activity against SH-SY5Y cell line. Comparing with reference compound taxol against MCF-7 and HepG2 lines （IC_{50} = 0.045 μM, IC_{50} = 0.032 μM，respectively), compounds **3c**, **3h**, **4c**, **8**, **9**, **10**, **11** present lower activities. However, their antitumor

potencies against SH-SY5Y cells were far better than the reference compound noscapine（IC_{50} = 80.3 μM）, especially the compound **3h** (IC_{50} = 0.4 μM). In addition, compound **19** seemed to have equipotent antitumor activity against SH-SY5Y cells (IC_{50} = 69.1 μM) compared to the control noscapine (IC_{50} = 80.3 μM). And compound **18** showed moderate activity on HepG2 cells (IC_{50} = 55.0 μM) and MCF-7 cells (IC_{50} = 89.2 μM).

The benzothiazole derivatives **3c**, **4c**, **8**, **9**, **10**, **11** which have sulfones, sulfoxides exhibited good antitumor activities against SH-SY5Y, HepG2 and MCF-7 cells. In addition, compounds **4c**, **9**, **11** with sulfone group present better biological properties than compounds **3c**, **8**, **10** which have sulfoxide group. While, benzothiazole derivatives **2c**, **6**, **7** without sulfone or sulfoxide groups showed no antitumor activity against three cell lines with IC_{50}＞120 μM. It also should be noted that compounds **3h**, one of benzoxazole derivative containing a sulfoxide group presented excellent potency against all tested cell lines. While **2h**, a benzoxazole derivative without sulfone or sulfoxide group had no toxicity towards three cancer cells; Compound **17** with poor solubility also had no inhibitory activity. From the above aspects, it could conclude that the introduction of a disulfide bond, S-C bond and S-N bond function on the benzothiazole or benzoxazole might produced inactive compounds **2c**, **2h**, **6**, **7**, **17** (**IC_{50}**＞120 μM**)**, while the introduction of sulfone or sulfoxide function might favors the anticancer activity as shown by compounds **3c**, **3h**,**4c**, **8**, **9**, **10**, **11**. The influence of substituents on benzothiazole group on the antitumor activity might in the order, sulfone > sulfoxide > S-N bond >other groups. In addition, thiazole compound **13b** also displayed some extent of antitumor activity .

Table 1.

In vitro cytotoxic of compounds **2a-19** against three cancer cell lines

Compd.	IC50 (μM) [a]		
	SH-SY5Y	HepG2	MCF-7
2a	＞120 [b]	＞120	＞120
2b	＞120	＞120	＞120
2c	＞120	＞120	＞120

2d	＞120	＞120	＞120
2e	＞120	＞120	＞120
2f	＞120	＞120	＞120
2g	＞120	＞120	＞120
2h	＞120	＞120	＞120
2i	＞120	＞120	＞120
3a	＞120	＞120	＞120
3b	＞120	＞120	＞120
3c	**7.0±0.5**	**4.7±0.1**	**8.6±0.7**
3d	＞120	＞120	＞120
3h	**0.4±0.9**	**5.6±0.2**	**4.5±0.1**
4a	＞120	＞120	＞120
4b	＞120	＞120	＞120
4c	**2.64±0.1**	**3.71±0.2**	**7.2±0.4**
4d	＞120	＞120	＞120
4e	＞120	＞120	＞120
4f	＞120	＞120	＞120
5a	＞120	＞120	＞120
6	＞120	＞120	＞120
7	＞120	＞120	＞120
8	**2.1±0.1**	**6.9±1.9**	**12.2±0.2**
9	**6.0±0.2**	**6.1±1.0**	**8.4±0.2**
10	**41.5±0.4**	**13.5±3.3**	**17.1±0.1**
11	**4.5±0.2**	**4.5±0.2**	**10.1±0.5**
13a	＞120	＞120	＞120

13b	**68.8±0.5**	**105.4±3.7**	**109.8±2.5**
14a	＞120	＞120	＞120
14b	＞120	＞120	＞120
15a	＞120	＞120	＞120
15b	＞120	＞120	＞120
16b	＞120	＞120	＞120
17	＞120	＞120	＞120
18	＞120	**55.00±2.6**	**89.2±3.2**
19	**69.1±0.8**	＞120	＞120
Taxol	NT [c]	**0.045**	**0.032**
Noscapine	**80.3±2.2**	NT	NT

[a] The cell were continuously treated with compounds for 48 h; [b] All data are expressed as means ± SD from three separate determinations. IC_{50} values were given only if they were less than 120 μM. [c] NT means not tested.

Among above compounds, seven compounds (**3c**, **3h**, **4c**, **8**, **9**, **10**, **11**) gave promising IC_{50} values on three cell lines. The dose-responsive curves (Figure 1) further indicated that inhibition rates of these compounds depended upon their concentrations. **3h**, **4c**, **8**, **10** displayed better selectivity than **3c**, **9**, **11** among SH-SY5Y, HepG2 and MCF-7 cells, especially at the concentrations around the IC_{50} values. It is a remarkable fact that at the concentration of 1μM, compounds **4c**, **8** did not lead to antitumor activity on MCF-7 cells, but the inhibition rates on SH-SY5Y cells were all about 50%. When the concentration of **3h** reached to 5μM, the inhibition rate on MCF-7 cells was only 20%, while the inhibition rates on SH-SY5Y and HepG2 cells were about 60%. When the concentration was 10μM, compound **10** showed better activity on HepG2 cells compared with SH-SY5Y and MCF-7 cells. Since the seven compounds (**3c**, **3h**, **4c**, **8**, **9**, **10**, **11**) showed good anti-tumor activity, especially **3h**, **4c**, **8**, **10** present better selectivity than compounds **3c**, **9**, **11** among these three cells, they worthy further research.

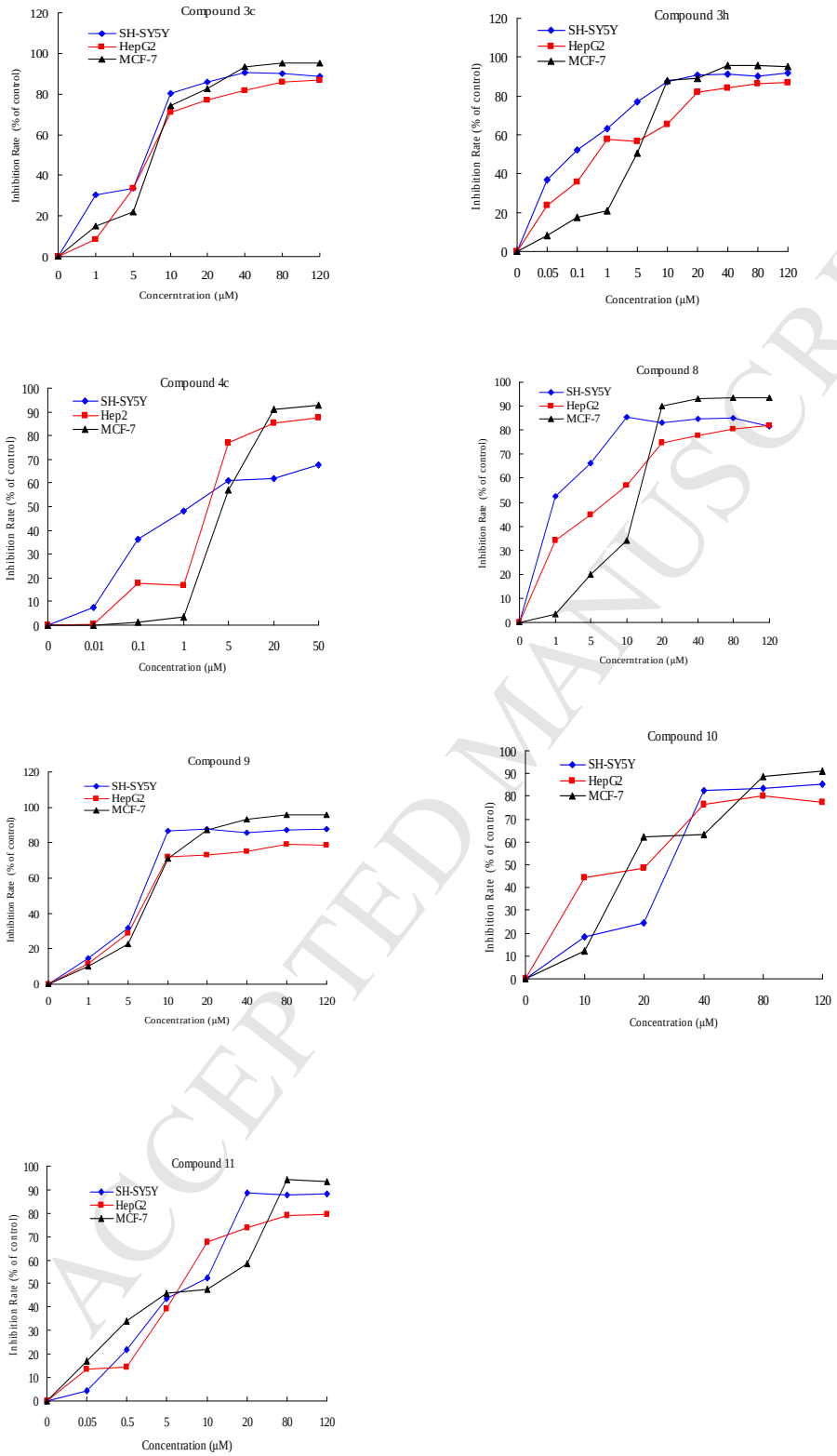

Fig. 1. The proliferation inhibition of compounds **3c, 3h, 4c, 8, 9, 10,11** assayed by MTT.

3. Conclusions

In summary, thirty-seven trifluorobutenyl derivatives have been synthesized for bioactivity assay. The synthesis strategy have the advantages with neutral reaction conditions and simple methodology. The biological activity evaluation indicated that seven of them have good anti-tumor activity compared to noscapine and taxol. And it was worth noting that the benzothiazole and benzoxazole derivatives with sulfones and sulfoxides (**3c**, **3h**, **4c**, **8**, **9**, **10**, **11** for example) exhibited good antitumor activities against SH-SY5Y, HepG2 and MCF-7 cells. Even though they have less activity than the reference compound taxol against MCF-7 and HepG2 lines, however they all showed higher activity than the reference compound noscapine on SH-SY5Y cells, especially the compound **3h** has excellent antitumor activity (IC_{50} = 0.4 μM) to SH-SY5Y cells, which revealed that this compound might be a good leading for anti-brain tumor. Besides, the seven title compounds (**3c**, **3h**, **4c**, **8**, **9**, **10**, **11**) showed good anti-tumor activity, especially **3h**, **4c**, **8**, **10** present better selectivity than compounds **3c**, **9**, **11** among these three cells, they have the potential to be leadings for anti-cancer agents and worthy further research.

4. Experimental Section

4.1. General Information

Melting points were determined in open capillary tubes and were uncorrected. The products were purified by column chromatography by using silica gel (200-300 mesh).^{1}H NMR spectra were run on a Varian-400 at room temperature with TMS as an internal standard and $CDCl_3$ as solvents. Mass spectra were recorded with a JEOL MS-D 300 mass spectrometer. The reactions were monitored by TLC with ultraviolet (UV) light; analytical thin-layer chromatography was carried out on silica gel GF_{254}. All raw materials were purchased from commercial sources. Reagents were all analytically or chemically pure. All the solvents and liquid reagents were dried by standard methods in advance or distilled before use. We designed and efficiently synthesized the compounds according to literature procedures.

4.2. General Procedure

4.2.1 General Procedure for the Synthesis of compounds **2a-2i**

Compound **1** (1 equiv), potassium carbonate (1.1 equiv) and 4-bromo-1,1,2-trifluorobutene-1-ene (1.1 equiv) are stirred in appropriate solvent at room temperature. After the reaction reagent was completed, it is filtered and the solvent is distilled off. The residue is dissolved in dichloromethane and washed with 5% aqueous solution of solution hydroxide and water in this order. It is dried over unhydrous sodium sulfate and purified by column chromatography to obtain the compounds **2a-2i**.

2-((3,4,4-trifluorobut-3-en-1-yl)thio)thiazole (**2a**). Yield: 69.3%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.79 (d, *J* = 22 Hz, 2H, CH_2), 3.04 (t, *J* = 7.2 Hz, 2H, CH_2-S), 7.24 (d, *J* = 3.2 Hz, 1H, CH-S), 7.68(d, *J* = 3.2 Hz, 1H, CH-N).

5-(pyridin-4-yl)-2-((3,4,4-trifluorobut-3-en-1-yl)thio)thiazole (**2b**). Yield: 69.6%; mp 35-36℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.89 (td, *J* = 4 Hz, *J* = 22 Hz, 2H, CH_2), 3.49 (t, *J* = 7.2 Hz, 2H, CH_2-S), 7.60 (s, 1H, CH-N), 7.74 (d, *J* = 1.6 Hz, 1H, CH), 7.75 (d, *J* = 1.6 Hz, 1H, CH), 8.65 (d, *J* = 1.6 Hz, 1H, CH-N), 8.67 (d, *J* = 1.6 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 26.3, 29.8, 116.0, 116.0, 120.3, 127.0, 140.6, 150.3, 150.4, 152.6, 153.6, 164.4. MS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_9F_3N_2S_2$: 302.0159. found: 303.0329.

2-((3,4,4-trifluorobut-3-en-1-yl)thio)benzothiazole (**2c**). Yield: 76.9%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.89 (m, 2H, CH_2), 3.54 (t, *J* = 6.8 Hz, 2H, CH_2-S), 7.31 (t, *J* = 3.2 Hz, H, CH), 7.42 (t, *J* = 3.2 Hz, H, CH), 7.76 (d, *J* = 8.4 Hz, H, CH), 7.87 (d, *J* = 8.4 Hz, H, CH).

2-((3,4,4-trifluorobut-3-en-1-yl)thio)-1H-benzoimidazole (**2d**). Yield: 76.9%; mp 124-125℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.82 (m, 2H, CH_2), 3.51 (t, *J* = 6.8 Hz, 2H, CH_2-S), 7.23 (m, 2H, CH_2), 7.51 (m, 2H, CH_2).

5-(difluoromethoxy)-2-((3,4,4-trifluorobut-3-en-1-yl)thio)-1H-benzoimidazole (**2e**). Yield: 65.6%; mp 35-36℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.82 (m, 2H, CH_2), 3.49 (t, *J* = 6.8 Hz, 2H, CH_2-S), 6.49 (t, *J* = 74 Hz, 1H, CH-O) 7.03 (m, H, CH), 7.28 (d, *J* = 17.2 Hz, 1H, CH) ,7.45 (d, *J* = 8.4Hz, 1H, CH) ^{13}C-NMR (400 MHz, $CDCl_3$). δ 26.3,

28.3, 106.0, 113.7, 115.5, 116.3, 118.9, 125.6, 128.0, 146.9, 150.4, 155.1; MS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_9F_5N_2OS$: 324.0356. found: 325.0263.

2-((3,4,4-trifluorobut-3-en-1-yl)thio)pyridine (**2f**). Yield: 68%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.72 (m, 2H, CH_2), 3.36 (t, *J* =7.2 Hz, 2H, CH_2-S), 6.99 (m, 1H, CH), 7.17 (d, 1H, CH), 7.48 (m, 1H, CH), 8.42 (d, 1H, CH).

5-((3,4,4-trifluorobut-3-en-1-yl)thio)-1,3,4-thiadiazole-2-thiol (**2g**). Yield: 55.6%; mp 66-67℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.78 (m, 2H, CH_2), 3.33 (m, 2H, CH_2-S), 11.03 (s, 1H, SH).

2-((3,4,4-trifluorobut-3-en-1-yl)thio)benzooxazole (**2h**). ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.91 (m, 2H, CH_2), 3.47 (t, *J* = 3.2 Hz, 2H, CH_2-S), 7.28 (m, 2H, 2 CH), 7.451 (m, 1H, CH), 7.60 (m, 1H, CH)

3-methyl-6-(pyridin-4-yl)-2-((3,4,4-trifluorobut-3-en-1-yl)thio)pyrimidin-4(3H)-one (**2i**). Yield: 76.5%; mp 120-121℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.86 (m, 2H, CH_2), 3.50 (t, *J* = 7.2 Hz, 2H, CH_2-S), 3.56 (s, 3H, CH_3-N), 6.75 (s, 1H, CH), 7.77 (d, *J* = 1.6 Hz, 1H, CH), 7.78 (d, *J* = 1.6 Hz, 1H, CH), 8.73 (d, *J* = 1.6 Hz, 1H, CH-N), 8.74 (d, *J* = 1.6 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 25.9, 28.1, 30.3, 106.1, 120.5, 127.0, 143.4, 150.5, 153.6, 156.4, 162.1, 162.2. MS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}F_3N_3OS$: 327.0653. found: 328.0764

4.2.2 General Procedure for the Synthesis of compounds **3a-3d**, **3h** and **10**.

To the solution of compounds **2** (1 equiv), 31% hydrogen peroxide water (1 equiv), acetic acid is mixture is added and stirred at ice cooling for certain hours. When the reagent was completed, the reaction mixture is cooling to 5□ and adjusted to pH 6 by adding an appropriate amount of an aqueous solution hydroxide, diluted with water and extracted three times with dichloromethane. The dichloromethane layer is washed with water, 10% sodium thiosulfate and water in this order and dried over unhydrous sodium sulfate. The solvent is distilled off and the concentrate is purified by column chromatography to obtain the compounds **3a-3d**, **3h** and **10**.

2-((3,4,4-trifluorobut-3-en-1-yl)sulfinyl)thiazole **(3a).** Yield: 66.7%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.76 (m, 2H, CH_2), 3.37 (m, 2H, CH_2-S), 7.68 (t, *J* = 3.2 Hz, 1H, CH-S), 7.99 (t, *J* = 3.2 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 18.3, 51.2, 124.1, 126.3, 145.2, 153.1, 174.5. MS (ESI): m/z $[M+H]^+$ calcd for $C_7H_6F_3NOS_2$: 240.9843. found: 241.9800.

5-(pyridin-4-yl)-2-((3,4,4-trifluorobut-3-en-1-yl)sulfinyl)thiazole (**3b**) Yield: 65.7%; mp 87-88℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.83 (m, 2H, CH_2), 3.44 (m, 2H, CH_2-S), 7.75 (d, *J* = 1.6 Hz, 1H, CH), 7.76 (d, *J* = 1.6 Hz, 1H, CH), 8.03 (s, 1H, CH-N), 8.71 (d, *J* = 1.6 Hz, 1H, CH-N), 8.72 (d, *J* = 1.6 Hz, 1H,CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 18.3, 51.4, 120.6, 120.7, 126.2, 140.3, 150.8, 153.1, 155.6, 175.7. MS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_9F_3N_2OS_2$: 318.0108. found: 319.0143

2-((3,4,4-trifluorobut-3-en-1-yl)sulfinyl)benzothiazole **(3c).** ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.83 (m, 2H, CH_2), 3.46 (m, 2H, CH_2-S), 7.51 (t, *J* = 7.2 Hz, 1H, CH), 7.58 (t, *J* = 7.2 Hz, 1H, CH), 8.01 (d, *J* = 8.0 Hz, 1H, CH), 8.08 (d, *J* = 8.0 Hz, 1H, CH). ^{13}C-NMR(400 MHz, $CDCl_3$), δ 18.4, 51.3, 122.5, 124.3, 125.5, 126.6, 127.3, 136.2, 153.2, 154.1, 176.2. MS (ESI): m/z [M+H]+ calcd for $C_{11}H_8F_3NOS_2$: 290.9999. found: 292.0088.

2-((3,4,4-trifluorobut-3-en-1-yl)sulfinyl)-1H-benzoimidazole (**3d**). Yield: 69.8%; mp 84-85℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.82 (m, 2H, CH2), 3.57 (m, 2H, CH2-S), 7.37 (m, 2H, 2CH), 7.59 (d, *J* = 7.6Hz, 1H, CH), 7.80 (d, *J* = 7.6Hz, 1H, CH), 11.87 (s, 1H, NH). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 18.5, 49.7, 112.0, 120.3, 123.4, 124.6, 127.2, 134.2, 144.1, 151.2, 152.9. MS (ESI): m/z [M+H]+ calcd for $C_{11}H_9F_3N_2OS$: 274.0388. found: 275.0472.

2-((3,4,4-trifluorobut-3-en-1-yl)sulfinyl)benzooxazole (**3h**). Yield: 28.6%; mp 66-68℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.93 (m, 2H, CH_2), 3.58 (m, 2H, CH_2-S), 7.48 (m, 2H, 2CH), 7.66 (d, *J* = 8.0 Hz, 1H, CH), 7.84 (d, *J* = 8.0 Hz, 1H, CH).

6-chloro-2-((3,4-dichloro-3,4,4-trifluorobutyl)sulfinyl)benzothiazole (**8**) Yield: 25.0%; mp 90-92℃; ^{1}H-NMR (400MHz, $CDCl_3$), δ 2.86 (m, 2H, CH_2), 3.58 (m, 2H, CH_2-S), 7.56 (d, *J* =8.8 Hz, 1H, CH), 8.00 (d, *J* =8.8 Hz, 1H, CH), 8.02 (s, 1H, CH). ^{13}C-NMR,

δ 28.8, 49.0, 109.8, 122.2, 125.1, 128.1, 128.4, 133.1, 137.4, 152.6, 176.4. MS (ESI): m/z [M+H]+ calcd for $C_{11}H_7Cl_3F_3NOS_2$: 394.8987. found: 395.9087.

2-((3,4-dichloro-3,4,4-trifluorobutyl)sulfinyl)benzothiazole (**10**). Yield: 31.5%; mp 70-72℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.73 (m, 2H, CH_2), 3.60 (m, 2H, CH_2-S), 7.53 (t, *J* = 7.2 Hz, 1H, CH), 7.60 (t, *J* = 7.2 Hz, 1H, CH), 8.03 (d, *J* = 7.2 Hz, 1H, CH), 8.10 (d, *J* = 7.2 Hz, 1H, CH); ^{13}C-NMR(400 M Hz, $CDCl_3$), δ 28.7, 48.7, 109.7, 122.3, 124.2, 125.2, 126.5, 127.2, 136.0, 153.9, 175.5. MS (ESI): m/z [M+H]+ calcd for $C_{11}H_8C_{l2}F_3NOS_2$: 360.9376. found: 361.9370.

4.2.3 General Procedure for the Synthesis of compounds **4a-4f** and **11**.

To the solution of compounds **2** (1 equiv), 31% hydrogen peroxide water (3 equiv), acetic acid is mixture is added and stirred at room temperature for certain hours. When the sulfoxide (the first product) is completed, the reaction mixture is cooling to 5□ and adjusted to pH 6 by adding an appropriate amount of an aqueous solution hydroxide, diluted with water and extracted three times with dichloromethane. The dichloromethane layer is washed with water, 10% sodium thiosulfate and water in this order, and dried over unhydrous sodium sulfate. The solvent is distilled off and the concentrate is purified by column chromatography to obtain the compounds **4a-4f**.

2-((3,4,4-trifluorobut-3-en-1-yl)sulfonyl)thiazole **(4a).** Yield: 60.5%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.76 (m, 2H, CH_2), 3.37 (m, 2H, CH_2-S), 7.68 (t, J = 3.2 Hz, 1H, CH-S), 7.99 (t, J = 3.2 Hz, 1H, CH-N), ^{13}C-NMR (400 MHz, $CDCl_3$), δ 18.2, 51.2, 124.2, 126.4, 145.2, 153.1, 174.4, MS (ESI): m/z $[M+H]^+$ calcd for $C_7H_6F_3NO_2S_2$: 256.9792. found: 257.9856.

5-(pyridin-4-yl)-2-((3,4,4-trifluorobut-3-en-1-yl)sulfonyl)thiazole (**4b**). Yield: 52.1%; mp 78-79℃; ^{1}H-NMR (400 MHz, $CDCl_3$) ,δ 2.98 (m, 2H, CH_2), 3.73 (t, *J* = 7.2Hz, 2H, CH_2-S), 7.80 (d, *J* = 1.6 Hz, 1H, CH), 7.81 (d, *J* = 1.6 Hz, 1H, CH), 8.11 (s, 1H, CH-N), 8.73 (d, *J* = 1.6 Hz, 1H, CH-N), 8.74 (d, *J* = 1.6 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 20.3, 50.7, 120.8, 122.8, 124.9, 139.7, 150.8, 153.0, 155.6, 165.6. MS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_9F_3N_2O_2S_2$: 334.0058. found: 335.0094

2-((3,4,4-trifluorobut-3-en-1-yl)sulfonyl)benzothiazole **(4c).** Yield: 63.9%; mp 52-54℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.97 (m, 2H, CH_2), 3.74 (t, *J* = 7.6 Hz, 2H,

CH_2-S), 7.64 (m, 2H, 2CH), 8.03 (d, *J* = 8.0 Hz, 1H, CH), 8.22 (d, *J* = 8.0 Hz, 1H, CH). ^{13}C-NMR(400 MHz, $CDCl_3$), δ 20.2, 50.6, 122.5, 125.4, 125.7, 128.0, 128.5, 136.9, 152.7, 153.2, 165.1.MS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_8F_3NO_2S_2$: 306.9949. found: 308.0064.

2-((3,4,4-trifluorobut-3-en-1-yl)sulfonyl)-1H-benzoimidazole (**4d**). Yield: 65.2%; mp 82-84℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.95 (m, 2H, CH_2), 3.74 (m, 2H, CH_2-S), 7.43 (m, 1H, CH), 7.49 (m, 1H, CH), 7.55 (d, *J* = 8 Hz, 1H, CH), 7.90 (d, *J* = 7.6 Hz, 1H,CH), 10.66 (s, 1H, NH). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 19.9, 50.6, 112.4, 121.8, 124.2, 124.6,126.8, 132.9, 142.9, 146.3, 152.9. MS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_9F_3N_2O_2S$: 290.0337. found: 291.0424.

5-(difluoromethoxy)-2-((3,4,4-trifluorobut-3-en-1-yl)sulfonyl)-1H-benzoimidazole (**4e**). Yield: 60.6%; mp 78-79℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.96 (m, 2H, CH_2), 3.74 (t, *J* = 7.6 Hz, 2H, CH_2-S), 6.56 (t, *J* = 73.2 Hz, 1H, CH-F) 7.27 (m, 1H, CH), 7.59 (m, 1H, CH), 7.86 (m, 1H, CH), 10.81 (s, 1H, NH). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 19.8, 50.6, 103.3, 112.7, 118.3, 122.9, 125.1, 130.5, 133.2, 140.3, 143.1, 147.7, 152.9. MS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_9F_5N_2O_3S$: 356.0254. found: 357.0566.

2-((3,4,4-trifluorobut-3-en-1-yl)sulfonyl)pyridine (**4f**). Yield: 51.3%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.83 (m, 2H, CH_2), 3.63 (t, *J* = 7.6Hz, 2H, CH_2-S), 7.60 (m, 1H, CH), 8.01 (m, 1H, CH), 8.11 (d, 1H, CH), 8.76 (d, 1H, CH). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 20.0, 47.7, 122.1,125.8, 127.8, 138.5, 150.4, 153.1, 157.1. MS (ESI): m/z $[M+H]^+$ calcd for $C_9H_8F_3NO_2S$: 251.0228. found: 252.0394.

6-chloro-2-((3,4-dichloro-3,4,4-trifluorobutyl)sulfonyl)benzothiazole (**9**) Yield: 29.6%; mp 118-120℃; ^{1}H-NMR (400MHz, $CDCl_3$), δ 3.00 (m, 2H, CH_2), 3.84 (m, 2H, CH_2-S), 7.63 (d, *J* =8.8 Hz, 1H, CH), 8.03 (s, 1H, CH), 8.15 (d, *J* =8.8 Hz, 1H, CH). ^{13}C-NMR, δ 30.6, 49.2, 109.3, 122.1, 125.3, 126.6, 129.3, 135.1, 137.9, 151.1, 165.3. MS (ESI): m/z [M+H]+ calcd for $C_{11}H_7Cl_3F_3NO_2S_2$: 410.8936. found: 411.9629.

2-((3,4-dichloro-3,4,4-trifluorobutyl)sulfonyl)benzothiazole (**11**). Yield: 38.5%; mp 87-88℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.96 (m, 2H, CH2), 3.87 (m, 2H, CH2-S), 7.65 (m, 2H, 2CH), 8.04 (d, *J*=8.0Hz, 1H, CH), 8.25 (d, *J*=8.0Hz, 1H, CH), ^{13}C-NMR

(400 MHz, $CDCl_3$), δ 30.5, 49.0, 109.1, 122.3, 125.1, 125.6, 127.9, 128.4, 136.6, 152.5, 164.6. MS (ESI): m/z [M+H]+ calcd for $C_{11}H_8Cl_2F_3NO_2S_2$: 376.9326. found: 377.9415.

4.2.4 General Procedure for the Synthesis of compounds **5a**, **6** and **7.**

To a stirred solution of compounds **2** (1 equiv)in carbon tetrachloride N-chlorosuccinimide (1.1 equiv) is added. The mixture was refluxed for appropriate hours by heating. As soon as the reaction has reached room temperature, the mixture is filtered and the solvent is distilled off. The concentrate is purified by column chromatography to obtain the compounds **5a**, **6** and **7**.

5-chloro-2-((3,4,4-trifluorobut-3-en-1-yl)thio)thiazole (**5a**). Yield: 66%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.76 (td, *J* = 4 Hz, J = 24.4 Hz, 2H, CH_2), 3.36 (t, *J* = 7.2 Hz, 2H, CH_2-S), 7.45 (s, 1H, CH-N).

6-chloro-2-((3,4-dichloro-3,4,4-trifluorobutyl)thio)benzothiazole (**6**) Yield: 27.5%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.86 (m, 2H, CH_2), 3.59 (m, 2H, CH_2-S), 7.38 (m, 1H, CH), 7.73 (m, 1H, CH), 7.77 (m, 1H, CH). ^{13}C-NMR(400 MHz, $CDCl_3$), δ 26.3, 36.8, 110.0, 120.6, 122.3, 125.4, 126.8, 136.4, 151.6, 162.5, 165.6. MS (ESI): m/z [M+H]+ calcd for $C_{11}H_7Cl_3F_3NS_2$: 378.9038. found: 379.9102.

2-((3,4-dichloro-3,4,4-trifluorobutyl)thio)benzothiazole (**7**). Yield: 33.6%; ^{1}H-NMR (400MHz, $CDCl_3$), δ 2.91 (m, 2H, CH_2), 3.61 (m, 2H, CH_2-S), 7.31 (t, *J* = 7.2 Hz, 1H, CH), 7.43 (t, *J* = 7.2 Hz, 1H, CH), 7.76 (d, *J* = 8.0 Hz, 1H, CH), 7.88 (d, *J* = 8.0 Hz, 1H, CH). ^{13}C-NMR, δ 26.5, 37.1, 110.2, 121.2, 121.9, 124.7, 125.7, 126.3, 135.5, 153.2, 165.1. MS (ESI): m/z [M+H]+ calcd for $C_{11}H_8Cl_2F_3NS_2$: 344.9427. found: 345.9492.

3.2.5 General Procedure for the Synthesis of compounds **13.**

To a stirred solution of compounds **12** (1 equiv) in absolute ethyl alcohol the malononitrile (1.1 equiv) was added. The mixture was stirred at room temperature for times . Without any further purification, the precipitate was filtered off to give the compounds **13**.

2-(thiazol-2-yμMethylene)malononitrile (**13a**). Yield: 70.3%; mp 143-145 ℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 7.88 (d, *J* = 3.2 Hz, 1H, CH-S), 8.02 (s, 1H, CH), 8.24 (d, *J* = 2.8 Hz ,1H, CH-N)

2-(1-(thiazol-2-yl)ethylidene)malononitrile (**13b**). Yield: 75.7%; mp 121-122 ℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.83 (s, 3H, CH_3), 7.81 (d, *J* = 3.2 Hz, 1H, CH-S), 8.18 (d, *J* = 3.2 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 22.0, 83.5, 112.6, 112.8, 126.0, 145.5, 160.5, 161.3. MS (ESI): m/z $[M+H]^+$ calcd for $C_8H_5N_3S$: 175.0204. found: 176.0279.

4.2.6 General Procedure for the Synthesis of compounds **14.**

To a stirred solution of compound **13** (1 equiv) in methyl alcohol a suspension of sodium borohydride (1.1 equiv) in methyl alcohol was added at ice bath. The reaction mixture was stirred for another 30 min as monitored by TLC and quenched with water 10% hydrochloric acid. After evaporation of volatile material in vacuo the remaining crude product was dissolved in dichloromethane. The organic layer was successively washed with 10% hydrochloric acid, a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography to give the compounds **14**.

2-(thiazol-2-yμMethyl)malononitrile (**14a**). Yield: 57.9%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 3.71 (d, *J* = 7.6 Hz, 2H, CH_2), 4.55 (t, *J* = 7.2 Hz, 1H, CH), 7.38 (d, *J* = 3.2 Hz, 1H, CH-S), 7.81 (d, *J* = 3.2 Hz, 1H, CH-N).

2-(1-(thiazol-2-yl)ethyl)malononitrile (**14b**). Yield: 62.1%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.78 (d, 3H, CH_3), 3.84 (m, 1H, CH-CH_3) 4.66 (d, 1H, *J* = 5.6 Hz, CH-CN), 7.38 (d, *J* = 3.2 Hz, 1H, CH-S), 7.80 (d, *J* = 3.2 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 17.8, 28.6, 39.0, 111.0, 111.9, 120.1, 143.0, 167.0. MS (ESI): m/z $[M+H]^+$ calcd for $C_8H_7N_3S$: 177.0361. found: 178.0495.

4.2.7 General Procedure for the Synthesis of compounds **15.**

The mixture of compounds **14** (1 equiv) and potassium carbonate (1.1 equiv) were dissolved in DMF (N,N-Dimethylf-ormamide) was stirred at certain temperature

for 1h under an argon atmosphere. Subsequently, 4-bromo-1,1,2-trifluorobutene-1-ene (1.1 equiv) were added and the mixture was stirred 10 hours at room temperature. After evaporation of volatile material in vacuo the remaining crude product was dissolved in dichloromethane, washed with water and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography to obtain the compounds **15**.

2-(thiazol-2-yμMethyl)-2-(3,4,4-trifluorobut-3-en-1-yl)malononitrile (**15a**). Yield: 29.5%; mp 49-51℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.37 (m, 2H, CH_2), 2.76 (m, 2H, CH_2), 3.72 (s, 2H, CH_2), 7.34 (d, *J* = 3.2 Hz, 1H, CH-S), 7.87 (d, *J* = 3.2 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 22.5, 33.0, 36.7, 39.6, 114.1, 121.2, 121.3, 126.1, 143.9, 153.2, 158.9. MS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_8F_3N_3S$: 271.0391. found: 272.0521.

2-(1-(thiazol-2-yl)ethyl)-2-(3,4,4-trifluorobut-3-en-1-yl)malononitrile(**15b**). Yield: 32.5%; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.84 (d, *J* = 7.2 Hz, 3H,CH_3), 2.21 (m,2H, CH_2), 2.71 (m, 2H, CH_2), 3.82 (q, 1H, CH), 7.42 (d, *J* = 3.2 Hz, 1H, CH-S), 7.84 (d, *J* = 3.2 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz,$CDCl_3$), δ 18.5, 22.7, 32.0, 42.6, 44.2, 113.5, 114.3, 120.6, 126.3, 143.3, 153.2, 165.5. MS (ESI): m/z [M+H]+ calcd for $C_{12}H_{10}F_3N_3S$: 285.0548. found: 286.0622.

4.2.8 Synthesis of compound **16b**.

To a stirred solution of compound **13b** (200mg, 1.14mmol) and a catalytic amount of copper (I) iodide in dry THF (6ml), a solution of methyl mangnesium iodide (4.46ml, 1.25mmol) in diethyl ether (prepared from 0.30 g of magnesium, 10ml of diethyl ether, and 0.86 ml of methyl iodide) was added at ice cooling under an argon atmosphere. The reaction mixture was stirred for another 1 h as monitored by TLC and quenched with water 10% hydrochloric acid. After evaporation of volatile material in vacuo the remaining crude product was dissolved in dichloromethane. The organic layer was successively washed with 10% hydrochloric acid, a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography to give the compounds **16b** (91mg).

2-(2-(thiazol-2-yl)propan-2-yl)malononitrile (**16b**). Yield: 41.7%; mp 46-48 ℃; ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.75 (s, 6H, $2CH_3$), 4.63 (s, 1H, CH-CN) 7.35 (d, *J* = 3.2 Hz, 1H, CH-S), 7.77 (d, *J* = 3.2 Hz, 1H, CH-N). ^{13}C-NMR (400 MHz, $CDCl_3$), δ 26.5, 34.5, 43.6, 111.5, 119.8, 119.9, 142.9, 172.1. MS (ESI): m/z $[M+H]^+$ calcd for $C_9H_9N_3S$: 191.0517. found: 192.0684.

4.2.8 Synthesis of 2,2'-Dithiobis(benzothiazole) (**17**).

To a stirred solution of benzothiazole-2-thiol(334 mg, 2 mmol) in acetonitril (3 mL), the catalyst (Fe/SBA-15, 30 mg, 0.02 mmol) and hydrogenperoxide (30% aqueous, 250 mg) were added. The reaction mixture was stirred for 15 min. After the completion of the reaction, which is associated with precipitation of disulfide and elimination of thiol odor. The precipitate was filtered off to give 2,2'-Dithiobis(benzothiazole) (228 mg). Yield: 68.6%; mp 177-179℃ (177-180℃ [23])

4.2.9 General Procedure for the Synthesis of compounds **18**,**19**.

To a stirred solution of benzothiazole-2-thiol(1 equiv) and cyclohexane (2.5 equiv), the sodium hypochlorite solution was added at 45℃. After the completion of the reaction, the reaction solution was cooled to room temperature and the products separated out. Without any further purification, the precipitate was filtered off to give the products.

N-cyclohexylbenzothiazole-2-sulphenamide (**18**). Yield: 65.7%; mp 100-102 ℃ (93-100℃[24])

N,N'-dicyclohexyl-2-Benzothiazole sulfenamide (**19**).Yield: 61.2%; mp 101-103℃ (102-104℃[24])

4.3. Cell Culture and Cell viability Assay

3.3.1 Cell culture. MCF-7 and SH-SY5Y cell lines were maintained in DMEM supplemented with 10% fetal bovine serum, 1% penicillin and streptomycin. The HepG2 cells were maintained in MEM supplemented with 10% fetal bovine serum, 1% penicillin and streptomycin. The cells were grown at 37 ℃ in an environment of 5% CO_2.

4.3.2 Cell viability assay. Cell viability was assessed by MTT assay. After grown overnight in 96-well plates, the cells were treated with indicated concentrations of compounds for 48 h in DMEM (MCF-7 and SH-SY5Y) or MEM (HepG2) supplemented with 10% fetal bovine serum. The cells were washed with PBS twice and then incubated with serum-free DMEM containing 0.5 mg/ml MTT for 4 h. Next, the cells were washed with PBS again and the formazan blue formed by living cells was dissolved in DMSO. Finally, the optical density was measured at 570 nm.

Supplementary Materials

Supplementary materials can be accessed at:

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Conflicts of Interest

The authors declare no conflict of interest.

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13C-NMR of compounds

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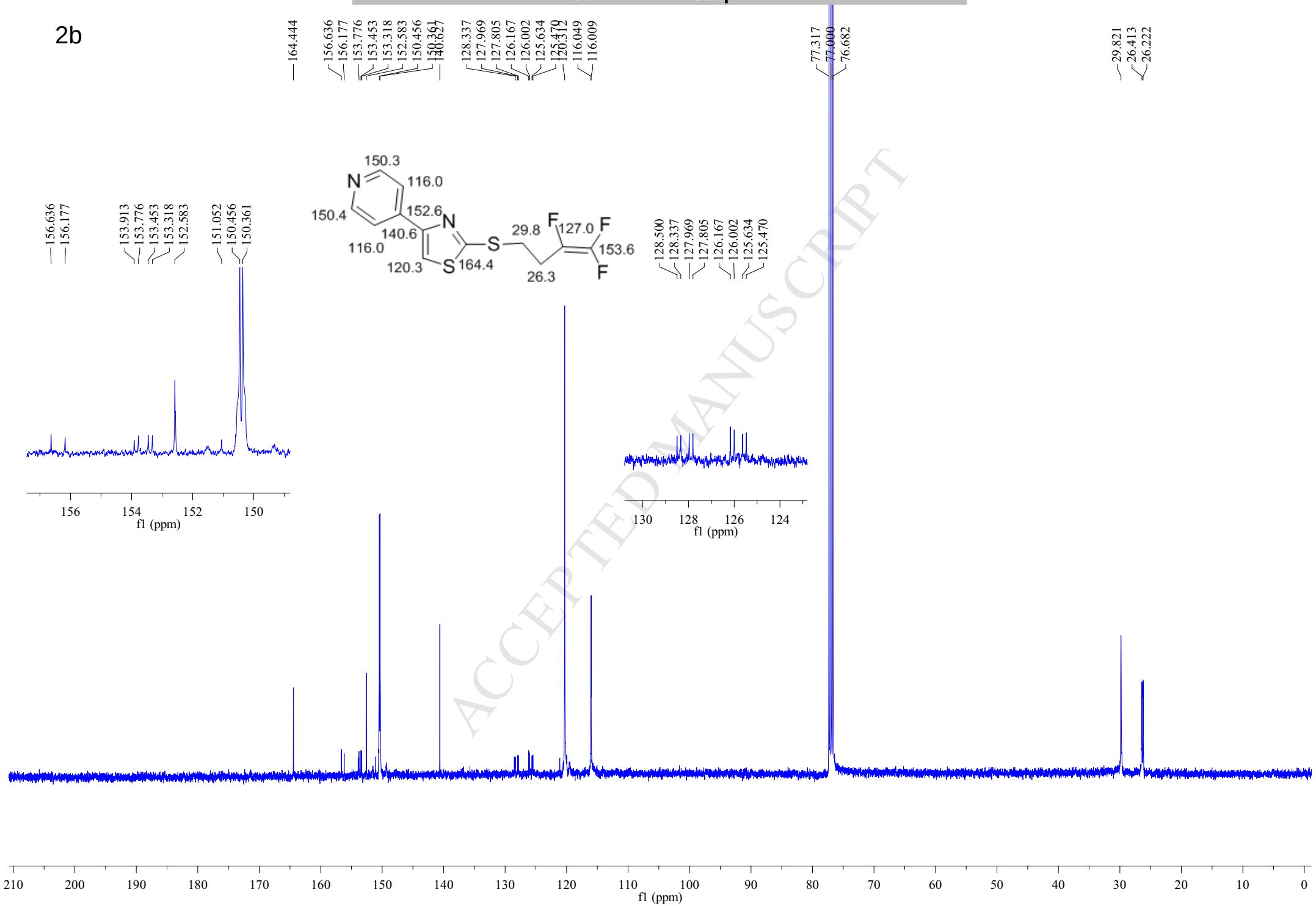

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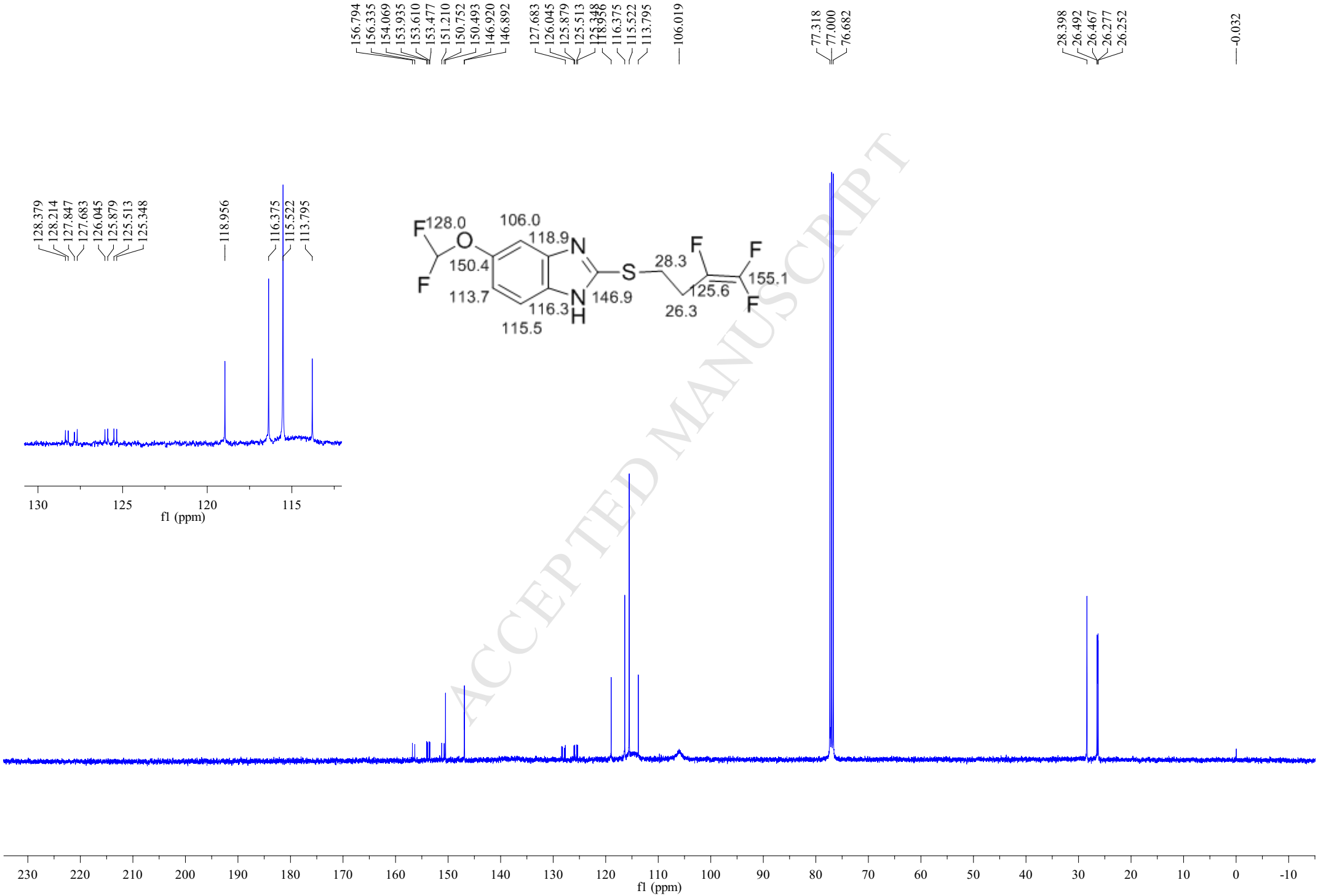

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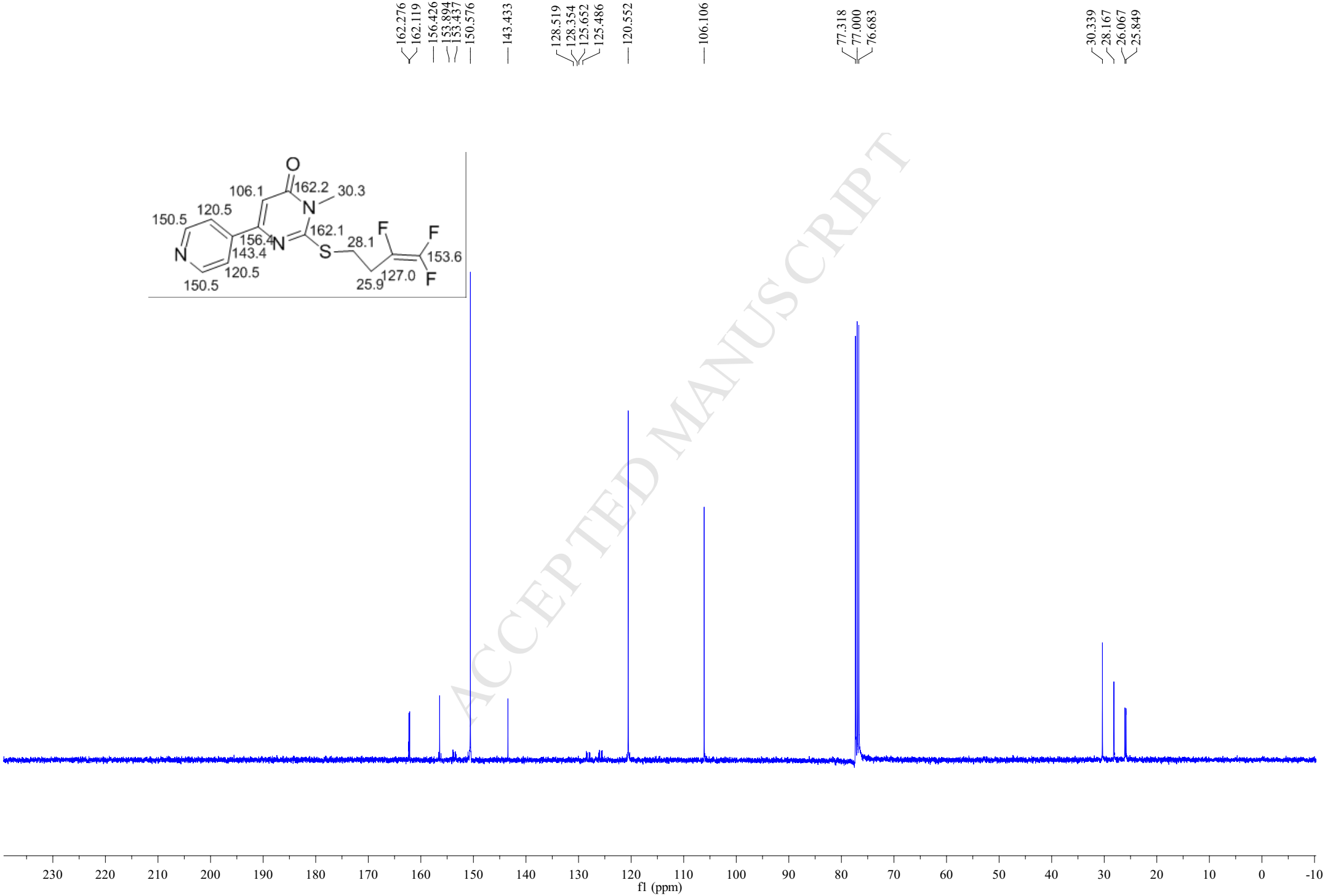

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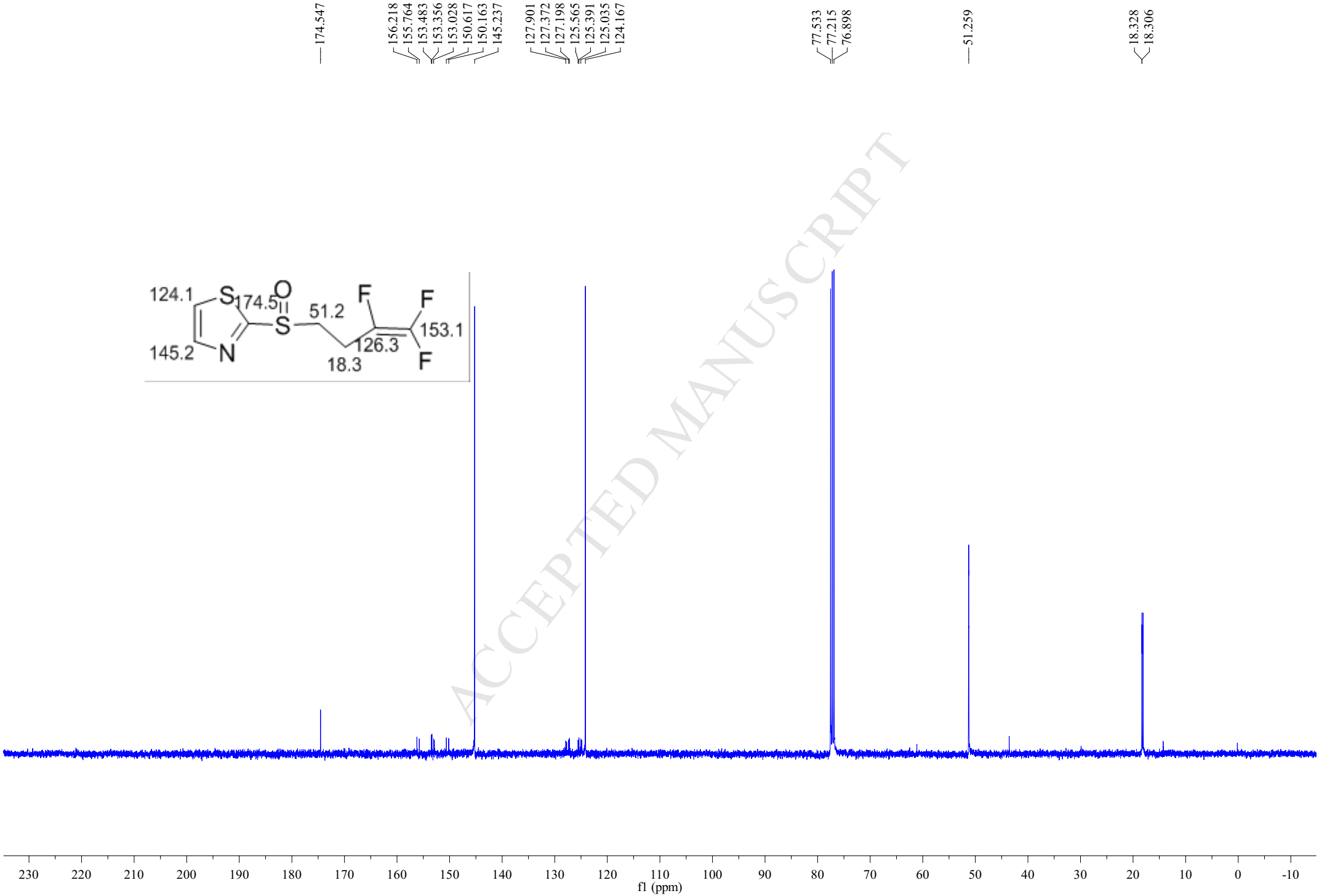

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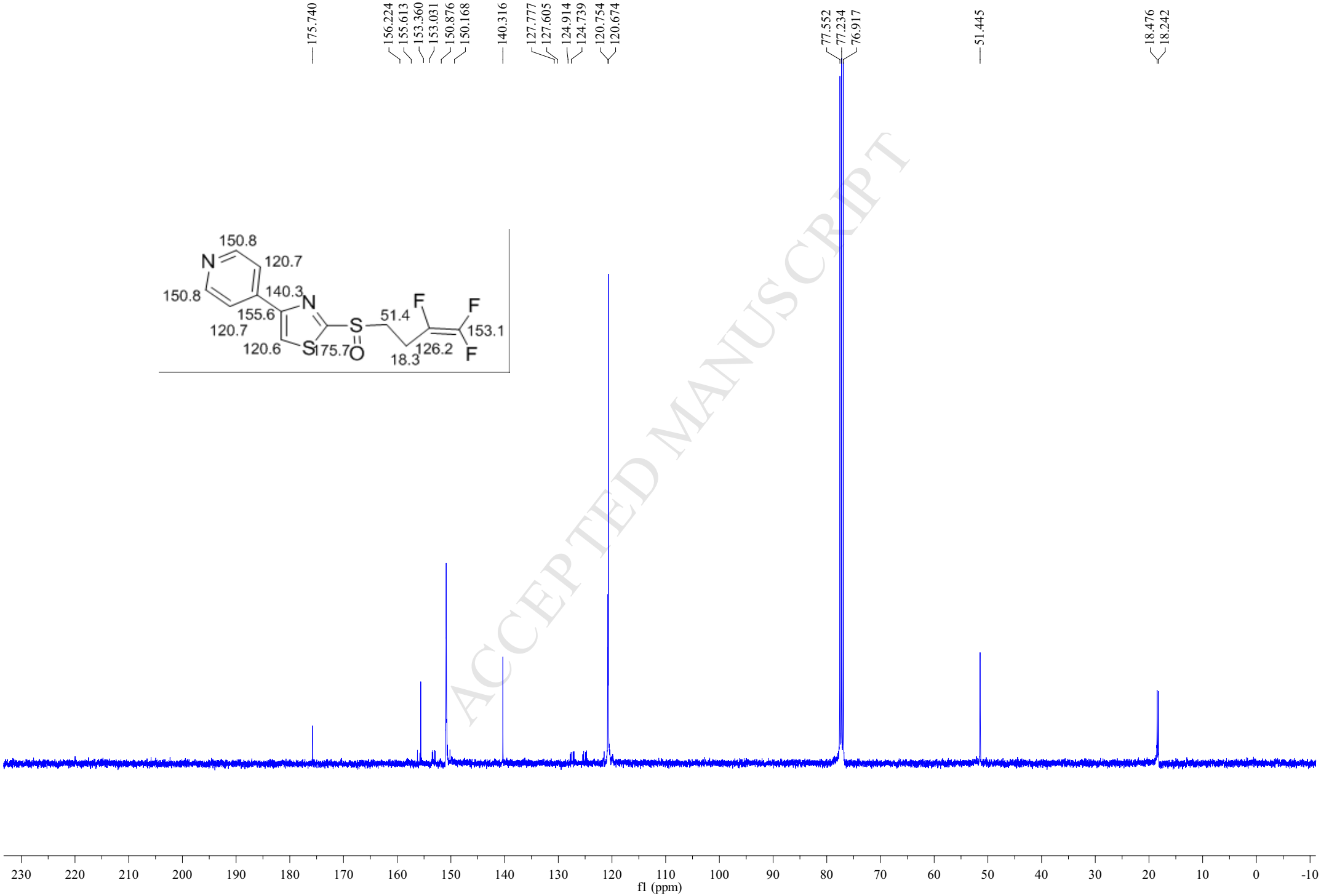

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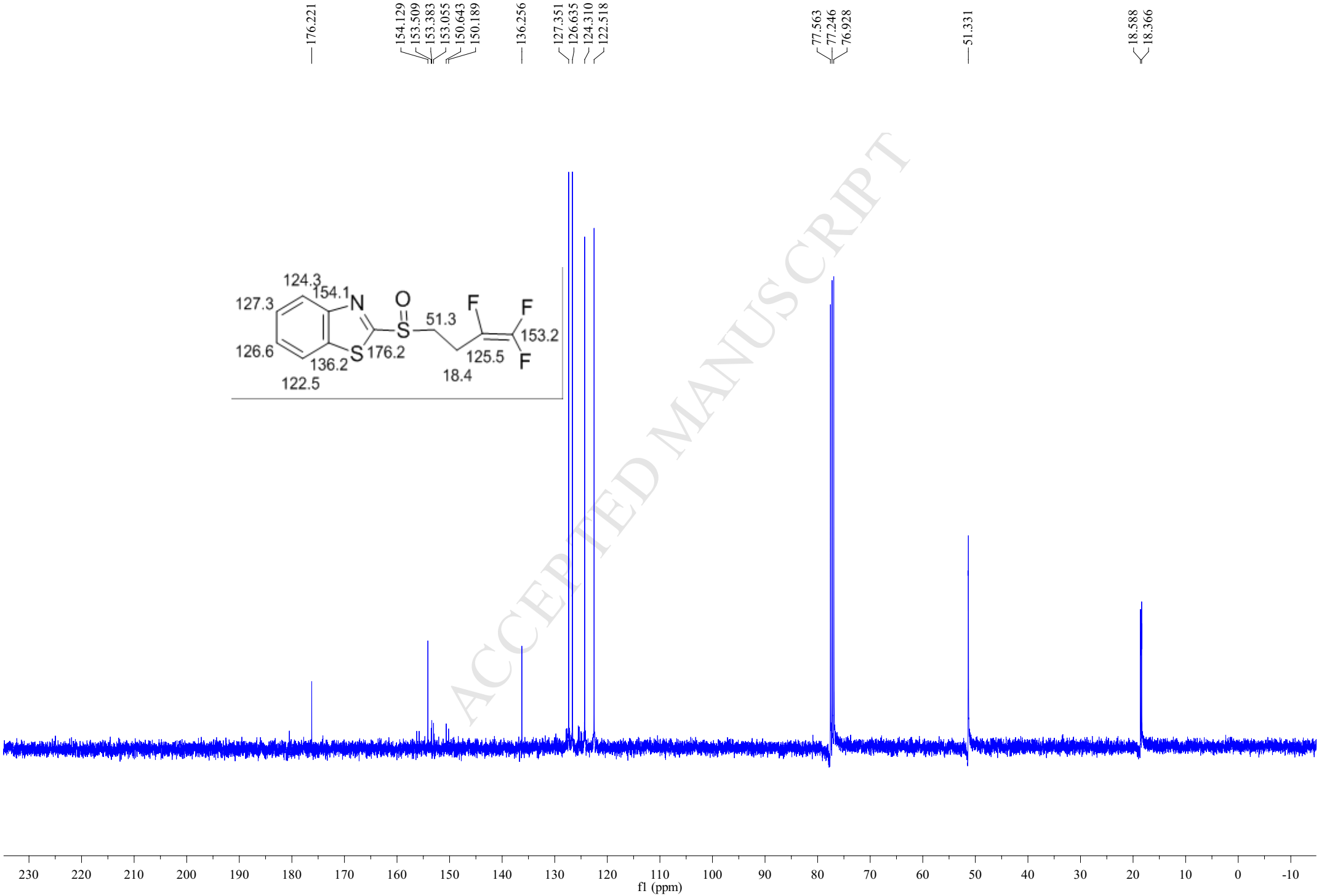

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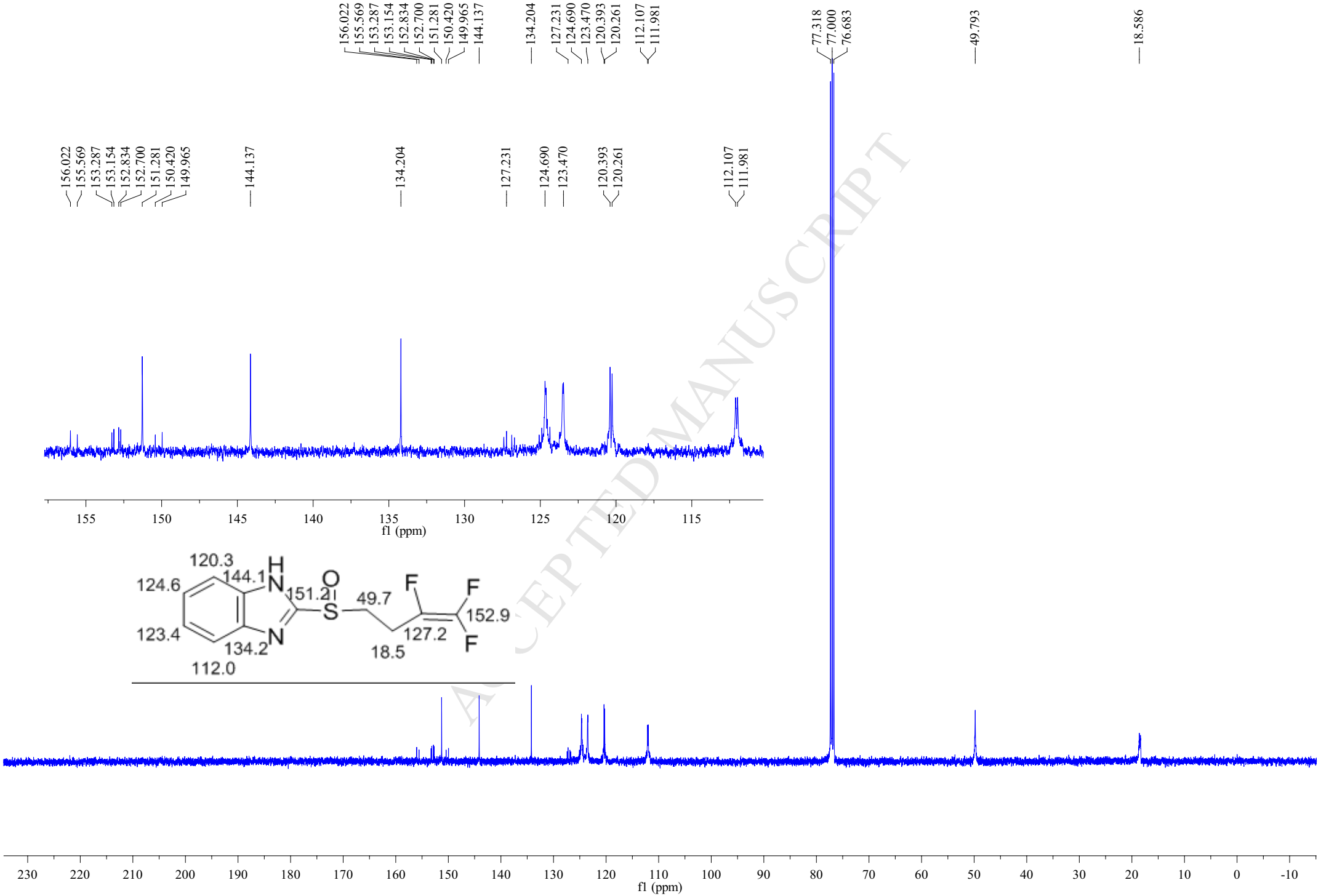

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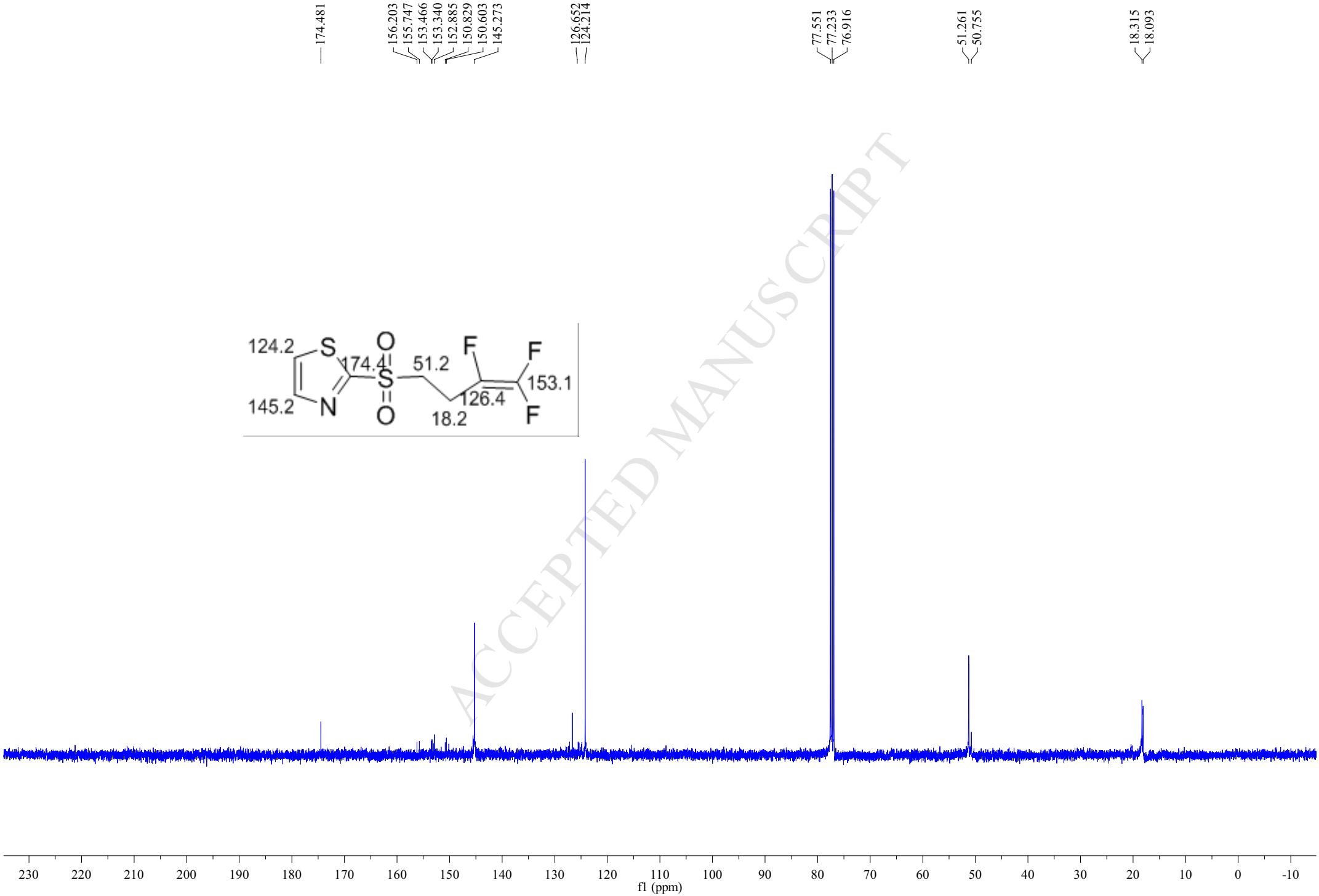

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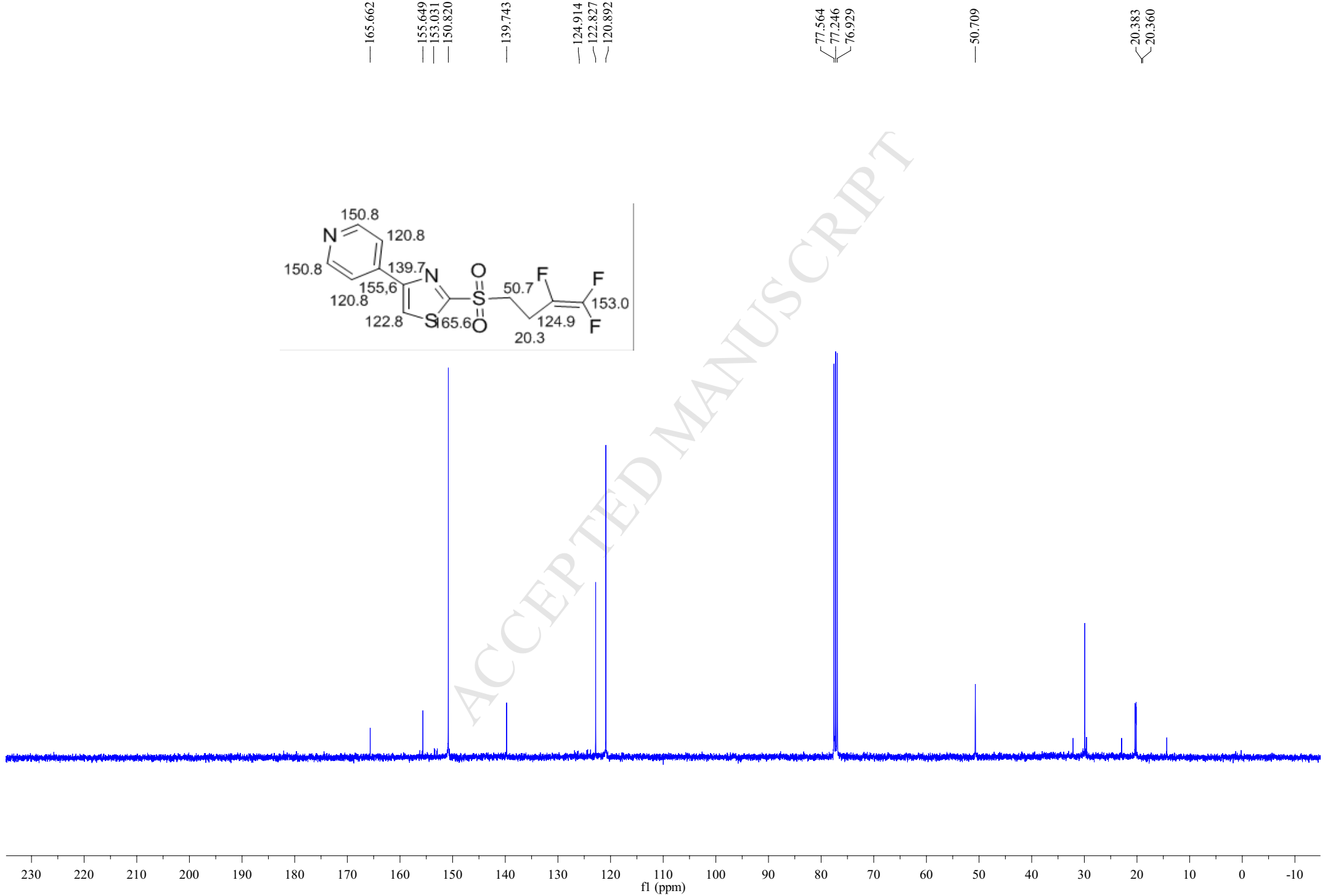

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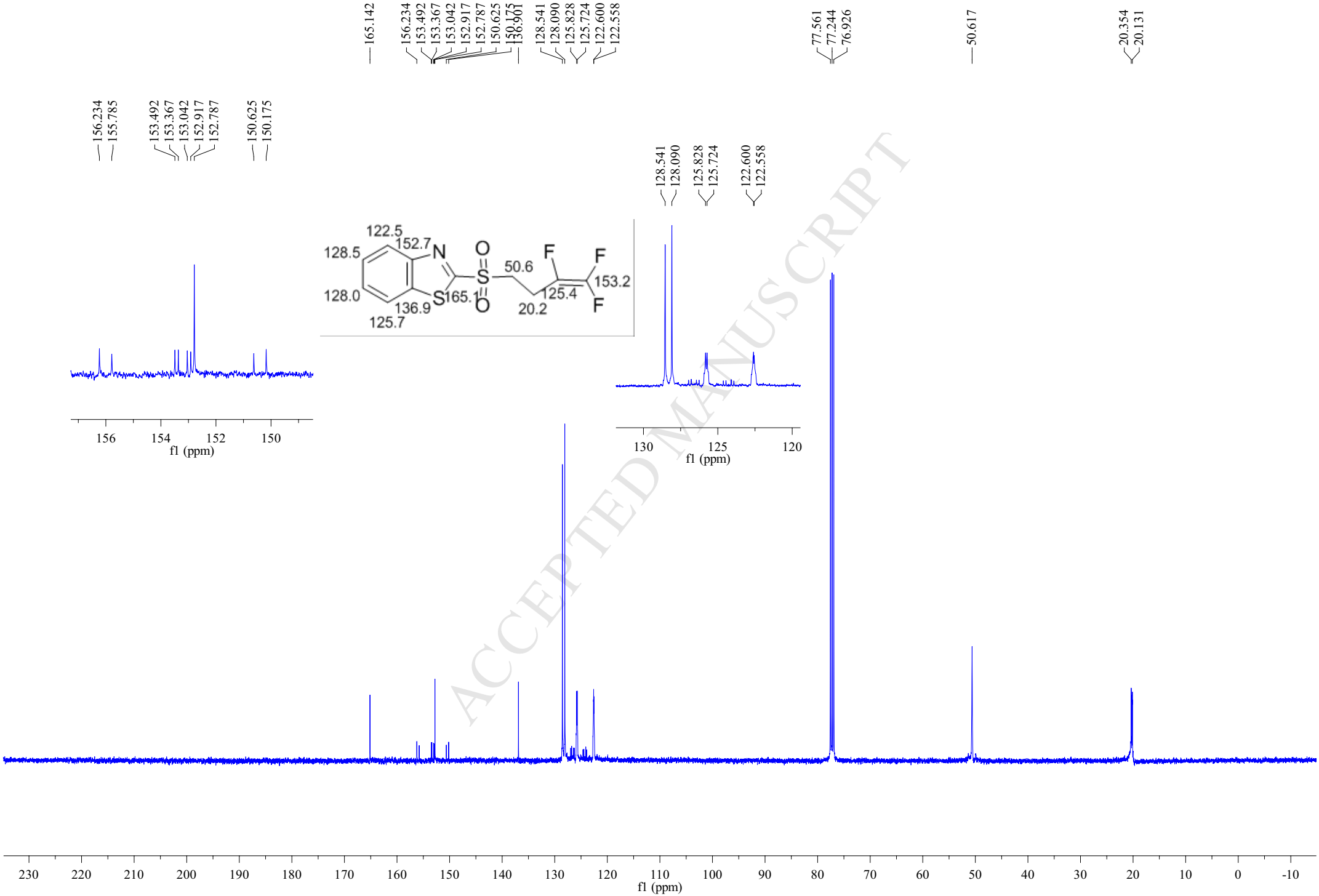

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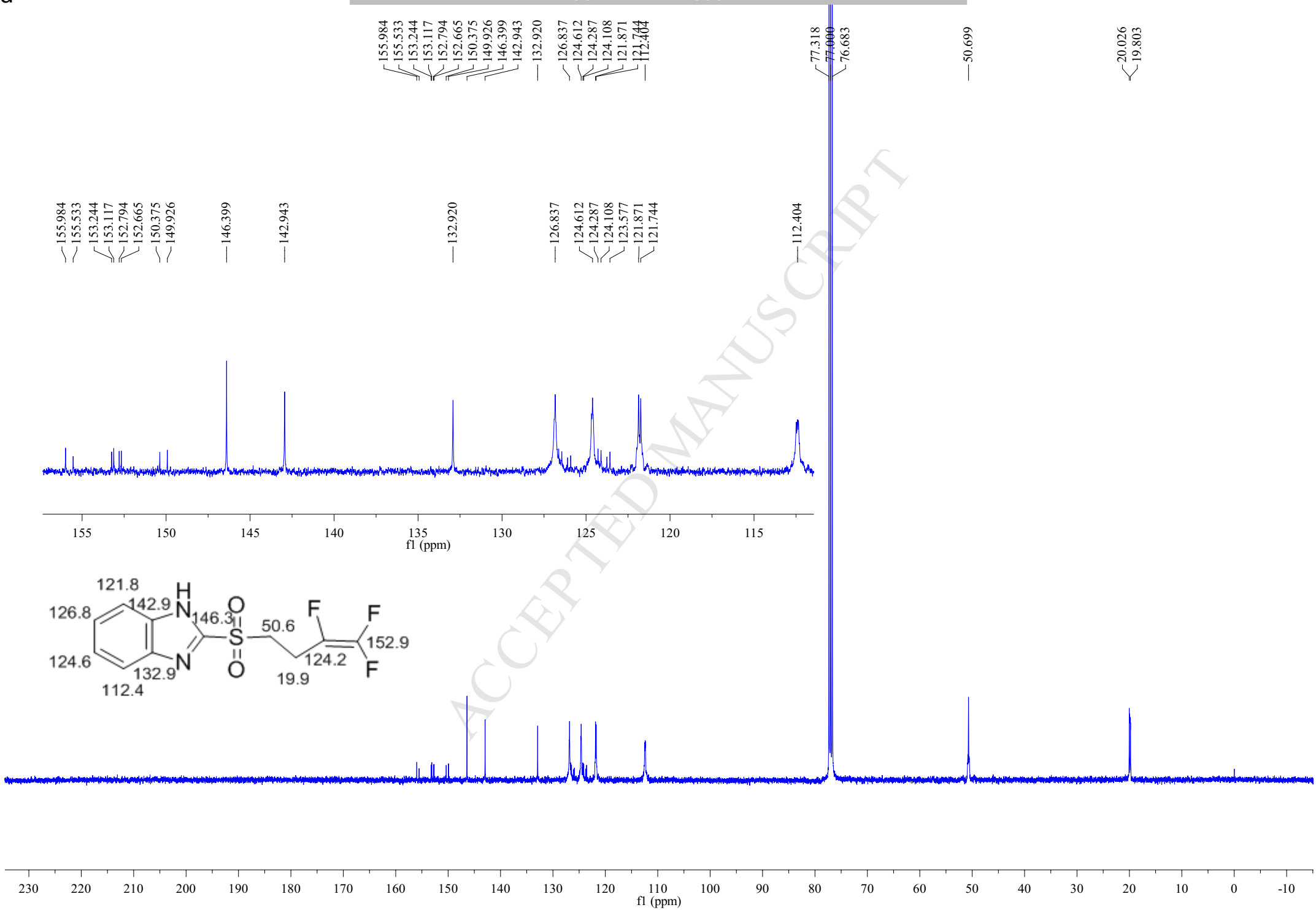

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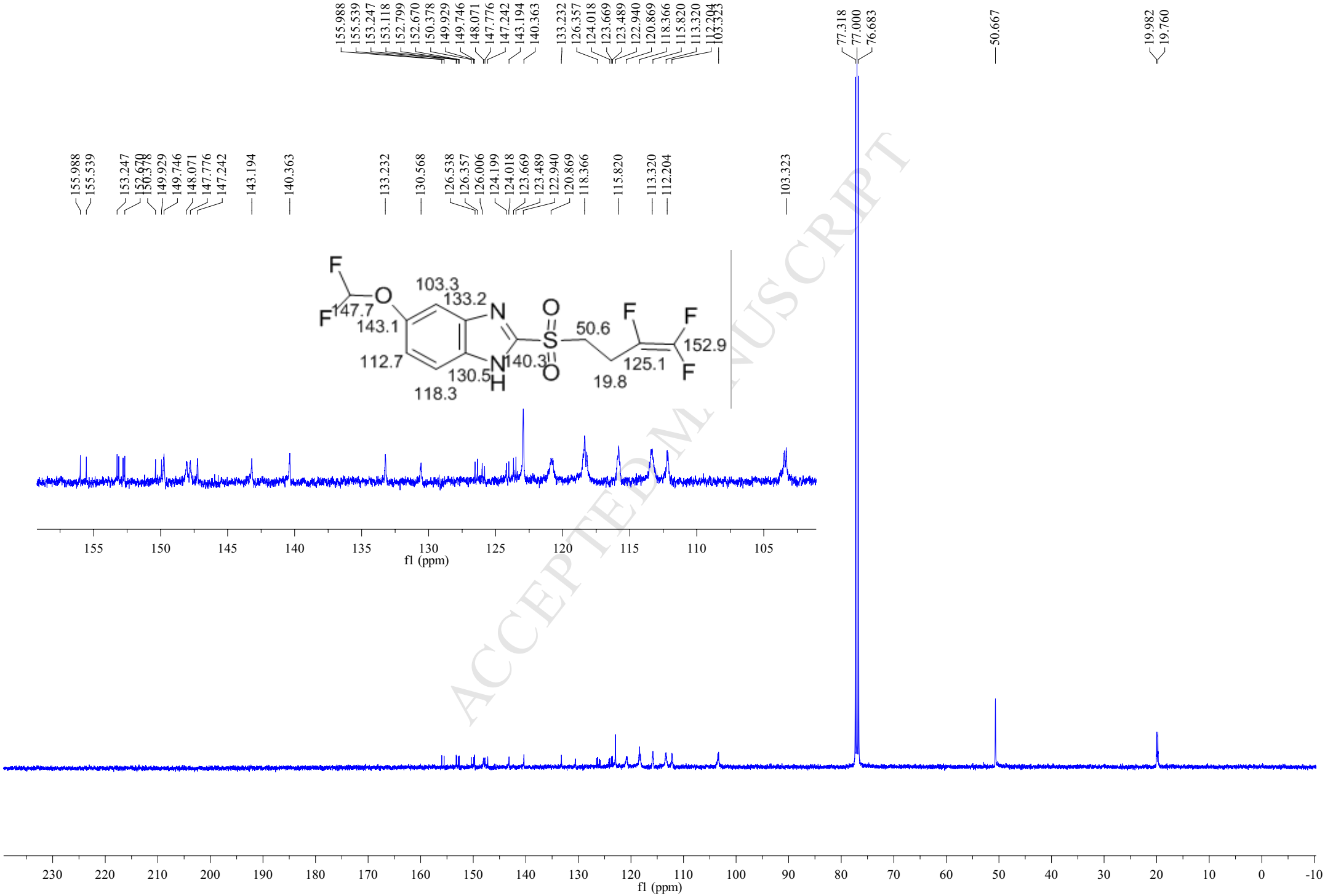

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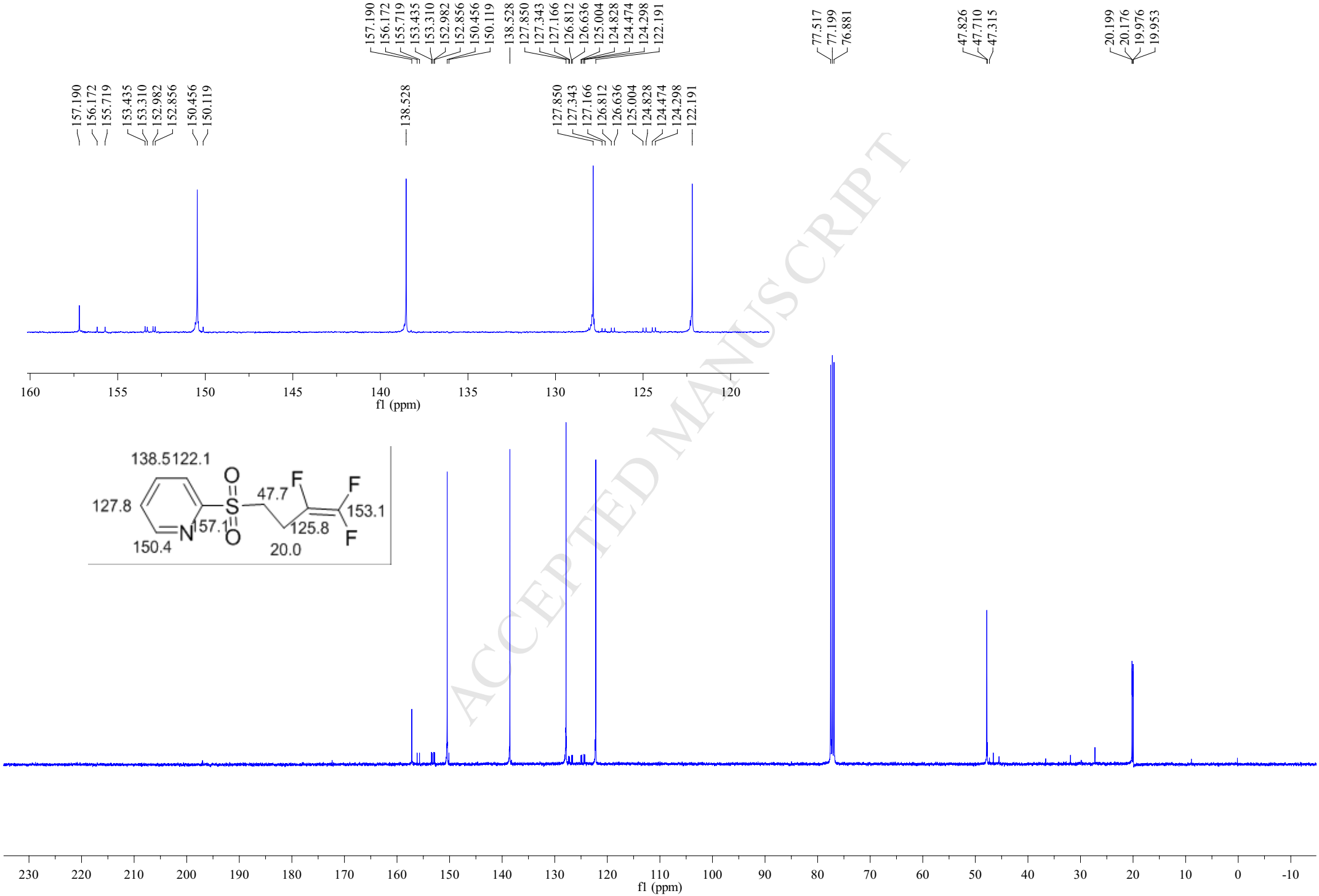

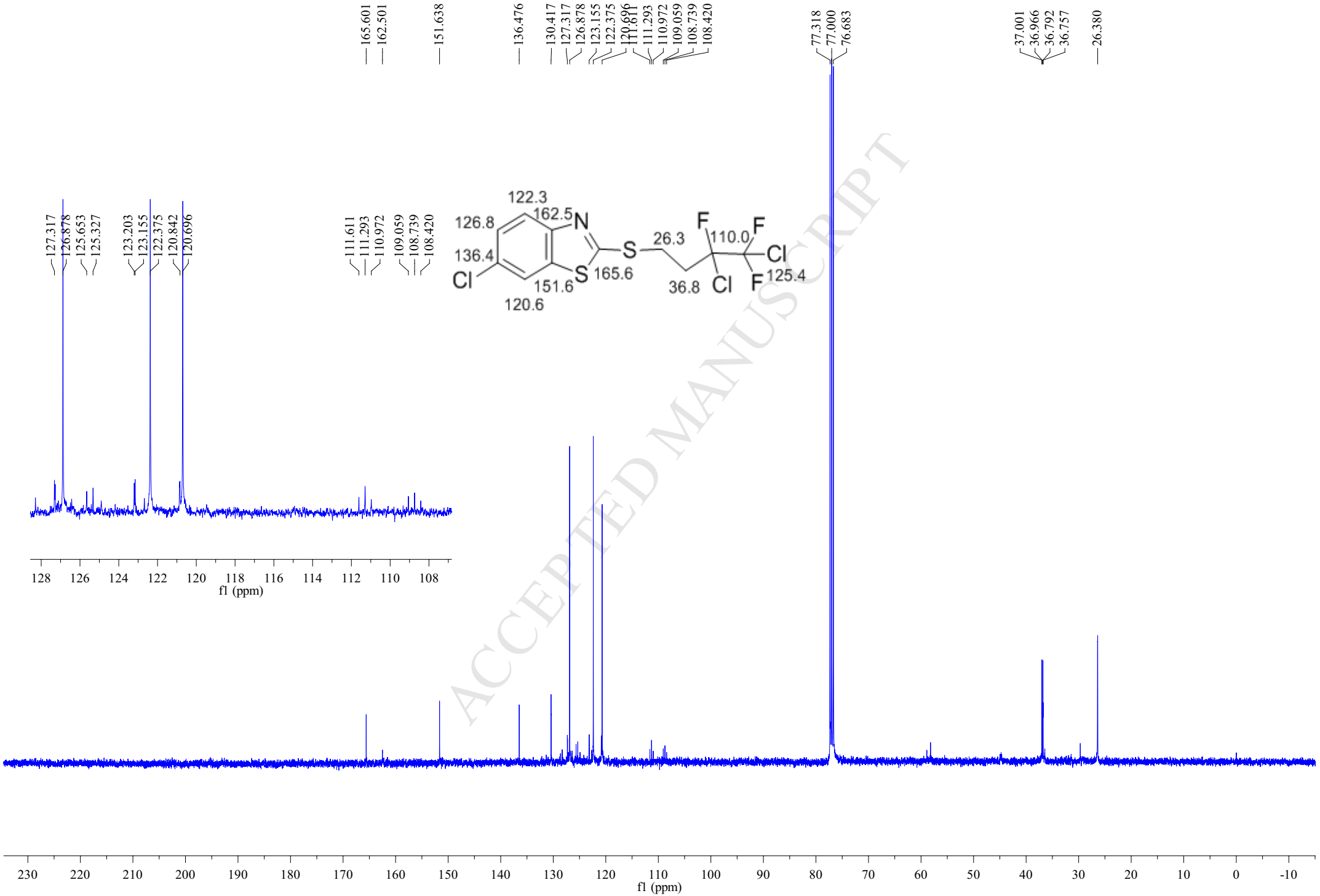

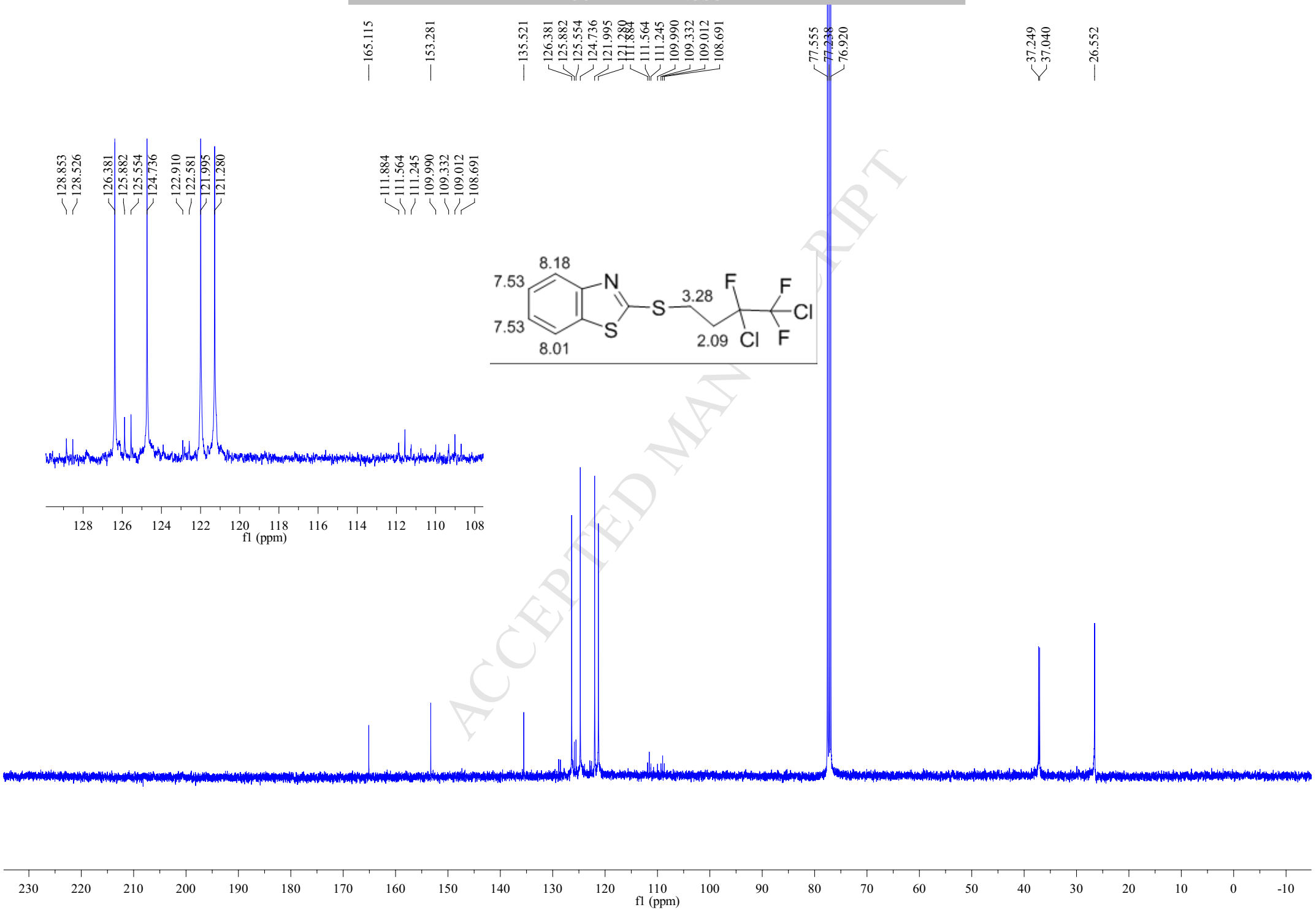

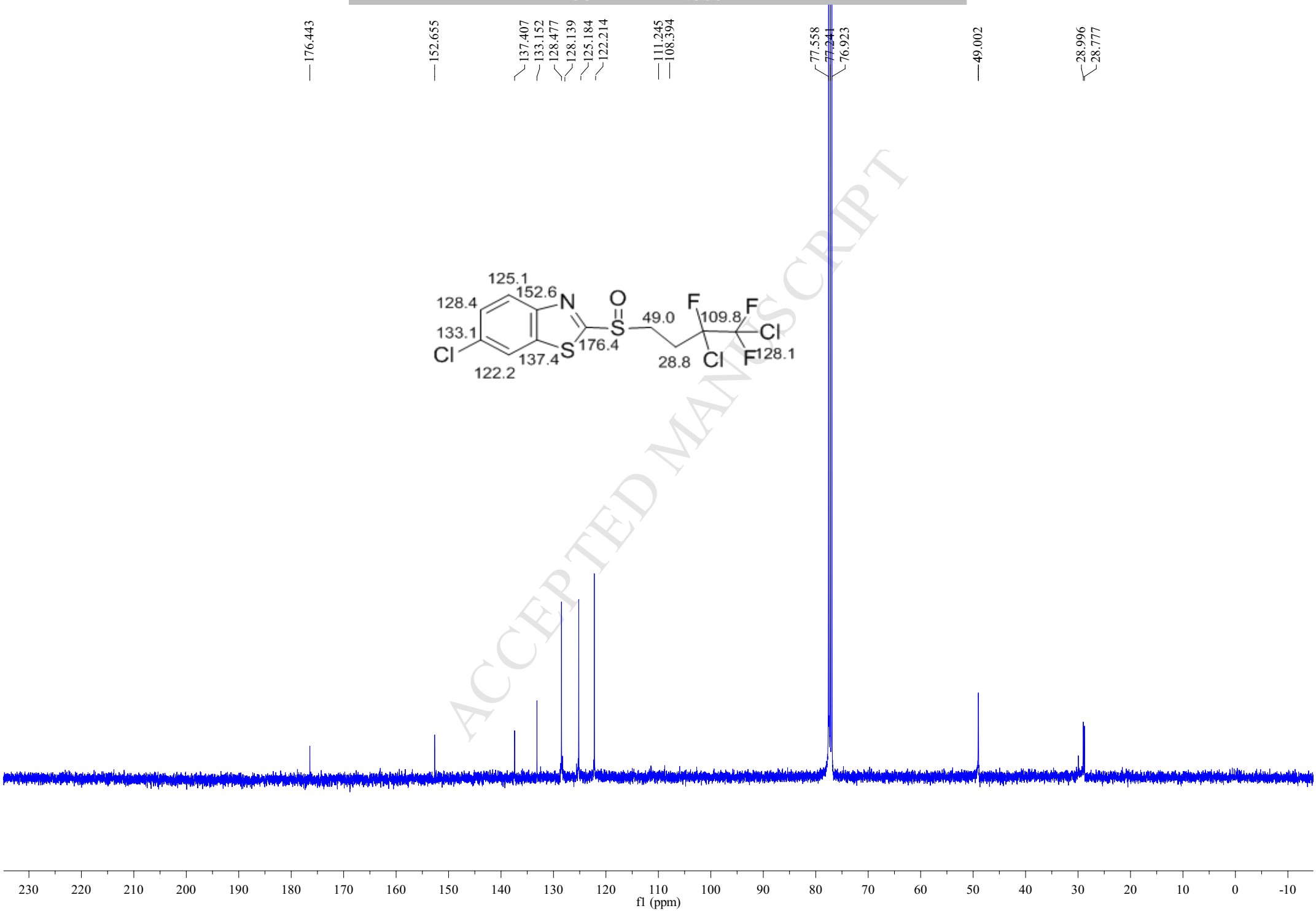

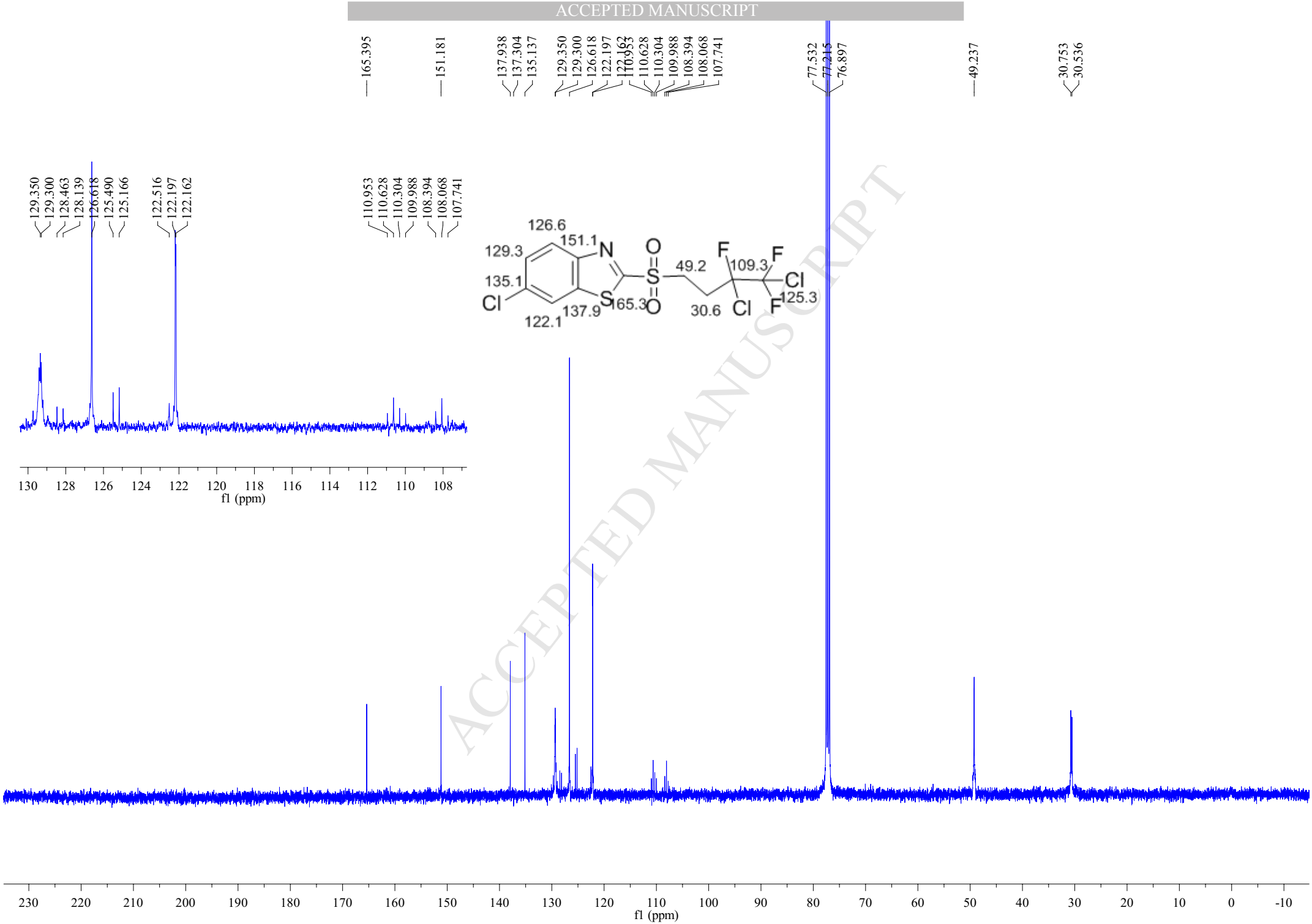

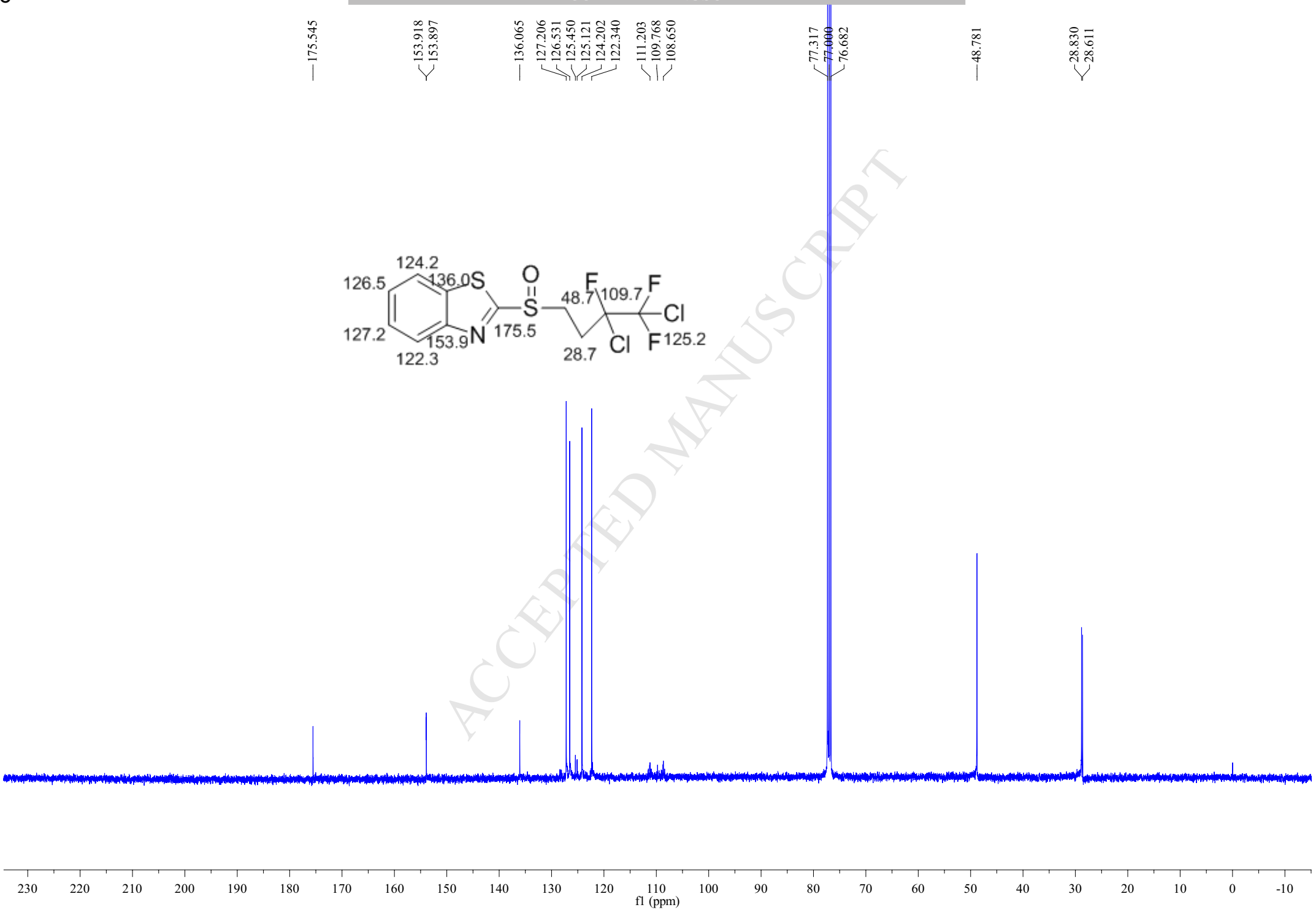

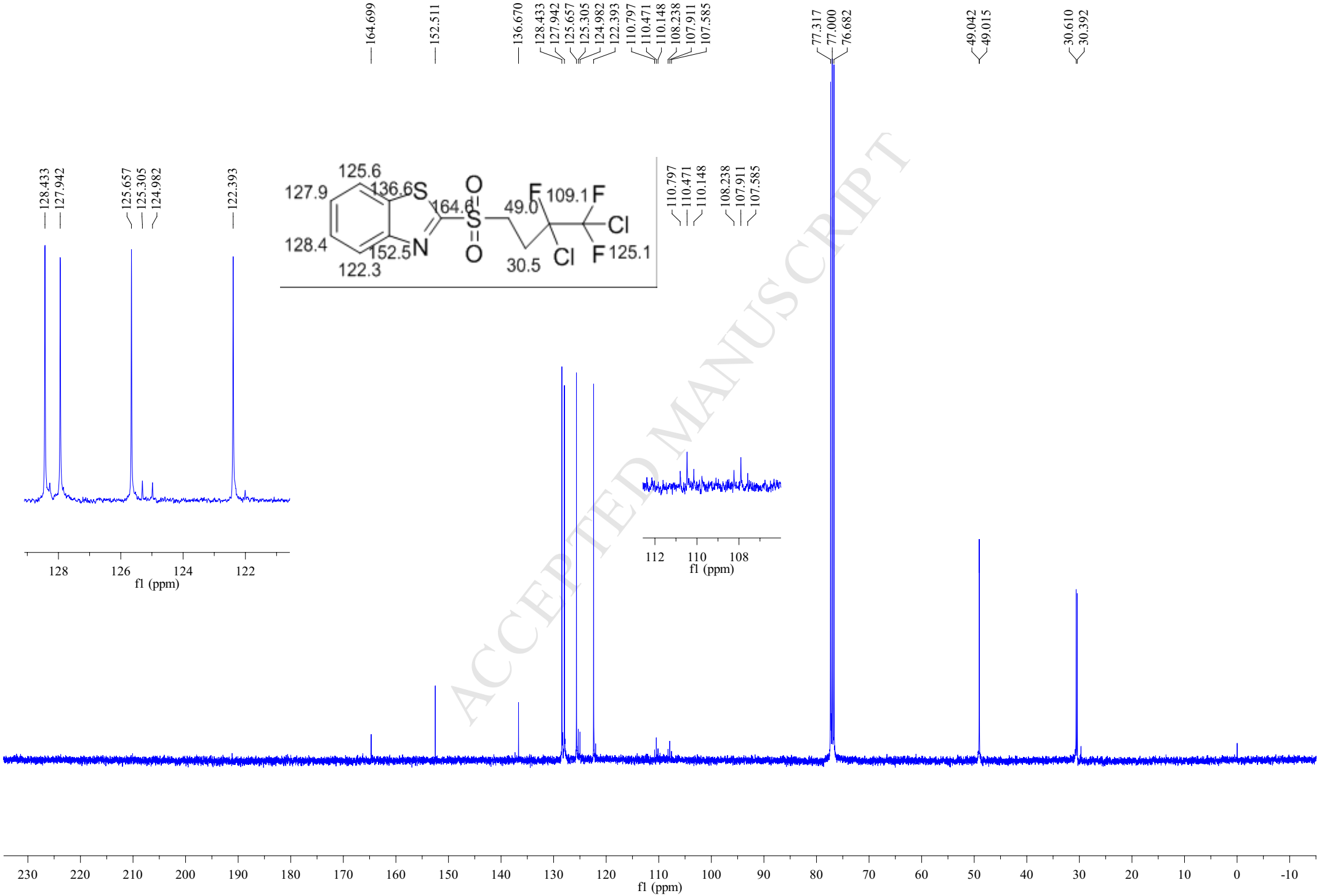

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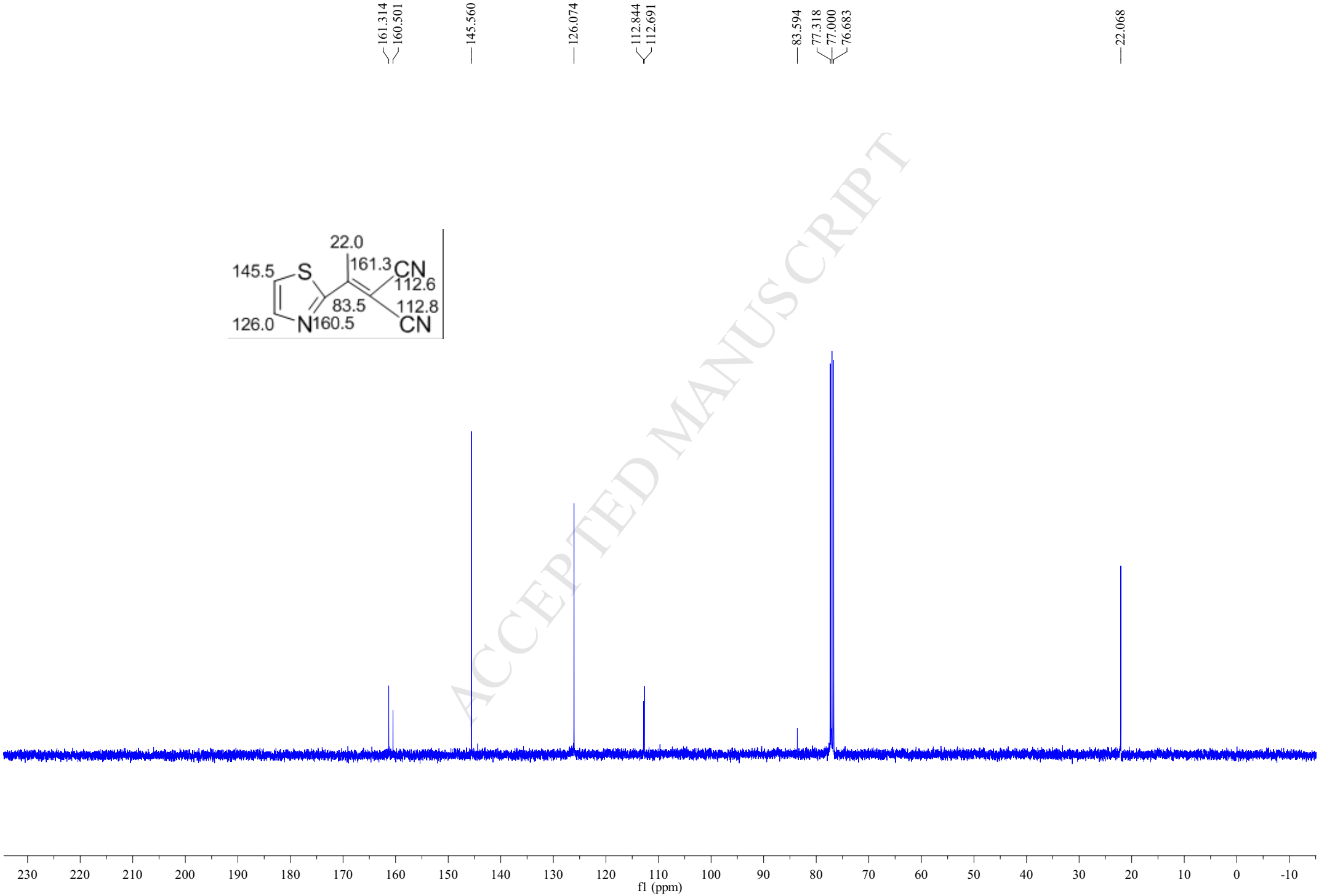

14b

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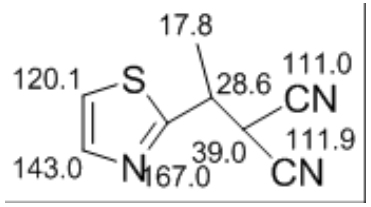
143.003
120.178
111.924
111.089
77.337
77.019
76.702
39.037
28.651
17.838



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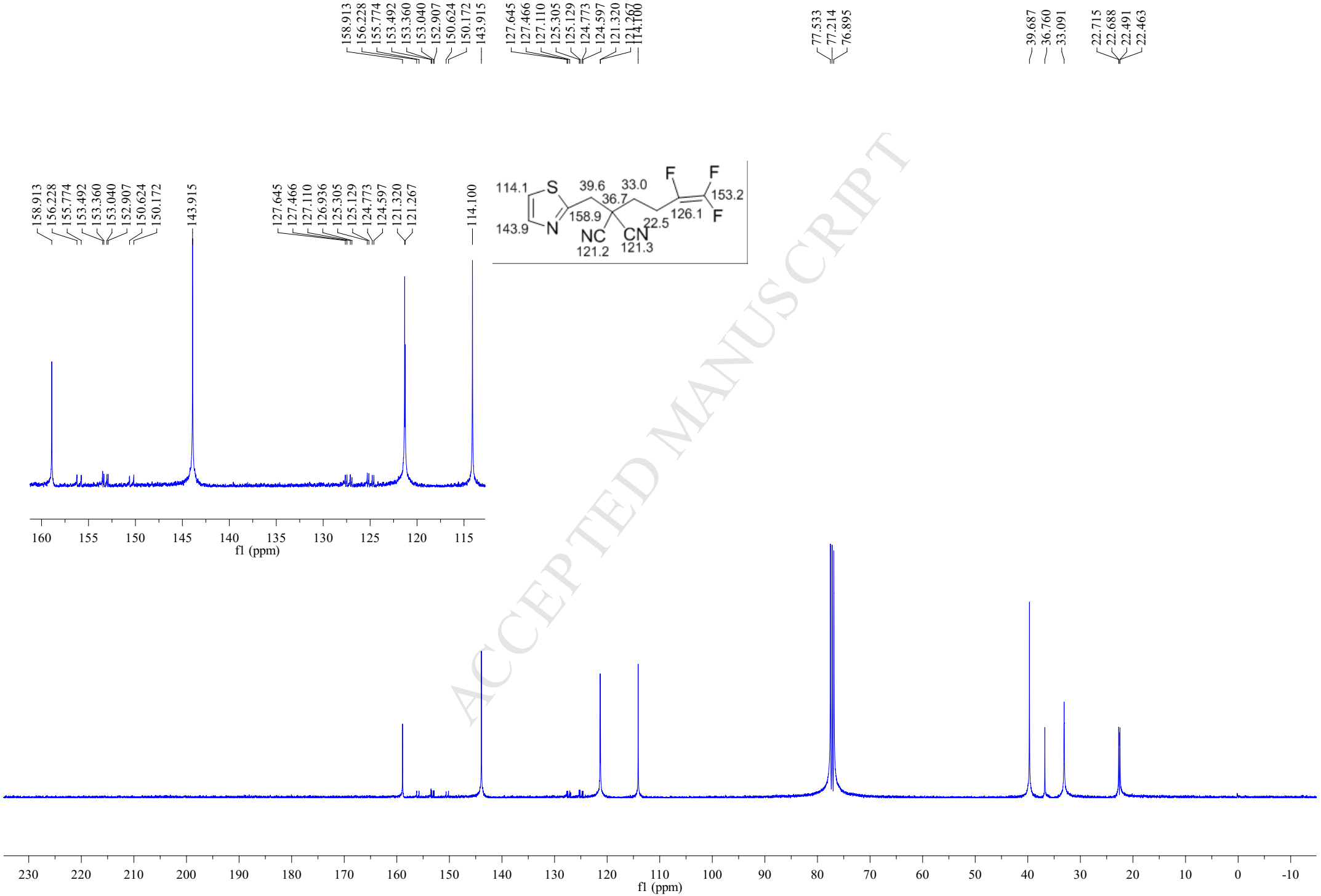
f1 (ppm)

15a



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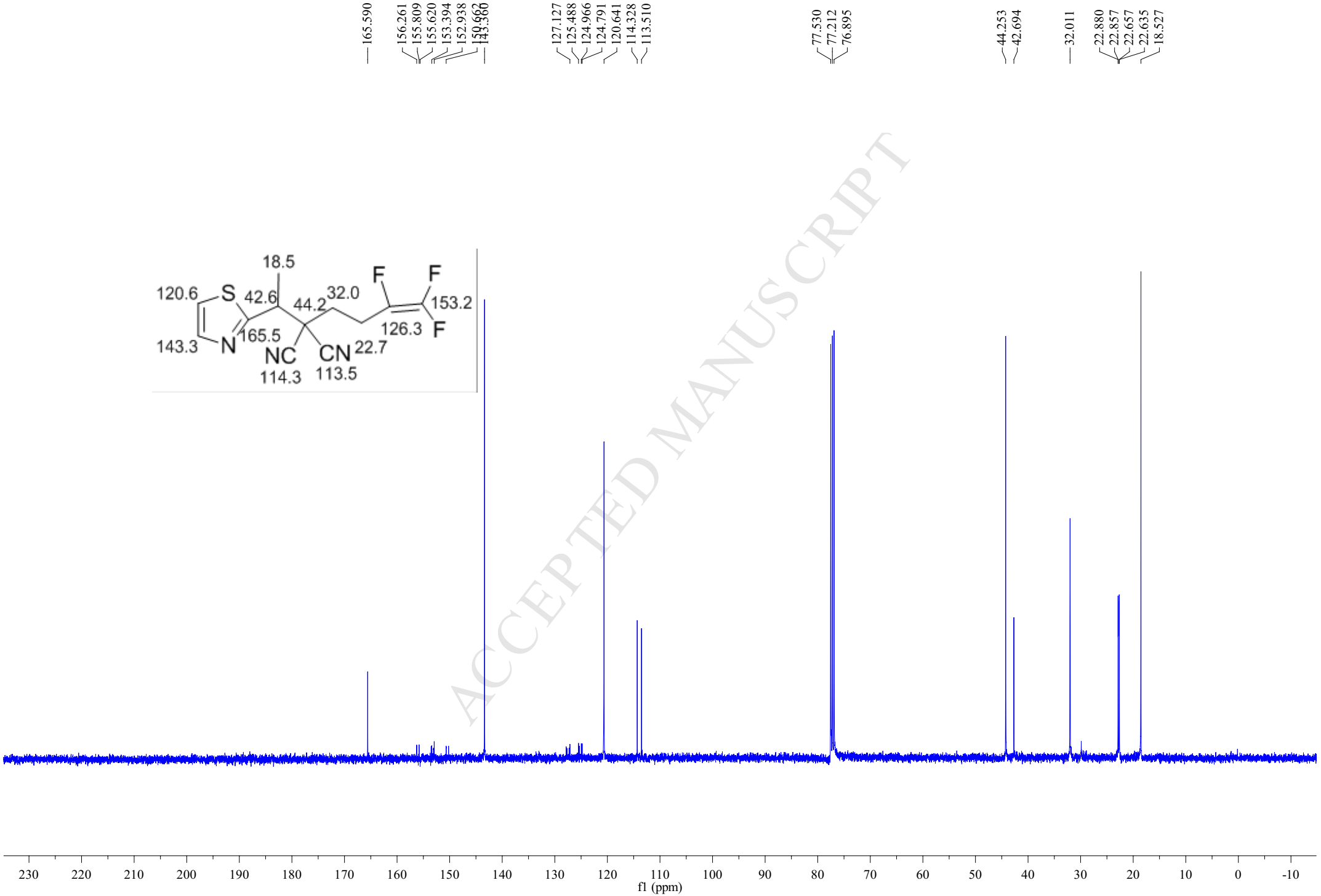

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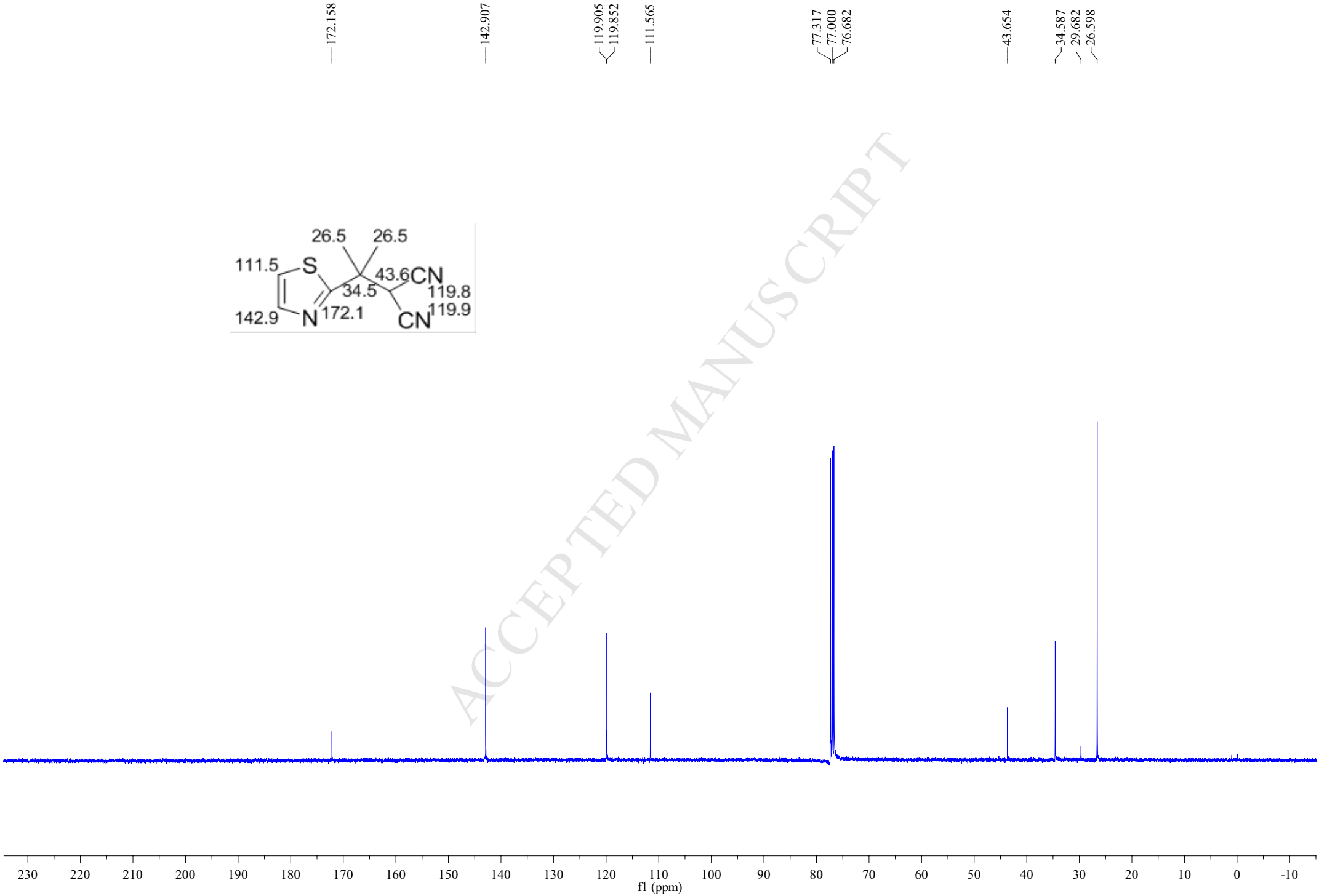

1H-NMR of compounds

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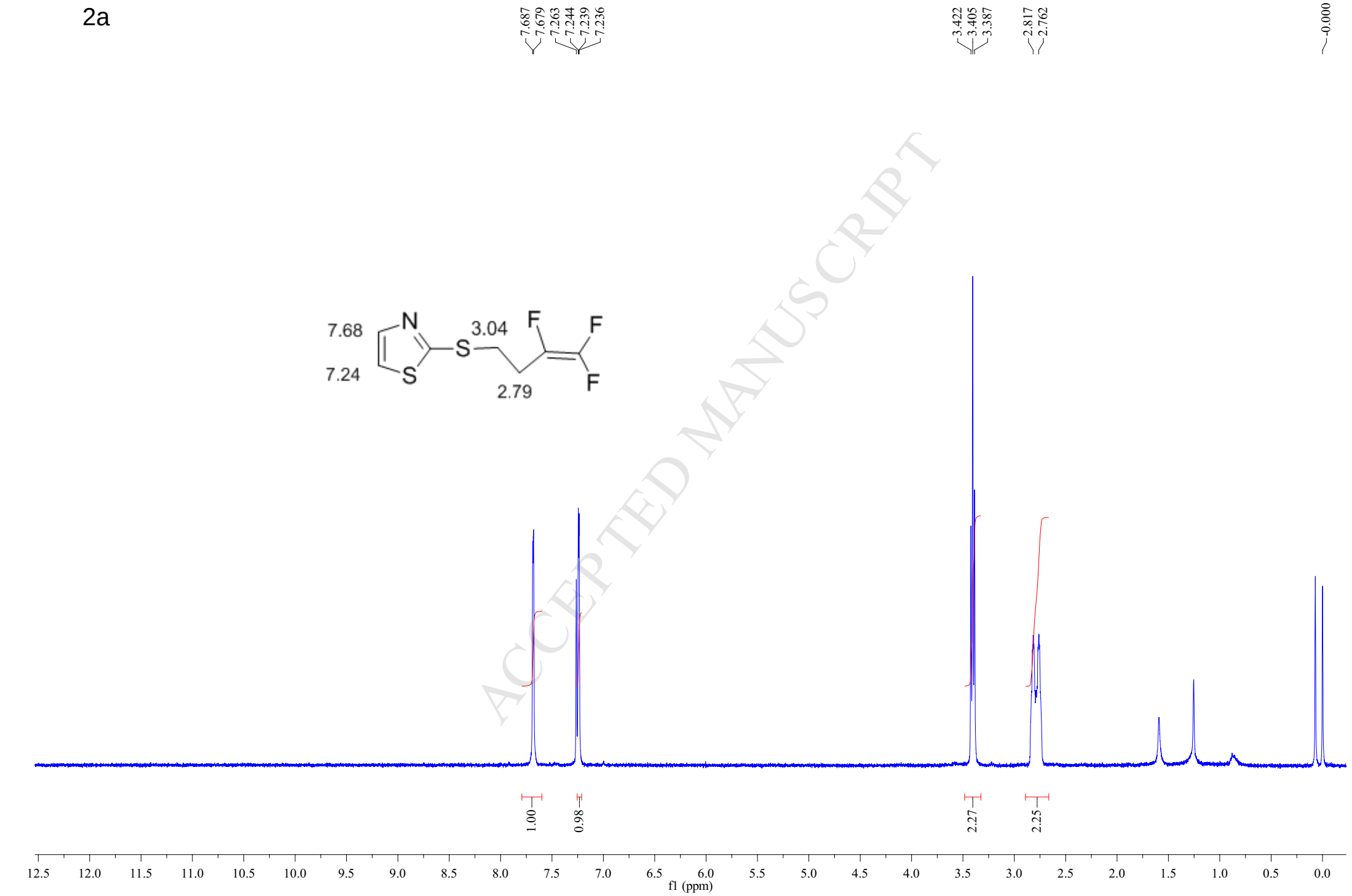

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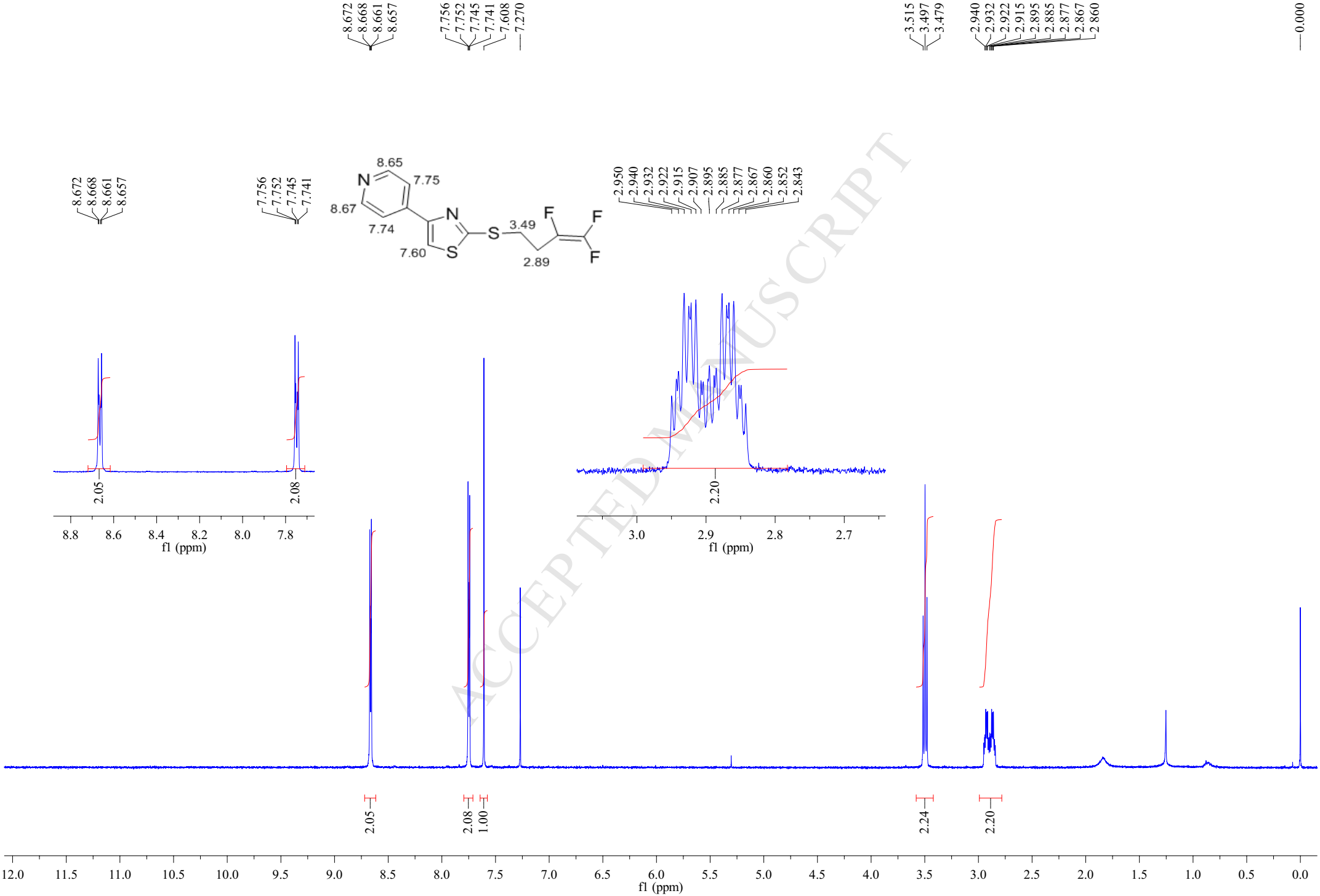

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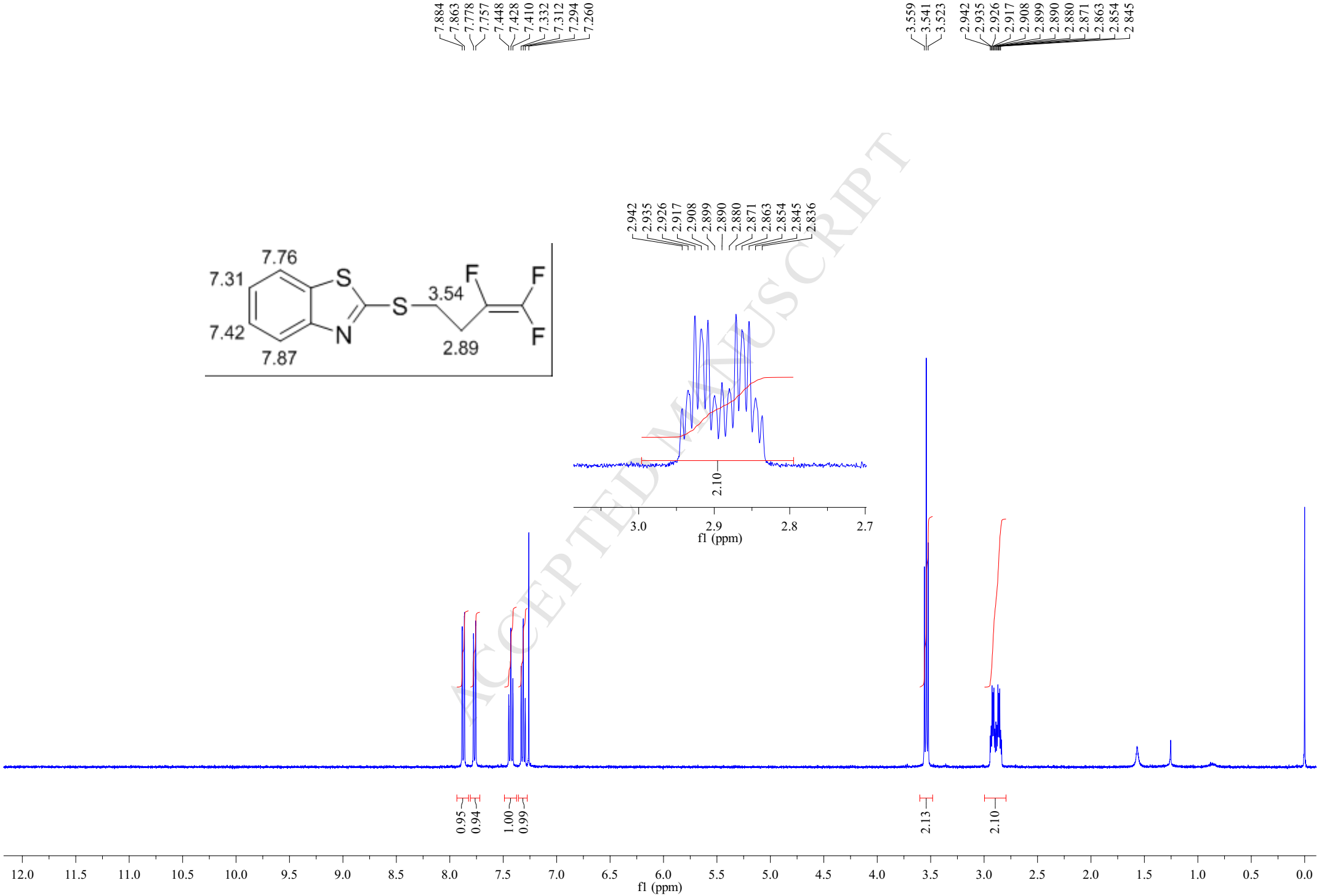

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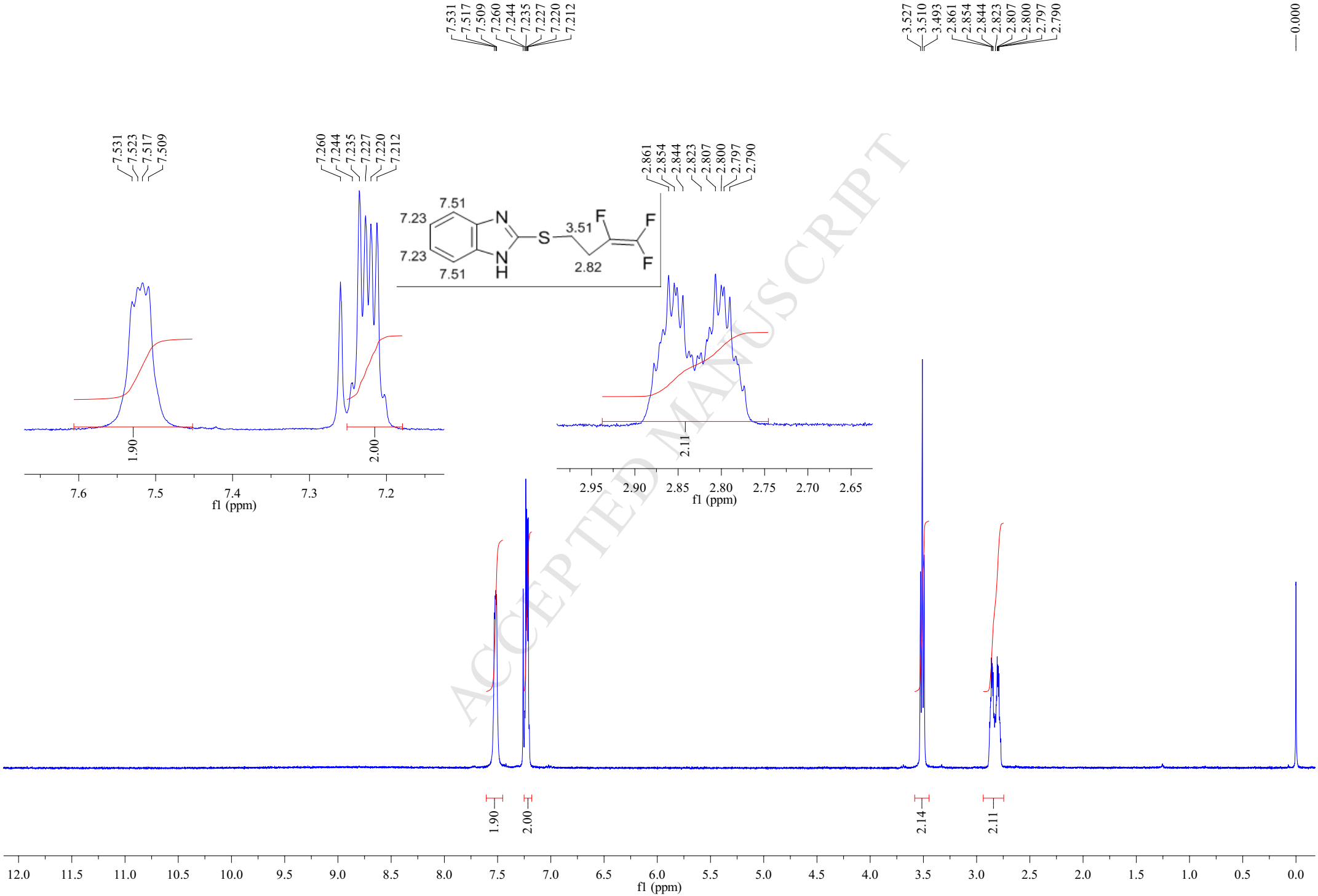

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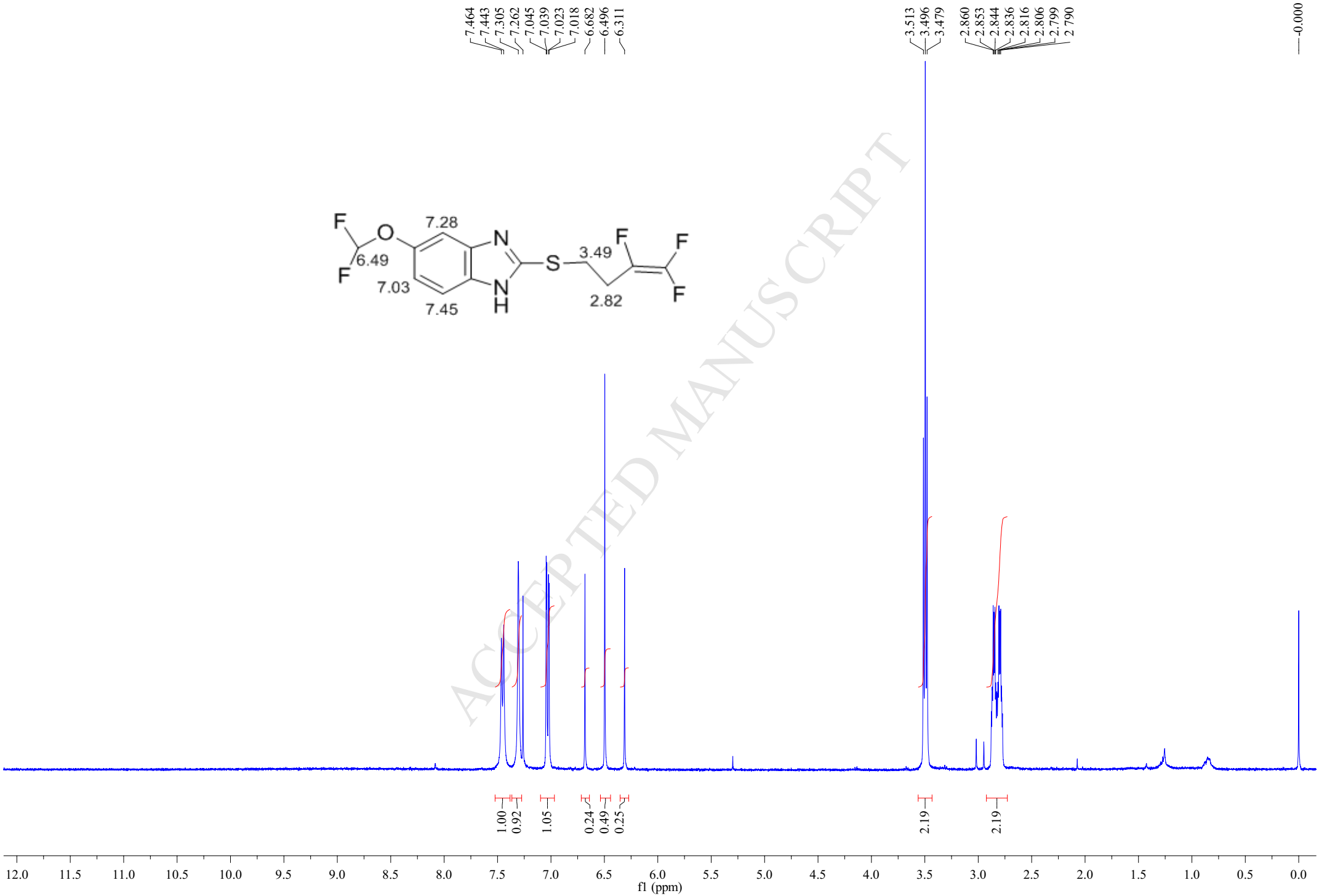

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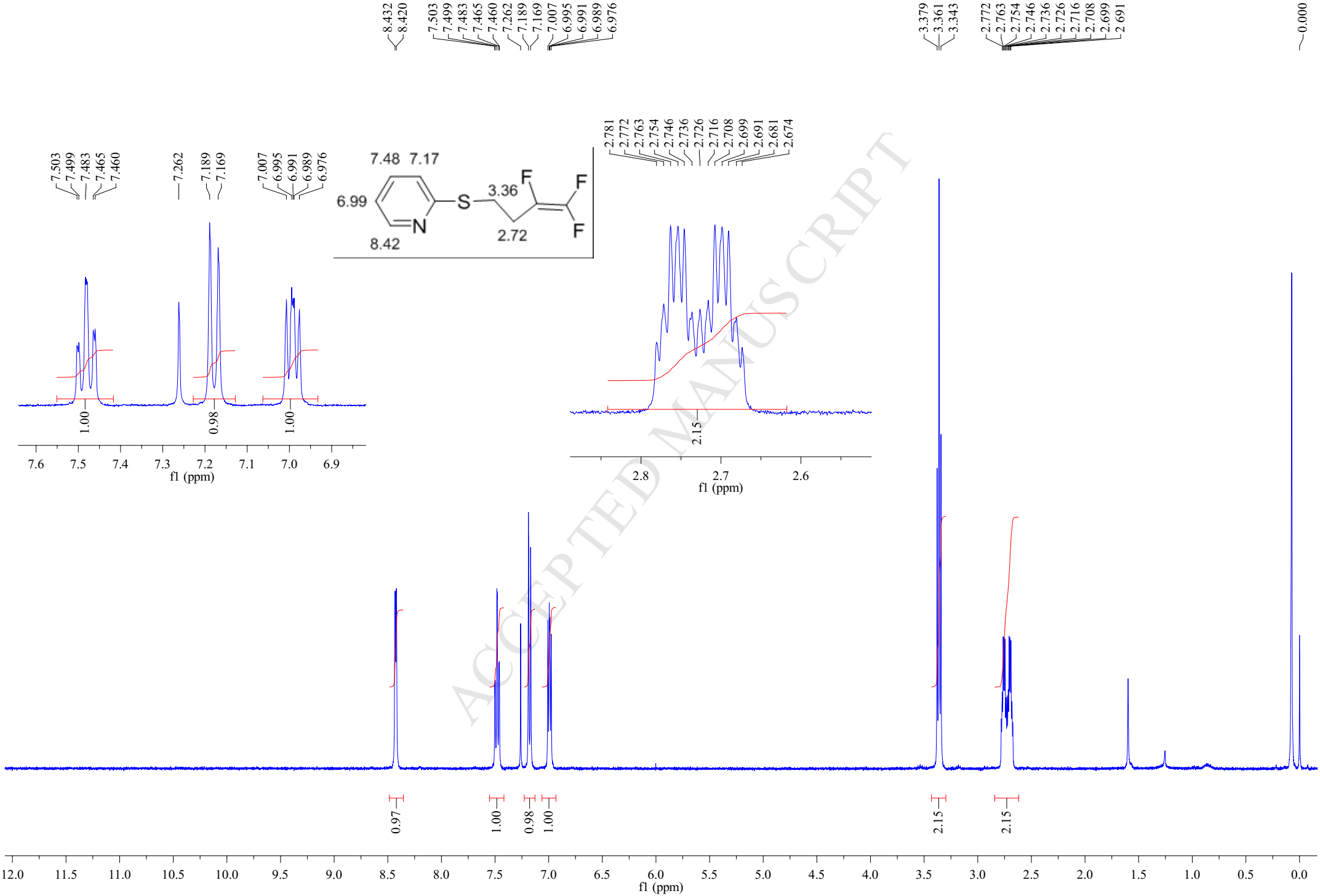

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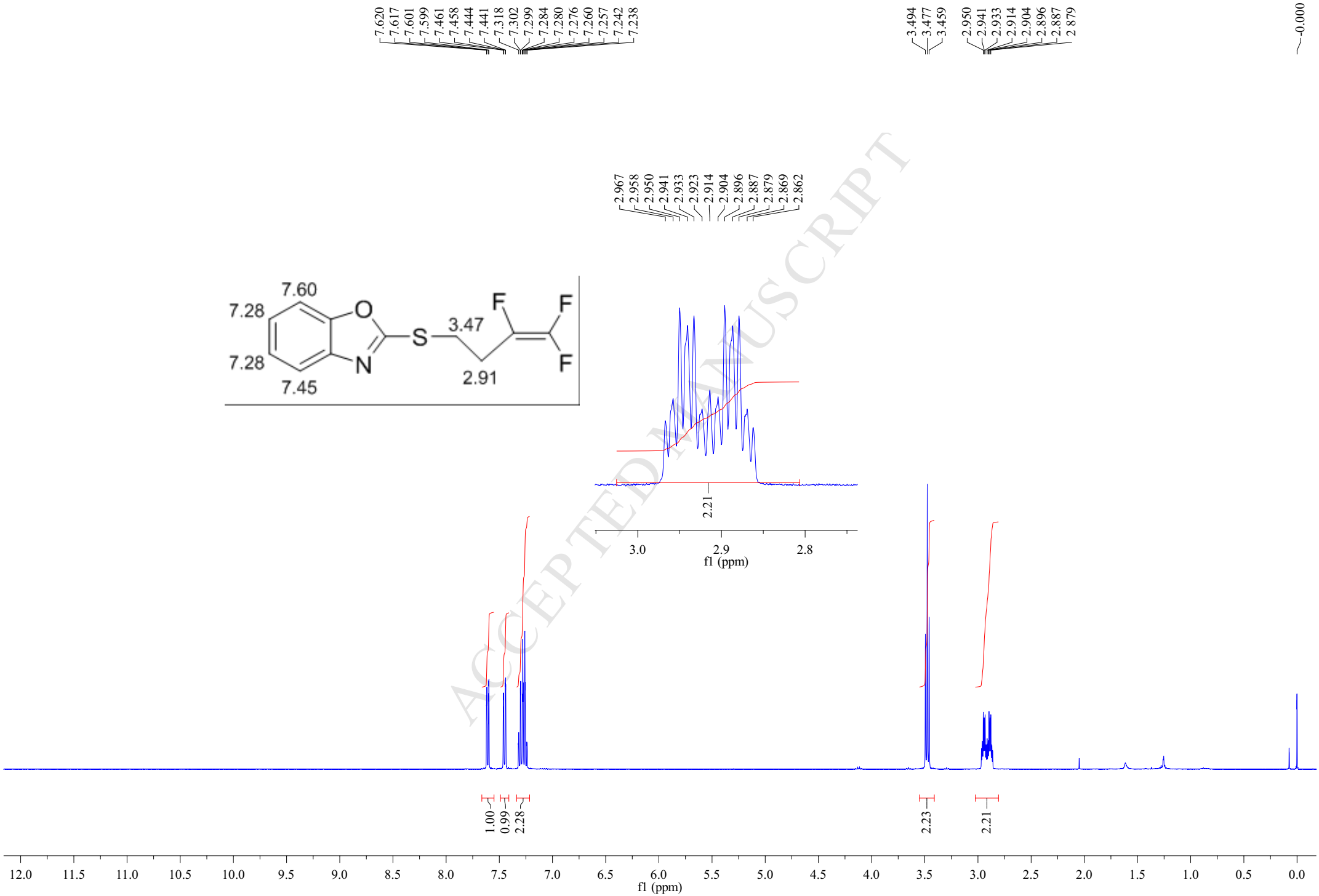

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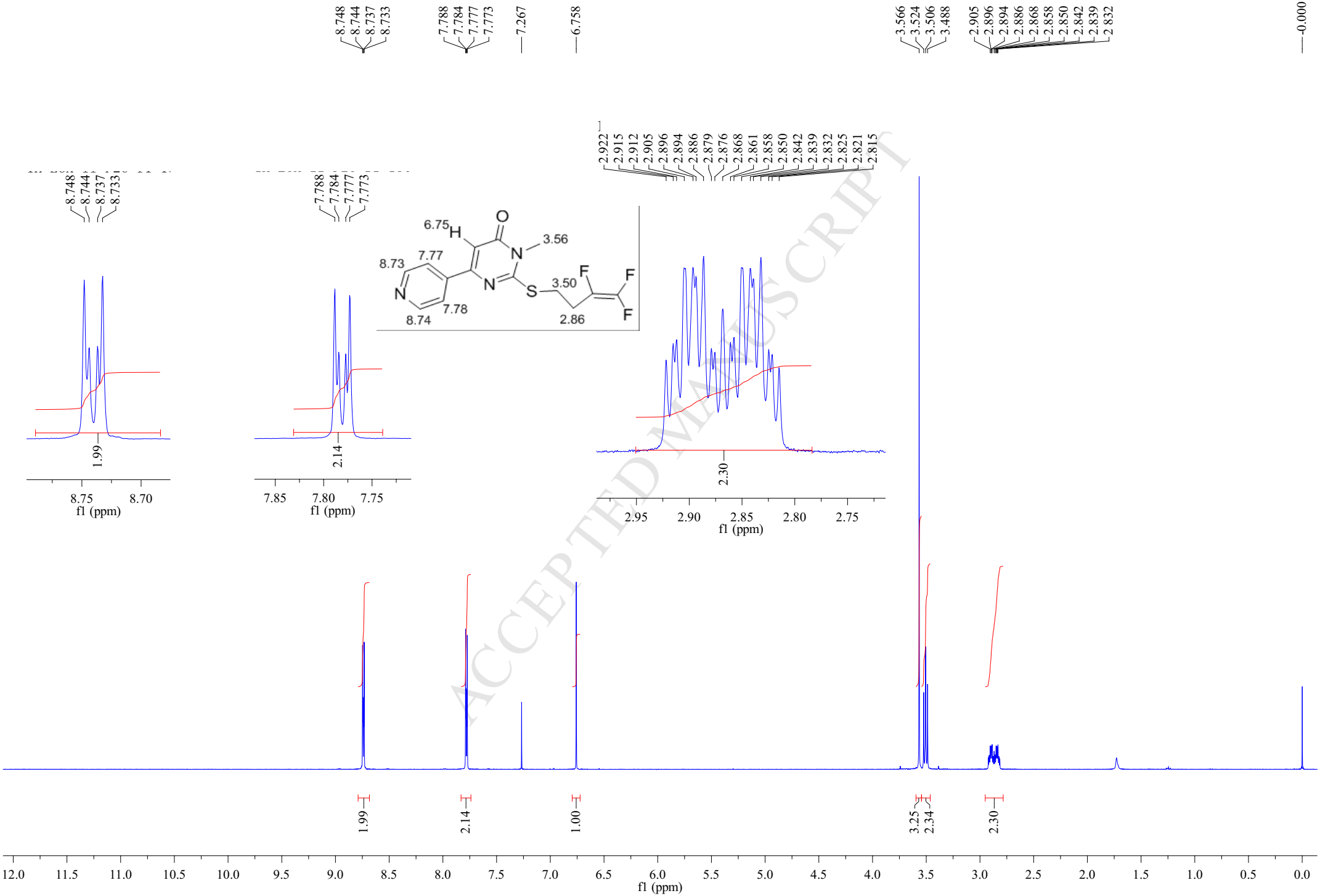

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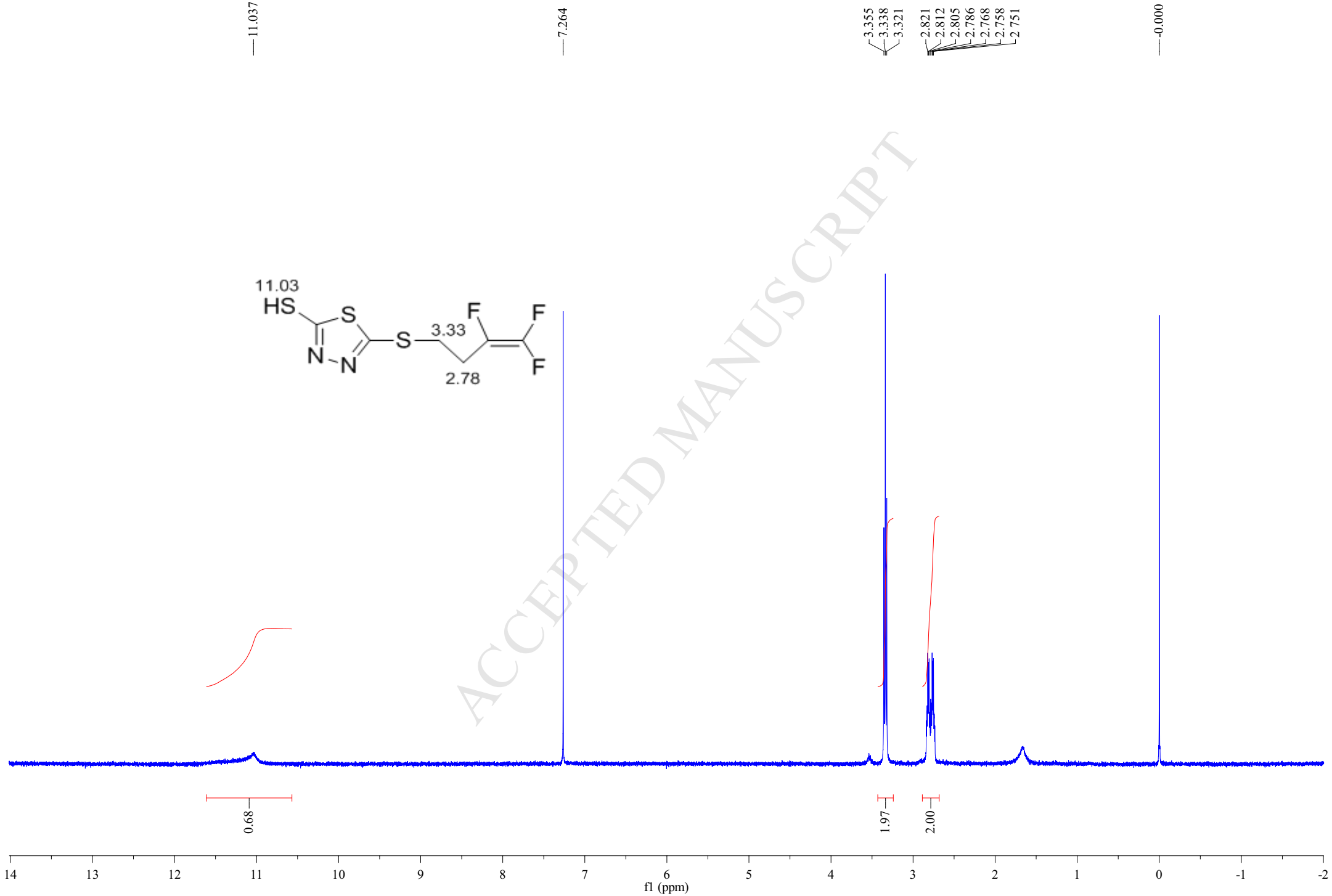

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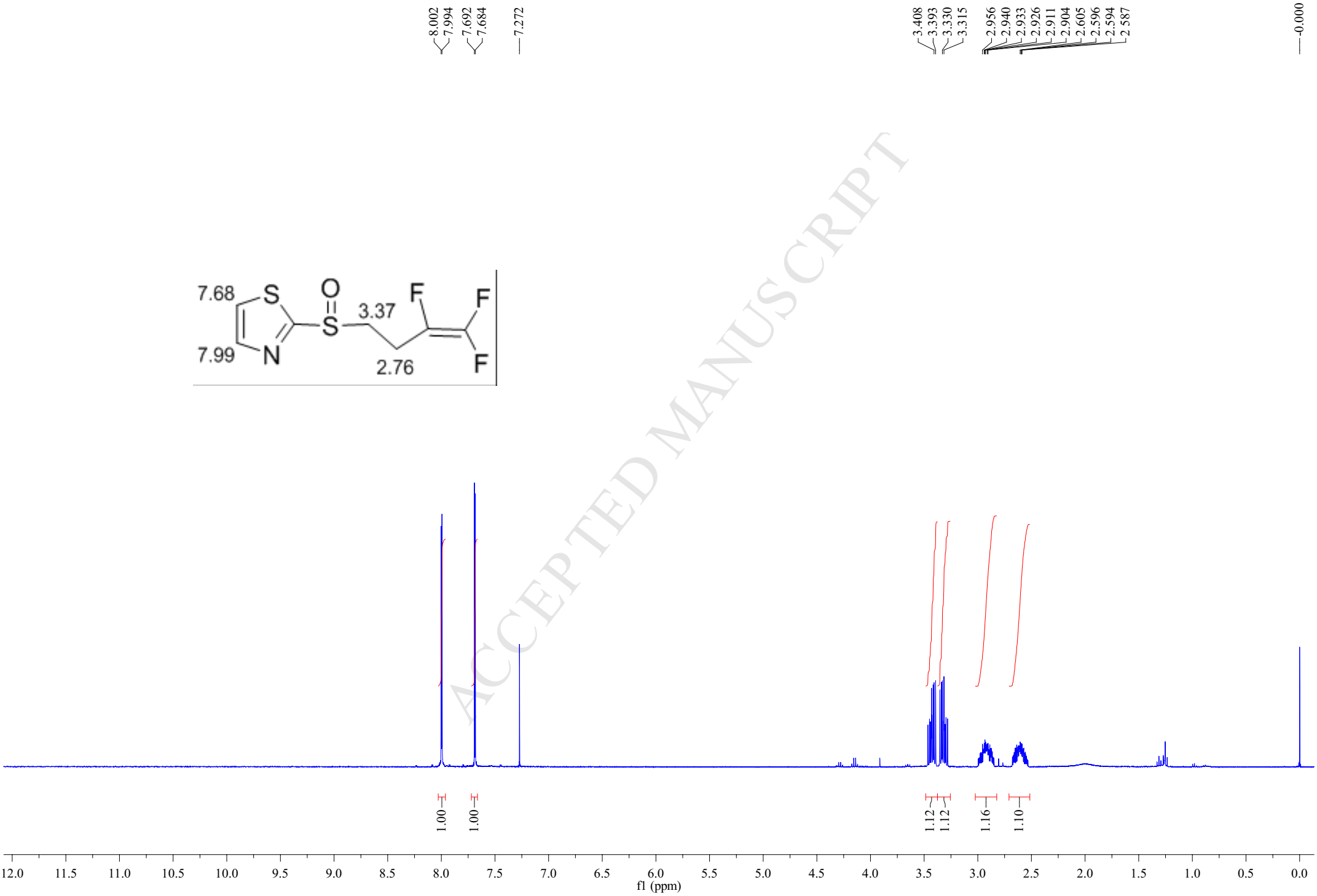

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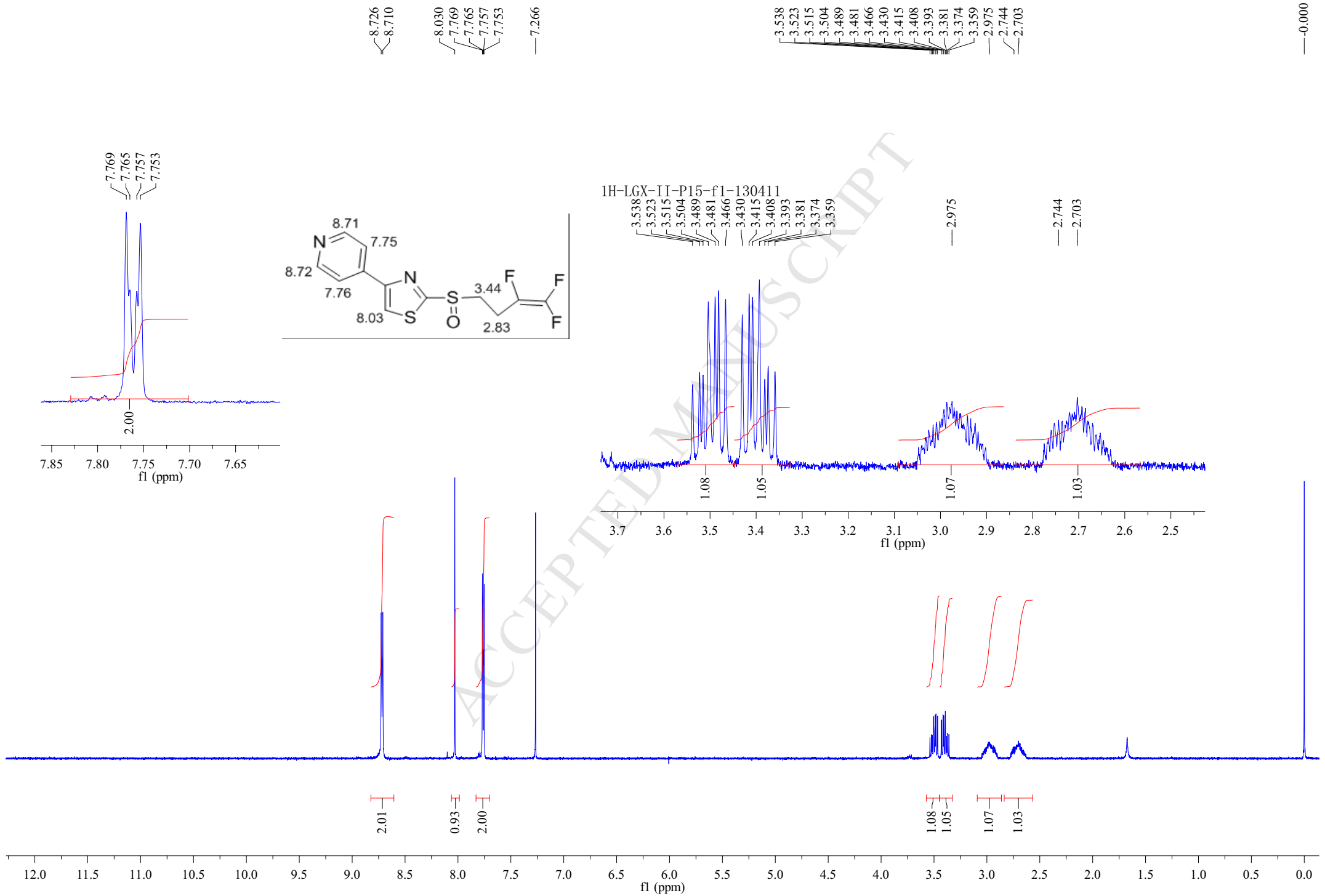

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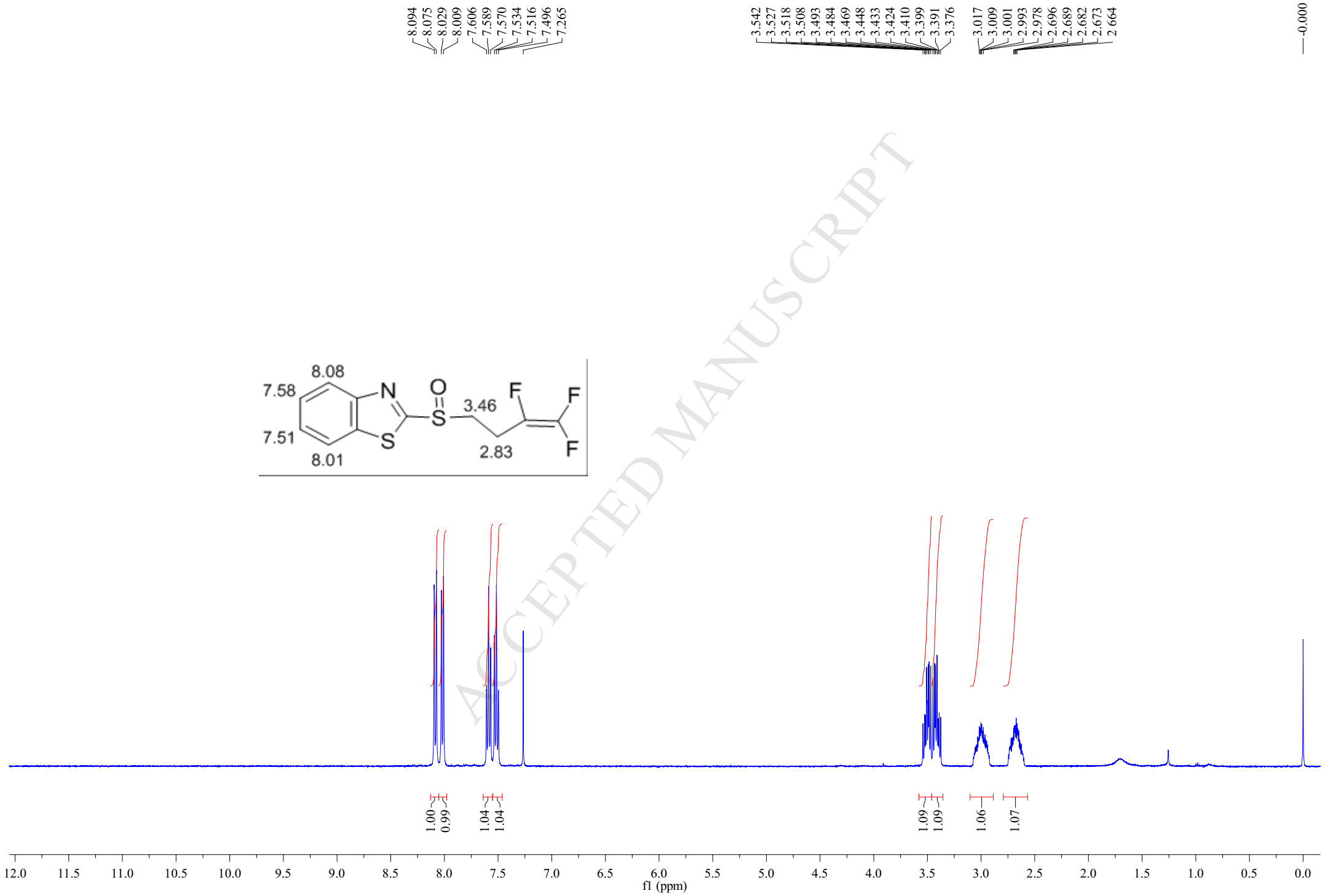

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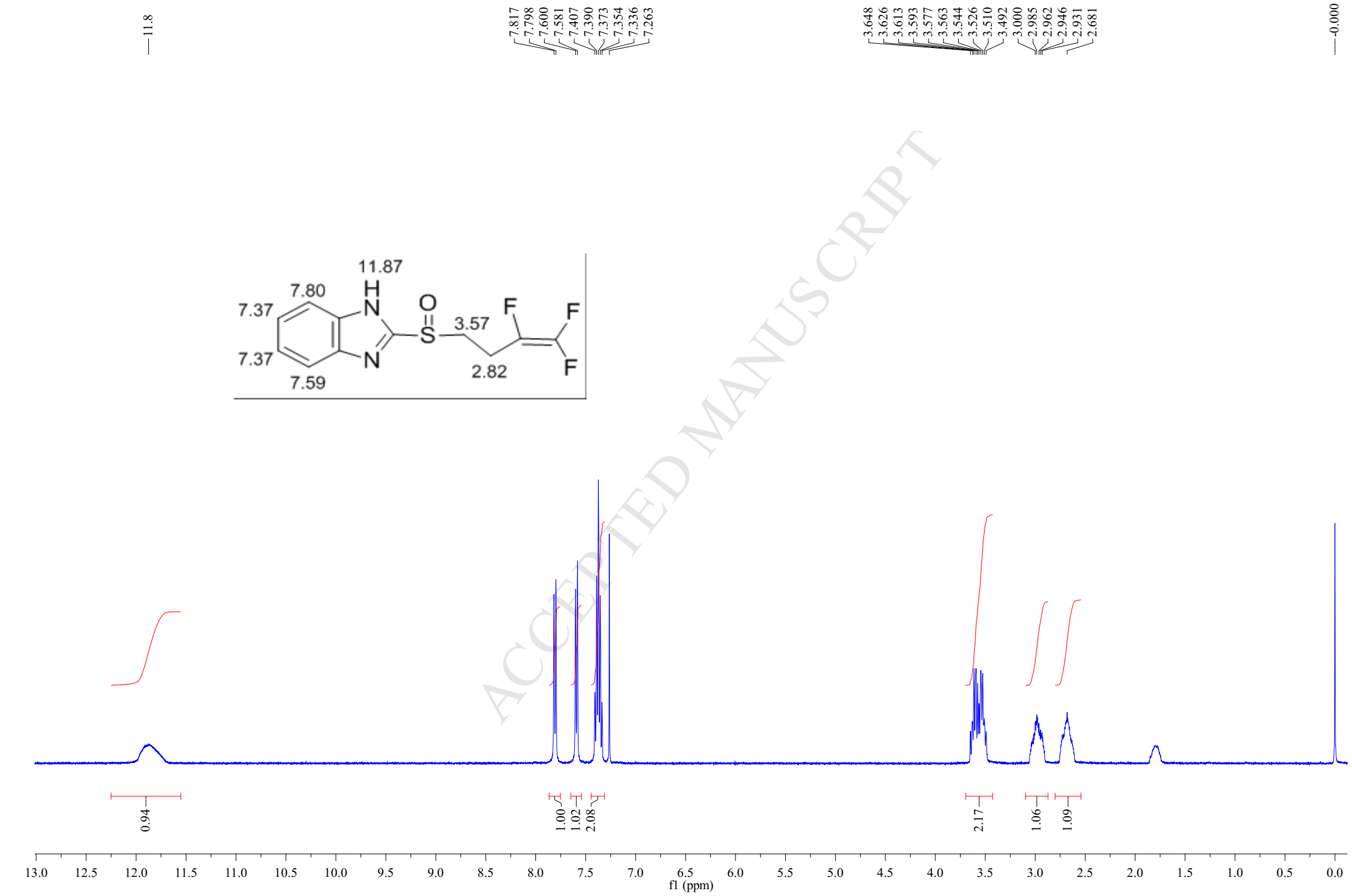

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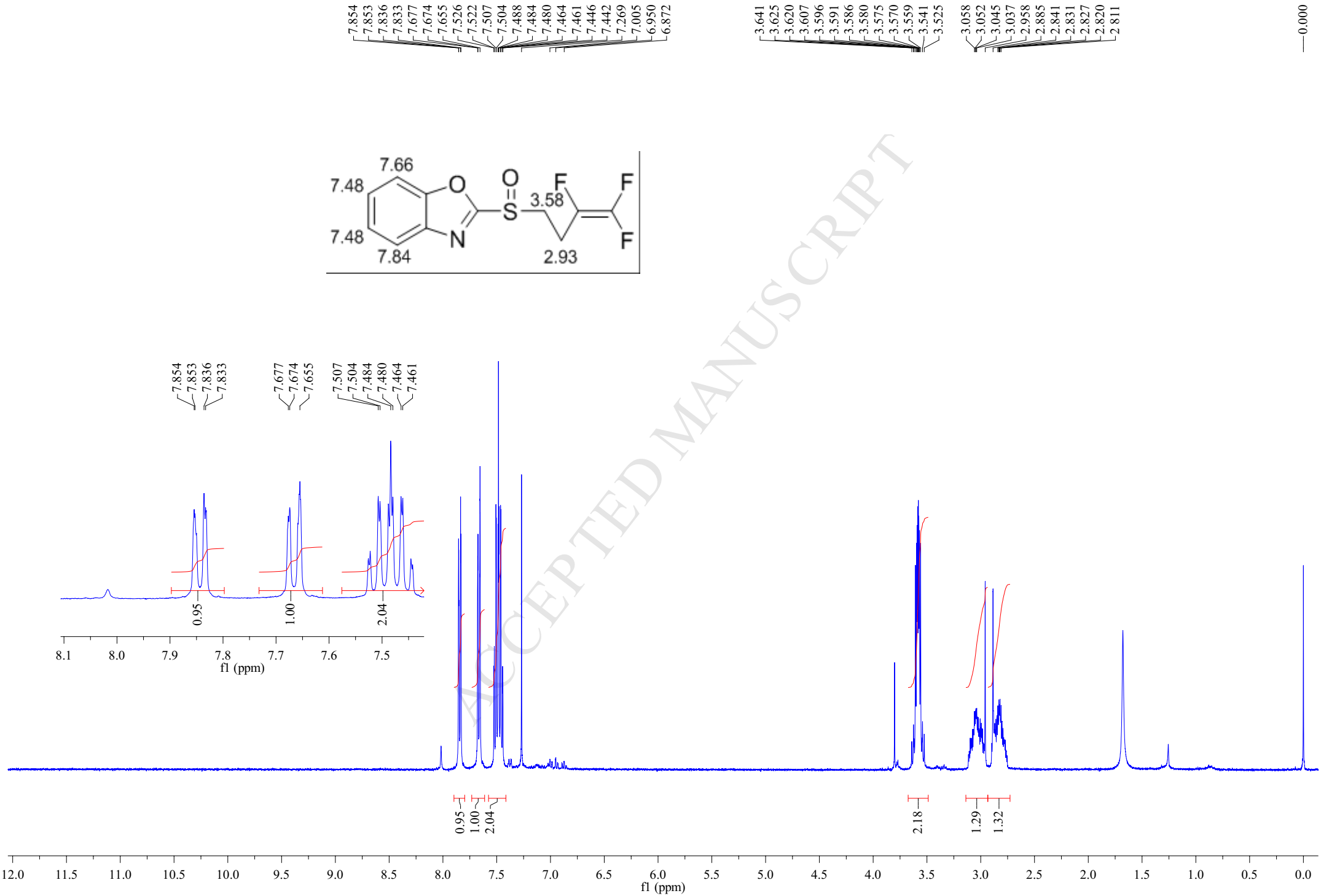

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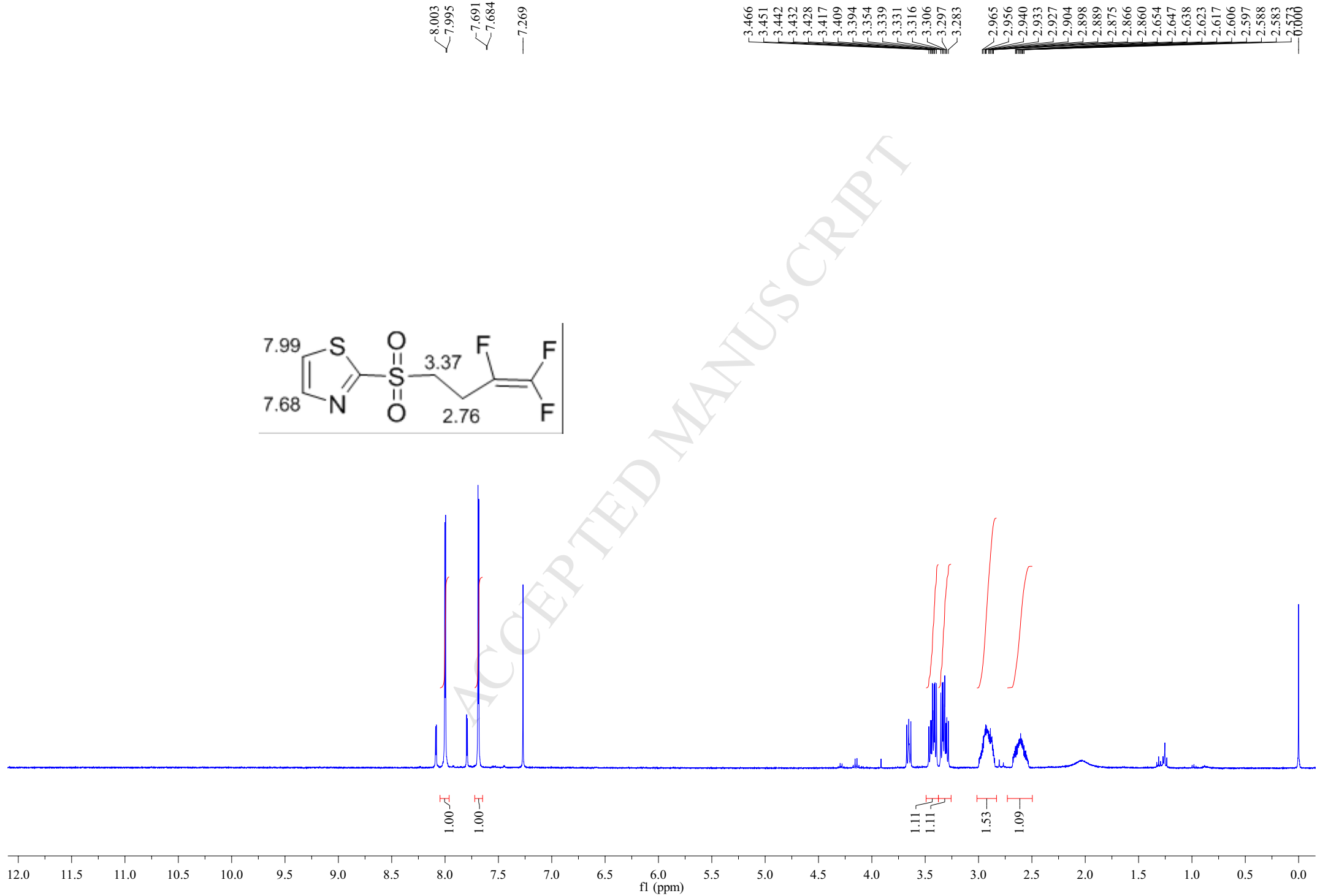

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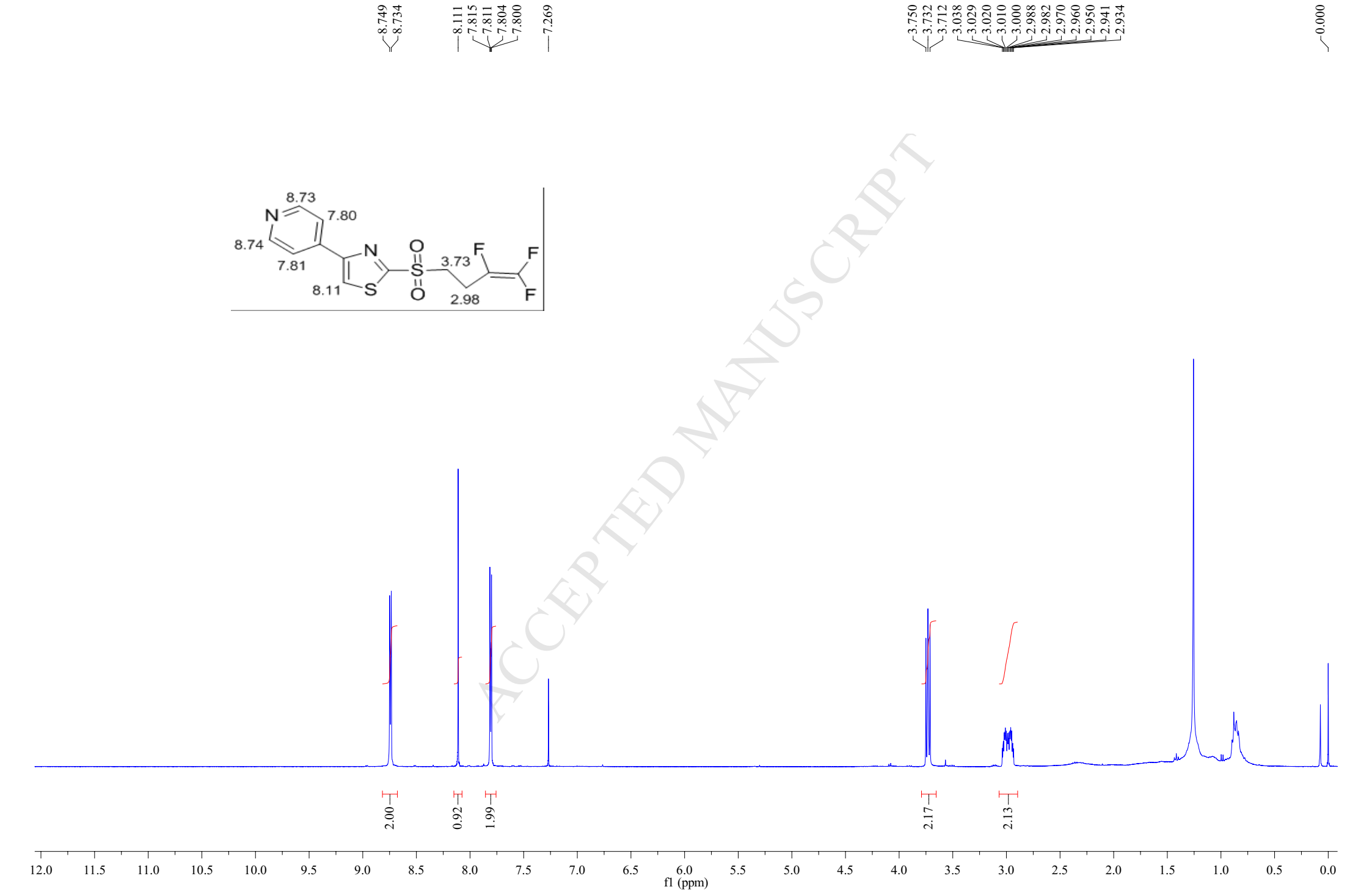

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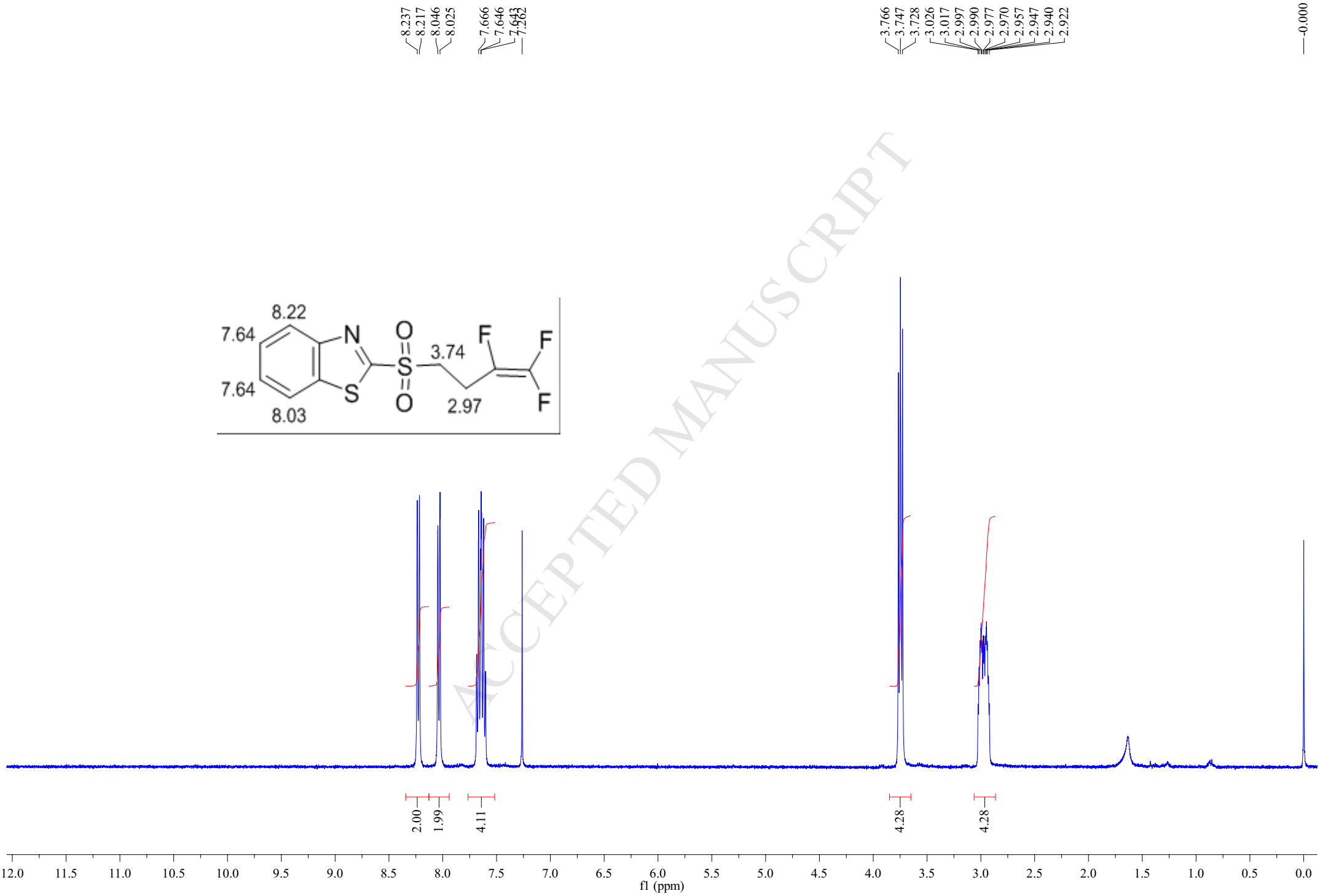

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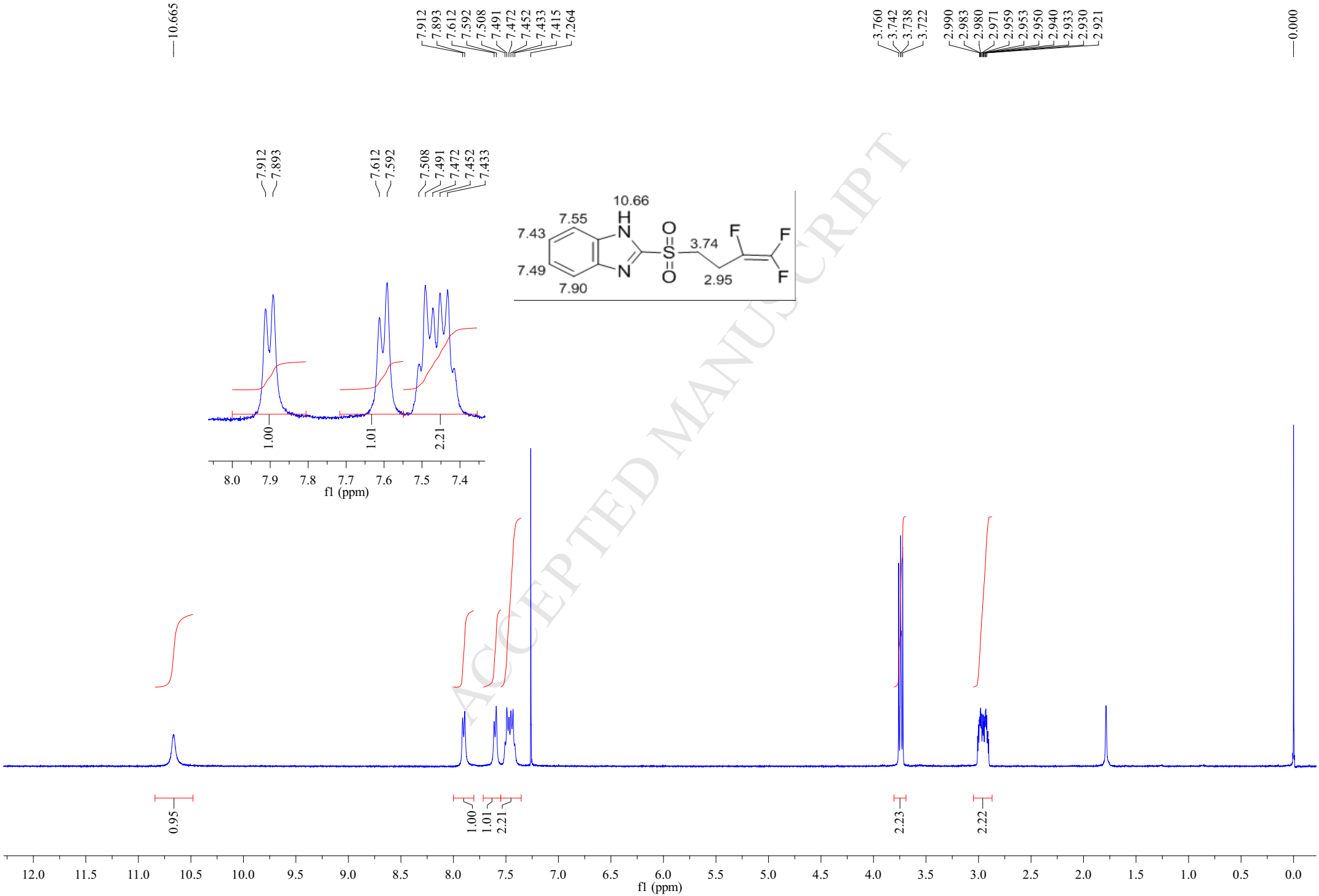

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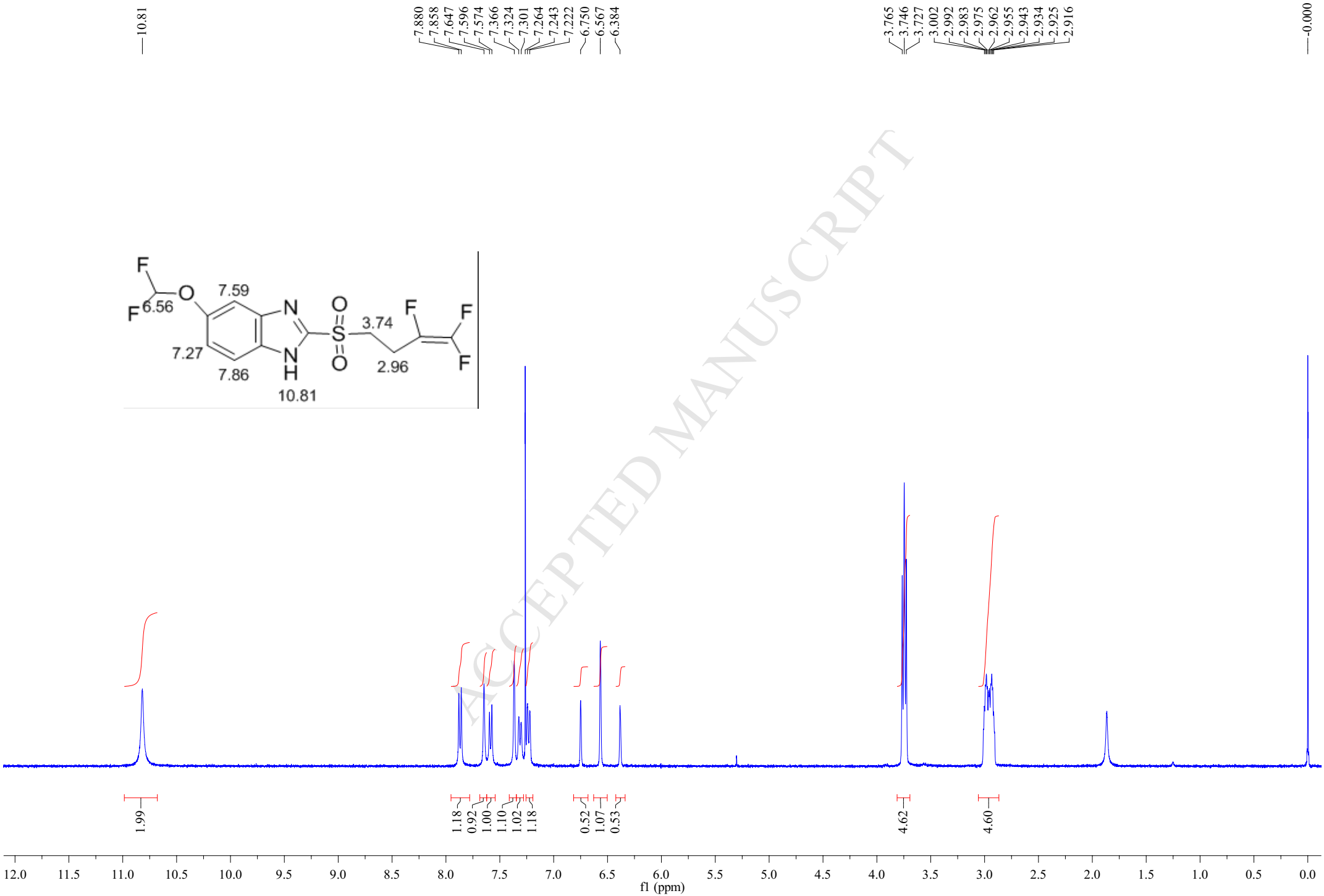

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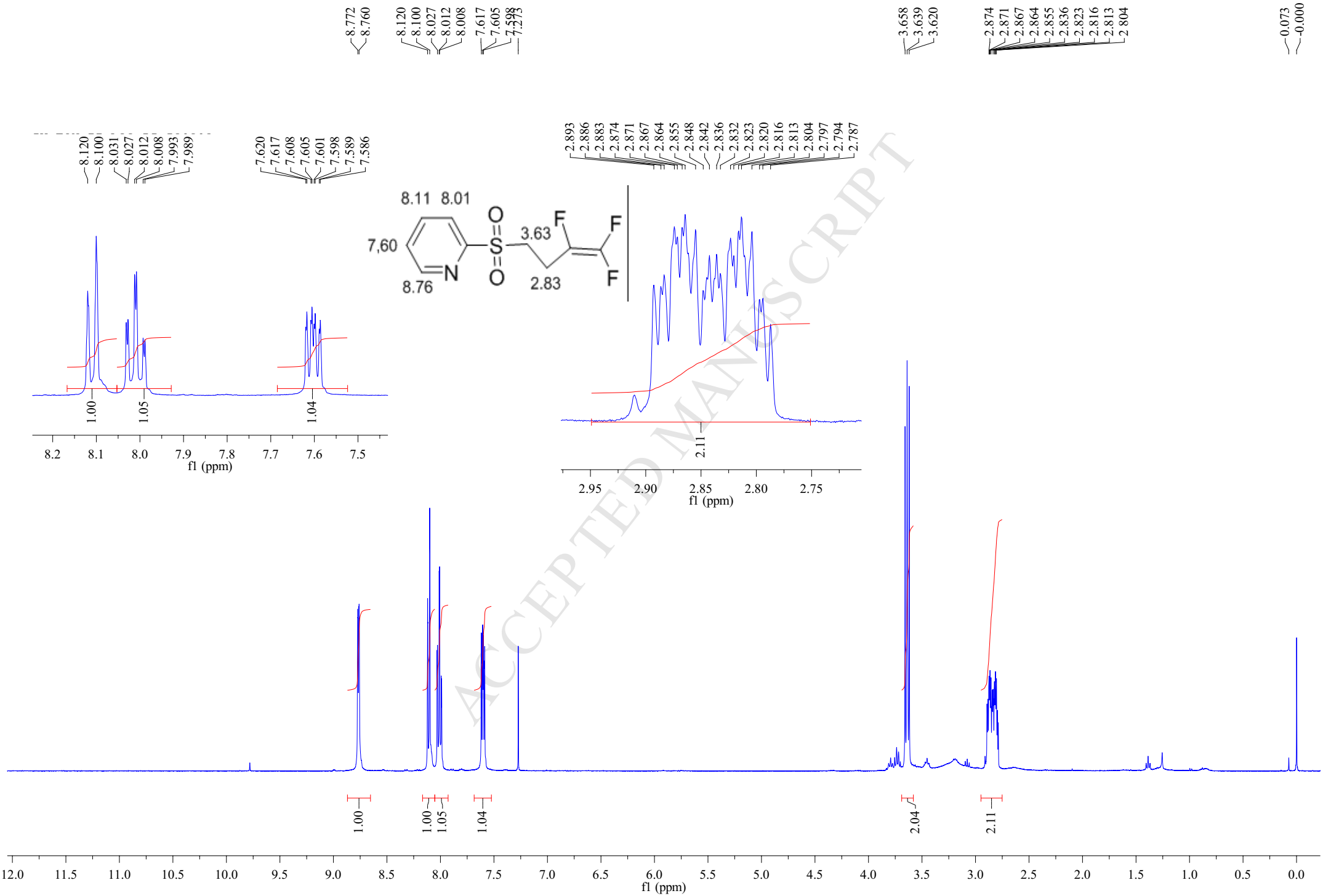

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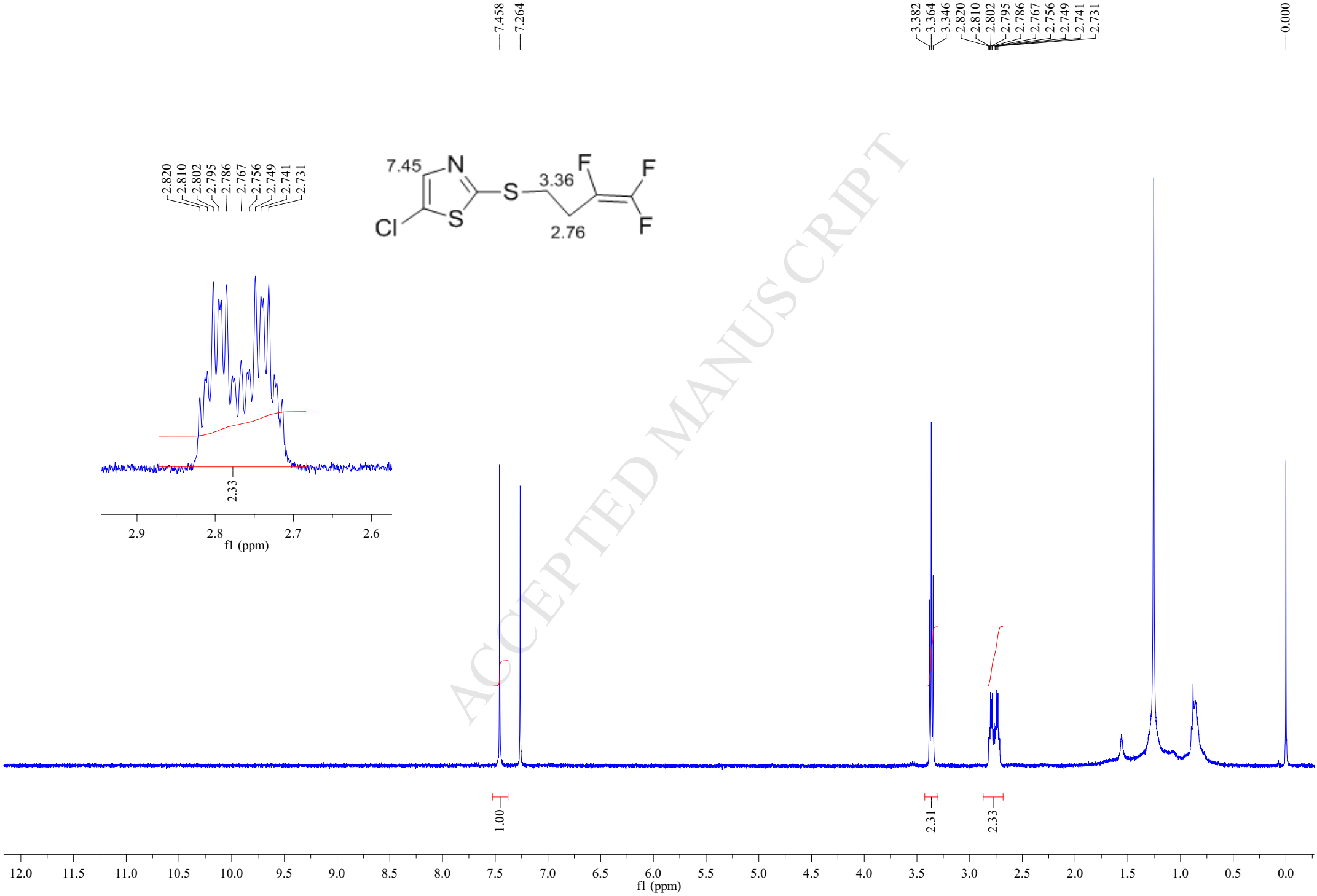

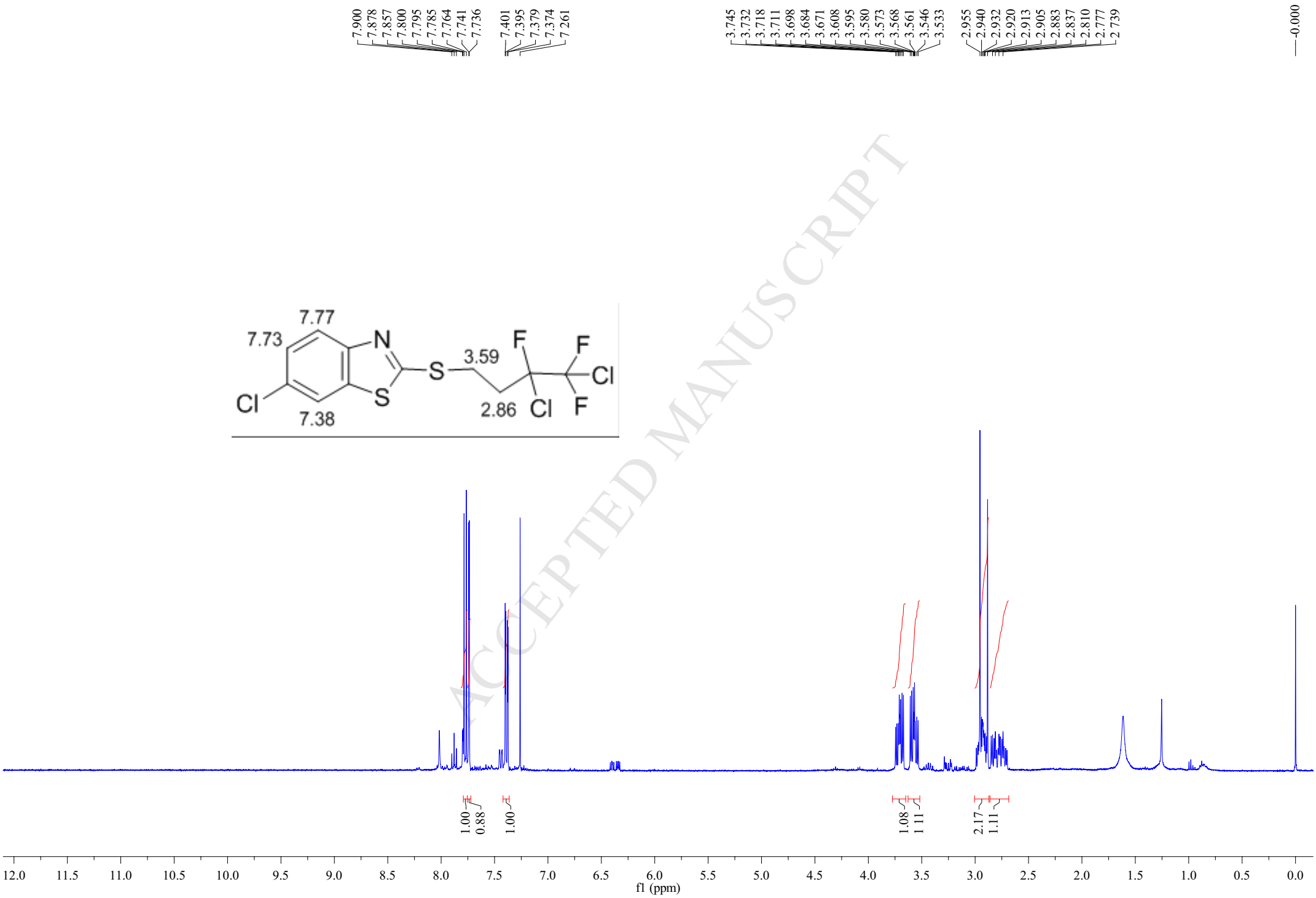

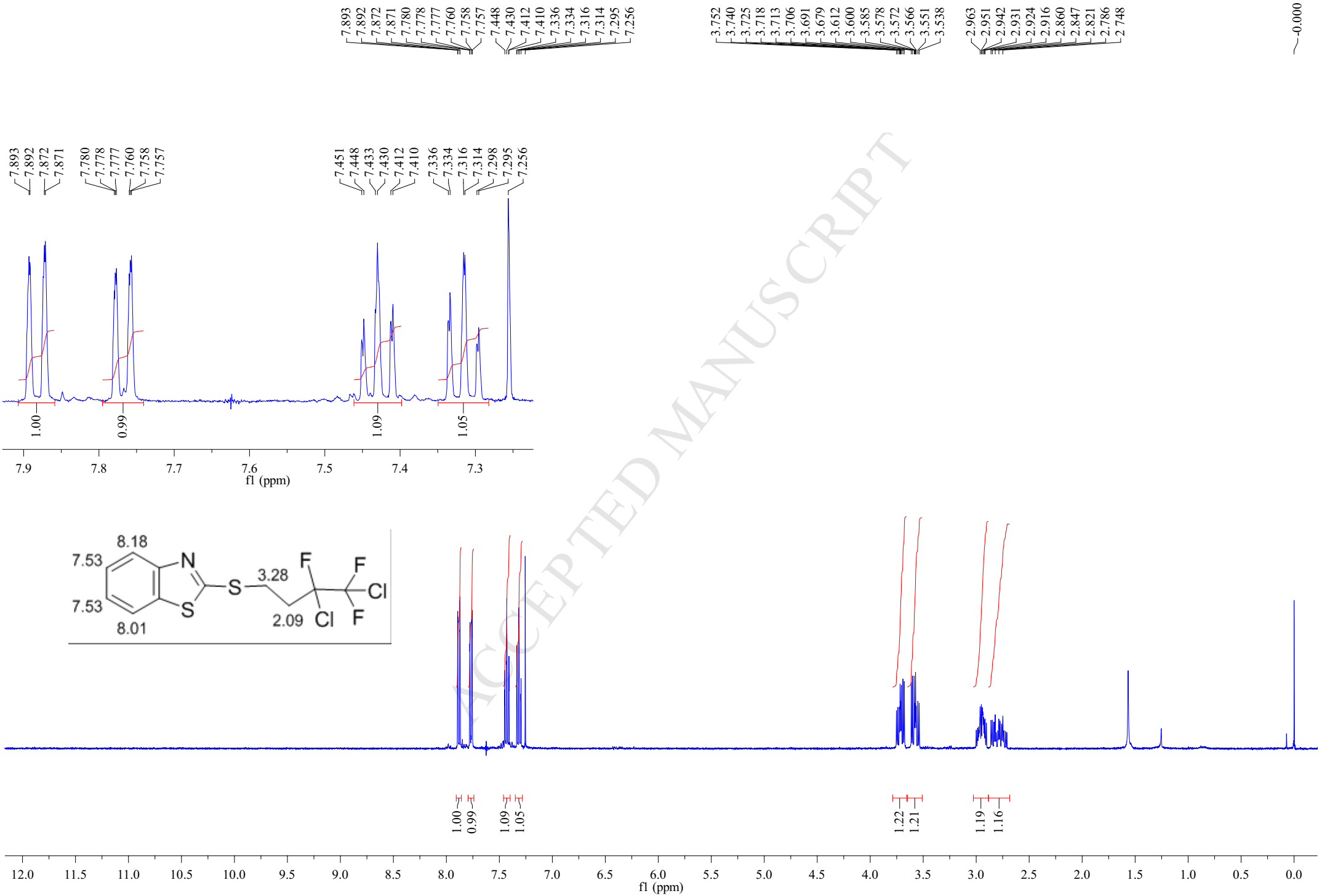

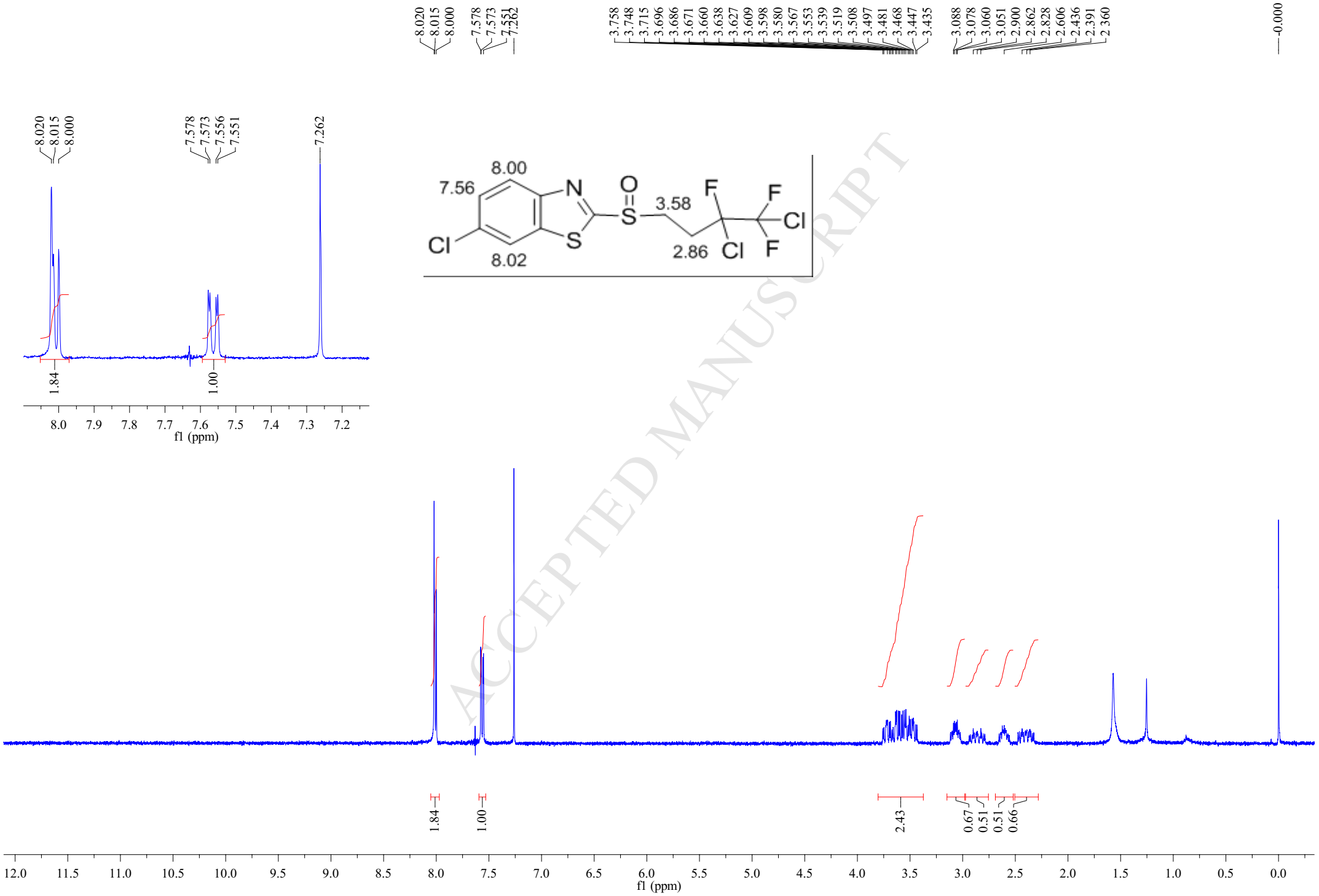

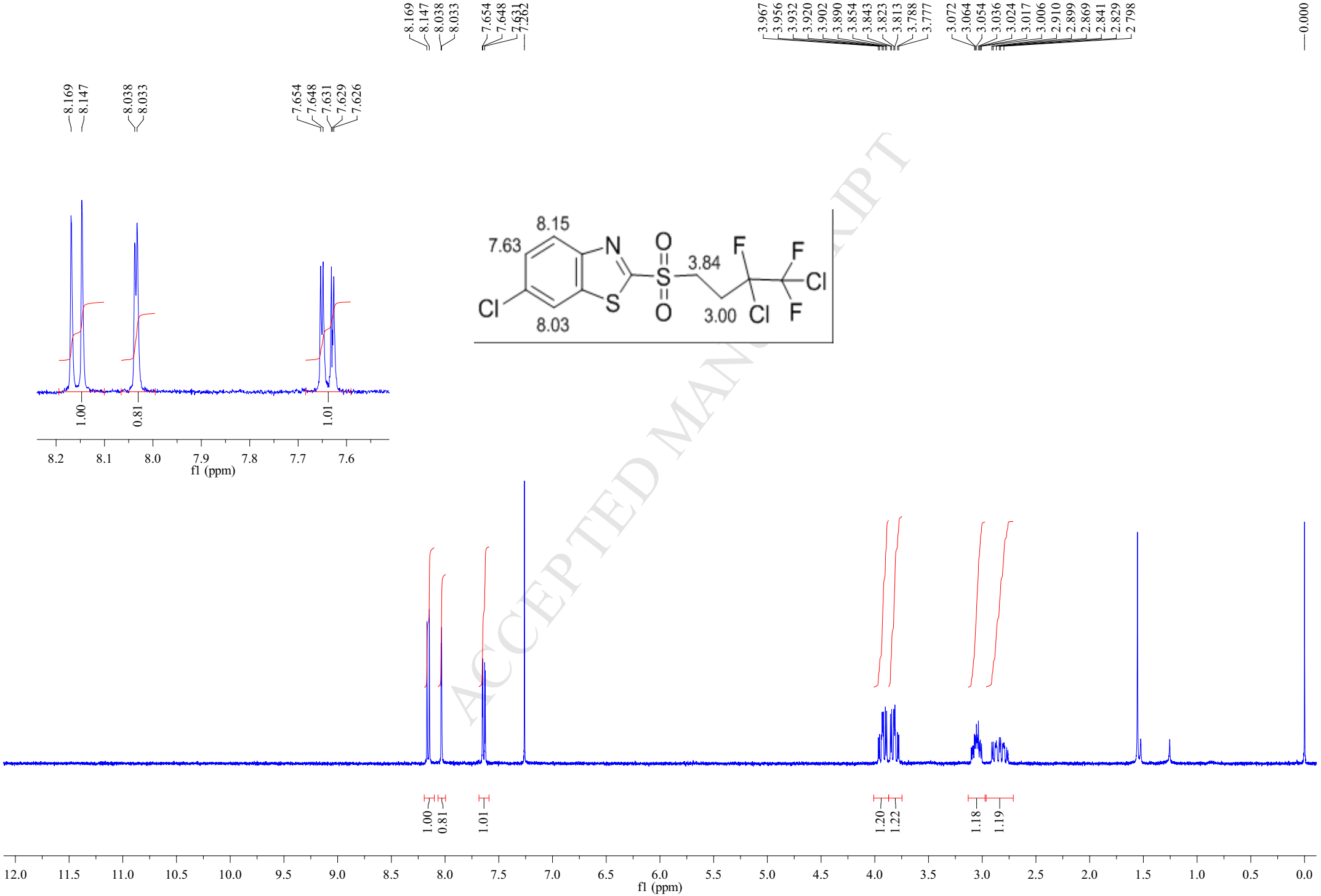

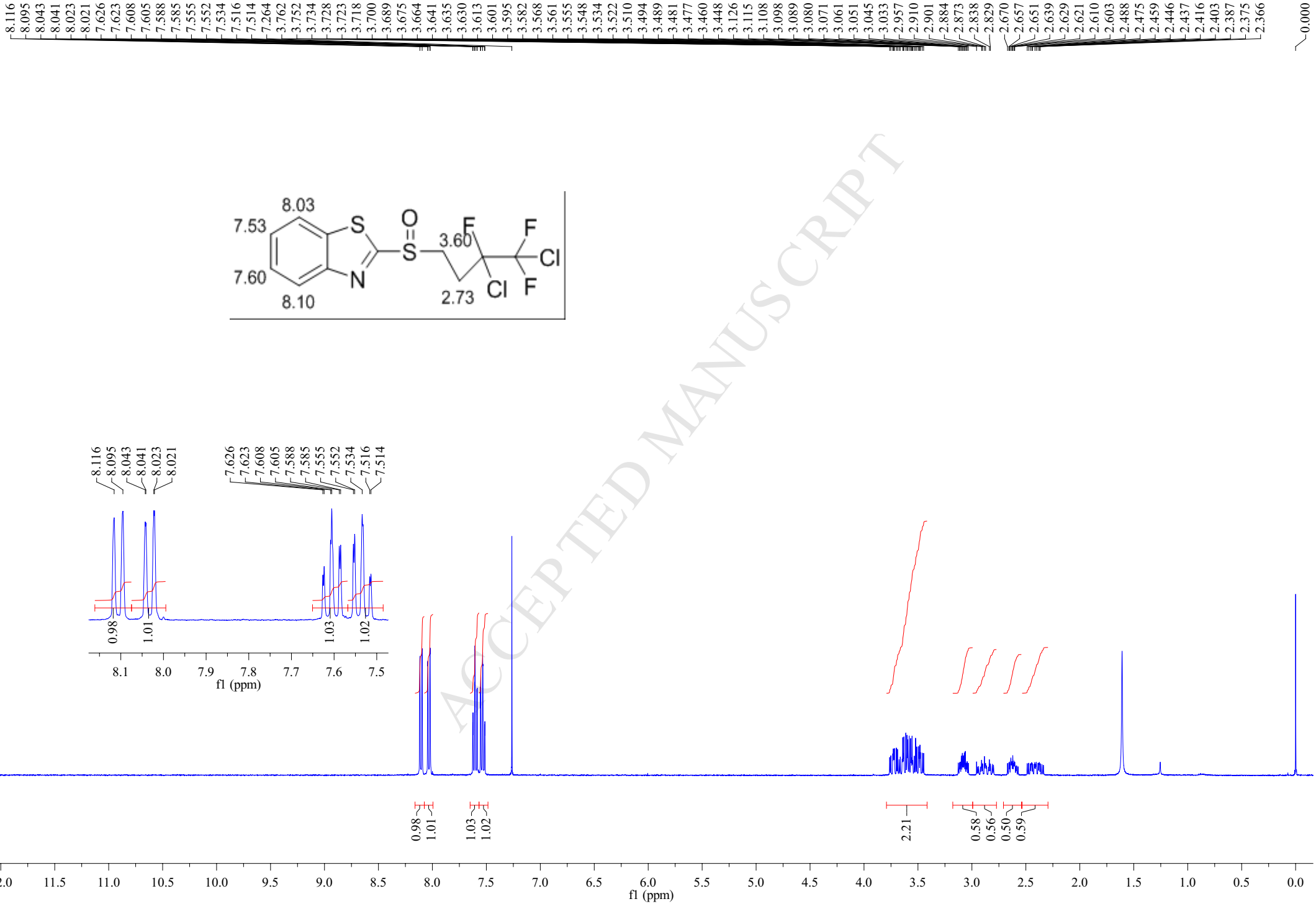

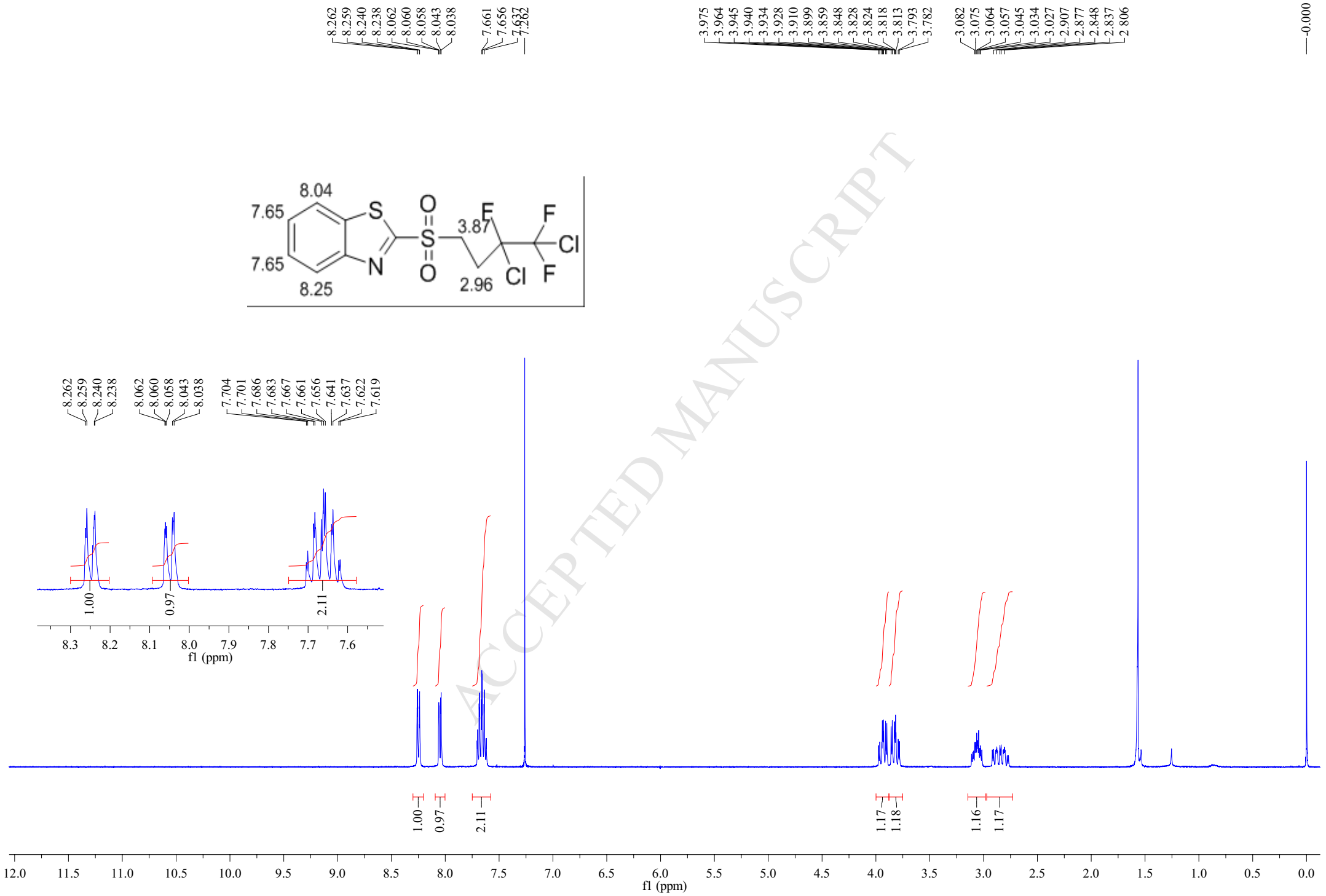

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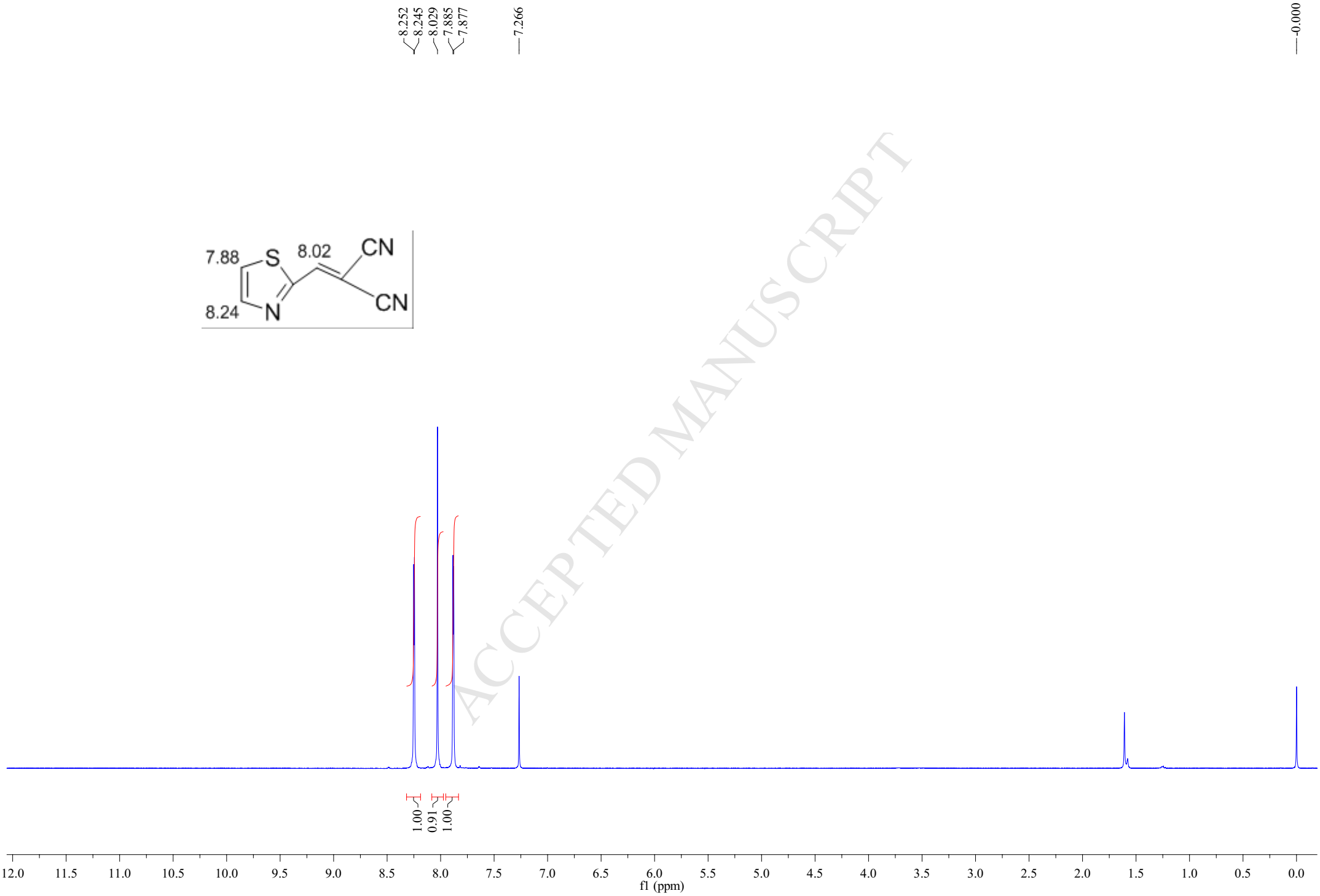

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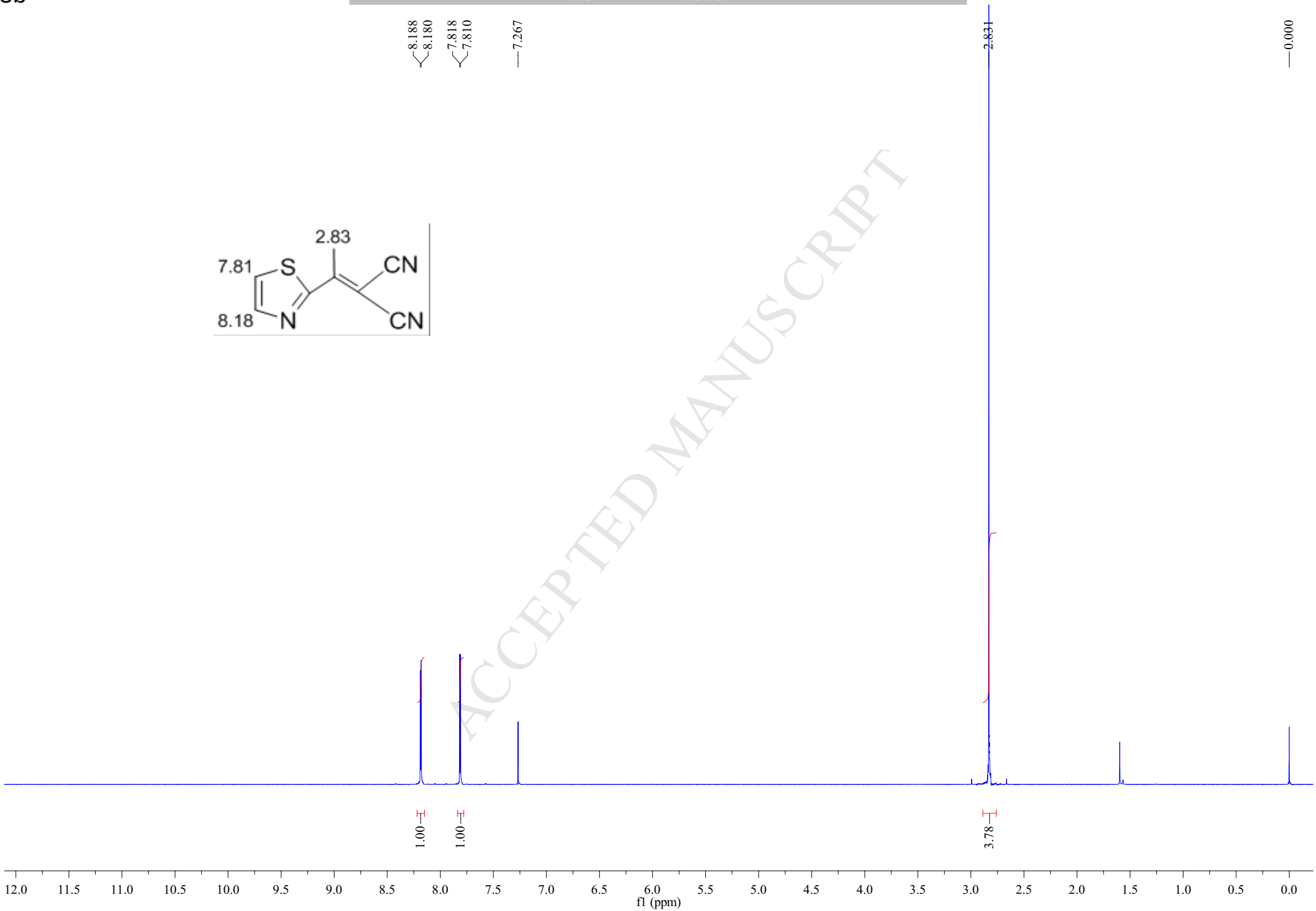

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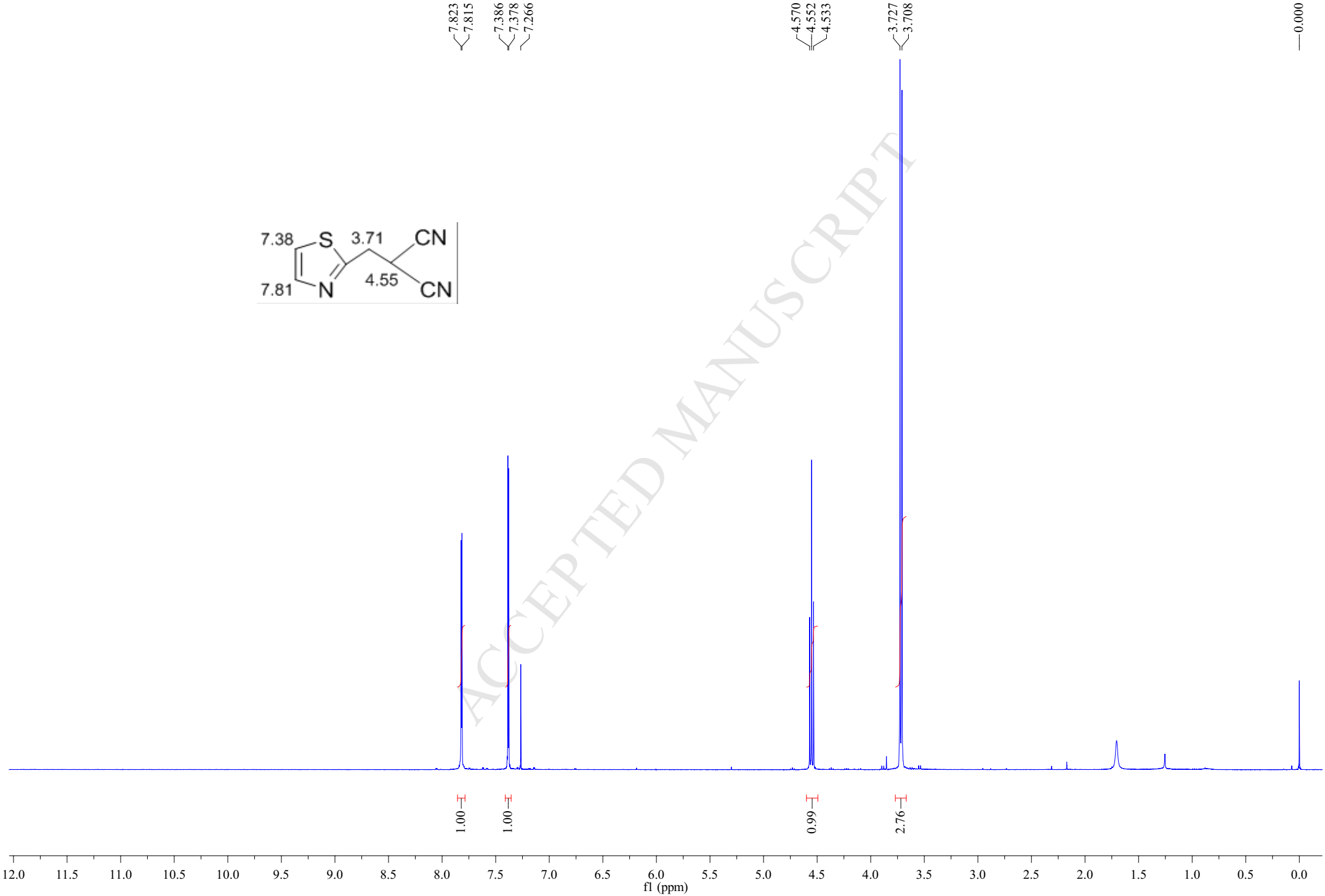

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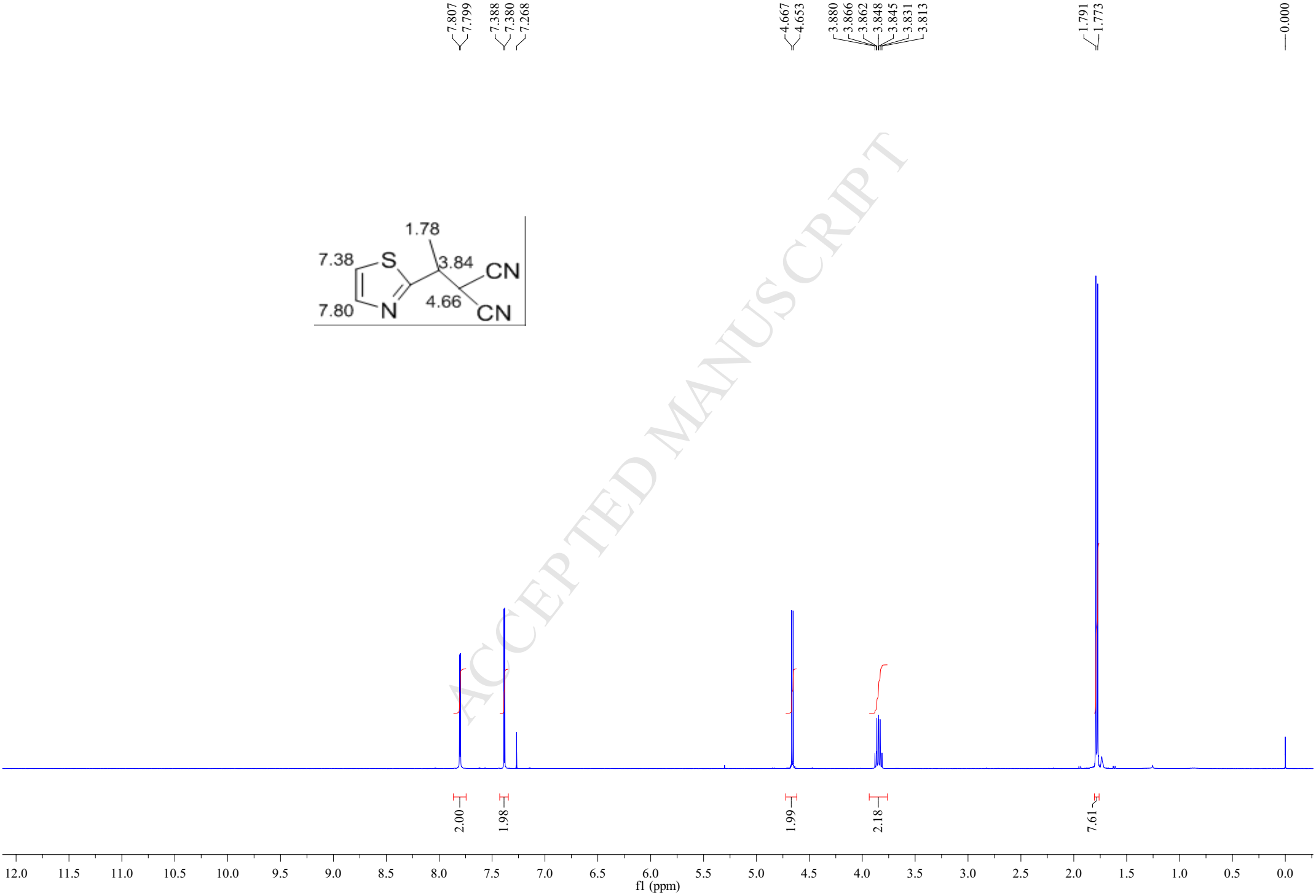

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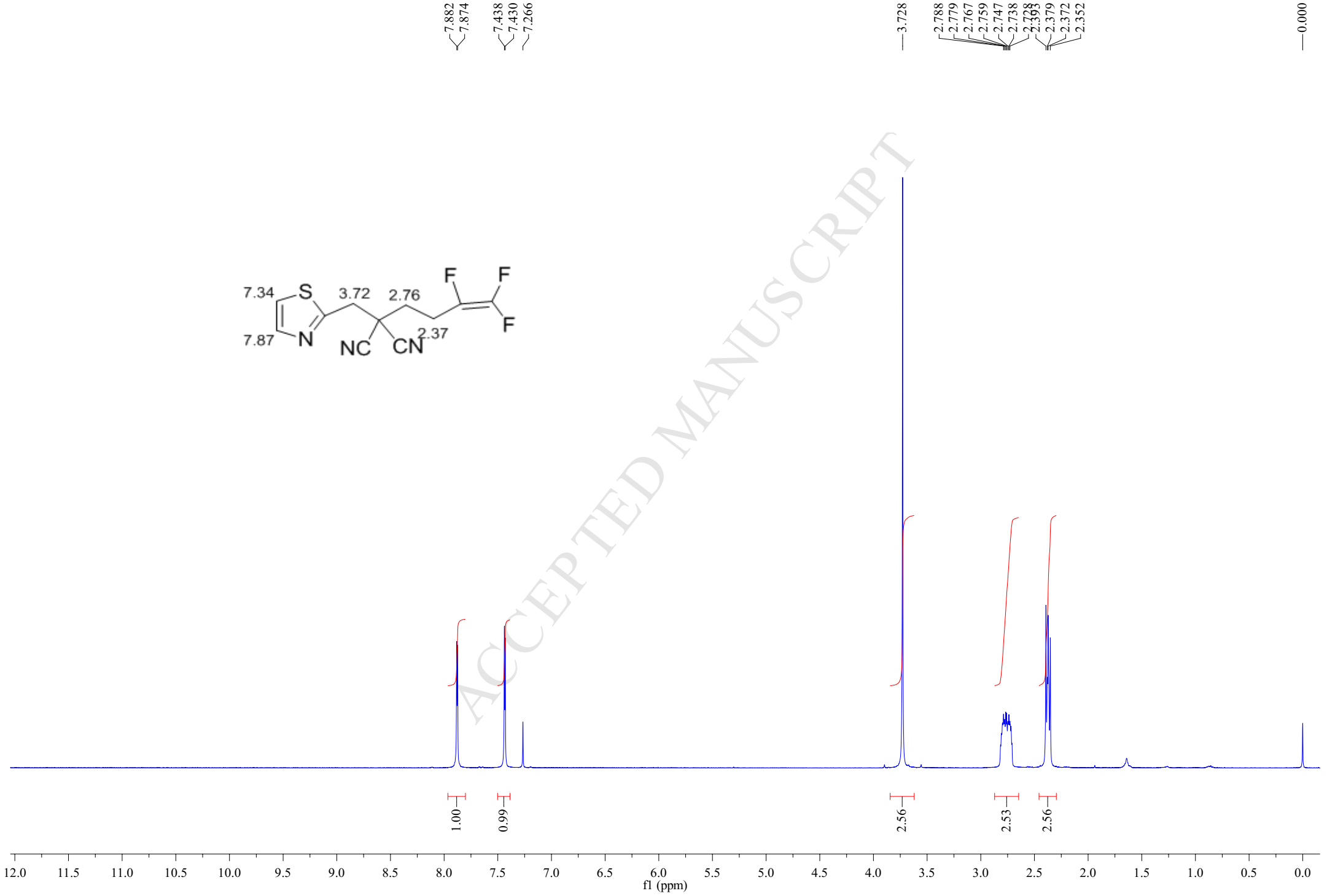

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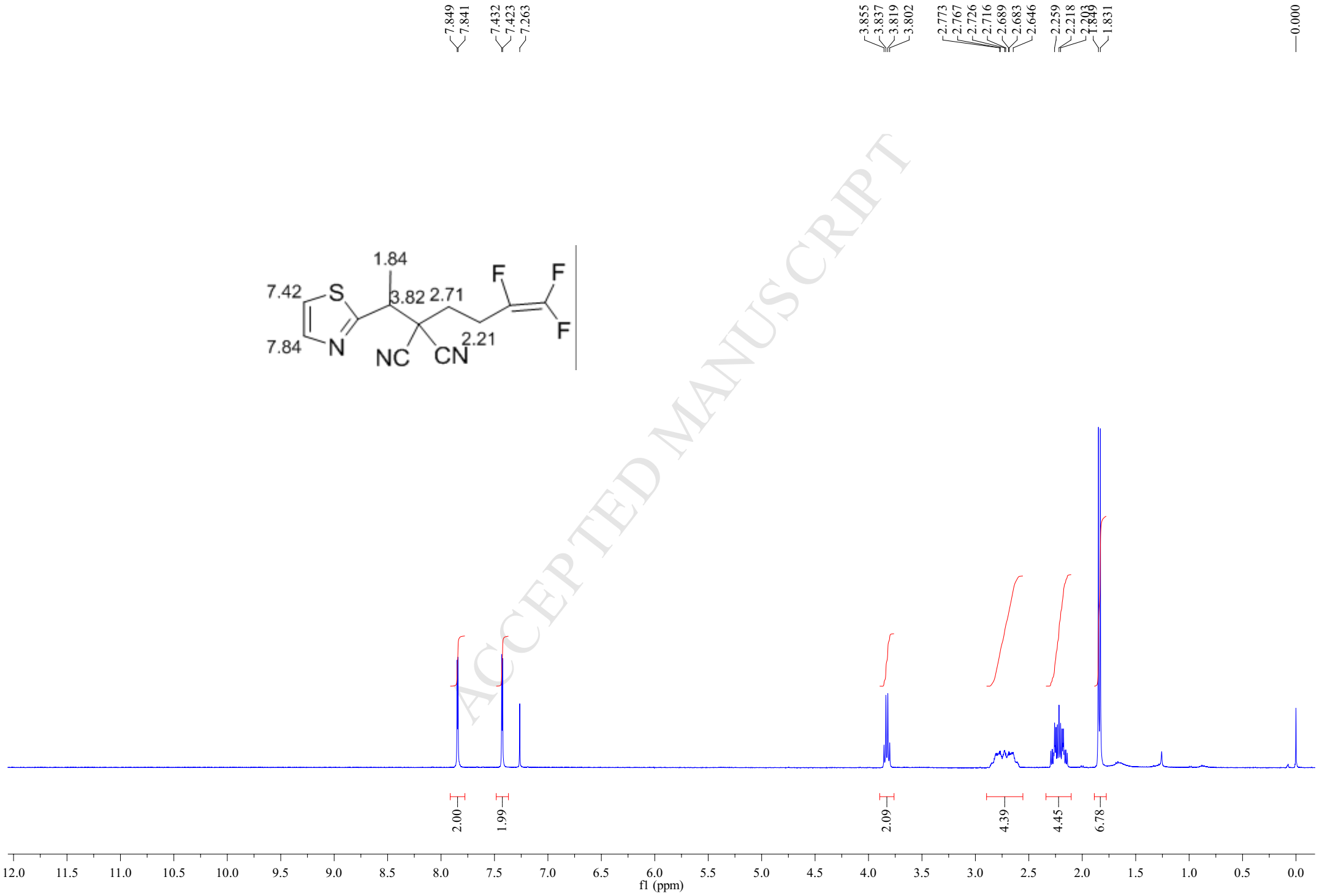

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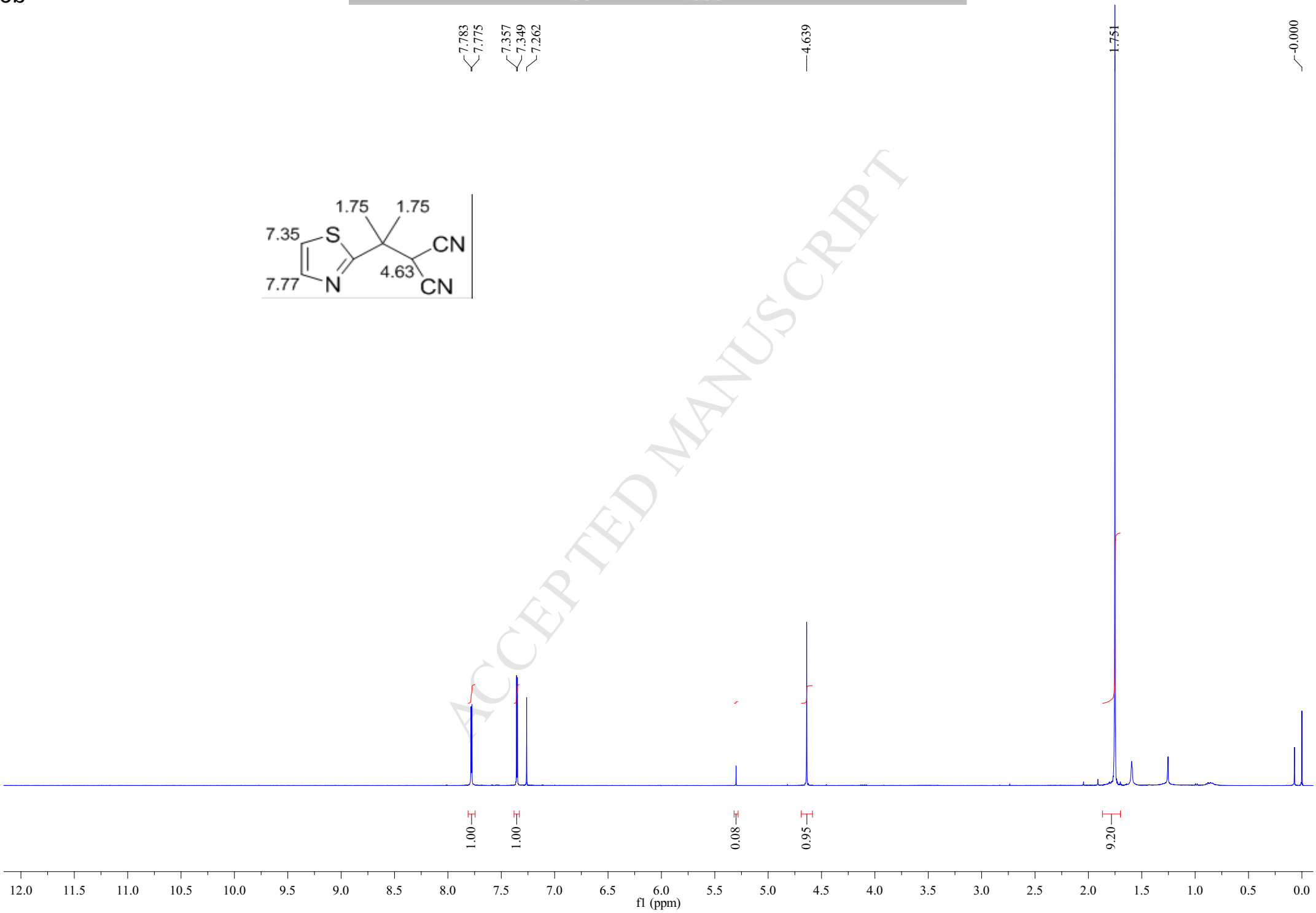

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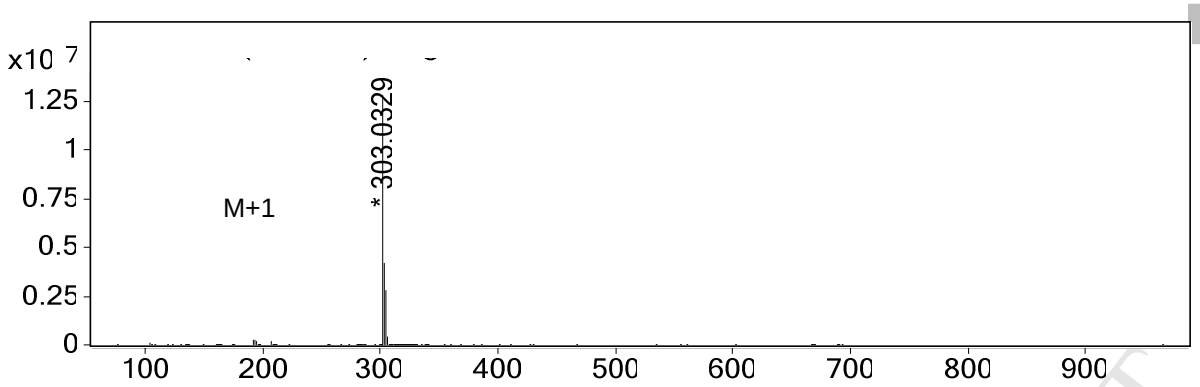

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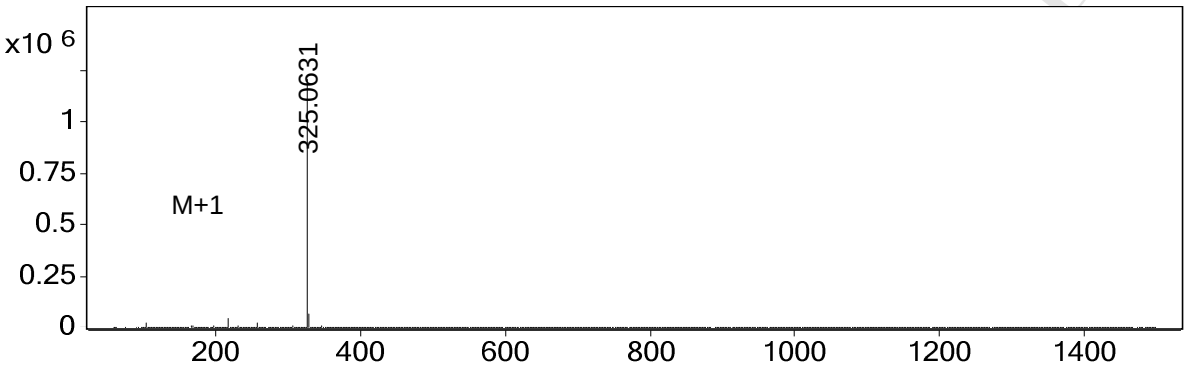

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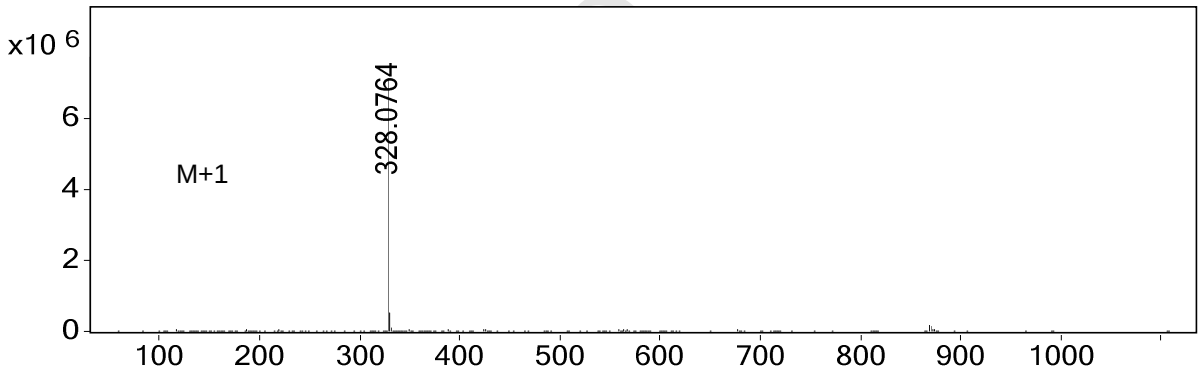

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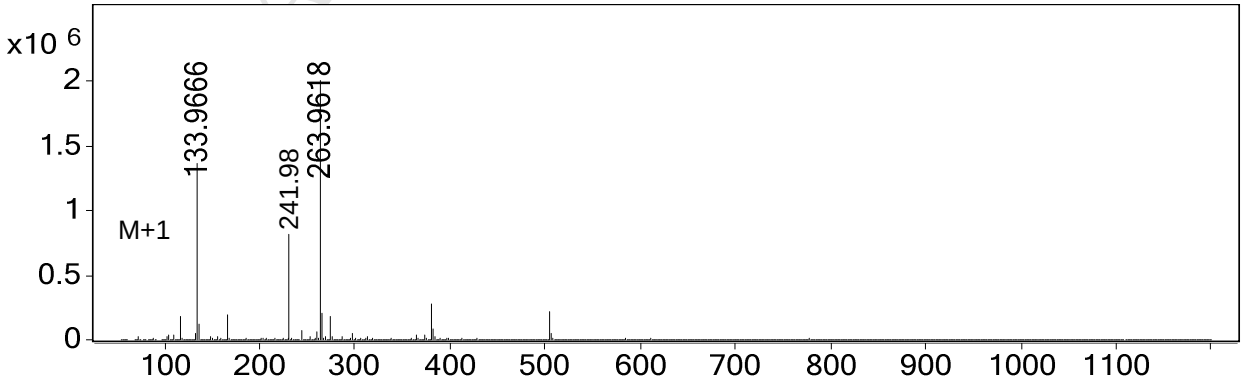

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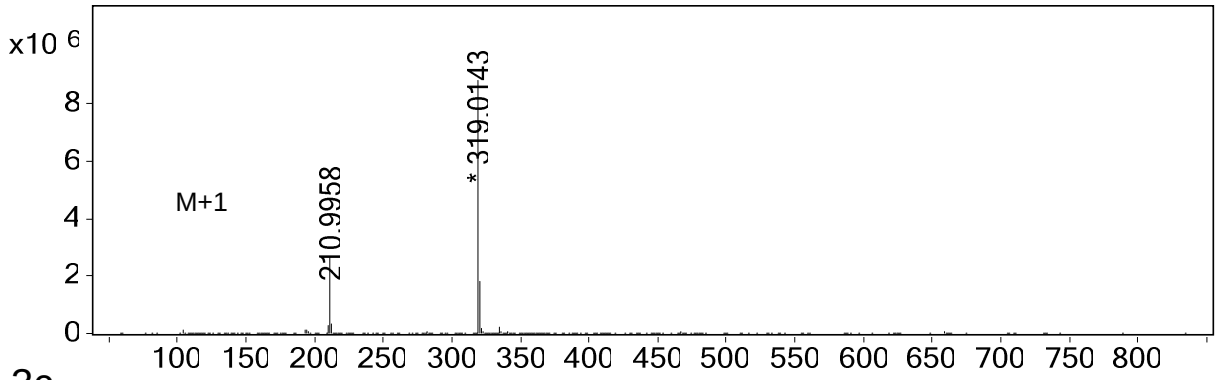

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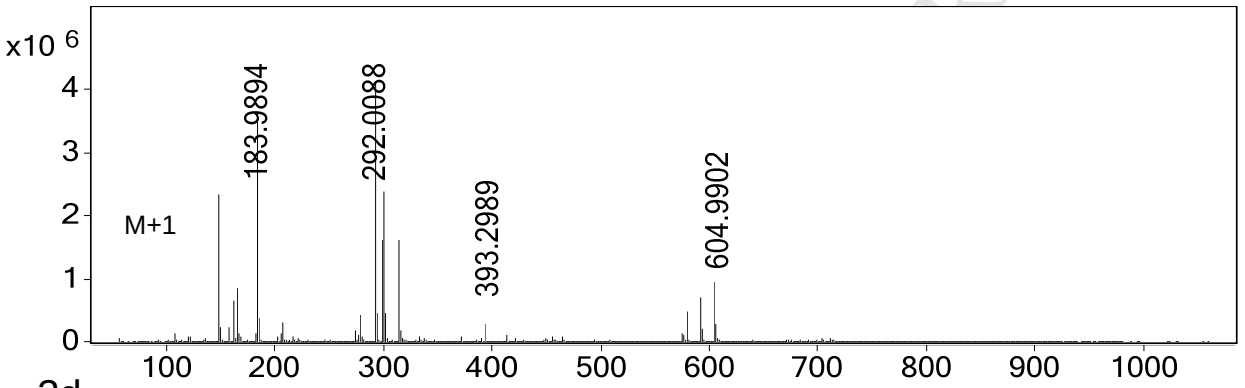

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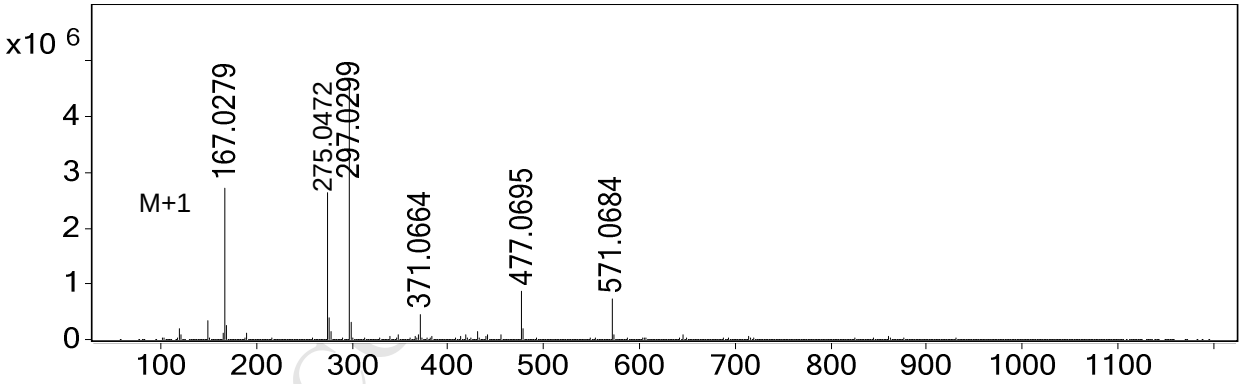

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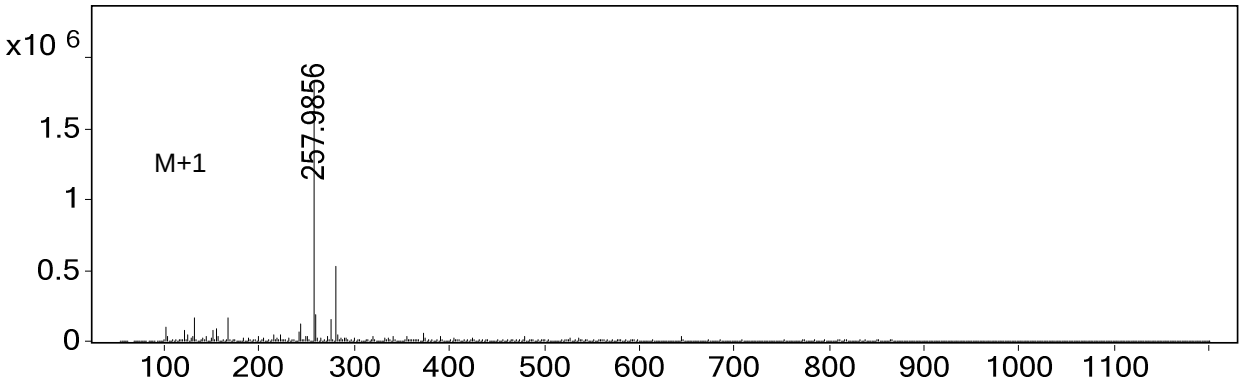

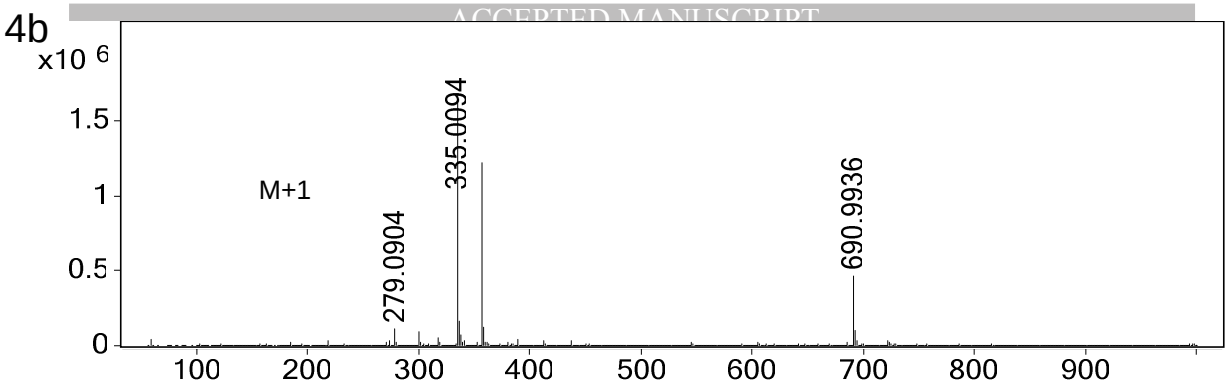

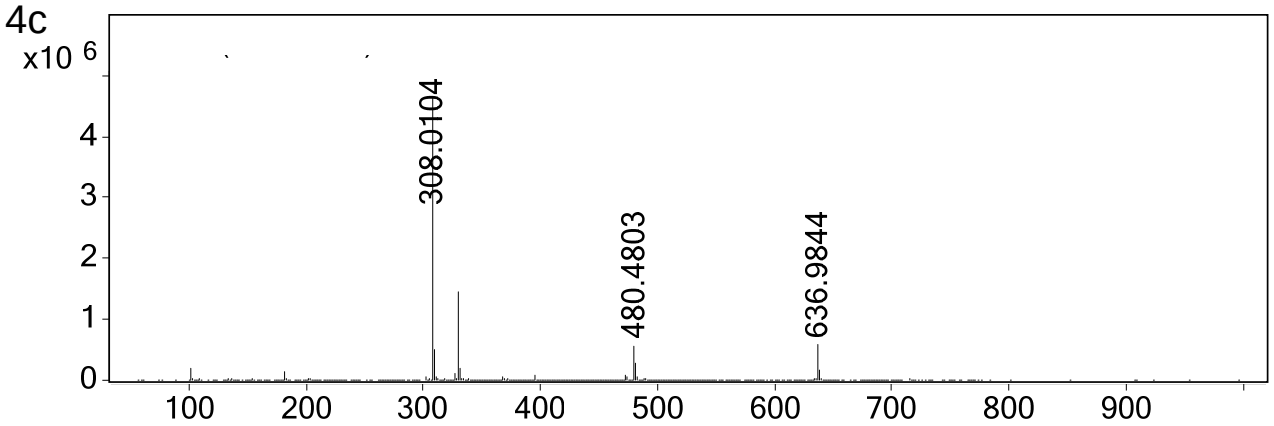

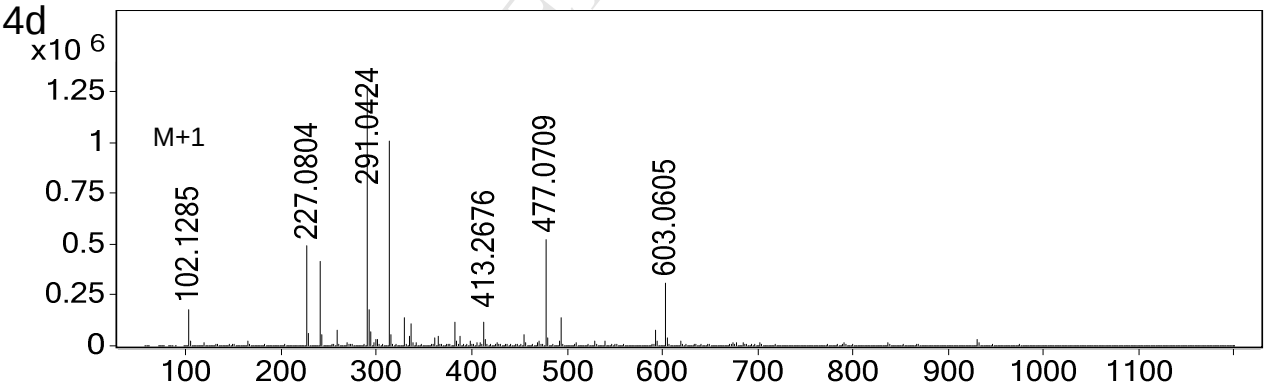

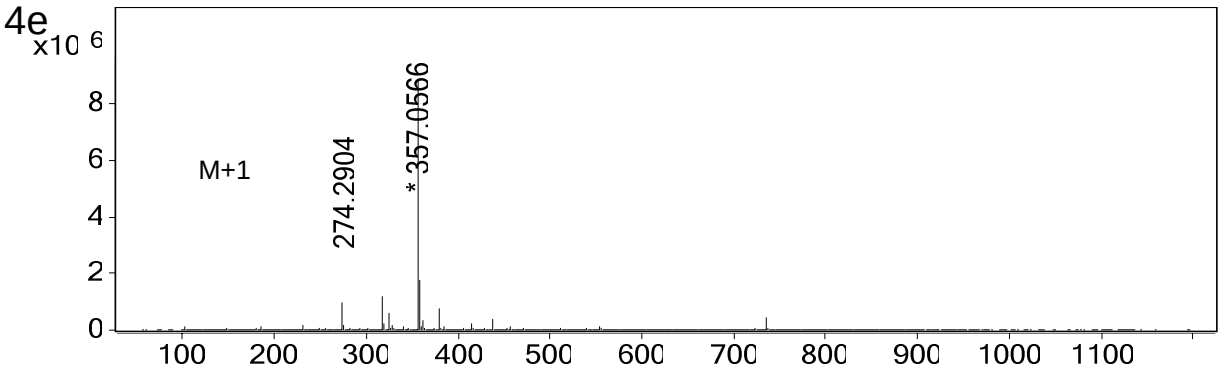

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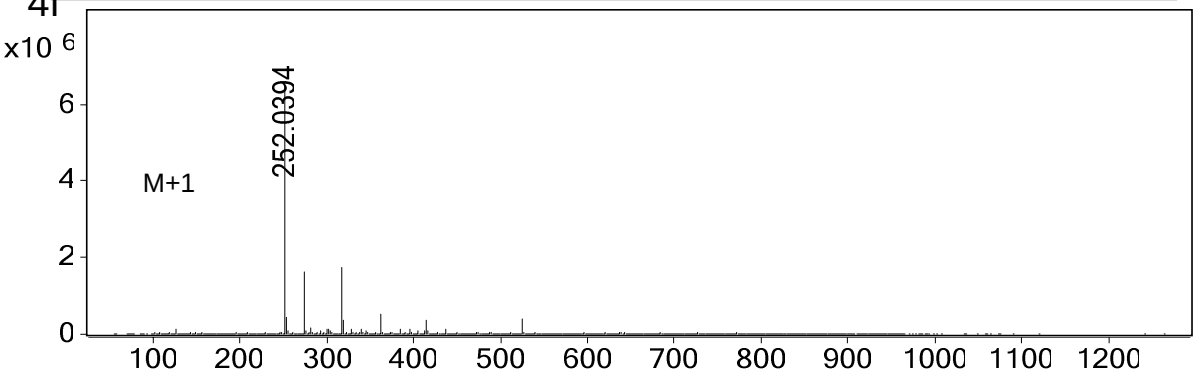

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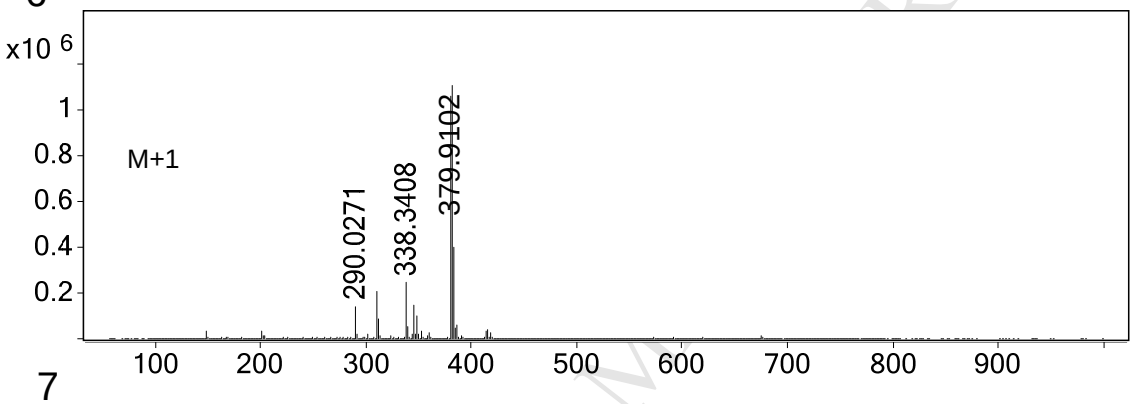

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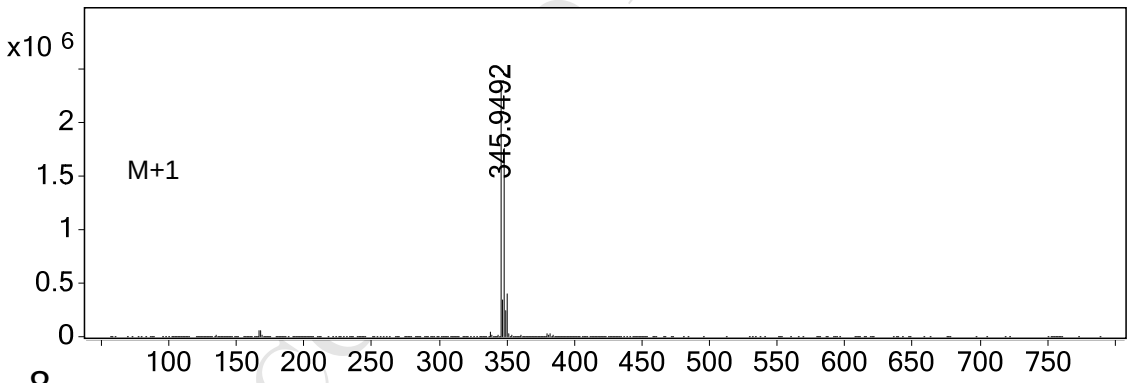

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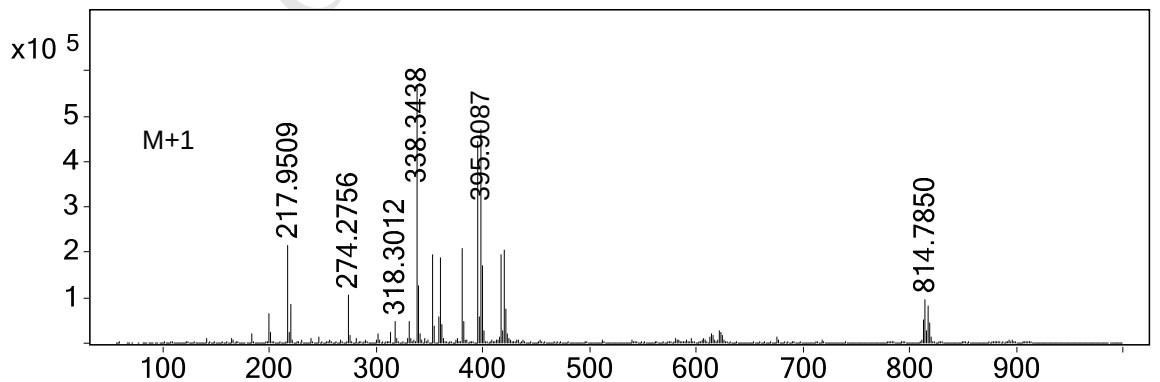

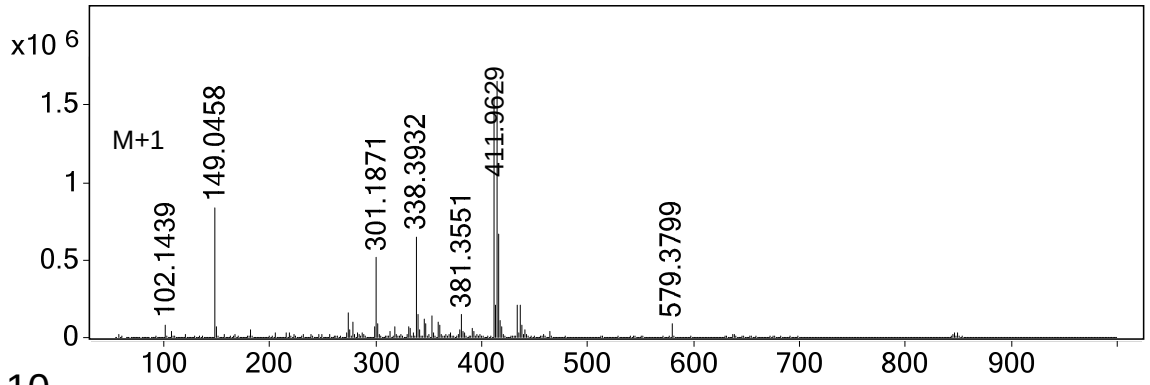
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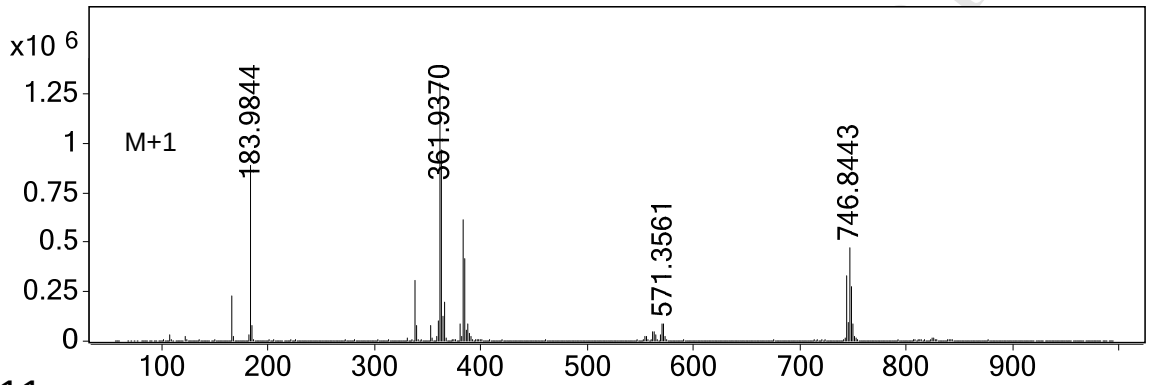
10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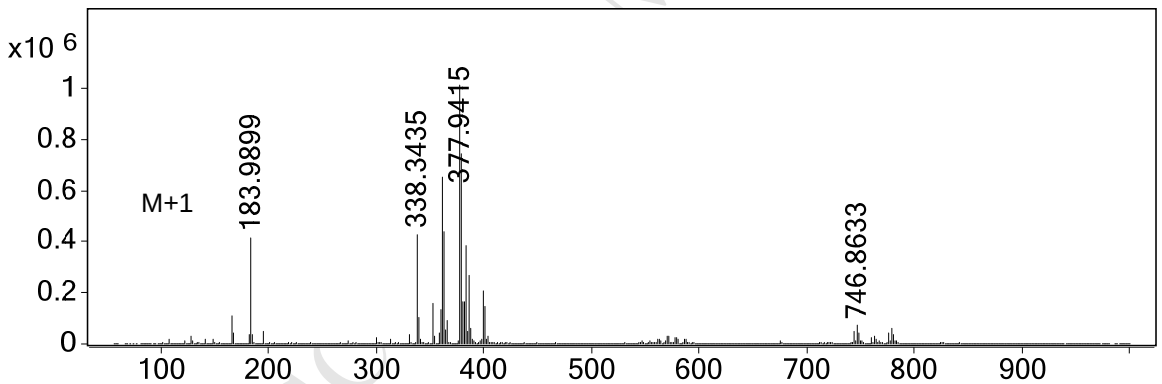
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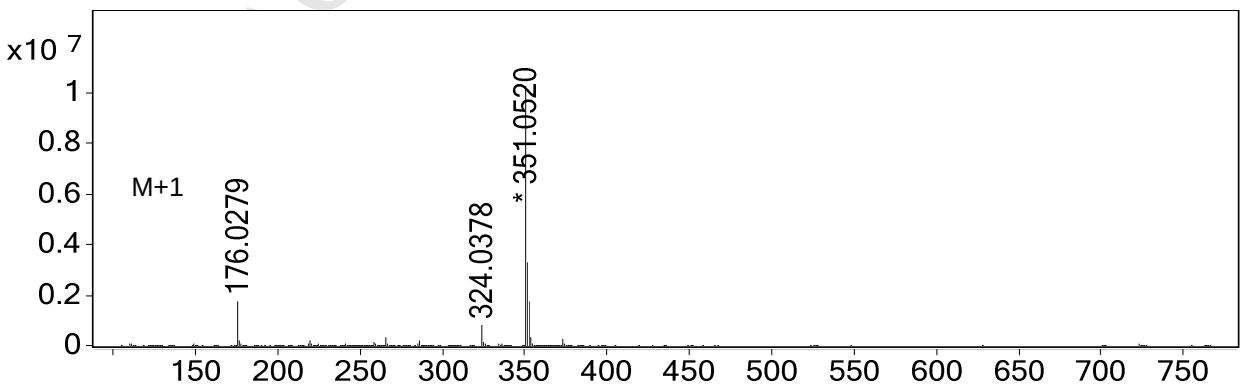
13b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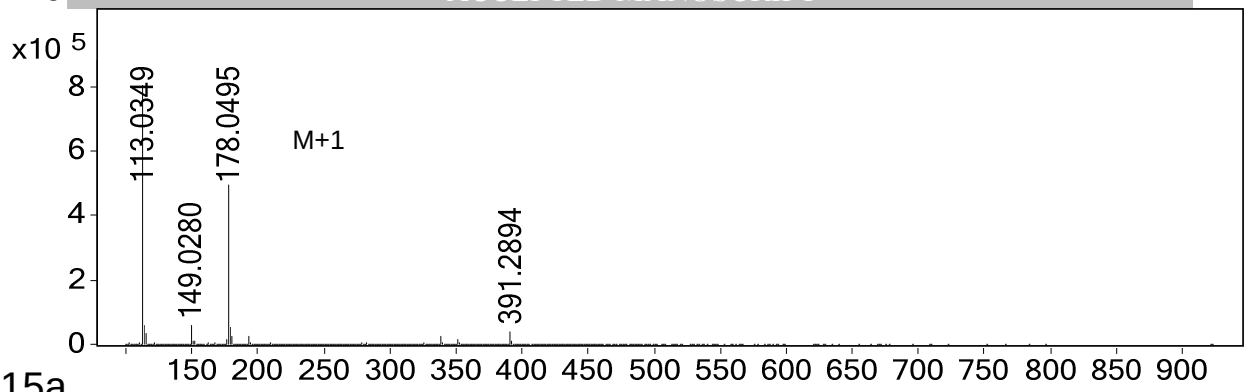
14b



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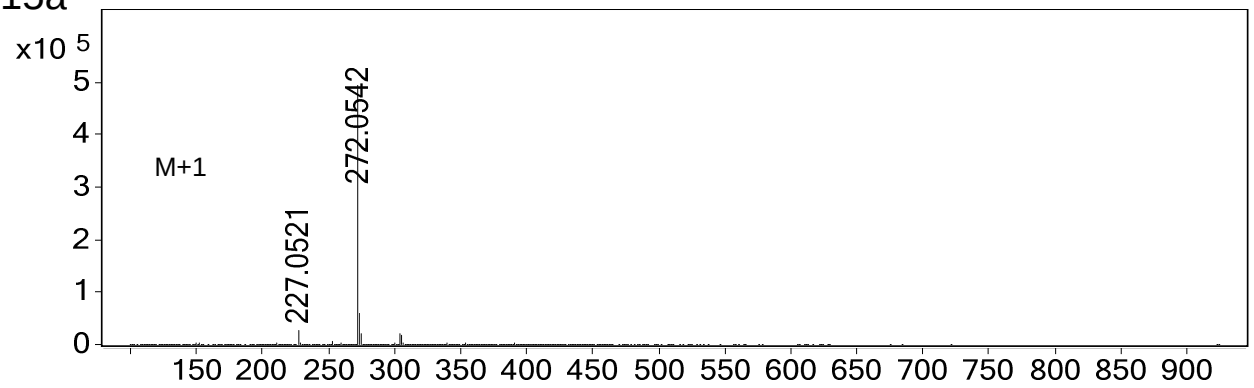

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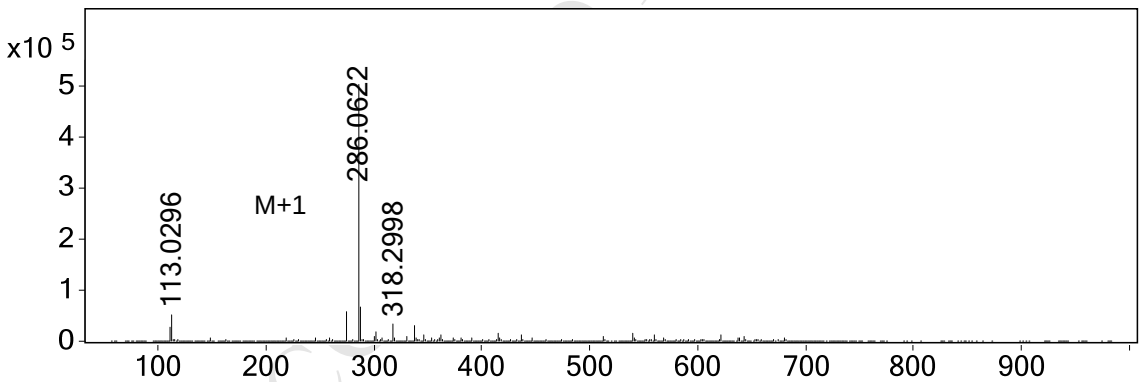

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