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Synthesis of novel pyrazoles incorporating a phenothiazine moiety: Unambiguous structural characterization of the regioselectivity in the 1,3-dipolar cycloaddition reaction using 2D HMBC NMR spectroscopy

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ABSTRACT

An efficient and attractive regioselective synthesis of a series of novel pyrazoles containing a phenothiazine moiety was achieved utilizing microwave irradiation. Unambiguous structural assignment of the obtained regioisomers were determined utilizing 2D HMBC NMR techniques as a valuable tool.

Keywords

microwave irradiation; phenothiazine; pyrazole; hydrazonyl halides; HMBC; regioselectivity

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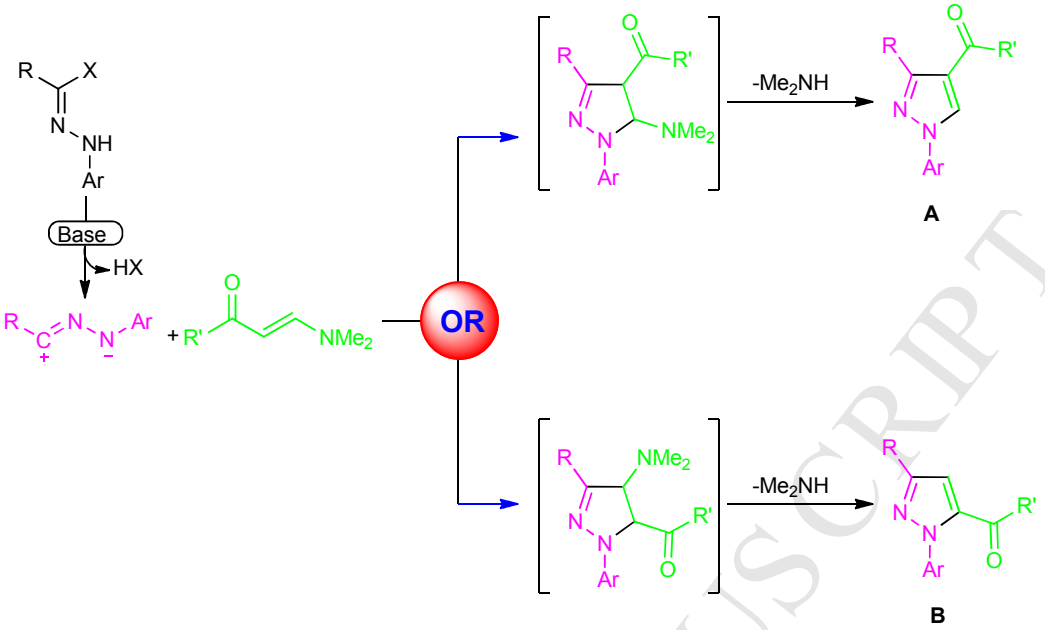
1. Introduction

The phenothiazine structure occurs in various neuroleptic drugs, e.g. chlorpromazine,[1] and antihistaminic drugs, e.g. promethazine.[2] The term "phenothiazines" describes the largest of the five main classes of neuroleptic antipsychotic drugs. These drugs have antipsychotic, and often antiemetic properties, although they may also cause severe side effects such as extrapyramidal symptoms (including akathisia and tardive dyskinesia), hyperprolactinaemia, and the rare but potentially fatal neuroleptic malignant syndrome, as well as substantial weight gain.[3] These side effects associated with phenothiazine drugs have raised a cautionary flag on these drugs.

Phenothiazine antipsychotics are classified into three groups that differ with respect to the substituent on the ring. Hence, there remains a demand for more efficacious and safer phenothiazine derivatives; this can be attained by the synthesis of a large number of novel phenothiazine derivatives for biological screening programmes.

On the other hand, enaminones have proven to be valuable synthons for a wide variety of biologically active heterocyclic ring systems.[4-8] One of these important classes is the pyrazole system.[9-12] Literature reports reveal many synthetic approaches used for the synthesis of pyrazole derivatives, one of the most important approach being the 1,3-dipolar cycloaddition utilizing nitrilimines (generated *insitu* by the action of base on the hydrazonoyl halide) and α,β-unsaturated carbonyl compounds (Scheme 1). [13-15]



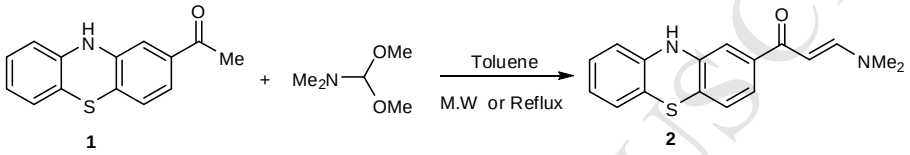
Scheme 1: 1,3-Dipolar cycloaddation reaction

The above reaction proceeds regioselectively to give only one product **A** or **B.** However, to the best of our knowledge, it is frequently difficult to present unequivocal proof of the reaction product structures for this 1,3-dipolar cycloaddition reaction. Therefore, it is crucial to rationalize the observed regioselectivity. Single crystal X-ray is a useful tool for the unambiguous structure determination of the obtained products, but it is sometimes difficult to access a single crystal of the formed product.

Motivated by the aforementioned findings, and in a continuation of our interest in the synthesis of a wide range of heterocyclic systems for biological screening in our laboratory,[16-31] we report herein on the 1,3-dipolar cycloaddition of some nitrilimines to the versatile, *hitherto* unreported *E*-3-(dimethylamino)-1-(10*H*-phenothiazin-2-yl) prop-2-en-1-one **(2)** under both microwave irradiation and conventional methods. This provides a convenient route for obtaining the novel phenothiazine derivatives bearing a pyrazole moiety. Unambiguous structure determination of the obtained regioisomers utilizing 2D NMR techniques as a valuable tool for the identification and characterization of pyrazoles was employed which could facilitate the work of the pharmacologist in the study of the structure activity relationship of bioactive molecules.

2. Results and discussion

The reaction of equimolar quantities of 1-(10*H*-phenothiazin-2-yl)ethanone **(1)** and dimethylformamide-dimethylacetal (*DMF-DMA*) was carried out in toluene under microwave irradiation. The key intermediate *E*-3-(dimethylamino)-1-(10*H*-phenothiazin-2-yl)prop-2-en-1-one **(2)** was obtained within 45 min. as evidenced by TLC (Scheme 2), while the same reaction carried out *via* reflux in toluene required 18 h.



Scheme 2: Synthesis of enaminone 2

The structure of the enaminone **2** was confirmed by its elemental analysis and spectroscopic data. Its ^{1}H NMR spectrum displayed two singlet signals at δ 2.88 and 3.13, due to the *N,N*-dimethyl protons, two doublets at δ 5.69 and 7.70 (*J* =12.4 Hz), due to the olefinic protons, in addition to aromatic proton signals in the region δ 6.66-7.30 and D_2O exchangeable singlet signal, due to the NH proton at δ 8.68. The value of the coupling constant (*J* =12.4 Hz) for the ethylenic protons indicates that the enaminone **2** exists exclusively in the *E*-configuration. The reactivity of enaminones, in general, can be attributed to the fact that they have two electron poor centers at C-1 and C-3 in addition to one electron-rich center at C-2, attributed by the delocalization of the lone pair of electrons on the nitrogen atom (Figure 1).

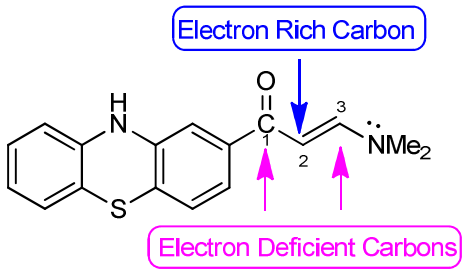
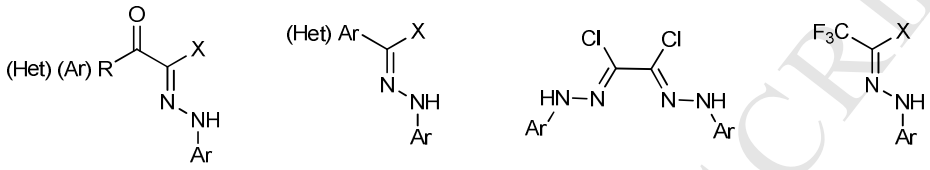


Figure 1: Structure of Enaminone 2

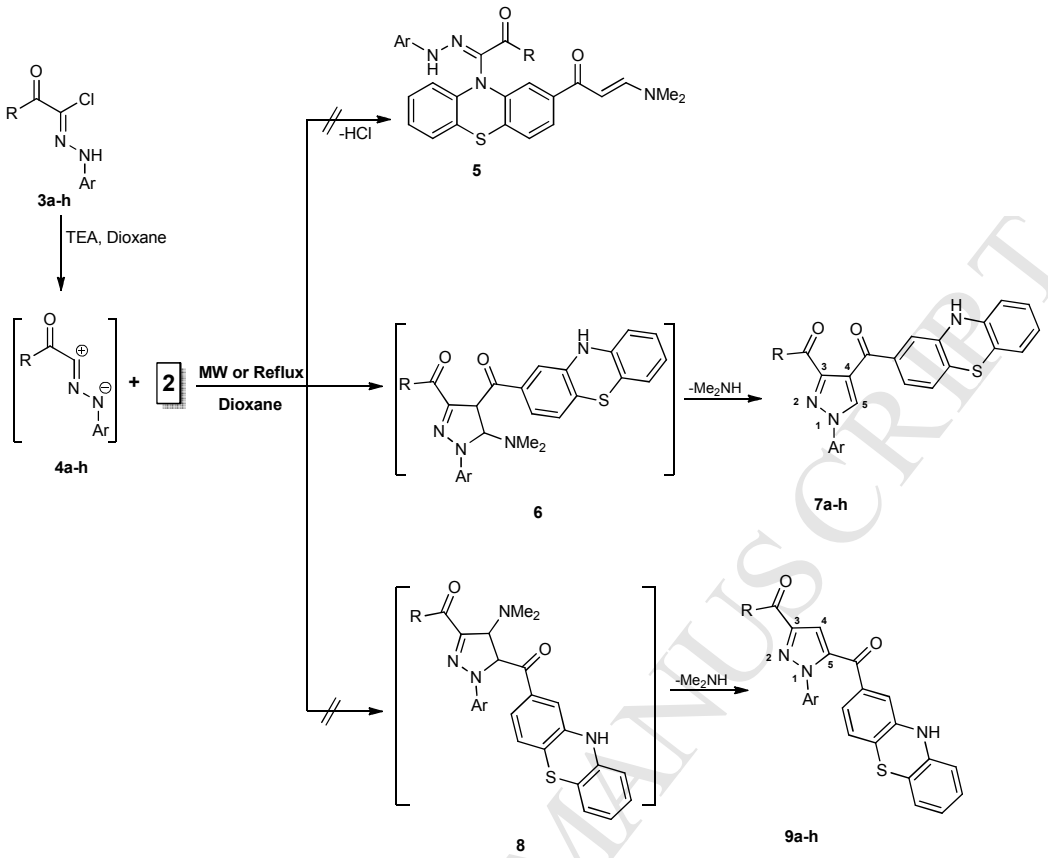
The double bond in compound **2** can be looked on as an electron-rich one that may enter into 1,3-dipolar cycloaddition reactions with hydrazonyl halides. On the other hand, there are many types of hydrazonyl halides as represented in Figure 2. Type I are *α*-ketohydrazonoyl halides, type II are *N*-arylbenzenecarbohydrazonoyl halide, type III are oxalodihydrazonyl dihalides and type IV are *N*-aryltrifluoromethylcarbohydrazonoyl halides



Type I **Type II** **Type III** **Type IV**

Figure 2: Some types of hydrazonyl halides

These hydrazonyl halides in presence of a base liberate *in situ*, intermediates known as nitrilimines. These can react easily with *α,β*-unsaturated ketones such as enaminones to afford a pyrazole *via* a 1,3-dipolar cycloaddition reaction. Therefore, our current research is directed to the study of the regioselectivity in the 1,3-dipolar cycloaddition of some nitrilimines (liberated *in situ* for hydrazonyl halides types I and III) with enaminone **2**. Thus, when compound **2** was allowed to react with the nitrilimine **4** (liberated, *in situ*, from the corresponding hydrazonyl halides (Type I) **3** by the action of triethylamine in dioxane under microwave irradiation), it afforded in each case, only one isolable product as shown by TLC analysis (Scheme 3). The times of reactions and yields are shown in Table 1.



Scheme 3: Reaction of hydrazony halids (type I) with enaminone 2

We have three possible products **5**, **7** or **9**. Amidrazone structure **5** was easily ruled out on the basis of the ^{1}H NMR spectra of the reaction products. In principle, two isomeric structures, **7a-h** or **9a-h** are possible for the product on the basis of elemental analysis and spectroscopic data of the isolated products. For example, the ^{1}H NMR spectra of the isolated products show, in each case, disappearance of NMe_2 signals, and the two doublets of the olefinic protons, and appearance of a singlet signal corresponding to pyrazole proton in the region δ 8.96-9.23. The IR spectra of the isolated products, in each case, showed the presence of two carbonyl absorption bands, and the presence of a band due to a NH group (Scheme 3).

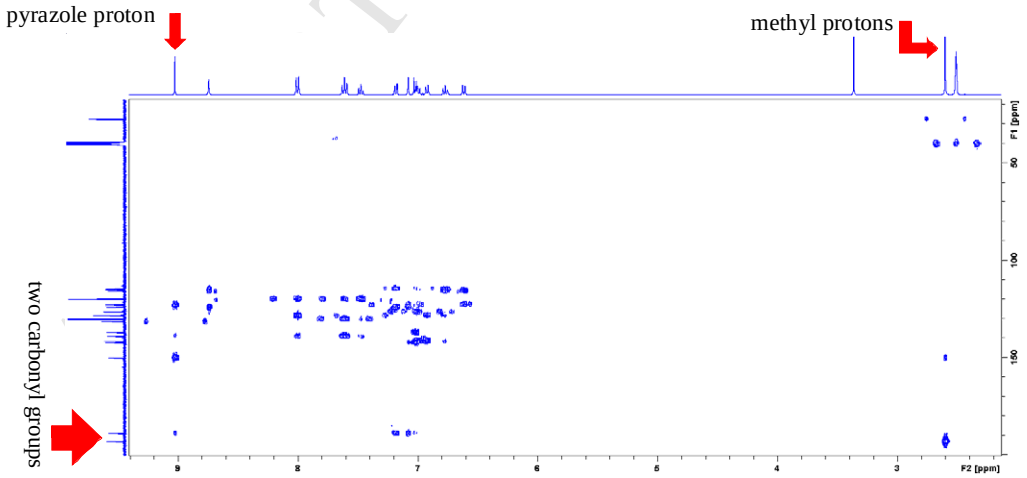
To our knowledge, the previously reported results[32-34] for similar reactions based on one dimension ^{1}H NMR spectroscopy assume that in the pyrazole ring system, C-4 is more electron-rich carbon than C-5; thus, H-4 is expected to appear at a higher field, typically at a lower chemical shift than H-5, which is

linked to a carbon attached to a nitrogen atom, and therefore is deshielded and typically appeared at a higher chemical shift.

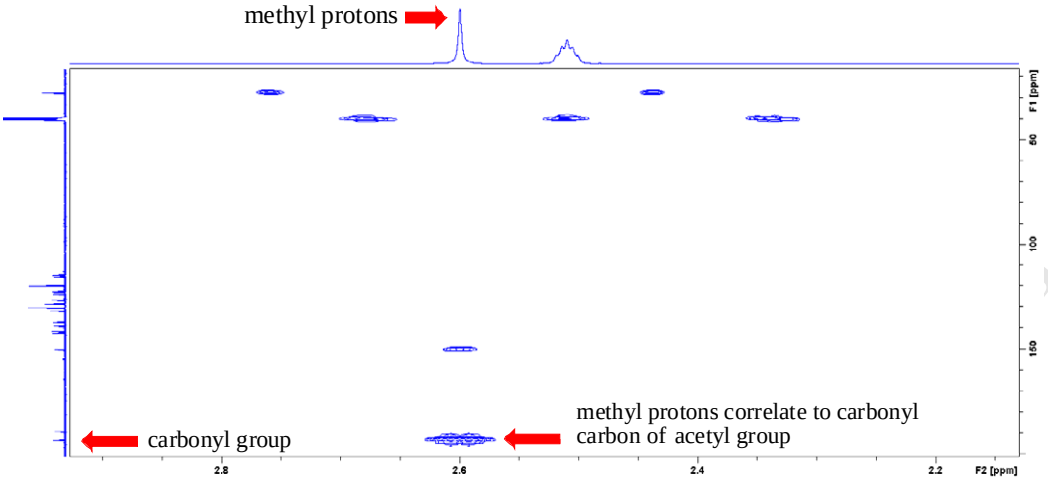
We agree with this assumption to some extent, if we can compare the spectra of two regioisomers. In the present case, we have only one ^{1}H NMR spectrum in view of the fact that the reaction proceeded in a regioselective manner. The chemical shift in NMR spectroscopy is considered a tensor not a scalar, so we can not decide if the obtained chemical shift of the pyrazole proton is a lower or higher value.

Therefore, distinction between the two possible regioisomers is very important, so we introduce here, a simple 2D-NMR experiment to unambiguouly elucidate the structure of the obtained regioisomer.

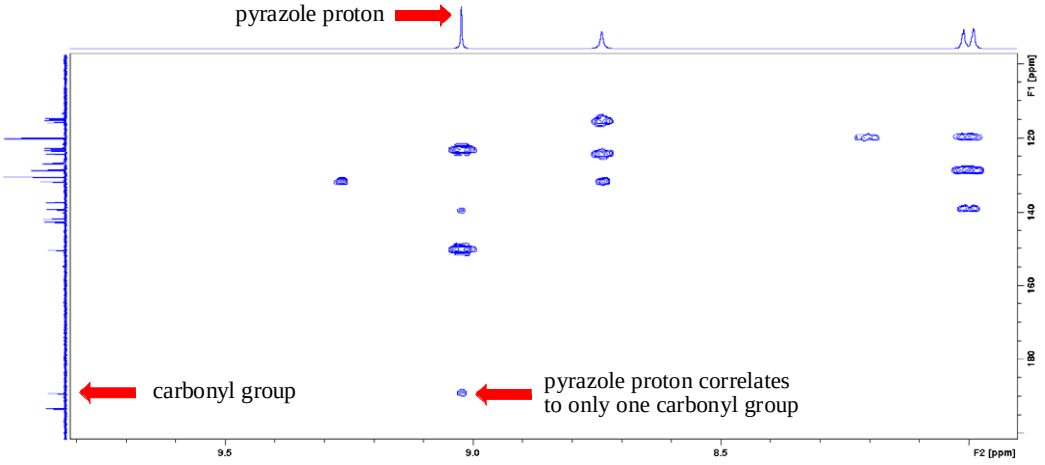
Structure elucidation was conveniently achieved on the basis of the long-range C–H connectivities *via* ^{1}H-^{13}C HMBC, (Figure 3a) depending on the correlation between the pyrazole proton with the carbons of the two carbonyl groups. For example, the ^{1}H-^{13}C HMBC spectrum of the isolated product **7a** or **9a**, shows a signal at δ 193.14 ppm corresponding to the carbonyl carbon due to its correlation peak with the signal at δ 2.59 ppm assigned to the methyl protons of the acetyl group (Figure 3b).



a



b



c

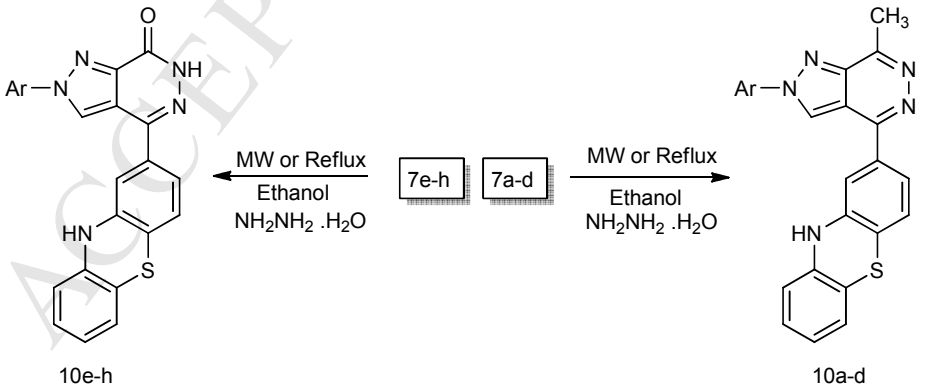
d

Figure 3: (a) the ^{1}H-^{13}C HMBC spectrum of the isolated regioisomer **7a** or **9a** (b) correlation between methyl protons and carbonyl group (c) correlation between pyrazol proton and carbonyl group (d) diagnostic correlations in the ^{1}H-^{13}C HMBC (red arrows) for two regioisomer **7a** and **9a**

On the other hand, the signal at δ 188.96 ppm is attributed to the other carbonyl group, owing to its correlation peak with the signal at δ 9.02 ppm, easily assigned to the pyrazole proton (Figure 3C). These observations indicate that only one carbonyl functional group correlates to the pyrazole proton ($^3J_{H\text{-}C}$), in accordance with the structure **7a**, in addition to the other observed correlations of the pyrazole protons with C-4 pyrazole ($^2J_{H\text{-}C}$), C-3 pyrazole ($^3J_{H\text{-}C}$) and the desheilded quaternary carbon of the phenyl group ($^3J_{H\text{-}C}$) (Figure 3c and Figure 3d). Therefore, these results confirm the existence of regioisomer **7a** and rule out the alternative structure **9a**.

The formation of novel pyrazole derivatives **7a-h** were assumed to be formed *via* initial 1,3-dipolar cycloaddition of the nitrilimines **4a-h** to the activated double bond in the enaminone **2** to afford the non-isolable dihydropyrazole intermediates **8**, followed by elimination of dimethylamine, yielding the pyrazole derivative **7a-h**.

It is noteworthy that the structure of pyrazole derivatives **7a-h** resulting from type I hydrazonyl halides can be confirmed chemically *via* the reaction of compounds **7a-h** with hydrazine to afford the pyrazolo[3,4-*d*] pyridazine derivatives **10a-h** in almost quantitative yields (Scheme 4). The time of reactions and yields are shown in Table 1.



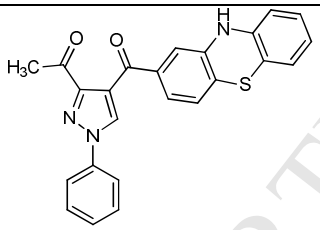
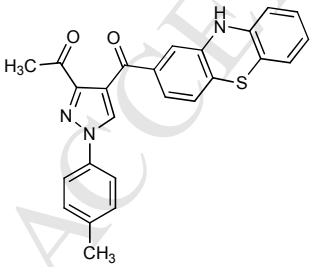
Scheme 4: Synthesis of pyrazolo[3,4-*d*] pyridazine derivatives 10a-h

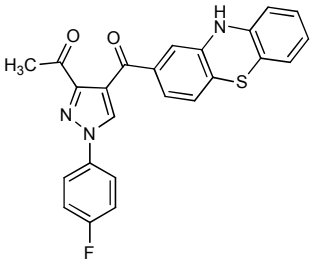
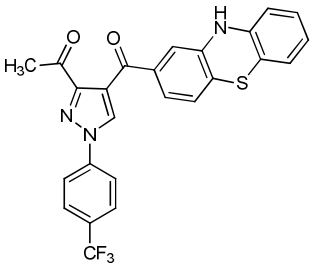
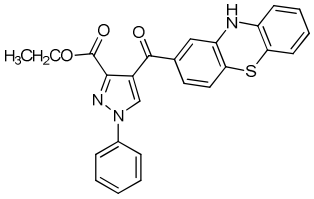
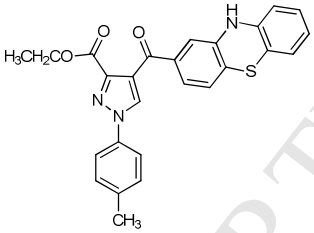
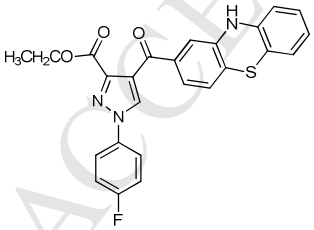
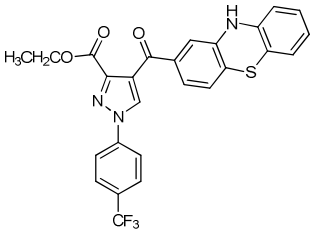
The structures of the products **10a-h** were confirmed based on their elemental analysis and spectrscopic data. The IR spectra of compounds **10a-d** showed disappearance of the two carbonyl absorption bands. Also, the IR spectra of

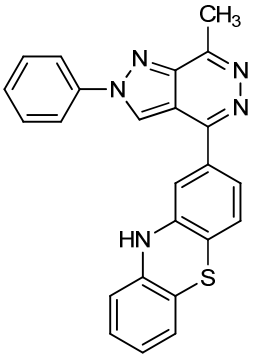
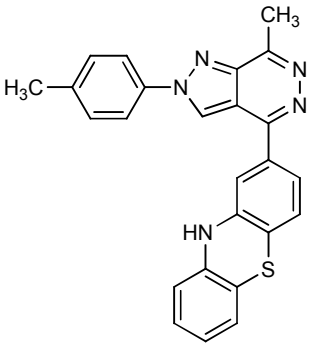
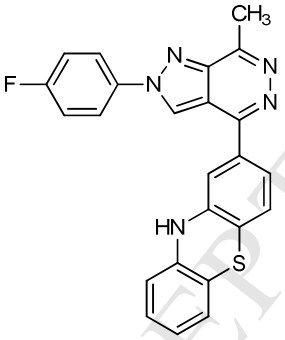
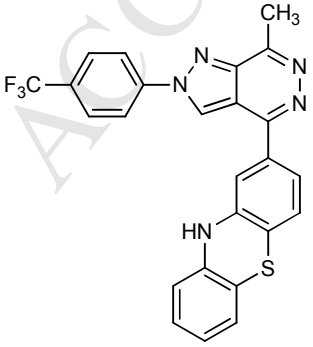
compounds **10e-h** showed appearance of two bands due to the two NH groups. The mass spectra of **10a** showed a peak corresponding to the molecular ion at 407 and its ^{1}H NMR spectrum revealed a singlet at δ 2.49 due to the methyl protons, a D_2O exchangeable singlet signal at δ 8.79 and a singlet signal at δ 9.56 due to the pyrazole H-5 proton in addition to aromatic multiplets.

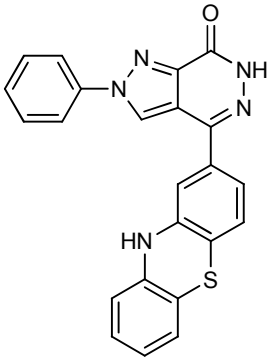
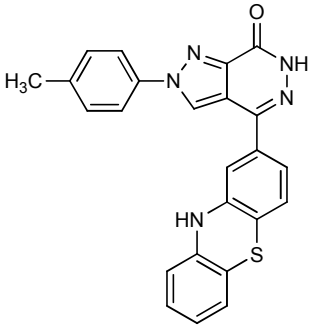
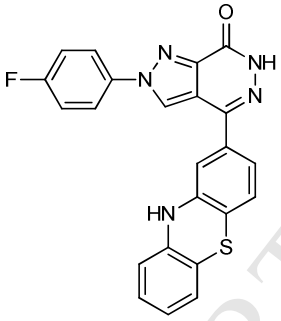
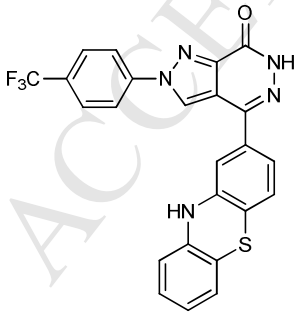
In order to address the advantage of microwave irradiation on the above mentioned reactions, all the previously mentioned reaction were carried out using conventional method *via* reflux in dioxane and/or ethanol (Table 1). The obtained results revealed that the reactions are took a longer time to attain a much lower yield than that obtained using the microwave protocol.

Table 1: Synthesis of pyrazole 7a-h pyrazolo[3,4-*d*]pyridazine derivatives 10a-h under both Microwave irradiation and conventional method

Entry	Product	Microwave Irradiation		Conventional Condition	
		Time (min.)	Yield %	Time (h)	Yield %
1	 **7a**	**120**	**91**	**48**	**69**
2	 **7b**	**120**	**93**	**48**	**70**

3	 **7c**	**120**	**93**	**48**	**65**
4	 **7d**	**90**	**89**	**48**	**62**
5	 **7e**	**120**	**90**	**48**	**65**
6	 **7f**	**100**	**91**	**48**	**62**
7	 **7g**	**120**	**90**	**48**	**62**
8		**120**	**88**	**48**	**58**

	7h				
9		**30**	**93**	**3**	**88**
	10a				
10		**30**	**95**	**3**	**85**
	10b				
11		**30**	**92**	**3**	**81**
	10c				
12		**30**	**89**	**3**	**85**
	10d				

13	 **10e**	**30**	**88**	**3**	**80**
14	 **10f**	**30**	**87**	**3**	**79**
15	 **10g**	**30**	**90**	**3**	**77**
16	 **10h**	**30**	**93**	**3**	**83**

Thus, microwave irradiation was found to have a beneficial effect on the synthesis of pyrazole derivatives**7a-h** and pyrazolo[3,4-*d*]pyridazine derivatives **10a-h**, in which there was a substantial decrease in the time of above reactions

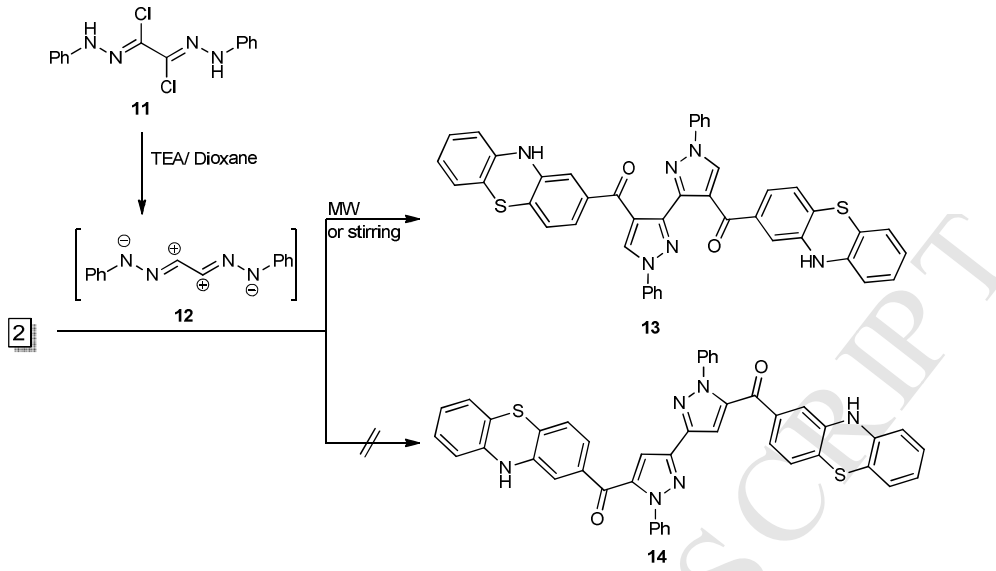
from 3-48 h under conventional heating to 30min.-2 h. In addation there was a noticeable improvement in the yields of the reactions under microwave irradiations.

Encouraged by the successful characterization of pyrazole derivatives **7a-h**, the reaction protocol was further extended to the reaction of other hydrazonyl halides of type III with enaminone **2**, in order to provide unambiguous structure determination of the obtained regioisomers. It is worth mentioning that the regioisomeric products in this case can not be proved chemically like the regioisomeric product of type I hydrazonyl halides with enaminone **2**.

It is important to mention here, that the reaction of oxalodihydrazonyl dichlorides **(11)** (Type III) with enaminone **2** afforded the regioselective bis pyrazole product **13** or **14**; however, oxalodihydrazonyl dichlorides **(11)** (Type III) were relatively more reactive and sensitive to heat than type I; it required less exposure time to MW irradiation at lower power for completion of the reaction.

The reaction was also performed under conventional conditions, by stirring the reactant at room temperature (Scheme 5).

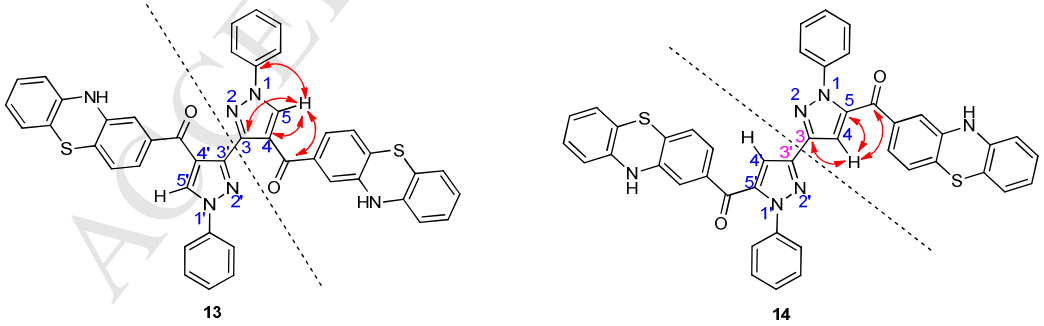
Reaction of oxalodihydrazonyl dichlorides **(11)** (Type III) with enaminone **2** under microwave irradiation also resulted in exclusive formation of a single regioisomer that may have structure **13** or **14** (Scheme 5). The challenge was to differentiate and determine its structure by NMR spectroscopy.



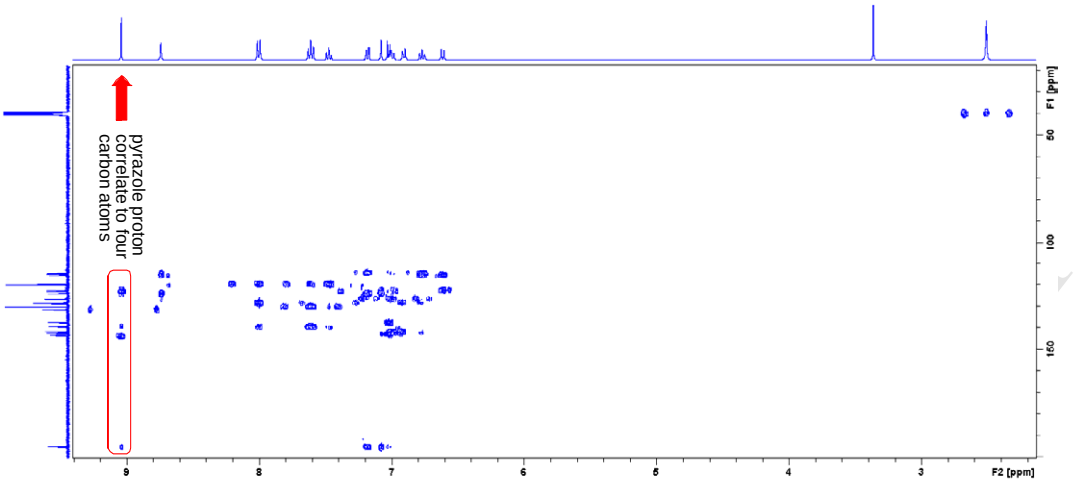
Scheme 5: Regioselective synthesis of bis-Pyrazole derivative 13

We found that ^{1}H-^{13}C HMBC is also a useful tool to unambigously assign the structure of isolated regioisomers unambiguously.

Structure elucidation of the isolated product **13** or **14** was achieved on the basis of the long-range C–H connectivities *via* ^{1}H-^{13}C HMBC, based on the number of correlations between the pyrazole proton towards carbons that are two and three bonds away (Figure 4a). The presence of four correlations in ^{1}H-^{13}C HMBC spectrum of the isolated product is conclusive evidence for the proposed structure **13** (Figure 4b).



a



b

Figure 4: (a) number of correlations between pyrazole proton towards carbons in the possible regioselective products **13** and **14**

(b) ^{1}H-^{13}C HMBC spectrum of the isolated product

Finally, our efforts will be extended to encompass unambiguous structural charactraization of the regioselectivity in 1,3-dipolarcycloaddation reactions with other types of hydrazonyl halides.

3. Conclusion

An efficient microwave-assisted protocol for the regioselective synthesis of a series of novel pyrazoles incorporating a phenothiazine moiety is reported. Microwave irradiation offered high yields of pyrazoles in a short reaction time, compared with classical heating. 2D (^{1}H–^{13}C) HMBC measurements can be readily utilized for the unambiguous structural characterization of the regioselectivity in the 1,3-dipolar cycloaddition reaction of hydrazonyl halides, type I and type III with enaminones.

4. Experimental section

4.1. General

All organic solvents were purchased from commercial sources and used as received unless otherwise stated. All other chemicals were purchased from Merck, Aldrich or Acros and used without further purification. Thin-layer chromatography (TLC) was performed on precoated Merck 60 GF254 silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer. The NMR spectra were recorded on on a Bruker Avance III 400 (9.4 Tesla, 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) spectrometer with a 5-mm BBFO probe, at 298 K. Chemical shifts (δ in ppm) are given relative to internal solvent, $CDCl_3$ 7.26 for ^{1}H and 77.0 for ^{13}C. (^{1}H–^{13}C) gs-HMBC was acquired and processed using standard Bruker NMR software (Topspin 3.2). Mass spectra were recorded on a Thermo ISQ Single Quadrupole GC-MS. Elemental analyses were carried out on a Euro*V*ector instrument C, H, N, S analyzer EA3000 Series.

Microwave experiments were performed using CEM Discover & Explorer SP microwave apparatus (300 W), utilizing 35 ml capped glass reaction vessels Automated power control based on temperature feedback.

α-Ketohydrazonoyl halides **3a-h**[35] and N,N-diphenyloxalodi-hydrazonoyl dichloride (**11**)[36] were prepared according to the reported literature.

4.2. General procedure and characterization data

4.2.1. Synthesis of E-3-(dimethylamino)-1-(10H-phenothiazin-2-yl)prop-2-en-1-one (2):

Method A: To a solution of 1-(10*H*-phenothiazin-2-yl)ethanone **(1)** (2.41g, 10 mmol) in toluene (30 mL), dimethylformamide-dimethylacetal (*DMF-DMA*)

(2.62 mL, 20 mmol) was added and refluxed for 18 h (untill no starting materials showed by in TLC). The excess toluene and *DMF-DMA* was distilled off under reduced pressure. The residual solid was taken up in ether (20 mL) and the resulting crystals were collected by filtration, washed thoroughly with ether, dried and finally recrystallized from dry benzene to afford the enaminone **3** in (2.58g, 87 % yield).

Method B: This process was performed using microwave irradiation (300 Watt, 100 ^{o}C) on the same scale described above. Here the reactants were dissolved in toluene and subjected to microwave irradiation for 45 min. until the starting materials were no longer detectable by TLC. The product was obtained and purified (2.75 g, 93% yield) as described above in conventional reaction .

Orange solid, mp 249-251 °C; IR (KBr) ν/cm^{-1}: 3256 (NH), 1636 (CO); ^{1}H NMR (DMSO-d_6): δ 2.88 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 5.69 (d, 1H, =CH-CO, *J* = 12.4 Hz), 6.66 (d, 1H, ArH, *J* = 8 Hz), 6.75 (t, 1H, ArH, *J* = 8 Hz), 6.91 (d, 1H, ArH, *J* = 8 Hz), 6.94 (d, 1H, ArH, *J* = 8 Hz), 6.99 (t, 1H, ArH, *J* = 8 Hz), 7.22 (s, 1H, ArH), 7.30 (d, 1H, ArH, *J* = 8 Hz), 7.70 (d, 1H, =CH-N, *J* = 12.4 Hz), 8.68 (s, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6): δ 14.16, 39.35, 62.14, 64.86, 116.03, 122.73, 124.31, 131.34, 132.36, 134.11, 137.80, 145.80, 146.31, 156.68, 161.47, 166.13; MS: M^+ (296); $C_{17}H_{16}N_2OS$ (296.39): Anal. Calcd: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found C, 68.83; H, 5.38; N, 9.40; S, 10.78%.

4.2.2.Typical procedure for the synthesis of pyrazole derivatives 7a-h

***Method A*:** To a mixture of enaminone **2** (2.96g, 10 mmol) and the appropriate hydrazonyl chloride **3a-h** (10 mmol) in dioxane (15 mL), an equivalent amount of triethylamine (10 mmol) was added. The total mixture was placed in a process vial in the microwave, and was irradiated with **a** power of 300 W to reach a reaction temperature of 140 ^{o}C under auto generated pressure. The vial was exposed to microwaves for the required time to complete the reaction. The progress of the reaction was monitored by TLC (eluent; ethylacetate: chloroform). Upon completion of the reaction, the solvent was evaporated under

reduced pressure. The obtained solid product was crystallized using ethanol to afford the corresponding pyrazole derivatives **7a–h**.

***Method B*:** To a hot solution of enaminone **2** (10 mmol) and the appropriate hydrazonyl halides **3a-h** (1.39 mL, 10 mmol) in dioxane (25 mL), triethylamine (10 mmol) was added. The reaction mixture was refluxed for 48 h. The solvent was evaporated under reduced pressure. The solid product was crystallized from ethanol to afford the corresponding pyrazole derivatives **7a–h**.

4.2.2.1. 1-(4-(10H-phenothiazine-2-carbonyl)-1-phenyl-1H-pyrazol-3-yl)ethanone (7a)

Orange solid, mp 258-260 °C; IR (KBr) ν/cm^{-1}: 3406 (NH), 1682, 1645 (CO), 1593 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.59 (s, 3H, CH_3CO), 6.61 (d, 1H, ArH, *J* = 8 Hz), 6.76 (t, 1H, ArH, *J* = 8 Hz), 6.92 (d, 1H, ArH, *J* = 8 Hz), 6.97-7.02 (m, 2H, ArH), 7.07 (s, 1H, ArH), 7.17 (d, 1H, ArH, *J* = 8 Hz), 7.47 (t, 1H, ArH, *J* = 7.6 Hz), 7.60 (t, 2H, ArH, *J* = 7.6 Hz), 7.99 (d, 2H, ArH, *J* = 8 Hz), 8.73 (s, 1H, NH, D_2O-exchangeable), 9.02 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 27.50, 114.59, 114.98, 115.55, 119.85, 122.63, 123.11, 123.19, 124.09, 126.60, 126.75, 128.49, 130.28, 131.56, 136.91, 137.06, 139.02, 141.59, 142.40, 150.30, 188.96, 193.14; MS: M^+ (411); $C_{24}H_{17}N_3O_2S$ (411.48): Anal. Calcd: C, 70.05; H, 4.16; N, 10.21; S, 7.79. Found C, 69.98; H, 4.12; N, 10.11; S, 7.71%.

4.2.2.2. 1-(1-(4-methylphenyl)-4-(10H-phenothiazine-2-carbonyl)-1H-pyrazol-3-yl)ethanone (7b)

Orange solid, mp 218-220 °C; IR (KBr) ν/cm^{-1}: 3402 (NH), 1682, 1647 (CO) , 1585 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 2.58 (s, 3H, CH_3CO), 6.60 (d, 1H, ArH, *J* = 8 Hz), 6.76 (t, 1H, ArH, *J* = 8 Hz), 6.91 (d, 1H, ArH, *J* = 8 Hz), 6.97-7.02 (m, 2H, ArH), 7.06 (s, 1H, ArH), 7.17 (d, 1H, ArH, *J* = 8 Hz), 7.40 (d, 2H, ArH, *J* = 8.4 Hz), 7.87 (d, 2H, ArH, *J* = 8.4 Hz), 8.74 (s, 1H, NH, D_2O-exchangeable), 8.96 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ

20.99, 27.49, 114.60, 114.98, 115.55, 119.71, 122.62, 123.01, 123.16, 124.03, 126.60, 126.75, 128.48, 130.62, 131.36, 136.81, 137.09, 138.06, 141.59, 142.38, 150.08, 189.01, 193.12; MS: *m/z* 425 (M^+); $C_{25}H_{19}N_3O_2S$ (425.50): Anal. Calcd: C, 70.57; H, 4.50; N, 9.88; S, 7.54. Found C, 70.50; H, 4.46; N, 9.83; S, 7.48%.

4.2.2.3. 1-(1-(4-fluorophenyl)-4-(10H-phenothiazine-2-carbonyl)-1H-pyrazol-3-yl)ethanone (7c)

Red solid, mp 253-255 °C; IR (KBr) ν/cm^{-1}: 3345 (NH), 1690, 1636 (CO) , 1594 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H, CH_3CO), 6.59 (d, 1H, ArH, *J* = 8 Hz), 6.75 (t, 1H, ArH, *J* = 8 Hz), 6.91 (d, 1H, ArH, *J* = 8 Hz), 6.98-7.03 (m, 2H, ArH), 7.10 (s, 1H, ArH), 7.19 (d, 1H, ArH, *J* = 8 Hz), 7.45 (d, 2H, ArH, *J* = 8 Hz), 7.83 (d, 2H, ArH, *J* = 8 Hz), 8.75 (s, 1H, NH, D_2O-exchangeable), 9.02 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 27.45, 114.63, 115.09, 115.65, 119.82, 122.60, 122.89, 123.19, 124.16, 126.66, 127.31, 128.51, 131.01, 131.43, 137.18, 141.05, 141.50, 142.41, 150.16, 160.97, 188.91, 193.14; MS: *m/z* 429 (M^+); $C_{24}H_{16}FN_3O_2S$ (429.47): Anal. Calcd: C, 67.12; H, 3.76; N, 9.78; S, 7.47. Found C, 67.06; H, 3.70; N, 9.75; S, 7.42%.

4.2.2.4. 1-(4-(10H-phenothiazine-2-carbonyl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)ethanone (7d)

Red solid, mp 270-272 °C; IR (KBr) ν/cm^{-1}: 3413 (NH), 1983, 1640 (CO) , 1606 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.61 (s, 3H, CH_3CO), 6.61 (d, 1H, ArH, *J* = 8 Hz), 6.76 (t, 1H, ArH, *J* = 8 Hz), 6.91 (d, 1H, ArH, *J* = 8 Hz), 6.98-7.03 (m, 2H, ArH), 7.08 (s, 1H, ArH), 7.18 (d, 1H, ArH, *J* = 8 Hz), 7.99 (d, 2H, ArH, *J* = 8.4 Hz), 8.24 (d, 2H, ArH, *J* = 8.4 Hz), 8.74 (s, 1H, NH, D_2O-exchangeable), 9.16 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 27.54, 114.46, 115.00, 115.53, 120.30, 122.65, 123.31, 123.49, 124.29, 126.62, 126.75, 127.58, 127.61, 128.50, 132.11, 136.91, 137.06, 141.54, 141.83, 142.42, 150.85, 188.72, 193.12; MS:

m/z 479 (M^+); $C_{25}H_{16}F_3N_3O_2S$ (479.47): Anal. Calcd: C, 62.62; H, 3.36; N, 8.76; S, 6.69. Found C, 62.57; H, 3.30; N, 8.73; S, 6.64%.

4.2.2.5. Ethyl 4-(10H-phenothiazine-2-carbonyl)-1-phenyl-1H-pyrazole-3-carboxylate (7e)

Yellow solid, mp 185-187 °C; IR (KBr) ν/cm^{-1}: 3302 (NH), 1717, 1671 (CO) , 1599 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.14 (t, 3H, CH_3, *J* = 7.2 Hz), 4.21 (q, 2H, CH_2, *J* = 7.2 Hz), 6.51 (d, 1H, ArH, *J* = 8 Hz), 6.78 (t, 1H, ArH, *J* = 8 Hz), 6.90 (d, 1H, ArH, *J* = 8 Hz), 6.92-6.96 (m, 2H, ArH), 7.11 (s, 1H, ArH), 7.21 (d, 1H, ArH, *J* = 8 Hz), 7.37 (t, 1H, ArH, *J* = 8 Hz), 7.46 (t, 2H, ArH, *J* = 8 Hz), 7.72 (d, 2H, ArH, *J* = 8 Hz), 8.76 (s, 1H, NH, D_2O-exchangeable), 9.19 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 13.82, 61.75, 114.13, 114.64, 116.65, 120.06, 122.40, 122.72, 123.80, 124.39, 125.92, 126.55, 127.78, 128.29, 129.64, 129.95, 137.19, 139.57, 141.41, 141.68, 143.83, 161.53, 188.43; MS: *m/z* 441 (M^+); $C_{25}H_{19}N_3O_3S$ (441.50): Anal. Calcd: C, 68.01; H, 4.34; N, 9.52; S, 7.26. Found C, 67.94; H, 4.29; N, 9.47; S, 7.22%.

4.2.2.6. Ethyl 1-(4-methylphenyl)-4-(10H-phenothiazine-2-carbonyl)-1H-pyrazole-3-carboxylate (7f)

Orange solid, mp 210-212 °C; IR (KBr) ν/cm^{-1}: 3290 (NH), 1717, 1669 (CO) , 1603 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.13 (t, 3H, CH_3, *J* = 7.2 Hz), 2.39 (s, 3H, CH_3), 4.24 (q, 2H, CH_2, *J* = 7.2 Hz), 6.52 (d, 1H, ArH, *J* = 8 Hz), 6.76 (t, 1H, ArH, *J* = 8 Hz), 6.88 (d, 1H, ArH, *J* = 8 Hz), 6.90-6.99 (m, 2H, ArH), 7.09 (s, 1H, ArH), 7.19 (d, 1H, ArH, *J* = 8 Hz), 7.40 (d, 2H, ArH, *J* = 8.4 Hz), 7.79 (d, 2H, ArH, *J* = 8.4 Hz), 8.71 (s, 1H, NH, D_2O-exchangeable), 9.16 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 13.79, 20.89, 61.70, 114.09, 114.60, 116.39, 119.88, 122.34, 122.67, 124.02, 124.41, 125.90, 126.48, 127.79, 128.11, 129.24, 130.10, 137.07, 139.23, 141.50, 141.80, 143.91, 161.37, 188.22; MS:

m/z 455 (M^+); $C_{26}H_{21}N_3O_3S$ (455.53): Anal. Calcd: C, 68.55; H, 4.65; N, 9.22; S, 7.04. Found C, 68.49; H, 4.58; N, 9.17; S, 7.00%.

4.2.2.7. Ethyl 1-(4-fluorophenyl)-4-(10H-phenothiazine-2-carbonyl)-1H-pyrazole-3-carboxylate (7g)

Red solid, mp 196-198 °C; IR (KBr) ν/cm^{-1}: 3289 (NH), 1721, 1663 (CO) , 1601 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 3H, CH_3, *J* = 7.2 Hz), 4.24 (q, 2H, CH_2, *J* = 7.2 Hz), 6.58 (d, 1H, ArH, *J* = 8 Hz), 6.82 (t, 1H, ArH, *J* = 8 Hz), 6.92-7.00 (m, 3H, ArH), 7.11 (s, 1H, ArH), 7.18 (d, 1H, ArH, *J* = 8 Hz), 7.61 (d, 2H, ArH, *J* = 8.4 Hz), 8.98 (d, 2H, ArH, *J* = 8.4 Hz), 8.75 (s, 1H, NH, D_2O-exchangeable), 9.23 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 13.83, 61.80, 113.98, 114.62, 116.47, 121.61, 122.05, 122.80, 123.86, 124.49, 125.82, 126.61, 127.53, 127.81, 130.07, 137.17, 139.60, 141.39, 141.82, 143.92, 160.90, 161.42, 188.29; MS: *m/z* 459 (M^+); $C_{25}H_{18}FN_3O_3S$ (459.49): Anal. Calcd: C, 65.35; H, 3.95; N, 9.14; S, 6.98. Found C, 65.29; H, 3.88; N, 9.09; S, 6.92%.

4.2.2.8. Ethyl 4-(10H-phenothiazine-2-carbonyl)-1-(4-(trifluoromethyl) phenyl)-1H-pyrazole-3-carboxylate (7h)

Orange solid, mp 202-204 °C; IR (KBr) ν/cm^{-1}: 3311 (NH), 1720, 1673 (CO) , 1606 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.13 (t, 3H, CH_3, *J* = 7.2 Hz), 4.19 (q, 2H, CH_2, *J* = 7.2 Hz), 6.66 (d, 1H, ArH, *J* = 8 Hz), 6.75 (t, 1H, ArH, *J* = 8 Hz), 6.90 (d, 1H, ArH, *J* = 8 Hz), 6.97-7.02 (m, 2H, ArH), 7.11 (s, 1H, ArH), 7.29 (d, 1H, ArH, *J* = 8 Hz), 7.98 (d, 2H, ArH, *J* = 8.4 Hz), 8.21 (d, 2H, ArH, *J* = 8.4 Hz), 8.77 (s, 1H, NH, D_2O-exchangeable), 9.22 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 14.13, 61.69, 114.46, 115.01, 115.52, 120.36, 121.34, 122.29, 122.67, 123.27, 124.34, 124.45, 126.68, 127.54, 128.20, 128.51, 132.34, 137.08, 140.02, 141.51, 142.13, 144.55, 161.30, 188.85; MS: *m/z* 509 (M^+); $C_{26}H_{18}F_3N_3O_3S$ (509.50): Anal. Calcd: C, 61.29; H, 3.56; N, 8.25; S, 6.29. Found C, 61.22; H, 3.49; N, 8.20; S, 6.23%.

4.2.3. Synthesis of pyrazolo[3,4-d]pyridazine derivatives 10a-h

Method A: To a solution of appropriate pyrazole derivatives **7a-h** (1 mmol) in ethanol (10 mL), hydrazine hydrate (98%) (2mL, 10 mmol) was added. The total mixture was placed in a process vial and was irradiated by microwaves with a power of 300 W to reach a reaction temperature of 140 °C under auto generated pressure for 30 min. The solid was filtered off, washed with ethanol and recrystallized from DMF to afford the corresponding pyrazolo[3,4-*d*]pyridazine derivatives **10a-h**.

Method B: A mixture of the appropriate pyrazole derivatives **7a-g** (1 mmol) and hydrazine hydrate (98%), (2mL, 10 mmol) was heated under reflux in ethanol (20 mL) for 3 hour then left to cool to room temperature. The precipitates were collected by filtration, washed with ethanol and dried. Recrystallization from dimethylformamide (DMF) afforded yellow crystals of the corresponding pyrazolo[3,4-*d*]pyridazine derivatives **10a-h**.

4.2.3.1. 2-(7-methyl-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-4-yl)-10H-phenothiazine (10a)

Orange solid, mp 284-286 °C; IR (KBr) ν/cm^{-1}: 1590 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.87 (s, 3H, CH_3), 6.71 (d, 1H, ArH, *J* = 8 Hz), 6.78 (t, 1H, ArH, *J* = 8 Hz), 6.95 (d, 1H, ArH, *J* = 8 Hz), 7.02 (t, 1H, ArH, *J* = 8 Hz), 7.10 (d, 1H, ArH, *J* = 8 Hz), 7.55-7.58 (m, 2H, ArH), 7.60-7.67 (m, 3H, ArH), 8.20 (d, 2H, ArH, *J* = 8 Hz), 8.79 (s, 1H, NH, D_2O-exchangeable), 9.56 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 18.48, 113.69, 115.01, 115.29, 116.20, 119.79, 121.85, 122.18, 122.40, 125.08, 126.75, 126.91, 128.24, 129.75, 130.24, 135.94, 139.59, 142.00, 142.78, 144.34, 151.76, 153.07; MS: *m/z* 407 (M^+); $C_{24}H_{17}N_5S$ (407.49):

Anal. Calcd: C, 70.74; H, 4.21; N, 17.19; S, 7.87. Found C, 70.69; H, 4.14; N, 17.14; S, 7.83%.

4.2.3.2. 2-(7-methyl-2-(4-methylphenyl)-2H-pyrazolo[3,4-d]pyridazin-4-yl)-10H-phenothiazine (10b)

Orange solid, mp 256-258 °C; IR (KBr) ν/cm^{-1}: 1587 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 6.70 (d, 1H, ArH, *J* = 8 Hz), 6.79 (t, 1H, ArH, *J* = 8 Hz), 6.94 (d, 1H, ArH, *J* = 8 Hz), 7.01 (t, 1H, ArH, *J* = 8 Hz), 7.12 (d, 1H, ArH, *J* = 8 Hz), 7.56-7.59 (m, 2H, ArH), 7.61 (d, 2H, ArH, *J* = 8 Hz), 8.10 (d, 2H, ArH, *J* = 8 Hz), 8.79 (s, 1H, NH, D_2O-exchangeable), 9.56 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 18.46, 20.87, 113.65, 115.01, 115.17, 116.18, 119.71, 121.83, 122.11, 122.38, 125.10, 126.76, 126.87, 128.25, 129.80, 130.33, 135.84, 140.06, 142.09, 142.71, 144.39, 151.75, 153.01; MS: *m/z* 421 (M^+); $C_{25}H_{19}N_5S$ (421.52): Anal. Calcd: C, 71.23; H, 4.54; N, 16.61; S, 7.61. Found C, 71.15; H, 4.50; N, 16.56; S, 7.57%.

4.2.3.3. 2-(2-(4-fluorophenyl)-7-methyl-2H-pyrazolo[3,4-d]pyridazin-4-yl)-10H-phenothiazine (10c)

Red solid, mp 261-263 °C; IR (KBr) ν/cm^{-1}: 1595 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.89 (s, 3H, CH_3), 6.73 (d, 1H, ArH, *J* = 8 Hz), 6.79 (t, 1H, ArH, *J* = 8 Hz), 6.95 (d, 1H, ArH, *J* = 8 Hz), 7.02 (t, 1H, ArH, *J* = 8 Hz), 7.13 (d, 1H, ArH, *J* = 8 Hz), 7.60 (s, 1H, ArH), 7.63 (d, 1H, ArH, *J* = 8 Hz), 7.78 (d, 2H, ArH, *J* = 8.4 Hz), 8.04 (d, 2H, ArH, *J* = 8.4 Hz), 8.78 (s, 1H, NH, D_2O-exchangeable), 9.61 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 18.51, 113.67, 115.01, 115.38, 116.17, 119.90, 122.45, 125.40, 126.10, 126.76, 126.93, 128.26, 129.61, 129.94, 135.77, 139.62, 142.34, 142.75, 144.39, 151.93, 153.31, 160.97; MS: *m/z* 425 (M^+, 22%); $C_{24}H_{16}FN_5S$ (425.48): Anal. Calcd: C, 67.75; H, 3.79; N, 16.46; S, 7.54. Found C, 67.70; H, 3.72; N, 16.41; S, 7.49%.

4.2.3.4. 2-(7-methyl-2-(4-(trifluoromethyl)phenyl)-2H-pyrazolo[3,4-d]pyridazin-4-yl)-10H-phenothiazine (10d)

Red solid, mp 290-292 °C; IR (KBr) ν/cm^{-1}: 1600 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.88 (s, 3H, CH_3), 6.72 (d, 1H, ArH, *J* = 8 Hz), 6.79 (t, 1H, ArH, *J* = 8 Hz), 6.96 (d, 1H, ArH, *J* = 8 Hz), 7.03 (t, 1H, ArH, *J* = 8 Hz), 7.12 (d, 1H, ArH, *J* = 8 Hz), 7.57 (s, 1H, ArH), 7.63 (d, 1H, ArH, *J* = 8 Hz), 8.06 (d, 2H, ArH, *J* = 8.4 Hz), 8.49 (d, 2H, ArH, *J* = 8.4 Hz), 8.81 (s, 1H, NH, D_2O-exchangeable), 9.75 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 18.49, 113.62, 115.03, 115.44, 116.15, 119.99, 122.42, 125.64, 126.00, 126.76, 126.94, 127.54, 127.57, 128.27, 129.50, 129.83, 135.78, 141.96, 142.41, 142.81, 144.58, 151.94, 153.27; MS: *m/z* 475 (M^+); $C_{25}H_{16}F_3N_5S$ (475.49): Anal. Calcd: C, 63.15; H, 3.39; N, 14.73; S, 6.74. Found C, 63.09; H, 3.32; N, 14.68; S, 6.70%.

4.2.3.5. 4-(10H-phenothiazin-2-yl)-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (10e)

Yellow solid, mp 281-283 °C; IR (KBr) ν/cm^{-1}: 3309, 3291 (NH), 1653 (CO) , 1601 (C=N); ^{1}H NMR (DMSO-d_6): δ 6.70 (d, 1H, ArH, *J* = 8 Hz), 6.80 (t, 1H, ArH, *J* = 8 Hz), 6.95 (d, 1H, ArH, *J* = 8 Hz), 7.02 (t, 1H, ArH, *J* = 8 Hz), 7.07 (d, 1H, ArH, *J* = 8 Hz), 7.28 (s, 1H, ArH), 7.39 (d, 1H, ArH, *J* = 8 Hz), 7.54 (t, 1H, ArH, *J* = 8 Hz), 7.64 (t, 2H, ArH, *J* = 8 Hz), 8.13 (d, 2H, ArH, *J* = 8 Hz), 8.75 (s, 1H, NH, D_2O-exchangeable), 9.35 (s, 1H, pyrazole-5-CH), 12.65 (s, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6): δ 113.02, 115.00, 116.24, 118.57, 118.73, 121.20, 122.32, 126.31, 126.76, 126.90, 128.22, 129.34, 130.25, 134.78, 139.45, 141.21, 141.99, 142.75, 143.24, 144.56, 156.36; MS: *m/z* 409 (M^+, 22%); $C_{23}H_{15}N_5OS$ (409.46): Anal. Calcd: C, 67.47; H, 3.69; N, 17.10; S, 7.83. Found C, 67.39; H, 3.60; N, 17.06; S, 7.75%.

4.2.3.6. 2-(4-methylphenyl)-4-(10H-phenothiazin-2-yl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (10f)

Yellow solid, mp > 300 °C; IR (KBr) ν/cm^{-1}: 3311, 3294 (NH), 1657 (CO) , 1603 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 6.68 (d, 1H, ArH, *J* = 8 Hz), 6.81 (t, 1H, ArH, *J* = 8 Hz), 6.95 (d, 1H, ArH, *J* = 8 Hz), 7.01 (t, 1H, ArH, *J* = 8 Hz), 7.09 (d, 1H, ArH, *J* = 8 Hz), 7.25 (s, 1H, ArH), 7.37 (d, 1H, ArH, *J* = 8 Hz), 7.42 (d, 2H, ArH, *J* = 8 Hz), 7.66 (d, 2H, ArH, *J* = 8 Hz), 8.72 (s, 1H, NH, D_2O-exchangeable), 9.32 (s, 1H, pyrazole-5-CH), 12.61 (s, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6): δ 18.47, 113.01, 115.05, 116.22, 118.53, 118.70, 121.24, 122.29, 126.27, 126.76, 126.91, 128.24, 129.32, 130.28, 134.75, 139.48, 141.26, 142.10, 142.83, 143.31, 144.55, 155.53; MS: *m/z* 423.49 (M^+); $C_{24}H_{17}N_5OS$ (423): Anal. Calcd: C, 68.07; H, 4.05; N, 16.54; S, 7.57. Found C, 68.00; H, 4.01; N, 16.45; S, 7.51%.

4.2.3.7. 2-(4-fluorophenyl)-4-(10H-phenothiazin-2-yl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (10g)

Orange solid, mp > 300 °C; IR (KBr) ν/cm^{-1}: 3315, 3301 (NH), 1660 (CO) , 1595 (C=N); ^{1}H NMR (DMSO-d_6): δ 6.73 (d, 1H, ArH, *J* = 8 Hz), 6.80 (t, 1H, ArH, *J* = 8 Hz), 6.95 (d, 1H, ArH, *J* = 8 Hz), 7.03 (t, 1H, ArH, *J* = 8 Hz), 7.12 (d, 1H, ArH, *J* = 8 Hz), 7.30 (s, 1H, ArH), 7.41 (d, 1H, ArH, *J* = 8 Hz), 7.76 (d, 2H, ArH, *J* = 8.4 Hz), 8.05 (d, 2H, ArH, *J* = 8.4 Hz), 8.76 (s, 1H, NH, D_2O-exchangeable), 9.32 (s, 1H, pyrazole-5-CH), 12.68 (s, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6): δ 113.11, 115.16, 116.18, 118.46, 119.02, 122.42, 126.11, 126.75, 126.93, 128.27, 129.51, 129.98, 134.86, 139.60, 141.32, 142.05, 142.75, 143.30, 144.50, 155.59, 161.09; MS: *m/z* 427 (M^+); $C_{23}H_{14}FN_5OS$ (427.45): Anal. Calcd: C, 64.63; H, 3.30; N, 16.38; S, 7.50. Found C, 64.57; H, 3.26; N, 16.36; S, 7.47%.

4.2.3.8. 4-(10H-phenothiazin-2-yl)-2-(4-(trifluoromethyl)phenyl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (10h)

Orange solid, mp > 300 °C; IR (KBr) ν/cm^{-1}: 3321, 3314 (NH), 1662 (CO) , 1603 (C=N); ^{1}H NMR (DMSO-d_6): δ 6.71 (d, 1H, ArH, *J* = 8 Hz), 6.79 (t, 1H, ArH, *J* = 8 Hz), 6.96 (d, 1H, ArH, *J* = 8 Hz), 7.05 (t, 1H, ArH, *J* = 8 Hz), 7.15 (d, 1H, ArH, *J* = 8 Hz), 7.33 (s, 1H, ArH), 7.46 (d, 1H, ArH, *J* = 8 Hz), 8.09 (d, 2H, ArH, *J* = 8.4 Hz), 8.43 (d, 2H, ArH, *J* = 8.4 Hz), 8.76 (s, 1H, NH, D_2O-exchangeable), 9.34 (s, 1H, pyrazole-5-CH), 12.64 (s, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6): δ 113.12, 115.10, 116.17, 118.85, 119.93, 121.20, 122.44, 124.60, 126.31, 126.76, 126.91, 128.23, 129.42, 130.11, 135.06, 139.66, 141.41, 142.09, 142.77, 143.34, 144.56, 155.54; MS: *m/z* 477 (M^+); $C_{24}H_{14}F_3N_5OS$ (477.46): Anal. Calcd: C, 60.37; H, 2.96; N, 14.67; S, 6.72. Found C, 60.31; H, 2.90; N, 14.62; S, 6.68%.

4.2.4. Synthesis of 4,4'-di(10H-phenothiazine-2-carbonyl)-1,1'-diphenyl-1H,1'H-3,3'-bipyrazole (13)

***Method A*:** To a mixture of enaminone **2** (2.96 g, 10 mmol) and the appropriate *N*,*N'*-diphenyloxalodihydrazonoyl dichloride (**11**) (1.54 g, 5 mmole) in dioxane (15 ml), an equivalent amount of triethylamine (10 mmol) was added. The total mixture was placed in a process vial and was irradiated by microwaves with a power of 50 W to reach a reaction temperature of 70 ^{o}C under auto generated pressure. The vial was exposed to microwaves for the required time to complete the reaction. The progress of the reaction was monitored by TLC (eluent; ethylacetate: chloroform). Upon completion of the reaction, the solvent was evaporated under reduced pressure to obtain the solid product in (3.28 g, 89% yield). The obtained solid product was crystallized using ethanol to afford the corresponding bipyrazole derivative **13**.

***Method B*:** This process was performed with stirring at room temperature on the same scale described above for the microwave reaction. The reactants were stirred in dioxane for 24 h until the starting materials were no longer detectable

by TLC. The product was obtained and purified (2.43 g, 66% yield) as described above in microwave reaction .

Brown solid, mp 152-154 °C; IR (KBr) ν/cm^{-1}: 3394 (NH), 1651 (CO), 1590 (C=N); ^{1}H NMR (DMSO`-d_6): δ 6.61 (d, 1H, ArH, *J* = 8 Hz), 6.76 (t, 1H, ArH, *J* = 8 Hz), 6.91 (d, 1H, ArH, *J* = 8 Hz), 6.98-7.03 (m, 2H, ArH), 7.08 (s, 1H, ArH), 7.18 (d, 1H, ArH, *J* = 8 Hz), 7.47 (t, 1H, ArH, *J* = 7.6 Hz), 7.60 (t, 2H, ArH, *J* = 7.6 Hz), 8.00 (d, 2H, ArH, *J* = 8 Hz), 8.74 (s, 1H, NH, D_2O-exchangeable), 9.03 (s, 1H, pyrazole-5-CH); ^{13}C NMR (DMSO-d_6): δ 114.55, 114.98, 115.56, 119.85, 122.68, 123.19, 123.24, 124.19, 126.65, 126.74, 128.49, 130.34, 131.66, 136.99, 137.08, 139.06, 142.56, 142.63, 143.42, 195.34; MS: M^+ (736); $C_{44}H_{28}N_6O_2S_2$ (736.86): Anal. Calcd: C, 71.72; H, 3.83**,** N, 11.41; S, 8.70. Found C, 71.66; H, 3.78; N, 11.39; S, 8.62%.

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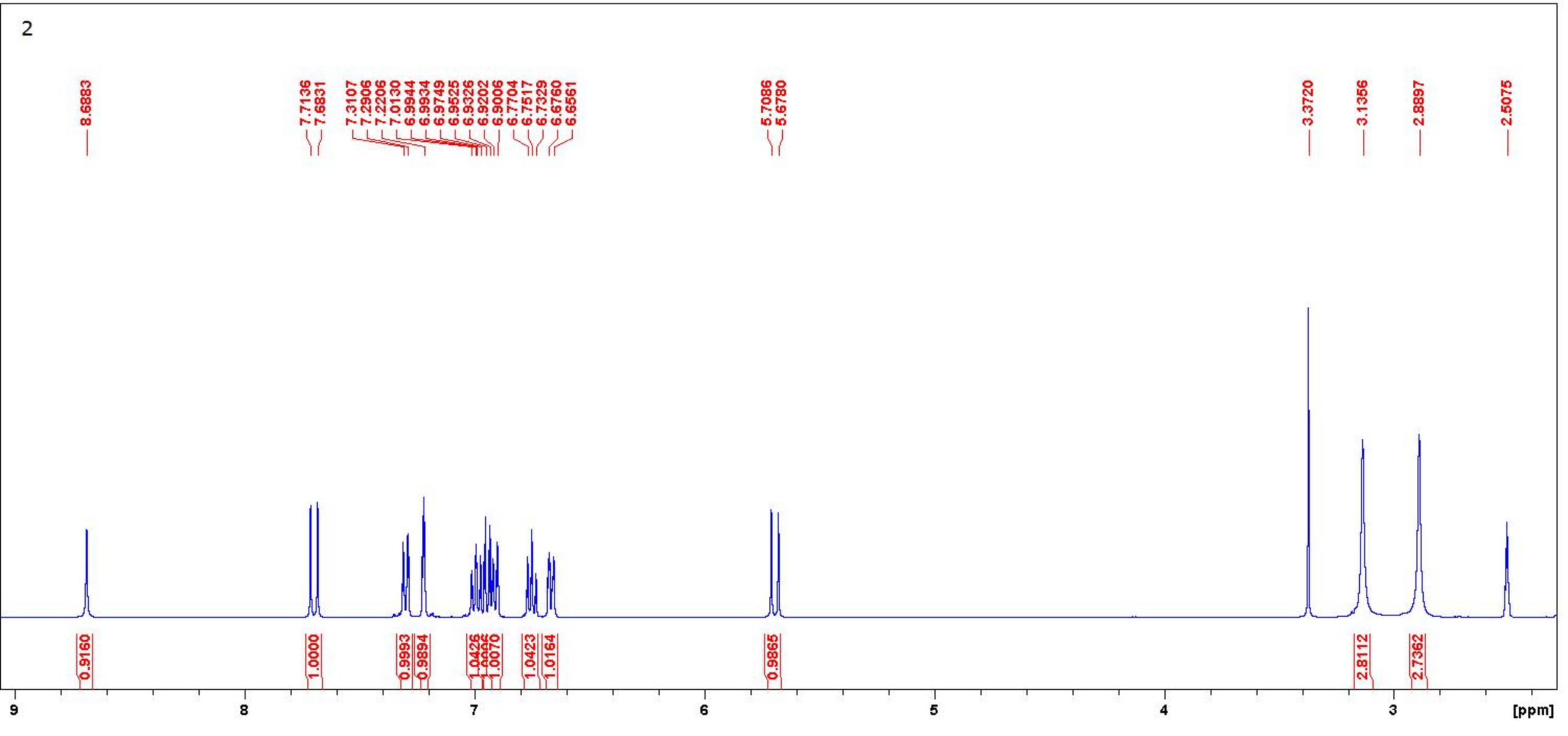
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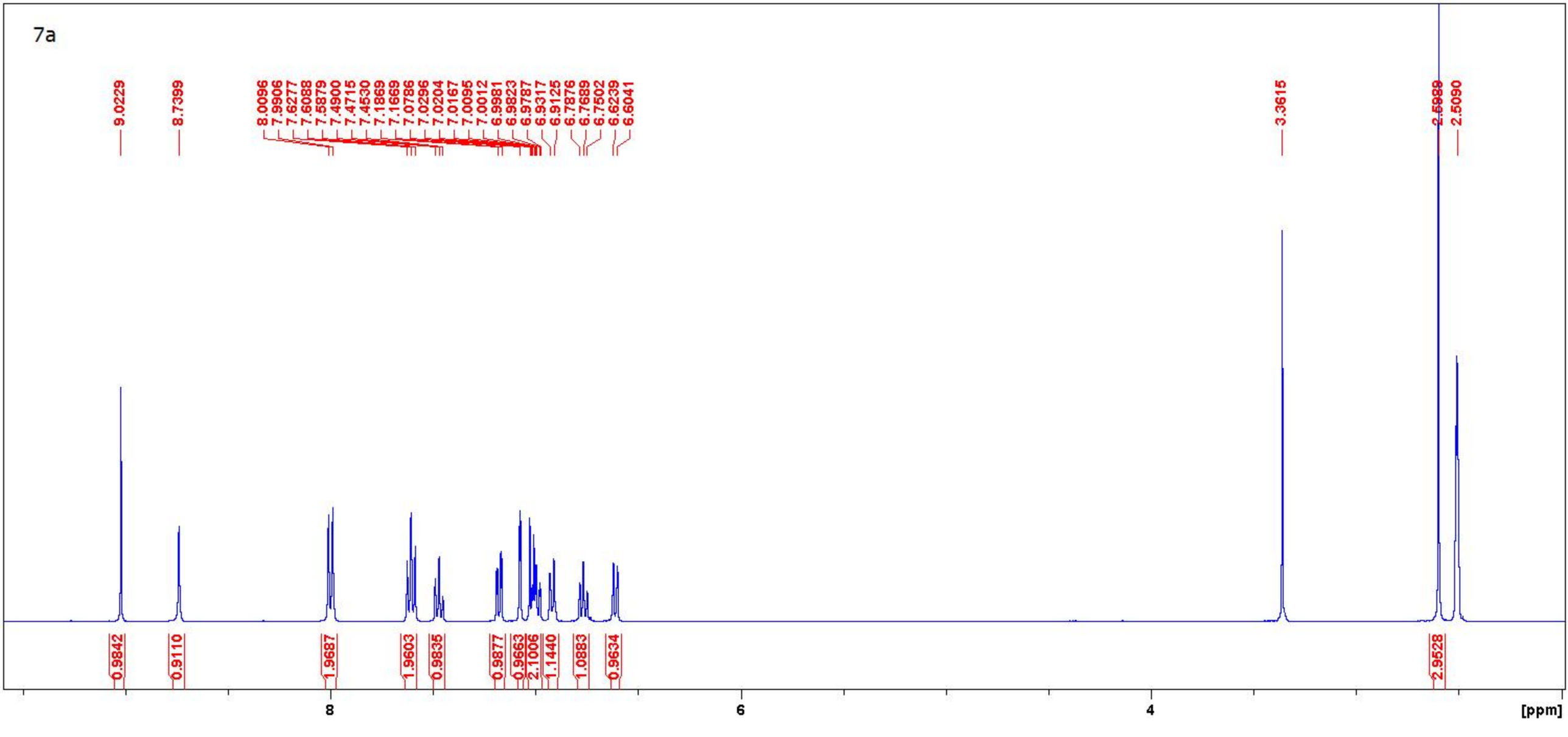
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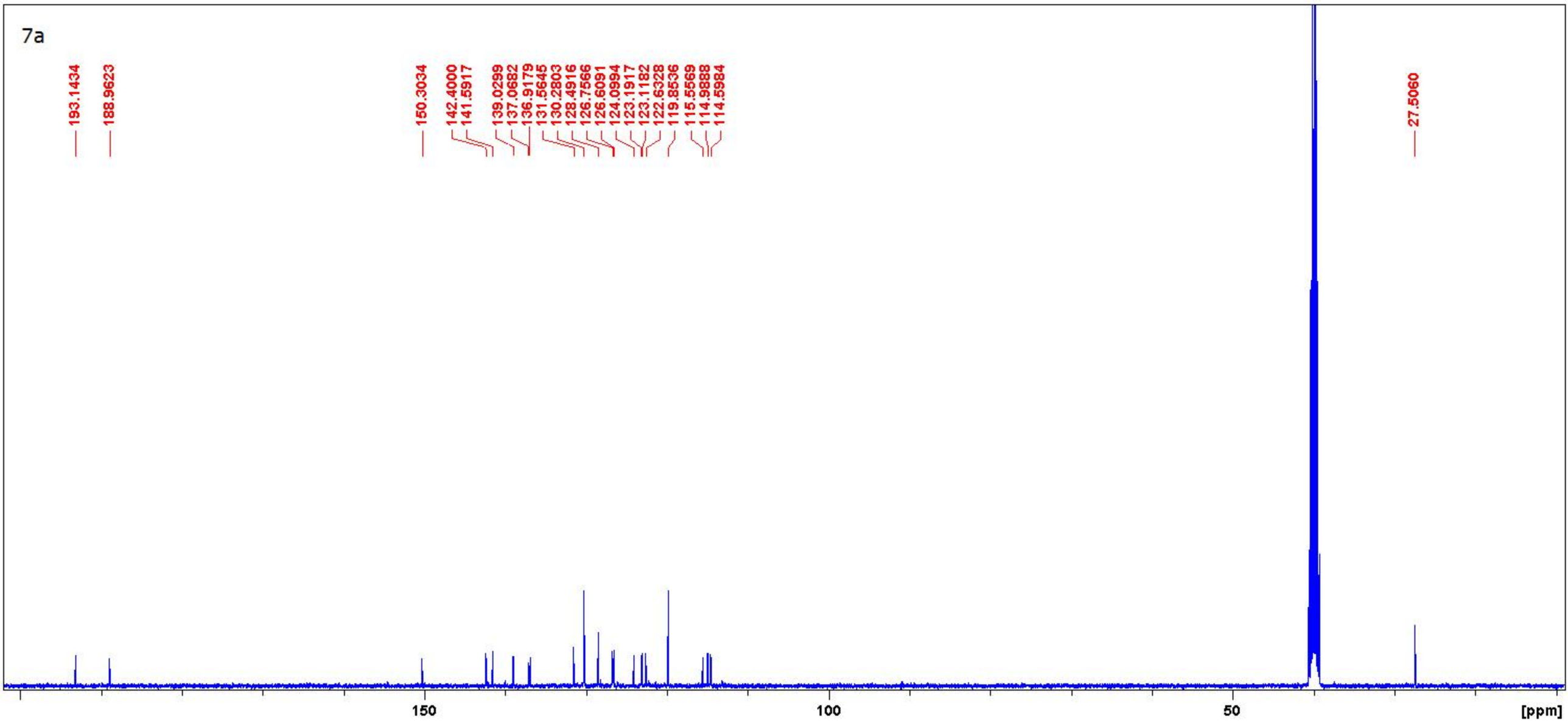
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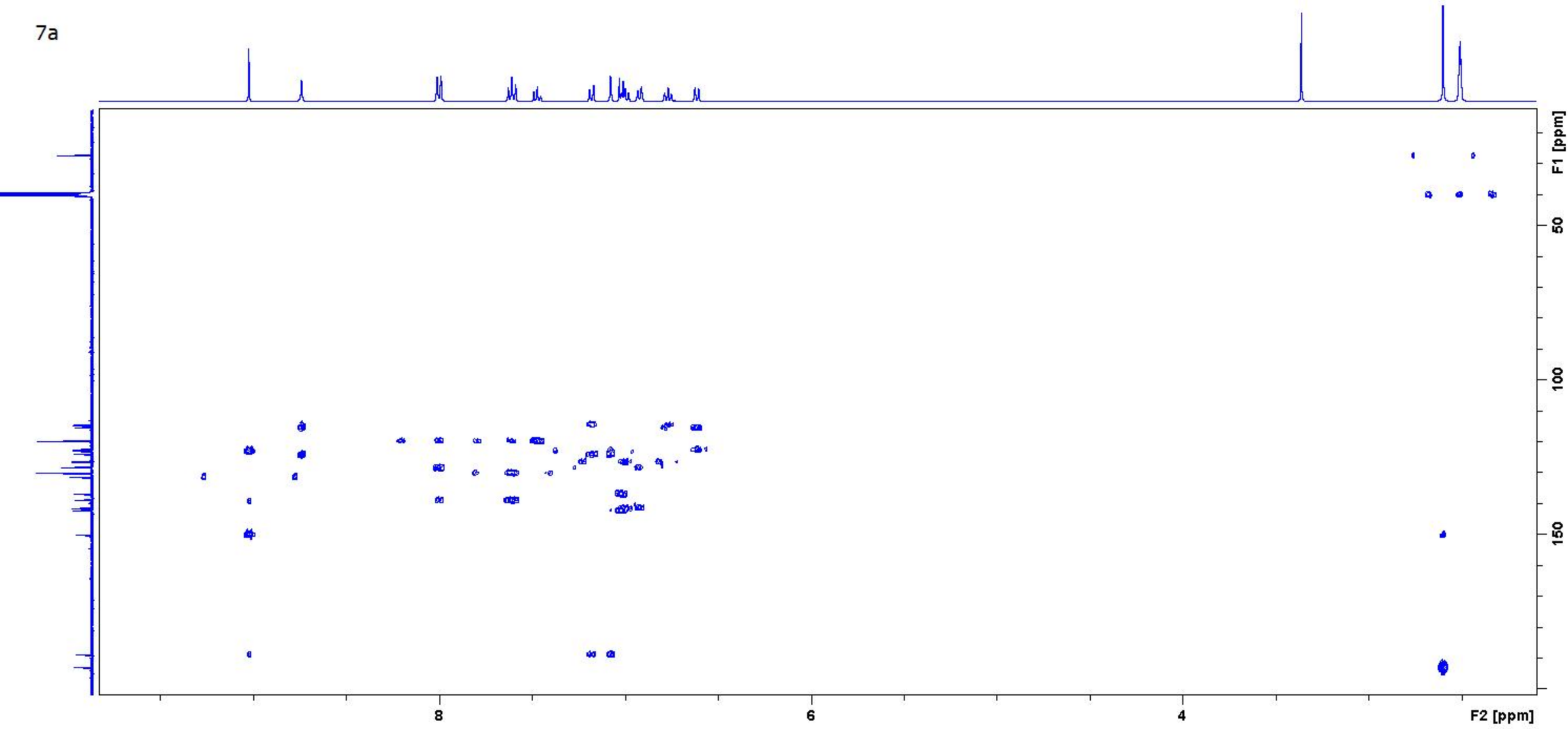
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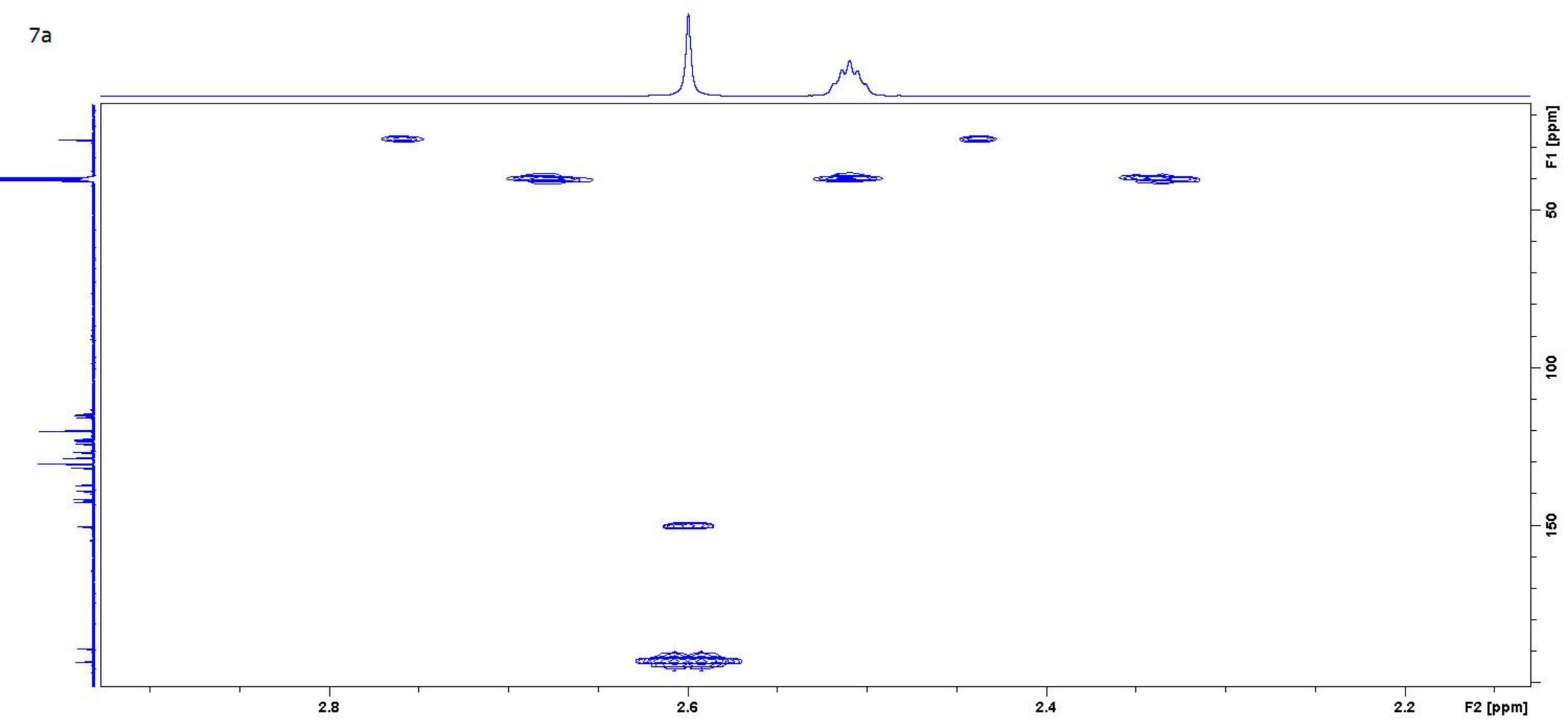

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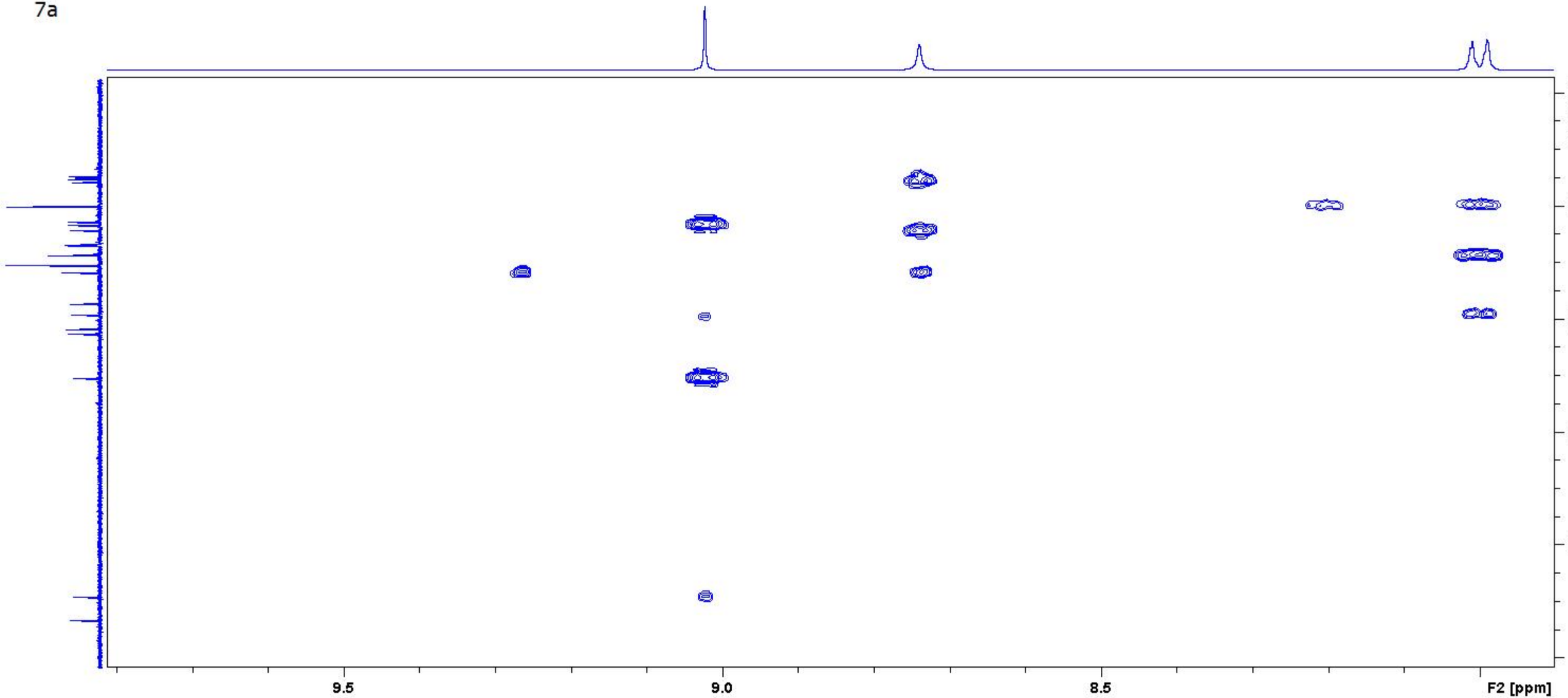

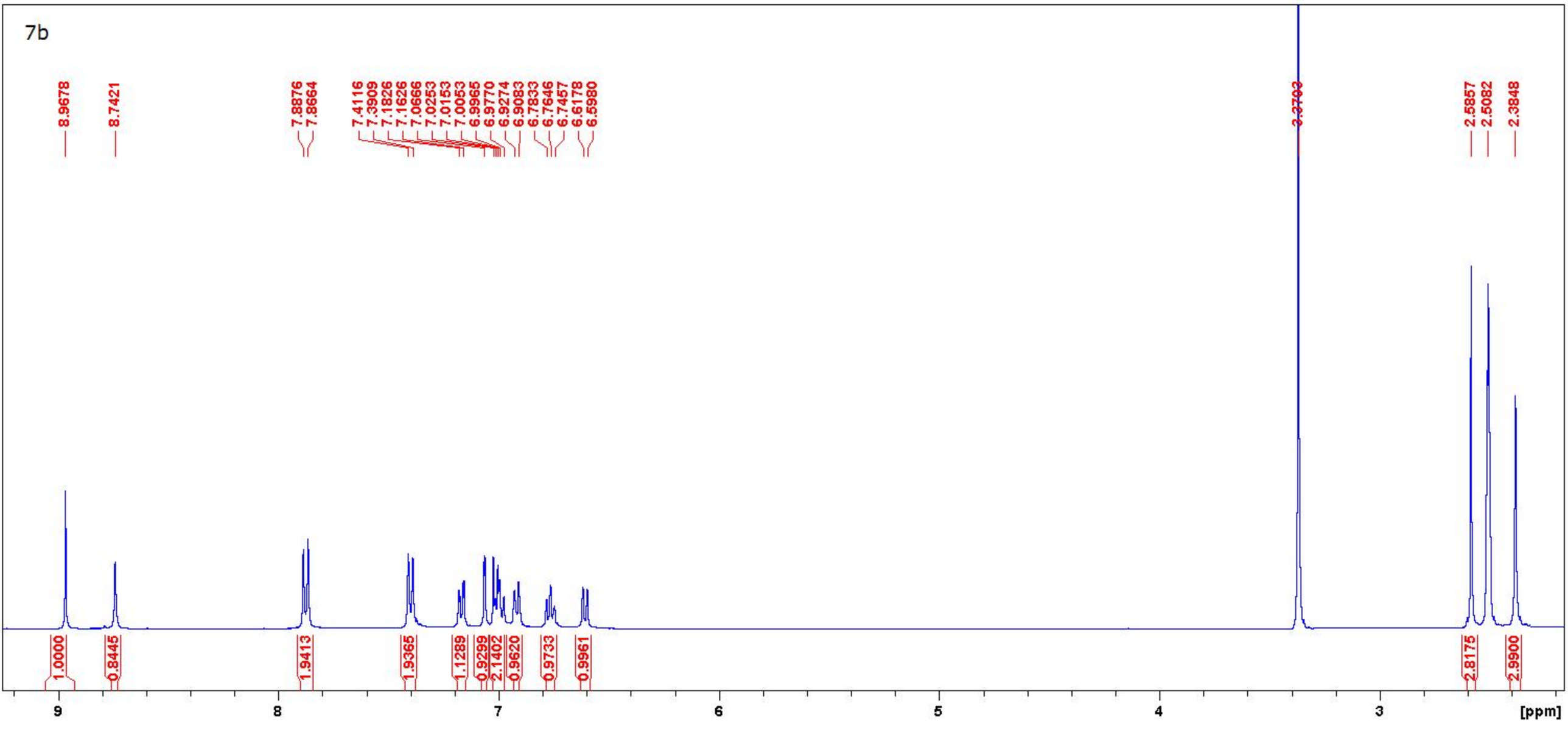
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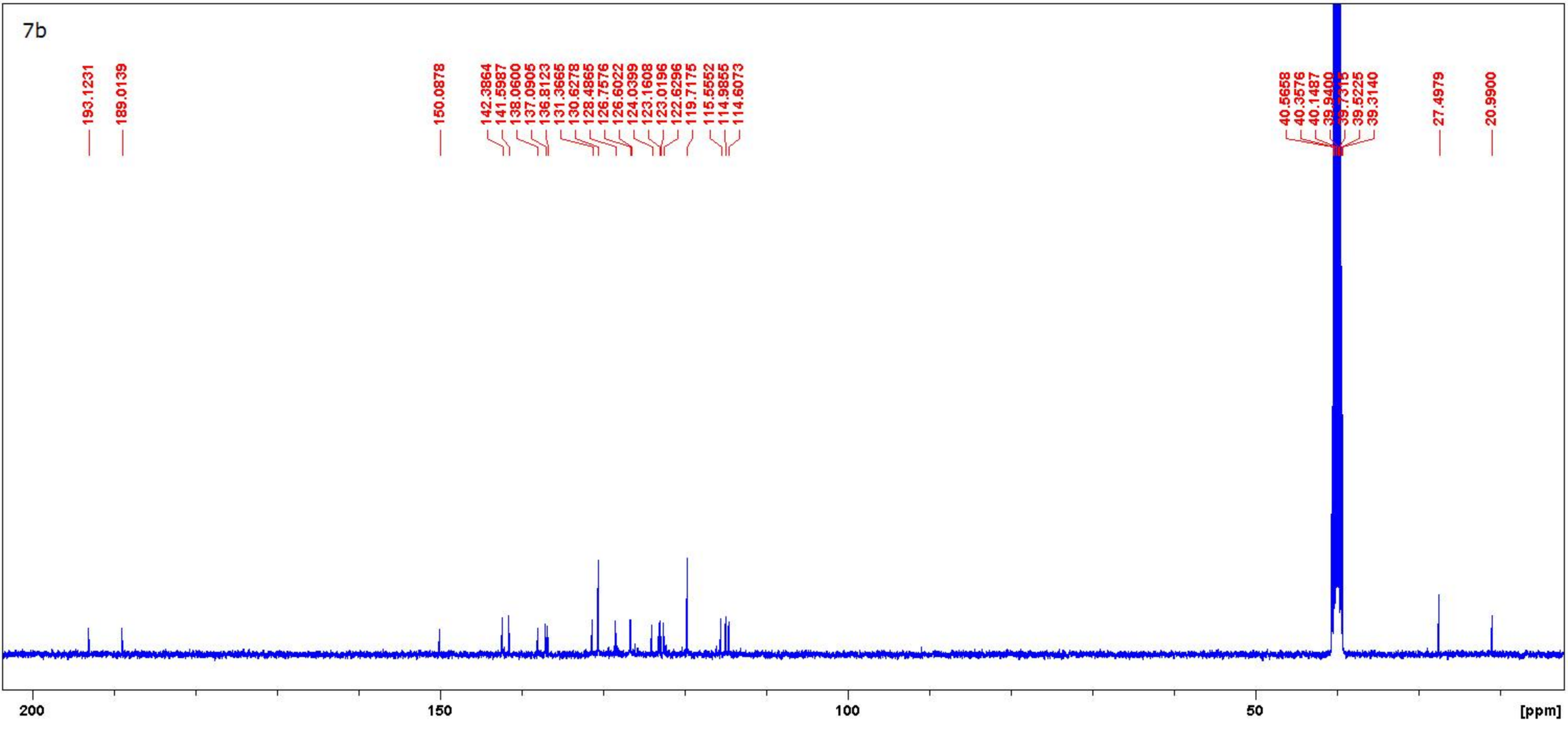
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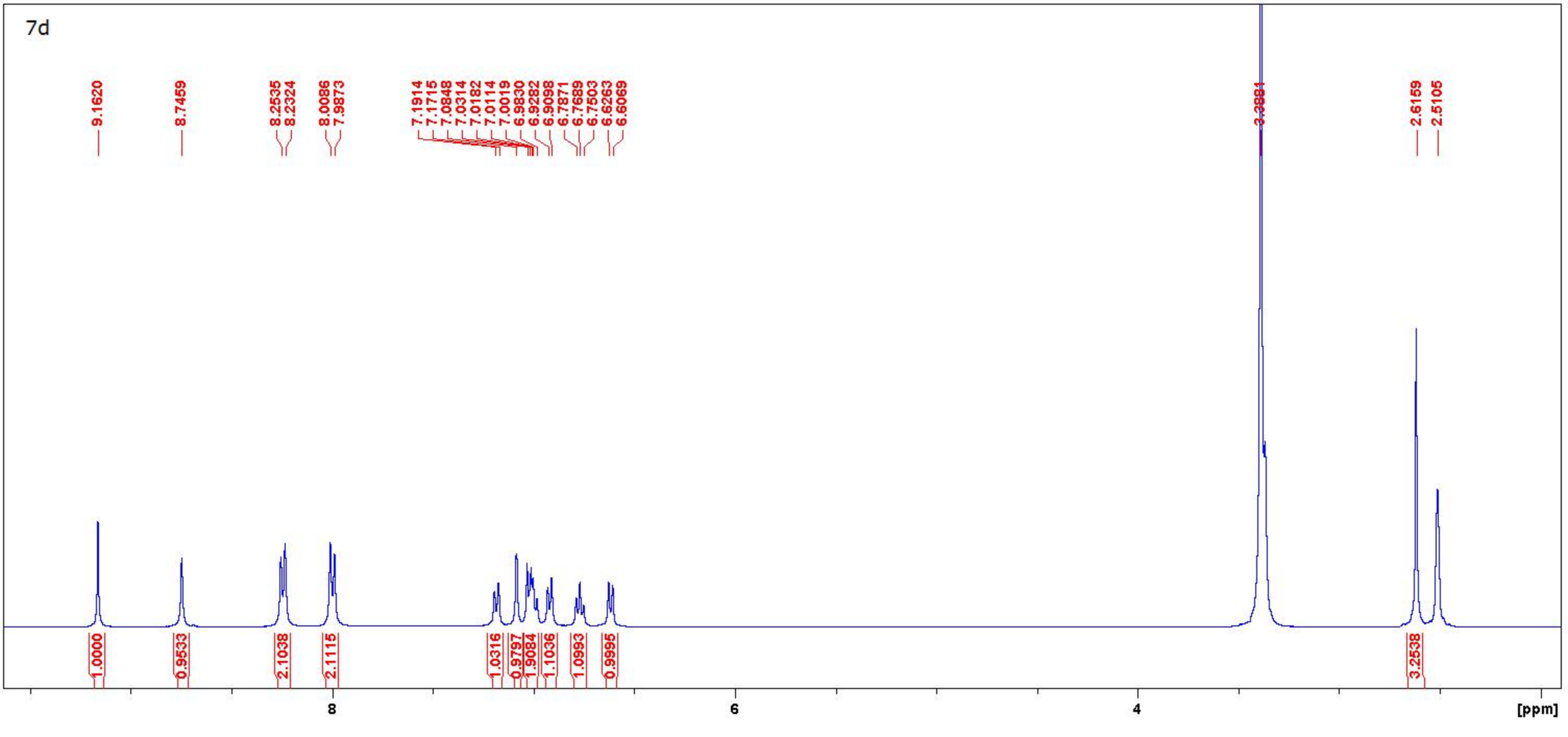
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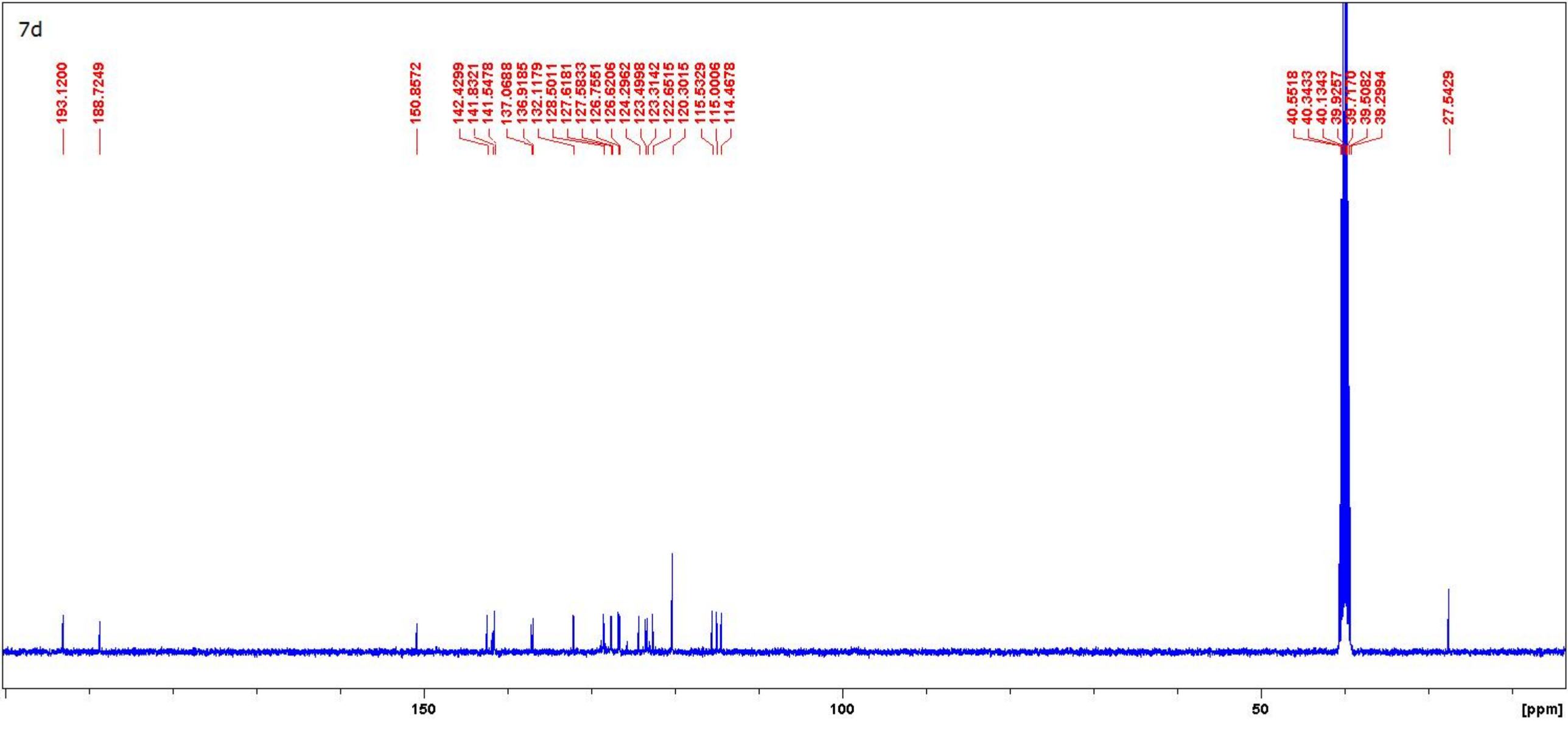
7d
193.1200
188.7249
150.8572
142.4299
141.8321
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137.0688
136.9185
132.1179
128.5011
127.6181
127.5833
126.7551
126.6206
124.2962
123.4998
123.3142
122.6515
120.3015
115.5329
115.0006
114.4678
40.5518
40.3433
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39.9257
39.7170
39.5082
39.2994
27.5429
150
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50
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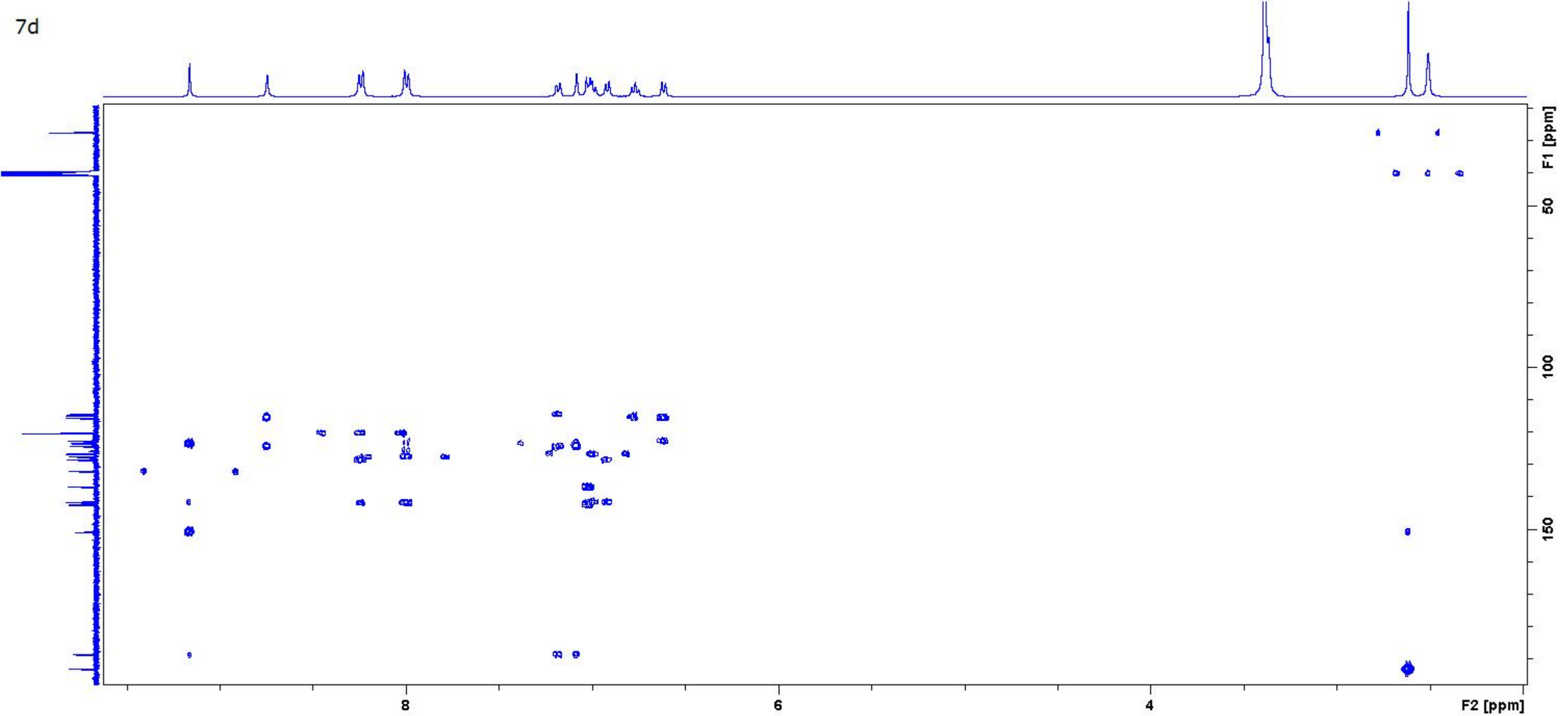
7d



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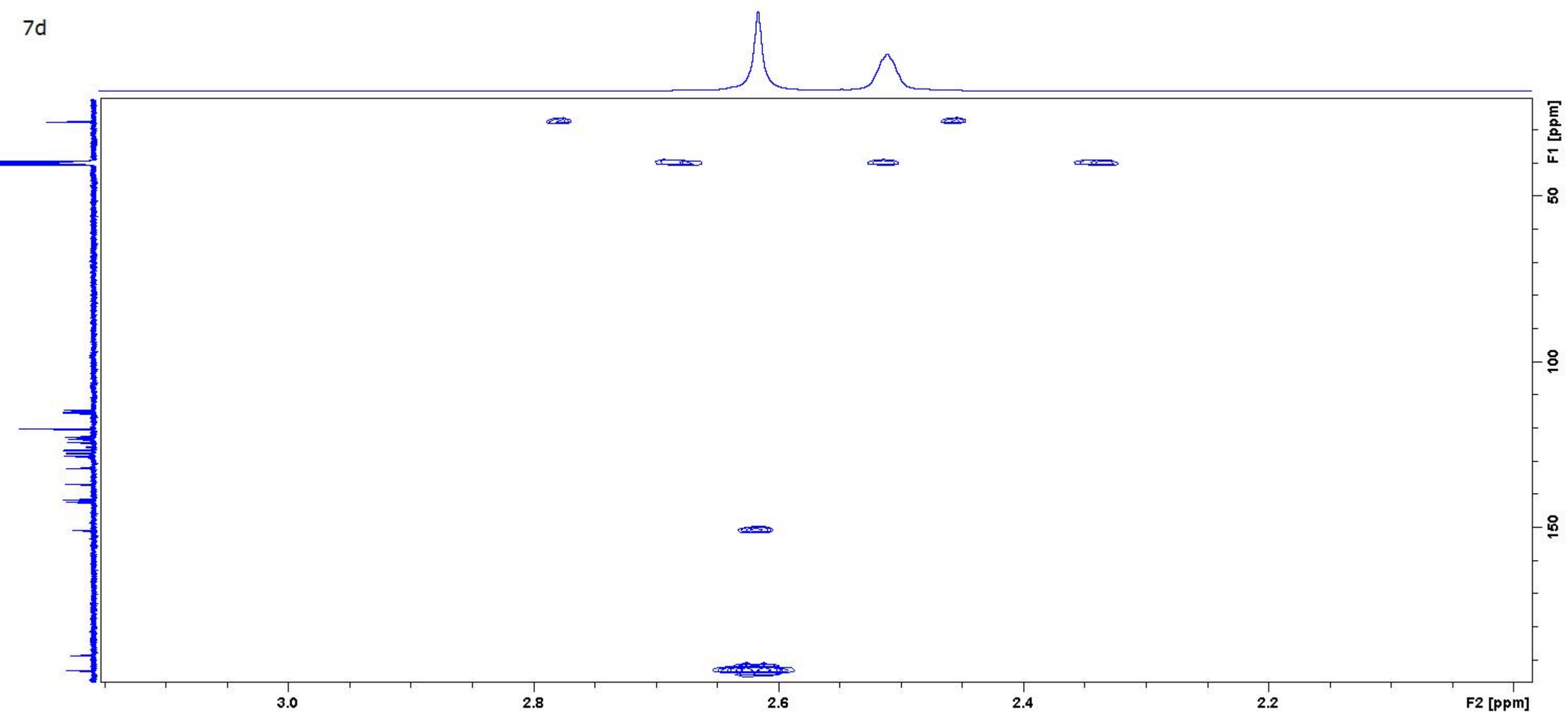
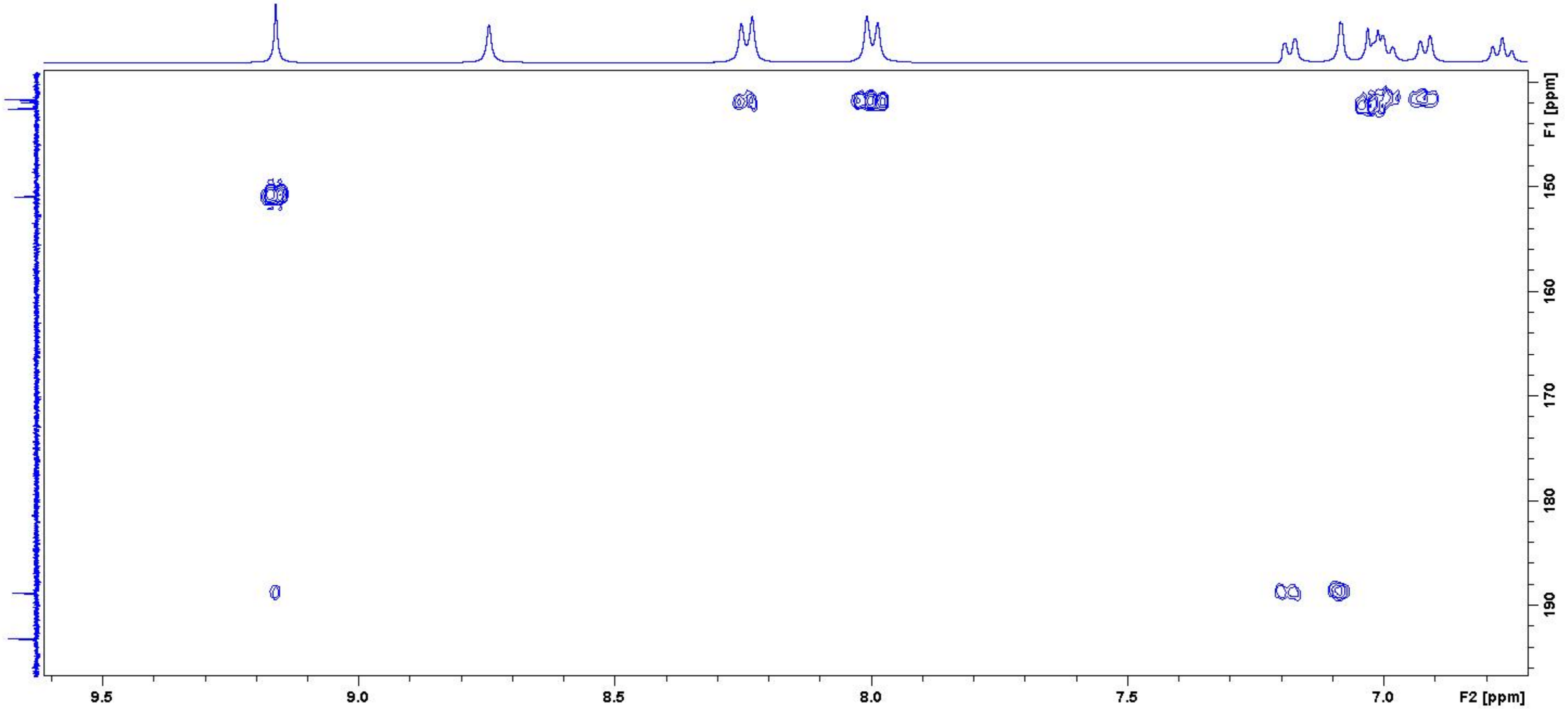
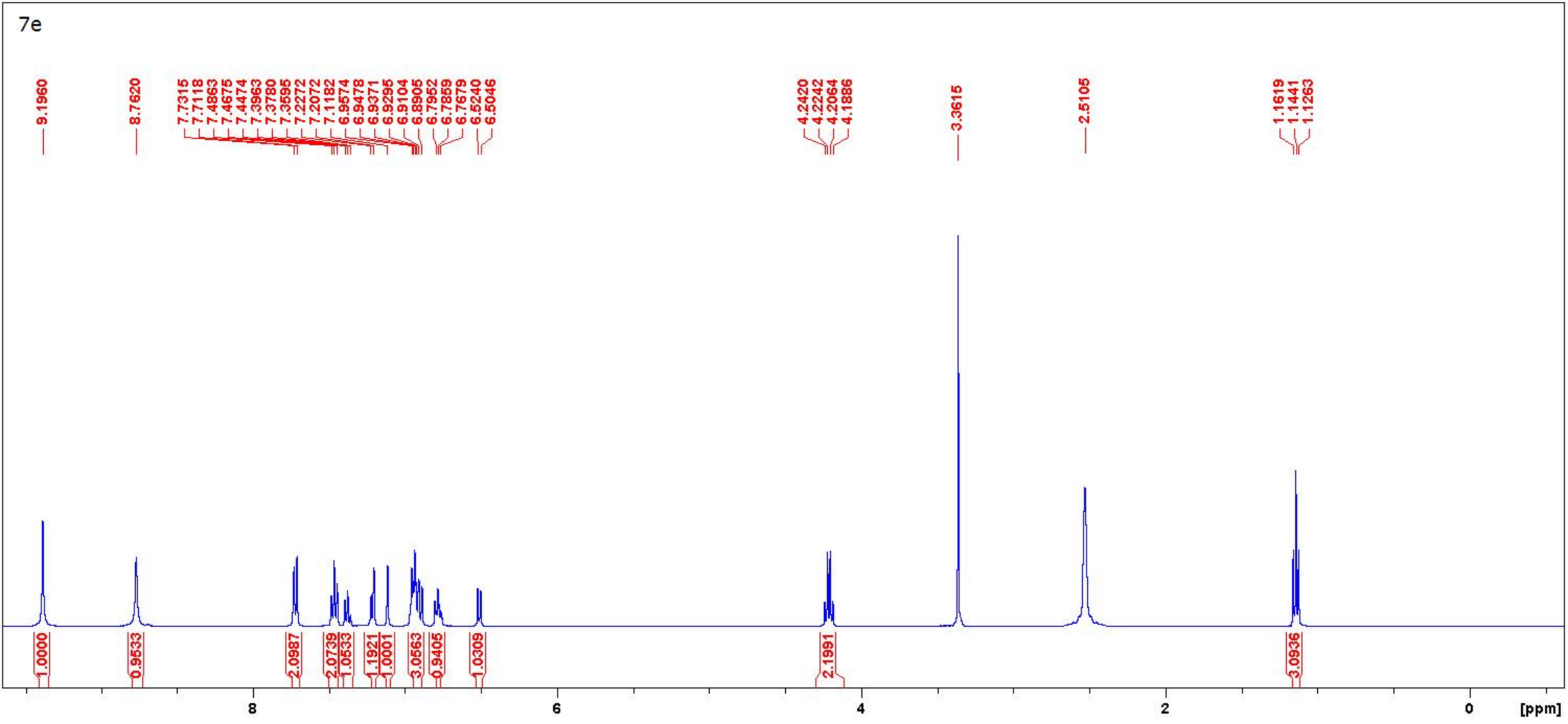


7d



7e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7.4863
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7.3780
7.3595
7.2272
7.2072
7.1182
6.9574
6.9478
6.9371
6.9295
6.9104
6.8905
6.7952
6.7859
6.7679
6.5240
6.5046
4.2420
4.2242
4.2064
4.1886
3.3615
2.5105
1.1619
1.1441
1.1263
1.0000
0.9533
2.0987
2.0739
1.0533
1.1921
1.0001
3.0563
0.9405
1.0309
2.1991
3.0936
8
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4
2
0
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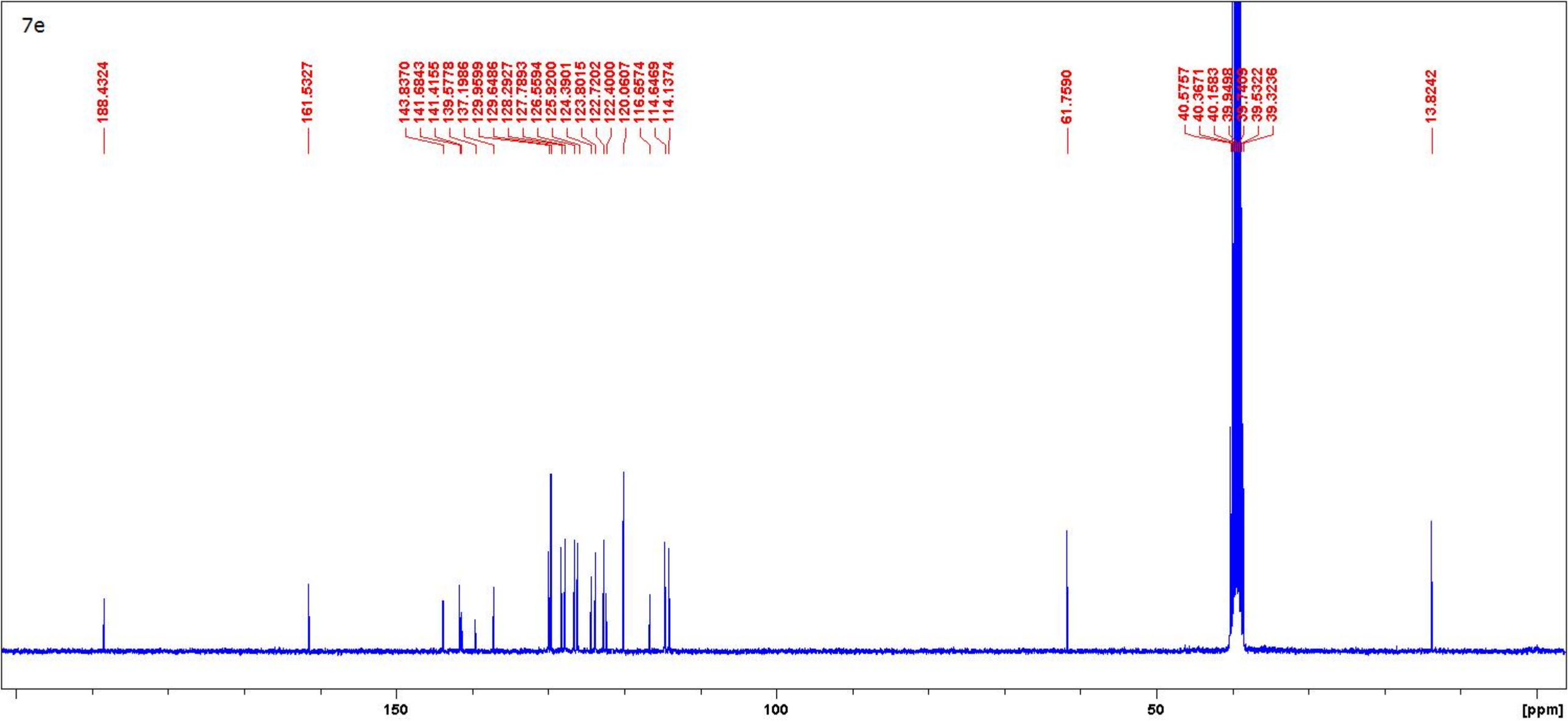
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188.4324
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141.6843
141.4155
139.5778
137.1986
129.9599
129.6486
128.2927
127.7893
126.5594
125.9200
124.3901
123.8015
122.7202
122.4000
120.0607
116.6574
114.6469
114.1374
61.7590
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40.3671
40.1583
39.9498
39.7403
39.5322
39.3236
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150
100
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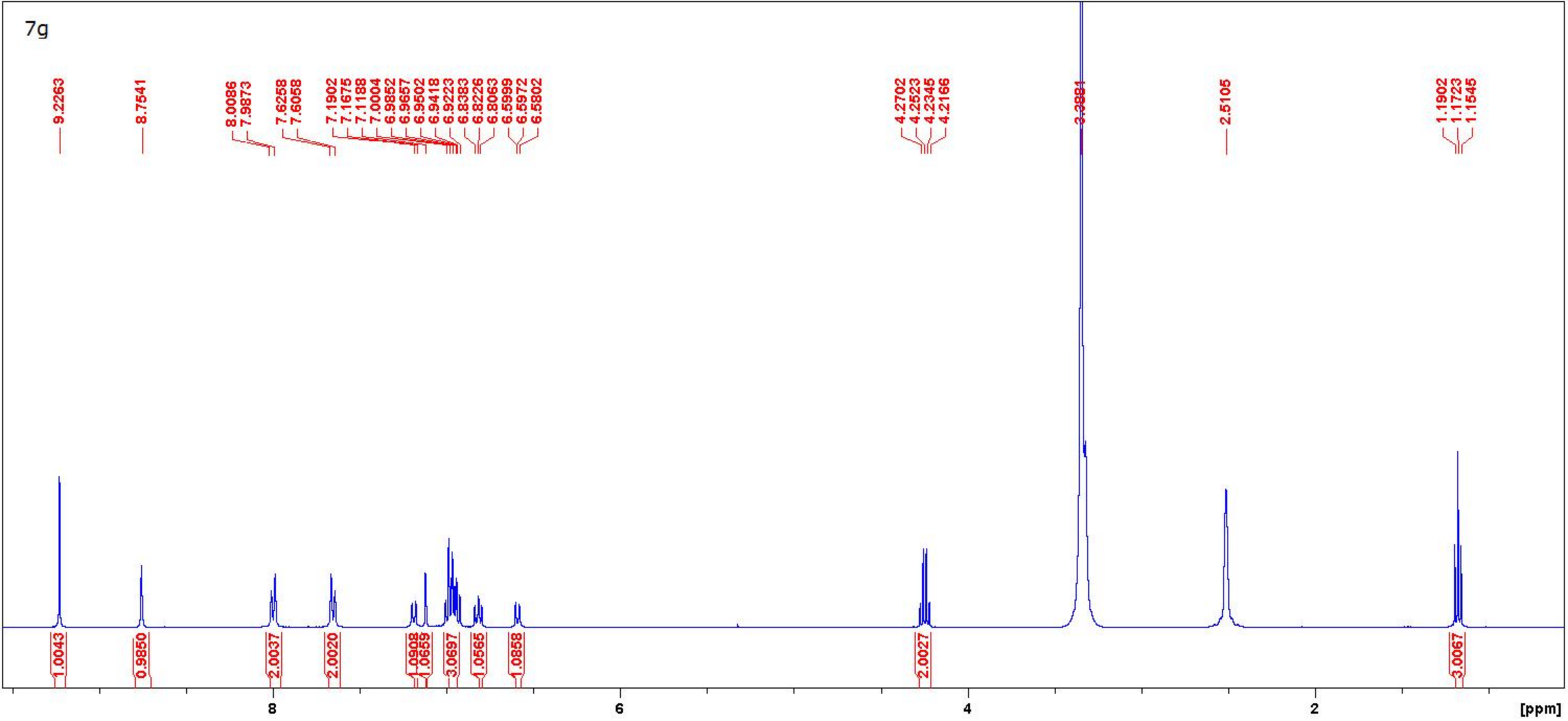
7g
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8.0086
7.9873
7.6258
7.6058
7.1902
7.1675
7.1188
7.0004
6.9852
6.9657
6.9502
6.9418
6.9223
6.8383
6.8226
6.8063
6.5999
6.5972
6.5802
4.2702
4.2523
4.2345
4.2166
3.3881
2.5105
1.1902
1.1723
1.1545
1.0043
0.9850
2.0037
2.0020
1.0908
1.0659
3.0697
1.0565
1.0858
2.0027
3.0067
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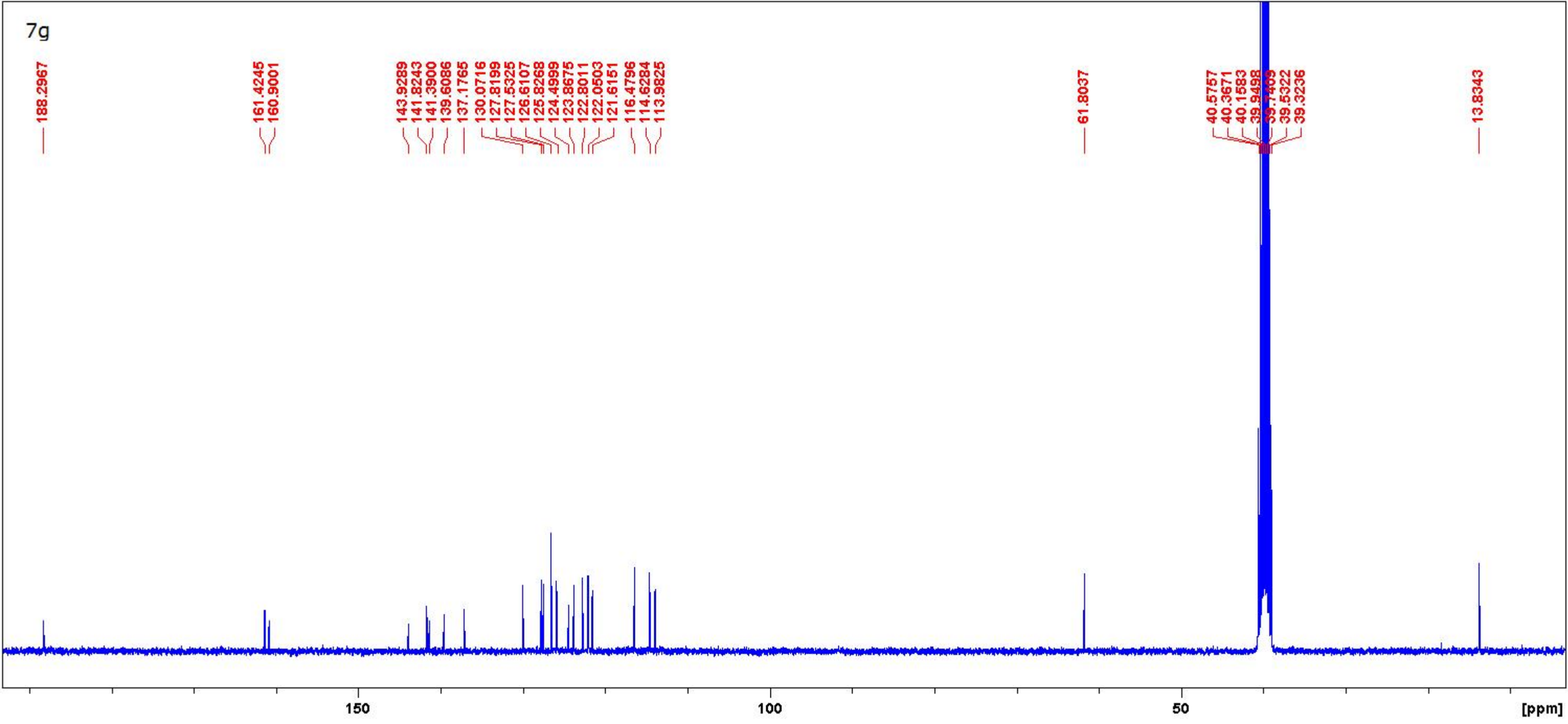
6
4
2
[ppm]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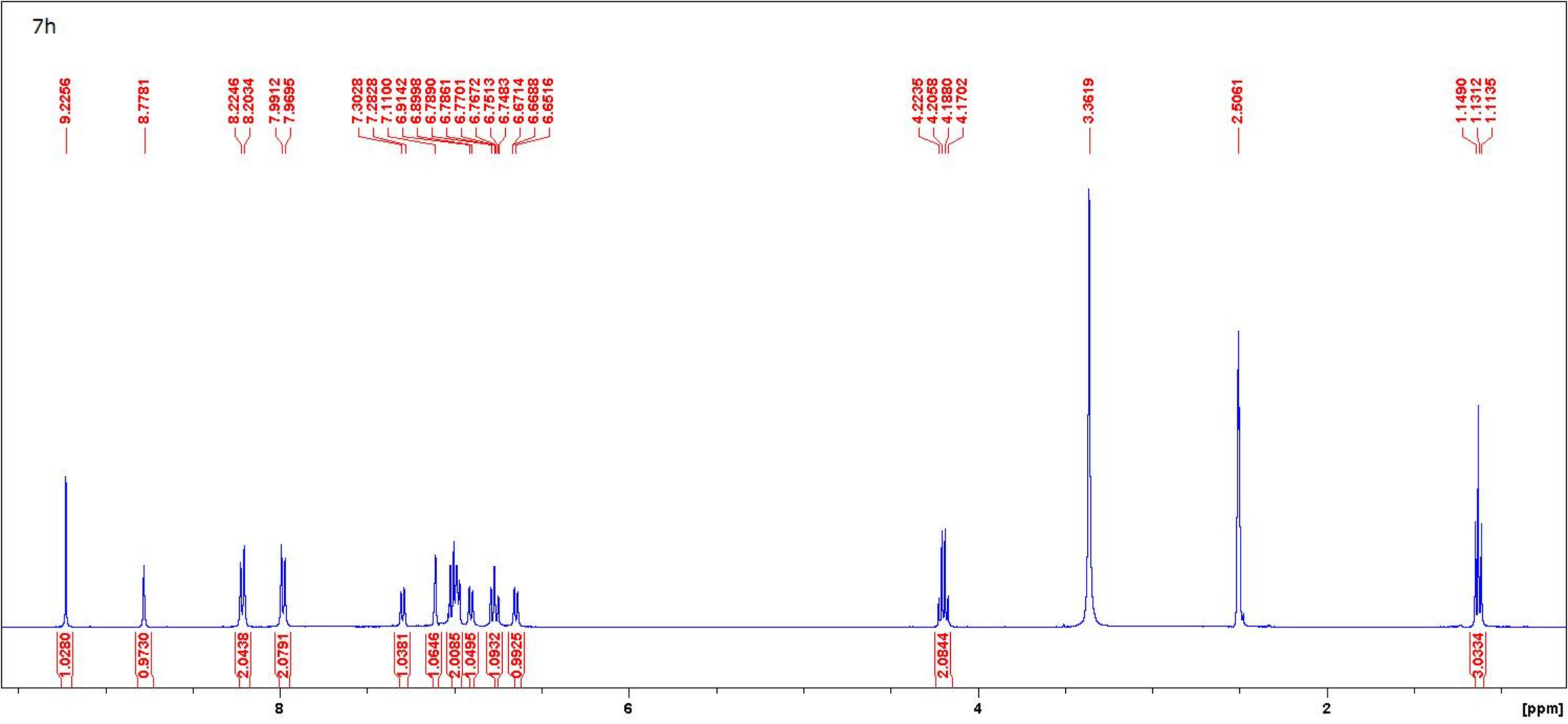
143.9289
141.8243
141.3900
139.6086
137.1765
130.0716
127.8199
127.5325
126.6107
125.8268
124.4999
123.8675
122.8011
122.0503
121.6151
116.4796
114.6284
113.9825
61.8037
40.5757
40.3671
40.1583
39.9498
39.7409
39.5322
39.3236
13.8343
150
100
50
[ppm]

7h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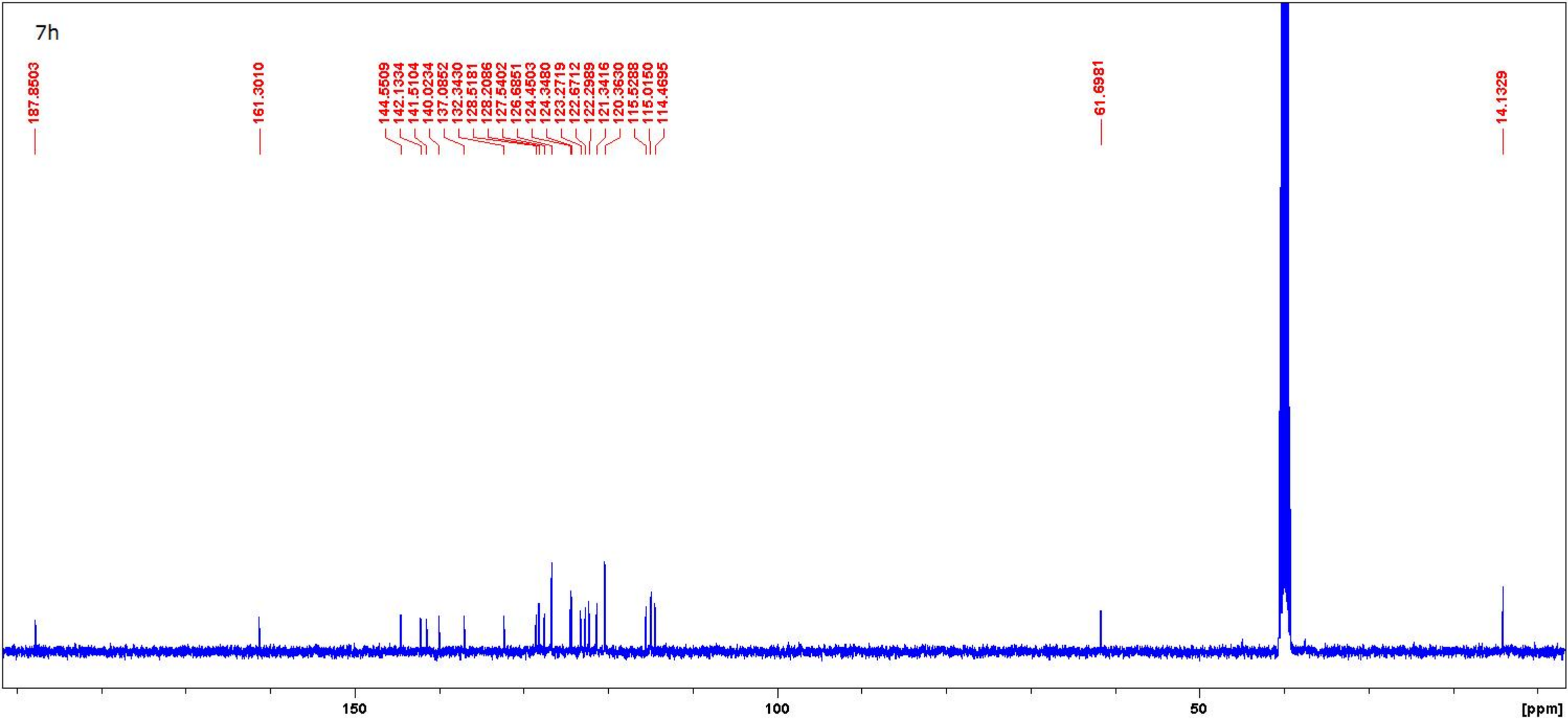
8.2246
8.2034
7.9912
7.9695
7.3028
7.2828
7.1100
6.9142
6.8998
6.7890
6.7861
6.7701
6.7672
6.7513
6.7483
6.6714
6.6688
6.6516
4.2235
4.2058
4.1880
4.1702
3.3619
2.5061
1.1490
1.1312
1.1135
1.0280
0.9730
2.0438
2.0791
1.0381
1.0646
2.0085
1.0495
1.0932
0.9925
2.0844
3.0334
8
6
4
2
[ppm]


7h
187.8503
161.3010
144.5509
142.1334
141.5104
140.0234
137.0852
132.3430
128.5181
128.2086
127.5402
126.6851
124.4503
124.3480
123.2719
122.6712
122.2989
121.3416
120.3630
115.5288
115.0150
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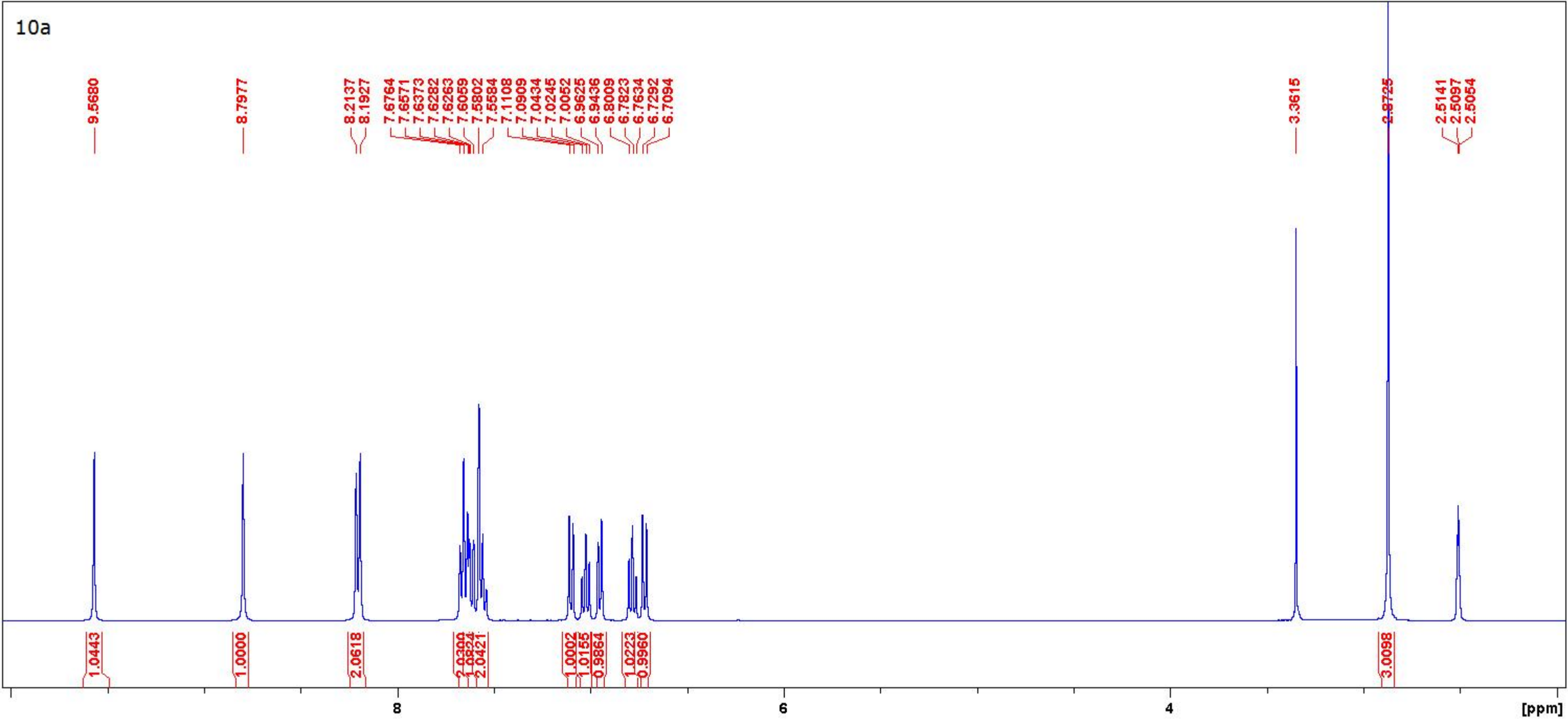
61.6981
14.1329
150
100
50
[ppm]


10a
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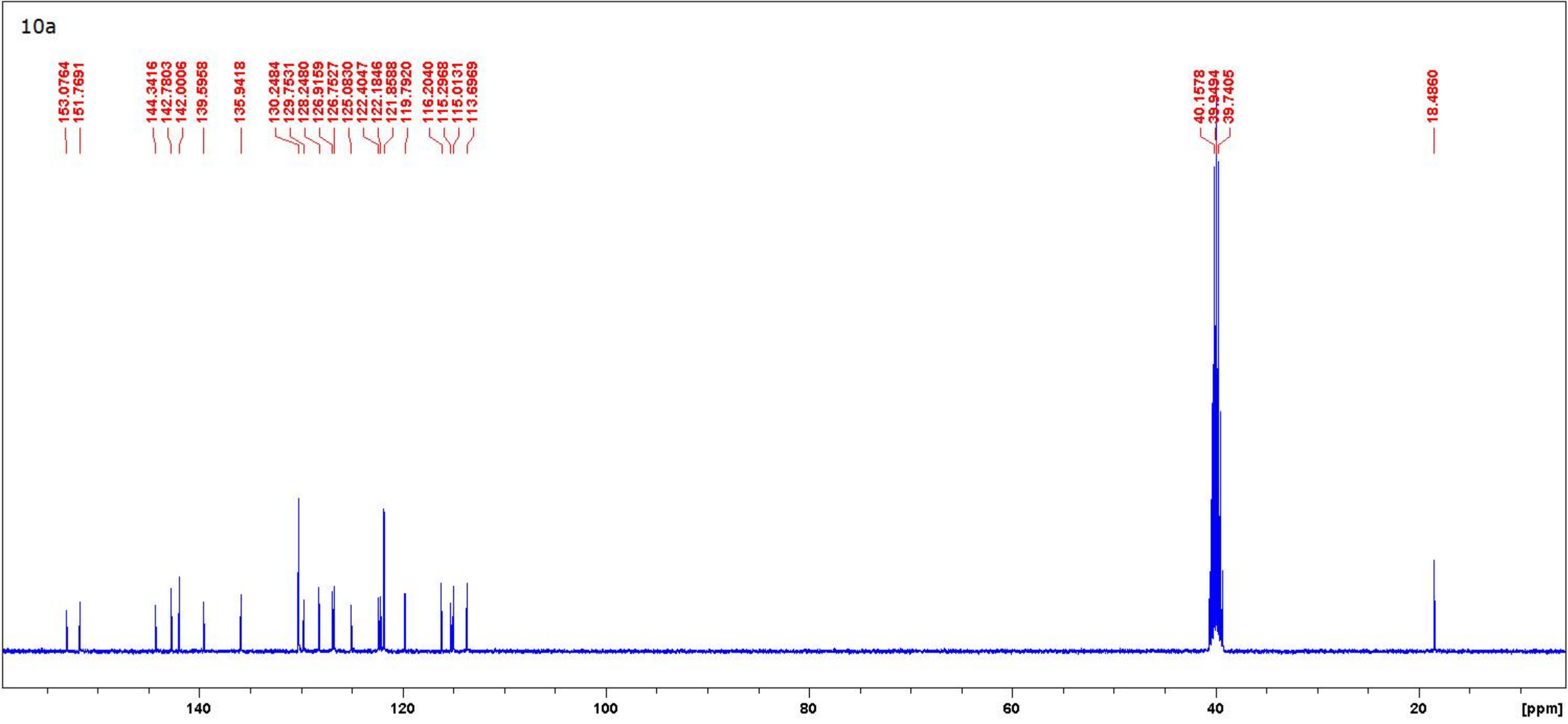
8.1927
7.6764
7.6571
7.6373
7.6282
7.6263
7.6059
7.5802
7.5584
7.1108
7.0909
7.0434
7.0245
7.0052
6.9625
6.9436
6.8009
6.7823
6.7634
6.7292
6.7094
3.3615
2.8725
2.5141
2.5097
2.5054
1.0443
1.0000
2.0618
2.0300
1.0824
2.0421
1.0002
1.0155
0.9864
1.0223
0.9960
3.0098
8
6
4
[ppm]


10a
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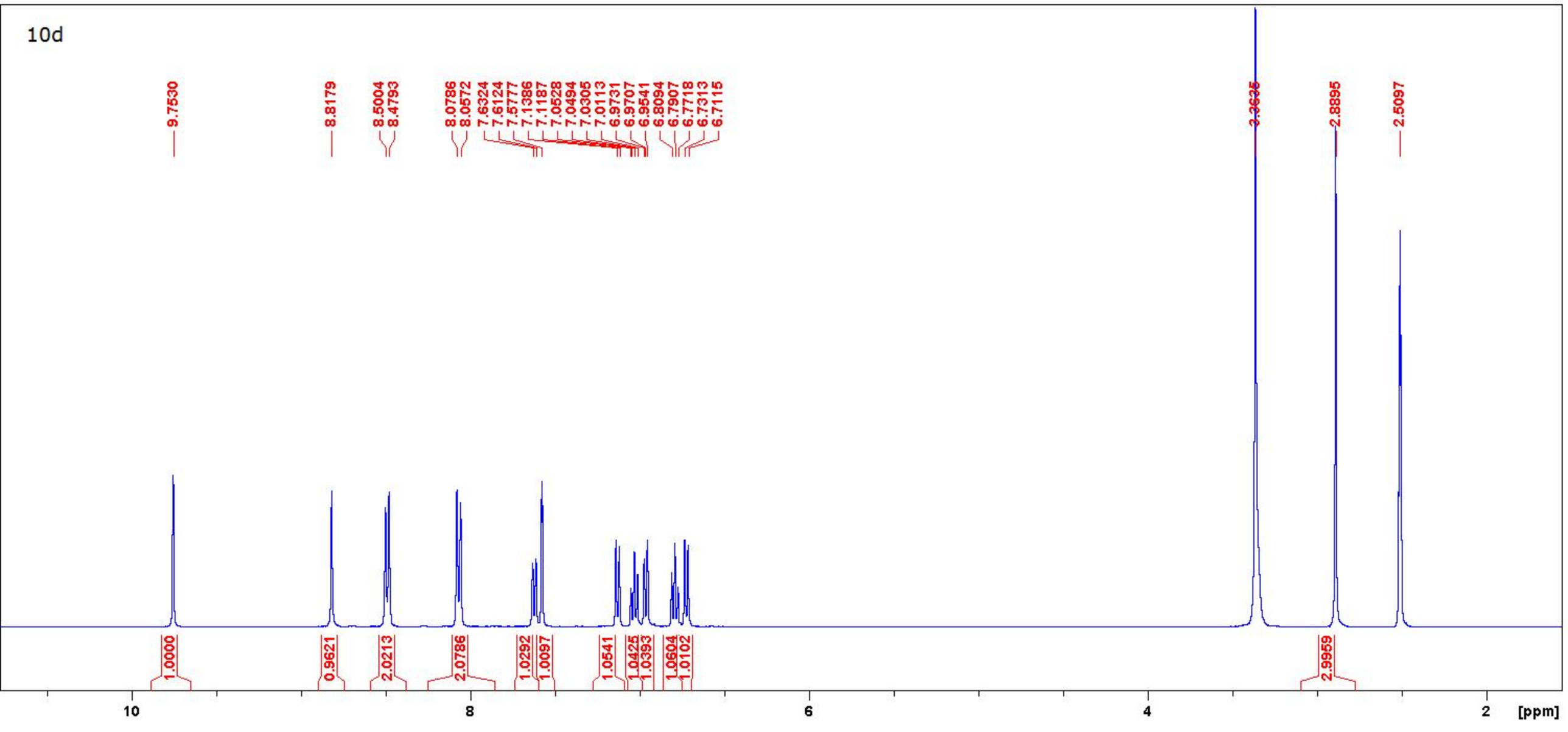
142.0006
139.5958
135.9418
130.2484
129.7531
128.2480
126.9159
126.7527
125.0830
122.4047
122.1846
121.8588
119.7920
116.2040
115.2968
115.0131
113.6969
40.1578
39.9494
39.7405
18.4860
140
120
100
80
60
40
20
[ppm]


10d
9.7530
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8.4793
8.0786
8.0572
7.6324
7.6124
7.5777
7.1386
7.1187
7.0528
7.0494
7.0305
7.0113
6.9731
6.9707
6.9541
6.8094
6.7907
6.7718
6.7313
6.7115
3.3635
2.8895
2.5097
1.0000
0.9621
2.0213
2.0786
1.0292
1.0097
1.0541
1.0425
1.0393
1.0604
1.0102
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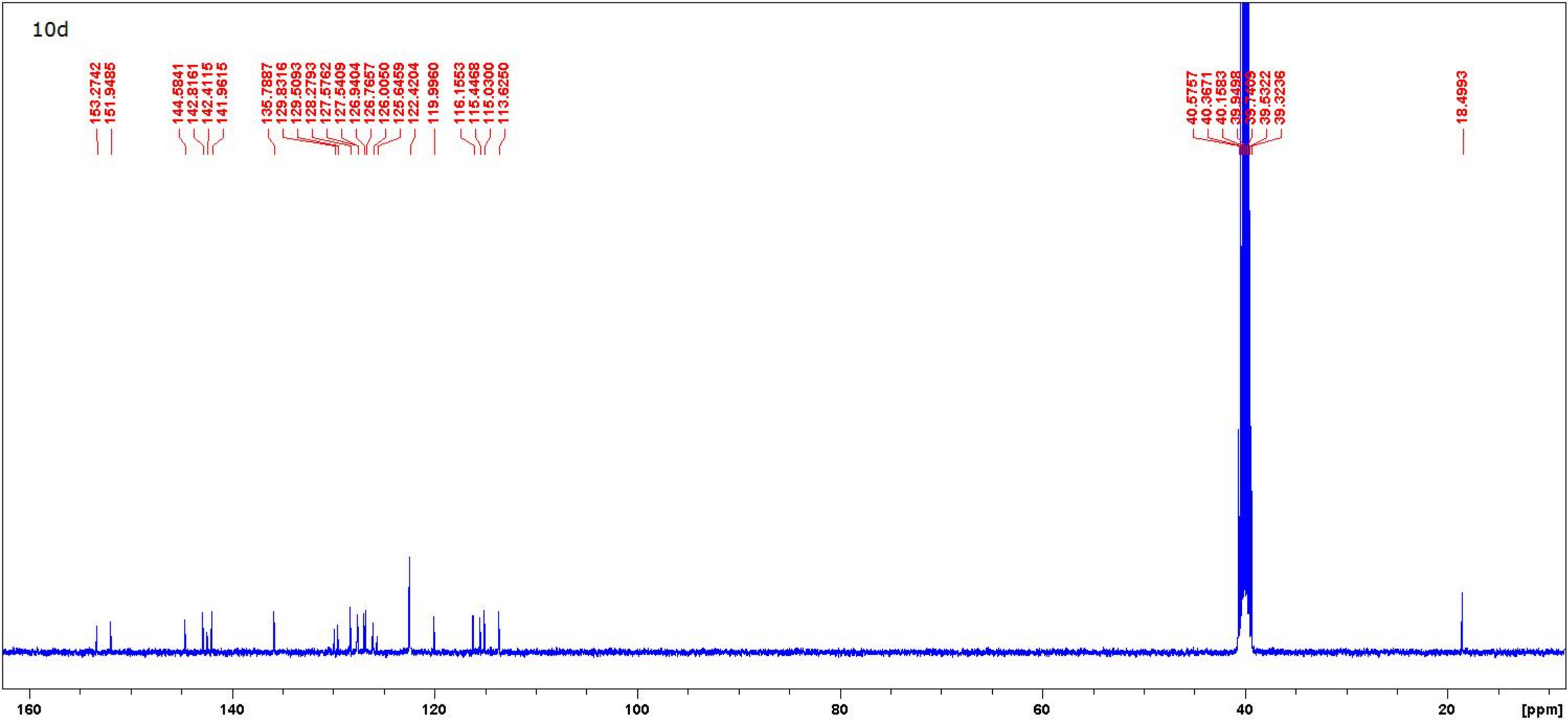
10
8
6
4
2
[ppm]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142.4115
141.9615
135.7887
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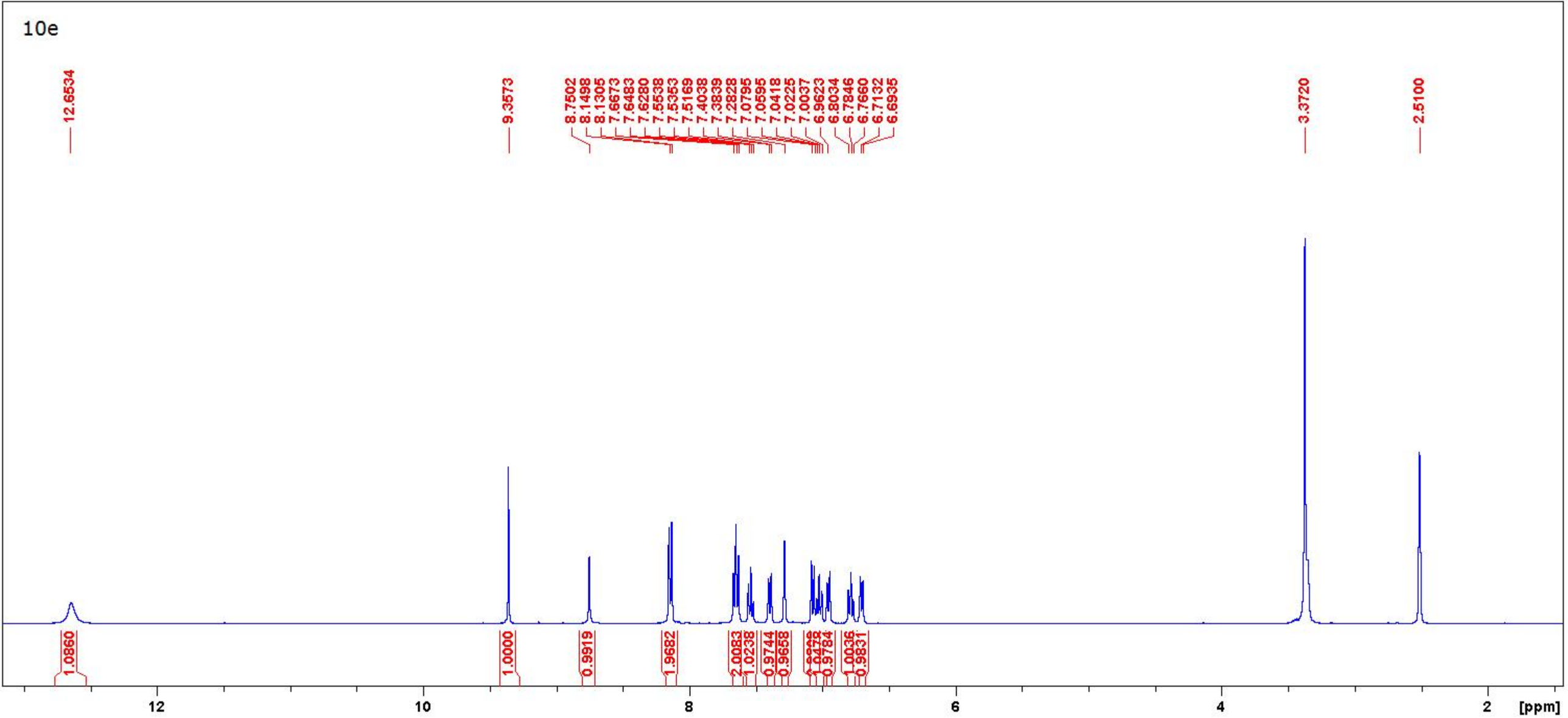
129.5093
128.2793
127.5762
127.5409
126.9404
126.7657
126.0050
125.6459
122.4204
119.9960
116.1553
115.4468
115.0300
113.6250
40.5757
40.3671
40.1583
39.9498
39.7409
39.5322
39.3236
18.4993
160
140
120
100
80
60
40
20
[ppm]


10e
12.6534
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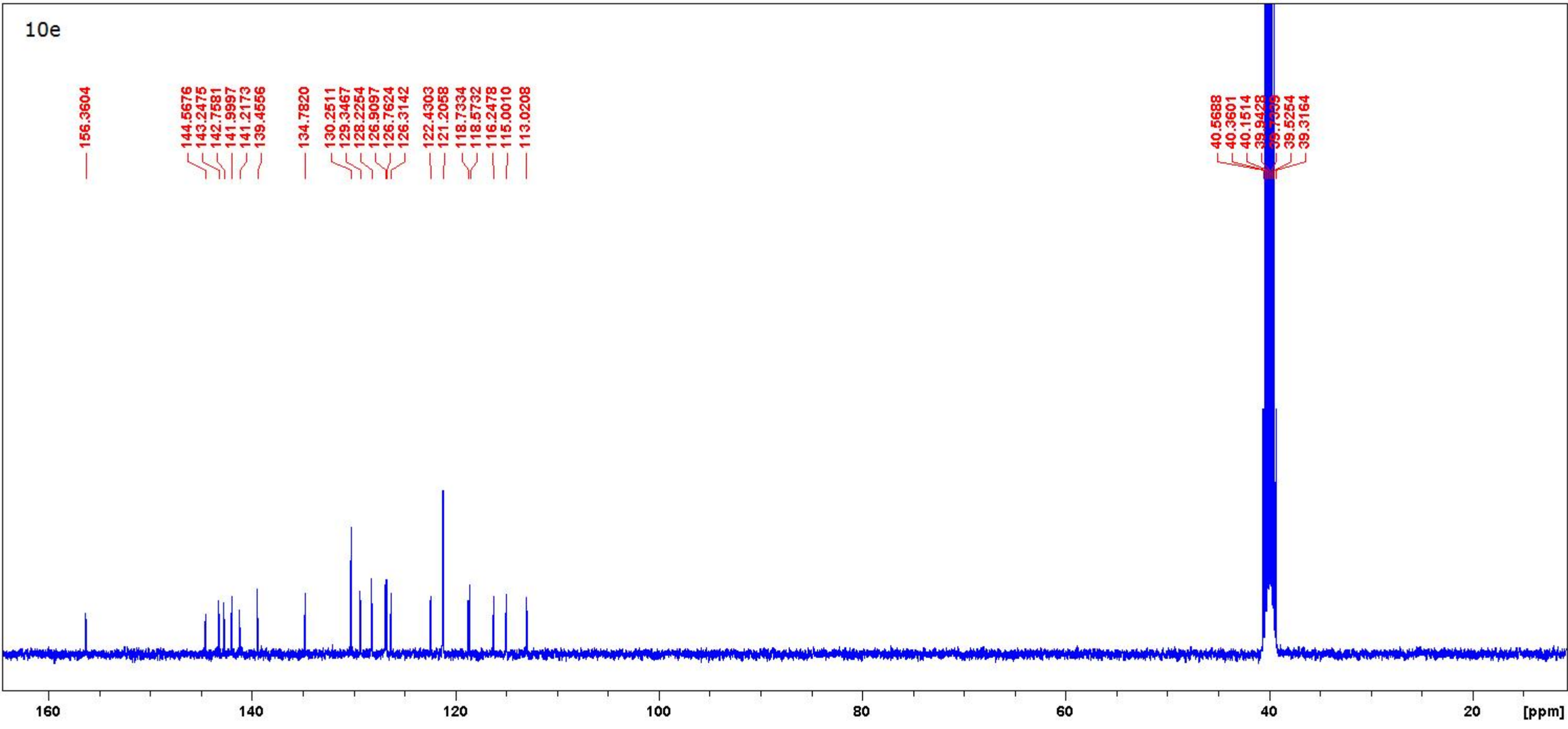
8.7502
8.1498
8.1305
7.6673
7.6483
7.6280
7.5538
7.5353
7.5169
7.4038
7.3839
7.2828
7.0795
7.0595
7.0418
7.0225
7.0037
6.9623
6.8034
6.7846
6.7660
6.7132
6.6935
3.3720
2.5100
1.0860
1.0000
0.9919
1.9682
2.0083
1.0238
0.9744
0.9658
0.9784
1.0036
0.9831
12
10
8
6
4
2
[ppm]


10e
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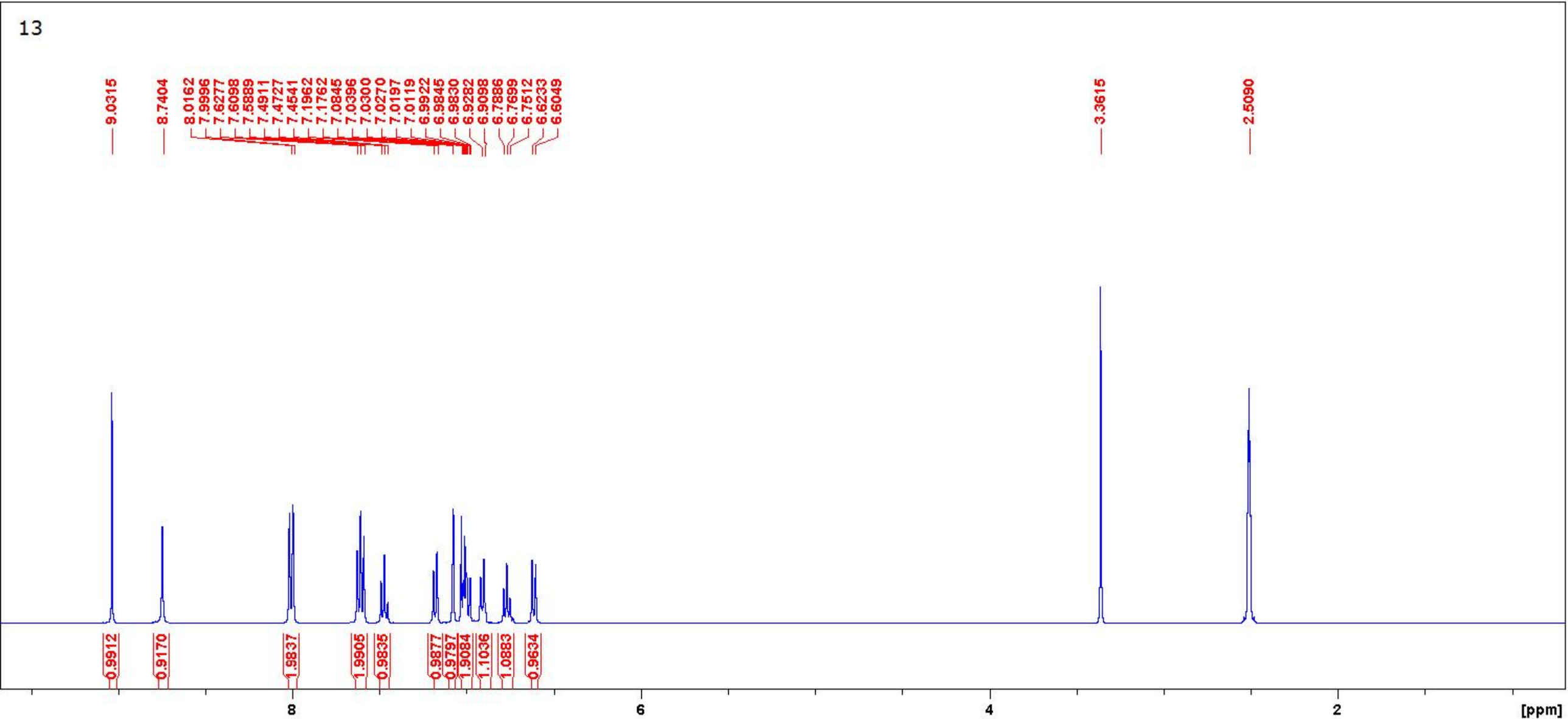
143.2475
142.7581
141.9997
141.2173
139.4556
134.7820
130.2511
129.3467
128.2254
126.9097
126.7624
126.3142
122.4303
121.2058
118.7334
118.5732
116.2478
115.0010
113.0208
40.5688
40.3601
40.1514
39.9428
39.7339
39.5254
39.3164
160
140
120
100
80
60
40
20
[ppm]

13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7.4541
7.1962
7.1762
7.0845
7.0396
7.0300
7.0270
7.0197
7.0119
6.9922
6.9845
6.9830
6.9282
6.9098
6.7886
6.7699
6.7512
6.6233
6.6049
3.3615
2.5090
0.9912
0.9170
1.9837
1.9905
0.9835
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0.9797
1.9084
1.1036
1.0883
0.9634
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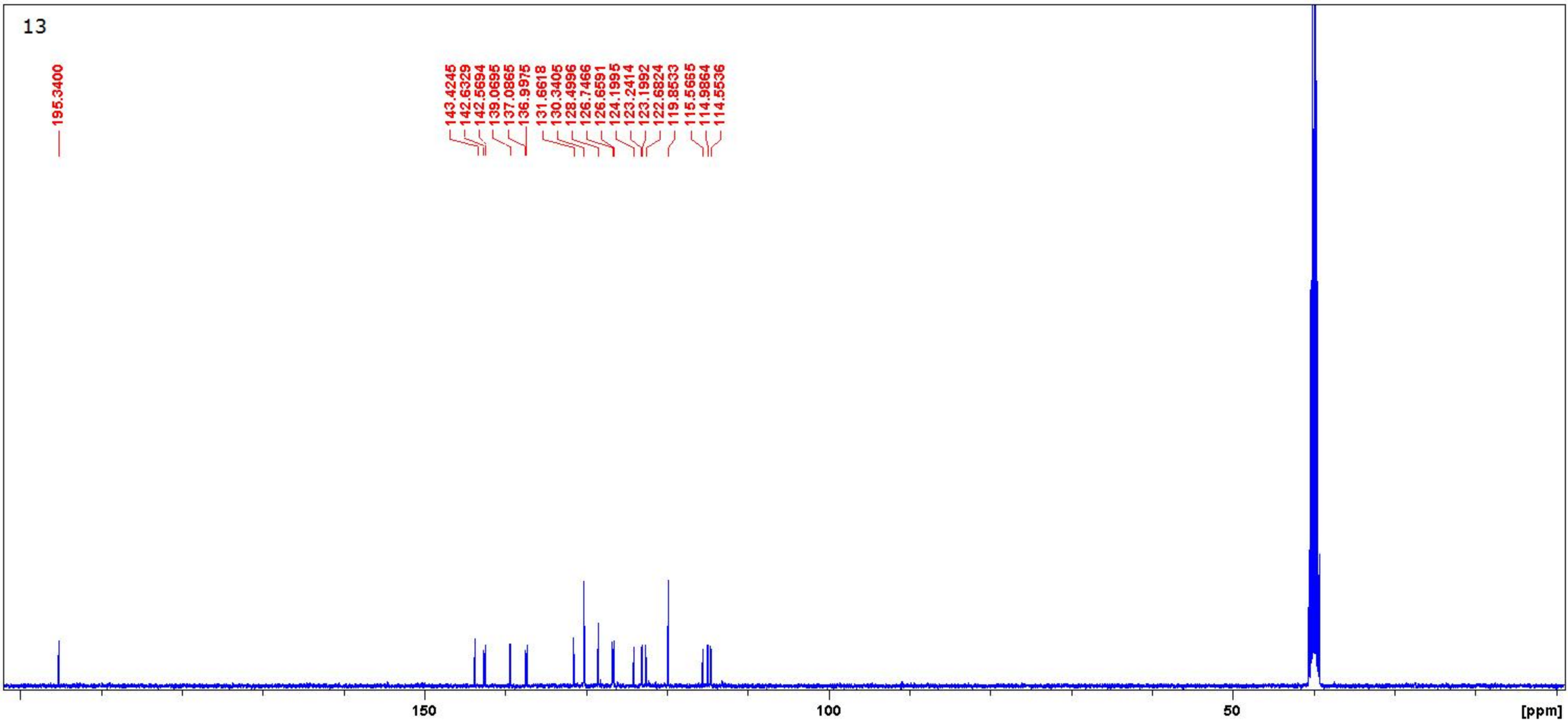
6
4
2
[ppm]


13
195.3400
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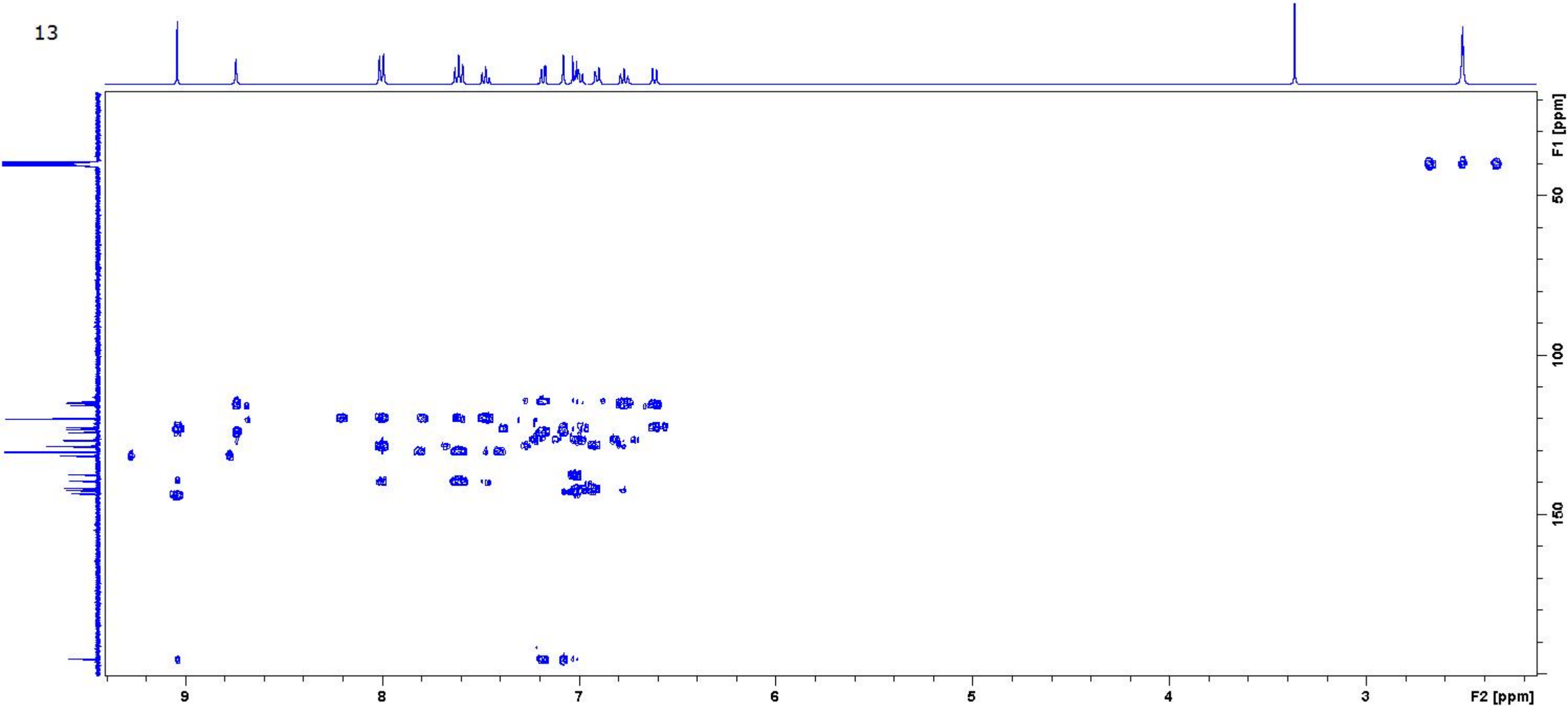
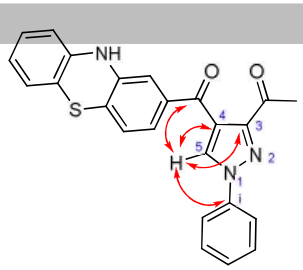
142.6329
142.5694
139.0695
137.0865
136.9975
131.6618
130.3405
128.4996
126.7466
126.6591
124.1995
123.2414
123.1992
122.6824
119.8533
115.5665
114.9864
114.5536
150
100
50
[ppm]

13

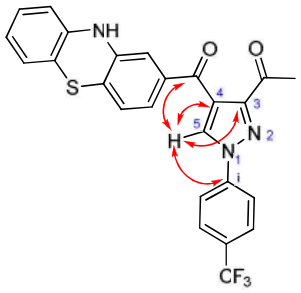




7a

Selected region for ^{1}H-^{13}C HMBC correaltions

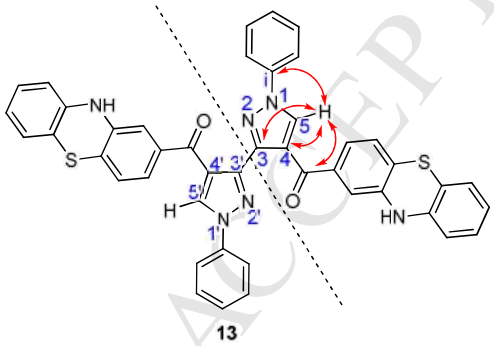
	δ	assign	HMBC
7a	2.59	CH_3	193.14 (CO), 150.30 (C-3)
	9.02	H-5	188.96 (CO), 150.30 (C-3), 139.02 (C-i), 123.11(C-4)



7d

Selected region for ^{1}H-^{13}C HMBC correaltions

	δ	assign	HMBC
7d	2.61	CH_3	193.12 (CO), 150.85 (C-3)
	9.16	H-5	188.72 (CO), 150.85 (C-3), 141.54 (C-i), 123.31(C-4)



13

Selected region for ^{1}H-^{13}C HMBC correaltions

	δ	assign	HMBC
13	9.03	H-5	195.34 (CO), 143.42 (C-3), 139.06 (C-i), 123.19(C-4)