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OPTION

Organic Chemistry

By

Boutelba Houria and Bousserou Assia

THEME

Green Efficient Synthesis, Crystal Structure and Spectroscopic Characterizations of Substituted 5-arylidene-1,3-thiazolidine-2,4-diones using Barium Hydroxide Catalyst.

Examining Committee Members :

Dr. YAHIA	MCA	Univ. of Skikda	President
Dr. BOUDERMINE	MCA	Univ. of Skikda	Examiner
Dr. BOUDEBBOUS	MCB	Univ. of Skikda	Rapporteur

03 July 2023

We dedicate this dissertation work :

To Our Parents

A special feeling of gratitude to our loving parents, thank you for making us what we are today.

To our sisters and brothers, thank you for the moral and physical support.

Assia & **Horia**

ACKNOWLEDGMENTS

This work was carried out at the " Pedagogical Laboratory " at the University of 20 August 1955-Skikda. We would like to thank all the people who took part in the development of this work. We would like to express our infinite gratitude and respect to our supervisor, **Dr. Khawla BOUDEBBOUS** for allowing us to work a part on an exciting and challenging scientific project. We particularly thank him for her valuable advices and her availability during the writing of the manuscript.

I address my sincere thanks to **Dr. Yahia** and **Dr. BOUDERMINE**, at University of 20 August 1955-Skikda, for having done us the honor to be the scientific examiners of this work.

We would like to say thanks to all our friends and colleagues for their precious support, thank you to all those who have crossed our path, and whose list would be far too long here, but who have contributed to making these finally pass in the best conditions possible.

General information

- The starting materials and reagents used in the reactions were supplied commercially by Aldrich, Acros, ABCR, and Merck.

- Nuclear magnetic resonance (^{1}H-NMR, ^{13}C-NMR) spectra were recorded using a Bruker Advance III 500 MHz spectrometer in DMSO-d_6. Chemical shifts are reported in parts per million (ppm), and the coupling constants (J) are expressed in Hertz (Hz). The addition of D_2O confirmed the assignment of exchangeable protons (NH).

- Melting points (mp) were measured in open capillary tubes and are uncorrected using a Gallenkamp MPD350.BM3.5 apparatus.

- Thin-layer chromatography (TLC) was performed on silica 60 F254.

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1 Introduction

The active methylene-containing compounds with both electrophilic and nucleophilic sites, has proved to be useful for the construction of a broad range of molecular system, particularly complex heterocyclic ring system **[1]**. A typical exemple of such compound is nitrogen sulphur containing heterocycles, which have recently attracted our interest, due to their exceptional bioactive behavior, mainly due to their unique structural features, especially with thiazole, that enable them to exhibit a broad spectrum of biological and pharmacological significance. Thiazolidine-2,4-dione (TZD), also known as Glitazone, is a five membered heterocyclic molecule containing thiazole nucleus with two carbonyl groups at the 2^{end} and 4^{th} positions. **[2]** Such compound are widely found in many natural product, biologically active and medicinal agents.**[3]** Therefore, it will be interesting and substantial to apply 1,3-thiazolidinedione in organic synthesis, as useful synthetic precursors of innovative and valuable complexes heterocyclic scaffolds. **[4-6]**

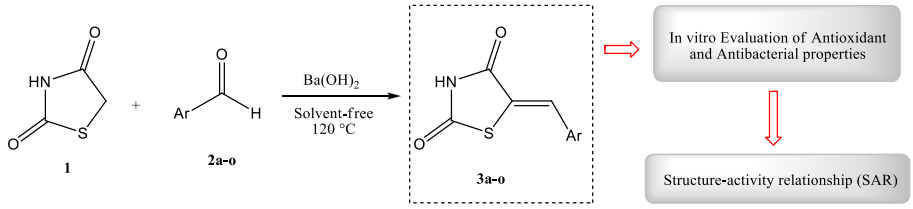
Among a versatile class of Sulfur-containing heterocyclic compounds, 5-arylidene-1,3-thiazolidine-2,4-diones. Many studies have described the biological properties of these compounds **[7]** which is widely found in many natural products, bioactive scaffolds possessing significant medicinal and biological activities **[8-11]**. On the other hand, the 5-arylidenethiazolidinediones are also useful synthetic precursors for versatile compounds **[12-14]** possessing substantial medicinal and pharmacological potencies **[15-18]**.

Therefore, in continuation of our research of new environmentally friendly synthesis procedures, for the synthesis of 5-arylidenethiazolidinediones in the aim of improving yields, reaction times and, as far as possible, respecting the environment. We report here, the preparation of title compounds by Knovenagel condensation between thiazolidinedione and arylaldehydes derivatives.

The literature reports several methods for the synthesis of 5-arylidene-2,4-thiazolidinediones, and which are often similar such as sodium acetate inacetic acid under reflux conditions **[19]**, KOH and ethanol under reflux **[20]**, piperidine in ethanol under reflux **[21–23]**, polyetheneglycol (PEG-300) under reflux **[24]** and ethylenediamine diacetateas catalyst at room temperature **[25]**.

First, we attempt to provide insight into both the historical conventional and the use of novel methodologies to synthesise the TZD core framework. Further to this, different therapeutic interests and synthetic procedures employed to substitute the TZD molecule at the activated methylene C5 and N3 position are reviewed.

Next, we will discussed the most important findings of our study in the Results section, using barium hydroxide ($Ba(OH)_2 \times 8H_2O$) as heterogeneous efficient catalyst toward the Knoevenagel condensation under solvent-free conditions. This method provides access to various substitued 5-arylidene-1,3-thiazolidine-2,4-diones in excellent yield.



Scheme 1.

Finally, the description of the various experimental protocols, will be detailed in the experimental section, as well as the spectroscopic and physical characteristics of synthesized compounds.

2 Bibliographic review

2.1 An overview on chemistry of thiazolidinedione (TZD)

Thiazolidine-2,4-dione (TZD), also known as Glitazone, is a five membered heterocyclic molecule containing thiazole nucleus with two carbonyl groups at the 2[end] and 4[th] positions. **[26]** The free –NH and $–CH_2$ moieties of thiazolidinedione nucleus are known as substitution positions, that have allowed access to a broad range of TZDs derivatives with interested pharmacological behavior. Variable substitutions appear at 3 and 5 positions, but significant change in structure and properties of thiazolidinedione is exerted by substitution at the carbon atom in the 2[end] position.

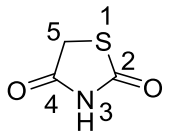


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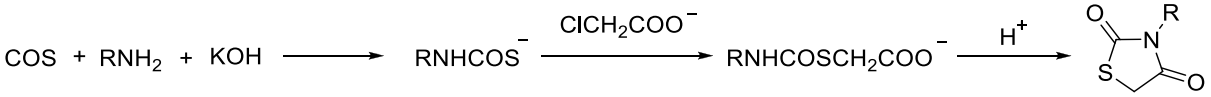
Figure 1 : Thiazolidine-2,4-dione

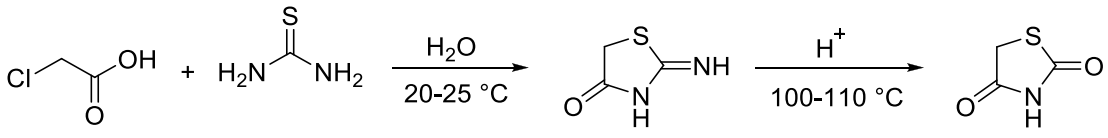
2.2 Synthesis : Possible ways to synthesize TZD nucleus

The synthesis of Thiazolidinedione (TZD) motif has been accomplished employing various starting substrates including thiocarbamates, thioureas, thiosemicarbazones and alkali thiocyanates, etc. The in situ synthesis of alkyl thiocabamate achieved by reacting carbonyl sulfide with primary amine in the presence of potassium hydroxide. These alkyl thiocarbamates are further reacted with α–haloalkanoic acids to yield thiolcarbamates, which cyclize to produce TZD nucleus (Scheme 2).**[27]**



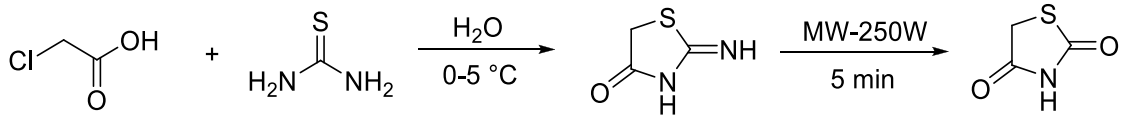
Scheme 2. Synthesis of thiazolidine-2,4-dione using thiocarbamate and chloroacetic acid.

The most frequently used synthetic approach is refluxing of α-chloroacetic acid with thiourea for 12 h that generates TZD nucleus via 2-imino-4-thiazolidinone intermediate as mentioned in (Scheme 3).**[28]**



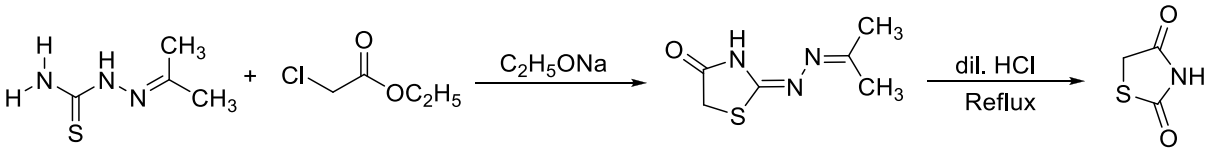
Scheme 3. Synthesis of thiazolidine-2,4-dione using thiourea and chloroacetic acid.

This reaction may be further accelerated involving microwave (MW) assisted technique, in which initially α-chloroacetic acid is reacted with thiourea under ice cold conditions to give 2-imino-4-thiazolidinone intermediate, which is further irradiated with microwave at 250 W for 5 min to yields white crystals of Thiazolidine-2,4-dione (Scheme 4).**[29]**



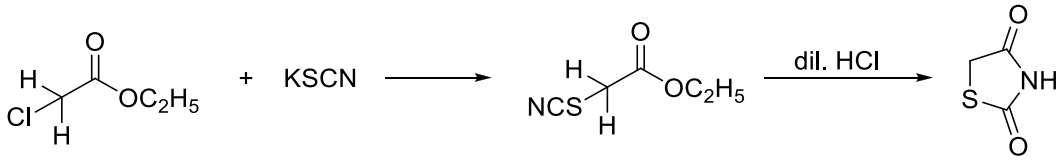
Scheme 4. Microwave assisted synthesis of thiazolidine-2,4-dione

Another reported synthetic protocol is the reaction mixture of thiosemicarbazone of acetone with chloroacetic acid ester, that, in the presence of sodium ethoxide yields 2-hydrazino-4-thiazolidinone which in turn yields TZD nucleus, in the presence of dilute hydrochloric acid, (Scheme 5).**[30]**



Scheme 5. Synthesis of thiazolidine-2,4-dione using thiosemicarbazone, chloroacetic acid ester and sodium ethoxide.

The other way to acquire TZD nucleus include acidification (i.e., with dilute HCl) of the product accessed from chemical reaction of ethylchloroacetate with potassium thiocyanate (Scheme 6).**[31]**

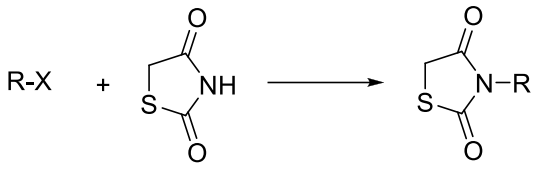


Scheme 6. Synthesis of thiazolidine-2,4-dione using ethyl chloroacetate and potassium thiocyanate.

2.3 Synthesis of various TZD derivatives

2.3.1 Substitutions at –NH moiety of TZD nucleus

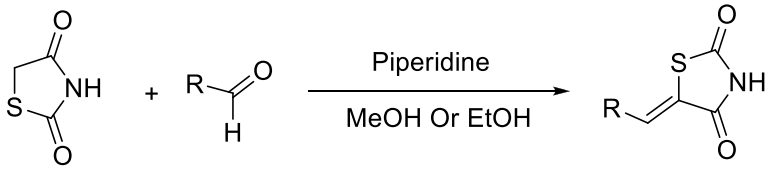
The free –NH moiety of TZD has mainly been alkylated adopting alkyl or aryl halides in the presence of alkali involving potassium carbonate **[32]** (Scheme 7), tetrabutylammonium iodide, **[33]** or sodium hydride **[34]** applying acetone or DMF as solvent.



Scheme 7. Substitution of –NH by alkyl or aryl group.

2.3.2 Substitution at free –CH_2 moiety of TZD nucleus

The free methylene moiety has mainly been substituted with aldehydes or ketones leading to formation of arylidene analogues, via 'Knoevenagel' condensation. The condensation reaction of aldehyde and thiazolidinedione has been accomplished under different reaction conditions involving, few drops of piperidine and using ethanol or methanol as solvents for 7-42 h **[35]** (Scheme 8), or anhydrous sodium acetate in glacial acetic acid **[36]** while condensation reaction of thiazolidinedione with ketones has been carried out in the presence of ammonium acetate or piperidinium acetate in toluene or ethyl acetate. **[37]** Attempts have also been made to create an environmentally friendly reaction condition for Knoevenagel condensation, employing L-tyrosine in water **[38]** or β-alanine in acetic acid, [39] or baker's yeast in ethanol. **[40]** These reactions have allowed TZD to be coupled to a variety of benzylidene derivatives as well as other heterocyclic ring moieties including chalcones, flavones, acridines, furfurals, and dibenzocycloheptanone, etc.



Scheme 8. Knoevenagel condensation of TZD with aldehyde group.

2.4 Pharmacological profile of thiazolidinediones derivatives : Application in medicinal chemistry

Due to its diverse and flexible nature **[41]**, TZD nucleus are found to exhibit a wide pharmacological profile and ability to inhibit various enzymes, **[2]** While TZDs are known to stimulate PPAR-ɤ (Peroxisome Proliferator Activated Receptor gamma) : a group of nuclear receptor regulates the genes controlling glucose homeostasis and lipid metabolism. Compounds containing thiazolidine-2,4-dione motif proved promising biological activities, including anti-hyperglycaemics, aldose reductase inhibitors, anti-cancer, anti-inflammatory, anti arthritics, anti-microbials, etc which attracted the attention of medicinal chemist for the development of new therapeutic agents. Some recent updates on synthesis and pharmacological advancements of compounds containing thiazolidine-2,4-dione nucleus are discussed in this section.

2.4.1 Antihyperglycemic agents

Hyperglycemia is a condition/lifestyle disease in which insulin resistance in peripheral tissue and liver causes a rise in glucose levels over time. Antihyperglycemic drugs work by reducing insulin resistance, increasing insulin secretion and encouraging glucose consumption in tissues. The interaction of antihyperglycemic drugs (TZD) with PPARɤ receptors is crucial for glucose metabolism regulation.**[42-44]**

Kar et al. in 2014, designed and synthesized novel glitazones containing thiazolidinedione ring structures as their basic scaffold for their antihyperglycemic inhibitory. Later, subjected to in vitro glucose uptake assay in the absence and presence of insulin to prove their antidiabetic potency involving rat hemi-diaphragm. Compound 1 exhibited as the most potent derivative with in vitro mean glucose uptake values of 34.71 mg/dl/45 min and 47.65 mg/dl/45min as in vitro mean glucose uptake values, in the absence and presence of insulin respectively, using Rosiglitazone as the reference drug with 36.00 mg/dl/45min and 50.50 mg/dl/45 min as in vitro mean glucose uptake values.**[45]** Acyl linker was found as an essential key feature for the activity and further modification as removal of bromine atom or replacement by methoxy, nitro or hydroxy group decreases the activity.

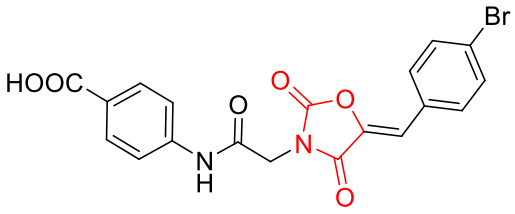


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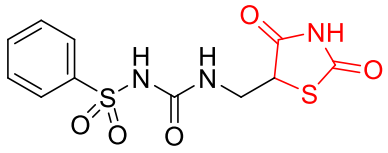
Figure 2. Potent Glitazone containing thiazolidinedione ring as potent antihyperglycemic agent

Jawale et al. in 2012 have reported the synthesis of thiazolidinedione derived sulfonylureas, by condensing various substituted sulfonamides and 5-(isocyanatomethyl) thiazolidine-2,4-dione. The isocyanomethyl thiazolidinedione was obtained by using the Curtius rearrangement, starting from known 2,4-dioxo-5-thiazolidineacetic acid. The synthesized compounds have been screened for the antihyperglycemic potency in sucrose loaded model (SLM) Sprague–Dawley strain male albino rats. Among these compounds 2, 3, 4 and 5 significantly inhibited the rise in postprandial hyperglycemia to the tune of 15.8 ($p < 0.01$), 17.2 ($p < 0.01$), 14.3 ($p < 0.01$) and 16.5 ($p < 0.01$) %, respectively towards Metformin as the reference drug with 27.0 % hyperglycemic activity.**[46]**



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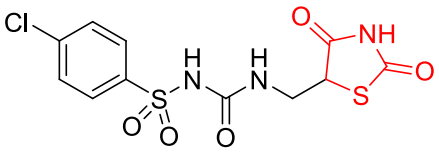

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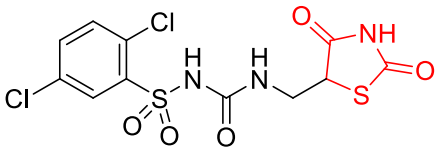

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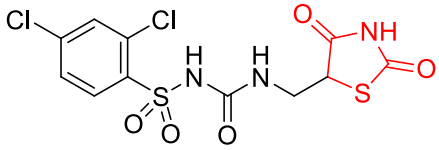

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Figure 3. Potent 1-((2,4-dioxothiazolidin-5-yl) methyl)-3-substitued benzene sulfonyl ureas as potent antihyperglycemic agents

2.4.2 Anticancer agents

K.W. Corigliano et al. in 2018 synthesized a new TZD-based compounds which were initially screened for their in vitro effect on cell viability, using MTT assays in MCF7 (breast cancer) and PC3 (prostate cancer) cells, that underwent treatment with 5 µM. Only set of three TZD

analogues 6, 7 and 8 were found to be the most promising, showing a 50% reduction of cell viability in both PC3 and MCF-7 cells after 48 h exposure to 5 µM concentration of each of the three drugs, when compared with standard drug Rosiglitazone. Although further research is required to understand their efficacy, We assume that these compounds have the potential to be further developed as a new adjuvant tool for anticancer treatment. **[47]**

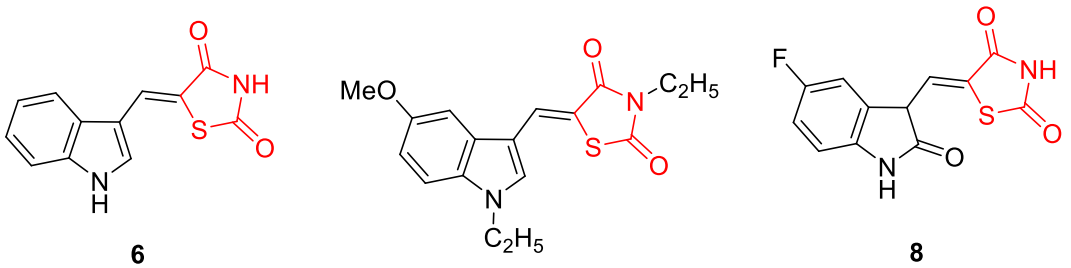

Figure 4. Potent Indole and 2,4-thiazolidinedione conjugates derivatives as anticancer agents

Metwally K. et al. in 2017 was prepared a new series of two thiazolidinedione scaffolds different in the position of the thiazolidinedione ring in the molecule (A-series where the thiazolidinedione ring is terminal, the B-series where the thiazolidinedione ring is located in the middle of the molecule). Then, they were screened their in vitro cytotoxic activity against a panel of human cancer cell lines namely, prostate cancer cells PC-3, breast carcinoma cells MDA-MB-231, and fibrosarcoma cells HT1080. Compound 9 and 10 was found to be most active. Doxorubicin is used as standard drug. **[48]**

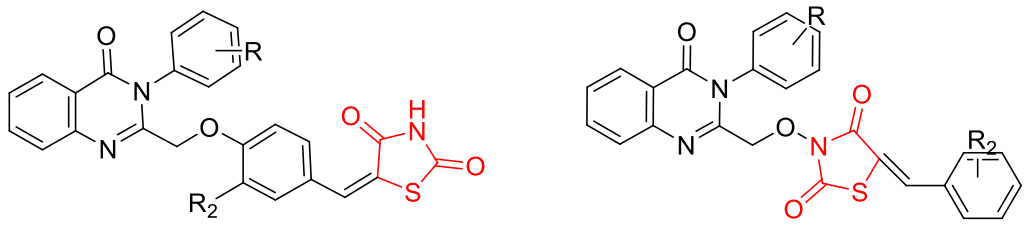

Figure 5. Potent 5-{[4-(substitutedphenyl-3,4-dihydro-4-oxoquinazolin-2-yl) methoxy] substitutedbenzylidene}-thiazolidine2,4-dione as anticancer agents

Sharma et al. in 2016 synthesized a series of novel benzimidazole thiazolidinedione derivatives and evaluated them towards human cancer lines prostate (PC-3 and DU-145), breast (MDA-MB-231), lung (A549) and one normal breast epithelial cell (MCF10A) employing MTT assay for their cytotoxic potential. Compound 11 exhibited as the most promising anticancer candidate, with an IC_{50} value of 11.46 ± 1.46 µM on A549 lung cancer

cell line and no substantial toxicity to MCF10A cells as compared to the reference drug 5-fluorouracil. [49]

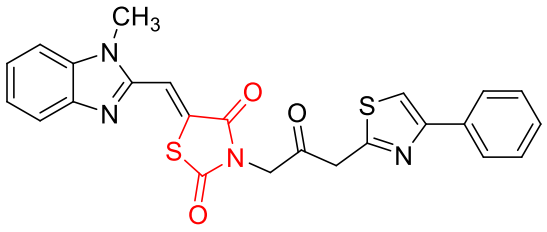

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Figure 6. Synthesis of benzimidazole-thiazolidinedione hybrids.

Anh et al. in 2015 synthesized a series of novel chromony thiazolidinediones derivatives via knoevenagel condensation reaction between 3-formyl-7-methoxy chromone and various thiazolidinedione derivatives. The intermediate compound and products, were evaluated for their cytotoxic effects against several human cancer cell lines, using the MTT [3-(4,5-dimethylthiazol-2-yl)- 2,5-diphenyl-2H-tetrazolium bromide] assay. The synthesized chromonylthiazolidines exhibited weak cytotoxic activities towards the tested cancer cell lines, while selective cytotoxic effects were observed. Compounds 12 and 13 displayed the most selective cytotoxic effects towards human epidermoid carcinoma with (IC_{50}= 44.1 ± 3.6 µg/mL) and breast cancer (IC_{50}= 32.8 ± 1.4 µg/mL) cell lines, respectively. It be concluded that chromoylthiazolidines are potential low-cost, and selective anticancer agents. **[50]**

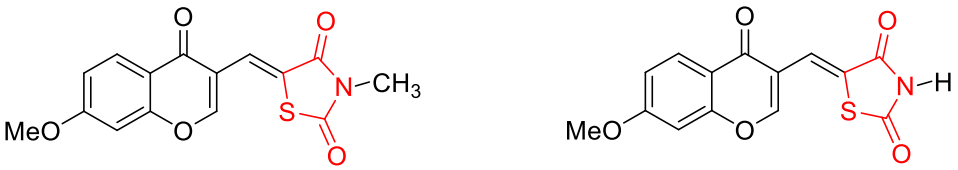

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Figure 7. Synthesis of 5-((7-Methoxy-4-oxo-4H-chromen-3-yl) methylene) substituted thiazolidine-2,4-dione

2.4.3 Antimicrobial and antiviral agents

Khan et al. designed and synthesized a series of novel biphenyl tetrazole thiazolidinedione hybrids, and screened them for their antimicrobial activity against Ciprofloxacin as the standard drug. Among the synthesized derivatives, compounds 14 (MIC-20.75, 35.41 µg/ml), **15** (MIC-19.41, 26.00 µg/ml), and 16 (MIC-8.58, 8.42µg/ml) were found to be most potent in vitro antimicrobial agents against bacterial strain (Escherichia coli, Bacillus subtilis). **[51]**

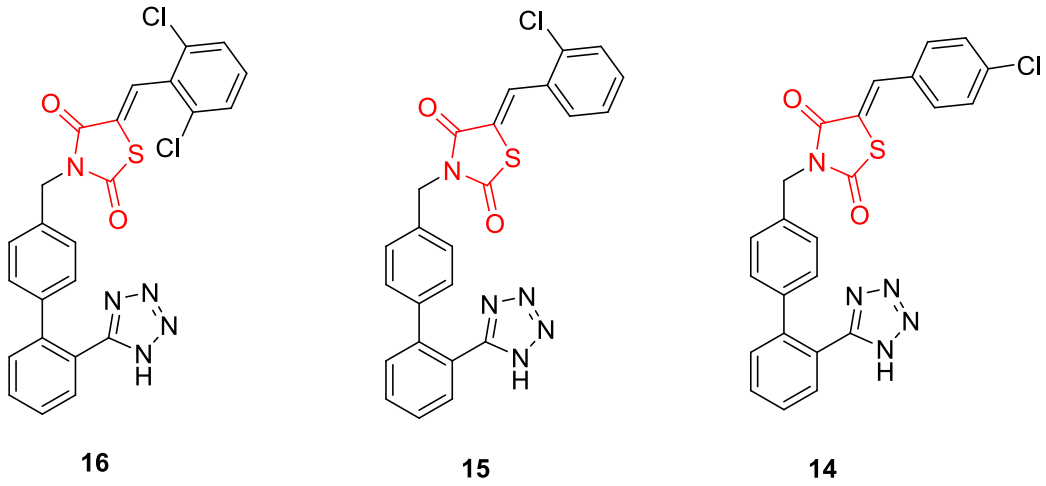


Figure 8. Potent Biphenyl tetrazole-thiazolidinediones as antibacterial agents

Nastas et al. synthesized a series of new 5-(Chromene-3-yl) methylene-2,4-thiazolidinedione derivatives. All new compounds were investigated for their in vitro antimicrobial activity, using diffusion method, towards two species of Gram-positive bacteria (Listeria monocytogenes, Staphylococcus aureus) and Gram-negative bacteria (Escherichia coli, Salmonella typhimurium) and fungi (Candida albicans). Antimicrobial potency result indicated that among the synthesized derivatives, compounds 17, 18 and 19 antimicrobial activity towards all tested bacteria and fungi, compared to those of Gentamicin and Fluconazole as the reference drugs. **[52]**

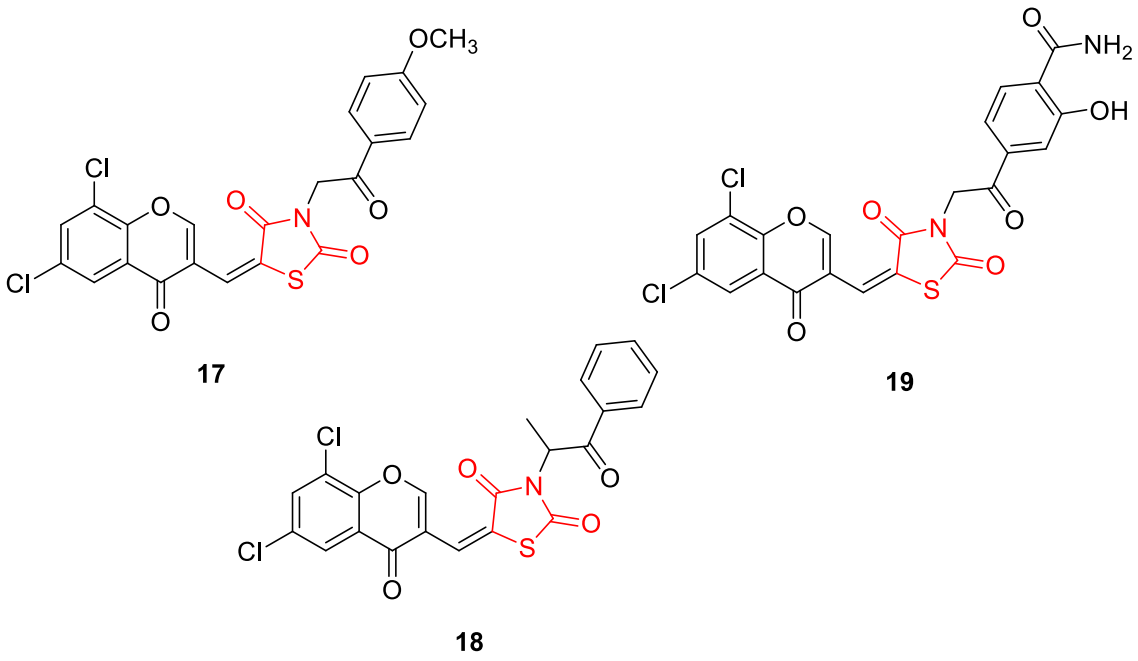
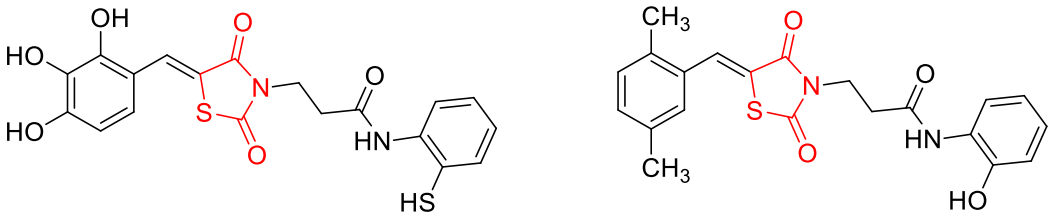


Figure 9. Potent 5-(Chromene-3-yl) methylene-2 ,4-thiazolidinediones as antimicrobial agents

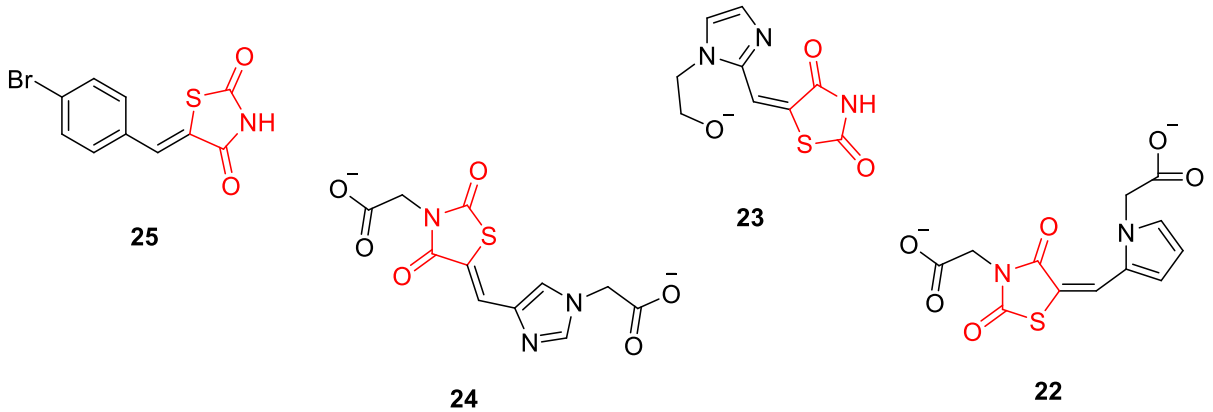
Bahare et al. synthesized a new series of substituted 2-(5- benzylidene-2,4-dioxothiazolidin-3-yl)-N-(phenyl) propanamide derivatives and tested them for antimicrobial (antibacterial and antifungal) activities and anti-viral (HIV-1 RT inhibitory activity). Compound 21 (MIC- 3.12, 6.25, 6.25, 6.25, 6.25, 6.25 µg/ml) exhibited excellent antibacterial potency towards S. aureus, B. subtilis, E. coli, P. aeruginosa, S. typhi and K. pneumonia, using Ciprofloxacin (MIC-0.78 µg/ml) as the standard drug, and antifungal activity of 12.5 µg/ml and 25 µg/ml against C. albicans and A. niger respectively, using Fluconazole as the reference drug with MIC value of 12.5 µg/ml for both strains. On the other hand compound 20 exhibited good HIV-1 RT inhibitory activity with 73% inhibition and IC_{50} value of 1.31 µM. **[53]**



20 **21**

Figure 10. Potent substituted 2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)-N-(phenyl-propanamide derivatives as antimicrobial agents

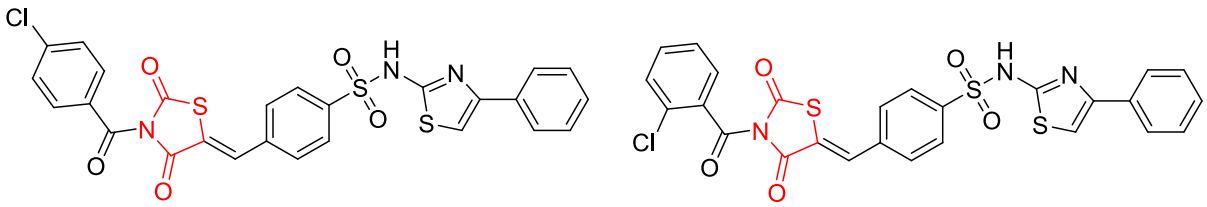
Moorthy et al. synthesized a series of novel imidazolyl thiazolidinedione derivatives and assessed them for their in vitro antimicrobial potency towards Ciprofloxacin and antifungal activity against Ketoconazole as the reference drugs. Among the synthesized derivatives, compound 22 showed significant antimicrobial potency (MIC- 3.8, 2.2, 1.6, 2.8, 7.9, 1.7 µg/ml) against S. aureus ATCC-9144, S. epidermidis ATCC-155, E. coli ATCC-25922, P. aeruginosa ATCC-2853, A. niger ATCC-9029, and A fumigatus ATCC-46645, respectively. Compounds 23, 24 and 25 showed good activity against all microorganism. **[54]**



25 **23** **24** **22**

Figure 11. Potent substituted 5-(Substituted benzylidene) thiazolidine-2,4-dione and imidazolyl thiazolidinedione derivatives as antimicrobial and antifungal agents

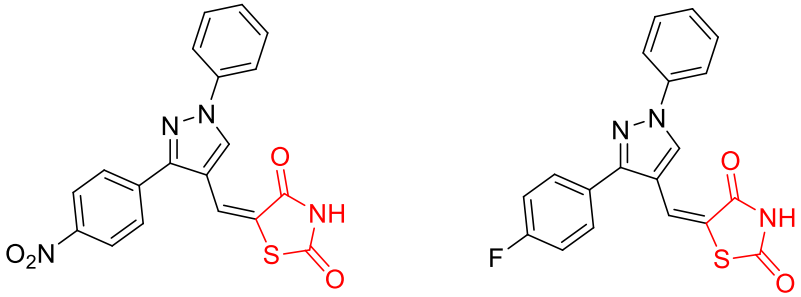
Parekh et al. reported benzoyl chloride substituted 2,4-thiazolidinedione derivatives and screened them for their in vitro antimicrobial and anti-tubercular activity. Compound 26 (MIC-12.5, 12.5, 6.25, 6.25 µg/ml) and 27 (MIC-25, 12.5, 6.25 & 6.25 µg/ml) were found to be most effective antimicrobial candidates towards E. coli, P. aeruginosa, S. aureus and B. subtilis, using Ciprofloxacin as the reference drug. Also 26 and 27 showed anti-tubercular activity towards M. tuberculosis (H37RV) with MIC values of 62.5 µg/ml for both compounds, employing Rifampicin and Isoniazid as the reference anti-tubercular drugs. **[55]**



27 **26**

Figure 12. Potent benzoyl chloride substituted 2,4-thiazolidinedione derivatives as antimicrobial and antifungal agents

Prakash et al. reported a series of 5-((3-aryl-1-phenyl-1H-pyrazol-4- yl) methylene) thiazolidine-2,4-diones through Knoevenagel condensation of pyrazole-4-carbaldehydes with thiazolidine-2,4-dione, and screend them for their antibacterial activity towards S. aureus, B. subtilis, P. aeruginosa and E. coli employing Ciprofloxacin as the reference drug and antifungal activity towards A. niger and A. flavus employing Fluconazole as reference drug. Compound 28 with 78.8 % and 82.5 % inhibition of mycelial growth, was emerged to be more potent than Fluconazole against A. flavus and A. niger, compared to Fluconazole's 77.7% and 81.1 percent inhibition. Whereas compound 29 exhibited the best antibacterial performance against S. aureus and B. subtilis, with MIC values of 16 µg/ml and 32 µg/ml, respectively. **[56]**

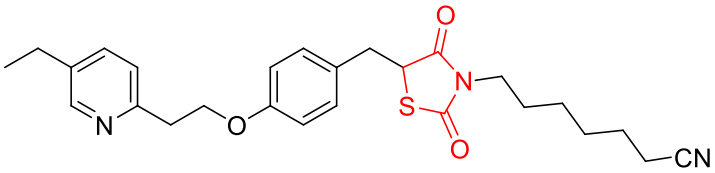


29 **28**

Figure 13. Potent 5-((3-aryl-1-phenyl-1H-pyrazol-4- yl) methylene) thiazolidine-2,4-diones derivatives as antimicrobial and antifungal agents

2.4.4 Antioxidant and xanthine oxidase inhibitors

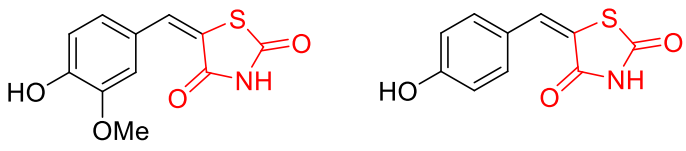
Xanthine oxidase (XO) is a complex metalloflavoprotein which catalyzes the alteration process of hypoxanthine to xanthine and xanthine to uric acid with concomitant manufacturing of hydrogen peroxide and superoxide anions. The overproduction of uric acid in serum usually leads to the deposition of micro and macroscopic deposits of sodium hydrogen urate monohydrate crystals in the joints of humans which leads to the pathological hyperuricemic condition namely gout. **[57]** Moreover, Inflammation, metabolic disorder, cellular aging, reperfusion damage, atherosclerosis, and carcinogenesis are all caused by atypical superoxide production. Begum et al. revealed the synthesis of N-substituted analogs of thiazolidinedione derivatives as antioxidant agents and effective new class of Xanthine Oxidase Inhibitors. Compound 30 exhibited better inhibitory, producing 72% inhibition towards human milk XO, using Allopurinol as the standard reference drug. **[58]**



30

Figure 14. potent 5-[4-[2-(5-Ethyl-2-pyridinyl) ethoxy] phenyl] methyl]-2, 4-thiazolidinedione derivative as antioxydant agent,

Hossain et al. described the synthesis of several 5-arylidene-2,4-thiazolidinediones analogue with geranyloxy or prenyloxy substituent on the 5-arylidene moiety of 5-arylidene-2,4-thiazolidinediones. The synthesized compounds were assessed for their radical scavenging inhibitories, using 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay which were expressed as IC_{50} (concentration required for 50% inhibition of 0.1 mM DPPH concentration) value. Several compounds displayed appreciable radical scavenging activities. The vanillin based thiazolidinedione compound 31 showed highest activity (IC_{50} = 2.49 μM) comparable to that of α-tocopherol (IC_{50} = 2.30 μM). But in vivo, compound 32 exhibited better results in inducing phase II detoxifying/antioxidative enzyme. **[59]**



31 **32**

Figure 15. Potent 5-arylidene-2,4-thiazolidinediones as antioxidant agent

2.4.5 α-glucosidase inhibitors

Chinthala et al. synthesized novel series of TZD's tagged with 1,2,3-triazoles and screened them for their in vitro a-glucosidase inhibition and anticancer activities. Compounds 33, 34 and 36 showed highly potential α-glucosidase inhibition with IC_{50} values ranging between 0.1 and 0.3 µg/ml, compared with the standard drug Acarbose (IC_{50} = 12.5 µg/mL). Whereas compounds 35, 36 and 37 have showed better anticancer activity towards human cancer cell lines IMR-32 (neuroblastoma), Hep-G2 (hepatoma) and MCF-7 (breast). Finally, molecules that showed potential a-glucosidase inhibition were subjected to docking studies using molecular modeling tools. These inhibitory results were further optimized by molecular docking studies, using molecular modeling tools. Docking studies revealed compounds 33, 34 and 36 are potent inhibitors of α-glucosidase and also exhibited compliance with standard parameters of drug likeness. **[60]**

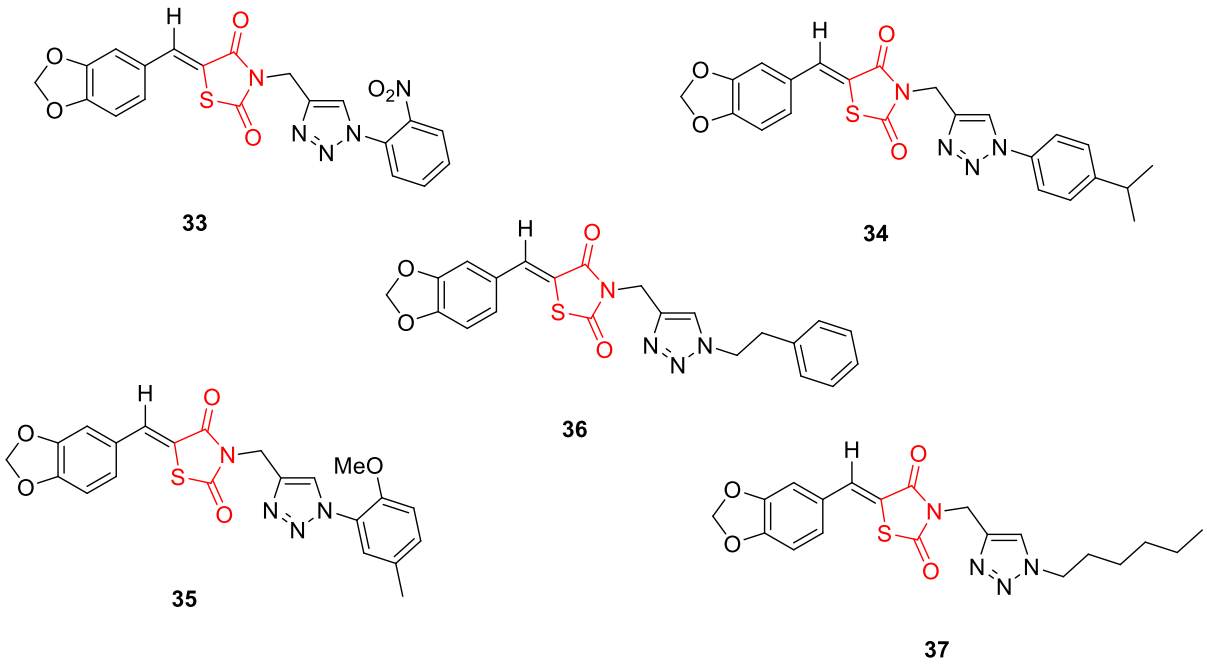
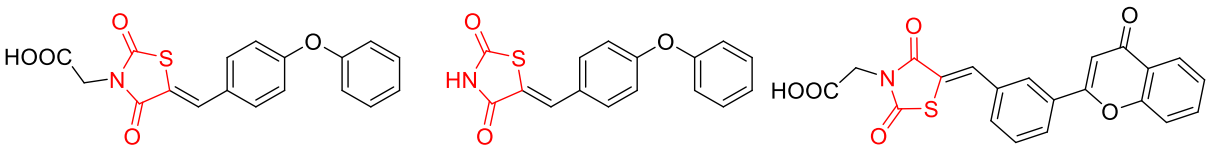


Figure 16. Potent 5-(benzo-[1,3]-dioxol-5-ylmethylene)-3-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl) thiazolidine-2,4-diones as α-glucosidase inhibitors

2.4.6 Aldose reductase inhibitors

Bruno et al. reported the synthesis of (Z)-5-arylidene-2,4-thiazolidinediones, and screened them for their aldose reductase inhibitory potency by varying substituents at the para position of benzylidene ring. The substitution of phenoxy group at the benzylidene ring found in the most effective compound of TZD class of ALR2 inhibitors, such as compound 38 (IC_{50} = 0.13 µM) against Tolrestat as the reference drug. **[61]** In addition, structure-activity relationship

analysis showed that introduction of an acetic acid chain in the -NH significantly enhanced aldose reductase potential inhibitory, and compound 39 (IC_{50} = 6.14 µM) was proved to be less effective compared to compound 38 **[62]** Thereafter, the SAR studies exerted in flavonyl substituted TZD derivatives, similar observations were recorded that methyl carboxylic acid substitution give also significant aldose reductase inhibitory (compound 40, IC_{50} = 0.41 µM).**[63]**



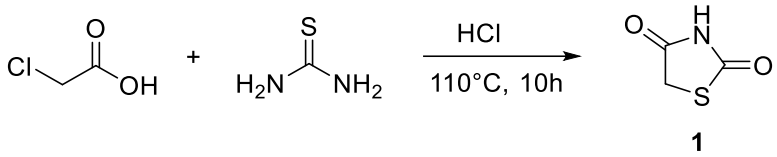
38 39 40

Figure 17. Potent (Z)-5-arylidene-2,4-thiazolidinediones derivatives as Aldose reductase inhibitors

3 Results and discussion

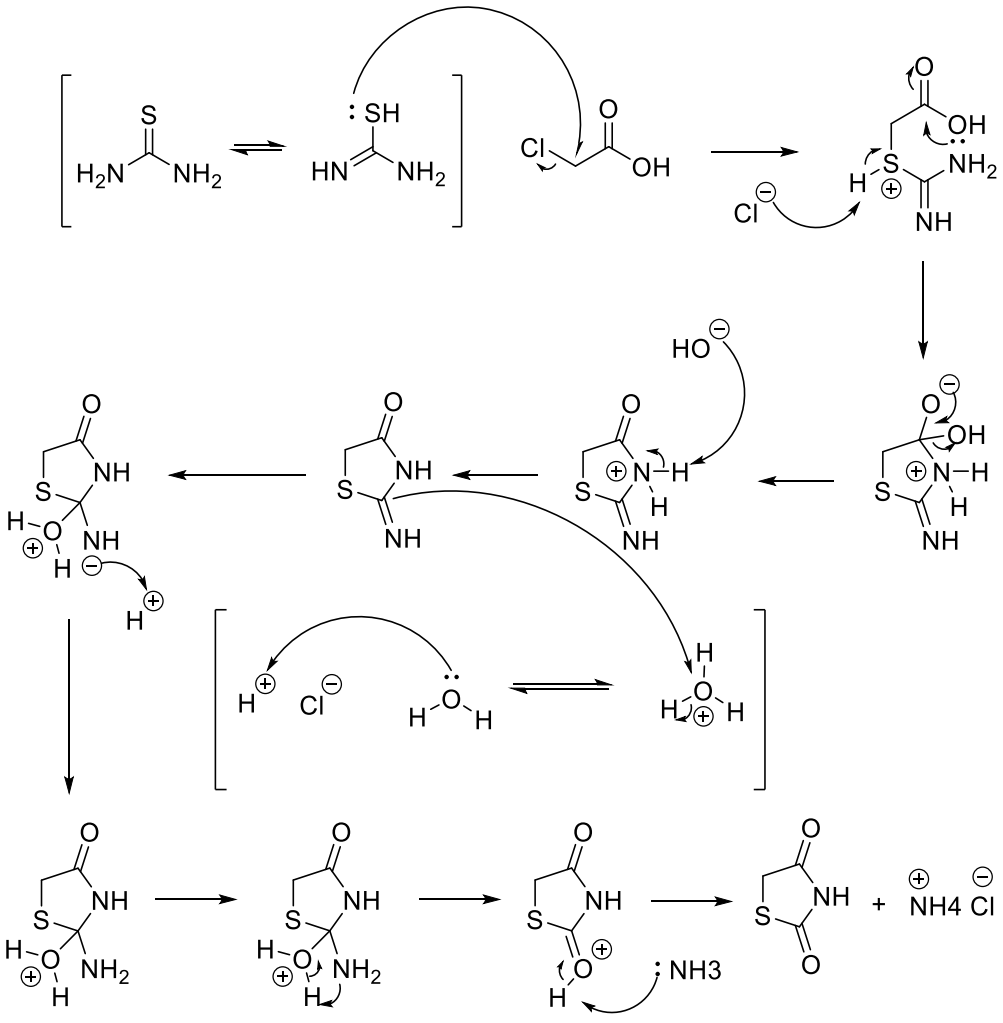
3.1 Preparation of Raw Material : Synthesis of 1,3-thiazolidine-2,4-dione (1)

1,3-thiazolidine-2,4-dione (**1**) was obtained in good yield (85%) by the action of thiourea on chloroacetic acid in the presence of hydrochloric acid [64]. The reaction mixture is heated for 10h at 110 °C, using water and conc. HCl as a solvent. The reaction scheme given below.



Scheme 9.

The following mechanism has been proposed :



Scheme 10.

The molecular structure of the desired compound (**1**) was elucidated by usual spectroscopic techniques such as FT-IR, ^{1}H NMR and ^{13}C NMR.

The NMR spectrum was recorded in DMSO d_6. The 1 H resonances were assigned on the basis of chemical shifts. The ^{1}H NMR spectrum exhibits two characteristic signals : a broad singlet at 10.98 ppm, attributed to the presence of NH group. Another signal in the form of a singlet at 3.98 ppm and which corresponds to the protons of the methylene group.

In the ^{13}C NMR spectrum, the signals resonated in the downfield region at 173.2 and 172.6 ppm are assigned to the two C=O amide functions. The appearance of signal at 35.7 ppm is assigned to the methylene group.

3.2 Barium hydroxide catalyzed solvent-free synthesis of 5-arylidene-1,3-thiazolidine-2,4-diones (3a-o)

To carry out our study, we chose as a model reaction, a mixture of 1,3-thiazolidinedione **1** (1.1 mmol) and *o*-tolualdehyde **2a** (1 mmol) in the presence of 20 mol% of the catalyst (Barium hydroxide) that we subjected to different operating conditions. At the first, To find a suitable reaction medium for the synthesis of the title compounds, the model reaction was performed in EtOH, in water, in a mixture of EtOH/H_2O and under solvent-free conditions at 80 °C. As it's clear from table 1, the best result were obtained under solvent-free as the reaction medium.

Table 1 A comparative study of efficiency of various catalysts for the synthesis of (Z)-5-(2-methylbenzylidene)thiazolidine-2,4-dione

Entry	Medium	Time (h)	Yield[b] (%)
1	EtOH	3	-
2	EtOH/Eau	3	10
3	Eau	3	21
4	Solvent-free	3	58

Réaction conditions : 1,3-thiazolidinedione (1.1 mmol); *o*-tolubenzaldehyde (1 mmol).
Catalyst $Ba(OH)_2$: 20 mol % ; Solvent-free, 80 °C
[b] Isolated pure product.

In a second step, involving the condensation reaction of 1,3-thiazolidinedione **1** (1.1 mmol), 2- methylbenzaldehyde **2a** (1 mmol) under thermal solvent-free conditions at 80 °C, several catalysts such as Boric and Ascorbic acid, Triethylamine (TMA) and Barium hydroxide were studied. As it is summarized from (table 2, entry 1-5), it was observed that catalytic systems triethylamine and Barium hydroxide efficiently accelerated the reaction towards the formation

of the desired product except for acid catalytic systems. The best yield of product **3a** (58%) was achieved under thermal solvent-free conditions at 80 °C, using 20 mol % of Barium hydroxide.

Table 2 A comparative study of efficiency of various catalysts for the synthesis of (Z)-5-(2-methylbenzylidene)thiazolidine-2,4-dione

Entry	Catalyst	Time (h)	Yield[b] (%)
1	-	3	-
2	Boric acid	3	-
3	Ascorbic acid	3	-
4	*Trimethylamine*	5	50
5	*Barium hydroxide*	3	58

Réaction conditions : 1,3-thiazolidinedione (1.1 mmol); *o*-tolubenzaldehyde (1 mmol). Catalyst : 20 mol %. Solvent-free, 80 °C

[b] Isolated pure product.

Next, we study the feasibility of Barium hydroxide as new catalyst for the synthesis of the desired compound, using different catalytic quantity 10, 20 and 30 mol %, under solvent-free conditions at 80 °C affording, 42, 58, and 19 % product yields, respectively. A further increase in amount of catalyst failed to improve the yield of the desired product. (Table 3, entries 1–3). An increase of the reaction temperature to 120 °C, lead to the apparent improvement of the reaction efficiency with significantly increased rates, and the desired products were obtained in very short times and excellent yields.

Table 3 Catalytic activity evaluation and the effect of temperature for the synthesis of (Z)-5-(2-methylbenzylidene)thiazolidine-2,4-dione

Entry	Catalyst (mol %)	Temperature (˚C)	Time (h)	Yield[c] (%)
1	10	80	3	42
2	20	80	3	58
3	30	80	3	19
4	20	100	1h 30 min	80
5	20	120	1	95

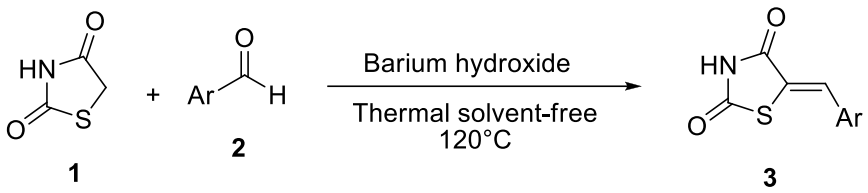
Réaction conditions : 1,3-thiazolidinedione (1.1 mmol); *o*-tolubenzaldehyde (1 mmol) under thermal solvent-free.

[b] Isolated pure product.

The reaction proceeds smoothly according to the previously defined optimum conditions, and excellent yields of multi-functionalized 1,3-thiazolidinediones derivatives were synthesized under thermal solvent-free using Barium hydroxide, for the first time. The obtained results are collated in Table 4 (entries 1–15). The structures of the synthesized molecules were

demonstrated by ^{1}H NMR, ^{13}C NMR spectroscopy, HRMS methods and further confirmed by single-crystal X-ray diffraction study performed for the compounds **3c**, **3i**, **3k** and **3m**.

Table 4 Thermal solvent-free synthesis of 5-arylidenethiazolidinediones derivatives in the presence of Barium hydroxide.

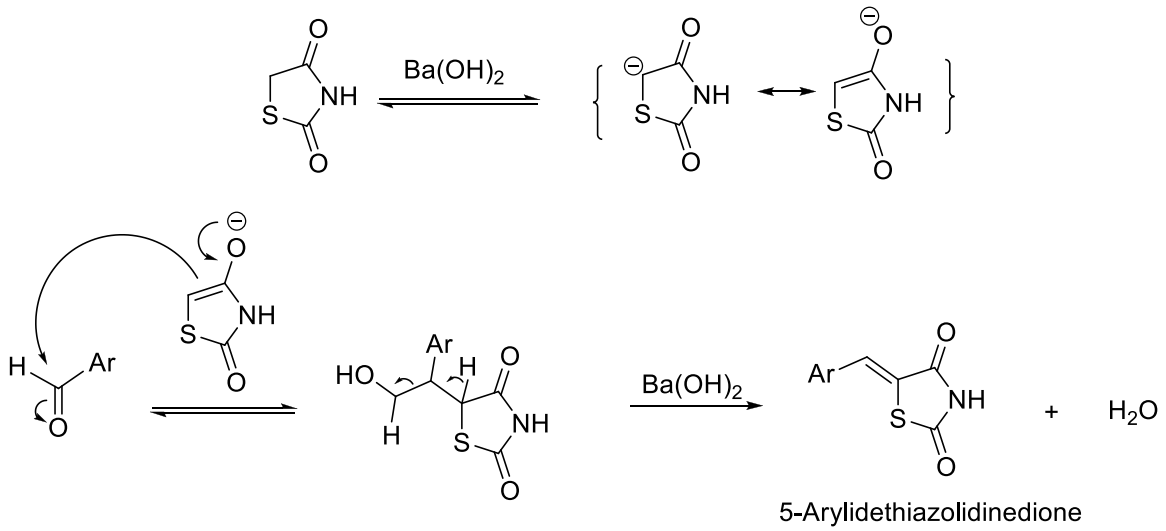


Scheme 11.

Entry	Ar	Compound	Time (h)	Yield [d] (%)	M.p. (˚C) Measured
1	2-Me-C_6H_4	3a	1	95	185-186
2	C_6H_5	3b	1	86	251-253
3	2,4-diMe-C_6H_3	3c	1	93	211-213
4	2,5-diMe-C_6H_3	3d	1	94	210-212
5	2,4-Cl_2-C_6H_3	3e	1	95	223-224
6	2,6-Cl_2-C_6H_3	3f	1	93	152-156
7	2,4-diOMe-C_6H_3	3g	1	90	220-222
8	3,4,5-TriOMe-C_6H_2	3h	1	87	185-187
9	3-Br-4-OMe-C_6H_3	3i	1	92	271-272
10	3-OMe-4-OH-C_6H_3	3j	1	95	228-229
11	3-OH-4-OMe-C_6H_3	3k	1	93	257-258
12	2-OH-C_6H_4	3l	1	90	255-256
13	2-OH-4-Br-C_6H_3	3m	1	92	248-250
14	2-OH-3-OMe-C_6H_3	3n	1	95	262-263
15	2,4-diOH-C_6H_3	3o	1	92	190 decomp

[d] Isolated pure product

A possible reaction mechanism is suggested :



Scheme 12.

3.3 Structural elucidation of the compound 3i (PR 10) taken as representative example

A structural analysis of (Z)-5-(3-bromo-4-methoxybenzylidene)thiazolidine-2,4-dione **3i**, taken as an example, was carried out. This compound has been experimentally characterized using, Nuclear Magnetic Resonance (NMR) spectroscopy and Mass Spectrometry. In addition, X-ray diffraction (XRD) was used for determining the atomic and molecular structure of this material.

Proton nuclear magnetic resonance

The NMR spectrum was recorded in DMSO d_6. The ^{1}H resonances were assigned on the basis of chemical shifts. The ^{1}H NMR spectrum exhibits a broad singlet at 12.59 ppm, attributed to the presence of NH group. Doublet signal at 7.86 ppm (J = 2.0 Hz) assigned to an aromatic proton. Characteristic signal that appear as singlet in 7.74 ppm (1H) correspond to ethylenic hydrogen. Additionally, aromatic proton shows doublet of doublet at 7.60 ppm with characteristic coupling constants of 8.7 and 2.0 Hz. A signal that appear as doublet in 7.28 ppm (1H) corresponds to the other aromatic hydrogen. The singlet peak at δ 3.92 ppm integrated for three protons was a characteristic peak of methoxy group.

Carbon nuclear magnetic resonance

In the ^{13}C NMR spectrum, the signals resonated in the downfield region at 167.8 and 167.6 ppm is assigned to the amide carbon. The appearance of a collection of signals in the region

134.9-111.4 ppm is ambiguously assigned to aryl carbons. Another signal resonated in the downfield region at 156.8 ppm belongs to C-OMe aryl carbon. In the aliphatic region, the signal at 56.6 ppm is assigned to the sole sp^3 hybridized carbon.

Crystallographic study of compound PR 10

Absolute structural determination is possible using single-crystal XRD data, the exact atomic positions can be observed, and thus bond lengths and angles can be determined.

Table 5. Crystal data and structure refinement for FB_PR 10

Empirical formula	$C_{11}H_8BrNO_3S$
Formula weight	314.15
Temperature [K]	296(2)
Crystal system	monoclinic
Space group (number)	$P2_1/c$ (14)
***a* [Å]**	7.3028(10)
***b* [Å]**	21.503(3)
***c* [Å]**	7.2715(7)
α [°]	90
β [°]	102.106(5)
γ [°]	90
Volume [Å^3]	1116.5(2)
Z	4
ρ_{calc} [gcm^{-3}]	1.869
μ [mm^{-1}]	3.862
***F*(000)**	624
Crystal size [mm^3]	0.720×0.110×0.080
Crystal colour	colourless
Crystal shape	stick
Radiation	MoK_α (λ=0.71073 Å)
2θ range [°]	5.71 to 54.94 (0.77 Å)
Index ranges	$-9 \le h \le 9$ $-26 \le k \le 27$ $-9 \le l \le 9$
Reflections collected	9810
Independent reflections	2535
Completeness to θ = 25.242°	99.4 %
Data / Restraints / Parameters	2535/0/158
Goodness-of-fit on F^2	1.328
Final *R* indexes [$I \ge 2\sigma(I)$]	R_1 = 0.0545 wR_2 = 0.1296

Final *R* indexes [all data]	R_1 = 0.0586 wR_2 = 0.1332
Largest peak/hole [eÅ^{-3}]	2.11/-1.31

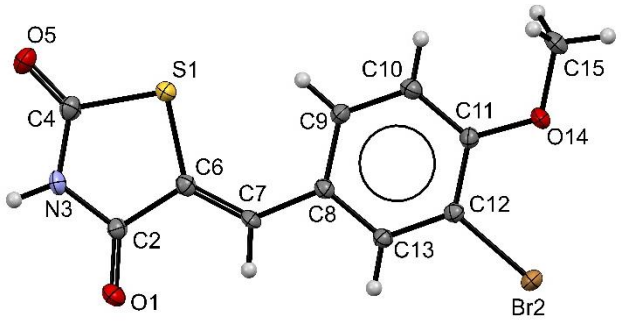


Figure 18. Crystallographic structure of the **PR 10** molecule

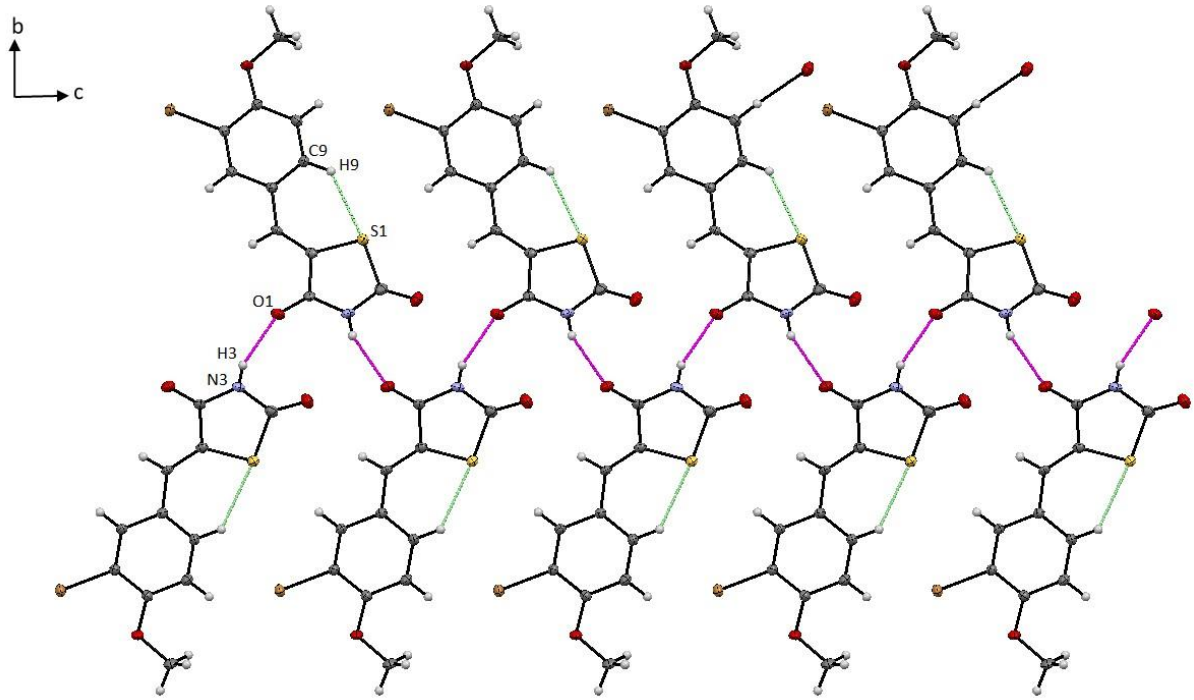


Figure 19 : The projection of the structure on the plan (bc).

Molecular stacking of title compound, presented in **Figure 19**, shows the existence of the two intermolecular and intramolecular hydrogen bonds of the type : N-H…O and C-H…S successive, that are sufficient to ensure cohesion of the crystalline structure (**Table 6**).

Table 6 : The list of hydrogen bonds existing in this compound.

	Hydrogen bond length (Å)			Angle (°)
D-H…A	**D-H**	**H…A**	**D…A**	**D-H…A**
N3-H3…O1	0,81(4)	2,12	2,888(3)	157(4)
C9-H9…S1	0,93	2,52	3,230(3)	134

4 Conclusion

In summary, we have developed a simple, rapid, and environmentally benign *protocol for the synthesis* of 5-Arylidene-2,4-thiazolidinediones **3a-o** derivatives, for the first time. *Inexpensive, widely available* Barium hydroxyde was employed to catalyze Knovenagel condensation reaction of thiazolidinediones and a wide range of functionalized aromatic aldehydes under solvent-free conditions. This new green synthesis has the rewards of ecologically benign, easy workup along with excellent yields. Readily available starting materials, atom-efficient routes employing more mild reaction conditions are the attracting features of this current protocol.

Moreover, selected compounds were screened towards antioxidant and antibacterial activities. In vitro studies showed that some synthesized 5-Arylidene-2,4-thiazolidinediones have significant inhibitory activities compared to reference drug. These preliminary results provide promising sources of multifunctional agents and sheds light on their potential usage in medicine and in the pharmaceutical industries.

The molecular structures of the synthesized compounds were fully elucidated by spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS methods and, for compounds **3c**, **3i**, **3k** and **3m** by single crystal X-ray diffraction analysis.

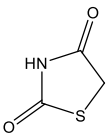
Experimental Section

5 Experimental Section

5.1 General procedure for the synthesis of 1,3-thiazolidine-2,4-dione (1)

In a 250 ml three-necked flasks was placed, a solution containing 56.5g (0.6M) of chloroacetic acid in 60 ml of water and 45.6g (0.6M) of thiourea dissolved in 60 ml of water. The mixture was stirred for 15 min to obtain a white precipitate, accompanied by considerable cooling. The 60 ml of concentrated hydrochloric acid from a drooping funnel was added slowly to the content of flask. The flask was then connected with a reflux condenser and gentle heat applied to effect complete dissolution, the solution is then brought to reflux for 8 to 10 hours. The residue in the form of white needles is filtered, washed with cold water to remove traces of hydrochloric acid. The residue is recrystallized from ethanol if necessary [64].

1,3-thiazolidine-2,4-dione (PR 19)



1

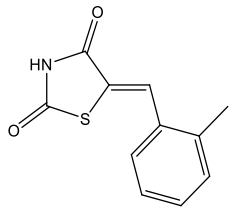
Yield = 85% as white crystals; $\mathbf{T_{fus.}}$= 124 °C (littérature = 123-125 °C, [64]); **IR** (KBr): ν (cm^{-1}): 1647, 1337, 1226, 1158, 787, 711, 617, 606; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 12.01 (s, 1H, -NH), 4.14 (s, 2H, -CH_2); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 173.9 (C=O), 173.1 (C=O), 35.8 (CH_2).

5.2 General procedure for the synthesis of 5-arylidene-1,3-thiazolidine-2,4-dione (3a-o)

Baryum hydroxide (0.2 mmol) was added to a mixture of aldehyde (1 mmol) and 1,3-thiazolidinedione (1.2 mmol). The resulted reaction mixture was magnetically heated at 120 ºC under solvent-free conditions for the appropriate time (Table 4). After completion (TLC), the reaction mixture was allowed to warm to room temperature, then 5 ml of hexane solvent was added while maintaining stirring for 30 min. The solid product was filtered and washed with *n*-Hexane, then with water to afford the final pure product.

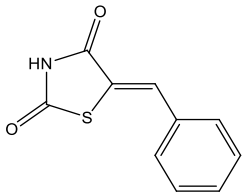
5.3 Spectral data for all synthesized compounds

(Z)-5-(2-methylbenzylidene) thiazolidine-2,4-dione (PR 1)



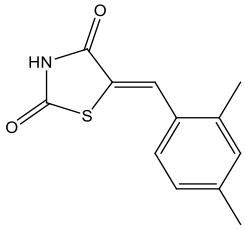
Yield= 95 % as white solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 7.83 (s, 1H, -CH), 7.42-7.41 (m, 1Har), 7.34-7.31 (m, 3Har), 2.38 (s, 3H, -CH_3); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 169.1, 169.0, 138.5, 132.5, 130.9, 130.0, 128.4, 127.1, 126.6, 35.8, 19.4.

(Z)-5-benzylidenethiazolidine-2,4-dione (PR 2)



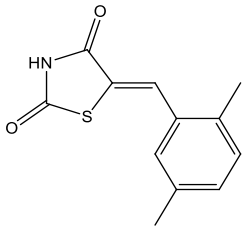
Yield= 86 % as white solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 12.45 (s, 1H, -NH), 7.74 (s, 1H, -CH), 7.60-7.45 (m, 5Har); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 169.0, 168.7, 133.3, 132.9, 130.8, 130.1, 130.0, 129.3, 128.6, 124.9, 35.8.

(Z)-5-(2,4-dimethylbenzylidene)thiazolidine-2,4-dione (PR 3)



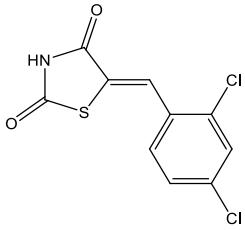
Yield= 93 % as beige solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 12.53 (s, 1H, -NH), 7.84 (s, 1H, -CH), 7.31 (d, J = 8.4 Hz, 1Har), 7.17-7.15 (m, 2Har), 2.36 (s, 3H, -CH_3), 2.30 (s, 3H, -CH_3); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 168.4, 167.8, 140.3, 138.7, 131.7, 129.3, 129.1, 127.2, 127.1, 124.3, 20.9, 19.3.

(Z)-5-(2,5-dimethylbenzylidene)thiazolidine-2,4-dione (PR4)



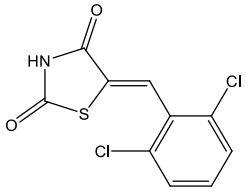
Yield= 94 % as beige solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 12.47 (s, 1H, -NH), 7.82 (s, 1H, -CH), 7.31 (d, J = 8.3 Hz, 1Har), 7.16-7.15 (m, 2Har), 2.35 (s, 3H, -CH_3), 2.30 (s, 3H, -CH_3); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 168.8, 168.5, 140.1, 138.6, 131.6, 129.4, 128.6, 127.2, 127.1, 124.9, 35.8, 20.9, 19.3.

(Z)-5-(2,4-dichlorobenzylidene)thiazolidine-2,4-dione (PR 6)



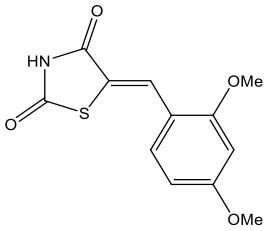
Yield= 95 % as white solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 7.84 (d, J = 1.8 Hz, 1Har), 7.82 (s, 1H, -CH), 7.61 (dd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1Har), 7.58 (d, J = 8.5 Hz, 1Har); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 168.0, 135.3, 135.2, 130.3, 130.0, 129.9, 128.3, 124.8.

(Z)-5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione (PR 7)



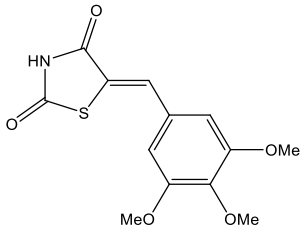
Yield= 93 % as white solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 7.71 (s, 1H, -CH), 7.57-7.55 (m, 2H), 7.45 (t, 1Har, J = 8.1 Hz); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 173.9, 170.2, 169.2, 135.8, 133.2, 132.4, 131.3, 128.7, 124.7, 35.8.

(Z)-5-(2,4-dimethoxybenzylidene)thiazolidine-2,4-dione (PR 8)



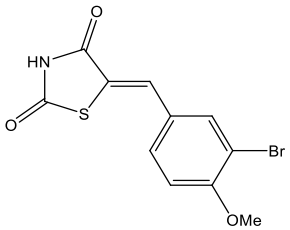
Yield= 90 % as beige solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 12.47 (s, 1H, -NH), 7.71 (s, 1H, -CH), 7.18-7.11 (m, 3Har), 3.82 (s, 3H, -OMe), 3.80 (s, 3H, -OMe); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 168.6, 150.6, 148.9, 131.4, 125.9, 123.6, 121.5, 113.2, 112.1, 55.7, 55.5.

(Z)-5-(3,4,5-trimethoxybenzylidene)thiazolidine-2,4-dione (PR 9)



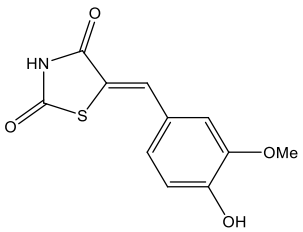
Yield= 87 % as yellow solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 7.66 (s, 1H, -CH), 6.91 (s, 2Har), 3.82 (s, 6H, 2-OMe), 3.72 (s, 3H, -OMe); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 169.2, 153.1, 139.0, 130.4, 129.1, 124.7, 107.3, 60.2, 56.1, 56.0, 35.8.

(Z)-5-(3-bromo-4-methoxybenzylidene)thiazolidine-2,4-dione (PR 10)



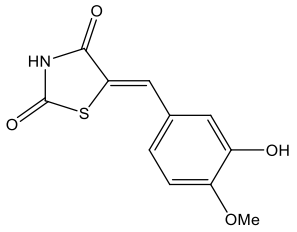
Yield= 92 % as greenyellow solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 12.59 (s, 1H, -NH), 7.86 (d, J = 2.0 Hz, 1Har), 7.74 (s, 1H, -CH), 7.60 (dd, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 1Har), 7.28 (d, J = 8.7 Hz, 1Har), 3.92 (s, 3H, -OMe); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 167.8, 167.6, 156.8, 134.9, 130.6, 130.1, 127.1, 122.3, 113.3, 111.4, 56.6; HRMS (ESI+): m/z $[M+H]^+$ Calc. Mass for $C_{11}H_9NO_3SBr$ 313.9487, found. 313.9488.

(Z)-5-(4-hydroxy-3-methoxybenzylidene)thiazolidine-2,4-dione (PR 12)



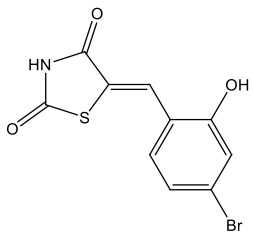
Yield= 95 % as yellow solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 12.44 (s, 1H, -NH), 9.92 (s, 1H, -OH), 7.69 (s, 1H, -CH), 7.16 (d, J = 1.2 Hz, 1Har), 7.06 (dd, J_1 = 8.3 Hz, J_2 = 1.2 Hz, 1Har), 6.92 (d, J = 8.3 Hz, 1Har), 3.82 (s, 3H, -OMe); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 168.4, 168.0, 149.3, 148.0, 132.3, 124.5, 124.1, 119.7,116.2, 114.1, 55.6.

(Z)-5-(3-hydroxy-4-methoxybenzylidene)thiazolidine-2,4-dione (PR 13)



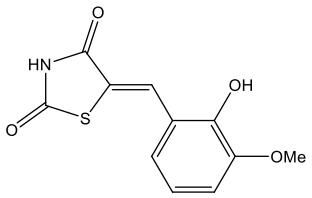
Yield= 93 % as beige solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 9.45 (s, 1H, -OH), 7.58 (s, 1H, -CH), 7.06-7.02 (m, 3Har), 3.82 (s, 3H, -OMe); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 169.1, 149.8, 146.9, 131.1, 126.1, 123.2, 115.8, 112.4, 55.7.

(Z)-5-(4-bromo-2-hydroxybenzylidene)thiazolidine-2,4-dione (PR 14)



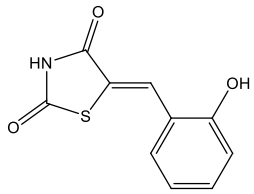
Yield= 92 % as goldenrod solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 10.69 (s, 1H, -OH), 7.77 (s, 1H, -CH), 7.43 (d, J = 2.3 Hz, 1Har), 7.40 (dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz, 1Har), 6.90 (d, J = 8.7 Hz, 1Har); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 174.0, 172.3, 170.1, 156.1, 133.4, 130.1, 127.8, 123.3, 122.3, 118.0, 110.4, 35.9; HRMS (ESI-): m/z $[M-H]^-$ Calc. Mass for $C_{10}H_5NO_3SBr$ 297.9174, found. 297.9175.

(Z)-5-(2-hydroxy-3-methoxybenzylidene)thiazolidine-2,4-dione (PR 15)



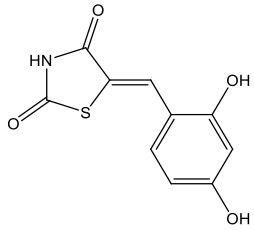
Yield= 95 % as yellow solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 12.41 (s, 1H, -NH), 9.57 (s, 1H, -OH), 7.97 (s, 1H, -CH), 7.05 (d, J = 7.2 Hz, 1Har), 6.97 (d, J = 7.2 Hz, 1Har), 6.90 (t, J = 8.0 Hz, 1Har), 3.83 (s, 3H, -OMe); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 147.9, 146.4, 125.2, 120.8, 119.5, 119.4, 113.5, 56.0, 35.9; HRMS (ESI+): m/z $[M+H]^+$ Calc. Mass for $C_{11}H_{10}NO_4S$ 252.0331, found. 252.0330.

(Z)-5-(2-hydroxybenzylidene)thiazolidine-2,4-dione (PR 16)



Yield= 90 % as goldenrod solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 10.42 (s, 1H, -OH), 7.96 (s, 1H, -CH), 7.35 (d, J = 7.1 Hz, 1Har), 7.27 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1Har), 6.96-6.91 (m, 2Har); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 170.1, 169.5, 157.1, 131.7, 128.2, 125.4, 124.0, 120.4, 120.0, 116.0, 35.9; HRMS (ESI-): m/z $[M-H]^-$ Calc. Mass for $C_{10}H_6NO_3S$ 220.0068, found. 220.0067.

(Z)-5-(2,4-dihydroxybenzylidene)thiazolidine-2,4-dione (PR 18)



Yield= 92 % as beige solid; **^{1}H NMR** (500.28 MHz, DMSO-d_6): δ (ppm): 7.92 (s, 1H, -CH), 7.17 (d, J = 7.2 Hz, 1Har), 6.40 (dd, J_1 = 7.2 Hz, J_2 = 2.2 Hz, 1Har), 6.38 (d, J = 2.2 Hz, 1Har), 4.12 (s, 2H, 2(-OH)); **^{13}C NMR** (125.8 MHz, DMSO-d_6): δ (ppm): 169.6, 169.3, 161.3, 159.2, 129.8, 126.3, 112.0, 108.2, 102.5, 36.0; HRMS (ESI-): m/z $[M-H]^-$ Calc. Mass for $C_{10}H_7NO_4S$ 236.0018, found. 236.0016.

References

[1] (a) S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto and V. Zanirato, *Chem. Rev*., **1995**, 95, 1065-1114; (b) C. Simon, T. Constantieux and J. Rodriguez, *Eur. J. Org. Chem*., **2004**, 4957; (c) H. Fujioka, K. Murai, O. Kubo, Y. Ohba and Y. Kita, *Org. Lett*., **2007**, 9, 1687-1690.

[2] M. J. Naim et al, *Eur. J. Med. Chem*.,**2017**, *129*, 218-250.

[3] (a) N. D. Sonawane and A. S. Verkman, *Bioorg. Med. Chem*., **2008**, 16, 8187-8195; (b) R. Maccari, R. Ottana, C. Curinga, M. G. Vigorita, ` D. Rakowitz, T. Steindl and T. Langer, *Bioorg. Med. Chem*., **2005**, 13, 2809; (c) A. Verma and S. K. Saraf, *Eur. J. Med. Chem*., **2008**, 43, 897-905; (d) B. Fabi ´ an, V. Kudar, A. Cs ´ ampai, T. Z. Nagy and P. ´ Sohar, ´ *J. Organomet. Chem*., **2007**, 692, 5621-5632; (e) R. Murugan, S. Anbazhagan and S. Sriman Narayanan, *Eur. J. Med. Chem*., **2009**, 44, 3272-3279; (f) B. R. Bhattarai, B. Kafle, J.-S. Hwang, D. Khadka, S.-M. Lee, J.-S. Kang, S. W. Ham, I.-O. Han, H. Park and H. Cho, Bioorg. *Med. Chem. Lett*., **2009**, 19, 6161-6165.

[4] H. Maruoka, M. Yamazaki, Y. Tomioka. *J. Heterocycl. Chem*. **2004**, 41, 641−646.

[5] V. S. Dofe, A. P. Sarkate, Z. M. Shaikh, C. K. Jadhav, A. S. Nipte, C. H. Gill. *J. Heterocycl. Chem*. **2018**, 55, 756−762.

[6] J. Sun, L. L. Zhang, E. Y. Xia, C. G. Yan. *J. Org. Chem*. **2009**, 74, 3398−3401.

[7] S.V. Jain, D.K. Vora, C.S. Ramaa, *Bioorg. Med. Chem*. **2013**, 21, 1599-1620.

[8] D. Kaminskyy, A. Kryshchyshyn, & R. Lesyk, *European journal of medicinal chemistry*. **2017**, 140, 542-594.

[9] C.D. Barros, A.A. Amato, K.B.R. Iannini, A.L. Silva, E.S. Leite, M.Z. Hernandes,M.C.A. Lima, S.L. Galdino, F.A.R. Neves, I.R. Pitta, *Bioorg. Med. Chem*. **2010**, 18, 3805-3811.

[10] S. Nakamura, K. Hayashu, H. Takizawa, T. Murase, K. Tsuruma, M. Shimazawa,H. Kakuta, H. Nagasawa, H. Hara, *Curr. Neurovasc. Res*. **2011**, 8, 25-34.

[11] V. Carbone, M. Giglio, R. Chung, T. Huyton, J. Adams, R. Maccari, R. Ottana, A.Hara, O. El-Kabbani, *Eur. J. Med. Chem*. **2010**, 45, 1140-1145.

[12] J. Liu, K. K. J. Chan, W. Chan, *Chem Res Toxicol*. **2016**, 29, 1865–1871.

[13] L. A. Bivona, F. Giacalone, L. Vaccaro, C. Aprile, M. Gruttadauria, *ChemCatChem*. **2015**, 7, 2526–2533.

[14] V. Kozell M. McLaughlin, G. Strappaveccia, S. Santoro, L. A. Bivona, C. Aprile, M. Gruttadauria, L. Vaccaro, *ACS Sustain Chem Eng*. **2016**, 4, 7209–7216.

[15] O. Bozdag-dündar, R. Ertan, H. Y. Aboul-Enein, A. Kładna, I. Kruk, *Luminescence*. **2011**, 26, 10–16.

[16] O. Bozdag-dündar, S. Gürkan, H. Y. Aboul-Enein, I. Kruk, A. Kładna, *Luminescence*. **2009**, 24, 194–201.

[17] B. De, I. Adhikari, A. Nandy, A. Saha, B. B. Goswami, *J Mol Struct*. **2017**, 1138, 17–26.

[18] S. Ueda, H. Terauchi, A. Yano, M. Matsumoto, T. Kubo, Y. Kyoya, K. Suzuki, M. Ido, M. Kawasaki, *Bioorg Med Chem*. **2014**, 12, 4101–4116.

[19] M. A. Ibrahim, M. Abdel-Megid, N. M. El-gohary, J. Braz, *Chem. Soc*. **2011**, 22, 1130-1139.

[20] S. Venkatesan, R. Singh, *Int. J. Chem. Pharm. Sci*. **2010**, 1, 17.

[21] S. S. Purohit, A. Alman, J. Shewale, *Int. J. Pharm. Pharm. Sci*. **2012**, 4, 273-276.

[22] G. Bruno, L. Costantino, C. Curinga, R. Maccari, F. Monforte, F. Nicolo, R. Ottana,M.G. Vigorita, *Bioorg. Med. Chem*. 2002, 10, 1077-1084.

[23] L. V. Sonawane, S. B. Bari, *Int. J. Biol. Chem*. **2011**, 5, 68-74.

[24] S. R. Mahalle, P. D. Netankar, S. P. Bondge, R. A. Mane, *Green Chem. Lett. Rev*. **2008**, 1, 103-106.

[25] Y. Zhang, Z. Zhou, Org. Chem. Int. 2012, 1-5.

[26] M. J. Naim et al. *Eur. J. Med. Chem*. **2017**, *129*, 218-250.

[27] S. Kallenbeg, S. Ber. *Deut. Chem. Ges*. **1923**, *56*, 316.

[28] O. Bozdag, G. Ayhan-Kilcigil, M. Tuncbilek, R. Ertan. *Turk. J. Chem*. **1999**, *23*, 163-169.

[29] B. R. Prashantha Kumar, S. Santhosh Kumar, Patel Viral, Ashish Wadhwani, R. Vadivelan, M. N. Satish Kumar, K. Elango, M. J. Nanjan. *J. Med. Chem. Res*. **2012**, *21*, 2689-2701.

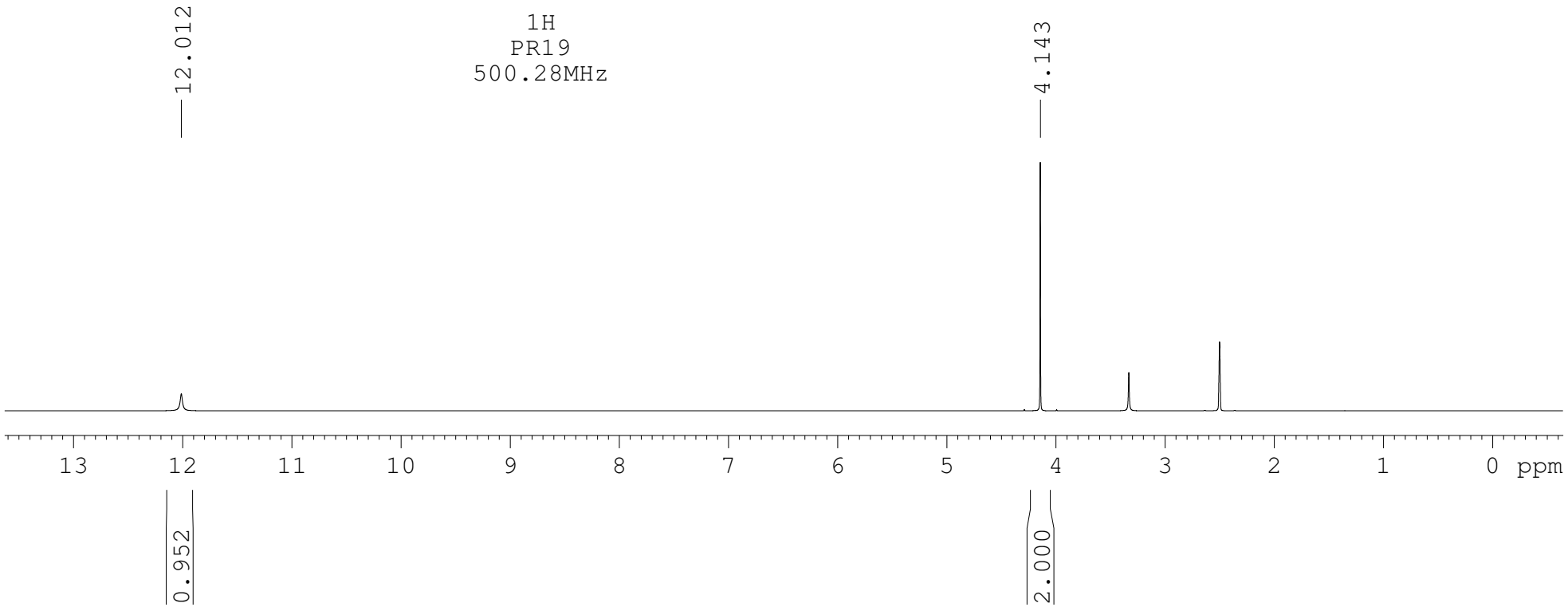
[30] J. Taylor. *J. Chem. Soc. Trans*. **1920**, 117, 4.

[31] W. Heintz. *Eur. J. Org. Chem*. **1865**, *136*, 213-223.

[32] E. S. Darwish, *Molecules*. **2008**, *13*, 1066-1078.

[33] W. Zhu, Y. Chong, H. Choo, J. Mathews, R. F. Schinazi, C. K. Chu, *J. Med. Chem.* **2004**, *47*, 1631-1640.
[34] M. J. Naim et al. *Eur. J. Med. Chem.* **2017**, *129*, 218-250.
[35] S. Kallenbeg, S. Ber. *Deut. Chem. Ges*. **1923**, *56*, 316.
[36] O. Bozdag, G. Ayhan-Kilcigil, M. Tuncbilek, R. Ertan. *Turk. J. Chem.* **1999**, *23*, 163-169.
[37] B. R. Prashantha Kumar, S. Santhosh Kumar, Patel Viral, Ashish Wadhwani, R. Vadivelan, M. N. Satish Kumar, K. Elango, M. J. Nanjan. *J. Med. Chem. Res.* **2012**, *21*, 2689-2701.
[38] J. Taylor. *J. Chem. Soc. Trans*. **1920**, 117, 4.
[39] W. Heintz. *Eur. J. Org. Chem.* **1865**, *136*, 213-223.
[40] B. Božić, J. Rogan, D. Poleti, M. Rančić, N. Trišović, B. Božić, G. Ušćumlić, *Arab J Chem*, **2013**.
[41] M. RASHID, N. SHRIVASTAVA, A. HUSAIN. *J. Chil. Chem. Soc*.**2020**, *65*,
[42] M. Laakso. Diabetes,**1999**, *48*, 937-942.
[43] T. Fujita, Y. Sugiyama, S. Taketomi, T. Sohda, Y. Kawamatsu, H. Iwatsuka, Z. Suzuoki. *Diabetes*, **1983**, *32* 804-810.
[44] Y. Sugiyama, S. Taketomi, Y. Shimura, H. Ikeda, T. Fujita. Arzneim. Forsch. **1990**, *40*, 263-267
[45] K. Kar, U. Krithika, P. Basu, S.S. Kumar, A. Reji, B.P. Kuma. *Bioorg. Chem*. **2014**, *56*, 27-33.
[46] D.V. Jawale, U.R. Pratap, N. Rahuja, A.K. Srivastava, R.A. Mane. *Bioorg. Med. Chem. Letts*, **2012**, *22*, 436-439.
[47] D.M. Corigliano, R. Syed, S. Messineo, A. Lupia, R. Patel, C.V.R. Reddy, A. Brunetti. *Peer J*. **2018**, *6*, 1-19.
[48] K. Metwally, H. Pratsinis, D. Kletsas. *Eur. J. Med. Chem*. **2017**, *133*, 340–350.
[49] P. Sharma, T.S. Reddy, D. Thummuri, K.R. Senwar, N.P. Kumar, V.G. Naidu, S.K. Bhargava, N. Shankaraiah. *Eur. J. Med. Chem*. **2016**, *124*, 608-621.
[50] H. L. T. Anh, N. T. Cuc, B. H. Tai, P. H. Yen, N. Xuan, D. T. Thao, N. H. Nam, C. V. Minh, P. V. Kiem, K. H. Kim. *Molecules*. **2015**, *20*, 1151–1160.
[51] F. A. K. Khan, K. S. Jadhav, R. H. Patil, D. B. Shinde, R. B. Arote, J. N. Sangshetti, *Biomed Pharmacother*. **2016**, *83*, 1146-1153.
[52] C. M. Nastasa, M. Duma, A. Pirnau, L. Vlase, B. Tiperciuc, Oniga. *Clujul Med*, **2016**, *89*, 122–127
[53] R. S. Bahare, S. Ganguly, K. Choowongkomon, S. Seetaha. *DARU J. Pharm. Sci*.**2015**, *23*, 1-15.
[54] P. Moorthy, S. P. Ekambaram, S. S. Perumal, *Arab. J. Chem*. **2014**, *8*, 1-7
[55] N.M. Parekh, K.V. Juddhawala, B.M. Rawal, *Med. Chem. Res*. **2013**, *22*, 2737-2745.
[56] O. Prakash, D.K. Aneja, P. Lohan, K. Hussain, S. Arora, C. Sharma, K.R. Aneja, *Med. Chem. Res*. **2012**, *21*, 2961-2968
[57] S. D. Beedkar, C. N. Khobragade, S. S. Chobe, B. S. Dawane, O. S. Yemul, *Int. J. Biol. Macromol*. **2012**, *50*, 947–956.
[58] A.B. Begum, M. Begum, V.L. Ranganatha, T. Prashanth, F. Zameer, R. Hegdekatte, S.A. Khanum. *Arch. Pharm*. **2014**, *347*, 247-255.
[59] S.U. Hossain, S. Bhattacharya. *Bioorg. Med. Chem. Letts*. **2007**, *17*, 1149-1154.
[60] Y. Chinthala, A.K. Domatti, A. Sarfaraz, S.P. Singh, N.K. Arigari, N. Gupta, S.K. Satya, J.K. Kumar, F. Khan, A.K. Tiwari, G. Paramjit. *Eur. J. Med. Chem*. **2013**, *70*, 308-314.
[61] G. Bruno, L. Costantino, C. Curinga, R. Maccari, F. Monforte, F. Nicolo, R. Ottana, M. Vigorita. *Bioorg. Med. Chem*. **2002**, *10*, 1077-1084.
[62] R. Maccari, R. Ottanà, C. Curinga, M. G. Vigorita, D. Rakowitz, T. Steindl, T. Langer. *Bioorg. Med. Chem*. **2005**, *13*, 2809-2823.
[63] O. Bozdag˘-Dündar, E. J. Verspohl, N. Das-Evcimen, R. M. Kaup, K. Bauer, M. Sarıkaya, B. Evranos, R. Ertan. *Bioorg. Med. Chem*. **2008**, *16*, 6747-6751.
[64] (a) T. Sodha, K. Mizuno, E. Imamiya, Y. Sugiyama, T. Fujita, et al, ChemPharm Bull., 1982, 30, 580- 600; (b) S. B. Radhe, V. M. Kulkarni, Der Pharma Chem.,2011, 3, 164-173.

APPENDIX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12
11
10
9
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7
6
5
4
3
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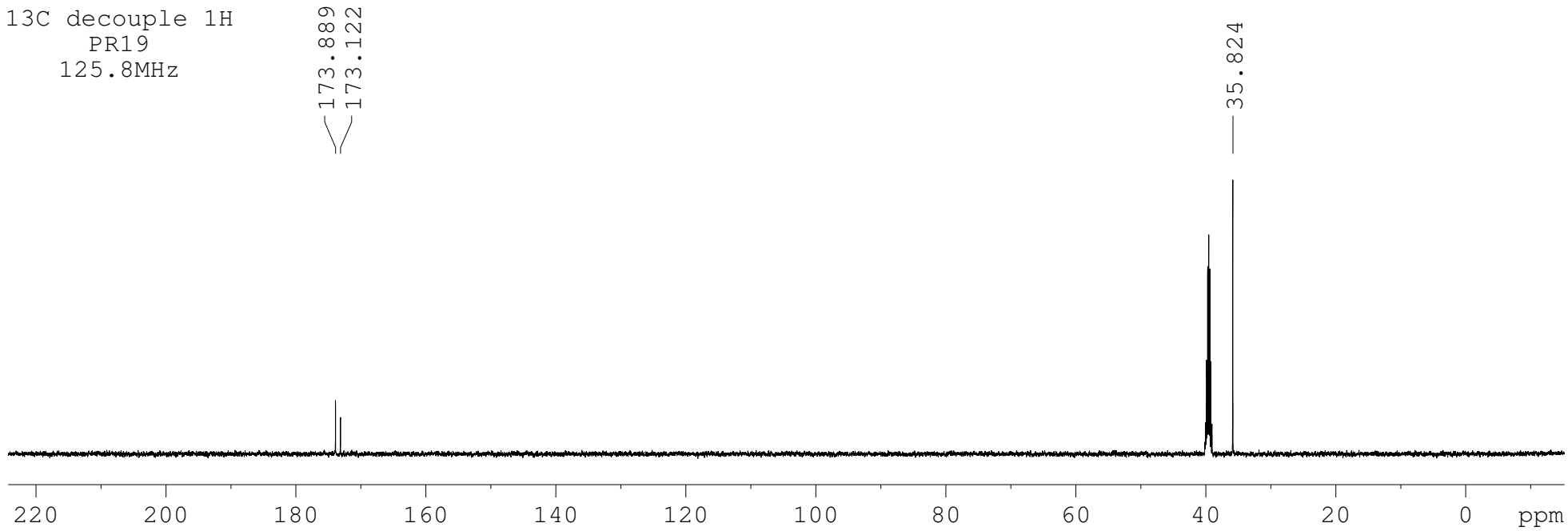
2.000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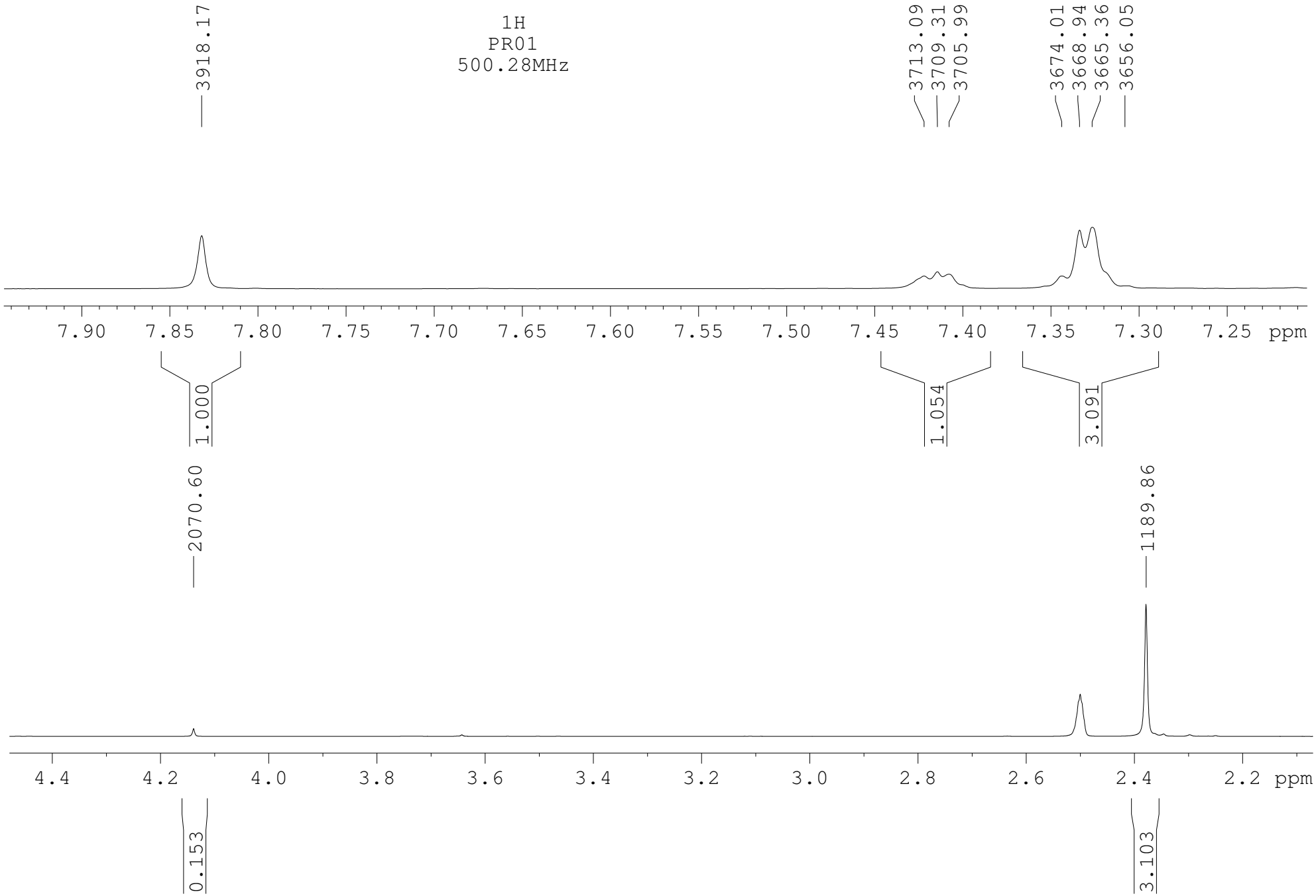
60
40
20
0
ppm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3665.36
3656.05
7.90
7.85
7.80
7.75
7.70
7.65
7.60
7.55
7.50
7.45
7.40
7.35
7.30
7.25
ppm
1.000
1.054
3.091
2070.60
1189.86
4.4
4.2
4.0
3.8
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3.4
3.2
3.0
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2.6
2.4
2.2
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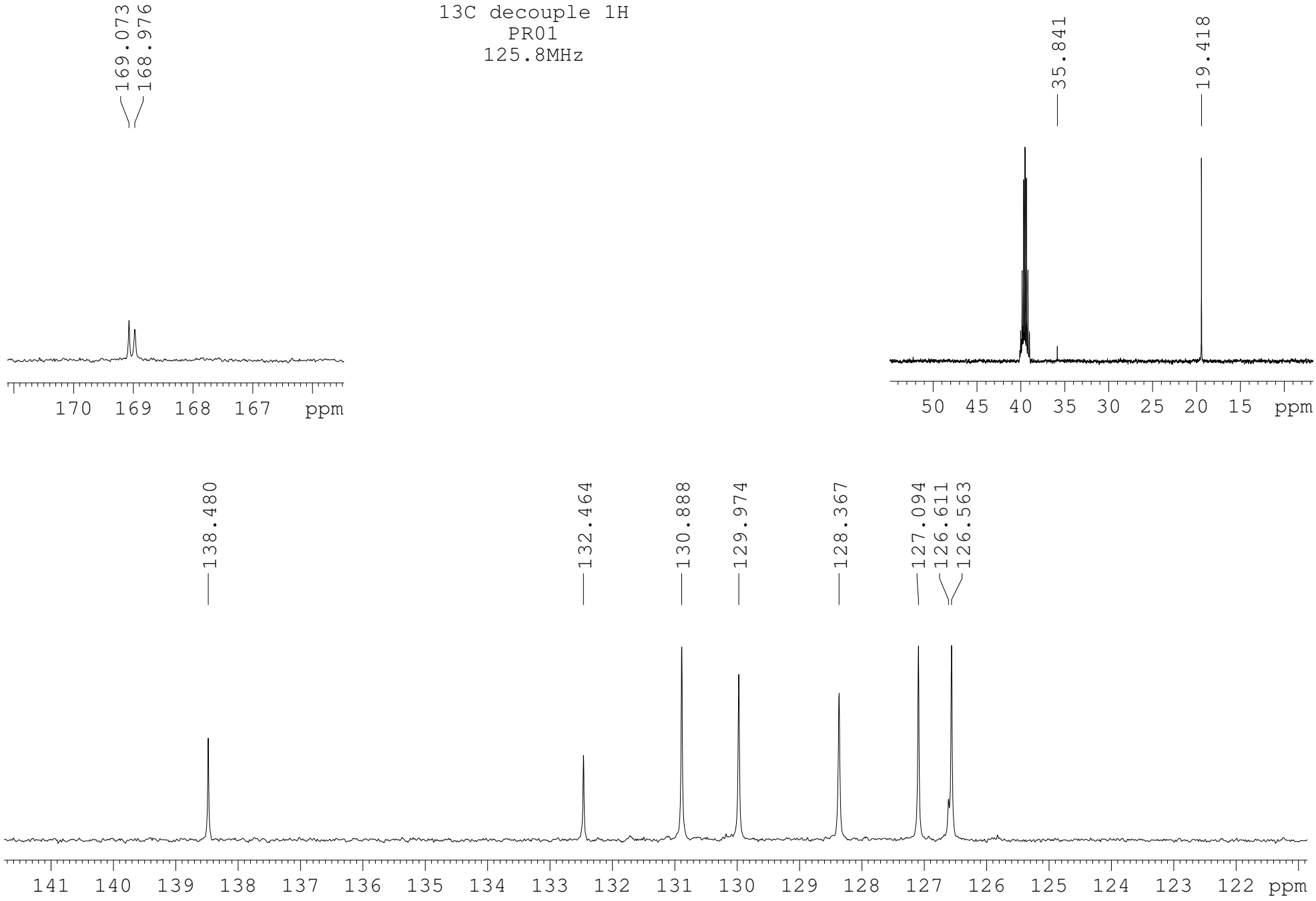
3.103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130.888
129.974
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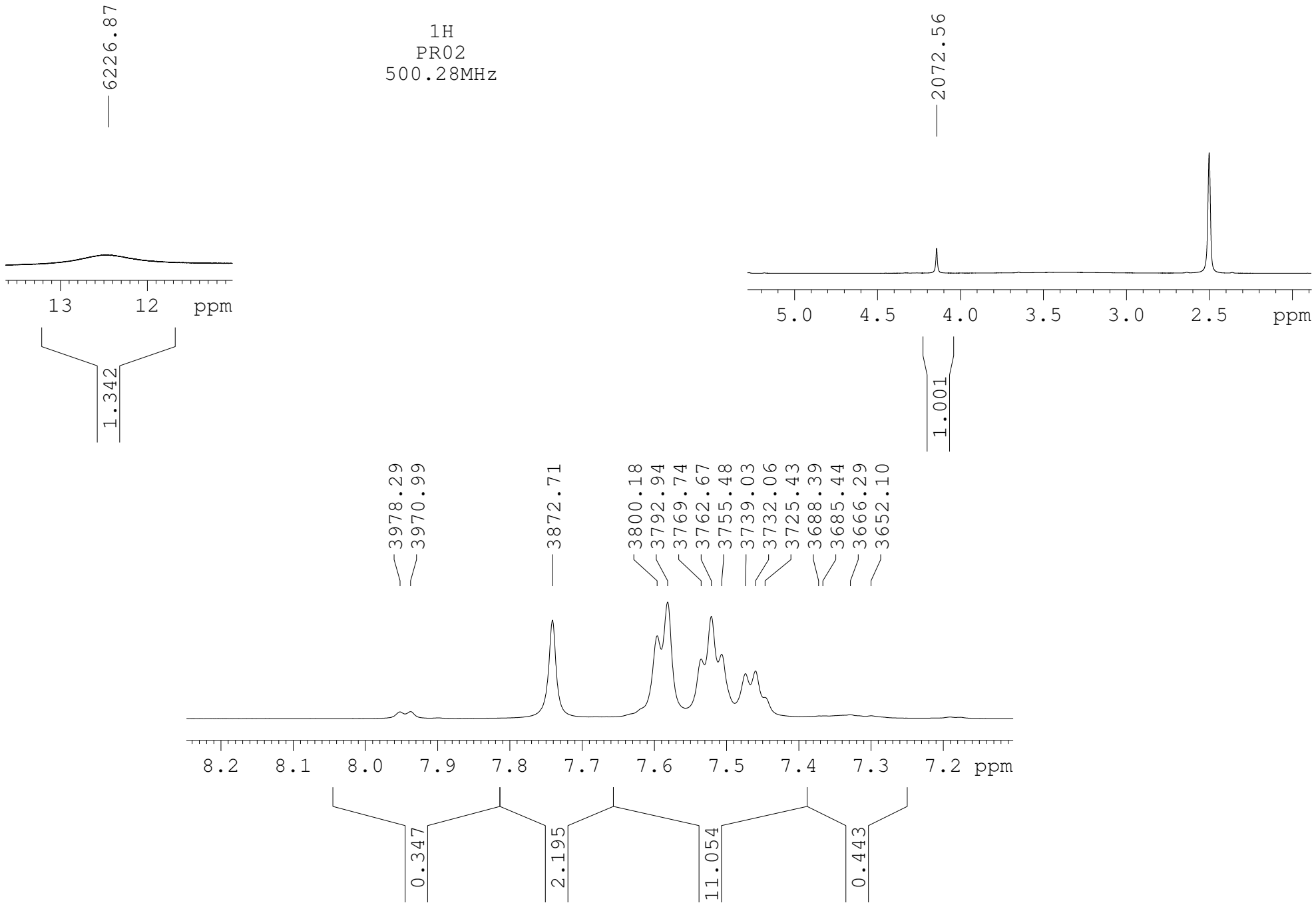
126.611
126.563
170 169 168 167 ppm
50 45 40 35 30 25 20 15 ppm
141 140 139 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122 ppm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3.0
2.5
ppm
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3978.29
3970.99
3872.71
3800.18
3792.94
3769.74
3762.67
3755.48
3739.03
3732.06
3725.43
3688.39
3685.44
3666.29
3652.10
8.2
8.1
8.0
7.9
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7.6
7.5
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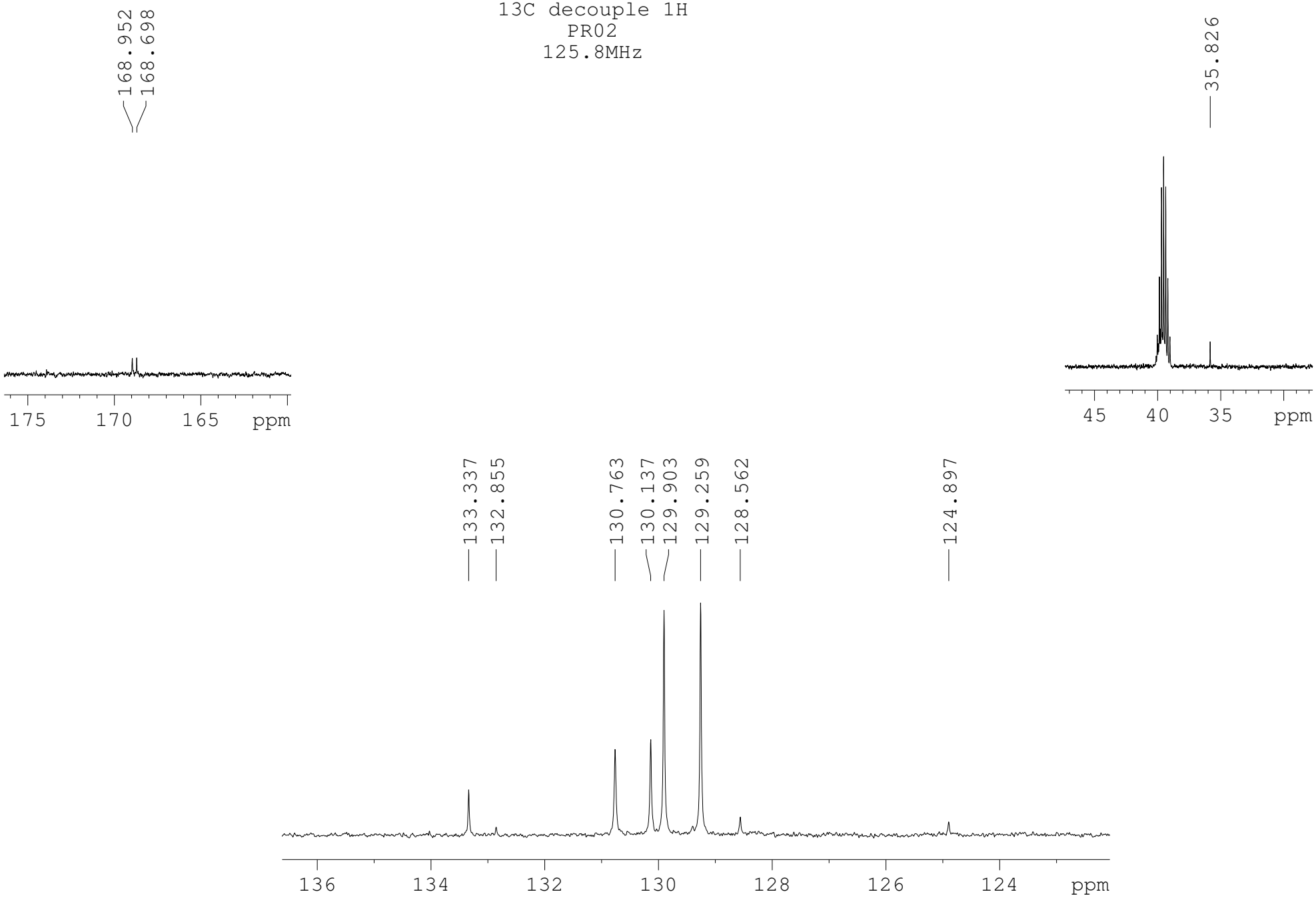
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129.903
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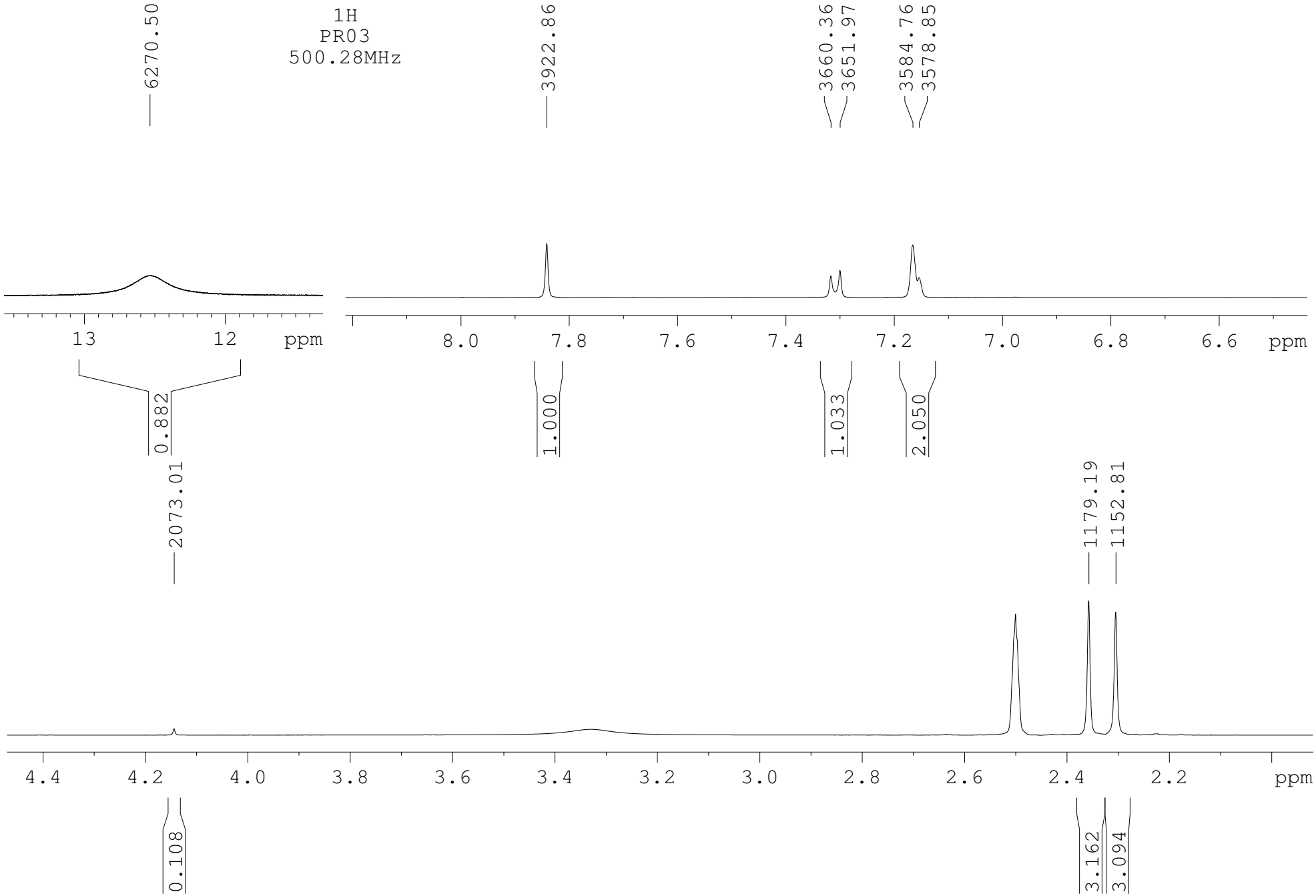
170
165
ppm
45
40
35
ppm
136
134
132
130
128
126
124
ppm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13
12
ppm
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
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1.033
2.050
2073.01
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4.4
4.2
4.0
3.8
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3.2
3.0
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2.2
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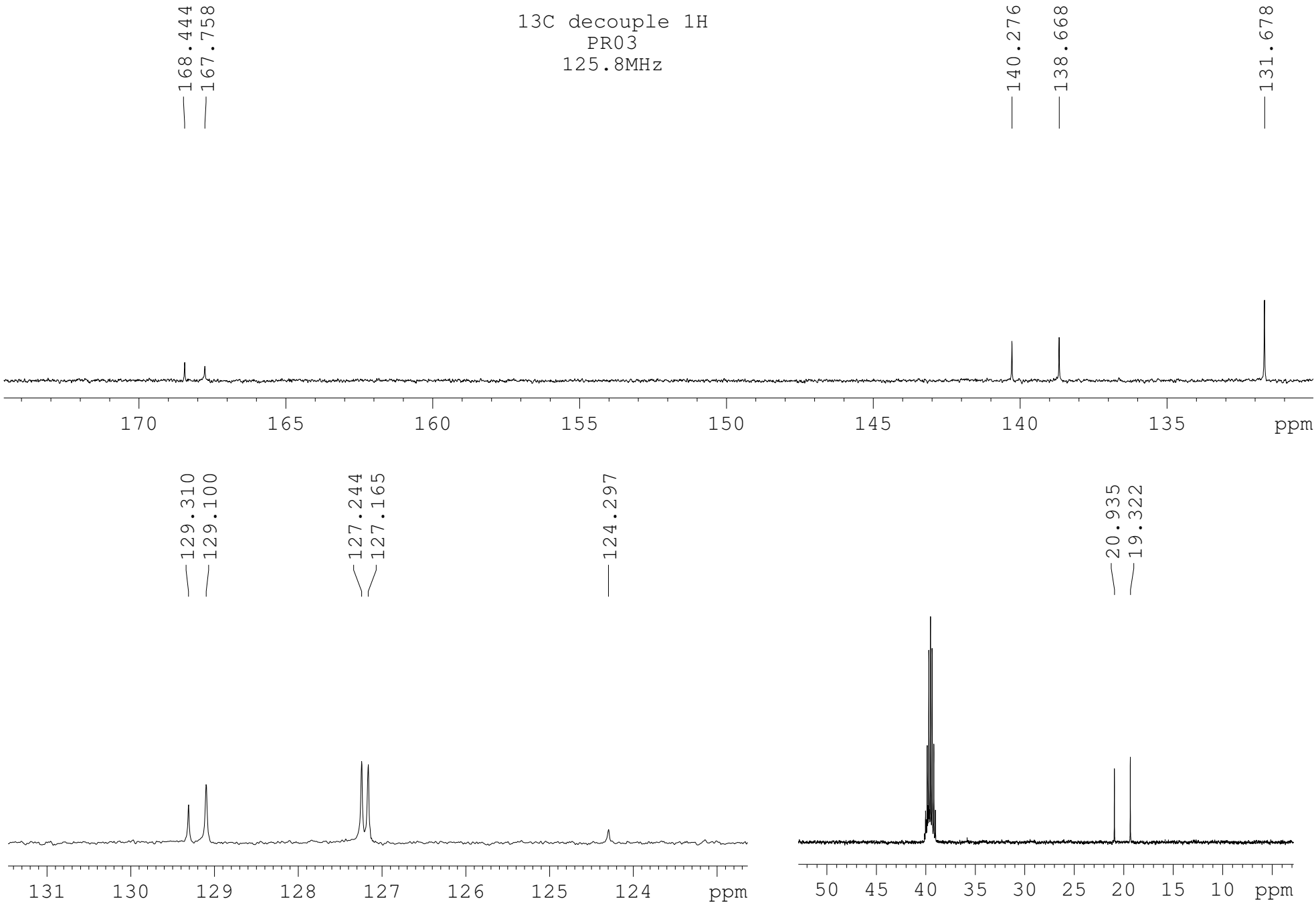
3.094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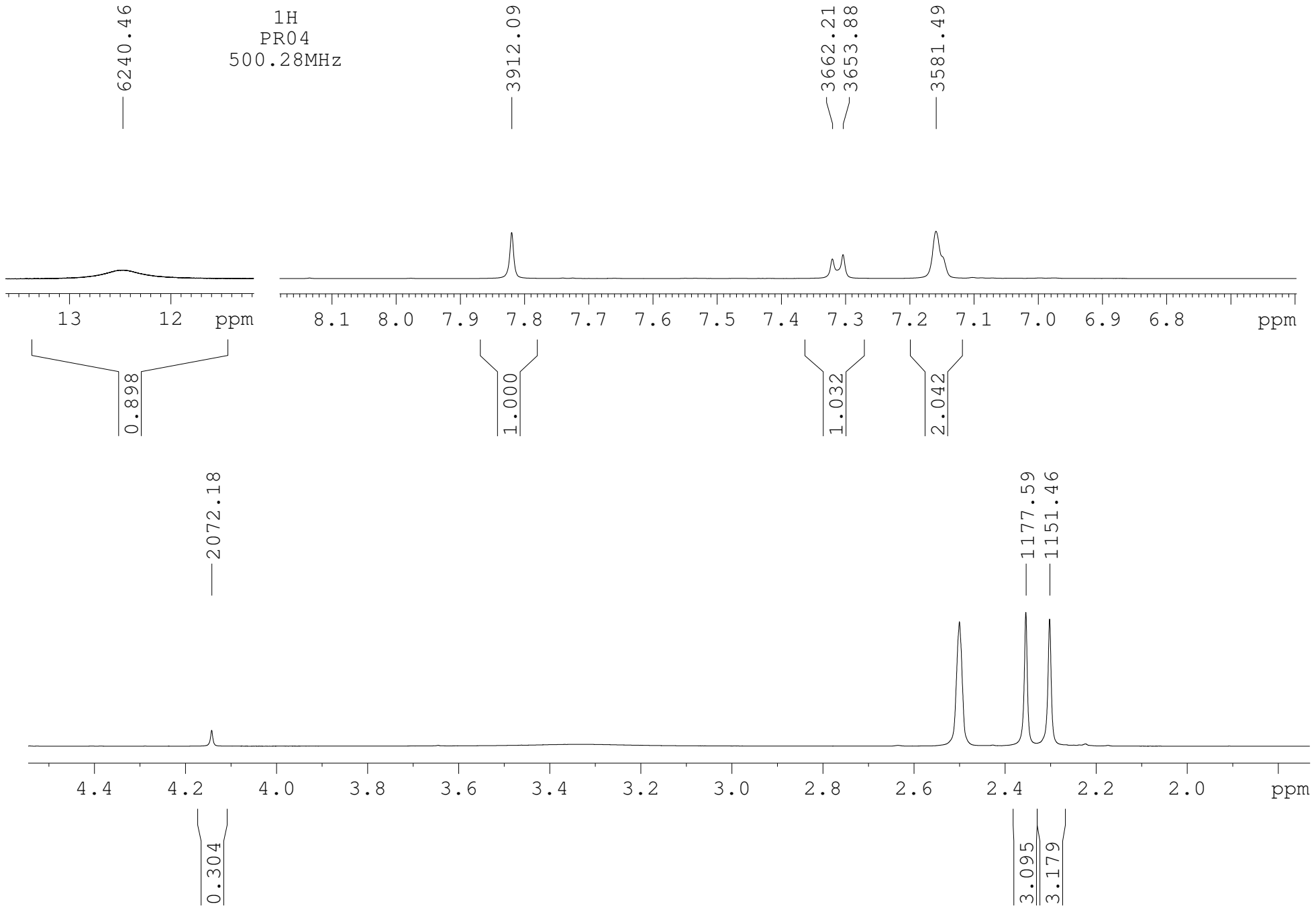
170
165
160
155
150
145
140
135
ppm
129.310
129.100
127.244
127.165
124.297
20.935
19.322
131
130
129
128
127
126
125
124
ppm
50
45
40
35
30
25
20
15
10
ppm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13
12
ppm
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8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
ppm
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
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3.095
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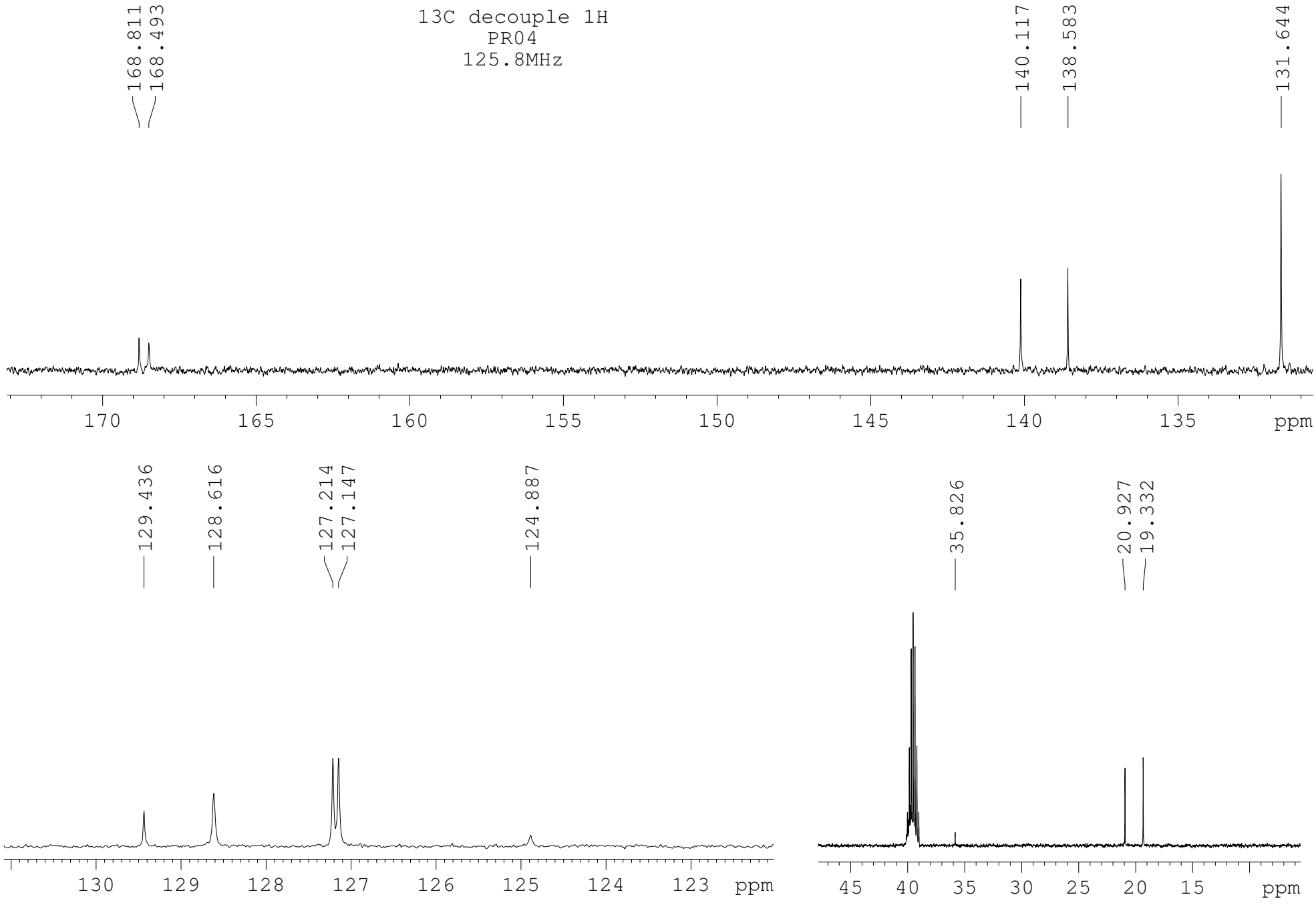
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170
165
160
155
150
145
140
135
ppm
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127.214
127.147
124.887
35.826
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128
127
126
125
124
123
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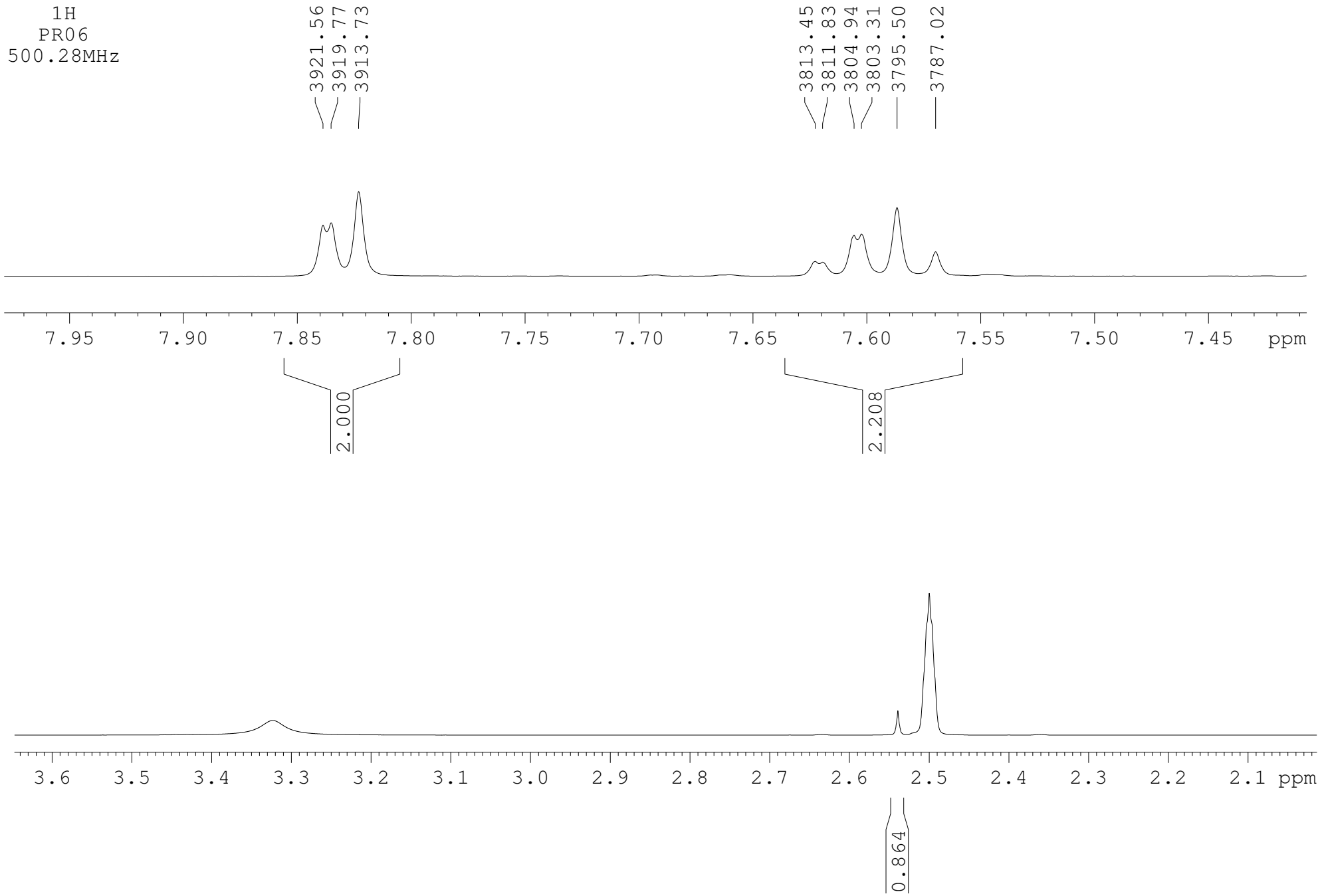
35
30
25
20
15
ppm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3803.31
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7.90
7.85
7.80
7.75
7.70
7.65
7.60
7.55
7.50
7.45
ppm
2.000
2.208
3.6
3.5
3.4
3.3
3.2
3.1
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2.5
2.4
2.3
2.2
2.1
ppm
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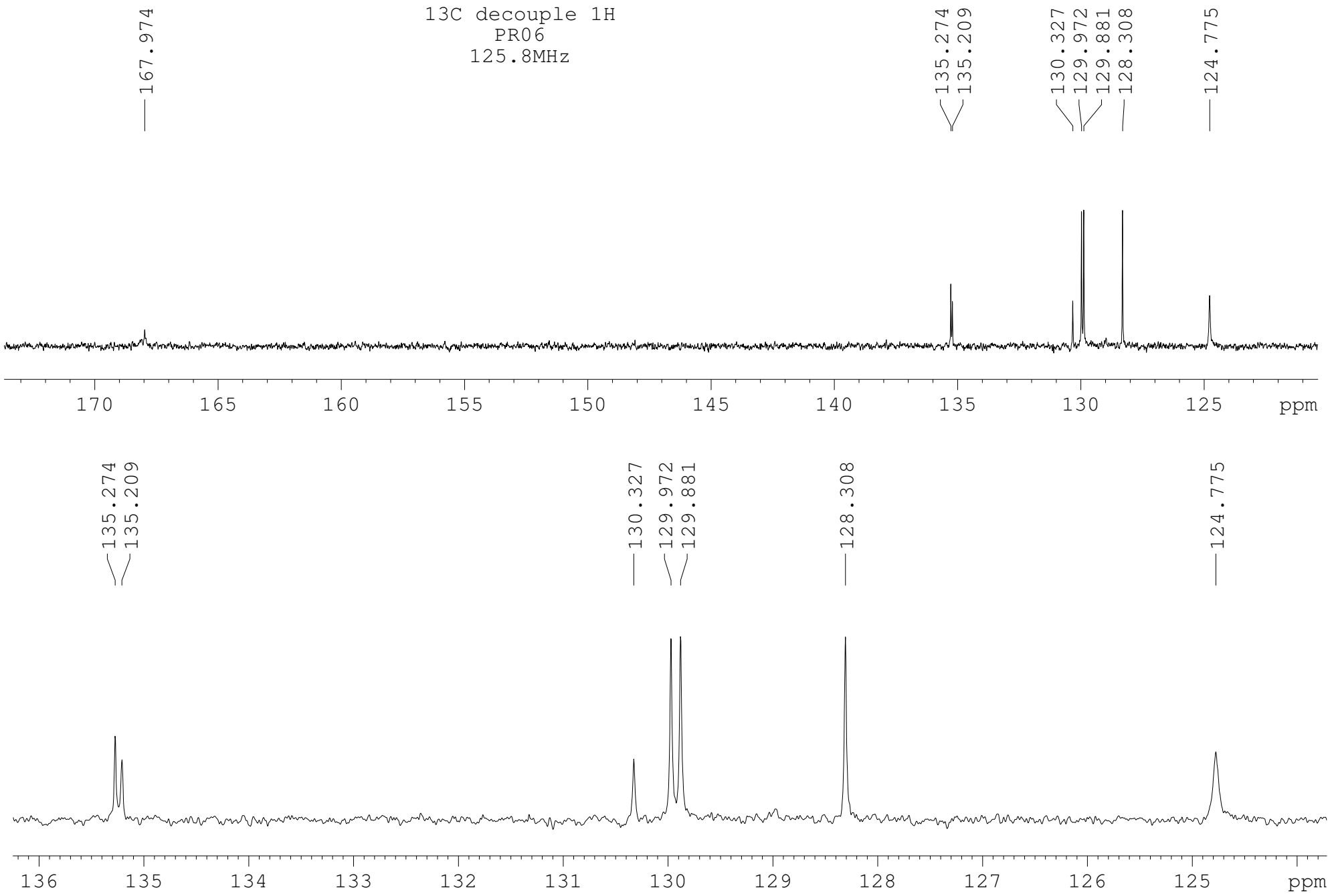
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128.308
124.775
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150
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135
130
125
ppm
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135.209
130.327
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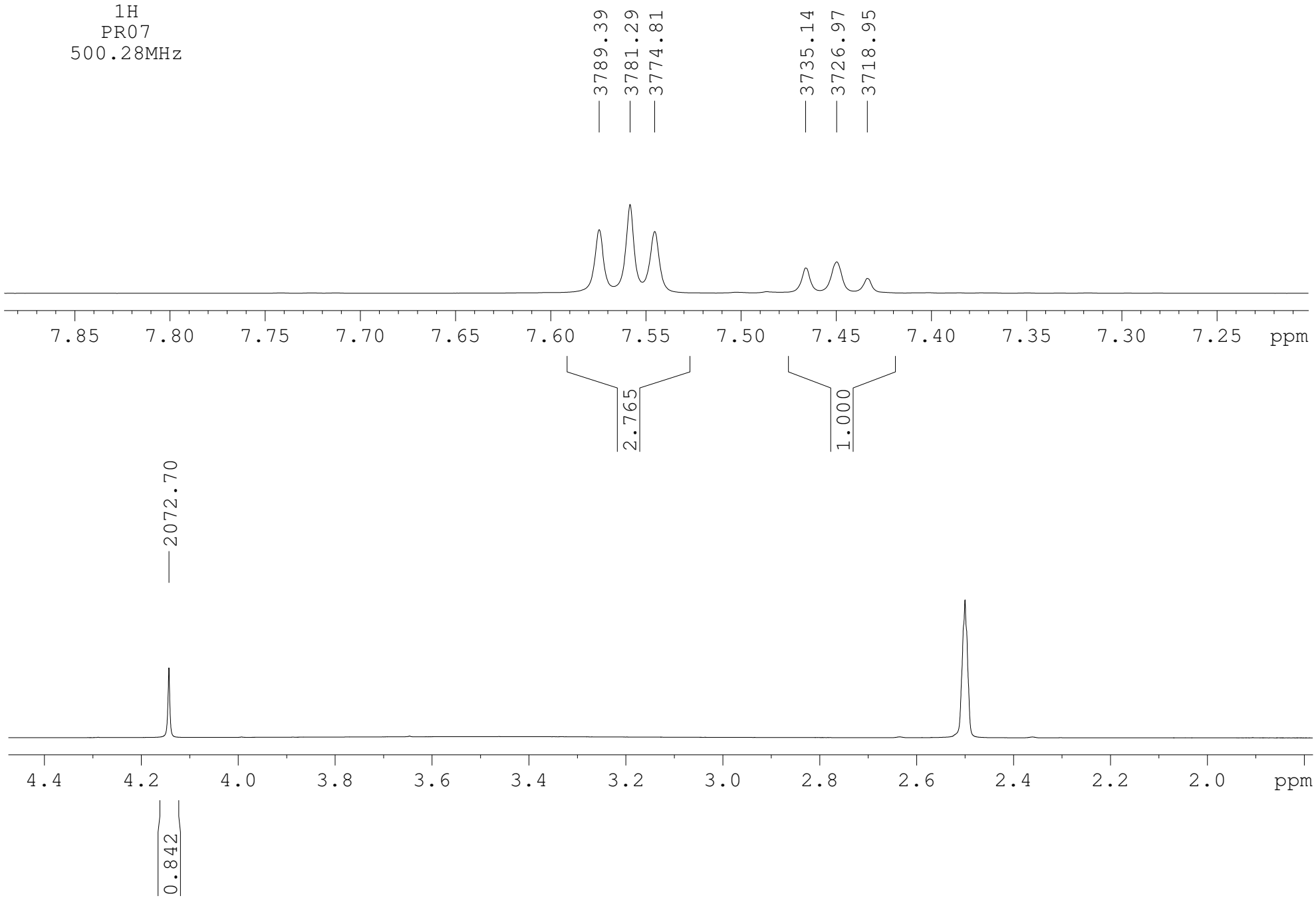
135
134
133
132
131
130
129
128
127
126
125
ppm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7.60
7.55
7.50
7.45
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7.35
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7.25
ppm
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3.4
3.2
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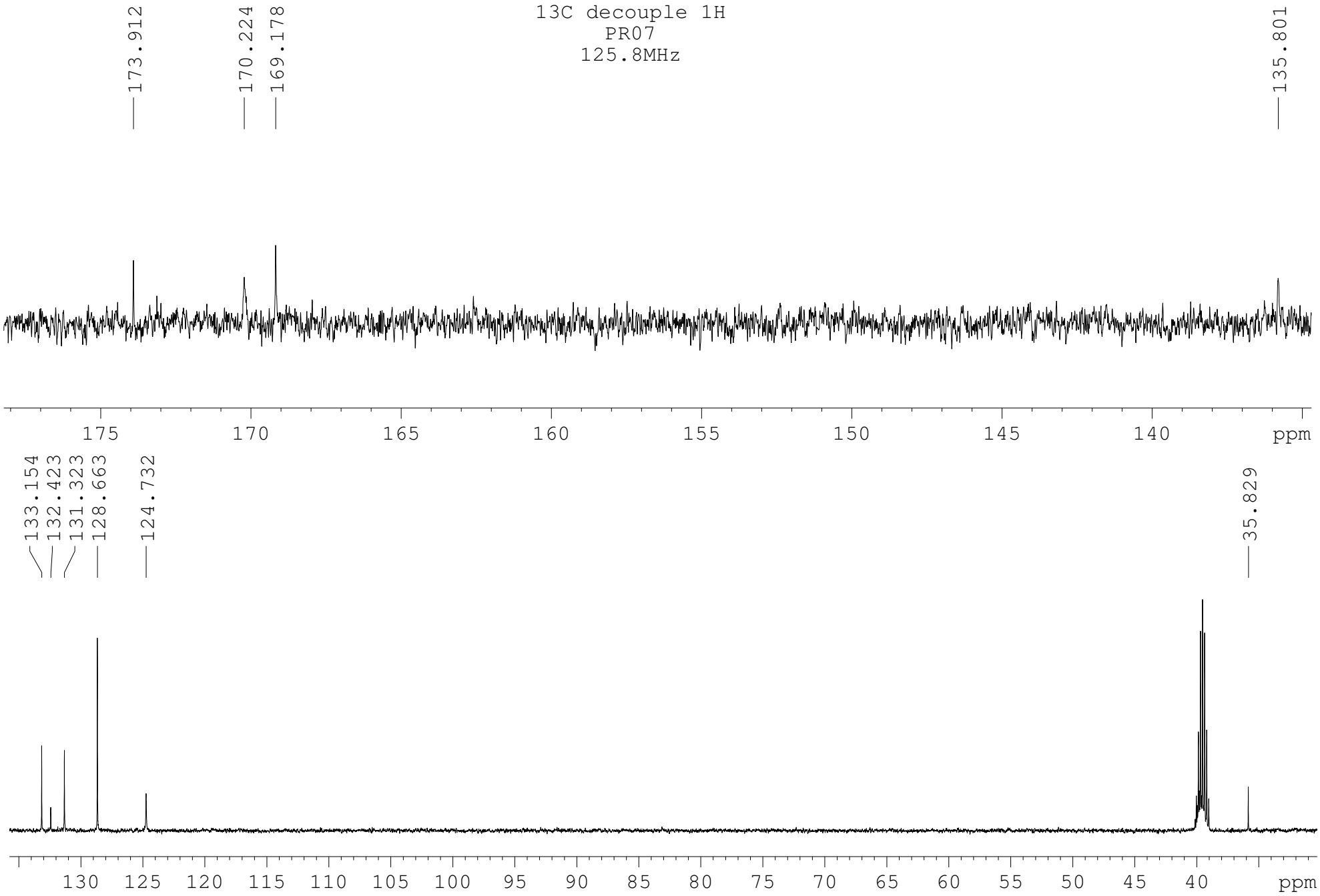
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165
160
155
150
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140
ppm
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132.423
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35.829
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110
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90
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80
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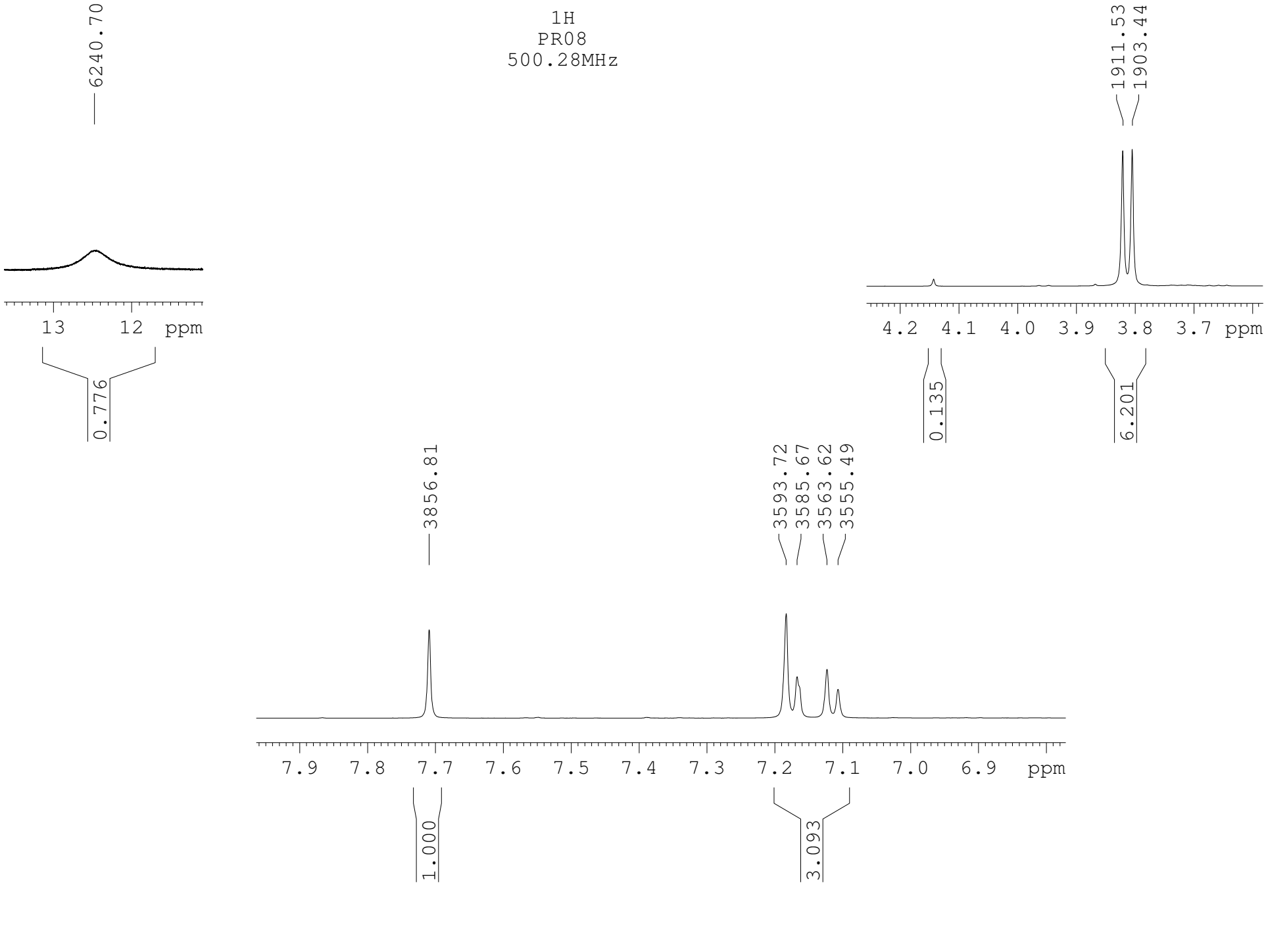
55
50
45
40
ppm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12
ppm
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4.0
3.9
3.8
3.7
ppm
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6.201
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3585.67
3563.62
3555.49
7.9
7.8
7.7
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7.5
7.4
7.3
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7.0
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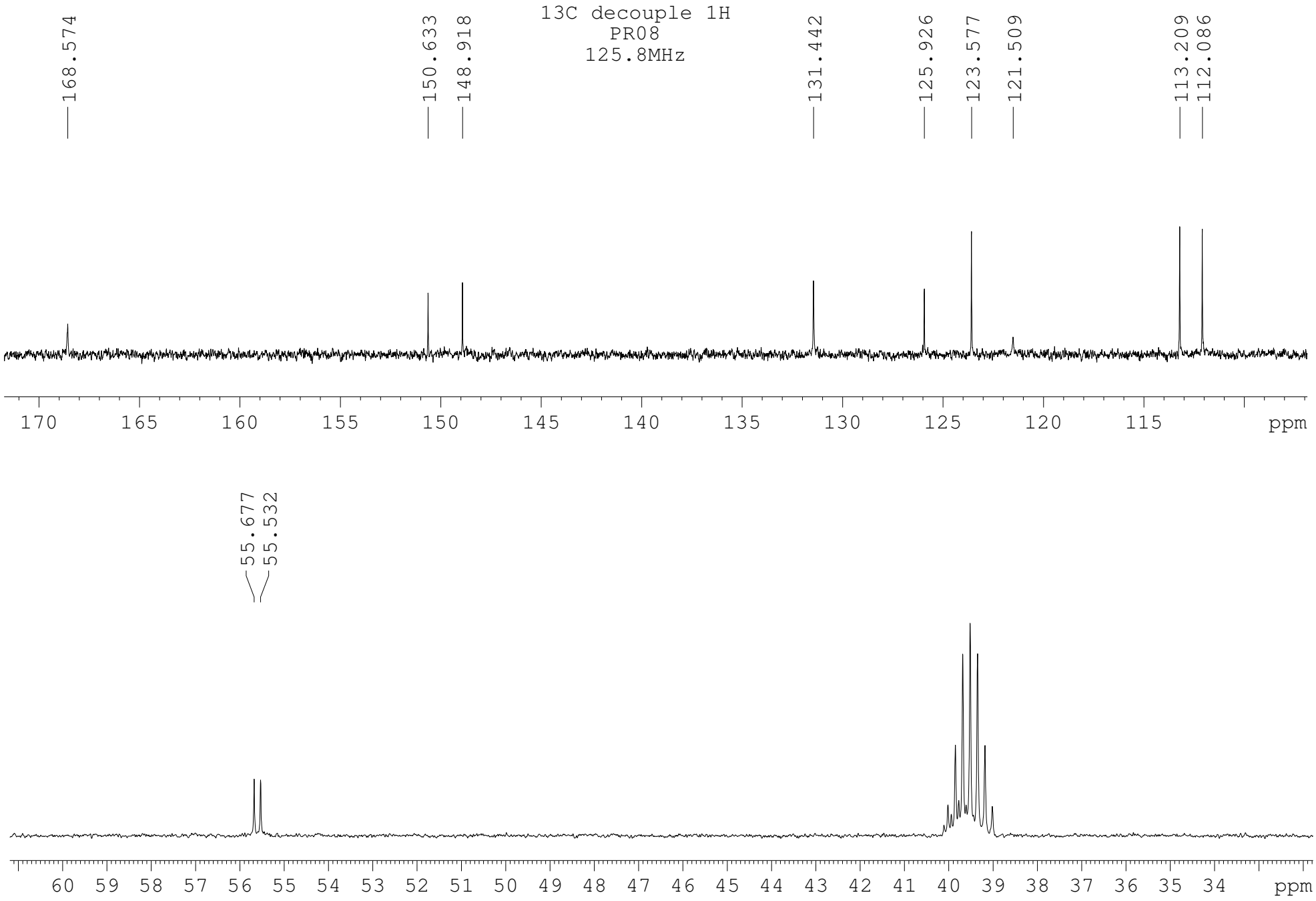
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113.209
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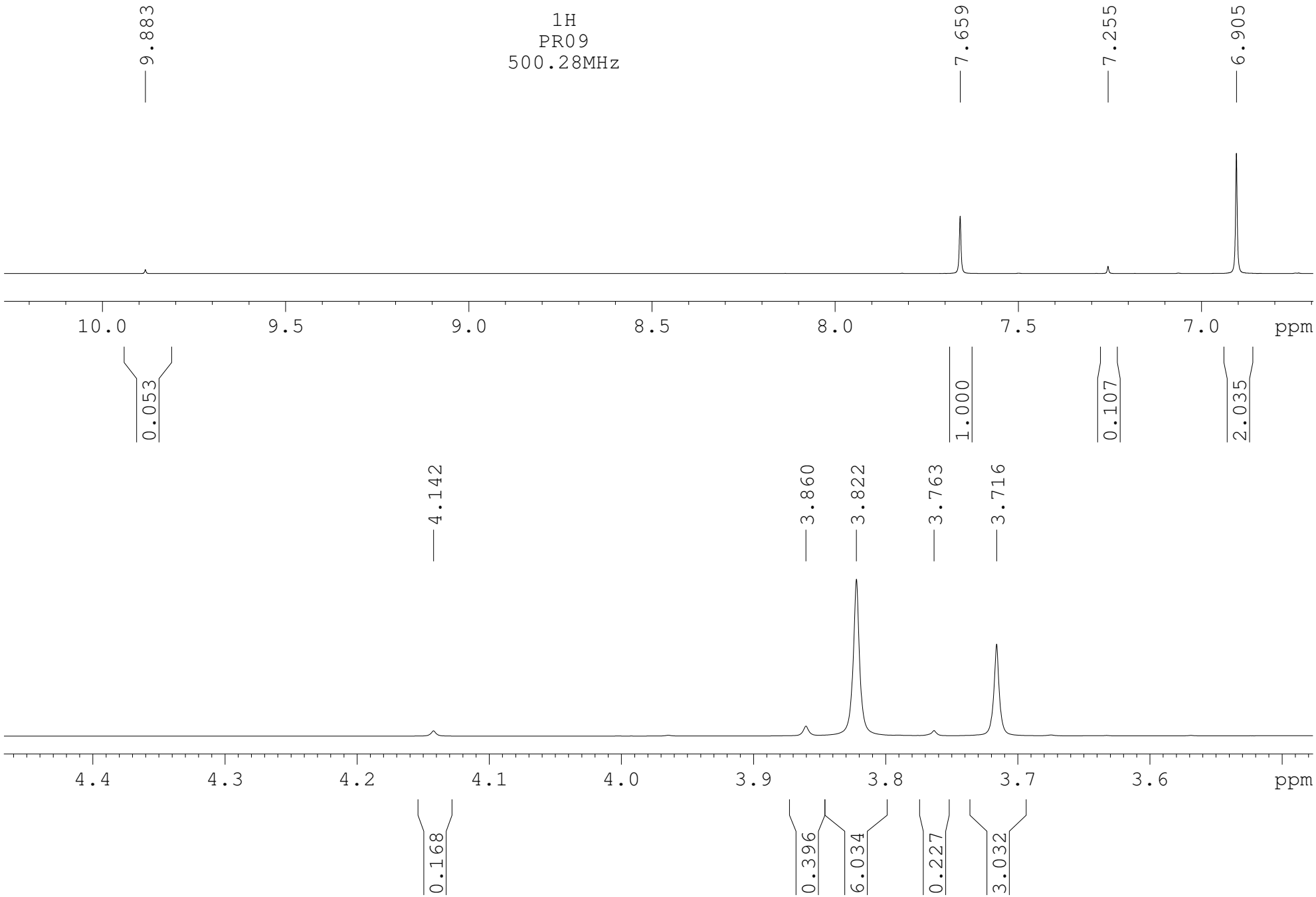
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9.5
9.0
8.5
8.0
7.5
7.0
ppm
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1.000
0.107
2.035
4.142
3.860
3.822
3.763
3.716
4.4
4.3
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3.8
3.7
3.6
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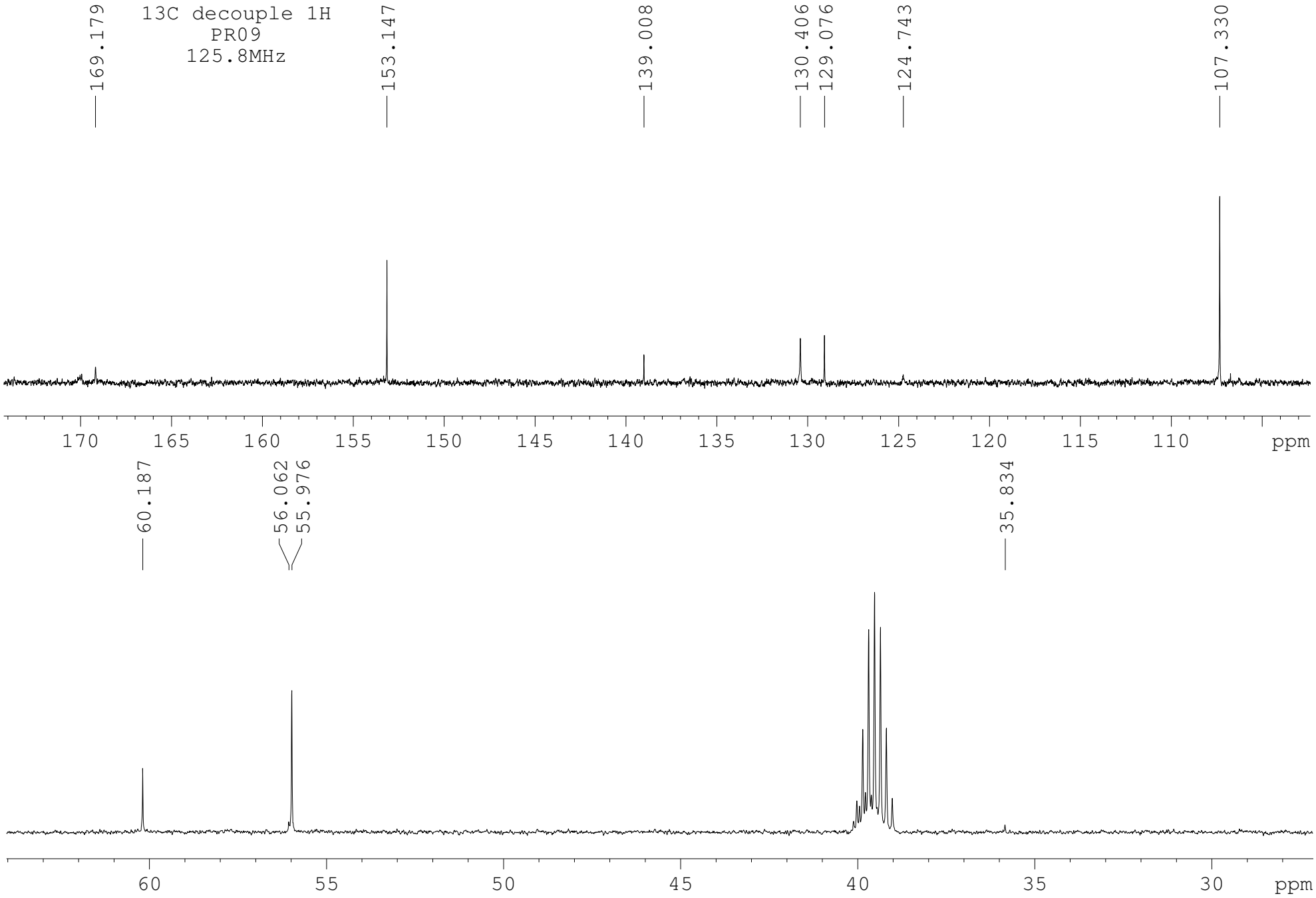
3.032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160
155
150
145
140
135
130
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120
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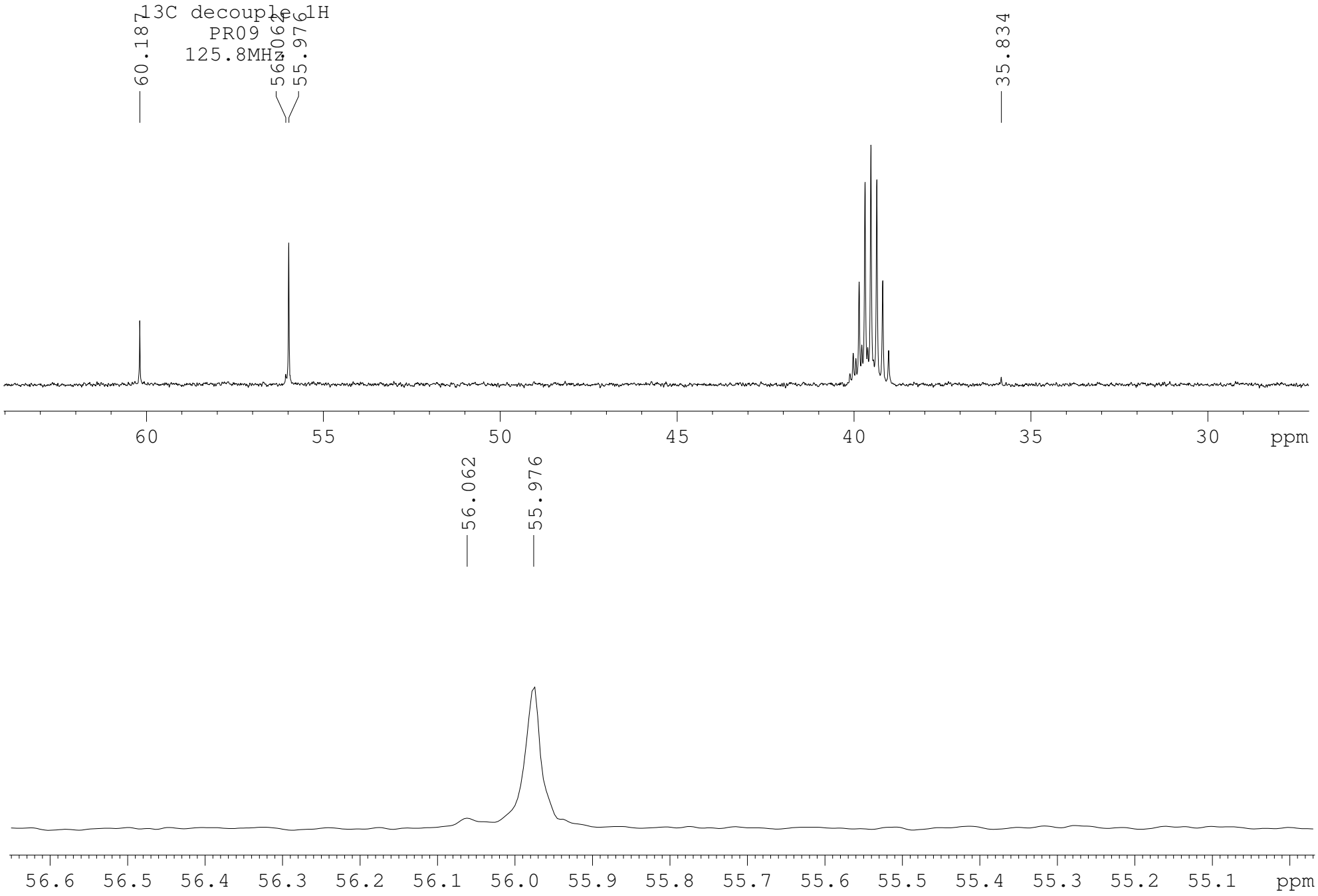
60
55
50
45
40
35
30
ppm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50
45
40
35
30
ppm
56.062
55.976
56.6
56.5
56.4
56.3
56.2
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55.8
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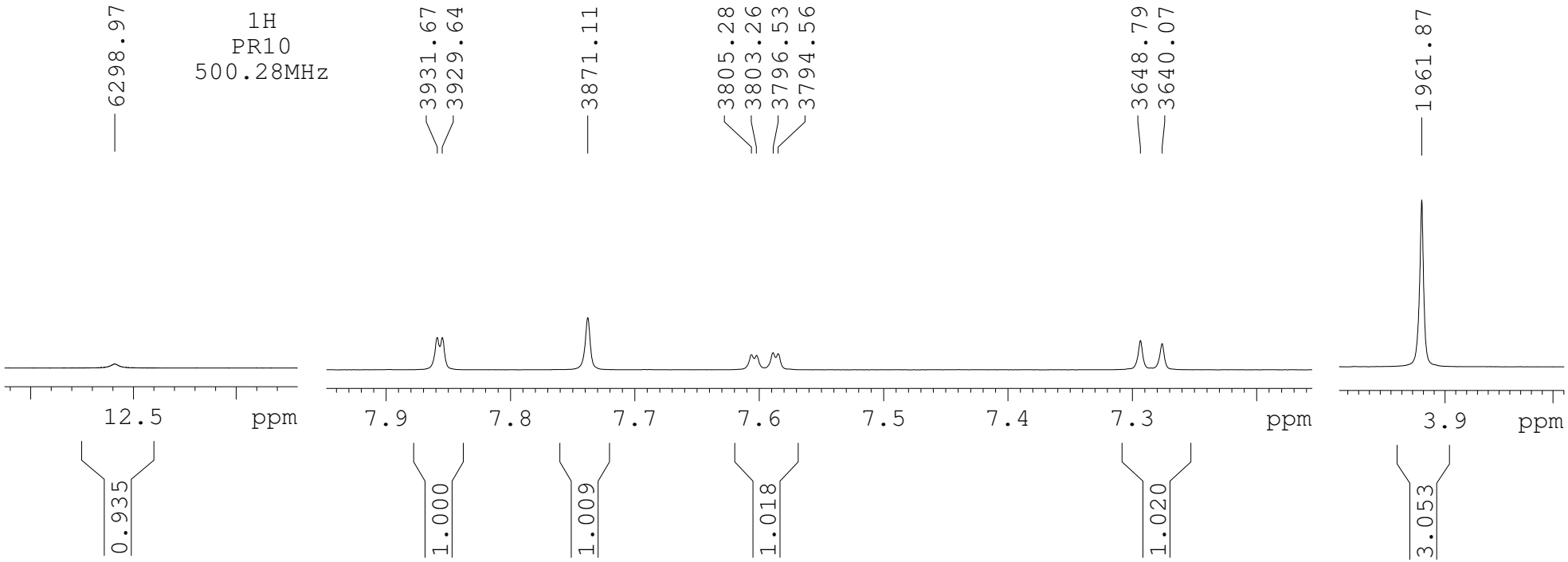
55.6
55.5
55.4
55.3
55.2
55.1
ppm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3794.56
3648.79
3640.07
1961.87
12.5
ppm
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7.8
7.7
7.6
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7.3
ppm
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ppm
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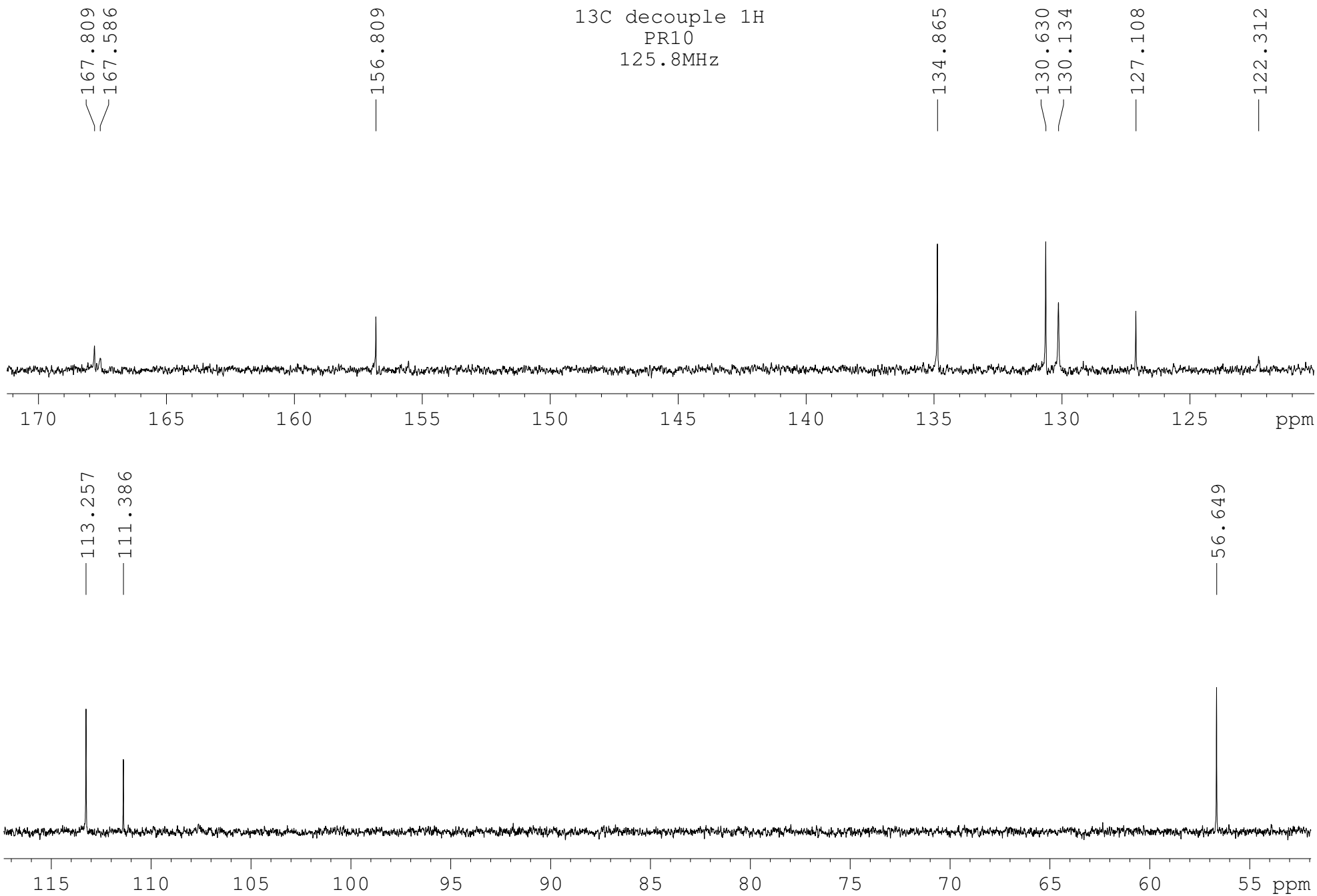
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165
160
155
150
145
140
135
130
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105
100
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90
85
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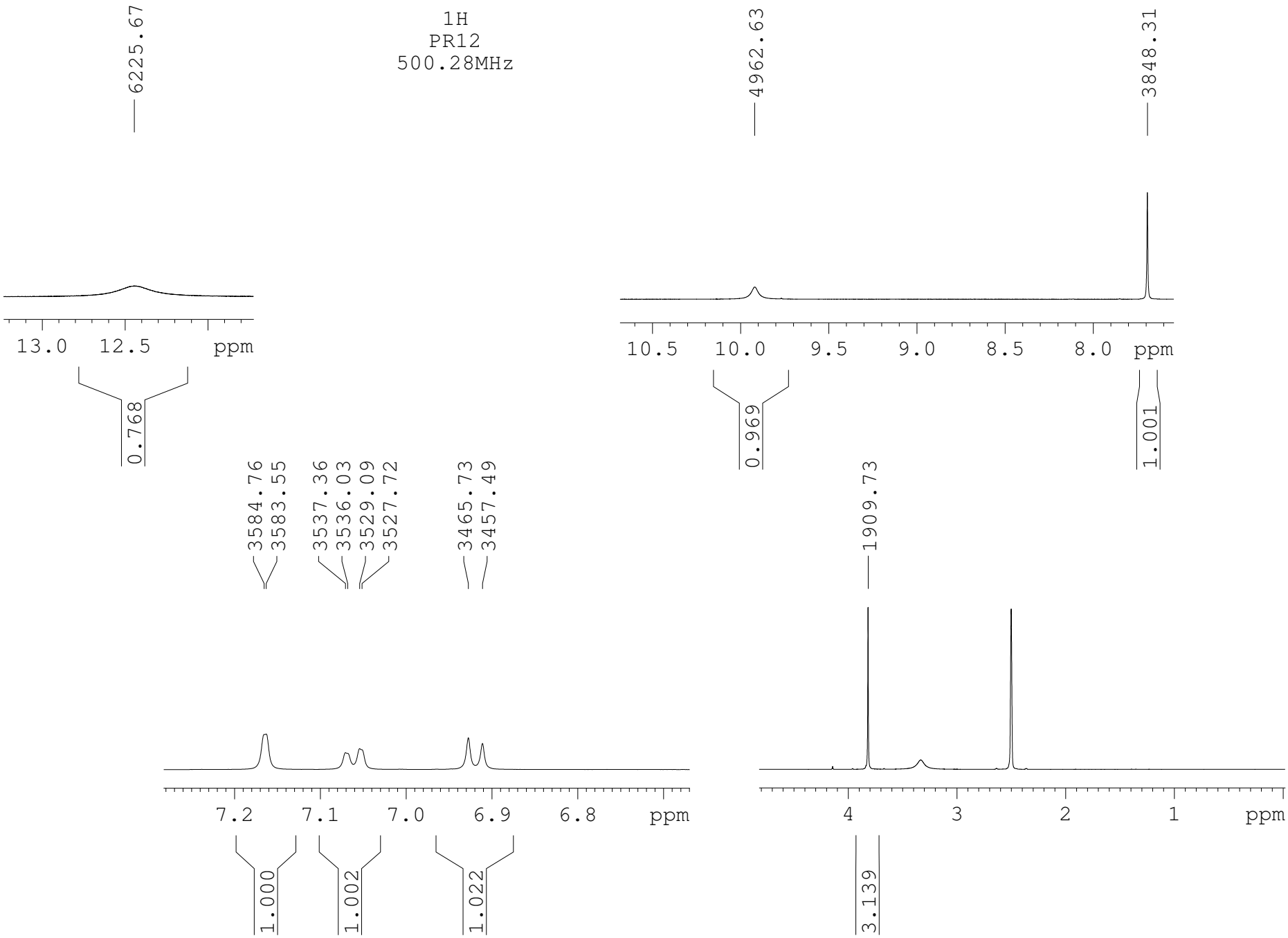
75
70
65
60
55 ppm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10.5
10.0
9.5
9.0
8.5
8.0
ppm
0.969
1.001
3584.76
3583.55
3537.36
3536.03
3529.09
3527.72
3465.73
3457.49
1909.73
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6.9
6.8
ppm
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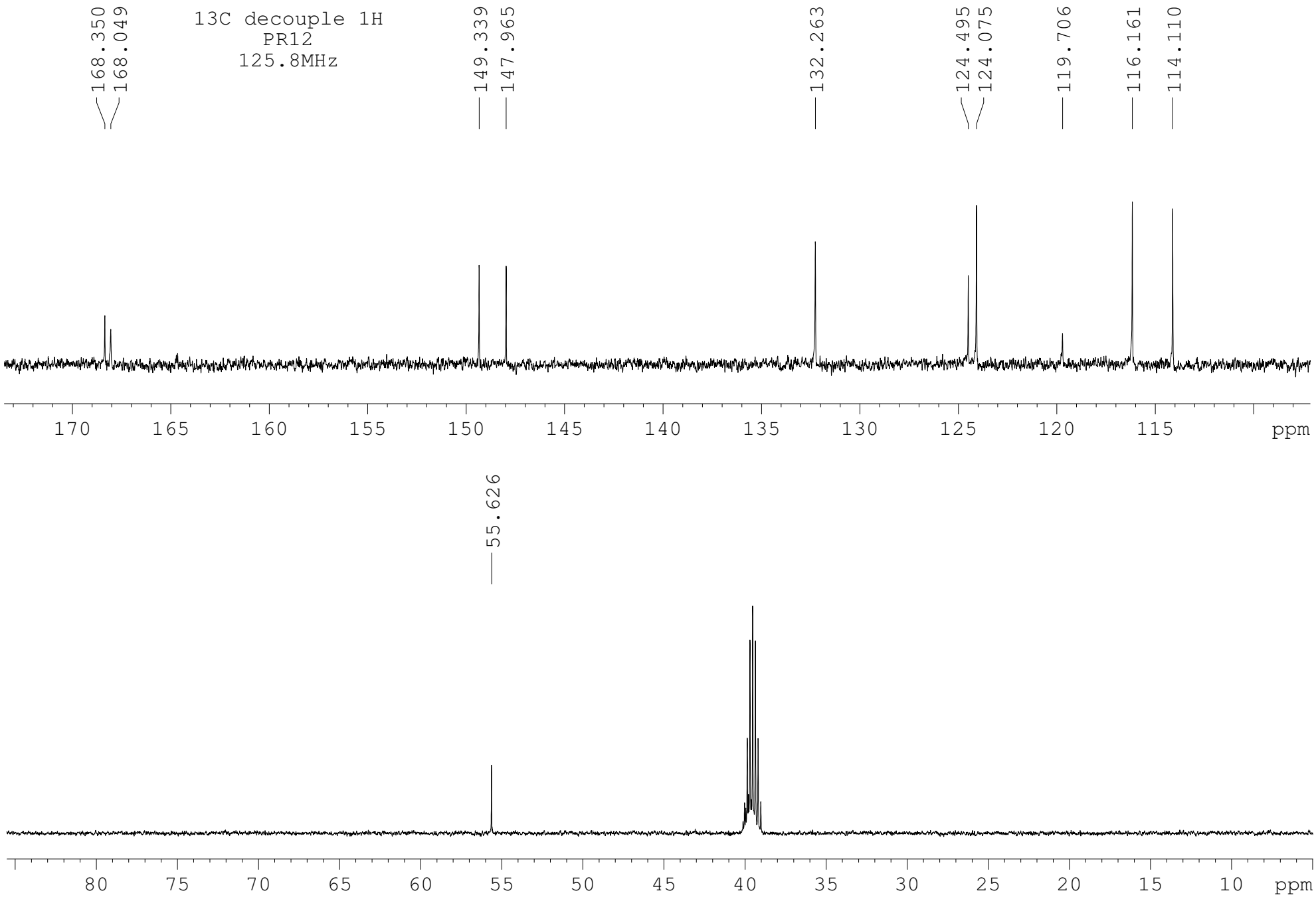
1.002
1.022
4
3
2
1
ppm
3.139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124.075
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40
35
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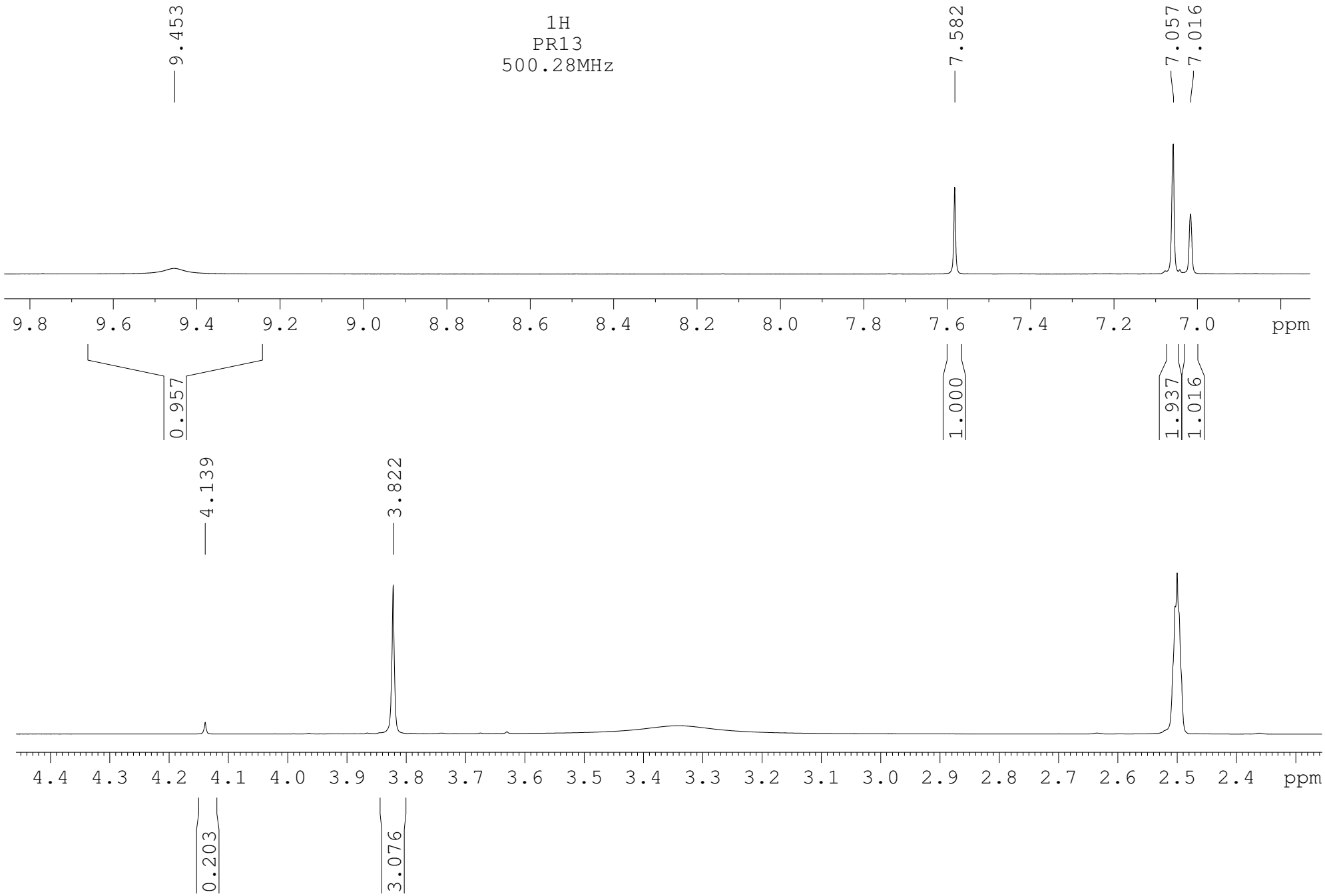
25
20
15
10
ppm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7.016
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1.000
1.937
1.016
4.139
3.822
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 ppm
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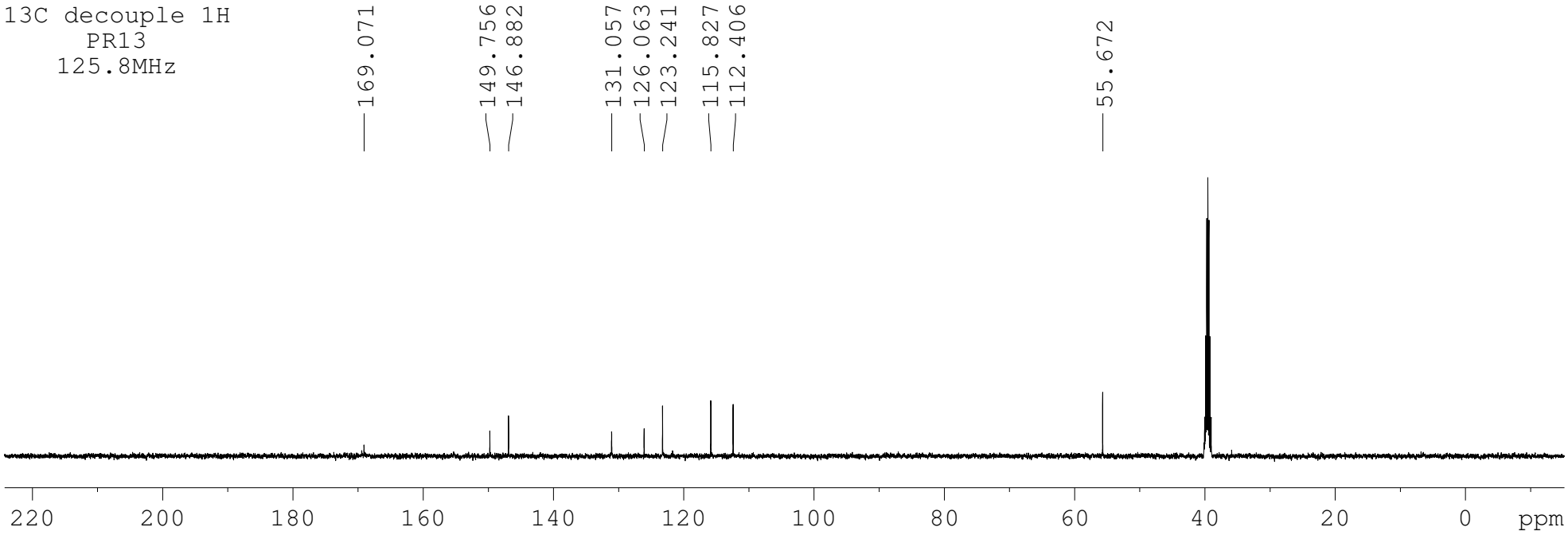
3.076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131.057
126.063
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180
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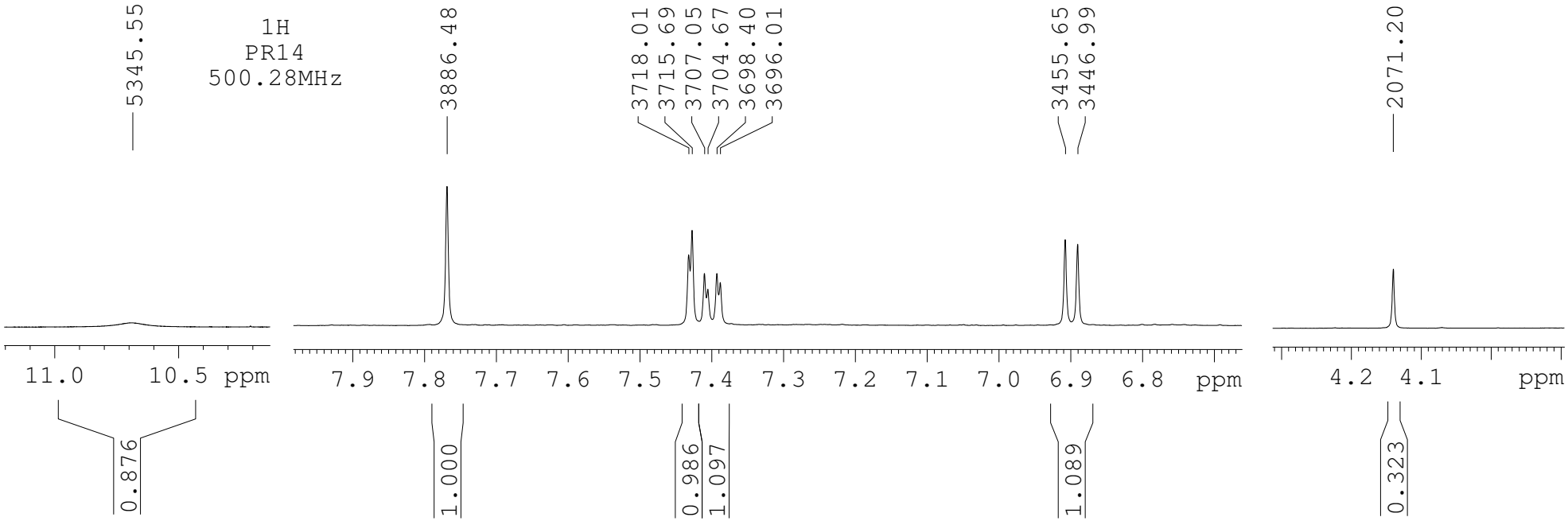
60
40
20
0
ppm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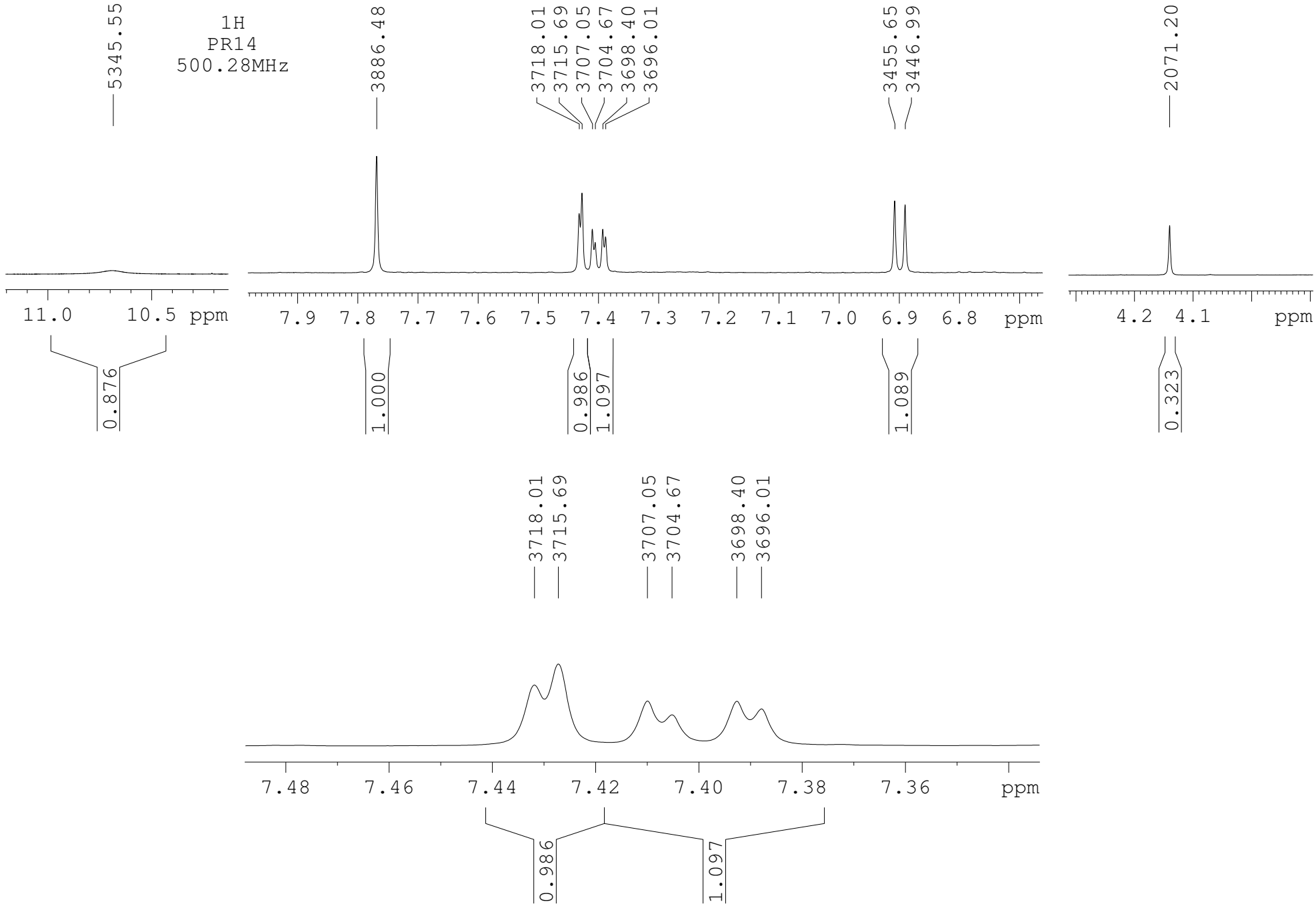
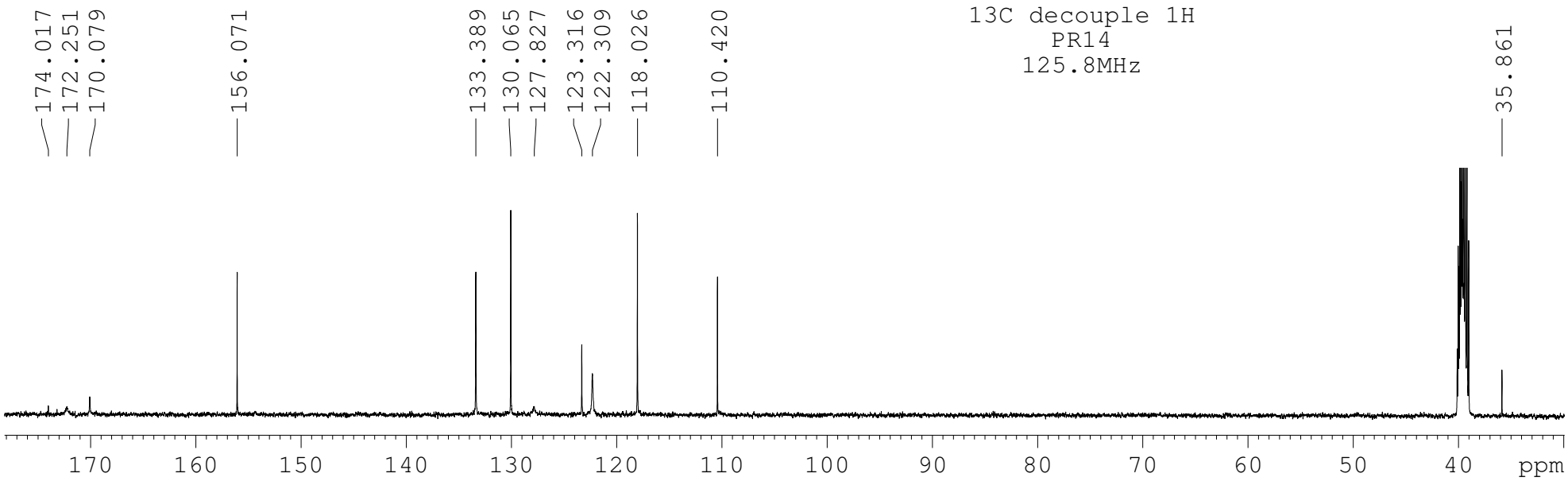
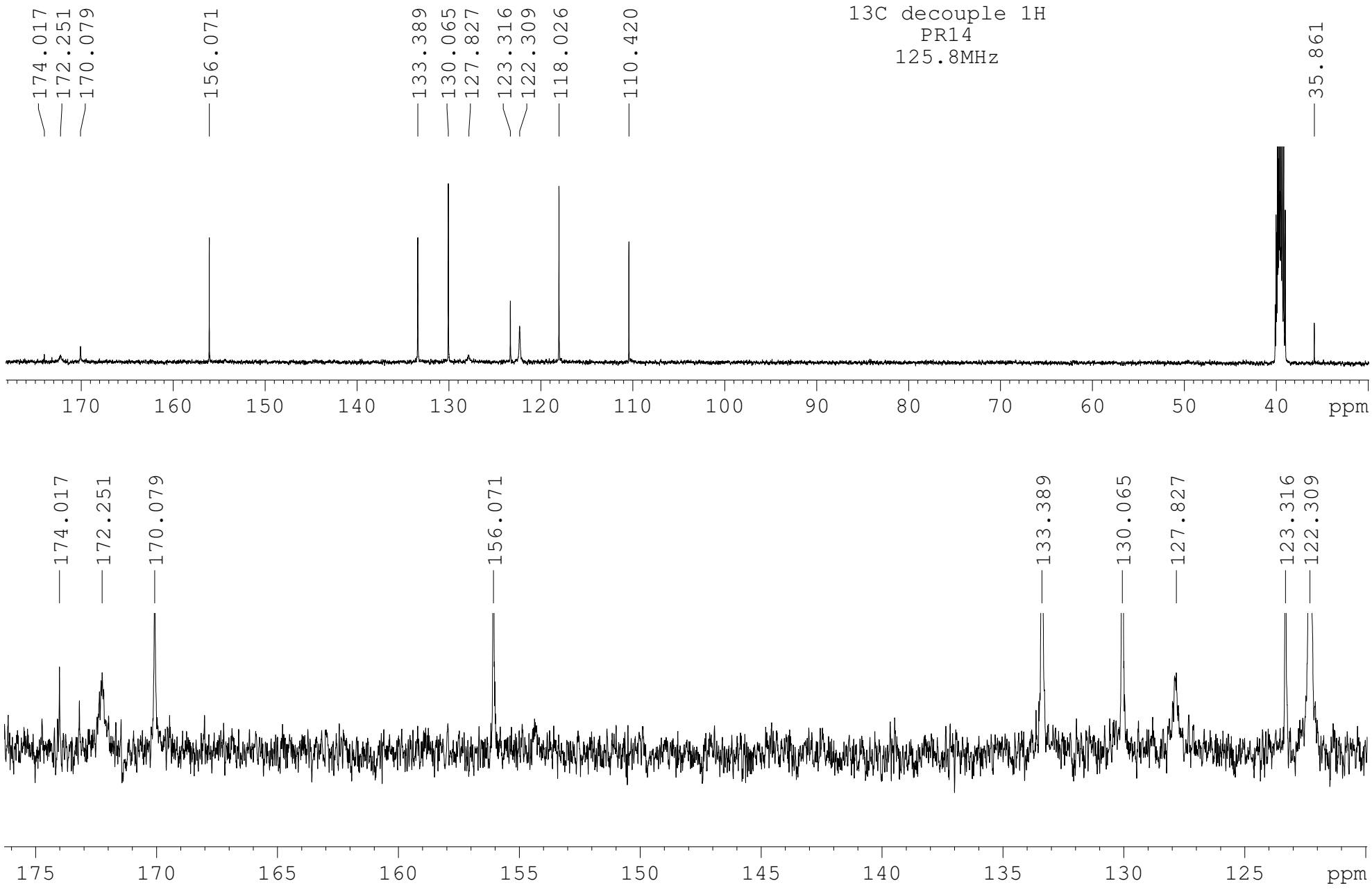
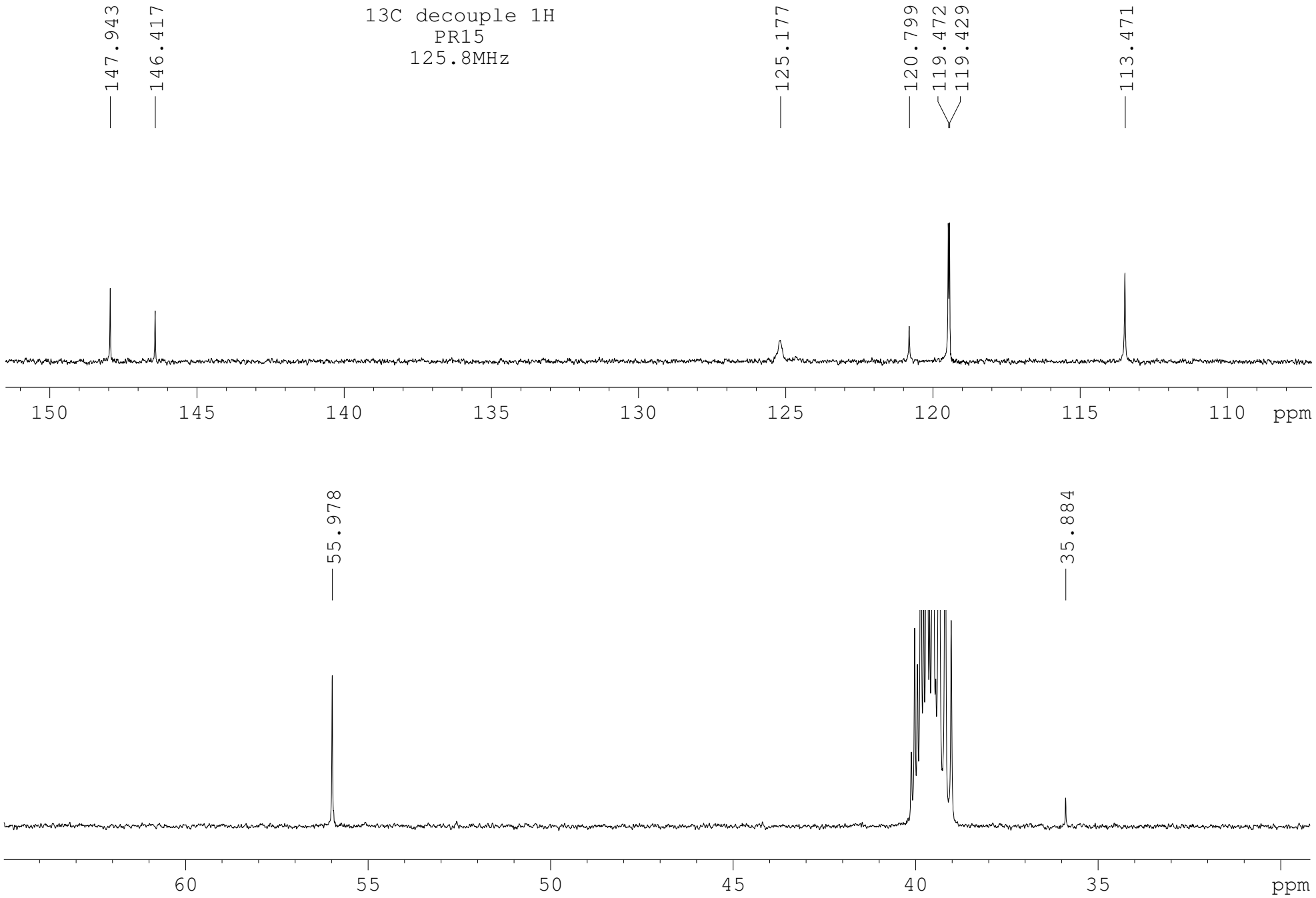
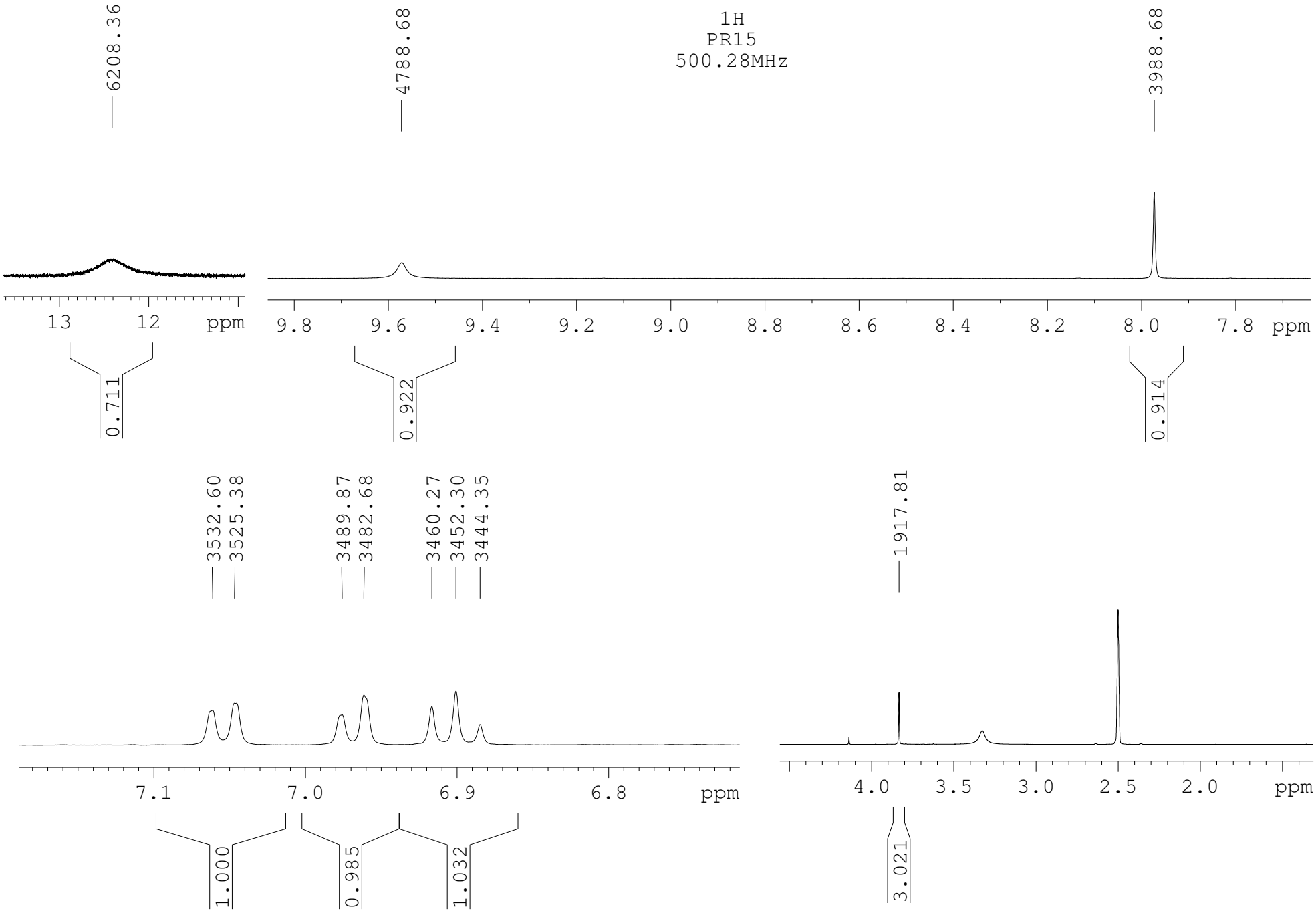
500.28MHz
5345.55
3886.48
3718.01
3715.69
3707.05
3704.67
3698.40
3696.01
3455.65
3446.99
2071.20
11.0
10.5
ppm
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
ppm
4.2
4.1
ppm
0.876
1.000
0.986
1.097
1.089
0.323

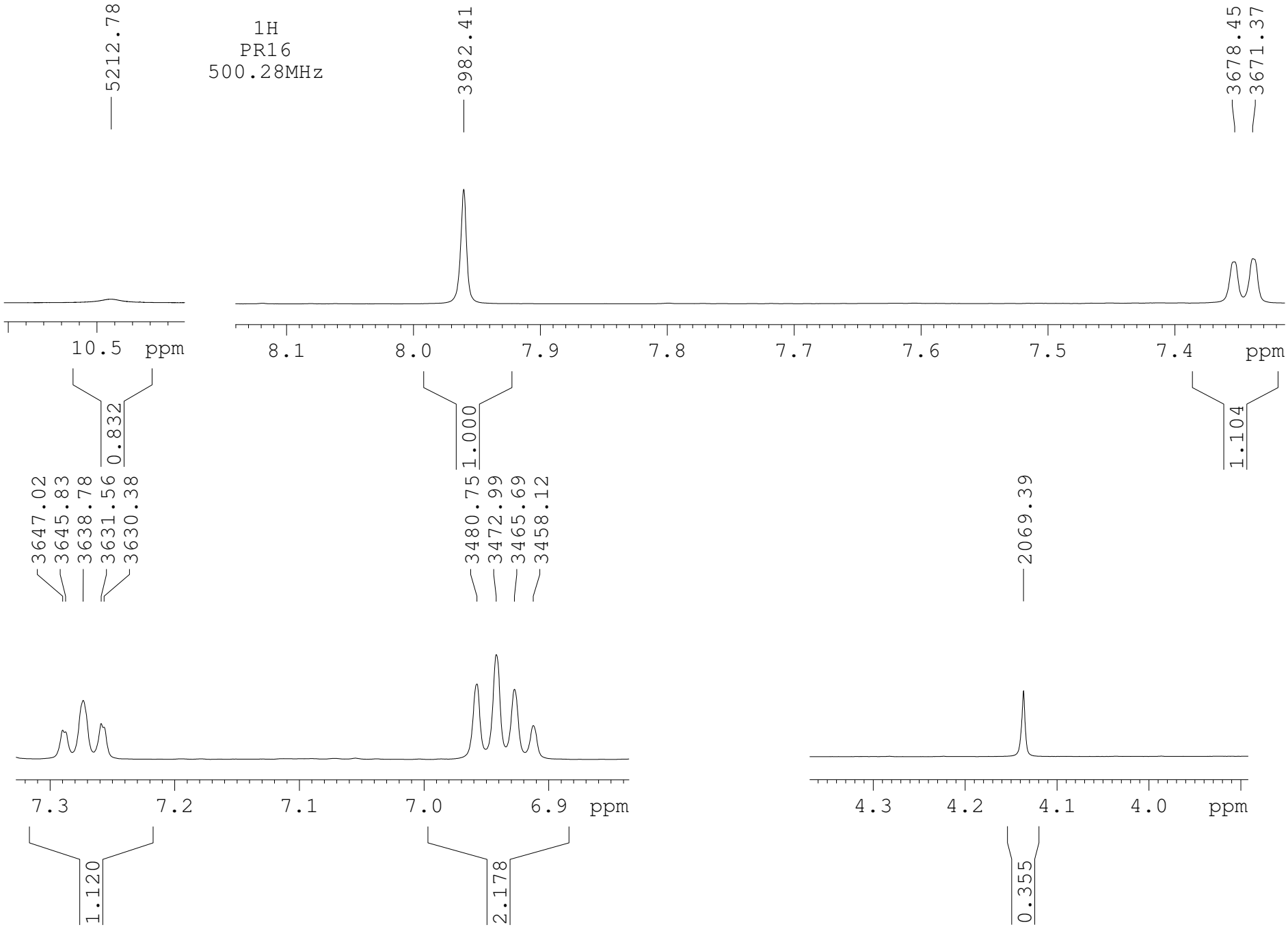

1H
PR14
500.28MHz
5345.55
3886.48
3718.01
3715.69
3707.05
3704.67
3698.40
3696.01
3455.65
3446.99
2071.20
11.0
10.5
ppm
0.876
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
ppm
1.000
0.986
1.097
1.089
4.2
4.1
ppm
0.323
3718.01
3715.69
3707.05
3704.67
3698.40
3696.01
7.48
7.46
7.44
7.42
7.40
7.38
7.36
ppm
0.986
1.097

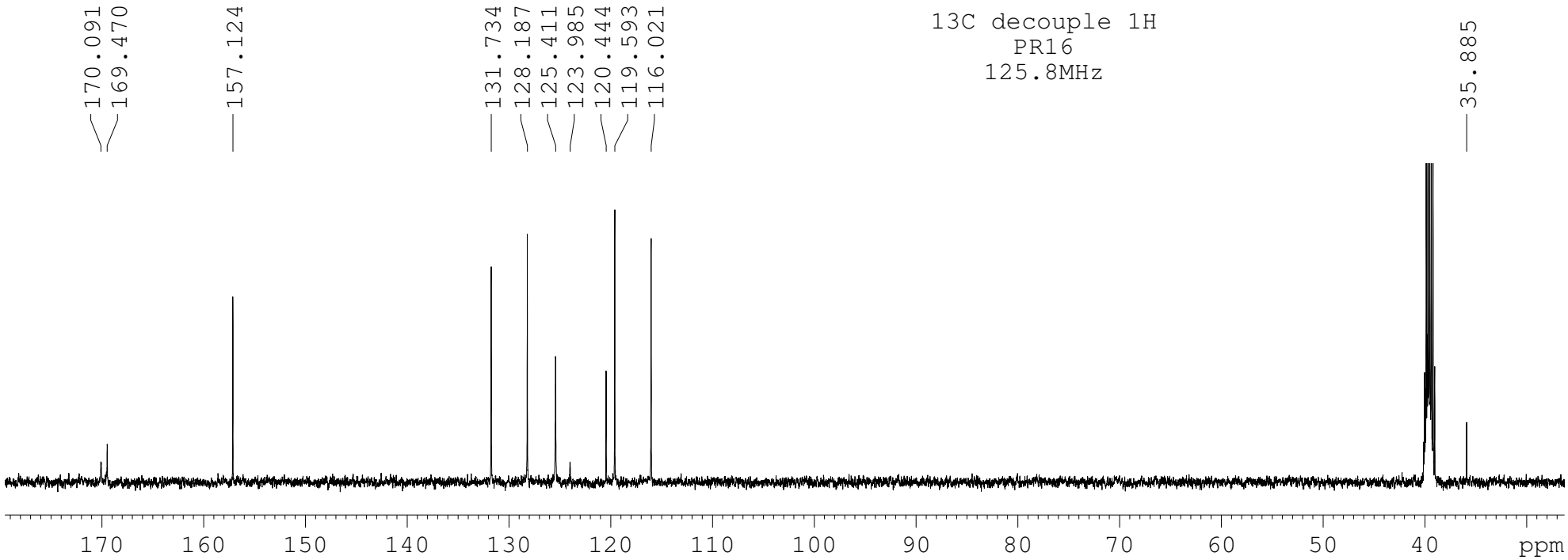

174.017
172.251
170.079
156.071
133.389
130.065
127.827
123.316
122.309
118.026
110.420
35.861
13C decouple 1H
PR14
125.8MHz
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

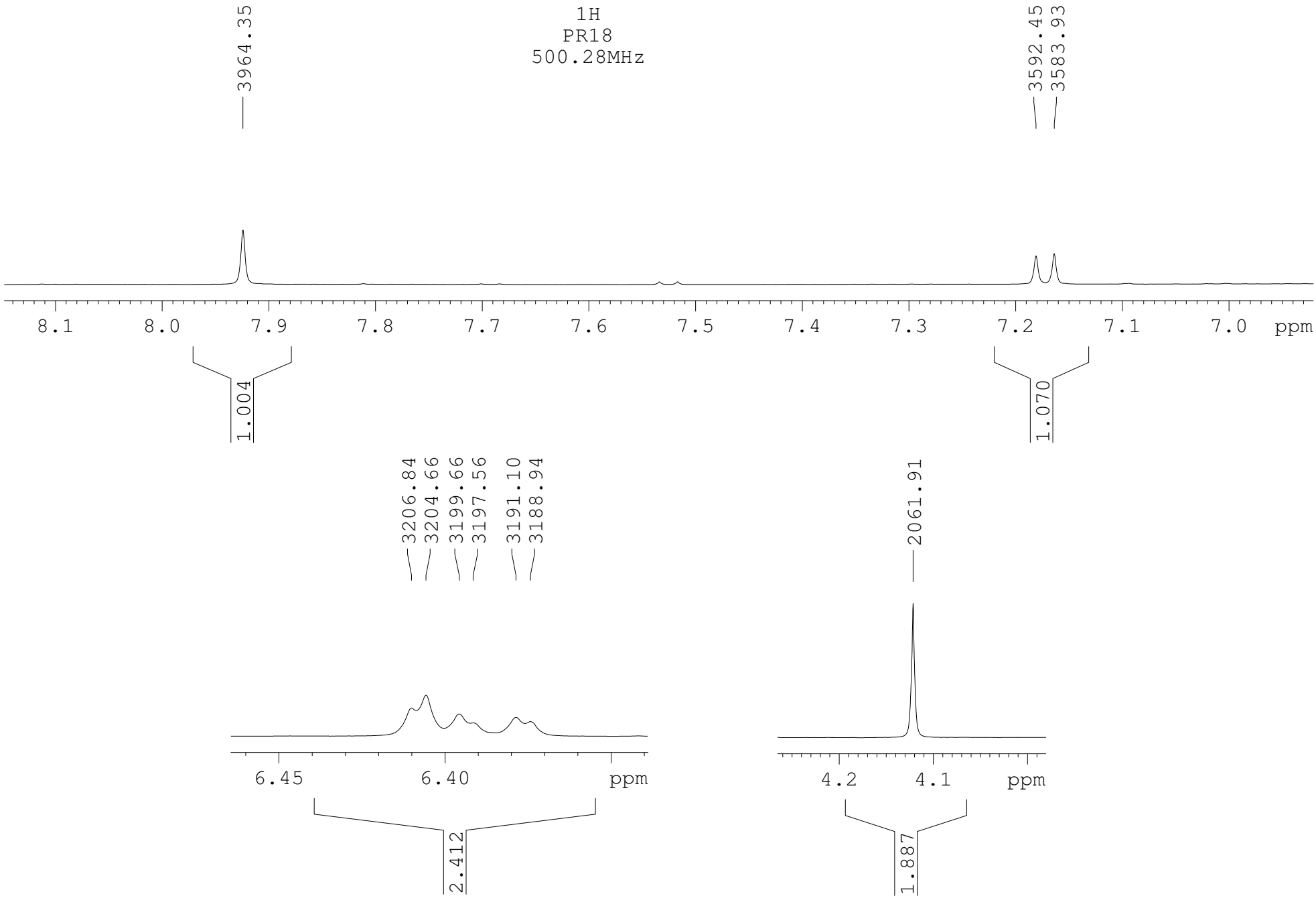

13C decouple 1H
PR14
125.8MHz
174.017
172.251
170.079
156.071
133.389
130.065
127.827
123.316
122.309
118.026
110.420
35.861
ppm
ppm

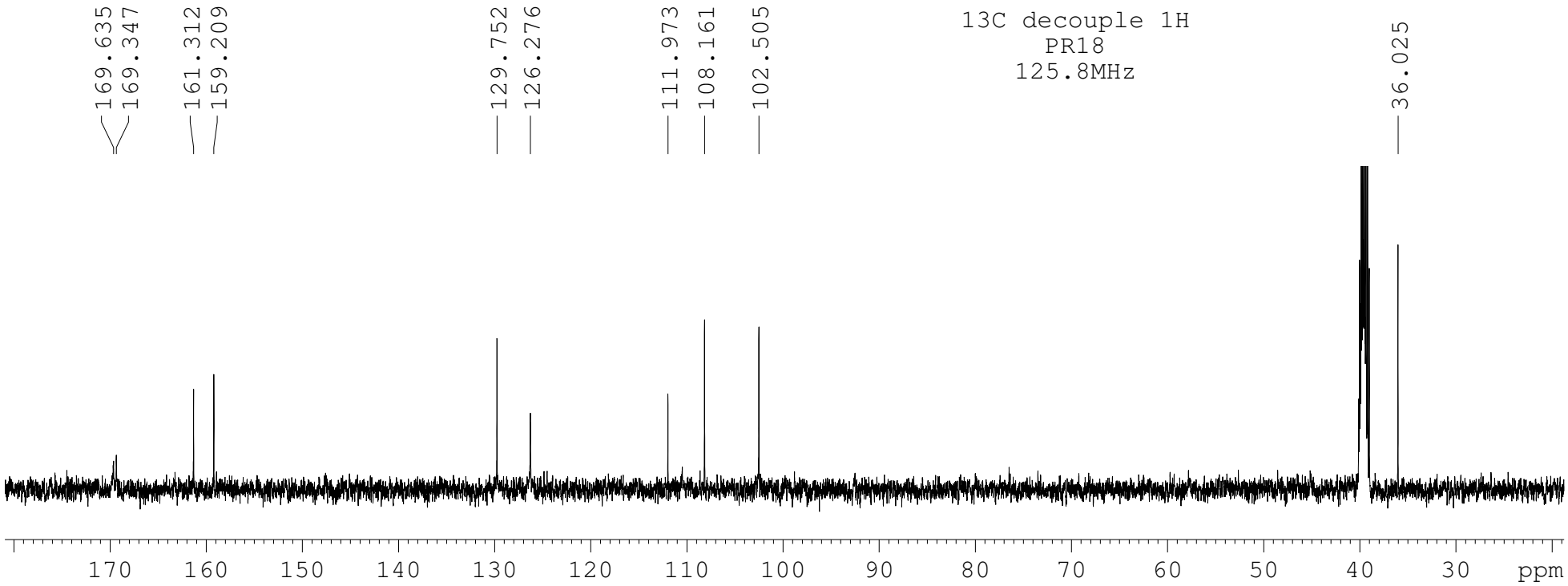

13C decouple 1H
PR15
125.8MHz
147.943
146.417
125.177
120.799
119.472
119.429
113.471
150
145
140
135
130
125
120
115
110
ppm
55.978
35.884
60
55
50
45
40
35
ppm


1H
PR15
500.28MHz
6208.36
4788.68
3988.68
13
12
ppm
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
ppm
0.711
0.922
0.914
3532.60
3525.38
3489.87
3482.68
3460.27
3452.30
3444.35
1917.81
7.1
7.0
6.9
6.8
ppm
4.0
3.5
3.0
2.5
2.0
ppm
1.000
0.985
1.032
3.021


1H
PR16
500.28MHz
5212.78
3982.41
3678.45
3671.37
10.5 ppm
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4 ppm
0.832
1.000
1.104
3647.02
3645.83
3638.78
3631.56
3630.38
3480.75
3472.99
3465.69
3458.12
2069.39
7.3
7.2
7.1
7.0
6.9 ppm
4.3
4.2
4.1
4.0 ppm
1.120
2.178
0.355


170.091
169.470
157.124
131.734
128.187
125.411
123.985
120.444
119.593
116.021
35.885
13C decouple 1H
PR16
125.8MHz
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


1H
PR18
500.28MHz
3964.35
3592.45
3583.93
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
ppm
1.004
1.070
3206.84
3204.66
3199.66
3197.56
3191.10
3188.94
2061.91
6.45
6.40
ppm
4.2
4.1
ppm
2.412
1.887


169.635
169.347
161.312
159.209
129.752
126.276
111.973
108.161
102.505
36.025
13C decouple 1H
PR18
125.8MHz
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm