UNIVERSITY OF TARTU
Faculty of Science and Technology
Institute of Technology

Intasar Ul Haq

Methanolysis of Benzoyl hydrazines in the presence of Trifluoromethanesulfonic acid

Bachelor's Thesis (12 ECTS)

Curriculum Science and Technology

Supervisor(s):
Lecturer, PhD Anton Mastitski

Tartu 2023

Methanolysis of benzoyl hydrazines in the presence of Trifluoromethanesulfonic acid

Abstract:

Methanolysis of variously substituted benzoyl hydrazines in the presence of CF_3SO_3H was explored for the first time. The effects of CF_3SO_3H acid concentration and substituents attached to benzoyl hydrazine on yield and reaction times were also examined. It was found that doubling the acid concentration results in an approximately four-fold decrease in reaction times. Moreover, reaction times are strongly dependent on the nature of substituents. Presence of electron-donating substitutes increases the reaction rate, while presence of electron-withdrawing groups has the opposite effect. The obtained results clearly demonstrate that acyl hydrazines could be converted to esters in good to excellent yields in the presence of 6-9 eq of CF_3SO_3H.

Keywords: Benzoyl hydrazines, CF_3SO_3H, esterification, methanolysis, methyl esters.

CERCS: P390 - Organic chemistry.

Bensoüülhüdrasiinide metanolüüs Trifluorometaansulfoonhappe juuresolekul

Lühikokkuvõte:

Käesoleva töö raames uuriti bensoüülhüdrasiinide metanolüüsi reaktsiooni CF_3SO_3H juuresolekul. Töös uuriti CF_3SO_3H kontsentratsiooni ja asendajate mõju bensoüülhüdrasiinide metanolüüsi reaktsiooni kiirusele. Tulemustest selgus, et happe kontsentrasiooni kahekordistamine tõstab reaktsiooni kiirust umbes 4 korda. Lisaks sellele reaktsiooni kiirus on väga sõltuv lähtehüdrasiinis olevatest asendajatest. Elektrondonoorsete asendajate juuresolekul reaktsiooni kiirus märkimisväärselt kasvab, elektronaktseptoorsed asendajad avaldavad vastupidist efekti. Saadud tulemused näitasid, et atsüülhüdrasiine saab konverteerida estriteks kasutades 6-9 ekv CF_3SO_3H. Saadud estrite saagised on head või suurepärased.

Märksõnad: Bensoüülhüdrasiinid, CF_3SO_3H, esterdamine, metanolüüs, metüülesterid.

CERCS: P390 – Orgaaniline keemia.

Table of Contents

1. Terms, Abbreviation and Notations

ACN – acetonitrile

Alk – alkyl

Ar – aryl

CGA - carboxyl group activation

DCM – dichloromethane

DMSO – dimethyl sulfoxide

DMAP – 4-(dimethylamino)pyridine

Et – ethyl

EtOAc – ethyl acetate

Et_2O – diethyl ether

Hex – hexane

HPLC – high performance liquid chromatography

IR – infrared

MeOH – methanol

NMR – nuclear magnetic resonance

PE – petroleum ether

Pr – propyl

R_f – retention factor

pTsOH – para-toluenesulfonic acid

TfOH – 2,2,2-trifluoromethanesulfonic acid (triflic acid)

TLC – thin layer chromatography

TMS – trimethylsilyl

UV – ultraviolet

2. Introduction

Esters have a widespread prevalence in several industries, including chemical, food, self-care and pharmaceuticals. Several methods have been developed and employed for ester synthesis. A classical method of ester production is Fischer esterification which uses large excess of alcohol reaction with a carboxylic acid in the presence of strong mineral acids (H_2SO_4, HCl). In addition to the classical acid-mediated approach, various methods have been reported for acylating alcohols. These methods include trans-esterification, acylation of alcohols by acid anhydrides and acyl halides. Additionally, carboxylate ions can be successfully alkylated by powerful alkylating reagents.

At the same time, esterification of nitriles and amides is not so common. However, a possible method of nitrile conversation using the Pinner reaction involves the production of toxic and corrosive HCl gas, thus making it inconvenient. Conversion of amides to esters has its own challenges due to amide bond strength and difficulty in selecting a proper catalyst.

However, synthesising complex and biologically active compounds bearing an ester functional group often proceeds via nitriles or amides, raising thus the demand for simple and general methods for the esterification of amides. Mastitski et al. have reported using a robust, reliable and convenient method for the esterification of various primary amides using TfOH as a catalyst. However, no scientific literature has previously been reported on the esterification of any other carboxylic acid derivates containing an amide moiety.

This thesis aims to fill this gap by studying the esterification of acid hydrazines using the method published by our research group. This work will also explore the implication of substituent groups attached to benzoyl hydrazine and the concentration of TfOH on the yield and rate of the methanolysis reaction.

3. Literature Review

Esters are organic compounds classified as derivates of carboxylic acids and alcohols with a general formula of $R^1COOR^{2,}$ where R^1 and R^2 could be identical or different aliphatic, aromatic, and heterocyclic groups. [1] (**Figure 1**)

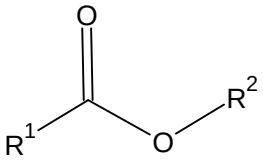


Figure 1 General Ester Structure

Esters are found abundantly in nature in fats, waxes, and fruit ethers. Esters contribute to the characteristic aroma of different fruits and flowers. For example, 3-Methylbutyl acetate and butyl acetate are responsible for the characteristic odour of bananas and pears, respectively.[2] Synthetic esters have several applications as solvents (e.g. Ethyl acetate), fragrances, and flavouring agents (e.g. Methyl butanoate in Apple and Pentyl butanoate in Apricot flavoured goods) [3]. Ingredients of everyday self-care products also possess esters, including surfactants in shampoos, antioxidants in anti-ageing creams and fragrances in perfumes.[4]

Esters are highly valued in organic synthesis as they serve as intermediates or starting materials for different syntheses. A typical example is the nucleophilic addition of hydroxide ions to esters. Similarly, polymer-based esters are extensively utilised in solid-phase peptide synthesis.[5] Moreover, esters can also act as a protective group for carboxyl groups. The common ester-protecting groups for carboxylic acids are methyl, allyl, and benzyl esters. In addition to protection, esters also aid in the resolution of enantiomers of carboxylic acids. [6]

The Ester group is present in a variety of bioactive compounds. Ester bonds are common in many medications available over the pharmacy counter, such as aspirin (**1, Figure 2**) or local anaesthetics like Chloroprocaine (**2, Figure 2**). Even specialised drugs for the treatment of COVID-19, such as Molnupiravir (**3, Figure 2**), contain ester bonds. This demonstrates the crucial role of ester synthesis methods in drug production. The following subchapter, **3.1,** will give an overview of the most important esterification methods.

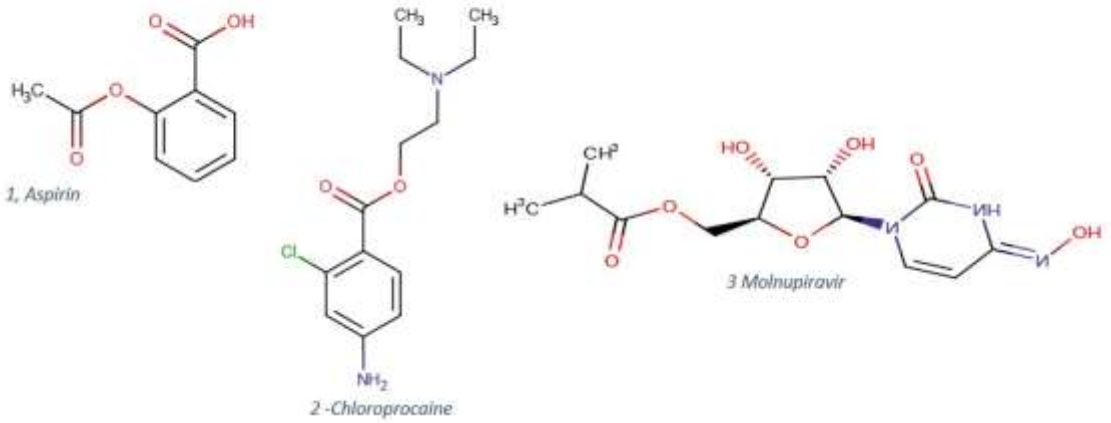


Figure 2 Active ingredients of drugs containing ester bonds.[7]

3.1 Preparation of esters

Several methods are available for preparing esters based on the desired end product and limitations posed by starting material or conditions. Generally, these methods can be organised broadly into two categories: 1) Activation of a carboxyl group (CGA) and subsequent reaction with alcohol; 2) Nucleophilic substitution reaction between carboxylate ion and alkyl sulfate/sulfonate or halide. However, the effectiveness of the nucleophilic substitution method can be affected by steric hindrance. [8]

The following subsections will delve into some standard industrial ester preparatory methods in more detail.

3.1.1 Fischer Esterification

Fischer esterification is a classical approach to the manufacturing of esters. This method involves reacting a carboxylic acid with excess alcohol at elevated temperature in the presence of a strong mineral acid (e.g. H_2SO_4, HCl, pTsOH), as shown in **Figure 3**.[8] Strong mineral acids are added to act as catalysts by providing H^+ ions. Protonation of carboxylic acid allows a nucleophilic attack on the positively polarised carbonyl group by alcohol. Ester and water are produced as products.

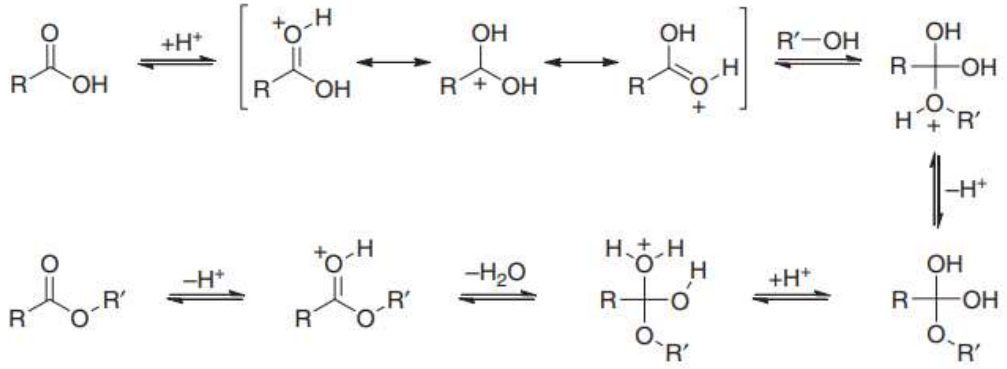


Figure 3 Fischer Esterification [8]

The main drawback of this method is being a reversible reaction, which also compromises product yield. As the reaction proceeds, equilibrium is established. For continuous product production, either one of the reactants should always be in excess, or products must be removed continuously as Le Chatelier's principle dictates. The generated water can be removed through azeotropic distillation. Similarly, water can be removed chemically using anhydrous salts or concentrated H_2SO_4 as a dehydrating agent. Molecular sieves are another effective way of water removal.[9]

A second major drawback of this method is its reaction kinetics, which depends on several factors such as temperature, catalyst efficiency and reactant structure. Primary alcohols react more quickly than secondary ones, and tertiary alcohols have the slowest reaction rate and undergo extended dehydration to alkenes.[8] In addition, the acid catalysed esterification suffers from several side reactions, such as dehydration, etherification, isomerisation, and oxidation. Application of Lewis acid catalysis (ex. $AlCl_3/ZnCl_2$) allows to perform esterification under much milder conditions.[10]

3.1.2 Transesterification

In this method, an ester is heated in the presence of a catalyst with excess alcohol or acid or another ester, respectively. This method uses milder reaction conditions compared to Fischer esterification and requires either acidic (e.g. HCl, $HClO_4$, pTsOH) or basic (Na) catalysis.[1] A simple transesterification using HCl as a catalyst is shown in **Figure 4**.

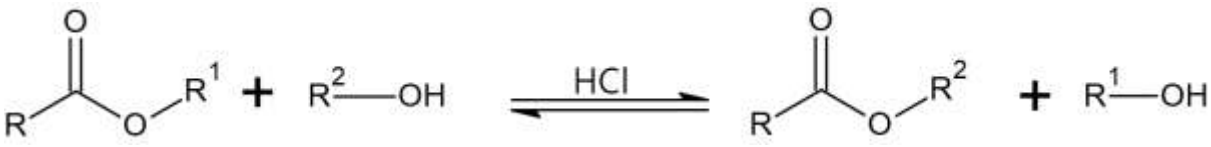


Figure 4 Transesterification

A Common Industrial application of transesterification includes biodiesel production [8] and poly(vinyl butyrate) production. [1] Analytical chemistry also widely uses transesterification to analyse alcohols, fats, and waxes. [1]

3.1.3 Acylation with Carboxylic Anhydrides

Carboxylic anhydrides readily and irreversibly react with alcohols in the presence of Brönsted or Lewis acids ($CoCl_2$, HCl, $HClO_4$) or basic (Pyridine, DMAP) catalysts. A perchloric acid-catalysed synthesis of benzoates is shown in **Figure 5**. Primary and secondary alcohols can be easily acylated in the presence of pyridine [11], while DMAP is more suitable for acylating tertiary alcohols. [12,13] On an industrial scale, this method is utilised to manufacture aspirin and produce cellulose acetate from cellulose and acetic anhydride. [1]

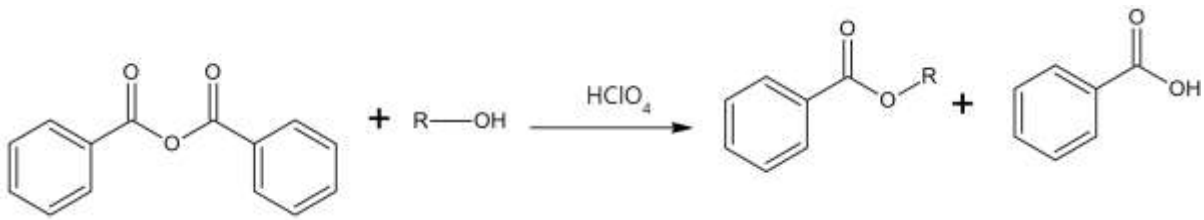


Figure 5 Acylation with Carboxylic Anhydrides

3.1.4 Acylation with Acyl Halides

Production of esters using acylation of alcohols with highly reactive acyl halides is a robust and reliable method having broad applications in analytical chemistry and organic synthesis. The carboxylic group can be converted to acyl halide by various reagents, including PCl_5, PBr_3, $SOCl_2$ or $(COCl)_2$. The acylation reaction is usually performed in the presence of weakly nucleophilic bases such as pyridine or tertiary amine (ex. DMAP) acting as catalysts and bounding the formed hydrogen halide. A simple acylation reaction using $SOCl_2$ as a reagent is shown in **Figure 6.** [14]

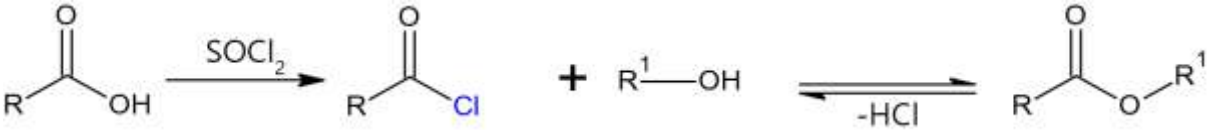


Figure 6 Acylation with Acyl Halide.

The reaction rate is fastest for primary and the less hindered alcohols, followed by secondary alcohols and slowest for tertiary alcohols. This method has the same advantages as the acylation of alcohols by carboxylic anhydrides, being fast, irreversible, and broadly applicable.

3.1.5 Alkylation of Carboxylate Anions

The alkylation of carboxylate anions can be classified as "Alkylation of oxygen" and is mainly employed in preparatory chemistry. In this method, the carboxylate anion acts as a nucleophile. Since carboxylates are resonance stabilised, they are weaker nucleophiles than alkoxides.[14] The reaction proceeds as the carboxylate ion attacks the electrophile by an SN2 mechanism, producing the desired ester. [8] This mild method is efficient in combination with primary alkyl halides or sulphates such as methyl iodide or dimethyl sulphate (DMS). The latter compound is a highly effective alkylating agent successfully employed to synthesise sterically hindered methyl esters.[15] A general principle of this method is demonstrated using methylation of cyclopentanecarboxylate, as is shown in **Figure 7**.

Figure 7 Alkylation of cyclopentanecarboxylate

3.2 Synthesis of esters from nitriles

Nitriles and alcohols can react in the presence of gaseous hydrogen chloride, producing imidate hydrochloride salts, as first reported by Pinner in 1877[16]. These salts can undergo acidic hydrolysis resulting in the formation of esters. A general scheme of the Pinner reaction leading to the formation of esters is shown in **Figure 8**.

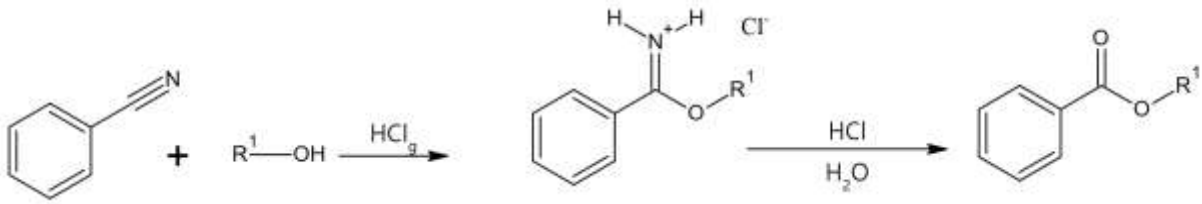


Figure 8 Pinner reaction

In addition to the formation of esters, the intermediate imidate salts might be converted to orthoesters by treatment with alcohols, reaction with primary amines or ammonia results in the formation of amidines, and, finally, heating allows to convert the imidate salt to amides.[17]

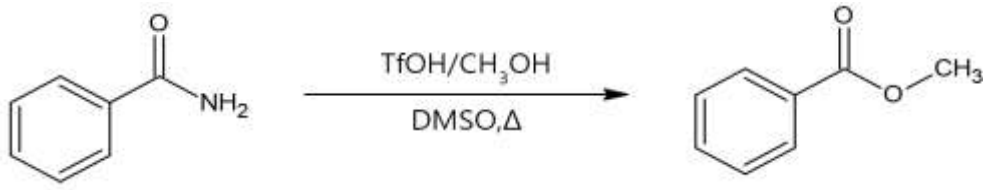
This method is not widely employed due to harsh reaction conditions, which are further made challenging by the use of large quantities of toxic and corrosive hydrogen chloride gas, the arduous handling it requires and slow reaction times. Luo et al. have successfully used trimethylsilyl chloride (TMS-Cl) and excess of ethanol for *in situ* generation of HCl(g).[18] Pfaff et al. reported a Lewis catalysed Pinner reaction using trimethylsilyl triflate (TMSOTf). This milder method gave good results using primary and secondary alcohols as well as aliphatic and aromatic nitriles as reaction substrates.[17]

3.3 Alcoholysis of amides

Amides, like esters, are prevalent in nature. The amide functional group is present in various peptides, proteins, and polymers.[19,20] Amides are thermodynamically stable compounds thanks to conjugation between the carbonyl group and the nitrogen atom. Amide resonance stabilisation inhibits their conversion to other groups under mild reaction conditions [21], thus making the alcoholysis of amides challenging. Despite chemical inertness, amides have emerged as popular acyl donors and can offer an alternative synthetic pathway towards acyl derivates. A reliable method of catalysing the esterification of amides in the presence of strong acids. Several catalysts have been reported for this method, including TMSCl [22], $KHSO_4$ [23], $SnCl_4$ [24], $Sc(OTf)_3$[25], N-protected secondary amides were converted to esters in the presence of K_3PO_4 [26], $Zn(OTf)_2$ [27] and $SOCl_2$ [28] have been utilised for converting amides to corresponding esters.

Triflic acid (TfOH) is a versatile synthetic catalyst in organic chemistry. Triflic acid is a thermally stable superacid with a pKa value of -14, which ensures effective protonation.[29] In terms of alcoholysis, Triflic acid can also significantly address the challenge of alcoholysis of sterically hindered amides or multiple protonation-centred compounds.[30] Vellemäe et al. were the first to report convenient esterification of the hindered α-aminoamide without requiring special equipment.[31] According to the reported procedure, the α-substituted primary amide was refluxed in a methanolic solution containing approximately 15% (by volume) of TfOH. The following reaction successfully converted sterically hindered amide to the corresponding methyl ester at atmospheric pressure with a yield of 65%.[31] Based on the prior results, Mastitski et al. have reported successful alcoholysis with n-substituted primary amides using TfOH as a catalyst in the presence of a small quantity of DMSO.[32] They initially optimised the reaction conditions using benzamide as the standard substrate and used

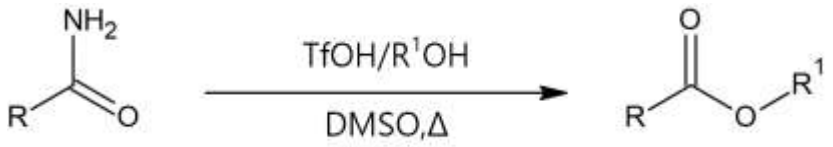
variable amounts of TfOH and methanol to find optimum reaction conditions, as shown in **Scheme 1**.



Scheme 1 Methanolysis of benzamide

According to the reported data [32], the amount of TfOH significantly affects the reaction time of benzamide methanolysis. For example, 15 mol eq of TfOH results in the completion of the reaction in 7 h compared to 24 h in the case of 2 mol eq of TfOH with the same amount of the applied methanol. Similarly, decreasing methanol content in the reaction mixture in the presence of 3 mol eq TfOH decreased the reaction time from 24 h (10 ml of methanol/100 mg of amide) to 8 h (1 ml/100 mg of amide). It was also reported that a very low volume of methanol could introduce a considerable margin of error in yield as methanol tends to vaporise in contact with TfOH without an efficient cooling mechanism. This is a highly exothermic reaction, and suitable cooling with dropwise addition of TfOH was highly recommended. [32]

After optimisation experiments, the group studied the alcoholysis of various primary amides, including alkyl, aryl and substituted aryl groups, as shown in **Scheme 2.**



Scheme 2. Alcoholysis of primary amides in a TfOH/R^1OH system

According to data reported by the group [32], methanolysis of different amides proceeded almost three times more quickly compared to alcoholysis with ethanol or n-propanol. Alcoholysis with benzyl alcohol resulted in the formation of dibenzyl ethers instead of esters. In general, as the molecular mass of alcohol increases, the reaction rate decreases. However, methanol was reported as an ideal reagent for the esterification of amides since it produces the highest yield and has short reaction times. Simultaneously, the group also studied the steric and electronic effects of different substituted groups on reaction rates and yields. It has been reported that electron-withdrawing groups (e.g. Nitro groups) attached to benzamide generally decrease reaction times. In contrast, electron-donating groups (e.g. methoxy) resulted in

extended reaction times. The group reported non-bulky/non-substituted amides esterified faster than benzamides with bulkier substitutions. [32]

The TfOH mediated alcoholysis is currently limited only to primary amides and has demonstrated selectivity in the presence of a cyclic tertiary amide moiety. At the same time, the amide moiety is present in several carboxylic acid derivatives such as acid hydrazides and only limited data is published about transformation of these compounds to esters. For example, selective and mild conversion of unsubstituted carboxylic acid hydrazides to the corresponding esters using acidic resins has been reported.[33] Encouraged by the recent development and the limited amount of literature data on the esterification of acid hydrazides, this thesis aims to build upon recent development and explore the possibility of conversion of acid hydrazides to esters using TfOH as a catalyst in the presence of DMSO.

4. Aim of the thesis

This thesis focuses on the methanolysis of carboxylic acid derivatives bearing an amide moiety, focusing on the conversion of carboxylic acid hydrazides to corresponding methyl esters using triflic acid as a catalyst and methanol acting both as a solvent and a reagent. This study aims to investigate the following:

I. Possibility of methanolysis of acid hydrazides.
II. Effect of different substituents on yield and reaction times of acid hydrazides methanolysis reaction.
III. Effects of the applied TfOH quantities on yield and reaction times.

5. Experimental Part

5.1 Instruments and Techniques

- TLC analyses have been performed on Sigma Aldrich silica gel plate 60 F254 UV 254 with pore size 60 Å. A UV lamp is utilised to detect UV-active compounds.
- NMR spectra measurements have been performed on a Bruker Instrument (700 MHz for ^{1}H spectra and 176 MHz for ^{13}C spectra) using $CDCl_3$ or DMSO-d^6 using solvent residual signals as an internal reference.
- HPLC analysis was conducted using a Shimadzu Prominence system fitted with a Phenomenex 2.6 µm (C18, 100 Å, 150 x 4.6 mm) column. The elution method employed was as follows: mobile phase A consisted of water with 0.1% trifluoroacetic acid (TFA), while mobile phase B comprised acetonitrile with 0.1% TFA. The gradient elution program involved the following steps: an initial 5-minute period with 5% B, followed by a 32-minute ramp from 5% to 100% B. The detection signal was monitored at 220 nm.
- Column chromatography has been performed using Merck Silica gel 60, mesh 70-230 (0.063-0.2 mm) in a ratio of about 1:30 (crude mixture: silica) by weight.
- Rotatory evaporation has been performed using BUCHI Rotavapor R-210 rotary evaporator, and Martin Christ Alpha 1-2 LD plus lyophiliser was used for ultralow vacuuming.

5.2 Physical Properties of Reagents and Solvents

Table 1. contains data collected from multiple sources [34, 35, 37].

Table 1. Physical properties of regent and solvent used.

Compounds	Molar Mass [g/mol]	Boiling Point [°C]	Melting Point [°C]	Density [g/ml]	Refractive Index n_D^{20}
Benzoyl hydrazine	136.15	267	112-114	1.178	1.546
Methanol	32.04	64.7	-98	0.791	1.329
Methyl benzoate	136.15	199	-12.35	1.084	1.857
DMSO	78.13	189	16	1.10	1.479
Ethyl acetate	88.11	76.5	-84	0.902	1.372
Ethanol 96%	46.07	78	-114	0.789	1.360
Diethyl Ether	74.12	34.6	-116	0.706	1.353

Ethyl-4-nitrobenzoate	195.17	186.3	57	-	-
Hexane	86.18	69	-95	0.659	1.375
Hydrazine hydrate (80%)	50.06	119	-51.7	1.030	-
Sulphuric acid 96%	98.08	290	-20	1.840	-
$NaHCO_3$	84.01	-	45	2.159	1.380
Methyl 3,4 - dimethoxybenozate	196.20	283	60.8	283	-
NaOH	40	-	318	-	-
Petroleum ether	82.20	40-60	-73	0.64	1.363
TfOH	158.08	160-162	-	-	-
3-Nitrobenzoyl hydrazine	181.15	279	153-154	1.406	-
Methyl-3-Nitrobenzoate	181.15	279	78-80	1.4283	1.5468
4-Nitrobenzoic acid	167.12	295.67	237-240	1.61	1.6280
Methyl-4-nitrobenzoate	181.15	314.24	94-96	1.4283	1.5468
4-Nitrobenzoylhydrazine	181.15	292.97	210-214	1.3539	1.5860
3,4-Dimethoxybenzoyl hydrazine	196.20	-	145	1.189	-

5.3 General synthetic procedures and characterisation of synthesised substances

5.3.1 Synthesis of 4-Nitrobenzoic acid

A measured amount of sodium dichromate (12.05g, 0.05 mol, 1.5 eq) was added into a conical flask and dissolved in water (30 ml) and followed by the addition of 4-nitrotoulene (4.66g, 0.034 mol, 1 eq) with stirring. Then, 20 ml of concentrated sulphuric acid (34 g, 0.347, 10 eq) was added to the solution slowly, followed by a gradual increase in heating via a hot plate. The mixture was heated at reflux for approx. 90 minutes. Upon completion, the reaction mixture was initially cooled to room temperature and ice-water mixture. The product was removed by filtration and was washed multiple times with cold water until the filtrate turned colourless. To completely remove chromium salts, the separated product was dissolved in 70 ml of 1 mol NaOH followed by filtration under reduced pressure and precipitation of the target 4-nitrobenzoic acid by the addition of conc. H_2SO_4 with pH checked using a universal indicator. The separated product was collected by vacuum filtration; the obtained solid was washed thoroughly with cold water three times and dried. The resulting solid has a light lemon colour with a melting point of 235-238, 238°C lit.[36] , with a yield of 51 %. (Ex. 1) Rf (EtOAc) = 0.15

(1) IR(cm^{-1}): 3117, 3063, 1684, 1604, 1538,1349, 1278, 930, 878, 800, 714
NMR(DMSO-d^6): ^1H (700 MHz) δ= 8.14 (d, 2H, J=9.1 Hz, Ar(H)), 8.28 (d, 2H, J=8.4 Hz, Ar(H)), 13.63 (s, 1H, OH); ^{13}C (176 MHz) δ= 123.70, 130.70, 136.40, 150.03, 165.81.

5.3.2 Esterification of 4-Nitrobenzoic acid

A stirrer bar and 4-Nitrobenzoic acid (2.05 g, n= 0.012, 1 eq) were added into a 50 ml round bottom flask, followed by the addition of 26 ml of CH_3OH (20.57 g, n=0.643, 52 eq). Stirring was started, and 4 ml of concentrated sulphuric acid (7.36, 0.075, 6 eq) was added dropwise. The reaction flask was equipped with a reflux condenser, and the mixture was refluxed for approx. 3 hours. The progress of the reaction was monitored by TLC. To perform TLC analysis, 0.5 ml of H_2O is added into a micro test tube, followed by 1-2 drops of the reaction mixture and the whole solution is topped with a 2-3 mm thick layer of EtOAc. A sample for TLC analysis was extracted from the top-formed layer after vigorous mixing by shaking. EtOAc: PE mixture 1:2 was used as eluent. Upon completion, the reaction mixture was concentrated on the rotatory evaporator up to = 50% of its initial volume. The concentrated reaction mixture was transferred to a 250 ml conical flask and treated with $NaHCO_3$ until the liberation of CO_2 ceased. A pH test was performed using a universal indicator paper to confirm neutralisation. The neutralised mixture was transferred into a separating funnel, and liquid-liquid extraction was performed twice using 50 ml of EtOAc each time. The combined organic layers were washed with 1 x20 ml brine and dried over anhydrous $MgSO_4$. The dried organic solution was decanted into a suitable round bottom flask and concentrated up to dryness using a rotatory evaporator. The resulting solid is light yellow with a melting point of 93-94°C, 96°C lit.[35],with a yield of 96 % (Ex. 2)
(2) IR(cm^{-1}): 3113, 3079, 2959 2854, 1716, 1608, 1521, 1441, 1345, 1271, 1101, 960, 876, 821, 717. NMR ($CDCl^3$): ^1H (700 MHz) δ= 3.97 (s, 3H, OCH_3), 8.20 (d, 2H, J=8.4 Hz, Ar(H)), 8.28 (d, 2H, J=9.1 Hz, Ar(H)); ^{13}C (176 MHz) δ= 52.96, 123.67, 130.84, 135.62, 150.68, 165.30.

5.3.3 Syntheses of Benzoyl Hydrazines

A starting ester (1 eq) was weighed into a round bottom flask, followed by the addition of hydrazine hydrate (5 eq used in Ex. 4,5,6 for syntheses of corresponding hydrazides, 10 mol eq was used in Ex.3 for benzoyl hydrazine synthesis) and the subsequent addition of 10 ml of methanol. The reaction flask was equipped with a reflux condenser, and the mixture was

refluxed until TLC analysis indicated the completeness of the reaction. To perform TLC analysis, 0.5 ml of H_2O is added into a micro test tube, followed by 1-2 drops of the reaction mixture and the whole solution is topped with a 2-3 mm thick layer of EtOAc. A sample for TLC analysis was extracted from the top-formed layer after vigorous mixing by shaking. As mentioned below, TLC eluent was prepared using EtOAc: PE in different ratios. Upon completion, the reaction mixture was initially cooled to room temperature and followed by further cooling via an ice bath or by keeping it in a refrigerator. The solution was crystallised to a solid state upon cooling. Crystallised solid was mixed with ice-cold methanol (approximately 3-5 ml) and filtered via vacuum filtration. The filter cake was washed with cold distilled water twice (approx. 5 ml used each time), and then the filter cake was transferred to a pre-weighed petri dish. The mother liquor is left to cool separately in a round bottom flask. Drying of filter cakes resulted in white to light yellow solids, with yields ranging from 62% to 88%, with a mean of 75%.

Benzoyl hydrazine (Ex. 3)

Yield 62 % as a white solid, mp. 113-116°C, 115°C lit.[35]. R_f (PE = 1) = 0.25

(3) IR(cm^{-1}): 3298, 3200, 3020, 2879, 1604, 1557, 1343, 1117, 985, 883, 671. NMR(DMSO-d^6): ^1H (700 MHz) δ= 4.49 (s, 2H, NH_2), 7.44 (t, 2H, J= 7 Hz, Ar(H)), 7.50 (t, 1H, J= 7 Hz Ar(H)), 7.82 (t, 2H, J= 1.4 Hz, Ar(H)), 9.77 (s, 1H, NH); ^{13}C (176 MHz) δ= 126.94, 128.29, 131.04, 131.31,165.91.

3,4-dimethoxy benzoyl hydrazine (Ex. 4)

Yield 75 % as a white solid, mp. 147°C, 145°C lit.[37]. R_f (EtOAc/PE 1/1) =0.75

(4) IR(cm^{-1}): 3306, 2939, 2845, 1626, 1577, 1496, 1324, 1236, 1148, 1017, 878, 834, 757. NMR(DMSO-d^6): ^1H (700 MHz) δ= 3.79 (d, 6H, J=2.1 Hz, 2 x OCH_3), 4.44 (s, 2H, NH_2), 6.99 (d, 1H, J= 8.4 Hz, Ar(H)), 7.44 (d, 1H, J= 1.4 Hz Ar(H)), 7.46 (dd, 1H, J= 8.4 Hz, J1= 1.4 Hz Ar(H)), 9.63 (s, 1H, NH); ^{13}C (176 MHz) δ= 55.53, 55.56, 110.33, 110.97, 120.18, 125.57 148.26, 151.13, 165.70.

3-Nitro benzoyl hydrazine (Ex.5)

Yield 80% as a light-yellow solid, mp. 152-153°C, 153.5°C lit.[35]. R_f (EtOAc) = 0.27

(5) IR(cm^{-1}): 3274, 3209, 3074, 2862, 1620, 1530, 1335, 1141, 992, 850, 715, 669 NMR(DMSO-d^6): 1H (700 MHz) δ= 4.63 (s, 2H, NH_2), 7.76 (t, 1H, J= 8.4 Hz, Ar(H)), 8.25 (d, 1H, J= 7.7 Hz Ar(H)), 8.35 (d, 1H, J= 7.7 Hz, Ar(H)), 8.63 (s, 1H, Ar(H)), 10.15 (s, 1H, NH); ^{13}C (176 MHz) δ= 121.79, 125.67, 130.13, 133.24, 134.74, 147.78, 163.57.

4-Nitro benzoyl hydrazine (Ex.6)

Yield 88 % as a light-yellow solid, mp. 210-212°C, 215.5°C lit.[35]. R_f (EtOAc) = 0.24

(6) IR(cm^{-1}): 3308, 3071, 2845, 1615, 1595, 1506, 1330, 1107, 929, 863,850, 731, 682. NMR(DMSO-d^6): ^1H (700 MHz) δ= 4.63 (s, 2H, NH_2), 8.04 (d, 2H, J= 8.4 Hz, Ar(H)), 8.30 (d, 2H, J= 8.4 Hz Ar(H)), 10.11 (s, 1H, NH); ^{13}C (176 MHz) δ= 123.51, 128.40, 138.98, 148.89, 163.85.

5.3.4 Methanolysis of Benzoyl Hydrazines

The starting benzoyl hydrazine (1 eq) was weighed into a round bottom flask and dissolved in a suitable amount of methanol (3 ml per 100 mg of benzoyl hydrazine), followed by the addition of DMSO (35 µl per 1 ml of methanol). The acquired solution flask was cooled in an ice-water bath for approximately five minutes. Afterwards, the desired amount of TfOH (3 eq or 6 eq or 9 eq) was added dropwise by automatic pipette into the stirring cold mixture. **Caution**: This is an intensely exothermic process! Fast addition may result in spilling and evaporation of the reaction mixture! After TfOH was added, the ice-water bath was removed, and the reaction flask was equipped with a reflux condenser. The mixture was refluxed until TLC or HPLC analysis indicated the completion of the reaction. To perform TLC analysis, 0.5 ml of $NaHCO_3$ is added into a micro test tube, followed by 3-4 drops of the reaction mixture and the whole solution is topped with a 2-3 mm thick layer of EtOAc. A sample for TLC analysis was extracted from the top-formed layer after vigour mixing by shaking. TLC eluent solvent was prepared using EtOAc: PE in different ratios, as mentioned in with products and starting hydrazine. For HPLC analysis, 50 µl of the sample was extracted using an automatic pipette from the top EtOAc layer prepared using the same procedure for TLC. The sample was evaporated to dryness using a Nitrogen gas stream unless. These residues were dissolved in 500 µl of HPLC-grade acetonitrile. HPLC analysis was conducted using a Shimadzu Prominence system using the elution method in the Instrument and Technique section.

Subsequently, the reaction mixture was cooled to room temperature, and the excess methanol was removed through rotatory evaporation. The concentrated reaction mixture was neutralised with slow addition of $NaHCO_3$ until the liberation of CO_2 ceased. $NaHCO_3$ is used to neutralise the excess of the TfOH. A pH test was conducted using universal indicator paper to confirm neutralisation. The acquired neutralised mixture was transferred into a separating funnel and extracted twice with EtOAc (approximately 20 ml of EtOAc each time). The combined organic layers were washed once with 20 ml brine and dried over anhydrous $MgSO_4$. The dried organic

solution was decanted into a suitable round bottom flask and rotary evaporated to dryness at 45 ºC. **Note**: A small amount of sodium triflate may partially extract into the organic layer; however, this impurity is subsequently removed using column chromatography.

Column chromatography on silica gel was performed to purify the crude mixture using an appropriate solvent for each compound. The specified solvents are listed below. The target fractions were evaporated, resulting in the desired esters. The esters ranged from a colourless, viscous oil to white or slightly yellow solids, with yields varying from 62 to 88%.

Methyl benzoate (Ex. 7,8,9)

Yield 78% as a colourless viscous oil [35]. R_f(EtOAc/PE 1/3) = 0.79

(7) IR(cm^{-1}): 3064, 2952, 2844, 1720, 1601, 1452, 1273, 1109, 1026, 707,687

NMR($CDCl_3$): ^1H (700 MHz) δ= 3.91 (s, 3H, OCH_3), 7.42 (t, 2H, J=7 Hz, Ar(H)), 7.54(t, 1H, J=7 Hz, Ar(H)), 8.03(d, 2H, J=7 Hz, Ar(H)); ^{13}C (176 MHz) = 52.16, 128.43, 129.65, 130.26, 132.98, 167.20.

Methyl 3,4-dimethoxy benzoate (Ex. 10,11,12)

Yield 89% as a white solid [35], mp. 60-61°C, 60.8°C lit.[35]. R_f(EtOAc/PE 1/2) = 0.73

(8) IR(cm^{-1}): 3009, 2958, 2841, 1716, 1594, 1514, 1431, 1270, 1228, 1105, 1018, 989, 758.

NMR($CDCl_3$): ^1H (700 MHz) δ= 3.87(s, 3H, OCH_3), 3.91(s, 6H, 2 x OCH_3), 6.86 (d, 1H, J=8.4 Hz, Ar(H)), 7.52 (d, 1H, J=2.1 Hz, Ar(H)), 7.66 (dd, 1H, J_1=8.4 Hz, J_2=2.1 Hz, Ar(H)); ^{13}C (176 MHz) δ= 52.05, 56.07, 56.08, 110.35, 112.05, 122.77, 123.65, 148.69, 153.04, 166.95.

Methyl 3-Nitrobenzoate (Ex. 13,14,15)

Yield 73% as a white solid, mp. 77-79°C, 78°C lit.[35]. R_f(EtOAc/PE 1/3) =0.66

(9) IR(cm^{-1}): 3093, 2961, 2869, 1716, 1526, 1439, 1350, 1290, 1268, 1194, 1134, 1102, 976, 823, 718. NMR($CDCl_3$): ^1H (700 MHz) δ= 3.98 (s, 3H, OCH_3), 7.65 (t, 1H, J=8.4 Hz, Ar(H)), 8.35 (m, 1H, Ar(H)), 8.40 (m, 1H, Ar(H)), 8.84 (t, 1H, J=2.1 Hz, Ar(H)); ^{13}C (176 MHz) δ= 52.88, 124.68, 127.47, 129.73, 131.97, 135.35, 148.37,165.03.

Methyl 4-Nitrobenzoate (Ex. 16,17,18,19)

Yield 83% as a light-yellow solid, mp. 93-94°C, 96°C lit.[35]. R_f(EtOAc/PE 1/3) =0.49

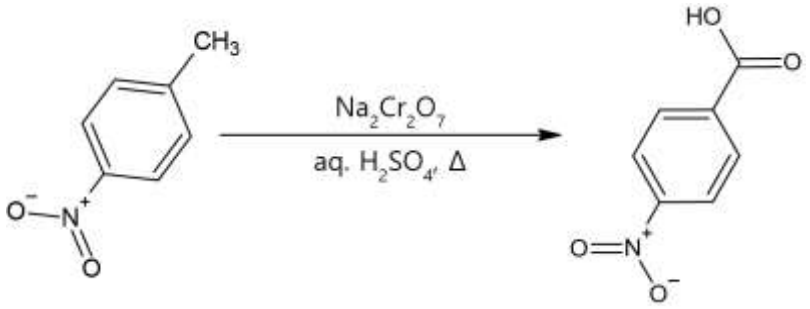
(10) IR(cm^{-1}): 3113, 3079, 2959 2854, 1716, 1608, 1521, 1441, 1345, 1271, 1101, 960, 876, 821, 717. NMR($CDCl_3$): ^1H (700 MHz) δ= 3.97 (s, 3H, OCH_3), 8.20 (d, 2H, J=8.4 Hz, Ar(H)), 8.28 (d, 2H, J=9.1 Hz, Ar(H)); ^{13}C (176 MHz) δ= 52.96, 123.67, 130.84, 135.62, 150.68, 165.30.

6. Result and Discussion

The primary objective of this work was to explore the prospect of conversion of acid hydrazides to corresponding esters. Given the limited scope and time constraints, the same optimised conditions are applied in this experiment set, as Mastitski et al. reported for alcoholysis with n-substituted primary amides. [32] The methanol concentration was kept constant at 3 ml per 100 mg of starting benzoyl hydrazine. 35 µl of DMSO was added per 1 ml of methanol in all reactions.

The initial methanolysis was successfully achieved by taking benzoyl hydrazine as a model substrate in 3 mol equivalence of TfOH. The reaction proceeded smoothly and yielded the desired methyl ester. The initial success prompted us to explore the methanolysis of variously substituted benzoyl hydrazine and evaluate the effect of varied amounts of 3 eq, 6 eq and 9 eq of applied TfOH on yield and reaction times.

6.1 Synthesis of 4-Nitrobenzoic acid



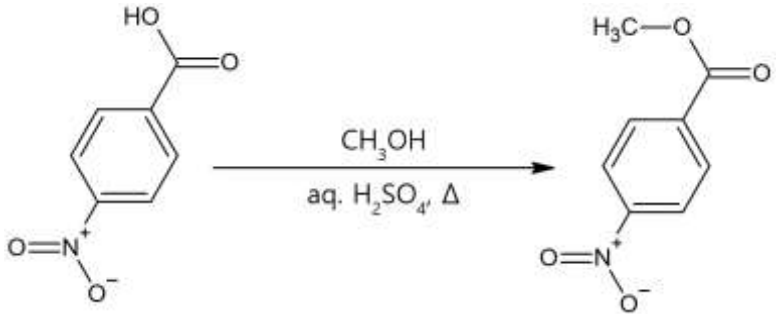
(1) - 51%

Figure 9 Oxidation of Toluene

This synthesis was performed as illustrated in **Figure 9,** following the procedure submitted initially by O. Kamm and A. O. Matthews [36]. However, all reactant amounts were decreased by a factor of 50. The obtained yield was 51%, lower than the expected range of 82-84%. A possible cause for this reduction is the volatile nature of nitrotoluene. Since a relatively small quantity was used, it might have vaporised upon the addition of concentrated sulphuric acid. Another possible reason for low yield is an incomplete conversion of starting 4-Nitrotoluene is non-continuous reflux leading to a decrease in reaction temperature and incomplete conversion. A relatively large excess of sulphuric acid in the reaction mixture greatly enhances the oxidising properties of dichromate, and a remarkable quantity of sulfuric acid is consumed during the

reaction. The purity of the obtained light lemon colour solid was checked with melting point measurement, which matches the published data.

6.2 Esterification of 4-Nitrobenzoic acid

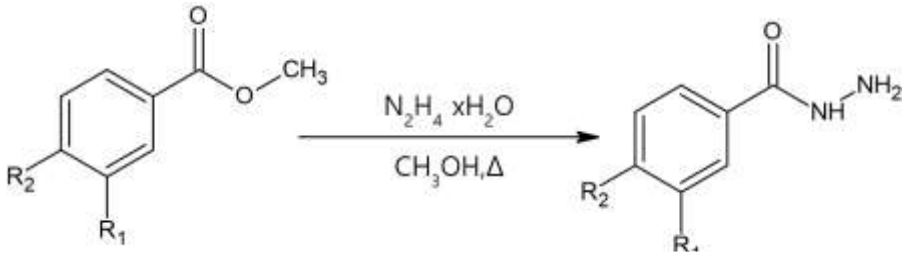


(2) - 96%

Figure 10 Esterification of 4-Nitrobenzoic acid

This synthesis was performed as illustrated in **Figure 10**. This synthesis is a standard Fischer esterification process where excess methanol ensures complete methanolysis of p-nitrobenzoic acid. Concentrated sulphuric acid acts as both a protonation catalyst and dehydrating agent. The reaction mixture was refluxed for approximately 3 hours, and the obtained mixture yielded 96% with a melting point of 93-94 °C. Although the melting point is slightly less than given in the literature, it is still within acceptable limits indicating the high purity of the product.

6.3 Syntheses of Benzoyl Hydrazines



(3) – 80%
(4) – 75%
(5) – 80%
(6) – 88%

Figure 11 General synthesis scheme of benzoyl hydrazines

This synthesis was performed as illustrated in **Figure 11**. Hydrazine hydrate is used in excess in all syntheses to ensure esters act as limiting reagents. Methanol is used as a solvent for dissolving the solid esters to optimise the reaction conditions. It is possible to use other alcohols as a solvent for dissolving the solid esters; however, this increases the risk of the trans-esterification reaction of starting ester. In order to avoid possible unwanted transesterification reactions, the same alcohol is usually used as a reaction media (methyl ester – methanol etc.)

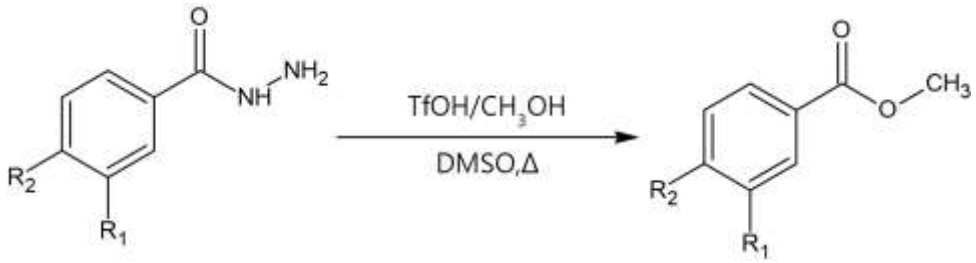
Hydrazine exhibits a great nucleophilic character due to the α-effect. In 1962, Pearson and Edwards coined the term α-effect to explain the increased reactivity of nucleophiles that possess an unshared pair of electrons at the atom adjacent to the nucleophilic centre.[38]

Table 2. Syntheses of Benzoyl hydrazines from esters

Experiment Number **(product code)**	Starting Material	R_1	R_2	Yield %
3 **(3)**	Methyl benzoate	H	H	62
4 **(4)**	Methyl 3,4-dimethoxy benzoate	O-CH_3	O-CH_3	75
5 **(5)**	Methyl 3-Nitrobenzoate	NO_2	H	80
6 **(6)**	Methyl 4 -Nitrobenzoate	H	NO_2	88

Electron donating/withdrawing groups affect only the reactivity since reactions were monitored until their completeness. Therefore the yields are only affected by the solubility of the products in their mother liquors. Hydrazines are miscible in water and have high solubility in methanol as well. The solubility of hydrazine in methanol varies depending on the hydrophilic or hydrophobic substituent attached to them. Usually, nitro-substituted compounds have poorer solubility, which explains the high yields for both nitro-substituted hydrazines comparatively.

6.4 Methanolysis of Benzoyl Hydrazines



(7) – 78%
(8) – 89%
(9) – 73%
(10) – 83%

Figure 12 General methanolysis scheme of Benzhydrazide

This synthesis was performed as illustrated in **Figure 12**. The reactions were carried out using benzoic acid hydrazide as a model substrate with excess methanol and a variable amount of TfOH (3 mol eq, 6 mol eq, and 9 mol eq). A small amount of DMSO was added to these organic

syntheses to prevent side reactions and enhance the purity of the final product. It prevented the oxidation of the starting acid hydrazine's amino group, which tends to have a strong reducing potential. This is essential as prolonged reaction time can lead to side reactions.

Table 3. Methanolysis of Benzoyl hydrazines from esters

Experiment Number and (**product code**)	Starting Material	R_1	R_2	TfOH (mol eq) used	Yield %	Reaction time h
7 **(7)**	Benzoyl hydrazine	H	H	3	71	68
8 **(7)**	Benzoyl hydrazine	H	H	6	59	28
9 **(7)**	Benzoyl hydrazine	H	H	9	78	10
10 **(8)**	3,4-dimethoxy benzoyl hydrazine	O-CH_3	O-CH_3	3	89	67
11**(8)**	3,4-dimethoxy benzoyl hydrazine	O-CH_3	O-CH_3	6	63	51
12 **(8)**	3,4-dimethoxy benzoyl hydrazine	O-CH_3	O-CH_3	9	79	51
13 **(9)**	3-Nitrobenzoyl hydrazine	NO_2	H	3	13*	235
14 **(9)**	3-Nitrobenzoyl hydrazine	NO_2	H	6	73	70
15 **(9)**	3-Nitrobenzoyl hydrazine	NO_2	H	9	71	70
16 **(10)**	4-Nitrobenzoyl hydrazine	H	NO_2	3	54	82
17 **(10)**	4-Nitrobenzoyl hydrazine	H	NO_2	6	71	66
18 **(10)**	4-Nitrobenzoyl hydrazine	H	NO_2	9	83	22
19 **(10)**	4-Nitrobenzoyl hydrazine	H	NO_2	13.5	66	22

*Spillage accident during transfer

According to the data collected in **Table 3**, the amount of TfOH has influenced the reaction times in all experiments of methanolysis of benzoyl hydrazines. Increasing acid concentration has resulted in a decrease in reaction time. However, the decrease in time is not uniform across the experimental sets. For the synthesis of methyl benzoate, the reaction time decreases almost seven-fold from approximately 70 h in the case of Ex. 7 (3 mol eq of TfOH) to 10 hours in the case of Ex. 9 (9 mol eq of TfOH). At the same time, for the synthesis of methyl 3,4-dimethoxy benzoate, where starting material contains electron-donating groups, the reaction time decreases by only 16 h from approximately 67 h in the case of Ex. 10 (3 mol eq of TfOH) to 51 hours in the case of Ex. 11 and Ex 12. (6 and 9 mol eq of TfOH, respectively). In this case, the increase in the concentration of TfOH does not influence reaction time when concentration increases from 6 to 9 mol eq of TfOH. A repeated, more close sampling set may produce a slight difference here. Simultaneously, the presence of the electron-withdrawing nitro group in the synthesis of methyl 3-Nitrobenzoate (Ex.13-15) and methyl 4-Nitrobenzoate (Ex.16-19) resulted in an increase in reaction time compared to the synthesis of methyl benzoate and methyl 3,4-dimethoxy benzoate for acid concentrations. In the case of the synthesis of methyl 3-Nitrobenzoate, reaction times decreased by four times as the concentration of TfOH acid increased from 3 mol eq (Ex. 13) to 6 mol eq(Ex. 14) and stabilised to the same reaction time for 9 mol eq(Ex. 15). In comparison, reaction time for methyl 4-Nitrobenzoate synthesis is only 82 h (Ex.16) compared to 235 h for methyl 3-nitrobenzoate (Ex. 13) upon application of 3 mol eq of TfOH. In the case of the synthesis of methyl 4-Nitrobenzoate, reaction times decreased by four times as the concentration of TfOH acid increased from 3 mol eq (Ex. 16) to 9 mol eq(Ex. 18) and stabilised to the same reaction time for 13.5 mol eq(Ex. 19). In the case of substituted benzoyl hydrazines, the electron effects worked in the opposite direction for 4-nitrobenzoyl hydrazines had the shortest reaction time at 9 mol eq. For 3 mol eq of TfOH, there are only minor differences in reaction times of benzoyl hydrazines. Such a minor effect is present because of a protonation centre (the free NH_2 group of hydrazide), and conjugation between the carbonyl group and the nitrogen atom makes nucleophilic addition of methanol to carbonyl carbon very difficult. These effects are much more assertive in comparison to electronic effects produced by electron donating/withdrawal groups. For higher concentrations of TfOH acid, other factors like specific solvation can affect the reaction times. Overall, at least six molar equivalence excess of acid must be utilised for general practical applications.

The pattern of yield production varies in different sets of experiments and does not have a clear pattern overall. The mean yield for this conversation was 78%. In conclusion, increasing the concentration of TfOH may not increase yield, but it would surely decrease reaction time.

7. Summary

The main goal of this thesis was to explore the possibility of esterification of benzoyl hydrazine using a selective method. In addition, the aim was to study the effect of benzoyl group substituents and TfOH concentrations on yield and reaction rate.

Firstly, the methanolysis of benzoyl hydrazine was achieved successfully. The reaction between benzoyl hydrazine and methanol resulted in the formation of methyl benzoate. The structure of methyl benzoate was confirmed using TLC, IR and NMR analyses.

Upon initial success, methanolysis of benzoyl hydrazines with different electronic and steric substitutions was studied. In the case of substituted benzoyl hydrazines, 4 Nitro benzoyl hydrazine had the shortest reaction time at 9 mol eq. The effect of substituted groups does not influence the reaction times significantly in case of 3 mol eq of TfOH therefore 6 mol eq of TfOH concentration founded ideal for practical application.

Further experiments were conducted to study the effect of TfOH concentration on yield and reaction rates for different substituents attached to the benzoyl group. It was observed that as the TfOH concentration increased, the reaction time for completion decreased. When the TfOH molar concentration is doubled, the reaction time decreases about four times. It was also noted that reaction rates plateau after a specific TfOH concentration increase, and a further increase in TfOH concentration does not result in a further decrease in reaction times.

The mean yield for methanolysis obtained was 78%. However, individual experimental yields vary. Variations in individual results may result from several factors, including the volatility of starting materials upon contact with TfOH. Low UV activity of final products may also have contributed to loss during column chromatography extractions. Other operational losses may have resulted during the vacuumation of products.

Esterification of benzoyl hydrazide using superacid has not been reported in scientific literature before. The obtained results clearly demonstrate that the alcoholysis of amide moiety in the presence of TfOH is not limited by applications in combination with primary amides but can be successfully used in combination with acyl hydrazines.

8. References

1. Riemenschneider, W.; Bolt, H. M. Esters, Organic. In Ullmann's Encyclopedia of Industrial Chemistry; Wiley-VCH: Weinheim, Germany, 2005; pp 245–266.
2. Carey, F. A., Giuliano, R. M., Allison, N. T., & Bane, T. S. L. (2020). 20. In Organic Chemistry (pp. 800–849). essay, McGraw-Hill Education.
3. Ouellette, R. J. (2018). Organic chemistry structure mechanism and synthesis. Elsevier.
4. Khan, N. R., & Rathod, V. K. (2015). Enzyme catalyzed synthesis of cosmetic esters and its intensification: A Review. Process Biochemistry, 50(11), 1793–1806. https://doi.org/10.1016/j.procbio.2015.07.014
5. Yang, J., Huang, H., & Zhao, J. (2023). Active ester-based peptide bond formation and its application in peptide synthesis. Organic Chemistry Frontiers, 10(7), 1817–1846. https://doi.org/10.1039/d2qo01686a
6. Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 5th ed.; Wiley: Hoboken, New Jersey, 2014.
7. Drug Structures. Uses, Interactions, Mechanism of Action | DrugBank Online. (n.d.). Retrieved April 29, 2023, from https://go.drugbank.com/drugs/DB15661
8. Siengalewicz, P., Mulzer, J., & Rinner, U. (2014). 6.09 synthesis of esters and lactones. Comprehensive Organic Synthesis II, 355–410. https://doi.org/10.1016/b978-0-08-097742-3.00612-1
9. Bruice, P. Y. (2017). Organic Chemistry. Pearson Education Limited.
10. Roy, H. N.; Mamun, A. H. A. Regiospecific Phenyl Esterification to Some Organic Acids Catalyzed by Combined Lewis Acids. Synth. Commun. 2006, 36 (20), 2975–2981.
11. Iqbal, J., & Srivastava, R. R. (1992). Cobalt(II) chloride catalyzed acylation of alcohols with acetic anhydride: Scope and mechanism. The Journal of Organic Chemistry, 57(7), 2001–2007. https://doi.org/10.1021/jo00033a020
12. Scriven, E. F. (1983). 4-dialkylaminopyridines: Super Acylation and alkylation catalysts. Chemical Society Reviews, 12(2), 129. https://doi.org/10.1039/cs9831200129
13. Kammoun, N., Le Bigot, Y., Delmas, M., & Boutevin, B. (2010). Cheminform Abstract: A new simplified method for esterification of secondary and tertiary alcohols. ChemInform, 28(42). https://doi.org/10.1002/chin.199742071
14. Ouellette, R. J., & Rawn, J. D. (2018). Carboxylic Acids. In Organic Chemistry: Structure, mechanism, synthesis (pp. 625–663). essay, Academic Press is an imprint of Elsevier.
15. Grundy, J., James, B. G., & Pattenden, G. (1972). Esterification of sterically hindered carboxylic acids using dimethyl sulphate. Tetrahedron Letters, 13(9), 757–758. https://doi.org/10.1016/s0040-4039(01)84430-0
16. Pinner, A., & Klein, F. (1877, July). Umwandlung der Nitrile in Imide. Berichte Der Deutschen Chemischen Gesellschaft, 10(2), 1889–1897. https://doi.org/10.1002/cber.187701002154
17. Pfaff, D., Nemecek, G., & Podlech, J. (2013, August 2). A Lewis acid-promoted Pinner reaction. Beilstein Journal of Organic Chemistry, 9, 1572–1577. https://doi.org/10.3762/bjoc.9.179
18. Luo, F. T., & Jeevanandam, A. (1998, December). Simple transformation of nitrile into ester by the use of chlorotrimethylsilane. Tetrahedron Letters, 39(51), 9455–9456. https://doi.org/10.1016/s0040-4039(98)02143-1
19. Benz, G. (1991). Synthesis of Amides and Related Compounds. Comprehensive Organic Synthesis, 381–417. https://doi.org/10.1016/b978-0-08-052349-1.00162-1
20. Kumar, V., Bhatt, V., & Kumar, N. (2018). Amides from plants: Structures and Biological Importance. Studies in Natural Products Chemistry, 287–333. doi:10.1016/b978-0-444-64058-1.00009-1

21. Toyao, T., Nurnobi Rashed, Md., Morita, Y., Kamachi, T., Hakim Siddiki, S. M., Ali, Md. A., Touchy, A. S., Kon, K., & Maeno, Z. (2018). Esterification of tertiary amides by alcohols through C−N bond cleavage over CEO 2. ChemCatChem, 11(1), 449–456. https://doi.org/10.1002/cctc.201801098
22. Xue, C., & Luo, F.-T. (2004). Transformation of amides into esters by the use of chlorotrimethylsilane. Journal of the Chinese Chemical Society, 51(2), 359–362. https://doi.org/10.1002/jccs.200400055
23. Sattenapally, N., Sharma, J., & Hou, Y. (2018). Selective conversion of primary amides to esters promoted by KHSO4. Arkivoc, 2018(5), 174–183. https://doi.org/10.24820/ark.5550190.p010.392
24. Fisher, L. E., Caroon, J. M., Stabler, S. R., Lundberg, S., Zaidi, S., Sorensen, C. M., Sparacino, M. L., & Muchowski, J. M. (1994). Mild hydrolysis or alcoholysis of amides. ti(iv) catalyzed conversion of primary carboxamides to carboxylic acids or esters. Canadian Journal of Chemistry, 72(1), 142–145. https://doi.org/10.1139/v94-022
25. Atkinson, B. N., & Williams, J. M. J. (2014). Scandium triflate catalyzed ester synthesis using primary amides. Tetrahedron Letters, 55(50), 6935–6938. https://doi.org/10.1016/j.tetlet.2014.10.124
26. Li, G., Lei, P., & Szostak, M. (2018). Transition-metal-free esterification of amides via selective N–C cleavage under mild conditions. Organic Letters, 20(18), 5622–5625. https://doi.org/10.1021/acs.orglett.8b02323
27. Nishii, Y., Hirai, T., Fernandez, S., Knochel, P., & Mashima, K. (2017). Zinc-catalyzed esterification of n-β-hydroxyethylamides: Removal of directing groups under mild conditions. European Journal of Organic Chemistry, 2017(34), 5010–5014. https://doi.org/10.1002/ejoc.201700748
28. Li, L.-C., Ren, J., Liao, T.-G., Jiang, J.-X., & Zhu, H.-J. (2007). A novel direct conversion of primary amides to their corresponding methyl esters. European Journal of Organic Chemistry, 2007(6), 1026–1030. https://doi.org/10.1002/ejoc.200600853
29. Simonato, Jp. (2005). Meet the industrial superacid. Chemistry & industry. 20-21.
30. Uchida, T., Somada, A., Kagoshima, Y., Konosu, T., & Oida, S. (2008). Carbon analogs of antifungal dioxane-triazole derivatives: Synthesis and in vitro activities. Bioorganic & Medicinal Chemistry Letters, 18(24), 6538–6541. https://doi.org/10.1016/j.bmcl.2008.10.055
31. Vellemäe, E., Mastitski, A., Järv, J., & Veli Hiltunen, J. (2018). A convenient methanolysis in the synthesis of carfentanyl. Organic Preparations and Procedures International, 50(5), 522–526. https://doi.org/10.1080/00304948.2018.1526034
32. Mastitski, A., Vellemäe, E., Smorodina, V., Konist, A., & Järv, J. (2023). Alcoholysis of primary amides in the presence of CF3so3H. Organic Preparations and Procedures International, 1–11. https://doi.org/10.1080/00304948.2023.2184997
33. Greenlee, W. J., & Thorsett, E. D. (1981). Mild conversion of carboxamides and carboxylic acid hydrazides to acids and esters. The Journal of Organic Chemistry, 46(26), 5351–5353. https://doi.org/10.1021/jo00339a019
34. Merck. Merck | Life Science Products & Service Solutions. (n.d.). https://www.sigmaaldrich.com/EE/en
35. Haynes, W. M. (2014). CRC Handbook of Chemistry and Physics, 95th edition. CRC Press Taylor & Francis Group.
36. P-nitrobenzoic acid. (1922). Organic Syntheses, 2, 53. https://doi.org/10.15227/orgsyn.002.0053
37. CAS SciFindern - Chemical Compound Database. CAS. (n.d.). https://www.cas.org/cas-scifindern-chemical-compound-database
38. Nigst, T. A., Antipova, A., & Mayr, H. (2012). Nucleophilic reactivities of hydrazines and amines: The futile search for the α-effect in hydrazine reactivities. The Journal of Organic Chemistry, 77(18), 8142–8155. https://doi.org/10.1021/jo301497g

9. Acknowledgement

I want to express my sincere appreciation to my respected supervisor **Anton Mastitski,** for allowing me to conduct my bachelor's thesis in his research lab. I consider myself exceptionally fortunate to have a supervisor who possesses an extraordinary level of patience coupled with a genuine passion for teaching. Anton's unwavering support and genuine regard for my progress allowed me to take my first steps into the captivating world of organic synthesis research.

I also sincerely thank my program director Ilona Faustova, whose unwavering support and constant encouragement were instrumental throughout my academic journey.

Furthermore, I cannot overlook my mother's immeasurable support and faith during all my life's highs and lows. Her unwavering dedication and encouragement have been a constant factor in my life.

Last but certainly not least, I extend my deepest thanks to Nadeem Natt (PhD), who has been my invaluable mentor. Despite the physical distance and seven time zones that separated us, Nadeem's unwavering guidance and support transcended all barriers, offering me guidance and wisdom on multiple occasions. I am profoundly grateful for his profound impact on my academic and personal growth.

10. Non-exclusive licence to reproduce the thesis and make the thesis public.

I, Intasar Ul Haq

1. grant the University of Tartu a free permit (non-exclusive licence) to:

reproduce, for the purpose of preservation, including for adding to the DSpace digital archives until the expiry of the term of copyright, my thesis

Methanolysis of Benzoyl hydrazines in the presence of Trifluoromethanesulfonic acid

supervised by Anton Mastitski

2. I grant the University of Tartu the permit to make the thesis specified in point 1 available to the public via the web environment of the University of Tartu, including via the DSpace digital archives, under the Creative Commons licence CC BY NC ND 4.0, which allows, by giving appropriate credit to the author, to reproduce, distribute the work and communicate it to the public, and prohibits the creation of derivative works and any commercial use of the work from 24/05/2026 until the expiry of the term of copyright,
3. I am aware that the author retains the rights specified in points 1 and 2.

4. I confirm that granting the non-exclusive licence does not infringe other persons' intellectual property rights or rights arising from the personal data protection legislation.

Intasar Ul Haq
08/06/2023

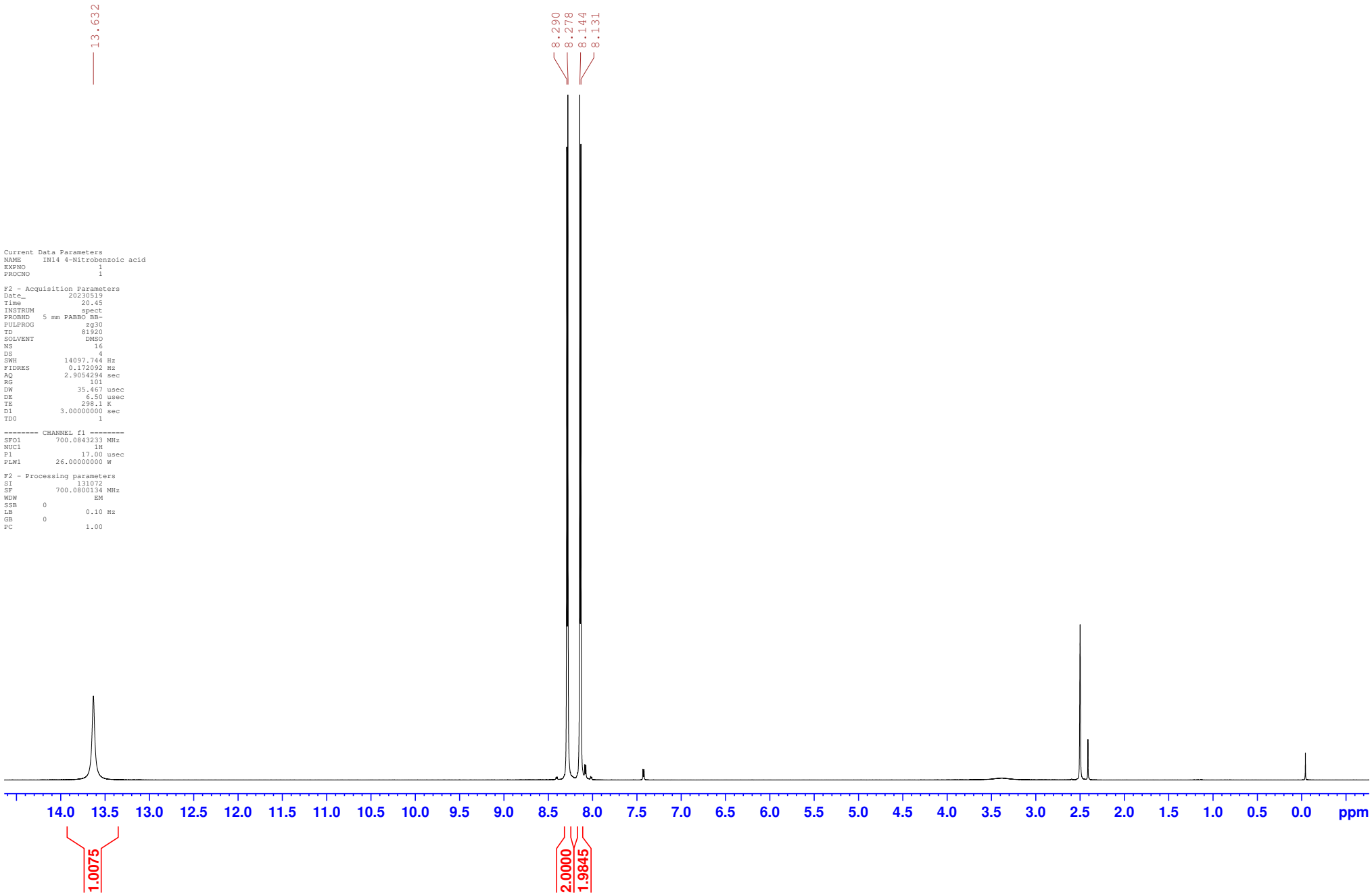
11. Appendices

11.1 NMR Supplement code table

Compound Code	NMR code	Compound name
1	IN 14	4-Nitrobenzoic acid
2	IN 18	Methyl 4-benzoate
3	IUH 01	Benzoyl hydrazine
4	IN 15	3,4-dimethoxy benzoyl hydrazine
5	IN 9	3-Nitrobenzoyl hydrazine
6	IN 16	4-Nitrobenzoyl hydrazine
7	IUH 03	Methyl benzoate
8	IN 8	methyl-3,4-dimethoxy benzoate
9	IN 12	Methyl 3 Nitrobenzoate
10	IN 18	Methyl 4-benzoate

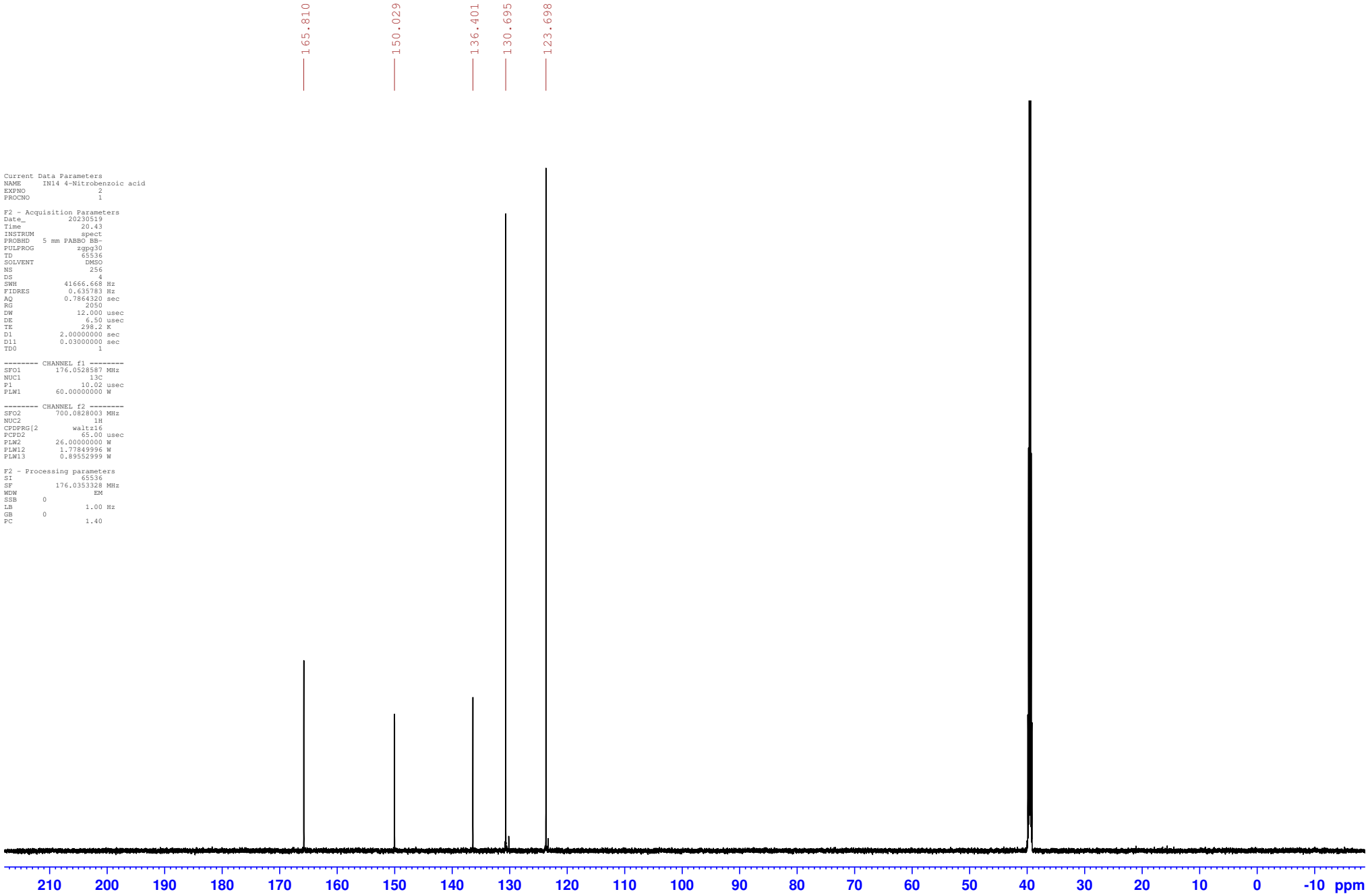
11.2 NMR Attachments

IN14 4-Nitrobenzoic acid 1H DMSO-d6
PROTON DMSO {C:\Spectra\data\AntonM\nmr} AntonM 8



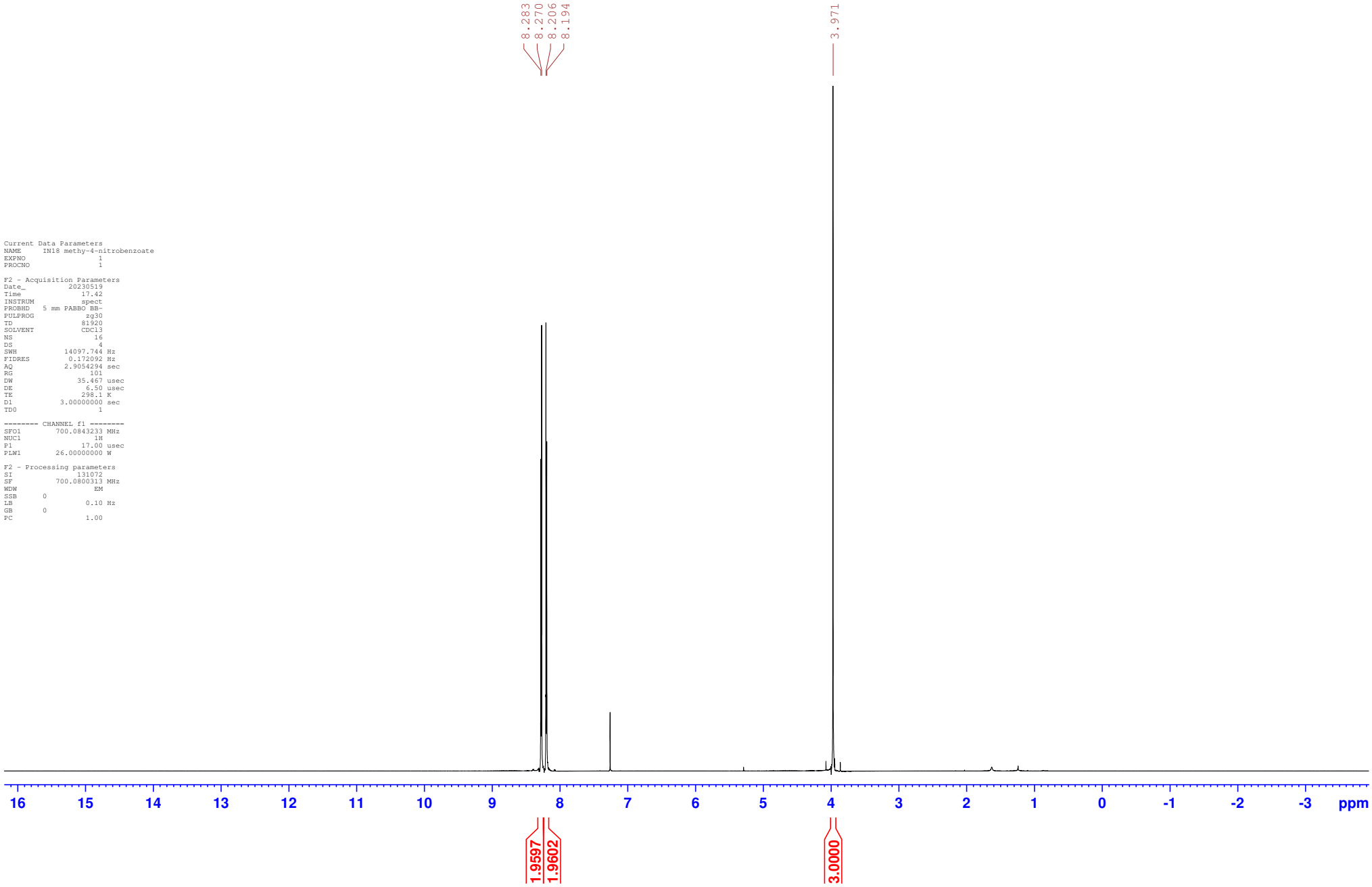

```
Current Data Parameters
NAME      IN14 4-Nitrobenzoic acid
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20230519
Time             20.45
INSTRUM          spect
PROBHD   5 mm PABBO BB-
PULPROG          zg30
TD              81920
SOLVENT           DMSO
NS                  16
DS                   4
SWH          14097.744 Hz
FIDRES        0.172092 Hz
AQ            2.9054294 sec
RG                 101
DW              35.467 usec
DE               6.50 usec
TE              298.1 K
D1           3.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1       700.0843233 MHz
NUC1               1H
P1              17.00 usec
PLW1       26.00000000 W

F2 - Processing parameters
SI              131072
SF         700.0800134 MHz
WDW                EM
SSB       0
LB              0.10 Hz
GB        0
PC              1.00
```

IN14 4-Nitrobenzoic acid C13 DMSO-d6
C13CPD DMSO {C:\Spectra\data\AntonM\nmr} AntonM 8



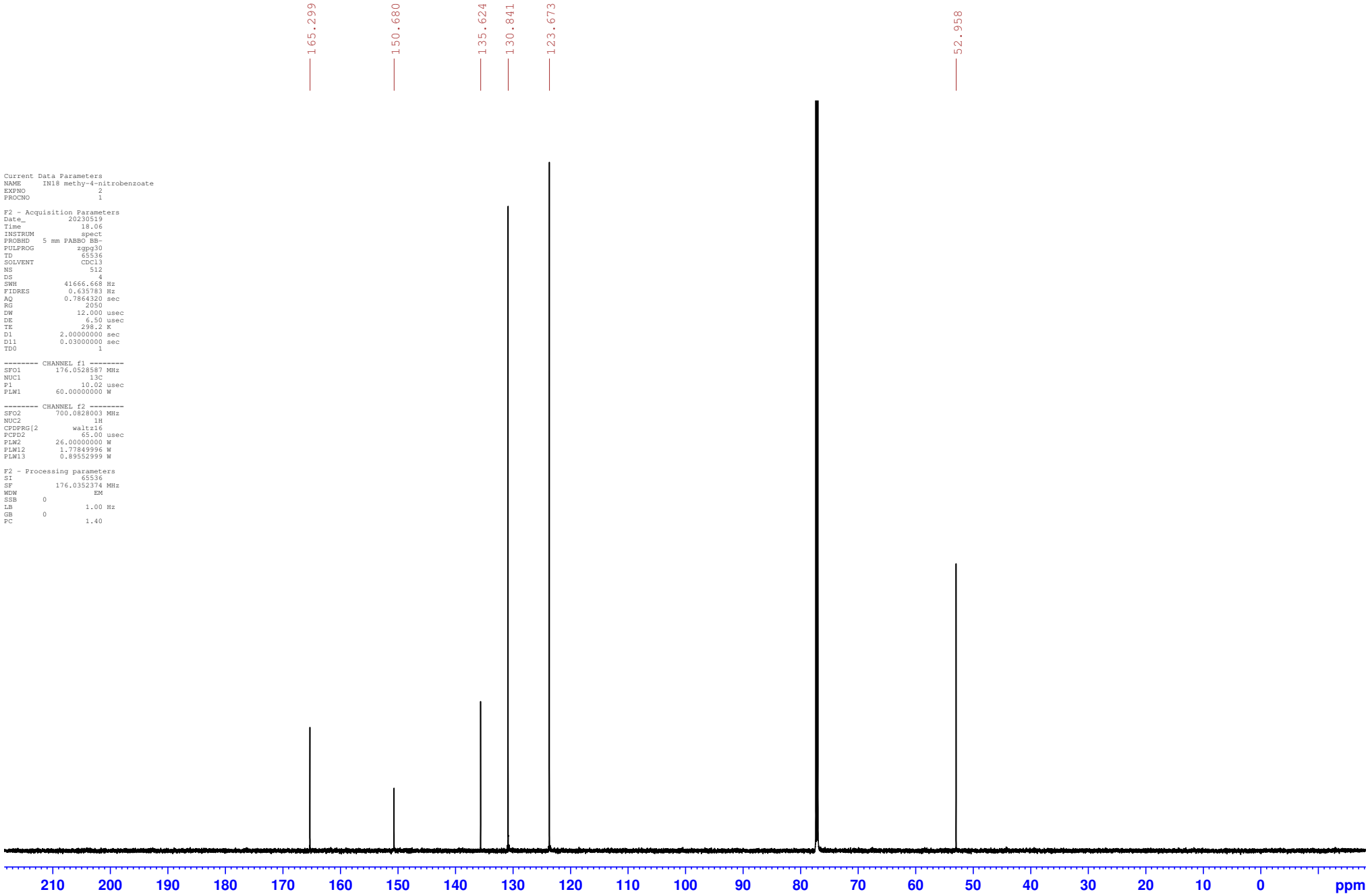

```
Current Data Parameters
NAME      IN14 4-Nitrobenzoic acid
EXPNO                2
PROCNO               1

F2 - Acquisition Parameters
Date_           20230519
Time              20.43
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT            DMSO
NS                   256
DS                     4
SWH           41666.668 Hz
FIDRES         0.635783 Hz
AQ            0.7864320 sec
RG                  2050
DW               12.000 usec
DE                6.50 usec
TE                298.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        176.0528587 MHz
NUC1                13C
P1                10.02 usec
PLW1        60.00000000 W

======== CHANNEL f2 ========
SFO2        700.0828003 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             65.00 usec
PLW2        26.00000000 W
PLW12        1.77849996 W
PLW13        0.89552999 W

F2 - Processing parameters
SI                 65536
SF          176.0353328 MHz
WDW                  EM
SSB      0
LB                1.00 Hz
GB       0
PC                1.40
```

IN18 methy-4-nitrobenzoate 1H CDCl3
PROTON CDCl3 {C:\Spectra\data\AntonM\nmr} AntonM 3



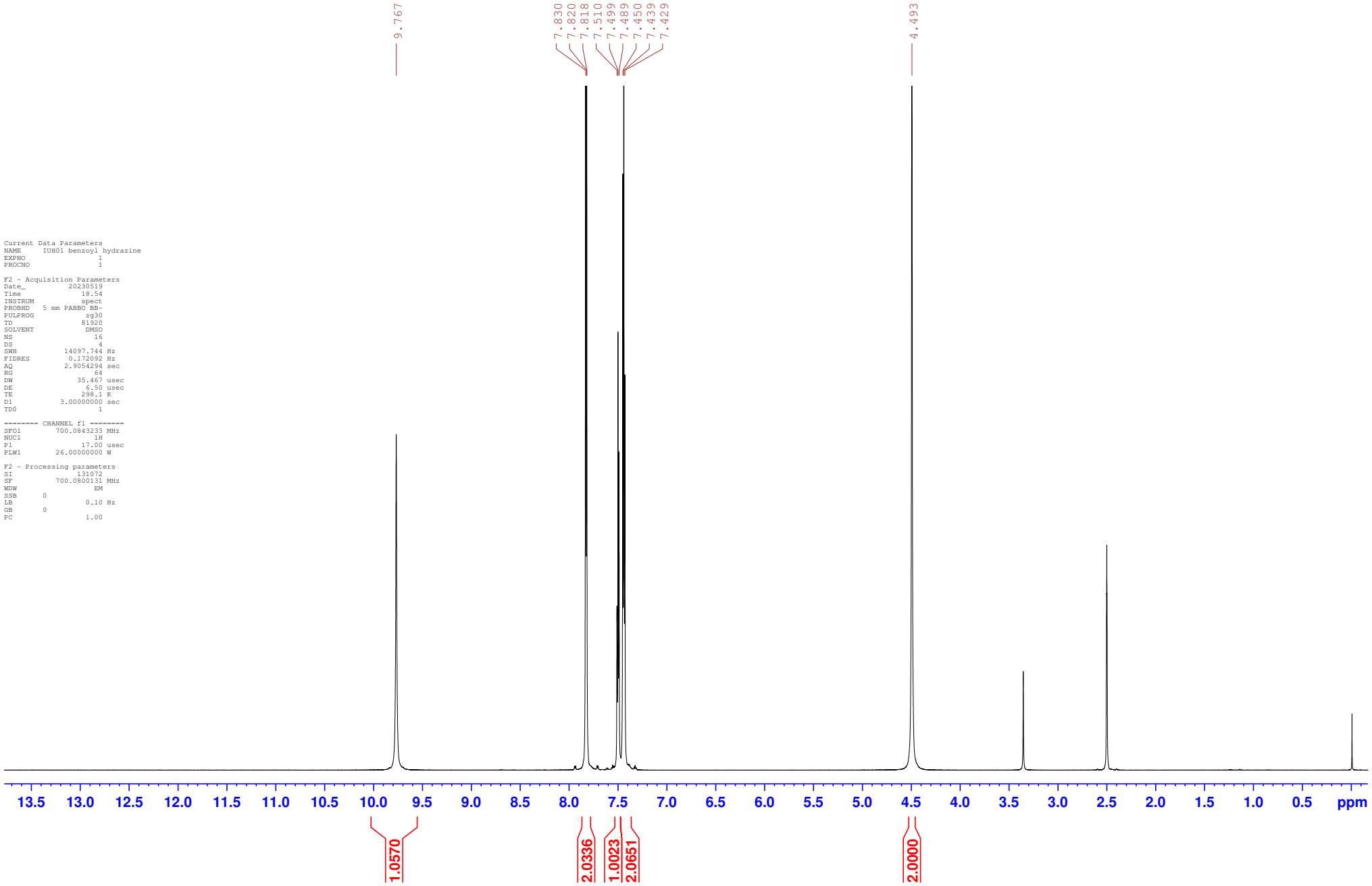

```
Current Data Parameters
NAME      IN18 methy-4-nitrobenzoate
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20230519
Time              17.42
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               81920
SOLVENT           CDCl3
NS                   16
DS                    4
SWH           14097.744 Hz
FIDRES         0.172092 Hz
AQ             2.9054294 sec
RG                 101
DW                35.467 usec
DE                 6.50 usec
TE                298.1 K
D1            3.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        700.0843233 MHz
NUC1                1H
P1                17.00 usec
PLW1        26.00000000 W

F2 - Processing parameters
SI                131072
SF          700.0800313 MHz
WDW                 EM
SSB       0
LB                 0.10 Hz
GB        0
PC                 1.00
```

IN18 methy-4-nitrobenzoate C13 CDCl3
C13CPD CDCl3 {C:\Spectra\data\AntonM\nmr} AntonM 3



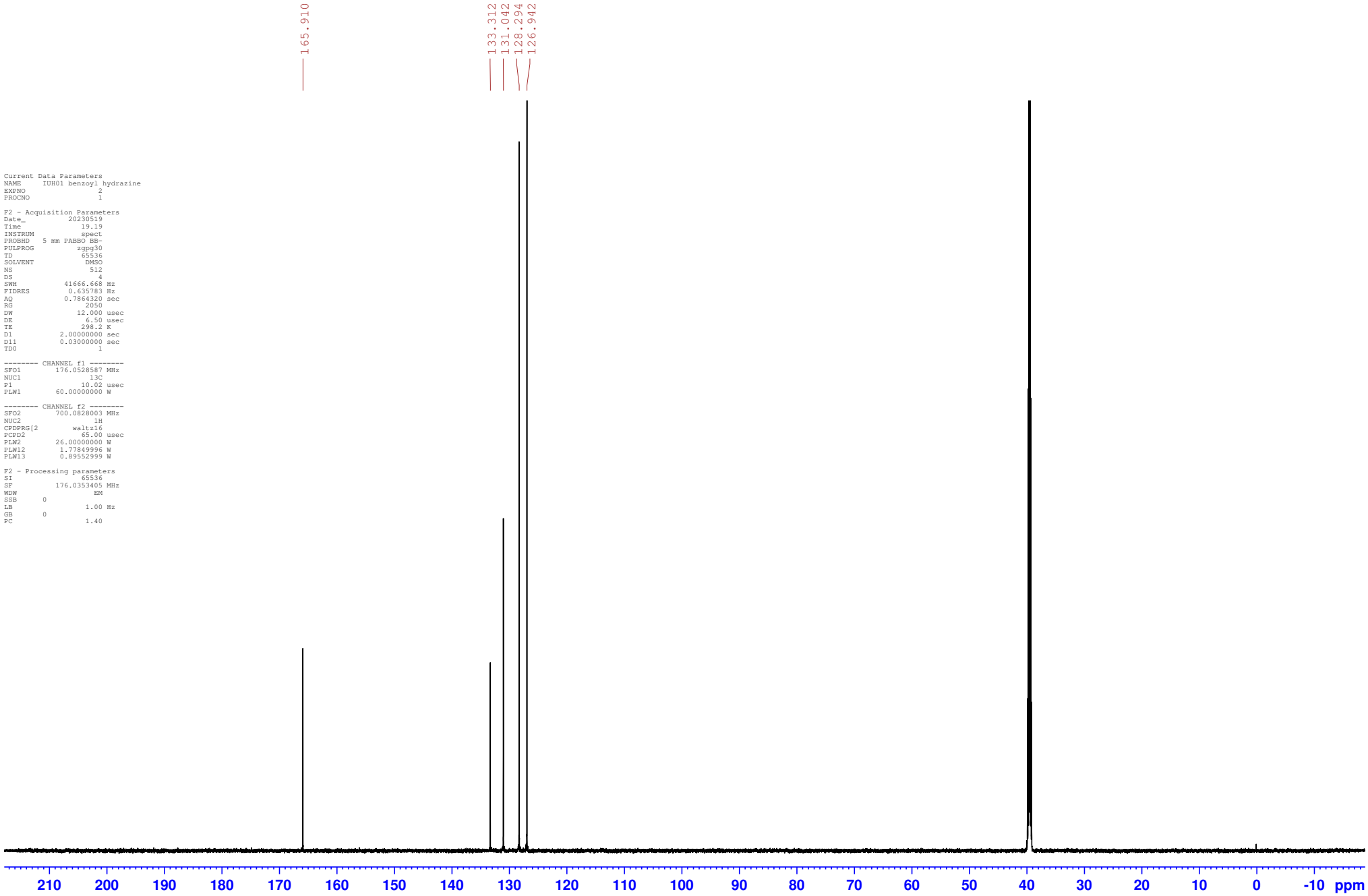

```
Current Data Parameters
NAME      IN18 methy-4-nitrobenzoate
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20230519
Time              18.06
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    4
SWH           41666.668 Hz
FIDRES        0.635783 Hz
AQ            0.7864320 sec
RG                 2050
DW               12.000 usec
DE                6.50 usec
TE                298.2 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        176.0528587 MHz
NUC1                13C
P1                10.02 usec
PLW1        60.00000000 W

======== CHANNEL f2 ========
SFO2        700.0828003 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             65.00 usec
PLW2        26.00000000 W
PLW12        1.77849996 W
PLW13        0.89552999 W

F2 - Processing parameters
SI                65536
SF          176.0352374 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

IUH01 benzoyl hydrazine 1H DMSO-d6
PROTON DMSO {C:\Spectra\data\AntonM\nmr} AntonM 5



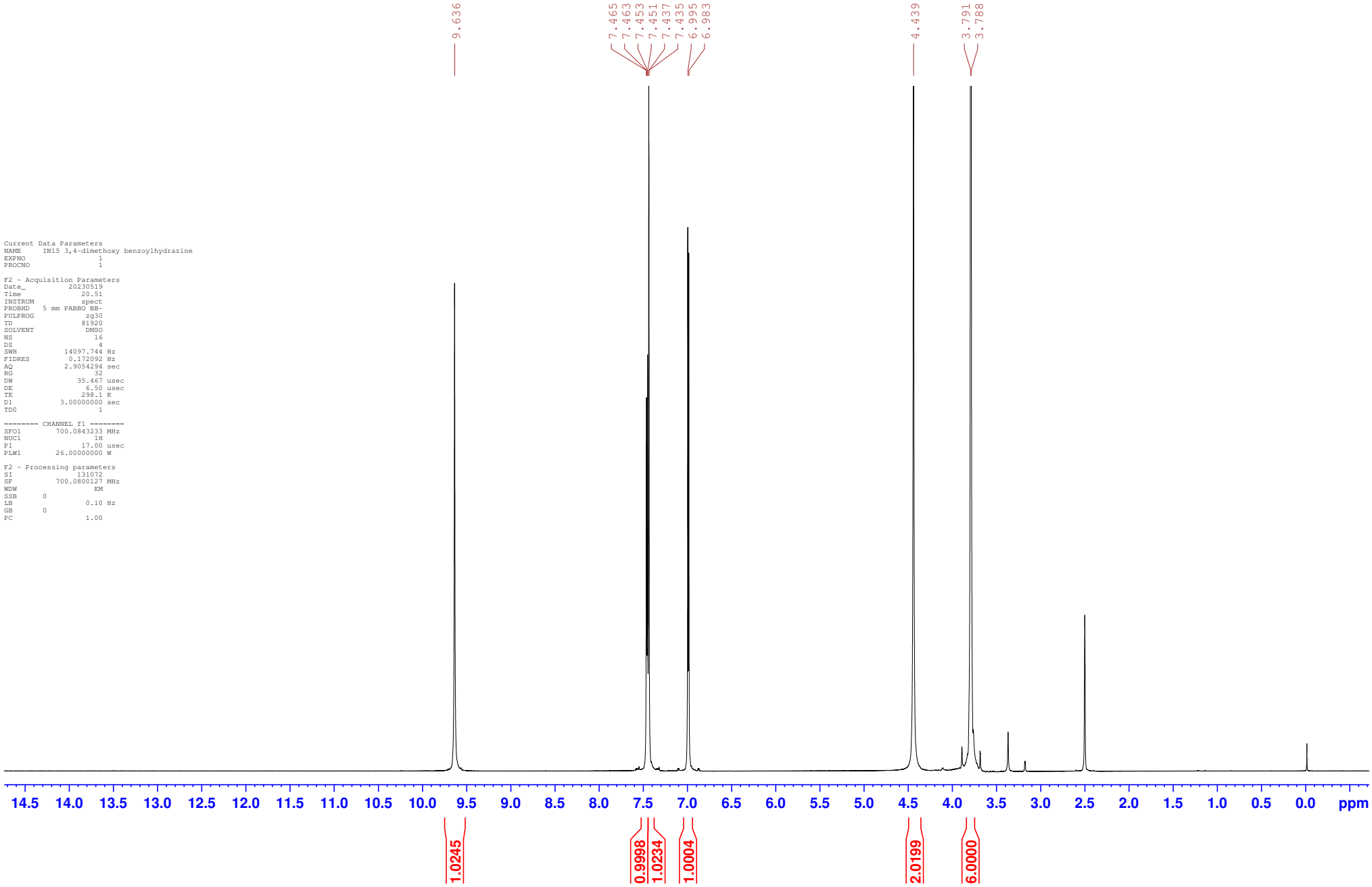

```
Current Data Parameters
NAME      IUH01 benzoyl hydrazine
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20230519
Time              18.54
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               81920
SOLVENT           DMSO
NS                  16
DS                   4
SWH          14097.744 Hz
FIDRES        0.172092 Hz
AQ            2.9054294 sec
RG                  64
DW             35.467 usec
DE              6.50 usec
TE              298.1 K
D1           3.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1       700.0843233 MHz
NUC1               1H
P1               17.00 usec
PLW1       26.00000000 W

F2 - Processing parameters
SI              131072
SF         700.0800131 MHz
WDW                EM
SSB       0
LB               0.10 Hz
GB        0
PC               1.00
```

IUH01 benzoyl hydrazine C13 DMSO-d6
C13CPD DMSO {C:\Spectra\data\AntonM\nmr} AntonM 5



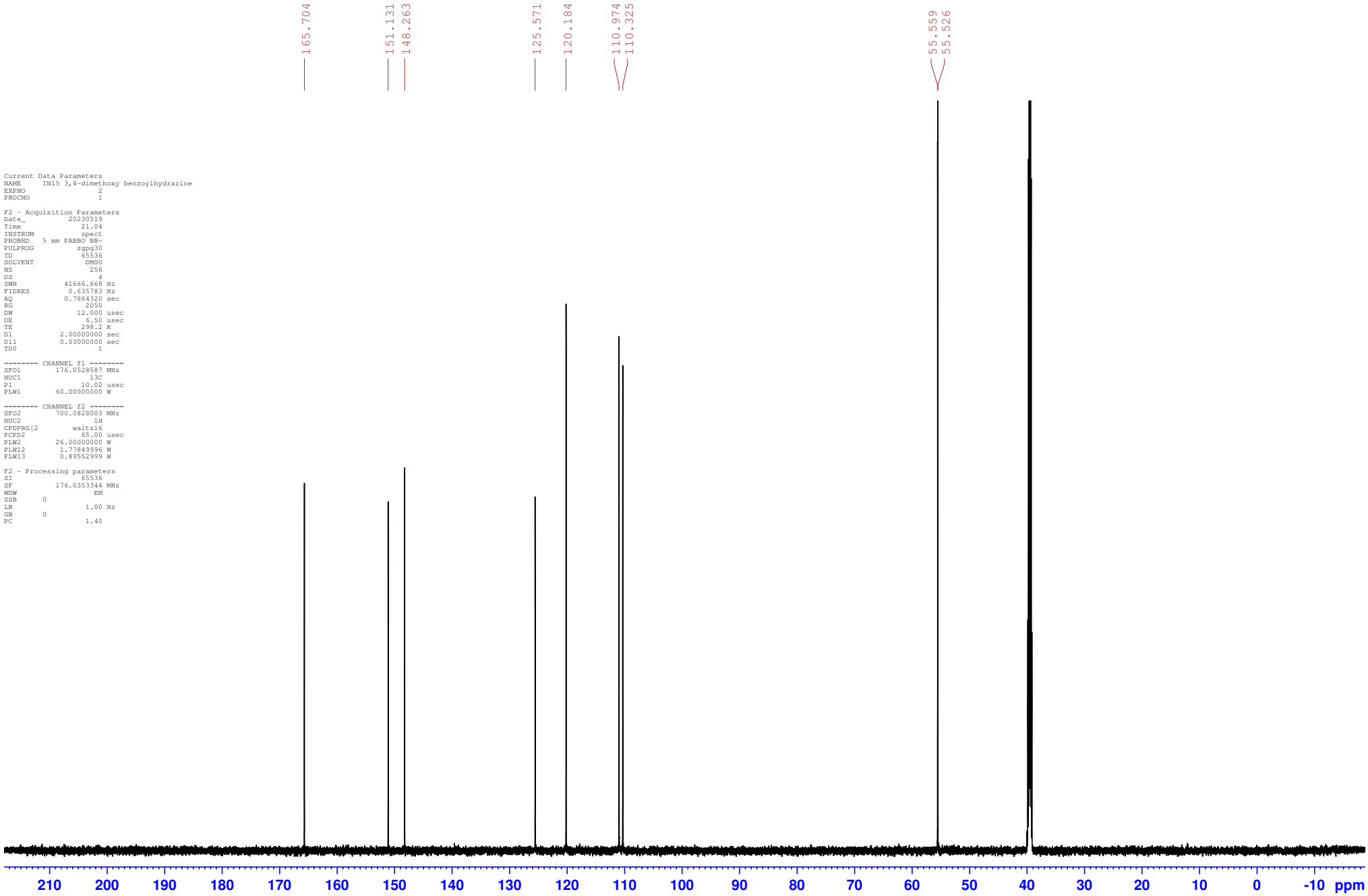

```
Current Data Parameters
NAME      IUH01 benzoyl hydrazine
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20230519
Time              19.19
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD                65536
SOLVENT             DMSO
NS                  512
DS                    4
SWH           41666.668 Hz
FIDRES         0.635783 Hz
AQ            0.7864320 sec
RG                 2050
DW               12.000 usec
DE                6.50 usec
TE                298.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        176.0528587 MHz
NUC1                13C
P1                10.02 usec
PLW1        60.00000000 W

======== CHANNEL f2 ========
SFO2        700.0828003 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             65.00 usec
PLW2        26.00000000 W
PLW12        1.77849996 W
PLW13        0.89552999 W

F2 - Processing parameters
SI                 65536
SF          176.0353405 MHz
WDW                  EM
SSB      0
LB                1.00 Hz
GB       0
PC                1.40
```

IN15 3,4-dimethoxy benzoylhydrazine 1H DMSO-d6
PROTON DMSO {C:\Spectra\data\AntonM\nmr} AntonM 9



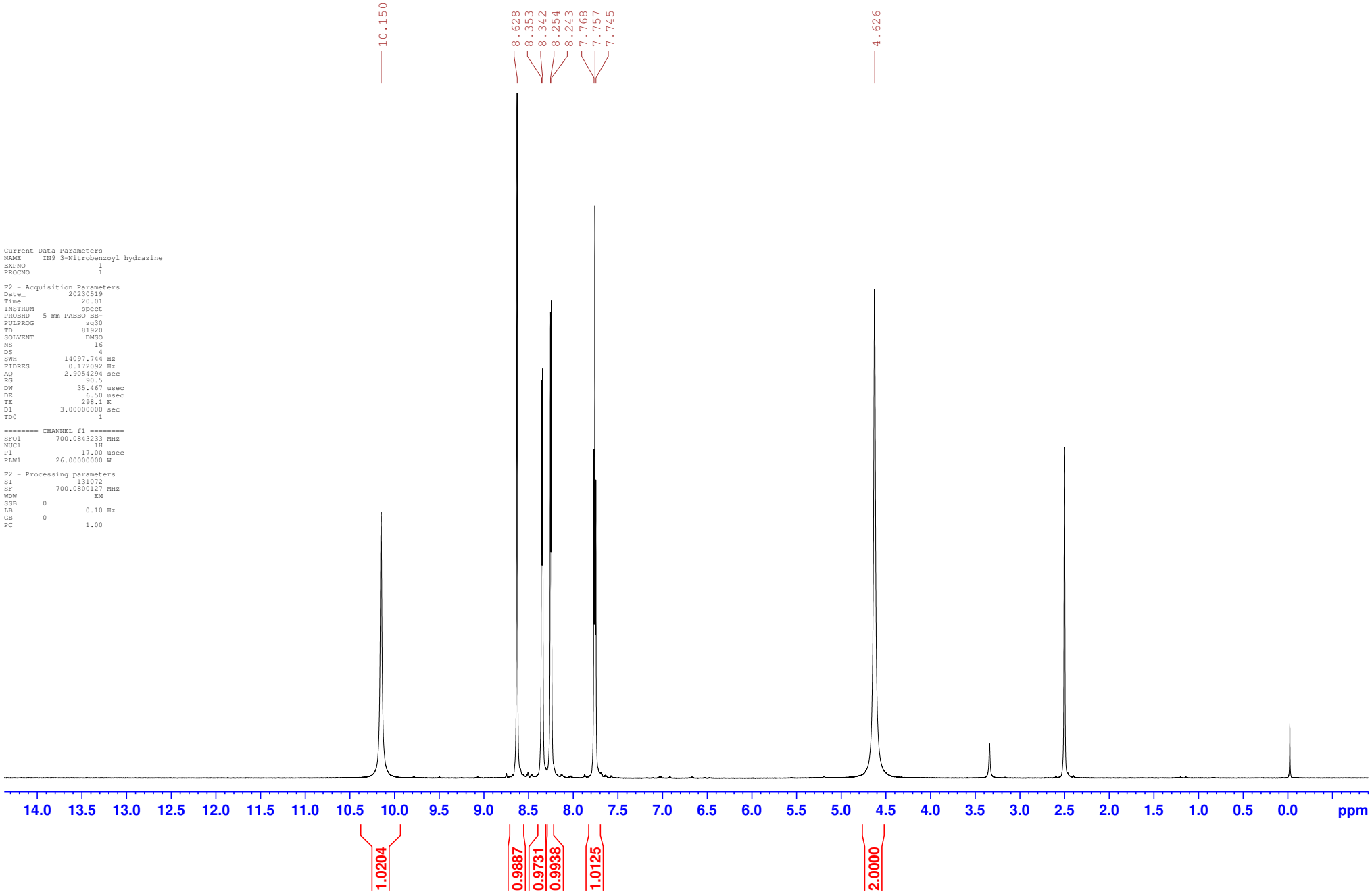

```
Current Data Parameters
NAME      IN15 3,4-dimethoxy benzoylhydrazine
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20230519
Time                 20.51
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    81920
SOLVENT                DMSO
NS                       16
DS                        4
SWH               14097.744 Hz
FIDRES            0.172092 Hz
AQ                2.9054294 sec
RG                       32
DW                  35.467 usec
DE                   6.50 usec
TE                  298.1 K
D1              3.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           700.0843233 MHz
NUC1                     1H
P1                   17.00 usec
PLW1          26.00000000 W

F2 - Processing parameters
SI                   131072
SF             700.0800127 MHz
WDW                     EM
SSB       0
LB                    0.10 Hz
GB        0
PC                    1.00
```

IN15 3,4-dimethoxy benzoylhydrazine C13 DMSO-d6
C13CPD DMSO {C:\Spectra\data\AntonM\nmr} AntonM 9



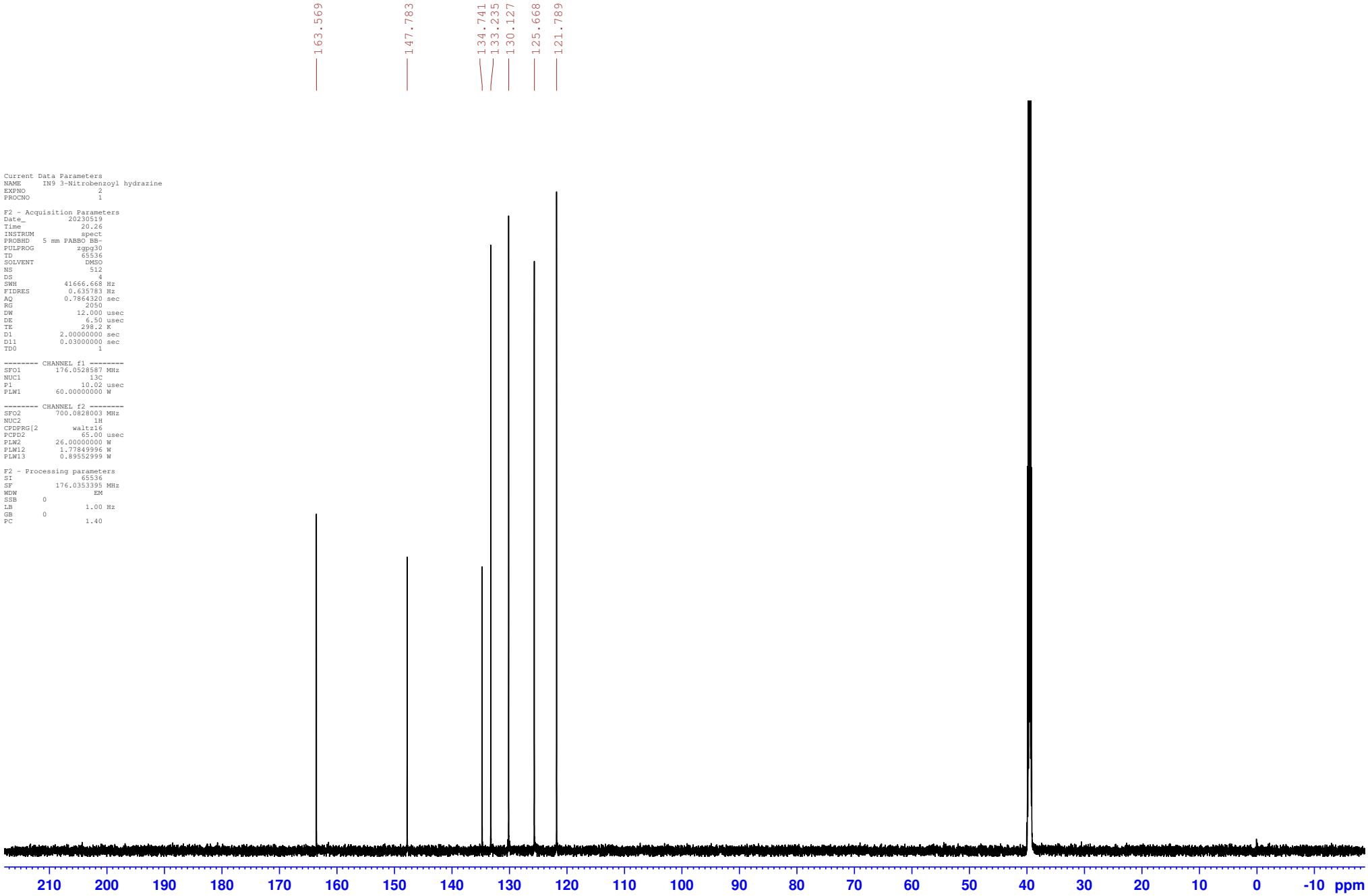

```
Current Data Parameters
NAME      IN15 3,4-dimethoxy benzoylhydrazine
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20230519
Time              21.04
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT            DMSO
NS                   256
DS                     4
SWH            41666.668 Hz
FIDRES             0.635783 Hz
AQ              0.7864320 sec
RG                  2050
DW                 12.000 usec
DE                  6.50 usec
TE                298.2 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         176.0528587 MHz
NUC1                 13C
P1                  10.02 usec
PLW1         60.00000000 W

======== CHANNEL f2 ========
SFO2         700.0828003 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2               65.00 usec
PLW2         26.00000000 W
PLW12         1.77849996 W
PLW13         0.89552999 W

F2 - Processing parameters
SI                   65536
SF           176.0353344 MHz
WDW                    EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```

IN9 3-Nitrobenzoyl hydrazine 1H DMSO-d6
PROTON DMSO {C:\Spectra\data\AntonM\nmr} AntonM 7



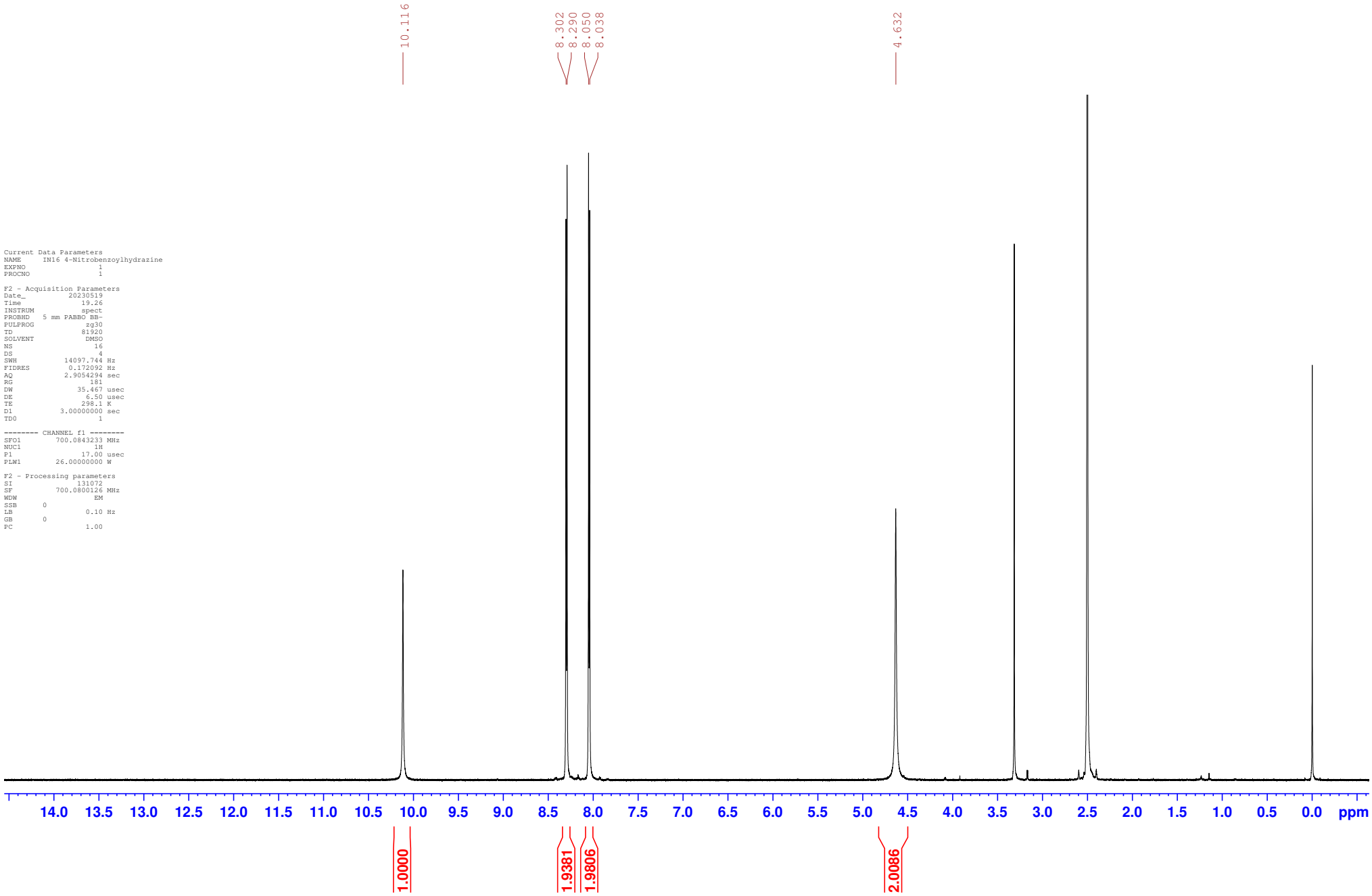

```
Current Data Parameters
NAME      IN9 3-Nitrobenzoyl hydrazine
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20230519
Time              20.01
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               81920
SOLVENT           DMSO
NS                  16
DS                   4
SWH           14097.744 Hz
FIDRES         0.172092 Hz
AQ            2.9054294 sec
RG                90.5
DW               35.467 usec
DE                6.50 usec
TE              298.1 K
D1            3.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        700.0843233 MHz
NUC1                1H
P1                17.00 usec
PLW1        26.00000000 W

F2 - Processing parameters
SI                131072
SF          700.0800127 MHz
WDW                 EM
SSB       0
LB                0.10 Hz
GB        0
PC                1.00
```

IN9 3-Nitrobenzoyl hydrazine 1H DMSO-d6
C13CPD DMSO {C:\Spectra\data\AntonM\nmr} AntonM 7



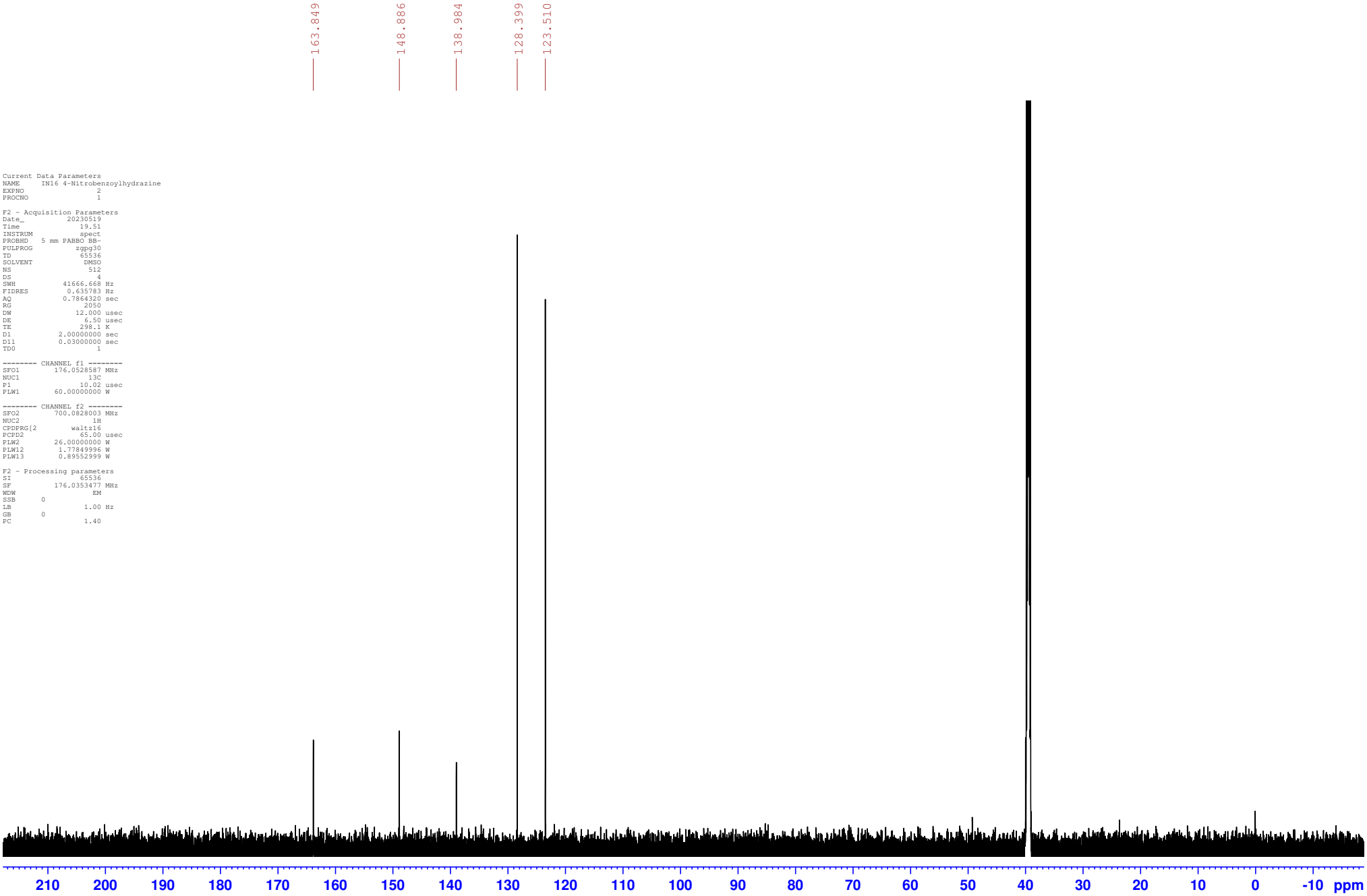

```
Current Data Parameters
NAME      IN9 3-Nitrobenzoyl hydrazine
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20230519
Time              20.26
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT             DMSO
NS                  512
DS                    4
SWH           41666.668 Hz
FIDRES            0.635783 Hz
AQ               0.7864320 sec
RG                 2050
DW                12.000 usec
DE                 6.50 usec
TE                298.2 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         176.0528587 MHz
NUC1                13C
P1                 10.02 usec
PLW1         60.00000000 W

======== CHANNEL f2 ========
SFO2         700.0828003 MHz
NUC2                1H
CPDPRG[2          waltz16
PCPD2              65.00 usec
PLW2         26.00000000 W
PLW12         1.77849996 W
PLW13         0.89552999 W

F2 - Processing parameters
SI                 65536
SF           176.0353395 MHz
WDW                  EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

IN16 4-Nitrobenzoylhydrazine 1H DMSO-d6
PROTON DMSO {C:\Spectra\data\AntonM\nmr} AntonM 6



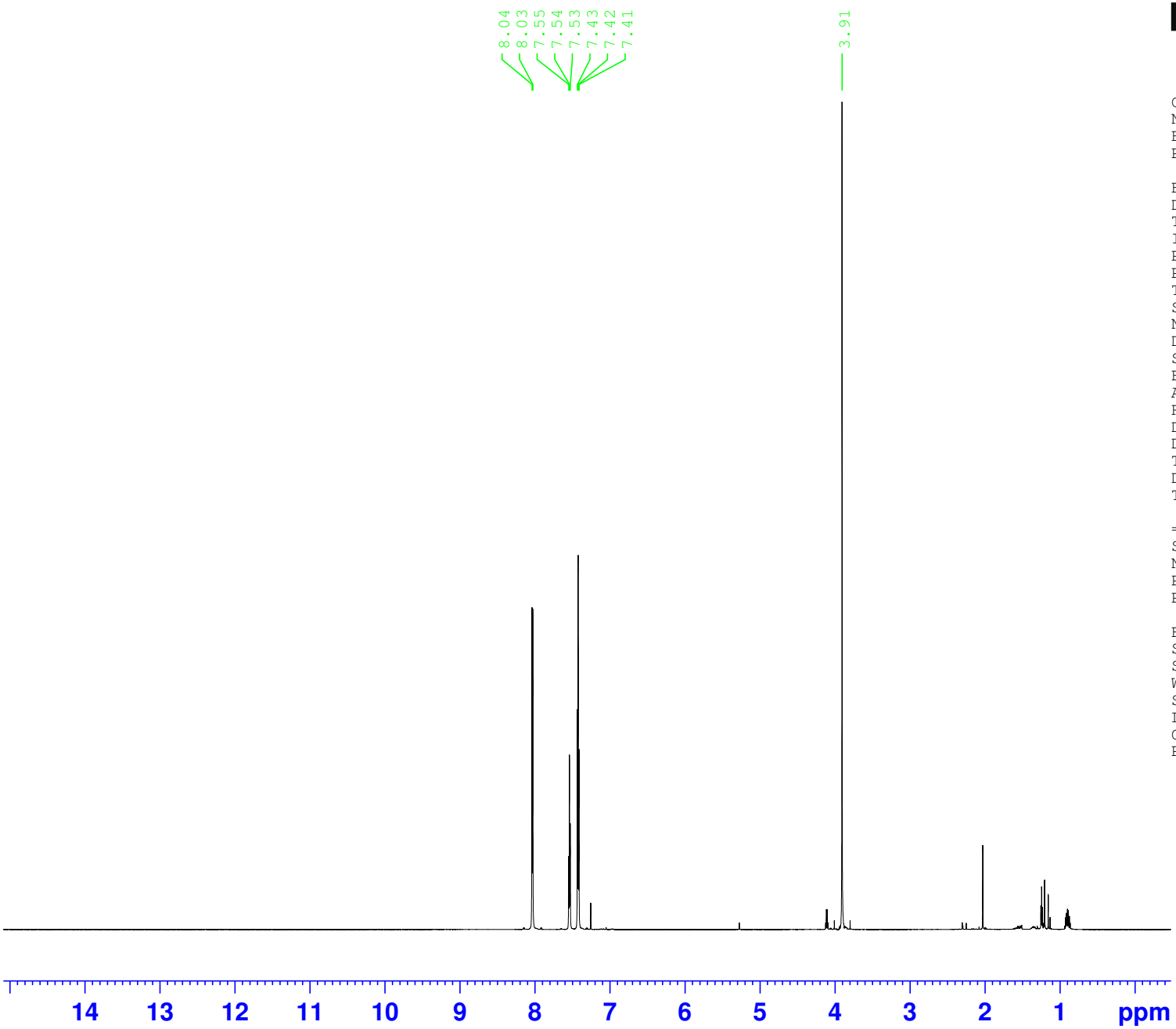

```
Current Data Parameters
NAME      IN16 4-Nitrobenzoylhydrazine
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20230519
Time              19.26
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               81920
SOLVENT           DMSO
NS                   16
DS                    4
SWH           14097.744 Hz
FIDRES         0.172092 Hz
AQ             2.9054294 sec
RG                 181
DW                35.467 usec
DE                 6.50 usec
TE                298.1 K
D1             3.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        700.0843233 MHz
NUC1                1H
P1                17.00 usec
PLW1        26.00000000 W

F2 - Processing parameters
SI                131072
SF          700.0800126 MHz
WDW                 EM
SSB       0
LB                 0.10 Hz
GB        0
PC                 1.00
```

IN16 4-Nitrobenzoylhydrazine C13 DMSO-d6
C13CPD DMSO {C:\Spectra\data\AntonM\nmr} AntonM 6




```
Current Data Parameters
NAME      IN16 4-Nitrobenzoylhydrazine
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20230519
Time              19.51
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT            DMSO
NS                   512
DS                     4
SWH           41666.668 Hz
FIDRES         0.635783 Hz
AQ            0.7864320 sec
RG                  2050
DW               12.000 usec
DE                6.50 usec
TE               298.1 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1        176.0528587 MHz
NUC1                  13C
P1                  10.02 usec
PLW1        60.00000000 W

======== CHANNEL f2 ========
SFO2        700.0828003 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2               65.00 usec
PLW2        26.00000000 W
PLW12        1.77849996 W
PLW13        0.89552999 W

F2 - Processing parameters
SI                   65536
SF          176.0353477 MHz
WDW                    EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```

IUH03 Methyl benzoate 1H CDCl3
PROTON CDCl3 {C:\Spectra\data\AntonM\nmr} AntonM 1



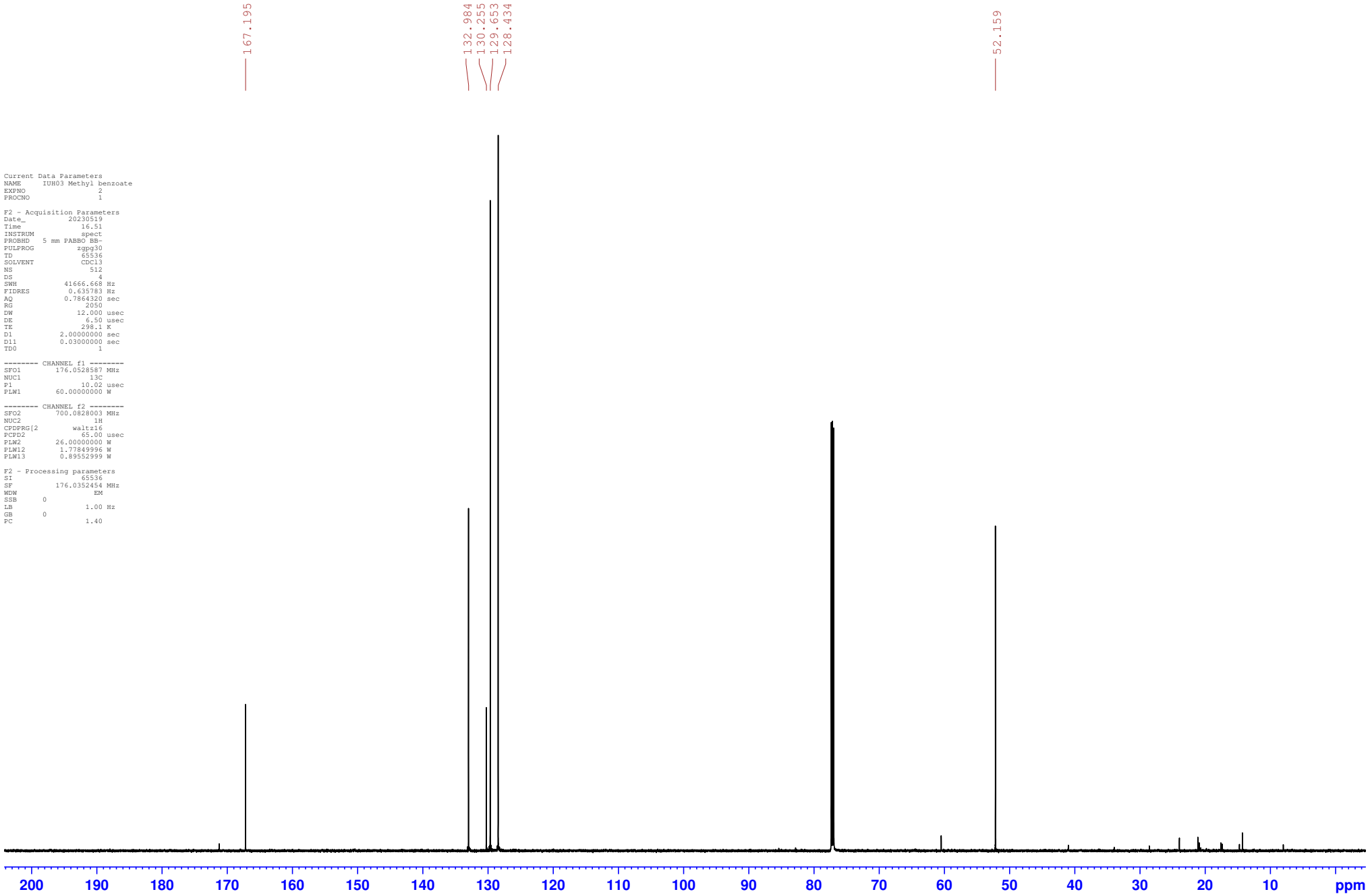
Current Data Parameters
NAME IUH03 Methyl benzoate
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230519
Time 16.26
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 81920
SOLVENT CDCl3
NS 16
DS 4
SWH 14097.744 Hz
FIDRES 0.172092 Hz
AQ 2.9054294 sec
RG 50.8
DW 35.467 usec
DE 6.50 usec
TE 298.1 K
D1 3.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 700.0843233 MHz
NUC1 1H
P1 17.00 usec
PLW1 26.00000000 W

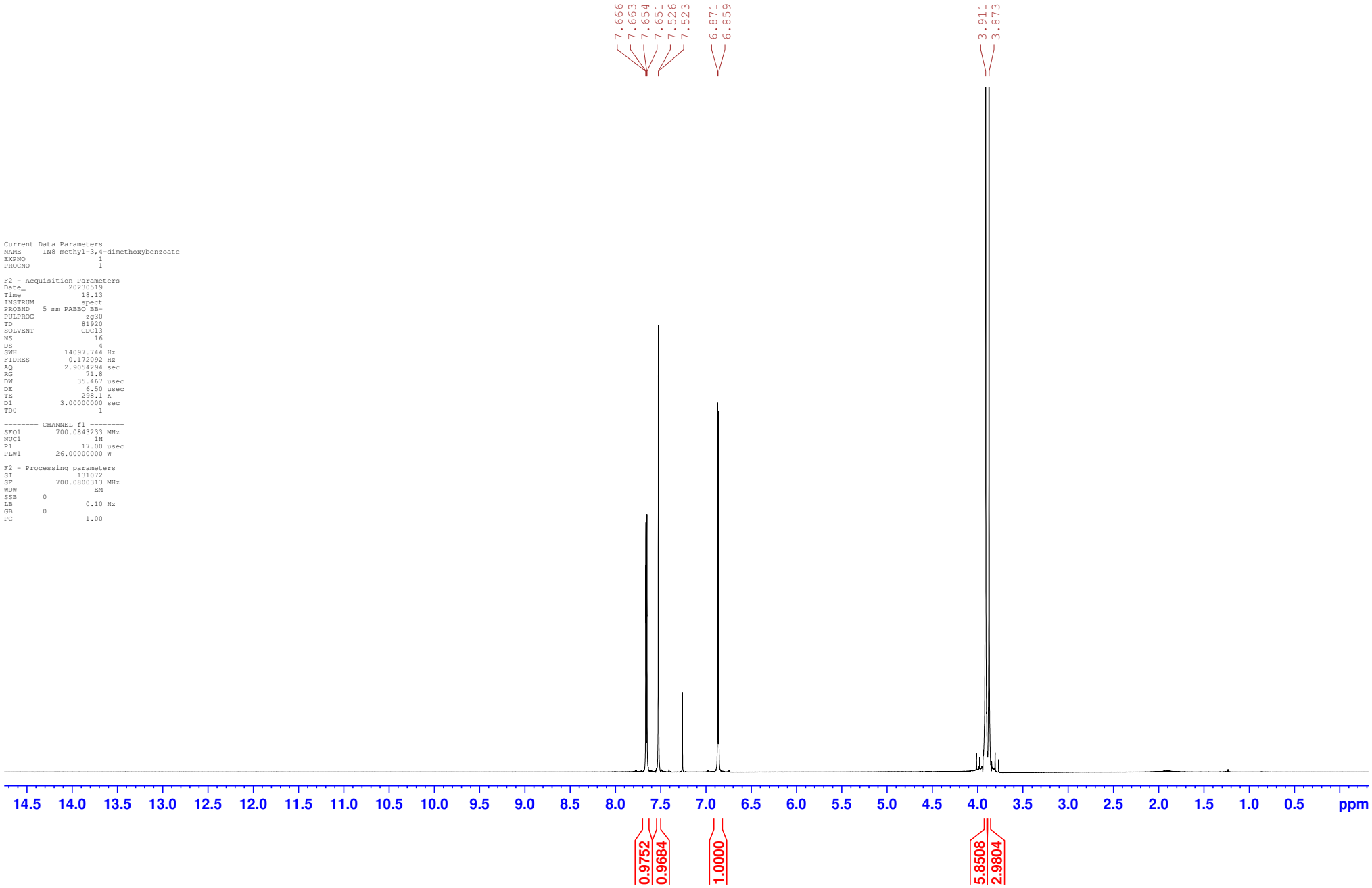
F2 - Processing parameters
SI 131072
SF 700.0800334 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

IUH03 Methyl benzoate 1H CDCl3
C13CPD CDCl3 {C:\Spectra\data\AntonM\nmr} AntonM 1



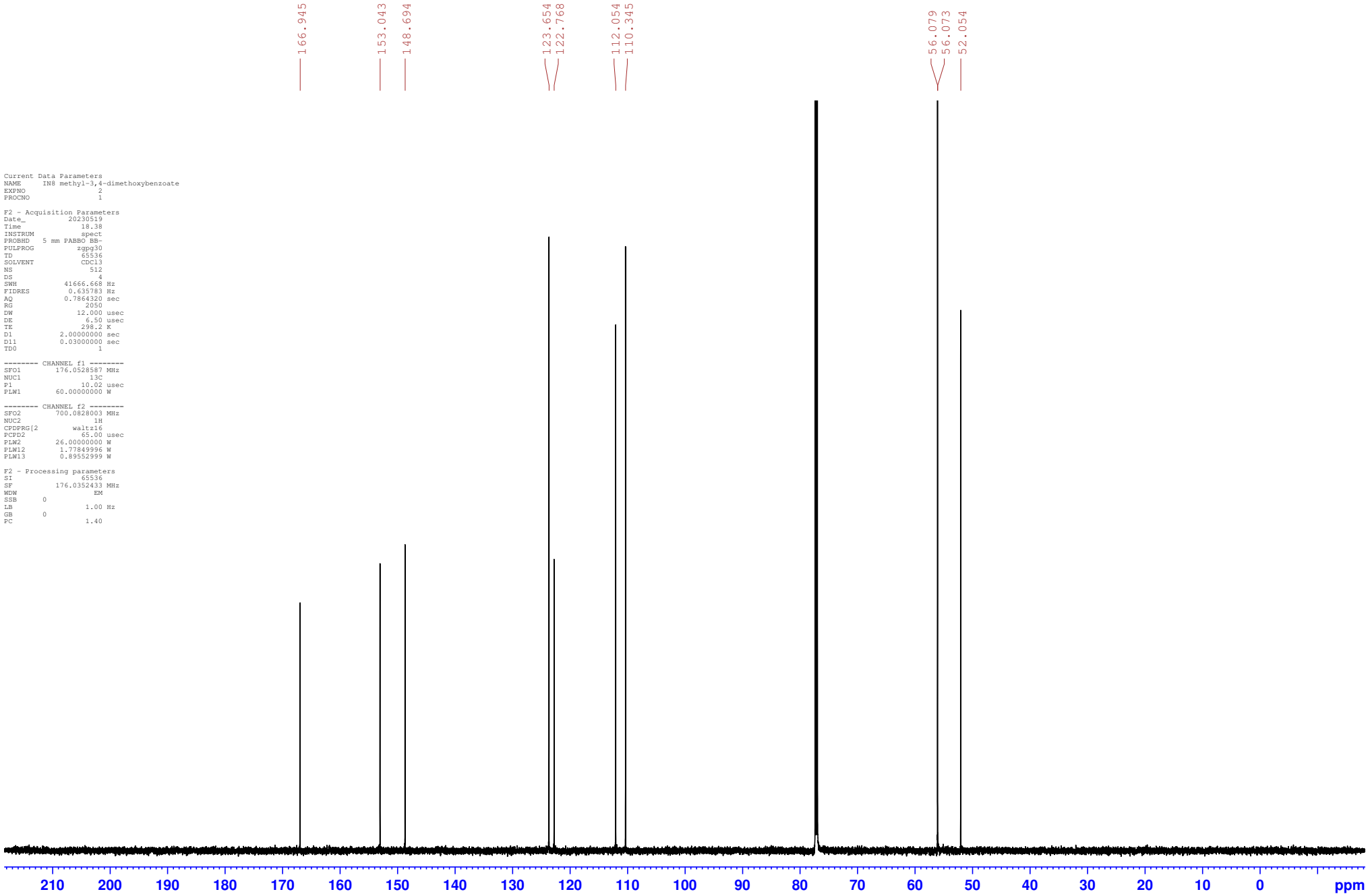

```
Current Data Parameters
NAME      IUH03 Methyl benzoate
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_           20230519
Time              16.51
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    4
SWH           41666.668 Hz
FIDRES         0.635783 Hz
AQ            0.7864320 sec
RG                 2050
DW               12.000 usec
DE                6.50 usec
TE                298.1 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        176.0528587 MHz
NUC1                13C
P1                10.02 usec
PLW1        60.00000000 W

======== CHANNEL f2 ========
SFO2        700.0828003 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             65.00 usec
PLW2        26.00000000 W
PLW12        1.77849996 W
PLW13        0.89552999 W

F2 - Processing parameters
SI                65536
SF          176.0352454 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

IN8 methyl-3,4-dimethoxybenzoate 1H CDCl3
PROTON CDCl3 {C:\Spectra\data\AntonM\nmr} AntonM 4



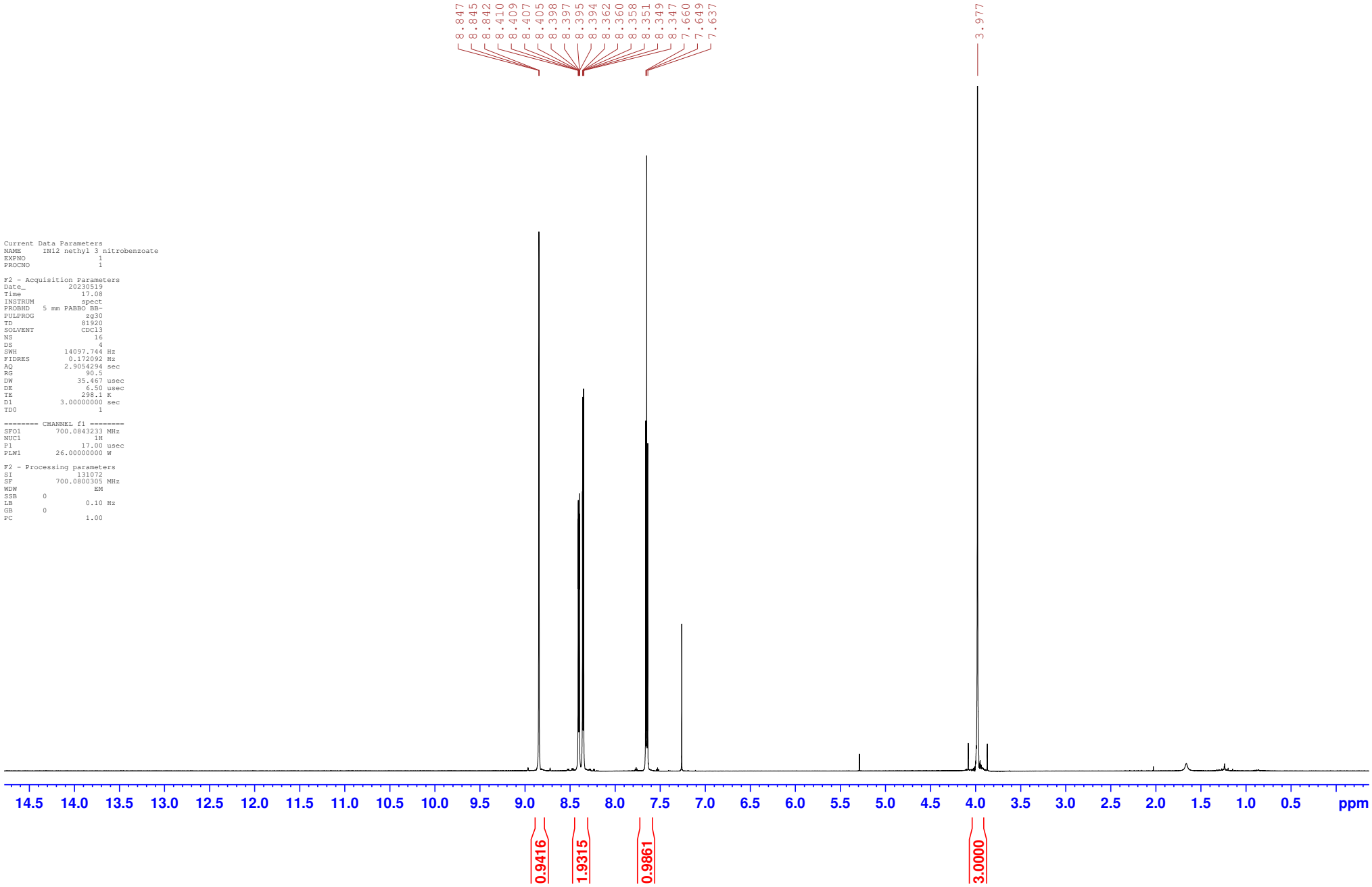

```
Current Data Parameters
NAME      IN8 methyl-3,4-dimethoxybenzoate
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20230519
Time                18.13
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 81920
SOLVENT            CDCl3
NS                    16
DS                     4
SWH            14097.744 Hz
FIDRES         0.172092 Hz
AQ             2.9054294 sec
RG                  71.8
DW                35.467 usec
DE                 6.50 usec
TE                298.1 K
D1            3.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         700.0843233 MHz
NUC1                   1H
P1                  17.00 usec
PLW1         26.00000000 W

F2 - Processing parameters
SI                 131072
SF           700.0800313 MHz
WDW                    EM
SSB       0
LB                  0.10 Hz
GB        0
PC                  1.00
```

IN8 methyl-3,4-dimethoxybenzoate C13 CDCl3
C13CPD CDCl3 {C:\Spectra\data\AntonM\nmr} AntonM 4



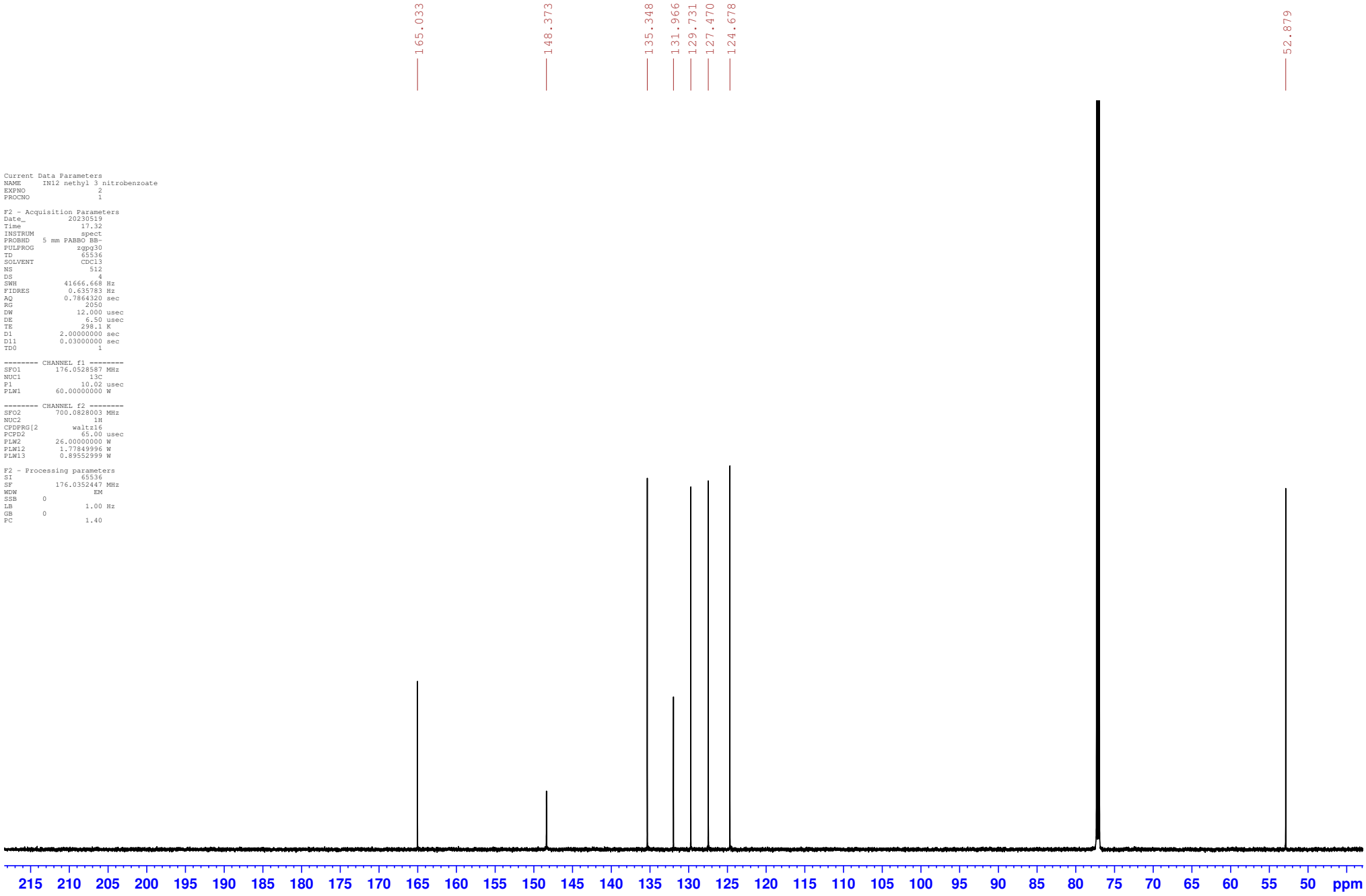

```
Current Data Parameters
NAME      IN8 methyl-3,4-dimethoxybenzoate
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20230519
Time              18.38
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    4
SWH           41666.668 Hz
FIDRES        0.635783 Hz
AQ            0.7864320 sec
RG                 2050
DW               12.000 usec
DE                6.50 usec
TE                298.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        176.0528587 MHz
NUC1                13C
P1                10.02 usec
PLW1        60.00000000 W

======== CHANNEL f2 ========
SFO2        700.0828003 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             65.00 usec
PLW2        26.00000000 W
PLW12        1.77849996 W
PLW13        0.89552999 W

F2 - Processing parameters
SI                65536
SF          176.0352433 MHz
WDW                 EM
SSB      0
LB                1.00 Hz
GB       0
PC                1.40
```

IN12 1H Methyl 3 Nitrobenzoate CDCl3
PROTON CDCl3 {C:\Spectra\data\AntonM\nmr} AntonM 2




```
Current Data Parameters
NAME      IN12 nethyl 3 nitrobenzoate
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20230519
Time              17.08
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               81920
SOLVENT           CDCl3
NS                   16
DS                    4
SWH           14097.744 Hz
FIDRES        0.172092 Hz
AQ            2.9054294 sec
RG                90.5
DW               35.467 usec
DE                6.50 usec
TE               298.1 K
D1            3.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        700.0843233 MHz
NUC1                1H
P1                17.00 usec
PLW1        26.00000000 W

F2 - Processing parameters
SI               131072
SF          700.0800305 MHz
WDW                 EM
SSB       0
LB                0.10 Hz
GB        0
PC                1.00
```

IN12 C13 Methyl 3 Nitrobenzoate CDCl3
C13CPD CDCl3 {C:\Spectra\data\AntonM\nmr} AntonM 2




```
Current Data Parameters
NAME      IN12 nethyl 3 nitrobenzoate
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20230519
Time              17.32
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 512
DS                   4
SWH           41666.668 Hz
FIDRES        0.635783 Hz
AQ            0.7864320 sec
RG                2050
DW               12.000 usec
DE                6.50 usec
TE                298.1 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        176.0528587 MHz
NUC1                13C
P1                10.02 usec
PLW1        60.00000000 W

======== CHANNEL f2 ========
SFO2        700.0828003 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             65.00 usec
PLW2        26.00000000 W
PLW12        1.77849996 W
PLW13        0.89552999 W

F2 - Processing parameters
SI                65536
SF          176.0352447 MHz
WDW                 EM
SSB      0
LB                1.00 Hz
GB       0
PC                1.40
```