Master's thesis:

Synthesis, Characterization and Derivatives Evaluation of Enamine

BY: Abdalhamid Al-arafi

منشورات البرنامج الوطني لتطوير المجلات العلمية

University of Benghazi

Faculty of Science

Department Of Chemistry

Synthesis, Characterization and Evaluation of Enamine Derivatives

By

Abdalhamid Al-arafi

Supervisor

Dr. Abdalla Gheath

Professor

This Thesis was Submitted in Partial Fulfillment of the Requirements for Master's Degree of Science in Chemistry.

Date: 4- 8- 2025

Declaration

I, Abdalhamid Al-arafi, hereby declare that the thesis entitled:

"Synthesis, Characterization, and Evaluation of Enamine Derivatives"

submitted to the Department of Chemistry, Faculty of Science, University of Benghazi, in partial fulfillment of the requirements for the Master's Degree of Science in Chemistry, is my own original work.

I further declare that this thesis has not been submitted previously, either in whole or in part, for the award of any degree at this or any other academic institution. All the sources of information and references used have been properly acknowledged.

Student's Name: Abdalhamid Al-arafi

Date: 4 – 8 – 2025

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This Thesis was Successfully Defended and Approved on

Supervisor

Dr. Abdalla Gheath

Signature:

…….

Dr. Naowara M. Al-arafi (Internal examiner)

Signature: …….

Dr. Abdul salam Al-salihin (Internal examiner)

Signature: …….

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All praise is due to Allah for His blessings and guidance

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***Abdulhamid* Al-arafi**

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List of Abbreviations and Symbols

Abbreviation/Symbol	Full Meaning
IR	**Infrared Spectroscopy**
NMR	**Nuclear Magnetic Resonance**
MS	**Mass Spectrometry**
MIC	**Minimum Inhibitory Concentration**
TLC	**Thin Layer Chromatography**
DMSO	**Dimethyl Sulfoxide**
$CDCl_3$	**Deuterated Chloroform**
°C	**Degrees Celsius**
D_2O	**Deuterium oxide**
EI	**Electronic impact ionization**
1Vqq	**Outer membrane osmoporin**
3uu2	**Penicillin-binding protein**
M.P	**Melting Point**
DMAP	4- **(Dimethylamino)pyridine**

Synthesis, Characterization and Derivatives Evaluation of Enamine

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Abstract

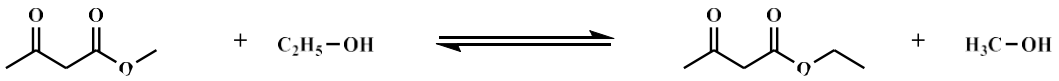
A series of compounds (I–XIII) were synthesized by reacting ethyl 2-oxocyclopentane-1-carboxylate (15) or ethyl 2-oxocyclohexane-1-carboxylate (23) with various diamines, including ethane-1,2-diamine (66), benzene-1,4-diamine (68), hydrazine hydrate (67), benzidine (70), N^1, N^3-bis(2-aminoethyl) malonamide (72), malonohydrazide (71), and piperazine (69). Most derivatives (I, II, III, VI, VII, VIII, X, XIII) adopted enamine structures via a 2:1 reaction ratio, whereas compounds IX and XI exhibited distinct structural frameworks due to a 1:1 reaction pathway. Notably, the reaction of β-keto ester (15) with hydrazine hydrate yielded enamine III as a minor product and pyrazolone IV as the major derivative, while the analogous reaction with compound (23) exclusively produced pyrazolone V. Additionally, the reaction of compound (23) with malonohydrazide afforded an azine derivative (XII). All syntheses proceeded under mild conditions with moderate yields, and the structures were characterized using melting point, TLC, IR, MS, ^{1}H-NMR (with D_2O exchange), ^{13}C-NMR, and APT analyses. Preliminary screening revealed antimicrobial activity in selected derivatives. Evaluation of antibacterial activity and molecular docking revealed that some compounds exhibited inhibitory effects.

Chapter 1

Introduction

1.1. Introduction

Esters act as important functional groups frequently observed in organic chemistry. One of the most common structural components in synthesizing different chemical molecules is the ester bond. In addition to condensing alcohol and acid to make esters, β-ketoesters have gained considerable attention due to their electrophilic and nucleophilic reactive sites, which can be utilized for synthesizing a wide range of complex natural products ***(Clemens & Hyatt, 1985; Witzeman & Nottingham, 1991)***. β-Ketoesters have been produced by reacting to diketene with alcohols ***(Rao & Sivakumar, 2006)***, or by using Claisen condensation to condense two esters in a basic medium ***(Fujita et al., 1997)***. Because diketene is highly reactive, caustic, and challenging to handle, its use as a starting material is limited. Another technique for synthesizing various commercial and non-commercial β-ketoesters is transesterification ***(Parmar et al., 1992)***. For over a century, scientists have been intrigued by the transesterification process, which produces β-ketoesters used as building blocks for various medicinal compounds. This reaction is simple, reliable, and involves widely available methyl/ethyl β-ketoesters. It substitutes an alkoxy group with an alcohol to create a new ester, making it valuable for synthesizing β-ketoesters that are hard to obtain commercially ***(Otera, 1993)***. The reaction has been extensively studied for applications in polymers, medicines, and bioactive substances ***(Niu et al., 2019)***. Recently, the transesterification reaction has become an important step in drug synthesis ***(Yadav et al., 2007)***



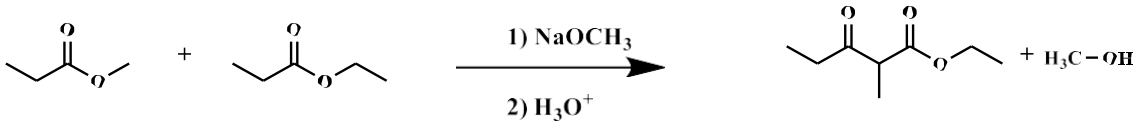
(1) (2) (3) (4)

1.2. Synthesis of β-ketoesters

In organic chemistry, β-ketoesters are strong synthons that can be essential for synthesizing several bioactive heterocyclic compounds. Numerous methods are available for the increase of β-Ketoesters, some of which are mentioned below.

1.2.1. Claisen Condensation

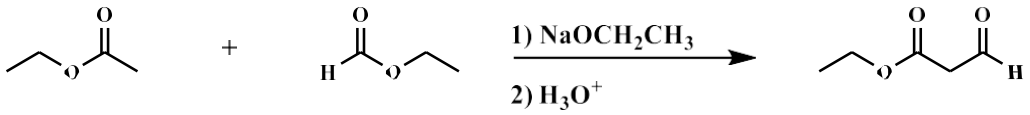
German chemist Rainer Ludwig Claisen is well-known for his pioneering work on the condensation of carbonyl compounds and sigmatropic rearrangements ***(Claisen & Claparède, 1881; Claisen, 1887)***. He was the first to synthesize β-ketoesters under fundamental conditions. In the Claisen condensation reaction, β-ketoesters or β-diketones are produced when a carbon-carbon bond forms between two distinct esters orbetween a carbonyl compound and an ester



(5) (6) (7) (4)

1.2.2. Mixed or Crossed Claisen Condensation

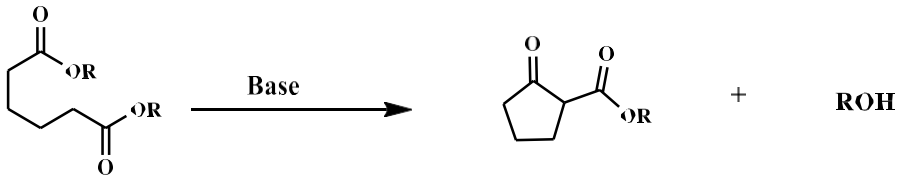
An enolizable ester or ketone molecule combines with another non-enolizable ester molecule to generate β-ketoesters in a process known as mixed Claisen condensation or crossed Claisen condensation reaction ***(Claisen, 1887).***



(8) (9) (10)

1.2.3. Dieckmann condensation

Dieckmann condensation is an intramolecular condensation catalyzed by a base ***(Schaefer & Bloomfield, 2004; Pallenberg, Dobhal, & Pandey, 2004)***. German scientist Walter Dieckmann developed a diester condensation, sometimes referred to as an intramolecular Claisen condensation, to synthesize cyclic β-ketoesters ***(Dieckmann, 1894)***. Five- or six-membered cyclic β-ketoesters are more efficiently prepared using the Dieckmann condensation (Scheme 6). Typically, sodium alkoxide in an alcoholic solvent facilitates the reaction. By removing the alkoxy group from the ester, the diester reactant undergoes internal cyclization under basic conditions to form cyclic β-ketoesters in this Dieckmann condensation process



(11) R = CH_3
(12) R = C_2H_5

(13) R = CH_3
(15) R = C_2H_5

(4) R = CH_3
(2) R = C_2H_5

1.3. Synthesis of cyclic five and six-membered rings

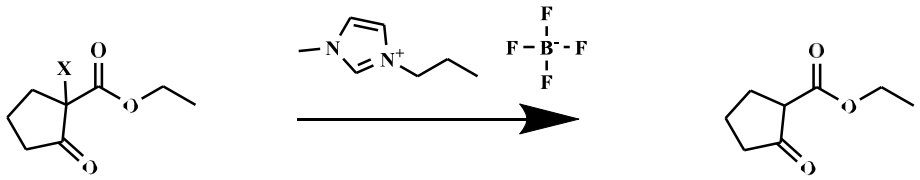
The synthesis of ethyl 2-oxocyclopentane-1-carboxylate (15) was carried out by reacting cyclopentanone (14) with diethyl carbonate (16) in the presence of sodium hydride, using toluene as a solvent at 100 °C for 2 hours ***(He et al., 2018).***

(14)

(16)

(15)

The synthesis of ethyl 2-oxocyclopentane-1-carboxylate (15) can also be achieved by dehalogenation of α-halo ketones and esters (17) and (18), catalyzed by 1-methyl-3-propylimidazolium tetrafluoroborate ***(Ranu,Chattopadhyay, & Jana, 2007)***

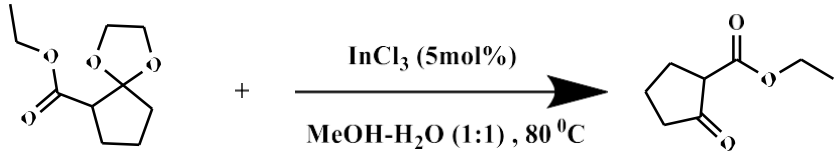


(17) X=Br
(18) X= I

(15)

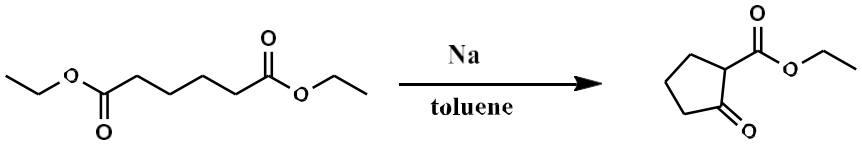
The present methodology, employing indium (III) chloride as a catalyst, provides a straightforward, efficient, and versatile approach for protecting various aldehydes and ketones by forming 1,3-dioxolanes and dialkyl acetals. Furthermore, the same catalyst has been successfully utilized for the deprotection of both dioxolanes and acetals in an

alternative solvent system ***(Ranu, Jana, & Samanta, 2004)***



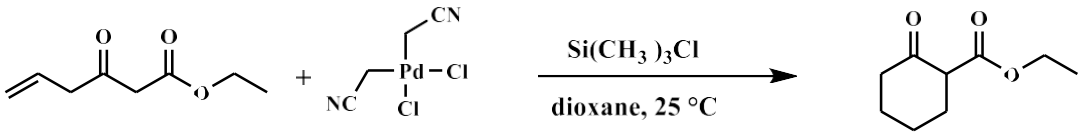
(19) **(15)**

2-Carbethoxycyclopentanone (15) was produced by Dieckmann cyclization of diethyl adipate (20) in the presence of sodium in toluene ***(Achanna & Suresh, 2013)***



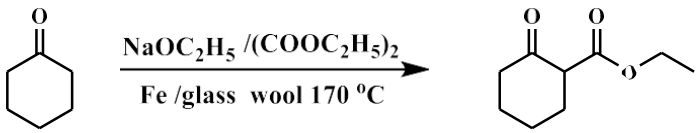
(20) **(15)**

synthesis of ethyl 2-oxocyclohexane-1-carboxylate (23) was achieved by reacting ethyl 3-oxohex-5-enoate (21) with bis(cyanomethyl)palladium(IV) chloride (22) in the presence of trimethylsilyl chloride, indioxane at 25 °C ***(Pei & Widenhoefer, 2002)***



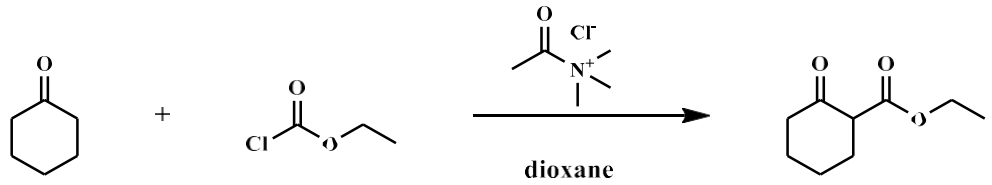
(21) **(22)** **(23)**

The reaction of cyclohexanone (24) with diethyl oxalate in the presence of sodium ethoxide, followed by pyrolysis with a catalytic amount of ground iron powder/glass wool at 170 °C gave ethyl 2-oxocyclohexanecarboxylate (23) in 45 % yield. ***(Achanna & Suresh, 2013)***



(24) **(23)**

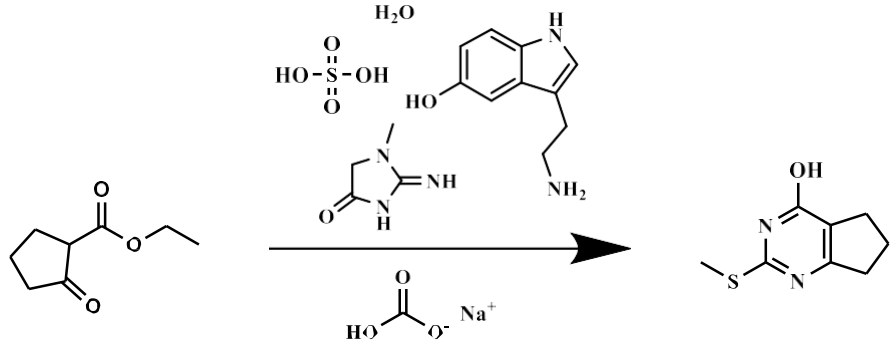
The reaction of one equivalent of ketones (24), an equimolar mixture of $CaCO_3$/CaO, one equivalent of acetyl trimethyl ammonium chloride, and one equivalent of ethyl chloroformate (25) was carried out in a flask containing dioxane to yield ethyl 2-oxocyclohexane-1-carboxylate (23) with a 95% yield after 3 hours ***(Pazdera & Simbera, 2011).***



(24) (25) (23)

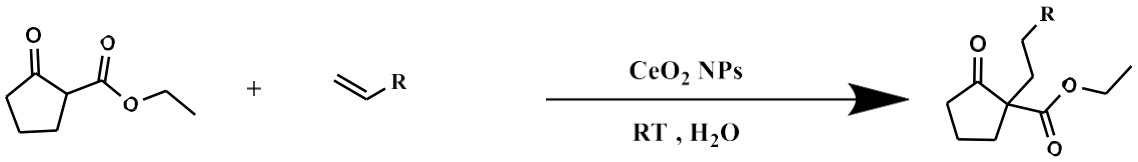
1.4 The reaction of five and six-membered rings

The compound (26) 2-(methylthio)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-ol was prepared by the reaction of ethyl 2-oxocyclopentane-1-carboxylate (15) with 2-methyl-2-thiopseudourea hemisulfate salt in sodium bicarbonate ***(Aware et al., 2015)***



(15) (26)

Cerium Oxide Nanoparticles are employed as a mild and neutral catalyst that can be easily synthesized at room temperature and reused multiple times. A reliable protocol has been developed for the selective bis-Michael addition and mono-allylation of active methylene compounds. These reactions are carried out under mild conditions in aqueous media at room temperature ***(Banerjee, 2015)***.

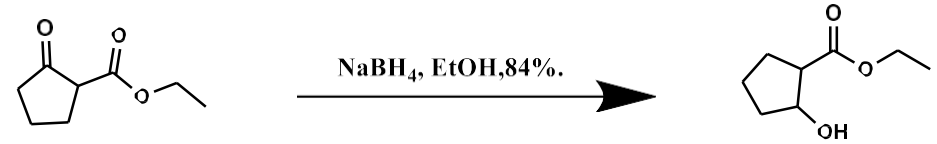


(15)

(27) R = COMe
(28) R= COOMe
(29) R= CN

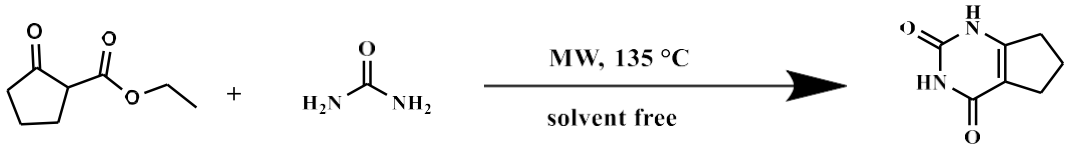
(30) R = COMe
(31) R= COOMe
(32) R= CN

Ethyl-2-hydroxycyclopentane-1-carboxylate (33) was prepared by solution of 2-oxo-cyclopentanecarboxylic acid ethyl ester (15) in ethanol, cooled to 0 °C, was treated with 98% sodium borohydride. The reaction mixture was stirred at 0 °C for 30 min ***(Sarabu et al., 2012).***



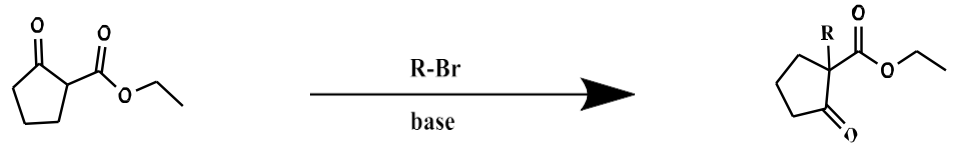
(15) (33)

The reaction between ethyl 2-oxocyclopentane-1-carboxylate (15) and urea (34) was carried out under microwave irradiation at 135 °C without the use of any solvent, resulting in the formation of 1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (35) with a 72% yield ***(Burgula, Radhakrishnan, & Kundu, 2012)***



(15) (34) (35)

The α-substituted β-keto ester derivatives (37a–d) were synthesized using ethyl 2-oxocyclopentanecarboxylate (15) as a starting material. The details of α-alkylation reactions with various alkyl bromides, 1 equivalent of the corresponding alkylating reagent, and potassium-tert-butylate as a base were used under reflux. The best yield (92%) was achieved with propargyl bromide ***(Tzvetkov et al., 2008)***.

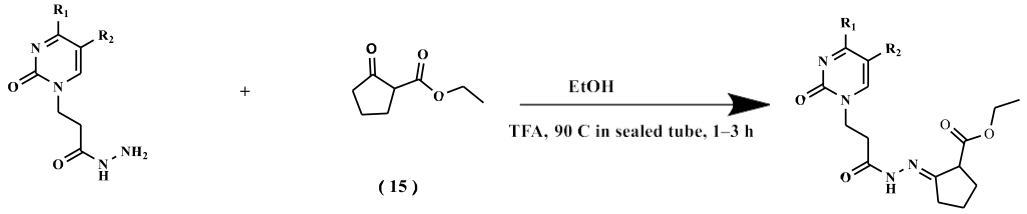


(15) (37) a-d

R =

36a 36b 36c 36d

The synthesis of (41) Uracil derivatives and (42) thymine derivatives and (43) cytosine derivatives from the reaction of ethyl 2-oxocyclopentane-1-carboxylate (15) with amide derivatives (38), (39), and (40) in ethanol or methanol, TFA, 90 °C in a sealed tube, 1–3 h ***(Bouhadir et al., 2016).***

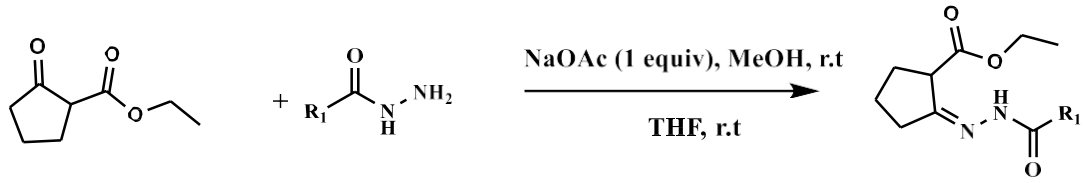


(15)

(38) R_1 = OH, R_2 = H
(39) R_1 = OH, R_2 = CH_3
(40) R_1 = NH_2, R_2 =H

(41) R_1 = OH, R_2 = H
(42) R_1 = OH, R_2 = CH_3
(43) R_1 = NH_2, R_2 = H

Their preparation proceeds using the reaction between cyclic β-ketoesters (15) and hydrazine derivatives (44,45) and one equivalent of tetrahydrofuran or methanol, at room temperature for 4 h, leading to the corresponding hydrazones (46,47) ***(Attanasi et al., 2006).***

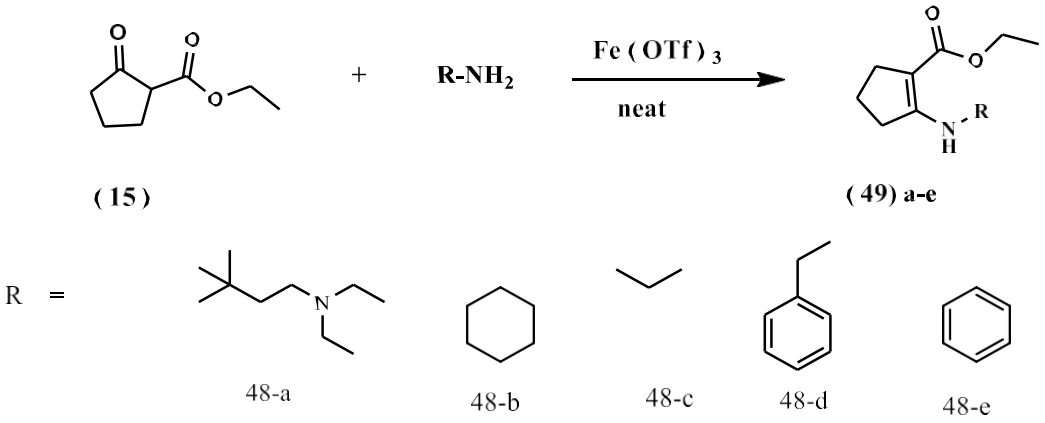


(15)

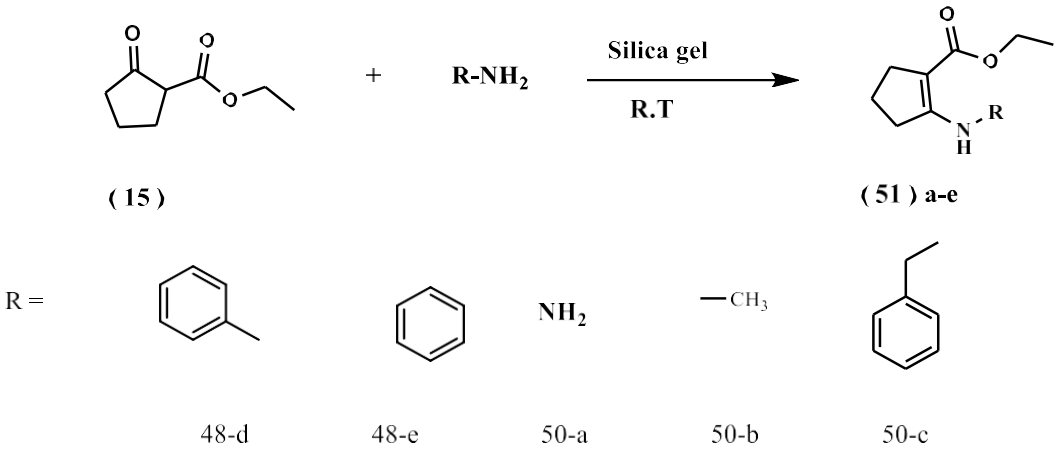
(44) R_1 = NH_2
(45) R_1 = Ot - Bu

(46) R_1 = NH_2
(47) R_1 = Ot - Bu

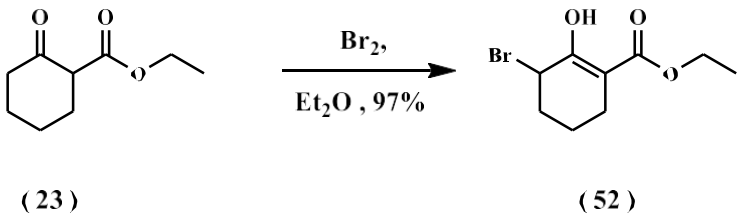
All secondary enamines were synthesized following the procedure reported in the literature (Li et al., 2019) , A mixture of primary amines and β-ketocarbonyl compounds was treated with iron(III) trifluoromethanesulfonate..



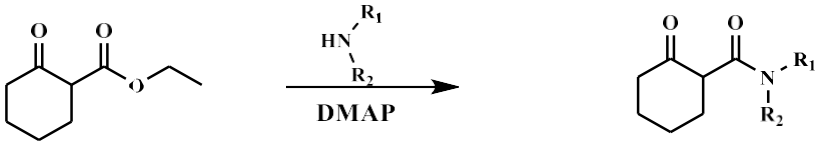
Amine was added dropwise to the suspension of silica gel for diketone in the dicarbonylic compound (and the resulting mixture was stirred at room temperature ***(Gao, Zhang, & Xu, 2004).***



brominating the compound (23) with bromine in diethyl ether, which selectively led to the formation of the monobromo derivative ***(Jourdan et al., 2013).***

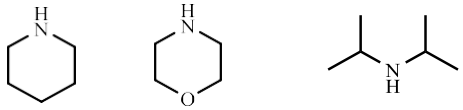


β-Keto amide (56 -58) can be synthesized by reaction of some secondary amines in 4-dimethylaminopyridine ***(Meyer, Piva, & Pete, 2000).***



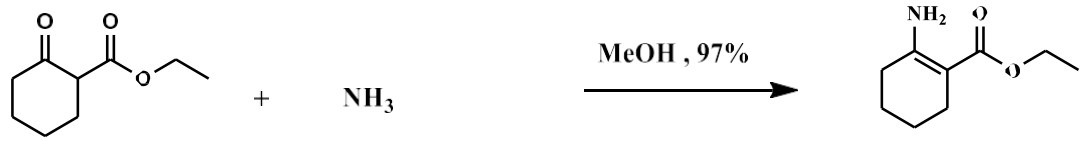
(23) **(56 -58)**

R =



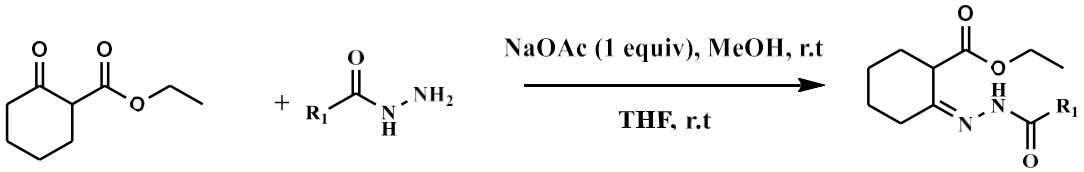
53 54 55

A mixture of ethyl 2-oxocyclohexanecarboxylate (23) and approximately 7 N ammonia (50a) solution in methanol was stirred in a closed vessel at room temperature for 24 hours, yielding (97%) of the known compound (51a) ***(Bobileva et al., 2014).***



(23) **(50 a)** **(51 a)**

The reaction between cyclic β-ketoesters (23) and hydrazine derivatives (44, 45) 1 equivalent, in tetrahydrofuran or methanol, at room temperature for 4 hours), resulted in the formation of the corresponding hydrazones (59, 60) ***(Attanasi et al., 2006).***

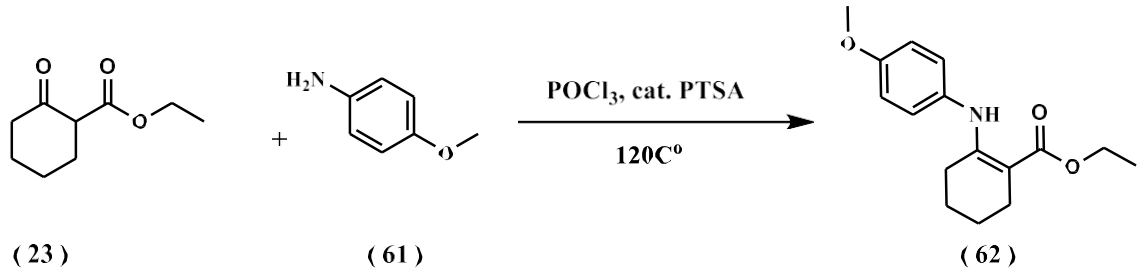


(23)

(44) = R_1 , NH_2
(45) = R_1, Ot - Bu

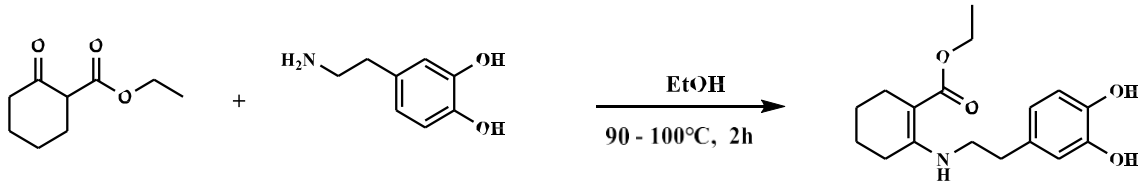
(59) = R_1 , NH_2
(60) = R_1, Ot - Bu

The ethyl 2-((4-methoxyphenyl) amino) cyclohex-1-ene-1-carboxylate (62) was synthesized by the reaction of ethyl 2-oxocyclohexane-1-carboxylate (23) and 4-methoxyaniline (61) ***(Attanasi et al., 2006).***



(23) (61) (62)

The reaction of ethyl 2-oxocyclohexane-1-carboxylate (23) with 4-(2-aminoethyl) benzene-1,2-diol (64) in ethanol at 90 - 100°C; for 2h to give the 1-(2-((3,4-dihydroxyphenethyl) amino) cyclohex-1-en-1-yl) butan-1-one (65) ***(Cuny et al., 2010)***



(23) (64) (65)

1.5 Biological activity of the enamine compounds

Enamine compounds are widely recognized for their broad biological activities, which can be attributed to their distinctive structural features, including a nitrogen-containing group conjugated with a carbon-carbon double bond. This structural configuration enables enamines to function as crucial intermediates in organic synthesis, facilitating strong interactions with biological targets. Numerous studies have demonstrated that enamine derivatives exhibit a wide range of pharmacological properties, such as antibacterial, antifungal, antiviral, anti-inflammatory, and anticancer activities. Specifically, their antibacterial activity is often linked to their ability to disrupt microbial enzymes or interfere with DNA synthesis. Furthermore, the presence of electron-donating or electron-withdrawing substituents on the enamine structure significantly influences their potency and selectivity. Given these attributes, enamine-based compounds are regarded as promising candidates for the development of new therapeutic agents, particularly in response to the growing challenge of antibiotic

Resistance ***(Singh & Mishra, 2021).***

1.6 Molecular Docking

Molecular docking is a computational technique used to predict the preferred orientation of one molecule (typically a small drug-like compound) when bound to a second molecule (usually a protein or enzyme) to form a stable complex. This method plays a critical role in drug discovery and structural molecular biology by providing insights into molecular interactions and binding affinities.

The goal of molecular docking is to:

1. Predict the binding mode of a ligand (small molecule) to a receptor (target protein).
2. Estimate the binding affinity, indicating how strongly the ligand binds to the target.
3. Identify potential lead compounds in drug development.

Docking involves two main components:

- Search algorithm: explores possible orientations and conformations of the ligand within the binding site.
- Scoring function: evaluates and ranks these poses based on predicted binding energy or other physicochemical criteria.

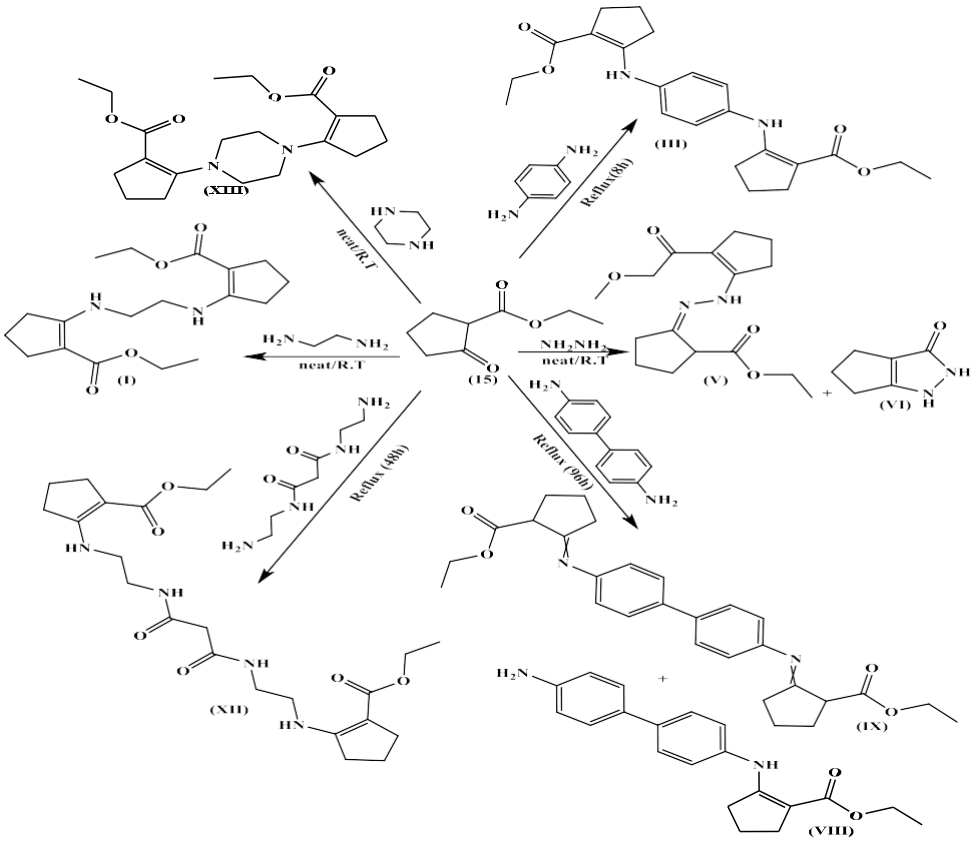
Molecular docking is widely used in virtual screening, structure-based drug design, and understanding biomolecular interactions. Popular docking software includes AutoDock, Molecular Operating Environment (MOE), Glide, and Dock ***(Lengauer & Rarey, 1996)***

Chapter 2

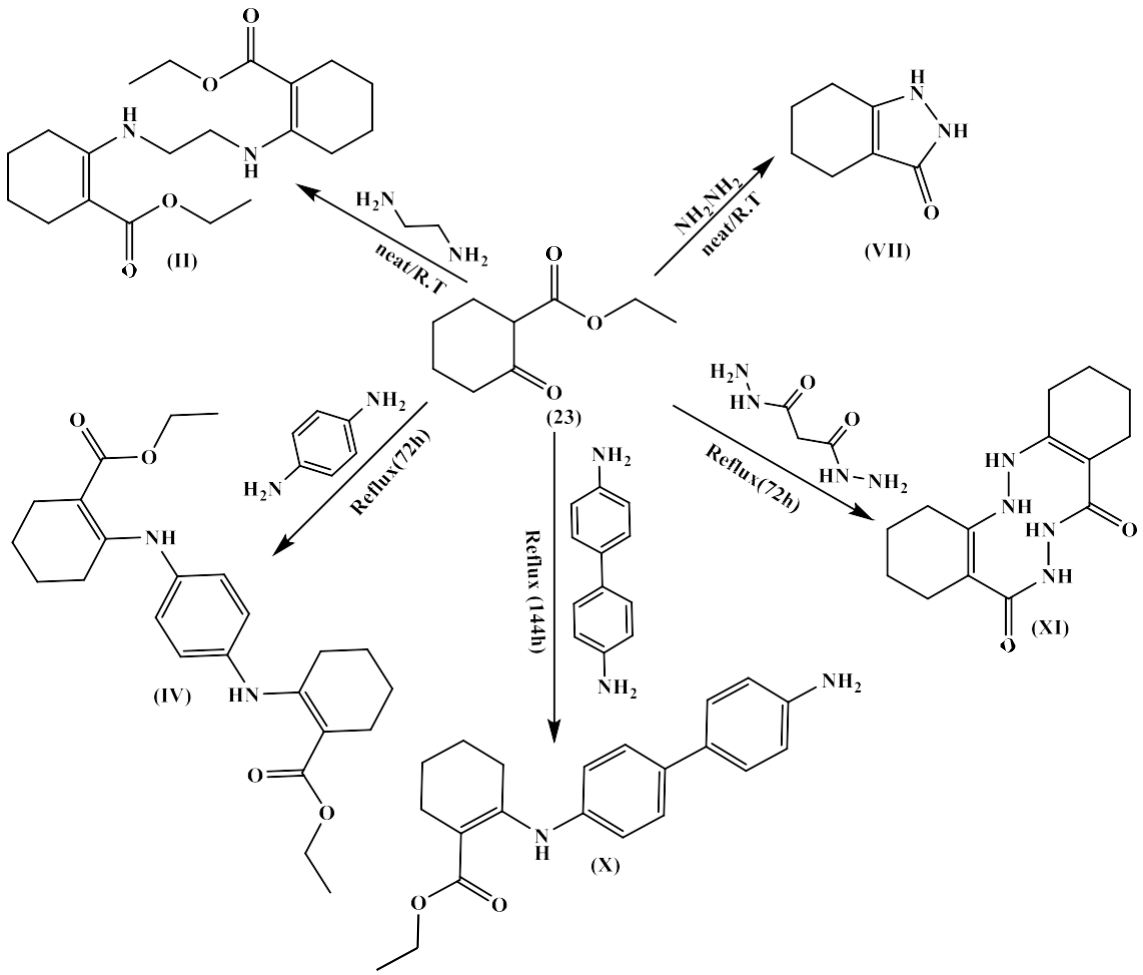
Discussion

2. " RESULTS AND DISCUSSION”

This work begins with an overview of enamine and imine chemistry, focusing on the synthesis of enamines through the reaction of cyclic β-ketoesters with various primary and secondary amines. In these transformations, amines served as nucleophiles, while cyclic β-ketoesters acted as electrophiles, enabling the formation of a new series of enamine-containing compounds (I–XIII). Specifically, ethyl 2-oxocyclopentane-1-carboxylate (15) and ethyl 2-oxocyclohexane-1-carboxylate (23) were reacted with a range of amines—including ethane-1,2-diamine (66), hydrazine hydrate (67), benzene-1,4-diamine (68), piperazine (69), benzidine (70), malonohydrazide (71), and N^1,N^3-bis(2-aminoethyl)malonamide (72)—under neat conditions at room temperature and under reflux in ethanol. Notably, no reaction was observed between ethyl 2-oxocyclohexane-1-carboxylate and either piperazine or N^1,N^3-bis(2-aminoethyl)malonamide under the tested conditions.



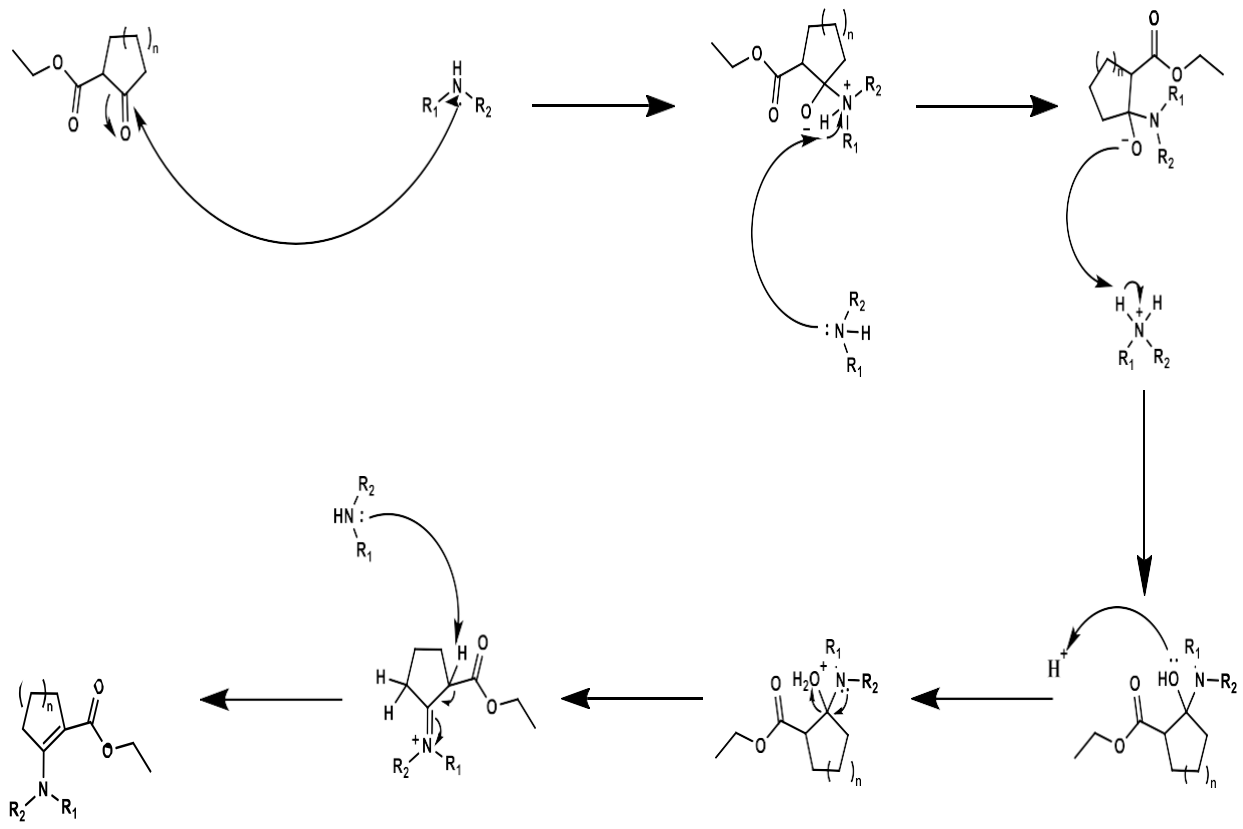
Scheme (2.1) Reaction of Ethyl 2-oxocyclopentane-1-carboxylate (15) with different diamines



Scheme (2.2) Reaction of Ethyl 2-oxocyclohexane-1-carboxylate (23) with different diamines

The Reaction Mechanism:

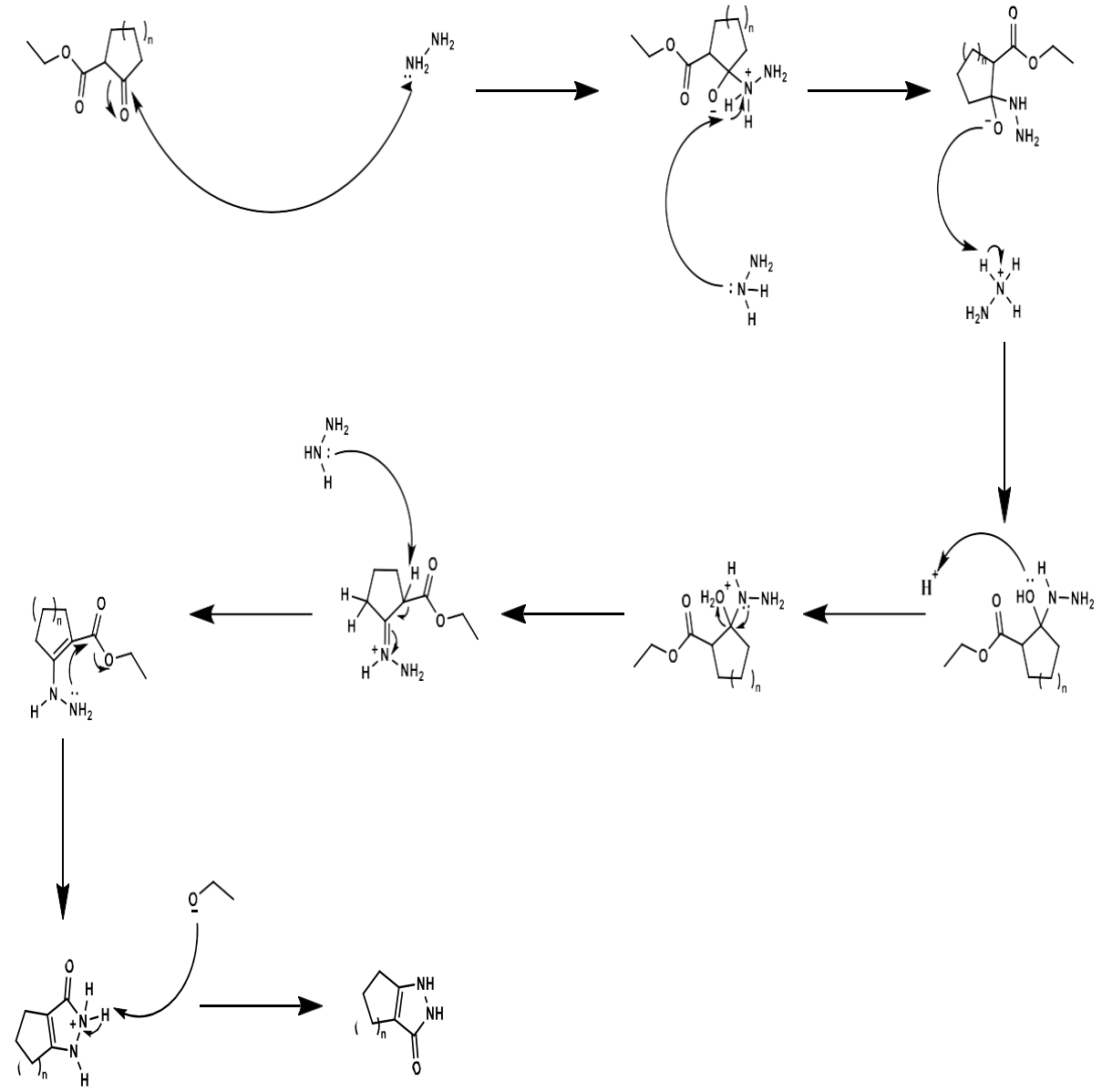
It is well-known that primary amines typically form imines, while secondary amines form enamines. However, some studies have suggested that primary amines can also form enamine compounds, particularly under specific conditions. In the scheme (2.3), we observed the mechanism of compounds (I, II, III, IV, V, VIII, IX, X, XII, XIII). In some of these compounds, the reaction occurred in a 1:1 and 2:1 ratio. Additionally, both imines and enamines were formed simultaneously, with imines appearing on one side and enamines on the other .



n = 1, 2

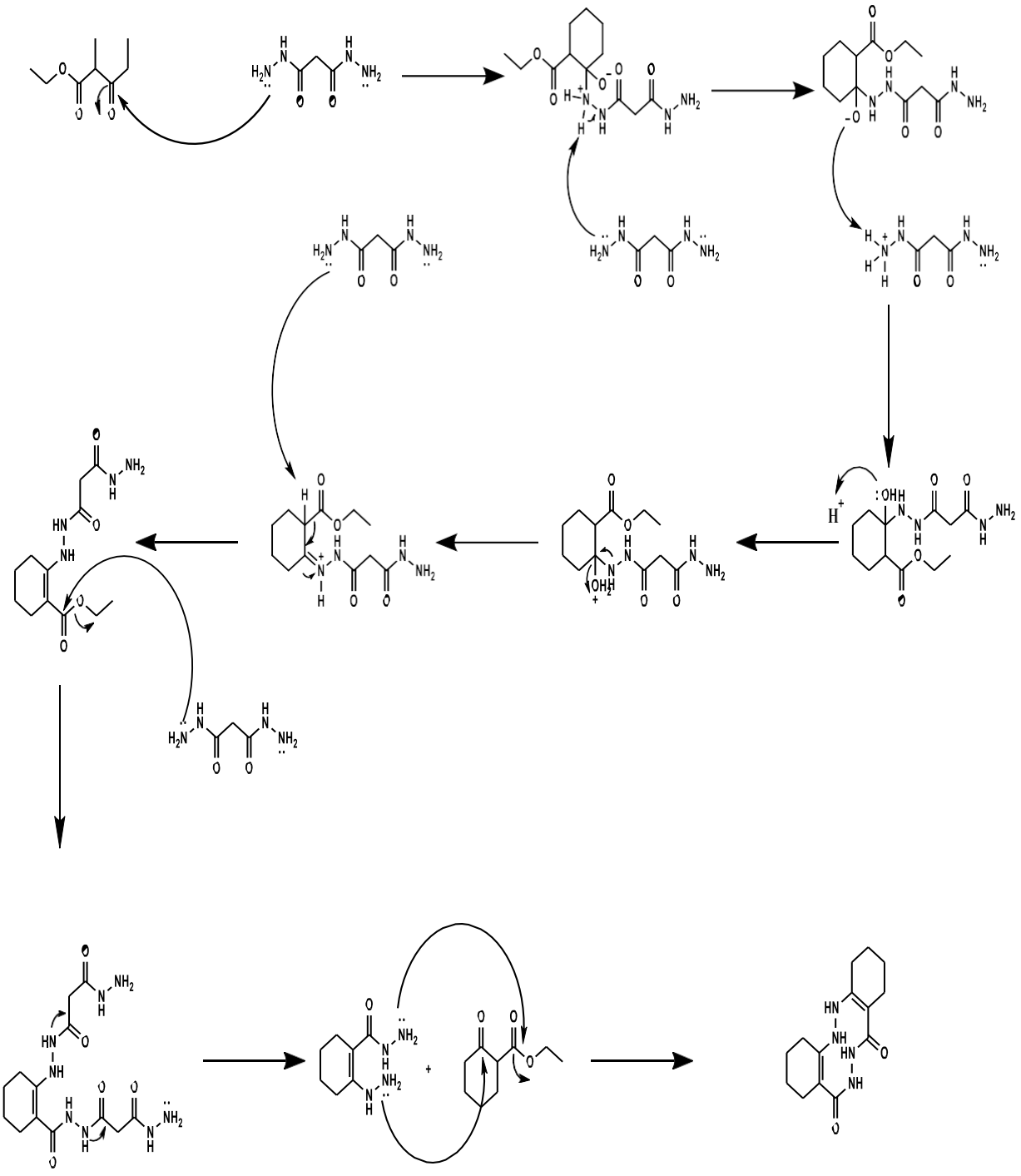
Scheme (2.3) The proposed mechanism of synthesis of compounds (I, II, III, IV, V, VIII, IX, X, XII, XIII)

As we notice in schemes (2.4) and (2.5), the enamine was formed, and then the ester group was attacked, and a heterocyclic ring was formed.



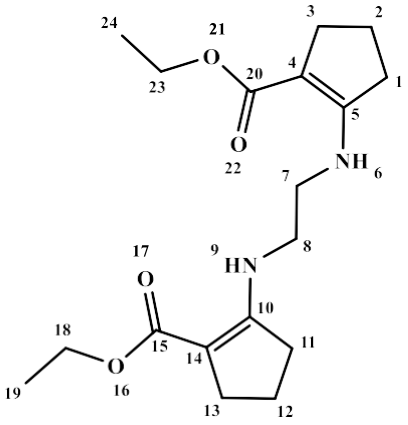
n = 1, 2

Scheme (2.4) The proposed mechanism of synthesis of compounds *(VI, VII)*



Scheme (2.5) : The proposed mechanism of synthesis of compound (XII)

The reaction of ethyl 2-oxocyclopentane-1-carboxylate (15) and ethyl 2-oxocyclohexane-1-carboxylate (23) with ethylenediamine under neat conditions, and with *p*-phenylenediamine under reflux, led to the formation of bis-enamine compounds (I), (II), (III), and (IV). Interestingly, all four reactions resulted in the formation of a single product in each case, yielding only one isolated compound per reaction.



The IR spectrum of compound (I) in figure (2.1a) determined the compound's identity as a sharp strong absorption band at 1591.53 cm^{-1} (C=C) and a sharp strong absorption band at 1644.40 cm^{-1} due to the carbonyl group of the ester function and a peak sharp at 3317.45 $cm^{-1\ 1}$ due to the NH. and peak at 2945.33 cm^{-1}CH aliphatic.

The ^{1}HNMR spectrum of compound (I) in $CDCl_3$ in figure (2.1b) showed a triplet signal at 1.26 ppm for the protons (24, 19) , A quartet signal at 4.12 ppm for protons (18, 23) because of the deshielding effect of an oxygen atom, which confirms the presence of the ethoxy group. Also, the singlet signal at 3.26 ppm is characteristic of protons (7, 8), and at 2.41 ppm, protons of cyclopentane (1, 11 , 3, 13) as a doublet of doublet for this signal. and the protons of cyclic (2, 12) appear as a quintet at 1.74 ppm. The NH signal appears as a singlet at 7.43 ppm, forming an enamine compound.

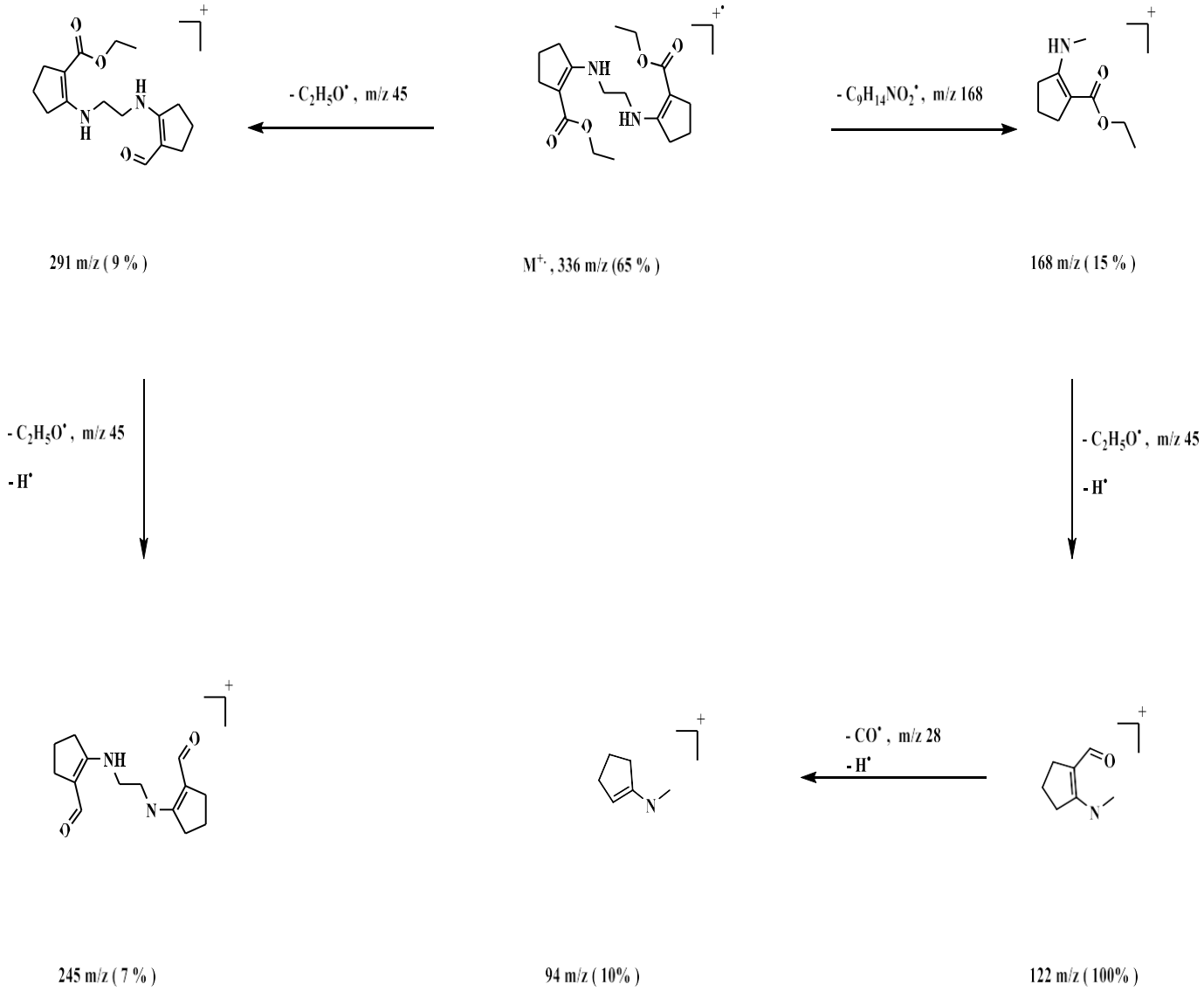
The D_2O spectrum in figure 2.1c) showed a disappearing proton for NH at 7.43 ppm and a new signal of hydrogen attached to (OD) at 4.72 ppm.

Carbon magnetic resonance spectral data of the compound (I) in figure (2.1d) is consistent with the proposed structure in which the carbons (19,24) appear at 14.68 ppm, followed by a signal at 20.88 ppm for carbons (12, 2). and carbons (3, 3) at 29.07. Carbons (11, 1) appear at 31.94 ppm, and signal at 64 ppm for carbons that are attached to nitrogen atoms (7, 8), and the signal at 58.44 ppm for the carbons (18, 23), the olefinic carbon that is attached by the carbonyl of ester (14,4) appears at 93.82 ppm. followed by a signal at 164.16 for olefinic carbon that is attached to an amino group (10, 5). while the carbonyl group of ester (15, 20) at 168.45 ppm.

The APT technique in Figure (2.1e) showed only carbons (19, 24) at down, representing CH_3, and the remaining carbons appeared up representing five CH_2 and three quaternary carbons

Further support of the compound **(I)** was obtained from its mass spectrum data in Figure 2.1 f). the possible fragmentation pathways are shown in Scheme (2.6) . The compound **(I)** gives an intense molecular ion peak at 336(65%). The molecular ion peak has two main fragmentation routes (2.4). The first route involves eliminating of $C_2H_5O^{\bullet}$ to give an intense peak at m/z 245 (7%). The other route of fragmentation is the expulsion of $C_9H_{14}NO_2^{\bullet}$from the molecular ion peak to the formation of cation as an intense peak at m/z 168 (15%), followed by loss of $C_2H_5O^{\bullet}$, and proton radicals as a molecule to give an intense peak at m/z 122 (100%) as base peak, and followed then the of CO and proton radical to provide a peak at m/z 94 (10%), All fragments are shown in Scheme (2.6) .

The IR spectra of compounds (II), (III), and (IV) exhibit similarities to that of compound (I). However, compounds (III) and (IV) show distinct absorption bands corresponding to the (=CH) stretching vibration at 3055.82 cm^{-1} and aromatic carbon stretching at 1572.24 cm^{-1} and 1511.67 cm^{-1}, The ^{1}H-NMR,^{13}C-NMR, APT, and D_2O spectrum for compounds (II), (III), and (IV) is similar of compound (I). different signal protons and carbons of cyclohexanone that appear in excess compared to cyclopentanone in aliphatic region, and differently for protons that are attached to the amine give the doublet of doublet signal at 3.29 ppm for compound (II), a result non-magnetic equivalent because rotation around a C–σ bond, and Compounds (III) and (IV) protons of aromatic that appear at region 6-8 ppm and carbons aromatic appear at region 110-140 ppm, The fragmentation of compound (II) , (III) and (IV) shows in scheme (2.7), (2.8) and (2.9), all these spectrum see in appendix page (89-112)



Scheme (2.6) The fragmentation *of compound (I)*

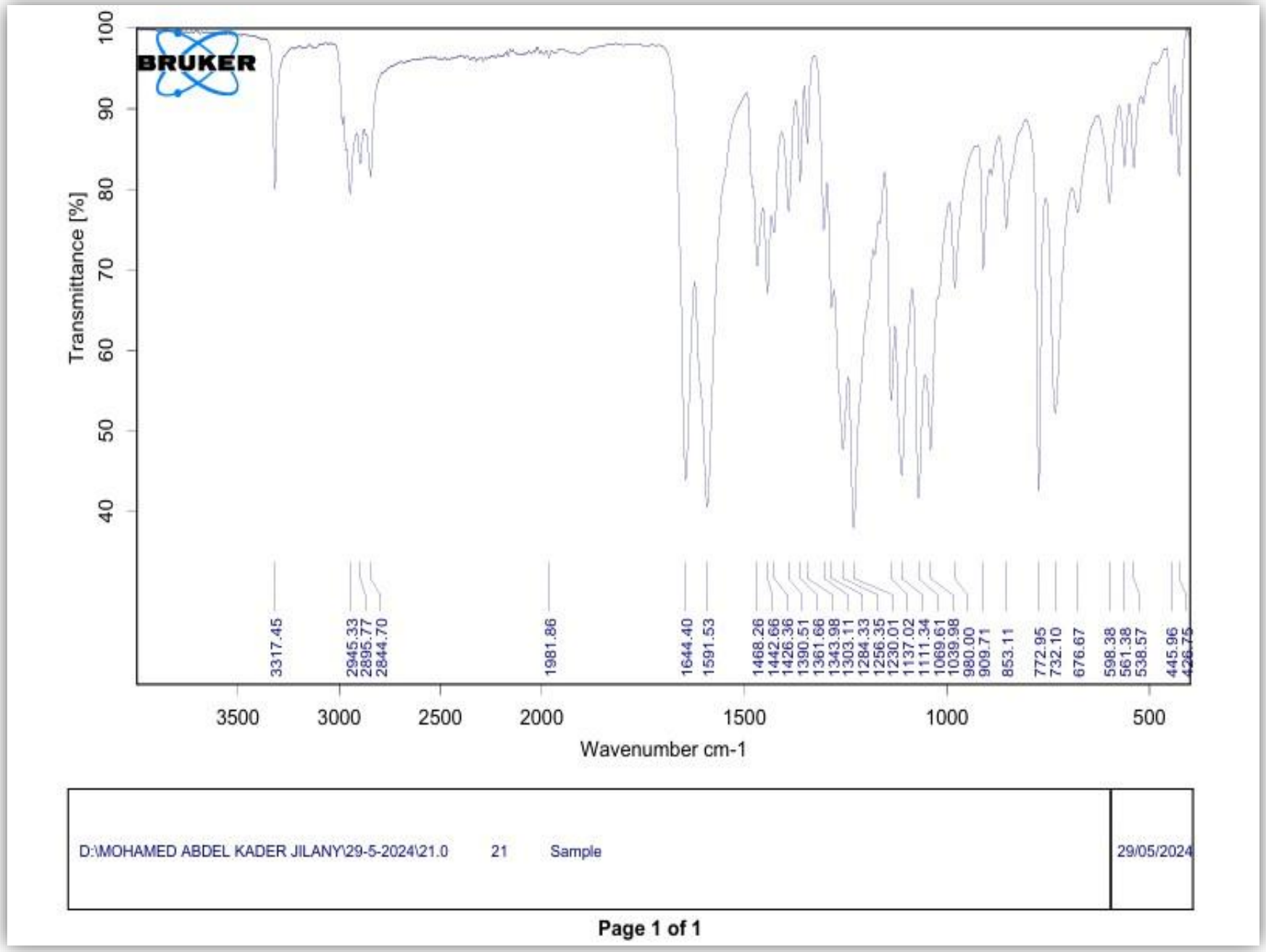


Figure (2.1a) FT-IR spectrum *of compound (I)*

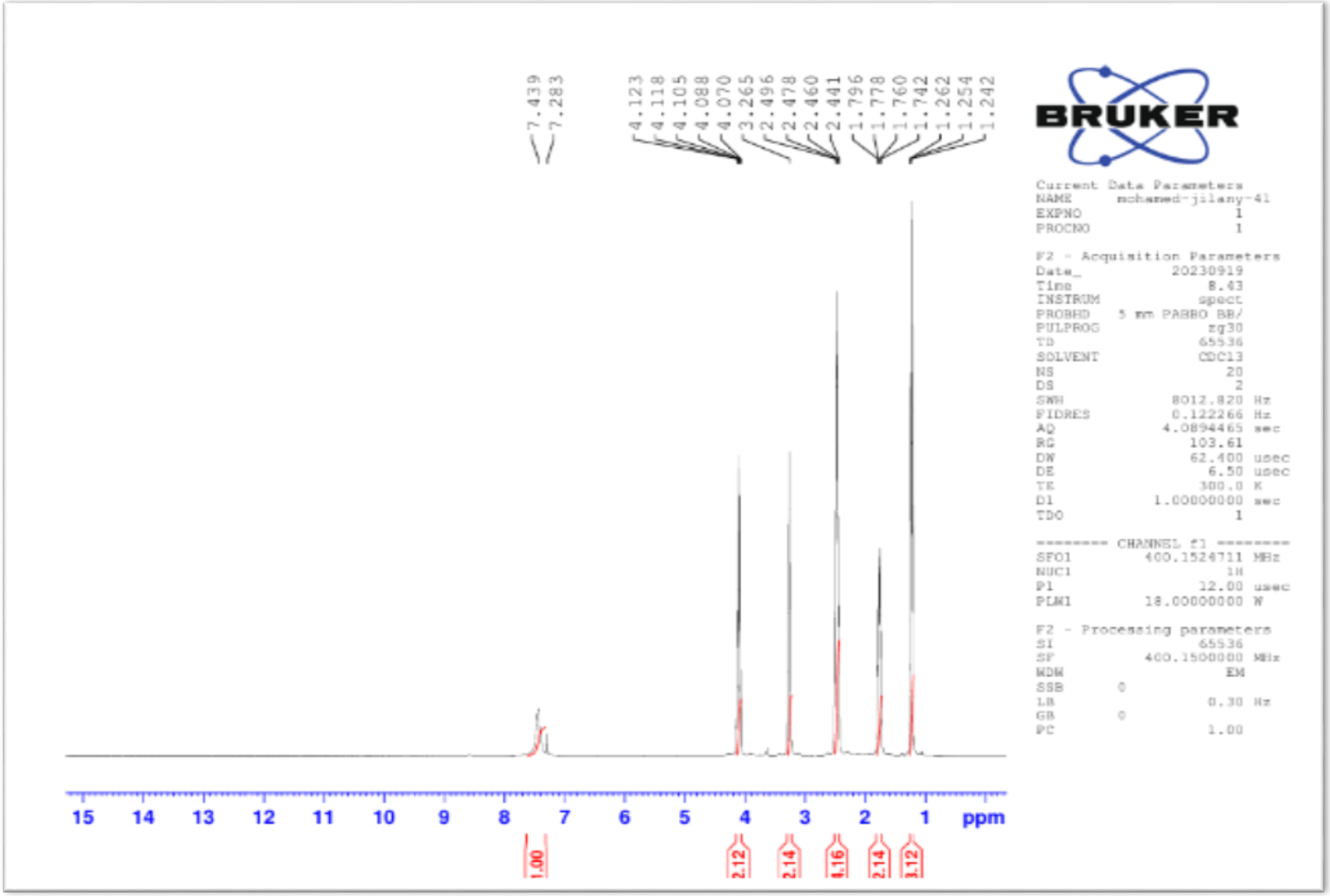


Figure (2.1b) ^{1}HNMR spectrum *of compound (I)*

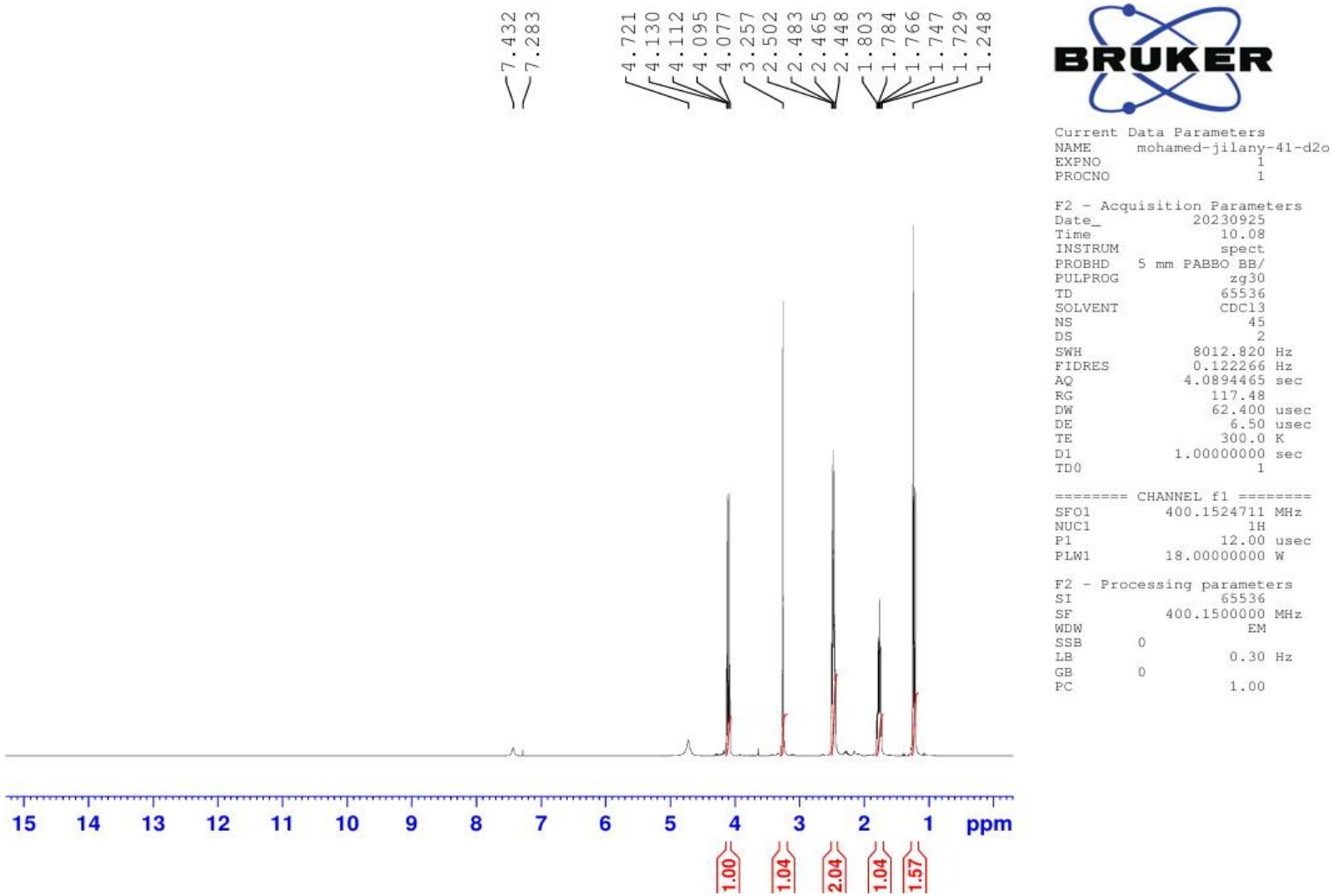


Figure (2.1c) D_2O spectrum *of compound (I)*

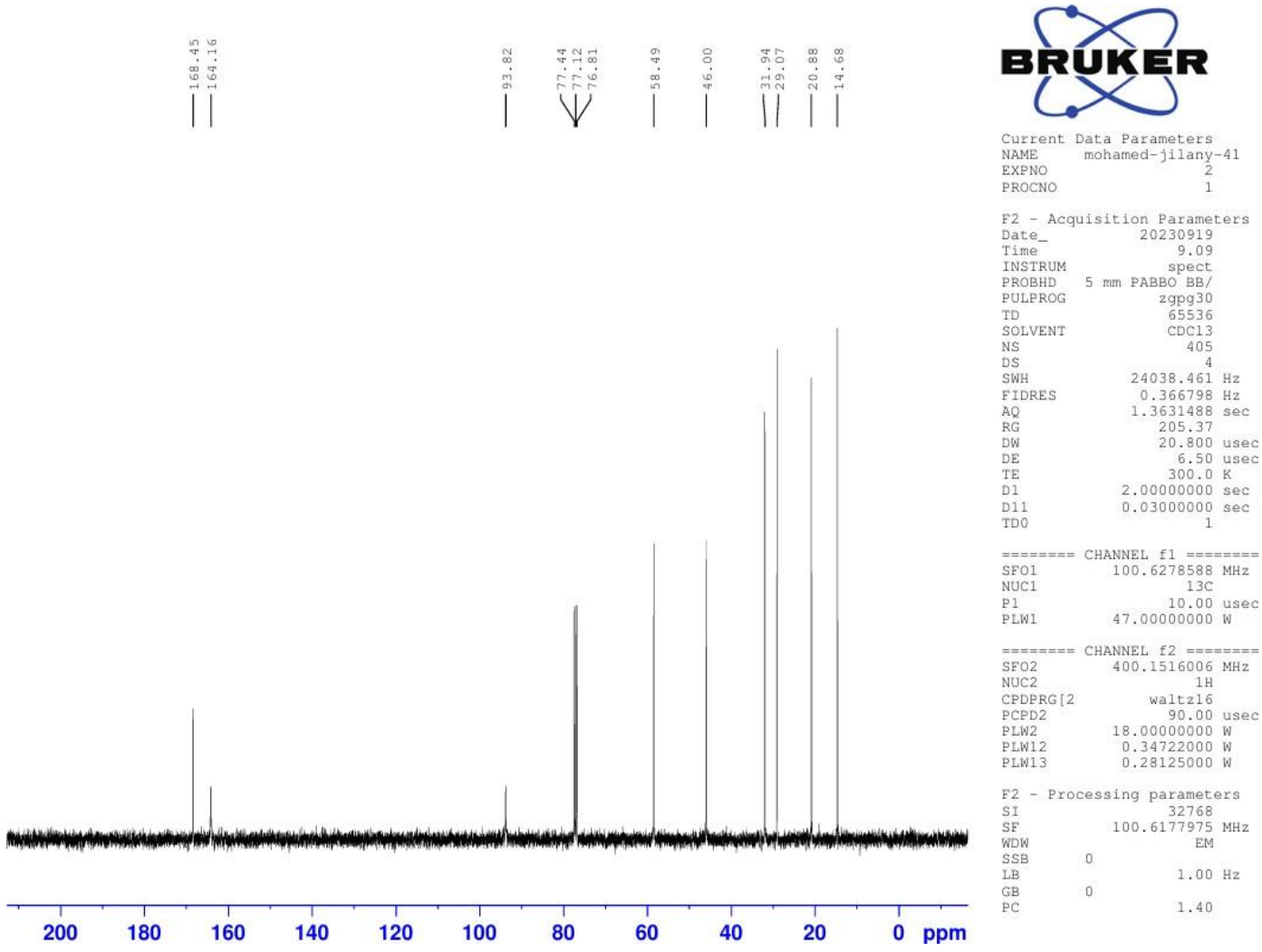


Figure (2.1d) ^{13}C-NMR spectrum *of compound (I) in CDCl* $_3$

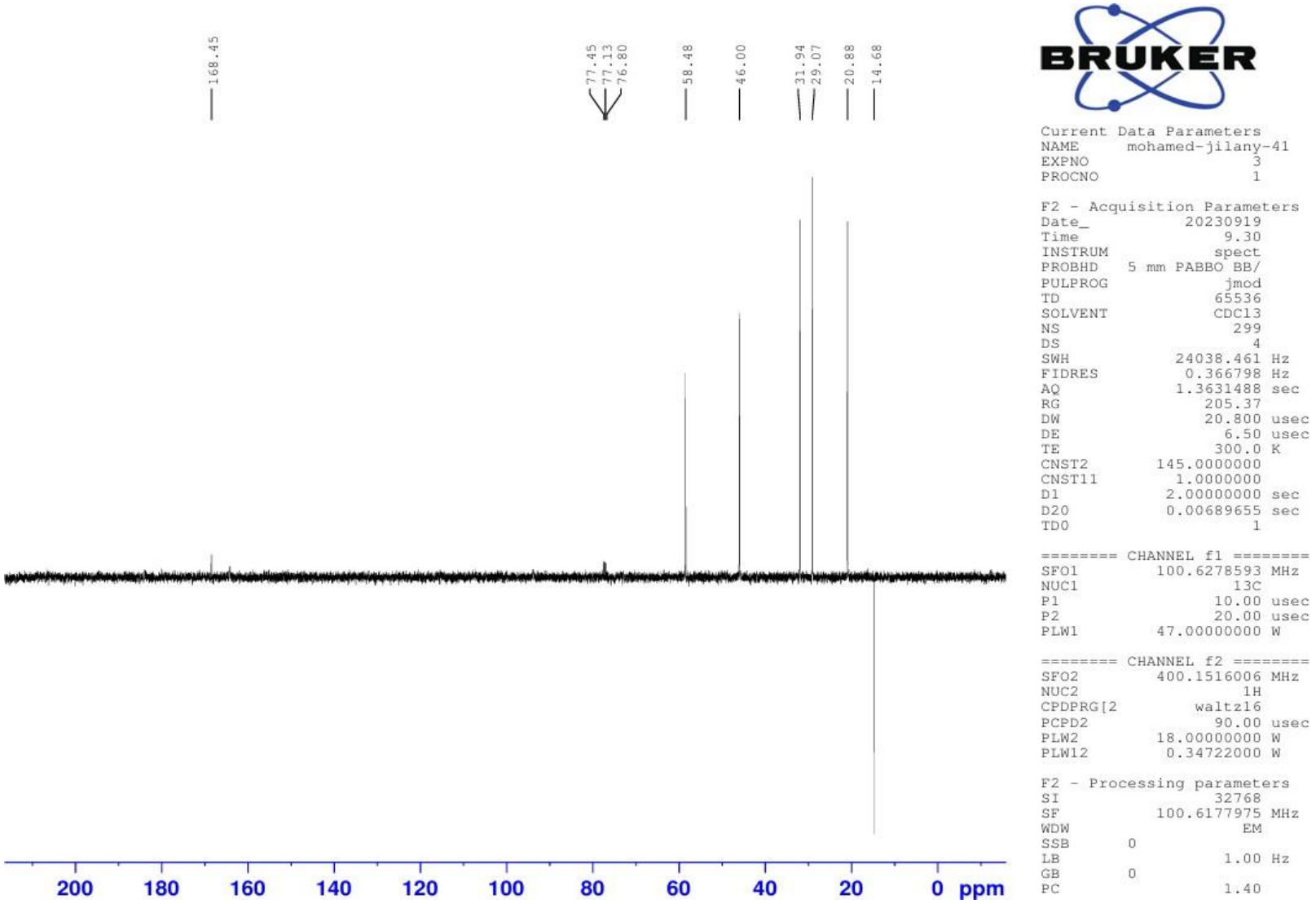


Figure (2.1e) APT spectrum *of compound (I) in CDCl* $_3$

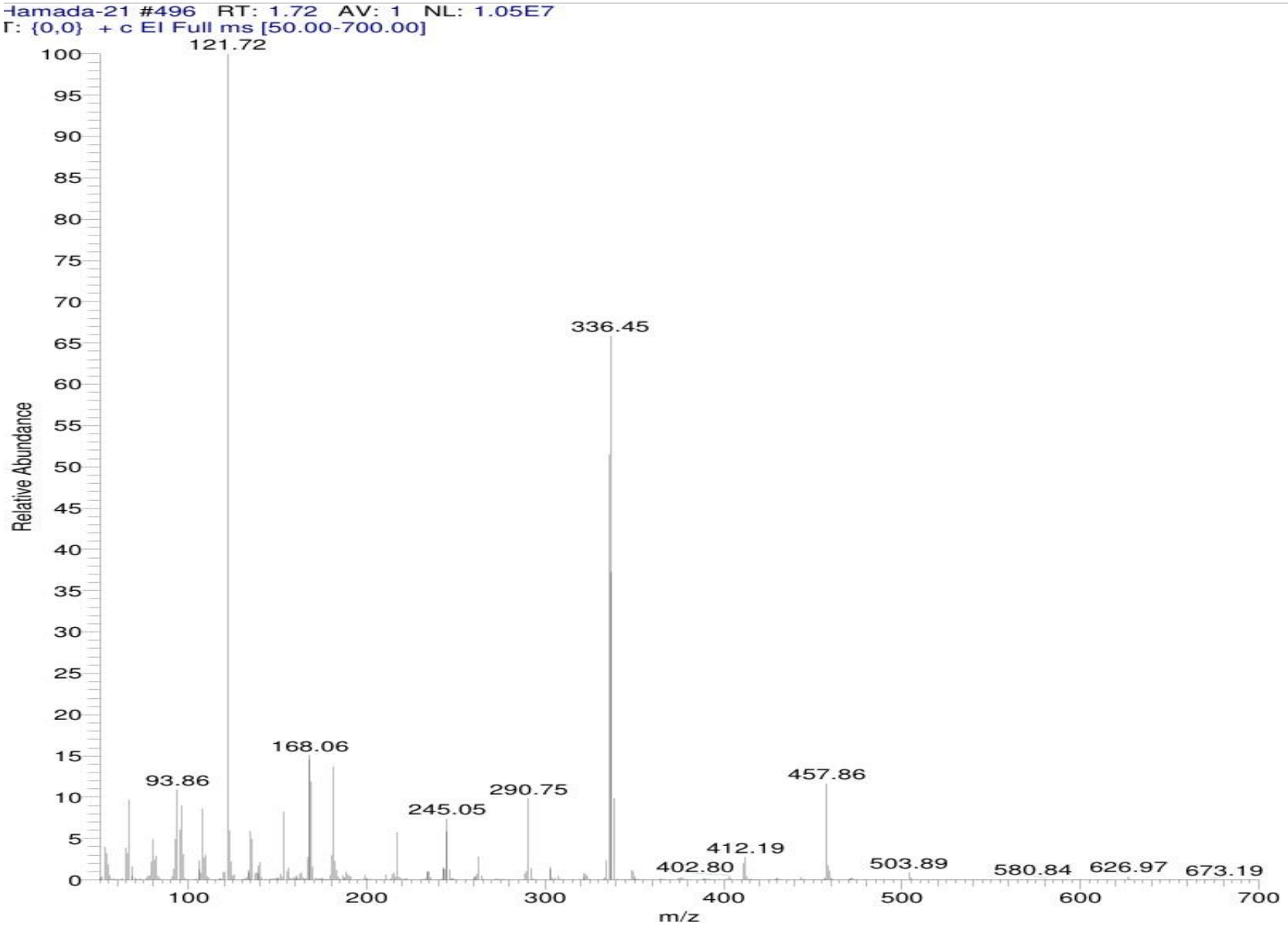
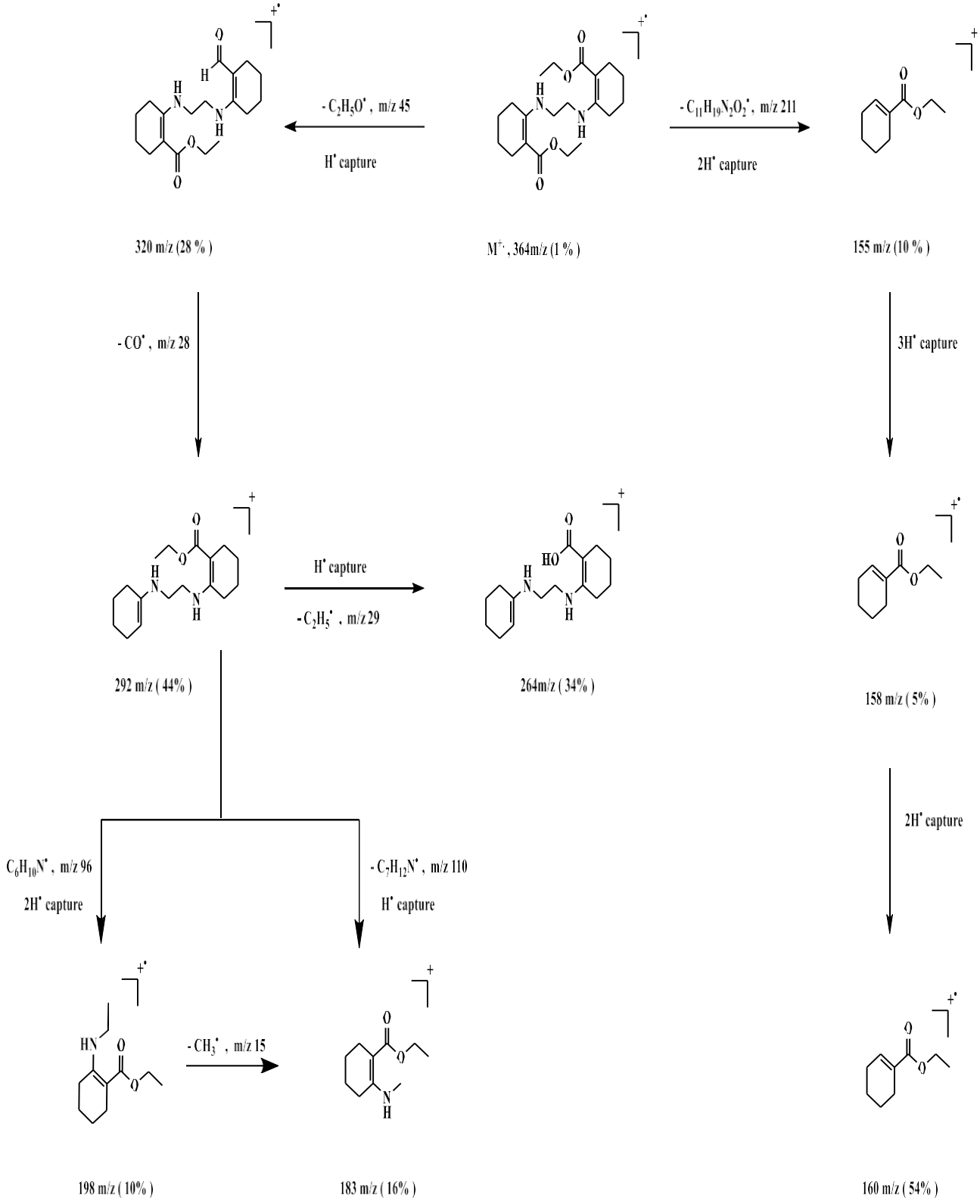
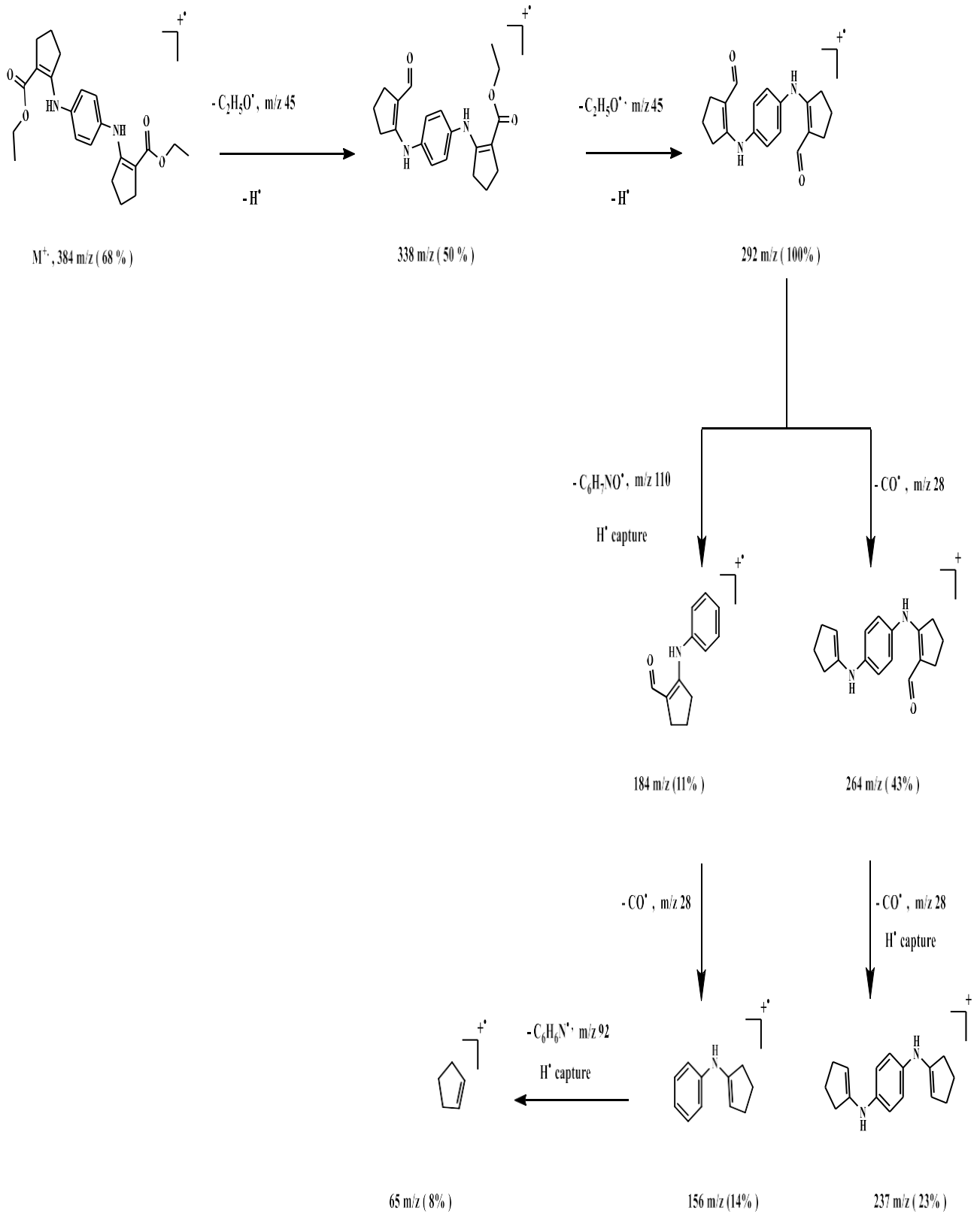


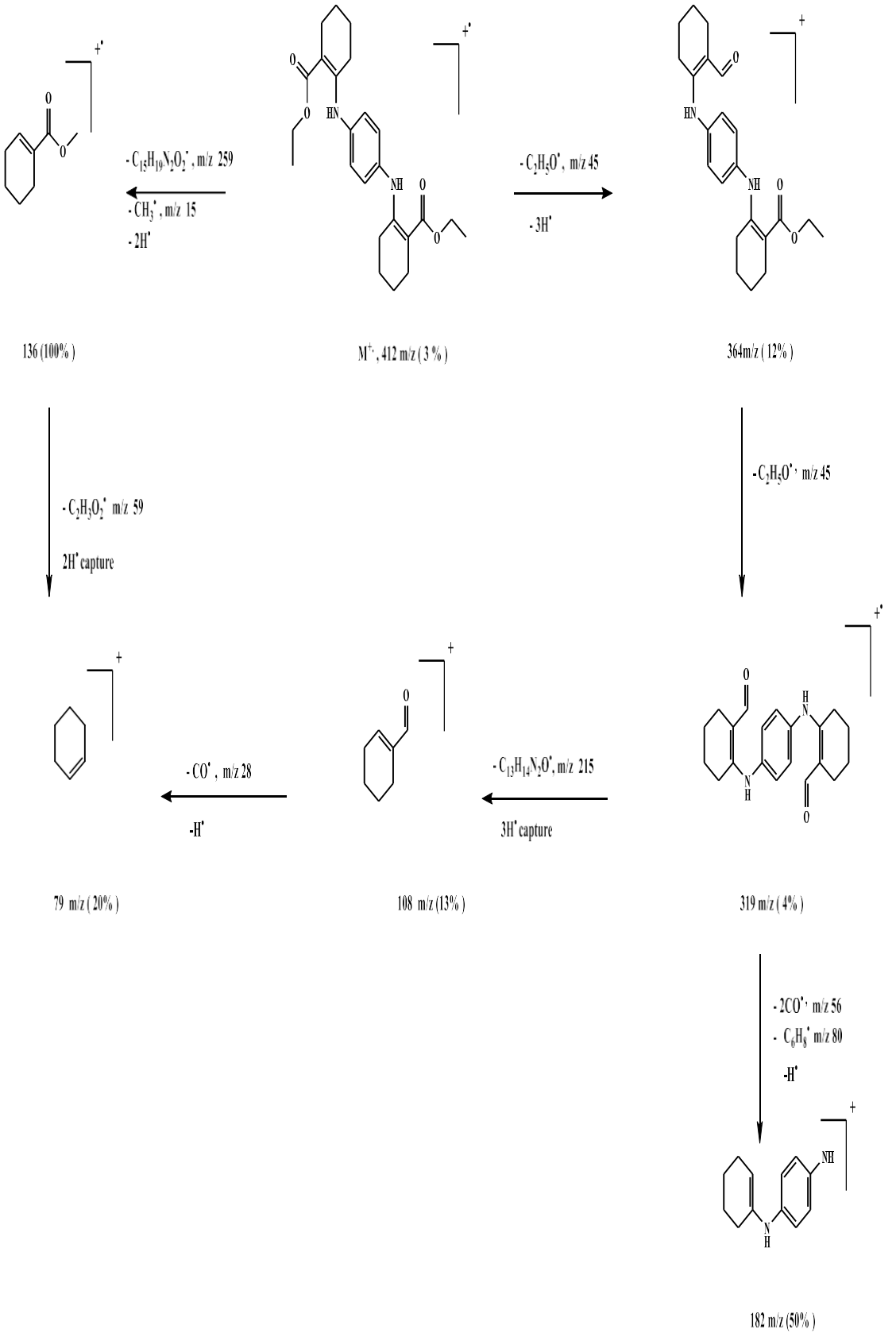
Figure (2.1f) Mass spectrum *of compound (I)*



Scheme (2.7) The fragmentation of compound (II)

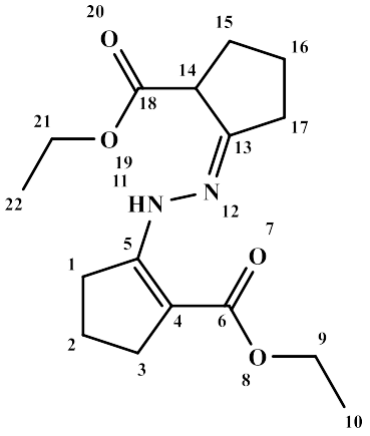


Scheme (2.8) The fragmentation of compound (III)



Scheme (2.9) The fragmentation of compound (IV)

The reaction of ethyl 2-oxocyclopentane-1-carboxylate (15) with hadrazine hydrate in neat conditions to produce two products, the major product of cyclic enamine 82% (V) and the minor product of bis-amine (14%) (VII), and the reaction of ethyl 2-oxocyclohexane-1-carboxylate (23) with hadrazine hydrate under neat conditions to produce one product of cyclic enamine, and The reaction of ethyl 2-oxocyclopentane-1-carboxylate with benzidine under reflux, led to the formation of two product, the major product of bis-enamine (IX) and the mainor product of mono-enamine (VIII) , while the reaction ethyl 2-oxocyclohexane-1-carboxylate (23) with benzidine to produce one product of mono-enamine (X).



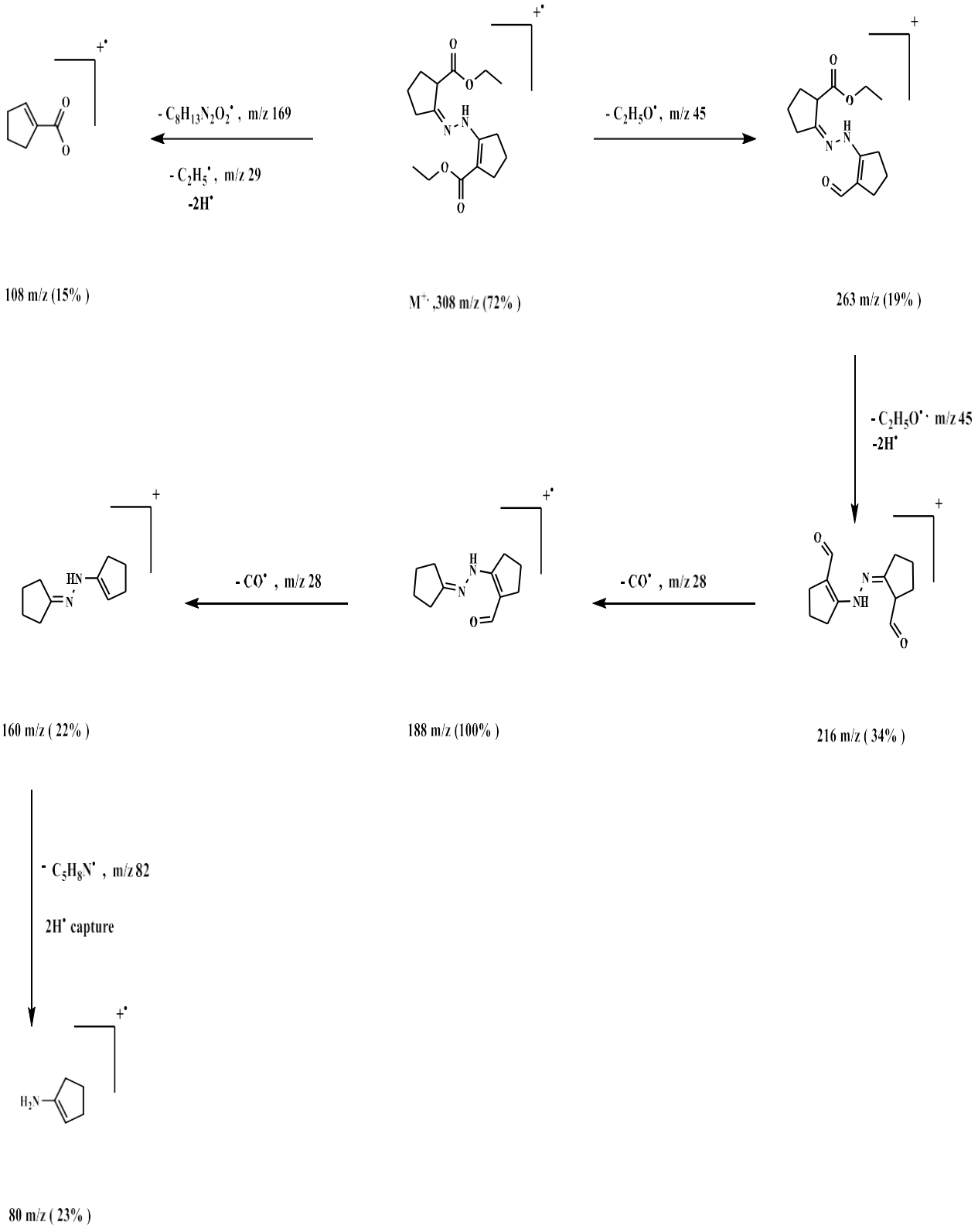
The IR spectrum of compound (V) in figure (2.5 a) determined the compound's identity as a sharp strong absorption band at 1604.55 cm^{-1} (C=C) and a sharp strong absorption band at 1647.36 and 1732.91 cm^{-1} due to the ester function and band sharp at 3259.78 cm^{-1} due to the NH. and 2966.13 cm^{-1}CH aliphatic

The ^{1} H NMR spectrum of compound (v) in $CDCl_3$ in figure (2.5 b) showed a two triplet signal at 1.30 ppm for the protons (10, 22) as non-equivalent protons. A two-quartet signal was shown at 4.26 for protons (9, 21 as non-equivalent protons), which confirms the presence of the ethoxy group. Also, the triplet signals at 3.15 ppm for protons (14). and at 1.83 to 3.15 ppm protons of cyclopentane (1, 2, 3 15, 16, 17). The NH signal appears as a singlet at 10 ppm. From this information we note that it has indeed been formed of enamine compound.

The D_2O spectrum in figure (2.5c) showed a disappearing proton for NH at 10 ppm and a new signal of hydrogen attached to (OD) at 4.76 ppm.

Carbon magnetic resonance spectral data of compound (V) in figure (2.5 d) showed a signal of carbons (10,22) appearing at 14.28 and 14.76 as non-equivalent carbon. And carbons (21, 9) appear at 61.36 and 59.15 ppm as non-equivalent carbon, which confirms the presence ethoxy group. a seven signal of cyclo pentane at region 23.22, 25.91, 27.05,29.36, 32.06, 37, 38.06 ppm. The olefinic carbon attached by carbonyl of ester (4) appears at 96.15 ppm. while the olefinic carbon that connected with the enamine appeared (5) at 156.28 ppm. Also carbons (13) appear at 161.20 ppm, finally carbonyl group of ester(6, 18) at 169.42 and 172.53 ppm as non-equivalent carbon

Further support for the structure of compound (V) was obtained from its mass spectrometry data shown in Figure (2.5e). The possible fragmentation pathways are depicted in Scheme 2.10. The compound (IV) produces a strong molecular ion peak at m/z 308 (72%). This molecular ion peak undergoes two main fragmentation routes (Scheme 2.10). The first pathway involves the elimination of a $C_2H_5O^{\bullet}$ group, resulting in an intense peak at m/z 263 (19%), followed by the further elimination of a $C_2H_5O^{\bullet}$ group, leading to a peak at m/z 216. This is followed by the loss of a $CO^{\bullet}$ group, giving the base peak at m/z 188 (100%). The second fragmentation pathway involves the expulsion of a $C_8H_{13}N_2O_2^{\bullet}$ group and an ethyl radical, leading to the formation of a radical cation with an intense signal at m/z 108 (15%). The remaining fragments are shown in Scheme (2.10).



Scheme (2.10) The fragmentation of compound (V).

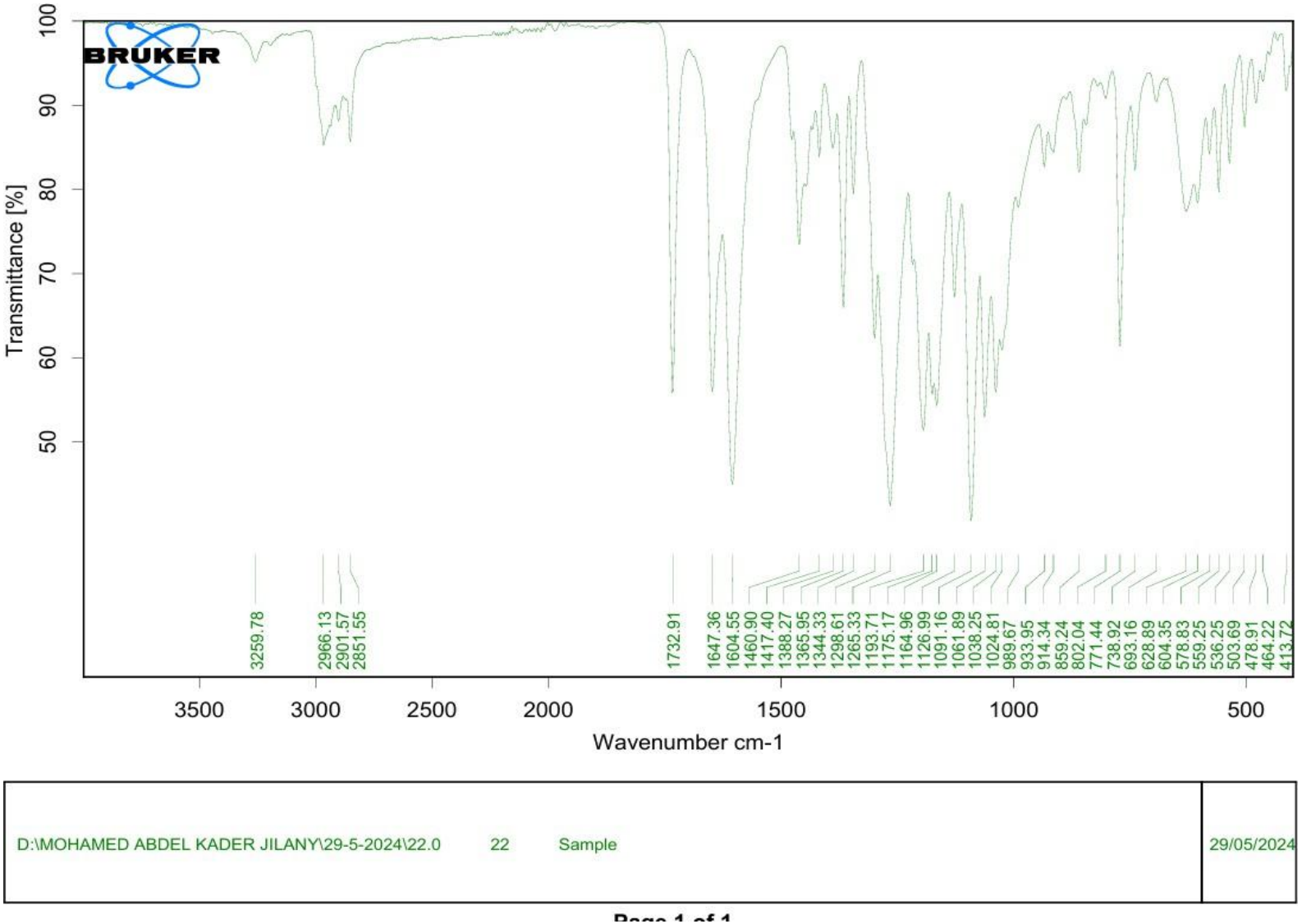


Figure (2.5 a) FT IR spectrum of compound (v)

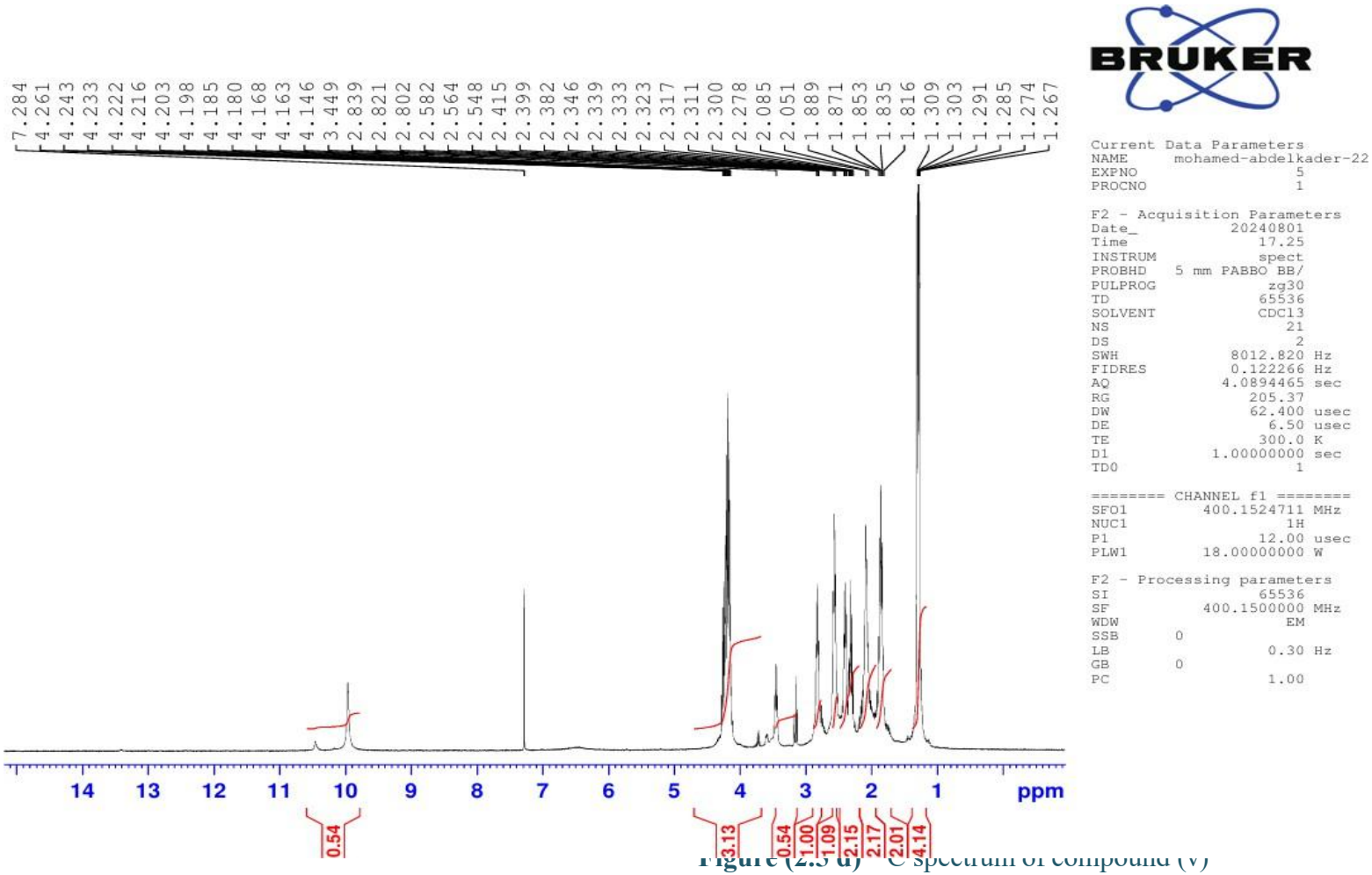


Figure (2.5 b) ^{1}HNMR spectrum of compound (v)

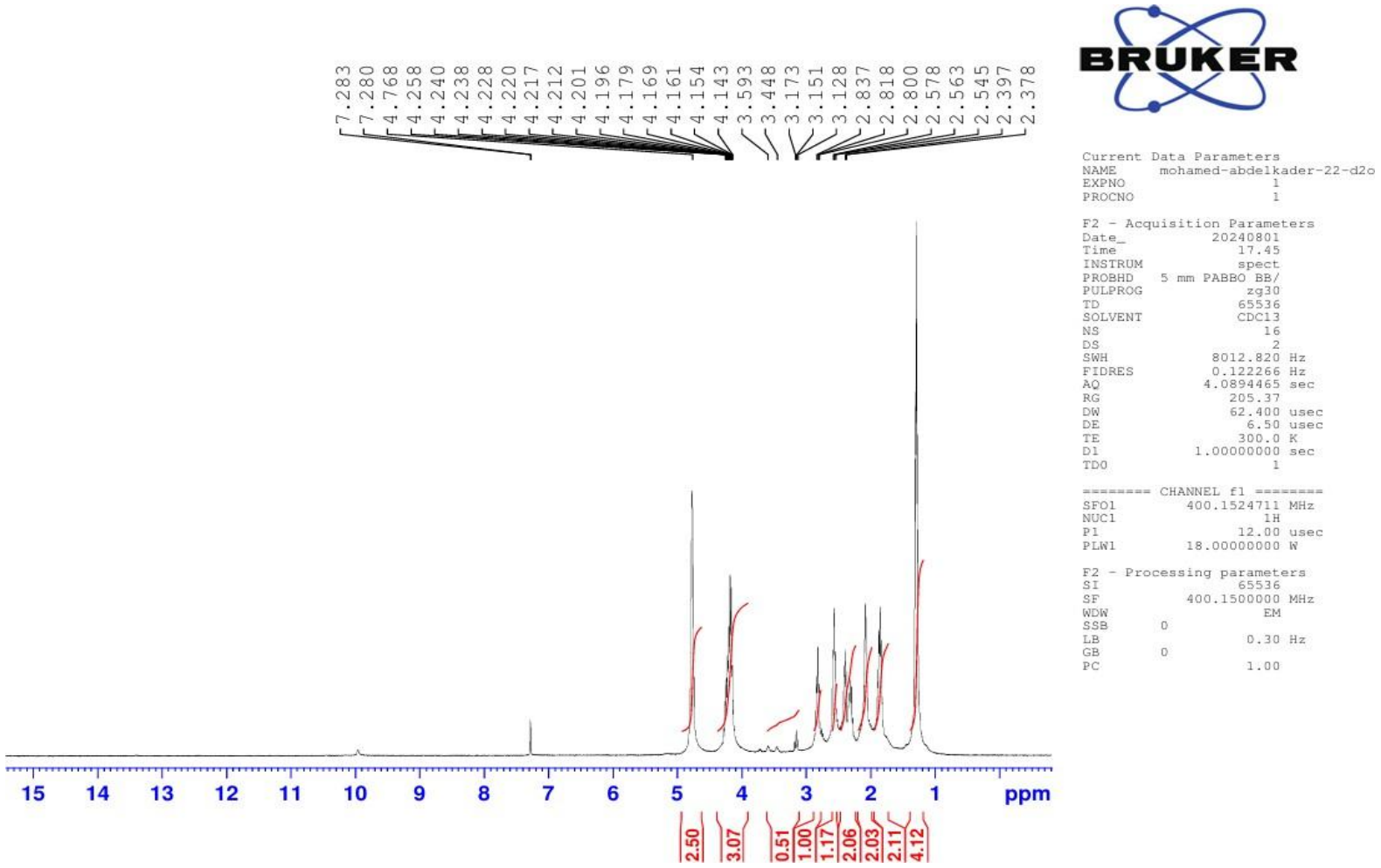


Figure (2.5 c) D_2O spectrum of compound (v)

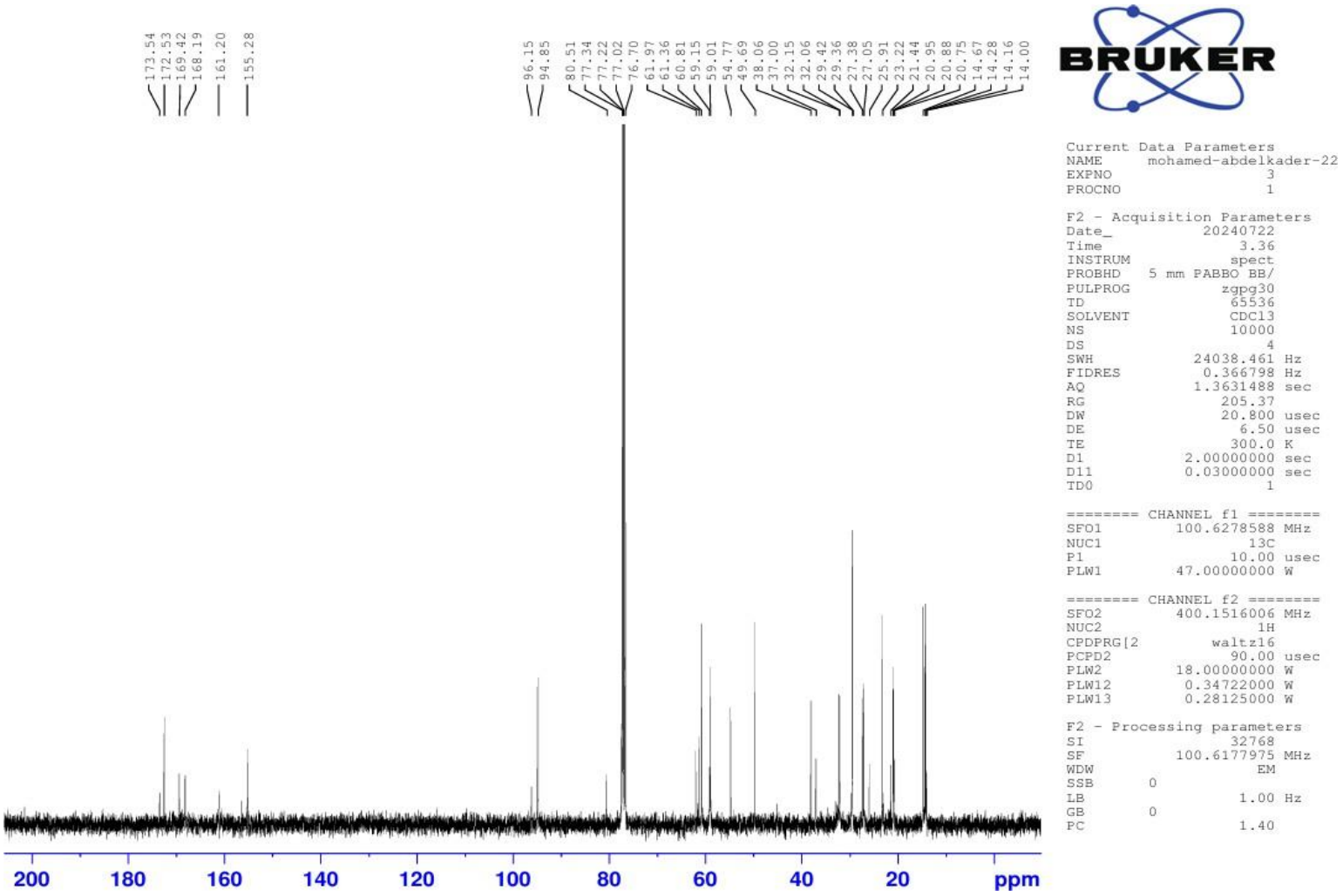



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Figure (2.5 d) C^{13}-NMR spectrum of compound (v)

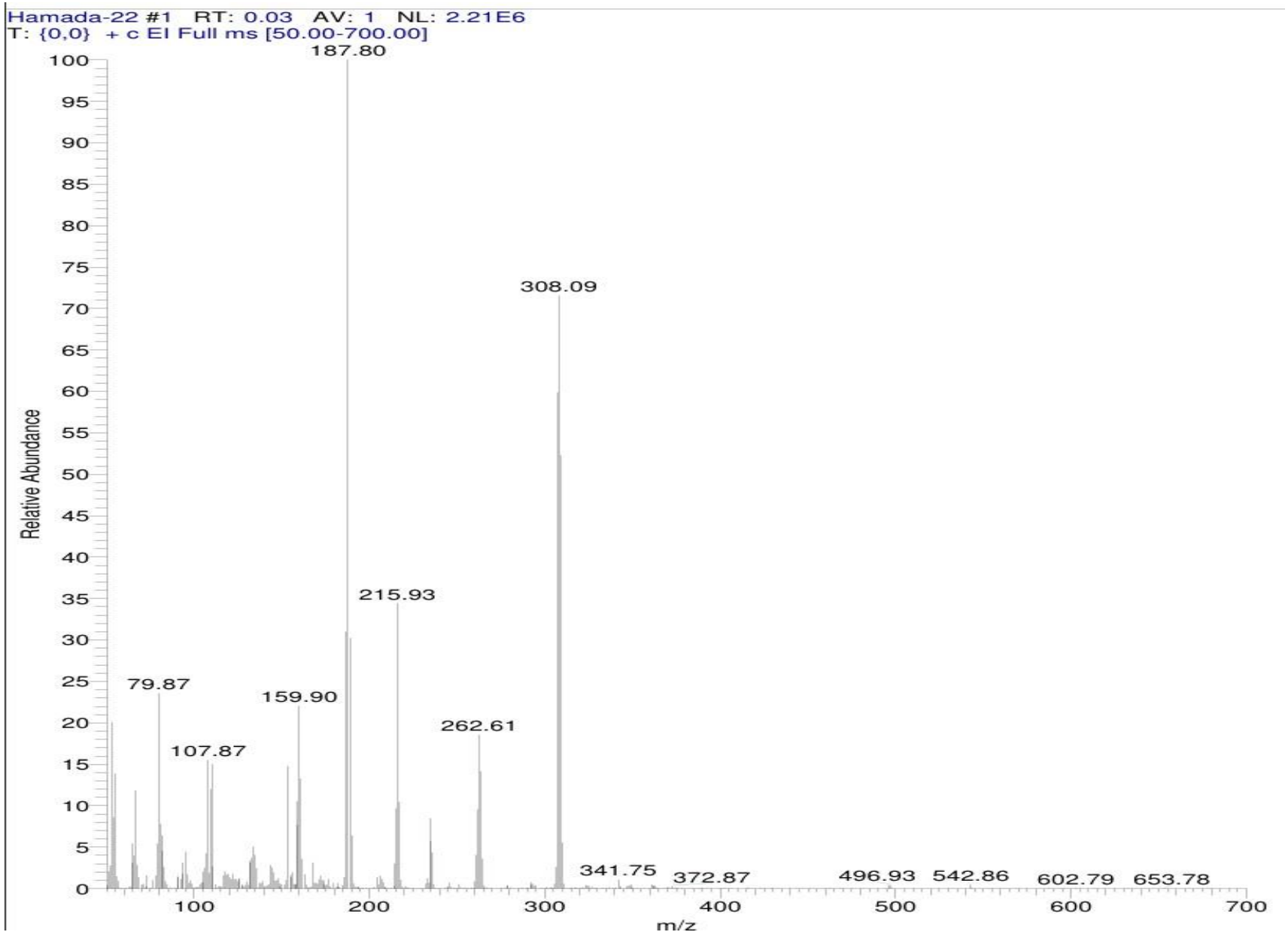
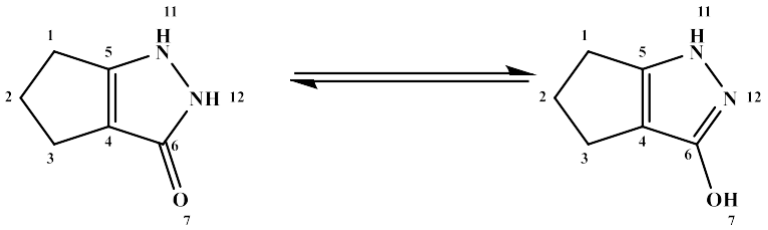


Figure (2.5 e) Mass spectrum of compound (v)



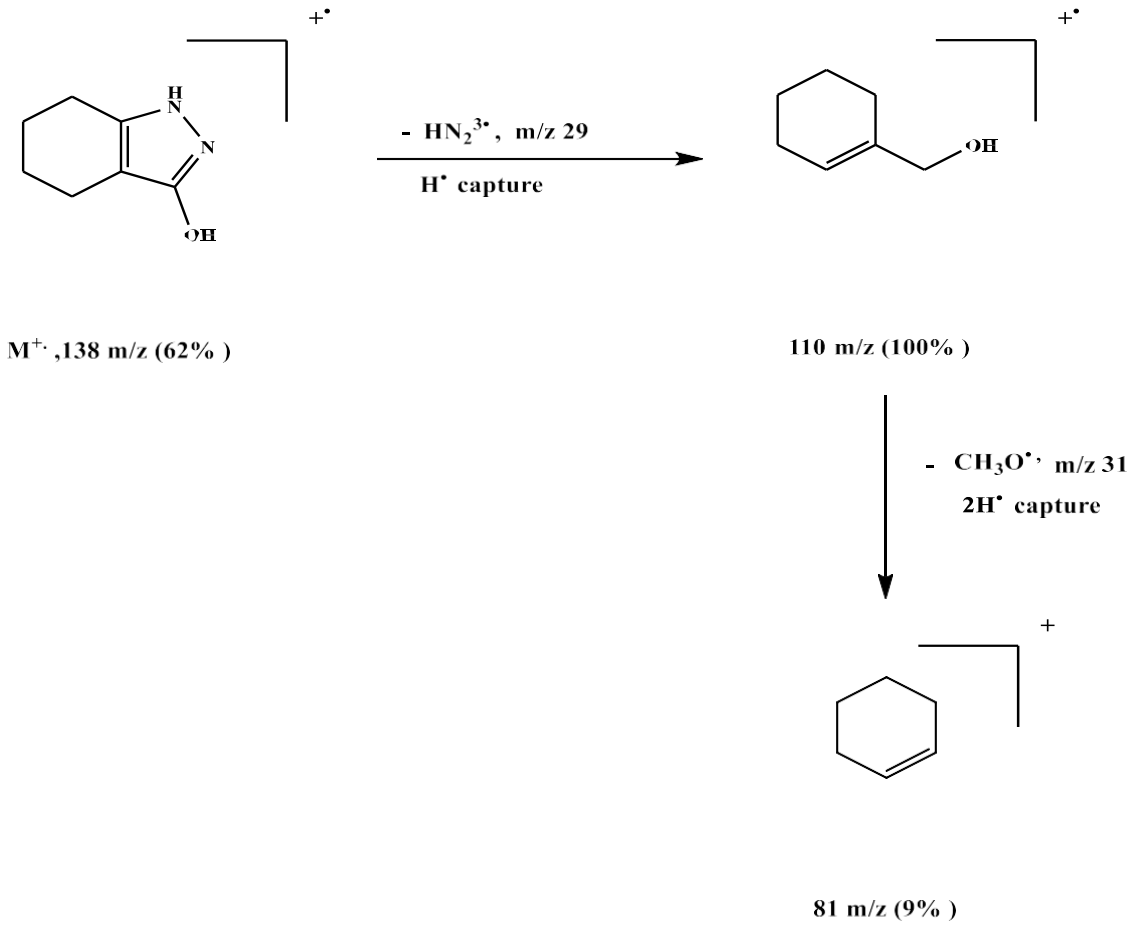
IR analysis in Figure (2.6a) indicates that the compound exists predominantly in the tautomeric form of 1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-ol. This is evidenced by a broad absorption band in the range of 3400–2500 cm^{-1}, attributed to the O–H stretch involved in intramolecular hydrogen bonding. Additionally, an absorption at approximately 3000 cm^{-1} corresponds to aliphatic C–H stretching. A strong band observed at 1590 cm^{-1} is assigned to the C=N stretching vibration, while the band at 1529 cm^{-1} is characteristic of C=C stretching

The ^{1}H-NMR spectrum of compound (VI) in DMSO-d_6 in figure (2.6 b) showed a multiplet signal at 2.46 ppm for the protons of cyclopentanone (1, 2, 3) as non-equivalent protons. At 10.51 ppm, acidic protons appear as a broad singlet signal for the nitrogen atom (11, 12). It is also noticed that the absence of peaks of the ethoxy group, which means that the ester group has been attacked and the pyrazolone ring has been formed.

Carbon magnetic resonance spectral data of compound (VI) in figure (2.6 c) showed a signal of carbons (2) appearing at 22.62 ppm. followed by signal carbon (3) appear at 24.48 ppm. while at 30.47 ppm appears signal of carbon (1). The olefinic carbon attached by carbonyl (4) appears at 107.57 ppm. while the olefinic carbon that connected with the amine appeared (5) at 153.75 ppm. Finally carbonyl group of amide(6) appear at 154.50 ppm

The APT technique in Figure (2.6 d) showed all carbons (1, 2, 3, 4, 5, 6) in the up .

The IR, ^{1}H-NMR, ^{13}C-Nmr, and APT, spectra of compounds (VII) are similar of compound (VI). different signal protons and carbons of cyclohexanone that appear in excess compared to cyclopentanone in the aliphatic region. The fragmentation of compound (VII) is shown in scheme (2.11) , all these spectra are seen in the appendix page (118-127)



Scheme (2.11) The fragmentation of compound (VII)

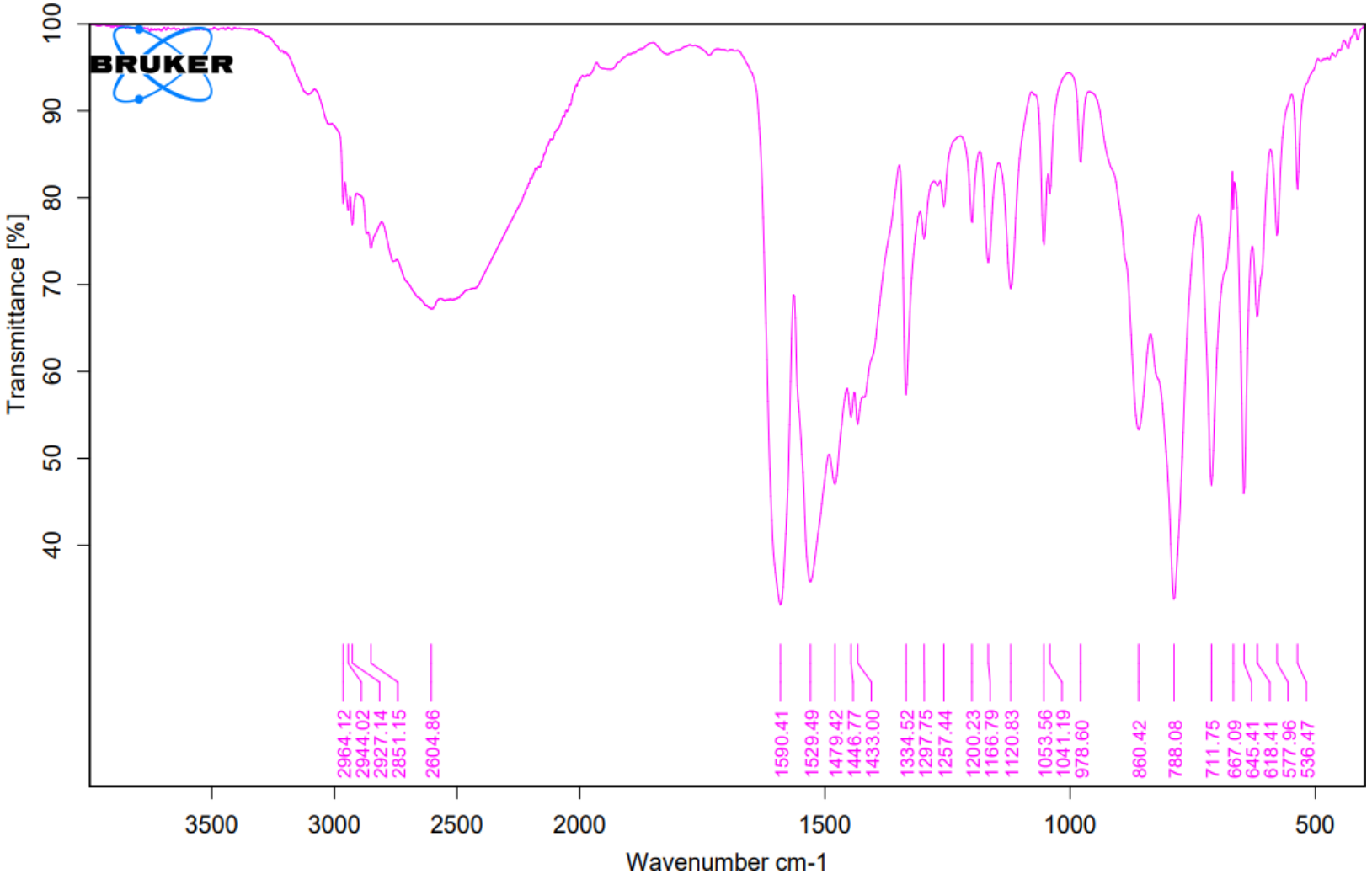


Figure (2.6 a) FT- IR spectrum of compound (VI)

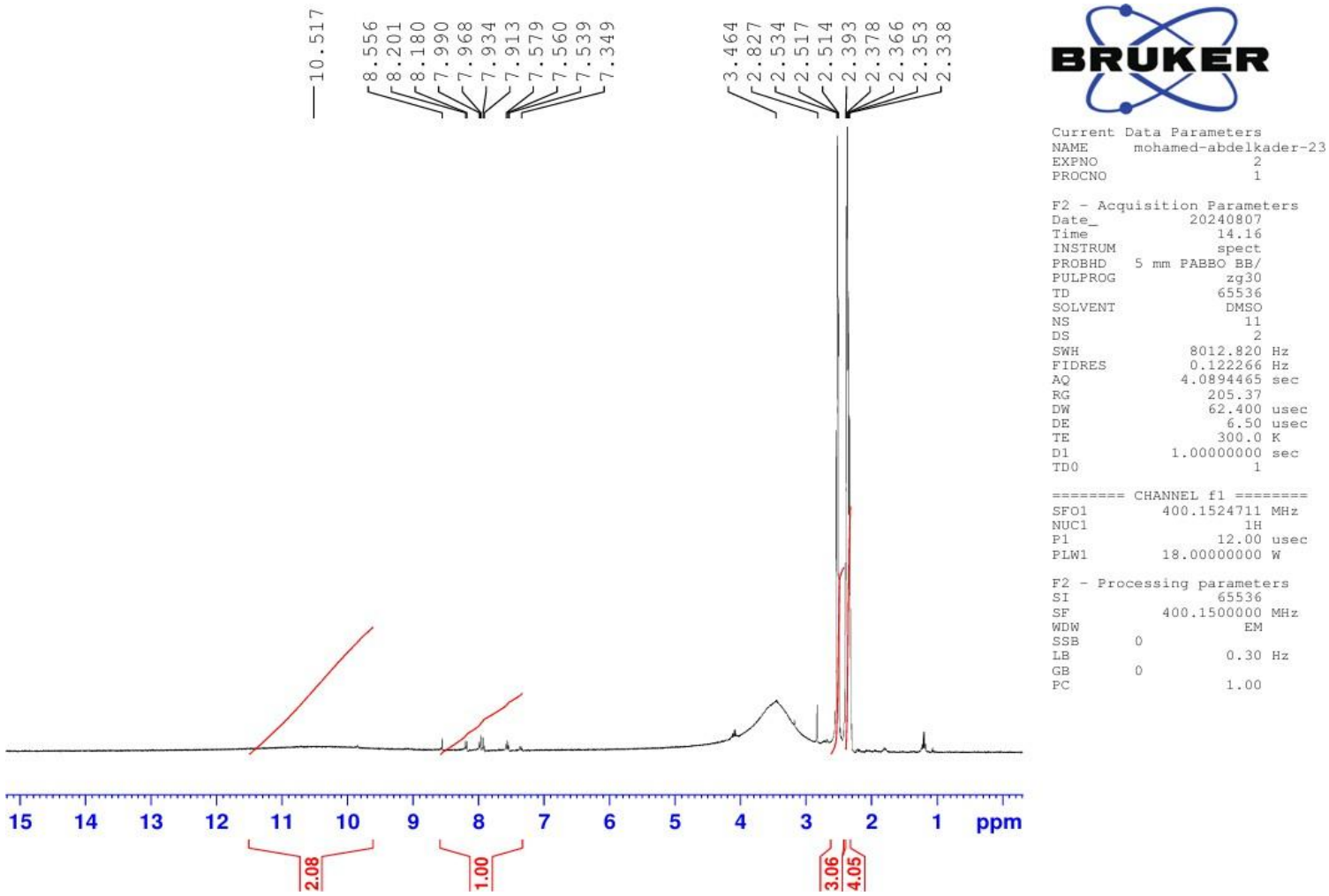


Figure (2.6 b) ^{1}HNMR spectrum of compound in DMSO-d_6 (VI)

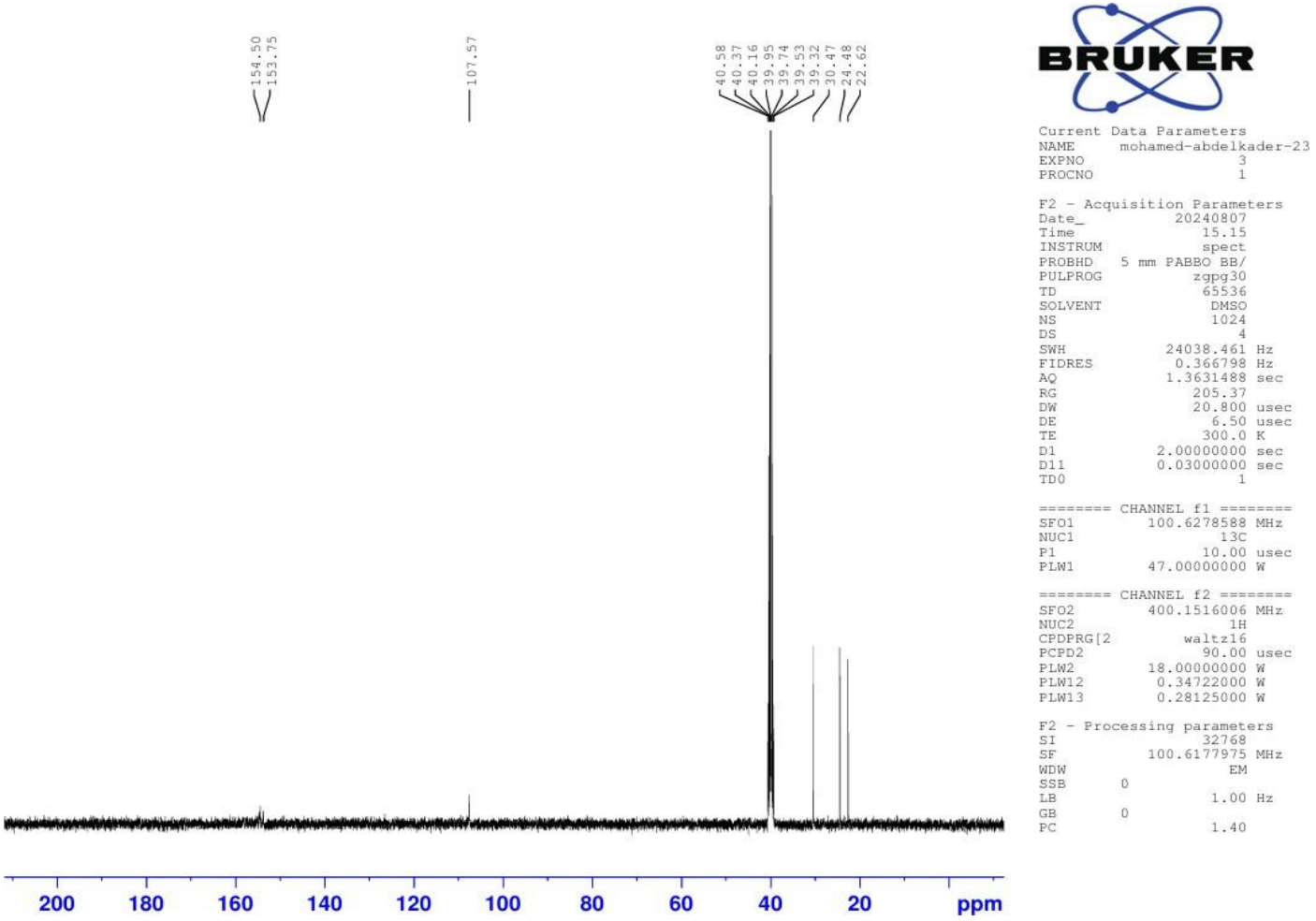


Figure (2.6 c) C^{13}-NMR spectrum of compound (VI) in DMSO-d_6

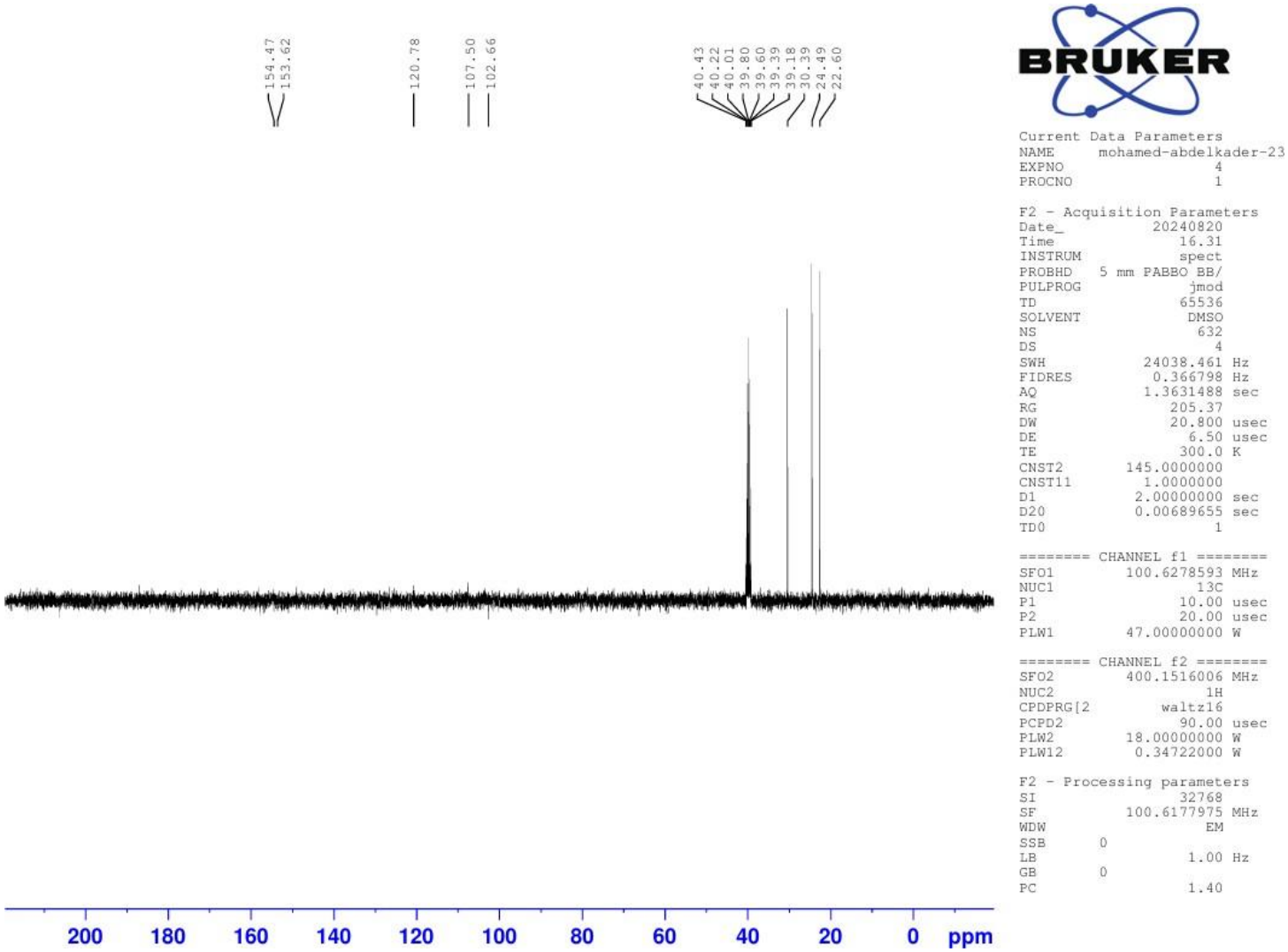
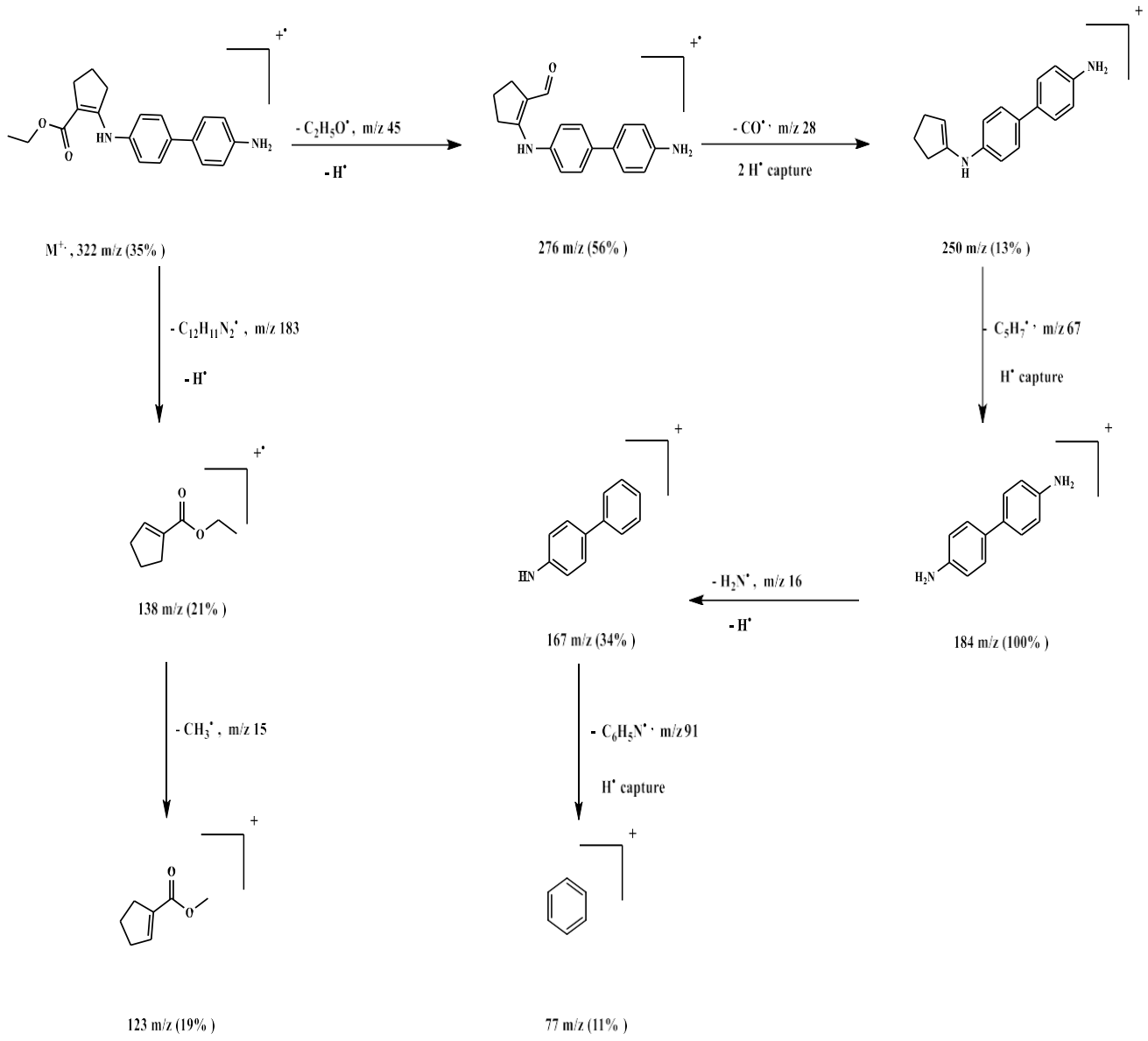
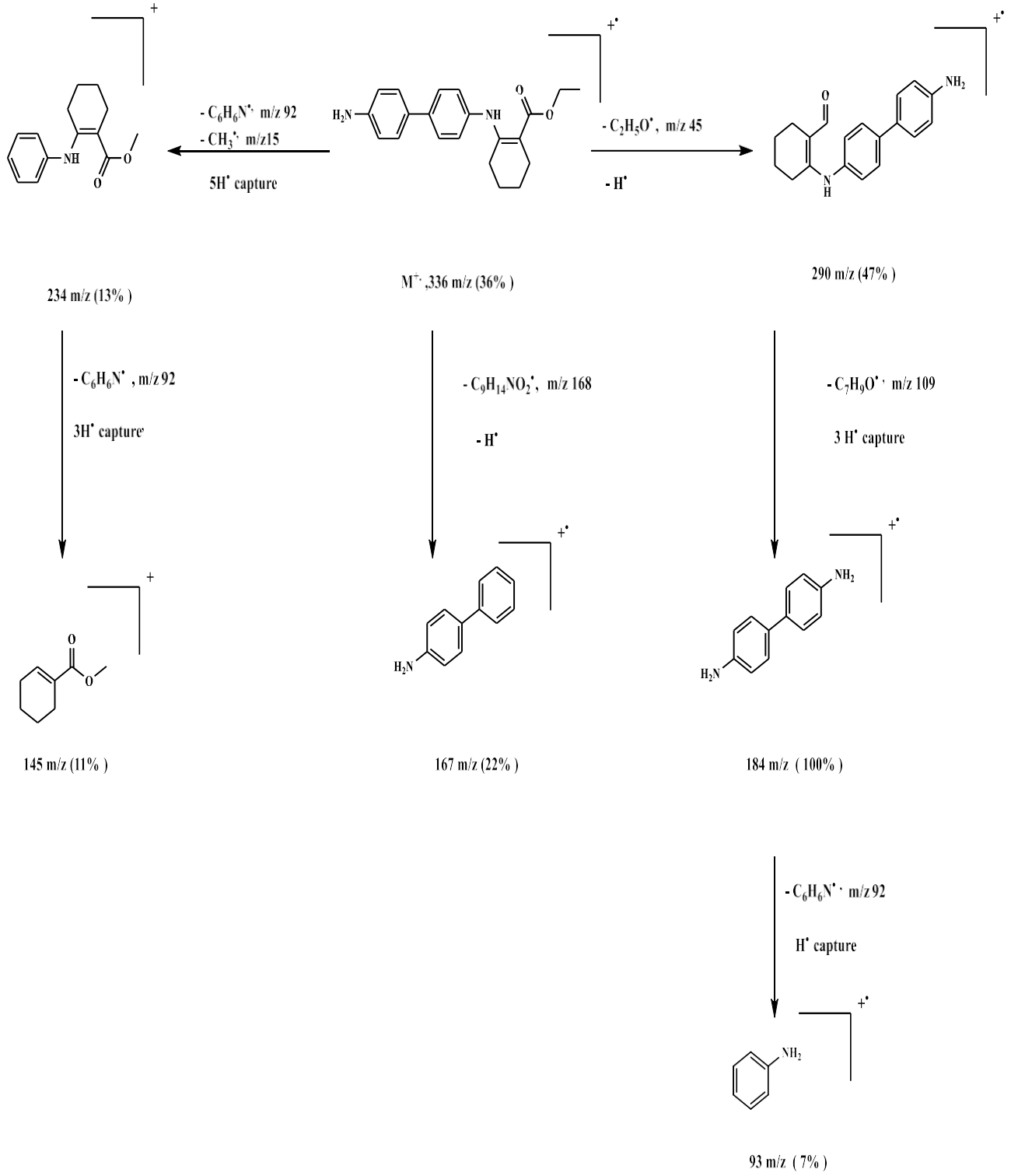


Figure (2.6 d) APT spectrum of compound (VI) in DMSO-d_6

The IR spectra of compounds (VIII), (IX), and (X) display general similarities to that of compound (I), but they also exhibit distinct absorption bands attributed to the stretching vibration of the (=CH) group and aromatic C=C bonds. Furthermore, the ^{1}H NMR, ^{13}C NMR, APT, and D_2O spectra of compounds (VIII), (IX) and (X) are comparable to that of compound (I), with notable differences. In the aliphatic region, signals corresponding to the protons and carbons of the cyclohexanone ring appear more than those of the cyclopentanone ring. Additionally, aromatic protons resonate in the region of downfield ppm, while aromatic carbon signals are observed in the 110–140 ppm range, The fragmentation of compound (VIII), and (X) shows in scheme (2.12), (2.13) and , all these spectrum see in appendix page (128-140)

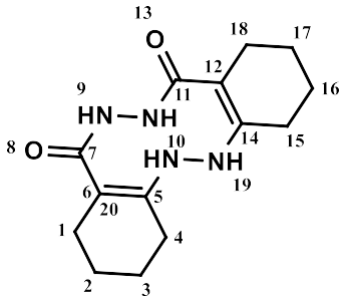


Scheme (2.12) The fragmentation of compound (VIII)



Scheme (2.13) The fragmentation of compound (X)

The reaction of ethyl 2-oxocyclopentane-1-carboxylate (15) with malonohydrazide resulted in the formation of multiple products, which could not be effectively separated by liquid-liquid extraction. In contrast, the reaction of ethyl 2-oxocyclohexane-1-carboxylate (23) with malonohydrazide yielded a single product, identified as the cyclic enamine compound (XI). The proposed reaction mechanism for the formation of compound (XI) is illustrated in Scheme (2.5).



The ^{1} H NMR spectrum of compound (XI) in DMSO-d_6 in figure (2.11 a) showed a multiplet signal at 1.63 ppm for the protons (3,2,16,17). A triplet siganle was shown at 2.22 for protons (4, 14 as equivalent protons) because of the resonance effect, and the absence of an ethoxy group, which confirms the attack on the ketone and then of the ester. Also, the triplet signal at 2.43 ppm has for protons (1,18). The NH signal (9, 10, 19, 20) appears as a singlet and is broad at 10.27 ppm. From this information, we note that it has indeed been formed of an enamine compound.

The D_2O spectrum in figure (2.11b) showed a disappearing proton for NH at 10.70 and a new

Carbon magnetic resonance spectral data of compound (XI) in figure (2.11c) showed a signal of carbons (2,17) appearing at 19.32 ppm as equivalent carbon. Followed by a signal of at 21.74, for carbons (3, 16) as equivalent carbon. and at 22.72 ppm appear signal of carbon (1, 18) as equivalent carbon. The carbons (4, 15) appear at 23.30 ppm as equivalent carbon. followed, the olefinic carbon attached by carbonyl of ester (12 ,6) appears at 99.03 ppm. while the olefinic carbon that connected with the amine appeared at 140.54 ppm. finally carbonyl group of ester (7, 11) appear at 159.04 ppm.

The APT technique in figure (2.11d) showed all carbons in the up direction .

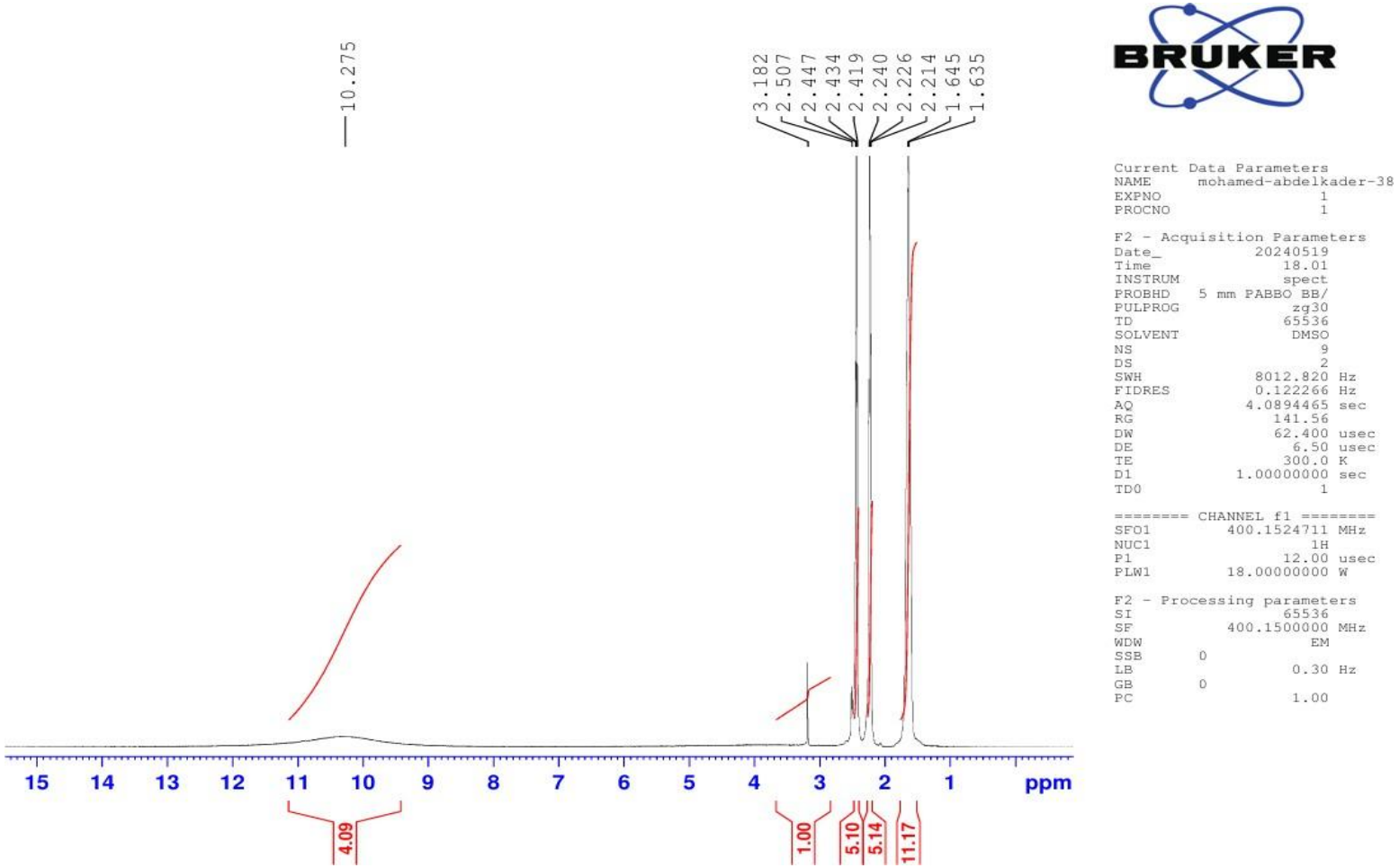



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Figure (2.11 a) ^{1}HNMR spectrum of compound (XI) in DMSO-d_6

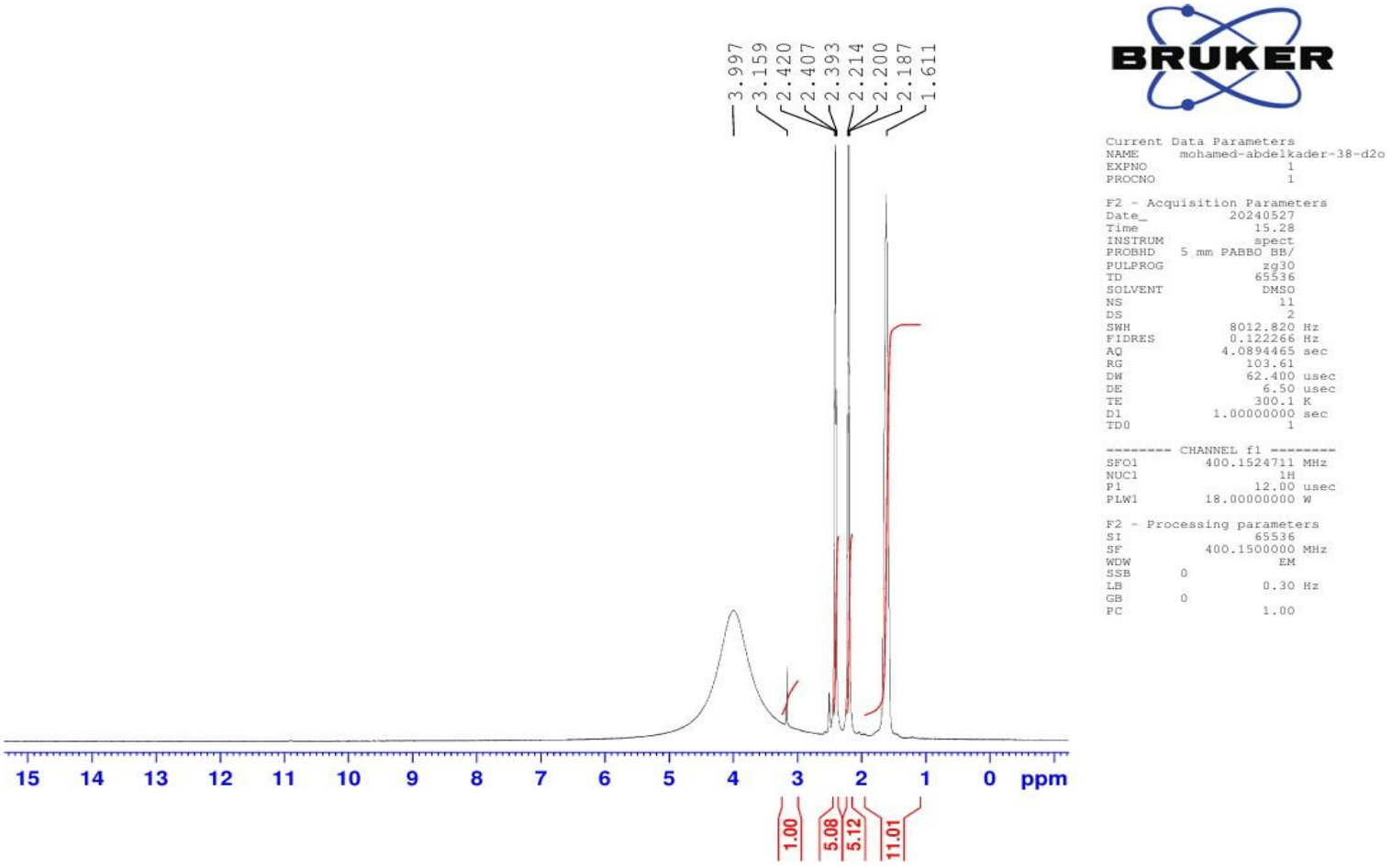


Figure (2.11 b) D_2O spectrum of compound (XI) in DMSO-d_6

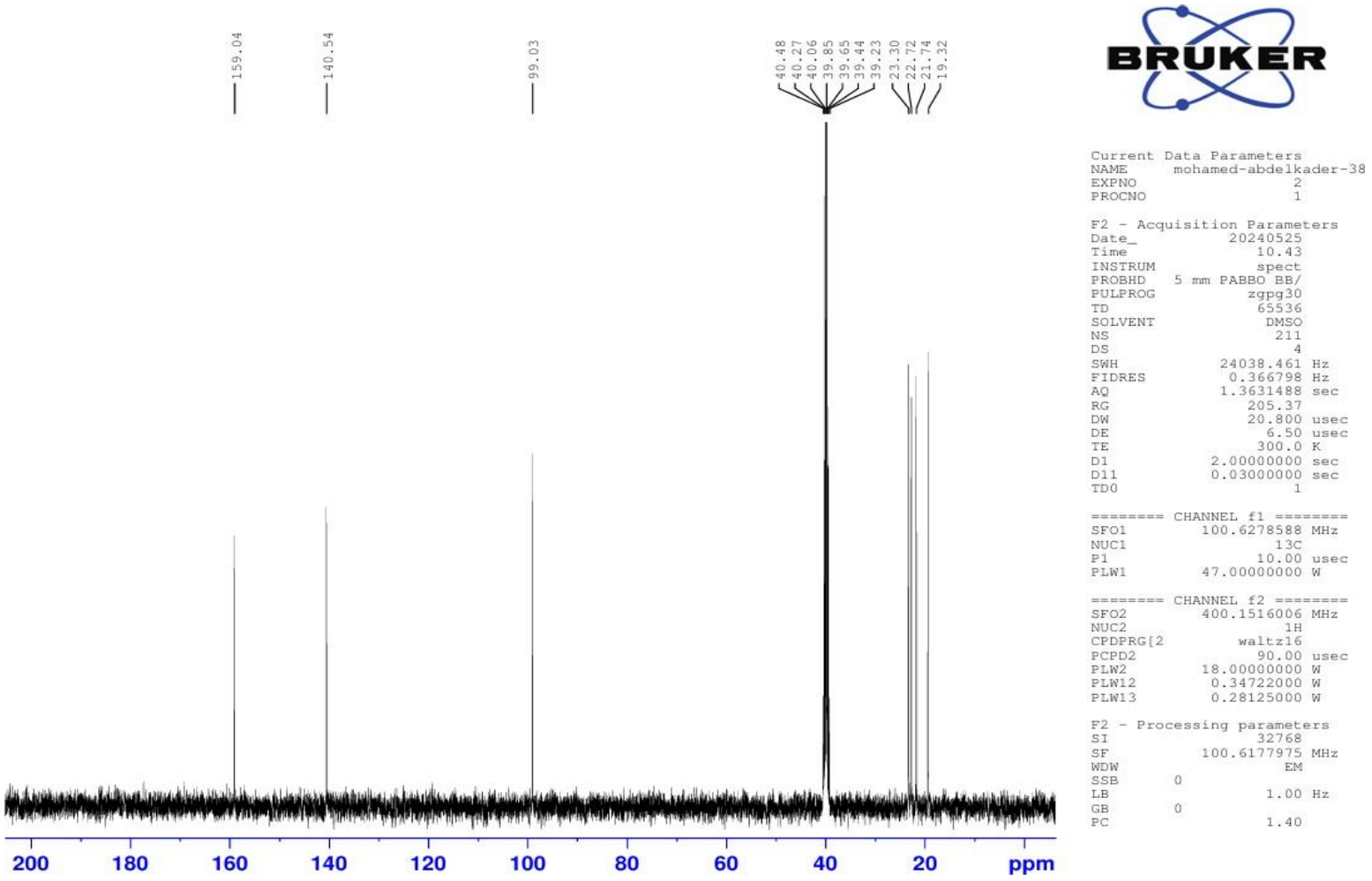
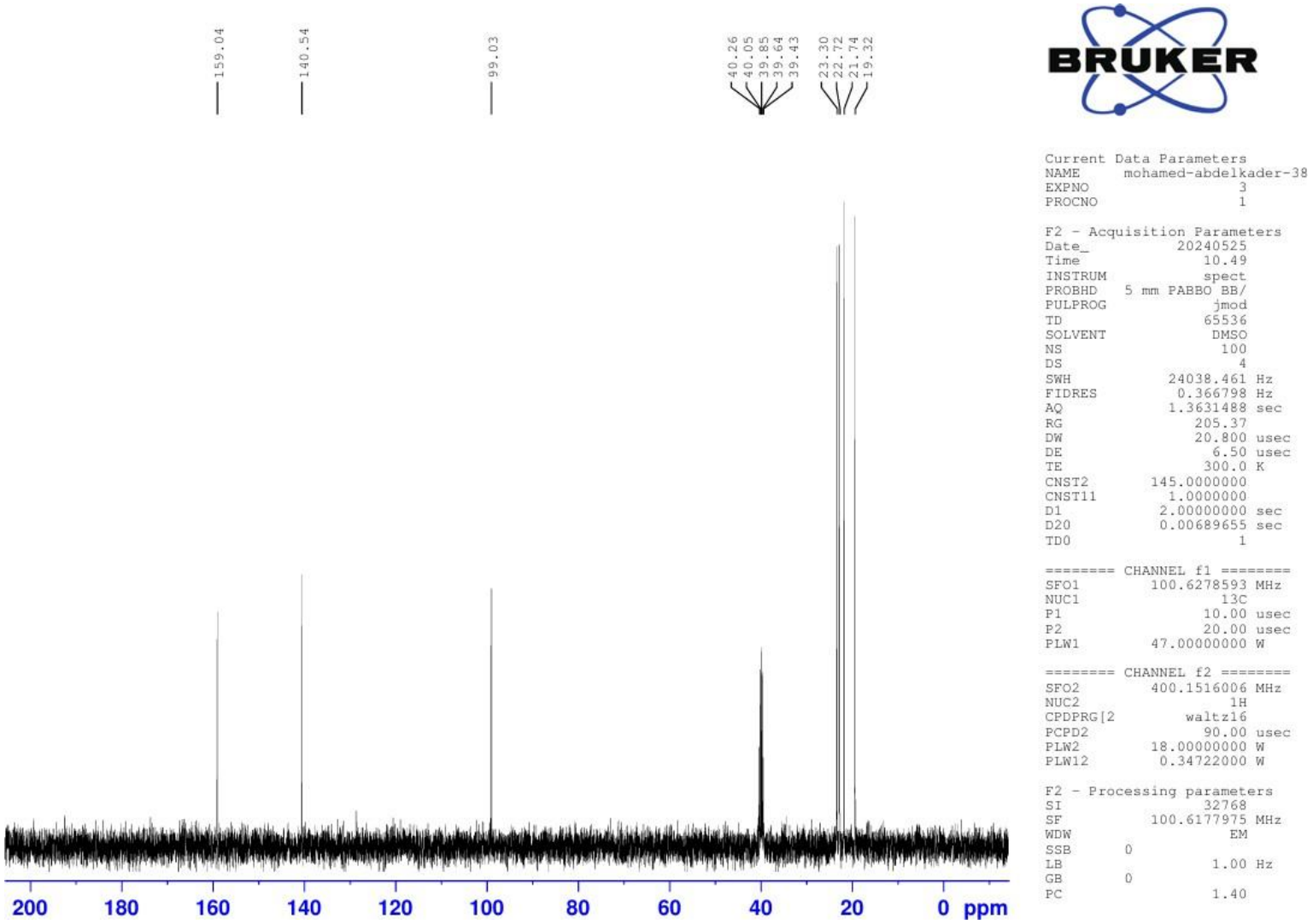


Figure (2.11 c) C^{13}-NMR spectrum of compound (XI) in DMSO-d_6

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CNST11             1.0000000
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CPDPRG[2             waltz16
PCPD2                 90.00 usec
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PLW12             0.34722000 W

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GB           0
PC                     1.40
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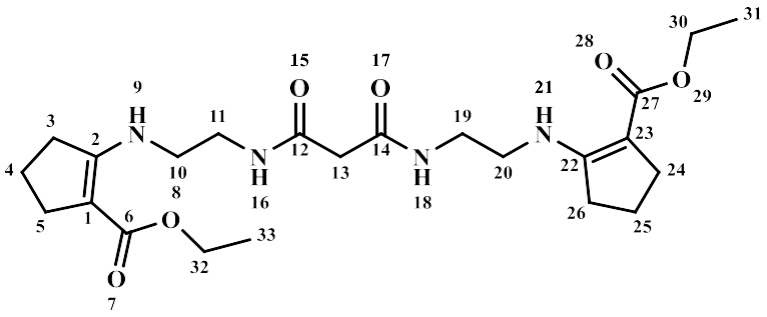
Figure (2.11 d) APT spectrum of compound (XI) in DMSO-d_6

The reaction of ethyl 2-oxocyclopentane-1-carboxylate (15) with N_1,N_3-bis(2-aminoethyl) malonamide resulted in one product of bis-enamine (XII) and one product with piprazine (XIII) , while ethyl 2-oxocyclohexane-1-carboxylate can not react with these amines because the cyclohexanone is low reactive than cyclopentanone a result ring strain due to its non-ideal bond angles and torsional strain for cyclopentanone, The spectrum analysis is shown in figure (2.12a) , (2.12b) , (2.13a) , (2.13c) , (2.13d)



The ^{1} H NMR spectrum of compound (XII) in DMSO-d_6 in figure (2.12 a) showed a signal at 1.16 ppm as triplet for protons (31, 33). and at 4.03 ppm appears signal as a quartet for protons (32, 30), which confirms presence ethoxy group in a compound. and at protons of cyclopentane (24, 25, 26,3,4,5) in regions 1.65 to 2.54 ppm as multiplet. And protons of (19,20 ,10, 11) appear in region 3.02 to 3.54 ppm as multiplet and followed protons (13) appear as singlet at, Finally, protons for enamine (18, 16) appear at 7.41 pm as singlet. followed by protons for (21, 9) as a singlet at 8.15 ppm.

Carbon magnetic resonance spectral data of compound (XII) in figure (2.12b) showed that of the, a signal of carbons (33, 31) appeared at 15.16 ppm. Followed by the 3 signals carbons (24, 25, 26, 3, 4, 5), which appear at 20.87, 29 .47, and at 31. 93 ppm.and carbons (19, 11) appear at 43.70 ppm. followed by carbons (20, 10) at 44 ppm. The carbon (13) appears at 45 .93 ppm. followed by a signal at 58.12 ppm for carbons (30, 32). The olefinic carbon attached by carbonyl of ester (23, 1) appeared at 91.83 ppm, while olefinic carbon attached by carbonyl of amine (2 ,22) appeared at 165.24 ppm. then carbonyl of amide (12, 14) is appeared at 167.62 ppm. Finally carbonyl of ester (6, 27) at 179.25 ppm.

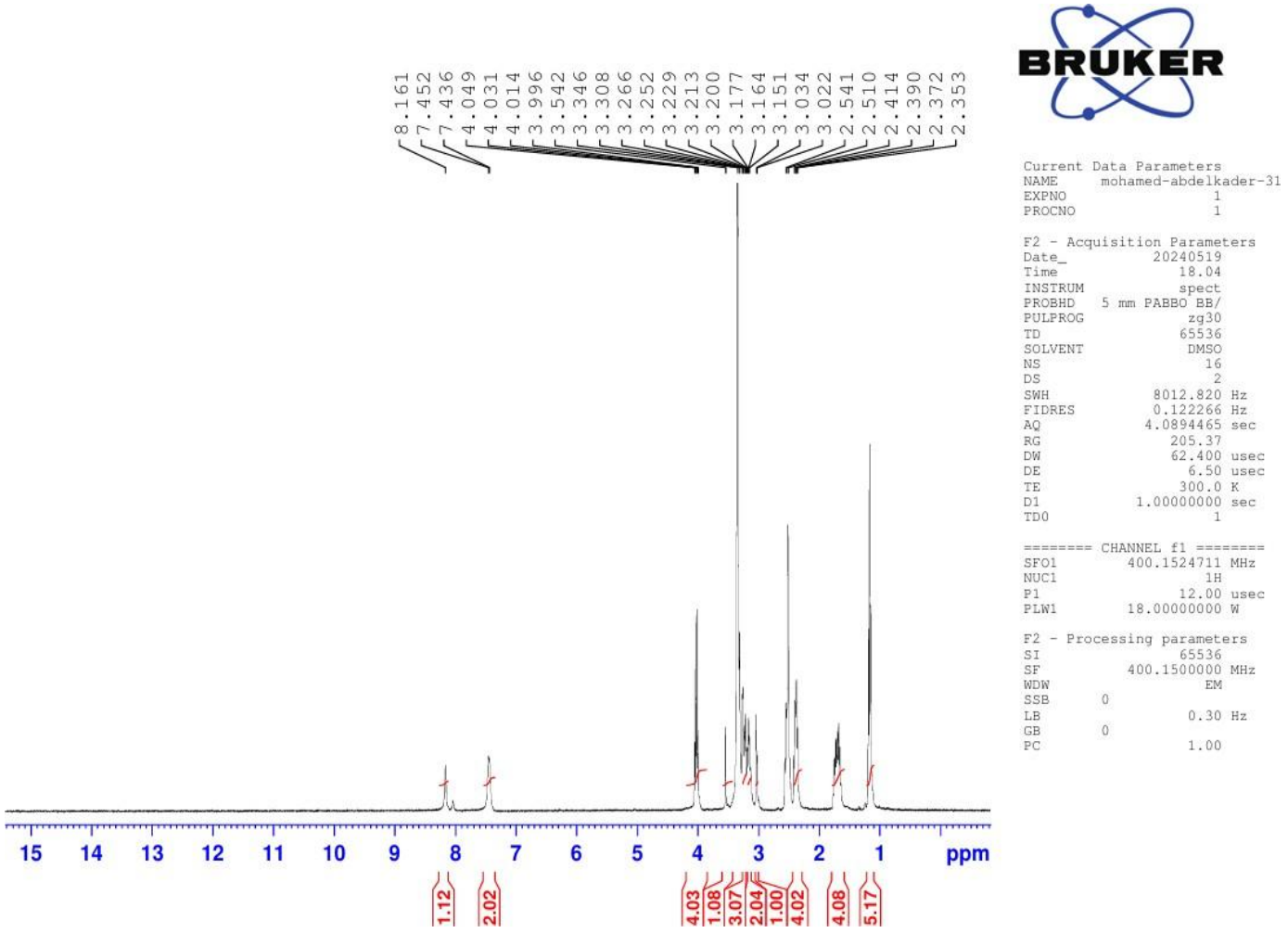


Figure (2.12 a) ^{1}HNMR spectrum of compound (XII) in DMSO-d_6

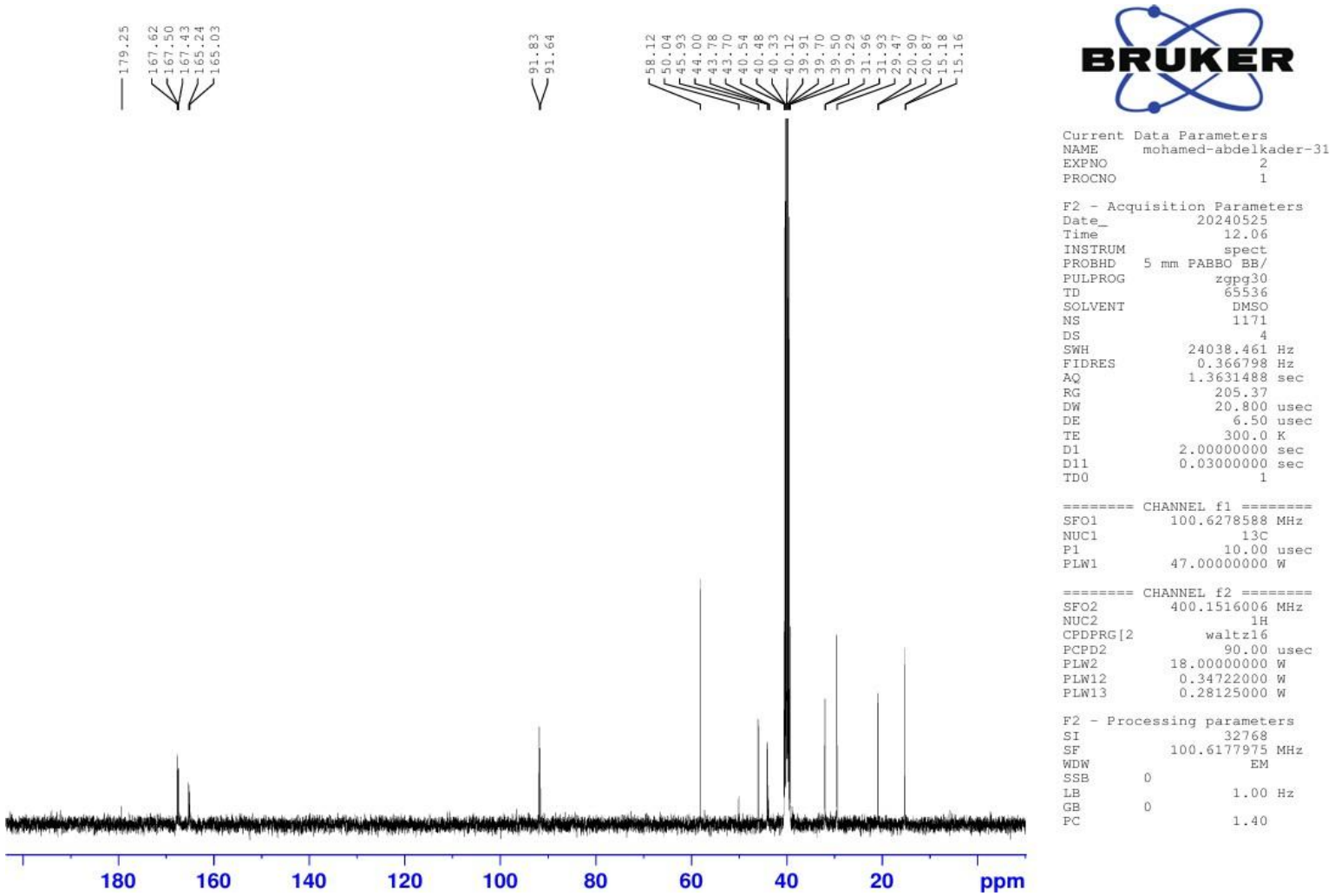
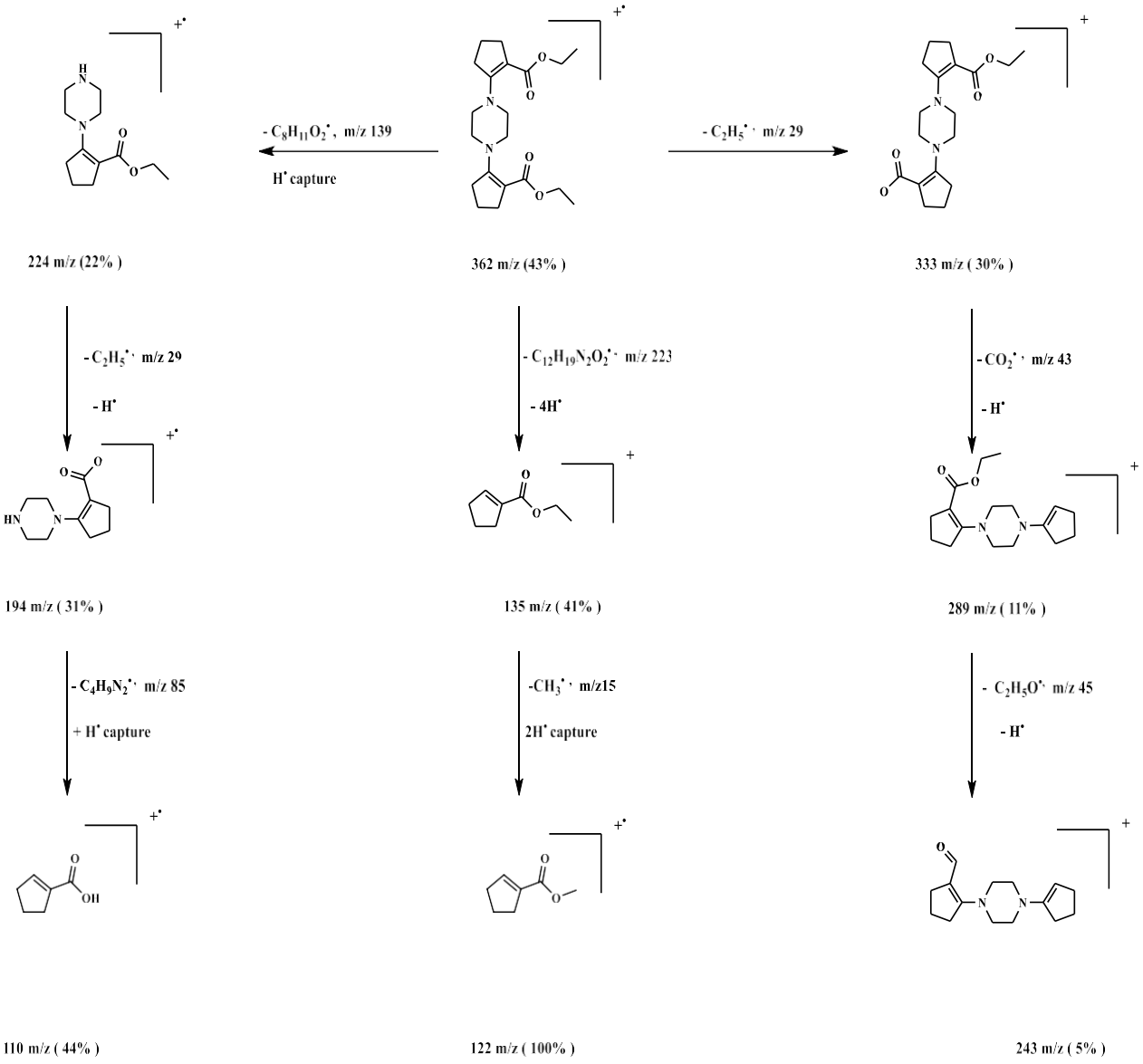


Figure (2.12 b) C^{13}-NMR spectrum of compound (XII) in DMSO-d_6

The IR spectrum of compound (XIII) is generally similar to that of compound (I), with the notable absence of the NH stretching absorption band, which confirms the successful formation of the bis-enamine structure. The ^{1}H NMR, ^{13}C NMR, and APT spectra also show overall similarity but with some distinct differences. In the aliphatic region, signals corresponding to the protons and carbons of the piperazine ring appear more prominently than those of the cyclopentanone ring. Additionally, a small peak is observed in the upfield region, which is attributed to dynamic interconversion caused by rotation around the sigma bond. The fragmentation of compound (XIII) is shown in scheme (2.14)



Scheme (2.14) The fragmentation of compound (XIII)

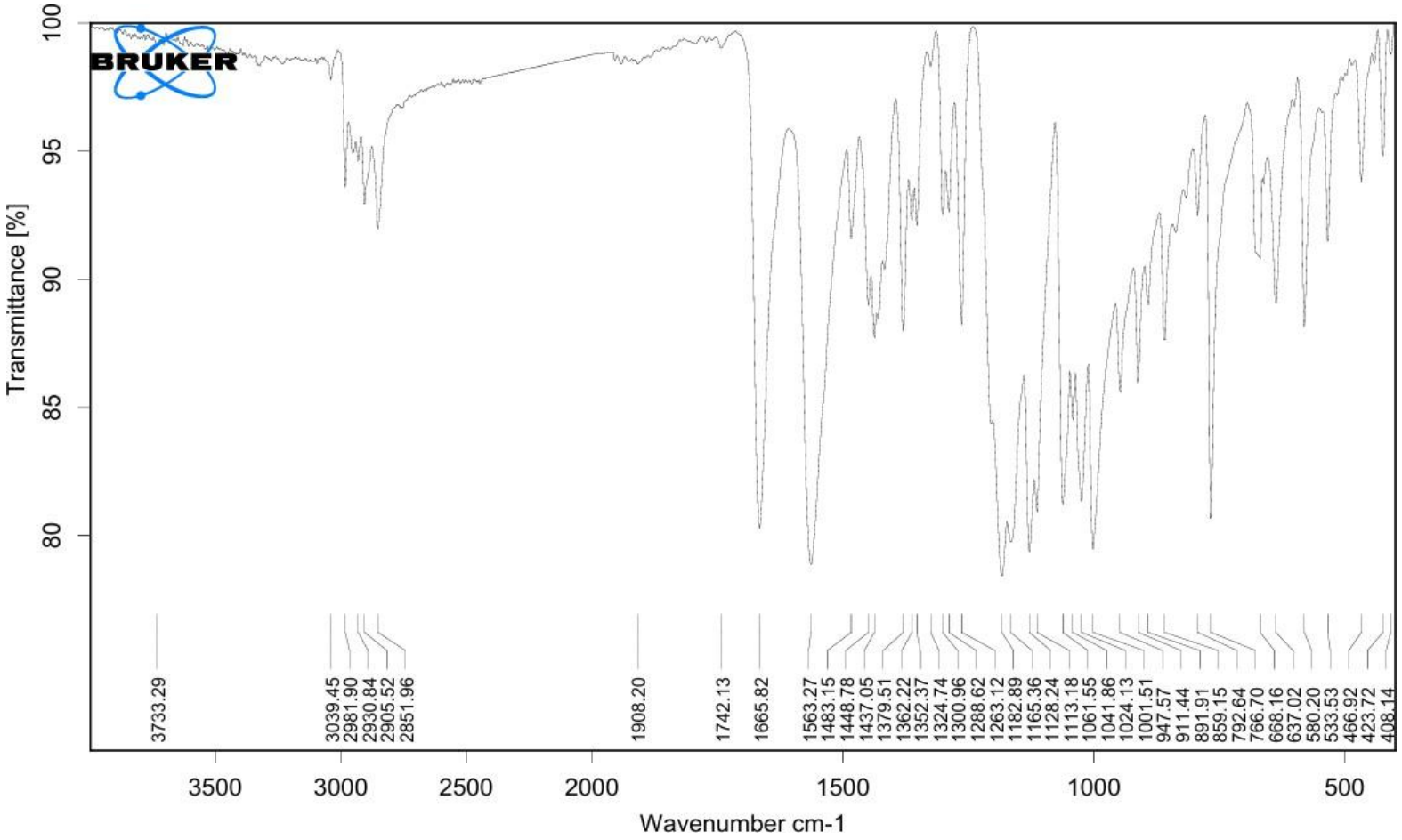


Figure (2.13 a) FT IR spectrum of compound (XIII)

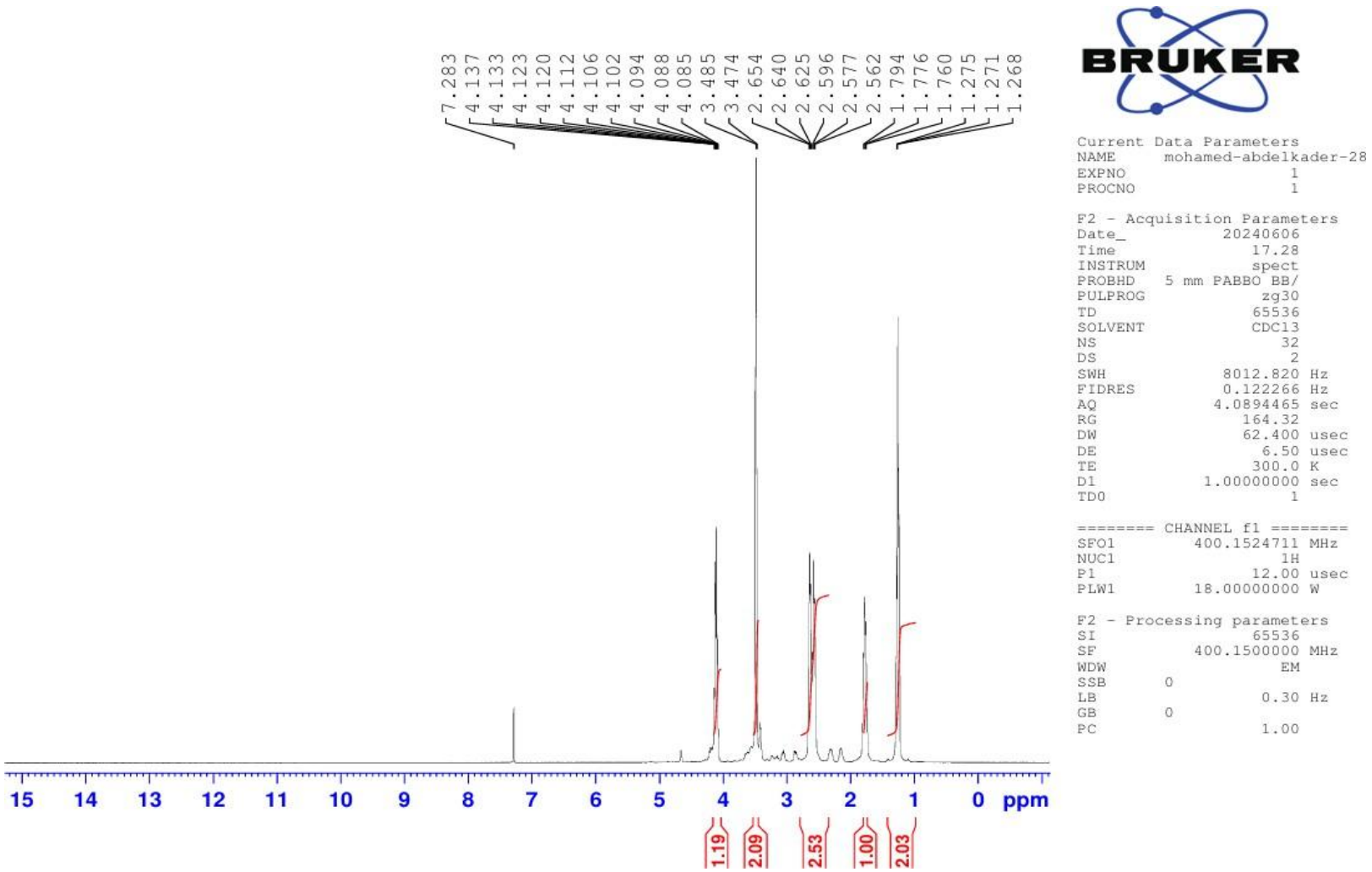
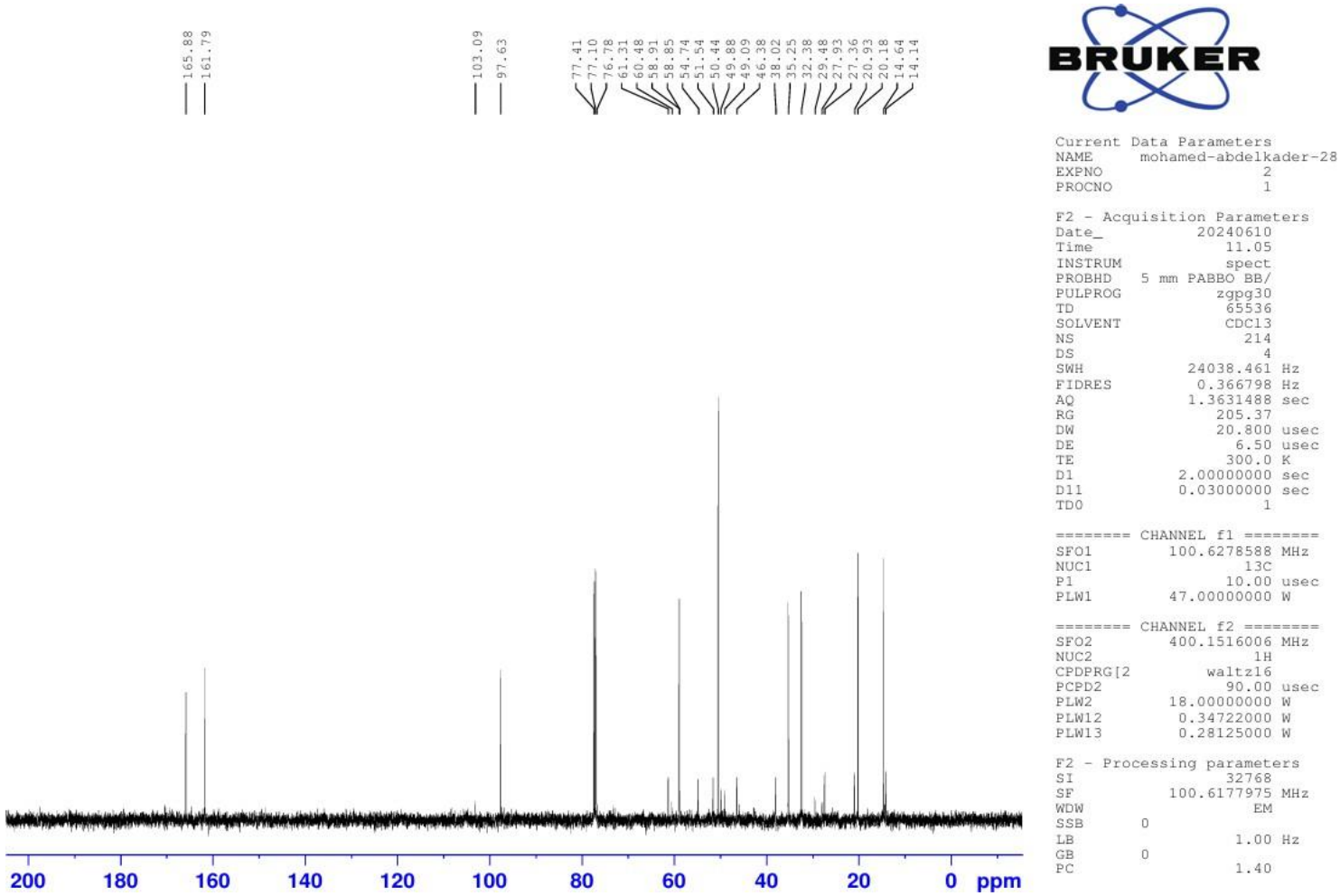


Figure (2.13b) ^{1}HNMR spectrum of compound (XIII) in $CDCl_3$



BRUKER

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TE                    300.0 K
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NUC2                    1H
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PLW2           18.00000000 W
PLW12           0.34722000 W
PLW13           0.28125000 W

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Figure (2.13c) C^{13}-NMR spectrum of compound (XIII) in $CDCl_3$

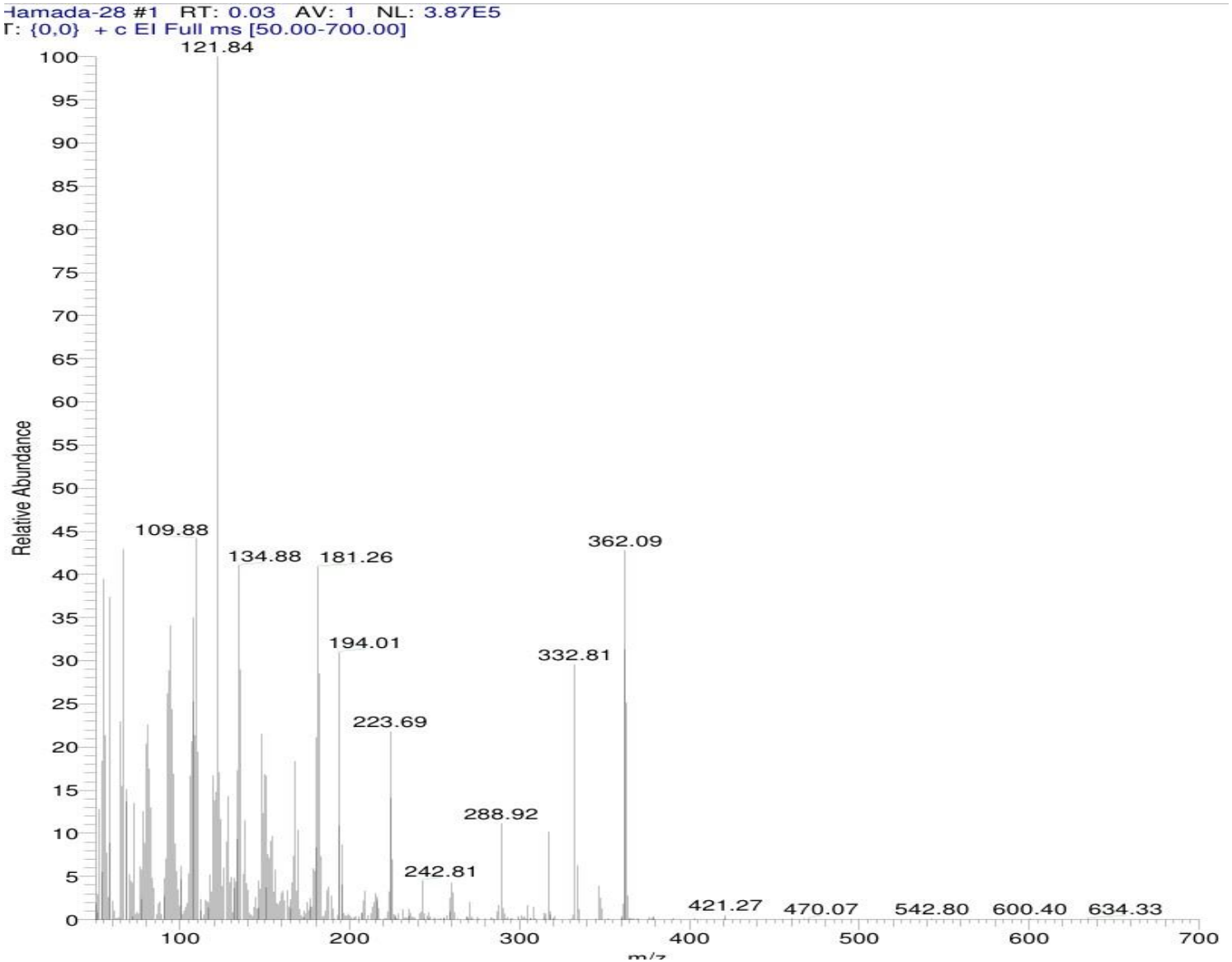


Figure (2.13d) Mass spectrum of compound (XIII)

2.1. Anti-bacterial activity

The antibacterial activity of the synthesized compounds was evaluated against four bacterial strains: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis*,using the well diffusion method. Ciprofloxacin (100 µg/mL) was used as a positive control and exhibited large inhibition zones (100 mm) against all tested bacteria, confirming the reliability and validity of the assay.

Upon analyzing the results:

- **All tested compounds displayed significantly lower antibacterial activity compared to ciprofloxacin.**
- Compounds **I, II, III, IV, V, XIII,** demonstrated similar levels of activity, with inhibition zones ranging between **5 and 8 mm**, indicating weak antibacterial effects against both Gram-negative and Gram-positive bacteria.
- **Compound VI** (1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3(2H)-one) showed the weakest antibacterial activity, with inhibition zones between **2 and 5 mm**, particularly against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, suggesting limited effectiveness.
- **Compound VII** (1,2,4,5,6,7-hexahydro-3H-indazol-3-one), despite containing the biologically potent indazole moiety, exhibited only modest antibacterial activity (4–5 mm) against all strains, indicating that further structural optimization may be necessary to enhance its antibacterial properties.

Additionally, Gram-negative bacteria (*E. coli* and *P. aeruginosa*) appeared relatively more susceptible to the tested compounds compared to Gram-positive strains (*S. aureus* and *E. faecalis*). This observation aligns with the known structural characteristics of bacterial cell walls, where the thick peptidoglycan layer in Gram-positive bacteria limits drug permeability and may contribute to reduced susceptibility.

Overall, although the tested compounds exhibited limited antibacterial effects, their basic activity suggests that further structural modifications—such as introducing more polar functional groups or enhancing cell wall permeability—may lead to the development of more potent antibacterial agents.

No of Compound	Bacteria Types			
	E.coli	*P.aeruginosa*	*S. aureus*	*E.faecalis*
	100	**100**	**100**	**100**
I	**6**	**5**	**8**	**6**
II	**6**	**5**	**8**	**6**
III	**6**	**5**	**8**	**5**
IV	**6**	**5**	**8**	**6**
V	**6**	**5**	**8**	**5**
VI	**4**	**2**	**2**	**5**
VII	**5**	**4**	**4**	**4**
XIII	**6**	**5**	**8**	**6**

Table2.1: **Anti-bacterial result**

2.2. Docking results

Compound	Binding affinity for Escherichia coli (3uu2) receptor	Binding affinity for Staphylococcus aureus(1vqq) receptor
I	-6.5	-6.7
II	-6.5	-7.2
III	-7.2	-7.6
IV	-7.2	-7.2
V	-6.8	-7.4
VI	-5.6	-5.6
VII	-5.9	-6.3
XIII	-6.9	-7.1

Table 2.2: Result of Molecular docking

This table shows that compound III has the highest binding affinity to the receptor 1VQQ, while compound IV and III shows the best binding affinity towards the 3UU2 receptor.

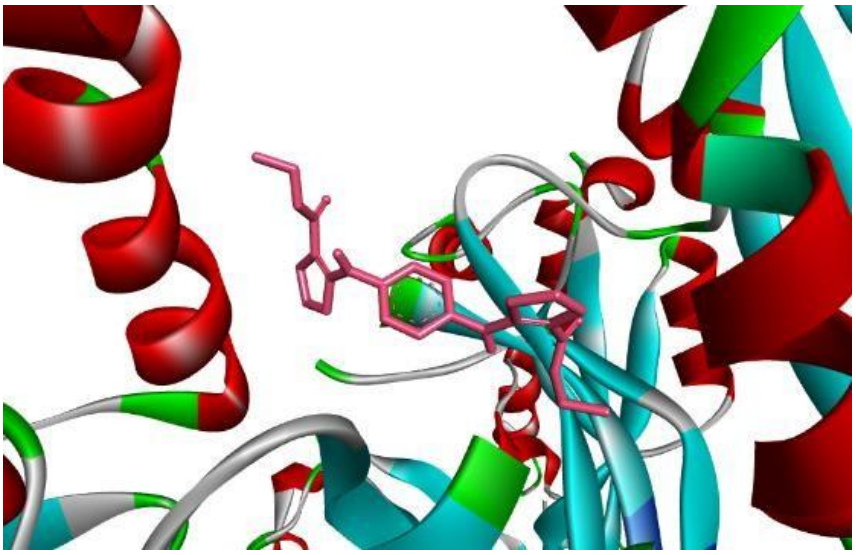


Figure (2.14a) shows the 3D interaction between compound III and the IVQQ RECEPTOR

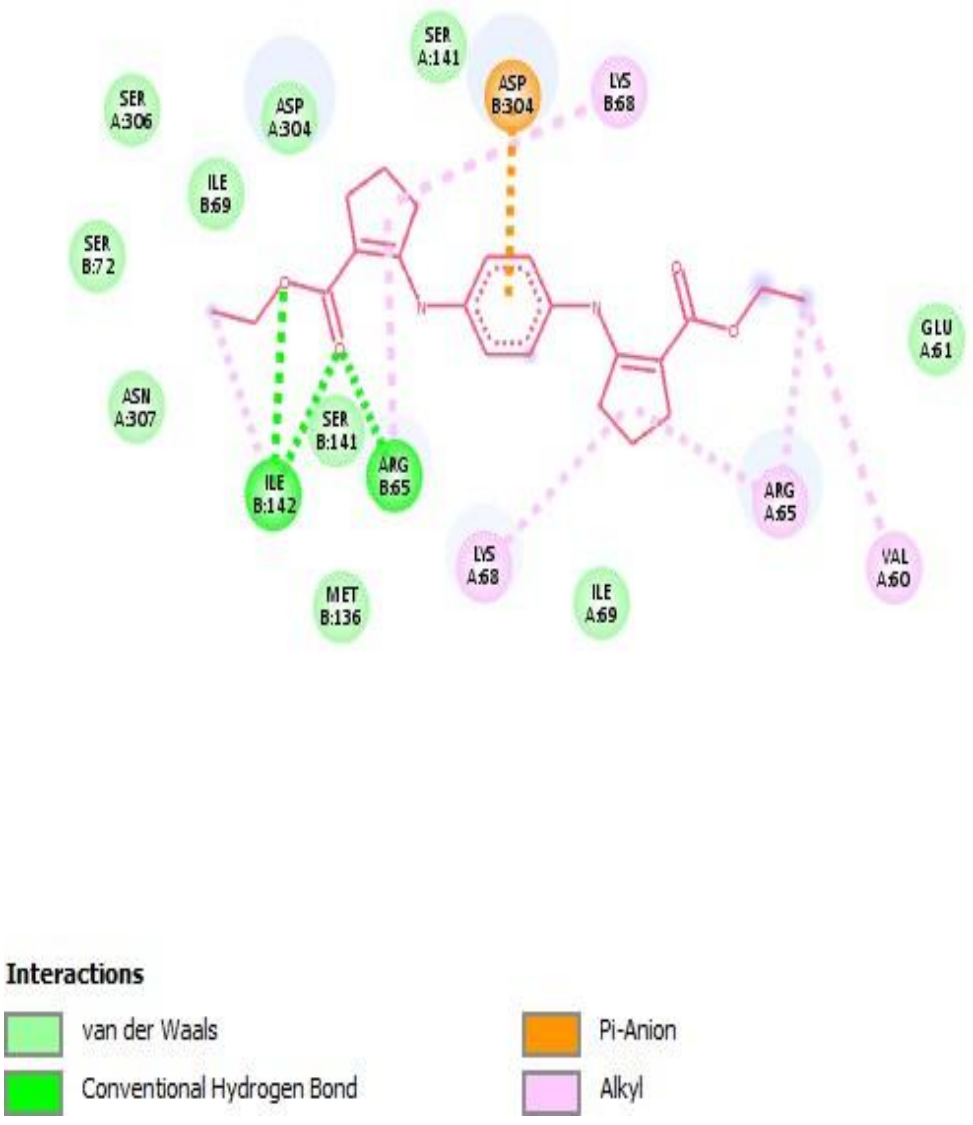


Figure (2.14b) shows the interacting atoms and the bonds between compound III and the receptor.

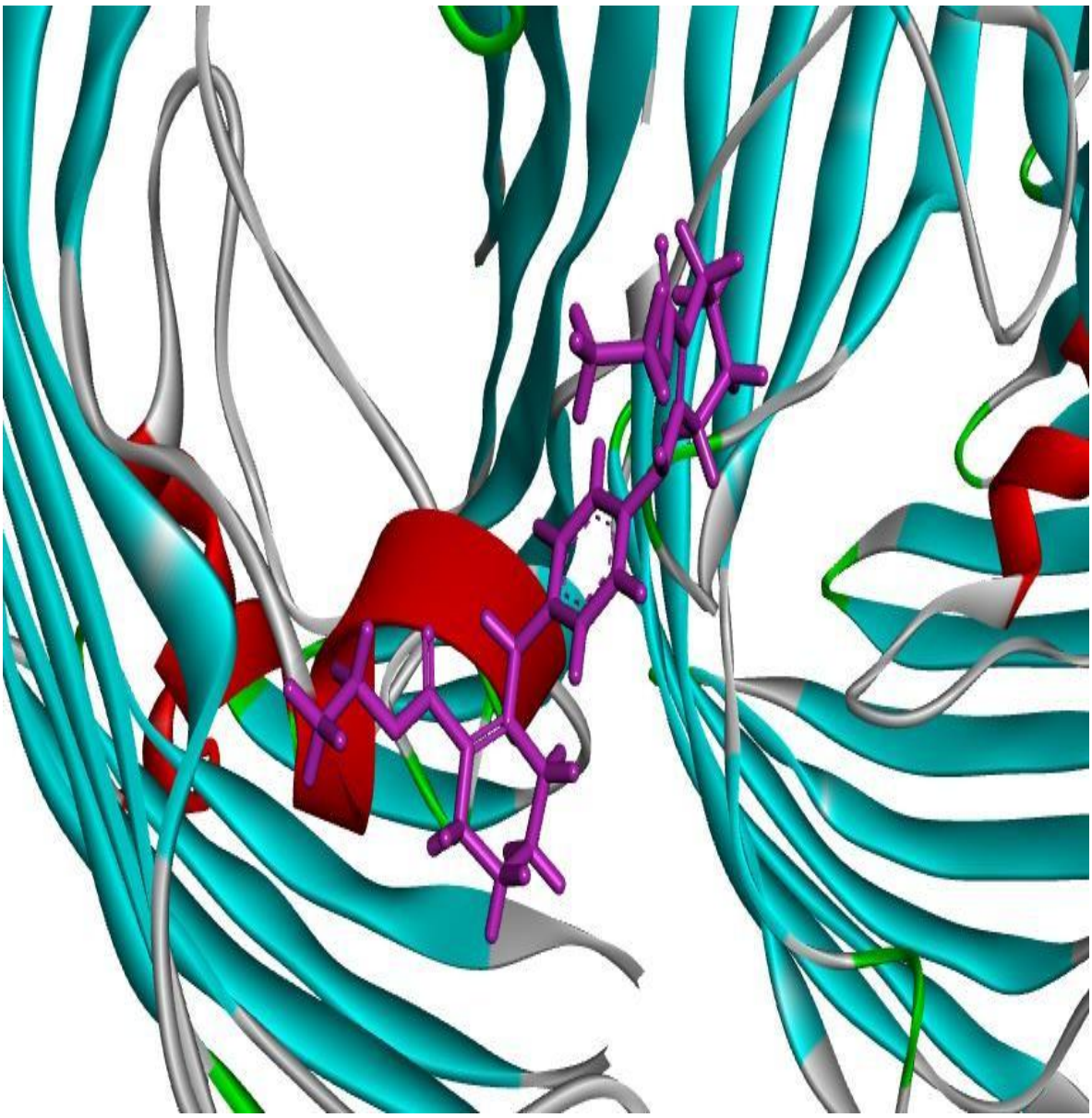


Figure (2.14c) shows the 3D interaction between compound IV and the 3uu2 receptor

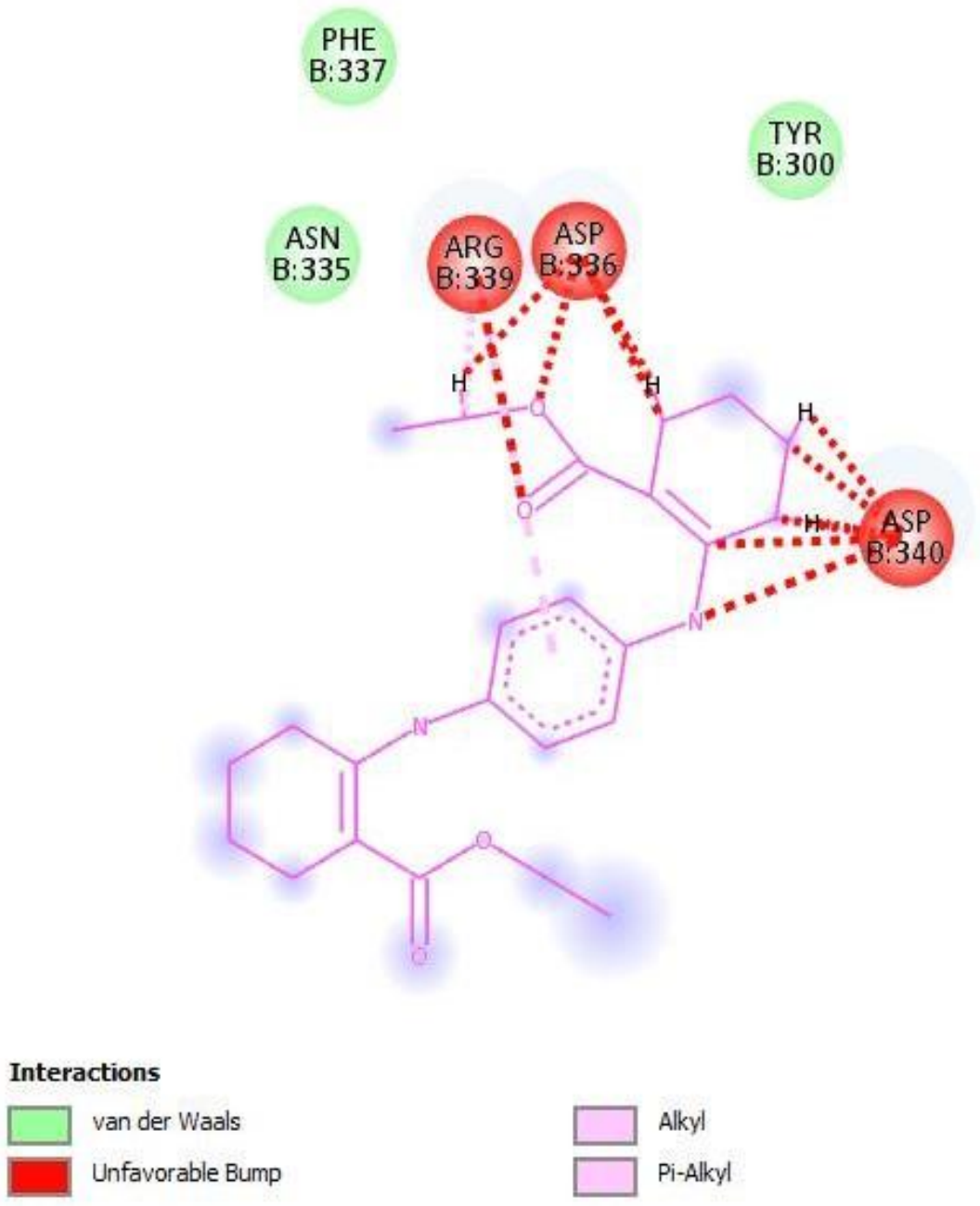


Figure (2.14d) shows the interacting atoms and the bonds between the compound IV and the receptor

2.3. Conclusion

In this study, a novel series of enamine derivatives was efficiently synthesized through the condensation of ethyl 2-oxocyclopentane-1-carboxylate (compound 1) or ethyl 2-oxocyclohexane-1-carboxylate (compound 2) with various diamines under mild conditions, affording the target products in high yields. Structural characterization using spectroscopic techniques—including IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry—confirmed the successful formation of the desired enamine scaffolds. The reactivity of the starting materials was found to be strongly influenced by both the ring size of the cyclic β-keto esters and the structure of the diamine reagents. Compound 23, derived from the six-membered cyclohexanone ring, predominantly yielded single products when reacted with ethane-1,2-diamine, 1,4-phenylenediamine, and benzidine, following 1:2 or 1:1 stoichiometries depending on the diamine. In contrast, reactions involving hydrazine hydrate or malonohydrazide led to the formation of cyclic products due to their bifunctional nucleophilicity, Compound 15, containing the more strained five-membered cyclopentanone ring, exhibited significantly higher reactivity, which in certain cases led to competing reaction pathways. For example, its reaction with benzidine afforded a mixture of 1:1 and 1:2 adducts, whereas treatment with hydrazine hydrate resulted in both pyrazolone and enamine derivatives. Nevertheless, reactions with other diamines proceeded selectively to give single 1:2 adducts. These findings underscore the crucial role of ring strain and steric hindrance in dictating the course of the reactions, with the cyclopentane-derived compound (15) showing a stronger propensity for multiple addition and cyclic product formation compared to the cyclohexane analogue (23) ,To evaluate the biological potential of the synthesized compounds, eight selected derivatives were tested for antibacterial activity against four bacterial strains—two Gram-positive and two Gram-negative—at a fixed concentration of 100 ppm. The inhibition zones observed ranged from approximately 5 to 8 mm. Among the tested compounds, the cyclic enamine derivative displayed the lowest antibacterial efficacy. Complementary computational studies were performed to assess the binding affinities of the synthesized compounds with two previously identified target proteins using molecular docking techniques. The compound derived from the reaction of *p*-phenylenediamine with cyclopentanone exhibited the highest binding affinity, which is attributed to the presence of an additional π-anion interaction that contributed to enhanced molecular recognition and stability within the active site.

Chapter 3

Experimental

3. Experimental

3.1. Instrumental:

3.1.1. Melting points:

Melting points (m.p) of the synthesized compounds were determined in capillary tubes using a Stuart Scientific melting point apparatus and are uncorrected.

3.1.2. Chromatography:

Analytical glass and aluminum plates were used with Silica gel G or GF 254 (Merck). The plates were run in the following systems:

1. Ethyl acetate.
2. Methanol – Hexane (different ratios)
3. Chloroform – Hexane (different ratios) , and examined under ultra-violet light Model UV GL-58/50 Hz Lampe

3.1.3. ^{1}H-NMR

Proton magnetic resonance spectra were carried out in the Centre for Drug Discovery Research & Development at Ain Shams University and proudly introduces deuterochloroform ($CDCl_3$) and hexadeuterodimethylsulfoxide (DMSO-d_6) solutions, on Brucker 400 MHz instruments, with chemical shift (δ) expressed in ppm downfield from tetramethyl silane as internal stand. The multiplicity of the signal is as follows: s (singlet), d (Doublet), t (Triplet), q (Quartet), m (multiplet).

3.1.4. ^{13}C-NMR

^{13}C-NMR spectra were carried out in the Centre for Drug Discovery Research & Development at Ain Shams University, proudly using 100 MHz and an internal reference

3.1.5. IR-Spectroscopy:

IR (KBr) measurements were made and recorded on the National Research Centre -Douqi . The positions of absorptions have been expressed in wave number units (cm^{-1}).

3.1.6 Mass spectroscopy

Mass spectroscopy was done using direct inlet in National Research Centre -Douqi mode : EI, Ionization voltage 70 ev

3.2. Solvents and Chemicals:

The following solvents and chemicals were used without further purification. The list of chemicals is shown in (Table 3.1).

Table (3.1): Solvents and chemicals used in the study.

Solvents and chemicals	Molecular formula	Company
Ethanol (99.9%)	C_2H_5O	MRS
Methanol (99.9%)	CH_4O	Fisher
Chloroform (99.5%)	$CHCl_3$	Euromedex
Acetone (99.5%)	CH_3COCH_3	Loba
Diethyl ether (98%)	$C_2H_5OC_2H_5$	CDH
Ethyl acetate (99%)	$C_4H_8O_2$	T-Baker
Hexane	C_6H_{14}	Sigma-Aldrich
ethyl 2-oxocyclopentane-1-carboxylate	$C_8H_{12}O_3$	Tcl chemicals
ethyl 2-oxocyclohexane-1-carboxylate	$C_9H_{14}O_3$	Alfa Aesar
malonic ester	$C_3H_4O_4$.	Sigma-Aldrich
Hydrazine hydrate	N_2H_6O	Merck
ethane-1,2-diamine	$C_2H_8N_2$	Acros Organics
Piperazine	$C_4H_{10}N_2$	Sigma-Aldrich
Benzidine	$C_{12}H_{12}N_2$	Tcl chemicals
benzene-1,4-diamine	$C_6H_8N_2$	Alfa Aesar

3.3.1 Reaction of cyclic beta-ketoesters with diamines.

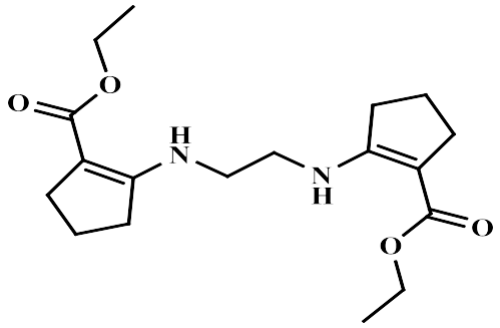
General procedure:

Two equivalents of ethyl 2-oxocyclopentane-1-carboxylate or ethyl 2-oxocyclohexane-1-carboxylate were added to one equivalent of the diamine and placed in a 100 ml beaker without any solvent, and the mixture was stirred at r.t. The solid formed was filtered and washed with ethanol, then dried on vacuum, giving a different color precipitate. The precipitate was recrystallized from ethanol to give compounds (I, II, V, VI, VII, XIII)

Table 3.2: The melting point, % yields and Color of synthesized compounds(I-II-V-VI-XIII)

Compounds	Yield (%)	m.p. (ºC)	Color	Reaction.time
I	36	110ºC	**White**	3h
II	**87**	**70-72 ºC**	**White**	48h
V	**14**	**71-73 ºC**	**Yellow**	72h
VI	**82**	**Dec at 245 ºC**	**yellow**	72h
VII	**48**	**Dec at 270ºC**	**white**	10min
XIII	85	113ºC	white	24h

diethyl 2,2'-(ethane-1,2-diylbis(azanediyl)) bis(cyclopent-1-ene-1-carboxylate) (I).



Mo. Formula: $C_{18}H_28N_2O_4$ (M.W = 336g/mol).

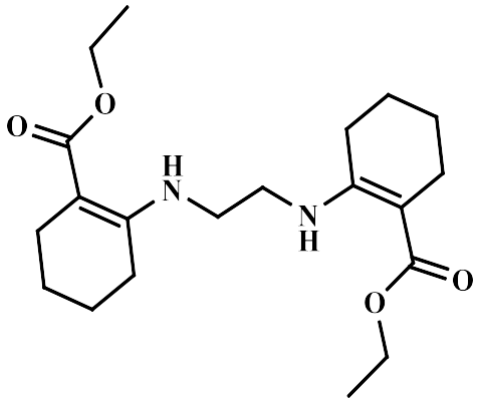
FT-IR υ_{max}**:**1591.53 cm^{-1} (C=C), 1644.40 cm^{-1} (ester CO), and 2945.33 cm^{-1}(CH aliphatic), 3317.45 cm^{-1} (NH amine)

^{1}H-NMR ($CDCl_3$): δ 7.43 (2H, S, NH), 4.12 (4H, q, CH_2-CH_3), 3.29 (4H, S, CH_2-NH),2.47 -2.41 (8H, dd, CH_2), 1.79 – 1.74 (4H, m, CH_2), 1.26 (6H, t, CH_3-CH_2)

^{13}C-NMR($CDCl_3$): δ 168.45 (CO), 164.16 (C=C-NH), 93.82, 58.49, 46 .00, 31.94, 29.07, 20.88, 14.68

MS EI m/z: $M^{+\cdot}$336, 168, 291, 245, 122, 94

diethyl 2,2'-(ethane-1,2-diylbis(azanediyl)) bis(cyclohex-1-ene-1-carboxylate) (II).



Mo. Formula: $C_{20}H_{32}N_2O_4$ (M.W = 364g/mol).

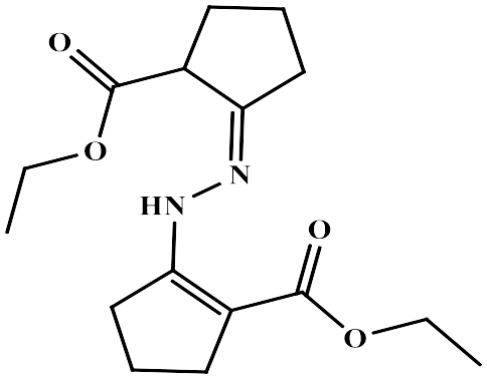
FT-IR υ_{max}: 1582.55 cm^{-1} (C=C), 1637.54 cm^{-1} (ester CO),), and 2973.32 cm^{-1}(CH aliphatic), 3252.81 cm^{-1} (NH amine)[1].

^{1}H-NMR ($CDCl_3$): δ 8.99 (2H, S, NH), 4.12 (4H, q, CH_2-CH_3), 3.29 (4H, dd, CH_2-NH), 2.26 (8H, m, CH2), 1.62 (8H, m, CH_2), 1.26(6H, t, CH_3-CH_2).

^{13}C-NMR($CDCl_3$): δ 170.86 (CO), 159.03 (C=C-NH), 90.60, 58.66, 43 .09, 26.24, 23.81, 22.59, 22.26, 14.62.

MS EI m/z: $M^{+\cdot}$ 364, 320, 292, 264, 198, 183, 158, 155.

ethyl (Z)-2-(2-(2-(ethoxycarbonyl)cyclopentylidene)hydrazineyl)cyclopent-1-ene-1-carboxylate (V).



Mo. Formula: $C_{16}H_{24}N_2O_4$ (M.W = 308g/mol).

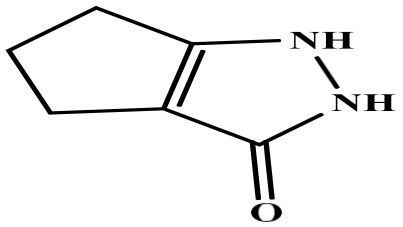
FT-IRυ_{max}: 1604.55 cm^{-1} (C=C) , 1647.36 and 1732.91 cm^{-1} (ester CO), , and 2996 cm^{-1}(CH aliphatic), 3259.78 cm^{-1} (NH amine)

^{1}H-NMR ($CDCl_3$): δ 10 (1H, S , NH), 4.14-4.26 (4H, m, CH_2-CH_3), 3.49 (1H, t , CH), 1.83-3.15 (12H, m, CH_2), 1.26-1.30(6H, m , CH_3-CH_2)

^{13}C-NMR($CDCl_3$): δ 173.54 (CO) , 169.42 (CO) , 161..20 (C=N) , 155.28 (N-C=C), 96 .15 (C=C), 61.97, 61.36, 38.06, 32.15, 27.38, 25.95, 25.91,23.22,21.44,14.67

MS EI m/z: $M^{+\cdot}$ 308, 263, 216, 188 , 160 , 108 , 80 .

1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3(2H)-one (VI)



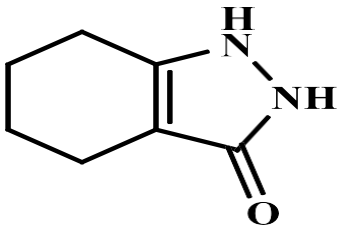
Mo. Formula: $C_6H_8N_2O$ (M.W = 124g/mol).

FT-IR (KBr) υ_{max}: broad band for OH from 3400 – 2500 cm^{-1}, 3000 cm^{-1} for CH aliphatic, and strong band at 1590 cm^{-1} for C=N, and at 1529 cm^{-1} for C=C

^{1}H-NMR ($CDCl_3$): δ 10.51 (2H, S,br, NH), 2.46 (2H, m, CH_2), 2.39-2.33(4H, m, CH2)

^{13}C-NMR($CDCl_3$): δ 154.50 (CO), 153.50 (C=C-NH), 107.50 (C=C-CO), 30.47, 24.48, 22.62

1,2,4,5,6,7-hexahydro-3H-indazol-3-one (VII)



Mo. Formula: $C_7H_{10}N_2O$(M.W = 138 g/mol).

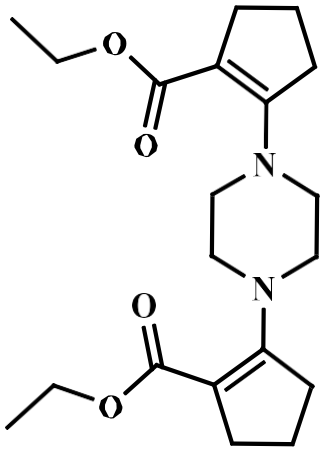
FT-IR (KBr) υ_{max}: broad band for OH from 3400 – 2500 $cm^{-1}$and a low frequency of 3000 cm^{-1} for CH aliphatic, and band at 1611 for NH binding cm^{-1}, and band 1560 cm^{-1} at for C=N, and at 1540 cm^{-1} for C=C.

^{1}H-NMR ($CDCl_3$): δ 10.26 (2H, br.S, NH), 2.5 (2H, t, CH_2), 2.41(2H, t, CH_2), 1.62 (4H, m, CH_2)

^{13}C-NMR($CDCl_3$): δ 158.95 (CO), 140.30 (C=C-NH), 98.94 (C=C-CO), 23.32, 22.75, 21.74,19.35.

MS EI m/z: $M^{+\cdot}$ 138, 110, 81.

diethyl 2,2'-(piperazine-1,4-diyl) bis(cyclopent-1-ene-1-carboxylate) (XIII)



Mo. Formula: $C_{20}H_{30}N_2O_4$ (M.W =362 g/mol).

FT-IR (KBr) υ_{max}: 1666.82 cm^{-1} (C=C), 1742.13 cm^{-1} (ester CO), and 2981.90 cm^{-1}(CH aliphatic).

^{1}H-NMR ($CDCl_3$): δ 4.13 (4H, q, CH_2-CH_3), 3.48 (6H, m, CH_2), 2.64(8H, m, CH_2), 1.79 (4H, m, CH_2) 1.26 (6H, t, CH_3).

^{13}C-NMR($CDCl_3$): 165.88 (CO), 161.79 (C=C-N), 103.09 (C=C-CO), 97.63(C=C-CO), 61.31 and 60.48, 49.88 and 49.09, 35.25 and 32.38, 20.93 and 20.18, 14.64 and 14.14.

MS EI m/z: $M^{+\cdot}$ 362, 333, 289, 224, 135, 243, 122, 194, 110.

3.3.2 Reaction of cyclic beta-ketoesters with di-amines.

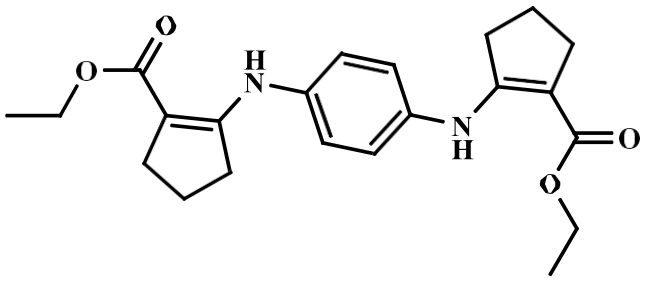
General procedure:

Two equivalents of ethyl 2-oxocyclopentane-1-carboxylate or ethyl 2-oxocyclohexane-1-carboxylate were added to one equivalent of the diamine with ethanol (20 ml), and the mixture was stirred and refluxing, The solid formed was filtered and washed with ethanol then dried on vacuum, giving a different color precipitate, the precipitate recrystallized from aquas ethanol to give compounds (III, IV, VIII, IX, X, XI, XII)

Table 3.3:The melting point , % yields and Color of synthesized compounds(III-IV-VIII-IX-X-XII)

Compounds	Yield (%)	m.p. (ºC)	Color	Reaction.time
III	**97**	**164-165ºC**	**purple**	8h
IV	**36**	**153-154ºC**	**gray**	72h
VIII	**12**	**169-170ºC**	**Yellow**	96h
IX	**18**	**154-160ºC**	**Yellow**	96h
X	**43**	**162-164ºC**	**Yellow**	144h
XI	**24**	**280-282ºC**	**White**	72h
XII	40	85-88ºC	White	48h

diethyl 2,2'-(1,4-phenylenebis(azanediyl)) bis(cyclopent-1-ene-1-carboxylate) (III)



Mo. Formula: $C_{22}H_{28}N_2O_4$ (M.W = 384g/mol).

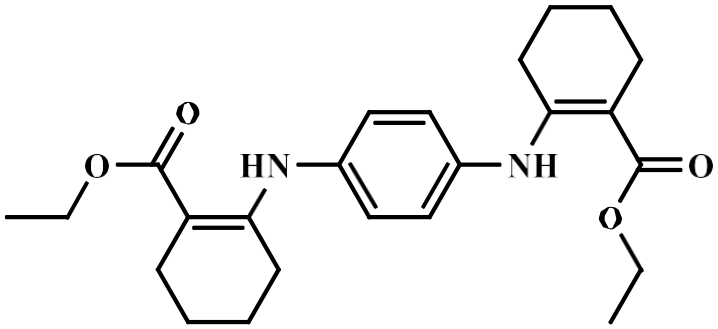
FT-IR υ_{max}**:** 1601.08 cm^{-1} (C=C), 1653.82 cm^{-1} (ester CO), and 2855.67 cm^{-1}(CH aliphatic), 3055.82 (=CH), 3295.97cm^{-1} (NH amine) c)

^{1}H-NMR ($CDCl_3$): δ 9.53 (2H, S, NH), 6.97 (4H, S, Ar-CH), 4.23 (4H, q, CH_2CH_3), 2.73 (4H, t, CH_2), 2.55-2.76 (4H, t, CH_2), 1.87 (4H, q, CH_2), 1.31 (6H, t, CH_3-CH_2)

^{13}C-NMR($CDCl_3$): δ 168.49. (CO), 160.57 (C=C-NH), 136.36, 121.90, 97.28, 58.94, 33.51, 28.79, 21.73, 14.68

MS EI m/z: $M^{+\cdot}$ 384, 338, 292, 264, 184, 237, 156.

Diethyl-2,2'-(1,4-phenylenebis(azanediyl))bis(cyclohex-1-ene-1-carboxylate) (IV)



Mo. Formula: $C_{24}H_{32}N_2O_4$(M.W = 412g/mol).

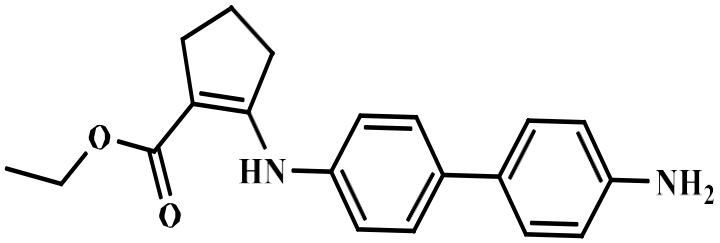
FT-IR υ_{max}: 1589.54 cm^{-1} (C=C), 1643.36 cm^{-1} (ester CO), and 2978.18 cm^{-1}(CH aliphatic), 3152.51cm^{-1} (=CH), 3207.53 cm^{-1} (NH amine).

^{1}H-NMR ($CDCl_3$): δ 10.70 (2H, S, NH), 6.98 (4H, S, Ar-CH), 4.22 (4H, q, CH_2CH_3), 2.37 (8H, m, CH_2), 1.62 (8H, m, CH_2), 1.29 (6H, t, CH_3-CH_2).

^{13}C-NMR($CDCl_3$): δ 170.84 (CO), 156.58 (C=C-NH), 136.23, 125.38, 93.04, 57.22, 29.96, 27.09, 23.85, 22.32, 14.59.

MS EI m/z: $M^{+\cdot}$ 412, 364, 319, 136, 108, 79.

ethyl 2-((4'-amino-[1,1'-biphenyl]-4-yl) amino) cyclopent-1-ene-1-carboxylate (VIII)



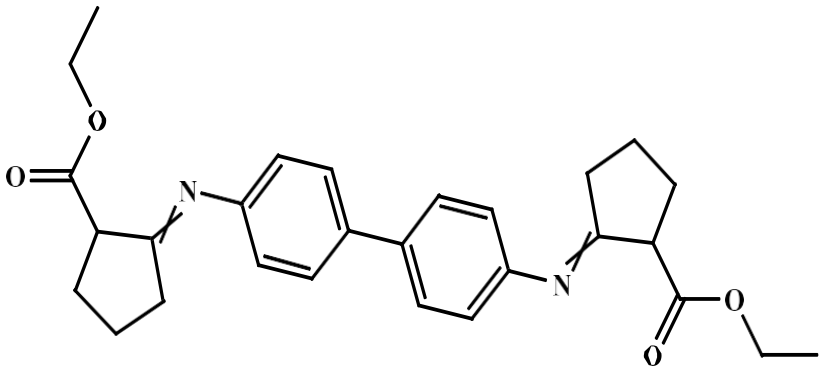
Mo. Formula: $C_{20}H_{22}N_2O_2$ (M.W =322 g/mol).

^{1}H-NMR ($CDCl_3$): 9.701 (1H, d, NH) 7.53-7.48 (8H, m, Ar-CH), 4.25 (2H, q, CH_2CH_3), 3.60(2H, br. S, NH_2), 2.89(2H, t, CH_2), 2.06(2H, t, CH_2) 1.93(2H, quintet, CH_2), 1.34 (3H, t, CH_3-CH_2).

^{13}C-NMR($CDCl_3$): 168.53, 160.47, 139.80, 135.03, 127.58, 126.98, 120.79, 115.46, 98.09, 59.03, 33.77, 28.74, 21.84, 14.68.

MS EI m/z: $M^{+\cdot}$ 322, 276, 250, 184, 167, 138, 123, 77.

diethyl-2,2'-([1,1'-biphenyl]-4,4'-diylbis(azaneylylidene)) bis(cyclopentane-1-carboxylate) (IX)

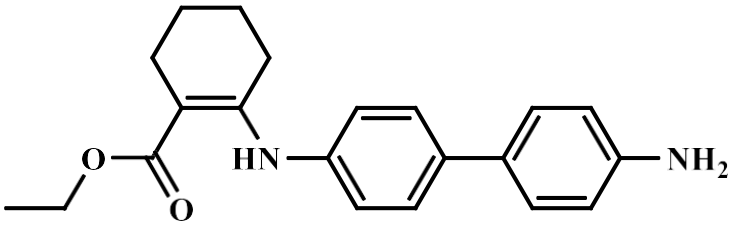


Mo. Formula: $C_{28}H_{32}N_2O_4$(M.W =460 g/mol).

^{1}H-NMR ($CDCl_3$): 9.69 (1H, S, NH) 6.84-7.50 (8H, m, Ar-CH), 4.26 (4H, q, CH_2CH_3), 2.87(4H, t, CH_2), 2.60 (4H, t, CH_2), 1.92 (4H, quintet, CH_2), 1.34 (6H, t, CH_3-CH_2) ((enamine))

^{13}C-NMR ($CDCl_3$) δ 173.55, 165.40, 137.85, 129.96, 125.33, 118.83, 54.64, 37.48, 33.30, 29.49, 21.82, 19.82, ((imine)).

ethyl 2-((4'-amino-[1,1'-biphenyl]-4-yl) amino) cyclohex-1-ene-1-carboxylate (X)



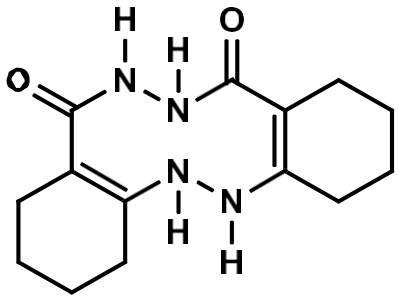
Mo. Formula: $C_{21}H_{24}N_2O_2$ (M.W =336 g/mol).

FT-IR (KBr) υ_{max}: 1578.29 cm^{-1} (C=C), 1631.60 cm^{-1} (ester CO), and 2980.96 cm^{-1}(CH aliphatic), and 3036.16 (=CH) 3223.09 cm^{-1} (NH amine) and 3350.92,3453.78 (NH_2).

^{1}H-NMR ($CDCl_3$): 10.87 (1H, d, NH) ,6.75-7.52 (8H, m, Ar-CH), 4.24 (2H, q, CH_2CH_3), 3.70 (2H, br. S, NH_2), 2.40 -1.62 (8H, m, CH_2), 1.32 (3H, t, CH_3-CH_2).

MS EI m/z: $M^{+\cdot}$ 336, 290, 184, 167, 234, 145, 91.

1,2,3,4,6,7,9,10,11,12,13,14-dodecahydrodibenzo[c,i][1,2,6,7] tetrazecine-5,8-dione (XI)

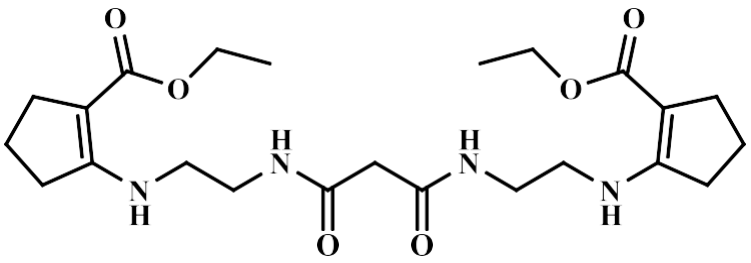


Mo. Formula: $C_{14}H_{20}N_4O_2$ (M.W =276 g/mol).

^{1}H-NMR ($CDCl_3$): δ 10.27 (4H, br,S, NH), 2.50-2.41 (4H, t, CH_2), 2.24-2.21 (4H, t, CH_2), 1.64-1.63 (8H, m, CH_2).

^{13}C-NMR($CDCl_3$): δ 159.04 (CO), 140.54 (C=C-NH), 99.03 (C=C-C=O), 23.30, 22.72, 21.74, 19.32.

ethyl(Z)-2-((2-(3-((2-((2-(ethoxycarbonyl) cyclopentylidene) amino) ethyl) amino)-3-oxopropanamido) ethyl) amino) cyclopent-1-ene-1-carboxylate (XII)



Mo. Formula: $C_{23}H_{36}N_4O_6$ (M.W =464 g/mol).

^{1}H-NMR ($CDCl_3$): 8.161 (1H, S, NH), 7.452 (2H, S, NH) 4.031 (4H, q, CH_2-CH_3), 3.02-3.65 (15H, m, CH_2), 2.35 -2.54(8H, m, CH_2), 1.18 (6H, t, CH_3-CH_2)

^{13}C-NMR($CDCl_3$): δ 179.25, 167.62, 167.50, 165.24, 91.83, 58.12, 45.15, 43.70, 40.54, 39.70, 39.29, 20.87, 15.18

3.4 In Vitro Anti-bacterial Activity for Products

3.4.1 Bacterial Strains Used in the Study

The antibacterial activity of the studied compounds was evaluated against four bacterial pathogens:

- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Escherichia coli*

The bacterial cultures were obtained from the Department of Microbiology, Al-Salim Medical Center, Benghazi, Libya. All the bacterial strains used in this study are clinical isolates. The cultures were incubated at 37°C for 24 hours on nutrient agar.

3.4.2 Preparation of Bacterial Suspensions

Fresh suspensions were prepared for each tested organism. A 24-hour bacterial growth was harvested and washed off using 100 mL sterile normal saline. The suspension was adjusted to McFarland 0.5 standard using sterile normal saline, giving a final bacterial concentration of approximately 10^8 CFU/mL.

3.4.3 Preparation of Chemical Compounds Solution

To study the antimicrobial activity, 0.001 g of each compound was dissolved in 10 mL of a mixture of chloroform and DMSO. Serial dilutions were prepared at concentrations of 100 μg/mL

3.4.4 Evaluation of Antimicrobial Activity of Tested Compounds

The antimicrobial activity of the tested compounds was evaluated using the well diffusion method. Mueller-Hinton Agar (MHA) plates were prepared and swabbed uniformly with 100 μL of the bacterial suspension. After allowing the plates to dry for 5 minutes, wells of 6–8 mm in diameter were punched into the agar using a sterile cork borer. Volumes ranging from 20 to 100 μL of the compound solutions were introduced into the wells. The plates were then incubated at 37°C for 24 hours. Ciprofloxacin was used as the standard antibiotic, while chloroform served as the negative control.

3.4.5 Determination of Inhibition Zones (mm)

After incubation, the inhibition zones were measured in millimeters using a zone reader. One plate was used for each concentration of the tested compounds against each bacterial strain.

3.5 *Molecular docking*

Protein Preparation: The protein targets, **Escherichia coli (3uu2) receptor and Staphylococcus aureus(1vqq) receptor,** were downloaded from the Protein Data Bank (PDB). Water molecules, ligands, and heteroatoms were removed during preparation using Biovia Discovery Studio.

Chemical Compounds: Chemical structures were drawn using ChemDraw.

Molecular docking studies were performed to evaluate the interaction between the chemical compounds and 3UU2, 1VQQ bacterial receptor proteins using PyRx 0.8 software. Visualization of the docking results was conducted using Biovia Discovery Studio

Chapter 4

Appendix

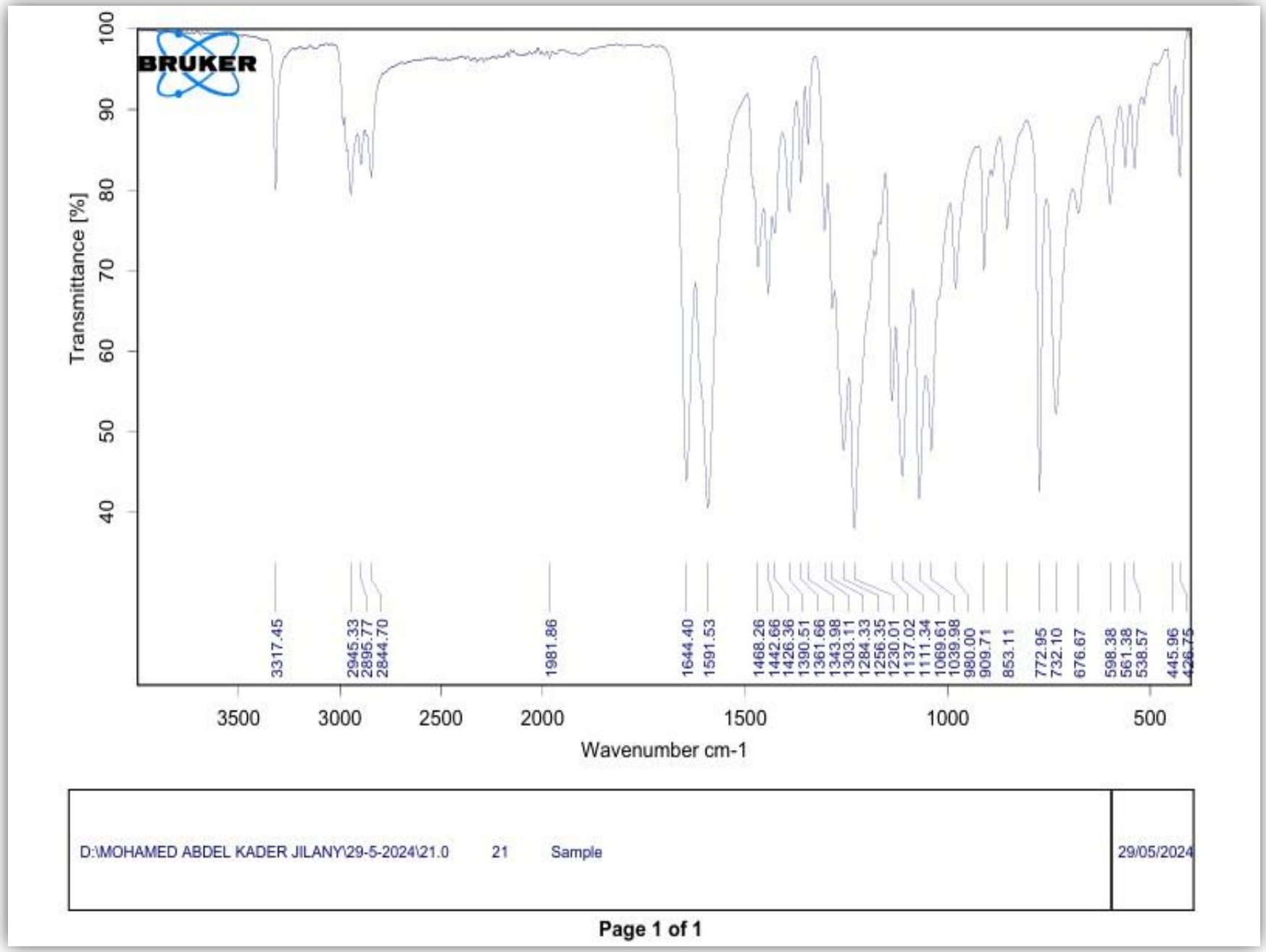


Figure (2.1a) FT-IR spectrum *of compound (I)*

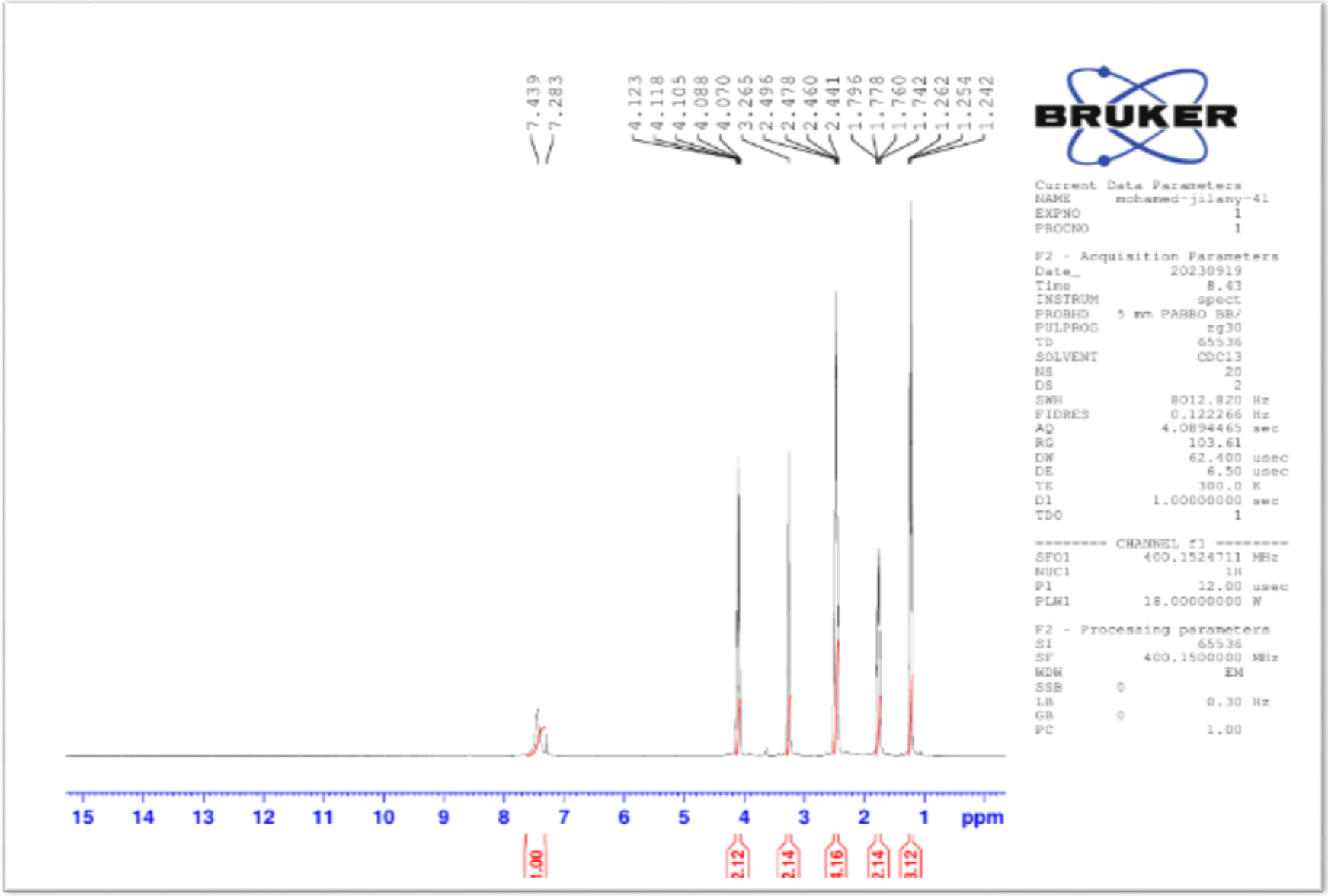


Figure (2.1b) ^{1}HNMR spectrum *of compound (I)*

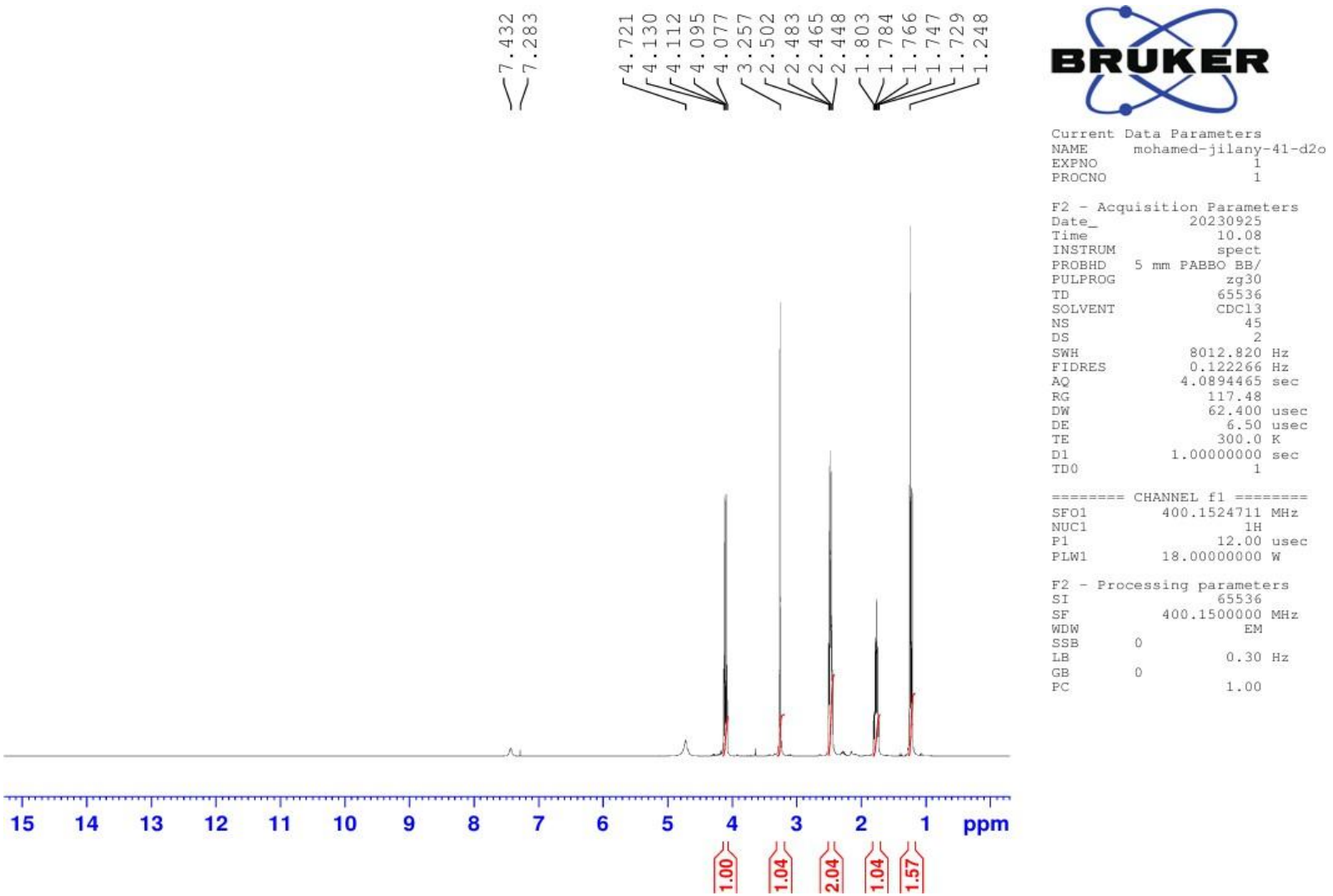
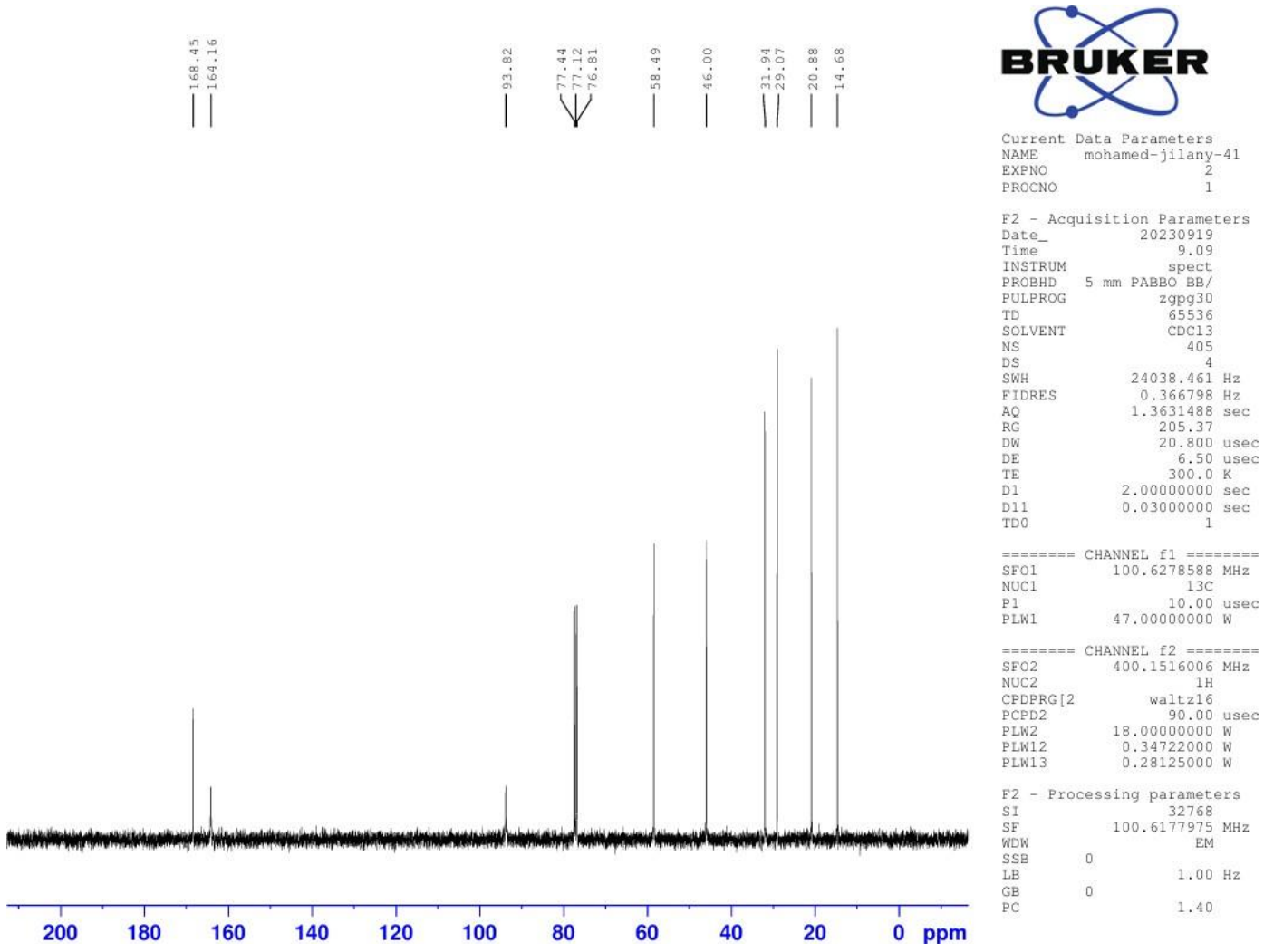


Figure (2.1c) D_2O spectrum *of compound (I)*



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PROCNO 1

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FIDRES 0.366798 Hz
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RG 205.37
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DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

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NUC1 13C
P1 10.00 usec
PLW1 47.00000000 W

======== CHANNEL f2 ========
SFO2 400.1516006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 18.00000000 W
PLW12 0.34722000 W
PLW13 0.28125000 W

F2 - Processing parameters
SI 32768
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SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure (2.1d)^{13}C-NMR spectrum *of compound (I) in CDCl* $_3$

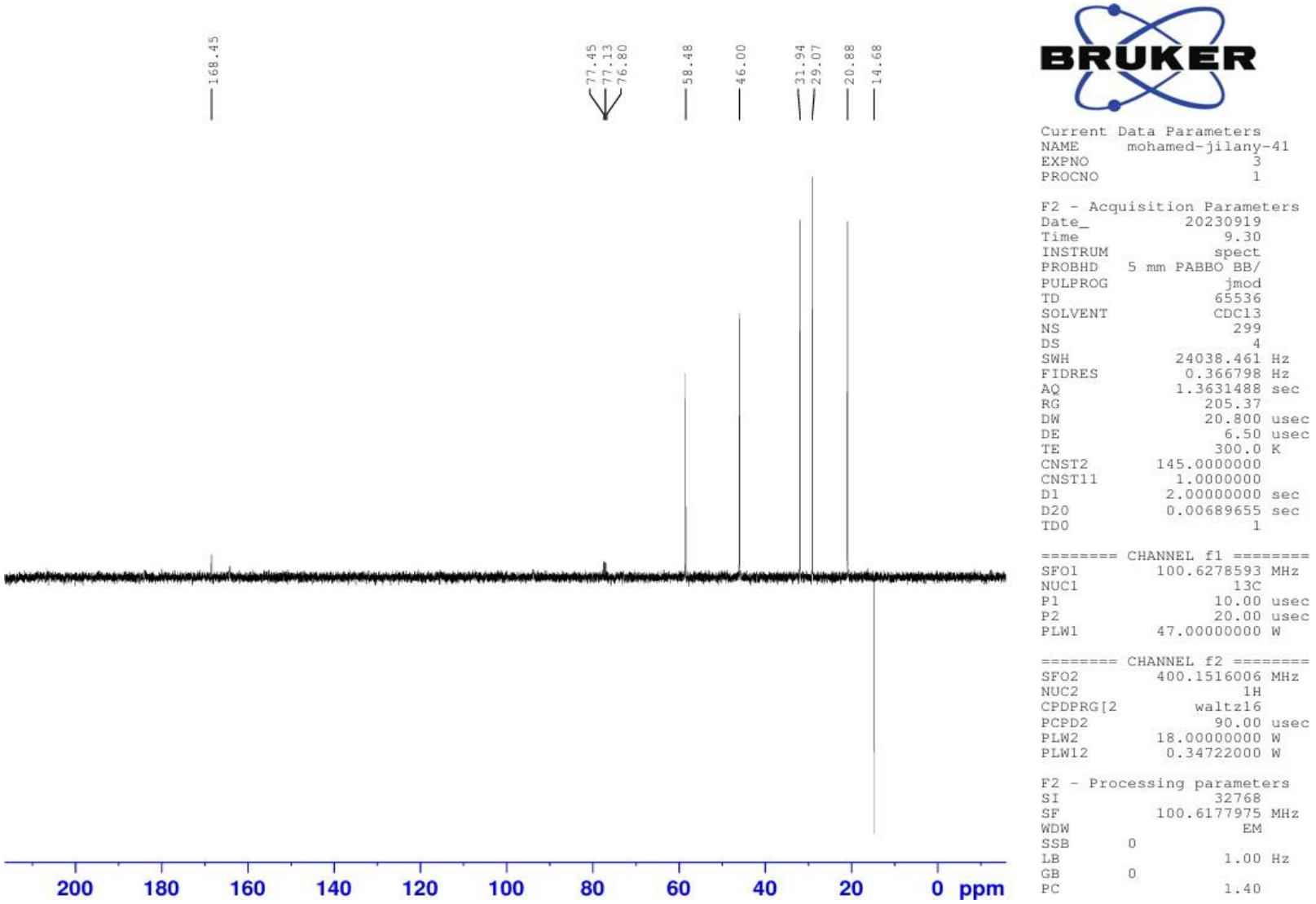


Figure (2.1e) APT spectrum *of compound (I) in CDCl* $_3$

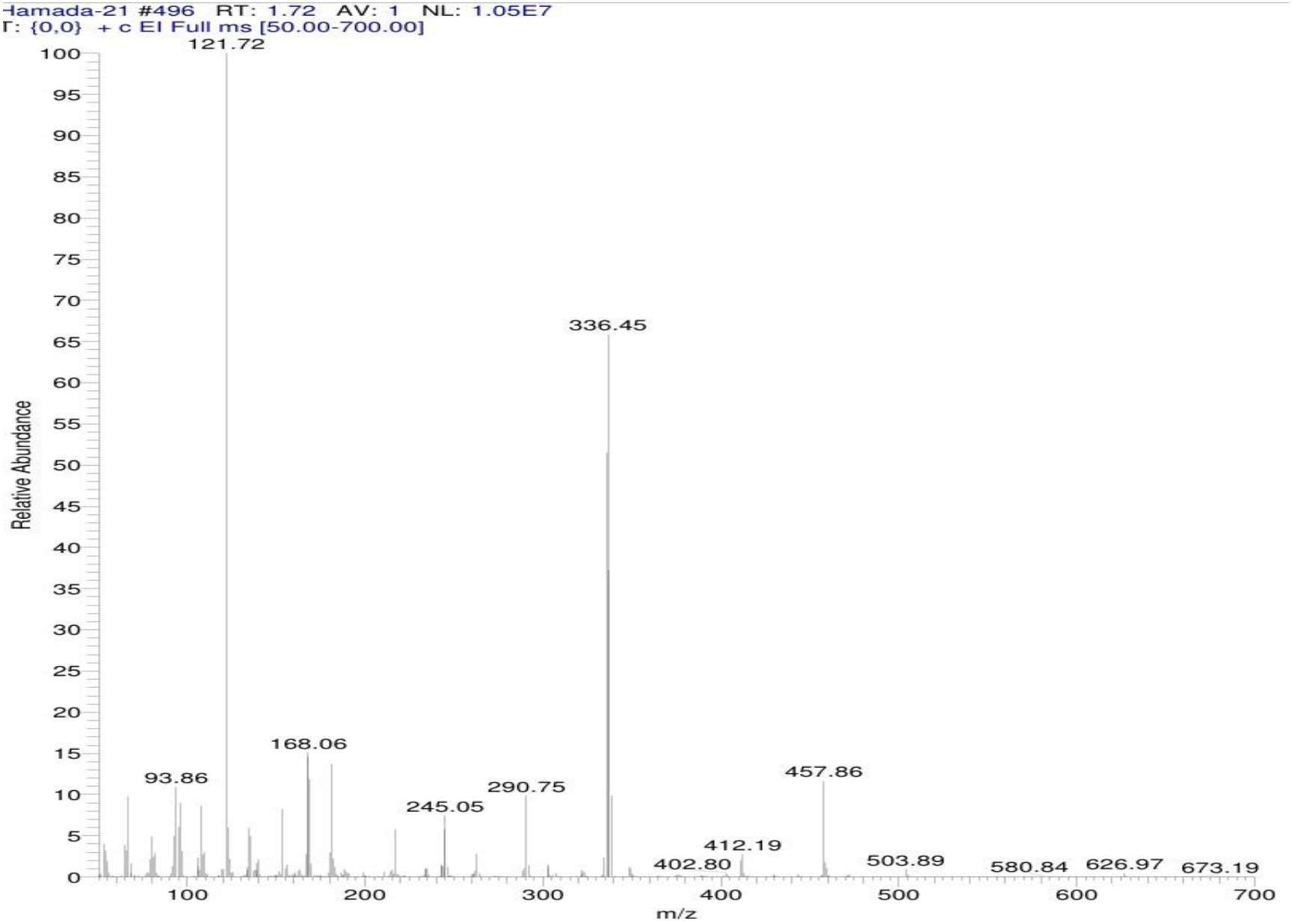


Figure (2.1f) Mass spectrum *of compound (I)*

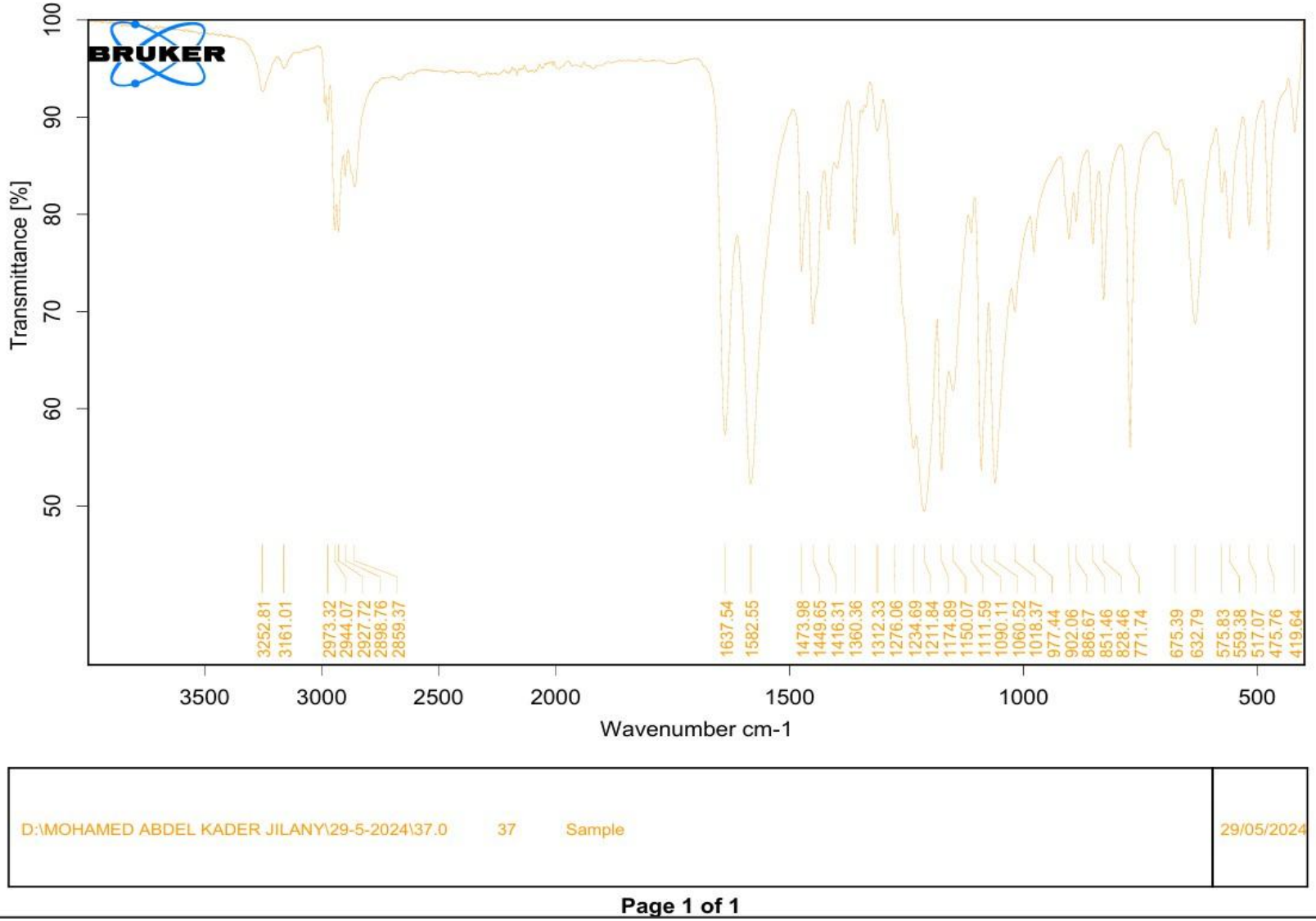


Figure (2.2 a)*FT- IR spectrum of compound (II)*

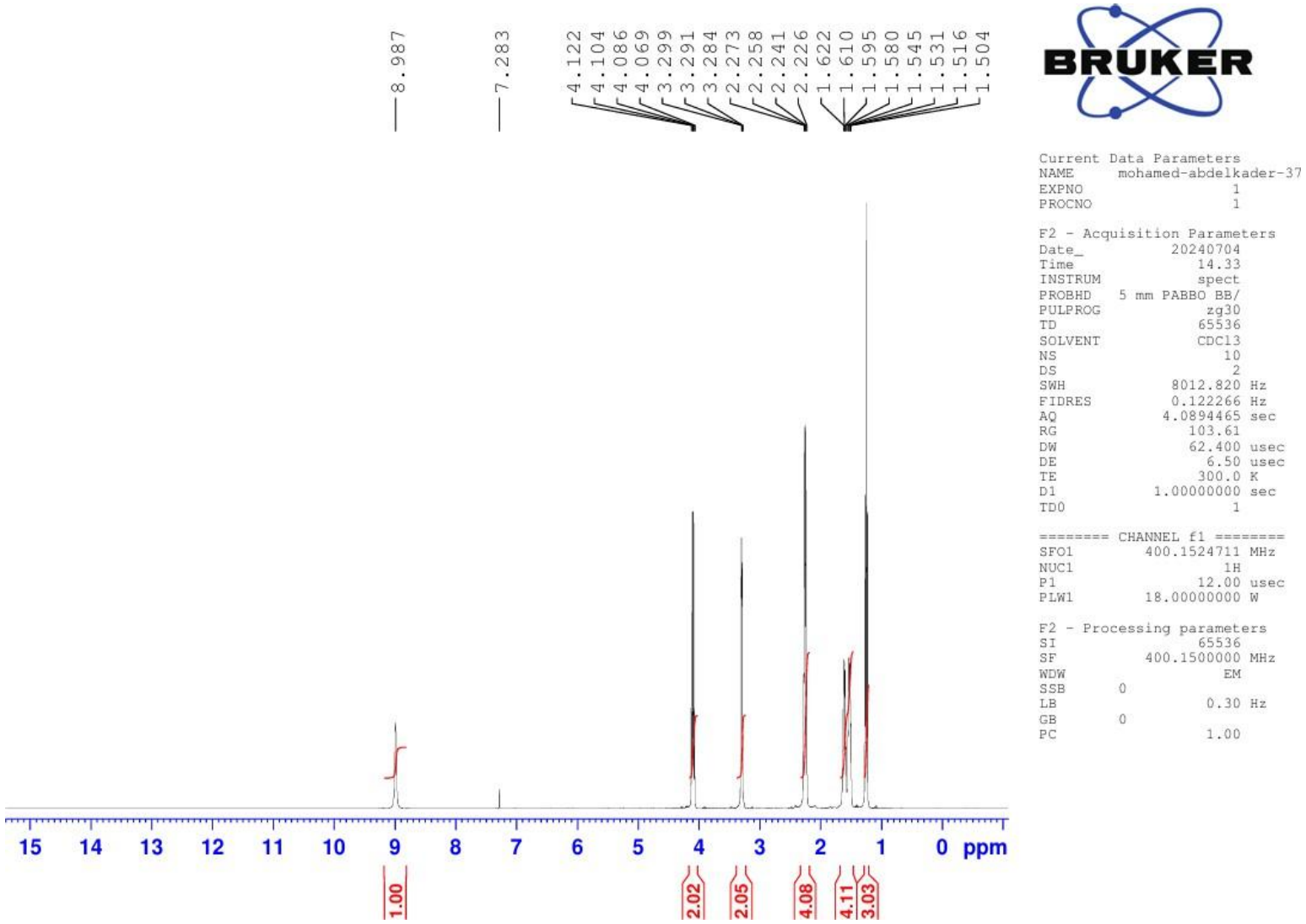


Figure (2.2 b) *[1]HNMR spectrum of compound (II) in CDCl 3*

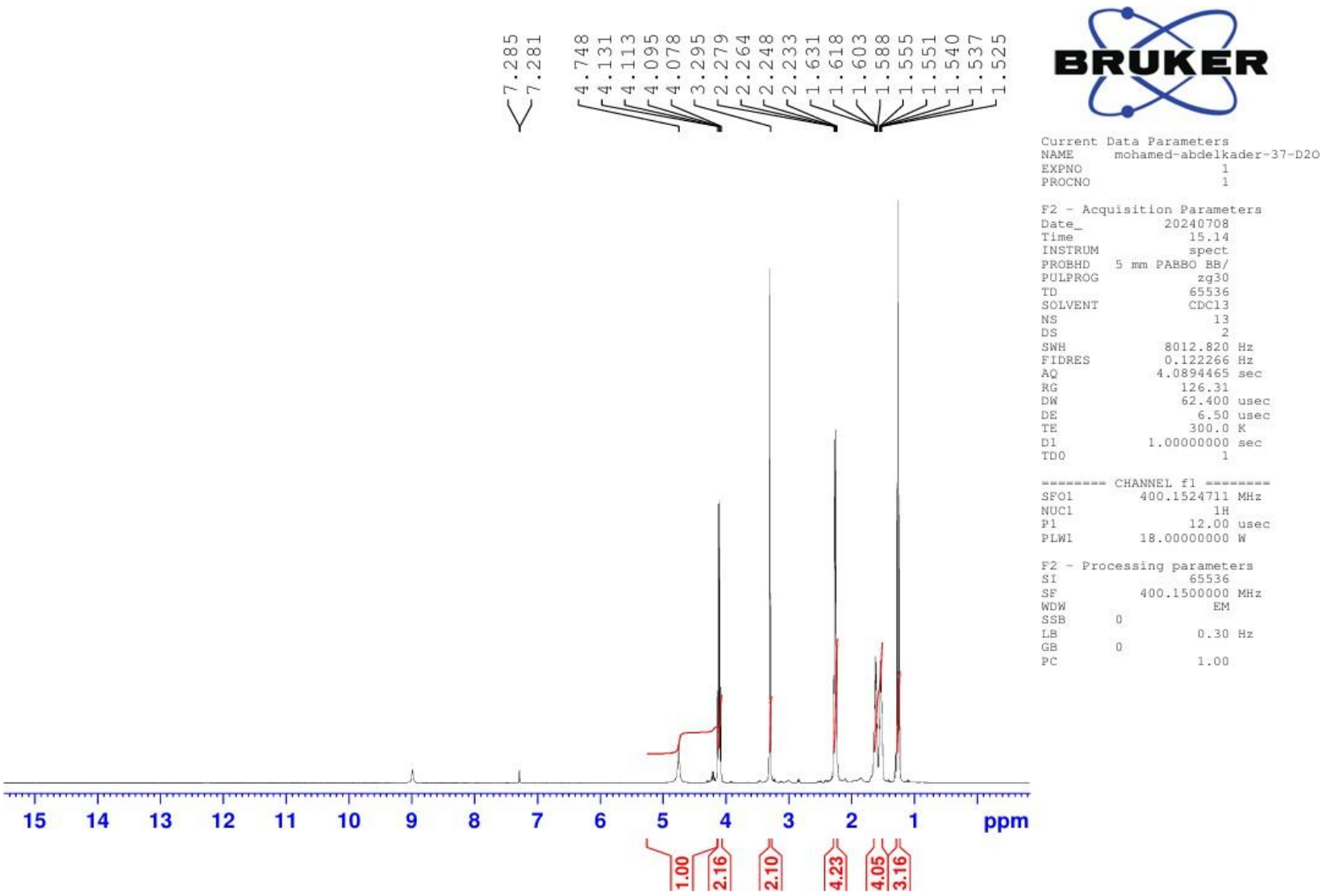


Figure (2.2 c) *D_2O spectrum of compound (II) in $CDCl_3$*

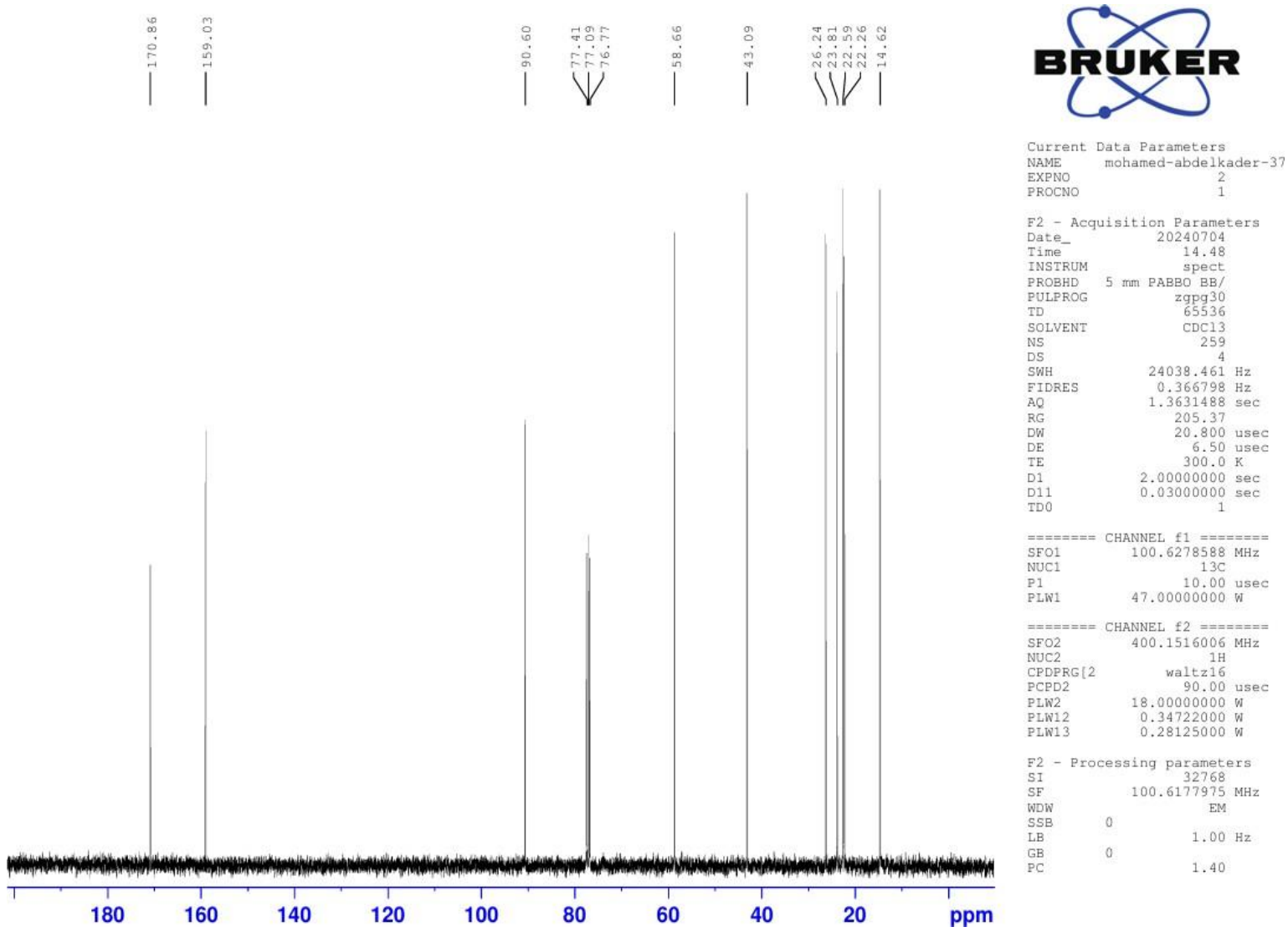


Figure (2.2 d) *^{13}C-NMR spectrum of compound (II) in CDCl $_3$*

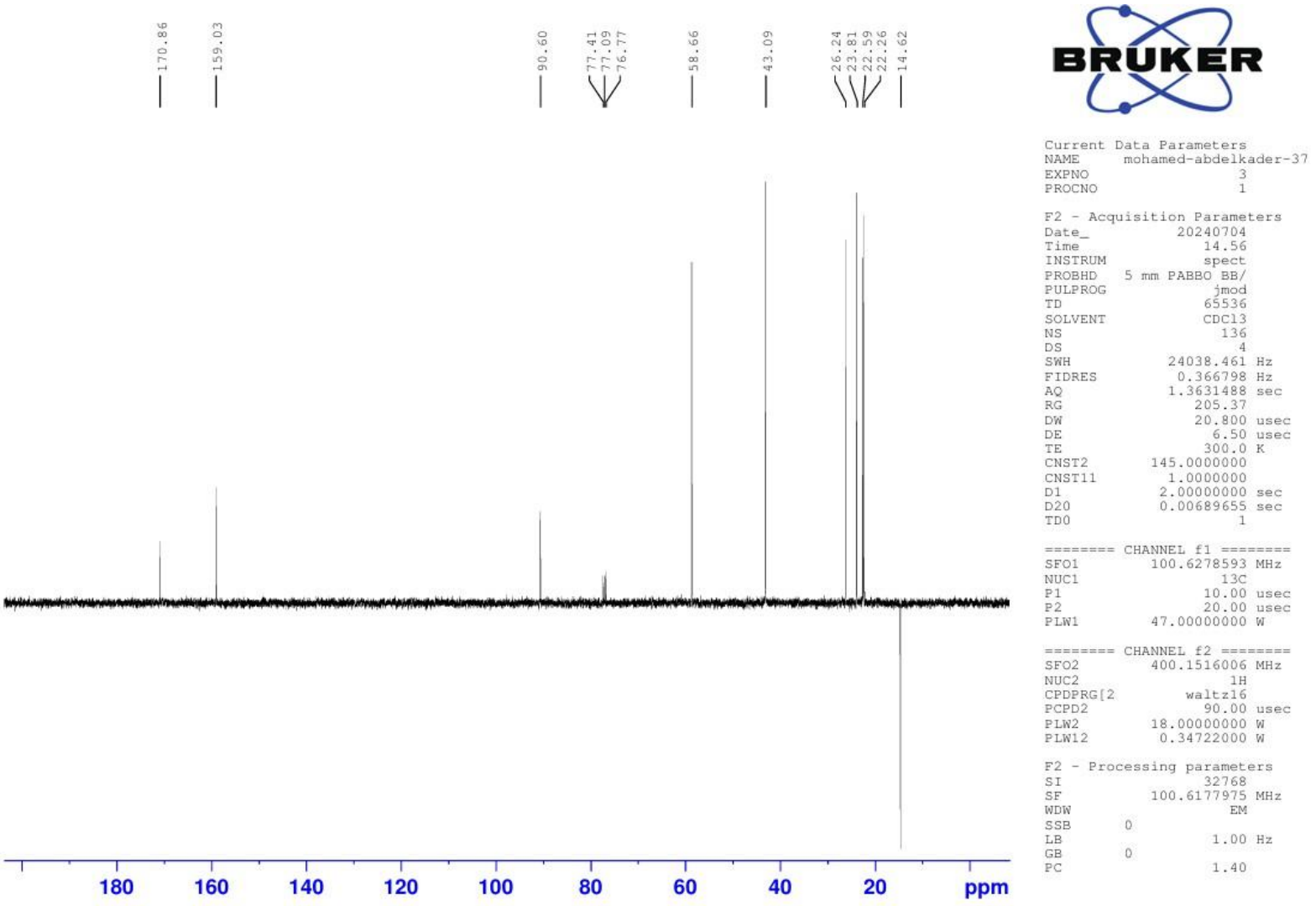


Figure (2.2 e) APT spectrum *of compound (II) in CDCl* $_3$

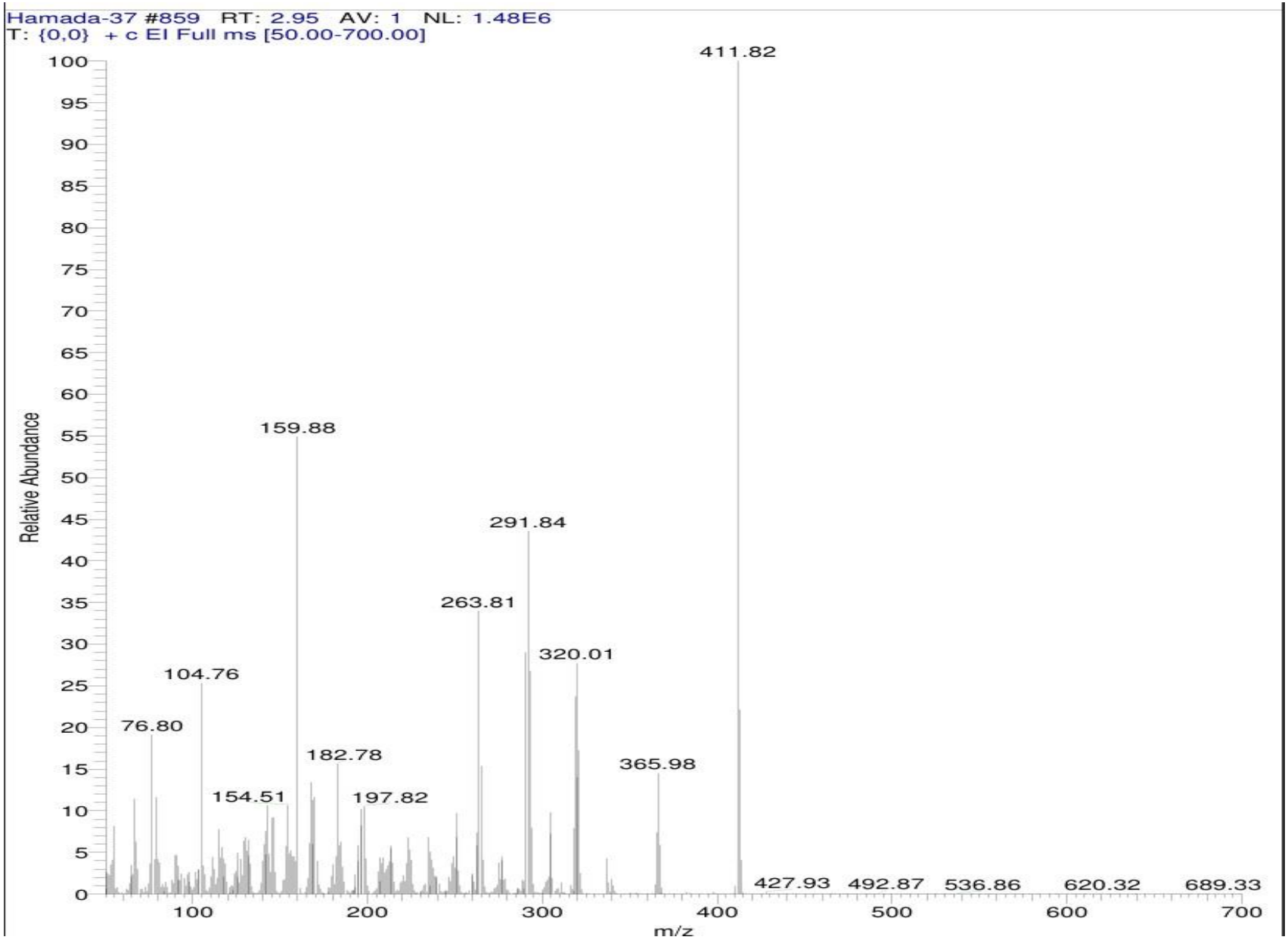


Figure (2.2f) *Mass spectrum of compound (II)*

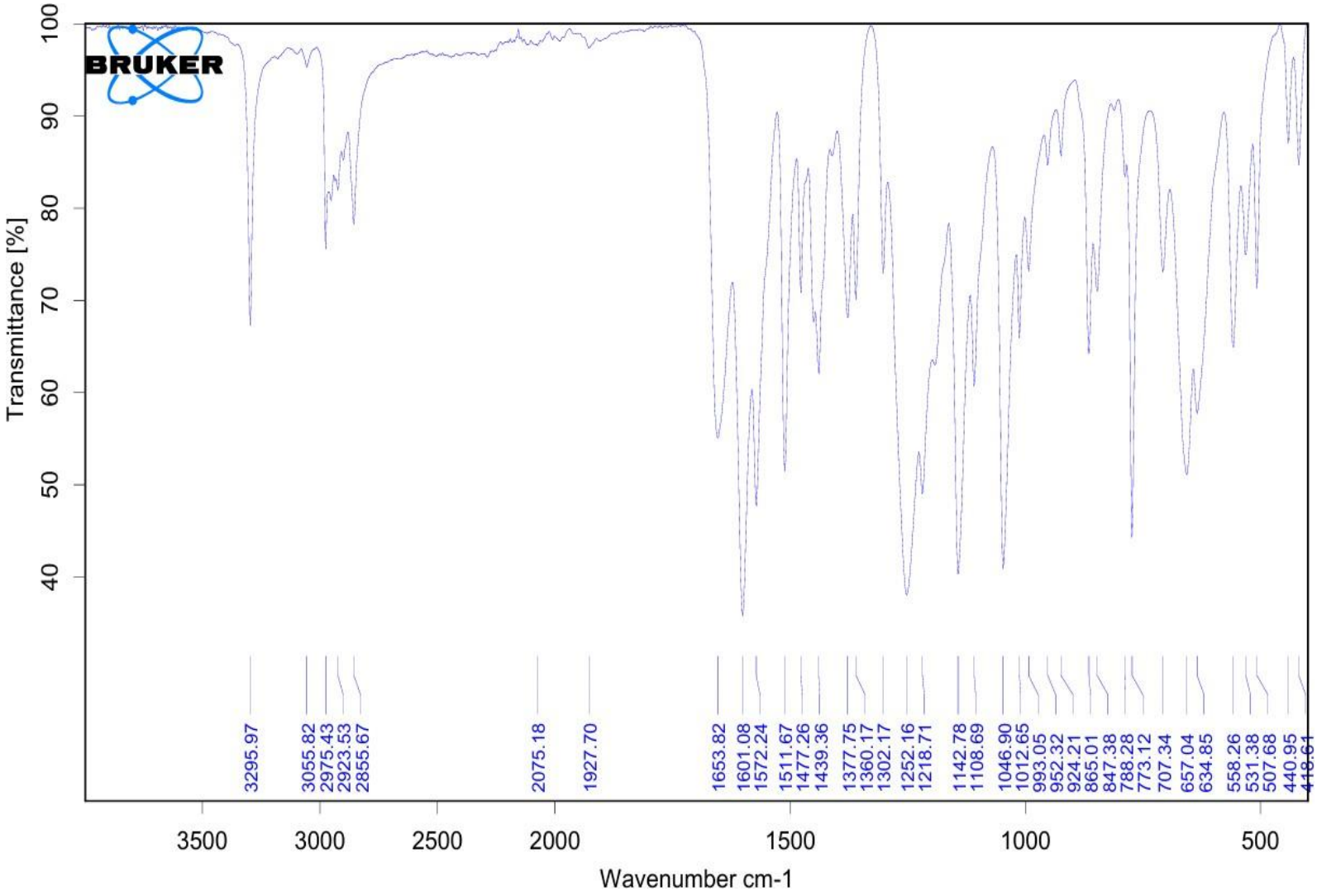


Figure (2.3a) FT-IR spectrum of compound (III)

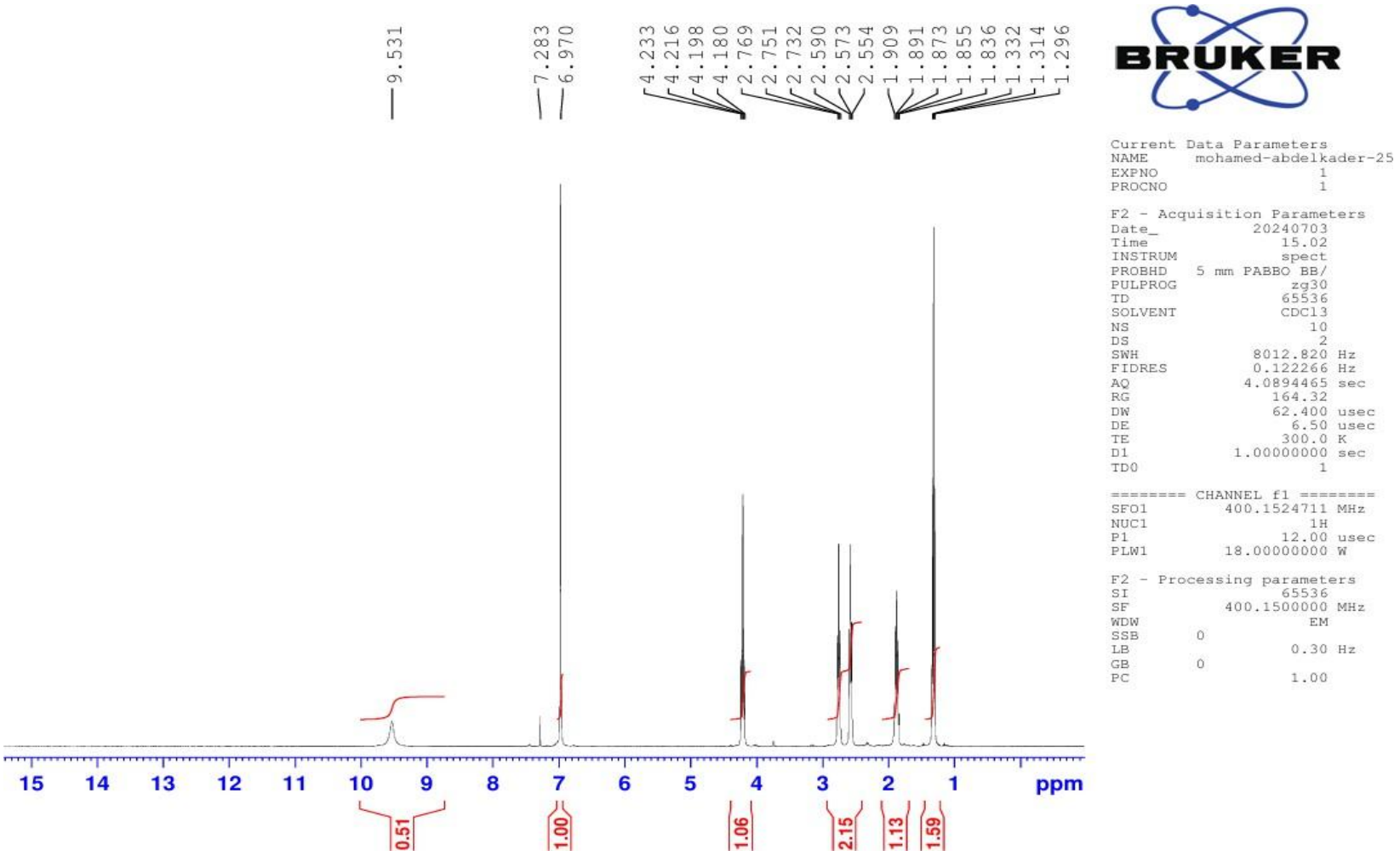


Figure (2.3b) ^{1}HNMR spectrum of compound (III) in $CDCl_3$

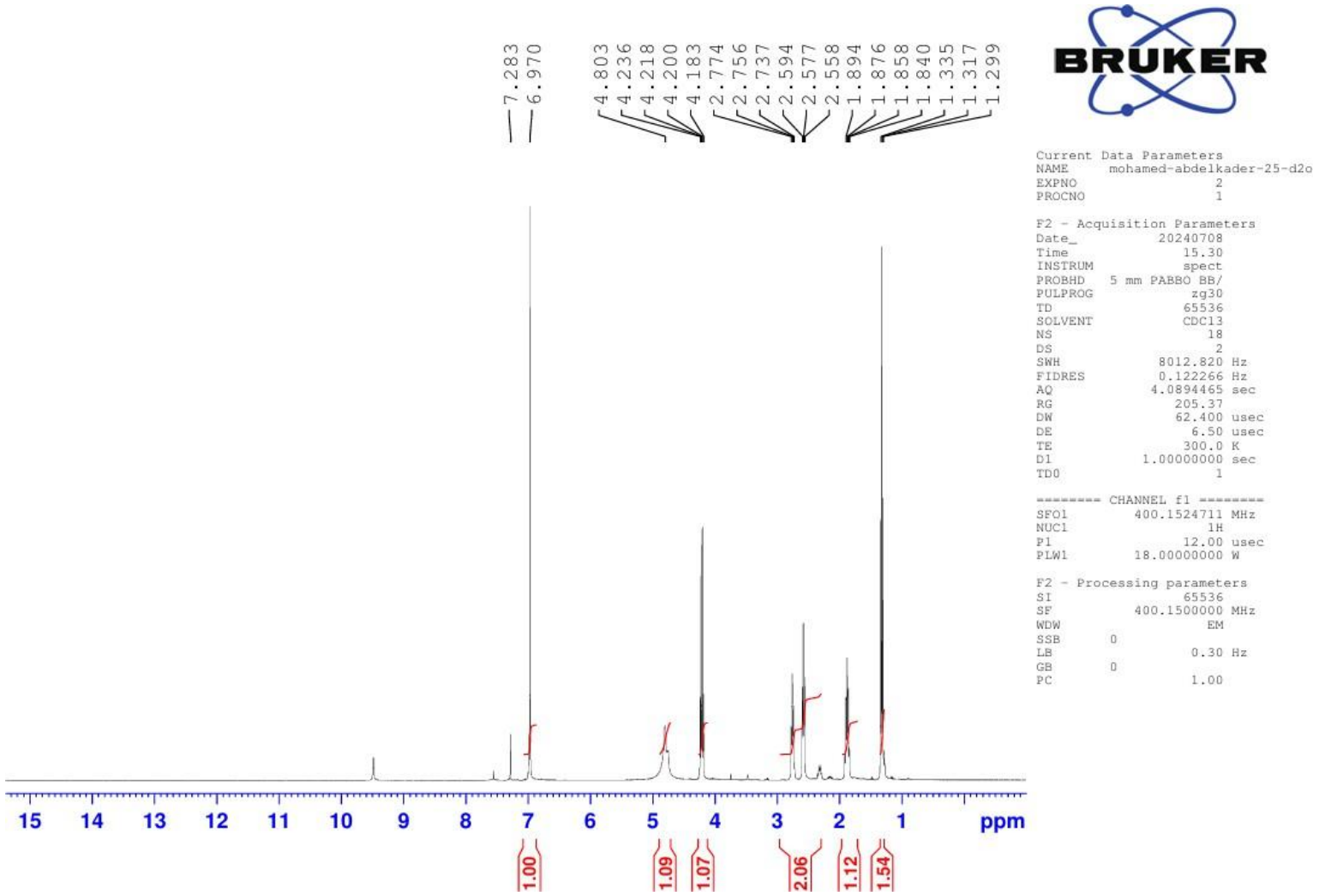
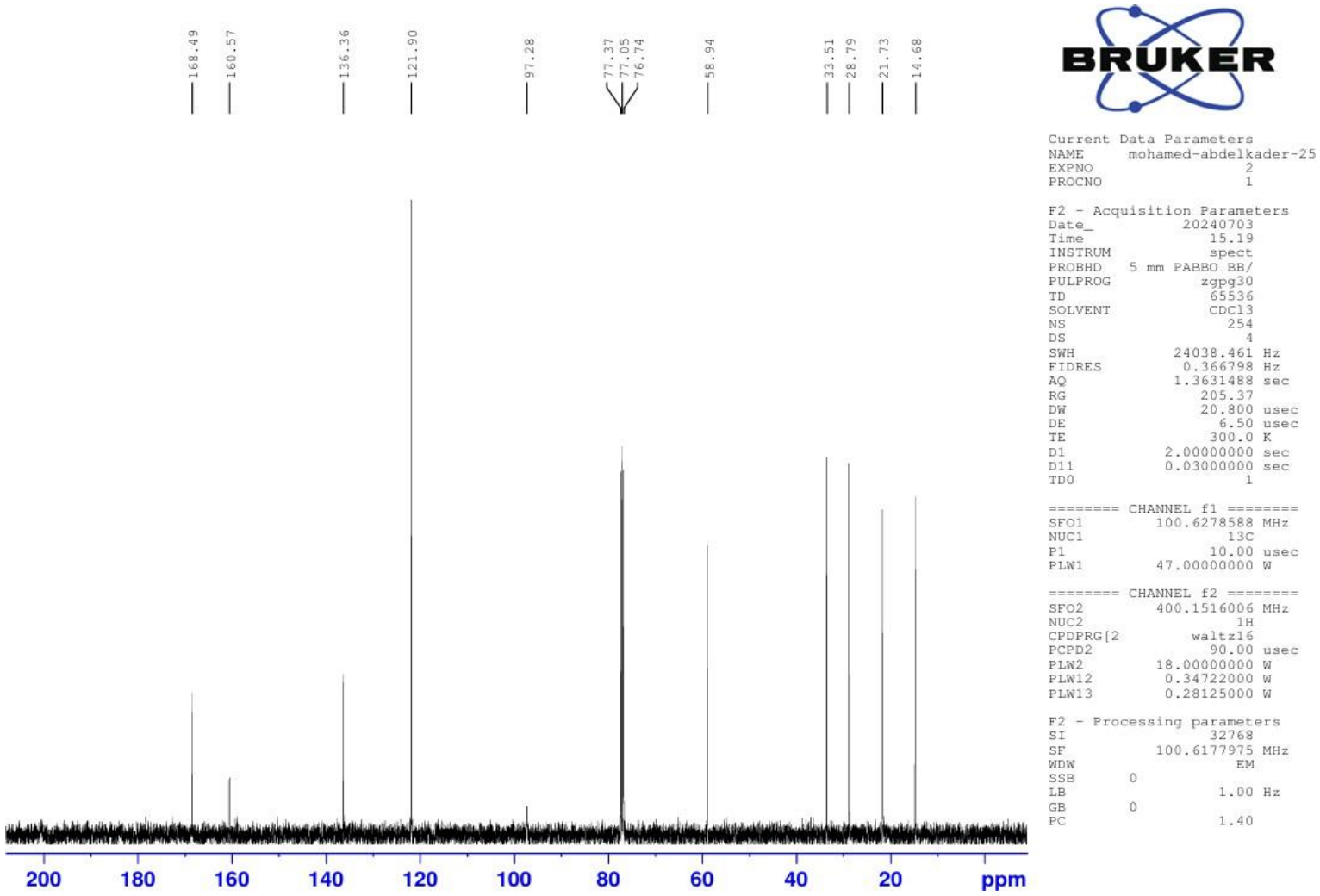


Figure (2.3c) D_2O spectrum of compound (III) in $CDCl_3$

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PROCNO                       1

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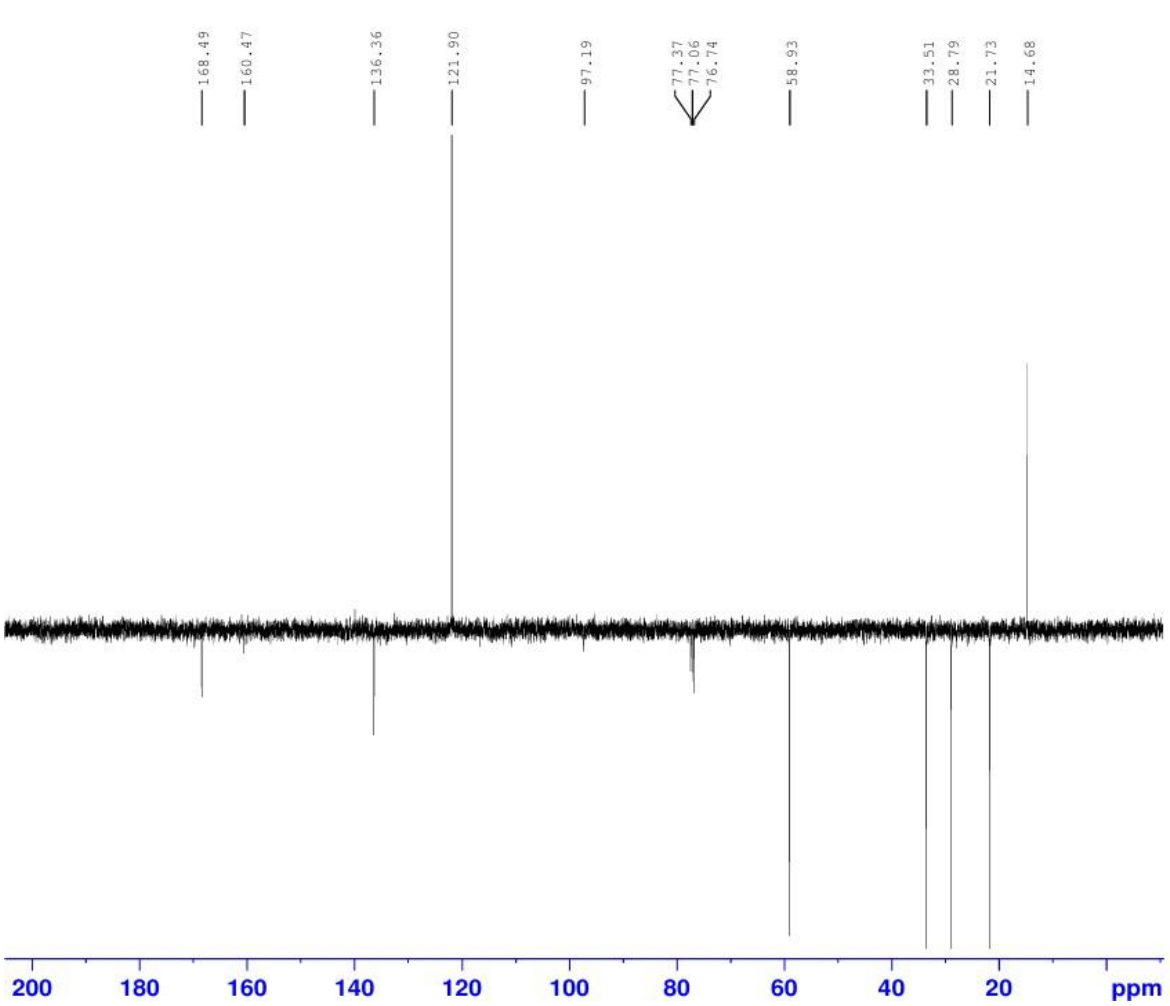
Time                  15.19
INSTRUM               spect
PROBHD    5 mm PABBO BB/
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     254
DS                       4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                   205.37
DW                   20.800 usec
DE                    6.50 usec
TE                   300.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           100.6278588 MHz
NUC1                    13C
P1                    10.00 usec
PLW1          47.00000000 W

======== CHANNEL f2 ========
SFO2           400.1516006 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                 90.00 usec
PLW2          18.00000000 W
PLW12          0.34722000 W
PLW13          0.28125000 W

F2 - Processing parameters
SI                    32768
SF             100.6177975 MHz
WDW                      EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

Figure (2.3d) *^{13}C-NMR spectrum of compound (III)*

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Current Data Parameters
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EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
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Time                   15.32
INSTRUM                spect
PROBHD    5 mm PABBO BB/
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                       227
DS                         4
SWH                24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                    205.37
DW                    20.800 usec
DE                     6.50 usec
TE                    300.0 K
CNST2             145.0000000
CNST11              1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                          1

======== CHANNEL f1 ========
SFO1              100.6278593 MHz
NUC1                      13C
P1                      10.00 usec
P2                      20.00 usec
PLW1              47.00000000 W

======== CHANNEL f2 ========
SFO2              400.1516006 MHz
NUC2                      1H
CPDPRG[2               waltz16
PCPD2                   90.00 usec
PLW2              18.00000000 W
PLW12              0.34722000 W

F2 - Processing parameters
SI                       32768
SF                100.6177975 MHz
WDW                         EM
SSB       0
LB                       1.00 Hz
GB        0
PC                       1.40
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Figure (2.3e) *APT spectrum of compound (III)*

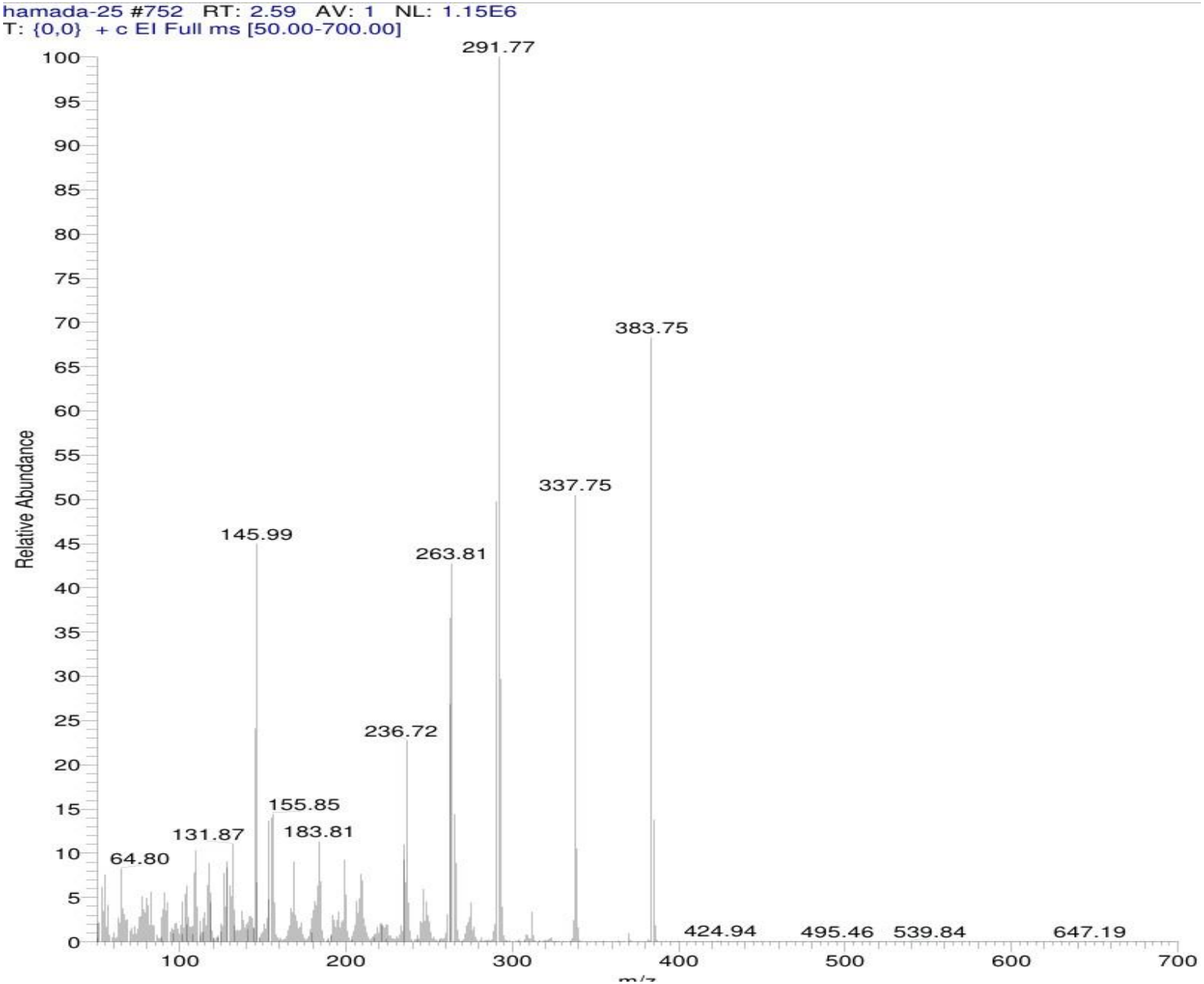


Figure (2.3f) *Mass spectrum of compound (III)*

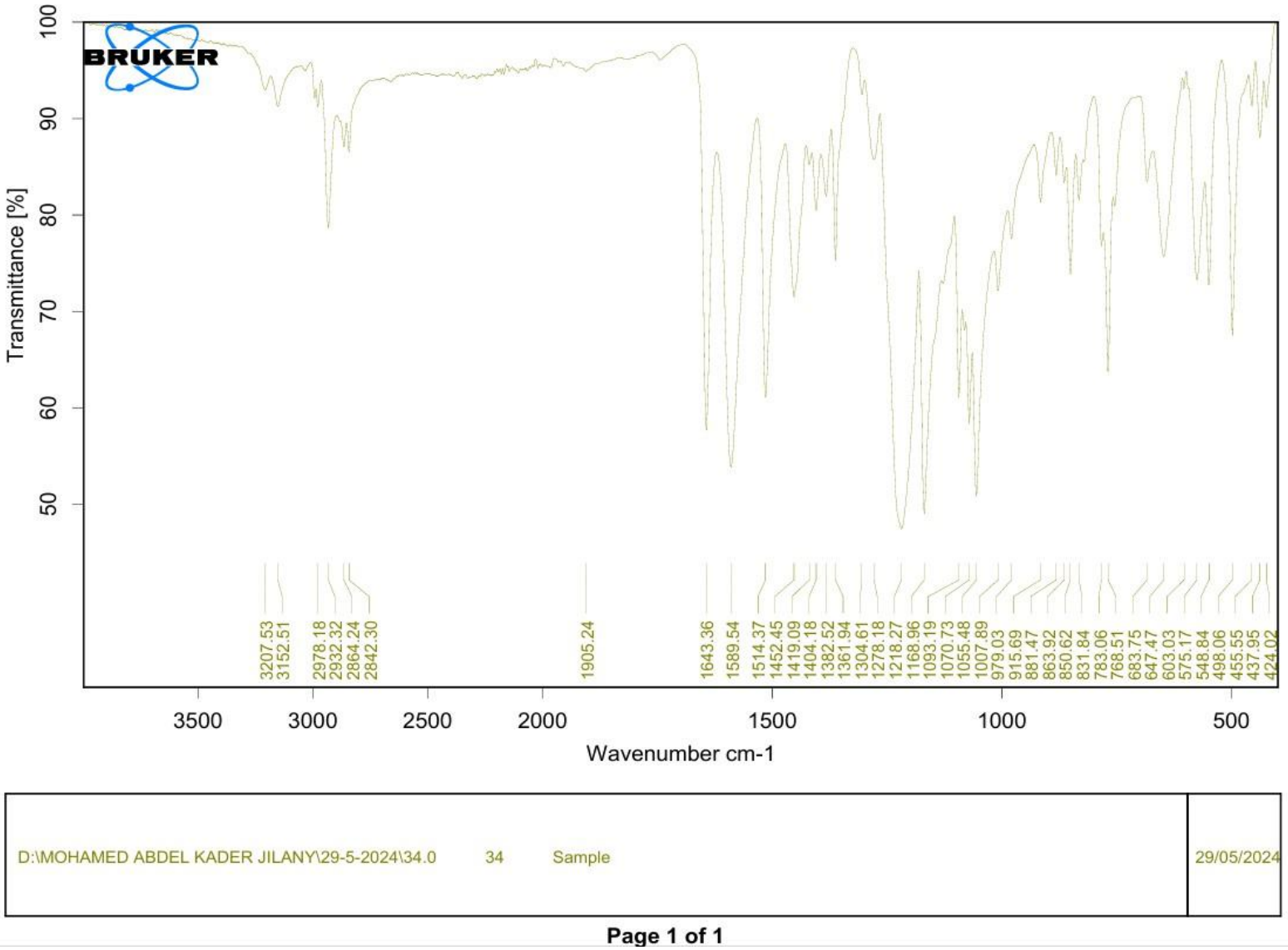


Figure (2.4 a) FT- IR spectrum of compound (IV) in $CDCl_3$

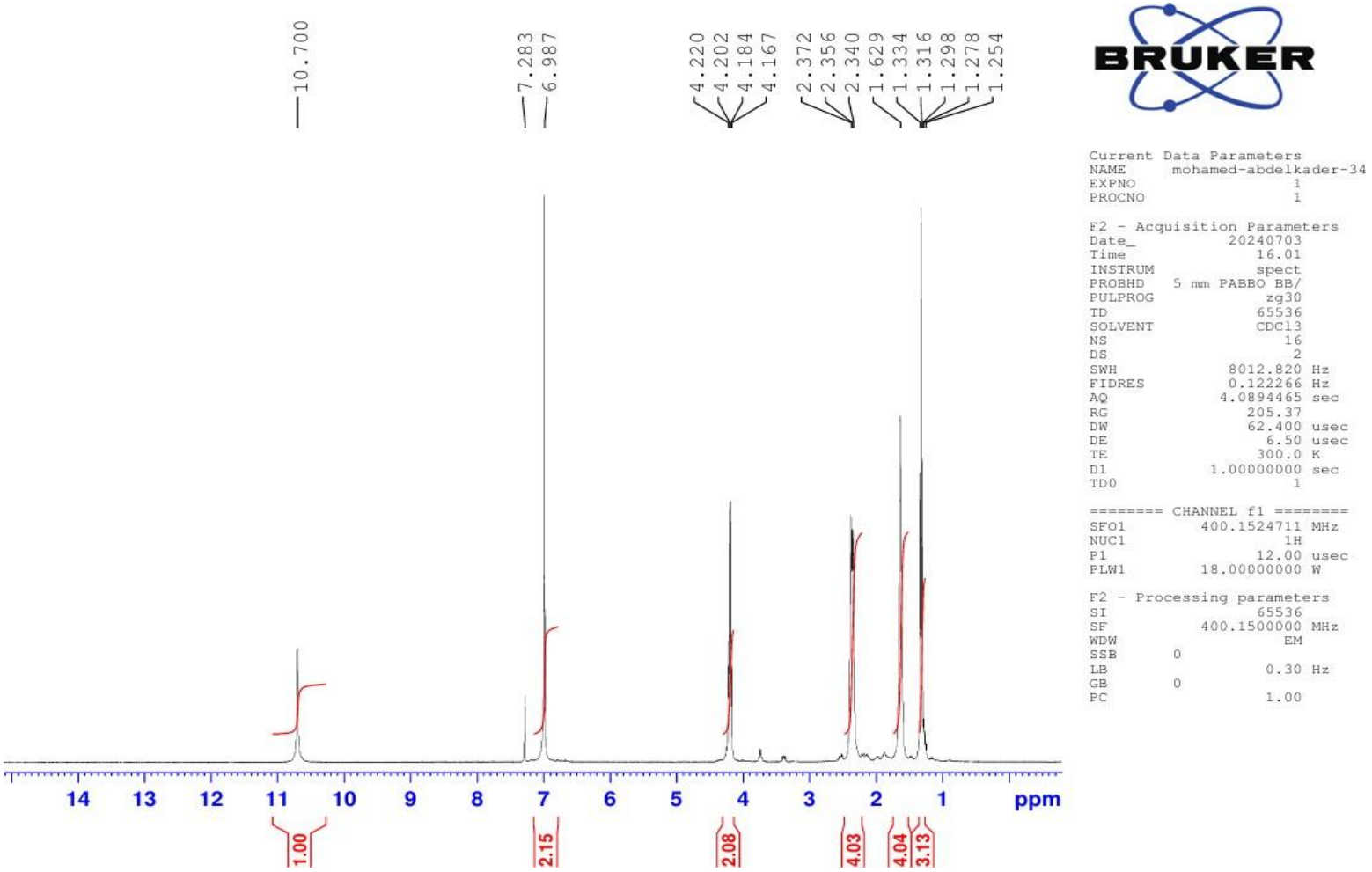


Figure (2.4 b) ^{1}HNMR spectrum of compound (IV) in $CDCl_3$

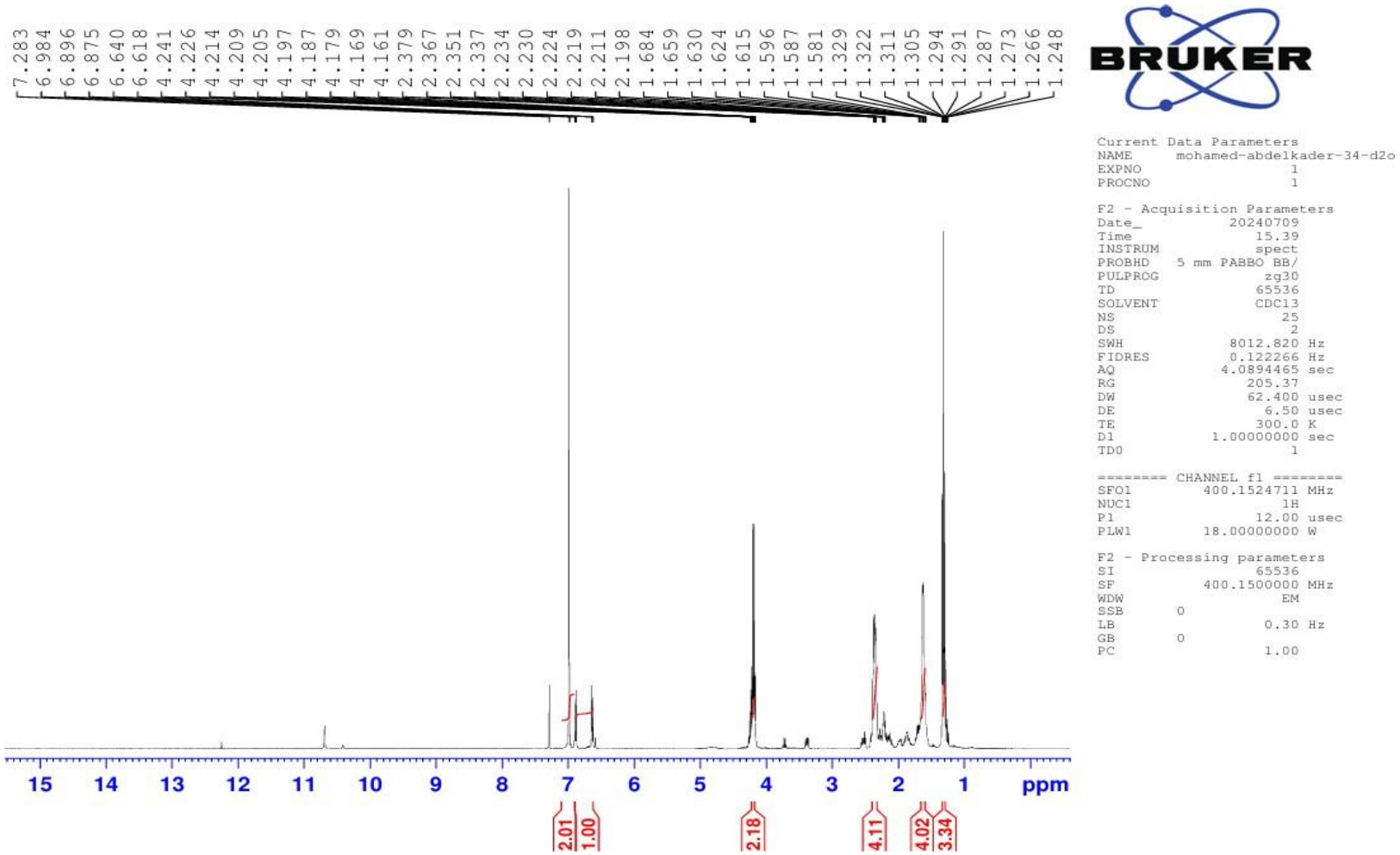
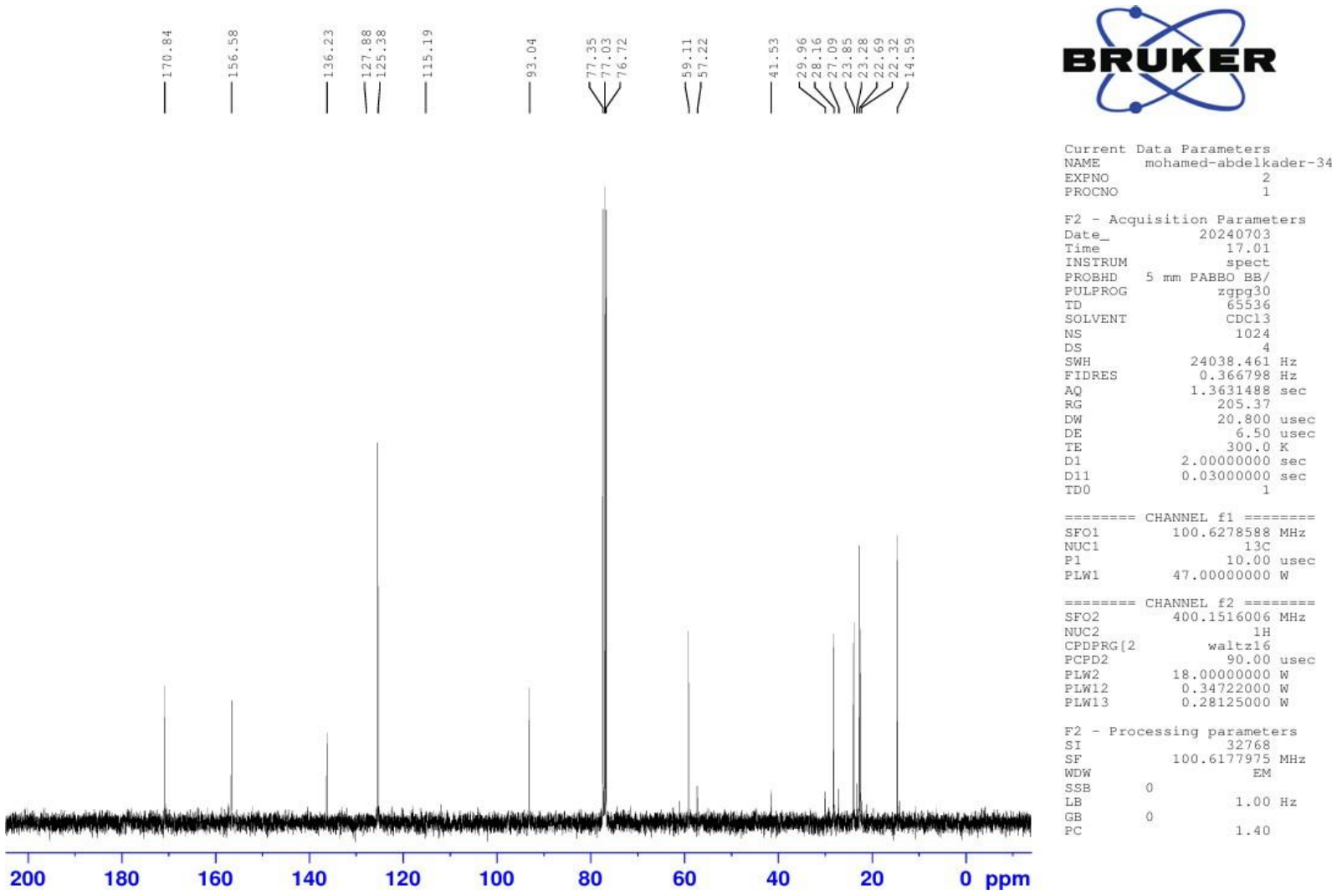


Figure (2.4 c) D_2O spectrum of compound (IV) in $CDCl_3$



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EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20240703
Time                 17.01
INSTRUM              spect
PROBHD    5 mm PABBO BB/
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631488 sec
RG                 205.37
DW                20.800 usec
DE                 6.50 usec
TE                300.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          100.6278588 MHz
NUC1                 13C
P1                10.00 usec
PLW1          47.00000000 W

======== CHANNEL f2 ========
SFO2          400.1516006 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2               90.00 usec
PLW2          18.00000000 W
PLW12          0.34722000 W
PLW13          0.28125000 W

F2 - Processing parameters
SI                   32768
SF            100.6177975 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

Figure (2.4 d) C^{13}-NMR spectrum of compound (IV) in $CDCl_3$

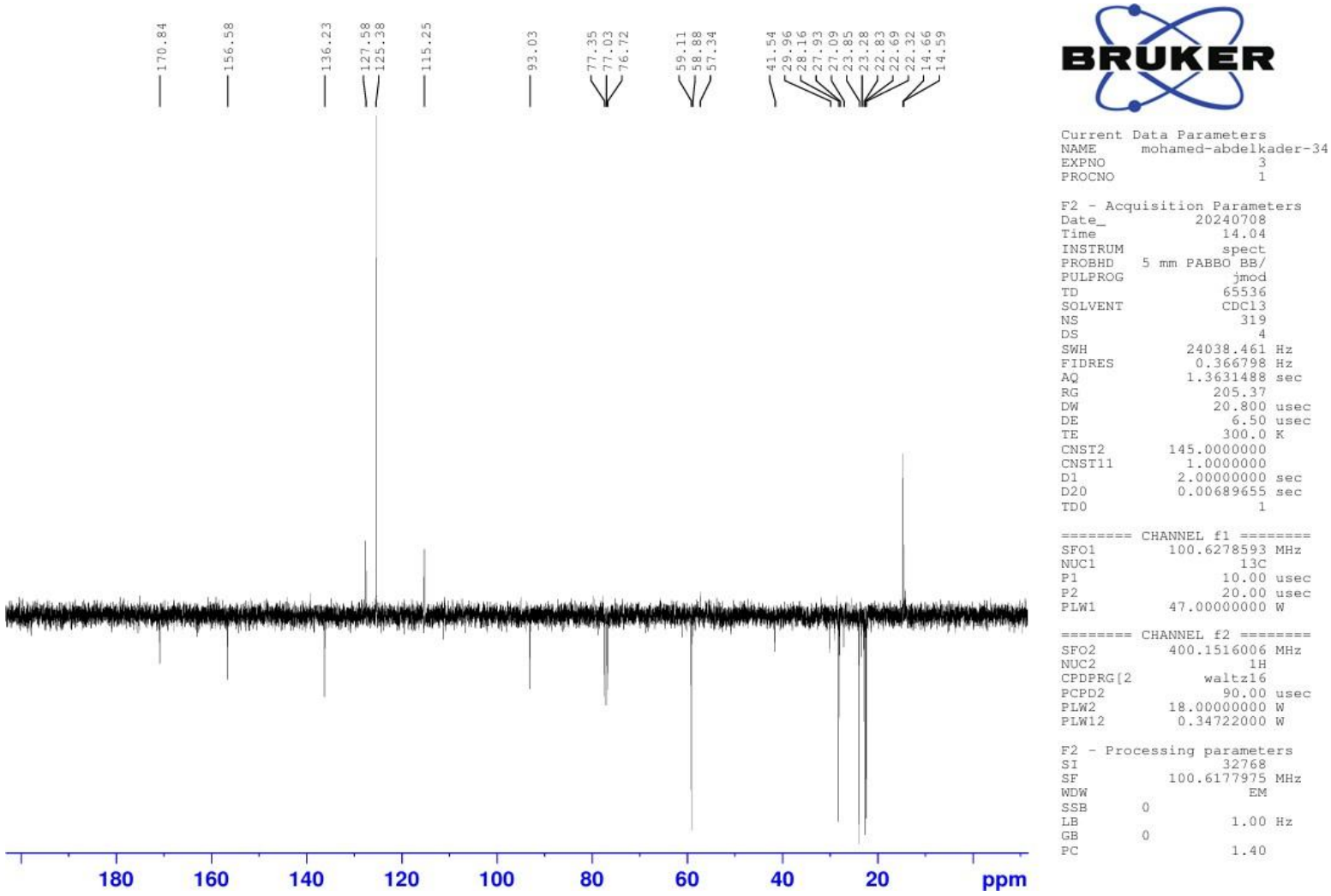


Figure (2.4 e) APT spectrum of compound (IV) in $CDCl_3$

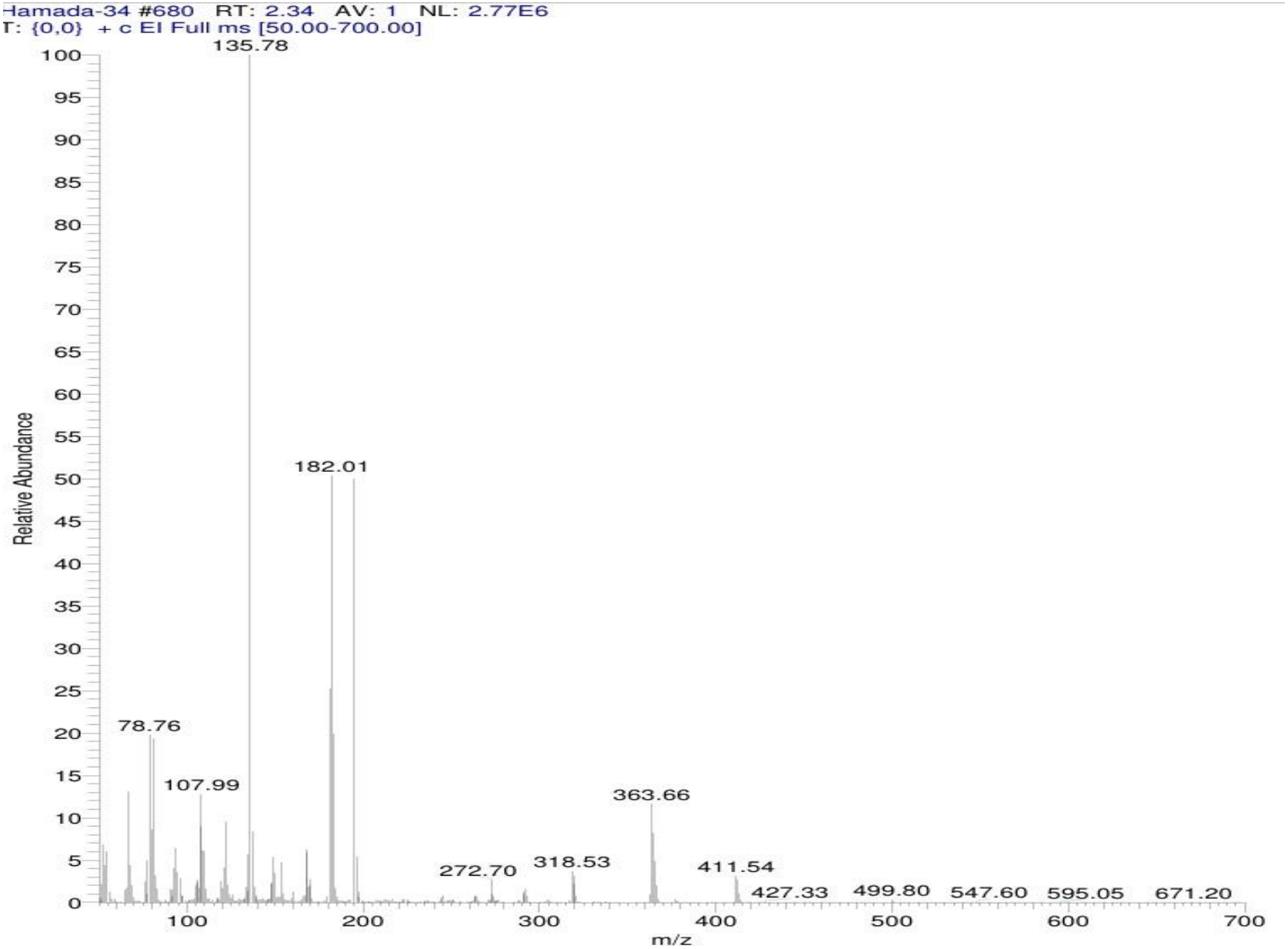


Figure (2.4 f) Mass spectrum of compound (IV)

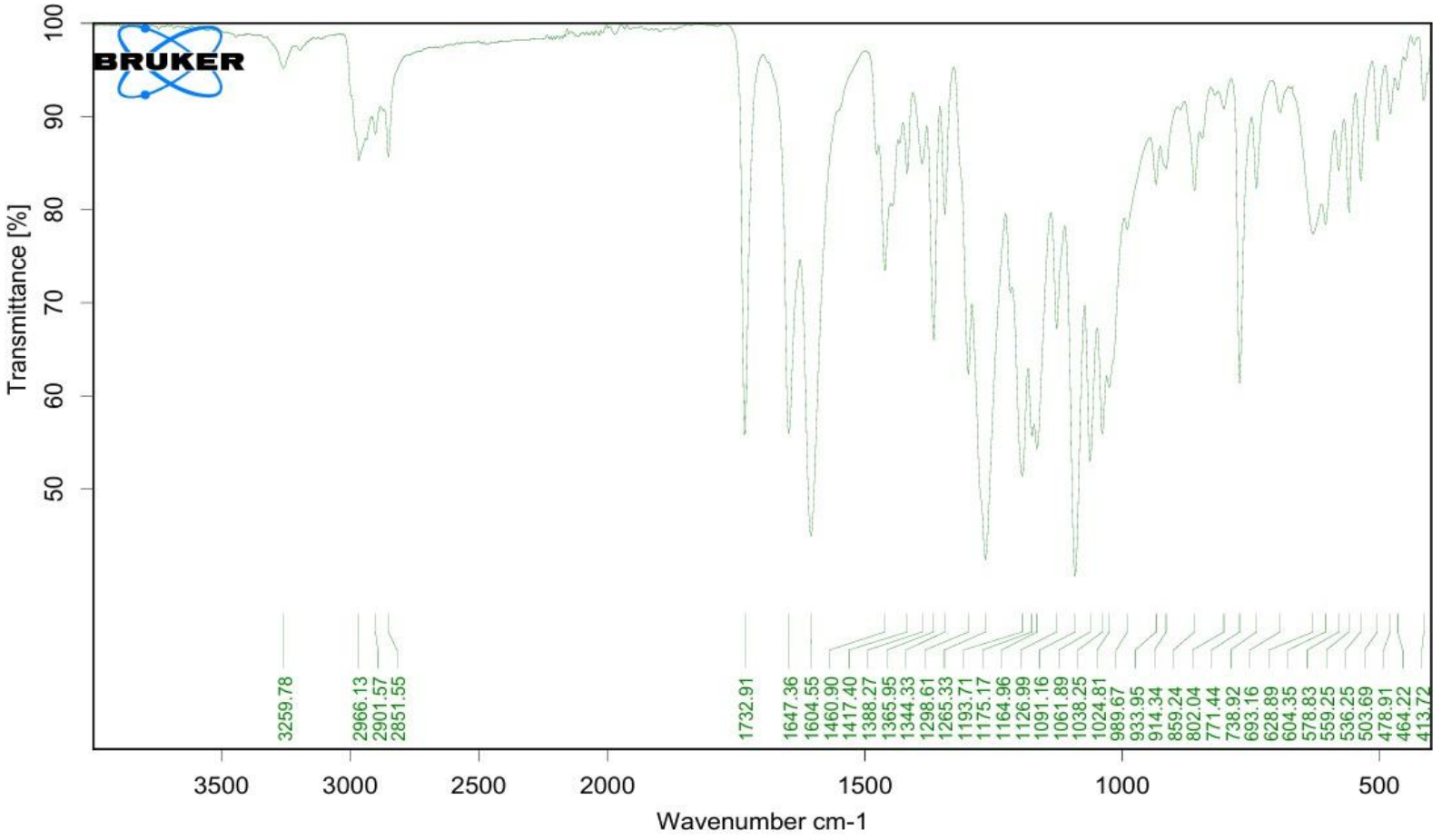


Figure (2.5 a) FT- IR spectrum of compound (v)

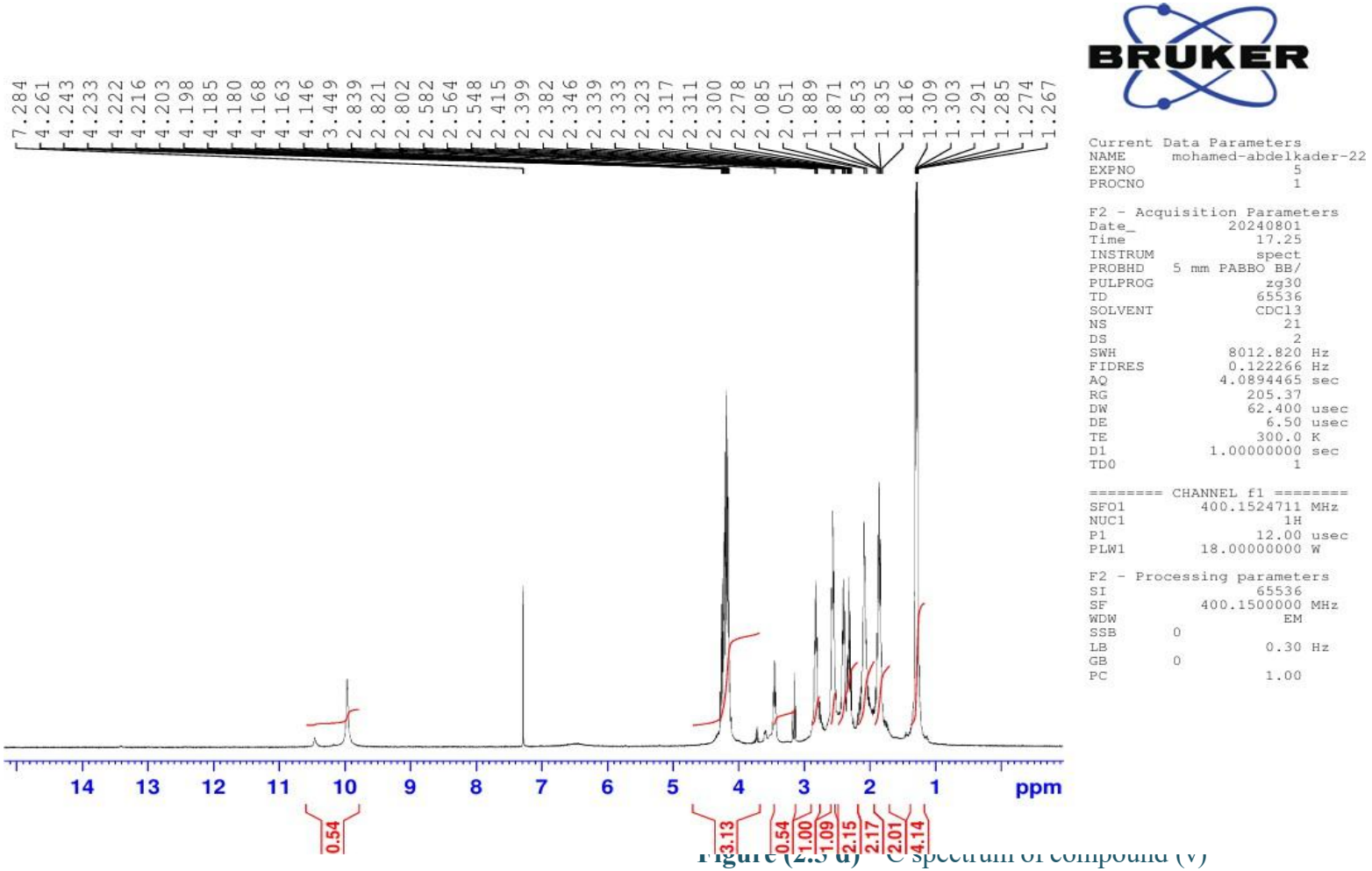


Figure (2.5 b) ^{1}HNMR spectrum of compound (v)

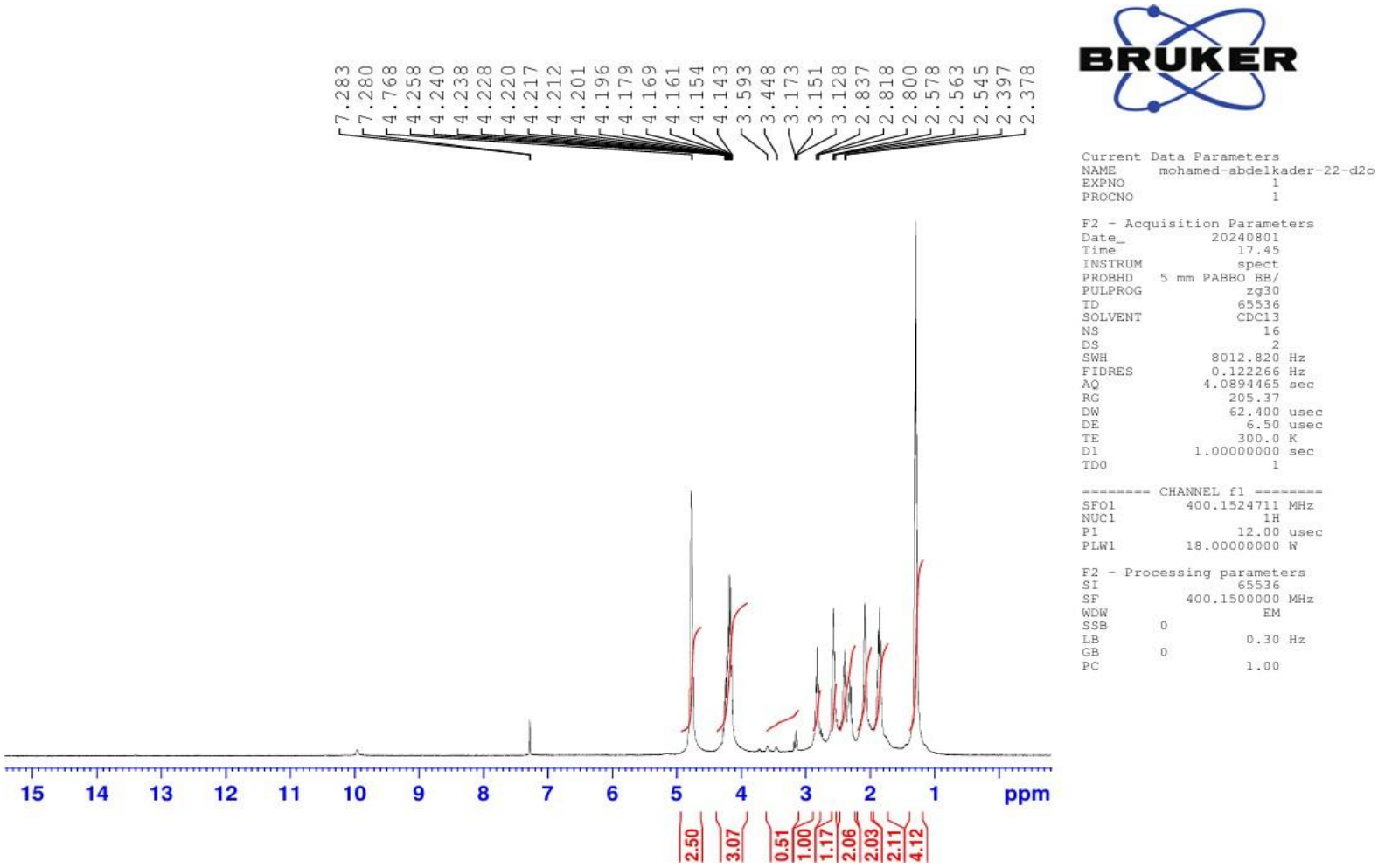
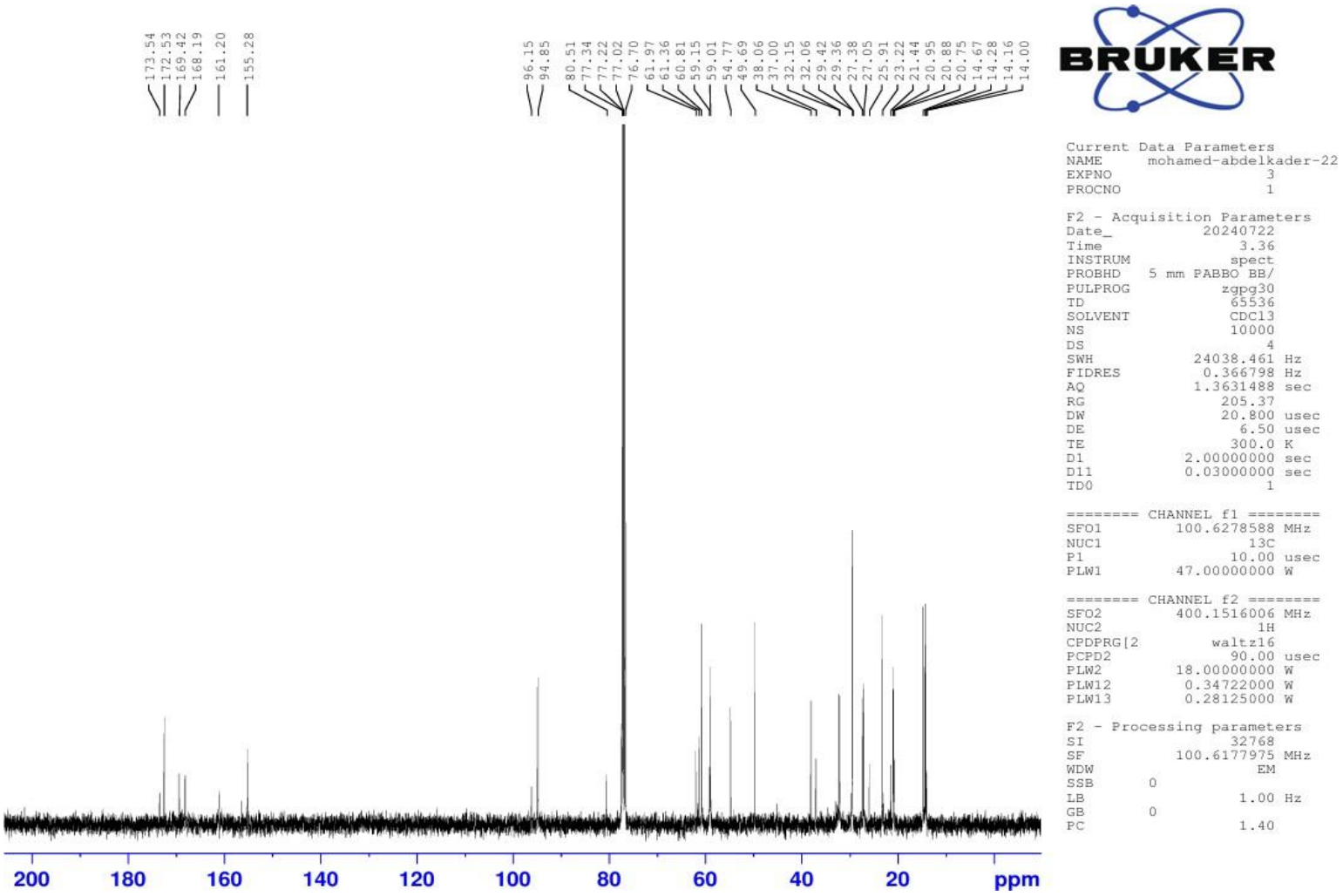


Figure (2.5 c) D_2O spectrum of compound (v)

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PROCNO                       1

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Time                   3.36
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PROBHD    5 mm PABBO BB/
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                   10000
DS                       4
SWH              24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631488 sec
RG                  205.37
DW                  20.800 usec
DE                   6.50 usec
TE                  300.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            100.6278588 MHz
NUC1                    13C
P1                    10.00 usec
PLW1           47.00000000 W

======== CHANNEL f2 ========
SFO2            400.1516006 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2           18.00000000 W
PLW12           0.34722000 W
PLW13           0.28125000 W

F2 - Processing parameters
SI                   32768
SF              100.6177975 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
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Figure (2.5 d) C^{13}-NMR spectrum of compound (v)

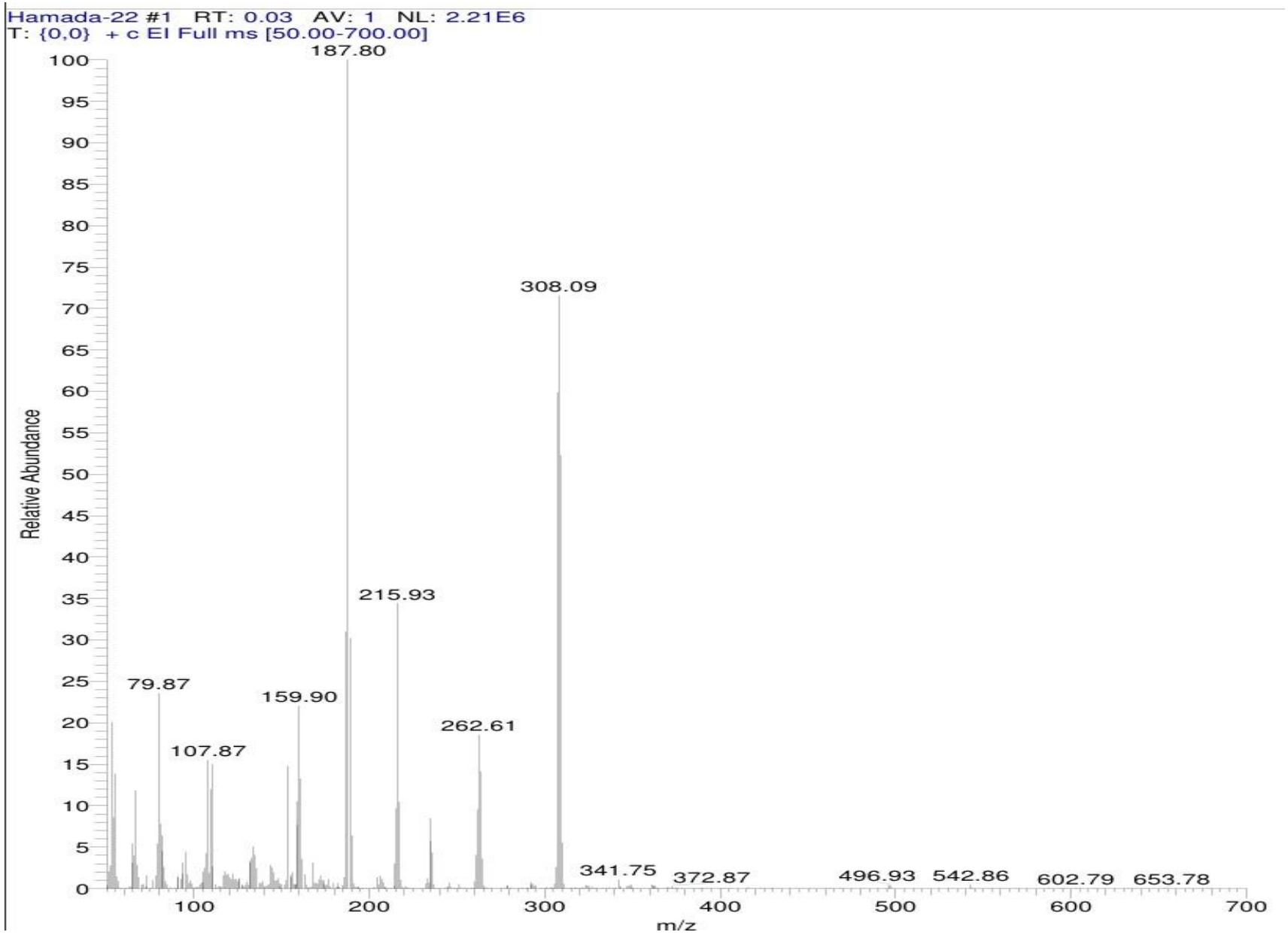


Figure (2.5 e) Mass spectrum of compound (v)

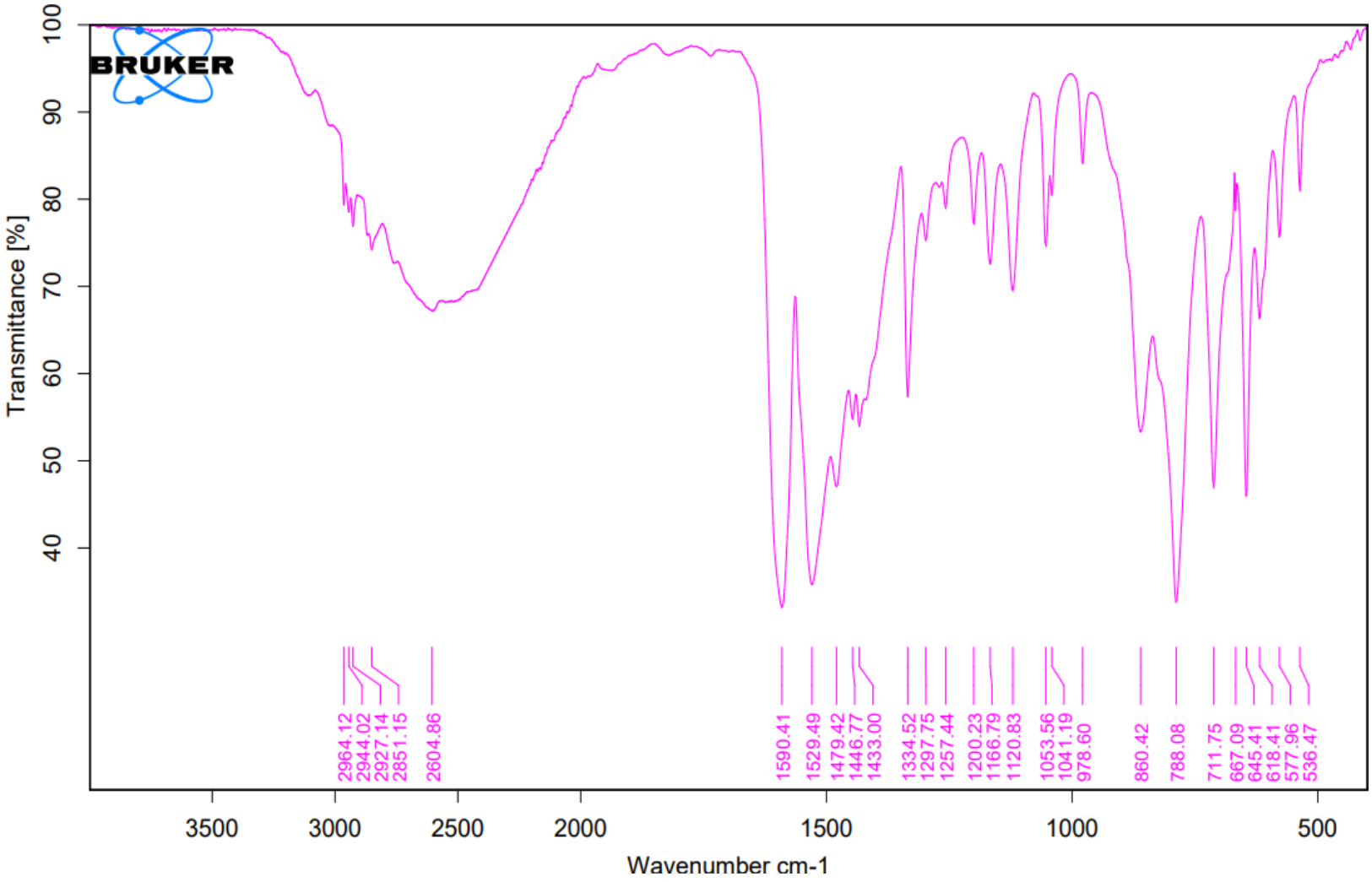


Figure (2.6 a) FT-IR spectrum of compound (VI)

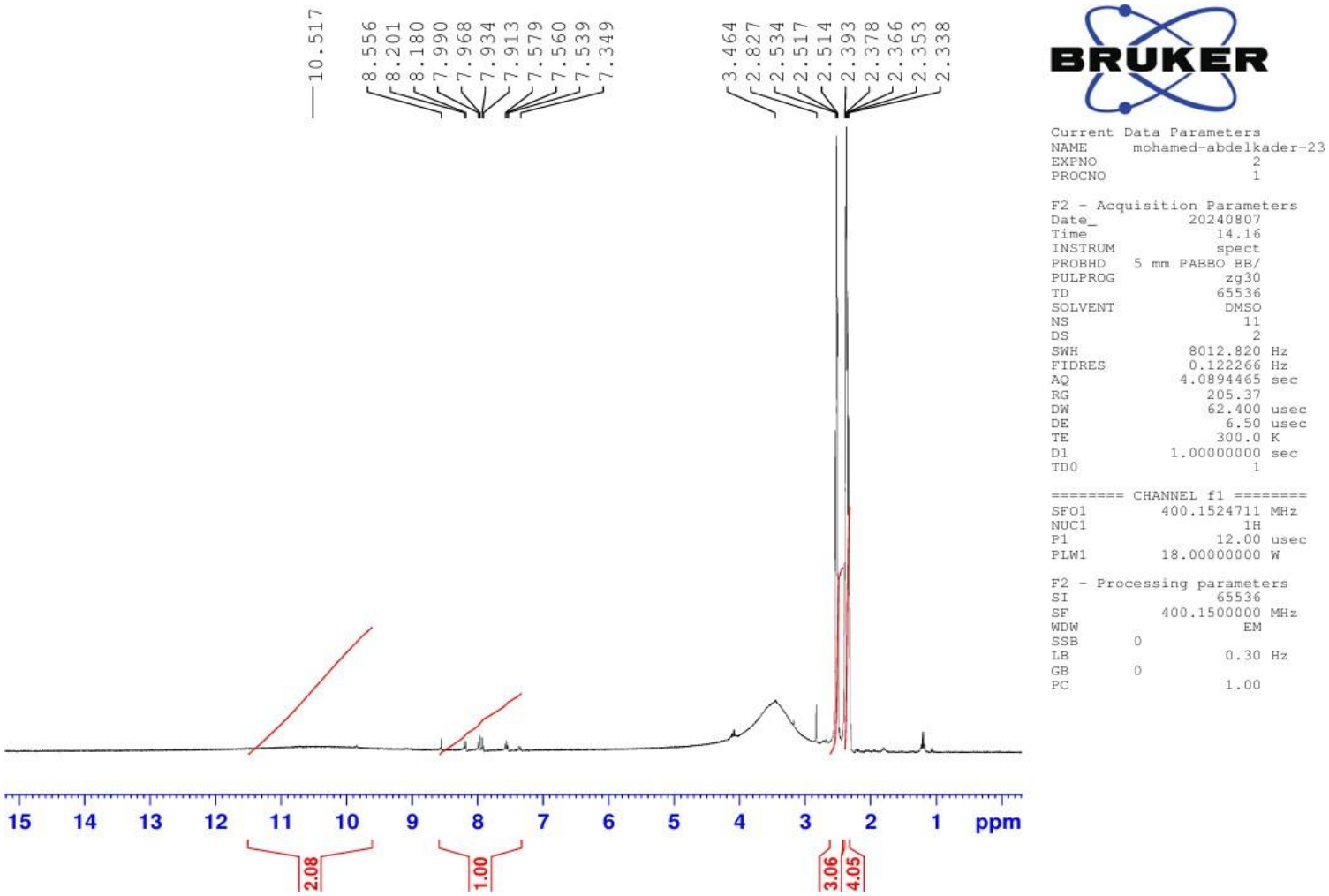
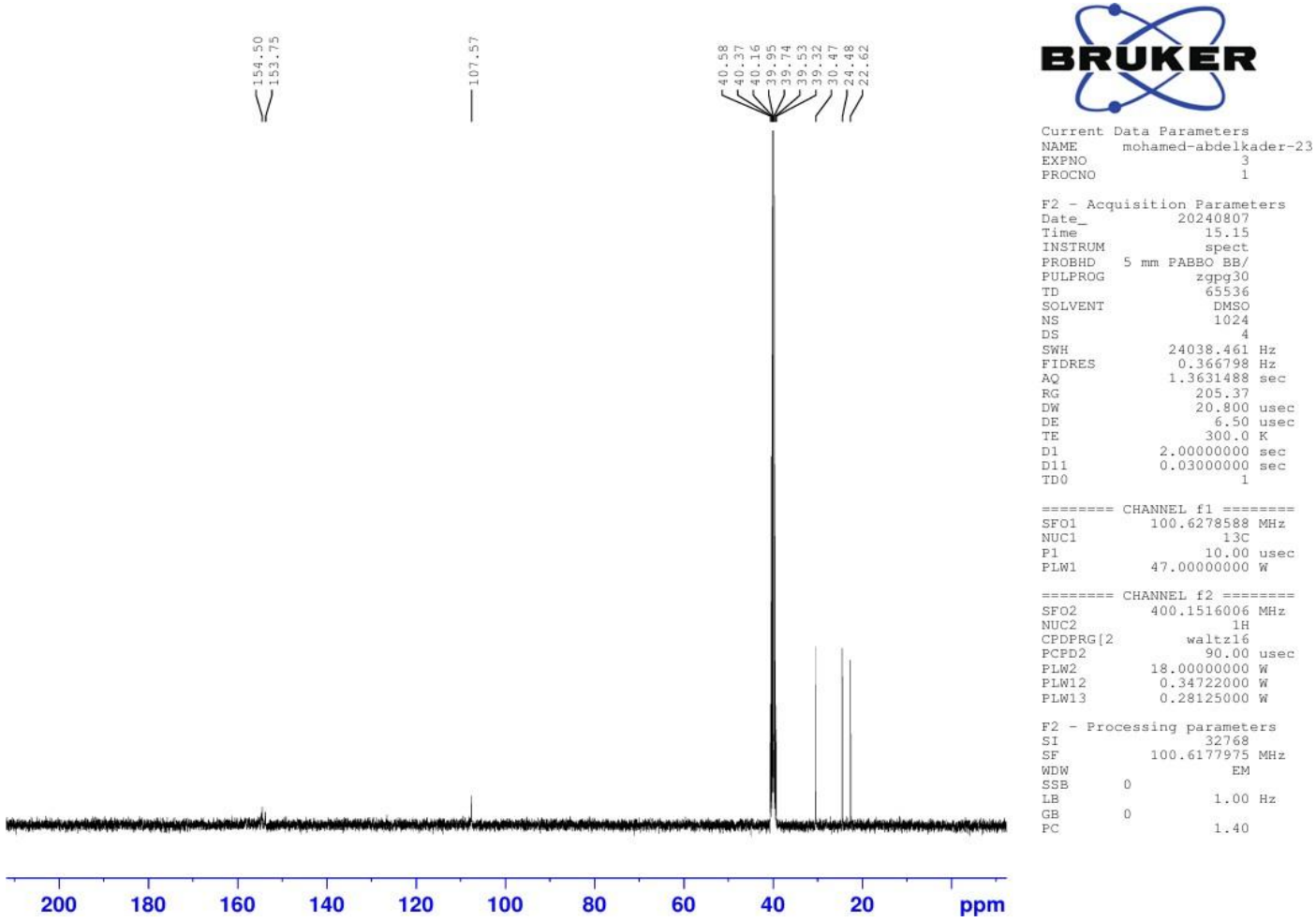


Figure (2.6 b) ^{1}HNMR spectrum of compound in DMSO-d_6 (VI)




```
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PROCNO                       1

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PROBHD    5 mm PABBO BB/
PULPROG            zgpg30
TD                  65536
SOLVENT               DMSO
NS                    1024
DS                       4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631488 sec
RG                  205.37
DW                  20.800 usec
DE                   6.50 usec
TE                  300.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          100.6278588 MHz
NUC1                   13C
P1                   10.00 usec
PLW1          47.00000000 W

======== CHANNEL f2 ========
SFO2          400.1516006 MHz
NUC2                   1H
CPDPRG[2           waltz16
PCPD2                90.00 usec
PLW2          18.00000000 W
PLW12          0.34722000 W
PLW13          0.28125000 W

F2 - Processing parameters
SI                   32768
SF            100.6177975 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```
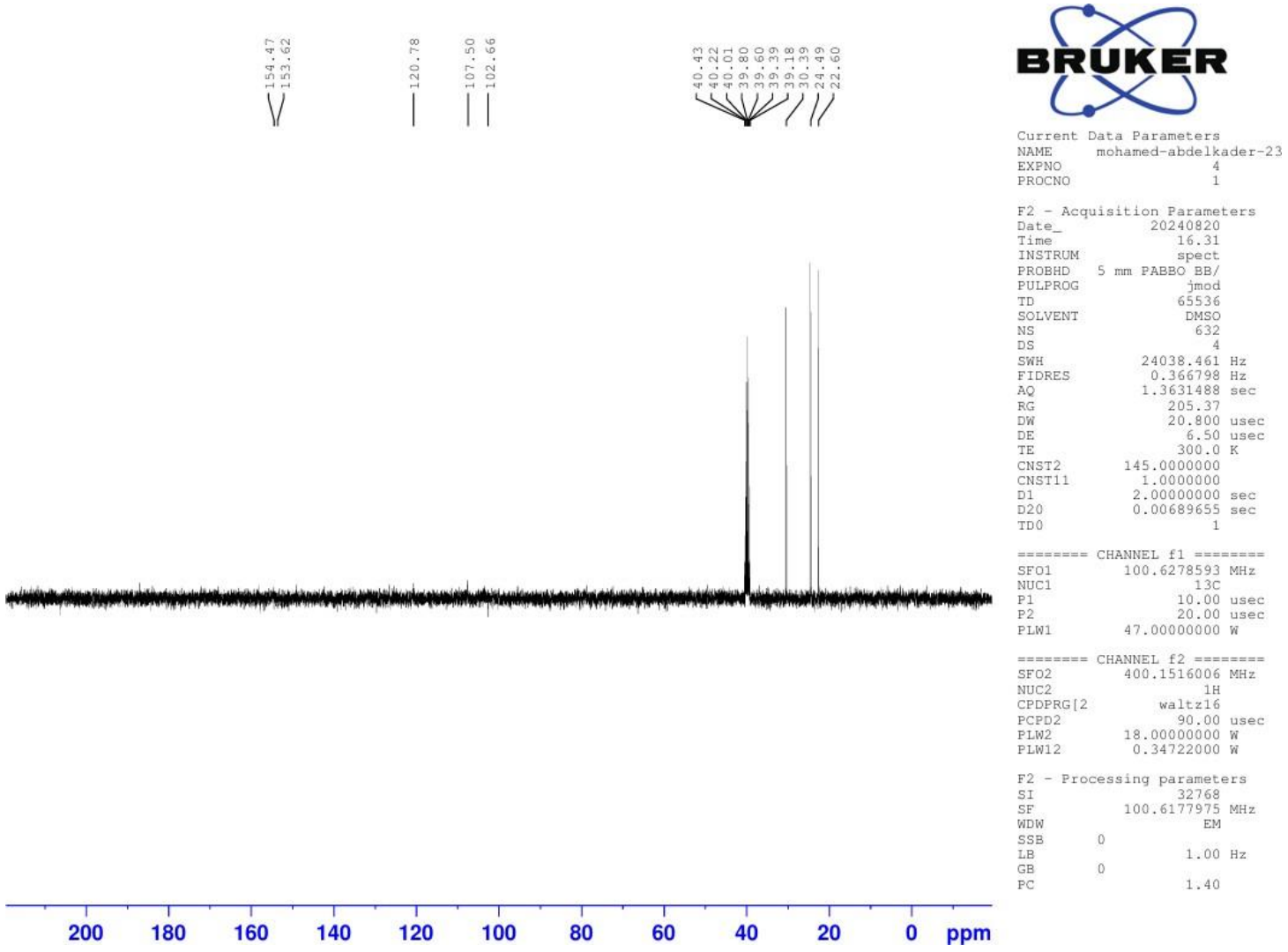

Figure (2.6 c) C^{13}-NMR spectrum of compound (VI) in DMSO-d_6

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NAME      mohamed-abdelkader-23
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_              20240820
Time                   16.31
INSTRUM                spect
PROBHD   5 mm PABBO BB/
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                      632
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                    205.37
DW                    20.800 usec
DE                     6.50 usec
TE                    300.0 K
CNST2            145.0000000
CNST11             1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             100.6278593 MHz
NUC1                    13C
P1                    10.00 usec
P2                    20.00 usec
PLW1            47.00000000 W

======== CHANNEL f2 ========
SFO2             400.1516006 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2            18.00000000 W
PLW12            0.34722000 W

F2 - Processing parameters
SI                     32768
SF               100.6177975 MHz
WDW                       EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

Figure (2.6 d) APT spectrum of compound (VI) in DMSO-d_6

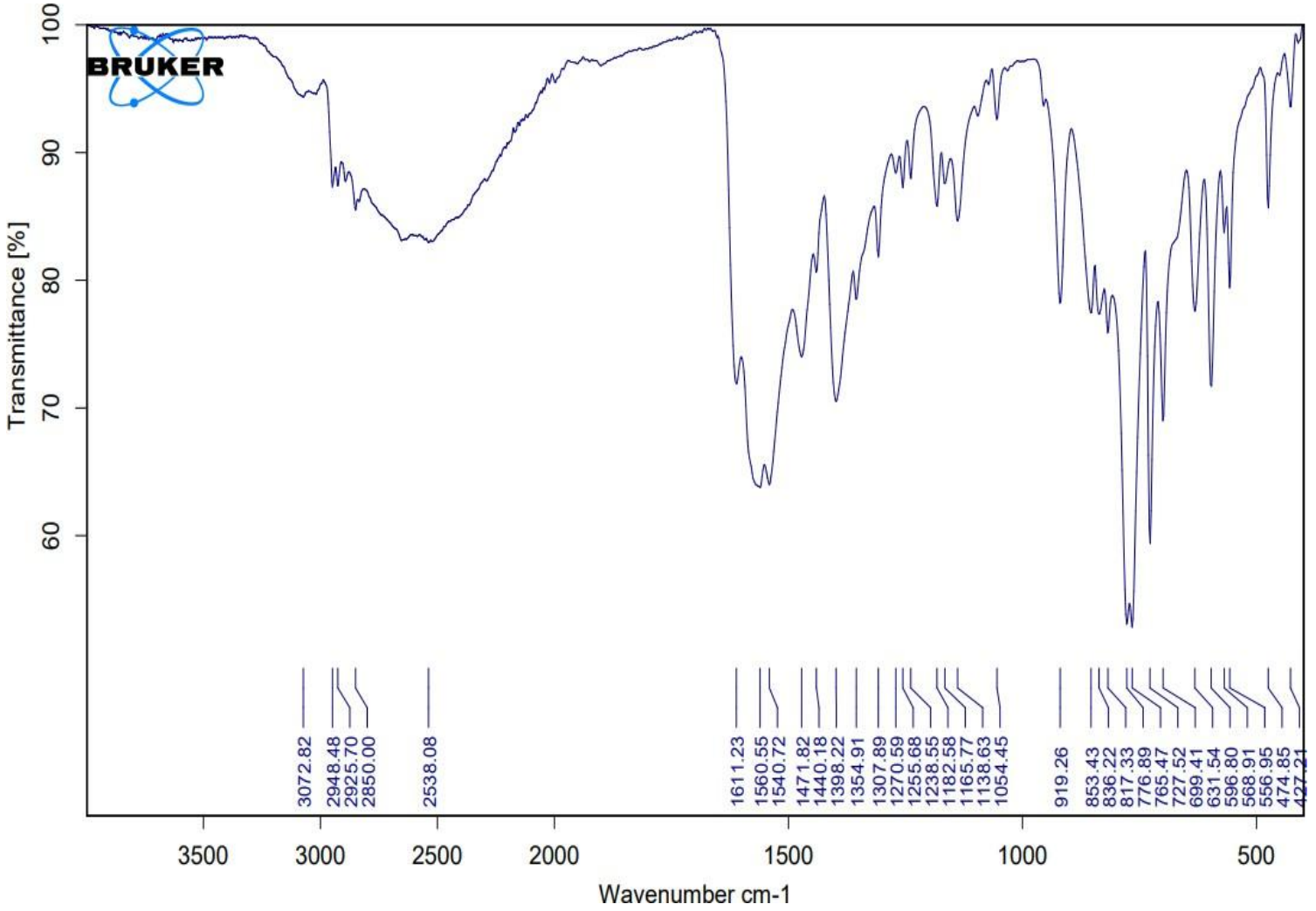


Figure (2.7a) FT-IR spectrum of compound (VII)

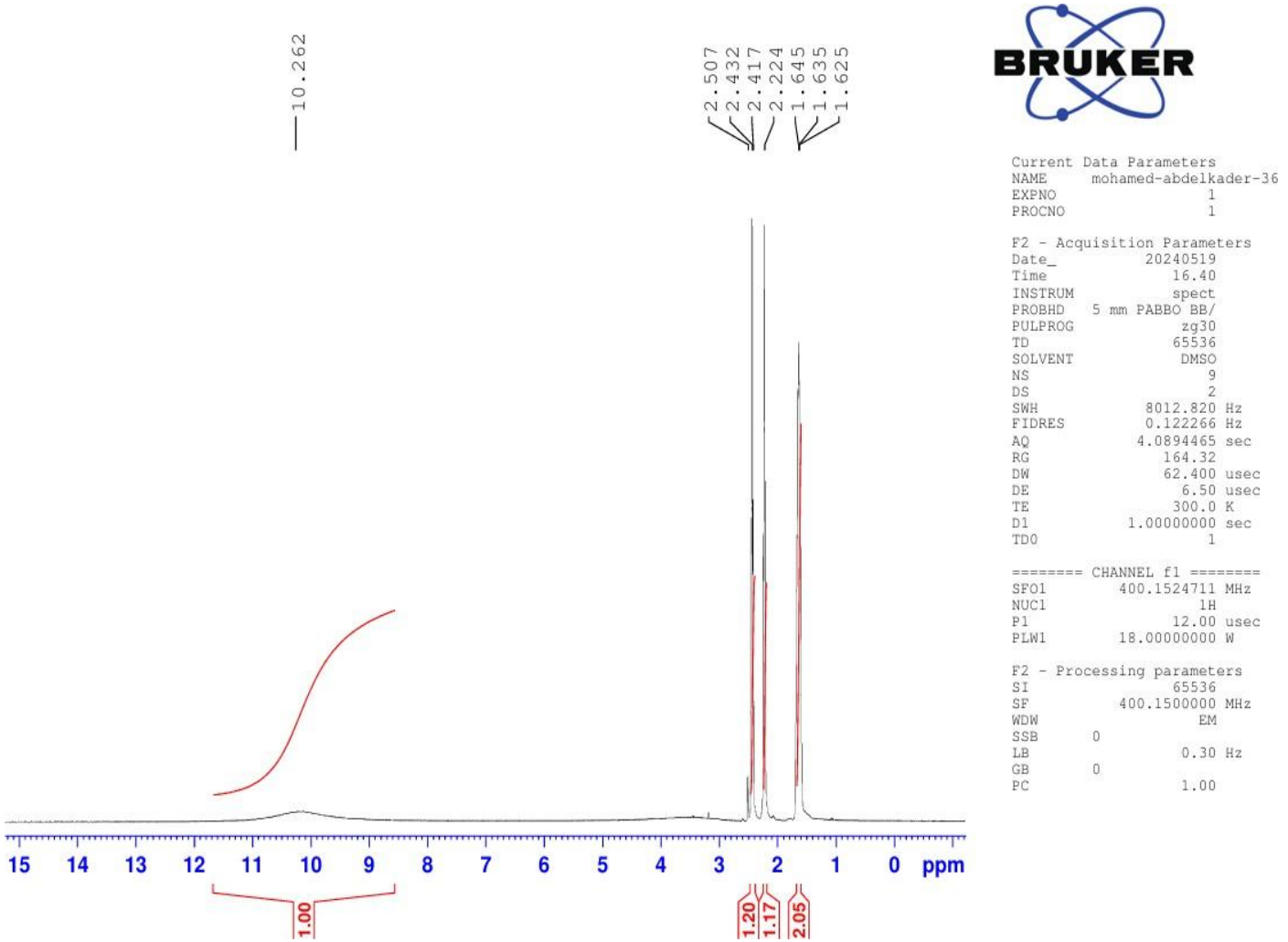


Figure (2.7b) ^{1}HNMR spectrum of compound (VII) in DMSO-d_6

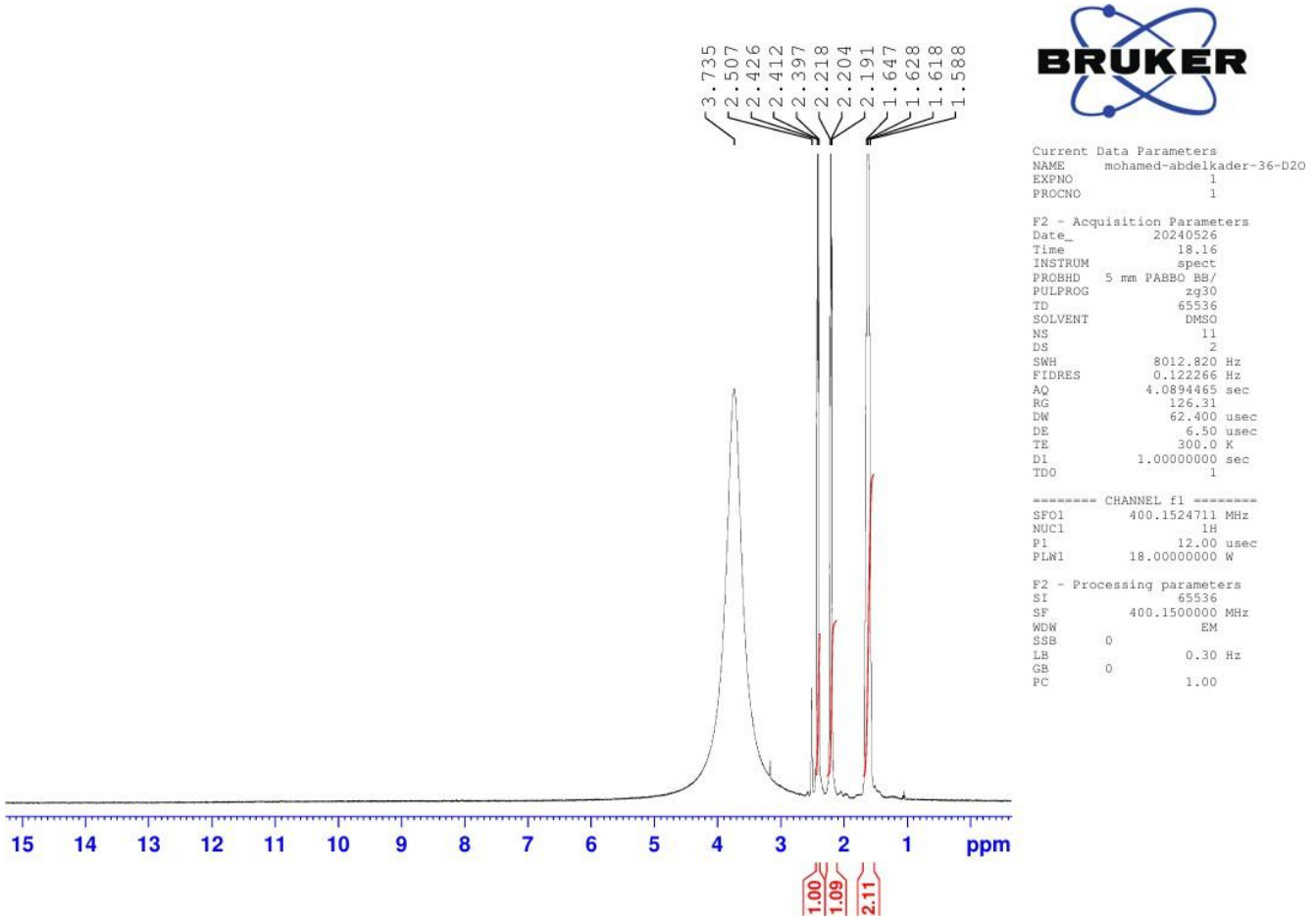


Figure (2.7c) D_2O spectrum of compound (VII) in DMSO-d_6

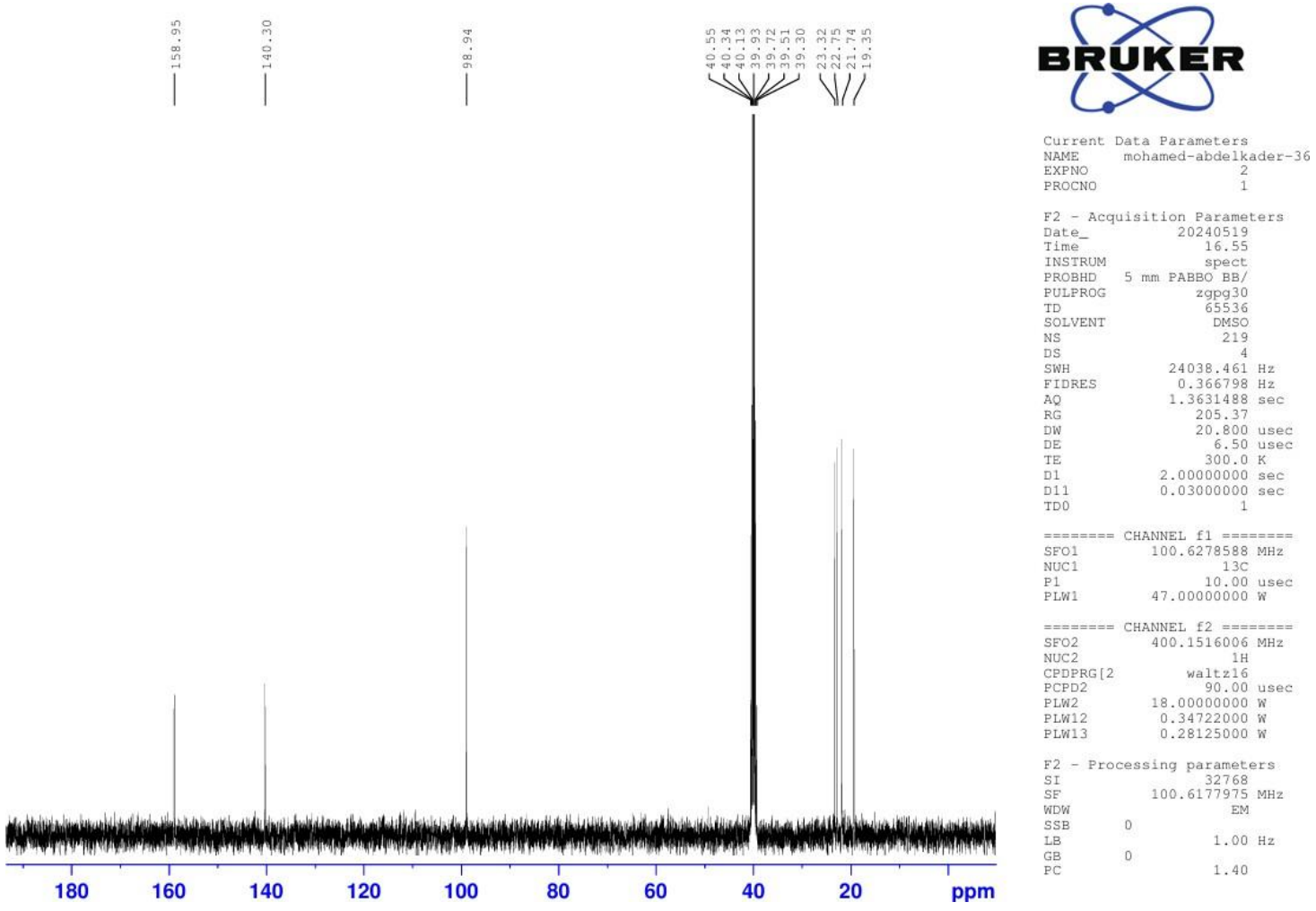
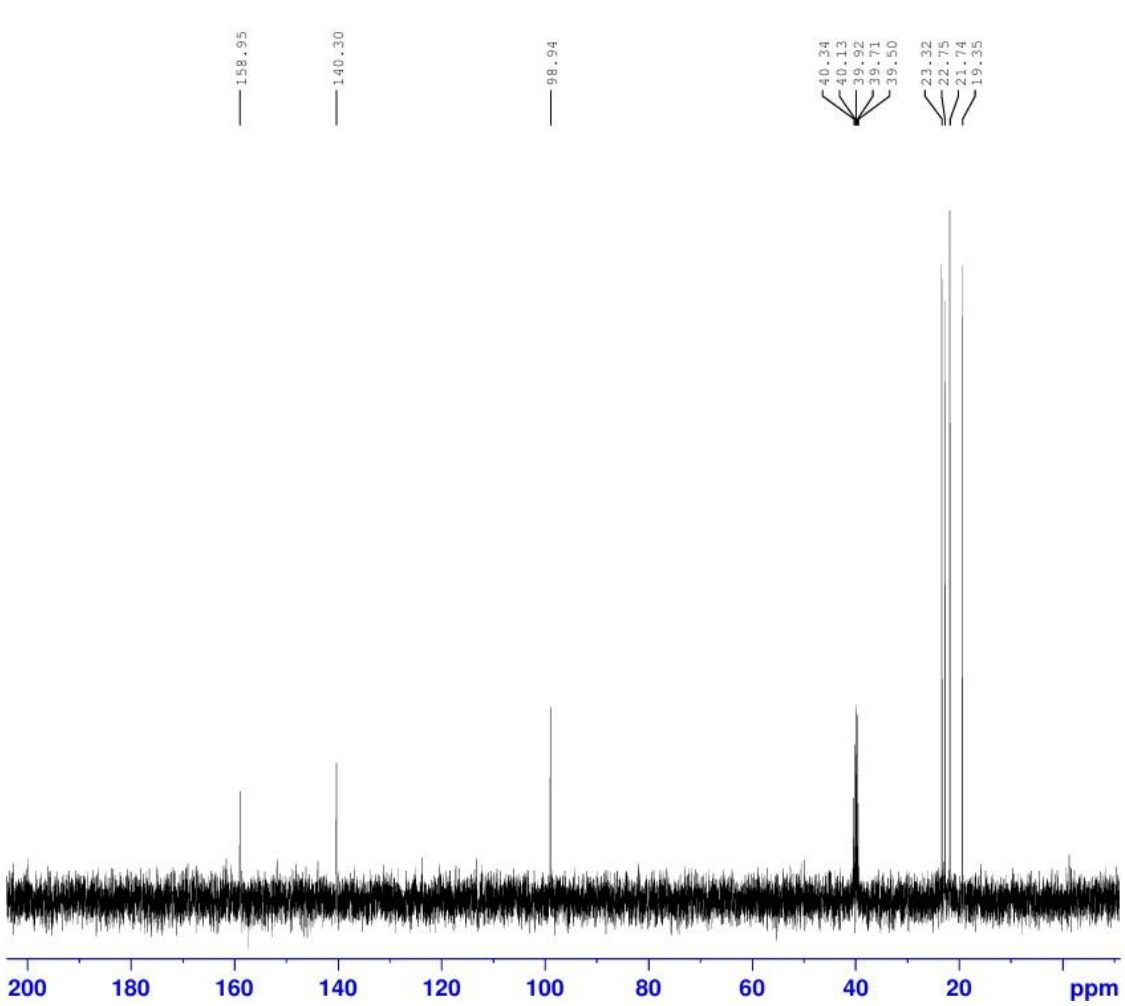


Figure (2.7d) C^{13}-NMR spectrum of compound (VII) in DMSO-d_6



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EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_              20240519
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INSTRUM               spect
PROBHD    5 mm PABBO BB/
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                      108
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                1.3631488 sec
RG                   205.37
DW                   20.800 usec
DE                    6.50 usec
TE                   300.0 K
CNST2            145.0000000
CNST11             1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                       1

======== CHANNEL f1 ========
SFO1            100.6278593 MHz
NUC1                    13C
P1                    10.00 usec
P2                    20.00 usec
PLW1           47.00000000 W

======== CHANNEL f2 ========
SFO2            400.1516006 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2           18.00000000 W
PLW12           0.34722000 W

F2 - Processing parameters
SI                    32768
SF              100.6177975 MHz
WDW                      EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

Figure (2.7e) APT spectrum of compound (VII) in DMSO-d_6

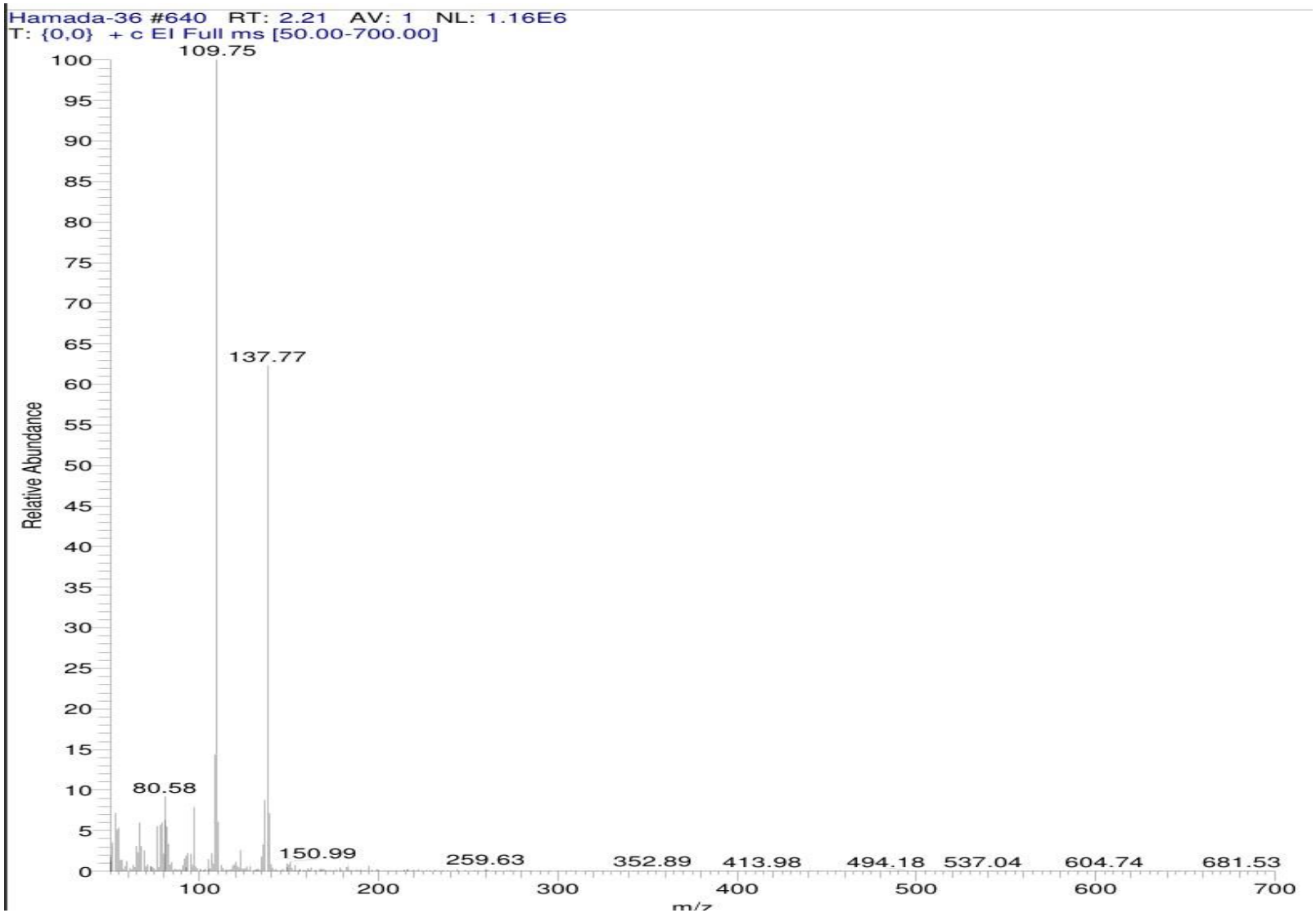


Figure (2.7 f) Mass spectrum of compound (VII)

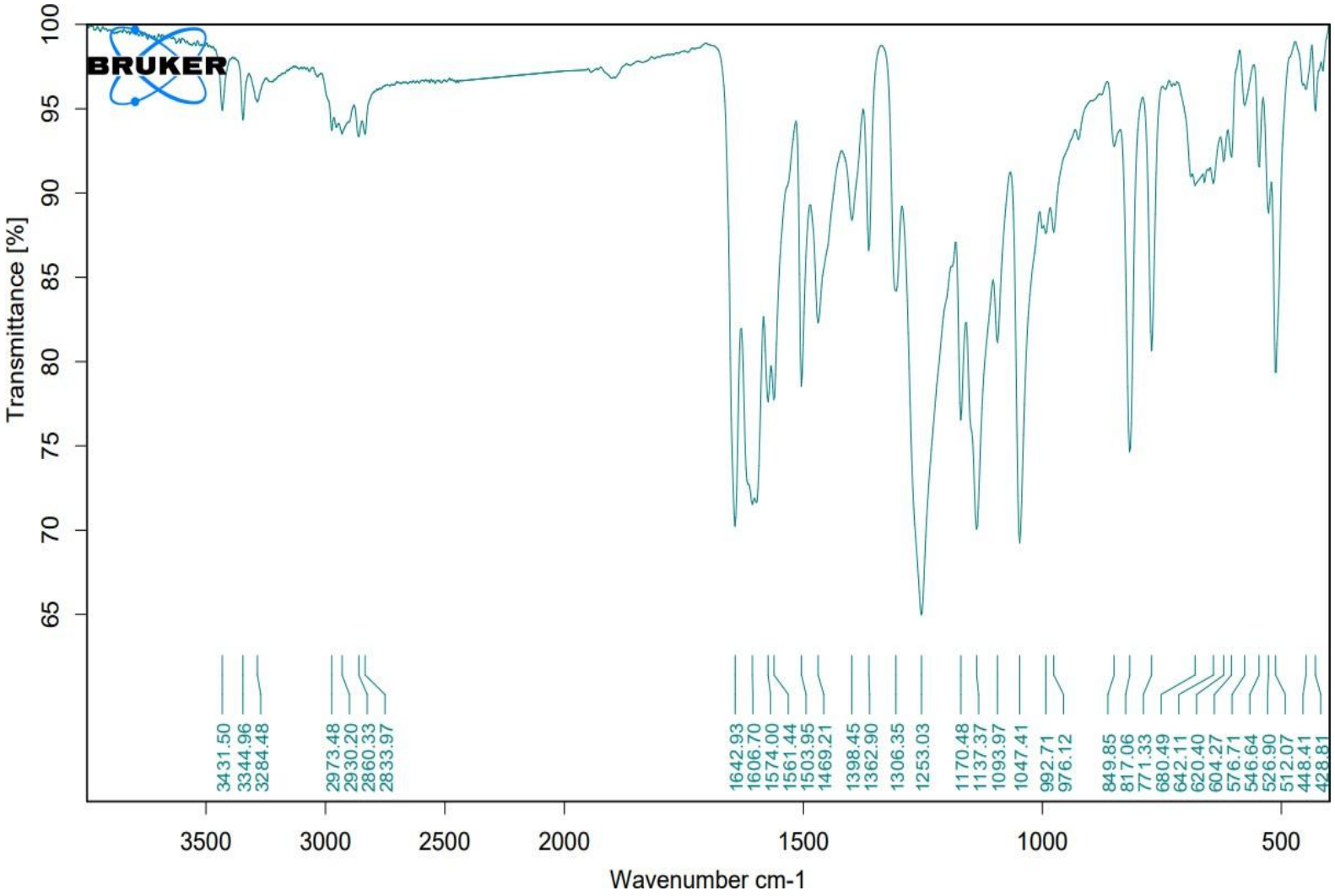
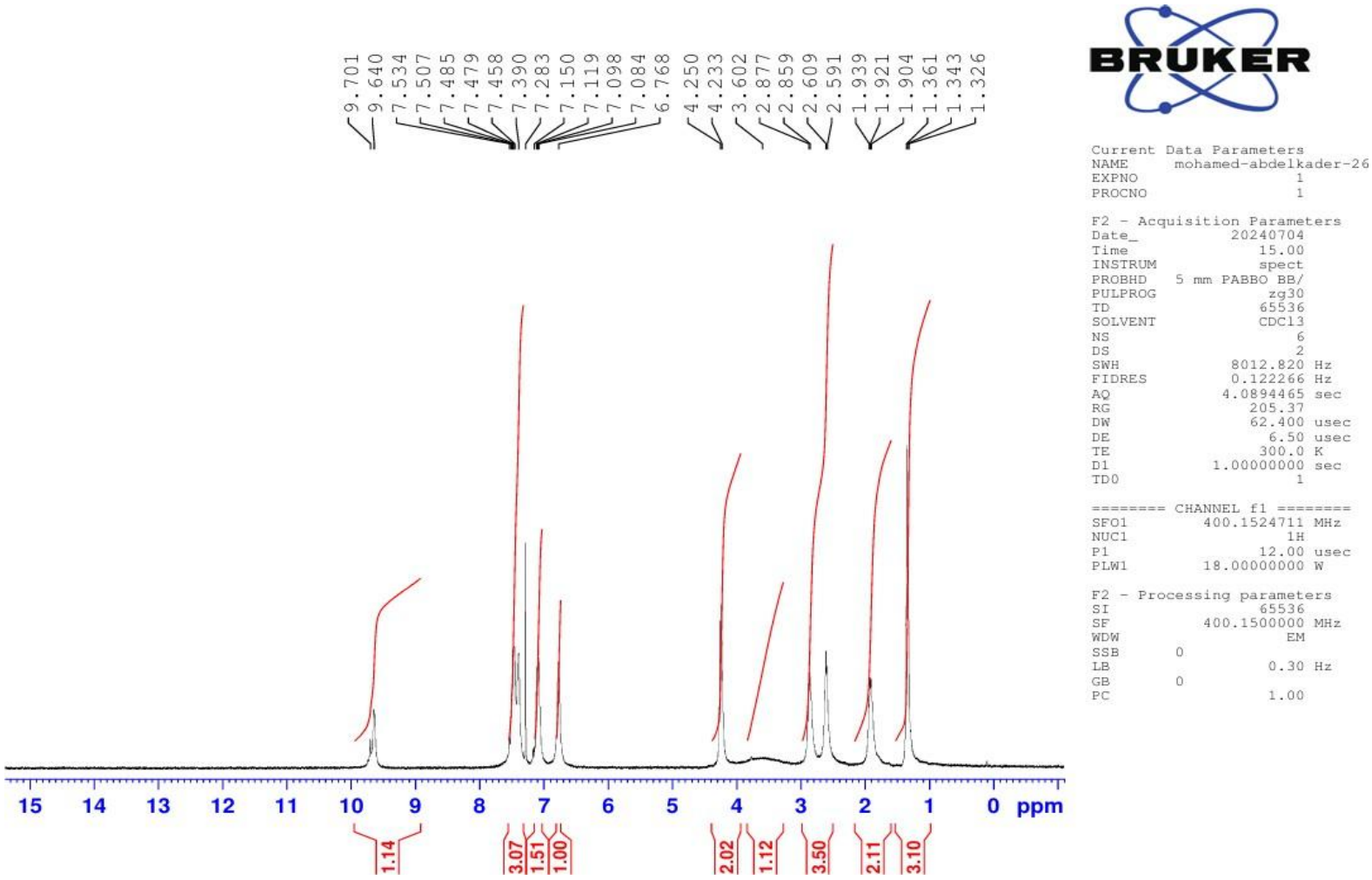


Figure (2.8 a) FT- IR spectrum of compound (VIII)



BRUKER

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Current Data Parameters
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EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20240704
Time              15.00
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                   6
DS                   2
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0894465 sec
RG               205.37
DW               62.400 usec
DE                6.50 usec
TE               300.0 K
D1            1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         400.1524711 MHz
NUC1                1H
P1                12.00 usec
PLW1        18.00000000 W

F2 - Processing parameters
SI                65536
SF           400.1500000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

Figure (2.8 b) ^{1}HNMR spectrum of compound (VIII) in $CDCl_3$

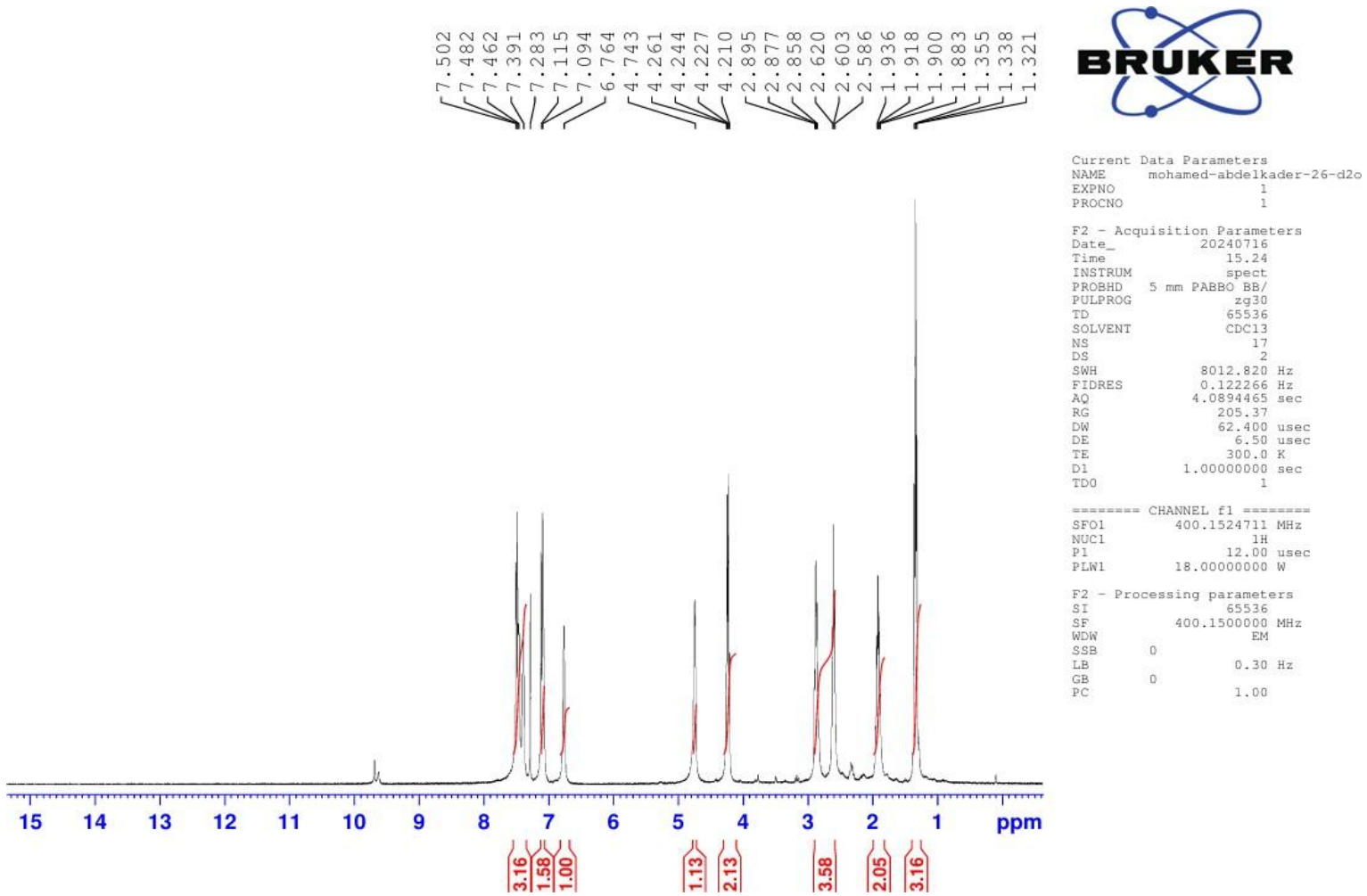
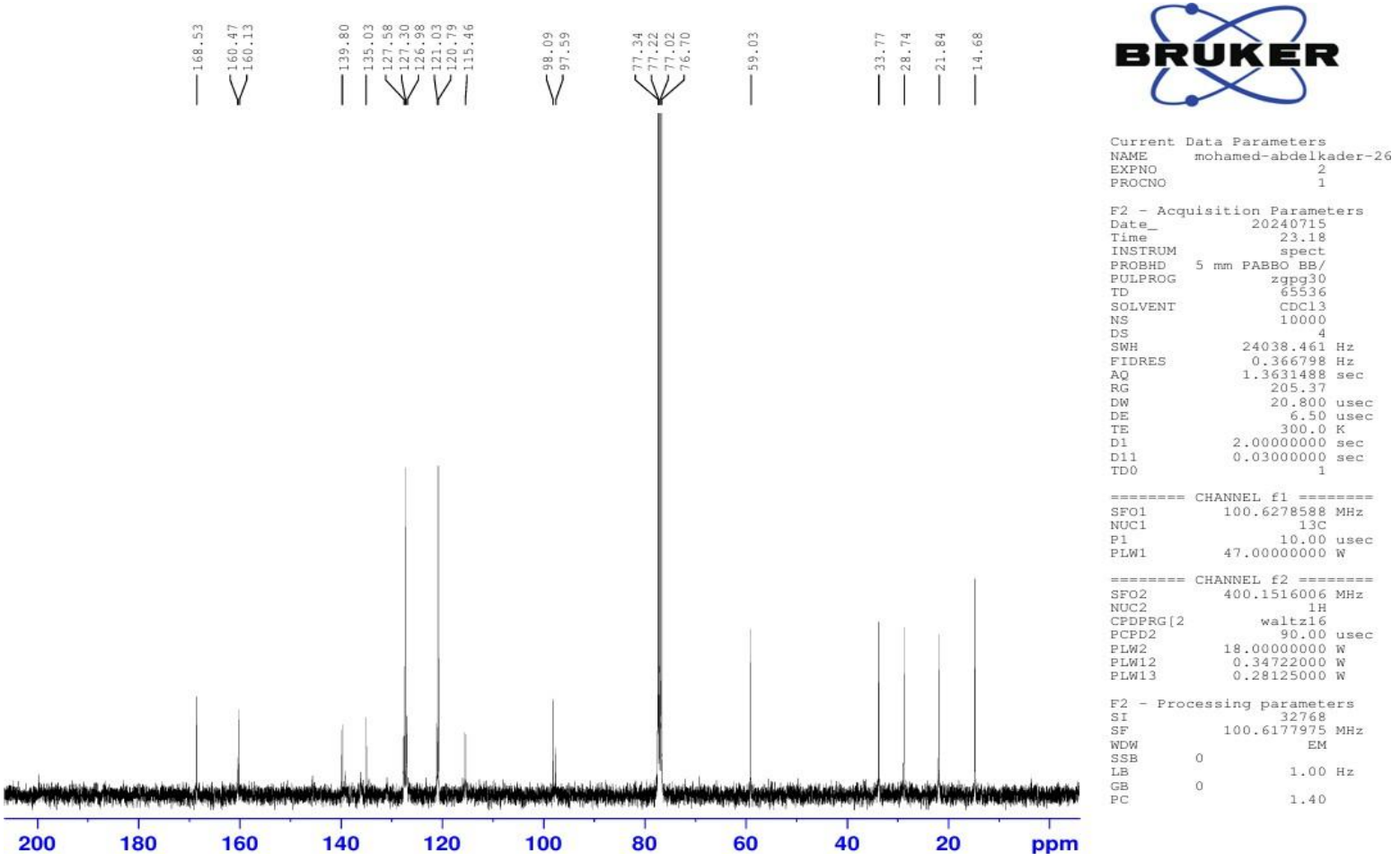


Figure (2.8 c) D_2O spectrum of compound (VIII) in $CDCl_3$

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Current Data Parameters
NAME      mohamed-abdelkader-26
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
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Time                  23.18
INSTRUM               spect
PROBHD    5 mm PABBO BB/
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                   10000
DS                       4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631488 sec
RG                  205.37
DW                  20.800 usec
DE                   6.50 usec
TE                  300.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          100.6278588 MHz
NUC1                   13C
P1                   10.00 usec
PLW1          47.00000000 W

======== CHANNEL f2 ========
SFO2          400.1516006 MHz
NUC2                   1H
CPDPRG[2           waltz16
PCPD2                90.00 usec
PLW2          18.00000000 W
PLW12          0.34722000 W
PLW13          0.28125000 W

F2 - Processing parameters
SI                   32768
SF            100.6177975 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

Figure (2.8 d) C^{13}-NMR spectrum of compound (VIII) in $CDCl_3$

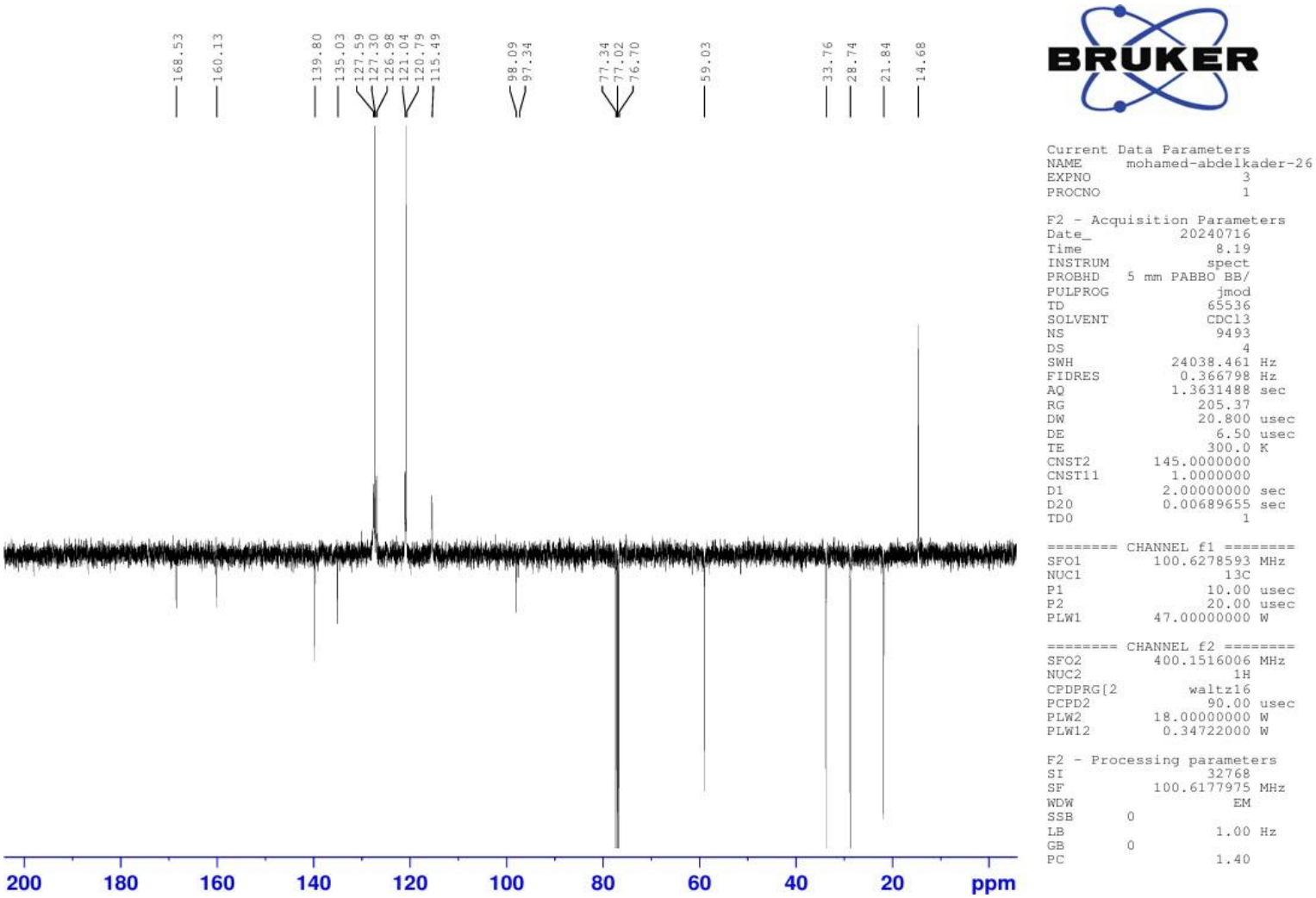


Figure (2.8 e) APT spectrum of compound (VIII) in $CDCl_3$

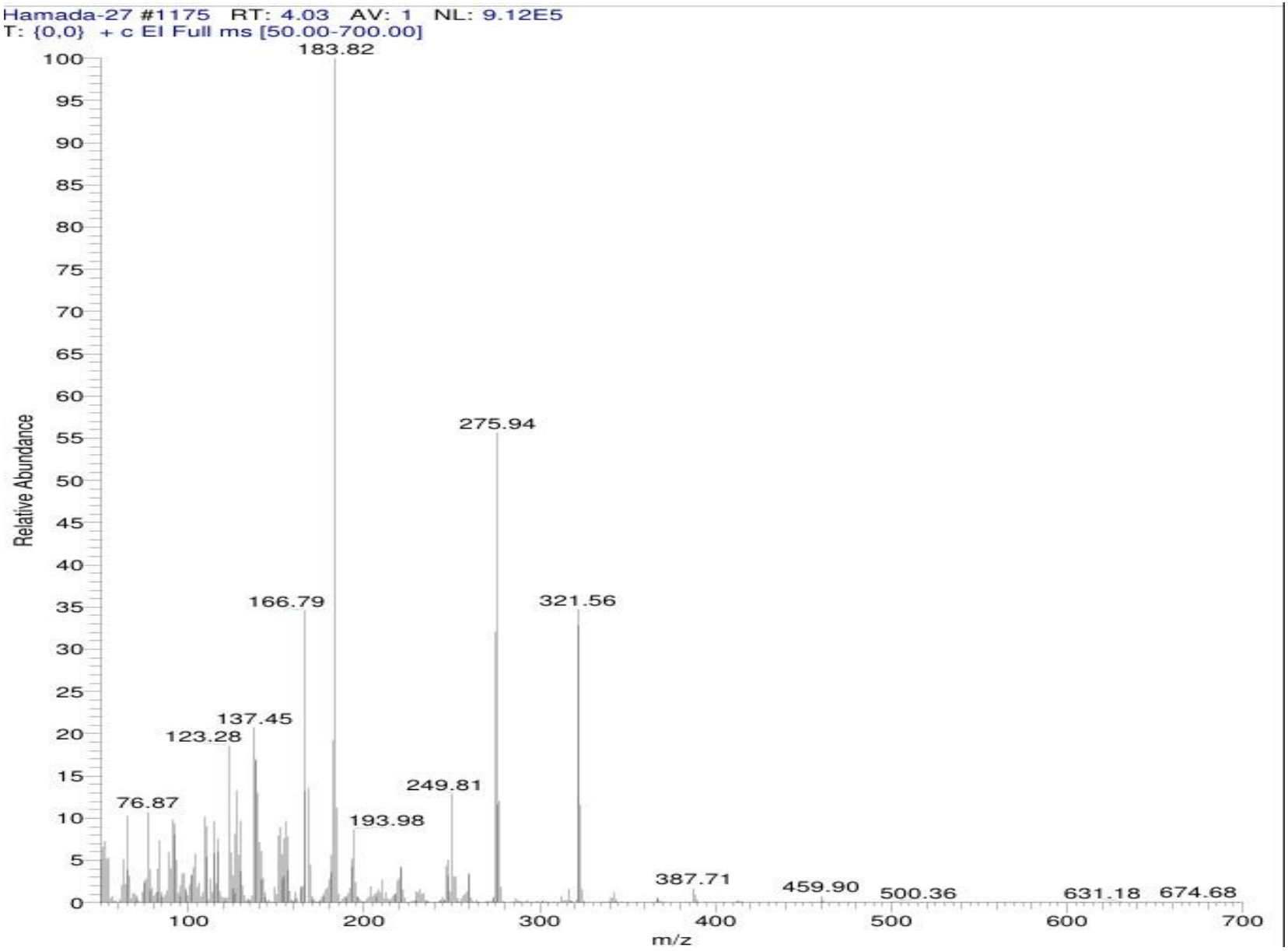


Figure (2.8 f) Mass spectrum of compound (VIII)

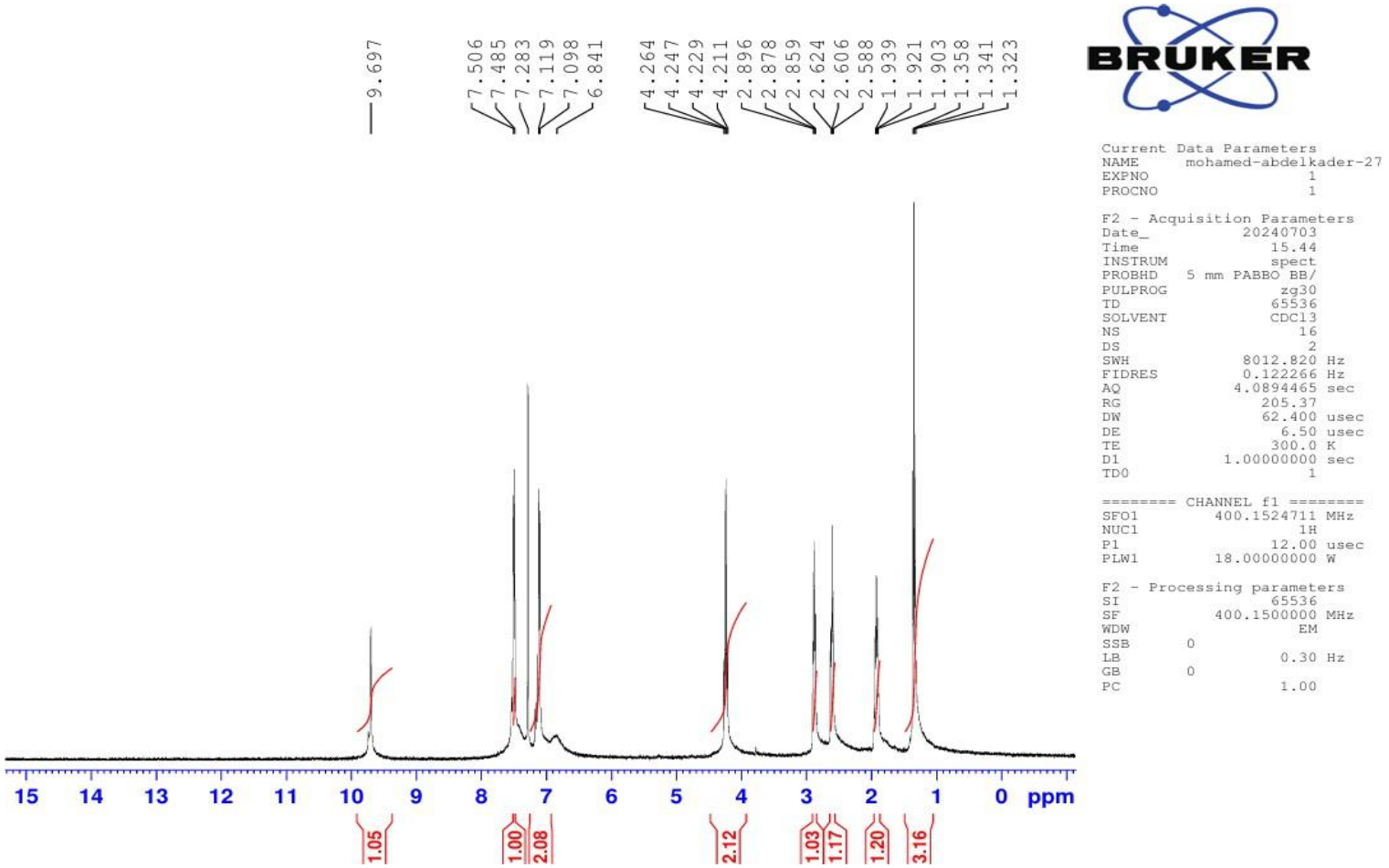
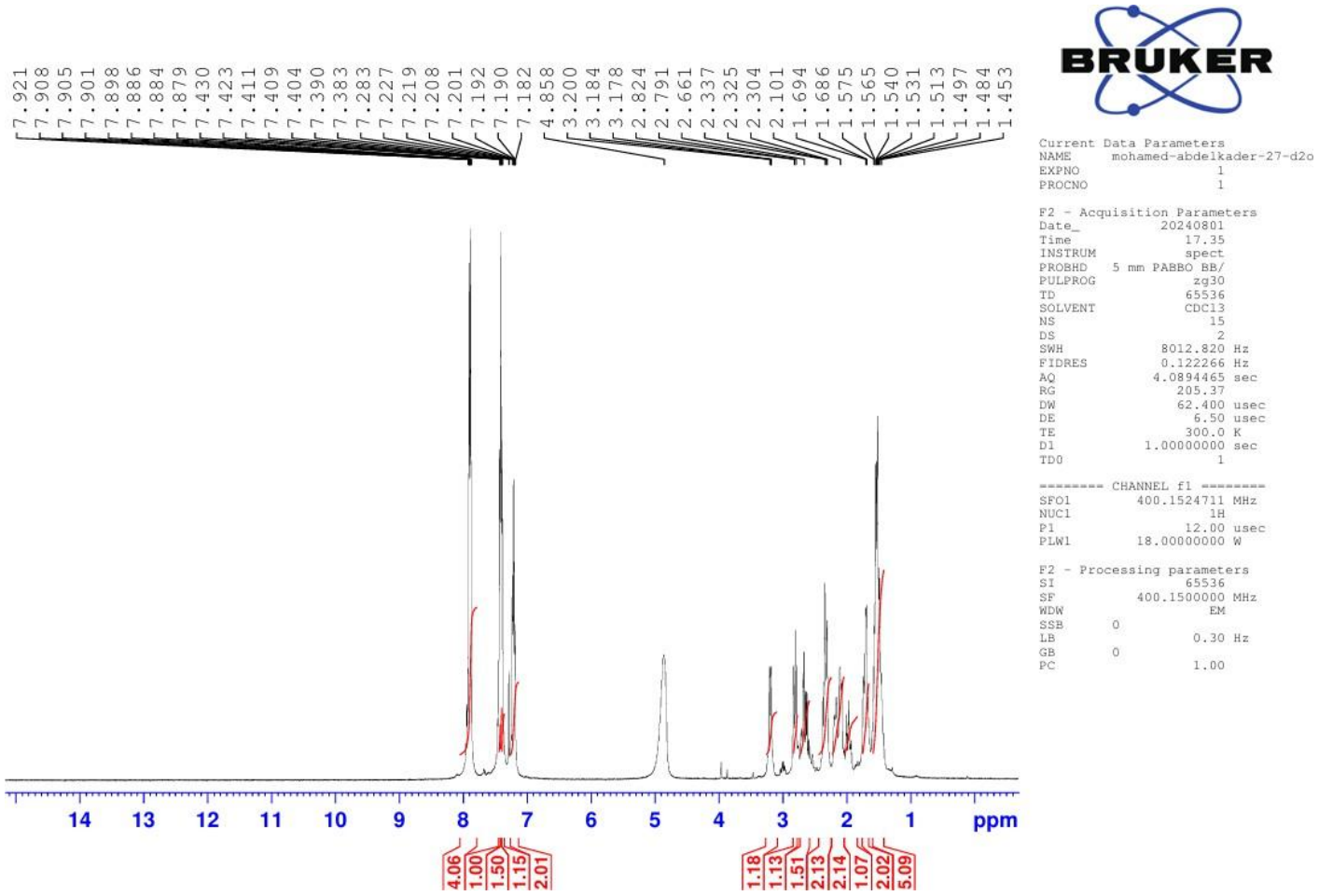


Figure (2.9 a) ^{1}HNMR spectrum of compound (IX) in $CDCl_3$



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Current Data Parameters
NAME      mohamed-abdelkader-27-d2o
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20240801
Time              17.35
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  15
DS                   2
SWH           8012.820 Hz
FIDRES        0.122266 Hz
AQ            4.0894465 sec
RG               205.37
DW               62.400 usec
DE                6.50 usec
TE               300.0 K
D1            1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        400.1524711 MHz
NUC1                1H
P1                12.00 usec
PLW1        18.00000000 W

F2 - Processing parameters
SI               65536
SF          400.1500000 MHz
WDW                 EM
SSB      0
LB               0.30 Hz
GB       0
PC               1.00
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Figure (2.9 b) D_2O spectrum of compound (IX) in $CDCl_3$

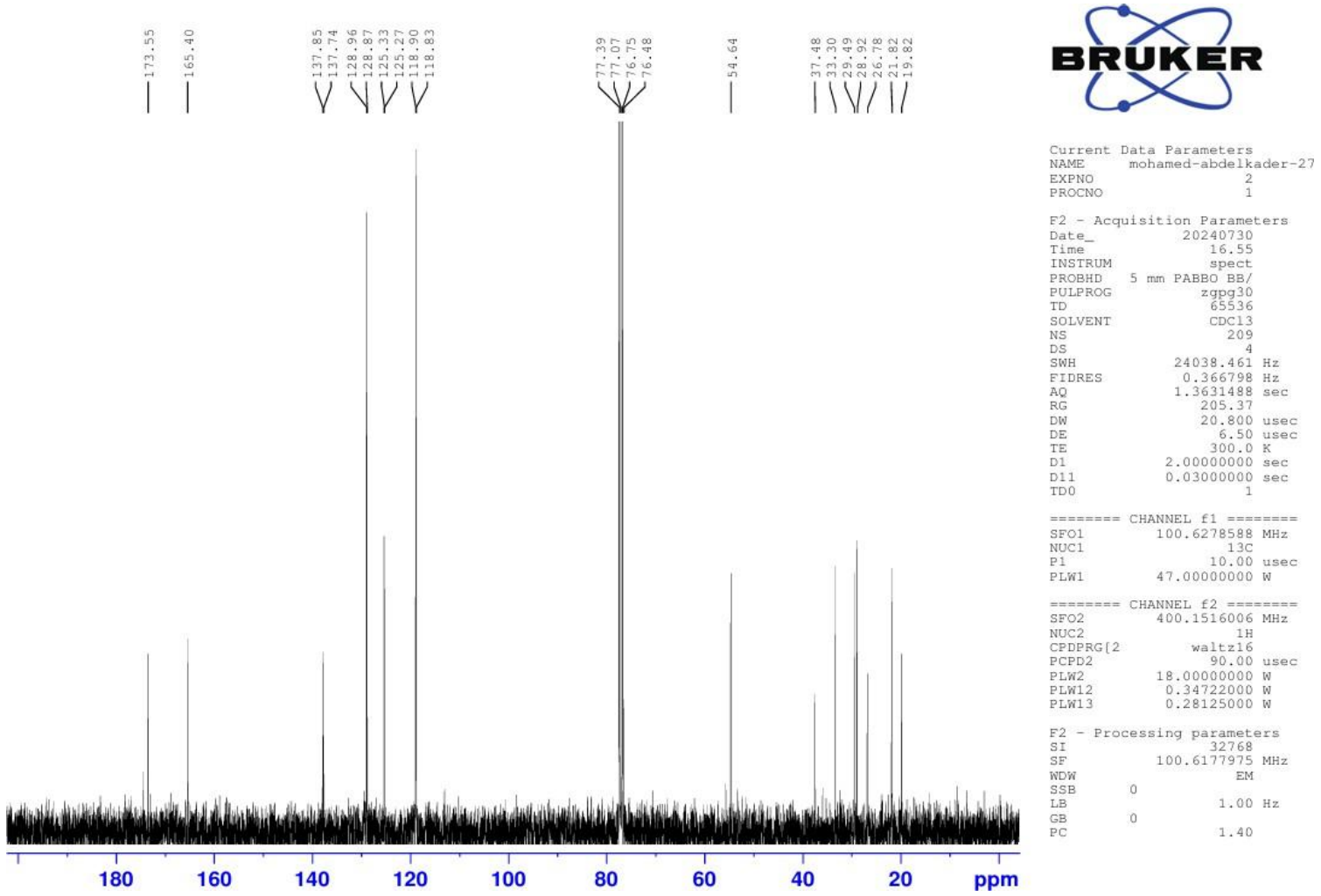


Figure (2.9 c) C^{13}-NMR spectrum of compound (IX) in $CDCl_3$

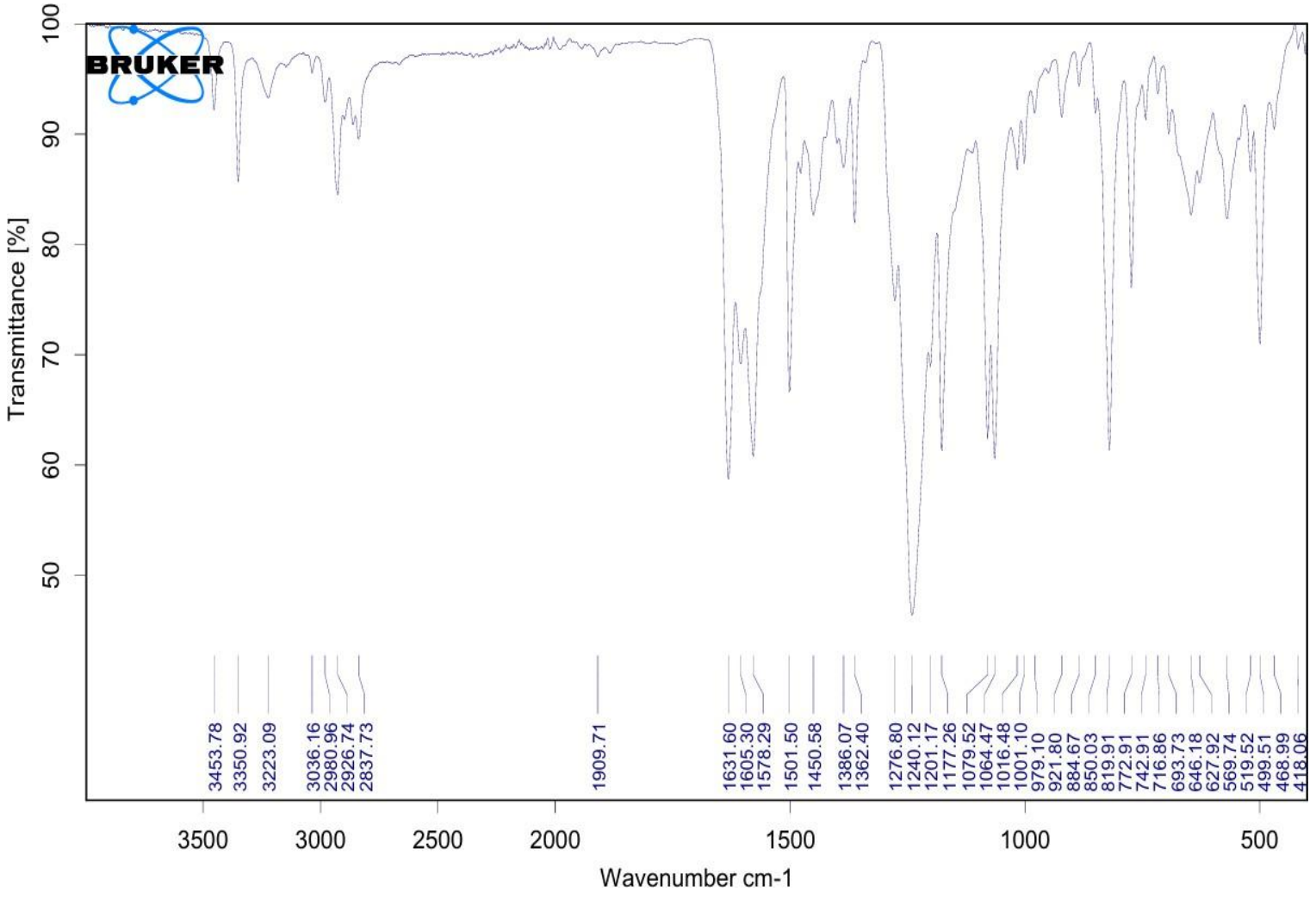
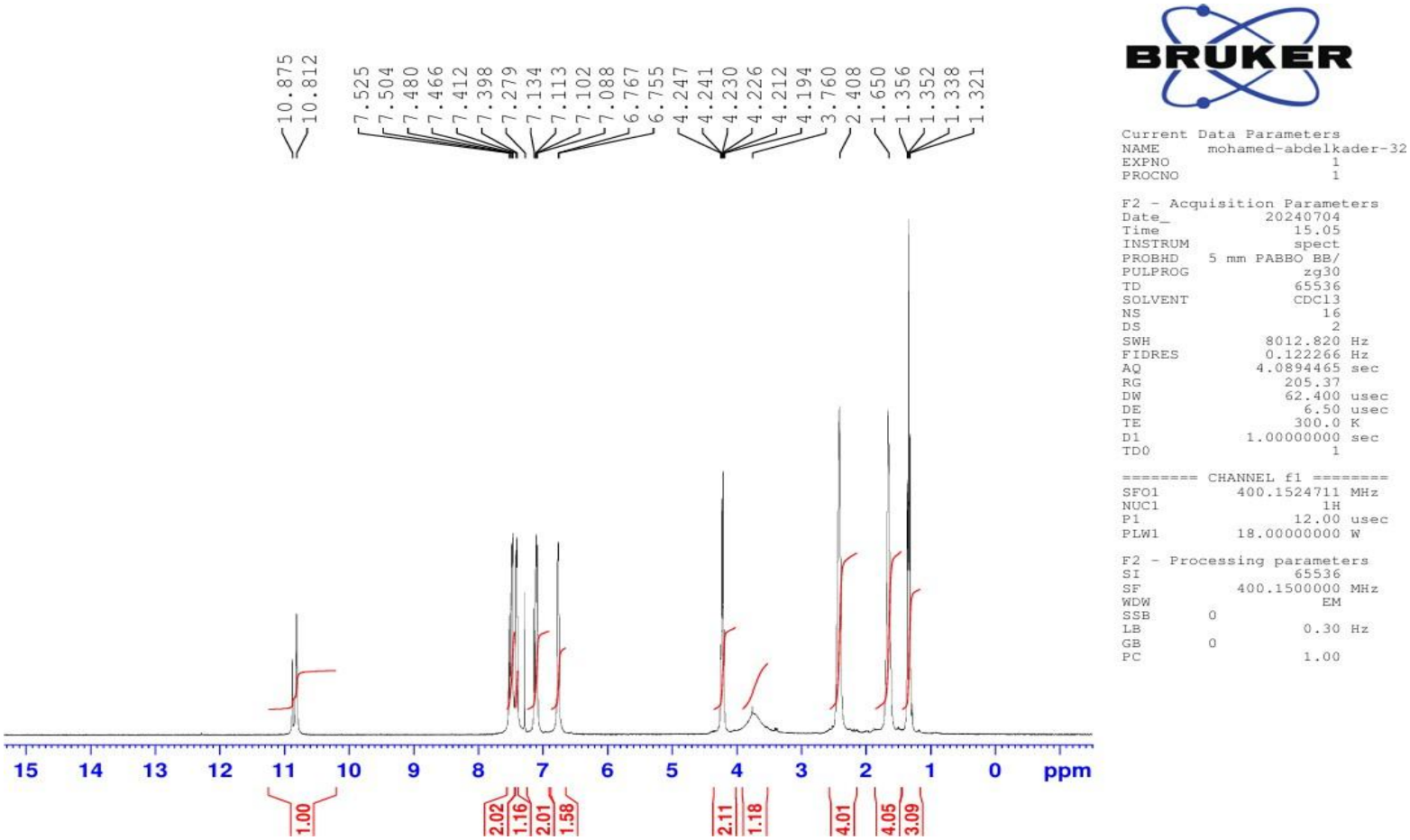


Figure (2.10 a) FT-IR spectrum of compound (X)

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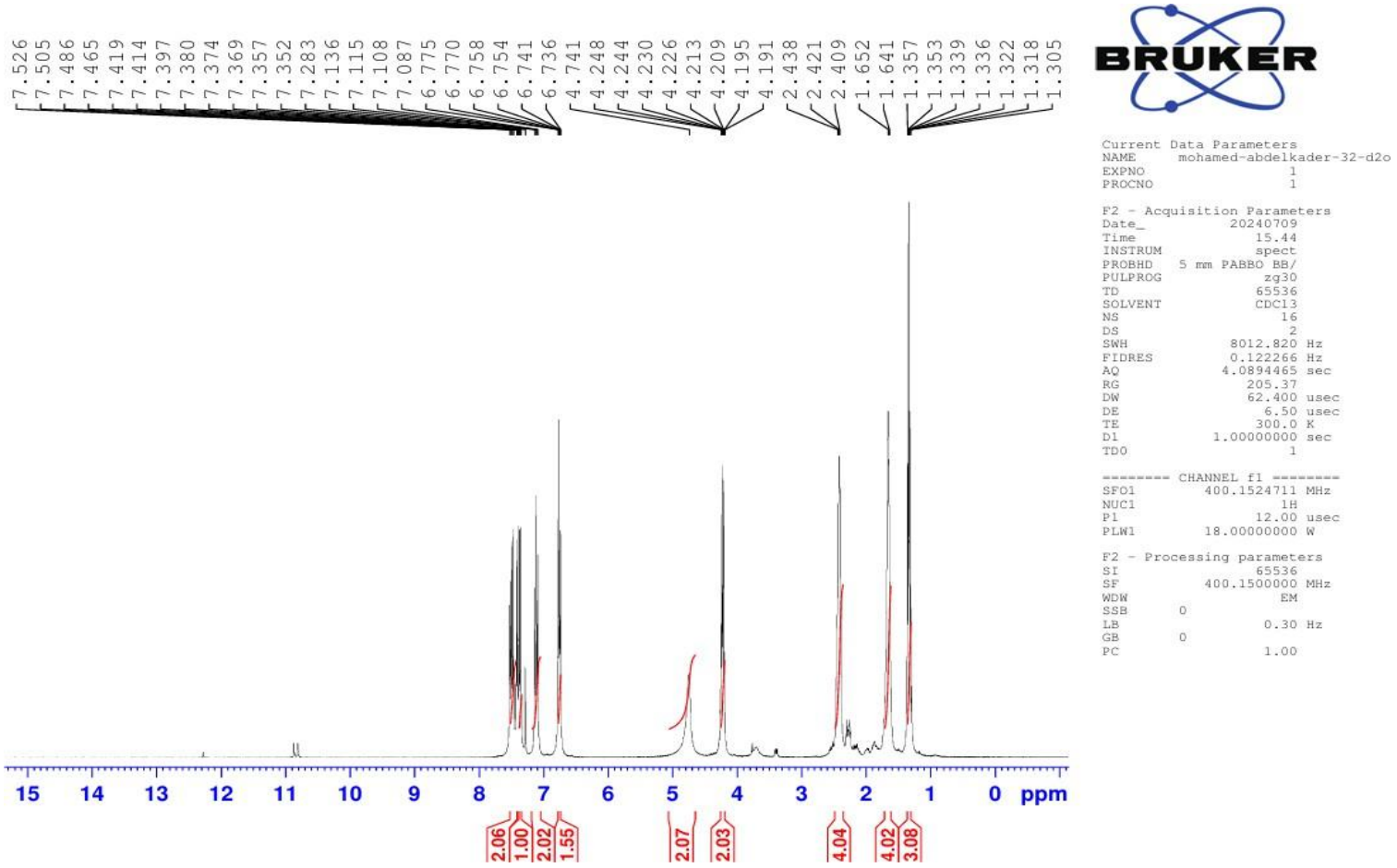
Current Data Parameters
NAME      mohamed-abdelkader-32
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20240704
Time                 15.05
INSTRUM              spect
PROBHD    5 mm PABBO BB/
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH               8012.820 Hz
FIDRES            0.122266 Hz
AQ                4.0894465 sec
RG                   205.37
DW                  62.400 usec
DE                   6.50 usec
TE                  300.0 K
D1              1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          400.1524711 MHz
NUC1                    1H
P1                   12.00 usec
PLW1          18.00000000 W

F2 - Processing parameters
SI                  65536
SF            400.1500000 MHz
WDW                    EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```

Figure (2.10 b) ^{1}HNMR spectrum of compound (X) in $CDCl_3$



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```
Current Data Parameters
NAME      mohamed-abdelkader-32-d2o
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20240709
Time              15.44
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH            8012.820 Hz
FIDRES        0.122266 Hz
AQ            4.0894465 sec
RG               205.37
DW               62.400 usec
DE                6.50 usec
TE               300.0 K
D1            1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         400.1524711 MHz
NUC1                1H
P1                12.00 usec
PLW1        18.00000000 W

F2 - Processing parameters
SI               65536
SF          400.1500000 MHz
WDW                 EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

Figure (2.10 c) D_2Ospectrum of compound (X) in $CDCl_3$

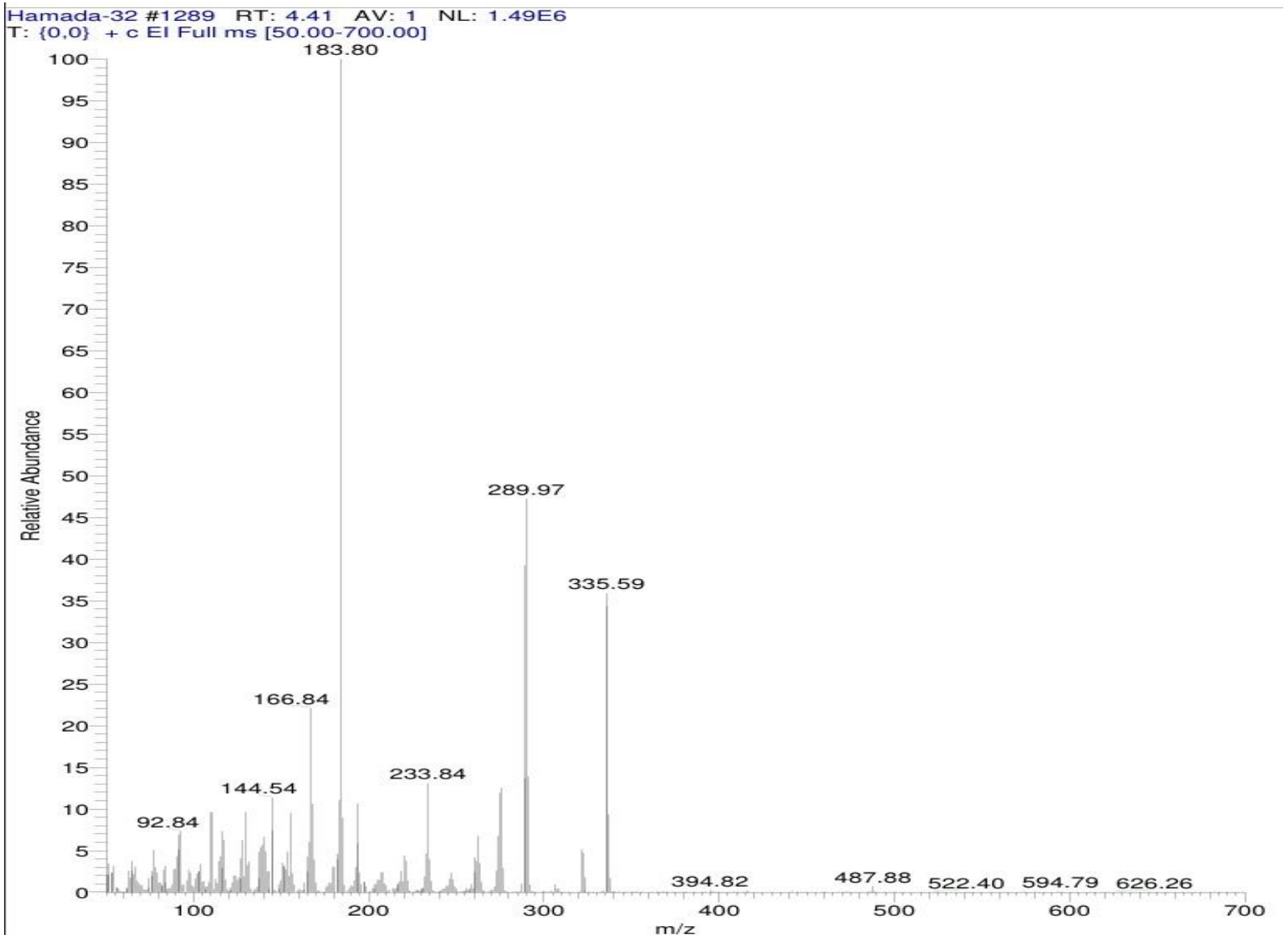
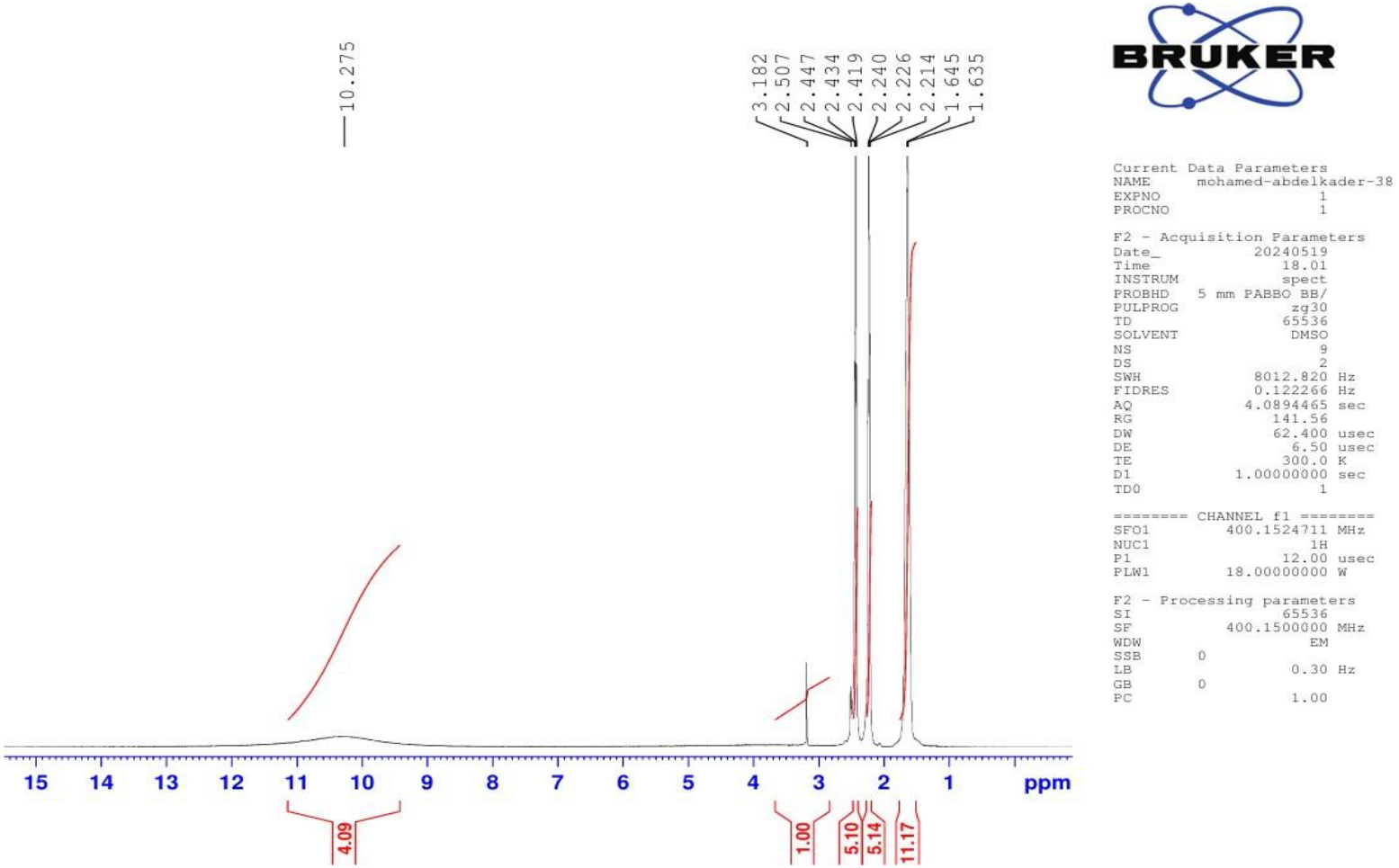


Figure (2.10 d) Mass spectrum of compound (X)

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Current Data Parameters
NAME      mohamed-abdelkader-38
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20240519
Time                 18.01
INSTRUM              spect
PROBHD    5 mm PABBO BB/
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                       9
DS                       2
SWH               8012.820 Hz
FIDRES               0.122266 Hz
AQ                4.0894465 sec
RG                   141.56
DW                   62.400 usec
DE                    6.50 usec
TE                   300.0 K
D1             1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          400.1524711 MHz
NUC1                    1H
P1                   12.00 usec
PLW1          18.00000000 W

F2 - Processing parameters
SI                    65536
SF            400.1500000 MHz
WDW                     EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.00
```

Figure (2.11 **a)** The [1] H NMR spectrum of compound (XI) in DMSO-d_6

Figure (2.11 a) HNMR spectrum of compound (XI) in DMSO-d_6

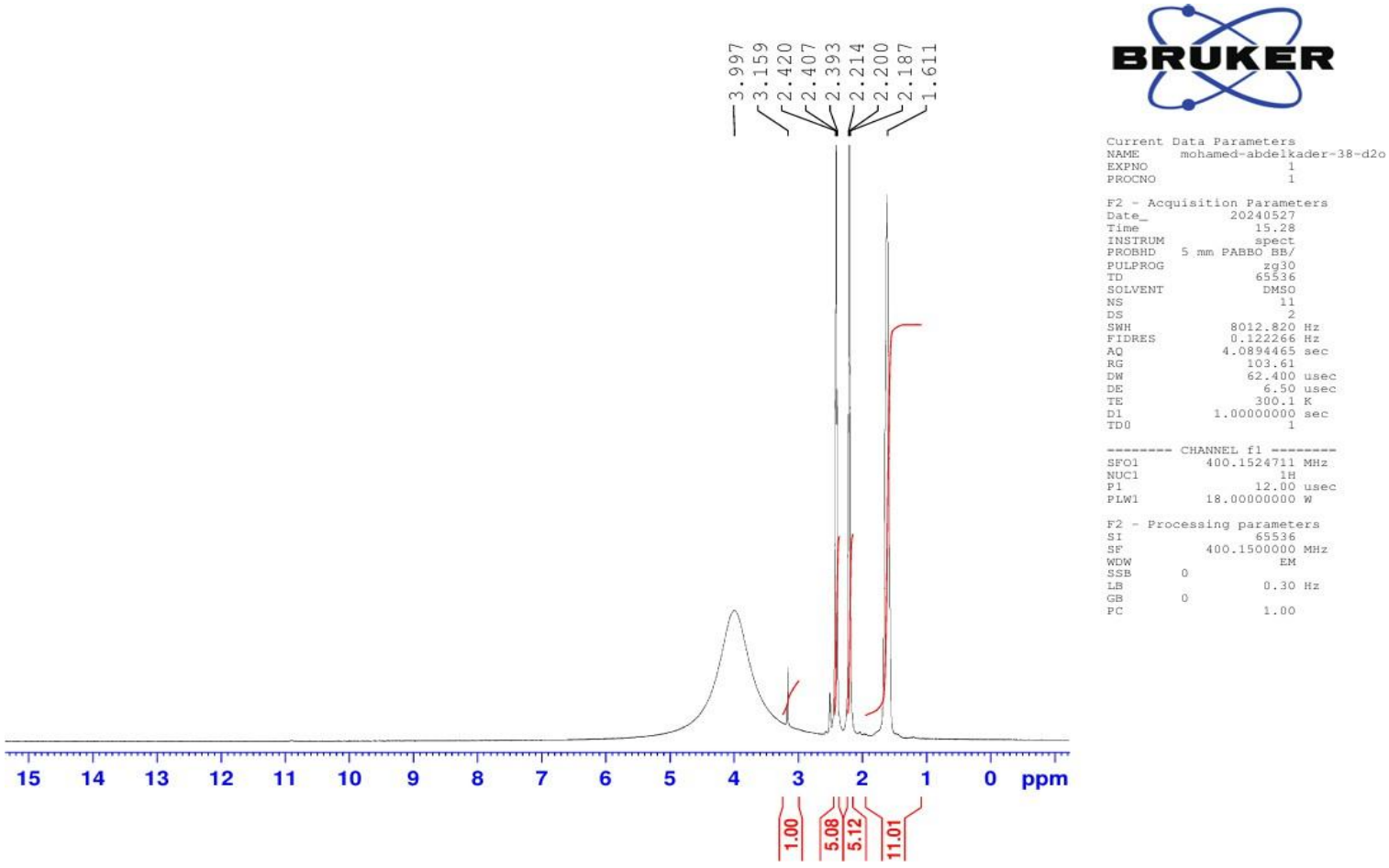


Figure (2.11 b) D_2O spectrum of compound (XI) in DMSO-d_6

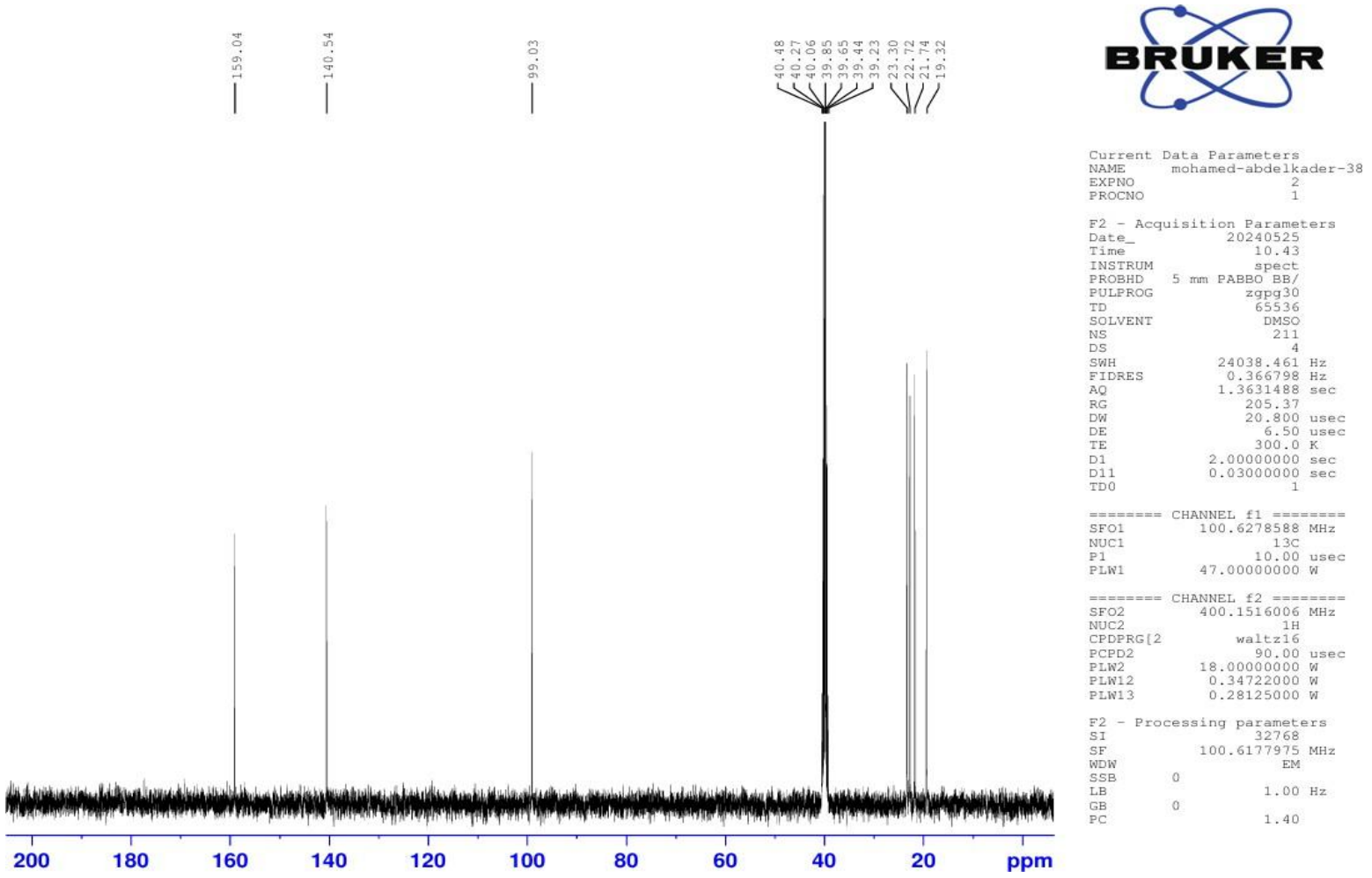
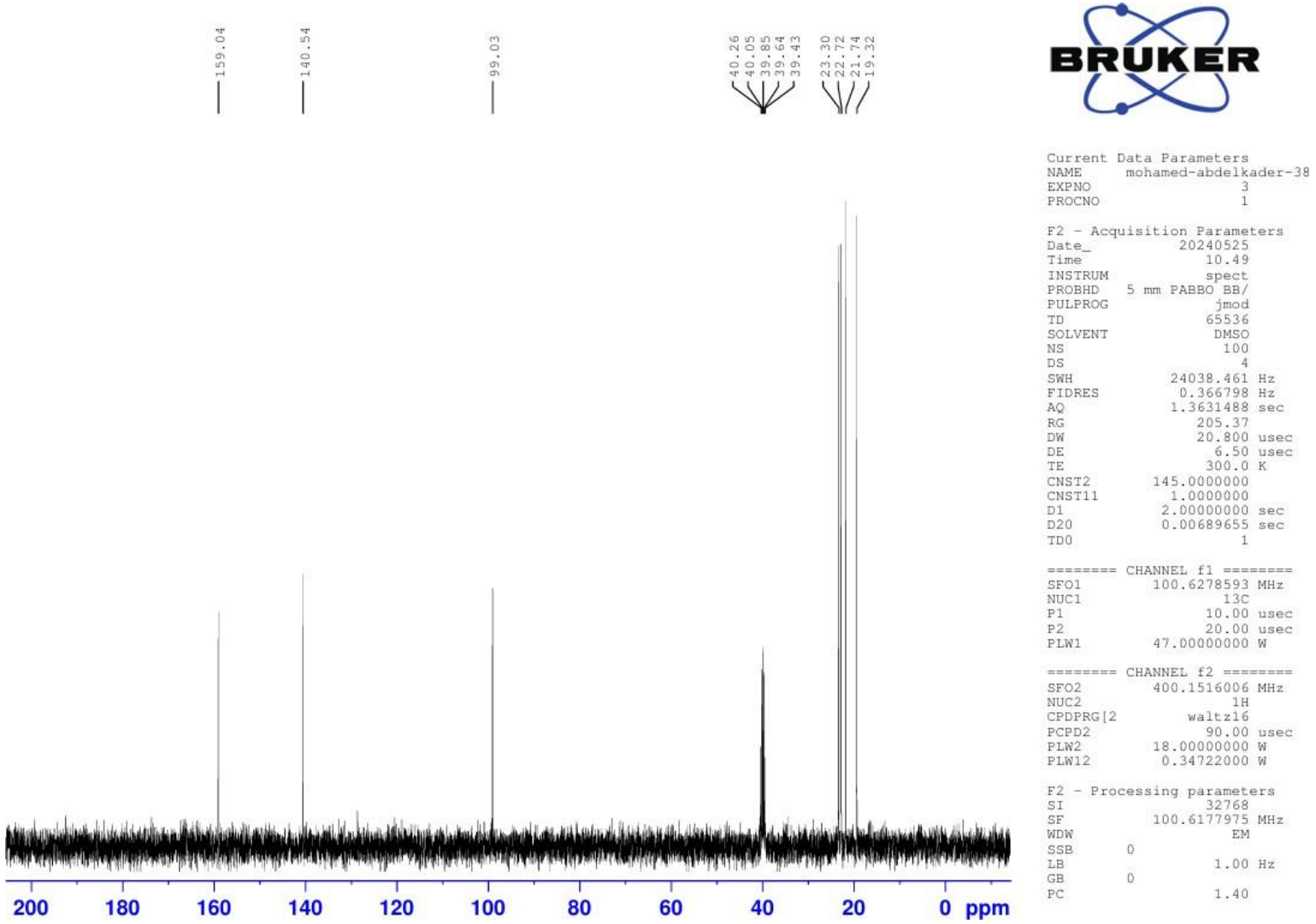


Figure (2.11 c) C^{13}-NMR spectrum of compound (XI) in DMSO-d_6

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Current Data Parameters
NAME      mohamed-abdelkader-38
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_              20240525
Time                  10.49
INSTRUM               spect
PROBHD    5 mm PABBO BB/
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                      100
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                    205.37
DW                    20.800 usec
DE                     6.50 usec
TE                    300.0 K
CNST2            145.0000000
CNST11             1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                          1

======== CHANNEL f1 ========
SFO1             100.6278593 MHz
NUC1                     13C
P1                     10.00 usec
P2                     20.00 usec
PLW1            47.00000000 W

======== CHANNEL f2 ========
SFO2             400.1516006 MHz
NUC2                     1H
CPDPRG[2              waltz16
PCPD2                  90.00 usec
PLW2            18.00000000 W
PLW12            0.34722000 W

F2 - Processing parameters
SI                       32768
SF               100.6177975 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

Figure (2.11 d) APT spectrum of compound (XI) in DMSO-d_6

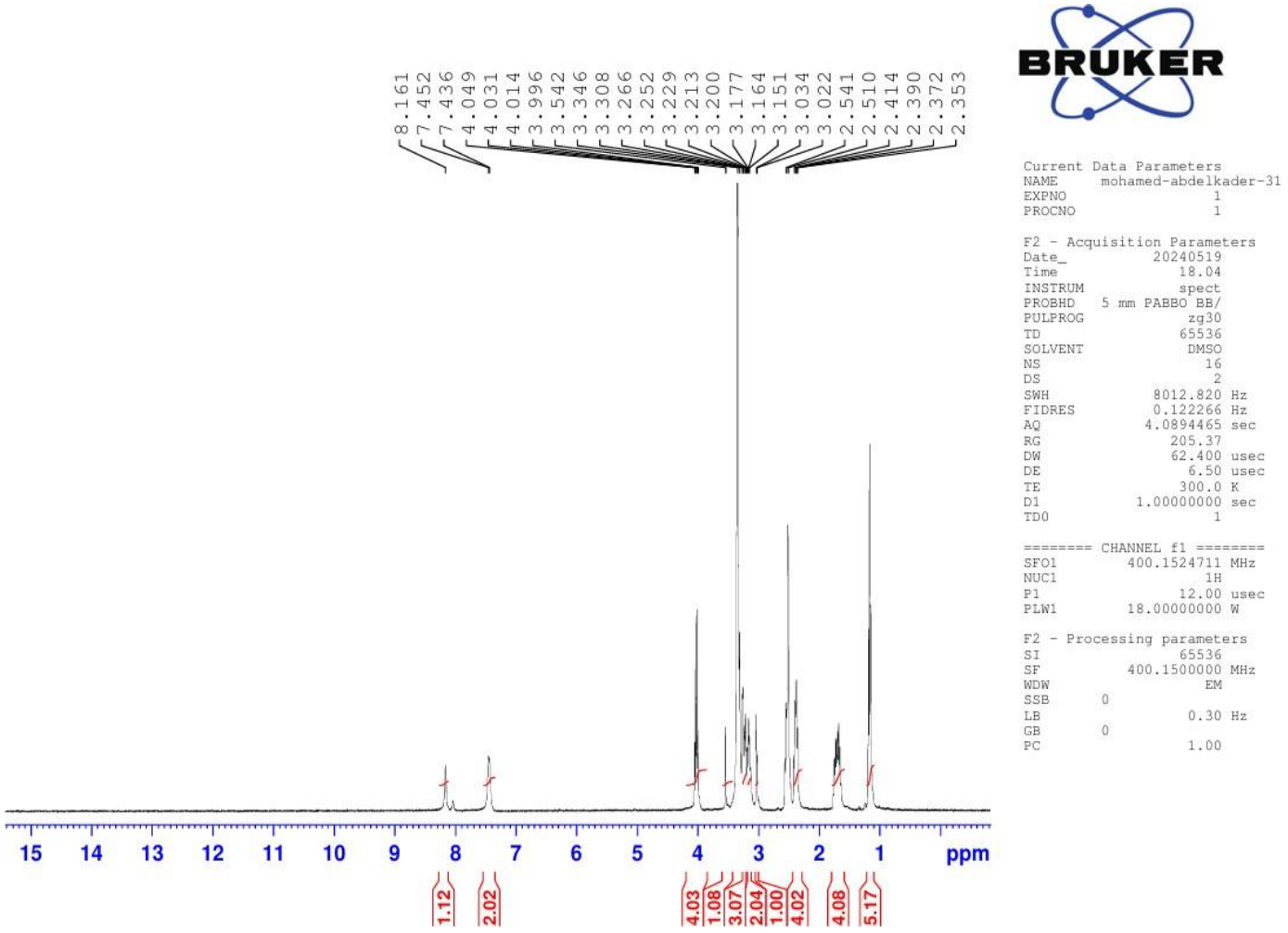
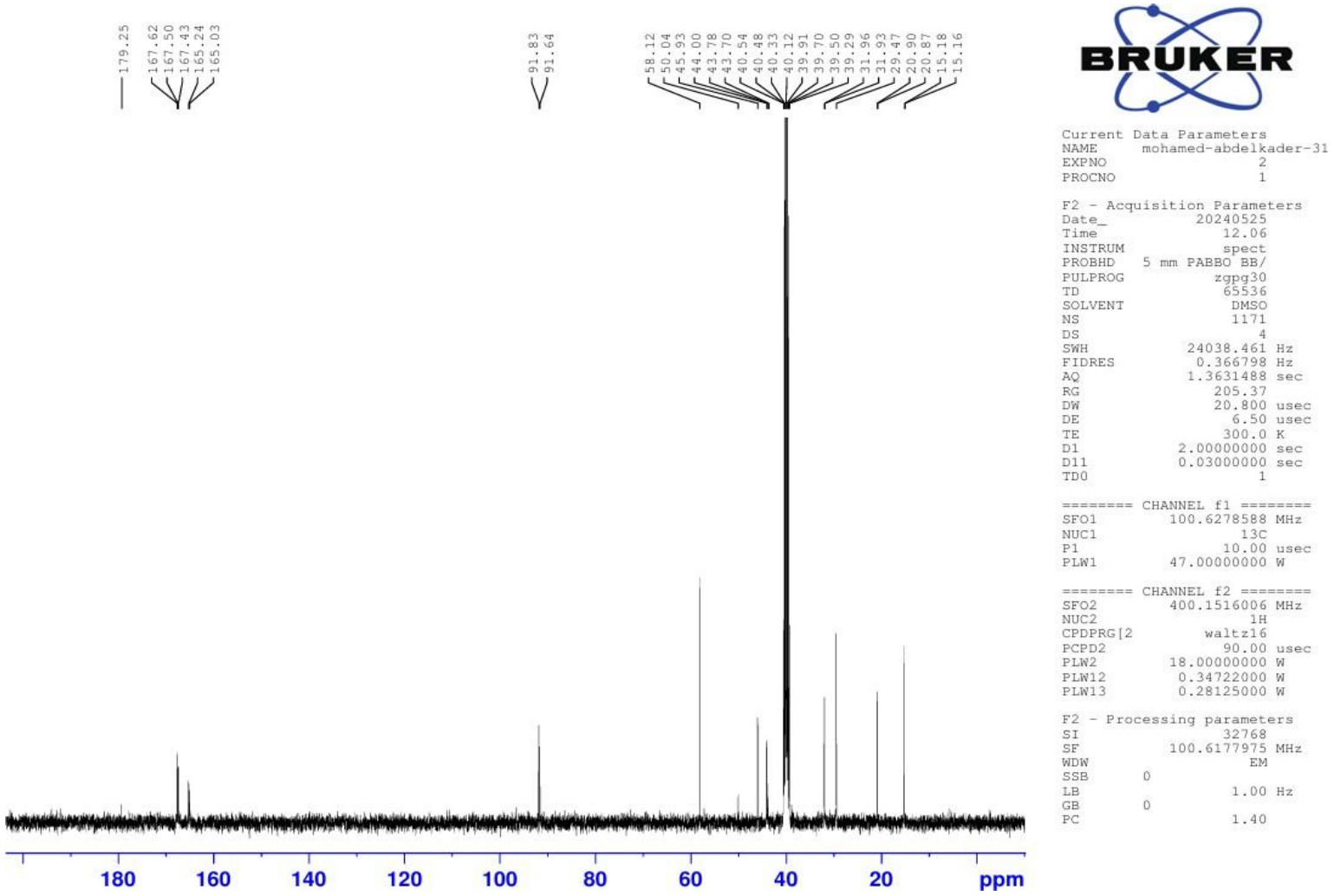


Figure (2.12 a) ^{1}HNMR spectrum of compound (XII) in DMSO-d_6



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```
Current Data Parameters
NAME      mohamed-abdelkader-31
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20240525
Time                  12.06
INSTRUM               spect
PROBHD    5 mm PABBO BB/
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                     1171
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                    205.37
DW                    20.800 usec
DE                     6.50 usec
TE                    300.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1            100.6278588 MHz
NUC1                    13C
P1                    10.00 usec
PLW1           47.00000000 W

======== CHANNEL f2 ========
SFO2            400.1516006 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2           18.00000000 W
PLW12           0.34722000 W
PLW13           0.28125000 W

F2 - Processing parameters
SI                    32768
SF              100.6177975 MHz
WDW                      EM
SSB       0
LB                     1.00 Hz
GB        0
PC                     1.40
```

Figure (2.12 b) C^{13}-NMR spectrum of compound (XII) in DMSO-d_6

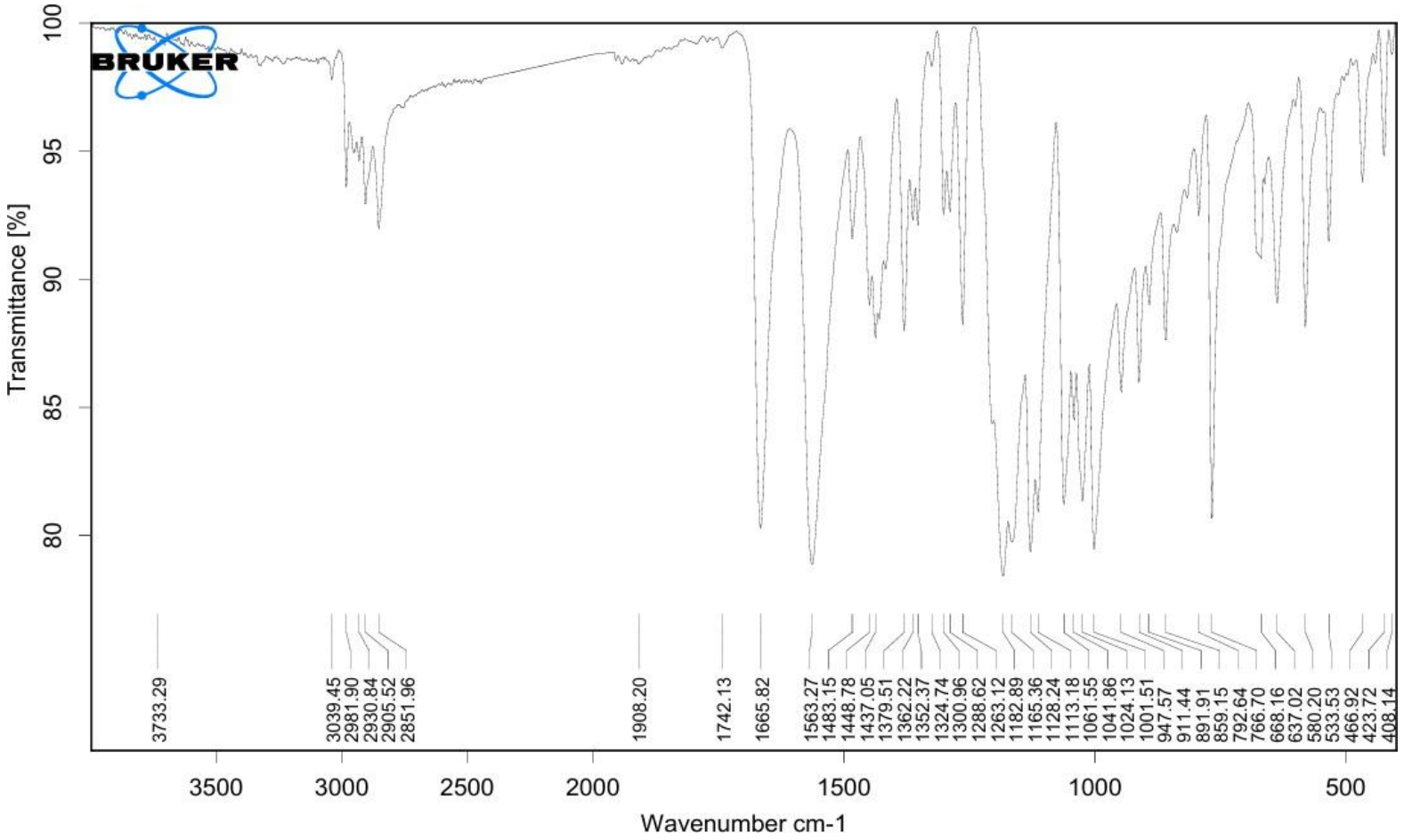


Figure (2.13 a) FT-IR spectrum of compound (XIII)

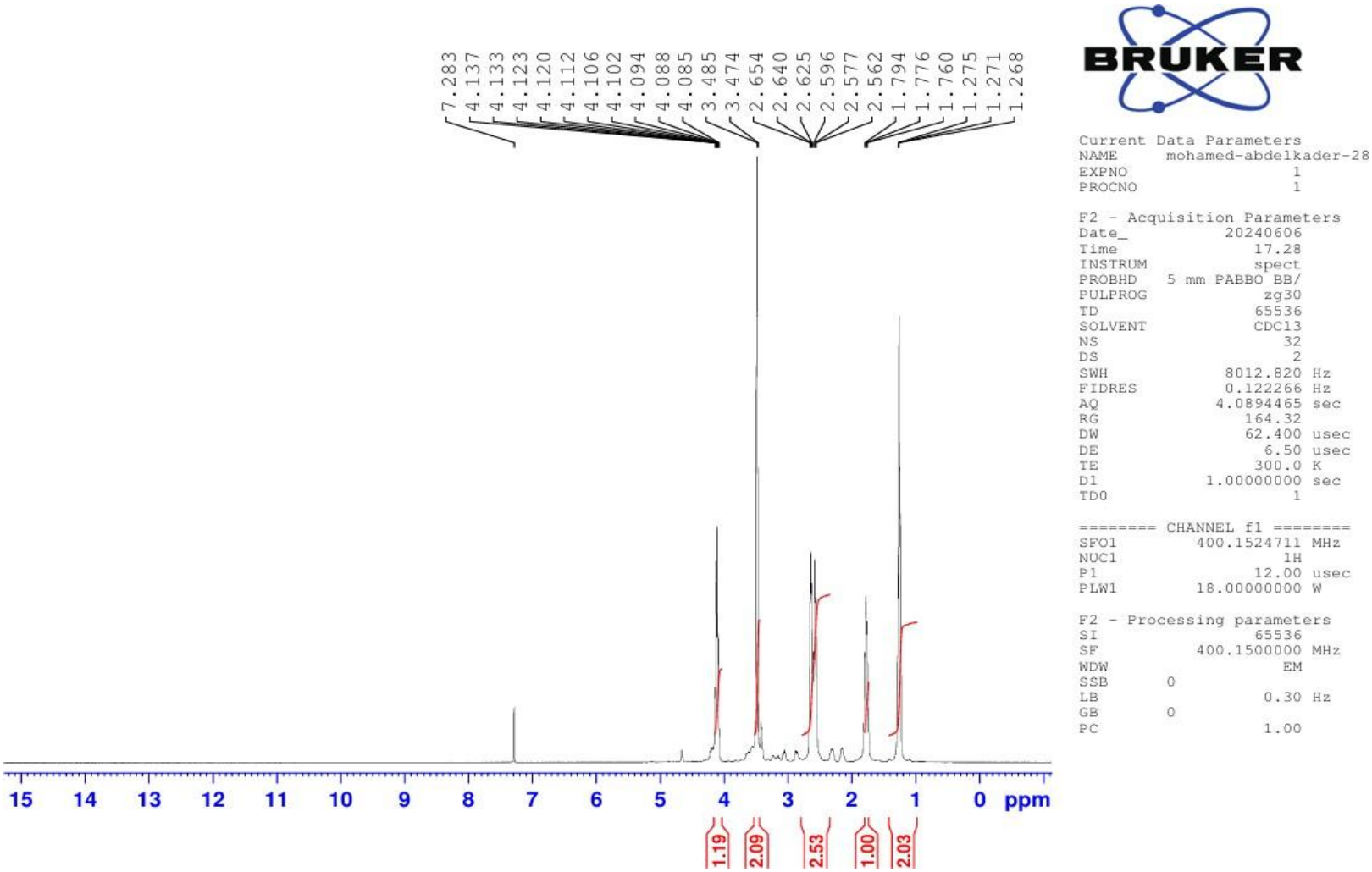
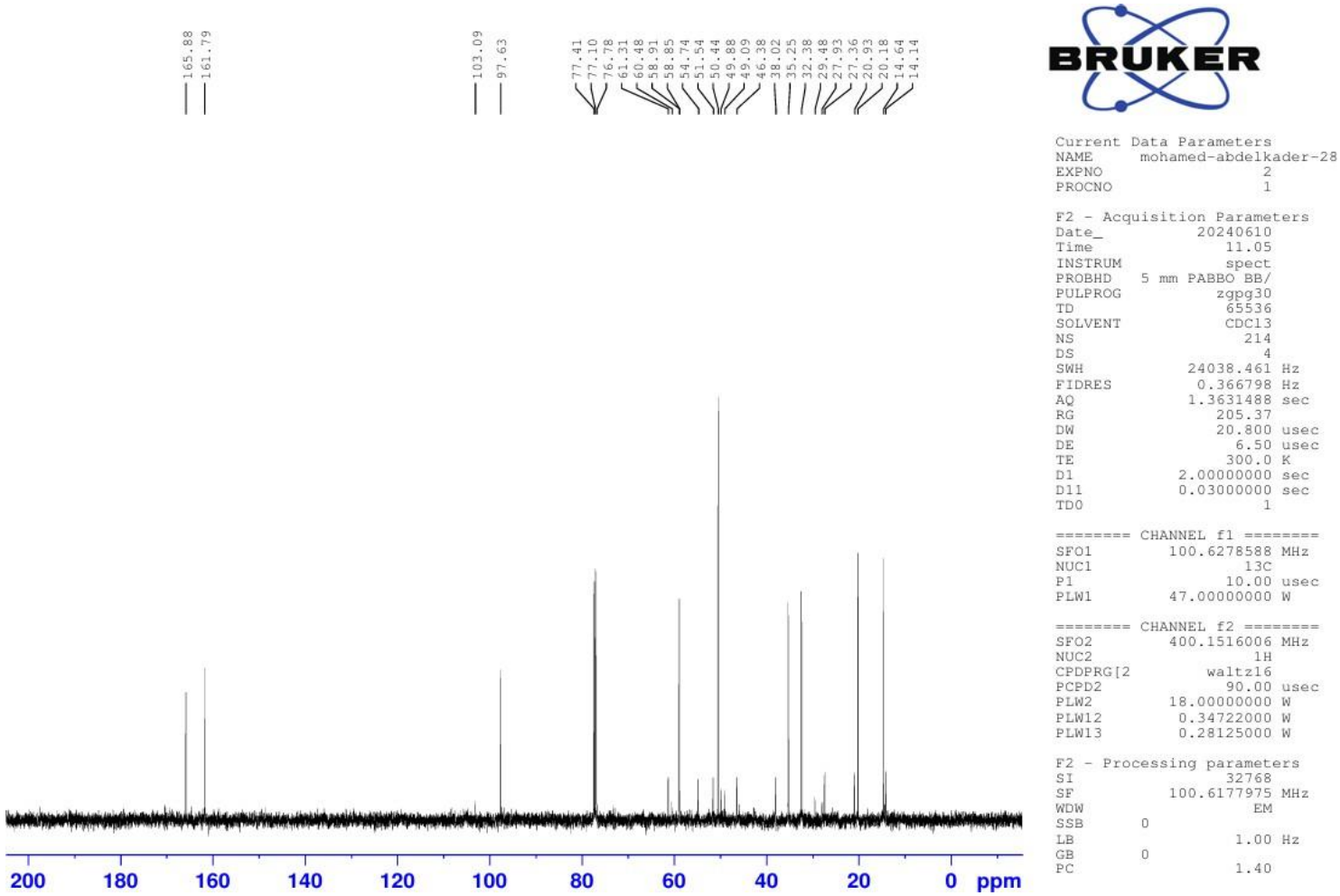


Figure (2.13b) ^{1}HNMR spectrum of compound (XIII) in $CDCl_3$

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Current Data Parameters
NAME      mohamed-abdelkader-28
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20240610
Time                  11.05
INSTRUM               spect
PROBHD    5 mm PABBO BB/
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      214
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                    205.37
DW                    20.800 usec
DE                     6.50 usec
TE                    300.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1           100.6278588 MHz
NUC1                    13C
P1                    10.00 usec
PLW1           47.00000000 W

======== CHANNEL f2 ========
SFO2           400.1516006 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2           18.00000000 W
PLW12           0.34722000 W
PLW13           0.28125000 W

F2 - Processing parameters
SI                    32768
SF             100.6177975 MHz
WDW                      EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

Figure (2.13c) C^{13}-NMR spectrum of compound (XIII) in $CDCl_3$

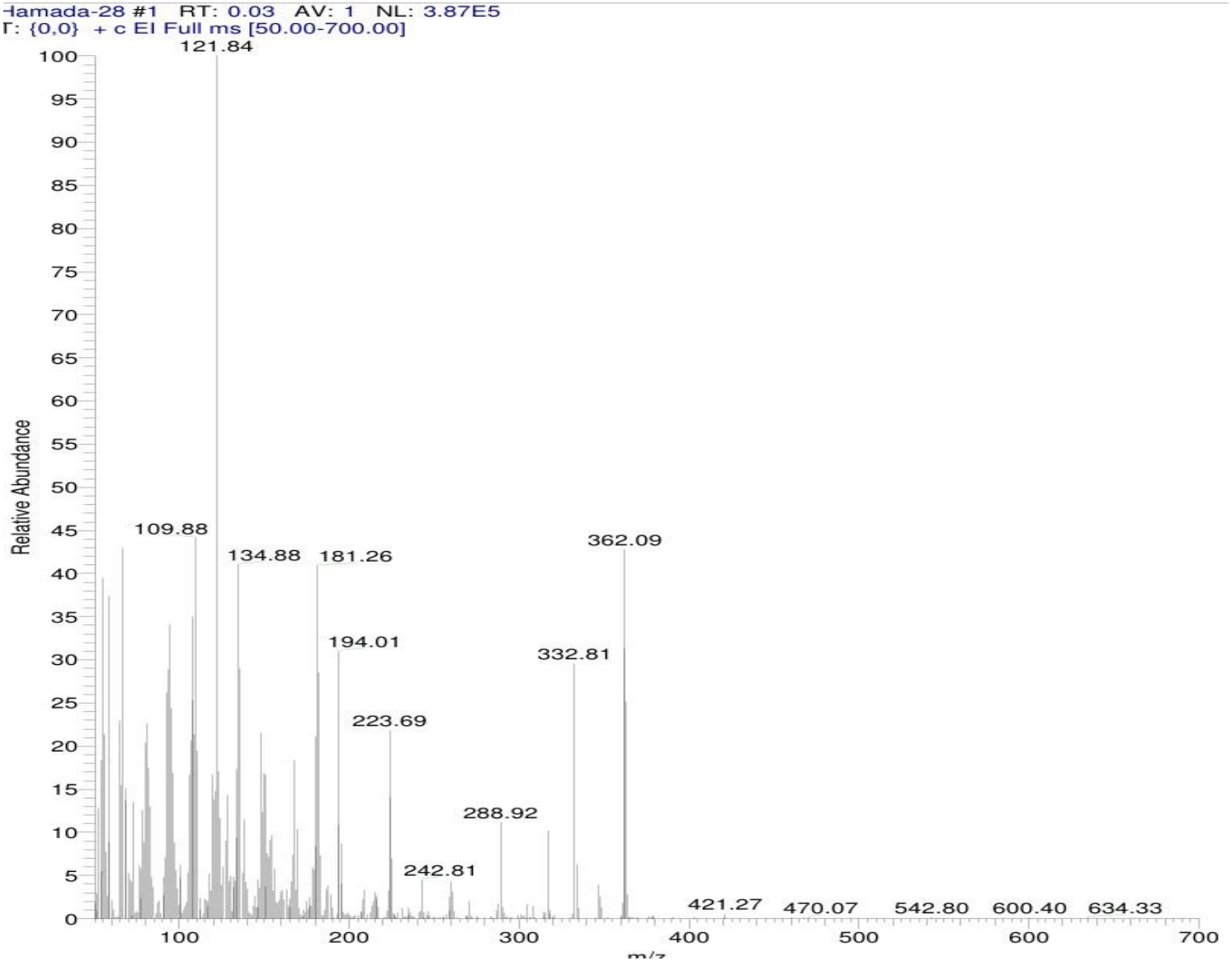

Figure (2.13d) Mass spectrum of compound (XIII)

Chapter 5

References

References

1. Achanna, V. M., & Suresh, H. (2013). Synthesis of five-and six-membered 2-trimethylsilyl-1,3,3-trimethylcycloalkenes: A novel preparation of alkyl/alkenyl/aryl-(1′, 3′, 3′-trimethylcyclopentenyl) ketones. *Journal of the Serbian Chemical Society, 78*(6), 759-768.
2. Attanasi, O. A., De Crescentini, L., Favi, G., Filippone, P., Golobič, A., Lillini, S., & Mantellini, F. (2006). Facile synthesis of new substituted tetrahydro-1H-indoles. *Synlett*, 2006(17), 2735-2738.
3. Attanasi, O. A., De Crescentini, L., Favi, G., Filippone, P., Golobič, A., Lillini, S., & Mantellini, F. (2006). Facile synthesis of new substituted tetrahydro-1H-indoles. *Synlett*, 2006(17), 2735-2738.
4. Aware, V., Gaikwad, N., Chavan, S., Manohar, S., Bose, J., Khanna, S., ... & Roychowdhury, A. (2015). Cyclopentyl-pyrimidine-based analogues as novel and potent IGF-1R inhibitors. *European Journal of Medicinal Chemistry, 92*, 246-256.
5. Banerjee, S. (2015). The remarkable catalytic activity of ultra-small free-CeO_2 nanoparticles in selective carbon–carbon bond formation reactions in water at room temperature. *New Journal of Chemistry, 39*(7), 5350-5353.
6. Bobileva, O., Bokaldere, R., Gailite, V., Kaula, I., Ikaunieks, M., Duburs, G., ... & Loza, E. (2014). Synthesis and evaluation of (E)-2-(acrylamido)cyclohex-1-enecarboxylic acid derivatives as HCA1, HCA2, and HCA3 receptor agonists. *Bioorganic & Medicinal Chemistry, 22*(14), 3654-3669.
7. Bouhadir, K. H., Koubeissi, A., Mohsen, F. A., El-Harakeh, M. D., Cheaib, R., Younes, J., ... & Eid, A. A. (2016). Novel carbocyclic nucleoside analogs suppress glomerular mesangial cells proliferation and matrix protein accumulation through ROS-dependent mechanism in the diabetic milieu. II. Acylhydrazone-functionalized pyrimidines. *Bioorganic & Medicinal Chemistry Letters, 26*(3), 1020-1024.
8. Burgula, L. N., Radhakrishnan, K., & Kundu, L. M. (2012). Synthesis of modified uracil and cytosine nucleobases using a microwave-assisted method. *Tetrahedron Letters, 53*(21), 2639-2642.
9. Claisen, L. (1887). Ueber die einführung von säureradicalen in ketone. *Berichte der deutschen chemischen Gesellschaft, 20*(1), 655-657.
10. Claisen, L., & Claparède, A. (1881). Condensationen von ketonen mit aldehyden. *Berichte der deutschen chemischen Gesellschaft, 14*(2), 2460-2468.

11. Clemens, R. J., & Hyatt, J. A. (1985). Acetoacetylation with 2,2,6-trimethyl-4H-1,3-dioxin-4-one: a convenient alternative to diketene. *The Journal of Organic Chemistry, 50*(14), 2431-2435.

12. Cuny, G. D., Robin, M., Ulyanova, N. P., Patnaik, D., Pique, V., Casano, G., ... & Higgins, J. M. (2010). Structure–activity relationship study of acridine analogs as haspin and DYRK2 kinase inhibitors. *Bioorganic & Medicinal Chemistry Letters, 20*(12), 3491-3494.

13. Dieckmann, W. (1894). *Ber. Dtsch. Chem. Ges.*, 27, 102–103.

14. Fujita, T., Tanaka, M., Norimine, Y., Suemune, H., & Sakai, K. (1997). Enantioselective synthesis of (−)-curcumanolide A using enzymatic transesterification of meso-spirodiol. *The Journal of Organic Chemistry, 62*(12), 3824-3830.

15. Gao, Y., Zhang, Q., & Xu, J. (2004). A Convenient and effective method for synthesizing β-amino-α,β-unsaturated esters and ketones. *Synthetic Communications, 34*(5), 909-916.

16. He, Q., Liu, J., Lan, J. S., Ding, J., Sun, Y., Fang, Y., ... & Xie, S. S. (2018). Coumarin-dithiocarbamate hybrids as novel multitarget AChE and MAO-B inhibitors against Alzheimer's disease: Design, synthesis and biological evaluation. *Bioorganic Chemistry, 81*, 512-528.

17. Jourdan, J. P., Rochais, C., Legay, R., de Oliveira Santos, J. S., & Dallemagne, P. (2013). An unusual boron tribromide-mediated, one-pot bromination/cyclization reaction. *Tetrahedron Letters, 54*(9), 1133-1136.

18. Lengauer, T., & Rarey, M. (1996). Computational methods for biomolecular docking. *Current Opinion in Structural Biology, 6*(3), 402–406.

19. Li, Y., Wang, D., Zhang, L., & Luo, S. (2019). Redox property of enamines. *The Journal of Organic Chemistry, 84*(18), 12071-12090.

20. Meyer, C., Piva, O., & Pete, J. P. (2000). [2+2] Photocycloadditions and Photorearrangements of 2-Alkenylcarboxamido-2-cycloalken-1-ones. *Tetrahedron, 56*(26), 4479-4489.

21. Niu, X., Wang, F., Li, X., Zhang, R., Wu, Q., & Sun, P. (2019). Using Zn^{2+} ionomer to catalyze transesterification reaction in epoxy vitrimer. *Industrial & Engineering Chemistry Research, 58*(14), 5698-5706.

22. Otera, J. (1993). Transesterification. *Chemical Reviews, 93*(4), 1449-1470.

23. Pallenberg, A. J., Dobhal, M. P., & Pandey, R. K. (2004). Efficient synthesis of pyropheophorbide-a and its derivatives. *Organic Process Research & Development, 8*(2), 287-290.

24. Parmar, V. S., Prasad, A. K., Sharma, N. K., Bisht, K. S., Sinha, R., & Taneja, P. (1992). Potential applications of enzyme-mediated transesterifications in the synthesis of bioactive compounds. *Pure and Applied Chemistry, 64*(8), 1135-1139.

25. Pazdera, P., & Simbera, J. (2011). Facile Carbethoxylation and Carbamoylation of Ketones. *Organic Preparations and Procedures International, 43*(3), 297-301.

26. Pei, T., & Widenhoefer, R. A. (2002). Palladium-catalyzed cyclization of alkenyl β-keto esters in the presence of chlorotrimethylsilane. *Chemical Communications*, (6), 650-651.

27. Rao, H. S. P., & Sivakumar, S. (2006). Condensation of α-aroylketene dithioacetals and 2-hydroxyarylaldehydes results in facile synthesis of a combinatorial library of 3-aroylcoumarins. *The Journal of Organic Chemistry, 71*(23), 8715-8723.

28. Ranu, B. C., Chattopadhyay, K., & Jana, R. (2007). Ionic liquid promoted selective debromination of α-bromoketones under microwave irradiation. *Tetrahedron, 63*(1), 155-159.

29. Ranu, B. C., Jana, R., & Samanta, S. (2004). A simple, efficient and general procedure for acetalization of carbonyl compounds and deprotection of acetals under the catalysis of indium (III) chloride. *Advanced Synthesis & Catalysis, 346*(4), 446-450.

30. Sarabu, R., Bizzarro, F. T., Corbett, W. L., Dvorozniak, M. T., Geng, W., Grippo, J. F., ... & Grimsby, J. (2012). Discovery of piragliatin—first glucokinase activator studied in type 2 diabetic patients. *Journal of Medicinal Chemistry, 55*(16), 7021-7036.

31. Schaefer, J. P., & Bloomfield, J. J. (2004). The Dieckmann Condensation (Including the Thorpe-Ziegler Condensation). *Organic Reactions, 15*, 1–203.

32. Singh, G., & Mishra, A. (2021). Recent advances in the pharmacological potential of enamine derivatives: A review. *Bioorganic Chemistry, 114*, 105030.

33. Tzvetkov, N. T., Waske, P. A., Neumann, B., Stammler, H. G., & Mattay, J. (2008). Photoinduced radical reactions of α-alkylated ethyl 2-oxo-1-cyclopentanecarboxylate derivatives: α-cleavage and cyclization to the skeleton of linear cyclohexano diquinanes. *Tetrahedron Letters, 49*(10), 1710-1713.

34. Witzeman, J. S., & Nottingham, W. D. (1991). Transacetoacetylation with tert-butyl acetoacetate: synthetic applications. *The Journal of Organic Chemistry, 56*(5), 1713-1718.

35. Yadav, J. S., Reddy, B. V. S., Krishna, A. D., Reddy, C. S., & Narsaiah, A. V. (2007). Triphenylphosphine: An efficient catalyst for transesterification of β-ketoesters. *Journal of Molecular Catalysis A: Chemical, 261*(1), 93-97.

جامعة بنغازي

كلية العلوم

قسم الكيمياء

تحضير والتعرف وتطبيقات مركبات الاينامين

قدمت من قبل:

عبد الحميد عبد الله العرفي

تحت إشراف:

د .عبد الله حمد غيث الدرسي أستاذ

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الإجازة العالية (الماجستير) في الكيمياء العضوية

بتاريخ : 4-8-2025

تحضير والتعرف وتطبيقات مركبات الاينامين

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الملخص:

تم تحضير سلسلة من المركبات من خلال تفاعل إيثيل 2-أوكوسايكلوبنتان-1-كاربوكسيلات أو إيثيل 2-أوكوسايكلوهكسان-1-كاربوكسيلات مع أنواع مختلفة من الأمينات الثنائية بما في ذلك إيثان-1،2-دايمين، بنزين-4،1-دايمين ، هيدرازين هيدرات ، بنزيدين , بيس (2-أمينو إيثيل) مالوناميد , مالونوهايدرازيد ، وبيبيرازين تبين أن معظم المشتقات اعتمدت على هياكل الإينامين من خلال نسبة تفاعل 2:1، في حين أظهرمركبين أُطُر هيكلية مميزة بسبب مسار تفاعل بنسبة 1:1 من الجدير بالذكر أن تفاعل بيتا كيتو الاستر(15) مع هيدرازين هيدرات أدى إلى تكوين الإينامين كمنتج ثانوي، والبيرازولون كمنتج كالمشتق الرئيسي، بينما أدى التفاعل النظير مع المركب (23) إلى إنتاج البيرازولون فقط , بالإضافة إلى ذلك، أدى تفاعل المركب (23) مع مالونوهايدرازيد إلى تكوين مشتق آزين , تمت جميع التفاعلات تحت ظروف معتدلة مع حصول على عوائد متوسطة، وتم تحديد الهياكل باستخدام نقطة الانصهار، TLC، الأشعة تحت الحمراء(IR) ، مطيافية الكتلة(MS) ، مطيافية الرنين المغناطيسي النووي للهيدروجين (^{1}H-NMR) مع تبادلD_2O ، مطيافية الرنين المغناطيسي النووي للكربون(^{13}C-NMR) ، وتحليلAPT , كشفت الفحوصات الأولية عن نشاط مضاد للميكروبات في بعض المشتقات المختارة، وأظهر تقييم النشاط المضاد للبكتيريا والدوكينج الجزيئي أن بعض المركبات أبدت تأثيرات مثبطة.