Master's Thesis :

SYNTHESIS, REACTIONS AND MICROBIAL STUDY OF SOME NOVEL BIS AMINO PYRROLES

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منشورات البرنامج الوطني لتطوير المجلات العلمية

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Synthesis, Reactions and Microbial Study of Some Novel Bis Amino Pyrroles

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

12 / October / 2025

DECLARATION

I, Mohammed Abd-alqadir Al-ajilani , hereby declare that the thesis entitled:
"Synthesis, Reactions and Microbial Study of Some Novel Bis Amino Pyrroles"
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.
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بسم الله الرحمن الرحيم

﴿ وَلَقَدْ آتَيْنَا دَاوُودَ وَسُلَيْمَانَ عِلْمًا وَقَالَا الْحَمْدُ لِلَّهِ الَّذِي فَضَّلَنَا عَلَىٰ كَثِيرٍ مِنْ عِبَادِهِ الْمُؤْمِنِينَ ﴾

صدق الله العظيم

{سورة النمل الآية 15 }

DEDICATION

TO MY FAMILY

Acknowledgements

Praise and thanks be to God that I have reached this stage after effort and exhaustion, so to you God be all praise. Secondly, I thank Dr. Naowara. M. Al-Arafi, the supportive doctor, and I thank her for the effort she made with me.

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Mohammed ABD-ALqadir AL-ajilani

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List of Abbreviations and Symbols

Abbreviation/Symbol	Full Meaning
IR	**Infrared Spectroscopy**
NMR	**Nuclear Magnetic Resonance**
MW	**Microwave**
TLC	**Thin Layer Chromatography**
DMSO	**Dimethyl Sulfoxide**
$CDCl_3$	**Deuterated Chloroform**
°C	**Degrees Celsius**
D_2O	**Deuterium oxide**
M.P	**Melting Point**
δ delta	**Used in NMR data report to signify chemical shift**
ppm	**Part per million**
U. V	**Ultra-violet**

Notes

- Compounds synthesized in this M.Sc. thesis are written in Roman number.

- Compounds which are known in literature and synthesized or used in parts of this work are written in Arabic numbers.

Synthesis, Reactions and Microbial Study of Some Novel Bis Amino Pyrroles

By

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Abstract

Various diamines, including ethane-1,2-diamine, hydrazine hydrate, o-phenylene diamine, m-phenylene diamine, p-phenylene diamine, and benzidine, were subjected to reactions with benzoin under the influence of malononitrile and a pyridine catalyst. As a result, bis-pyrrole derivatives (I, III, IV, and VI) were predominantly formed. Interestingly, ethane-1,2-diamine also yielded a furan derivative (II) as the major product. On the other hand, reactions involving hydrazine hydrate and o-phenylene diamine deviated from the formation of bis-pyrroles, producing a hydrazone derivative (V) and a quinoxaline derivative (VII), respectively.

Subsequently, bis-pyrrole derivatives (I and IV) and compound (II) were reacted with acetic anhydride to afford corresponding amide derivatives (VIII, IX, and X). All syntheses were conducted under mild conditions using straight forward procedures, yielding moderate yields. The synthesized compounds (I-X) were characterized using melting Point TLC, IR, ^{1}H NMR (including D_2o exchange) ^{13}C NMR and Apt techniques. Evaluation of antimicrobial activity revealed that Some compounds exhibited inhibitory effects.

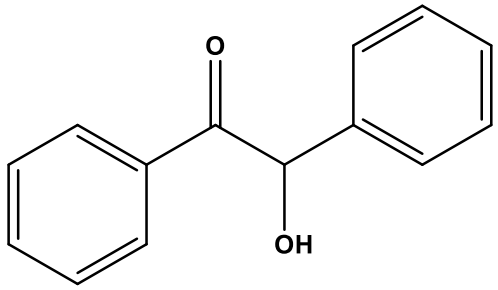
Chapter 1

INTRODUCTION

1. Introduction

1.1. Benzoin:

Benzoin (1) is an organic compound that has several names 2-hydroxy-2-phenylacetophenone,2-hydroxy-1, 2-diphenylethanone, alcohol or bitter almond oil camphor consisting of an ethylene bridge flanked by phenyl groups with a hydroxyl and a ketone functional group ***(Prasanth and Vijayalakshmi, 2018)***. The general structure of the compound is shown below:



(1)

It comes as off-white to yellow crystalline with an odor of camphor. Slightly acrid taste. When broken the fresh surfaces have a milky-white color and solube in warm alcohol and carbon disulfide; insolube in water, and has a melting point (137°C) .***(Pubchem, 2012) (Honjo, 2007 and Iwamoto, 2006 et al)***

Benzoin (1) was mentioned for the first time in 1832 by Justus Von Liebig and Friedrich Fuller in their research on bitter almond oil ***(Anderson and Jacobson, 1922)***. Benzoin (1) is a naturally occurring compound derived from plants referred to as vegetable gums or balsams ***(Rosemary and John, 2003)***. The chemical constituent present in the benzoin are cinnamic, benzoic and sumaresinolic acid esters, benzoic acid, cinnamic acid, sumaresinolic acid, benzaldehyde and vanillin ***(Jadhav and Pharmacophore, 2015)***.

Benzoin (1) sometimes known as the benzaldehyde. It is the condensation between aromatic aldehydes to form α-hydroxyl ketones (i.e., benzoins) in the presence of a catalyst ***(Estager et al, 2007)***. The benzoin (1) condensation is one of the most important reactions of biochemistry ***(Estager et al, 2007)***. The benzoin (1) condensation is a unique reaction for benzaldehyde ***(Mayo and Trumper, 2005) (Edwin and Scott, 2016)***.

1.1.1. Synthesis of benzoin:

A typical of unpolung strategy is the benzoin (1) condensation reaction, cyanide ion catalyzed dimerization of two aldehydes, which was fortuitously discovered by Liebig and Wohler in 1832. Benzoin (1) condensation is an important strategy to create new C-C bonds leading the formation of α-functionalized carbonyl compounds. This unique process and its mechanism have been intensively studied ***(Eymur et al, 2013)***.

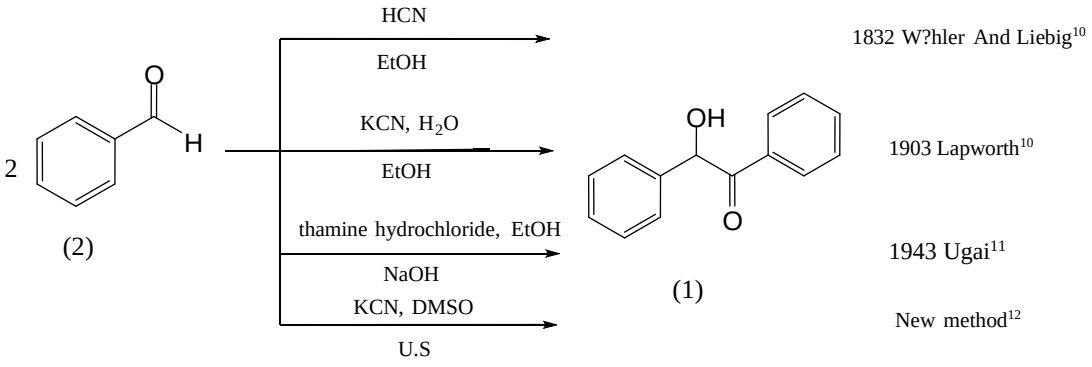
In 1903, Lapworth was the first to establish the mechanism of cyanide ion catalyzed benzoin (1) condensation and determine the formation of crucial carbanion intermediate ***(Eymur et al, 2013)***.

The Benzoin (1) and its derivatives were synthesized by conventional method using sodium cyanide and ethanol with strong heating for the longer time which is found to be hazardous and slower conversion. An alternative facile route of green approach, eco-friendly and solvent-free reaction procedure with very simple workup conditions is needed for organic synthesis. ***(Hadapsar, 2015)***.

In 1943 Ugai, synthesized benzoin and its substituted derivatives includes three component coupling reaction of benzaldehyde (2), ethanol and sodium hydroxide. The ice-cold clear solution of thiamine hydrochloride in aqueous ethanol was added to that this ice cooled freshly prepared sodium hydroxide solution. Then Fresh bidistilled benzaldehyde or substituted benzaldehyde was added to the reaction mixture. The mixture was heated gently on a water bath for about 60 min. The mixture was cooled to room temperature ***(Hadapsar, 2015)***.

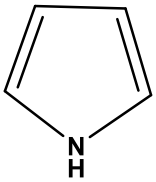
A rapid, highly efficient and mild green synthesis of symmetrical and unsymmetrical benzoin derivatives was achieved from the reaction of benzaldehyde (2) derivatives with potassium cyanide in dimethyl sulfoxide under argon gas. This simple method affords benzoin derivatives at room temperature in short reaction times with high yield and purity ***(Safari and Moshtael et al, 2011).***

Electron-donating substituents on the phenyl ring inhibit benzoin condensation because the carbanion intermediate is destablized. Conversely, electron-withdrawing groups on the phenyl ring stabilize the analogous carbanion and subsequent nucleophilic addition reaction will not occur.It is chiral and exists as pair of enantiomers (R,S)-benzoin ***(Mayo and Trumper, 2005)***.



1.2. Pyrrole:

Pyrrole (3) is an organic compound that is both heterocyclic and aromatic. It has a five-membered ring with the chemical formula C_4H_4NH. In its pure form, it is a colorless liquid that easily darkens when exposed to air. Substituted versions of pyrrole, such as N-methylpyrrole ($C_4H_4NCH_3$), are also referred to as pyrroles. Porphobilinogen, a pyrrole with three substituents, serves as the precursor for numerous natural products, including heme ***(Marc, 2002) (*****Lehninger** ***and Nelson et al, 2000)***.



(3)

Pyrrole (3) is typically purified by distillation before use, and it is known for its nutty odor. It belongs to a class of 5-membered aromatic heterocycles, similar to furan and thiophene ***(Wilfred et al, 2003)*** Pyrrole (3) exhibits aromatic character due to the partial delocalization of lone pairs of electrons on the nitrogen atom into the ring, resulting in a 4n + 2 aromatic system according to Hückel's rule. In terms of aromaticity, pyrrole (3) is considered modest compared to benzene but comparable to related heterocycles such as thiophene and furan ***(Smith et al, 2007)***. Its melting point is -23 °C (-9 °F; 250 K).

In 1834, F.F. Runge first detected pyrrole as a constituent of coal tar. Later, in 1857, it was isolated from the pyrolysate of bone. The name "pyrrole" originates from the Greek word "pyrrhos," meaning "reddish, fiery," which refers to the red color it imparts to wood when moistened with hydrochloric acid ***(Runge, 1834) (Albrecht, 2000)***.

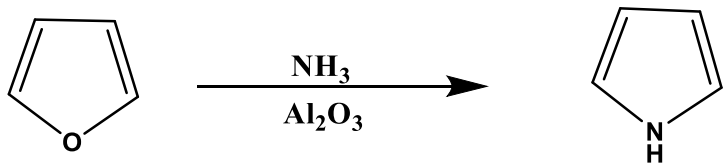
While pyrrole (3) itself is not naturally occurring, many of its derivatives can be found in various cofactors and natural products. Examples of naturally produced molecules containing pyrroles include vitamin B_{12}, bile pigments such as bilirubin and biliverdin, as well as the porphyrins found in heme, chlorophyll, chlorins, bacteriochlorins, and porphyrinogens. Additional pyrrole-containing secondary metabolites include PQQ, makaluvamine M, ryanodine, rhazinilam, lamellarin, prodigiosin, myrmicarin, and sceptrin. The synthesis of pyrrole-containing haemin, carried out by Hans Fischer, was recognized with a Nobel Prize ***(Jusélius, 2000)***.

1.2.1. Synthesis of pyrrole:

Pyrrole (3) and its derivatives are crucial heterocyclic compound with significant applications in pharmacenticals, agrochemicals, and materials science. several synthetic strategies have been developed for their preparation including ***(Harreus, 2012)***:

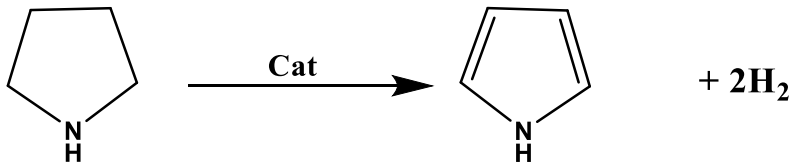
Classical Approaches to Pyrrole Synthesis:

In industry, pyrrole (3) is produced by treatment of furan (4) with ammonia in the presence of solid acid catalysts, like SiO_2 and Al_2O_3 ***(Harreus, 2012)***.



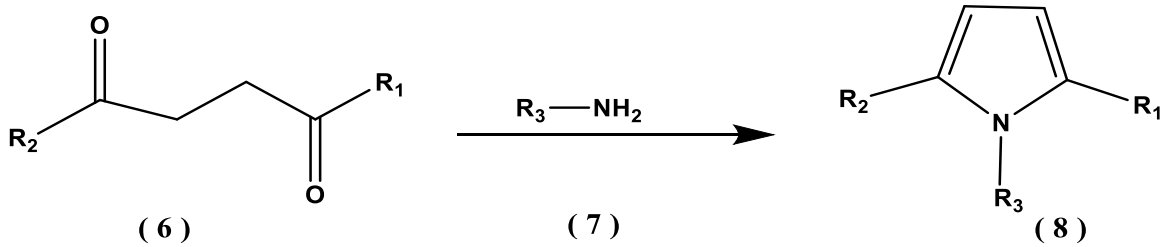
(4) **(3)**

Pyrrole (3) can also be obtained through the catalytic dehydrogenation of pyrrolidine (5) ***(Harreus, 2012)***.



(5) **(3)**

The Paal-Knorr synthesis is the most widely used method for synthesizing pyrroles, as well as their derivatives. This well-known technique involves reacting a 1,4-dicarbonyl compound (6a, b) with ammonia or a primary amine (7a, b). As a result, pyrrole and substituted pyrrole (8a, b) are formed ***(Paal, 1884) (Knorr, 1884)***.



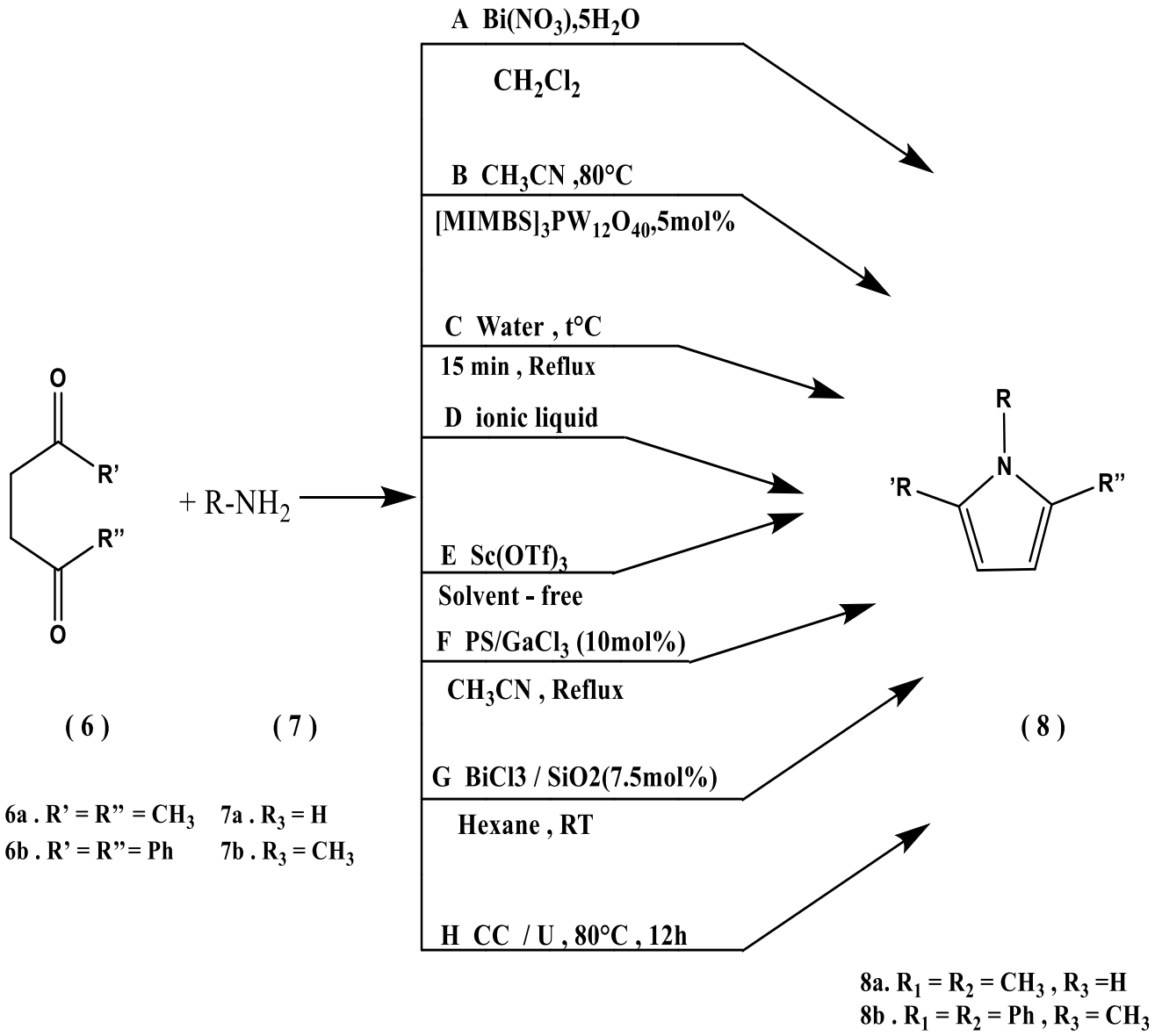
(6) **(7)** **(8)**

6a . $R_1 = R_2 = CH_3$
6b . $R_1 = R_2 = Ph$

7a . $R_3 = H$
7b . $R_3 = CH_3$

8a . $R_1 = R_2 = CH_3$, $R_3 = H$
8b . $R_1 = R_2 = Ph$, $R_3 = CH_3$

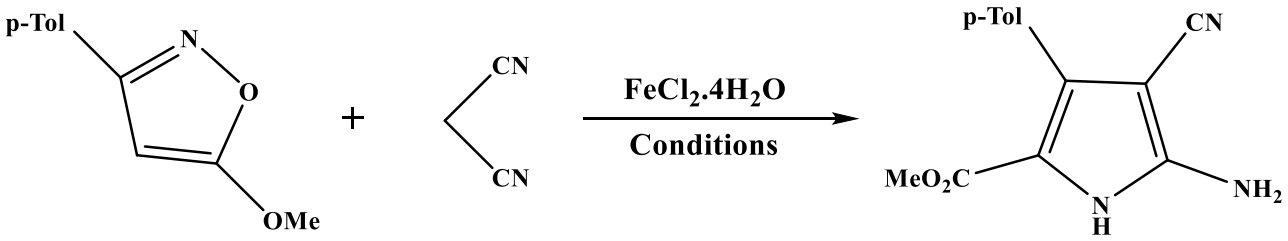
Changes in the synthesis of Paal-Knorr pyrrole Several modifications to the initial reagents and/or reaction conditions have been made to the traditional Paal-Knorr technique in order to optimize it. displayed on the scheme **1** ***(Tzankova, et al, 2018)***.



Scheme 1. Modifications in Paal-Knorr pyrrole synthesis ***(Tzankova, et al, 2018)***.

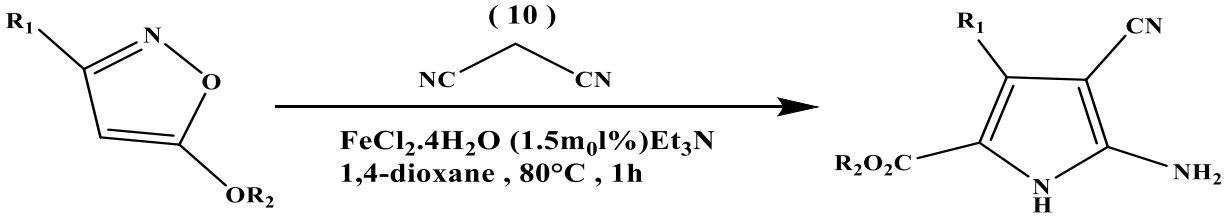
A complete atom-efficient domino technique has been established for creating alkyl 5-amino-4-cyano-1H-pyrrole-2-carboxylates (11). This is done through the transannulation of 5-alkoxyisoxazoles (9) with malononitrile (10) using Fe (II) as a catalyst. These alkyl 5-amino-4-cyano-1H-pyrrole-2-carboxylates (11) serve as valuable building blocks for a variety of annulation processes, which result in novel derivatives of 1H-pyrroloimidazole and pyrrolopyrimidine ***(Anastasiya et al, 2021)***.

Fe (II) complexes and salts are frequently employed as efficient catalysts for the N–O bond breakage in 5-alkoxyisoxazoles, as detailed in an array of publications, whereas Ni (II) complexes and salts are effectively used to produce pyrroles by the interaction of isoxazoles with methylene active chemicals ***(Anastasiya et al, 2021)***.



(9) **(10)** **(11)**

The reaction tolerates a variety of donor- and acceptor-substituted aryl, alkyl, and 2-thienyl groups at the 3 position (R_1) and alkoxy substituents at the 5 position (R_2O) of isoxazole (12a-e) and affords the desired products (13a-e) in generally good yields (55–95%). The relatively low yields of pyrroles are due to the instability of isoxazoles leading to resinification of the corresponding reaction mixtures and the need to isolate pyrroles using chromatography***(Anastasiya et al, 2021)***.

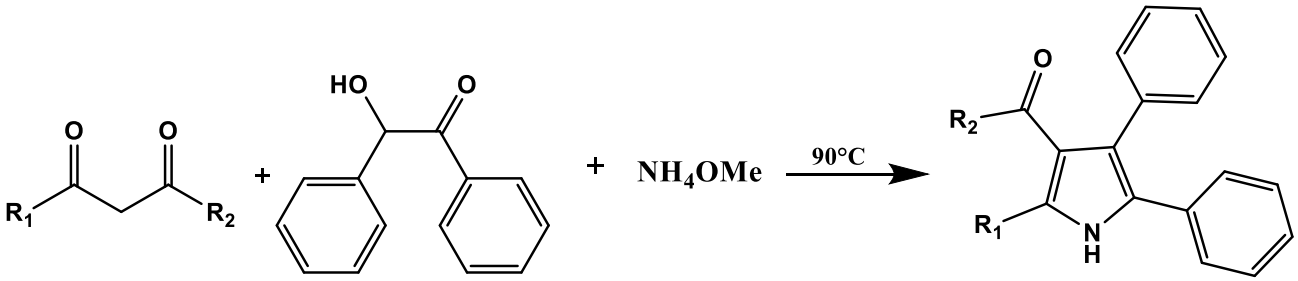


(12) **(13)**

12a . R_1= C_6H_5
12b . R_1 =C_6H_4-pNO_2
12c . R_1 = C_6H_4-pCH_3
12d . R_1 = C_6H_4-pF
12e . R_1 = C_6H_4-pBr
$12_{(a,e)}$. R_2 = CO_2CH_3

13a . R_1= C_6H_5
13b . R_1 =C_6H_4-pNO_2
13c . R_1 = C_6H_4-pCH_3
13d . R_1 = C_6H_4-pF
13e . R_1 = C_6H_4-pBr
$13_{(a,e)}$. R_2 = CO_2CH_3

A straightforward one-pot technique that uses a reaction involving 1,3-dicarbonyl compounds (14a-d), benzoin (1) and ammonium acetate (15) at 90°C was developed for the regioselective synthesis of tetrasubstituted pyrroles (16a-d) without the need for a solvent or catalyst ***(Bhat, 2013)***.

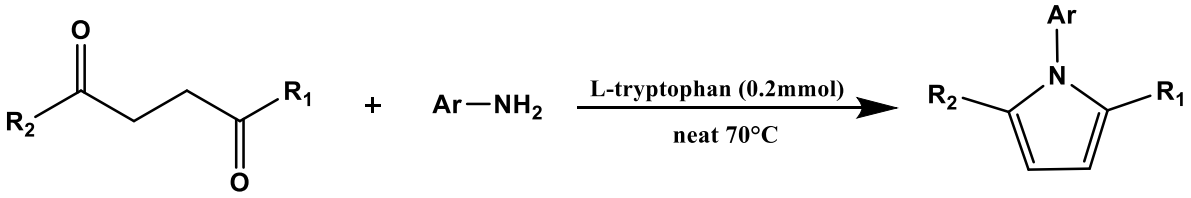


(14) **(1)** **(15)** **(16)**

14a. $R_2 = CO_2C_2H_5$
14b. $R_2 = CO_2CH_3$
14c. $R_2 = CO_2C_4H_9$
14d. $R_2 = COC_6H_5$
$14_{(a,d)}$. $R_1 = CH_3$

16a. $R_2 = CO_2C_2H_5$
16b. $R_2 = CO_2CH_3$
16c. $R_2 = CO_2C_4H_9$
16d. $R_2 = COC_6H_5$
$16_{(a,d)}$. $R_1 = CH_3$

For the first time, a solvent -free paal-knorr reaction employing L-tryptophan as a biodegradable organo catalyst has been developed**,** This green protocol facilitates the condensation of 2,5-dicarbnyl (6a, b) compounds.With primary aromatic amines (17a-e) to afford pyrrole (18a-e) in high yields, eliminating the need for toxic solvents or metal catalysts ***(Bhat, 2013)***.



(6) **(17)** **(18)**

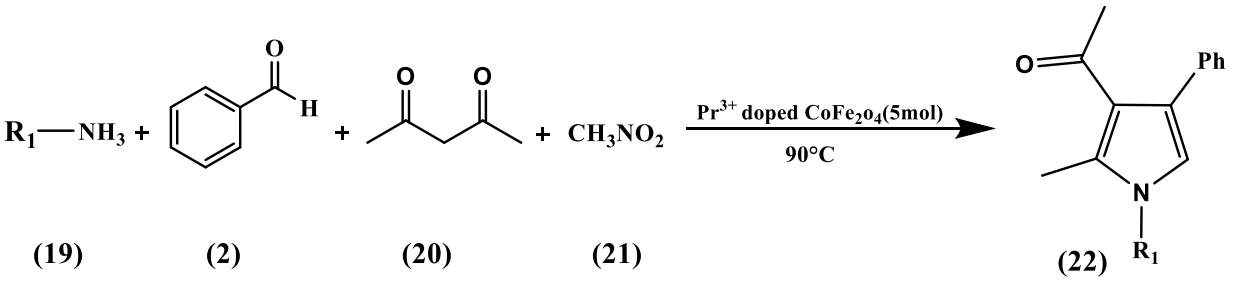
6a. $R_1 = R_2 = CH_3$
6b. $R_1 = R_2 = Ph$

17a. $Ar = C_6H_5$
17b. $Ar = 4\text{-}OMeC_6H_4$
17c. $Ar = 4\text{-}MeC_6H_4$
17d. $Ar = 4\text{-}BrC_6H_4$
17e. $Ar = 3,4\text{-}(Cl)_2C_6H_4$

18a. $Ar = C_6H_5$
18b. $Ar = 4\text{-}OMeC_6H_4$,
18c. $Ar = 4\text{-}MeC_6H_4$
18d. $Ar = 4\text{-}BrC_6H_4$
18e. $Ar = 3,4\text{-}(Cl)_2C_6H_4$
$18_{(a,e)}$. $R_1 = R_2 = CH_3$
$18_{(a,e)}$. $R_1 = R_2 = Ph$

Khan et al. introduced a synthetic approach to synthesize multisubstituted pyrrole derivatives (22a, b). this strategy involved a four-component, one-pot, solvent-free reaction using a Pr^{3+} doped $CoFe_2O_4$

catalyst. Notably, this catalyst was both reusable and magnetically facile The researchers highlighted that the reaction demonstrated robustness, eco-friendliness, and achieved high yields within a short reaction time. The four components used in the one-pot reaction were primary aromatic amines (19a,b), benzaldehyde (2), acetylacetone (20), and nitromethane (21) ***(Khan, et al, 2016)***.

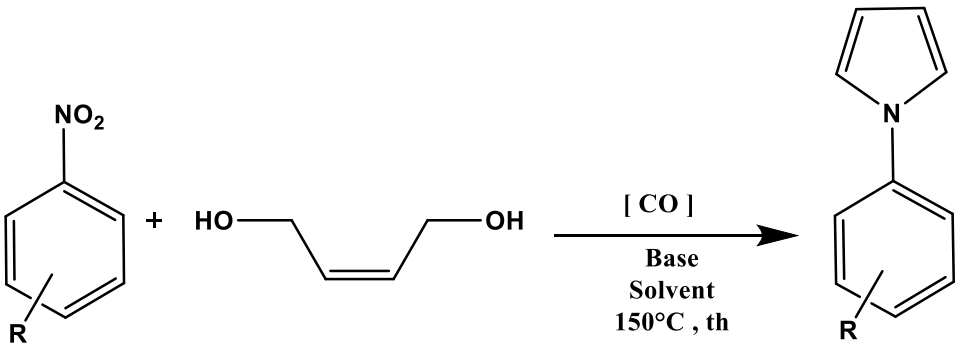


(19) **(2)** **(20)** **(21)** **(22)**

19a. R_1= 4-FC_6H_4
19b. R_2= 4-$NO_2C_6H_4$

22a. R_1= 4-FC_6H_4
22b. R_2= 4-$NO_2C_6H_4$

Employing bio-waste caffeine carbon-supported heterogeneous cobalt catalyst, synthesis of various substituted pyrrole derivatives is reported. In this methodology, pyrroles (25a, b) were synthesized through coupling between nitroarenes (23a, b) and (Z)-but-2-ene-1,4-diol (24) in a tandem manner ***(Panja, et al, 2021)***.

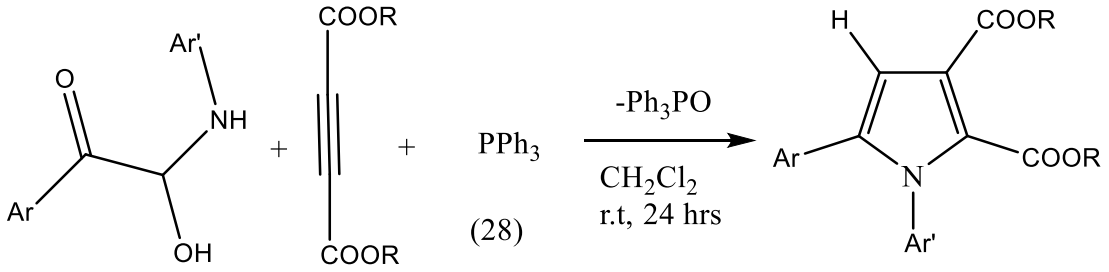


(23) **(24)** **(25)**

23a. R= 4-OCH_3
23b. R= 3-Cl-4-OCH_3

25a. R= 4-OCH_3
25b. R= 3-Cl-4-OCH_3

Some polyfunctionalized pyrrole derivatives (29a-d) were synthesized by triphenyl phosphineoxide-promoted (28) condensation reaction between dialkyl acetylene dicarboxylates (27a, b) and 1-aryl-2-(arylamino)-2-hydroxyethanones (26a-d) ***(Mendel and Lillquist, 1979)***.



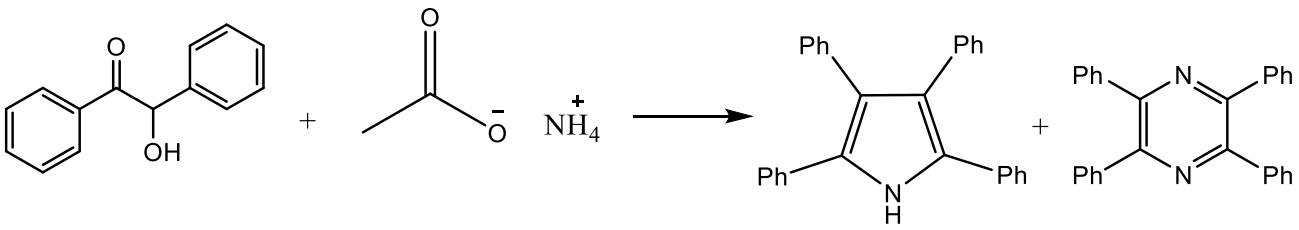
(26) (27) (29)

	Ar	Ar'
26a.	4-BrC_6H_4	4-$NO_2C_6H_4$
26b.	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$
26c.	4-ClC_6H_4	4-$NO_2C_6H_4$
26d.	4-ClC_6H_4	3-$NO_2C_6H_4$

	R
27a.	Me
27b.	Et

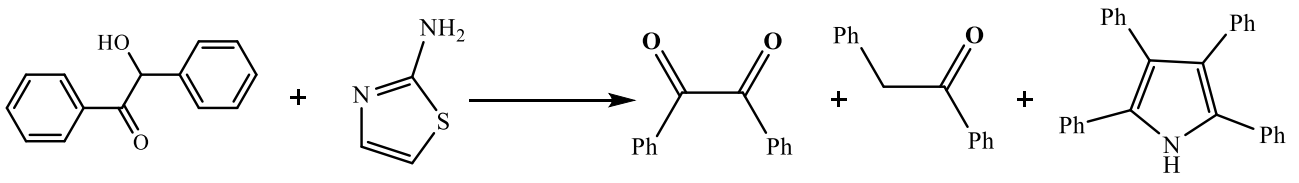
	R	Ar	Ar'
29a.	Me	4-BrC_6H_4	4-$NO_2C_6H_4$
29b.	Me	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$
29c.	Me	4ClC_6H_4	4-$NO_2C_6H_4$
29d.	Et	4-ClC_6H_4	3-$NO_2C_6H_4$

Reaction of benzoin (1) with ammonium acetate (15) only led to 2,3,5,6-tetraphenyl pyrazine (31) and 2,3,5,6-tetraphenylpyrrole (30) ***(Mendel and Lillquist, 1979)***.



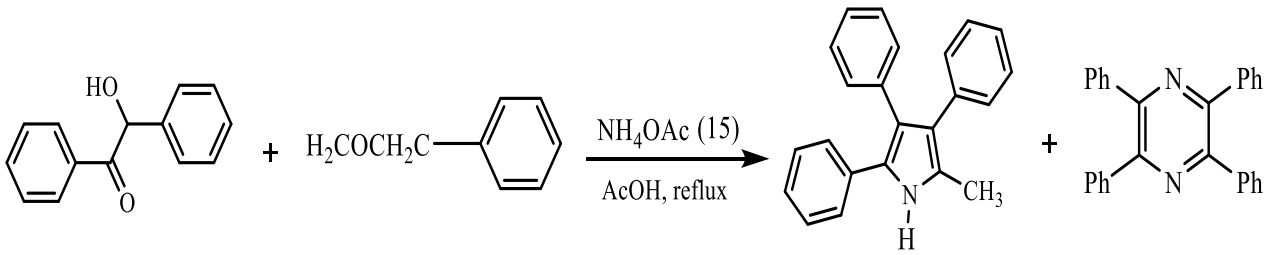
(1) (15) (30) (31)

Also, when benzoin (1) was heated with 2-aminothiazole (32), benzil (33), desoxybenzoin (34), and 2,3,5,6-tetraphenyl pyrrole (30) were formed ***(Mendel and Lillquist, 1979)***.



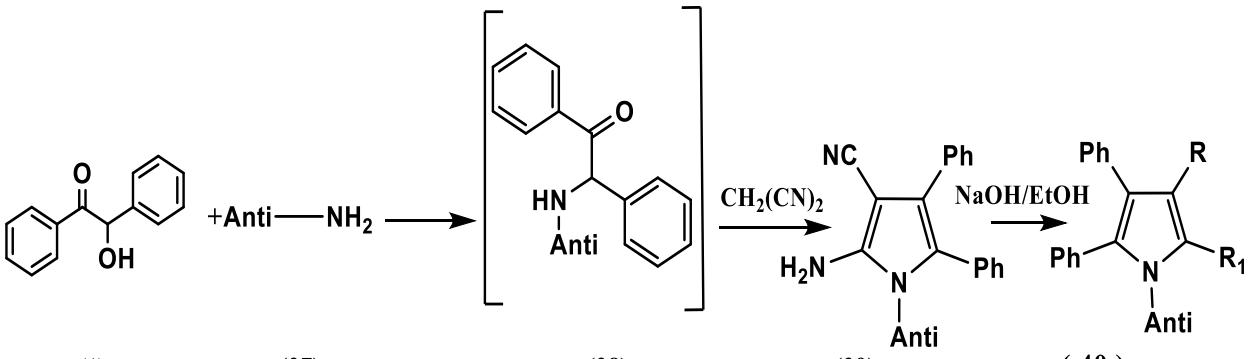
(1) (32) (33) (34) (30)

An anti-hyper glycemic agent, 2-methyl-3,4,5-triphenyl pyrrole derivative (36) synthesized by refluxing a mixture of benzoin (1), benzyl methyl ketone (35) and ammonium acetate (15) in acetic acid. It was also reported that this reaction also lead to a minor by product which was possibly formed due to self-condensation of benzoin (1) with ammonium acetate (15) in presence of acetic acid and air ***(Varun et al, 2015)***.

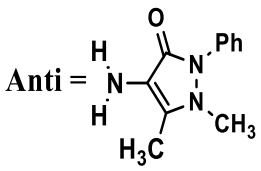


(1) (35) (36) (31)

The reaction of benzoin (1) with antipyrine amine (37) and malononitrile (10) in non-polar solvent gave the pyrrole derivative (39) which was further utilized for the preparation of pyrrole derivatives (40a-c) using appropriate reagents and reaction conditions ***(Varun et al, 2015)***.



(1) **(37)** **(38)** **(39)** **(40)**

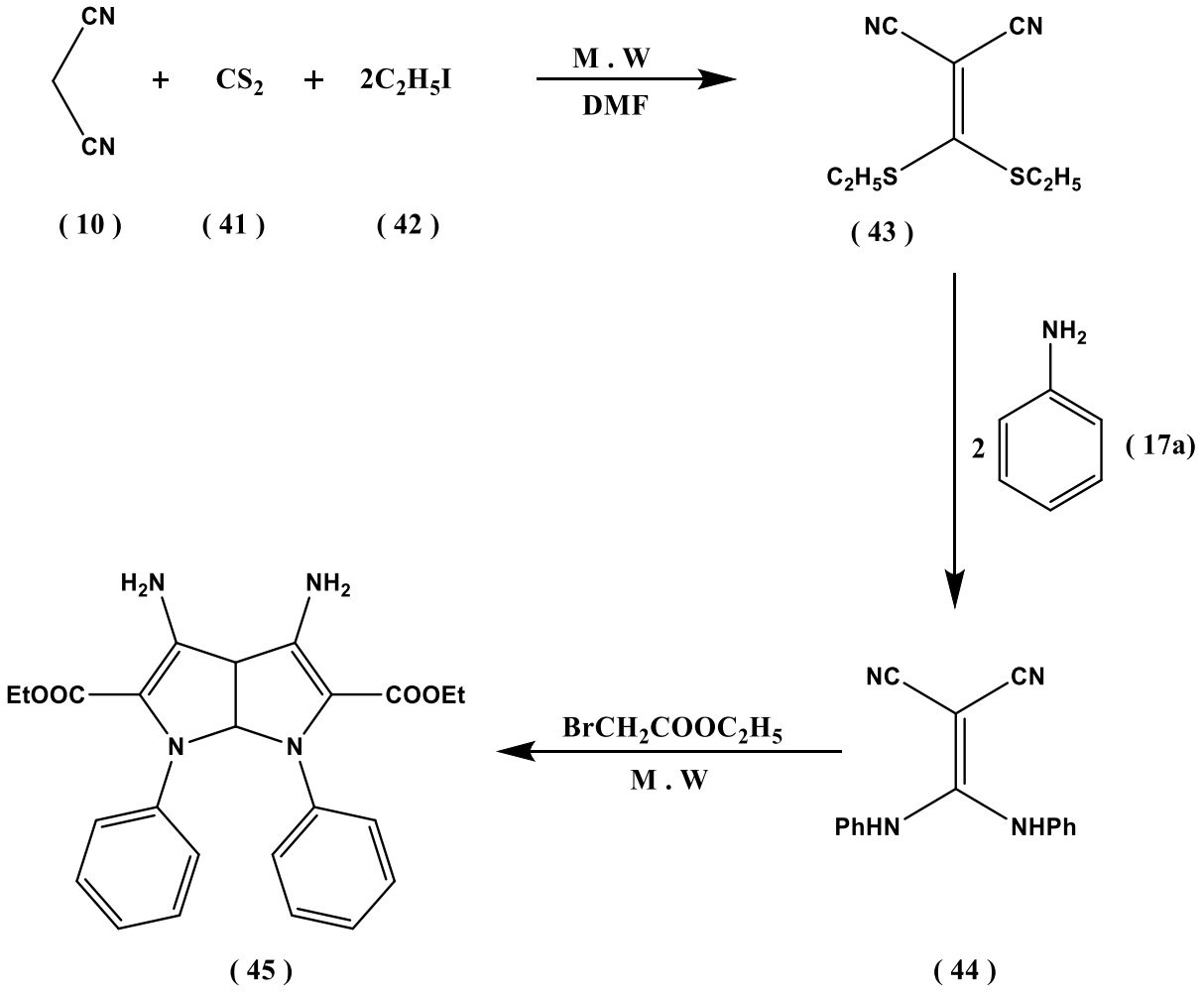


40a. R = CN R_1 = $NHCOCH_3$
40b. R = CN R_1 = CHOEt
40c. R = $CONH_2$ R_1 = NH_2

1.2.2. Synthesis of bis amino pyrrole:

Bis amino pyrrole refers to a class of organic compounds containing two pyrrole rings, each substituted with on amino group (-NH_2) or aderivative there of (e.g.,−HNR or −NR_2) these compounds are part of the broader family of nitrogen containing heterocycles, with are significant in medicinal chemistry, materials science, and dye synthesis ***(Shokr et al, 2021)***.

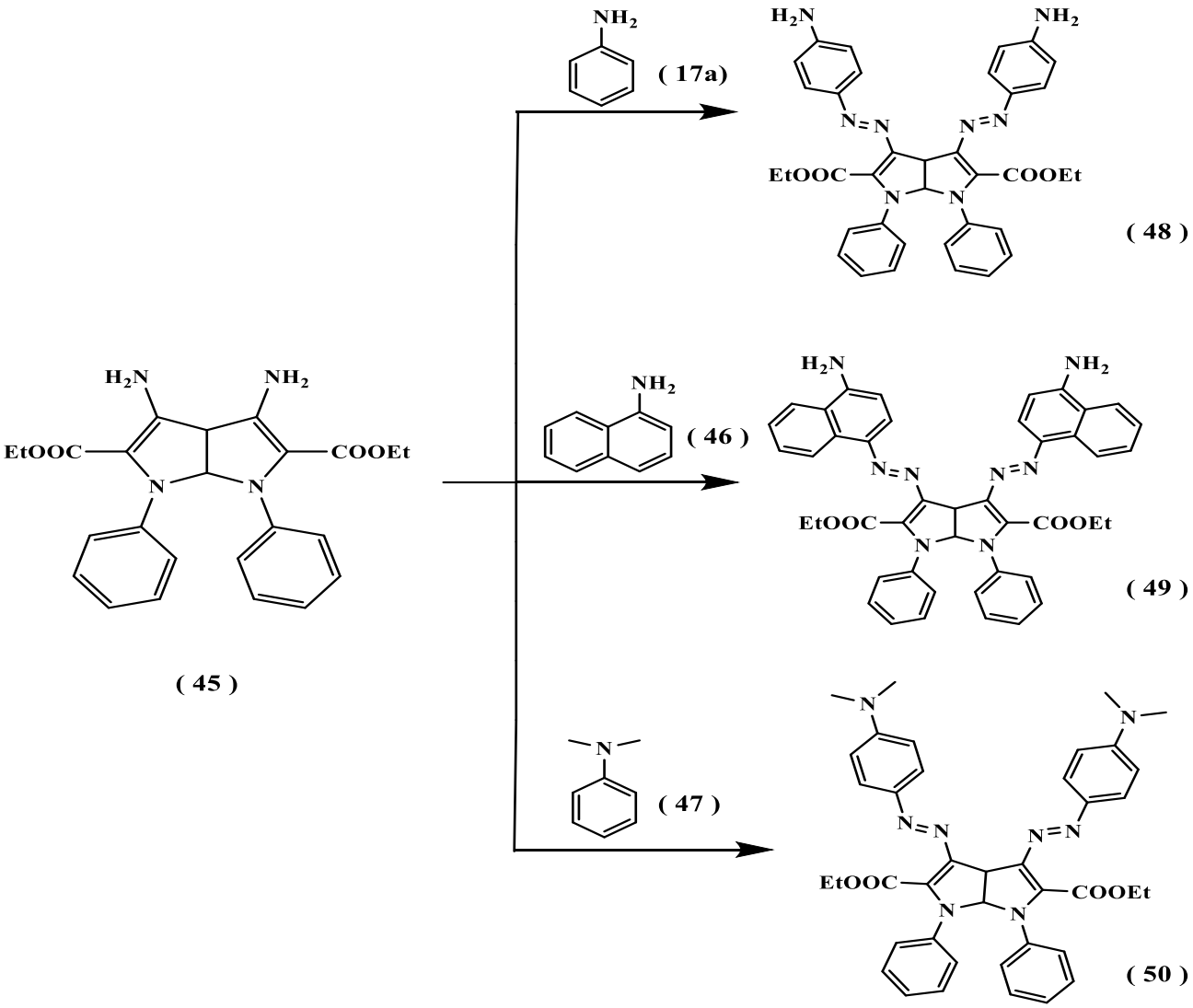
Shokr etal. Successfully synthesized novel bis amino pyrrole compounds for use as dyes in their stady. The synthesis was achieved via microwave irradiation by reaction malononitrile (10), carbon disulfide (41), and ethyl iodide (42). to form an S, S-acetal (43), inter mediate. subsequent reflux of this inter mediate with aniline (17a) for 24 hours resulting in for mation of 2-(bis (phenyl amino) methylene) malononitrile (44). finally, heating the obtained product with bromo acetat under microwave Conditions for 5 minutes facilitated cyclization to afford the target bis-amino pyrrole derivatives (45) This methodology highlights the efficieng of microwave- assisted synthesis in a ccelerating reaction times and improving yields for complex hetorocyclic systems ***(Shokr et al, 2021)***.



1.2.2.1 Reactions of bis amino pyrroles:

Dihydro pyrrolo [2,3-b] Pyrrole derivatives were synthesized in excellent yields (70-75%) under mild, convenient reaction Conditions via a diazonium salt inter mediate. The synthesis bigan with the preparation of the diazonim salt from diethyl 3,4-diammo-1,6-diphenyl-1, 6-dihydropyrrolo[2,3-b] pyrrole-2,5-dicarboxylate (45). This intermediate subsequent underwent an azo Coupling reaction with aromatic amine anilin (17a), I-naphthy amine (46) and N, N-dimethyl aniline (47), to afford the target Compone (48) (49) and (50) respectively ***(Shokr et al, 2021)***.

This reaction protocol demonstrates efficient acess to structurally diverse dihydro pyrrolo [2,3-b] Pyrrole systems through a rapid and high- yielding process, The mild reaction conditions, Short reaction time, and versatility of amin coupling partners highlight the praticality of this approach for Synthesizing functionalized heterocyclic architectures with pot Potential applications in materila or pharmaceutical chemistry ***(Shokr et al, 2021)***.



1.3. Biological Activity:

Heterocyclic compounds containing nitrogen nucleus plays most important role in the field of medicinal chemistry. It shows wide range of activities for medication purpose ***(Patil et al, 2009)***.

A large number of Bis amino pyrrole compounds have been synthesized and evaluated for their different biological activities. Some marketed nitrogen nucleus containing drugs have different types of pharmacological activities ***(Patil et al, 2009) (Pyo et al, 2008)***. Thus, the Bis amino pyrrole skeleton is frequently encountered in medicinal chemistry.

Bis amino pyrroles demonstrate a variety of biological functions, such as antibacterial, antiviral, antifungal, anti-inflammatory, and anticancer effects. These compounds are present in many natural, synthetic, and semi synthetic materials. The different groups within these compounds are crucial in shaping their biological characteristics ***(Da Silva et al, 2011)***.

Chapter 2

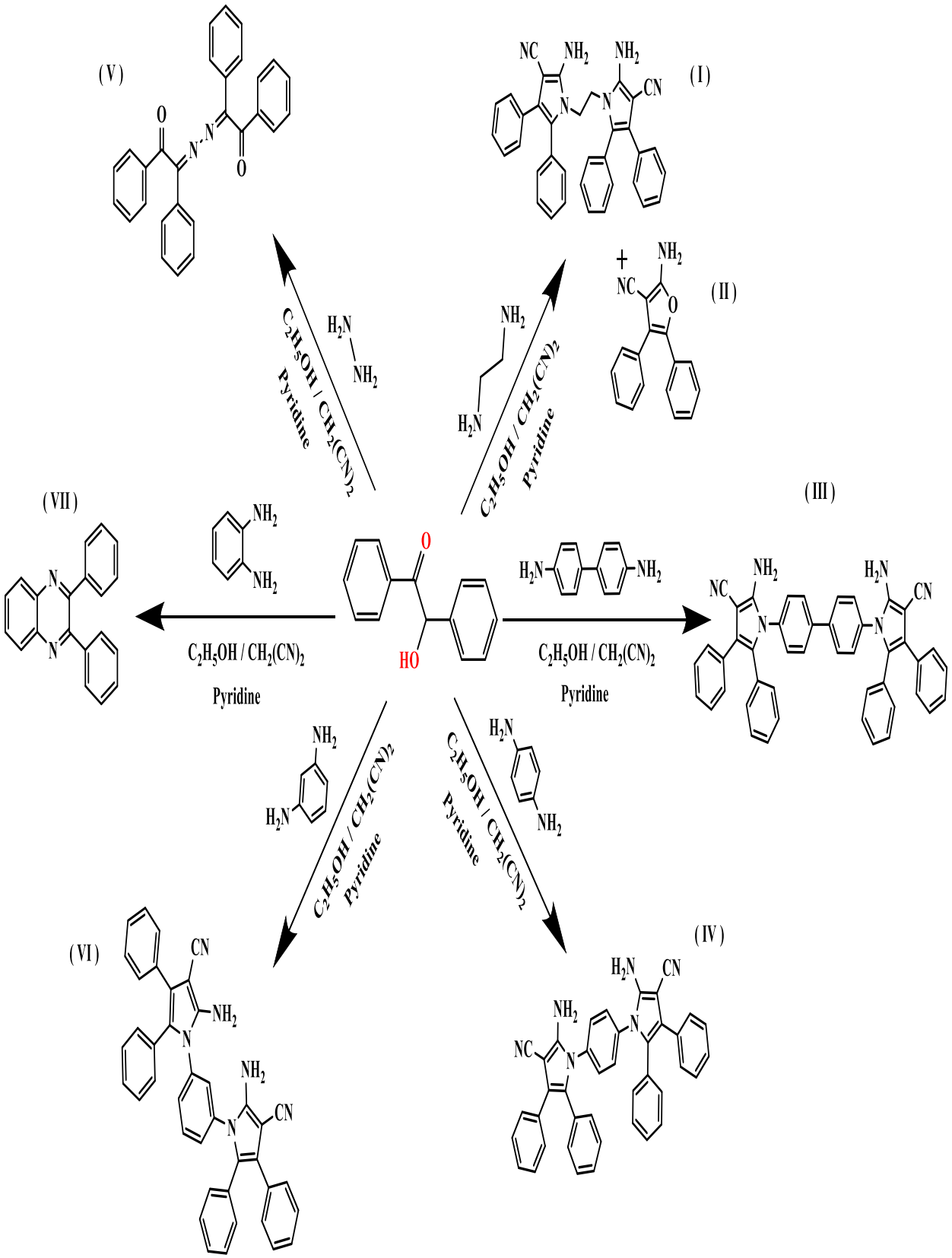
Discussion

2. Discussion:

2.1. Reaction of benzoin with diamines:

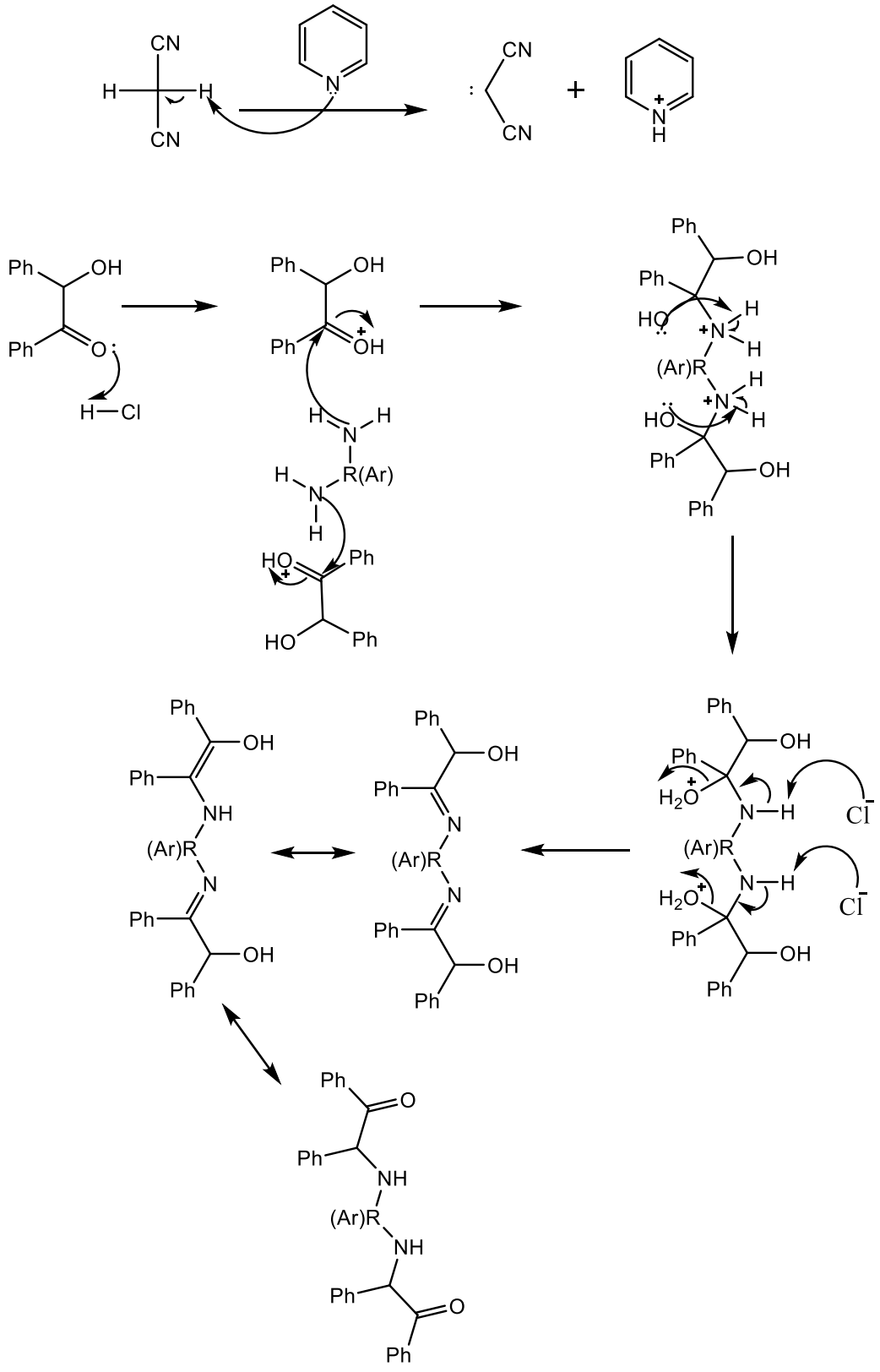
The synthesis of 1H-pyrrole derivatives has garnered considerable attention due to their broad biological and medicinal applications. In this study, benzoin (1) served as an electrophilic center, reacting with various aromatic diamines (e.g., ethane-1,2-diamine, benzidine, p-phenylenediamine, m-phenylenediamine) and malononitrile as a nucleophile under optimized conditions (ethanol/pyridine) to afford novel heterocyclic compounds incorporating the 1H-pyrrole core (I, III, IV, VI). (Scheme 2.1)

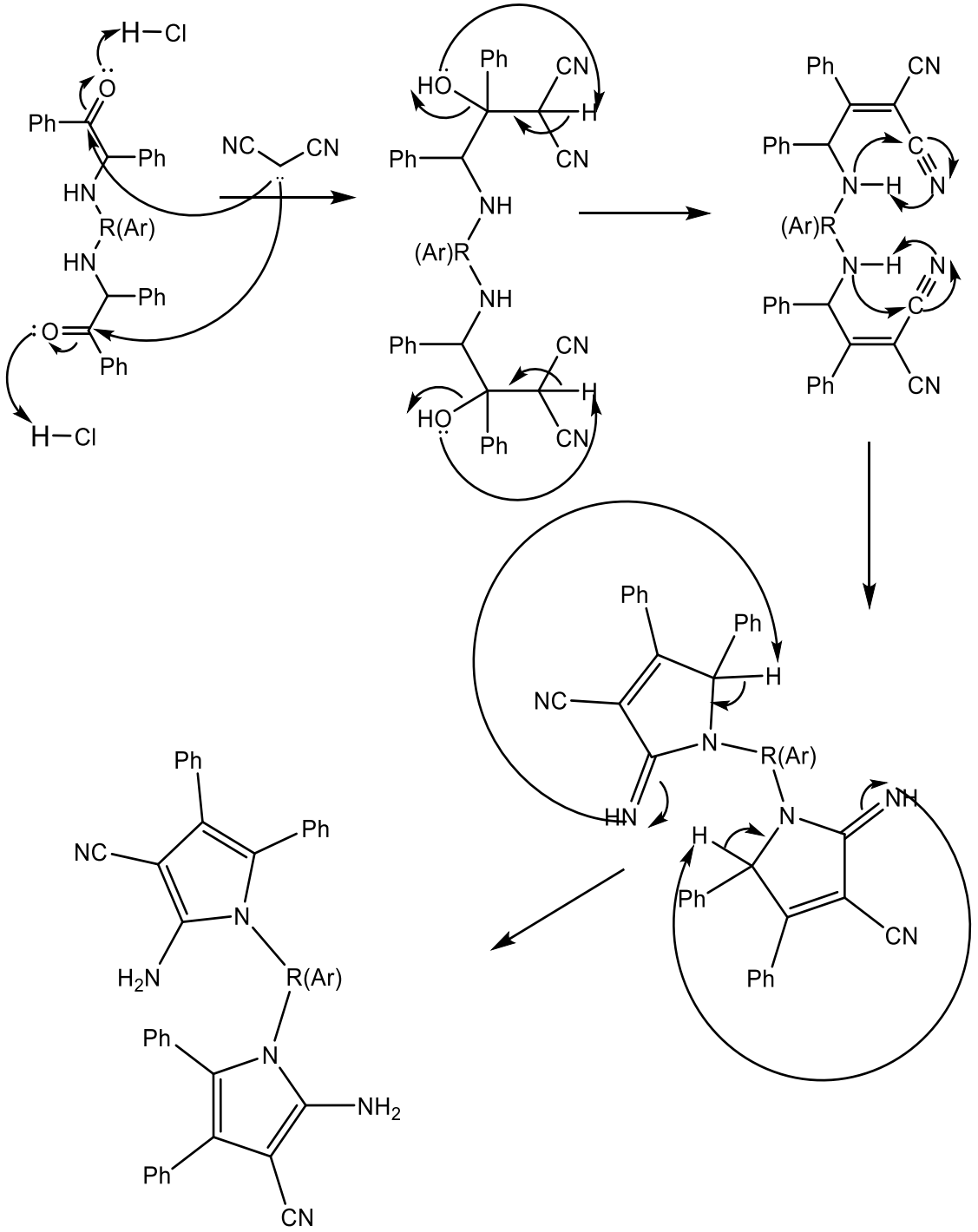
The synthesis of I, III, IV, and VI proceeds via nucleophilic attack of the diamine on benzoin's carbonyl group, generating an α-amino ketone intermediate, which undergoes in situ condensation with malononitrile to afford moderate yields of the target bis(1H-pyrrole) compounds (scheme 2.2). The use of pyridine as a base in ethanol likely facilitates enolization and subsequent cyclization. However, deviations from this pathway were observed with ethylenediamine, hydrazine, and o-phenylenediamine, emphasizing the role of reactant geometry and electronic effects.



Scheme 2.1: Reaction of benzoin with diamines.

The Reaction Machanism:

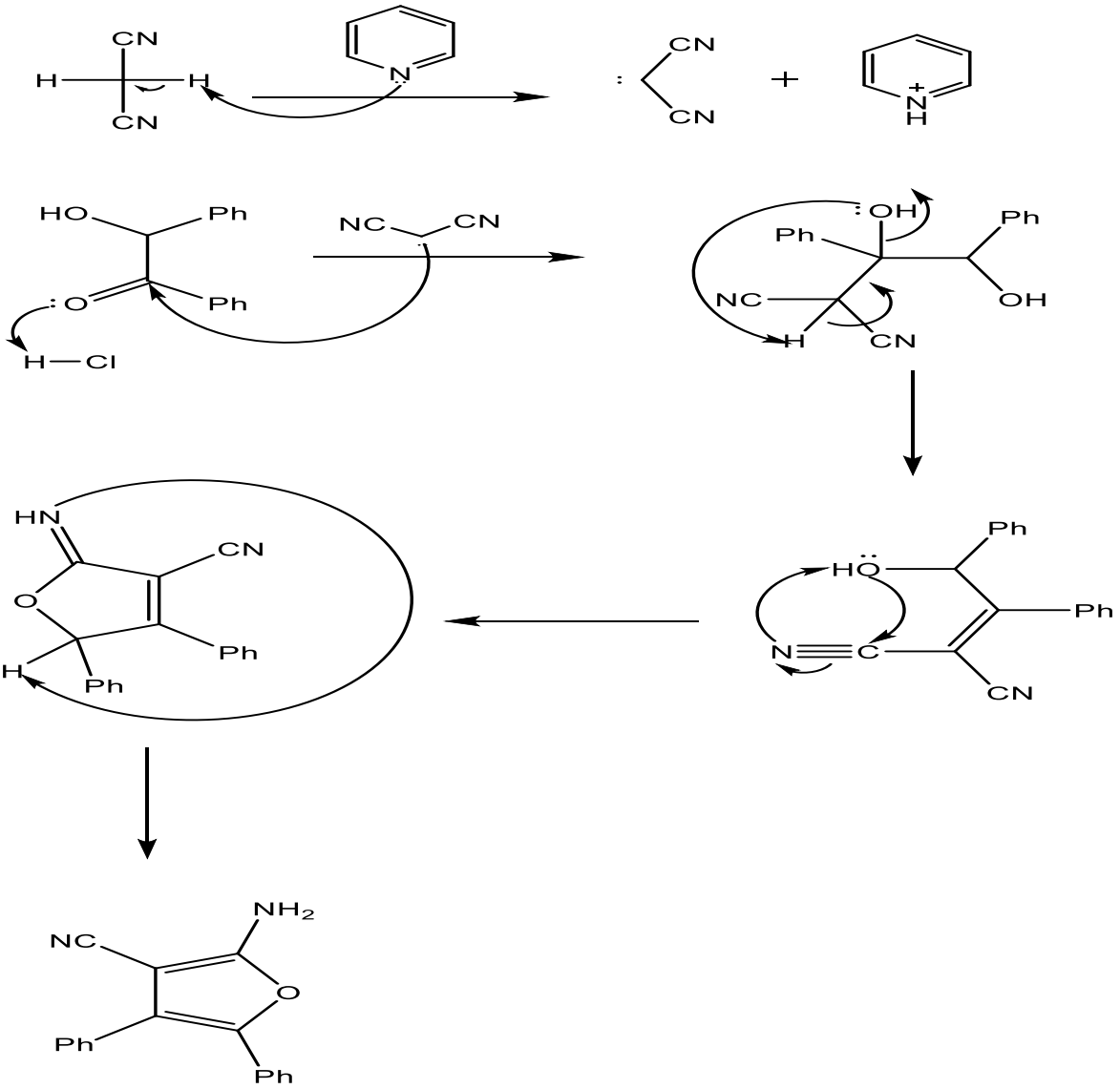




Scheme 2.2: The proposed mechanism of synthesis of compounds I, III, IV and VI

This study demonstrates the divergent reactivity of benzoin (1) with diamines, where steric and electronic factors critically govern the formation of heterocyclic products. When ethylenediamine was employed, both the expected bis-pyrrole (I) and an unexpected furan derivative (II) formed. The latter likely arises via a Knoevenagel condensation between benzoin and malononitrile, followed by intramolecular cyclization as illustrated in (Scheme 2.3). This side reaction highlights the competitive pathways accessible under the given conditions, where the nucleophilicity of the amine and the electrophilicity of the carbonyl group direct product distribution.

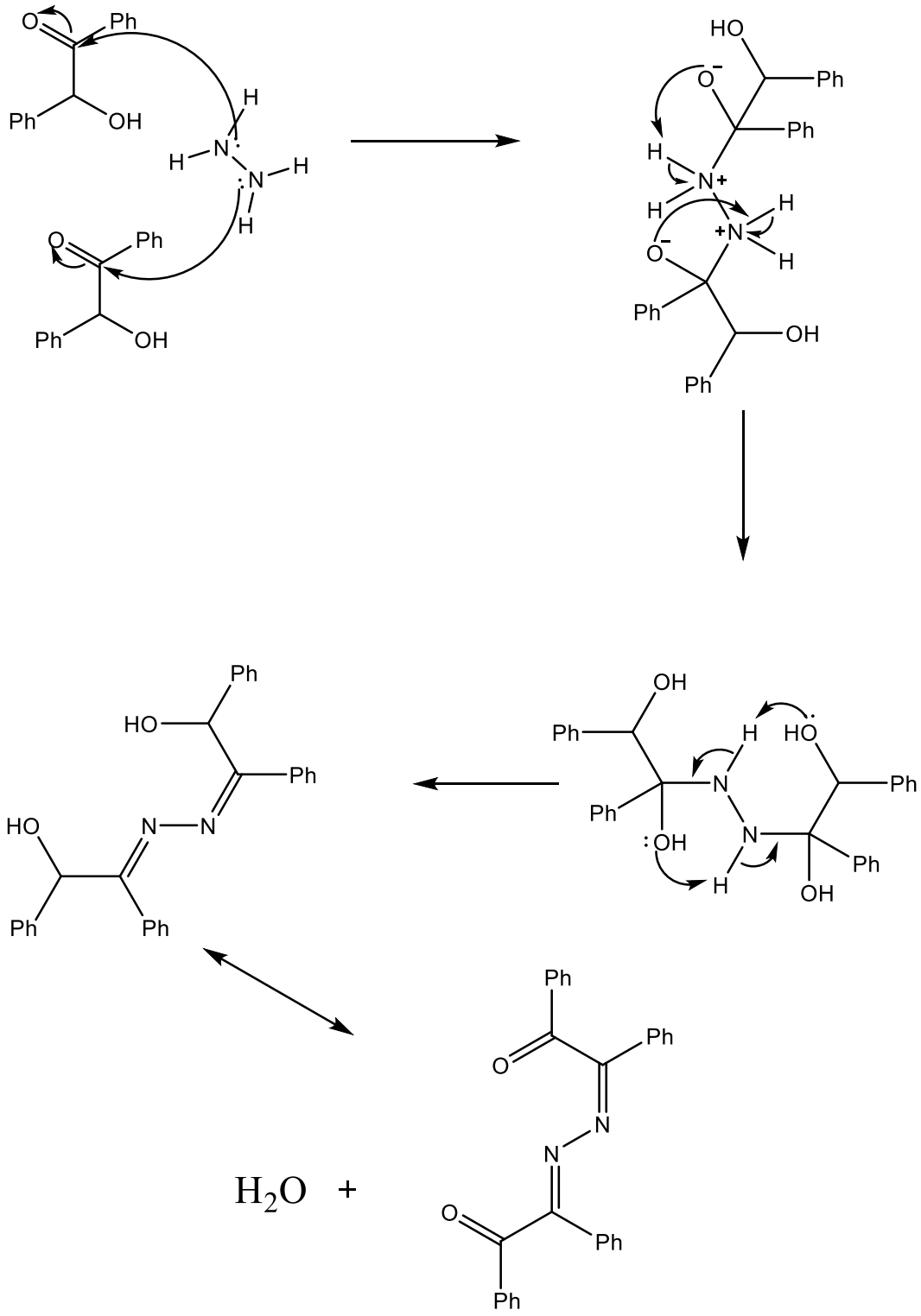
<u>The Reaction Machanism:</u>



Scheme 2.3: The proposed mechanism of synthesis of compound II

In contrast, the reaction with hydrazine proceeded exclusively to form 2,2'-(hydrazine-1,2-diylidene) bis(1,2-diphenylethan-1-one) (V), bypassing pyrrole formation entirely. This transformation, which occurs even in the absence of malononitrile, underscores the unique reactivity of hydrazine as a bifunctional nucleophile. The mechanism involves initial attack on the carbonyl carbon, followed by dehydration and intramolecular cyclization as shown in (Scheme 2.4) The absence of competing pathways here suggests that the rigidity of the hydrazine-derived intermediate favors this thermodynamic product.

The Reaction Machanism:

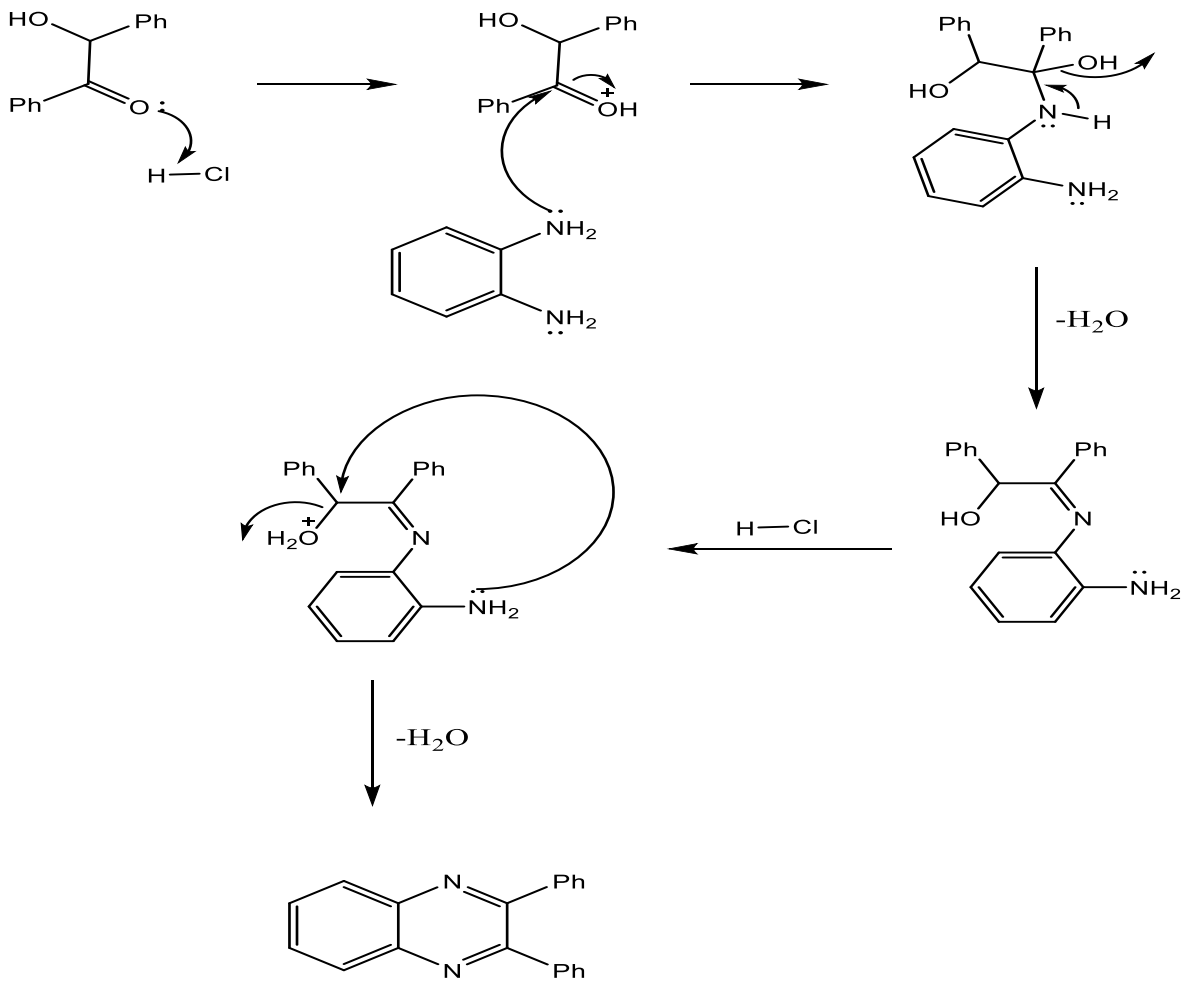


Scheme 2.4: The proposed mechanism of synthesis of compound V

Notably, o-phenylenediamine exclusively yielded 2,3-diphenylquinoxaline (VII), with no evidence of pyrrole formation. This selectivity is attributed to the proximity of the amino groups, which facilitates imine formation and subsequent cyclization into a quinoxaline framework (Scheme 2.5). The aromatic conjugation and high thermodynamic stability of the quinoxaline ring further drive this preference, overriding potential alternative pathways.

These observations underscore the delicate balance between kinetic and thermodynamic control in heterocyclic synthesis. The unexpected formation of VII emphasizes how intramolecular cyclization dominates when using ortho-substituted diamines due to geometric constraints.

<u>The Reaction Machanism:</u>



Scheme 2.5: The proposed mechanism of synthesis of compound VII

The contrasting outcomes between aliphatic and aromatic diamines highlight the importance of rigidity in directing cyclization. Aromatic diamines with para- or meta-substitution favor pyrrole formation due to their ability to stabilize the intermediate without imposing excessive steric strain. In contrast, ethylenediamine's flexibility and o-phenylenediamine's constrained geometry led to alternative pathways.

The reaction of benzoin with ethylene diamine yielded two distinct products, with Compound (II) being the major product (44% yield) and Compound (I) forming as a minor product (39% yield). Comprehensive spectroscopic analyses, including IR, ^{1}H NMR, and ^{13}C NMR, were employed to confirm the structures of these compounds, providing insight into their formation and the reaction pathway.

The IR spectrum of Compound (I) (Figure 1) exhibited characteristic absorption bands corresponding to primary amine (NH_2) and nitrile ($C\equiv N$) functional groups. The presence of two distinct NH_2 stretching vibrations (3215.37 cm^{-1} and 3366.87 cm^{-1}) and a sharp nitrile absorption (2187.47 cm^{-1}) confirmed the expected functional groups. The ^{1}H NMR spectrum (Figure 2) further supported the proposed structure, displaying signals for CH_2 protons (2.80 and 3.96 ppm), NH_2 protons (6.34 and 8.04 ppm), and aromatic protons (7.08–7.39 ppm). Notably, the spectrum suggested an asymmetric structure, likely due to restricted rotation around a C–σ bond, leading to non-equivalent proton environments. The ^{13}C NMR spectrum (Figure 3), while showing fewer signals than expected (14 distinct peaks for 36 carbon atoms), indicated symmetry or overlapping chemical shifts, consistent with the proposed structure. additionally, the APT technique was used (Figure 4) and Additionally D2O (Figure 5).

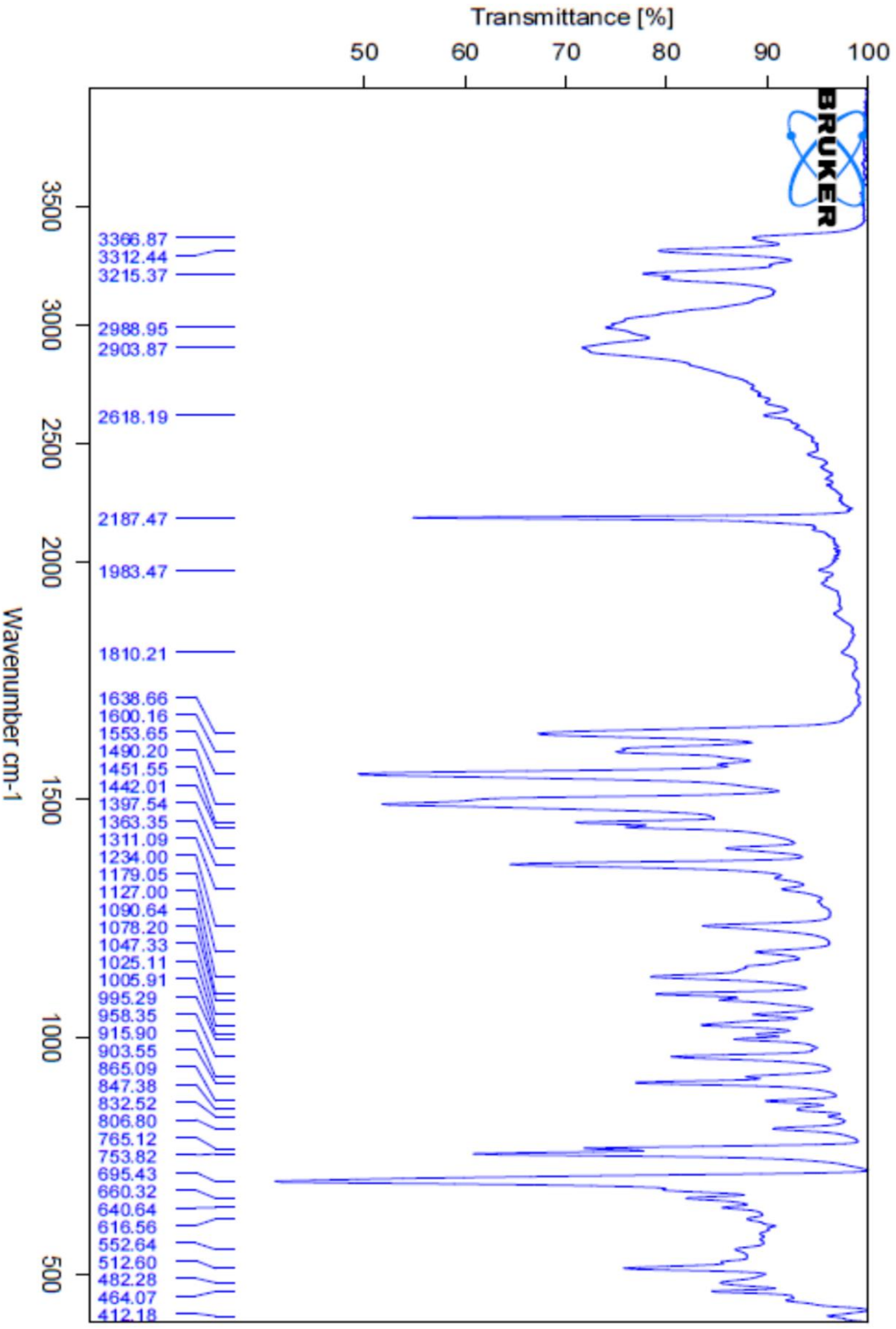


Fig 1: FT-IR spectrum of compound (I)

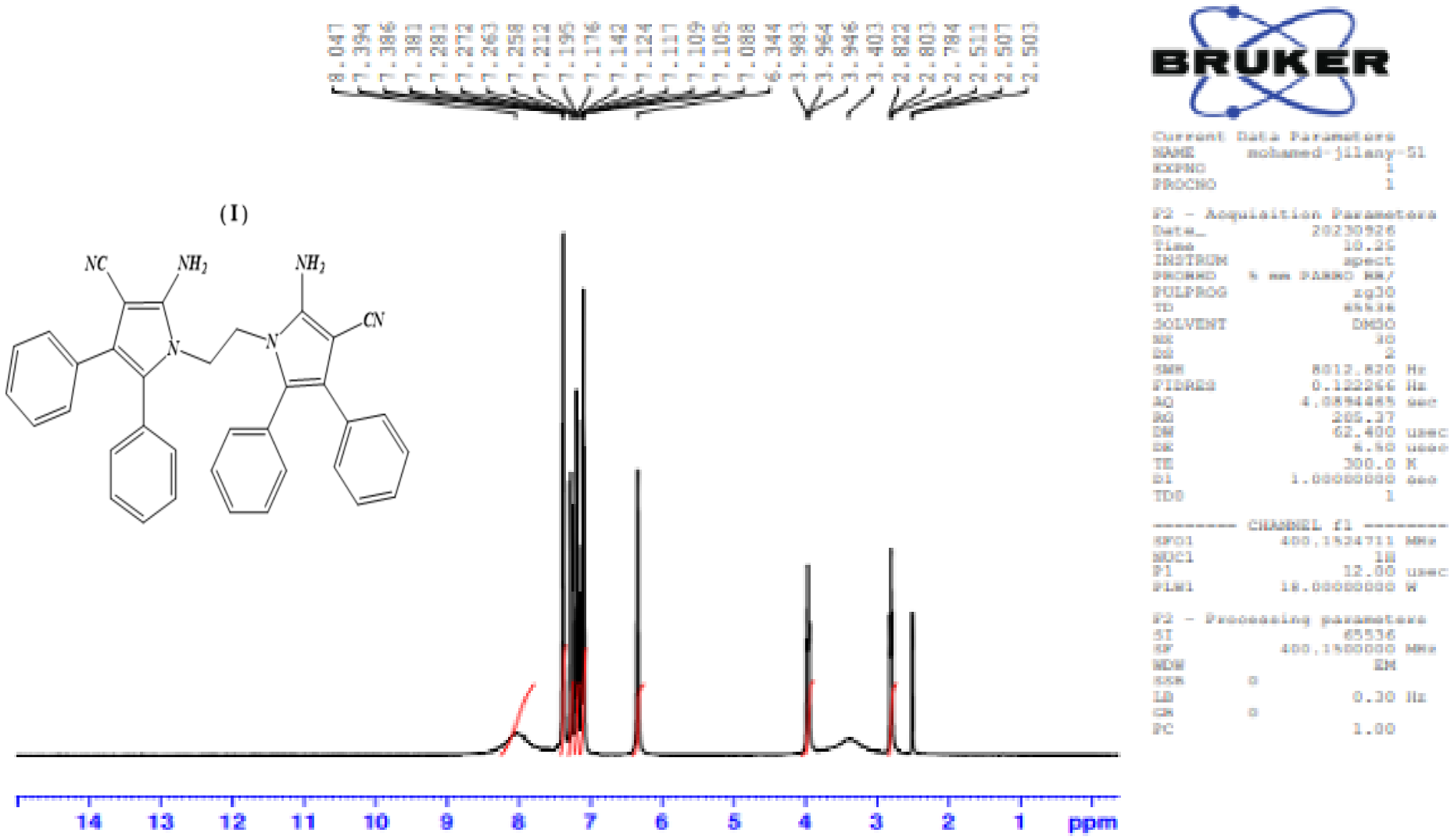


Fig 2: ^{1}H-NMR spectrum of compound (I)

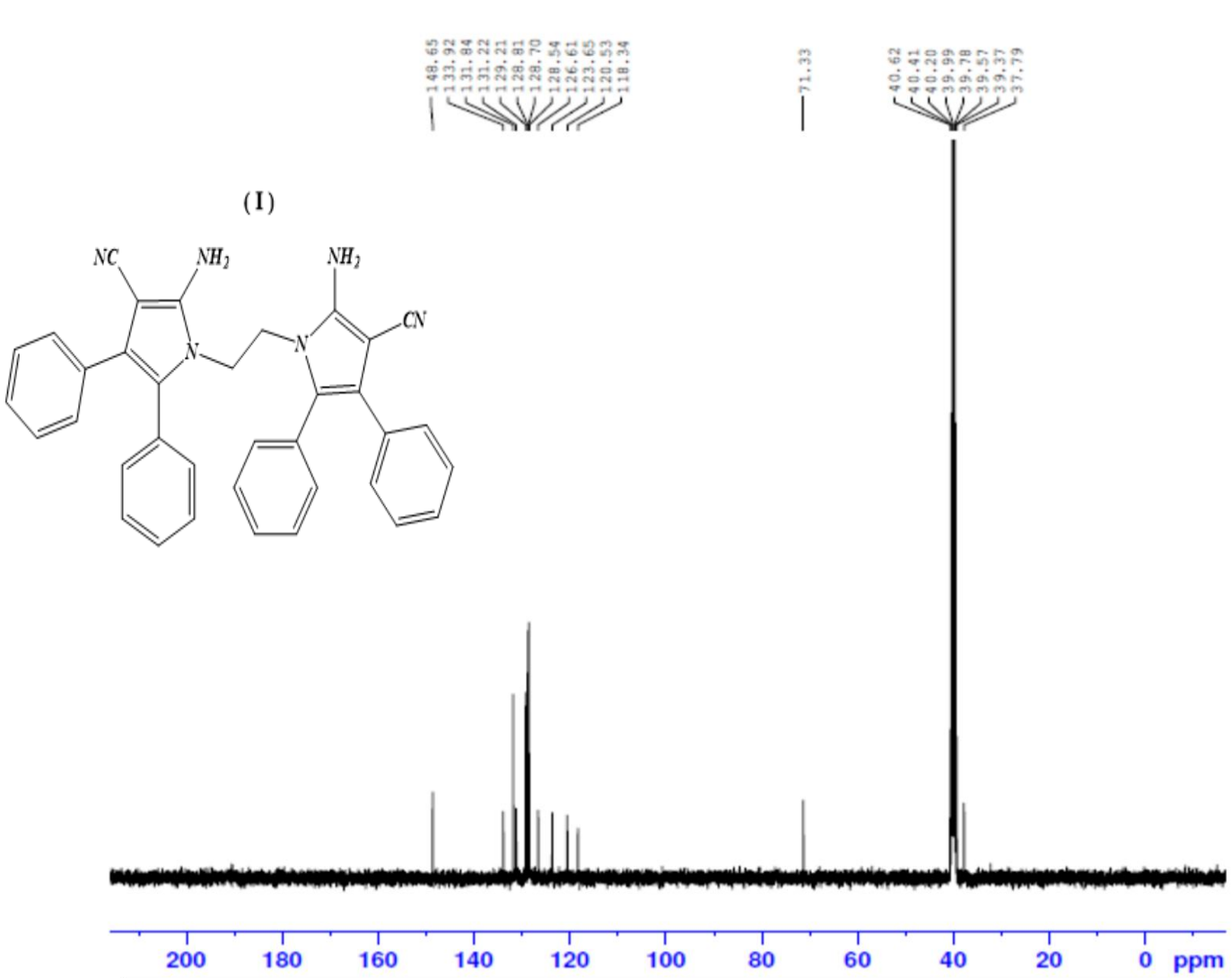


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Fig 3: ^{13}C-NMR spectrum of compound (I)

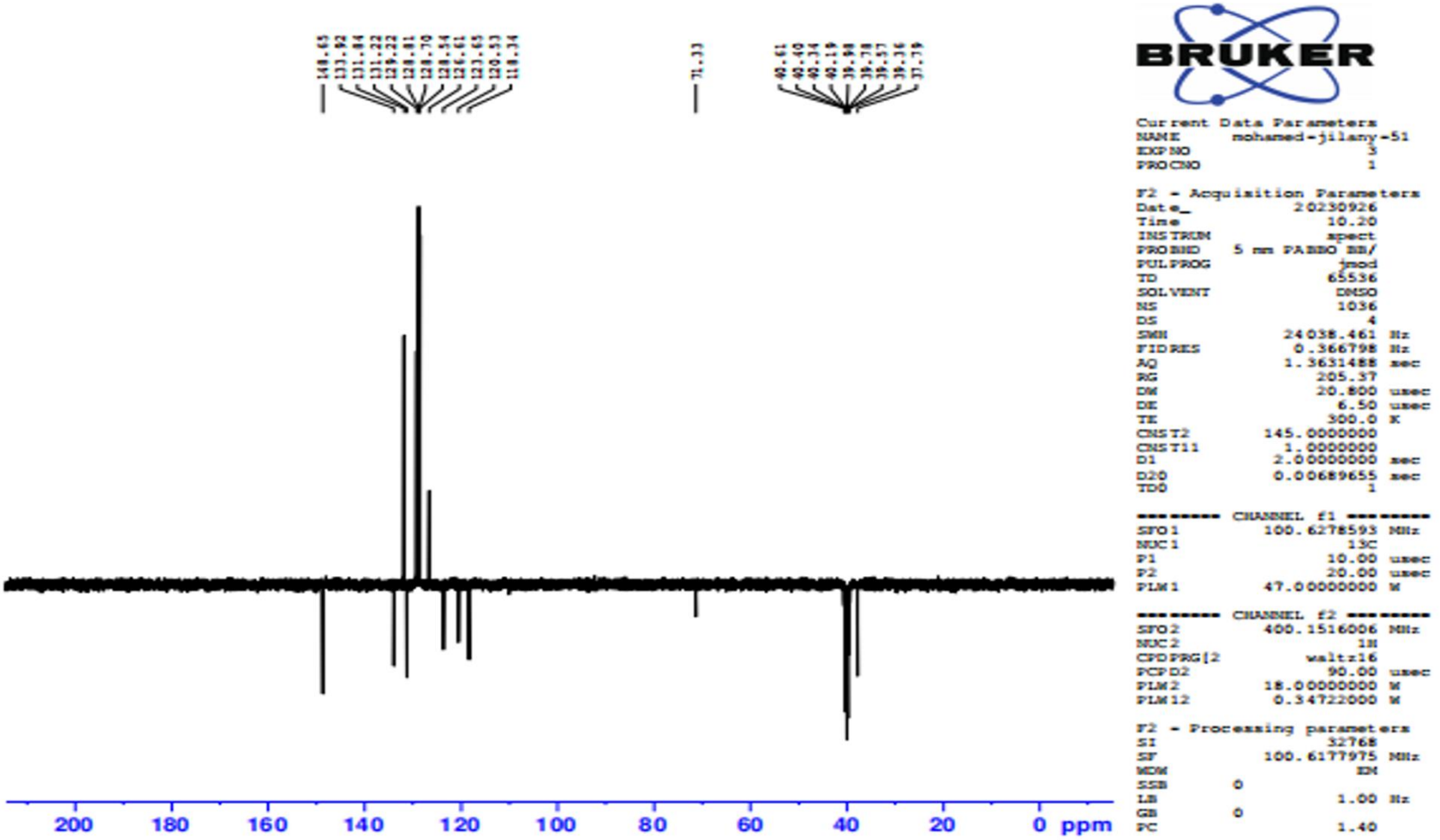

Fig 4 : APT spectrum of compound (I)

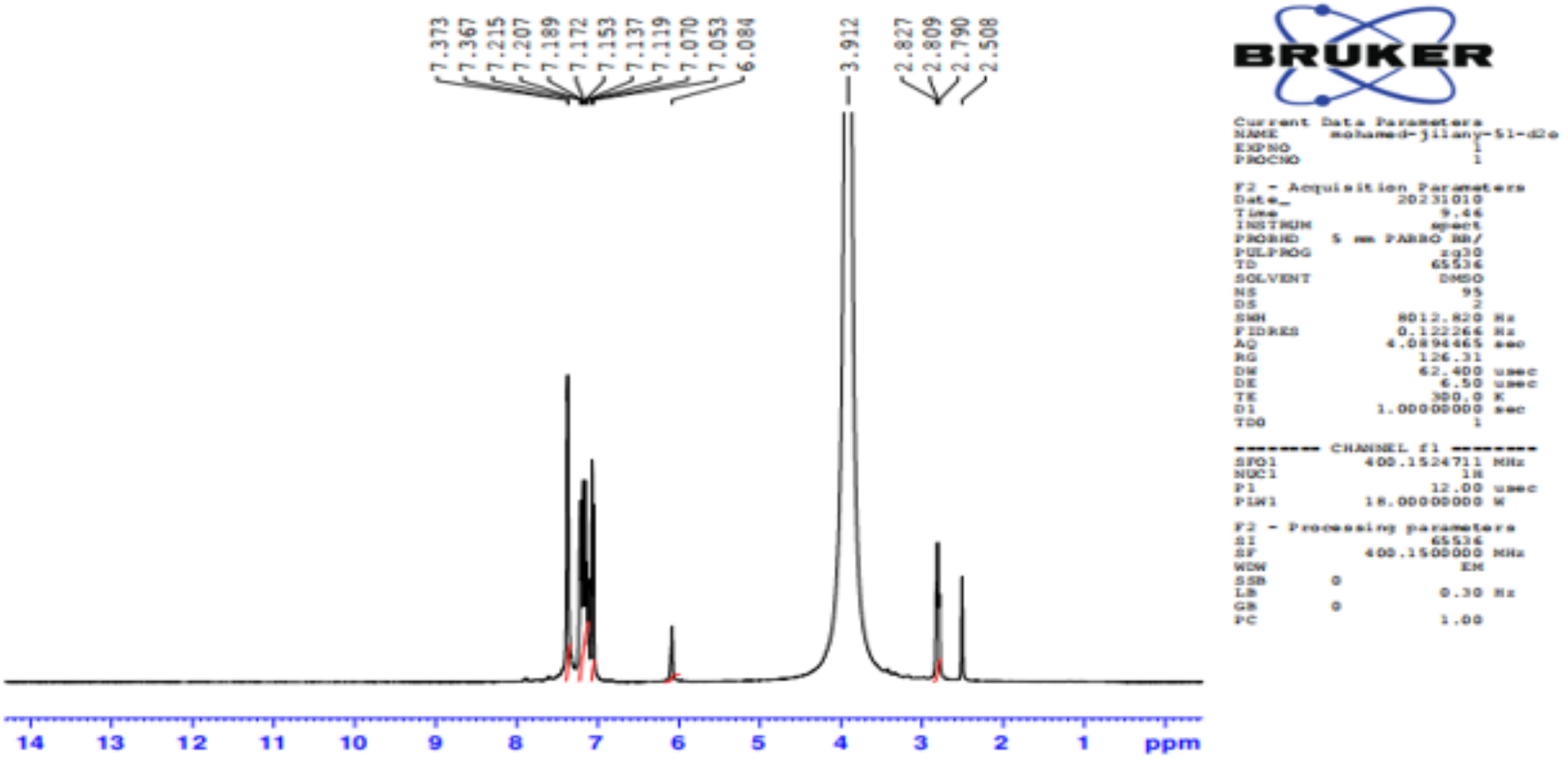

Fig 5 :D_2O spectrum of compound (I)

In contrast, Compound (II) was identified as the major product, with spectroscopic evidence strongly supporting its formation. The IR spectrum (Figure 6) further corroborated the structure, with absorptions corresponding to NH_2 (3311.02–3464.24 cm^{-1}), C≡N (2213.68 cm^{-1}), and aromatic C–H (3061.05 cm^{-1}) stretches. The disappearance of CH_2 signals and the retention of aromatic protons strongly indicate intramolecular cyclization leading to a furan ring. The ^{1}H NMR spectrum (Figure 7) revealed the absence of CH_2 protons, suggesting their involvement in ring formation, while the aromatic region (7.15–7.47 ppm) displayed 10 protons, consistent with a symmetrically substituted furan ring. A singlet at 7.73 ppm was assigned to an NH proton, confirming the presence of a single amine group. additionally, the ^{13}C NMR and APT technique was used (Figure 8-9) and Additionally D2O (Figure 10).

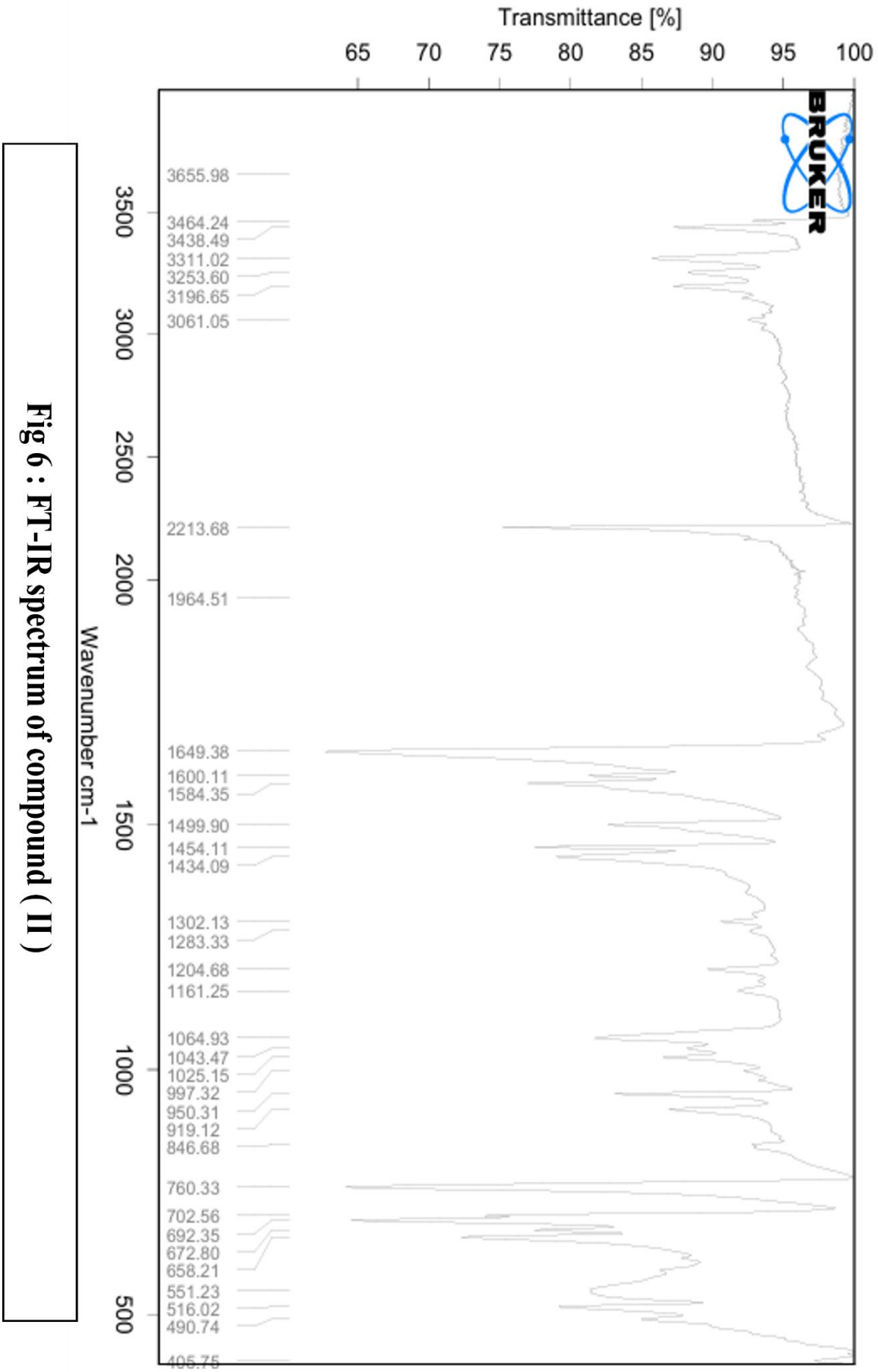

Fig 6 : FT-IR spectrum of compound (II)

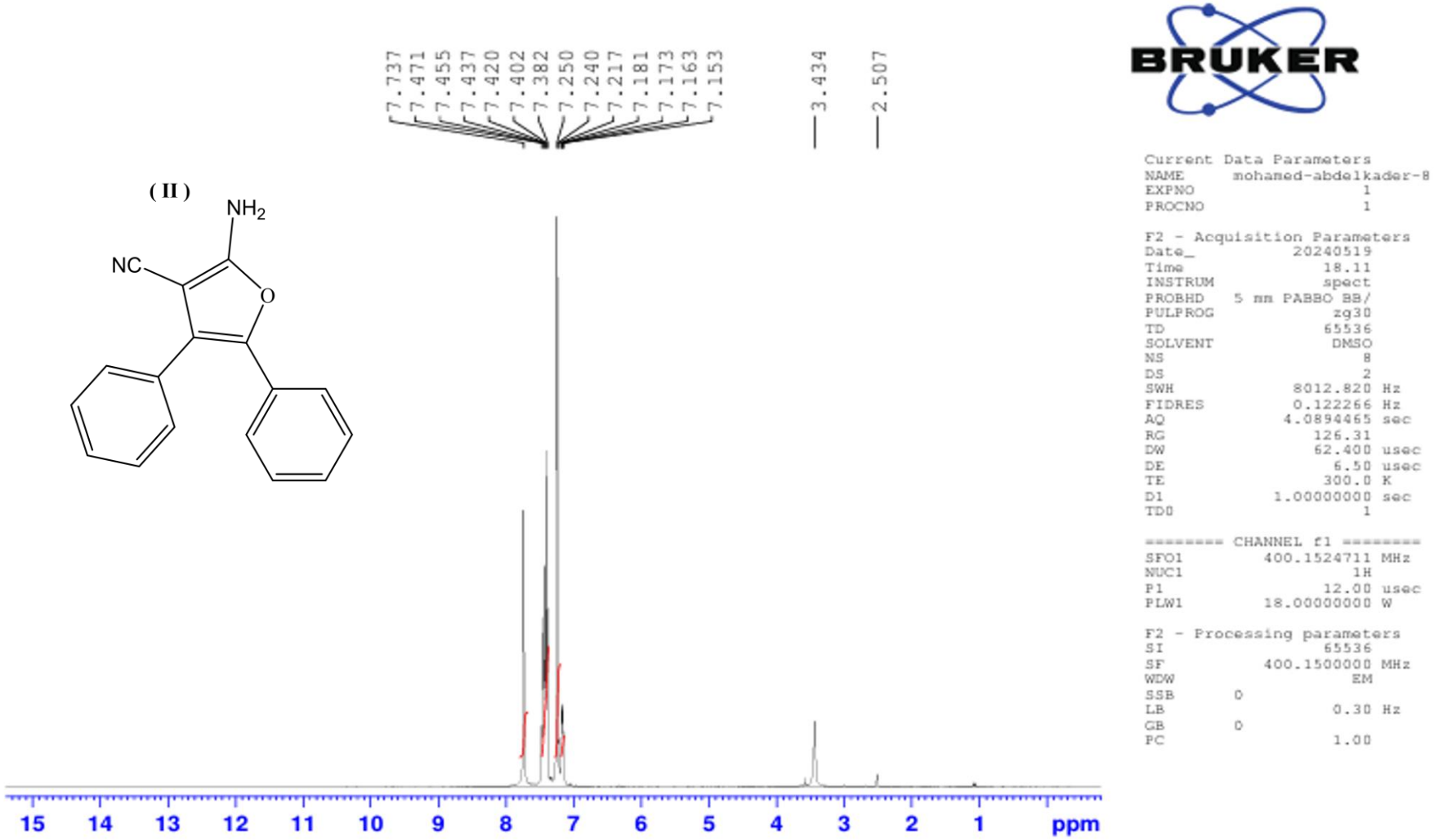

Fig 7 : ^{1}H-NMR spectrum of compound (II)

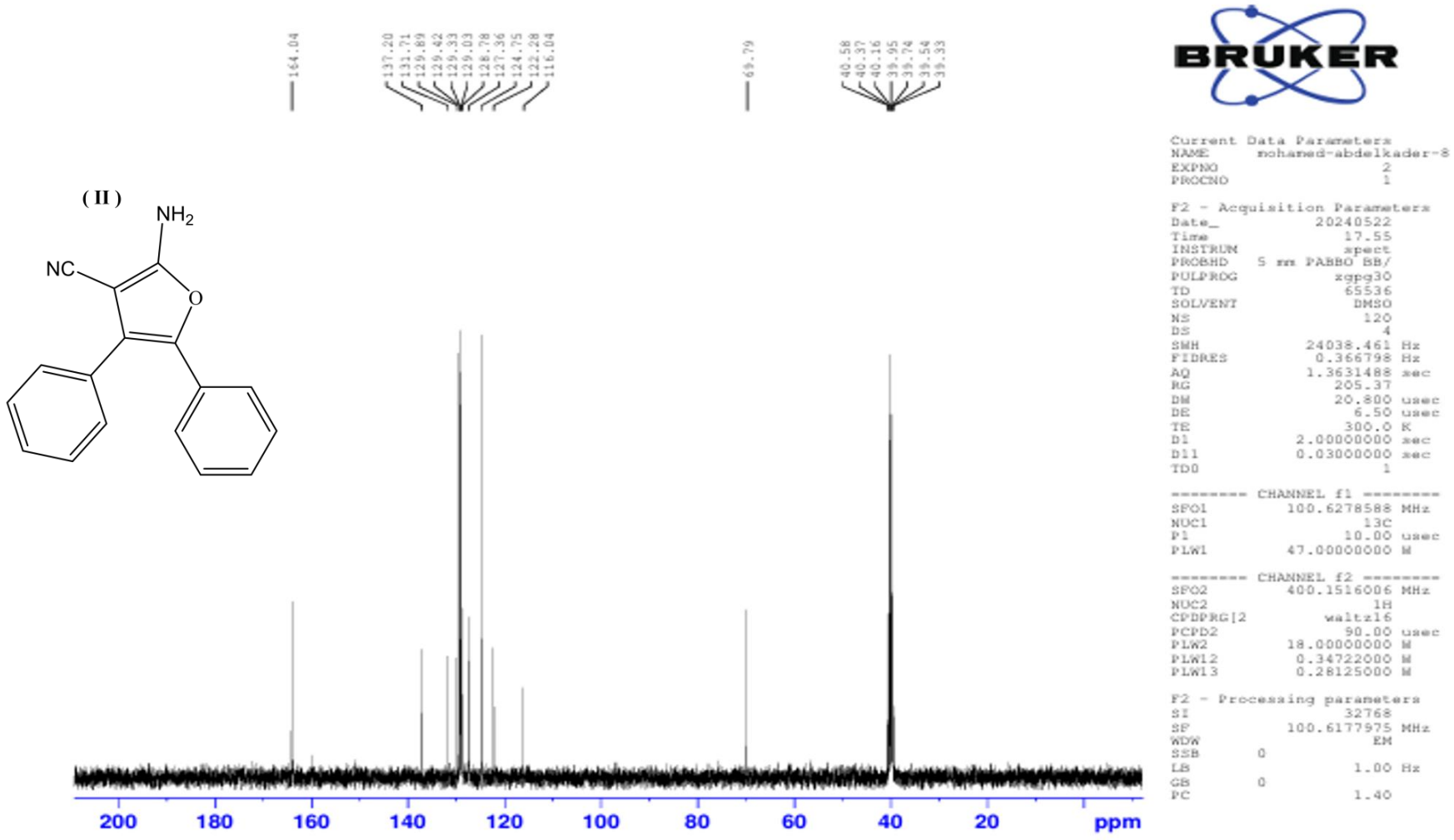

Fig 8 : ^{13}C-NMR spectrum of compound (II)

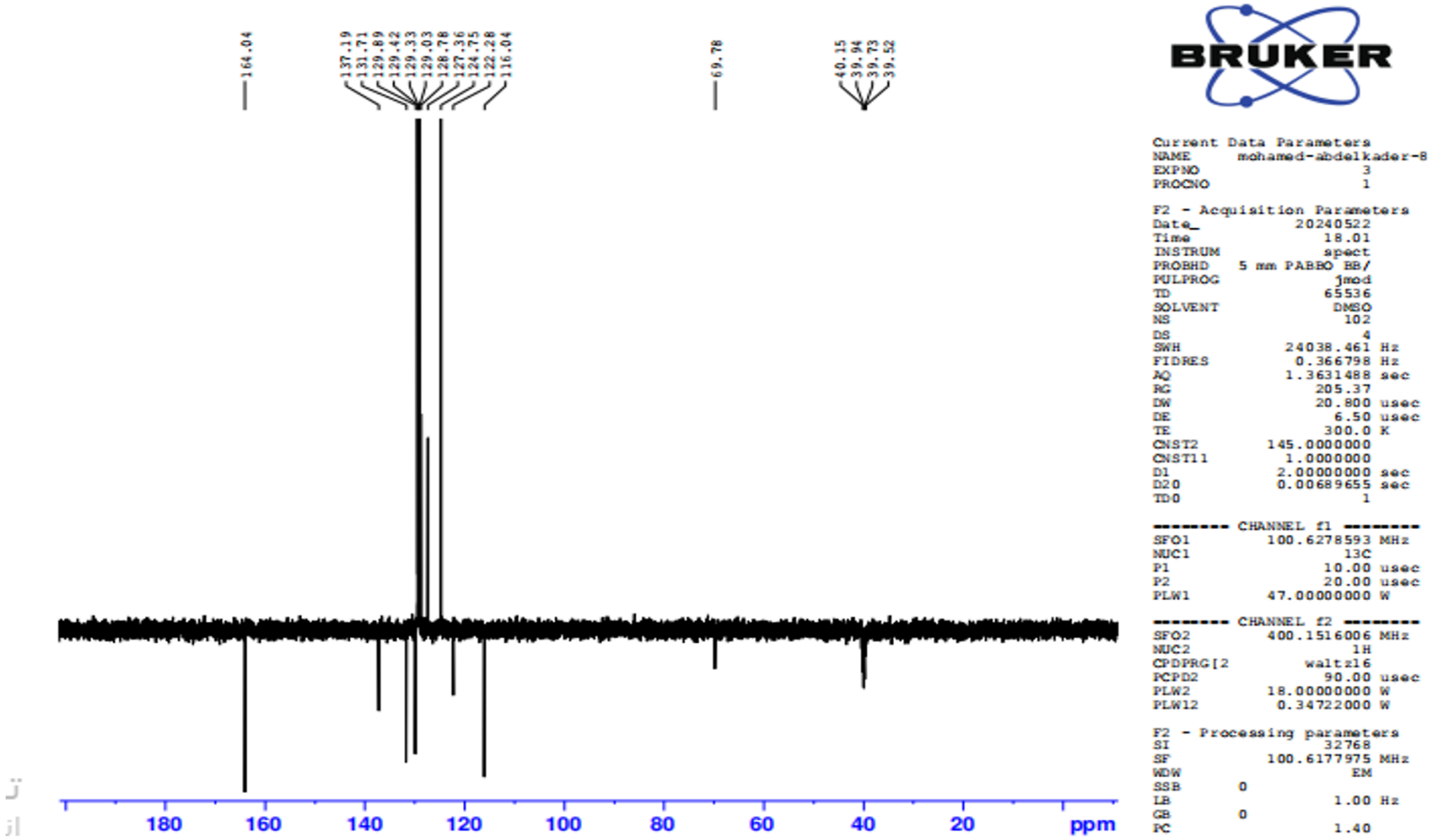


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Fig 9 : APT spectrum of compound (II)

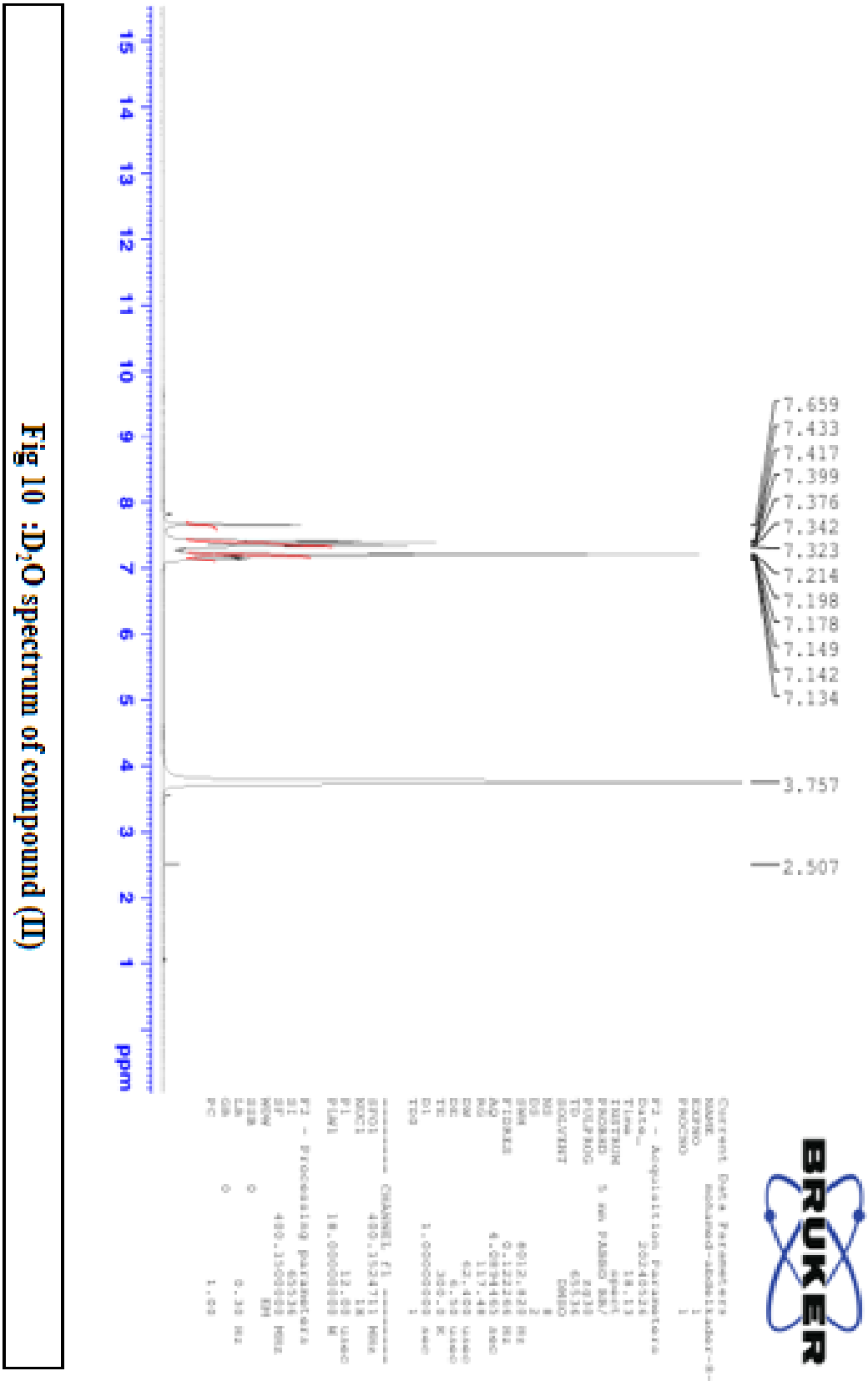

Fig 10 :D_2O spectrum of compound (II)

The preferential formation of Compound (II) (44% yield) over Compound (I) (39%) suggests that the reaction pathway favors furan ring formation under the given conditions. This selectivity may arise from its greater stability due to aromaticity or lower activation energy for cyclization. The absence of CH_2 protons in Compound (II) supports an intramolecular cyclization process, whereas Compound (I) retains the CH_2 groups, indicating an alternative pathway without ring closure. The spectroscopic data conclusively confirm the structures of both products, with Compound (II) being the dominant product due to favorable cyclization.

The aromatic regions of the spectra exhibit complex multiplet patterns, with proton counts matching the expected aromatic systems for each compound. The slight variations in chemical shifts among III, IV, and VI likely arise from subtle differences in electronic environments introduced by their respective substituents. Further confirmation is derived from the ^{13}C NMR spectra, where the number of observed signals corresponds precisely to the predicted carbon counts for each structure. The absence of extraneous peaks suggests high purity in the synthesized compounds, with no detectable impurities or byproducts. Collectively, the IR, ^{1}H NMR, and ^{13}C NMR data provide a coherent and convincing argument for the structural integrity of III, IV, and VI. The consistency across all spectroscopic methods underscores the reliability of the synthetic approach and the accuracy of the proposed molecular frameworks. (see Figure 11-15 and Appendixes 36-40, 41-44).

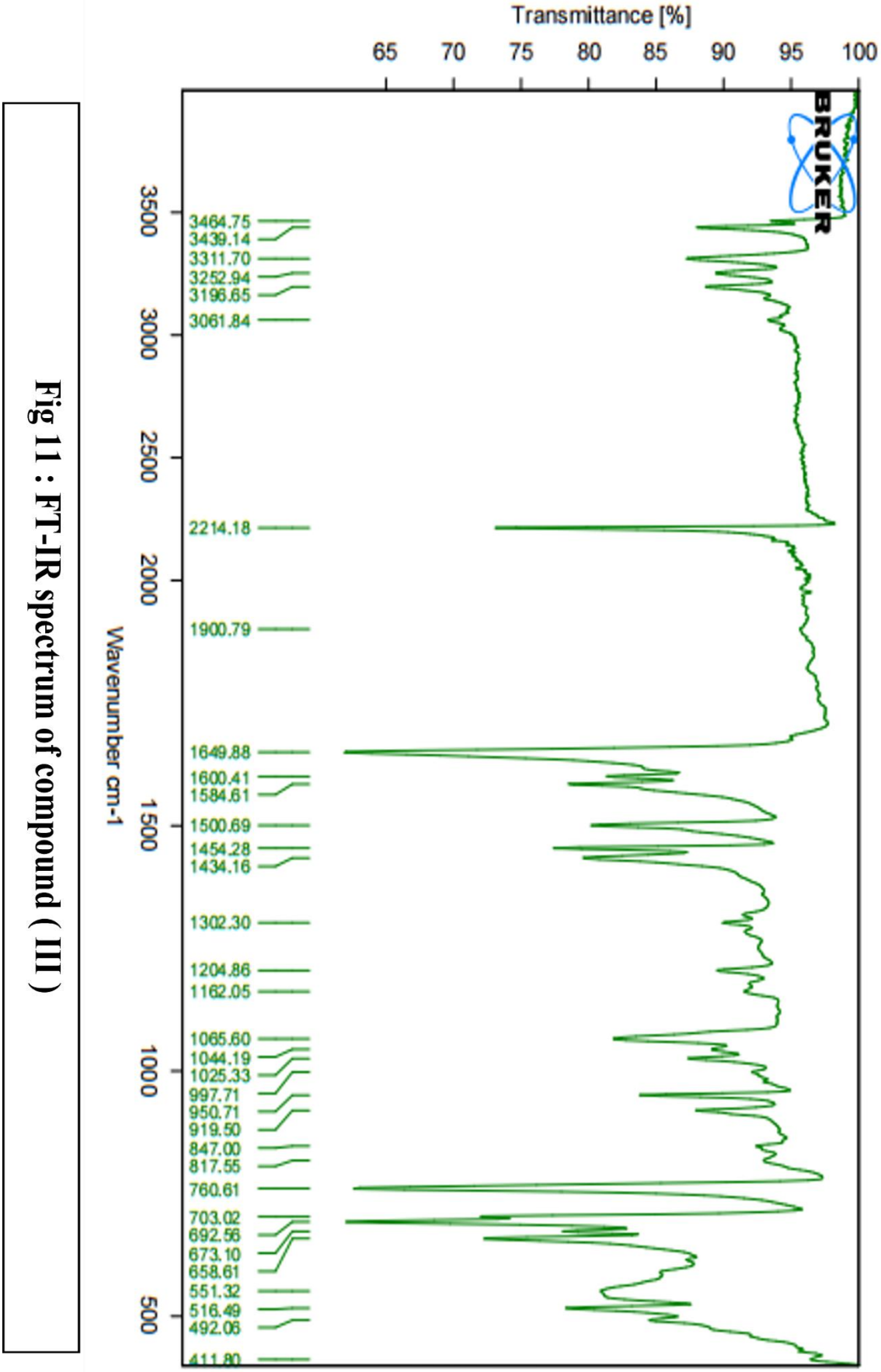

Fig 11 : FT-IR spectrum of compound (III)

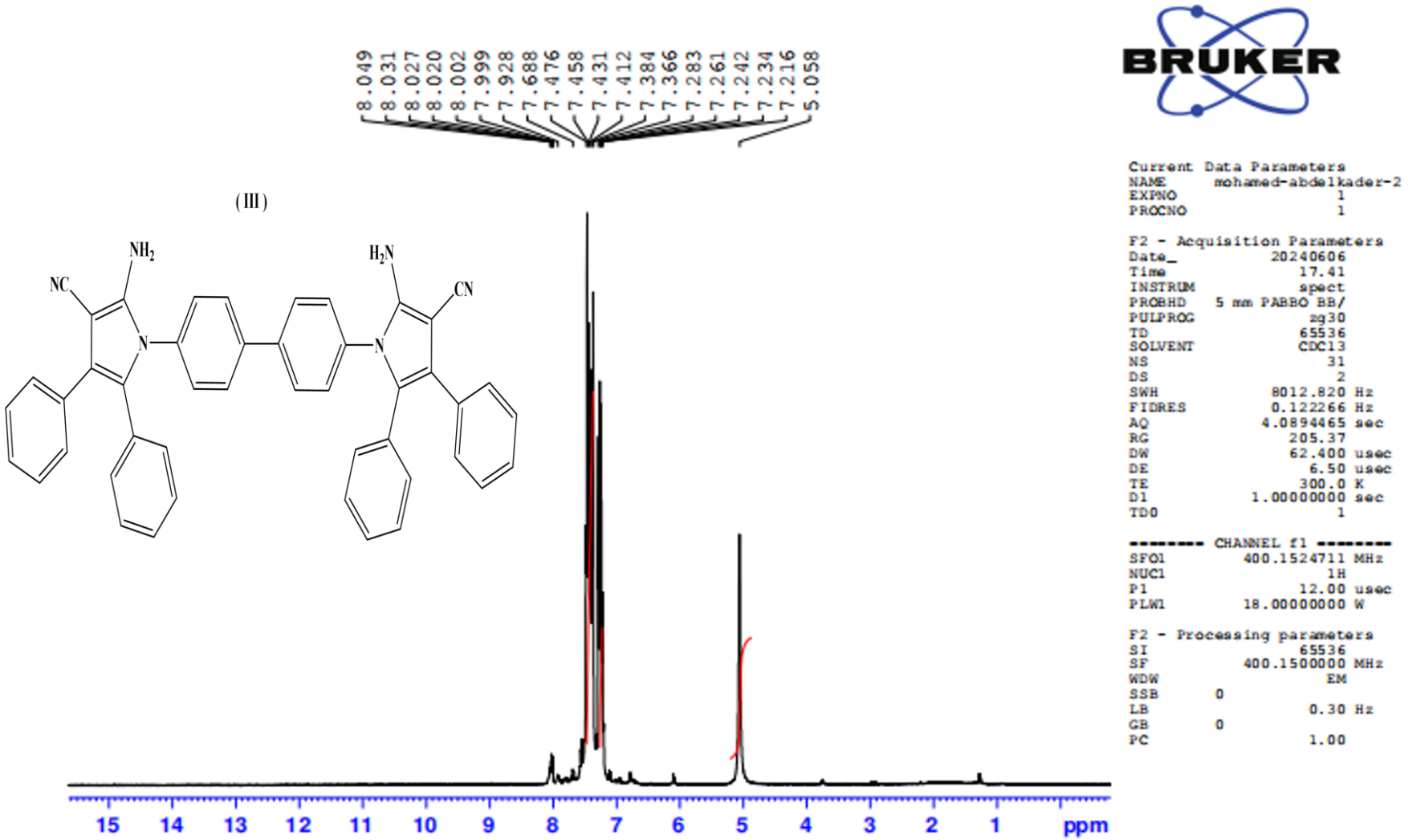


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Fig 12 : ^{1}H-NMR spectrum of compound (III)

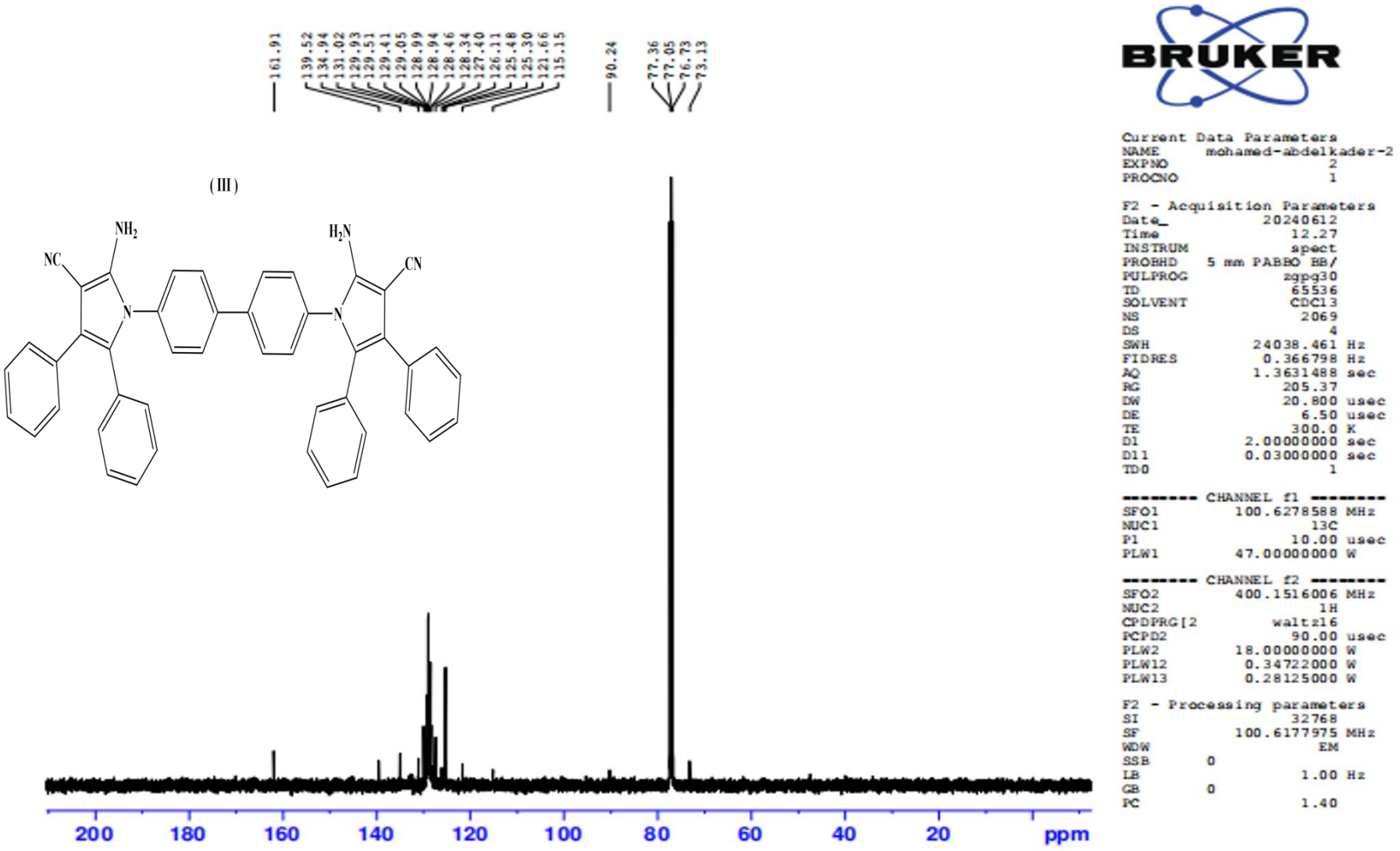


Fig 13 : ^{13}C-NMR spectrum of compound (III)

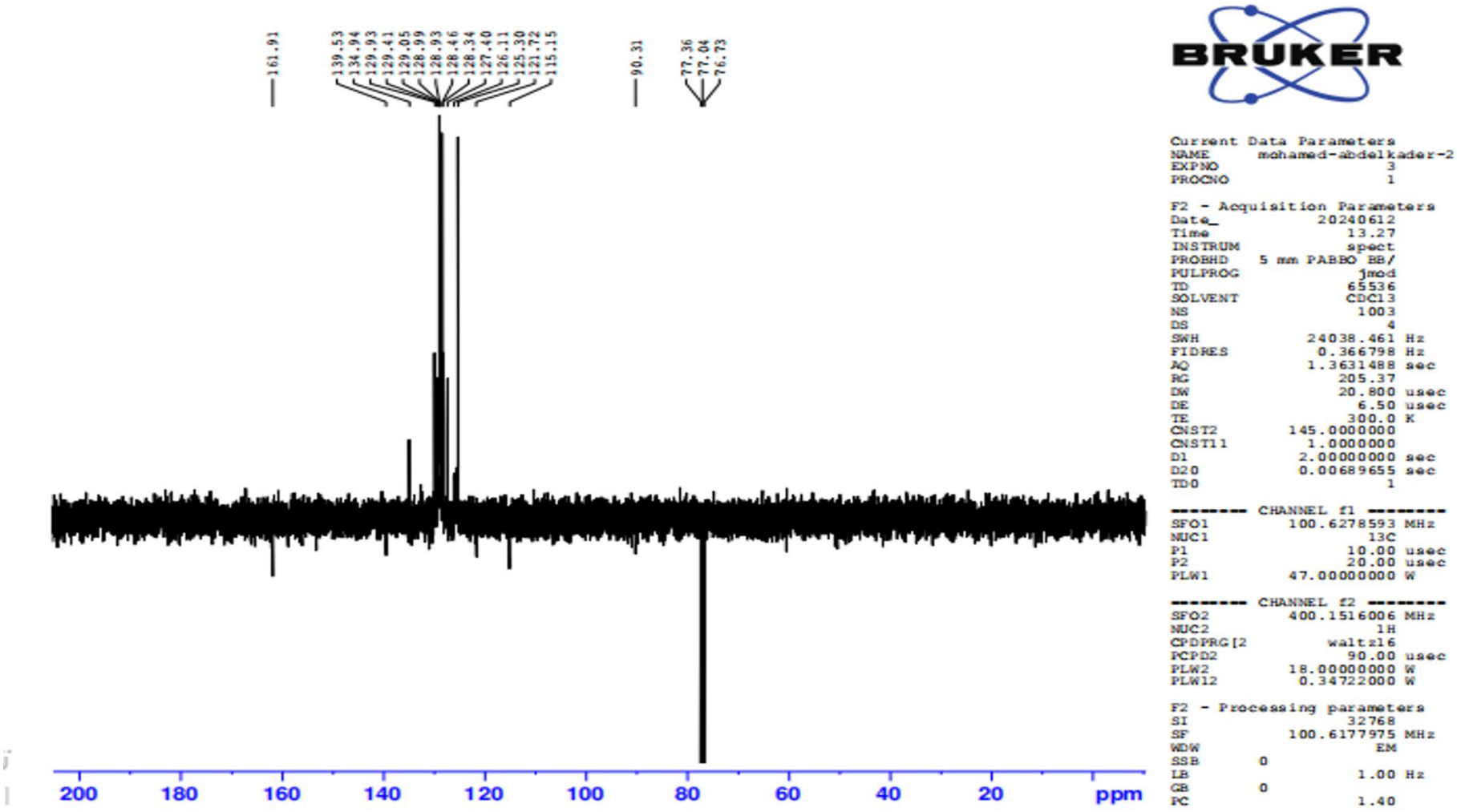


Fig 14 : APT spectrum of compound (III)

Fig 15: D_2O spectrum of compound (III)

On the other hand, the analytical results for compounds V and VII revealed a distinct divergence from the previously studied compounds (I, III, IV, and VI). The initial objective of the reaction between benzoin with hydrazine and ortho-phenylenediamine was the synthesis of a bis pyrrole derivative. However, this target compound was not successfully obtained; instead, compounds V and VII were formed. Compound V was characterized by IR spectroscopy, which exhibited a carbonyl (C=O) absorption band at 1677.22 cm^{-1} and a C=N stretching frequency at 1593.26 cm^{-1}. The absence of NH_2 protons in the ^{1}H NMR spectrum, along with the presence of only one type of aromatic proton with matching integration values, further supported the proposed structure to compound (V) and (VII). The ^{13}C NMR analysis confirmed the structure of compound V, revealing two distinct carbonyl carbons at 197.42 ppm (ketonic C=O) and two imine carbons (C=N) at 167.08 ppm. The observed carbon count aligned with the proposed structure, corroborating the successful formation of compound V. Similarly, the structural elucidation of compound VII was consistent with the analytical data, demonstrating the formation of an alternative product rather than the intended bis pyrrole (see Figure 16-19, 20 - 22).

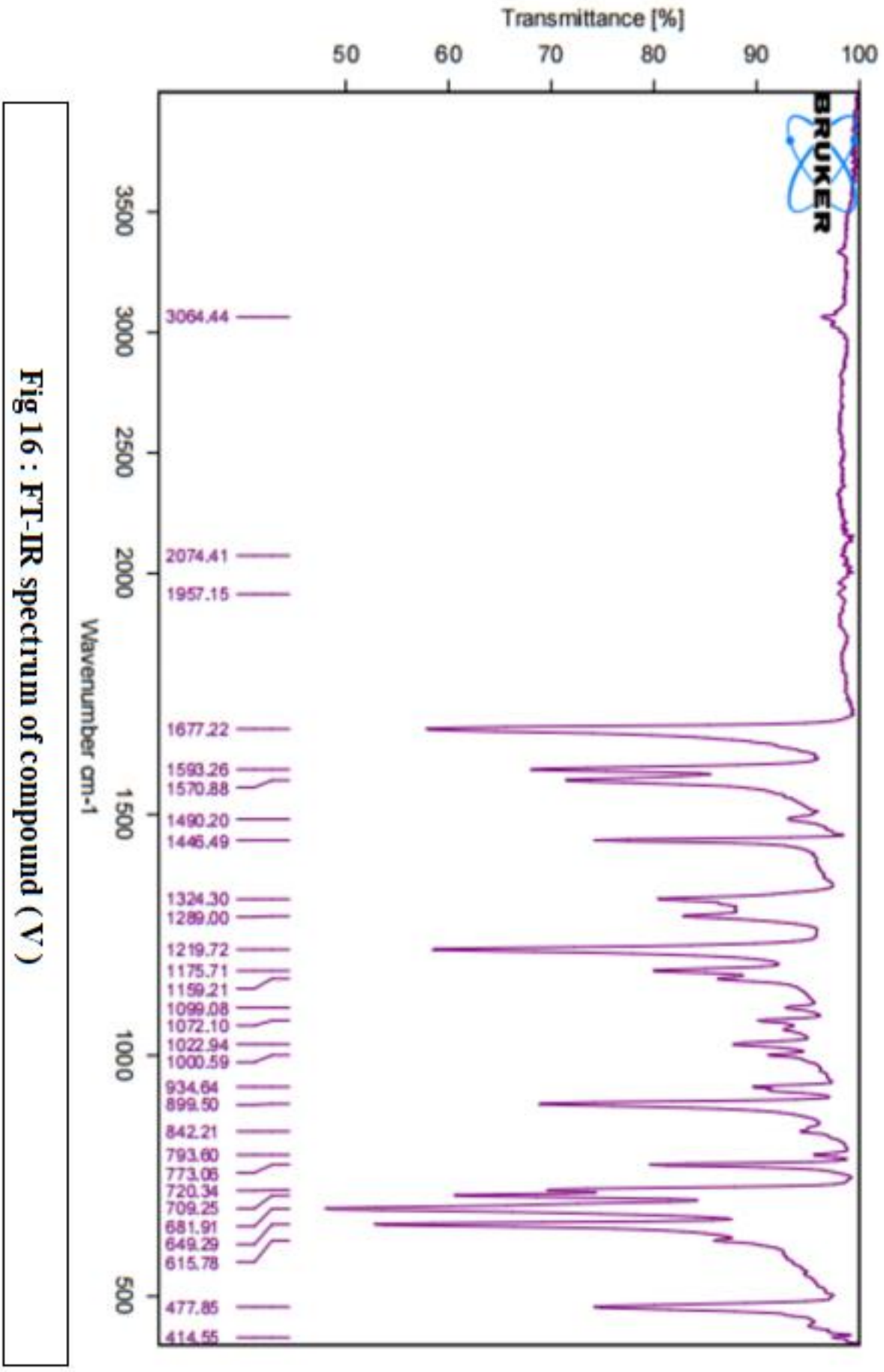
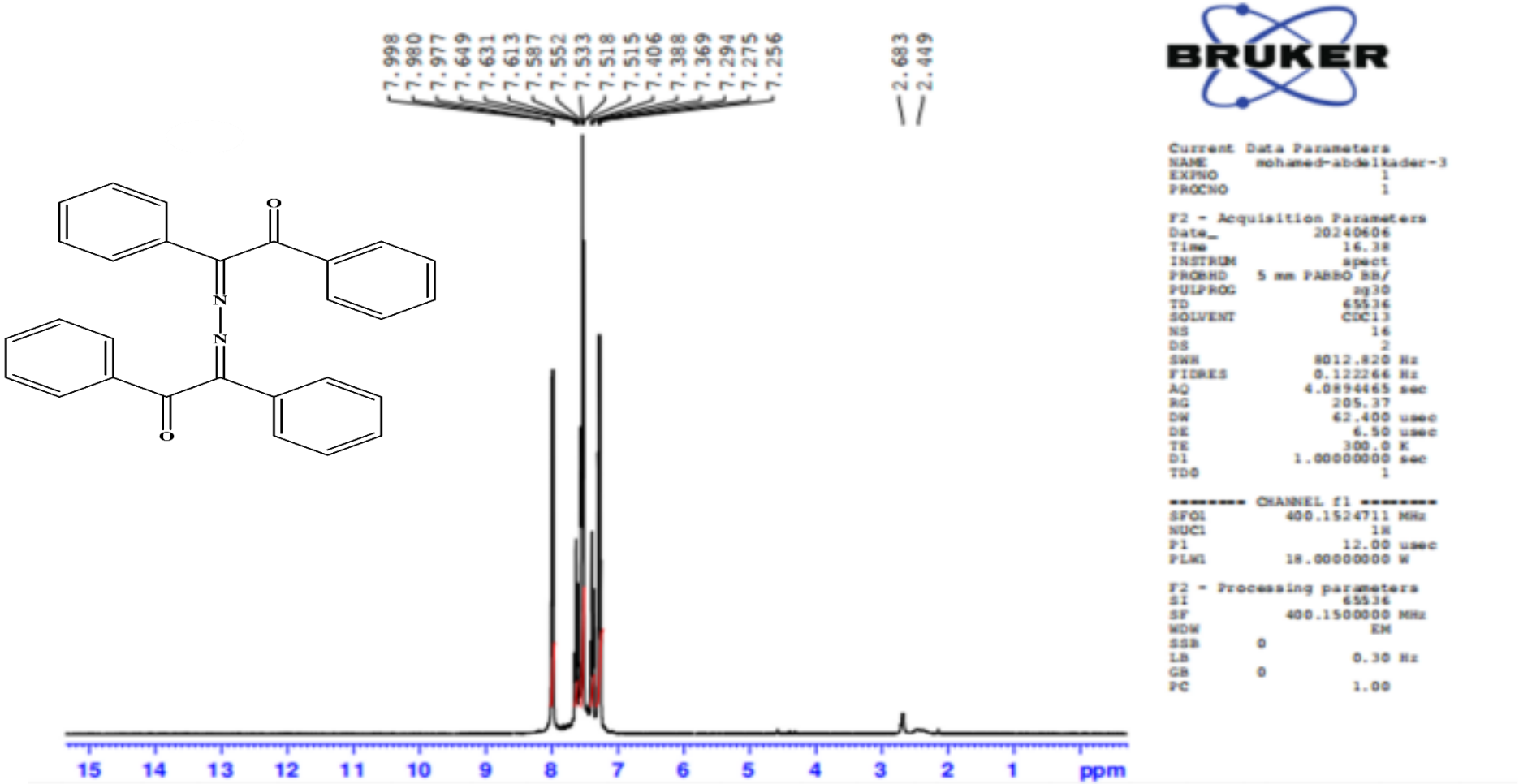


Fig 16 : FT-IR spectrum of compound (V)



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P1                   12.00 usec
PLW1            18.00000000 W

F2 - Processing parameters
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Fig 17 : ^{1}H-NMR spectrum of compound (V)

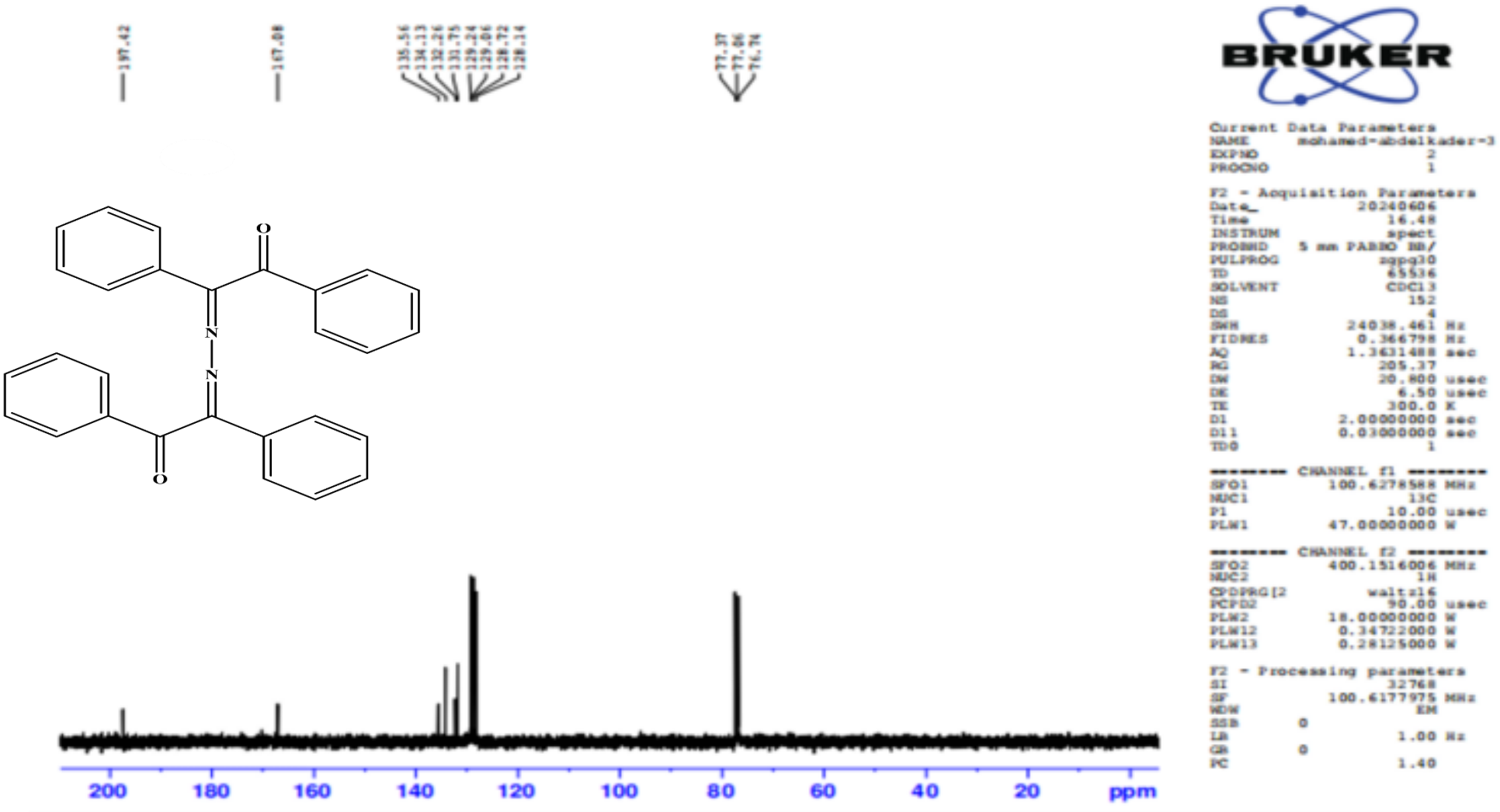
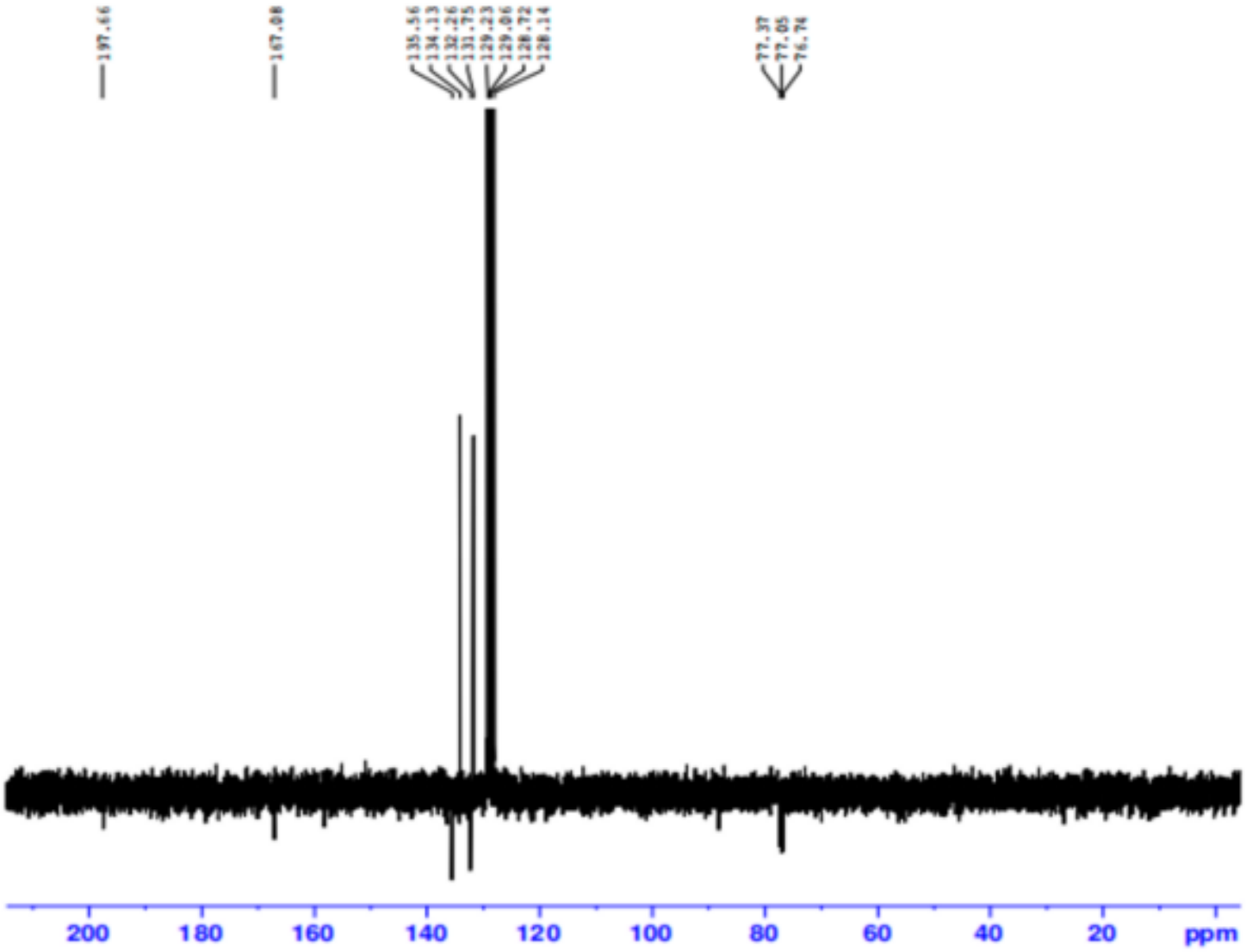


Fig 18 : ^{13}C- NMR spectrum of compound (V)



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AQ                1.3631488 sec
RG                   205.37
DW                   20.800 usec
DE                    6.50 usec
TE                   300.0 K
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P2                     20.00 usec
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PCPD2                  90.00 usec
PLW2           18.00000000 W
PLW12           0.34722000 W

F2 - Processing parameters
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WDW                        EM
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LB                      1.00 Hz
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PC                      1.40
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Fig 19 : APT spectrum of compound (V)

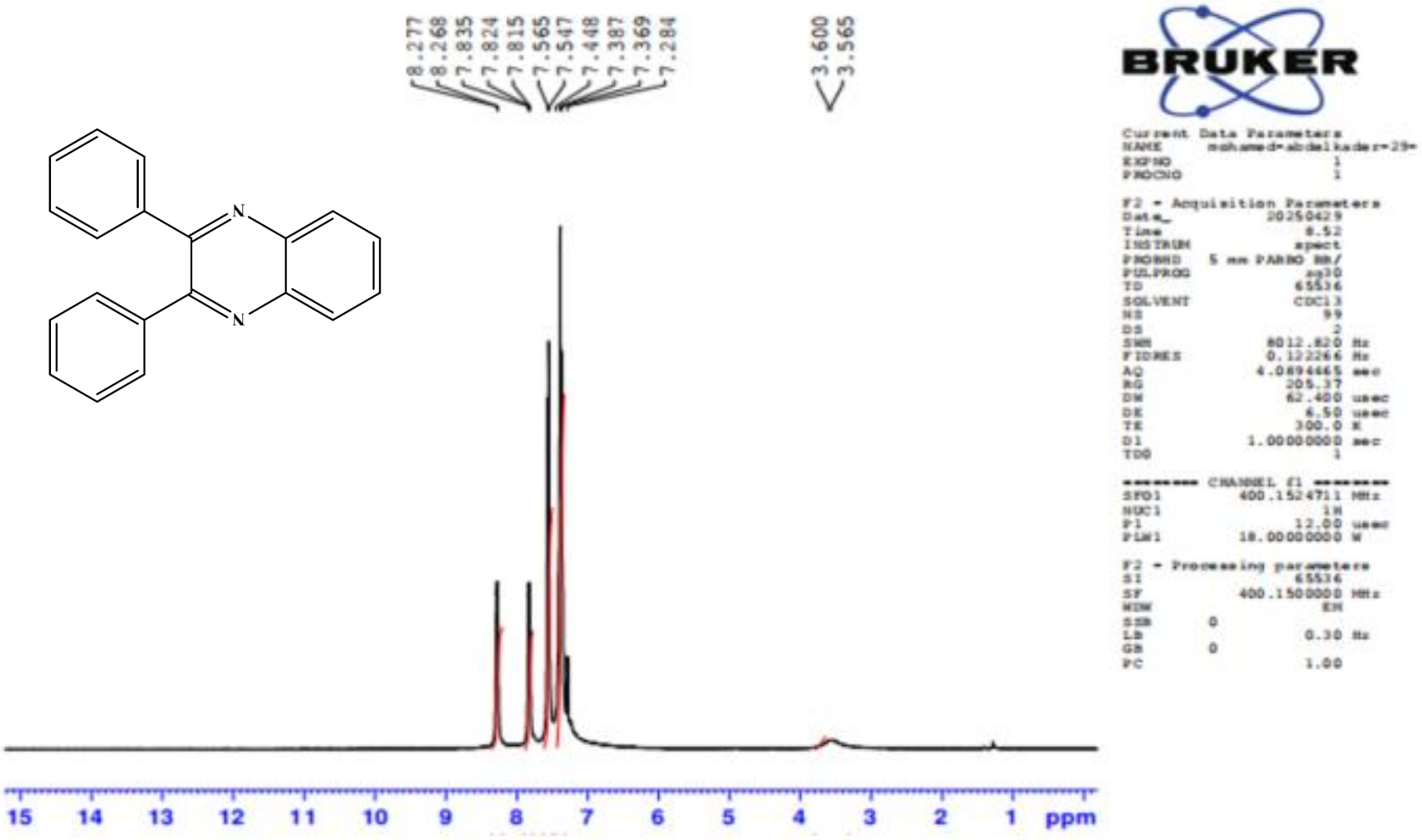
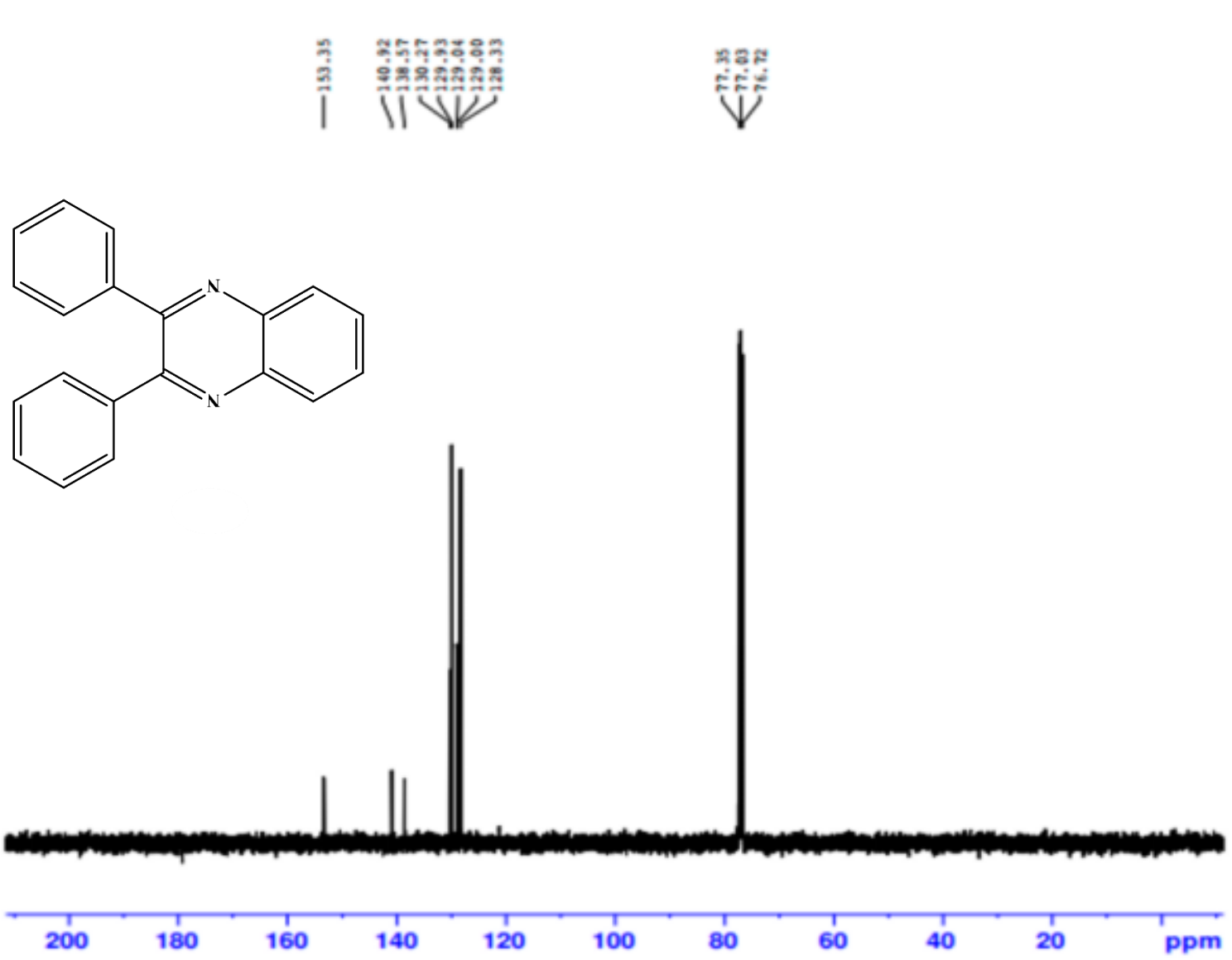


Fig 20 : ^{1}H-NMR spectrum of compound (VII)

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NS                      1064
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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 =======
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NUC1                    13C
P1                    10.00 usec
PLW1           47.00000000 W

======== CHANNEL f2 =======
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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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WDW                       EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

Fig 21 : ^{13}C- NMR spectrum of compound (VII)

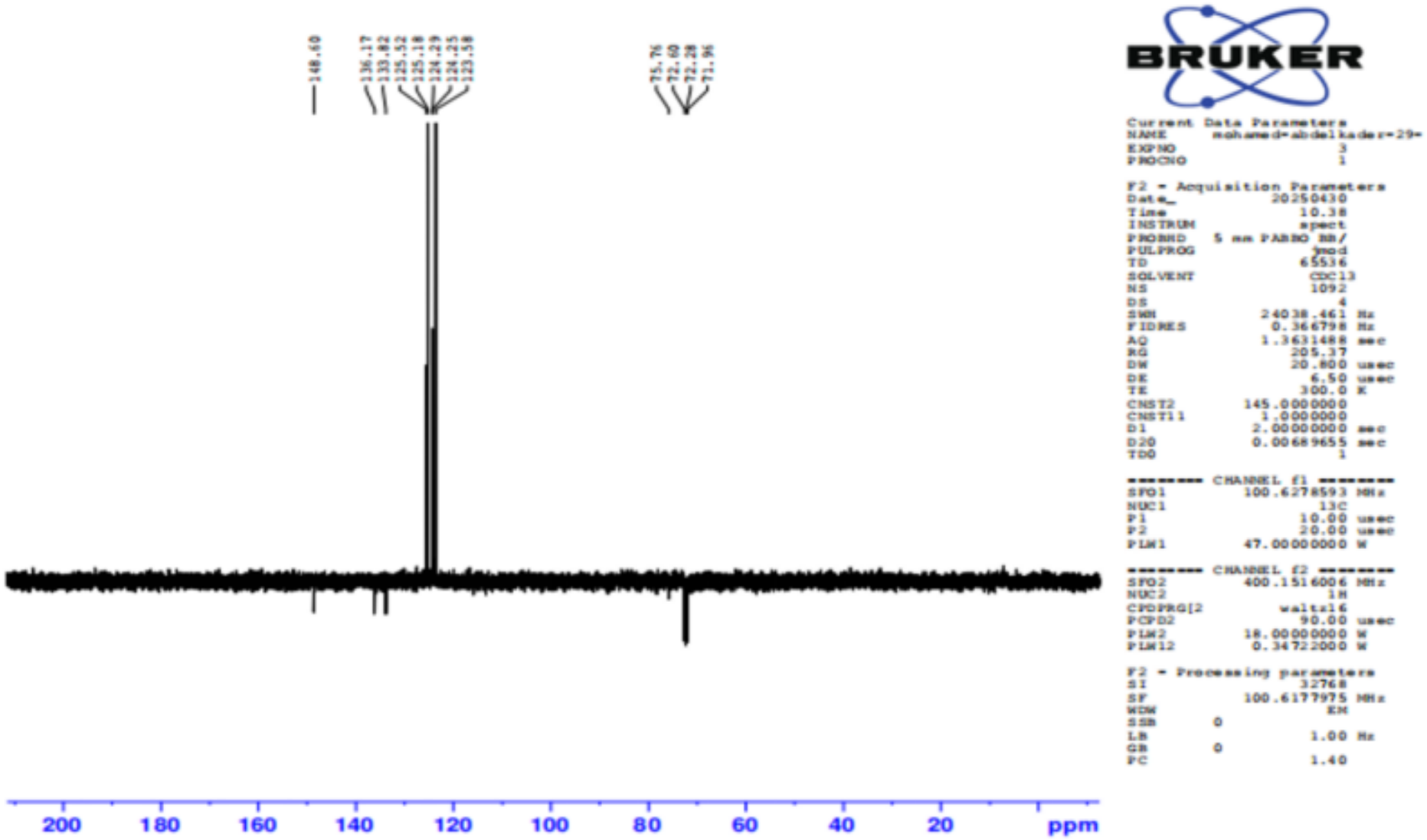
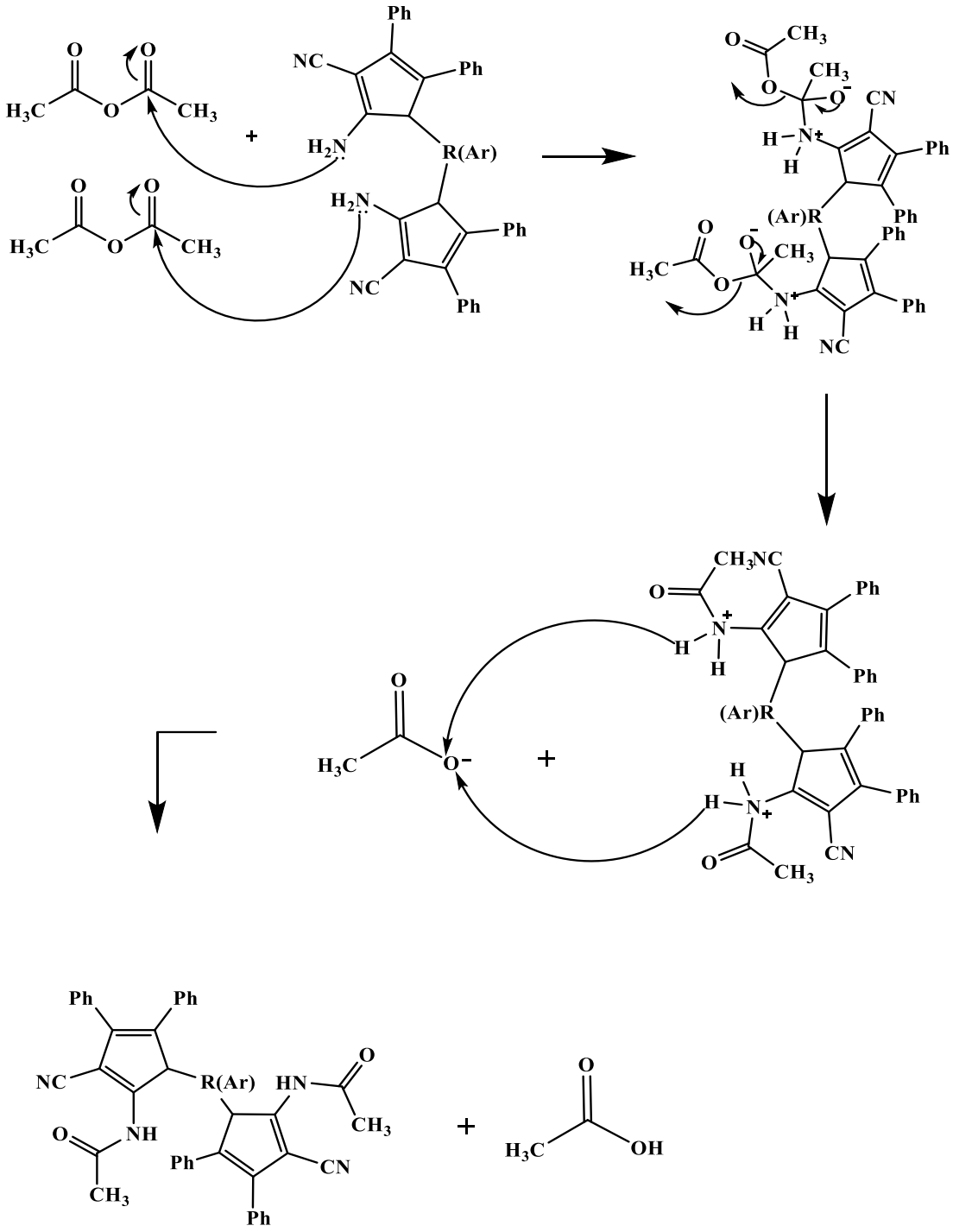


Fig 22: APT spectrum of compound (VII)

2.2. Reaction of compounds I, II and IV with acetic anhydride:

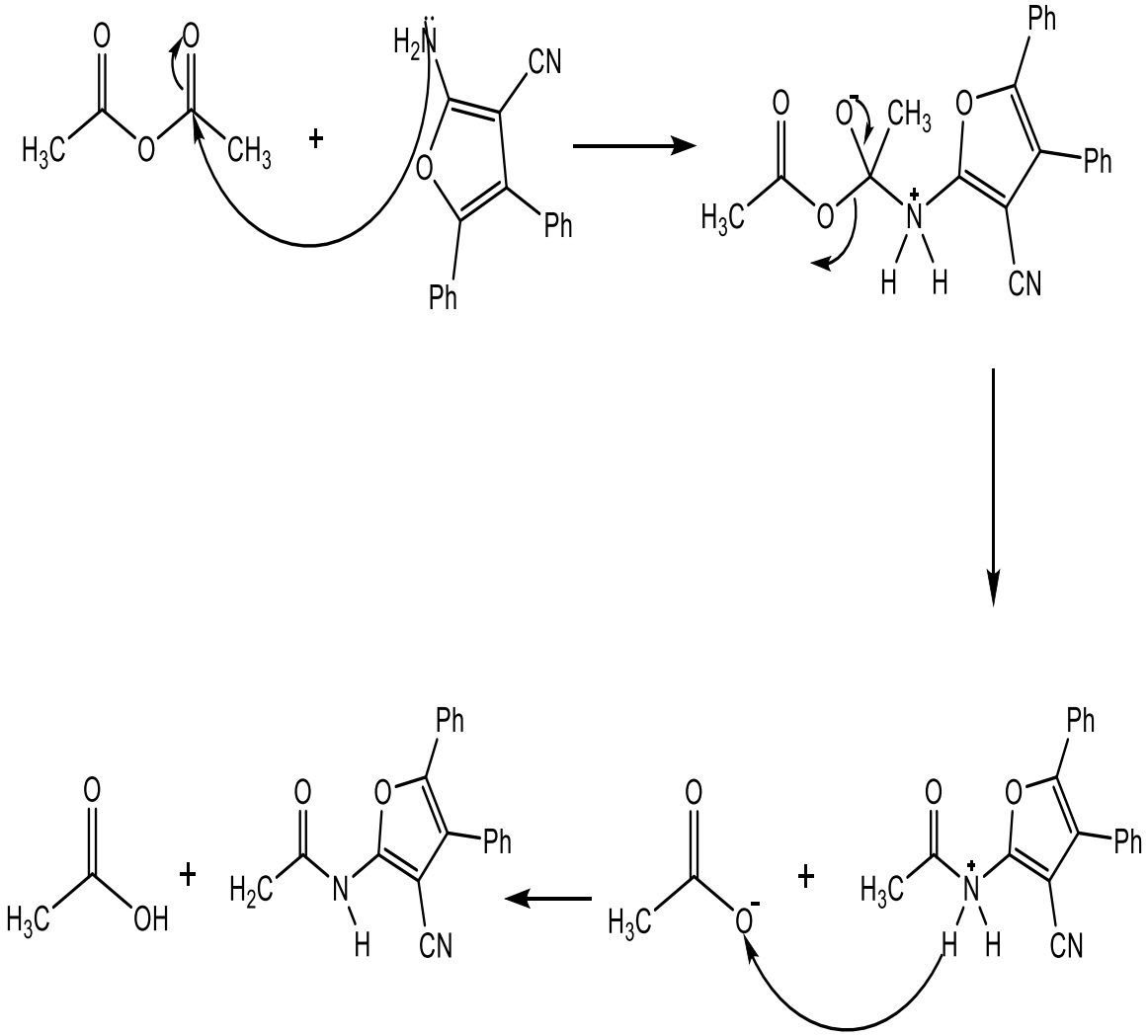
The second step of this research involves the successful acylation of the primary amine groups in compounds I, II and IV to form the corresponding amide derivatives VIII, IX, and X demonstrates the efficiency of acetic anhydride as an acylating agent under mild conditions. The reaction proceeded smoothly at room temperature over 24 hours, suggesting that the nucleophilic acyl substitution mechanism is highly favorable for these substrates (Scheme 2.6 and Scheme 2.7). The absence of harsh conditions or additional catalysts highlights the practicality of this approach for modifying amine-containing compounds, particularly in the context of bis pyrrole derivatives.

The Reaction Machanism:



Scheme 2.6: The proposed mechanism of synthesis of compounds VIII and X

<u>The Reaction Machanism:</u>



Scheme 2.7: The proposed mechanism of synthesis of compound IX

Spectroscopic analyses provided conclusive evidence for the formation of the amide linkages. The disappearance of primary amine signals in the ^{1}H NMR spectra (Figures 23, 28 and 32), coupled with the appearance of new singlets corresponding to the methyl protons of the acetyl groups and the amide NH protons, strongly supports the proposed structural changes. Notably, the chemical shifts of the amide NH protons (ranging from 7.86 to 10.10 ppm) are consistent with hydrogen bonding and the deshielding effects typical of amide functionalities. The distinct methyl singlets observed in each derivative further confirm the incorporation of the acetyl groups, with variations in chemical shifts likely arising from differences in the electronic environments of the parent compounds. The IR spectra (Figure 27) further corroborated the acylation, with the appearance of a characteristic amide carbonyl stretch at 1694 cm^{-1} for compound IX. This value aligns with the expected range for amide C=O vibrations, though the slight variations compared to typical amide absorptions (usually around 1650–1680 cm^{-1}) may reflect conformational constraints or hydrogen bonding interactions within the molecular framework. The ^{13}C NMR data (Figure 24, 29 and 33) provided additional confirmation, with the amide carbonyl carbons appearing between 150–183 ppm. The significant downfield shift observed for compound X (182.98 ppm) suggests a highly deshielded carbonyl environment, possibly due to adjacent electron-withdrawing effects or intramolecular interactions. The consistency between the spectroscopic data and the expected structural modifications underscores the reliability of this acylation method. The clean conversion, absence of side products, and high specificity for the amine groups indicate that the reaction is both selective and efficient. These findings are particularly relevant for the design of functionalized bis pyrrole derivatives, as the introduced amide groups may enhance solubility, stability, or further reactivity for subsequent transformations. Moreover, the successful application of this acylation strategy opens avenues for diversifying the structural modifications of similar amine-containing scaffolds. The robustness of this method, combined with its simplicity, makes it a valuable tool in synthetic organic chemistry, particularly in the development of novel heterocyclic compounds with potential applications in medicinal chemistry. the APT technique was used (Figure 25, 30, 34) and Additionally D2O (Figure 26, 31, 35).

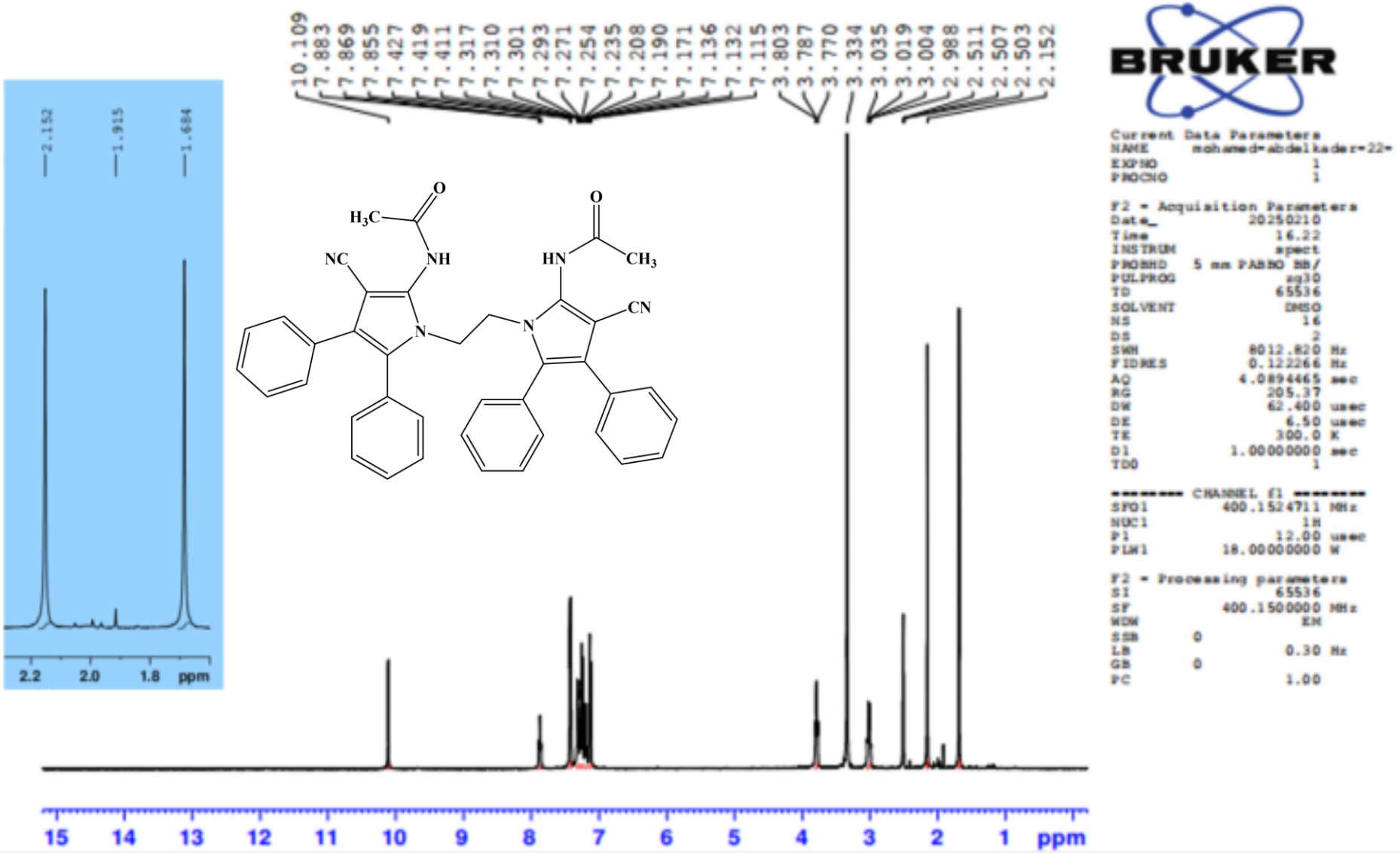


Fig 23 : ^{1}H-NMR spectrum of compound (VIII)

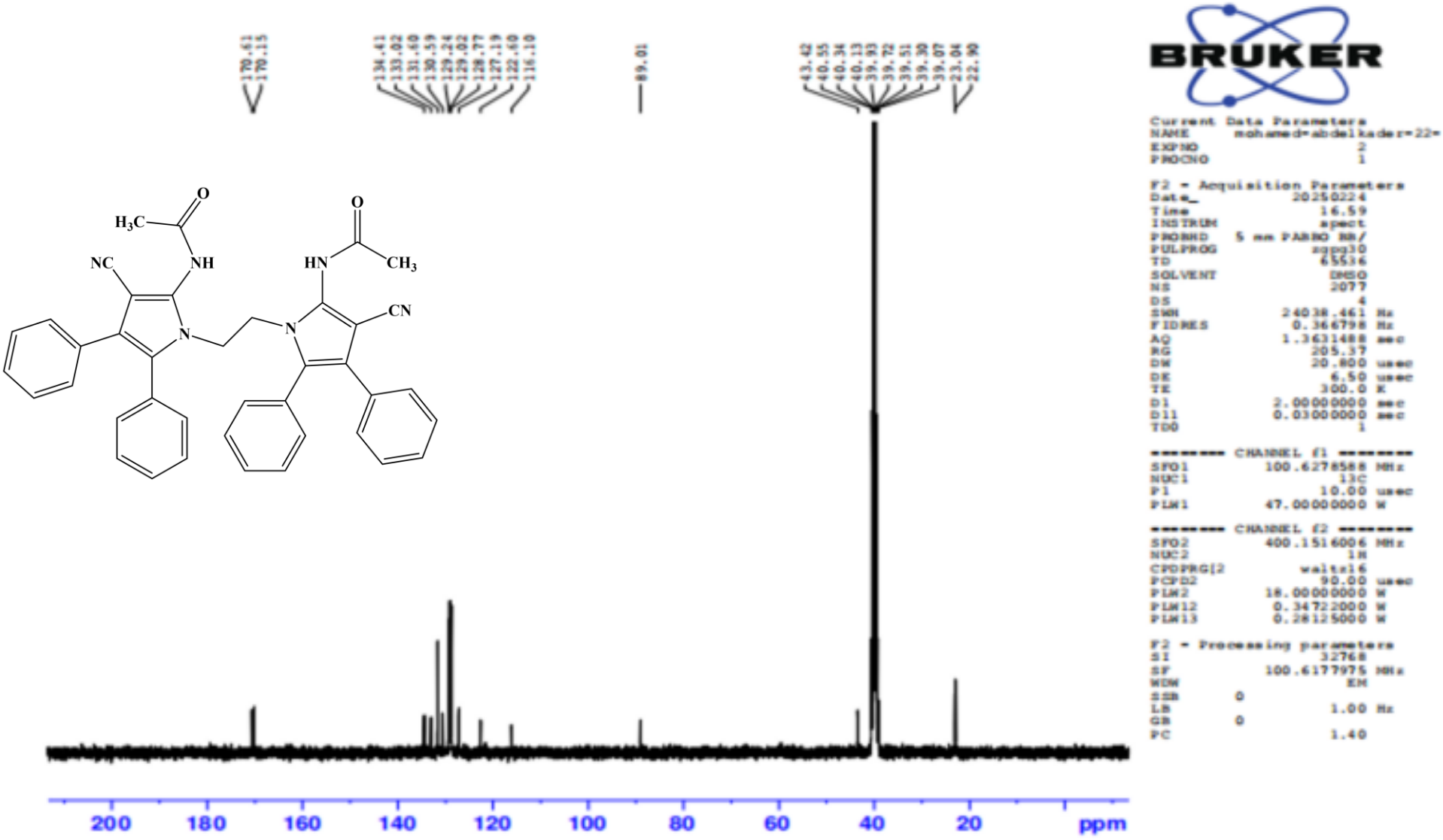
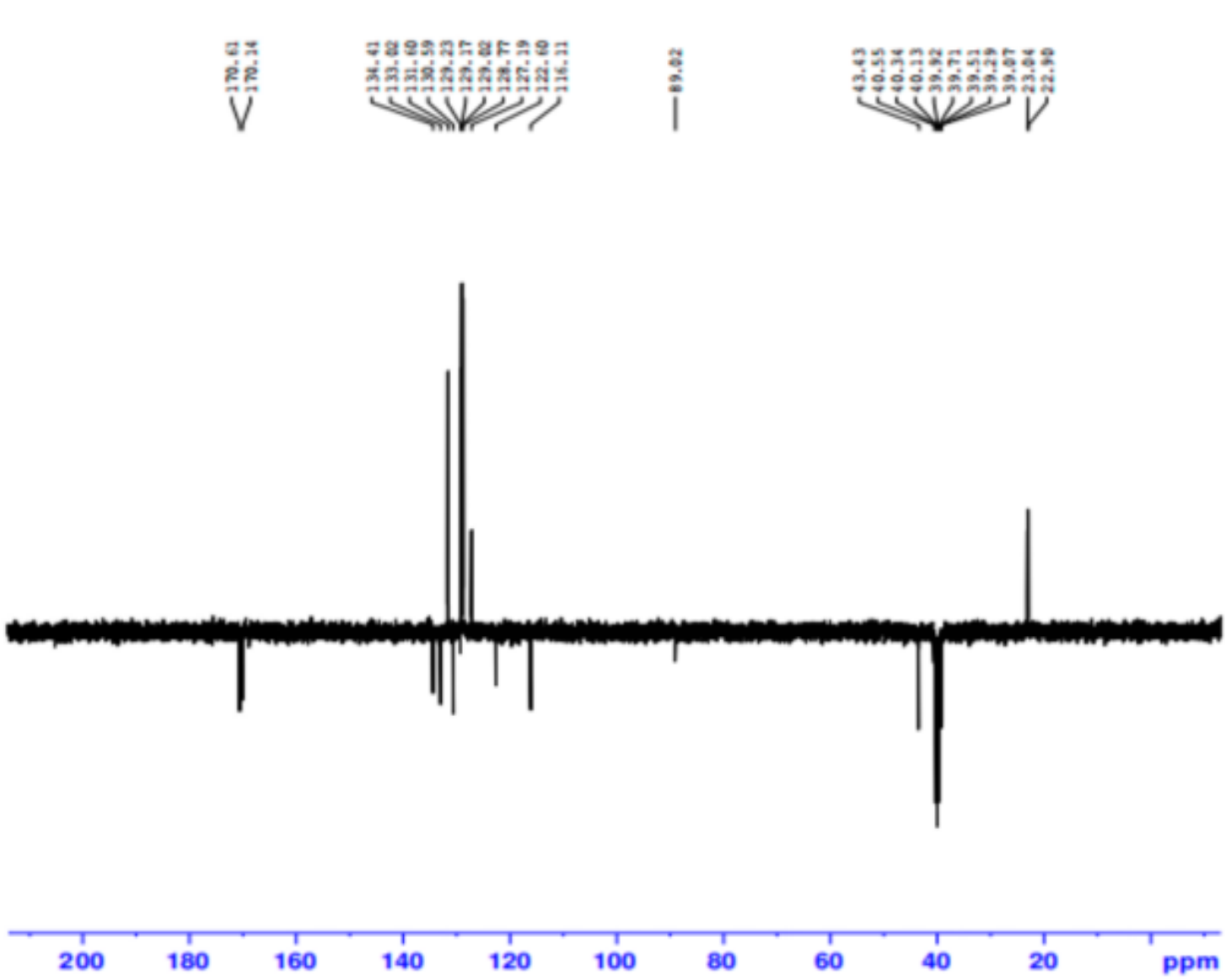


Fig 24 : ^{13}C- NMR spectrum of compound (VIII)



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SOLVENT                DMSO
NS                      1000
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 ========
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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
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WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
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Fig 25: APT spectrum of compound (VIII)

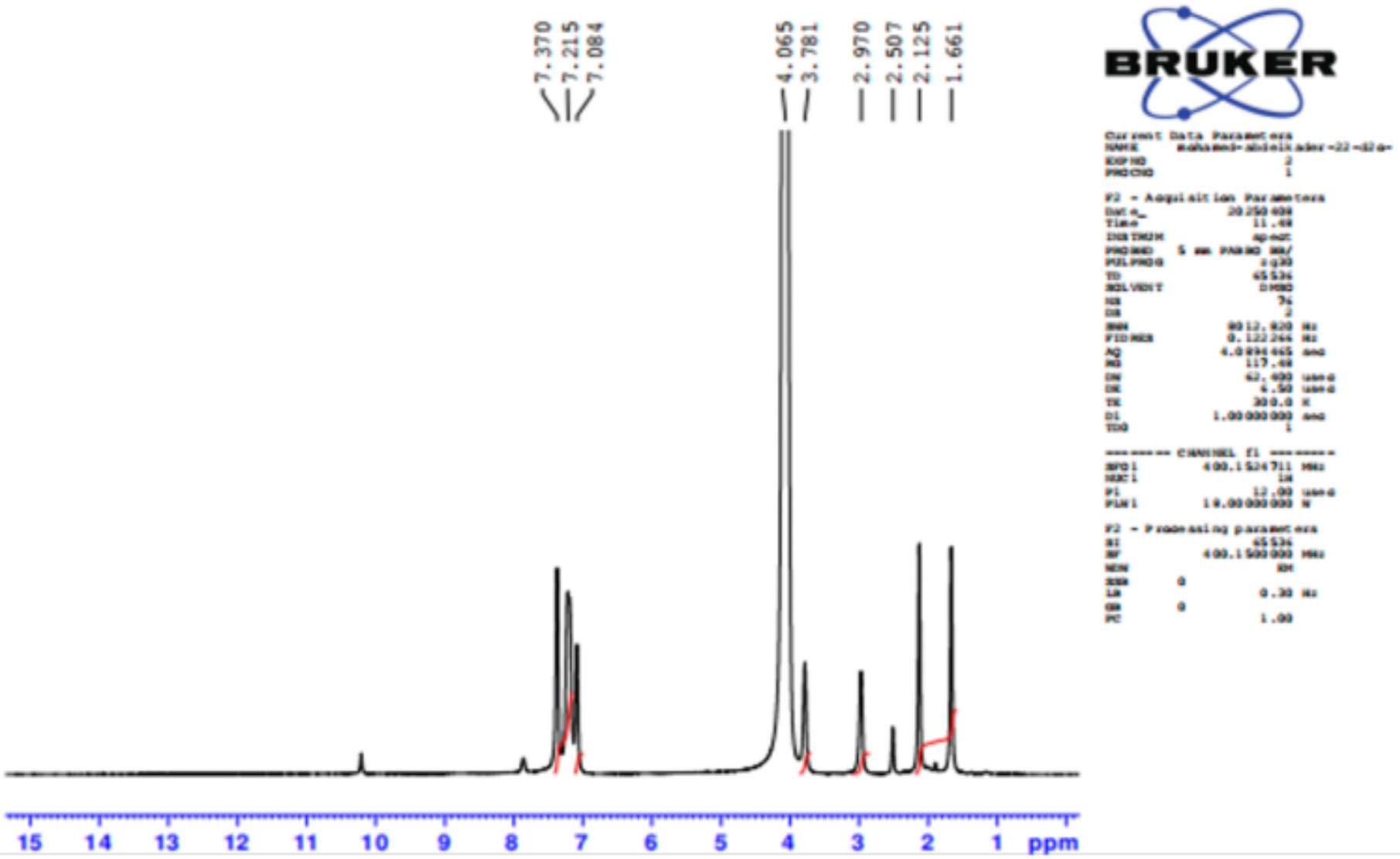


Fig 26: D_2O spectrum of compound (VIII)

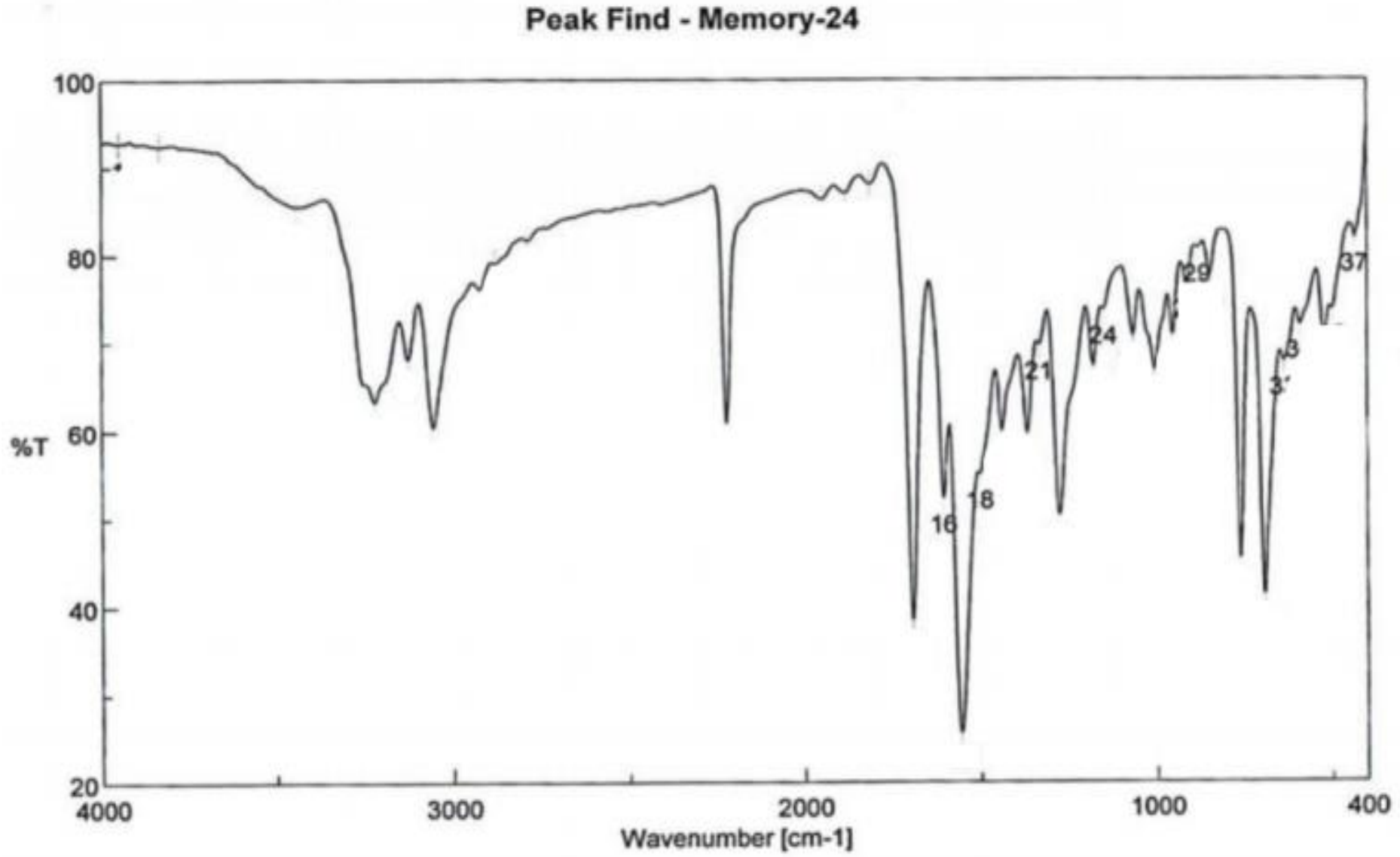


Fig 27 : FT-IR spectrum of compound (IX)

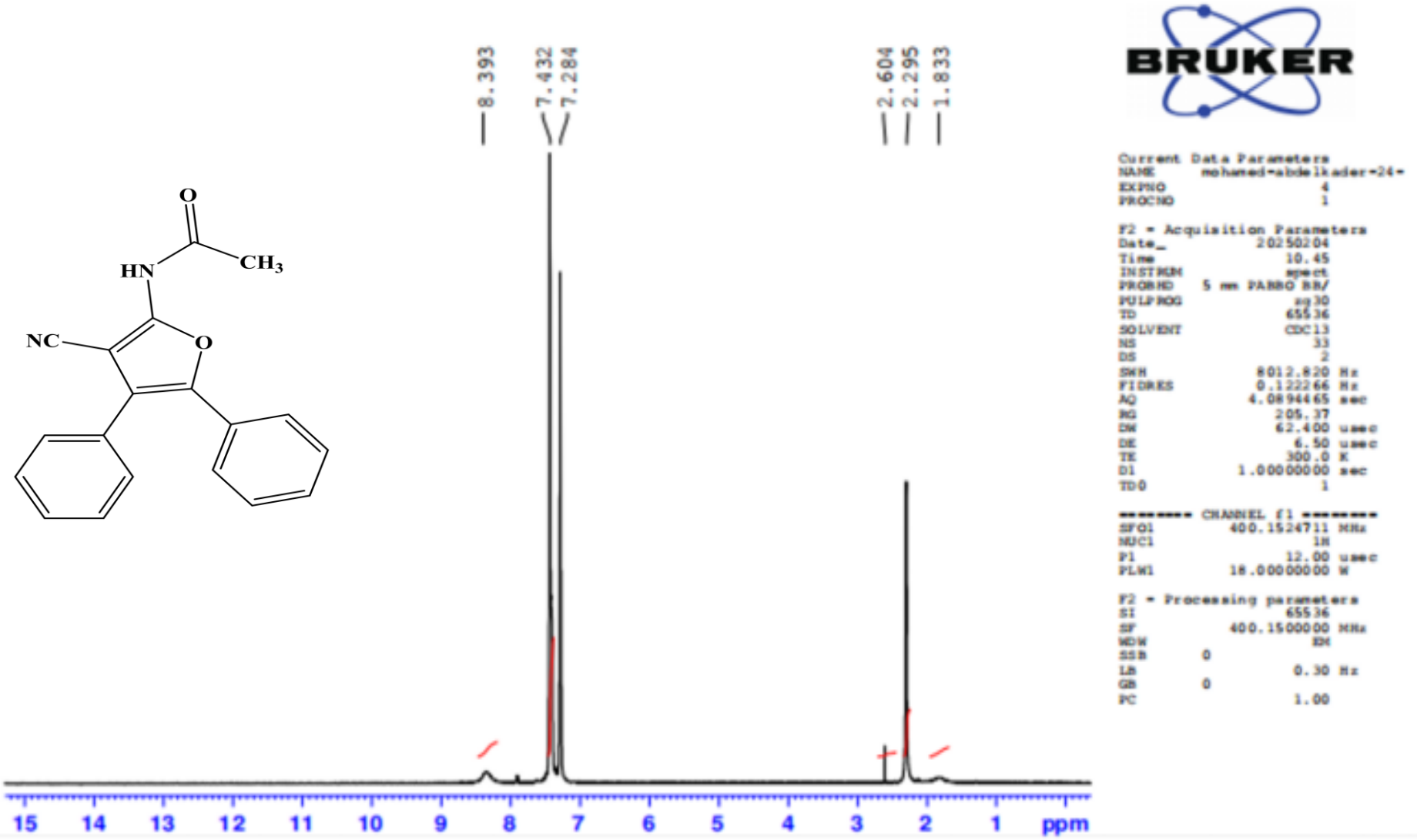


Fig 28 : ^{1}H-NMR spectrum of compound (IX)

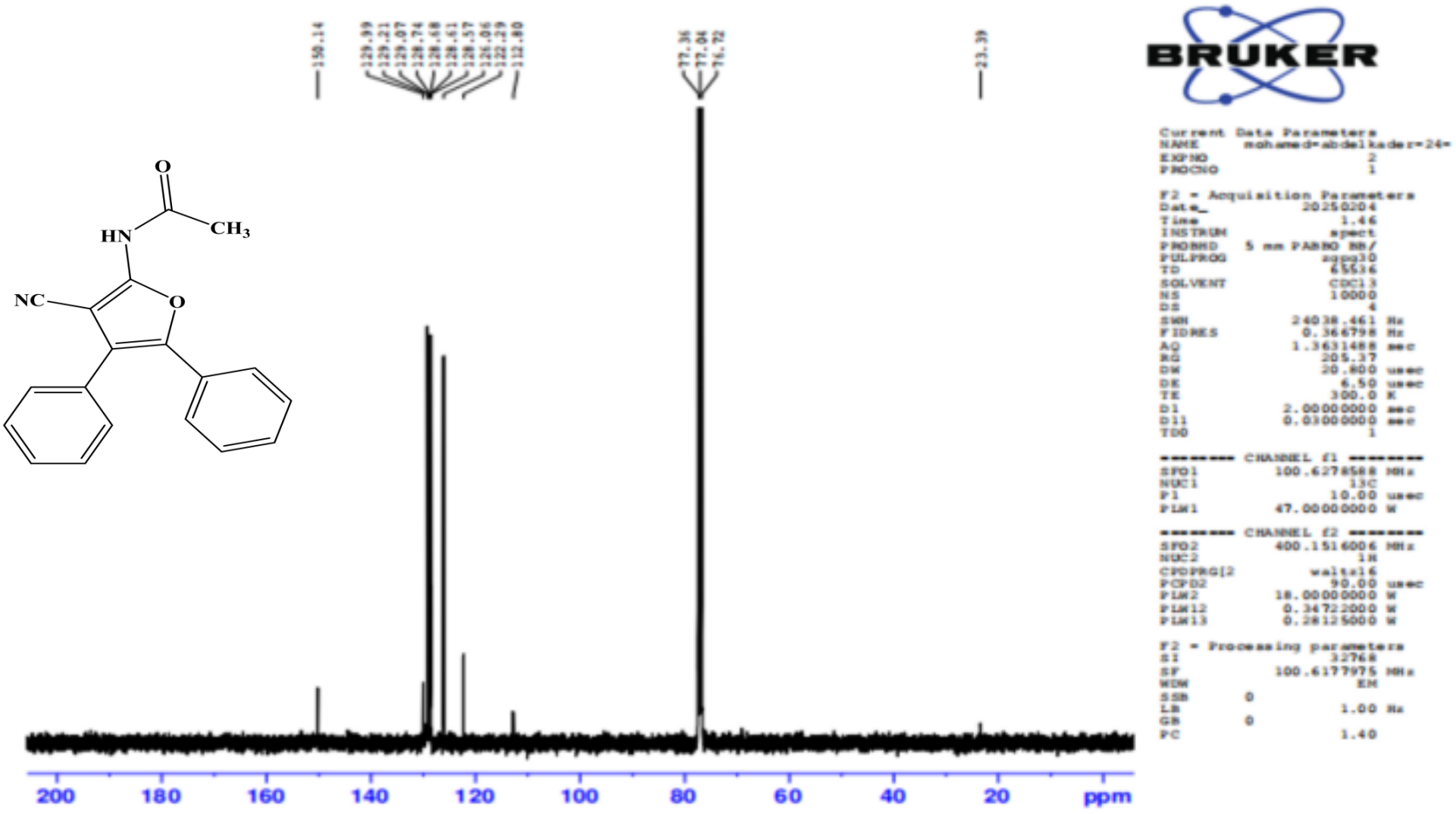


Fig 29 : ^{13}C- NMR spectrum of compound (IX)

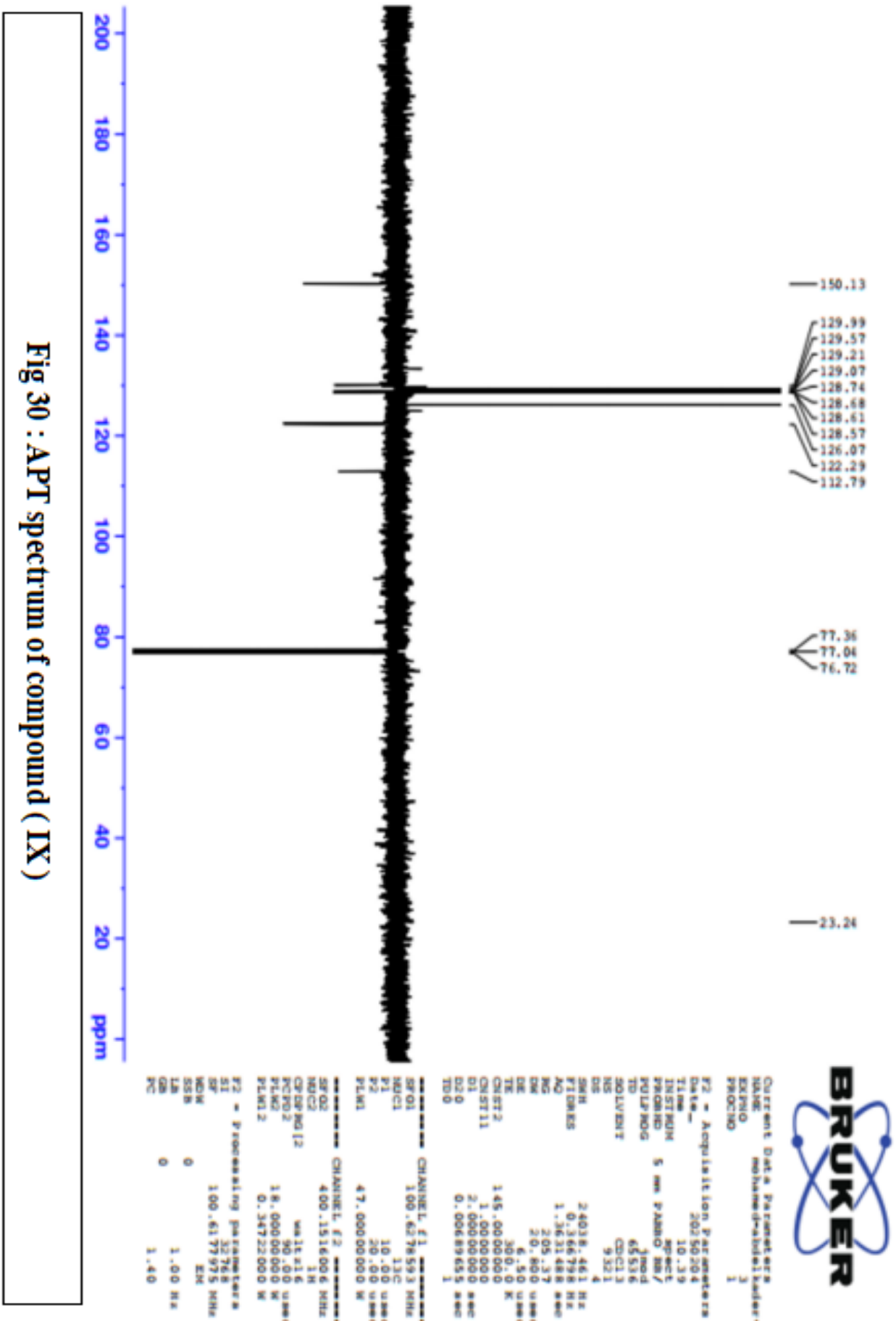


Fig 30 : APT spectrum of compound (IX)

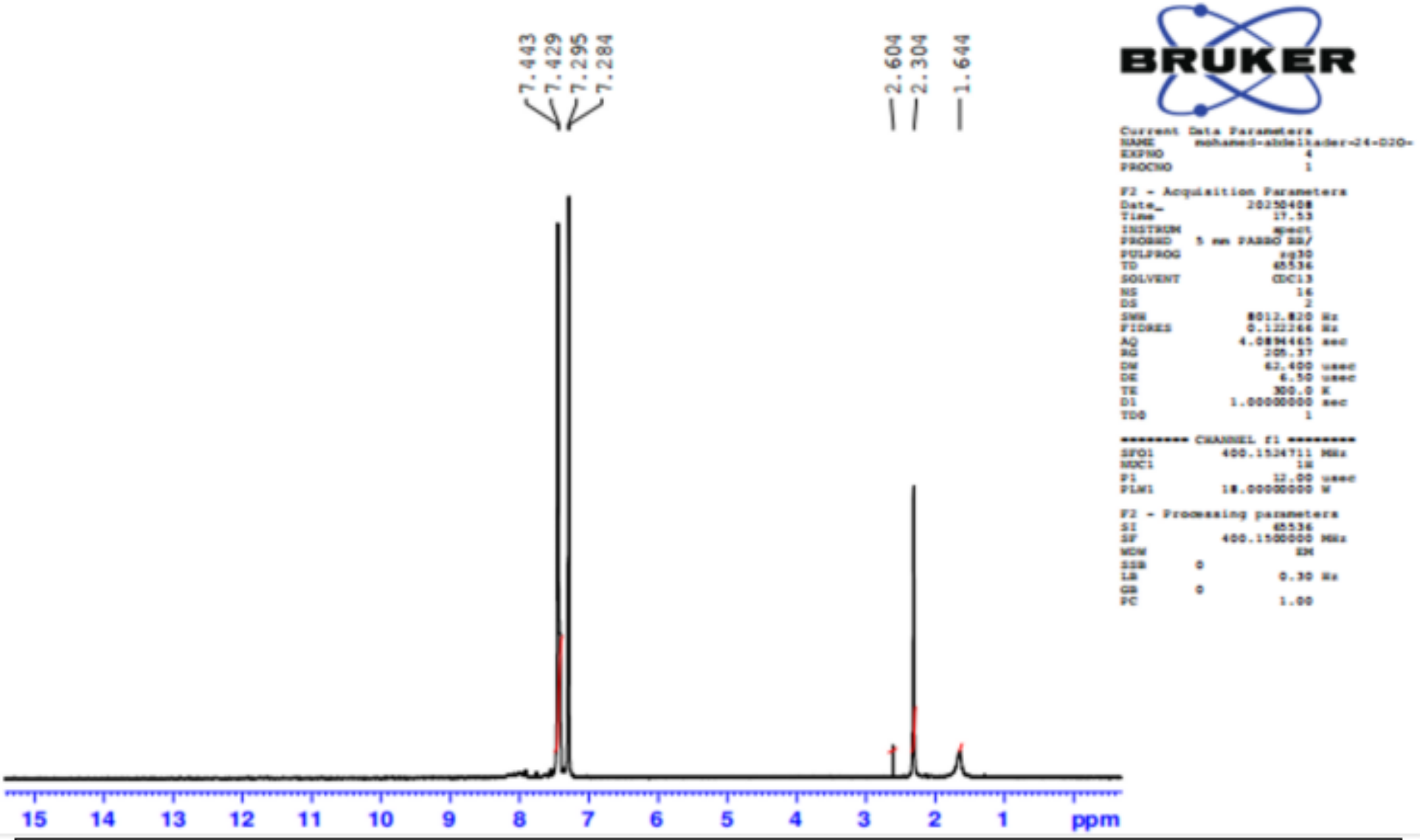


Fig 31: D_2O spectrum of compound (IX)

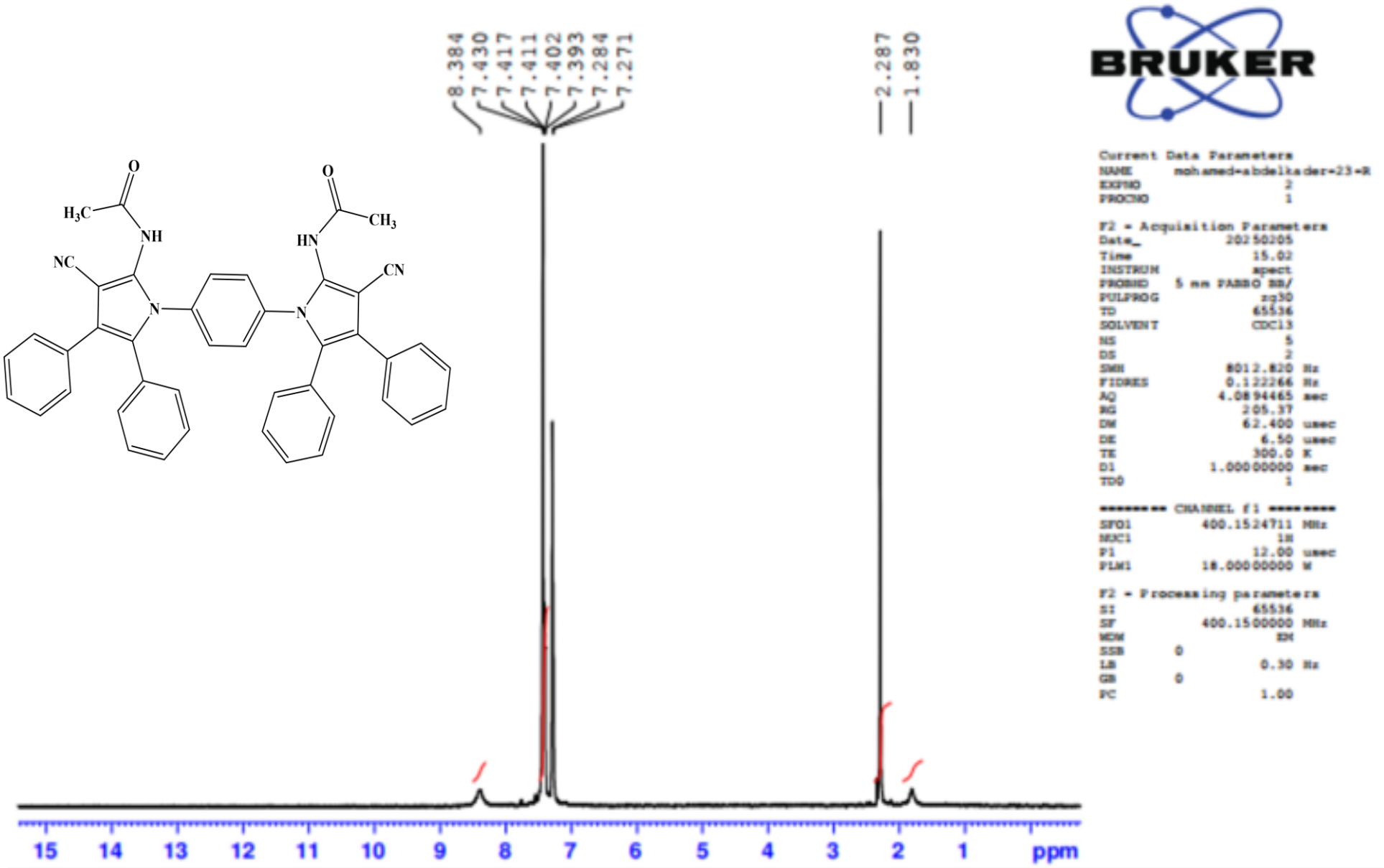


Fig 32 : ^{1}H-NMR spectrum of compound (X)

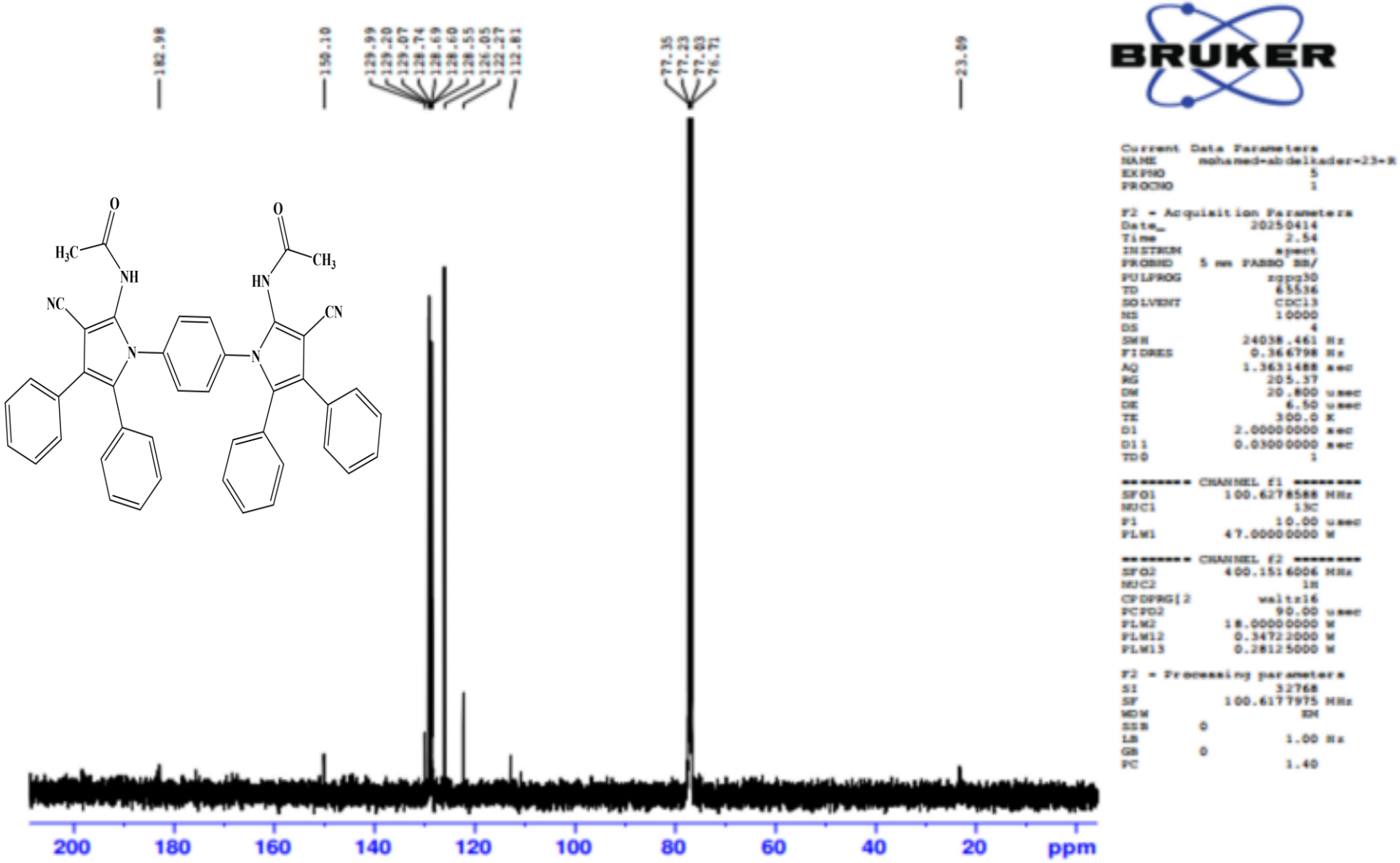


Fig 33 : ^{13}C- NMR spectrum of compound (X)

Fig 34 : APT spectrum of compound (X)

Fig 35: D_2O spectrum of compound (X)

2.3. Biological evaluation:

The antibacterial activity of the synthesized compounds was evaluated against four bacterial strains: ***Escherichia coli***, ***Pseudomonas aeruginosa***, ***Staphylococcus aureus***, and ***Enterococcus faecalis***, using the disc 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.as shown in table 2.1:

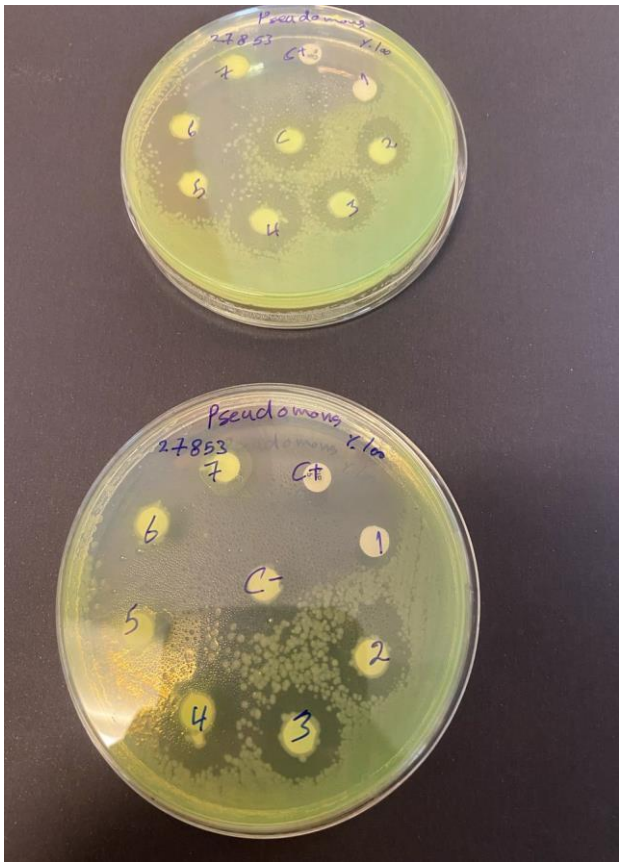
No of Compound	Bacteria Types							
	E. coli		P.aeruginosa		S. aureus		E.faecalis	
	100	50	100	50	100	50	100	50
I	8	4	8	0	0	0	0	0
II	8	4	8	5	9	5	7	4
III	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0
IV	4	0	0	0	0	0	0	0
VI	0	0	5	0	0	0	0	0
VII	0	0	5	0	4	0	0	0

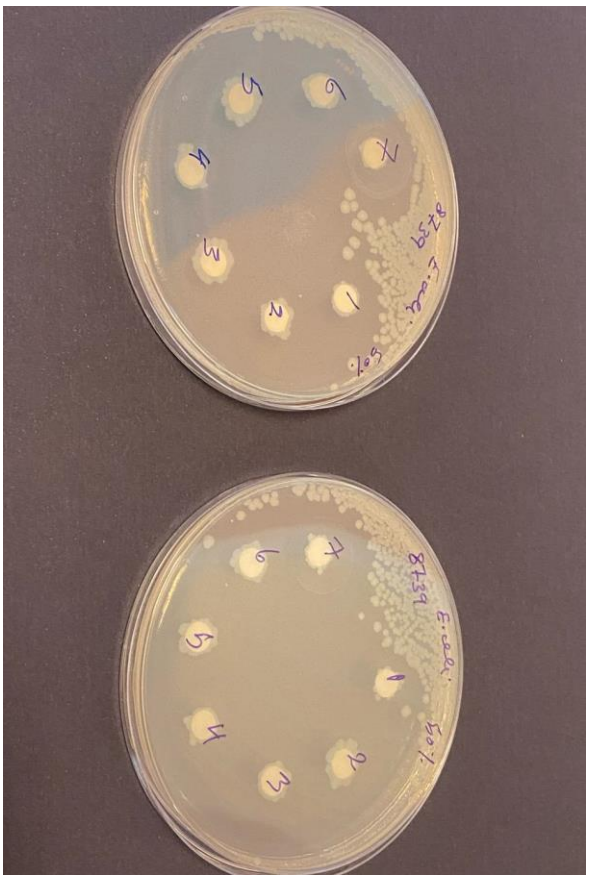
Table2.1: Anti-microbial result

All tested compounds displayed significantly lower antibacterial activity compared to ciprofloxacin.

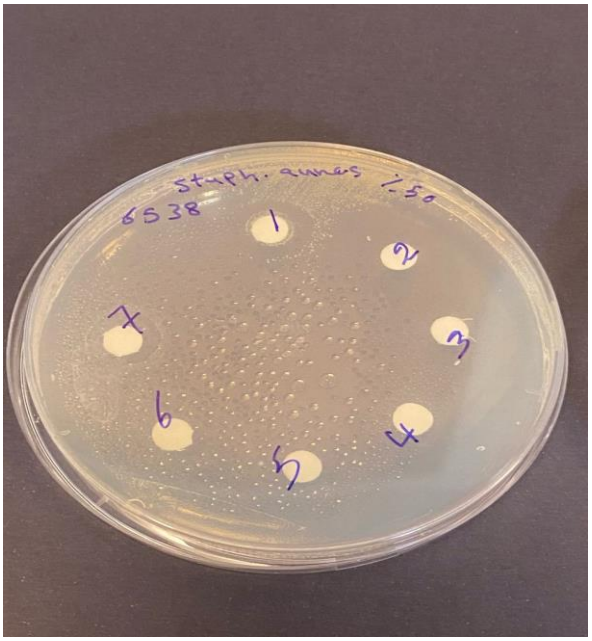
Some compounds exhibited activity against both Gram-positive and Gram-negative bacteria. Compound **(II)** showed significantly higher activity than the others against all selected microbes. It was observed that compounds **(III)** and **(V)** displayed weaker activity against all investigated microbes, while compounds **(IV)** and **(VI)** showed less than moderate activity against bacteria. Compounds **(I)** and **(VII)** demonstrated moderate activity against bacteria.

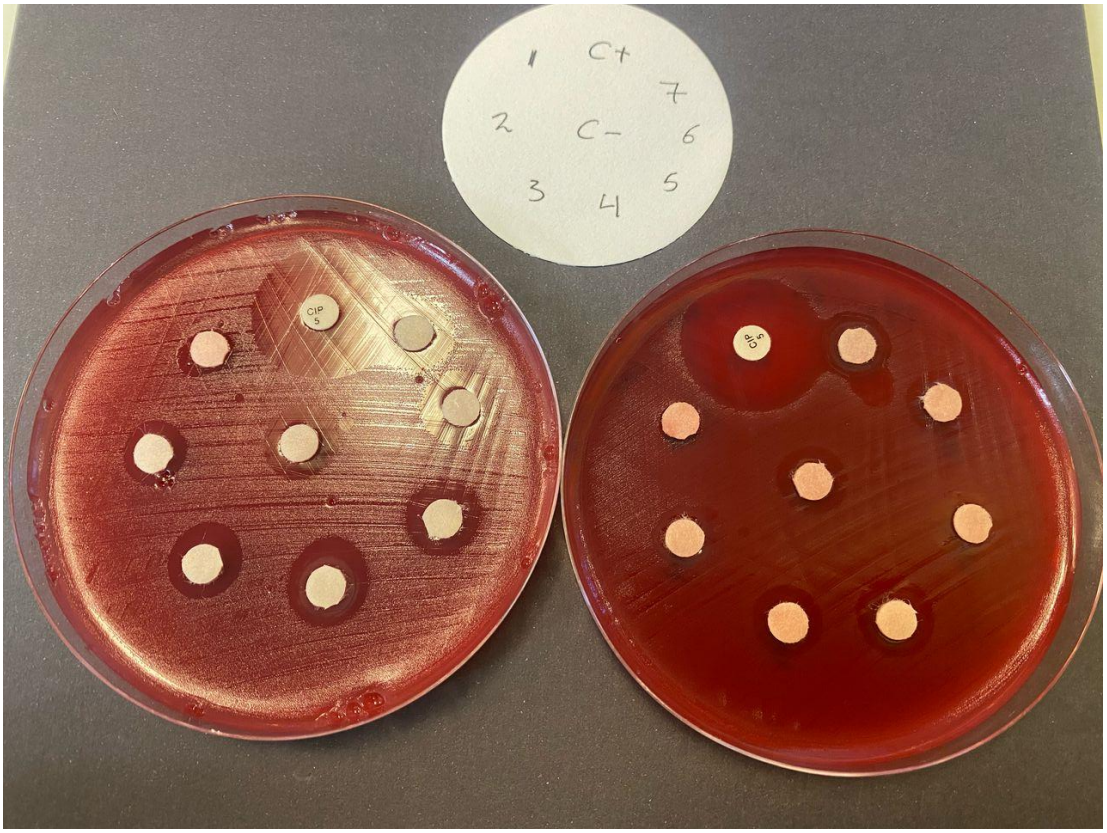
Overall, although the tested compounds exhibited limited antibacterial effects, their basic activity suggests that further structural modifications—such as introducing more polar functional groups or enhancing cell wall permeability—may lead to the development of more potent antibacterial agents.





Some images of types of bacteria





Some images of types of bacteria

2.4. Conclusion:

This study highlights the controlled divergent reactivity of benzoin with different diamines and malononitrile, leading to the selective formation of bis-pyrrole derivatives (I, III, IV, and VI) under optimized ethanol/pyridine conditions. The reaction pathway was governed by steric and electronic factors, with ethylenediamine yielding both pyrrole (I) and furan (II) products, where the latter dominated (44%) due to favorable intramolecular cyclization. In contrast, hydrazine exclusively produced the hydrazone-linked (V) bypassing pyrrole formation entirely, while o-phenylenediamine favored quinoxaline (VII) due to geometric constraints promoting intramolecular cyclization. Spectroscopic characterization (IR, ^{1}H NMR, ^{13}C NMR) confirmed the structural identities of all synthesized compounds, with distinct functional group signatures supporting the proposed mechanisms. The acylation of primary amines (I, II, IV) with acetic anhydride successfully generated amide derivatives (VIII, IX, X), demonstrating an efficient and mild functionalization strategy. These findings underscore the critical influence of reactant geometry, rigidity, and electronic effects on product distribution, providing key insights for designing heterocyclic frameworks.

Beyond synthetic utility, the preliminary antimicrobial screening revealed promising biological activity, particularly for the furan derivative (II), which exhibited superior efficacy against all tested microbial strains. This structure-activity relationship provides a valuable cornerstone for future medicinal chemistry efforts. Collectively, these findings offer fundamental insights and a robust, tunable platform for the rational design of complex heterocyclic frameworks with potential applications in pharmaceutical development and materials science.

Chapter 3

Experimental

3. Experimental

3.1. General Remarks:

The chemical analysis were used in the identification of the organic compounds.

3.1.1. ^{1}H-NMR

Proton magnetic resonance spectra were carried out in the Centre for drug discovery research & development at ain shams university in deuterochloroform ($CDCl_3$) and hexadeuterodimethylsulfoxide (DMSO-d_6) solutions, on Brucker 400 MHz instruments, with chemical shift (δ) expressed in ppm down field from tetramethylsilane as internal stand (δ TMS=0). The multiplicity of the signal is as follow: s (Singlet), d (Doublet), t (Triplet), q (Quartet), m (Multiplet).

3.1.2. ^{13}C-NMR

^{13}C-NMR spectra were carried out in the Centre for drug discovery research & development at ain shams university on Brucker 100 MHz and internal reference TMS=0. Signal multiplicities were measured by APT spectroscopy.

3.1.3. IR-Spectroscopy:

FT-IR measurements were measured recored on the National Research Centre (NRC) at Giza using a Perkin Elmer 2000 FT-IR system. The positions of absorptions have been expressed in wave number units (cm^{-1}).

3.1.4. Melting points:

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

3.1.5. Chromatography:

Analytical aluminum plates were used with Silica gel G, and the plates were run in the following systems**:**

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

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: Solvent and chemical 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
Ethane-1,2-diamine	$C_2H_8N_2$	Aldrich
o-phenylenediamine	$C_6H_4(NH_2)_2$	Aldrich
m-phenylenediamine	$C_6H_4(NH_2)_2$	Aldrich
p-phenylenediamine	$C_6H_4(NH_2)_2$	Aldrich
1,1'-biphenyl-4,4'-diamine (Benzidine)	$C_{12}H_{12}N_2$	Ferakberlin
Hydrazine	N_2H_4	Aldrich

Benzoin (99%)	$C_{14}H_{12}O_2$	Scharlau
Hydrochloric acid (37%)	HCl	Carlo-Erba
Pyridine	C_5H_5N	BDH
Malononitrile (99%)	$CH_2(CN)_2$	Aldrich
Acetic anhydride	$C_4H_6O_3$	BDH

3.3. Synthesis of products.

3.3.1. Reaction of benzoin with diamines:

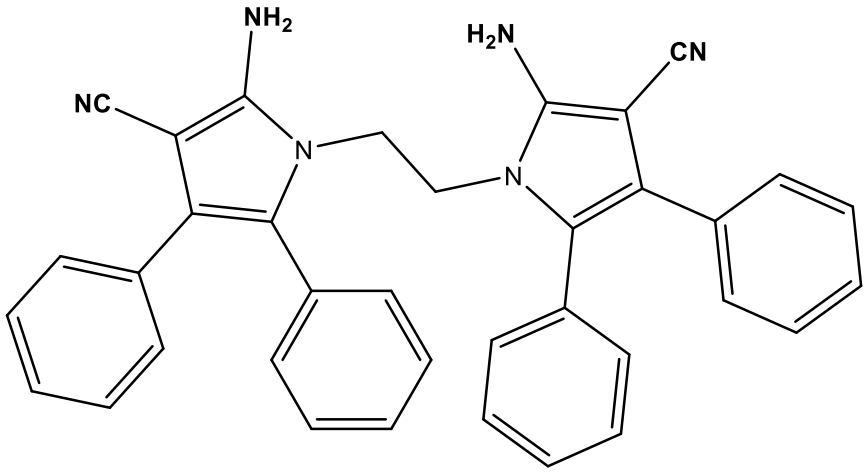
General procedure:

In a 100 ml round-bottom vial with a capacitor and a magnetic drive, a mixture of benzoin (0.02 mol), suitable diamine derivatives (0.01 mol), concentrated hydrochloric acid (10-14 drops) in ethanol (30 ml) were heated under reflux for eight minutes, Malanonitrile (0.66 ml, 0.02 mol), followed by drops (1 ml) of pyridine were added as a catalyst and left to reflux until a solid formed. The resulting solid was filtered, dried and purified by recrystallization from ethanol to afford compounds (I-VII), as shown in Table (3-2).

Table 3.2: The melting point, % yields and Color of synthesized compounds(I-VII)

Compounds	Yield (%)	m.p. (°C)	Color	Reaction.time
I	39.25	299 - 300	White	6 h
II	44.11	201 - 203.5	White	6 h
III	14.2	188 - 190	Orange	50 h
IV	8.5	191.8 - 193	Gray	34 h
V	18.6	202.7 - 203.7	Yellow	12 h
VI	14.4	189.5 - 190.5	Gray	18 h
VII	25.3	123.5 - 125.5	White	16 h

1,1'-(ethane-1,2-diyl)bis(2-amino-4,5-diphenyl-1H-pyrrole-3-carbonitrile) (I)



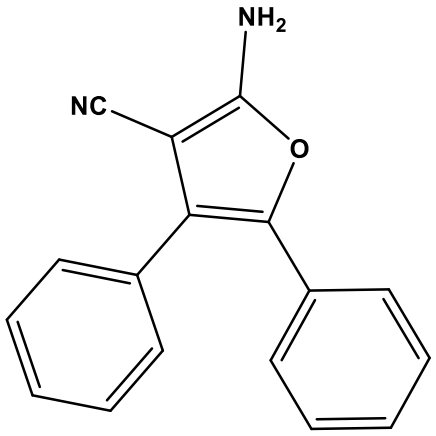
Mol . Formula: $C_{36}H_{28}N_6$ (M.W = 544.65g/mol).

FT-IR: ν (cm^{-1}): 1234.00 (C-N), 2187.47 (CN), 3215.37 – 3366.87 (NH_2).

^{1}H-NMR (DMSO-d_6): δ: 2.80 (t, 2H, CH_2) ,3.96 (t, 2H, CH_2) 6.34 (s, 2H, NH_2) 7.08 – 7.39 (m, 20H, Ar-H), 8.04 (s, 2H, NH_2).

^{13}C-NMR (DMSO-d_6): δ: 37.79 (2C), 71.33 (2C), 118.34 (2C), 120.53 (2C), 123.65 (2C), 126.61 (2C), 128. 54 (4C), 128.70 (4C), 128.81 (4C), 129.21 (4C) ,131.22 (2C), 131.84 (2C) ,133.92 (2C), 148.65 (2C).

2-amino-4,5-diphenylfuran-3-carbonitrile (II)



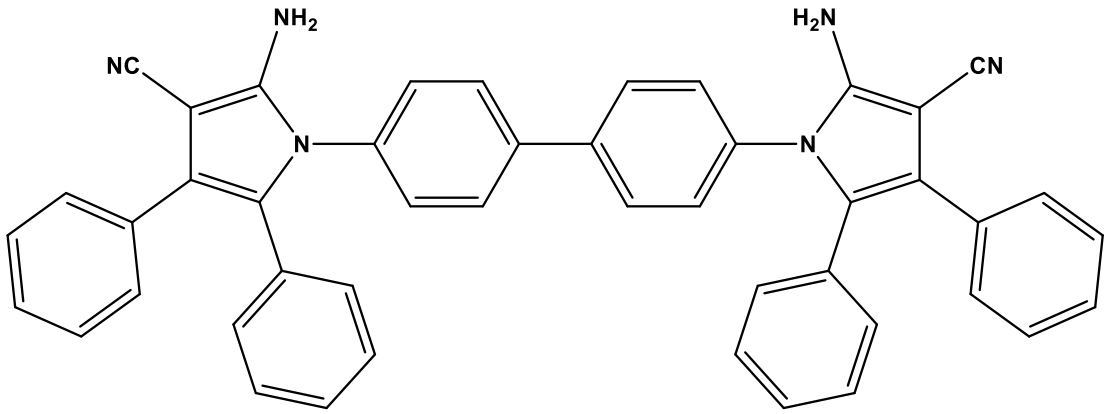
Mol . Formula: $C_{17}H_{12}N_2O$ (M.W = 260.29 g/mol).

FT-IR: ν (cm^{-1}): 2213.68 (CN), 3061.05 (Ar-CH), 3311.02 – 3464.24 (NH_2).

^{1}H-NMR (DMSO-d_6): δ: 7.15 – 7.47 (m, 10H, Ar-H), 7.73 (s, 2H, NH_2).

^{13}C-NMR (DMSO-d_6): δ: 69.79 (1C), 116.02 (1C), 122.28 (1C), 124.75 (2C), 127.36 (1C), 128.78 (4C), 129.03 (1C), 129.33 (1C), 129.42 (1C), 129.89 (1C), 131.71 (1C), 137.20 (1C), 164.04 (1C).

1,1'-([1,1'-biphenyl]-4,4'-diyl)bis(2-amino-4,5-diphenyl-1H-pyrrole-3-carbonitrile) (III)



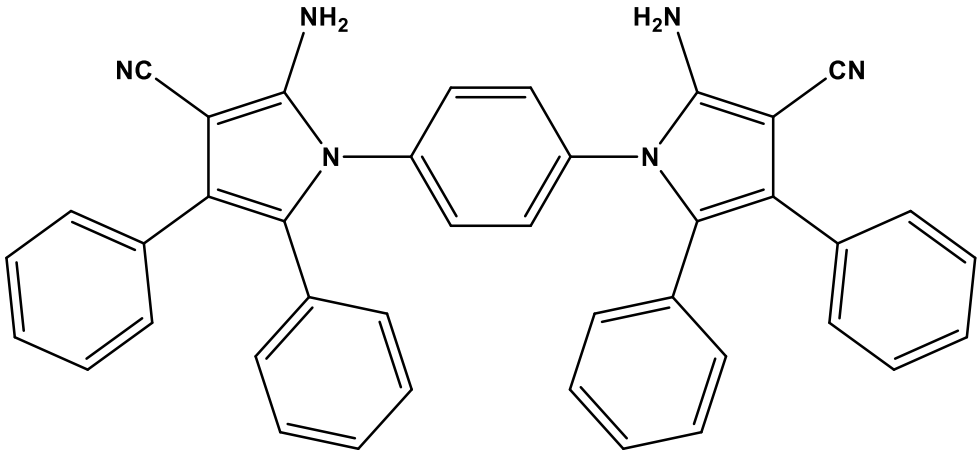
Mol. Formula: $C_{46}H_{32}N_6$ (M.W = 668.79g /mol)

FT-IR: ν (cm^{-1}): 1204.86 (C-N), 2214.18 (CN), 3061.84 (Ar-CH), 3311.70 – 3439.14 (NH_2).

^{1}H-NMR ($CDCl_3$): δ: 5.05 (s, 4H, NH_2), 7.21-7.28 (m, 14H, Ar-H), 7.36- 7.47 (m , 14H , Ar-H) .

^{13}C-NMR ($CDCl_3$): δ: 73.13 (2C), 115.15 (2C), 121.66 (4C), 125.30 (4C), 125.48 (2C), 126.11 (2C), 127.40 (2C), 128.34 (4C), 128.46 (4C), 128.94 (2C), 128.99 (2C), 129.05 (2C), 129.41 (2C), 129.51 (2C), 129.93 (2C), 131.02 (2C), 134.94 (2C), 139.52 (2C), 161.91 (2C).

1,1-'(1,4-phenylene)bis(2-amino-4,5-diphenyl-1H-pyrrole-3-carbonitrile) (IV)



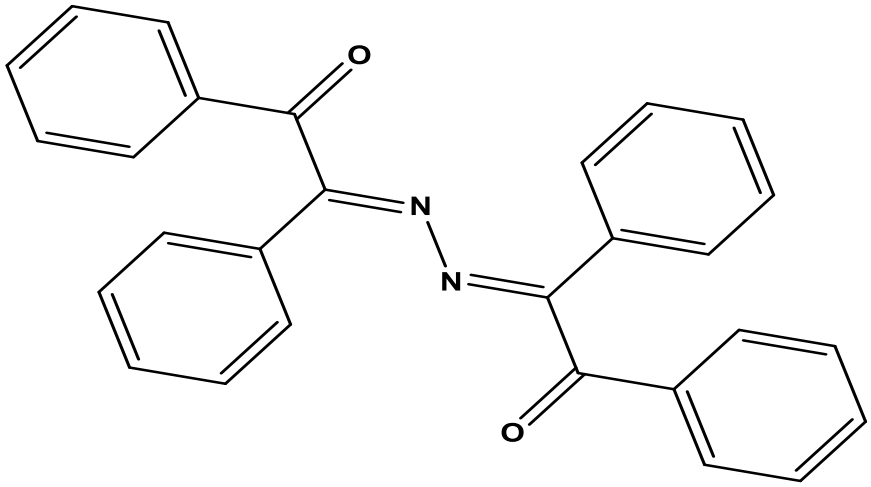
Mol. Formula: $C_{40}H_{28}N_6$ (M.W = 592.69g /mol)

FT-IR: ν (cm^{-1}): 1205.31 (C-N), 2214.68 (CN), 3061.70 (Ar-CH), 3312.94-3440.19 (NH_2).

^{1}H-NMR ($CDCl_3$): δ: 4.91 (s, 4H, NH_2), 7.20 – 7.28 (m, 12H, Ar-H), 7.36-7.47 (m, 12H, Ar-H).

^{13}C-NMR ($CDCl_3$): δ: 115.12 (2C), 121.67(2C), 125.30 (2C), 125.45 (2C), 127.41 (4C) ,128.35 (4C), 128.46 (2C), 128.95 (4C), 129.00 (4C), 129.51 (4C), 131.02 (2C), 132.50 (2C), 139.55 (4C) , 161.86 (2C) .

2,2'-(hydrazine-1,2-diylidene)bis(1,2-diphenylethan-1-one) (V)



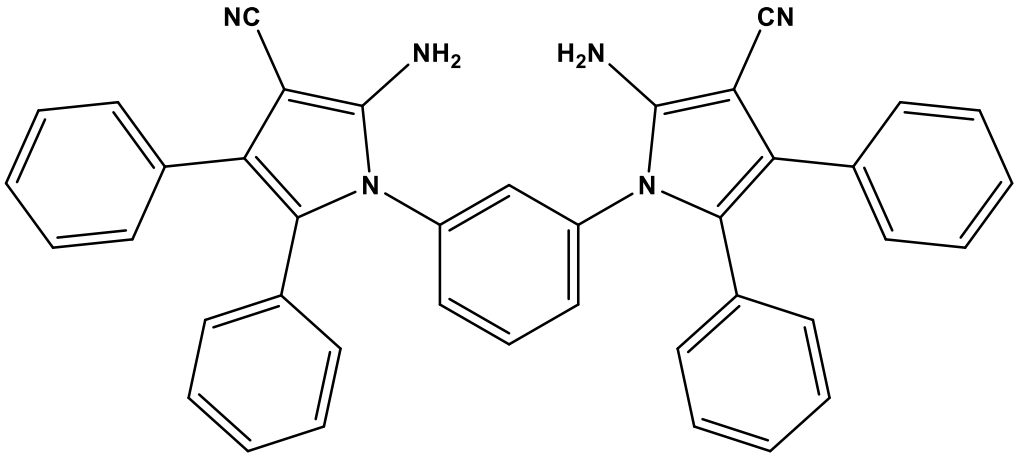
Mol. Formula: $C_{28}H_{20}N_2O_2$ (M.W = 416.47 g /mol)

FT-IR: ν (cm^{-1}): 1593.26 (C=N), 1677.22 (C=O), 3064.44 (Ar- CH).

^{1}H-NMR ($CDCl_3$): δ: 7.25-7.40 (m, 6H, Ar-H), 7.51 – 7.64 (m, 10H, Ar-H), 7.97 – 7.99 (m, 4H, Ar-H).

^{13}C-NMR ($CDCl_3$): δ: 197.42 (2C), 167.08 (2C), 135.56 (2C), 134.13 (2C), 132.26 (2C), 131.75 (4C), 129.24 (2C), 129.06 (4C), 128.72 (4C), 128.14 (4C).

1,1-'(1,3-phenylene)bis(2-amino-4,5-diphenyl-1H-pyrrole-3-carbonitrile) (VI)

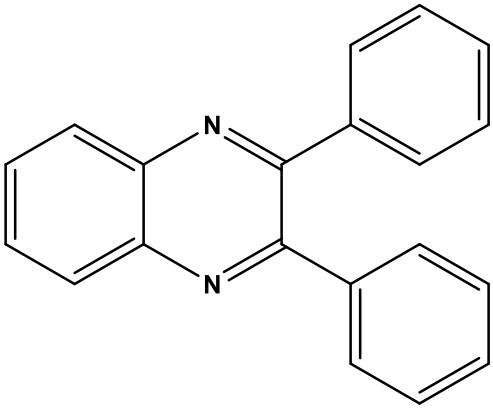


Mol. Formula: $C_{40}H_{28}N_6$ (M.W = 592.69g /mol)

^{1}H-NMR ($CDCl_3$): δ: 4.96 (s, 4H, NH_2), 7.22 – 7.28 (m, 12H, Ar-H), 7.36-7.45 (m , 12H , Ar-H) .

^{13}C-NMR ($CDCl_3$): δ: 90.19 (2C) ,113.11 (3C), 125.47(1C), 125.76 (1C), 125.87 (1C) ,128.25 (2C), 128.35 (2C) ,128. 50 (4C), 128.71 (2C), 128.98 (2C), 129.03 (1C), 129.21 (1C), 129.30 (1C), 129.48 (1C), 129.53 (1C), 129.64 (1C) ,130.14 (4C), 132.68 (2C), 132.82 (2C) ,134.35 (2C) ,137.32 (2C), 169.96 (2C).

2,3-diphenylquinoxaline (VII)



Mol. Formula: $C_{20}H_{14}N_2$ (M.W = 282.35g /mol)

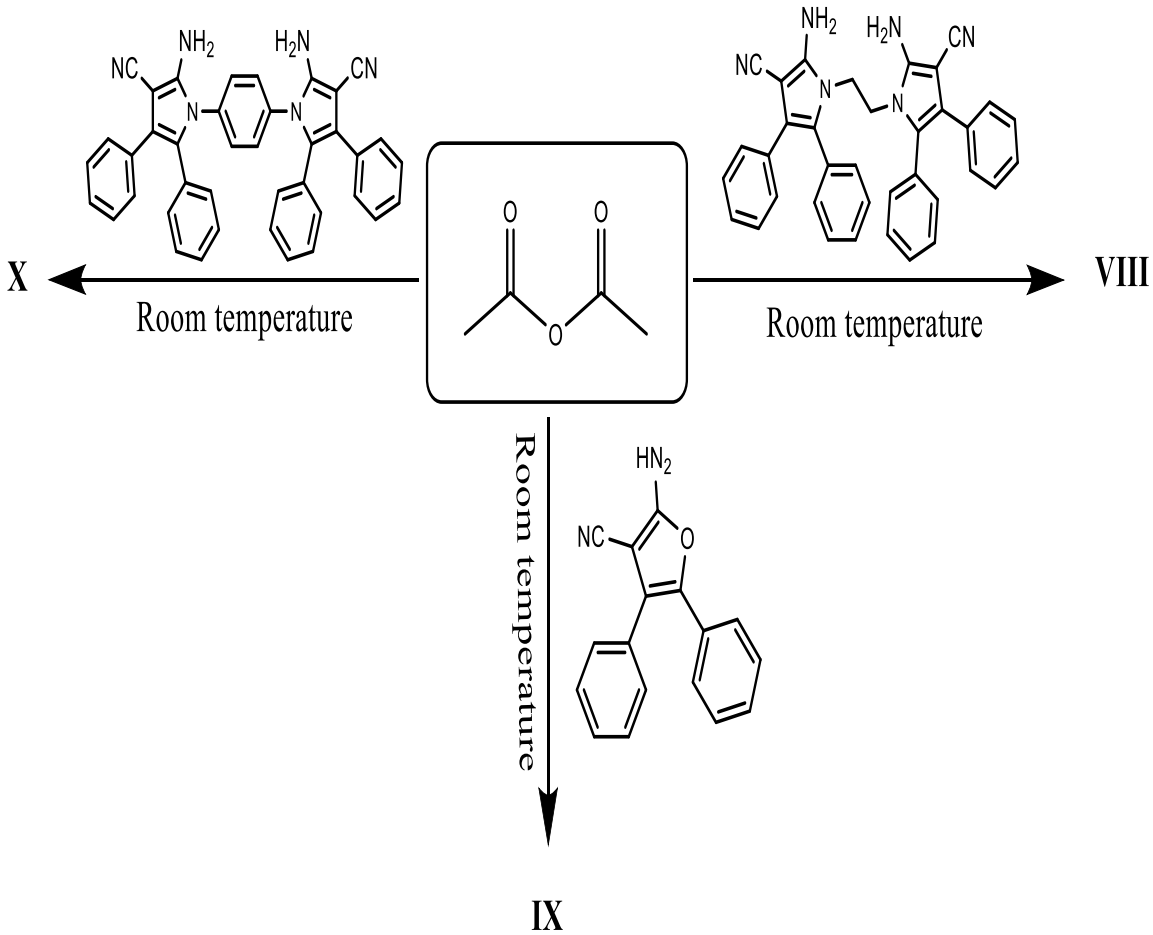
^{1}H-NMR ($CDCl_3$): δ: 7.28 –7.44 (m, 6H, Ar-H), 7.54 –7.56 (m, 4H, Ar-H), 7.81–7.83 (m, 2H, Ar-H), 8.26–8.27 (m, 2H, Ar-H).

^{13}C-NMR ($CDCl_3$): δ: 128.33 (4C), 129.00 (2C), 129.04 (2C), 129.93 (2C), 130.27 (4C), 138.57 (2C), 140.92 (2C), 153.35 (2C).

3.3.2. Reaction of acetic anhydride with Compounds I, II and IV:

General procedure:

Compounds I, II and IV (0.01 mol) were dissolved in excess acetic anhydride and stirred at room temperature for 24 hours until precipitation occurred. The resulting precipitate was filtered under vacuum thoroughly washed and dried then recrystallized from an appropriate solvent to afford pure Compound VIII, IX. and X as shown in Table (3-3) and scheme (3.1).

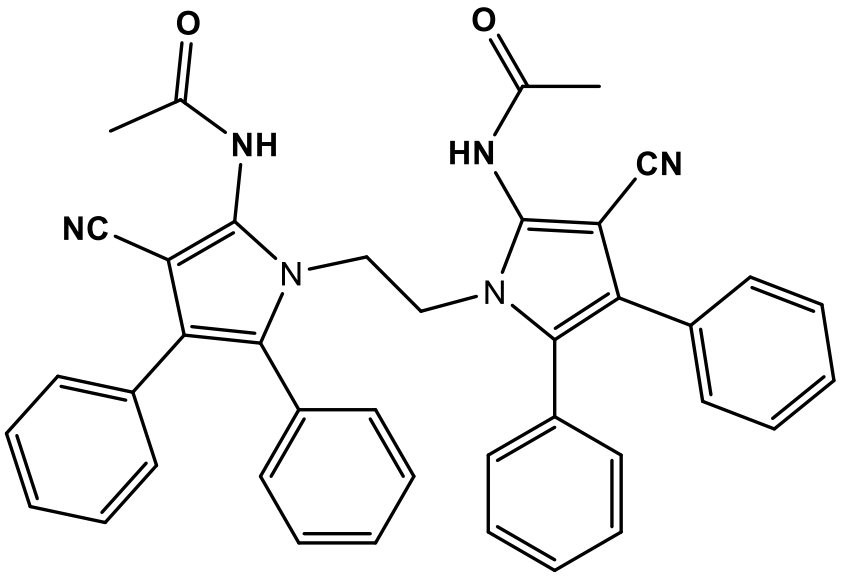


Scheme 3.1: Reaction of acetic anhydride with Compound I , II and IV

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

Compounds	Yield (%)	m.p.(°C)	Color
VIII	15.2	272 - 274	White
IX	15.8	193.5-195	White
X	9.5	192 - 194	White

N,N'-(ethane-1,2-diylbis(3-cyano-4,5-diphenyl-1H-pyrrole-1,2-diyl))diacetamide (VIII)

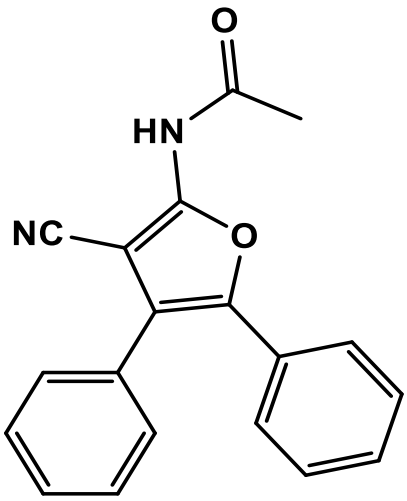


Mol. Formula: $C_{40}H_{32}N_6O_2$ (M.W = 628.72g / mol).

^{1}H-NMR ($CDCl_3$): δ: 1.68 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.00 – 3.01 (d, d, 2H, CH_2), 3.78 (t, 2H, CH_2), 7.11 – 7.42 (m, 20H, Ar-H), 7.86 (t, 1H , NH) , 10.10 (s , 1H , NH) .

^{13}C-NMR ($CDCl_3$): δ: 22.90 (1C), 23.04 (1C), 43.42 (2C) , 89.01 (2C) , 116.10 (2C) , 122.60 (2C) , 127.19 (4C) , 128.77 (4C) , 129.02 (4C) , 129.24 (4C) , 130.59 (4C) ,131.60 (2C) , 133.02 (2C) , 134.41 (4C) 170.15 (1C) , 170.61 (1C) .

N-(3-cyano-4,5-diphenylfuran-2-yl)acetamide (IX)



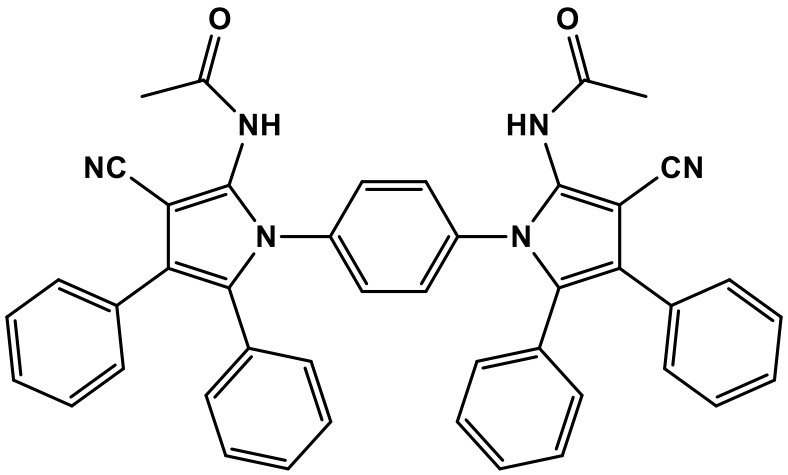
Mol. Formula: $C_{19}H_{14}N_2O_2$ (M.W = 302.33 g / mol) .

FT-IR: ν (cm^{-1}): 1694.16 (C=O) , 2223.52 (CN) , 3057.58 (Ar-CH) , 3223.43-3443.28 (NH).

^{1}H-NMR ($CDCl_3$): δ: 2.29 (s , 3H , CH3) , 7.38 – 7.43 (m , 10H , Ar-H), 8.39 (s , 1H , NH).

^{13}C-NMR ($CDCl_3$): δ: 23.39 (1C) , 112.80 (1C) , 122.29 (1C) , 126.06 (2C) , 128.57 (2C) , 128.61 (2C) , 128.68 (2C) , 128.74 (2C) , 129.07 (2C) , 129.21 (2C) , 129.99 (1C) , 150.14 (1C) .

N,N'-(1,4-phenylenebis(3-cyano-4,5-diphenyl-1H-pyrrole-1,2-diyl))diacetamide (X)



Mol. Formula: $C_{44}H_{32}N_6O_2$ (M.W = 676.76 g / mol) .

^{1}H-NMR ($CDCl_3$): δ: 2.28 (s , 6H . CH_3), 7.27 – 7.34 (m , 24H , Ar-H) , 8.38 (s , 2H , HN)

^{13}C-NMR ($CDCl_3$): δ: 23.09 (2C) , 112.81 (2C) , 122.27 (2C) , 126.05 (2C) , 128.55 (8C) , 128.60 (6C) , 128.69 (6C) , 128.74 (4C), 129.07 (2C) , 129.20 (2C) , 129.99 (4C) , 150.10 (2C) , 182.98 (2C) .

3.4. In Vitro Antimicrobial 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:

- **Gram positive**

  Staphylococcus aureus

  Enterococcus faecalis

- **Gram negative**

  Escherichia coli

  Pseudomonas aeruginosa

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 extract was dissolved in 10 mL of a mixture of chloroform and DMSO. Serial dilutions were prepared at concentrations of 100 µg/mL and 50 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.

Chapter 4

Appendix

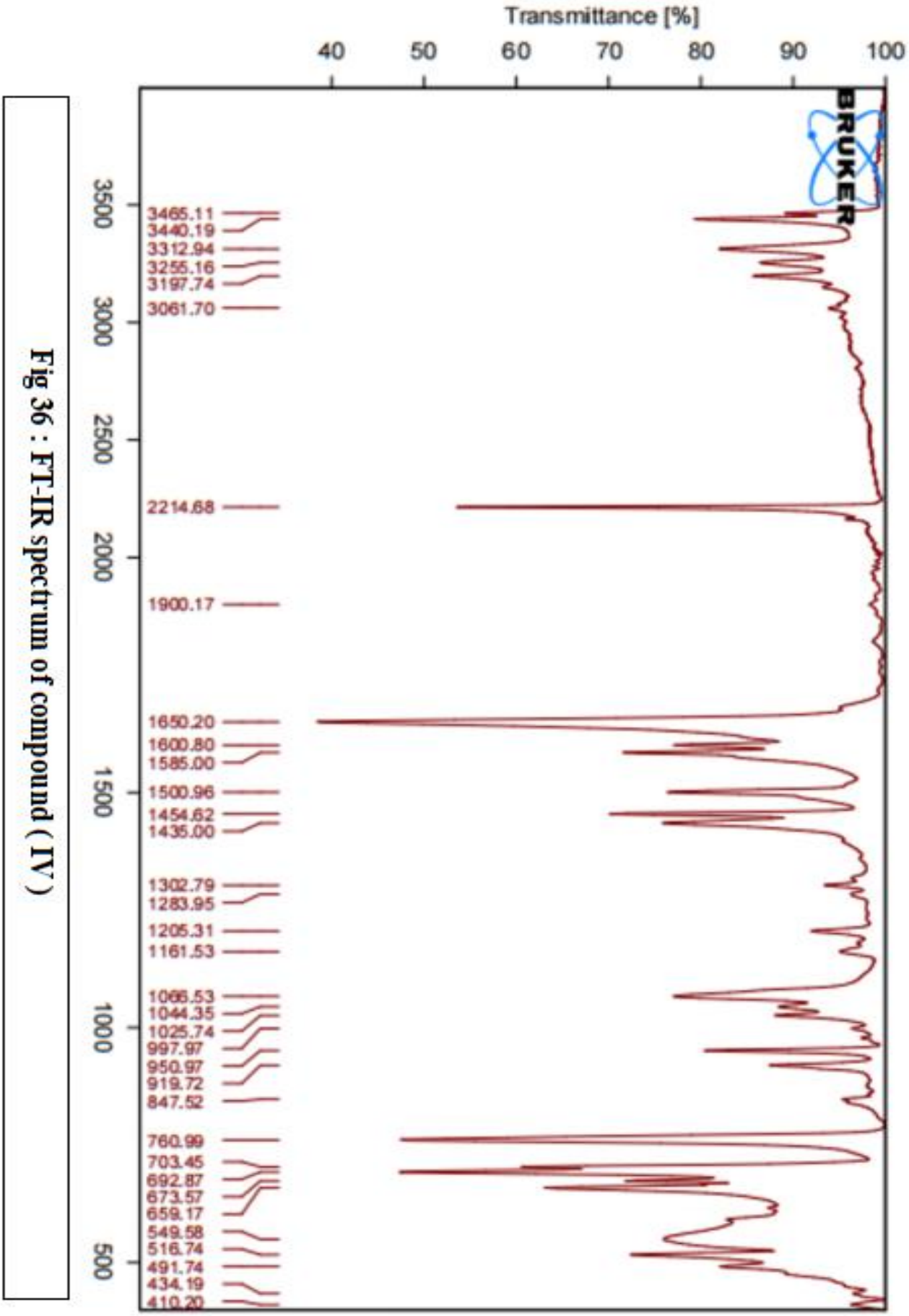
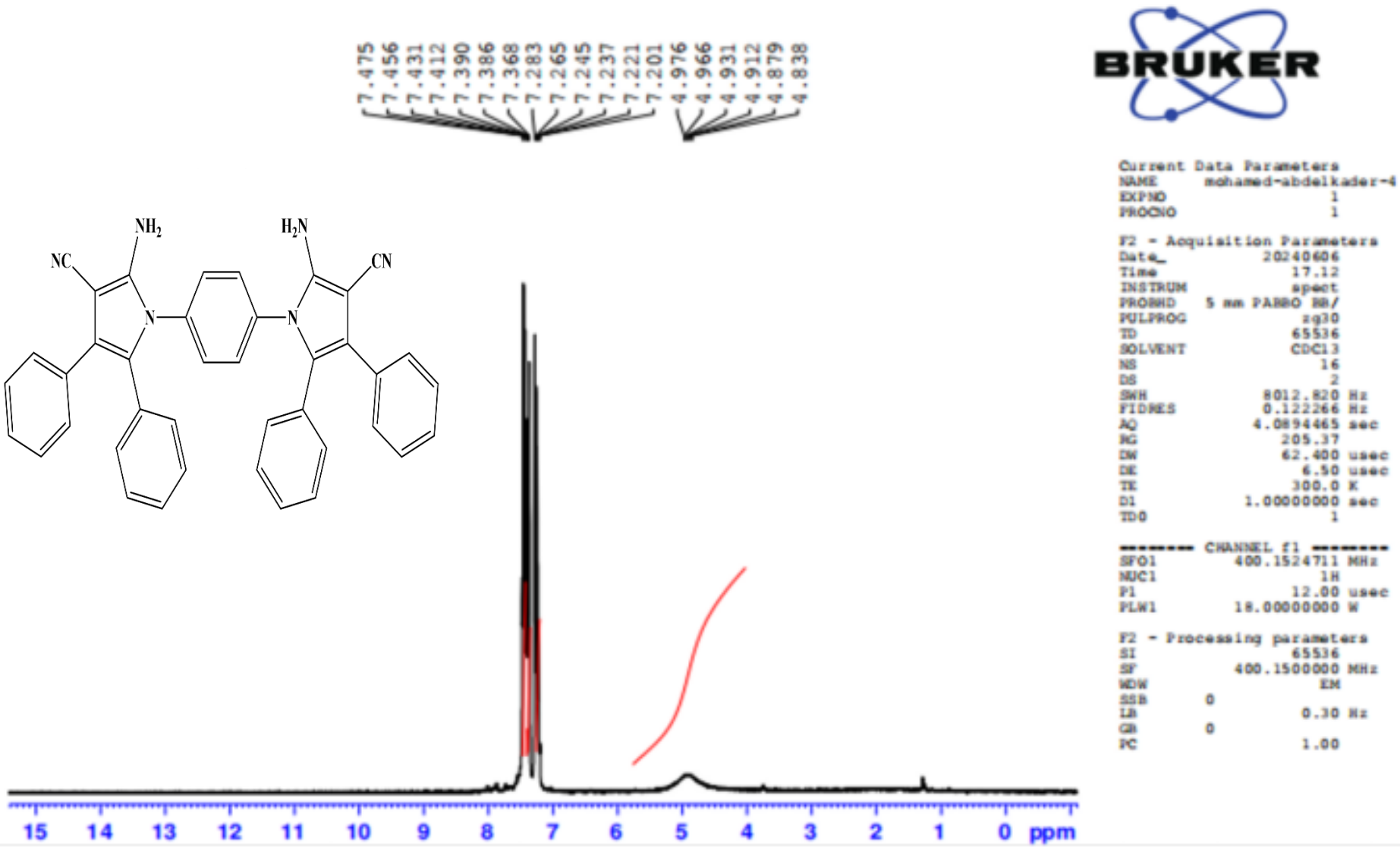


Fig 36 : FT-IR spectrum of compound (IV)



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PROCNO                       1

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PULPROG              zg30
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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 ========
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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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Fig 37 : ^{1}H-NMR spectrum of compound (IV)

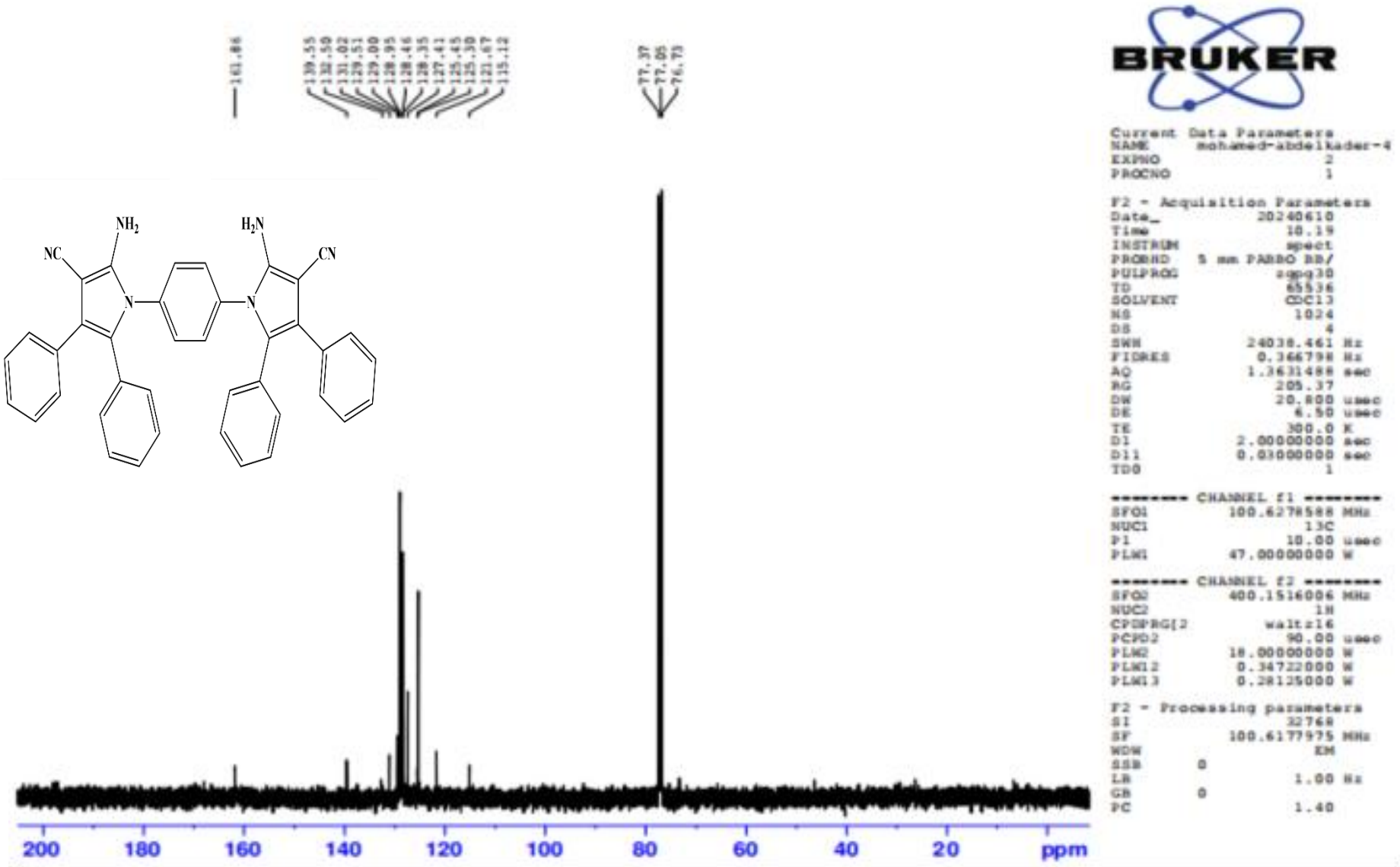
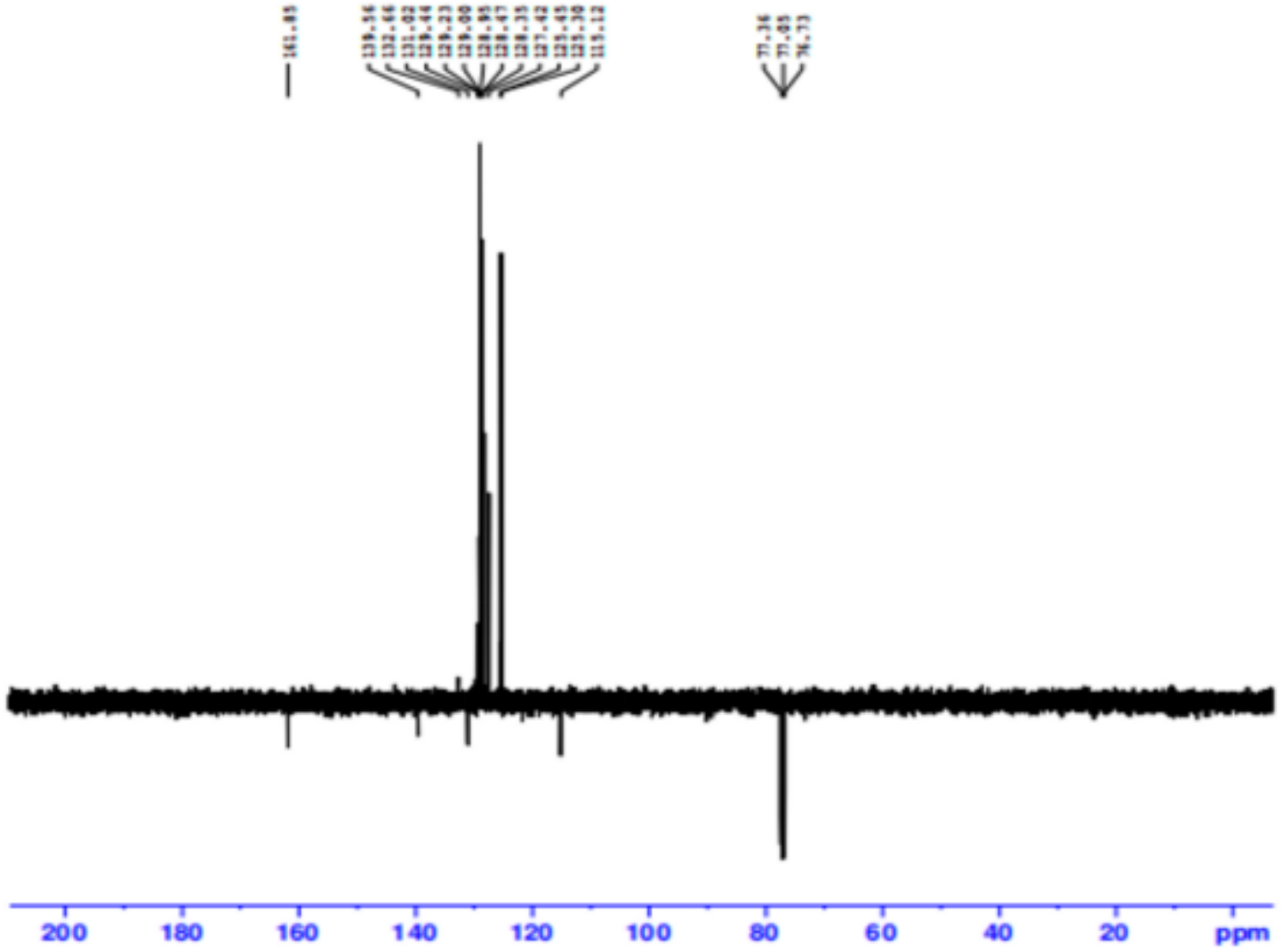


Fig 38 : ^{13}C- NMR spectrum of compound (IV)



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PROCNO                         1

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SOLVENT                    CDCl3
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DS                             4
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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
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SF                   100.6177975 MHz
WDW                           EM
SSB                 0
LB                         1.00 Hz
GB                  0
PC                         1.40
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Fig 39 : APT spectrum of compound (IV)

Fig 40: D_2O spectrum of compound (IV)

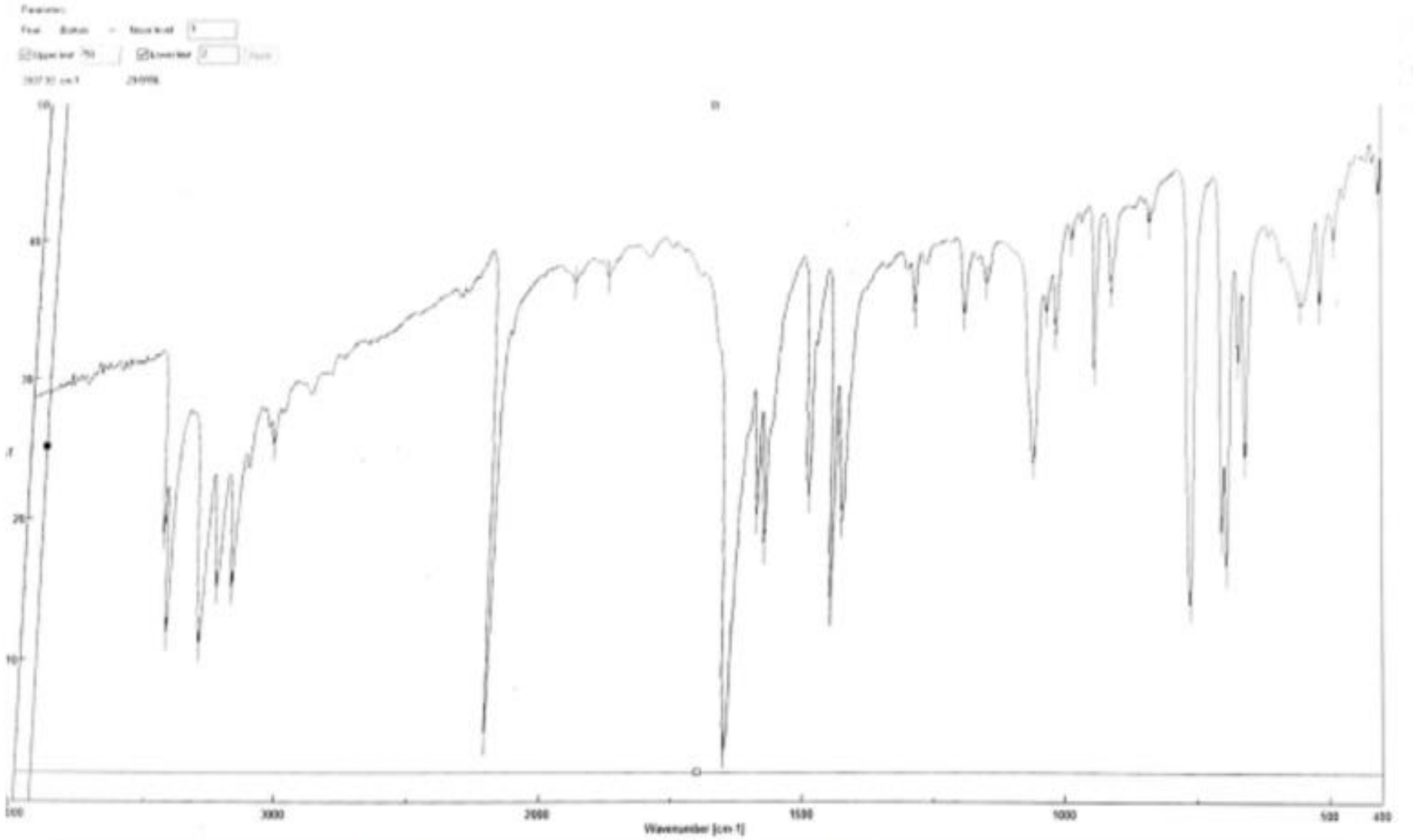


Fig 41 : FT-IR spectrum of compound (VI)

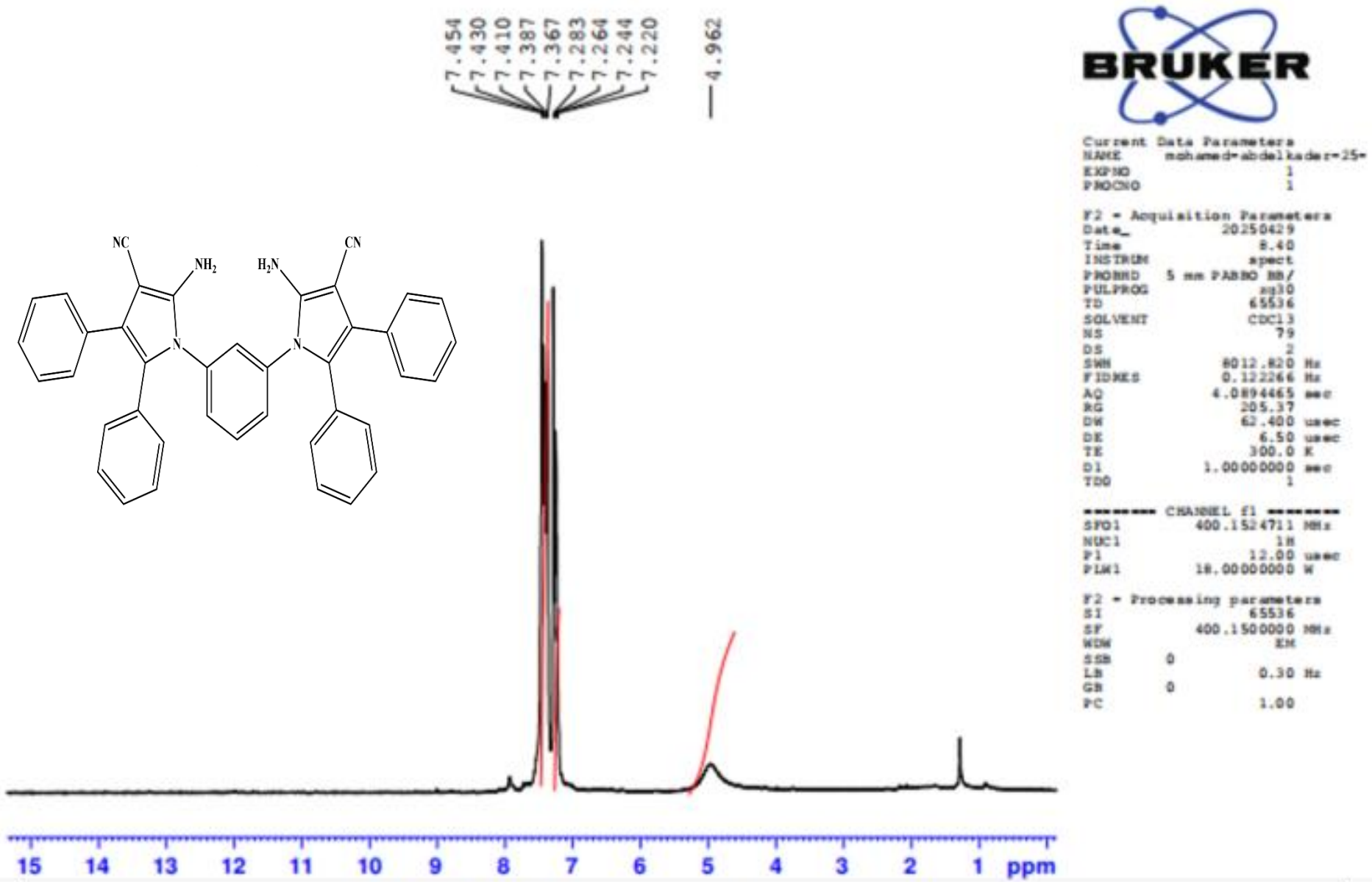
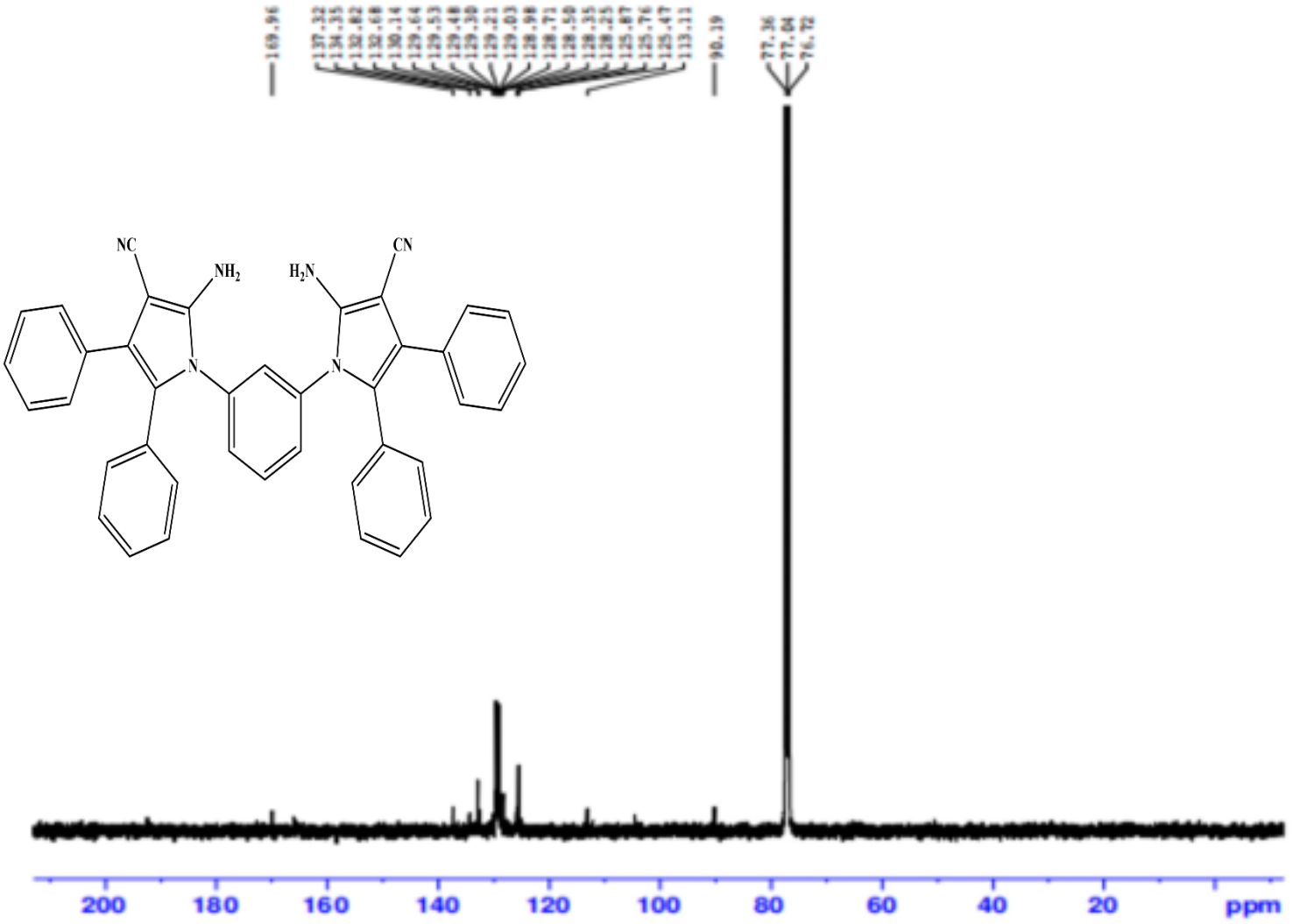


Fig 42: ^{1}H-NMR spectrum of compound (VI)



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PROCNO                           1

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SOLVENT                      CDCl3
NS                             19977
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
```

Fig 43 : ^{13}C- NMR spectrum of compound (VI)

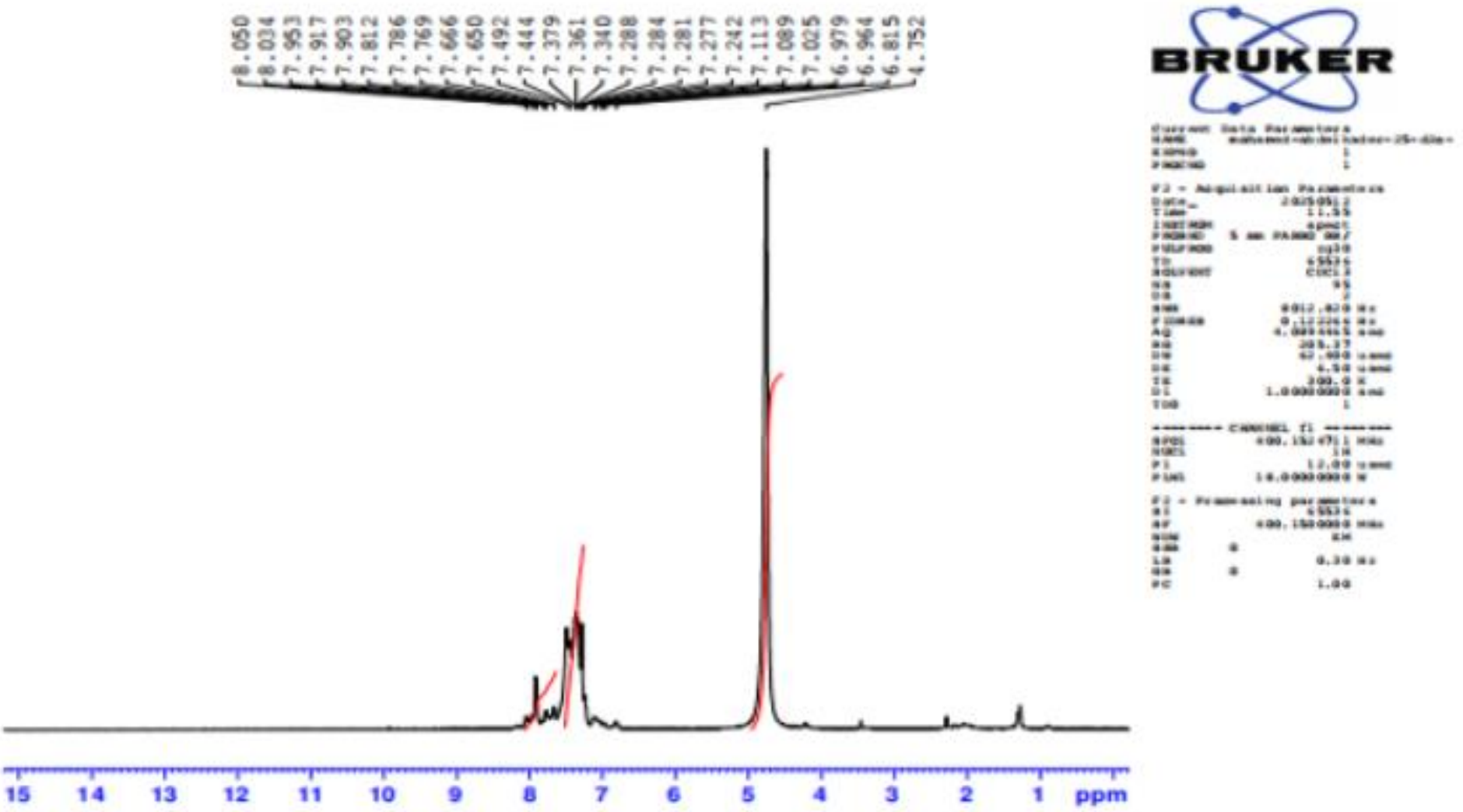

Fig 44: D_2O spectrum of compound (VI)

Chapter 5

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قدمت من قبل:

محمد عبد القادر الجيلاني

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

في الكيمياء

12 / أكتوبر/ 2025

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الملخص

تم تفاعل سلسلة من ثنائيات الامين الإيثان-2,1-ثنائي الامين، هيدرات الهيدرازين، 2,1- فينلين ثنائي الامين، 3,1- فينلين ثنائي الامين، 4,1- فينلين ثنائي الامين والبنزيدين مع البنزوين فى وجود مركب مالونونيتريل وحفاز البيريدين. أسفر التفاعل بشكل اساسي عن مشتقات ثنائي البيرول (I, III , IV و VI) ومع ذلك ، نتج عن تفاعل الايثان-1,2-ثناني الأمين ايضا المركب (II) كناتج أساسي.

علي النقيض من ذلك، لم تنتج تفاعلات هيدرات الهيدرازين و2,1- فينلين ثنائي الامين مركبات ثنائي البيرول بل تكون مشتق الهيدرازون (V) والكينوكسالين (VII) على التوالي.

بعد ذلك تم تفاعل مركبات ثنائي البيرول (I،IV) والمركب (II) مع أنهيدريد حمض الخليك للحصول على مشتقات الأميد المقابلة (VIII، IX، X). تم تنفيذ جميع عمليات التخليق تحت ظروف معتدلة باستخدام طرق مباشرة، وأعطت نتائج متوسطة النتائج. تم توصيف المركبات المُخلَّقة (I - X) باستخدام نقاط الانصهار، وكروماتوغرافيا الطبقة الرقيقة (TLC)، ومطياف والأشعة تحت الحمراء (IR)، والرنين المغناطيسي النووي للبروتون (^{1}H-NMR) (بما في ذالك تبادل D_2O) والرنين المغناطيسي النووي للكربون (^{13}C-NMR)، وتقنية APT. بالإضافة إلى ذلك، كشف تقييم النشاط المضاد للميكروبات عن ان بعض المركبات أظهرت تأثيرات مثبطة.