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Synthesis of some curcumin derivatives by reaction with ammonia derivatives and study its biological efficiency.

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

﴿ يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ
دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ ﴾

[المجادلة ،الآية 11]

صدق الله العظيم

الإهداء

إلى من غرسوا في نفسي حب العلم والعمل

أمي وأبي و إخوتي و زوجي وأبنائي

إلى من كانوا خير عون وسند ليّ

أصدقائي و أساتذتي

شكر وتقدير

فبتوفيق من الله تعالى تم اعداد هذا البحث فالحمد لله رب العالمين الذي هدانا لهذا وماكنا لنهتدي لولا ان هدانا الله فالشكرلله والصلاة والسلام على رسول الله.

ولان من لم يشكرالناس لم يشكرالله لايسعني في هذا المقام الا ان اتقدم ببالغ الشكروالتقدير لأستاذي الفاضل "أ.د.خيري محمد حمزة"على مابذله من جهد ومتابعة مدة الاشراف على الرسالة.

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كما أتقدم بجزيل الشكر والعرفان"لأسرتي"التي رافقتني ودعمتني في مسيرتي هذه و أتوجه بالشكرالى"كلية التربيه الزاويه"و"قسم الكيمياء جامعة طرابلس"على مدهم ليد العون لي.

كما لاانسى ان أتقدم بجزيل الشكر والعرفان لكل من ساهم بشكل أوباخر في إتمام هذا البحث.

والحمد لله..... و الله ولي التوفيق .

LIST OF CONTENTS

LIST OF CONTENTS		
Subject	**Page number**	
Acknowledgement	**I**	
List of contents	**III**	
List of tables	**VII**	
List of Figures	**VII**	
Abstract	**X**	
NO.	**CHAPTER ONE**	**page**
1.0	**Introduction**	**1**
1.1	**Background**	**1**
1.2	**Turmeric**	**2**
1.2.1	**Turmeric, general features**	**2**
1.2.2	**Constituents of turmeric**	**2**
1.2.3	**Botanical description of Curcuma longa L.**	**3**
1.2.4	**Chemical constituents of Curcuma longa L.rhizome**	**3**
1.2.5	**Chemical structure and properties of curcuminoids**	**4**
1.3	**Curcumin**	**6**
1.3.1	**HISTORY OF CURCUMIN**	**6**
1.3.2	**Chemical Properties of Curcumin**	**6**
1.3.3	**Biosynthesis**	**8**

1.3.4	**Synthetic derivatives of curcumin**	**10**
1.3.5	**Toxicity**	**15**
1.3.6	**Pharmacological activity of curcuminoids**	**15**
1.3.8	**Biological activities of curcumin**	**16**
1.4	**Schiff base derivatives of curcumin**	**20**
1.4.1	**Synthesis of Schiff Base**	**22**
1.4.2	**Mechanism of Schiff Base Formation**	**22**
1.4.3	**Biological Applications**	**23**
1.5	**Hydrazone derivatives of curcumin**	**24**
1.5.1	**Hydrazone**	**24**
1.6	**Oxime derivatives of curcumin**	**32**
1.7	**amino acids derivatives of curcumin**	**33**
	AIMS OF THE Study	**39**
NO.	**CHAPTER TWO**	**page**
2.0	**Characterization methods**	**41**
2.1	**General Experimental**	**42**

2.1.1	**Reaction of curcumin with various ammonia derivatives 89-100.**	**42**
2.1.2	**General Procedure**	**42**
2.1.3	**With aromatic amines**	**42**
2.1.4	**With Aliphatic Amines**	**46**
2.1.5	**With amino acids**	**49**
2.1.6	**with Hydrazine Derivatives**	**50**
2.1.7	**With Secondary Amines**	**51**
2.2	**Reaction of curcumin derivatives with alkyl halides**	**52**
2.2.1	**General Procedure**	**52**
2.3	**Antimicrobial activity**	**56**
	CHAPTER THREE	**page**
	RESULTS AND DISCUSSIONS	**55**
3.1	**Reaction of curcumin with ammonia derivatives**	**58**
3.1.1	**Reaction of curcumin with amines**	**59**

3.1.2	**Reaction of curcumin with amino acids**	**62**
3.1.3	**Reaction of curcumin with Hydrazine Derivatives**	**64**
3.1.4	**Reaction of curcumin derivatives With alkyl halides**	**66**
3.1.5	**Reaction of curcumin derivatives With Aromatic Secondary Amines**	**69**
3.2	**Biological results**	**72**
3.2.1	**Antimicrobial Activity of Synthesized Compounds**	**74**
3.2.2	**Antioxidant Activity**	**75**
	Conclusion	**77**
	Recommendations	**78**
	Reference	
	الملخص باللغة العربية	

LIST OF TABLES

No	Table	page
Table(1)	Chemical and physical characteristics of curcuminoids	5
Table(2)	The percentage yield and reaction time for the synthesis of curcumin analogues (89-100)	52
Table(3)	The percentage yield and reaction time for the synthesis of curcumin analogues(98 ,99)	54
Table(4)	Analytical data for the newly prepared compounds [89-100]	55
Table(5)	Table(5):Spectral data of compounds [89-100]	79-84
Table(6)	Antibacterial activity of the compounds by well diffusion method	72-74

LIST OF FIGURES

No	FIgure	page
Figure.1	Curcuma longa L.	3
Figure.2	Chemical structure of curcumin and its essential functional moieties.	7
Figure.3	Donation of H−atom from active methylene group	8
Figure.4	Schematic showing multiple biological activities of turmeric/curcumin.	16

Figure.5	**Percentage of DPPH inhibition for curcuminderivatives for Compounds at different concentrations[89] ,[90],[95].**	**75**
Figure.6	**Percentage of DPPH inhibition for curcumin derivatives for Compounds at different concentrations [98],[94],[91], [92].**	**76**
Figure.7	**Percentage of DPPH inhibition for curcumin derivatives for Compounds at different concentrations [93] ,[96],[100],[99].**	**76**
Figure. (8-51)	**The IR spectrum of compound, The ^{1}H NMR spectrum of compound, The ^{13}C-NMR spectrum of compound, The Mass spectrometry of compound.**	**85-140**

LIST OF SCHEMES

Scheme.1	**Biosynthetic pathways to curcuminoids in turmeric.Major(thick arrows) and Minor (thin and dotted arrows)**	**9**
Scheme.2	**Mechanistic explanation of the formation of Schiff base.**	**23**
Scheme.3	**Synthesis of curcumin phosphorylated derivatives**	**29**
Scheme.(4, 5,6,7).	**Mechanism of the reaction of curcumin with ammonia derivatives**	**64,66, 69,71.**

ABBREVIATION'S	
SYMBOLS	**NAME'S**
FTIR	**Fourier-transform infrared spectroscopy**
^{1}H-NMR	**Proton Nuclear Magnetic Resonance**
^{13}C-NMR	**Carbon-13 Nuclear Magnetic Resonance**
TMS	**Tetramethylsilane**
δ	**Chemical shift**
ppm	**Parts per million**
S	**Singlet**
d	**Doublet**
q	**Quartet**
m	**Multiplet**
MS	**Mass spectrum**
TLC	**Thin layer chromatography**
p.m	**Melting Point**
g	**Gram**
h	**Hrs**
DMSO	**Dimethyl sulfoxide**
%	**Percentage**
^{0}C	**Degree Celsius**
µg	**Microgram**

µM	**Micromole**
IC50	**Half maximal inhibitory concentration**
DMF	**Dimethylformamide**
DPPH	**2,2-diphenyl-1-picrylhydrazyl**
Ar	**Aromatic**
mL	**Milliliter**
nm	**Nanometer**
OTs	**Tosyl**
cm	**Centimeter**
CM	**Curcumin**

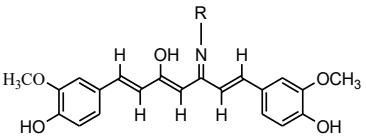
ABSTRACT

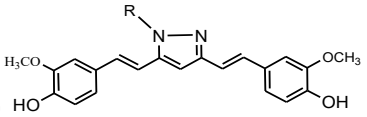
Synthesis, Characterization and Biological Activity Study of a New Class some curcumin derivatives by reaction with ammonia derivatives.

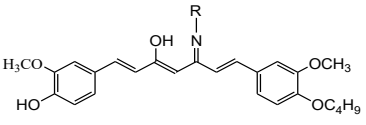
Abstract

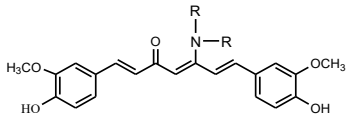
In summary, curcumin has desirable medicinal value with multiple therapeutic effects on cellular biochemical , physiological regulation ,infection suppression and immunomodulation . This had drawn great interest by the scientific community in gaining more understanding on the mechanistic basis of its therapeutic action. It is inevitable to perform such task without the knowledge on its structure-activity relationship . This chapter addressed this point by reviewing our current understanding on the structural details of curcumin and its analogs with relation to its observed biological activities.

This work supposes that chemical stability and biological activities may act as a template to design and synthesize new CM analogues which can serve better in therapeutics. a number of curcumin derivatives (89-100) were prepared Where it gave the expected results A, B, C, and D. Purified products were analyzed by various analytical and spectroscopic techniques, such as: melting point, TLC, ^{1}H- NMR, ^{13}C- NMR, IR, and mass spectroscopic . In all cases, results are consistent with the expected structures. All compounds were obtained in acceptable yield (54% to 87%).

(A) 

(B) 

(C) 

(D) 

The biological activity of these compounds was evaluated against four strains of bacteria at three different concentrations:100 ppm,200 ppm,300 ppm. The results showed remarkable effectiveness against bacteria . The antioxidant activity of these compounds was also evaluated by measuring their ability to reduce DPPH , The results showed a clear antioxidant capacity of these compounds.

CHAPTER ONE

INTRODUCTION

CHAPTER ONE

INTRODUCTION

1.1-Background

Islamic law emphasizes practices that maintain the human body in a robust and healthy state , free from illness and weakness. It is undeniable that Islam introduced an integrated approach to body strengthening, hygiene, prevention, and treatment because one of the Sharia's most important goals is self-preservation, which is the subject of assignment with integrity. All of this makes it possible for a person to fully embrace life with all of its vitality and activity and to master the worship of God Almighty[1,2].

Diseases and dangerous microorganisms have plagued humanity since ancient times. The discovery of antibacterial agents in the 20th century alleviated, at least partially, the burden of infectious diseases. Numerous antibacterial agents have been created since then and applied in clinical settings. But resistance to the antibacterial agents was also noted almost as rapidly as they were created[3].

The idea of "superbugs," which are immune to all antibacterial agents, is becoming increasingly plausible as the twenty-first century goes on, particularly since bacteria may now invade the entire human body[4,5]. Natural plant-based products and their synthetic and semi-synthetic counterparts have been noted to be crucial in the development of novel and improved chemotherapy medicines. Curcumin is a natural substance, and its semi-synthetic counterparts (Figure1.1)[6,7].

1.2 -Turmeric

1.2.1 -Turmeric, general features

Curcuma longa L., or turmeric, is a member of the Zingiberaceae family, which includes over 80 species of rhizomatous perennial herbs[8]. It is widely found in the tropics of Asia, Africa, and Australia[9]. It is commonly used as a spice and medicine, especially in Asian countries, where it is primarily grown in China and India. More than 2,000 years ago, turmeric was utilized in Asia for cooking, medicinal, cosmetics, and fabric dyes[10].

It wasn't until the 14th century A.D. that turmeric became widely accepted in European society." Turmeric is known by various names such as ukon , Indian saffron , kurkum, yellow ginger, and kunyit basah, reflecting its widespread cultural and culinary significance. Turmeric is used in basic food preparation in at least 20 countries, according to a conservative estimate by Ravindran[11]. Because of its economic significance worldwide," daily [12].C.longa has been thoroughly researched[13]. Nepal and other oriental countries[14] employ its rectangular, ovate, pyriform, and frequently short-branched rhizomes as a home medicine. With a slender stem, this perennial herbaceous plant can grow up to 1 m in height (Figure 1).

Rhizomes are cylindrical, aromatic, yellow-to-orange, and heavily branched[15]. Early in 1900, Lampe and Milobedzka[16] discovered curcumin, the main active ingredient that gives plants their yellow hue. Since ancient times, turmeric has been known to have a "magic touch" in treating a wide range of illnesses because of its diverse range of pharmacological properties[17].

1.2.2 - Constituents of turmeric

Curcumin, turmeric oil, and total extracts of turmeric are all recognized for their therapeutic qualities. However, these components' and their constituents' biological activity vary greatly[18]. According to reports, the ratios of curcuminoids are crucial for turmeric's maximum bioprotective effects. Curcuminoids[19] are found in Curcuma longa's yellow-pigmented portion. In turmeric, curcuminoids typically vary from 3 to 5%. The three main components of curcuma longa extracts are curcumin, demethoxycurcumin, and bisdemethoxy-curcumin[20].

1.2.3 - Botanical description of Curcuma longa L.

Scientific name: Curcuma longa L. **Family name**: Zingiberaceae.

Genus : Curcuma. **Synonym**: Curcuma domestica Val.

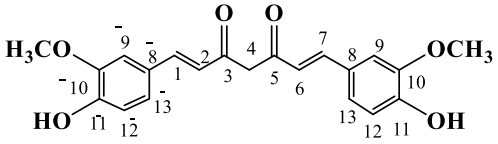
Figure .1: Curcuma longa L.

1.2.4 -Chemical constituents of Curcuma longa L. rhizome.

Numerous substances were extracted from the rhizomes of C. longa for the phytochemical investigations, including fatty acids, monoterpenoids, steroids, sesquiterpenoids, diarylpentanoids, and diarylheptanoids [21, 22].

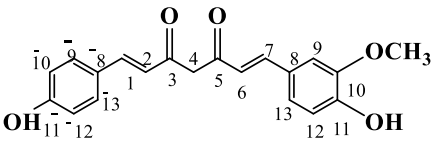
1.2.5-Chemical structure and properties of curcuminoids

A yellow-orange powder, curcumin is insoluble in water, soluble in acetone, dioxane, ethanol, and dimethyl sulfoxide[23], and only weakly soluble in ether. In commercial curcuminoid, curcumin I makes up 77%, curcumin II makes up 17%, and curcumin III makes up 3%. As seen below, Curcumin is least soluble in aqueous solution in the pH range of 1 to 6, but it is most stable at these values .The chemical and physical properties of curcuminoids are as summarized in Table (1) [24] .



Curcumin I

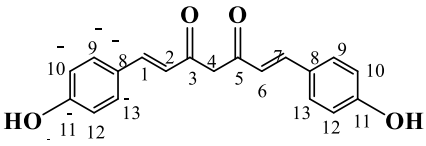
[1]



Curcumin II

Demethoxycurcumin

[2]



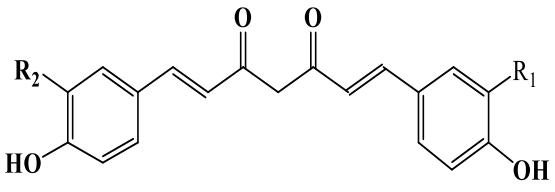
Curcumin III

Bis-demethoxycurcumin

[3]

Table (1): Chemical and physical characteristics of curcuminoids.

Particulars	Curcuminoids		
	Cu I	Cu II	Cu III
Structure	$R_1 = R_2 = OCH_3$	$R_1 = OCH_3$, $R_2 = H$	$R_1 = R_2 = H$
IUPAC name	1,7-bis- 4-hydroxy-3-methoxyphenyl hepta- 1, 6 - diene – 3, 5-dione.	1-4- hydroxy -3-methoxyphenyl-7- 4-hydroxyphenyl-hepta-1,6-diene - 3,5 -dione.	1,7- bis- 4 hydroxy phenyl-hepta-1,6-diene-3,5 -dione .
Chemical formula	$C_{21}H_{20}O_6$	$C_{20}H_{18}O_5$	$C_{19}H_{16}O_4$
Molecular Weight (g / mol)	368	338	308
PK a	8.54	9.30	10.69
Melting Point(ºC)	183.0-186.0	172.5-174.5	224.0
Solubility in Alcohol or Acetone	Soluble	Soluble	Soluble
Solubility in hexane or Ether	Insoluble	Insoluble	Insoluble



Cu I , $R_1 = R_2 = OCH_3$

Cu II , $R_1 = OCH_3$, $R_2 = H$

Cu III , $R_1 = R_2 = H$

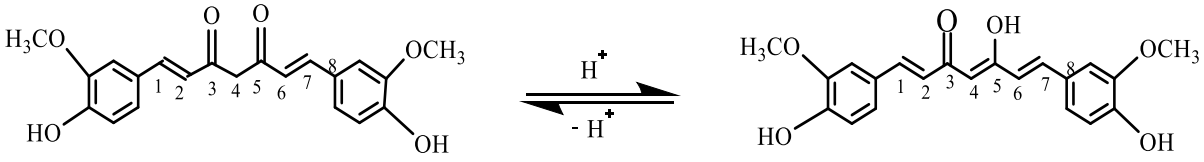
1.3 - Curcumin

1.3.1 -History of Curcumin

Henri Auguste Vogel and Pierre Joseph Pelletier documented the first isolation of a "yellow coloring-matter" from the rhizomes of turmeric in 1815, leading to the naming of curcumin. Eventually, it was discovered to be a blend of turmeric oil and resin. Milobedzka and Lampe (1910) claimed that curcumin's chemical structure was diferuloylmethane[25]. The chemical was synthesized later in 1913 by the same group (Figure 2).

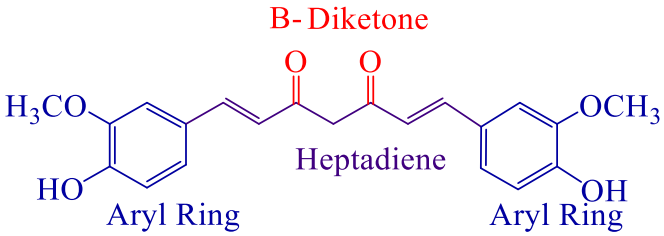
1.3.2 -Chemical Properties of Curcumin

The polyphenol molecule curcumin , sometimes called diferuloylmethane ($C_{21}H_{20}O_6$), has a low molecular mass (368.37 g/mol) and a melting point of roughly 183°C (Table1)[26]. As the first diarylheptanoid ever discovered, it belongs to the class of diarylheptanoid compounds.A seven-carbon linker and three main functional groups are included in curcumin: an aromatic O-methoxy-phenolic group and an α,β-unsaturated β-diketone moiety (Figure 2). Two α,β-unsaturated carbonyl groups bind the aromatic ring systems, which are phenols. It is a diketone tautomer that shows up in water in keto form and in enolic form in organic solvents. Diketones are easily deprotonated to create enolates and form stable enols.The chemical structures of curcumin [I] in its keto and enol forms are illustrated in equation (1). The carbonyl group that is α,β-unsaturated is a good Michael acceptor and is added nucleophilically. Although curcumin is hydrophobic, it dissolves well in organic solvents[27] but poorly in water.



[1] **Keto form** **[1]** **Enol form**

Eq (1)



[1]

Figure 2: Chemical structure of curcumin and its essential functional moieties.

The literature has long known that curcumin exists in a stable crystalline form. A diketone that is stable in the enol state and readily deprotonated to the keto state is one of the several tautomeric states of curcumin. In contrast to the stable form[28], two novel metastable polymorphs of curcumin (enol form) have recently been reported to have greater solubility.Curcumin's keto enol tautomerism results from the presence of carbonyl groups on heptadiene's carbon numbers three and five, as indicated by equation [1]. The carbony double bond conjugates with the enol double bond and a pi orbital system, stabilizing the enol tautomer in relation to the keto tautomer i.e. phenyl group in conjugation with the conjugated C=C double bonds .

The enol tautomer is characterized by the formation of strong intramolecular hydrogen bonding compared to intermolecular hydrogen bonding which exists in the keto form[29,30] .

a -Role of methylene group in curcumin.

Curcumin's keto form (1) has an active methylene group in the heptadienone bond that connects the two methoxyphenol rings. By donating an H-atom from the methylene[31], Jovanovic et al. demonstrated that curcumin had antioxidant properties only when it is in the keto form.

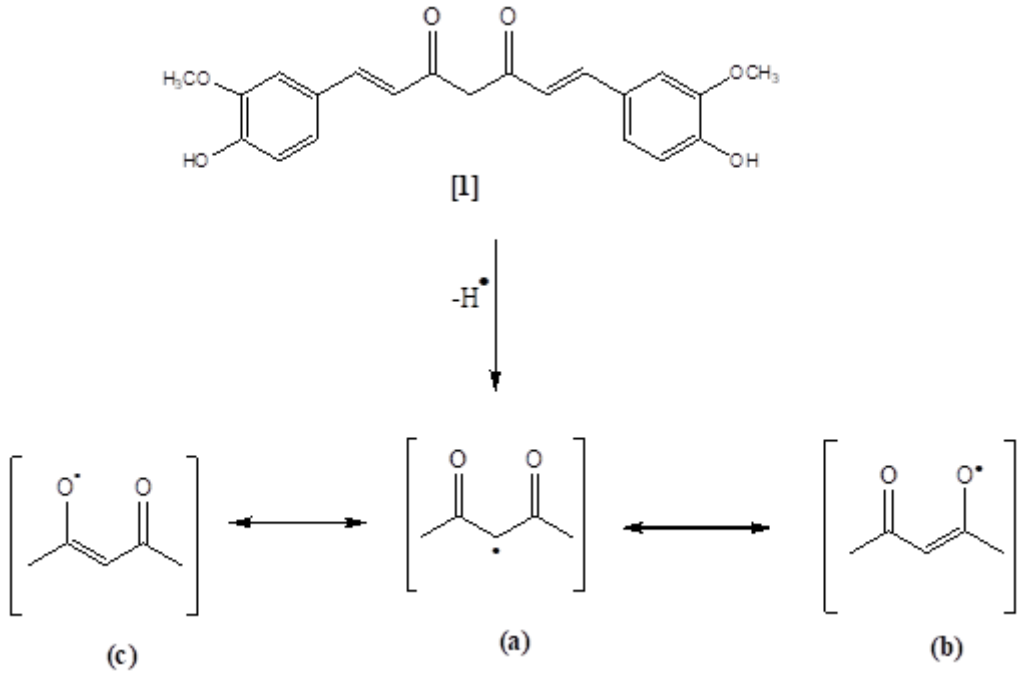
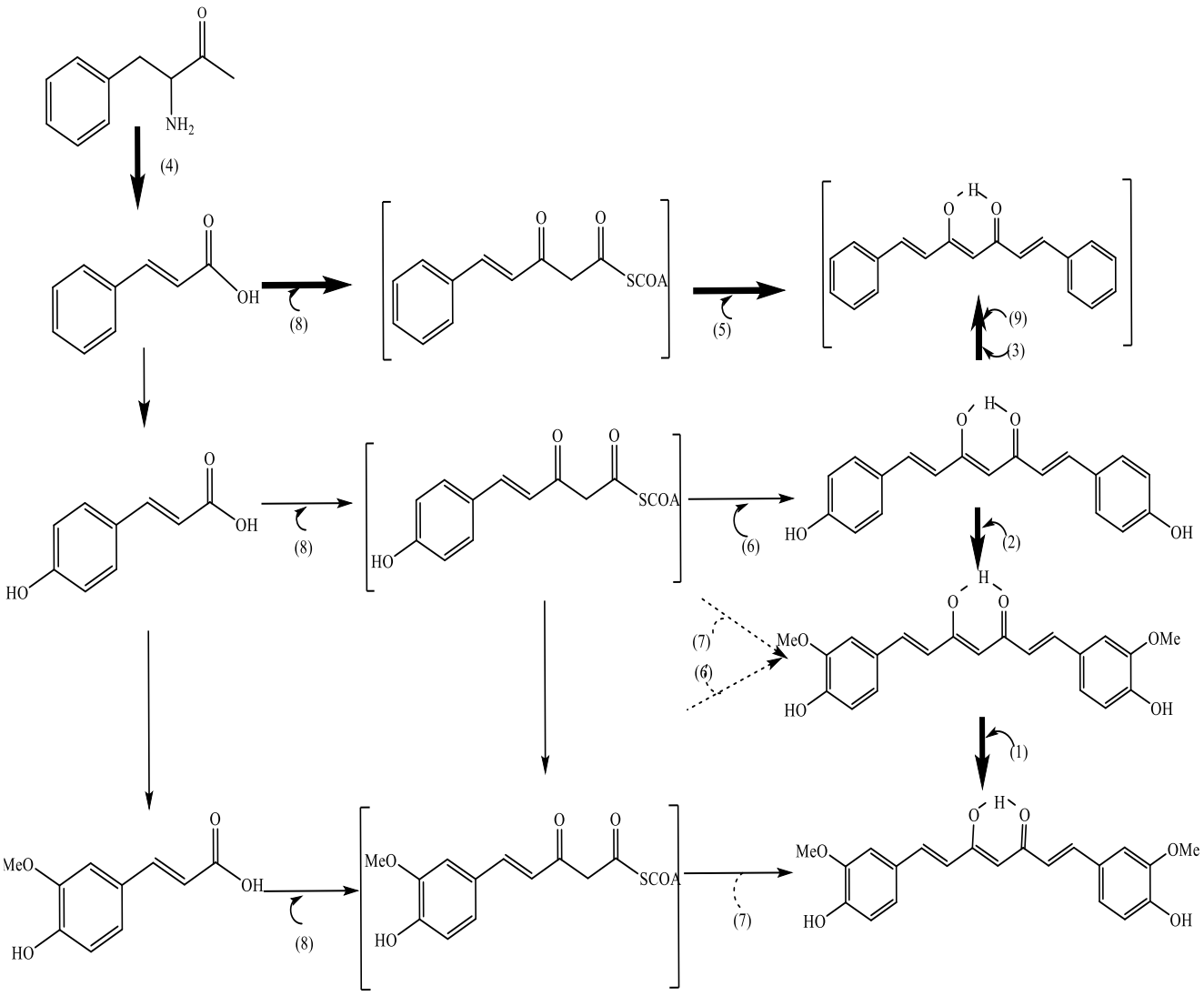


Figure 3 : Donation of H-atom from active methylene group

1.33- Biosynthesis.

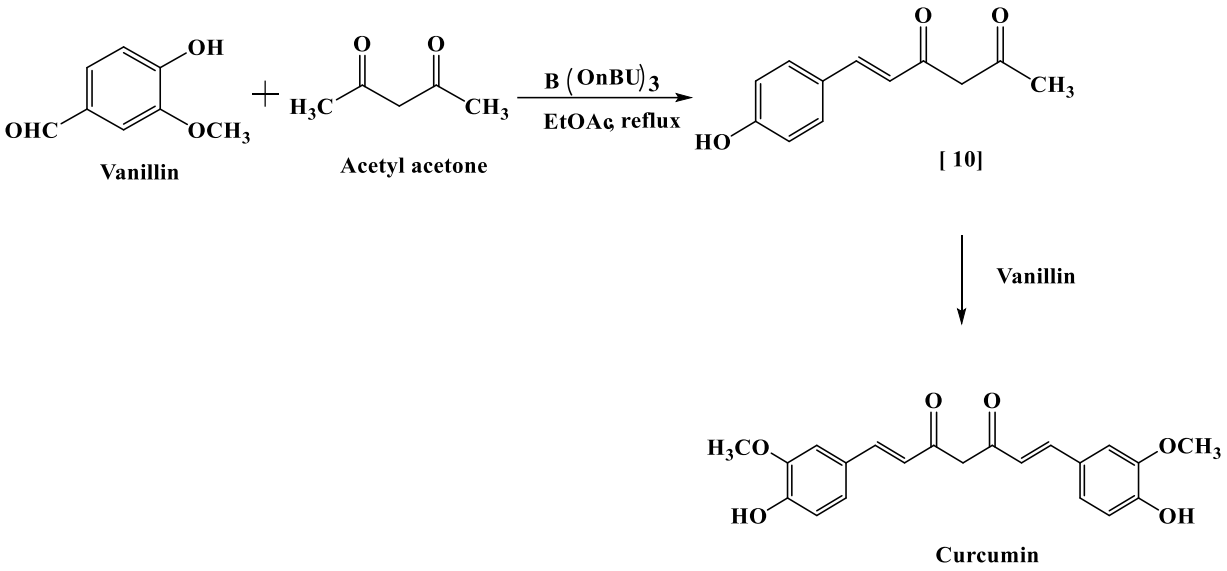
Beginning with cinnamic acid, which is produced from phenylalanine, Roughley and Whiting postulated two synthetic methods in 1973. The hydroxy and methoxy functional groups on the aromatic rings were added after the curcuminoid scaffold was formed, and two cinnamonoyl CoAs and one malonyl CoA were utilized in the production of the curcuminoids as summarized in (Scheme.1)[32].



Scheme.1: Biosynthetic pathways to curcuminoids in turmeric.Major(thick arrows) and Minor (thin and dotted arrows)

(4) phenylalanine; (5), cinnamic acid; (6), p-coumaric acid; (7), ferulic acid;(8), malonic acid;(9), putative curcuminoid skeleton intermediate: bisdeshydroxy bisdes methoxycurcumin (BDH BDMC) ; (3), bisdesmethoxycurcumin (BDMC) ; (2), desmethoxycurcumin (DMC) ; (1), curcumin.

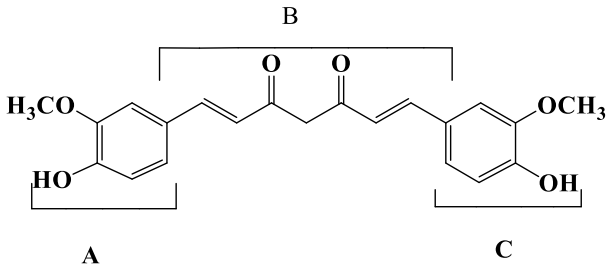
Synthesis of curcumin by can also be via the condensation of acetyl acetone with two equivalent of aromatic aldehyde (vanillin) as summarized in **(**equation 2) [33] .



Eq (2)

1.3.4- Synthetic derivatives of curcumin

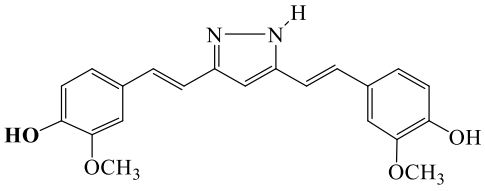
Several derivatives of curcumin [1] have been synthesized since its diverse biological functions were first reported[34]. We describe here the alteration of the di keto group in the current study. The key structural areas of curcumin's pharmacophoric properties [1] are depicted in the generalized form below. Curcumin's molecular structure [1] is composed of three primary regions: a conjugated diketone (B)[35,36] connects two substituted aromatic rings (A and C). The produced derivatives exhibit molecular modifications in one or more of these region .



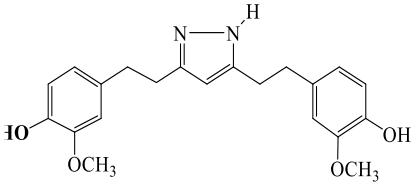
[1]

A - Derivatization at keto-enolic position of curcumin

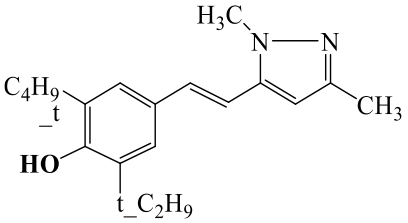
In 1991, Flynn et al. from the Warner-Lambert Company's Parke-Davis Pharmaceutical Research Division reported the first synthesis of the N-unsubstituted pyrazole derived from curcumin [1]. It was tested as a 5-lipoxygenase and cyclooxygenase inhibitor in combination with the hemicurcuminoid pyrazoles, as indicated below the series from pyrazoles derived from curcumin and curcuminoids[37].



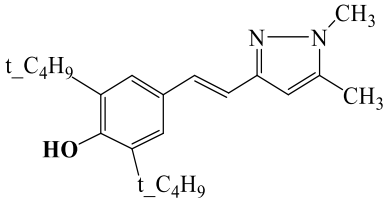
[11]



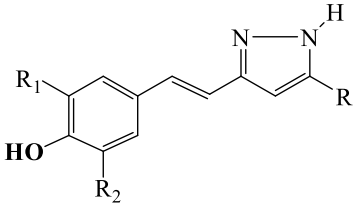
[12]



[13]



[14]

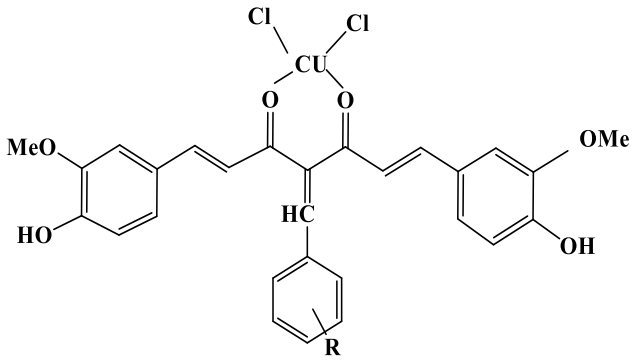


[15]

[16], $R_1 = OCH_3$, R_2 = H, R = CO_2H **[18] , $R_1 = R_2 = i\text{-}C_3H_7$, R = CH_3** **[20] , R1 = R2 = R = CH3**

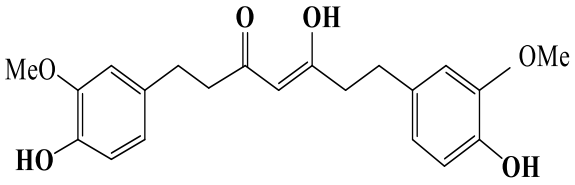
[17], $R_1 = R_2 = OCH_3$, R = CH_3 **[19] , $R_1 = R_2 = t\text{-}C_4H_9$, R = CH_3**

(Zambre, et al., 2006)[38]. reported the synthesis of Copper(II) conjugates (Fig 7) of Curcumin [21] and its derivatives are synthesize structurally characterized and evaluated for their potential of inhibiting.



[21]

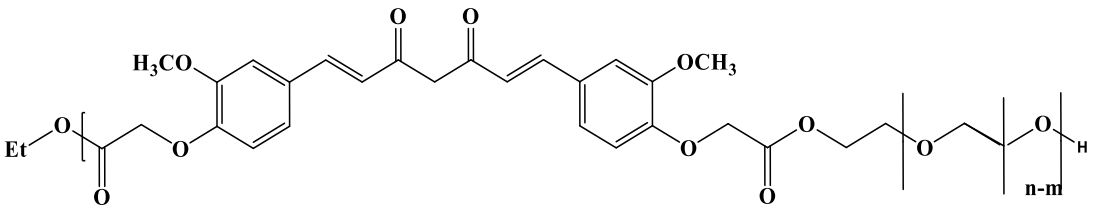
Selective hydrogenation of α,β-unsaturated olefinic bonds in curcumin, affords tetrahydrocurcumin [22], a colorless derivative of curcumin Pattekhan, *et al*. 2005 .



[22]

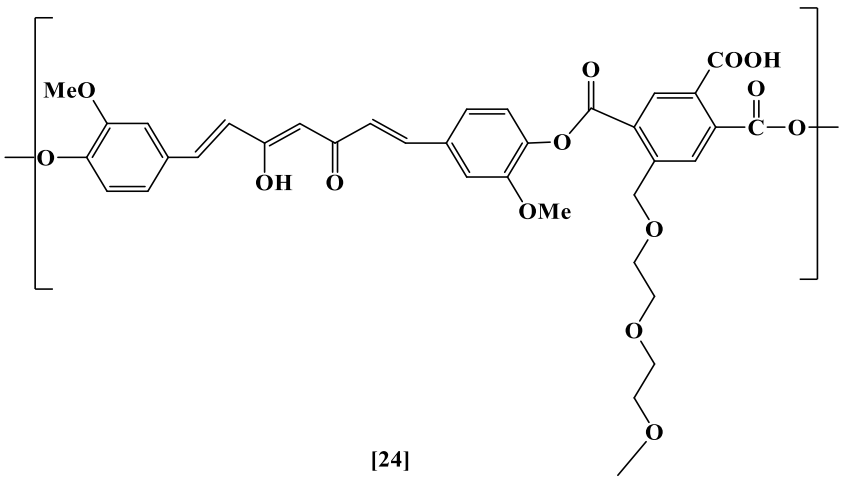
B- Derivatizations at phenolic position of curcumin

Synthesis of polymerization of curcumin diester with poly (ethylene glycol) and copolymer curcumin were carried out by Pandey [23] as (anticancer agent).



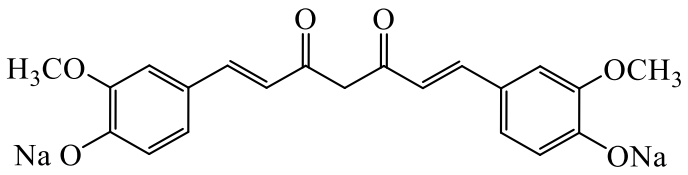
[23]

Tang have made high molecular weight curcumin polymers (polycurcumins) by condensation polymerization of curcumin [24] as (anticancer agent[39]).



[24]

Mukophadhyay et al[40]. demonstrated the activity of curcumin anti-inflammatory and other semi-synthetic analogues (sodium curcuminate [25], diacetyl curcumin, triethyl curcumin and tetrahydro curcumin) however the sodium curcuminate was the most potent analogue and was more water-soluble than curcumin.

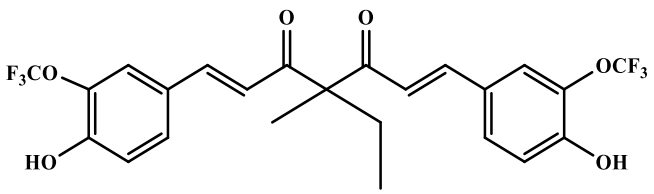


[25]

C - Modifications of the methoxy phenolic units

D.Yanagisawa *et al*[41]. described the synthesis of a new curcumin derivative with fixed keto forms, 1,7-bis(4′-hydroxy-3′-trifluoromethoxy) phenyl-4-ethyl-4-methyl-1,6-heptadiene-3,5-dione[26]. The findings suggested that the keto forms of curcumin derivatives have a lot of promise as a medicinal drug and imaging probe that targets Aβ oligomers.

Non-fibrillar soluble Aβ oligomers are especially hazardous, and β-amyloid (Aβ) aggregates build up in the brain early in the course of Alzheimer's disease (AD). In order to create imaging probes and therapeutic medicines that target Aβ oligomers in the brain, the keto form of curcumin derivatives, such as compound [26], may be a suitable seed chemical.



[26]

1.3.5 -Toxicity

When curcumin was administered orally, it was found to be safe in both animal and human models of toxicity. Curcumin has been demonstrated to be safe, even at relatively high doses, in studies involving rats, monkeys, and guinea pigs. Nonetheless, a few studies noted minor adverse effects, such as dermatitis, diarrhea, and headache[42].

1.3.6 - Pharmacological activity of curcuminoids

The finest source of many medications may be medicinal herbs. Many scholars throughout the world have looked into medicinal herbs because of their many therapeutic qualities. Biochemically speaking, plant-based medications might be far more suitable than synthetic ones. In contemporary medicine, numerous investigations have been carried out to determine the possible impacts of different therapeutic herb extracts that are essential to both human and animal health. Turmeric is a highly researched medicinal herb that contains several phytochemicals[43].

1.3.7 - Therapeutic uses of Curcuma longa

Curcuma longa was used for therapeutic purposes as early as 1748. Curcumin was extracted from Curcuma longa rhizomes by Vogel and Pelletier in the century that followed. In 1949, an article about curcumin's antibacterial properties was published in "Nature."[44]. Adding heteroaryl or long chain substituents to curcumin analogs may increase their antibacterial activity, according to a number of studies. Because they have been shown to provide a broad range of pharmacological effects, curcuminoids are the most bioactive ingredients. It has been demonstrated that curcumin has stronger biological effects than demethoxy curcumin and bisdemethoxy curcumin .

Srimal and Dhawan (1973)[45] have investigated the pharmacological effects of curcumin as an anti-inflammatory agent According to this study's authors, the substance worked effectively in both acute and chronic inflammatory models. Huang and colleagues (1992) noted that curcumin was less harmful than the reference medication. Huang studied the inhibitory effects of curcumin on vascular smooth muscle cell and blood mononuclear cell growth.

Curcumin was shown to negatively affect blood mononuclear cells' responses to the alloantigen MLR[46] and the mi togen PHA. Curcumin may be used clinically to treat transplant atherosclerosis, according to the researchers. Demethoxy curcumin , bisdemethoxy curcumin, and diacethyl curcumin are the three derivatives of curcumin that have been examined for their antioxidative qualities by Unnikrishnan and Rao (1995). The authors proved that these compounds safeguard hemoglobin against oxidation[47].

1.3.8 -Biological activities of curcumin

Curcumin's diverse range of biological activities, including its anti-inflammatory, antiviral, antifungal, antioxidant, and anti-atherosclerotic properties, have been documented in over 4,000 studies[48](Figure 4). The following conditions have been demonstrated to benefit with curcumin: lung fibrosis, inflammatory bowel disease, nephrotoxicity, arthritis, psoriasis, diabetes, cardiovascular disease, multiple sclerosis, and allergies. Curcumin has a very complicated structure, but it also possesses several unique biochemical properties[49].

The diketone moiety of curcumin appears to play a crucial role in its anticancer activity . Curcumin is regarded as one possible perfect anti-cancer medication in chemotherapy activities due to its low molecular weight, hypotoxicity, and distinct biological action. Aggarwal and associates[50] (2003). Numerous research teams have therefore regarded curcumin as an excellent lead molecule for creating a wide range of analogs as possible novel anticancer medications.

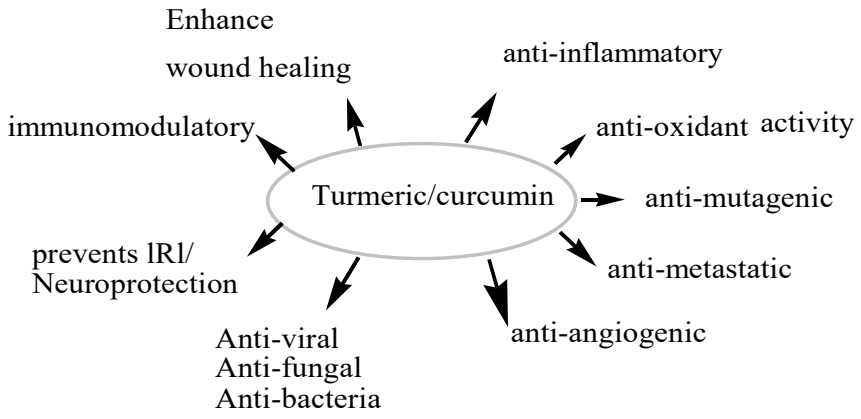


Figure .4: Schematic showing multiple biological activities of turmeric/curcumin.

According to Aggarwal and Harikumar[51], curcumin may be used to treat a number of illnesses, including rheumatoid arthritis, Alzheimer's disease, metabolic syndrome, neurodegenerative diseases, and cardiovascular disorders.

Antioxidant effects

Multiple disorders, such as cardiac ischemia, hemorrhage and shock, cerebral ischemia, neuronal cell injury, hypoxia, and cancer, are largely caused by oxidative stress. The antioxidant activity of curcumin is robust and on par with that of vitamin C and vitamin E[52].

The phenolic protons and methylene group of curcumin[53] are responsible for its antioxidant qualities and actions on free radicals . Curcumin donates protons to reactive oxygen and nitrogen species , neutralizing them through electron transfer and hydrogen atom abstraction[54], thereby acting as an effective free radical scavenger.

and curcumin may be a more potent free radical scavenger than vitamin E. It does this by promoting the body's natural production of glutathione (GSH), an antioxidant that shields cells and tissues from damage caused by free radicals. Experiments on animals and cells in vitro further demonstrate that curcumin can increase the activity of superoxidase dismutase (SOD) and raise serum and cell GSH levels. Once blood flow has been restored, these ischemic reperfusion tissues frequently generate too many free radicals, which lead to oxidative stress and damage. By scavenging free radicals, curcumin administration can lessen the harm that these toxins do to tissue cells (Dinkova-Kostova and Talalay, 2008)[55,56].

Antimicrobial effects

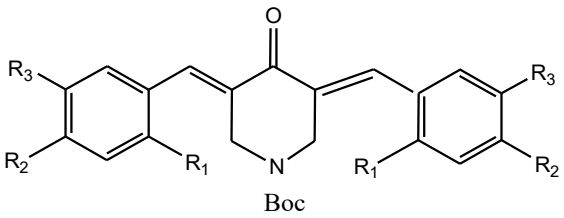
This compound's numerous biological and pharmacological characteristics, such as its antioxidant and anticancer effects, have drawn the attention of numerous contemporary biochemical studies. Sadly, its low bioavailability and limited therapeutic use are caused by its poor water solubility and insufficient absorption in vivo[57,58] .

Curcumin's deficiencies along with its structural simplicity and nontoxicity made it a suitable lead ingredient for the creation of possible antioxidant and cancer chemopreventive agents[59]. A lot of interest has been shown in amino acid schiff bases and their derivatives due to their high biological activity and biosolubility [60].

Curcumin analogs and Cancer

Kuttan and colleagues originally reported on curcumin's anti-cancer properties in humans in 1987.

Ocasio-Malavé et al[61], revealed in a recent study that Boc-piperidone chalcones have the potential to be innovative cytotoxic agents against highly metastatic cancer cells. Compounds [27,28,29] shown cytotoxicity towards highly metastatic prostate cancer[62] while also inducing apoptosis.



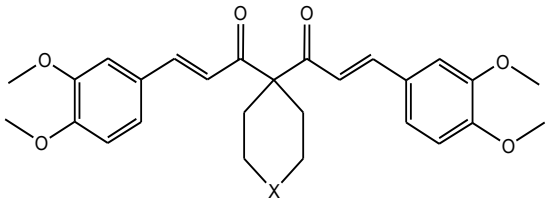
[27], a:R_1=R_2=F,R_3=OH

[28], b:R_1=CH_3,R_2=R3=H

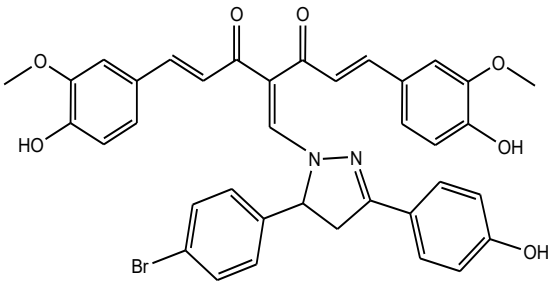
[29] c:R_1=R_3=OCH_3,R1=H

pancreatic cancer cells' net cell proliferation was decreased by compound [33], a synthetic curcumin analog. It is a new mono-carbonyl curcumin analog that exhibits exceptional cytotoxicity against a number of cancer cell lines [32].

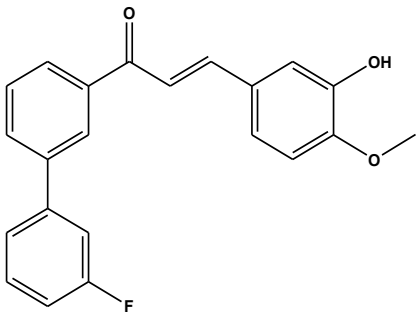
By causing cancer cells to undergo apoptosis, the compound's proapoptotic activity [31] has demonstrated exceptional results. Cytotoxic curcumin analogs' structures are displayed [63, 64].



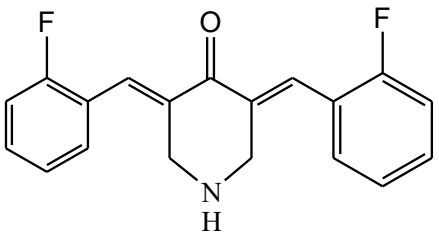
[30], X=CH_2,O



[31]



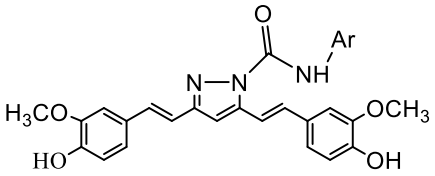
[32]



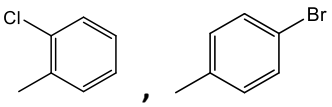
[33]

Antimalarial activity

Malaria is a potentially fatal illness that is spread by vector-infected Anopheles mosquitoes from five different parasite species. An estimated 3.4 billion individuals are at risk of contracting malaria, and the disease is endemic in 107 countries and territories. The schizonticidal and parasiticidal activity of the curcumin analogues was reported by Parveen et al. (2013), with an IC50 ranging from 1.48 to 23.09 μM[65].



[34],[35] Ar =



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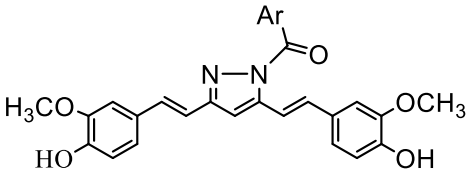
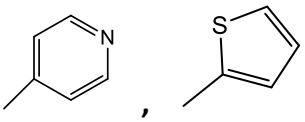


[36] ,[37] Ar =



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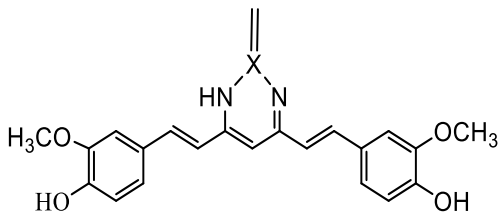
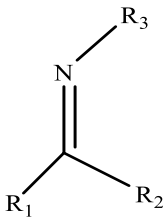


[38],[39] X = O , S

1.4 - Schiff base derivatives of curcumin

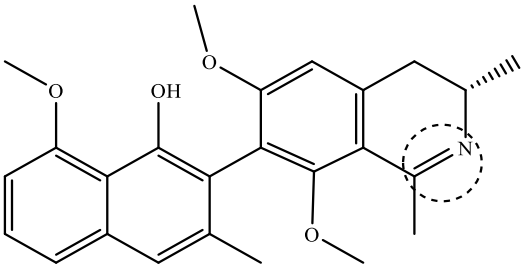
The first person to create Schiff's base using azeotropic distillation was Hugo Schiff in 1864, utilizing primary amine and aldehyde or ketone . The general structure for a Schiff base as shown below[66] .

As stated below, Schiff bases are classified as chemical compounds (imines) that have a hydrocarbyl group on the nitrogen atom, in accordance with the IUPAC recommendation. Anils, imines, and azomethine are other names for these compounds[67].



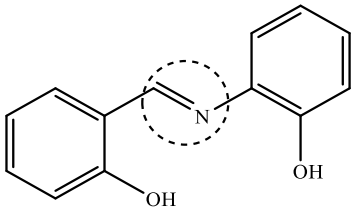
where R_1, R_2 and R_3 are alkyl or (more often) aryl groups. R_1 or/and R_2 may also be hydrogen atoms.

Schiff bases are currently the subject of much research because of their ease of synthesis, vast diversity of color configurations, and increased interest in the field of thermochromic materials[68]. Schiff bases with aryl substituents are significantly more stable and easier to manufacture than those with alkyl substituents, which are comparatively unstable. These compounds [34] and [41] are examples of bioactive Schiff bases, where the azomethine group (-C=N) is present in every molecular structure. The azomethine group in Schiff base compounds plays a significant role in many areas[69].



[40]

Ancistrocladidine 1
(Antibacterial activity)
Natural product compound

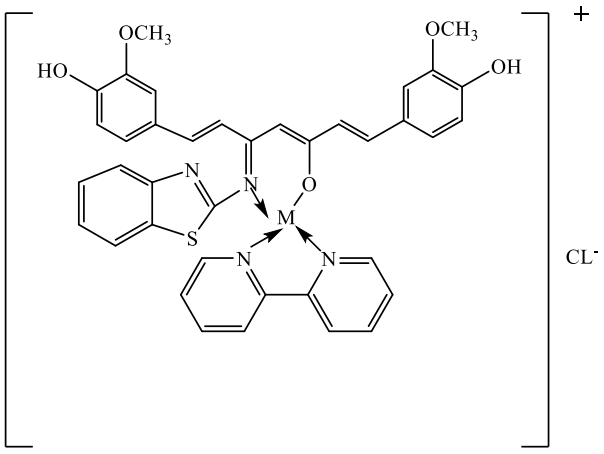


[41]

N-(Salicylidene)-2hydroxyaniline(4)
(antimalarial activity)
Non-natural compound

Metal complex of curcumin

In 2017, Raman et al[70]. explained how to create a Schiff base ligand with a 2-aminobenzothizole moiety and its metal complexes using 2,2 ⁄-bipyridine as a co-ligand, as demonstrated in the molecule [42].

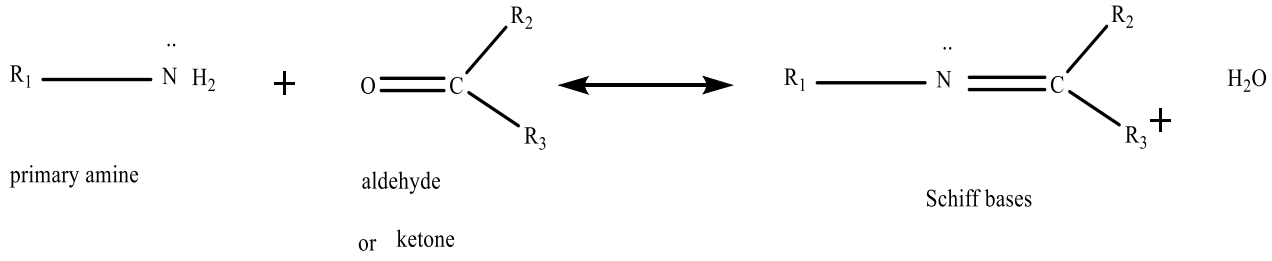


M =CU(II) , Ni(II), and Zn(II)

[42]

1.4 .1 - Synthesis of Schiff Base.

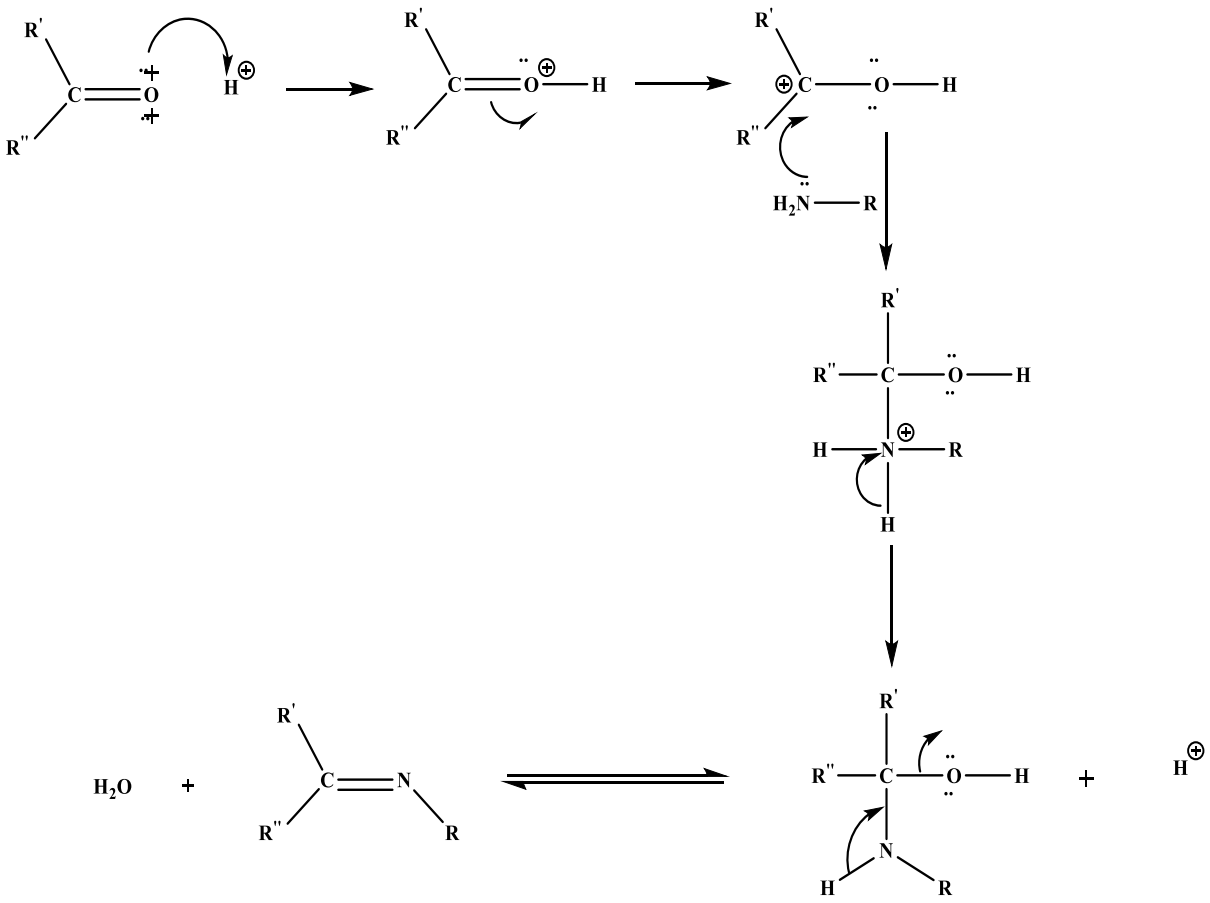
These compounds can be produced by a one-step condensation process, as described in equation (3), between a primary amine and a carbonyl compound (aldehyde and ketones) under standard laboratory conditions[71]. Typical Schiff bases are solid crystals[72].Schiff bases can be employed as ligands to prepare metal complexes with a variety of distinct structures or as intermediaries in the synthesis of amino acids.



Eq[3]

1.4.2 - Mechanism of Schiff Base Formation

An amine is added nucleophilically , and water is then removed, forming the double bond (imine) C=N between the ketone or aldehyde and the main amine. Addition followed by elimination is the sequence of two types of reactions that actually make up the Schiff base formation. For many Schiff bases, aqueous acid or base can hydrolyze them back to their aldehydes, ketones, and amines[73,74].



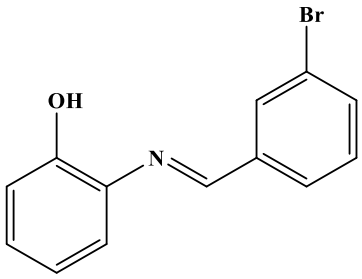
Scheme .2: Mechanistic explanation of the formation of Schiff base.

1.4.3- Biological Applications.

Antimicrobial agents, antifungal activity, antibacterial, antiviral, anticancer, and enzyme inhibition are among the potential properties of schiff bases and their derivatives [75,76,77]. and have been instrumental in several excellent discoveries of novel treatments in this field [78].

Antioxidan

Schiff bases' antioxidant and free radical scavenging properties are demonstrated by a variety of instances. A compound that has been described in the literature as a strong antioxidant agent[79] is [43].



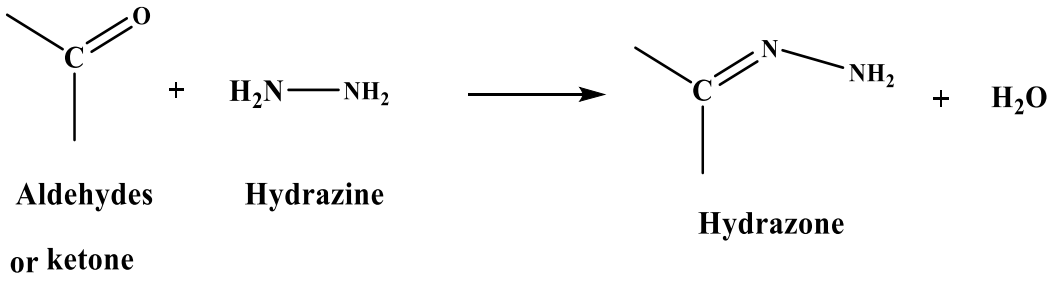
[43]

In order to counteract excessive levels of reactive oxygen species, the human body employs an antioxidant system that includes enzymes like superoxide dismutases , glutathione peroxidases, and catalases as well as a variety of non-enzymatic small molecules that are widely present in the biological system, including glutathione, ascorbic acid, α-tocopherol, β- caroten and selenium [80].

1.5.Hydrazone derivatives of curcumin

1.5.1 Hydrazone

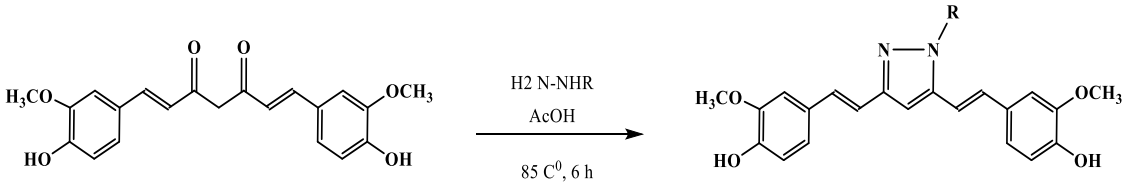
A type of Schiff bases with the formula $C{=}NNH_2$ is hydrazones, which are created when aldehydes or ketones react with hydrazine. Aldehydes and ketones can react with hydrazine (H_2NNH_2) to produce a hydrazone derivative. equation (4) describes hydrazone creation, which is a variant of the imine forming reaction that was previously studied[81].



[44]

Eq . 4

J. R. Fuchs et al[82]. prepared the Compounds [11] and [45] were obtained by treating curcumin with hydrazine and N-methylhydrazine in acetic acid, respectively. as illustrated in equation (5)

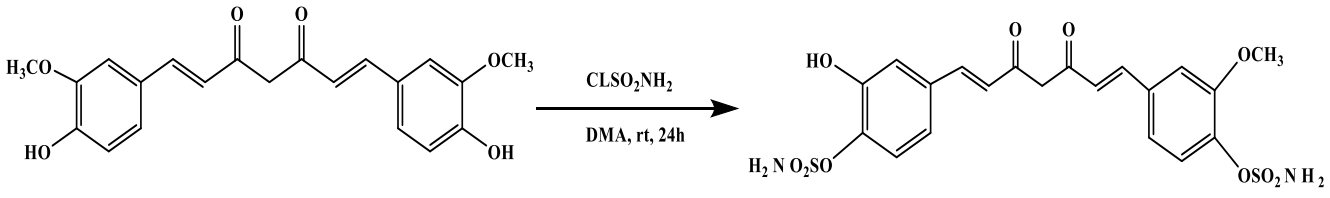


[11], R = H

[45], R = CH 3

Eq.5

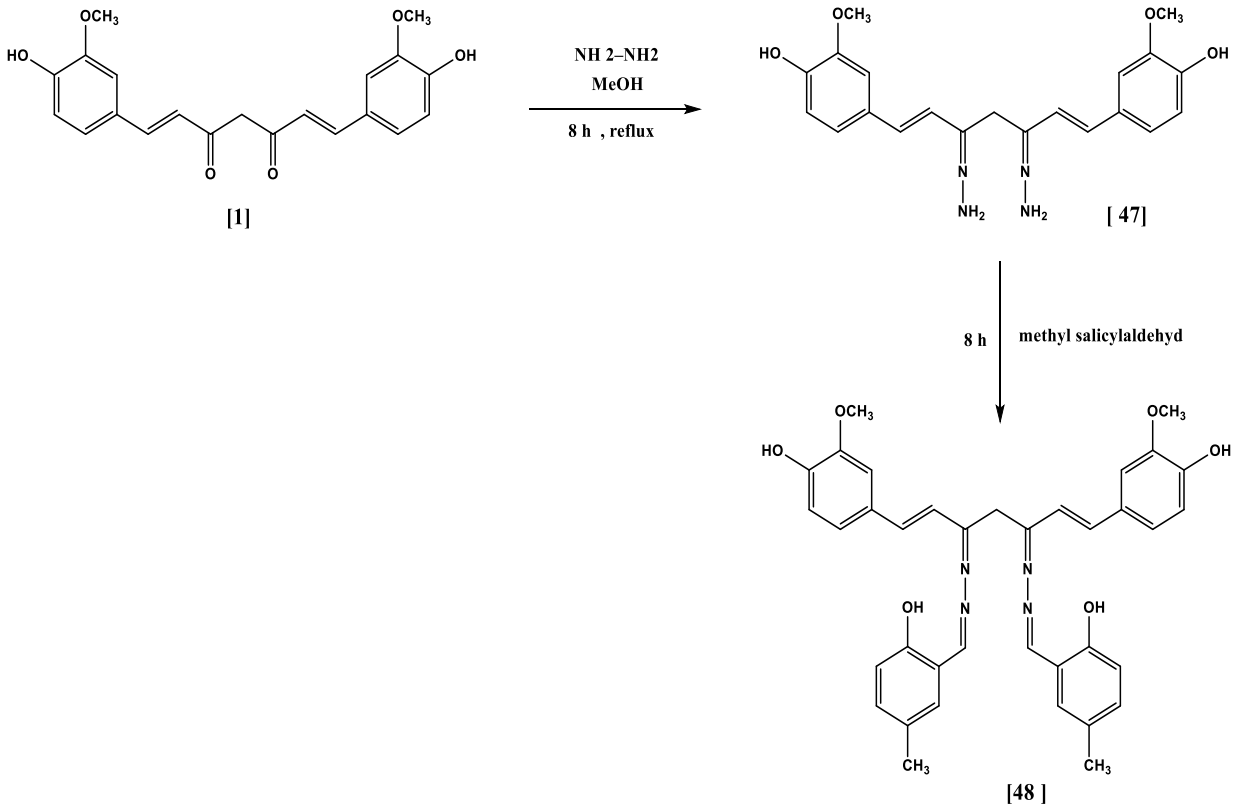
Additionally, a well-established method was used to synthesize sulfamoylated curcumin analogues by employing chlorosulfonamide ($CLSO_2NH_2$) in dimethyl acetamide (DMA) at room temperature for 24 hours. In equation (6), the synthesis of compound [46] [83] from curcumin is displayed.



[1] **[46]**

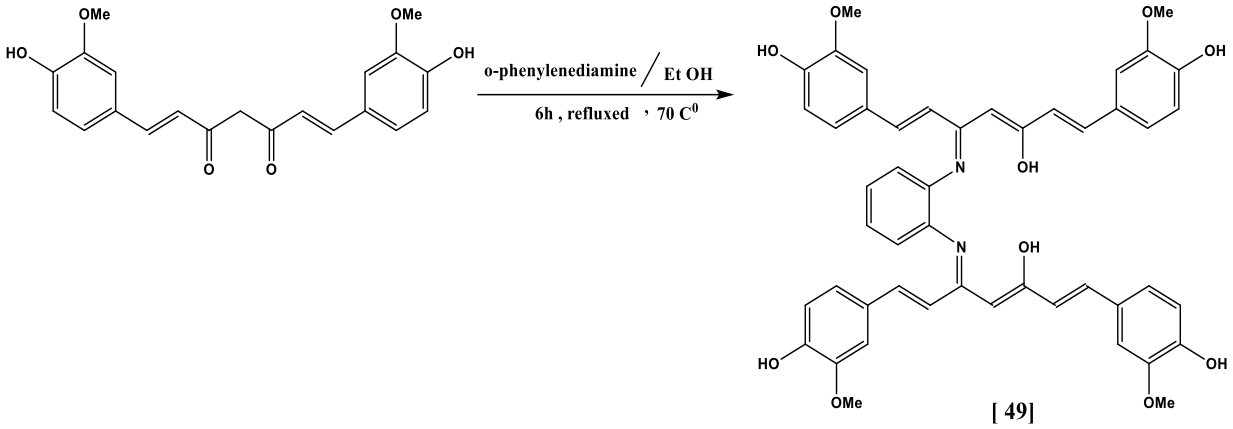
Eq.6

Venkatesh et al[84]. synthesized the curcumin derivative [47] by reacting curcumin with hydrazine hydrate in a methanol solution before it condensed. Subsequent condensation of derivative [47] with methyl salicylaldehyde produced the Schiff base ligand [48]. according to the equation that follows (7).



Eq.7

C.C.Christopher et al[85] . equation (8) demonstrates the one-step synthesis of curcumino-2 phenylenediimine by reacting curcumin (I) with o-phenylenediamin in ethanol and refluxing for six hours at 70 ℃ .

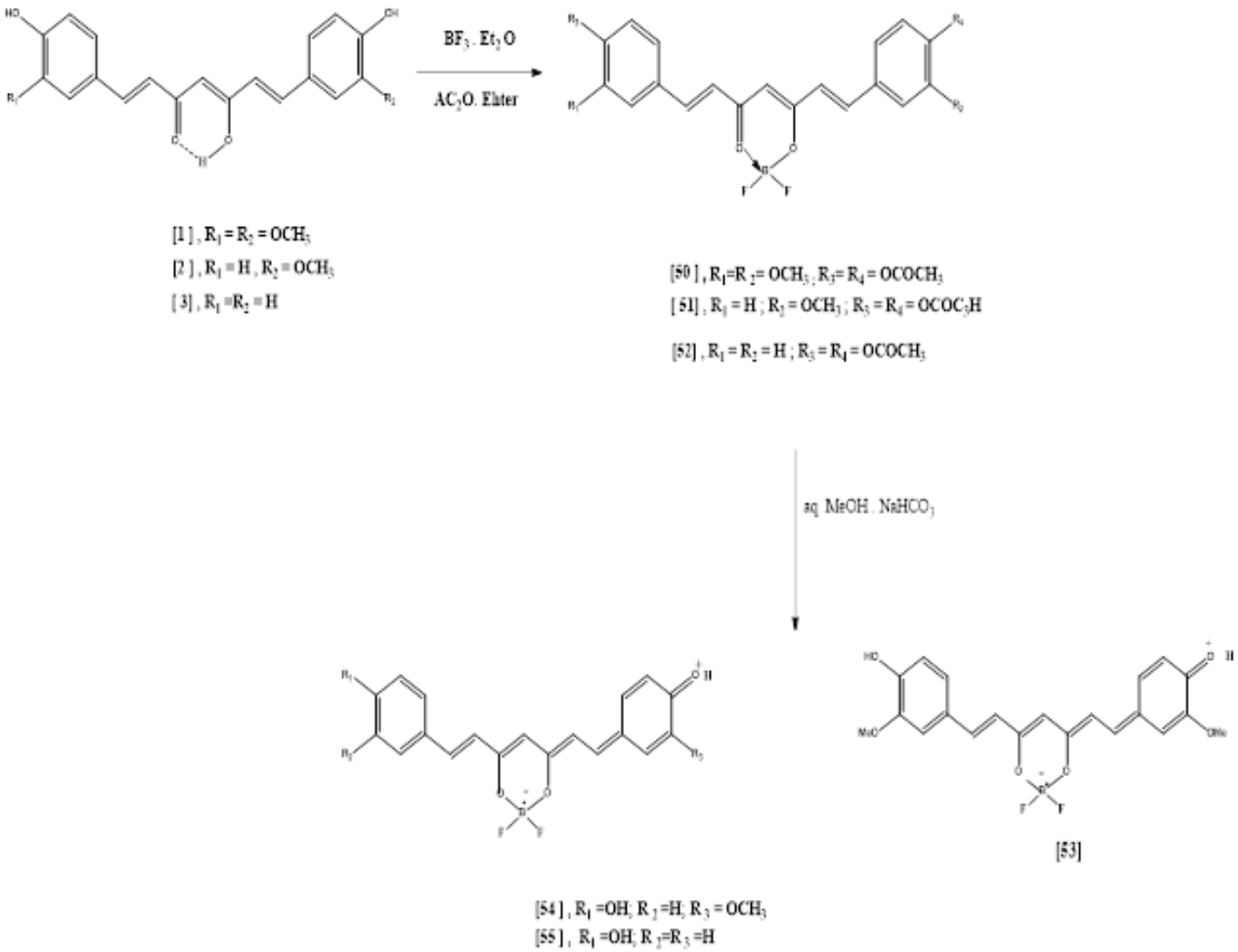


[49]

85%

Eq.8

E. Venkata rao and P. Sudheer[86] reported the synthesis of diacetylcurcuminoid difluoroboronites[53],[54] and [55] as shown in equation (9) .



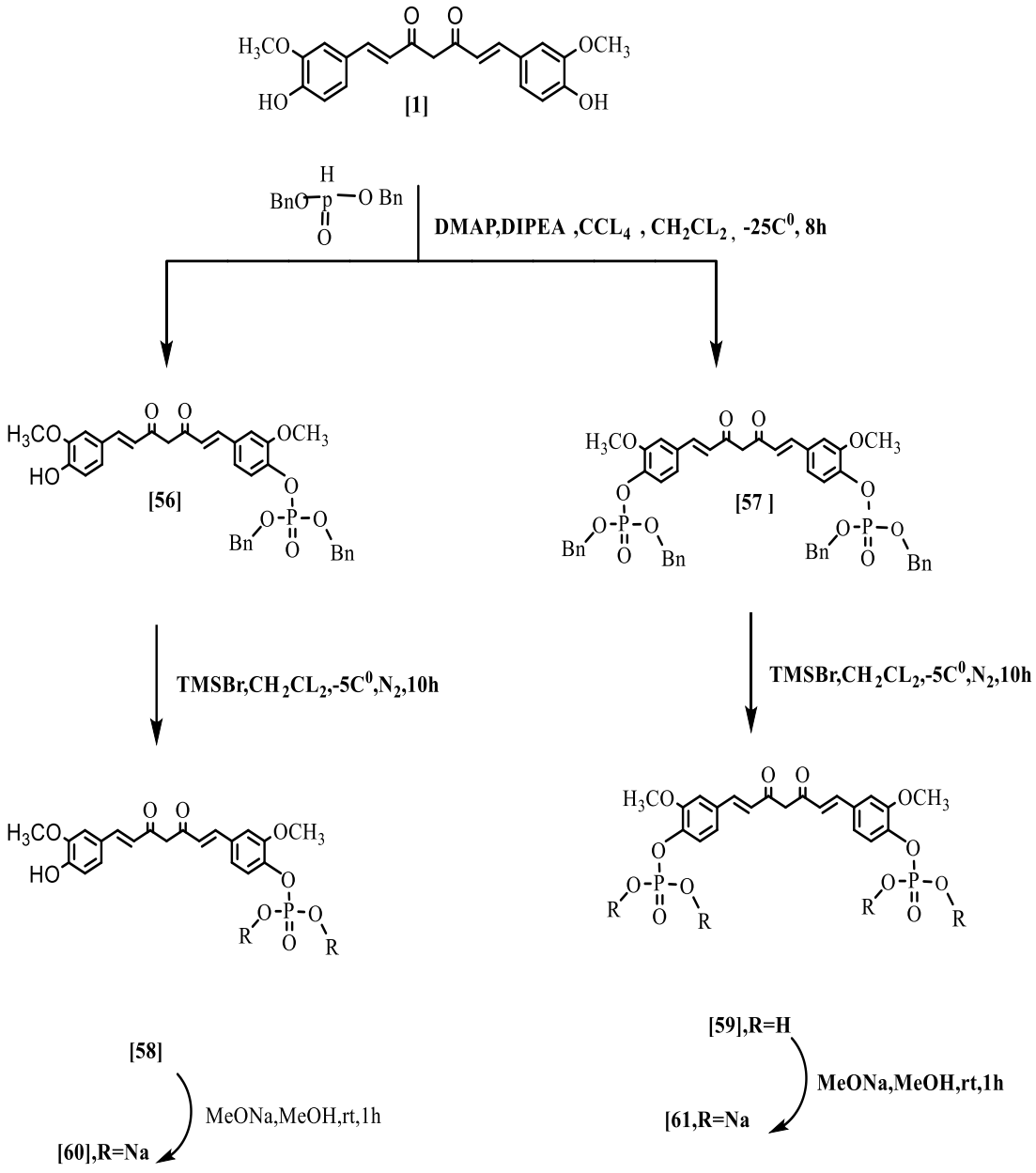
Eq.9

Luyang Ding and Shuli Ma et al[87] . Curcumin's solubility in aqueous media was enhanced by the synthesis of Three different curcumin derivative series phosphorylated, etherified, and esterified products were created, and their anti-tumor properties were evaluated against breast cancer in humans. The anticancer cell line growth activities against HeLa cells were greater for compounds 58, 63, and 9 than for curcumin. as seen in equations (10) and (14) as well as in Scheme (3).

A - Synthesis of curcumin phosphorylated derivatives

To create compounds [56] and [57], curcumin was reacted with dibenzyl phosphate in anhydrous ethyl acetate at -25 ℃ in a N_2 atmosphere. When 56 or 57 are debenzylated in anhydrous dichloromethane at -5 ℃ in a N_2 atmosphere, trimethylbromosilane (TMSBr) treatment produces the compound [58].

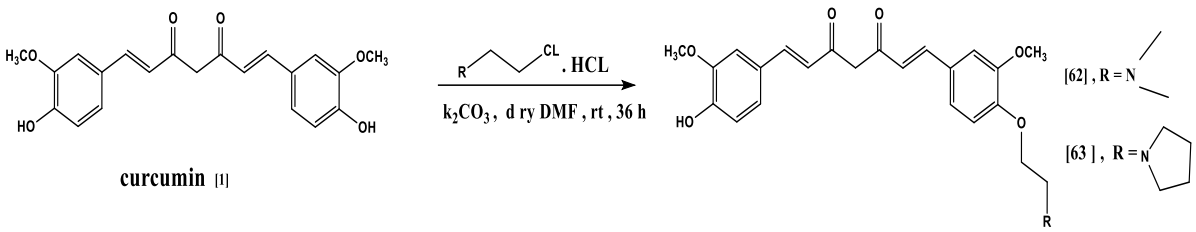
Compounds 60 and 51 were obtained by a reaction of 58 and 59 with MeONa in MeOH solution, respectively, for 1 h. The solubility of compounds 58, 59, 60, or 61 in water was greatly increased. As shown in the Scheme(3).



Scheme .3: Synthesis of curcumin phosphorylated derivatives

B – Synthesis of curcumin etherified derivatives.

Scheme shows how to create the curcumin etherification derivatives synthetically. Compounds 62 and 63 are much more soluble in water now that nitrogen polar groups have been added. According to equation (10).



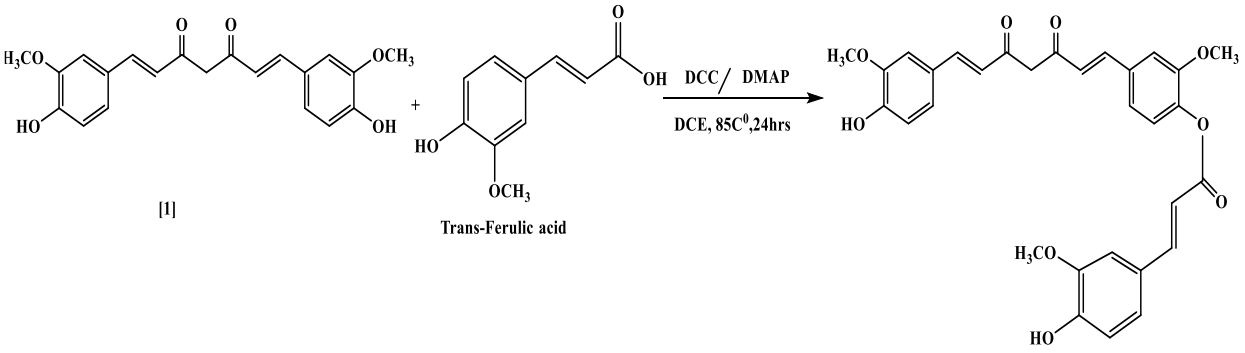
Eq.10

C - Synthesis of curcumin esterified derivatives.

Equation (14) of Curcumin Amino Acid Derivatives shows that the last series of derivatives were created by condensation between the phenolic group of curcumin and the carboxylic group of an amino acid.

Siukan Law , et al[88] . reported the synthesis of ferulic acid curcumin, isovanillin curcumin, 4-methoxy- 1-naphthaldehyde curcumin, were designed and synthesized successfully with the percentage yield of 15.0%, 29.6%, and 52.0%, respectively. as shown in equations(11a,11b,11 c).

a - Synthesis of ferulic acid curcumin



[1]

Trans-Ferulic acid

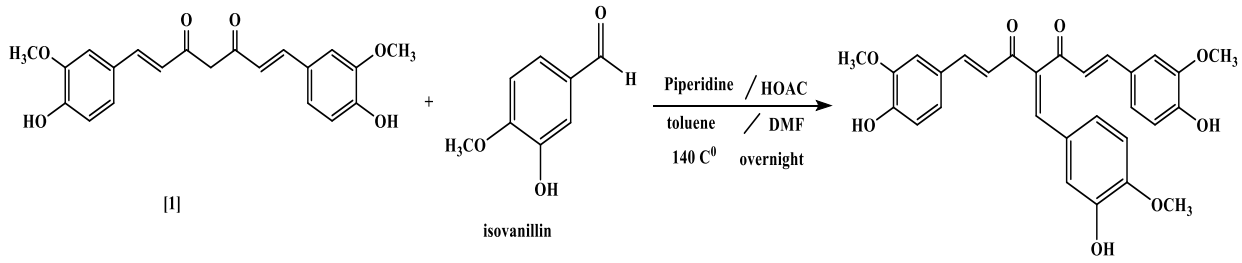
ferulic acid curcumin

[64]

15.0%

Eq.11a

B - Synthesis of isovanillin curcumin



[1]

isovanillin

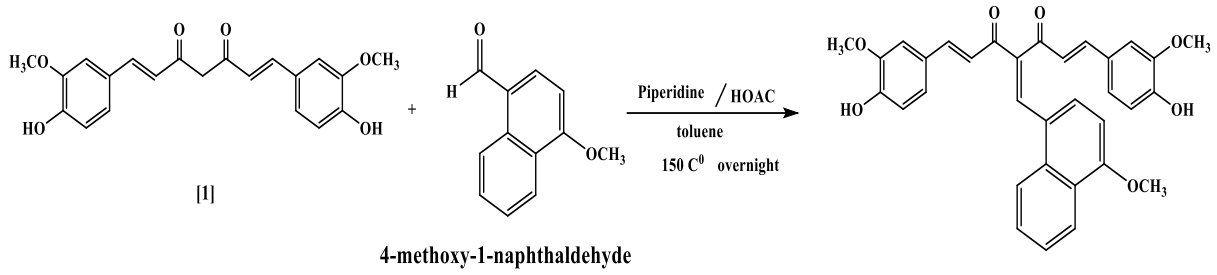
isovanillin curcumin

[65]

29.6%

Eq.11b

C - Synthesis of 4-methoxy-1-naphthaldehyde curcumin



[1]

4-methoxy-1-naphthaldehyde

4-methoxy-1-naphthaldehyde curcumin

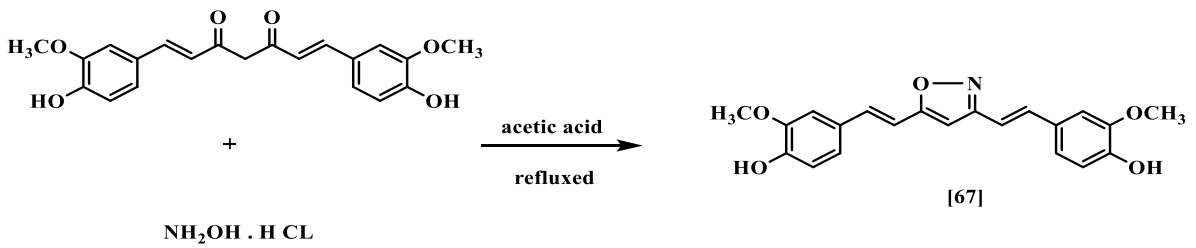
[66]

52.0%

Eq.11c

1.6 - Oxime derivatives of curcumin

Oximes, an acronym for oxy-imine, which exhibits a wide spectrum of pharmacological and biological properties. In 2001, Dutta et al. produced the first oxime analogue of curcumin by condensing curcumin and hydroxylamine hydrochloride in glacial acetic acid[90].the reaction is summarized as illustrated in equation (12)

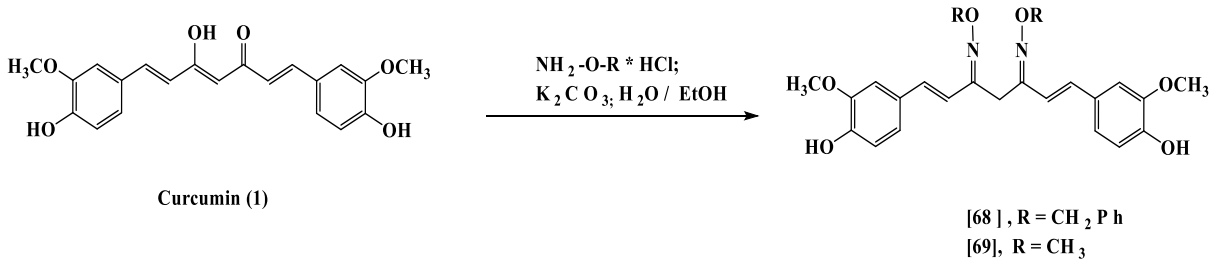


NH_2OH . H CL

[67]

Eq.12

D. Simoni et al[91]. reported that dioxime analogs 68 and 69 could be created by mixing a solution of potassium carbonate in water with a solution of curcumin and O-methyl or O-benzylhydroxylamine hydrochloride in 25% water–ethanol. After 25 minutes of refluxing, cooling, and vacuoconcentration, the mixture was cleared of the majority of the ethanol, leaving behind a residue. The mixture of analogs 68 or 69 was obtained by chromatographic separation from unreacted curcumin in 40% and 32% yield, respectively. as shown in equations (13).



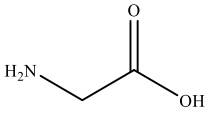
Curcumin (1)

[68] , R = CH_2Ph
[69], R = CH_3

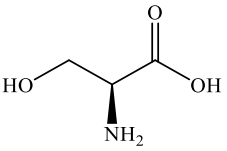
Eq.13

1.7 - Amino acids derivatives of curcumin

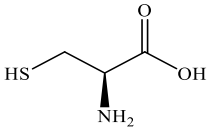
Due to their high biological activity and biosolubility, amino acid schiff bases and their derivatives have garnered a lot of interest. Amino acids are molecules with two functional groups: an amine group and a carboxylic moiety. The amino acids that have the general formula $H_2NCHRCOOH$ are known as α-amino acids. When β-diketones and active chemotherapy medicines are combined with amino acids, Schiff base production can occur.The body need 20 different kinds of amino acids to develop and work correctly, and these amino acids come in two different configurations (L and D). Of them, nine amino acids are deemed essential[92]. Various functional groups were conjugated with curcumin. Additionally, curcumin-amino acid conjugates were produced by employing various substitution In this study, we examine how natural curcumin compounds and their conjugates interact with amino acids[93] . In this work, the use som of basic amino acids(as shown below the Chemical structure of amino acids) to improve the physicochemical properties of curcumin .



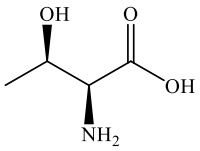
[70] Glycine (Gly)



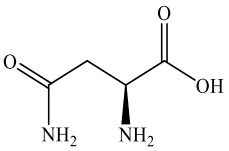
[71] L-Serine (Ser)



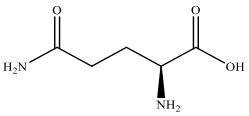
[72] L-Cysteine(Cys)



[73] L-Threonine (Thr)

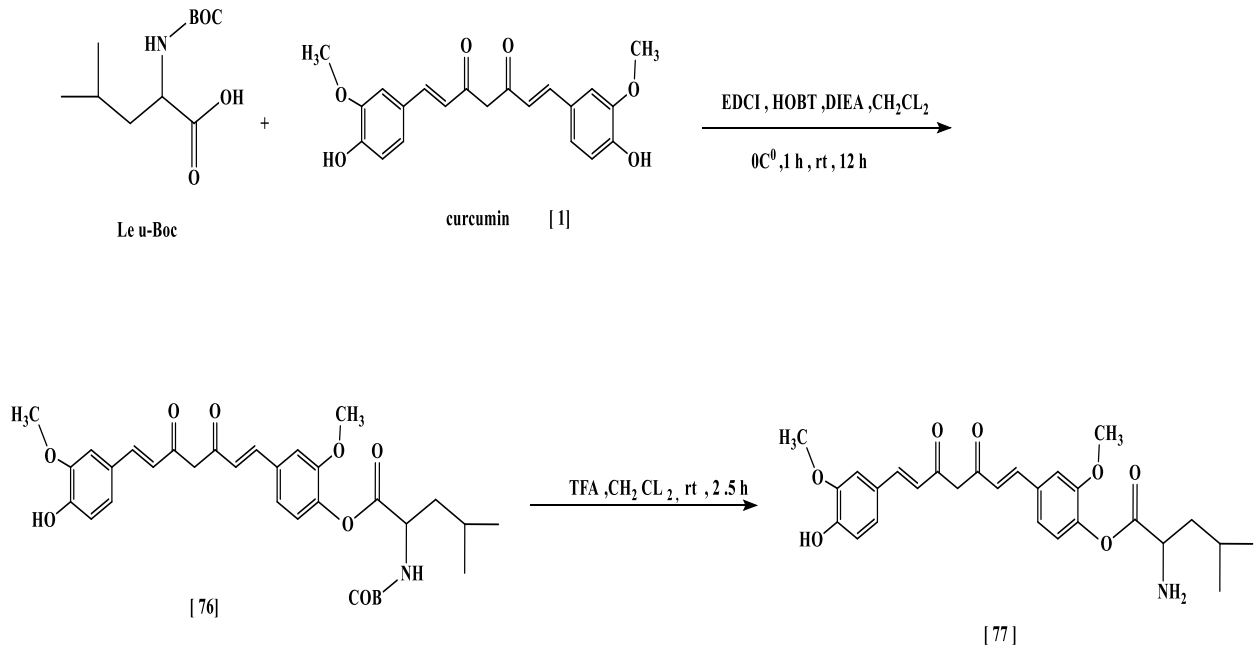


[74] L-Asparagin (Asn)



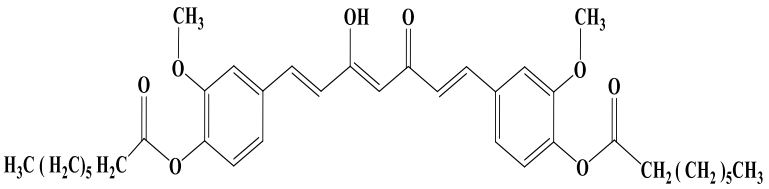
[75] L-Glutamine (Gln)

Shuli Ma, Hongxiang Lou and Luyang Ding[94] reported the synthesis of compounds [76] and[77] by the Leu-Boc, were reacted with curcumin in the presence of EDCI / HOBT to give [76], By using trifluoroacetic acid (TFA) to remove the protective tert-butyloxycarbonyl (Boc) group from [76] in anhydrous dichloromethane, the end product [77] was produced . As shown in equation (14).

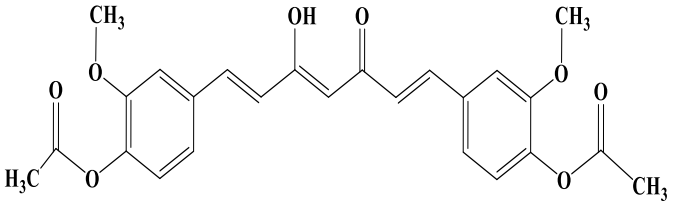


Eq.14

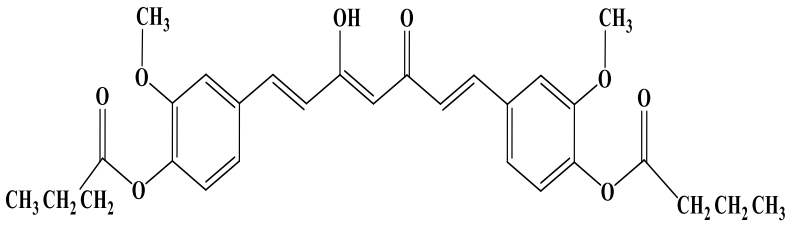
Furthermore, a study by Zarei et a[95] . (2024) has recently reported the synthesis of curcumin dioctanoate (78), curcumin diacetate (79) and curcumin dibutanoate (80) .through the interaction of curcumin with the appropriate aldehydrides when 4-dimethylaminopyridine (DMAP) is present in a catalytic amount. Curcumin dibutanoate (80) demonstrated a markedly enhanced solubility in food-grade oils. It had a strong antioxidant activity of 1.92% when tested using the DPPH technique. Compared to curucmin, curcumin dibutanoate demonstrated greater stability against heat and oxidation.



[78]



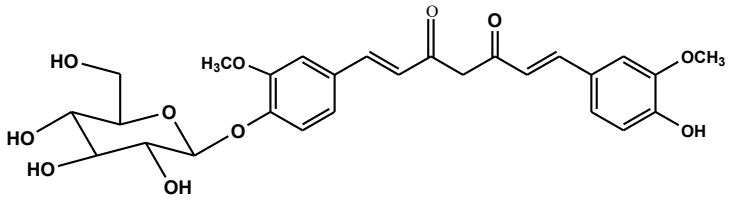
[79]



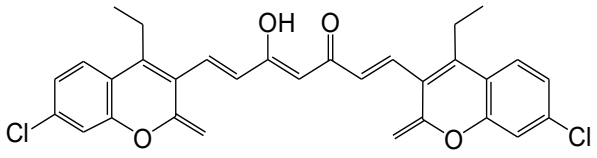
[80]

Curcumin has an ability to affect multiple biological targets and has been shown to exhibit activity against various diseases, including (cancer, cardiovascular disease, neurological and autoimmune diseases)[96,97,98,99] .

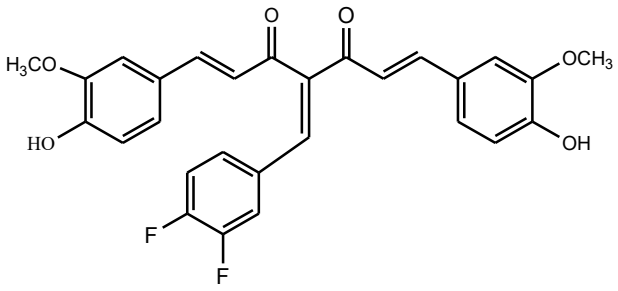
Recently, much attention has been paid to pharmacological properties of curcumin because of its potential to be a very useful drug. Curcumin has been widely studied for its ant oxidative, anticancer, and anti-inflammatory Anti-Allergic Activity effects. Curcumin 4'-O-β-glycosides(81) showed acted as potential anti-allergic agents[100], The afforded analog exhibited compound (82) higher aqueous solubility and more potent antibacterial activity than curcumin versus standard bacterial strains including Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumonia and Haemophilus influenza, Curcumin derivatives with anti-pancreatic cancer activity, in vitro studies of a curcumin derivative called difluorinated-curcumin (CDF) (83) on various pancreatic cancer cell lines have proven its ability to inhibit the growth and survival of these cancer cells GO-Y030 (84) is another curcumin derivative which has a more significant ability for inhibiting the pancreatic cell lines than curcumin[101].



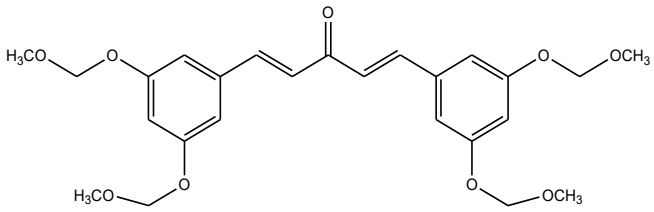
[81]



[82]

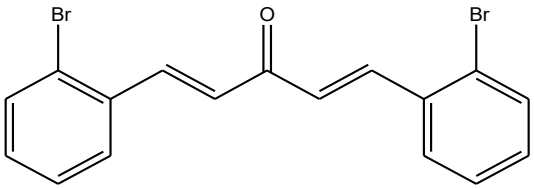


[83]



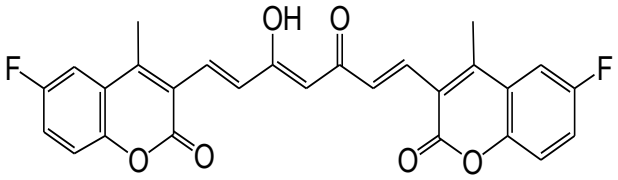
[84]

the curcumin analogue [85] inhibits Nasopharyngeal carcinoma (NPC) in two human NPC cell lines, CNE_2 and CNE_2R. After treatments for 48 h, both [85]and curcumin caused inhibition of cell viability in the two NPC cell lines. However, [85] exhibited greater inhibition than curcumin. IC50 values for [85] were 1.1 μM in the CNE_2 cells and 0.9 μM in the CNE_2R cells, respectively, which were substantially more potent than curcumin (IC50 values 8.1 and 6.7 μM) [102].

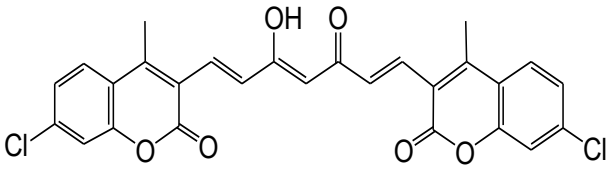


[85]

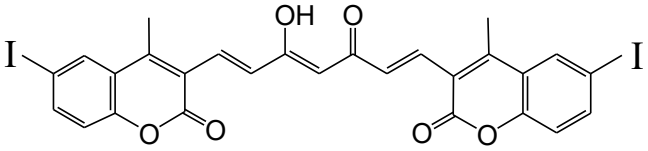
compounds that offer antioxidants [86], [87], and [88] Analogs with fluoride substitutions, in particular, have better antioxidant and anticancer properties than CM, according to biological investigations conducted on them [103,104].



[86]



[87]



[88]

AIMS OF THE study

AIMS OF STUDY

As mentioned earlier in the introduction, Curcumin is a very important class of organic compounds Curcumin was chosen for this study for several reasons , and among these are:

It is safe even when consumed at a daily dose of 12 g for 3 months as was shown in several studies. It has been utilized for centuries in Eastern medicine as a topical treatment for wounds, inflammation, and tumors. It showed several activities as an anti-inflammatory, anti-viral, anti-oxidant, antibacterial, wound healing, hypocholesterolemic effects in diabetic patients.

Curcumin has been shown to suppress carcinogenesis in several tissues including the skin, liver, lung, colon, stomach and breast. The di ketone functional group in curcumin is very useful in organic synthesis it could be converted to several ther functional groups ,among which are amines , alcohols and imines.

In this study curcumin will be incorporated with ammonia derivatives to from Schiff base formation . as mentioned earliar in the introduction. and the prepared compounds are summarized in the Chapter two .

The overall aims of this study are:

1. Design and synthesis of some hydrogen bonding which exists in the keto form based on ammonia derivatives with antibacterial activities and anti-oxidant.

2. Characterize the prepared compounds by various spectroscopic methods including ^{1}H-NMR, ^{13}C- NMR, IR spectroscopy and mass spectroscopy.

3. Assess the antibacterial potency and Anti-microbial activity , Antioxidant Activity.

4. synthesis of the curcumin etherification derivatives by the reaction of curcumin derivative prepared with alkyl halide , to raise and improve the biological and medical properties.

CHAPTER TWO

EXPERIMENT

CHAPTER TWO

EXPERIMENTAL

2. Characterization methods

All new compounds were characterized by ^{1}H- NMR, ^{13}C-NMR , FT- IR , and mass spectroscopy **.**

Nuclear Magnetic Resonance spectra NMR were recorded on Varian Gemini 4000, 300 MHz instrument.

All (^{1}H-NMR) experiments were reported in δ units, parts per million (ppm) downfield from tetramethylsilane (TMS) .

Chemical shifts are presented in ppm (δ) with internal TMS as standard reference . the following appreciation are used :

S= singlet d = doublet q = quartet m = multiplet

All ^{13}C- NMR spectra were reported in ppm relative to deuterated chloroform ($CDCl_3$, 77.0 ppm).

Infra-red spectra (IR) were recorded on a Shimadzu 820 PC FT-IR spectrometer, samples were run as K Br disk in the range of 4000-200 cm^{-1}.

Mass spectrum of the compound were recorder using VG 7070 E.G.C mass spectrometer.

Thin layer chromatography was performed using silica gel 60 F 254 per coated aluminum sheets.

Samples purifications was carried out by recrystallization from suitable solvents.

Melting Points were determined using an open capillary method.

2.1-General Experimental

All chemicals used were purchased commercially from ALDRICH and FLUKa Chemicals. Some materials were also obtained from Al Zawya Oil Refining Company. Assay (≥99.5-98 %),With further refinement.

2.1.1-Reaction of curcumin with various ammonia derivatives [89-100].

2.1.2- General Procedure

For preparation of curcumin derivatives Compounds [89-100]:

The general experimental procedure for the preparation of compounds [89-100] was as follows: In a round bottom flask equipped with magnetic stirring bar and a condenser, curcumin (1.5 mmol, 0.5 g) was dissolved in glacial acetic acid (8 ml). To the solution of curcumin in acetic acid was added the desired ammonia derivatives (amines derivatives ,hydrazine derivatives) (1.5 mmol) followed by sodium acetate (0.2 g).

The produced solution was refluxed for 14 hrs. The progress of the reaction was monitored by TLC analysis. After complete conversion (6-14h), as shown in the following table (2) the mixture was cooled down to room temperature and then neutralized with ammonium hydroxide. The produced solid was collected by suction filtration and purified by recrystallization from suitable solvents, Melting point were determined by open capillary method.

2.1.3- With aromatic amines.

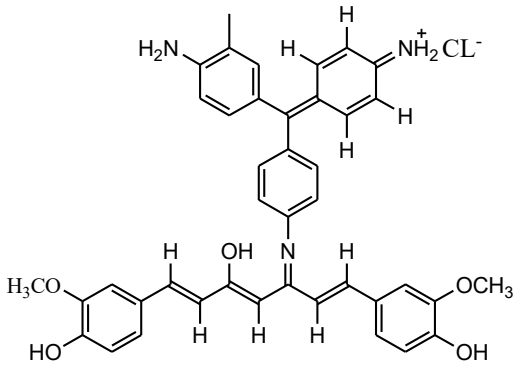
a- Preparation of 4-((4-amino-3-methylphenyl)(4-((1E,4Z,6E) -5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-ylideneamino)phenyl)methylene) cyclohexa-2,5-dieniminium[89]

Curcumin (1.5 mmol, 0.5 g) was dissolved in glacial acetic acid (8.0mL), and ***rosaniline hydrochloride*** (0. 33g) was added to the solution followed by sodium acetate (1.5 m mole, 0.2 g). The mixture was refluxed for16 hrs. Then neutralized with ammonium hydroxide to produce light greenish precipitate which was collected by suction filtration and purified by recrystallization from suitable solvents (Ethanol) . The product weight was 0.68 g (73%) , m .p.(156 -158 ^{o}C).

IR(cm^{-1}):1583 cm^{-1} (C=N) , 1025 cm^{-1} (OCH_3) , 1626 (C=C aliphatic) , 3188-3327 (NH_2), 3327.5-3188.4 (O-H of phenol) .

^{1}H- NMR (DMSO-d6): δ 3.78 (s, 6H, OCH3) , 8.8-9.45 (s, 2H, OH), 4.0 (S, 2H,NH_2) , 5.9 (s, 2H ,OH), 7.30 (S,2 H, A r-H), 7.14(d, *J* = 8.3 Hz, 2H , A r- H) , 7.53 (d, *J* = 15.8 Hz, 2H,Ar-H), 3.36(s,3CH_3), 6.03 (S, 1H-4), 7.82 – 6.25 (m, 11H Ar-H), 6.78 (d , *J* = 33.9, 12.1 Hz, 4H).

^{13}C-NMR (DMSO) δ 183.66, 149.99, 148.53, 141.14, 128.94, 126.78, 123.58, 121.58, 116.25, 113.14, 111.96, 101.21, 56.23, 40.68, 40.47, 40.26, 40.05, 39.84, 39.63, 39.42, 21.83.



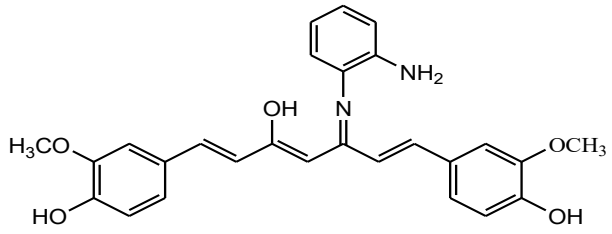
[89]

4-((4-amino-3-methylphenyl)(4-((1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-ylideneamino)phenyl)methylene)cyclohexa-2,5-dieniminium

b- Preparation of 4-((1E,3Z,6E)-5-(2-aminophenylimino)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,3,6-trienyl)-2-methoxyphenol . [90]

Curcumin (1.5 mmol, 0.5 g) was dissolved in glacial acetic acid (8.0 mL), and **o-Phenylenediamine** (0.1g) was added to the solution followed by sodium acetate (1.5 m mole, 0.2 g). The mixture was refluxed for 11 hrs. Then neutralized with ammonium hydroxide to produce light brown precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (n-butanol) , The product weight was 0.418 g , (67 %), m.p.(141-143 ºC) .

IR (cm^{-1}) : 1557 (C=N) , 1025 (OCH_3), 1625 (C=C aliphatic),3190 (2O-H of phenol),2300 (NH_2) .



[90]

4-((1E,3Z,6E)-5-(2-aminophenylimino)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,3,6-trienyl)-2-methoxyphenol

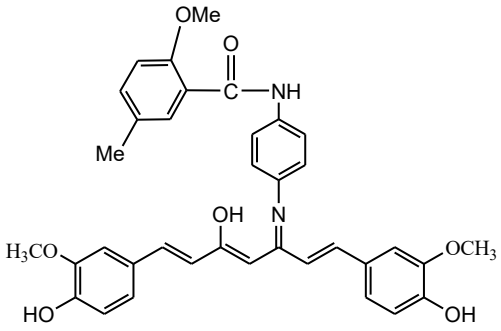
c- Preparation of N-(4-((1E,4Z,6E) - 5 -hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,4,6 – trien-3-ylideneamino)-3-methoxyphenyl) benzamide.[91]

Curcumin (1.5 mmol, 0.8g) was dissolved in glacial acetic acid (8.0 mL), and **(4-Benzoylamino-2-methoxy-5-methyl benzen amine)** (0.556 g) was added to the solution followed by sodium acetate (1.5 mmol, 0.2 g). The mixture was refluxed for16 hrs. Then neutralized with produce ammonium hydroxide to produce precipitate dark brown which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (Ethanol) , The product weight was 0.913 g (71 %), m .p. 84-88 ^{o}C .

IR (cm^{-1}): 1555.97 (C=N), 1028.33 (C-O ether) of (OCH_3), 1624.1(C=C aliphatic), 3179.9 (O-H of phenol) , 3700 (CONH amide).

^{13}C-NMR (DMSO) δ 183.69, 149.86, 148.51, 141.16, 131.65, 128.77, 127.94, 123.56, 121.63, 116.23, 115.51, 111.95, 110.74, 56.23, 40.67, 40.46, 40.25, 40.05, 39.84, 39.63, 39.42, 17.64.

^{1}H-NMR(DMSO)δ4.743.73(s,6H,OCH_3),5.56(S,2H,2OH),6.98(S,2H,ArH)7.04(d,J=15.8,Hz,2H,Ar-H)7.15(d,*J*=14.33Hz,2H,Ar-H),6.07(S,1H.4),9.5 (S,1H,OH) 7.57– 6.07(m, 4H), 8.99 (S,1H, NH), 8.29-7.24(m,8H-Ar)



[91]

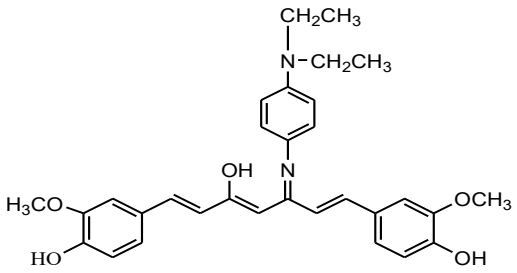
N-(4-((1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-ylideneamino)-3-methoxyphenyl)benzamide

e- Preparation of 4 -((1E,3Z,6E)-5 - (4(diethylamino)phenylimino)- 3 -hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,3,6-trienyl)-2-methoxyphenol.[92]

Curcumin (0.8g) was dissolved in glacial acetic acid (8.0 mL), and **N,N-Diethyl-p-phenylenediamine** (0.356 g) was added to the solution followed by sodium acetate (1.5 mmol , 0.2 g). The mixture was refluxed for15 hrs. Then neutralized with ammonium hydroxide to produce light brown precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (n-butanol), The product weight was 0.66 g (59 %), m .p.-125 123 ºC . IR (cm^{-1}) : 1557 (C=N) , 1027.23 (OCH_3), 1625.8 (C=C aliphatic), 3360-3484 (2O-H of phenol) .

^{1}H-NMR (DMSO) δ 4.32 -3.70(s, 6H, OCH3), 5.50 (S,2H, 2OH), 6.68(S,2H,Ar-H),6.77(d,J=15.5,Hz,2H,ArH)7.15(d,*J*=14.32Hz,2H,ArH),6.07(S,1H4),9.68(S,1H,OH),6.46.51(m,4H),1.97-1.03(q,4H,CH_2),3.37-3.17(t,6H,CH_3).

^{13}C-NMR (DMSO) δ 186.94, 183.66, 159.32, 149.84, 148.74, 148.50, 148.37, 141.14, 137.76, 135.84, 130.75, 127.55, 127.05, 126.85, 123.54, 122.47, 122.15, 121.95, 121.61, 116.22, 111.94, 111.44, 110.85, 101.23, 96.98, 68.25, 56.22, 56.14, 40.64, 40.43, 40.22, 40.01, 39.81, 39.60, 39.39, 30.91, 19.56.



[92]

4-((1E,3Z,6E)-5-(4-(diethylamino)phenylimino)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,3,6-trienyl)-2-methoxyphenol.

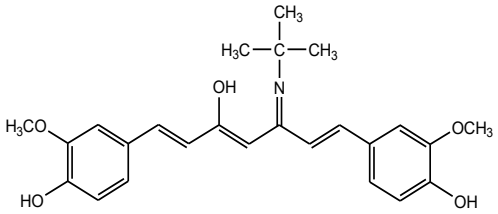
2.1.4- With Aliphatic Amines.

a- Preparation of 4-((1E,3Z,6E)-5-(tert-butylimino)-3-hydroxy-7-(4-hydroxy3-methoxyphenyl)hepta-1,3,6-trienyl)-2 methoxyphenol.[93]

Curcumin (1.5 mmol, 0.5 g) was dissolved in glacial acetic acid (8.0 mL), and ***tert-Butylamine*** (0.25g) was added to the solution followed by sodium acetate (1.5 mmol , 0.2 g). The mixture was refluxed for 12hrs. Then neutralized with ammonium hydroxide to produce orange-red precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (Ethanol), The product weight was 0.421 g (74 %),m .p 170-172 ºC .IR (cm^{-1}): 1567 (C=N), 1028 (OCH_3) , 1622 (C=C aliphatic) , 3189.27 (O-H of phenol).

^{1}H-NMR (DMSO-d6): δ 3.84 -3.45(s, 6H, OCH_3) , 9.87-9.66 (S,1H,OH), 4.15(S,2H, 2OH), 6.68 (S,2H, Ar-H),7.55(d, *J* = 15.7, Hz, 2H ,A r-H),7.33(d „*J* =14.66 Hz, 2H,Ar-H), 6.06 (S,1H_4), 6.86 – 6.77 (m, 4H), 1.31-0.93(S,9CH_3).

^{13}C-NMR (DMSO) δ 183.67, 149.83, 148.50, 141.15, 130.76, 126.85, 123.55, 121.62, 116.22, 111.92, 101.24, 56.23, 40.61, 40.40, 40.19, 39.98, 39.78, 39.57, 39.36.



[93]

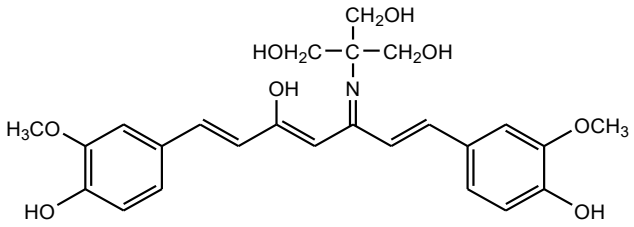
4-((1E,3Z,6E)-5-(tert-butylimino)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,3,6-trienyl)-2-methoxyphenol

b- Preparation of 4-((1E,3Z,6E)-5-(1,3-dihydroxy-2-(hydroxymethyl)propan-2-ylimino)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,3,6-trienyl)-2-methoxyphenol.[94]

Curcumin (1.5 mmol, 0.5 g) was dissolved in glacial acetic acid (8.0 mL), and **Tris(hydroxymethyl)aminomethane**(THAM) (0.12 g) was added to the solution followed by sodium acetate (1.5 m mole, 0.2 g). The mixture was refluxed for 14 hrs. Then neutralized with ammonium hydroxide to produce dark orange precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (Ethyl acetate), The product weight was 0.49 g (77%), m.p.150-152 ºC .IR (cm^{-1}) : 1557 (C=N) , 1025 (OCH_3), 1625 (C=C aliphatic), 3667 (2O-H of phenol).

^{1}H-NMR(DMSO-d6): δ3.84 -3.04 (S, 6H, OCH_3) , 9.87-9.66 (S,1H,OH),4.15(S,2H,2OH), 7.55 - 6.33 ,6.06(S,1H-4),7.56-7.47(m,4H),1.99-1.16(S,3H,OH),1.26-1.13(m,6H,CH_2).

^{13}C-NMR(DMSO) δ 183.67, 149.85, 148.50, 141.14, 130.76, 126.86, 123.54, 121.62, 116.40, 116.23, 111.96, 101.22, 56.23, 40.67, 40.46, 40.26, 40.05, 39.84, 39.63, 39.42.



[94]

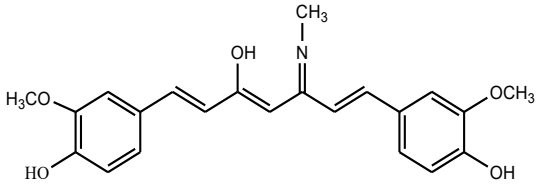
4 -((E,3Z,6E)-5-(1,3-dihydroxy-2-(hydroxymethyl)propan-2-ylimino)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,3,6-trienyl)-2-methoxyphenol

c- Preparation of 4-((1E,3Z,6E)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-5-(methylimino)hepta-1,3,6-trienyl)-2-methoxyphenol.[95]

Curcumin (1.5 mmol, 0.5 g) was dissolved in glacial acetic acid (8.0 mL), and **Methylamine** (0.31g) was added to the solution followed by sodium acetate (1.5 m mol , 0.2 g). The mixture was refluxed for 11 hrs. Then neutralized with ammonium hydroxide to produce light greenish precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (n-butanol), The product weight was 0.443 g (86 %), m.p.156 -158 ºC .IR (cm^{-1}): 1567.73 (C=N) , 1029.11 (OCH_3) , 1622.75 (C=C aliphatic), 3316.2(O-H of phenol).

^{1}H- NMR (DMSO-d6): δ 4.32 -3.02(s, 6H, OCH_3), 9.68 (S,1H,OH), 5.50-5.13 (S,2H, 2OH), 6.68(S,2H,Ar-H),6.75(d, J = 15.7, Hz, 2H,Ar-H)6.79(d ,*J* =14.66 Hz, 2H,Ar-H),6.06 (S,1H-4), 7.75–6.68(m, 4H), 1.31-1.02(S,3H) .

^{13}C -NMR (DMSO) δ 183.68, 149.84, 148.50, 141.15, 126.86, 123.56, 121.62, 116.22, 111.94, 101.23, 56.23, 40.65, 40.44, 40.23, 40.02, 39.81, 39.60, 39.39.



[95]

4-((1E,3Z,6E)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-5-(methylimino)hepta-1,3,6-trienyl)-2-methoxyphenol

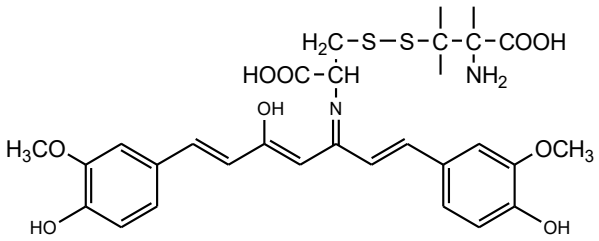
2.1.5- With amino acids.

Preparation of (R)-2-amino-3-(2-(2-carboxy-2-((1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-ylideneaminoethyl) disulfanyl)-2,3-dimethylbutanoic acid.[96]

Curcumin (1.5 mmol, 0.5 g) was dissolved in glacial acetic acid (8.0 mL), and **L-Cystine** (0.24 g) was added to the solution followed by sodium acetate (1.5 mmole, 0.2 g). The mixture was refluxed for 14 hrs. Then neutralized with ammonium hydroxide to produce dark brown precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (n-brobanol), The product weight was 0.626g (74 %),m.p.89-90ºC. IR(cm^{-1}):1558(C=N),1029 (OCH_3) ,1623.22(C=Caliphatic),3331(2O-H of phenol),2935.04(NH_2).

^{1}HNMR(DMSOd6):δ4.653.66(S,6H,OCH_3),9.67(S,1H,OH),4.15(S,2H,2OH),(S,2H,ArH)7.55(d,J=15 .7,Hz,2H,ArH),7.33(d,*J*=14.66Hz,2H,ArH),6.06(S,1H_4),6.076.69(m,4H),9.87(S,2H,COOH),2.61(S,1 H),1.921.04(m,9$H_{11,12}$),3.36-2.67(d,2H_8),2.34(S,2H,NH_2).

^{13}C- NMR (DMSO) δ 183.67, 149.85, 148.50, 141.14, 126.85, 123.55, 121.62, 116.23, 111.95, 101.21, 56.23, 40.67, 40.46, 40.25, 40.04, 39.83, 39.62, 39.41.



[96]

(R)-2-amino-3-(2-(2-carboxy-2-((1E,4Z,6E)-5-hydroxy-1,7-bis

(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-ylideneamino)ethyl)disulfanyl)-2,3-dimethylbutanoic acid

2.1.6- with Hydrazine Derivatives.

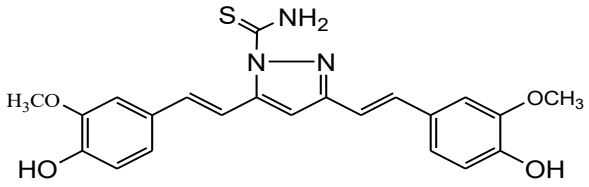
Preparation of 3,5- bis((E)- 4 -hydroxy-3 -methoxystyryl-1H-pyrazole-1-carbothioamid.[97]

Curcumin (2.5 mmol,1g) was dissolved in glacial acetic acid (8.0 mL), and **Thiosemicarbazide** (0.246 g) was added to the solution followed by sodium acetate (1.5 m mole, 0.2 g). The mixture was refluxed for 16 hrs. Then neutralized with ammonium hydroxide to produce light greenish precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (Acetic acid) , The product weight was 0.681 g (60 %), m.p.115-118ºC .

IR (cm^{-1}) : 1551.57-1586.53(C=N) ,1028.65(OCH_3),1624.57(C=C aliphatic) , 3194.4 (2O-H of phenol) , 1204.9(C-N) , 3194.32(NH_2).

^{1}H- NMR (DMSO) δ 4.14 -3.66(s, 6H, OCH_3), 5.56-5.13 (S,2H, 2OH), 6.68(S,2H,Ar-H),7.55(d, J = 15.8, Hz, 2H,Ar-H)7.16 (d „*J*=14.33 Hz,2H,Ar-H),6.62 (S,1H-4), 7.57– 6.62(m, 4H),2.09 (S,2H,NH_2).

^{13}C- NMR (DMSO) δ 149.82, 148.50, 141.14, 126.86, 123.55, 121.62, 116.22, 111.89, 56.22, 40.58, 40.37, 40.16, 39.95, 39.74, 39.54, 39.33.



[97]

3,5- bis ((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-carbothioamide

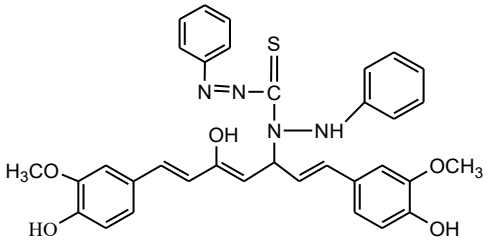
2.1.7 - With Secondary Amines .

Preparation of 2 - ((1E,4Z,6E)- 5 - hydroxy-1,7- bis (4-hydroxy- 3 - methoxyphenyl)hepta -1,4,6-trien-3-yl) -1,5 diphenylthiocarbazone.[100]

Curcumin (1.5 mmol, 0.8g) was dissolved in glacial acetic acid (8.0 mL), and **Dithizone** (0.556 g) was added to the solution followed by sodium acetate (1.5 m mole, 0.2 g). The mixture was refluxed for 12hrs. Then neutralized with ammonium hydroxide to produce precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (n-butanol) , The product weight was 0.0129 g (87 %), m .p 140- 143ºC . IR (cm^{-1}) : 1264.55-1206.11 (C-N) , 1025 (OCH_3), 1624.93(C=C aliphatic),3607 (2O-H of phenol),1728.7(C=O),1206.11(C=S).

^{1}H-NMR (DMSO-d6): δ 4.42-3.15(s,6H,OCH_3), 5.56-5.14 (S,2H,2OH), 6.98(S,2H,Ar-H) ,7.04 (d,J15.8,Hz,2H, Ar-H) 7.15 (d,*J* =14.33Hz, 2H,A r-H),6.07(S,1H-4),9.86(S,1H,OH) 6.93– 6.55(m, 4H), 4.42 (S,1H, NH), 8.29-7.74-6.69(m,10H-Ar).

^{13}C-NMR (DMSO) δ 148.50, 130.07, 128.07, 123.57, 122.90, 116.23, 114.53, 111.95, 68.24, 56.23, 40.67, 40.46, 40.25, 40.04, 39.83, 39.62, 39.41, 30.91, 19.56.



[100]

2-((1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-yl)-1,5-diphenylthiocarbazone

Table (2) The percentage yield and reaction time for the synthesis of curcumin analogues [89-100].

Compound.NO	Time of reaction (hrs)	Yield %
89	16	73
90	11	67
91	16	71
92	15	59
93	12	74
94	14	77
95	11	86
96	14	74
97	16	60
100	12	87

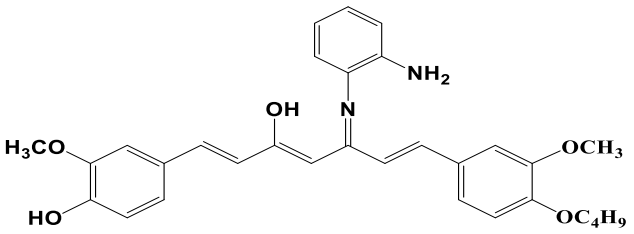
2.2- Reaction of curcumin derivatives with alkyl halides .

2.2.1-General Procedure

A mixture of curcumin derivatives was dissolved in Acetone(C_3H_6O) and was added alkyl halides to the solution followed in the presence of anhydrous potassium carbonate (K_2CO_3) as a base . The mixture was refluxed for (48 hrs), as shown in the following table (3) the mixture was cooled down to room temperature to produce precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents .

a- Preparation of 4-((1E,3Z,6E)-5-(2-aminophenylimino)-7-(4-butoxy-3-methoxyphenyl)-3-hydroxyhepta-1,3,6-trienyl)-2-methoxyphenol.[98]

curcumin derivatives [90] (0.137) was dissolved in Acetone(C_3H_6O) and was added **1-Chloro-butane** (0.0185) to the solution followed in the presence of anhydrous potassium carbonate (K_2CO_3) as a base . The mixture was refluxed for 48 hrs to produce precipitate which was collected by suction filtration The solid product was purified by ecrystallization from suitable solvents (n-butanol), The product weight was 0.1183 g (77%) , m.p (117-119 ºC) .IR (cm^{-1}) : 1587.65 (C=N) , 1026.96 (OCH3), 1623.93 (C=C aliphatic), 3230 (2O-H of phenol),2600-2800(NH_2) amine . ^{1}H-NMR (DMSO-d6): δ 3.32 -3.17(S, 6H, OCH_3), 9.68 (S,1H,OH), 5.50-5.13 (S,2H, OH), 6.68(S,2H,Ar-H),6.75(d, J = 15.7, Hz, 2H,Ar-H)6.79(d ,*J* =14.66 Hz, 2H,Ar-H),6.06 (S,1H-4), 7.75–6.68(m, 4H), 1.76-1.06(S,9H)



[98]

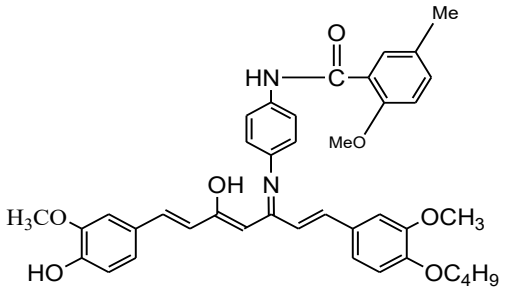
4- ((1E,3Z,6E)-5-(2-aminophenylimino)-7-(4-butoxy-3-methoxyphenyl)-3-hydroxyhepta-1,3,6-trienyl)-2-methoxyphenol.

b- Preparation of N-(4-((1E,4Z,6E)-1-(4-butoxy-3-methoxyphenyl)-5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-ylideneamino)phenyl)-2-methoxy-5-methylbenzamide.[99]

curcumin derivatives [91] (0.4 g) was dissolved in Acetone(C_3H_6O) and was added **1- Chloro - butane** (0.061 g) to the solution followed in the presence of anhydrous potassium carbonate (K_2CO_3) as a base . The mixture was refluxed for 48 hrs to produce precipitate which was collected by suction filtration The solid product was purified by recrystallization from suitable solvents (Acetic acid) , The product weight was 0.236 g (54%) , m.p (111-113 ºC).IR (cm^{-1}) : 1573.65 (C=N) , 1027.96 (OCH_3), 1624.93 (C=C aliphatic), 1728.7 (2O-H of phenol**) .**

^{1}H- NMR (DMSO-d6): δ 4 .42-3.38(s, 6H, OCH_3), 5.67-5.09 (S,2H, 2OH), 6.98- 7.74 aromatic ring (m, Ar-H),6.07(S,1H-4), 9.85 (S,1H,OH) 6.93– 6.55(m, 4H), 4.42 (S,1H, NH), 4.64-1.14 (m,9H).

^{13}C- NMR (DMSO) δ 148.50, 130.07, 128.07, 123.57, 122.90, 116.23, 114.53, 111.95, 68.24, 56.23, 40.67, 40.46, 40.25, 40.04, 39.83, 39.62, 39.41, 30.91, 19.56.



[99]

N-(4-((1E,4Z,6E)-1-(4-butoxy-3-methoxyphenyl)-5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-ylideneamino)phenyl)-2-methoxy-5-methylbenzamide

Table (3) The percentage yield and reaction time for the synthesis of curcumin analogues[98 ,99]

Compound.NO	Time of reaction (h r s)	Yield %
98	48	77
99	48	54

Table(4) : Analytical data for the newly prepared compounds [89-100].

Compoud. NO	Yield (%)	Color	Solvent for Recrystallization	Melting point (^{0}C)	Molecular Formula
89	73%	Light green	Ethanol	156-158	$C_{41}H_{38}N_3O_5^+Cl$
93	74%	Orange-red	Ethanol	170-171	$C_{25}H_{29}NO_5$
90	67%	Olive	n-butanol	141-143	$C_{27}H_{26}N_2O_5$
94	77%	Orange	Ethyl acetate	150-152	$C_{25}H_{29}NO_8$
96	74%	Brown	n-brobanol	89-90	$C_{30}H_{36}N_2O_9S_2$
95	86%	Yellow- orange	n-butanol	156-158	$C_{22}H_{23}NO_5$
97	60%	Light brown	Acetic acid	115-118	$C_{22}H_{21}N_3O_4S$
91	71%	Dark brown	Ethanol	84-88	$C_{36}H_{34}N_2O_7$
92	59%	Light brown	n-butanol	123-125	$C_{31}H_{34}N_2O_5$
100	87	Red	n-butanol	140-143	$C_{34}H_{32}N_4O_5S$
98	77%	Dark grey	n-butanol	117-119	$C_{31}H_{34}N_2O_5$
99	54%	Dark brown	Acetic acid	111-113	$C_{40}H_{42}N_2O_7$

2.3-Antimicrobial activity

The natural components from plants are considerable antimicrobial agents may that can substitute the current antibiotics, which are facing increasingly evolving resistance by microorganisms.

Testing for Antibacterial Activity :

Materials:

Culture media: Mueller-Hinton, Tryptic Soy Broth (Hylabs , Israel) Antibiotic.

Microorganisms used:

Bacterial strains used in the study were Gram – positive bacterial **(**Staphylococcus aureus , Staphylococcus agalacteae) and Gram- negative bacterial (Escheria coli , Klebsiella pneumonia).

Screening for Antimicrobial activity :

In vitro biological screening effects of the investigated compounds were tested against the bacteria , Escheria coli, Klebsiella pneumonia (gram- negative) and Staphylococcus aureus ,Staphylococcus agalacteae (gram - positive).

The stock solutions were prepared by dissolving the compounds in Dimethyl sulfoxide (DMSO) . It is serially diluted and used to found the minimum inhibitory concentration values. In a typical procedure , 6 mm diameter well was made on the agar medium inoculated with the microorganism.

The well was filled with test solution using amicropipette and the plates were incubated at $35C^0$ for 24 h for the bacteria During this period, the test solution was diffused through the medium and the growth of the inoculated **microorganisms was affected**. The inhibition zone developed on the plate was measured and reported in the Table[6].

Antioxidant Activity

The antioxidant activity of the curcumin derivatives samples was determined using the DPPH radical-scavenging activity values.

DPPH Free Radical-Scavenging Activity

The antioxidant activities of all curcumin derivatives were evaluated according to the DPPH radical-scavenging activity as described by Braca et al.

Applied procedures

Briefly,1 mL of the curcumin derivatives was mixed with 1 mL of 0.003% DPPH in methanol at varying concentrations (20– 50 μg /mL) The absorbance of the reaction solution was recorded after 30 minutes at a wavelength of 517 nm. Ascorbic acid was prepared as a sample compared at the same concentrations in methanol . The percentage of DPPH inhibition was calculated using the following equation:

$$\% \text{ of DPPH inhibition} = \left[\left(\frac{A_{DPPH} - AS}{A_{DPPH}} \right) \right] X \ 100$$

CHAPTER THREE

RESULTS AND DISCUSSION

CHAPTER THREE

RESULTS AND DISCUSSIONS

3.1 - Reaction of curcumin with ammonia derivatives

We extended our work to variety of aromatic amines , Aliphatic amines to react with curcumin and Likewise, hydrazine derivatives interact with curcumin , This work reported the synthesis of curcumin analogues from simple phenols through many serial reactions interaction of curcumin derivatives with(alkyl halides). According to the biological studies performed on these analogues, it is concluded that these analogues have improved antioxidant and Antimicrobial activity.

The studied reaction of curcumin with ammonia derivatives will be categorized into five categories:

1- With Aromatic primary and Secondary Amines.

2-With Aliphatic Amines.

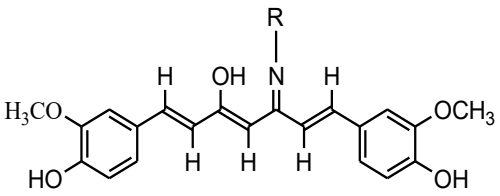
3- With amino acids.

4- with Hydrazine Derivatives.

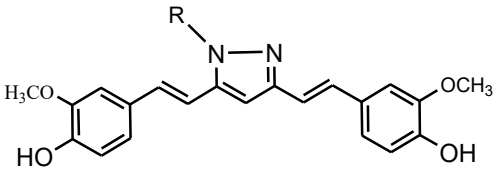
5-The reaction of curcumin derivatives With alkyl halides.

In this procedure, curcumin (compound1) was refluxed with various ammonia derivatives in acidic media, which performs dual function as catalyst and solvent. The progress of the reaction was monitored by TLC. The produced solid was collected by suction filtration and purified by recrystallization from suitable solvents, Melting point were determined by open capillary method. Some reactions required more reflux time than the others.Followed procedure produced only the expected product curcumin derivatives compounds of type **(A)** resulted synthesized by the one step condensation reaction between a primary amine and a carbonyl compound at ordinary laboratory conditions and releasing water, to form double bond imine (C=N) is a reaction; nucleophilic addition of an amine followed by elimination of water and a Schiff base of the type **(B)**; resulted

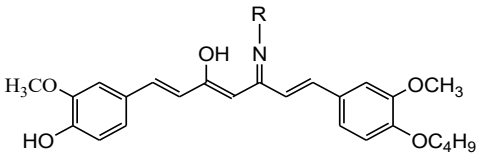
from the reaction with Hydrazine. The Schiff base formation is really a sequence of of two types of reactions ,i.e. addition Followed by elimination ,the curcumin derivatives compounds of type **(C)** result through modifications to the aromatic side chain by substituting the phenolic -OH with different linkers. While the reaction with secondary amines is expected to give the possible product **(D)** enamines (R_2N- $CR=CR_2$).



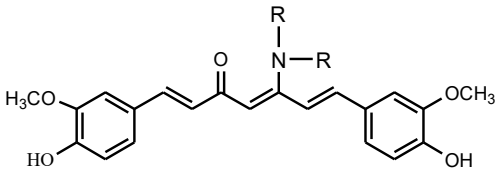
(A)



(B)



(C)

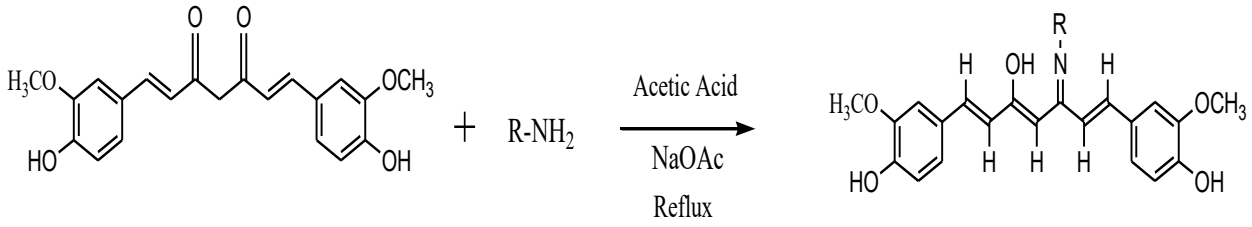


(D)

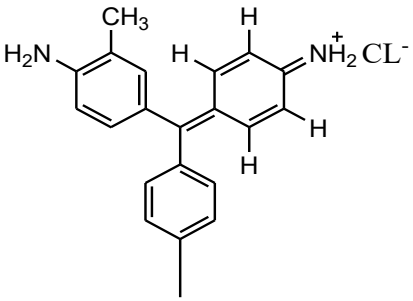
then analyzed by various spectroscopic techniques, such as; In all cases results are consistent with the expected structures. All compounds were obtained in acceptable yield (54% to 87%).

3.1.1- Reaction of curcumin with amines.

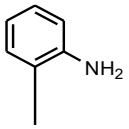
The reaction of curcumin with primary amines of the type R-NH_2 in glacial acetic acid as the following scheme shows was studied.



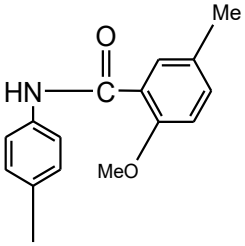
[89];R=



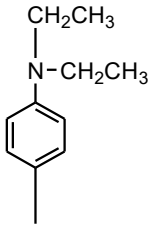
[90];R=



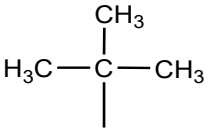
[91];R=



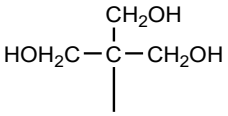
[92];R=



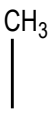
[93];R=



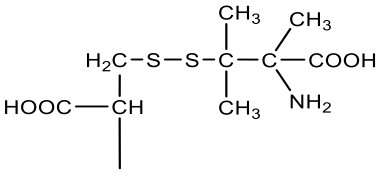
[94];R=



[95];R=



[96];R =



The reaction of curcumin (1) with aromatic amines was conducted in acetic acid thus with; rosaniline hydrochloride , o –Phenylenediamine , (4-Benzoyl amino-2-methoxy-**5-**methyl) benzen amined , N,N-Diethyl-p-phenylenediamine . The reactants were refluxed for 8-16 hr afforded in each case a solid product in about 59-73% yield

The reaction is summarized as the scheme shows . IR spectrum **(Fig.8)** shows a characteristic peak at 1583.82 ,1567.55,1555.97 and 1585.67 cm^{-1} respectively. Indicating the presence of imine group and the absence of C=O carbonyl group and appearance of OH hydroxyl group in the region 3072-350 cm^{-1} . , and the of (C=C) stretching of the aliphatic at 1626.60,1623.45,1624.14 and 1625.83 cm^{-1} respectively ,a band at 1025.91,1028.56, 1028.33 and 1027.23cm^{-1} respectively for (C-O ether) of methoxy group, and band at 3190.23-2848.23$cm^{-1}$for (O-H) phenol. The ^{1}H- NMR spectrum in (d_6-DMSO) of products **, (Fig.9. 9/ ,15.15/,19)** shows the following NMR data which are consistent with the structure of compounds **[89,91]** and **[92]**. show one proton singlet at δ 6.03,6.07and 6,07 ppm for compounds**[89],[91]** and **[92]** ,for H- 4 in products of type (A), and three proton singlet at δ 3.78 ,3.73 , and 3.70 ppm for compounds **[89],[91]**,and**[92]** ,for assigned (s, 6H, $2OCH_3$), and one proton singlet at δ 5.9, 5.56 and 5.50 ppm for compounds **[89],[91]** and **[92]** , for (2OH) phenol group, and two proton singlet at δ 4.0 ppm for assigned($2NH_2$) of amine group for compound **[89]** , the aromatic rings protons gave multiplet signals in the aromatic region δ 6.68 -7.82 and another multiplet at δ 7.16 ppm for protons of the aromatic rings. At for the rest of spectra see table(5).

On the other hand,^{13}C- MNR spectra in (d_6-DMSO) of compounds**[89, 91 ,92]** , shows number of resolved carbon signals, **(Fig.10,16,20)** shows the following data which are consistent with the structure of compounds **[89],[91]**, and**[92]** ,the imine carbon signal was observed at δ 141.14,141.16, and 141.14 respectively , and the methyl carbon ($O-CH_3$) signal was observed at δ 56.23,56.23, and 56.22 respectively, and the hydroxyl carbon(C-OH) signal was observed at δ 183.66,183.69, and 183.66, and rest of the resolved carbon signals are corresponding to the aromatic carbon atoms of the product . Mass spectrum of the compounds **[89]**,**[91]** and **[92]**,**(fig.11,17),** and **(21)** respectively ,clearly show a peak at 650.49,606.67 and 514.25. These results indicate the formation of a Schiff base these compounds can only arise if the starting amines react with the keton form of the curcumin, Through SN^2 nucleophilic substitution reaction on carbon number 3,5.

The reaction of curcumin(1) with aliphatic amine tertButylamine Tris(hydroxymethyl)aminomethane ,Methylamine in glacial acetic acid a solid product was obtained in about 74-86% yield, IR spectrum **(Fig 22,26,30)** shows a characteristic peak at 1557.37,1567.55,1567.73cm^{-1} respectively. Indicating the presence of imine group and the absence of C=O group and appearance of OH group in the region 4.15,4.15.5.5$cm^{-1}$and the of (C=C) stretching of the aliphatic at 1625.93 ,1622.72,1622.75 cm^{-1},a band at 1025.81, 1028.68,1029.11cm^{-1} for (C- O ether) of methoxy group respectively , and band at 3189-3667,7 $cm^{-1}$for (2O-H) phenol. The ^{1}H NMR spectrum in (d_6-DMSO) of products , **(Fig. 23,23$^{/}$,27$^{/}$ 27$^{//}$,31,31$^{/}$)** shows the following NMR data which are consistent with the structure of compounds .

show one proton singlet at δ 6.06,6.05 and 6,06 ppm for compounds **[93]**,**[94]** and **[95]** ,for H- 4 in products of type (A),and three proton singlet at δ 4.15 -3.36 ppm for compounds**[93],[94]**,and**[95]** ,for assigned (s, 6H, 2OCH_3), and one proton singlet at δ 5.50, 6.06 and 5.50 ppm for compounds **[93]**,**[94]** and **[95]** ,for (2OH) phenol group, the aromatic rings protons gave multiplet signals in the aromatic region δ 6.68 -7.82. At for the rest of spectra see table(5).

On the other hand,^{13}C- MNR spectra in (d_6-DMSO) of compounds**[93, 94 ,95]** , shows number of resolved carbon signals, **(Fig.24,28,32)** shows the following data which are consistent with the structure of compounds **[93]**,**[94]** ,and**[95]** ,the imine carbon signal was observed at δ 141.15,141.14, and 141.15 respectively , and the methyl carbon (O-CH_3) signal was observed at δ 56.23,56.23, and 56.23 respectively , and the hydroxyl carbon(C-OH) signal was observed at δ 183.67,183.67, and 183.68 respectively, and rest of the resolved carbon signals are corresponding to the aromatic carbon atoms of the product. Mass spectrum of the compounds **[93]**,**[94]**, and **[95]**,**(fig25),(fig. 29)**,and **(fig. 33)** respectively ,clearly show a peak at 424.5 , 470.73 and 381.18. Also these results indicate the formation of a Schiff base.

3.1.2 -Reaction of curcumin with amino acids

The reaction of curcumin with hydrazine derivatives in glacial acetic acid as the following scheme shows was studied. Many of these compounds were prepared by the classical method of reacting hydrazines with β – dicarbonyl compounds; since curcumin is “symmetrical” only one tautomer (R = 97).

The reaction of curcumin with primary amines of the type R-NH2 in glacial acetic acid as the explained previously .

The reaction of curcumin (1) with L - Cystine The reactants were refluxed for14 hr afforded in each case a solid product in about 74% yield , IR spectrum**(Fig. 34)** shows a characteristic peak at 1558 .07 cm^{-1} Indicating the presence of imine group and the absence of C=O two groups , and band 1623.22 cm^{-1} the of (C=C) stretching of the aliphatic , and band at 1029.22 cm^{-1} for (C-O ether) of methoxy group, and band at 3331.09 cm-1for (O-H) phenol, and band at 2935.04cm^{-1}(COOH) of compound **[96]** ,The ^{1}H- NMR spectrum in (d6-DMSO) of products , **(Fig.35,35$^{/}$,35$^{//}$)** shows the following NMR data which are consistent with the structure of compounds **[96]**show one proton

singlet at δ 6.03 ppm for compound **[96]**, for H- 4 in products of type (A), and three proton singlet at δ 3.36 ppm for compound **[96]** for assigned (s, 6H, 2OCH_3), and one proton singlet at δ6.07 ppm for compounds **[96]**for (2OH) phenol group ,for the rest of spectra see table (5).

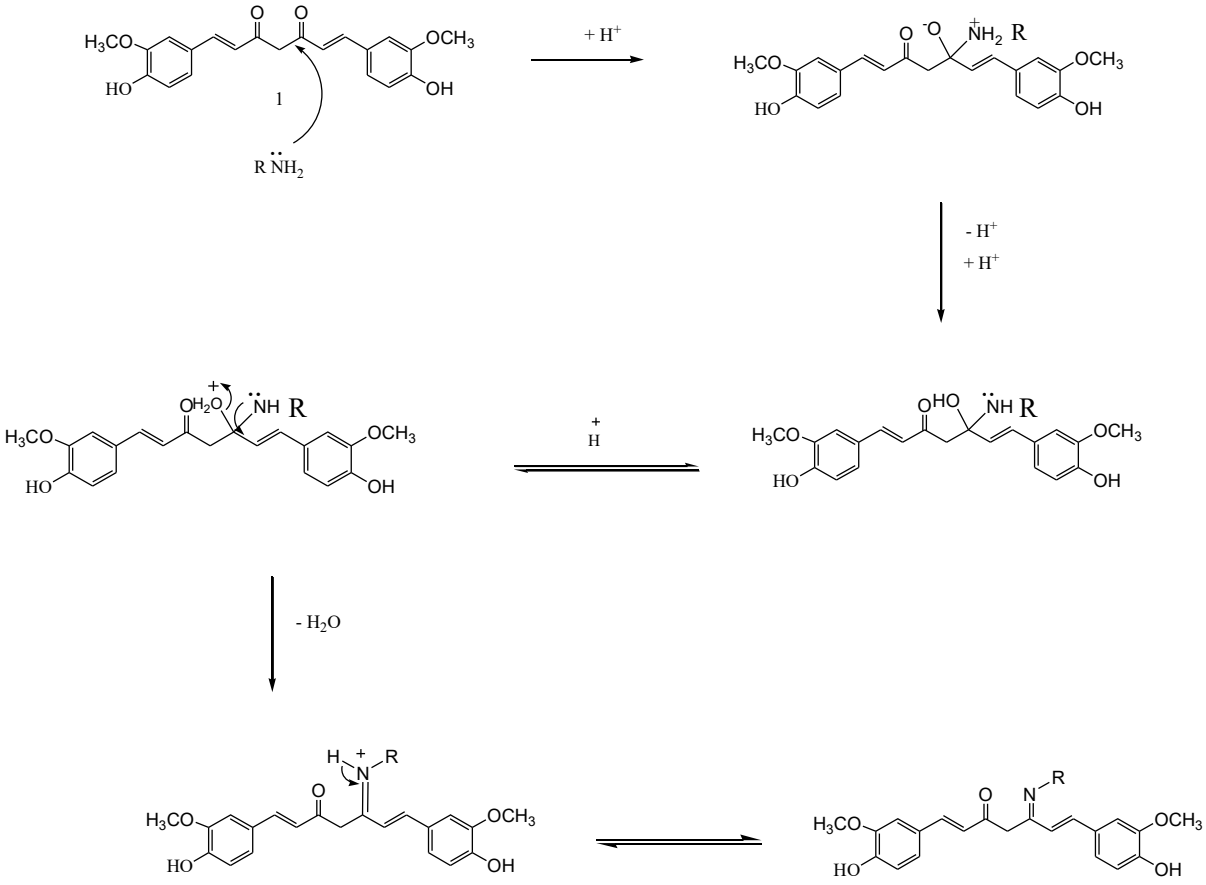
On the other hand,^{13}C- MNR spectra in (d6-DMSO) of compound **[96]** shows number of resolved carbon signals, **(Fig. 36)** shows the following data which are consistent with the structure of compound **[96]**, the imine carbon signal was observed at δ 141.14 , and the methyl carbon (O-CH_3) signal was observed at δ 56.23 , and the hydroxyl carbon(C-OH) signal was observed at δ 183.67, and rest of the resolved carbon signals are corresponding to the aromatic carbon atoms of the product.

Mass spectrum of the compounds **[96] (fig.37)** ,clearly show a peak at 604.89 Also these results indicate the formation of a Schiff base.

Both IR and NMR and Mass spectral data are in agreement with the possible structure of the product compounds .The formation of this product is thought to be through nucleophilic attack of the amines strong nucleophile[Kb= $1.09 \times 10^{3-}$], and no steric affect at carbonyl group to yield Schiff ,s base.

Reaction mechanism

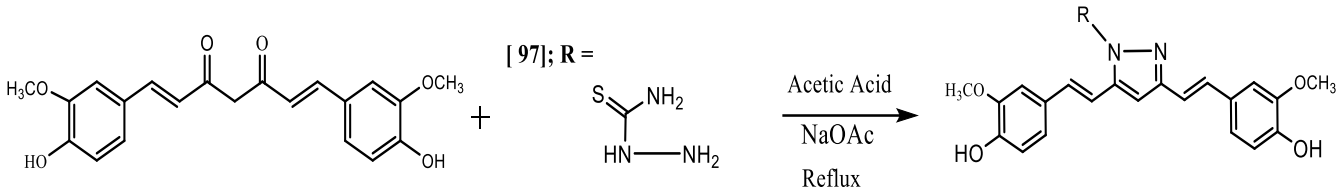
A . The mechanism for reaction of curcumin with amines of the type R-NH2 as shown in scheme (4) .



Scheme. 4 : mechanism for reaction of curcumin with amines of the type R-NH2

3.1.3- Reaction of curcumin with Hydrazine Derivatives.

The reaction of curcumin with hydrazine derivatives in glacial acetic acid as the following scheme shows was studied. Many of these compounds were prepared by the classical method of reacting hydrazines with β – dicarbonyl compounds; since curcumin is "symmetrical" only one tautomer (R = 97).



The reaction of curcumin(1) with thiosemicarbazide afforded in each case a solid product in about 60-87% yield. IR spectrum **(Fig.38)** shows a characteristic peak at 1586.53 cm^{-1} Indicating the presence of imine group and the absence of C=O two groups **[97]** , and the of (C=C) stretching of the aliphatic at 1624.57, band at 1028.65 cm^{-1} for (C-O ether) of methoxy group, and band at 3194.32 $cm^{-1}$for (O-H) phenol , and band at 3005.40 cm^{-1}(NH_2) of compound **[97]** and band at 1728.72 cm^{-1}(C= O) of compound **[97]** The ^{1}H NMR spectrum in (d6-DMSO) of product , **(Fig.39,39$^/$,39$^{//}$)** shows the following NMR data which are consistent with the structure of compound **[97]**. show one proton singlet at δ6.06 ppm compound **[97]** for H- 4 in products of type (B), and three proton singlet at δ 4.14 -3.36 ppm for compound **[97]**, for assigned (s, 6H, 2OCH_3), and one proton singlet at δ 5.56 ppm for compounds **[97]** (2OH) phenol group, the aromatic rings protons gave multiplet signals in the aromatic region δ 6.69 -7.76. At for the rest of spectra see table(5).

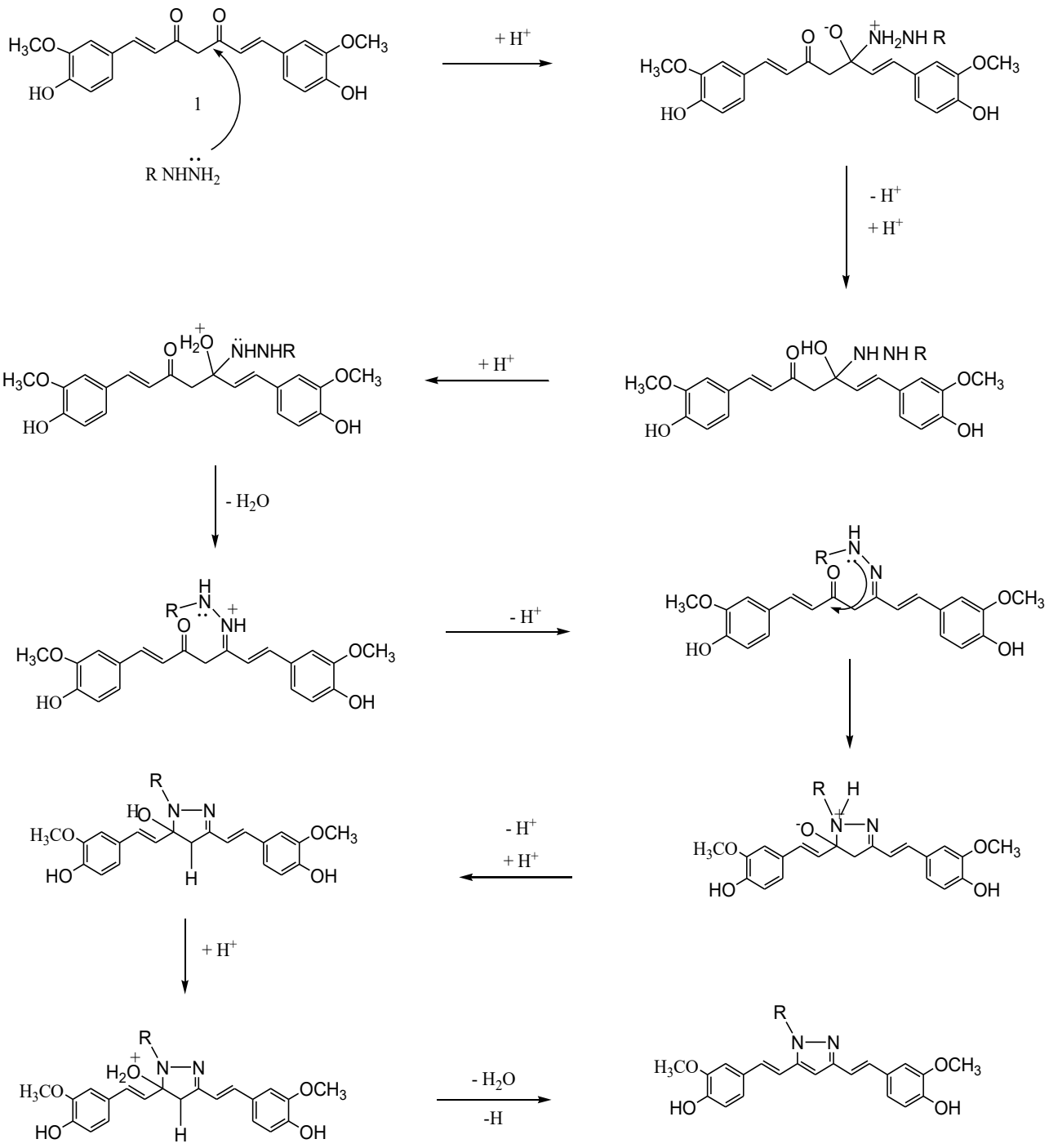
On the other hand,^{13}C- MNR spectra in (d6-DMSO) of compound **[97]**, shows number of resolved carbon signals, **(Fig.40)** shows the following data which are consistent with the structure of compound **[97]** , the imine carbon signal was observed at δ 141.15 for **[97]** and the methyl carbon (O-CH_3) signal was observed at δ 56.23 , and the rest of the resolved carbon signals are corresponding to the aromatic carbon atoms of the product.

Furthermore, the mass spectra of the isolated product **[97] ,(fig. 41) ,** clearly show a peak at 423 , Fragment at and a peak at (M-191) due to loss of (E)-4-(3-iminobut-1-en-1-yl)-2-methoxyphenol ($C_{11}H_{13}NO_2$) and a peak at (M-149) due to 2-methoxy-4-vinylphenol($C_9H_{10}O_2$) for the rest of spectrum **(fig.42)** .

these result indicate the formation of a Schiff base , Through the reaction of the ketone group with hydrazine to give the hydrazone, which is called Schiff bases In the presence of another ketone group, water is removed and the compound is cyclized and a pyrazole compound is formed. This synthesis undergoes schiff base reaction as described by the proposed reaction mechanism .

Reaction mechanism

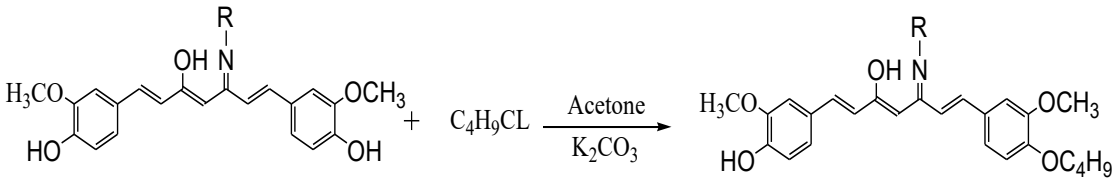
B. Mechanistically, the coupling between curcumin and hydrazines is expected to proceed as shown in scheme (5). Both amino groups of hydrazine make ucleophilic attack on the carbonyl groups of the curcumin followed by loss of two water molecules.



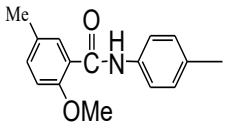
Scheme. 5 : Mechanism of coupling between curcumin and hydrazine

3.1.4- Reaction of curcumin derivatives With alkyl halides.

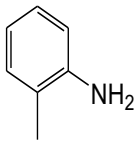
The reaction of curcumin derivatives with alkyl halides in acetone . as the following scheme shows was studied. Due to the importance of the hybridization process and its properties in raising and improving biological and medical properties, the alkylation process was carried out in Acetone as a solvent or in a mixture of acetone and acetonitrile (CN_3CH), route to the curcumin etherification derivatives.



[98]; R =



[99]; R =



The reaction of curcumin derivatives compound **[91,90]**with Butyl chloride And give hybrid curcumin analogues . The S-alkylation reactions were done in the presence of K_2CO_3 in acetone or DMF afforded in each case a solid product in about 55-77% yield. IR spectrum **(Fig. 50)** shows a characteristic peak at,1574.47and 1574.47 cm^{-1} Indicating the presence of imine group and the absence of C=O group and appearance of OH group in the region 3072-2604cm^{-1}, band at 1026.75 cm^{-1} for (C- O ether) of methoxy group and 1005.92 cm^{-1} of Buthoxy group.

The ^1H NMR spectrum in (d6-DMSO) of products , **(Fig.43)** shows the following NMR data which are consistent with the structure of compounds **[98],[99]** . show one proton singlet at δ 6.06,6.07 ppm for compounds[98],[99] and ,for H- 4 in products of type (B), and three proton singlet at δ 4.14 -3.36 ppm for compounds **[98],[99]** for assigned (s, 6H, $2OCH_3$), and one proton singlet at δ5.56, 5.56 ppm for compounds **[98]**, **[99]**for (2OH) phenol group, ^{13}C- MNR spectra in (d6-DMSO) of compounds **[98 , 99]** , shows number of resolved carbon signals, shows the

following data which are consistent with the structure of compounds **[98],[99]** ,the imine carbon signal was observed at δ 141.15,141.14 respectively , and the methyl carbon (O-CH_3) signal was observed at δ 56.23,56.23 , respectively and the hydroxyl carbon(C-OH) signal was observed at δ 183.67, 183.67 respectively, and rest of the resolved carbon signals are corresponding to the aromatic carbon atoms of the product .

Furthermore, the mass spectra of the isolated product**[99] (fig.44) ,** clearly show a peak at 666.3 , Fragment a peak at at(M-192) due to loss of $C_{11}H_{12}O_3$ (M-150) due to $C_9H_{10}O_2$ cation and for the rest of spectrum **(fig.45).**

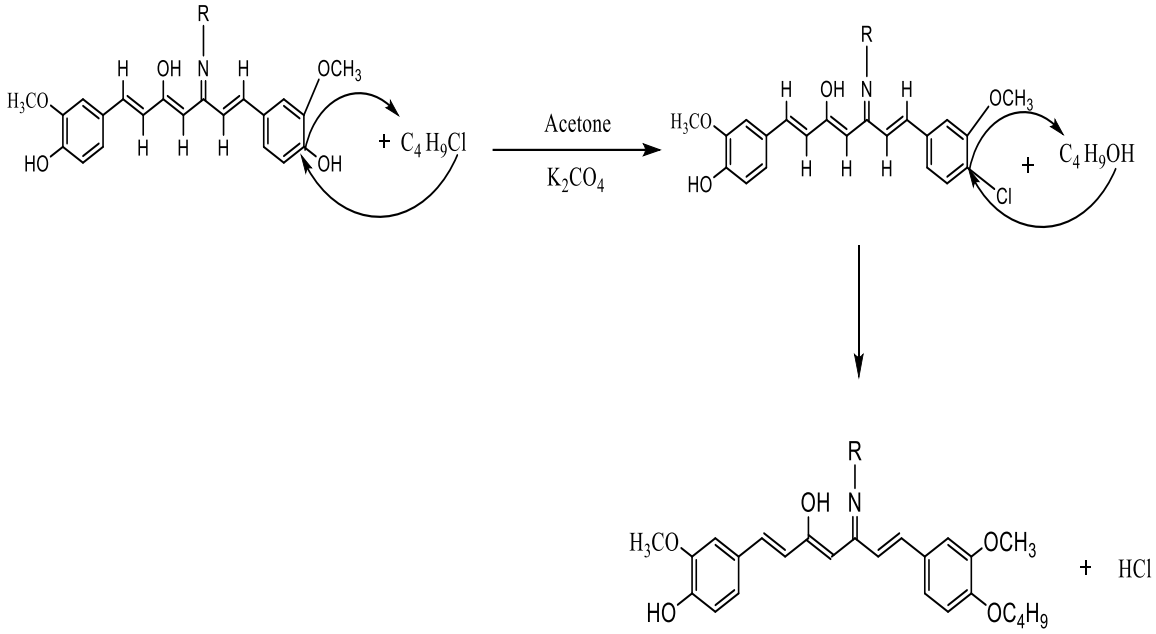
Both IR and NMR and Mass spectral data are in agreement with the possible structure of the product compounds . The results showed the formation of the corresponding ether.

The products were prepared in conditions of power outages. This may lead to a difference in the production rate and an increase in the reaction time.

As a result of the success of the reaction, researchers can continue this reaction and introduce more active groups than the butyl group.

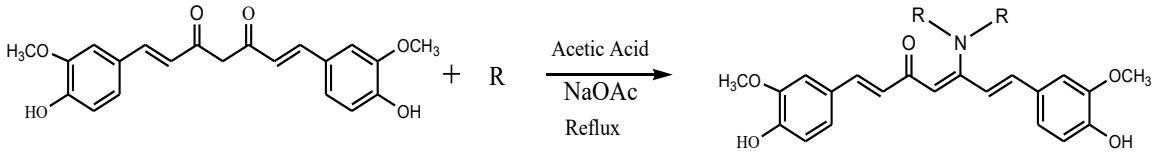
Reaction mechanism

C. The mechanism for reaction of curcumin derivatives with alkyl halides as shown in scheme (6).

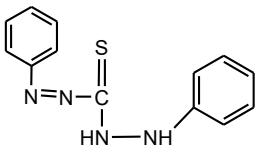


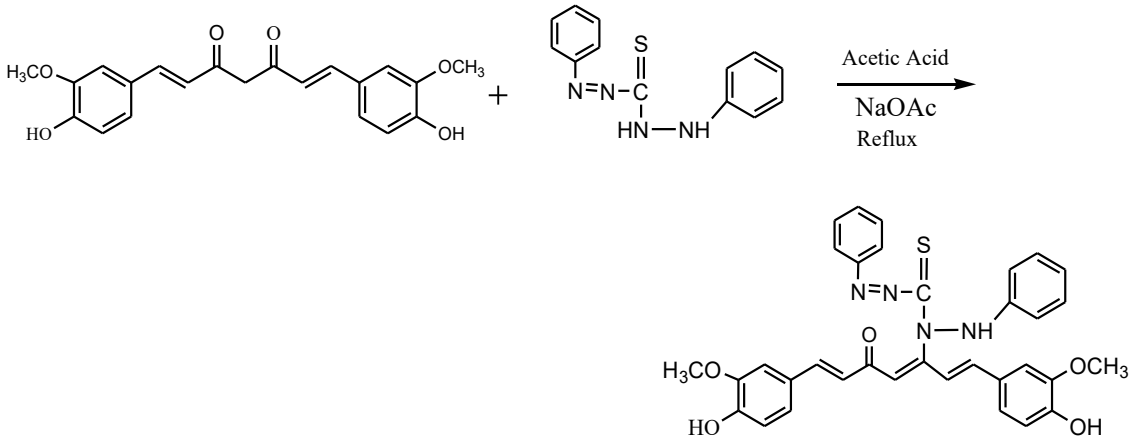
3.1.5- Reaction of curcumin derivatives With Aromatic Secondary Amines

The reaction of curcumin with Secondary amines of the type R_2-NH in glacial acetic acid as the following scheme shows was studied.



[100];R=





The reaction of curcumin(1) with 1,5-diphenylthiocarbazone afforded in each case a solid product in about 60-87% yield. IR spectrum **(46)** shows a characteristic peak at 1573.56 cm^{-1} Indicating the presence of imine group and the absence of C=O two groups **[100]** , and the of (C=C) stretching of the aliphatic at 1624.57, band at 1027.96 cm^{-1} for (C-O ether) of methoxy group, and band at 3266.20 $cm^{-1}$for (2O-H) phenol , and band at 1728.72 cm^{-1}(C= O) of compound **[100]** . The ^{1}H NMR spectrum in (d6-DMSO) of products , **(Fig.47,47/)** shows the following NMR data which are consistent with the structure of compound [100].show one proton singlet at δ6.06,6.07ppm compound [100] for H- 4 , and three proton singlet at δ 4.14 -3.36 ppm for compound ,**[100]**, for assigned (s, 6H, $2OCH_3$), and one proton singlet at δ 5.56 ppm for compound **[100]**for (2OH) phenol group, the aromatic rings protons gave multiplet signals in the aromatic region δ 6.69 -7.76. At for the rest of spectra see table(5).

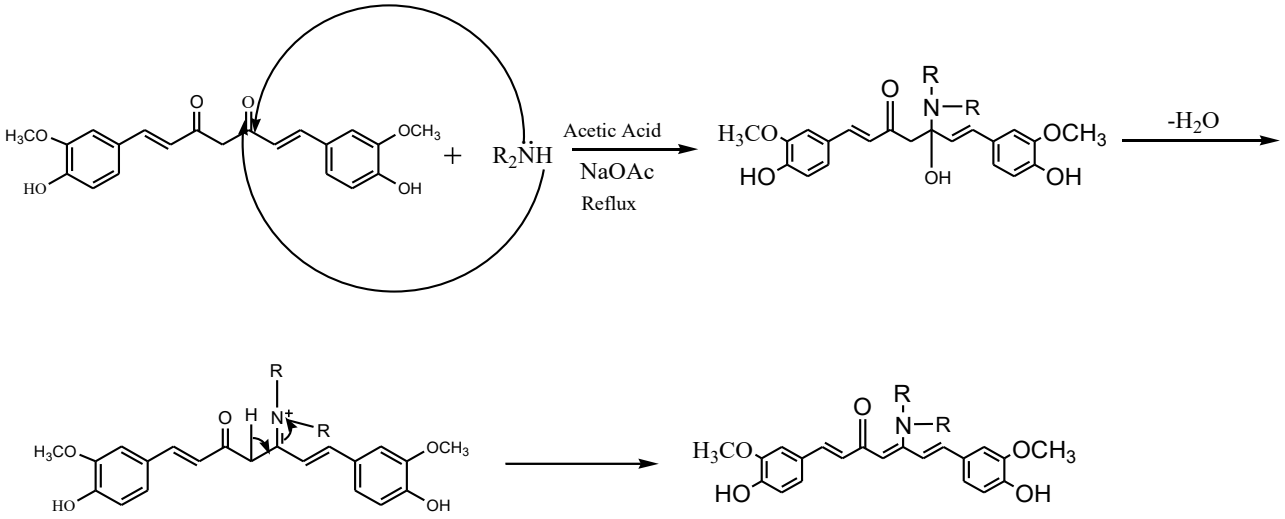
On the other hand,^{13}C- MNR spectra in (d6-DMSO) of compound **[100]** , shows number of resolved carbon signals, shows the following data which are consistent with the structure of compound **[100]**, the enamine carbon signal was observed at the C-N for [100] at δ 68.24 in products of type (D) and the methyl carbon (O-CH_3) signal was observed at δ 56.23, and the rest of the resolved carbon signals are corresponding to the aromatic carbon atoms of the product.

Furthermore, the mass spectra of the isolated product[100] **(fig.48) ,** clearly show a peak at m/z = 608.21 $C_{34}H_{32}N_4O_5S$, Fragment a peak at (M- 432.16) due to 2-((E)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-yl)-1,5-diphenylthiocarbazone ($C_{24}H_{24}N_4O_2S$) cation and (E)-4-(but-1-en-3-yn-1-yl)-2-methoxyphenolate ($C_7H_5N_2S^{+}$) a peak at (M- 149.02) and apeak at (M-173.o6) due to loss of 2-methoxy-4-vinylphenolate ($C_{11}H_9O^{2-}$) and for the rest of spectrum **(fig.49).**

These result for compound **[100]** rule out the possibility of Schiff base, The reason is that the reaction with primary amines gives imines $R_2C=NR$ while the reaction with secondary amines gives enamines R_2N- $CR=CR_2$ and the reaction is favoured at pH=4.5 initially forming a tetrahedral intermediate.

Reaction mechanism

D. Mechanistically, the coupling between curcumin and Secondary Amines is expected to proceed as shown in scheme (7)



3.2-Biological results

3.2.1- Antimicrobial Activity of Synthesized Compounds

Screening Results :

In vitro biological screening effects of the investigated compounds were tested against the bacteria , Escheria coli, Klebsiella pneumonia (gram- negativ) and Staphylococcus aureus ,Staphylococcus agalacteae (gram - positive). The results of the prepared compounds(89-100) for antibacterial testing are shown in Table (6).

The result of antimicrobial activity showed clearly that all tested compound exhibited antibacterial activity of the compounds showed a good activity against the four used strains.

Table [6] : Antibacterial activity of the compounds by well diffusion method.

Screening results (Zone of inhibition mm)[100 ppm]

Compound No.	E. coli	Klebsiella pneumoniae	Staphylococcus aureus	Staphylococcus agalacteae
89	10	11	12	0
93	12	12	12	11
90	11	11	10	12
94	12	11	12	15
96	0	0	0	0
95	12	14	12	11
97	11	11	11	13
91	11	10	11	0
92	11	12	10	12
100	10	10	10	12
99	0	0	0	0

Table [6] : Antibacterial activity of the compounds by well diffusion method.

Screening results (Zone of inhibition mm)[200 ppm]

Compound No.	E. coli	Klebsiella pneumoniae	Staphylococcus aureus	Staphylococcus agalacteae
89	14	12	14	0
93	13	13	13	11
90	12	12	12	13
94	13	13	13	15
96	0	0	11	0
95	14	16	14	11
97	12	13	12	14
91	12	11	13	0
92	12	13	11	13
100	11	11	11	13
99	0	0	10	0

Table [6] : Antibacterial activity of the compounds by well diffusion method.

Screening results (Zone of inhibition mm)[300 ppm]

Compound No	E. coli	Klebsiella pneumoniae	Staphylococcus aureus	Staphylococcus agalacteae
89	15	14	15	0
93	14	14	13	12
90	12	13	14	14
94	15	14	15	17
96	0	12	12	0
95	15	16	16	12
97	12	14	14	15
91	12	13	13	0
92	13	14	12	14
100	12	11	12	15
99	11	11	11	0

Compounds (99) did not show activity when using a concentration of [100 ppm] and gave good activity at concentrations [200,300 ppm]. Also, compound 96 did not give a good response except at a concentration of [300 ppm] against the two types of bacteria, Klebsiella pneumoniae and Staphylococcus aureus, and at a concentration of [200 ppm] it gave a good response against Staphylococcus aureus only. The remaining compounds gave a good response against the four types of bacteria at all concentrations. The highest response was for compounds 95 and 94.

3.2.2- Antioxidant Activity

Biological activities of the synthesized analogues were studied by comparing their activities with those of curcumin. This biological assessment included examining the antioxidant capacity via DPPH and hydroxyl radical scavenging activity tests, t was found that these analogues have the comparable antioxidant activities but with better stability and water solubility in comparison with curcumin . It is postulated that such analogues may be useful clues to improve the therapeutic applications of curcumin **Fig [5,6,7]** . The reaction of the antioxidant with DPPH reduces the purple color of the DPPH solution to a colorless color, which can be measured spectrophotometrically at a wavelength of 517 nm, indicating the presence of antioxidant activity and a certain strength of this substance. By evaluating the antioxidant activities of the prepared curcumin derivatives, it was found that the lower the concentration, the more the purple color disappears and the absorption increases (the lower the concentration, the greater the ability of the derivative to reduce the DPPH compound), meaning strong antioxidant activity.

According to the results shown in Figure (20, 21, 22), compounds 100, 94, and 91 gave the strongest antioxidant activity, while compound 96 had the lowest antioxidant activity, compared to ascorbic acid (1A).

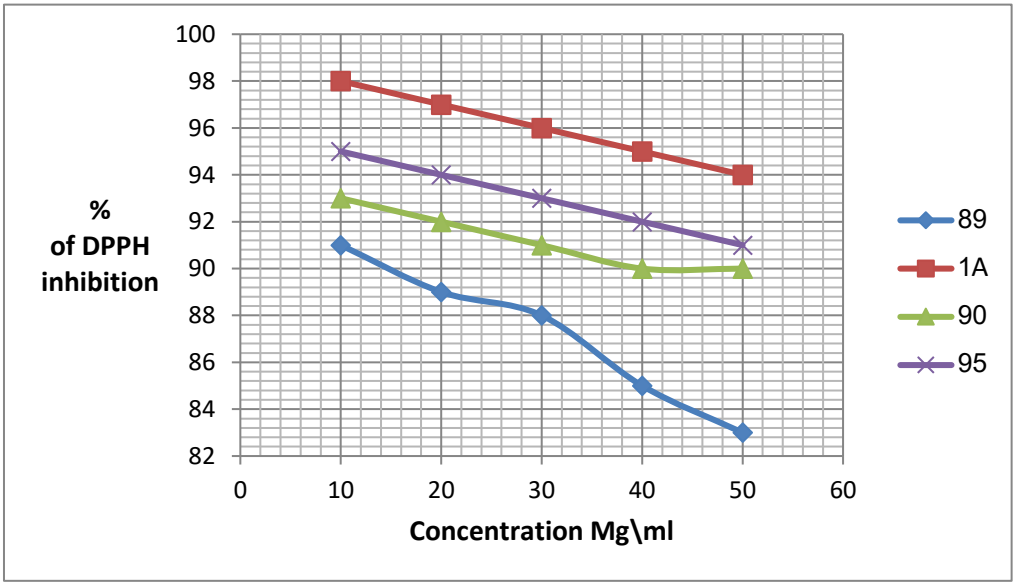


Fig.5 - Percentage of DPPH inhibition for curcumin derivatives

for Compounds at different concentrations [89] ,[90],[95]

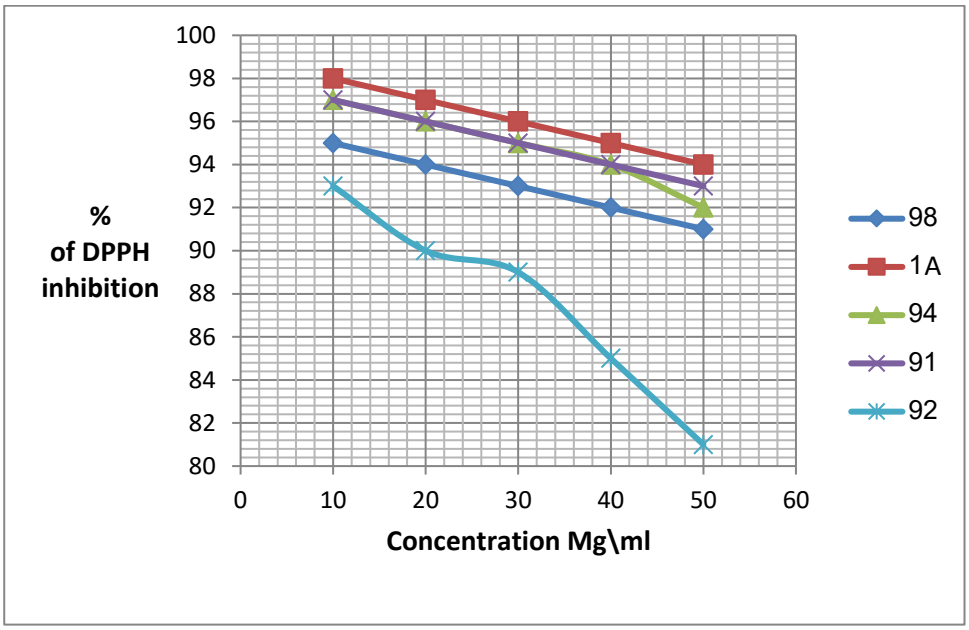


Fig.6 - Percentage of DPPH inhibition for curcumin derivatives for Compounds at different concentrations [98] ,[94],[91],[92]

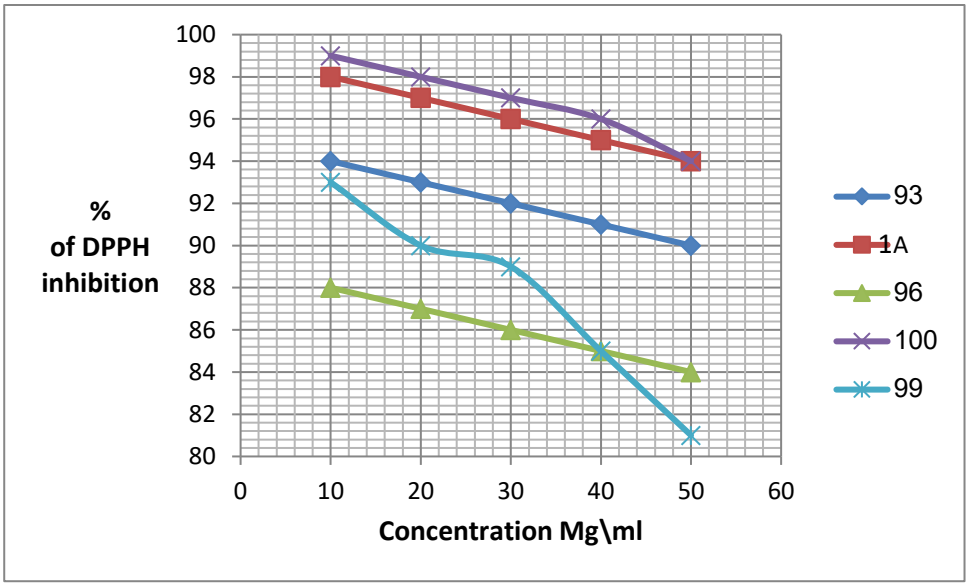


Fig.7- Percentage of DPPH inhibition for curcumin derivatives for Compounds at different concentrations [93] ,[96],[100],[99]

CONCLUSION

In this study, a number of curcumin derivatives (89-100) were prepared by steps **A, B, C,** and **D**. In step **A**, we obtained compounds 89-96 by reacting curcumin with some primary aromatic and aliphatic ammonia derivatives , We obtained compound 100 in step **D**, where curcumin reacted with a secondary ammonia derivative. In step **B**, we obtained compound 97 from the reaction of curcumin with a hydrazine derivative. As for compounds 98 and 99, we obtained them in step **C** from the reaction of derivatives 90 and 93 with an alkyl halide.

Then these compounds (89-100) were characterized using were analyzed by various analytical and spectroscopic techniques, such as: melting point, TLC, ^{1}H- NMR, ^{13}C- NMR, IR, and mass spectroscopic . In all cases, results are consistent with the expected structures. All compounds were obtained in acceptable yield (54% to 87%).

The biological activity of these compounds was evaluated against four strains of bacteria (Staphylococcus aureus , Staphylococcus agalacteae , Escheria coli , Klebsiella pneumonia) At three different concentrations: 100 ppm, 200 ppm, 300 ppm. The results showed remarkable effectiveness against bacteria, especially compound 95.

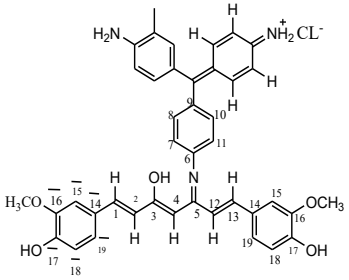
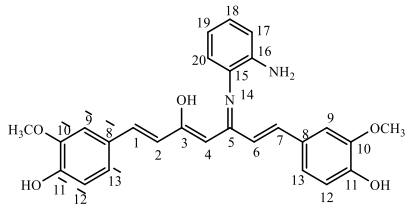
The antioxidant activity of these compounds was also evaluated by measuring their ability to reduce DPPH. The results showed a clear antioxidant capacity of these compounds, especially compounds 100 and 96.

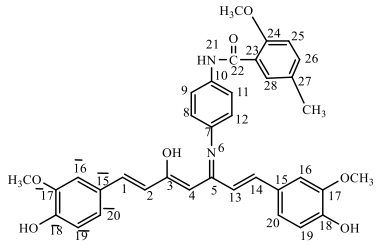
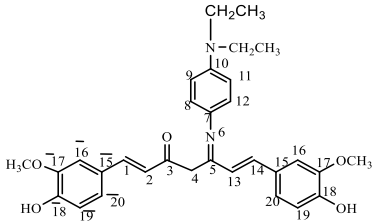
Recommendations

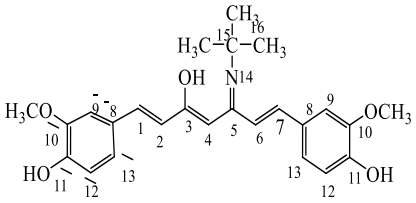
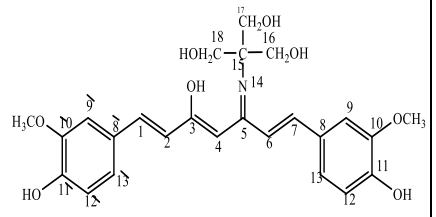
Exploring innovative curcumin derivatives offers promising strategies to address the challenges associated with its bioavailability and efficacy and valuable insights for future research directions.

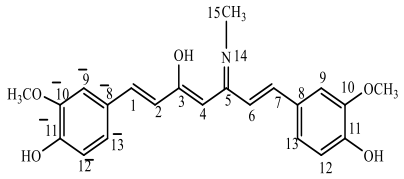
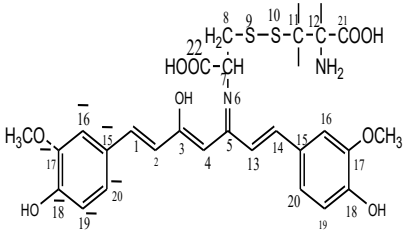
Future research should be focused on bringing this fascinating molecule to the forefront of therapeutic agents for the treatment of human diseases.

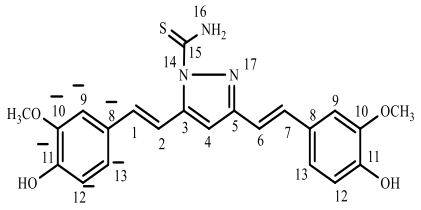
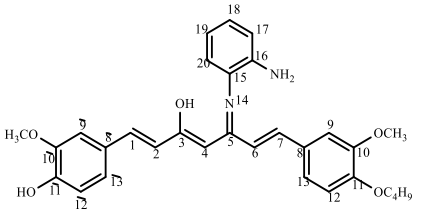
Table(5):Spectral data of compounds [89-100]

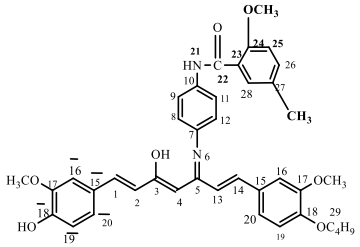
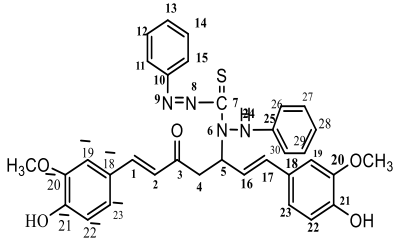
Compound No.	IR (K Br) v cm^{-1}	^{1}H-NMR(400 MHz)d_6-DMSO δ(ppm)	^{13}C-NMR(101MHz)d_6-DMSO δ (ppm)
 **89**	1583.82(C=N),1025.91 (OCH_3),1626(C=Caliphatic) , 3188-3327 (NH_2) , 2639 (O-H of phenol) .	3.78 (s, 6H, OCH3) , 8.8-9.45 (s, 2H, OH), 4.0 (S, 4H,NH_2) , 5.9 (s, 2H ,OH), 7.30 (S,2H, Ar-H), 7.14(d, *J* = 8.3 Hz, 2H , Ar-H) , 7.53 (d, *J* = 15.8 Hz, 2H,Ar-H), 3.36(s, CH_3), 6.03 (S, $1H_4$), 7.82 – 6.25 (m, 11H Ar-H), 6.78 (d , *J* = 33.9, 12.1 Hz, 4H).	56.23(OCH_3),149.99(C_{17},C_{17}),148.53(C_{16},C_{16}),141.14(C_5),101.21(C_4), 111.96-149.99 (C-aromatic).
 **90**	1567 (C=N) , 1028 (OCH3) , 1623(C=Caliphatic), 3190 (O-H of phenol),2300 (NH_2).		

 **91**	1555.97 (C=N) , 1028.3 3 (OCH3),1624.1(C=Caliphatic) 3179.9-(O-H of pheno 1202.23(C-N)1624.14(C=O) amid grop .	4.74−3.73(s, 6H, OCH3), 5.56 (S,2H, 2OH), 6.98 (S,2H,Ar−H) ,7.04 (d, J = 15.8, Hz, 2H,ArH)7.15(d,J=14.33Hz,2H,ArH),6.07(S,1H_4), 9.5 (S,1H,OH) 7.57− 6.07(m, 4H), 8.99(S,1H,NH), 8.29−7.24(m,8H−Ar),	56.23(OCH_3), 149.86(C_{17},C_{17}^-), 148.51(C_{16},C_{16}^-),141.16(C_5) ,101.22(C_4),110.74−149.86 (C−aromatic),17.64(CH_3)
 **92**	1585.67 (C=N) , 1027.23 (OCH3) , 1625.83 (C=C aliphatic) , 3360-3484 (2O-H of phenol),1266-1231.8(C-N),1732.8(C=O) .	4.32 −3.70(s, 6H, OCH3), 5.50 (S,2H, 2OH), 6.68(S,2H,Ar−H),6.77(d, J = 15.5, Hz, 2H,Ar−H)7.15 (d,J=14.32Hz,2H,ArH),6.07(S,1H_4),9.68 (S,1H,OH), 6.84− 6.51(m, 4H), 1.97−1.03 (q,4H,CH_2), 3.37−3.17(t,6H,CH_3).	56.22(OCH_3), 159.32(C_{17},C_{17}^-), 148.50(C_{16},C_{16}^-),141.14(C_5) ,101.23(C_4),110.85−159.32 (C−aromatic),30.91(CH_2), 19.56(CH_3),96.98−68.25(C_7).

 **93**	1567(C=N),1028(OCH3),1622 (C=Caliphatic), 3189.27(O-H of phenol).	3.84 -3.45(s, 6H, OCH3) , 9.87-9.66 (S,1H,OH), 4.15(S,2H, 2OH), 6.68 (S,2H, Ar-H),7.55(d, *J* = 15.7, Hz, 2H ,Ar-H),7.33(d,*J* =14.66 Hz, 2H,Ar-H), 6.06 (S,1H$_4$), 6.86 – 6.77 (m, 4H), 1.31-0.93(S,9CH$_3$).	56.23 (OCH$_3$) , 149.83 (C$_{17}$,C$_{17}$), 148.50 (C$_{16,}$C$_{16}^-$), 141.15 (C$_5$) , 101.21(C$_4$), 111.92-149.83 (C-aromatic),19.90(CH$_3$).
 **94**	1557 (C=N) , 1025(OCH3) , 1625 (C=C aliphatic),3667.7 (O-H of phenol)	3.84 -3.04(S, 6H, OCH3) , 9.87-9.66 (S,1H,OH),4.15(S,2H,2OH),(S,2H,Ar-H)7.55 (d, J = 15.7, Hz, 2H,Ar-H),7.33(d,*J* =14.66 Hz,2H,Ar-H),6.06(S,1H$_4$),7.56-7.47(m,4H), 1.99-1.16(S,3H,OH), 1.26 – 1.13 (m, 6H, CH$_2$).	56.23(OCH$_3$), 149.85(C$_{17}$,C$_{17}^-$), 148.50(C$_{16,}$C$_{16}^-$),141.14(C$_5$) , 101.22(C$_4$),111.96-149.85 (C-aromatic) .

 **95**	1567.73 (C=N),1029.1(OCH3), 1622.75(C=Caliphatic),3316.2 (O-Hof phenol).	4.32 -3.02(s, 6H, OCH3), 9.68 (S,1H,OH), 5.50-5.13 (S,2H, 2OH), 6.68(S,2H,Ar-H),6.75(d, J = 15.7, Hz, 2H,Ar-H)6.79(d,*J* =14.66 Hz, 2H,Ar-H),6.06 (S,1H_4), 7.75–6.68(m, 4H), 1.31-1.02(S,3H) .	56.23(OCH_3), 149.84(C_{17},C_{17}^-), 148.50(C_{16},C_{16}^-),141.14(C_5) , 101.23(C_4),111.94-149.85 (C-aromatic),20.49(CH_2) .
 **96**	1558 (C=N) , 102 9(OCH3), 1623.22 (C=C aliphatic), 2935.04 (NH_2), 3331(O-H of phenol) ,	4.65-3.66(S,6H,OCH3),9.67(S,1H,OH),4.15(S, 2H,2OH),(S,2H,Ar-H)7.55 (d, J = 15.7, Hz, 2H,ArH),7.33(d,*J*=14.66Hz,2H,ArH),6.06(S,1H_4),6.076.69(m,4H),9.87(S,2H,COOH),2.61(S,1H), 1.92-1.04(m,9$H_{11,12}$),3.36-2.67(d,2H_8),2.34 (S,2H,NH_2).	56.23(OCH_3), 149.85(C_{17},C_{17}^-), 148.50(C_{16},C_{16}^-),141.14(C_5) , 101.21(C_4),111.95-149.85 (C-aromatic), 20.56(CH_2), (CH_3)19.95, 183.67(COOH).

 **97**	1586.53-1551.57(C=N) ,1028.65(OCH3),1624.57(C=C aliphatic) , 3194.4 (2O-H of phenol) , 3194.32(NH2).	4.14 -3.66(S, 6H, OCH3), 5.56-5.13 (S,2H, 2OH), 6.68(S,2H,Ar-H),7.55(d, J = 15.8, Hz, 2H,Ar-H)7.16 (d,*J*=14.33 Hz,2H,Ar-H),6.62 (S,1H_4), 7.57– 6.62(m, 4H),2.09 (S,2H,NH_2).	56.22(OCH_3), 149.82(C_{17},C_{17}^-), 148.50(C_{16},C_{16}^-),141.14(C_5) , 101.22(C_4),111.89-149.82 (C-aromatic),1820 -1840 (C = S) .
 **98**	1587.65 (C=N) , 1026.96 (OCH3),1623.93(C=Caliphati), 3230(2O-H of phenol), 2600-2800 (NH_2) amine.	3.32 -3.17(S, 6H, OCH_3), 9.68 (S,1H,OH), 5.50-5.13 (S,2H, OH), 6.68(S,2H,Ar-H),6.75(d, J = 15.7, Hz, 2H,Ar-H)6.79(d ,*J* =14.66 Hz, 2H,Ar-H),6.06 (S,1H-4), 7.75– 6.68(m, 4H), 1.76-1.06(S,9H)	

 **99**	1573.65(C=N),1027.96(OCH3) , 1624.93 (C=Caliphatic),3266. (2O-Hof phenol),1728.7(C=O).	4.42-3.38 (s, 6H, OCH3) , 5.67-5.09 (S,2H, 2OH),6.98(S,2H,ArH),7.04(d,J15.8,Hz,2H,ArH) 7. 15(d,„*J*=14.33Hz,2H,ArH),6.07(S,1H_4), 9.85 (S,1H,OH) 6.93– 6.55(m, 4H), 4.42 (S,1H, NH), 7.74-6.69(m,10H-Ar), 4.64-1.14 (m,9H).	56.23(OCH_3), 149.85(C_{17},C_{17}-), 148.50(C_{16},C_{16}-),141.14(C_5) , 101.22(C_4),111.96-149.85 (C-aromatic) .
 **100**	1264.55-1206.11(C-N), 1027.96(OCH3),1624.93(C=C aliphati)3607(2OHof phenol), 1728.72 (C=O).	4.42-3.15(s,6H,OCH3), 5.56-5.14 (S,2H,2OH), 6.98(S,2H,ArH),7.04(d,J15.8,Hz,2H,ArH)7.15(d „*J*=14.33Hz,2H,Ar H),6.07(S,1H_4),9.86(S,1H,OH) 6.93– 6.55(m, 4H), 4.42 (S,1H, NH), 8.29-7.74-6.69(m,10H-Ar).	56.23(OCH_3), 141.14(C_5) , 68.24(C_4),111.95-148.50 (C-aromatic),30.91(C_7), 19.56(C_{25}) .

Appendix of Spectral Data

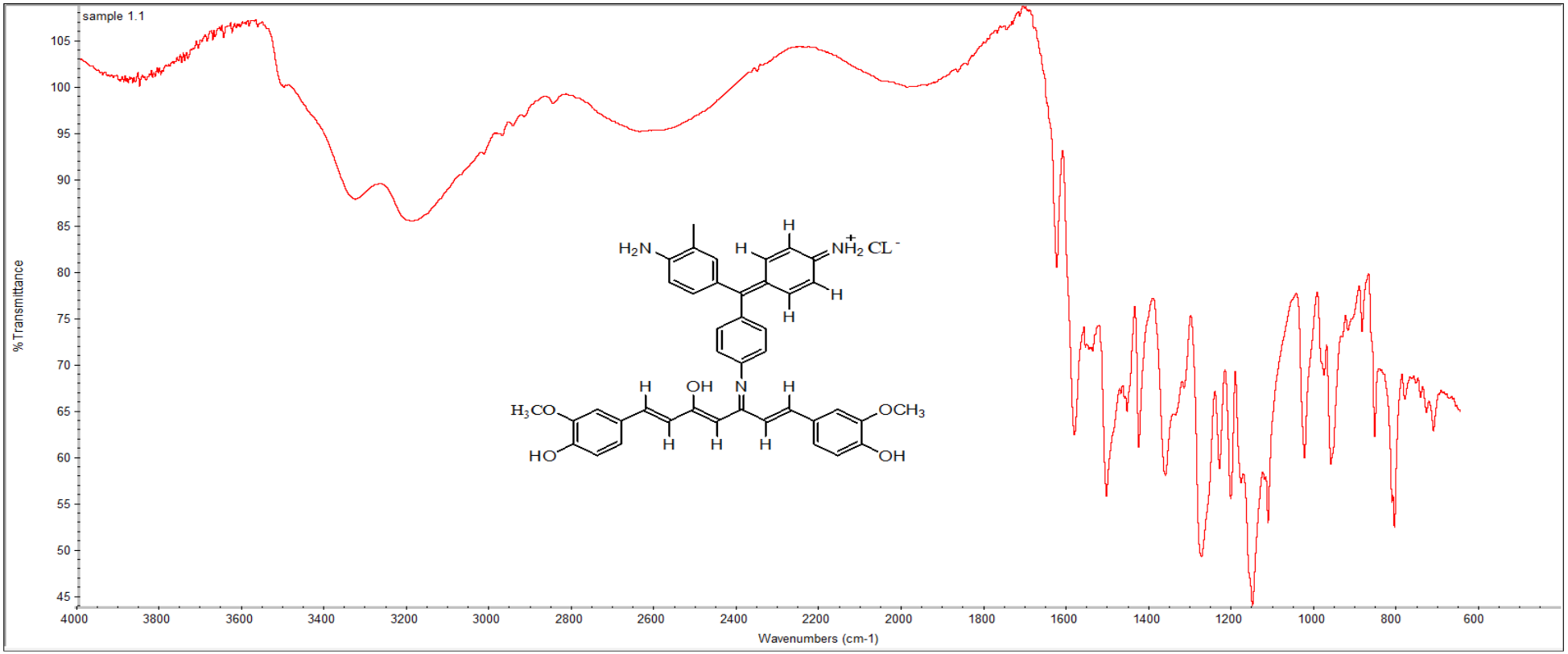


Figure. 8: The IR spectrum of compound [89].

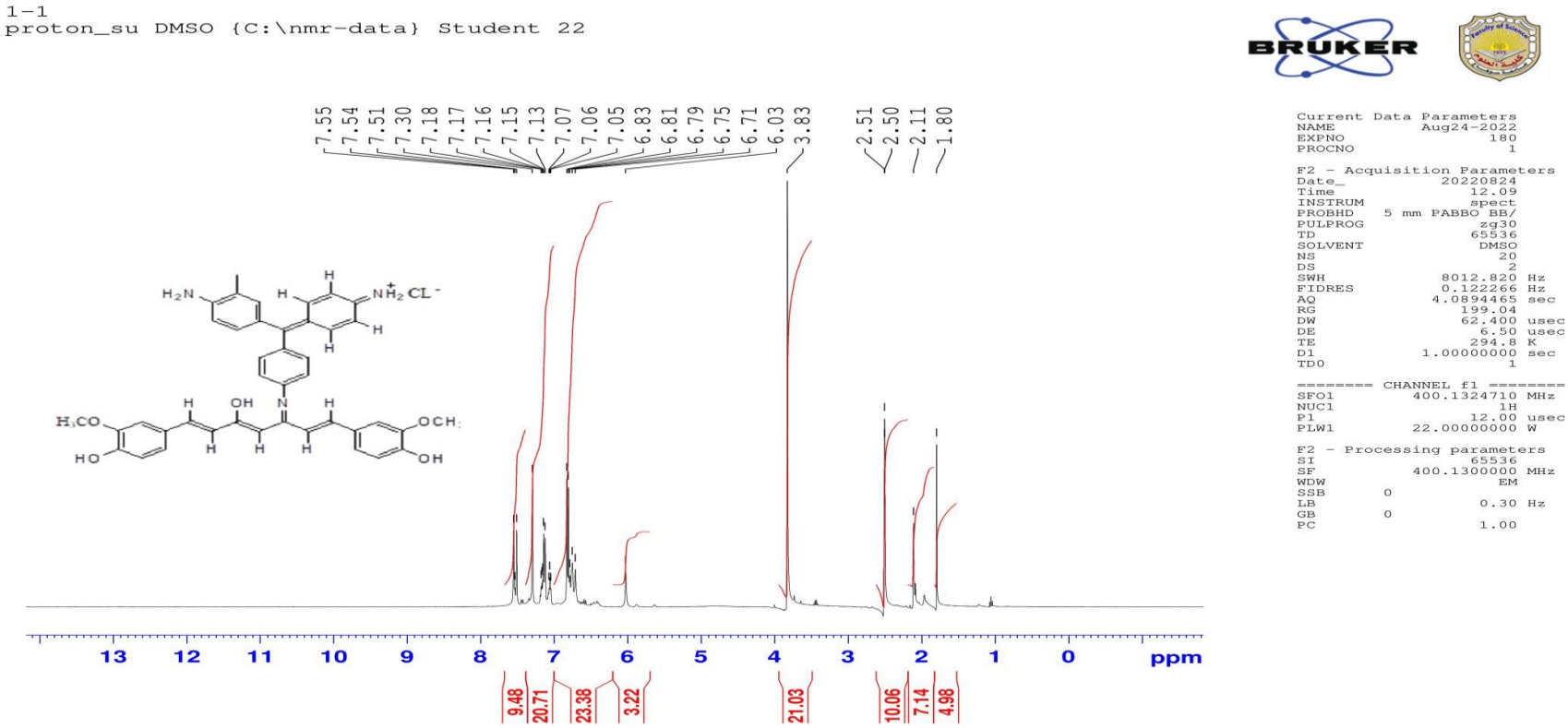


Figure.9 : The[1]H- NMR spectrum of compound [89]

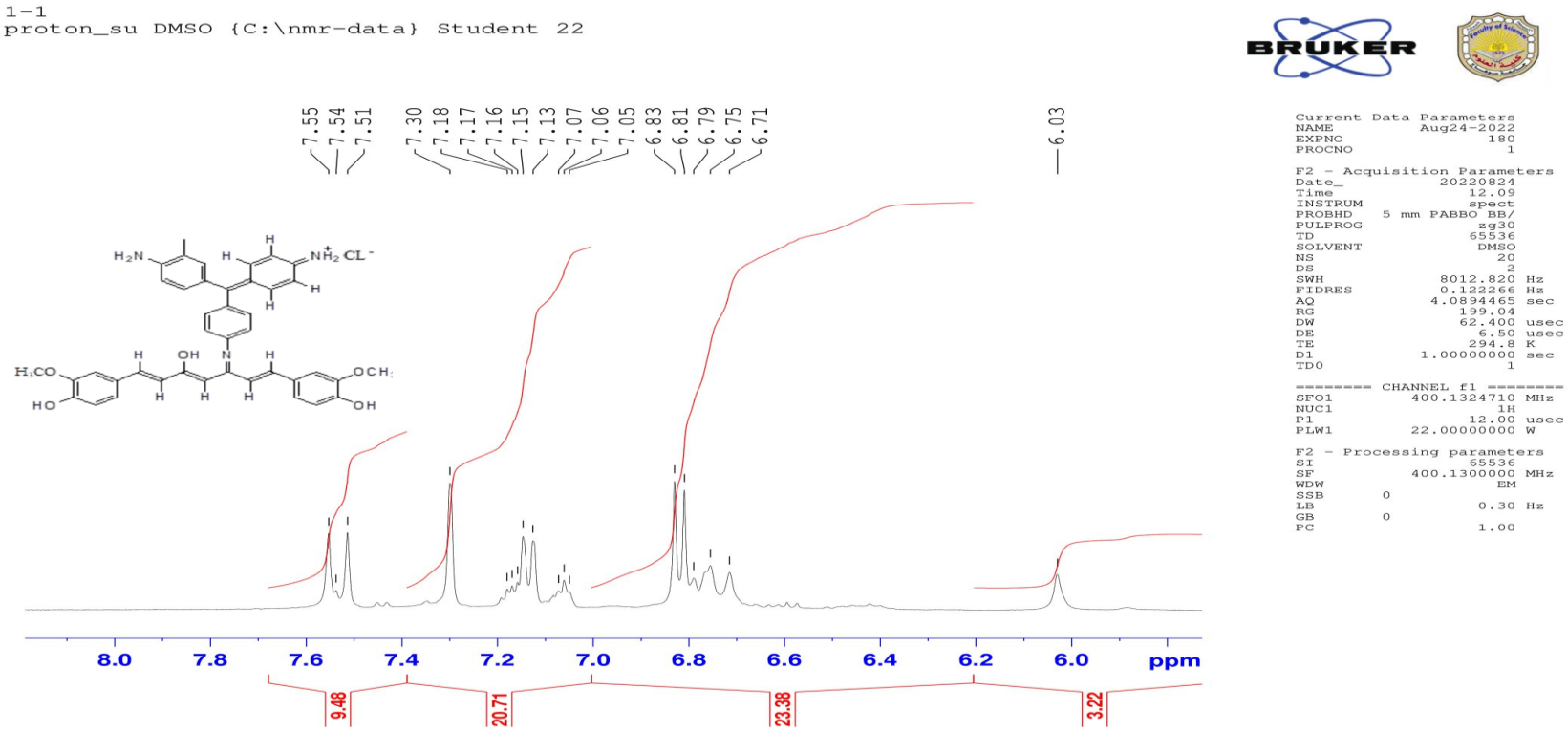


Figure .9/ : The ^{1}H NMR spectrum of compound [89].

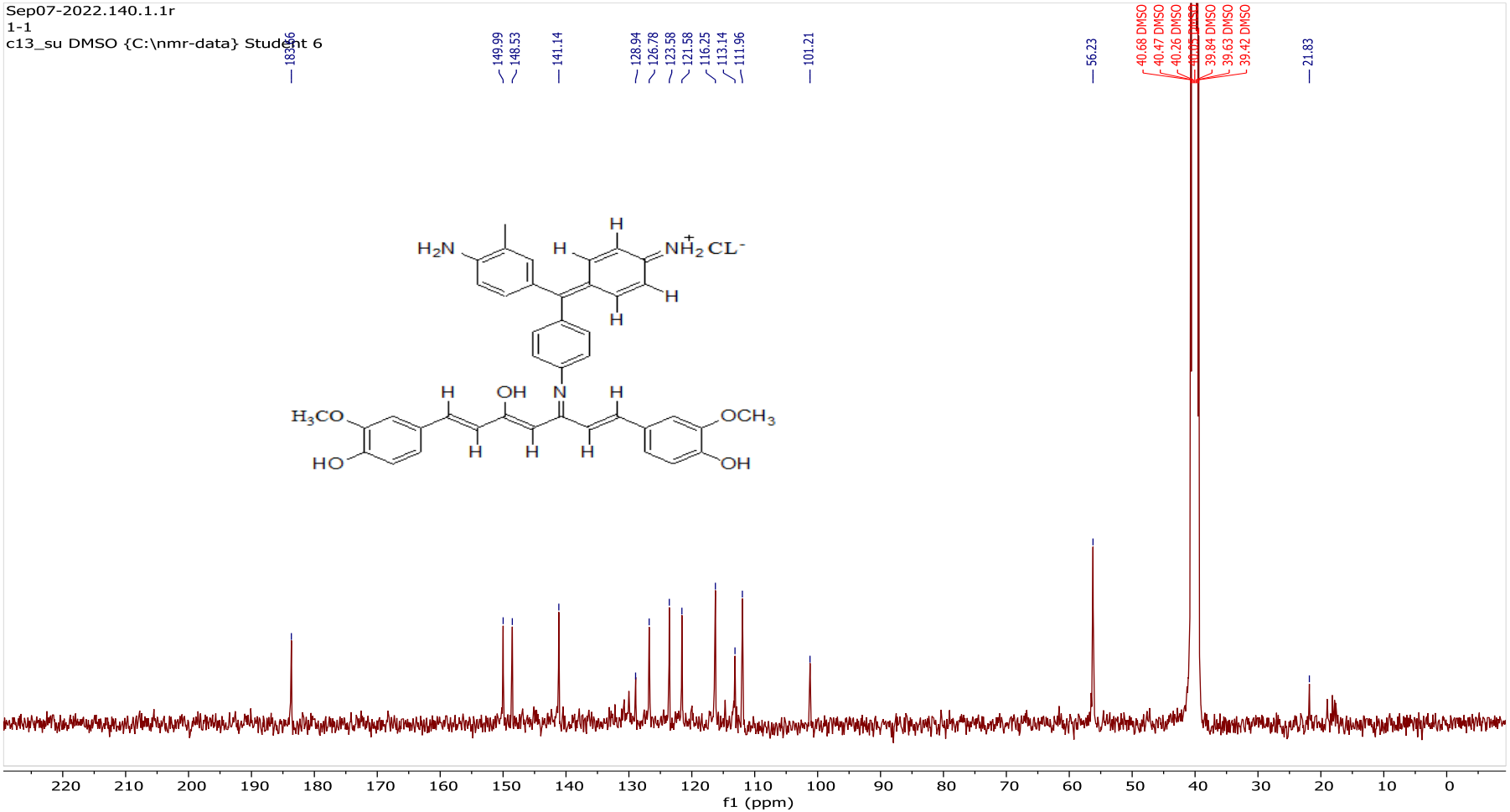


Figure. 10: The^{13}C- NMR spectrum of compound [89]

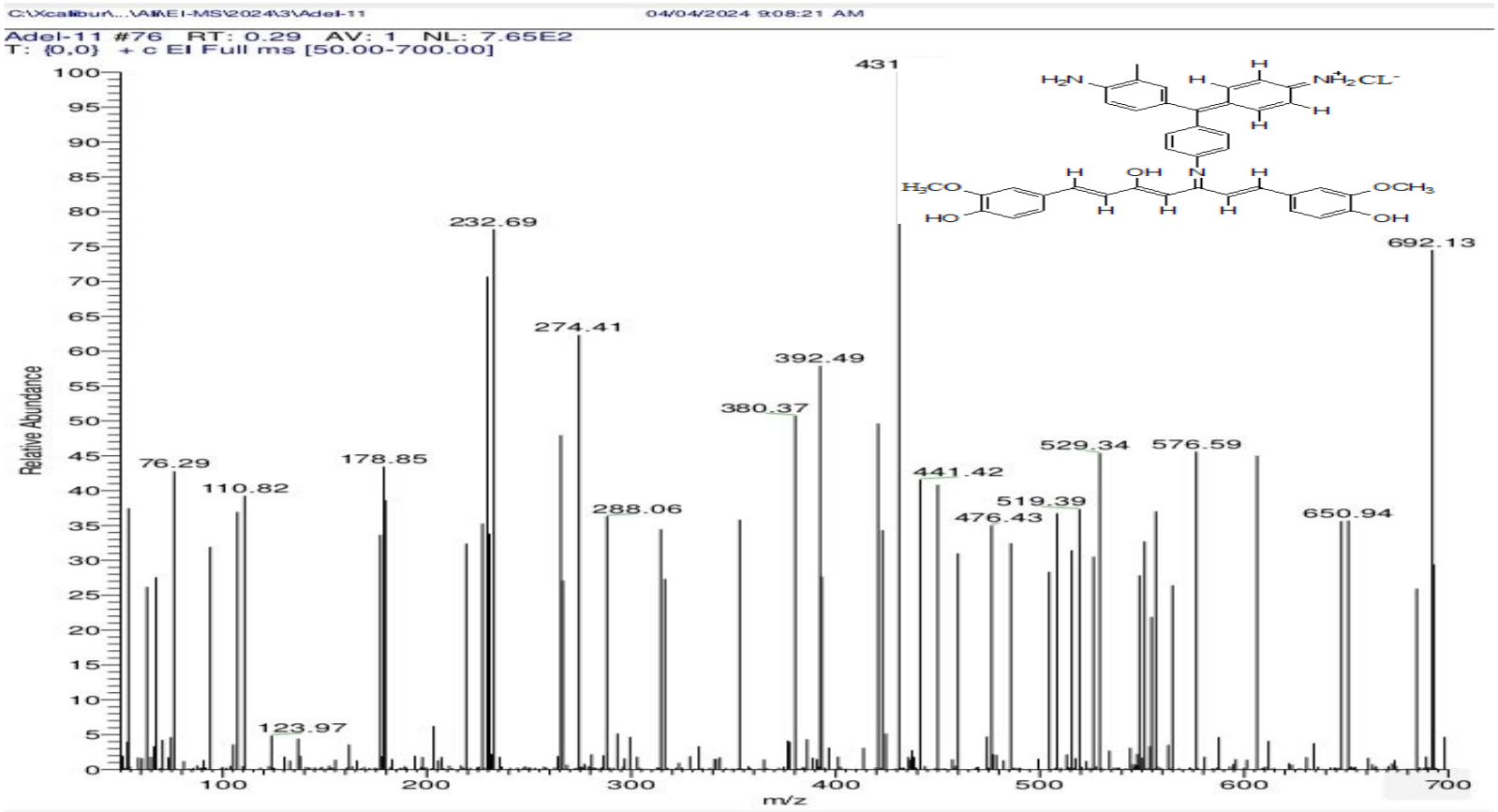


Figure.11 : The Mass spectrometry of compound [89].

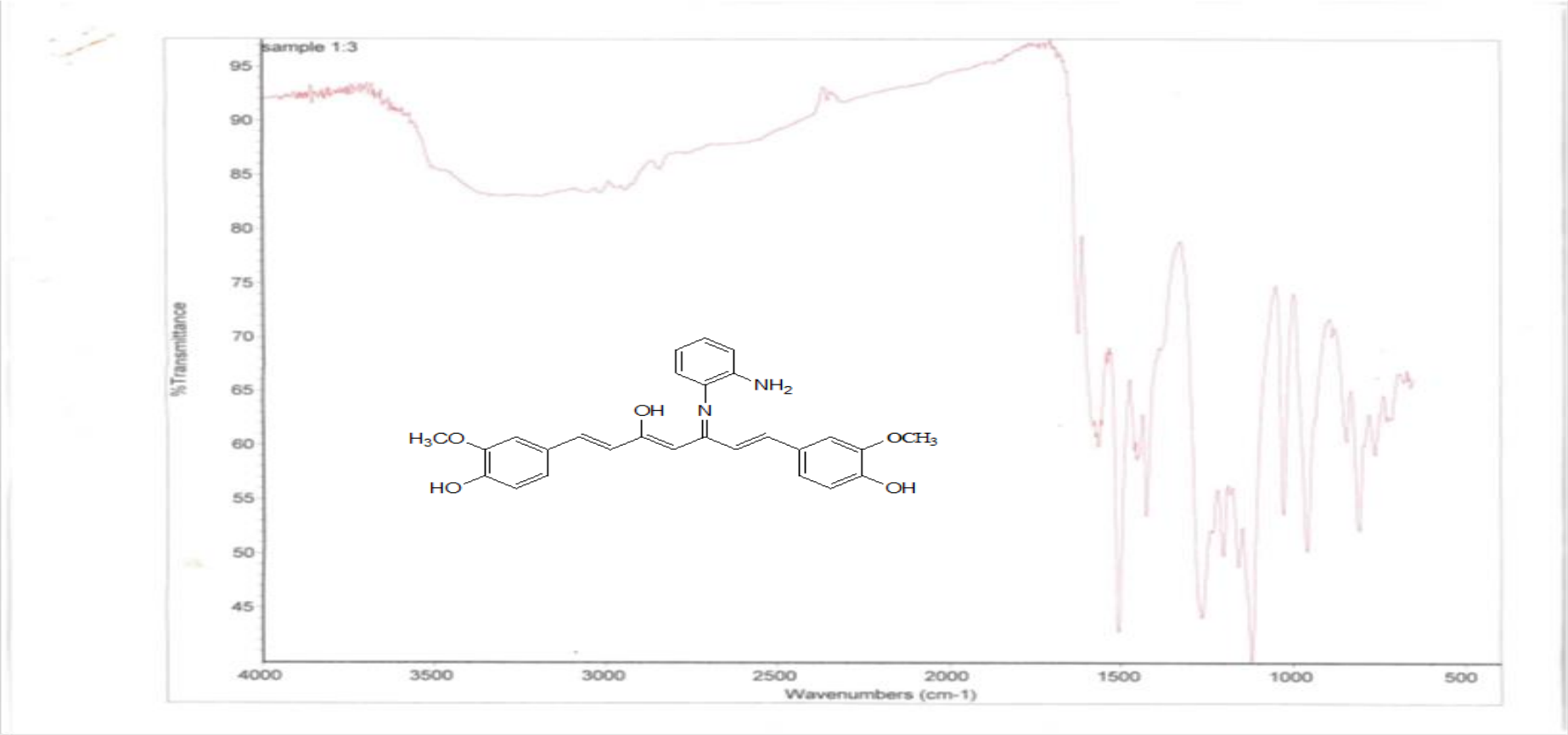


Figure. 12: The IR spectrum of compound [90].

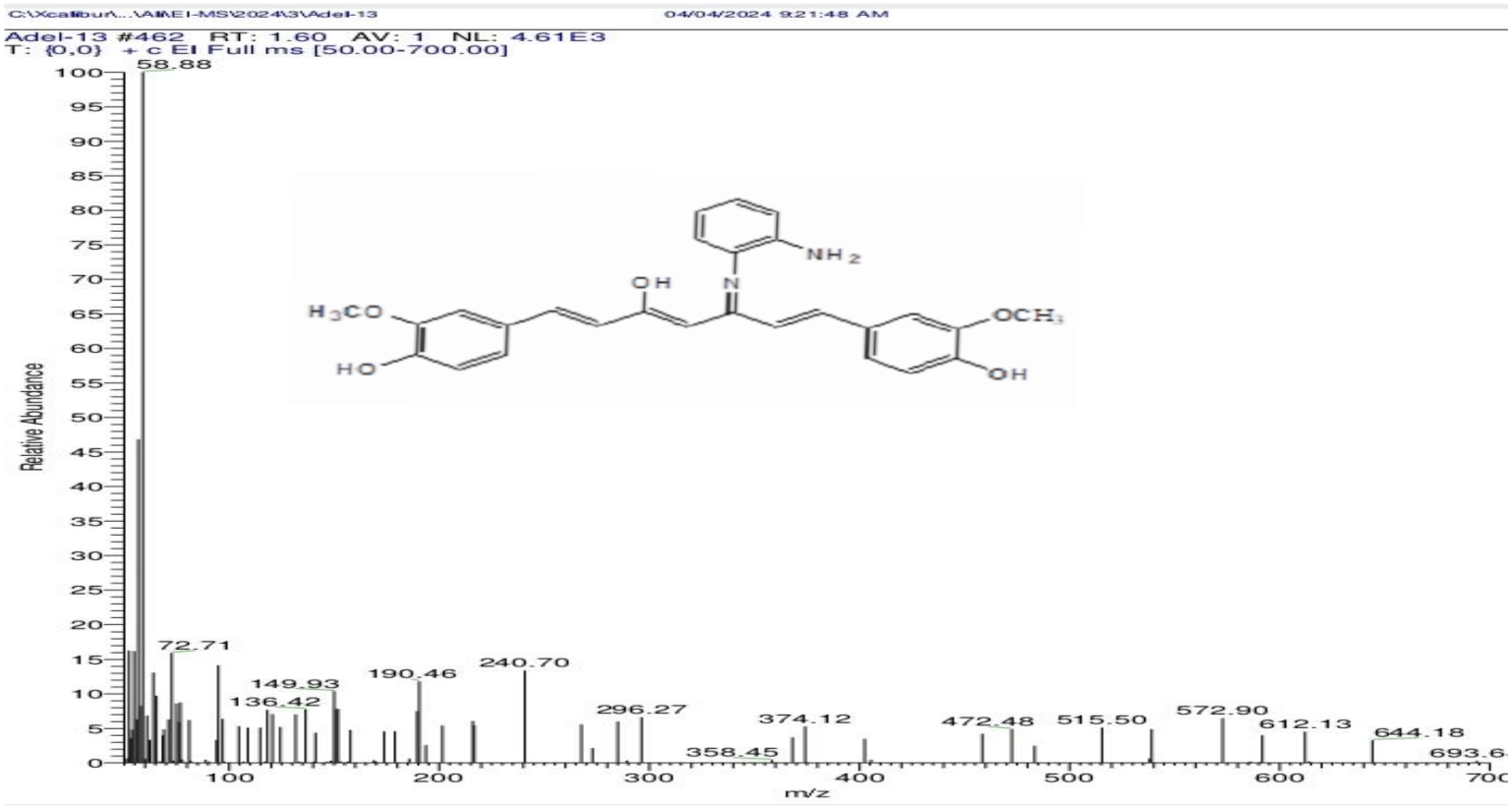


Figure. 13 : The Mass spectrometry of compound [90].

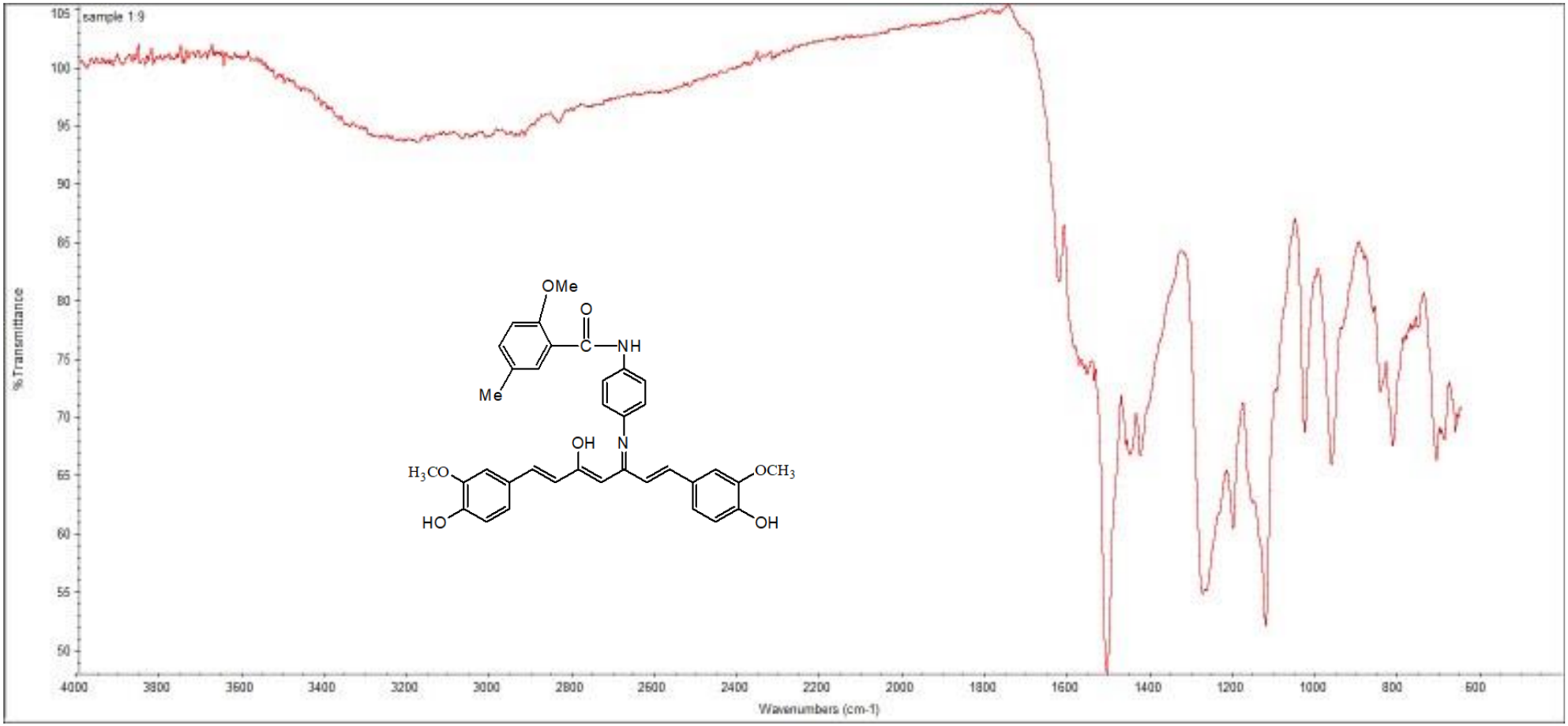


Figure. 14: The IR spectrum of compound [91]

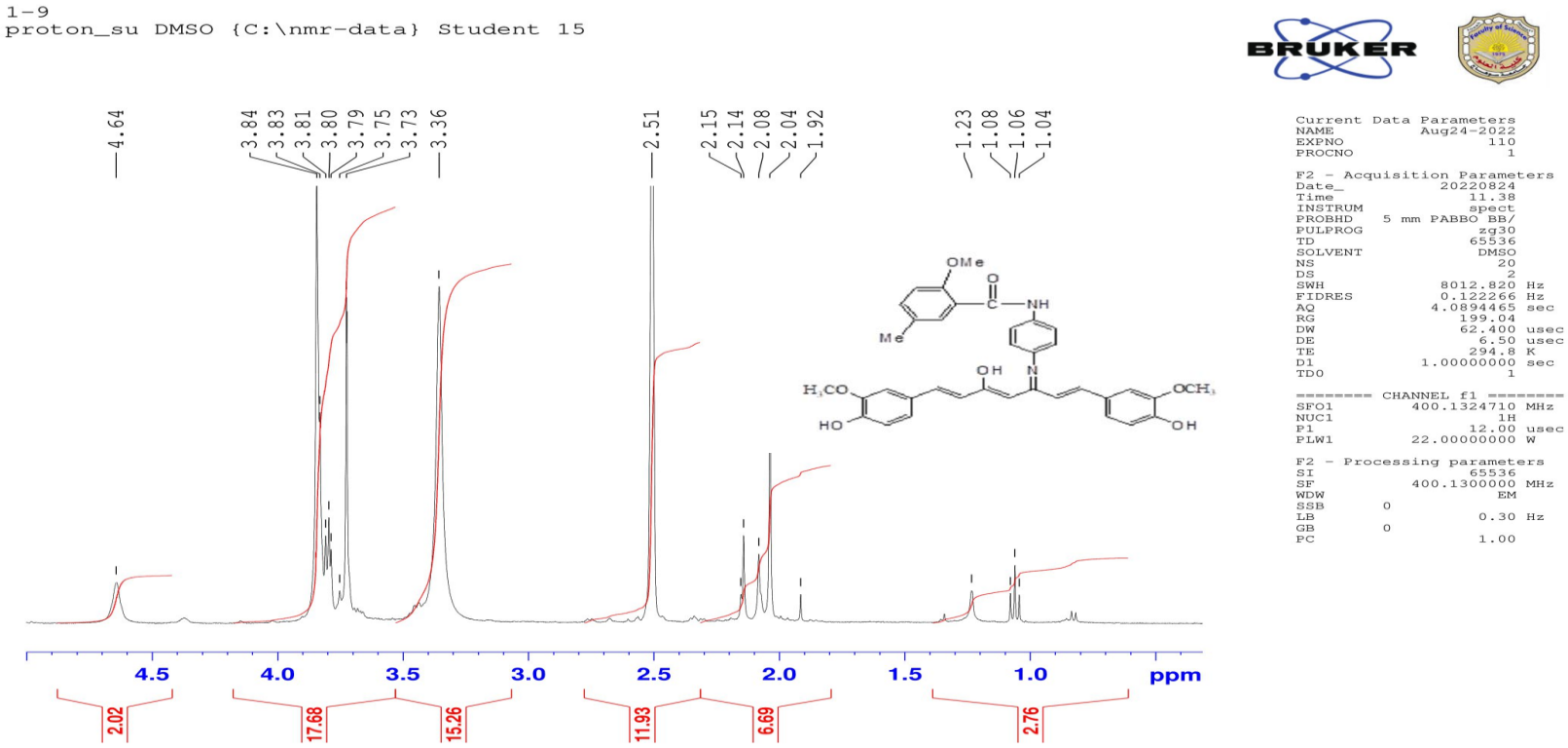


Figure.15 : The ^{1}H –NMR spectrum of compound [91]

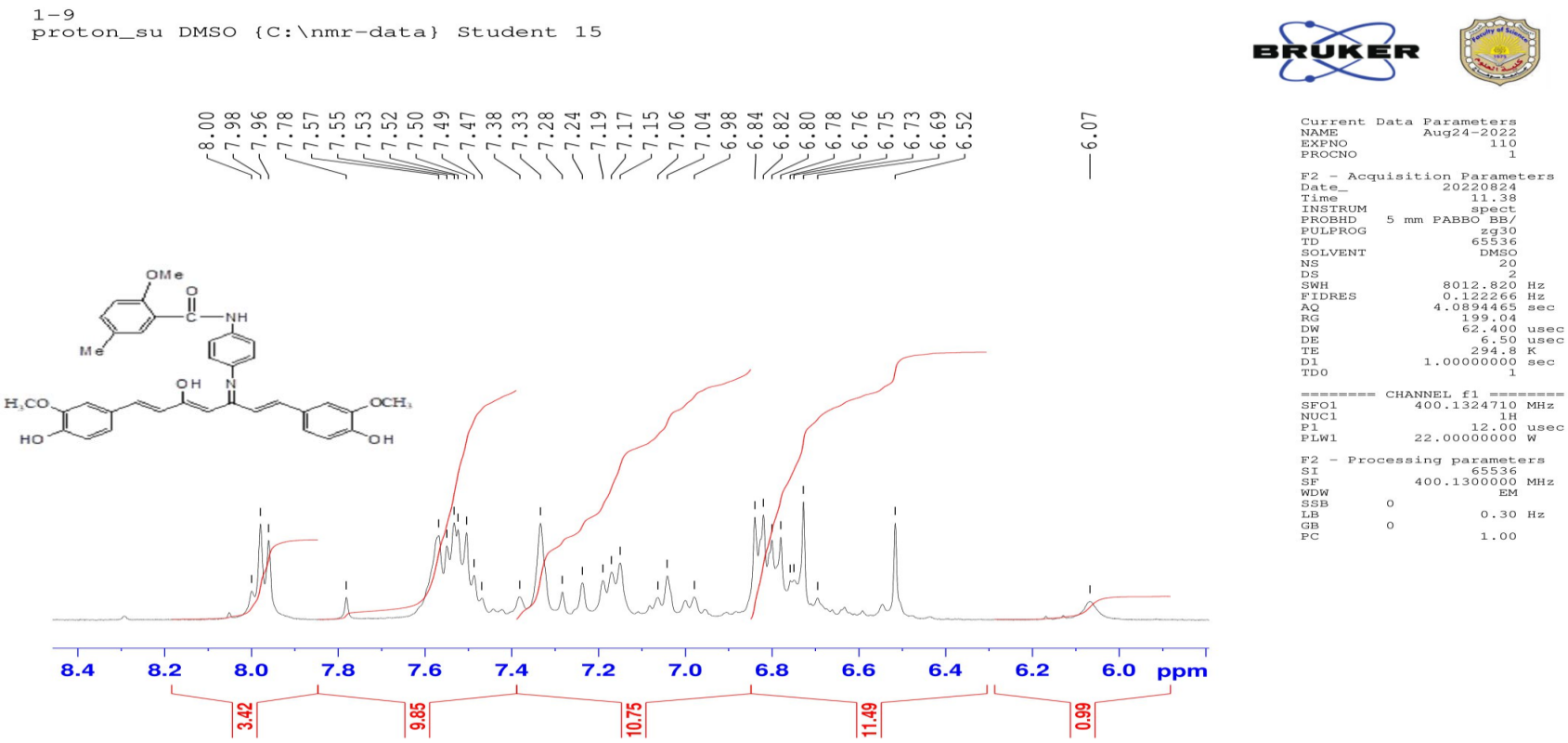


Figure. 15/: The ^{1}H- NMR spectrum of compound [91]

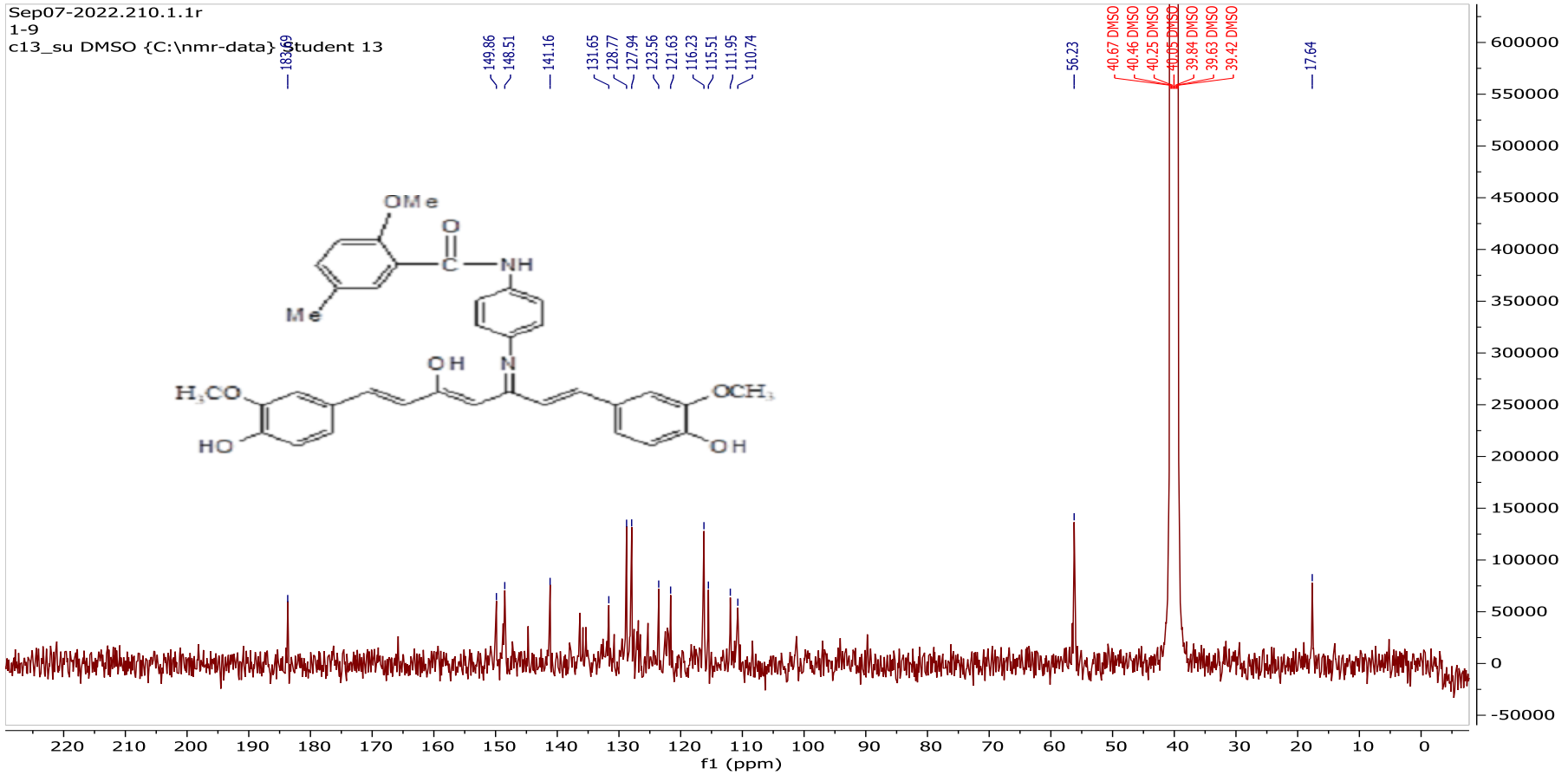


Figure.16 :The^{13}C –NMR spectrum of compound [91].

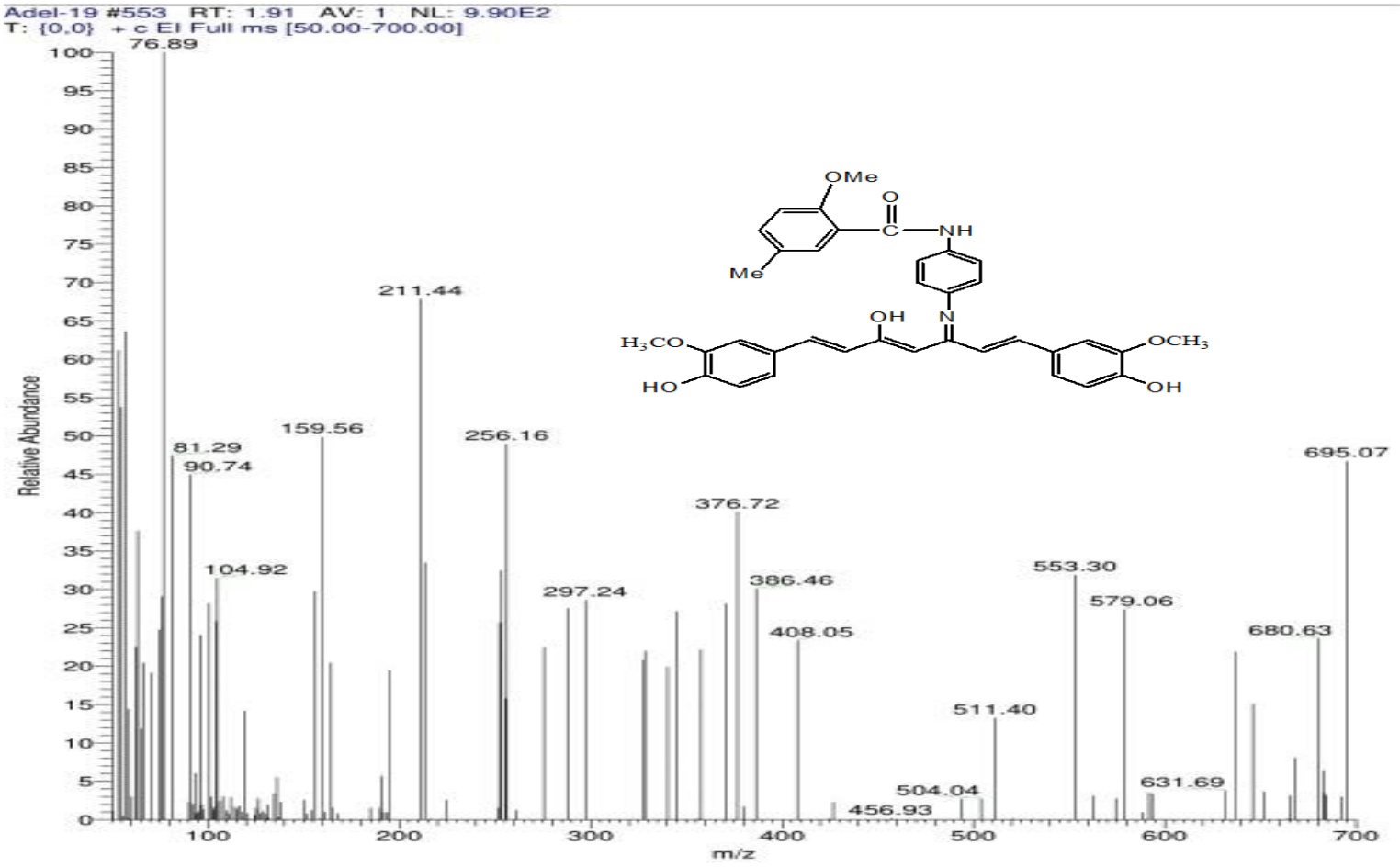


Figure. 17 : The Mass spectrometry of compound [91].

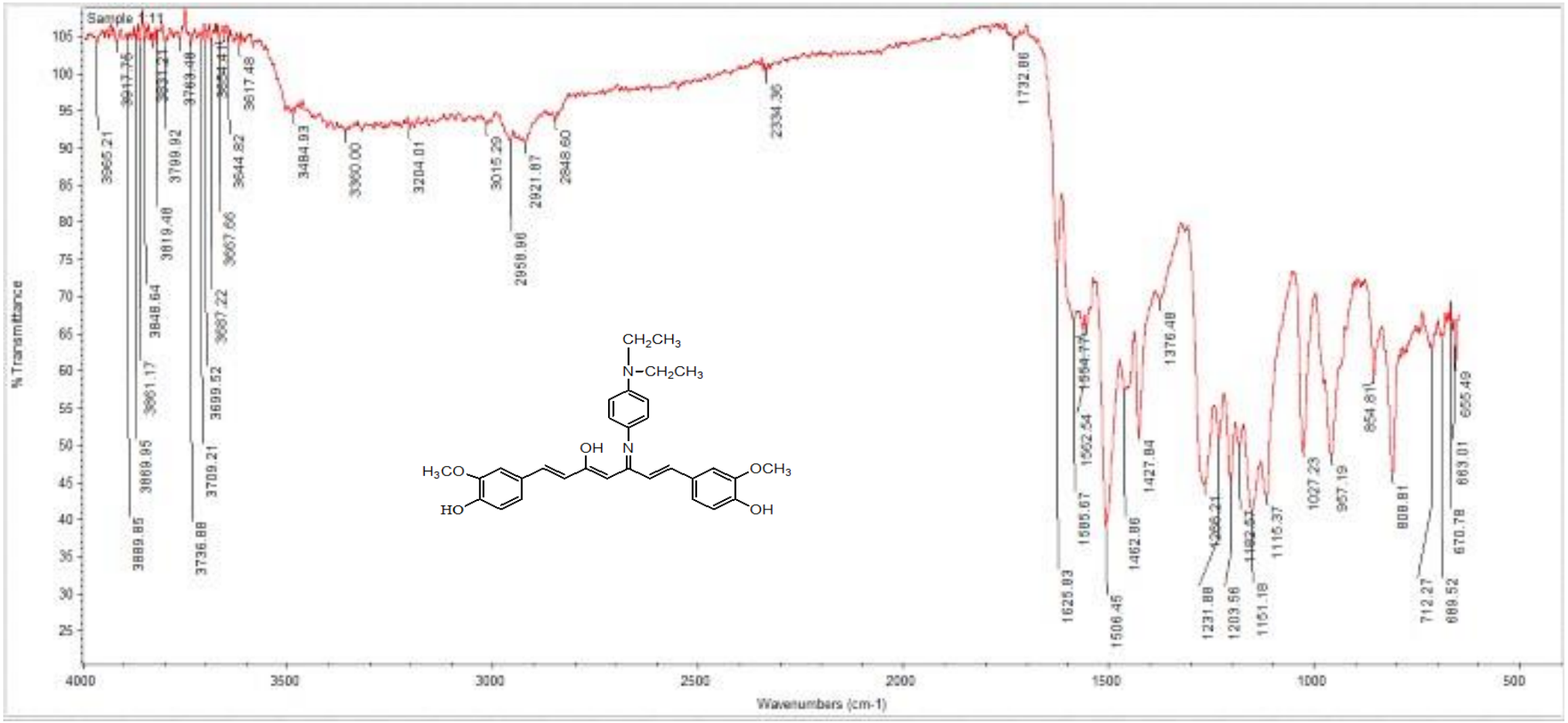


Figure. 18: The IR spectrum of compound [92]

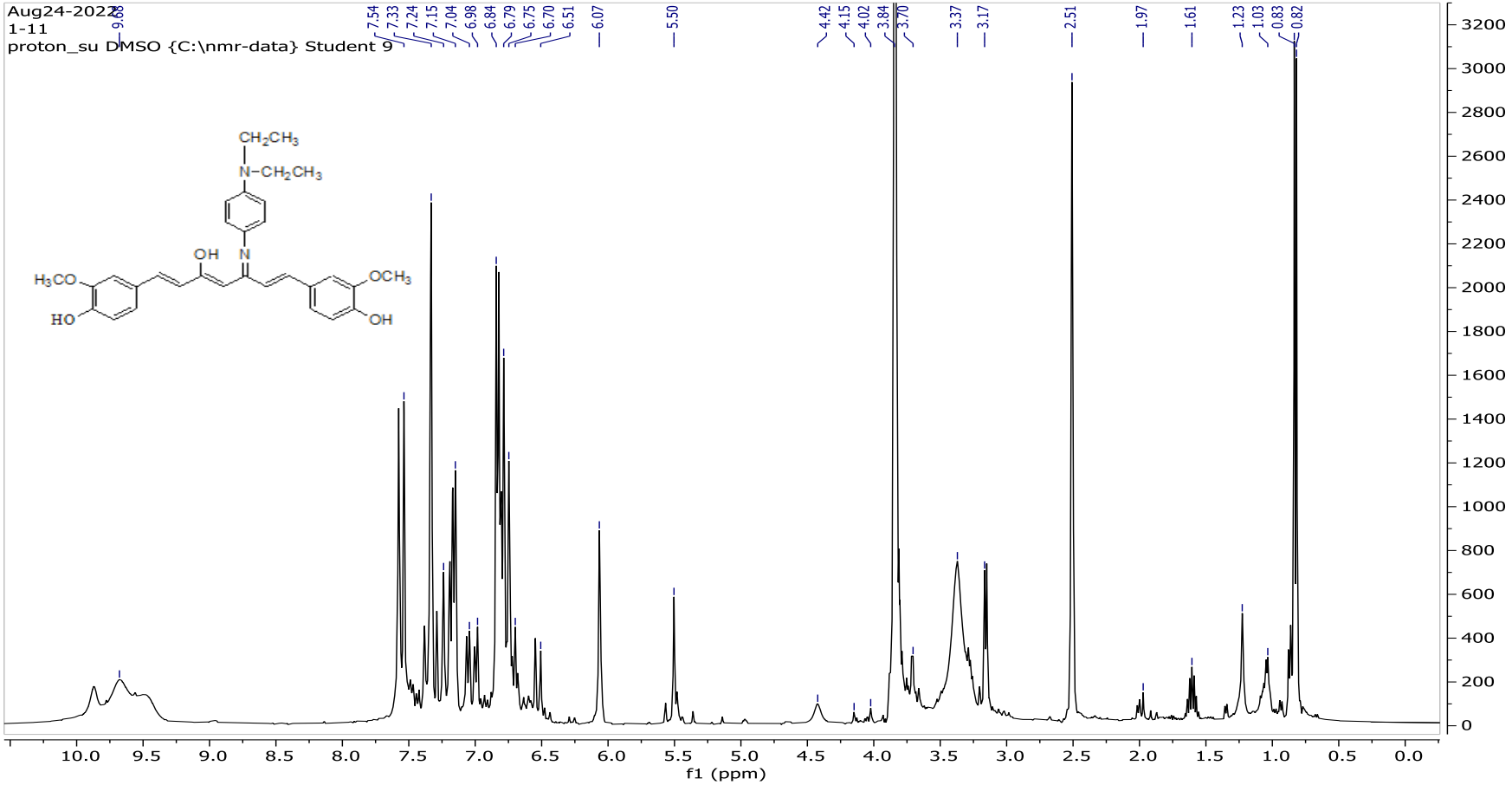


Figure.19 :The ^{1}H- NMR spectrum of compound [92].

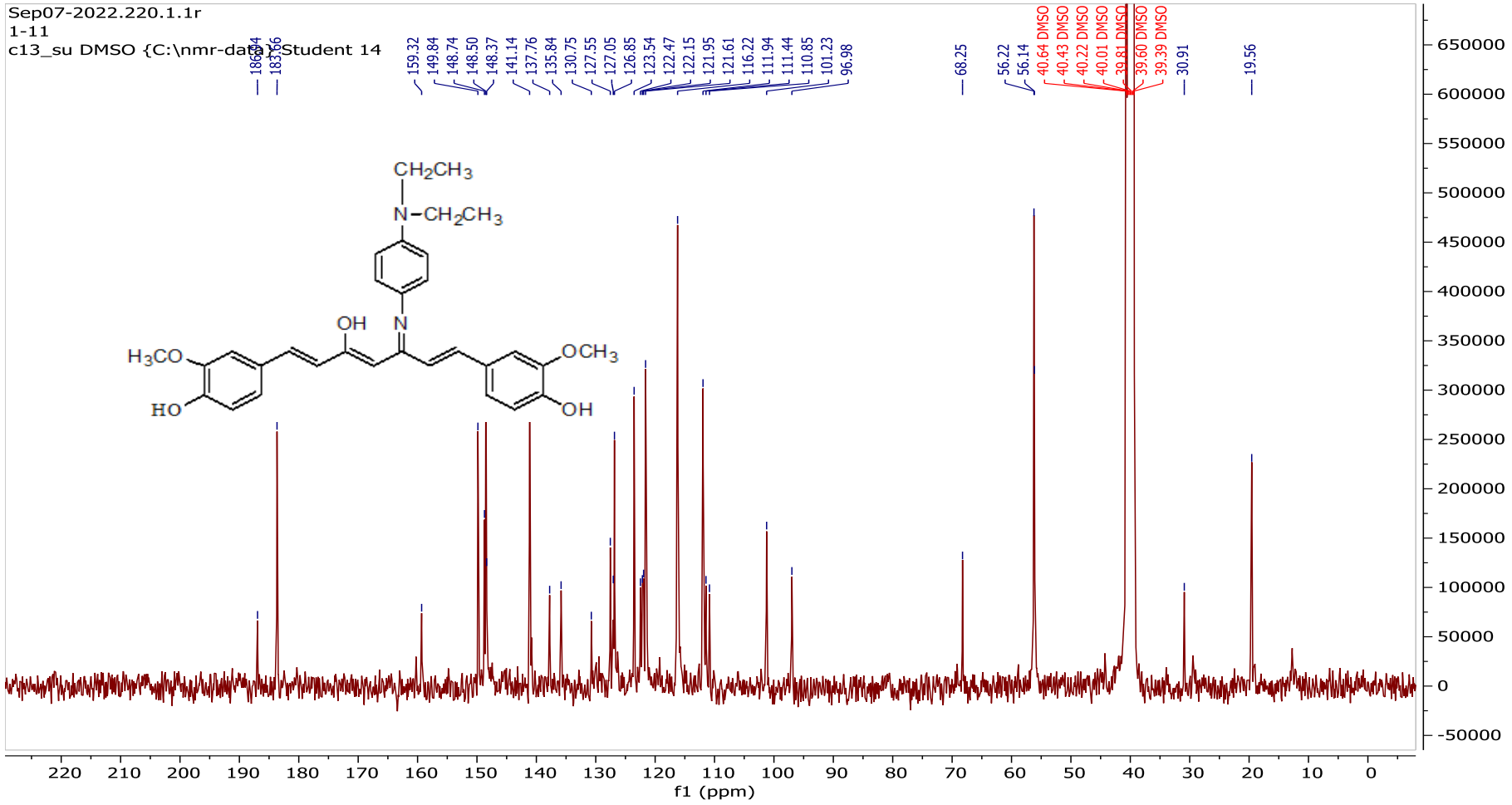


Figure .20 : The^{13}C- NMR spectrum of compound [92].

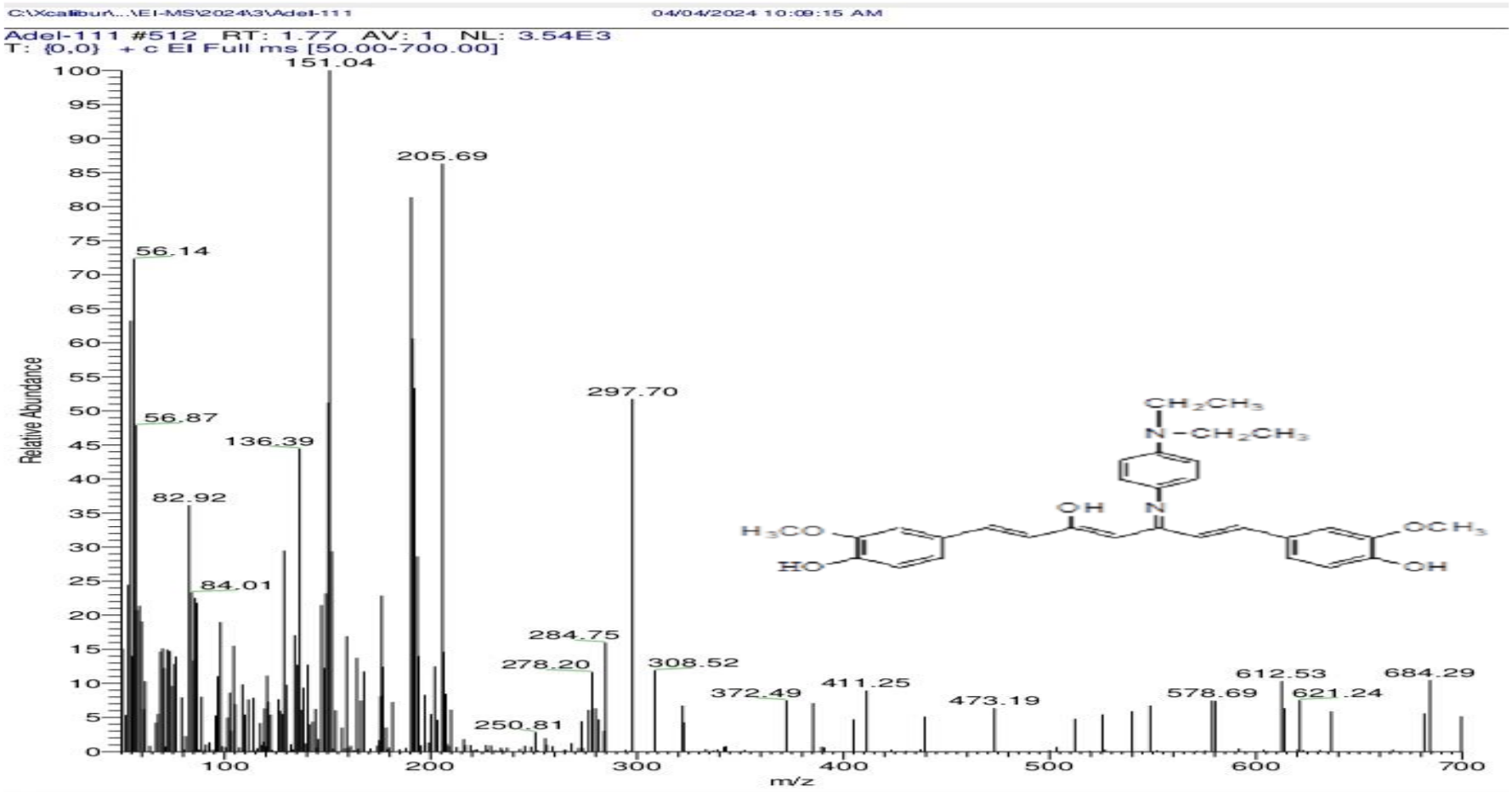


Figure.21 : The Mass spectrometry of compound [92].

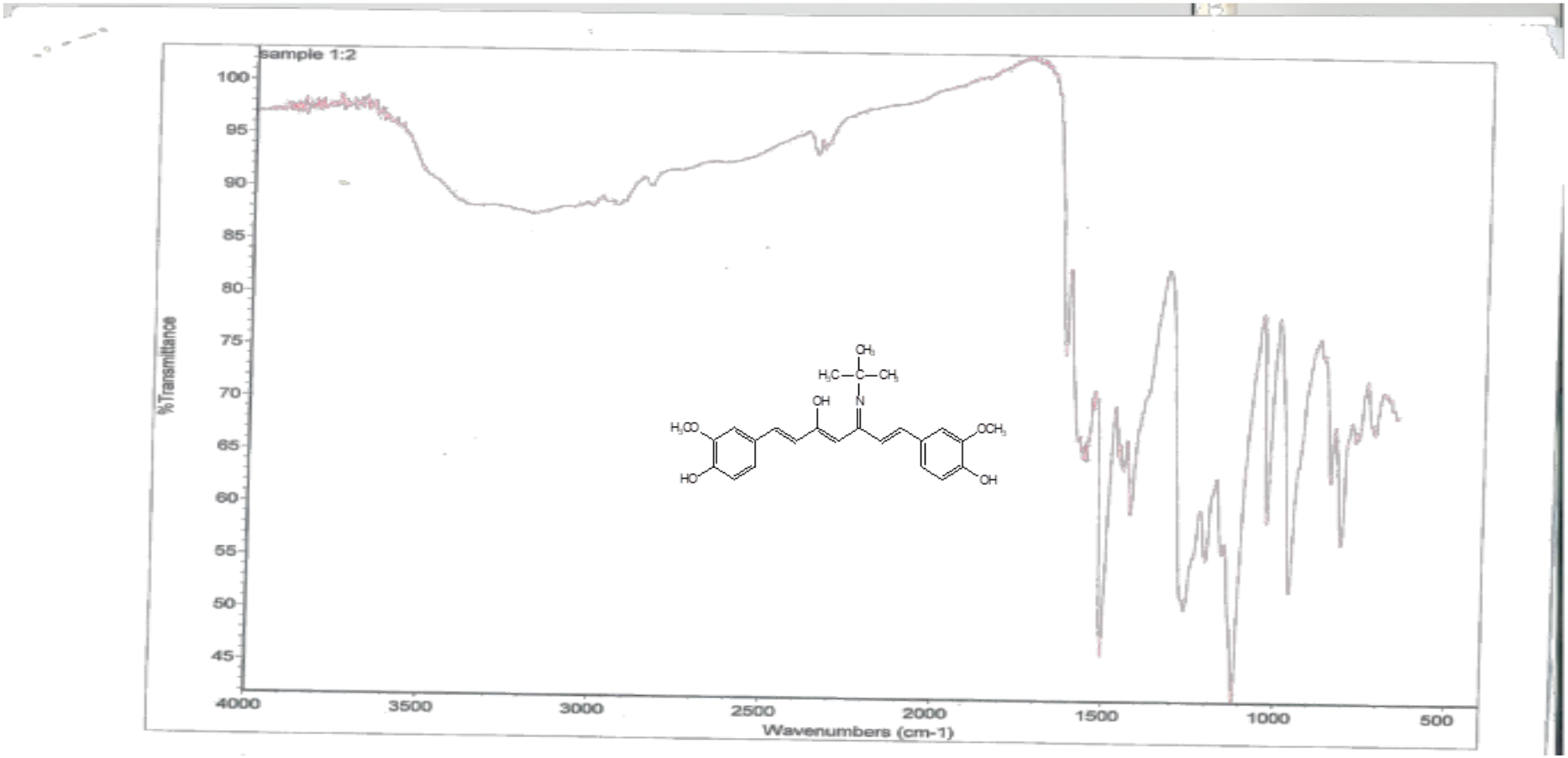


Figure. 22: The IR spectrum of compound [93].

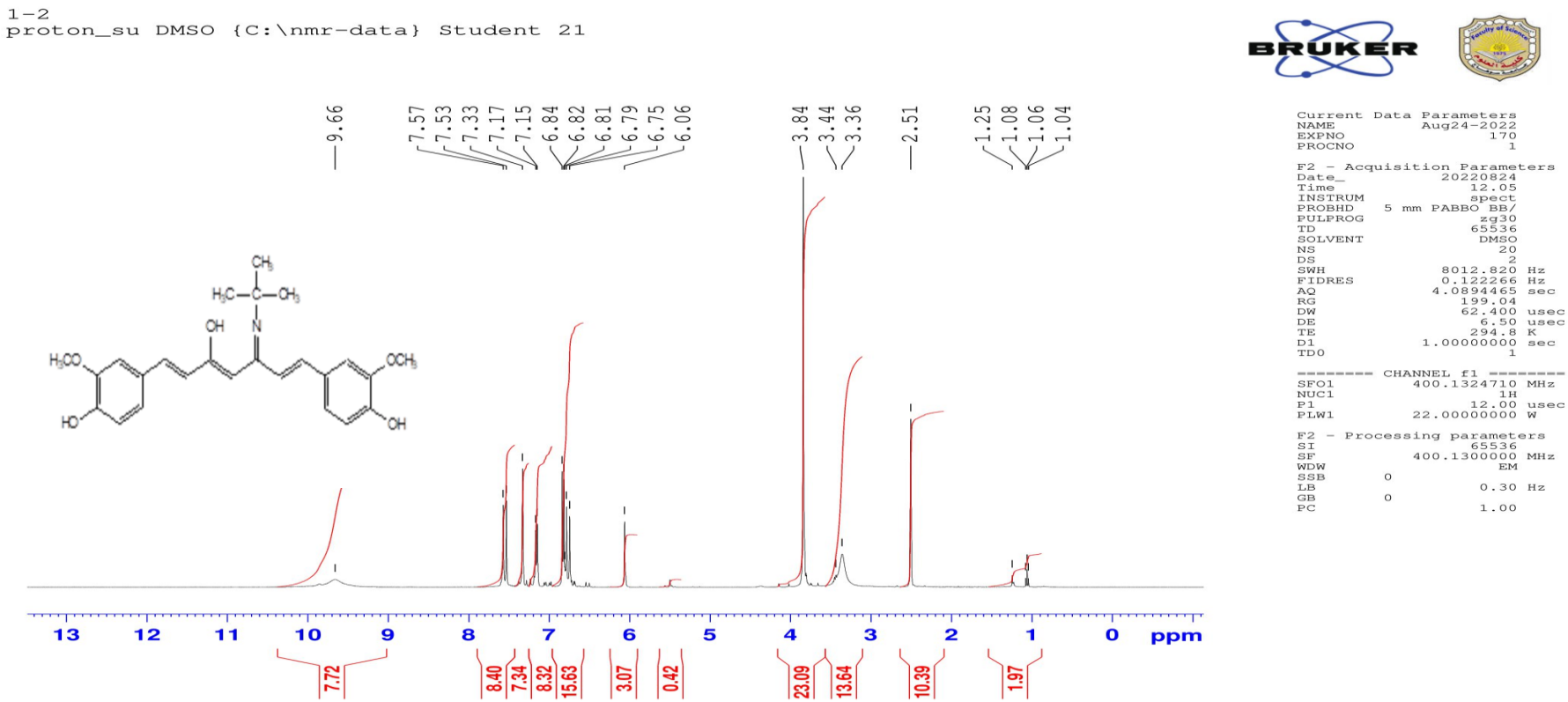


Figure. 23 : The ^{1}H- NMR spectrum of compound [93].

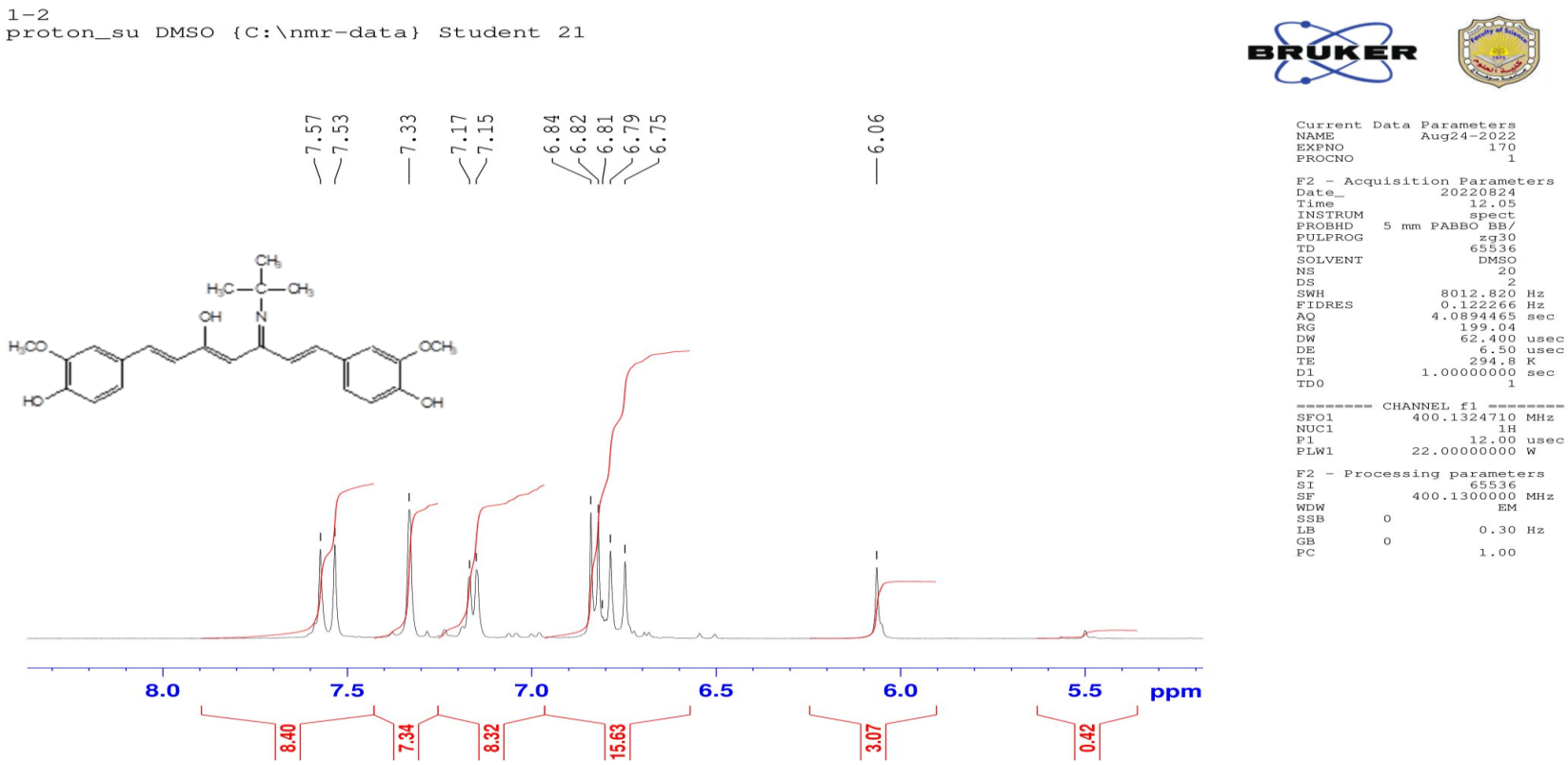


Figure .23/ : The^{1}H –NMR spectrum of compound [93]

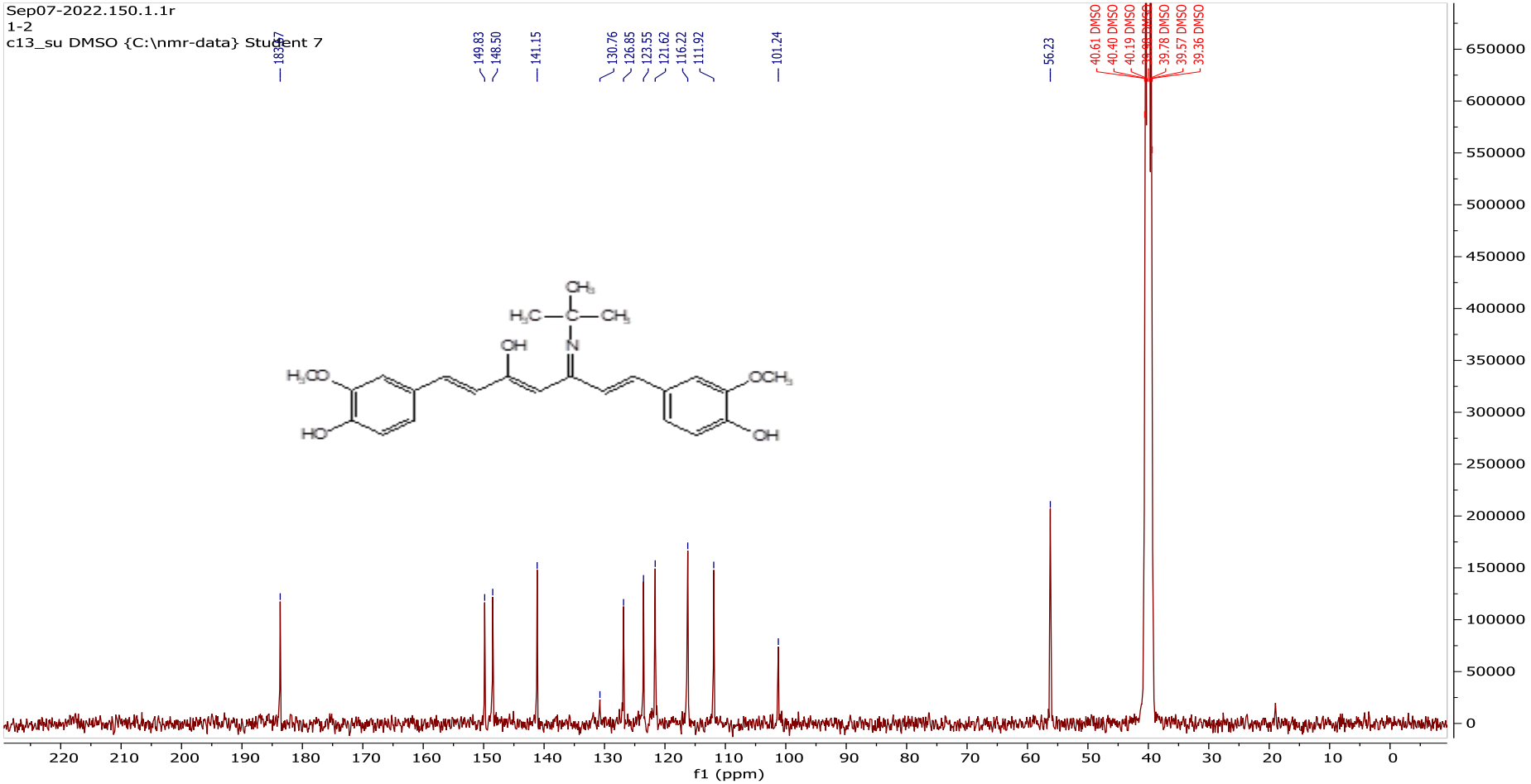


Figure.24 : The^{13}C –NMR spectrum of compound [93].

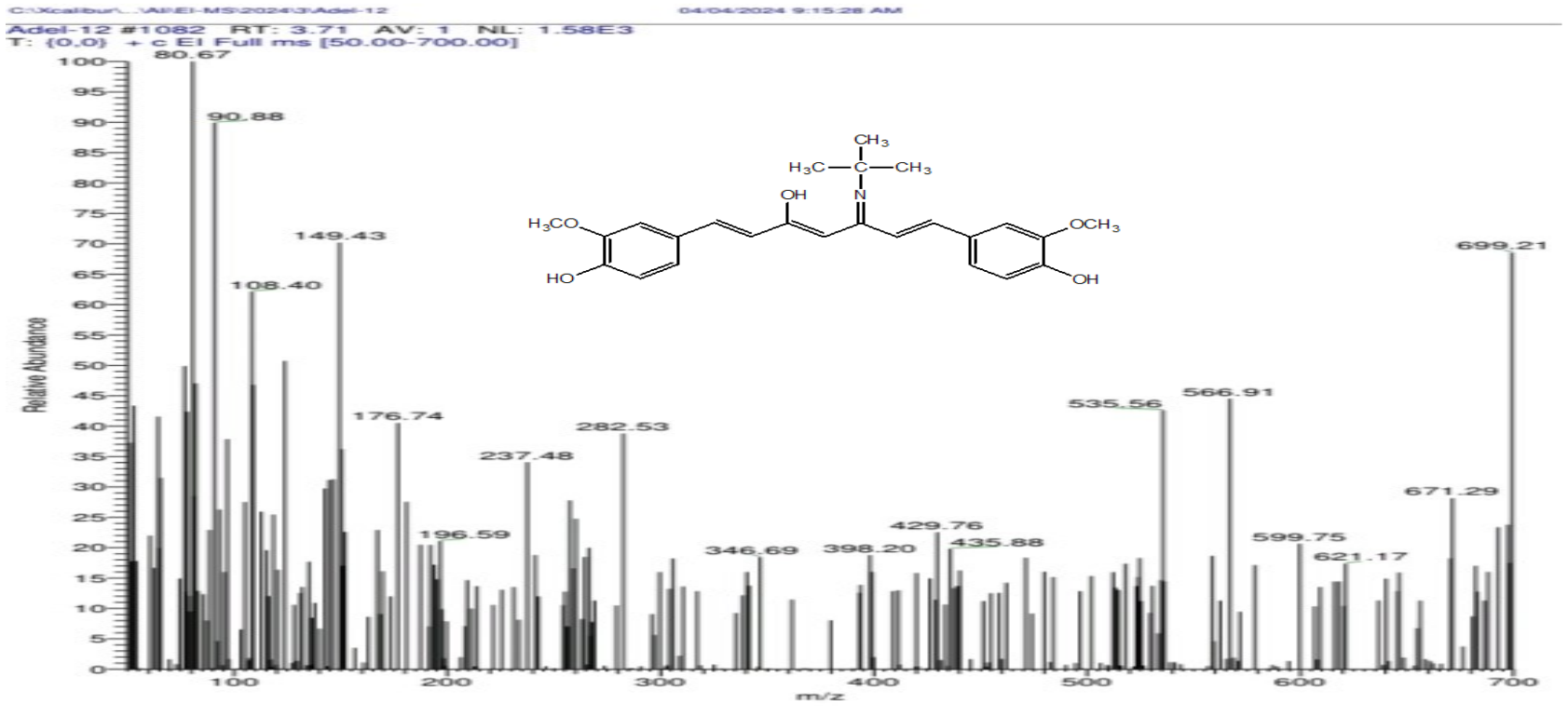


Figure.25: The Mass spectrometry of compound [93].

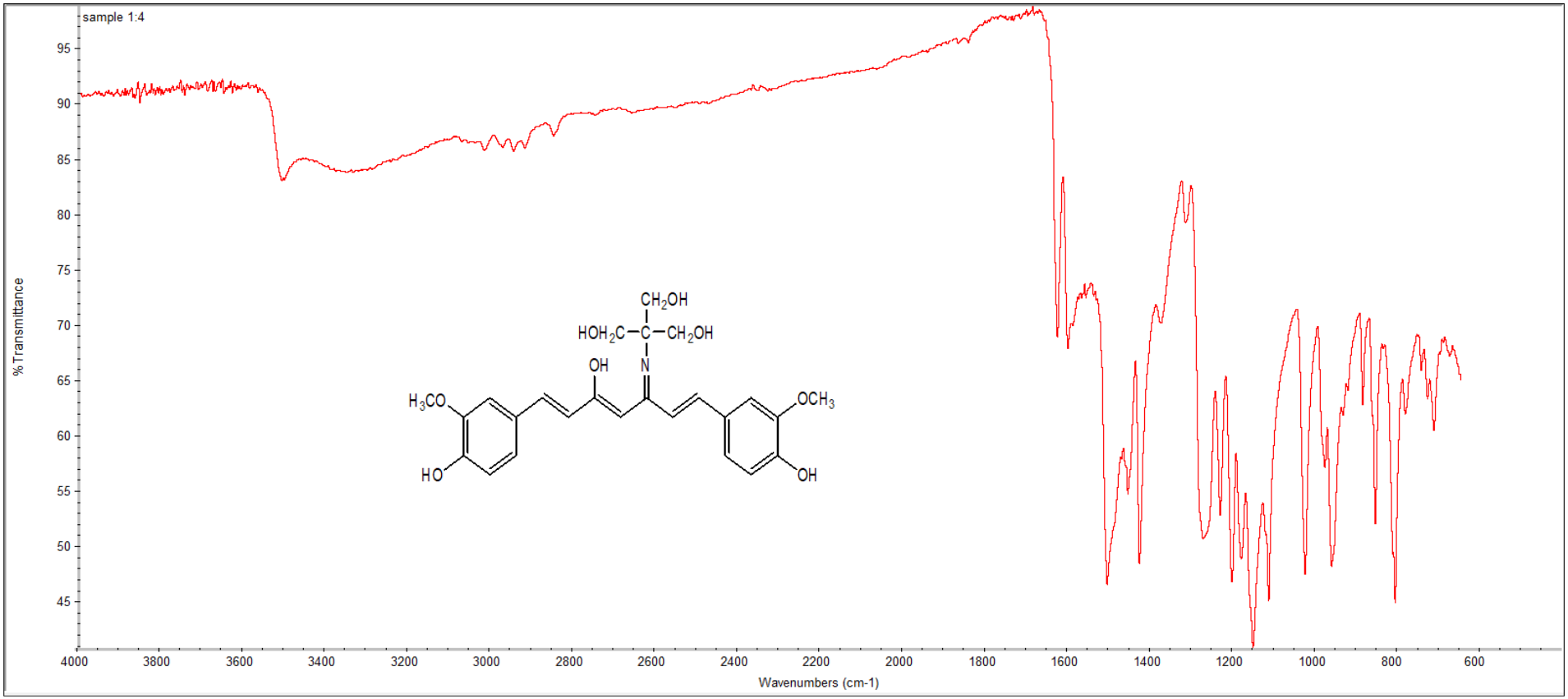


Figure .26 : The IR spectrum of compound [94].

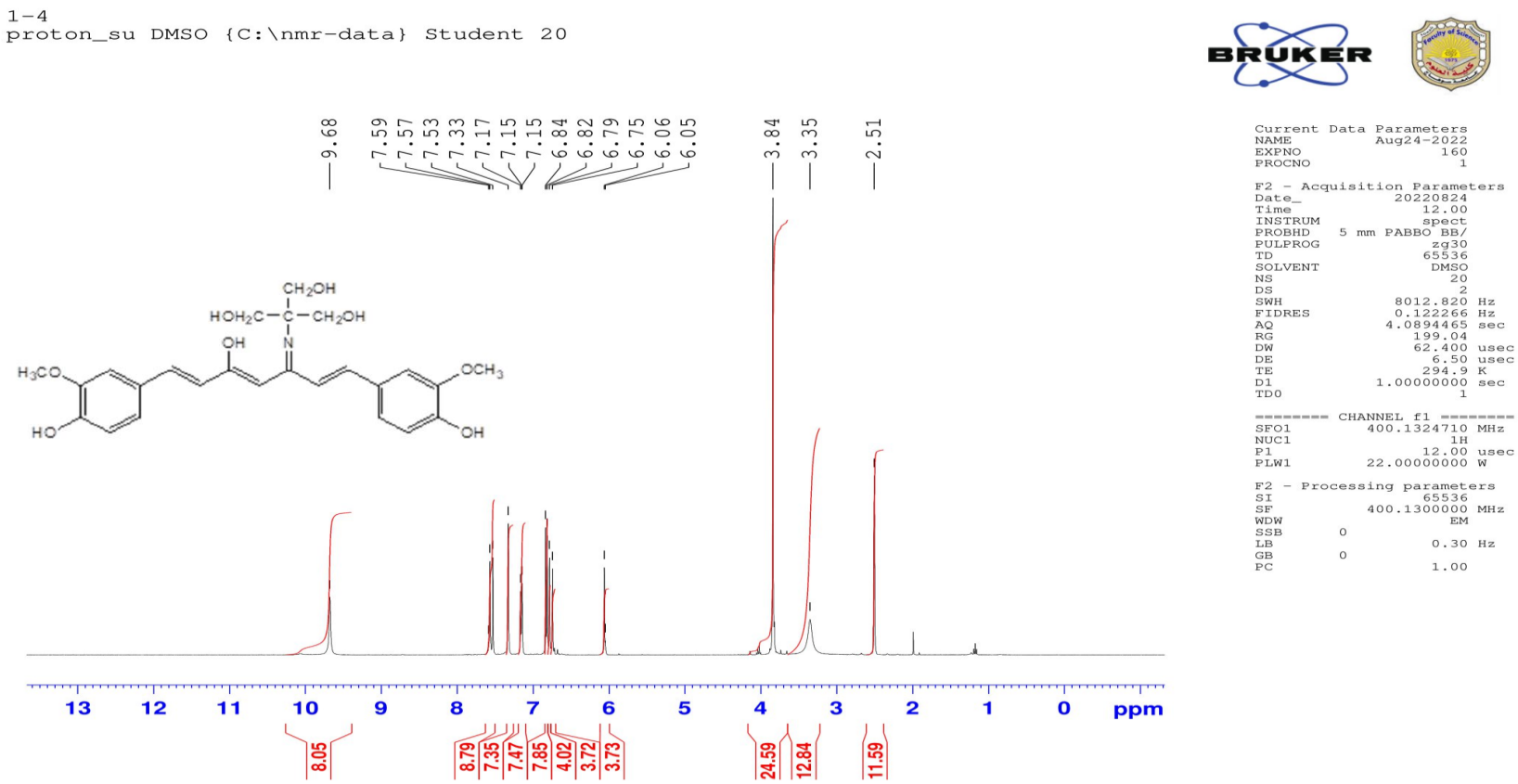


Figure. 27 : The^{1}H –NMR spectrum of compound [94].

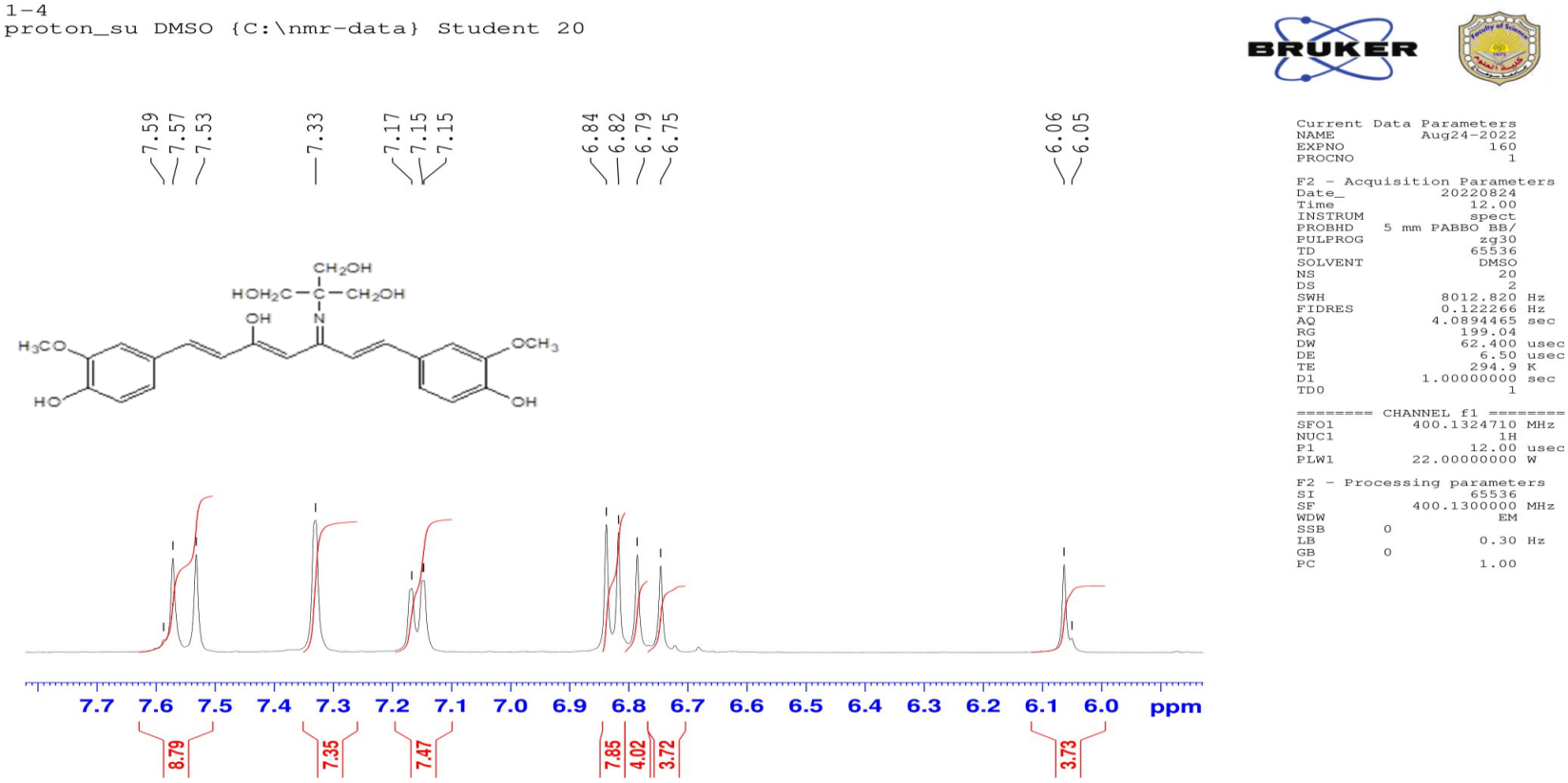


Figure.27/ : The^{1}H –NMR spectrum of compound [94].

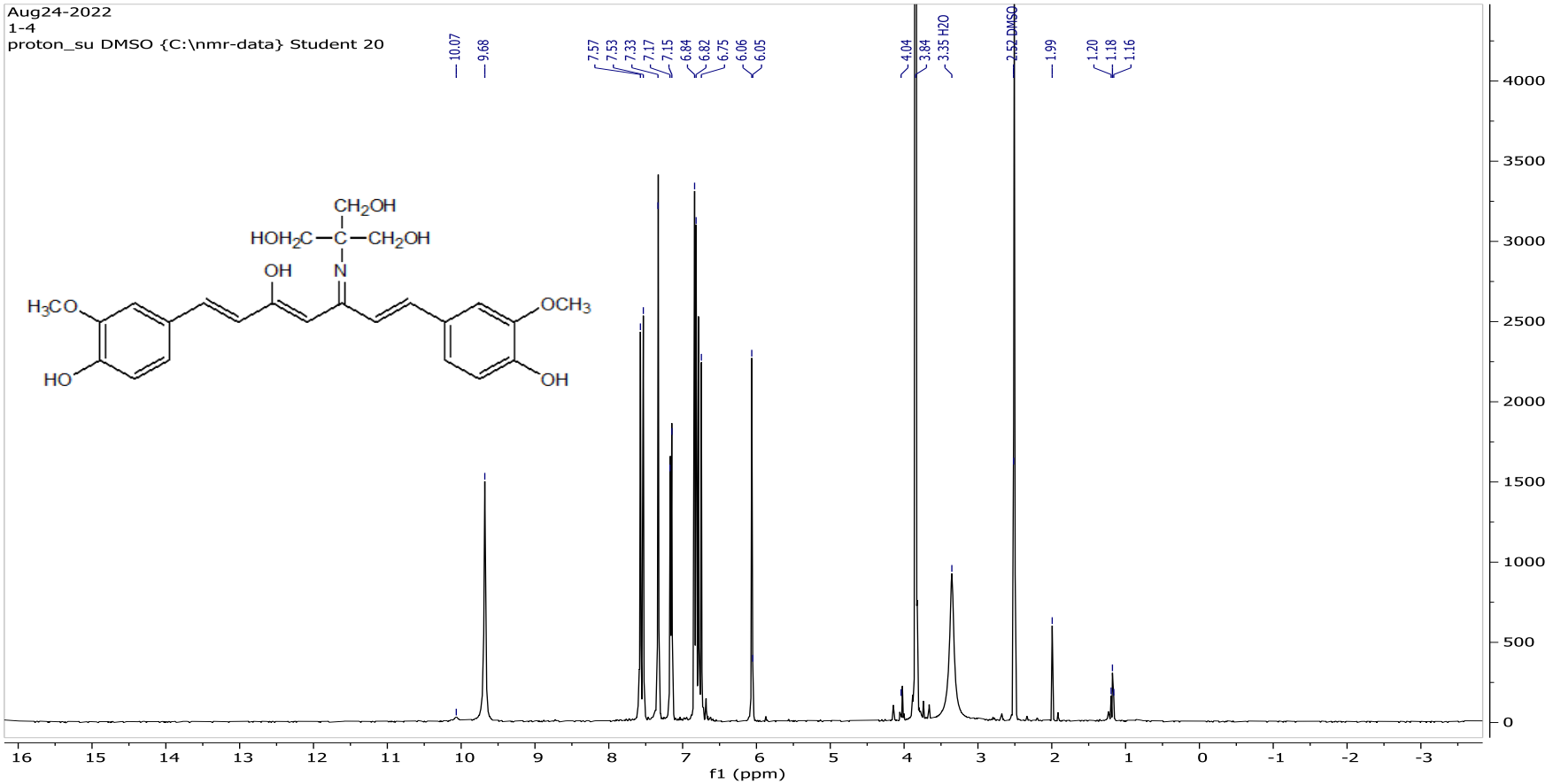


Figure.27// : The^{1}H- NMR spectrum of compound [94].

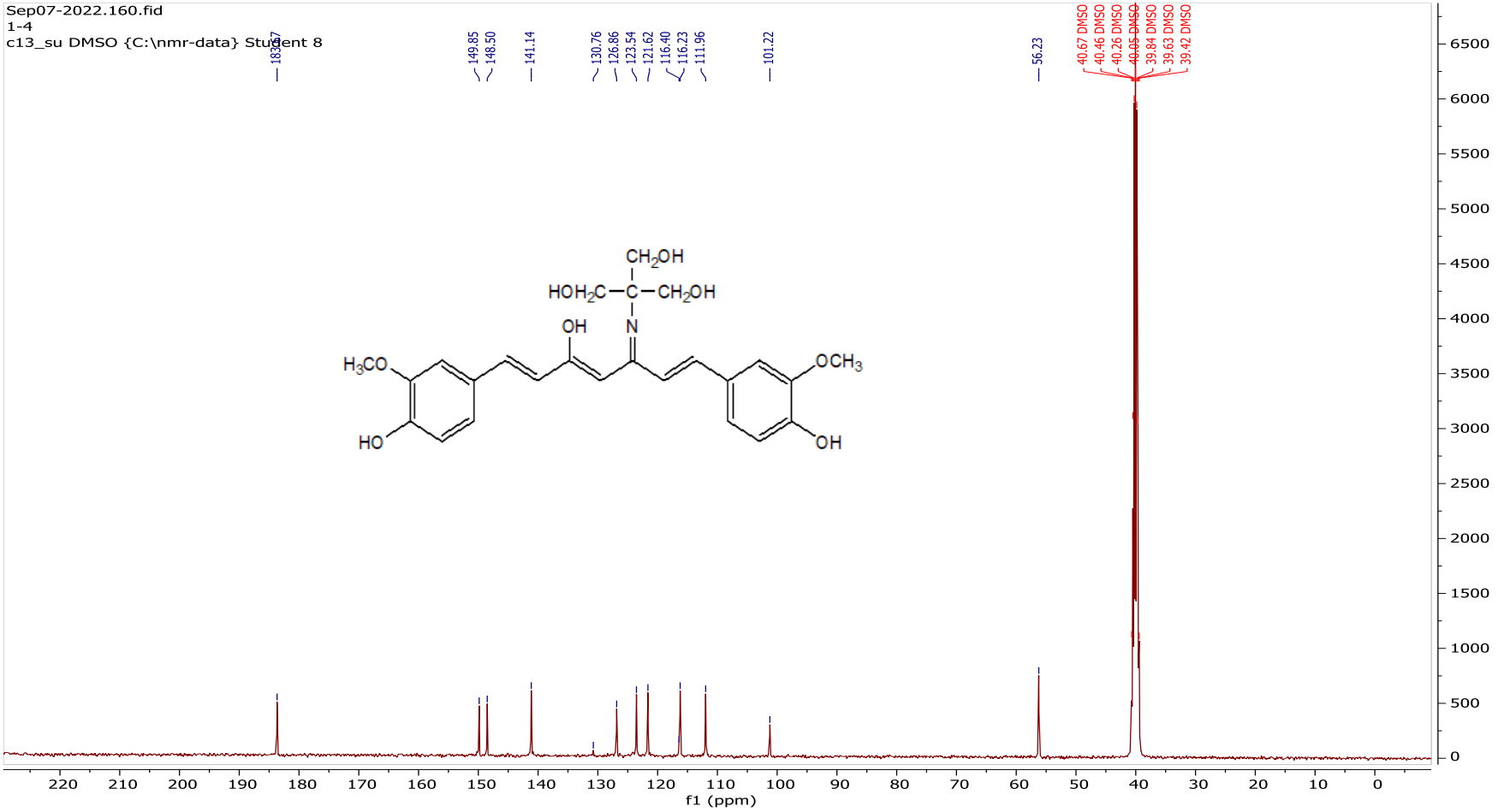


Figure.28:The ^{13}C- NMR spectrum of compound [94].

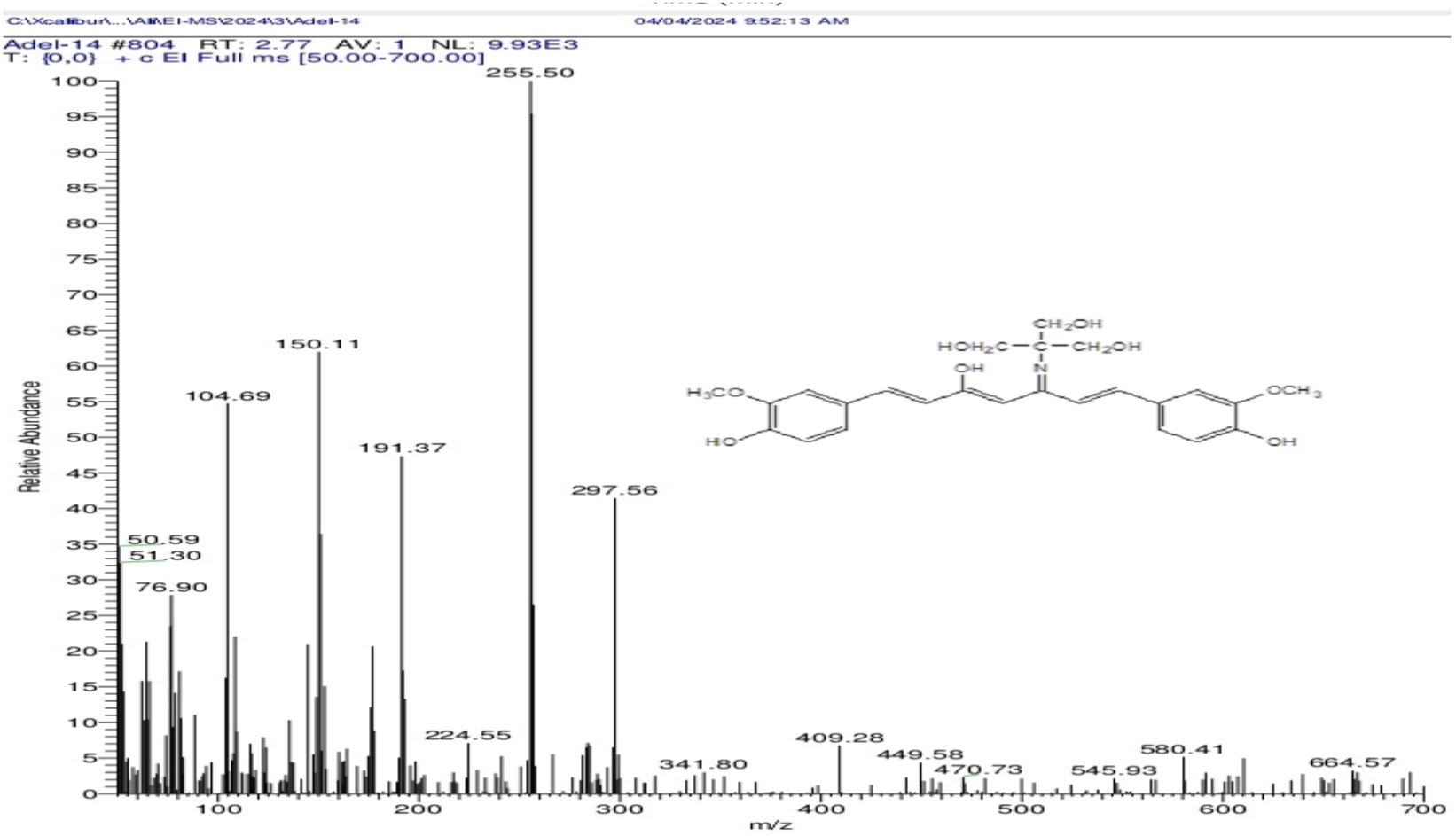


Figure.29: The Mass spectrometry of compound [94].

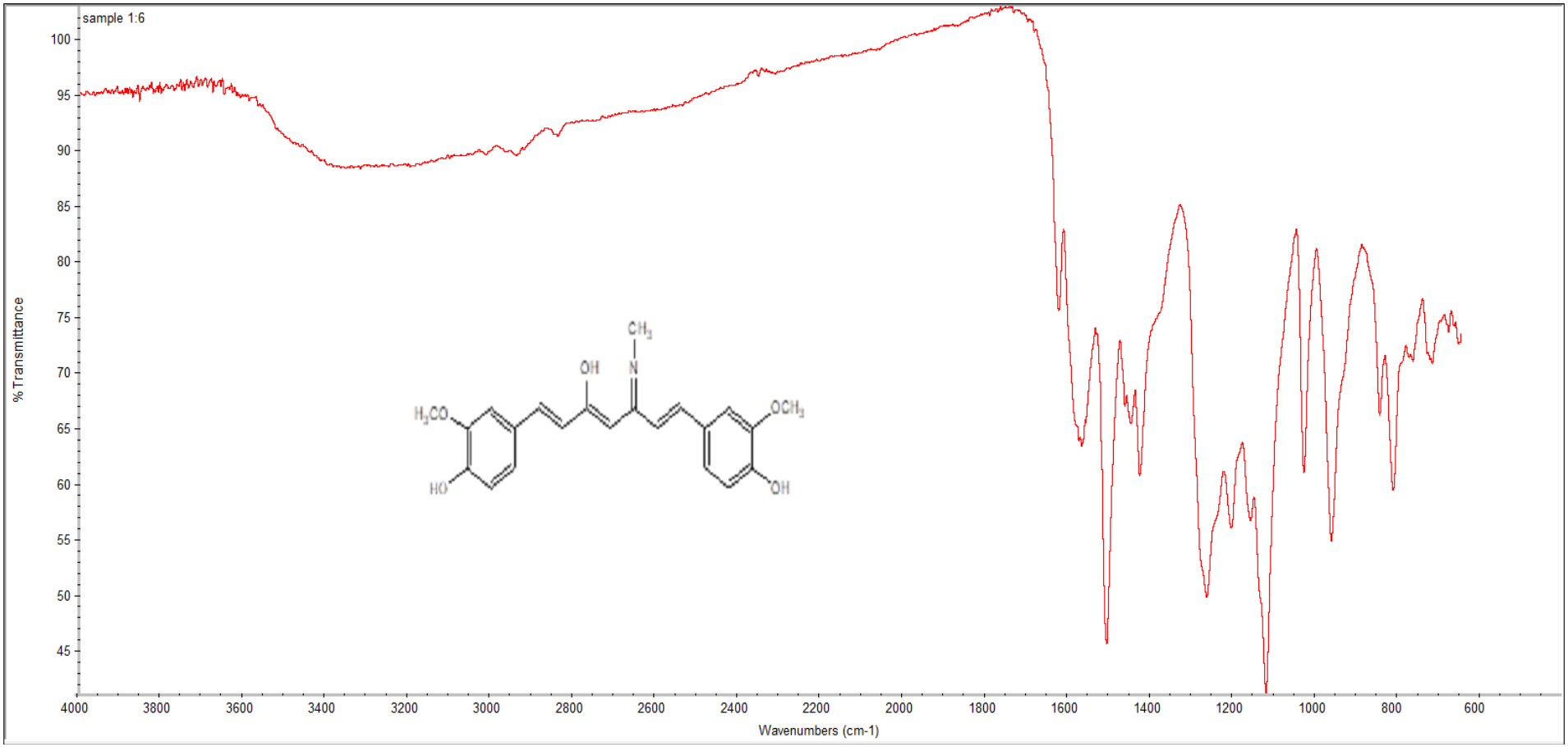


Figure .30 : The IR spectrum of compound [95]

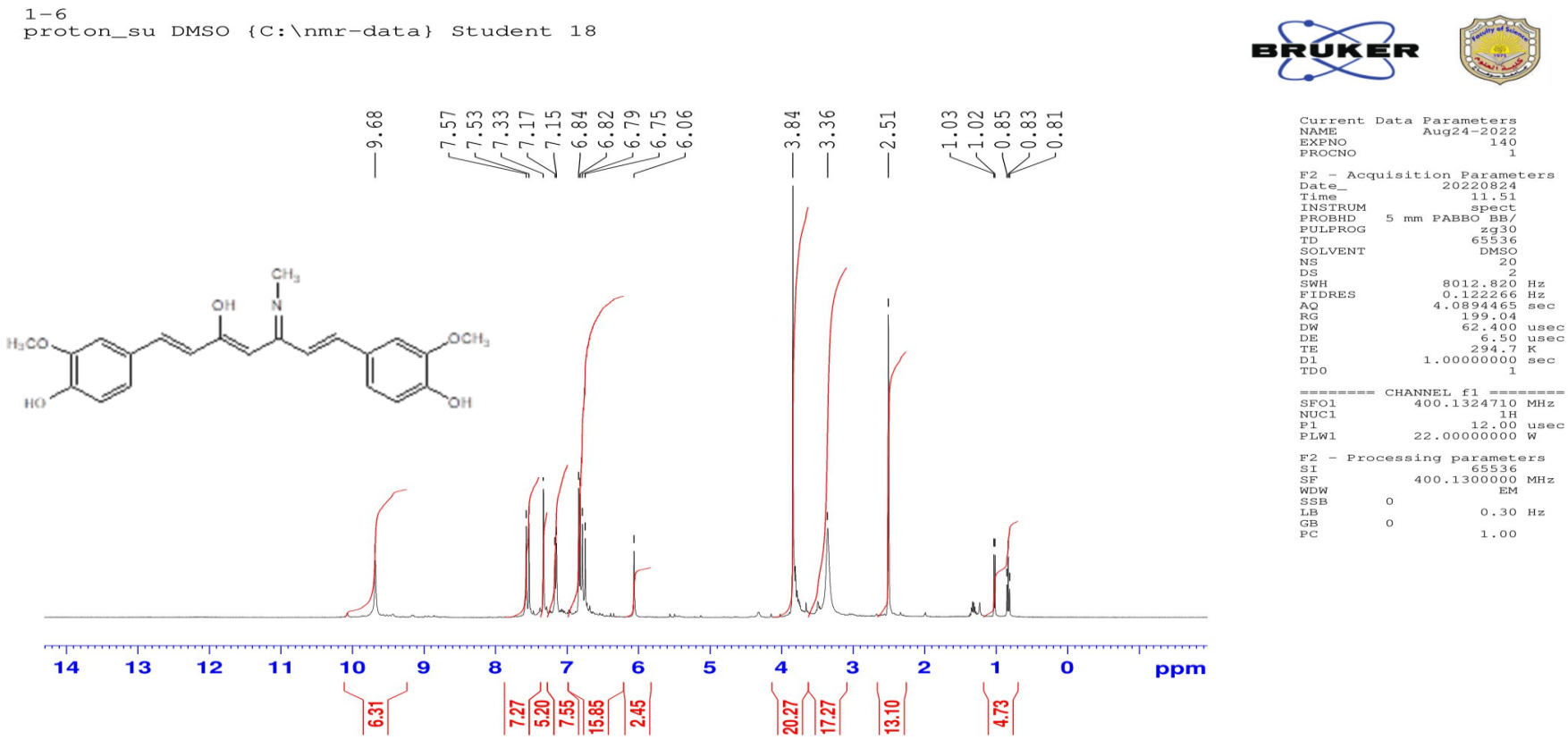


Figure.31 : The ^{1}H- NMR spectrum of compound [95].

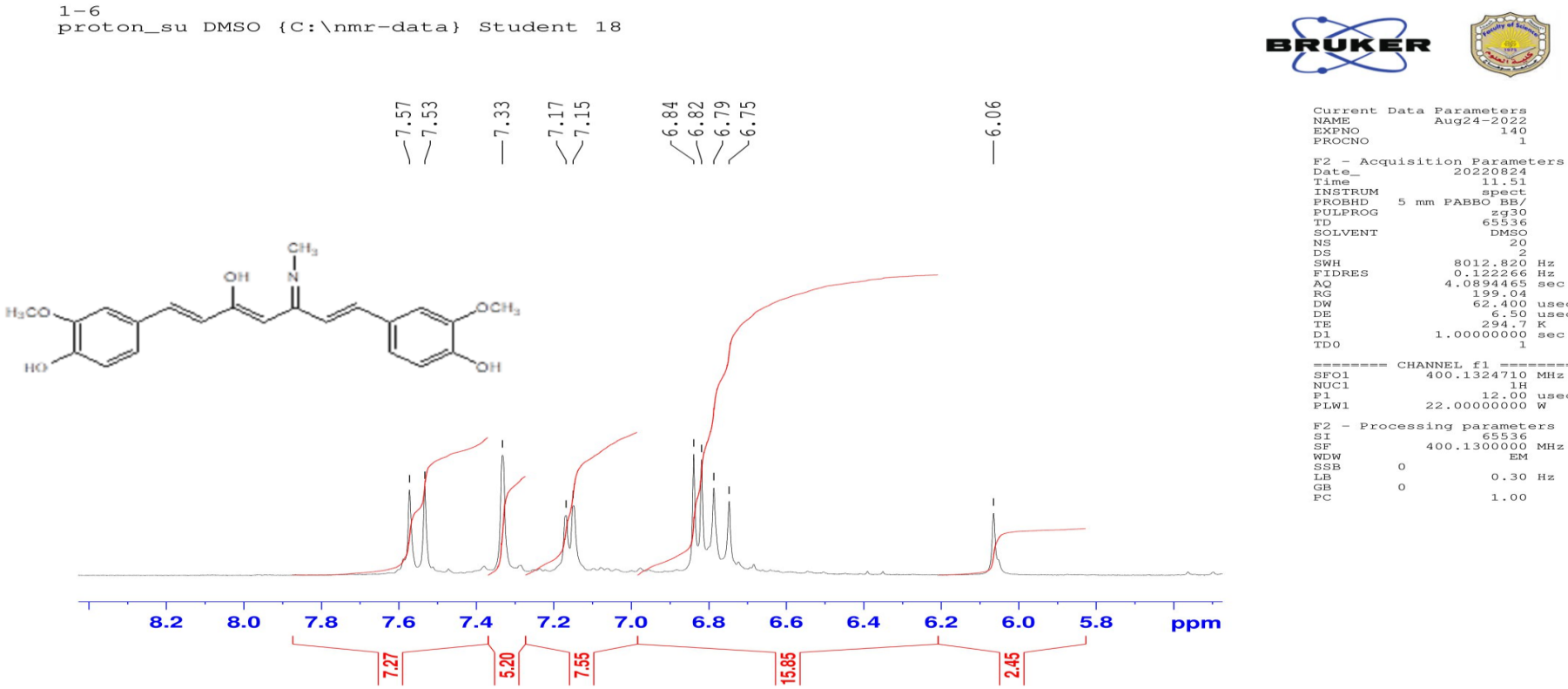


Figure.31/ : The ^{1}H –NMR spectrum of compound [95].

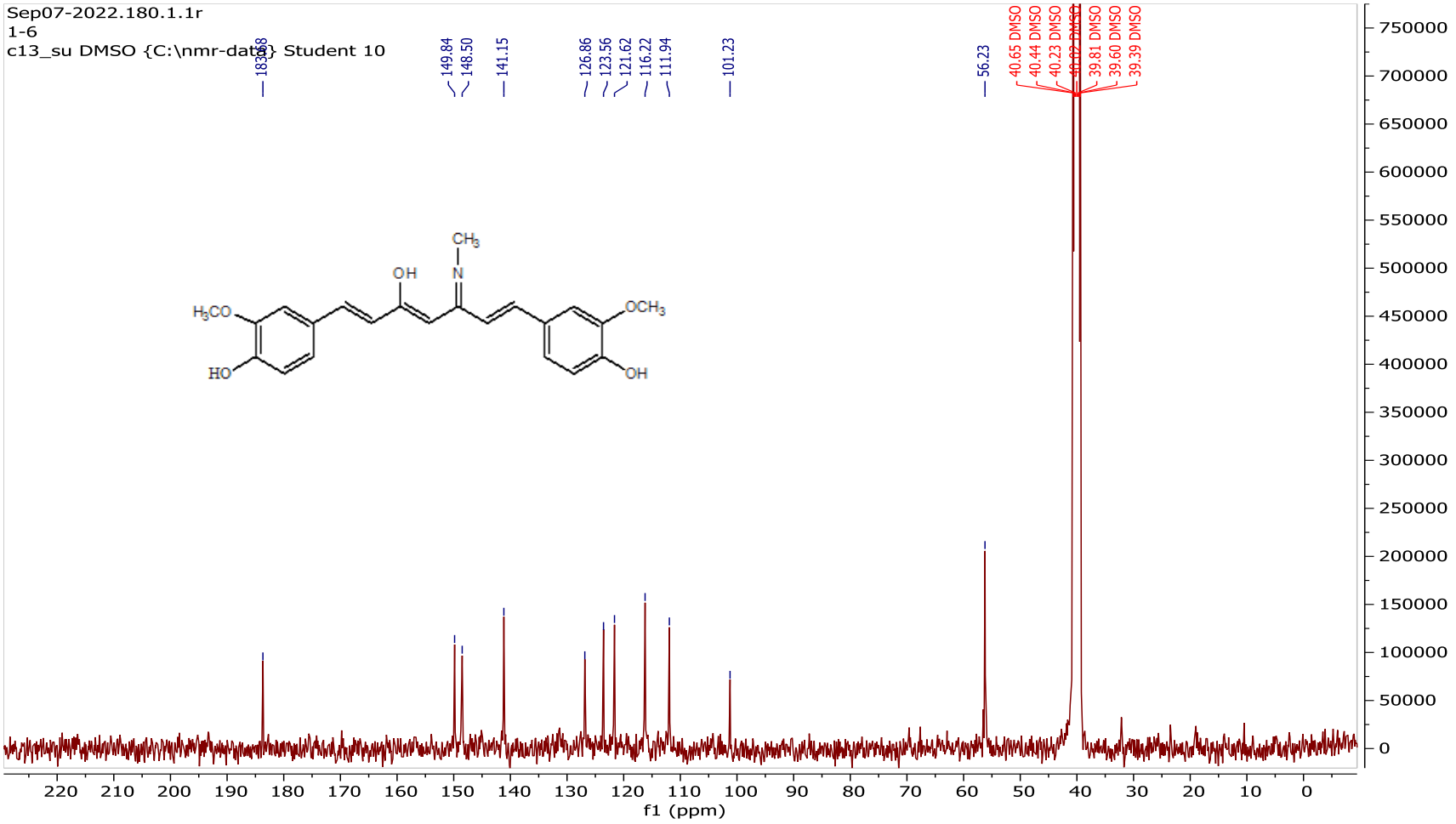


Figure .32: The^{13}C –NMR spectrum of compound [95].

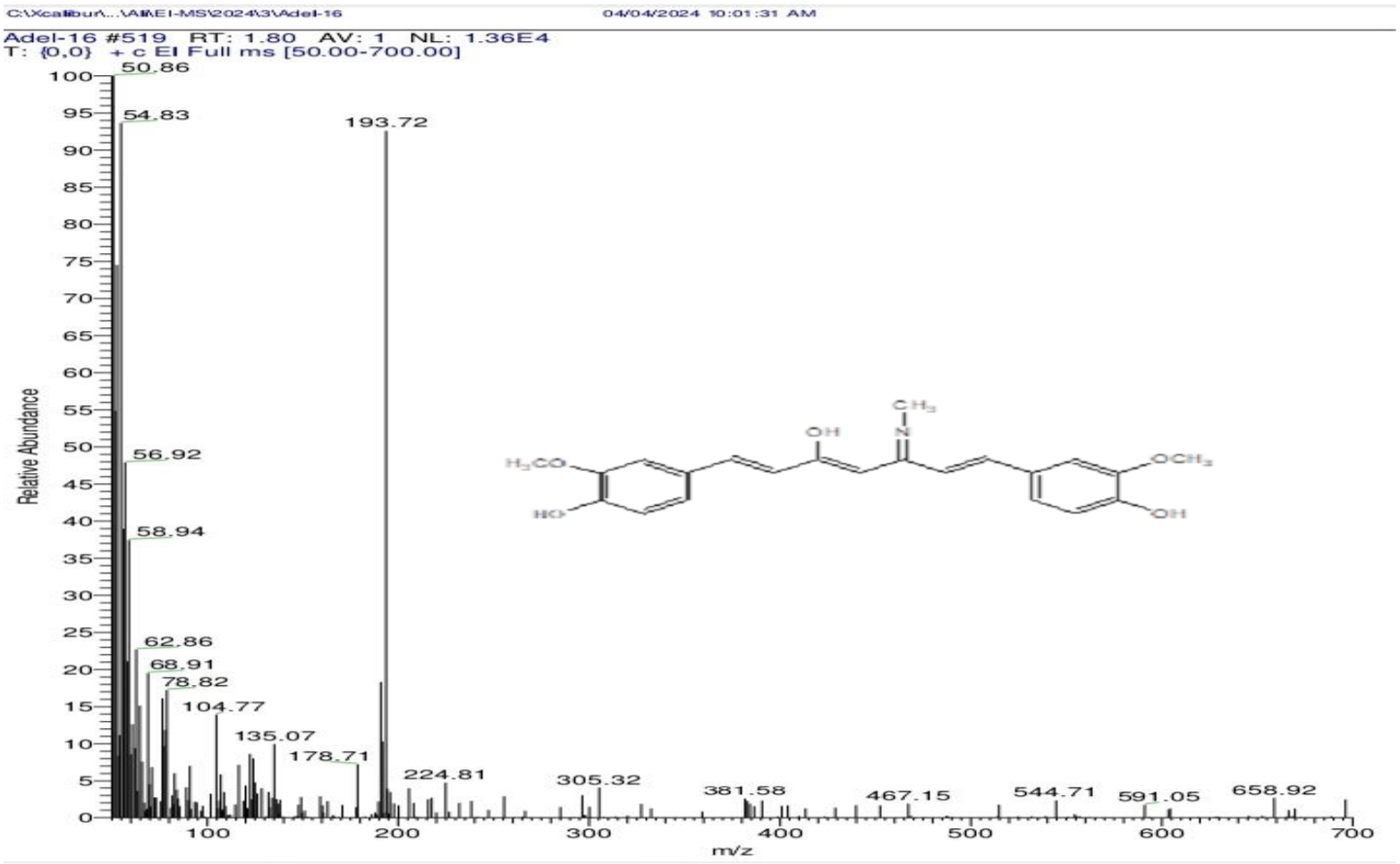


Figure.33 : The Mass spectrometry of compound [95].

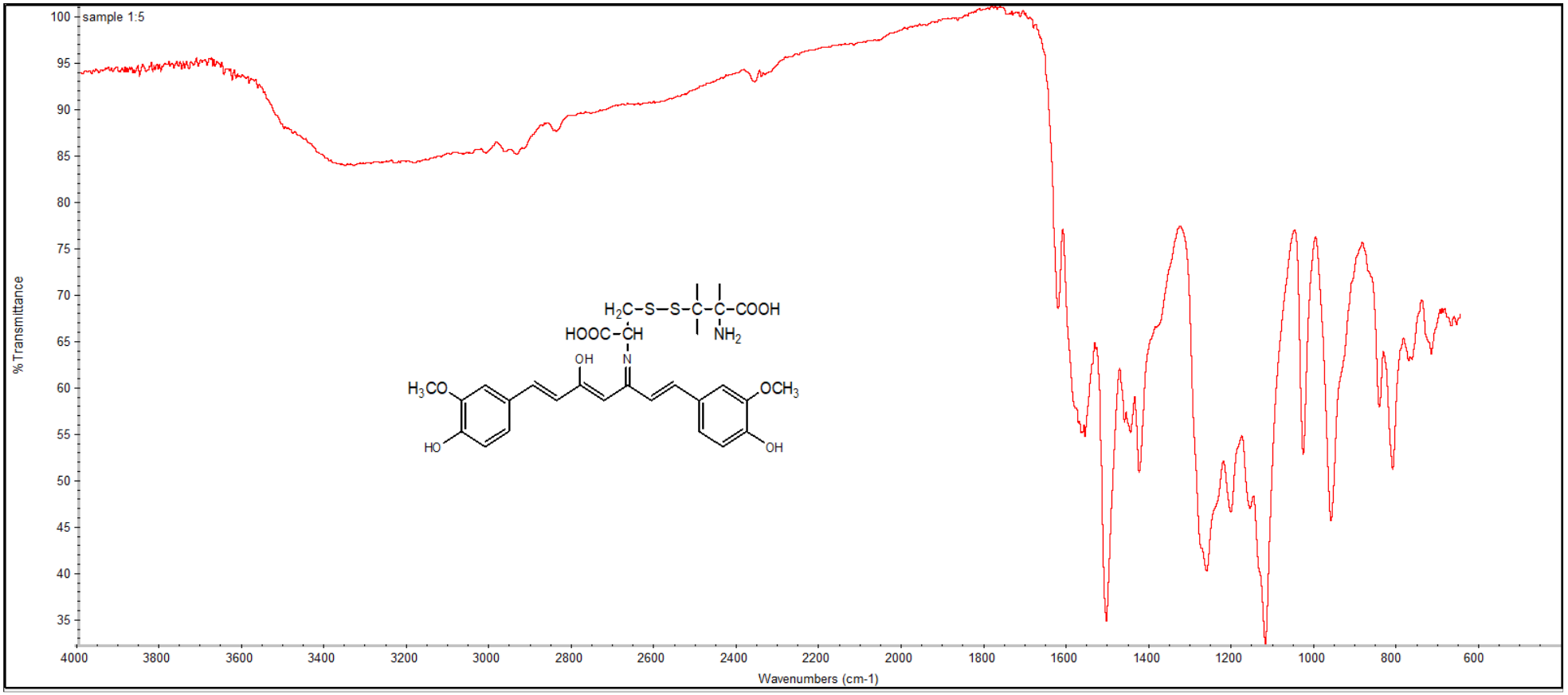


Figure .34: The IR spectrum of compound [96].

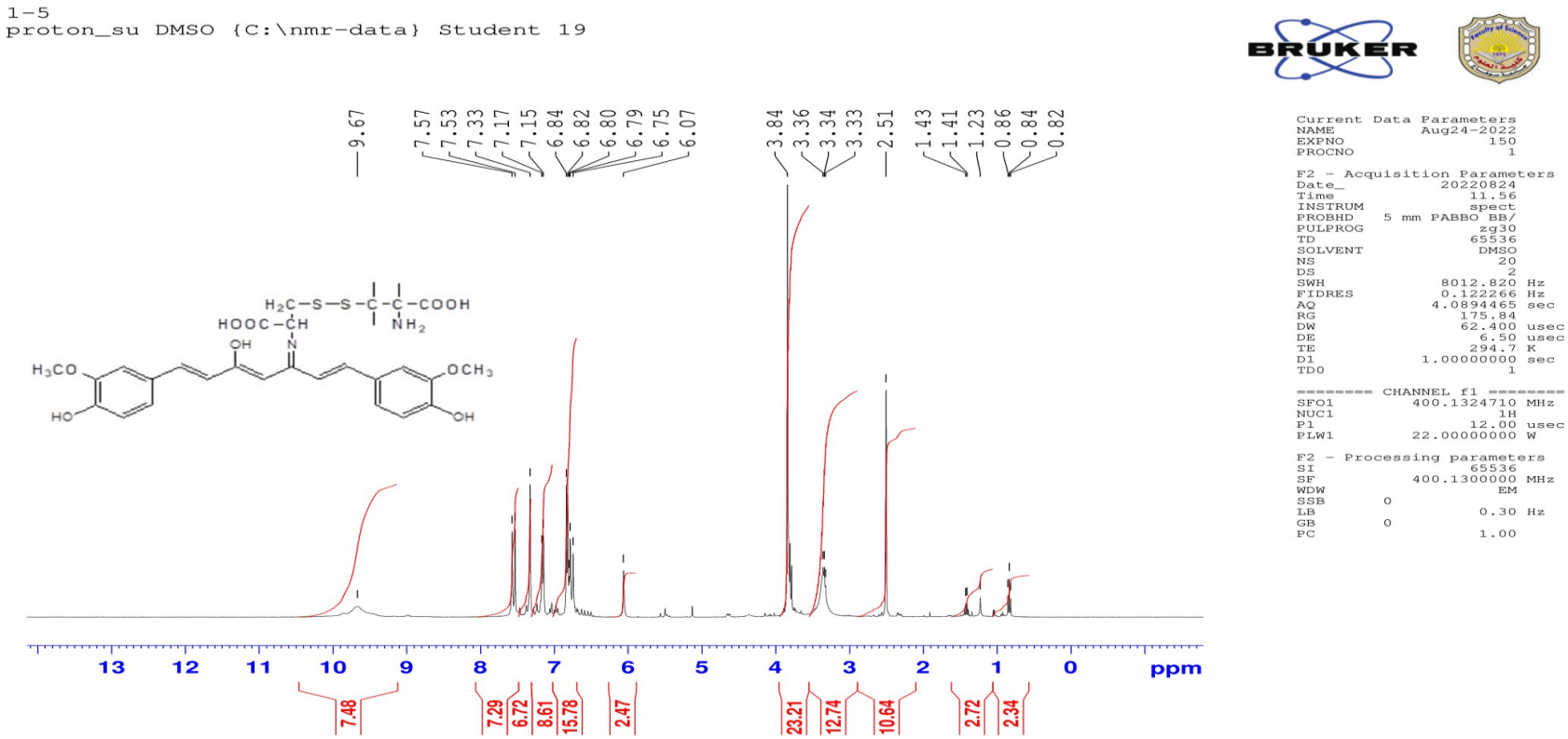


Figure.35 : The ^{1}H -NMR spectrum of compound [96].

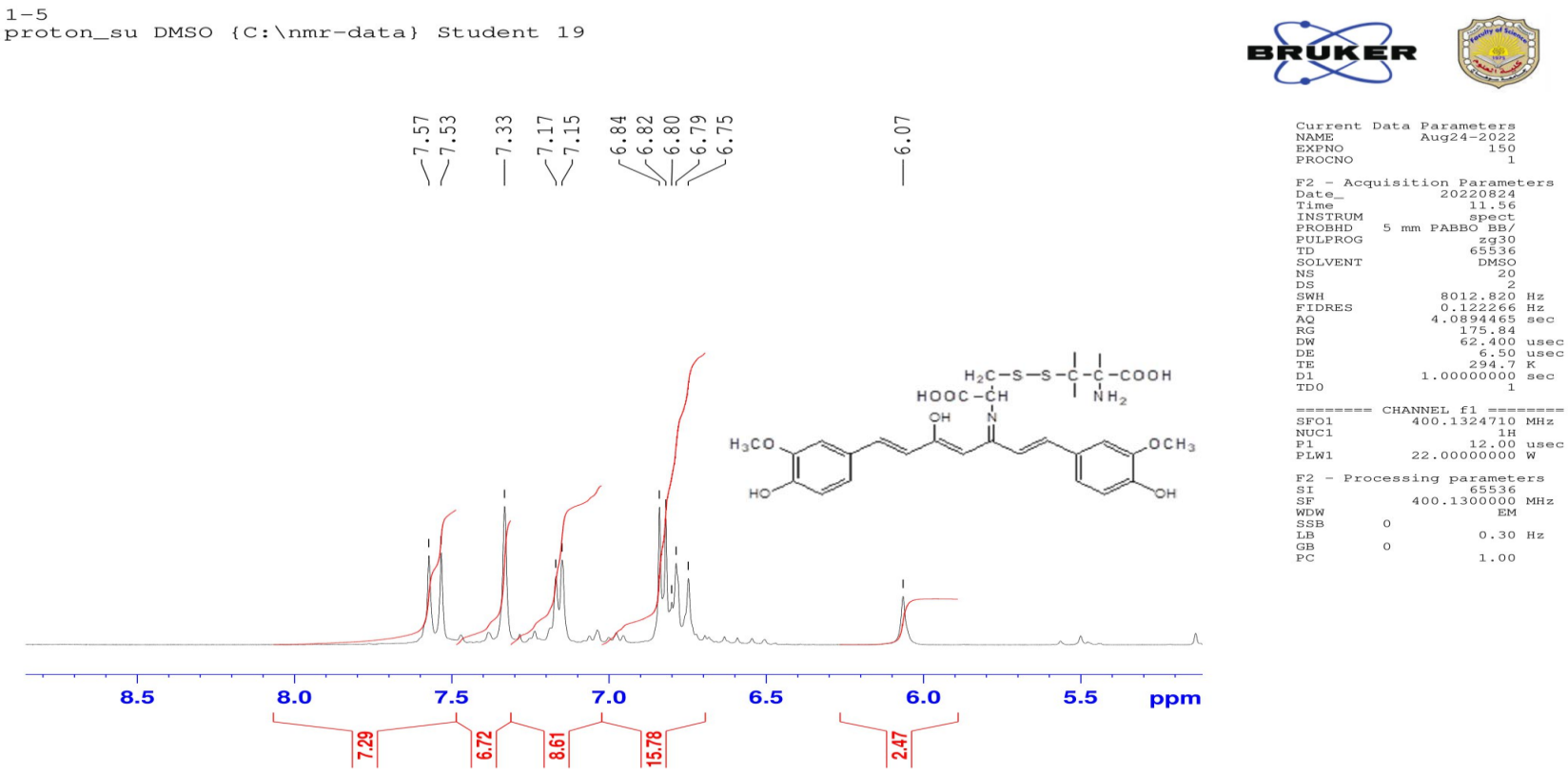


Figure.35/ : ^{1}H –NMR spectrum of compound [96].

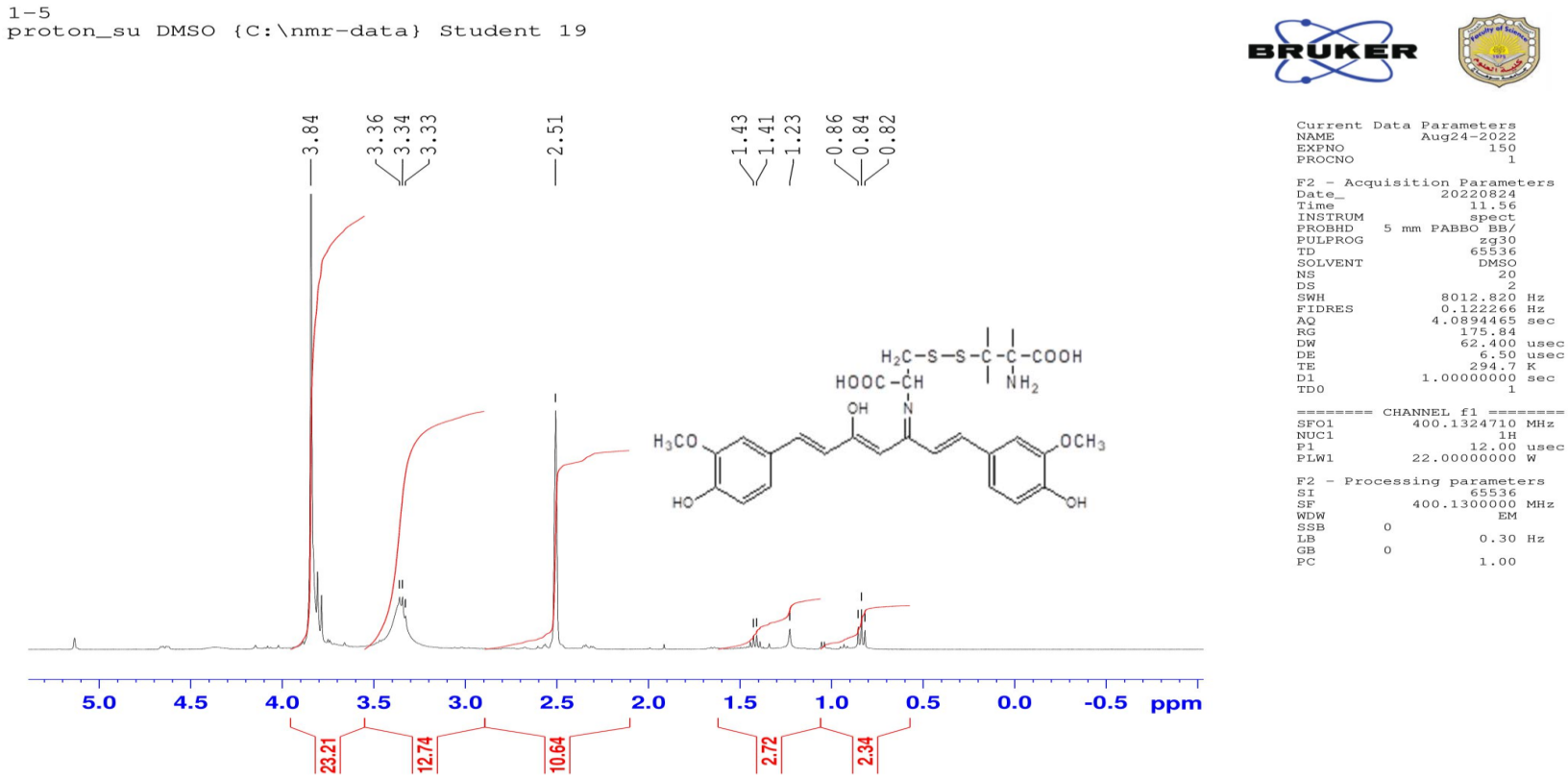


Figure.35// : The^{1}H –NMR spectrum of compound [96].

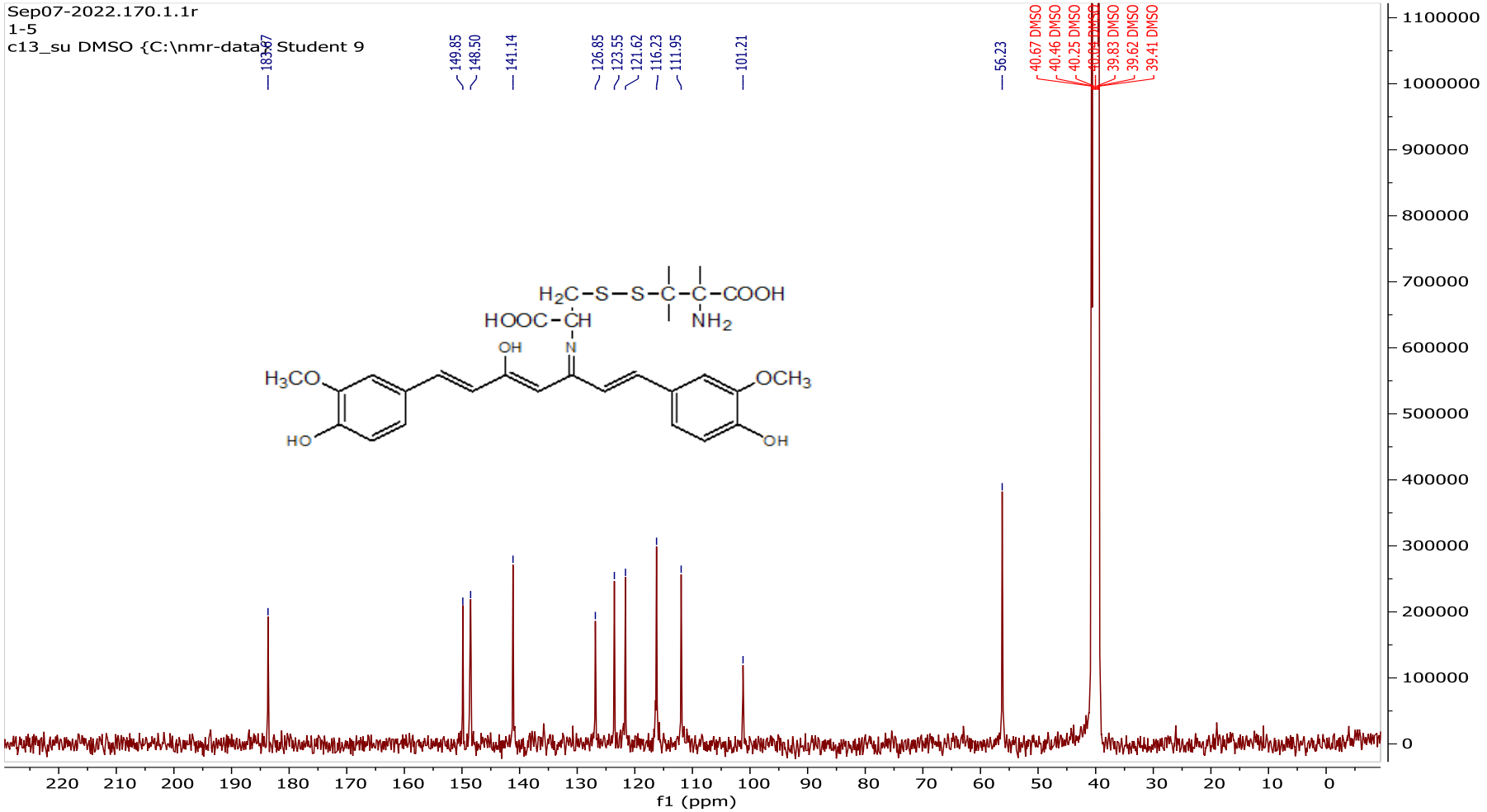


Figure.36 :The ^{13}C- NMR spectrum of compound [96].

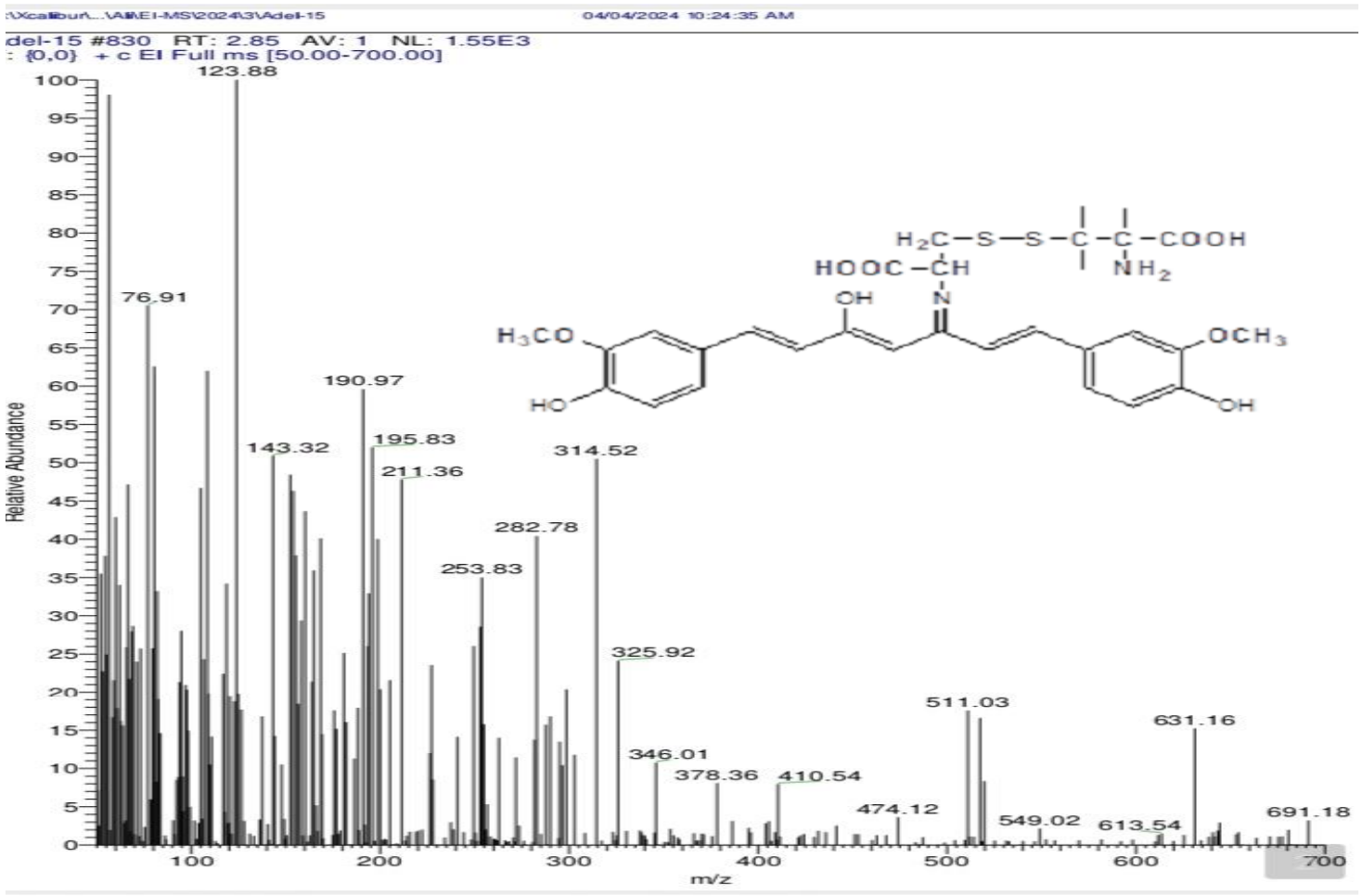


Figure.37 : The Mass spectrometry of compound [96].

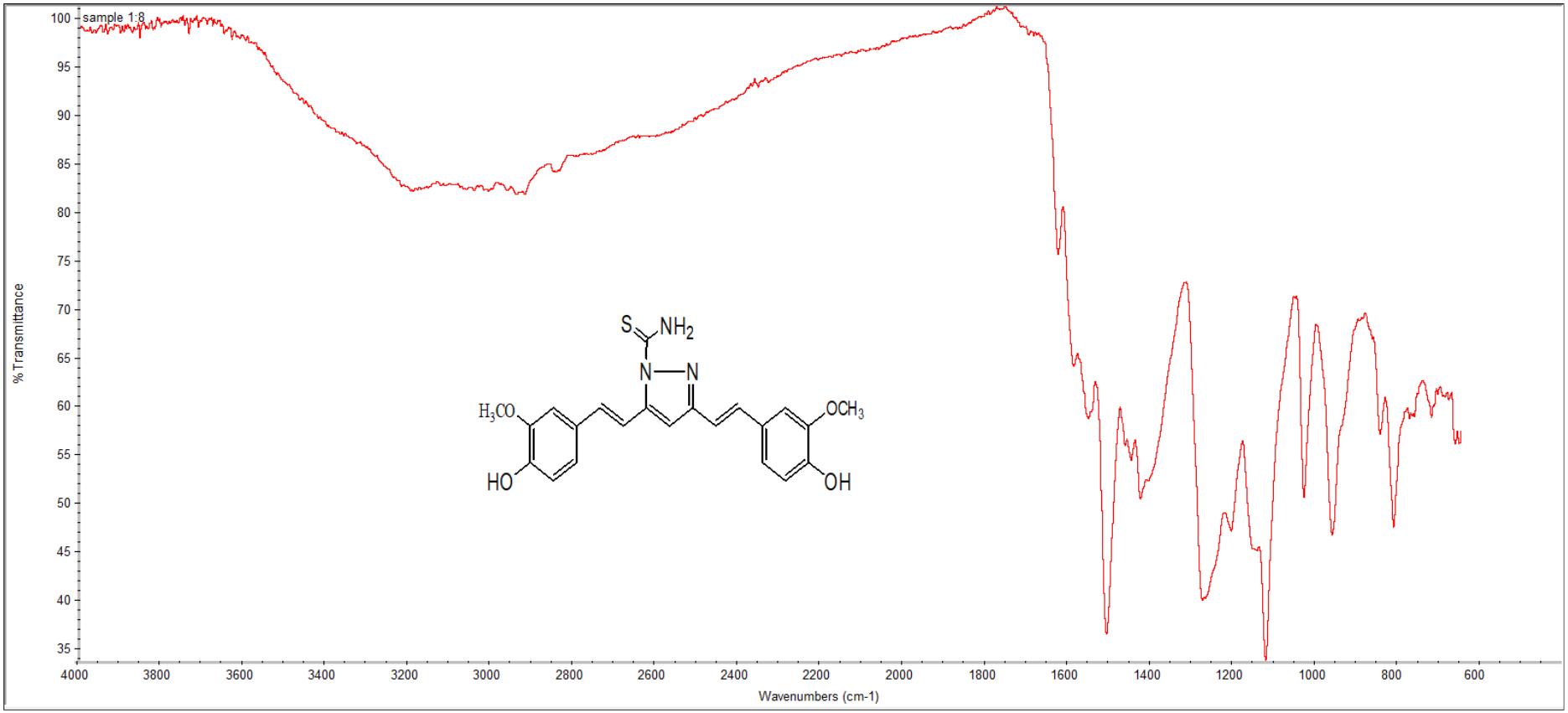


Figure. 38 : The IR spectrum of compound [97].

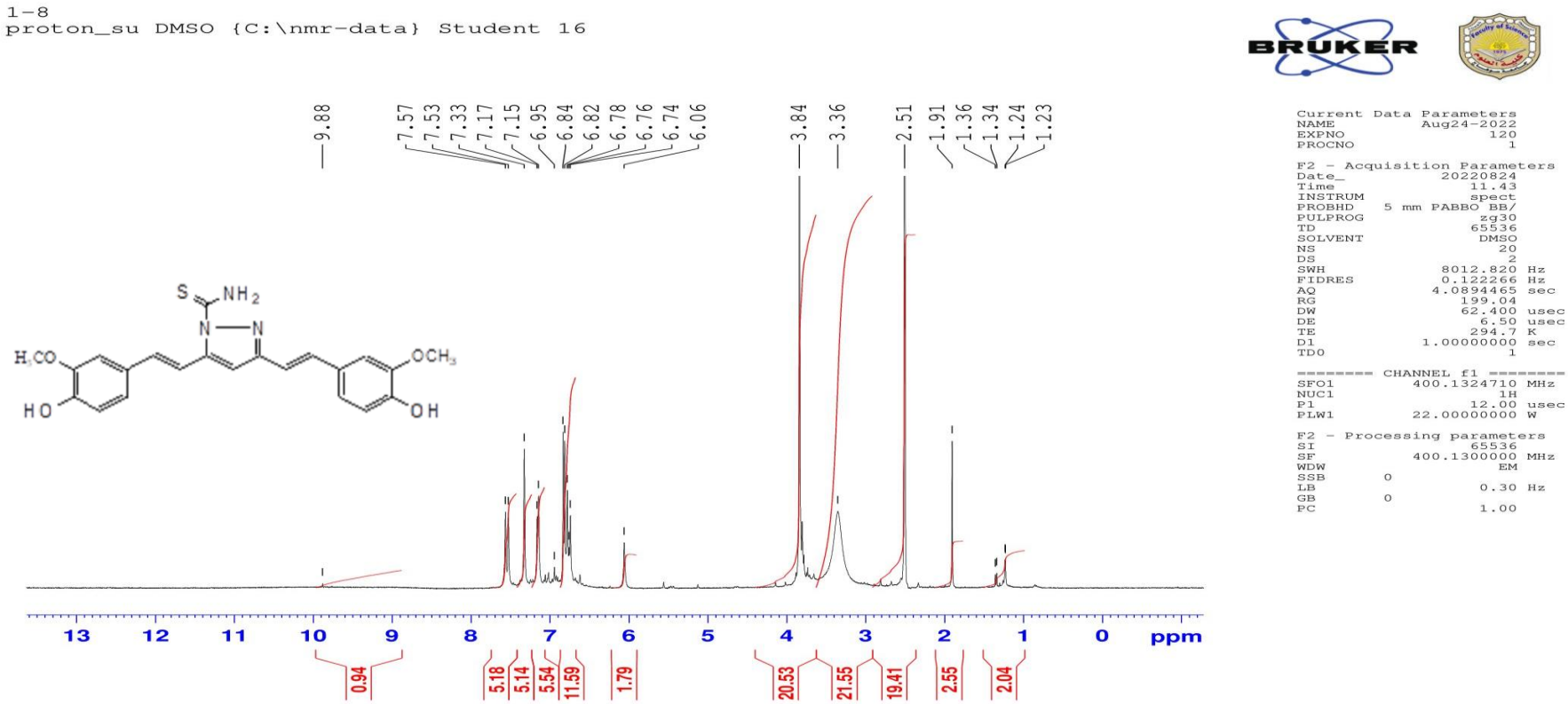



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Figure.39 : The ^{1}H NMR spectrum of compound [97].

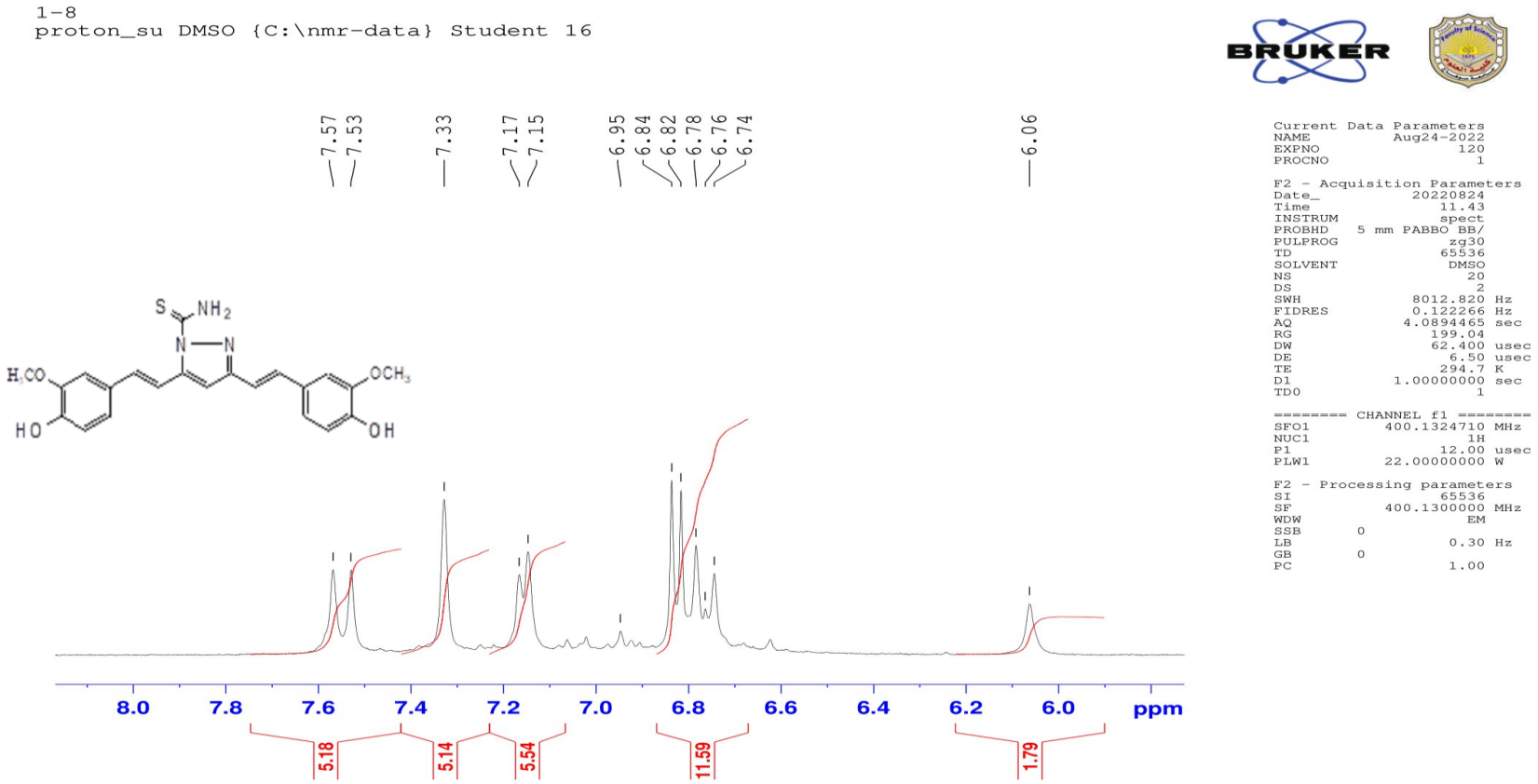


Figure.39/ : The ^{1}H NMR spectrum of compound [97]

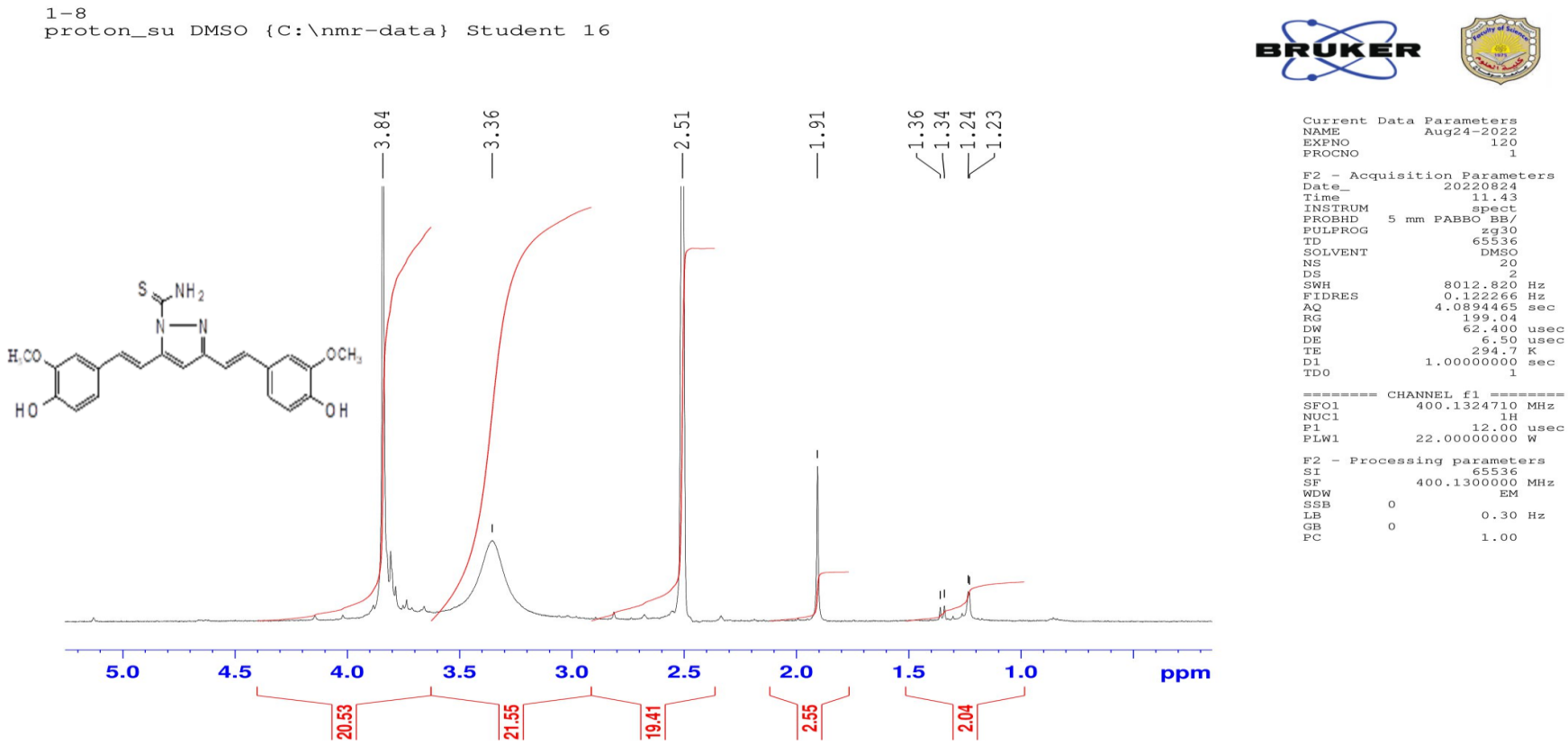


Figure.39// : The ^{1}H NMR spectrum of compound [97].

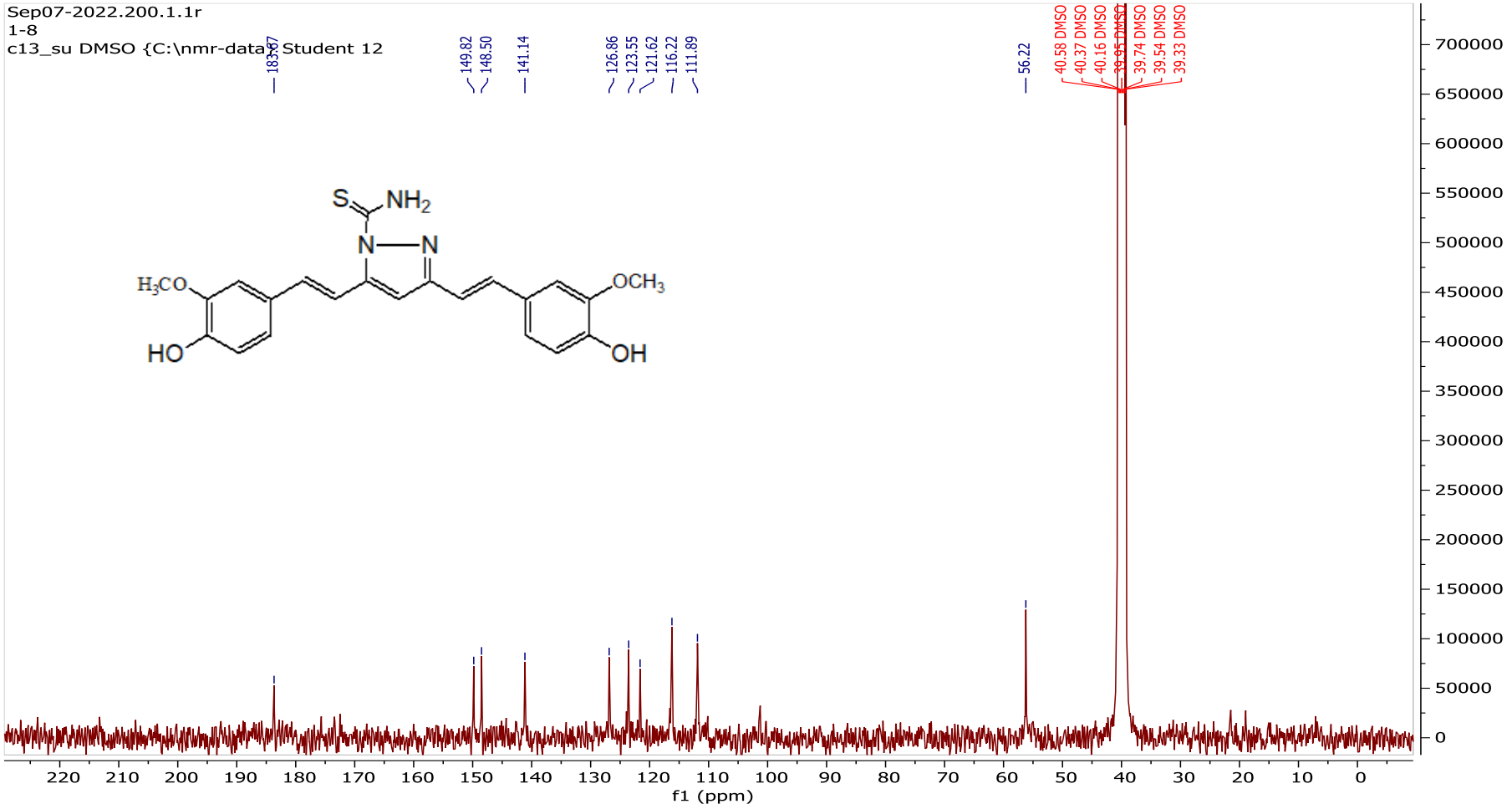


Figure.40: The ^{13}C-NMR spectrum of compound [97].

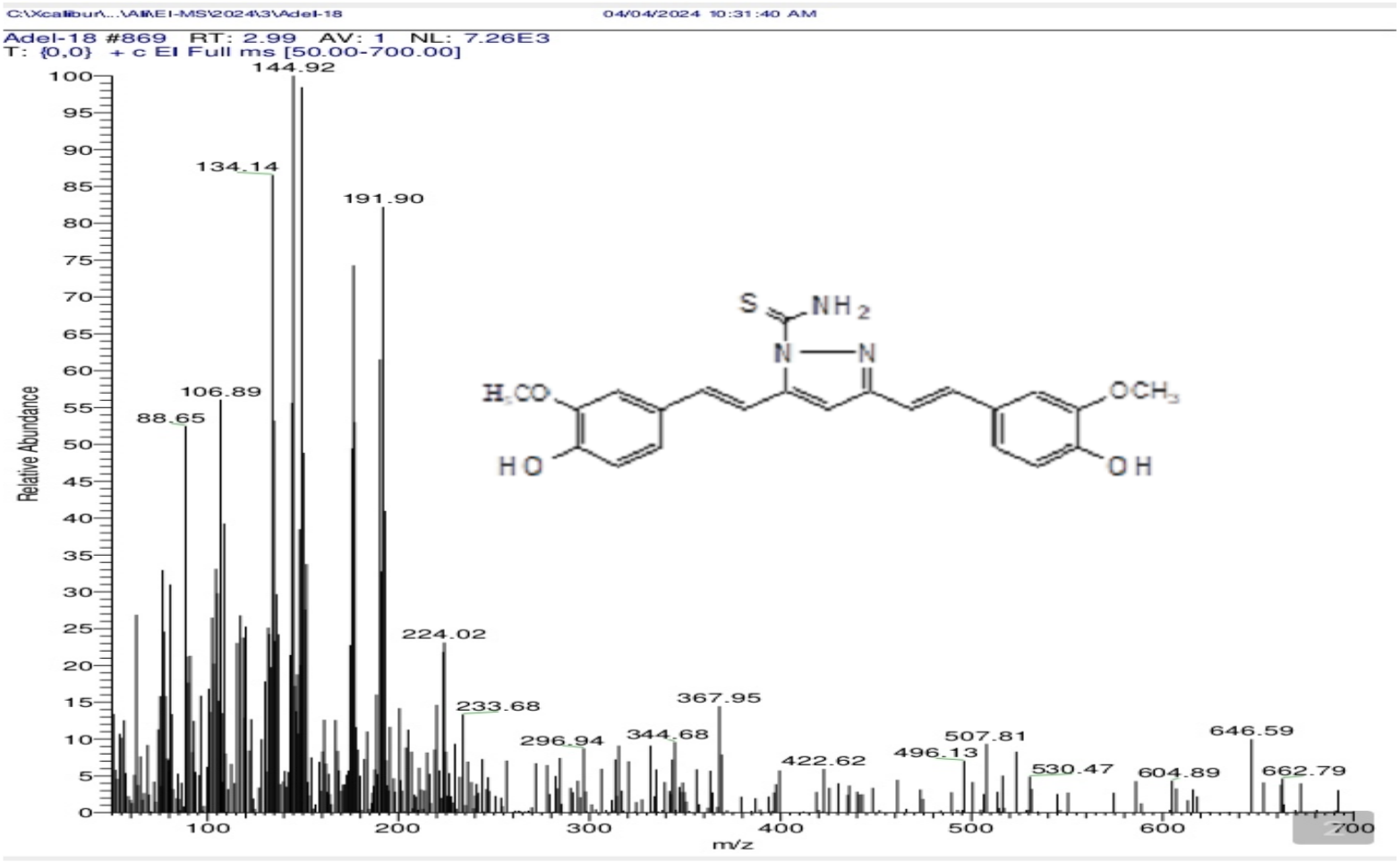


Figure.41 : The Mass spectrometry of compound [97]

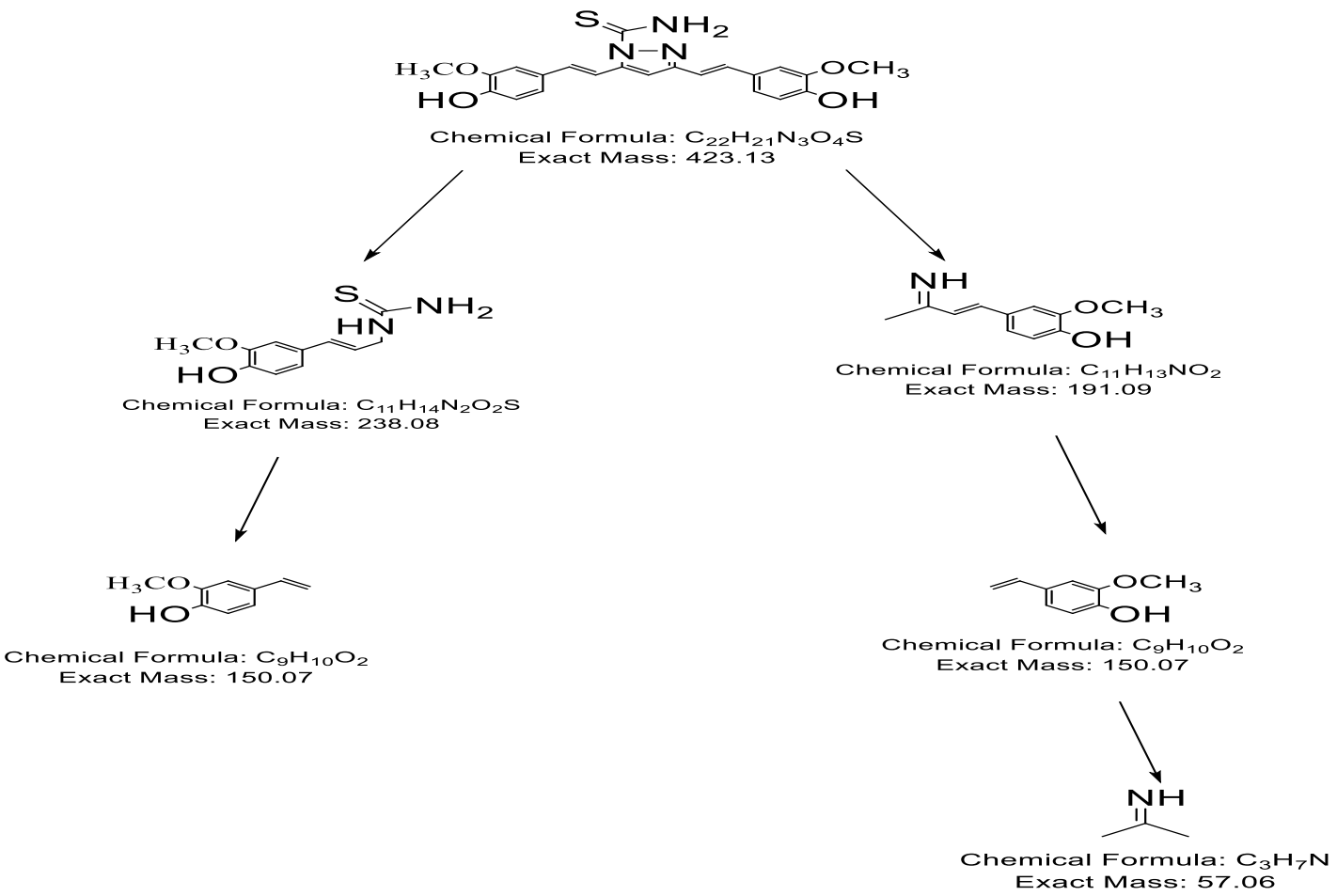
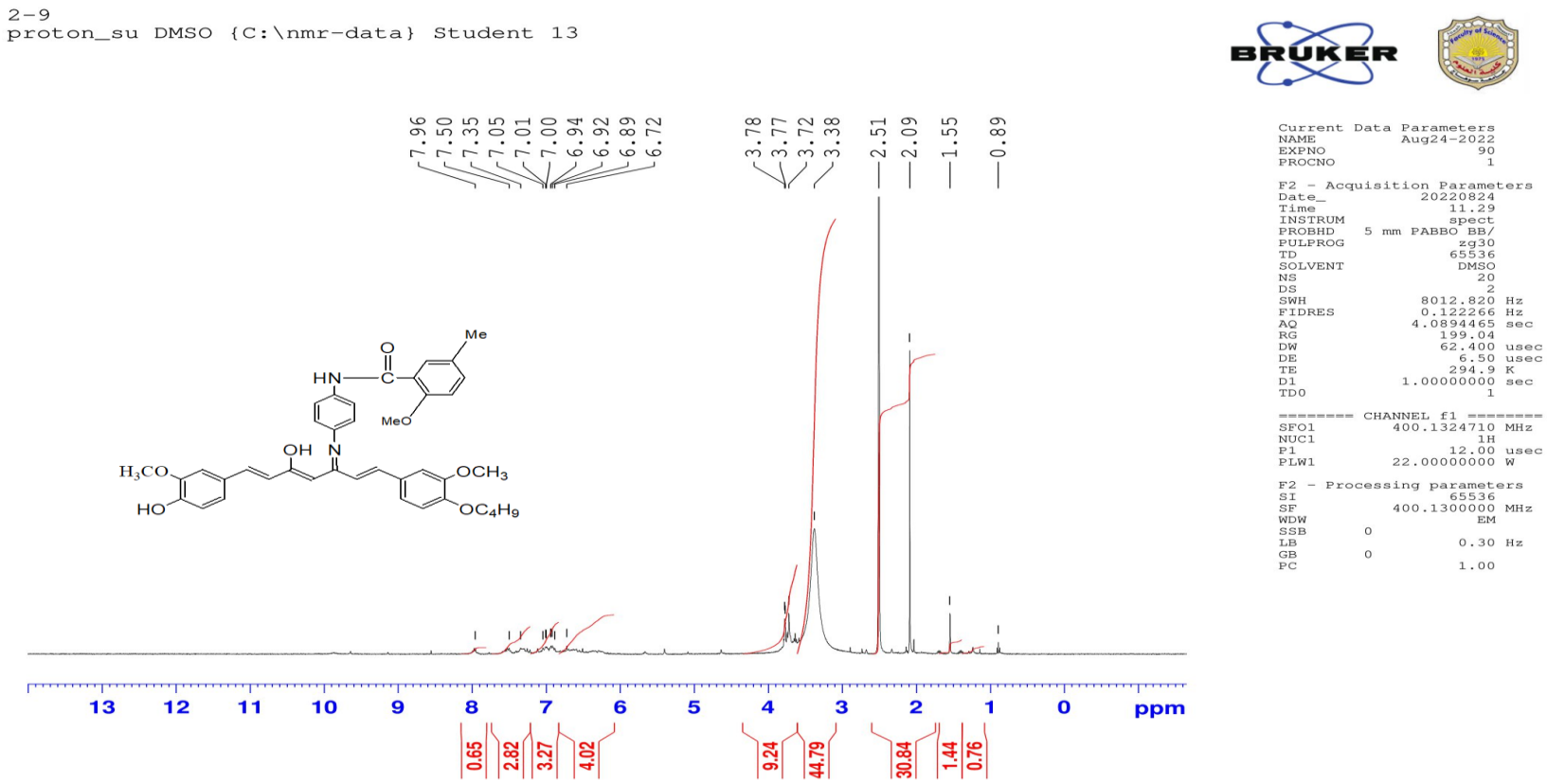


Figure.42 : Fragmentation patterns for compound [97].

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DE                          6.50 usec
TE                         294.9 K
D1                      1.00000000 sec
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Figure.43 : The ^{1}H- NMR spectrum of compound [99].

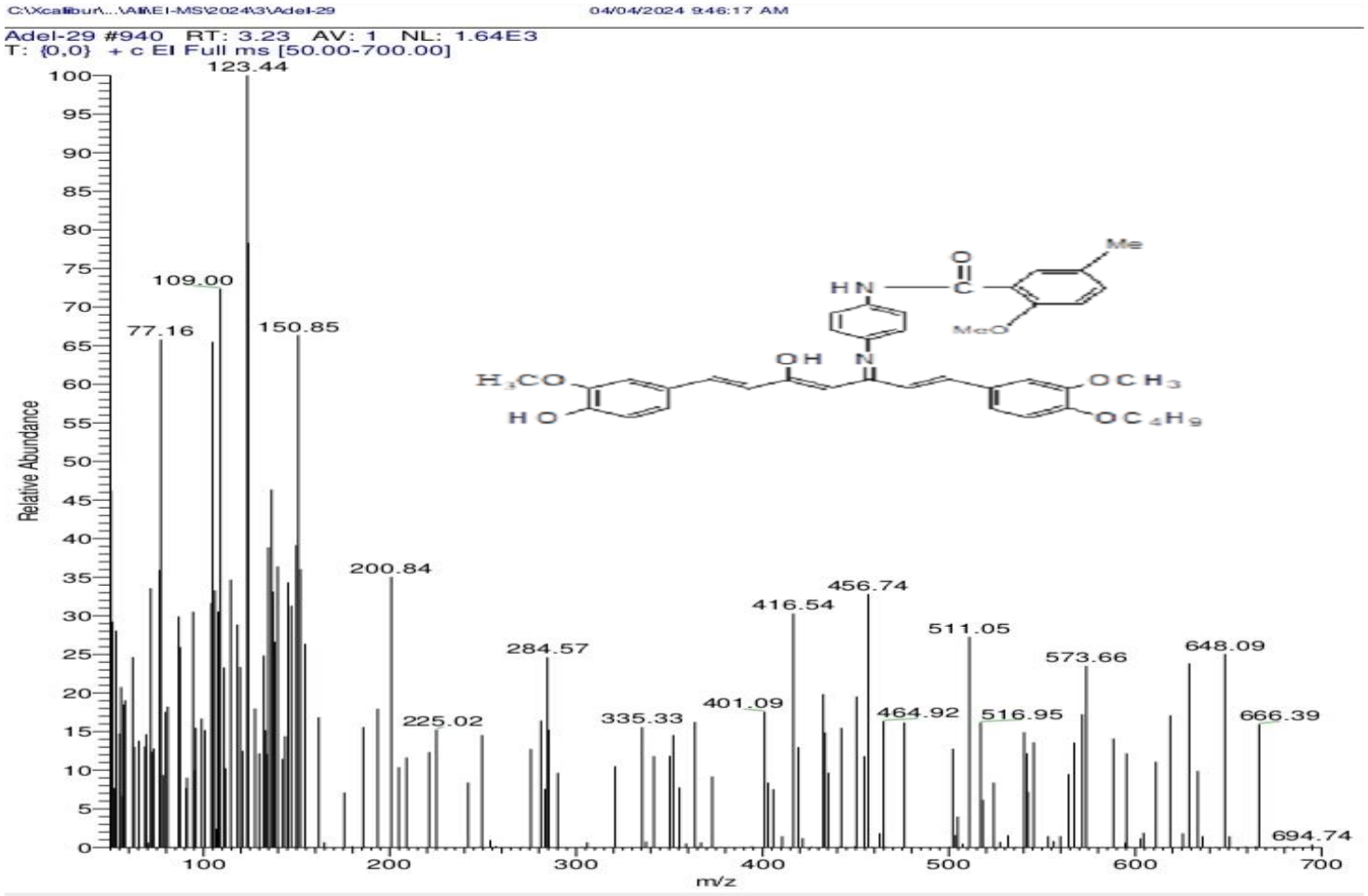


Figure.44 : The Mass spectrometry of compound [99]

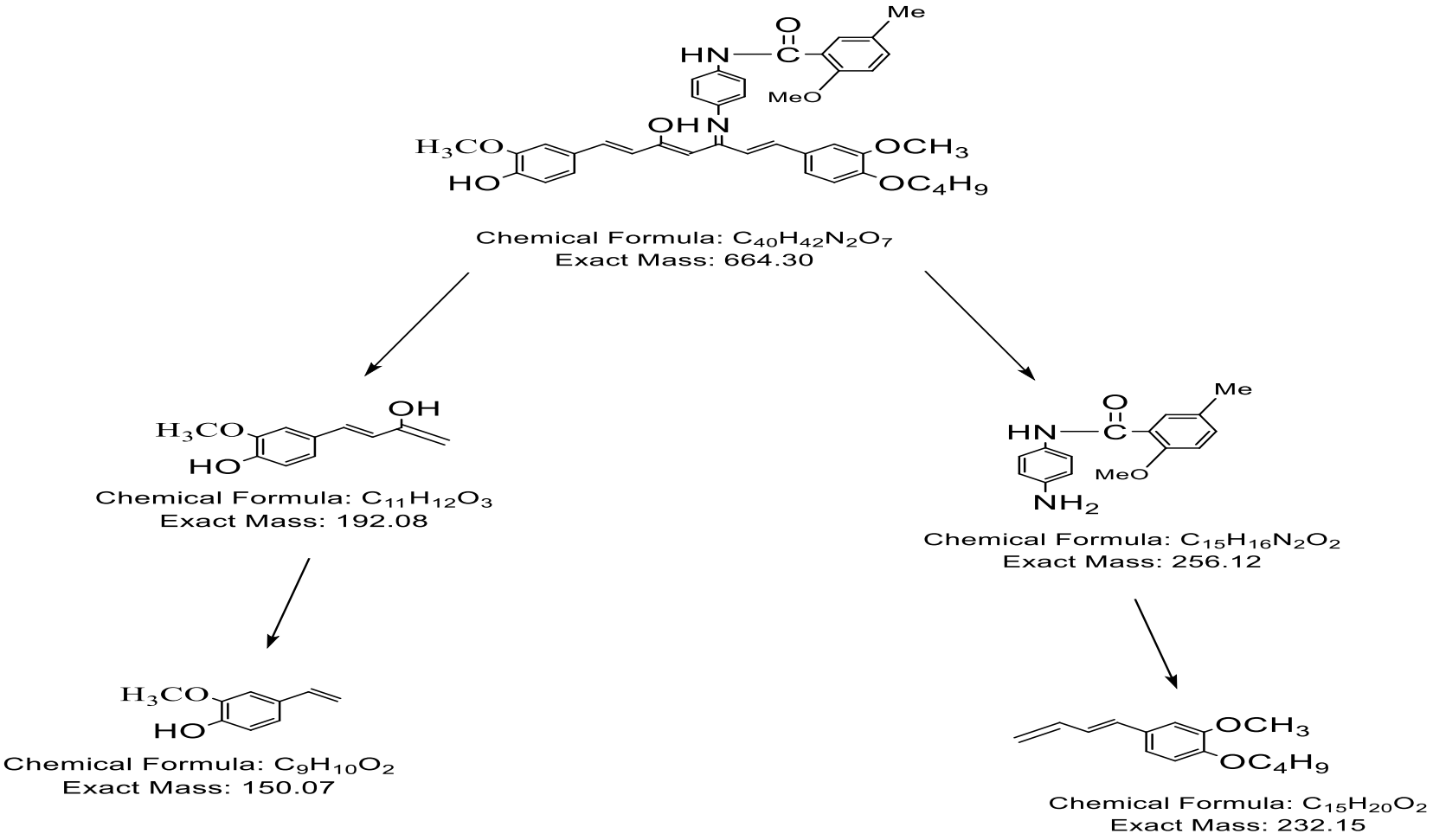


Figure.45 : Fragmentation patterns for compound [99].

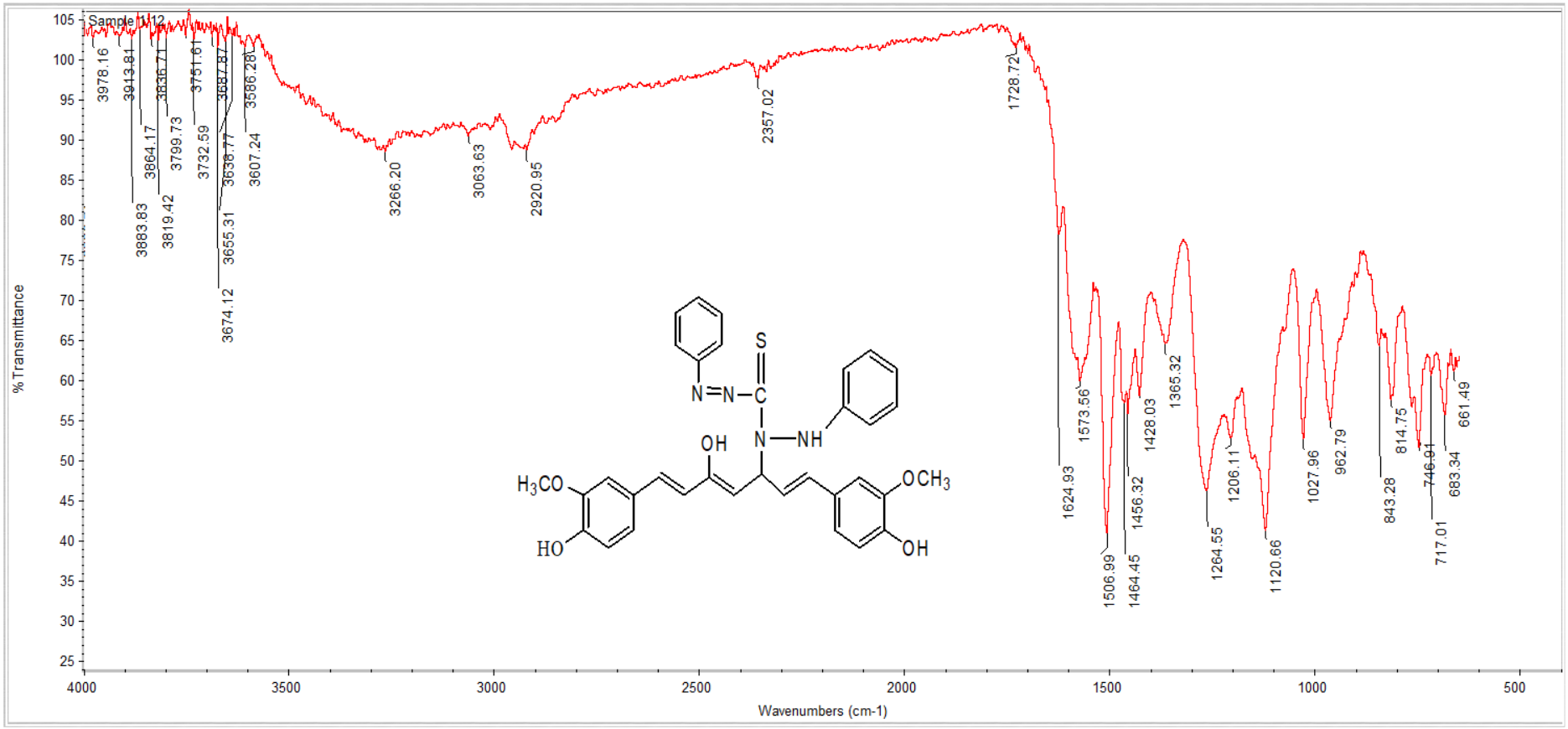
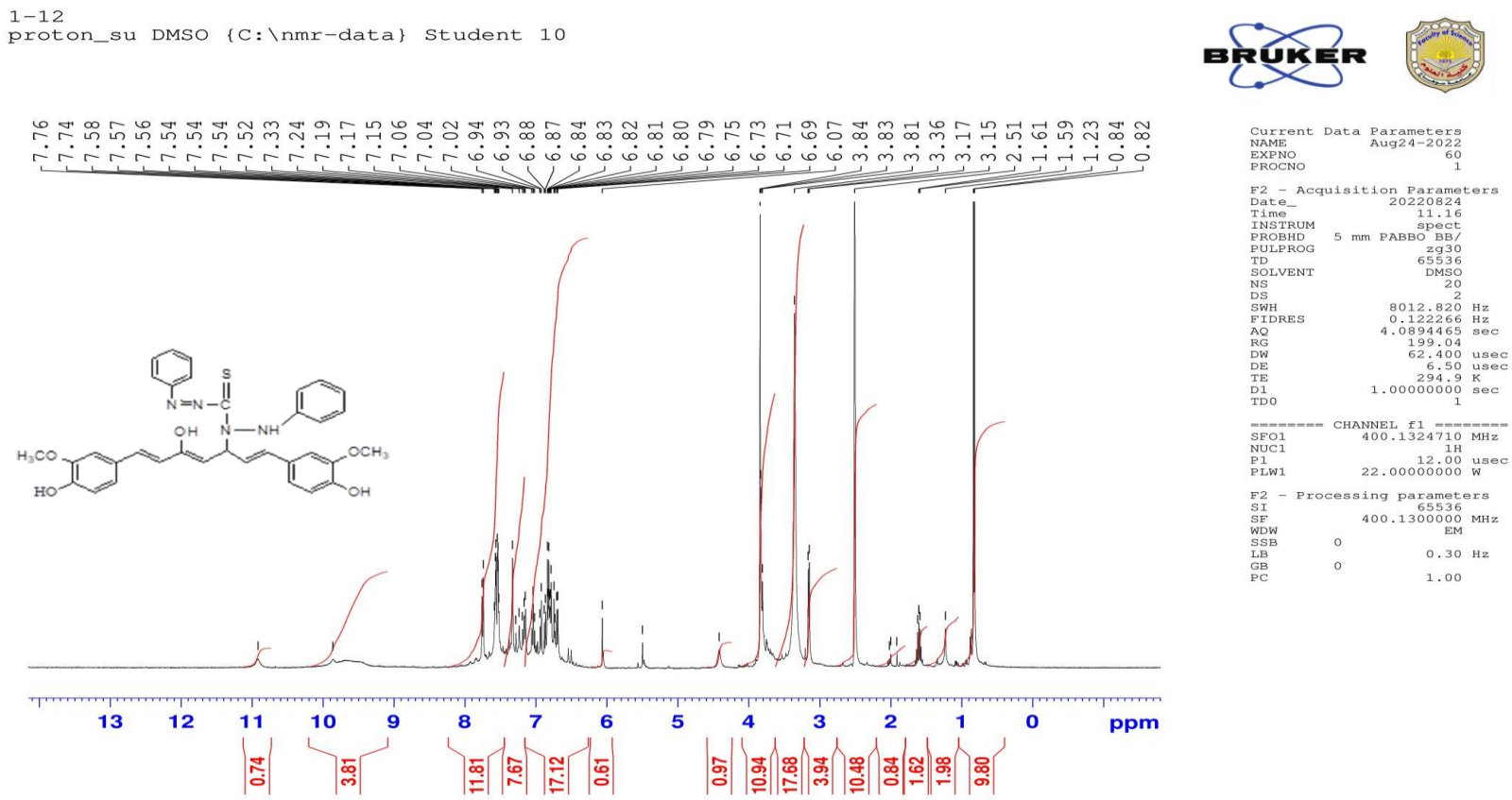


Figure.46 : The IR spectrum of compound [100]

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FIDRES                  0.122266 Hz
AQ                      4.0894465 sec
RG                         199.04
DW                         62.400 usec
DE                          6.50 usec
TE                         294.9 K
D1                    1.00000000 sec
TD0                            1

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NUC1                         1H
P1                         12.00 usec
PLW1                22.00000000 W

F2 - Processing parameters
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LB                         0.30 Hz
GB                  0
PC                         1.00
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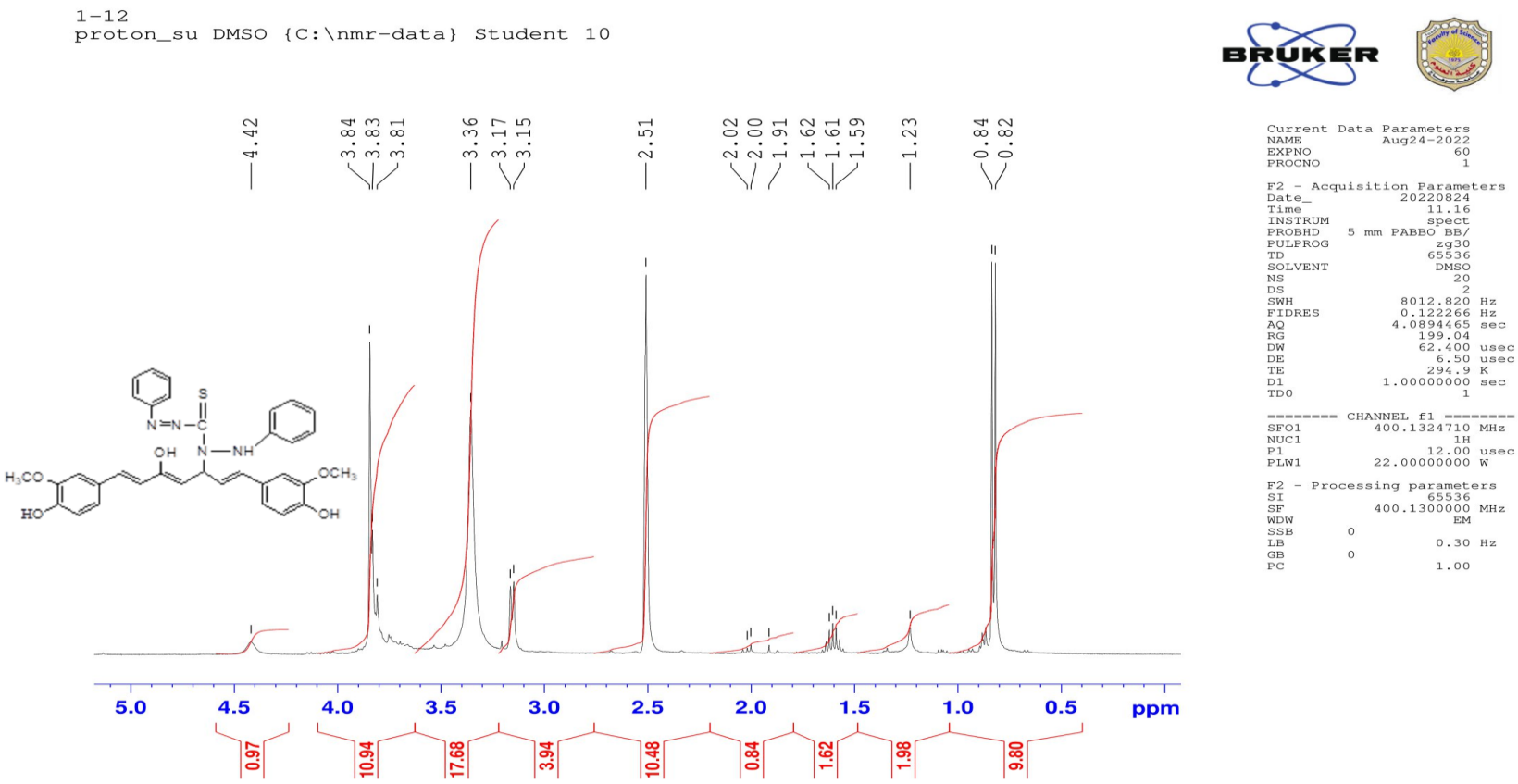
Figure.47: The ^{1}H- NMR spectrum of compound [100]

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SWH                     8012.820 Hz
FIDRES                  0.122266 Hz
AQ                      4.0894465 sec
RG                         199.04
DW                         62.400 usec
DE                          6.50 usec
TE                         294.9 K
D1                      1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
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NUC1                          1H
P1                         12.00 usec
PLW1                   22.00000000 W

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Figure.47/: The ^{1}H NMR spectrum of compound [100]

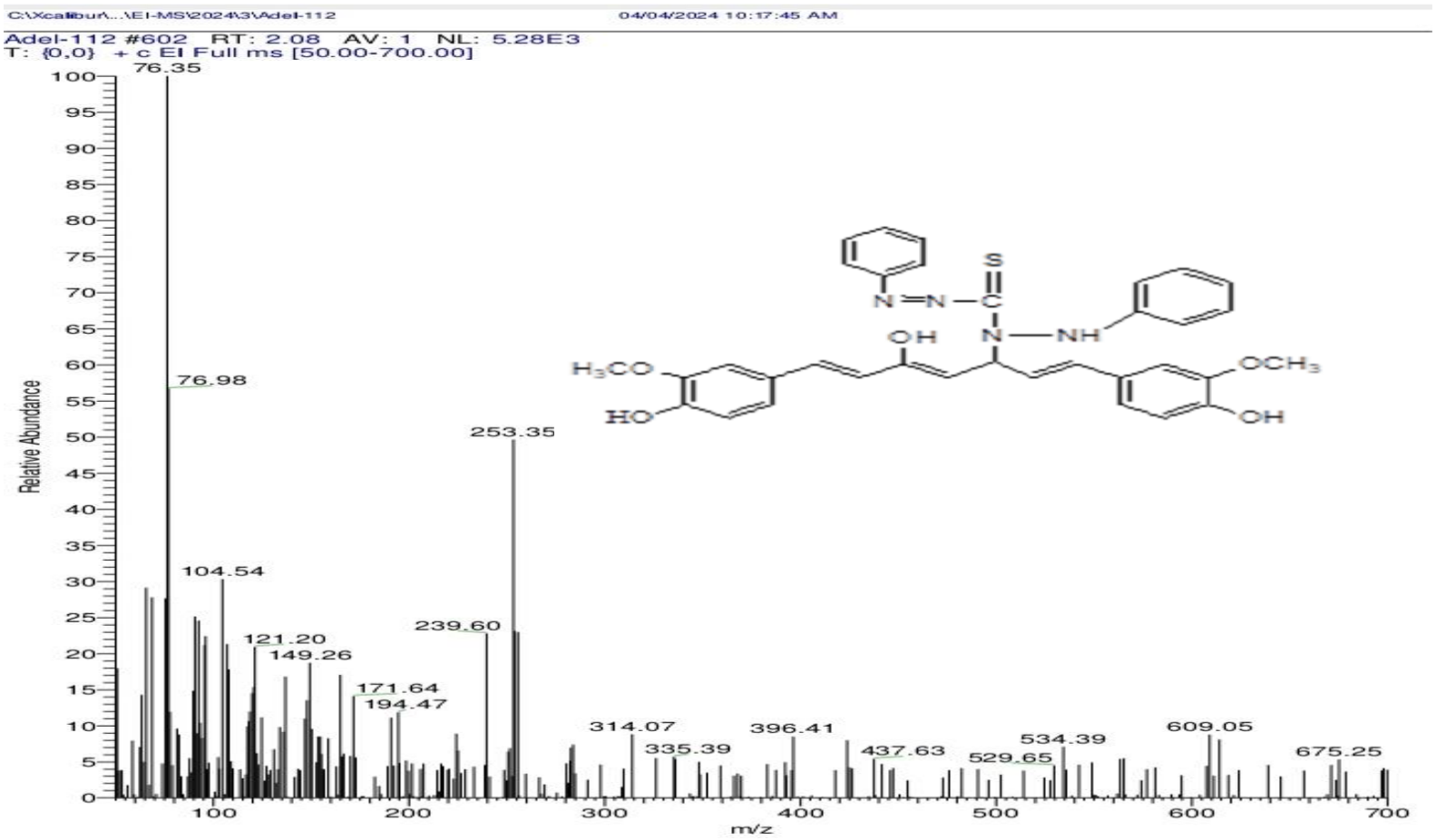

Figure.48: The Mass spectrometry of compound [100]

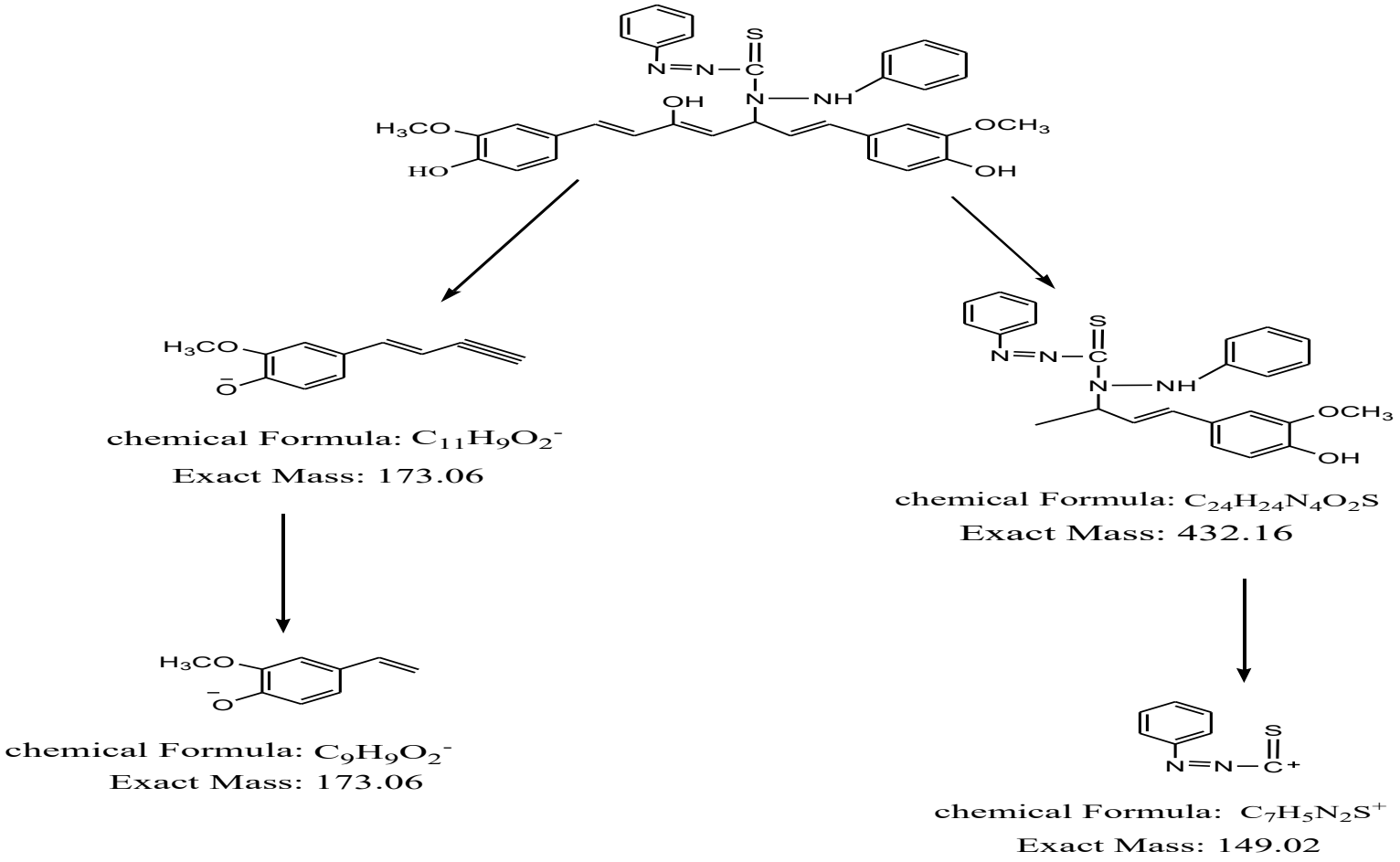

Figure.49 : Fragmentation patterns for compound [100]

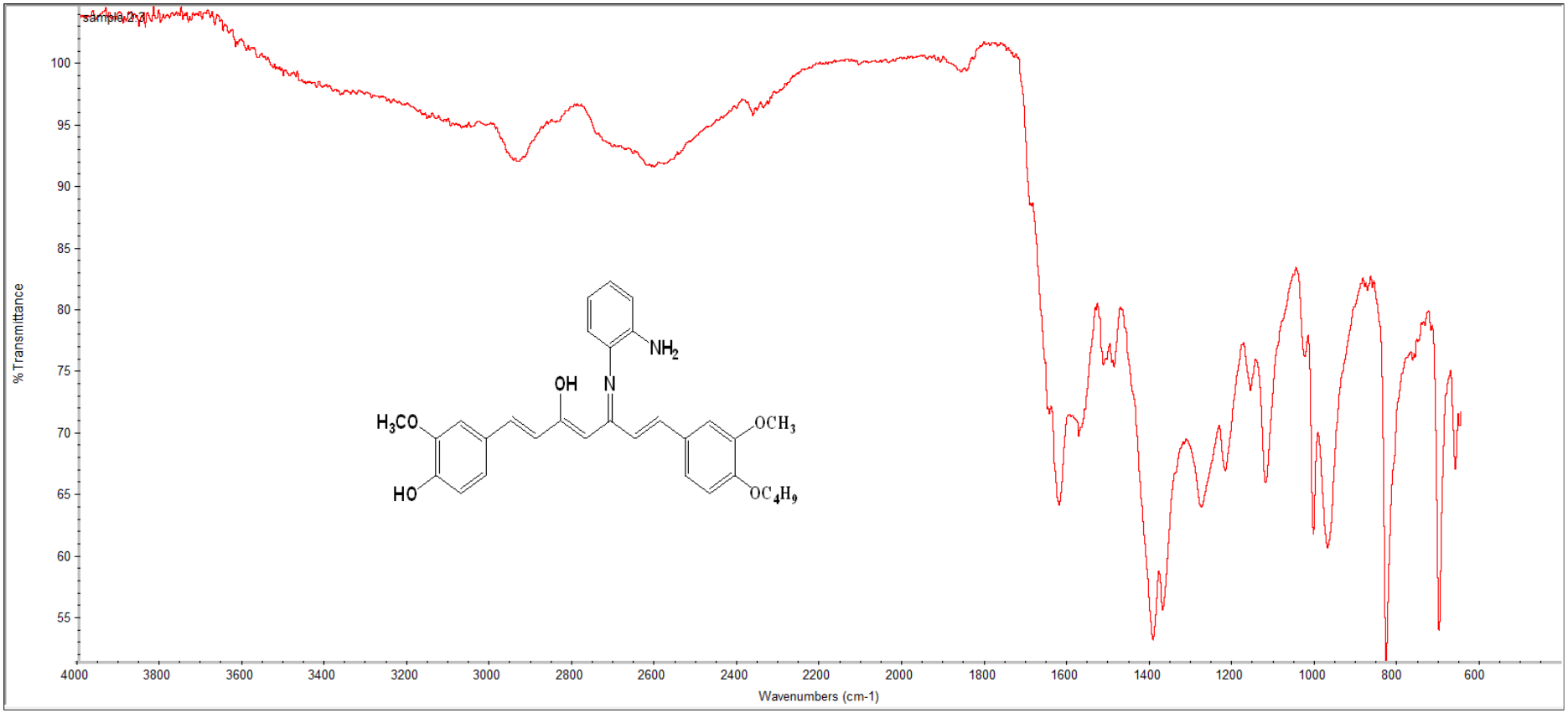

Figure.50 : The IR spectrum of compound [98]

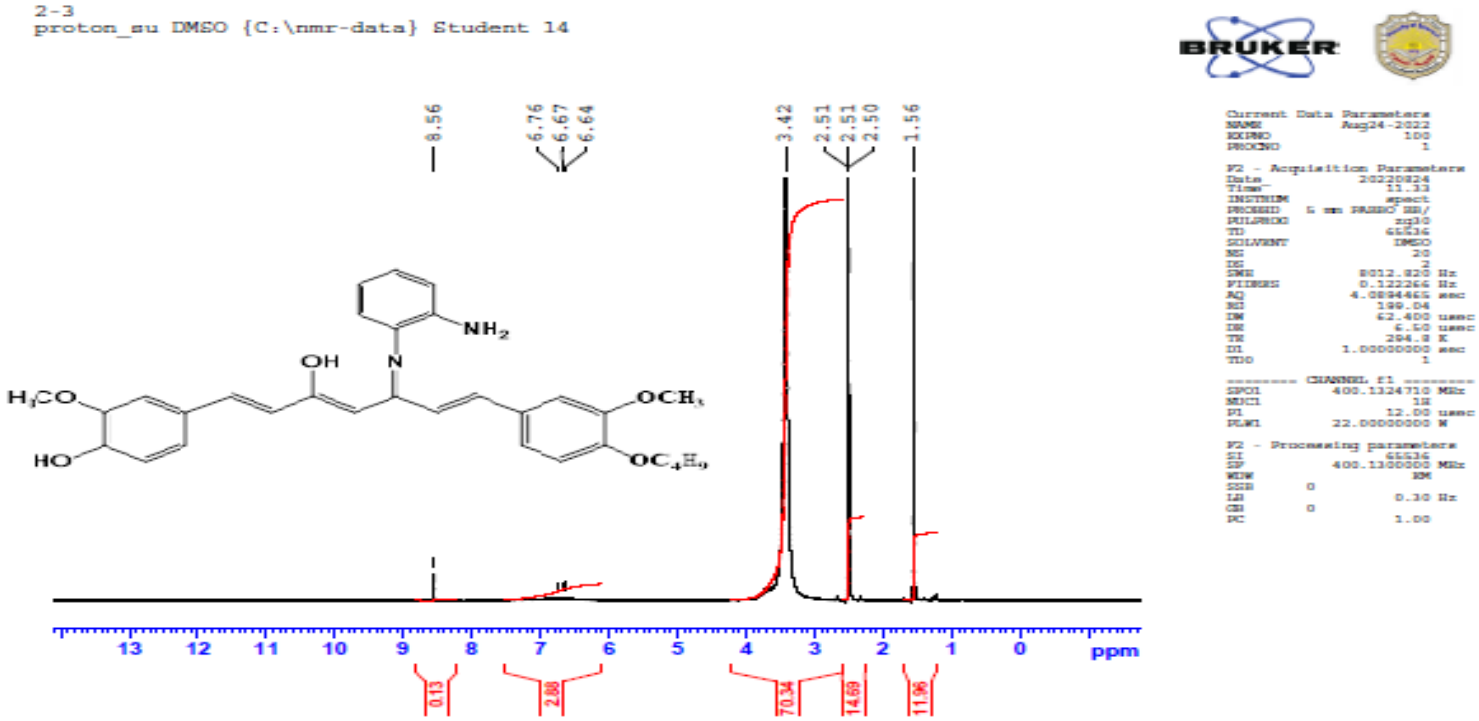

Figure.51: The ^{1}H- NMR spectrum of compound [98]

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رسالة لنيل الإجازة العالية الماجستير

بعنوان

تخليق بعض مشتقات الكركمين بتفاعله مع مشتقات الامونيا ودراسة فاعليتها البيولوجية

إعداد الطالبة :

نعيمة امحمد سالم احفيظة

تحت إشراف الأستاذ الدكتور البروفسور:

خيري محمد الصادق حمزة

للعام الجامعي 2024-2025 م

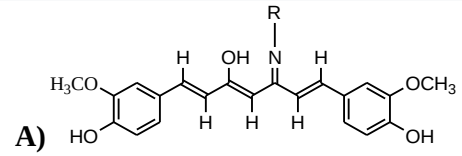
الملخص العربي

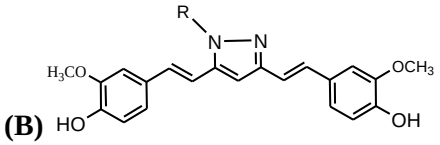
تخليق وتوصيف ودراسة النشاط البيولوجي لفئة جديدة من بعض مشتقات الكركمين عن طريق التفاعل مع مشتقات الأ مونيا.

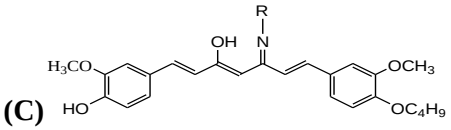
ملخص الرسالة

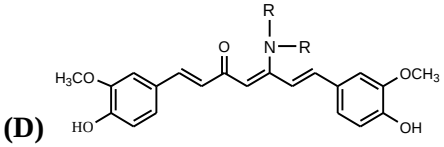
باختصار، للكركمين قيمة طبية مرغوبة، وله تأثيرات علاجية متعددة على التنظيم الكيميائي الحيوي الخلوي، والتنظيم الفسيولوجي، وتثبيط العدوى، وتعديل المناعة. وقد أثار هذا اهتمامًا كبيرًا من المجتمع العلمي، سعيًا لفهم آلية تأثيره العلاجي. ولا مفر من القيام بهذه المهمة دون معرفة العلاقة بين بنيته ونشاطه. وقد تناول هذا الفصل هذه النقطة بمراجعة فهمنا الحالي للتفاصيل البنيوية للكركمين ونظائره، وعلاقتها بأنشطته البيولوجية المرصودة.

يفترض هذا العمل أن الاستقرار الكيميائي والأنشطة البيولوجية قد تُشكلان نموذجًا لتصميم وتصنيع نظائر جديدة للكركمين، والتي تُحسّن من استخدامها في العلاجات. تم تحضير عدد من مشتقات الكركمين (89-100)، حيث أعطت النتائج المتوقعة (أ، ب، ج، د). تم تحليل النواتج المنقاة ، باستخدام تقنيات تحليلية وطيفية متنوعة، مثل: نقطة الانصهار، كروماتوجرافيه الطبقة الرقيقة (TLC), مطيافية الرنين النووي المغناطيسي للبروتون (^{1}H NMR), مطيافية الرنين المغناطيسي النووي للكربون-13 (^{13}C NMR) الأشعة تحت الحمراء، ومطيافية الكتلة . في جميع الحالات، كانت النتائج متوافقة مع التركيب المتوقع,تم الحصول على جميع المركبات بنسبة إنتاج مقبولة (54% إلى 87%).









تم تقييم النشاط البيولوجي لهذه المركبات ضد أربع سلالات من البكتيريا بثلاثة تركيزات مختلفة: (100ppm، 200 ppm و 300ppm). أظهرت النتائج فعالية ملحوظة ضد البكتيريا. كما تم تقييم النشاط المضاد للأكسدة لهذه المركبات من خلال قياس قدرتها على تقليل DPPH، وأظهرت النتائج قدرة مضادة للأكسدة واضحة لهذه المركبات.