University of Kerbala

College of Science

Department of Chemistry

Synthesis of Schiff Bases Derivatives from Adamantane

A Thesis

Submitted to the Council of the College of Science / University of Kerbala as a Partial Fulfillment of the Requirements for the Degree of Master of Science in Chemistry

Written By

Zainab Mohammed Ali Saadon

B. Sc. in Chemistry (2007) /University of Kerbala

Supervised by

Prof. Dr. Rahman Tama Al-Tamimi

September **2024 A.D** Rabi Al-Awwal **1446 A.H**

﴿بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ﴾

﴿وَلَقَدْ آتَيْنَا دَاوُودَ وَسُلَيْمَانَ عِلْمًا ۖ

وَقَالَا الْحَمْدُ لِلَّهِ الَّذِي فَضَّلَنَا عَلَىٰ كَثِيرٍ مِّنْ

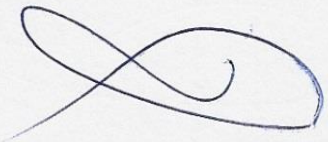
عِبَادِهِ الْمُؤْمِنِينَ﴾

صدق الله العظيم

سورة النمل اية(15)

Supervisor Certification

I certify that this thesis " Synthesis of Schiff Bases Derivatives from Adamantane " was conducted under my supervision at the Chemistry Department, College of Science, University Karbala, as a partial requirement for the degree of Master of Science in Chemistry.



Signature:
Name: Dr. Rahman Tama Al-Tamimi
Title: Professor
Address: University of Kerbala, College of Sciences,
Department of Chemistry
Date: 1 / 10 / 2024

Report of the Head of the Chemistry Department

According to the recommendation presented by the Chairman of the Postgraduate Studies Committee, 1 forward this thesis" Synthesis of Schiff Bases Derivatives from Adamantane" for examination.

Signature:

Assist. Prof. **Dr. Thaer Mahdi Madlool**

Head of Chemistry Department

Address: University of Kerbala, College of Science, Department of Chemistry

Date: 11 / 8 / 2024

Kerbala University
Science College
Asst. Prof. Dr. Thaer M. M. Al-Rammahi
Head of Chemistry Department

Examination Committee Certification

We certify that we have read this entitled " Synthesis of Schiff Bases Derivatives from Adamantane "as the examining committee, examined the student " Zainab Mohammed Ali Saadon" on its contents, and that in our opinion, its adequate for the partial fulfillment of the requirements for the Degree of Master in science of chemistry

Signature:
Name: Dr.Haitham Dalol Hanoon
Title: Professor
Address: University of Kerbala, College of Science, Department of Chemistry.
Date: 1 / 10 / 2024
(Chairman)

Signature:
Name: Dr. Ban Hasan Taresh
Title: Assistant Prof
Address: University of Kerbala, College of Science, Department of Chemistry.
Date: 1 / 10 / 2024
(Member)

Signature:
Name: Dr. Ahmed Thamer Salim
Title: Assistant Prof
Address: AL - Nahrain University College of Pharmacy.
Date: / / 10 / 2024
(Member)

Signature:
Name: Dr. Rahman Tama Al-Tamimi
Title: Professor
Address: University of Kerbala, College of Science, Department of Chemistry.
Date: 1 / 10 / 2024
(Member & supervisor)

Approved by the council of the College of Science
Signature:
Name: Dr. Hassan Jameel Al-Fatlawy
Title: Professor
Address: Dean of College of Science, University of Kerbala.
Date: / / 2024

Dedication

To those who, without their presence, God would not have created a built sky and not earth, praiseworthy, the ships of deliverance, Ashab Al-Kisa' (Companions of the Cloak), peace be upon them…

To population of my heart …

To the one who taught me to give without waiting…To the one who's I carry his name with all pride…. I hope that God has mercy on you and accepts you as one of the martyrs, and your words will remain stars that guide me today and tomorrow and forever my dear father may god have mercy on him…. To the spring that watered me with the water of tenderness, and from under its foot my Lord made the heavens, and in her I find safety when fear …. To my kind mother. To the symbol of loyalty. To the rose of my life. To the companion of my life…. My dear husband may God protect him from all evil…To my children my liver buds and the apple of my eye (Shamms and Reda). And to those who have given color to life and to those who supported me and helped me to my brothers and my sisters.

Lastly, to any book, person, word who have credited with teaching us. I dedicate this humble effort to everyone we ask god Almighty to benefit him. He is the hearer and the Answerer.

Zainab

Acknowledgment

Praise be to Allah, who has valued everything, and showed His good kindness in shapes, meaning and covering faults, and blessings and peace be upon the best of creatures and human beings, Prophet Mohammed (the chosen) of the elite of mankind and upon his good family members and followers until the Day of Judgment.,

*I present my sincere thanks and great gratitude to my distinguished professor, the supervisor (**Prof. Dr. Rahman Tama Al-Tamimi**) for his scientific patronage and valuable guidance throughout the period of research completion. My thanks, appreciation and gratitude are due to the Presidency of the University of Kerbala - Deanship of the Faculty of Science and the head of the Department of Chemistry for giving me the opportunities to complete my studies. Moreover, I am pleased to present my sincere thanks and appreciation to my distinguished staff members of the Department of Chemistry, for what they showed and helped to facilitate my research.*

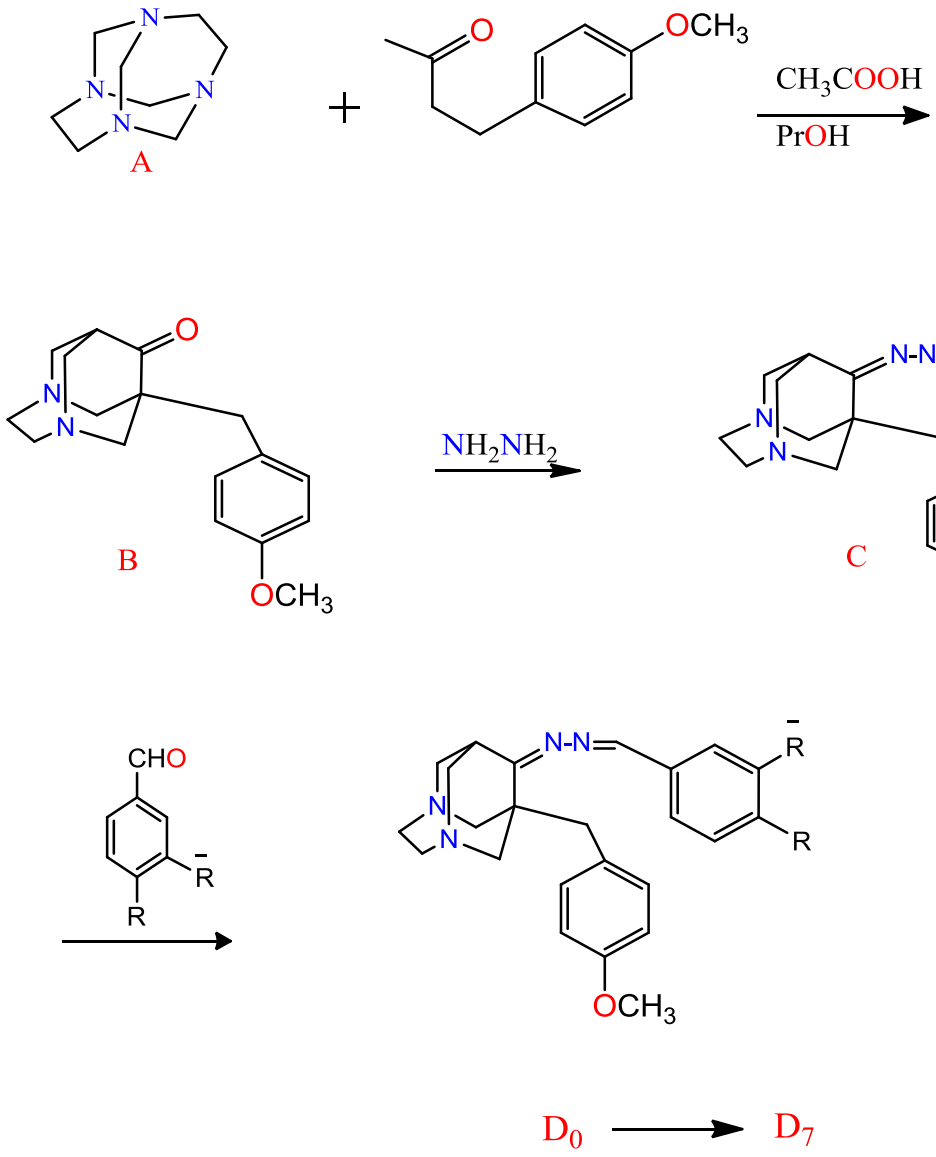
I would like to express my thanks and gratitude to everyone who showed help and assistance during the period of research, and in particular to all my fellow postgraduate students., in gratitude for their attitude,

and finally, I would like to thank (my honorable family especially my husband) everyone who raised their eyes to heaven and their hands praying for me, asking the Lord to reward them on behalf of me, the best reward.

The researcher

Abstract

This study included preparation of 1-(4-Methoxybenzyl)-3,6-diazahomoadamantan-9-one and synthesis of new azomethine compounds for 1-(4-Methoxybenzyl)-3,6-diazahomoadamantane-9-one derivatives. Condensation of ethylene diamine with paraformaldehyde produced teotropine. Reaction of **1,3,6,8 Tetraazatricyclo [4.4.1.1(3,8)] dodecane (teotropine) A** with anisyl acetone produced **1-(4-Methoxybenzyl)-3,6-diazahomoadamantan-9-one B** which was reacted with hydrazine hydrate produced **1-(4-Methoxybenzyl)-3,6-diazahomoadamantan-9-one hydrazone C** and the latter was subjected to transformation of 1-(4-Methoxybenzyl)-3,6-diazahomoadamantan-9-one compound over hydrazine to obtain derivatives of 1-(4-Methoxybenzyl)-3,6-diazahomoadamantane. Heating of 1-(4-Methoxybenzyl)-3,6-diazahomoadamantan-9-one hydrazone with aldehyde derivatives consisting of (*p*-benzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-nitroenzaldehyde,3-chlorobenzaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, 4-carboxybenzaldehyde) using reflux in ethyl alcohol to **imines Diazahomoadamantane D_0 –D_7.** The new produced compounds were identified by FT-IR, ^{1}H NMR, ^{13}C-NMR, Mass spectra. Antibacterial study of the new produced compounds (**A, D_0-D_7**).The Compound **A** and **D_2** showed high activities against, ***Staphylococcus aureu*s** while compound **D_4** showed high activities against ***Escherichia coli*** bacteria. The inhibition zone findings were compared to the reference antibiotic (Gentamycin) as a control drug. Below are the prepared compounds;



$D_0 \longrightarrow D_7$

R = $\bar{R}$=H (D_0) R=4Cl (D_1)$\bar{R}$=H , R=4NO_2(D_2) $\bar{R}$ =H ,R=4Br(D_3) $\bar{R}$=H ,$\bar{R}$=3Cl

(D_4) R=H ,R= 4OH(D_5) $\bar{R}$=H , $\bar{R}$ = 3OH (D_6)R=H , R=4COOH (D_7) $\bar{R}$=H

List of Contents

List of Tables

List of Figures

Abbreviations

Symbol	Definition
BHI	Brain Heart Infusion
CSA	Camphor Sulfonic Acid
^{13}C-NMR	Carbon Nuclear Magnetic Resonance
DAMP	2,4-Diamino-5-Adamantyl-6-Methyl pyrimidine
DMSO	Dimethyl Sulfoxide
EAC	Ehrlich Ascites Carcinoma
EtOH	Ethanol
FT-IR	Fourier Transform Infrared
^{1}H NMR	Proton Nuclear Magnetic Resonance
HL-60	Human Leukemia cells
MP	Melting Point

MHz	Megahertz
MIC	Minimum Influenced Concentration
n-butyl	Normal Butyl
OM	Organic Matter
OLED	Organic light emitting diodes
PAHs	Polycyclic Aromatic Hydrocarbons
Ph	Phenyl
ppm	Part Per Million
SBs	Schiff Bases
Str.	Stretching
sy	Symmetric
TNF-α	Tumor Necrosis Factor
TAAD	Tetra azadamantane
TMS	Tetra Methyl Silane
TMEDA	Tetra Methylethane-1,2-Diamine
TLC	Thin Layer Chromatography
t-Bu	Tertiary Butyl
ν	Stretching Vibration

Chapter One

Introduction

1.1 Organic Compounds

Aquatic organic matter is predominantly formed by carbon atoms linked to oxygen, hydrogen, nitrogen, sulfur and other atoms. These combined elements can be originated either by multiple allochthonous and autochthonous natural sources or anthropogenic inputs Organic matter (OM) of natural origin is primarily formed by biogeochemical processes such as photosynthesis, excretion of organisms, bio-mass decay, or diagenesis [1].Nitrogen ``containing organic compounds such as amines and heterocyclic compounds are used as inhibitors for protecting the copper surface from corrosion in aggressive acid solutions [2].Organic compounds are any chemical compounds in which one or more carbon atoms are covalently connected to the atoms of other elements. however, this does not mean that any carbon-containing substance, such as cyanides, carbonates, and carbides, is considered organic. Methane is the greatest example of the simplest organic chemical. Cyclohexane, ethylene, ethane, and ethane are some examples of organic compounds. Organic compounds are divided into two categories[3].

i.Acyclic or Open Chain Compounds

ii.Closed-Chain or Cyclic Compounds

i.Acyclic or open chain compounds: Because thes molecules do not form a ring, acyclic compounds are the polar opposite of cyclic compounds. Because they have a linear structure, they are referred to as open chain compounds. Acyclic aliphatic chemicals and alkanes are the greatest examples of these compounds.

ii. Closed chain or cyclic compounds: "Ring compounds" are another name for cyclic compounds. Cyclic compounds, as their second name implies, are those in which one or more than one number of atoms are joined to form a closed ring. It is not necessary for all of these compounds' rings to be the same size [3].

1.2. Heterocyclic Compounds

Heterocyclic compounds containing nitrogen, sulfur, or oxygen are an important class of groundwater contaminants related to the production and use of manufactured gas, heavy oils,

and coal tar [4] heterocyclic compounds resemble cyclic organic compounds that incorporate only carbon atoms in the rings but the presence of the heteroatoms gives heterocyclic compounds physical and chemical properties that are often quite distinct from those of their all-carbon-ring analogs [5].The heterocycles exhibit diverse properties including electrophilic and nucleophilic action, oxidizing and reducing properties, and acidic and basic attributes which are associated with the electronic arrangements in their chemical structures [6].Heterocyclic chemistry is a key source of compounds for drug discovery due to the capability of the resulting molecules to imitate the structure of endogenous ligands and bind to a variety of biological targets [7] .Some of these compounds enjoy the stability of aromatic compounds and are called hetero cyclo aromatic compound, such as Pyrrole and Indole [8].

1.3. Classification of Heterocyclic Compounds

Heterocyclic compounds can be divided to many types ;

1.3.1. Aliphatic Heterocyclic Compounds

The activation of C–H bonds in aliphatic and other compounds for their ox functionalization is of great interest for the chemical industry. Those bonds are thermodynamically strong and rather inert and, therefore, their activation is an intricate task**.** The addition of oxygen to aliphatic hydrocarbons and bio based lipids, which are cheap and widespread feedstock's, may convert them into very valuable compounds, such as building blocks or pharmaceuticals [9]**.**

1.3.2. Aromatic Heterocyclic Compounds

Heterocyclic compounds are aromatic and non-aromatic compound. Physical and chemical properties of non-aromatic compound that are differential of the particular heteroatom. Non-aromatic heterocyclic containing only one heteroatom are, Oxirane, Thiirane, and Aziridine. In heteroatom’s of nitrogen, oxygen, or sulfur are most common heterocyclic compounds containing five or six-member rings [10]. Aromatic compounds are pyridine, and pyrrole, furan and thiophen are examples of heteroaromatic compound Figure1.1The aromatic heterocycles play a major role in drug design for medicinal chemistry. Most natural products

have aromatic heterocycles in their structure. We designed our super halogens by using heterocyclic compounds that are aromatic since they obey Huckel's rule of aromaticity [11]. The compounds that are monocyclic and aromatic generally follow the Huckel's Rule. The rule given by Huckle states that an organic compound that has cyclic and aromatic properties must have the 4 n + 2 π electrons, Thus according to this rule it is propounded that the most of the aromatic compound must contain 6 π electrons when n is taken equal to 1. The Huckel's rule also has some exceptions like furan, thiophen, and pyrrole [12] .

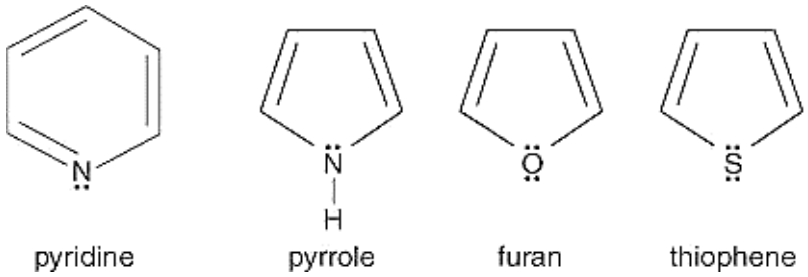
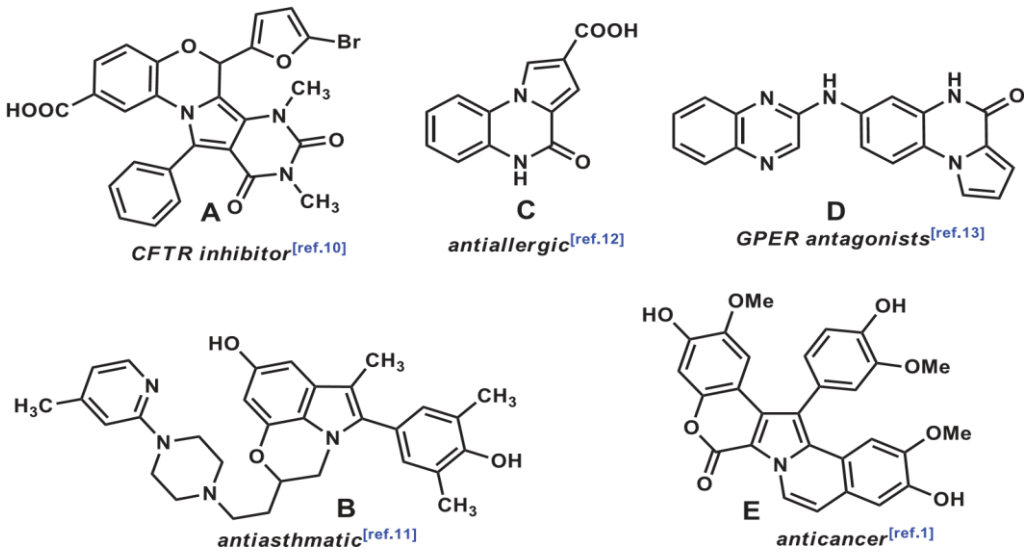


Figure 1.1 Heterocyclic Compounds

The fused heterocyclic compounds are widely investigated in pharmacology as often specific drug-receptor interactions are attained via predisposing such heterocycles in the molecular architecture. Pyrrole-fused benzoxazinones and benzoxazepines attracted wide attention owing to diverse pharmacological activities. For example, a benzopyrimido-pyrrolo-1,4-benzoxazine (A) was proved to be a potent CFTR inhibitor (Scheme1. 1)[13].



Scheme 1.1 Some of The Biologically Important Byrrole-Fused Compounds

1.4. Polycyclic Aromatic Compounds

The term polycyclic aromatic hydrocarbon (PAH) refers to a ubiquitous group of several hundred chemically-related, environmentally persistent organic compounds having various structures and varied toxicity[14].Polynuclear aromatic hydrocarbons (PAHs) are hydrophobic organic compounds comprising of two or more fused aromatic rings that may be released into the environment from both natural and anthropogenic sources [15].The group of polycyclic aromatic hydrocarbons (PAH) is an extensively studied class of compounds in many fields of work, but the designation PAC is less used and hardly known despite its usefulness. It Polycyclic aromatic hydrocarbons are formed during the incomplete combustion of organic material. Environ- mental sources of polycyclic aromatic hydrocarbons include industrial air pollution, urban air pollution, tobacco smoke [16]. For years human exposure to polycyclic aromatic hydrocarbons (PAHs) has been a concern as a result of the widespread occurrence of these compounds and their adverse impacts on ecosystem and human health [17]. Aromatic compounds are important in industry and play roles in the biochemistry of all living things, whereas solar cells and photovoltaic, organic light emitting diodes (OLEDs), thin film transistors [18].The Pentacycloundecylamines are polycyclic cag amines derived from reductive amination of Cookson's "birdcage" diketone (Figure4,1).A prominent biologically active Pentacycloundecylamines, is NGP1-01 (Figure 4, 2) Some as a Pentacycloundecylamines have been tested in vivo in an effort to develop cocaine addiction therapeutics. Two metafluoro substituted aromatic

Pentacycloundecylamines (Figure4, 5 and 6) were evaluated together with cocaine in behavioral studies with rats[19].

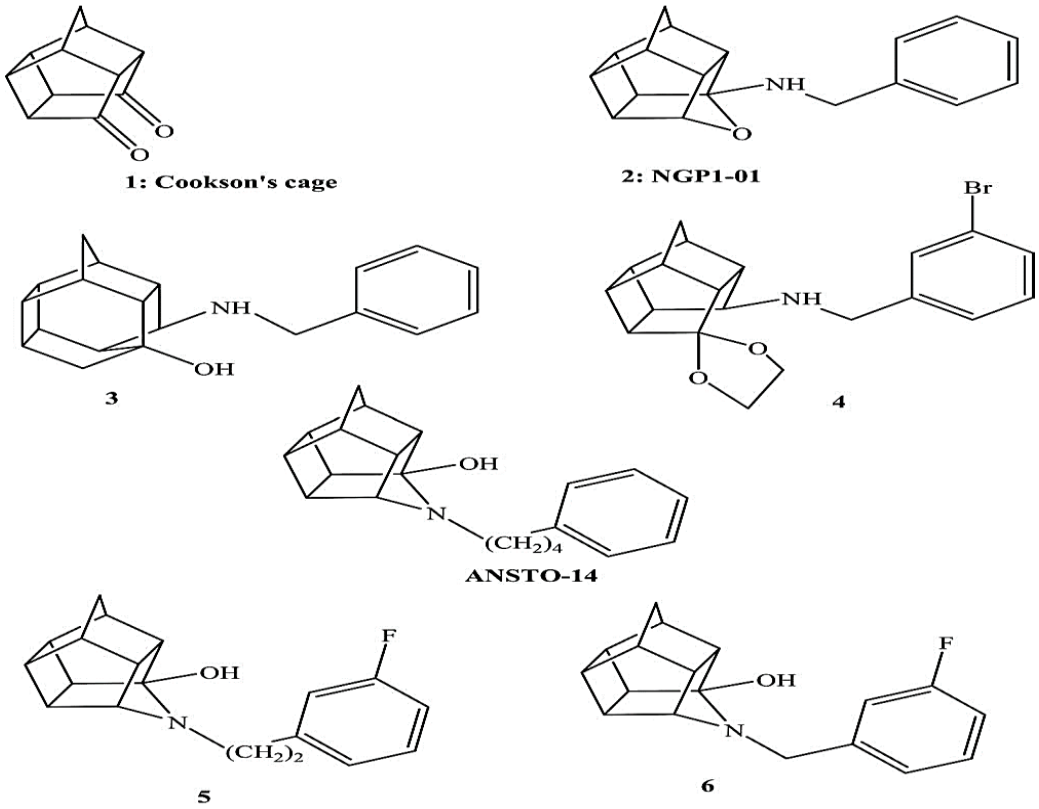
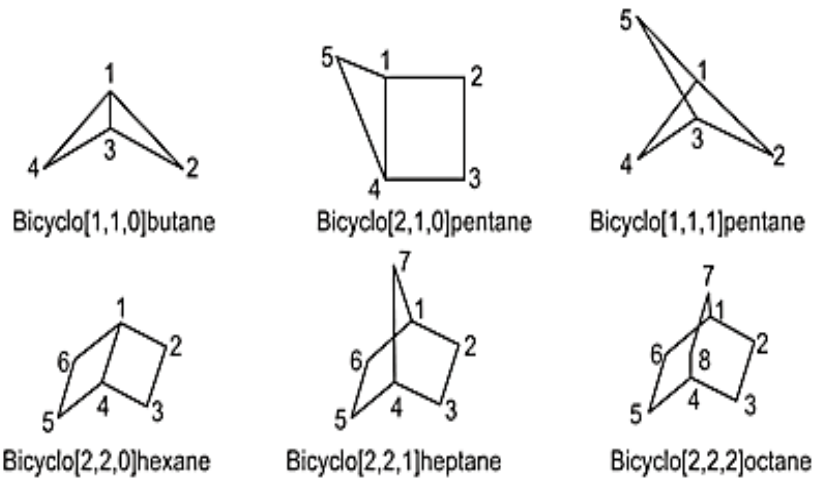


Figure 1.2 Pentacycloundecylamines

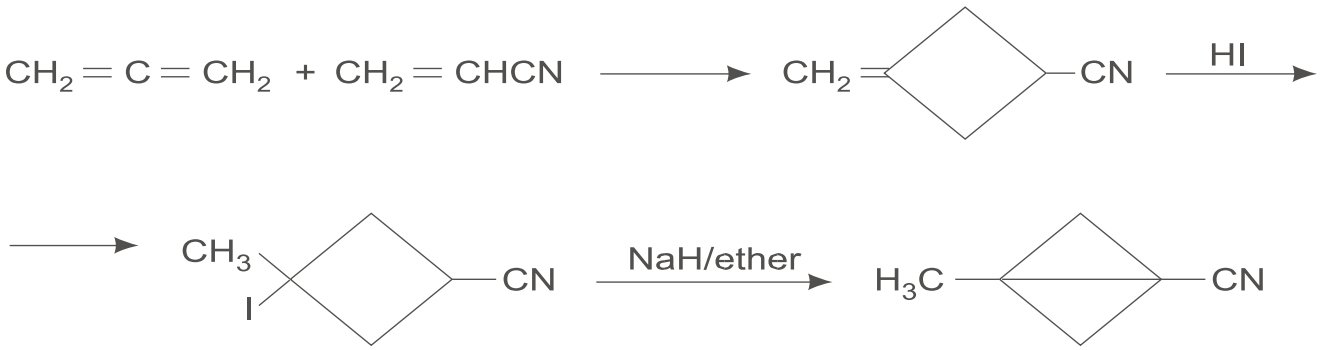
1.5. Bi cyclic

Bridged ring compounds contain two or more rings fused together. A study of these compounds is special interest in relation to ring strain and their characteristic properties. Some typical examples are discussed below. These compounds are named as derivatives of butane, pentane, hexane, heptane, octane, etc., depending on the total number of carbon atoms in their rings combined together. The following examples illustrate the nomenclature of bridged rings (Scheme1. 2).



Scheme 1.2 Examples of Bicyclic

1,3-Disubstituted bicyclo[1,1,0]butane can be synthesized by the following cycloaddition reaction[20].



Scheme 1.3 Synthesized of 1,3-Disubstituted Bicycle [1,1,0] Butane

1.6. Camphor

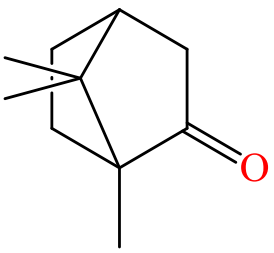
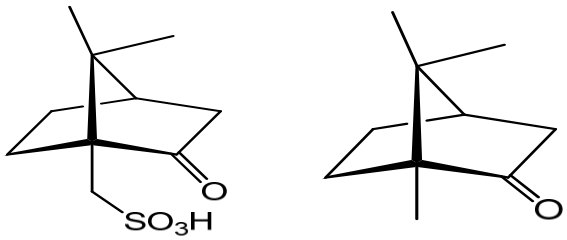


Figure 1. 3 Structure of Camphor

Camphor, 1,7,7-trimethylbicyclo [2.2.1] heptan-2-one, is a natural product used since antiquity in a wide range of applications, such as in food flavourings, fumigants, perfumes, cosmetics, household cleaners, and topically applied analgesics [21]. Camphor is a highly toxic ingredient that can be found in commonly used rubs and preparations such as tiger balm and Vicks [22]. It is a white, crystalline substance with a related trees of laurel family. Camphor tree is native to of Camphor laurel (Cinnamomum camphora) and other strong odor and pungent taste, derived from the wood United States and a variety There are many pharmaceutical applications for sublimation of wood, twigs and bark of the tree [23] Camphor is the main component in the majority of plant essential oils used in medicine and cosmetics. The insecticidal and insect-expelling efficacy of camphor has been widely confirmed [24]. Camphor (Figure1.4) is a natural product (also produced by synthetic means) with very ancient applications as an insect repellent, muscular relaxant, and anesthetic and is currently used as a cough suppressant and decongestant according to conditions established by the Food and Drug Administration [25].



Camphor sulfonic acid **Camphor**

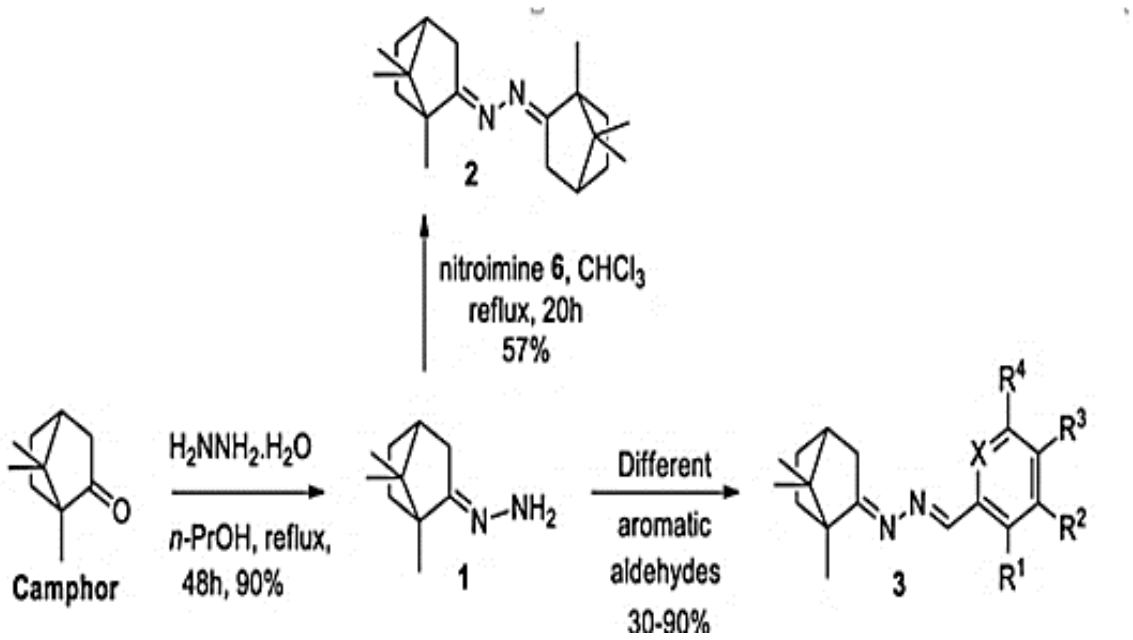
Figure 1.4 Molecular Structures of Camphor and Camphor Sulfonic Acid.

Camphor and its derivatives such as camphor sulfonic acid (CSA), which are readily available in optically pure forms for both of the enantiomers, are widely used synthons in asymmetric synthesis [26].

1.7. Reaction of Camphor

Studies on the synthesis of N, O and S-heterocyclic compounds from camphor mono-terpenes are reported. Most of the reported compounds were found to have good biological

activities against human cancer cell lines, influenza virus, Gram-positive and Gram-negative bacteria [27].



Scheme 1. 4 General Synthetic Scheme for the Camphor Derivatives

1.8. Tricyclic

Nitrogen-containing bi-and tricyclic heterocycles bearing diazepine, diazocine, and Benz imidazole moieties are of current research interest because of their pharmacological properties. Bicyclic and tricyclic cores are also common in a large number of natural products and pharmacologically active compounds [28]. Tricyclic compounds are sometimes considered as synonima of drugs healing central nervous system pathologies, although there are some well-known examples of tricyclic derivatives marketed for different indications, such as antihistamines, antivirals and antiulceratives [29].Also (Isotwistane is tricyclo[4.3.1.$0^{3,7}$] decane; for clarity, Isotwistane numbering is also used for the diaza analog [30].

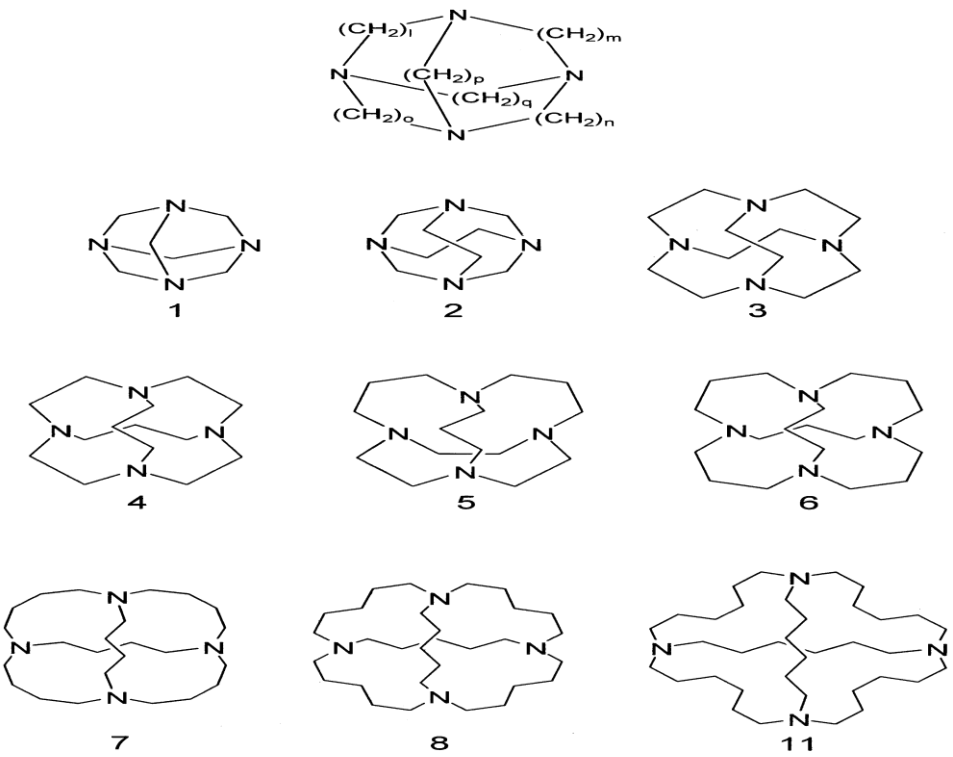


Figure 1.5 Examples of Macro Tricyclic Compounds

1.9. Adamantane

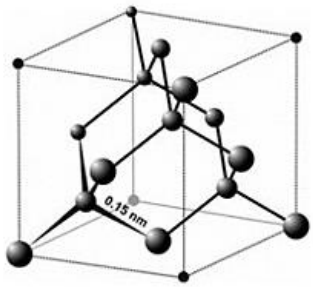


Figure 1. 6 Structure of Diamond Crystal lattice

More cage hydrocarbons with a structure superimposable with that of a diamond lattice have emerged, forming a family of compounds called diamondoids, also known as nano diamonds due to their nature of being nanometresized diamonds terminated by carbon-hydrogen bonds[31].Adamantane, a polycyclic cage molecule with high symmetry and remarkable properties. It was first isolated in 1933 from crude oil [32]. a diamond is not only

measured by its weight in carats, the color, or the perfection of the stone but rather in its value as a material for research and technology [33]. Larger diamondoids ,such as 10 diamantine, triamantane, and higher polymantanes, are obtained by incorporating additional carbon cages to adamantane Diamondoids [34]. Diamondoids are defined as a group of nanometer–size saturated hydrocarbons whose structures resemble part of the diamond lattice,i.e.,these are hydrogen–terminated nanodiamonds Figure1. 7 [35]. Introduction of a nitrogen atom into the lipophilic adamantane molecule should give cage-like heterocyclic compounds with analogous properties [36].The genesis of the cage hydrocarbons adamantanes and diamantanes, in particular, the formation of these structures from compounds that are feasible for production from juvenile carbon and hydrogen, was of interest [37].Adamantane, 10diamantine and triamantane, the smallest diamondoids, with chemical formulas $C_{10}H_{16}$,$C_{14}H_{12}$, and $C_{18}H_{24}$, respectively[38]. Figure 1.7

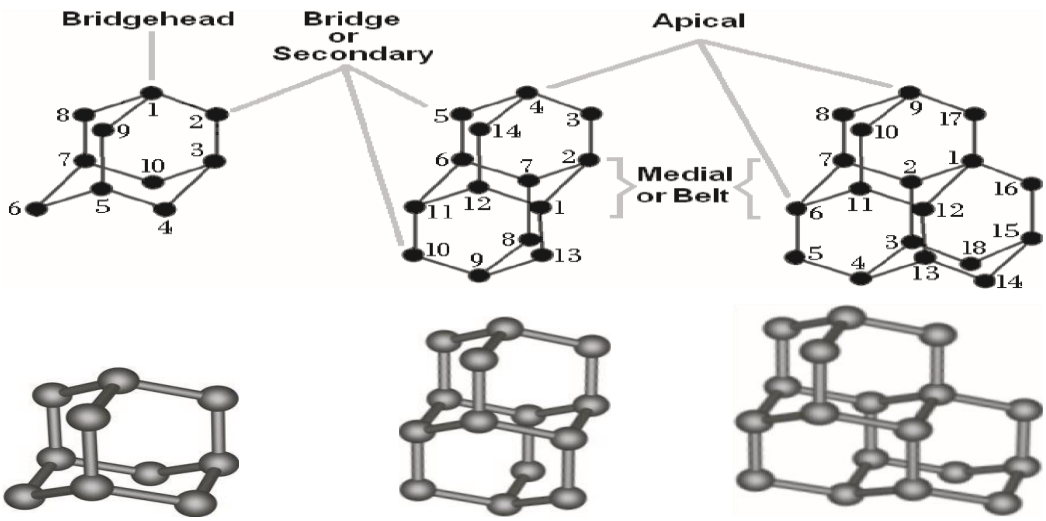


Figure 1.7 Three-Dimensional Molecular Structures of (from left to right) Adamantane, Diamantane and Triamantane

1.10. Synthesis of Adamantane

Schleyer introduced a Lewis acid-catalyzed rearrangement to produce adamantane A Lewis acid is any acid that can accept a pair of electrons and form a coordinate covalent bond According to Schleyer endo-trimethylenenorbornane, which could be produced readily, rearranged to adamantane when refluxed overnight with aluminum chloride ($AlCl_3$) .This reaction allowed a simple preparation of adamantane with 10% overall yield, which was

unprecedented at that time, and opened up the field of diamondoids synthesis and application for further studies worldwide. For example, the number of patents related to adamantane increased rapidly after the publication of Schreyer's synthesis of adamantane Fig1.8 [38].

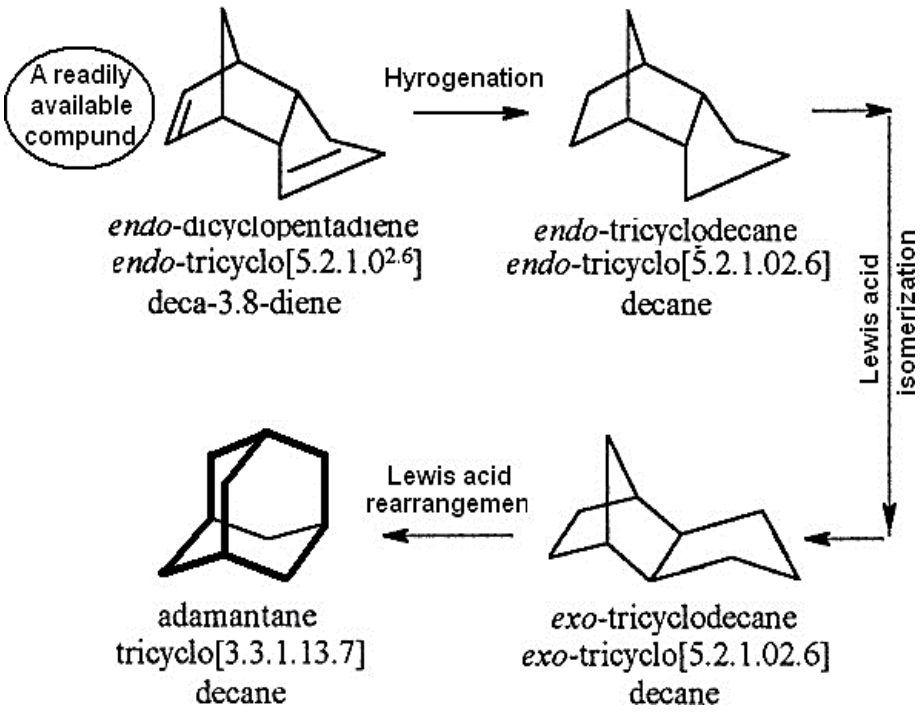


Figure 1. 8 Various Stages in Synthesis of Adamantane

1.11. Adamantane Derivatives

Derivatives of adamantane have found numerous applications in medicinal chemistry and material science. Especially for the latter applications, tetra substituted Adamantane are valuable scaffolds because they are mechanically rigid and conformation ally well defined [39]. Adamantane is a member of a class of molecules called diamondoids, which are molecules possessing at least one adamantane unit which are totally or largely superimposable on the diamond lattice. Family are face-fused polymantanes, often referred to as “higher-order diamondoids”, with examples such as diamantane 6 or triamantane 7 which are formed of two and three face-fused adamantane units respectively (Figure1. 9).These structural motifs are comparatively less used in drug design and still need to prove their worth as useful pharmacophore add-ons .There is a growing interest in materials

chemistry in the use of diamondoids for diamond formation, which is an area of research that we are focused on. In recent years, it has been shown that diamondoids such as adamantane (poly)haloadamantanes azaadamantanes, adamantane carbonitrile or pentamantane can be used as precursors or seeds of nano diamonds under high-pressure high-temperature conditions [40] .The introduction of the adamantane motif led to higher antitrypanosomal activity and better selectivity of the new derivatives in comparison to the parent compound [41].

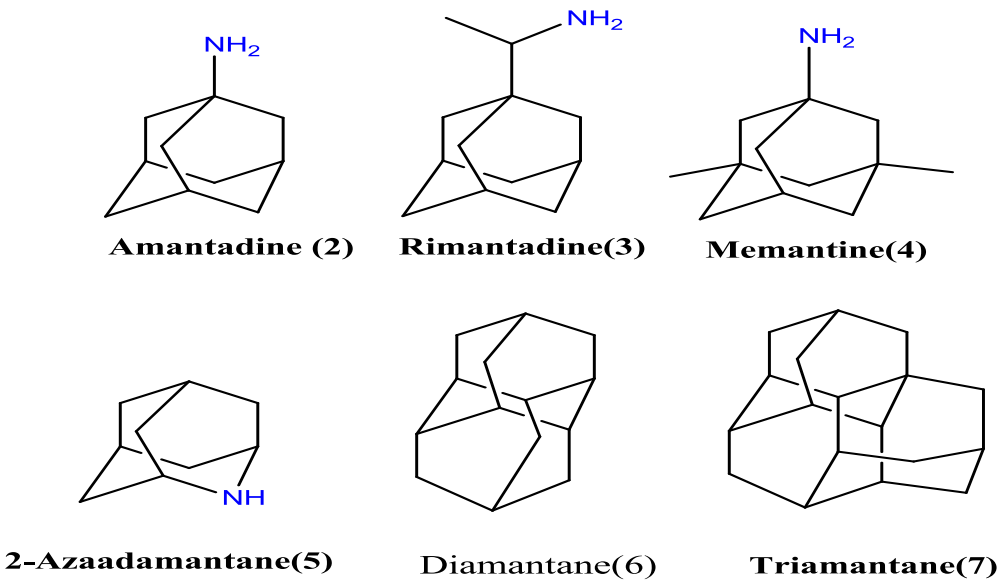


Figure 1. 9 The Structure of Pharmaceuticals Derived from Adamantane and Diamondoids

Many adamantane derivatives have interesting biological properties. The most famous medicine is the antiviral drug 1-aminoadamantane (amantadine) Amantadine and many similar compounds with three-dimensional 'box-like' adamantane structure are employed in the treatment of certain neurological disorders. The combination of such aliphatic core with phthalimide ring gives biologically active compounds. For instance, *N*-adamantylphthalimide induces tumor necrosis factor (TNF-α) in human leukemia HL-60 cells while 1-adamantylmaleinimide and its derivatives, show anticancer activity in mice and inhibition of herpes simplex virus in vitro [42].The antiviral drug rimantadine, neurotropic drugs amantadine (or midantane) and memantine are used in medical practice. The latter is employed to treat Alzheimer's disease [43].Many viruses already are shown resistance

against adamantine derivatives amantadine and rimantadine[44].Recently, amino aromatic adamantane and disubstituted adamantane derivatives, with marked antiproliferative activity on different human cell lines [45].

1.12. Physical and Chemical Properties

The special structure of adamantane gives it many useful chemical and physical properties [46] .Pure adamantane is a colorless crystalline solid with a characteristic camphor smell. It is practically insoluble in water, but readily soluble in nonpolar organic solvents. However, adamantane slowly sublimes even at Elastic constants of adamantane were measured using large (centimeter-sized) single crystals and the ultrasonic echo technique only σ-bonds are relatively inert chemically. However, adamantane and its derivatives are highly reactive[47].Adamantane possesses a unique rigid but strain-free ring system, composed of three fused chair cyclohexane rings. Have shown that adamantane crystallizes in a face centered cubic lattice (extremely unusual for an organic compound) and four molecules per unit cell. All carbon- carbon bond lengths are 1.54 ± 0.01 A. and all C-C-C angles 109.5 ± 1.5°. The molecule therefore should be completely free from both angle and torsional strain. At the beginning of growth, crystals of adamantane show only cubic and octahedral faces, as expected for a face-centered cubic lattice with only forces between nearest neighbor's effective The effects of this unusual structure upon physical properties are striking. As has been previously remarked, adamantane is one of the highest melting hydrocarbons known, mp. 269°, yet it sublimes readily, even at atmospheric pressure and room temperature. The boiling point, of course, is undeterminable directly. However, adamantane, present in a mixture of hydrocarbons being fractionally distilled, is found in the cuts of b.p. near 190°C Unfortunately, he molar heat of combustion of solid adamantane, AH°= -1451.7 kcal [48].

1.13. Adamantanone

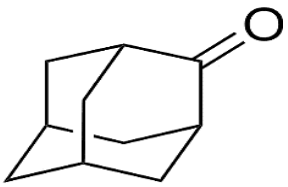
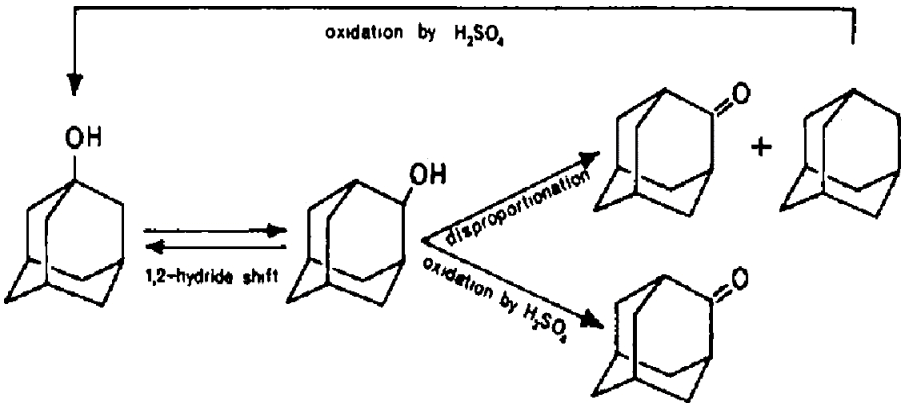


Figure 1.10 Structure of 2-Adamantanone

Adamantanone is the ketone of adamantane can be synthesized from 1-hydroxyadamantane or from adamantane in good yields by treatment with concentrated sulphuric acid. The formation of the ketone is due to disproportionation and oxidation reactions. The oxidation of adamantane to 1-hydroxyadamantane by means of sulphuric acid. Homologues of Adamantanone can also be formed by analogous reactions in sulphuric acid. Intermolecular hydride transfer reactions of 1-hydroxy and 2-hydroxyadamantane resulting [49].

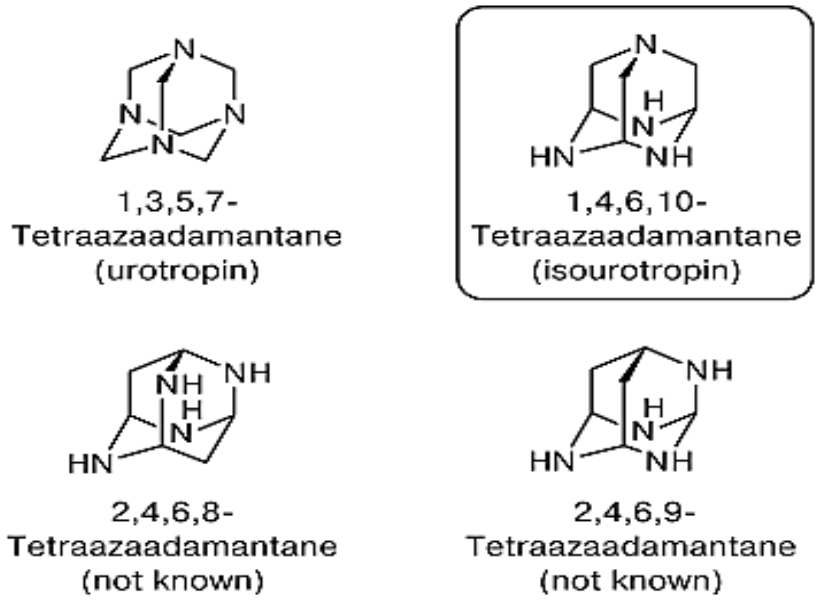


Scheme 1.5 The Oxidation of Adamantane to 1-Hydroxyadamantane and Adamantanone by Means of Sulphuric Acid[49].

2-Adamantanone is a key intermediate in the synthesis of 2-substituted adamantane-based medications (kemantan, bromantane, *etc.*) Its thermodynamic properties in the condensed and gaseous phase state, such as heat capacity in the condensed phase state, sublimation thermodynamics, statistical-thermodynamic calculations [50].

1.14. Tetrazadamantane

Urotropin or 1,3,5,7-Ttrazadamantane is the best known of this class and has been used as an antigout agent in pharmacology and with various additives for the prevention and treatment of influenzas [51]. 1,3,5,7 tetra azadamantanes (Urotropin), one of the first heteroadamantanes, was synthesized back by Alexander Butlerov. This compound for a long time was the only known isomer out of four possible tetra azadamantanes without nitrogen—nitrogen bonds. Recently we have discovered an unusual intramolecular cyclotrimerization of the oximino groups in tris (β oximinoalkyl) amines which led to 1,4,6,10 tetra azadamantanes derivatives a new heterocage system isomeric to Urotropin (Scheme 1.6).This strategy was used to obtain unsubstituted 1,4,6,10 tetra azadamantane (the so called "Iso Urotropin") and showed that its structure and properties significantly differ from those characteristics of isomeric Urotropin [52].



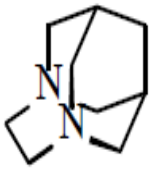
Scheme 1.6 Structures of Tetrazadamantane Derivatives[52]

The synthesis of bimacrocycles, i. e. molecules containing two covalently linked, potentially chelating subunits, has received much attention in recent years .One such class of

compounds involves a linkage between one nitrogen atom from each ring [53]. TAAD was used to improve the thermal and photo chemical stability of perovskite films (most likely through coordination of Pb(II) ions) [54]. Hexamethylenetetramine (Urotropin) was first reported in the scientific literature over 140 years ago .It is an important industrial chemical that is produced commercially via the reaction of formaldehyde and ammonia [55].

1.15. Diazadamantane

1,3-Diazadamantane



3,6- Diazahomoadamantane

Figure 1.11 Structure of Diazadamantane and Diazahomoadamantane

Azadamantanes and polyazaadamantanes continue to play important roles in organic and medicinal chemistry. Among the most useful members of the azaadamantane family are the azadamantanes [56]. Adamantane and its derivatives have fascinating structures due to their various physiological, pharmaceutical, and medical activities[57].Azadamantanes are nitrogenous analogs of adamantine, which contain one or more nitrogen atoms instead of carbon atoms. These compounds have been known since the 50s of the last century. Some Diazadamantane derivatives have been found in nature, e.g. the alkaloids acosmine, acosmine acetate, and panacosmine isolated from the Acosmium panamense seed extract and dasycarpumine isolated from the Acosmium dasycarpum extract. Acosmine and its derivative bowdichine. It should be noted that the biological role of these compounds is not yet clear, and their biological activity has not been studied [58].

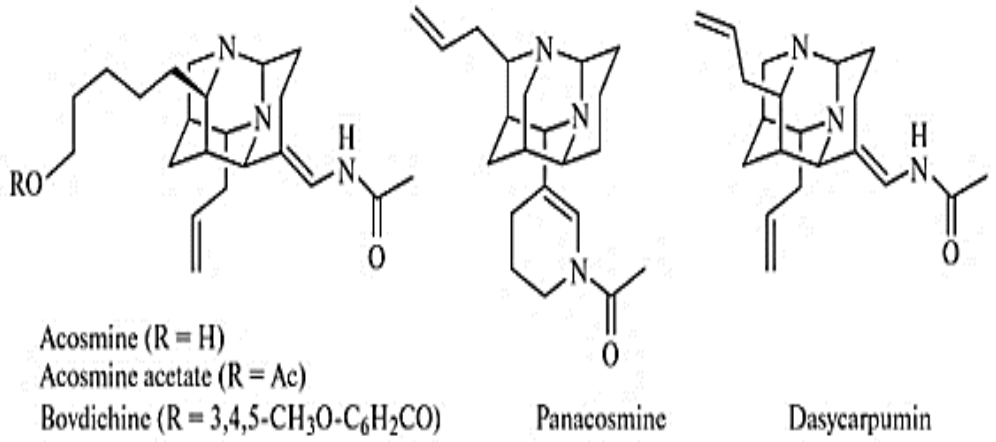
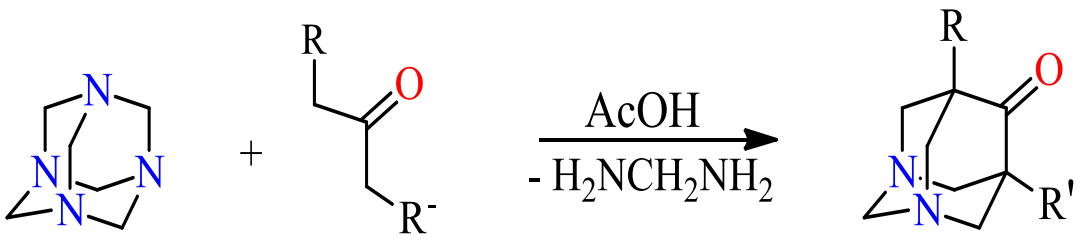


Figure 1. 12 Examples of Azadamantanes Structure Some Natural Diazadamantane Derivatives[58]

1.16. Synthesis of 1,3-diazadamantane

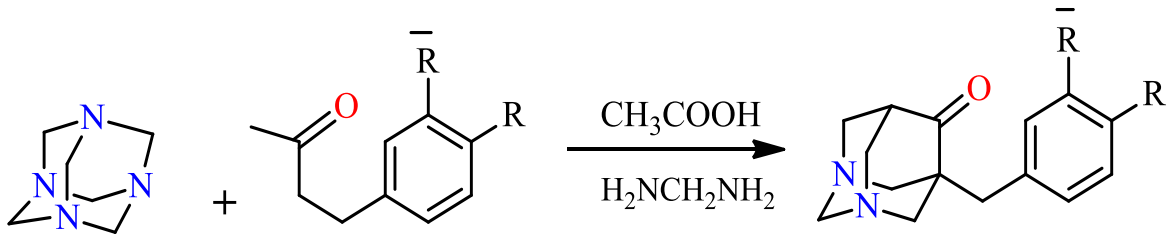
1,3-Diazaadamantan-6-ones are the most available derivatives of 1,3-diazaadamantane, which are obtained by the condensation of hexamethylenetetramine with ketones of the formula RCH_2COCH_2R This method was used to synthesize in good yields a number of diazaadamantanones with two substituents at the bridgehead positions 5 and 7 (Scheme 1.7). The condensation with hexamethylenetetramine makes it possible to incorporate ketone molecules into the structure of 1,3-diazaadamantane, that can be a useful approach in the developing molecular technology. Possessing a specific odor, fragrant ketones are means of commu nication between individuals of their species and carriers of another significant biological information[59].



R^- =H, R= $PhCH_2$

Scheme 1.7 Synthesis of 1,3-Diazadamantanes by Condensation of Ketones with Urotropin

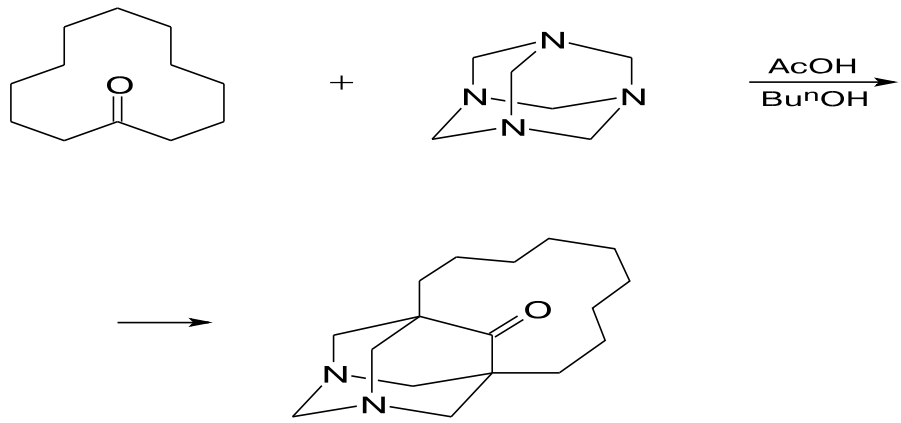
In order to trace the changes in the odor upon incorporation of ketone molecules in the structure of Diazadamantane, we have chosen as the starting methyl ketones synthetically feasible benzyl acetone and its derivatives at the benzene ring,4-(4-hydroxyphenyl) butan-2-one, 4-(4-methoxyphenyl)butan-2-one and 4-(4-hydroxy-3-methoxyphenyl)butan-2-one known for their specific odor, biological activity, and a wide application in cosmetics, perfumery, medicine, and food industry [59].



R = R´ = H (a), R = OH, R´ = H (b), R = OMe, R´ = H (c), R = OH, R´ = OCH_3 (d)

Scheme 1.8 Synthesis of 1,3-Diazadamantanes by Condensation of Benzyl Acetone with Urotropin

1,3-Diazadamantan-6-ones are the most easily accessible 1,3-diazadamantane derivatives. These compounds are synthesized by condensation of hexamethylenetetramine (adamanzane) with acyclic ketones. for example condensation of cyclododecanone with hexamethylenetetramine(adamanzane) in refluxing *n* butanol in the presence of AcOH .5,7-nonamethylene-1,3-diazadamantan-6-one was first synthesized in 15% yield (Scheme1.9)[60].



Scheme 1.9 Synthesis of 5,7- Nonamethylene-1,3-Diazadamantan-6-one

1.17. 1,3,6,8-Tetrazatricyclo [4.4.1. (13,8)] dodecane

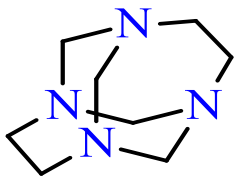
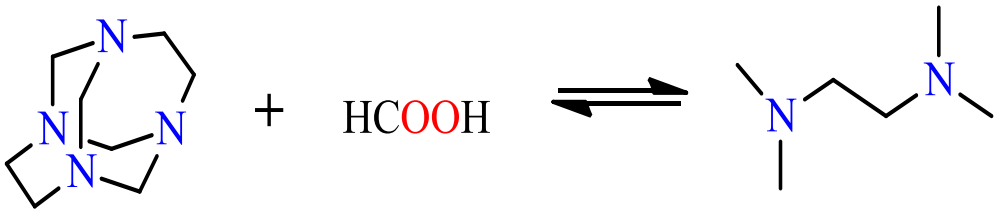


Figure 1.13 Structure of 1,3,6,8- Tetrazatricyclo [4.4.1.13,8] Dodecane

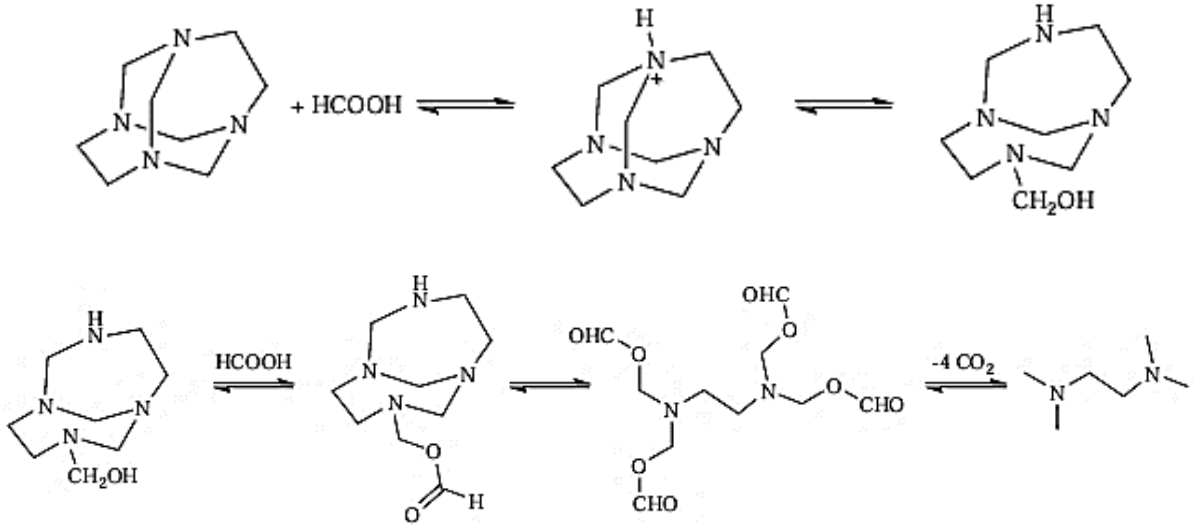
1,3,6,8-Tetrazatricyclo [4.4.1.1(3,8)] dodecane (TATD) is a tricyclic alkanic tetra amine an adamanzane cage structure containing four nitrogen atoms in an approximate tetrahedral arrangement around each nitrogen atom [61] .1,3,6,8-tetraazatricyclo [4.4.1. I (3,8)] dodecane, which contains only seven-membered rings. Condensation of ethylene diamine with formaldehyde occurs easily and yields a crystalline product $C_8H_{16}N_4$ [62]. It has been used in organic synthesis and in the preparation of resins based on phenol, urea, or melamine [63]. Syntheses of symmetrical and unsymmetrical *N,N*-tetra substituted 1,2-diamines are well known. By comparison, syntheses of tri substituted and tetra substituted 1,2-diamines involving the reduction of aminals are much less well documented. Most of the methods found in literature involve the use of sodium borohydride or lithium aluminum hydride as reducing agents but treatment of TATD with an excess of this reducing agent followed by hydrolysis afforded only the starting aminal. Next we choose hydrogenation with Pd as a catalyst in MeOH or Raney/Ni in EtOH, but these were also found to not be good methods for the reduction TATD.

1.17.1. Reaction of Tetramethylenediethylenetetramine with formic acid

The reduction of TATD was only achieved when formic acid was used, and the reduction product isolated in good yield was the diamine *N,N,N´,N´*- tetramethylethane-1,2-diamine (TMEDA) (Scheme1.10)[64].



Scheme1.10 Reduction of TATD with Formic Acid



Scheme 1.11 Possible non-ionic pathway[64]

1.18. 3,6-Diazahomoadamantane

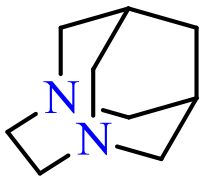
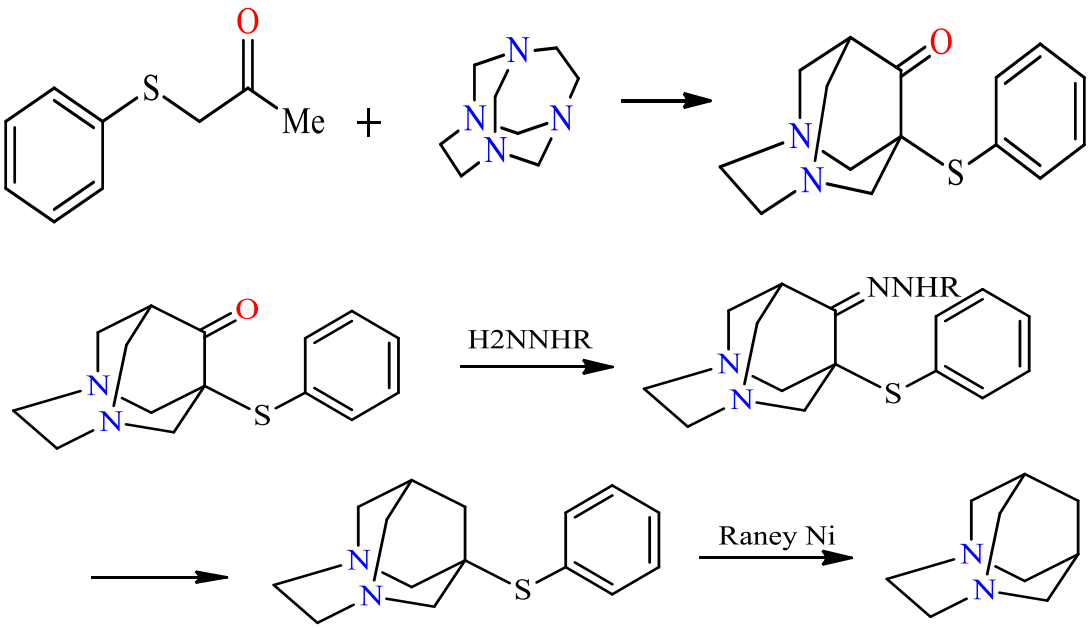


Figure 1.14 Structure of 3,6- Diazahomoadamantane

1.19. Synthesis of 3,6-diazahomoadamantane

By condensation of methyl ketones with 1,3,6,8- Tetrazatricyclo [4.4.1.1(3,8)] dodecane and subsequent Wolff–Kishner reduction of the resulting 3,6-diazahomoadamantan-9-ones we obtained a number of 3,6-diazahomoadamantane derivatives as initial ketone we used 1-phenylsulfanyl propan-2-one its condensation with 1,3,6,8-tetraazatricyclo- [4.4.1.13,8]

dodecane in propan-2-ol afforded more than 60% of 1-phenylsulfanyl-3,6-diazahomoadamantan-9-one (Scheme10). Ketone was reduced to 1-phenylsulfanyl-3,6-diazahomoadamantane in two ways: through 1-phenylsulfanyl-3,6-diazahomoadamantan-9-one hydrazone according to Wolff–Kishner and by reduction of 1-phenylsulfanyl-3,6-diazahomoadaman-tan-9-one p-tolylsulfonylhydrazone with sodium tetrahydridoborate in acetic acid desulfurization of 1-phenylsulfanyl-3,6-diazahomoadamantane by heating over Raney nickel according to the procedure described in gave previously unknown unsubstituted 3,6-diazahomoadamantane which was isolated as a readily sublimable white crystalline substance with mp 250–251°C [65].



Scheme 1.12 Synthesis of 3,6-Diazahomoadamantane

1.20. 3,6-Diazahomoadamantane-9-one

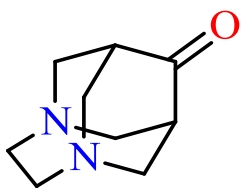
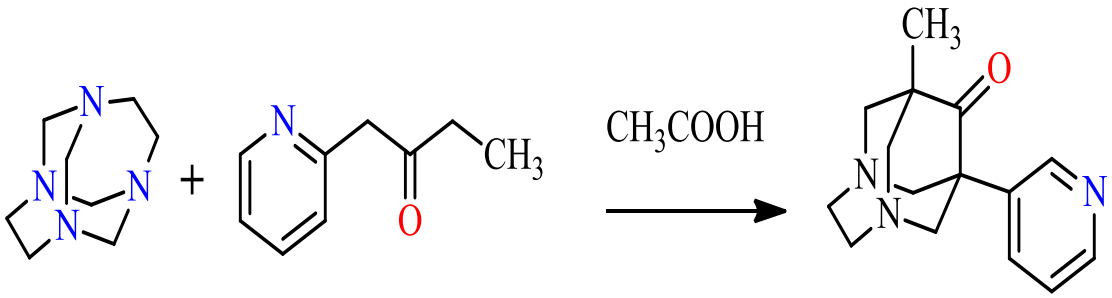


Figure 1.15 Structure of 3,6-Diazahomoadamantane-9-one

Diazahomoadamantane is a complex polycyclic framework molecular. It is well-know that by condensing a cyclic ketone with 1,3,6,8- tetra azatricyclo[4.4.1.1(3,8)] in the presence of acetic acid by mannich,s reaction can give 3,6-diazahomoadaman-9-one and its derivatives with substituent's in the nodal (scheme 1.12)[66].

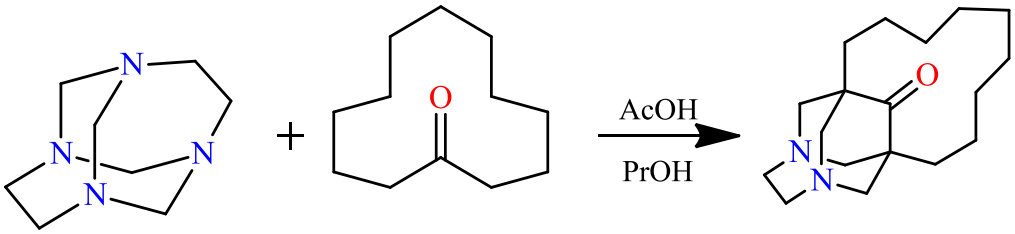


Scheme 1.13. Condensing a Cyclic Ketone with 1,3,6,8 -Tetra Azatricyclo [4.4.1.1(3,8)]

1.21. Synthesis of 3,6-Diazahomoadamantane-9-one

1.21.1. Synthesis of 1,8-Nonamethylene-3,6-Diazahomoadamantan-9-one

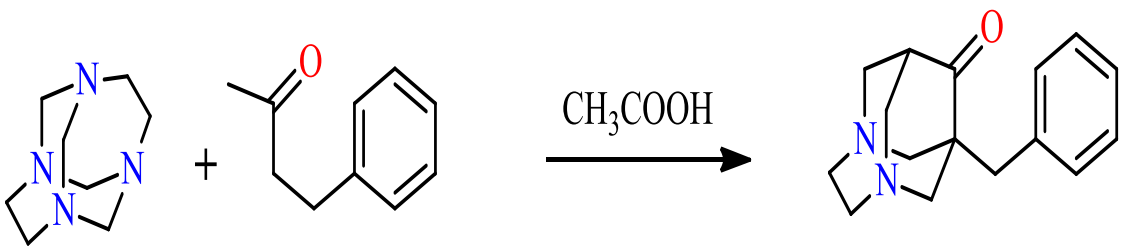
By ketones condensation with 1,3,6,8-tetraza tricyclo[4.4.1.1(3,8)]dodecane(tetramethelend iethyelenetetramine) in 2-propanol in the presence of acetic acid we formerly obtained 3,6-diazahomoadamantan-9-one and its derivatives with substituents in the nodal positions [1–3] the synthesis by similar procedure of 13,16 Diaza tetracyclo[9.6.1.11,13.111,16]-eicosan-18-one(1,8-nonamethylene-3,6-diazahomoadamantan-9-one) by the condensation of cyclododecanone with tetramethylenediethylenetetramine [67].



Scheme 1.14 Synthesis of 1,8-Nonamethylene-3,6-Diazahomoadamantan-9-one

1.21.2. Synthesis of 1-Benzyl-3,6- Diazahomoadamantan-9-one

New derivatives of 3,6-diazahomoadamantane we obtained by the condensation of 4-phenylbutan-2-one with tetramethylenediethylenetetramine and the resulting product was 1-benzyl-3,6-diazahomoadamantan-9-one [68].



Scheme 1.15. Synthesis of 1-Benzyl-3,6- Diazahomoadamantan-9-one.

1.22. Schiff Bases

Schiff base stands for an imperative type of ligand in chemical coordinating to find comprehensive enforcement in diverse domains as biological, inorganic, analytical, and artificial chemistry branches [69]. Since their discovery by the German chemist Hugo Schiff. Schiff bases (imines), scaffolds with high chemical reactivity, and their metal complexes have been very well known for catalysis in various synthetic processes and for their biological properties. The general structure of a Schiff base is shown in Figure1.16, R^1, R^2 and R^3 being an alkyl or aryl moiety[70]. They have drawn considerable research attention of

scientists owing to the ease of synthesis and metal complexation [71]. Malonoyldihydrazide and 2-aminobenzaldehyde compounds are capable to form complexes with transition metal ions in the form Schiff bases [72].Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable While those of aromatic aldehydes having effective conjugation are more stable [73]. Schiff base metal complexes have interested for their noteworthy contributions in magnetism, material science and catalysis such as carboxylation, reduction, oxidation, epoxidation, and hydrolysis reactions [74].

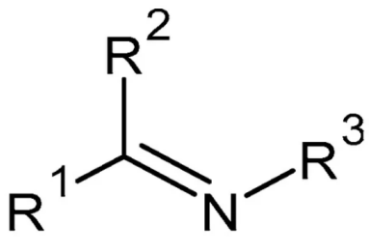


Figure 1.16 The General Structure of a Schiff Base

Schiff bases (SBs) are organic compounds characterized by an imine or azomethine group (>C=N–) that are widely used as pigments and dyes, catalysts, polymer stabilizers luminescence chemo sensors and intermediates in organic synthesis. Schiff bases can also be used as corrosion inhibitors for different metal electrolyte systems, since they adsorb and form a corrosion-mitigating surface film through their electron-rich centers, including the imine moiety In fact, this moiety can offer strong bonding with metallic ions because of its π-acceptor properties .Moreover, several studies addressed the tribological activities of SBs and their role as bio lubricant additives .Additionally, the use of SBs as catalysts in fixation of CO_2 to mitigate its accumulation in the atmosphere has been widely described .SBs have also been studied in the carbohydrate research field in relation to Amadori products .and in material chemistry for applications in photoactive solar energy Figure1.17 [75].

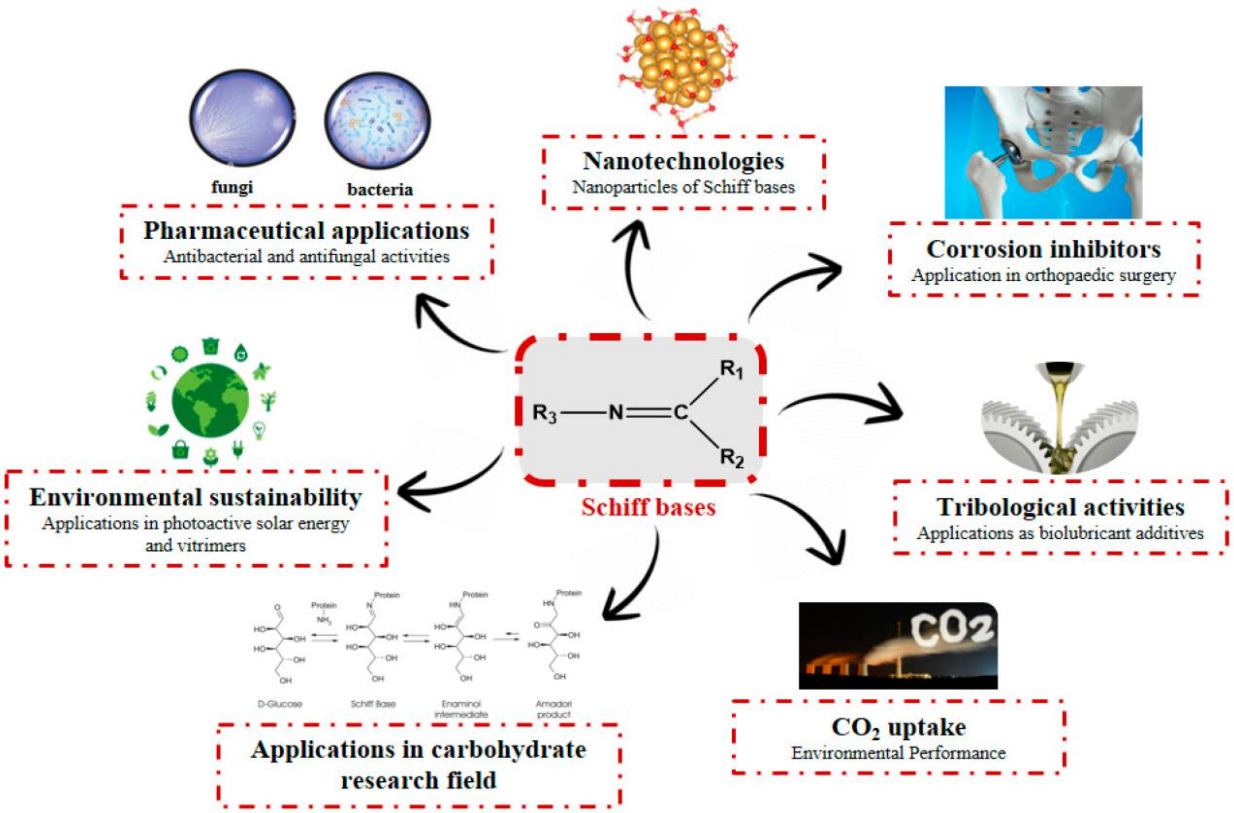
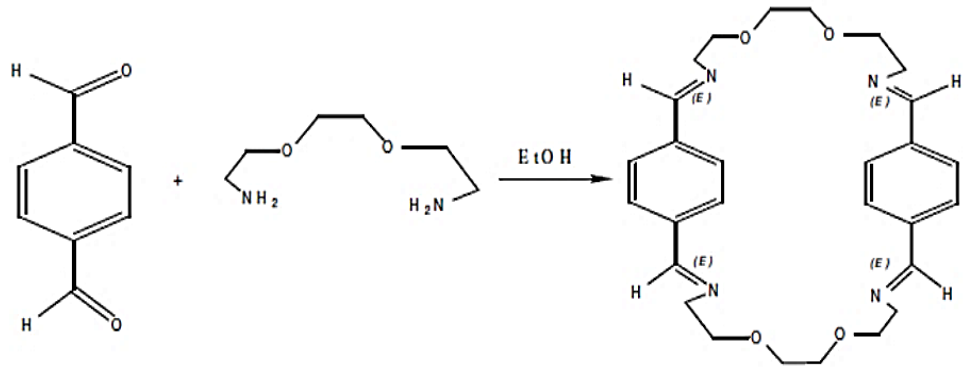


Figure 1.17 Main Properties and Uses of Schiff Bases

Schiff bases are important due to their ability to stabilize metal ions of various oxidation states, participation in numerous catalytic and industrial applications and broad spectrum biological activities [76]. Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base [77] .



Scheme 1.16 Macro Cyclic Schiff Base

The symmetrical 2 : 1 Schiff bases derived from salicylic aldehyde and aliphatic and aromatic 1,2-diamines, often referred to as salen and salophen, have attracted a great deal of interest in recent years due to their synthetic accessibility, their rich coordination chemistry, as well as their relevance to catalysis1,2 and materials science [78].

1.23. Biological Activities of Schiff Bases

Schiff bases have been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial antiproliferative, anti-inflammatory, antiviral, and antipyretic properties Imine or azomethine groups are present in various natural, natural derived, and non-natural compounds (see Fig.1.18 for some examples) [79]. Hydrazones possesses an azomethine –NHN=CH- proton which is an important constituent for new drug development for the biological activities like anti-microbial [80].

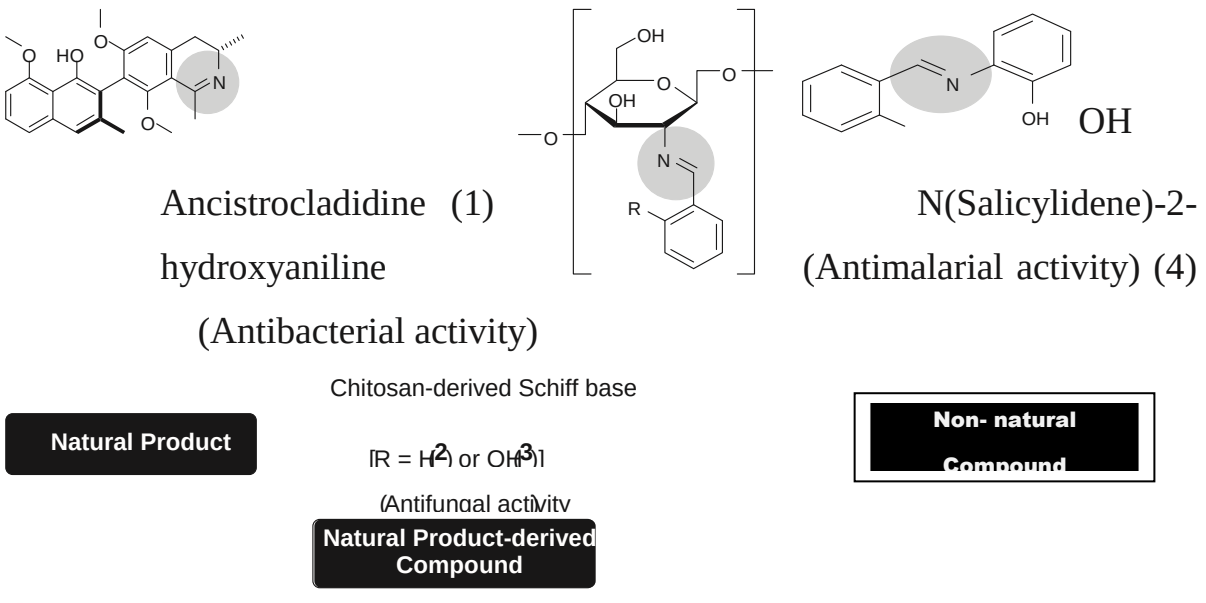


Figure 1.18 Examples of Bioactive Schiff Bases. The Imine or Azomethine Group Present in each Molecular Structure is Shaded.

Metal complexes with these bases have numerous applications, such as, in the treatment of cancer as antibactericide agents as antivirus agents as fungicide agents [81]. It has been shown that Schiff base complexes derived from 4-hydroxysalicylaldehyde and amines have strong anticancer activity, e.g. against Ehrlich Ascites Carcinoma (EAC)[82]. Many Schiff bases complexes were used to synthesis medication compounds and this is because the reactive interacting of the Schiff base ligand with the metal ion and become more effective if compared with the free metal Schiff bases.The objective of this paper is the present of biological activity of the Schiff base complexes and ligand against the bacterial and fungal [83]. Only limited progress has been made in research into antibacterial drugs with new mechanisms and core structures. Amoxicillin, noroxacin, and ciprooxacin are the commonest drugs used to treat bacterial infection, but are associated with severe side effects [84].Interest in the use of transition metal complexes with Schiff bases in medicine began to develop in the second half of the 19th century. Co(II), Ni(II), Cu(II) and Zn(II) complexes exhibit exceptional biological activity [85].

1.24. Synthesis of Schiff Bases

Schiff base is a condensation product of any primary amine with an active carbonyl group of an aldehyde or a ketone under optimum conditions and contain the azomethine group (−CH=N− or >C=N−)The Schiff base was prepared by mixing stoichiometric ratio of p-Hydroxybenzaldehyde in ethanol with ethanoic solution of 4-aminobenzoic acid. p-hydroxybenzaldehyde [86].

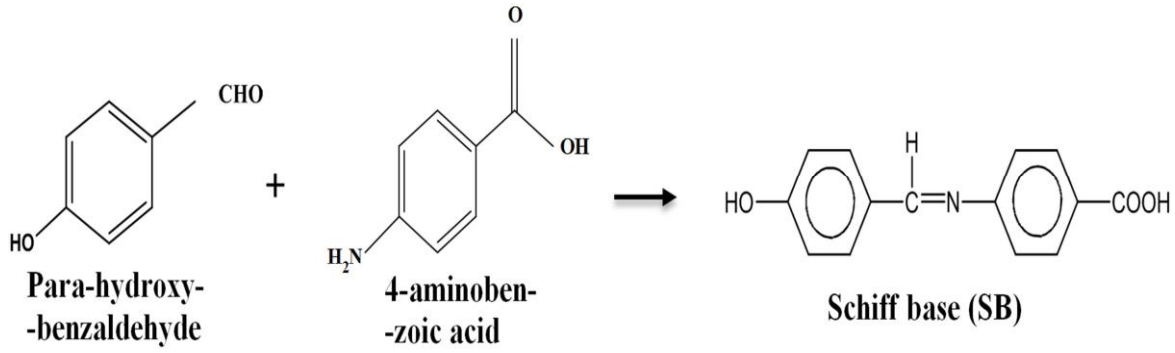


Figure 1.19 Reaction Scheme for The Preparation of Schiff Base.

The general mechanism of imine formation a carbinolamine. A carbinolamine is a nucleophilic compound addition to the carbonyl group. In amine group ($-NH_2$) $-NHR$ or $-NR$) and a hydroxyl group to this case, the nucleophile is the amine, which reacts with the same carbon as in Figure 1.20 [86].

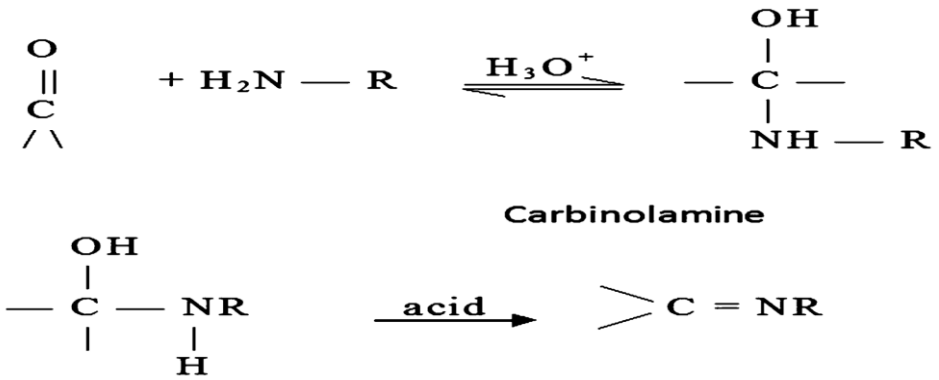


Figure 1.20 Reaction Mechanism for The Formation of Azomethine Group (−CH=N− or >C=N-) in Schiff Base.

1.25. Application of Schiff Base

1.26. Catalysis

The Schiff base transition metal complexes are cheap, easy to synthesize, and their chemical and thermal stability make them a family of attractive oxidation catalysts for a variety of organic substrates. Important oxidation reactions include the oxidation of sulfides to sulfoxides, the activation of hydrocarbons, alkenes to epoxides and diols, and the transformation of alcohols to either the corresponding carbonyl compounds or carboxylic acids. The catalytic activities of the Cu (II), Co (II), Fe (III), and Mn (II) complexes are observed for the phenol hydroxylation reaction. The activities of these cobalt complexes are slightly lower than that of manganese (II), iron (II), and copper (II) analogs of the investigated Schiff bases. Catechol was found as the major product of the reaction [87].

1.27. Biological Activity of Adamantane and Azadamantanes

The adamantane nucleus is an established pharmacophore in numerous chemotherapeutic agents. The adamantane-based analogues exhibited significant antiviral activity against influenza Avirus human immunodeficiency viruses and herpes simplex viruses. Anticancer activity was reported for some adamantane derivatives (Figure ١. 21) [88].

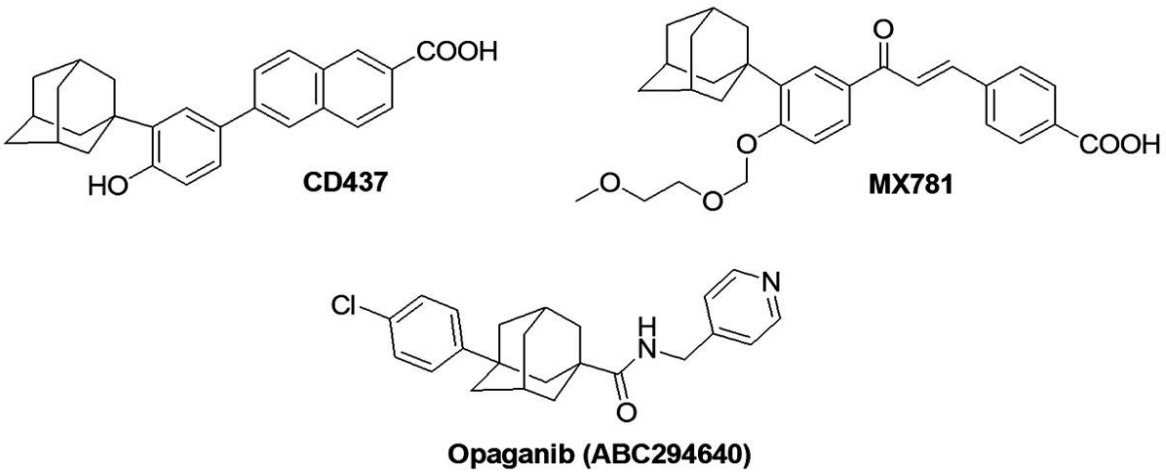


Figure 1. 21 Adamantane-Based Anticancer Agents

Adamanzane were got so interesting, because of their bioactive verves parable antibacterial and anti-fungal. Adamanzane are also appeared antidiabetic, anti-tumor, and anti-inflammatory [89].1,3-Diazaadamantane-6-one derivatives have attracted considerable attention for diverse applications [90].1,3-Diaza-adamantane derivatives exhibit antibacterial and psychotropic activity [91]. Derivatives of 1,3-diazaadamantane are distinguished from the chemically inert conjugates of adamantane by the presence of two ternary nitrogen atoms in the backbone, which allows for the former to be isolated in a water soluble hydrochloride form. These two nitrogen atoms provide for chemical activity of 1,3-diazaadamantanes[92]. Some derivatives of amino adamantane are known as efficient treatments for neurodegenerative diseases [93].The most known of the clinically useful imides is the antiviral drug amantadine (1-aminoadamantane).Another field where amantadine and many related derivatives are successfully employed, is the treatment of certain neurological disorders, e.g. Parkinson's disease. There are only few papers concerning the antimicrobial

activity of adamantane derivatives. In this study we show that certain easily Synthesise 1-adamantanemethanol esters of various N-substituted phthalimide 4-carboxyl- ate exhibit a distinct antimicrobial activity. It is worth to note that among structurally similar compounds N-(1-adamantyl) maleimide shows anticancer activity in mice and inhibits herpes simplex virus replication in vitro [94]. In 1971 Jonak et al. Designed a novel growth inhibitor of mouse mammary adenocarcinoma cells ñ 2,4-diamino-5-adamantyl-6-methyl pyrimidine (DAMP) and found it to be a potent, lipid-soluble antifolate [95]. An adamantane moiety in the molecules often has a substantial effect on the biological properties[96].

Aims of The Study

1. Synthesis of new 3,6-diazahomoadamantane derivatives bearing ketone, hydrazone or Schiff basses
2. Preparation of new azomethine compounds for 1-(4-Methoxybenzyl)-3,6-diazahomoadamantane-9-one derivatives.
3. Evaluating antibacterial action for target compounds against Gram-positive and Gram-negative bacteria and comparing results with that of control drug.

Chapter Two

Experimental Part

2.1. Materials

All chemicals, reagents and solvents were provided from the commercial sources summarized in Table (2-1)

Table (2-1) : Chemicals and Their Commercial Sources

Chemicals	Molecular formula	M.Wt. g/ mole	Purity %	Supplied companies
Paraformaldehyde	$CH_2O)_nH(HO$	30.03	97	Sigma Aldrich
Ethane diamine	$C_2H_8N_2$	60.098	99	GCC, Germany
Ethanol (absolute)	C_2H_6O	46.06	99.9	Hayaman
Aluminum oxide	Al_2O_3	101.96	99	Riedel-Dehaenag Seelze-Hannover
Hydrazine hydrate	H_6N_2O	50.06	98	Thomas Baker
Acetic acid	$C_2H_4O_2$	60.051	99	BDH, England
Butanol	$C_4H_{10}O$	74.121	99	Sigma Aldrich
Hexamine	$C_6H_{12}N_4$	140.19	99	Sigma Aldrich
Heptane	C_7H_{16}	100.201	99.7	Sigma Aldrich
Diethyl ether	$C_4H_{10}O$	74.12	99.5	Scharlau, Spain

Iso propanol	C_3H_8O	60.10	98	India
Benzaldehyde	C_6H_5CHO	106.13	98	BDH, England
p-Chloro benzaldehyde	ClC_6H_4CHO	140.57	98	BDH, England
m-Chloro benzaldehyde	ClC_6H_4CHO	140.57	98	BDH, England
p-Hydroxy benzaldehyde	HOC_6H_4CHO	122.12	98	HI media
m-Hydroxy benzaldehyde	HOC_6H_4CHO	122.12	98	BDH, England
4-Nitro benzaldehyde	$NO_2C_6H_4CHO$	151.12	98	BDH, England
4-Bromo benzaldehyde	BrC_6H_4CHO	185.02	98	BDH, England
p-Carboxy benzaldehyde	$OCHC_6H_4CO_2H$	150.133	98	BDH, England
4-Methoxyphenyl-2-butanon	$C_{11}H_{14}O$	178.23	98	Sigma Aldrich
3-Pentanon	$C_5H_{10}O$	86.134	99	Sigma Aldrich

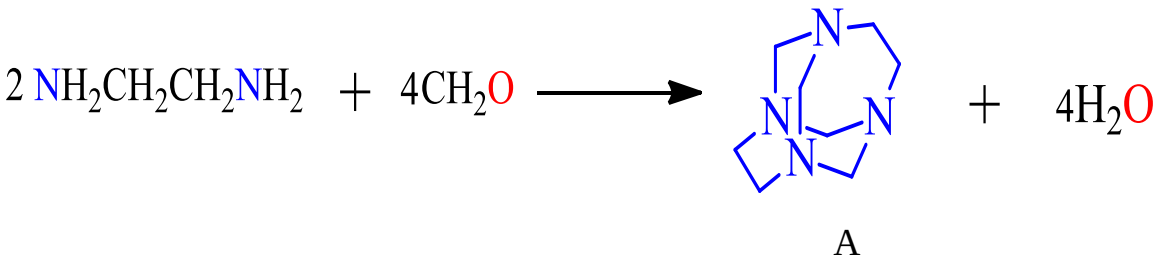
2-Butanon	C_4H_8O	72.11	98	India
Methanol	CH_3OH	32.O4	99.83	GCC, Germany
Iodine	I_2	253.80	99.5	GCC, Germany
Toluene	C_7H_8	92.14	97	GCC, Germany
Chloroform	$CHCl_3$	119.38	99.4	Sigma Aldrich

2.2. Equipments

1. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F_{254}). The reactions were monitored by TLC and visualized by development of the TLC plates with Iodine vapor.
2. Melting points were recorded using an Electro thermal Stuarts MP 30 capillary melting point apparatus.
3. FT-Infrared spectra were recorded on SHIMADZU FTIR-8400S Infrared Spectrophotometer as potassium bromide discs at the University of Kerbala
4. Mass spectra were measured on an instrument Finnigan MAT 90 with a direct admission into the ion source of 200$_{\circ C}$ at Russian Technological, College MRussia the Federation - Moscow.
5. ^{1}H NMR (300 MHz) and spectral data have been measured on a Bruker DPX 300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) using $CDCl_3$ as a solvent and TMS as an internal benchmark at Russian Technological, College MRussia the Federation - Moscow. Chemical shifts were recorded as δ (ppm) adjacent to TMS, which was utilized as an internal standard. Coupling constants (*J*) were displayed in Hertz.
6. Elemental analysis measurements were done by Perkin Elmer 300A College MRussia the Federation – Moscow.
7. Autoclave, supplied from Prestige Medical-England, was used to sterilize agar media.

2.3. The Preparation Methods;

2.3.1. Preparation of Tetramethylenediethylenetetramine(Teotropine)(A)

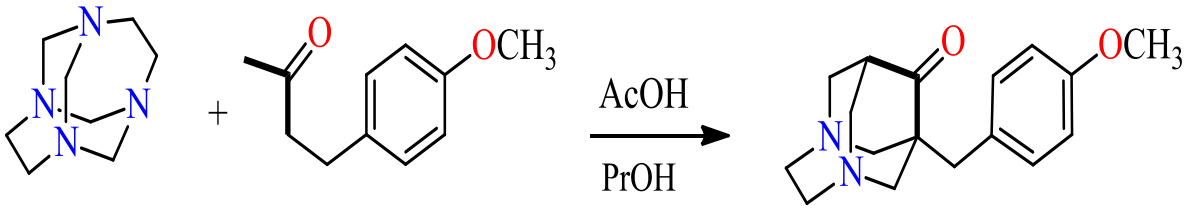


A

equation (2-1) [97]

Tetramethylenediethylenetetramine preparation from (7.5mL,1mol) of ethylene diamine with vigorous stirring in small portions, without allowing the temperature to rise above 50°C, (6.44g ,2 mol) of paraformaldehyde were added within 6 hours. After complete dissolution of paraformaldehyde, the reaction mixture was stirred another 30 min and left for 12 h. White crystals, (71%) mp.183-184°C.

2.3.2. Preparation of 1-(4-Methoxybenzyl)-3,6-Diazahomoadamantan -9-one (B)

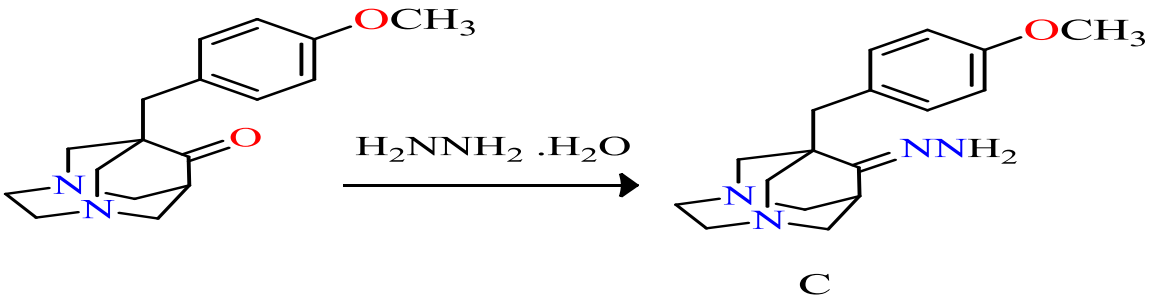


B

equation (2-2) [97]

Mixture of (14.30 g ,85mmol) of Tetramethylenediethylenetetramine (14.10g ,95 mmol) of 4-(4-methoxy phenyl)-2-butanone and (15.30g ,260 mmol) of acetic acid in 130 mL of 2-propanol was heated for 30 min at 60-70°C. The reaction mixture was concentrated in vacuum; the viscous residue was treated with hot heptane (4 x50 mL). The warm extract was purified by filtration through layer of anhydrous aluminum oxide 10g, placed on a glass frit filter. The solvent was distilled off, the residue was recrystallized from heptane. The yield was 4.88g (34%) white crystals, mp.102-104°C [68].

2.3.3. Preparation of 1-(4-Methoxybenzyl)-3,6-Diazahomoadamantan-9-one Hydrazone (C)

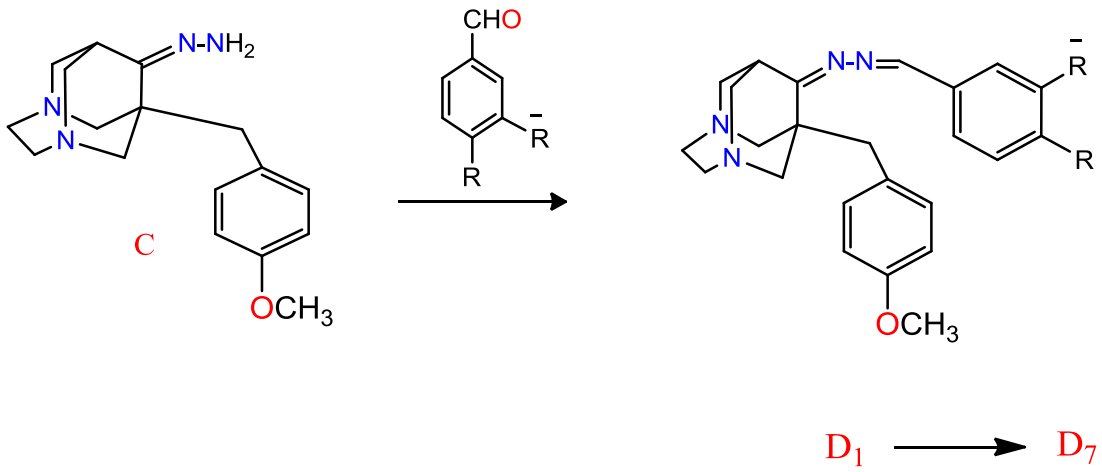


C

equation (2-3)

A solution of (1.30g ,4.8 mmol) of ketone (1-(4-methoxybenzyl)-3,6 diazahomoadamantan-9-one) in 10 mL solution of hydrazine hydrate was boiled for 3h. The reaction was monitored by TLC (Chloroform: methanol 5:1) the residue was recrystallized from toluene. The yield was 1.15 g(80%) white crystals, mp 178-180°C [68].

2.3.4. Preparation of imines Diazahomoadamantane (Schiff Bases)(general synthesis) (D_0-D_7) [98].



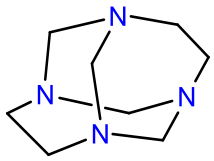
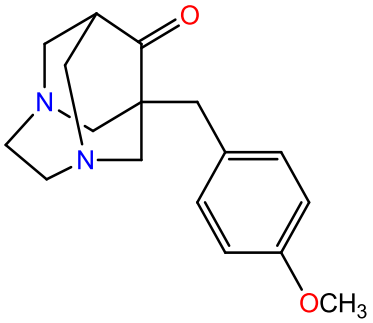
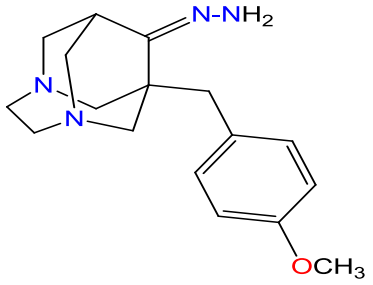
R = R=H (D_0) R=4Cl (D_1)R=H , R=4NO_2(D_2) R=H ,R=4Br(D_3) R=H ,R=3Cl

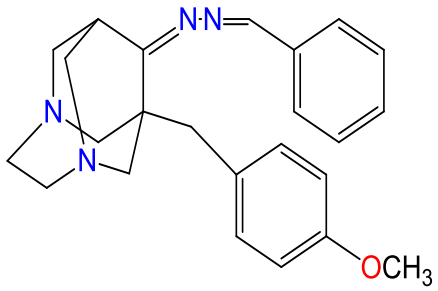
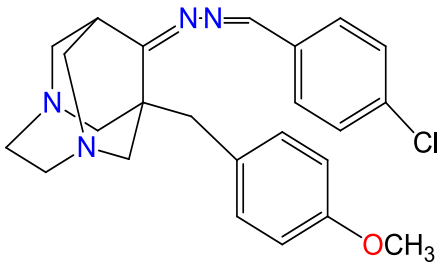
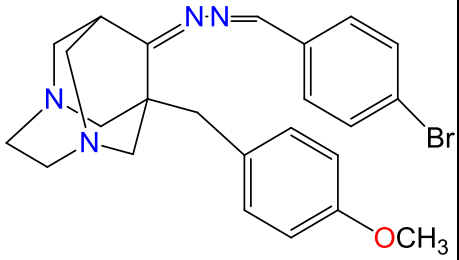
(D_4) R=H ,R= 4OH(D_5) R=H , R = 3OH (D_6)R=H , R=4COOH (D_7) R=H

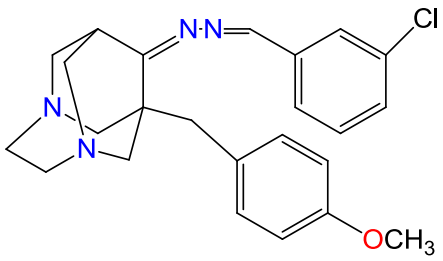
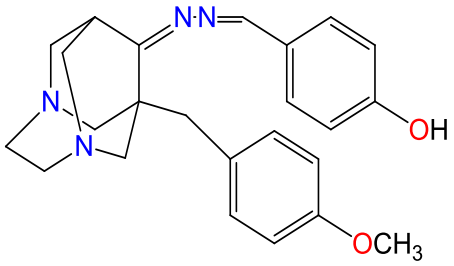
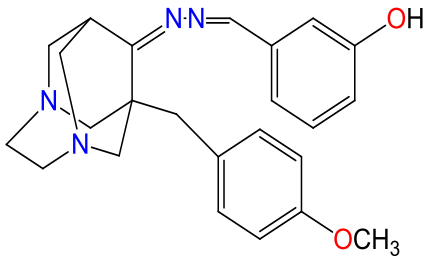
equation (2-4)

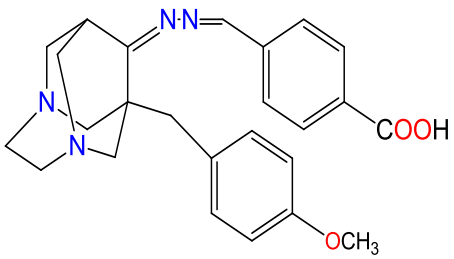
(1mmol) of benzaldehyde derivatives was taken in 20 mL of methanol and (1mmol) of hydrazone was dissolved in 20 mL of methanol. The solution was mixed together and heated at a temperature of 65°C for 3h. The reaction was monitored by TLC and the precipitate was filtered and recrystallized with absolute ethanol.

Table (2-2): Some Physical Properties and other Characteristics for Compounds(A-D_7).

Com. No.	Structure	Molecularformula	M.Wt.g/mole	Color	M.P. ºC	Nomenclature	Yield %
A		$C_8H_{16}N_4$	168.24	White	183-184	Tetramethylenediethylenetetramine	71
B		$C_{17}H_{22}N_2O_2$	286.38	White	112-114	1-(4-methoxybenzyl)-3,6 -diazahomoadamantan -9-one	34
C		$C_{17}H_{24}N_4O$	300.41	White	178-180	1-(4-methoxybenzyl) 3,6-diazahomoadamantan-9-one hydrazone (II)	80

D_0		$C_{24}H_{28}N_4O$	388.52	yellow	110-112	N-Benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.$1^{3,8}$] undec-9-ylidene] hydrazine	77
D_1		$C_{24}H_{27}ClN_4O$	422.96	Pale Orange	162-164	N-4-chloro Benzyliden [(9)-1-(4-methoxybenzyl)-3,6 diazatricyclo [4.3.1.$1^{3,8}$] undec-9-ylidene] hydrazine	71
D_3		$C_{24}H_{27}BrN_4O$	467.41	Pale yellow	182-184	N-4-Bromo Benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.$1^{3,8}$] undec-9-ylidene] hydrazine	80

D_4		$C_{24}H_{27}ClN_4O$	422.96	Pale Orange	188-190	N-3-Chloro Benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.$1^{3,8}$] undec-9-ylidene] hydrazine	74
D_5		$C_{24}H_{28}N_4O_2$	404.51	yellow	240-244	N-4-Hydroxy Benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.$1^{3,8}$] undec-9-ylidene] hydrazine	76.9
D_6		$C_{24}H_{28}N_4O_2$	404.51	Pale yellow	229-231	N-3- Hydroxy Benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.$1^{3,8}$] undec-9-ylidene] hydrazine	76

D_7		$C_{25}H_{28}N_4O_3$	432.52	Pale yellow	286-287	N-4- Carboxy Benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.$1^{3,8}$] undec-9-ylidene] hydrazine	71

2.4 Antibacterial Study

2.4.1. Preparing Mc Farland Solution

The Mc Farland solution (tube No. 0.5) is made up of two parts: solution (A) and solution (B). Solution (A) was made by adding 1 mL of concentrated H_2SO_4 to 100 mL of distilled water after 1.75g of barium chloride $BaCl_2H_2O$ was dissolved. At once, 99.5 mL of solution (B) and 0.5 mL of solution (A) were combined. Using this final solution as a reference, the approximate amount of germ cells (1.5×10^{-8} cells/mL) in the bacterial cell suspension utilized for antibacterial activity was determined [99].

2.4.2. Preparing Bacterial Suspension

The examined bacterial isolates were added to Brain Heart Infusion Broth (BHI) broth, which was then incubated at 37°C for 24 h. The turbidity of the broth was then measured and compared to the standard McFarland solution No. (0.5). Next, 0.1 mL of isolates broth, which contained roughly 1.5×10^{-8} cells/mL, was spread onto a Muller Hinton agar plate using a cotton swab and the plate tilted 60 degrees in each direction. The plates were then left to stand upside down at room temperature for 10 min. After that, they were incubated at 37 °C for 24 h, and the diameter of the inhibition zone was measured using a sterile rule [99].

2.4.3. Preparing Implant Mediums (Agar)

In order to prepare the Muller Hinton agar medium, 38g were dissolved in 1000 mL of distilled water, brought to a boil to completely dissolve the agar, autoclaved at 121°C for 10 min, and then allowed to cool to 45°C . When it's ready to use, the agar will pour into Petri plates after that [99].

2.4.4. Antibacterial Tests Method

In order to apply the disc diffusion method, the antibacterial test was conducted. All target compounds (**A, D_0, D_1, D_2, D_3, D_4, D_5, D_6, D_7**) have had their antibacterial efficacy tested *invitro* against the Gram-positive Bacteria *Staphylococcus aureus*, *Streptococcus mutants* and the Gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*. The cultures of the investigated bacteria were uniformly surface-inoculated onto the agar plates. Five-mL-diameter holes were cut in the solidified material, spaced appropriately apart. (20 mg of each compound dissolved in 1 mL of DMSO) were added to the holes. All types of bacteria were cultured on the plates for 24 h at 37°C. The measurement of the zones that prevent bacterial growth surrounding the discs has been established in mm [99].

Chapter Three

Results

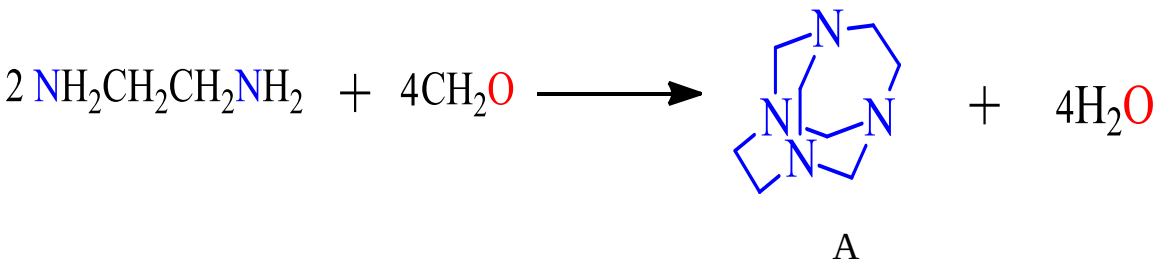
and

Discussion

3-1 Synthesis of Compounds

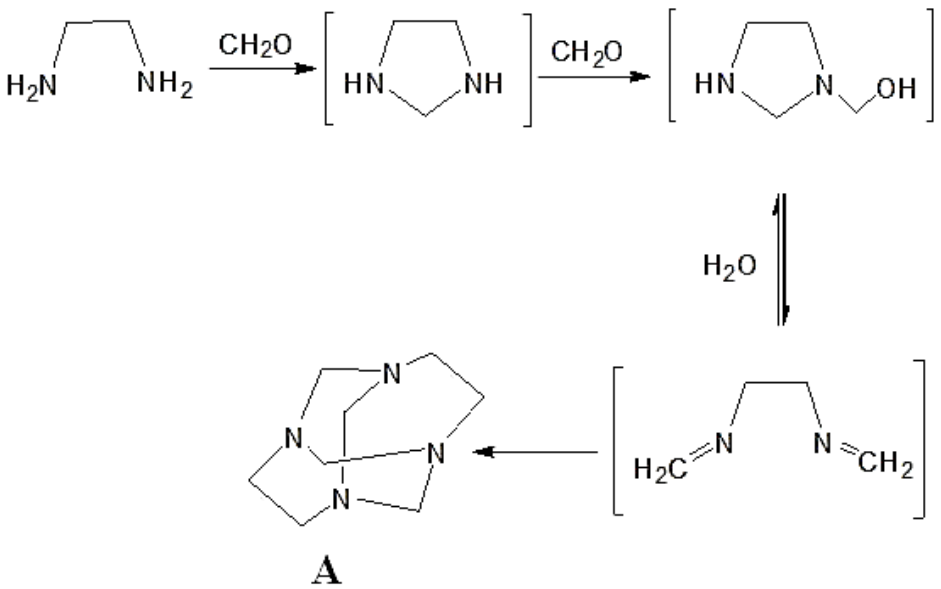
3-1-1- Preparation of Tetramethylenediethylenetetramine (Teotropine)A

1,3,6,8 -Tetra azatricyclo {4.4.1.1 (3,8)} dodecane prepared from ethylene diamine with vigorous stirring in small portions of paraformaldehyde were added within 6 h. After complete dissolution of paraformaldehyde, the reaction mixture was stirred another 30 min and left for 12 h. equation (3-1).



A

equation (3-1) [97]

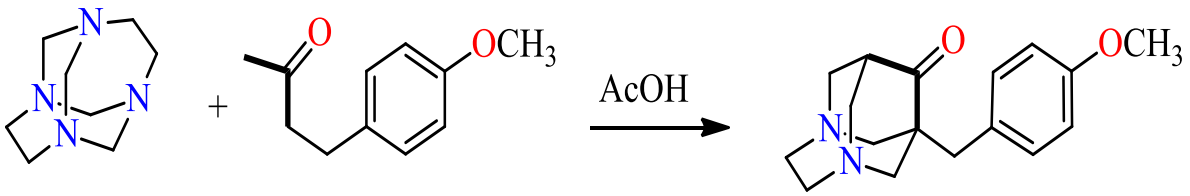


A

Scheme (3-1) Mechanism of (Teotropine)A[100]

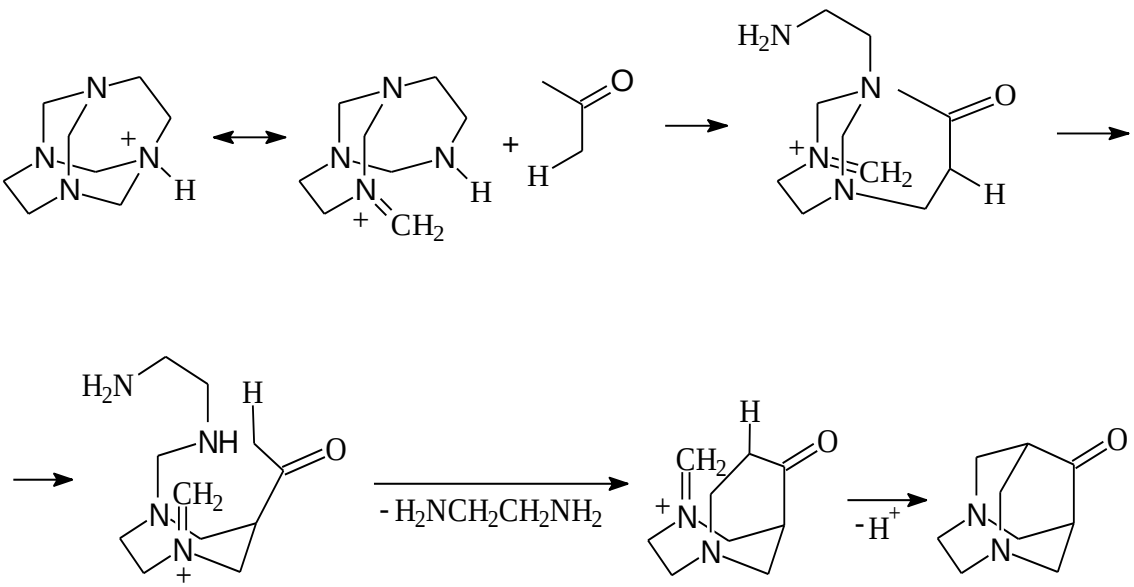
3-1-2- Preparation of 1-(4-Methoxybenzyl)-3,6-Diazahomoadamantan-9-one (B)

Mixture of tetramethylenediethylenetetramine and 4-(4-methoxy phenyl)-2-butanone and of acetic acid in 2- propanol was heated for 30 min. The reaction mixture was concentrated in vacuum; the viscous residue was treated with hot heptane. The warm extract was purified by filtration through layer of anhydrous aluminum oxide placed on a glass frit filter. The solvent was distilled off the residue was recrystallized from heptane[68].



B

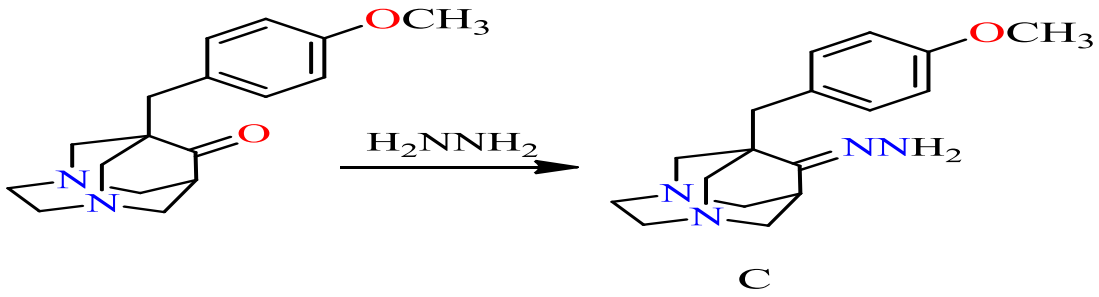
equation (3-2) [97]



Scheme (3-2) Proposed Mechanism of 1-(4-Methoxybenzyl)-3,6 Diazahomoadamantan-9-one formation.

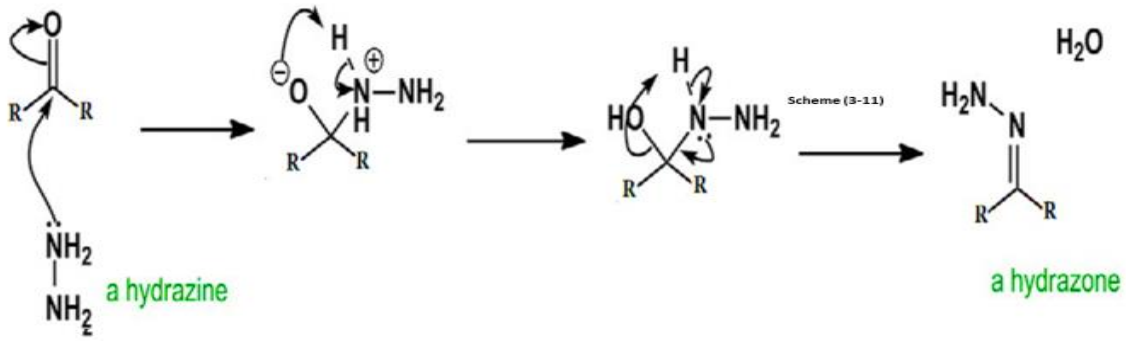
3-1-3- Preparation of 1-(4-Methoxybenzyl)-3,6-Diazahomoadamantan-9-one hydrazone(C)

A solution of ketone(1-(4-methoxybenzyl)-3,6 diazahomoadamantan-9-one) was boiled in a solution of hydrazine hydrate for 3h. the residue was recrystallized from toluene. The reaction was monitored by TLC [68].



C

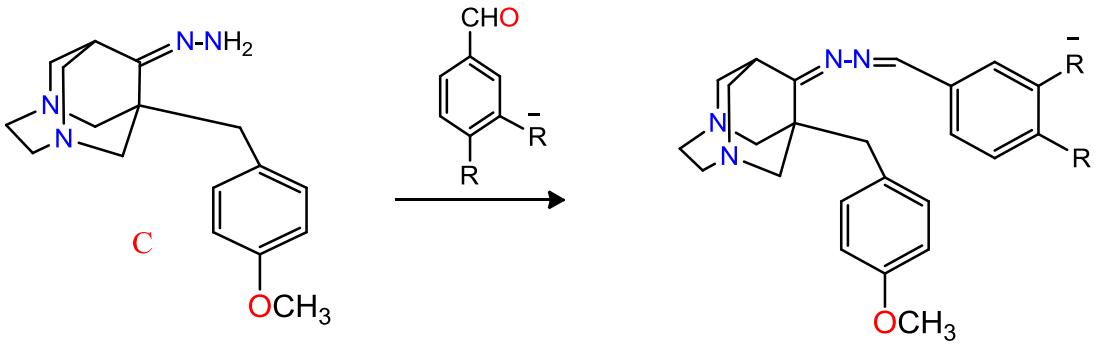
equation (3-3)



Scheme (3-3) General Mechanism for the Synthesis of hydrazone

3-1-4- Preparation of imines diazahomoadamantane (Schiff Bases)(general synthesis) (D_0-D_7) [98]

Benzaldehyde derivatives was reacted with hydrazone and the mixture dissolved in methanol. The reaction was monitored by TLC and the precipitate was filtered and recrystallized with absolute ethanol.



D_0 ⟶ D_7

R = $\bar{R}$=H (D_0), R=4Cl (D_1) $\bar{R}$=H , R=4NO_2 (D_2) $\bar{R}$ =H ,R=4Br(D_3) $\bar{R}$=H ,$\bar{R}$=3Cl

(D_4) R=H ,R= 4OH (D_5) $\bar{R}$=H , $\bar{R}$ = 3OH (D_6) R=H , R=4COOH (D_7) $\bar{R}$=H

equation (3-4)

3.2. Characterization of Synthesized Compounds

3.2.1. FT-IR Spectra

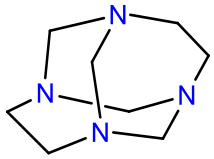
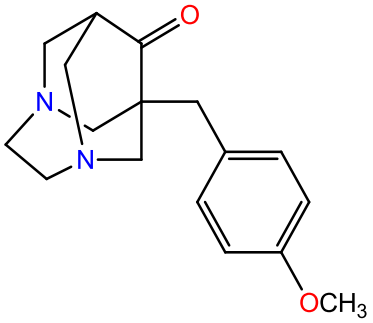
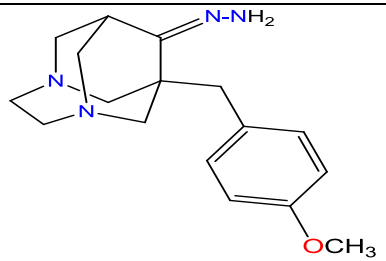
3.2.1. 1. FT-IR Spectra of 3,6 Diazahomoadamantane Derivatives (B-C)

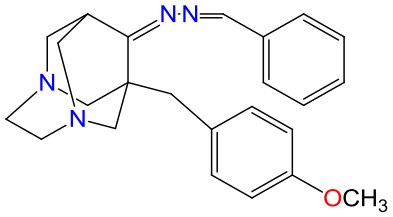
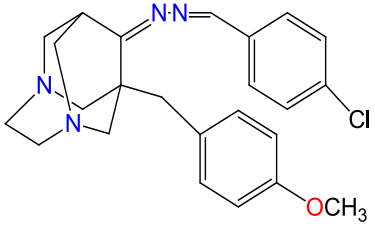
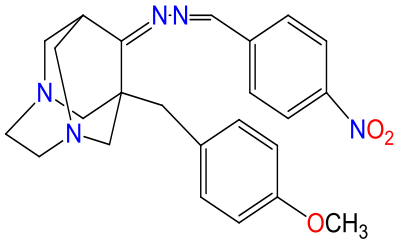
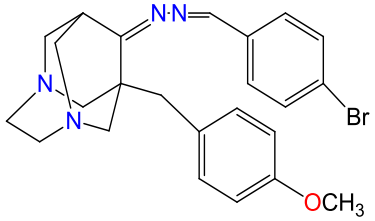
The weak bands of these compounds (B-C) are absorbed in the range (1512,1446), (1512,1442) cm^{1} belonging to the (C=C) stretching vibration aromatic rings, while the aromatic(C-H) stretching vibration band can be seen in the range of (3001-3063) cm^{-1}, as well as in the range (3232-3390) cm^{-1}du to (NH_2) stretching were attributed to compound (C) and (1708) cm^{-1} du to (C=O) were attributed to compound (B).

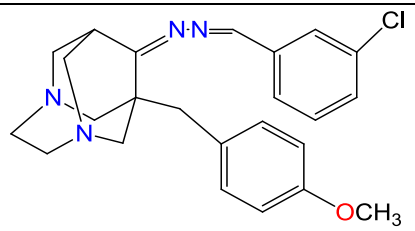
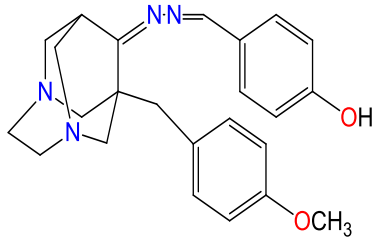
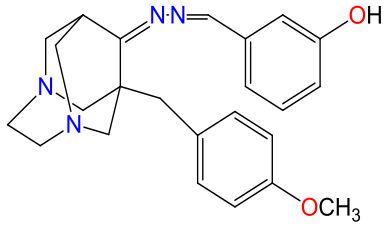
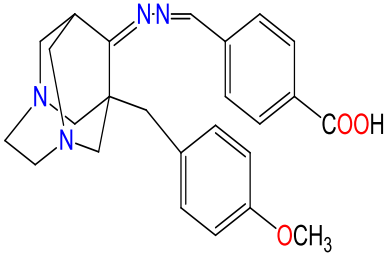
3.2.1.2. FT-IR Spectra of Schiff Bases Compounds (D_0-D_7)

The IR spectra of the prepared Schiff base compounds showed in Figure (3-4) to (3-12) showed the disappearance of the amine band in the region (3232-3390) cm^{-1} for benzaldehyde derivatives(D_0-D_7). Anew distinct medium to strong intensity band appeared in the spectrum due to the stretching frequency of the azomethine group . And the appearance of the band C=O at (1706) cm^{-1} were attributed to compound D_7. Table (3-1) displays the results for these chemicals absorption bands.

Table (3-1): The FT-IR Data of Compounds (A-D_7)

Com.No.	Structure	C=C Arom.	C=N	CH_2 asy Aliphatic	CH_2 sy Aliphatic	CH Aromatic	C-N	C-O-C	Others
A		-	-	2935	2862	-	1276	-	-
B		1512,1446	-	2931	2850	3001	١٣٠٠	(1249)asy, (1022) sy $vOCH_3$	$vC=O(1708)$ cm^{1}
C		1512,1442	1639	2912	2843	٣١٠٠	١٣٠٠	(1238) asy,(1033)sy $vOCH_3$	(3390-3232) cm^{-1} for the (NH_2)

D_0		1508,1446	1620	2931	2847	٣٠٥٩	١٢٩٦	1249 asy, 1026 sy, ($vOCH_3$)	-
D_1		1512,1446	1624	2908	2843	3100	١٢٩٦	1246 asy, 1037 sy, ($vOCH_3$)	613 cm^{-1} vC-Cl)
D_2		1516,1446	1616	2928	2843	٣٠٣٦	١٣٠٠	1246 asy, 1033sy ($vOCH_3$)	1516,1342 cm^{-1} (vNO_2,)
D_3		1512,1442	1620	2935	2847	3001	١٣٠٠	1249 asy,1037 sy ($vOCH_3$)	740 cm^{-1} (vC-Br)

D_4		1512,1450	1620	2924	2843	٣٠٦٣	١٢٩٦	1249 asy,1030 sy ($vOCH_3$)	756 cm^{-1} (v C-Cl)
D_5		1508,1454	1635	2939	2847	3059	١٣٧٣	1246 asy,1033 sy ($vOCH_3$)	-
D_6		1508,1454	1608	2931	2847	3039	1300	1242 asy,1033 sy($vOCH_3$)	-
D_7		1508,1446	1624	2943	2847	٣٠٦٣	١٣٠٠	1246 asy,1033 sy($vOCH_3$)	1706(vC=O)

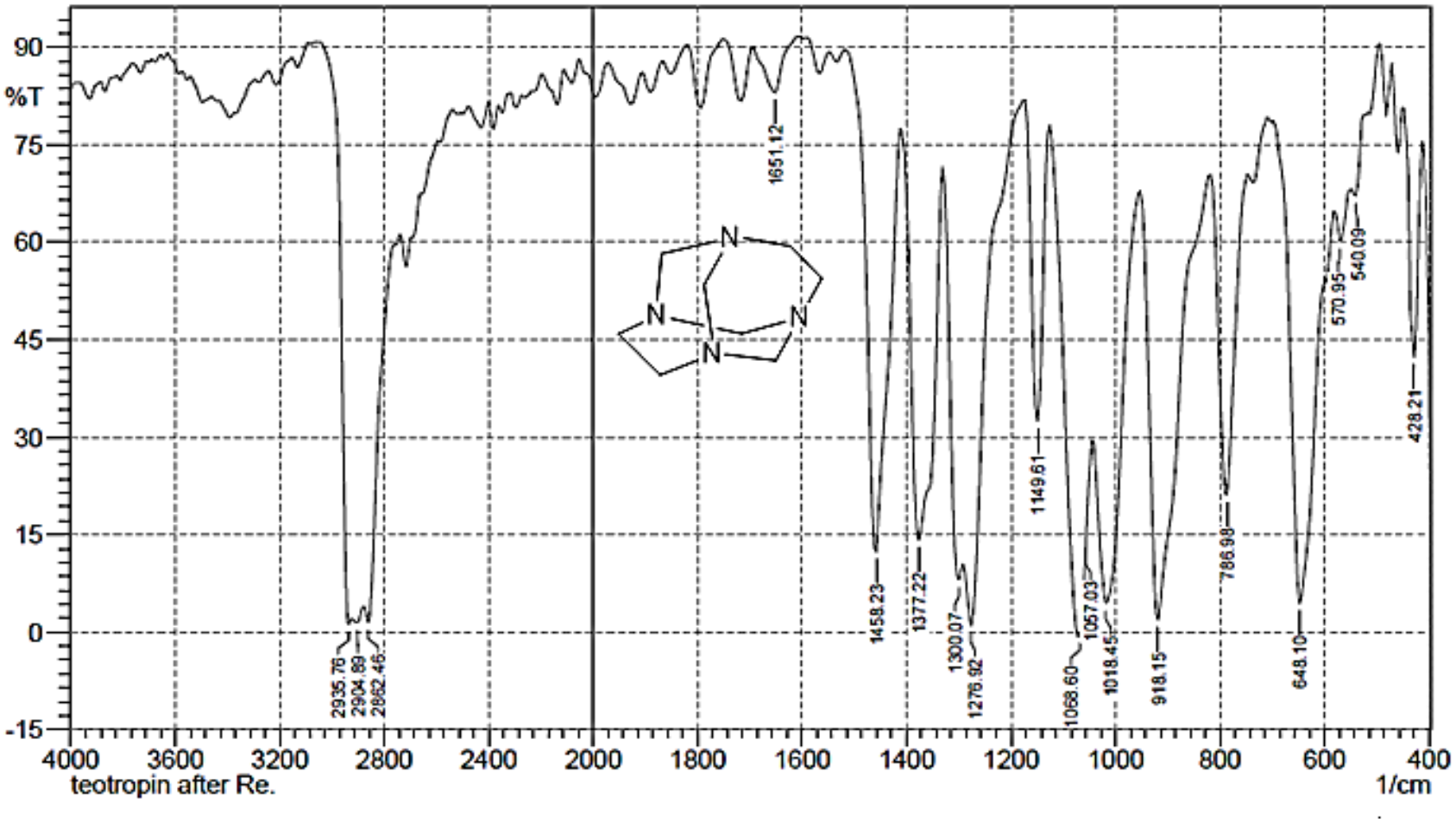


Fig. (3-2) FT-IR Spectrum of Compound (A)

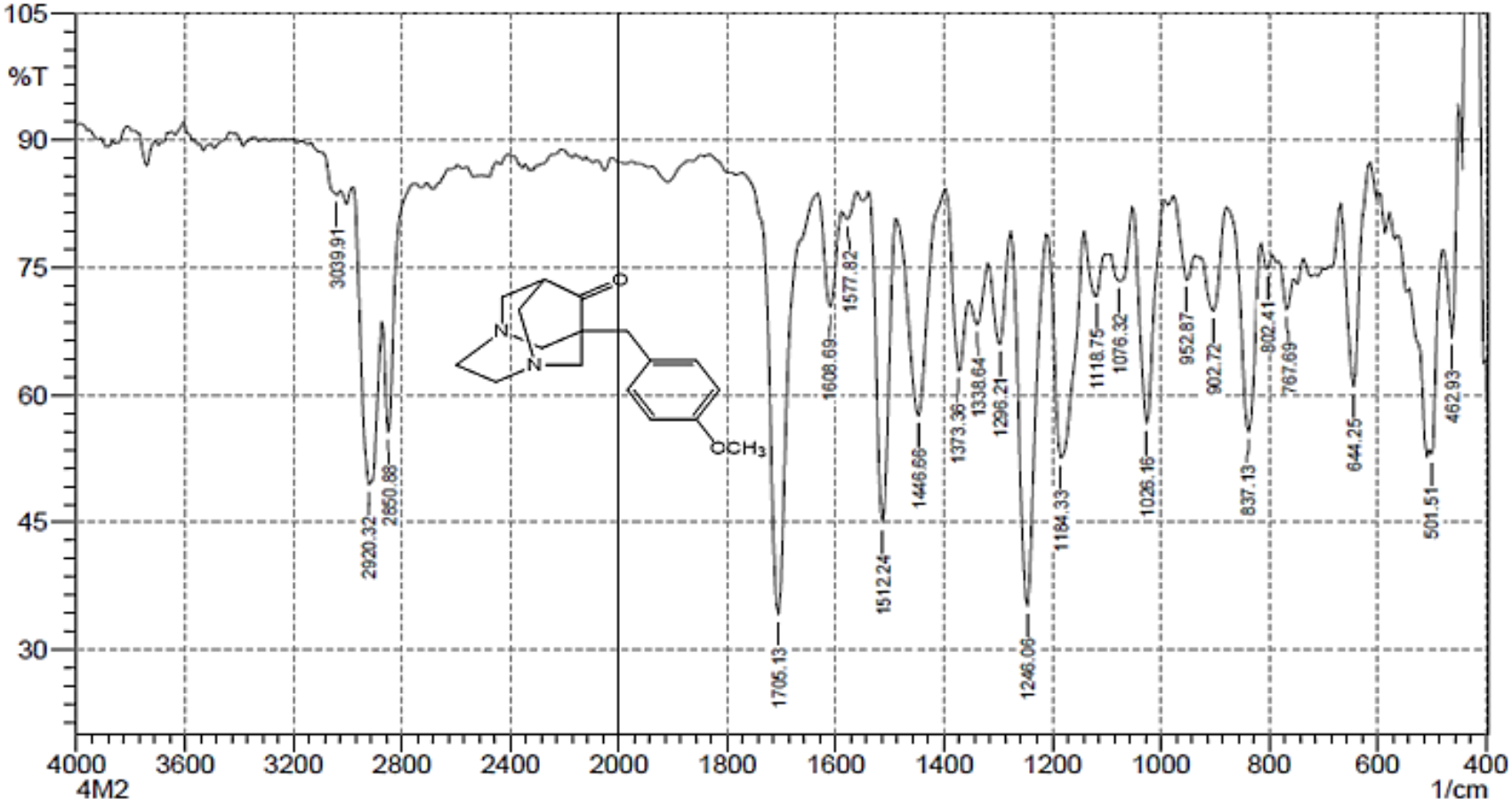


Fig. (3-3) FT-IR Spectrum of Compound (B)

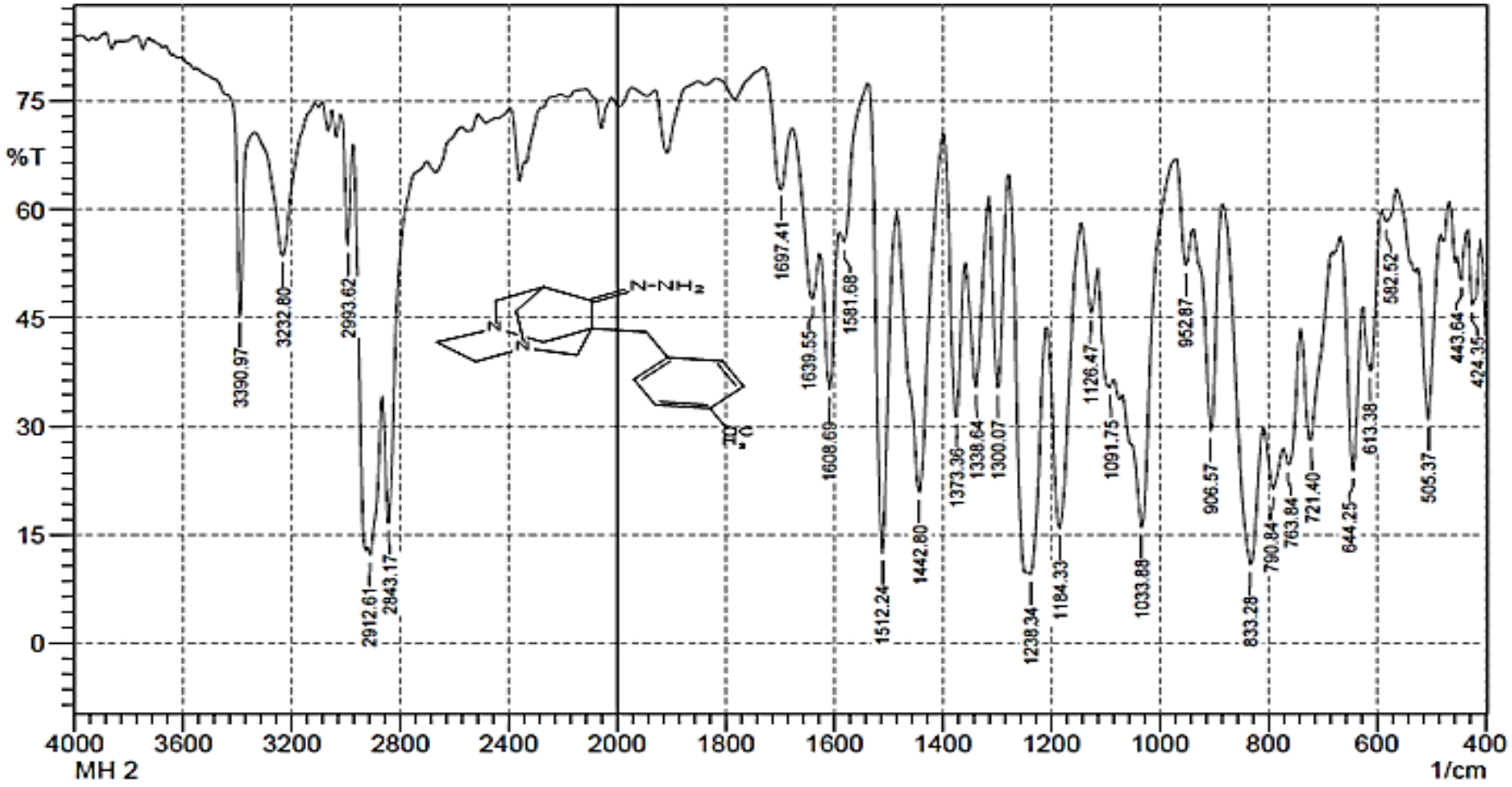


Fig. (3-4) FT-IR Spectrum of Compound(C)

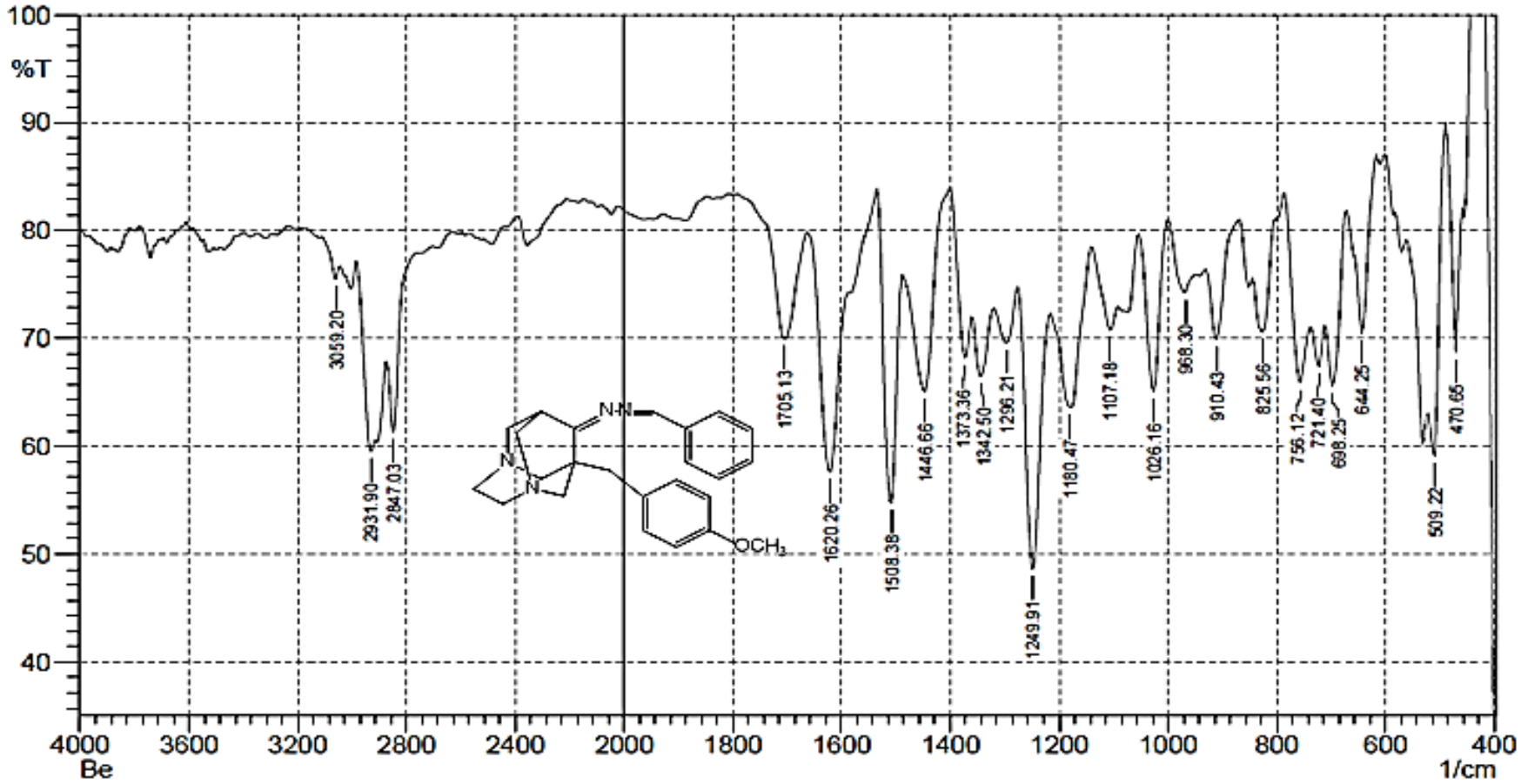


Fig. (3-5) FT-IR Spectrum of Compound(D_0)

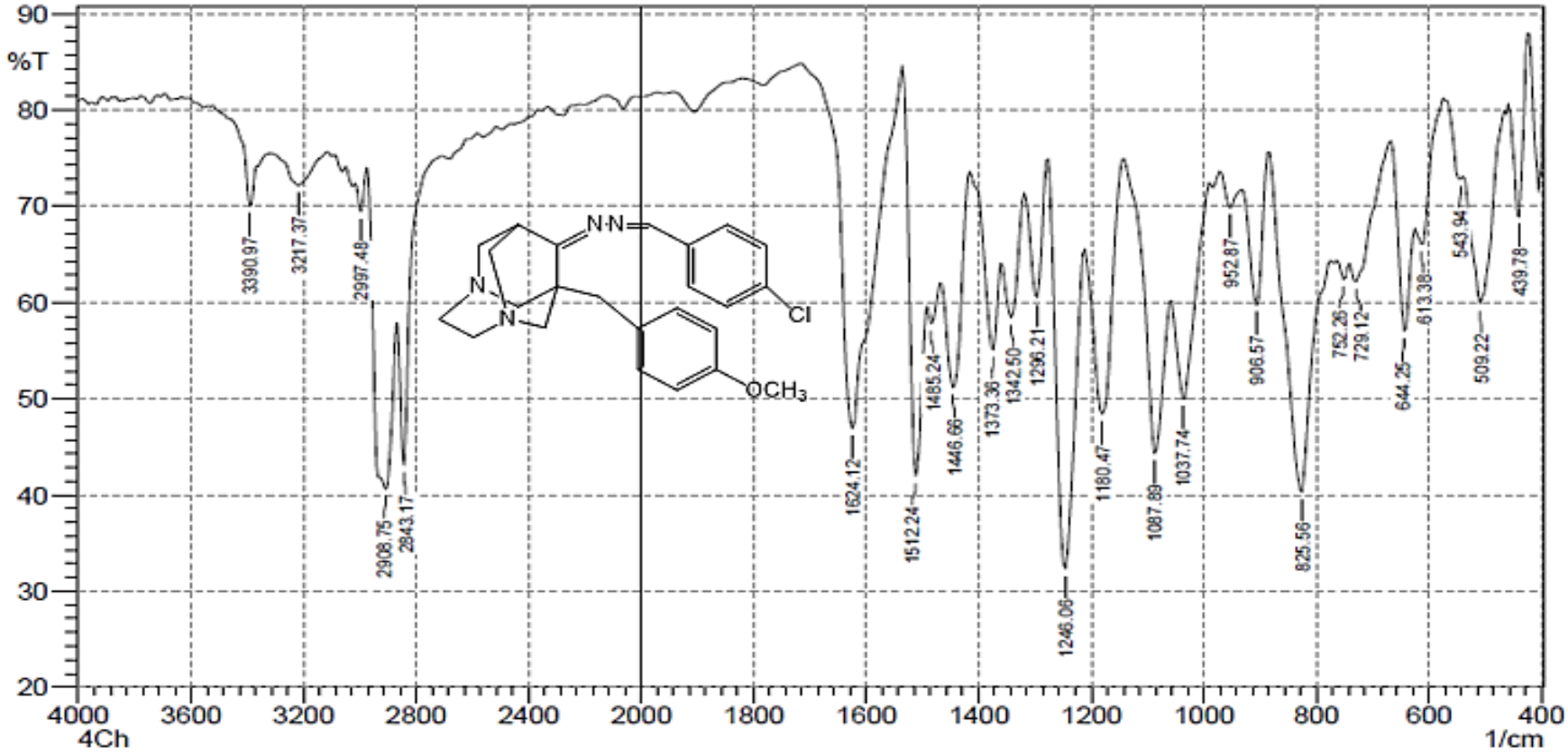


Fig. (3-6) FT-IR spectrum of compound(D_1)

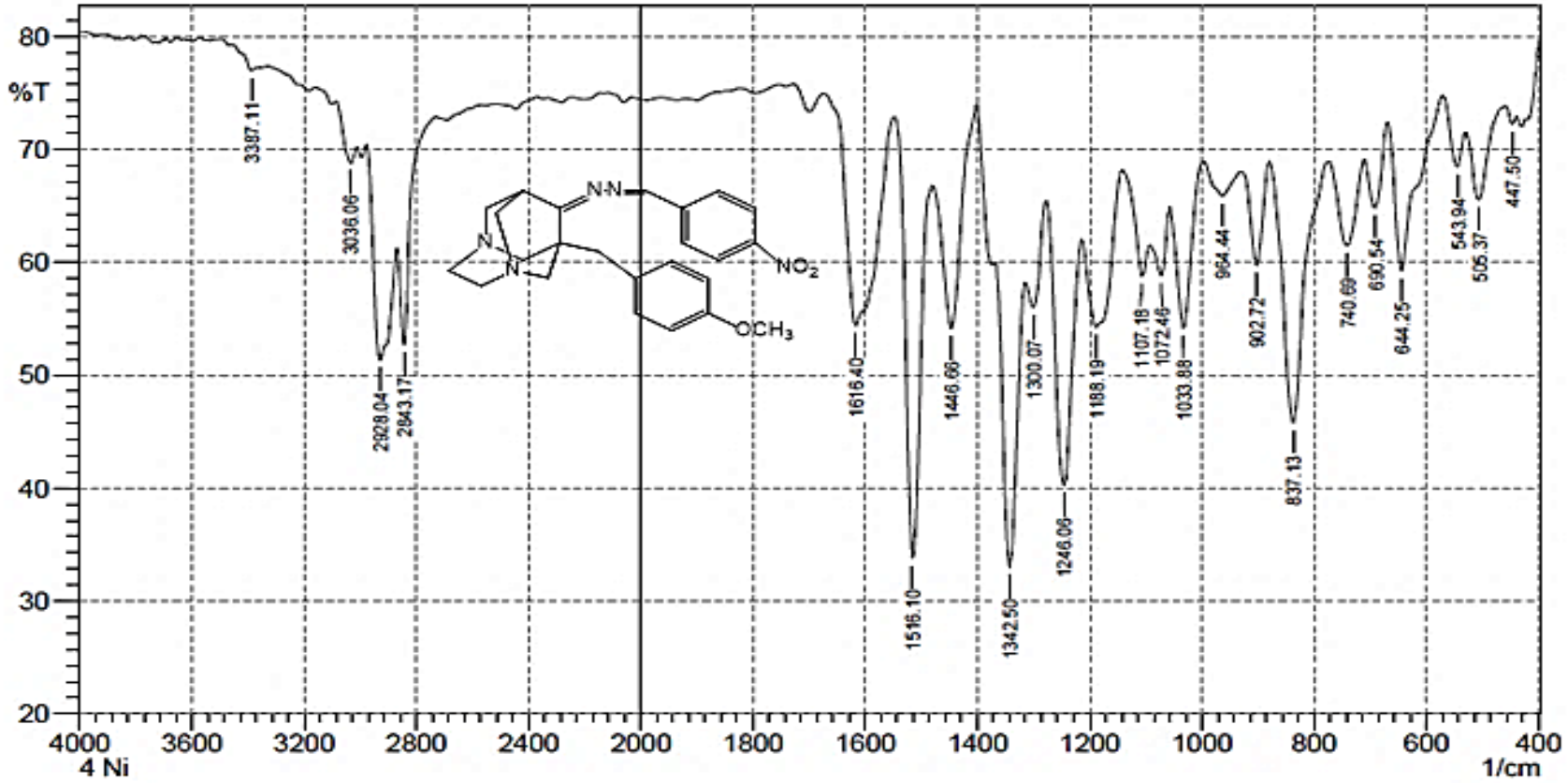


Fig. (3-7) FT-IR Spectrum of Compound(D_2)

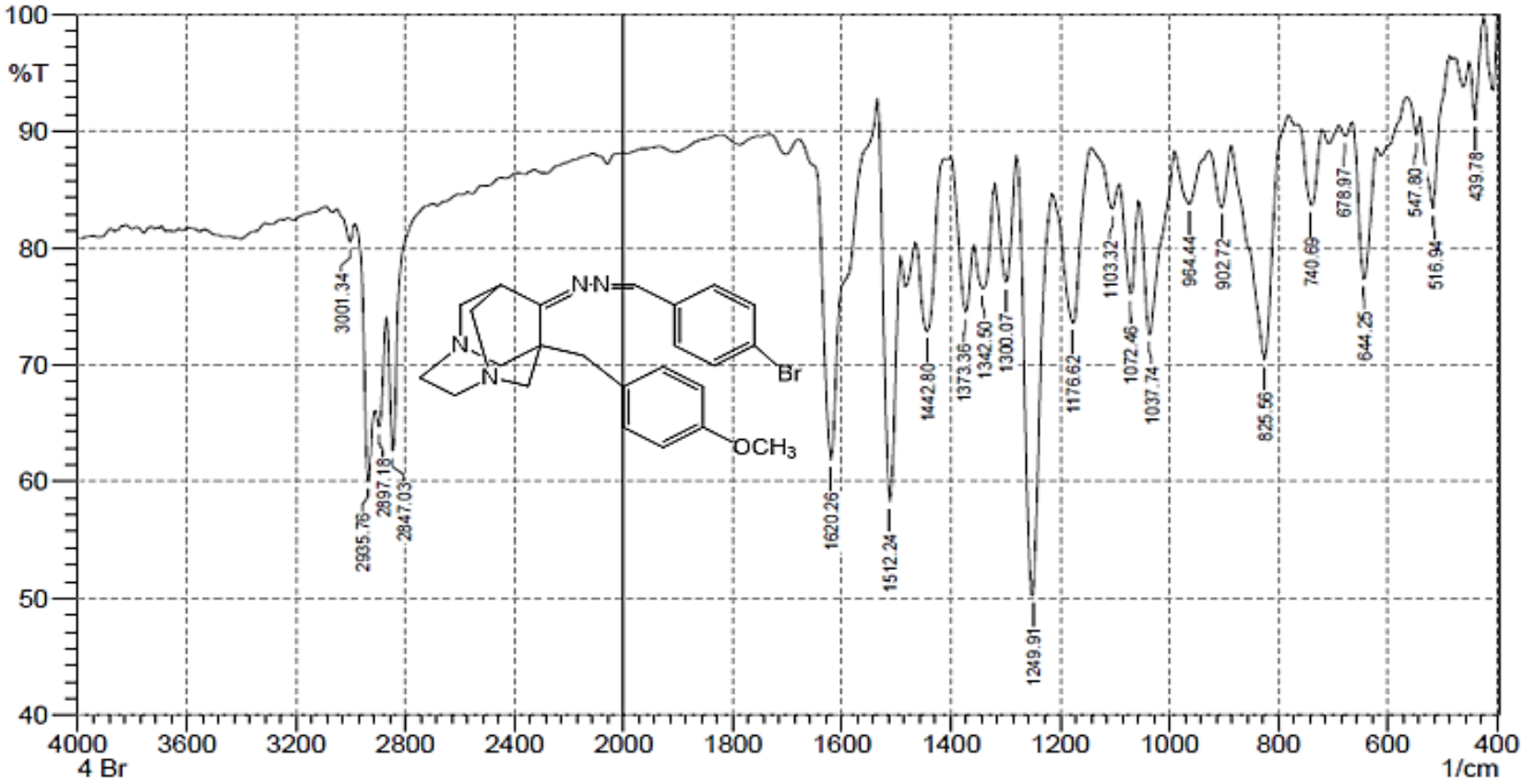


Fig. (3-8) FT-IR Spectrum of Compound(D_3)

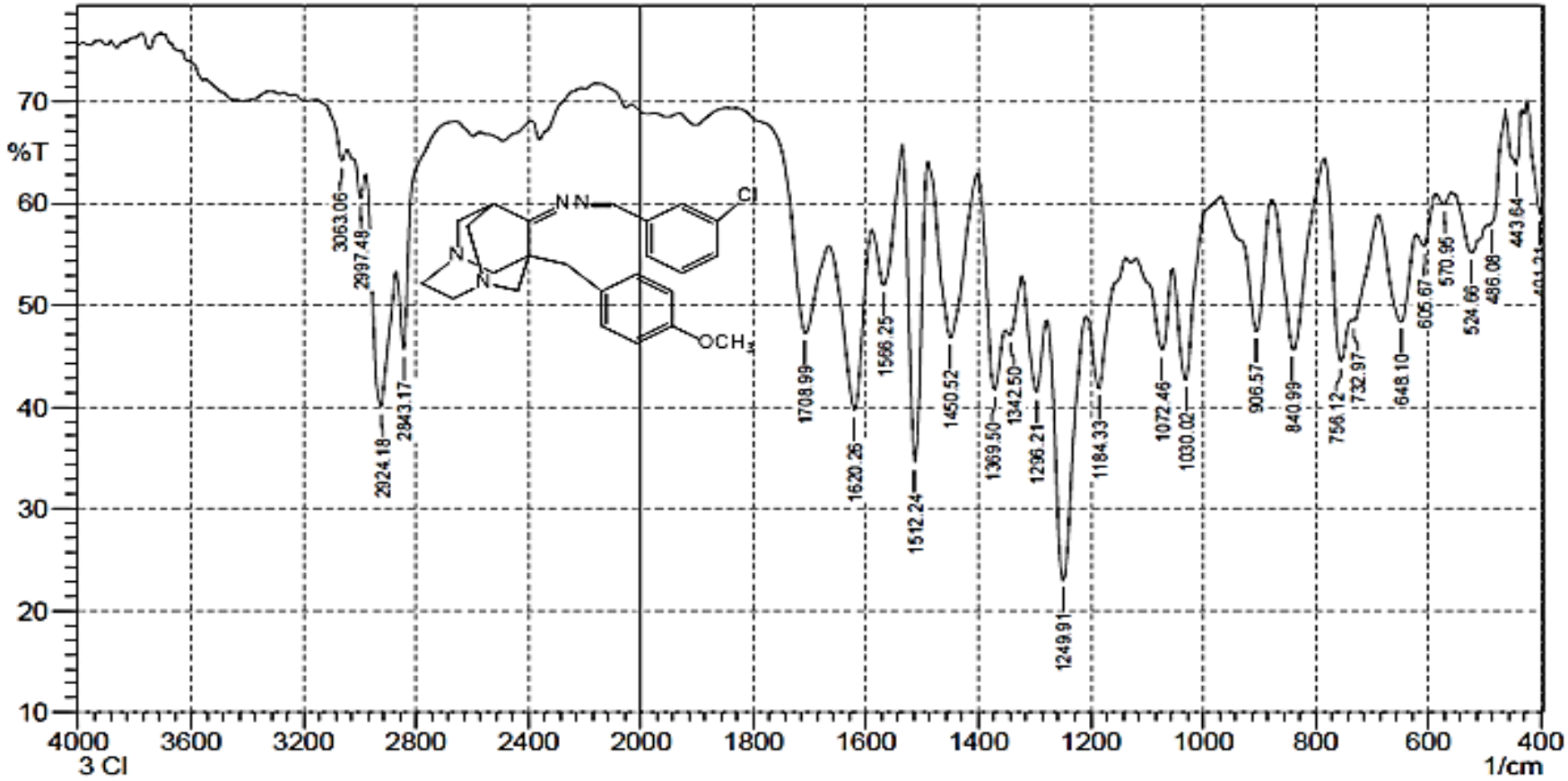


Fig (3-9) FT-IR Spectrum of Compound(D_4)

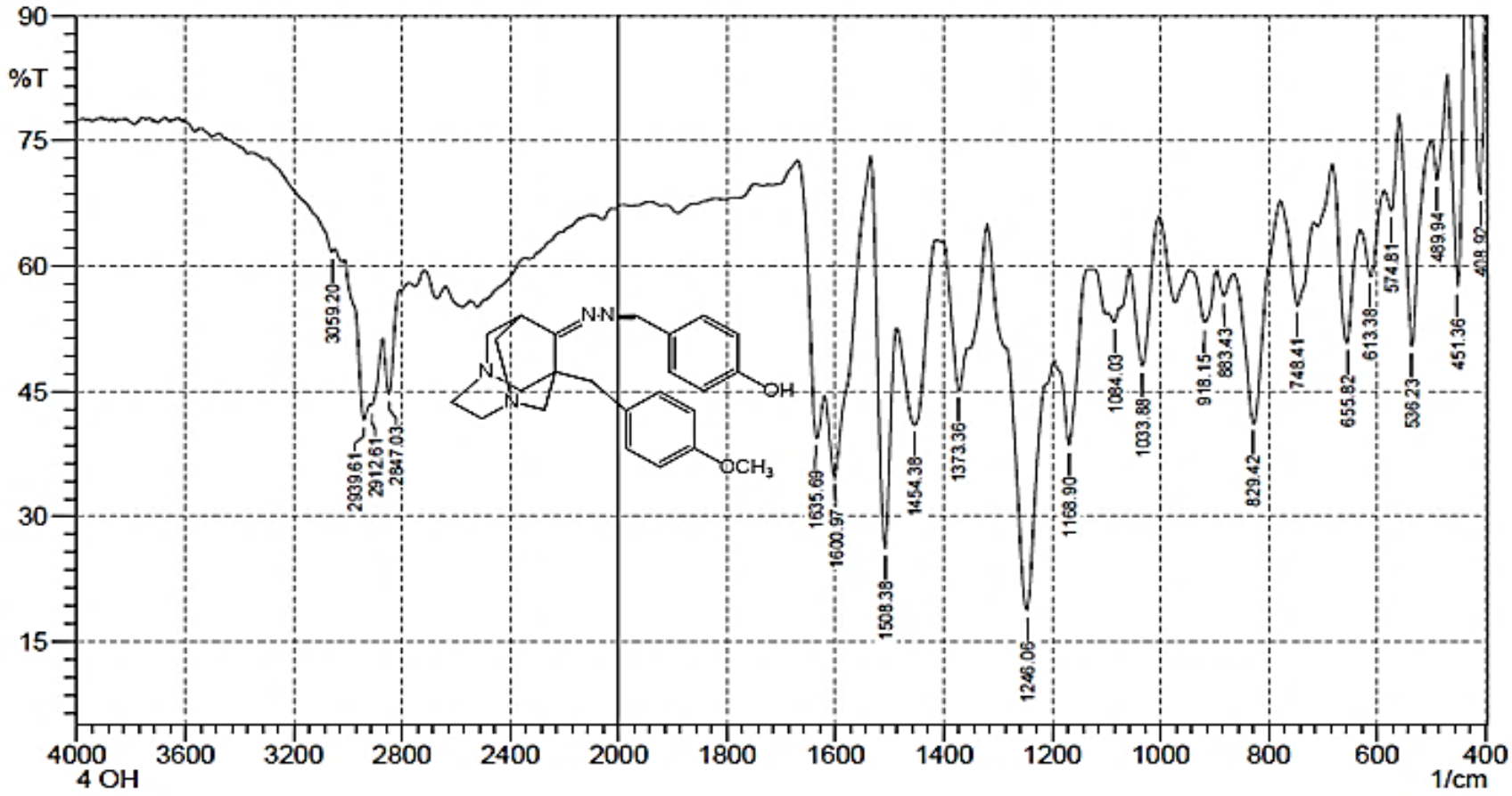


Fig. (3-10) FT-IR Spectrum of Compound (D_5)

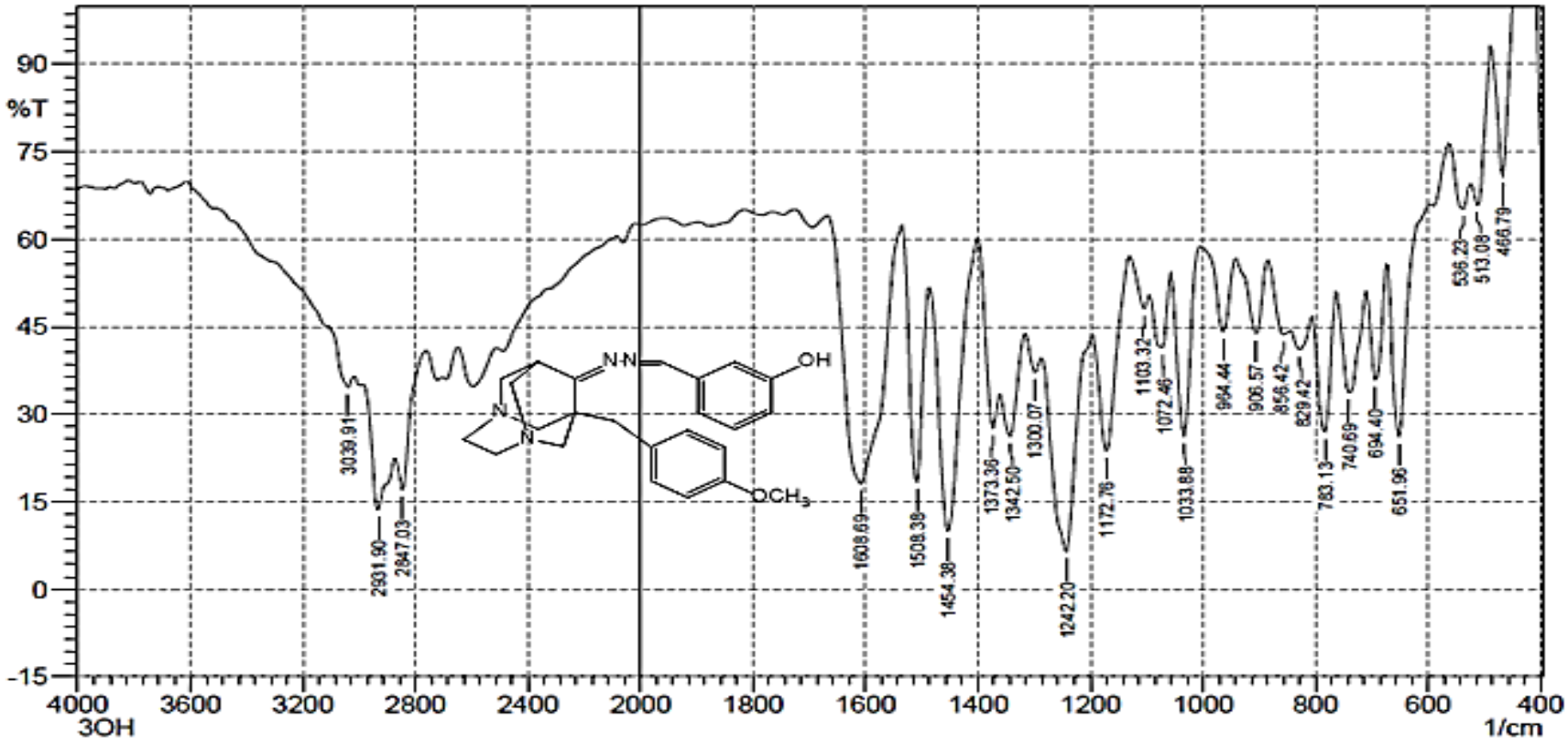


Fig. (3-11) FT-IR Spectrum of Compound (D_6)

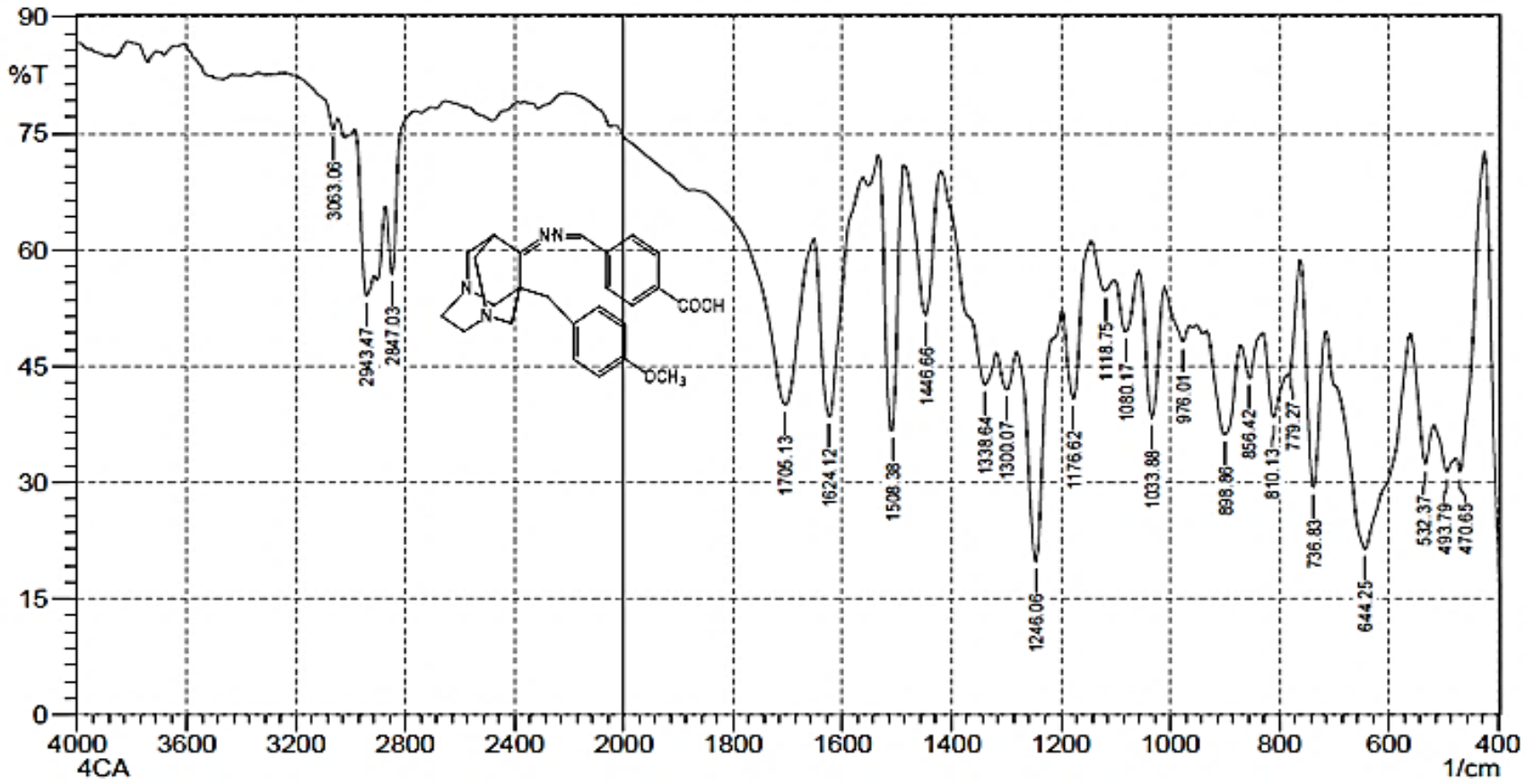


Fig. (3-12) FT-IR Spectrum of Compound (D_7)

3.2.2 ^{1}HNMR Spectrum

^{1}HNMR spectra of synthesized compounds was showed in compounds from (B-D_7) ^{1}HNMR spectra was recorded in DMSO solvent and $CDCl_3$ using tetra methyl silane (TMS) as internal standard. The ^{1}HNMR spectrum of the indicated compound indicates compatibility with the proposed structure. Chemical shifts of various protons are show in Table (3-1) and (3-2).

3.2.2.1 HNMR Spectrum of the 3,6-Diazahomoadamantane Derivatives Compounds (B, C) and Schiff Bases Compounds (D_0-D_7)

In The ^{1}HNMR spectra of synthesized compounds (B-D_7) a group of signals is present characteristic of the diazahomoadamantan-9-one scaffold consisting of two AB system of NC H_2C, protons of aminal ethylene groups NCH_2CH_2N. ^{1}HNMR spectrum 1-(4-methoxybenzyl)-3,6-diazahomoadamantan-9-one (B) showed the following characteristic chemical shifts ($CDCl_3$ as solvent and DMSO) singlet signal at the rang (1.87-1.89) ppm belong to proton of (CH) for compounds (B-D_7.) The 4-methoxybenzyl group signal manifests as two doublets of the benzene group protons in the range of (6.80–6.97) to (6.88 - 7.53) ppm, a singlet of the methylene a the rang (2.32-2.85) ppm, a singlet signal δ (5.01) ppm due to the amine groups(2H) for compound(C). The spectrum also showed doublet signal and multiplet belong to the proton of (NCH_2C). The ethylene bridge's proton multiplet, NCH_2CH_2N and the expanded singlet at 1.87 ppm. The compounds from (B to D_7) contains highest peak a singlet signal due to the protons (OCH_3) groups it within the range (3.80-3.81) ppm. It was also observed that multiplet and doublet signals appeared due to the protons of the aromatic rings. while in compounds (D_5, D_6, D_7) a singlet signal appears at (5.85) (5.73) (12.04) ppm due to the hydroxyl groups. The ^{1}HNMR spectra of Schiff bases prepared in compounds (D_0-D_7) showed the disappearance of the singlet signal that belongs to the amine group for compound 1-(4-methoxybenzyl)-3,6-diazahomoadamantan-9-one hydrazone(C).This indicates the interaction of the amine group with carbonyl group of aldehyde compounds .It was also found the emergence of a new signal belonging to the azomethine group within the range (9.31-9.03)ppm as shown in the table below (3-3).

Table (3-2): The Chemical Shifts Values of ^{1}H-NMR spectrum for Compounds B and C

Com. No.	structure	1H(CH)	Ar-H	(2H)CH_2	(3H)OCH_3	(4H)NCH_2CH_2N	8H (4NCH_2)	Other

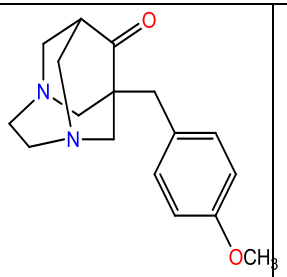
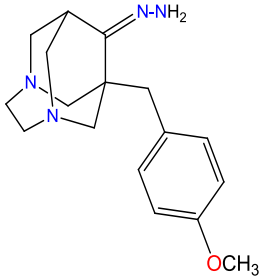
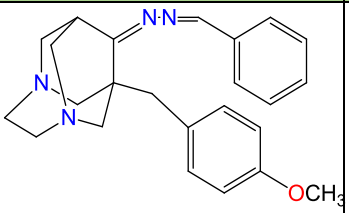
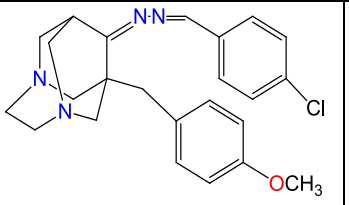
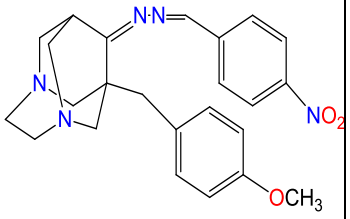
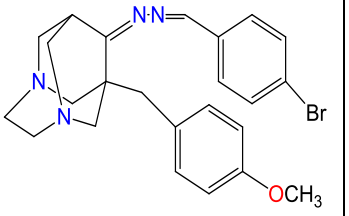
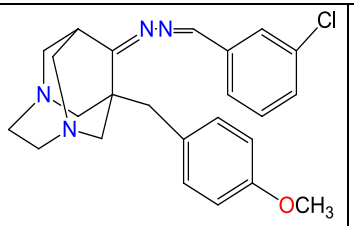
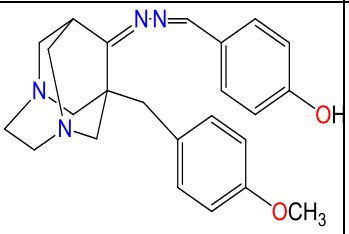
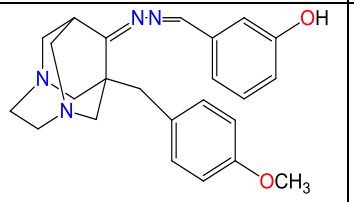
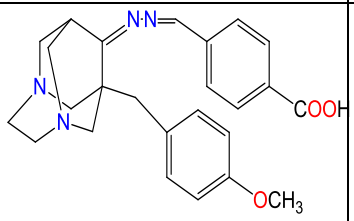
B		1.87s	6.80-6.97 d (4H)	2.32s	3.80s	3.07m	2.58, 2.72 d, *J* = 4.0 Hz , 2.94 ,3.15 d , *J* = 4.0 Hz	-
C		3.09s	6.87-7.21 d *J* (4H), *J* =8.8 Hz	3.15s	3.80s	3.34m	3.27-3.37m ,3.48 d 3.70 d, *J* = 14.0 Hz	5.01 br. s(2H, NH_2)

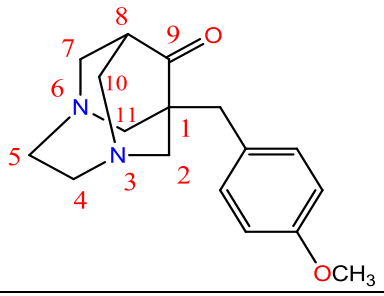
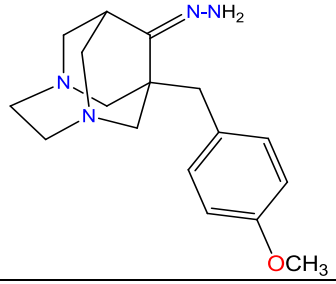
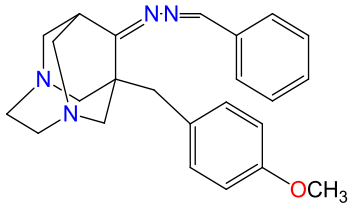
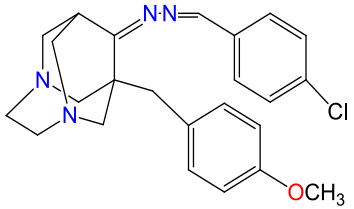
Table (3-3): The Chemical Shifts Values of H-NMR spectrum for Schiff Bases Compounds (D_0-D_7)

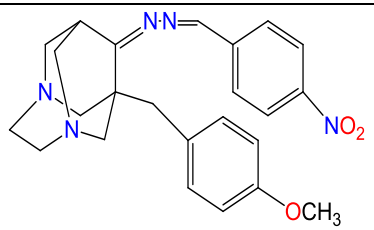
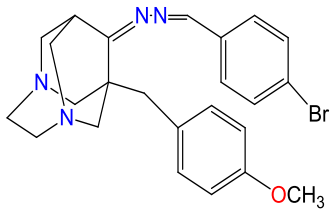
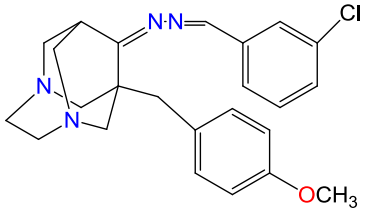
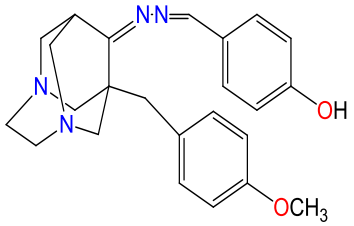
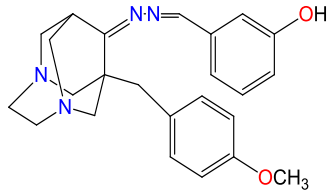
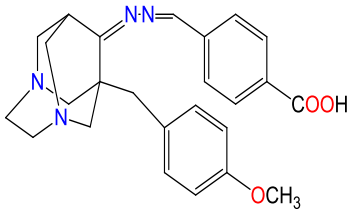
Com. No.	structure	(1H)CH	Ar-H	(2H)CH_2	(3H)OCH_3	(4H)NCH_2CH_2N	8H(4NCH_2)	CH=N (2H)	Other
D_0		2.37s	6.84 -7.42 m(9H)	2.89s	3.81s	3.12m	3.34 d, 3.21 d *J* =14.0 Hz, ,2.92-3.16 m	9.31s	-
D_1		2.94s	6.84- 7.88 m(8H)	2.84 s	3.82s	3.14m	3.08-3.40 m,6.84 -7.88m	9.06s	-
D_2		2.91s	6.83 -7.82 m (8H)	2.80 s	3.81s	3.07 m	3.12 d, *J*= 14.0 Hz, 3.02-3.12 m, 3.26 d, *J*= 14.0	9.00s	-
D_3		2.91s	6.83 -7.82 m (8H)	2.80 s	3.81s	3.07m	3.02-3.12 m, 3.12 d, 3.26 d, *J*= 14.0 Hz	9.00s	-

D_4		2.78s	7.09 -7.73 m (8H)	2.83 s	3.81s	3.04 m	2.94-3.30 m	9.38s	-
D_5		2.74s	6.79 -7.27 m (8H)	2.37 s	3.84s	3.29 m	3.19-3.82 m	8.98s	5.85 br. s (1H, OH)
D_6		2.74s	6.79 -7.27 m (8H)	2.37 s	3.84s	3.29 m	3.19-3.82 m (8H)	8.98s	5.73 br. s (1H, OH)
D_7		1.89s	6.88 -7.53 m (8H)	2.85 s	3.81s	3.03 m	2.82-3.69 m	9.03s	12.04 s (1H, OH)

D= doublet M= multiplet S= singlet

Table (3-4): The ^{13}C- NMR data of Compounds (B-D_7) (75 MHz, $CDCl_3$)

Com.No.	structure	C^9	Ph C=N	$\underline{C}OCH_3$	$\underline{C}$-Ph	$C^{2,10}$	$C^{4,5}$	$C^{7,11}$	$O\underline{C}H_3$	C^1	C^8	$\underline{C}H_2Ph$
B		214	-	185	131,129,113	61	57	56	55	48	45	52
C		158	-	153	139,130,126	64	60	57	65	55	52	36
D_0		163	158	153	139,138,133,130,129,128 ,121	64	60	57	66	55	52	39
D_1		164	162	158	149,141,138,133,128, 128,121	60	57	55	64	50	52	33

D_2		163	158	153	145,139,136,133,130,128 ,126	46	60	57	68	55	53	39
D_3		177	169	162	143,139,137,133,130,128 ,126,121	64	60	57	67	55	53	39
D_4		169	162	160	148,141,136,133,130,128 ,126	64	60	57	68	55	53	33
D_5		162	159	153	146,139,136,130,128,126 ,121	64	60	57	68	55	52	39
D_6		166	163	158	143,141,136,130,129,126 ,122	61	60	57	67	55	50	30
D_7		177	162	157	146,140,136,133,130,128 ,126,121	62	60	57	67	55	49	32

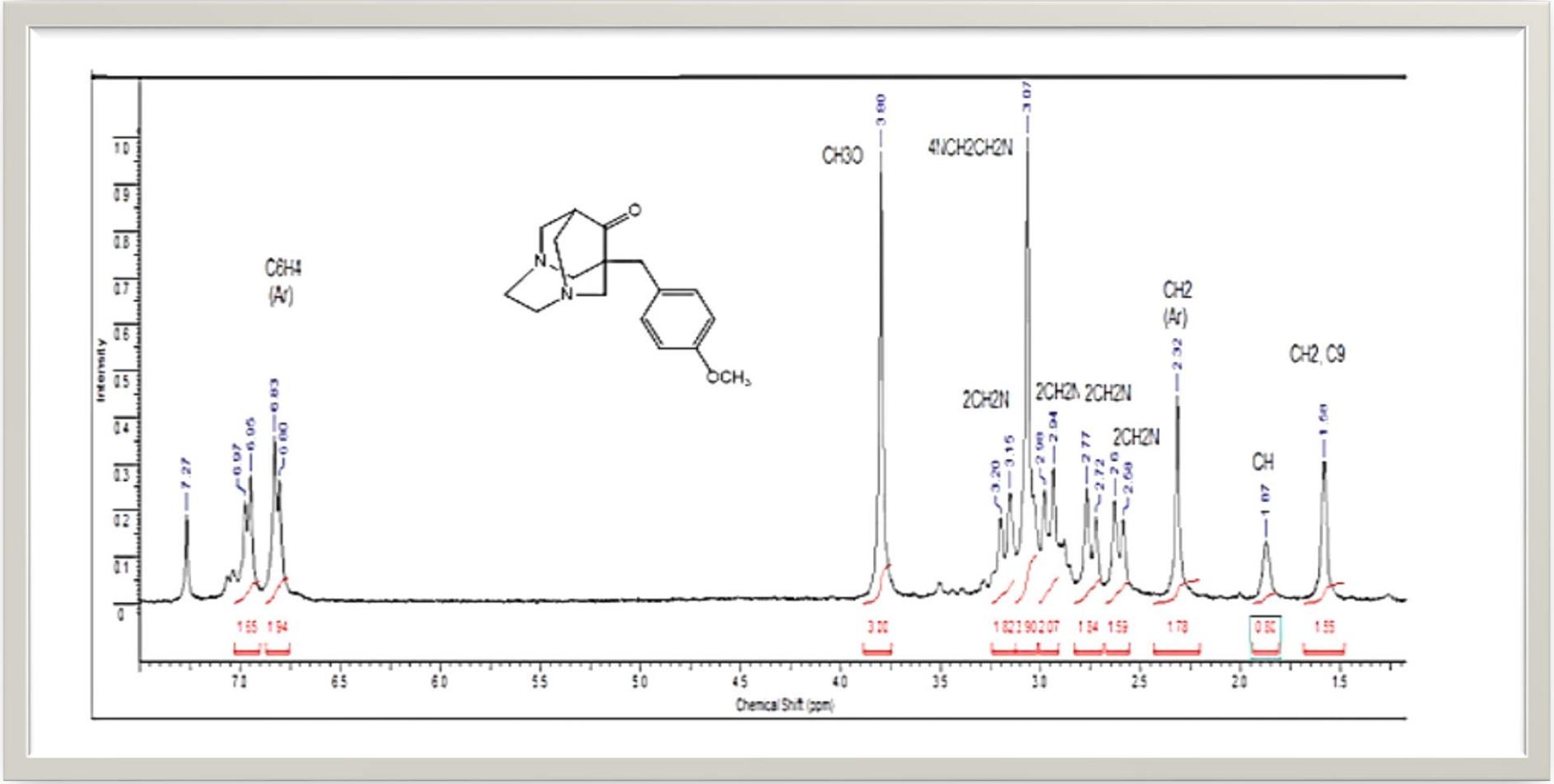


Figure (3-13) ^{1}H-NMR Spectrum of Compound (B)

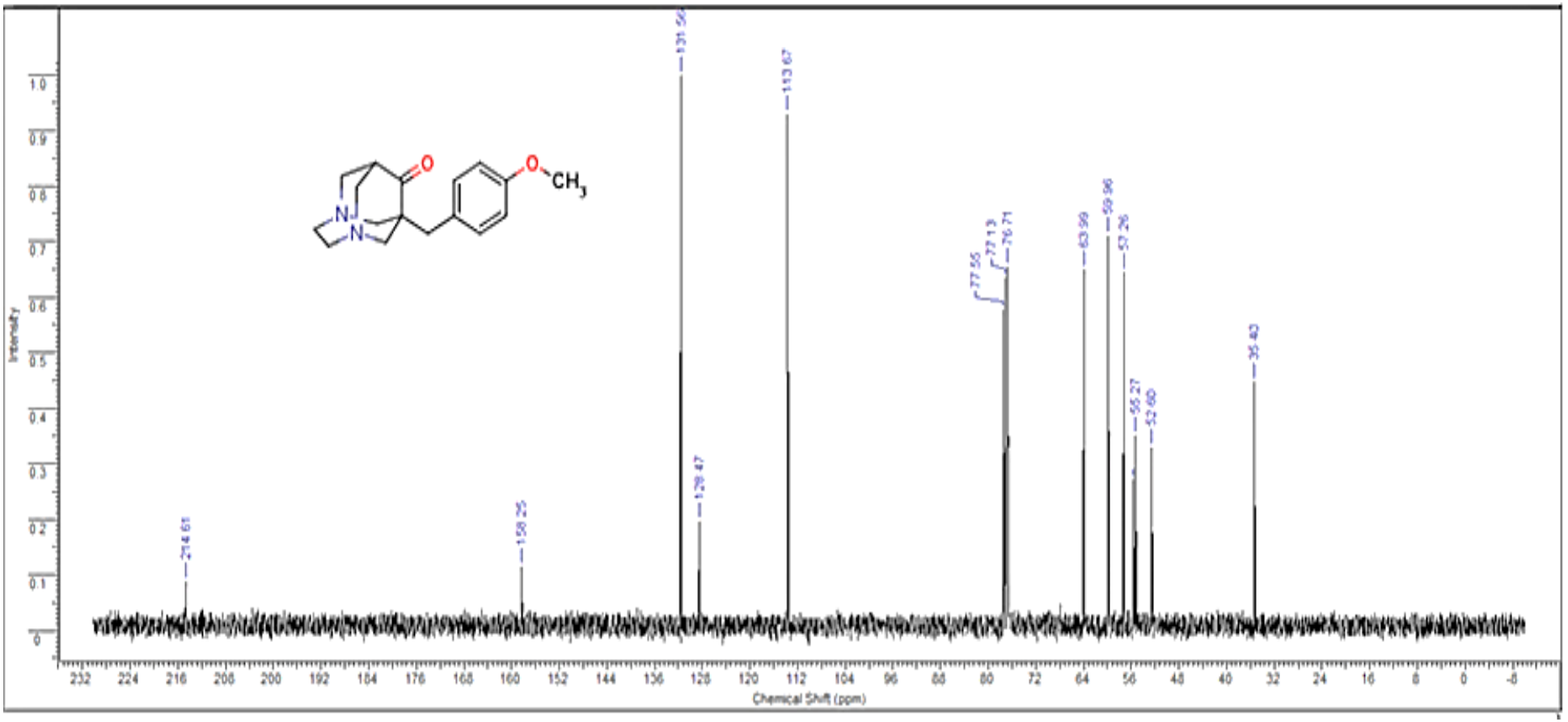


Figure (3-14) ^{13}C-NMR Spectrum of Compound (B)

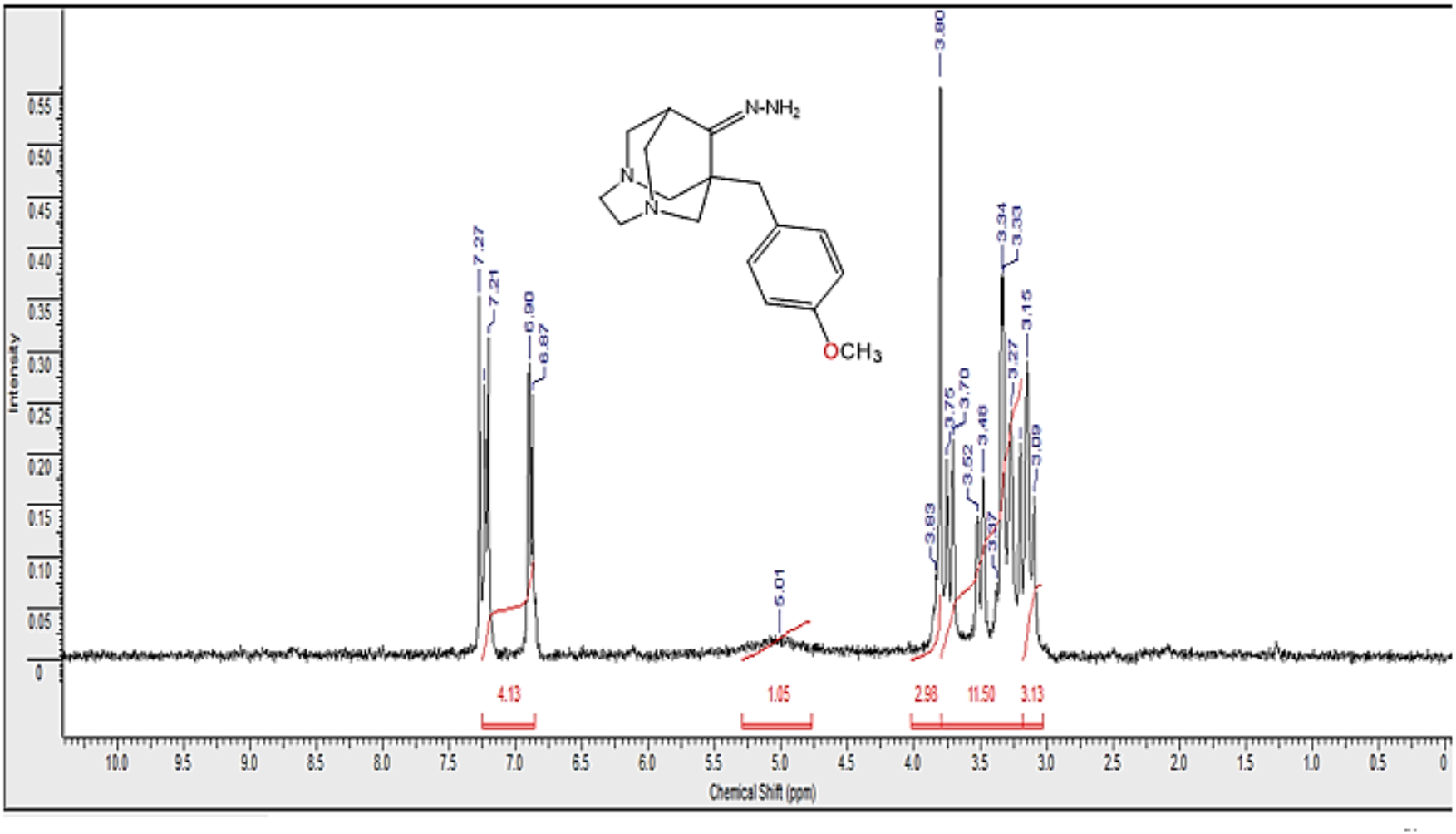


Figure (3-15) ^{1}H-NMR Spectrum of Compound (C)

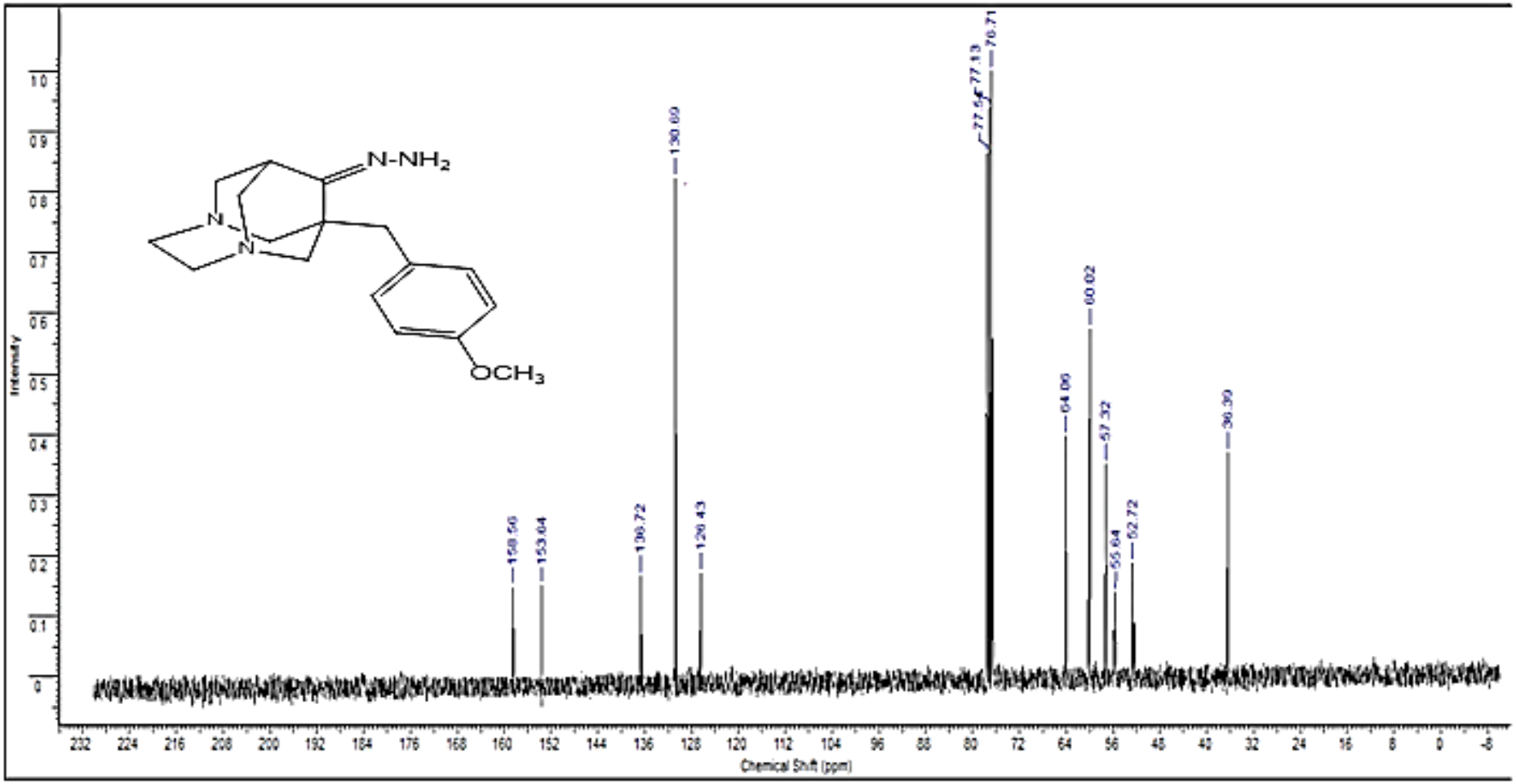


Figure (3-16) ^{13}C-NMR Spectrum of Compound (C)

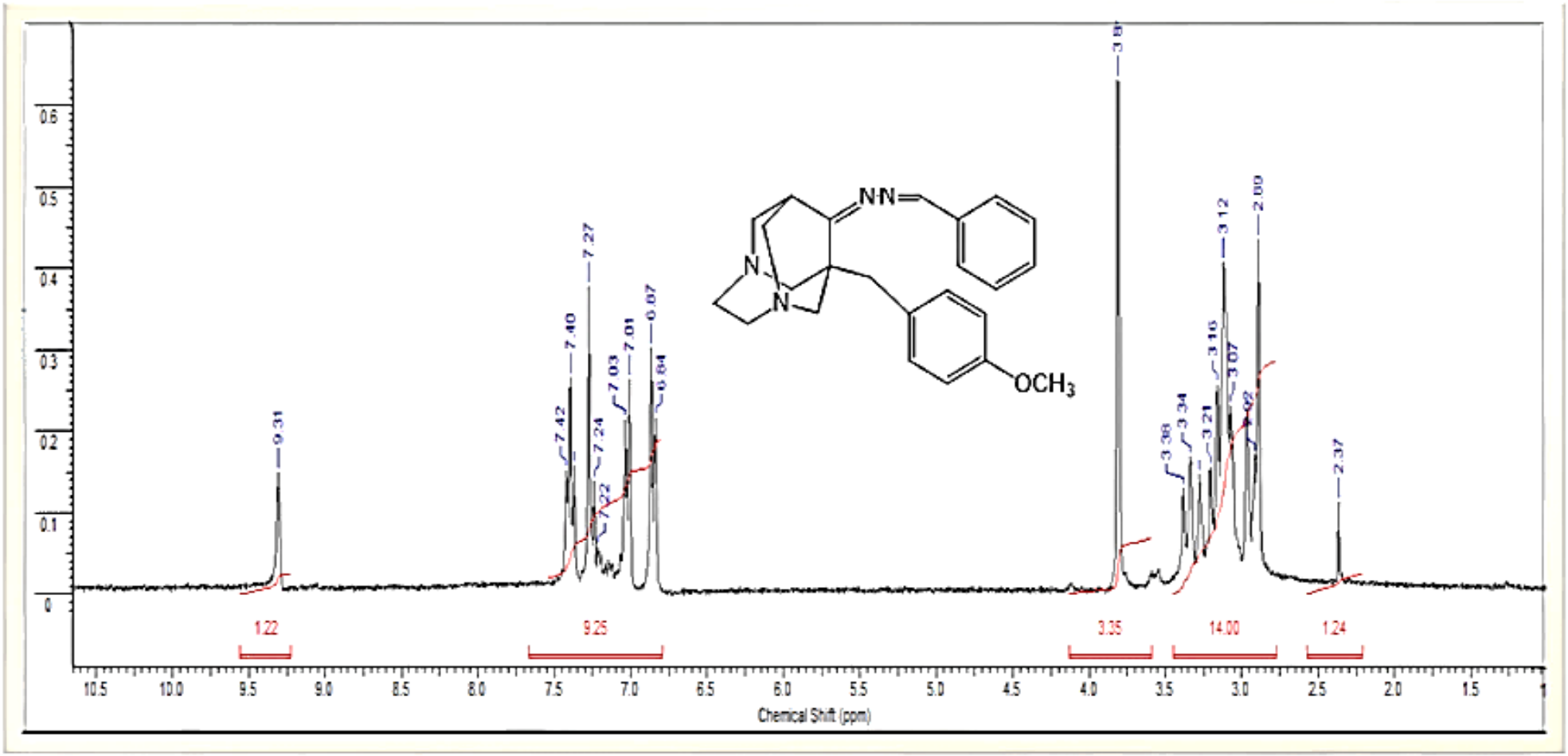


Figure (3-17) ^{1}H-NMR Spectrum of Compound (D_0)

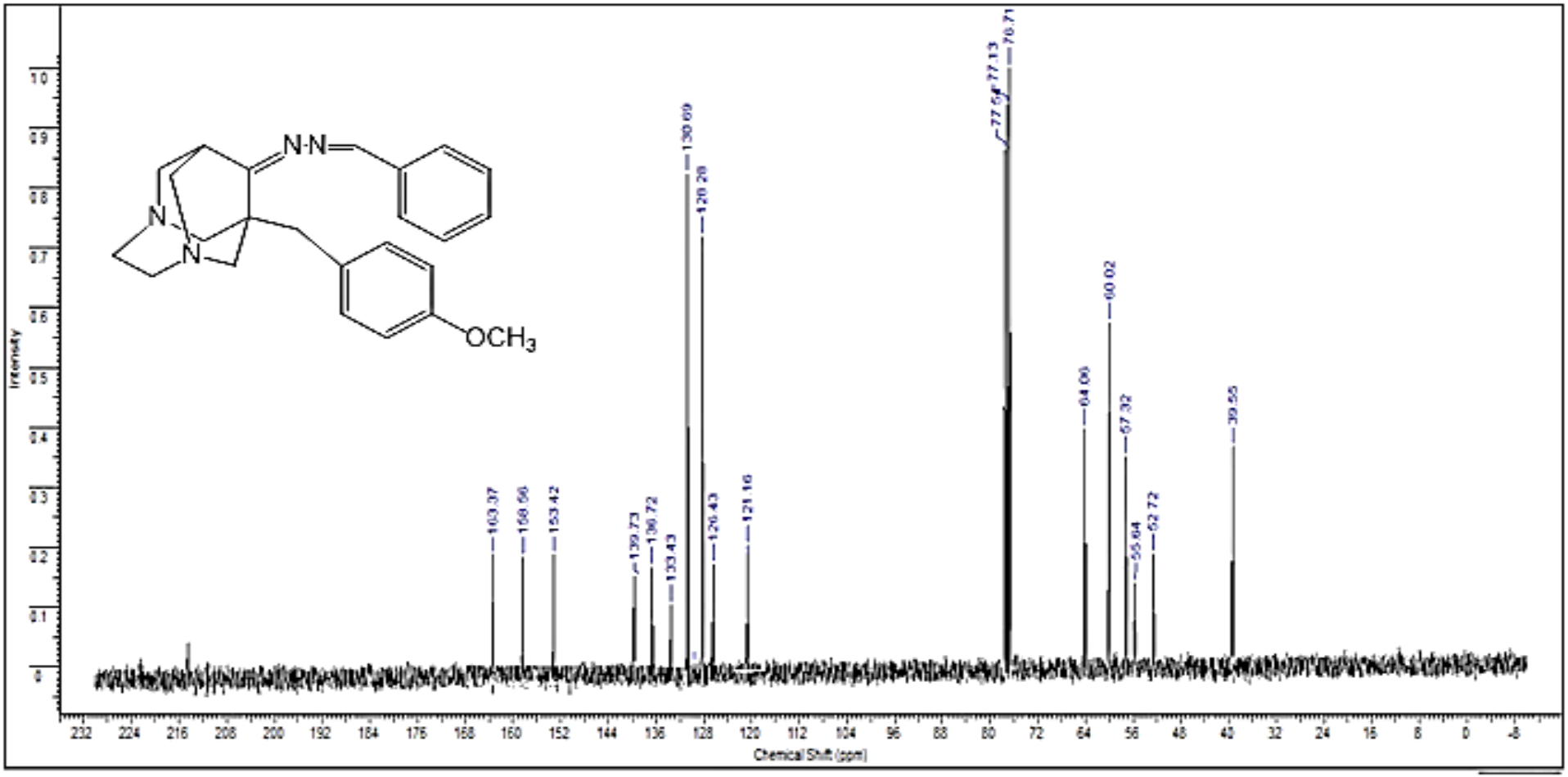


Figure (3-18) ^{13}C-NMR Spectrum of Compound (D_0)

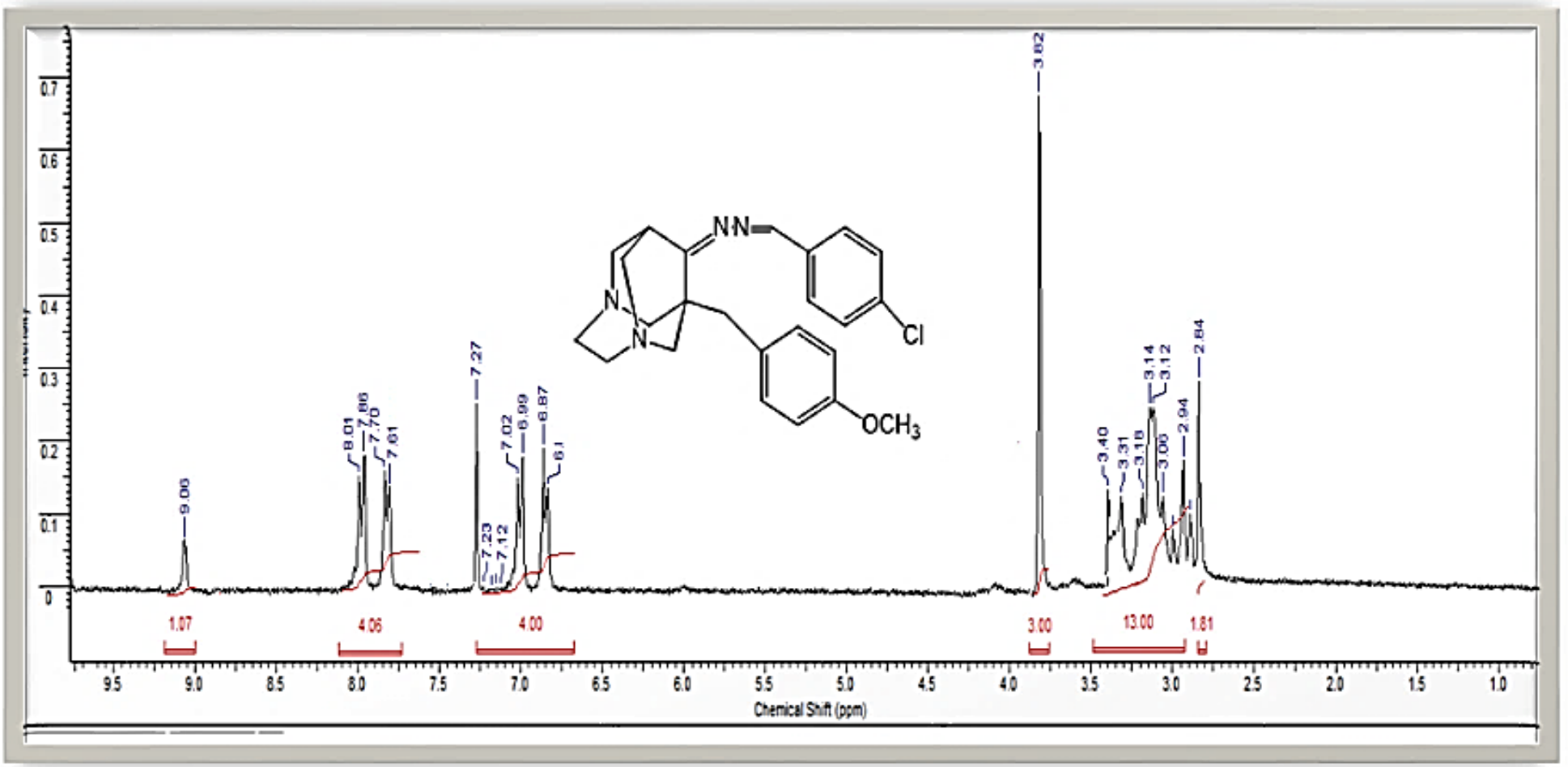


Figure (3-19) ^{1}H-NMR Spectrum of Compound (D_1)

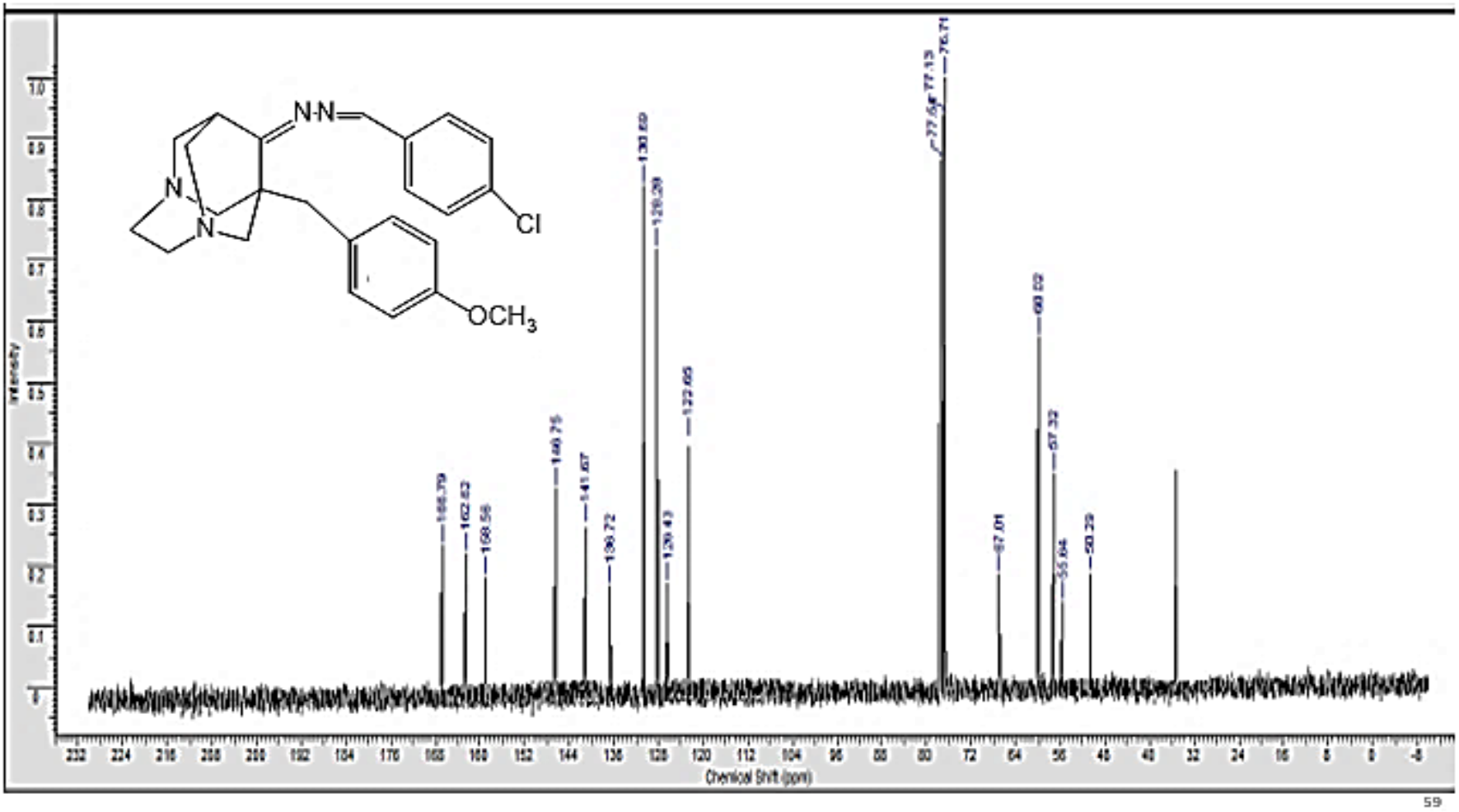


Figure (3-20) ^{13}C-NMR Spectrum of Compound (D_1)

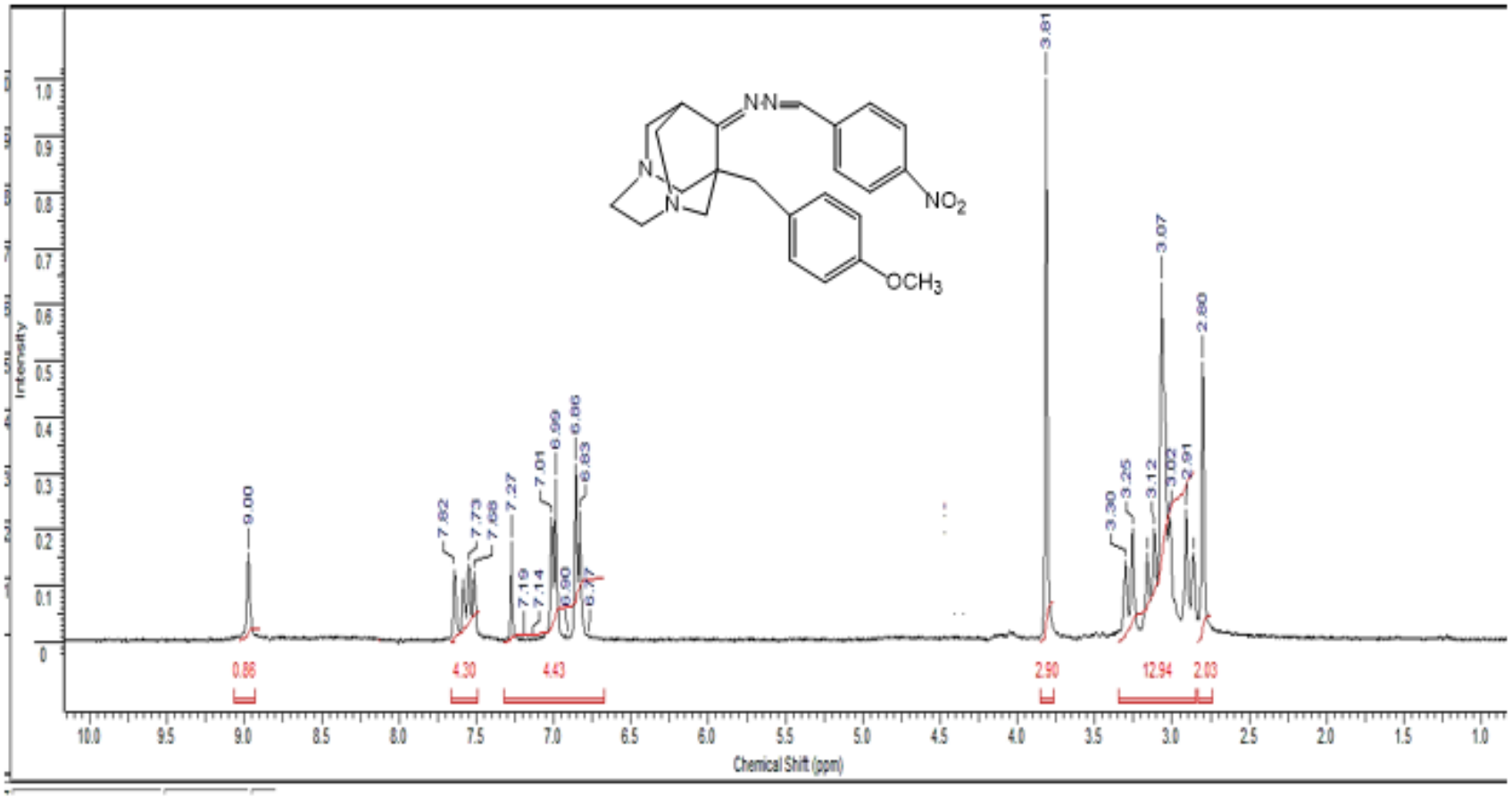


Figure (3-21) ^{1}H-NMR Spectrum of Compound (D_2)

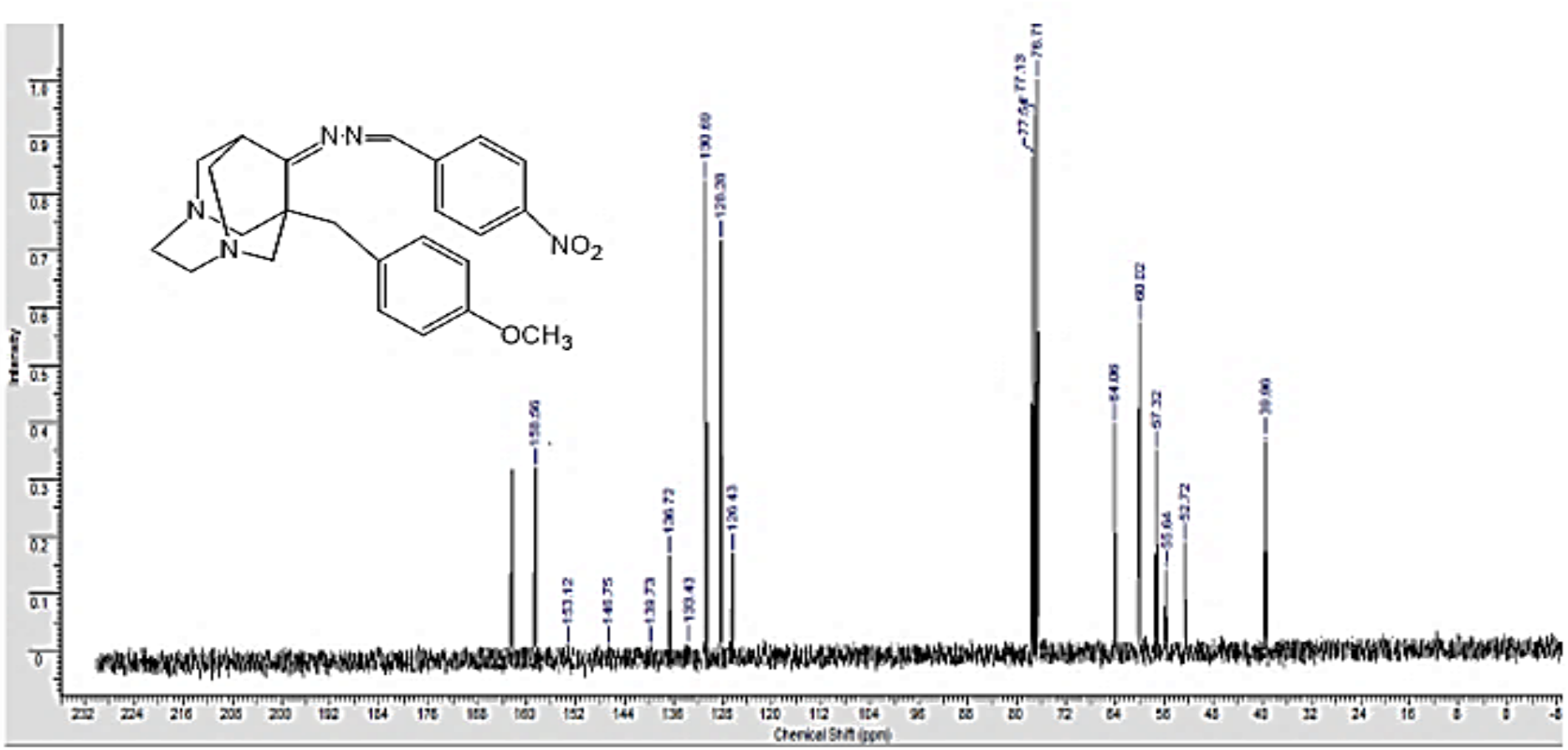


Figure (3-22) ^{13}C-NMR Spectrum of Compound (D_2)

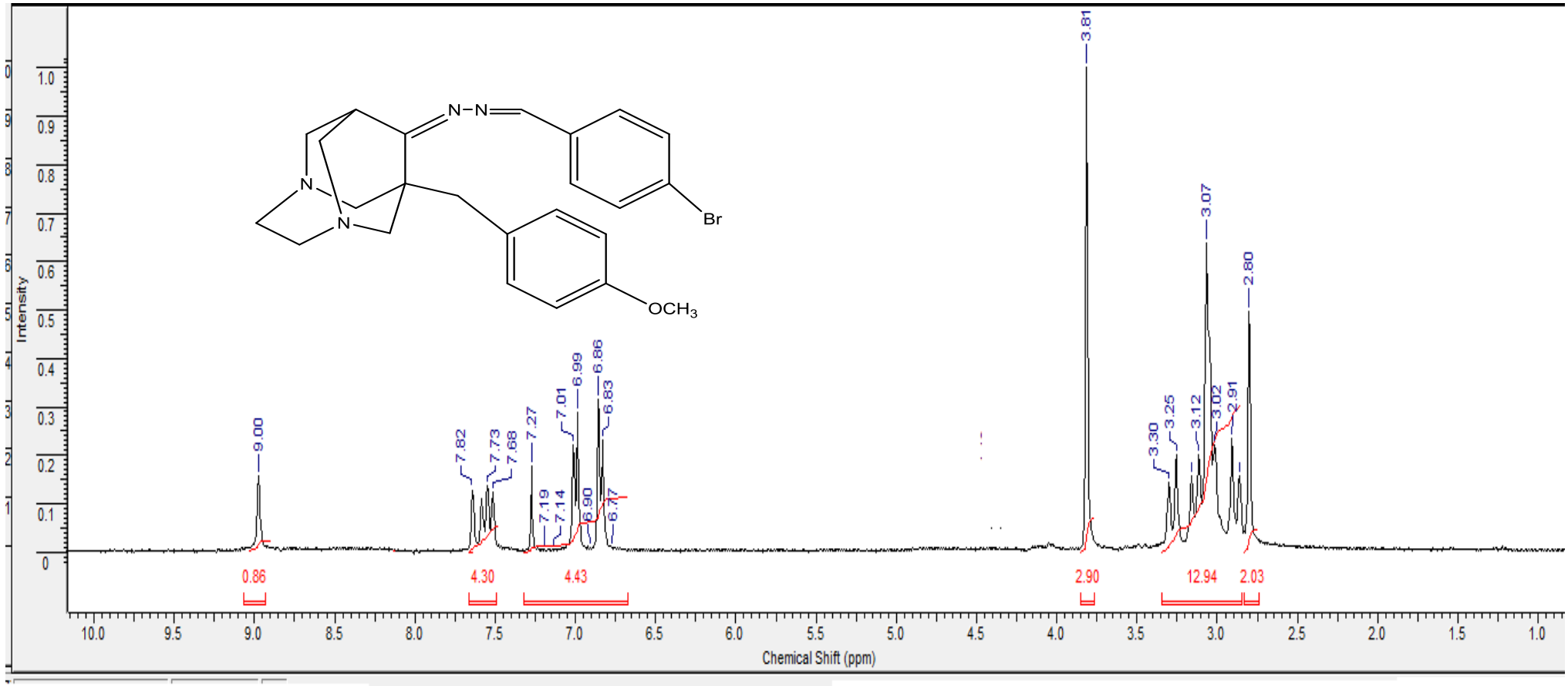


Figure (3-23) ^{1}H-NMR Spectrum of Compound (D_3)

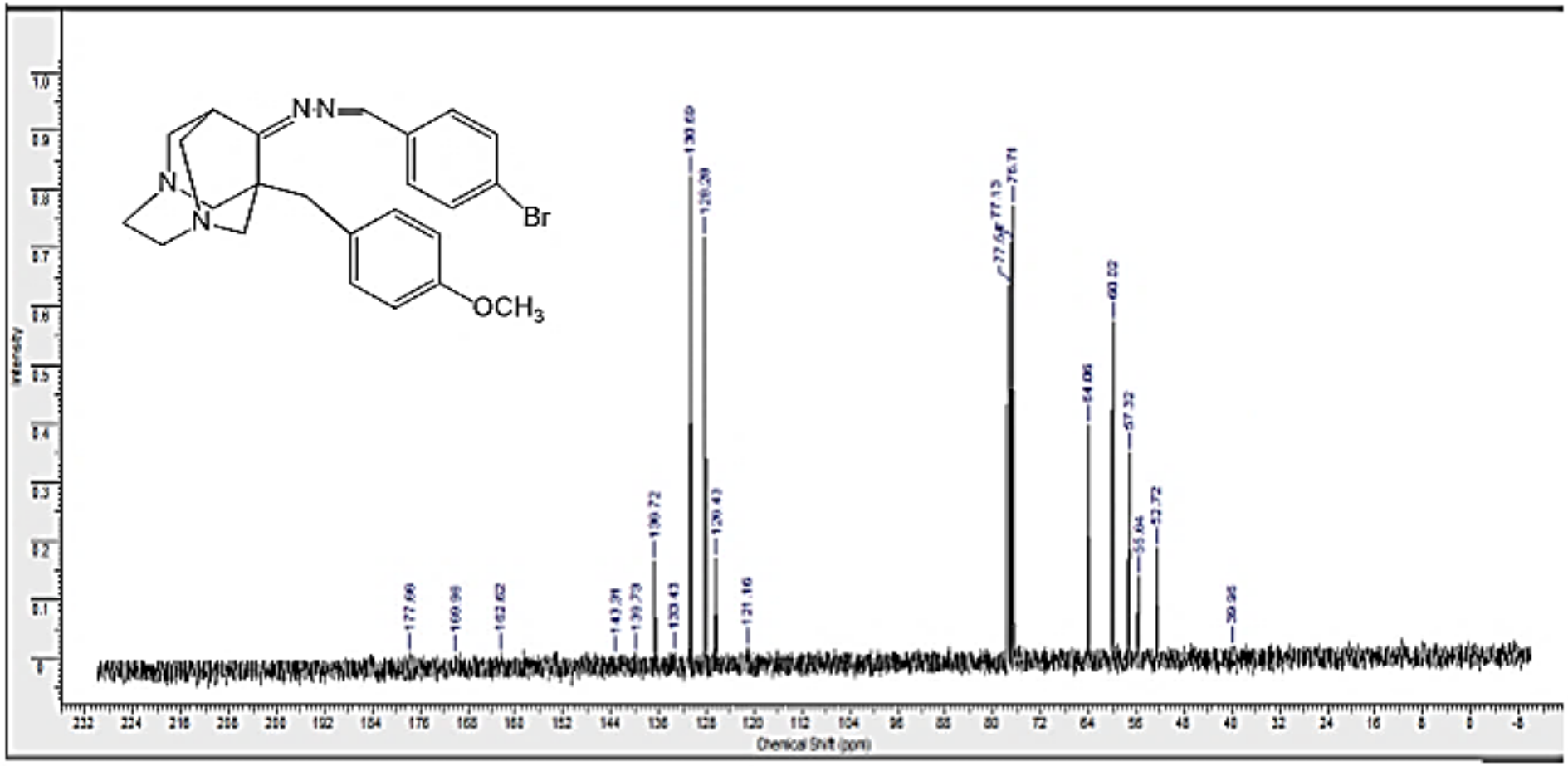


Figure (3-24) ^{13}C-NMR Spectrum of Compound (D_3)

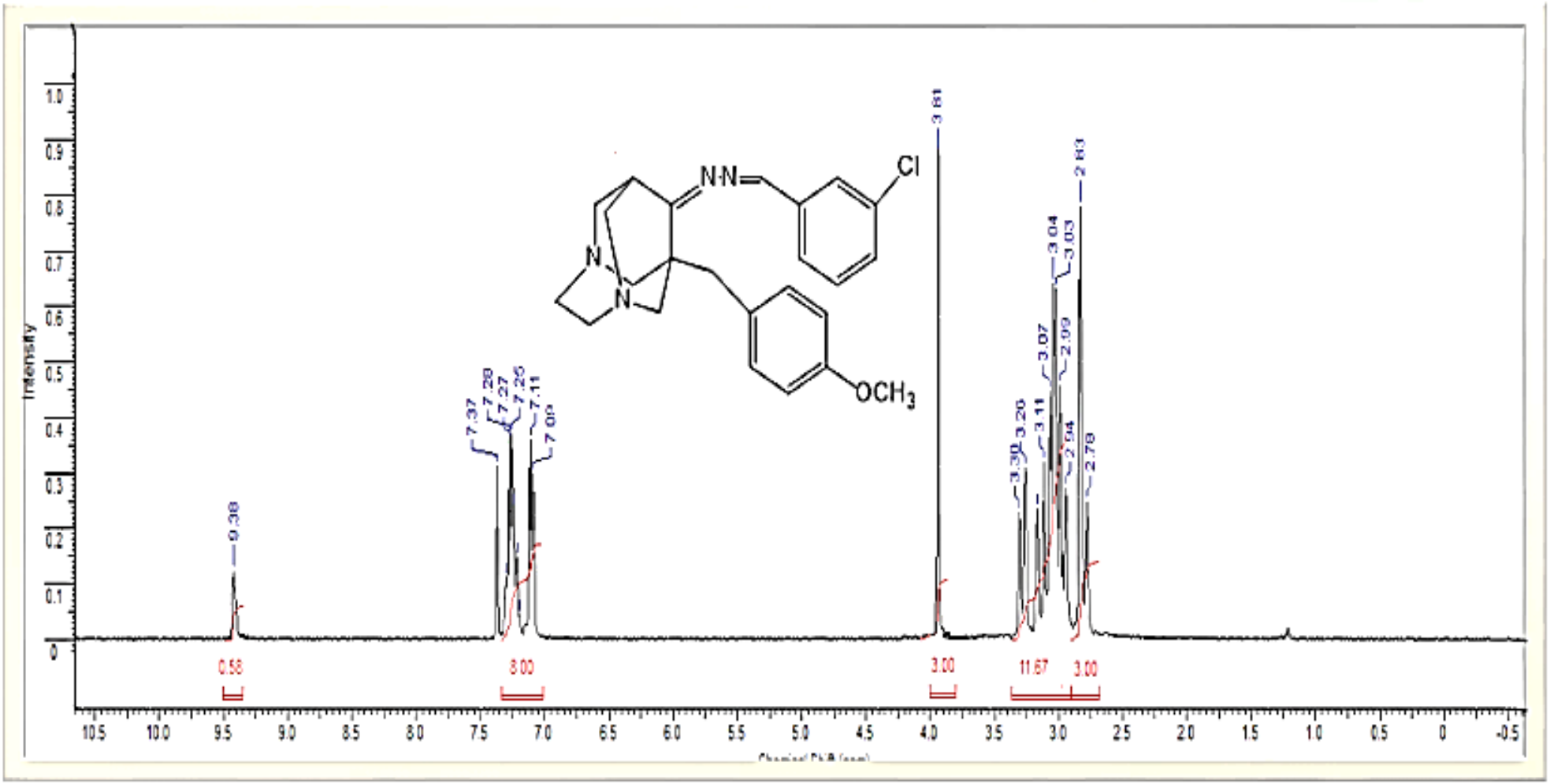


Figure (3-25) ^{1}H-NMR Spectrum of Compound (D_4)

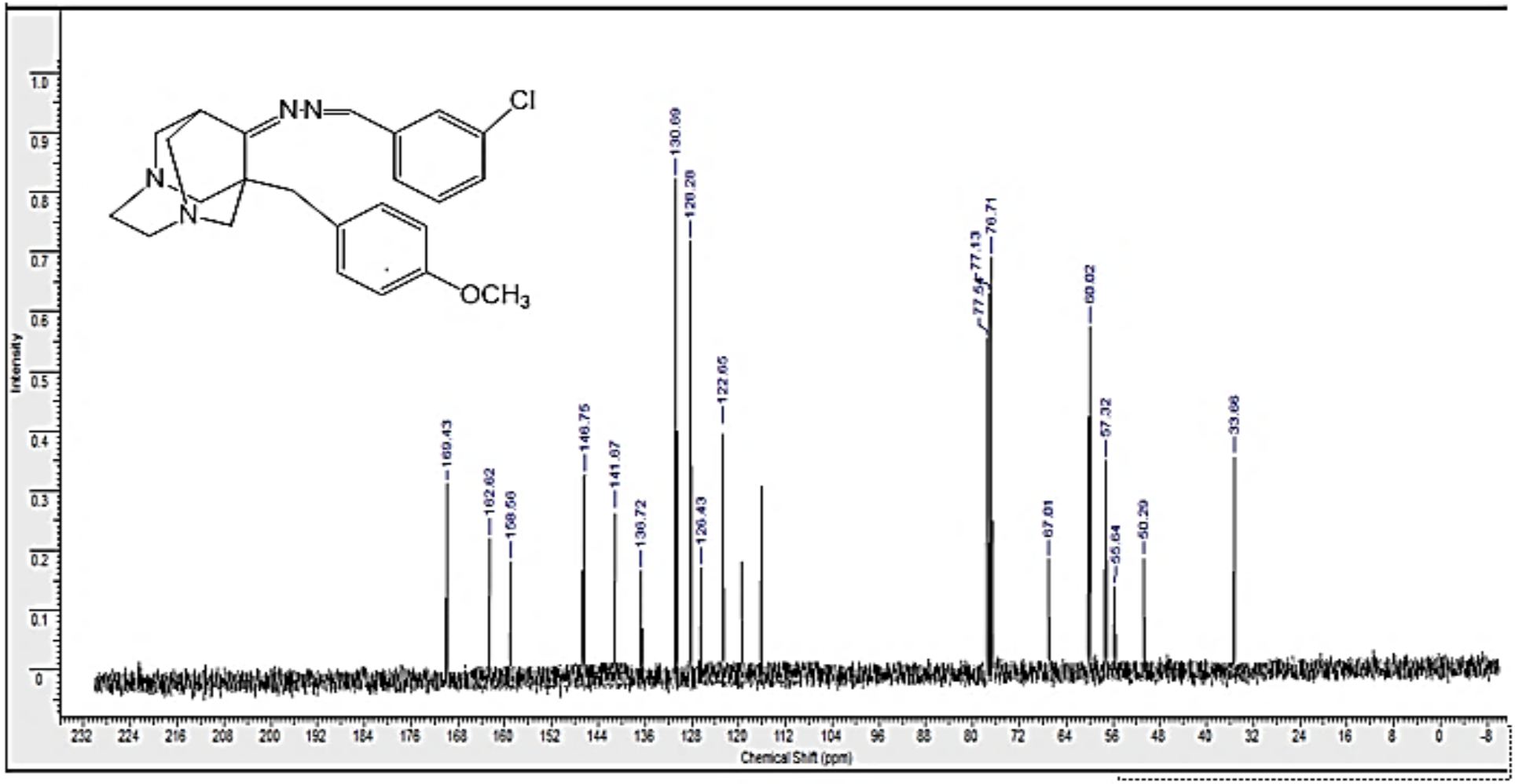


Figure (3-26) ^{13}C-NMR Spectrum of Compound (D_4)

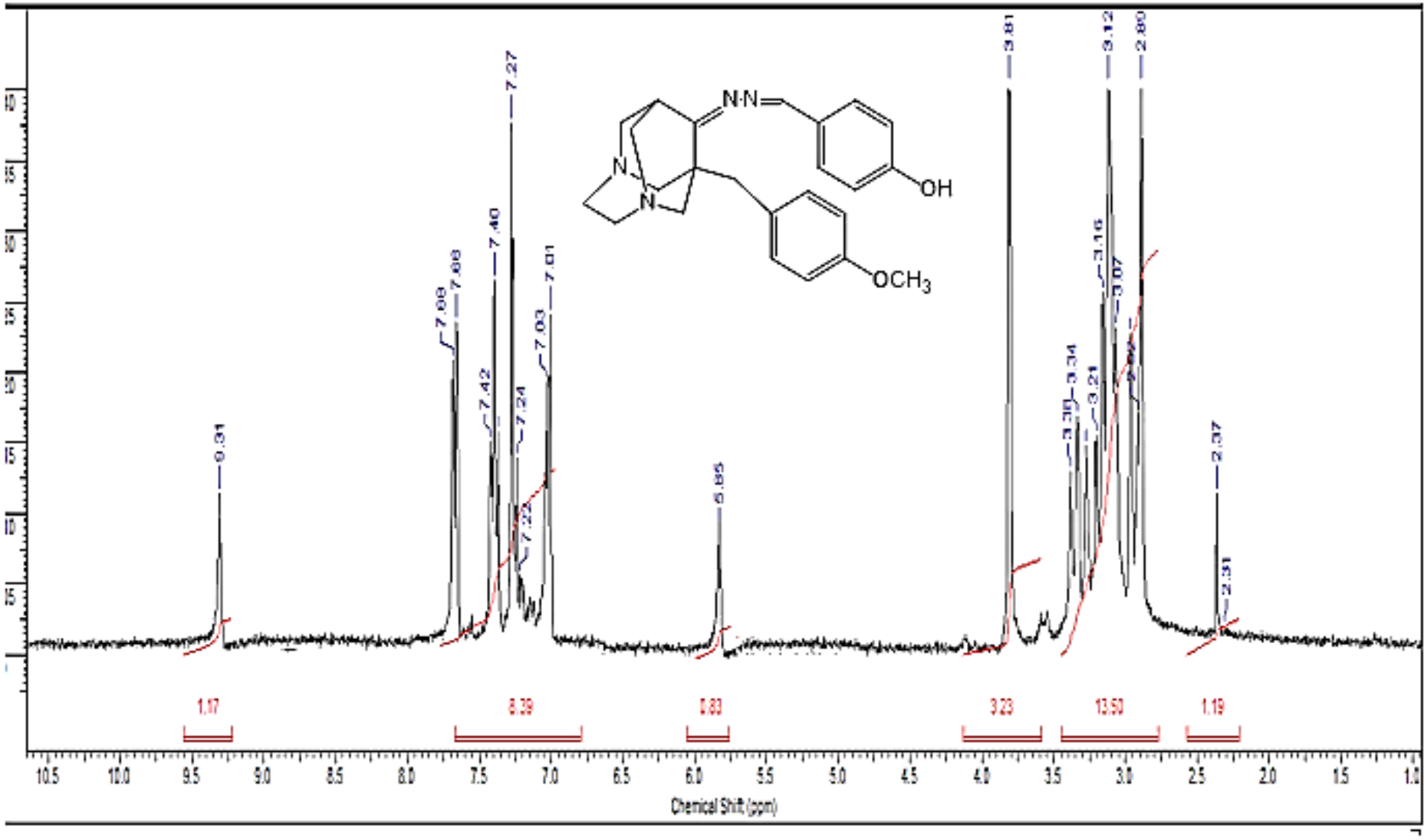


Figure (3-27) ^{1}H-NMR Spectrum of Compound (D_5)

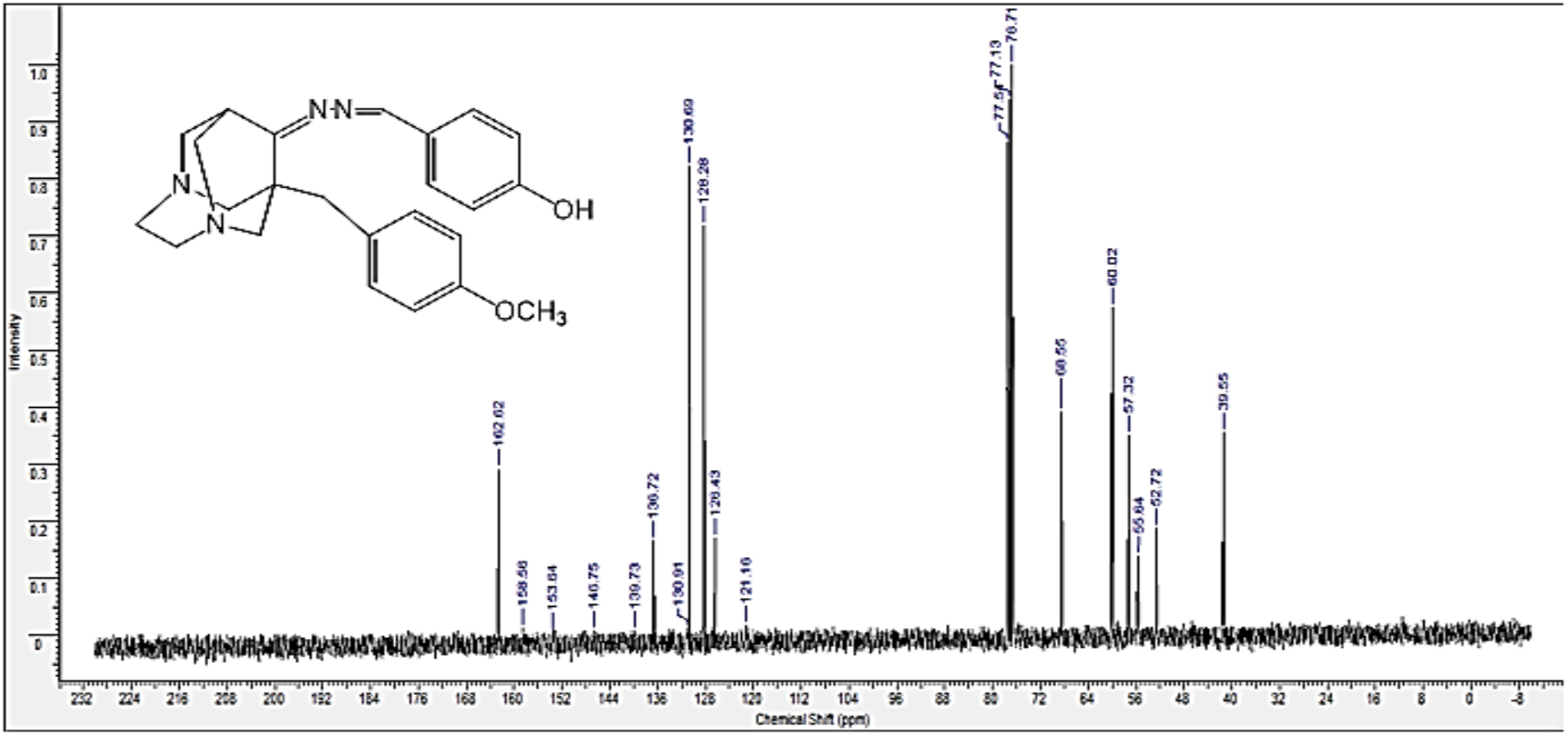


Figure (3-28) ^{13}C-NMR Spectrum of Compound (D_5)

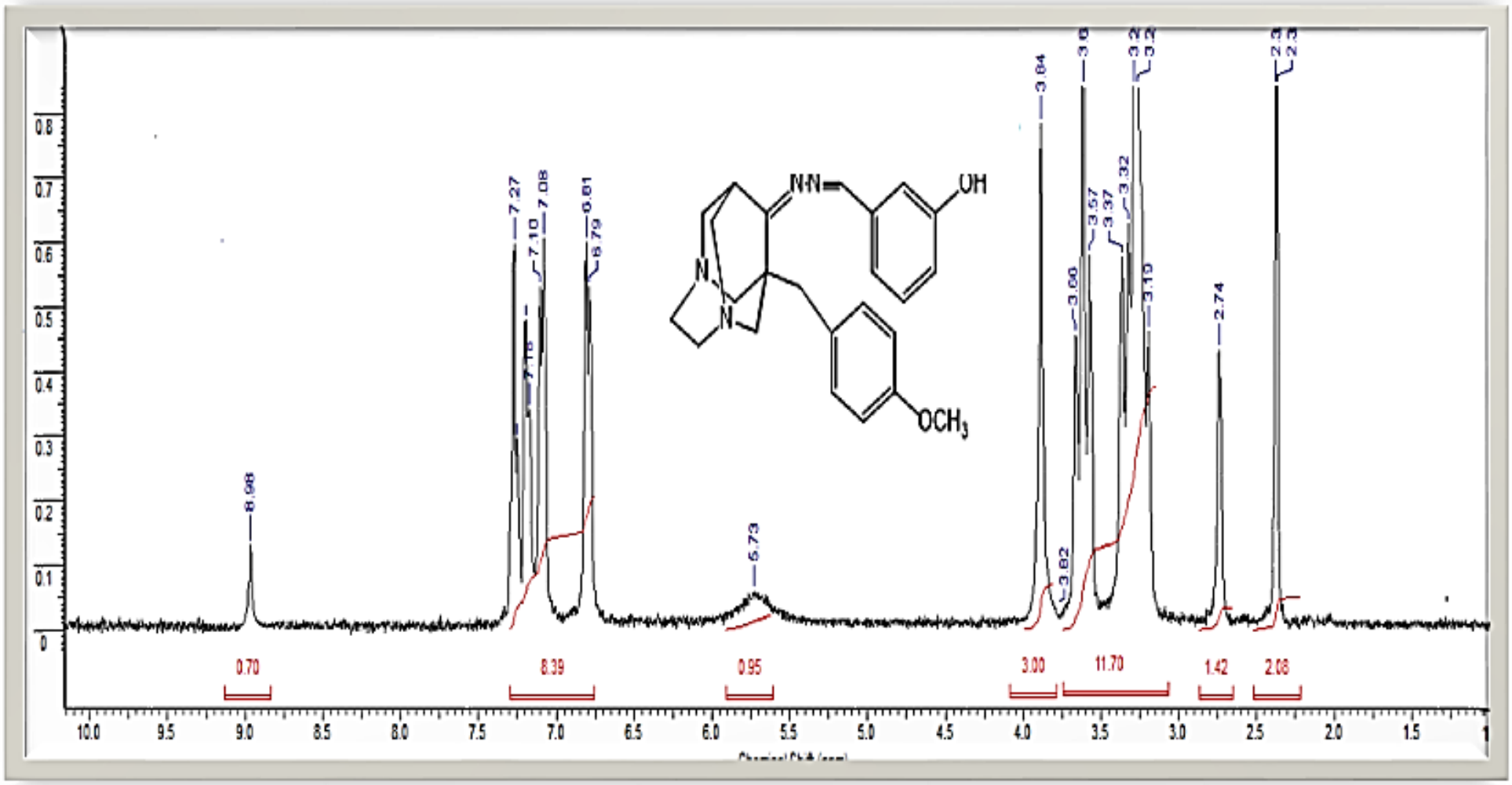


Figure (3-29) ^{1}H-NMR Spectrum of Compound (D_6)

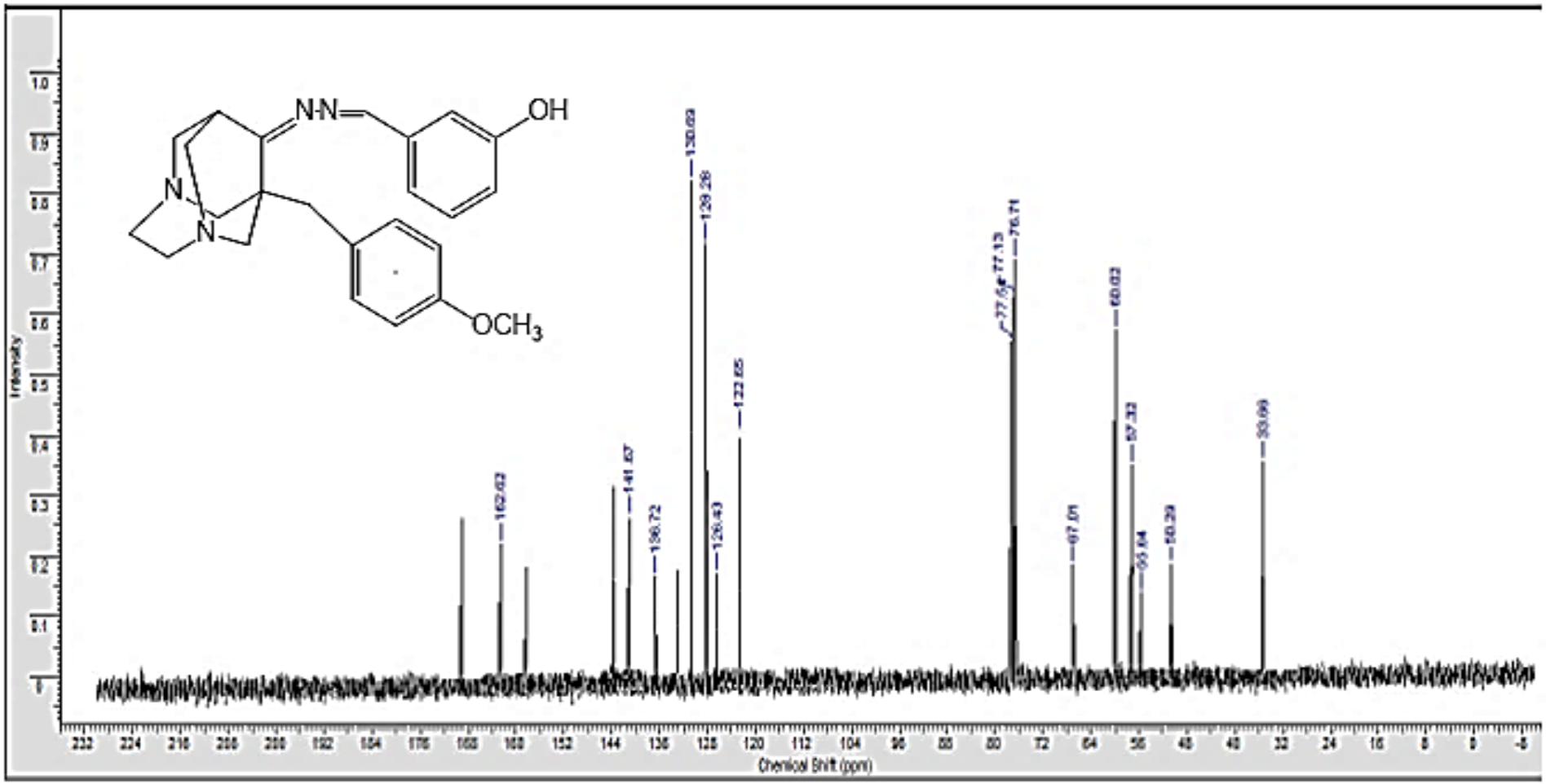


Figure (3-30) ^{13}C-NMR Spectrum of Compound (D_6)

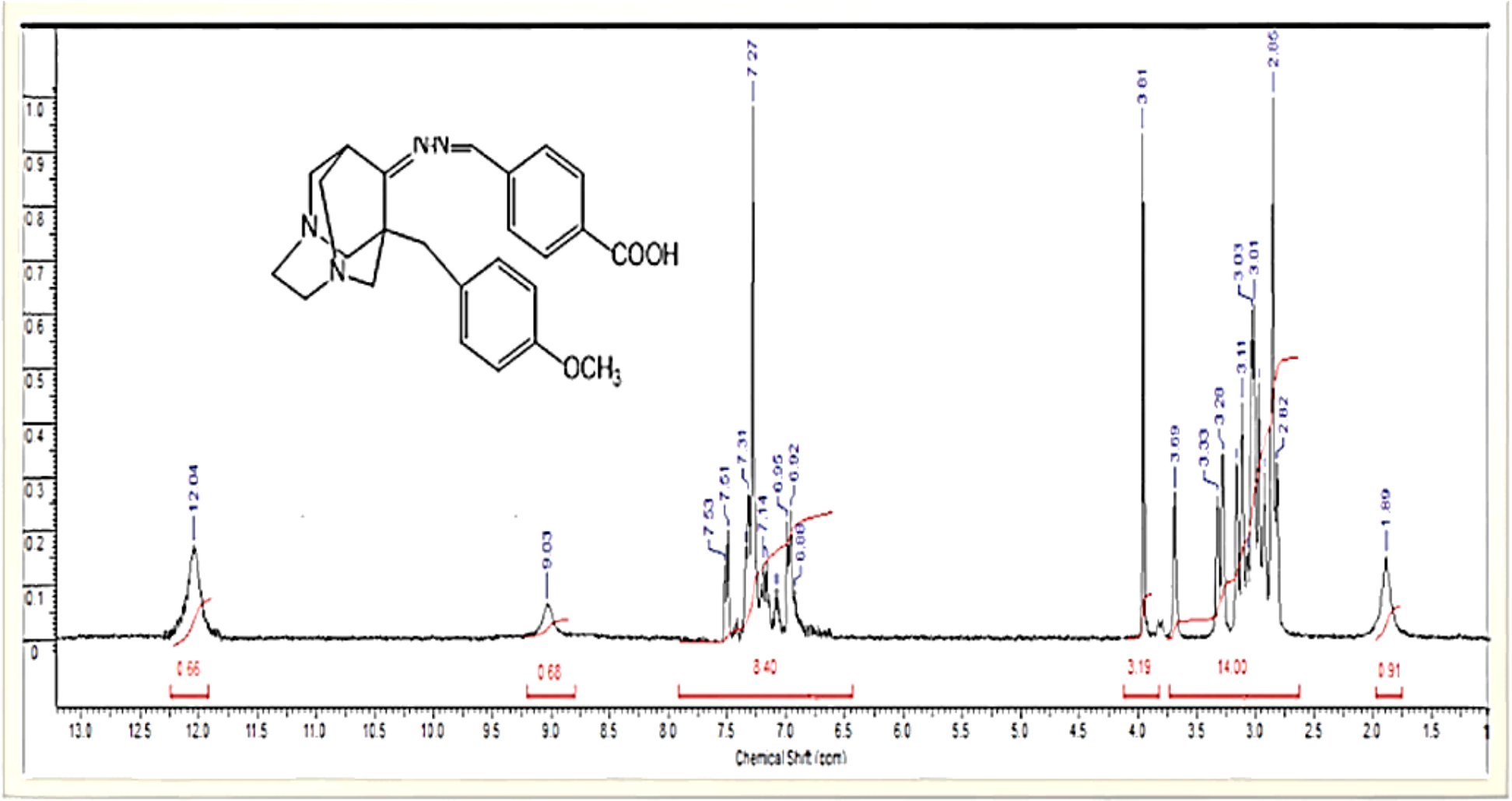


Figure (3-31) ^{1}H-NMR Spectrum of Compound (D_7)

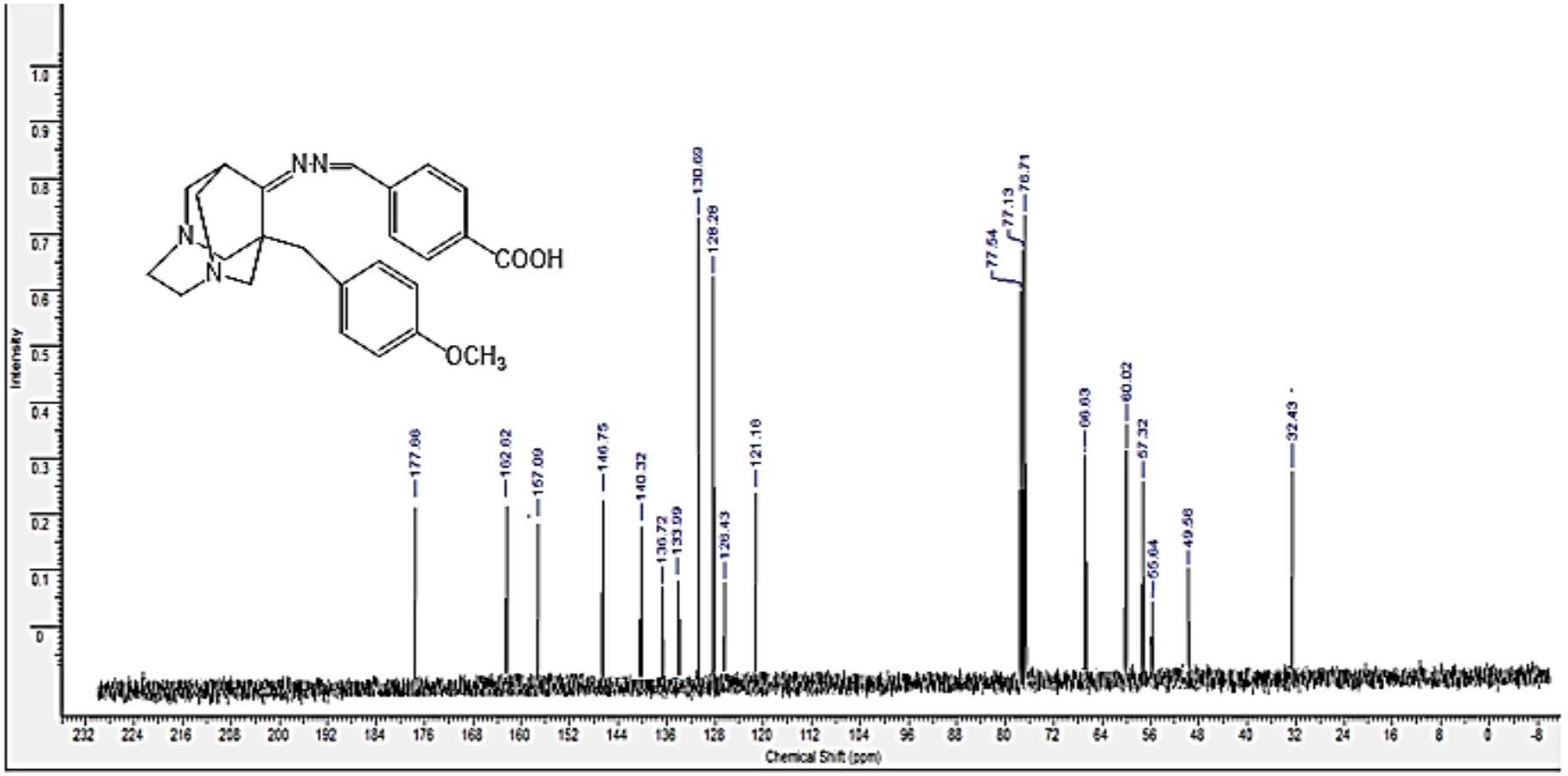


Figure (3-32) ^{13}C-NMR Spectrum of Compound (D_7)

3.2.3. Mass Spectra of the Synthesized Compounds (B-D_7)

The results of the mass spectrometry of the prepared compounds showed that the molecular ion peaks of the Schiff basses compounds and Diazahomoadamantane derivatives match the chemical calculations of the molecular weight. This match proof of the validity of the prepared structures. Mass spectra of compounds obtained contain intensive and the most intensive peaks of ions $^{+}$[M].The fragmentation of $^{+}$[M] ions of compounds result in the formation of common for the prepared structures ions .Molecular ion peak ($^{+}$[M] 286) in the mass spectrum of compound(B) and ($^{+}$[M] 300) in the mass spectrum of compound (C) is mostly fragmented as a result of skeleton degradation and cation production at m/z 72 and 57 and (m/z 284 NH_2 in compound C) .The other directions of $^{+}$[M] decomposition in these compounds are governed by the nature of the functional substituent in the position **C_9** of the Schiff bases. All mass spectra of the synthesized compounds appeared the molecular ion peak at (m/z) value is equal to the corresponding exact mass as indicated in Table (3-5).

Table (3-5): The Exact Mass and Measured Molecular Ion Mass (m/z) of the Synthesized Compounds(B-D_7)

Com. No.	Chemical Formula	Molecular weight g/mole	Exact Mass	Molecular ion Mass (m/z)
B	$C_{17}H_{22}N_2O_2$	286.38	286.17	286
C	$C_{17}H_{24}N_4O$	300.41	300.20	300
D_0	$C_{24}H_{28}N_4O$	388.52	388.23	388
D_1	$C_{24}H_{27}CLN_4O$	422.96	422.19	422
D_2	$C_{24}H_{27}N_5O_3$	433.51	433.21	433
D_3	$C_{24}H_{27}BrN_4O$	467.41	466.14	467
D_4	$C_{24}H_{27}CLN_4O$	422.96	422.19	422
D_5	$C_{24}H_{28}N_4O_2$	404.51	404.22	404
D_6	$C_{24}H_{28}N_4O_2$	404.51	404.22	404
D_7	$C_{25}H_{28}N_4O_3$	432.52	432.22	432

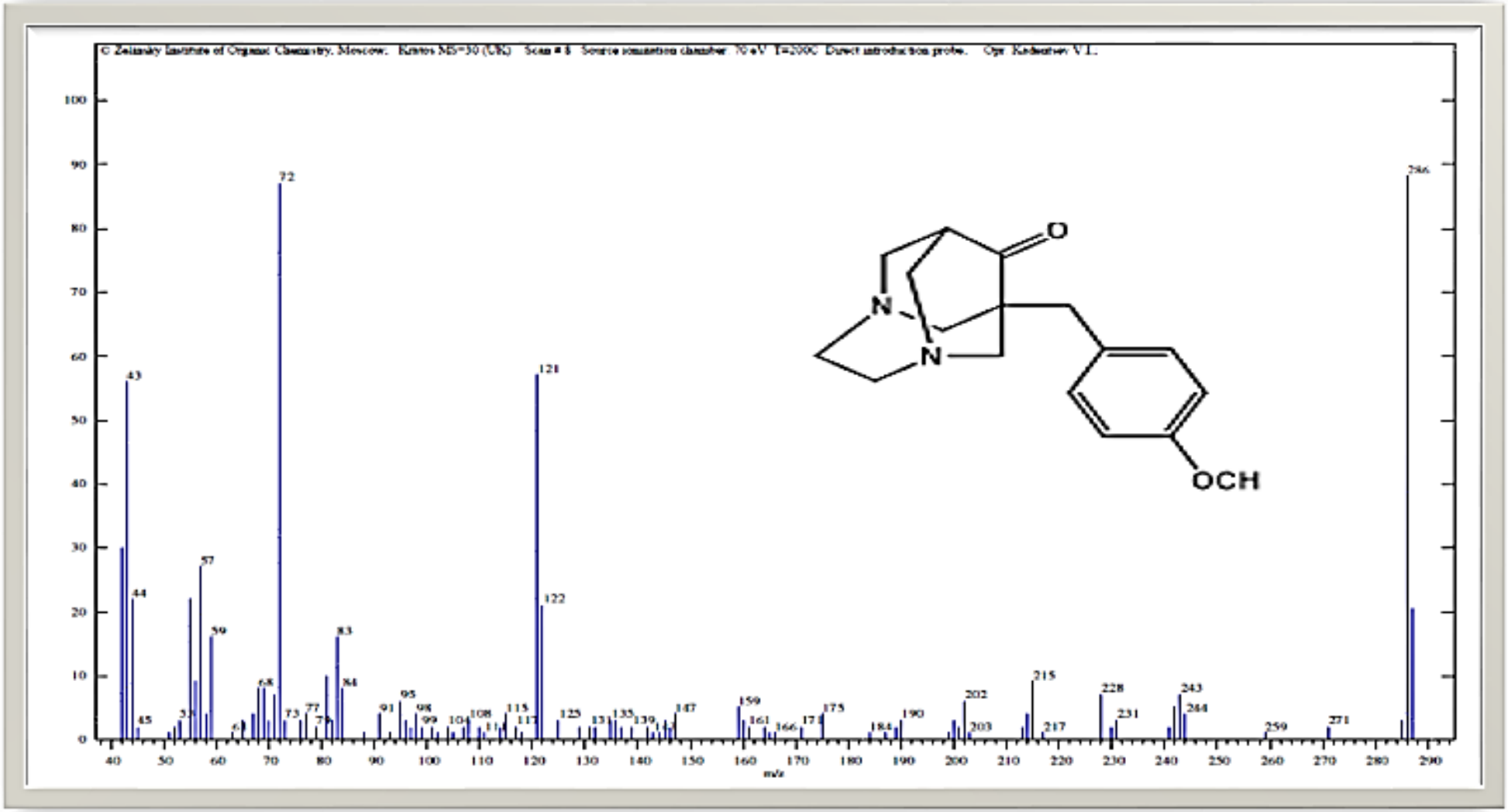


Figure (3-33) Mass Spectra of Compound (B)

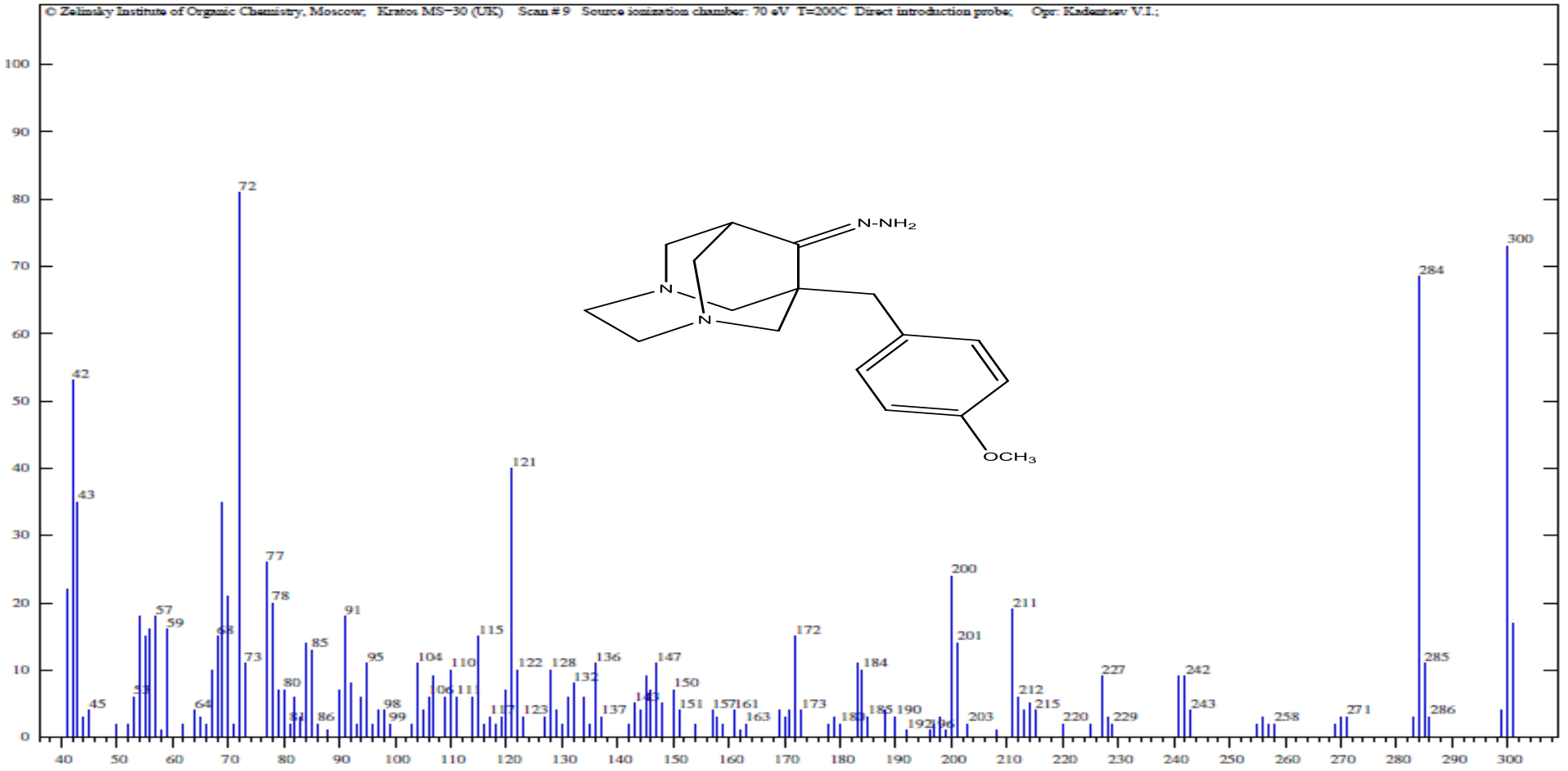


Figure (3-34) Mass Spectra of Compound (C)

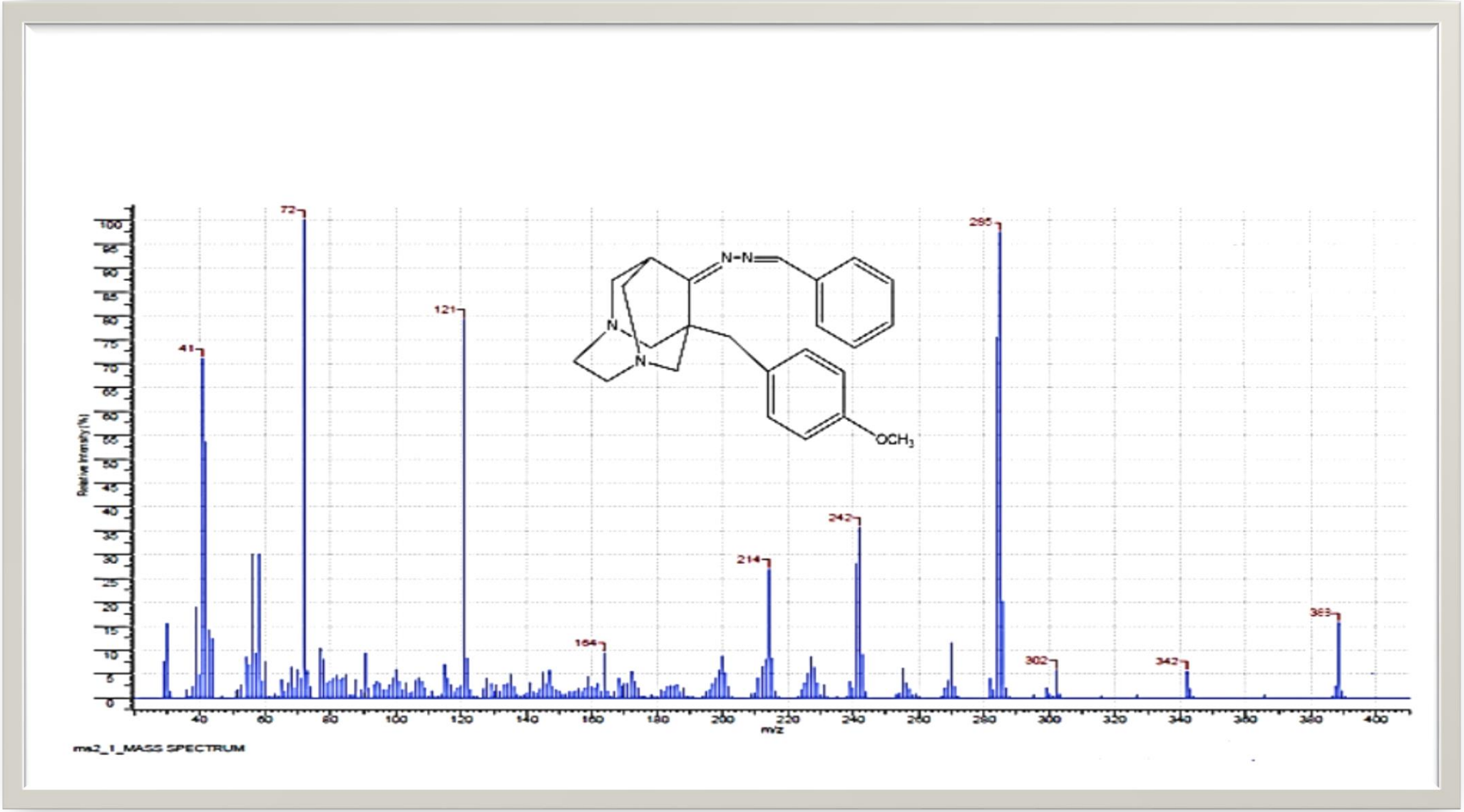


Figure (3-35) Mass Spectra of Compound (D_0)

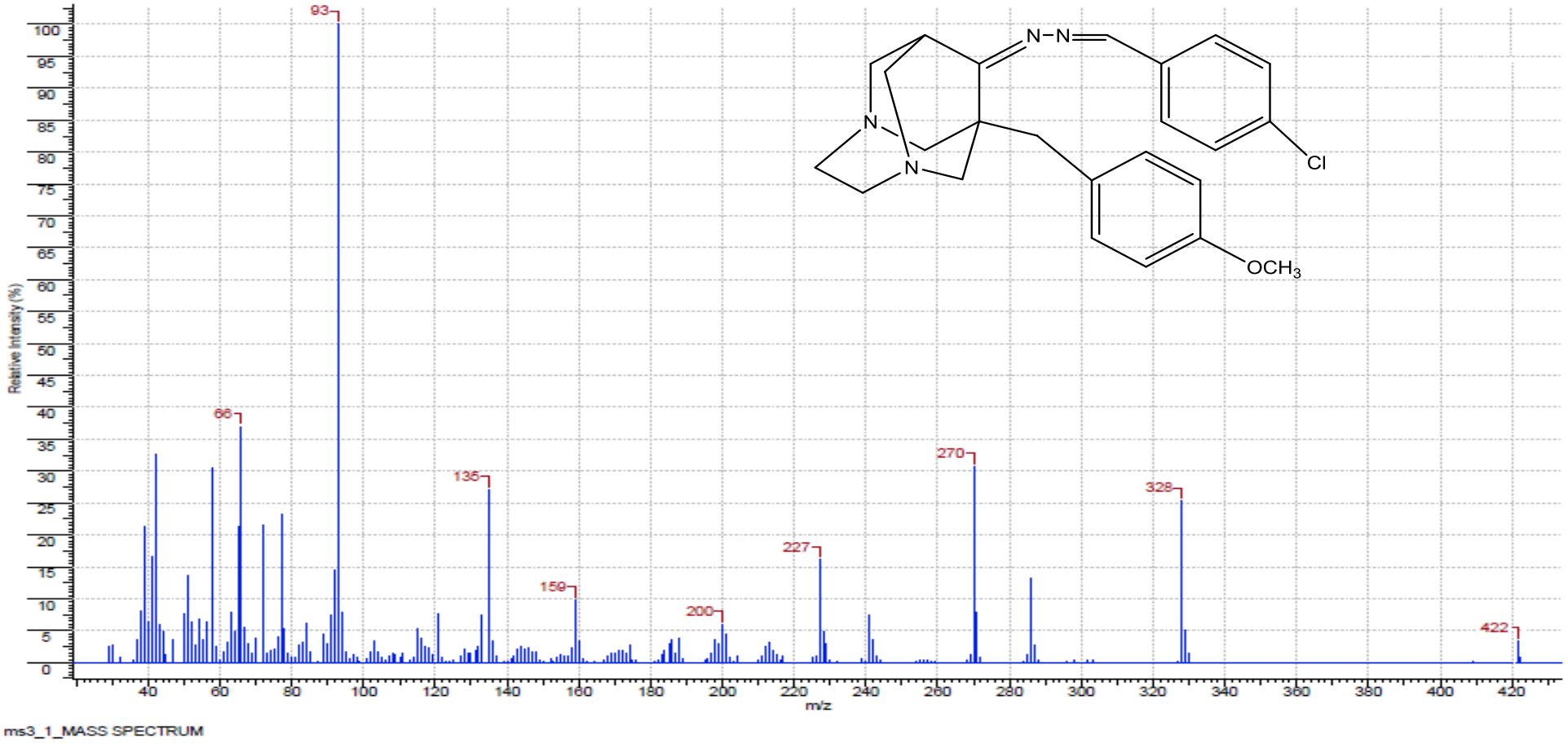


Figure (3-36) Mass Spectra of Compound (D_1)

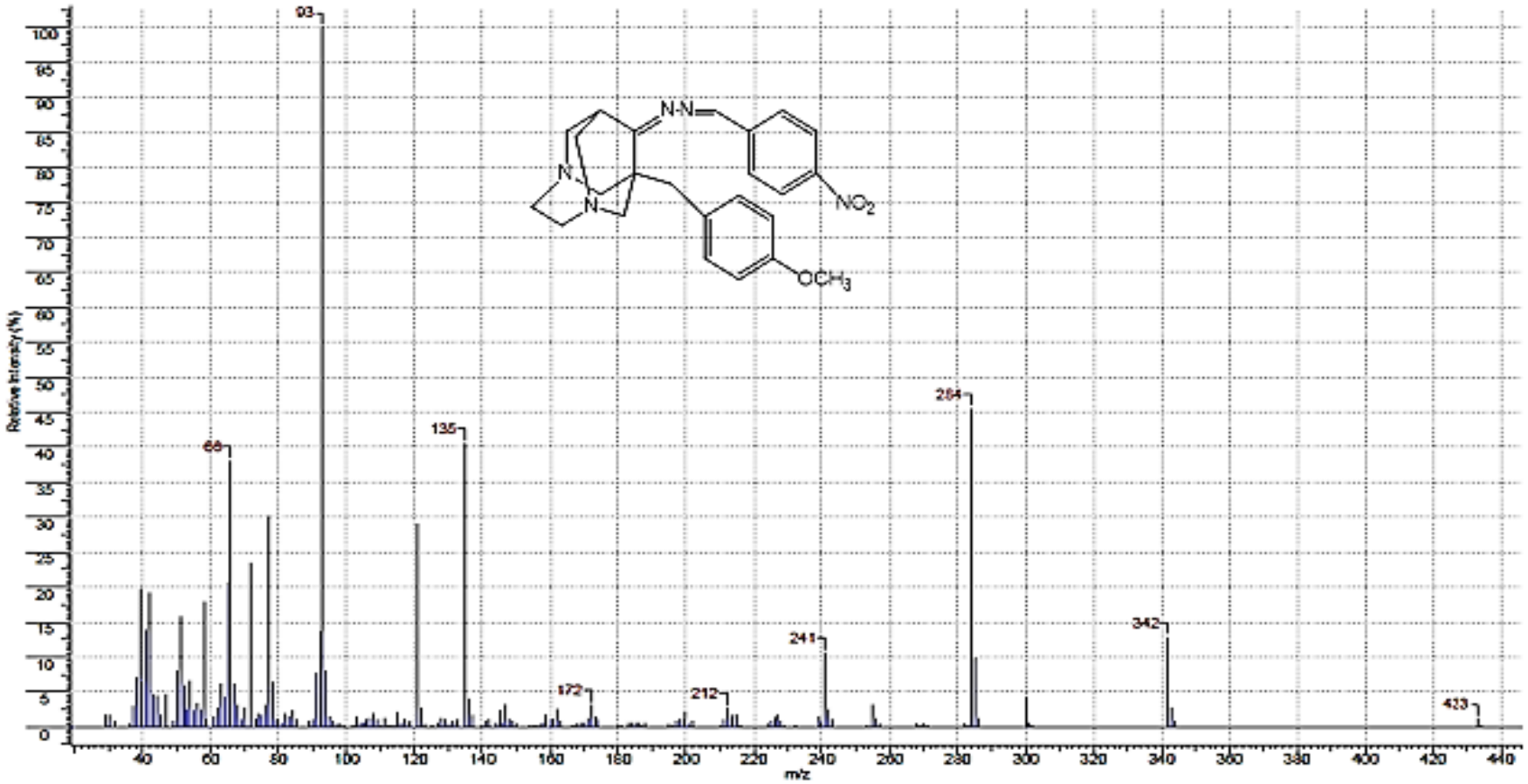


Figure (3-37) Mass Spectra of Compound (D_2)

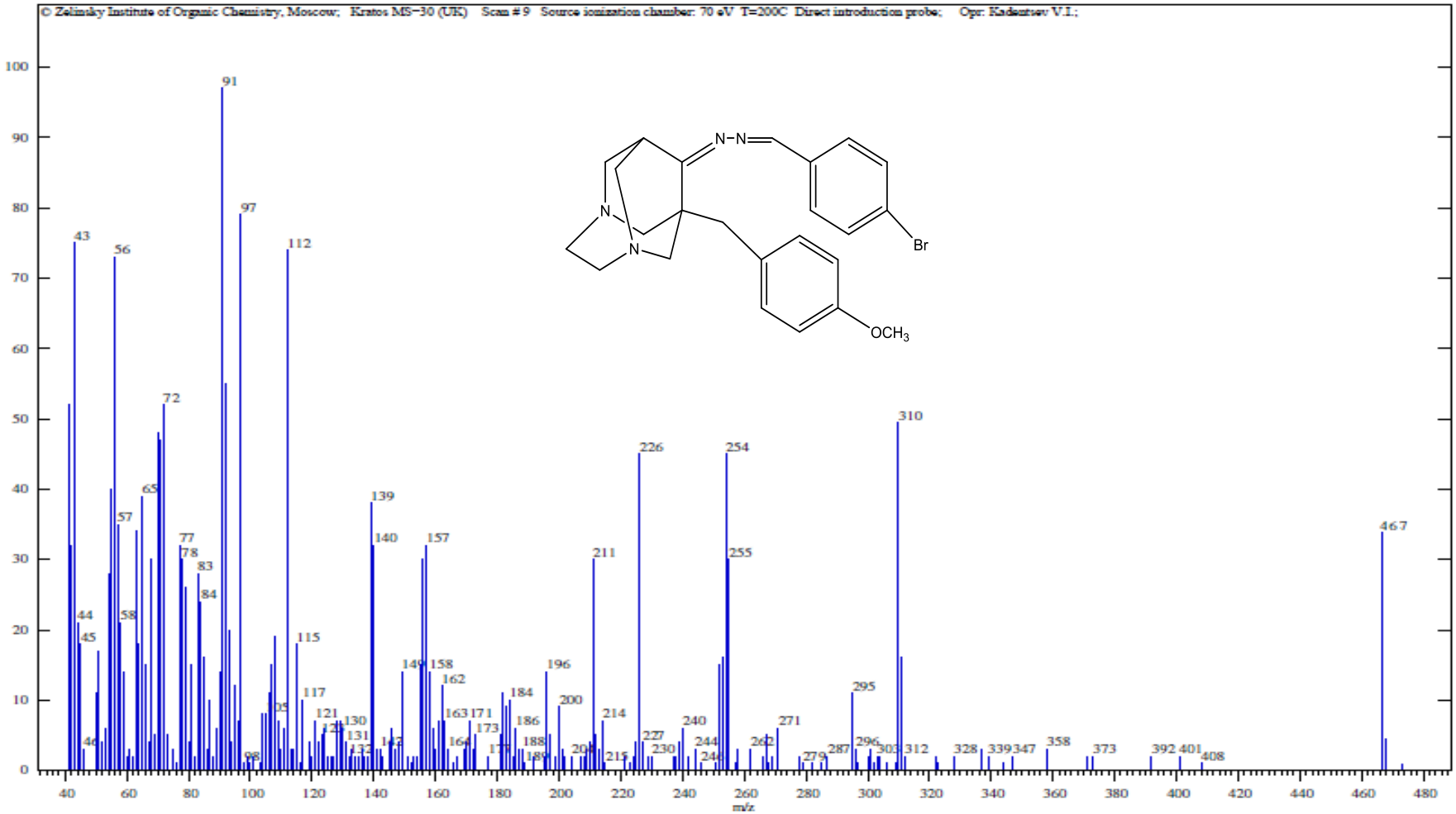


Figure (3-38) Mass Spectra of Compound (D_3)

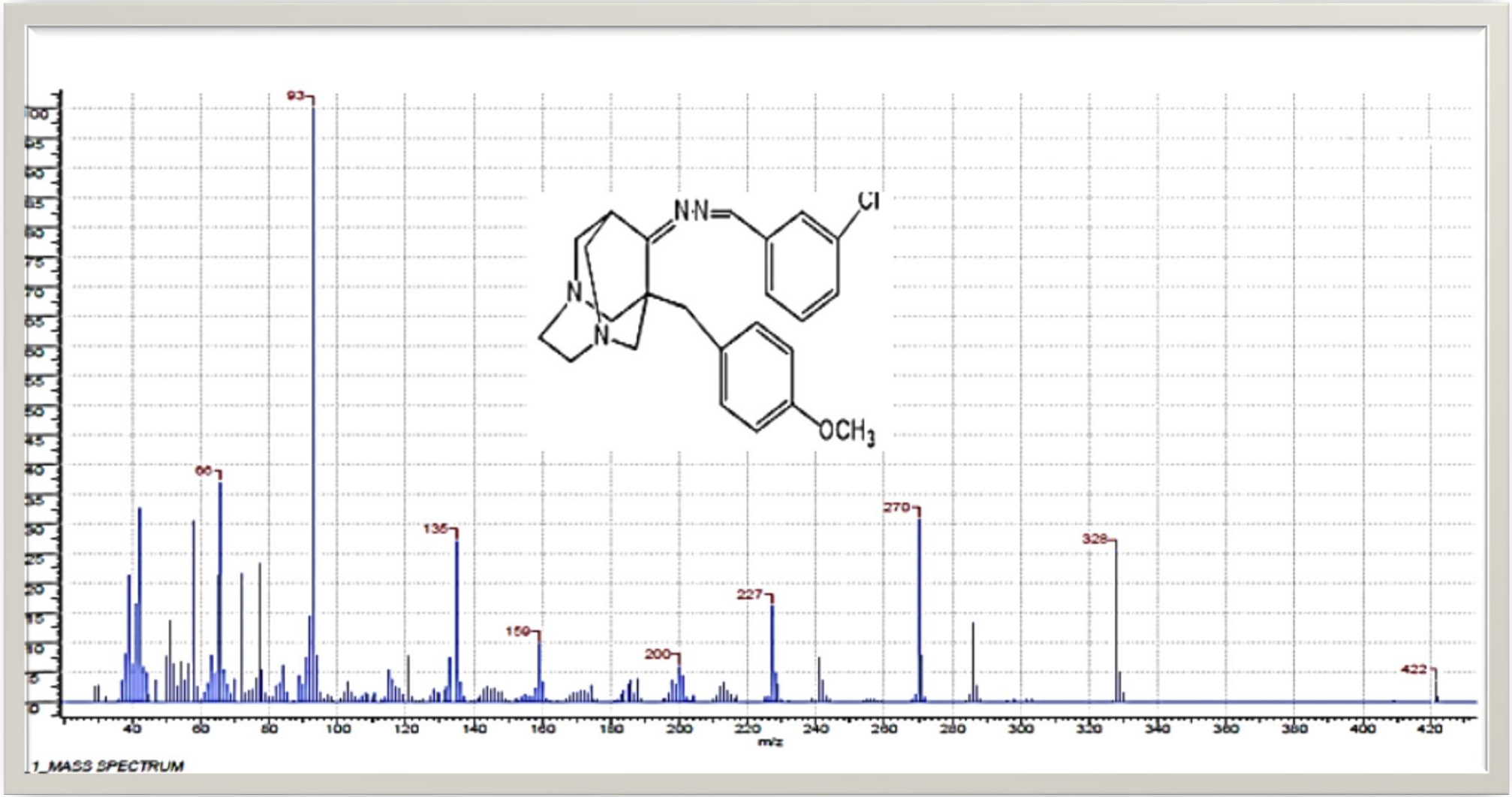


Figure (3-39) Mass Spectra of Compound (D_4)

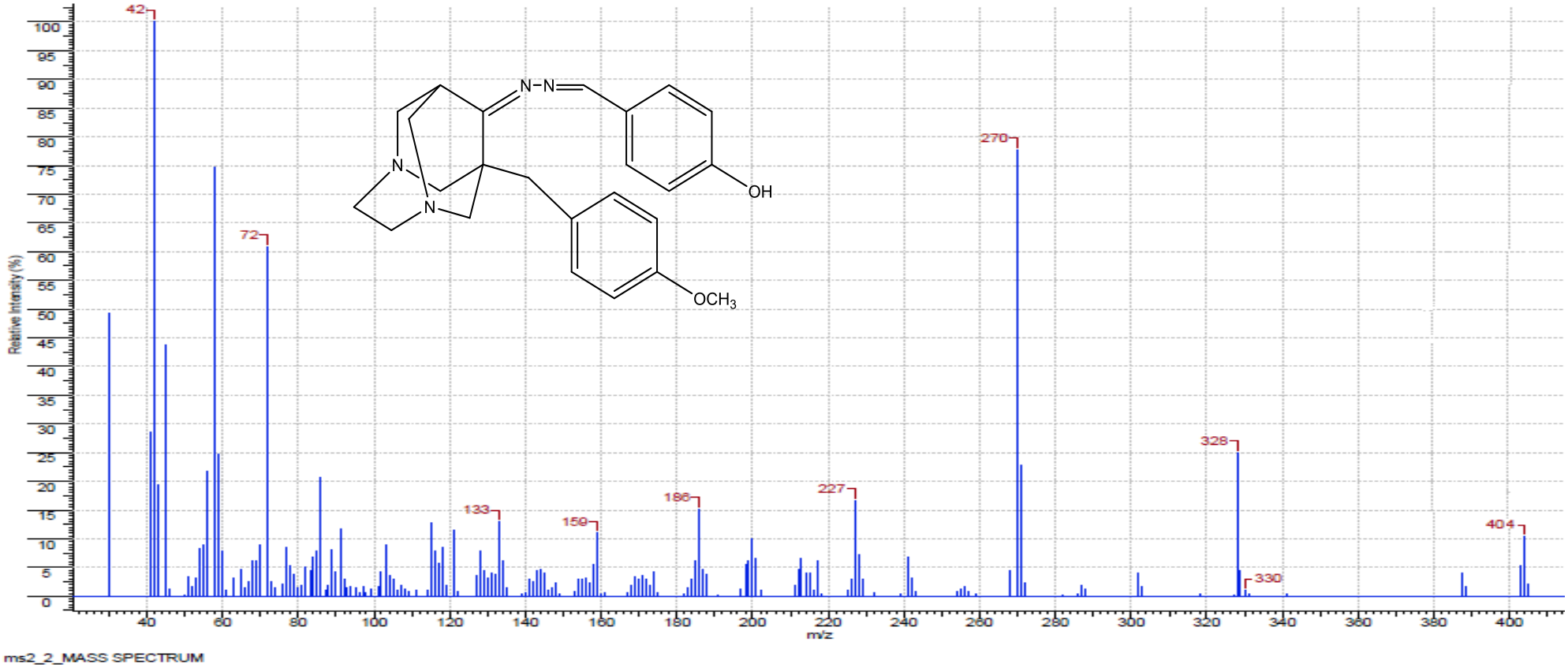


Figure (3-40) Mass Spectra of Compound (D_5)

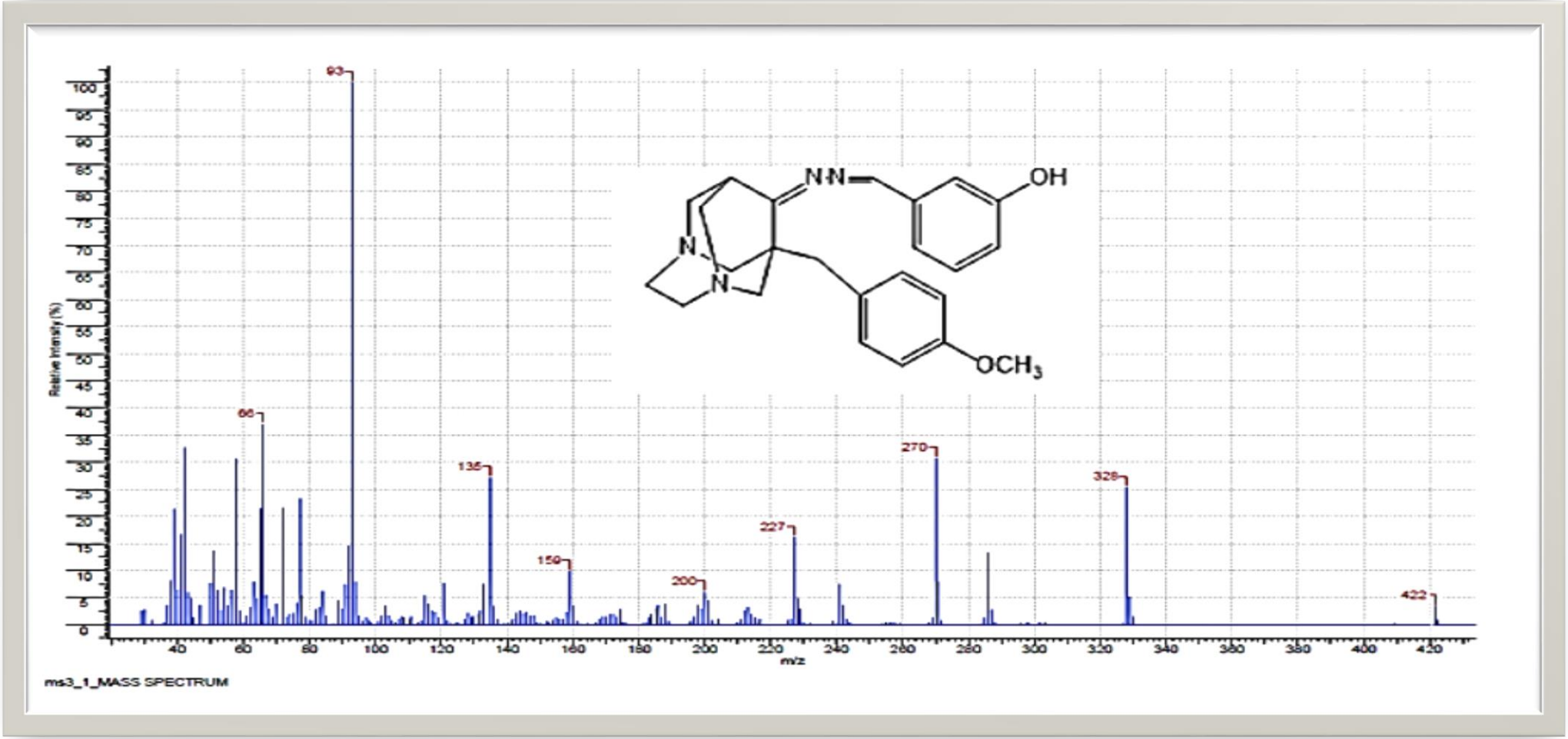


Figure (3-41) Mass Spectra of Compound (D_6)

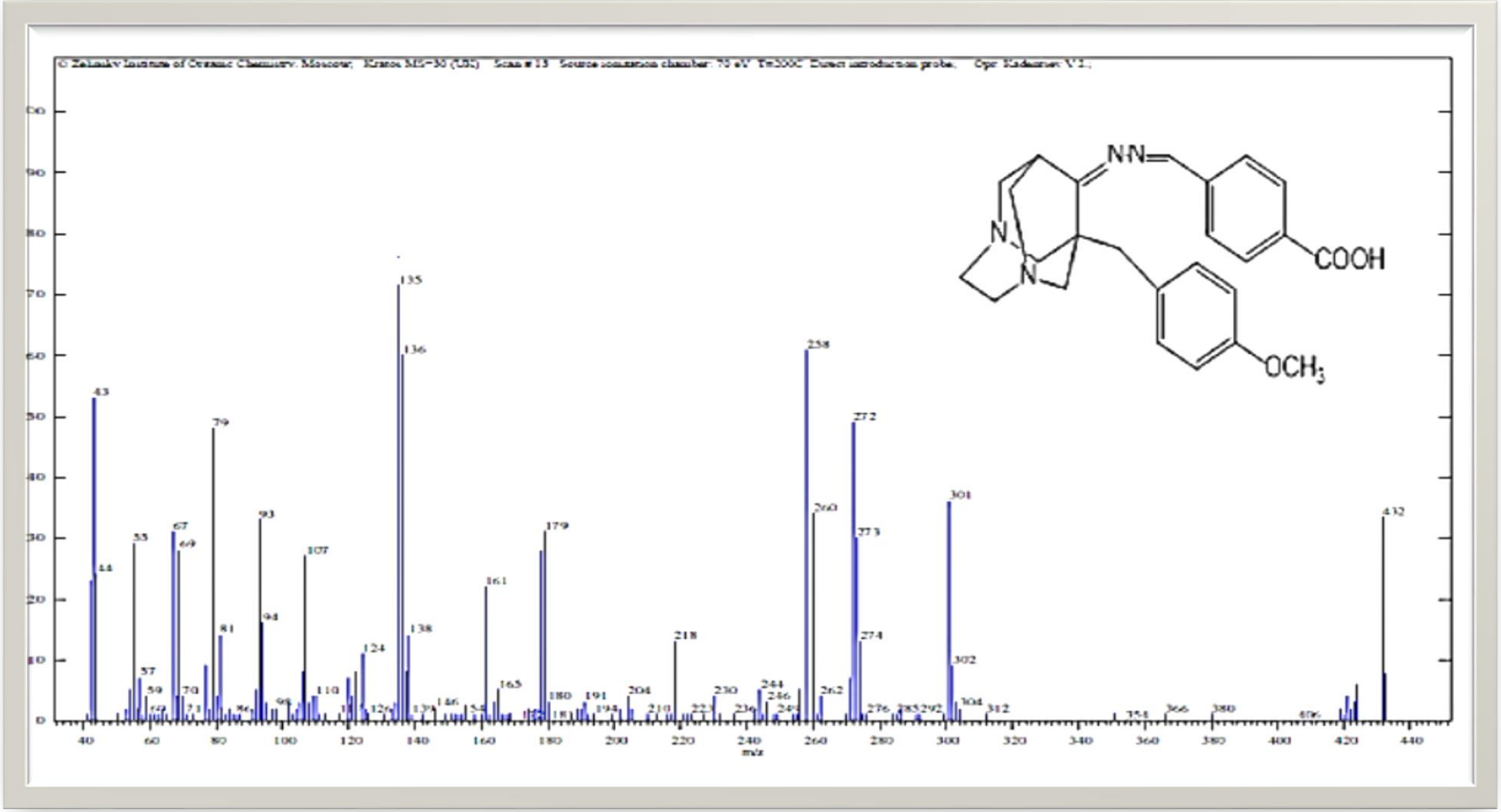


Figure (3-42) Mass Spectra of Compound (D_7)

3.3. (CHN) Elemental Analysis of Schiff Bases and 3,6-Diazahomoadamantane Derivatives.

The (CHN) elemental microanalysis measurements of the final Schiff bases and 3,6-diazahomoadamantane derivatives. compounds showed good agreement between calculated and observed values, Table (3-6)

Table (3-6): (CHN) Elemental Analysis of Compounds (B-D_7)

Entry	Calculated %			Found %		
	C	H	N	C	H	N
B	71.30	7.74	9.78	71.12	7.77	9.80
C	67.97	8.05	18.65	67.84	8.16	18.54
D_0	74.20	7.26	14.42	74.09	7.36	14.56
D_1	68.15	6.43	13.25	68.07	6.36	13.41
D_2	71.26	6.98	13.85	71.13	7.10	13.37
D_3	61.67	5.82	11.99	61.85	5.90	12.15
D_4	69.42	6.53	12.95	69.96	6.68	12.74
D_5	71.26	6.98	13.85	71.43	7.13	13.67
D_6	71.26	6.98	13.85	71.13	7.10	13.37
D_7	69.42	6.53	12.95	69.96	6.68	12.74

3.4. The Antibacterial Activities

Using the agar diffusion technique, [101] *Staphylococcus aureus*, *Streptococcus mutants* (Gram-positive) and *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative) bacteria were employed to evaluate the antibacterial effect of the target compounds 3,6-diazahomoadamantane derivatives **A** and Schiff bases $\mathbf{D_0}$-$\mathbf{D_7}$ in 1 mL of DMSO, 20 mg of each tested compound were resolved. . The compound **A** and $\mathbf{D_2}$ showed high activities against *S. aureus* bacteria, while compound $\mathbf{D_4}$ showed high activities against *E. coli* bacteria less than gentamycin. The inhibition zone findings were compared to the reference antibiotic (Gentamycin) as a control drug. Table (3-7) show the inhibition zone of each tested compounds.

Table (3-7): The Antibacterial Activity of Compounds (A-D_7)

Bacteria Type	***Staphylococcus Aureus* (G+)**	***Escherichia Coli*(G-)**	***Streptococcus mutants***	***Pseudomonas aeruginosa***
Compound No.	*Inhibitory zone (diameter) (mm)*			
A	12	7	9	8
D_0	7	8	9	8
D_1	9	9	8	7
D_2	12	10	10	9
D_3	10	8	8	8
D_4	4	12	9	7
D_5	6	8	6	6
D_6	8	7	6	7
D_7	10	10	9	8
Gentamycin	22	20	18	18
DMSO	0	0	0	0

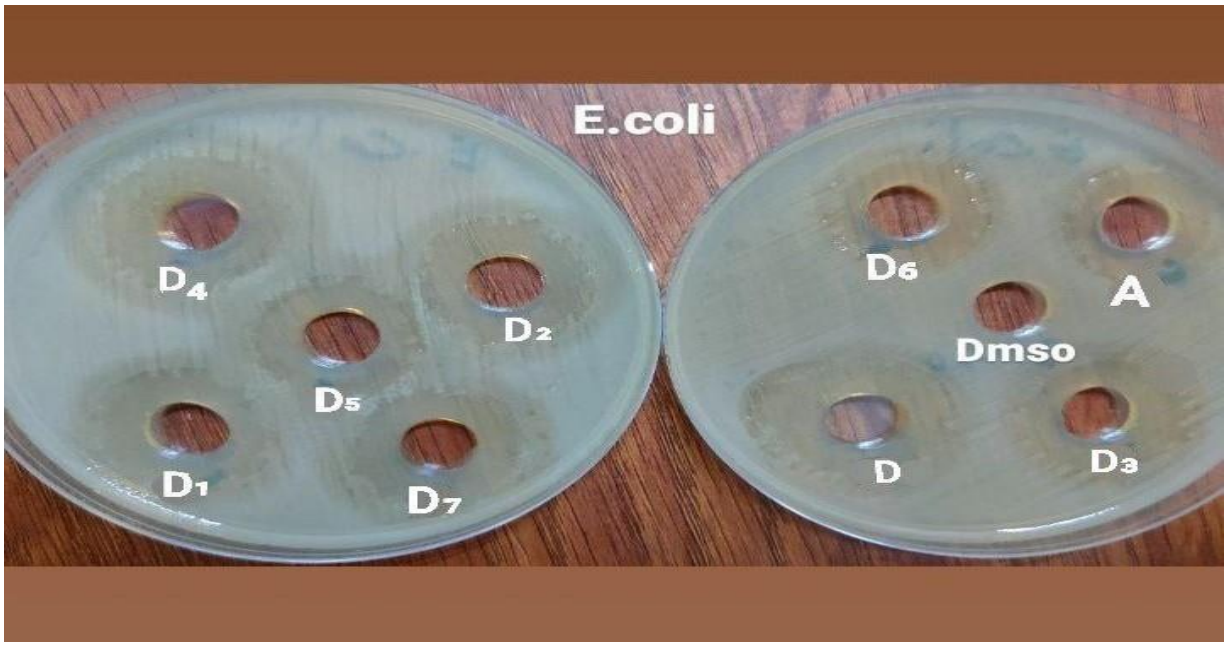


Figure (3-43): Antibacterial Photographs of 3,6-Diazahomoadamantane Derivatives and Schiff Bases (D_0-D_7 and A) Against *E. coli*.

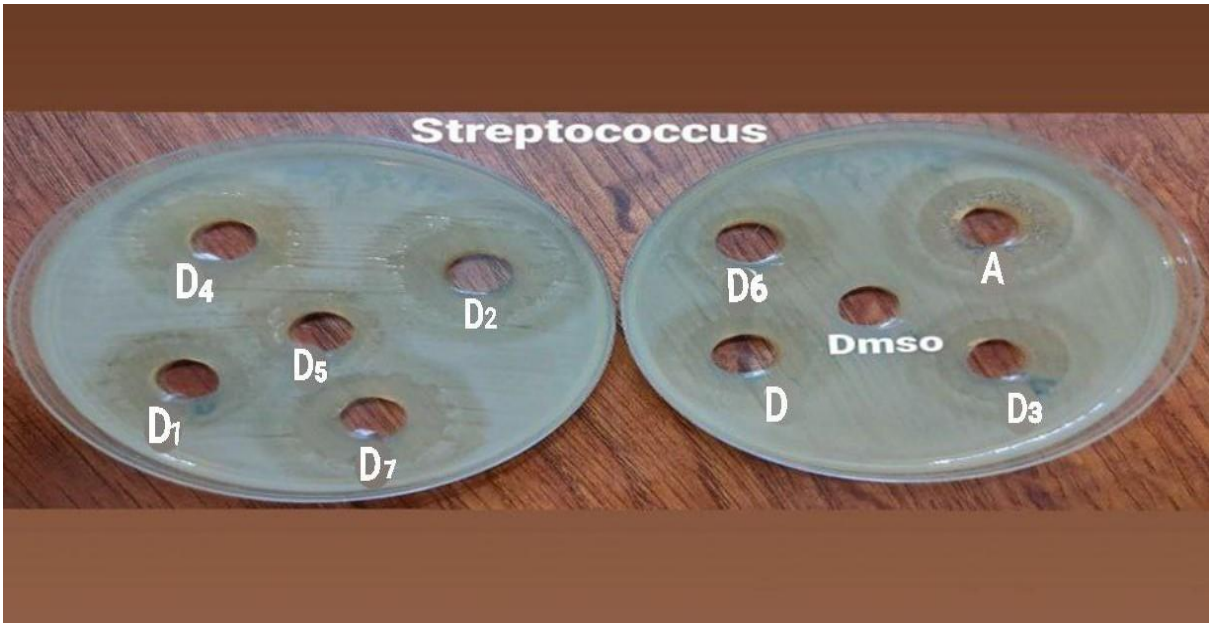


Figure (3-44): Antibacterial Photographs of 3,6-Diazahomoadamantane Derivatives and Schiff Bases (D_0-D_7 and A) Against *Streptococcus Mutants*

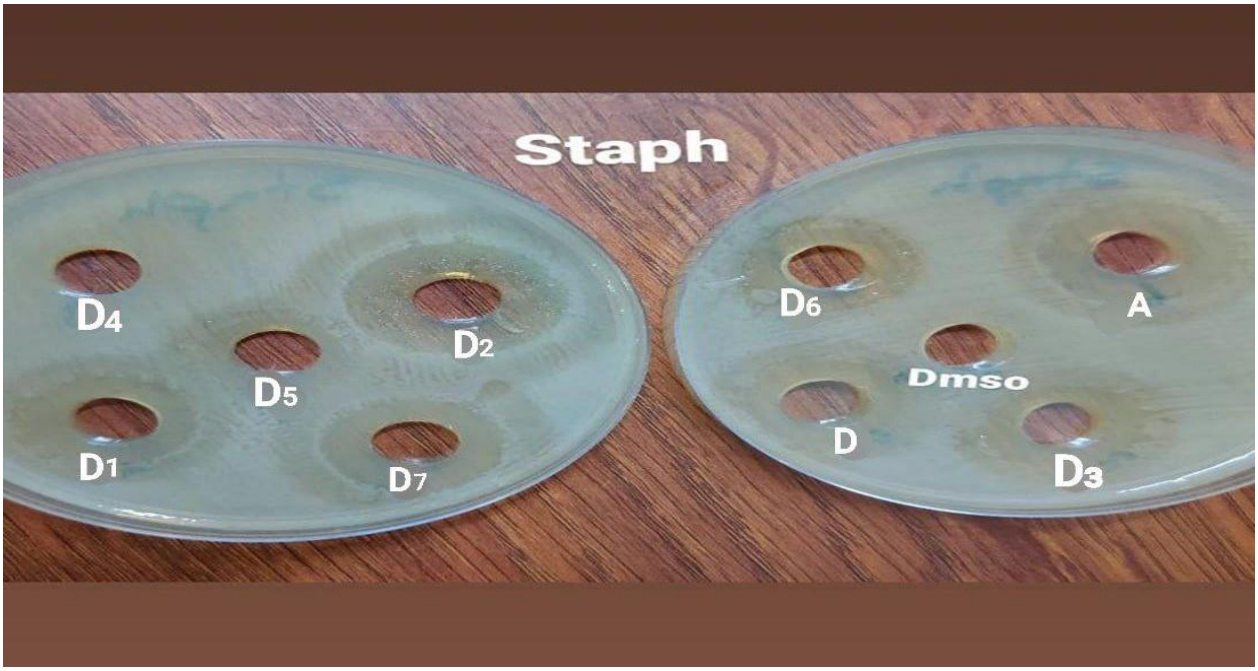


Figure (3-45): Antibacterial Photographs of 3,6-Diazahomoadamantane Derivatives and Schiff Bases (D_0-D_7 and A) Against *Staphylococcus Aureus*

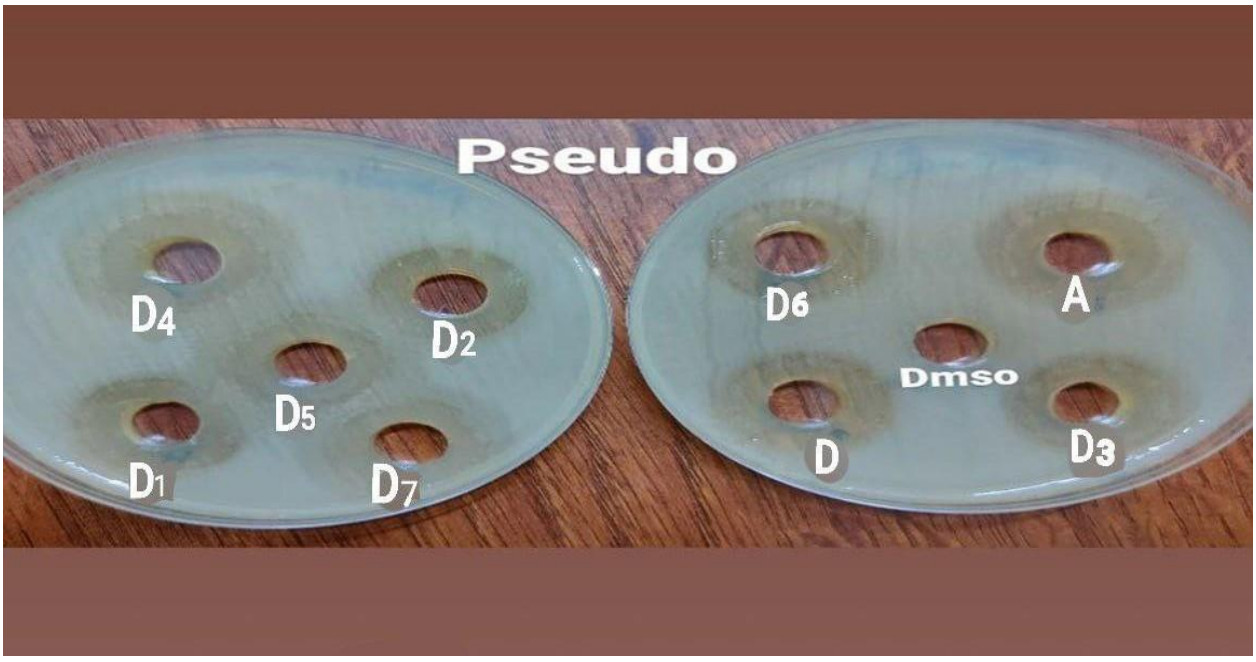


Figure (3-46): Antibacterial Photographs of 3,6-Diazahomoadamantane Derivatives and Schiff Bases (D_0-D_7 and A) Against *Pseudomonas Aeruginosa*

Conclusions

1. The prolonged conjugation of the produced teotropin with the ketone group gives them a great degree of stability.
2. All of the generated compounds were resonance stable and had relatively high melting points, as evidenced by their levels of stability.
3. The reflux is an efficient technique, suitable reaction time and good yield with prepared Schiff bases 3,6-diazahomoadamantan-9-one.
4. All synthesis of the 3,6-diazahomoadamantane derivatives were characterized using FTIR, ^{1}HNMR,^{13}C-NMR and Mass spectra.
5. This study gives important molecular insights that may be used to test the antibacterial activity of the newly synthesized compounds.

Future Work

1 .Synthesis of other heterocyclic compounds using the new 3,6-diazahomoadamantan-9-one.

2 . Applying green chemistry, microwave irradiation helped generate the imines compounds in just a brief period of time with an acceptable yield.

3 .The investigation of the biological effects of synthetic chemicals on various bacteria, fungi, viruses, and illnesses affecting animal tissues.

References

[1] V. Artifon, E. Zanardi-Lamardo, and G. Fillmann, “Aquatic organic matter: Classification and interaction with organic microcontaminants,” *Sci. Total Environ.*, vol. 649, pp. 1620–1635, 2019.

[2] G. Karthik, M. Sundaravadivelu, P. Rajkumar, and M. Manikandan, “Diaza-adamantane derivatives as corrosion inhibitor for copper in nitric acid medium,” *Res. Chem. Intermed.*, vol. 41, pp. 7593–7615, 2015.

[3] M. Mcguire, “Organic Chemistry : Current Research Classification of Organic Compounds,” vol. 11, p. 1000302, 2022.

[4] E. Bi, T. C. Schmidt, and S. B. Haderlein, “Environmental factors influencing sorption of heterocyclic aromatic compounds to soil,” *Environ. Sci. Technol.*, vol. 41, no. 9, pp. 3172–3178, 2007.

[5] P. Arora, V. Arora, H. S. Lamba, and D. Wadhwa, “Importance of Heterocyclic Chemistry: a Review,” Ijpsr, vol. 3, no. 9, pp. 2947–2954, 2012.

[6] M. Chauhan and R. Kumar, “A comprehensive review on bioactive fused heterocycles as purine-utilizing enzymes inhibitors,” *Med. Chem. Res.*, vol. 24, no. 6, pp. 2259.

[7] L. Crocetti, G Floresta, S Nazir, C Vergelli, A Bhogal, C Biancalani, N Cesari, MP Giovannoni., “Synthesis and inverse virtual screening of new bi-cyclic structures towards cancer-relevant cellular targets,” *Struct. Chem.*, vol. 33, no. 3, pp. 769–793, 2022.

[8]N. A. Alsaady, A. A. Alsaady, H. A. Kazem, Z. A. A. Alreda, and Z. A. Mohammed, “Biochemical Application of New Synthetic Compounds of Pyridine Derivatives Incorporating on Tetrazole Moieties,” vol. 2, no. 1, pp. 17–23, 2024.

[9] C. Aranda ,J Carro, A González-Benjumea, ED Babot, A Olmedo, D Linde, AT Martínez ,“Advances in enzymatic oxyfunctionalization of aliphatic compounds,” *Biotechnol. Adv.*, vol. 51, no. xxxx, 2021.

[10] R. M. Fikry, “Synthesis of some New Pyrimidine and Condensed Pyrimidine Derivatives,” *J. Indian Chem. Soc.*, vol. 73, no. 12, pp. 698–699, 1996.

[11] G. N. Reddy and S. Giri, “Super/hyperhalogen aromatic heterocyclic compounds,” *RSC Adv.*, vol. 6, no. 52, pp. 47145–47150, 2016.

[12] S. Tiwari and S. Talreja, “A Study on Aromatic Heterocyclic Organic Compounds,” *J. Pharm. Res. Int.*, no. June, pp. 36–40, 2022.

References

[13] S. Selvendran and S. Rajendran, “Lewis acid-promoted synthesis of highly substituted pyrrole-fused benzoxazinones and quinoxalinones,” *Synth. Commun.*, vol. 51, no. 3, pp. 437–445, 2021.

[14] T. Rengarajan, P. Rajendran, N. Nandakumar, B. Lokeshkumar, P. Rajendran, and I. Nishigaki, “Exposure to polycyclic aromatic hydrocarbons with special focus on cancer,” *Asian Pac. J. Trop. Biomed.*, vol. 5, no. 3, pp. 182–189, 2015.

[15] P. Ghosh and S. Mukherji, “Environmental contamination by heterocyclic Polynuclear aromatic hydrocarbons and their microbial degradation,” *Bioresour. Technol.*, vol. 341, no. July, p. 125860, 2021.

[16] J. P. Lowe and B. D. Silverman, “Carcinogenicity of polycyclic aromatic hydrocarbons: A dialogue,” *J. Mol. Struct. THEOCHEM*, vol. 179, no. 1, pp. 47–81, 1988.

[17] Y. Zhang, S. Tao, J. Cao, and R. M. Coveney, “Emission of polycyclic aromatic hydrocarbons in China by county,” *Environ. Sci. Technol.*, vol. 41, no. 3, pp. 683–687, 2007.

[18] R. K. Mohammad, R. A. Madlol, N. M. Umran, and F. I. Sharrad, “Structure and electronic properties of substitutionally doped Cycloheptane molecule using DFT,” *Results Phys.*, vol. 6, pp. 1036–1043, 2016.

[19] C. J. Van der Schyf and W. J. Geldenhuys, “Polycyclic Compounds: Ideal Drug Scaffolds for the Design of Multiple Mechanism Drugs?,” *Neurotherapeutics*, vol. 6, no. 1, pp. 175–186, 2009.

[20] V. K. Ahluwalia and R. Aggarwal, “Bridged Rings,” *Alicyclic Chem.*, vol. 1, pp. 177–190, 2023.

[21] E. T. da Silva Araújo, AM Moraes, LA De Souza, MC Silva Lourenco, “Synthesis and biological activities of camphor hydrazone and imine derivatives,” *Sci. Pharm.*, vol. 84, no. 3, pp. 467–483, 2016.

[22] S. G. Jabbour, N. A. Mawlawi, M. W. Kuthbudeen, and S. Y. Aljanaahi, “Camphor Oil Toxicity: A Case Report,” *Cureus*, vol. 15, no. 10, pp. 2–5, 2023.

[23] R. Hamidpour, S. Hamidpour, M. Hamidpour, and M. Shahlari, “ Camphor (Cinnamomum camphora), a traditional remedy with the history of treating several diseases ,” *Int. J. Case Reports Images*, vol. 4, no. 2, p. 86, 2013.

[24] A. Berthiaume, E. Galarneau, and G. Marson, “Polycyclic aromatic compounds (PACs) in the Canadian environment: Sources and emissions,” *Environ. Pollut.*, vol. 269, p. 116008, 2021.

[25] J. H. Leitão, S. A. Sousa, S. A. Leite, and M. F. N. N. Carvalho, “Silver camphor imine complexes: Novel antibacterial compounds from old medicines,” *Antibiotics*, vol. 7, no. 3, 2018.

[26] H. He, B. J. Pei, H. H. Chou, T. Tian, W. H. Chan, and A. W. M. Lee, “Camphor sulfonyl hydrazines (CaSH) as organocatalysts in enantioselective Diels-Alder reactions,” *Org. Lett.*, vol. 10, no. 12, pp. 2421–2424, 2008.

[27] E. S. Alwan, M. S. Bayoumy, and R. M. Mohareb, “Synthesis of heterocyclic compounds from camphor,” *Org. Commun.*, vol. 16, no. 2, pp. 54–74, 2023.

[28] M. Elagawany, M. A. Ibrahim, and S. S. Panda, “One-pot synthesis of bi- and tricyclic heterocyclic compounds using benzotriazole chemistry,” *Tetrahedron Lett.*, vol. 57, no. 44, pp. 4910–4913, 2016.

[29] V. Fedi, A. Guidi, and M. Altamura, “Tricyclic structures in medicinal chemistry: an overview of their recent uses in non-CNS pathologies,” *Mini Rev. Med. Chem.*, vol. 8, no. 14, pp. 1464–1484, 2008.

[30] I. M. McDonald, A. Ng, J. Cutrone, R. Mate, and R. E. Olson, “Novel tricyclic diamines 1. Synthesis of 1,4-diazaisotwistane and 1,4-diazahomoisotwistane as constrained 3-aminoquinuclidine isosteres,” *Tetrahedron Lett.*, vol. 59, no. 8, pp. 747–750, 2018.

[31] Mathew and Todd, “Diploma thesis Supervisor: doc. Mgr. Radim Hrdina, Prague, 2023.

[32] A. Štimac, M. Šekutor, K. Mlinarić-Majerski, L. Frkanec, and R. Frkanec, “Adamantane in drug delivery systems and surface recognition,” *Molecules*, vol. 22, no. 2. 2017.

[33] H. Schwertfeger, A. A. Fokin, and P. R. Schreiner, “amonds are hemist’sDia c best friend: Diamondoid chemistry beyond adamantane,” *Angew. Chemie - Int. Ed.*, vol. 47, no. 6, pp. 1022–1036, 2008.

[34] J. C. Garcia, J. F. Justo, W. V. M. MacHado, and L. V. C. Assali, “Functionalized adamantane: Building blocks for nanostructure self-assembly,” *Phys. Rev. B - Condens.*

Matter Mater. Phys., vol. 80, no. 12, 2009.

[35] A. A. Fokin, TS Zhuk, AE Pashenko "Functionalization of homodiamantane: Oxygen insertion reactions without rearrangement with dimethyldioxirane," *J. Org. Chem.*, vol. 79, no. 4, pp. 1861–1866, 2014.

[36] N. V Averina, G. S. Borisova, and N. S. Zefirov, "(4-Azahomoadamantane) Derivatives," *Russ. J. Org. Chem.*, vol. 37, no. 7, 2001.

[37] G. N. Gordadze and M. V. Giruts, "Synthesis of adamantane and diamantane hydrocarbons by high-temperature cracking of higher n-alkanes," *Pet. Chem.*, vol. 48, no. 6, pp. 414–419, 2008.

[38] G. A. Mansoori, *Chapter 1: Molecular Structure and Chemistry of Diamondoids From Diamondoid Molecules*, vol. 1. 2007.

[39] W. Maison, J. V. Frangioni, and N. Pannier, "Synthesis of rigid multivalent scaffolds based on adamantane," *Org. Lett.*, vol. 6, no. 24, pp. 4567–4569, 2004.

[40] M. Bonsir, A. R. Kennedy, and Y. Geerts, "Synthesis and Structural Properties of Adamantane-Substituted Amines and Amides Containing an Additional Adamantane, Azaadamantane or Diamantane Moiety," *ChemistryOpen*, vol. 11, no. 10, 2022.

[41] J. Rudolfová, V. Kryštof, M. Nečas, R. Vícha, and M. Rouchal, "Adamantane-Substituted Purine Nucleosides: Synthesis, Host–Guest Complexes with β-Cyclodextrin and Biological Activity," *Int. J. Mol. Sci.*, vol. 23, no. 23, 2022.

[42] A. Orzeszko, B. Kamińska, G. Orzeszko, and B. J. Starościak, "Synthesis and antimicrobial activity of new adamantane derivatives II," *Farm.*, vol. 55, no. 9–10, pp. 619–623, 2000.

[43] Q. A. Gevorkyan, A. D. Arutyunyan, G. L. Arutyunyan, S. P. Gasparyan, and G. G. Danagulyan, "Synthesis of novel pyrazolyl derivatives of 1,3-diazaadamantane," *Chem. Heterocycl. Compd.*, vol. 53, no. 2, pp. 192–195, 2017.

[44] I. Stankova , K Chuchkov, R Chayrov, L Mukova, A Galabov, D Marinkova, D Danalev "Adamantane Derivatives Containing Thiazole Moiety: Synthesis, Antiviral and Antibacterial Activity," *Int. J. Pept. Res. Ther.*, vol. 26, no. 4, pp. 1781–1787, 2020.

[45] I. Papanastasiou, A. Tsotinis, N. Kolocouris, S. P. Nikas, and A. Vamvakides, "New

aminoadamantane derivatives with antiproliferative activity," *Med. Chem. Res.*, vol. 23, no. 4, pp. 1966–1975, 2014.

[46] H. Zhu, J. Guo, C. Yang, S. Liu, Y. Cui, and X. Zhong, "Synthesis of adamantane-based trimeric cationic surfactants," *Synth. Commun.*, vol. 43, no. 8, pp. 1161–1167, 2013.

[47] R. T. Alasadi, V. V. Burmistrov, D. A. Pitushkin, A. I. Kuznetsov, and G. M. Butov, "Reactions of Isocyanatoadamantanes with 3,6-Diazahomoadamantan-9-ylidene-substituted Hydrazines and Oximes," *Russ. J. Org. Chem.*, vol. 56, no. 5, pp. 729–734, 2020.

[48] R. C. Fort and P. R. Von Schleyer, "Adamantane: Consequences of the diamondoid structure," *Chem. Rev.*, vol. 64, no. 3, pp. 277–300, 1964.

[49] H. W. Geluk and J. L. M. A. Schlatmann, "Hydride transfer reactions of the adamantyl cation-I. A new and convenient synthesis of adamantanone," *Tetrahedron*, vol. 24, no. 15, pp. 5361–5368, 1968.

[50] Ala Bazyleva [a], Dzmitry H. Zaitsau [b], Gennady J. Kabo [c 1] "Thermochemical study of 2-adamantanone" J.Chemical Thermodynamics,vol .186. no.10, pp .107134,2023.

[51] G. L. Balaji, S. Sarveswari, and V. Vijayakumar, "Synthesis of diversely substituted adamantanes as a new class of antimicrobial agent," *Res. Chem. Intermed.*, vol. 41, no. 9, pp. 6765–6776, 2015.

[52] A. N. Semakin, I. S. Golovanov, A. Y. Sukhorukov, S. L. Ioffe, and V. A. Tartakovsky, "Synthesis of 1,4,6,10-tetraazaadamantane quaternary derivatives," *Russ. Chem. Bull.*, vol. 65, no. 9, pp. 2270–2277, 2016.

[53] M. Ciampolini, L. Fabbrizzi, and A. Perottib, "I (2 1," no. 998, pp. 4–5, 1984.

[54] A. N. Semakin, I. S. Golovanov, Y. V. Nelyubina, and A. Y. Sukhorukov, "1,4,6,10 Tetraazaadamantanes (TAADs) with N-amino groups: synthesis and formation of boron chelates and host–guest complexes," *Beilstein J. Org. Chem.*, vol. 18, pp. 1424–1434, 2022.

[55] J. O. Jensen, "Vibrational frequencies and structural determinations of hexamethylenetetraamine," *J. Mol. Struct. THEOCHEM*, vol. 686, no. 1–3, pp. 159–163, 2004.

[56] J Wu, DA Leas, Y Dong, X Wang, EL Ezell, DE Stack, JL Vennerstrom , "Synthesis of 2-Azaadamantan-6-one: A Missing Isomer," *ACS Omega*, vol. 3, no. 9, pp. 11362–11367, 2018.

[57] H. Fadhil, A. Hassan, and R. T. Al-tamimi, "Theoretical study on molecular structure

and electronic properties of new 1,3-diaza-adamantan-6-ones derivatives" *Indon . J. Chem.*,vol.20, no. 3, pp.638-644,2020.

[58] E. V. Suslov, K. Y. Ponomarev, K. P. Volcho, and N. F. Salakhutdinov, "Azaadamantanes, a New Promising Scaffold for Medical Chemistry," *Russ. J. Bioorganic Chem.*, vol. 47, no. 6, pp. 1133–1154, 2021.

[59] J. E. Meyer, "Brief Communications," *Psychiatry (New York)*, vol. 24, no. 4, pp. 357–360, 1961.

[60] I. O. Razenko,a T. M. Serova,b , A. I. Kuznetsova"Synthesis of 5,7-nonamethylene-1,3-diazaadamantan-6-one" *Russian Chemical Bulletin* ., vol. 65, no. 10, pp. 2458–2460, 2016.

[61] A. Rivera, J. M. Uribe, J. Ríos-Motta, and M. Bolte, "Effect of protonation on the structure of 1,3,6,8-tetraazatricyclo[4.4.1.13,8] dodecane (TATD) adamanzane: Crystal structure and DFT analysis of 3,6,8-triaza-1-azoniatricyclo[4.4.1.13,8]dodecane 4-nitrophenolate 4-nitrophenol," *J. Struct. Chem.*, vol. 58, no. 4, pp. 789–796, 2017.

[62] P. Murray-Rust, "Crystal and molecular structure of 1,3,6,8-tetra-azatricyclo [4.4.1.1 (3,8)]-dodecane, the 2:1 condensation product of formaldehyde and 1,2-diaminoethane, and the conformation of this system," *J. Chem. Soc. Perkin Trans. 2*, no. 10, pp. 1136–1141, 1974.

[63] A. Rivera, M. E. Núñez, M. S. Morales-Ríos, and P. Joseph-Nathan, "Preparation of cage amine 1,3,6,8-tetraazatricyclo[4.3.1.1 (3,8)]undecane," *Tetrahedron Lett.*, vol. 45, no. 41, pp. 7563–7565, 2004.

[64] A. Rivera and J. Rios-Motta, "Unusual reactivity patterns of 1,3,6,8-tetraazatricyclo-[4.4.1.1 (3,8)]-dodecane (TATD) towards some reducing agents: Synthesis of TMEDA," *Molecules*, vol. 12, no. 7, pp. 1471–1481, 2007.

[65] A. I. Kuznetsov, I. M. Senan, A. K. Shukkur, I. A. Azzheurova, and T. M. Serova, "Synthesis of 3,6-diazahomoadamantane," *Russ. J. Org. Chem.*, vol. 48, no. 1, pp. 119–122, 2012.

[66] Ansam .F .Noamane "Bromination of Diazahomoadamantane with liqiude bromine and Synthesis of New its , Derivatives " O International, , no. V, pp. 1–10, 2016.

[67] A. I. Kuznetsov, A. K. Shukkur, and T. M. Serova, "Synthesis of 1,8-nonamethylene-3,6-diazahomoadamantan-9-one," *Russ. J. Org. Chem.*, vol. 44, no. 5, p. 763, 2008.

References

[68] R. T. Alasadi and A. Shukkur, "Synthesis of 1-Benzyl-3,6-diazahomoadamantane," *Russ .J. Org. Chem.,* vol .49, no.11, pp. 9–15, 2013.

[69] A. K. Chakraborti, S. Bhagat, and S. Rudrawar, "Mahdi, S.H. and Karem, L.A., 2018. Synthesis, spectral and biochemical studies of new complexes of mixed ligand Schiff base and anthranilic acid" *Orien. J. Chem.*, 34(3), pp.1565-1572., *Tetrahedron Lett.*, vol. 45, no. 41, pp. 7641–7644, 2004.

[70] D. Iacopetta, J Ceramella, A Catalano, C Saturnino, MG Bonomo, C Franchini, MS Sinicropi "Schiff bases: Interesting scaffolds with promising antitumoral properties," *Appl. Sci.*, vol. 11, no. 4, p. 1877, 2021.

[71] T. Article, "Submission Files Included in this PDF A survey of metal Schiff base complexes for energy-related applications is provided," 2017.

[72] R. Rajavel, M. S. Vadivu, and C. Anitha, "Synthesis, physical characterization and biological activity of some schiff base complexes," *E-J.l Chem.*, vol. 5, no. 3, pp. 620–626, 2008.

[73] SA Dalia, F Afsan, MS Hossain, MN Khan, C Zakaria, MKE Zahan, M Ali "A short review on chemistry of schiff base metal complexes and their catalytic application," *Int. J. Chem. Stud.*, vol. 6, no. 3, 2018.

[74] P. Ekmekcioglu, N. Karabocek, S. Karabocek, and M. Emirik, "Synthesis, structural and biochemical activity studies of a new hexadentate Schiff base ligand and its Cu(II), Ni(II), and Co(II) complexes," *J. Mol. Struct.*, vol. 1099, pp. 189–196, 2015.

[75] J. Ceramella, D. Iacopetta, A. Catalano, F. Cirillo, R. Lappano, and M. S. Sinicropi, "A Review on the Antimicrobial Activity of Schiff Bases: Data Collection and Recent Studies," *Antibiotics*, vol. 11, no. 2, 2022.

[76] A. Z. El-Sonbati, W. H. Mahmoud, G. G. Mohamed, M. A. Diab, S. M. Morgan, and S. Y. Abbas, "Synthesis, characterization of Schiff base metal complexes and their biological investigation," *Appl. Organomet. Chem.*, vol. 33, no. 9, pp. 1–16, 2019.

[77] S. Arulmurugan, H. P. Kavitha, and B. R. Venkatraman, "Biological activities of schiff base and its complexes: A review," *Rasayan J. Chem.*, vol. 3, no. 3, pp. 385–410, 2010.

References

[78] D. Pawlica, M. Marszałek, G. Mynarczuk, L. Sieroń, and J. Eilmes, "New unsymmetrical Schiff base Ni(II) complexes as scaffolds for dendritic and amino acid superstructures," *New J. Chem.*, vol. 28, no. 12, pp. 1615–1621, 2004.

[79] CM Da Silva, DL da Silva, LV Modolo, RB Alves, MA de Resende, CVB Martins, Â de Fátima, "Schiff bases: A short review of their antimicrobial activities," *J. Adv. Res.*, vol. 2, no. 1, pp. 1–8, 2011.

[80] R. Pawar and J. Parikh, "Study of Anti-bacterial Activities of dihydrazide-dihydrazone Derivatives of Adamantly Moiety Containing Nitro Group," *Int. J. Renew. Energy Exch.*, vol. 10, no. 11, pp. 27–39, 2022.

[81] B. Ambrozini, E. R. Dockal, and É. T. G. Cavalheiro, "Thermal behavior of tetradentate Schiff base chromium(III) complexes," *J. Therm. Anal. Calorim.*, vol. 115, no. 2, pp. 979–986, 2014.

[82] B Samanta, J Chakraborty, CR Choudhury, SK Dey, DK Dey, SR Batten, P Jensen, GPA Yap "New Cu(II) complexes with polydentate chelating Schiff base ligands: Synthesis, structures, characterisations and biochemical activity studies," *Struct. Chem.*, vol. 18, no. 1, pp. 33–41, 2007.

[83] F. M. Ibrahim and S. M. Abdalhadi, "Performance of Schiff Bases Metal Complexes and their Ligand in Biological Activity: A Review," *Al-Nahrain J. Sci.*, vol. 24, no. 1, pp. 1–10, 2021.

[84] J. Zhu, G. Teng, D. Li, R. Hou, and Y. Xia, "Synthesis and antibacterial activity of novel Schiff bases of thiosemicarbazone derivatives with adamantane moiety," *Med. Chem. Res.*, vol. 30, no. 8, pp. 1534–1540, 2021.

[85] E. Raczuk, B. Dmochowska, J. Samaszko-Fiertek, and J. Madaj, "Different Schiff Bases—Structure, Importance and Classification," *Molecules*, vol. 27, no. 3, 2022.

[86] M. Motahar Hossain, "Preparation, Physical Characterization and Antibacterial Activity of Ni (II), Cu (II), Co (II), Cd (II), Zn (II) and Cr (III) Schiff Base Complex Compounds," *Sci. J. Chem.*, vol. 6, no. 2, p. 17, 2018.

[87] T. Akitsu, *Schiff Base in Organic, Inorganic and Physical Chemistry*. BoD–Books on Demand, 2023.

[88] H. M. Hassan, L. H. Al-Wahaibi, G. S. Shehatou, and A. A. El-Emam, "Adamantane-linked isothiourea derivatives suppress the growth of experimental hepatocellular carcinoma via inhibition of TLR4-MyD88-NF-κB signaling.," *Am. J. Cancer Res.*, vol. 11, no. 2, pp. 350–369, 2021.

[89] R. T. Alasadi and Z. H. Abood, "Synthesis of diazahomoadamantane derivative," *AIP Conf. Proc.*, vol. 2144, pp. 1–5, 2019.

[90] H. Abdulhasan, A. Al-Yasari, and R. Alasadi, "Theoretical study on molecular structure and electronic properties of new 1,3-diaza-adamantan-6-ones derivatives," *Indones. J. Chem.*, vol. 20, no. 3, pp. 638–644, 2020.

[91] Y. Sharabi-Ronen, S. Levinger, M. Ben-Dahan Lellouche, and A. Albeck, "Anti-neoplastic activity of 1, 3-diaza-2-functionalized-adamantan-6-one compounds against melanoma cells," *Med. Chem. (Los. Angeles).*, vol. 10, no. 1, pp. 27–37, 2014.

[92] OK Mamaeva, AG Gabrielyan, GL Arutyunyan, TN Bocharova, EA Smirnova, AA Volodin, "Promoting DNA molecules association by amphiphilic derivatives of 1,3-diazaadamantanes containing hydrophobic side chains," *Mol. Biol.*, vol. 48, no. 5, pp. 741–748, 2014.

[93] E. Ivanova, I. Kapitsa, E. Valdman, and T. Voronina, "Comparison of the Analgesic Activity of Antiparkinsonian Aminoadamantane Derivatives Amantadine and Hemantane," *Adv. Park. Dis.*, vol. 05, no. 03, pp. 50–60, 2016.

[94] A. Orzeszko, B. Kaminska, and B. J. Starociak, "Synthesis and antimicrobial activity of new adamantane derivatives III," *Farmaco*, vol. 57, no. 8, pp. 619–624, 2002.

[95] B Orzeszko, M Fedoryński, AE Laudy, BJ Starościak, A Orzeszko, "Full Paper Synthesis and Atibacterial Activity of 5-Adamantan-1-Yl- Methyl A nalogues of Trimethoprim," no. C, pp. 374–377.

[96] A. Shokova and V. V. Kovalev, "Biological Activity of Adamantane-Containing Mono- and Polycyclic Pyrimidine Derivatives* (A Review)," *Pharm. Chem. J.*, vol. 50, no. 2, pp. 63–75, 2016.

[97] I. Edition, M. Region, R. Federation, "Synthesis of fragrant 3,6 diazahomoadamantan 9 ones," *Russ. Chem. Bulletin.*, vol. 64, no. 4, pp. 6–8, 2015.

[98] W. A. Al Masoudi, H. T. Mohammad, and A. A. Hama, "Synthesis, Characterization

and Pharmacological Study of New Schiff Base Derived From Amoxicillin Drug," *Int. Res. J. Pharm.*, vol. 6, no. 6, pp. 386–389, 2015.

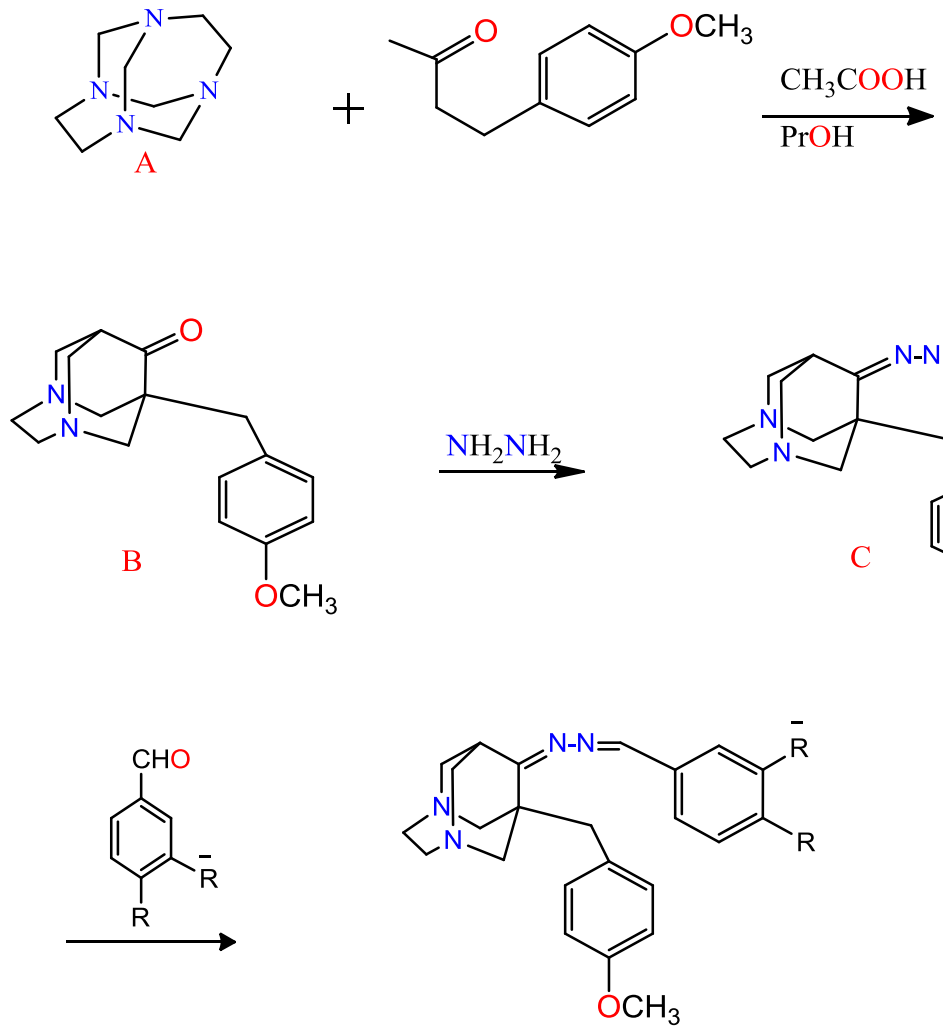
[99] H. H. Abbas, "Synthesis and Evaluation of Antibacterial Activities for Some New Thiazolidinone Derivatives of Thiadiazole," 2023.

[100] D. Johannes and S. Turid, "Condensation of Alkanediamaines with formaldehyde; intramolecular disproportionate of m-hydroxymethyl groups into N-Methyl and N-Formyl groups", Chem. *Scand*., Vol .45,P1064-1070." pp. 1064–1070, 1991.

[101] J. Tokyo, "Theory of Agar Diffusion Methods for Bioassay," *J. Article.,* vol. 15, no. 1, pp. 975–977, 1992.

الخلاصة

تضمنت هذه الدراسة تحضير مركبات أزوميثين لمشتقات ١- (٤-ميثوكسي بنزايل) -٣،٦-ديازاهومودامانتان-٩-اون وتحضير ١- (٤-ميثوكسي بنزايل) -٣،٦- ديازاهومودامانتان-٩-اون . تكاثف الاثيلين ثنائي الأمين مع البارافورمالديهايد ينتج التيوتروبن. تفاعل ٨,٦,٣,١ رباعي أزا تراي سايكلو [١٣.1.٤.٤] دوديكان **A** مع أنيسيل أسيتون أنتج ١- (٤-ميثوكسي بنزايل) -٣،٦- ديازاهومودامانتان-٩-اون **B** الذي تفاعل مع هيدرازين هيدرات أنتج ١- (٤-ميثوكسي بنزايل) -٣،٦-ديازاهومودامانتان-٩-اون هيدرازون **C** وتعرض الأخير لتحويل ١- (٤-ميثوكسي بنزايل) -٣،٦-ديازاهومودامانتان-٩- اون مركب فوق هيدرازين للحصول على مشتقات ١- (٤-ميثوكسي بنزايل) -٣،٦-ديازاهومودامانتان. تسخين ١- (٤-ميثوكسي بنزايل) -6،٣- ديازاهومودامانتان-٩-اون هيدرازون مع مشتقات ألالديهايدات التي تتكون من بارا - بنزالديهايد، ٤-كلوروبنزالديهايد، ٤-بروموبنزالديهيد، ٤-نيتروبنزالدهيد، ٣-كلوروبنزالدهيد، ٣-هيدروكسي بنزالديهايد، ٤-هيدروكسي بنزالديهايد، ٤-كربوكسي بنزالديهايد (باستخدام التصعيد بوجود الكحول الإيثيلي إلى أمينات ديازاهومودمنتان.**(D_7-D_0)** تم تحديد المركبات المنتجة الجديدة بواسطة FT-IR و ^{1}H-NMR, ^{13}C- NMR وطيف الكتلة , دراسة مضادة للبكتيريا للمركبات المنتجة الجديد**(D_7-D_0, A)** أظهر المركب **A** و**D_2** فعالية ضد بكتيريا ***Staphylococcus aureus***، بينما أظهر المركب **D_4** فعالية ضد بكتيريا ***Escherichia coli***تمت مقارنة نتائج منطقة التثبيط بالمضاد الحيوي المرجعي (جنتاميسين) كدواء ضابط. فيما يلي المركبات المعدة .



$D_0 \longrightarrow D_7$

R = $\bar{R}$=H (D_0) R=4Cl (D_1)$\bar{R}$=H , R=4NO_2(D_2) $\bar{R}$ =H ,R=4Br(D_3) $\bar{R}$=H ,$\bar{R}$=3Cl

(D_4) R=H ,R= 4OH(D_5) $\bar{R}$=H , $\bar{R}$ = 3OH (D_6)R=H , R=4COOH (D_7) $\bar{R}$=H

جامعة كربلاء

كلية العلوم

قسم الكيمياء

تحضير مشتقات قواعد شيف من الادمنتان

رسالة مقدمة الى

مجلس كلية العلوم / جامعة كربلاء وهي جزء من متطلبات

نيل درجة الماجستير في علوم الكيمياء

كتبت من قبل

زينب محمدعلي سعدون

بكالوريوس علوم كيمياء (٢٠٠٧) / جامعة كربلاء

بأشراف

د. رحمن طعمة التميمي

ايلول ٢٠٢٤ م

ربيع الاول ١٤٤٦هـ