Republic of Iraq

Ministry of Higher Education

and Scientific Research

University of Babylon

College of science for women

Department of Chemistry

Synthesis and Characterization of bis Tetrazole derivatives based on adamantan's derivatives Schiff bases

A Thesis

Submitted to the Council of the College of science for women / The University of Babylon as a Partial Fulfillment of the Requirements for the Degree of Master of Science/ Chemistry

By

Ansam Abd-Alkadhim kumaet Al-Ajili

B. Sc. Chemistry. College of Science

Babylon University (1999)

Supervised by

Prof. Dr. : Sadiq Abdul Hussain Karim

2023 A **1444 H**

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

هُوَ الَّذِي بَعَثَ فِي الْأُمِّيِّينَ رَسُولًا مِنْهُمْ يَتْلُو عَلَيْهِمْ آيَاتِهِ وَيُزَكِّيهِمْ وَيُعَلِّمُهُمُ الْكِتَابَ وَالْحِكْمَةَ وَإِنْ كَانُوا مِنْ قَبْلُ لَفِي ضَلَالٍ مُبِينٍ ﴿2﴾

صدق الله العلي العظيم

سورة الجمعة- الآية ﴿2﴾

Supervisor's Certification

I, certify thesis entitle

"Synthesis and Characterization of bis Tetrazole derivatives based on adamantan's derivatives Schiff bases"

by **Ansam Abd-Alkadhim kumaet Al-Ajili** under my supervision at the Department of Chemistry/ College of Science WSCI/University of Babylon as a partial fulfillment of the requirements for the Degree of Master in Science / Chemistry

Signature:

Name: Dr. Sadiq A. Karim

Scientific Degree: Professor

Address: College of science WSCI /Department of Chemistry

Date: / 4 / 2023

Recommendation of Head of Chemistry Department

According to the available recommendation , I forward this thesis for Discussion

Signature of Chemistry Department

Name: Dr. Sadiq A. Karim

Scientific Degree : Professor

Address : Head of Chemistry Department

University of Babylon / College of Science for Woman

Date: / 4 / 2023

Dedication

To my

Dear Parents

My Brothers and Sisters

To my support in life..... my husband

To the adornment and joy of my life....my children

To all those who stood by my side ……

To everyone who has a place in my heart ……

To everyone who has supported me even with a word ……

To all the family and friends……

Ansam

ACKNOWLEDGEMENTS

Praise be to ***Allah***, Lord of the worlds. Praise be to ***Allah***, who helped me and gave me the strength, to complete this thesis. I would like to extend my special thanks and appreciation to my supervisor, ***Prof. Dr. Sadiq A. Karim***, for his suggestion and for providing his continuous advice and valuable guidance, without his guidance and close supervision of the work, it would have never been achieved.

I also express my thanks and gratitude to the deanship of the college of science for women, and all my professors who helped me and provided their valuable pieces of advice.

Also, I would like to extend my sincere thanks and appreciation to ***professor Dr. Ayad Alkaim*** for their help in this work .

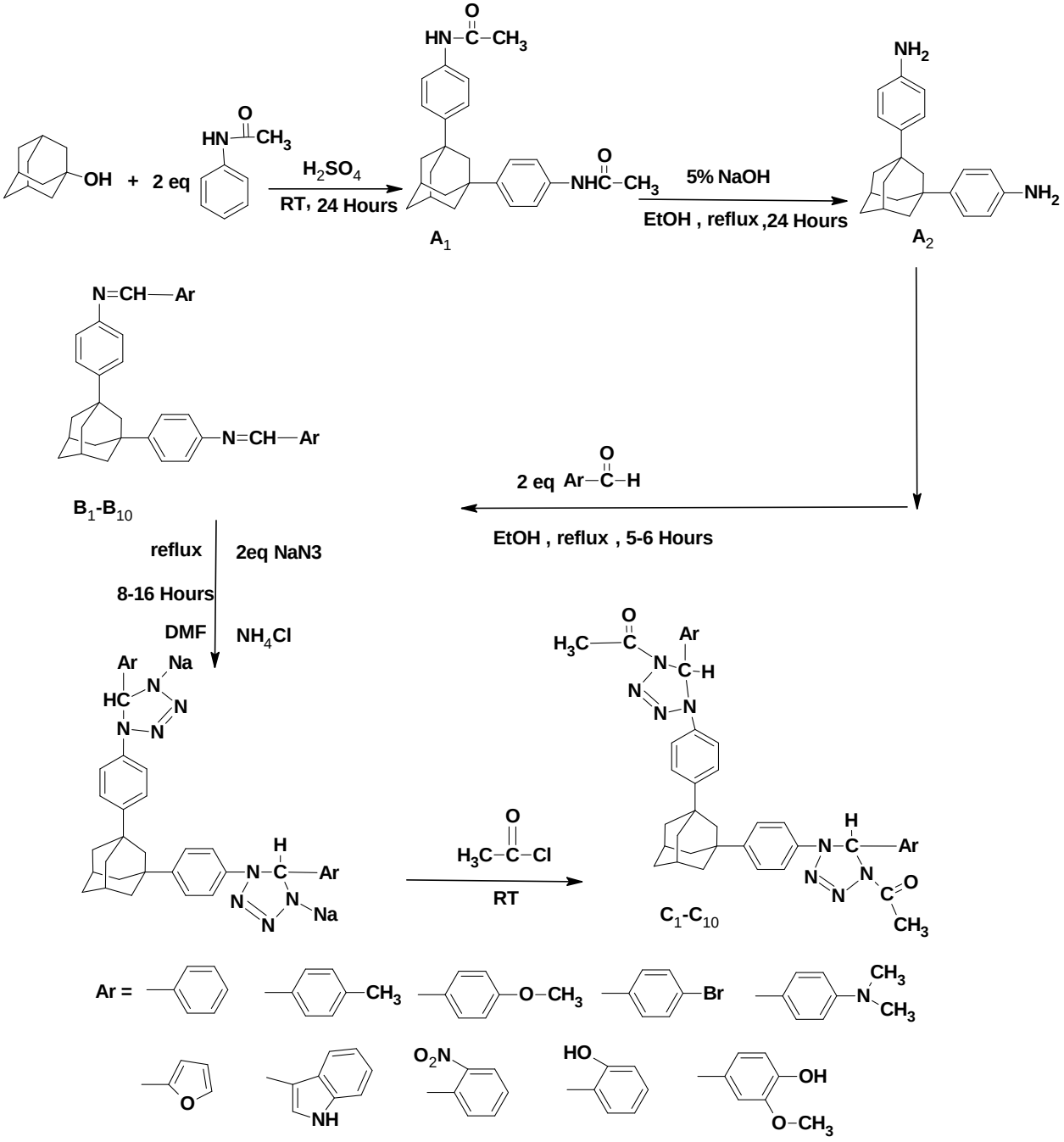
Finally, I would like to express my sincere thanks and appreciation to the members of my family and my husband, who has been a support throughout this period until I reached this stage.

Ansam

Summary

Synthesis of new Schiff base derivatives contain adamantane skeleton in their structures by using adamantanol as initial material. adamantanol undergo to the two reaction steps; first step reacts adamantanol with acetanilide in acidic medium to produce adamantine salt of acetanilide and the second step; adamantane salt undergoes to the deportation reaction in basic medium to produce adamantane derivative (amine). These amine derivative react with several different aromatic aldehyde to produce new compound contains bis-Schiff base group and adamantane cage in the same molecule as shown in scheme below.

As well as, synthesized new heterocyclic compound contains tetrazole ring in their structure by reaction Schiff base derivatives mentioned above with sodium azide as first step, after that the product react with acetyl chloride to produce tetrazole derivative compounds as second step as shown in scheme below. All new derivative compounds were characterized by using Melting points, FT-IR, Mass Spectroscopy, (^{1}H and ^{13}C) NMR spectroscopy. The synthesis compounds(Schiff bases) were tested for their antioxidant activity, as well as estimated of some new synthesized compound against of antimicrobial activity. It was observed that the Schiff base derivatives exhibit high value of inhibition against 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical, and some of new compounds exhibit have good inhibitory action against *candida albicans*, and weak-moderate inhibitory action against *Staphylococcus aureus* Gram positive and *Escherichia coli* Gram negative.



Scheme(I):Synthesis route for all synthesized compounds(B1-B10) and(C1-C10)

List of Content

List of tables

List of Figures

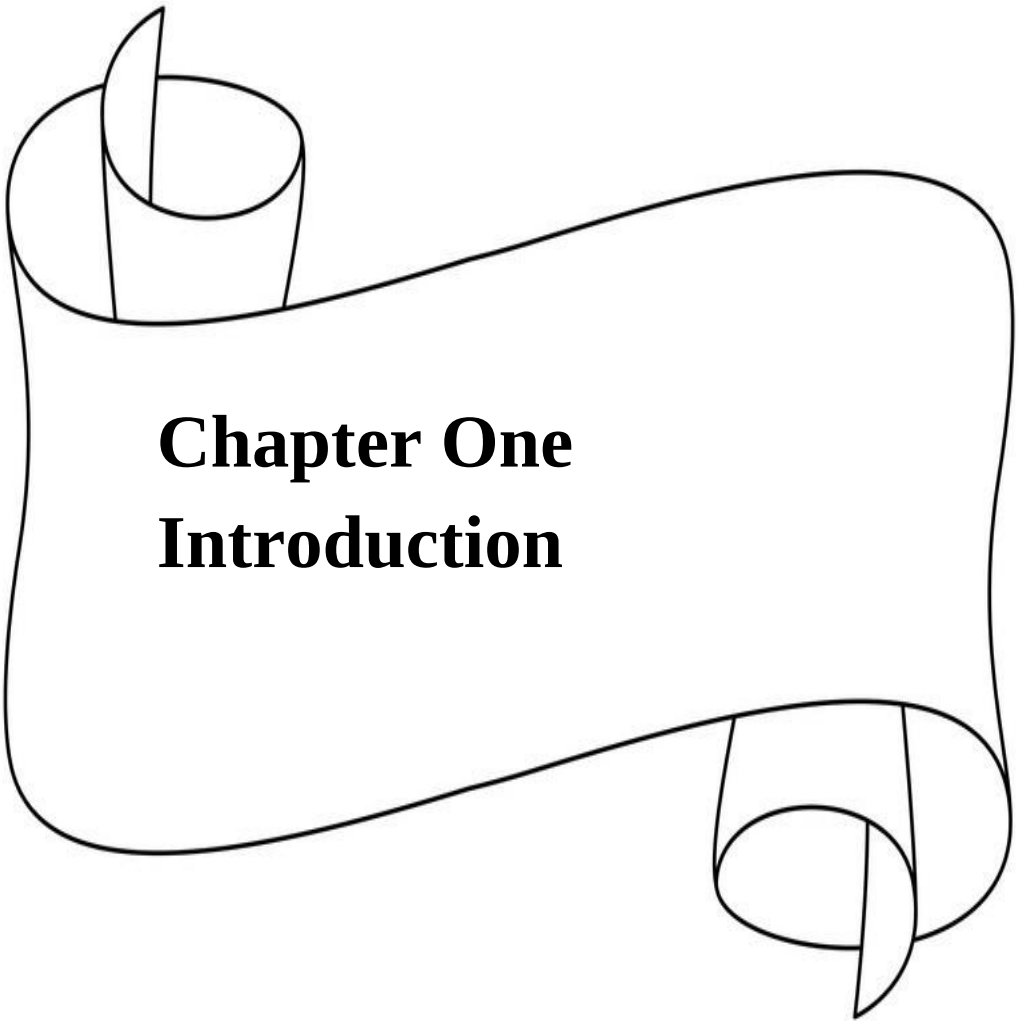
List of Scheme

List of Equation

List of Image

List of abbreviations

Shorten	Full name
AcoH	Aceticacid
Abs. EtOH	Absolut ethanol
C_{Ar}	Aromatic carbon
C_{Al}	Aliphatic carbon
HCoV-OC43	Human respiratory coronavirus OC43
EtOH	Ethanol
DMSO	Dimethyl Sulfoxide
DMF	Dimethylformamide
RT	Room temperature
ROS	Reactive oxygen species
Ref	Reflux
11β-HSD1	11β hydroxysteroid dehydrogenase type 1



Chapter One
Introduction

1.1. Adamantane

Four cyclohexane rings are joined to form the polyhedral organic compound adamantane [$(CH)_4(CH_2)_6$] as shown in figure (1.1), It is a colorless, crystalline substance with a camphor-like flavor [1].

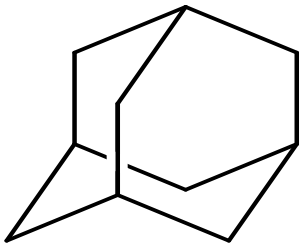
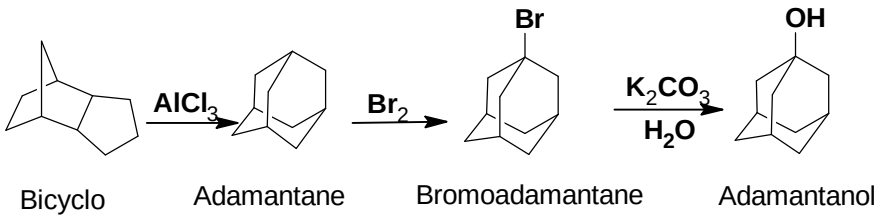


Figure 1.1: Adamantane

In 1933 Adamantane isolated from petroleum chemically synthesis in the first time in 1941, and some properties of chloroadamantanes were studied in 1959 as insecticide, after Schleyer's synthesis scheme(1.1) [2], made adamantane widely accessible, pharmaceutical research on adamantane and its functionalization was limited. Today, syntheses of adamantane derivatives continue to support these investigation [3]. It is a thermodynamically stable compound like cage structure that has the same framework as a "diamond lattice" and is a highly symmetric cycloaliphatic hydrocarbon [4-6]. The adamantane unique structure imparts many useful physical and chemical properties, such as high thermal ,oxidative stabilities, low surface energy, extreme lipophilicity, thermal conductivity, and high density, adamantane and its derivatives have wide range in lubricants and pharmaceuticals applications [7]. It has four bridgehead location that can be simply substituted by Friedel–Craft chemistry[7, 8]. It has four tertiary carbons and six secondary carbons. So, the hydrogen's attached to the four tertiary carbons are relatively more active, and could be easily functionalization [2, 9]. For example, It's feasible to create derivatives of 1 that include four distinct tertiary substituents.



Scheme 1.1: Adamantane synthesis by Schleyer's synthesis

These compounds are chiral, however due to their close to spherical form, the separation are difficult, recent mechanistic studies using adamantane as a model were able to explain and forecast how higher diamondoids will behave in the presence of radical, electrophilic, and oxidative reagents [10].

Multisubstituted adamantane are particularly adaptable scaffolds because of their mechanical rigidity, well-defined structure, and sterically bulky nature. Adamantane chemistry has been investigated and reviewed in great detail over the past 50 years[6, 11]. It's attractive bulky molecule due to the unique chemical and physical properties because of its tetrahedral form, it is an excellent building block for metal-organic frameworks(MOFs) also organic polymers with micropores [9]. Adamantane moiety is a part of structural backbone of many compounds, substances and its discovery led to the development of a new branch of chemistry that focuses on the methods of synthesis as well as the physical, chemical, and biological characteristics of organic polyhedral compounds with applications in the pharmaceutical sector [12]. The thermal stability and mechanical characteristics of polymers including adamantyl groups can be greatly improved [13]. Numerous antiviral medications have been found to have the adamantane nucleus. This is as a result of it's several virus-specific modes of action. In many instances, adding an adamantyl moiety to a pharmacologically active molecule improved the original drug's therapeutic profile [14].

1.1.2. Adamantane Derivatives

Adamantyl moiety integration produces compounds with a comparatively high lipophilicity, which can change the biological availability of these molecules, an adamantyl-containing molecule will nearly always be more lipophilic than the des-adamantyl analog, the adamantyl group influences the therapeutic index of several experimental compounds through a number of methods in addition to raising the partition coefficient, scientists have been interested in adamantane derivatives as possible chemotherapy drugs, this led to the development of various medications that are already on the market[15]. Numerous uses in medical chemistry and material sciences have been developed for stiff, tetrahedrally symmetric molecules with two- or three-dimensional scaffolds known as adamantane derivative [16]. When adamantane fragments are added to pharmaceuticals, the stability and lipophilicity of the drugs are improved. For examples adamantane pharmaceuticals derivatives containing nitrogen are abundant and typically have antiviral[17], anti-Parkinsonian[18], or anti-Alzheimer properties, Fundamentally straightforward examples include "amantadine 2, rimantadine 3, or memantine 4" figure (1.2) Adamantane also has the potential to superimpose itself onto the diamond lattice; in fact, it's the tiniest molecular member of the diamond family [19]. Research on the synthesis of new adamantane-containing compounds is stimulated by the great medicinal utility of adamantane derivatives [20]. The diamond-like cage structure of Adamantane is comparatively insensitive to reactions of degradation due to electrophilic, nucleophilic, or elimination reactions[5]. Targeted drug distribution and surface recognition are two areas in which our recently developed idea of using adamantane as an anchor in the lipid bilayer of liposomes has interesting applications [21]. The influenza medication that is officially approved A viral

infection prevents the reproduction of the virus by inhibiting the M2 proton channel, which is essential for the virus's life cycle [22]. The benefit of the adamantyl group gives increased potency for medications that include it [23]. Studies on these derivatives were done in an effort to identify novel chemicals and biological functions, as a result, various adamantane compounds were found to have a variety of biological functions[24], including antimicrobial, anticancer, antidiabetics, anti-inflammation [25], angiogenesis inhibition [36], 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibition[26], actoprotective antituberculosis, cannabimimetic properties[27], and tyrosinase inhibition activities [28]. In order to boost the lipophilicity of medications that are already active and to enhance their pharmacological effects, the adamantane moiety is typically added to their structures nowadays [21, 28].

1.1.3. Pharmaceuticals Derived from Adamantane

A number of adamantanes have developed defenses against coronaviruses. Human respiratory coronavirus HCoV-OC43 can be effectively treated with rimantadine ,amantadine, bananins, and the structurally similar drug memantine[29]. Numerous surface recognition investigations and novel drug delivery system design and production include the adamantane moiety [21]. Adamantyl groups are frequently added to the molecular structures of other compounds to enhance their biological activity. Because the adamantyl group has relatively good fat solubility, it can significantly increase a compound's membrane permeability. The development of drugs for antibacterial with new structures is crucial to research for clinical application [30].

1.1.3.1. Amantadine (1-aminoadamantane)

Since its discovery in the 1960s, amantadine (Amt) and its adamantane-based derivatives have shown to be effective medicines for treating a variety of clinical conditions [31]. Many researchers have been interested in the biological activities and synthesis of adamantane derivatives since the first adamantane derivative, (amantadine) was shown to show antiviral activity [27]. As a result, several adamantane derivatives were found to have different biological functions [26], as shown in Figure (1.2).

1.1.3.2. Rimantadine (Rim)

The first derivatives of adamantane used in medical practice exhibiting antiviral activity against influenza(A strains). Rimantadine (Rim) as shown in Figure (1.2) also used since the start of the 1980s to prevent and treat influenza A infection[27]. The influenza A virus's proton conduction channel (M2) is

connected to the drug's mode of action. These medications are unsuccessful against influenza (B virus) because it lacks the M2 ion channel [25].

1.1.3.3. Memantine

Memantine as shown in Figure (1.2) are frequently used to treat neurodegenerative illnesses, and a pathophysiologic connection between amantadine's antiviral and anti-Parkinson effects has been proposed [29].

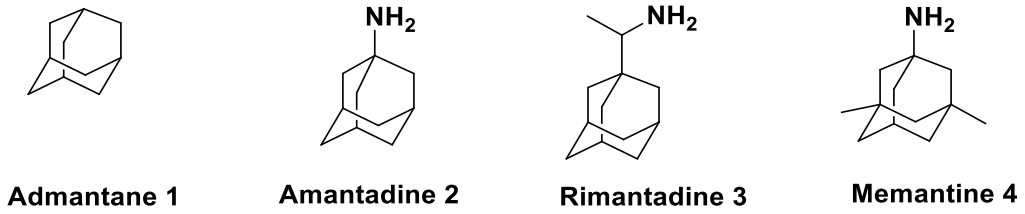


Figure 1.2: Pharmaceuticals derivatives from adamantane

1.1.4. Adamantane-Containing Polymers

Adamantane-containing polymers have received a lot of interest recently since it is anticipated that they would not only have a large free volume but will also enhance special physical and chemical characteristics[6]. The incorporation of the adamantane unit into polymers has been proven to considerably increase the stability of polymers, including improving their glass transition temperature, increasing their heat resistance, and lowering their dielectric constant [32]. Due to adamantane's strong hydrophobicity and symmetrical, inert cage structure, which inhibits degradative processes like oxidation and elimination, these polymers have increased stability [33]. The remarkable physical and thermal characteristics of adamantane and its derivatives have led to its incorporation into several polymers during the past few years, its rigid, spherical form gives the parent molecule an extremely high melting point (269°C) and outstanding thermal stability for a

hydrocarbon [4, 7, 34-36]. Polymers including polyamides, polysulfones, polyesters, and polyimides have adamantyl groups inserted into the side groups or main chain [35].

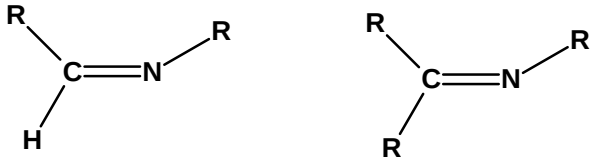
1.1.5. Adamantane Derivatives Application as Catalyst

Adamantane is a prime candidate to be used in the construction of catalysts due to its accessibility, low cost, stereoelectronic characteristics, and simplicity of functionalization[2]. In recent years, literature has risen about the idea of hybrid molecules as an effective technique of drug design that allows ligands to interact with a variety of interesting targets. In this method, two pharmacophoric moieties are combined into a single structural framework [37].

1.2. Schiff Bases

Schiff bases are a diverse class of substances distinguished by the existence of a double bond between the carbon and nitrogen atoms, their diversity is produced by the numerous ways in which different alkyl or aryl substituents can be combined, both naturally occurring and artificially created compounds of this class can be discovered, many chemists and biochemists have long found inspiration in Schiff bases[38] . Hugo Schiff first discovered the reversible condensation reaction between "primary amine and carbonyl compounds" in 1864, and since then, Schiff base compounds have received substantial research due to their wide variety of biological uses, chelating properties, stability, and simplicity of manufacture [39]. Due to their widespread applications and simplicity of manufacture, derivatives of Schiff-based have drawn a lot of interest, and it has found use in a variety of fields, including analytical, biological, and inorganic chemistry, which is mostly due to the existence of carbon-nitrogen double bonds, photochromic and thermochromic characteristics have also been seen in the solid state. Additionally, it has been

demonstrated that these molecules serve as significant intermediates in a variety of enzymatic processes that involve the interaction of the enzyme with the carbonyl or amino group of the substrate [40]. The imine bond produce by reaction of aldehyde and amine is called aldimine, while the imine bond produce by reaction of ketone is called ketamine as shown in figure(1.3) [41]. Since aromatic aldehyde Schiff bases have a strong conjugation mechanism, they are more stable than aliphatic aldehyde Schiff bases, which are unstable and readily polymerizabl [42]. The crosslinking of amine groups and aldehyde groups creates a dynamic covalent imine bond as part of the chemical process known as the Schiff reaction [43] .



aldimine ketamine

Figure 1.3 : Two type of Schiff base

1.2.1. Application of Schiff Bases in Medicine

Schiff base compounds has been shown to have a variety of biological effects, containing antifungal, antibacterial, and anti-inflammatory effects [39, 44-47], ureases inhibitory, anti-ulcerogenic, antioxidant, pesticidal, cytotoxic, and anticancer including DNA damage, the kind of substituted aromatic ring depends on biological activity [48-50]. Only a little amount of progress has been achieved in the past 30 years in the study of antibacterial medications with novel mechanisms and core structures; Schiff bases have a range of biochemical, clinical, and pharmacological features, these compounds exhibit several biological features mostly because of the imine group's presence, one of the organisms' built-in processes for self-healing is a Schiff reaction with dynamic equilibrium [51]. The

presence of imine or azomethine groups is seen in a variety of natural, naturally-derived [45].

1.2.2. Application of Schiff Bases in Industry

Schiff bases act as substrates in many preparation of biologically active and industrial compounds by cycloaddition or replacement reaction [50, 52]. Bactericides, Pesticides, herbicides, insecticides, and growth regulating have all been made from Schiff bases and their metal complexes [46]. Additionally, they were used in the production of automotive anti-glare mirrors and high-temperature, organic semiconductors, deodorants, light stabilizers, filaments, cross-linked polymers, dental materials, corrosion inhibitors, and perfumes, as well as other crucial fields like catalysis, photography, paints, pigment [53-55], and food industry[56]. Schiff bases, which have four, five, and seven-membered rings and exhibit biological activities based on their spectra, and have a wide range of industrial and medicinal uses[57]. By adding them to polymer films, they help to photostabilize polymer [58]. In scientific investigations, it has also been employed effectively as a very effective and selective sensing material for electrochemical, optical, and membrane sensors, multiidentate ligand Schiff base complexes have a high propensity to bind any metal ion [59, 60]. Recent studies have looked at a number of Schiff bases as corrosion inhibitors for different metals and alloys in acid conditions; these compounds typically work by adhering to the metal surface [61].

1.2.3. Application of Schiff Bases as Catalyst

At high temperatures, several Schiff bases operate well as catalysts [47]. They are also receiving more attention as a result of their amazing catalytic and

biological uses [48]. In a recent spate of studies, synthesis structural analysis, and catalytic activity of oxovanadium Schiff base complexes [62].

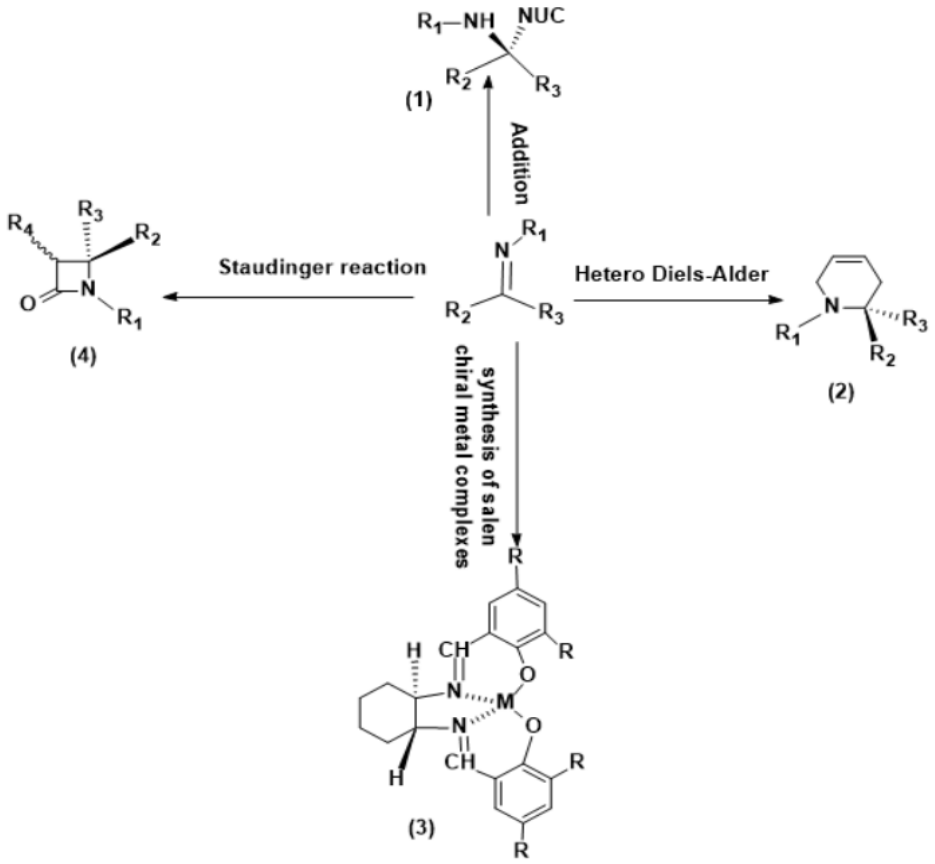
1.2.4. Application of Schiff Bases in Metal Complexes

As a result of their ability to form complexes with metal ions, Schiff base ligands are frequently utilized in the development of inorganic chemistry and coordination chemistry [47], they have significantly contributed to the development of modern coordination chemistry [63]. Several distinctive biological features of Schiff bases are due to the nitrogen found in the imine groups (C=N) in these compounds' metallic forms and their chelating abilities [64]. Additionally, it would be intriguing to look into the biological effects of this novel Schiff base molecule and its lanthanide complexes, including their potential antimicrobial, antifungal, antioxidant, and anticancer effects [39]. They are known as auxiliary ligands because in contrast to reactive ligands, they do not themselves go through irreversible changes but instead affect the structural reactivity of the transition metal ion at the heart of the complex [39]. The study of coordination chemistry of Schiff base has grown significantly. Schiff base complexes provide advantages for biological applications [65], supramolecular chemistry, material science, catalysis, separation [66]. Due to their simplicity in synthesis and capacity to form complexes with practically all metals, Schiff base ligands have drawn a lot of attention from researchers [67].

1.2.5. Application of Schiff Bases as Intermediate in Organic Synthesis

The imine group, which is defined by a double bond between carbon and nitrogen atoms, is thought to play a vital role in the advancement of chemical research. The reaction of Schiff base is crucial for the production of C-N bonds

during of synthesize of organic compounds[59]. It has a useful precursor in synthesis of organic compound to produce of Intermediates and Products, we can identify, in an generalization, four different kinds of reactions in which Schiff bases have been found very important applications: (A) addition reaction of organometallic or hydride reagents to C=N bond as in structure(1); (B) hetero Diels-Alder reaction to produce heterocyclic compounds as in structure (2); (C) synthesis of salen chiral metal complexes (3); (D) synthesis of significant biologically β-lactam ring by Staudinger reaction with ketene (4),as shown in Scheme(1.2)**.** Schiff bases as intermediates in bio-processes existing as transamination reaction[68], Moreover the reactions of azomethine throughout ring closing to generation a wide range of five , six and seven members ring of heterocyclic organic molecules[69], such as the derivatives of Oxazepines, Tetrazole, Thiazolidinone [70, 71], Oxadiazole, Azetidinone, and Benzoxazole [72]. Due to the nitrogen atom's lone pair of electrons and the double bond's overall electron-donating nature, the chemistry of the (C=N) group has been actively involved in the development of chemical sciences. These substances have a wide range of uses in the science of chemistry, such as fine chemicals, medicinal substrates, or as a building block in the synthesis of significant pharmaceuticals[73]. When the OH groups are positioned correctly in relation to the C=N functionality, both intramolecular and intermolecular H-bonds may be seen [74]. Generally speaking, heterocyclics with nitrogen atoms are present in the structures of the majority of medicinally significant compounds for pharmacological activities ranging from antibacterial to anticancer. The development of microorganism resistance to the majority of existing antimicrobial drugs is a problem for global health. There is a growing need to create novel antibacterial compounds to address this issue [75].



Scheme 1.2: Application of Schiff base in organic synthesis

1.2.6. Application of Schiff Bases as Antioxidant

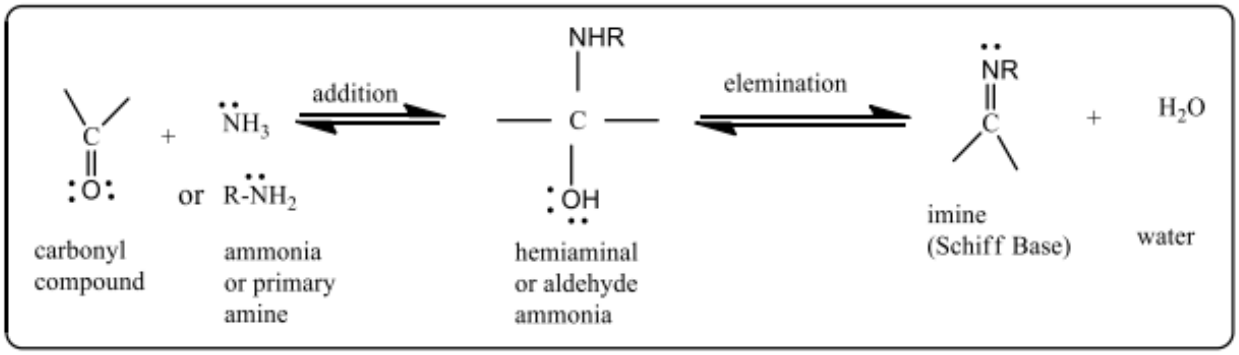
Antioxidants are chemical compounds found in nature that shield the living organism from harm from dangerous chemicals known as free radicals. Free radicals play a crucial part in the etiology of many illnesses[76], including cancer, diabetes, liver damage, autoimmune disorders, heart diseases, atherosclerosis, and aging. These are formed by body cells in reaction to free radicals, antioxidants which have the ability to scavenge free radicals are therefore crucial for the treatment and prevention of various disorders. They are frequently employed as catalysts in industries like anticorrosion and in antibiotics like anti-inflammatory, antifungal, antibacterial, and antiviral. Because they are more affordable and

efficient than natural antioxidants, synthetic antioxidants are widely used nowadays[48]. Numerous studies on how free radicals interact with biological systems including lipids, DNA, and protein are now being conducted [77]. A free radical is any type of chemical species that may live independently and has an unpaired electron in an atomic orbital. Most radicals have a few like characteristics that are brought by the presence of unpaired electrons. Many radicals have a high reactivity and instability threshold. By either donating or accepting an electron from other molecules, they can behave as either reductant or oxidants [78]. These are so reactive substances that may damage physiologically Important elements found in cell membranes and the nucleus include proteins, DNA, lipids, and carbohydrates. By attacking crucial macromolecules, free radicals, which can harm cells and disturb homeostasis. Every sort of molecule in the body is susceptible to damage by free radicals. Proteins, lipids, and nucleic acids are the main targets among them[78]. Free radicals are created from molecules by redox processes, the cleavage of radicals into additional radicals, and the breaking of chemical bonds so that each fragment retains one electron [79]. Synthetic antioxidants are being utilized extensively because they are more efficient and affordable than natural antioxidants, Several Schiff-base metal complexes are being researched right now as efficient ROS scavengers and antioxidants [80].

1.2.7. Synthesis of Schiff Base and Mechanism

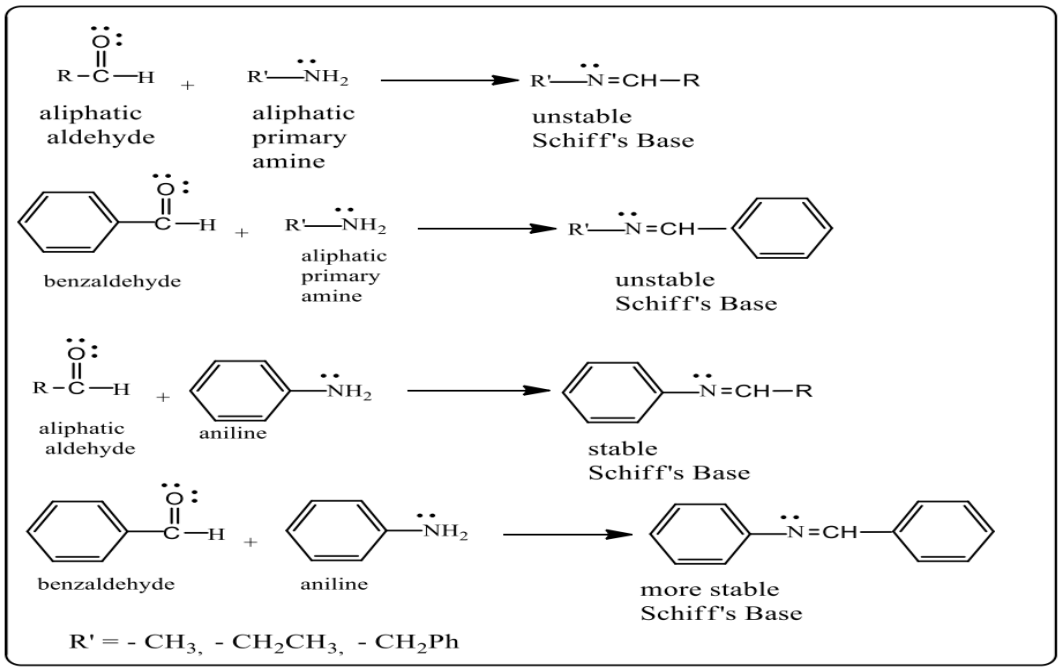
Adding nucleophiles to carbonyl group are one of the most significant types of reactions[81]. In order to create a hemiaminal, an aromatic amine's double electronic amino group (NH_2) is attacked by a nucleophile addition to carbonyl group (C=O) of aromatic aldehyde's, this unstable intermediate convert to Schiff base by removed water molecule as shown in Scheme (1.3) [82]. Aqueous acid or

base can hydrolyze several Schiff bases to return them to their aldehydes, ketones, and amines[83].



Scheme 1.3 :Mechanism of Schiff base synthesis

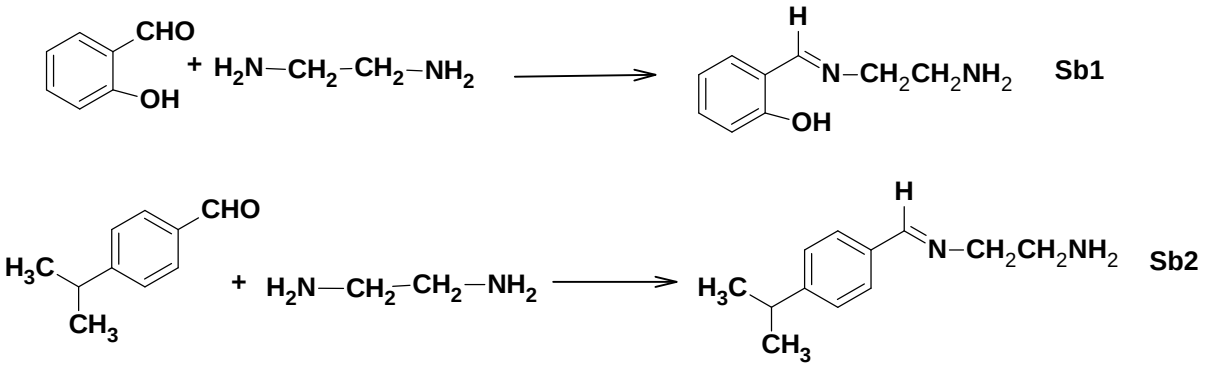
The stability of the finished product depends on the nature of the initial aldehyde or ketone and the amine. In general, the resultant imine is unstable. The following classes of chemicals can be used to create stabilized Schiff bases, it can be said. as shown in Scheme (1.4) [84].



Scheme 1.4 :Stability of Schiff bases depend on the structure of carbonyl compound and amine

1.2.8. Synthesis of Schiff Bases Historically

Sheheryar et al. (2022) [85] studied and synthesized new two Schiff base ligands,(E)-2-(4-aminobut-1-enyl) phenol(Sb1) by condensation reaction between ethylene diamine and salicyldehye and (E)-2-(4-aminobut-1enyl)-5-methylaniline(Sb2) from 4-dimethylaminobenzaldehyde and ethylene di-amine as shown in equation(1.1) and evaluate biological activity of this ligands.



Equation 1.1: New two Schiff base ligands Sb1 & Sb2

Hemalatha et al. (2022)[86] synthesis Schiff bases Isoniazid,(E)-N'-((1H-Pyrrol-2-yl)methylene)isonicotinohydrazide (S1) and (E)-N'-(thiophen-2-yl-methylene) isonicotinohydrazide (S2) as shown in Figure(1.4), by the reaction of Isonicotinohydrazide with heterocyclic carbaldehyde, this compound have specific HC=N-NH-C=O group, these specific group leads to formation "intermolecular and intramolecular hydrogen bonding" which, as a result of strong interact between binding sites and cells of target tumor, promotes biological activity.

S1

S2

((1*H*-pyrrol-2-yl)methylene)isonicotinohydrazide (Thiophen-2-ylmethylene)isonicotinohydrazide

Figure 1.4: Structures of compound (S1) & (S2)

Osman et al.(2021) [37] In order to create a hybrid compound that is an effective drug design strategy which allows interaction between ligands and multiple targets of interest as shown in figure(1.5), this strategy involves the combination of two pharmacophoric moieties in a one structural framework. It has been established that the idea of "one-drug-one-target-one-disease" is inadequate for treating this heterogeneous disease. Additionally, studies on the effectiveness of new antiepileptic medications in effectively treating seizures have been mixed [37, 87].

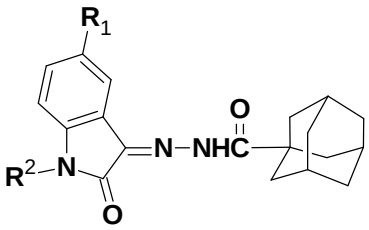
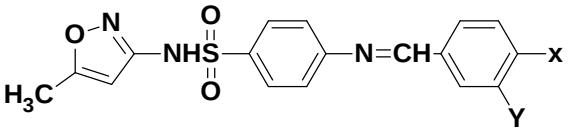


Figure 1.5: Schiff base derivative from adamantane-1-carbohydrazide and isatin derivative

Mousa et al.(2021)[88] As shown below, the study included the synthesis of a new Schiff base compounds from the reaction of the drug sulfamethoxazole with some aromatic aldehydes as shown in Figure(1.6), using the classical Schiff base method, as well as the examination of the biological activity of the prepared compound in comparison to the biological activity of the parent drug.

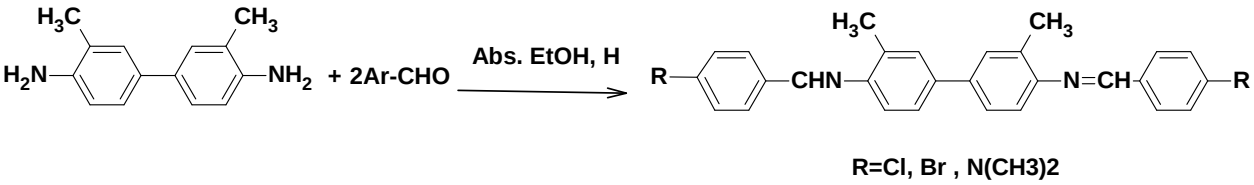


X = OH, Br, Cl, CHO, NO2

Y = H, OCH3

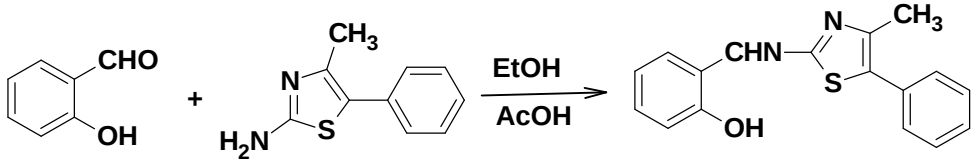
Figure 1.6: Schiff derived from sulfamethoxazol drug and aromatic aldehydes

Al-Labban, H. (2017)[89] synthesis of new Schiff bases derivatives by condensation reaction of o-tolidine with many aromatic aldehydes as shown in equation (1.2).



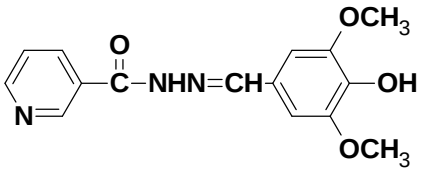
Equation 1.2: Schiff base derivative from *o*-tolidine

Abd-Elzaher et al.(2016)[90] Using a condensation reaction between salicylaldehyde and 2-amino-4-phenyl-5-methyl thiazole as shown in equation (1.3), this report created a Schiff base ligand in good yield. It also examined the anticancer properties of the compounds created in comparison to various human tumor cell lines.

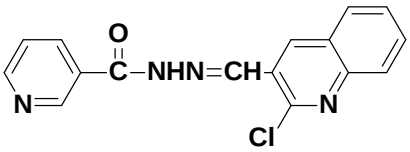


Equation 1.3: Synthesis of Schiff base derivative from salicylaldehyde and 2-amino-4-phenyl-5-methyl thiazole

Desai et al.(2015)[91]A series of Schiff bases derived from nicotinic acid hydrazide and variety of aldehydes using natural catalyst lemon juice, which exhibit biological activity in moderate to good yields, which have been exhibited excellent anti-tubercular activity in compared with standard drugs used.such as Nicotinic acid (4-hydroxy-3,5-dimethoxy-benzylidene)-hydrazide and Nicotinic acid (2-chloro-quinolidene)-hydrazide as shown in figure (1.7).



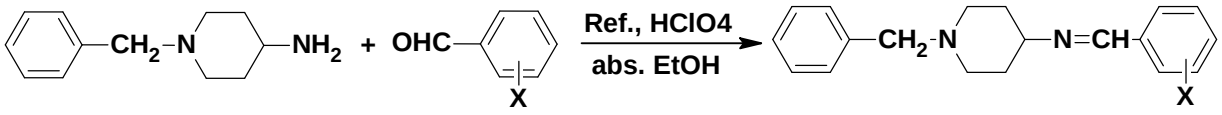
Nicotinic acid(4- hydroxy-3,5-dimethoxy-benzylidene)hydrazide



Nicotinic acid(2-chloro-quinolidene)hydrazide

Figure 1.7: Schiff base based on Nicotinic acid

Mayavel et al .(2014)[92]in this report a series of Schiff's bases (aryl E-imines) have been synthesized by condensation of aryl amines and benzaldehyde derivatives in perchloric acid as catalyst equation(1.4), in good yield Schiff's bases approximate 80%.



x=H ,CH3 ,OCH3 ,F ,Cl ,Br ,NO2 ,N(CH3)2

Equation 1.4: Preparation of Schiff base used perchloric acid as a catalyst

Pandey et al.(2012) [93] Schiff bases synthesis and research Using various aromatic aldehydes, generated from 2-amino-5-aryl-1,3,4-thiadiazole derivatives have been produced as shown in Figure(1.8) , Due to their intriguing physiological characteristics, several five-membered aromatic systems with three hetero atoms in the symmetrical position have been explored. The 1, 3, 4-thiadiazole derivatives were recognized to have a wide range of pharmacological properties, including analgesic, antibacterial, anti-convulsant, anti-inflammatory , and antimicrobial properties. Drugs containing thiadiazole have also been found to have anti-tubercular, diuretic, anticancer, and anthelmintic properties.

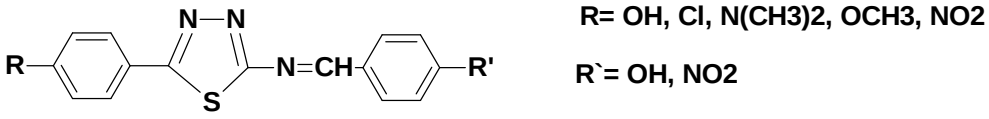


Figure 1.8: Schiff bases derived from 2-amino-5-aryl-1,3,4-thiadiazol derivatives with aromatic aldehydes

Khedr et al .(2005)[94] new Schiff bases synthesized from azo compound 5-[3-(1,2,4-triazolyl-azo]-2,4-dihydroxy-benzaldehyde (TA) and 1,3-diaminopropane(TAAP) compound or 1,6-diaminohexane (TAAH) compound figure(1.9).

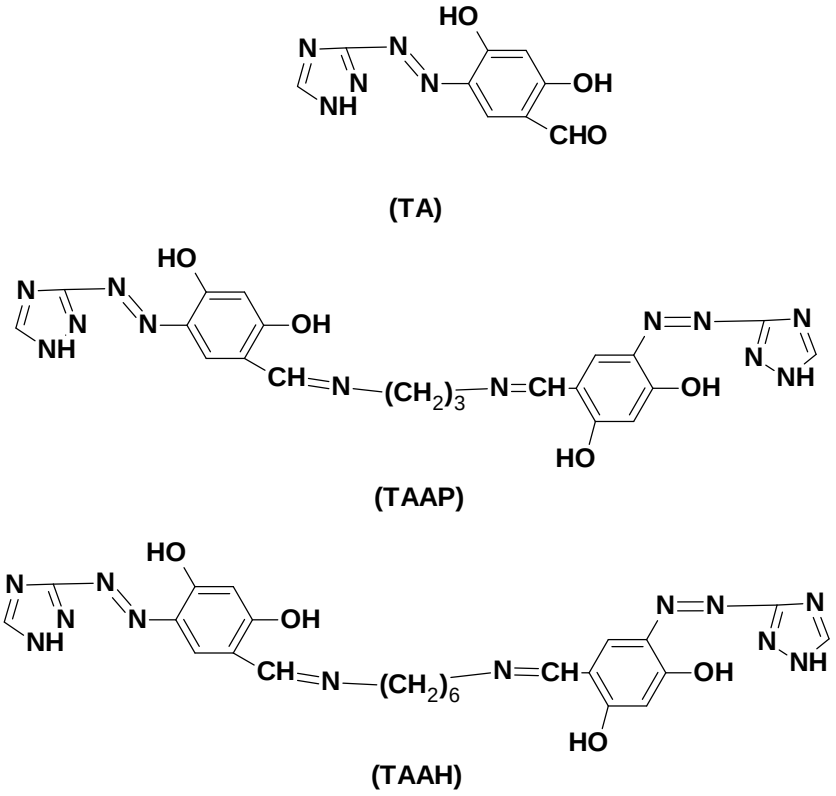


Figure 1.9: Several Schiff bases compounds contain azo dyes

1.3. Heterocyclic Compounds

The most frequent heteroatoms are oxygen, nitrogen, and sulfur, while heterocyclic rings including additional hetero elements are also well-known. Heterocyclic compounds are cyclic organic molecules that contain at least one hetero atom [95, 96], Due to its involvement in several diseases, heterocyclic compounds are regarded as one of the essential types of organic chemicals that are employed in numerous biological areas. The heterocyclic ring is a fundamental structural component of many biological compounds, including RNA, and DNA, hemoglobin, chlorophyll, and vitamins[97]. Amino acids as histidine, proline, and tryptophan, in addition to vitamin and coenzyme precursors from the riboflavin, folic acid, thiamine ,pyridoxine, biotin, B12, and E family of vitamins, are some of the major heterocyclic compounds utilized in medications. There are several heterocyclic compounds that are pharmacologically active, many of which are used often in therapeutic settings [98]. The essential structural components of many bioactive natural compounds, such as alkaloids and macrolides, as well as many physiologically significant and important molecules are represented by the heterocyclic frameworks such as furan , pyrrole , thiophene , pyridine, piperidine , oxazepine, thiazolidinedione, benzoxazole, oxadiazole, and azetidinone as shown in Figure (1.10) [99, 100].

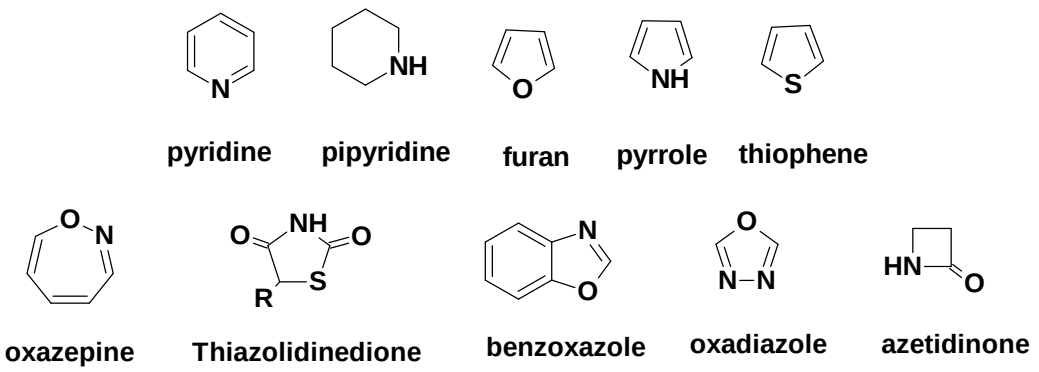


Figure 1.10: Different heterocyclic ring with one, two, and three heteroatom

1.3.1. Cycloaddition Reaction

A cyclic adduct is created in a family of chemical reactions known as cycloaddition when two or more unsaturated molecules combine. Due to it's capacity to produce many C-C and C-heteroatom bonds in a single step, cycloaddition reactions are regarded as the most important bond-forming processes in organic chemistry. A cycloaddition process has been classified as "(m+n)-cycloaddition" depend on the characteristics of the reacting systems involved. "m" and "n" stand for the number of atoms from each of the reacting partners participating during the cycloaddition reaction (typically m > n). One of the most well-known cycloaddition reactions is the "Diels-Alder reaction (D-A)", which is a [4+2]-cycloaddition reaction between a diene (4-component) and a dienophile (2-component). Diels and Alder made the initial discovery of the D-A reaction in 1928, and in 1950, they were jointly awarded the Nobel Prize. The most popular hetero-Diels-Alder (HDA) reactions used to create six-membered heterocyclic systems including pyrans, piperidines, and other compounds. In addition to D-A processes, [3+2] cycloaddition reactions provide a flexible method for producing five-membered heterocyclic compounds with high levels of stereo- and regio selectivity, including triazoles, oxazoles, imidazoles isoxazoles, and tetrazoles. For

the synthesis of heterocyclic natural products or medicinal compounds, these reactions have frequently been exploited as key reactions. The heterocyclic frameworks (furan, pyrrole, quinolone, indole, imidazole, oxazole, triazole, etc.) represent the key structures of medicinal, pharmaceutical, and biologically important molecules as well as many bioactive natural products, for example, alkaloids and macrolides [99].

1.3.2. Tetrazole Ring System

Tetrazole is a five-membered heterocyclic molecule containing a carbon atom and four nitrogen atoms. Theoretically, tetrazole has 3 isomers: 1H-tetrazole(1), 2H-tetrazolium(2), and 5H-tetrazole (3) as shown in figure (1.11) [101, 102]

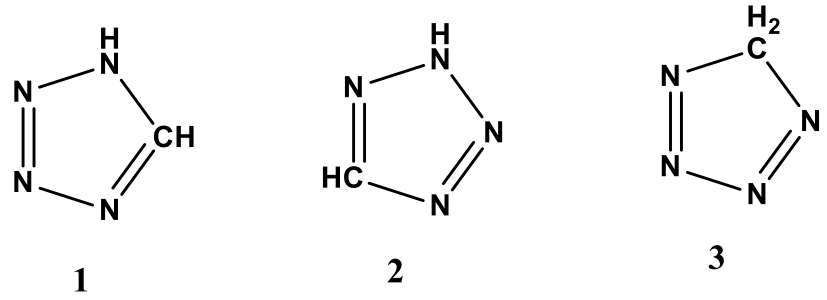


Figure 1.11: Structure of the regioisomeric tetrazole rings

Tetrazole rings are major factors in new drug design descriptors since they are included in the majority of active pharmaceutical ingredients (API), Numerous investigations on the synthesis of tetrazole derivatives are being conducted in light of its significance, It's synthesis involves [3+2] cycloaddition reaction [103]. Tetrazole's heteroaromatic five-membered ring, which has four nitrogen atoms, produces nitrogen-rich planar structural characteristics. Additionally, tetrazoles'

acidic character results from the free N-H present in their structure[104], and this trait can cause nucleophilic substitution to generate more complicated aliphatic and aromatic heterocyclic compounds, in fact, the heterocyclic tetrazole moiety exhibits the identical pKa values for the respective carboxylic acids[105] , it also has roughly the same needs for planar delocalized system space and offered the highest nitrogen concentration of any heterocyclic molecule. Tetrazole derivatives have both acceptor and donor electrical characteristics due to the nitrogen-rich multi-electron conjugated system and planar ring skeleton structure [102]. The tetrazole ring's bigger size as compared to the carboxylate anion might lower it's binding affinity at the active site. This might be due to "steric hinrance" or improper grouping of the active site's functional [106], and can stabilize the negative charge of the corresponding anion through charge displacement Tetrazoles also demand approximately the same amount of electrical space as carboxylates and have a larger nitrogen concentration than other heterocycles, as a result, these qualities have increased their use in a variety of fields, including as materials research, coordination chemistry, pharmaceuticals and drug design, the food industry and agrochemicals [107], polymers, gas generators, rocket propellants, chemicals for photography and photoimaging, and explosives[108]. Nitrogen-rich compound and derivatives are a favorable components of ecofriendly energetic compositions[109], an important group of poly-aza-heterocyclic chemicals, tetrazoles were mostly found in nature. Tetrazoles have attracted a lot of interest lately because of their broad range of medical and biological uses, including as anticancer, antiviral, antiallergic, antibiotic, and anti-HIV agents [110]. Due to their great density, good positive enthalpy of formation, extraordinary detonation capability, and high thermal stability, nitrogen-rich compounds have received a lot of interest in energetic materials [111]. The

Tetrazole group has improved bioavailability and metabolic stability, and the four nitrogen atoms in the Tetrazole ring can provide a more even distribution of charges[100].

1.3.3. Biological Activity of Tetrazole Compound

One of the most pressing objectives in contemporary chemistry and materials science is the development of innovative functional organic materials. These substances include a broad range of typically conjugated organic compounds with various chemical and physical characteristics. Tetrazoles, which are classified as carboxylic acid bioisosteres [112], are present in a variety of pharmacological processes, including several therapeutically effective medications[113, 114], improve lipophilicity, bioavailability Tetrazole, and lessen adverse effects[115] . due to the produced compounds exhibited anti-bacterial, anti-fungal, and anti-viral. Recent findings from multiple research teams throughout the globe have proven that adding a nitrogen heterocyclic motif typically improves the quality of materials compared to their carbocyclic analogs action, tetrazole compounds and their products were extremely important, particularly in the biological area. It was furthermore utilized in the creation of medications used to treat chronic illnesses[116] , anticonvulsant and diabetic kidney disease activities[114], it has also exhibit analgesic, anti-inflammatory, anti-cancer, anti-hypertensive, hypoglycemic, antiparasitic, and antiviral properties, the aforementioned characteristics and the ability to modify the biological or physico-chemical characteristics of these compounds by adding a variety of structurally different substituents to the heterocycle ring have led to the use of this heterocycle as a template in numerous research projects aimed at creating new bioactive compounds[102]. Tetrazole derivatives created by the cyclic addition reactions

between Schiff bases and sodium azide [116]. There are several examples of commercial medications with the tetrazole ring-like structure, including cilostazol, pentylenetetrazol, losartan, candesartan, and valsartan, which are all used in clinical practice to treat various diseases figure (1.12). Because it is the bioisosteric analog of cis-amide and a carboxylic acid and has good metabolic stability, the tetrazole ring is also exploited in the development of novel medications, tetrazoles also have interactions with electron-donating and electron-withdrawing groups and exhibit stacking interactions with receptor recognition sites that are present in target tissues[117]. More than 20 pharmaceuticals containing tetrazole motifs are readily accessible on the market, treating a variety of medical conditions[118].

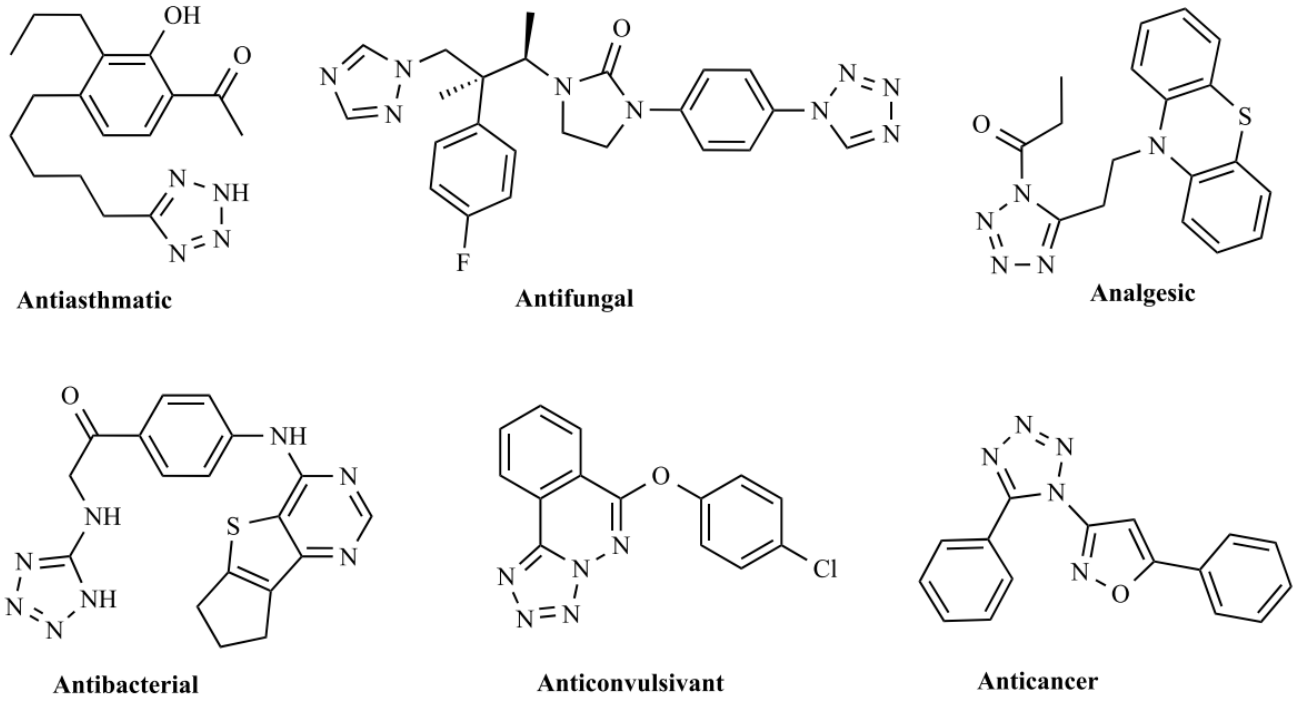
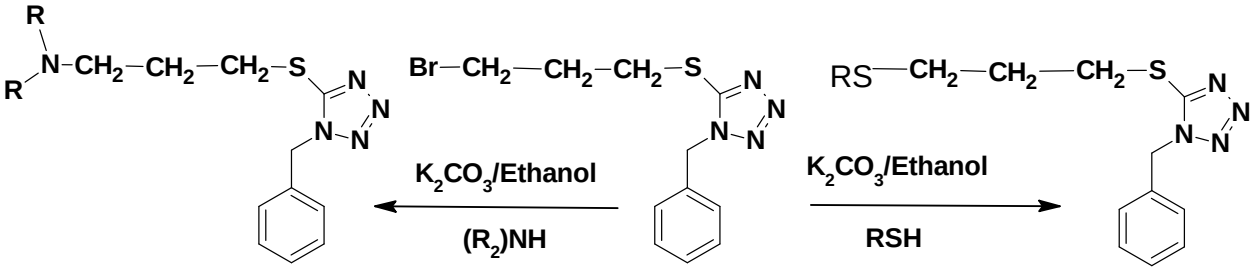


Figure 1.12 Public drugs having the tetrazole ring.

1.3.3.1. Antifungal and Antibacterial Activity

Several tetrazole hybrids were created, manufactured, and tested for their antifungal properties; some of them shown promising action against both drug-resistant and drug-susceptible fungi for example Dhayanithi et al .(2011) New 5-thio-substituted tetrazole derivatives as shown in equation(1.5) were effectively produced and studied antifungal and antibacterial activities all the Synthesized substances show middle to excellent effectiveness against the examined organisms [105].



Equation 1.5: Synthesis of 5-thio-substituted tetrazole

1.3.3.2. Analgesic and Anti-Inflammatory Activity

In both natural and synthesized pharmaceuticals, nitrogen heterocycles are the most crucial structural components[119]. Bekhit et al .(2004) synthesized a series compounds involved both the tetrazole ring and quinoline in the same skeleton structure as shown in figure(1.13), as well as evaluation of anti-inflammatory and antibacterial properties of the recently synthesized compounds [120].

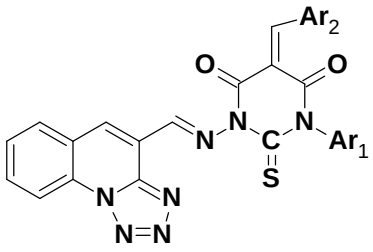
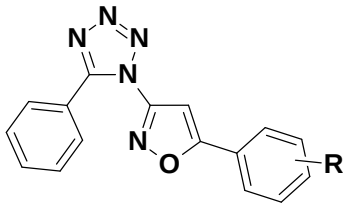


Figure 1.13: Schiff base derivative containing tetrazole ring and quinolone

1.3.3.3. Anticancer Activity

One of the most terrifying diseases that affects both humans and animals is cancer, which is one of the major causes of mortality globally. As a result, in order to effectively inhibit proliferative pathways and cell clonal growth, new anticancer medication molecules must be found, created, and improved. Additionally, it is essential to create new structural heterocyclic moieties in order to create potential anticancer agents with intriguing biological applications. An important worldwide public health concern is cancer. One of the most popular forms of treatment for breast cancer is chemotherapy. Negative side effects of this therapy are often reported, ranging from nausea to bone marrow failure and the emergence of multidrug resistance[121]. Tetrazole moiety insertion into therapeutic molecules has lately received research and may increase the medicine's efficacy and bioavailability[122]. Bhaskar et al .(2010) synthesis of new derivatives as shown in figure(1.14)with anticancer activity containing tetrazole ring from benzonitrile [123].



R= H, Br, Cl, CH3, OCH3, NO2, N(CH3)2

Figure 1.14: New derivatives with anticancer activity containing tetrazole ring from benzonitrile

1.3.3.5. Anti-Corrosion Activity

Conjugated double bonds, aromatic rings, heterocyclic rings, which serve as the fundamental building blocks of organic molecules, as well as N, P, O, and S, provide inhibitors a robust platform for metal adsorption. The effective stalling of corrosive attack can be facilitated by the well-organized self-assembly of organic molecules on the metal surface , Qiang et al. (2020) explored the mechanism by which the S-linker affects the ability of tetrazole compounds to control copper corrosion and recommended two tetrazole derivatives as inhibitors in sulfuric acid solutions[124]. Tetrazole's chemistry is being monitored to evolve dynamically, Compounds containing tetrazole and compositions based on them are used as corrosion inhibitors[125].

1.3.4. Synthesis of Tetrazole Compound

Tetrazoles can exist as anions, cations, and other tautomeric forms. 1,4 Dihydrotetrazoles 1 and 2 are examples of partly hydrogenated tetrazoles in this context as shown in figure(1.15) [126].

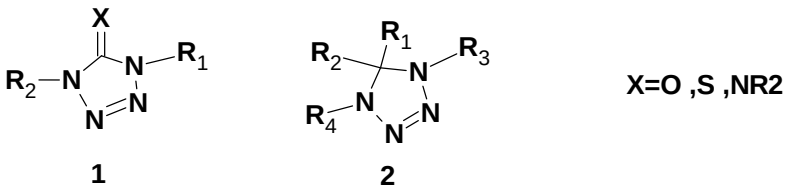
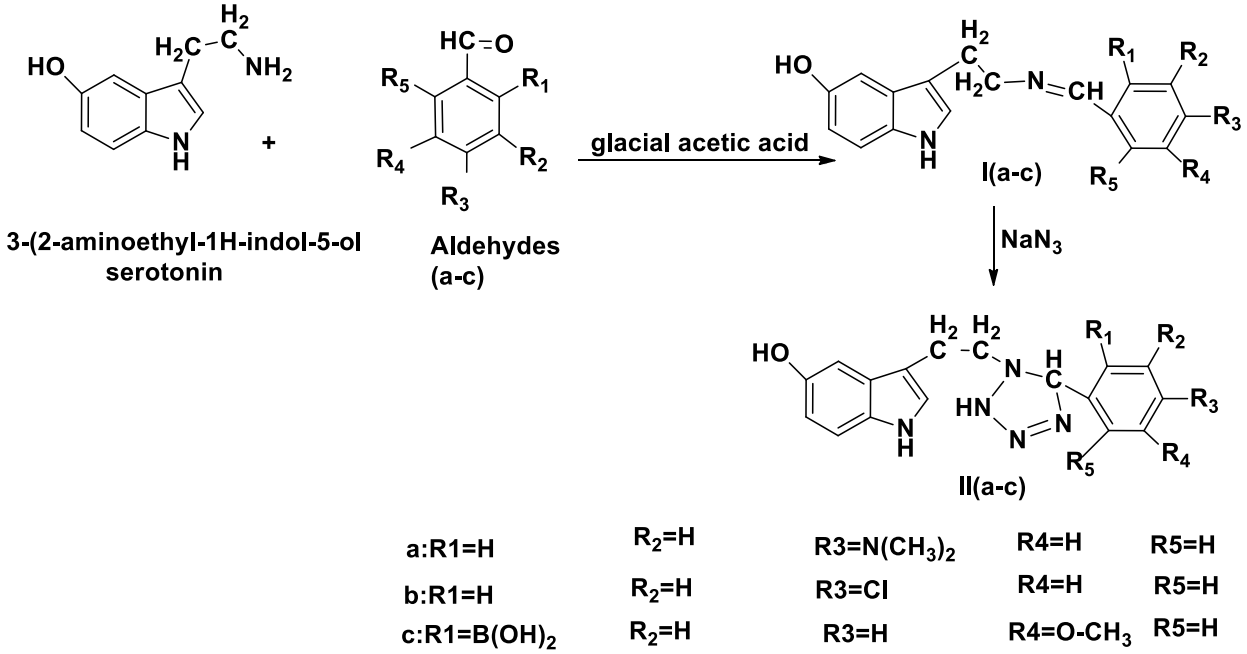


Figure 1.15 Tetrazole forms partially hydrogenated

Saleh et al. (2021)[127] synthesis and the study of new Derivatives of Serotonin having tetrazole Moiety and estimated antimicrobial activity of synthesizes compounds as shown in scheme(1.5).



Scheme 1.5 Synthesis Tetrazole derivatives serotonin

Alsahib et al .(2021)[128] synthesize a series of tetrazole derivatives compound from Schiff base derived from 2-(pyrimidin-2-ylamino) acetohydrazide with various aromatic aldehydes ,these Schiff base derivatives react with sodium azide to produced tetrazole compound as shown in figure (1.16).

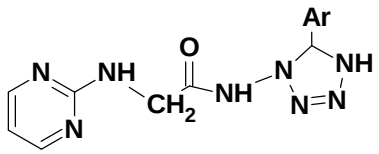


Figure 1.16: Tetrazole derivatives compound from Schiff base and sodium azide

Ahmed et al .(2019)[52] Synthesis of new tetrazole derivatives compound from Schiff base derivatives of (1-amino-4-methyl-6-phenylpyrimidine-2-(1H)-thione)as shown in figure (1.17).

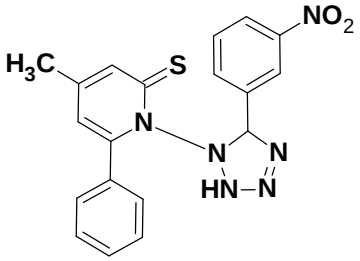
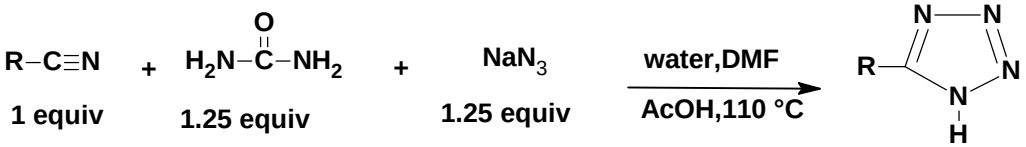


Figure 1.17: New tetrazole derivatives compound from (1-amino-4-methyl-6-phenyl pyrimidine-2-(1H)-thione

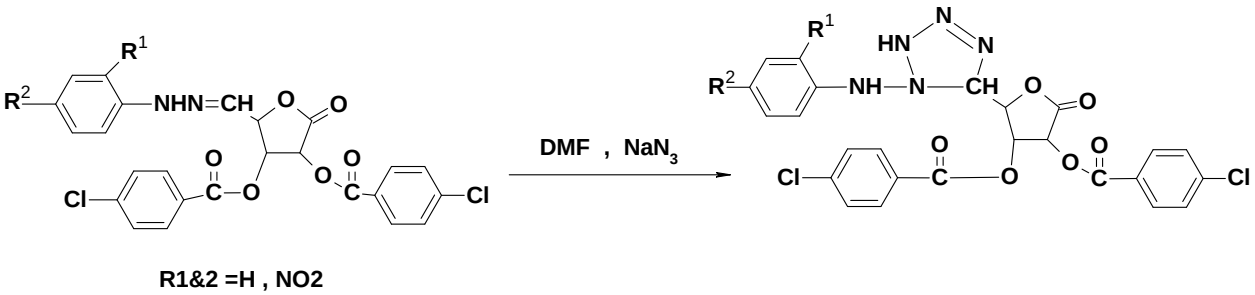
Yakambram et al.(2018)[129] The development of an excellent to high yield method for synthesizing 5-substituted 1H-tetrazoles utilizing a variety of nitriles and sodium azide in the presence of urea and acetic acid as shown in equation(1.6).



R=aryl,hetro cyclic,etc

Equation 1.6: Synthesis 5-substituted 1H-tetrazoles from different nitriles and urea

Mosa et al .(2019)[130] synthesis of 2,5-Dihydrotetrazole derivatives by cycloaddition reaction between schiff base and sodium azide as shown in equation (1.7) and evaluated of biological activity of derivative compounds.



Equation 1.7: Synthesis of 2,5-dihydrotetrazole derivatives

Alfatlawi et al . (2018)[131]synthesis of new derivative of Schiff base from 2-Aminonitrobenzothiazole, these derivative then react with sodium azide to produced tetrazole derivative as shown in figure(1.18)

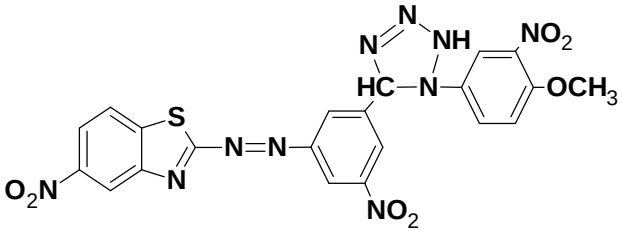
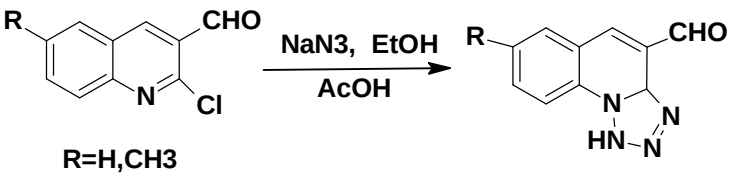


Figure 1.18: New tetrazole derivative from Amino nitro benzothiazole

Bhuva et al .(2012)[132] Synthesis of tetrazol derivative from 2-chloro quinoline-3-carbaldehyde derivatives as shown in equation (1.8).



Equation 1.8: Preparation of tetrazole derivative from 2-chloro quinoline-3-carbaldehyde

Al-Juburi, R .(2012)[133] a series of new Schiff base synthesized from benzidine and aromatic aldehydes, then react with sodium azid in THF as solvent to produce tetrazole derivatives as shown in figure (1.19), and estimated the biological activity of these compounds.

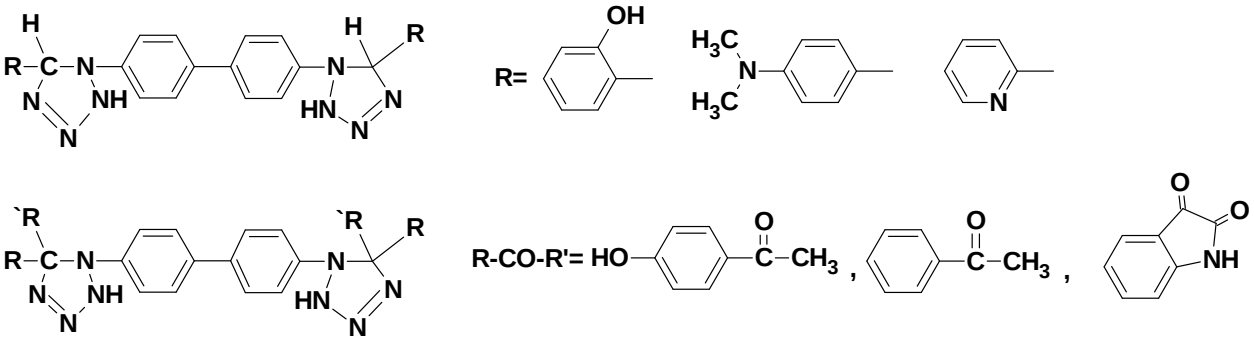


Figure 1.19: Tetrazole derivatives based on benzidine

Umarani et al .(2010)[134] synthesis of new Schiff bases containing tetrazole quinoxalines in skeleyon structures, as well as estimated of biological activity of synthesized compounds figure (1.20).

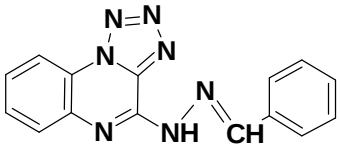


Figure 1.20: New Schiff bases containing tetrazolo quinoxalines

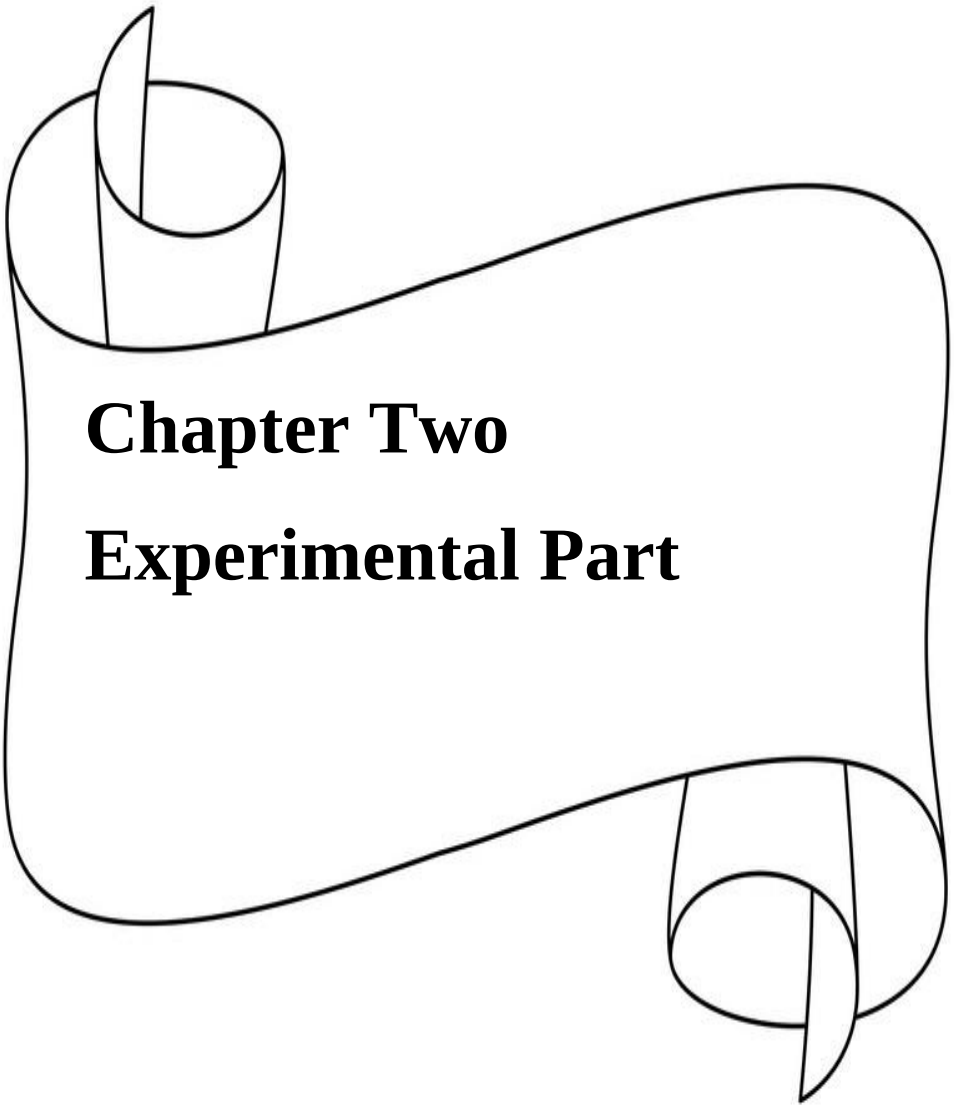
1.4. Aims of the Work

1-Synthesis of new Schiff base derivatives compounds containing adamantane moiety in skeleton structure.

2-Synthesis of new heterocyclic compounds containing bis tetrazole ring from Schiff bases which prepared previously.

3-Estimated of antioxidant activity of all Schiff base derivatives .

4-Evaluation of biological activity of some synthesized compound.



Chapter Two

Experimental Part

2.1. Chemical Materials

The manufacture company, relative purity, molecular formula and Chemical materials as shown in table(2.1).

Table 2.1: The manufacture company, relative purity, molecular formula and Chemical materials

NO	Material	Molecular Formula	Company	Purity
1.	Adamantanol	$C_{10}H_{16}O$	CDH	99%
2.	Acetanilide	C_8H_9NO	CDH	99%
3.	Ammonium chloride	NH_4Cl	CDH	98%
4.	Acetyl chloride	C_2H_3ClO	Alpha	99%
5.	Benzaldehyde	C_6H_5CHO	CDH	99%
6.	4- Bromobenzaldehyde	C_7H_5BrO	CDH	98%
7.	Dimethylformamide (DMF)	C_3H_7NO	CDH	99%
8.	Ethanol	C_2H_5OH	SPI	99.9%
9.	Furan-2-carbaldehyde	$C_5H_4O_2$	CDH	97%
10.	4-hydroxy-3-methoxybenzaldehyde	$C_8H_8O_3$	CDH	97%
11.	Indol-3-carboxaldehyde	C_9H_7NO	EMD	97%
12.	4-Methylbenzaldehyde	C_8H_8O	CDH	97%

13.	4-Methoxybenzaldehyde	$C_8H_8O_2$	CDH	98%
14.	N,N-Dimethylamino benzaldehyde	$C_9H_{11}NO$	CDH	99%
15.	*O*-Nitrobenzaldehyde	$C_7H_5NO_3$	Thomasbakr	99%
16.	Pyridine	C_5H_5N	CDH	97%
17.	Sodium hydroxide	NaOH	Sigma-Alderch	97%
18.	Sulfuric acid	H_2SO_4	BaKER	98%
19.	2- hydroxybenzaldehyde	$C_7H_6O_2$	SGMA	98%
20.	Sodium azide	NaN_3	CDH	99%

2.2. Instrument Evaluation and Apparatus

2.2.1. Device of Melting Points

SMP30 melting point device ,College of Science for Women/ Babylon University.

2.2.2. FT-IR Spectra (Fourier Transform Infrared) Device

FT-IR (Fourier Transform Infrared) 8400s Shimadzu (Japan) spectrophotometer, College of Science for Women/ Babylon University.

2.2.3. (^{1}H, ^{13}C) NMR Spectra Measurements

The nuclear magnetic resonance spectra were measured at Isfahan University of Technology (IUT) Iran using an instrument Bruker at (400mHz) Switzerland with (DMSO-*d6)*

2.2.4. Mass Spectrometric

Agilent Technology (HP) Model: 5973 Network Mass Selective Detector, at Isfahan University of Technology (IUT) , and DI Analysis Shimadzu QP-2010-Plus(E170Ev) Spectrometer, the measurements were taken at laboratories of Turkey University, Micro analytical center.

2.2.5. Oven Heating

Oven Heating materials 2009 Binder(Germany) , College of Science for Women/ Babylon University.

2.2.6 UV-vis spectrophotometer

UV-vis spectrophotometer at a λmax of 517 nm

2.3. Synthesis Route of Schiff Base Derivatives from Adamantanol

2.3.1. Preparation of 1,3-Bis(4-acetanilide) Adamantane(A1)

Mixed 1 equivalent of adamantanol (15g, 0.0985 mol) with 2 equivalent of acetanilide(26.6 g ,0.197 mol) then added 300 ml from H_2SO_4, as solvent and oxidation agent with drop-wise under stirring vigorously for 24 hours at room temperature(32°C). After that, produced mixture is poured into water ice with stirring for 30 minutes, then the precipitate is washed by water for several times after filtration to remove the residue of the acid, then the product is dried as a white powder, 87% yield, melting point (115-116 °C), as shown in figure (2.1). This method according to Habib, A et al. (2021) [1].

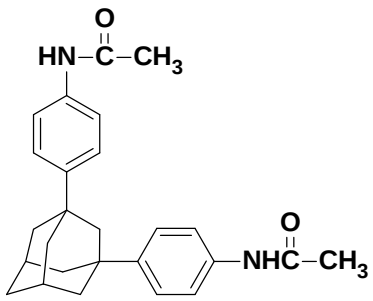


Figure 2.1: 1,3-Bis(4-acetanilide) adamantane(A1)

2.3.2. Preparation of 1,3-bis(4-aminophenyl) Adamantane(A2)

The adamantane salt of acetanilide(1eq) mixed with aqueous solution of sodium hydroxide(5%), then added 250 ml of ethanol the reaction happen under reflux condition(78°C) for(24 hours), there for the mixture poured into ice water with stirring for 30 minutes, then the precipitate is washed for several times after filtration to remove the residue of the base, the precipitate is dried as a Light brown

powder, 85% yield و melting point (120-122°C), This method according to Habib, A et al. (2021) [1], figure (2.2)show the structure of adamantane derivative(A2).

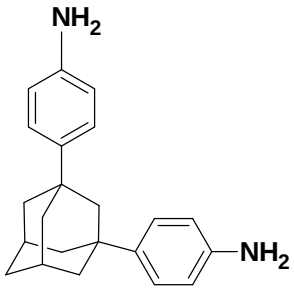


Figure 2.2: 1,3 bis (4-aminophenyl) adamantane(A2)

2.3.3. General procedure of Synthesis of Schiff base Derivatives(B1-B10)

The adamantane derivative(A2) react with several aromatic aldehyde where, 1eq of prepared amine mixed with 2eq of aromatic aldehyde in 35ml of absolute ethanol as a solvent and 0.5ml of pyridine as (basic medium) catalyst, the reaction occur under reflux condition (78°C) for 5-6 hours, then the mixture is filtered and recrystallization by absolute ethanol. This method according to Hemalatha et al.(2022) [86], product dried by oven heating at 70 °C. General formula of Schiff base derivatives (B1-B10)shown in figure(2.3).

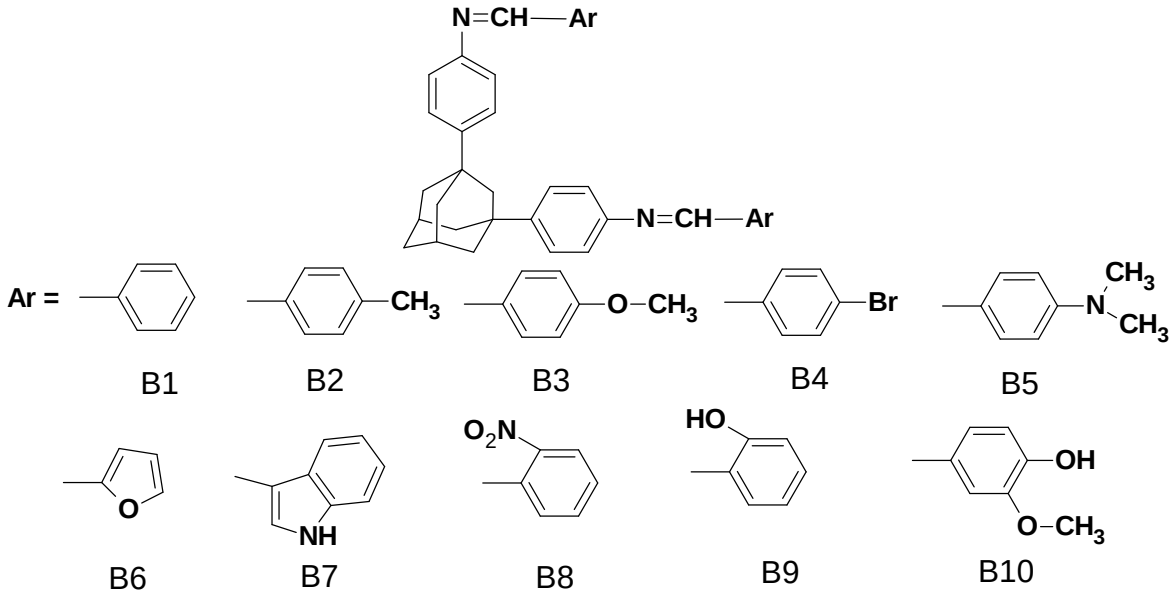


Figure 2.3: General formula of Schiff base derivatives

2.3.3.1. Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-benzylidene)aniline) (B1)

General procedure was followed by using (3gm , 0.00942mol) from adamantane derivative amine(A2) and (1.922 ml, 0.01884mol) from benzaldehyde to produce 2.6 gm from Schiff base derivative(B1) as shown in figure(2.4), as an off-white color powder 55.8% yield , melting point(155-156 °C).

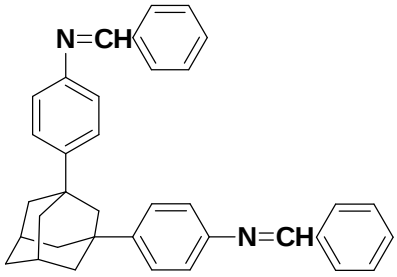


Figure 2.4: Structure of 4,4'-(adamantane-1,3-diyl)bis(N-benzylideneaniline)(B1)

2.3.3.2. Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(4-methyl-benzylidene)aniline) (B2)

General procedure was followed by using (4gm, 0.0125mol) from adamantane derivative(amine) A2 and (2.95ml, 0.025 mol) from 4-methyl benzaldehyde to produce 4.5 gm from Schiff base derivative (B2) as shown in figure(2.5), as an off- white color powder, 68.5% yield , melting point 142-144°C.

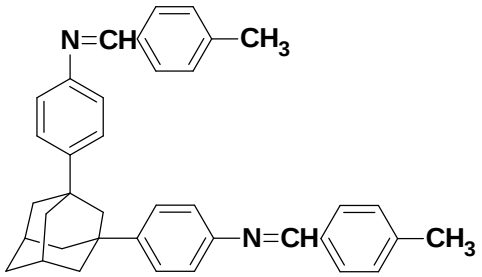


Figure 2.5: Structure of 4,4'-(adamantane-1,3-diyl)bis(N-(4-methylbenzylidene)aniline)(B2)

2.3.3.3. Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(4-methoxy-benzylidene)aniline) (B3)

General procedure was followed by using (4gm, 0.0125mol) from adamantane derivative(amine)A2 and (3.1ml, 0.0255 mol) from 4-methoxy benzaldehyde to produce 5.1 gm from Schiff base derivative (B3) as shown in figure(2.6), as an off- white color powder, 72% yield, melting point 130-132°C.

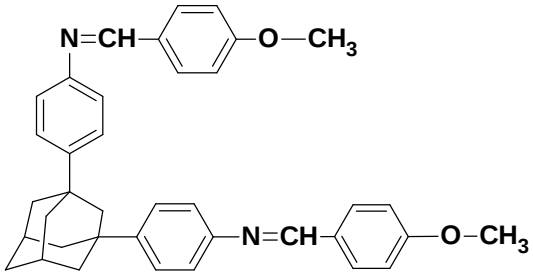


Figure 2.6: Structure of 4,4'-(adamantane-1,3-diyl)bis(N-(4-methoxybenzylidene)aniline)(B3)

2.3.3.4. Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(4-bromo-benzylidene)aniline) (B4)

General procedure was followed by using (4 gm, 0.0125mol) from adamantane derivative (amine) A2 and (4.64 gm, 0.0251 mol) from 4- bromo benzaldehyde to produce 5.6 g from Schiff base derivative (B4) as shown in figure(2.7), as an off- white color powder, 69.1% yield, melting point 204-206°C.

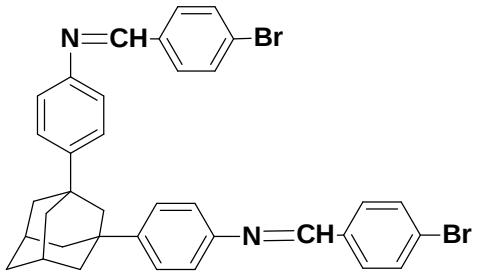


Figure 2.7: Structure of 4,4'-(adamantane-1,3-diyl)bis(N-(4-bromo-benzylidene)aniline) (B4)

2.3.3.5. Synthesis of 4,4'-((adamantane-1,3-diyl)bis(4,1-phenylene)) bis(azanylylidene))bis(methanylylidene)bis(N,N-dimethylaniline) (B5)

General procedure was followed by using (4g ,0.0125mol) from adamantane derivative(amine)A2 and (3.74 g ,0.0251 mol) from 4- N,N dimethyl benzaldehyde to produce 4.9 g from Schiff base derivative(B5) as shown in figure(2.8),as a light yellow color powder, 67.3% yield , melting point 158-160°C.

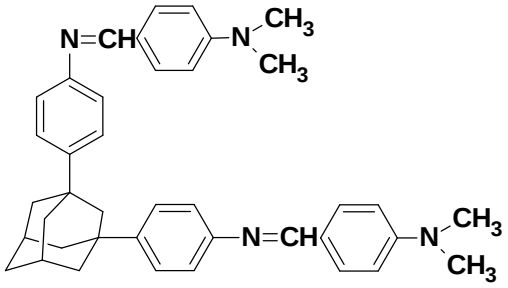


Figure 2.8: Structure of 4,4'-((adamantane-1,3-diyl)bis(4,1-phenylene)) bis(azanylylidene)) bis(methanylylidene)bis(N,N-dimethylaniline)(B5)

2.3.3.6. Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(furan-2-yl methylene)aniline)(B6)

General procedure was followed by using (4g, 0.0125mol) from adamantane derivative(amine)A2 and (2.1 ml, 0.0251 mol) from furfural to produce 2.6 g from Schiff base derivative(B6) as shown in figure(2.9), as a brown color powder, 43.6% yield, melting point 164-166° C.

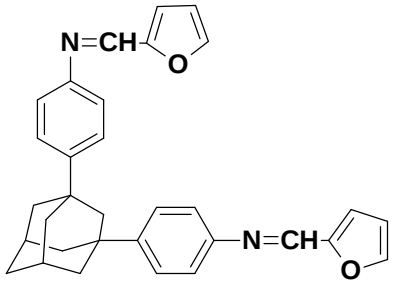


Figure 2.9: Structure of 4,4'-(adamantane-1,3-diyl)bis(N-(furan-2-ylmethylene)aniline)(B6)

2.3.3.7. Synthesis of (N-((1H-indol-3-yl)methylene)-3-(4-(((1H-indol-3-yl)methylene)amino)phenyl)adamantan-1-yl)aniline (B7)

General procedure was followed by using (2g, 0.00628mol) from adamantane derivative(amine) A2 and (1.8gm, 0.0125 mol) from indol-3-carboxaldehyde to produce 1.65g from Schiff base derivative (B7) as shown in figure(2.10), as a yellow color powder 45.8% yield , melting point 163-165° C.

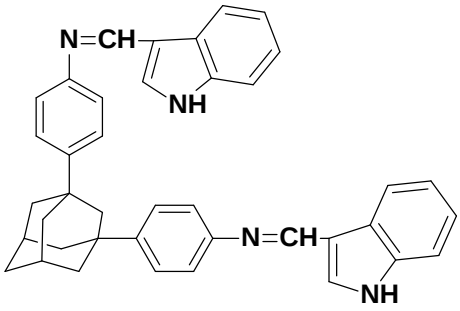


Figure 2.10: Structure of (N-((1H-indol-3-yl)methylene)-3-(4-(((1H-indol-3-yl)methylene) amino)phenyl)adamantan-1-yl)aniline (B7)

2.3.3.8. Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(2-nitro -benzylidene)aniline) (B8)

General procedure was followed by using (3gm, 0.00942mol) from adamantane derivative(amine)A2 and (2.84gm, 0.01884 mol) from o-nitro benzyaldehyde to produce 3gm from Schiff base derivative (B8) as shown in figure(2.11),as a dark yellow color powder 54.5% yield, melting point 137-139° C.

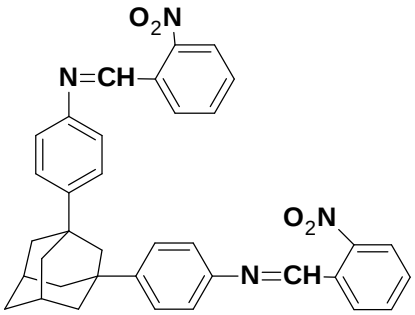


Figure 2.11: Structure of 4,4'-(adamantane-1,3-diyl)bis(N-(2-nitro - benzylidene)aniline)(B8)

2.3.3.9. Synthesis of 2,2'-(((adamantane-1,3-diyl)bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))diphenol (B9)

General procedure was followed by using (2.5gm, 0.00785mol) from adamantane derivative(amine) A2 and (1.64ml, 0.0157 mol) from salicylaldehyde to produce 2.43gm from Schiff base derivative (B9) as shown in figure (2.12), as a dark yellow color powder 58.7% yield , melting point 111-112° C.

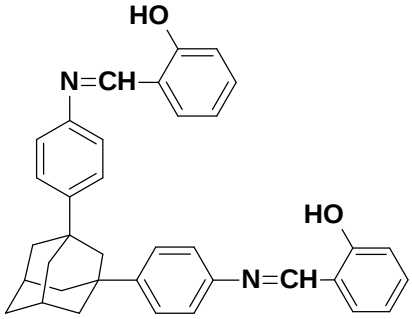


Figure 2.12: Structure of 2,2'-(((adamantane-1,3-diyl)bis(4,1-phenylene)) bis(azanylylidene))bis(methanylylidene))diphenol (B9)

2.3.3.10. Synthesis of 4,4'-(((adamantane-1,3-diyl)bis(4,1-phenylene)) bis(azanylylidene))bis(methanylylidene))bis(2-methoxyphenol) (B10)

General procedure was followed by using (2.5gm, 0.00785mol) from adamantane derivative(amine)A2 and (2.38 gm, 0.0157 mol) from vanillin to produce 1.7gm from Schiff base derivative(B10) as shown in figure(2.13), as a brown color powder 36.9% yield, melting point 210-211° C.

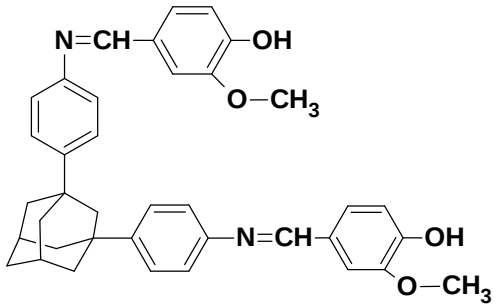


Figure 2.13: Structure of 4,4'-(((adamantane-1,3-diyl)bis(4,1-phenylene)) bis(azanylylidene)) bis(methanylylidene))bis(2-methoxyphenol) (B10)

2.4. General Procedure of Synthesis of Tetrazole Derivatives from Schiff Bases

Mixed 1 eq of Schiff base derivatives with 2 eq of sodium azide and 0.5-1 gm from ammonium chloride in 15 ml of dimethylformamide (DMF) as a solvent the reaction occur under reflux conditions (150°C) for 8-16 hours, the mixture leave to evaporate more amount of solvent then poured into ice water at 0-5°C , after that, filtered and washed by water and sodium bicarbonate and filtered for second time, and recrystallization with absolute ethanol. The method described by Mohite et al. (2009)[135], then the drying powder treated with excess amount of acetyl chloride with continuous stirring for 5 minutes, after that the mixture is left until the residue of acetylchloride is vaporized to produce tetrazole derivatives

as powder solid. Figure (2.14)show the general formula of tetrazole derivatives(C1-C10).

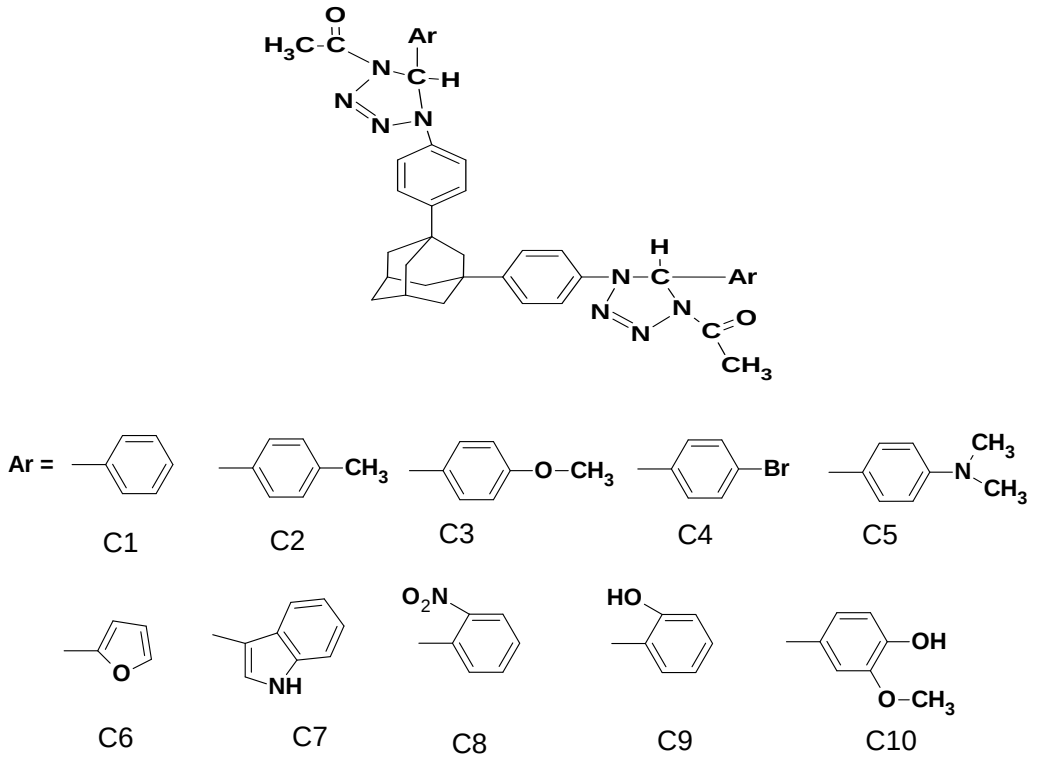


Figure 2.14: General formula of tetrazole derivatives(C1-C10).

2.4.1. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diylbis(4,1-phenylene)) bis(5-phenyl-4,5-dihydro-1H-tetrazole-4,1-diyl))diethanone (C1)

General procedure was followed by using (1.7gm, 0.00343 mol) from Schiff base derivative (B1) and (0.44gm, 0.00687) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative (C1) as shown in figure(2.15), as a yellow color powder 23%, melting point 92-94° C.

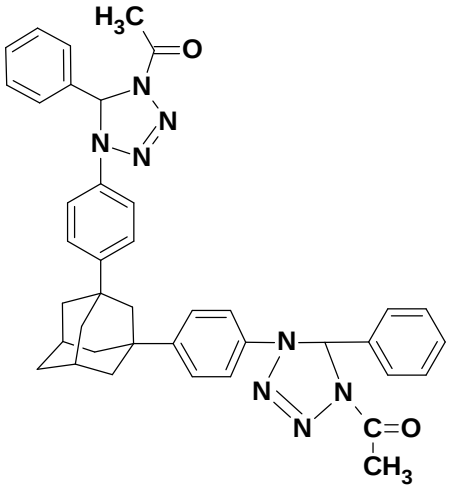


Figure 2.15: Structure of C1

2.4.2. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diyl)bis(4,1-phenylene)) bis(5-(p-tolyl)-4,5-dihydro-1H-tetrazole-4,1-diyl))diethanone (C2)

General procedure was followed by using (1 gm, 0.0018 mol) from Schiff base derivative (B2) and (0.23 gm, 0.0036 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative(C2) as shown in figure (2.16), as a greenish-yellow color powder 32%, melting point 82-84° C.

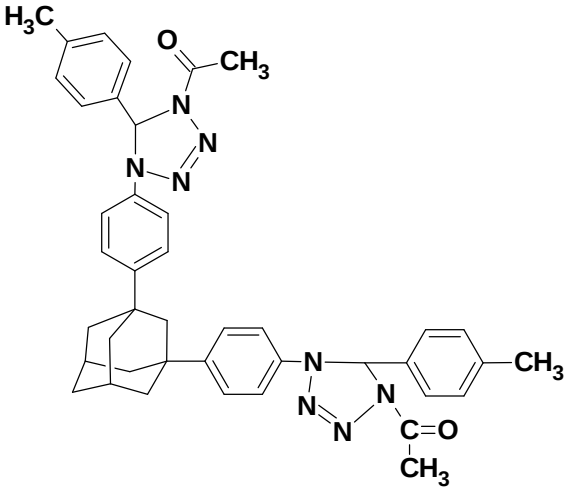


Figure 2.16: Structure of C2

2.4.3. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diyl)bis(4,1-phenyl -ene))bis(5-(4-methoxyphenyl)-4,5-dihydro-1H-tetrazole-4,1-diyl)) diethanone (C3)

General procedure was followed by using (2gm, 0.0036 mol) from Schiff base derivative (B3) and (0.46 gm, 0.0072 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative(C3) as shown in figure(2.17), as a greenish-yellow color powder 34%, melting point 68-70° C.

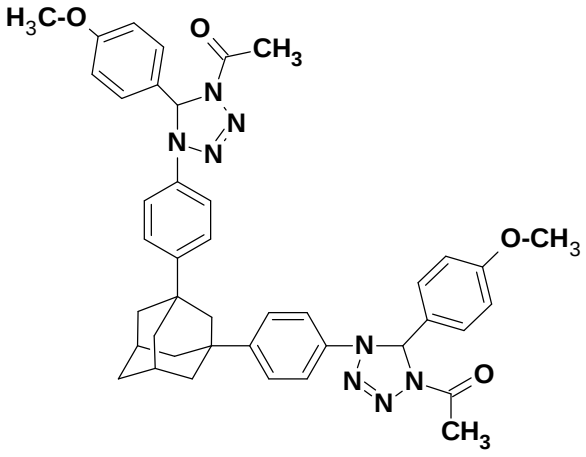


Figure 2.17: Structure of C3

2.4.4. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diyl)bis(4,1-phenylene)) bis(5-(4-bromophenyl)-4,5-dihydro-1H-tetrazole-4,1-diyl)) diethanone (C4)

General procedure was followed by using (1.5gm, 0.0029 mol) from Schiff base derivative (B4) and (0.29 gm, 0.0045 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative (C4) as shown in figure(2.18), as an orange color powder 27%, melting point 167-168° C.

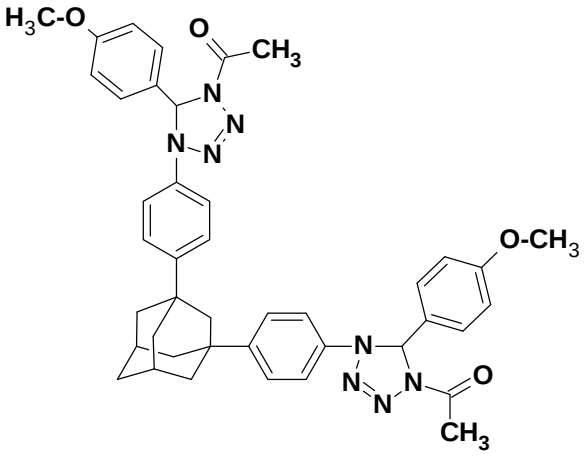


Figure 2.18: Structure of C4

2.4.5. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diyl)bis(4,1phenylene)) bis(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-tetrazole-4,1-diyl)) diethanone (C5)

General procedure was followed by using (1.5gm, 0.0025 mol) from Schiff base derivative (B5) and (0.33 gm, 0.00516 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative (C5) as shown in figure (2.19), as a red color powder 32%, melting point 161-162° C.

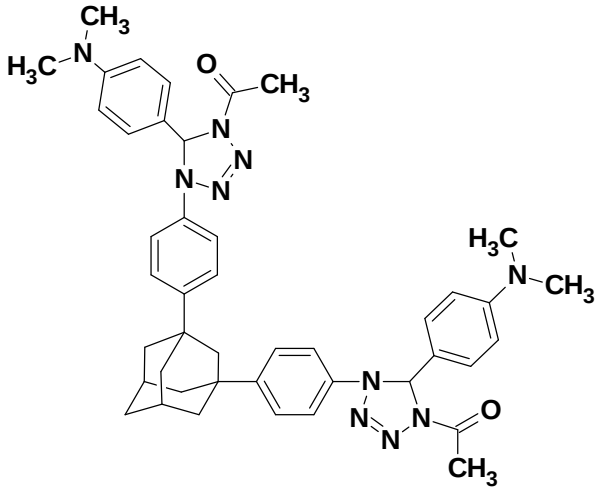


Figure 2.19: Structure of C5

2.4.6. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diyl)bis(4,1phenylene)) bis(5-(furan-2-yl)-4,5-dihydro-1H-tetrazole-4,1-diyl))diethanone(C6)

General procedure was followed by using (2gm, 0.0042 mol) from Schiff base derivative (B6) and (0.54 gm, 0.00842 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative(C6) as shown in figure(2.20), as a dark brown-color powder 12.2%, melting point 139-140° C.

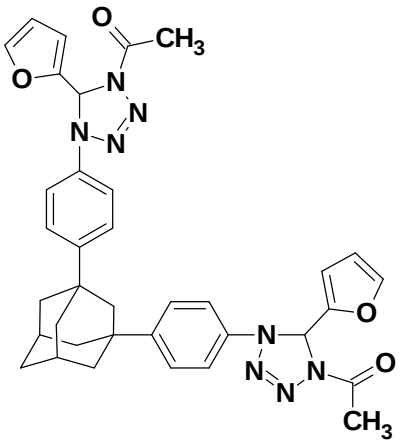


Figure 2.20: Structure of C6

2.4.7. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diyl)bis(4,1phenylene)) bis(5-(1H-indol-3-yl)-4,5-dihydro-1H-tetrazole-4,1-diyl))diethanone (C7)

General procedure was followed by using (1.65gm, 0.00288 mol) from Schiff base derivative (B7) and (0.37 gm, 0.00576 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative (C7) as shown in figure(2.21), as a dark-red color powder 15.49%, melting point 188-190° C.

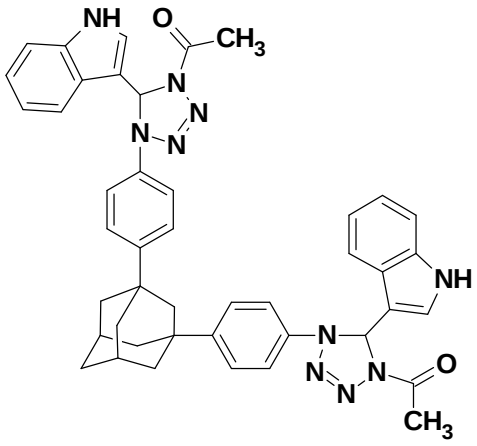


Figure 2.21: Structure of C7

2.4.8. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diyl)bis(4,1phenylene)) bis(5-(2-nitrophenyl)-4,5-dihydro-1H-tetrazole-4,1-diyl))diethanone (C8)

General procedure was followed by using (1.5gm, 0.00256 mol) from Schiff base derivative (B8) and (0.33 gm, 0.00513 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative(C8) as shown in figure(2.22), as a dark-brown color powder 22.3%, melting point 72-74° C.

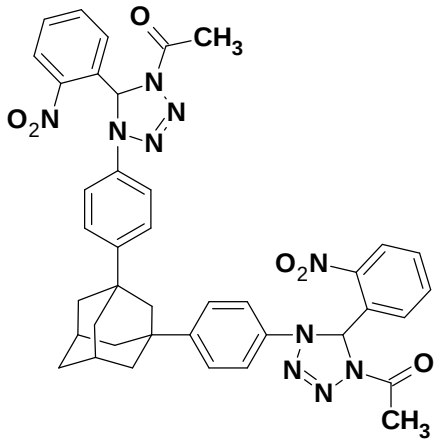


Figure 2.22: Structure of C8

2.4.9. Synthesis of 1,1' (4,4'-(adamantane-1,3-diyl)bis(4,1-phenylene))bis(1-acetyl-4,5-dihydro-1H-tetrazole-5,4-diyl))bis(2,1-phenylene) diacetate (C9)

General procedure was followed by using (1.5gm, 0.00284 mol) from Schiff base derivative (B9) and (0.37 gm, 0.00569 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative(C9) as shown in figure (2.23) as a greenish-yellow color powder 35.3%, melting point 88-90° C.

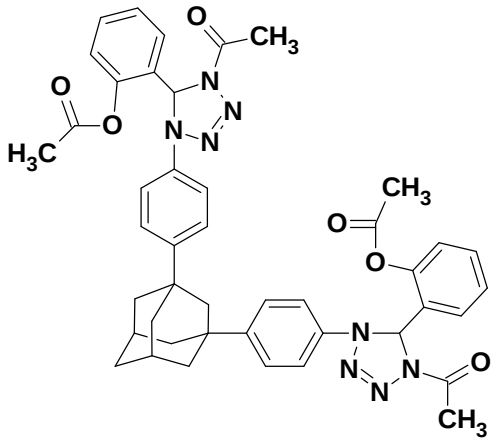


Figure 2.23: Structure of C9

2.4.10. Synthesis of 1,1'-(4,4'-(adamantane-1,3-diyl)bis(4,1-phenylene))bis(5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-tetrazole-4,1-diyl))diethanone (C10)

General procedure was followed by using (1.2gm, 0.00204 mol) from Schiff base derivative (B10) and (0.26 gm, 0.00409 mol) from sodium azide and appropriate amount from acetylchloride to produce tetrazole derivative(C10) as shown in figure (2.24) as a brown color powder 26.6%, melting point 177-178° C.

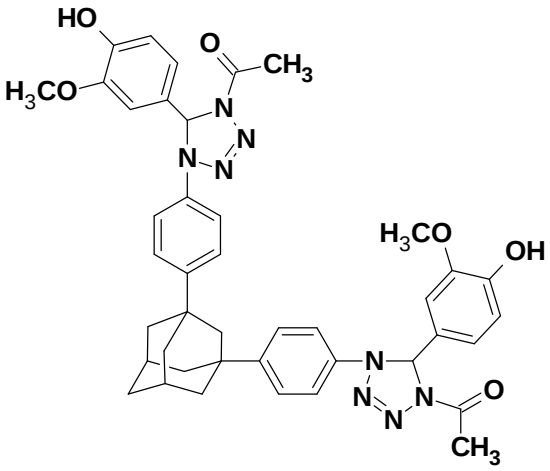
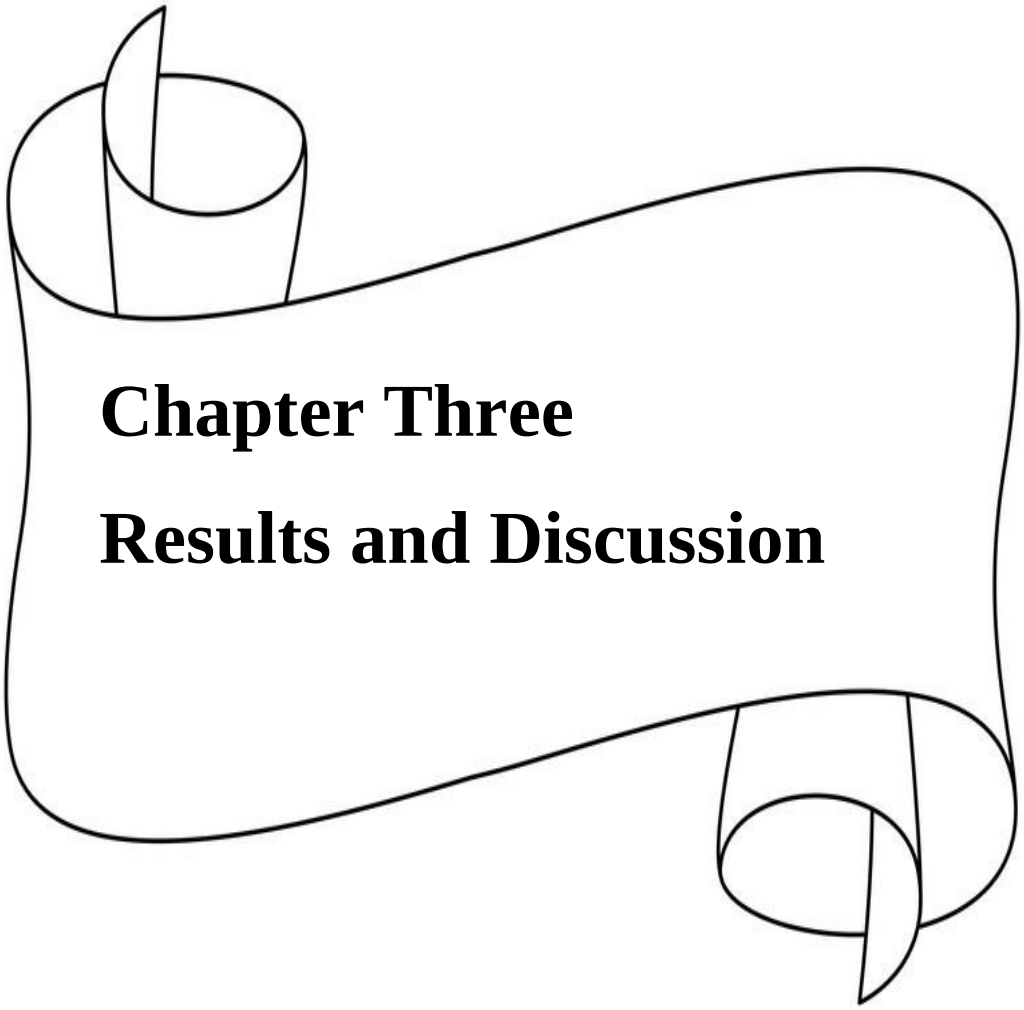


Figure 2.24: Structure of C10



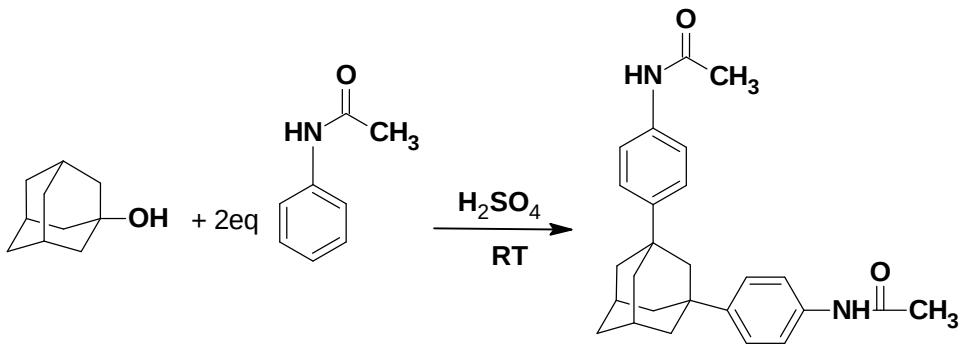
Chapter Three

Results and Discussion

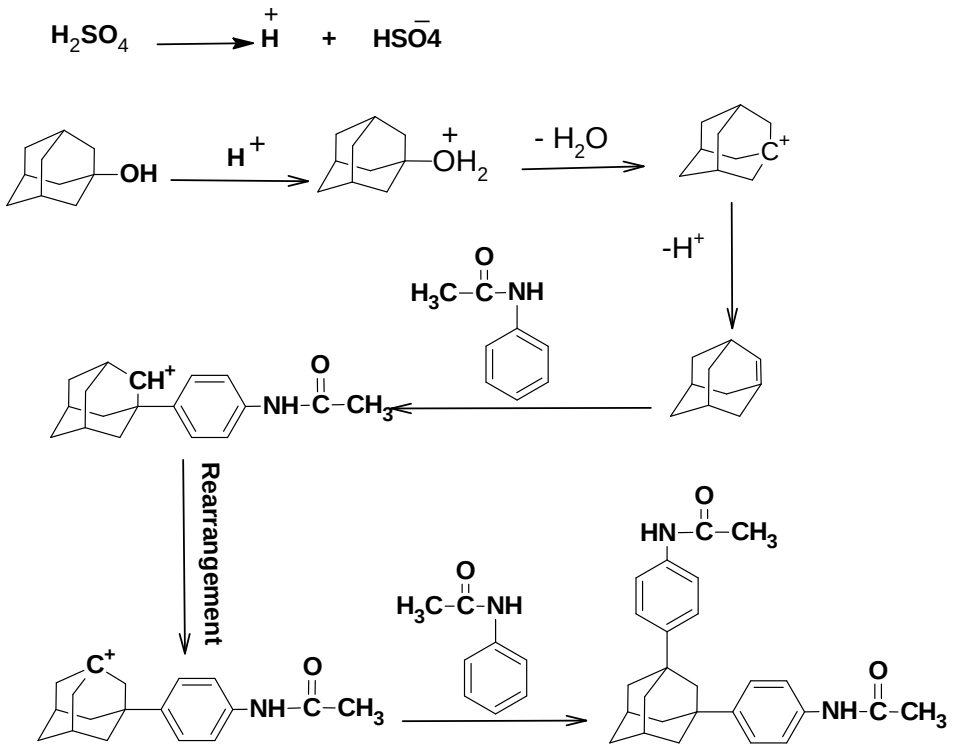
3. Results and Discussion

3.1. Preparation of 1,3 bis(4-acetamido-1-phenyl)adamantane(A1)

Adamantane salt of acetanilide prepared in strong acidic medium equation (3.1) to get a very good yield ,in this reaction we used acetanilide because of their high stability under these conditions, suggestion mechanism of this reaction shown in scheme (3.1). FT-IR Spectrum of adamantane salt show many specific peak such as peaks at(3055,3115) cm^{-1} indicate to C-H aromatic , peaks at (2848,2904)cm^{-1} refers to the stretching vibration of C-H bond of adamantane, peaks at (1516-1600) cm^{-1} indicate to C=C aromatic, peak at (3298cm^{-1}) indicate to the stretching vibration of N-H bond from amide, peak at (1666cm^{-1}) indicate to amide carbonyl group as shown in figure(3.1).



Equation 3.1: Preparation of compound A1



Scheme 3.1: Suggestion mechanism of prepration 1,3 bis(4-acetamido-1-phenyl)adamantane(A1)

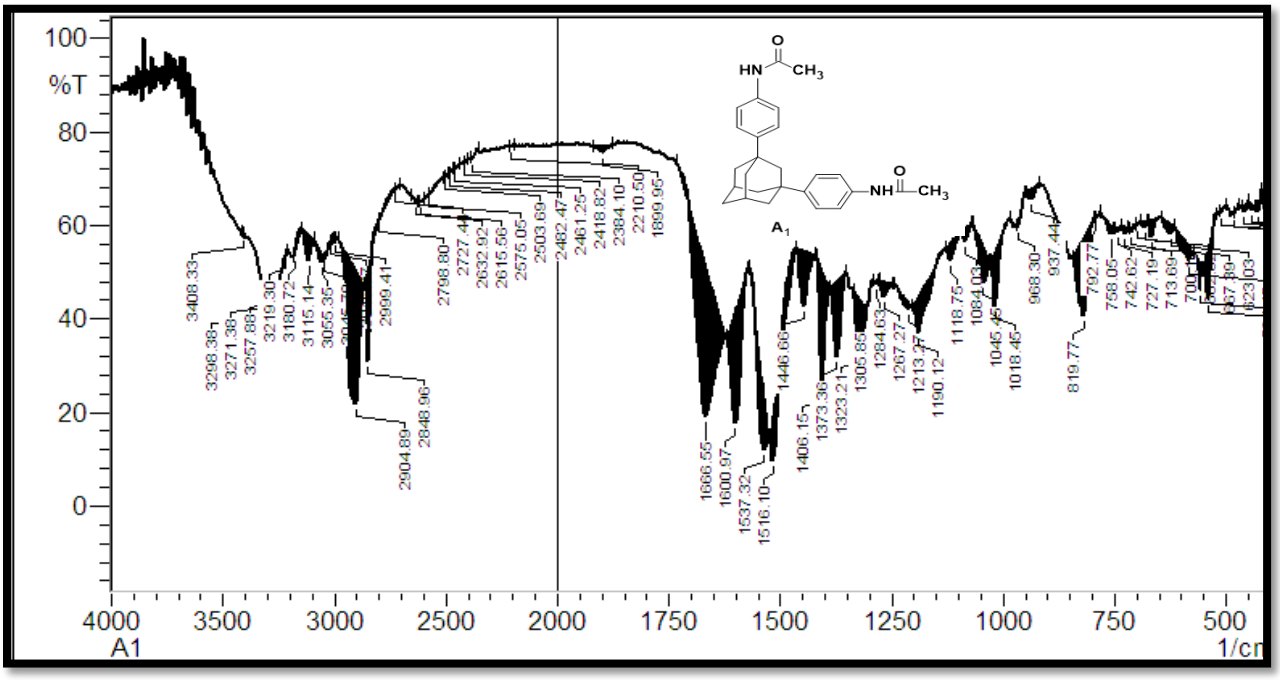
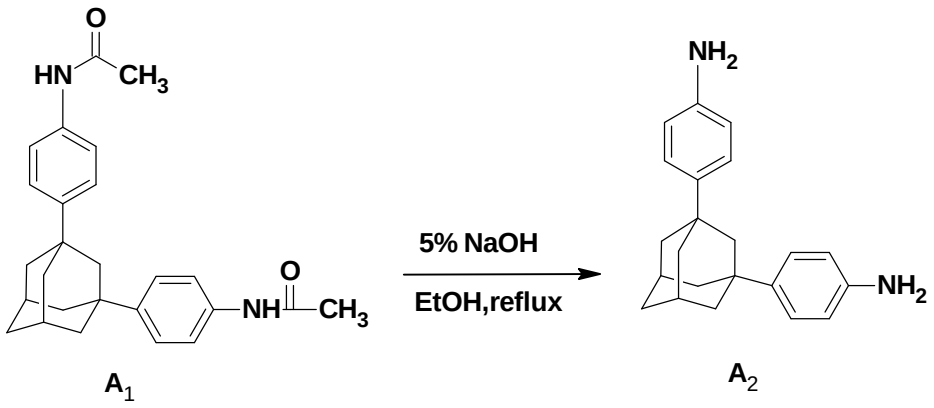


Figure 3.1: FT-IR Spectrum of compound A1

3.2. Preparation of 1,3 bis (4-amino phenyl)adamantane (A2)

The adamantane salt (A1) can be undergoes to de-protection reaction by react with aqueous solution of sodium hydroxide(5%) under reflux condition in ethanol for 24 hours as shown in equation(3.2), FT-IR spectrum of adamantane derivative (A2) shows specific peak such as 3012 cm^{-1} indicates to the C-H aromatic, two peaks at (2901,2847) cm^{-1} indicate to C-H for adamantane , peak for C=C at 1516 cm^{-1}, sharp and double peak at 3344-3421 cm^{-1} indicate to the formation of primary amine, as well as disappearance peak of N-H bond from amide as shown in figure (3.2).



Equation 3.2: Preparation of compound A2

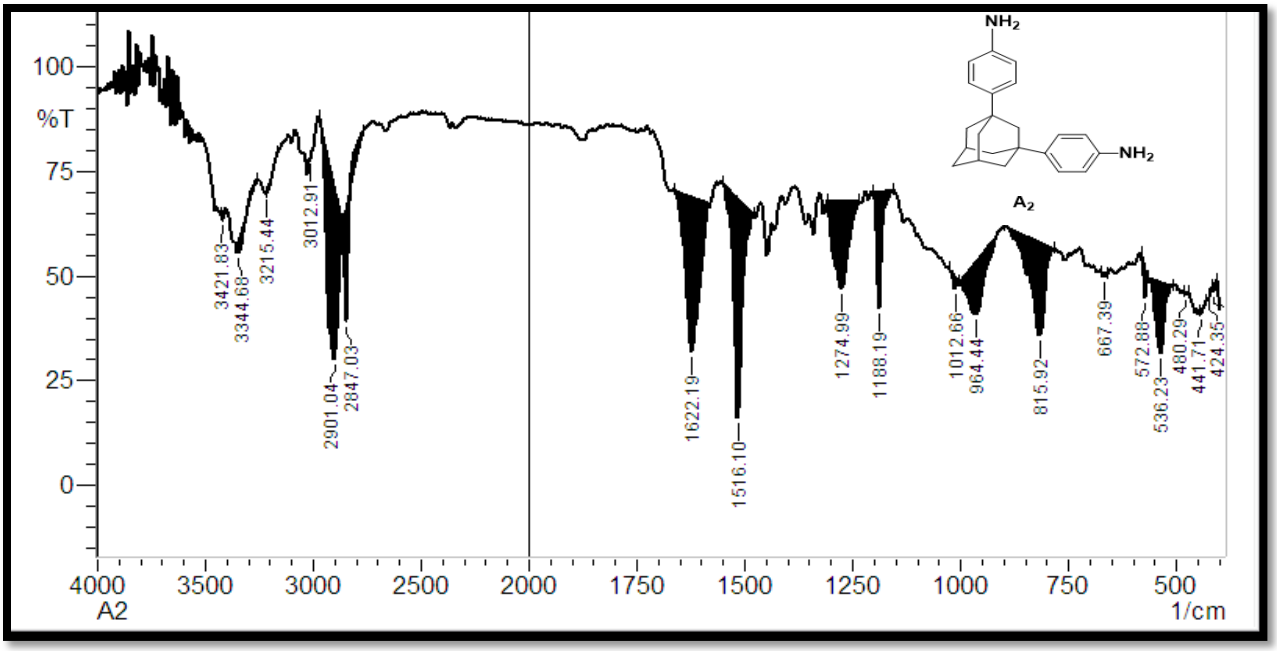


Figure 3.2: FT-IR Spectrum of compound A2

3.3. Schiff base Derivatives

3.3.1. Solubility and Physical Properties of Schiff Base Derivatives

Schiff base derivatives(B1-B10) soluble in many organic solvent ,however insoluble of water as inorganic solvent. Melting point, colors, yield and solubility of all Schiff base derivatives listed below in table (3.1).

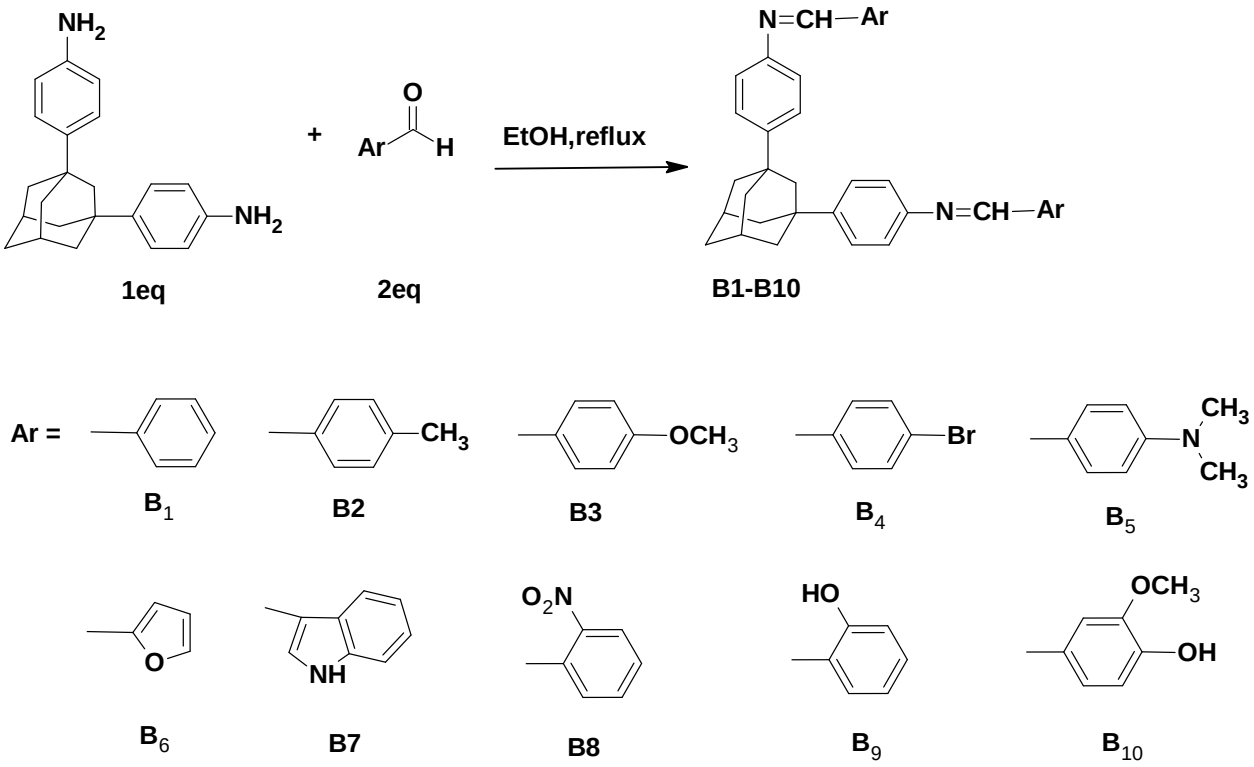
Table 3.1: Solubility and Physical properties of Schiff base derivatives

Comp.	M.P (°C)	Color	Yield (%)	Solubility					
				water	ethanol	benzene	dioxane	DMF	DMSO
B1	155-156	Off-white	56	–	–	+	δ	+	+
B2	142-144	Off-white	68	–	–	+	δ	+	+
B3	130-132	Off-white	72	–	–	+	δ	+	+
B4	204-206	Off-white	69	–	–	+	δ	+	+
B5	158-160	Pale-yellow	67	–	–	+	δ	+	+
B6	164-166	Light-brown	43.6	–	–	+	δ	+	+
B7	163-165	Yellow	45.5	–	–	+	δ	+	+
B8	137-139	Dark-yellow	54.5	–	–	+	δ	+	+
B9	111-112	Light-yellow	58.7	–	–	+	δ	+	+
B10	210-211	Dark-yellow	36.9	–	–	+	δ	+	+

partial= δ

3.3.2. Synthesis of Schiff Base Derivatives

The amine derived from adamantane undergoes to condensation reaction with different aromatic aldehyde to produce new Schiff base derivatives (B1, B2. B3, B4, B5, B6, B7, B8, B9, B10) as shown in equation(3.3) .All Schiff base derivatives synthesized characterization by FT-IR, Mass spectroscopy and (^{1}H-^{13}C) NMR.



Equation 3.3: Synthesis of Schiff base derivative (B1-B10)

3.3.3. FT-IR Spectrum

Information regarding the makeup and structure of functional groups can be obtained from the infrared spectrum. The functional group section of the spectrum is the high-frequency zone, in this region of the spectrum 4000-1300 cm^{-1}, the distinctive stretching frequencies for significant functional groups including OH, NH, and carbonyl group may be found. The "finger print" area is the common name for the middle part of the spectrum, which spans 1300-900 cm^{-1}[136].

3.3.3.1. FT-IR Spectra of Schiff Base Derivatives(B1-B10):

The fundamental bands that distinguish synthesize compound (Schiff base derivatives) listed below in table(3.2),we observe appearances strong band at (1600-1626 cm^{-1}) indicates to C=N group and disappearances medium and sharp double peaks which indicates to stretching vibration of primary amine[137], table(3.2) at υ (cm^{-1}) (KBr) summarizes other distinctive bands.

Table 3.2: Fundamental bands of Schiff base derivatives in FT-IR spectra

Comp.	C-H Aromatic(cm-1)	C-H Aliphatic(cm-1)	C=N Imine(cm-1)	C=C Aromatic(cm-1)	Other band(cm-1)
B1	3101,3010	2918,2847	1627	1577,1500,1450	
B2	3045,3010	2918,2897, 2900	1626	1597,1570,1512	
B3	3050,3035	2908, 2847	1624	1597,1575,1512	1251(C-O)
B4	3083,3026	2899,2848	1626	1585,1566,1498	705(C-Br)
B5	3050,3034	2847,2897	1608	1599,1554,1525	1100(C-N)
B6	3080	2899,2847	1622	1516,1475,1446	1250(C-O)
B7	3030	2920,2897,2847	1618	1593,1575,1496 1446	3396(N-H) indole, 1246(C-N)
B8	3020	2912,2846	1616	1570,1442	1519(NO2) 1010(C-N)
B9	3100	2848,2901	1618	1599,1573,1491 1456	3400(OH) 1278(C-O)
B10	3000	2920,2846	1600	1589,1508,1415	3371(OH)

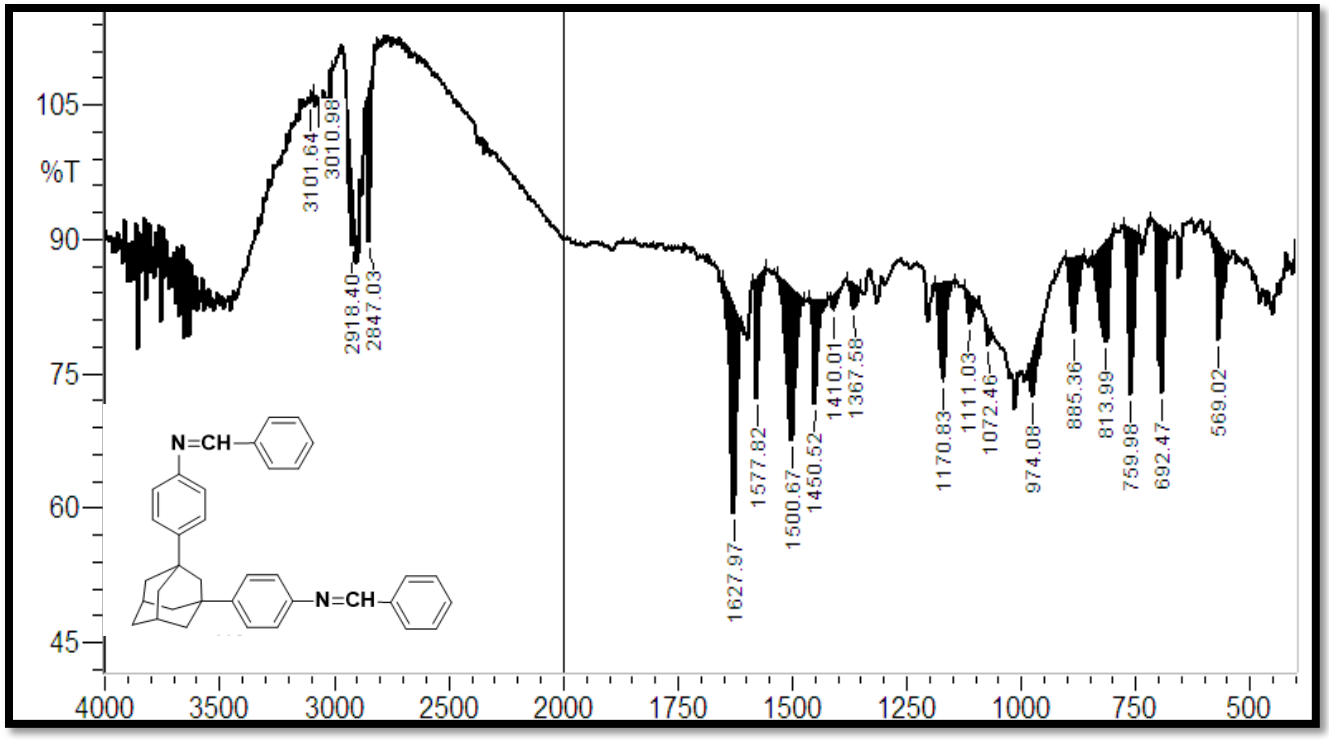


Figure 3.3: FT-IR Spectrum of Schiff base derivative B1

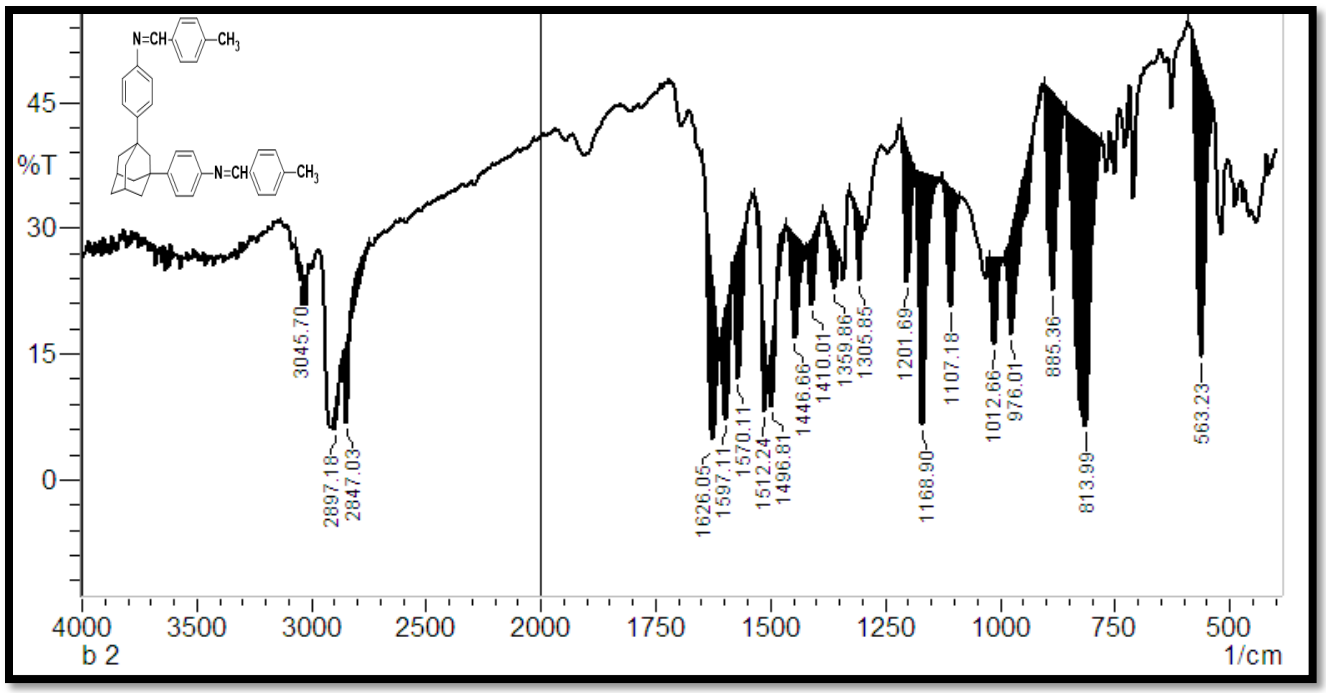


Figure 3.4: FT-IR of Spectrum Schiff base derivative B2

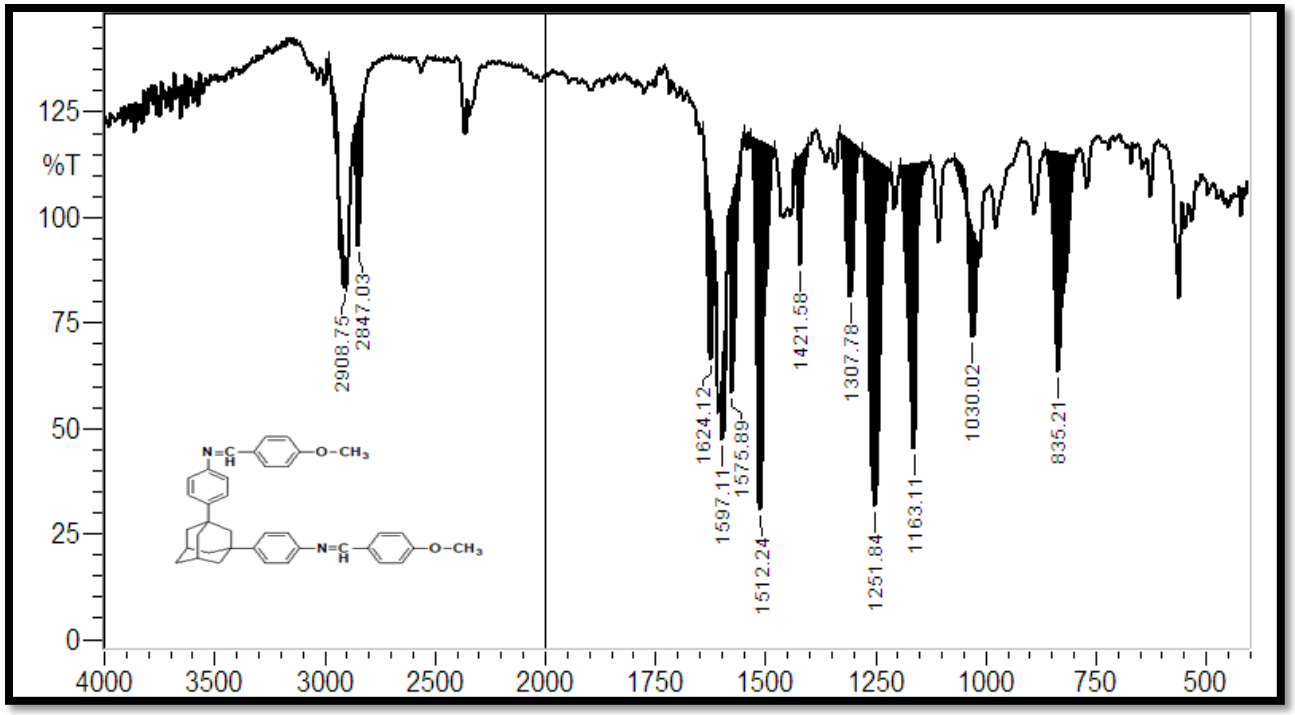


Figure 3.5 : FT-IR Spectrum of Schiff base derivative B3

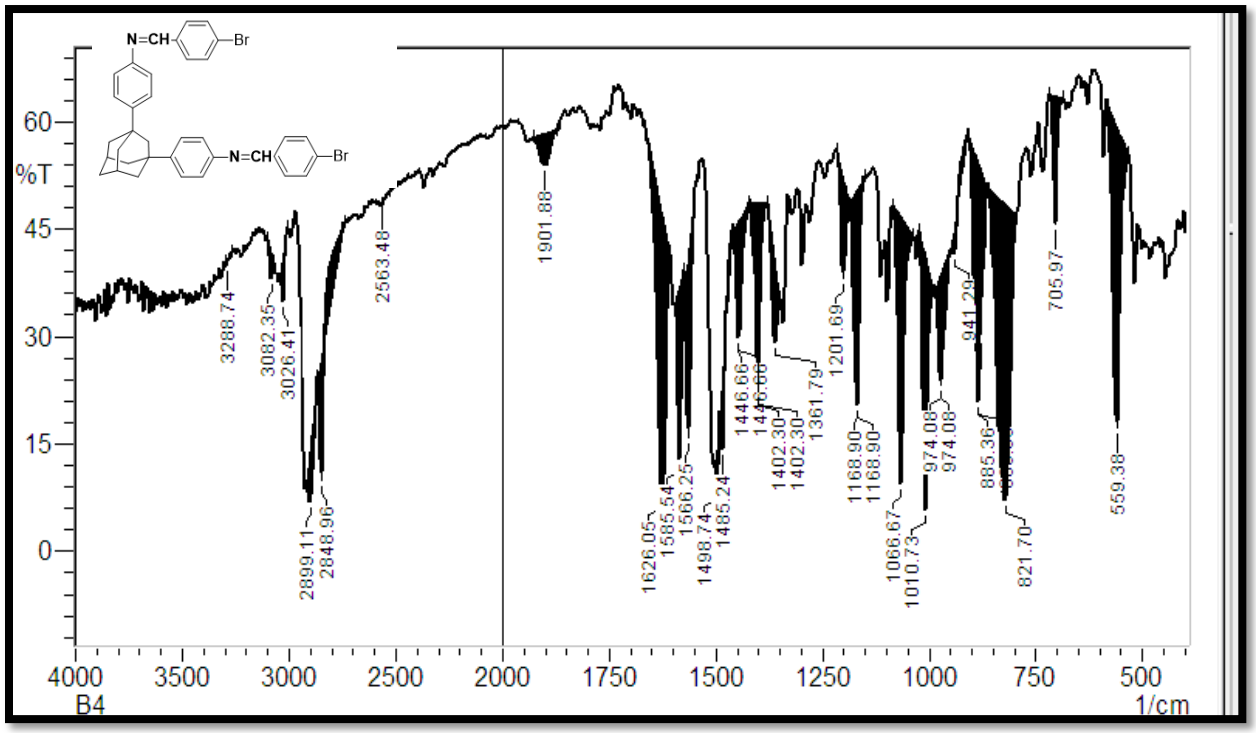


Figure 3.6: FT-IR Spectrum of Schiff base derivative B4

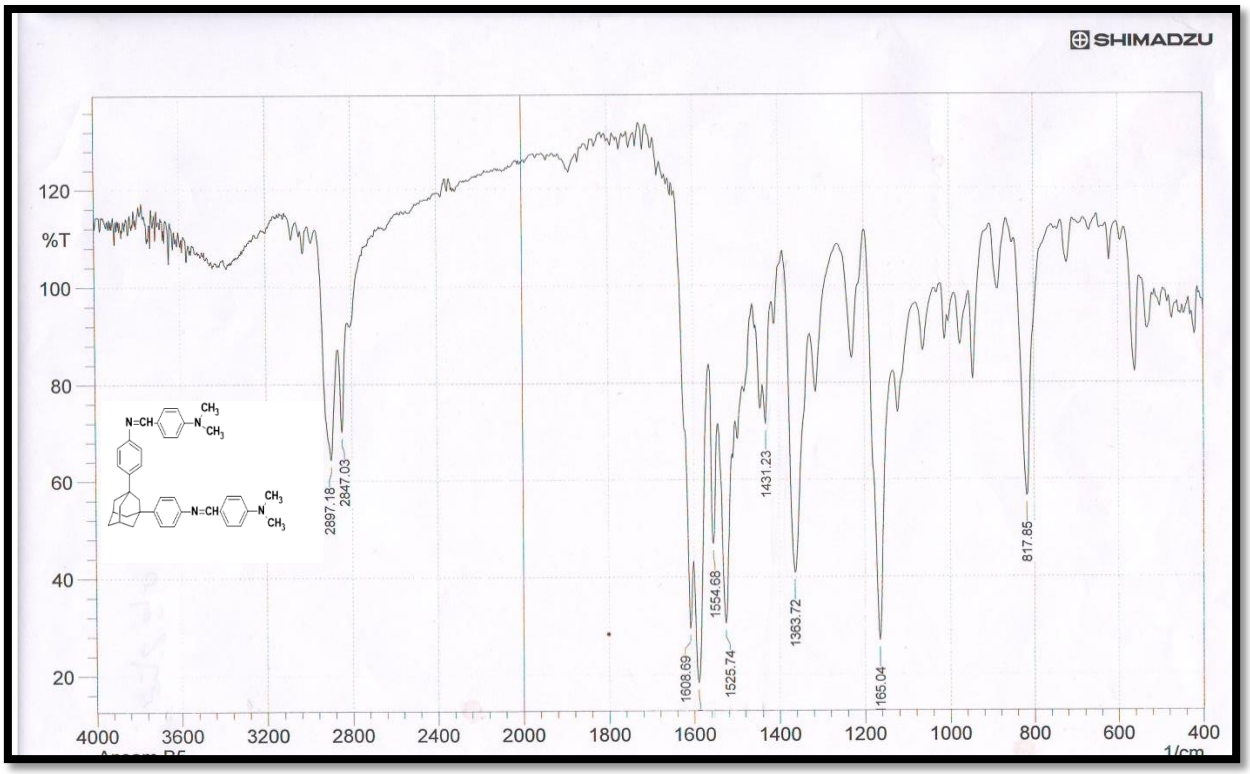


Figure 3.7: FT-IR Spectrum of Schiff base derivative B5

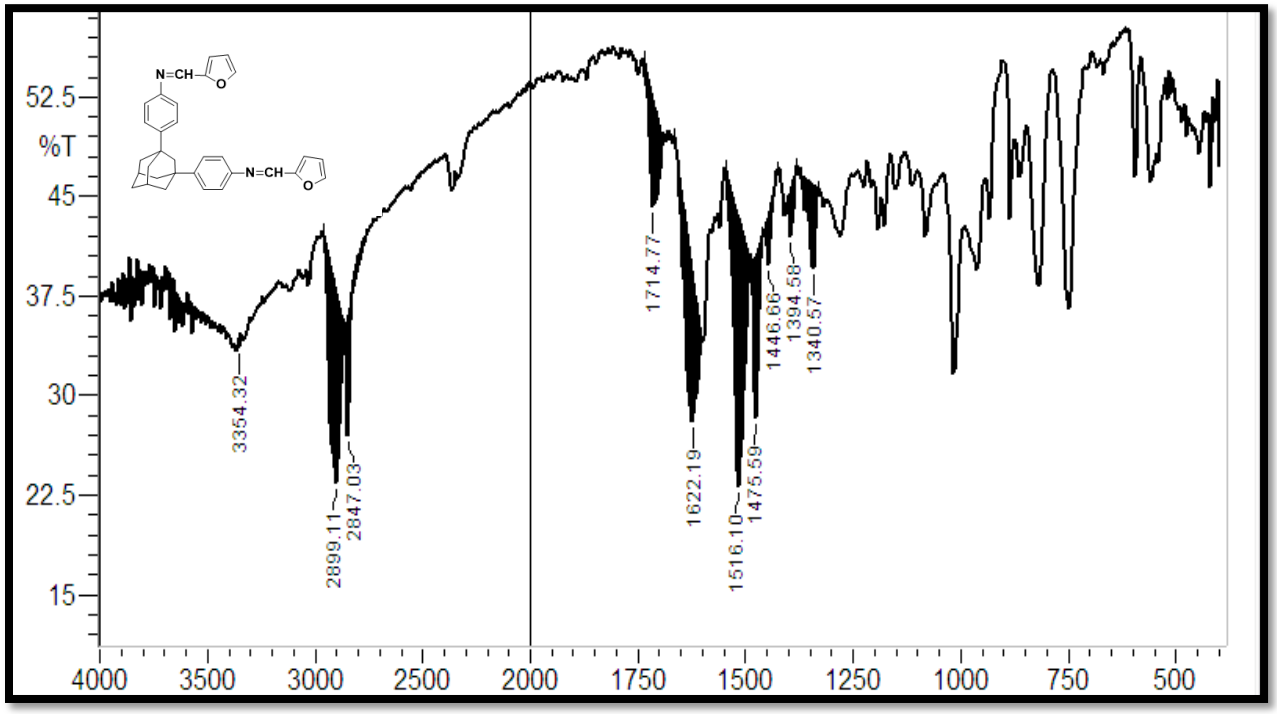


Figure 3.8: FT-IR Spectrum of Schiff base derivative B6

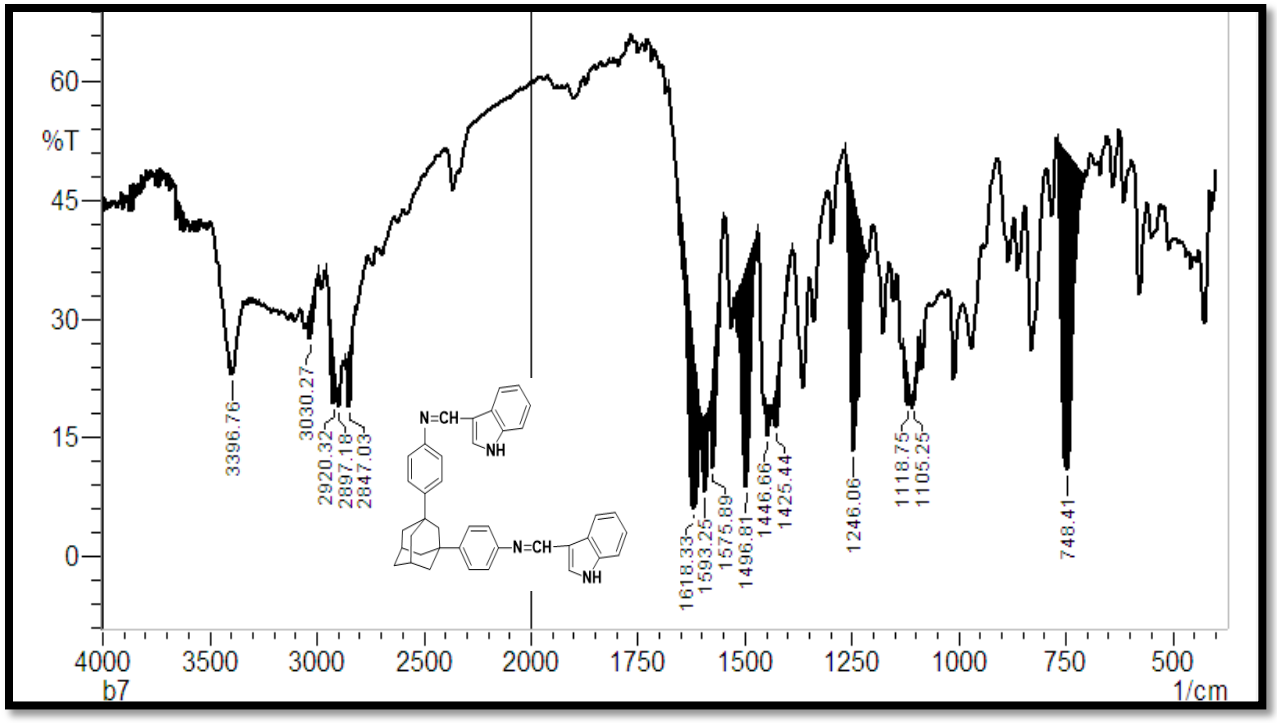


Figure 3.9: FT-IR Spectrum of Schiff base derivative B7

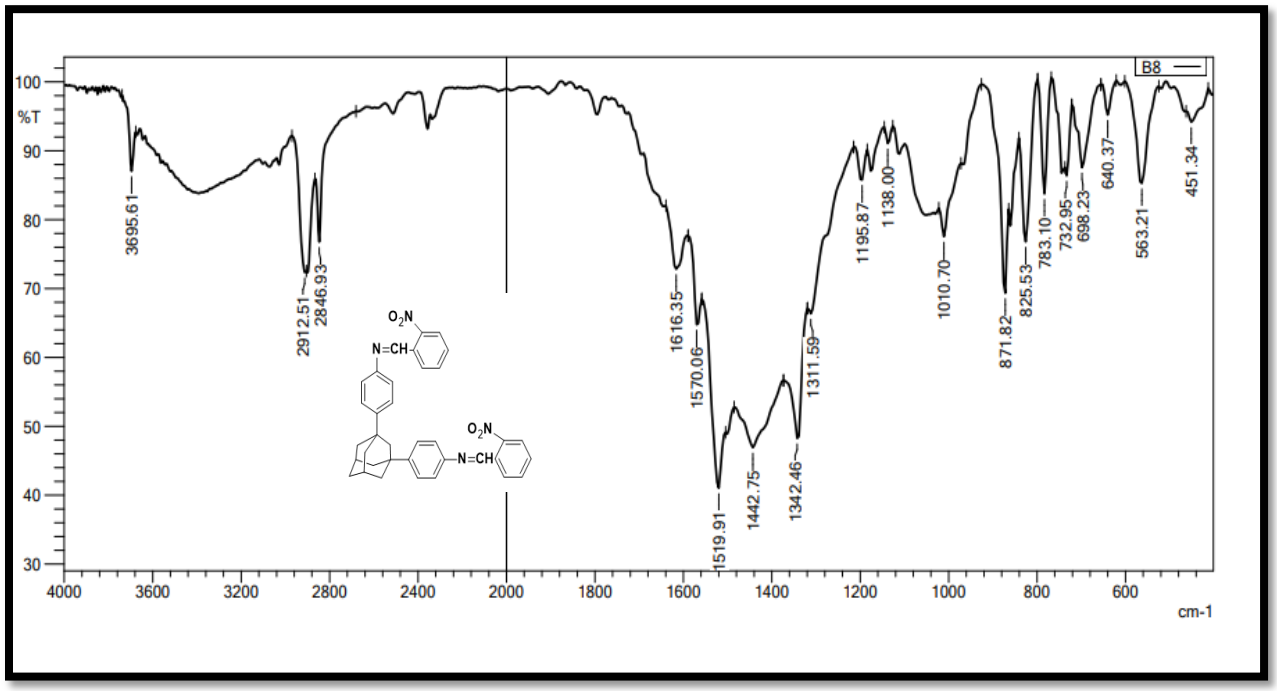


Figure 3.10: FT-IR Spectrum of Schiff base derivative B8

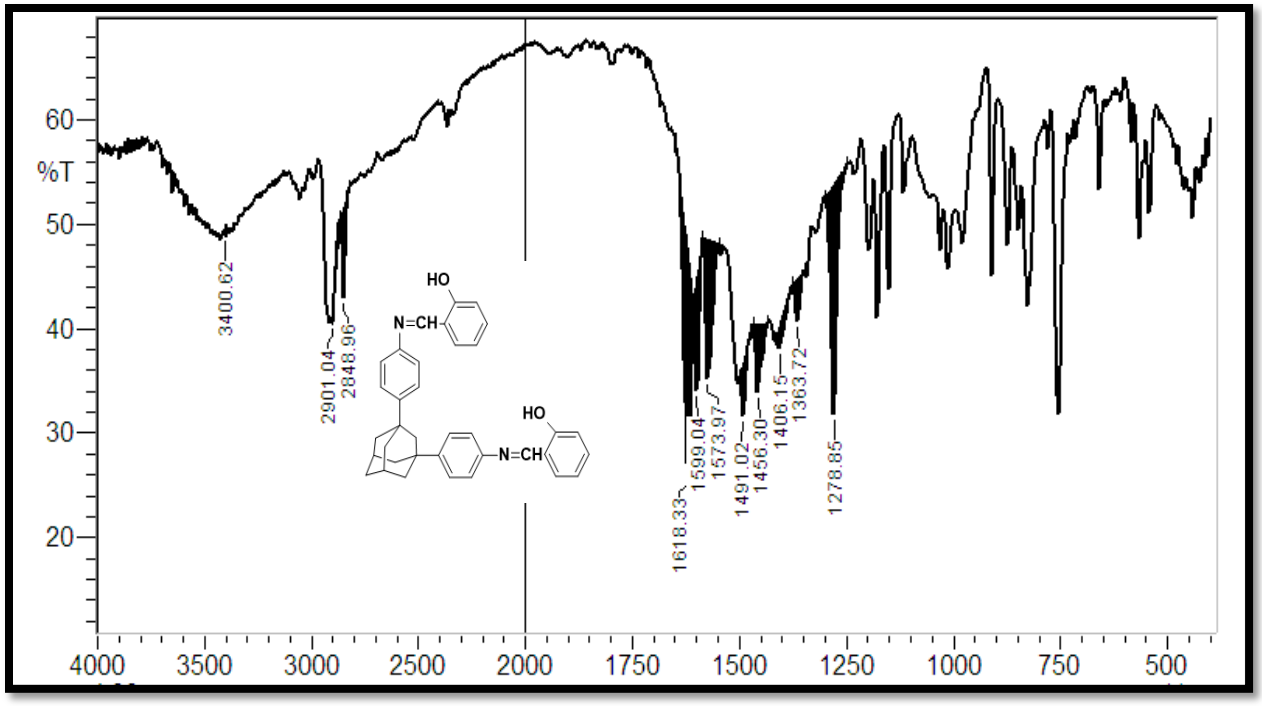


Figure 3.11: FT-IR Spectrum of Schiff base derivative B9

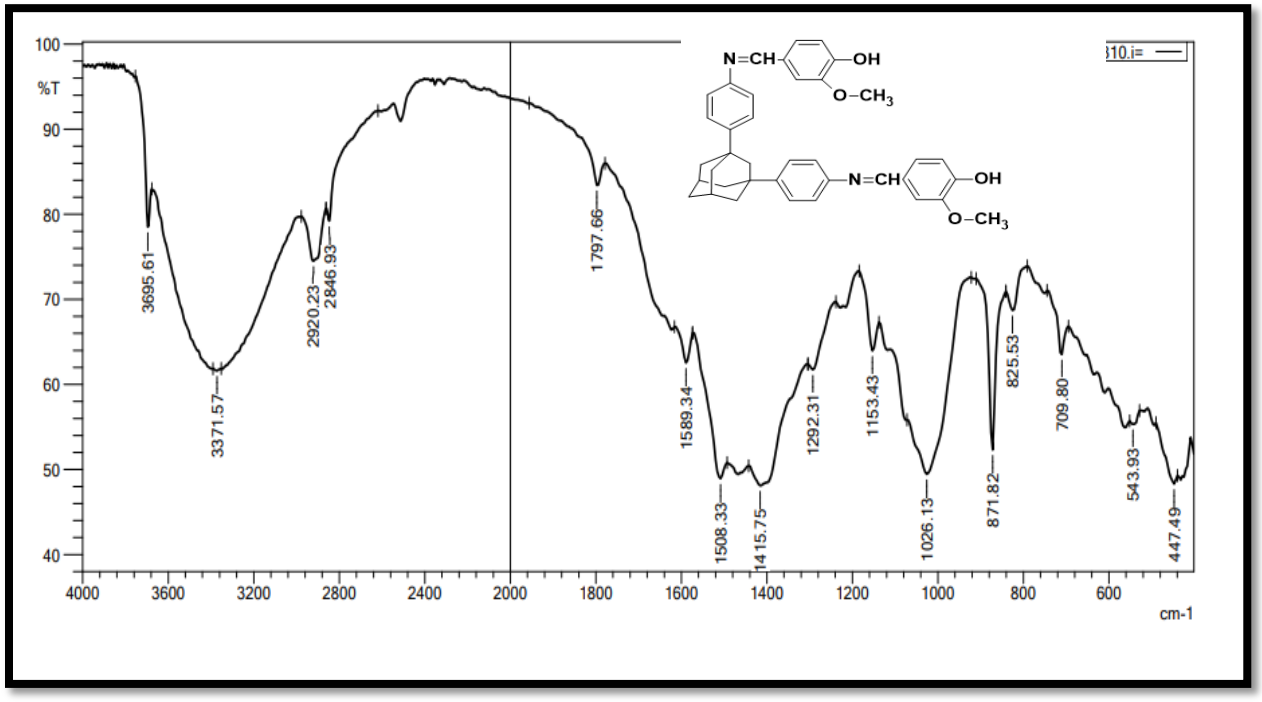


Figure 3.12: FT-IR Spectrum of Schiff base derivative B10

3.3.4. Characterization of Schiff Base Derivatives by Mass Spectrometry

Mass spectrometry is based on a rather straightforward idea: A substance is ionized using the "ionization method," the ions are separated based on their mass/charge ratio using the "ion separation method," and the number of ions representing each mass/charge unit is then recorded as a spectrum. The intensity of the molecular ion peak depends on the stability of the molecular ion[136]. Some of the Schiff base derivatives(B1,B2,B3,B5,B8,B9) listed in table(3.3) have parent ion and base peak in the same value ,which indicate to the stability of these compounds.

Table 3.3: Fundamental band of Schiff base derivatives in Mass spectrum

Compound	M.wt	m/z found	Base peak	First fragment	Last fragment
B1	494.66	494.3	494.3	465.3	65.1
B2	522.7	522.4	522.4	494.3	65.1
B3	554.7	554.4	554.4	525.3	65
B4	652.4	652.1	274	595.1	65.1
B5	580.8	580.4	580.4	565	55
B6	474.59	474.3	396.3	446.3	55.1
B7	572.7	572.3	446.3	565.3	55.1
B8	584.66	584.3	584.3	565.3	55.1
B9	526.6	526.3	526.3	498.3	65.1
B10	586.7	586.3	151	526.3	57

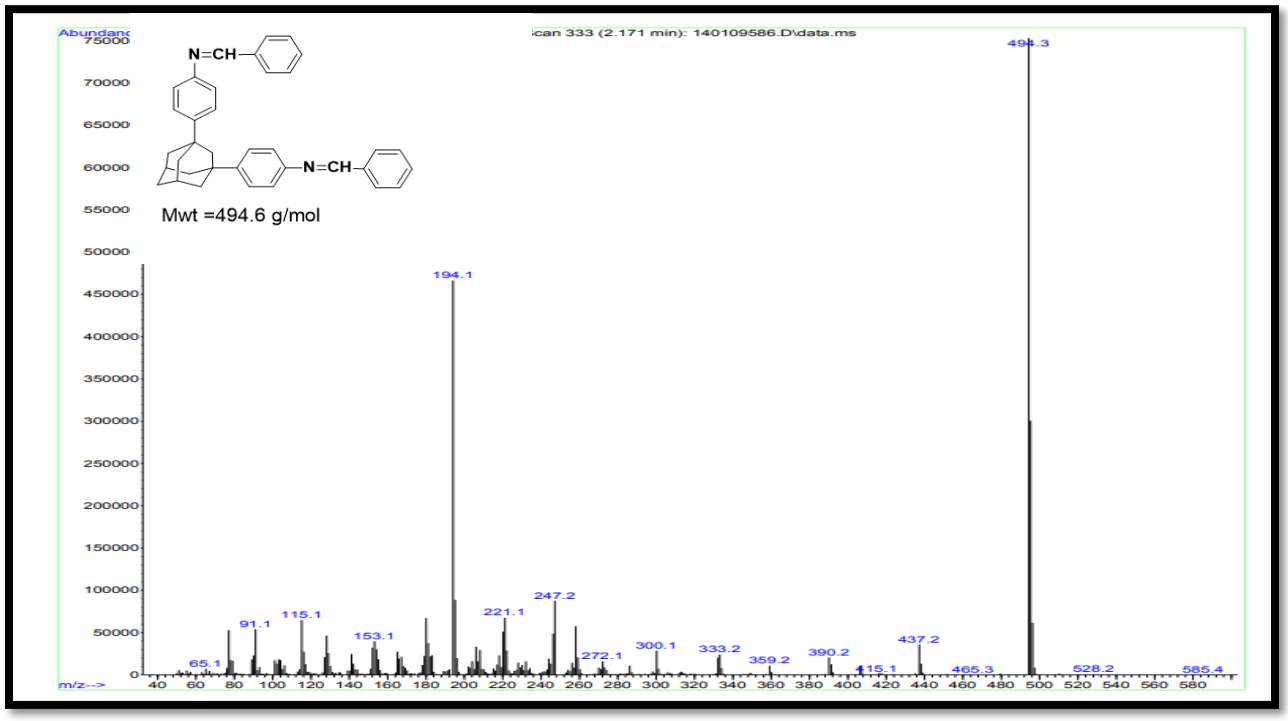


Figure 3.13: Mass Spectra of Schiff base derivative B1

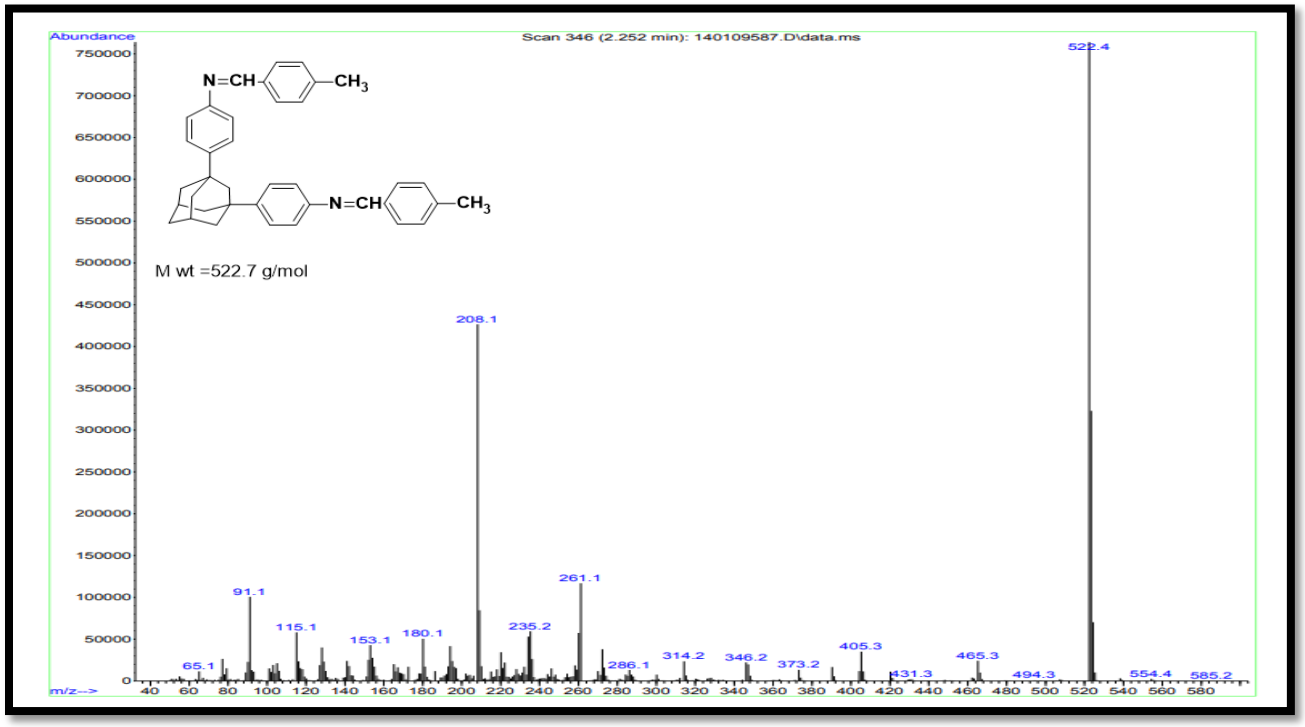


Figure 3.14: Mass Spectra of Schiff base derivative B2

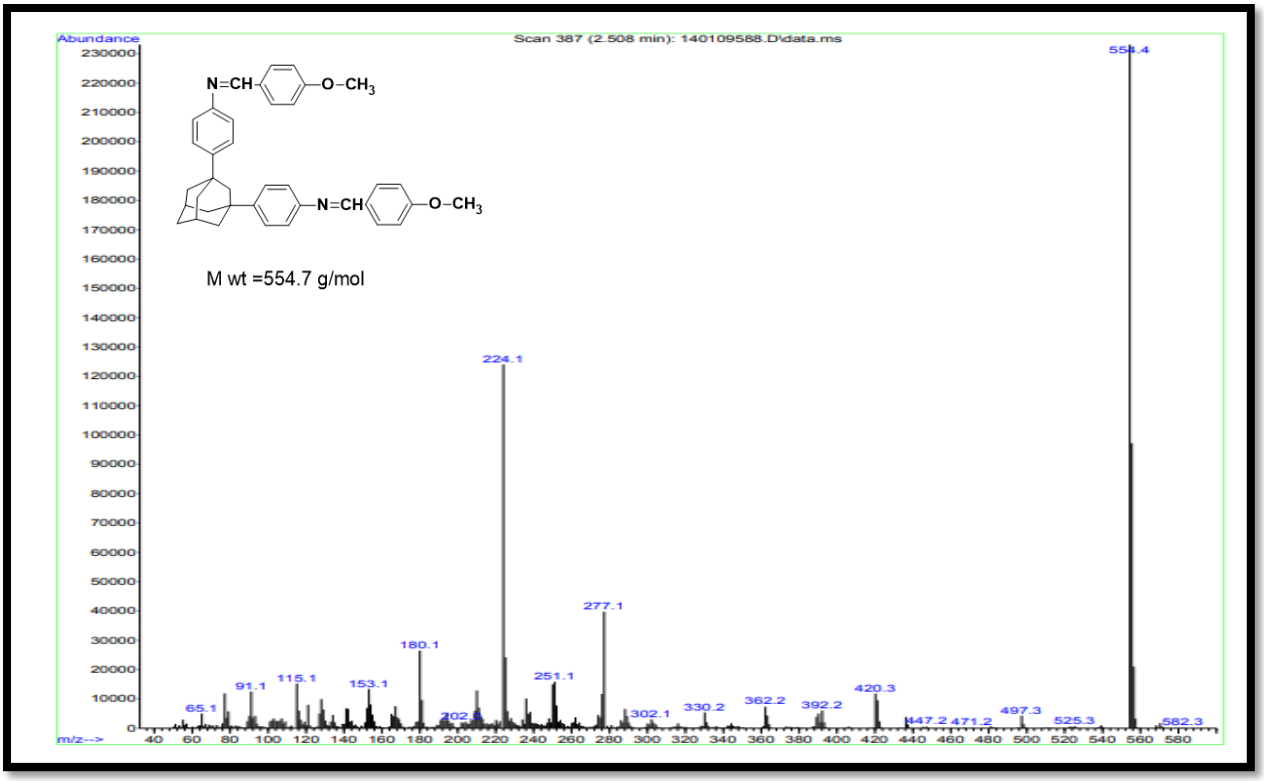


Figure 3.15: Mass Spectra of Schiff base derivative B3

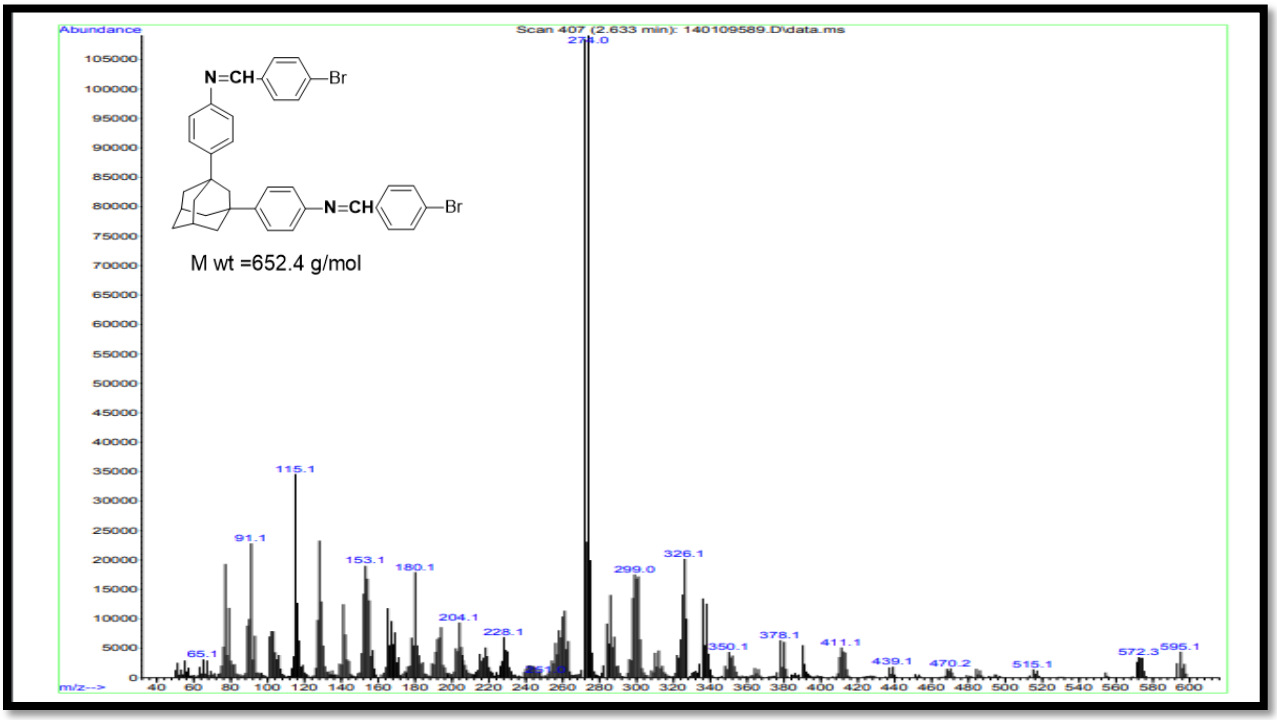


Figure 3.16: Mass Spectra of Schiff base derivative B4

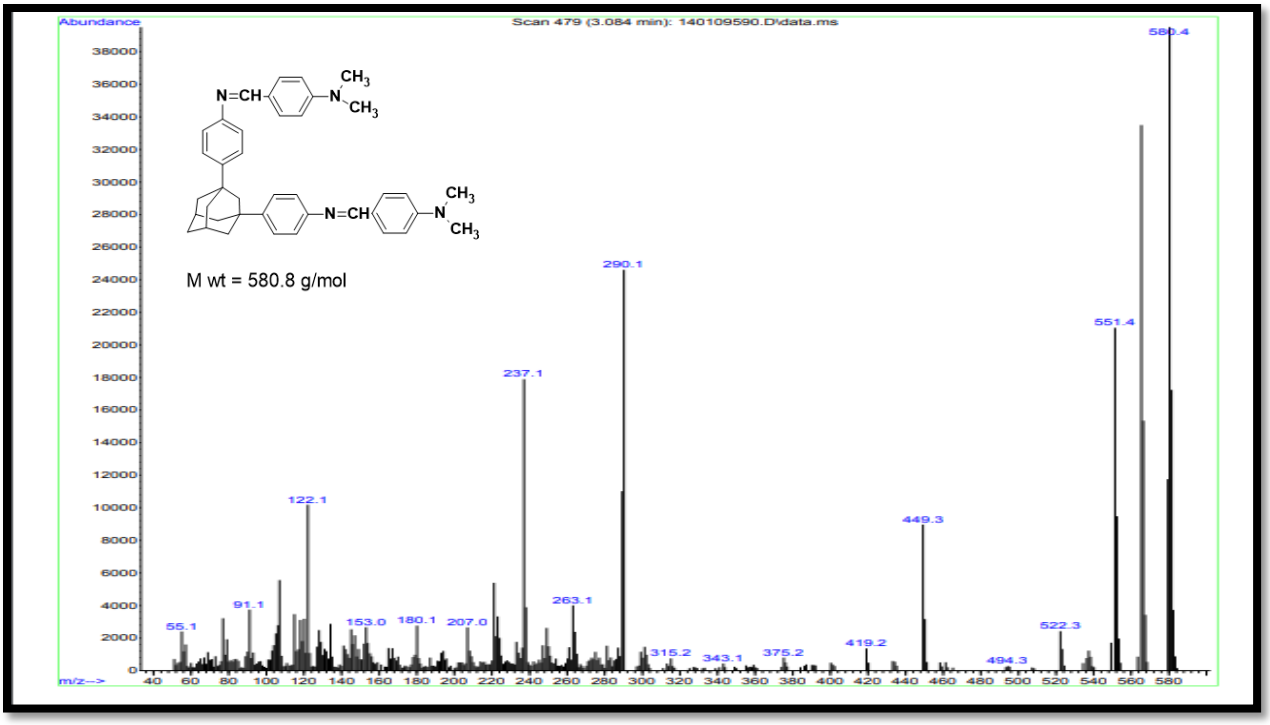


Figure 3.17: Mass Spectra of Schiff base derivative B5

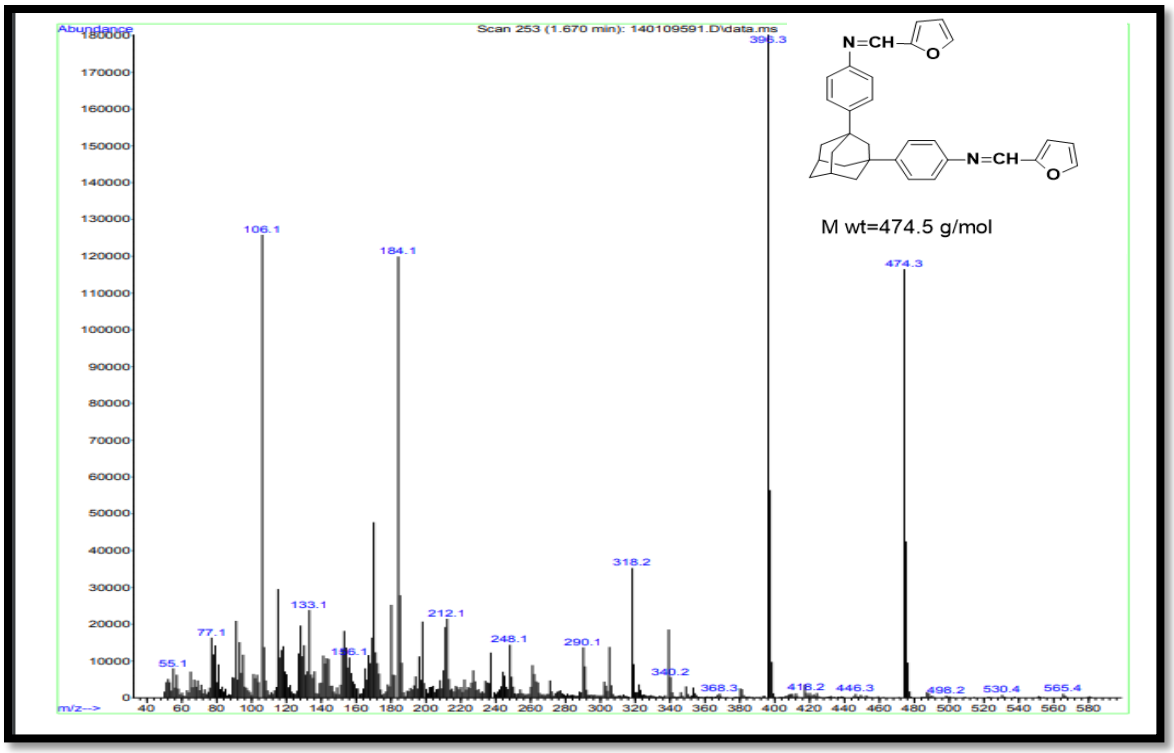


Figure 3.18: Mass Spectra of Schiff base derivative B6

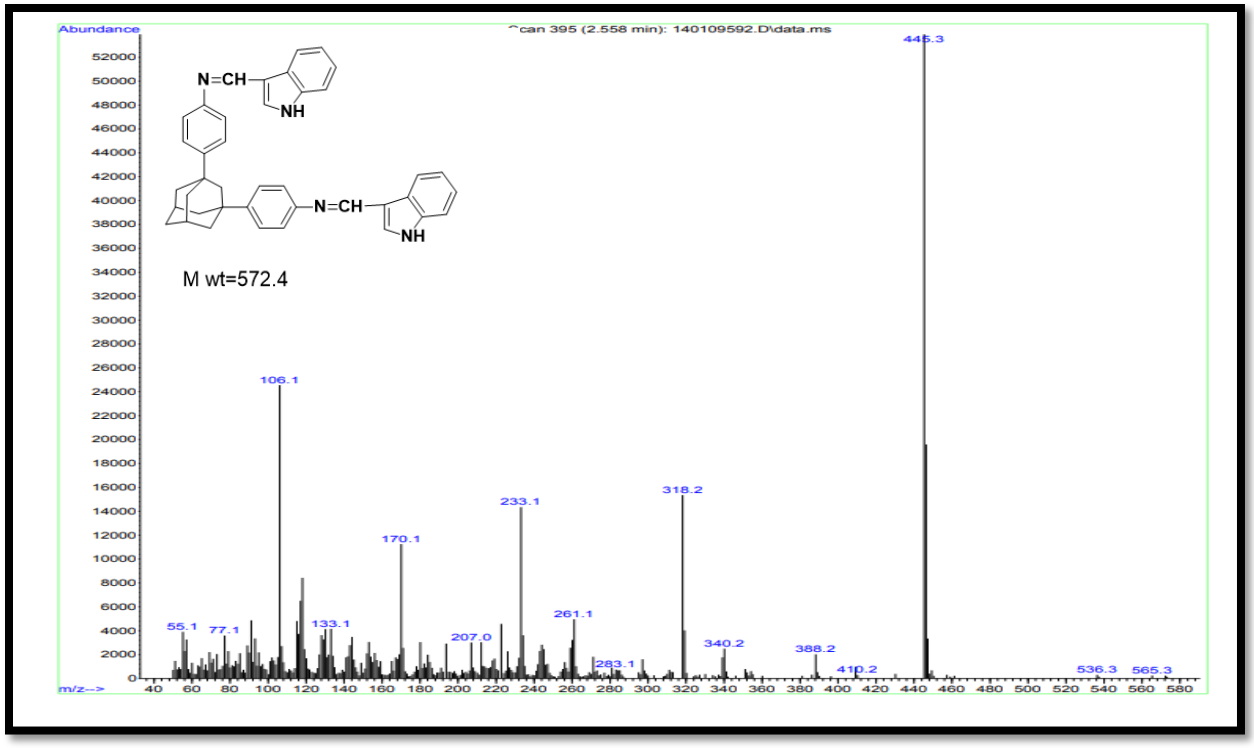


Figure 3.19: Mass Spectra of Schiff base derivative B7

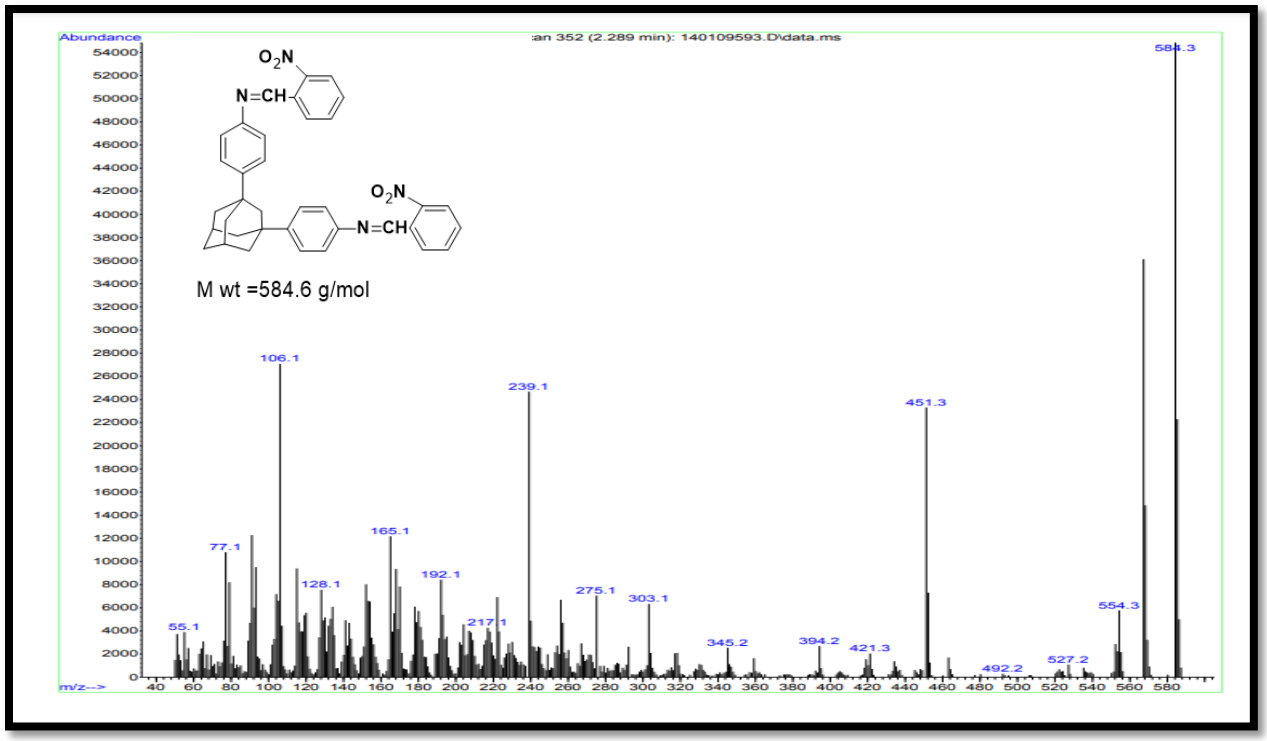


Figure 3.20: Mass Spectra of Schiff base derivative B8

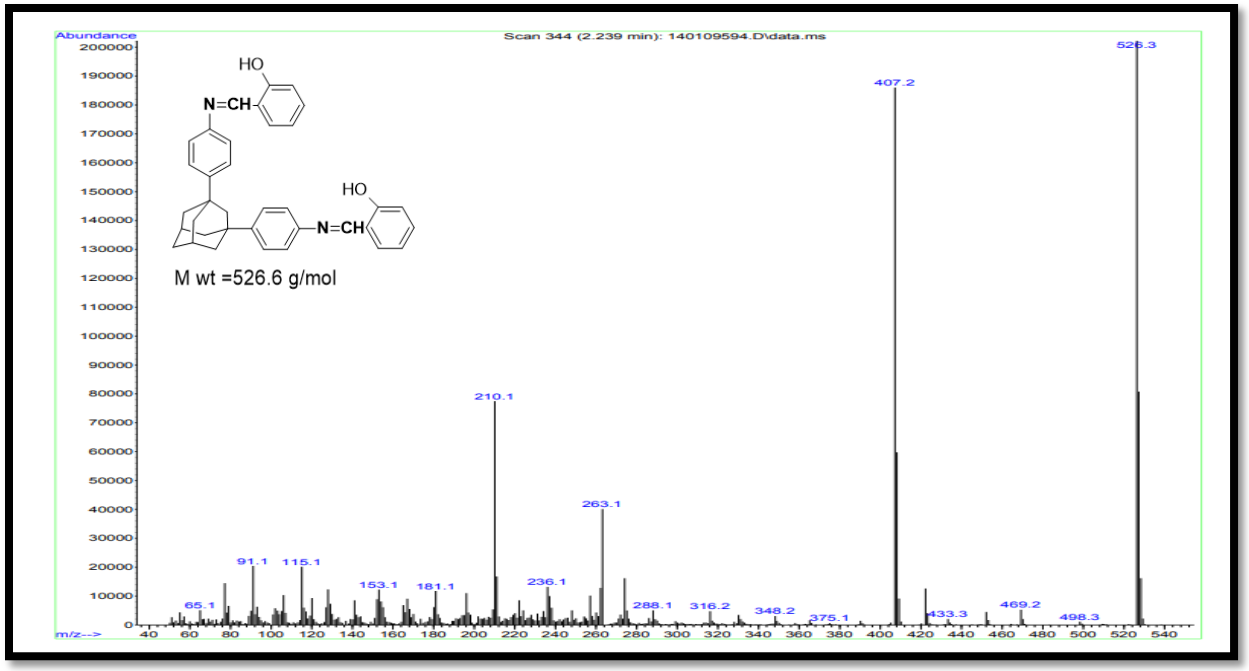


Figure 3.21: Mass Spectra of Schiff base derivative B9

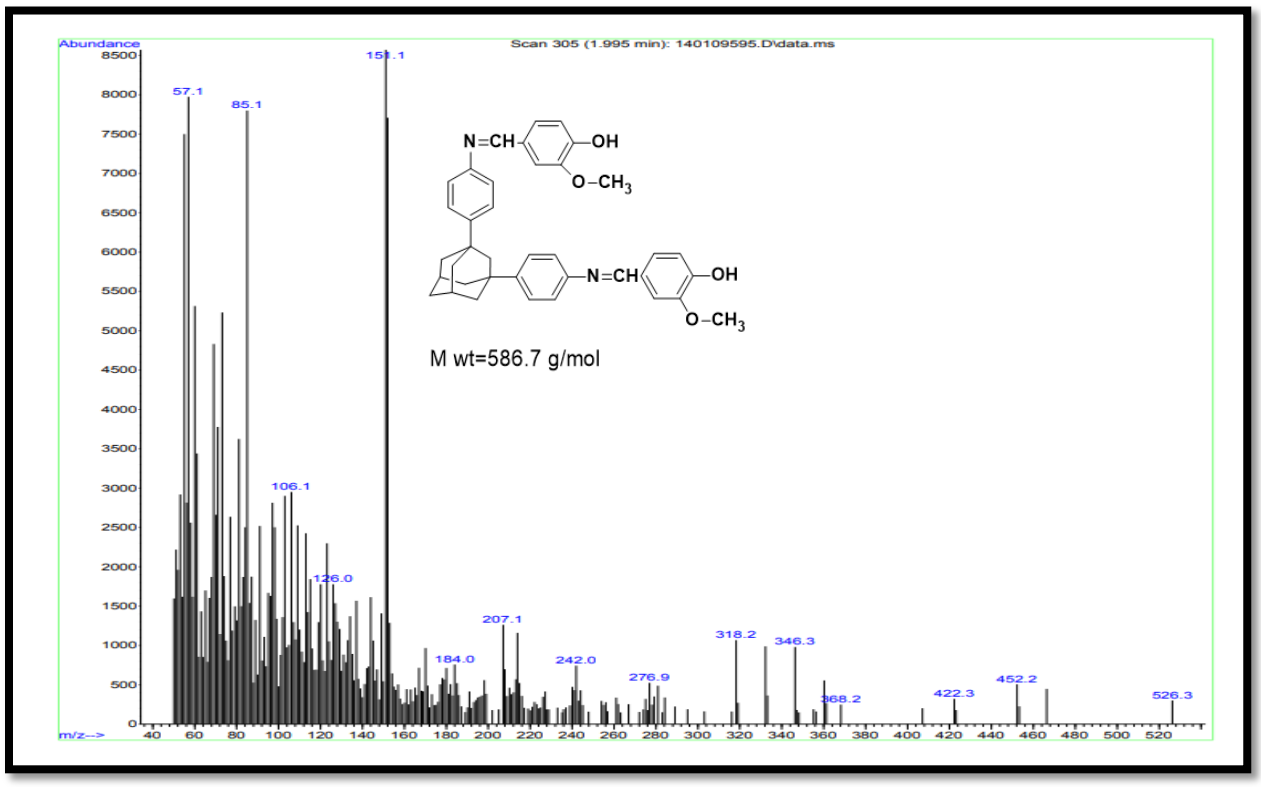


Figure 3.22: Mass Spectra of Schiff base derivative B10

3.3.5. ^{1}H-NMR Spectrum of Schiff Base Derivatives

^{1}H-NMR Spectrum (DMSO-*d6*) for new Schiff base showed the specific signals such as singlet peak at region δ (8 -8.6)ppm indicates to proton imine group[42], multi peak at region δ (1.75-2) ppm indicate to protons of adamantane structure and multi peaks at region δ (6.5-8) ppm refer to aromatic protons. The chemical shift of all type of protons for Schiff base derivatives listed in table(3.4) .

Table 3.4 : Chemical shift(ppm) in ^{1}H-NMR spectrum of schiff base derivatives(B1-B10)

Comp.	Aliphatic protons	Aromatic protons	Proton of imine group	Other protons
B1	1.24-2.48	7.1-7.9	8.6	
B2	1.23-2.38	7-7.8	8.5	
B3	1.24-2.27	7-7.8	8.5	3.8 protons of($O-CH_3$)
B4	1.24-2.29	7.2-7.9	8.6	
B5	1.25-2.27	6.7-7.7	8.4	3.03 protons of($N-CH_3$)
B6	1.7-2.96	6.3-7.9	8.4	
B7	1.23-2.27	6.5-7.5	8.4	4.87 proton of indole
B8	1.74-2.4	7.2-8	8.8	
B9	1-2.15	7-8	8.6	6.8 proton of (OH)
B10	1.2-3	6.5-7.5	8.46	4.6 proton of (OH) 3.8 proton of($O-CH_3$)

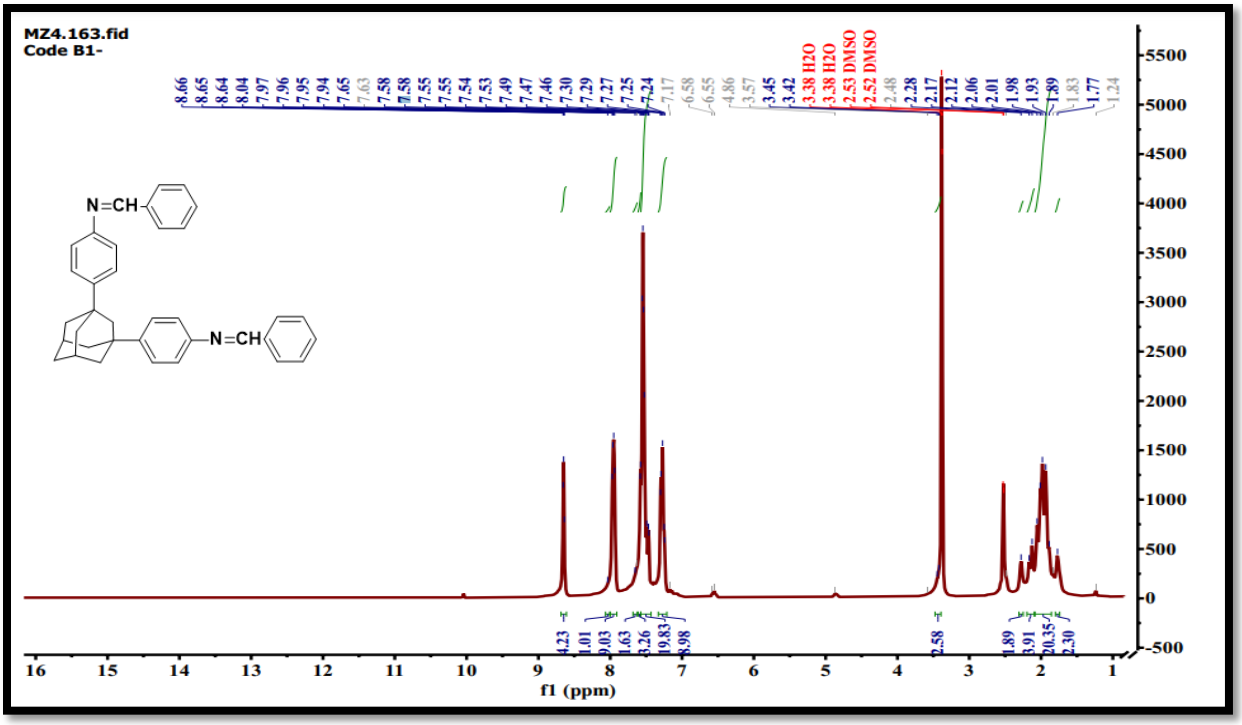


Figure 3.23: ^{1}H-NMR spectrum of Schiff base derivative B1

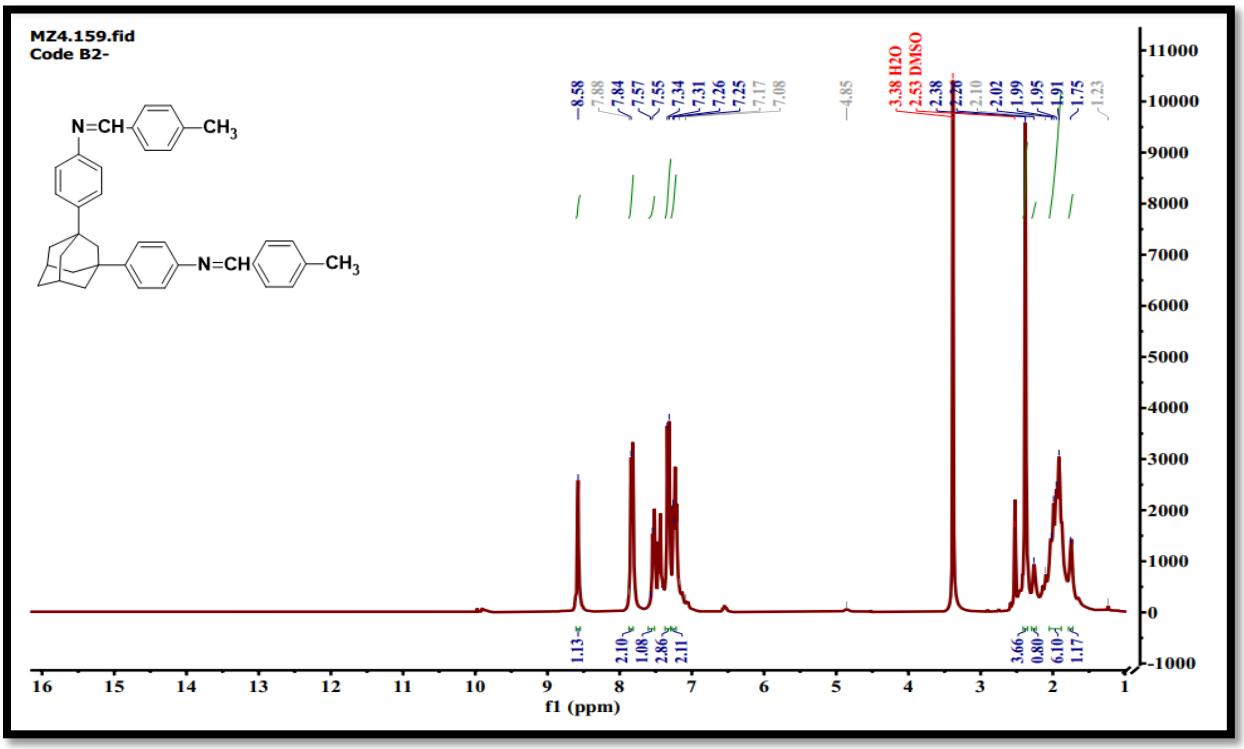


Figure 3.24: ^{1}H-NMR spectrum of Schiff base derivative B2

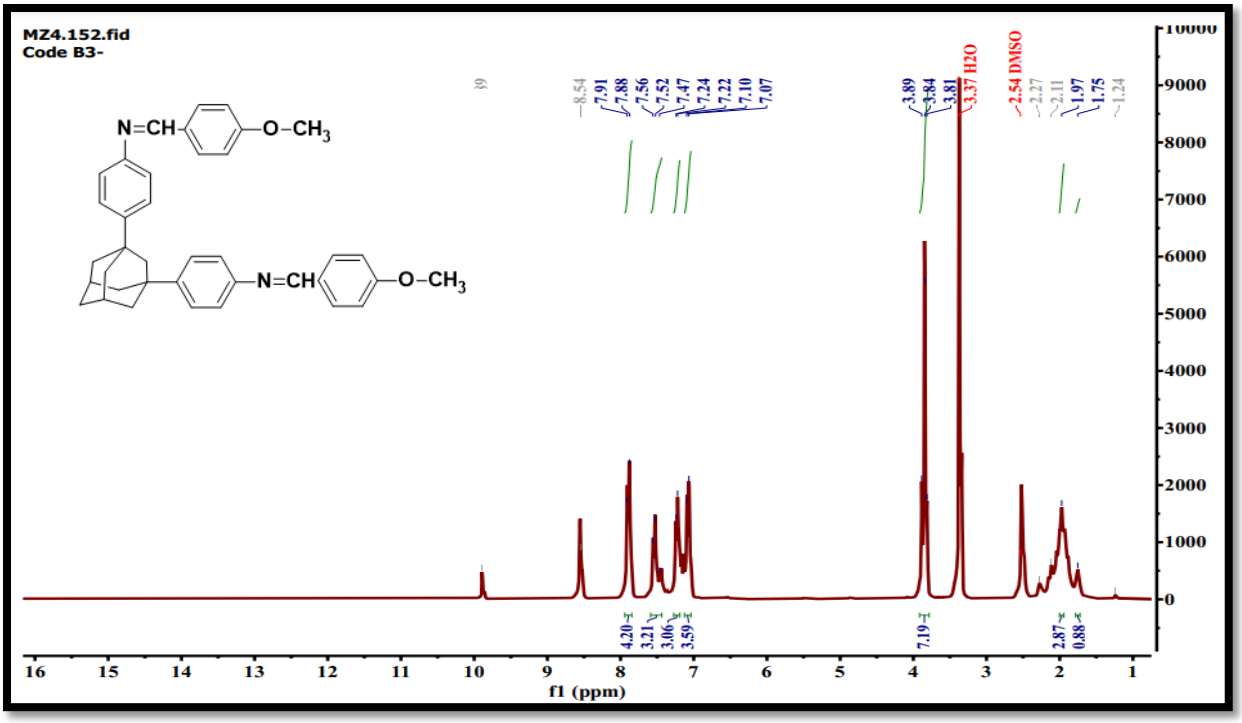


Figure 3.25: ^{1}H-NMR spectrum of Schiff base derivative B3

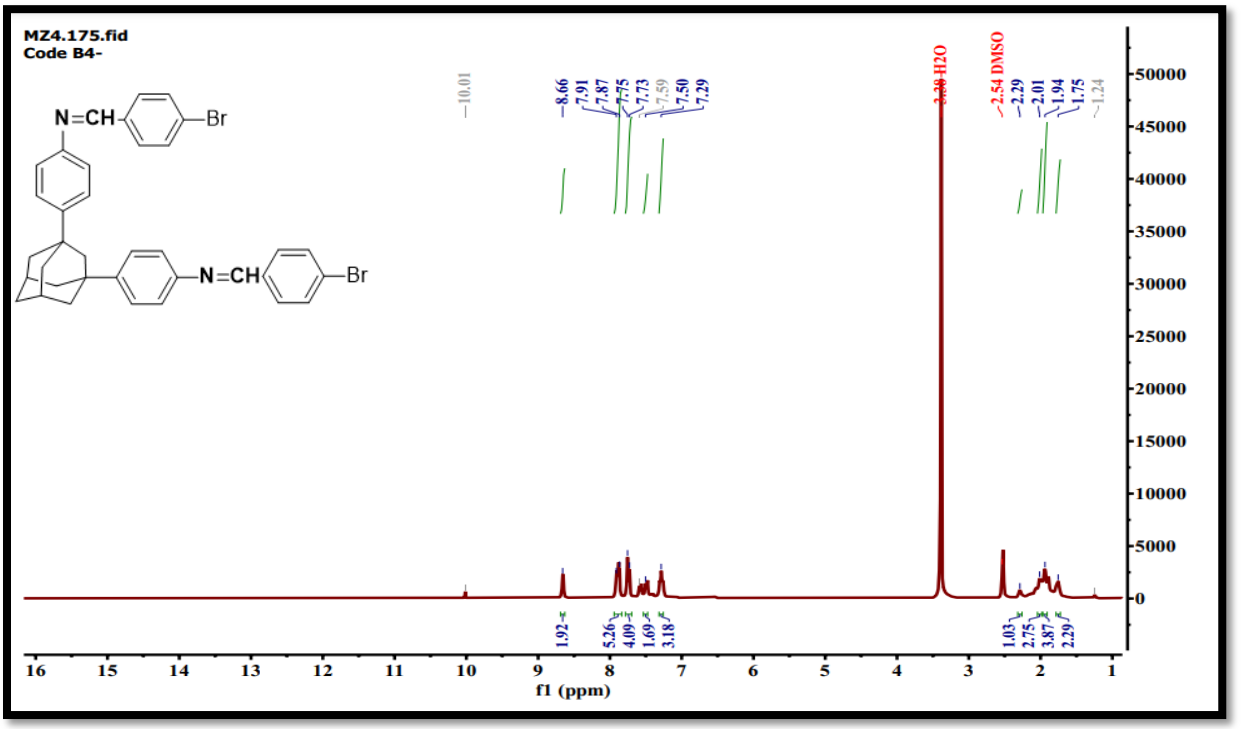


Figure 3.26: ^{1}H-NMR spectrum of Schiff base derivative B4

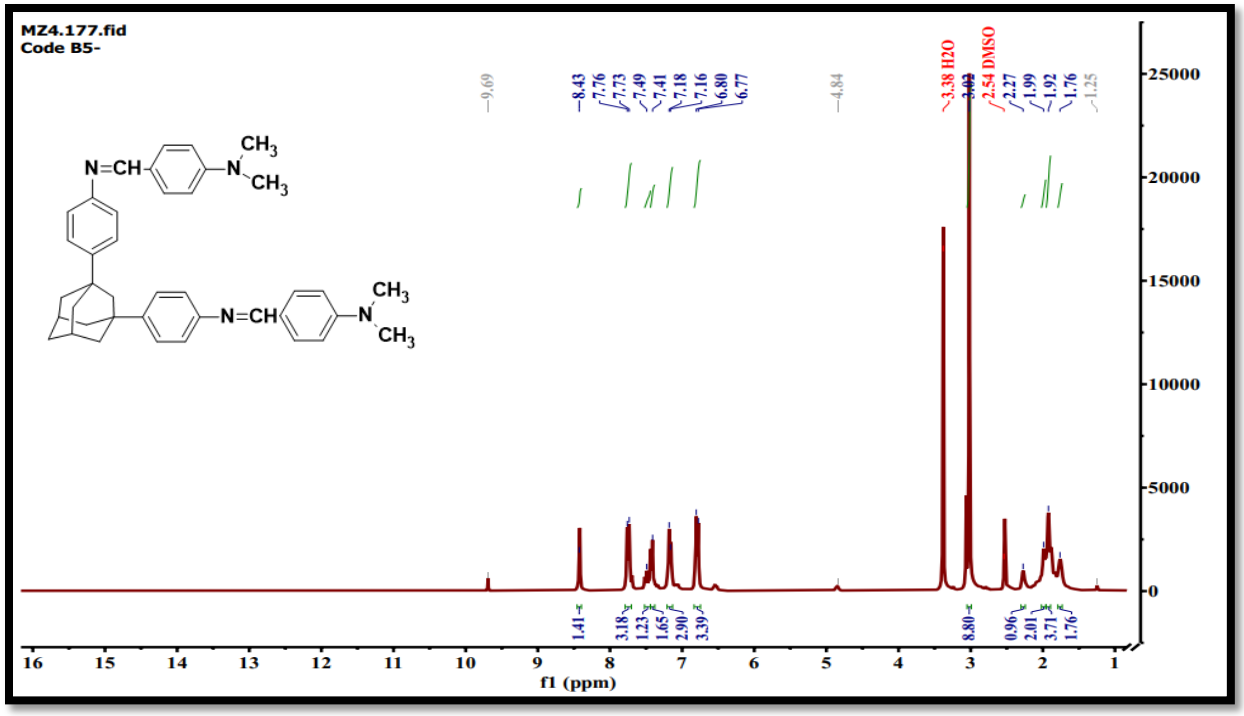


Figure 3.27: ^{1}H-NMR spectrum of Schiff base derivative B5

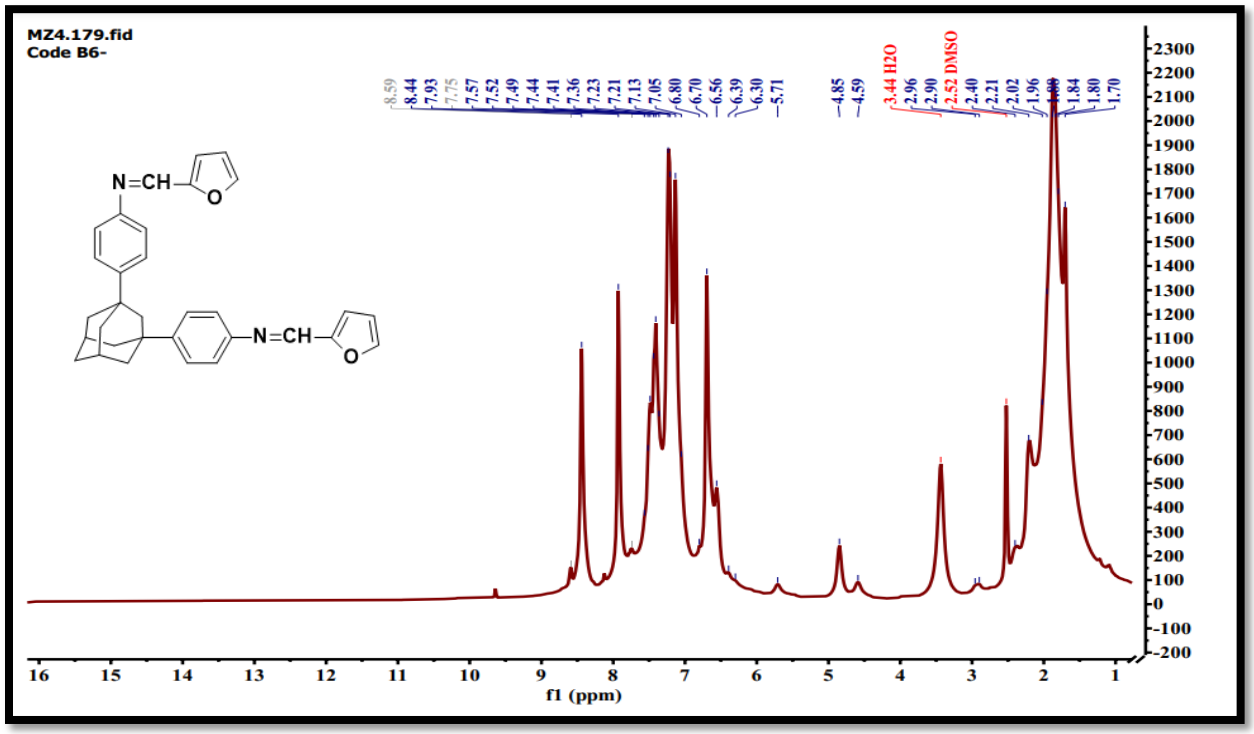


Figure 3.28: ^{1}H -NMR spectrum of Schiff base derivative B6

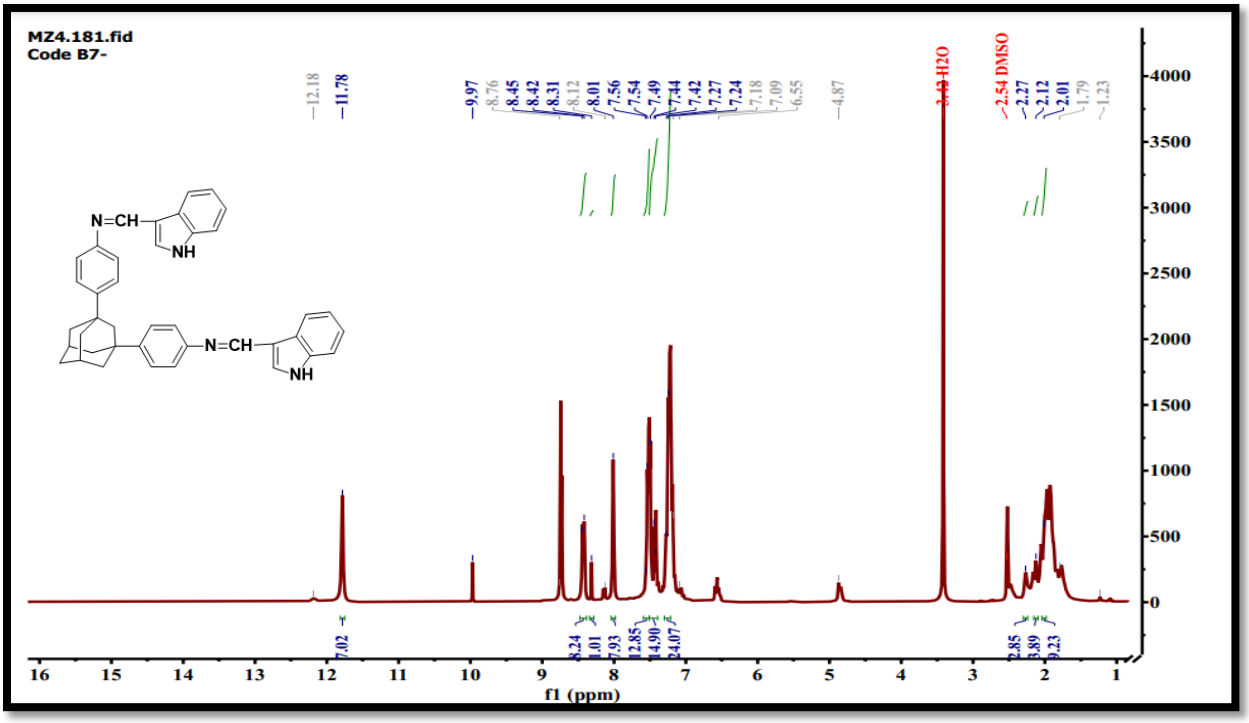


Figure 3.29: ^{1}H-NMR spectrum of Schiff base derivative B7

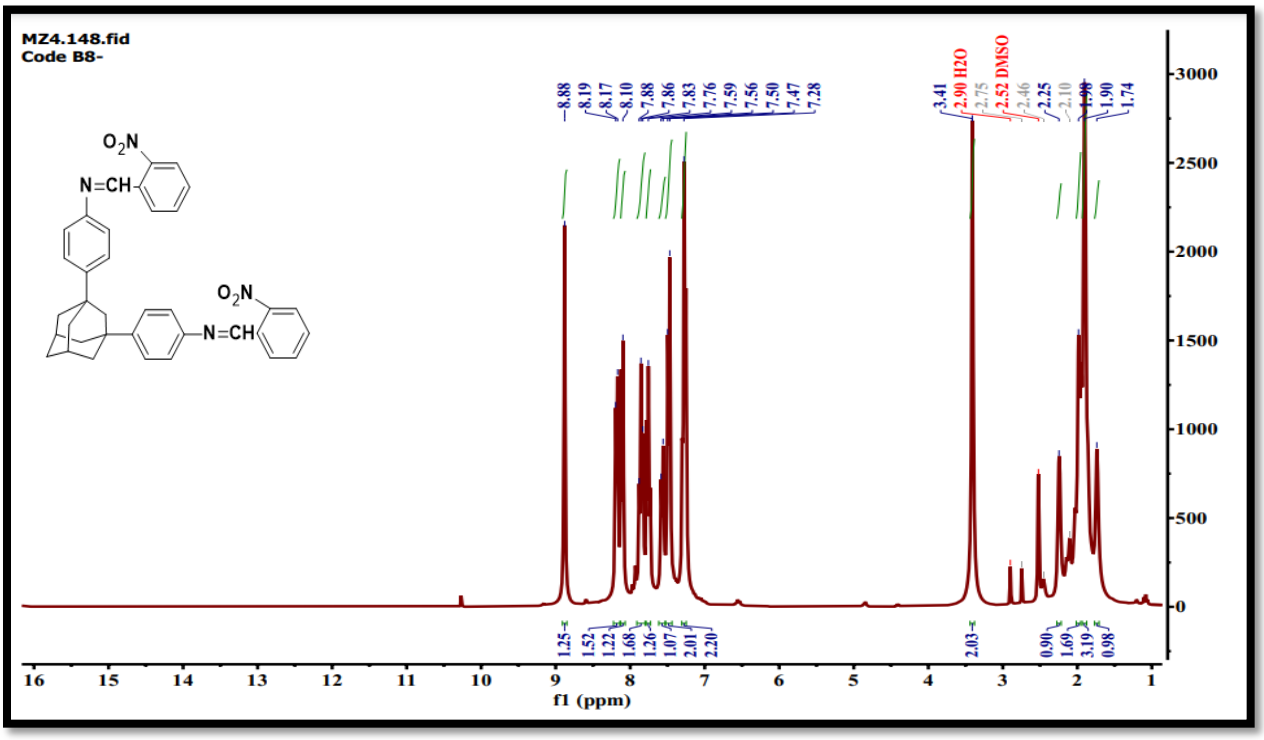


Figure 3.30: ^{1}H-NMR spectrum of Schiff base derivative B8

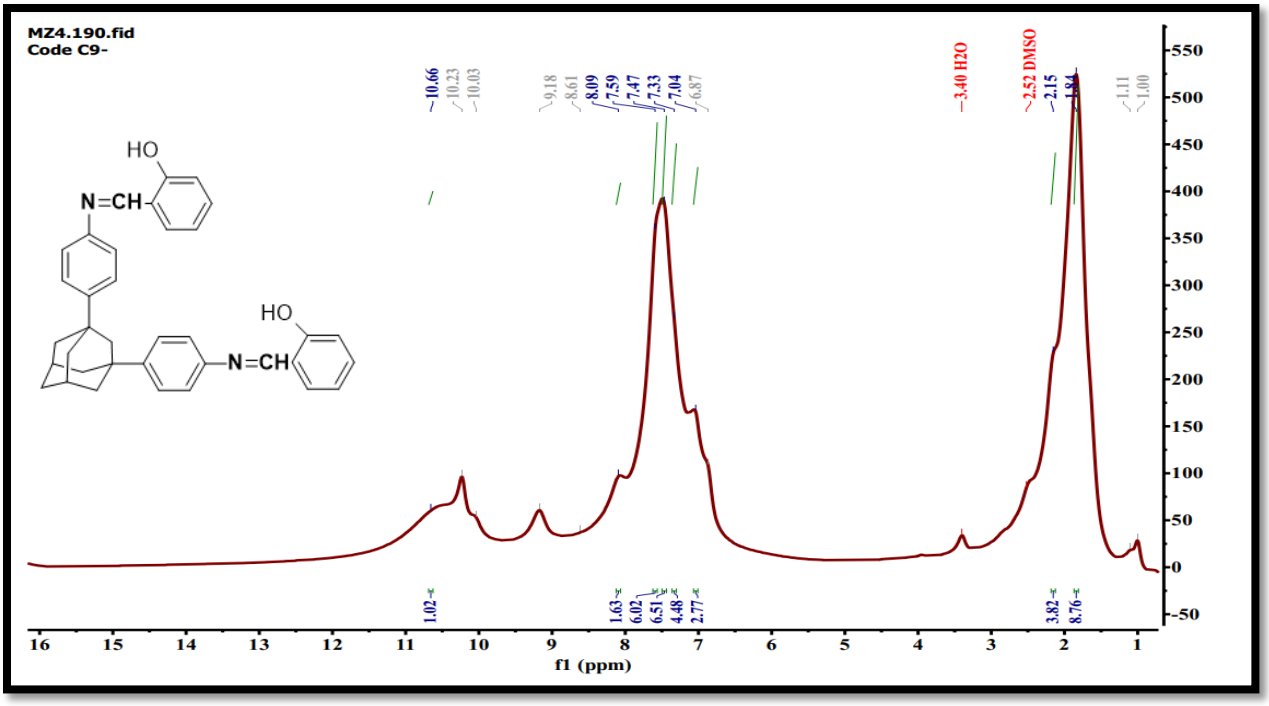


Figure 3.31: ^{1}H-NMR spectrum of Schiff base derivative B9

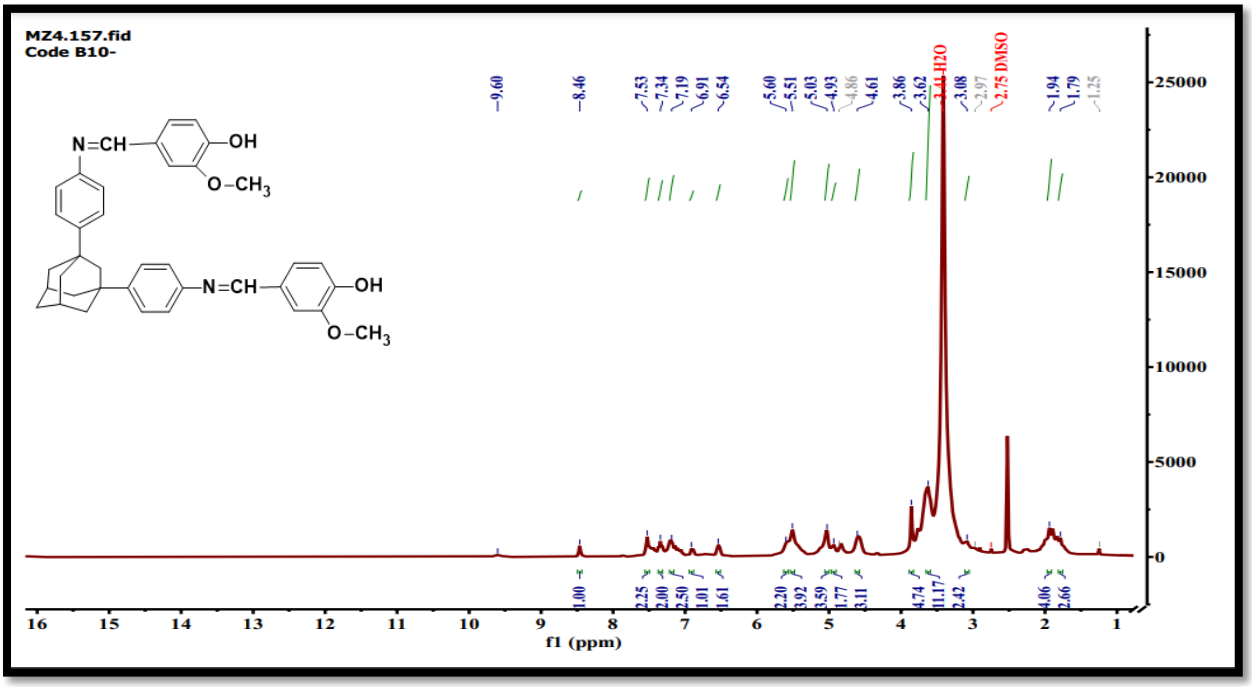


Figure 3.32: ^{1}H-NMR spectrum of Schiff base derivative B10

3.3.6. ^{13}C-NMR Spectrum of Schiff Base Derivatives

^{13}C-NMR Spectrum(ppm) (DMSO-*d6*) of Schiff base derivatives characterized by the presence of carbon of imine group (C=N) which is observed at the range 152-160 ppm, and chemical shift between 29 and 38 indicate to carbons of adamantane, while the chemical shift at range 110-150 indicate to the aromatic carbons. The chemical shift of all type of carbons for Schiff base derivatives listed in table(3.5).

Table 3.5 :Chemical shift(ppm) in ^{13}C-NMR spectrum of Schiff base derivatives

Comp.	Aliphatic carbons (ppm)	Aromatic carbons (ppm)	Carbon of imine group (ppm)	Other carbons (ppm)
B1	37-38.3	121-149.5	160.45	
B2	21.6-38.2	121.2-149.6	160.1	
B3	22-3.9	114-132	159.6	55.87 of C-O
B4	37.2	121-135	159	149 of C_{Ar}-Br
B5	29-40.2	111.5-130.6	159	$C_{Al.}$-N(42.2), $C_{Ar.}$-N(147-152)
B6	29.5-38	112.9-126	152	$C_{Ar.}$-O(146-149)
B8	29.4-38.3	121-134	156	C_{Ar}-NO_2(148-149)
B9	29.4-37.2	117-145	160	$C_{Ar.}$-O(149)

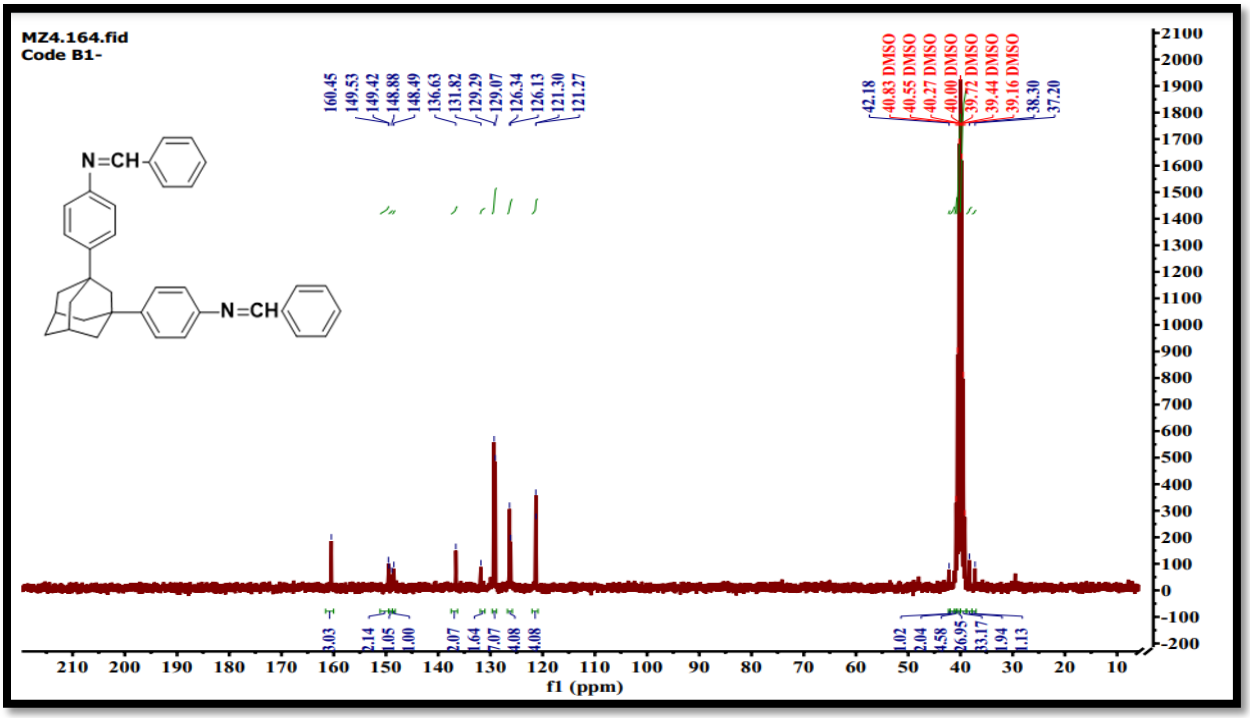


Figure 3.33: ^{13}C-NMR spectrum of Schiff base derivative B1

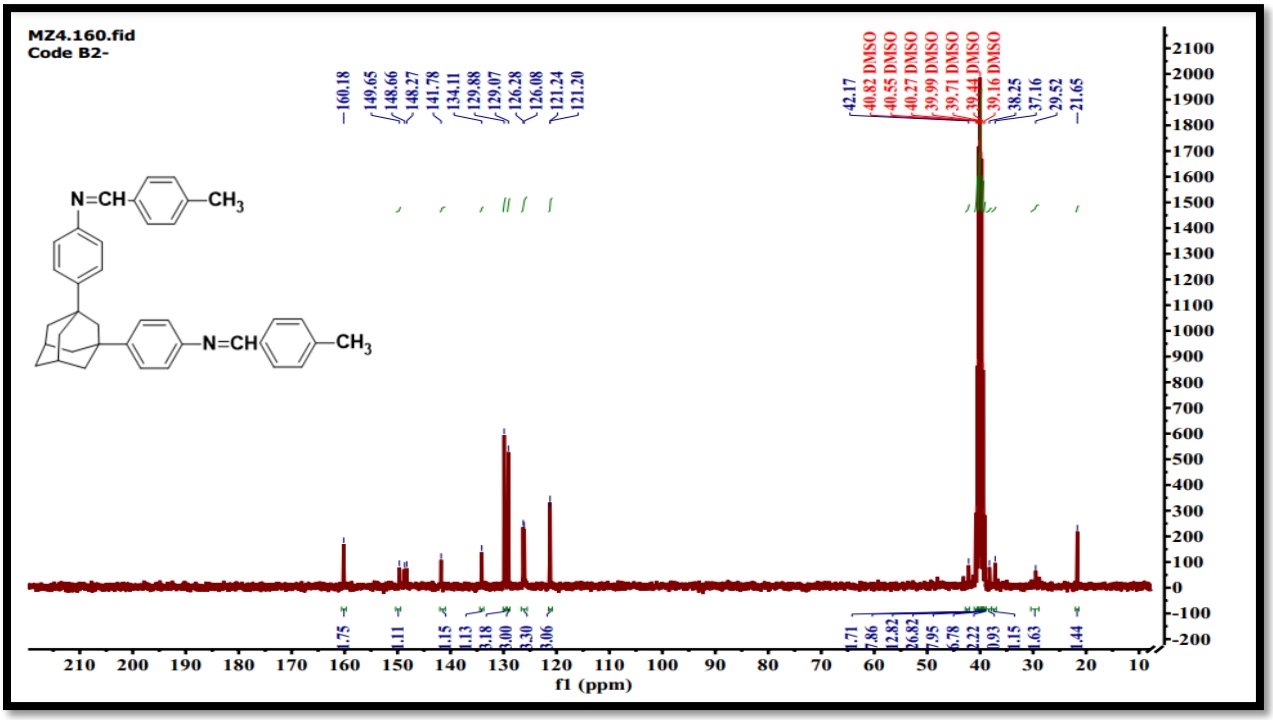


Figure 3.34: ^{13}C-NMR spectrum of Schiff base derivative B2

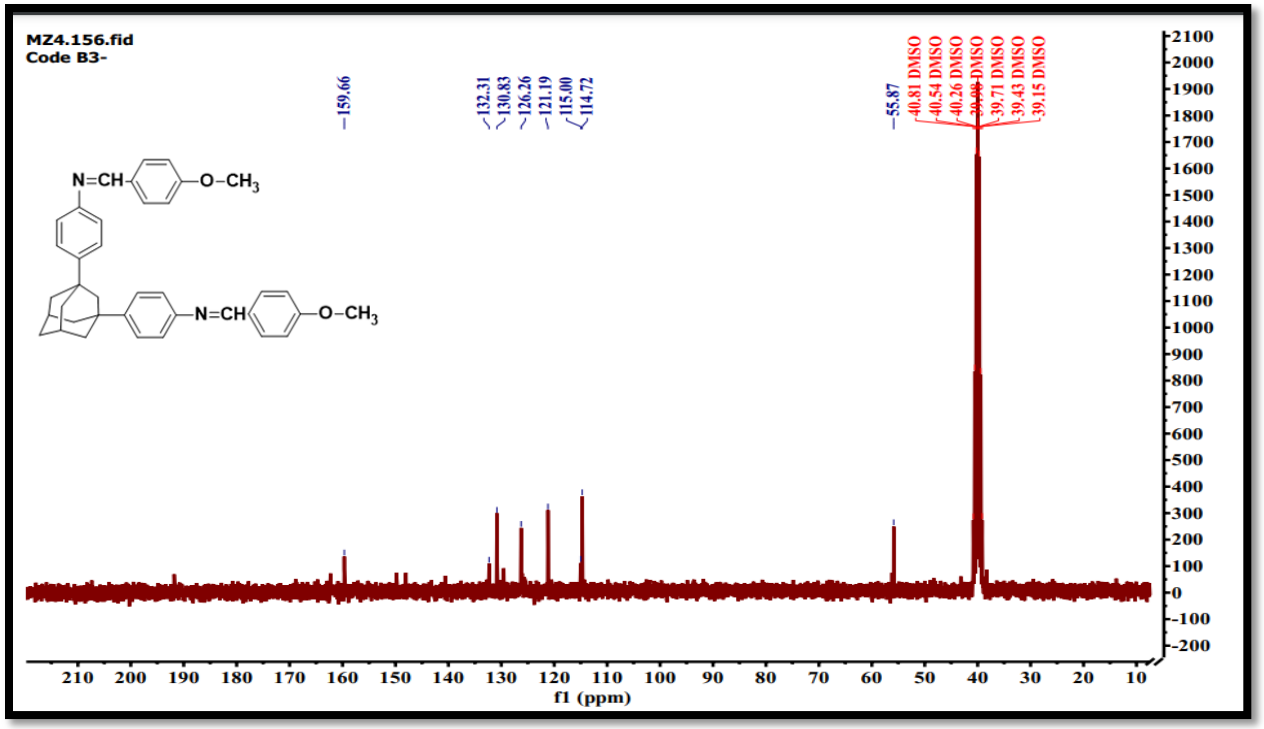


Figure 3.35: ^{13}C-NMR spectrum of Schiff base derivative B3

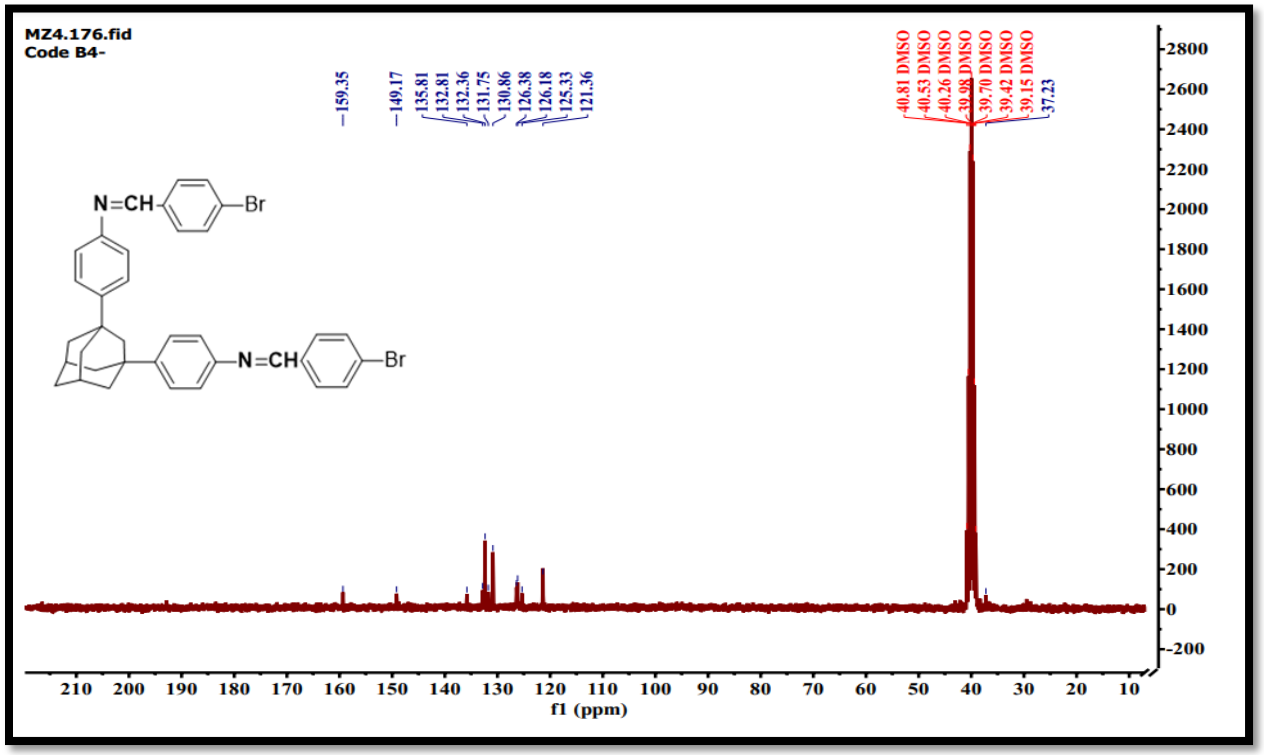


Figure 3.36: ^{13}C-NMR spectrum of Schiff base derivative B4

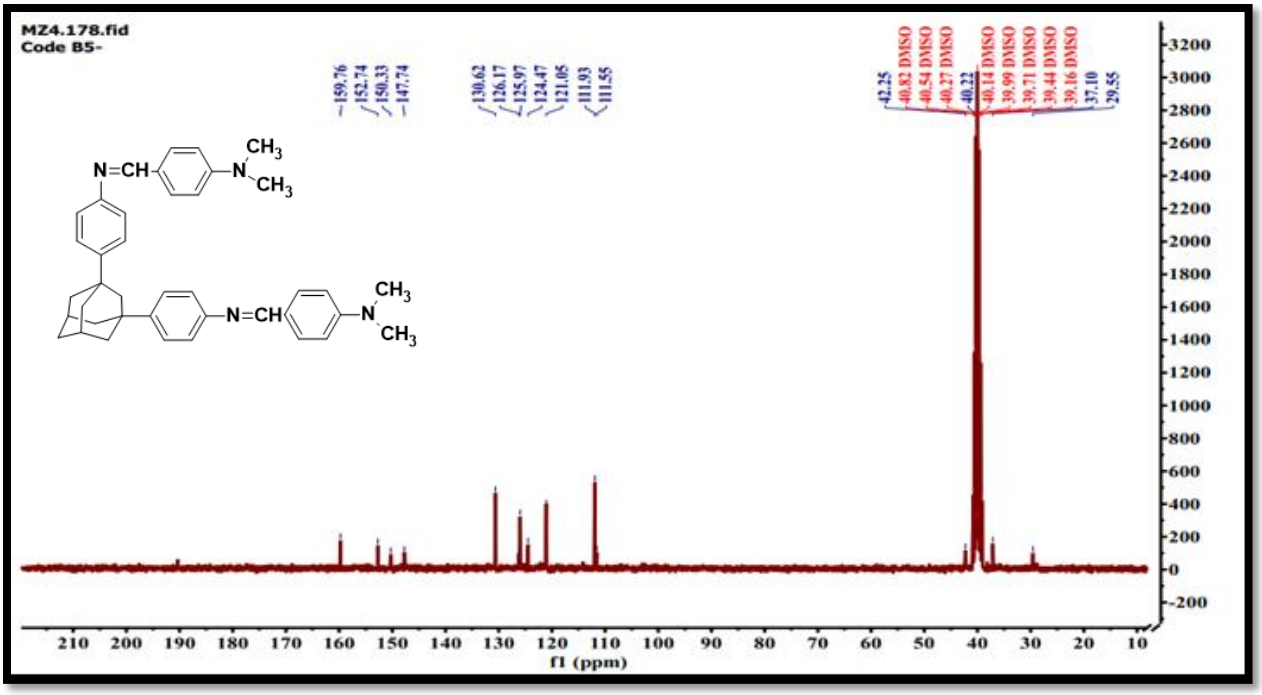


Figure 3.37: ^{13}C-NMR spectrum of Schiff base derivative B5

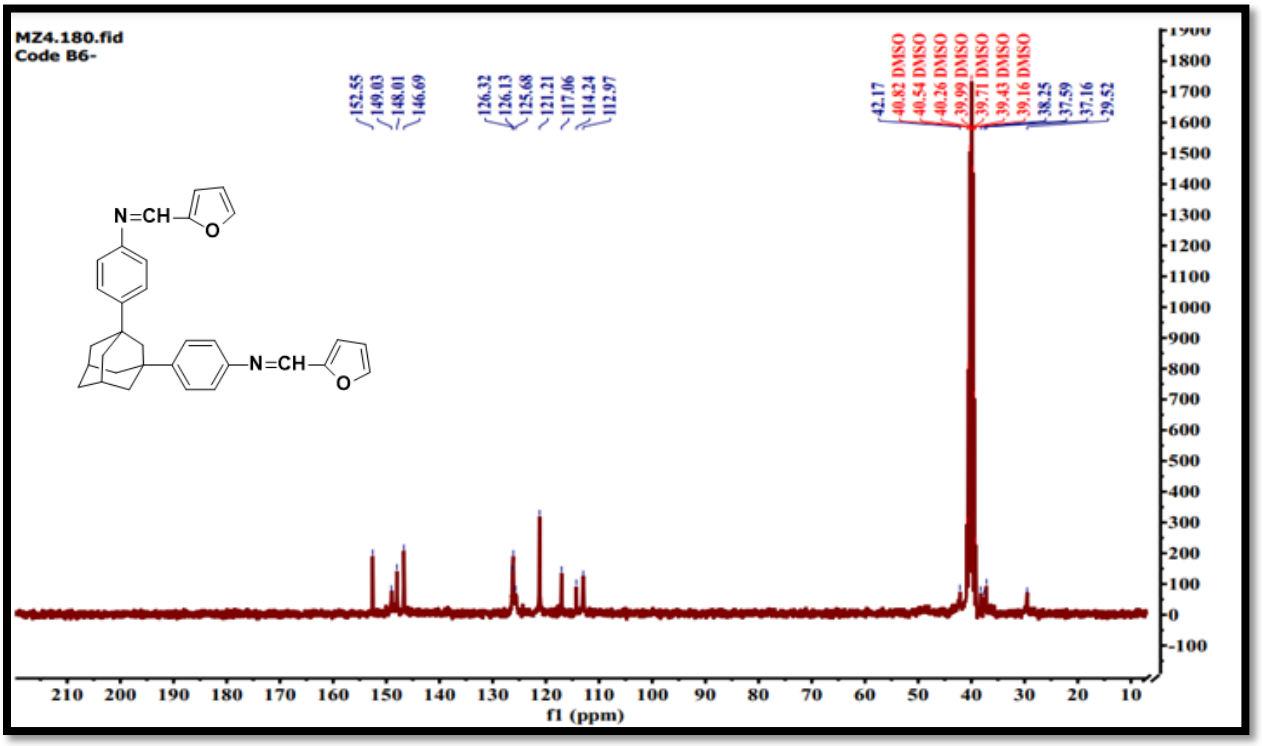


Figure 3.38: ^{13}C-NMR spectrum of Schiff base derivative B6

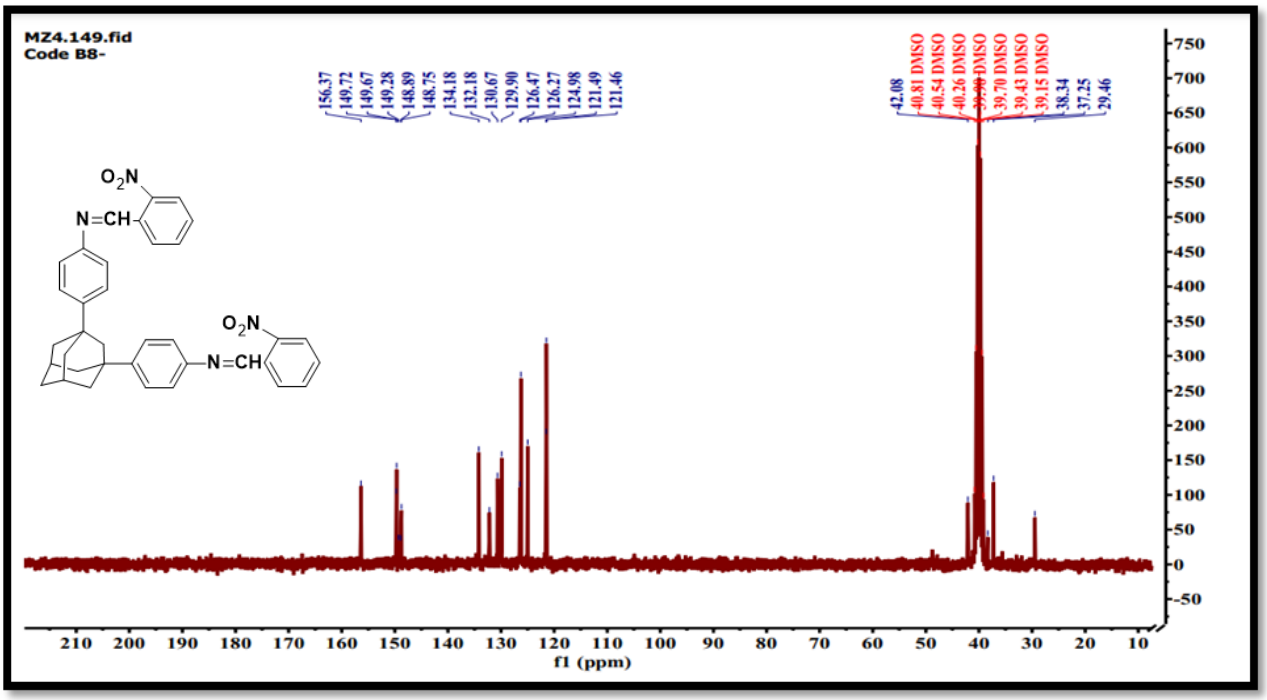


Figure 3.39: ^{13}C-NMR spectrum of Schiff base derivative B8

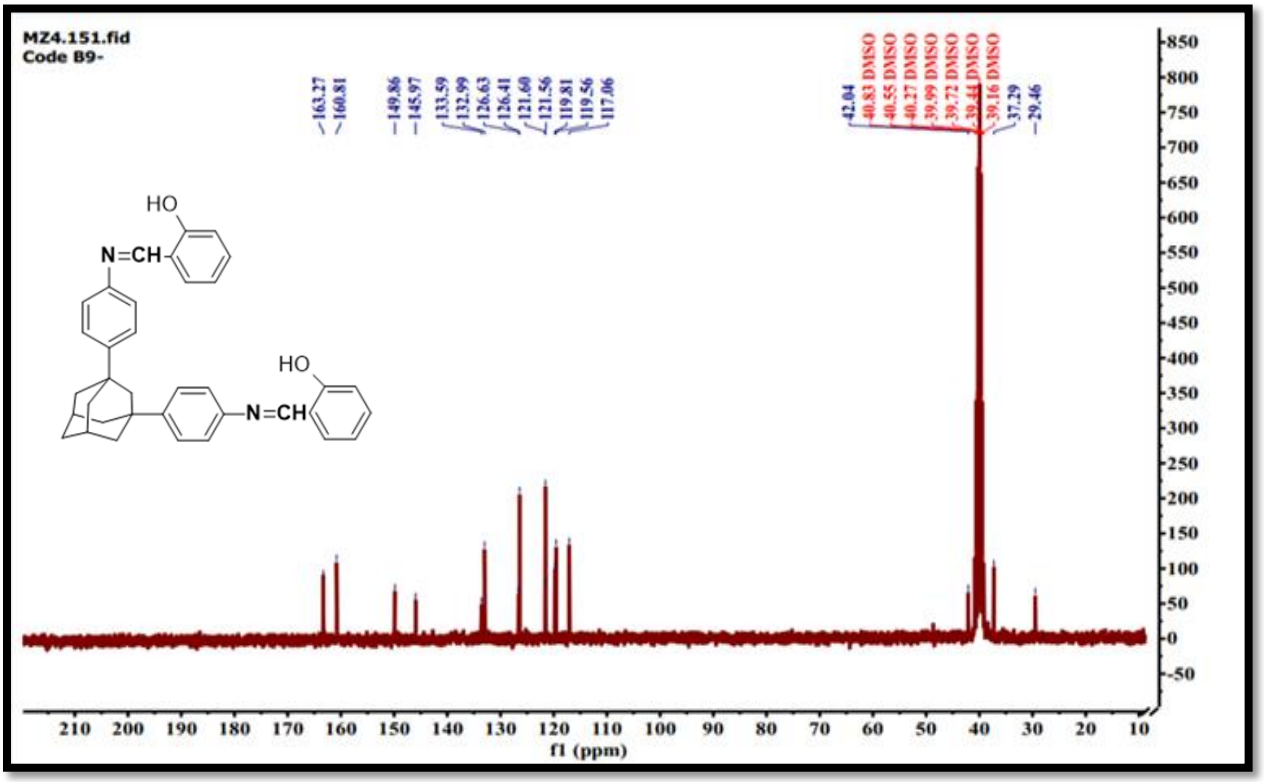


Figure 3.40: ^{13}C-NMR spectrum of Schiff base derivative B9

3.3.7. Antioxidant Activity of Schiff Base Derivatives

According to table(3.6)Schiff base derivatives synthesized (B1-B10) exhibited high inhibition percentage against DPPH(1,1-diphenyl-2-picrylhydrazyl) free radical from less value 80.5 % in compound B7 to higher value 89.9% in compound B3 at high concentration 1 mg/ml, as well as the percent inhibition decreased with decrease concentration in all compounds. Image (3.1) illustrated change in color of all compounds in different concentration. These change proves radicals scavenging ability of all compounds. The substituent on aromatic ring and their position also make an influence on the scavenging ability.

Table 3-6: values of antioxidants activity of Schiff base derivatives by DPPH scavenging assay

Comp	1 mg/ml absorbance	% inhibition	0.5 mg/ml absorbance	% inhibition	0.25 mg/ml absorbance	% inhibition	0.125 mg/ml absorbance	% inhibition
B1	0.2854	87.8	0.3254	86.1	0.3952	83.1	0.425	81.8
B2	0.3254	86.1	0.3564	84.8	0.4952	78.8	0.5027	78.5
B3	0.2354	89.9	0.2465	89.4	0.2846	87.8	0.3685	84.2
B4	0.4315	81.6	0.4658	80.1	0.4885	79.1	0.5124	78.1
B5	0.435	81.4	0.4578	80.4	0.4851	79.3	0.5022	78.5
B6	0.4354	81.4	0.4658	80.1	0.5624	76	0.6356	72.9
B7	0.4568	80.5	0.5074	78.3	0.5687	75.7	0.6245	73.3
B8	0.4135	82.3	0.4754	79.7	0.5246	77.6	0.5486	76.6
B9	0.2745	88.3	0.3564	84.8	0.3812	83.7	0.4135	82.3
B10	0.2564	89	0.2954	87.4	0.3512	85	0.3914	83.3
Absorbance of control solution(DPPH + methanol) =2.3464								

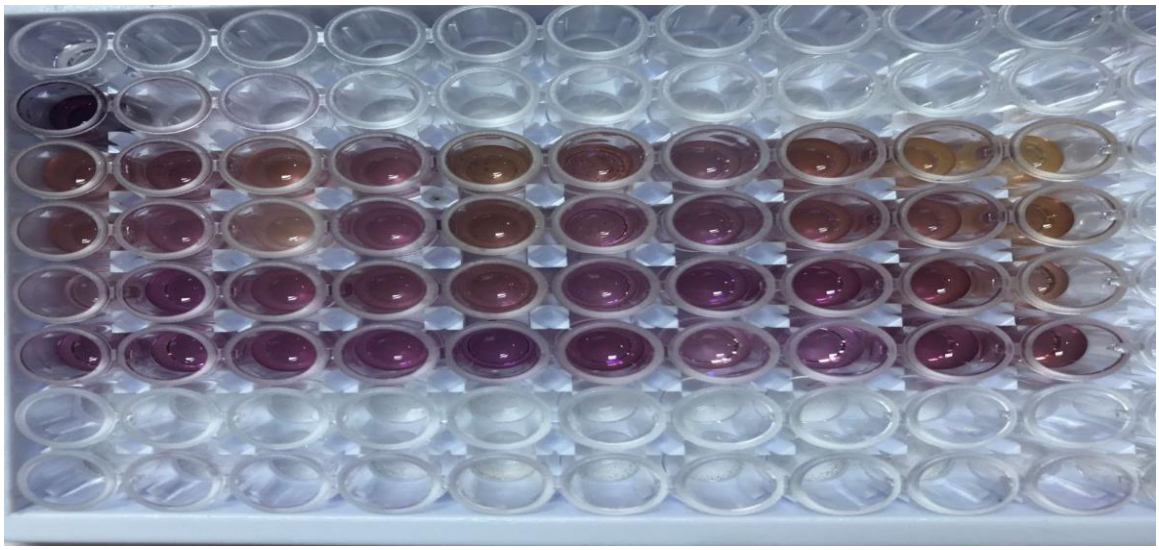


Image 3.1: Change in color of DPPH at different concentration of all Schiff base derivatives

3.4 .Tetrazole Derivatives

Tetrazole chemistry has mostly been influenced by the widespread use of these groups of chemicals in biochemistry, agriculture, and medicine, heterocyclic derivatives are often utilized as antibacterial agents. Several substances containing tetrazole have been employed as antibacterial and anticancer agents[138].

3.4.1. Solubility and Physical Properties of Tetrazole Derivatives

The tetrazole derivatives which Synthesized have been tested against many organic solvent such as Ethanol, DMF, Benzene as shown in table(3.7).

Table 3.7: Solubility and physical properties of Tetrazole derivatives

Comp.	M.P (°C)	color	Yield %	Solubility			
				EtOH	DMSO	C_6H_6	DMF
C1	92-94	Yellow	23	+	+	δ	+
C2	82-84	Greenish- yellow	32.2	+	+	δ	+
C3	68-70	Greenish- yellow	34	+	+	+	+
C4	167-168	Orange	27	+	+	δ	+
C5	161-163	Dark- red	32	+	+	δ	+
C6	139-141	Dark- brown	12.2	+	+	_	+
C7	188-190	Dark- red	15.4	+	+	_	+
C8	72-74	Dark- brown	22.3	+	+	_	+
C9	88-90	Greenish- yellow	35.3	+	+	δ	+
C10	177-179	Dark-brown	23.6	+	+	_	+

partial= δ

3.4.2. General Mechanism of Tetrazole Derivatives

Reactions in 1,3-Dipolar Cycloaddition reactions (1,3-DPCA) are a broad family of concerted reactions that are similar to the Diels-Alder reaction. For each 1,3-dipole, there is at least one charge-separated resonance structure with dipolar charges. This class of reactants is referred to as 1,3-dipoles as a result of its structural characteristics. While bonds are not necessary for dipolarophiles to operate, additional multiply bonded functional groups like carbonyl, imine, azo, and nitroso may Dipolarophiles are frequently substituted alkenes or alkynes. Dipolarophiles respond differently depending on the type of 1,3-dipole involved in the reaction, as well as the substituents that are present on the bond. The 1,3-DPCA reaction is incredibly helpful for creating five-membered heterocyclic rings. The figure (3.41) that follows illustrates how 1,3-DPCA reactions can be depicted. The 1,3-dipole is the thing a-b-c, and the dipolarophile is d-e[81].

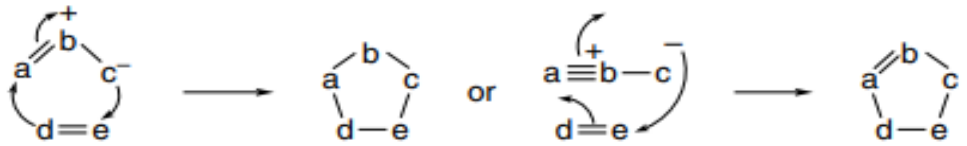


Figure 3.41: 1,3-Dipolarophiles reaction

The mechanism of cycloaddition reaction of 1,3 dipole(sodium azide) with Schiff base derivatives (dipolarophile) can be illustrated in figure (3.42).

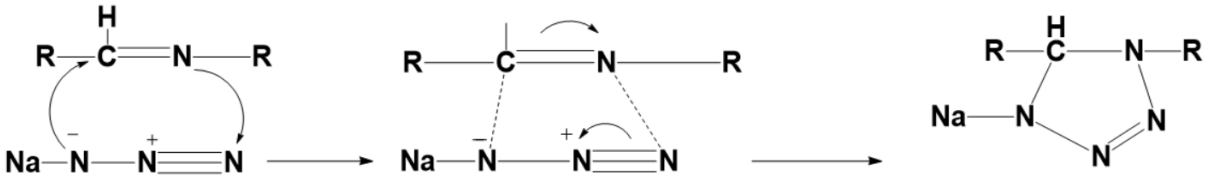
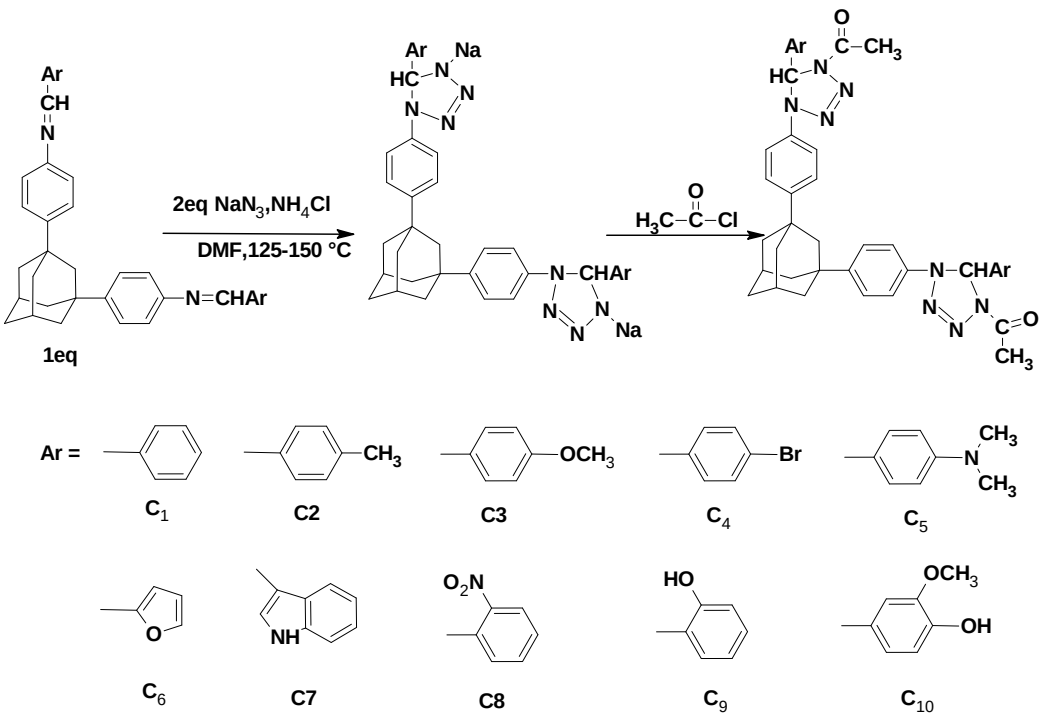


Figure 3.42: Mechanism of cycloaddition reaction of sodium tetrazole

3.4.3. Synthesis of Tetrazole Derivatives

According to the 1,3 dipole cycloaddition reaction (3+2) Schiff base derivatives react with sodium azide with yield percent from (12%-35%) as first step, tetrazole ring have partial solubility in water ,as well as the present of N-Na bond on the tetrazole ring that have ionic characters lead to increase of partial solubility in water. Therefore , yield percentage is low due to the losses of product through washing in water. Second step the product reacts with acetyl chloride in order to remove sodium atom from tetrazole ring and produces tetrazole derivatives(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10) as shown in figure(3.1) .



Scheme 3.1: Synthesis of tetrazole derivatives (C1-C10)

3.4.4. FT-IR Spectrum of Tetrazole Derivatives(C1-C10):

The FT-IR spectrum υ (cm-1) (KBr) of tetrazole derivatives that illustrated in figures below shows disappearance imine group (C=N), as well as appearance several bands of peaks such as weak peak at approximately 1404-1500 cm^{-I} indicates to azo group (N=N), strong peak at range 1635-1658 cm^{-1} indicates to amide carbonyl group , strong–medium two peaks 2843-2847cm^{-1}, 2897-2920cm^{-1} indicate of C-H aliphatic of adamantane structure, and other band such as C=C aromatic at rang 1450-1600 cm^{-1}. The fundamental band of all tetrazole derivatives listed in table (3.8).

Table 3.8: Fundamental bands in FT-IR spectrum of tetrazole derivatives(C1-C10)

Comp.	C-H Aromatic (cm-1)	C-H Aliphatic (cm-1)	C=O Amid (cm-1)	N=N Azo (cm-1)	C=C Aromatic (cm-1)	Other bands (cm-1)
C1	3080	2846, 2900	1658	1446	1597,1512	
C2	3039	2846, 2897	1654	1446	1600,1512	
C3	3043	2846, 2900	1654	1440	1597,1581	1276 (C_{Ar}-O)
C4	3043	2846, 2900	1654	1446	1589,1512	748(C_{Ar}-Br)
C5	3048	2897, 2843	1647	1500	1597,1543	1172($C_{Al.}$-N) 1200($C_{Ar.}$-N)
C6	3036	2846, 2900	1647	1500	1597,1512	1250 ($C_{Ar.}$-O)
C7	3051	2847, 2897	1643	1435	1581,1500	1222($C_{Ar.}$-N)
C8	3042	2846, 2897	1637	1404	1512	1527 (NO_2) 1188($C_{Ar.}$-NO_2)
C9	3032	2846,2900	1643	1469	1608,1577	1200 (C_{Ar}-O)
C10	3035	2846,2920	1635	1458	1543	1200($C_{Ar.}$-O) 1053($C_{Al.}$-O)

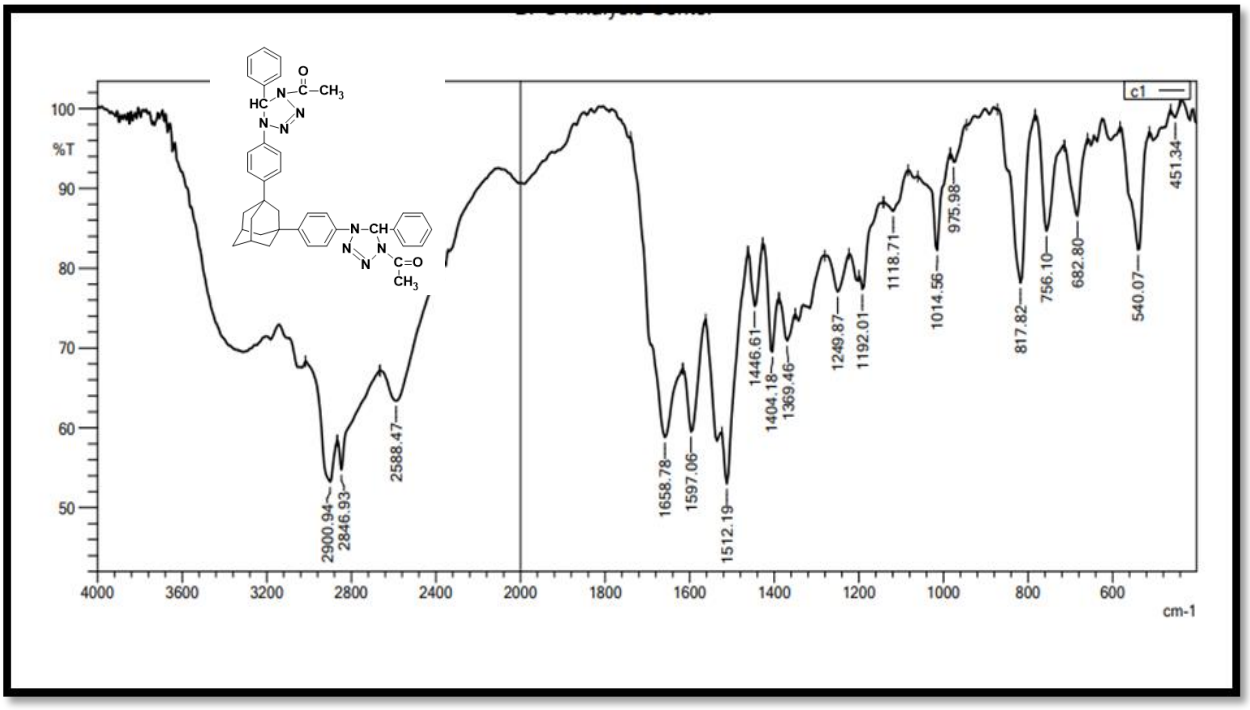


Figure 3.43: FT-IR Spectrum of tetrazole derivative C1

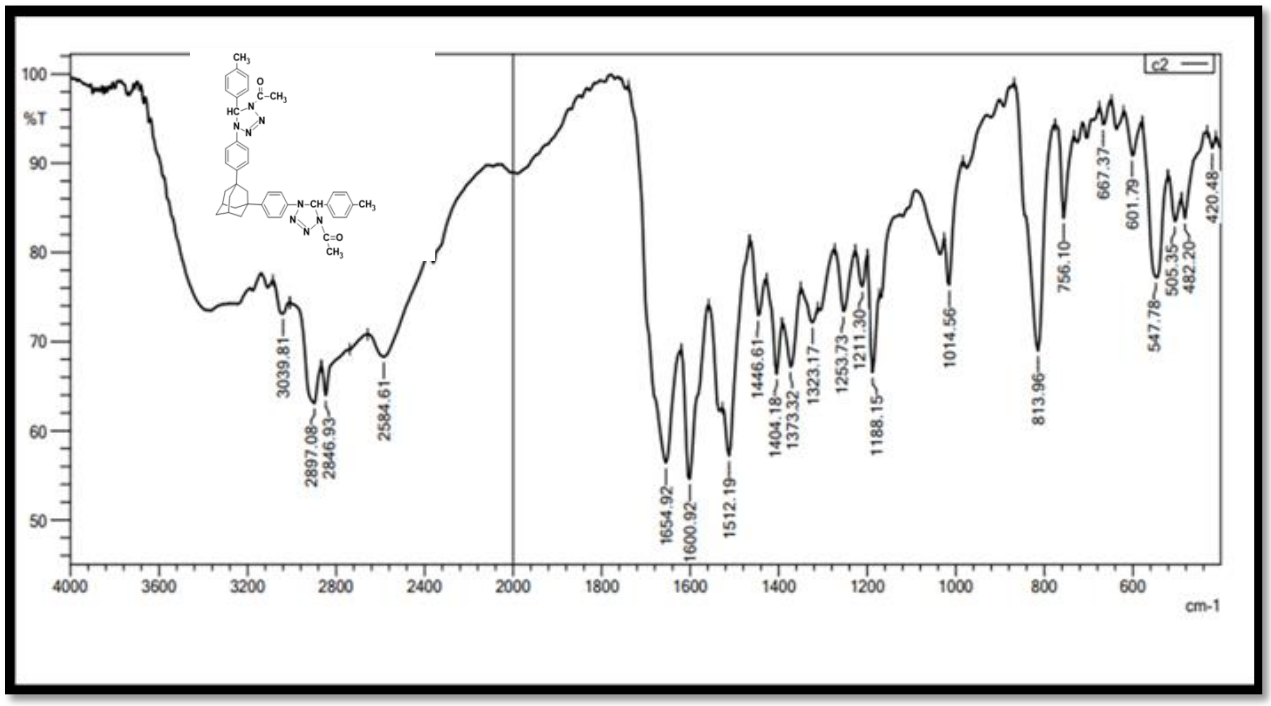


Figure 3.44 : FT-IR Spectrum of tetrazole derivative C2

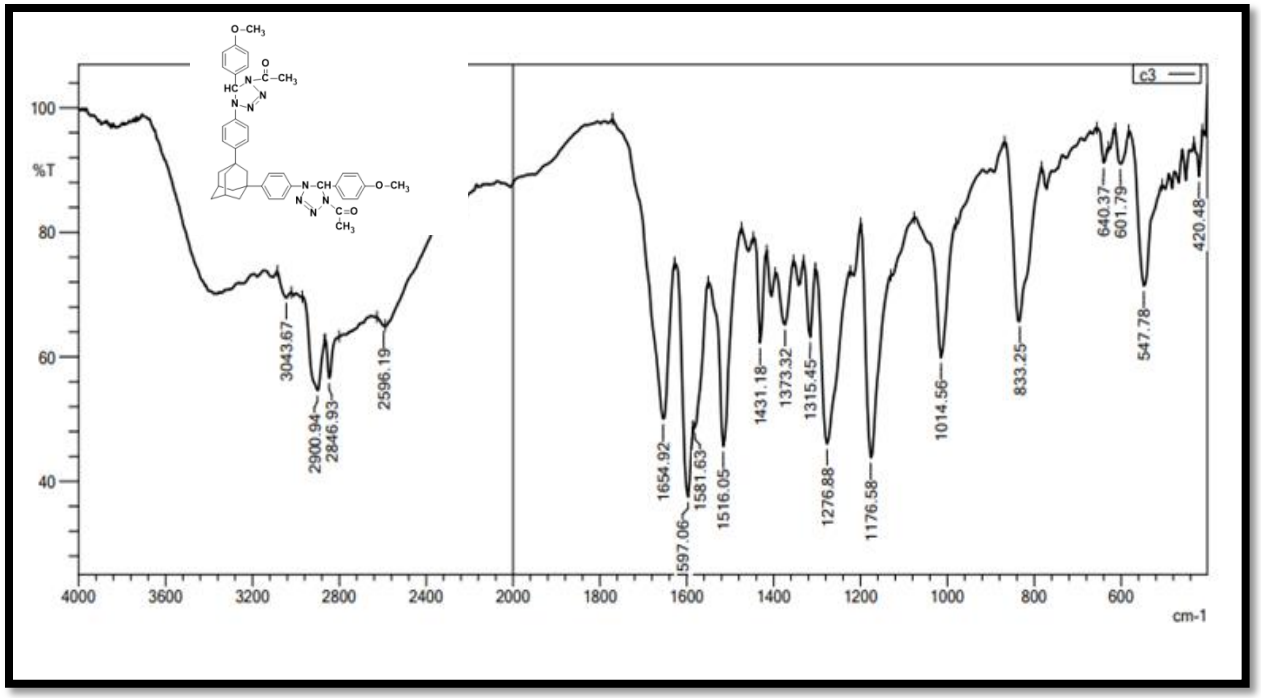


Figure 3.45 : FT-IR Spectrum of tetrazole derivative C3

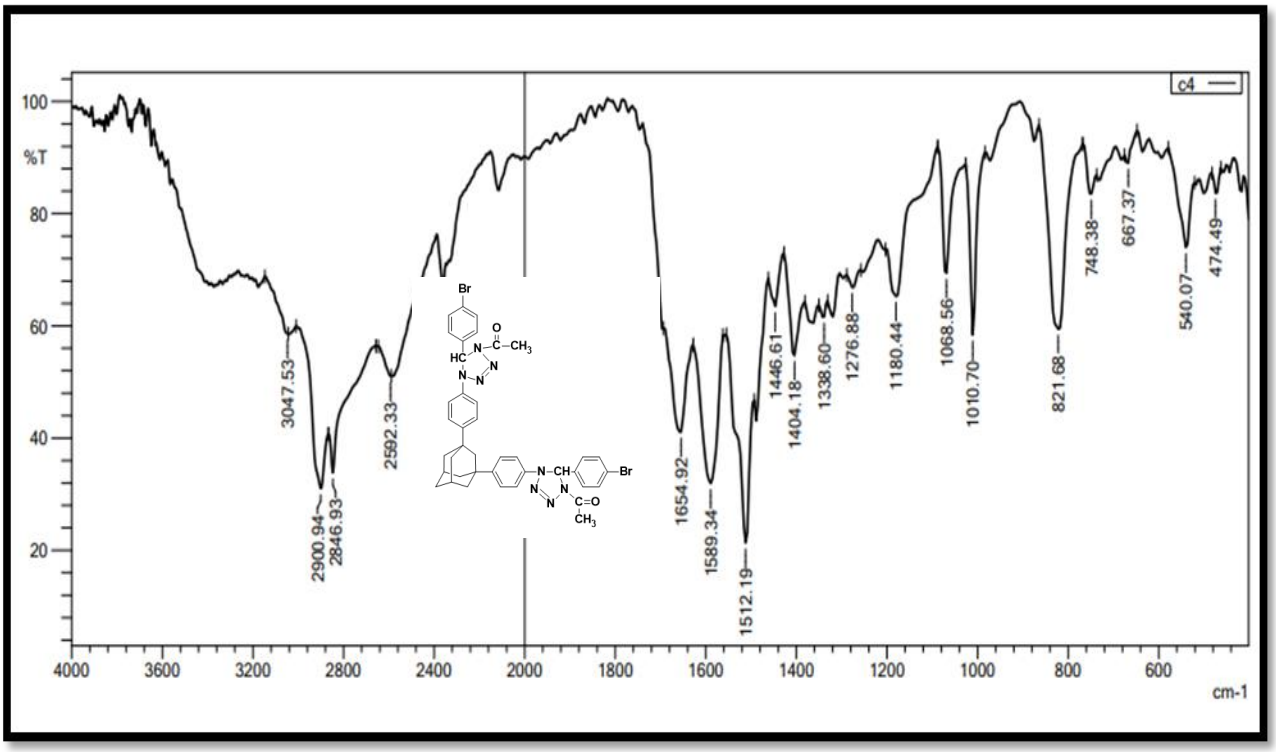


Figure 3.46: FT-IR Spectrum of tetrazole derivative C4

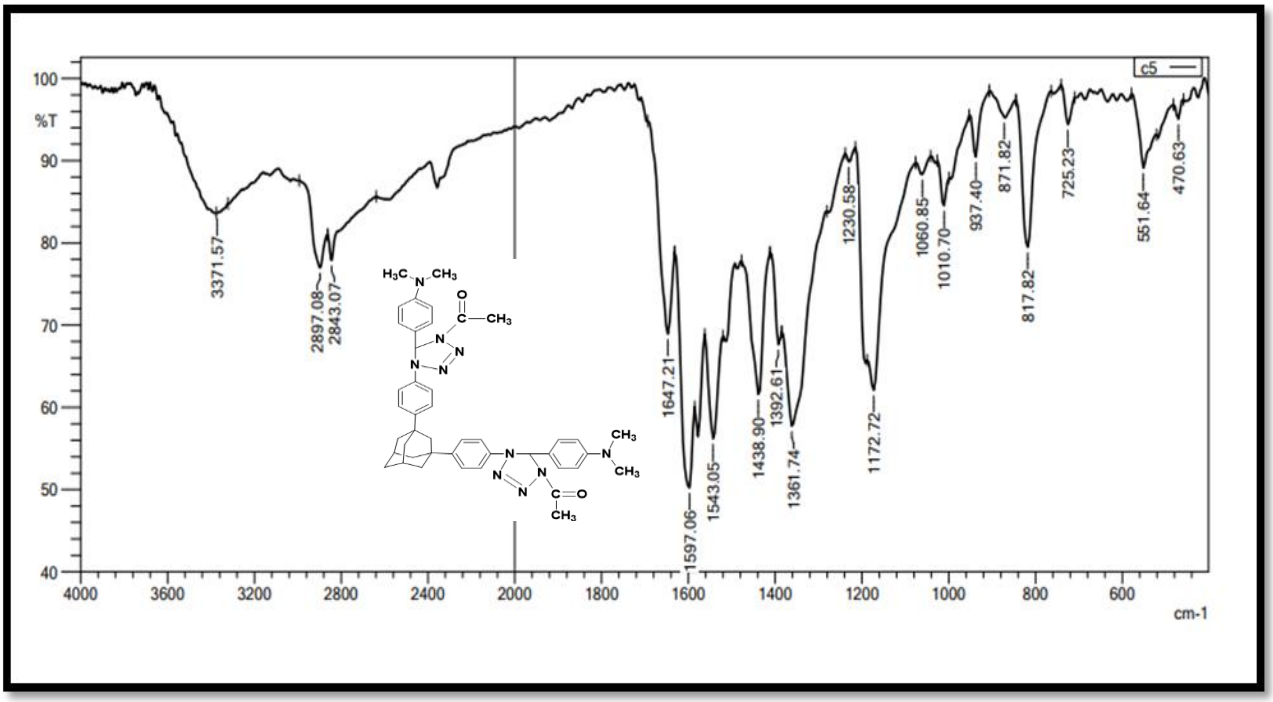


Figure 3.47: FT-IR Spectrum of tetrazole derivative C5

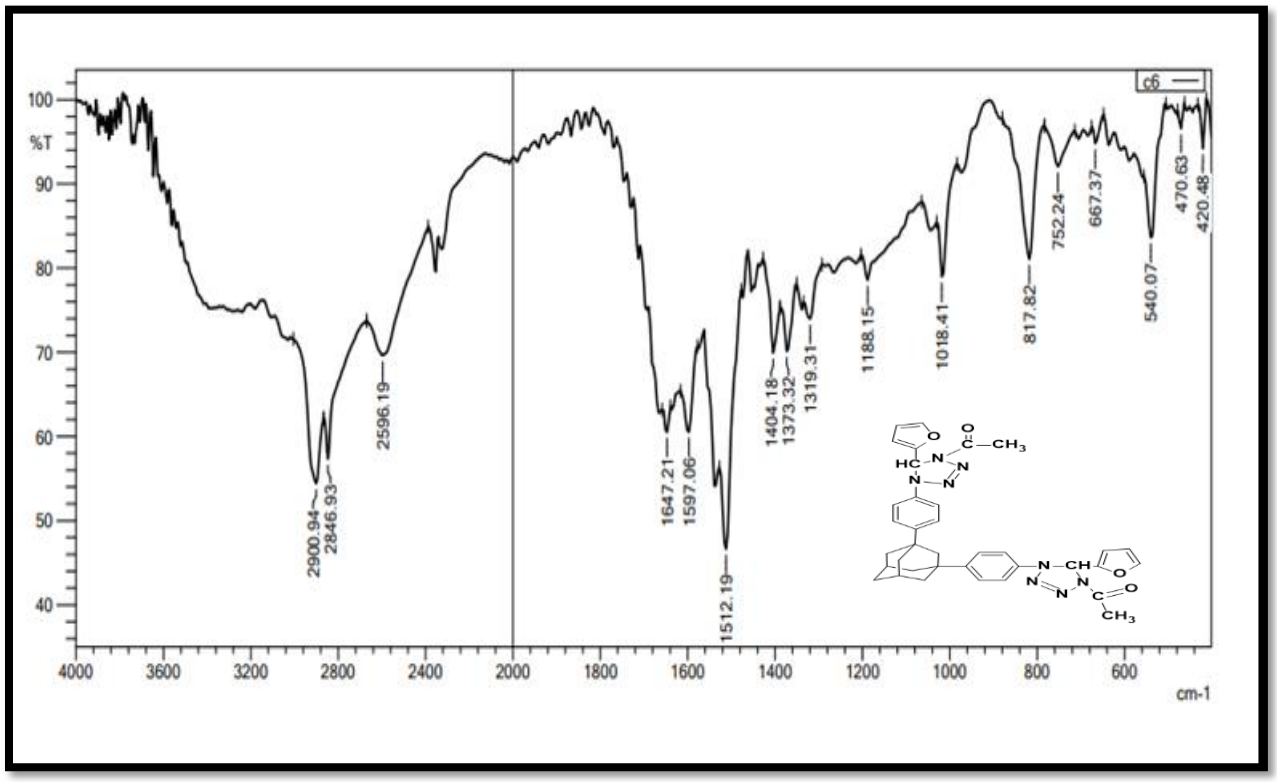


Figure 3.48: FT-IR Spectrum of tetrazole derivative C6

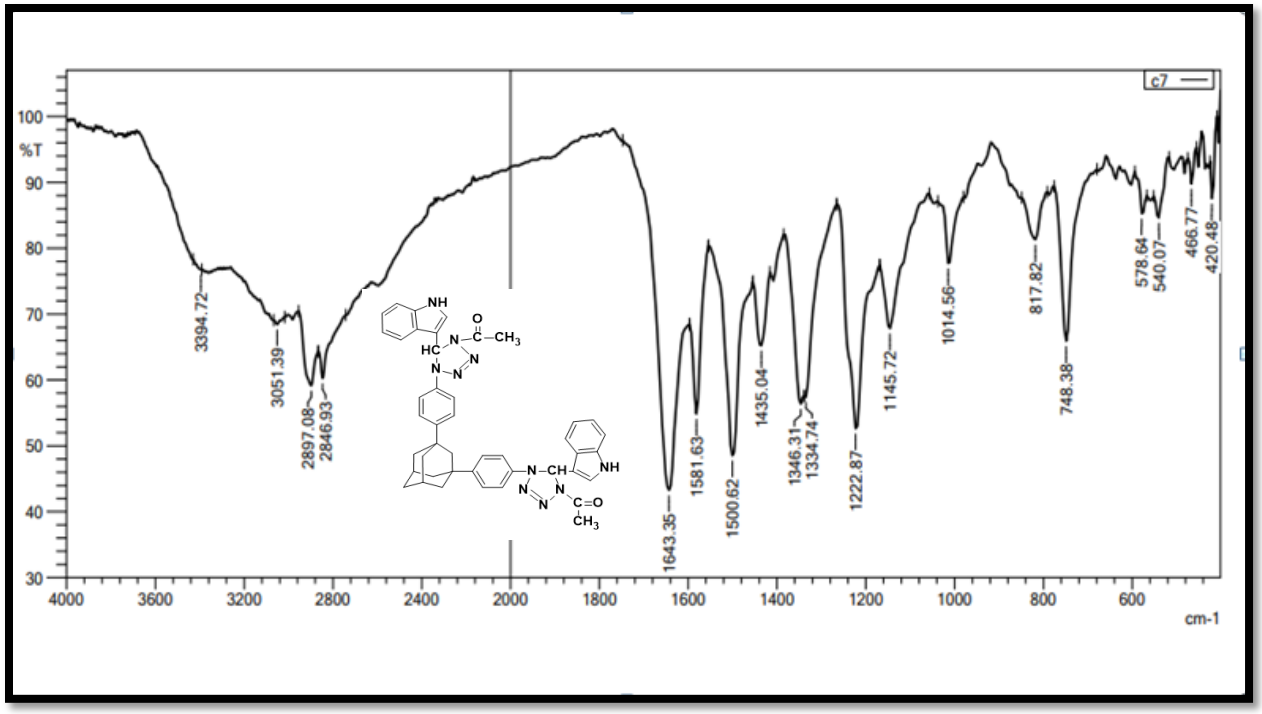


Figure 3.49: FT-IR Spectrum of tetrazole derivative C7

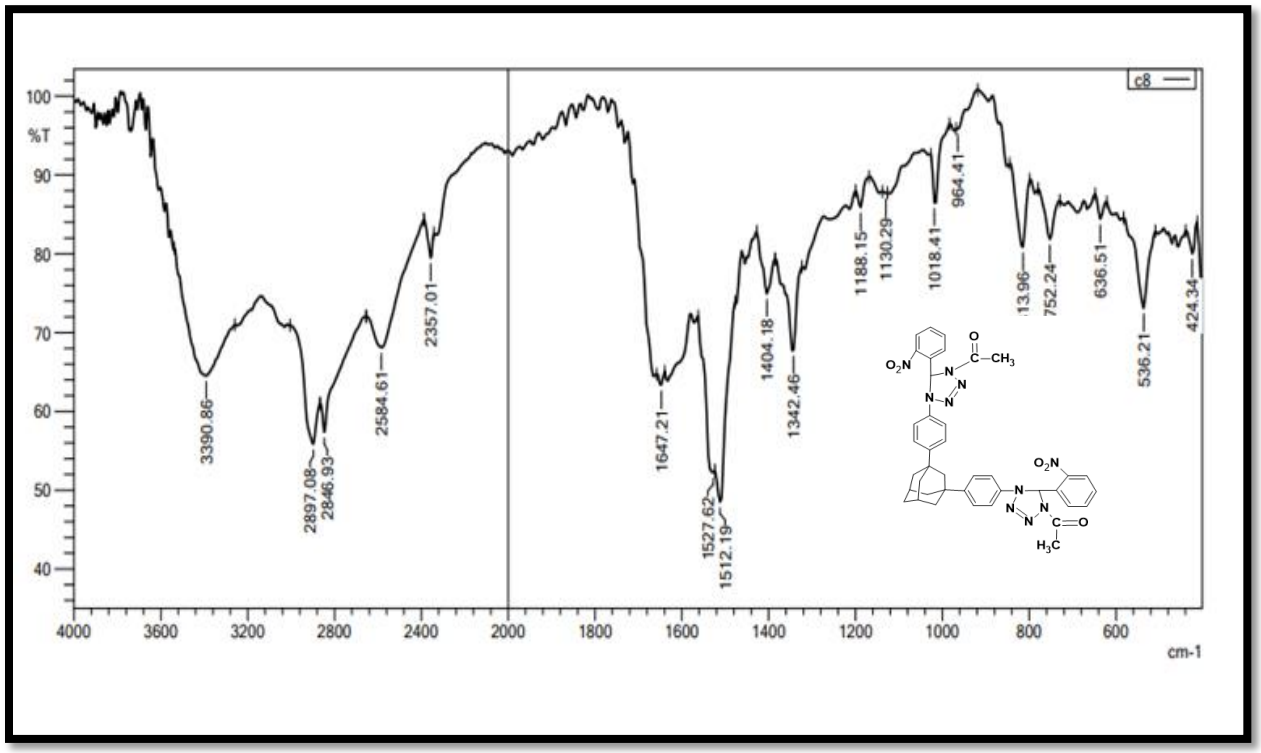


Figure 3.50: FT-IR Spectrum of tetrazole derivative C8

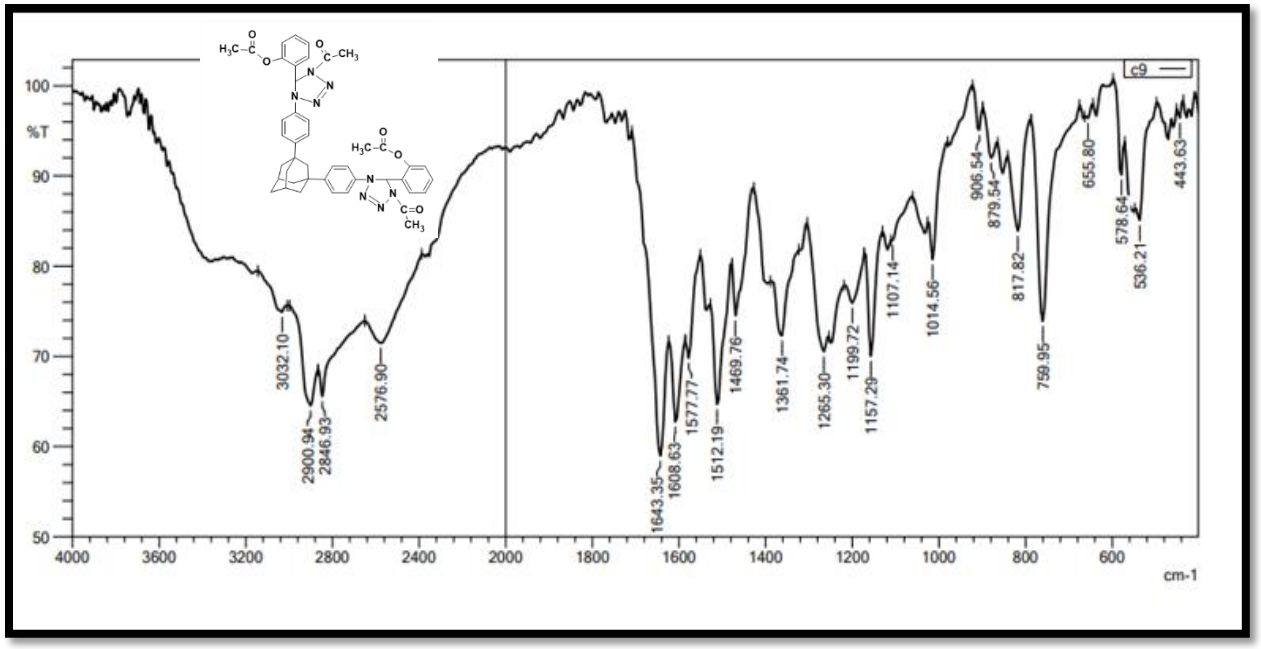


Figure 3.51: FT-IR Spectrum of tetrazole derivative C9

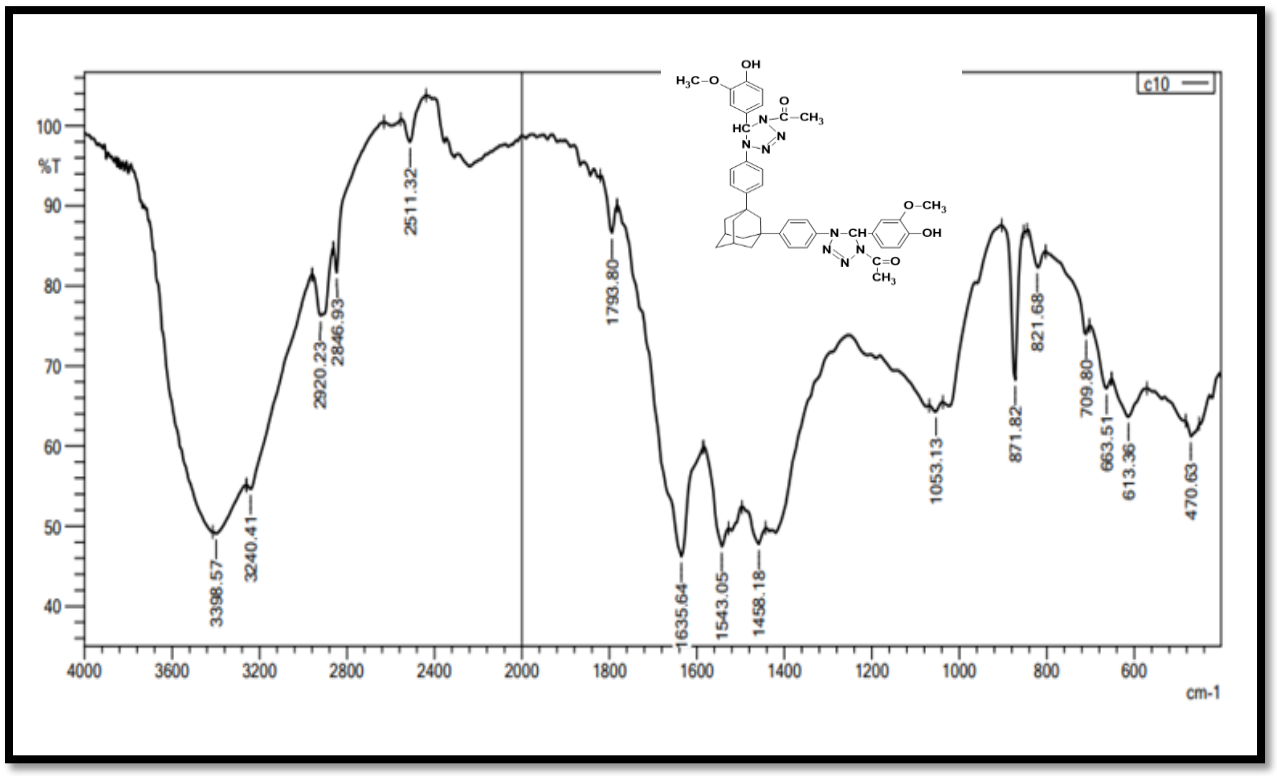


Figure 3.52: FT-IR Spectrum of tetrazole derivative C10

3.4.5. Characterization of Tetrazole Derivatives by Mass Spectrometry (C1-C10)

The term "mass spectrum" refers to a plot of the masses of the particles that have positively charged. Every peak in the spectrum, including the molecular ion peak, has an intensity that is measured as a percentage of the base peak, which has the maximum intensity and is assigned a value of 100%. The intensity of the molecular ion peak depends on the stability of the molecular ion[136]. The mass spectrum of tetrazole derivatives shown in figures below.

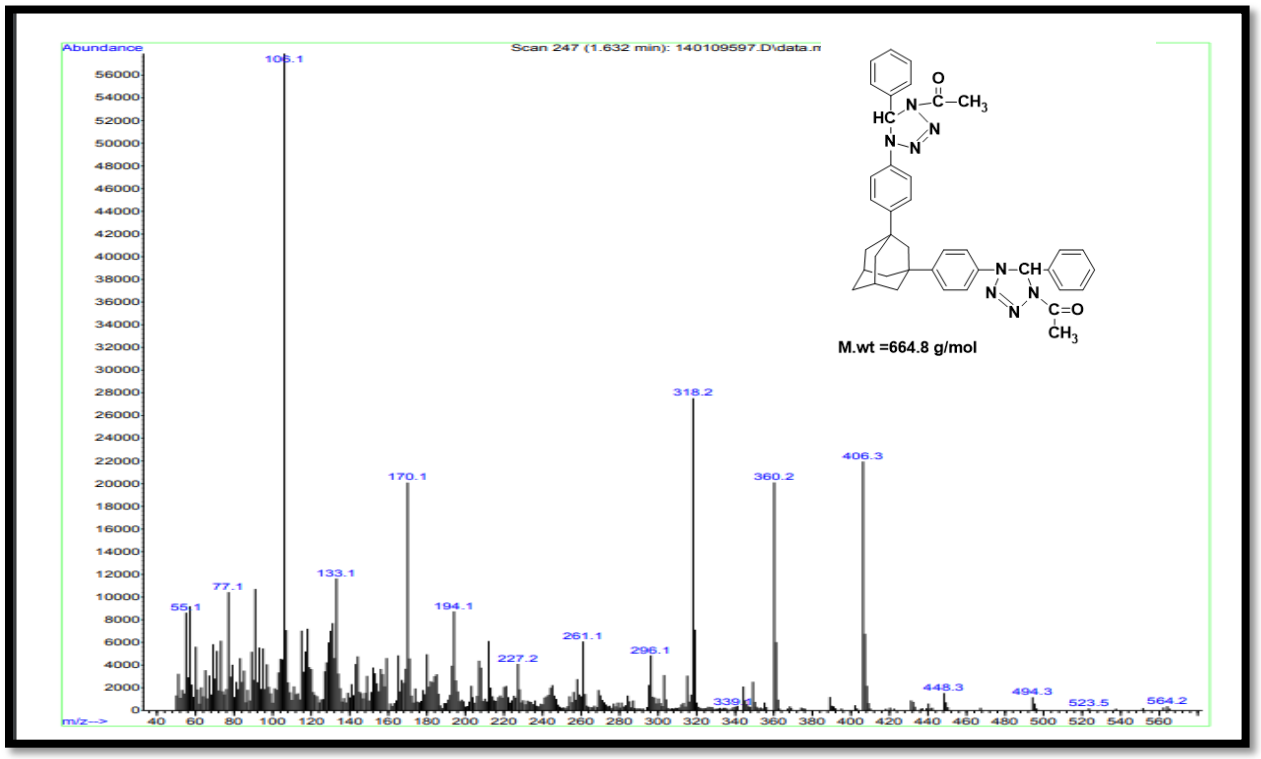


Figure 3.53: Mass spectra of tetrazole derivative C1

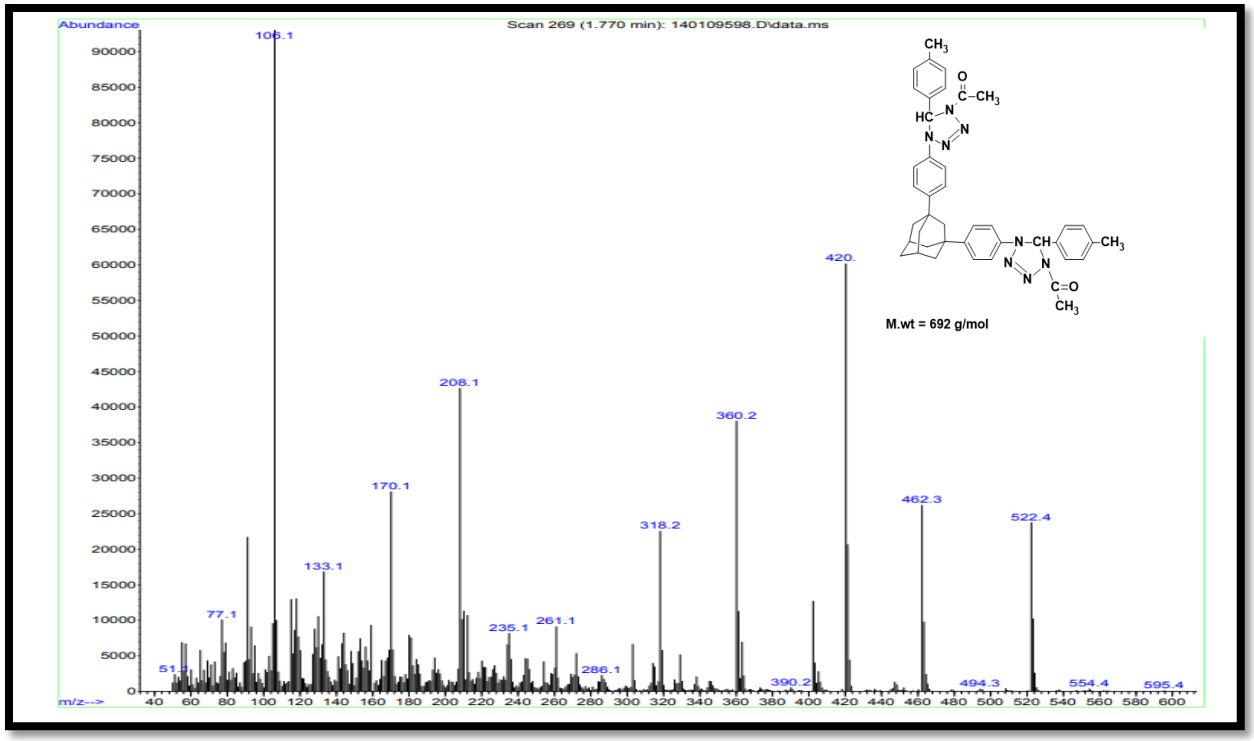


Figure 3.54: Mass spectra of tetrazole derivative C2

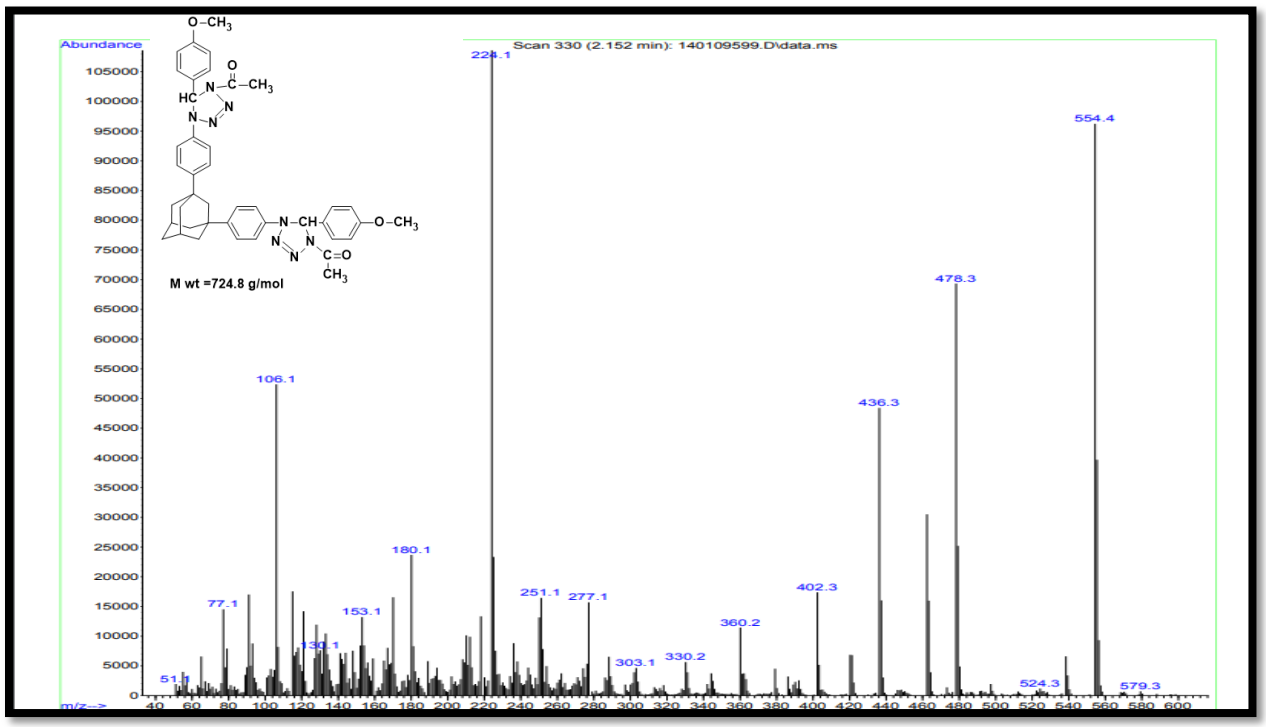


Figure 3.55: Mass spectra of tetrazole derivative C3

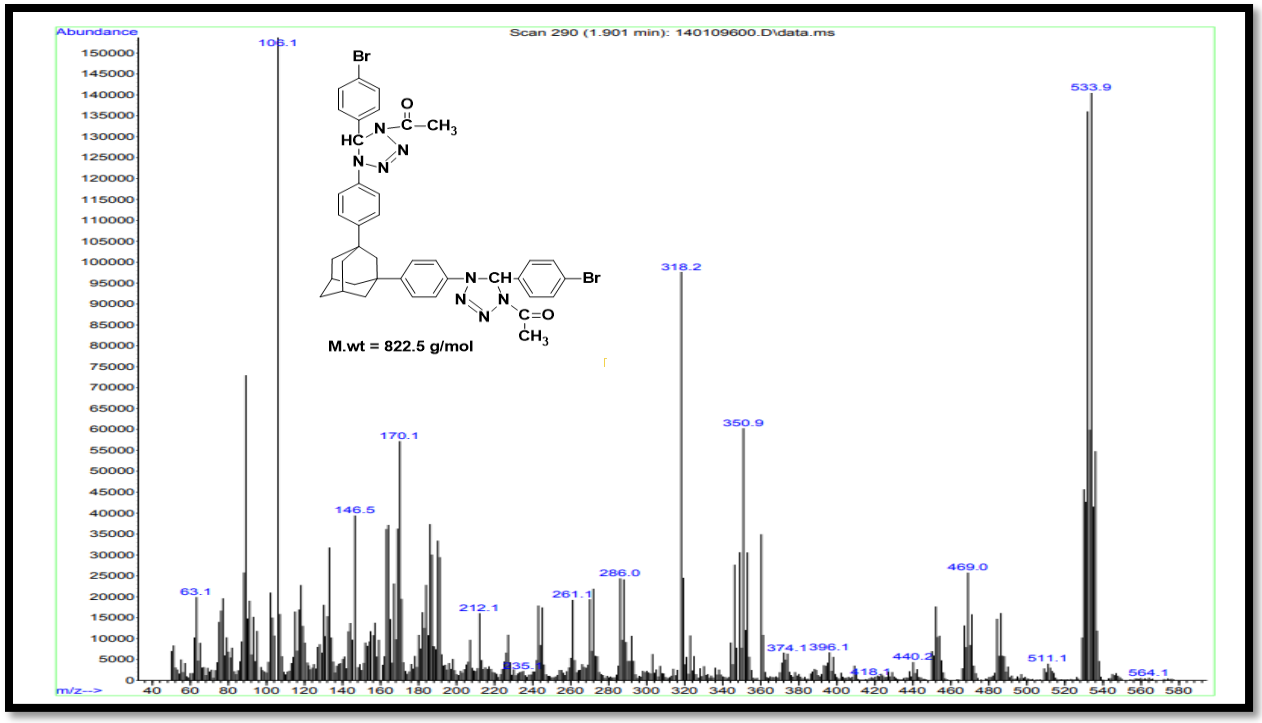


Figure 3.56 :Mass spectra of tetrazole derivative C4

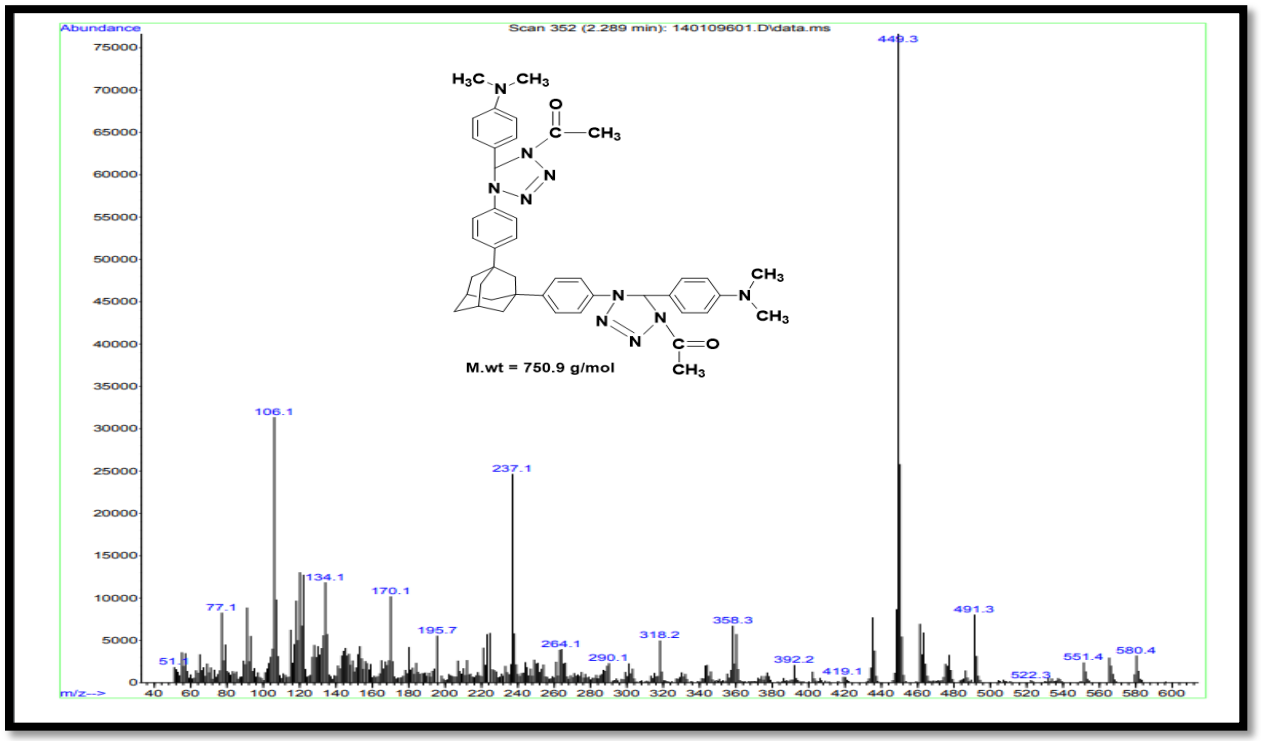


Figure 3.57: Mass spectra of tetrazole derivative C5

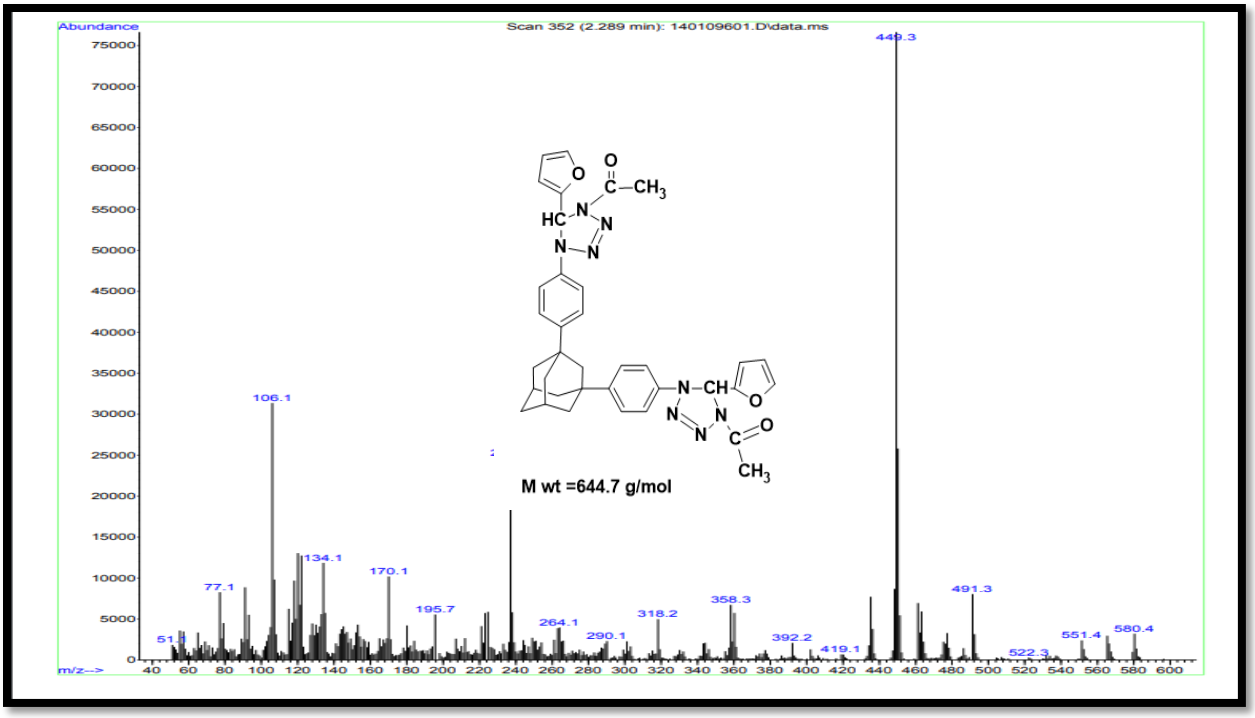


Figure 3.58: Mass spectra of tetrazole derivative C6

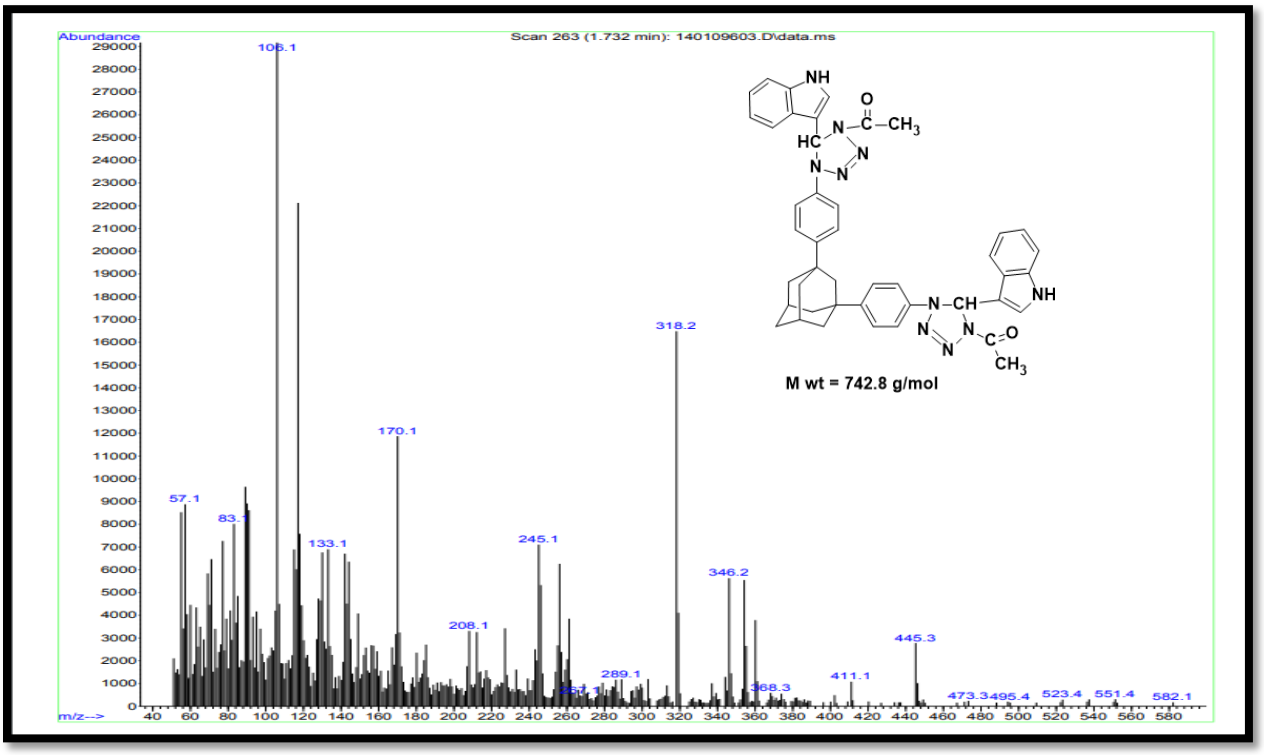


Figure 3.59: Mass spectrum of tetrazole derivative C7

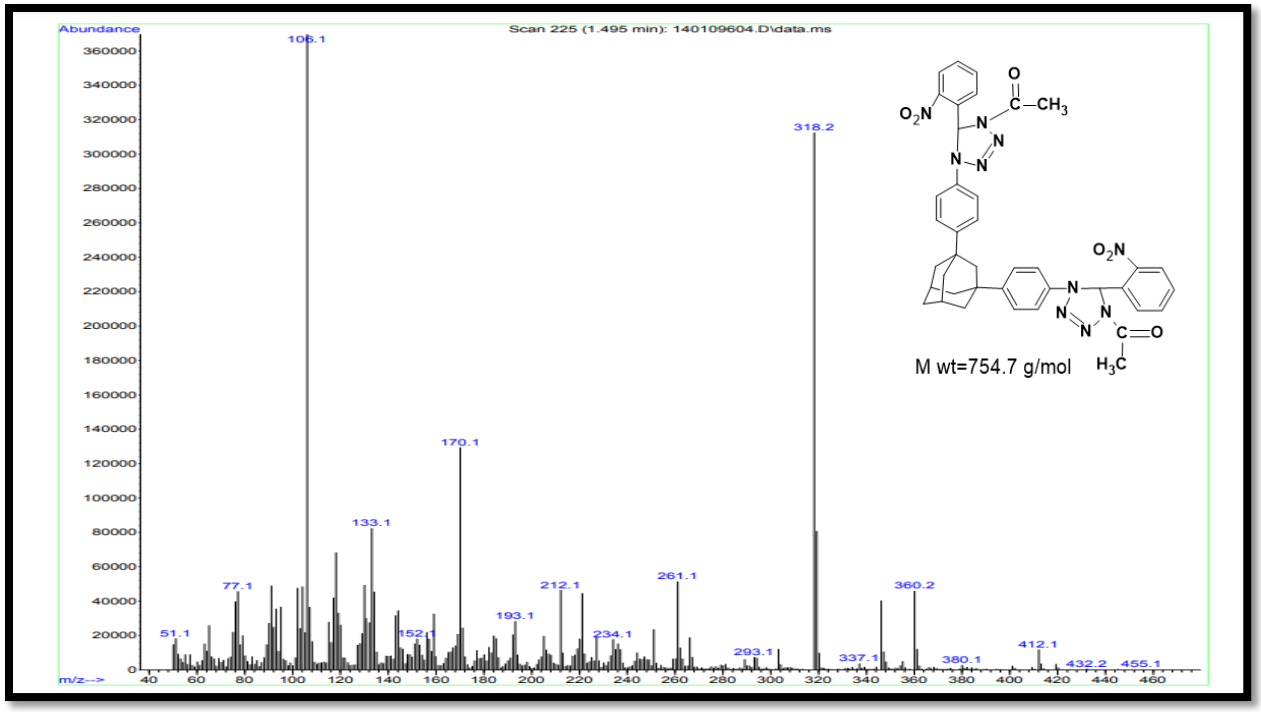


Figure 3.60: Mass spectrum of tetrazole derivative C8

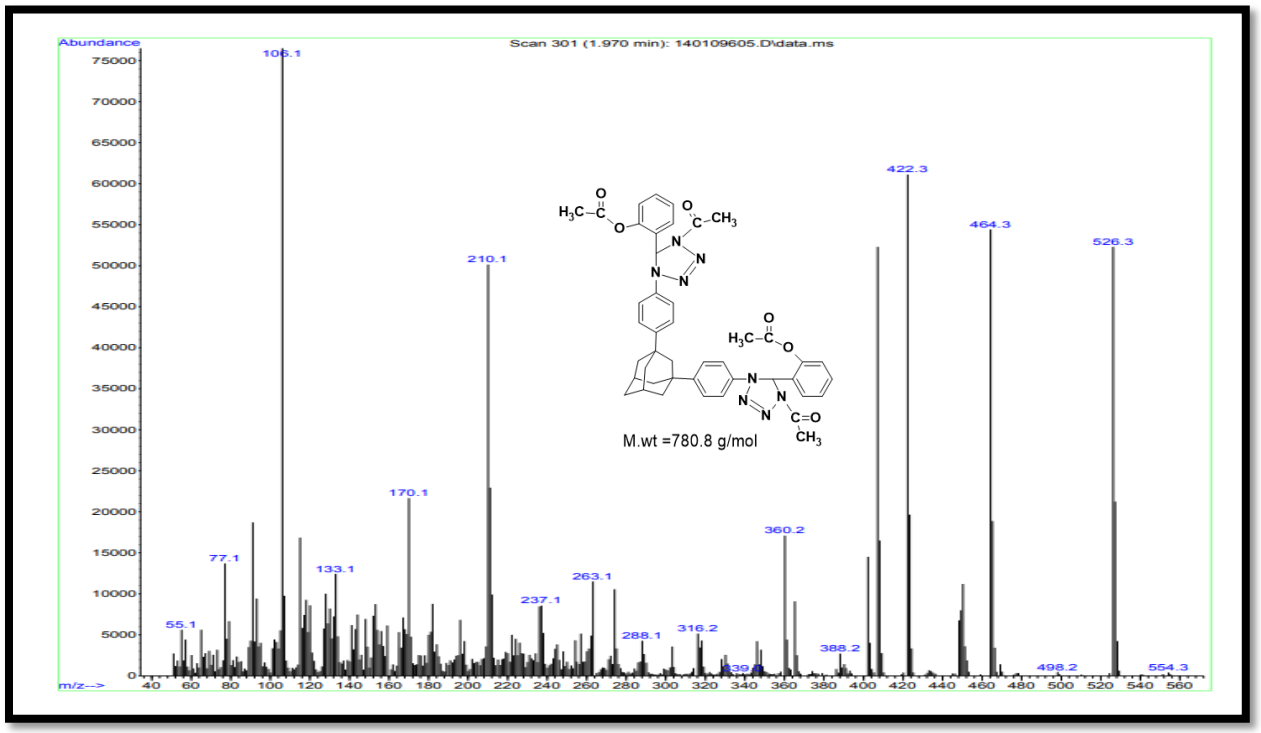


Figure 3.61: Mass spectrum of tetrazole derivative C9

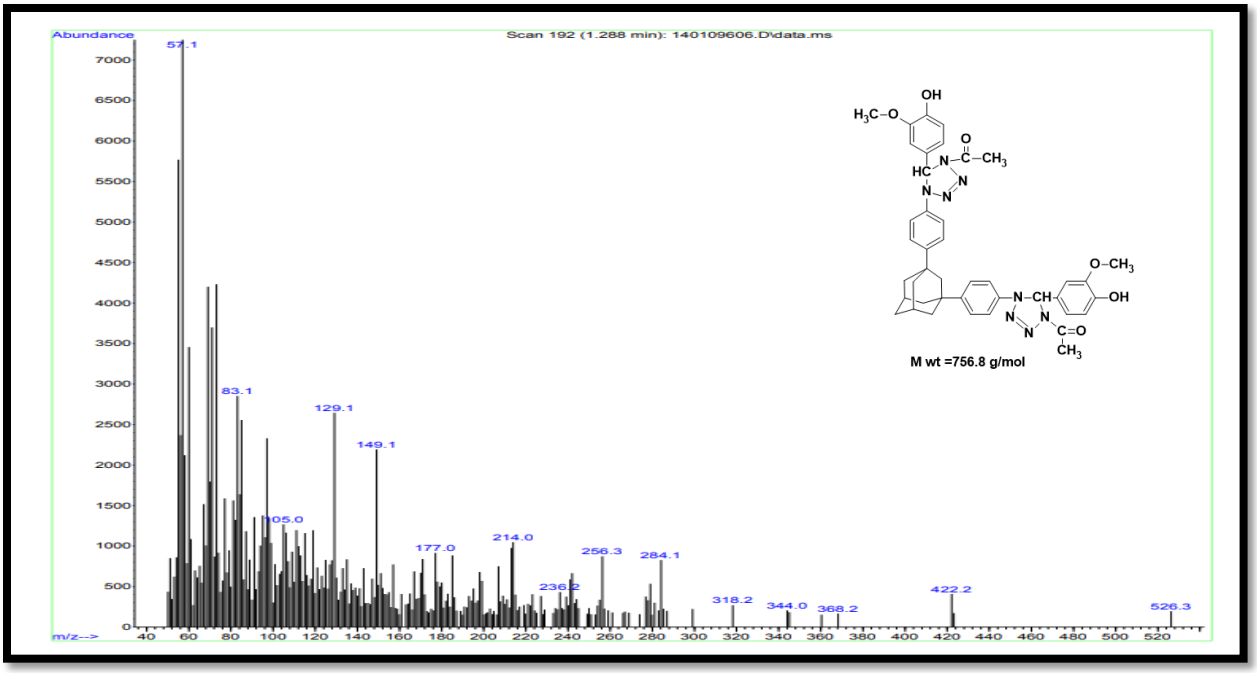


Figure 3.62: Mass spectrum of tetrazole derivative C10

3.4.6. Liquid chromatography mass spectrometry (LC-Mass) of Some Tetrazole Derivatives Compound(C1,C8,C9)

We observed the calculation value closed to the found value of all three compound, which indicates that the reaction took place as planned. In tetrazole derivative C9 the OH group substituted on the benzene ring react too with acetyl chloride due to the reactivity of phenolic OH group to produced ester group, this side reaction can be proved by LC-Mass chart of this compound as shown in figure(3.65) below. Table (3.9) explain the fundamental band of tetrazole derivatives(C1,C8,C9) in LC-Mass spectrum.

Table 3.9: the fundamental band of tetrazole derivatives(C1,C8,C9) in LC-Mass spectrum

Compound	M.wt	m/z Found	Base Peak	First Fragment	Last Fragment
C1	664.8	666.01	168.1	575.24	96.23
C8	754.7	755.06	205.02	661.02	99.49
C9	780.8	780.41	135.1	700	135.1

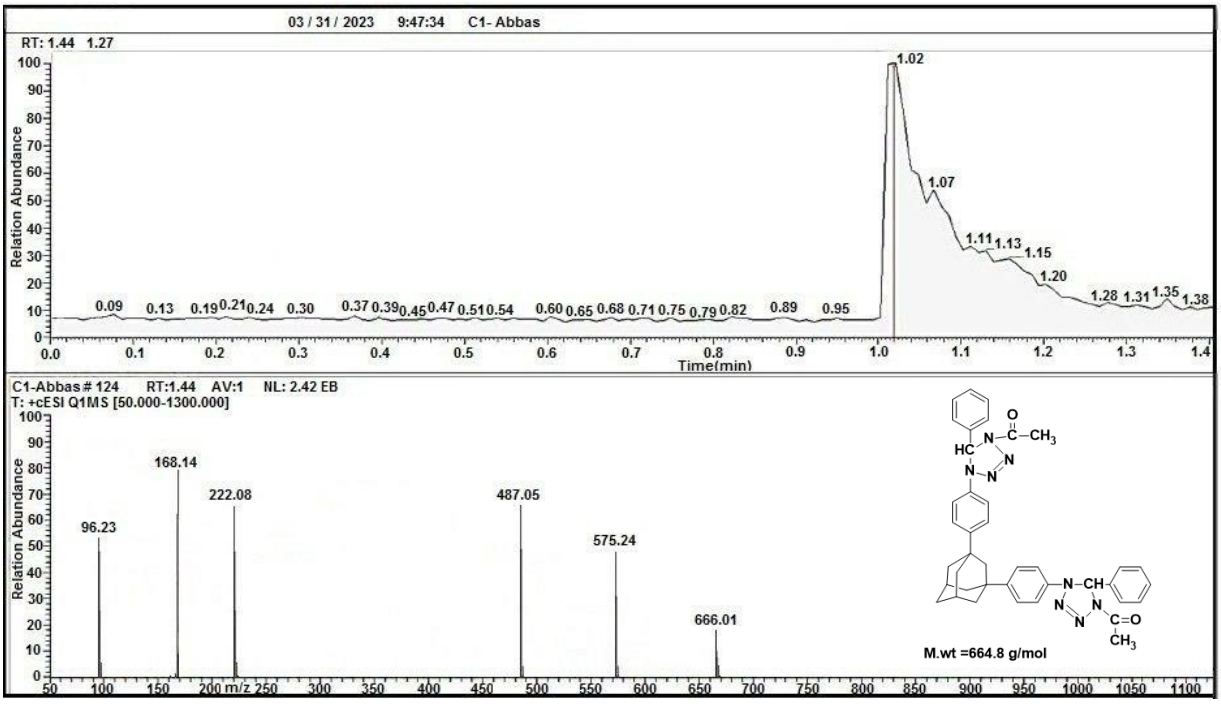


Figure 3.63: LC-Mass Spectrum of tetrazole derivative C1

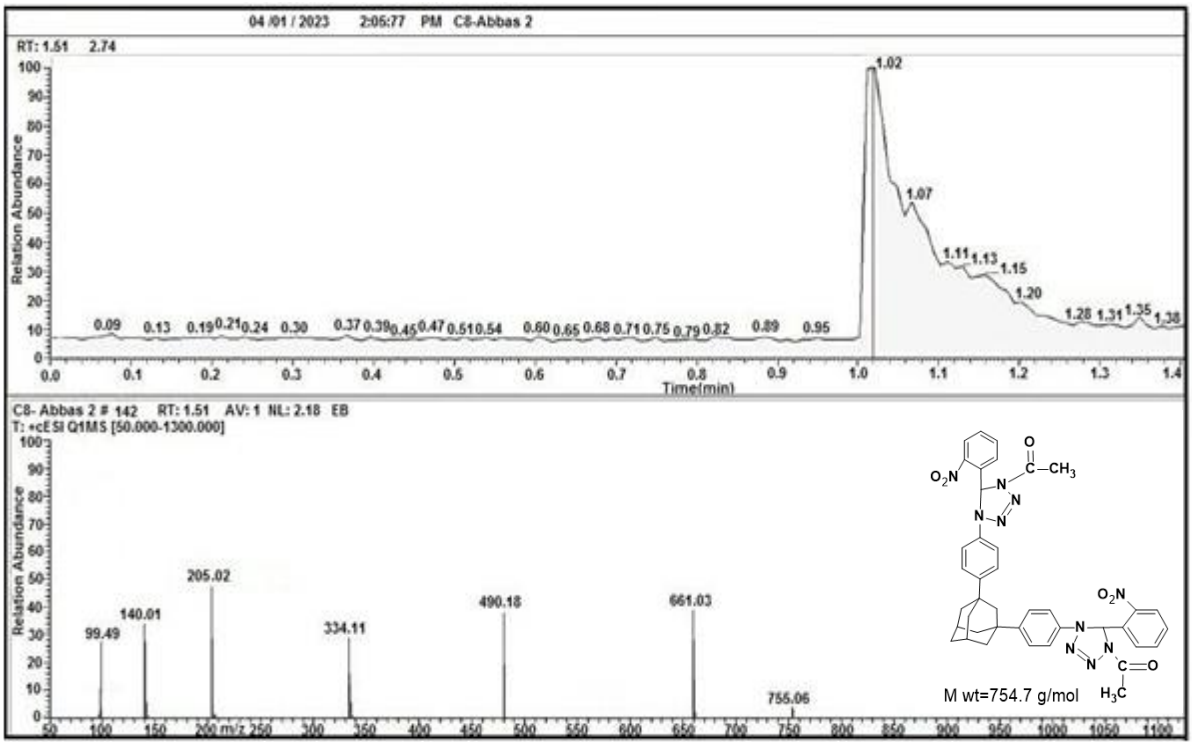


Figure 3.64: LC-Mass Spectrum of tetrazole derivative C8

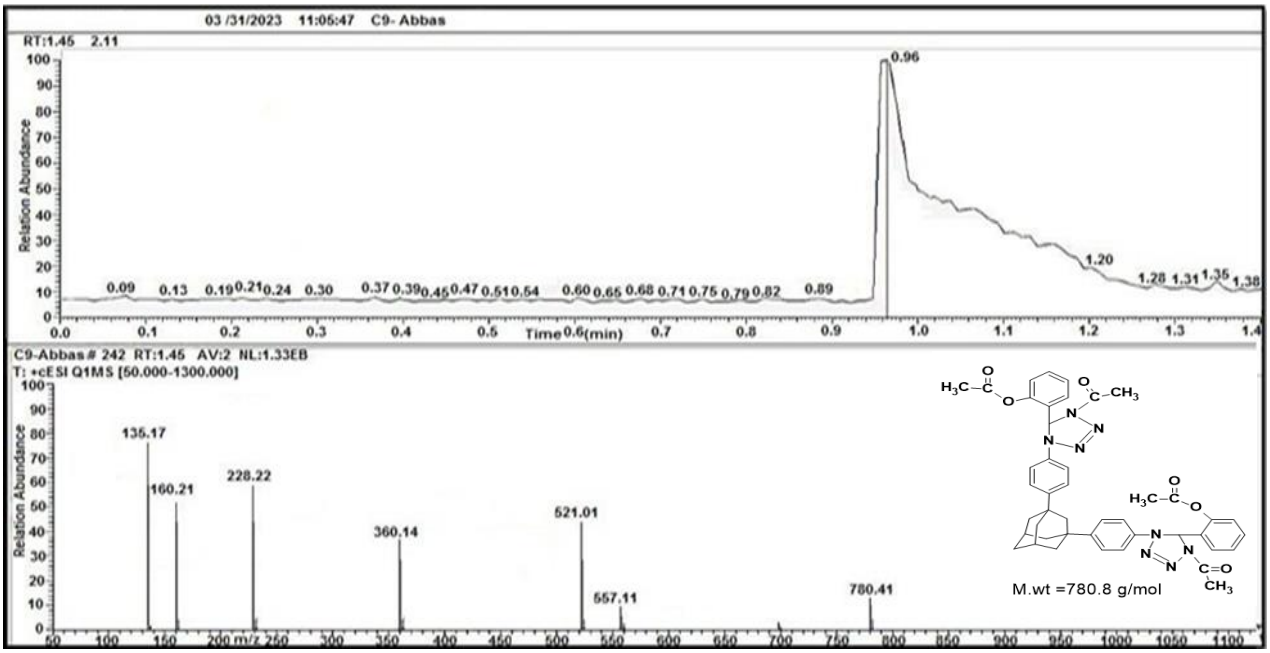


Figure 3.65: LC-Mass Spectrum of tetrazole derivative C9

3.4.7. ^{1}H-NMR Spectra of Tetrazole Derivatives(C1-C10)

^{1}H-NMR Spectrum (DMSO-*d6*) for new tetrazole showed the specific signals such as multi peaks at region δ (1.0-2)ppm indicate to protons of adamantane structure , singlet peak at region δ (2.4-3.9)ppm indicates to proton of tetrazole and multi peaks at region δ (6-8.9)ppm refer to protons on the aromatic ring, as well as singlet peak at region close to proton of adamantane region indicate to protons of CH_3 that bonded with carbonyl amide. The chemical shift of all type of protons explain in table (3.10), ^{1}H-NMR Spectra of tetrazole derivatives(C1-C10) shown in figures below.

Table 3.10 :Chemical shift in ^{1}H-NMR spectrum of tetrazole derivatives(C1-C10)

Comp.	Aliphatic protons (ppm)	Proton of tetrazole ring(ppm)	Aromatic Protons (ppm)	Protons from CH3C=O group(ppm)	Other protons (ppm)
C1	1.1-1.8	2.7	6-8.9	2-2.3	
C2	1.7-1.9	2.7	7.2-8.4	2-2.38	2.5(CH_3-ph)
C3	1.6-2	3.9	7-7.9	2.1	3.6-3.9(CH_3-O)
C4	1.2-1.9	2.8	6-8.8	2.7	
C5	1.2-1.9	3.02	6.8-8.4	2-2.2	3-3.2(CH_3-N)
C6	1-1.9	2.4	6.7-7.8	2-2.2	
C7	1.1-1.97	2.4	6.98-8.87	2-2.2	4.69(N-H)
C8	1-1.9	3.7	7.3-8.9	2.8	
C9	1-1.84	2.7	6.8-8.6	2.15	
C10	1.15-1.77	2.8	6.9-8.2	2.16	6.5(OH)

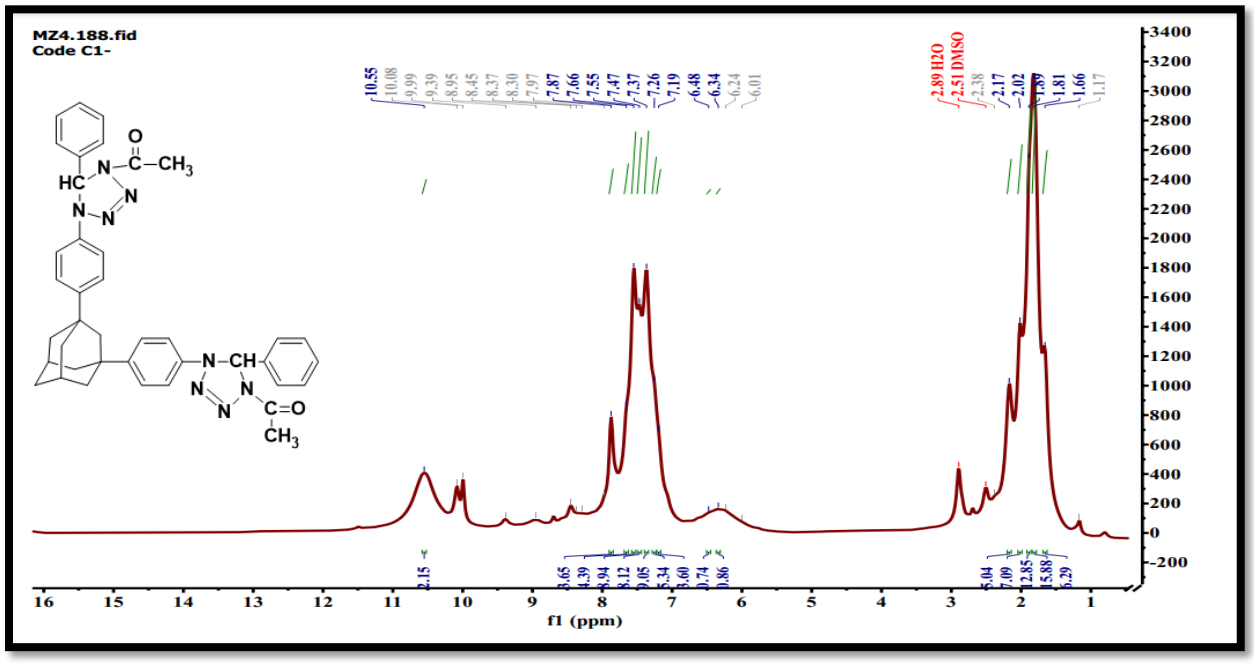


Figure 3.66: ^{1}H-NMR Spectrum of tetrazole derivative C1

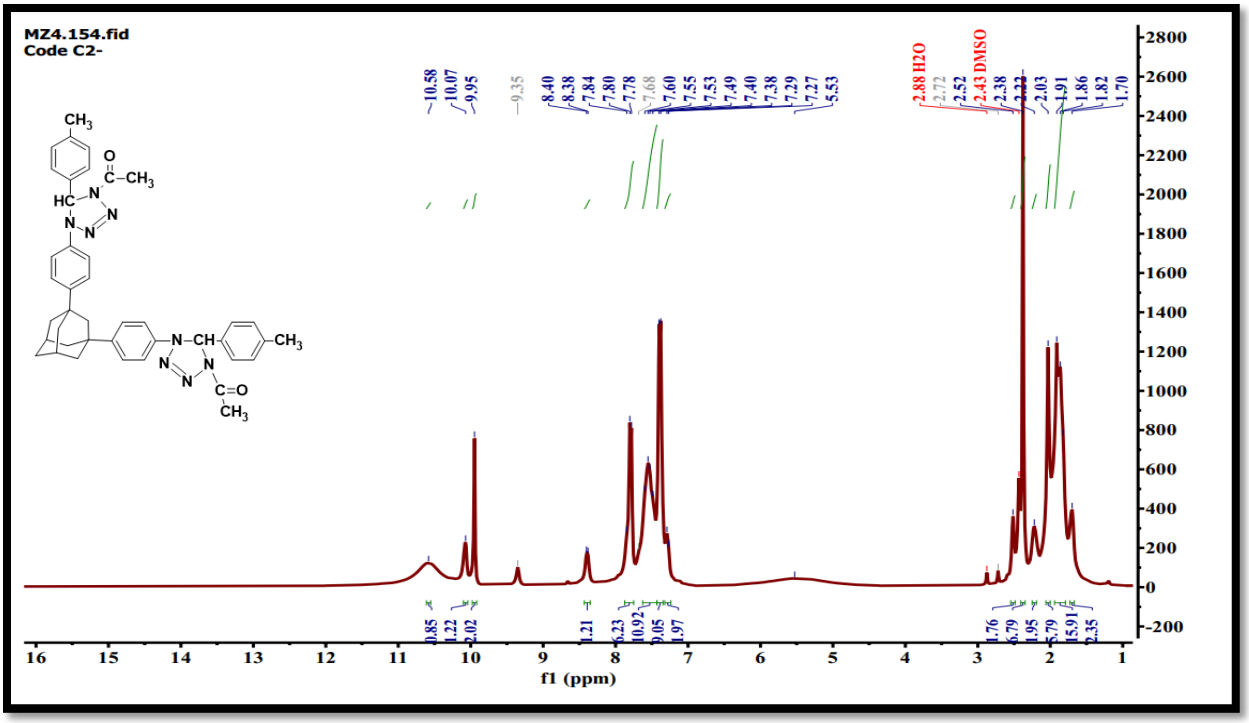


Figure 3.67: ^{1}H-NMR Spectrum of tetrazole derivative C2

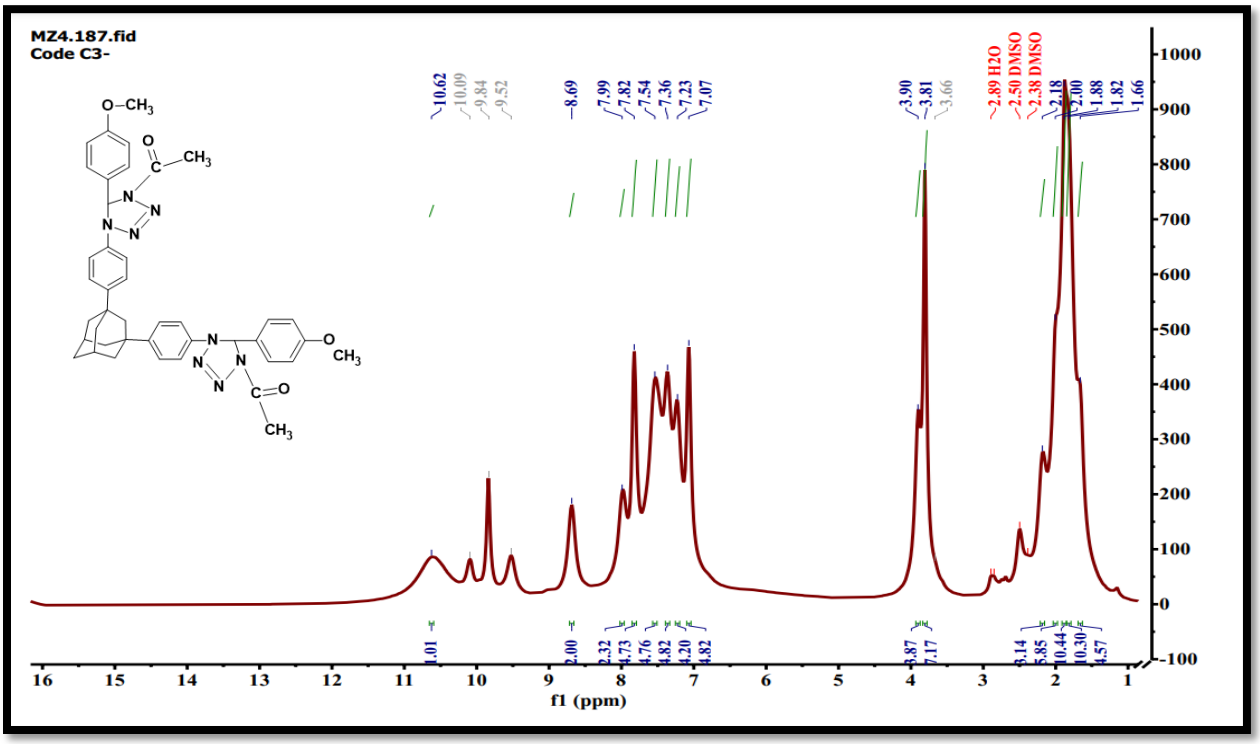


Figure 3.68: ^{1}H-NMR Spectrum of tetrazole derivative C3

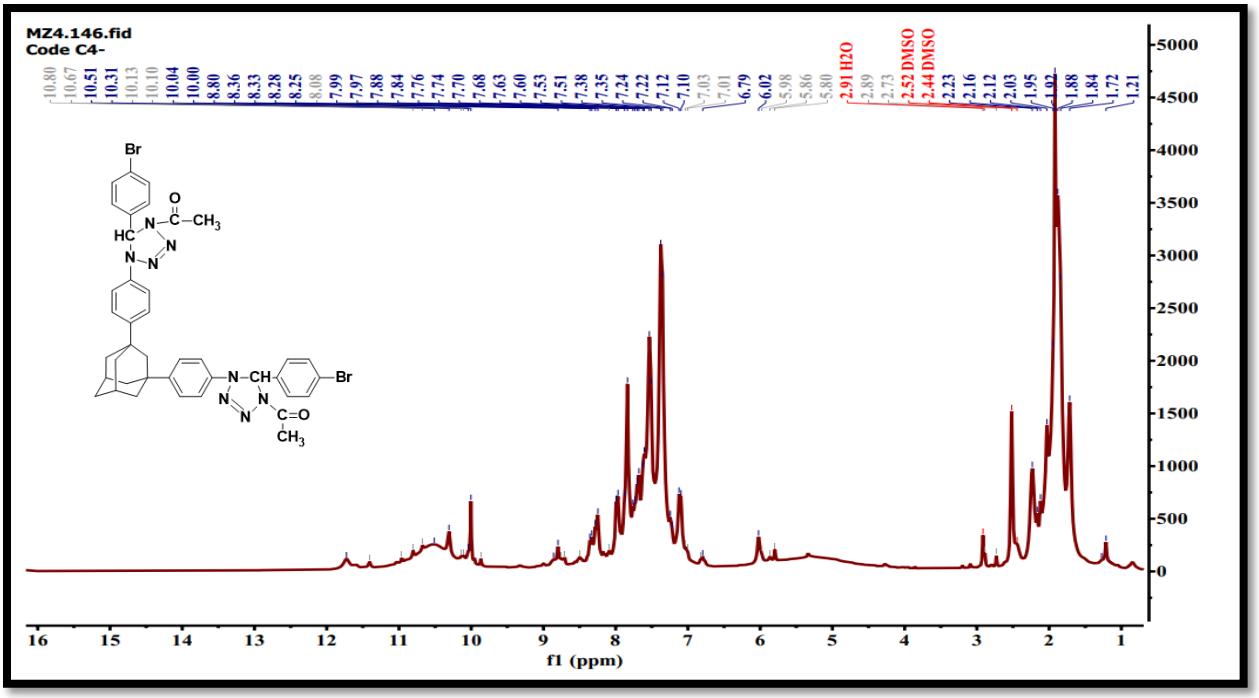


Figure 3.69: ^{1}H-NMR Spectrum of tetrazole derivative C4

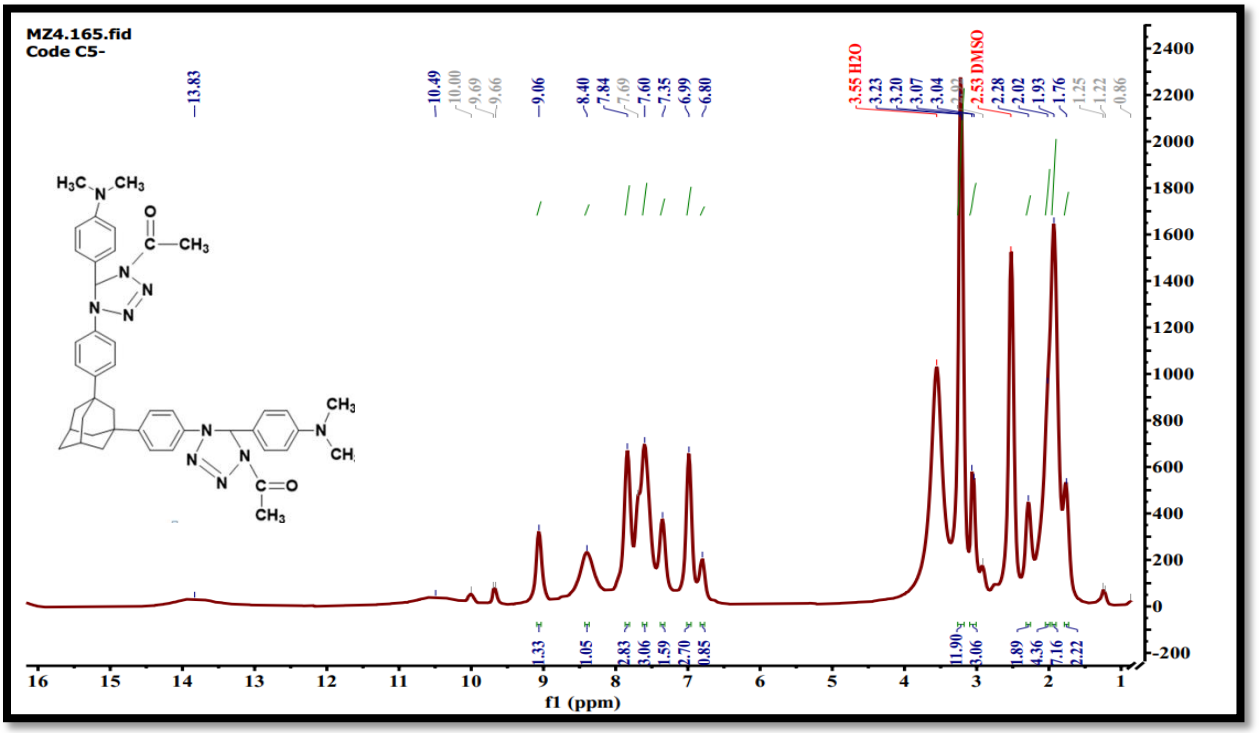


Figure 3.70: ^{1}H-NMR Spectrum of tetrazole derivative C5

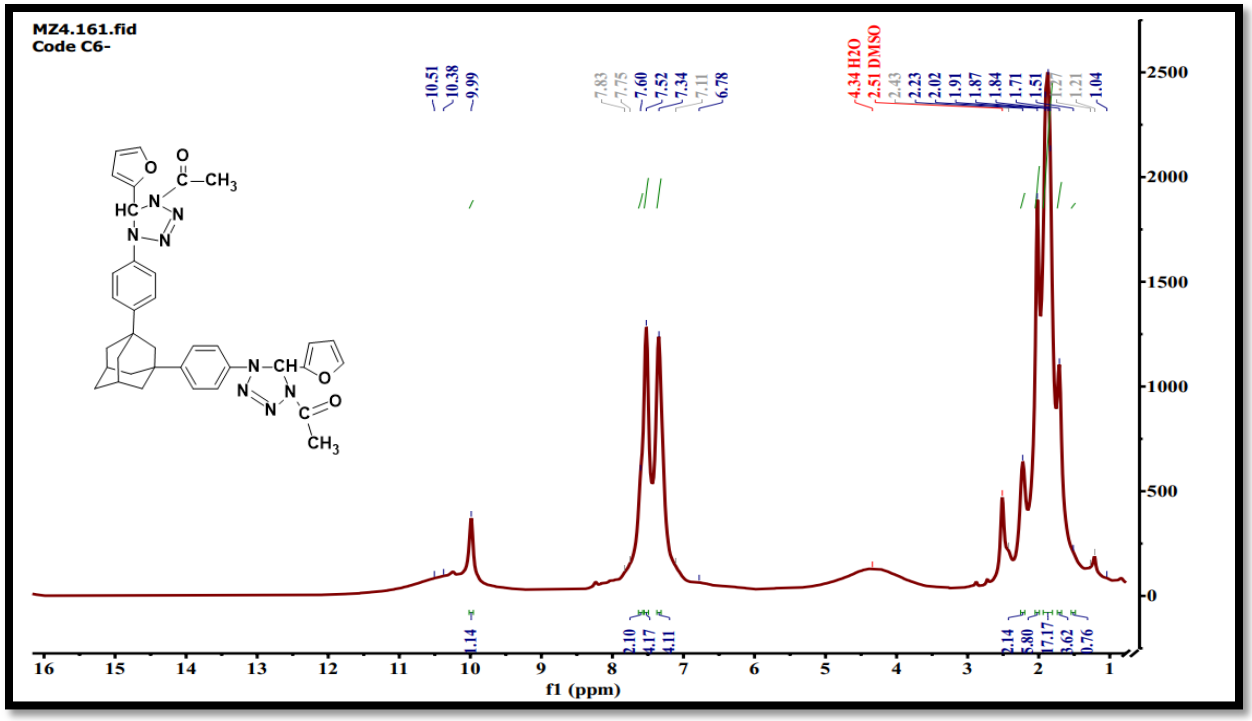


Figure 3.71: ^{1}H-NMR Spectrum of tetrazole derivative C6

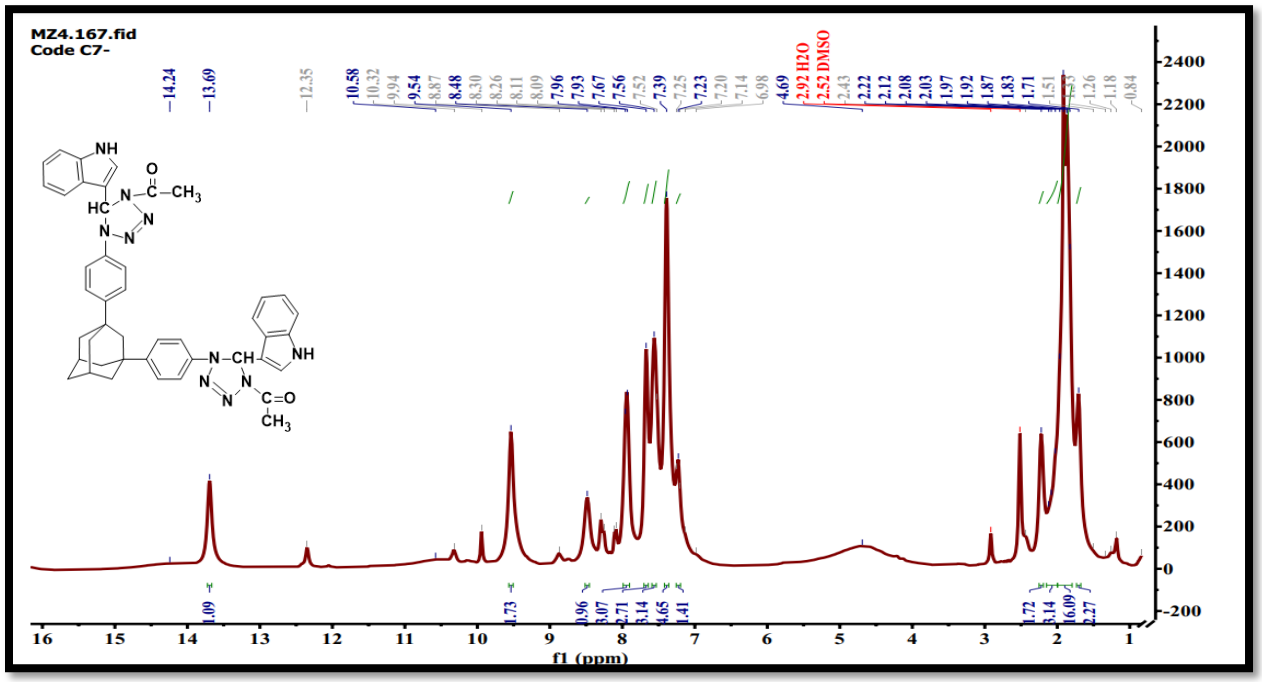


Figure 3.72: ^{1}H-NMR Spectrum of tetrazole derivative C7

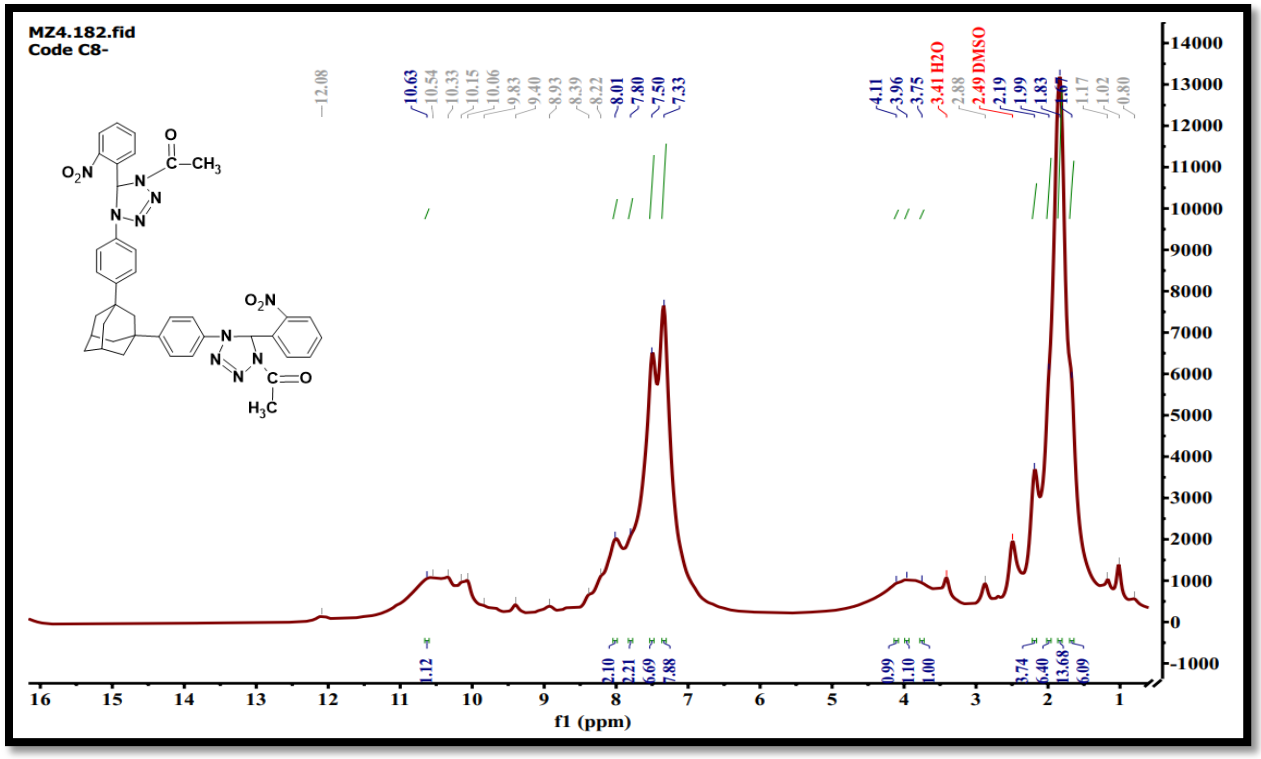


Figure 3.73: ^{1}H-NMR Spectrum of tetrazole derivative C8

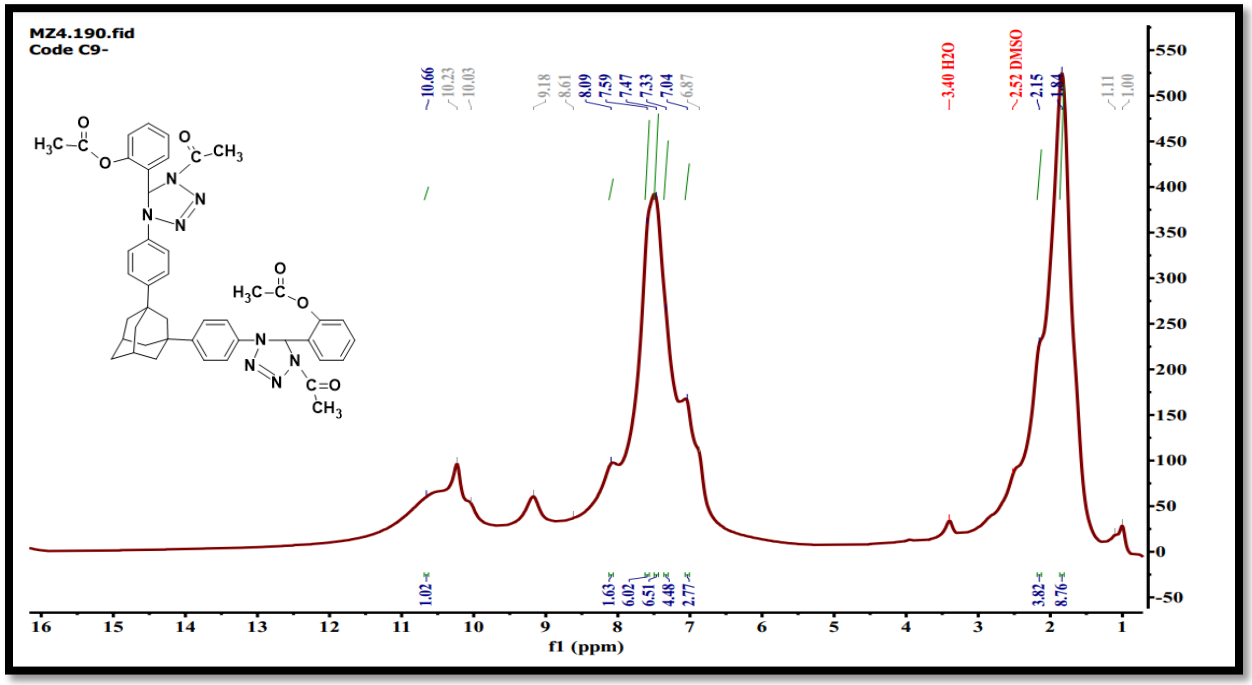


Figure 3.74: ^{1}H-NMR Spectrum of tetrazole derivative C9

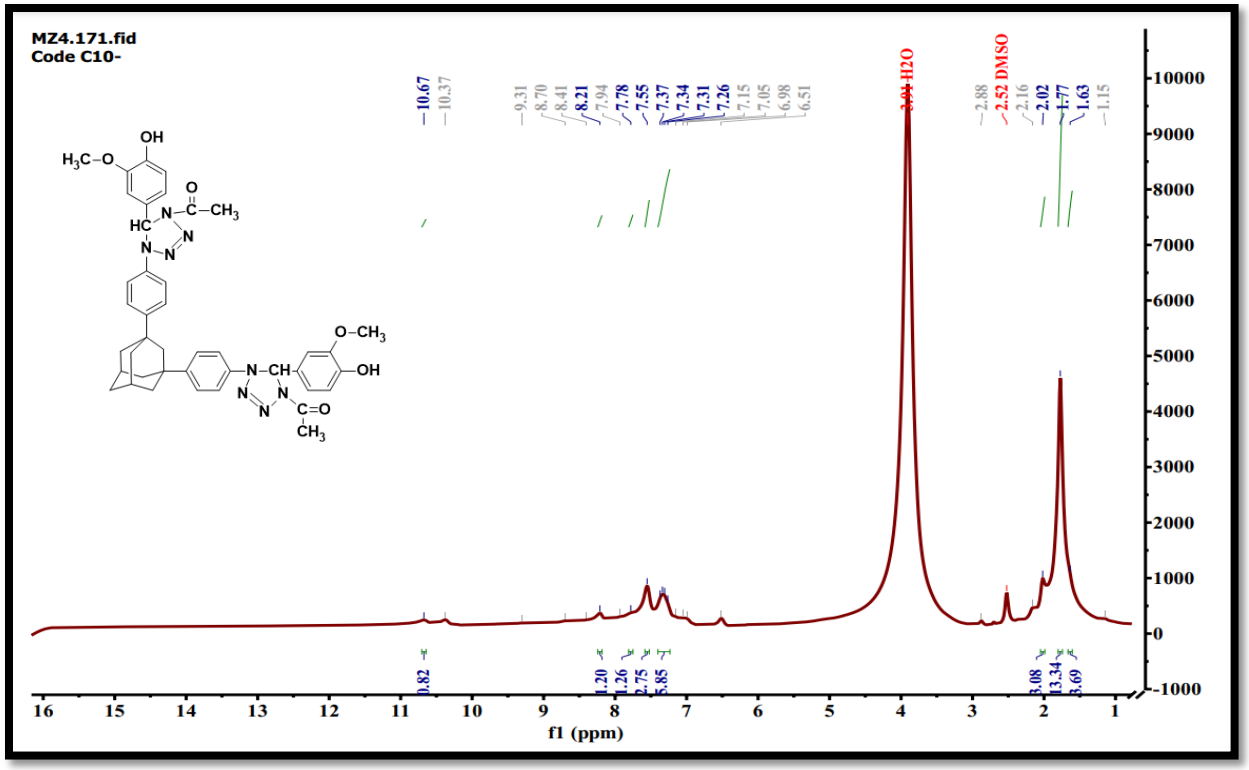


Figure 3.75: ^{1}H-NMR Spectrum of tetrazole derivative C10

3.4.8. ^{13}C -NMR Spectrum of Tetrazole Derivatives(C1-C10)

^{13}C-NMR Spectra (DMSO-*d6*) for new tetrazole derivatives showed the specific signals such as peaks of carbons for adamantane structure at region δ (24-38)ppm, and peak at region δ (41-42.2) ppm refers to the carbon of tetrazole ring, multiple peaks at region δ (108.8-139) ppm indicate to the carbons of aromatic rings, and peak of carbon for amide appearance at δ (159-178.5) ppm . chemical shift of all type of carbon in ^{13}C-NMR spectrum of tetrazole derivatives shown in table (3.11), ^{13}C-NMR Spectra of tetrazole derivatives(C1-C10) shown in figures below.

Table 3.11: Chemical shift in ^{13}C-NMR spectrum of tetrazole derivatives

Comp.	Aliphatic carbons (ppm)	Carbon of tetrazole ring (ppm)	Aromatic carbons (ppm)	Amide carbon(ppm)	Other carbons (ppm)
C1	24.5-37	42	118-136	168.6	
C2	21.6-38.3	42.2	119-134.4	168.6	
C3	24.5-37	41.9	115-137	164.6	56-57(C_{Al}-O) 137(C_{Ar}-O)
C4	21.6-38.3	41.9	118-135	172.4	135(C_{Ar}-Br)
C5	29.3-37.2	41.1	111.6-136.5	159	40.7(C_{Al}-N) 136.5(C_{Ar}-N)
C6	24.4-37.2	41	119.3-129.7	168.5	
C7	21.6-37.4	41.8	108.8-139	178.5	
C8	24.8-37.2	41.9	118-129.6	173	129.6 C_{Ar}-NO_2
C10	24.3-37	41.6	114-125	177	125(C_{Ar}-O)

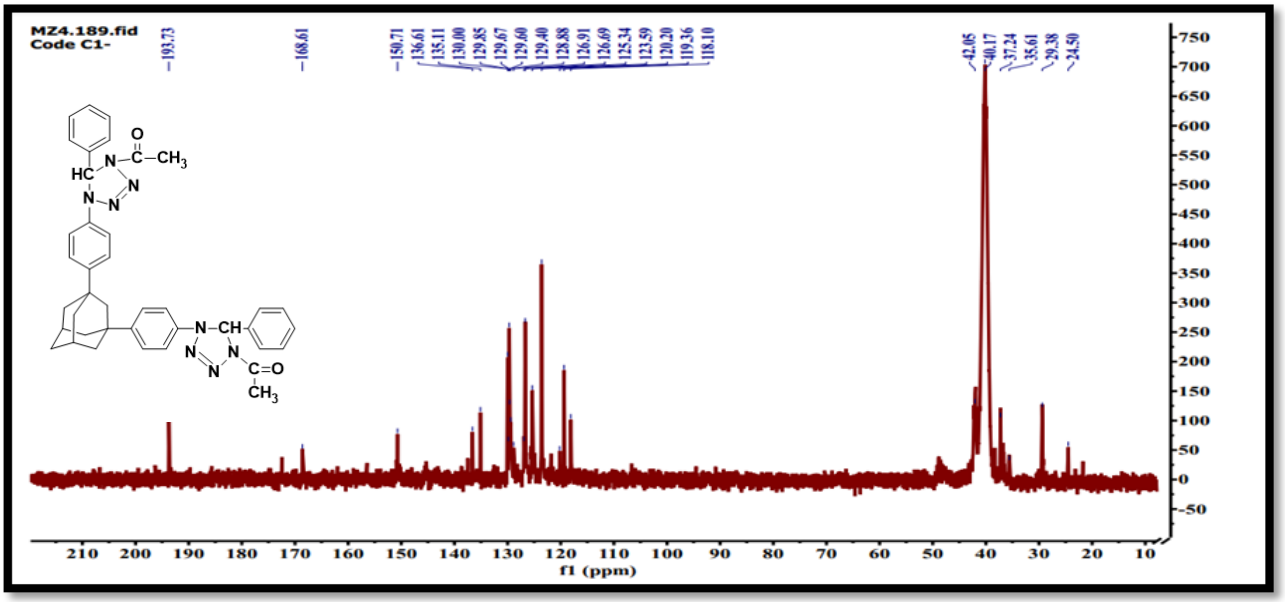


Figure 3.76: ^{13}C-NMR Spectrum of tetrazole derivative C1

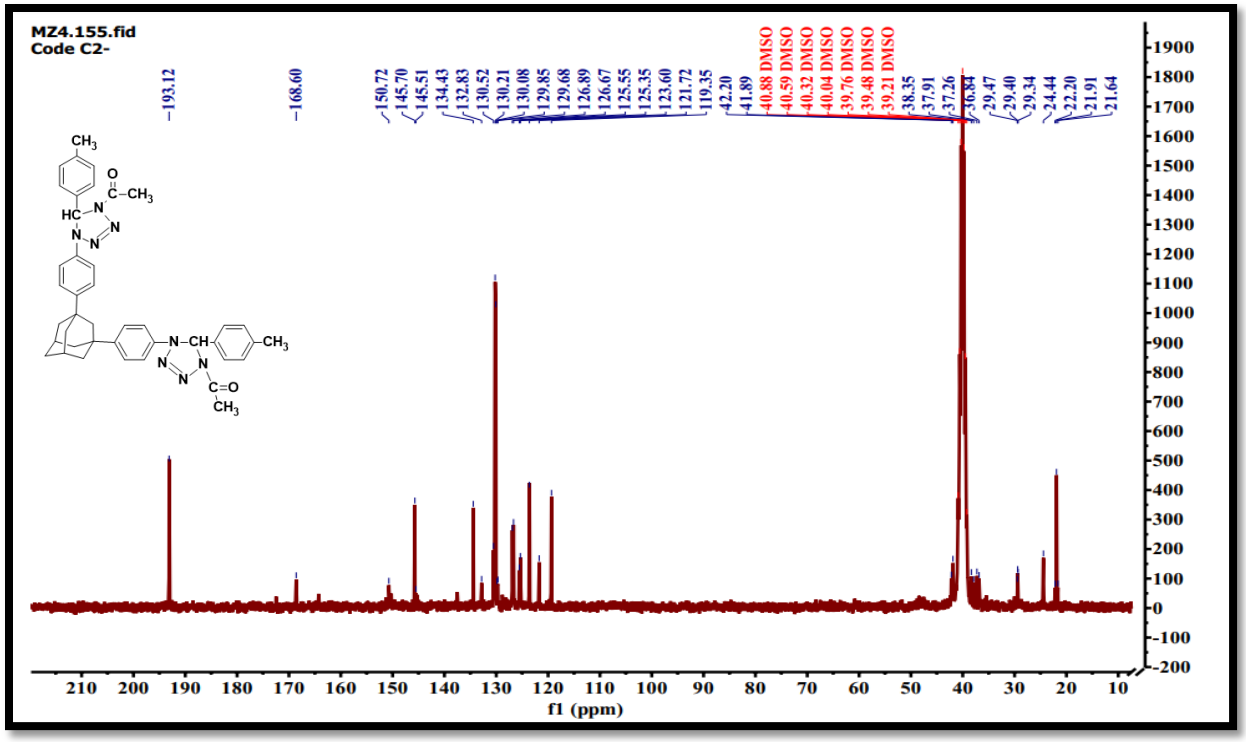


Figure 3.77: ^{13}C-NMR Spectrum of tetrazole derivative C2

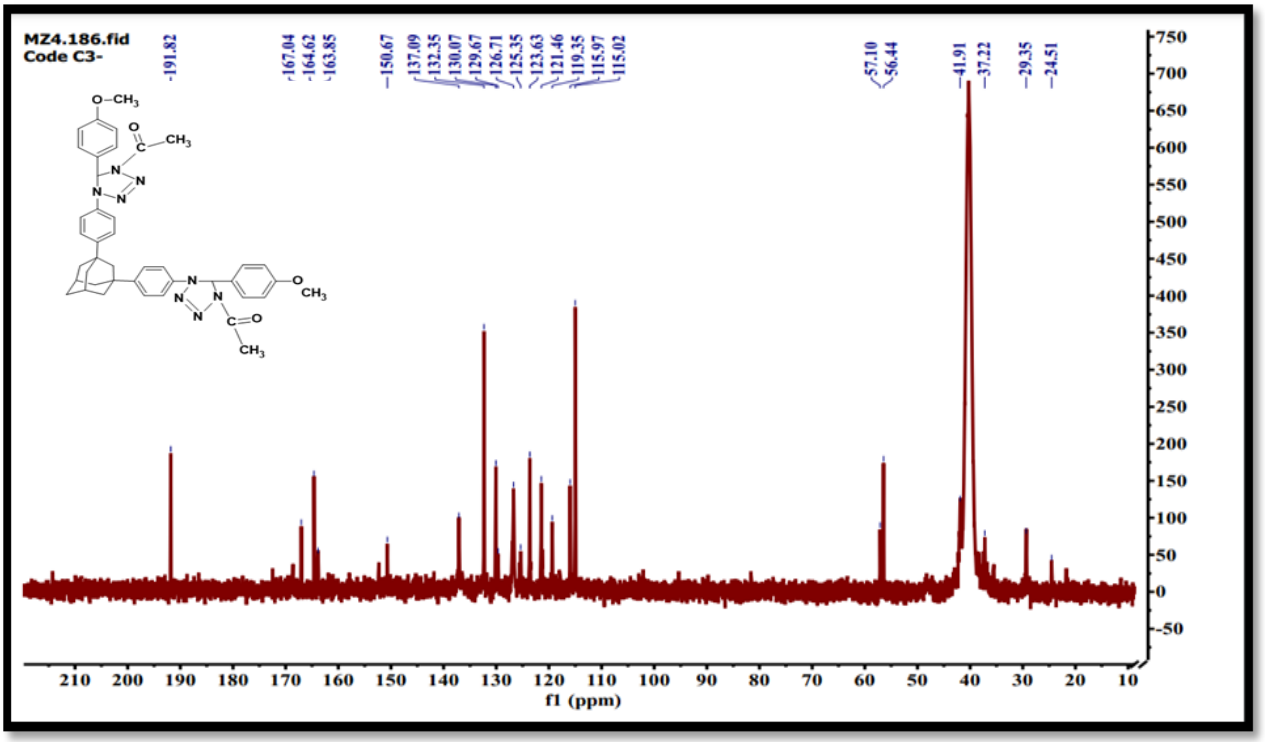


Figure 3.78: ^{13}C-NMR Spectrum of tetrazole derivative C3

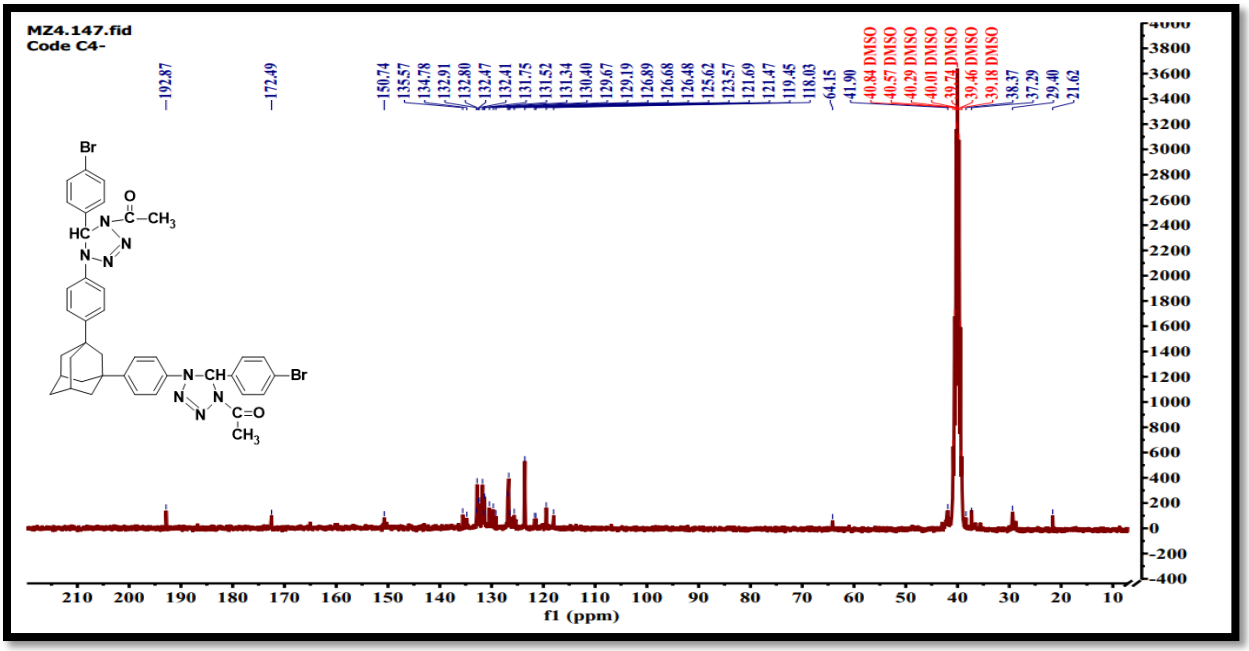


Figure 3.79: ^{13}C-NMR Spectrum of tetrazole derivative C4

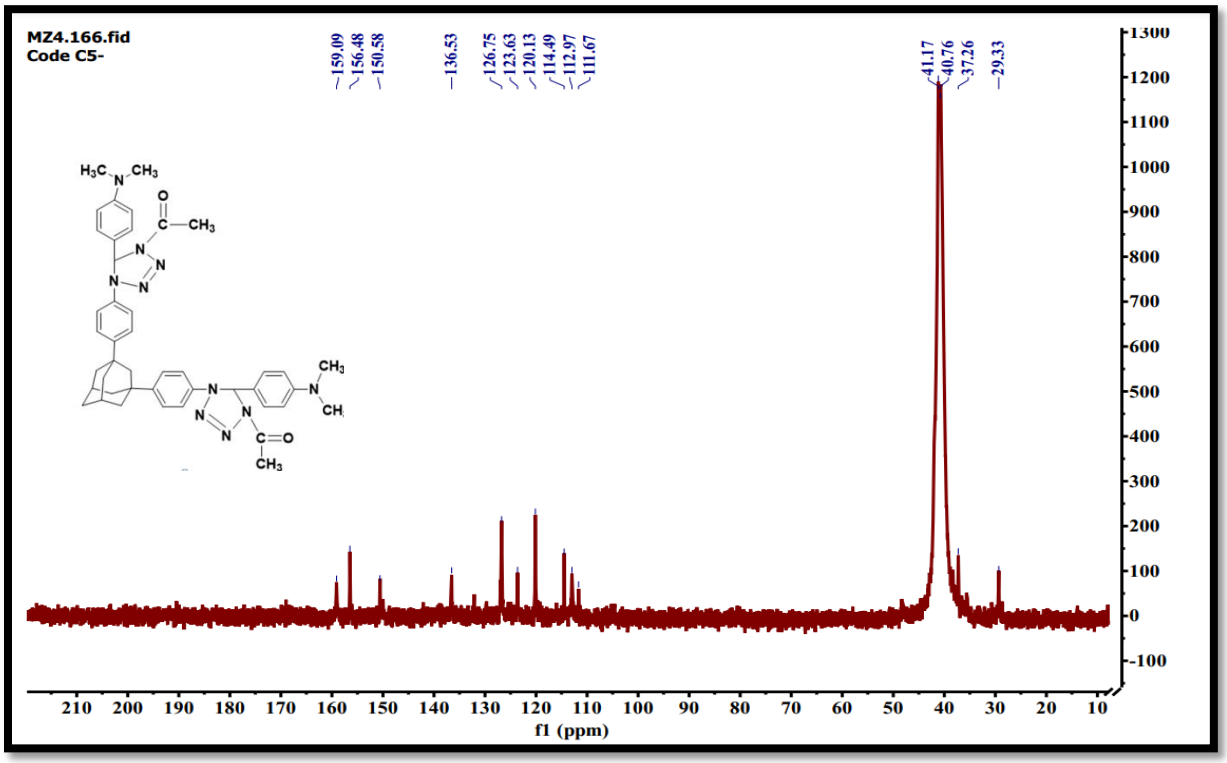


Figure 3.80: ^{13}C-NMR Spectrum of tetrazole derivative C5

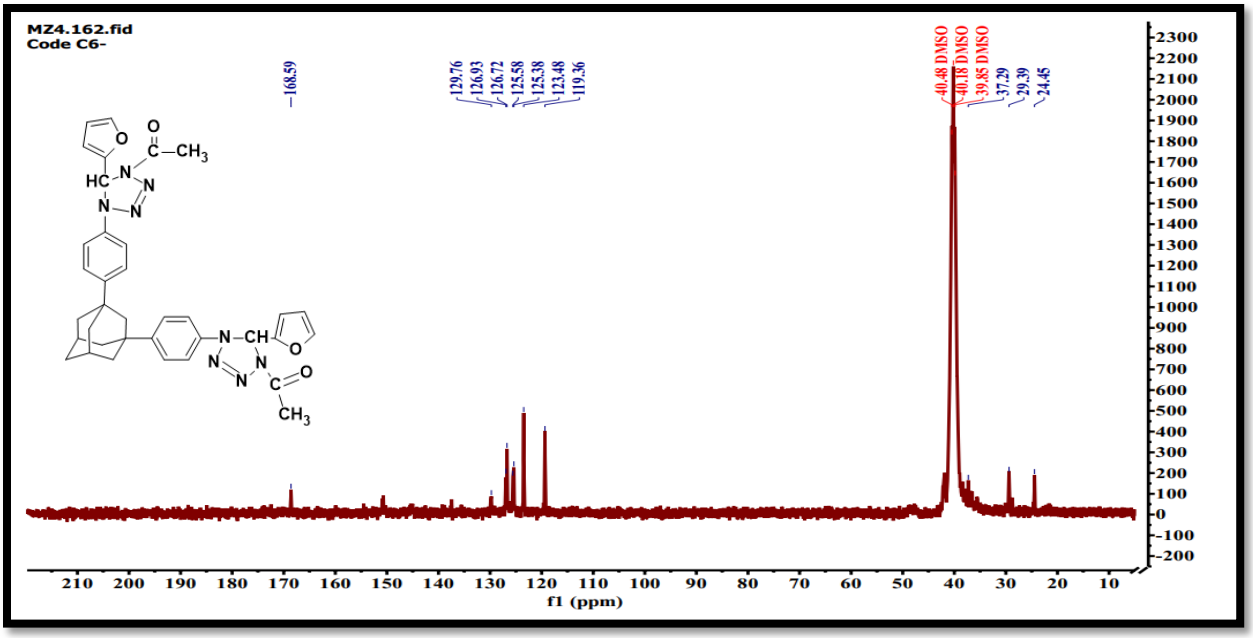


Figure 3.81: ^{13}C-NMR Spectrum of tetrazole derivative C6

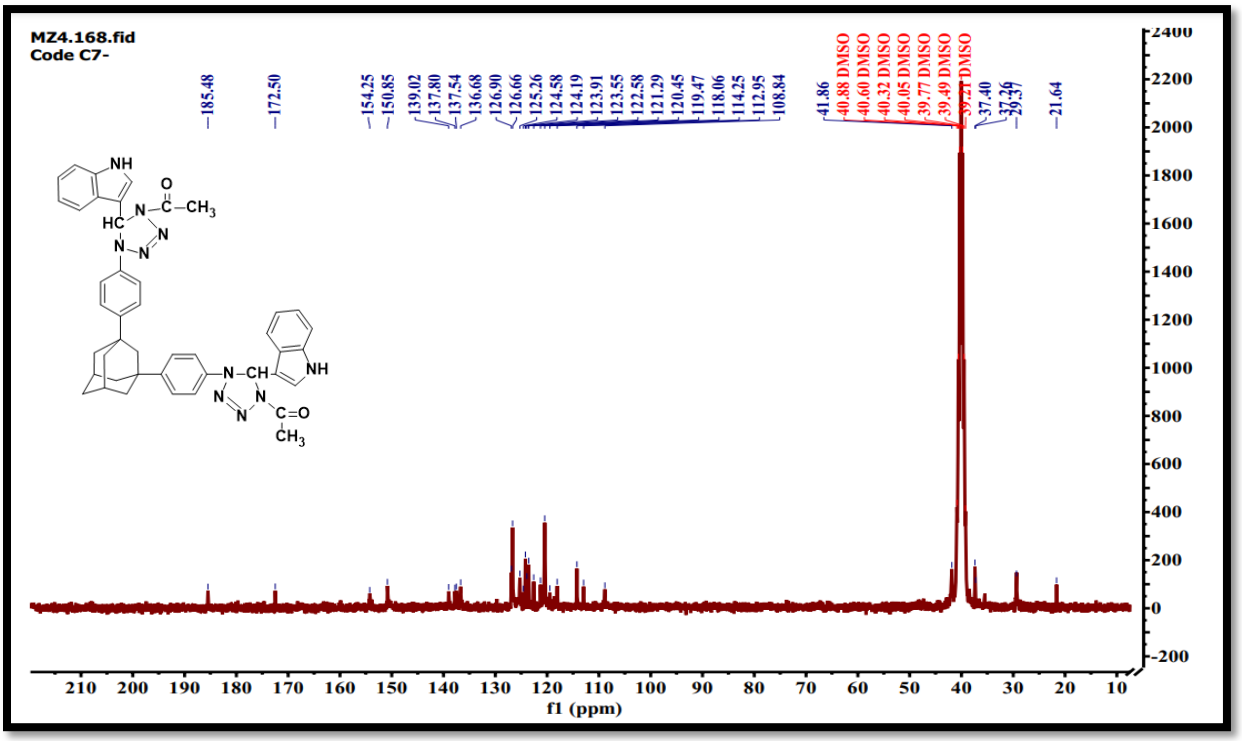


Figure 3.82: ^{13}C-NMR Spectrum of tetrazole derivative C7

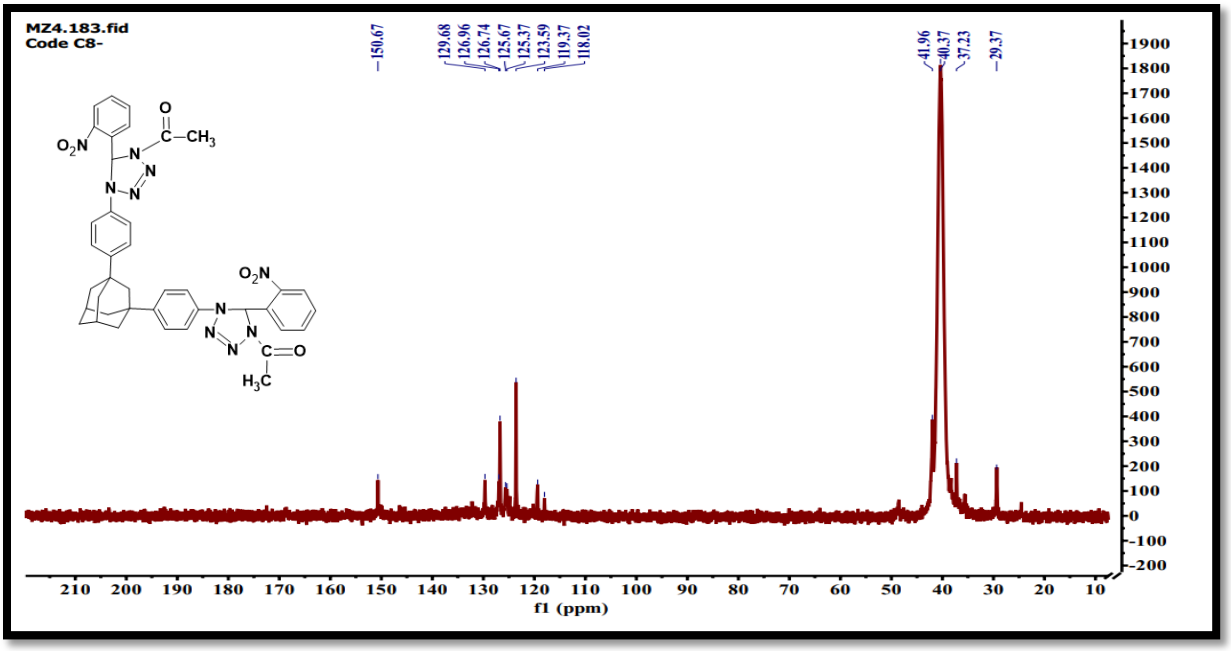


Figure 3.83: ^{13}C-NMR Spectrum of tetrazole derivative C8

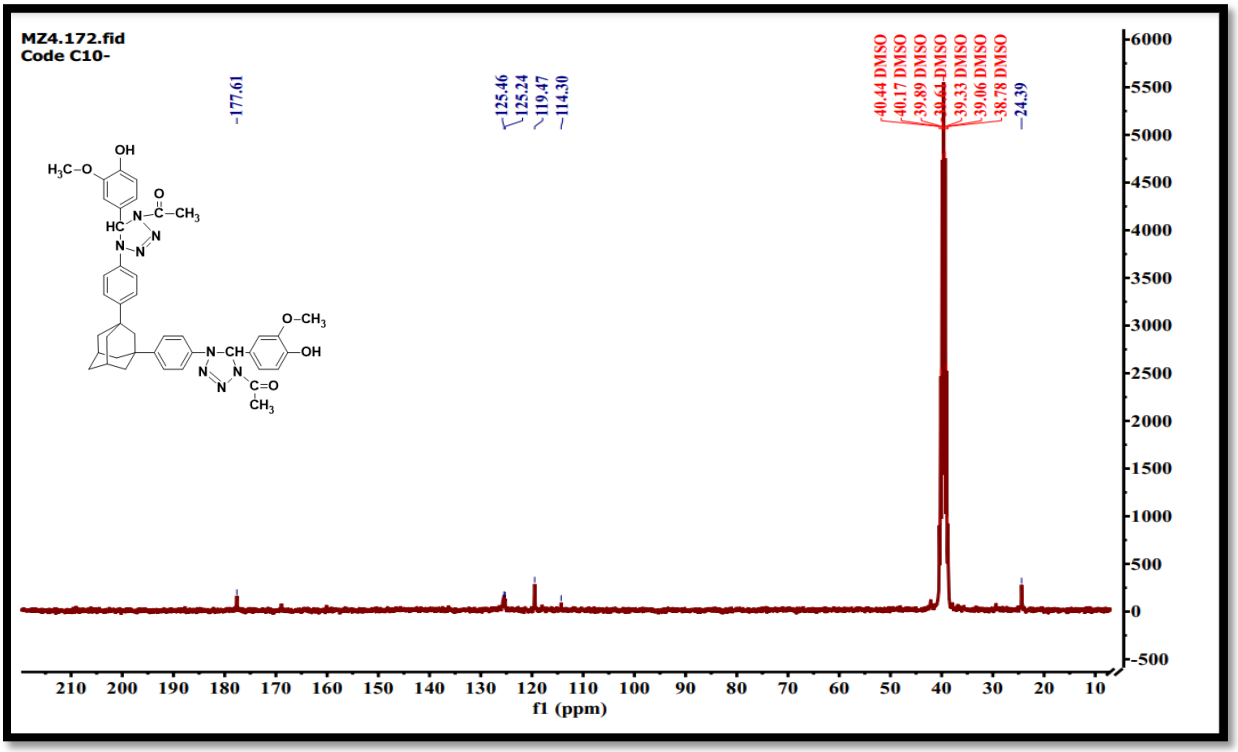


Figure 3.84: ^{13}C-NMR Spectrum of tetrazole derivative C10

3.4.9. Study of the Antimicrobial Activity of Some New Schiff Base and Tetrazole Derivatives by Using Well-Diffusion Assay (WDA)

1- Bacterial isolate (***Staphylococcus aureus*** and ***Escherichia coli***) was activated overnight in Brain heart infusion broth at 37 ºC.

2- Culture was washed twice with sterile normal saline then centrifuged at 12000 rpm for 10 min and re suspended in normal slain. The turbidity of suspension was adjusted to 0.5 McFarland in to prepare the inoculums.

3- A sterile swab was used to obtain an inoculum from the bacterial suspension. These inoculums were streaked on a Mueller-Hinton agar plate and left to dry.

4- Wells cut into the plates with 5mm sterile cork borer were loaded with 100 µl of the sample.

5- Inhibition zones were measured using a ruler

In vitro Antimicrobial activity a series of some new synthesized compounds tested for their antimicrobial activity against *staphylococcus aureus* , *Escherichia coli* and *Candida albicans*, table (3.12) explain zoom inhibition of some synthesized compounds against of two kinds of bacterial(*staphylococcus aureus* , *Escherichia coli*) and one kind of fungi(candida albicans) at concentration 0.001M in DMF as a solvent. It was observed that some of the synthesized compounds have good inhibitor action against *candida albicans* (B5, B8, B9, C7, C8), and weak-moderate activity against *staphylococcus aureus* , *Escherichia coli* in compounds (B1, B4, B5, B8, C1, C4, C5, C7, C8), compound B9 have good activity against *staphylococcus aureus* and *candida albicans* , as well as moderate activity against *Escherichia coli* Bactria due to the present of OH group substituent on the benzene ring.

Table 3.12: Zoom inhibition of some synthesized compound against two kinds of bacterial and one kind of fungi

Sample at 0.001 mol/L In DMF	Zoom inhibition(mm) *Staphylococcus aureus*	Zoom inhibition(mm) *Escherichia coli*	Zoom inhibition (mm) *Candida albicans*
B1	9	15	10
B4	15	12	19
B5	9	16	21
B8	16	13	22
B9	20	15	21
C1	9	15	15
C4	16	16	13
C5	17	17	12
C7	13	8	23
C8	10	12	22
DMF	Zero	Zero	Zero

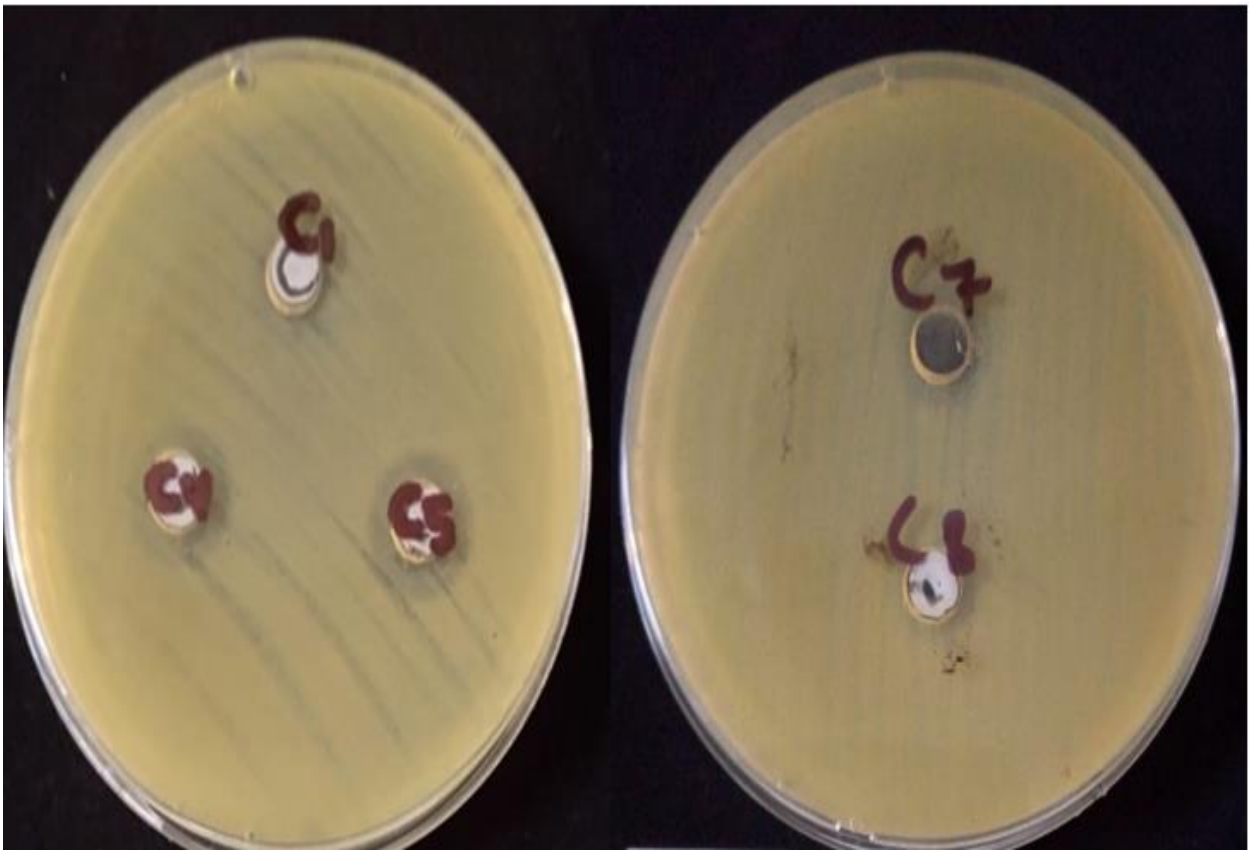


Image 3.2: Biological activity of some synthesized compound against of *staphylococcus aureus* Bactria

Image 3.3: Biological activity of some synthesized compound against *Staphylococcus aureus* Bactria

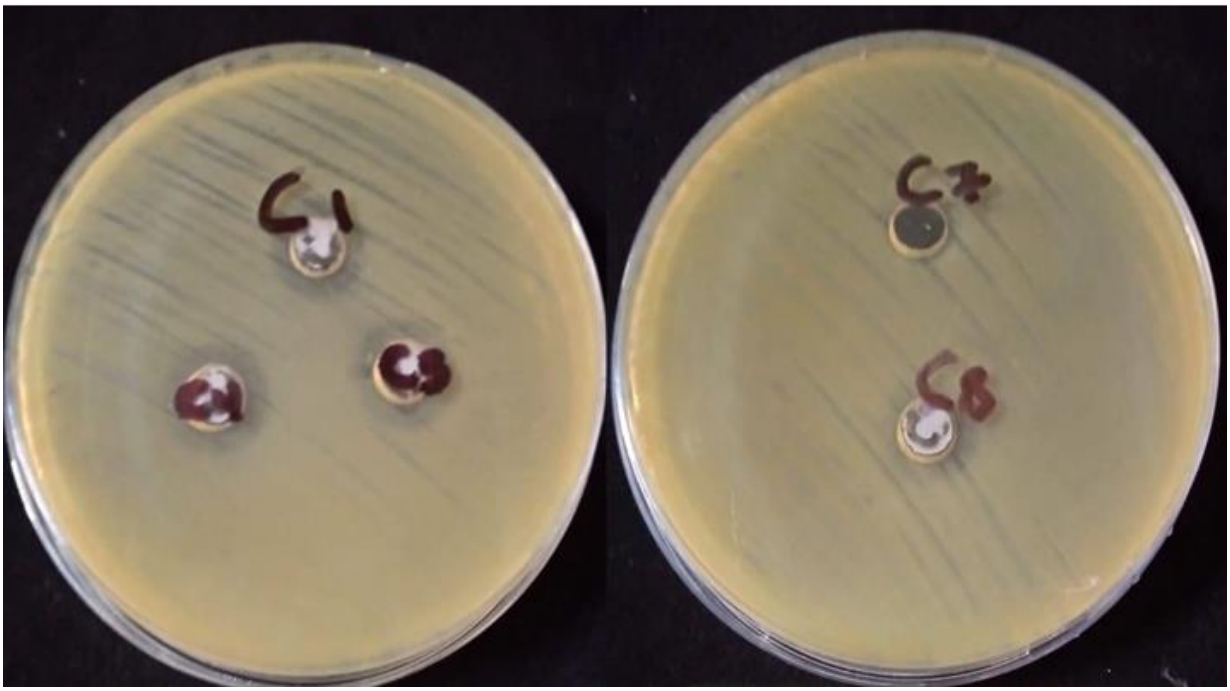


Image 3.4: Biological activity of some synthesized compound against *Escherichia coli* Bactria

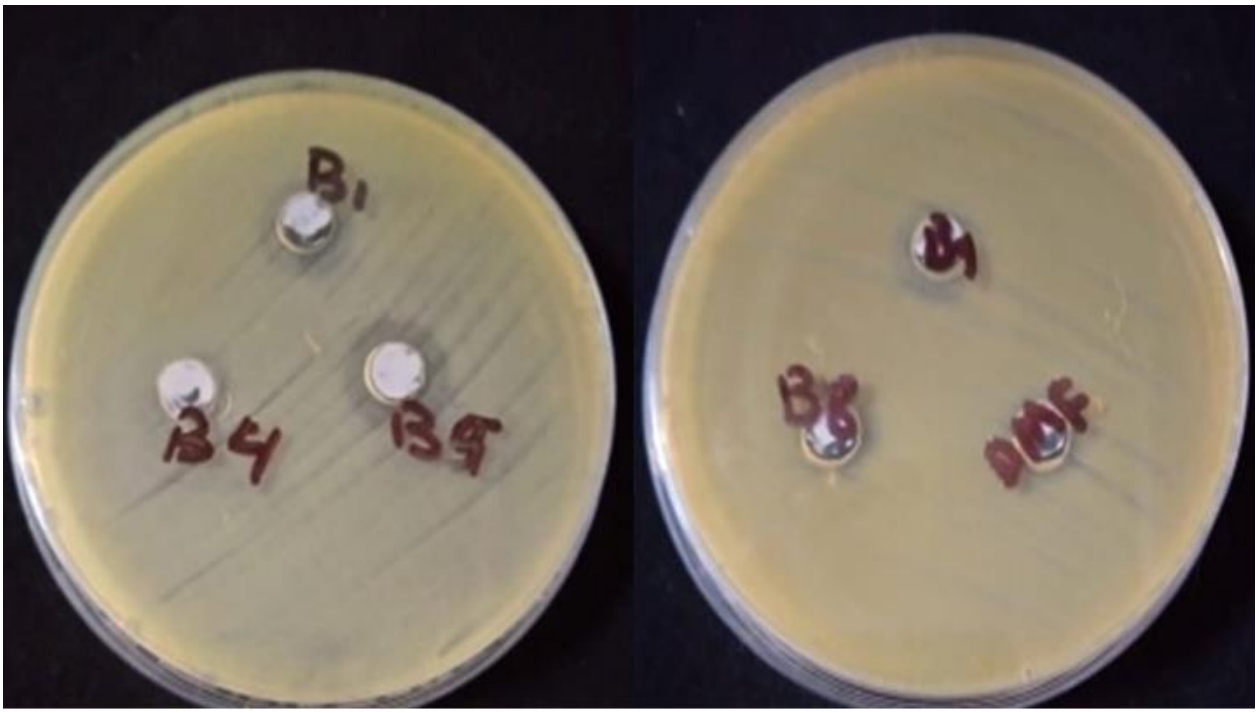


Image 3.5: Biological activity of some synthesized compound against *Escherichia coli* Bactria

Image 3.6: Biological activity of some synthesized compound against *Candida albicans* fungi

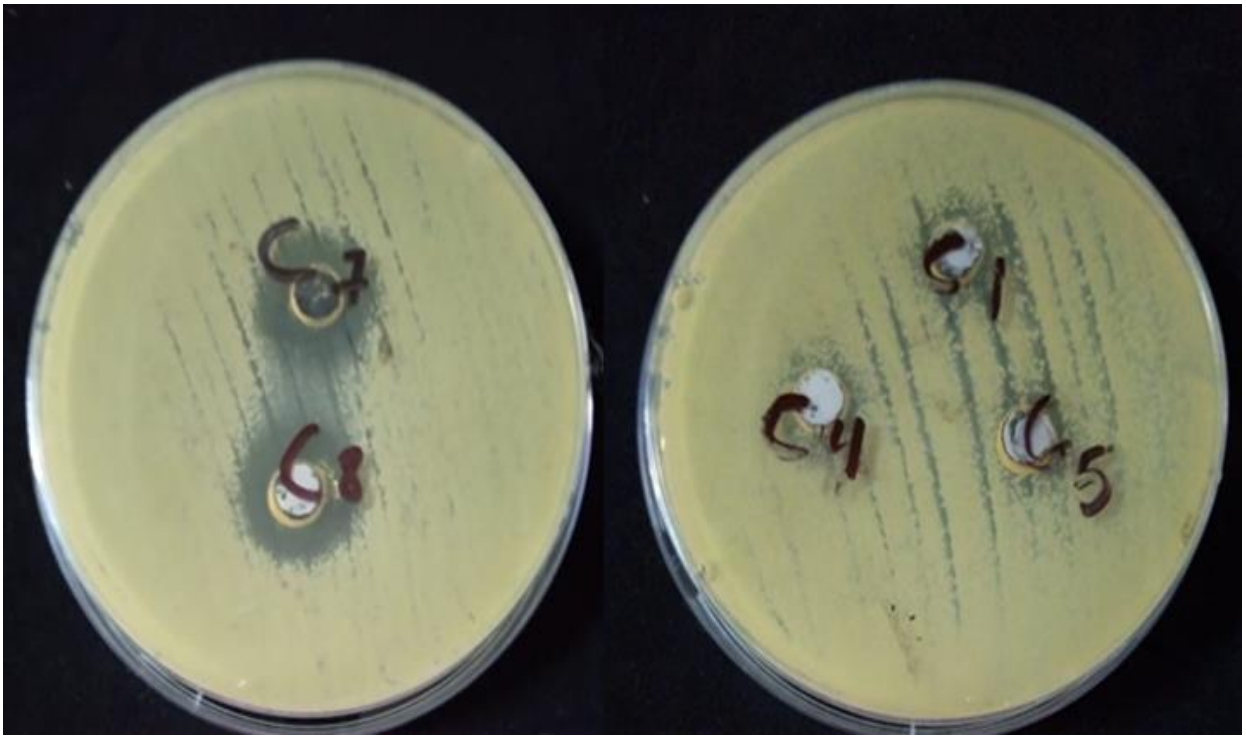


Image 3.7: Biological activity of some synthesized compound against *Candida albicans* fungi

3.5. Conclusions:

1. Preparation of adamantane salt of acetanilide by reaction of adamantanol with acetanilide in acidic medium, and preparation of adamantane derivative (amine) by basic hydrolysis of adamantane salt with good yield.

2. Successfully synthesis of a new ten Schiff base derivatives from react adamantane derivative amine with different aromatic aldehyde with yield percent range from (36-72)%, these different in yield percentage caused by nature of aromatic aldehyde; such as type of the ring , substituent (electron withdrawing or electron donating group) and their position on the ring make this different.

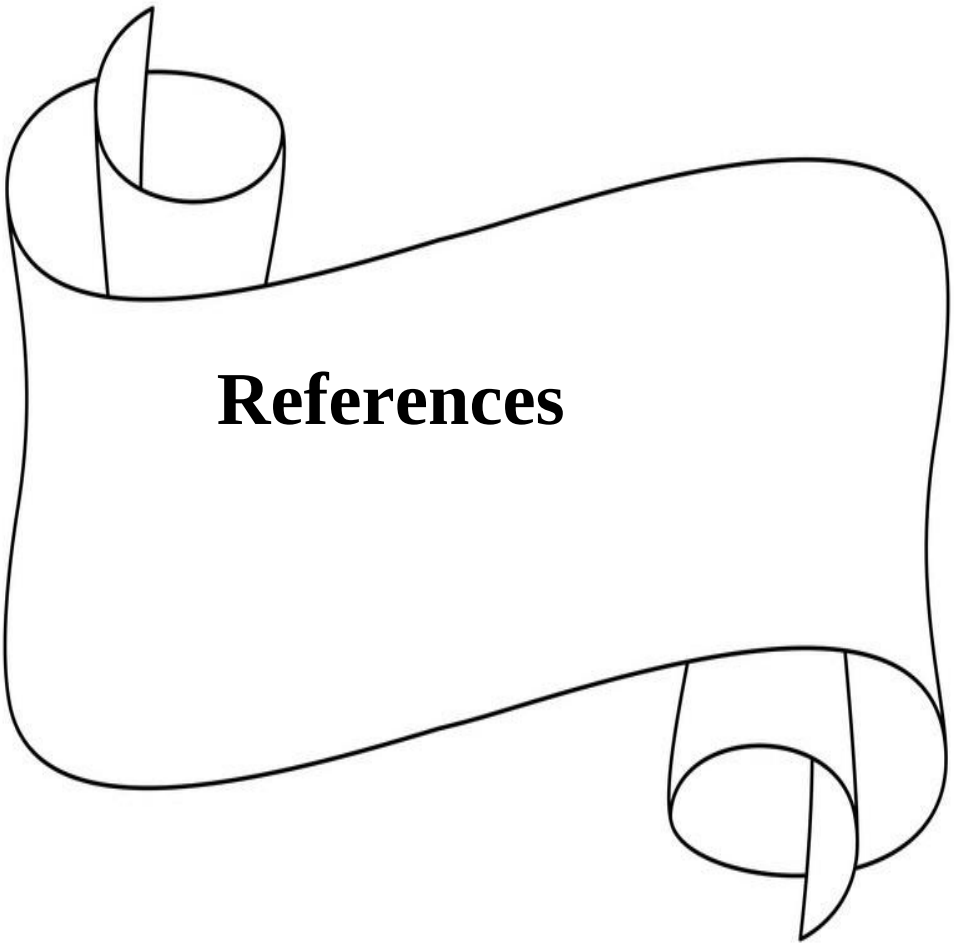
3. Successfully Synthesis of a new tetrazole derivatives compound from react Schiff base derivatives with sodium azide with yield percent range from(12-35)% as a first step, second step the product react with acetylchlorid to produce tetrazole derivatives compounds.

4. Evaluation of antioxidant activity against DPPH free radical of synthesized Schiff base derivatives (B1-B10),where all compounds exhibit high inhibition percentage from range (80.5-89.9)% at high concentration 1 mg/mL in methanol.

5. Estimation of biological activity of some new derivatives compound against two types of bacteria and one type of fungi. Some of tested compounds exhibit good inhibition activity against ***candida albicans*** (B5, B8, B9, C7, C8), and weak-moderate activity against ***staphylococcus aureus*** , ***Escherichia coli*** in compounds (B1, B4, B5, B8, C1, C4, C5, C7, C8). Compound B9 have good activity against *staphylococcus aureus* and *candida albicans* as well as moderate activity against *Escherichia coli* Bactria due to the present of OH group substituent on the benzene ring.

3.6. Suggestion for Future Work:

1. Synthesis new derivatives of Schiff base by using different aromatic aldehydes or ketones.
2. Synthesis different heterocyclic compounds from Schiff base derivatives.
3. We Suggest tested synthesized compound with different types of bacteria or fungi.
4. We suggest evaluation of biological activity in different concentration of compounds.
5. Testing the efficiency of derivative compounds as anticancer assay.
6. Synthesis new azo derivative compounds form adamantane derivative amine.
7. Synthesis of polyamid from adamantane derivative amine.



References

4. References

1. Habib, A.K. and S.A. Karim, *The Synthesis of a New Aliphatic Polyamide Based on Some Adamantane's Derivatives.* 2021. **11**(3): p. 842-845.
2. Agnew-Francis, K.A. and C.M. Williams, *Catalysts Containing the Adamantane Scaffold.* Advanced Synthesis & Catalysis, 2016. **358**(5): p. 675-700.
3. Wanka, L., K. Iqbal, and P.R. Schreiner, *The lipophilic bullet hits the targets: medicinal chemistry of adamantane derivatives.* Chem Rev, 2013. **113**(5): p. 3516-604.
4. Hsiao, S.-H. and C.-T.J.M. Li, *Synthesis and Characterization of New Adamantane-Based Polyimides.* 1998. **31**(21): p. 7213-7217.
5. Mathews, A.S., I. Kim, and C.-S. Ha, *Fully aliphatic polyimides from adamantane-based diamines for enhanced thermal stability, solubility, transparency, and low dielectric constant.* Journal of Applied Polymer Science, 2006. **102**(4): p. 3316-3326.
6. Kanehashi, S., S. Konishi, K. Takeo, K. Owa, H. Kawakita, S. Sato, T. Miyakoshi, and K. Nagai, *Effect of OH group on the water vapor sorption property of adamantane-containing polymer membranes.* Journal of Membrane Science, 2013. **427**: p. 176-185.
7. Allcock, H.R. and W.E.J.M. Krause, *Polyphosphazenes with Adamantyl Side Groups.* 1997. **30**(19): p. 5683-5687.
8. Mugisawa, M., K. Ueno, K. Hamazaki, and H. Sawada, *Synthesis and Properties of Novel Cross-Linked Fluoroalkyl End-Capped Oligomeric Nanoparticles Containing Adamantane Units*. Macromolecular Rapid Communications, 2007. **28**(6): p. 733-739.
9. Shen, C., Y. Bao, and Z. Wang, *Tetraphenyladamantane-based microporous polyimide for adsorption of carbon dioxide, hydrogen, organic and water vapors.* Chem Commun (Camb), 2013. **49**(32): p. 3321-3.
10. Schwertfeger, H., A.A. Fokin, and P.R. Schreiner, *Diamonds are a chemist's best friend: diamondoid chemistry beyond adamantane.* Angew Chem Int Ed Engl, 2008. **47**(6): p. 1022-36.
11. Masahide Tominaga, K.K., and Isao Azumaya*, *Pseudopolymorph and Charge-Transfer Co-Crystal of Disubstituted Adamantane containing Dimethoxyphenol Moieties.* Crystal Growth &Design, 2009. **9**: p. 3692-3696.
12. Spilovska, K., F. Zemek, J. Korabecny, E. Nepovimova, O. Soukup, M. Windisch, and K.J.C.M.C. Kuca, *Adamantane–a lead structure for drugs in clinical practice.* 2016. **23**(29): p. 3245-3266.

13. Shi, X.J., G.J. Chen, Y.W. Wang, L. Yuan, Q. Zhang, D.M. Haddleton, and H. Chen, *Control the wettability of poly(n-isopropylacrylamide-co-1-adamantan-1-ylmethyl acrylate) modified surfaces: the more Ada, the bigger impact?* Langmuir, 2013. **29**(46): p. 14188-95.
14. Hassan, G.S., A.A. El-Emam, L.M. Gad, and A.E.M.J.S.P.J. Barghash, *Synthesis, antimicrobial and antiviral testing of some new 1-adamantyl analogues.* 2010. **18**(3): p. 123-128.
15. Munkuev, A.A., E.S. Mozhaitsev, A.A. Chepanova, E.V. Suslov, D.V. Korchagina, O.D. Zakharova, E.S. Ilina, N.S. Dyrkheeva, A.L. Zakharenko, J. Reynisson, K.P. Volcho, N.F. Salakhutdinov, and O.I. Lavrik, *Novel Tdp1 Inhibitors Based on Adamantane Connected with Monoterpene Moieties via Heterocyclic Fragments.* Molecules, 2021. **26**(11).
16. Tominaga, M., H. Masu, and I. Azumaya, *Construction and charge-transfer complexation of adamantane-based macrocycles and a cage with aromatic ring moieties.* J Org Chem, 2009. **74**(22): p. 8754-60.
17. Pham, V.H., T.P.D. Phan, D.C. Phan, and B.D. Vu, *Synthesis and Bioactivity of Thiosemicarbazones Containing Adamantane Skeletons.* Molecules, 2020. **25**(2).
18. Danysz, W., A. Dekundy, A. Scheschonka, and P. Riederer, *Amantadine: reappraisal of the timeless diamond-target updates and novel therapeutic potentials.* J Neural Transm (Vienna), 2021. **128**(2): p. 127-169.
19. Bonsir, M., 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, 2022: p. e202200031.
20. Kuznetsov, N.Y., R.M. Tikhov, I.A. Godovikov, M.G. Medvedev, K.A. Lyssenko, E.I. Burtseva, E.S. Kirillova, and Y.N. Bubnov, *Stereoselective synthesis of novel adamantane derivatives with high potency against rimantadine-resistant influenza A virus strains.* Org Biomol Chem, 2017. **15**(15): p. 3152-3157.
21. Stimac, A., M. Sekutor, K. Mlinaric-Majerski, L. Frkanec, and R. Frkanec, *Adamantane in Drug Delivery Systems and Surface Recognition.* Molecules, 2017. **22**(2).
22. Wang, J., J.R. Schnell, and J.J. Chou, *Amantadine partition and localization in phospholipid membrane: a solution NMR study.* Biochem Biophys Res Commun, 2004. **324**(1): p. 212-7.
23. Wassel, M.M.S., Y.A. Ammar, G.A.M. Elhag Ali, A. Belal, A.B.M. Mehany, and A. Ragab, *Development of adamantane scaffold containing 1,3,4-thiadiazole derivatives: Design, synthesis, anti-proliferative activity*

and molecular docking study targeting EGFR. Bioorg Chem, 2021. **110**: p. 104794.

24. Krinochkin, A.P., D.S. Kopchuk, K. Giri, Y.K. Shtaitz, E.S. Starnovskaya, I.A. Khalymbadzha, R.A. Drokin, E.N. Ulomsky, S. Santra, G.V. Zyryanov, V.L. Rusinov, and O.N. Chupakhin, *A PASE Approach towards (Adamantyl-1)-, Alkyl- and (Het)Aryl-Substituted [1, 2,4]triazolo[1, 5-d][1, 2,4]triazines: A Sequence of Two Solvent-Free Reactions Bearing Lower E-Factors.* ChemistrySelect, 2018. **3**(28): p. 8202-8206.
25. Chayrov, R., N.A. Parisis, M.V. Chatziathanasiadou, E. Vrontaki, K. Moschovou, G. Melagraki, H. Sbirkova-Dimitrova, B. Shivachev, M. Schmidtke, Y. Mitrev, M. Sticha, T. Mavromoustakos, A.G. Tzakos, and I. Stankova, *Synthetic Analogues of Aminoadamantane as Influenza Viral Inhibitors-In Vitro, In Silico and QSAR Studies.* Molecules, 2020. **25**(17).
26. Shehadi, I.A., F.A. Delmani, A.M. Jaber, H. Hammad, M.A. AlDamen, R.A. Al-Qawasmeh, and M.A. Khanfar, *Synthesis, Characterization and Biological Evaluation of Metal Adamantyl 2-Pyridylhydrazone Complexes.* Molecules, 2020. **25**(11).
27. Keita, H., *Adamantane-Functionalized Phthalimide Scaffold: Pathways to Supramolecular Interactions and Drug Discovery.* Organics, 2021. **2**(4): p. 388-394.
28. Pham, V.H., T.P.D. Phan, D.C. Phan, and B.D. Vu, *Synthesis and Bioactivity of Hydrazide-Hydrazones with the 1-Adamantyl-Carbonyl Moiety.* Molecules, 2019. **24**(21).
29. Butterworth, R.F., *Potential for the Repurposing of Adamantane Antivirals for Covid-19.* Drugs R D, 2021. **21**(3): p. 267-272.
30. Zhu, J., G. Teng, D. Li, R. Hou, and Y. Xia, *Synthesis and Antibacterial Activity of Novel Schiff Bases of Thiosemicarbazone Derivatives With Adamantane Moiety.* 2021.
31. El-Emam, A.A., E. Saveeth Kumar, K. Janani, L.H. Al-Wahaibi, O. Blacque, M.I. El-Awady, N.H. Al-Shaalan, M.J. Percino, and S. Thamotharan, *Quantitative assessment of the nature of noncovalent interactions in N-substituted-5-(adamantan-1-yl)-1,3,4-thiadiazole-2-amines: insights from crystallographic and QTAIM analysis.* RSC Adv, 2020. **10**(17): p. 9840-9853.
32. Geng, Z., Y. Lu, S. Zhang, X. Jiang, P. Huo, J. Luan, and G. Wang, *Synthesis and characterization of novel adamantane-based copoly(aryl ether ketone)s with low dielectric constants.* Polymer International, 2014. **63**(2): p. 333-337.

33. Liao, X.X., T. Wang, J. Wang, J.C. Zheng, C. Wang, and V.W. Yam, *Optoelectronic properties of a fullerene derivative containing adamantane group.* ACS Appl Mater Interfaces, 2013. **5**(19): p. 9579-84.
34. Mathias, L.J., C.M. Lewis, and K.N.J.M. Wiegel, *Poly(ether ether ketone)s and Poly(ether sulfones) with Pendent Adamantyl Groups.* 1997. **30**(19): p. 5970-5975.
35. Chern, Y.T., H.C.J.M.c. Shiue, and physics, *Low dielectric constant polyimides derived from 1,3- bis(4-aminopheny1)adamantane.* 1998. **199**(6): p. 963-969.
36. Han, D.W. and J.A. Moore, *Synthesis and characterization of adamantane-containing poly(enaminonitriles).* Polymer, 2009. **50**(12): p. 2551-2557.
37. Osman, H.M., T. Elsaman, B.A. Yousef, E. Elhadi, A.A.E. Ahmed, E.M. Eltayib, M.S. Mohamed, M.A. Mohamed, and P.M. Mancini, *Schiff Bases of Isatin and Adamantane-1-Carbohydrazide: Synthesis, Characterization and Anticonvulsant Activity.* Journal of Chemistry, 2021. **2021**: p. 1-11.
38. Raczuk, E., B. Dmochowska, J. Samaszko-Fiertek, and J. Madaj, *Different Schiff Bases-Structure, Importance and Classification.* Molecules, 2022. **27**(3).
39. Abu-Yamin, A.A., M.S. Abduh, S.A.M. Saghir, and N. Al-Gabri, *Synthesis, Characterization and Biological Activities of New Schiff Base Compound and Its Lanthanide Complexes.* Pharmaceuticals (Basel), 2022. **15**(4).
40. Boussadia, A., A. Beghidja, L. Gali, C. Beghidja, M. Elhabiri, P. Rabu, and G.J.I.C.A. Rogez, *Coordination properties of two new Schiff-base phenoxycarboxylates and comparative study of their antioxidant activities.* 2020. **508**: p. 119656.
41. Berber, N., *Synthesis of New Schiff Base Compounds and Identification of Their Structures.* Adıyaman University Journal of Science, 2020.10(1):p.179-188.
42. Rumez, R.M.J.j.o.t.c.o.b.e., *Synthesis and Characterization of New Oxazepines Compounds Derived From D-Galactose.* 2015. **20**(87).
43. Xu, J., Y. Liu, and S.H. Hsu, *Hydrogels Based on Schiff Base Linkages for Biomedical Applications.* Molecules, 2019. **24**(16).
44. Iacopetta, D., J. Ceramella, A. Catalano, C. Saturnino, M.G. Bonomo, C. Franchini, and M.S. Sinicropi, *Schiff Bases: Interesting Scaffolds with Promising Antitumoral Properties.* Applied Sciences, 2021. **11**(4).
45. Bhoi, M.N., M.A. Borad, N.K. Panchal, and H.D. Patel, *2-Aminobenzothiazole Containing Novel Schiff Bases Derivatives: Search for New Antibacterial Agents.* International Letters of Chemistry, Physics and Astronomy, 2015. **53**: p. 106-113.

46. Khdeaur Abbas, S.J.j.o.k.u., *Synthesis and Characterization of New Oxazepine and Oxazepane Derived From Schiff Bases.* 2016. **12**(2): p. 96-125.
47. Verma, R., N.P. Lamba, A. Dandia, A. Srivastava, K. Modi, M.S. Chauhan, and J. Prasad, *Synthesis of N-Benzylideneaniline by Schiff base reaction using Kinnow peel powder as Green catalyst and comparative study of derivatives through ANOVA techniques.* Sci Rep, 2022. **12**(1): p. 9636.
48. Shah, S.S., D. Shah, I. Khan, S. Ahmad, U. Ali, and A.U.J.R.A.C. Rahman, *Synthesis and Antioxidant Activities of Schiff Bases and Their Complexes: An Updated Review.* Biointerface Research in Applied Chemistry, 2020. **10**(6): p. 6936-6963.
49. Wei, L., W. Tan, J. Zhang, Y. Mi, F. Dong, Q. Li, and Z. Guo, *Synthesis, Characterization, and Antifungal Activity of Schiff Bases of Inulin Bearing Pyridine ring.* Polymers (Basel), 2019. **11**(2).
50. Abid, O.H., H.M. Tawfeeq, and R.F. Muslim, *Synthesis and characterization of novel 1,3-oxazepin-5(1h)-one derivatives via reaction of imine compounds with isobenzofuran-1(3h)-one.* ACTA Pharmaceutica Sciencia, 2017. **55**(4).
51. Ismailova, D.S., A.A. Ziyaev, K.M. Bobakulov, S.A. Sasmakov, U.S. Makhmudov, E.G. Yusupova, and S.S. Azimova, *The new Schiff bases of 2-alkylthio-5-(4-aminophenyl)-1,3,4-oxadiazoles and their antimicrobial activity.* Journal of the Iranian Chemical Society, 2018. **16**(3): p. 545-551.
52. Ahmed, A.A., N.G. Ahmed, A.K.J.P.J.o.S. Ahmad, and I.R.S.A.P. Sciences, *Synthesis of New Substituted Tetrazole and 4-Thiazolidinone from Schiff's Bases: Synthesis of New Substituted Tetrazole Compounds* 2019. **63**(1): p. 1-11.
53. Jadhav Sheetal, P. and H. Kapadnis Kailas, *Synthesis and Characterization of Schiff bases of Benzaldehyde with Nitroanilines and their Cobalt, Nickel and Copper metal Complexes.* 2018.
54. Abid, O.H. and A.k. Ramadan, *Preparation and Identification of Novel 1, 3-Oxazepine Derivatives by Cycloaddition Reactions [2+5] of Selected Carboxylic Acid Anhydrides with Imines Derived from 4-methyl aniline.* Al-Mustansiriyah Journal of Science, 2018. **29**(2): p. 93-100.
55. Yadav, M., S. Sharma, and J. Devi, *Designing, spectroscopic characterization, biological screening and antioxidant activity of mononuclear transition metal complexes of bidentate Schiff base hydrazones.* Journal of Chemical Sciences, 2021. **133**(1).
56. Mahmood, A.A.J.I.J.o.P., *Green synthesis of Schiff bases: a review study.* 2022. **18**(2): p. 180-193.

57. Al-Sultani, K.T.A., *Synthesis, Identification and Evaluation the Biological Activity for Some New Heterocyclic Compounds Derived from Schiff Bases.* Iosr Journal of Pharmacy and Biological Sciences, 2017. **12**(02): p. 39-47.
58. Hussain, Z., E. Yousif, A. Ahmed, A.J.O. Altaie, and m.c. letters, *Synthesis and characterization of Schiff's bases of sulfamethoxazole.* 2014. **4**(1): p. 1-4.
59. Ghanghas, P., A. Choudhary, D. Kumar, and K. Poonia, *Coordination metal complexes with Schiff bases: Useful pharmacophores with comprehensive biological applications.* Inorganic Chemistry Communications, 2021. **130**.
60. Nartop, D. and H. ÖĞÜTcÜ, *Potansiyel Antimikrobiyal Ajanlar Olarak Yeni Asimetrik Schiff Bazlarının Sentezi.* Sinop Üniversitesi Fen Bilimleri Dergisi, 2020.
61. Kf, H. and E. Hh, *Synthesis, Characterization, Biological Evaluation and Anti Corrosion Activity of Some Heterocyclic Compounds Oxazepine Derivatives from Schiff Bases.* Organic Chemistry: Current Research, 2013. **2**(3).
62. Grivani, G., G. Bruno, H.A. Rudbari, A.D. Khalaji, and P. Pourteimouri, *Synthesis, characterization and crystal structure determination of a new oxovanadium(IV) Schiff base complex: The catalytic activity in the epoxidation of cyclooctene.* Inorganic Chemistry Communications, 2012. **18**: p. 15-20.
63. Wahba, O., A.M. Hassan, A. Naser, and A.J.E.J.o.C. Hanafi, *Preparation and spectroscopic studies of some copper and nickel Schiff base complexes and their applications as colouring pigments in protective paints industry* 2017. **60**(1): p. 25-40.
64. Soroceanu, A. and A. Bargan, *Advanced and Biomedical Applications of Schiff-Base Ligands and Their Metal Complexes: A Review.* Crystals, 2022. **12**(10).
65. Warad, I., O. Ali, A. Al Ali, N.A. Jaradat, F. Hussein, L. Abdallah, N. Al-Zaqri, A. Alsalme, and F.A. Alharthi, *Synthesis and Spectral Identification of Three Schiff Bases with a 2-(Piperazin-1-yl)-N-(thiophen-2-yl methylene)ethanamine Moiety Acting as Novel Pancreatic Lipase Inhibitors: Thermal, DFT, Antioxidant, Antibacterial, and Molecular Docking Investigations.* Molecules, 2020. **25**(9).
66. Anuse, D.G., V.J. Desale, B.R. Thorat, D.D. Anuse, S.G. Jagadhani, K.G. Abraham, and R.S. Yamagar, *Synthesis and Screening of Biologically Active Schiff bases of Benzothiazoles and its Zinc and Lanthanum Metal Complexes.* Oriental Journal Of Chemistry, 2021. **37**(1): p. 187-193.

67. Berhanu, A.L., Gaurav, I. Mohiuddin, A.K. Malik, J.S. Aulakh, V. Kumar, and K.-H. Kim, *A review of the applications of Schiff bases as optical chemical sensors.* TrAC Trends in Analytical Chemistry, 2019. **116**: p. 74-91.
68. Qin, W., S. Long, M. Panunzio, and S.J.M. Biondi, *Schiff bases: A short survey on an evergreen chemistry tool.* 2013. **18**(10): p. 12264-12289.
69. Mahrath, A.J., S. Aboluse, and S.N.J.J.o.B.u. Kamil, *Synthesis and spectroscopic studies of some Schiff bases derived from Benzidine and their conversion to 1, 3-oxazepine derivatives throughout [2+5] cycloaddition reactions (II)* 2012. **20**(8).
70. Mahmoud, M., S.R. Mmohammed, and A.A. Dawood, *Synthesis, Identification and Biological Activity of New Heterocyclic Compounds from Reaction of New Schiff-Bases with Phathalic Anhydride.* Science Journal of University of Zakho, 2020. **8**(1): p. 12-18.
71. Ahmed, A.A., N.G. Ahmed, A.K.J.P.J.o.S. Ahmad, and I.R.S.A.P. Sciences, *Synthesis of New Substituted Tetrazole and 4-Thiazolidinone from Schiff's Bases: Synthesis of New Substituted Tetrazole Compounds.* 2020. **63**(1): p. 1-11.
72. Desai, V. and R.J.I.J.P. Shinde, *Green synthesis of nicotinic acid hydrazide schiff bases and its biological evaluation.* 2015. **5**: p. 930-935.
73. Nief, O.A., H.N. Salman, and L.S.J.I.J.o.S. Ahamed, *Synthesis, Characterization, Biological Activity Studies of Schiff Bases and 1,3-Oxazipene Derived from 1,1 -Bis (4-aminophenyl) -4-Phenyl Cyclohexane.* 2017. **58**: p. 1998-2011.
74. Berkesi, O., T. Körtvélyesi, C. Hetényi, T. Németh, and I. Pálinkó, *Hydrogen bonding interactions of benzylidene type Schiff bases studied by vibrational spectroscopic and computational methods.* Phys. Chem. Chem. Phys., 2003. **5**(10): p. 2009-2014.
75. Mohammed, I.A., M. Ahmed, R. Ikram, M.A. Qadir, and R.J.L.A.J.o.P. Hussain, *1,3-Oxazepine Compounds Derived from Azomethine: Synthesis, Characterization and Antibacterial Evaluation.* 2018. **37**(3): p. 540-6.
76. Kumar, M., T. Padmini, and K. Ponnuvel, *Synthesis, characterization and antioxidant activities of Schiff bases are of cholesterol.* Journal of Saudi Chemical Society, 2017. **21**: p. S322-S328.
77. Cheng, L.X., J.J. Tang, H. Luo, X.L. Jin, F. Dai, J. Yang, Y.P. Qian, X.Z. Li, and B. Zhou, *Antioxidant and antiproliferative activities of hydroxyl-substituted Schiff bases.* Bioorg Med Chem Lett, 2010. **20**(8): p. 2417-20.

78. Lobo, V., A. Patil, A. Phatak, and N.J.P.r. Chandra, *Free radicals, antioxidants and functional foods: Impact on human health.* 2010. **4**(8): p. 118.
79. Pham-Huy, L.A., H. He, and C.J.I.j.o.b.s.I. Pham-Huy, *Free radicals, antioxidants in disease and health.* 2008. **4**(2): p. 89.
80. Kostova, I. and L.J.C.m.c. Saso, *Advances in Research of Schiff-Base Metal Complexes as Potent Antioxidants.* 2013. **20**(36): p. 4609-4632.
81. Carey, F.A. and R.J. Sundberg, *Advanced organic chemistry: part A: structure and mechanisms*. 2007: Springer Science & Business Media.
82. Ayfan, A.K.H., R.F. Muslim, and N.S. Noori, *Preparation and Characterization of Novel disubstituted 1, 3-Oxazepine-tetra-one from Schiff bases reaction with 3-methylfuran-2, 5-dione and 3-Phenyldihydrofuran-2, 5-dione.* Research Journal of Pharmacy and Technology, 2019. **12**(3).
83. Hossain, M.S., P.K. Roy, C. Zakaria, and M.J.I.J.C.S. Kudrat-E-Zahan, *Selected Schiff base coordination complexes and their microbial application: A review.* 2018. **6**(1): p. 19-31.
84. Hussein, I.A., S.F. Narren, I.M.M. Hasan, A.M.J.J.o.P.S. Saleh, and Research, *Synthesis and biological activities of some new derivatives based on bis (4, 4'-diamino phenoxy) ethane containing Oxazpines, Terazole rings* 2018. **10**(10): p. 2461-2469.
85. Sheheryar and M.U. Shah, *synthesis-characterization-and-antibacterial-activity-two-new-schiff-bases-devired-from-e22aminoethyl-imino-methyl-pheno.pdf.* 2022. **15**(1).
86. Hemalatha, G.M., K. Thirunavukkarasu, and C.R. Kumar, *Isoniazid-Based Schiff's Bases in Bone Cancer Studies Using Mg-63 Cell Lines.* International Journal of Applied Pharmaceutics, 2022: p. 168-174.
87. Choudhary, N. and V. Singh, *Insights about multi-targeting and synergistic neuromodulators in Ayurvedic herbs against epilepsy: integrated computational studies on drug-target and protein-protein interaction networks.* Sci Rep, 2019. **9**(1): p. 10565.
88. Mousa, E.F., I.K.J.I.J.o.M.R. Jassim, and C. Protection, *Synthesis, Characterization, and Study the Biological Activity of Some Schiff's Bases, and 1,3 - Oxazepine Compounds Derived from Sulfamethoxazole Drug.* 2021. **13**(1): p. 43-54.
89. Al-Labban, H.M.Y., *Synthesis, characterization and study of biological activity of some new 1, 2, 3, 4-Tetrazole derivatives.* Research Journal of Pharmacy and Technology, 2017. **10**(10).
90. Abd-Elzaher, M.M., A.A. Labib, H.A. Mousa, S.A. Moustafa, M.M. Ali, A.A.J.b.-s.u.j.o.b. El-Rashedy, and a. sciences, *Synthesis, anticancer activity*

and molecular docking study of Schiff base complexes containing thiazole moiety. 2016. **5**(1): p. 85-96.

91. Desai, V. and R.S.J.I.J. Pharm., *Green synthesis of nicotinic acid hydrazide schiff bases and its biological evaluation.* 2015. **5**: p. 930-935.
92. Mayavel, P., K. Thirumurthy, S. Dineshkumar, and G.J.A.U.M.C.-S. Thirunarayanan, sectio AA–Chemia, *Perchloric acid catalyzed condensation of amine and aldehydes: Synthesis and antibacterial activities of some aryl (E)-imines.* 2014. **69**(1-2).
93. Pandey, A., R. Rajavel, S. Chandraker, and D.J.E.-J.o.C. Dash, *Synthesis of Schiff bases of 2-amino-5-aryl-1, 3, 4-thiadiazole and its analgesic, anti-inflammatory and anti-bacterial activity.* 2012. **9**(4): p. 2524-2531.
94. Khedr, A., M. Gaber, R. Issa, and H. Erten, *Synthesis and spectral studies of 5-[3-(1,2,4-triazolyl-azo]-2,4-dihydroxybenzaldehyde (TA) and its Schiff bases with 1,3-diaminopropane (TAAP) and 1,6-diaminohexane (TAAH). Their analytical application for spectrophotometric microdetermination of cobalt(II). Application in some radiochemical studies.* Dyes and Pigments, 2005. **67**(2): p. 117-126.
95. Adnan, S.J. and K.J.f. Chemistry, *Synthesis, Identification and Study The Biological Activity of Some Tetrazole Derivatives From Imidazole Derivative*. 2017. **2**(2).
96. Ranjith, R.J.J.o.C. and p. Research, *The chemistry and biological significance of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone nucleus* 2016. **8**(5): p. 505-526.
97. Al-Mulla, A.J.D.P.C., *A review: biological importance of heterocyclic compounds.* 2017. **9**(13): p. 141-147.
98. Saini, M.S., A. Kumar, J. Dwivedi, and R.J.I.J.P.S.R. Singh, *A review: biological significances of heterocyclic compounds.* 2013. **4**(3): p. 66-77.
99. Baire, B., R. Gardas, and S.J.G.s.a.f.b.r.h. Gandhi, *Cycloaddition reactions in ionic liquids for the synthesis of biologically relevant heterocycles.* 2021: p. 249-295.
100. Arora, P., V. Arora, H. Lamba, D.J.I.J.o.P.S. Wadhwa, and Research, *Importance of heterocyclic chemistry: a review* 2012. **3**(9): p. 2947.
101. Ibrhem , R.A. and S.F.N. Al.Zobadyi *Synthesis of New β-Lactam, Tetrazole, Thiazolidinone, and Oxazepine Compounds from Schiff Bases and Study of Their Biological Activity*. Journal of Medicinal and Chemical Sciences, 2023. **6**(3).
102. Wei, C.X., M. Bian, and G.H. Gong, *Tetrazolium compounds: synthesis and applications in medicine.* Molecules, 2015. **20**(4): p. 5528-53.

103. Vishwakarma, R., C. Gadipelly, and L.K.J.C. Mannepalli, *Advances in Tetrazole Synthesis–An Overview.* 2022. **7**(29): p. e202200706.
104. Varala, R. and B.H.J.M.D. Babu, *A click chemistry approach to tetrazoles: recent advances.* 2018.
105. Dhayanithi, V., S. Shafi, K. Kumaran, S. Jai, V. Ragavan, K. Goud, S. Kumari, and H. Pati, *Synthesis of selected 5-thio-substituted tetrazole derivatives and evaluation of their antibacterial and antifungal activities.* Journal of the Serbian Chemical Society, 2011. **76**(2): p. 165-175.
106. Mittal, R. and S.K. Awasthi, *Recent Advances in the Synthesis of 5-Substituted 1H-Tetrazoles: A Complete Survey (2013–2018).* Synthesis, 2019. **51**(20): p. 3765-3783.
107. Safapoor, S., M.G. Dekamin, A. Akbari, and M.R. Naimi-Jamal, *Synthesis of (E)-2-(1H-tetrazole-5-yl)-3-phenylacrylenenitrile derivatives catalyzed by new ZnO nanoparticles embedded in a thermally stable magnetic periodic mesoporous organosilica under green conditions.* Sci Rep, 2022. **12**(1): p. 10723.
108. Chandgude, A.L. and A. Dömling, *Convergent Three-Component Tetrazole Synthesis*. 2016, Wiley Online Library.
109. Gorn, M.V., N.P. Gritsan, C.F. Goldsmith, and V.G. Kiselev, *Thermal Stability of Bis-Tetrazole and Bis-Triazole Derivatives with Long Catenated Nitrogen Chains: Quantitative Insights from High-Level Quantum Chemical Calculations.* J Phys Chem A, 2020. **124**(38): p. 7665-7677.
110. Mashhoori, M.S. and R. Sandaroos, *New ecofriendly heterogeneous nano-catalyst for the synthesis of 1-substituted and 5-substituted 1H-tetrazole derivatives.* Sci Rep, 2022. **12**(1): p. 15364.
111. Luo, Y., W. Zheng, X. Wang, and F. Shen, *Nitrification Progress of Nitrogen-Rich Heterocyclic Energetic Compounds: A Review.* Molecules, 2022. **27**(5).
112. Roh, J., K. Vávrová, and A. Hrabálek, *Synthesis and Functionalization of 5-Substituted Tetrazoles.* European Journal of Organic Chemistry, 2012. **2012**(31): p. 6101-6118.
113. Bystrov, D.M., A.N. Pivkina, and L.L. Fershtat, *An Alliance of Polynitrogen Heterocycles: Novel Energetic Tetrazinedioxide-Hydroxytetrazole-Based Materials.* Molecules, 2022. **27**(18).
114. Safapoor, S., M.G. Dekamin, A. Akbari, and M.R. Naimi-Jamal, *Synthesis of (E)-2-(1H-tetrazole-5-yl)-3-phenylacrylenenitrile Derivatives Under Green Conditions Catalyzed by New Thermally Stable Magnetic Periodic Mesoporous Ognosilica Embedded With ZnO Nanoparticles.* 2021.

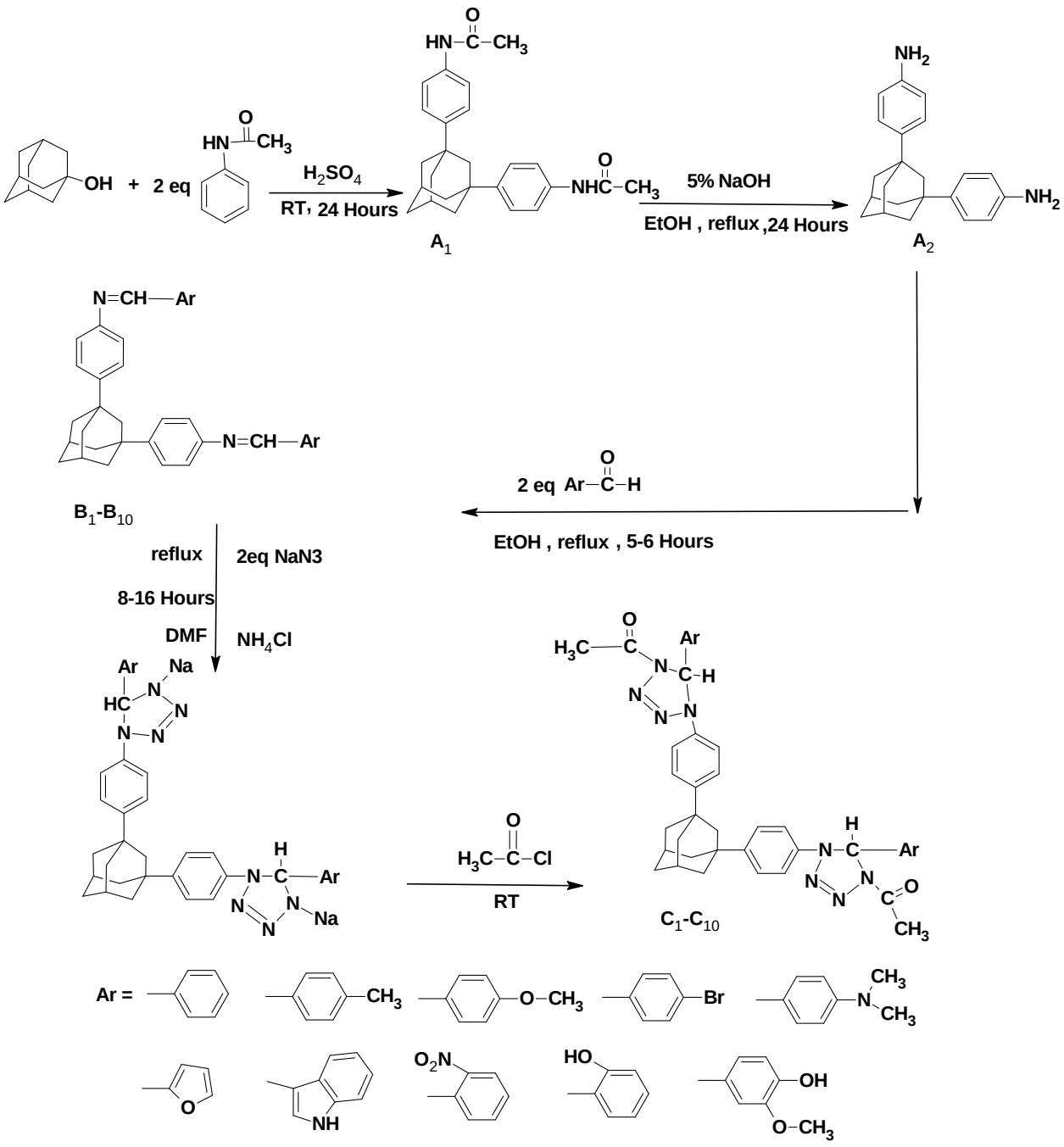
115. Gao, C., L. Chang, Z. Xu, X.F. Yan, C. Ding, F. Zhao, X. Wu, and L.S. Feng, *Recent advances of tetrazole derivatives as potential anti-tubercular and anti-malarial agents.* Eur J Med Chem, 2019. **163**: p. 404-412.
116. Faraj, E.M. and F.H.J.M.T.P. Jumaa, *Preparation, diagnostics and biological evaluation of new Schiff base and tetrazole derivatives.* 2022. **49**: p. 3549-3557.
117. Leyva-Ramos, S. and J. Cardoso-Ortiz, *Recent Developments in the Synthesis of Tetrazoles and their Pharmacological Relevance.* Current Organic Chemistry, 2021. **25**(3): p. 388-403.
118. Zhang, Y., J.C.H. Lee, M.R. Reese, B.P. Boscoe, J.M. Humphrey, and C.J. Helal, *5-Aryltetrazoles from Direct C-H Arylation with Aryl Bromides.* J Org Chem, 2020. **85**(8): p. 5718-5723.
119. Shaabani, S., A. Shaabani, M. Kucerakova, and M. Dusek, *A One-Pot Synthesis of Oxazepine-Quinazolinone bis-Heterocyclic Scaffolds via Isocyanide-Based Three-Component Reactions.* Front Chem, 2019. **7**: p. 623.
120. Bekhit, A.A., O.A. El-Sayed, E. Aboulmagd, and J.Y. Park, *Tetrazolo[1,5-a]quinoline as a potential promising new scaffold for the synthesis of novel anti-inflammatory and antibacterial agents.* Eur J Med Chem, 2004. **39**(3): p. 249-55.
121. Alasadi , Y.K., F.H. Jumaa, A.H. Dalaf, S.M. Shawkat , and M.G. Mukhif, *Synthesis, Characterization, and Molecular Docking of New Tetrazole Derivatives as Promising Anticancer Agents.* Journal of Pharmaceutical Negative Results, 2022. **13**(3).
122. Dhiman, N., K. Kaur, and V. Jaitak, *Tetrazoles as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies.* Bioorg Med Chem, 2020. **28**(15): p. 115599.
123. Bhaskar, V. and P.J.J.O.B.M. Mohite, *Synthesis, characterization and evaluation of anticancer activity of some tetrazole derivatives.* 2010. **2**(4): p. 249-259.
124. Qiang, Y., H. Li, and X. Lan, *Self-assembling anchored film basing on two tetrazole derivatives for application to protect copper in sulfuric acid environment.* Journal of Materials Science & Technology, 2020. **52**: p. 63-71.
125. Vasilyev, A., R. Trifonov, A. Lisakova, D. Ryabukhin, V. Ostrovskii, and I. Boyarskaya, *Hydroarylation of (E)-5-(2-Arylethenyl)-2-methyl-2H-tetrazoles under Superelectrophilic Activation.* Synthesis, 2016. **49**(03): p. 579-586.
126. Ostrovskii, V.A., R.E. Trifonov, and E.A. Popova, *Medicinal chemistry of tetrazoles.* Russian Chemical Bulletin, 2013. **61**(4): p. 768-780.

127. Saleh, M.A., B.M. Abd Razik, K.F.J.N.-N.V. Ali, E.O. Journal, and NVEO, *Synthesis, Characterization, Molecular Docking Study And Biological Activity Of Serotonin Derivatives Containing Tetrazole Moiety*. 2021: p. 2447-2460.
128. Alsahib, S.A. and R.M. Dhedan, *Synthesis and Characterization of some Tetrazole Derivatives and Evaluation of their Biological Activity.* Egyptian Journal of Chemistry, 2021. **0**(0): p. 0-0.
129. Yakambram, B., A. Jaya Shree, L. Srinivasula Reddy, T. Satyanarayana, P. Naveen, and R. Bandichhor, *Urea mediated 5-substituted-1H-tetrazole via [3 + 2] cycloaddition of nitriles and sodium azide.* Tetrahedron Letters, 2018. **59**(5): p. 445-449.
130. Mosa, I.A.A.-Z. and R.M. Rumez, *Synthesis, Characterization and Evaluation The Biological Activity of New Five and Seven Heterocyclic Compounds Derived from L-Ascorbic Acid*. 2019.
131. Alfatlawi, I.O., E.H. Sahab, N.M.J.R.J.o.P. Aljamali, and Technology, *Synthesis of (Tetrazole, Oxazepine, Azo, Imine) Ligands and Studying of Their (Organic Identification, Chromatography, Solubility, Physical, Thermal Analysis, Bio-Study).* 2018. **11**(7): p. 2821-2828.
132. Bhuva, S.V. and M.P. Patel, *A three component one-pot synthesis and biological studies of some new octahydroacridine-1, 8-dione derivatives containing tetrazolo [1, 5-a] quinoline moiety* 2012.
133. Al-Juburi, R.M.J.A.-N.J.o.S., *Synthesis and Characterization of Some Heterocyclic Compounds (Oxazepine, Tetrazole) Derived from Schiff Bases.* 2012. **15**(4): p. 60-67.
134. Umarani, N., K. Ilango, and N.K.J.D.P.C. Singh, *A facile design and efficient synthesis of schiff's bases of tetrazolo [1,5-a] quinoxalines as potential anti-inflammatory and anti-microbial agents.* 2010. **2**(1): p. 159-167.
135. Mohite, P., R. Pandhare, S. Khanage, and V.J.D.J.N.B. Bhaskar, *Anovel Approach for Synthesis of Substituted Tetrazoles*. 2009. **4**(4): p. 803-807.
136. Silverstein, R.M., F.X. webster, and D.J. Kiemle, *Spectrometric Identification of Organic Compounds*, ed. S. Edition. 2005: John Wiley& Sons,Inc.
137. Abbs, S.K. and Z.H. Abood, *Synthesis and studies of biological activity of -1,3oxazepine-4,7-dione derivitives "*, in *Thesis*. 2014, University of Kerbala.
138. Varadaraji, D., S.S. Suban, V.R. Ramasamy, K. Kubendiran, J.S.K. Raguraman, S.K. Nalilu, and H.N.J.O.C. Pati, *Synthesis and evaluation of a series of 1-substituted tetrazole derivatives as antimicrobial agents.* 2010. **3**(3).

الخلاصة

تم تصنيع مشتقات قواعد شيف جديدة تحتوي على هيكل الادمانتان في تركيبها بواسطة استخدام الادمانتانول كمادة اولية. الادمانتانول يخضع الى تفاعلين : الاول تفاعل الادمانتانول مع الاستنالايد بوسط حامضي لتحضير ملح الادمانتان للاستنالايد التفاعل الثاني ملح الادمانتان يخضع الى تفاعل ازالة الحماية بوسط قاعدي لتحضير الامين المشتق من الادمانتان. ومن ثم يتفاعل الامين المحضر مع عدد من الالديهايدات الاروماتية لتحضير مركبات تحتوي على مجموعتين ايمين وهيكل الادمانتان بنفس الجزيئة كما في المخطط ادناه.

كذلك تخليق مركبات حلقية غير متجانسة تحتوي على حلقة التترازول بواسطة تفاعل مشتقات شيف المذكورة اعلاه مع ازيد الصوديوم كخطوة اولية, بعد ذلك الناتج المتكون يعامل مع الاسيتايل كلورايد لتحضير مركبات مشتقات التترازول كخطوة ثانية كما في المخطط ادناه. كل المركبات المحضرة يتم تشخيصها بواسطة جهاز قياس درجة الانصهار, مطيافية الاشعة تحت الحمراء ,مقياس طيف الكتلة, مطيافية الرنين النووي المغناطيسي .وتقدير فعالية مشتقات قواعد شيف الجديدة كمضاد للأكسدة, الى جانب تقدير الفعالية ضد الميكروبات لبعض من المركبات المحضرة, حيث لوحظ ان مشتقات قواعد شيف تمتلك فعالية جيدة ضد تثبيط الجذر الحر (DPPH), وايضا بعض المركبات المحضرة امتلكت فعالية جيدة ضد فطر الكانديدة الى جانب فعالية ضعيفة الى متوسطة ضد البكتريا سالبة الغرام *Escherichia coli* وموجبة الغرام*staphylococcus aureus* .



Scheme(I):Synthesis route for all synthesized compounds(B1-B10) and(C1-C10)

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة بابل/ كلية العلوم للبنات

قسم الكيمياء

تحضير وتشخيص لمشتقات التترازول الثنائية بالاعتماد على مشتقات الادمانتان لقواعد شيف

رسالة

مقدمة الى مجلس كلية العلوم للبنات-جامعة بابل

من متطلبات نيل شهادة الماجستير في العلوم / كيمياء

من قبل

أنسام عبد الكاظم كميت العجيلي

بكالوريوس علوم كيمياء . كلية العلوم

جامعة بابل(1999)

إشراف

أ.د. صادق عبد الحسين كريم

1444 هـ 2023 م