Ministry of Higher Education

and Scientific Research

University of Diyala

College of Science

Department of Chemistry

Synthesis and Biological Activity of Some Heterocyclic from Hydrazone Derivatives

A Thesis Submitted to the

Council of College of Science, University of Diyala in Partial Fulfillment of the Requirements for the degree of Master of Science in Chemistry

by

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B.Sc. Chemistry Science/ University of Diyala 2015

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2022 A.D **1443 A.H**

بسم الله الرحمن الرحيم

{يَسْأَلُونَكَ عَنِ الْأَنفَالِ ۖ قُلِ الْأَنفَالُ لِلَّهِ وَالرَّسُولِ ۖ فَاتَّقُوا اللَّهَ وَأَصْلِحُوا ذَاتَ بَيْنِكُمْ ۖ وَأَطِيعُوا اللَّهَ وَرَسُولَهُ إِن كُنتُم مُّؤْمِنِين}

صدق الله العظيم

(سورة الانفال / الأية1)

Dedication

Dedicated To you . . .

To the one who makes me proud to bear his name, my dear father, to the one who possesses heaven under her feet, my lovely mother, to my brothers and sister. . .

To my grandmother, aunts and uncles please do not forget to help me during my studies . . .

To all loved ones and friends. . . .

to best friend (Mariyam Mussa) .

ANFAL

Acknowledgement

I am grateful to my parents for everything they have given me ……there are no words that fulfill your right. I would like to be grateful to all my family for their support and assistance throughout the period of writing the thesis work and study.

Thanks and appreciation for the efforts made by my supervisor Dr. Luma Salman Abd for the comments and directions she provided for the completion of this project, you have my deepest thanks, appreciation and respect, Dr. Luma.

Thank you, our departed role model from the life that remains in our minds you will not be our doctor in science but our doctor is in high morals, humility, and the beautiful manner in your dealing with us(May God have mercy on you, our honorable doctor Dr. Fadhil Lafta Faraj)

Thank you……

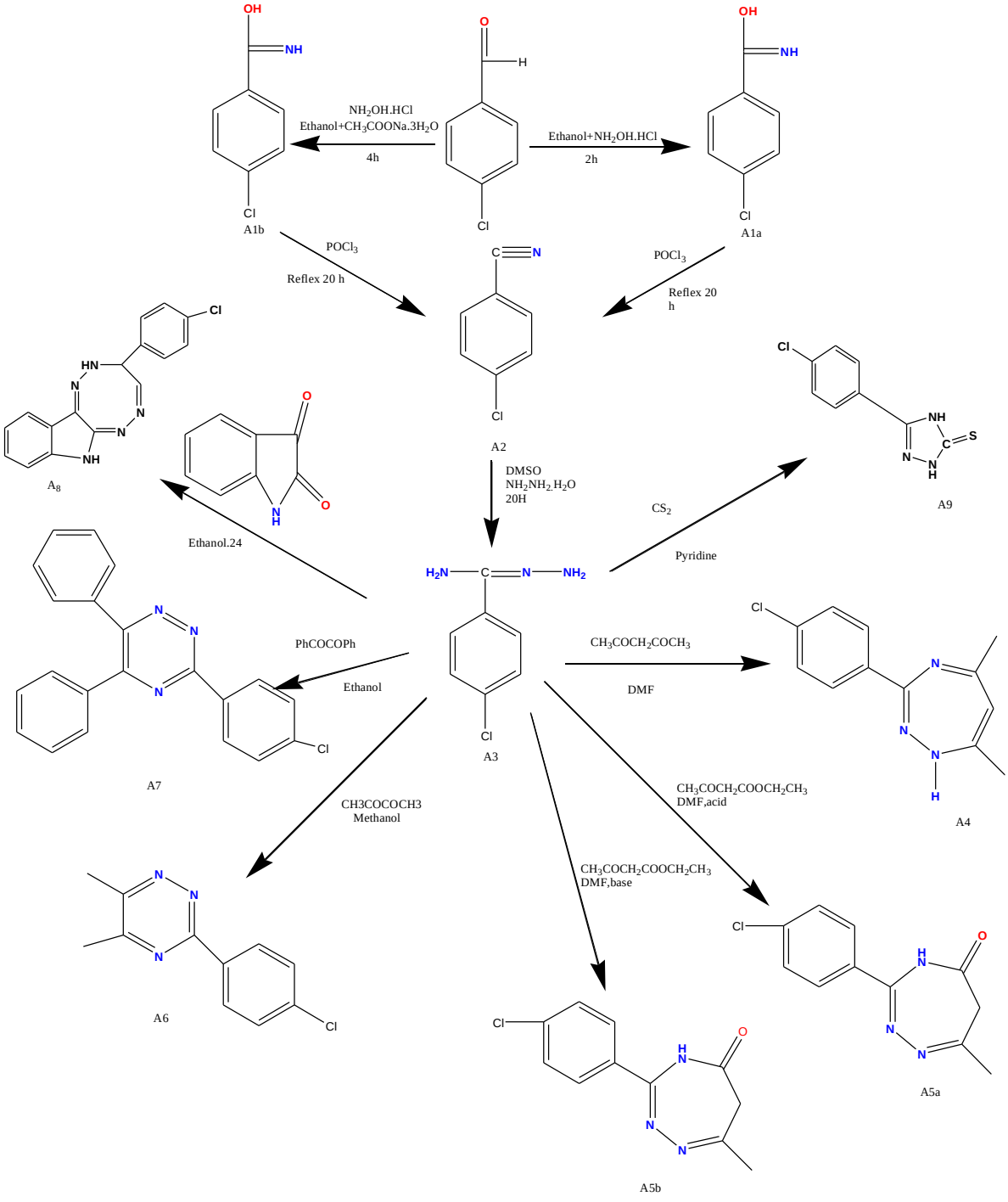
Abstract

The work in this thesis describes approaches towards synthesis of substituted hydrazone amide as intermediates in the synthesis of hydrazone derivitaes.

The initial approach to the synthesis of 4-chlorobenzohydrazon amide. focused on the synthesis of oxime on suitable scale followed synthesis of 4-chlorobenzonitrile that would enable the synthesis of the 4-chlorobenzohydrazon amide.

- The first step started from reaction of 4-chlorobenzaldehyde with hydroxylamine hydrochloride and sodium acetate tri-hydrate in ethanol to form oxime
- Synthesis of 4-chlorobenzo nitrile was accomplished in one step by reaction of oxime with phosphoryl chloride $POCl_3$ as solvent.
- The required 4-chlorobenzo hydrazone amide was obtained after subjected 4-chlorobenzo nitrile to reaction with hydrazine hydrate 88% in Dimethyl sulfoxide(DMSO) .
- Synthesis hydrazone derivatives were achieved through the reaction of 4-chlorobenzohydrazon amide with different di-ketone compounds and CS_2using different solvent .

The chemical structures of all new compounds have been characterized and confirmed by spectroscopic techniques such as, (FT- IR, ^{1}H-NMR, ^{13}C-NMR and APT ^{13}C-NMR). Their purity was tested by thin layer chromatography (TLC). Two new synthesized compounds **(A_4 and A_7)** was evaluated for their cytotoxic activity against *bacteria* and *fungi.*



The general scheme shown synthesized compounds(A_1-A_9)

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List of scheme

List of Abberviations

°C	Degree Celsius
Eπ	Ione pair of orbital P electrons
EAS	Electrophilic Aromatic Substitution
DFT	Discrete Fourier Transform
Kcal.mol	Kilo calories.Mole
A	*Alfa*
ß	*Beta*
DMF	Dimethyle formamide
CNS	Central nervous system
TLC	Thin Layer Chromatography
FTIR	Fourier-Transform Infrared
^{1}H – NMR	Proton Nuclear Magnetic Resonance Spectrometer
^{13}C – NMR	Carbon Nuclear Magnetic Resonance Spectrometer
APT ^{13}C NMR	Attached Proton Test ^{13}C- Nuclear Magnetic Resonance Spectrometer
ML	Milliter
Mmol	Millimole
MLT	Medical Labtory Thchnicim
DMMS	Medical landmarks
IC50	Value represents the minimal concentration of adrug the is required for 50y inhibition in vitro this value is expressed as a molar concentrate
h, hrs	Hour, Hours

G	Gram
M.p.	Melting point
Cm	Centimeter
MHz	Megahertz
DMSO	Dimethyl Sulfoxide
Δ	Chemical shift
Ppm	Part per million
S	Singlet
D	Doublet
T	Triplet
M	Multiplet
TMS	Tetramethylsilane
Ar	Aromatic ring
Rf	Retetion factor
E.coli	Escherichia coli
S.aureus	Staphylococcus aureus

Chapter One

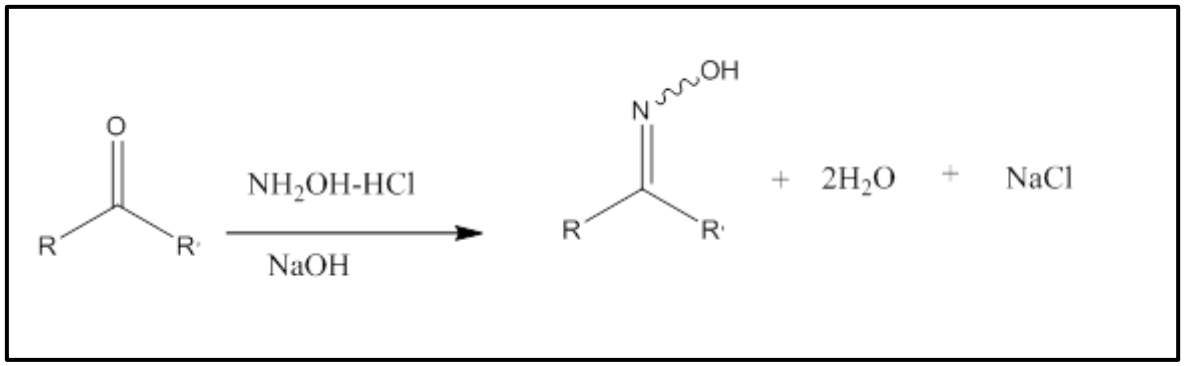
(Perface & Literature review)

1.1.Perface:

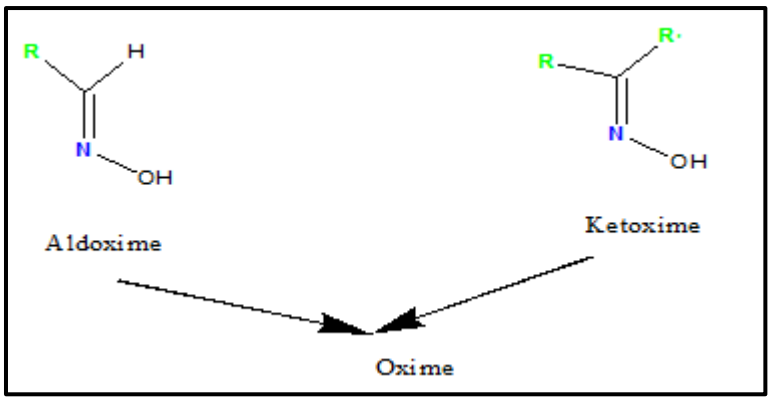
Oximes have been considered an important focus in many chemical and pharmaceutical research, one of whose alternatives contains an amino group and characterized by its simple structure, as it has proven biological and clinical importance.

For example entered into the preparation of many important medicines, including heart disease medicines as well as anti-inflammatory medicines.

Oxime and its derivatives have been used in the treatment of many viruses, including viruses that infect agricultural crops, plant growth regulation herbicide and antimicrobial, including derivatives that contain thiazoles in their composition, oxime can be classified into two types(Aldoxime and Ketoxime), according to the substance in the preparation of oxime, whether it is aldehyde or ketone[1-3]. Scheme (1-1)(Fig1-1).



Scheme(1.1): Scheme Showing the Synthesis of oxime

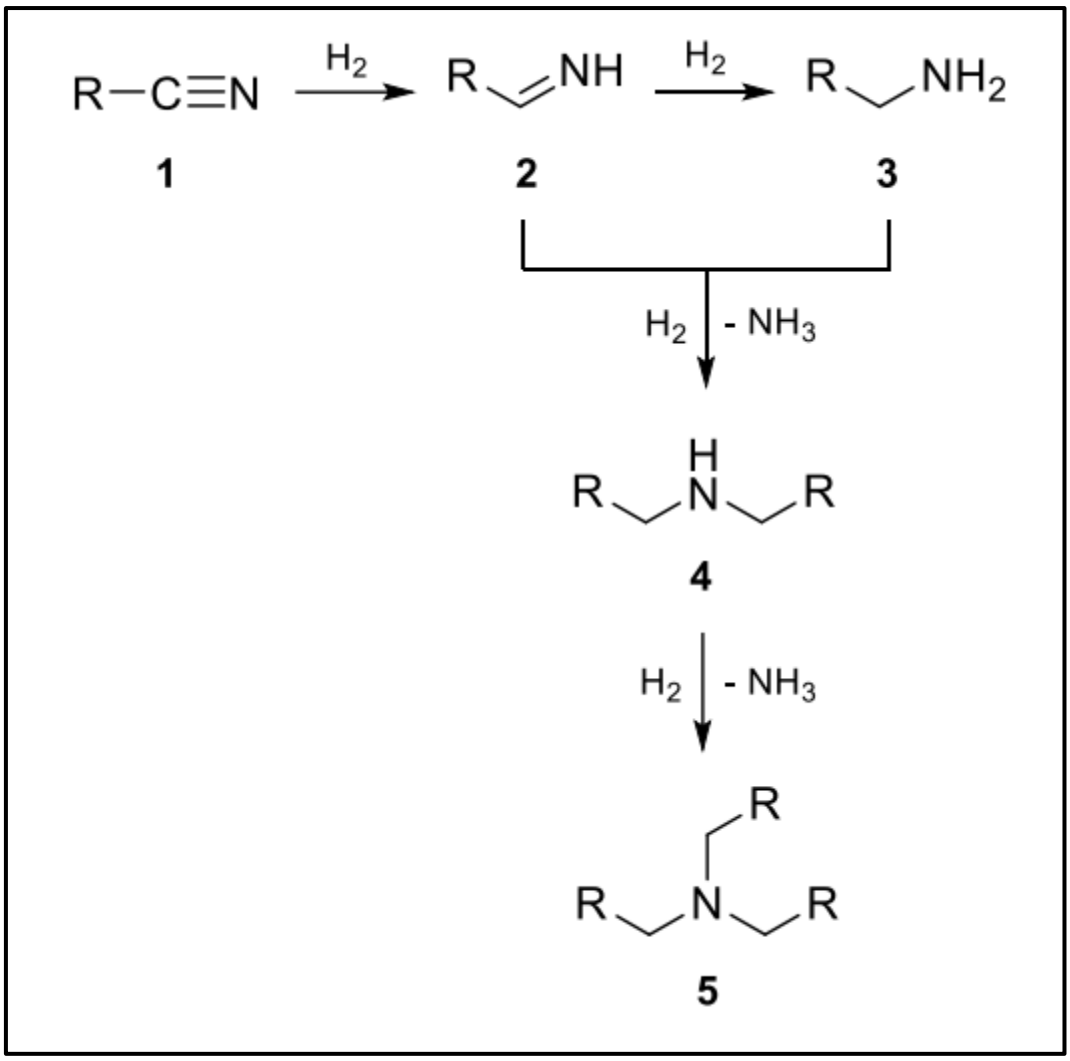


Figure(1-1): showing kinds of oxime from aldehyde and ketone

1.1.1.Nitrile

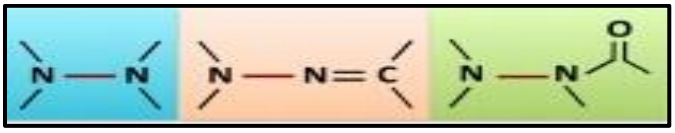
Nitriles are kind of organic compounds that has cyanide C≡N group[(4)]. It is important functional groups in organic synthesis due to their unique reactivity and activating ability[(5)].

For in organic chemistry they are extremely important because they are the building blocks of the life sciences industries for medicines and agrochemicals, preparation of amines by nitrile hydrogenation is a valuable method[(6-7)]. This process is often done in the industrial field with catalysts such as Rani nickel or cobalt[(8)].A mixture of primary, secondary and tertiary amines is formed at the nitrile hydrogenation, because of the highly reaction of the amino medium[(9)] .



Scheme(1.2): pathways to the hydrogenation of nitriles.

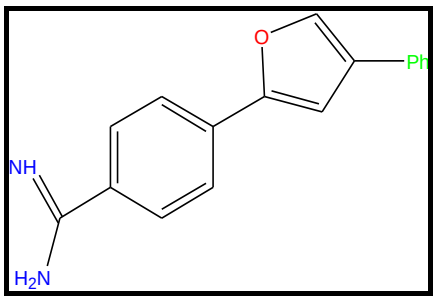
1.1.2-Hydrazine-Hydrazone derivatives



Hydrazine Hydrazon Hydrazide

Hydrazides and hydrazones are available in a significant number of the bioactive hetrocyclic compounds with a wide range of applications due to their organic and clinical properties .Because of their properties ,these compounds has received much attention from synthetic chemists in the past few years

During the past years, compounds with a variety of hydrazide derivatives were synthesized and evaluated for their various biological activities such as anticancer, anti-HIV, anthelntic antimycobacterial and antimalarial activitives[10-12] . Benzamidine derivatives have been found as competitive inhibitors of trypsin, plasmin and thrombin proteolytic enzymes[13]. ***Alnabulsi et al*** have demonstrated in their lab that non-symmetrical furanamidine (Figure1-2) was found as a novel compound to inhibit the enzymatic activity of NQO2(N-Ribosyldihydoriecion amide:Qunone) with both anti-cancer and anti-malarial activity[14].

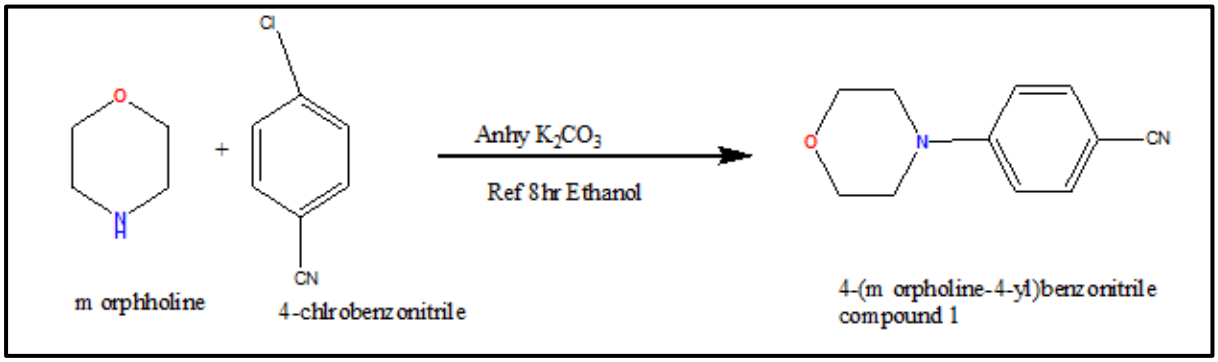


Figure(1.2) : showing structure novel compound to inhibit the enzymatic activity of NQO2

1.2 . Literature review

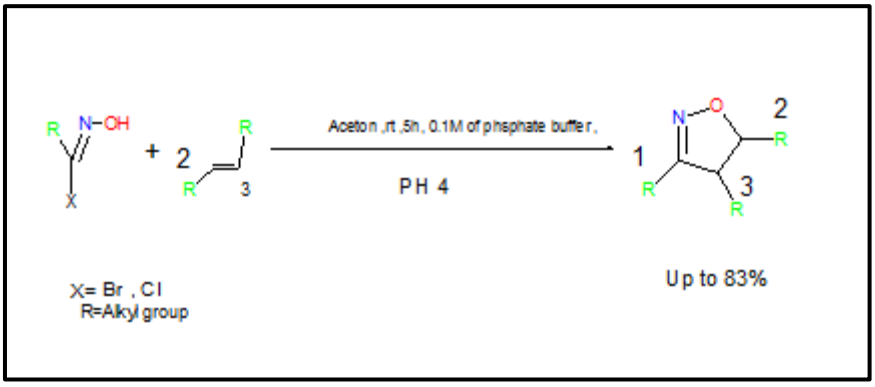
Wang .L.S et al in (2015): studied the preparation a number of new pyrazole oxime derivatives with an oxazole ring have been developed and produced., the title compounds were structurally confirmed by ^{1}HNMR-^{13}CNMR Preliminary bioassay results, as well as spectra and elemental studies, revealed that some of the title compounds had promise fungicidal action insecticidal and acarie fungicidal activity against cucumber pesudoperonospora cubensis has insecticidal efficacy against Aphis craccivora and Nilaparvata lugens in addition to other insects [15].

Somashekhar .M et al in (2013): prepare compound 4-(Morpholin-4-yl)benzo nitrile through interaction morpholine with 4-chloro benzo nitrile[16] .



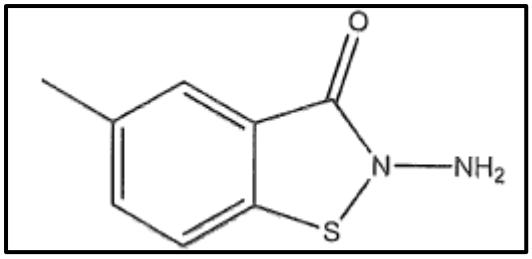
Scheme (1.3): showing prepare 4-(morpholin-4-yl)benzo nitrile.

Liao and et al in published a review highlighting the main achievements since 2010 in the development of methodologies for the synthesis of isoxazolines. According to the reaction mechanism, oxime-participated synthesis of isoxazolines is mainly classified into four reaction type[17].



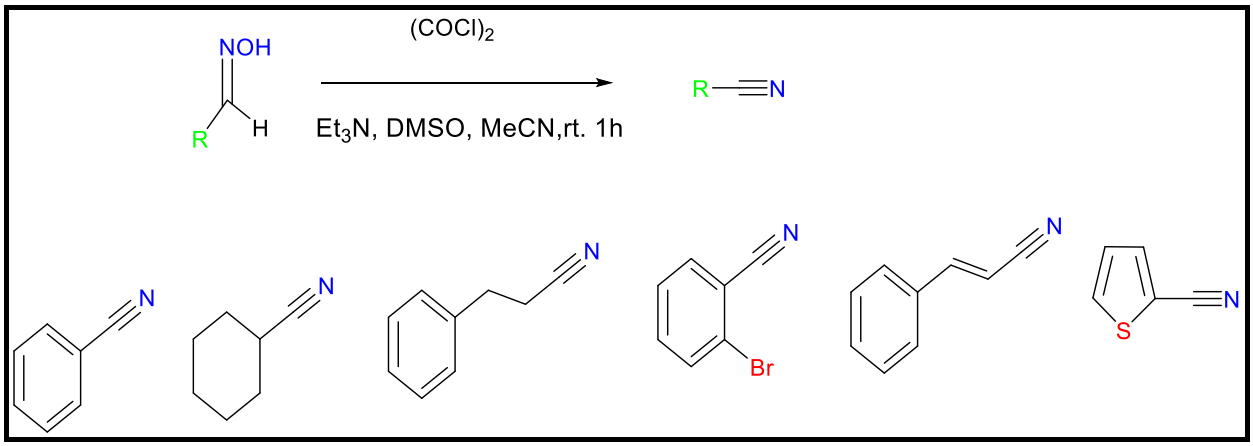
Scheme(1-4): [3+2] cycloaddition of nitrile oxides to construct Isoxazolines

Narasimhan .B etal (2010): **:**synthesized heterocyclic hydrazone derivatives, the most important of which is 2-amino-5-methyl-benzo{d}iso thiazol-3-one[18] Figure(1-3).



Figure(1-3): **Figure showing structure of 2-amino-5-methyl-benzo{d}iso thiazol-3-one**

Ding and et al in (2018) reported Using oxalyl chloride and a catalytic quantity of dimethyl sulfoxide in the presence of Et_3N, nitriles can be made from primary amides or aldoximes. At room temperature, the reactions were complete within 1 hour. A wide range of cyano compounds, including aromatic, heteroaromatic, cyclic, and acyclic aliphatic species, were produced in good to exceptional yields [(19)].

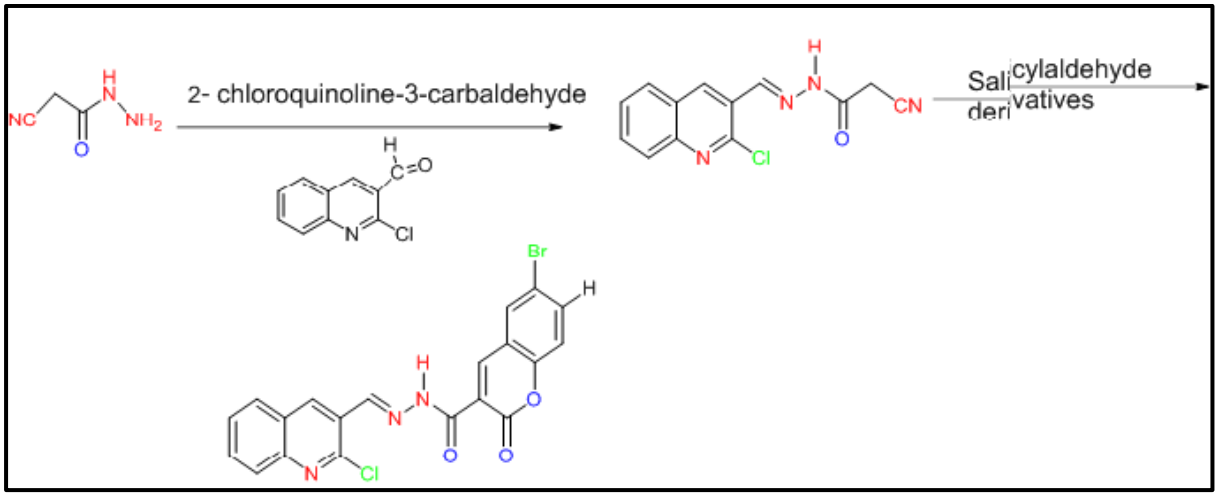


Scheme(1-5): preparation of nitriles

In 2018 new series of coumarin compounds with hydrazide-hydrazone and amide substitutes has been produced. ***by Nasr and et al*** and evaluation for their antitumor *in vitro* was also investigate.

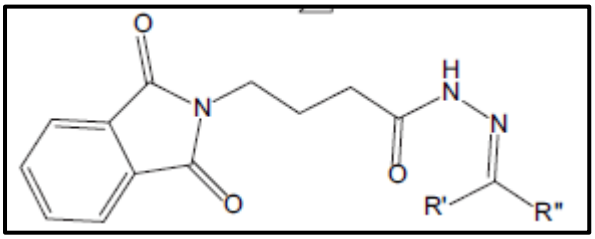
Among these compounds The mechanism of action of bromo coumarin hydrazide hydrazone derivative was explored after it demonstrated outstanding effectiveness against resistant pancreatic cancer (Panc-1), hepatocellular

carcinoma (HepG2), and leukemia (CCRF) cell lines. They also demonstrated that compound might act as a chemical carrier for 99mTc and 99mTc in vivo [(20)].



Scheme(1-6):compounds Bromo coumarin hydrazide hydrazone

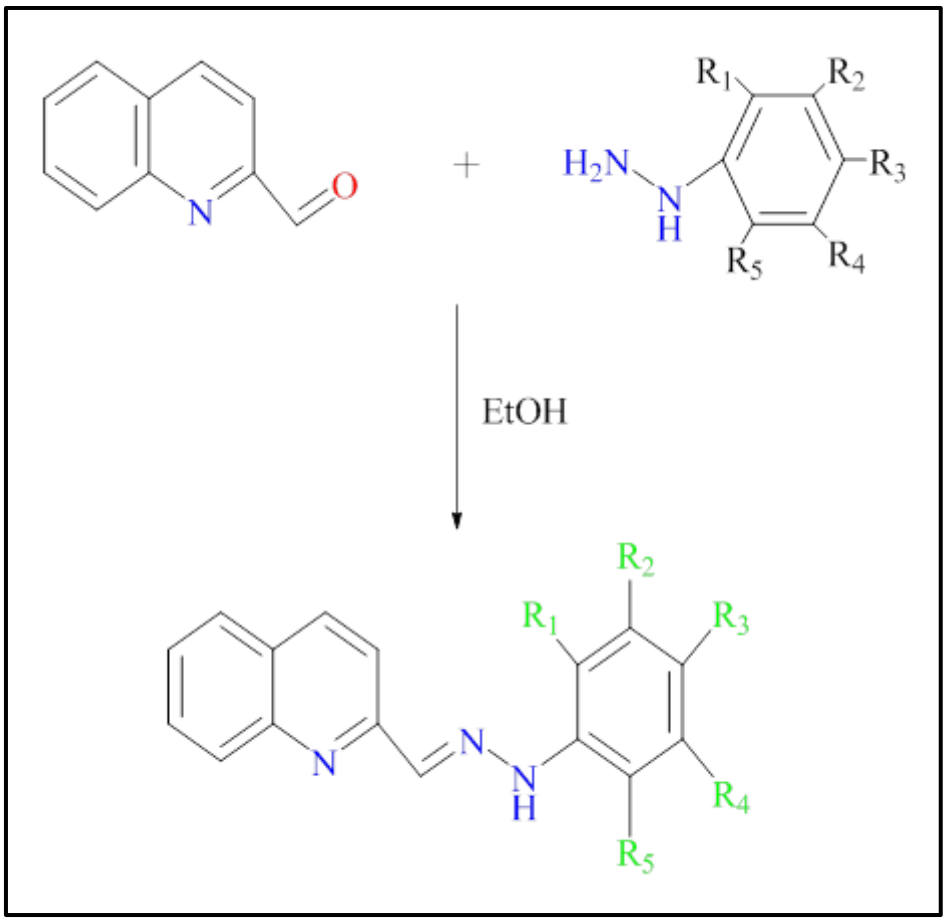
Ragavendran .V.J et al (2007):synthesized N-aryl or alkyl idene-4-(1,3-dioxo -1,3 di hydro-2H-iso-indol-2-yl)butanoyl hydrazone from reaction of 4-amino butyric acid with hydrazine hydrate[(21)].Figure(1-4)



Figure(1-4) showing structure of N-aryl or alkyl idene-4-(1,3-dioxo -1,3 di hydro-2H-iso-indol-2-yl) butanoyl hydrazone.

Puskullu M. O et al in(2016) was reported a series of new quinoline-2-carbaldehyde hydrazones using simple reaction strategies that was developed as an isotope biosynthesis for MLT(Medical Labtory Thchnicim). Targeted

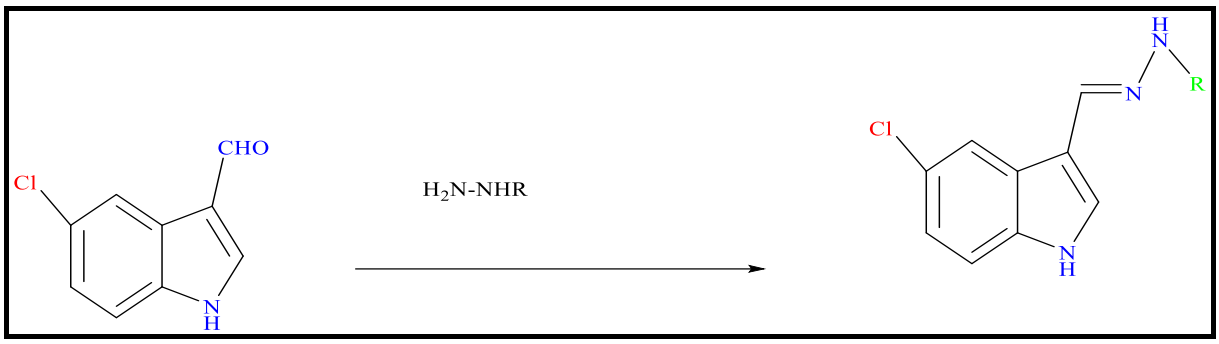
hydrazones derived from quinoline-2-carboxaldehyde and suitable hydrazine derivatives were heated in the presence of EtOH and the new compounds was characterized using IR, ^{1}H-NMR ,^{13}C-NMR and elemental analyses[(22)].



Scheme (1.7): Synthesis of quinoline-2- carbaldehyde hydrazones

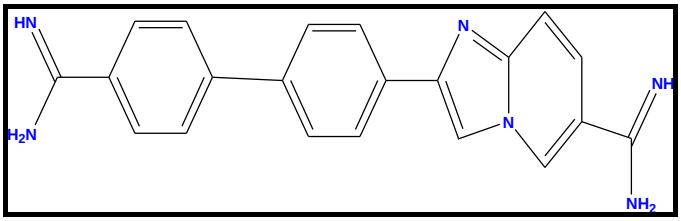
Ayse D. Yılmaz et al in (2012) was reported melatonin analogue indole hydrazide / hydrazone derivatives of compounds. The antioxidant activity was examined in vitro against MLT (Medical Labtory Thchnicim) and BHT(rancid substance).All the compounds were characterized using ^{1}H and ^{13}C-NMR, Mass, FT-IR spectra, and elemental analyses. At 1 m concentration, the majority of the substances had a strong inhibitory effect on the superoxide radical scavenging experiment. (79-95%).Almost all tested compounds

possessed a robust cleaning activity against DPPH(rickets) radical scavenging activity at values of {IC_{50}} {(2 to 60 µm)} [23]



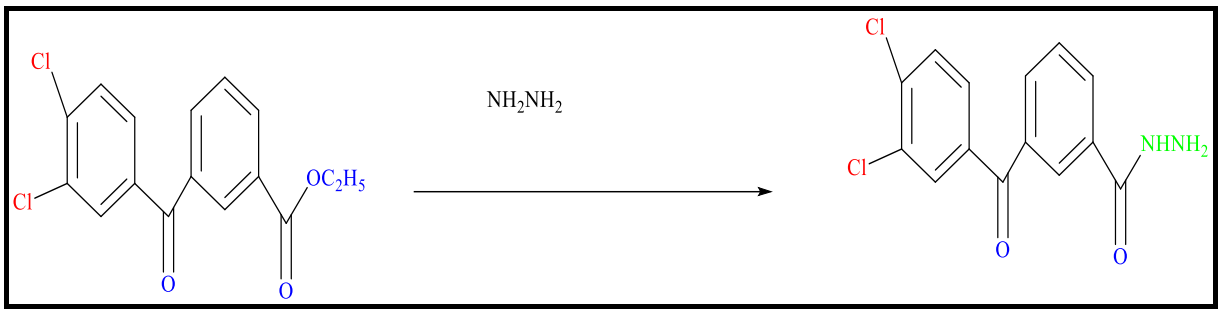
Scheme (1.8): Synthesised 5-chloro indole derivatives.

Soeiro et al in (2013): reported a review including new amidines and their analogues compounds as notable agents against intracellular parasites that cusses a wide range of infectious. Extremely active imidazo[1,2-a]pyridines compound is one of these compounds that prepared through three steps via a diamidoxime [24] .Figure(1.5) .



Figure(1.5) : showing structure of imidazo derivatives.

Bushra P. and Arvind K. (2020) synthesized novel hydrazone derivatives, starting from 2-(3,4-Dichloro-benzoyl)-benzoic acid and converting to 2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester, then to 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide with substituted aromatic substituents ketones [25]



Scheme(1.9): Synthesis of 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide.

1.3 Aim of this project

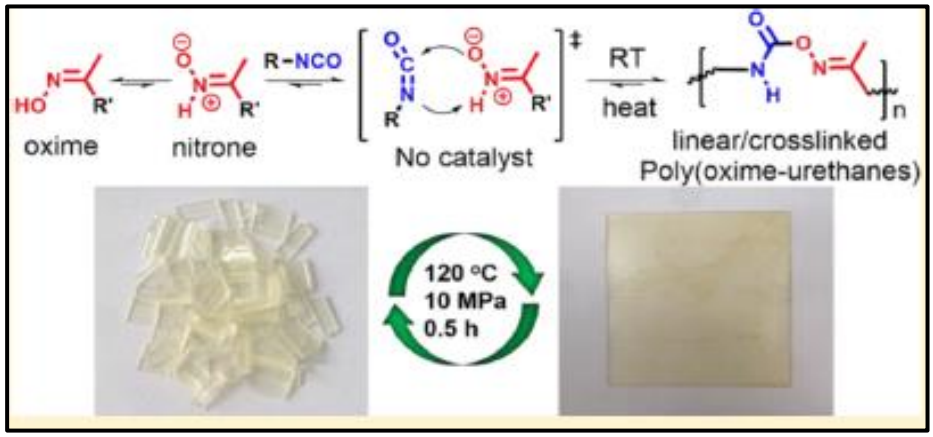
1. Synthesis a series of new Hydrazone derivatives.
2. Identification the chemical structures of the synthesizd compounds by various spectroscopic techniques such as Nuclear Magnetic Resonance Spectroscopy ^{1}H-NMR, APT ^{13}C-NMR and Fourier Transform infrared Spectroscopy (FT-IR).
3. Evaluation the biological activity of some newly synthesized compounds against bacteria and fungi

Chapter Two

(Theoretical Part)

2.1.Oxime

Oxime was discovered in the 1880s, where oxime compounds received wide attention due to the importance of the covalent bond in it (NH-OH) and its importance. This bond entered into the manufacture of polymers, including poly oxime[(26)] Figure(2.1). and also in optical imaging by integrating its bonds within oxime estar[(27)] .



Figure(2.1): Figure showing the synthesis of poly oxime.

The importance of oxime comes in biology and its vital activity is proven by the presence of the neutral acid group-OH- and slightly basic –N-atoms and its importance as inhibitors of enzymes, biosynthesis media, many treatments including chelating as drugs[(28)]and inhibition of cancer cells[(29)].

Hydroxy amino(oxime) is an important intermediate acid for the synthesis of many oxides, including N-oxide and Pyrazine and it was identified from the most important oxides that were considered as components of various peptide antibiotics[(30)].

In view of the importance of the oxime compounds in organic chemistry, many synthetic chemists have been concerned with facilitating the synthesis of oxime, unless the method of interaction of carbonyl(aldehydes or ketones)with hydroxyl ammonium hydrochloride is one of the most important methods for preparing oxime[(31,32)].

The oxime was previously created through the reduction of RNO_2 to amines with iron carbonyl[33], or through the (ammoximation reaction), which includes the ketone conversion reaction to the corresponding oxime.

One of the most important conditions for this is the reaction of the presence of ammonia at a concentration of 1%, where the ketone reacts with hydrogen peroxide and ammonia in the presence of a crystalline titonosiliate as a catalyst for the reaction[34].

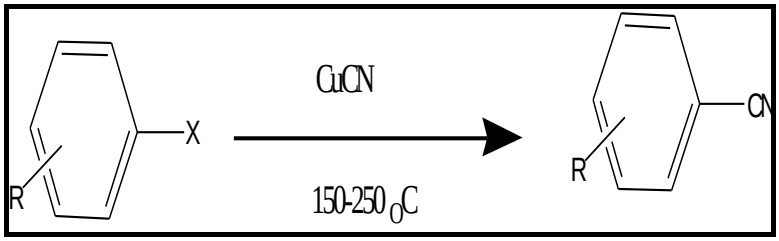
2.2.Nitriles

Nitriles are type of organic compounds that has cyanide group[35]that attracts the importance of this group in the effective organic composition[36].Nitriles are found in the synthesis of light emitting diodes[37].

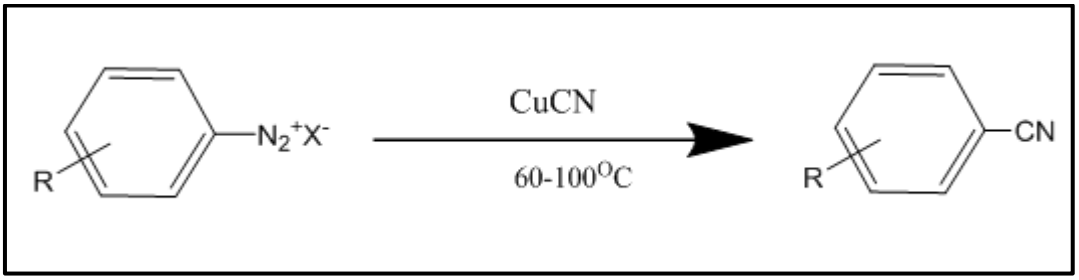
The importance of nitriles in organic chemistry comes industrially through it is hydrogenation into amines ,there are several catalyst factors, such as Rani nickel or cobalt. A mixture of primary, secondary and tertiary amines is formed at the nitrile hydrogenation, because of the highly reaction of the amino medium[38-41].

Nitriles are industrially established by the Rosenmund-von Braun reaction using CuCN as stoichiometric reactions and Sandmayer reaction, and also metal-catalyzed cyanation reactions of aryl halides or aryl triflates using toxic cyanide reagents such as NaCN , KCN , CuCN , $Zn(CN)_2$ and Me_3SiCN[42,43].

a- the Rosenmund-von Braun reaction:



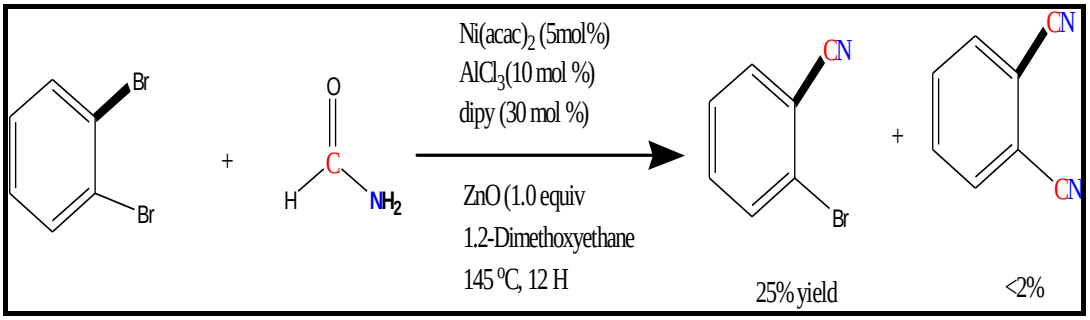
b- Sandmayer reaction:



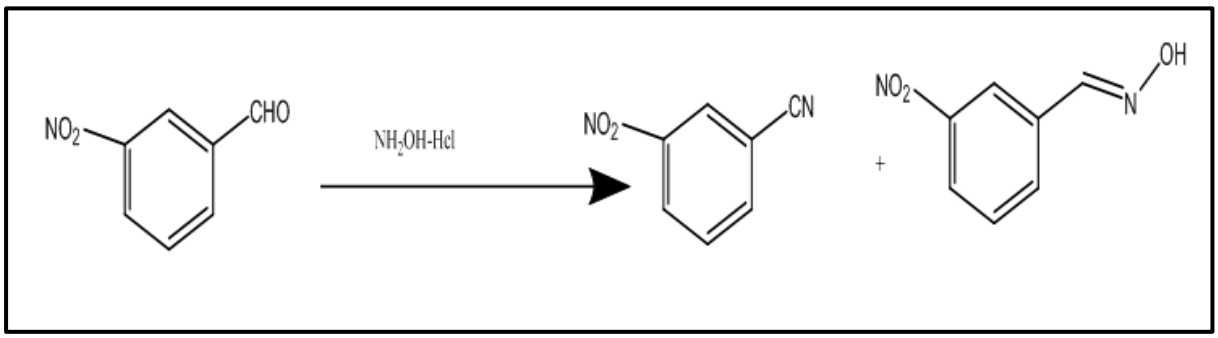
2.3.Preparation of nitriles

Many methods have been developed to produce nitriles such as aldoximes synthetic strategies include halide-CN exchange. or dehydration of aldoxime , oxidation of amines and amides[(44)].

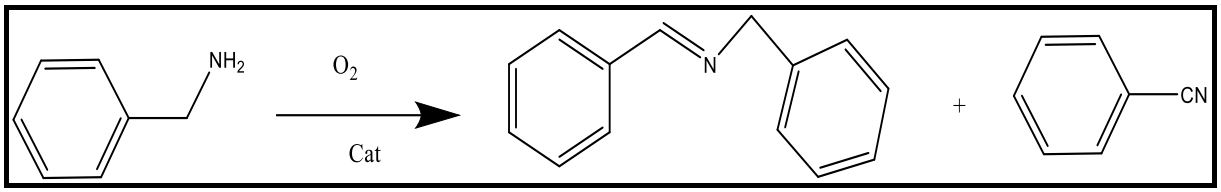
2.3.1-Halide-CN exchange[(45)].



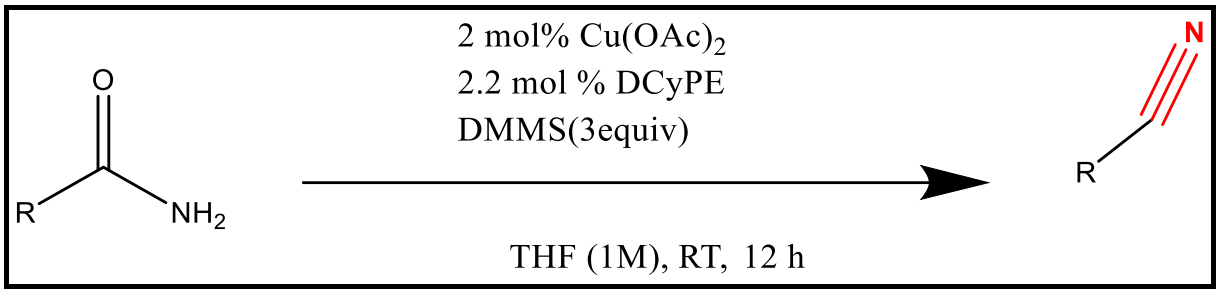
2.3.2-Dehydration of aldoxime[(46)].



2.3.3-Oxidation of amines[47].

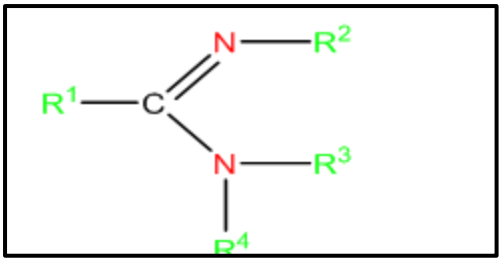


2.3.4-Oxidation of amides[48].



2.4.Hydrazone and Hydrazone derivatives

Hydrazone and hydrazone derivatives play significant position in synthetic and medicinal chemistry. Hydrazone moiety constitute an "azomethine" group which may be derivatives of aldehydes and ketones by replacement of oxygen atom with the $=NNH_2$ group. Hydrazones also act as intermediate for development of novel drugs [49,50] (Fig2.2), The C=N double bond in hydrazones are important compounds in drug design as they act as ligands for metal complexes, organocatalysis and synthesis of organic compounds[51, 52]. The C=N bond of hydrazone and terminal nitrogen atom containing a lone pair of electron is responsible for the physical and chemical properties. The C-atom in hydrazone has both electrophilic and nucleophilic character and both the N-atoms are nucleophilic although the amino type nitrogen is more reactive[53, 5 4]. Because of these properties hydrazones and its derivatives are widely used in organic synthesis [55,56]. (Fig2.3) R, R_1, R_2, R_3represent hydrogen, alkyl or aryl radicals and their substitution products.



Figure(2.2):The structure of an amidine derivatives.

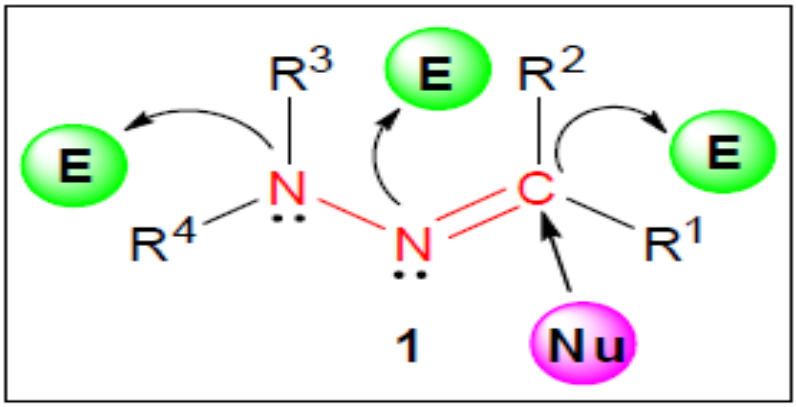
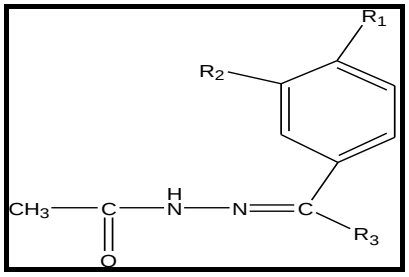
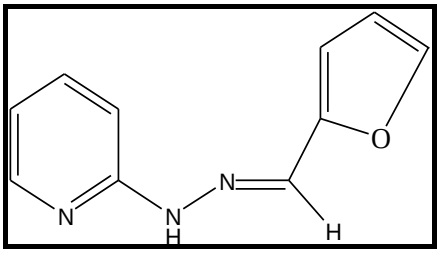


Figure (2.3) :Classifacation of active centers.

Furthermore hydrazone and it is analogs possess wide range of biological activites [57,58],such as anti-tumor[59, 60],hypoallergenic and hypotensive[61],anti-inflammatory[62],anti-convulsant,anti-malarial[63],anti-bacterial[64] and anti-fungal[65], the derivative (Acetyl Hydrazone) was consider an Hydrazone was considered an effective anti-inflammatory[66] (Fig2.4). While the derivaties of hydrazone that has proven effective as an anti-gonist according to spectroscopy HNMR is the derivative (2-formyl furyl)Pyridyl hydrazone[67]. (Fig2.5)



Figure(2.4):The chemical structure of acetyl hydrazine.



Figure(2.5):The chemical structure of 2-(2-formyl furyl)pyrdiyl hydrazone.

2.4.1.Properties of hydrazone derivatives.

Hydrazone is soluble in water and organic solvent, its aqueous solutions are not emissive under ultraviolet light[(68)]. Among the most important organic solvents that have been effective in dissolving hydrazone are $CuCl_2(DMSO)_2$ and DMF/MeOH[(69)].

2.5.Di ketone compound

Di ketones are organic compounds that have strong mineral properties and are non-toxic and chemically stable[(70)]These compounds have biological activity against cancerous cells, including carcinogenic liver cells[(71)],as well as infected lung cells[(72)]and carcinogenic skin cells[(73)].

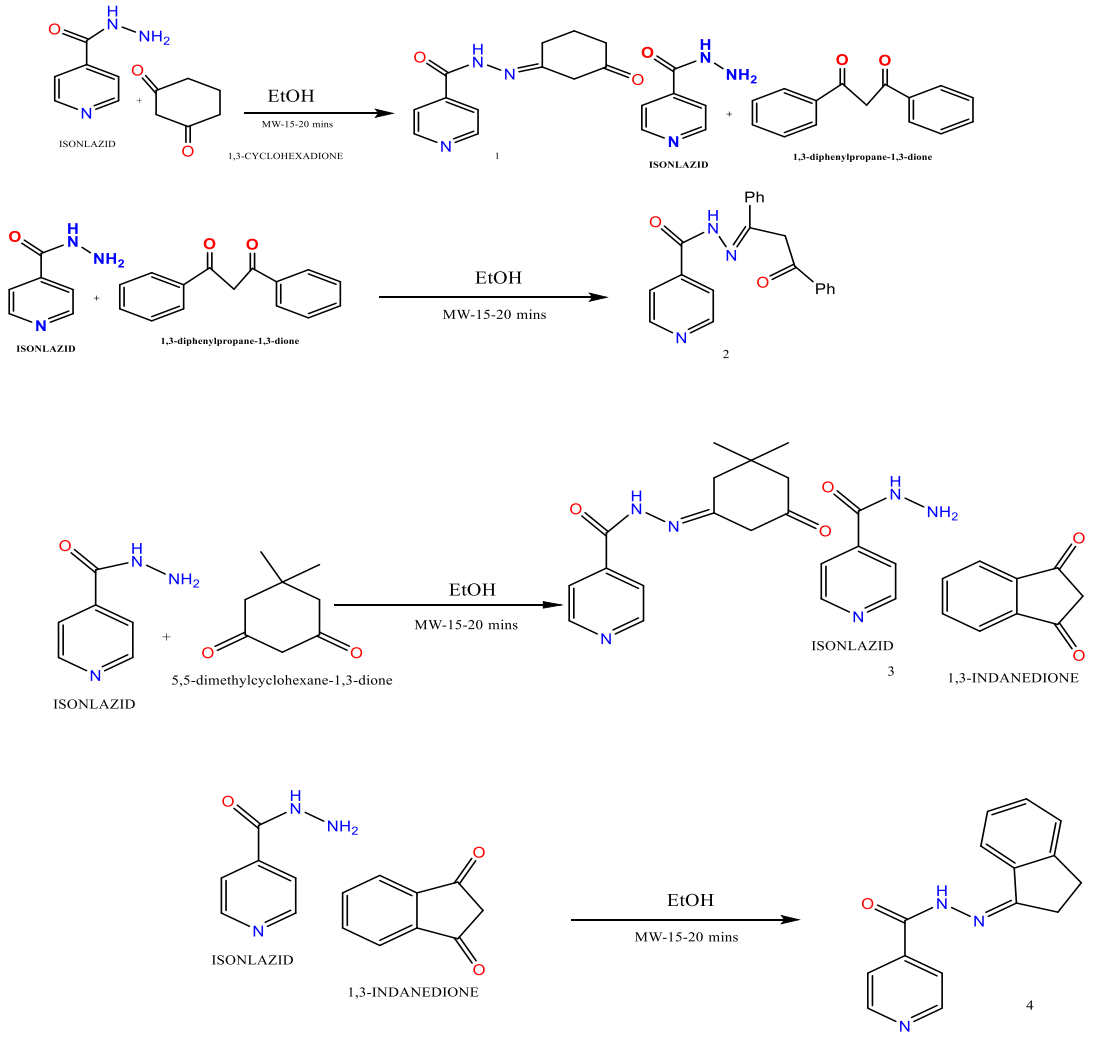
It was also used in the preparation of many primary drugs and the treatment of many diseases, including arthritis and arteriosclerosis[(74)].

On the other hand, it proved its importance in coordination chemistry through its association with groups that have the ability to dissolve in water. Through this property, I was able to prepare hydrophilic ligand that consider this type of ligand as a common solvent in biological processes[(75)].

Di ketones are important in producing energy for many animals and can replace glucose in the brains of these animals[(76)],as well as its importance in the synthesis of biologically active amines of high purity, which were used as biologically important factors[(77)].

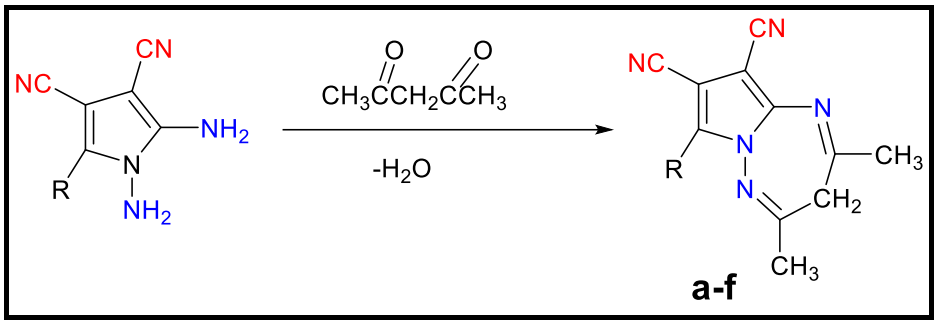
Among the most important reactions experienced by this type of compounds are the aldol reactions to form an enolate as well as the reduction reactions using different boron complexes through which the reduction and fluorination reactions take place [78-80].

In 2020 Ameen and et al published a series of β-diketone hydrazones that synthesized via condensation of isoniazid with series of β-diketone. The structures of the Schiff bases are established by elemental and spectroscopic techniques. The prepared compounds were screened for antibacterial and antioxidant potential by DPPH free-radical scavenging activity and Ferric reducing antioxidant power (FRAP) assays, and showed good radical scavenging activity[81]. Schem (2-1).



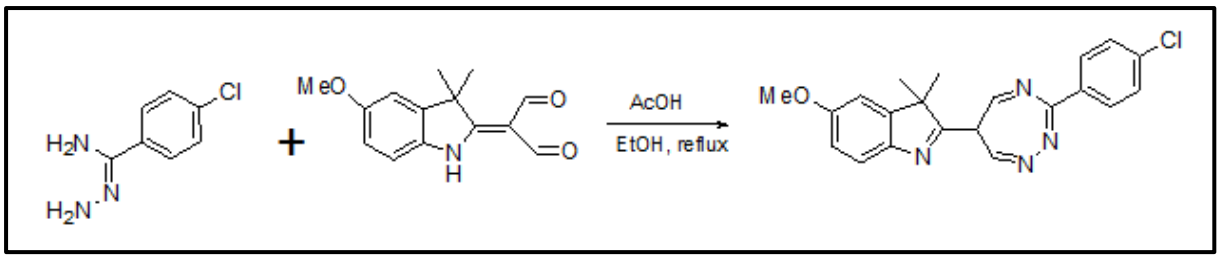
Schem (2-1). series of β-diketone hydrazones that synthesized via condensation of isoniazid

Elattar and et al published a review including the literature survey of 1,2,4-triazepines. One of compound that related to our work was synthesis Pyrrolo[1,2-b][1,2,4]triazepine that accomplished by boiling pyrroles in acetylacetone containing a catalytic amount of p-toluenesulfonic acid for 2–4 hours[82] (Scheme 2-2).



Scheme(2-2) Synthesis of pyrrolo[1,2-b][1,2,4]triazepines. (a) R Me (88%); (b) R Pr (50%); (c) R C_5H_{11} (55%); (d) R Ph (52%); (e) R 4-$MeOC_6H_4$ (77%); (f) R 2-furyl (22%)

In 2020, Nassrulla and et al was published synthesis of 7- membered heterocycles of triazepines skeleton, using 2-(5-methoxy-3,3-dimethyl-1,3-dihydro-indol -2-ylidene)-malonaldehyde and 4-chlorobenzamidiene triazepines skeleton was tested for their antibacterial activity against microorganisms representing (Gram +ve)bacteria two kinds of bacteria such as *Staphylococcus aureus* and *Escherichia coli* (Gram –ve)and its shows moderated bacteriostatic properties Scheme (2-3) [83].



Scheme(2-3). published synthesis of 7- membered heterocyclesof triazepines skeleton

2.6.Biological Activity

2.6.1.Bactiria Activity

Recently, a major problem has emerged around the world in the resistance of bacteria to antibiotics, as ***Escherichia Coli*** was considered one of the most important of these bacterial resistant to antibiotics[(84-86)].

This type of bacteria is found in the intestines of humans and many animals, and there are some beneficial and harmful ones[(87)].

There are two types of *E.Coli*: Gram-negative bacteria, which are more prevalent in winter, and Gram-positive bacteria, which are more common in summer, where Gram-negative bacteria are 2-10 smaller than the gram-positive strain[(88,89)].

The standard isolate of this bactria has been used as microorganisms for sensitivity tests such as disk agar methods and minimum inhibitory concentration[(90)].Its strains were developed by cloning RNA in several prokaryotic stages[(91)].

Staphylococcus aureus, which is one of the most important mutated strains and anti-drug for many drugs, is one of the causes that lead to bacterial diseases in humans[(92)]. One of the damage caused by bacteria to plants and humans is that it affects the banana plant that infects its leaves, which leads to yellowing

and necrosis of the leaves and changing the color of the fruit and vascular tissues, which will lead to human infection with bacterial blood diseases[(93)].

2.6.2.Fungi Activity

Fungi are considered to be triple bonds, as they were first examined by optical microscopy by Smith in (1994).

6000 species of fungi have been detected and it is possible to increase this number according to partial techniques and analytical techniques through which other types of fungi can be detected[(94-96)].

More than one of the most prevalent types of fungi is soil fungi, as it was proven through rapid and accurate changes in microbial complexes, as well as the type of fungi that infects plants, by isolating the immature infected plant part, the type of *fungi* causing damage to it can be determined[(97, 98)].

There are diseases caused by fungi to humans hypersensitivity pneumonitis (HP) is a complex syndrome caused by an exaggerated immune response to the inhalation of a large variety of organic particles.

Furthermore it causes a birds disease that is transmitted to humans, and this disease which called (pigeon breeders' disease).Many studies found that tobacco infection play an important role in farmers lung [(99)]. Tree leaves could be affected, including watermelon leaves, where the infection with white spot on the lower surface of the leaf and increased in size with the passage of time and led to the formation of a white crust formation on the upper surface called Amemaria cuumerina [(100)].

Chapter Three

(Experimental Part)

3.1.Chemistry part:

3.1.1.Materials

All of the project's beginning components and solvents were bought from various suppliers. as listen in the ***Table (3.1*)**

Table (3.1): Chemicals and solvents used in the chemistry part.

No	Chemical	Purity	Molecular Formula	Company
1	3-Oxo-butyric acid ethyl estar	99%	$C_6H_{10}O_3$	Sigma Aldrich
2	4-Chlorobenzaldehyde	99.5%	C_7H_5OCl	Merck
3	Acetic acid	98%	$C_2H_4O_2$	Merck
4	Benzil	99.9%	$C_{14}H_{10}O_2$	Sigma Aldrich
5	Butane-2,3-dione	99.8%	C_4H_6O2	Sigma Aldrich
6	Carbon disulfide	98%	CS_2	Merck
7	Di ethyl ethar	99%	$C_4H_{10}O$	Sigma Aldrich
8	Dimethyl formamide	99.9%	C_3H_7NO	Romil
9	Dimethyl sulfoxide	99%	C_2H_6OS	Sigma Aldrich
10	Ethanol	99%	C_2H_6O	Scharlau
11	Ethyl acetate	99%	$C_4H_8O_2$	Romil
12	Hydrazine hydrate	99%	N_2H_6O	Sigma Aldrich
13	hydroxylamine hydrochloride	98%	NH4OCl	Thomas Baker
14	Isatin	98%	$C_8H_5NO_2$	Merck
15	Methanol	99%	CH_3OH	GCC
16	n-Hexane	99%	C_6H_{14}	Sigma Aldrich
17	Pentane-2,4-dione	99.5%	$C_5H_8O_2$	Merck

18	Phosphoryl Chloride	99.5%	$POCl_3$	Merck
19	Potassium carbonate	98%	K_2CO_3	Sigma Aldrich
20	Potassium manganite	99%	$KMnO_4$	GCC
21	Pyridine	99%	CN_5H_5	Merck
22	Silica gel	99%	SiO_2	Merck
23	Sodium acetate tri hydrate	99%	$C_2H_3NaO_2$	Merck
24	Sodiumhydroxide	99%	NaOH	Merck
25	Triethylamine	99%	$N_{15}H_6C$	Merck

3.1.2.Instruments

Fourier-transform infrared spectroscopy (FTIR): IR spectra recorded on a Perkin-Elmer Spectrum version 10.02 by using KBr disk in the Department of Chemistry, College of Science- University and IR spectra recorded on a (Shimadzu FT-IR spectrophotometer at the Chemistry department / College of education for pure science/ University of Diyala).

Thin Layer Chromatography (TLC): Thin layer Chromatography (TLC) was performed using alumina plates (size20x20) percolated with silica gel with using fluorescence indicator . TLC plates were developed either by the quenching of UV fluorescence or by treatment with a basic $KMNo_4$ solutions or vanill, and heating in Department of Chemistry, College of Science, University of Diyala.

Melting Point: The melting Point of the synthesized compounds were determined by using the stuart SMP^{10} electronic apparatus, at the the Department of Chemistry, College of Science, University of Diyala and Chemistry department / College of education for pure science/ University of Diyala.

Nuclear Magnetic Resonance Spectrometer (NMR): ^{1}H NMR, ^{13}C NMR and APT ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in University of Science and Technologe, College of Science, lrbid City, Jordn and ^{1}H NMR spectra was recorded on a Varian 499.44MHz spectrometer in University of Tehran , Iran.

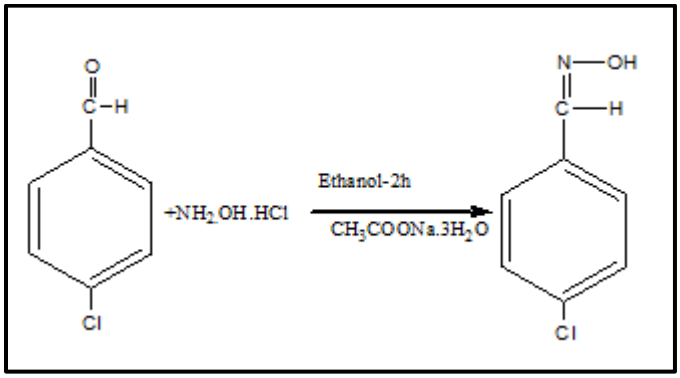
Nuclear Magnetic Resonance Spectrometer (NMR): ^{1}H NMR spectra was recorded on a Didaku 500.1MHz spectrometer in University of Mashhad , Iran.

Antibacterial Activity: The antibacterial activity of compounds was evaluated at the University of Baghdad Center for Biological Research.

3.1.3.Synthetic methods

3.1.3.1. Synthesis of 4-chlorobenzaldoxime(A_1a-A_1b)

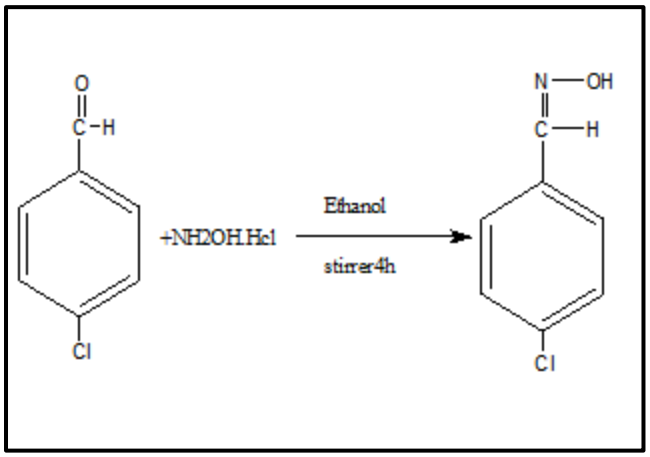
3.1.3.1.1 Synthesis of 4-chlorobenzaldoxime(First method A_1a)



Scheme (3.1): .Synthesis 4-chlorobenzaldoxime

Solution of hydroxyl ammonium hydrochloride (1gm , 0.01mol) and (2gm 0.014mol) of sodium acetate tri-hydrate in distilled water(5ml) at room temperature , was added to a solution of substituted 4-chlorobenzaldehyde (0.5gm 0.003mol) in 20 ml ethanol . After constant stirring in a water bath at 75°C for 2-hours, TLC (1:1) hexane: ethyl acetate with pre-coated silica gel was used to monitor the reaction's completion ,the resulting mixture was cooled in ice bath , bright white precipitate was formed direct, filtered off, and recrystallized from hot ethanol and cold water to afford pure white precipitate. Yield (94%), m.p. 106-107ºC[101,102].

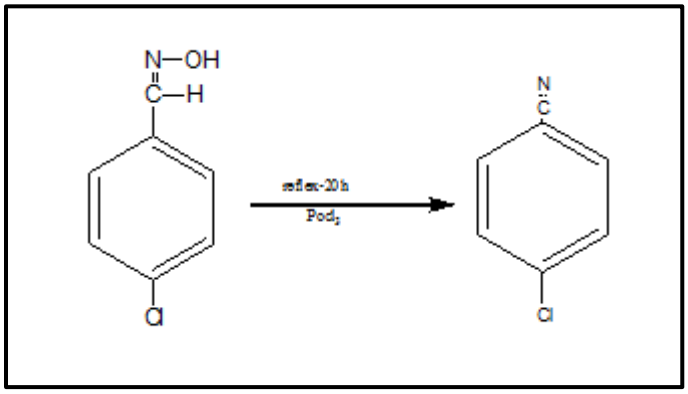
3.1.3.1.2 Synthesis of 4-chlorobenzaldoxime (Second methodA_1b)



Scheme(3.2): Synthesis of 4-chlorobenzaldoxime(A_1b)

Mixture of 4-chlorobenzaldehyde (0.5gm, 0.003mol) and hydroxyl ammonium chloride (1gm, 0.01mol) was dissolved in (15ml ethanol), and the mixture was left stirred in water bath at 75°C for 4-hours , the reaction was cooled in ice bath and solid obtained was filtered out, rinsed with ethanol, and recrystallized from hot ethanol. Yield (82%) . m.p. 106-107ºC.

3.1.3.2. Synthesis of 4-chloro benzonitrile (A_2)



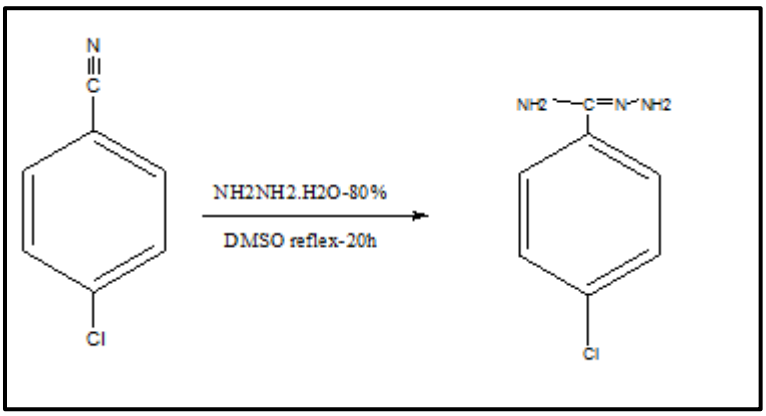
Scheme(3.3): .Synthesis of 4-Chloro- benzonitrile.

To a round bottom flask was added 4-chlorobenzaldoxime (0.74gm 0.0047mol) and (15mL) of $POCl_3$, The solution was stirred at reflux for 20 hours in oil bath at 150 ºC. TLC (1:1) hexane: ethyl acetate with pre-coated silica gel was used to check reaction completion. then the reaction was cooled to

room temperature overnight and poured into H_2O (10 mL). The resulting precipitate was collected by filtration, recrystallized from hot ethanol to afford pure brown precipitate that dried in oven. Yield (81%), m.p 97-98ºC.

3.1.3.3Synthesis of 4-Chloro benzo hydrazonamide (A_3a-A_3b

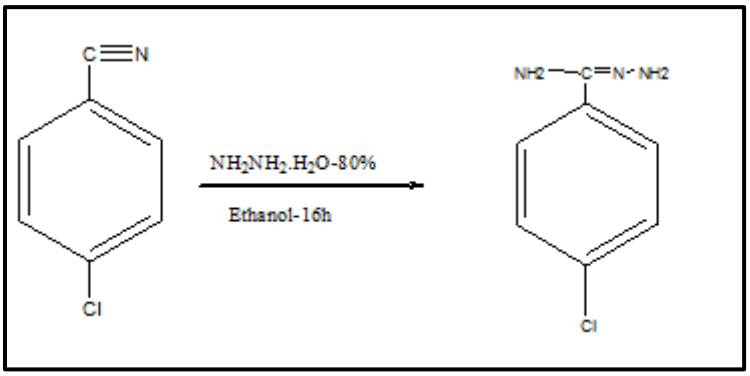
3.1.3.3.1.Synthesis of 4-Chloro benzo hydrazonamide(First method A_3a)



Scheme (3.4): Synthesis 4-Chlorobenzohydrazon amide (A_{3A})

To a round bottom flask was added (0.07gm 0.0005 mol) of 4-chlorobenzonitrile, $N_2H_4.H_2O$ 80% (1 mL) and DMSO (15 mL). The solution was stirred under reflux for 20 hours, TLC (1:1) hexane: ethyl acetate with pre-coated silica gel was used to monitor the reaction's completion. The reaction was poured into (10 ml)of H_2O, and the white precipitate was filtered off. and recrystallized from ethanol to afford pure white precipitate that dried in oven Yield (91%) , m.p. 172-173ºC.

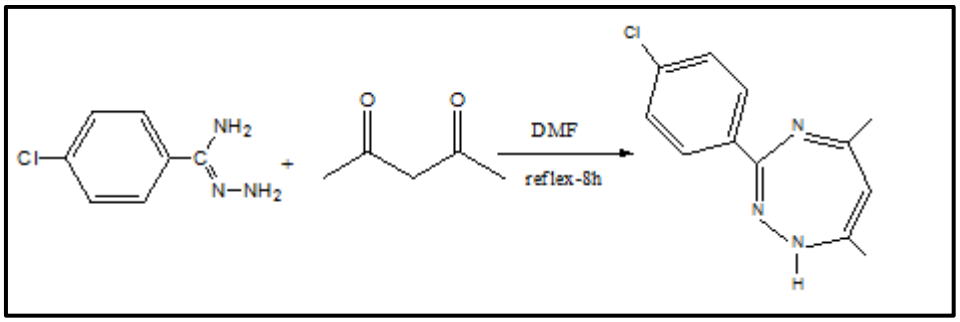
3.1.3.3.2.Synthesis of 4-Chloro benzo hydrazonamide(Second methodA_3b)



Scheme (3.5): Synthesis 4-Chlorobenzohydrazon amide (A_{3B})

A mixture of 4-chlorobenzonitrile(0.68gm 0.005mol) and (1ml) of hydrazine hydrate (80%) in ethanol (15mL) was left stirring under reflux , for 16 hours at 75 ºC, completion of the reaction was monitored by TLC (1:1) hexane: ethyl acetate with pre-coated silica gel. After that, the reaction mixture was poured in to cold water and the resulting precipitate was collected by filtration . The crud material was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate 1:1 to afford the desired pure product as pink crystal precipitate . Yield (82%), m.p. 174-176ºC.

3.1.3.4-synthesis of 3-(4-Chloro-Phenyl) 5-7-dimethyl-1H {1,2,4}triazepine (A_4)

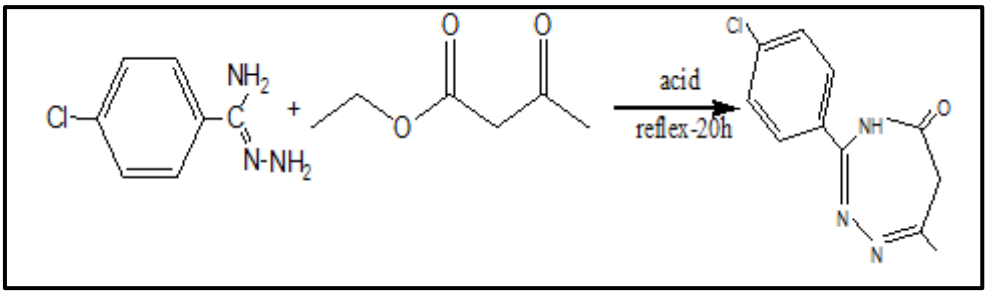


Scheme (3.6): .Synthesis 3-(4-Chloro-Phenyl) 5-7-dimethyl-1H-{1,2,4}tri azepine.

To a mixture solution of 4-Chlorobenzohydrazonamide (0.2gm 0.0012mol) and (15mL) of DMF was added (1mL) of pentane 2-4-dione. The mixture was heated at reflux for 8 hours, using an oil bath at 120 ºC, completion of the reaction was monitored by TLC (1:1) hexane: ethyl acetate with pre-coated silica gel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). to obtain the organic mixture extracts, they were dried over Na_2SO_4 and concentrated in a vacuum, The product was white crystals , Yield (78%), m.p. 192-193ºC.

3.1.3.5. -Synthesis3-(4-Chlorophenyl)-7-methyl-5-methylene-5,6-di hydro-4H-{1,2,4}triazepine(A_5a-A_5b)

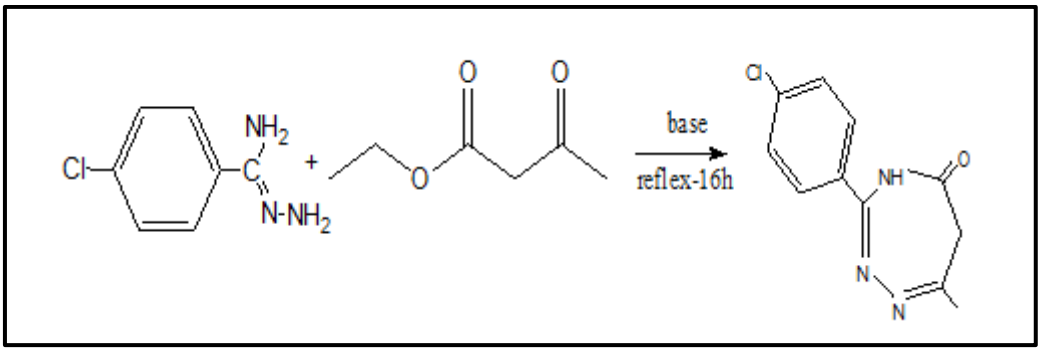
3.1.3.5.1. -Synthesis3-(4Chlorophenyl)-7-methyl-4H-methylene1,2,4}triazepine -5-one(First method A_5a).



Scheme(3.7): Synthesis3-(4Chlorophenyl)-7-methyl-4H-methylene1,2,4}triazepine -5-one

To a round bottomed flask was added 4-chlorobenzohydrazonamide (0.1gm 0.00061mol) , (0.1ml) of (3-oxo-butyric acid ethyl estar) and DMF (8ml) . To the stirred solution, 5drop of acetic acid was added and the mixture was heated at reflex for 20 hours, completion of the reaction was monitored by TLC (1:1) hexane: ethyl acetate with pre-coated silica gel. The mixture was allowed to cool to room temperature and the residual, was separated and the aqueous layer was extracted with ethyl acetate (3x30 ml). The combined organic extracts were dried over Mg_2SO_4 and concentrated under vaccum to afford the product as yellow solid . Yield (88%), m.p. 230-231ºC.

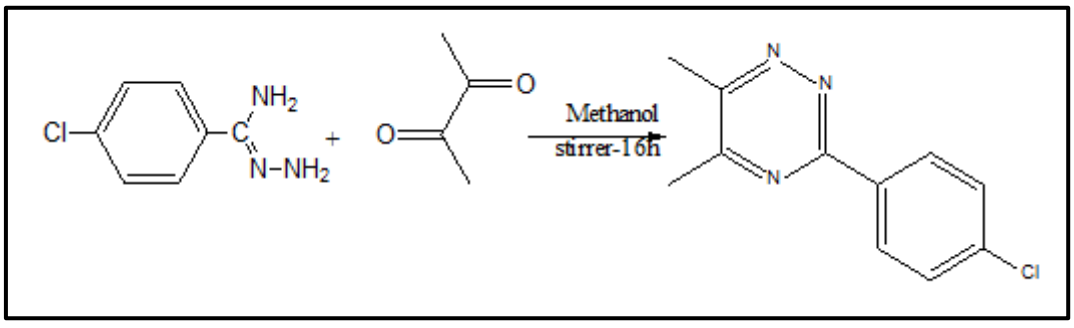
3.1.3.5.2. Synthesis3-(4Chlorophenyl)-7-methyl-4H-methylene1,2,4}triazepine -5-one (Second methodA_5b)



Scheme(3.8): Synthesis3-(4Chlorophenyl)-7-methyl-4H-methylene1,2,4}triazepine -5-one -

To stirred solution of 4-chlorobenzohydrazonamide (0.1gm, 0.00061mol) and 3-oxo-butyric acid ethyl estar. in (8ml) DMF was added catylast amount of triethylamine (0.1ml). The mixture was heated at reflux for 16 hours completion of the reaction was monitored by TLC (1:1) hexane: ethyl acetate with pre-coated silica gel. The flask was allowed to cool to room temperature and the residual, The aqueous layer was separated and extracted with ethyl acetate (3x30 mL). The organic extracts were mixed and dried on Mg_2SO_4 before being concentrated under vacum to afford the product as orange solid Yield (72%), m.p. 232-235ºC.

3.1.3.6. Synthesis3-(4-Chloro-phenyl)-5,6-dimethyl-{1,2,4}triazine (A6)

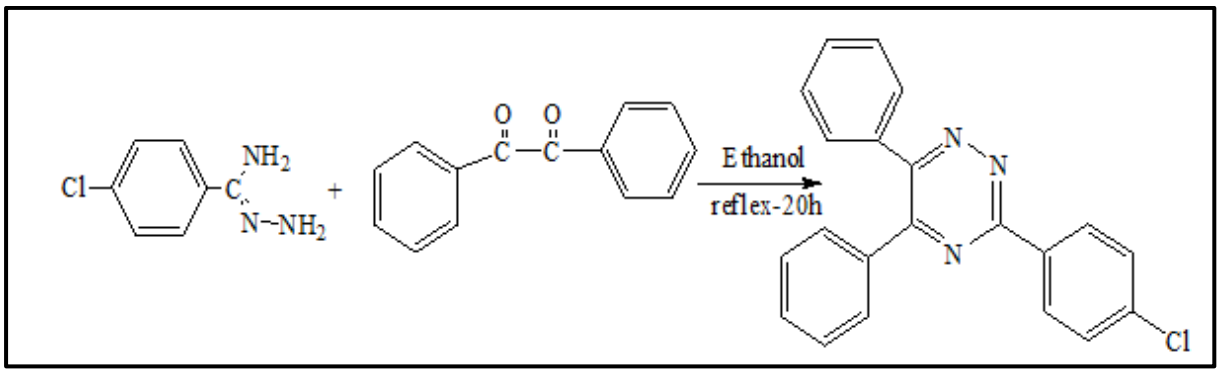


Scheme(3.9): Synthesis3-(4-Chloro-phenyl)-5,6dimethyl-{1,2,4}triazine.

A mixture of 4-chlorobenzohydrazon amide (0.1gm 0.0006mol) and 0.1 mL of butane-2,3-dione in (10 m L) methanol, was treated with catalyst amount of

of acetic acid. The mixture was left stirrer for16 hours at room temperature , TLC was used to monitor the end of reaction(1:1) ethyl acetate: hexane with pre-coated silica gel. The reaction mixture then poured into cold water, filtered off , dried in oven and recrystallized by hot ethanol to afford pure pale yellow precipitate . Yield (84%), m.p. 198-199ºC.

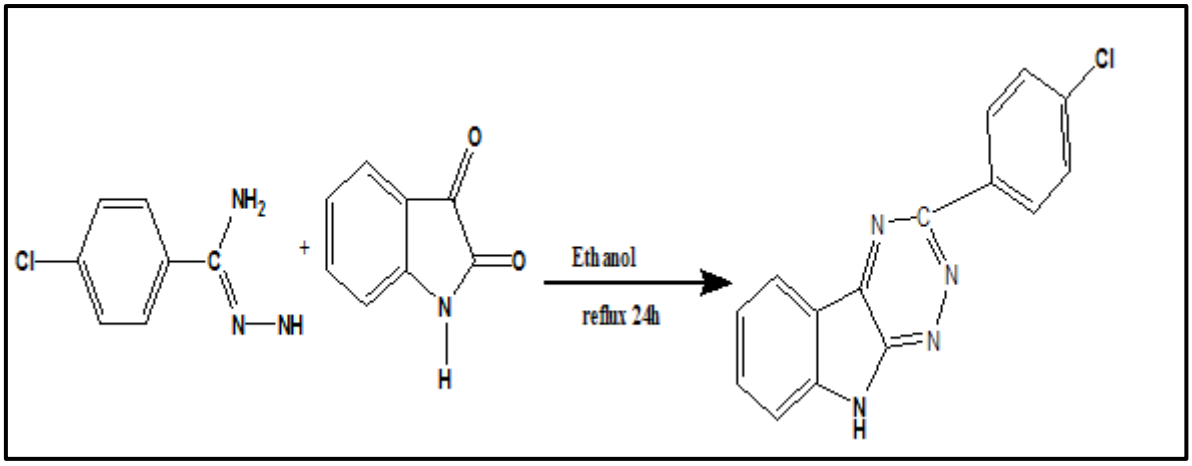
3.1.3.7. Synthesis 3-(4-Chloro-phenyl)-5,6-di phenyl {1,2,4}triazine(A_7)



Scheme(3.10): Synthesis 3-(4-Chloro-phenyl)-5,6-di phenyl-{1,2,4}triazine.

To a mixture of 4-chlorobenzohydrazonamide (0.18gm 0.001mol) and (0.14gm, 0.00066mol) of benzil in(15 mL) ethanol was added couple drops of acetic acid, the resulting solution was heated at reflex for 20 hours at 75 ºC , completion of the reaction was monitored by TLC (1:1) hexane: ethyl acetate with pre-coated silica gel. before being placed into cold water, the reaction was brought to room temperature. The forming yellow precipitate was then filtered and washed with distilled water before being baked in the oven to yield the desired pure chemical yellow precipitate Yield (87%), m.p. 291-292ºC

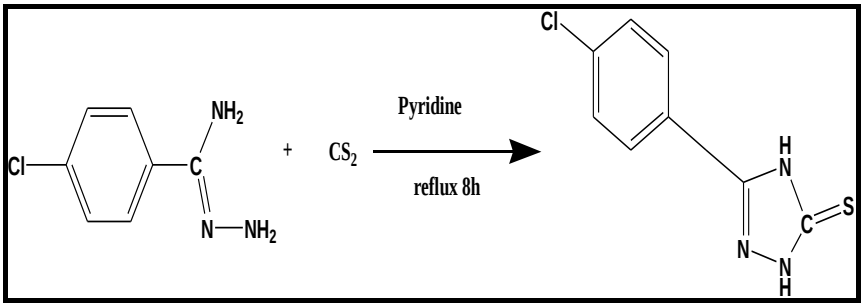
3.1.3.8. Synthesis of 3-(4-chlorophenyl)-9H-{1,2,4}tetrazepino{5-6b}indole (A_8)



Scheme(3.11): Synthesis of 3-(4-chlorophenyl)-9H-{1,2,4}tetrazepino{5-6b}indole (A_8)

To a stirrer round bottom flask was added a mixture of (0.14gm 0.0008 mol) 4-chlorobenzohydrazonamide, (0.14gm 0.001mol) of isatin and 3 drops of acetic acid in (15mL) ethanol , then, the reaction mixture was stirred at reflux for 24 hours. completion of the reaction was monitored by TLC (1:1) hexane: ethyl acetate with pre-coated silica gel. The reaction was allowed to cool to room temperature, the orange precipitate was collected by filtration and dried in oven. The crud material was purified by flash column chromatography on silica gel, eluting of hexane-ethyl acetate 1:1 to afford the desired pure product as a orange crystal precipitate . Yield (78%) m.p 287-288.

3.1.3.9. Synthesis of 5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (A_9)



Scheme(3.13): Synthesis of 5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

A mixture of 4-chlorobenzohydrazonamide(0.38gm 0.002mol) and CS_2 (0.5ml) in (15ml) pyridine was refluxed for (8) hours, completion of the reaction was monitored by TLC (1:1) hexane: ethyl acetate with pre-coated pre -coated silica gel, then poured onto an ice-water combination with 3 drops of Hcl. The resulting white solid was filtered off, washed with water, dried, and recrystallized in hot ethanol. Yield (67%), m.p. 220-224ºC.

Chapter Four

(Results and discussion)

4.1.Introduction

The main goal of this work is a proposed approach to the synthesis of new heterocyclic activate bio compounds. Our initial studies focused on obtaining the best reaction conditions for the synthesis of oxime using para-chlorobenzaldehyde as substrate**.**

The physical properties of compounds ***(A$_1$-A$_9$)*** were registered ***in Table (4. 1).***

4.2.Synthesis and identification of 4-chlorobenzaldoxime (A$_1$a andA$_1$b) .

4.2.1-Compound (A$_1$a-A$_1$b)

A mixture of hydroxyl ammonium chloride , P-chloro benzaldehyde and sodium acetate trihydrate was dissolved in distilled water (5 mL) and to this solution was added (20ml) of ethanol until solution occurs. After stirred 2 hours in water bath, The TLC analysis showed that a new compound had been formed, with completely consumed of starting material as evidenced by a strong absorption corresponding to the OH group at 3301cm^{-1} and 1564 cm^{-1} corresponding to the C=N group and disappearing carbonyl group of benzaldehyde group. **(Fig 4.2).** The ^{1}HNMR spectrum **(Fig4.3)** showed a clean singlet signal of proton of N-OH , HC=N group at δ 11.43 ppm and δ 8.41 ppm} respectively Zhang ,L et al [(103)]. A signal in the ATP^{13}C NMR spectrum **(Fig4-4)** at δ 147.10 ppm corresponding to the C=N group was observed

.It is important to mention that the oximes were obtained as *Z/E* mixtures as determined by analysis of ^{1}HNMR spectra that showed doubling up of all peaks signal such as N-OH proton at δ 11.86 and 11.43 ppm.

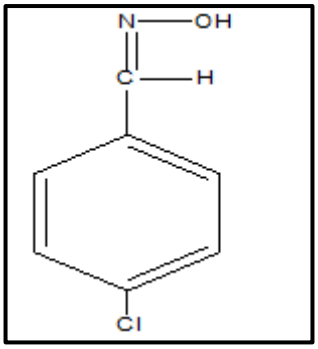


Figure (4. 1): The chemical structure of A_{1a} and A_1b

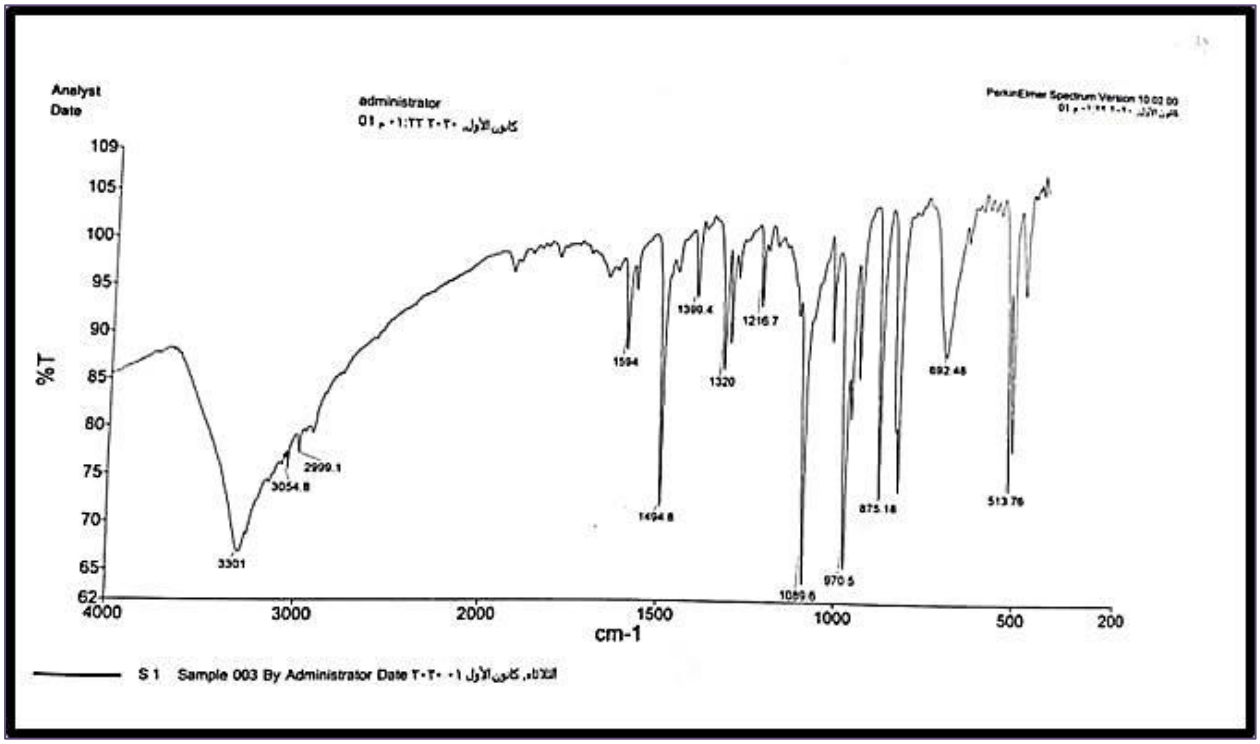


Figure (4. 2): FT-IR spectrum in of (A_{1a}) compound

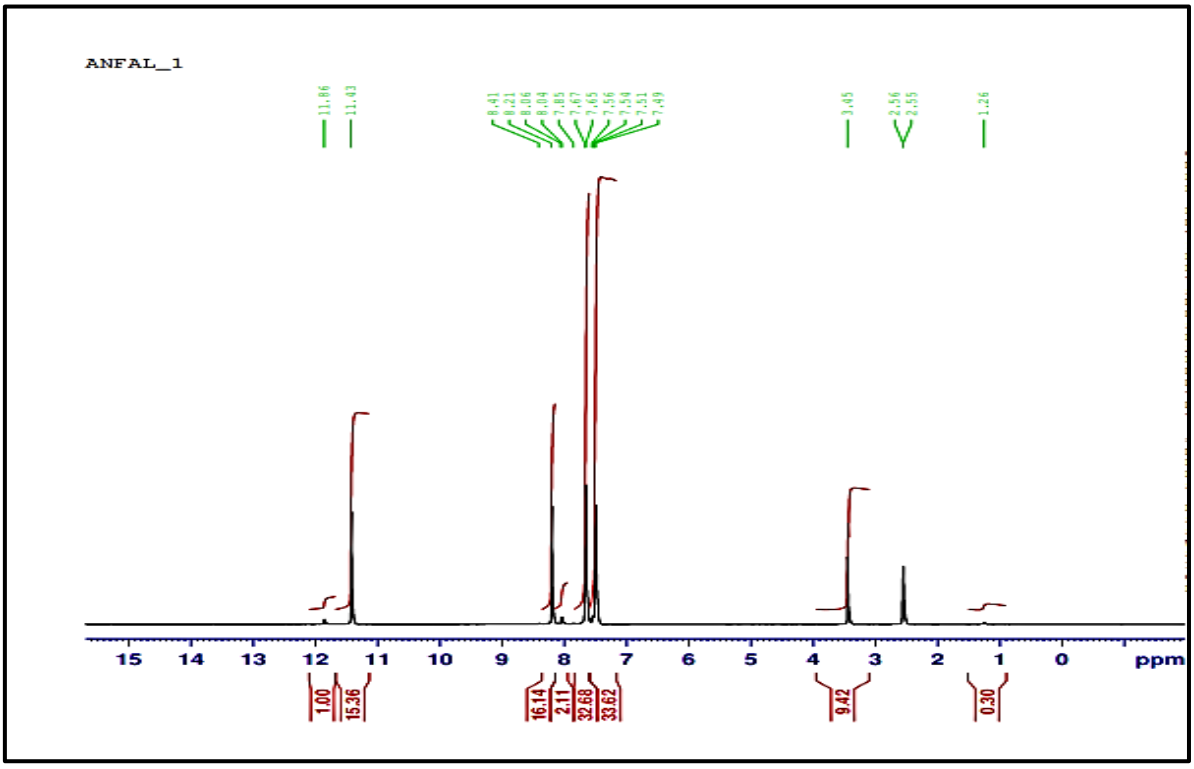


Figure (4. 3): ^{1}H NMR spectrum of (A_{1a}) compound

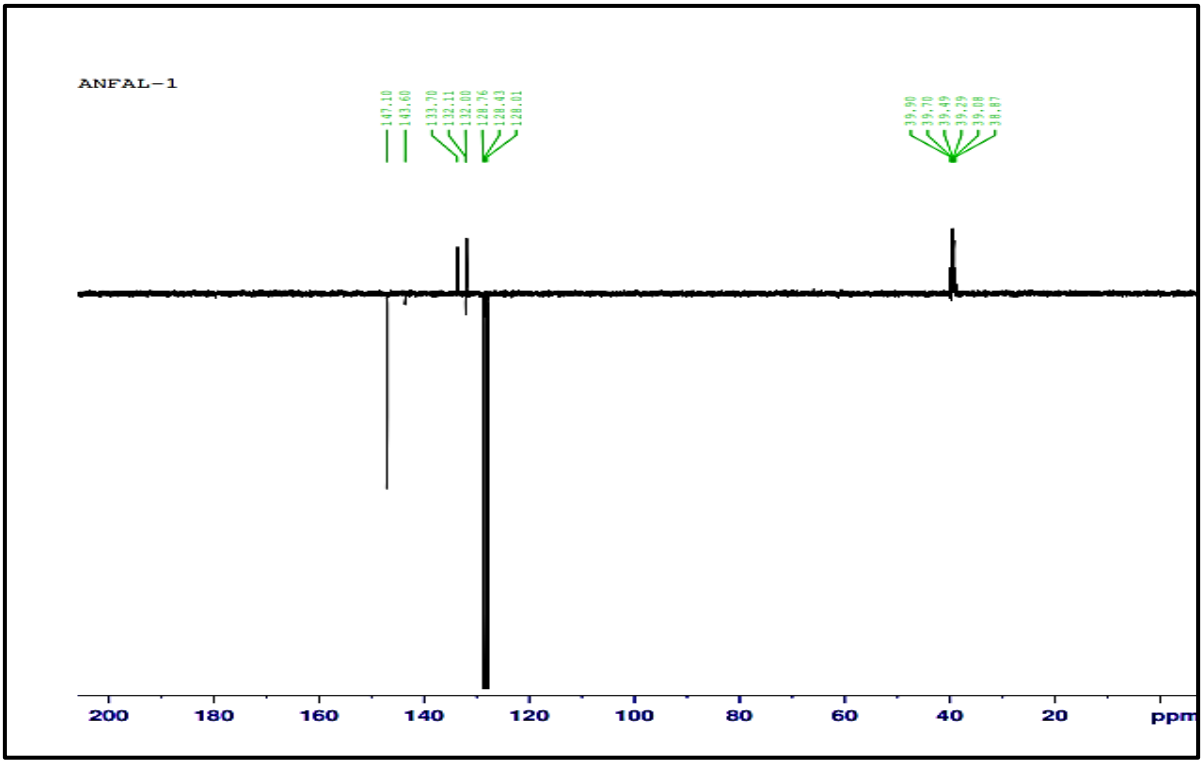


Figure (4. 4): ATP ^{13}C-NMR spectrum of (A_{1a})

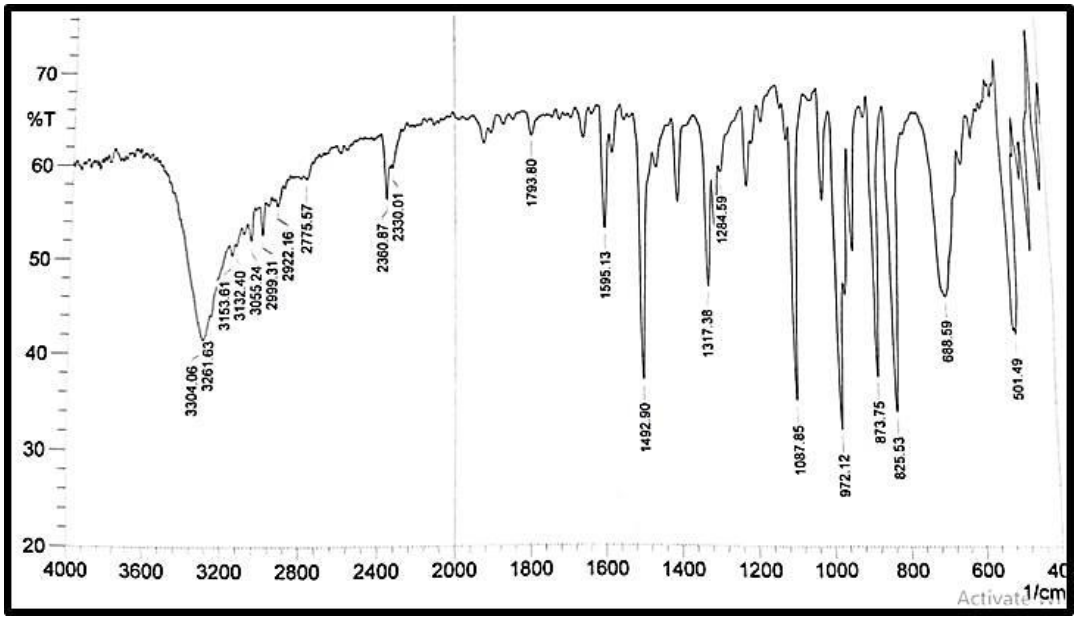


Figure (4. 5): FT-IR spectrum of compound (A_{1b})

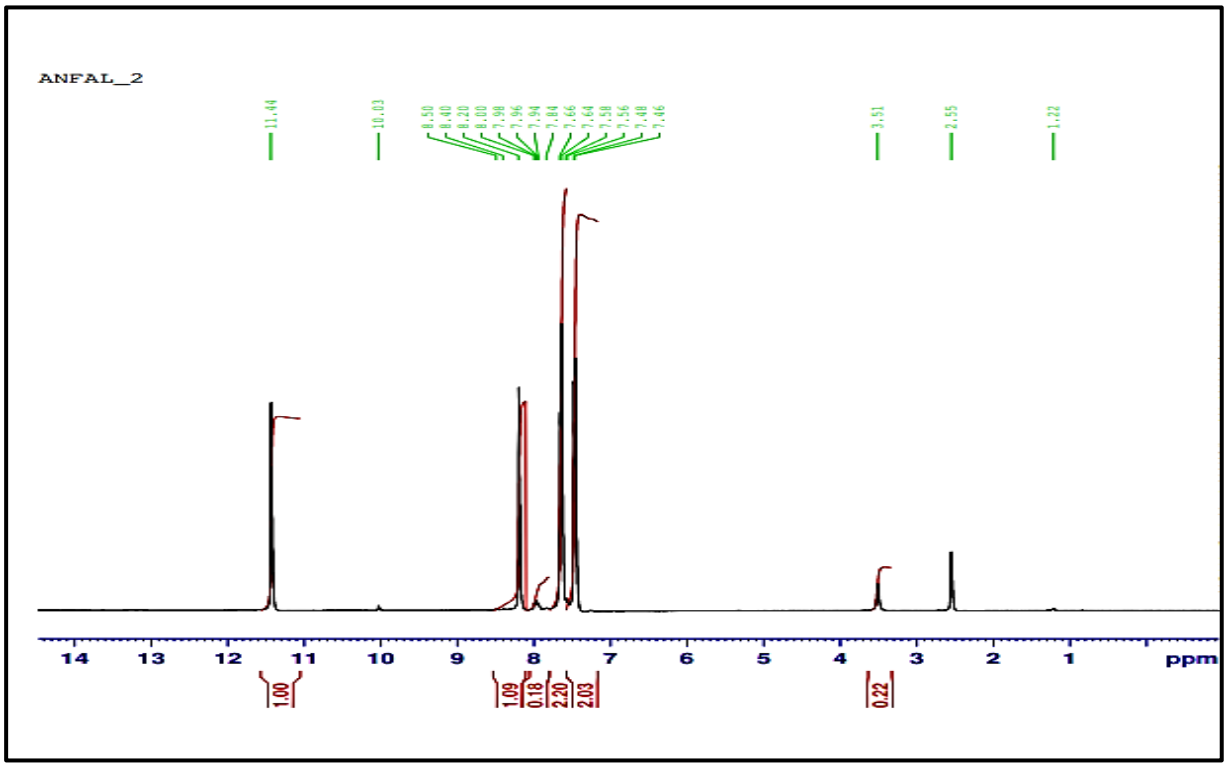


Figure (4. 6): ^{1}H NMR spectrum of (A_{1b}) compound

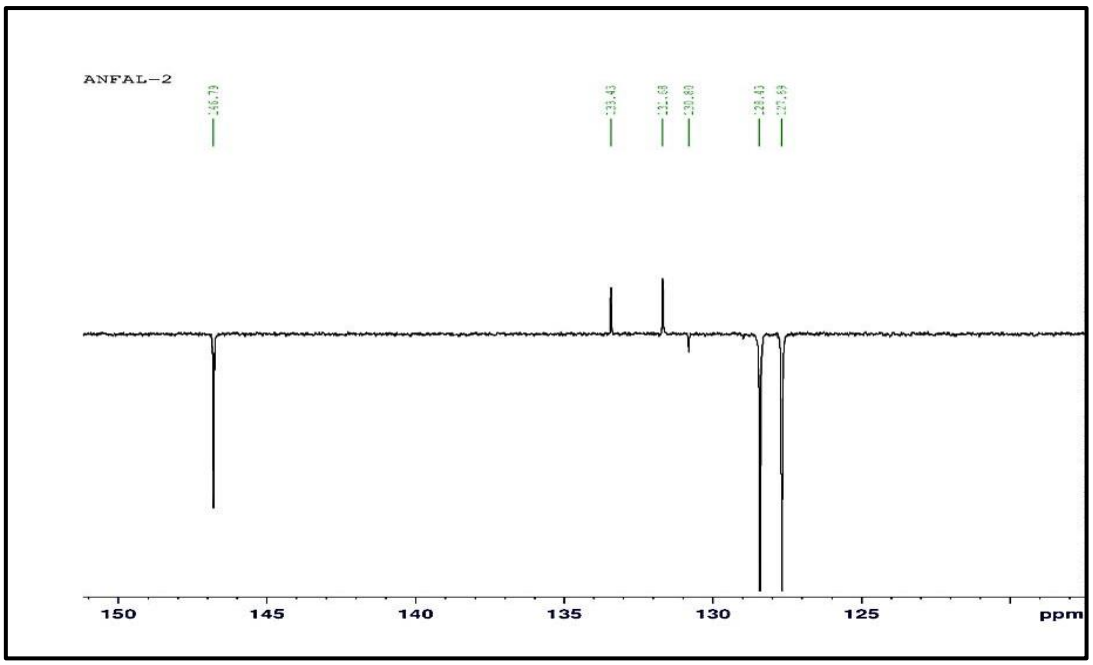


Figure (4.7): ATP ^{13}C-NMR spectrum of (A_{1b}) compound

4.3.Synthesis and identification of 4-chlorobenzonitrile (A_2)

The synthesis of P-chlorobenzonitrile from aldoximes was achieved using procedure of (15 mL) of $POCl_3$ and *Para*-chlorobenzaldoxime was left under reflux for 20 hours. The TLC analysis showed the presence of a new material with consume of starting material and the target compound was obtained as brown precipitate in 81% yield.

Peak at 3456.2 cm^{-1} in the FT-IR spectra **(Fig4-9)**probably return to nitrile group. In spite of the peak of nitrile group was observed higher than expected, however the ^{1}H NMR of the product confirm the product that showed signals referred to the aromatic protons at δ 8.13-7.52 ppm. with disappearing the N-OH and HC=N group of starting material. **(Fig4-10).** Regarding the broad singlet at 6.54 ppm in the ^{1}HNMR spectrum we thing that the chlorine and cyanide substituents are acting very similarly electronically and so giving quasi symmetry to the molecule and the protons ate appearing as a broad singlet rather than AA′ BB′ system[(104)].

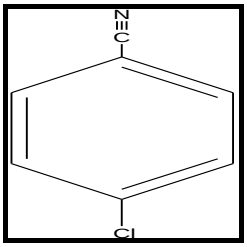


Figure (4.8): The chemical structure of compound A_2

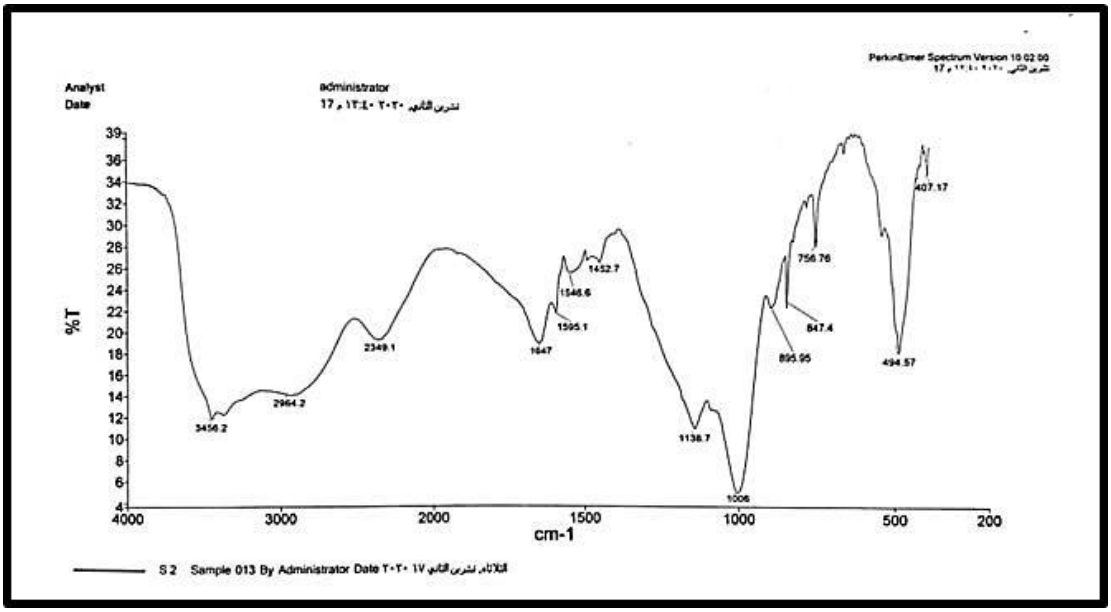


Figure (4.9): FT-IR spectrum in of (A_2) compound

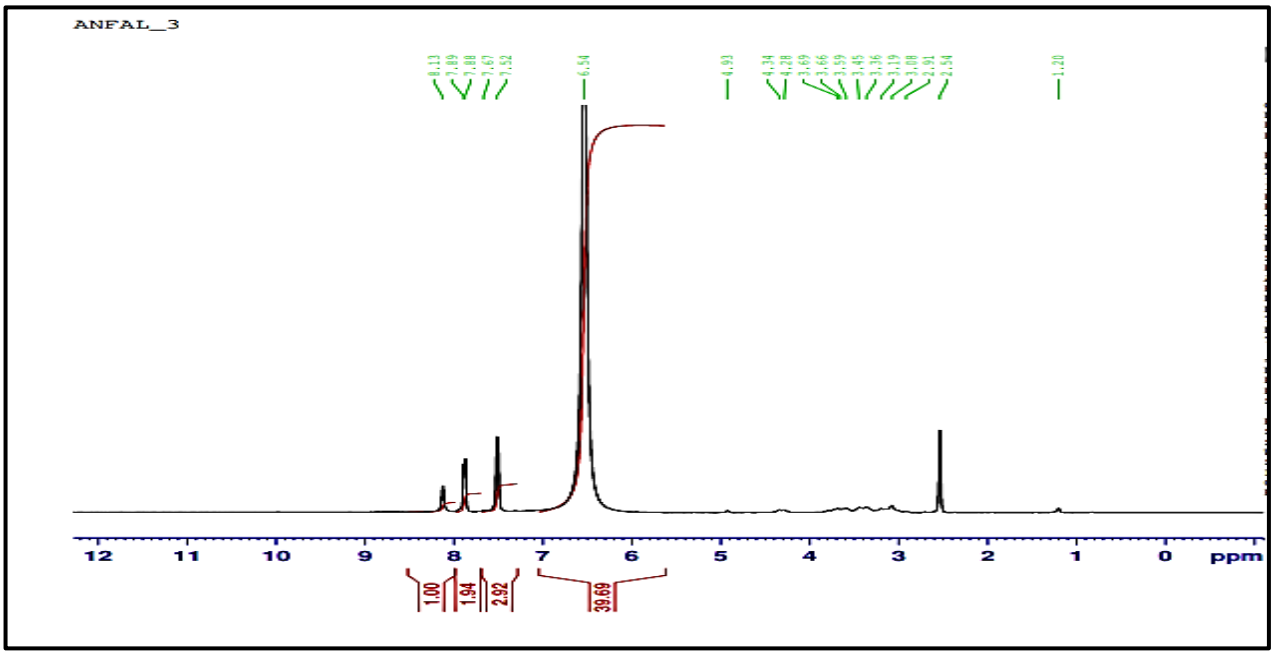


Figure (4. 10): ^{1}H NMR spectrum of(A_2) compound

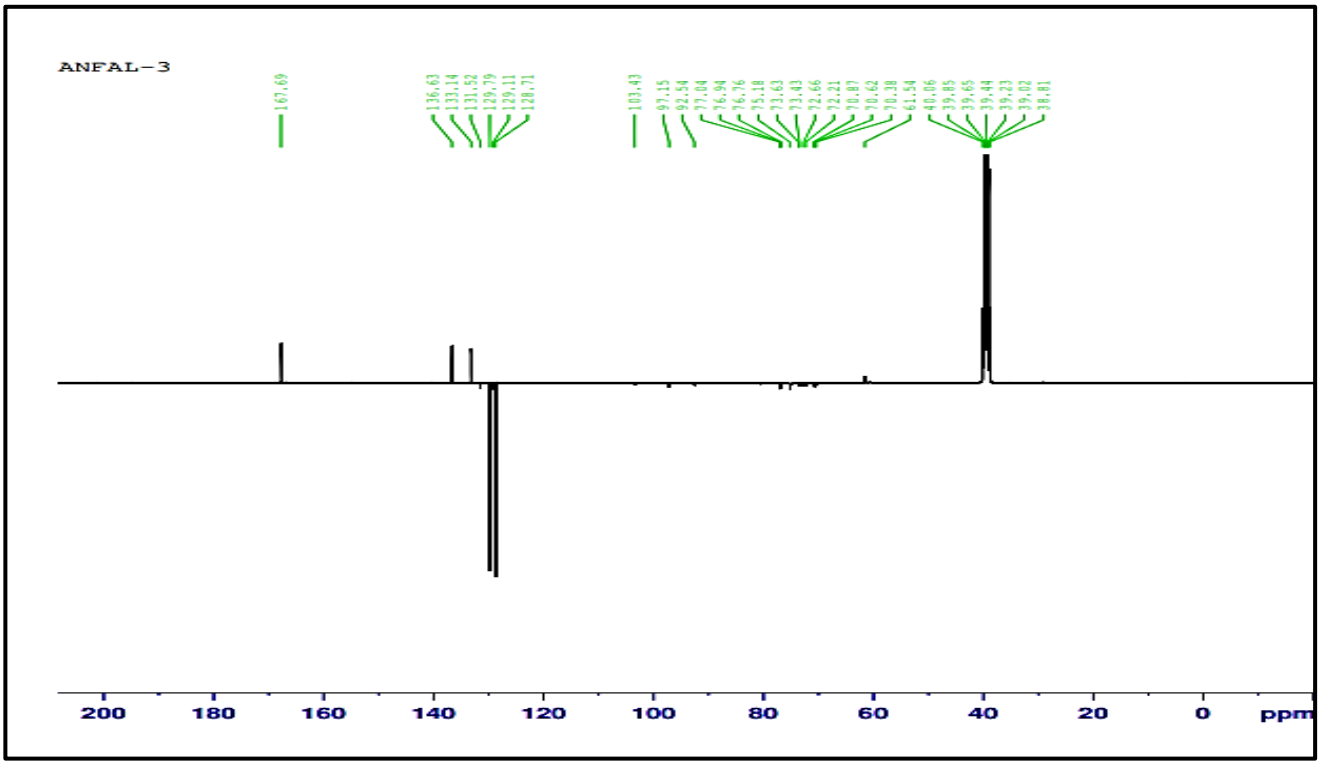


Figure (4. 11): ^{13}C-NMR spectrum of (A_2)

4. 4 Synthesis and identification of4-Chloro benzo hydrazon amide [A_{3A}]

The next step including converting the nitrile group to useful intermediate imine group for synthesis different compounds, 0.05 mol of 4-chlorobenzonitrile treated with 1ml of hydrazine hydrate 80% in 15ml of DMSO and the reaction mixture heated under reflux for 20 hours .The TLC analysis showed the presence of a new material with complete consumption of starting material . FT-IR **(Fig 4-13)** and ^{1}HNMR (Fig **4-14)** used to identification of the desired new compound The IR spectrum displayed two stretching bands at 3333.8 and 3191.1 cm^{-1} belong to the amine group , in addition absorption band at 1637.21 belonged to (C=N) . Finally, A new feature in the ^{1}H NMR spectrum was a pair of double at δ 7.90 and δ 7.54 ppm corresponding to the four protons of the aromatic ring along with resonances at δ 5.19 ppm corresponding to the protons of NH_2-

the integration values from the ^{1}H NMR spectra for the product agreed with the number of protons proposed for the respective structures.

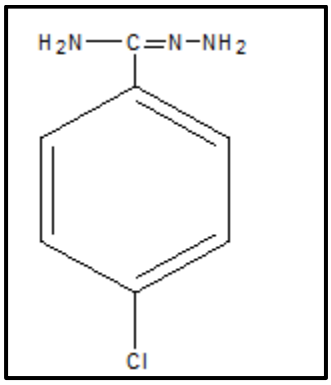


Figure (4. 12): The chemical structure of compound (A_3).

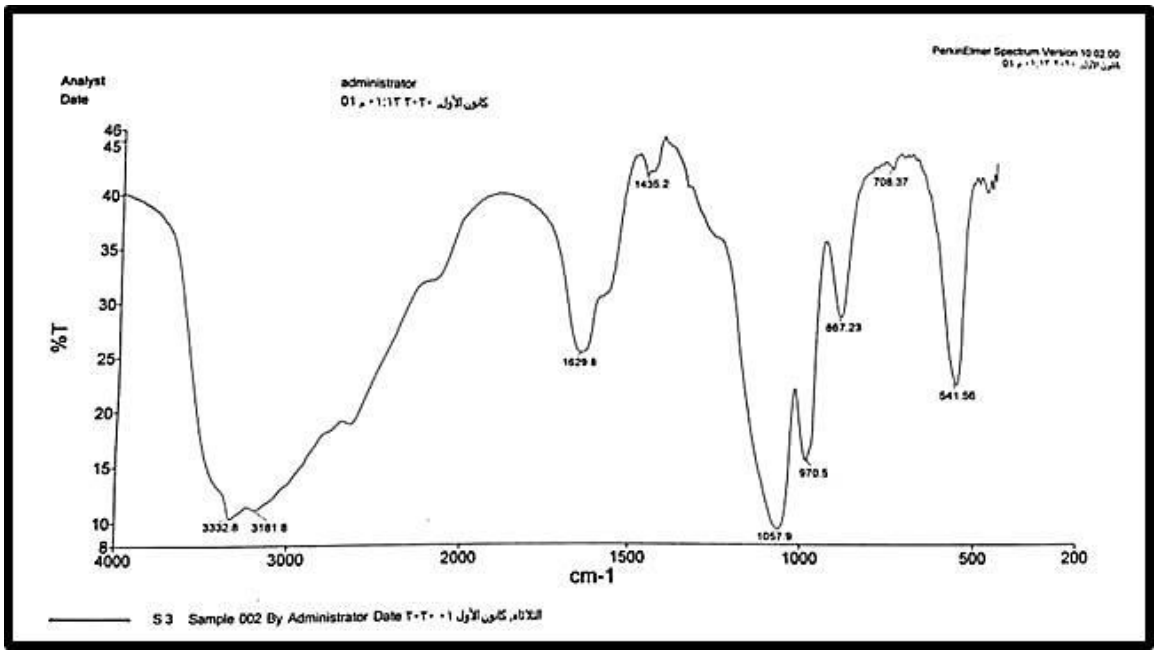


Figure (4. 13): FT-IR spectrum in of compound (A_3a)

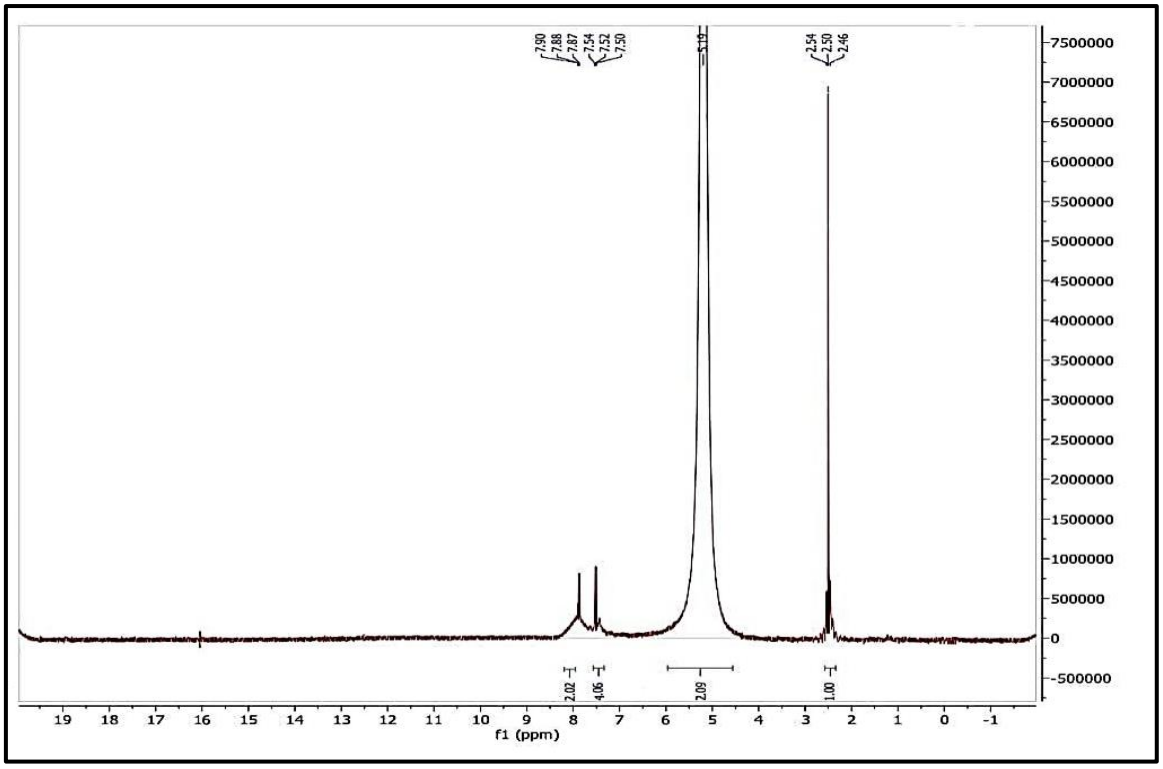


Figure (4. 14): ^{1}H NMR spectrum of compound(A_{3a}).

4. 5 Synthesis and identification of 4-Chloro benzo hydrazon amide [A_{3B}]

Compound (A_{3b}) was synthesized through the reaction 4-chlorobenzonitrile with hydrazine hydrate (80%) in ethanol (15ml) under reflux , for 16 hours at 75 ºC, The TLC analysis showed the presence of a new material with consume of starting material and the desired pure product was obtained as pink crystal precipitate in yield of (82%), after purification by column chromatography on silica gel, eluting with hexane-ethyl acetate 1:1. The FT-IR **(Fig 4-15)** and ^{1}HNMR **(Fig4-16)** allowed the identification of the desired new compound The IR spectrum displayed stretching bands at 33300, and 1642, belong to the amine group and (C=N) group respectively, with completely disappear starching of nitrile group. A new feature in the ^{1}H NMR spectrum was resonances at δ 5.76 ppm corresponding to the protons of NH_2-N=C. A signal in the ^{13}C NMR spectrum**(Fig4-17)** at δ 165.25 ppm corresponding to the carbon of imine group was observed that confirming that hydrazon compound was

indeed synthesized with no signals for any starting material whether aldehyde group or cyanide group. It is important to mention, that synthesis of nitrile compound was carry out from reaction of one equivilant of para chlorobenzaldehyde with 1.1 equivalent of$NH_2OH.HCl$ in DMSO at 100°C and the mixture was left under heated for 8 hours . The structure of the nitrile compound was supported bythe observation of a nitrile CN absorption at 2225 cm^{-1} and 1593 referred to (C=C) groups, Finally, a band at 828 attributed to(C-Cl) .

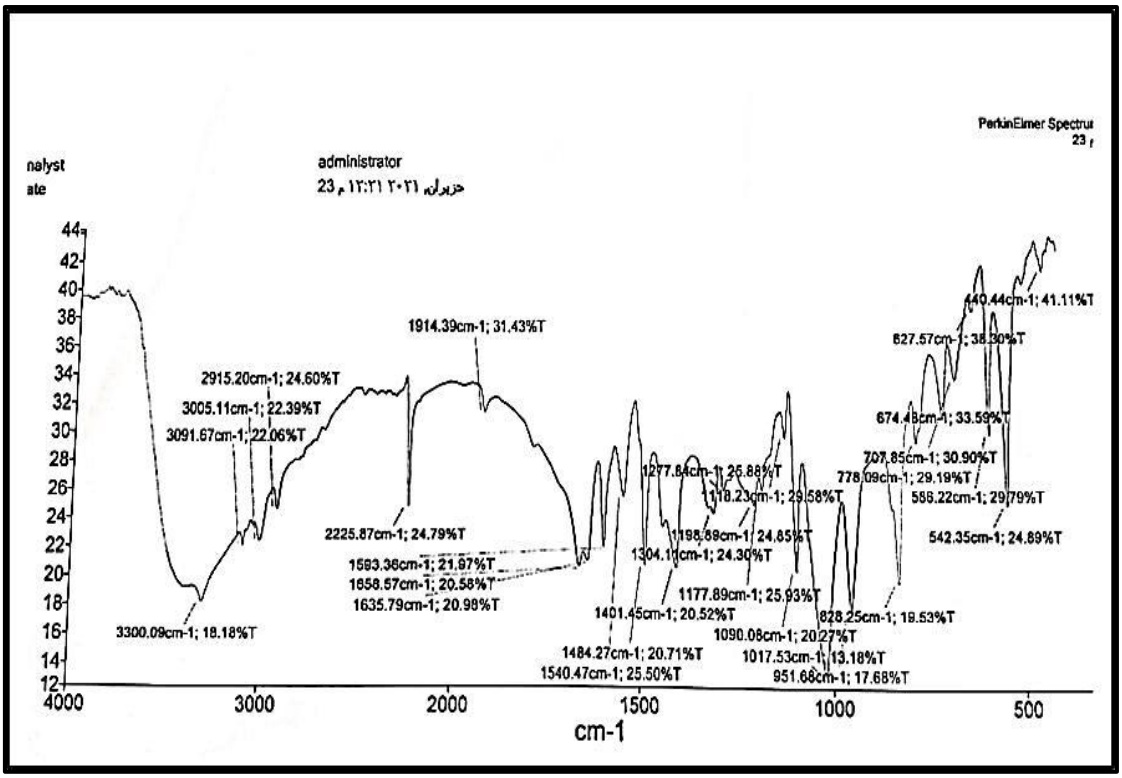


Figure (4. 15): A -FT-IR spectrum of (A_{3b}) compound.

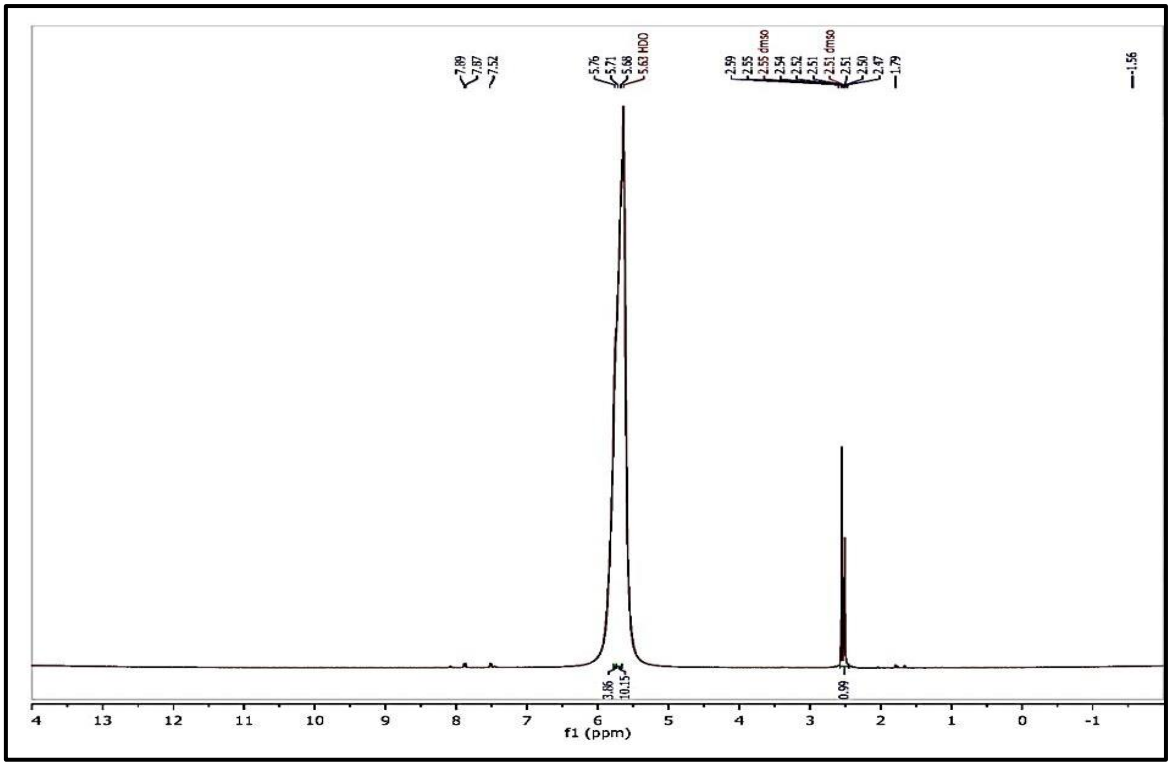


Figure (4. 16): ^{1}H NMR spectrum of compound(A_{3b}).

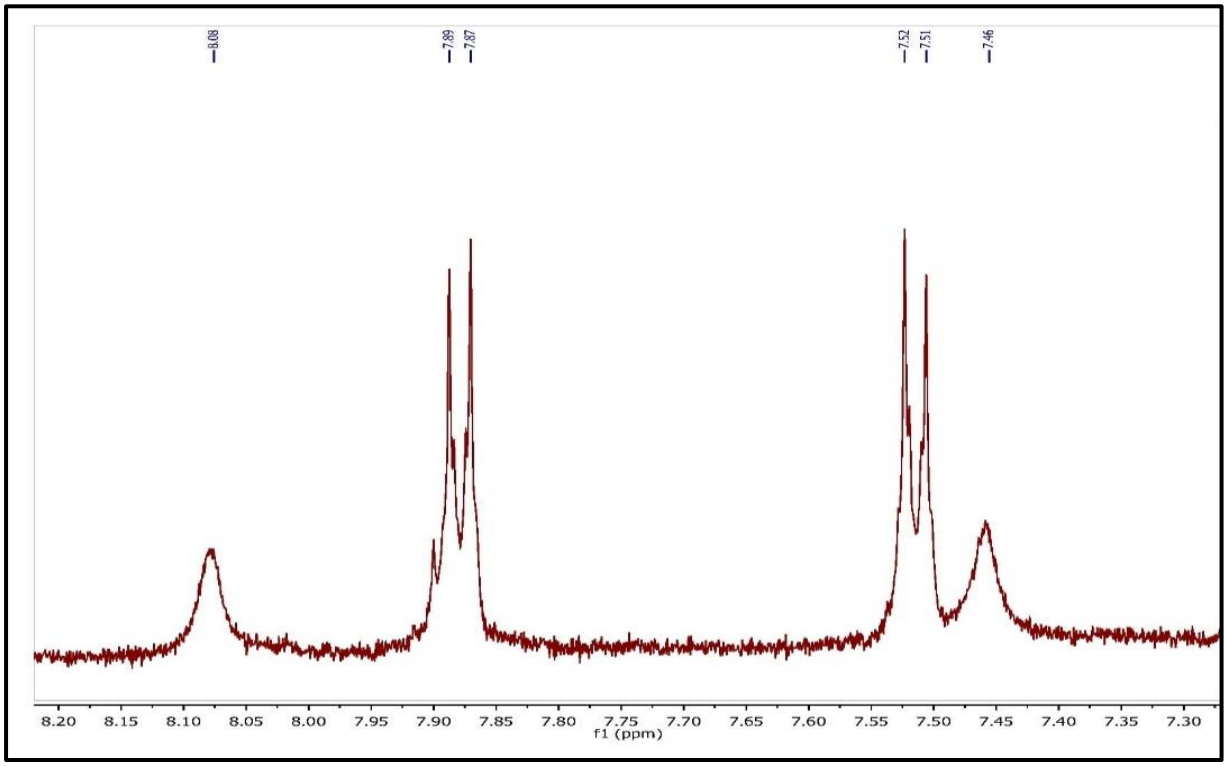


Figure (4.17): Zoom of ^{1}H NMR spectrum of compound(A_{3b}).

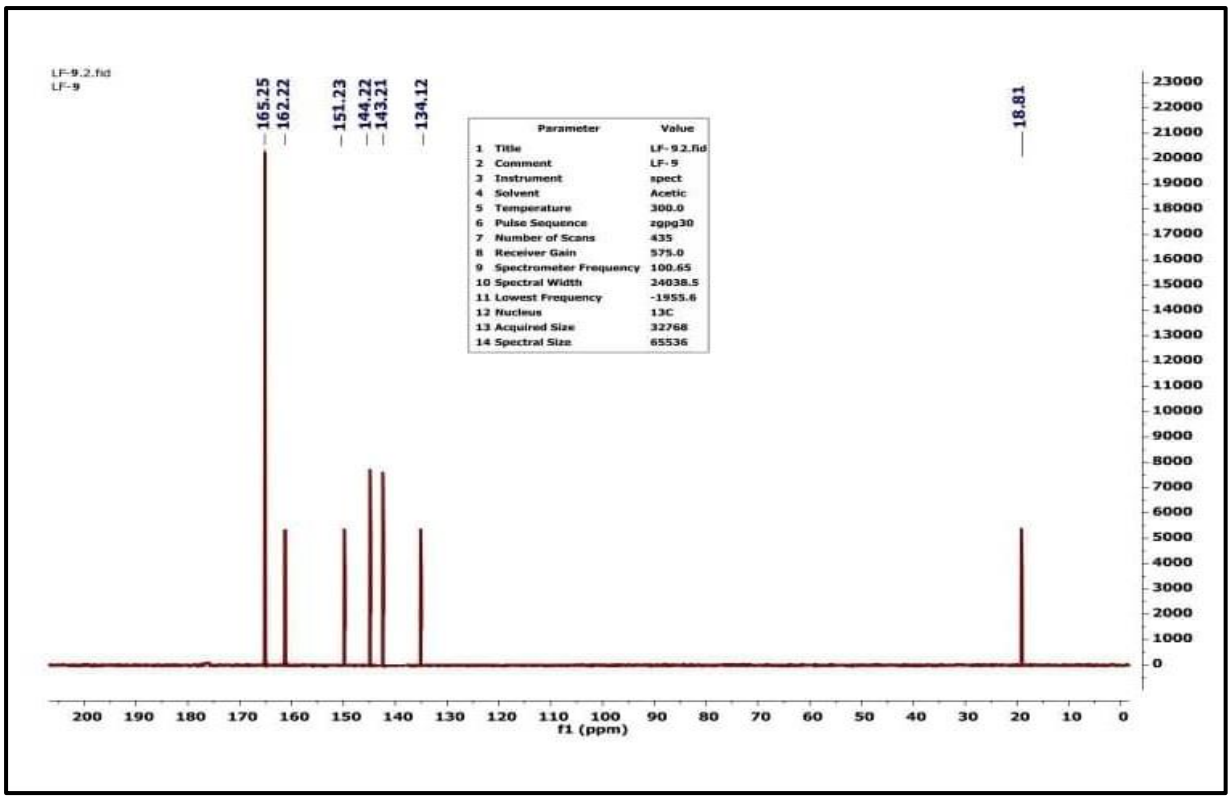


Figure (4.18): ^{13}C-NMR spectrum of (A_3b) compound

4. **6 Synthesis and identification of of3-(4-Chloro-Phenyl) 5-7-dimethyl-1H-{1,2,4}tri azepine (A4).**

Compound (A_4) Preparation from reaction of hydrazone amide with pentane -2,4-dione in DMF under reflux for 8 hours afforded single product triazepine as white crystal in yield of 78% .The formation of the product was supported by observation band at 3456 and 1691 cm^{-1} for NH and C=N group· Two starching bond at 1565.5 and 1416cm^{-1} were assigned to aromatic (C=C) group and CH_3 group respectively. **Fig (4-20)**. In addition formation of compound **(A_4)** was confirmed through examination of its ^{1}H NMR spectrum. The ^{1}HNMR spectrum **(Fig4-21)** showed a clean singlet signal of proton of NH group at δ10.58 ppm, with additional peaks at δ2.01, 1.83 and 5.55 ppm corresponding to the two methyl group and C=CH of triazepine ring .

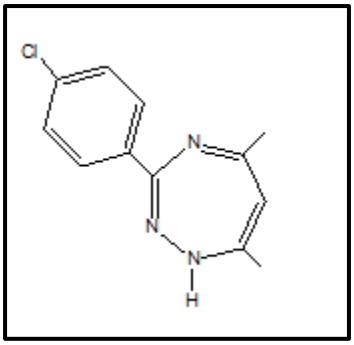


Figure (4.19): The chemical structure of compound(A_4).

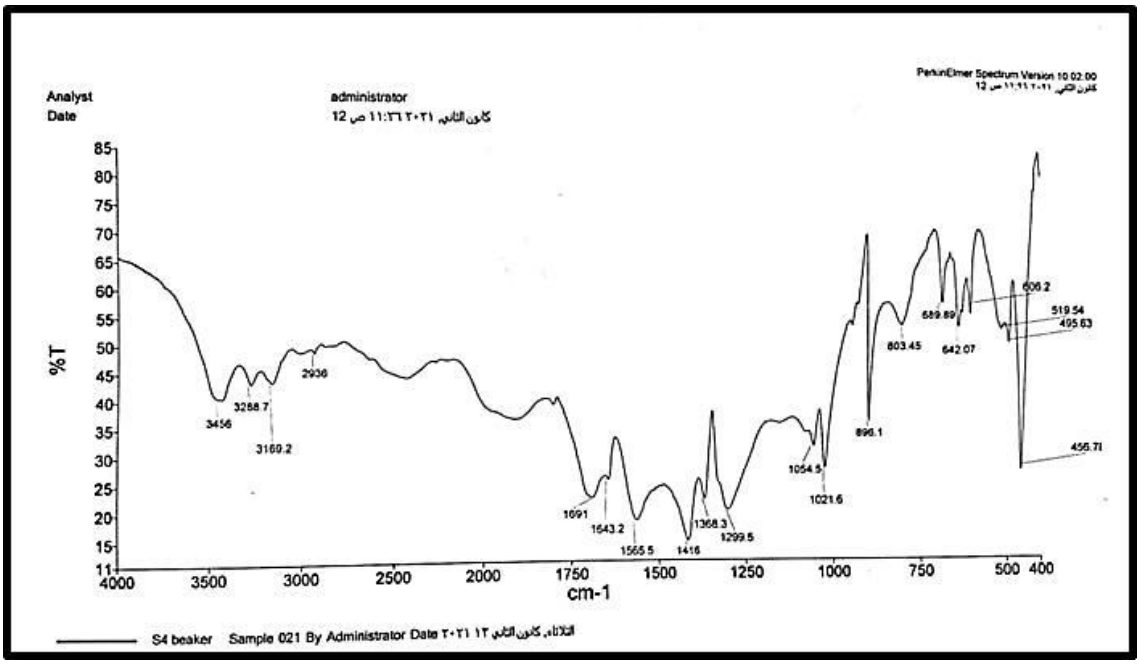


Figure (4.20): FT-IR spectrum of (A_4) compound.

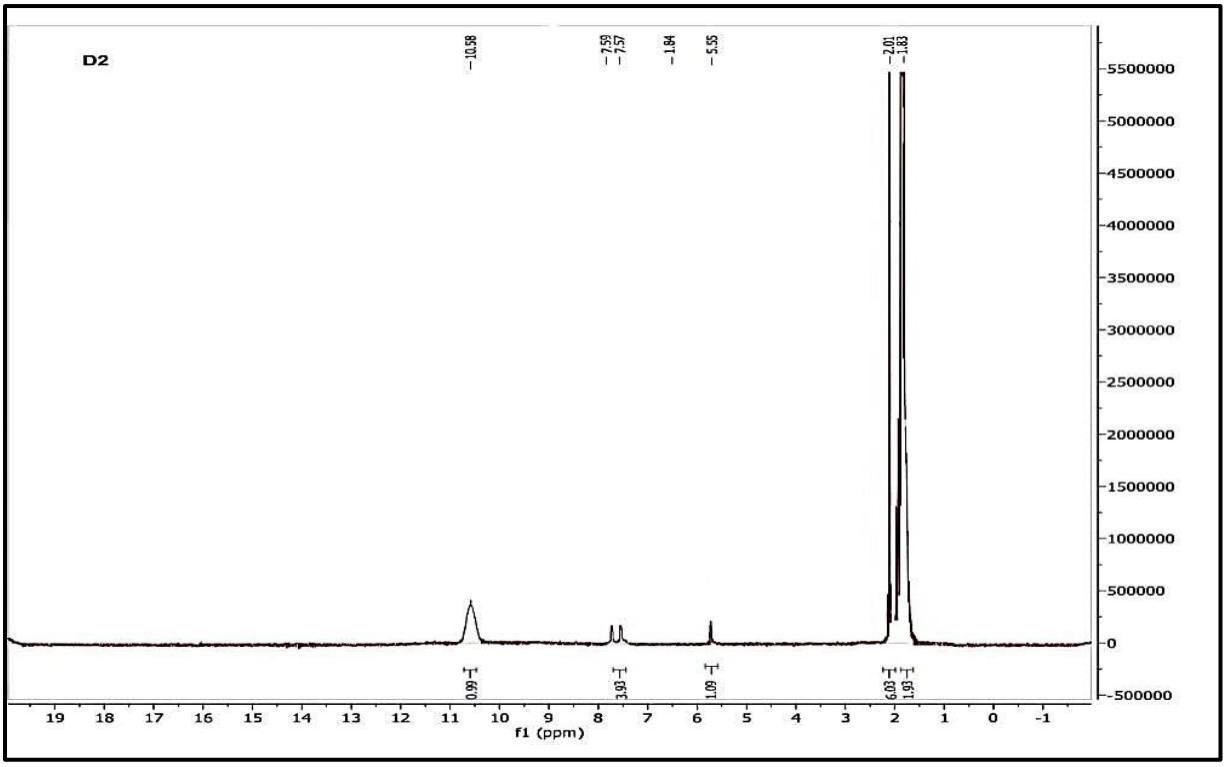


Figure (4.21): ^{1}H NMR spectrum of of 3-(4-Chloro-Phenyl) 5-7-dimethyl-1H-{1,2,4}triazepine (A_4)

4. 7- Synthesis and identification of Synthesis3-(4Chlorophenyl)-7-methyl-4H-methylene1,2,4}triazepine -5-one (A_5a-A_5b)

The compound (A_5a) was synthesized by the reaction of (A_3) and ethyl 3-oxobutanoate in an acid medium with a structure appears in **(Fig4. 22).**

The compound (A_5b) was synthesized by the reaction of (A3) and ethyl 3-oxobutanoate in an base medium with a structure appears in **(Fig4. 22)**

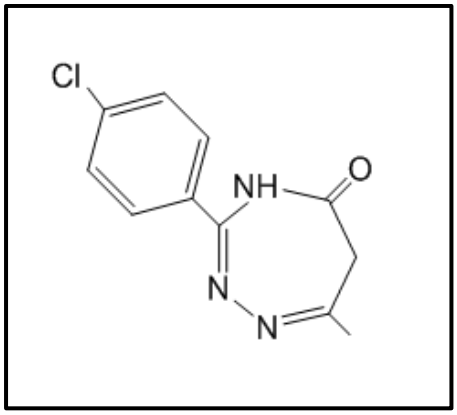


Figure (4.22): The structures of (-A_5a- A_5b).

To prepare the desired seven member heterocyclization of hydrazon amide with 1,3-bifunctional reagent resulting in the formation of (triazepine) nucleus . Thus , the triazepine derivative **(A_5a-A_5b)** were obtained by condensation of compound **A_3** with ethyl acetoacetate in acidic and basic media. In acidic media IR spectrum showed absorption band at 3205, 1703 and 1607 cm^{-1} for NH , C=O and C=N group respectively the ^{1}HNMR**(Fig4-24)** spectrum showed two singlets at δ 8.68, 3.17 and 2.05 ppm for NH, CH_2 and CH_3 respectively. A second attempt at this reaction was carried out in basic media the TLC analysis showed one spot with completely consume of starting material. the^{1}HNMR spectrum also showed three singlets at δ 8.81, 2,8 and 2.04 ppm for NH, CH_2 and CH_3 respectively. The structure of the product was also supported by the FT-IR spectrum that showed band at 3432 and 1628.3 cm^{-1} for NH and C=N group.

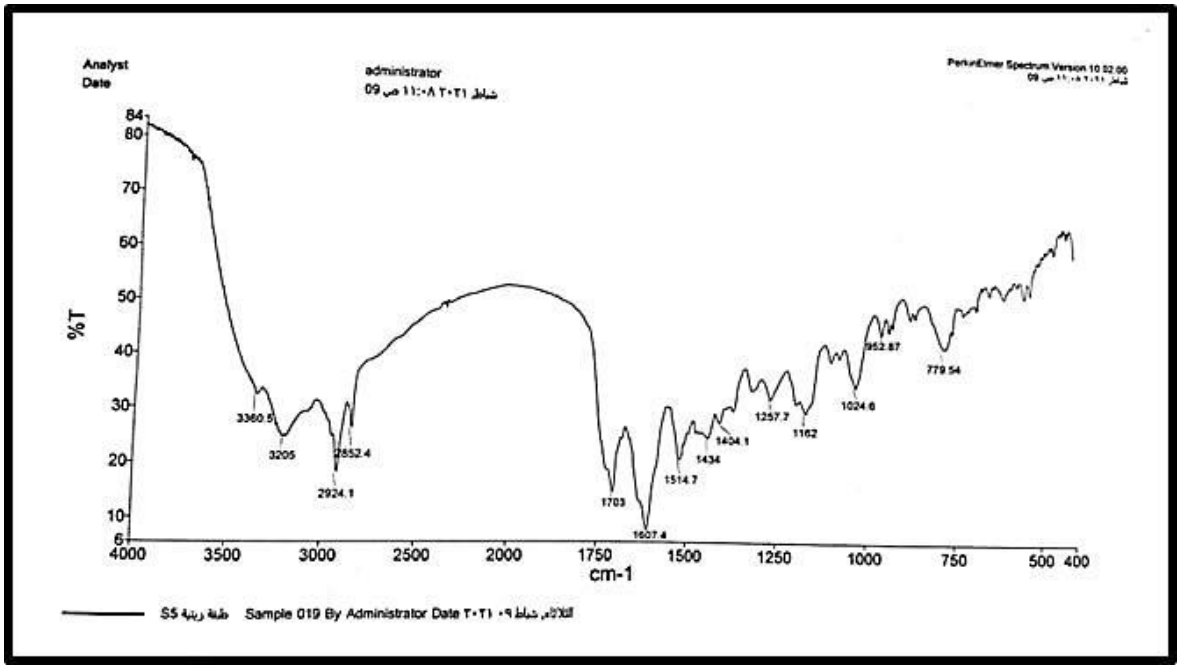


Figure (4. 23): FTIR Spectrum in of (A_5a) compound.

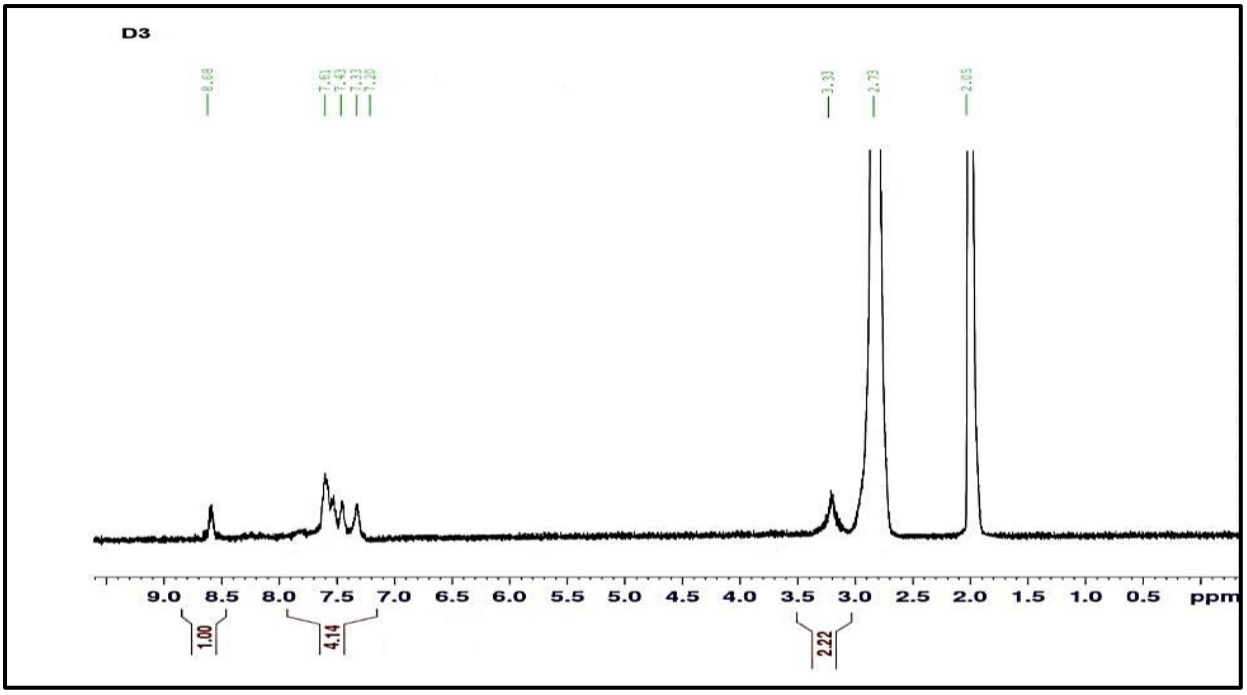


Figure (4. 24): ^{1}H NMR spectrum of(A_5a).

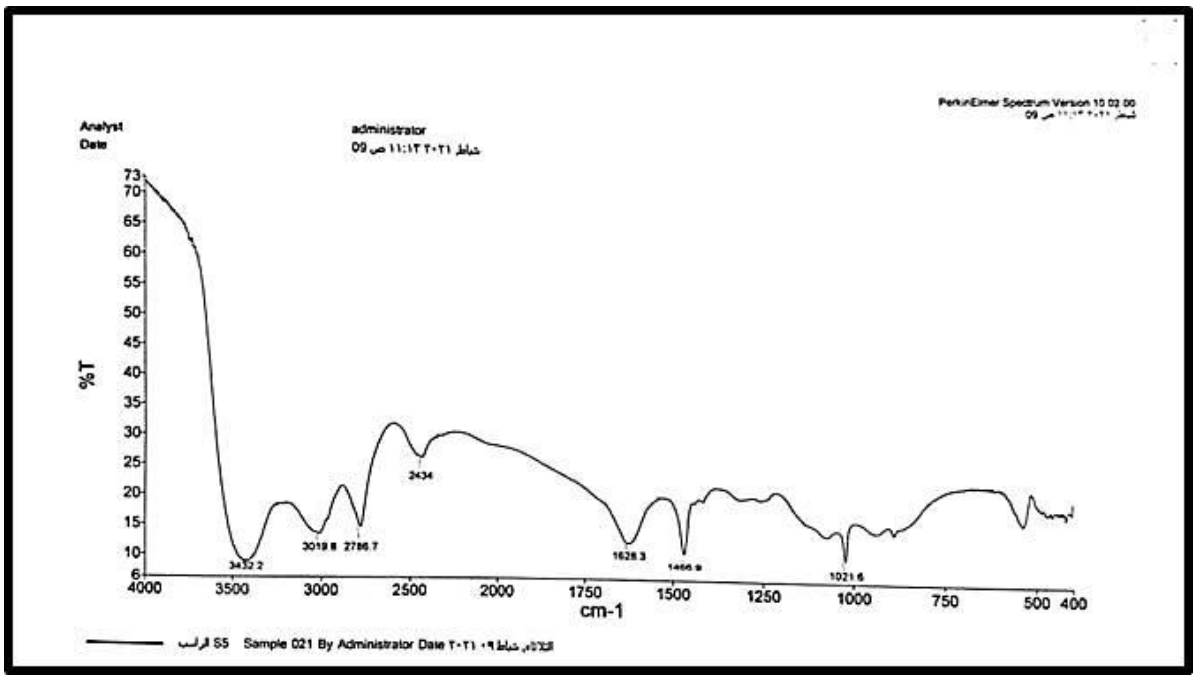


Figure (4. 25): FT-IR spectrum of (A_5b) compound

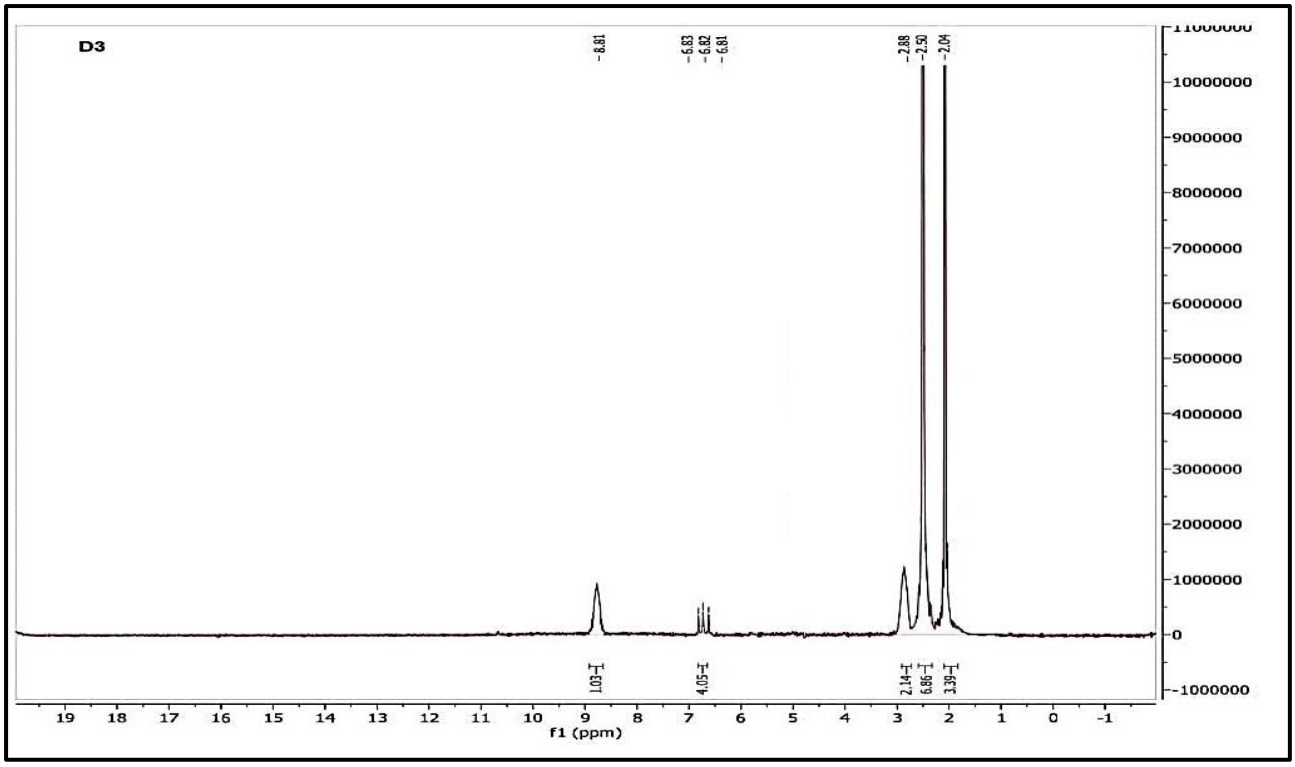


Figure (4. 26)(A)^{1}H NMR spectrum of(A_5b)

4. 8- Synthesis and identification of 3-(4-Chloro-phenyl)-5,6-dimethyl-{1,2,4}triazine [A_6]

compound (A_6) was synthesized through the reaction of (A_3) and butane 2-3-dione , with a structure appears in **(Fig 4.27).**

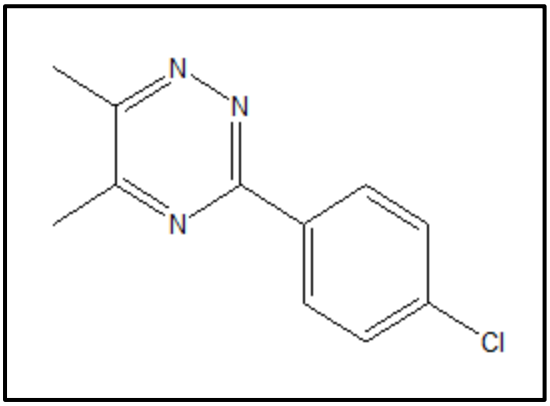


Figure (4.27): The chemical structures of compound (A_6)

The IR spectrum of compound A_6 (Fig4-28) exhibited characteristic absorption band at 1697.8 cm^{-1} for C=N group. The product also was characterized by the appearance in its ^{1}HNMR spectrum Fig(4.29) of singlet signals due to resonance of proton of methyl groups at 1.88 and 1.28 ppm .

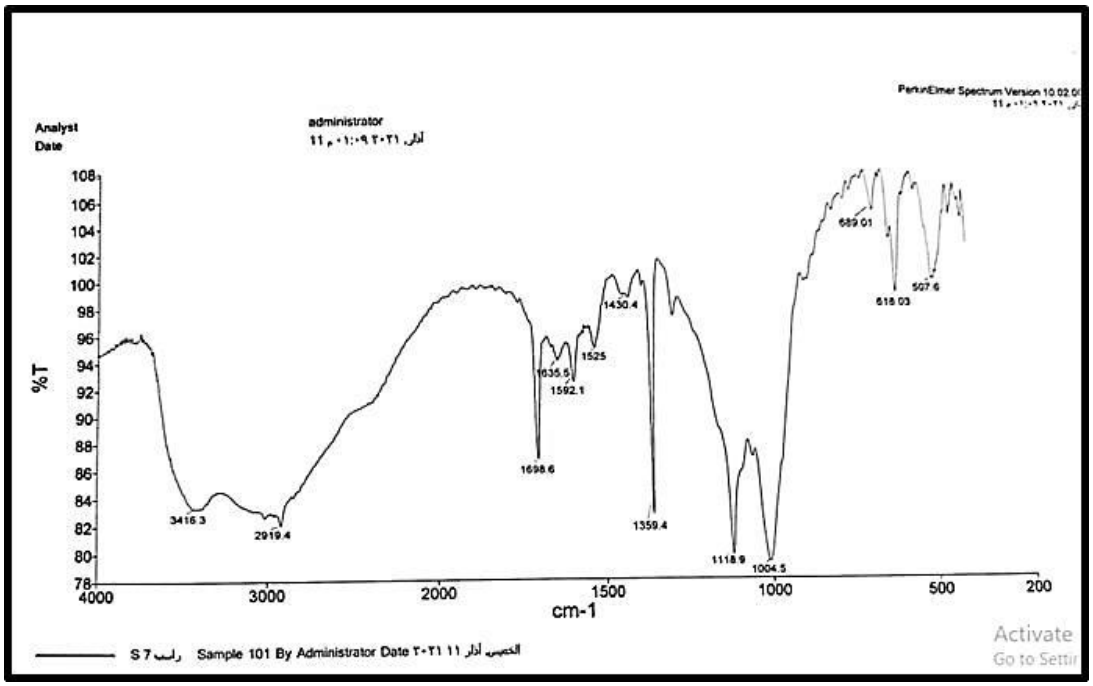


Figure (4. 28): FT-IR spectrum in of (A_6) compound

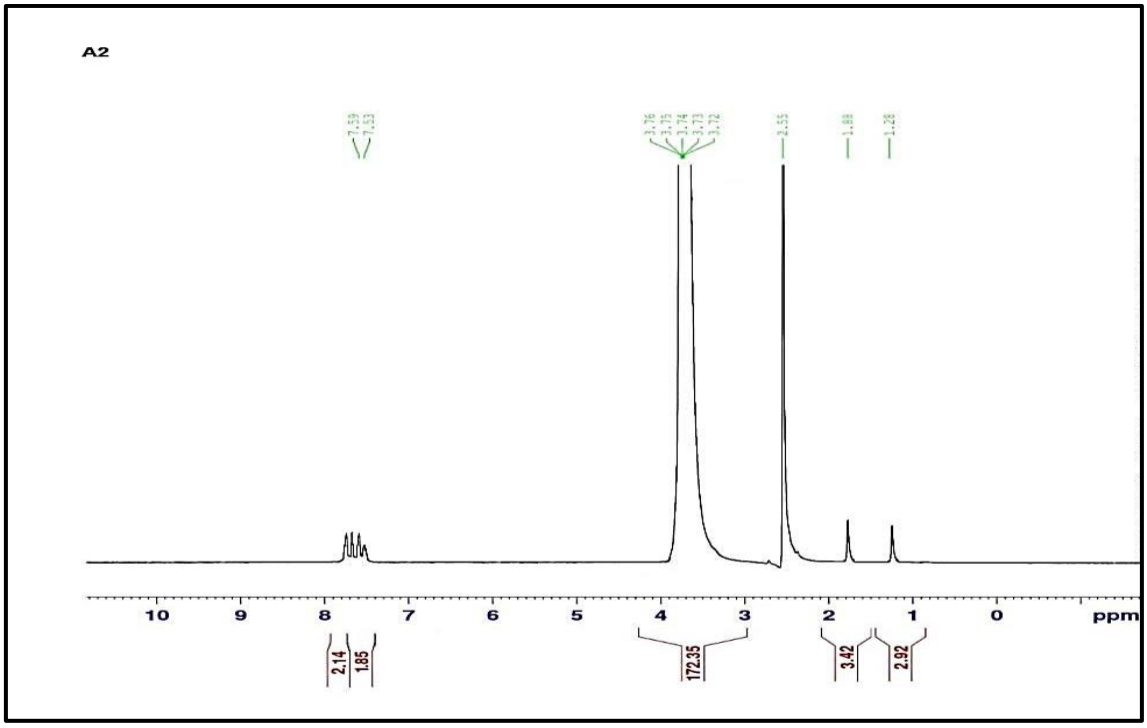


Figure (4.29) HNMR of (A_6) compound

4.9 -Synthesis and identification of 3-(4-Chloro-phenyl)-5,6-di phenyl-{1,2,4}triazine(A_7)

Compound (A_7) was synthesized through the reaction of (A_3)with benzil, with a structure appears in ***(Fig 4.30).***

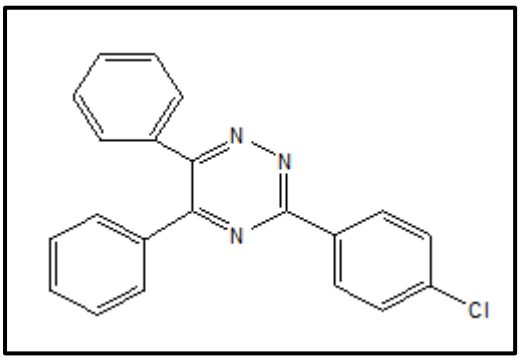


Figure (4. 30): The chemical structures of compound (A_7)

Furthermore, we also investigated the reactivity of A_3 with 1,2-diphenylethane-1,2-dione. After work up the crude product did not showed any signals other than the signals referred to the aromatic protons at δ 7.61-6.91ppm as multiplet in its ^{1}HNMR. In addition IR spectrum confirm the absence of two NH_2 group and appear peak at 1676 cm^{-1} corresponding to C=N group.

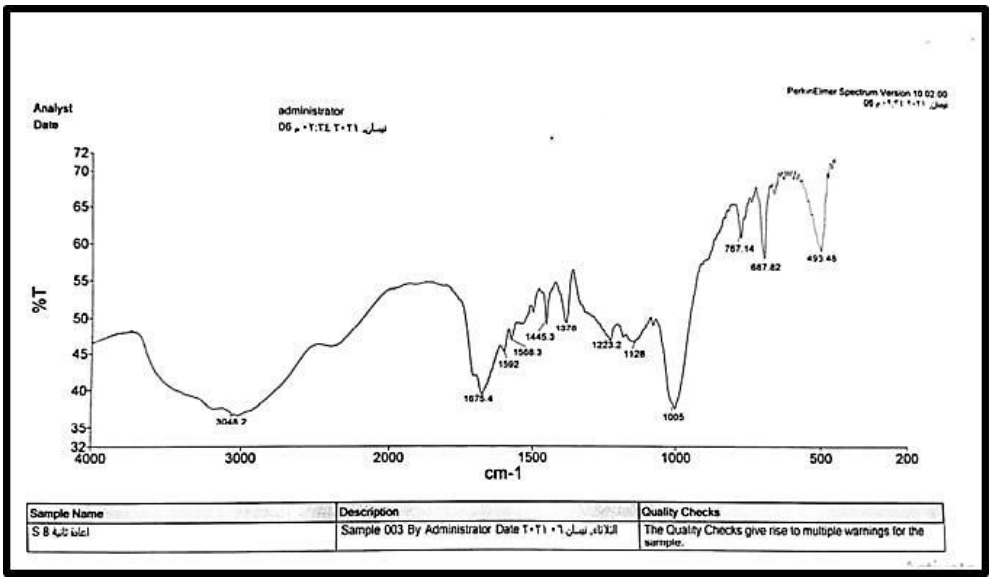


Figure (4. 31): FT-IR spectrum of (A_7) compound.

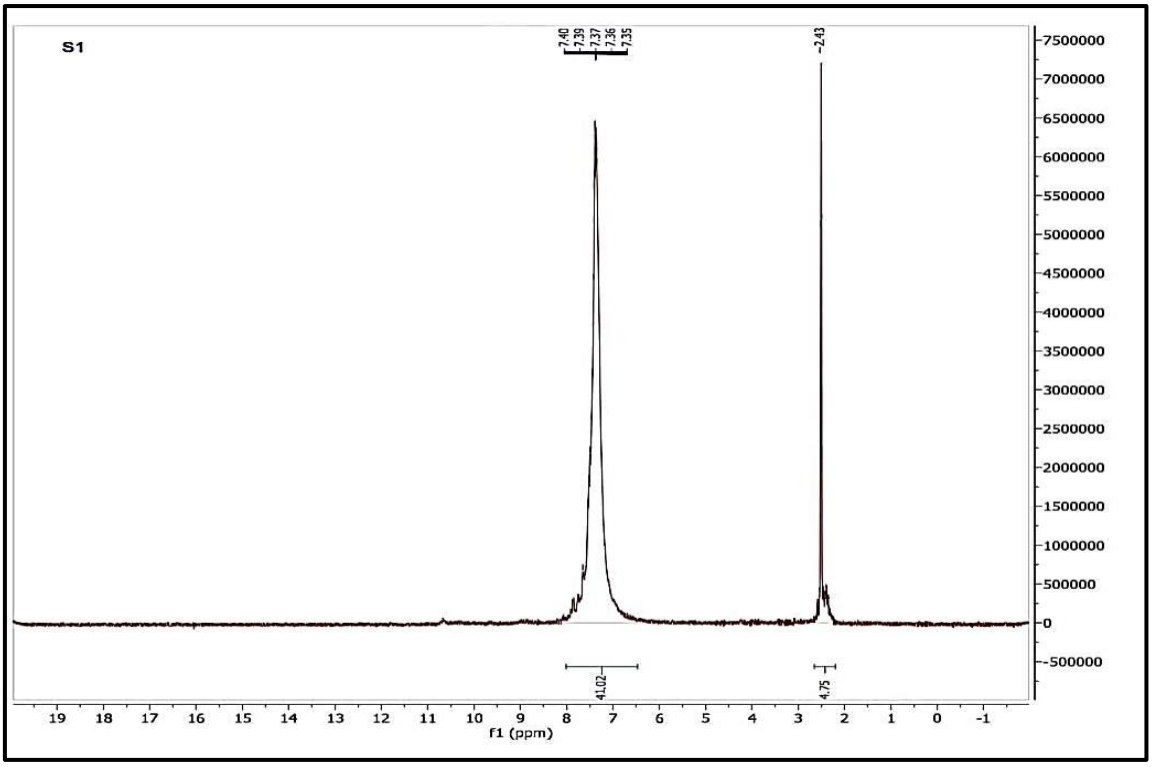


Figure (4. 32): ^{1}H NMR spectrum of 3-(4-Chloro-phenyl)-5,6-di phenyl-{1,2,4}triazine compoundd (A_7).

4.10.Synthesis and identification of 3-(4-chlorophenyl)-9H-{1,2,4} tetrazepino {5-6b}indole (A_8)

Compound (A_8) was synthesized through the reaction of isatin with (A_{3b}), a structure appears in ***(Fig 4.33).***

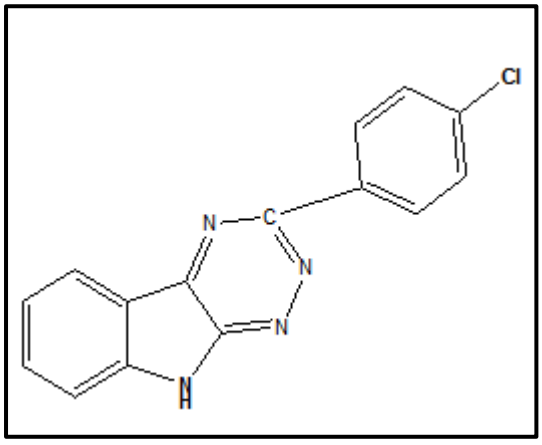


Figure (4.33): The chemical structure of compound (A_8)

Also, analogous cyclization may occur by nucleophiles react with heterocyclic 1,2 diketone isatin. A mixture of 4-chlorobenzohydrazonamide A_3 and (Isatin) in ethanol containing few drops of acetic acid was left under reflux for 24hours. TLC analysis indicated that the reaction had produced a new compound with completely consume of starting material.

the crud material product was purified by column chromatography on silica gel, eluting of hexane-ethyl acetate 1:1 to afford the desired pure product as a orange crystal precipitate in yield of 78%.

FT-IR spectrum **(Fig4-34)** of the new compound showed absorption at 1697,1618cm^{-1} that referred C=N· Absorption starching.

The ^{1}H NMR spectrum**(Fig4-35)** of the first fraction obtained after column chromotograpy showed multi signals at δ 8.12-7.11 ppm due to aromatic proton, and singlet signal at 10.36 ppm due to N-H proton. The^{13}C spectrum display many signals ranging from δ172.27-128.12 ppm corresponding to triazin and aromatic rings.

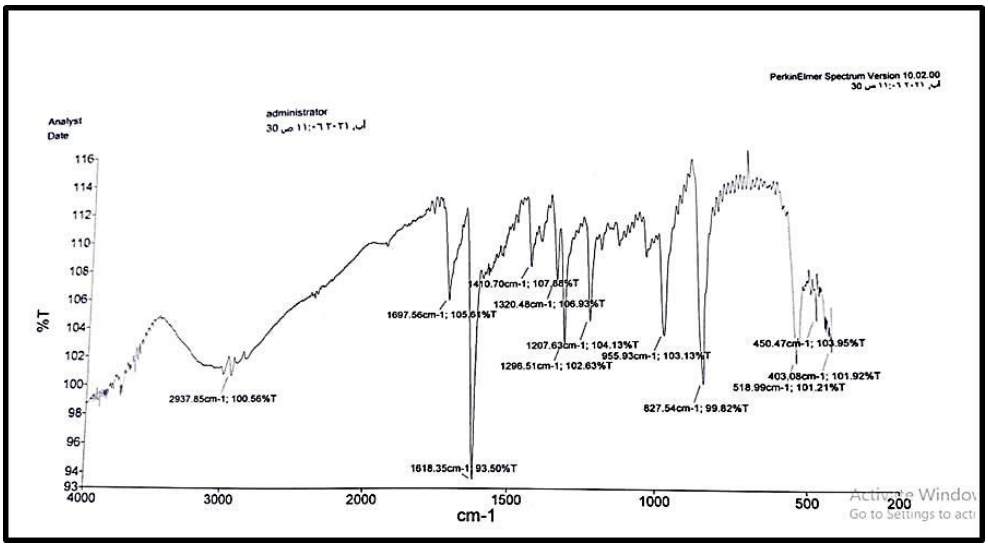


Figure (4.34): FT-IR spectrum of (A_8) compound

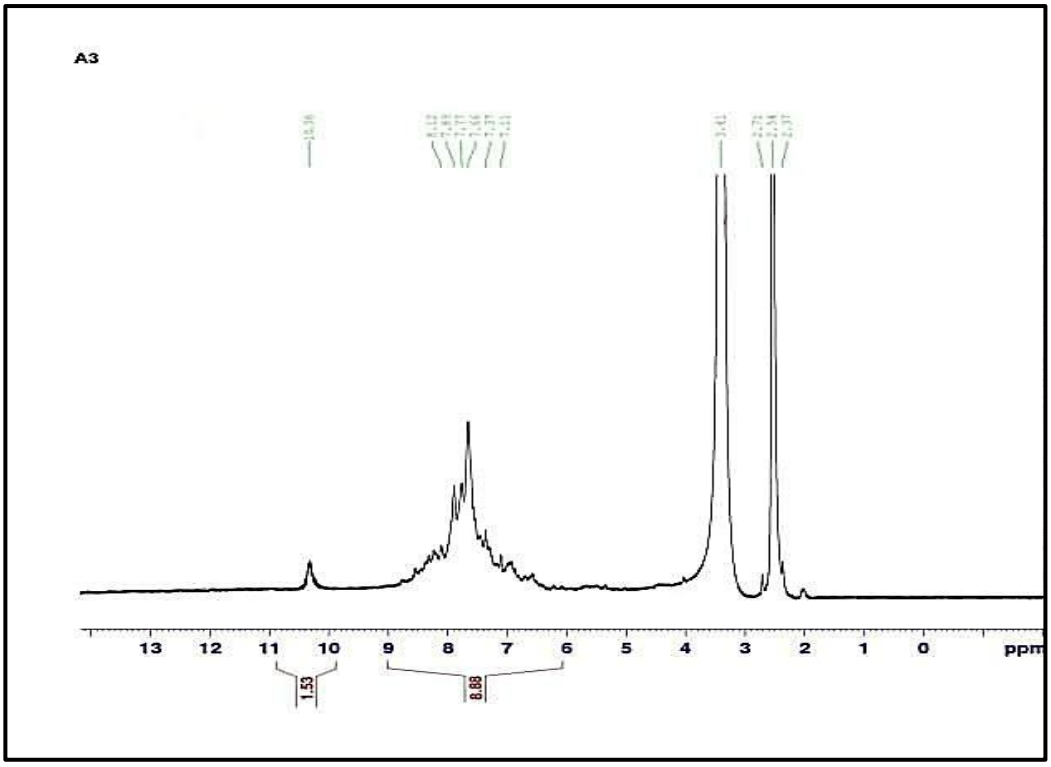


Figure (4.35): ^{1}H NMR spectrum of compound (A_8)

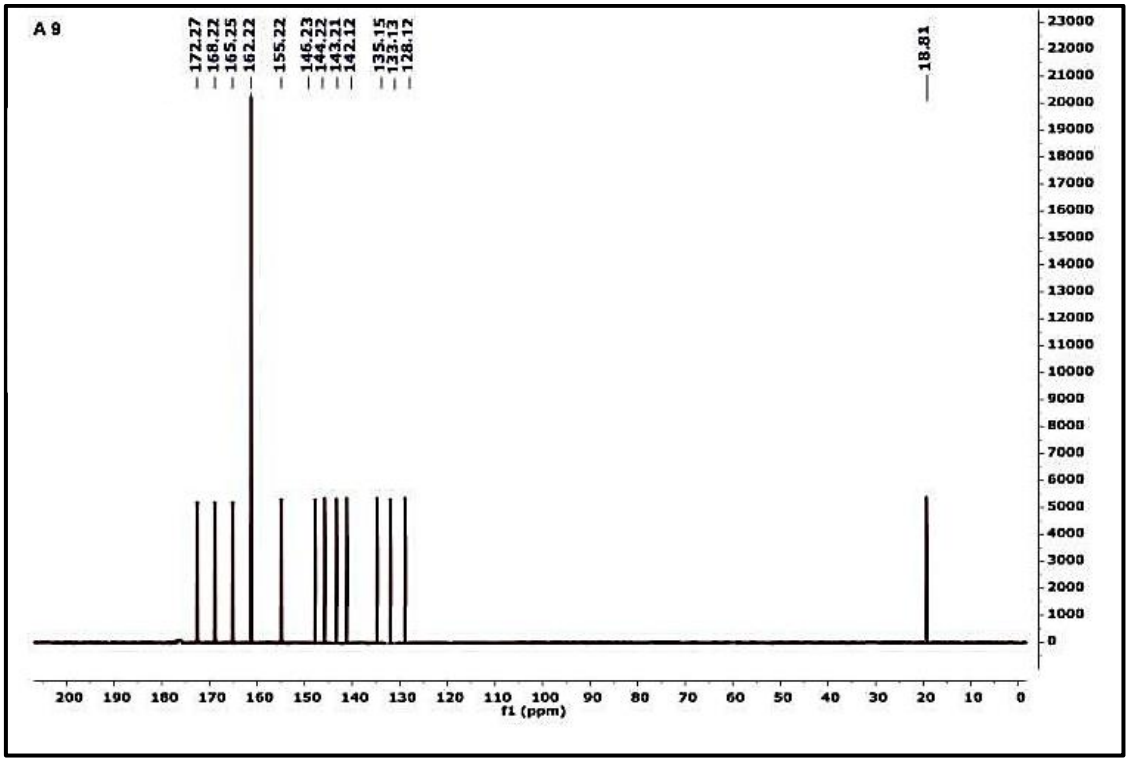
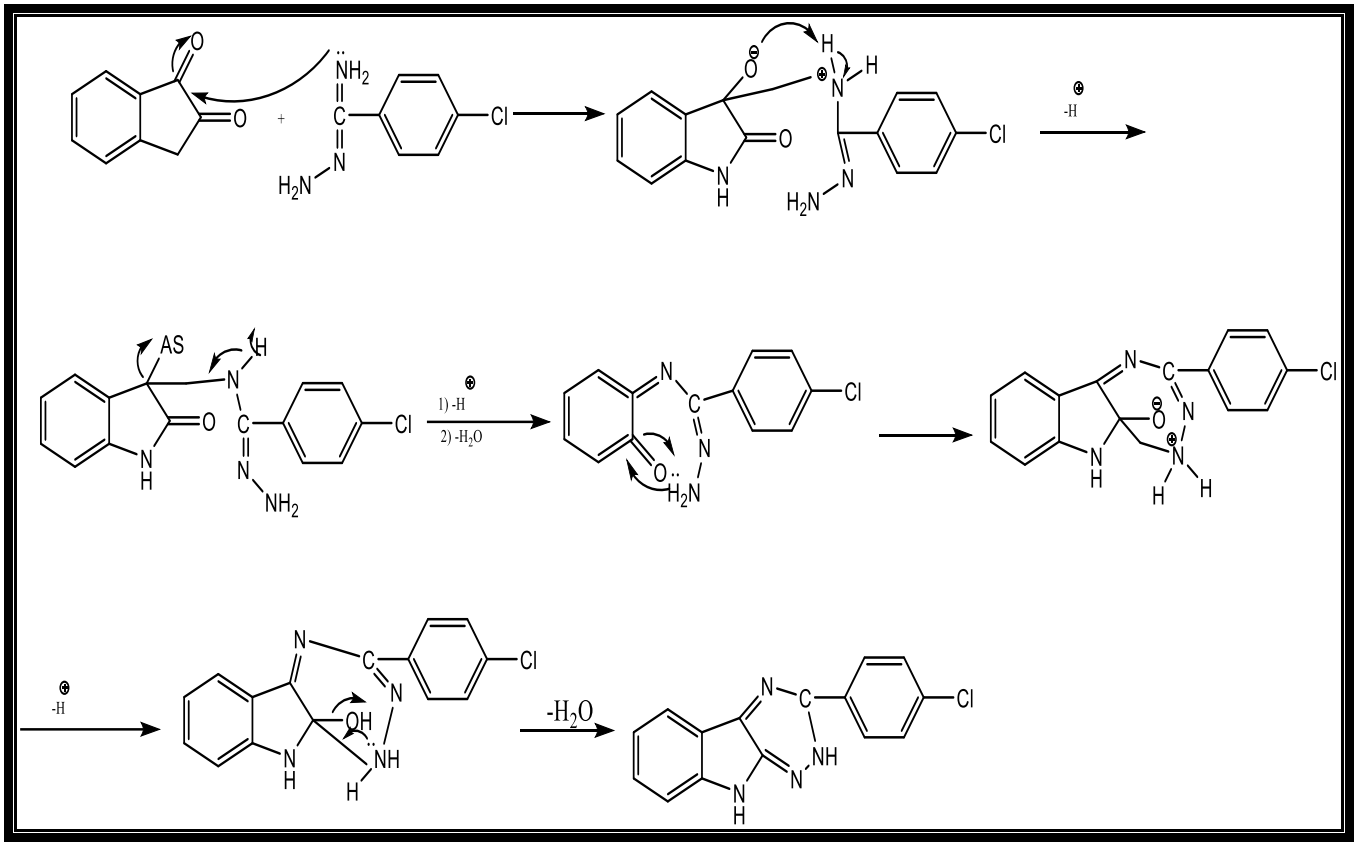


Figure (4.36): ^{13}C NMR spectrum of compound (A_8)



Scheme(4.37): Mechanism of compound A_8 synthesis

4.11-Synthesis and identification of 5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (A_9)

Compound (A_9) was synthesized through the reaction of CS_2 with (A_3b), with a structure appears in **(Fig4.38).** The FT-IR spectrum of compound (A_9) **(Fig4 . 39)**

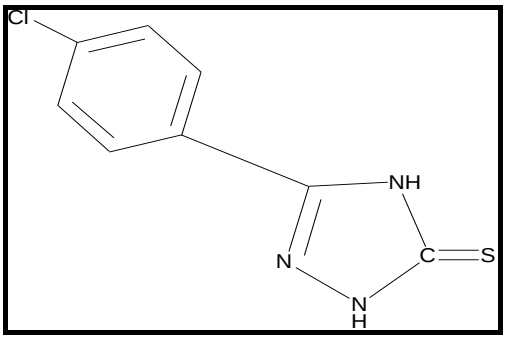


Figure (4.38): The chemical structure of compound (A10)

IR spectrum of A_{10} showed absorption band at 3316.4 and 3243cm-1 corresponding to (2NH) group, as well as a peak at 1239 that belong to C=S group. Its ^{1}H NMR spectrum showed two singlet signals at δ 9.77-9.44 ppm due to two proton, of N-H proton of triazole ring.

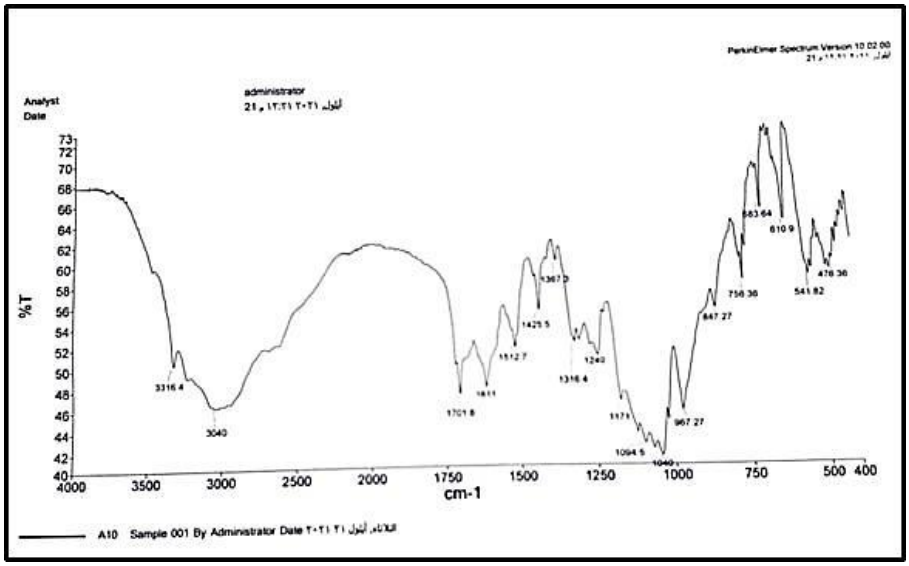


Figure (4. 39): FT-IR spectrum of (A_9) compound

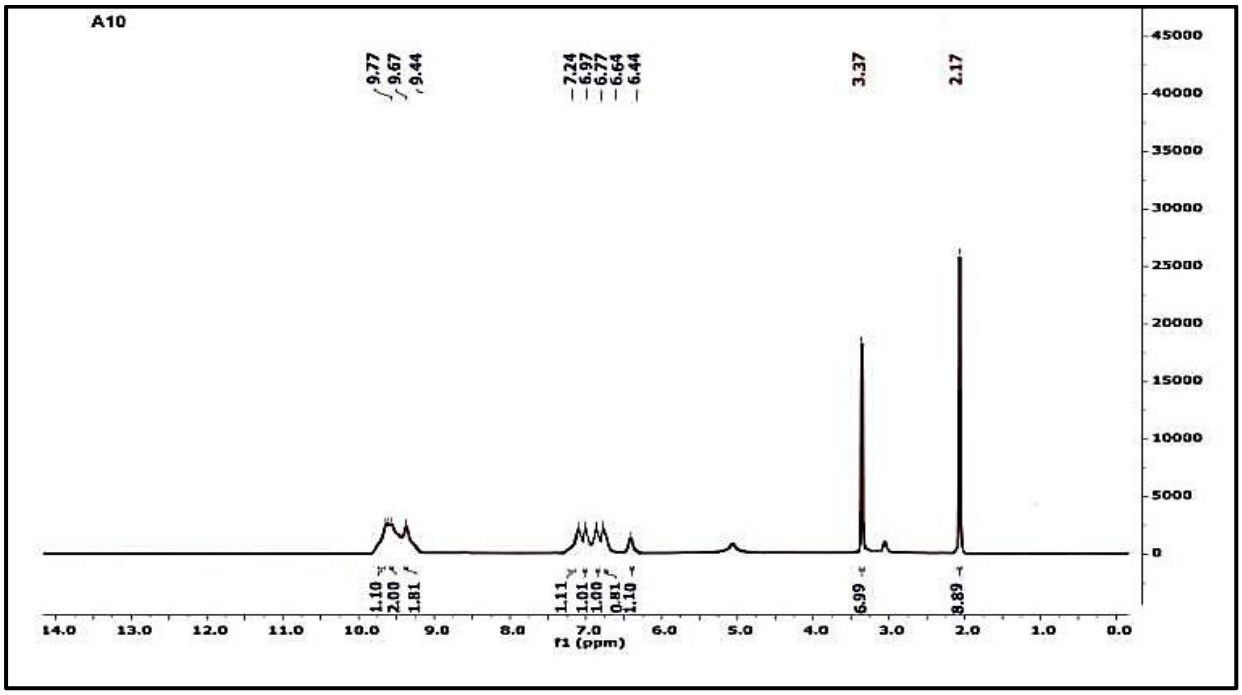


Figure (4.40): HNMR spectrum of (A_9) compound

Table (4.1): Physical Properties of –new compounds A_1 to A_9

Comp. Symbol	Molecular Formula	M. Wt ($g.mol^{-1}$)	Color	M.P. ° C	Yield %
A_1a	**C_6H_6ClNO**	***155.58***	Bright white	**106-107**	***94***
A_1b	**C_6H_6ClNO**	***155.58***	White	**106-107**	***82***
A_2	**C_6H_4ClCN**	***137.57***	Brown	**97-98**	***81***
A_3a	**$C_6H_8ClN_3$**	***161.49***	White	**172-173**	***91***
A_3b	**$C_6H_8ClN_3$**	***161.49***	Pink	**174-176**	***82***
A_4	**$C_{12}H_{11}N_3Cl$**	***232.96***	White crystals	**192-193**	***78***
A_5a	**$C_{12}H_{11}N_3OCl$**	***248.69***	Yellow	**230-231**	***88***
A_5b	**$C_{12}H_{11}N_3OCl$**	***248.69***	Orange	**233-235**	***72***
A_6	**$C_{11}H_{10}N_3Cl$**	***219.67***	Pale yellow	**198-199**	***84***
A_7	**$C_{21}H_{15}N_3Cl$**	***344.82***	Yellow	**291-292**	***87***
A_8	**$C_{15}H_9N4Cl$**	***280.72***	Orange	**287-288**	***78***
A_9	**$C_8H_6N_3SCl$**	***211.67***	White	**220-224**	***67***

4. 12 - Biological activity

Material and Methods

Staphylococcus aureus isolate was cultured on Blood agar and Mannitol salt agar. *Escherichia coli* isolate was cultured on MacCkonky agar and Eosin methylene blue. *Candida albicans* isolate was cultured on Sabouraud dextrose agar and Candida chromogenic agar.

MacFarland turbidity standard

The preparing solution from the company (Biomeriex) was used in calibrating the number of bacterial cells, as it gives an approximate number of cells 1.5 x 10^8 cells/ml.

1- Muller Hinton agar

This medium was prepared by dissolving 38 gm in 1L of distillated water and sterilized by autoclave at 121 °C and under pressure 15 pounds for 15 minutes cooled and poured into sterile dishes and kept in the refrigerator until use.

2- Determination the Antimicrobial activity of(A_4 and A_7) by agar well diffusion method

1- A number of bacteria colonies were transported by loop to prepare the suspended bacteria and put it in tubes contain brain heart infusion broth to activate the bacteria. The tubes were incubated for (18 - 24) h at 37 °C. The suspended bacteria was compared to the standard MacFarland solution (1.5 x $10^{8)}$ cells/ml. After that the bacteria suspended was spread by Sterile Swab, it was spread on the plates containing Muller Hinton agar and then left the plate for a while to dry.

2- A holes were made with a diameter of 5 mm in the culture media by using sterilized a cork borer

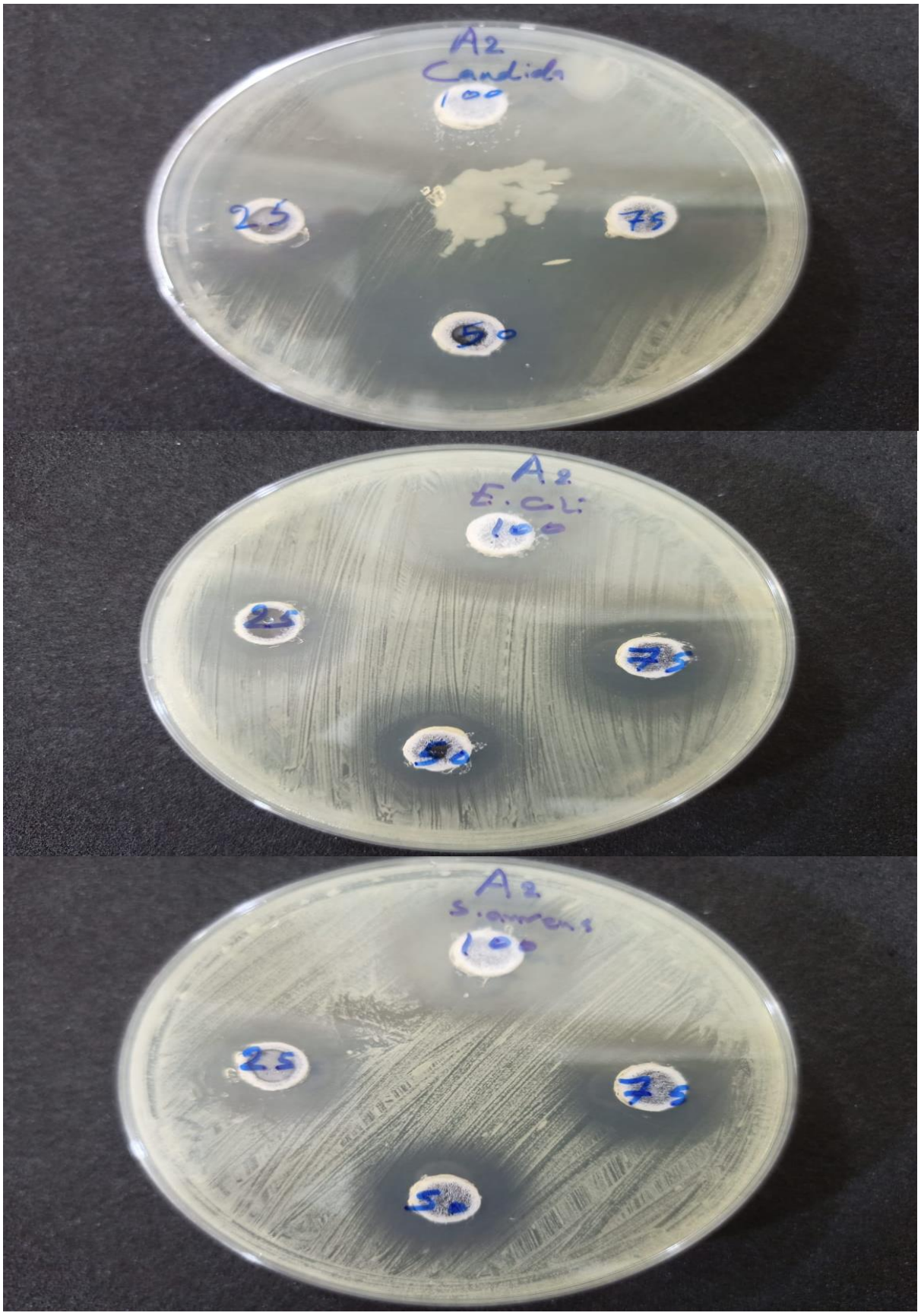
3- 100 µl of the material were added to each hole individually by micropipette.

4-The effectiveness of each concentration was determined by measuring the diameter of the inhibition zone around each hole.

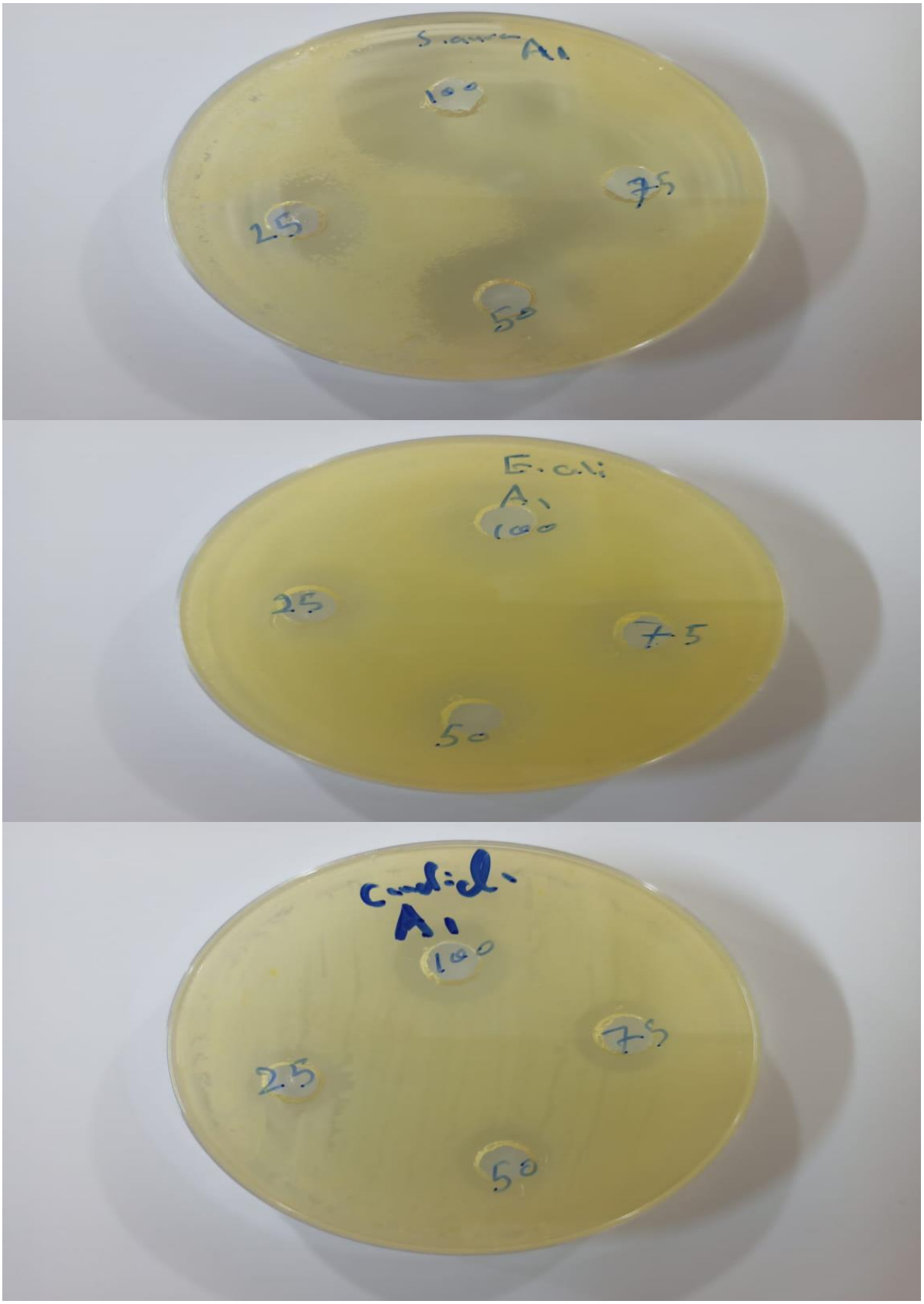
Results

Table(4.2): Results of Biological activity

Microorganism / **Tested materials**	*C. albicans*				*E. coli*				*S. aureus*			
	25	50	75	100	25	50	75	100	25	50	75	100
A1=A7	12	14	15	17	19	20	22	23	18	25	33	35
A2=A4	24	26	32	40	21	22	26	30	17	19	23	24



Figure(4-41):Effects of the tested (A_4) against *S. aureus* and *E.coli*.



Figure(4-42):Effects of the tested (A7) against *S. aureus* and *E.coli*.

4.13-Conclusion

1. The synthesis and purification by column chromatography eluting with hexane - ethyl acetate (1:1) of 4-chlorobenzohydrazonamide as precursor to built the hydrazone derivative was successful
2. These compounds were obtained as solid state and the purity of each synthetic compounds were confirmed by thin layer chromatography.
3. Their chemical structures were identified by inspection of its spectral techniques for instant FT-IR, ^{1}H-NMR ^{13}C-NMR and APT ^{13}C-NMR .
4. Synthesis seven new compounds in good yield through the reaction of 4-chlorobenzohydrazonamide with 1.2-diketone and aldehyde .
5. Two of the synthesized compounds **(A4, A7)**. Were examined for their antibacterial and antifungal activities result indicated that, compound (A4) showed pronounced activity against *Candida albicans*

4.14-Suggestions for Future work

1 - We have achieved an efficient (3steps) route to the key precursor hydrazone amide from 4-chlorobenzaldehyde.

2- Now we would seek to apply this route to synthesis different heterocyclic compound on large scale and evaluation their biological activity against different kind of cancer cells, bacteria or fungus.

3- It may will be that the specific reaction conditions developed in this area could be applied with success to this work

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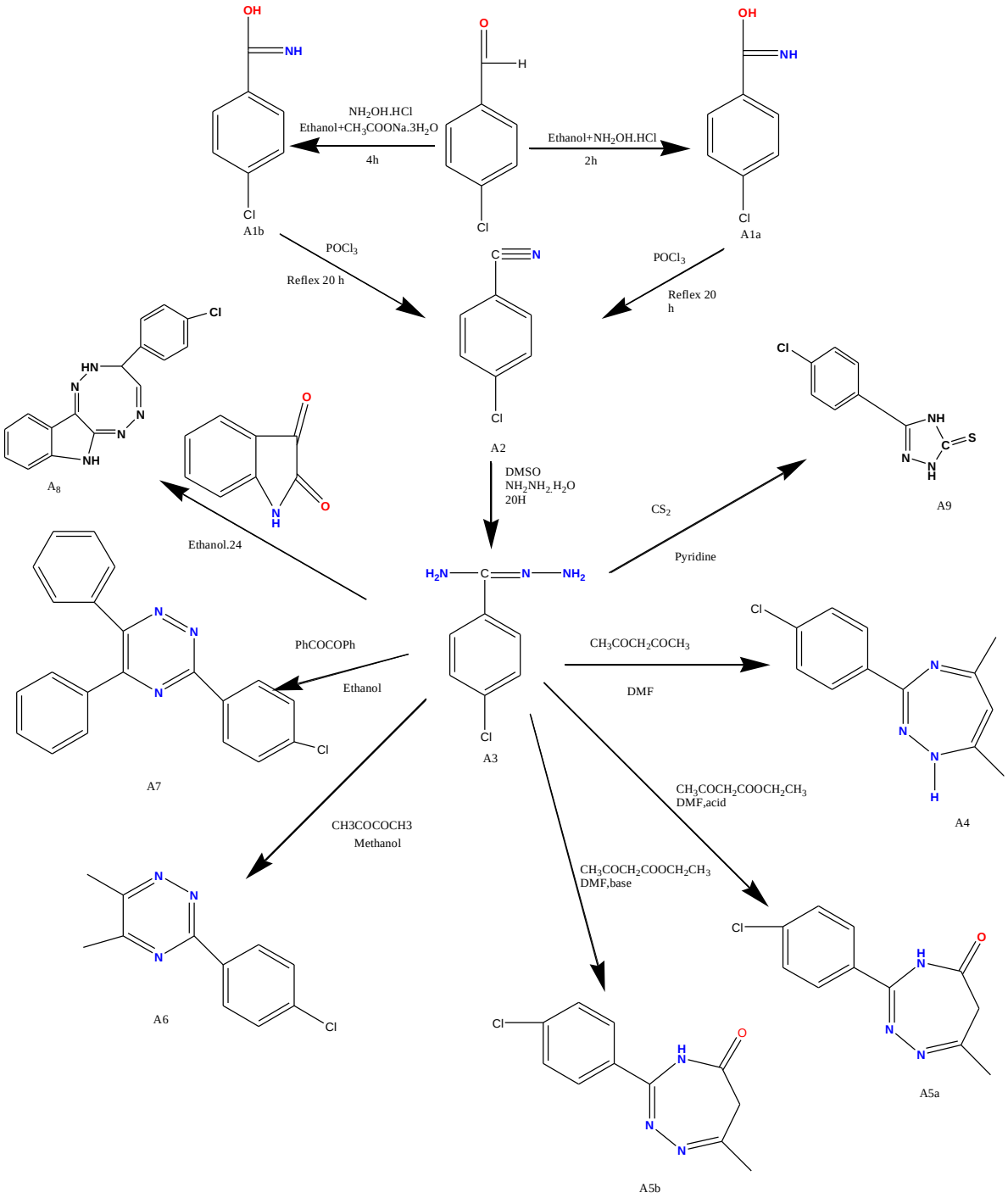
الخلاصة

يصف العمل في هذه الرسالة طريقة تحضير الهيدرازون امايد كحالة وسطية في تحضير مشتقات الهيدرازون

المسار الاول تضمن تحضير 4-كلوروهيدرازون امايد من تحضير الاوكسيم بنسبة ناتج جيدة تتبعه تحضير 4-كلورونتريل لكي يتيح لنا تحضير 4-كلورو هايدرازون امايد

1- بدأت الخطوة الأولى من تفاعل 4-- كلورو بنزالديهايد مع هيدروكسيل الامونيوم هيدروكلوريك وثلاثي هيدرات اسيتات الصوديوم في الايثانول لتكوين الاوكسيم .
2- تم تحضير 4-كلوروبنزونتريل في خطوة واحدة بتفاعل الاوكسيم مع كلوريد الفوسفوريل
3- تم الحصول على المركب المطلوب 4-كلوروبنزوهيدرازون امايد بعد تفاعل 4-كلورونتريل مع الهايدرازين بوجود داي مثيل سلفوكسايد
4- تم تصنيع مشتقات الهيدرازون امايد من خلال تفاعل 4-كلوروبنزوهيدرازون امايد مع مركبات داي كيتون ومركب كاربون داي-سلفايد باستخدام اوساط مختلفة
5- المركبات تم تشخيصها واثبات تركيبها الكيمياوي بالتقنيات الطيفية مثل طيف الاشعة تحت الحمراء(FT- IR) وطيف الرنين المغناطيسي للبروتون والكاربون (^{1}H-NMR, APT ^{13}C-NMR), تم اختبار نقاوتها بواسطة كروموتوكرافيا الطبقة الرقيقة وتم تقييم مركبين جديدين لنشاطهما السمي ضد بكتريا (موجبة وسالبة الغرام)والفطريات. وتم الحصول على نتائج جيدة



مخطط يوضح المركبات التي تم تحضيرها

وزارة التعليم العالي والبحث العلمي

جامعة ديالى / كلية العلوم

قسم الكيمياء

التحضير و الفعالية البايولوجية لبعض المركبات الحلقية غير المتجانسة من مشتقات الهيدرازون

مجلس كلية العلوم / جامعة ديالى

وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

كيمياء عضوية

من قبل الطالبة

أنفال عمر علي

بكالوريوس في علوم الكيمياء 2015

جامعة ديالى ـ كلية العلوم

بأشراف

أ.م.د. لمى سلمان عبد

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