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Synthesis, Characterization and Evaluation of Biological Activity of Some Isatin Derivatives

A Thesis Submitted to The Council of the College of Sciences, University of Diyala in Partial Fulfillment of the Requirements for the Degree of Master of Science in Chemistry

By

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بسم الله الرحمن الرحيم

﴿ يَرْفَعِ ٱللَّهُ ٱلَّذِينَ ءَامَنُواْ مِنكُمْ وَٱلَّذِينَ أُوتُواْ ٱلْعِلْمَ دَرَجَٰتٍ ۚ وَٱللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ ﴿١١﴾ ﴾

صدق الله العظيم

(سورة المجادلة- الأية)

Dedication

I dedicate my thesis ……..

The last of the prophets and messengers, our noble messenger and our example, Muhammad(peace be upon him).

The source of my strength and pride, and my family, who deserve all the thanks and gratitude, especially my beloved mother, my husband, sisters, idedicate my message to my father and my daughter and finally all thanks to my dear supervisor (Asst. Prof. Dr. wassan Baqir Ali) for the burden they have carried with me in order to achieve my dream.

RUSUL

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First of all, I thank Allah for helping me to overcome obstacles that stood in my way during the research.

I would like to express my special thanks to my parents and my sisters for their invaluable support and encouragement.

I would like to sincerely thank my supervisor Asst. Prof. Dr. wassan Baqir. Ali for her guidance and support throughout this study, especially for her confidence in me.

Sincere thanks are also to the Dean of the College of Science/ University of Diyala. I express my thanks to the Head and the staff of the Chemistry Department for their help

Also I would like to direct my deep thanks to my husban.

To all my friends ,thank you for your understanding and encouragement in my many moments of crisis, your friendship makes my life a wonderful experience . I cannot list all the names here, but they are always in my mind

RUSUL

Abstract

In this thesis, new compounds have been successfully synthesized from isatin **,** and their purity confirmed by thin layer chromatography**.** The chemical structures of the synthesized compounds (R_1- R_9) were determined by some spectroscopy techniques such as [FTIR ,^{1}H-NMR and ^{13}C-NMR]. The reactions were followed up by thin layer chromatography (T.L.C), some physical properties of synthesized compounds were determined such as melting points and colors**.** The new synthesized compounds (R_1- R_9) were tested for antibacterial efficacy against gram-negative and gram-positive bacteria, respectively, ***E. coli and S. aureus***. Most of these compounds exhibited good to acceptable antibacterial activity against two strains of the tested bacteria**.** The current study included these steps **:**

1- Synthesis of compound (Z)-3-(benzo[d]thiazol-2-ylimino)indolin-2-one[R_1] by the reaction of isatin with, 2-aminobenzothazole**.**

2- Synthesis of (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-chloroacetyl) indolin- 2-one[R_2] by the reaction of [R_1] with chloroacetyl chloride and triethylamine.

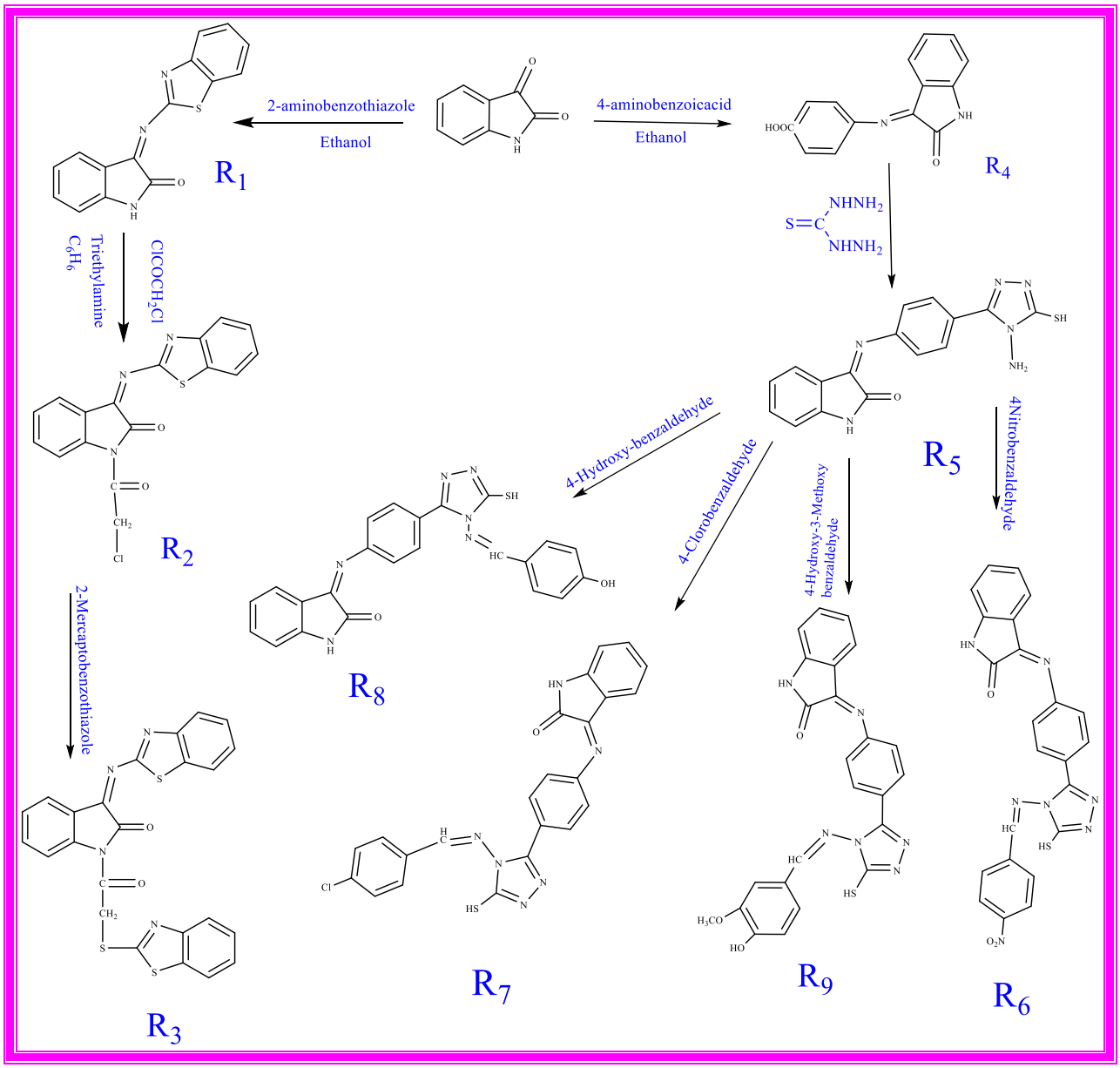
3- Synthesis of compound (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-(benzo[d]thiazol-2-ylthio)acetyl)indolin-2-one by the reaction of [R_2] with 2-mercaptobenzothazole.

4- Synthesis of compound (Z)-4-((2-oxoindolin-3-ylidene)amino)benzoic acid [R_4] through the reaction of isatin with 4-amino benzoic acid.

5- Synthesis of compound (z)-3-((4-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one [R_5] by the reaction of[R_4]with thiocarbohydrazide .

6- New schiff bases [R_6 -R_9] were synthesized through the reaction of the compound [R_5] with different aromatic aldehydes**.**

Scheme (1): General scheme of the synthesized compounds



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List of abbreviations

Abbreviation	Meaning
^{1}H-NMR	*Proton Nuclear Magnetic Resonance*
F.T-IR	*Fourier-transform infrared*
DMSO	*Dimethyl sulfoxide*
M.P.	*Melting point*
M. Wt	*Molecular weight*
TLC	*Thin layer chromatography*
&	*And*
Ar	*Aromatic ring*
E. coli	*Escherichia coli*
Cm	*Centimeter*
G	*Gram*
µm	*Micrometer*
%	*Percent (per cent)*
Δ	*Chemical shifts*
H	*Hour(s)*
Min	*Minute*
MHz	*Megahertz*
Ppm	*Parts per million*
S	*Singlet*
Cal	*Calculated*
Λ	*Wave length*
Cond.	*Conductivity*
CT	*Charge Transfer*
^{0}C	*Degree Celsius*

$\bar{\upsilon}$	*Wave number*
μeff	*Magnetic torque*
Mmol	*Millimol*
B.M	*Bohr Magneton*
Mm	*Millimeter*
^{13}C-NMR	Carbon Nuclear Magnetic Resonance Spectrometer

CHAPTER ONE

Preface & Literature review

1.1. Preface

Heterocyclic chemistry has now become a separate field of chemistry with long history, present society and future prospects. Nitrogen, oxygen and sulfur are considered the most hetero atoms known. Heterocyclic compounds are considered one of an important type of organic compounds due to their implication in drugs and industrial studies[1]. As they find wide application as analgesic agents, tranquilizers, neurotransmitters besides other pharmacologically active products Amoxycillin, an antibiotic; ranitidine, an antagonist of the H_2 histamine receptor for the treatment of gastric ulcers; hydrochlorothiazide and florosenide, diuretics; acetaminophen,an analgesic; digoxin, a cardiac glycoside; pencillin-V, an antibiotic; etc. contain heterocyclic ring as a part of their structures . Heterocycles are synthesized with a focus on studying the physiological effects that these compounds can trigger and the synthetic routes that can provide with greater supply of these compounds than that nature can produce. Thiadiazoles, oxadiazoles and triazoles are five membered rings associated with diverse biological and pharmacological properties ,Thiadiazoles are any of several isomeric five membered heterocycles having two carbon atoms, two nitrogen atom, one sulphur atom and two double bond. Oxadiazolines are five membered heterocycles having two carbon atoms, two nitrogen atom, one oxygen atom and two double bond [2]. Indole, an important class of nitrogen, containing heterocyclic with wide variety of biological activities. Isatin is a derivative of indole which is indole-2,3-dione. Isatin is reported for antitubercular activity[3]. Isatin's synthetic adaptability has led to a wide range of uses in organic synthesis, with the medicinal and pharmacological aspects of its derivatives being actively researched. A number of Schiff bases generated from Isatin and Imesatin derivatives have been reported to exhibit antibacterial, antifungal,

and antiviral activities, as well as central nervous system (CNS) depressant, anti-HIV, anti-inflammatory, analgesic, and anticancer agents **[4-7].** Schiff base reactions are useful in organic synthesis for forming carbon-nitrogen bonds and are a crucial intermediary in a variety of enzyme processes. Reactions in which an enzyme interacts with an amino or carbonyl group in the substrate. In an enzyme, the condensation of a primary amine, usually a lysine residue, occurs. One of the most important types of catalytic mechanisms in biological processes is the formation of schiff base or Imesatin with a carbonyl group of the substrate. Azoles such as isoxazole, thiazole, pyrazole, tetrazole, and triazole, are nitrogen-containing heterocyclic compounds that are increasingly used in the current field of research and development of novel drugs. 1,2,4 triazoles are among these azoles are a significant moiety of medicinal compounds that meet the criteria for novel medication development. The compounds of [1,2,4] triazole have a high potential of biological activity antifungal, antibacterial**[8]** anticonvulsant, antipsychotic**[9]** and antitumour properties**[10]**

1.2. Literature review

Pandeya S. N. et al (2005) Synthesized aseries of condensed compounds by reacting a heterocyclic system like isatin or 5-fluro isatin with ethyl cyano acetate and substituted ketones by Jain. This compound showed anticonvulsant activity in rats **[11]** Fig (1.1)

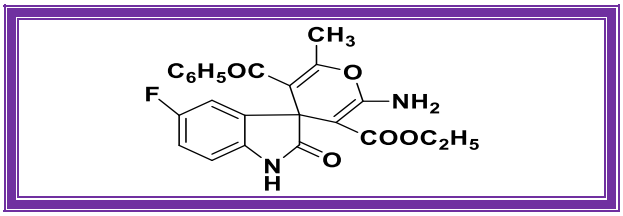
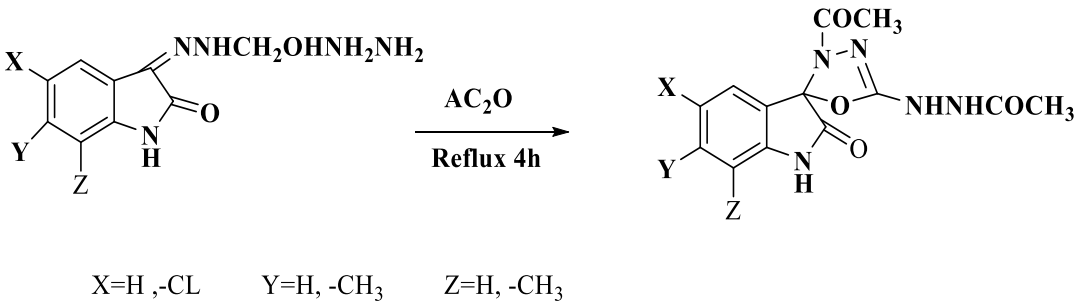


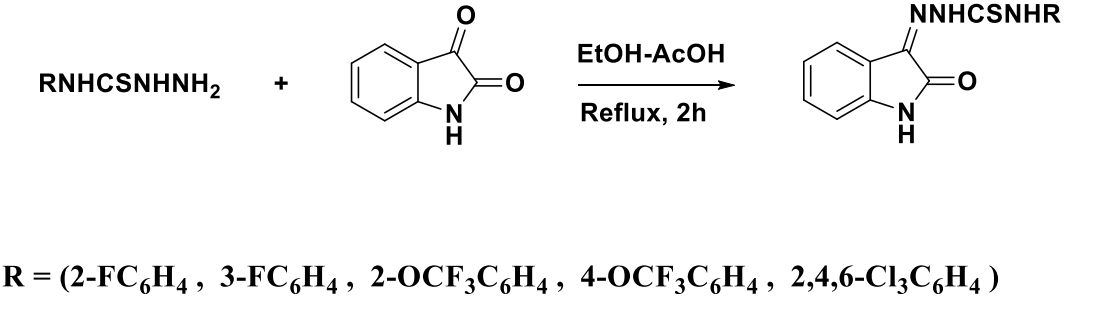
Fig. (1.1): Heterocyclic derivatives of isatin

Md. Rabiul Islam et al.(2007) have created chalcone-based heterocyclic compounds with five membered rings, such as pyrrole, furan, and thiophene. The goal is to improve the antifungal activity of some produced compounds, as well as to study these compounds using theoretical programs and demonstrate that they have new antifungal activity **[12]** . As show in Scheme (1.1).



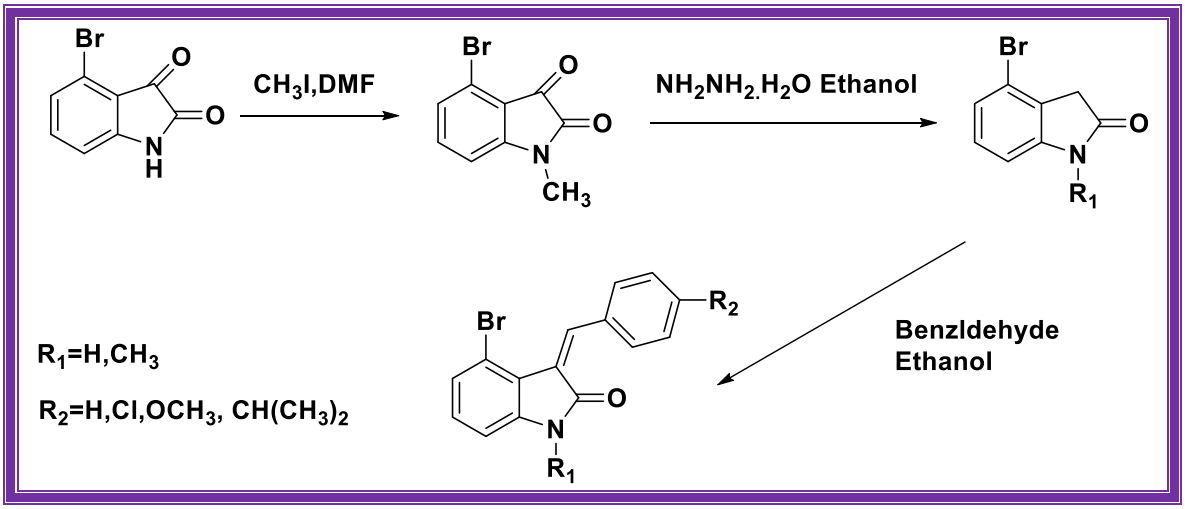
Scheme (1.1): Synthesis of Heterocyclic derivatives of isatin

Humayun pervez et al.(2009) have synthesized characterized and screened a new series of N4-substituted isatin-3-thiosemicarbazones for in vitro cytotoxic, phytotoxic and urease inhibitory effects. All the compounds proved to be active in the brine shrimp bioassay. All the synthetic compounds showed weak to moderate (10–40%) phytotoxicity at the highest tested concentration (500 mg/mL) indicating their usefulness as inhibitors of soil ureases **[13]**. As show in Scheme (1.2).



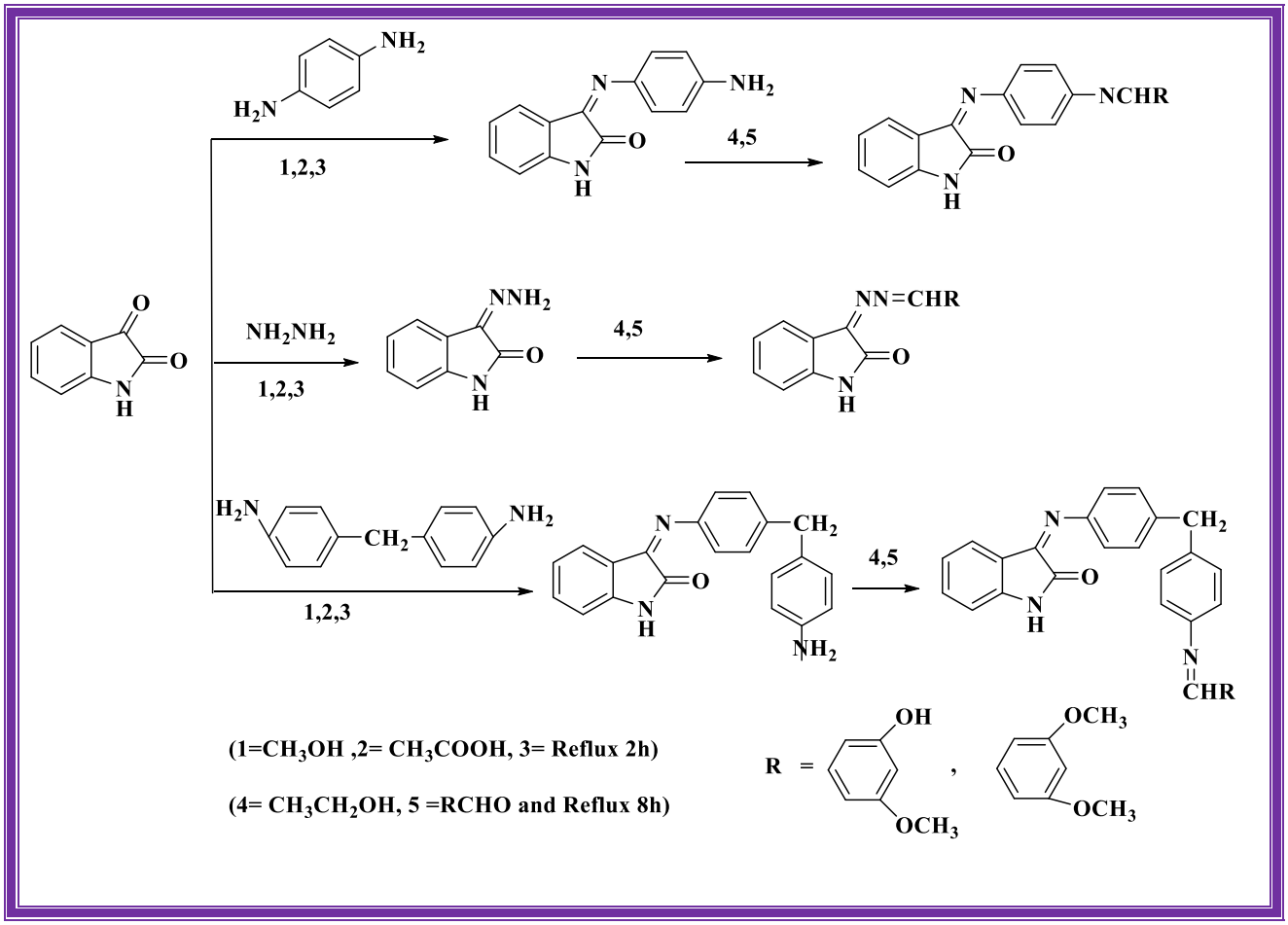
Scheme (1.2). Synthesis N4-substituted isatin-3-thiosemicarbazones

Yuou Teng et al (2013) produced heterocyclic compounds with 4-Bromo substitution on the basis of isatin . The goal is to boost the cytotoxic activity of the substance anticancer activity and selectivity of some prepared compounds **[14]** Scheme (1.3).



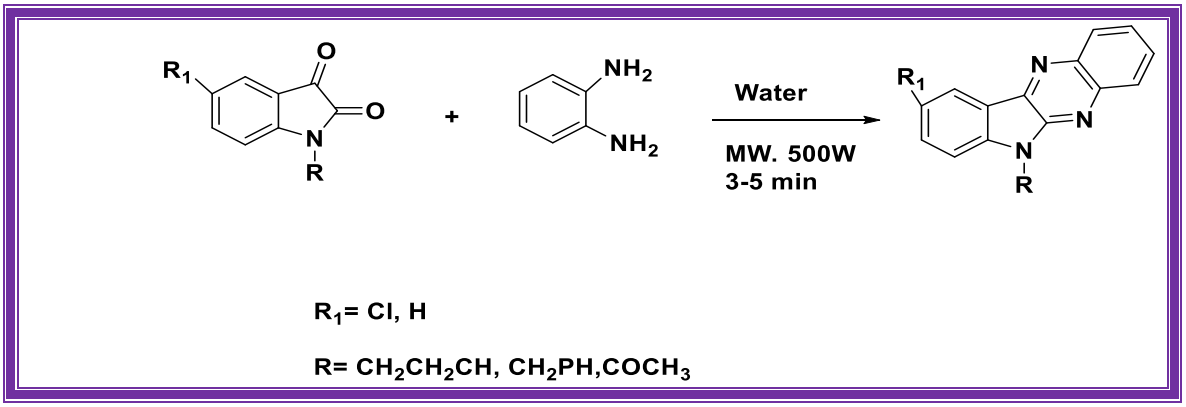
Scheme (1.3): Synthesis route of 3-substituted 4-Bromo isatin derivatives

Olubunmi S. Oguntoye et al.(2016) have synthesized the reaction of Hydrazine monohydrate, p-phenylenediamine, and 4,4-diaminodiphenylmethane with isatin yielded a range of novel schiff bases of imesatin and isatin derivatives, which were previously synthesized. The synthesized schiff bases were obtained in moderate to excellent yields and purity **[15]**. As show in scheme (1.4).



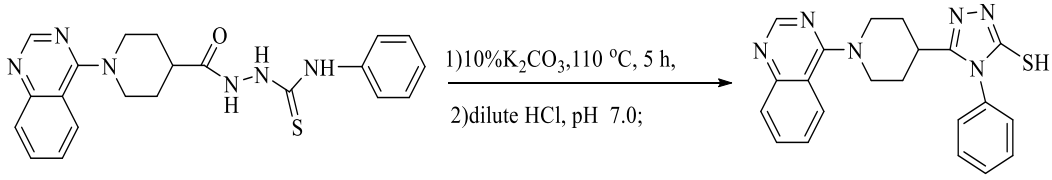
Scheme (1.4): synthesis of the Schiff bases of isatin and Imesatin derivatives

Bajpai, et al (2017) used isatin derivatives with o-phenylenediamine in water under microwave irradiation Scheme (1.5). The presented method is mild, environmentally friendly, inexpensive and highly effective to give products in good to excellent yields **[16]**.



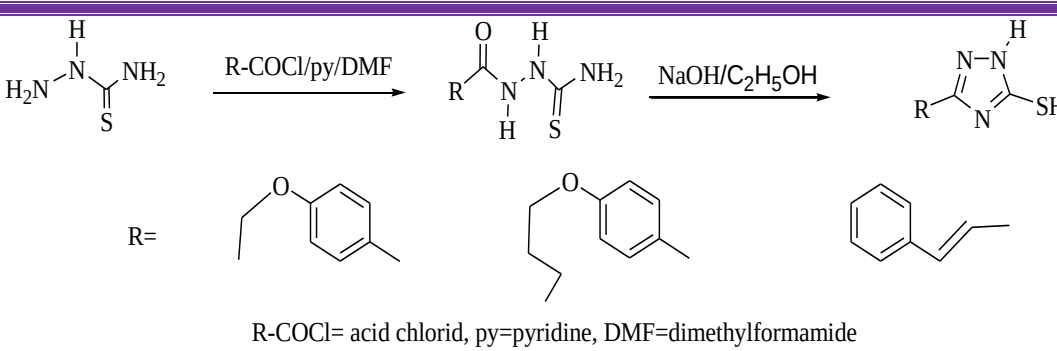
Scheme (1.5): The reaction consists in the condensation of the Benzene-1,2diamine groups on the C_2 and C_3 carbonyl functions of isatin.

Yang. et al(2017) Synthesized a 4-phenyl-5-(1-(quinazolin-4-yl)piperidine-4-yl)-4H-1,2,4-triazole-3-thiol from reaction N-phenyl-2-(1-(quinazolin-4-yl)piperidine-4-carbomyl)hydrazine-1-carbothioamide in the presence of K_2CO_3, HCl **[17]** As show in scheme (1.6).



Scheme (1.6). Synthesis of 4-phenyl-5-(1-(quinazolin-4- yl)piperidine-4-yl)-4H-1,2,4-triazole-3-thiol

Mioc et al . (2017) synthesized a 1H-3-R-5-mercapto-1,2,4-triazoles by acylation of thiosemicarbazide with the corresponding acid chloride and pyridine in N,N-dimethylformamide, followed by the cyclisation reaction of the resulted 1-acyl-thiosemicarbazides in ethanolic NaOH, at reflux **[18]** As show in scheme (1.7).



Scheme (1.7). Synthesis of 1H-3-R-5-mercapto-1,2,4-triazoles

Al-Azawi (2018) successfully synthesized as Isatin-aniline compound, namely ethyl 4-aminoN-(3-isatinyl) benzoate in high yield and its inhibition impact on corrosion of MS (mild steel) in hydrochloric acid as corrosive solution was examined via weight loss and scanning electron microscope techniques Fig (1.2) **[19]**

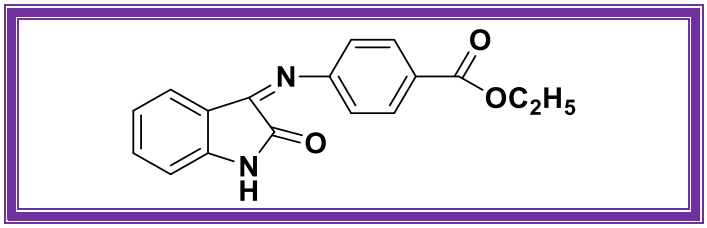
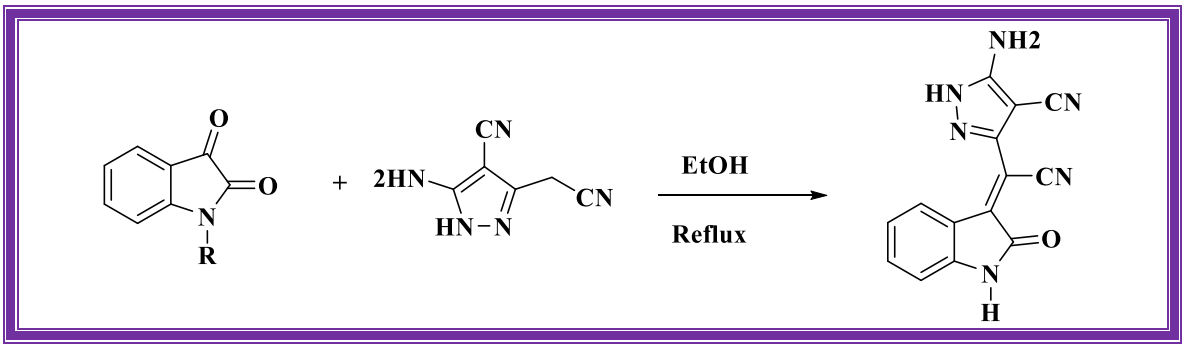


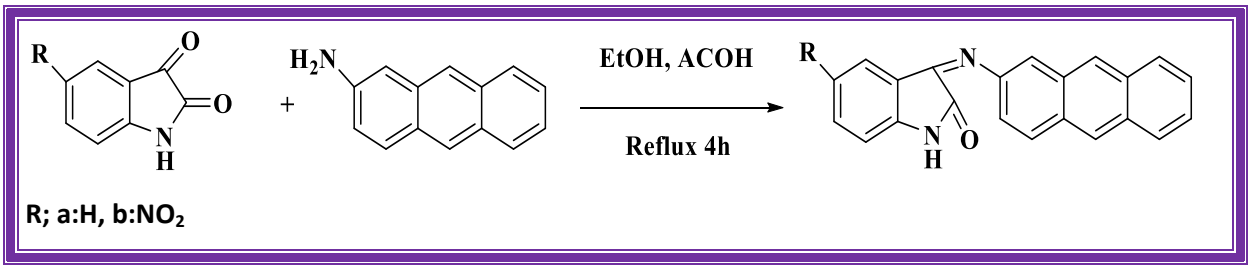
Fig (1.2): Synthesis of the inhibitor (ethyl 4-amino-N-(3- isatinyl)benzoate

Mohamed I. Hassan (2019) have synthesized a 5-amino-3-(cyano(2oxoindolin-3-ylidene)methyl)-1H-pyrazole4-carbonitrile form reaction Isatin with 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile in absolute ethanol was heated under reflux for 3 hours and show its new activity as antibacterial activities **[20]** Scheme (1.8).



Scheme (1.8): Synthesis of Heterocyclic derivatives of isatin

Inci Selin, D. et al (2019) Used an isatin (1H-indole-2,3-dione) as a reagent in a large number of synthesis due to its biological properties. In addition, it is a heterocyclic ring system used for obtaining and other reactions of indole and quinoline derivatives. In this study, two new Schiff base compounds were synthesized by the reaction of 2-aminoantracene with an isatin/5-nitroisatin **[21]** the structure of the synthesized compounds as show in scheme (1.9).



Scheme (1.9). Synthesis of new isatin derivatives

1 .3. The aim of the study

The main objectives of this study are the following:

1- The synthesis of Schiff base indole derivatives.

2- Characterization of the synthesized compounds by some spectroscopy techniques such as [FTIR ,^{1}H-NMR and ^{13}C-NMR].

3- Measurement of the biological activity of all prepared compounds and testing their effectiveness against both bacteria of types positive and negative gram .

CHAPTER TWO

INTRODUCTION

2.Introduction

2.1. Heterocyclic compound

Heterocyclic chemistry is an essential field in the chemical sciences and it accounts for a large portion of the current research being conducted around the world **[22].** Cyclic compounds in which one or more of the ring atoms are different atom other than carbon are called heterocyclic compounds which may have N, O, S and less frequently phosphorous, boron and silicon **[23].** The heteroatom is a Greek word which means different **[24].** Heterocyclic compounds can be aromatic in nature according to their chemical structure such as pyrrole, furan, and thiophene or aliphatic like pyrrolidine and tetrahydrofuran. The aromatic heterocyclic rings can be five or six-membered. They may contain one heteroatom such as pyrrole , furan, and thiophene, or two heteroatom as in imidazole which comprises of two nitrogen atom, or oxazole ring which contains nitrogen and oxygen. These heterocyclic rings could be fused with benzene ring to form one compound, for example, Indoles compounds and their derivatives as illustrate in Fig (2.1) **[25].**

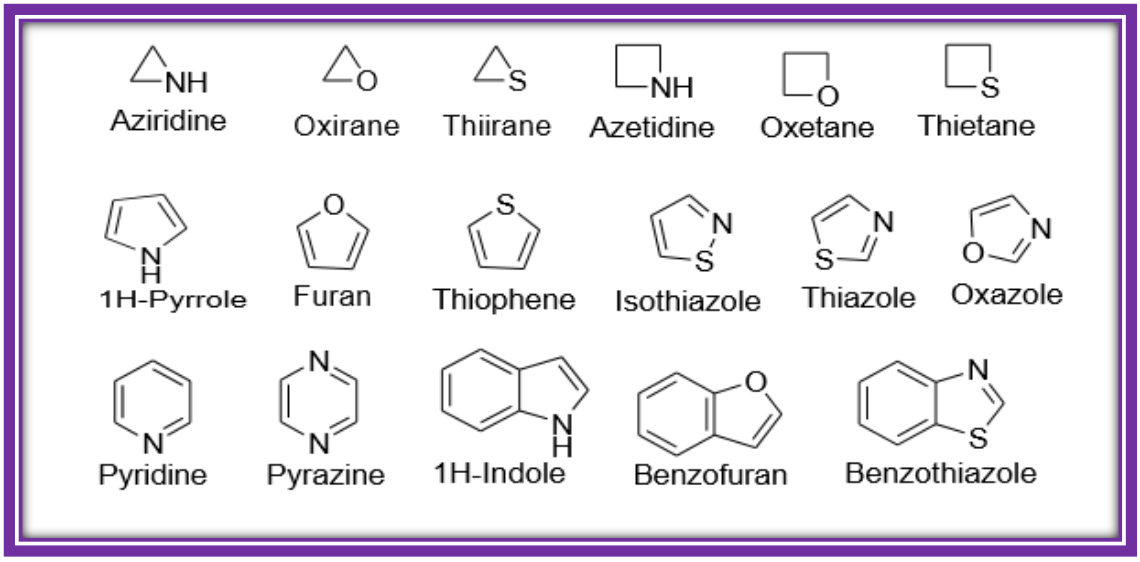


Fig (2.1): Simple aromatic rings and nonaromatic rings

Heterocyclic compounds containing 5- or 6-membered ring are important due to their diverse biological activities **[26].** These are represent a large group of heterocyclic compounds, have been extensively explored for developing pharmaceutically molecules **[27].** Organic chemists have been making extensive efforts to produce these compounds are abundant in nature and great more to life because of many natural products contains many subunits in their structure such as hormones, vitamins, and antibiotics **[28].** Therefore, they have attracted significant attention in the composition of many important biological molecules. Because of their extensive distribution in nucleic acid structures and involvement in most physiological processes in plants and animals, nitrogen heterocycles are the most frequent among the huge number of heterocycles discovered in nature, especially those incorporating oxygen or sulphur **[29].**

2.2. Isatin

Isatin (1H-indole-2, 3-Dione) consist of indole nucleus and two types of carbonyl groups i.e. keto and lactam group Fig (2.2). It has been discovered 150 years ago and now known as oxindole and Endogenous polyfunctional heterocyclic compounds. It was first investigated by Erdman and Laurent in 1841 as a product from the oxidation of indigo using nitric and chromic acids **[30].** Various substituted isatins have also been identified in plants, fungi and symbiotic bacteria **[31].** Isatin and its derivatives have a wide spectrum of biological and pharmacological properties, and they are commonly employed as starting materials for the synthesis of heterocyclic compounds and as drug synthesis substrates **[32].**

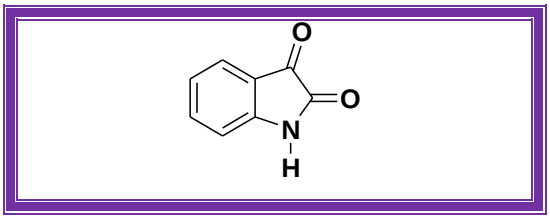


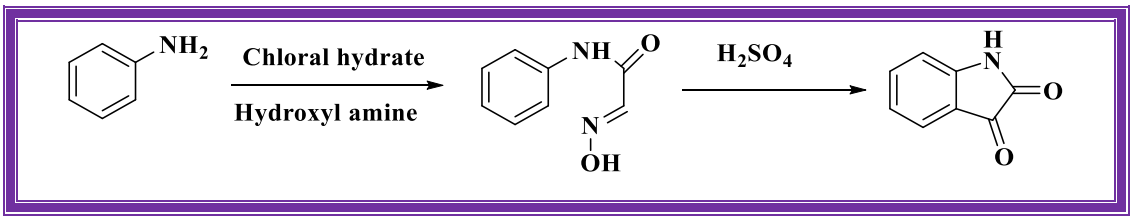
Fig (2.2): The chemical structures of isatin

The biological activities of isatin and its derivatives have been known for a long time. Isatin itself exhibited range of actions such as CNS-MAO inhibition, sedative, anticonvulsant and anxiogenic activities. Similarly, isatin derivatives are known to possess awide spectrum of pharmacological properties including anthelmintic, antibacterial, anticonvulsant, anti-fungal, antineoplastic, antiviral, cysticidal, herbicidal, hypotensive and enzymatic inhibition **[33].**

2.3.General methods for synthesis of Isatin

2.3.1.Sandmeyer Synthesis

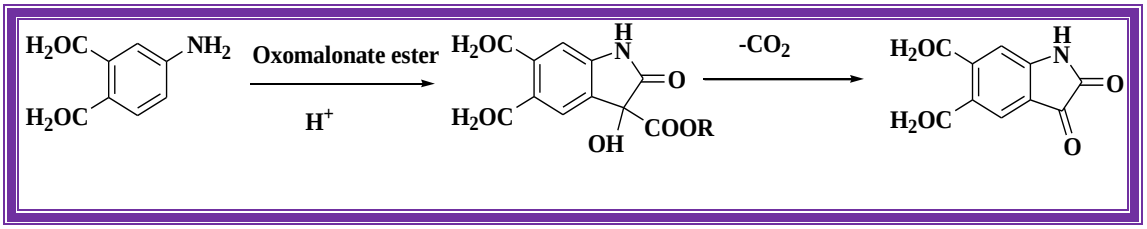
The reaction of chloral hydrate, hydroxylamine, and a primary aryl amine to produce -isonitrosoacet anilide and -isonitrosoacet anilide is used to make isatin derivatives .The Sandmeyer isatin synthesis is the result of electrophilic cyclization in the presence of a strong acid, such as concentrated sulfuric acid (Scheme 2.1). This method is suitable for anilines with electron withdrawing substituents, such as 2-fluoroaniline **[34 -36].**



Scheme (2.1) :Sandmeyer isatin synthesis

2.3.2.Martinet isatin synthesis

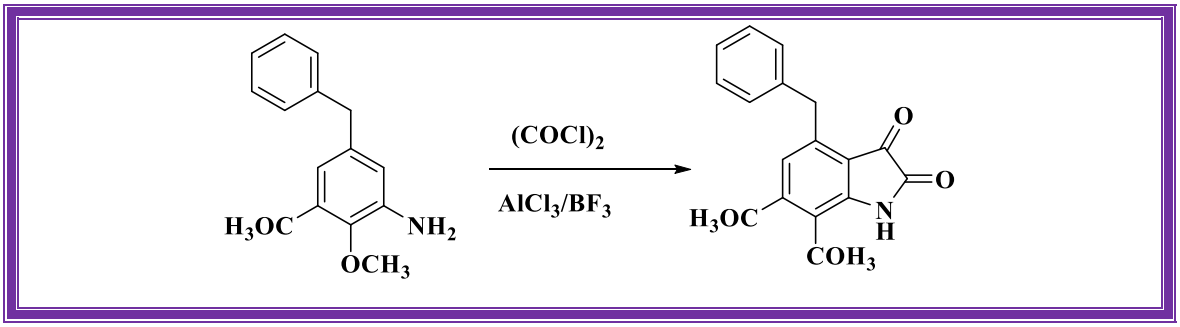
The Martinet method (Scheme 2.2) for the synthesis of isatins in the presence of an acid, an amino aromatic molecule reacts with either an oxomalonate ester or its hydrate to produce a 3-(3-hydroxy-2-oxindole) carboxylic acid derivative, which is then oxidatively decarboxylated to yield the respective isatin **[37].**



Scheme (2.2): Martinet isatin synthesis

2.3.3.Stolle method

The Stolle method is the most important alternative to Sandmeyer synthesis (Scheme 2.3).anilines are reacted with oxalyl chloride to produce an intermediate chlorooxalylanilide, which can then be cyclized in the presence of a Lewis acid, commonly aluminium chloride, to produce the matching isatin **[38-39].**

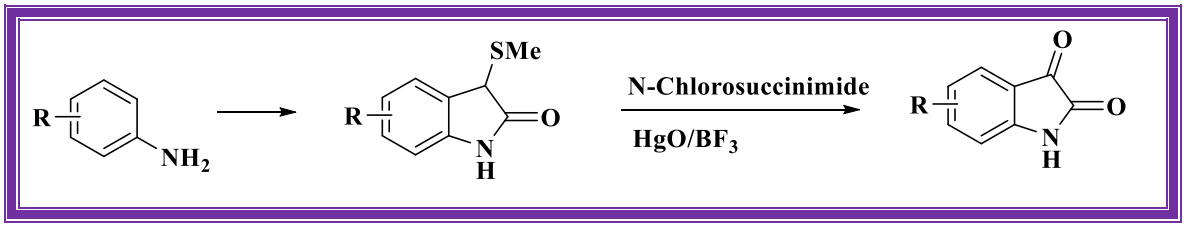


Scheme (2.3) : Stolle method for isatin synthesis

2.3.4.Gassman method

The synthesis and subsequent oxidation of an intermediate 3-methylthio-2-oxindole yields the substituted isatins in this approach (Scheme 2.4). When electron withdrawing groups are present, two complementary techniques for the synthesis of 3-methylthio-2-oxindoles have been devised. The oxindole derivative can be generated via an N-chloroaniline intermediate, which then interacts with a nitrogen atom. To make an azasulfonium salt, combine a methyl thioacetate ester with a methyl thioacetate ester. When electron donating groups destabilize the N-

chloro intermediate, reacting the chlorosulfonium salt with the suitable aniline generates higher quantities of 3-methylthio-2-oxindoles [40].

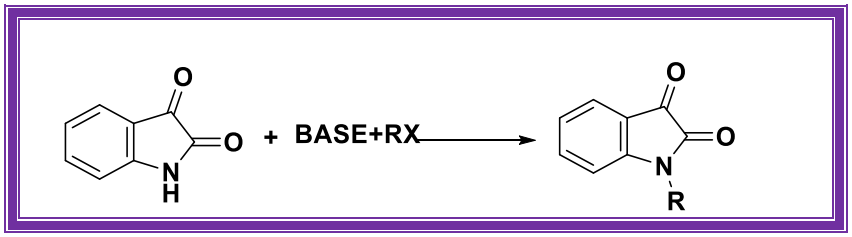


Scheme (2.4) : Gassman method for isatin synthesis

2.4. General reaction of isatin

2.4.1 N-Alkylation

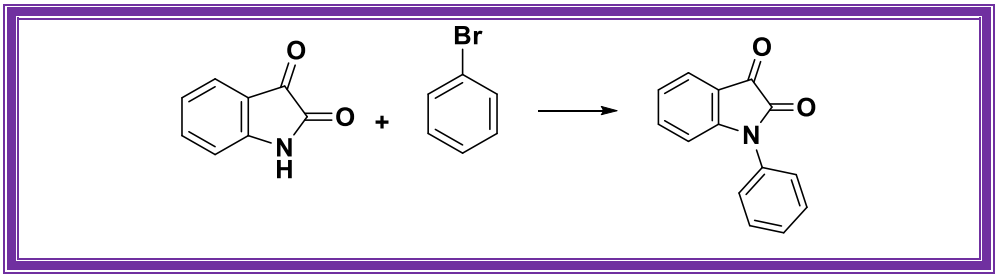
N- Alkyl isatin is prepared by reacting sodium salt with sulphates or alkyl halides (Scheme 2.5) [41].



Scheme (2.5) : N-Alkylation of isatin

2.4.2. N-Arylation

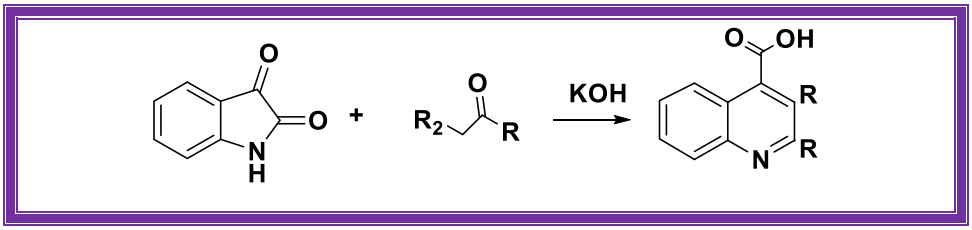
N-Arylisatin is prepared from reaction with triphenyl bismuth actetate ($Ph_3Bi(OAc)_2$ and copper oxide(CuO) under inert atmosphere or from arylbromide and copper oxide (Scheme 2.6) [42].



Scheme (2.6) : N-Arylation of isatin

2.4.3. Pfitzinger reaction

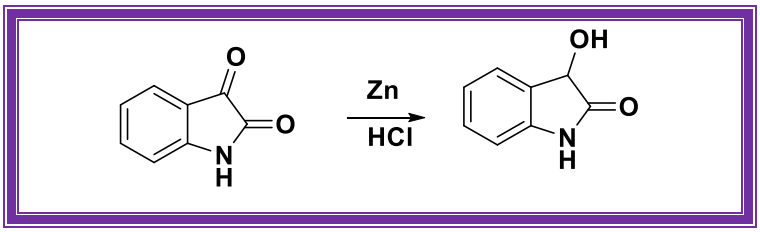
Isatin reacted with a carbonyl compound in presence of a base will give substituted quinoline-4-carboxylic acid (Scheme 2.7) [43].



Scheme (2.7) : : Pfitzinger reaction of isatin

2.4.4. Reduction of Isatin

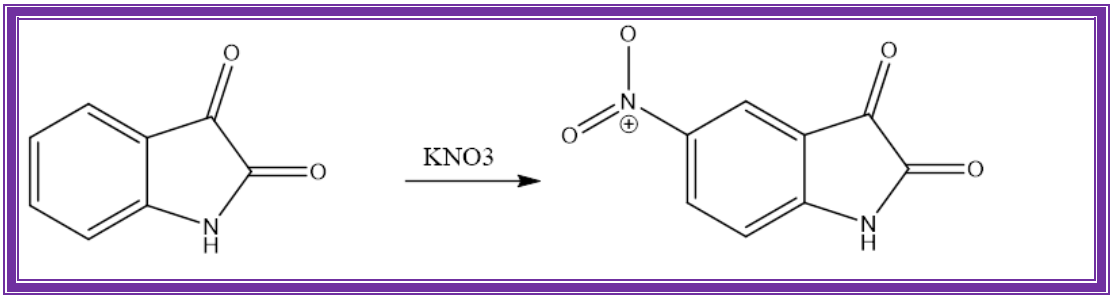
Isatin undergo reduction in presence of reducing agent such as Zn and HCl to yield 3-hydroxy-1, 3-dihydro-2H-indol-2-one-methane (Scheme 2.8) [44].



Scheme (2.8) : Reduction of isatin

2.4.5 Nitration

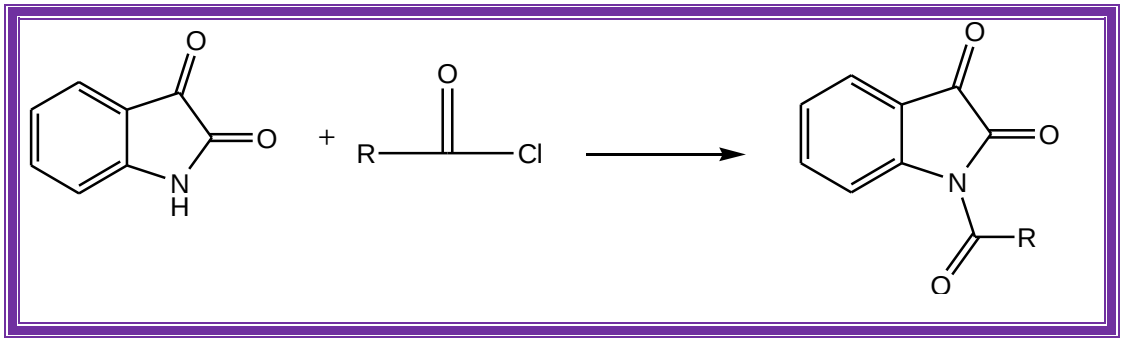
5-Nitroisatin is produced by adding con.H_2SO_4 drop wise to a solution of Isatin at 0-50℃ over a time period of 1 hour (Scheme 2.9) [45].



Scheme (2.9) : Nitration of isatin

2.4.6. N-Acylation

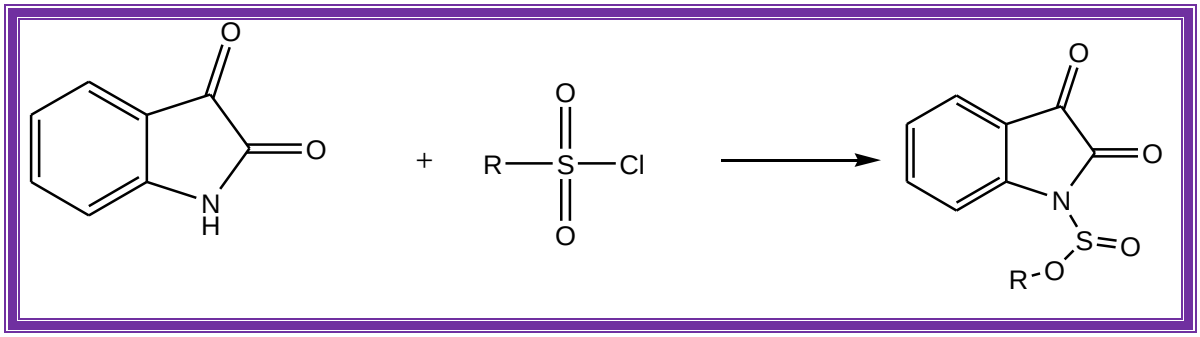
N-Acylation is synthesized by using sodium salt of isatin and acyl chloride or anhydride under reflux(Scheme 2.10) **[46].**



Scheme (2.10) : N-Acylation of isatin

2.4.7. N-Sulfonylation

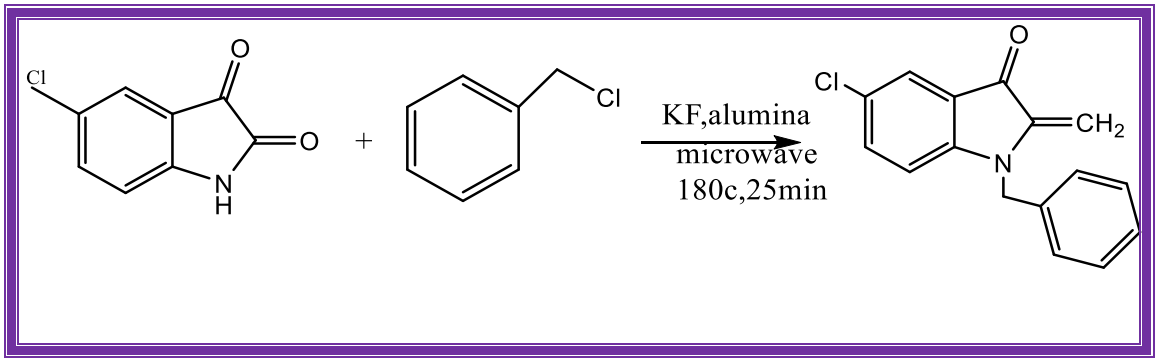
The reaction between sulfonyl chloride and isatin yields N-sulphonylisatin (Scheme 2.11) **[47].**



Scheme (2.11) : **N-Sulfonylation of isatin**

2.4.8. N- Benzylation

Isatin 1-a, b is N-benzylated by reacting it with chlorobenzyl or bromobenzyl under microwave irradiation or on a solid support of KF/alumina. (Scheme 2.12) **[48].**

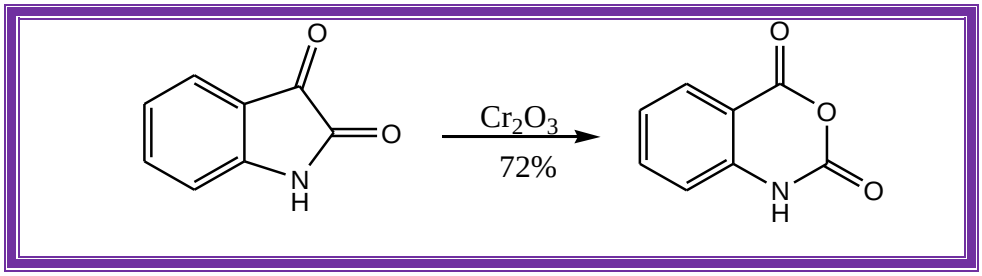


Scheme (2.12) : **N-Benzylation of isatin**

2.4.9. Oxidation

Isatin in presence of chromium trioxide converted into isatoic anhydride, the anhydride form of isatin.

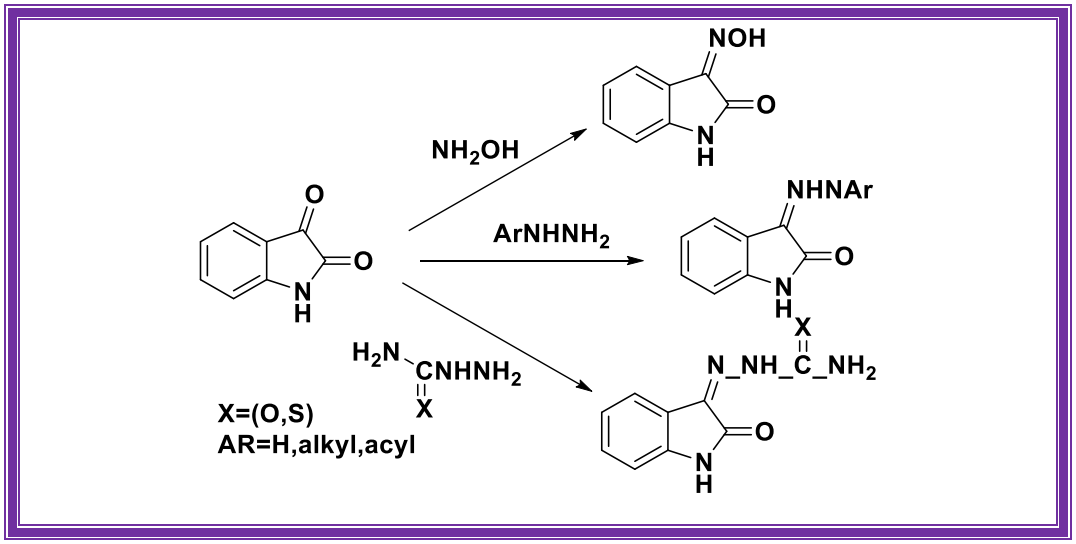
The oxygen atom introduced between two adjacent carbonyl group is obtained from the oxidizing agent. This should not cause significant decomposition to the system (Scheme2.13) **[49].**



Scheme (2.13) : Oxidation of isatin

2.4.10. Reactions of carbonyl groups.

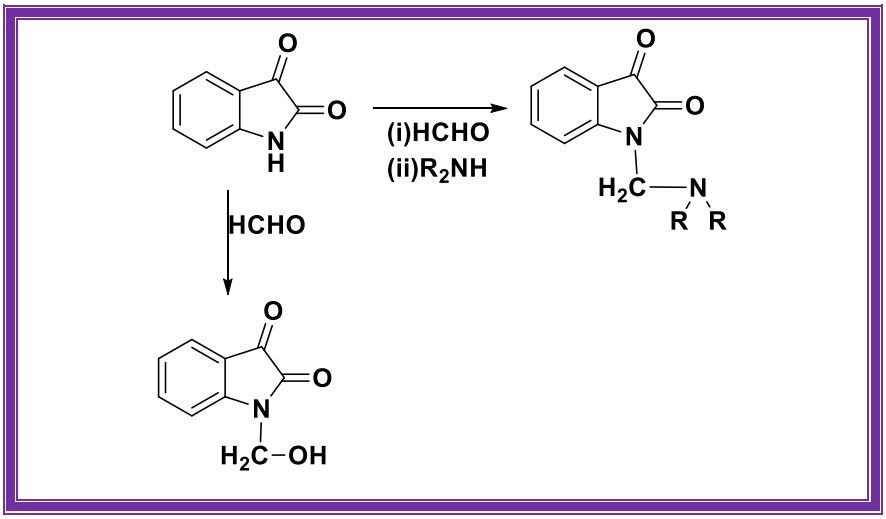
With ketonic reagents such as hydroxylamine, phenyl hydrazine, and semicarbazide, the reactive carbonyl group at position-3 undergoes normal reactions as illustrate in(Scheme 2.14) The carbonyl group at position-2 is less active and has less ketonic character compared with carbonyl group at C3 **[50].**



Scheme (2.14) : Reactions of carbonyl groups of isatin

2.4.11. Mannich reaction.

In the Mannich reaction, isatin reacts with formaldehyde and a variety of amines to produce their respective Mannich bases; in the absence of an amine, isatin and substituted isatin with formaldehyde yield their respective Mannich bases **[51] .** Hydroxymethyl isatins as illustrate in (Scheme 2.15).

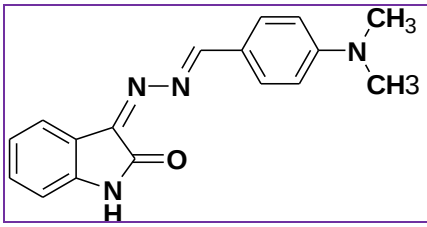
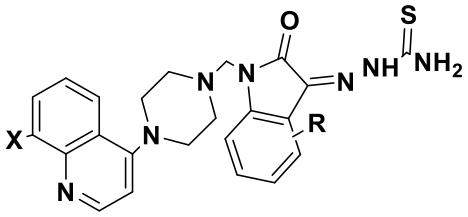
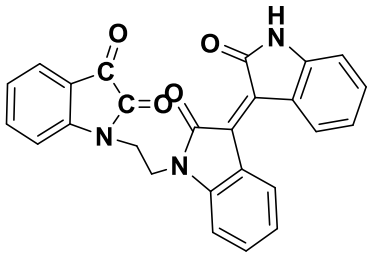
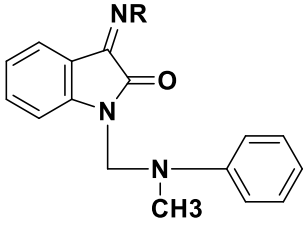


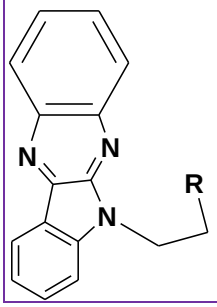
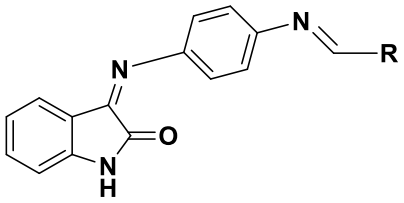
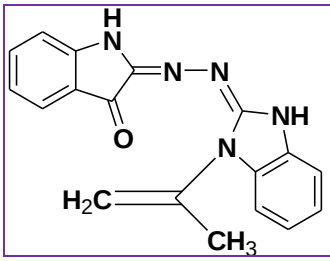
Scheme (2.15) : Mannich reaction of isatin

2.5. Biological activity of isatin

Isatin is a versatile precursor for many biologically active molecules and its diversified nature makes it a versatile substrate for further modifications. This review provides a brief overview on the recent advances and future perspectives on pharmacological aspects of isatin and its derivatives that reported in the last decade **[52].**

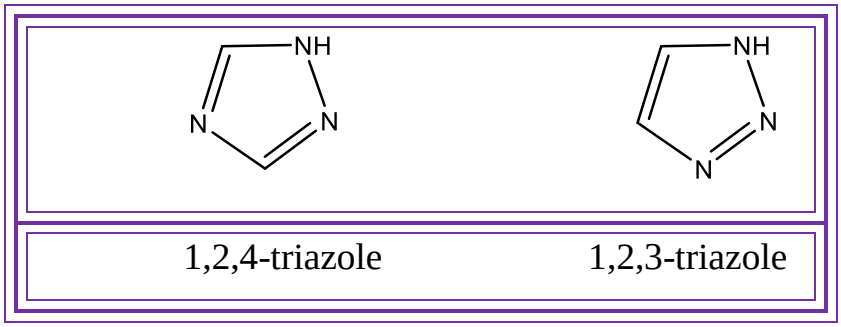
Table (1.1):Biological activity of some isatin and its derivatives.

Bioactivity	Structures	References
Antituberculasis activity		53
Anticancer activity		54
antifungal activity		55
anti-inflammatory activity		56

Antiviral activity		57
Antioxidant activity		58
Antimicrobial Activity		59

2.6. Triazole

The organic heterocyclic compound triazole, also known as pyrrodiazole, has a five-membered diunsaturated ring structure with three nitrogen atoms and two carbon atoms in nonadjacent places . Triazole is the most basic type of the triazole family. Triazole is a crystalline solid that is white to pale yellow in color and has a mild, distinctive odor. It is soluble in water and alcohol, melts at 120°C, and boils at 260°C. 1,2,3-triazole and 1,2,4-triazole are two isomeric chemical compounds that occur together. Bladin was the first scientist to define the carbon nitrogen ring system ($C_2N_3H_3$) (triazole) and to describe triazoles derivatives represented by two isomers: 1,2,3-triazoles and 1,2,4-triazoles are two types of triazoles **[60].** As illustrated in fig (2.3).



1,2,4-triazole 1,2,3-triazole

Fig (2.3): Isomers: 1,2,3- triazoles and 1,2,4-triazoles

2.7. 1,2,4-Triazoles

1,2,4-Triazoles and their derivatives are important group of heterocyclic compounds characterized by a five-membered ring of two carbons and three nitrogen atoms **[61].** The chemistry of five-member N-heterocycle compounds, primarily tetrazole (CH_2N_4), triazoles ($C_2H_3N_3$), and their substituted derivatives, is of great significance. Nitrogen heterocycles with five members are essential structural components and physiologically active molecules **[62]**, corrosion inhibitors **[63],** pesticides **[64],** dyes **[65],** and other industrial chemicals. 1,2,3-triazole is used as antibacterial **[66],** antifungal **[67],** antioxidant **[68],** anti- malarial and anti-leishmanial drugs **[69].** 1,2,4-triazole is employed as a factor in drug structures much more than 1,2,3-isomer. The synthesis of both simple and fused triazole systems attracted the interest of the chemical industry **[70].** After discovering that certain triazoles can prevent fog formation in photographic emulsions **[71]**, and that others can be used as herbicides and convulsants.

2.7.1 Physical properties of 1,2,4-triazoles

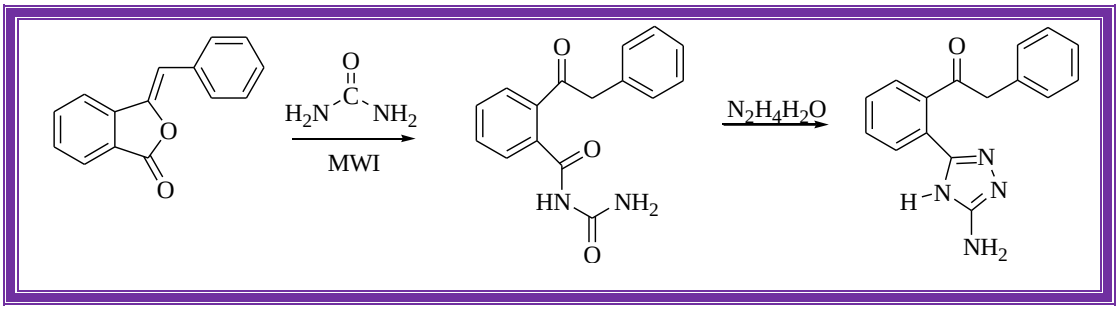
At room temperature, almost all 1,2,4-triazoles are solid. They range in color from white to pale yellow. They are soluble in polar solvents such as ethanol, chloroform, dimethyl sulfoxide, and dimethyl formamide, but not in non-polar solvents such as ethers. Because protonation and deprotonation produce salts,1,2,4-triazoles are soluble in both acidic and basic conditions [72] .

2.7.2. Synthesis Methods of 1,2,4-Triazole

Synthesizing the 1,2,4-triazole nucleus can be done in many ways. The following are some of the methods that have been discussed:-

2.7.2.1 Synthesis from Urea

Younisb (2011) synthesized 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)2-phenylethanone by reaction of 3-benzylidene phthalide with urea under micro wave irradiation (MWI) gave 1-(2-(αphenylacetyl)benzoyl)urea and further cycloaddition reaction with hydrazine hydrate to give the yield [73]. as shown in (Scheme 2.16).

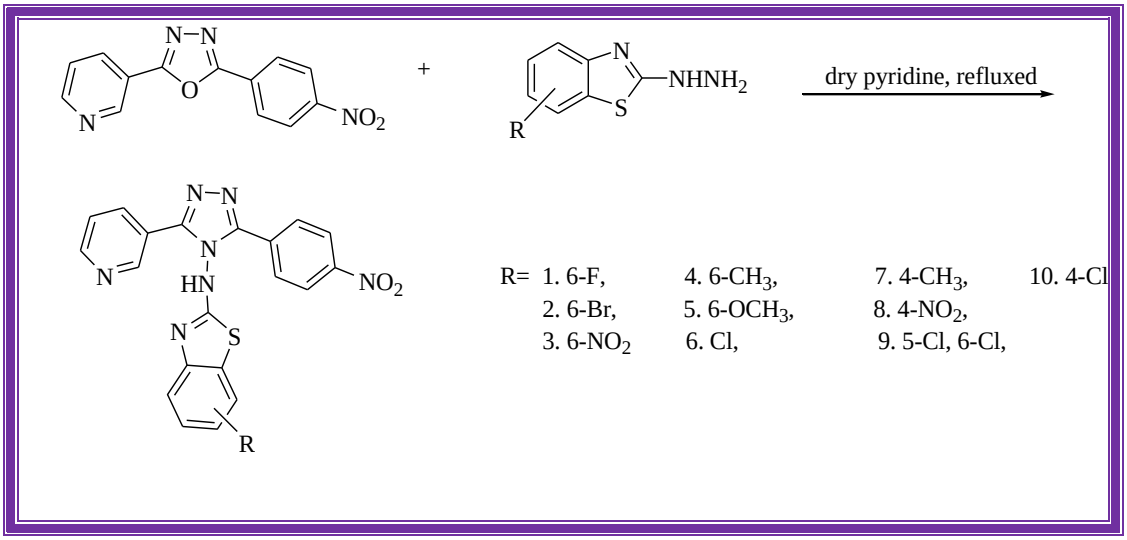


Scheme (2.16): Synthesis of 1-[2-(5-Amino-4H-[1,2,4]triazol-3-yl)-phenyl]-2-phenyl-ethanone

2.7.2.2. Synthesis from 1,3,4-oxadiazol

Patel, et al. (2011) synthesized of 3-(3-pyridyl)-5(4-nitrophenyl)-4-(N-substituted-1,3-benzothiazol-2amino)-4H-1,2,4-triazole by reaction 2-(3-pyridyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole

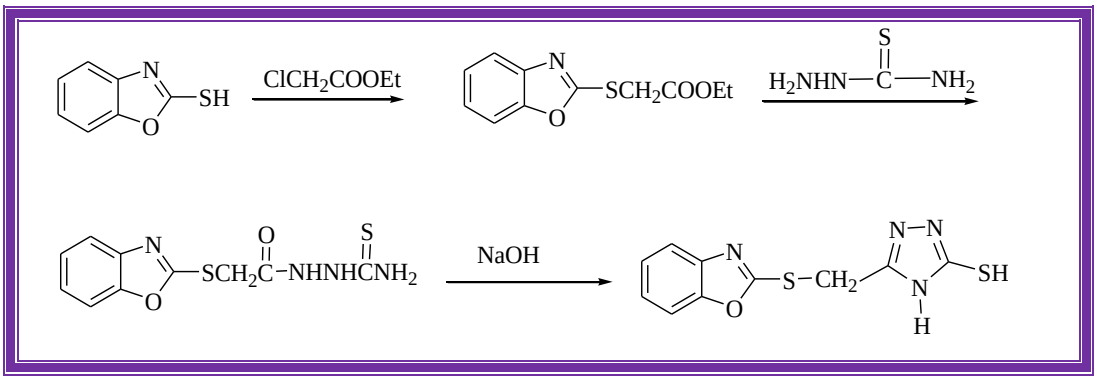
with substituted 2-hydrazino-1,3-benzothiazole in dry pyridine [74] as shown in (Scheme 2.17).



Scheme (2.17): Synthesis of 3-(3-pyridyl)-5(4-nitrophenyl)-4-(N-substituted-1,3-benzothiazol-2amino)-4H-1,2,4-triazole

2.7.2.3. Synthesis from Oxazole

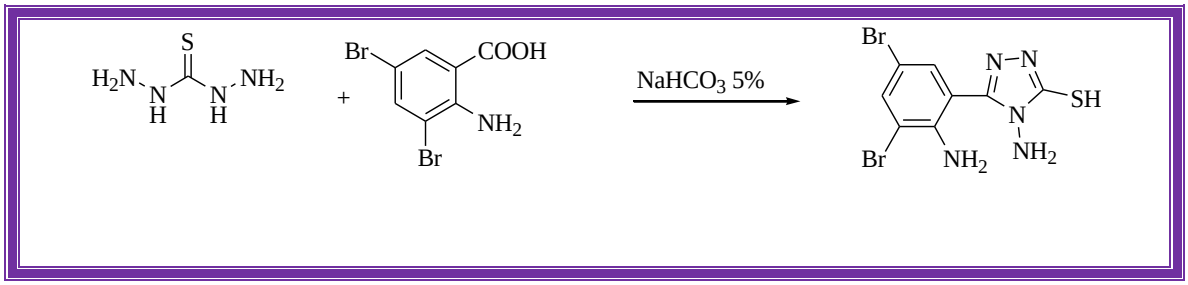
***Askar et al.* (2013)** synthesized of 5-(benzoxazole-2-ylthio methyl)-(4H), 1,2,4-triazole-3thiol by a reaction between 2-mercapto benzoxazole with Ethyl chloro acetate, followed by a reaction with thiosemicarbazide to produce 2-[(benzoxazole-2-ylthio) acetyl] hydrazine carbothioamide, which in turn reacts with NaOH [75] as shown in (Scheme 2.18).



Scheme (2.18): Synthesis of 5-(benzoxazole-2-ylthio methyl)-(4H), 1,2,4-triazole-3thiol

2.7.2.4. Synthesis from thiocarbohydrazide

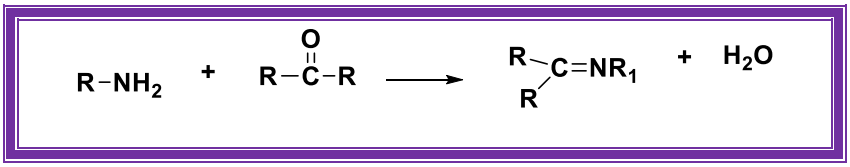
Udupi et al. (2018) synthesized of 3- (2́ –amino–3́,5́– dibromo phenyl)–4-amino-5-mercapto-1,2,4–triazole of the combination of thiocarbohydrazides with 3,5–dibromoanthranilic acid in equimolar proportion was fused for 2 hrs. It was cooled, washed with sodium bicarbonate 5% solution, washed then again water and the dried compound was recrystallized from ethanol this is a usual synthetic method **[76],** as shown in (Scheme 2.19).



Scheme (2.19): Synthesis of 3- (2́ –amino–3́,5́– dibromo phenyl)–4-amino-5-mercapto-1,2,4–triazole

2.8.Schiff base.

Condensation of an aldehyde or ketone with a primary amine produces a Schiff base as illustrate in (Scheme 2.20) **[77].**



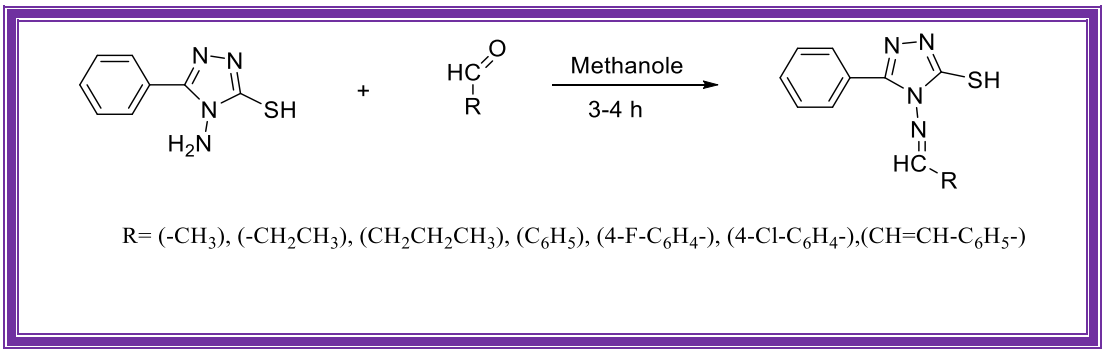
Scheme (2.20) :The reaction of Schiff base

where R is aryl, alkyl, cycloalkyl or heterocyclic groups that are of different substitutes . In the Present time chemists still prepare diverse Schiff base ligands referred . These compounds are also know as anils, imines or azomethines. They were first reported by Hugo Schiff in 1864 **[78].** Schiff bases are an important class of chemicals in the medicinal and pharmaceutical sciences because they have been found to have a wide

range of biological activities, including antifungal properties **[79],** antibacterial **[80],** anti-inflammatory **[81],** anticancer **[82],** antimicrobial **[83, 84],** antiviral **[85],** antiproliferative **[86],** analgesic **[87],** Antioxidants **[88]** .

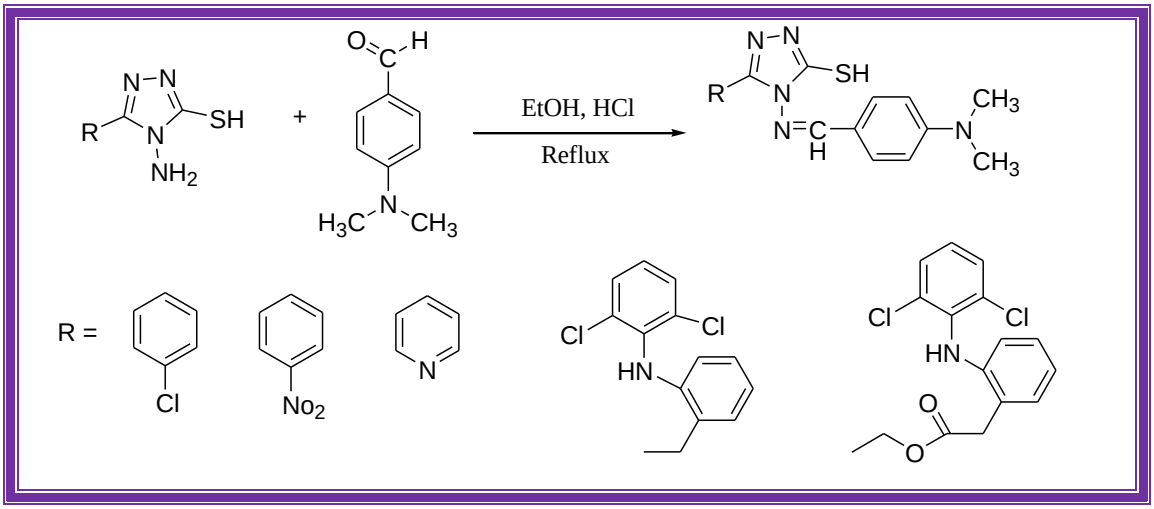
2.8.1 Synthesis Methods of Schiff bases

Singh et al. (2018) designed and synthesized Schiff bases by refluxing the reaction mixture of 4-amino-5-pyridin-4-yl-1,2,4-triazole-3-thiol with various aldehyde in methanol in presence of a few drops of concentrated hydrochloric acid as a catalyst, as shown in equation**[89]** (Scheme 2.21).



Scheme (2.21): Synthesis Schiff bases of triazole

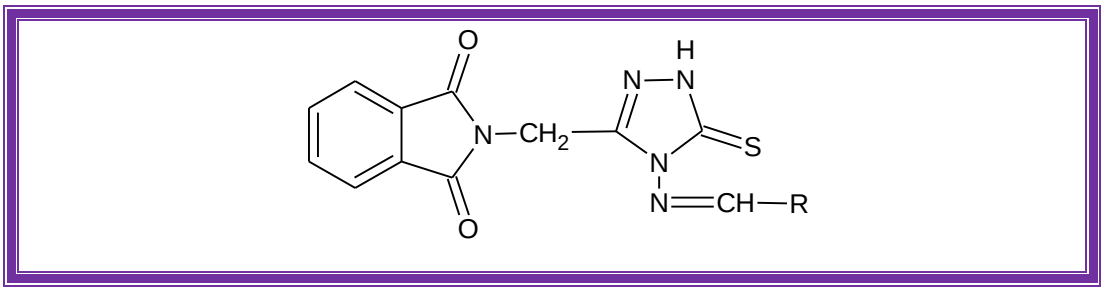
***Parjanya, et al.*(2014)**synthesized a series of Schiff base of reaction 1,2,4Triazole and 4-Dimethylamine benzaldehyde in ethanol was treated with concentrated HCl and refluxed for 2h. Once cooled, the reaction mixture was filtered and recrystallized from ethanol to give 4-[(4-Dimethylamino-benzylidene)-amino]-5-subsituted-3,4-dihydro-2H[1,2,4]triazole-3-thiol **[90]** , as shown in (Scheme 2.22).



Scheme(2.22): Synthesis schiff bases of triazole

2.8.2: Biological Activity of Schiff's Bases

The compounds carrying azomethine functional group –C=N– which are known as Schiff bases have gained importance in medicinal and pharmaceutical fields due to the most versatile organic synthetic intermediates and also showing a broad range of biological activities, such as antituberculosis **[91],** anticancer **[92],** analgesic and anti-inflammatory **[93],** anticonvulsant **[94],** antibacterial and antifungal activities **[95].** Schiff bases derived from triazole (3) found excellent antibacterial activity against four *Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa, Enterobacter cloacae, and Klebsiella pneumonia) and one Gram-positive strain (Staphylococcus aureus)* **[96].**



R: phenyl, 2 –hydroxyphenyl, 3 –pyridyl, 3 –nitrophenyl, 4 –chlorophenyl

CHAPTER THREE

Materials and Methods

3.1.Chemicals

All materials and solvents used in this study were purchased from different companies, as listed in Table (3.1). These materials used as it is without any purification or modification .

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

No.	Chemicals	Chemical formula	Supplied from	Purity%
1	2-amino benzothiazole	$C_7H_6N_2S$	Aldrich	99.5
2	2-mercapto benzothiazole	$C_7H_5NS_2$	Aldrich	99.9
3	4-amino benzoic acid	$C_7H_7NO_3$	Aldrich	98
4	4-Chloro benzaldehyde	C_7H_5OCl	Aldrich	97
5	4-hydroxy benzaldehyde	$C_7H_6O_2$	CHD	97
6	4-Hydroxy-3-methoxy-benzaldehyde	$C_8H_8O_3$	Aldrich	99
7	4-nitro benzaldehyde	$C_7H_5NO_3$	Aldrich	98
8	Benzene	C_6H_6	United Kingdom	99.7
9	Carbon disulfide	CS_2	Thomas Baker	99
10	Choro acetyl chloride	$ClCOCH_2Cl$	Aldrich	99
11	Dimethyl formamide (DMF)	C_3H_7NO	Merck	99
12	Dimethyl sulfoxide (DMSO)	C_2H_6OS	BDH	98
13	Ethanol	C_2H_6O	Scharlu	99.7
14	Ethyl acetate	$C_4H_8O_2$	Aldrich	80
15	Glacial acetic acid	$C_2H_4O_2$	BDH	98
16	Hexane	C_6H_{14}	BDH	99.5
17	Hydrazine hydrate	$N_2H_4.H_2O$	Merck	98
18	Isatin	$C_8H_5NO_2$	Aldrich	97
19	Methanol	CH_3OH	GCC	98
20	Tri ethylamine	$N(CH_2CH_3)_3$	Fluka	98

3.2. Instruments

• Melting Points: The melting points of the produced compounds were obtained using the following method using the Stuart SMP[10] Electronic Apparatus, at Chemistry Department , College of Science, University of Diyala

• FT- IR Spectra: Infrared spectra of the prepared compounds were recorded on (KBr) disc by using PERKIN ELMER SPEACTRUM-65/ Germany at Chemistry Department, College of Science, University of Diyala.

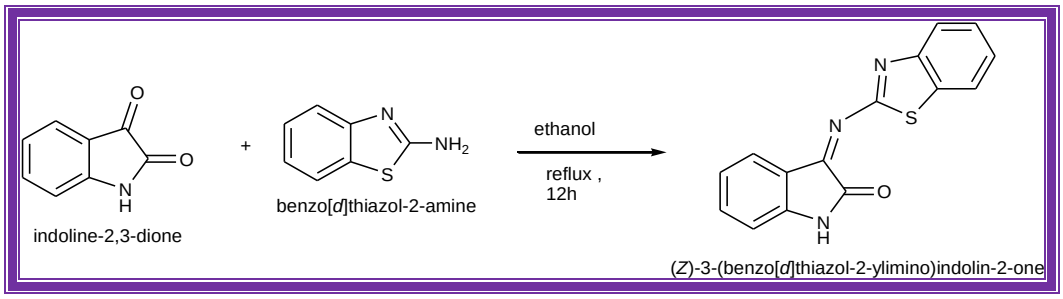
• Nuclear Magnetic Resonance Spectrometer (NMR): ^{1}H NMR and ^{13}C NMR the spectra were recorded on a Bruke 500 MHz spectrometer at University of Science and Technology, College of Science, Tehran Iran.

•Antibacterial Activity: The compound's antibacterial activity was tested at the University of Diyala .Center for Biological Research.

• Ultraviolet Cabinet: Thin Layer Chromatography (T.L.C) for organic compounds was performed by using CM-10A /SPECTROLINE /USA and mixture of solvents (Ethyl acetate and n-hexane) at Chemistry Department, College of Science, University of Diyala.

3.3 Synthetic methods of the compounds.

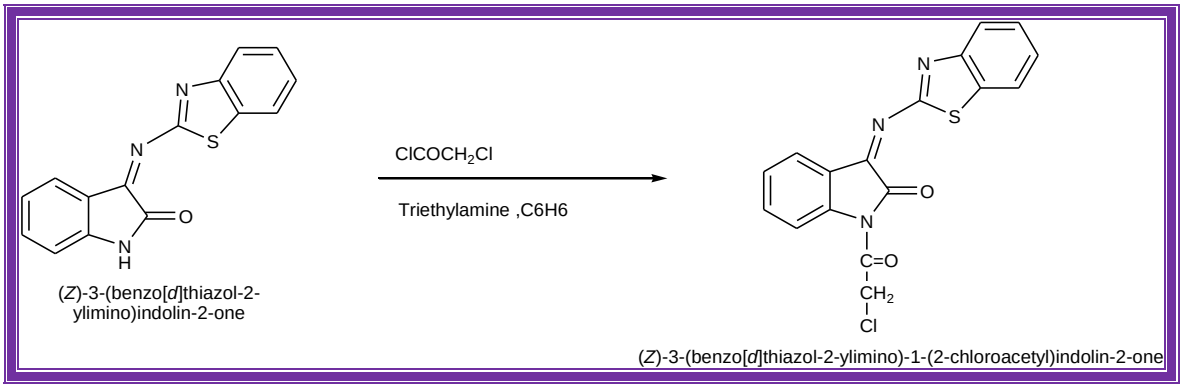
3.3.1. Synthesis of (Z)-3-(benzo[d]thiazol-2-ylimino)indolin-2-one[R_1]



Equation (3.1):The synthetic pathway of (Z)-3-(benzo[d]thiazol-2-ylimino)indolin-2-one[R_1]

2-Aminobenzothazole (1.88 g, 13.2 mmol) was added to isatin (1.71 g, 11.6 mmol) in 99.9% (ethanol) 30 ml and the combination was refluxed for 12 hours T.L.C was used to ensure that the reaction was completed(mobile phase: ethyl acetate :hexane 1:3). Under the reduced pressure, the solvent evaporated, and the precipitate was filtered and washed with water. To obtain pure [R_1] the precipitate was dried and recrystallized from (Ethanol) **[97].**

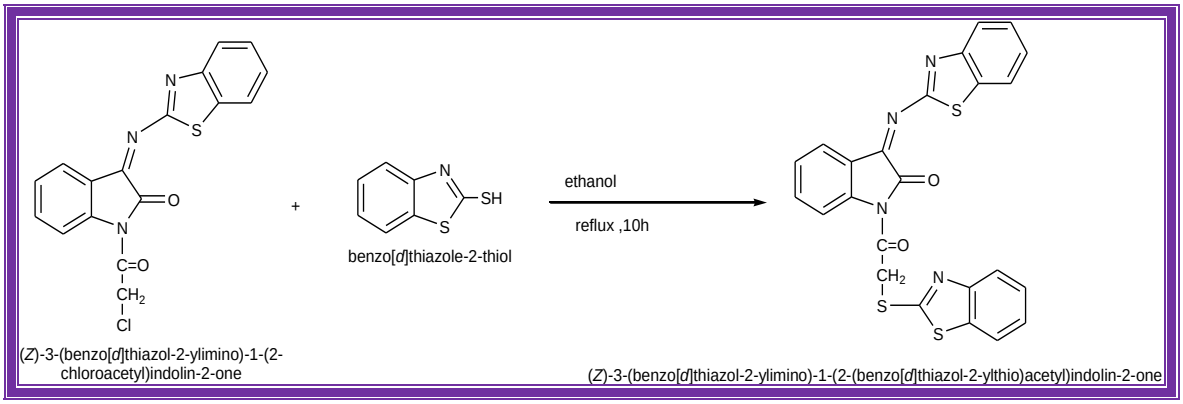
3.3.2.Synthesisof(Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-chloroacetyl)indolin-2-one[R_2]



Equation (3.2): The synthetic pathway of (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-chloroacetyl)indolin-2-one[R_2]

In 30 ml (benzene),a combination of (Z)-3-(benzo[d]thiazol-2-ylimino)indolin-2-one[R_1] (0.22 g,0.867 mmol) and triethylamine(0.08 g, 10.867 mmol) was added drop by drop for about 30 minutes, followed by chloroacetyl chloride (0.09 g,0.867 mmol) In 25 ml benzene. The reaction mixture was then strirred for 6 hours at room temperature before being refluxed for 10 hours. T.L.C was used to track the reaction's progress, with a (3:1 hexane: ethyl acetate) combination as the mobile phase. The reaction mixture was quenched in ice cold water and filtered once the reaction was completed. To obtain pure [R_2] the precipitate was dried and recrystallized from (Ethanol) **[98].**

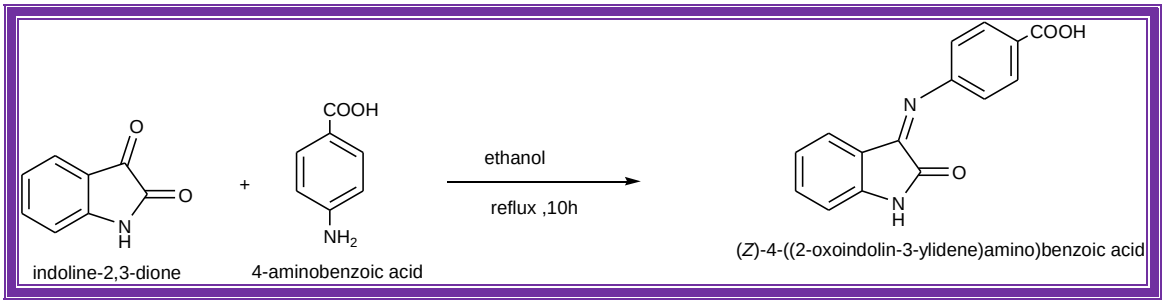
3.3.3. Synthesis of (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-(benzo[d]thiazol-2-ylthio)acetyl)indolin-2-one[R_3]



Equation (3.3): The synthetic pathway of (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-(benzo[d]thiazol-2-ylthio)acetyl)indolin-2-one[R_3]

In absolute (ethanol) 30 ml, a mixture of (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-chloroacetyl)indolin-2-one[R_2] (0.5g, 1.7mmol.) with 2-mercaptobenzothiazole (0.15g, 9mmol) was added with constant stirring, and the resulting liquid was refluxed on a water bath for 10 hours. T.L.C was used to track the reaction's progress, with a(3:1 hexane: ethyl acetate) combination as the mobile phase. Precipitate was generated after the mixture was cooled. [R_3]was obtained by filtering, drying, and recrystallizing the precipitate from (Ethanol) **[99].**

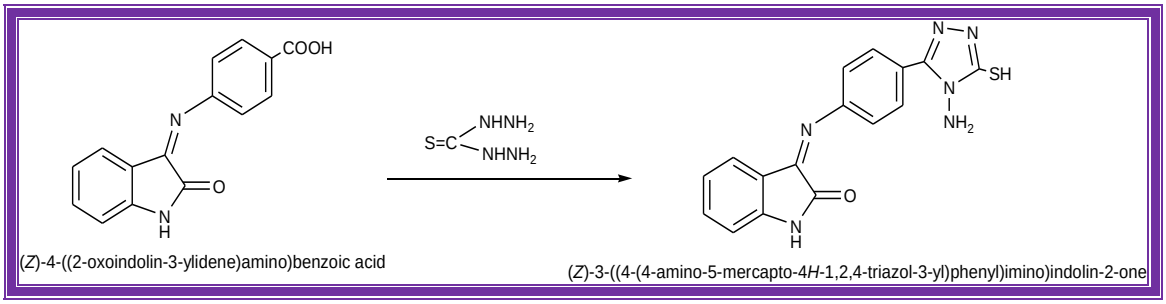
3.3.4 The synthesis of (Z)-4-((2-oxoindolin-3-ylidene)amino)benzoic acid[R_4]



Equation (3.4): The synthetic pathway of (Z)-4-((2-oxoindolin-3-ylidene)amino)benzoic acid [R_4]

2-Amino benzoic acid (0.087 g, 0.65mmol) was added to isatin (0.2 g, 0.65mmol) in absolute(ethanol 50ml) , and the combination was refluxed for 10 hours T.L.C was used to ensure that the reaction was completed (mobile phase :ethyl acetate :hexane 1:3). The solvent evaporated under low pressure once. After the reaction was finished, the precipitate was filtered and washed with water. To obtain pure [R4] the precipitate was dried and recrystallized from (Ethanol) **[100].**

3.3.5. Synthesis of (z)-3-((4-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one [R_5]



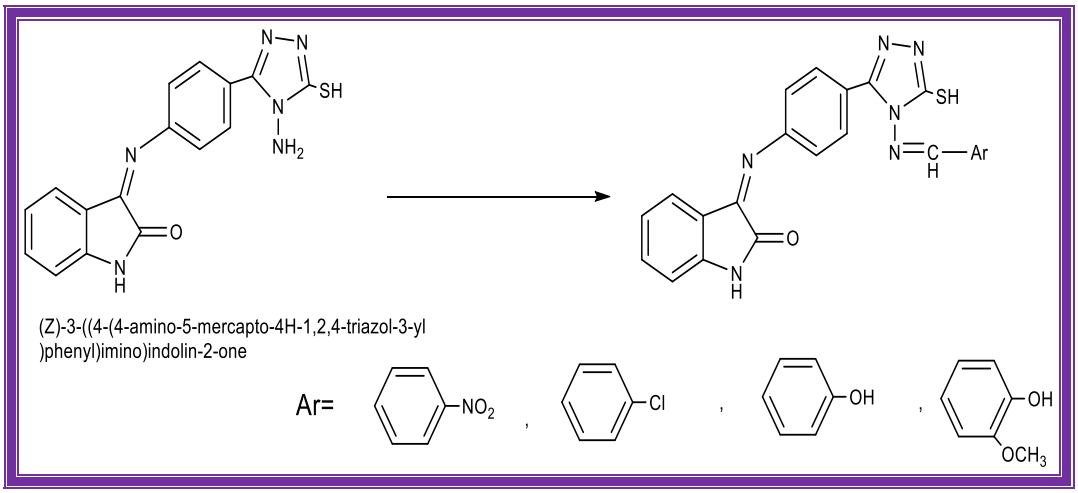
(*Z*)-4-((2-oxoindolin-3-ylidene)amino)benzoic acid

(*Z*)-3-((4-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one

Equation (3.5): The synthetic pathway of (z)-3-((4-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one [R_5]

In a round bottom flask, a combination of compound [R_4] (1.23g, 0.01mmol.) and thiocarbohydrazide (1.59g, 0.015mmol.) was heated until the contents of the flask were melted. After cooling, the product was treated with (sodium bicarbonate) solution to neutralize any remaining carboxylic acid. After that, it was washed with water and filtered. T.L.C was used to ensure that the reaction was completed and that the chemical was pure (mobile phase Hexane: Ethyl acetate 1:2). The title compounds [R5] were obtained by recrystallizing the result from (Ethanol)**[101].**

3.3.6. **Synthesis** the derivatives of the Schiff bases [R_6-R_9].



Equation (3.5): The synthetic pathway of [R_6 - R_7 – R_8- R_9]

To a solution of compound [R_5] (0.2g, 0.65mmol) in (ethanol) 25ml, with different aromatic aldehyde (4-nitro-benzaldehyde, 4-Chlorobenzaldehyde, 4-hydroxybenzaldehyde, 4-hydroxy-3-methoxy-benzaldehyde) (0.65mmol) was added with (2-3 drops) of (glacial acetic acid). In a water bath, the reaction mixture was refluxed for 10-14 hours. T. L.C is used to monitor the reaction's progress, with a(3:1 hexane :ethyl acetate) combination as the mobile phase. The solution was then cooled to room temperature. The precipitate was produced, filtered, washed, and recrystallized from (Ethanol).

3. 4. Biological activity

3.4.1. 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.

3.4.2. 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 compounds by agar well diffusion method

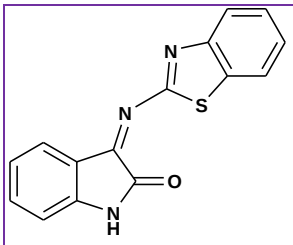
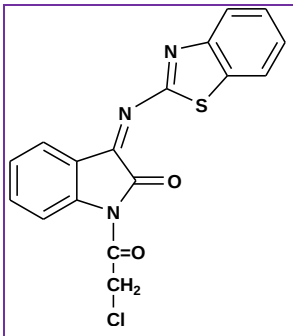
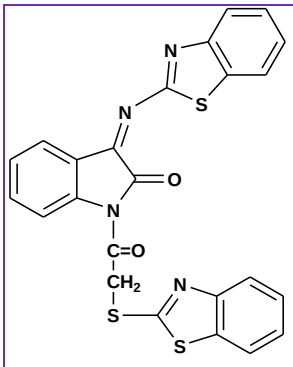
1- A number of bacteria colonies were transported by loop to prepare the suspended bacteria and put it in tubes contain brain heart infusion broth to activate the bacteria. The tubes were incubated for (18 - 24) h at 37 °C. The suspended bacteria was compared to the standard Mac Farland solution (1.5 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.

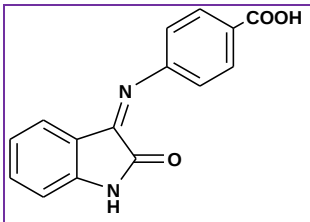
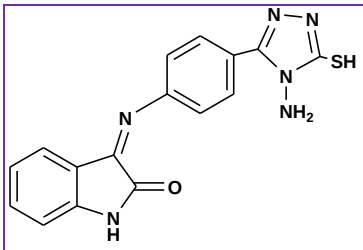
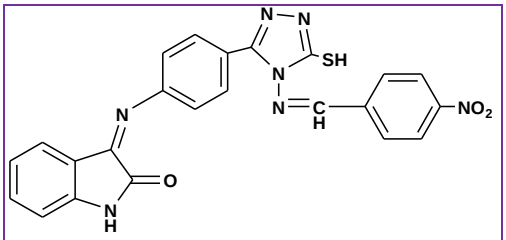
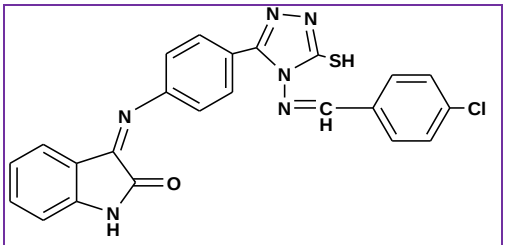
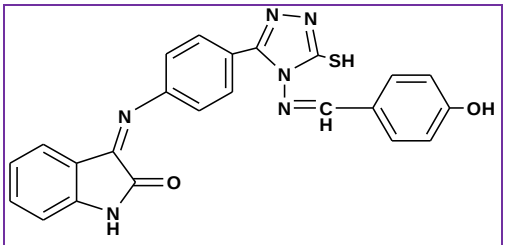
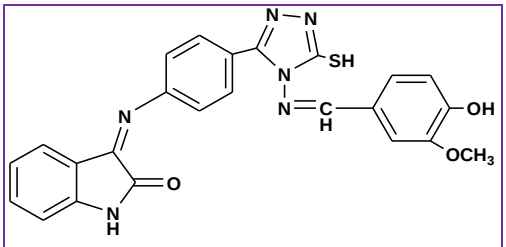
2- A holes were made with a diameter of 5 mm in the culture media by using sterilized a cork borer

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.

Table (3.3) : The structures and nomenclatures of the synthesized compounds

Comp. No.	Comp. Structure	Comp. Name
R_1		**(Z)-3-(benzo[d]thiazol-2-ylimino)indolin-2-one**
R_2		**(Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-chloroacetyl)indolin-2-one**
R_3		**(Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-(benzo[d]thiazol-2-ylthio)acetyl)indolin-2-one**

R_4		**(Z)-4-((2-oxoindolin-3-ylidene)amino)benzoic acid**
R_5		**(Z)-3-((4-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one**
R_6		**(3Z)-3-((4-(5-mercapto-4-((4-nitrobenzylidene)amino)-4H-1,2,4-triazol-3-yl)phenyl)imine)indolin-2-one**
R_7		**(3Z)-3-((4-(4-((4-chlorobenzylidene)amino)-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one**
R_8		**(3Z)-3-((4-(4-((4-hydroxybenzylidene)amino)-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino-2-one**
R_9		**(3Z)-3-((4-(4-((4-hydroxy-3-methoxybenzylidene)amino)-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin -2-one**

CHAPTER FOUR

RESULTS & DISCUSSION

4.1 Introduction

The Schiff bases and the other heterocyclic compounds derived from it are important organic compounds in the organic synthesis and many derivatives showed biological effect against many diseases. Therefore, we synthesized a series of new schiff bases compounds form isatin derivatives that are widely used in pharmaceutical chemistry and the development of drugs. The physical properties of compounds (**R_1 – R_9**) were listed in **Table (4.2). P.P(59)**

4.2 Synthesis and identification of (Z)-3-(benzo[d]thiazol-2- ylimino) indolin-2-one[R_1]

The compound [R_1] was synthesized through the reaction of isatin with 2-aminobenzothiazole as shown in **Fig (4.1)**

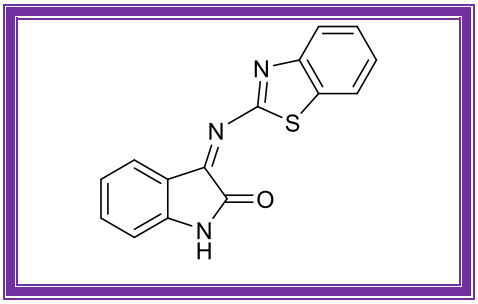
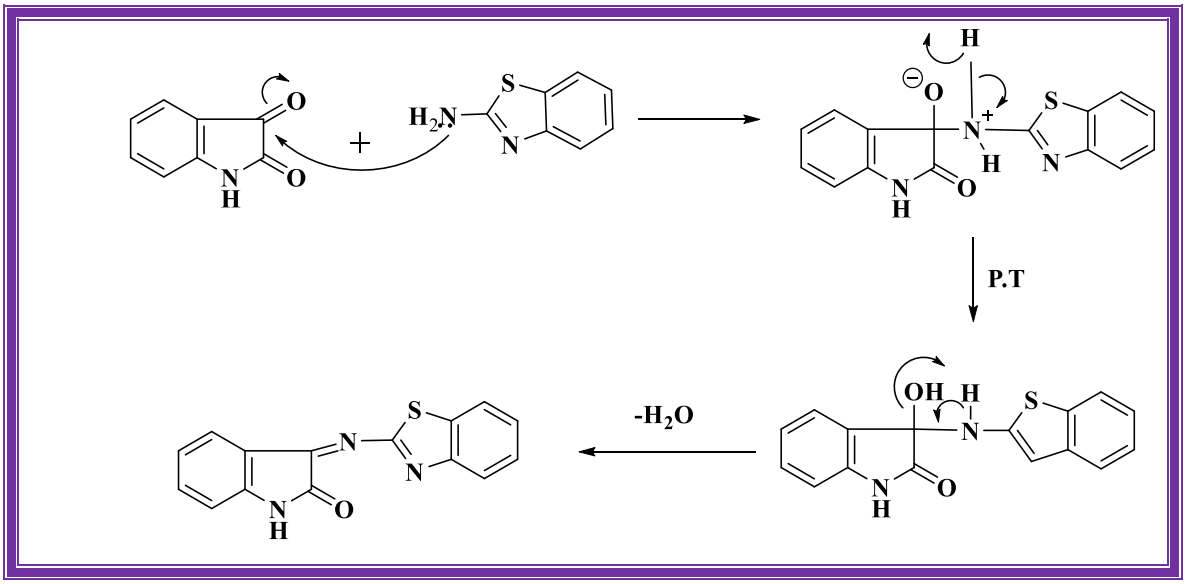


Fig (4.1): The chemical structure of compound (R_1)

The mechanism Suggested for the synthesis of compound R_1 is given in **scheme (4.1).**



Scheme (4.1): The mechanism for the synthesis of compound (R_1).

The structure of the compound [R_1]was proved by FT-IR, ^{1}HNMR,^{13}C-NMR spectroscopy. The FT-IR spectrum as illustrated in Fig (4.2) and Table (4.1) P.P(58) shows disappearance of the stretching vibration bands for (asymmetric and symmetric) for NH_2 group of 2-aminobenzothiazole and appearance absorption band at 3185 cm^{-1} was attributed to N-H group. New clear absorption band at 1619 cm^{-1} was due to C=N stretching vibration . Absorption band at 1736 cm^{-1} was due to stretching vibration of C=O. The bands at 1535 cm^{-1} and 1463cm^{-1} are due to the C=C aromatic **[103].**

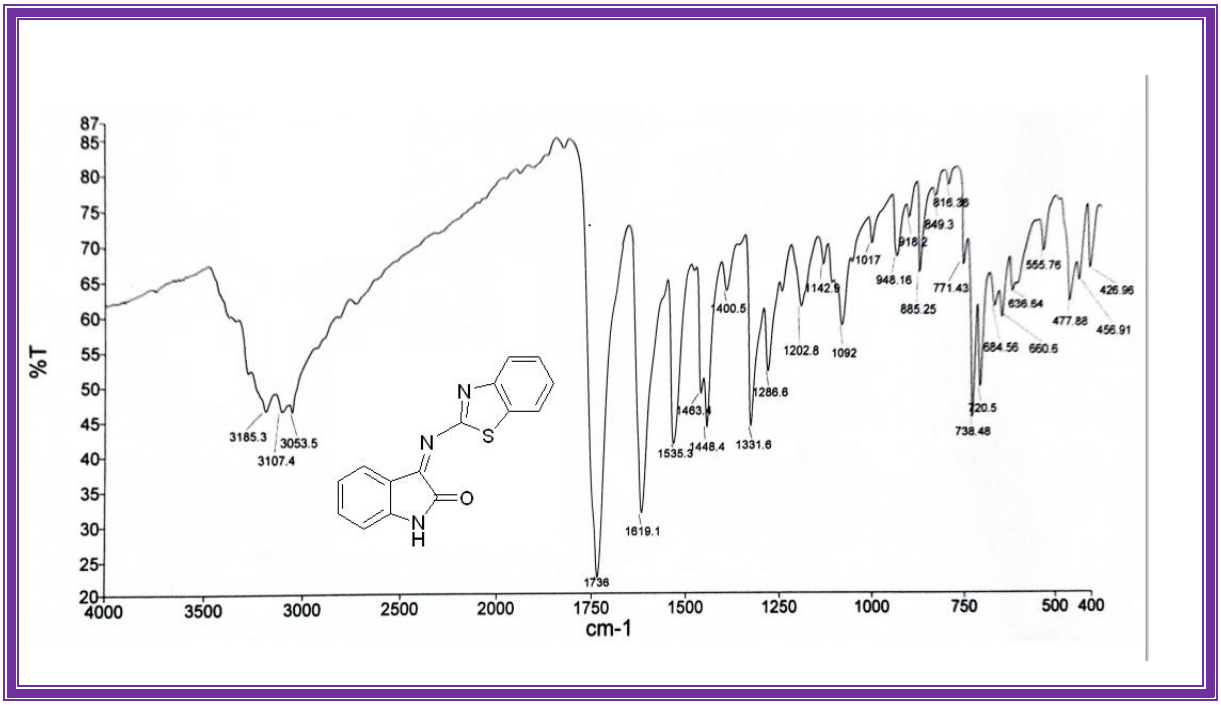


Fig (4.2): FT-IR spectrum of compound (R_1)

The ^{1}H-NMR spectra of the compound [R_1], Figure (4.3)shows the following chemical shifts (DMSO-d_6, ppm): 11.04 (s, 1H,NH) , 7.66-6.91 (m,8H,Ar-H) .

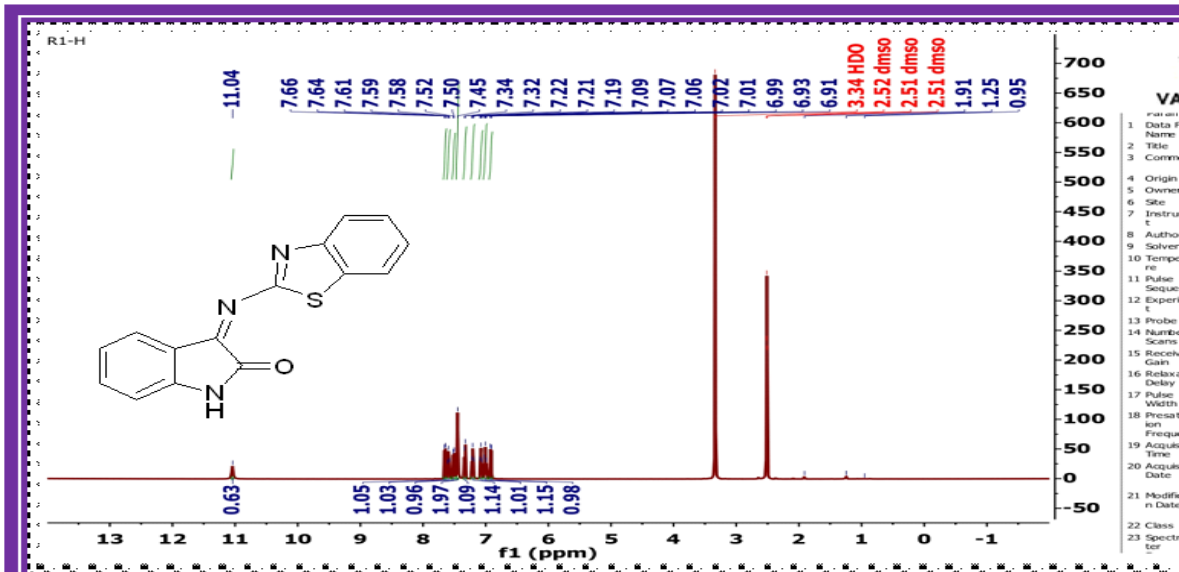


Fig (4.3): ^{1}H NMR spectrum of compound (R_1)

^{13}C-NMR spectra of the same compound [R_1], Fig (4.4) exhibited the chemical shifts (DMSO-d_6, ppm): 112.67-125.87 (C-Ar), 138.85 (C=N benzothiazole), 153.30 (C=N), 166.87 (C=O).

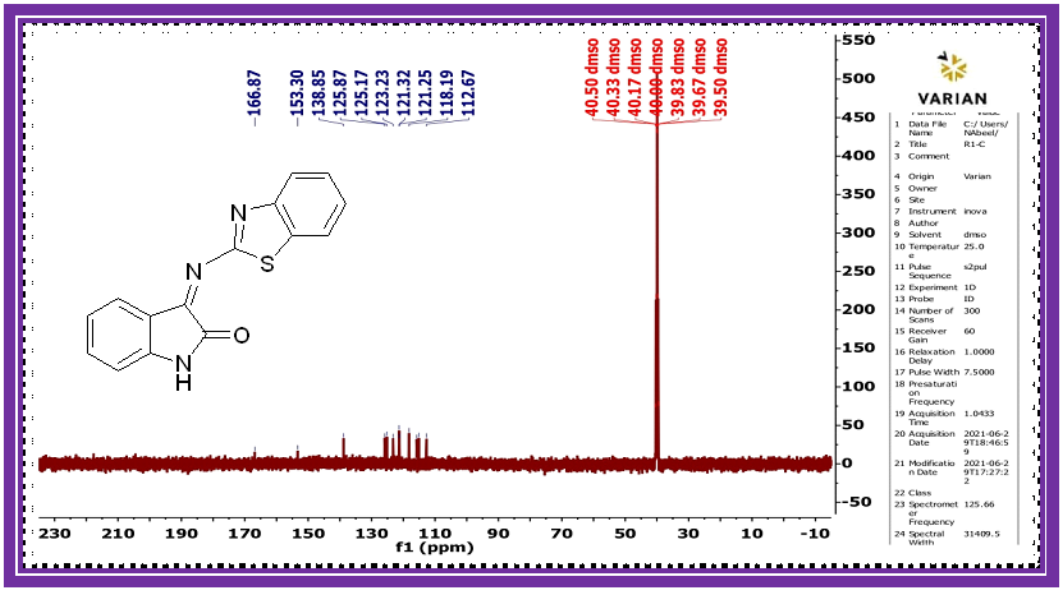


Fig (4.4): ^{13}C-NMR spectra of compound (R_1)

4.3 Synthesis and identification Of (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-chloroacetyl)indolin-2-one[R_2]

The compound [R_2] was synthesized through the reaction of (Z)-3-(benzo[d]thiazol-2- ylimino)indolin-2-one[R_1] with chloroacetyl chloride and triethylamine as illustrated in **Fig (4.4)**

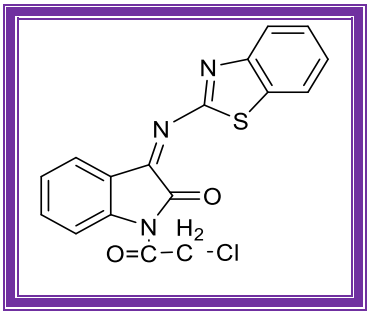
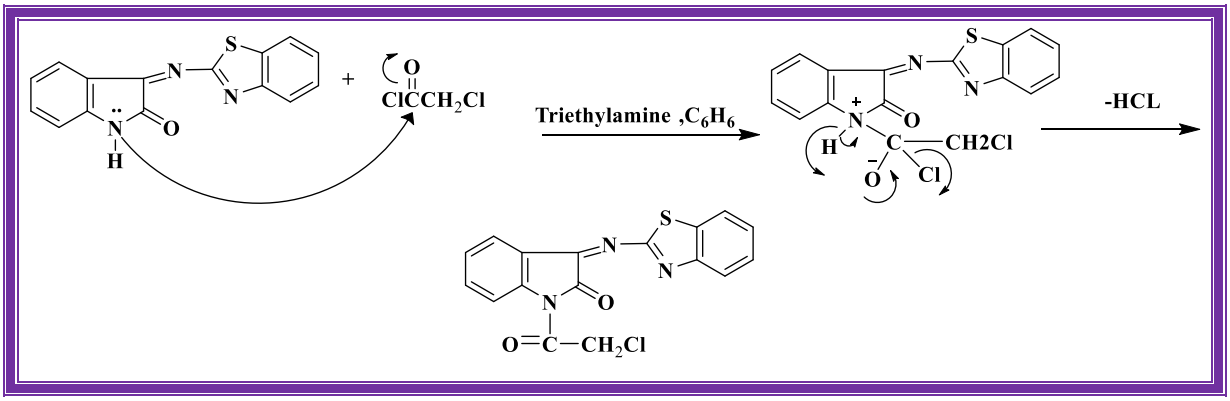


Fig (4.5): The chemical structure of compound (R_2)

The mechanism Suggested for the synthesis of compound R_2 is given in **scheme (4.2).**



Scheme (4.2): The mechanism for the synthesis of compound (R_2).

The FT-IR spectrum of compound [R_2]Fig (4.6) and Table (4.1) show disappearance of the characteristic absorption bands at 3185 cm^{-1} due to NH group in compound[R_1]and emergence of new clear absorption band at 1649 cm^{-1} was due to (C=O amid) stretching vibration. absorption band at 3053 cm^{-1} was attributed to C-H aromatic. Absorption band at 1619 cm^{-1} was due to C=N stretching vibration. Bond absorption at 1736 cm^{-1} was due to stretching vibration of C=O (isatin).The bands at 2945 cm^{-1} and 2800cm^{-1} are due to the CH_2 group **[104].**

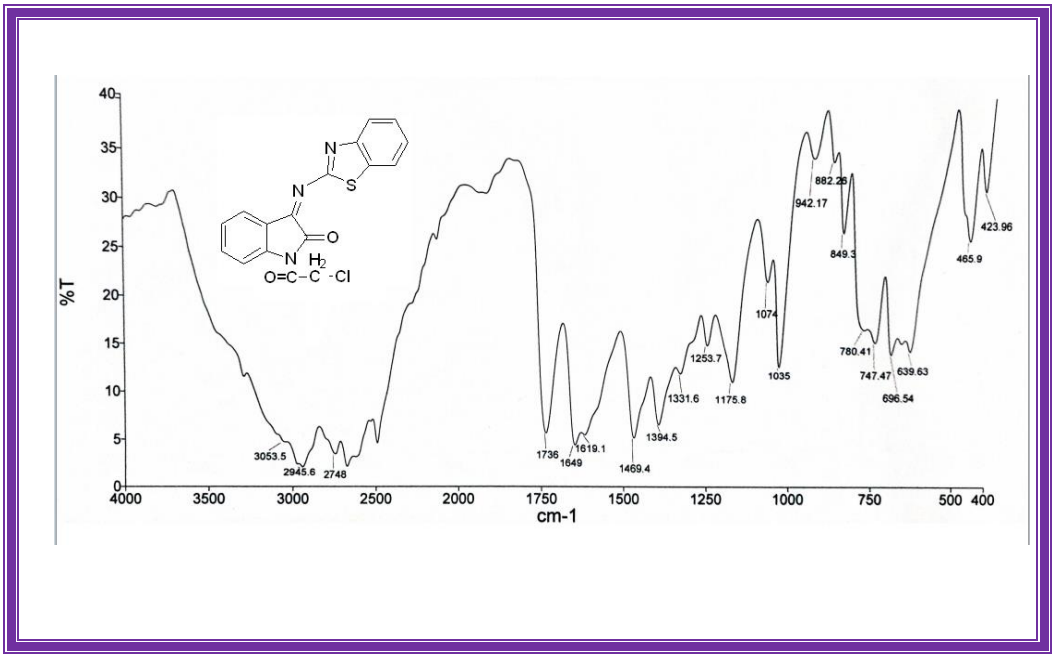


Fig (4.6): FT-IR spectrum in of compound (R_2)

The ^{1}H-NMR spectrum of compound [R_2] Fig (4.7) shows the chemical shifts (DMSO-d_6, ppm): 4.20 (s,2H,CH_2), 7.09 -7.98 (m,8H,Ar-H)

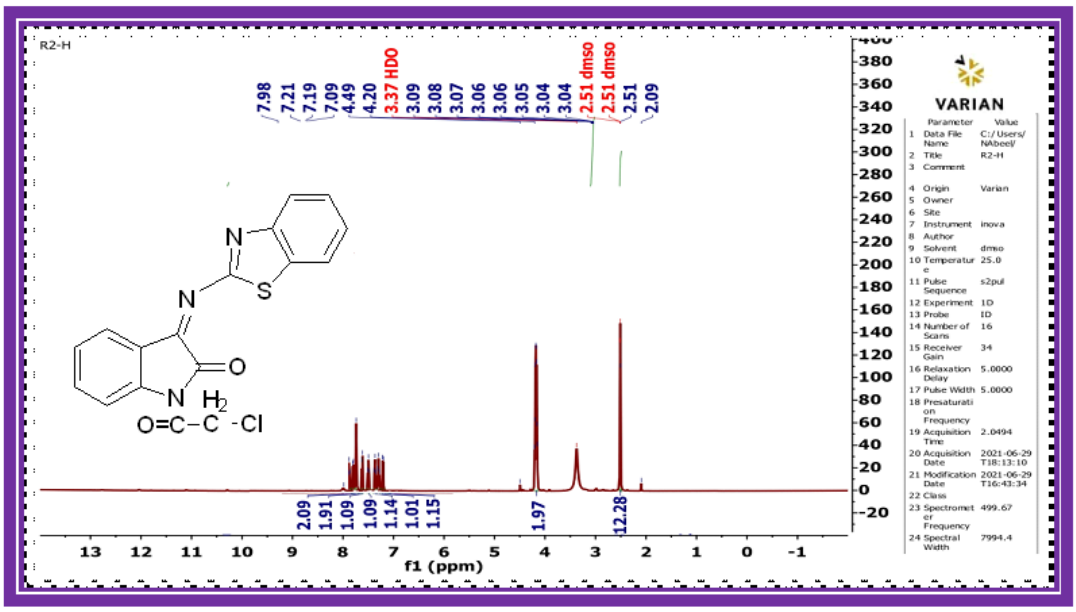


Fig (4.7): ^{1}HNMR spectrum of compound (R_2)

4.4 Synthesis and identification of (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-(benzo[d]thiazol-2-ylthio)acetyl)indolin-2-one[R_3]

The compound [R_3] was synthesized through the reaction of compound [R_2] with 2-mercaptobenzothiazole as illustrated in **Fig (4.8)**.

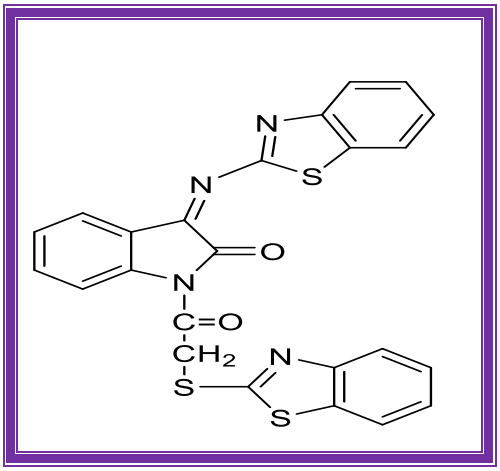


Fig (4.8): The chemical structure of compound (R_3)

The FT-IR spectrum of compound [R_3] Fig (4.9) and Table (4.1) . absorption band at 1596 cm^{-1} was due to C=N stretching vibration .The

bands at 1454 cm^{-1} and 1494cm^{-1} are due to the C=C aromatic. The bands at 1738 cm^{-1} due to the stretching vibration of C=O. Also appearance absorption band at 1643 cm^{-1} which attributed to group N-C=O **[105].**

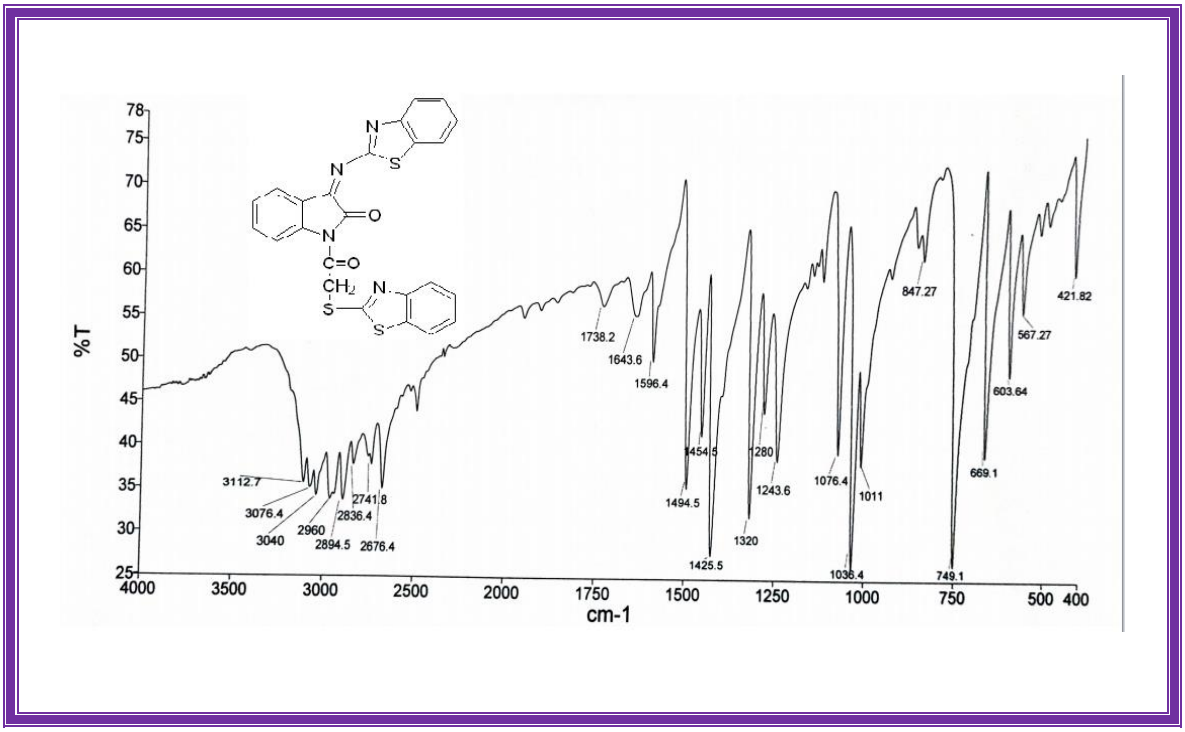


Fig (4.9): FT-IR spectrum in of compound (R_3)

The ^{1}H-NMR spectrum of compound [R_3] Fig (4.10) shows the chemical shifts (DMSO-d_6, ppm): 8.13 – 7.28 (m,12H,Ar-H), 4.36 (s,2H, CH_2).

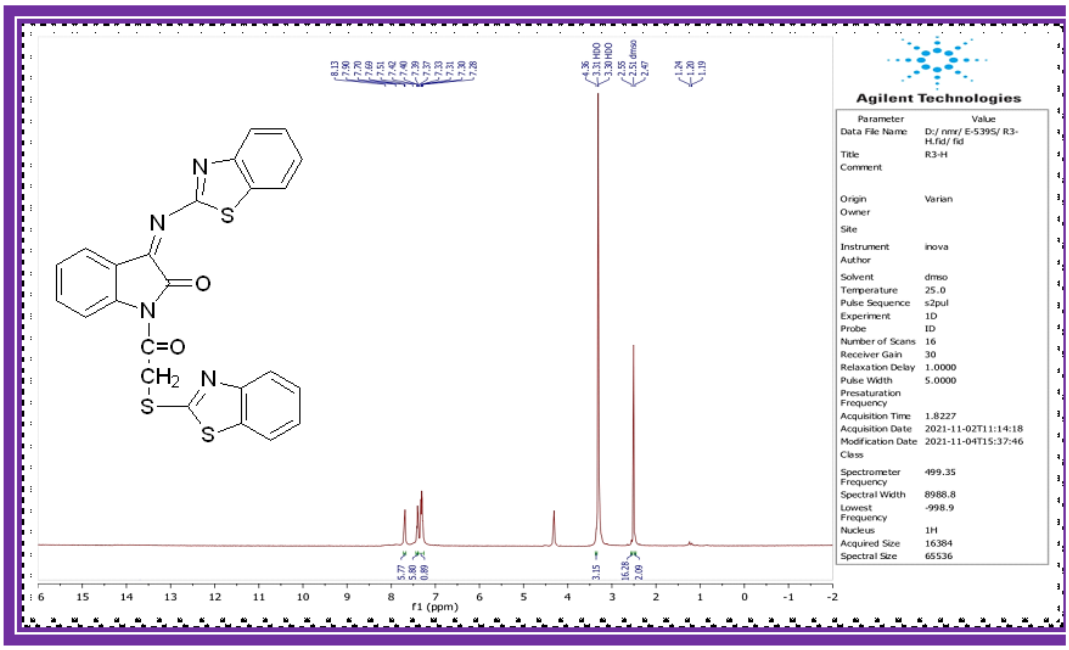


Fig (4.10): ^{1}HNMR spectrum in of compound (R_3)

4.5 Synthesis and identification of(Z)-4-((2-oxoindolin-3-ylidene) amino)benzoic acid[R_4]

The compound [R_4] was prepared by the reaction of the isatin and 4-aminobenzoicacid with a structure appears in **Fig (4.11)**

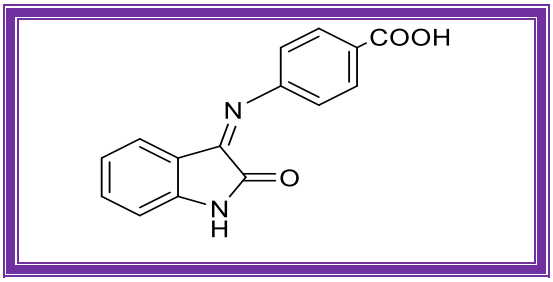


Fig (4.11): The Chemical structures of compounds (R_4)

The FT-IR spectrum of compound [R_4] Fig (4.12) and Table (4.1) shows the appearance absorption band range between (3251- 2999cm $^{-1}$) was due to OH. absorption band at 3191cm^{-1} was attributed to banding of NH group. Absorption band at 1616 cm^{-1} was due to C=N stretching vibration .The bands at 1739 cm^{-1} due to the stretching vibration of C=O group of isatin. Also appearance absorption band at 1688 cm^{-1} which

attributed to C=O of carboxylic group. The bands absorption at 1598 cm^{-1} and 1466cm^{-1} are due to the C=C aromatic **[106].**

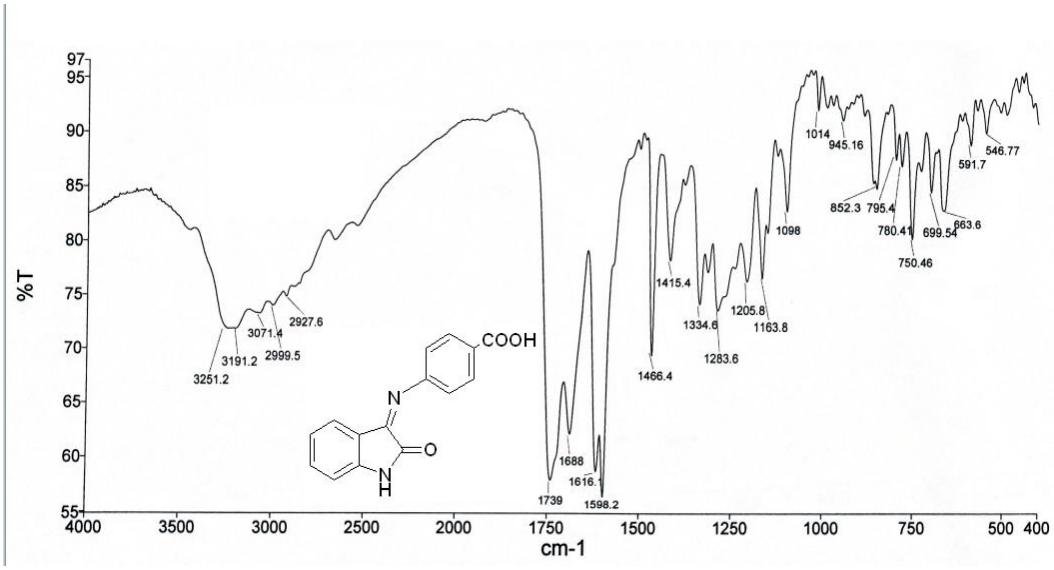


Fig (4.12): FT-IR spectrum in of compound (R_4)

The ^{1}H-NMR spectrum of compound [R_4] Fig (4.13) shows the chemical shifts (DMSO-d_6, ppm):12.92 (s,1H,OH),10.93 (s,1H,NH), 7.89-6.31(m,8H,Ar-H)

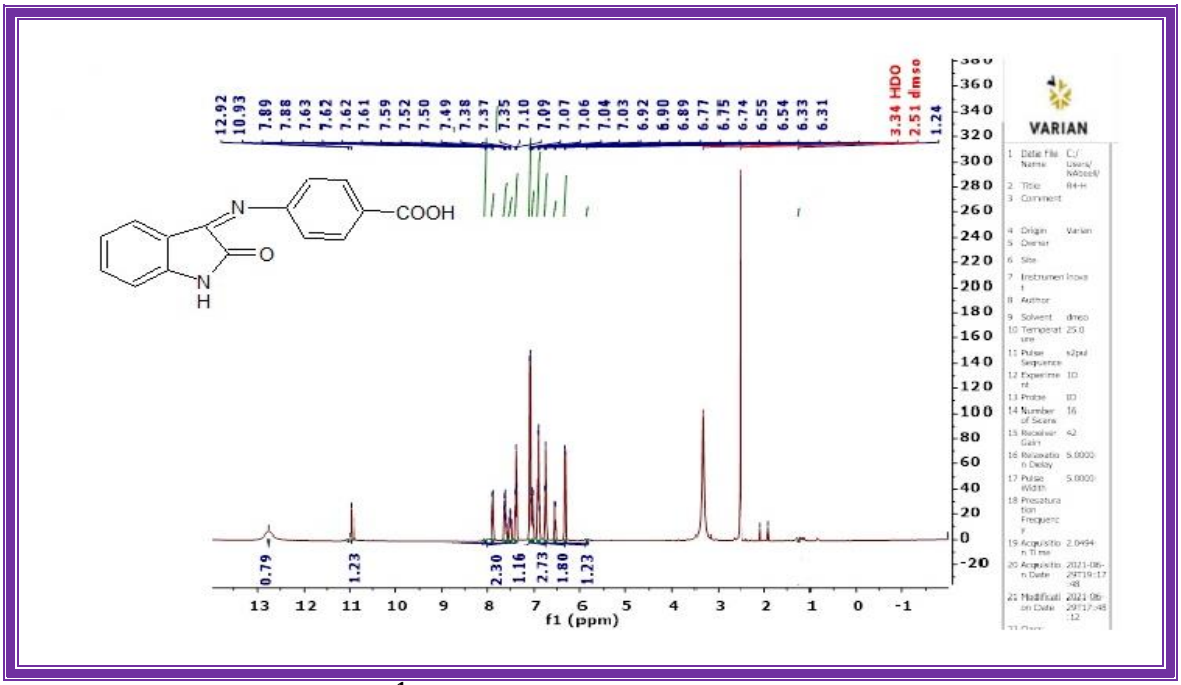


Fig (4.13): ^{1}HNMR spectrum in of compound (R_4)

^{13}C-NMR spectra of the same Compound [R_4], Fig (4.14) exhibited the chemical shifts (DMSO-d_6, ppm): 112.12-155.01 (Ar-C), 155.55(C=N), 163.69(C=O), 167.43(COOH).

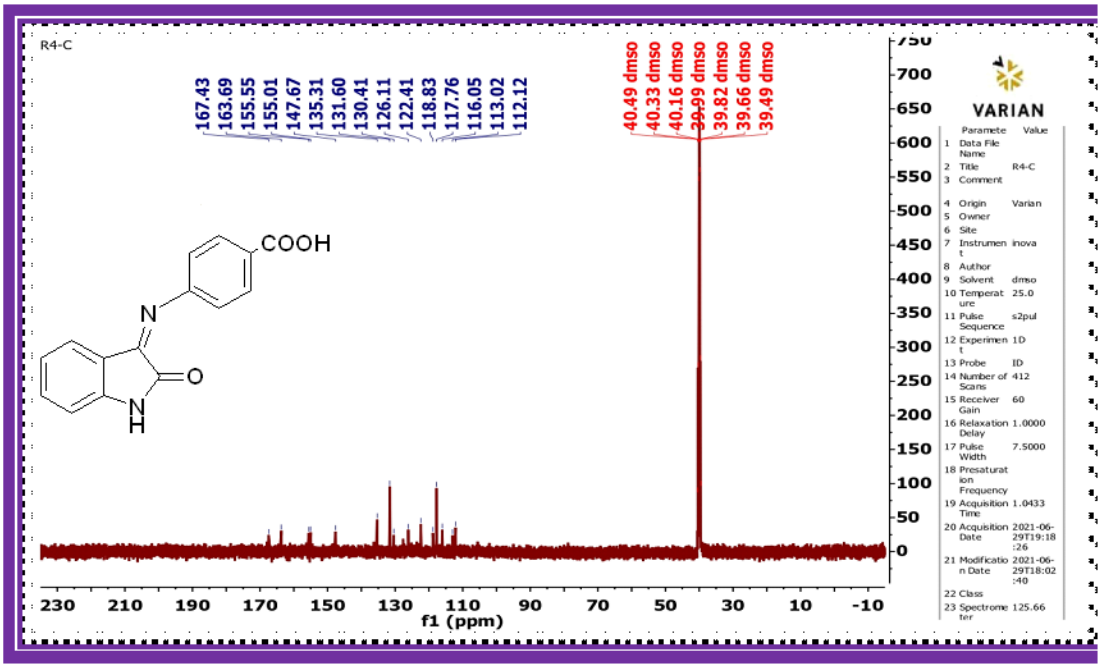


Fig (4.14): ^{13}C-NMR spectra of compound (R_4)

4.6 Synthesis and identification of(z)-3-((4-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one [R_5]

The compound [R_5] was prepared by the reaction of the R_4 with thiocarbohydrazide as illustrated in **in Fig(4.15).**

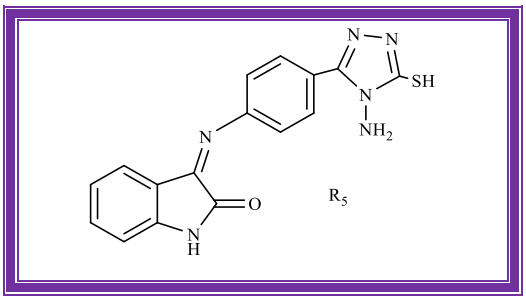
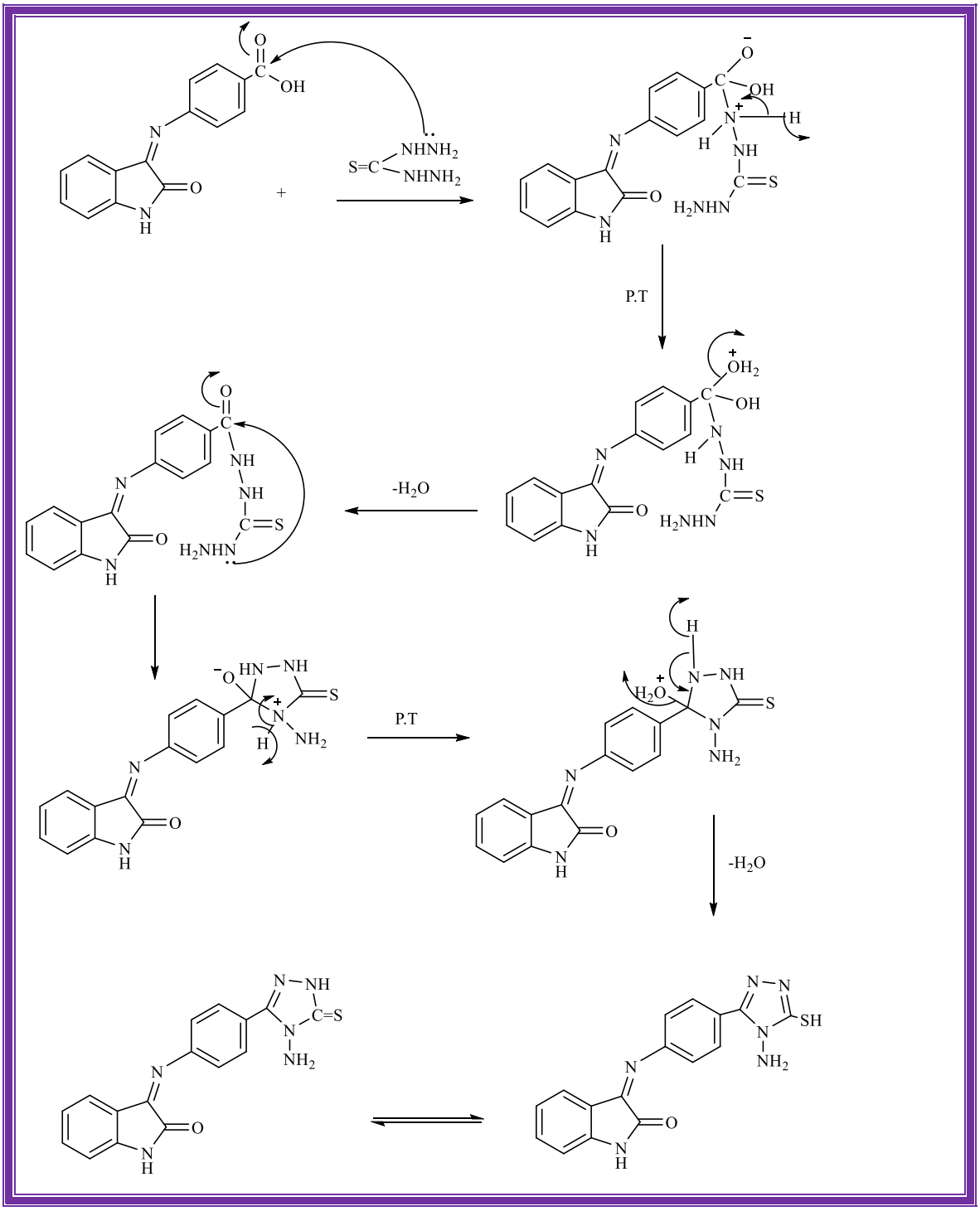


Fig (4.15): The Chemical structures of compound (R_5)

The mechanism Suggested for the synthesis of compound R_5 is given in **scheme (4.3).**



Scheme (4.3): The mechanism for the synthesis of compound (R_5).

The FT-IR spectrum of compound (R_5) Fig (4.16) and Table (4.1) shows absorption bands at 3448 cm^{-1} was attributed to banding of NH_2 group. Whereas absorption bands at 3395 was attributed to banding of NH group. Absorption band at 1568 cm^{-1} was due to C=N stretching vibration. The bands at 1655 cm^{-1} due to the stretching vibration of C=O . The band 1415 cm^{-1} absorption are due to the C=C aromatic **[107].**

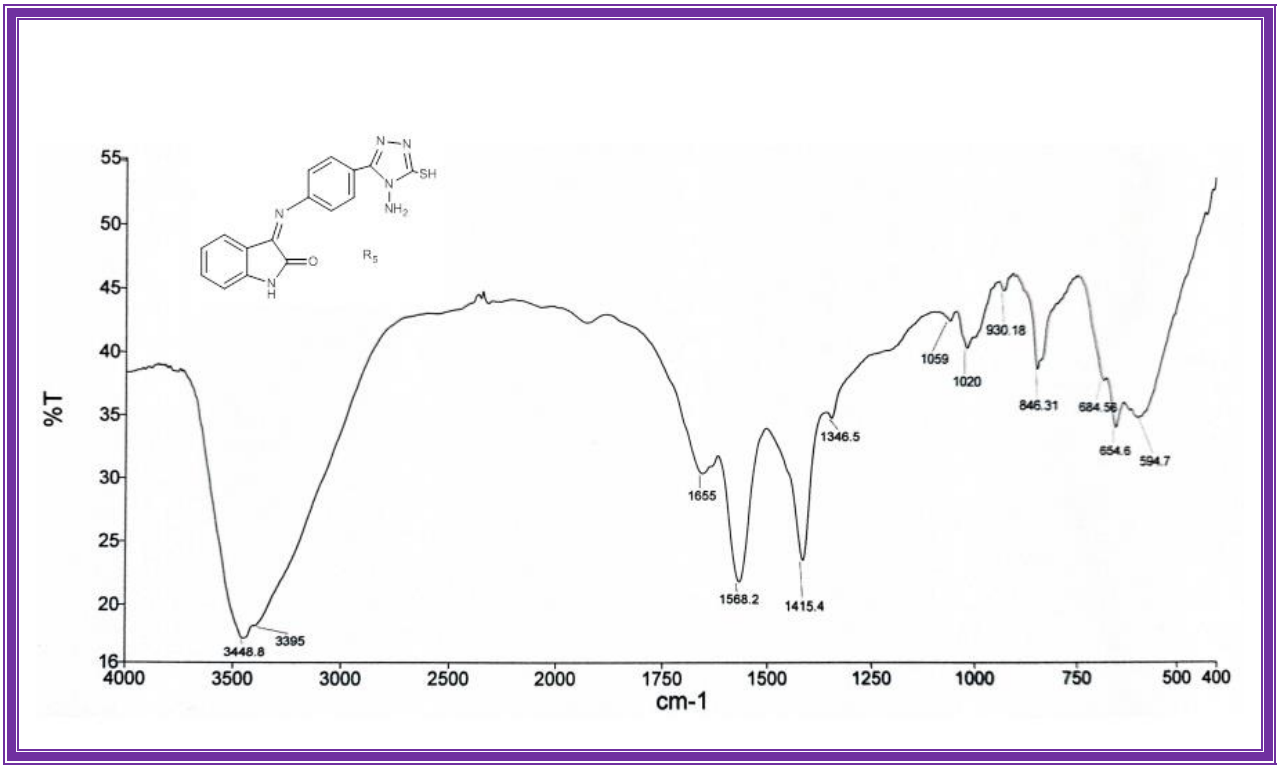


Fig (4.16): FT-IR spectrum in of compound (R_5)

The ^{1}H-NMR spectrum of compound (R_5) Fig(4.17) shows the chemical shifts (DMSO-d_6, ppm): 13.01 (s,1H,SH), 11.33 (s,1H,NH), 7.62-6.54

(m,8H,Ar-H) 5.87 (s,2H,NH_2) .

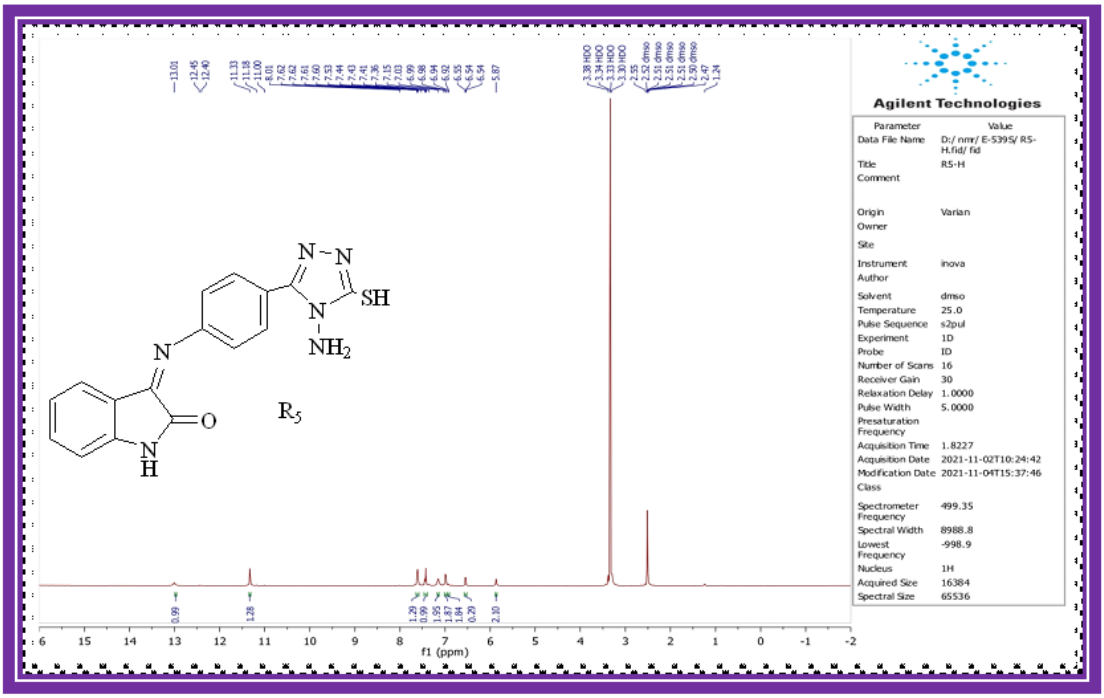


Fig (4.17): ^{1}HNMR spectrum in of compound (R_5)

4.7 Synthesis and identification of Schiff base (3z)-3-((4-(5-mercapto-4-((4-nitrobenzylidene)amino)-4H-1,2,4-triazol-3-yl)phenyl) imine) indolin-2-one [R_6]

The compound [R_6] were prepared by the reaction of the [R_5]with 4-nitrobenzaldehyde, the structure illustrated **in Fig (4.18).**

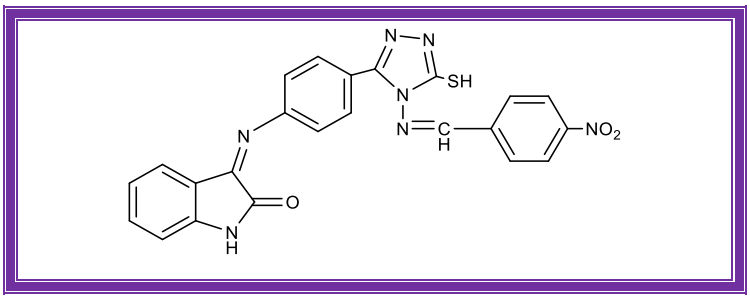


Fig (4.18): The Chemical structures of compounds (R_6)

The FT-IR spectrum of compound [R_6] Fig (4.19) and Table (4.1) shows absorption band at 3005 cm^{-1} was due to C-H aromatic . Band absorption at 1577 cm^{-1} was due to C=N stretching vibration. Absorption

band at 1709 cm^{-1} due to the stretching vibration of C=O. Absorption bands at 3424 cm^{-1} was attributed to stretching vibration of N-H. The band at 1421 cm^{-1} are due to the C=C aromatic **[108].**

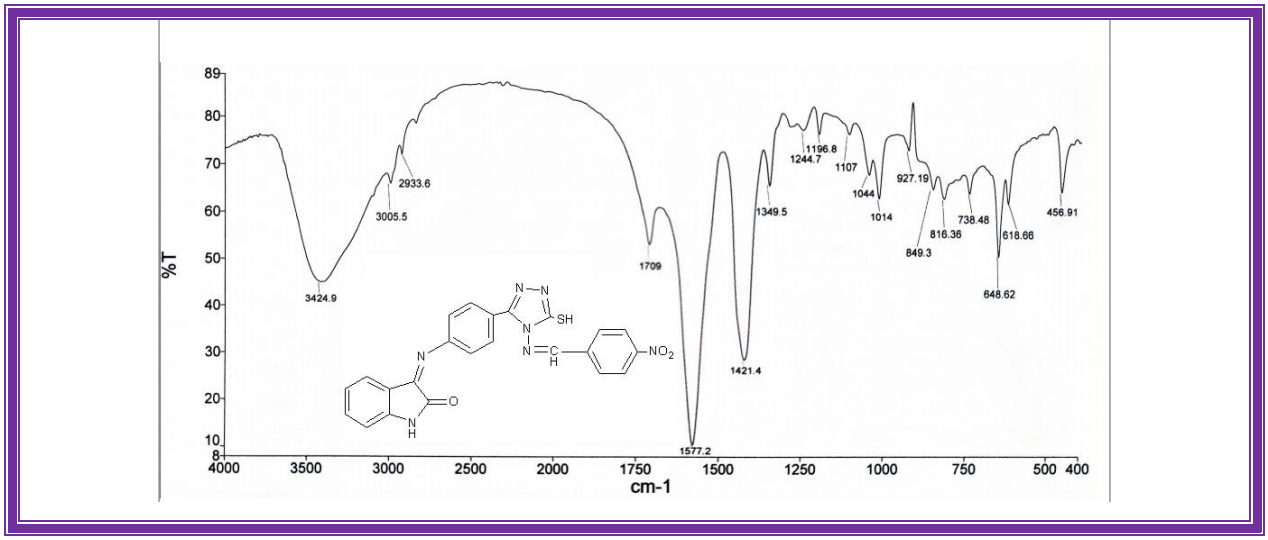


Fig (4.19): FT-IR spectrum in of compound (R_6)

The ^{1}H-NMR spectrum of compound [R_6] Fig (4.20) shows the chemical shifts (DMSO-d_6, ppm): 10.74 (s,1H,SH), 10.18 (s,1H,NH), 8.47 (s,1H,N=CH), 8.44-8.04 (m,12H,Ar-H).

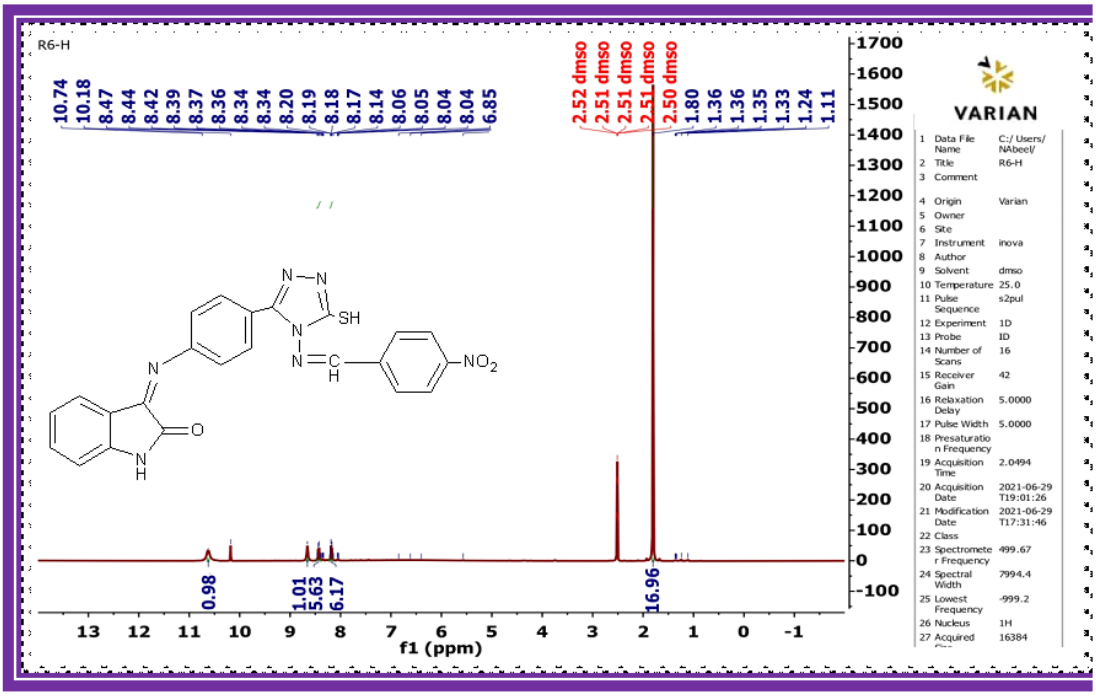


Fig (4.20): ^{1}HNMR spectrum in of compound (R_6)

4.8 Synthesis and identification of Schiff base (3z)-3-((4-(4-((4-chlorobenzylidene)amino)-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one [R_7]

The compound [R_7] was prepared by the reaction of the [R_5] with 4-chlorobenzaldehyde , and the structure appears in **Fig (4.21)**.

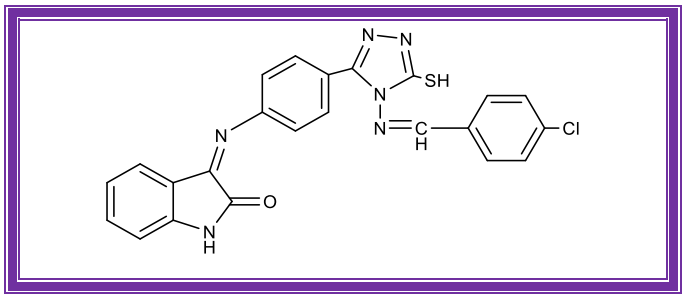
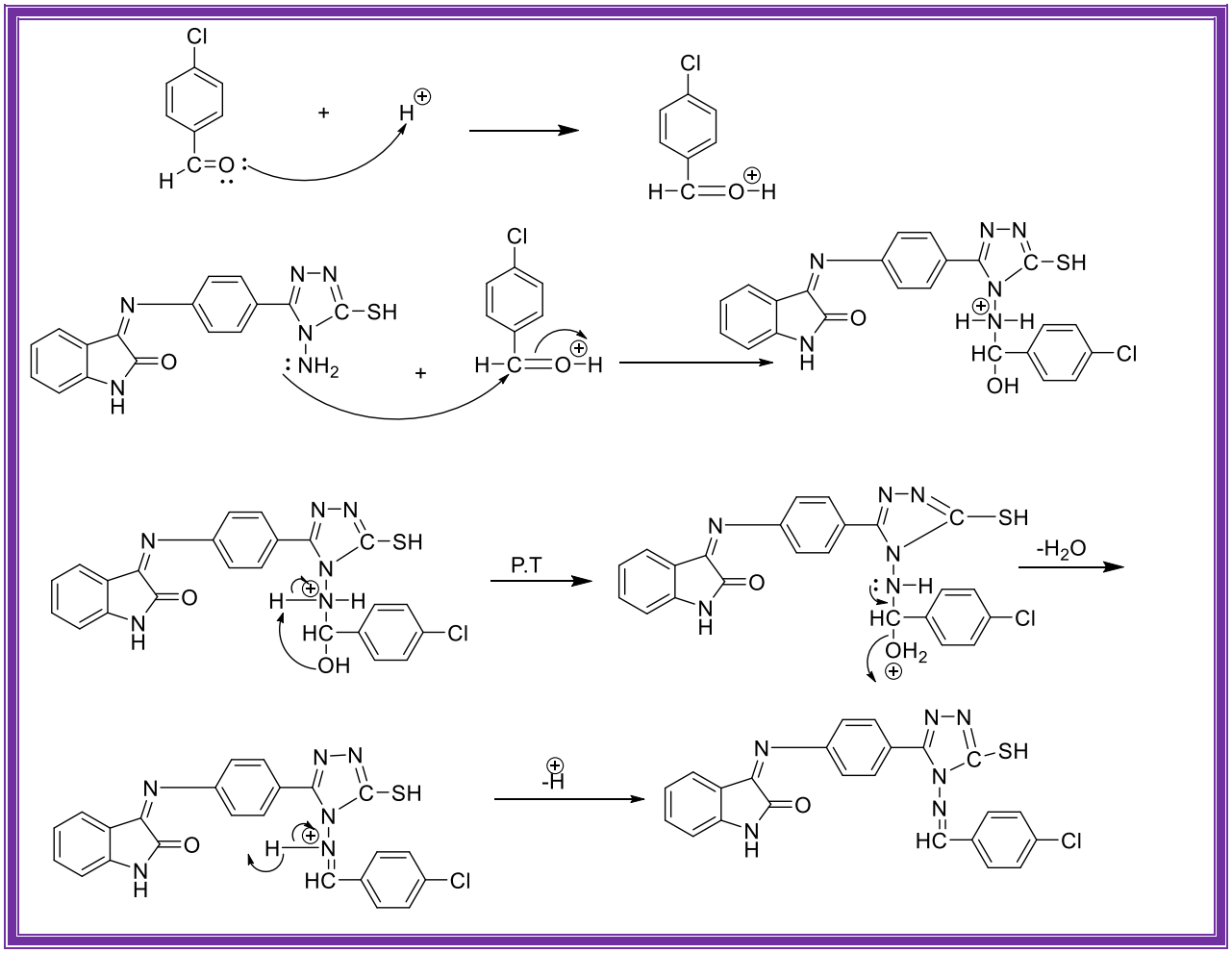


Fig (4.21): The Chemical structures of compounds (R_7)

The mechanism Suggested for the synthesis of compound R_7 is given in **scheme (4.4).**



Scheme (4.4): The mechanism for the synthesis of (R_7) compound.

The FT-IR spectrum of compound [R_7] Fig(4.22) and Table (4.1) shows absorption band at 3062 cm^{-1} was due to C-H aromatic . Absorption band at 1625 cm^{-1} was due to C=N stretching vibration .The bands absorption at 1503 cm^{-1} and 1460cm^{-1} are due to the C=C aromatic. The bands at 1704 cm^{-1} due to the stretching vibration of C=O. Absorption bands at 3157 cm^{-1} was attributed to stretching vibration of N-H **[109].**

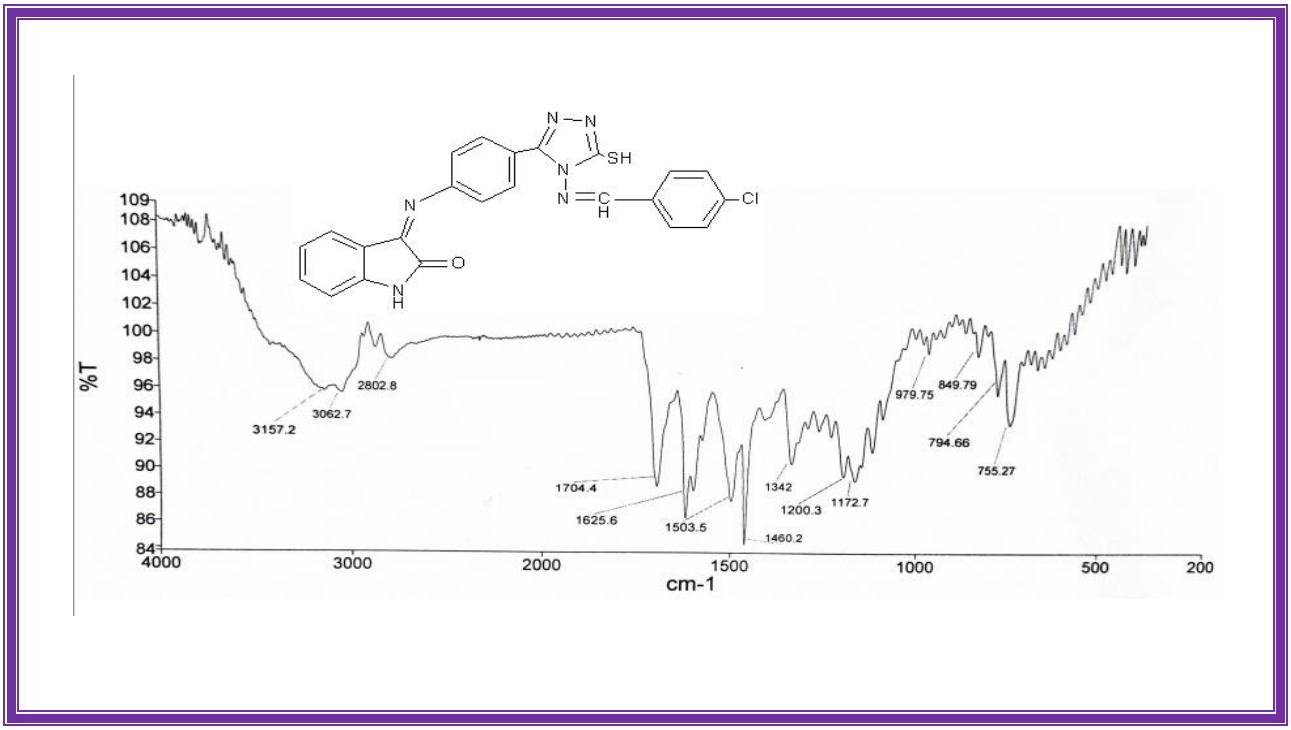


Fig (4.22): FT-IR spectrum in of compound (R_7)

The ^{1}H-NMR spectrum of compound [R_7] shows the chemical shifts (DMSO-d_6, ppm): 13.01 (s,1H,SH), 11.33 (s,1H,NH), 8.00 (s,1H,N=CH),6.53-7.71 (m,12H,Ar-H)

4.9 Synthesis and identification of Schiff base (3z)-3-((4-(4-((4-hydroxybenzylidene)amino)-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino-2-one[R_8]

The compound [R_8] was prepared by the reaction of the[R_5]with 4-hydroxbenzaldehyde, with a structure appears **in Fig (4.23).**

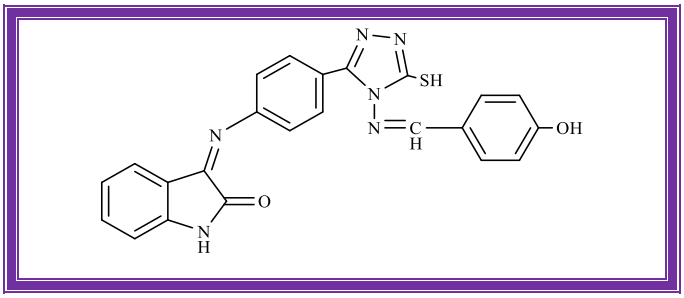


Fig (4.23): The Chemical structures of compounds (R_8)

The FT-IR spectrum of compound [R_8] Fig(4.24) and Table (4.1) shows absorption band at 3070 cm^{-1} was due to C-H aromatic . Absorption band at 1621 cm^{-1} was due to C=N stretching vibration . Absorption band at 3212 cm^{-1} was due to bonding of OH group. The bands at 1700 cm^{-1} due to the stretching vibration of C=O. The bands at 1582 cm^{-1} and 1507cm^{-1} are due to the C=C aromatic **[110].**

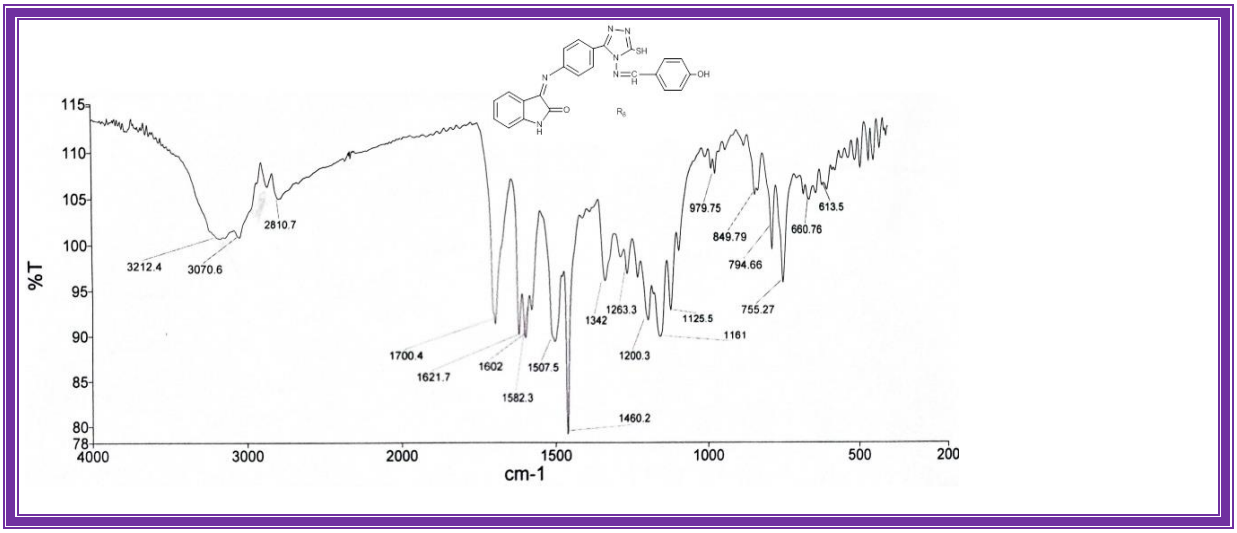


Fig (4.24): FT-IR spectrum in of compound (R_8)

The ^{1}H-NMR spectrum of compound [R_8] Figure (4.25) shows the chemical shifts (DMSO-d_6, ppm): 13.01 (s,1H,SH), 7.96 (s,1H,NH), 7.60

(s,1H,N=CH), 7.46 -7.28 (m,12H,Ar-H) , 10.64 (s,1H,OH)

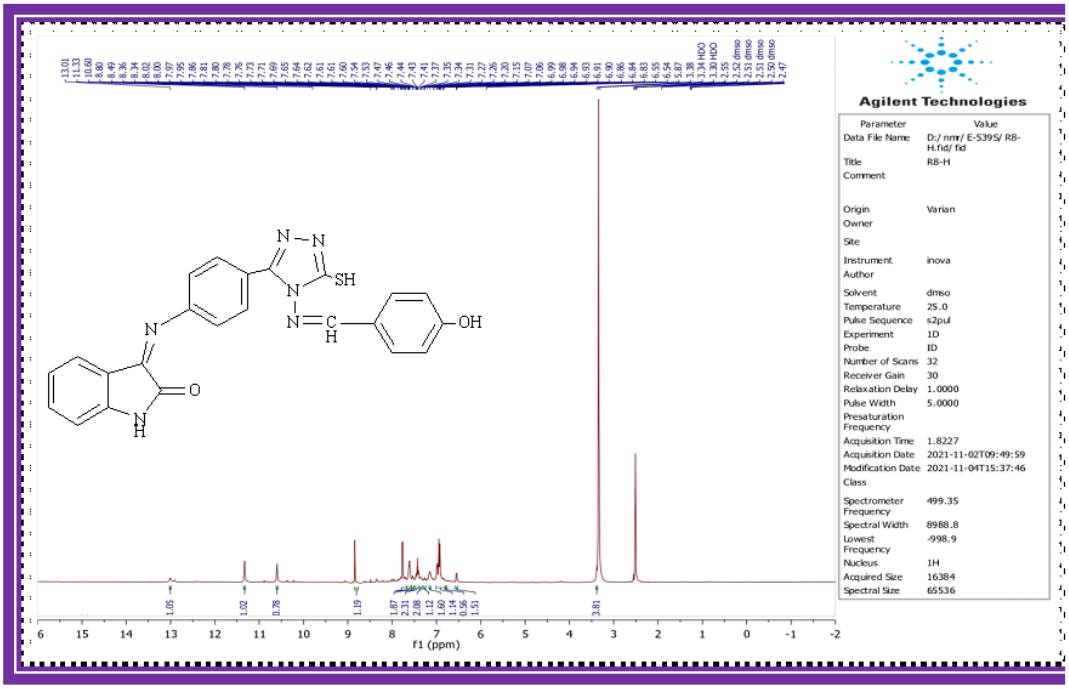


Fig (4.25): ^{1}HNMR spectrum in of compound (R_8)

4.10 Synthesis and identification of Schiff base (3z)-3-((4-(4-((4-hydroxy-3-methoxybenzylidene)amino)-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin -2-one[R_9]

The compound [R_9] was prepared by the reaction of the [R_5]with 4-hydroxy-3-methoxybenzaldehyde, with a structure appears in **Fig (4.26).**

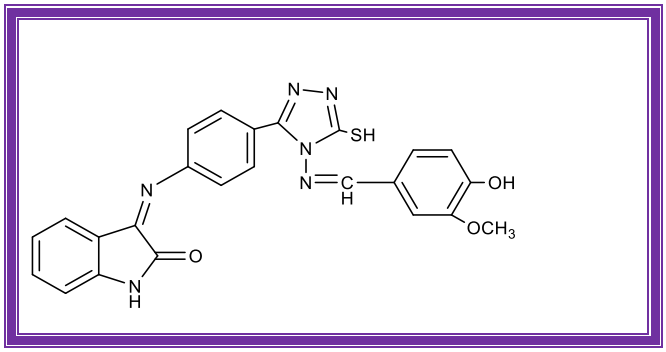


Fig (4.26): The Chemical structures of compounds (R_9)

The FT-IR spectrum of compound [R_9] Fig(4.27) and Table (4.1) shows absorption band at 3065 cm^{-1} was due to C-H aromatic and absorption band at 2927 cm^{-1} was due to C-H aliphatic. Absorption band at

1622 cm^{-1} was due to C=N stretching vibration .The bands at 1505 cm^{-1} and 1460cm^{-1} are due to the C=C aromatic. Absorption band at 3257 cm^{-1} was due to bonding of OH group. Appearance absorption bands at 3191 cm^{-1} was attributed to N-H group. . The bands at 1700 cm^{-1} due to the stretching vibration of C=O **[111-112]**

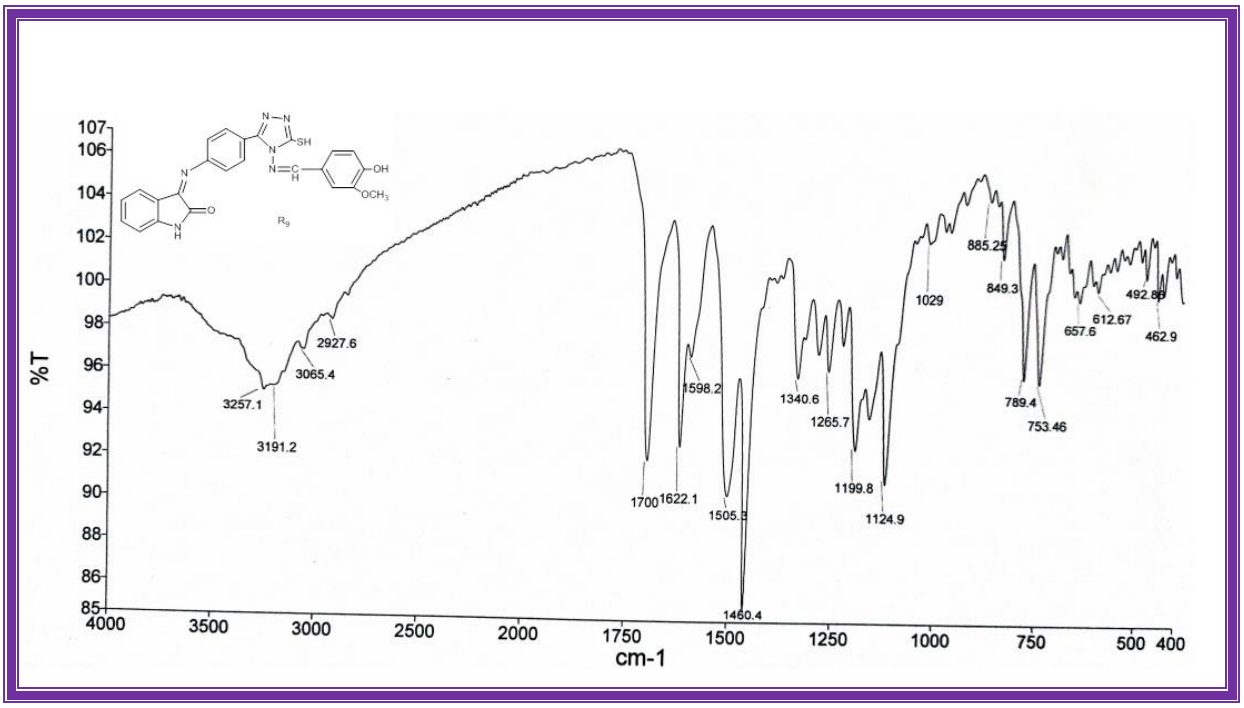


Fig (4.27): FT-IR spectrum in of compound (R_9)

The ^{1}H-NMR spectrum of compound [R_9] Fig (4.28) shows the chemical shifts (DMSO-d_6, ppm): 13.00 (s,1H,SH), 11.33 (s,1H,NH), 10.26 (s,1H,OH) 8.57 (s,1H,N=CH), 8.57-6.54 (m,11H,Ar-H) , 3.93

(s,1H,OCH_3).

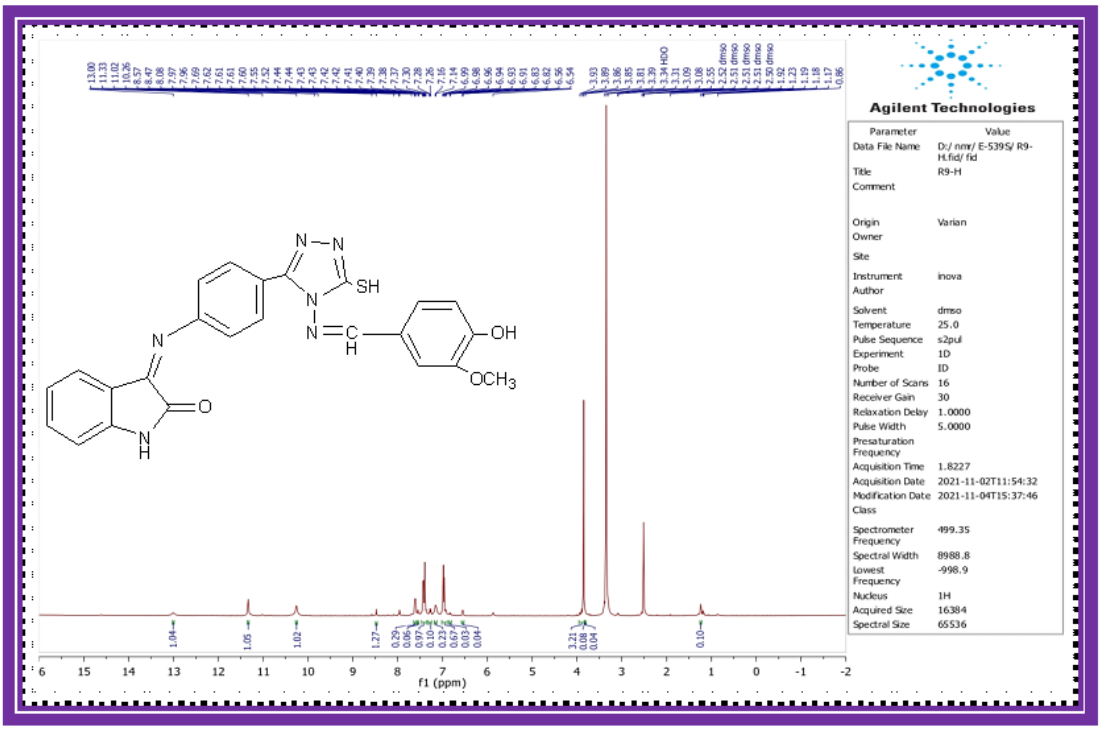


Fig (4.28): ^{1}HNMR spectrum of compound (R_9)

Table (4.1):The most diagnostic FT-IR bands of the compounds (R_1-R_9) in (cm^{-1}).

Comp.No.	νC-H arom.	ν C=O	ν C=N	ν C=C	N-H	Others
R_1	-------	1736	1619	1535-1463	3185	-----
R_2	3053	1735	1619	1459	-----	ν C=O amide 1649 ν CH2 group 2945-2748
R_3	3076	1738	1596	1454-1494	-----	ν C=O amide 1642
R_4	-----	1739	1616	1598-1466	3191	ν OH 2999-3251 ν COOH 1688
R_5	------	1655	1568	1415	3395	ν NH_2 3448
R_6	3005	1709	1577	1421	3424	------
R_7	3062	1704	1625	1460-1503	3157	------
R_8	3070	1700	1621	1507-1582	------	ν OH 3212
R_9	3065	1700	1622	1460-1505	3191	ν OH 3257 ν C-H Aliphatic 2927

Table (4.2): Physical Properties of compounds (R_1 – R_9)

)Comp. symbol	Molecular Formula	m. W t (g. mol^{-1})	Color	M .p. ^{o}c	Yield %	Recry. Solvent
R_1	$C_{15}H_9N_3OS$	279.32	Light orange	182-184	93	Ethanol
R_2	$C_{17}H_{10}ClN_3O_2S$	355.80	Light brown	200-203	90	Benzene
R_3	$C_{24}H_{14}N_4O_2S_3$	486.58	Brown	250-251	98	Ethanol
R_4	$C_{15}H_{10}N_2O_3$	266.26	Light yellow	280-281	88	Ethanol
R_5	$C_{18}H_{12}M_6OS$	336.37	Orange black	288-289	75	Ethanol-water
R_6	$C_{23}H_{15}N_7O_3S$	469.48	Yellow	<296	70	Ethanol – water
R_7	$C_{23}H_{16}N_6O_2S$	440.48	Brown	250-251	66	Ethanol-water
R_8	$C_{23}H_{15}ClN_6OS$	458.92	Light brown	282-284	60	Ethanol-water
R_9	$C_{24}H_{18}N_6O_3S$	470.51	Light brown	<290	78	Ethanol-water

4. 11 Biological activity

The disk diffusion method was used to test the antibacterial activity of most of the targeted compounds against one gram-negative bacteria *(E. coli)* and one gram-positive bacteria *(S. aureus).* DMSO was used to dissolve the test substances. As a comparative benchmark, two conventional antibiotics (STREPTOMTCIN) were utilized. The compounds' zones of inhibition were measured in Figures (4. 29), (4.30) (mm). Table (4. 3) lists the antibacterial activity data of the produced compounds. The test chemicals' antibacterial properties are briefly displayed here.

The result indicated that the activity against *S. aureus* bacteria was high for (R_1-R_3), low for compound (R_5) and no activity has appeared for (R_4), The

resu it is also confirmed the activity against (E. coli) bacteria of the compounds (R_1 ,R_2 ,R_3 ,R_6) , whereas the compounds (R_4 ,R_5 ,R_7 ,R_8 ,R_9) showed no activity against this type of bacteria.

Table(4. 3) : The inhibition zones of the compounds(R_1-R_9)

Microorganism / Tested materials	*E. coli*				*S. aureus*			
	100	75	50	25	100	75	50	25
R_1	33	31	27	24	23	23	21	16
R_2	13	12	11	R	20	20	19	17
R_3	25	23	24	22	22	21	23	21
R_4	-	-	-	-	-	-	-	-
R_5	-	-	-	-	13	12	12	11
R_6	21	18	16	14	19	16	15	14
R_7	-	-	-	-	20	20	19	17
R_8	-	-	-	-	21	20	19	19
R_9	-	-	-	-	17	15	15	14

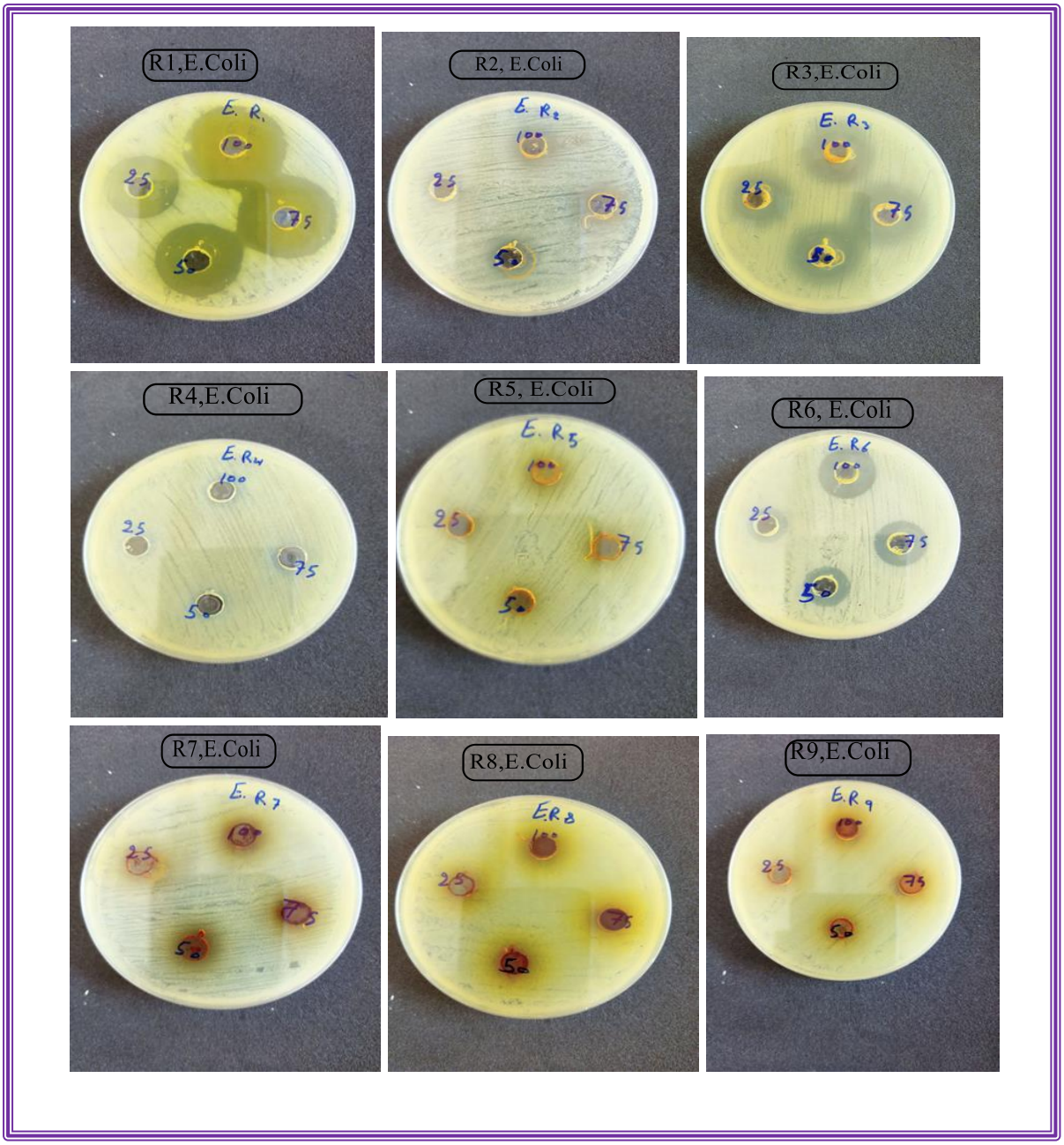


Fig (4. 29): The compounds' zones of inhibition were measured .

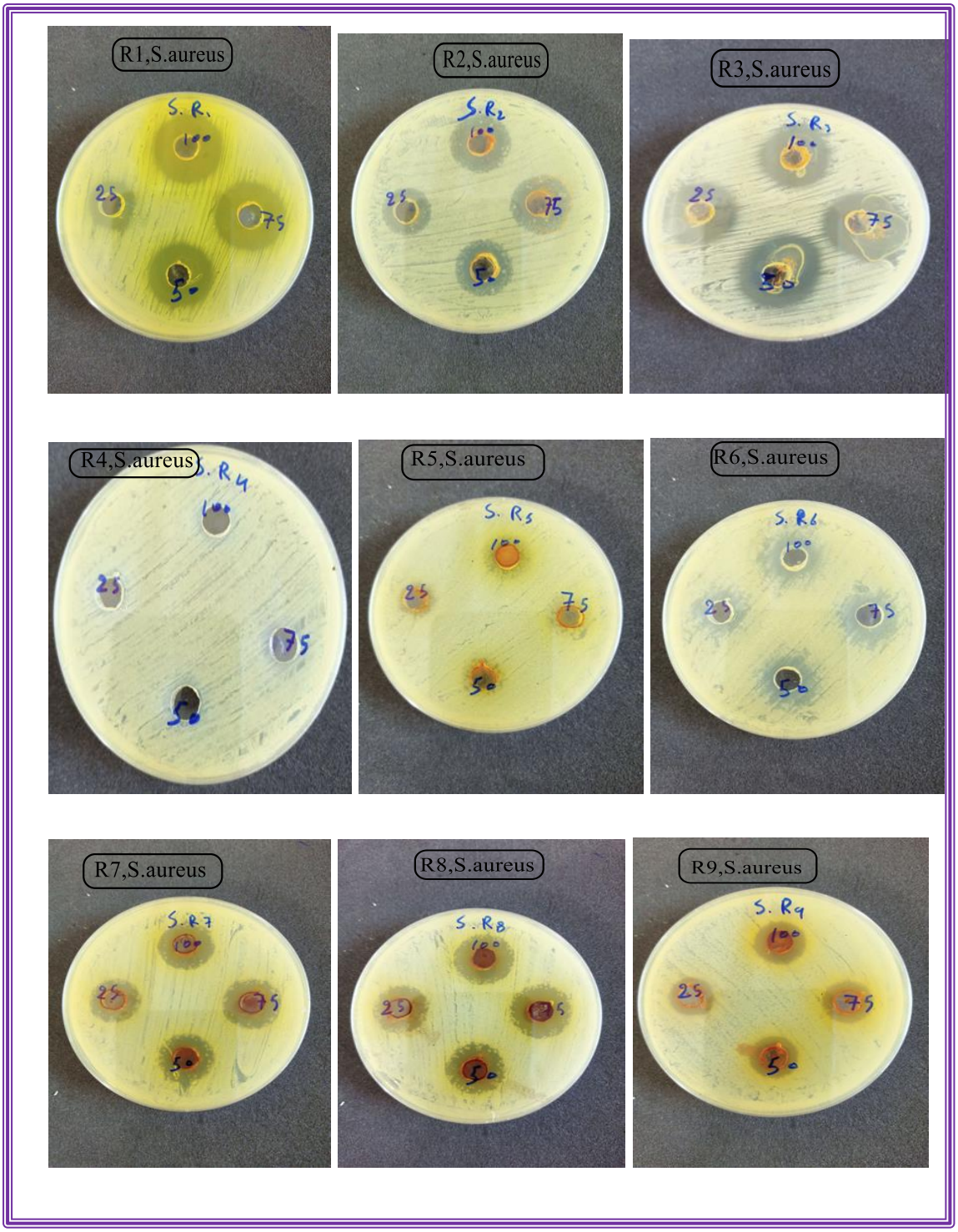


Fig (4. 30): The compounds' zones of inhibition were measured

Conclusion

The present study concluded the following:

1. Synthesis of nine derivatives (R_1-R_9) from the reaction of isatin with different primary amine, then preparation of Schiff bases that identified by melting point, FT-IR, ^{1}HNMR and ^{13}C-NMR spectroscopy techniques.

2. Some of the prepared compounds were examined for their antibacterial activities toward two strains of bacteria ***(E. coli)*** and ***(S. Aureus).*** The result indicated that the activity against (*S. aureus)* bacteria was high for (R_1-R_3), low for the compound (R_5) and no apparent activity for (R_4), also the data proved the activity against (*E. coli*) bacteria for compounds (R_1,R_2 ,R_3 ,R_6), whereas the compounds (R_4,R_5,R_7,R_8,R_9) showed no activity against this type of bacteria.

Suggestions for future work:

1. Synthesis of a new series of Schiff bases containing 1,2,4- triazole-3-thiole derivatives from the reaction of the compounds [R_5] with other different aldehydes.

2. Synthesis of a series of new complexes for synthesized compounds with different transition metal ions and evaluate their biological activities.

3. Study of biological activity of the derivatives against other types of bacteria and fungi.

4. Investigate of some industrial applications of these derivatives and their complexes.

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الخلاصة

الخلاصة

في هذه الرسالة ، تم تحضير مركبات بنجاح من الايساتين ، تم تحديد التركيب الكيميائي للمركبات المحضرة (R_1- R_9) بواسطة بعض تقنيات التحليل الطيفي مثل^{1}H-NMR, FTIR] and ^{13}C-NME]. تمت متابعة التفاعل بواسطة كروماتوغرافيا الطبقة الرقيقة (TLC) ، وتم تحديد الخواص الفيزيائية للمركبات المحضرة مثل درجات الانصهار والألوان. تم تقييم الفعالية البيولوجية للمركبات المحضرة لمعرفة نشاطها المضاد لنوعين من البكتريا ***E. coli and S. aureus*** بكتيريا سالبة الغرام وموجبة الغرام ، على التوالي. حيث أظهرت معظم هذه المركبات نشاطًا مضادًا للبكتيريا جيدًا إلى مقبول ضد سلالتين من البكتيريا المستخدمة. وتضمنت الدراسة الحالية الخطوات التالية:

1- تحضير المركب [R_1] (Z)-3-(benzo[d]thiazol-2-ylimino)indolin-2-one ، بتفاعل الايساتين مع 2-امينو بنزوثايزول.

2- تحضير المركب Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-chloroacetyl)indolin-2-one[R_2] عن طريق تفاعل المركب [R_1]مع كلورو أسيتيل كلوريد وثلاثي إيثيل أمين.

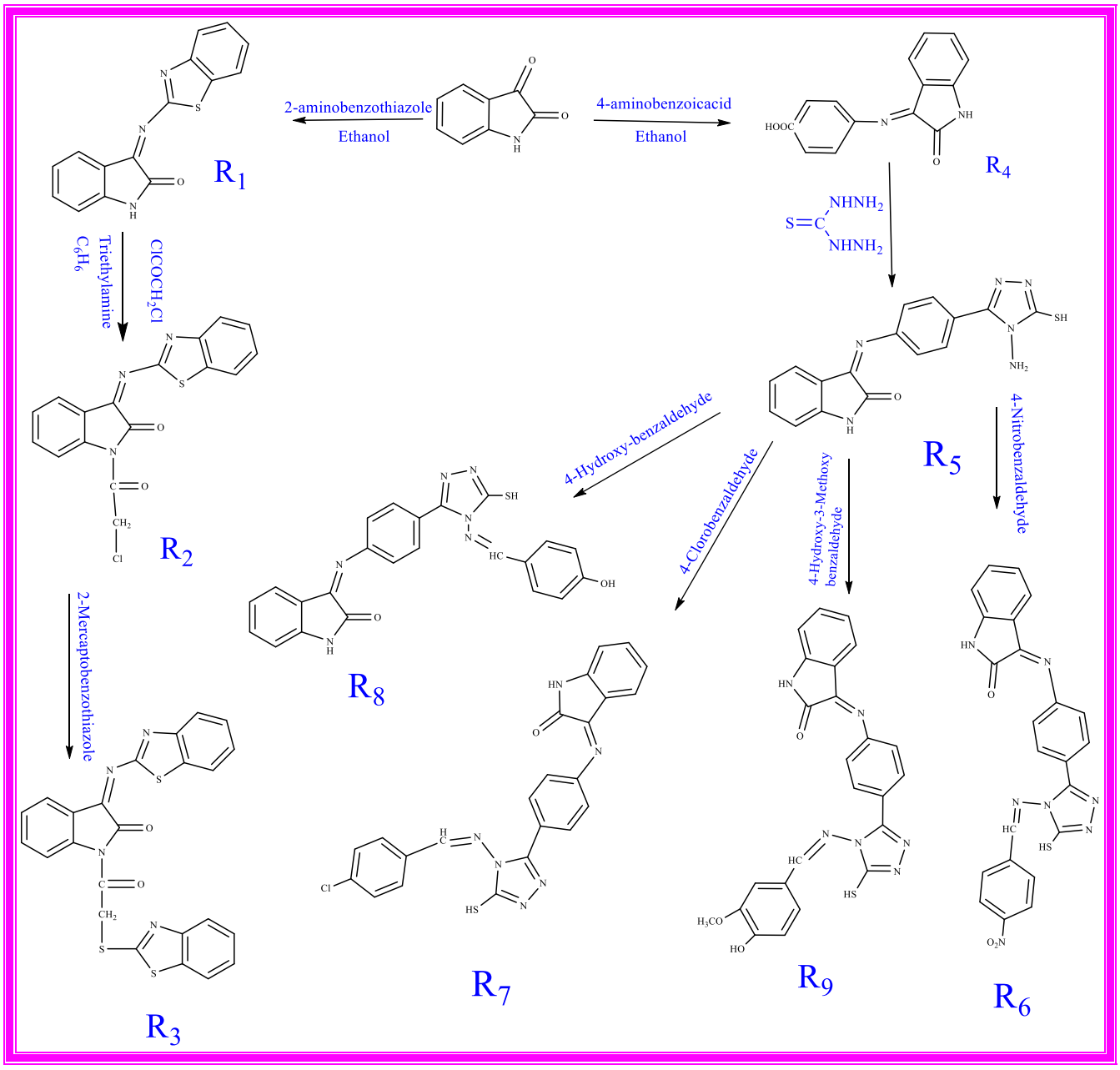
3- تحضير المركب (Z)-3-(benzo[d]thiazol-2-ylimino)-1-(2-(benzo[d]thiazol-2-ylthio)acetyl)indolin-2-one بواسطة تفاعل [R_2] مع 2-مركبتوبنزوثيازول.

4- تحضير المركب[R_4] (Z)-4-((2-oxoindolin-3-ylidene)amino)benzoic acid

من تفاعل الايساتين مع 4-amino benzoic acid

5- تحضير المركب[R_5] (z)-3-((4-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)phenyl)imino)indolin-2-one من خلال تفاعل المركب[R_4] مع ثايوكربوهيدرازيد.

6- تم تحضير قواعد شيف الجديدة [R_6-R_9] من خلال تفاعل المركب [R_5]مع الالديهايدات الاروماتية المختلفة.



المخطط(1): يوضح المركبات المحضرة

وزارة التعليم العالي والبحث العلمي

جامعة ديالى/ كلية العلوم

قسم علوم الكيمياء

تحضير و تشخيص وتقييم الفعالية البايلوجية لبعض مشتقات الايزاتين

رسالة مقدمة الى

مجلس كلية العلوم/ جامعة ديالى

وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

من قبل الطالبة

رسل شكر محمود وهاب

بكالوريوس في علوم الكيمياء

كلية العلوم/ جامعة ديالى 2018

بإشراف

أ. م. د. وسن باقر علي

1443هـ **2022 م**