Ministry of Higher Education
and Scientific Research
University of Diyala
College of Science
Department of Chemistry

Synthesis of New Schiff Base Derivatives From Indole and Evaluation Their Biological Activity

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

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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

Dedication

To whom God has sent as a mercy to the worlds and a beacon for the righteous, the teacher of the first nation, the master of the messengers and the seal of the prophets, our master Muhammad and his pure family. (God prays on him).

To those whose main concern was my education, so that I could move forward among the students to the reason for my existence in life.... My father (God handed him an asset to us).

To whom God made heaven under her feet, my beloved mother.

To all of the academic professors especially **Dr. Fadhil Lafta Faraj**, to my colleagues and companions on the path, and to everyone who stood with me during the study period.

Acknowledgements

First of all, I would like to thank Allah for giving me the strength and energy to accomplish this work, thank you God to all things that you give me in all my life I am using this opportunity to express my deepest gratitude I can't find words that express what I feeling so I should thank my teacher and special thanks to **Dr. Fadhil Lafta Faraj**

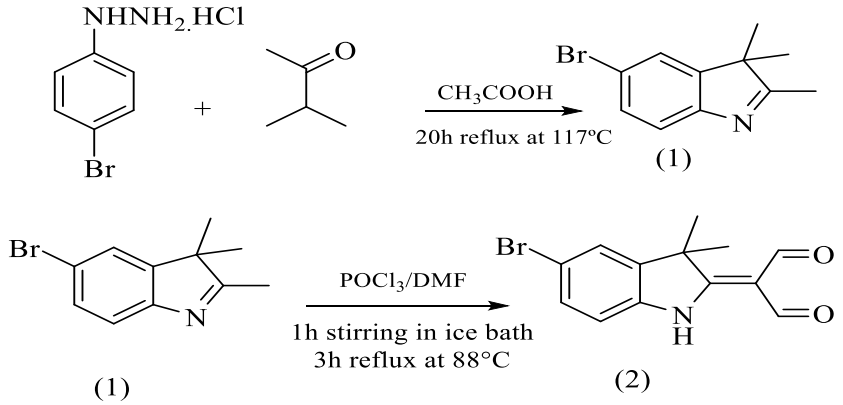
Supreme words of thanking and appreciation to the Dean, chairman, and the staff of the Chemistry Department, College of Science, Diyala University.Finally nothing of this work could have been done without the moral support of my dear friends.

ABSTRACT

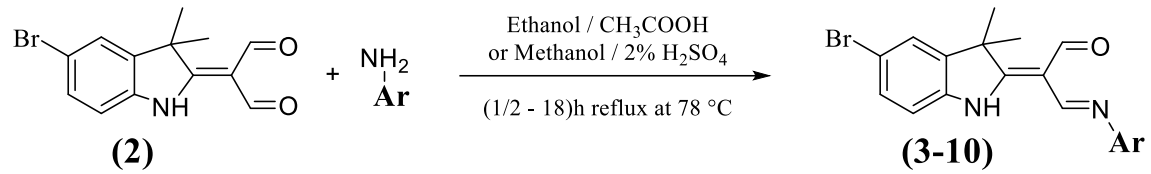
In this thesis, a series of new Schiff bases have been successfully synthesized, their purity were confirmed by thin layer chromatography, The chemical structures of the synthesized compound were charictrazation by some spectroscopic techniques like, FT-IR and ^{1}H-NMR, as well as some of their physical properties were determined such as, melting points. The synthesized compounds were divided into two sections:

The first section; includes synthesis of new starting material, 5-bromo-2,3,3-trimethyl -3*H*-indole **(1)** and 2-(5-bromo-3,3- dimethyl-1,3-dihydroindol-2-ylidene)-malonaldehyde **(2).**

The first compound, 5-Bromo-2,3,3-trimethyl -3*H*-indole **(1)** has been synthesized by Fischer indole synthesis via reaction of 4-bromophenylhydrazine hydrochloride with methyl isopropyl ketone in the presence of glacial acetic acid as a catalyst. The **second compound**, 2-(5-Bromo-3,3- dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde **(2)** has been synthesized by Vilsmeier Haack reaction via reaction of 5-Fluoro-2,3,3-trimethyl-3*H*-indole **(1)** with Phosphoryl chloride (POCl3) in a presence of N, N-dimethyl formamide (DMF).

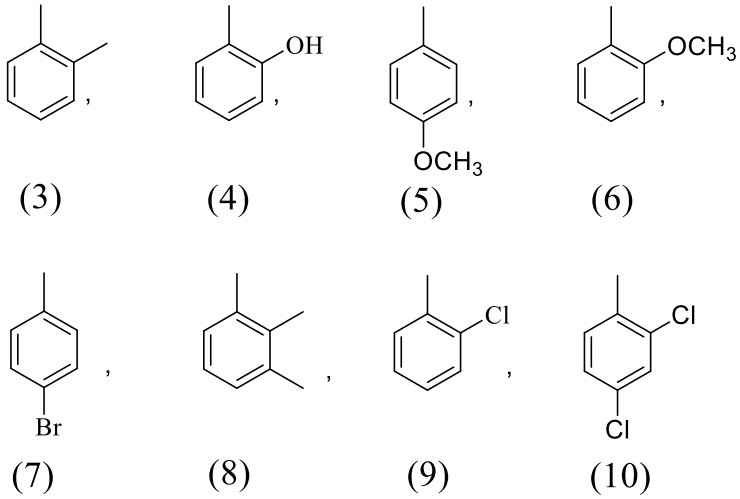


The second section; includes synthesis of new Schiff bases via reaction of compound 2-(5-Bromo-3,3-dimethyl-1,3- dihydroindol-2-ylidene)-malonaldehyde (**2**) with various aniline substitutes, in absolute ethanol or methanol as a solvent.



(2) **(3-10)**

where **Ar =**



(3) (4) (5) (6)

(7) (8) (9) (10)

The two new synthesized compounds 4 and 6 were evalutated for biological activity against two types of bacteria gram-negative (G-) *E. coli* and gram-positive (G+) *S. aureus*. Where compound 4 showed an inhibitory effect on activity of bacteria.

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List of Symbols and Abbreviations	
α	Alpha
β	Beta
cm	Centimeter
δ	Chemical Shift
CMC	Compehrnsive Medicinal Chemistry
°C	Degree Celsius
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DPPH	Diphenyi-1-picrylhydrazyl
d	Doublet
CHN	Elemental analyses
E. coli	Escherichia coli
EtOH	Ethanol
FT-IR	Fourier-Transform Infrared
g	Gram
h, hrs	Hour, Hours
HCT	Hematocrit
LSD	Lysergic acid diethylamide
MHz	Megahertz
m. p.	Melting Point
µg	Micro gram
mL	Milliliter
mmole	Millimole
m	Multiplet
ppm	Part per million
%	Percent
π	Pi
^{1}H-NMR	Proton Nuclear Magnetic Resonance Spectrometer
σ	Sigma
s	Singlet
S. aureus	Staphylococcus aureus
TMS	Tetramethylsilane
TLC	Thin Layer Chromatography
t	Triplet

CHAPTER ONE

PREFACE AND LITERATURE

Chapter One: Preface and Literature review

1.1 . Preface

In our daily lives, heterocyclic compounds has great interest which contian one or more hetero atoms. Heterocyclic compounds can be used in a variety of ways. Pharmaceuticals, agrochemicals, and veterinary items are the most common applications. They are also used as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, and dye materials. They are used in the synthesis of other organic compounds as vehicles. Some natural products, such as antibiotics like penicillin and cephalosporin, and alkaloids like vinblastine, morphine, and reserpine, include heterocyclic moiety. [1] For a long time, medicinal chemistry has been fascinated by the chemistry and biology of heterocyclic molecules. A number of heterocyclic derivatives with a nitrogen atom serve as unique and adaptable scaffolds for drug development in the laboratory. Since indole was first extracted by treating indigo dye with oleum, the name indole is derived from the words indigo and oleum. The study of the dye indigo sparked the development of indole chemistry. [2] At room temperature, the indole ring is a white powder that is an aromatic heterocyclic molecule C_8H_7N is the chemical formula for indole. It has an aromatic bicyclic structure with a five-membered pyrrole ring fused to a benzene ring to produce two isomeric benzopyrrole. A functional group containing a carbon nitrogen double bond with the nitrogen atom linked to an aryl or alkyl group but not hydrogen is known as an azomethine group. The most common way to make stabilized Schiff bases is to combine aromatic primary amines with the active carbonyl group of aromatic aldehydes and ketones. [3]

The indole Schiff bases were known as a significant class of heterocyclic organic compounds which have wide applications in many fields for examples

anti-inflammatory activity [4], antimicrobial activity‘[5] antibacterial, antifungal, antitumor activity [6] and antioxidant [7]

Recently, many efforts have been dedicated by chemists and biologists on the modification of indole Schiff bases for the development of pharmaceutical, biological and medicinal compounds.

This study focused on the use of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-(o-tolylimino)propanal (2) and various substituted aniline to synthesize new indole Schiff bases compounds and spectroscopic techniques were used to characterize the chemical structures of all of these novel substances.

Chapter One: Preface and Literature review

1 .2 . Literature review

Ghaidan, A. F. (2018) Series of new compounds of indole Schiff base derivatives have been synthesized by reaction of 2-(5-Chloro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde with aniline substituted. The chemical structures of the synthesized compounds were characterized by TLC, FT-IR, 1H, 13C NMR and APT 13C NMR.The in vitro anticancer activity of the new synthesized compounds tested against– AMJ breast cancer cell line. The revealed data showed that compounds have promising anticancer activity against AMJ13 cell line at low concentrations. [8]

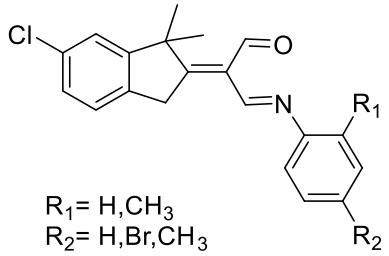


Figure (1.1) 2-(5-Chloro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-3-(2,4- disubstituted phenylimino)-propionaldehyde derivatives

Abdelmadjid, A. et al.(2021) A brand-new Schiff base The reaction between2,4-diaminotoluene and2-hydroxy-5-methoxy benzaldehyde produced 2,2'-((1E,1'E)-((4-methyl-1,3-phenylene)bis(azaneylylidene)) bis(methaneylylidene)) bis(4-methoxyphenol). The compound was characterized by using IR, UV-Vis, 1H, and ^{13}C NMR techniques. The structure of the ligand was determined by X-Ray Diffraction method (XRD). The electrochemical properties were studied through the cyclic voltammetry. Several experiments were used to assess the antioxidant properties of the synthesized Schiff base.[13]

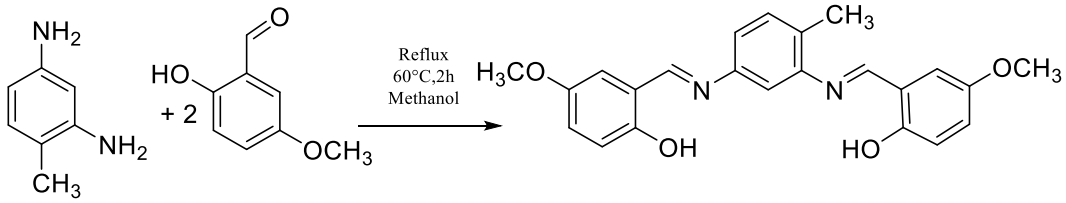


Figure (1.2) Synthesis of 2,2'-((1E,1'E)-((4-methyl-1,3-phenylene)bis(azaneylylidene)) bis(methaneylylidene)) bis(4-methoxyphenol).

Saleem, M. F. et al.(2021) Four Schiff base derivatives of gabapentin, were synthesized by condensation with benzoin, vanillin, acetophenone, and benzophenone, respectively. Their chemical identities were established by FT-IR, ^{1}H-NMR and ^{13}C-NMR techniques. The new compounds were screened for antibacterial activity using agar well method, antioxidant activity by DPPH assay, and anticonvulsant activity against pentylenetetrazole (PTZ) induced seizures in mice.[14]

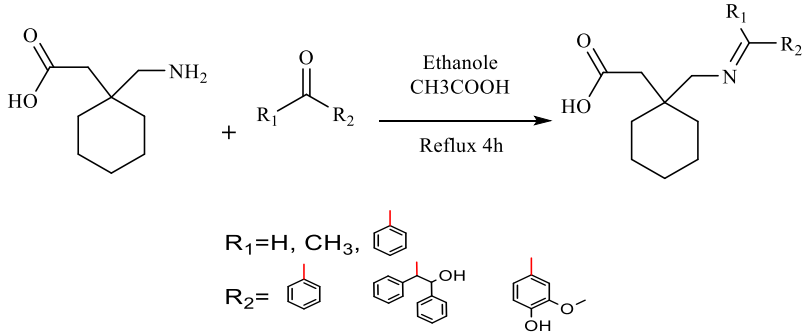


Figure (1.3) Chemical reaction showing synthesis of gabapentin Schiff base compound

Jameel, D. A et al.(2020) Series of new indole based Schiff base derivatives were designed and synthesized by reacting 2-(1,1-dimethyl- 1,3-dihydro-2H-benzo[e]indole-2-ylidene)malonaldehyde with different substituted aniline. Spectroscopic techniques were used to confirm and characterize the chemical structure of the substances (FT-IR, ^{1}H-NMR and APT ^{13}C-NMR). The cytotoxicity activity of the target compounds at various doses was tested against the AMJ-13 breast cancer cell line. The findings revealed that compounds have promising cytotoxic activity against AMJ13 cell line

particularly compound (3) showed highest inhibition at 100 μg/ml rate among the tested compounds with diffrent concentration. [9]

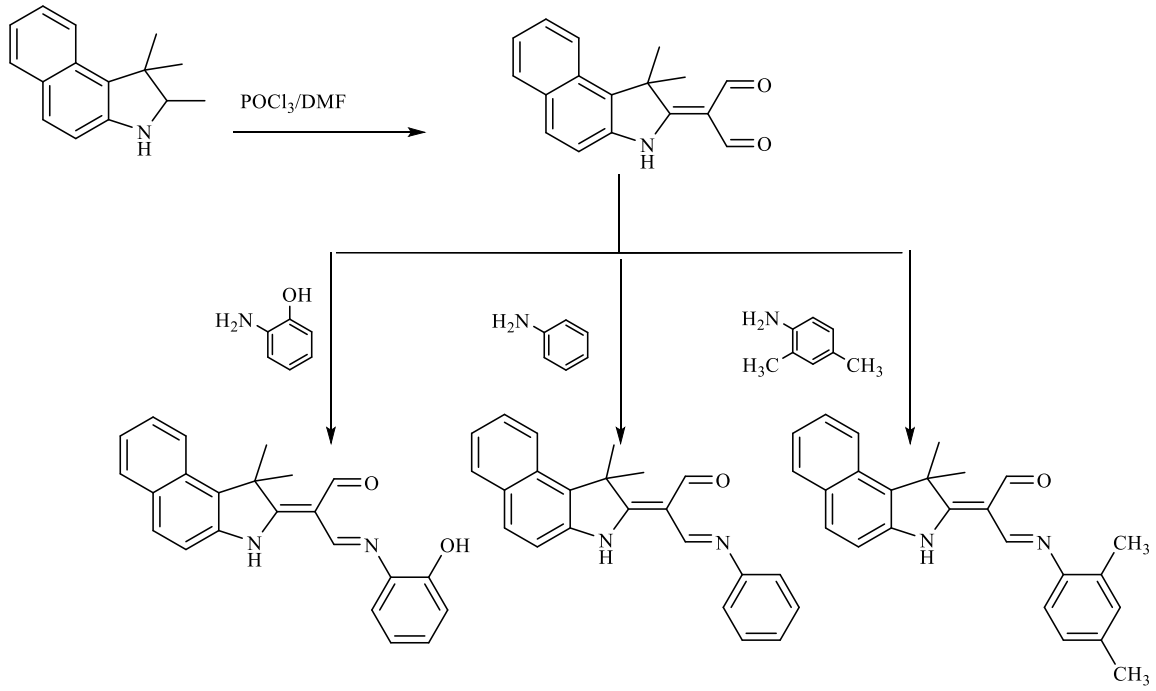


Figure (1.4) The general scheme of synthesis of the three new indole Schiff bases derivatives

Al-Azawi K.F. (2018) Synthesized successfully new compound, ethyl 4-amino N-(3-isatinyl) benzoate in high yield from reaction of ethyl 4-aminobenzoate with isatin in (1:1) molar ratio , Weight loss and scanning electron microscopy techniques were used to investigate the effect of the inhibitor on corrosion of MS (mild steel) in hydrochloric acid as a corrosive solution.[15]

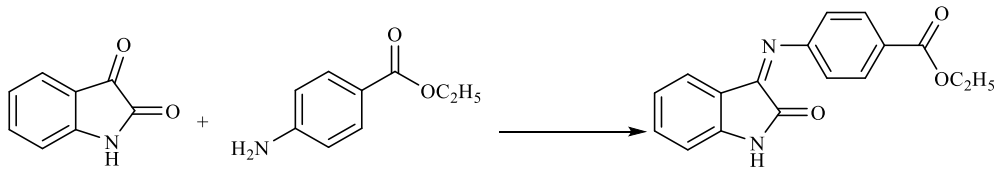


Figure (1.5) Synthesis of inhibitor (ethyl 4-amino *N*-(3-isatinyl) benzoate).

Fatemeh H. et al.(2017) synthetic compound, 2-(1,1-Dimethyl-1,3-dihydro-benzo[e]indol-2-ylidene)-3-(2-hydroxyphenylimino)-propionaldehyde, abbreviated as DBID a substance that has been synthesized reaction of 2-(1,1-dimethyl-1,3- dihydro-benzo[e]indol-2-ylidene)-malonaldehyde with 2-aminophenol. FT-IR, ^{1}H NMR, ^{13}C NMR, and APT-NMR, as well as elemental analyses (CHN), were used to describe and confirm the chemical structure of the synthesized molecule. The chemical was tested for antiproliferative activity against the HCT 116 colorectal cancer cell line, and a putative mechanism of action was discovered. The MTT assay was performed to estimate the IC_{50} value, and its apoptosis-inducing impact was studied. [10]

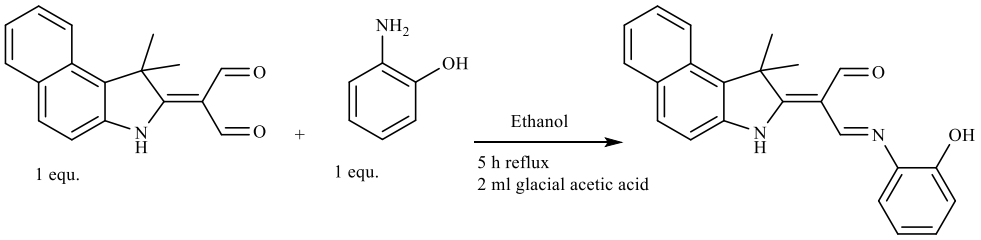


Figure (1.6): Synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-benzo[e]indole- 2-ylidene)-3-(2-hydroxy-phenylimino)-propionaldehyde (DBID).

Aghdam, R. et al.(2013) Fischer synthesis with isopropylmethylketone yielded4,7-dichloro-2,3,3-trimethyl-3H-indole from 1-(2,5-dichlorophenyl)hydrazine. When indolenine was exposed to the vilsmeier reagent, amino methylene malondialdehyde was formed, which then interacted with hydrazine, arylhydrazine, urea, cyanoacetamide, and thiourea to produce pyrazols, pyrimidones, and thiopyrimidone, respectively.[11]

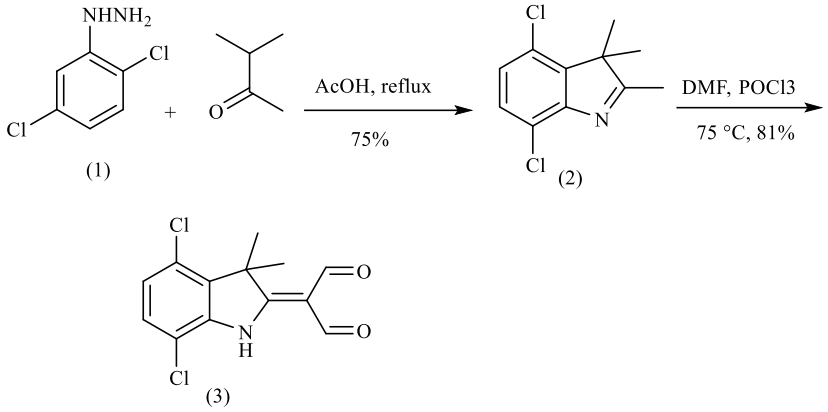


Figure (1.7) The synthetic pathway of 2-(4,7-dichloro-3,3-dimethylindolin-2-ylidene)malonaldehyde

Saundane, A. R., et al. (2015) synthesized *N*'-[(5-substituted-2-phenyl-1*H*-indole-3-yl)methylene] 2-oxo-2*H*-chromene-3- carbohydrazides and were screened for their antimicrobial and antioxidant activities. The synthesized derivatives showed acceptable activities as antimicrobial and antioxidant agents figure (1. 7). [12]

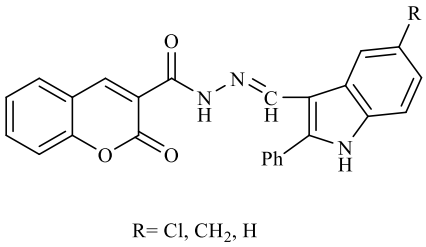


Figure (1. 8): *N*'-[(5-substituted-2- phenyl-1*H*-indol-3-yl)methylene] 2-oxo-2*H*-chromene-3-carbohydrazides

Roohi, L. et al. (2013) The reaction of 4-chloro-2,3,3-trimethyl-7-phenoxy-3H-indole with Vilsmeier reagent resulted At 75°C, in good diformylation of the imine-methyl group. Malonaldehyde's structure was confirmed by its spectral data. (FT-IR, ^{1}H-NMR and ^{13}C-NMR).[16]

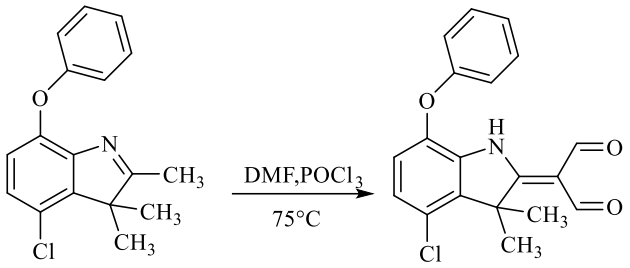


Figure (1. 9): The synthetic of 2-(4-chloro-3,3-dimethyl-7-phenoxyindolin-2-ylidene)malonaldehyde

Ashraf, M. A. et al. (2011) R_1N=CHR_2 is the generic formula for three new series of biologically active amino substituted Schiff bases. R_1 stands for 2-amino-benzthiazole, 4-amino-salicylic acid, and 4-aminophenol, respectively. The reactions of three distinct amino substituted chemicals and substituted aldehydes in ethanol yielded R_2 =4-chlorobenzaldehyde, 2-chlorobenzaldehyde, salicylaldehyde, vanillin, and benzaldehyde. Different physico-chemical techniques, such as melting point, elemental analysis, and multinuclear NMR, were used to characterize these compounds (^{1}H, ^{13}C). The biological activity of the free ligands and their metal complexes against bacteria, fungus, and yeast were tested in vitro. When opposed to Schiff base ligands, metal complexes have more powerful actions.[17]

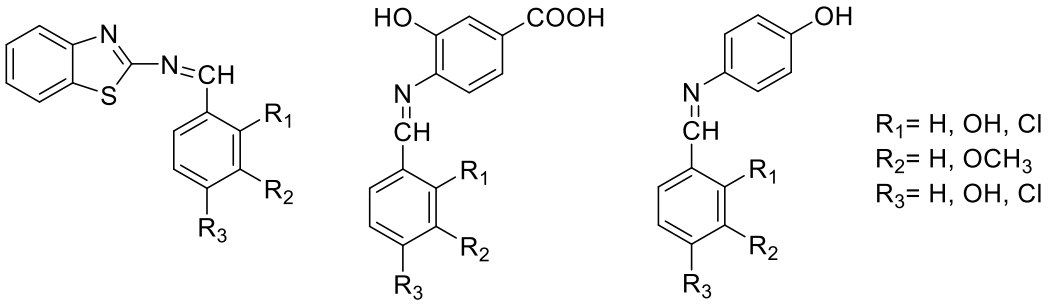


Figure (1. 10): New synthesized Schiff bases

1. 3. Aim of the work

The objectives of this study are: -

1) To synthesize a series of new Indole Schiff base derivatives.
2) Using spectroscopic techniques such as nuclear magnetic resonance spectroscopy (^{1}H-NMR) and Fourier Transform infrared spectroscopy (FT-IR), determine the chemical purity and structures of the produced compounds as well as to validate their identity physical properties.
3) To evaluate the biological activity of the newly synthesized compound anti two types of becteria.

CHAPTER TWO

INTRODUCTION

Chapter Two: Introduction

2. 1 Heterocyclic Compounds

A heterocyclic compound is a cyclic compound with an element other than carbon in one or more of the ring atoms. A heteroatom is a ring atom that is not carbon. The word heteros, which meaning "different," is derived from the greek language. *N*, O, and S are the most prevalent heteroatoms found in heterocyclic compounds.[18] Heterocyclic compounds offer a wide range of applications, but medical chemistry and industrial applications are of special interest. [19,20] Heterocyclic compounds, such as pyrrole, furan, and thiophene, can be aromatic in nature, as evidenced by their chemical structure. Figure (2. 1) or aliphatic compounds like pyrrolidine and tetrahydrofuran Figure (2. 2).

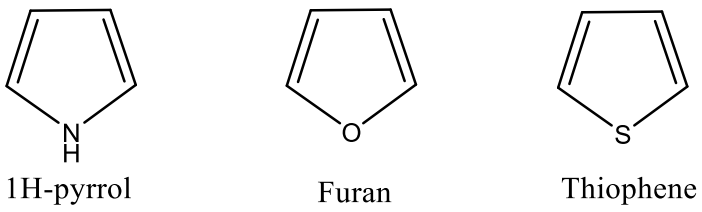


Figure (2. 1): The chemical structure of pyrrole furan, and thiophene

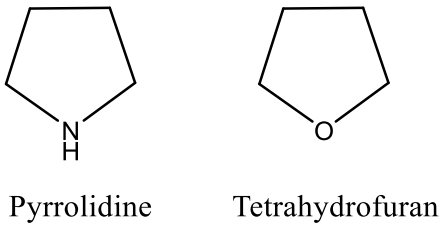


Figure (2. 2): The chemical structure of pyrrolidine and tetrahydrofuran

The aromatic heterocyclic rings can be five-membered. They may include one heteroatom such as pyrrole, furan, and thiophene, or two heteroatom as in oxazole ring which comprises of one oxygen atom and one nitrogen atom, or in thiozole which contains one nitrogen atom and

one sulfur atom, and in imidazole ring which comprises of two nitrogen atoms figure (2. 3).

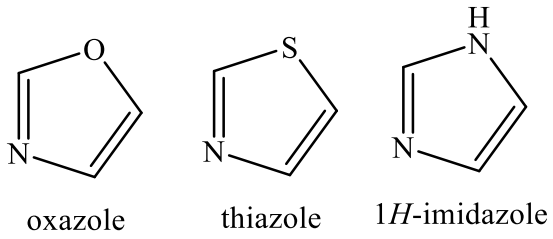


Figure (2. 3): The chemical structure of oxazole, thiozole and 1H-imidazole

These heterocyclic rings could be fused with benzene ring to give compounds like indole, benzofuran, and benzothiophene.[21] figure (2. 4).

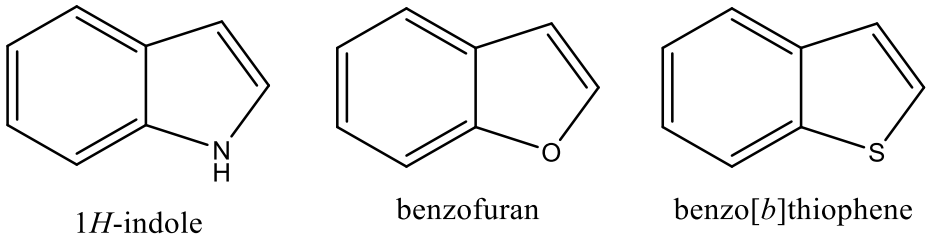


Figure (2. 4): The chemical structure of indole, benzofuran, and benzothiophene

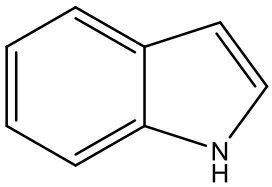
The majority of medications and physiologically active agrochemicals are heterocyclic, as are several additives and modifiers used in industrial applications ranging from cosmetics to reprography, data storage, and polymers. [22]

At organic chemistry, heterocyclic compounds had been one of the most active research topics [23]. They have performed a significant role in the evolution of pesticides, medicines and pharmaceutical applications. [24,25] Heterocycles have antiviral, antibiotic, antidepressant, antihypertensive, and anticancer activities. More than 67% percent of the compounds listed in the Comprehensive Medicinal Chemistry (CMC) database have heterocyclic rings. A wide range of carbon, hydrogen, and

heteroatom combinations can be created, resulting in compounds with a wide range of physical, chemical, and biological properties. [26,27] Five and six-membered heterocycles are abundant in nature and have a significant impact on life because of many natural products contains many subunits in their structure such as hormones, vitamins, and antibiotics. Therefore, they ave drawn a lot of significant attention in the composition of many important biological molecules. A practical method for the synthesis of such compounds is a great interest in synthetic organic chemistry. Among the all heterocyclic, pyrazoline and pyrazole are a class of compounds with biological activities, such as antitumor, antioxidant, antimicrobial, calcium channel modulators and antipyretic. [28]

2. 2 Indole

Indole is an aromatic heterocyclic organic molecule that is a white solid compound at room temperature. The indole chemical formula is C_8H_7N. It has a bicyclic structure, consisting of a benzene ring and a pyrrole nucleus are joined at 2,3 places of the pyrrole ring Figure (2. 5).



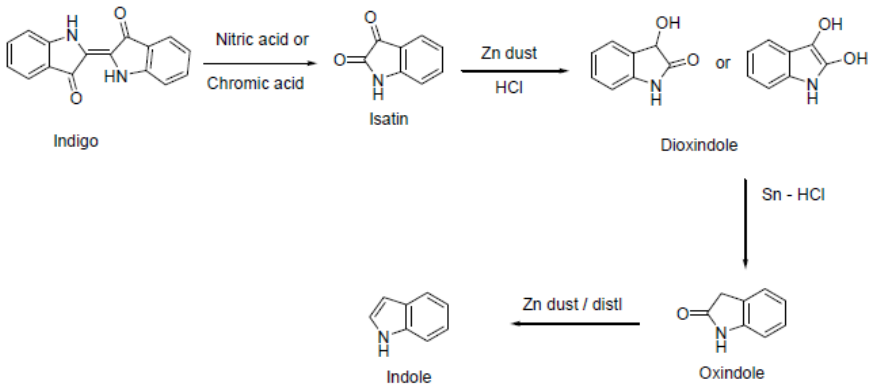
1*H*-indole

Figure (2. 5): The chemical structures of indole ring

The words indigo and oleum are combined to form the name indole. Indole is a nitrogenous non-basic chemical. The study of the dye indigo sparked the development of indole chemistry. Indole is derived from the term India, which refers to a blue dye brought from India called Indigo.

Chapter Two: Introduction

[29] ***Adolf von Baeyer*** used zinc dust to convert oxindole to indole in 1866. Indigo can be turned to isatin, which can subsequently be transformed to oxindole. [30]. in 1869; he proposed a formula for indole.



Scheme (2. 1) Adolf von Baeyer indole synthesis

The Indole is an important heterocyclic system because it contains the skeleton of indole alkaloids, which are biologically active chemicals found in plants, such as strychnine. figure (2. 6) and Lysergic acid diethylamide (LSD) figure (2. 7), because it is the basis of drugs like indomethacin, and it is also found in proteins in the form of the amino acid tryptophan. [31]

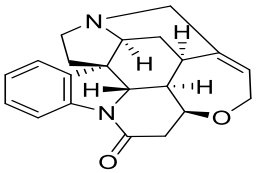


Figure (2. 6): The chemical structure of strychnine

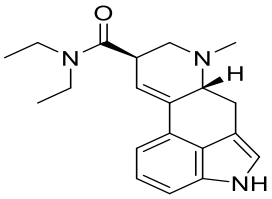


Figure (2. 7): The chemical structure of Lysergic acid diethylamide (LSD)

Chapter Two: Introduction

Indole and its derivatives can be found in a variety of plants, including unripe bananas, broccoli, clove, practically all essential oil on flower (such as jasmine and orange blossoms), and coal tar. [32] Thus, indole derivatives are a typical class of organic heterocyclics that have gained in popularity in recent years because to their wide range of biological and pharmacological actions, including anticancer, antihypertensive, antiproliferative, antiviral, and antitumor properties [33,34], anti-inflammatory [35], anti-depressant [36], antimicrobial [37], antifungal [38] and tuberculostatic activities [39]. For these reasons they have attracted the attention of biologists, pharmacists and chemists.

According to Huckel's rule, the indole nucleus is an aromatic molecule since it is a planar bicyclic molecule with 10 electrons (8 electrons from double bonds and 2 electrons from a lone pair of electrons from nitrogen). It works as a weak base that only protonates when exposed to strong acids. [40]

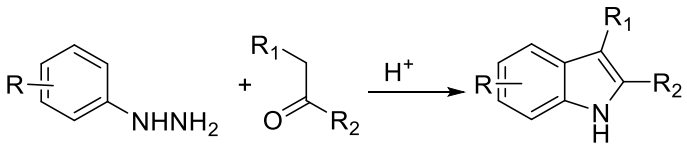
2. 2. 1. Previous synthetic methods of indole ring.

The preparation of indole ring considered to be one of the most exciting reactions in organic chemistry. The following reactions are the most famous synthesizing of indole ring [41]

2. 2. 1. 1. Fischer indole synthesis

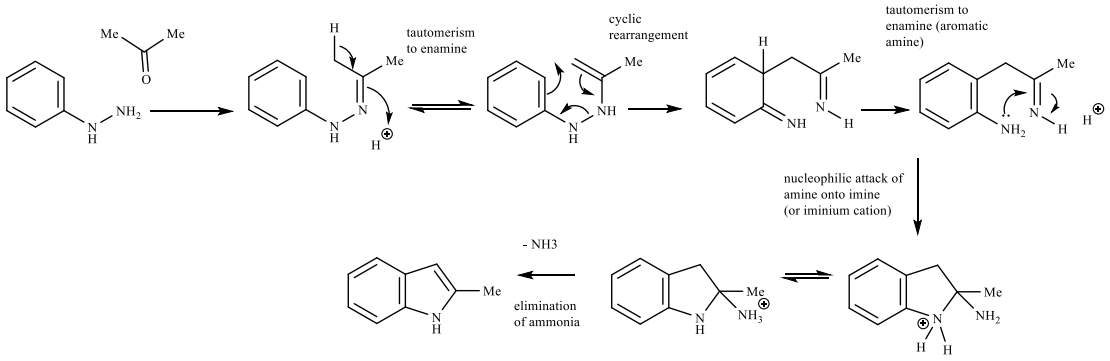
The Fischer indole synthesis, in which an aromatic phenylhydrazone is heated in acid, is the most useful route to indoles. The condensation result of a phenylhydrazine and an aldehyde or ketone is phenylhydrazone. A cyclic rearrangement procedure is used to close the ring. When hydrazine reacts with a carbonyl molecule, it creates an imine-like product called hydrazone. The enamine tautomer of this hydrazone undergoes the cyclic rearrangement, which occurs because the cyclic flow of electrons

generates a strong C–C link while cleaving a weak N–N bond. This appears to be the formation of a di-imine. One of these is engaged in rearomatization, which results in the production of an aromatic amine. The other imine function is subsequently attacked, yielding the nitrogen equivalent of a hemiketal. Finally, the aromatic indole system is formed by acid-catalyzed ammonia elimination. [42,43]



R, R_1, R_2 = Alkyl or Aryl

Scheme (2. 2) Fischer indole synthesis

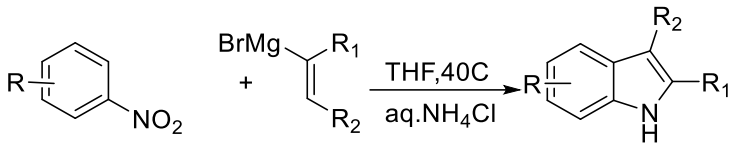


Scheme (2. 3) Mechanism of Fischer indole synthesis

2. 2. 1. 2. Bartoli indole synthesis.

The Bartoli indole is an organic reaction where a substituted nitroarene is turned to an indole using an excess of a vinyl Grignard reagent succeeded by an acid workup. The yield of this reaction has affected by the substituents on the nitroarene, and the highest yield observed with ortho substituted reagents and the bulky groups. Scheme (2. 4) [44]

Chapter Two: Introduction

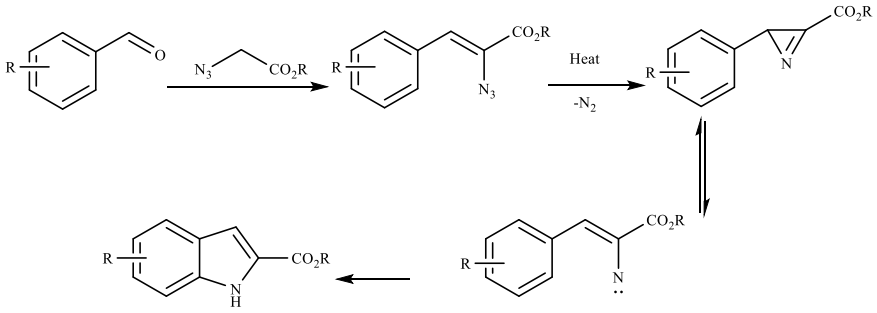


R_1, R_2 = Alkyl or Aryl

Scheme (2. 4) Bartoli indole synthesis.

2. 2. 1. 3. Hemetsberger indole synthesis

Thermal degradation of -styryl azides to the corresponding 2H-azirines occurs readily in equilibrium with the vinyl nitrene isomer, followed by electrocyclization onto the aromatic ring. The C3–C3a bond is already present in the precursor for the Hemetsberger reaction, unlike in the Fischer or Bischler indole syntheses; it is thus particularly suited to the regio specific synthesis of 4- or 6-substituted indoles from ortho- or para-substituted benzaldehydes Scheme (2. 5) [45]

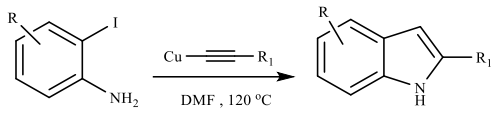


R = Alkyl or Aryl

Scheme (2. 5) Hemetsberger indole synthesis

2. 2. 1. 4. Castro indole synthesis

The 5-endo-dig cyclization of alkynylaniline, a condensation product of o-iodoaniline with cuprous acetylides, is used to make Castro indole. The onstruction of numerous indole derivatives becomes possible as a result of this cyclization. Scheme (2. 6) [46]



R, R_1 = Alkyl or Aryl

Scheme (2. 6) Castro indole synthesis

2.2.2. Pharmacological activities of indole derivatives

Indole analogues accountable for anti-cancer, anti-convulsant, anti-microbial, anti-tubercular, anti-malarial, antiviral, anti-diabetic. as shown in Figure (2.8) [47,48]

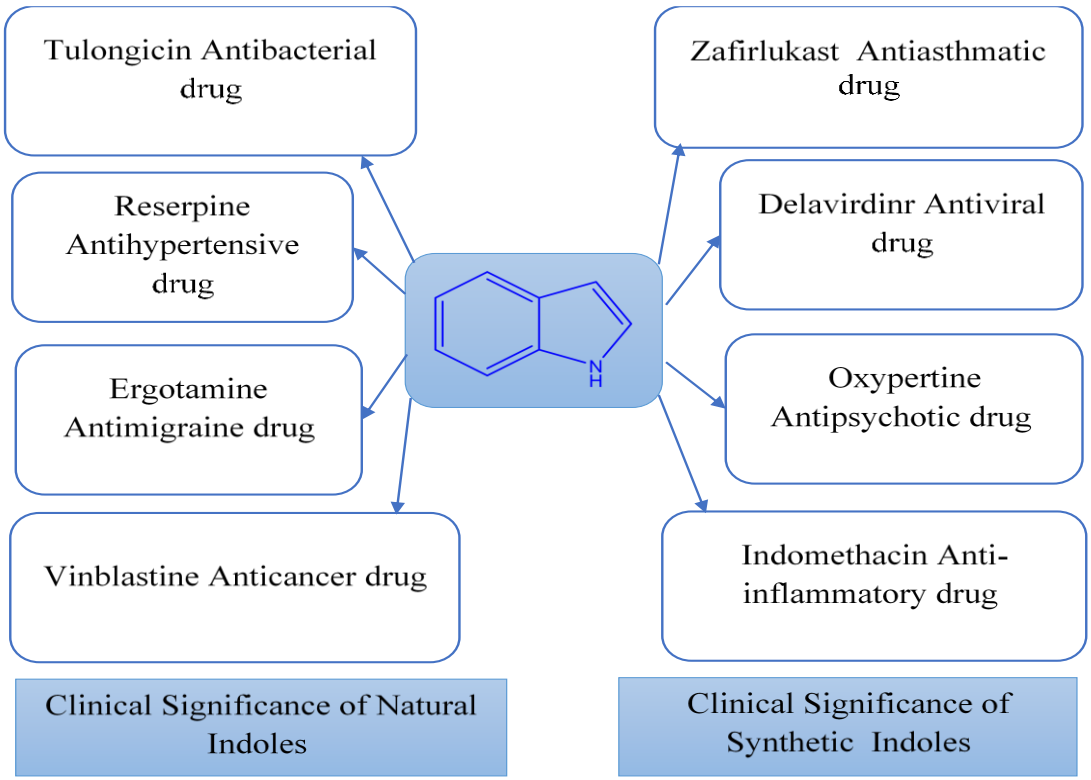


Figure (2.8): Pharmacological activities of indole derivatives

2.2.3 Reactivity of indole as aromatic ring

Indole is an aromatic heterocyclic compound with a unique reactivity. Here are a few general rules. [49,50]

• The nitrogen is not basic. (pKa= 3.6) .

• Aromatic electrophillic replacement of indole is a simple process. The C3 position, followed by the N and C2 locations, is the most nucleophilic.

• The C2 and C3 bonds frequently react in the same way that alkenes do.

• At nitrogen, indole can be deprotonated. The salts that arise can be effective nucleophiles.

• N substitution is favored by highly ionic salts (e.g. Li+, K+).

• C3 substitution is favored by softer counter ions.

• C2 can be deprotonated when N is substituted.

2. 3. Vilsmeier– Haack.

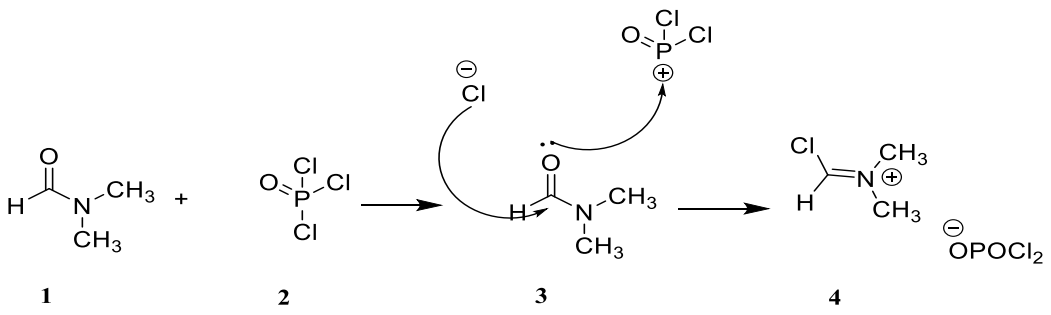
Since 1927, the discovery of Vilsmeier-Haack reagent (e.g. $POCl_3$+DMF) has piqued the interest of synthetic organic chemists. Because it is one of the most prevalent functional groups for carbon-carbon bond formation, it is most commonly employed to introduce the CHO group into aromatic rings. DMF, $POCl_3$ serves as both a reagent and a solvent in the Vilsmeier-Haack reaction. $POCl_3$ is a very toxic solvent that is harmful to one's health and pollutes the environment. [51] The Vilsmeier reaction was originally developed to formylate activated aromatic substrates and carbonyl compounds; nevertheless, it is now widely used to synthesize heterocyclic compounds such as quinolines, indoles, quinozolines, and pyridines. Vilsmeier reaction-based synthesis of different substituted chloronicotinaldehydes has received far less attention in the literature. Under Vilsmeier reaction conditions, Meth-Cohn and Westwood synthesized 2-chloropyridines, pyridones, and quinolines utilizing enamides. [52]

Chapter Two: Introduction

2. 3. 1. The Vilsmeier– Haack constituting.

The Vilsmeier– Haack (VH) reagent is a halomethyleniminium salt made up of Lewis acids like $POCl_3$, $COCl_2$, and $SOCl_2$ and organic bases like N-N'-dimethyl formamide (DMF), NN'-dimethyl acetamide (DMA), or comparable N-N'-dialkyl amides. On a synthetic basis, VH reactions with organic molecules in general and hydrocarbons with abundant π-electrons in particular are particularly easy to formylate. [53]

The Vilsmeier–Haack reagent has become increasingly popular in domino reactions, particularly in the synthesis of heteroaromatic compounds, in recent years. It has been feasible to generate a vast variety of different heterocyclic compounds under mild circumstances and with high yields. [54] The Vilsmeier-Haack reaction can also be used to add an acetyl group to activated aromatic or hetero aromatic compounds, as well as a variety of other conversions. The reaction is named after Anton Vilsmeier and Albrecht Haack. *N*,*N* dimethylformamide (DMF) (1) and phosphorus oxychloride ($POCl_3$) (2) are used to make a halomethyleniminium salt (4), which is employed in the synthesis of a wide range of heterocyclic compounds. The Vilsmeier reaction produces an aldehyde when Vilsmeier reagent is used in the process. As a result, the Vilsmeier reaction is also known as Vilsmeier reagent formylation. [55]



Scheme (2. 7) The Vilsmeier– Haack constituting.

Chapter Two: Introduction

2. 4. Schiff base.

Schiff bases are compounds containing an azomethine functional group (C=N-R) that have been produced by combining primary amines with an aldehyde or ketone. [56].

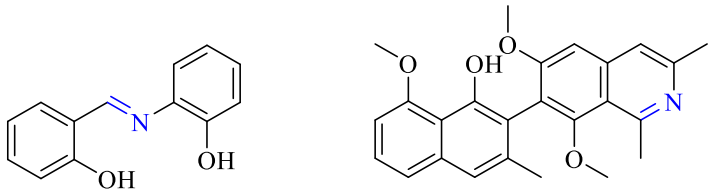
Schiff bases were named after the German chemist Hugo Schiff [57] A Schiff base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been replaced with an imine or azomethine group.

The bases Schiff derived from aldehydes are known as aldimine, and those derived from ketones are known as ketamine. [58]

Schiff bases are a class of chemical molecules that are commonly employed. Various natural, natural-derived, and non-natural substances have imine or azomethine groups. The presence of an imine group in these compounds has been proven to be important for their biological actions. [59] Schiff reported the first preparation of imines in the 19th century (1864). Since then, a number of imine synthesis methods have been described. [60]

Schiff bases are used in a variety of fields, including biology, analytical chemistry, organic, inorganic, and material chemistry [61,62]. Antibacterial, antihypertensive, antipyretic, anticancer, anti-inflammatory, and anti-HIV properties have been discovered [63,64]. Additionally, in the solid state, several Schiff bases have photochromic, thermochromic, solvatochromic, and thermochromic characteristics [65]. Schiff bases containing a sulfur atom were considered an important molecules in pharmacological and medical applications, including antifungal [66], antibacterial [67], anticancer [68], and herbicidal [69]. In

addition, certain bioactive compounds derived from natural sources, with Schiff base in their structure [70].

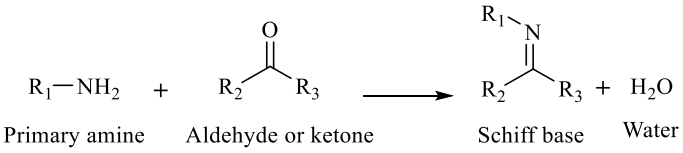


Antibacterial activity Antimalarial activity

Figure (2.9): Bioactive Schiff base compounds

2. 4. 1. Synthesis of Schiff bases

A Schiff base reaction is an acid-catalyzed reversible condensation of a primary amine (not ammonia) with an aldehyde or ketone. The nitrogen analogue of an aldehyde or ketone is a Schiff base, in which the carbonyl group is substituted by an imine group (C=N-R), which is shown in scheme (2.8) where R may be an alkyl or an aryl group.



Primary amine Aldehyde or ketone Schiff base Water

R_1, R_2, R_3 = Alkyl or Aryl

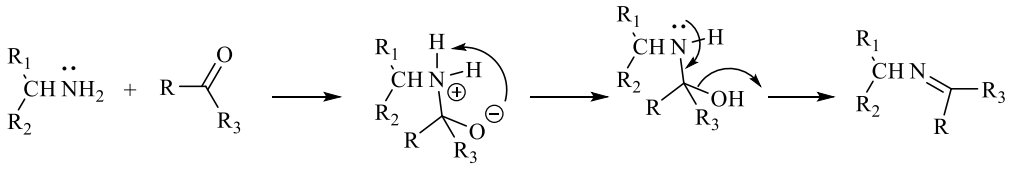
scheme (2.8): Preparation of Schiff base

Schiff bases with aryl substituents are more stable and straightforward to make than those with alkyl substituents. This means that aliphatic aldehyde Schiff bases are less stable and polymerize more easily than aromatic aldehyde conjugate compounds. [71,72]

2.4. 2. General formation of Schiff base

The formation of Schiff base is usually catalyzed by acids or bases, or by heat. [73] There are two phases in the creation of an azomethine

group. The amine nitrogen works as a nucleophile in the first stage, nucleophilically adding to the electrophilic carbonyl carbon of aldehydes or ketones to produce a hemiaminal. The nitrogen is deprotonated in the second step, resulting in the formation of a C=*N* double bond (azomethine) and the displacement of a water molecule. [74]

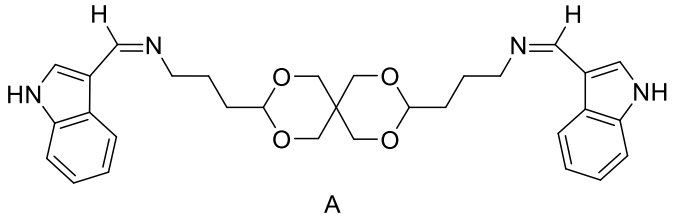


R_1, R_2 , R_3 = Alkyl or Aryl

scheme (2.9): General of Schiff base formation

2.5. The Biological Active of Some Indole Schiff Bases

In particular, the indole Schiff bases have been shown to possess the diverse biological properties. For example, the bis-indole Schiff base (A) displays analgesic and anti-inflammatory activity. Furthermore, indole-3-carbaldimines (B, C, and D) formed by the condensation of 3-formyl indole with various amino acids, exhibit antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus polymyxa* (Figure 1.12).[75]



A

(1H-Indol-3-ylmethylene)-[3-(9-{3-[(1H-indol-3-ylmethylene)-amino]-propyl}-2,4,8,10-tetraoxaspiro[5.5]undec-3-yl)-propyl]-amine

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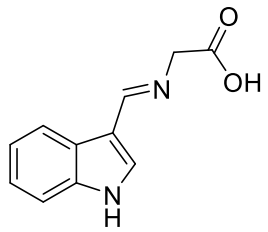
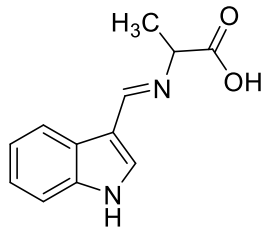


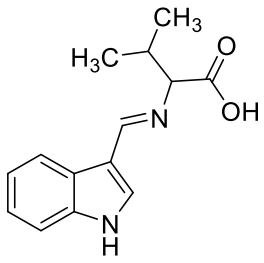
B

[(1*H*-indol-3-ylmethylene)-amino]acetic acid



C

2-[(1*H*-indol-3-ylmethylene)-amino]propanoic acid



D

2-[(1*H*-indol-3-ylmethylene)-amino]-3-methylbutanoic acid

Figure (2.10): The Biological active of some indole schiff bases

CHAPTER THREE

EXPERIMENTAL PART

Chapter Three: Experimental Part

3. 1. Chemistry part.

3. 1. 1. Materials.

Table (3.1) presented the chemicals and solvents utilized in the chemistry section were bought from various company providers. They were used without additional purification as received. The melting points of the synthesized compounds were evaluated using an open capillary melting point device, and the purity of the produced compounds was checked using a thin layer chromatography (TLC) sheet.

Table (3. 1). In the chemistry section, chemicals and solvents were used.

Materials and chemicals	**Molecular formula**	**Company**
4-Bromoaniline	C_6H_6BrN	Merck
4-Bromophenylhydrazinhydrochlorid	$C_6H_8BrN_2Cl$	Merck
4-Chloroaniline	C_6H_6ClN	BDH
2,4-Dichloroaniline	$C_6H_5Cl_2N$	Fulka
2,3-Dimethylaniline	$C_8H_{11}N$	Merck
Dimethylformamide	C_3H_7NO	Romil
Ethanol	CH_3CH_2OH	Scharlaw
Ethyl acetate	$C_4H_8O_2$	Chem lab
Glacial acetic acid	CH_3COOH	Chem lab
Hexane	C_6H_{14}	Chem lab
2-Hydroxy anilin	C_6H_7NO	Merck
Methanol	CH_3OH	GCC
2-Methoxyaniline	C_7H_9NO	Merck
4-Methoxyaniline	C_7H_9NO	Merck
2-Methylaniline	C_7H_9N	Merck
Methyl isopropyl ketone	$C_5H_{10}O$	Merck
Phosphoryl chloride	$POCl_3$	Merck
Sodium hydroxide	NaOH	Thomas Baker
Sodium sulfate	Na_2SO_4	Loba Chemie
Sulfuric acid	H_2SO_4	Scharlaw

Chapter Three: Experimental Part

3. 1. 2. Instruments.

3. 1. 2. 1. Fourier Transform Infrared Spectrophotometer (FT-IR):

IR spectra achieved on a Perkin-Elmer Spectrum version 10.02 by using a disk of KBr for solid substance in Department of Chemistry, College of Sciences, University of Diyala.

3. 1. 2. 2. Nuclear Magnetic Resonance Spectrometer (NMR):

^{1}H NMR spectra were recorded on a Bruker (400 MHz,DMSO δ in ppm) spectrometer at the Faculty of Science, University of Tehran

3. 1. 2. 3. Thin Layer Chromatography (TLC):

The new compounds have taken to purification by using Silica gel plates, and the spots have detected by using a fluorescence analysis cabinet Model CM10, In Department of Chemistry, College of Sciences, University of Diyala .

3. 1. 2. 4. Melting Point:

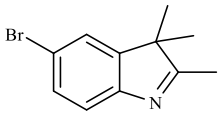
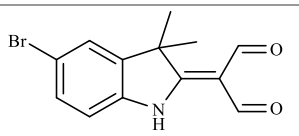
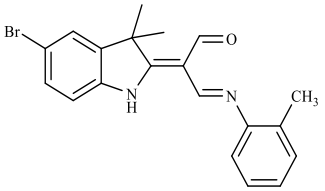
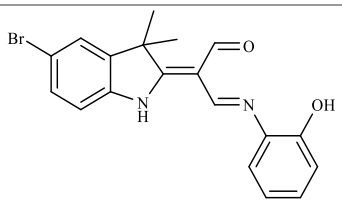
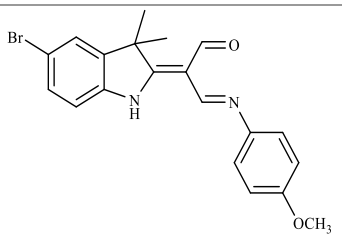
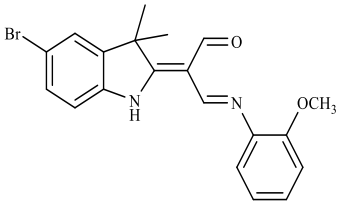
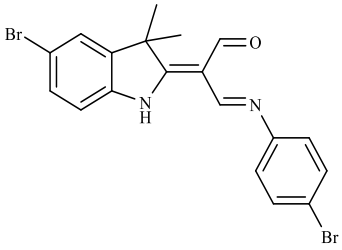
The melting points of the synthesized compounds were determined by open capillary tubs by using the stuart melting point apparatus SMP10 UK, in the Chemistry Department, College of science, Diyala University .

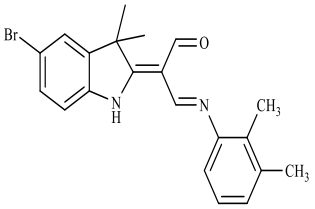
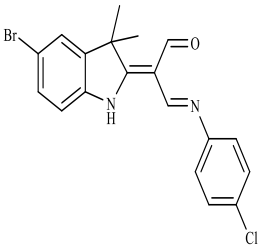
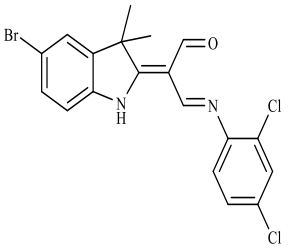
3. 1. 2. 5. Rotary Evaporator:

The solvent was evaporated by using Heldove apparatus, HeiVAP, Germany in the Chemistry Department, College of Science, Diyala University.

Chapter Three: Experimental Part

Table 3.2 : The structures and nomenclatures of the synthesized compounds

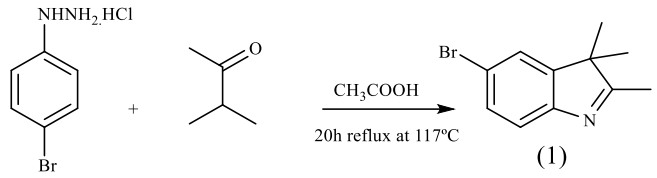
Comp No.	Comp. Structure	Molecular Formula	Comp. name
1		$C_{11}H_{12}BrN$	5-bromo-2,3,3-trimethyl -3H-indole
2		$C_{13}H_{12}BrNO_2$	2-(5-bromo-3,3-dimethylindolin -2-ylidene)malonaldehyde
3		$C_{20}H_{19}BrN_2O$	2-(5-bromo-3,3-dimethylindolin-2-ylidene) -3-(o-tolylimino)propanal
4		$C_{19}H_{17}BrN_2O_2$	2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal
5		$C_{20}H_{19}BrN_2O_2$	2-(-5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-methoxyphenyl)imino)propanal
6		$C_{20}H_{19}BrN_2O_2$	2-(-5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2-methoxyphenyl)imino)propanal
7		$C_{19}H_{16}Br_2N_2O$	2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-bromophenyl)imino)propanal

8		$C_{21}H_{21}BrN_2O$	2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal
9		$C_{19}H_{16}BrClN_2O$	2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-chlorophenyl)imino)propanal
10		$C_{19}H_{15}BrCl_2N_2O$	2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,4-dichlorophenyl)imino)propanal

Chapter Three: Experimental Part

3. 1. 3. Synthetic methods:

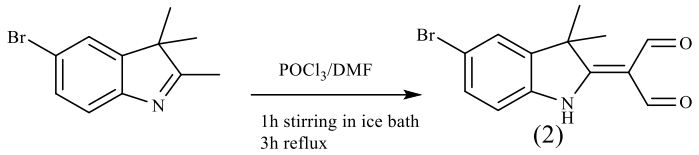
3. 1. 3. 1. Synthesis of 5-bromo-2,3,3-trimethyl-3*H*-indole (1)



Scheme (3-1): The synthetic pathway of compound (1)

A mixture of (1g, 4.5mmol) of (4-bromo-phenyl)-hydrazine hydrochloride and isopropyl methyl ketone (0.57 g, 6.75 mmol) was dissolved in (30 mL) of glacial acetic acid and the mixture was refluxed in oil path at 117 ºC for 20h. Then the product was cooled by addition it in the icy distilled water, and neutralized with 25% NaOH aqueous, then extracted with ethyl acetate (3×25mL). The organic layer dried over Na2SO4 and the solvent was evaporated. The product is a viscous oil of indolenine (1). Yield (1.17g 99%).

3. 1. 3. 2. Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene) malonaldehyde (2)

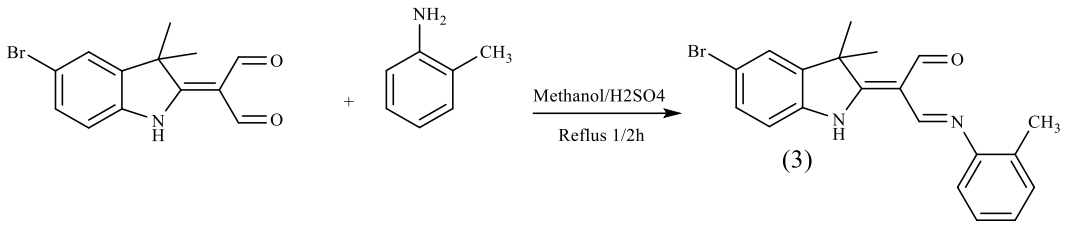


Scheme (3-2): The synthetic pathway of compound (2)

A (3.5mL) of *N*, *N*-dimethyl formamide (DMF) cooled in an ice bath then (1.35mL, 14.7mmol) of Phosphoryl chloride ($POCl_3$) added dropwise with stirring under 7°C for 10 minutes , Then a solution of (1.17g, 4.9 mmol) indolenine (1) in DMF (3.5mL) was added dropwise for 10 minutes under 7°C , The reaction mixture stirred in ice bath for 1h. Then refluxed for 3h, at 85-90ºC. The resulting solution was poured on icy distill water and neutralized with aqueous 25% NaOH. The resulting is a brown precipitate was filtered off, washed with hot distill water and dried in oven then recrystallized from ethanol to give Pure of 2-(5-bromo-3,3-dimethylindolin-2-ylidene) malonaldehyde (2) The purity of this compound checked by using TLC (3:1) hexane: ethyl acetate as an eluent, with precoated silica gel, which gave one spot on polar area. Yield: (1.2g, 83%), m.p. 159-161 ºC.

Chapter Three: Experimental Part

3. 1. 3. 3. Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-(o-tolylimino)propanal (3)

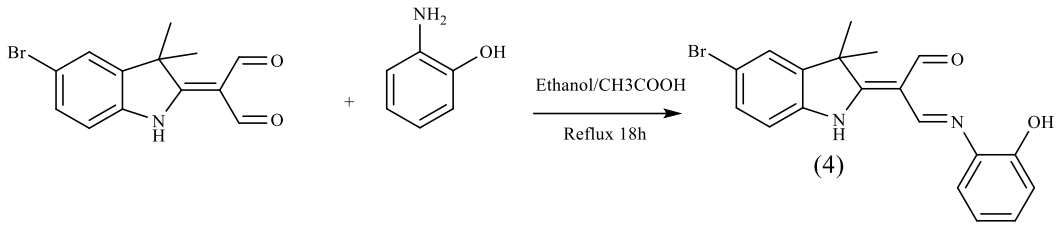


Scheme (3-3): The synthetic pathway of compound (3)

A solution of (0.15g, 0.5mmol) of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in methanol 15mL and (0.054g, 0.5mmol) of o-tolylamine was dissolved in methanol 15mL and then added 3 drops of 2% H2SO4 to the solution. The mixture was refluxed in a water bath at 78 ºC for 1/2hrs. A solvent was reduced to one quarter; yellow precipitate was formed direct, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The purity of this compound was determined by using TLC (3:1) hexane: ethyl acetate, which gave one spot. Yield (0.17g 87%) m.p. 262-267 ºC.

Chapter Three: Experimental Part

3. 1. 3. 4. Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal (4)



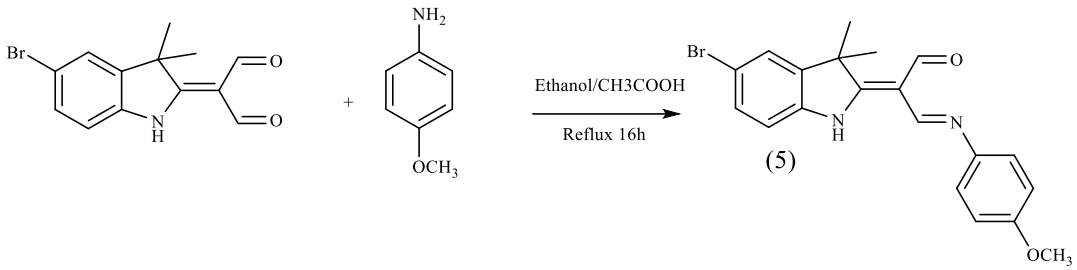
(4)

Scheme (3-4): The synthetic pathway of compound (4)

A solution of (0.15 g, 0.5 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 mL and (0.055 g, 0.5 mmol) of 2-hydroxy aniline was dissolved in ethanol 10mL and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 18hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.149 g, 76%), m.p. 117-119 ºC.

Chapter Three: Experimental Part

3. 1. 3. 5. Synthesis of 2-(-5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-methoxyphenyl)imino)propanal (5)

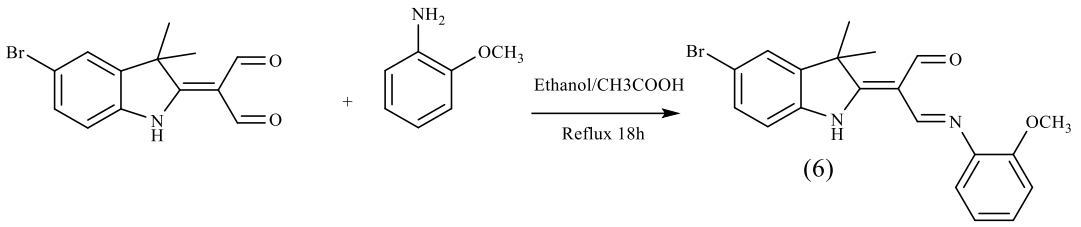


Scheme (3-5): The synthetic pathway of compound (5)

A solution of (0.15 g, 0.5 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 mL and (0.062 g, 0.5 mmol) of 4-methoxyaniline was dissolved in ethanol 10mL and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 16hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.14 g, 80%), m.p. 152-155 ºC.

Chapter Three: Experimental Part

3. 1. 3. 6. Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2-methoxyphenyl)imino)propanal (6)

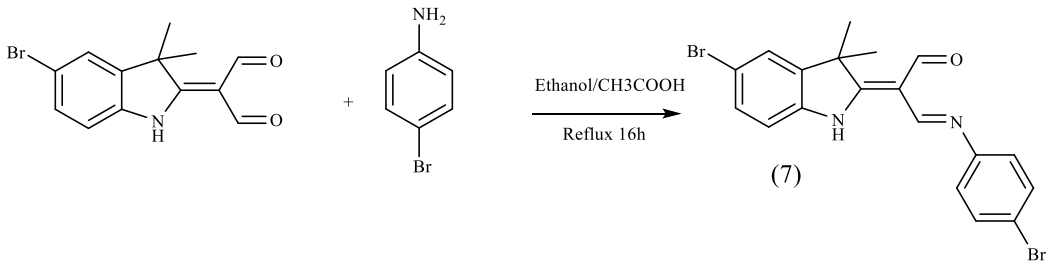


(6)

Scheme (3-6): The synthetic pathway of compound (6)

A solution of (0.15 g, 0.5 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 mL and (0.062 g, 0.5 mmol) of 4-methoxyaniline was dissolved in ethanol 10mL and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 16hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.14 g, 80%), m.p. 161-163 ºC.

3. 1. 3. 7. Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-bromophenyl)imino)propanal (7)

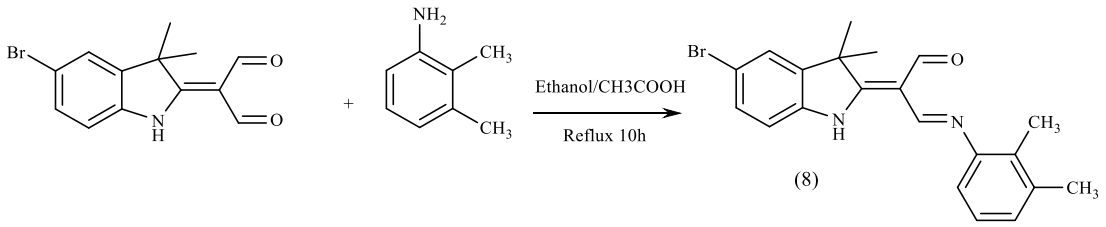


(7)

Scheme (3-7): The synthetic pathway of compound (7)

A solution of (0.15 g, 0.5 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 mL and (0.087 g, 0.5 mmol) of 4-bromoaniline was dissolved in ethanol 10mL and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 16hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.14 g, 63%), m.p. 166-168 ºC.

3. 1. 3. 8. Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal (8)

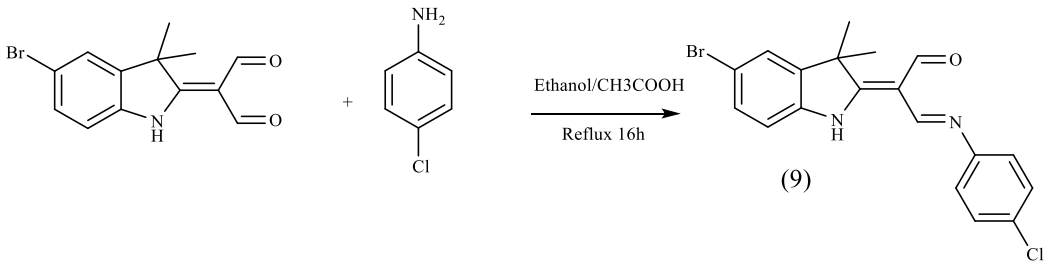


Scheme (3-8): The synthetic pathway of compound (8)

A solution of (0.15 g, 0.5 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 mL and (0.061 g, 0.5 mmol) of 2,3-dimethylaniline was dissolved in ethanol 10mL and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 16hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.14 g, 70%), m.p. 141-143 ºC.

Chapter Three: Experimental Part

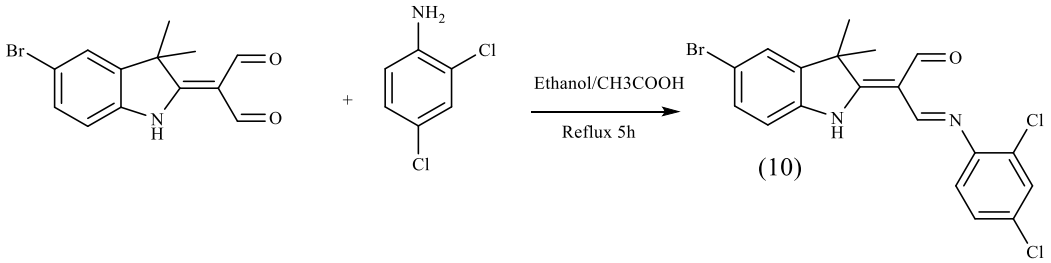
3. 1. 3. 9. Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-chlorophenyl)imino)propanal (9)



Scheme (3-9): The synthetic pathway of compound (9)

A solution of (0.15 g, 0.5 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 mL and (0.063 g, 0.5 mmol) of 4-chloroaniline was dissolved in ethanol 10mL and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 16hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.149 g, 72%), m.p. 179-181 ºC.

3. 1. 3. 10. Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,4-dichlorophenyl)imino)propanal (10)



Scheme (3-10): The synthetic pathway of compound (10)

A solution of (0.1 g, 0.33 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene) malonaldehyde was dissolved in ethanol 15 mL and (0.05 g, 0.33 mmol) of 2,4-chloroaniline was dissolved in ethanol 10mL and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 16hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield(0.174 g, 78%), m.p. 177-179 ºC.

Chapter Three: Experimental Part

3.2. Biological part.

3.2.1. Material and Methods

Staphylococcus aureus was cultured and identified on blood agar and mannitol salt agar. *Escherichia coli* isolate was cultured and identified on macckonky agar and eosin methylene blue.

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 CFU/mL.

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 petri dishes and kept in the refrigerator until use.

Determination the Antimicrobial activity of synthesized 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 MacFarland solution (1.5 x 10^8 CFU/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. After then, incubate the dishes at (37 °C) for (24 h).

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

CHAPTER FOUR

RESULTS AND DISCUSSION PART

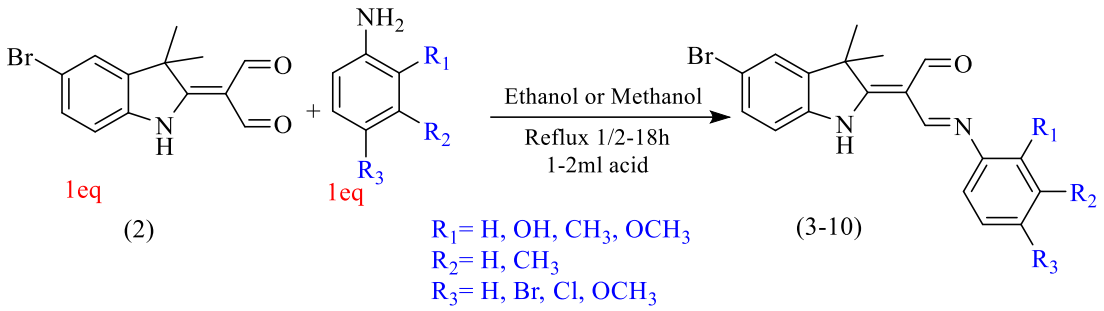
Chapter Four: Results and Discussion Part

4. Results and discussion

4. 1. Chemistry Part

4. 1. 1. Methodology

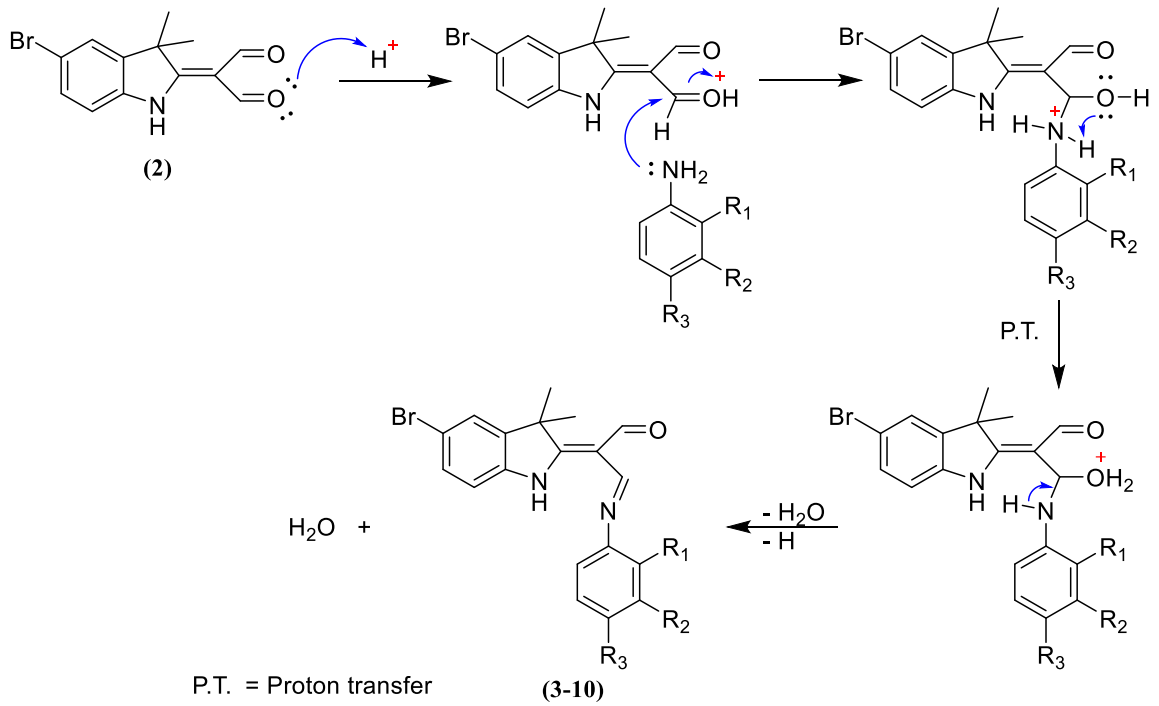
A series of new Schiff bases have been synthesized from 2-(5-bromo- 3,3-dimethyl-1,3-dihydro -indol-2-ylidene) malonaldehyde (2) by the condensation reaction of this compound with substituents of aniline according to synthetic pathway as shown in scheme (4.1).



Scheme (4.1): synthetic pathway of Schiff bases (3-10)

Chapter Four: Results and Discussion Part

The proposed mechanism of formation of the new compounds as illustrated in scheme (4.2)



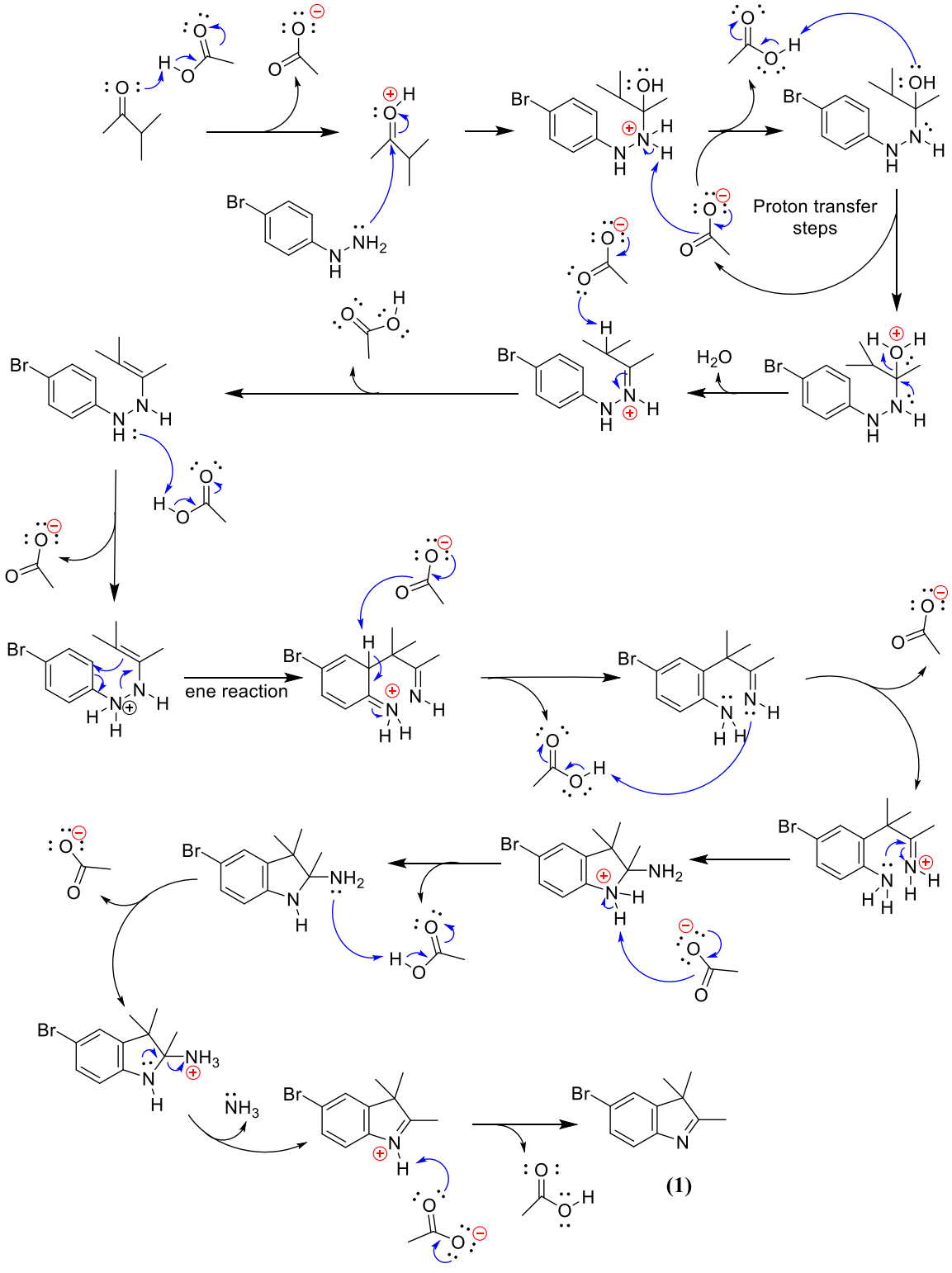
Scheme (4.2): Mechanism for synthesis of new Schiff bases (3-10).

The compound 2-(5-bromo- 3,3-dimethyl-1,3-dihydro- indole-2-ylidene) malonaldehyde (2) was synthesized by two steps:

The first step: Fischer indole synthesis of 5- bromo-2, 3, 3-trimethyl-3*H*-indole (indoline) **(1)** by reacting 4-bromophenyl hydrazine hydrochloride with methyl isopropyl ketone in perfect yield, as shown in Scheme (3.1).

The mechanism for the formation of indoline **(1)** is proposed by Fischer, E. (1883) [76] as shown in Scheme (4.3).

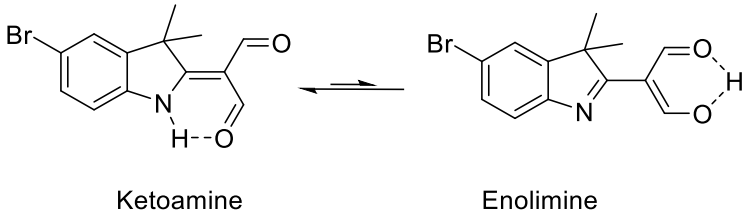
Chapter Four: Results and Discussion Part



Scheme (4.3): Mechanism of Fischer reaction to form 2, 3, 3-trimethyl-5- bromo-3*H*-indole (indoline) (1)

The second step: Vilsmeier-Haack reaction of indoline **(1)** with phosphoryl chloride ($POCl_3$) in the presence of *N*,*N*-dimethyl formamide (DMF) to form starting material 2-(5-bromo- 3,3-dimethyl-1,3-dihydro-indole-2-ylidene) malonaldehyde **(2)** in a good yield, as shown in scheme (3.2).

The compound **(2)** found as keto-amine, enol-imine tautomer forms, as shown in scheme (4.4) [77].



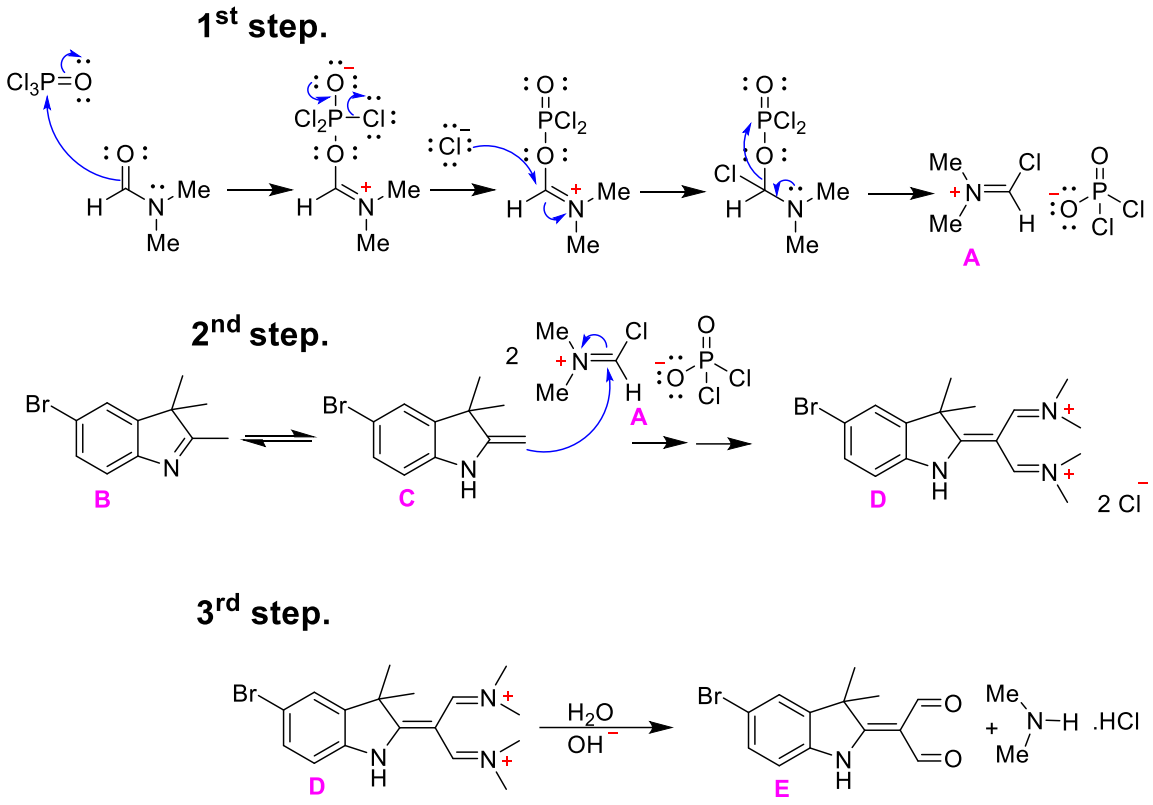
Scheme (4.4): Tautomer forms of 2-(5-bromo- 3,3-dimethyl-1,3-dihydro-indole-2-ylidene) malonaldehyde (2).

The mechanism of the formation of 2-(5-bromo- 3,3-dimethyl-1,3-dihydro-indole-2-ylidene) malonaldehyde **(2)** involves three steps as shown in scheme (4.5). [78]

In the first step: Combination of DMF with $POCl_3$ to formation of chloro-iminium ion **(A_1)**.

In the second step: The reaction of chloro-iminium ion **A** with 2, 3, 3-trimethyl-5- bromo -3*H*-indole (indoline) **B**, but the compound **B** in the equilibrium with enamine tautomer **C**. So **C** will react with. Later the chloro-iminium ion **A** forms the first step attacked to create the intermediate **D**.

In the therd step: Involves the hydrolysis of intermediate **D**, to produce **E**, which its 2-(5-bromo- 3,3-dimethyl-1,3-dihydro-indole-2-ylidene) malonaldehyde (2)



Scheme (4.5): Mechanism of the Vilsmeier-Haack reaction to form the compound (2).

The newly synthesized compounds are colored, stable in air, Soluble in DMSO and have tested by TLC, FT-IR and ^{1}H-NMR . The physical properties such as the melting point and percentage yield of the new compounds represented in the table (4. 1)

Chapter Four: Results and Discussion Part

Table (**4. 1**): Physical properties of the synthesized compounds (**1**-**10**)

Compound No.	Molecular formula	Percentage Yield	Melting Point ºC	Molecular Weight g/mol
1	$C_{11}H_{12}BrN$	99%	oily	238.13
2	$C_{13}H_{12}BrNO_2$	83%	159-161 ºC	294.15
3	$C_{20}H_{19}BrN_2O$	87%	262-264 ºC	383.29
4	$C_{19}H_{17}BrN_2O_2$	76%	117-119 ºC	385.26
5	$C_{20}H_{19}BrN_2O_2$	80%	152-155 ºC	399.29
6	$C_{20}H_{19}BrN_2O_2$	80%	161-162 ºC	399.29
7	$C_{19}H_{16}Br_2N_2O$	63%	166-168 ºC	448.16
8	$C_{21}H_{21}BrN_2O$	70%	141-143 ºC	397.32
9	$C_{19}H_{16}BrClN_2O$	72%	179-181 ºC	403.70
10	$C_{19}H_{15}BrCl_2N_2O$	78%	177-179 ºC	438.15

Chapter Four: Results and Discussion Part

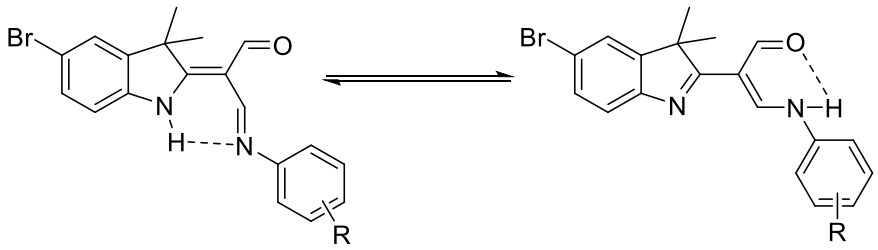
4. 1. 2. Spectral study of the new synthesized compounds (1-10)

4. 1. 2. 1. FT-IR Study

The IR measurements for the new synthesized compounds showed absorption bands rang from 4000 to 400 cm^{-1}.

The FT-IR spectral data of new synthesized compounds (2-10) are listed in table (4.2).

The new compounds (3 conformed that the absorption bands of the (NH_2) group, which belong to substituted aniline, had disappeared and that new absorption bands of imino group (-CH=N-) had appeared at rang (1614-1633) cm^{-1}, indicating that the production of these new compounds had been done successfully. In addition, some of these new compounds **(3-10)** did not show absorption bands that were attributed to the (NH) group for the indole ring because these new compounds were stabilized by intramolecular hydrogen bonds as shown in Scheme (4.6).



Scheme (4.6): Tautomer forms of new compounds (3-10).

Table (4.2): FT-IR spectral data for compounds (2-10).

Comp. No.	Characteristic bands of FT-IR spectra (ν in cm^{-1}, KBr disc)								
	C-H Ar.	C-H Alip.	C-H Alde.	C=O	C=N	C=C Ar.	CH_3	C-N	Others
2	2984	2850 2755	2708	1657 1633	-	1609-1468	1369	1220	3141(N-H) 822 (C-Br) 735 (C-H Bend)
3	2976	2928 2858	2708	1669	1625	1594-1491	1326	1231	806(C-Br) 755 (C-H Bend)
4	3086	2921 2858	2747	1657	1621	1582-1495	1342	1243	1168(C-O) 818 (C-Br) 755 (C-H Bend)
5	3062	2984 2842	2716	1669	1629	1519-1448	1342	1259	818 (C-Br) 778 (C-H Bend)
6	2976	2936 2850	2739	1665	1621	1590-1460	1342	1255	818 (C-Br) 747 (C-H Bend)
7	-	2960	2724	1669	1621	1582-1448	1334	1231	814(C-Br) 767 (C-H Bend)
8	3062	2968 2865	2708	1669	1625	1582-1460	1330	1220	810 (C-Br) 763 (C-H Bend)
9	2960	2960 2873	2739	1669	1625	1586-1444	1334	1227	818(C-Br) 767 (C-H Bend)
10	-	2960	2724	1669	1625	1586-1440	1330	1227	818(C-Br) 767 (C-H Bend)

Chapter Four: Results and Discussion Part

FT-IR for the compound 2-(5-bromo- 3,3-dimethyl-1,3-dihydro -indol-2-ylidene) malonaldehyde (2)

The structure of the compound **(2)** was confirmed by FT-IR spectrum as illustrated in Figure (4.1) and Table (4.2). The FT-IR spectrum shows an absorption bands at (2984 cm^{-1}) which referred to the aromatic (C-H), (2850 and 2755 cm^{-1}) to the aliphatic (C-H), and (2708 cm^{-1}) to the aldehyde (C-H). Also, (1657 cm^{-1}) for the (C=O) group (strong absorption band). The stretching frequency at (1609-1468 cm^{-1}) is due to the (C=C) aromatic [79,80]. The absorption bands that appeared at (1365 cm^{-1}) related to the CH_3 group [81], and at (1220 cm^{-1}) which was attributed to the (C-N) group [82]. Also, the absorption bands at (822cm^{-1}) are assigned to(C-Br). A sharp peak at (735 cm^{-1}) is attributed to the out-of-plane (C-H) group [10] and at (3141 cm^{-1}) for N-H group.

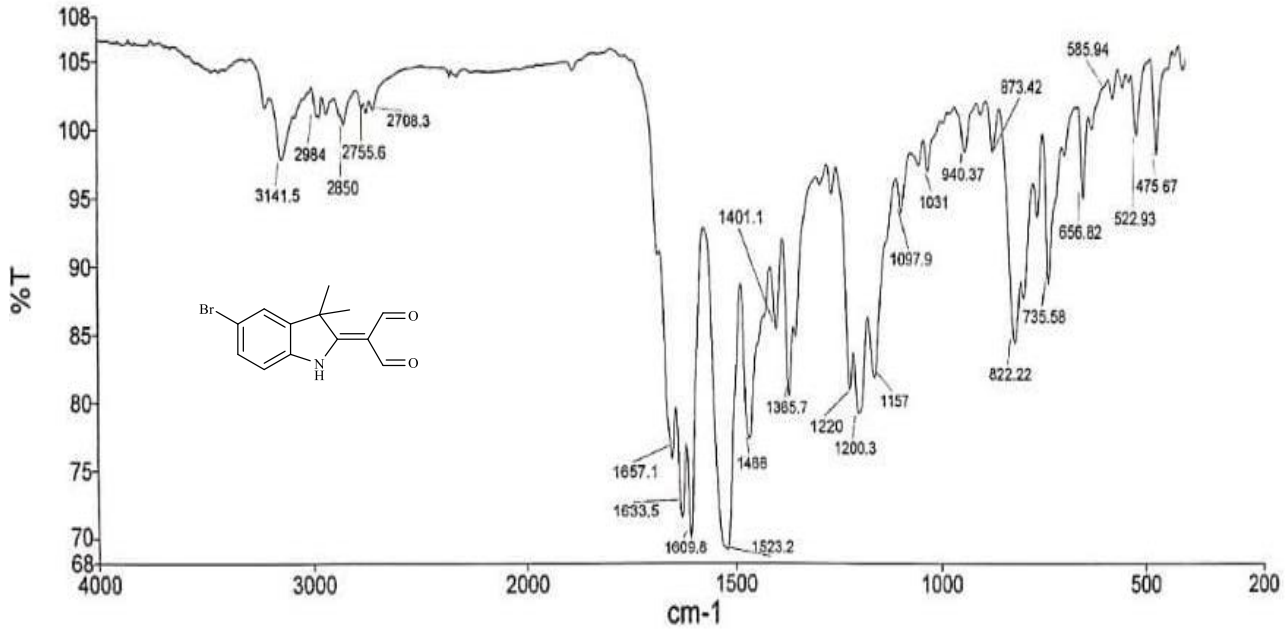


Figure (4.1): The FT-IR spectra of the compound (2).

Chapter Four: Results and Discussion Part

FT-IR for the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-(o-tolylimino)propanal (3)

The structure of the compound **(3)** was confirmed by FT-IR spectrum as illustrated in Figure (4.2) and Table (4.2). The FT-IR spectrum shows an absorption band at (2976 cm^{-1}) which referred to the aromatic (C-H), (2928 and 2858 cm^{-1}) to the aliphatic (C-H), and (2708 cm^{-1}) to the aldehyde (C-H). Also, (1669 cm^{-1}) for the (C=O) group (strong absorption band), and (1625 cm^{-1}) for the (C=N) azomethine group. The stretching frequency at (1594-1491 cm^{-1}) is due to the (C=C) aromatic. The absorption bands that appeared at (1326 cm^{-1}) related to the CH_3 group, and at (1231 cm^{-1}) which was attributed to the (C-N) group. Also, the absorption bands at (806cm^{-1}) are assigned to(C-Br). Finally, a sharp peak at (755 cm^{-1}) is attributed to the out-of-plane (C-H) group.

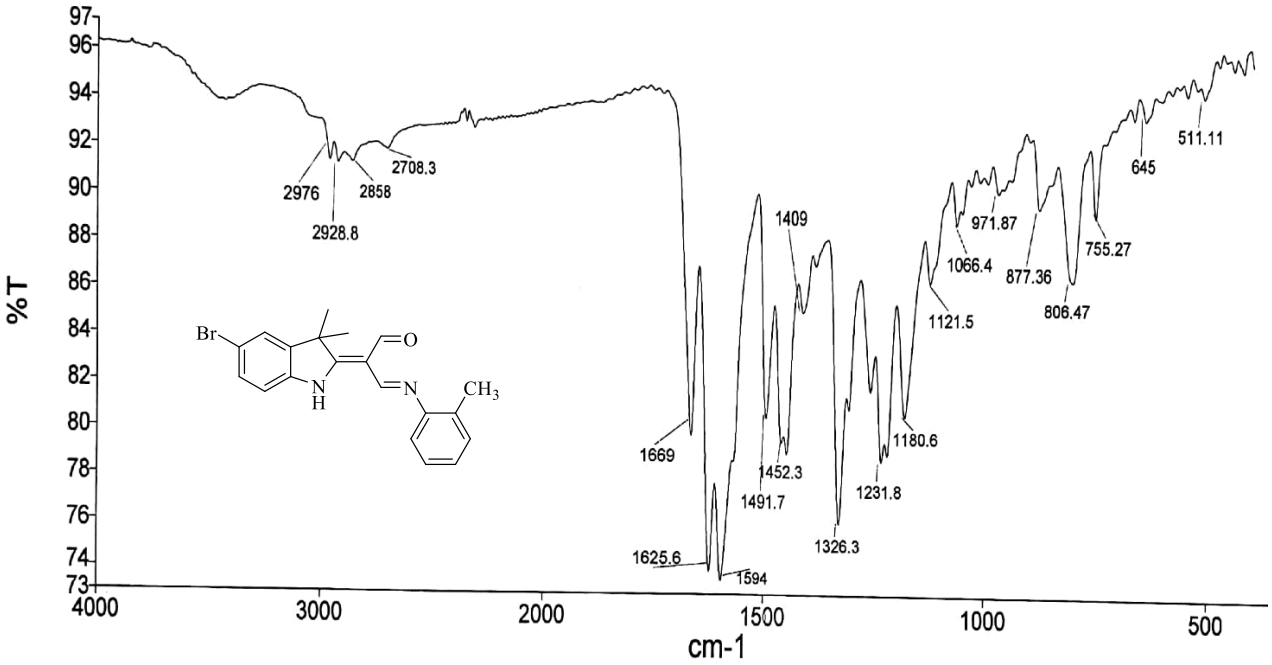


Figure (4.2): The FT-IR spectra of the compound (3).

Chapter Four: Results and Discussion Part

FT-IR for the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal. (4)

The structure of the compound **(4)** was confirmed by FT-IR spectrum as illustrated in Figure (4.3) and Table (4.2). The FT-IR spectrum shows an absorption band at (3086 cm^{-1}) which referred to the aromatic (C-H), at (2921 and 2858 cm^{-1}) to the aliphatic (C-H), and (2747 cm^{-1}) to the aldehyde (C-H). Also, (1657 cm^{-1}) for the (C=O) group (strong absorption band), and (1621 cm^{-1}) for the (C=N) azomethine group. The stretching frequency at (1582-1495 cm^{-1}) is due to the (C=C) aromatic. The absorption bands that appeared at (1342 cm^{-1}) related to the CH_3 group, and at (1243 cm^{-1}) which was attributed to the (C-N) group. A peak at (1168 cm^{-1}) is accounted to the (C-O) group [82]. Also, the absorption bands at (818 cm^{-1}) are assigned to(C-Br). Finally, a sharp peak at (755 cm^{-1}) is attributed to the out-of-plane (C-H) group.

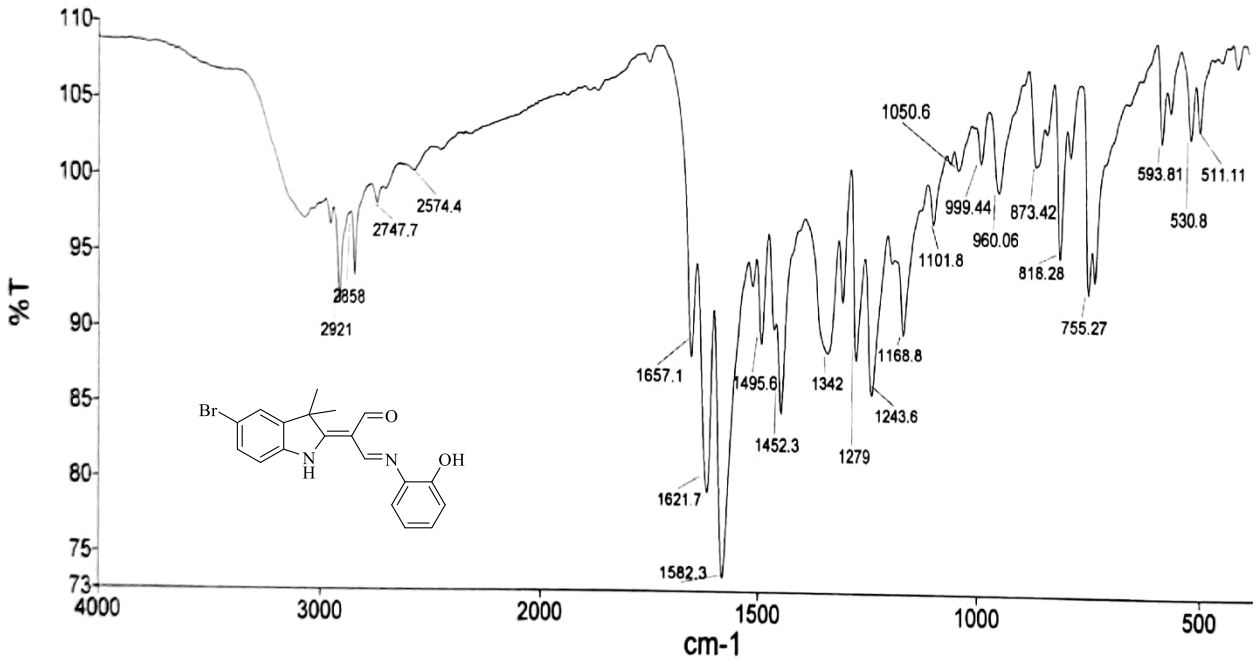


Figure (4.3): The FT-IR spectra of the compound (4).

FT-IR for the compound 2-(-5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-methoxyphenyl)imino)propanal (5)

The structure of the compound **(5)** was confirmed by FT-IR spectrum as illustrated in Figure (4.4) and Table (4.2). The FT-IR spectrum shows an absorption band at (3062 cm^{-1}) which referred to the aromatic (C-H), (2984 and 2842 cm^{-1}) to the aliphatic (C-H), and (2716 cm^{-1}) to the aldehyde (C-H). Also, (1669 cm^{-1}) for the (C=O) group (strong absorption band), and (1629 cm^{-1}) for the (C=N) azomethine group. The stretching frequency at (1519-1448 cm^{-1}) is due to the (C=C) aromatic. The absorption bands that appeared at (1342 cm^{-1}) related to the CH_3 group, and at (1259 cm^{-1}) which was attributed to the (C-N) group. Also, the absorption bands at (818cm^{-1}) are assigned to(C-Br). Finally, a sharp peak at (778 cm^{-1}) is attributed to the out-of-plane (C-H) group.

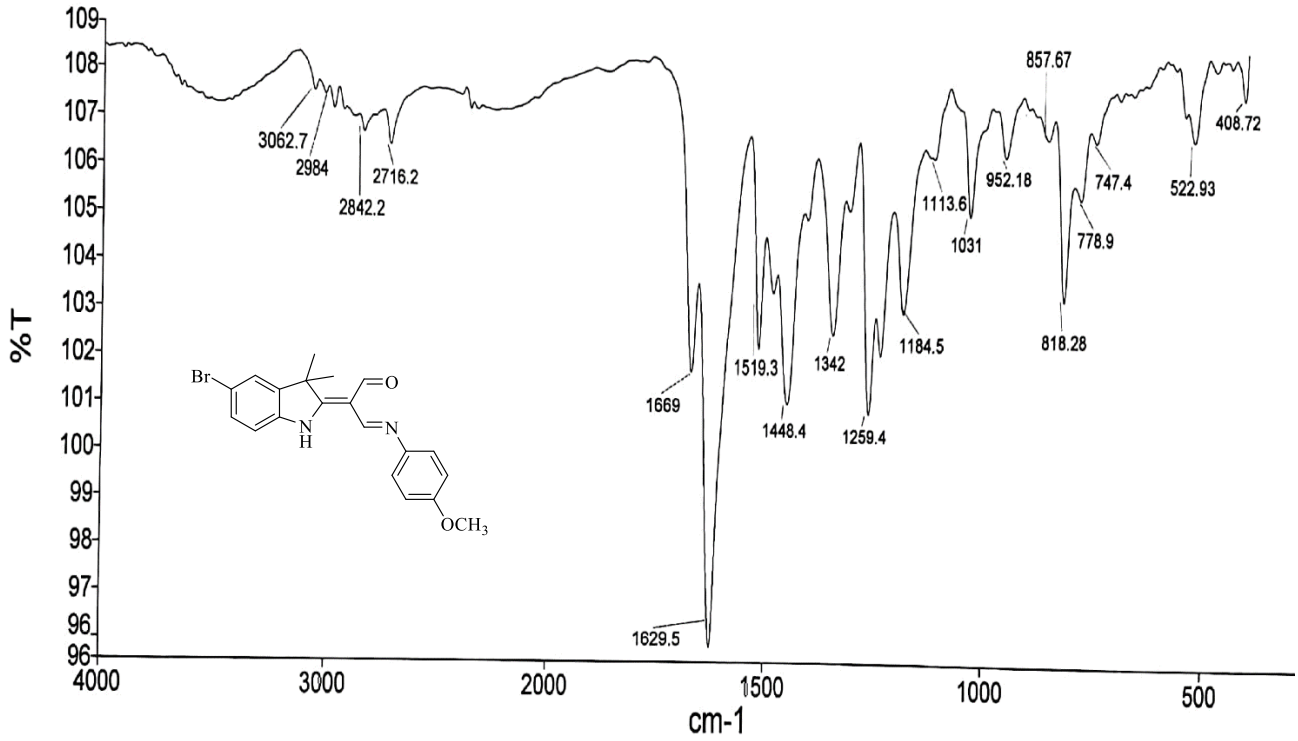


Figure (4.4): The FT-IR spectra of the compound (5).

FT-IR for the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2-methoxyphenyl)imino)propanal (6)

The structure of the compound **(6)** was confirmed by FT-IR spectrum as illustrated in Figure (4.5) and Table (4.2). The FT-IR spectrum shows an absorption band at (2976 cm^{-1}) which referred to the aromatic (C-H), at (2936 and 2850 cm^{-1}) to the aliphatic (C-H), and (2739 cm^{-1}) to the aldehyde (C-H). Also, (1665 cm^{-1}) for the (C=O) group (strong absorption band), and (1621 cm^{-1}) for the (C=N) azomethine group. The stretching frequency at (1590-1460 cm^{-1}) is due to the (C=C) aromatic. The absorption bands that appeared at (1342 cm^{-1}) related to the CH_3 group, and at (1255 cm^{-1}) which was attributed to the (C-N) group. Also, the absorption bands at (818 cm^{-1}) are assigned to(C-Br). Finally, a sharp peak at (747 cm^{-1}) is attributed to the out-of-plane (C-H) group.

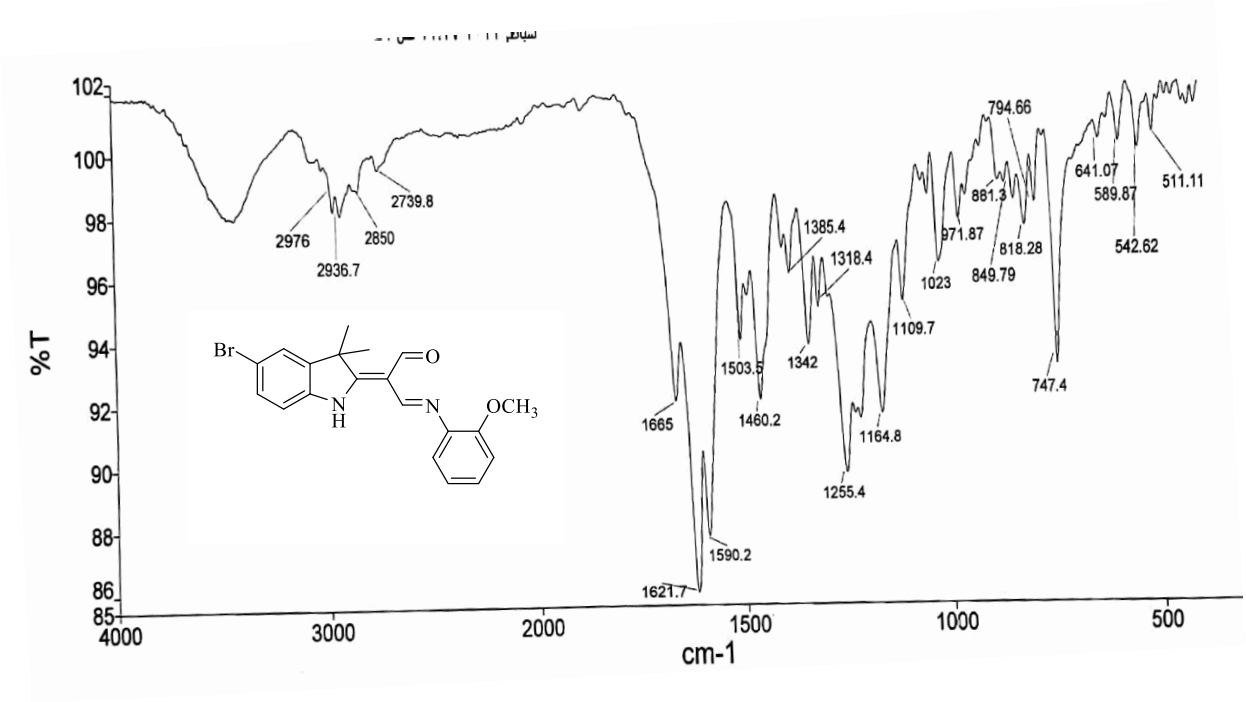


Figure (4.5): The FT-IR spectra of the compound (6).

Chapter Four: Results and Discussion Part

FT-IR for the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-bromophenyl)imino)propanal (7)

The structure of the compound **(7)** was confirmed by FT-IR spectrum as illustrated in Figure (4.6) and Table (4.2). The FT-IR spectrum shows an absorption band at (2960 cm^{-1}) to the aliphatic (C-H), and (2724 cm^{-1}) to the aldehyde (C-H). Also, (1669 cm^{-1}) for the (C=O) group (strong absorption band), and (1621 cm^{-1}) for the (C=N) azomethine group. The stretching frequency at (1558-1448 cm^{-1}) is due to the (C=C) aromatic. The absorption bands that appeared at (1334 cm^{-1}) related to the CH_3 group, and at (1231cm^{-1}) which was attributed to the (C-N) group. Also, the absorption bands at (814 cm^{-1}) are assigned to(C-Br). Finally, a sharp peak at (767 cm^{-1}) is attributed to the out-of-plane (C-H) group.

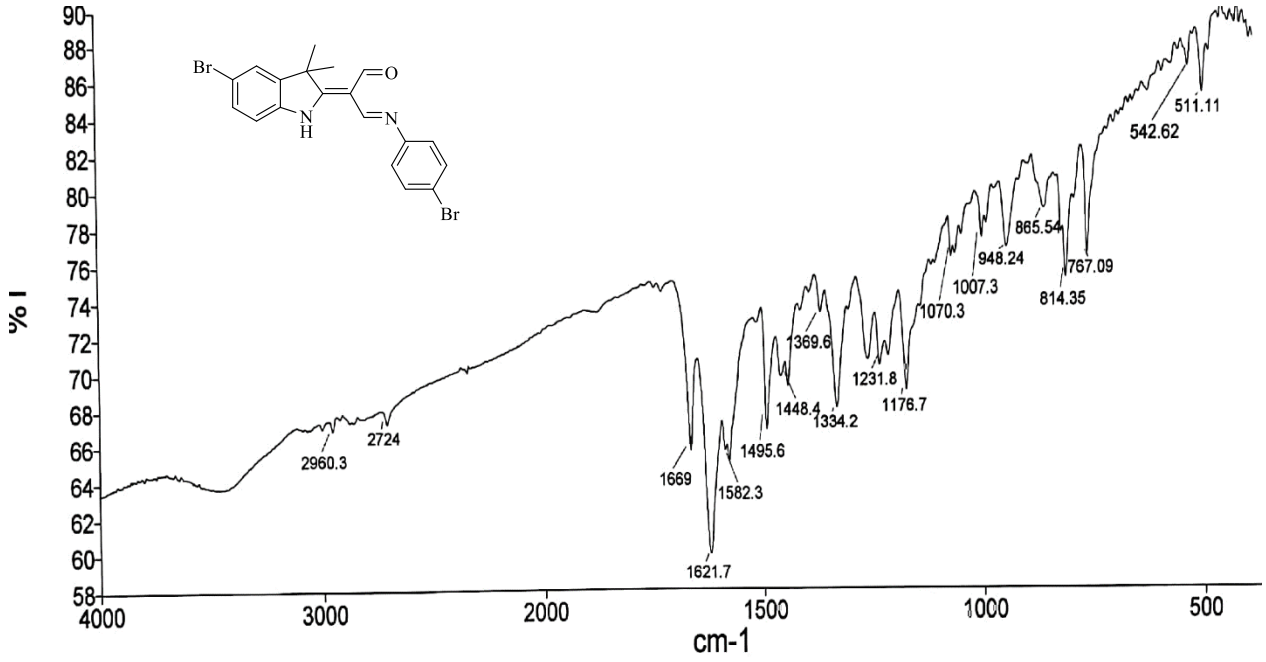


Figure (4.6): The FT-IR spectra of the compound (7).

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FT-IR for the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal (8)

The structure of the compound **(8)** was confirmed by FT-IR spectrum as illustrated in Figure (4.7) and Table (4.2). The FT-IR spectrum shows an absorption band at (3060 cm^{-1}) which referred to the aromatic (C-H), at (2968 and 2865 cm^{-1}) to the aliphatic (C-H), and (2708 cm^{-1}) to the aldehyde (C-H). Also, (1669 cm^{-1}) for the (C=O) group (strong absorption band), and (1625 cm^{-1}) for the (C=N) azomethine group. The stretching frequency at (1582-1460 cm^{-1}) is due to the (C=C) aromatic. The absorption bands that appeared at (1330 cm^{-1}) related to the CH_3 group, and at (1220 cm^{-1}) which was attributed to the (C-N) group. Also, the absorption bands at (810 cm^{-1}) are assigned to(C-Br). Finally, a sharp peak at (763 cm^{-1}) is attributed to the out-of-plane (C-H) group.

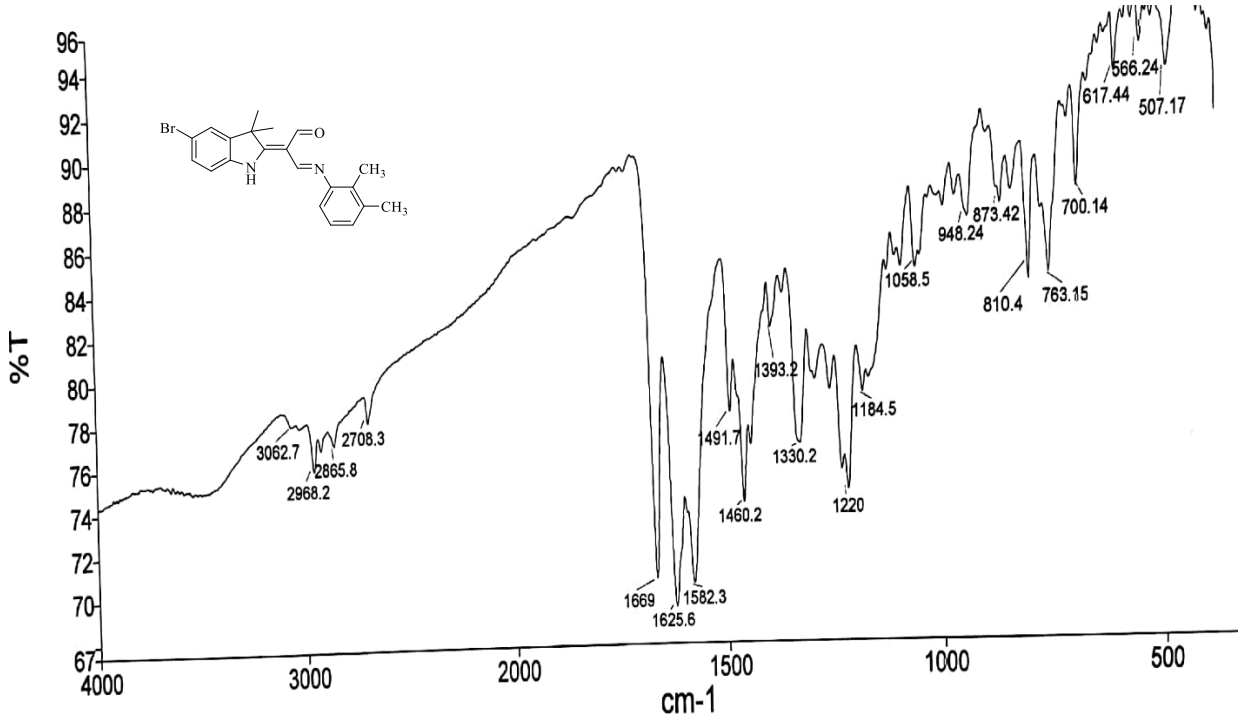

Figure (4.7): The FT-IR spectra of the compound (8).

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FT-IR for the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-chlorophenyl)imino)propanal (9)

The structure of the compound **(9)** was confirmed by FT-IR spectrum as illustrated in Figure (4.8) and Table (4.2). The FT-IR spectrum shows an absorption band at (2960 cm^{-1}) which referred to the aromatic (C-H), at (2960 and 2873 cm^{-1}) to the aliphatic (C-H), and (2739 cm^{-1}) to the aldehyde (C-H). Also, (1669 cm^{-1}) for the (C=O) group (strong absorption band), and (1625 cm^{-1}) for the (C=N) azomethine group. The stretching frequency at (1586-1444 cm^{-1}) is due to the (C=C) aromatic. The absorption bands that appeared at (1334 cm^{-1}) related to the CH_3 group, and at (1227 cm^{-1}) which was attributed to the (C-N) group. Also, the absorption bands at (818 cm^{-1}) are assigned to(C-Br). Finally, a sharp peak at (767 cm^{-1}) is attributed to the out-of-plane (C-H) group.

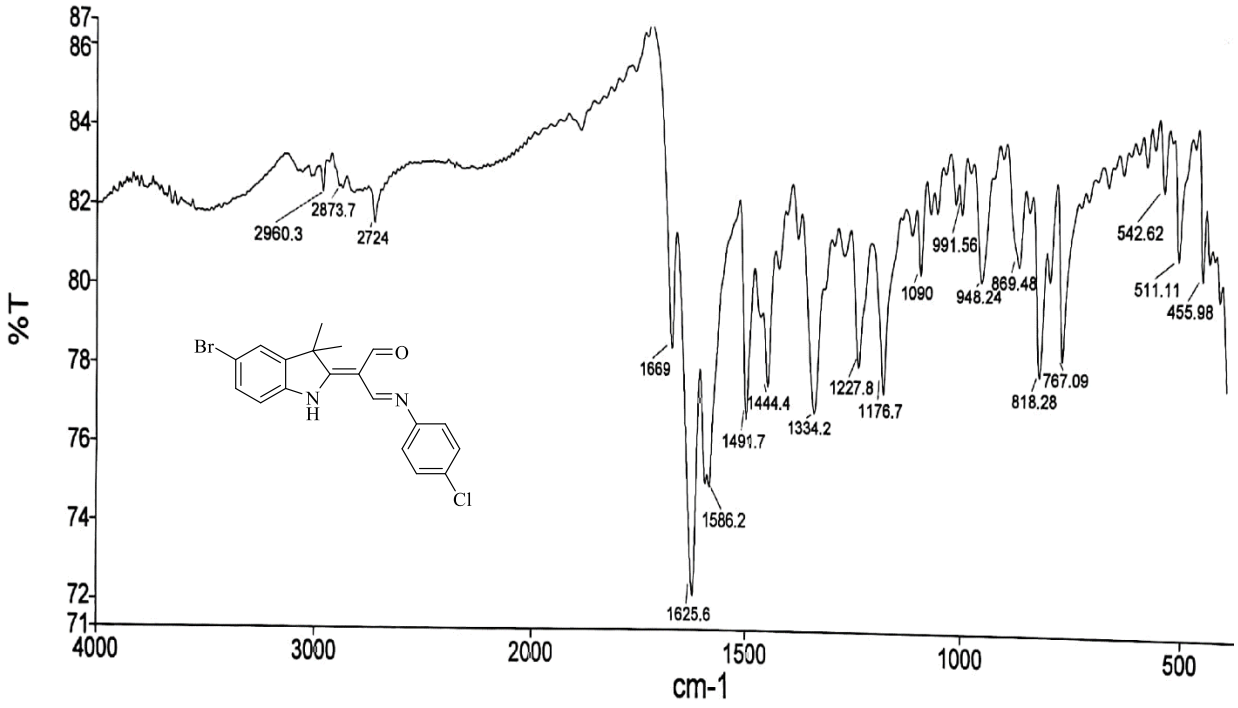

Figure (4.8): The FT-IR spectra of the compound (9).

FT-IR for the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,4-dichlorophenyl)imino)propanal (10)

The structure of the compound **(10)** was confirmed by FT-IR spectrum as illustrated in Figure (4.9) and Table (4.2). The FT-IR spectrum shows an absorption band at (2960 cm^{-1}) to the aliphatic (C-H), and (2724 cm^{-1}) to the aldehyde (C-H). Also, (1669 cm^{-1}) for the (C=O) group (strong absorption band), and (1625 cm^{-1}) for the (C=N) azomethine group. The stretching frequency at (1586-1440 cm^{-1}) is due to the (C=C) aromatic. The absorption bands that appeared at (1330 cm^{-1}) related to the CH_3 group, and at (1227 cm^{-1}) which was attributed to the (C-N) group. Also, the absorption bands at (818 cm^{-1}) are assigned to(C-Br). Finally, a sharp peak at (767 cm^{-1}) is attributed to the out-of-plane (C-H) group.

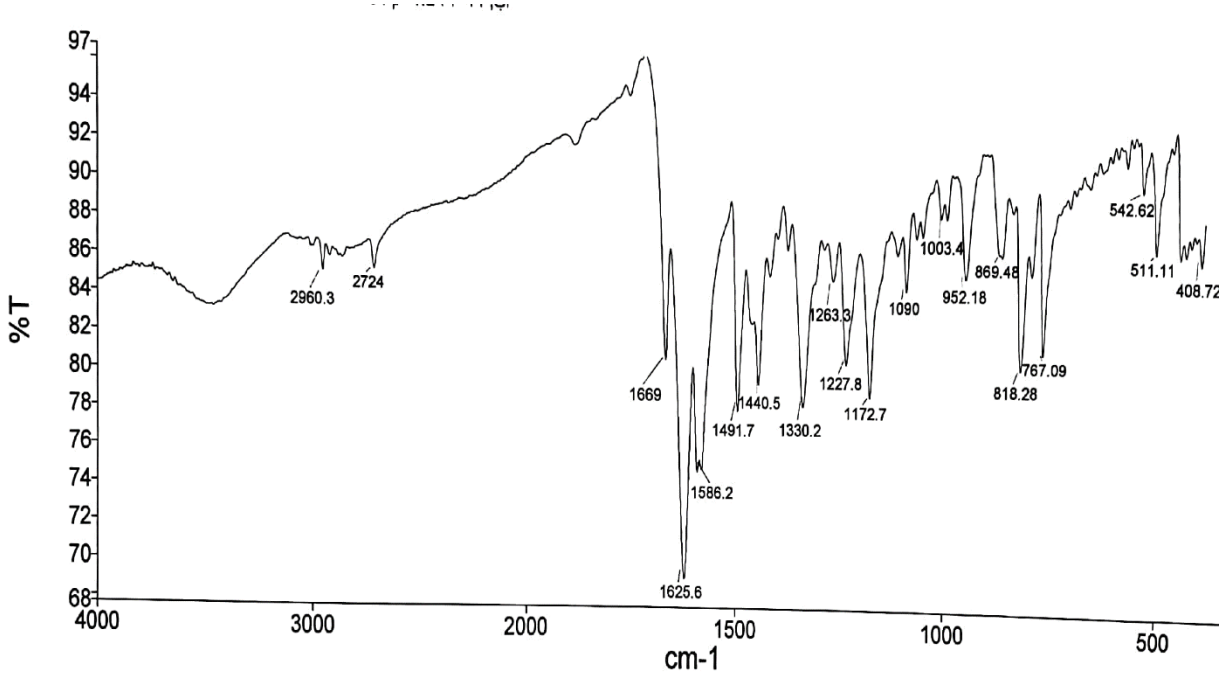

Figure (4.9): The FT-IR spectra of the compound (10).

4.1.2.2. ^{1}H-NMR Study.

^{1}H-NMR spectra was detected in DMSO (dimethyl sulfoxide) with chemical shifts in ppm and using TMS (tetramethylsilane) as standard.

Table (4.3) list the ^{1}H-NMR spectral data of newly produced substances (2-10)

Table (4.3): The chemical shifts in ppm to ^{1}H-NMR results for compounds (2-10).

Comp. No.	N-H	HC=O	-OH	HC=N	Ar.-H	-OCH$_3$	Ortho CH$_3$	Meta CH$_3$	6H, 2x CH$_3$
2	7.81	9.80			7.68-7.33				1.81
3	7.81	9.47		8.80	7.73-7.38			2.57	1.64
4	7.71	9.41	10.48	8.68	7.64-6.92				1.60
5	7.66	9.40		8.58	7.54-7.02	3.80			1.60
6	7.50	9.42		8.74	7.42-7.10	4.05			1.61
7	7.73	9.44		8.68	7.71-7.48				1.60
8	7.69	9.43		8.69	7.56-7.10		2.35	2.40	1.62
9	7.69	9.42		8.67	7.62-7.50				1.60
10	7.68	9.44		8.69	7.62-7.31				1.60

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The ^{1}H-NMR spectrum of the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene) malonaldehyde (2)

Figure (4.10) shows chemical shifts δ at 7.81 (s, 1H, NH), 9.80 (s, 2H, -CH=O), 7.68 – 7.33 (m, 3H, Ar-H), 1.66 (s, 6H, 2x CH_3).

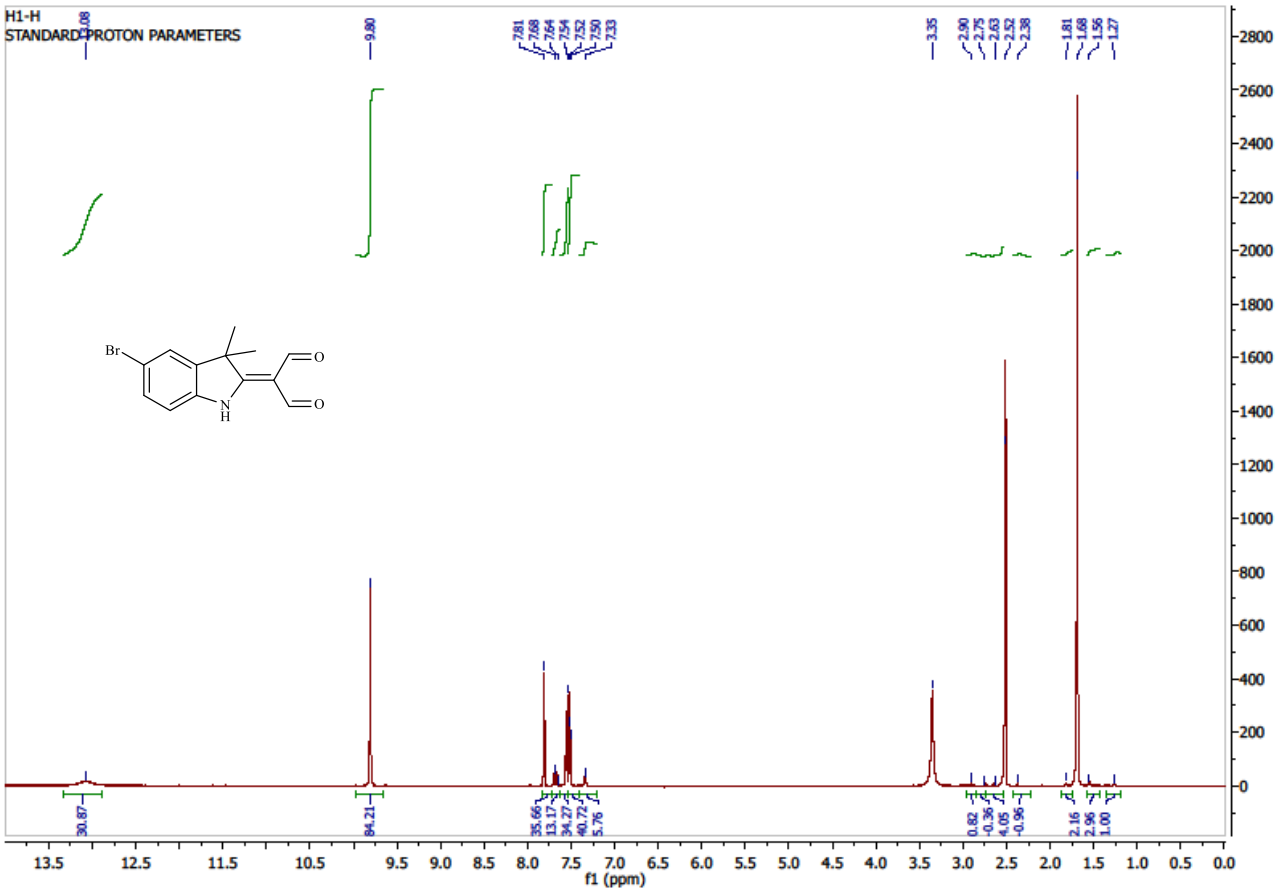

Figure (4.10): The ^{1}H-NMR spectra of the compound (2).

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The ^{1}H-NMR spectrum of the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-(o-tolylimino)propanal (3)

Figure (4.11) shows chemical shifts δ at 7.81 (s, 1H, NH), 9.47 (s, 1H HC=O), 8.80 (s,1H HC=N), 7.73 _7.38 (m, 7H Ar.-H) 2.57 (s, 3H, CH_3), 1.64 (s, 6H 2x CH_3).

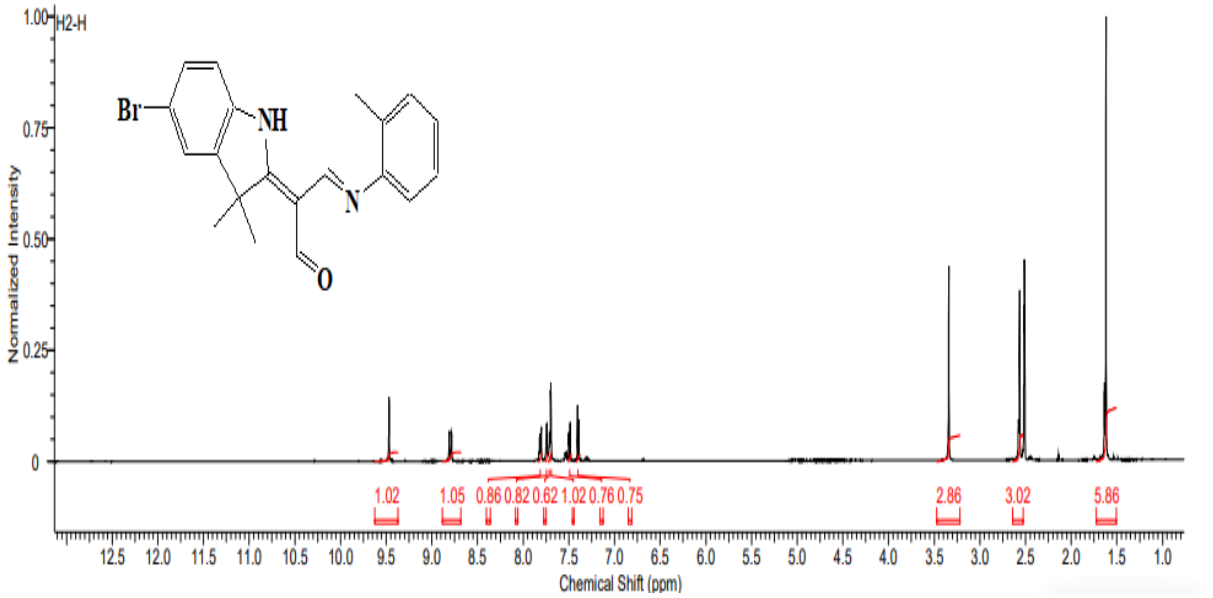

Figure (4.11): The ^{1}H-NMR spectra of the compound (3).

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The ^{1}H-NMR spectrum of the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal. (4)

Figure (4.12) shows chemical shifts δ at 7.71 (s, 1H, NH), 10.48 (s, 1H OH), 9.41 (s, 1H -CH=O), 8.68 (s, 1H HC=N), 7.64 _6.92 (m, 7H Ar.-H), 1.60 (s, 6H 2x CH_3).

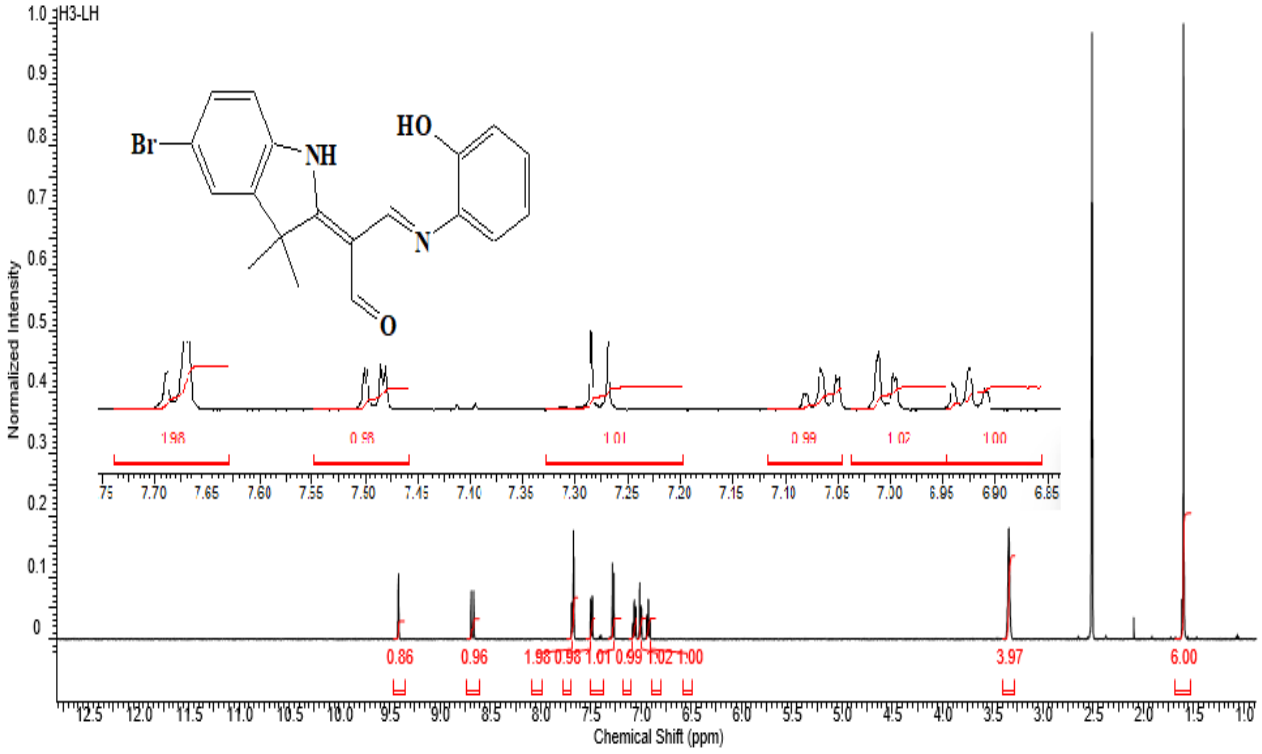

Figure (4.12): The ^{1}H-NMR spectra of the compound (4).

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The ^{1}H-NMR spectrum of the compound 2-(-5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-methoxyphenyl)imino)propanal (5)

Figure (4.13) shows chemical shifts δ at 7.66 (s, 1H, NH), 9.40 (s, 1H, -CH=O), 8.58 (s,1H_HC=N), 7.54 – 7.02 (m, 7H, Ar-H), 3.80 (s,3H -OCH3),1.60 (s, 6H, 2x CH_3).

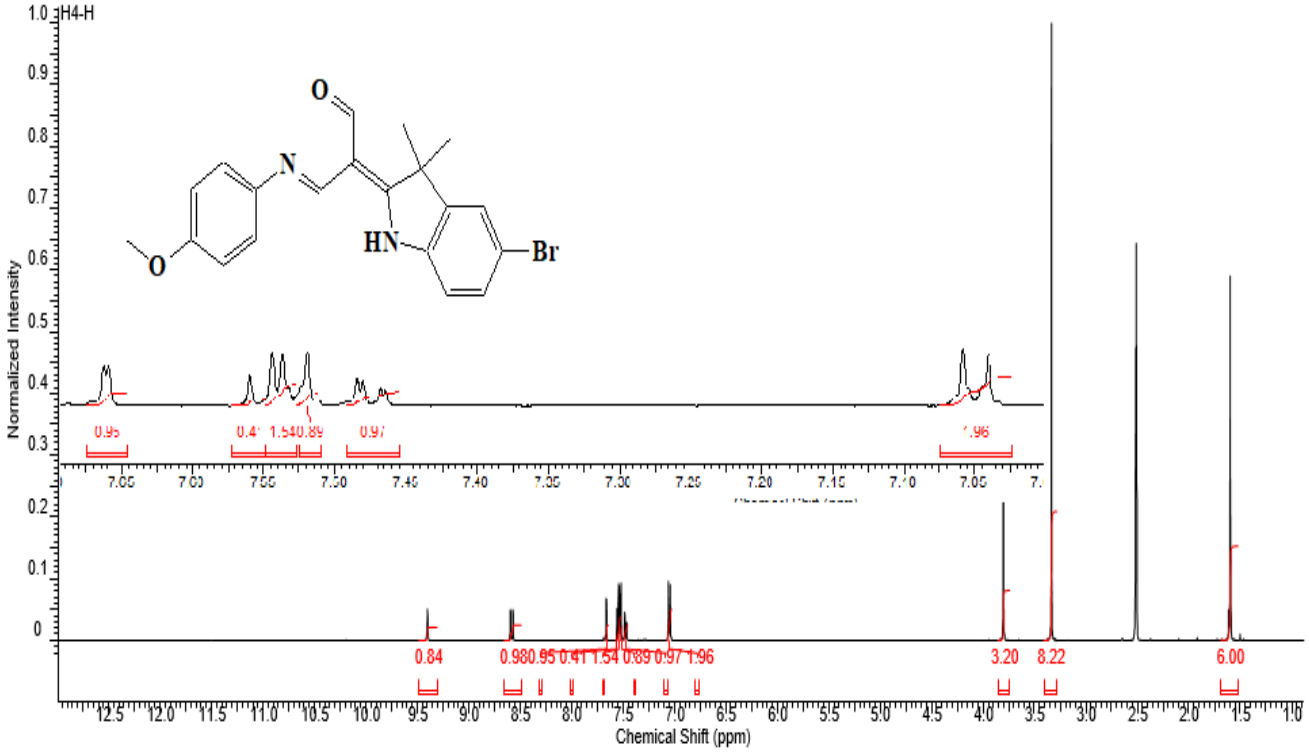

Figure (4.13): The ^{1}H-NMR spectra of the compound (5).

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The ^{1}H-NMR spectrum of the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2-methoxyphenyl)imino)propanal (6)

Figure (4.14) shows chemical shifts at 7.50 (s, 1H, NH), 9.42 (s, 1H -CH=O), 8.74 (s, 1H HC=N), 7.42 _7.10 (7H Ar.-H), 4.05 (s,3H -OCH3), 1.61 (s, 6H 2x CH_3).

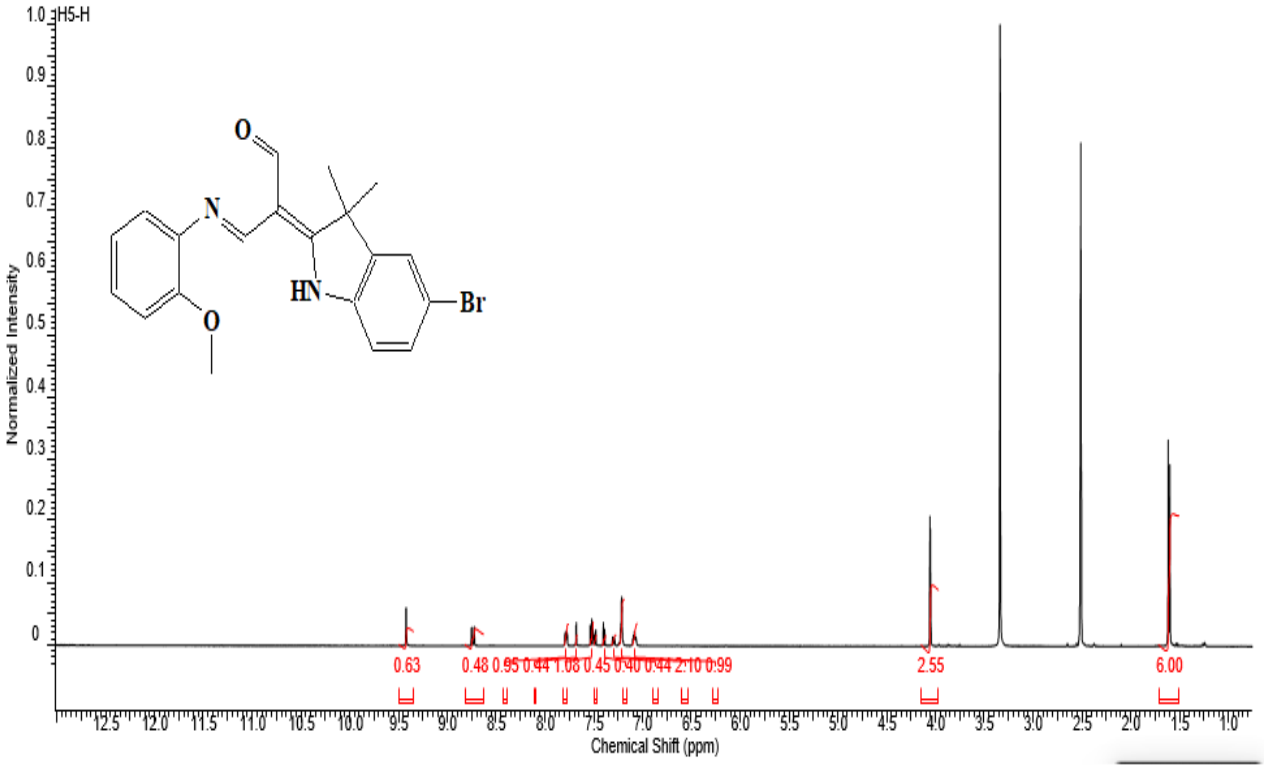

Figure (4.14): The ^{1}H-NMR spectra of the compound (6).

The ^{1}H-NMR spectrum of the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-bromophenyl)imino)propanal (7)

Figure (4.15) shows chemical shifts at 7.73 (s, 1H, NH), 9.44 (s, 1H -CH=O), 8.68 (s, 1H HC=N), 7.71 _7.48 (7H Ar.-H), 1.60 (s, 6H 2x CH_3).

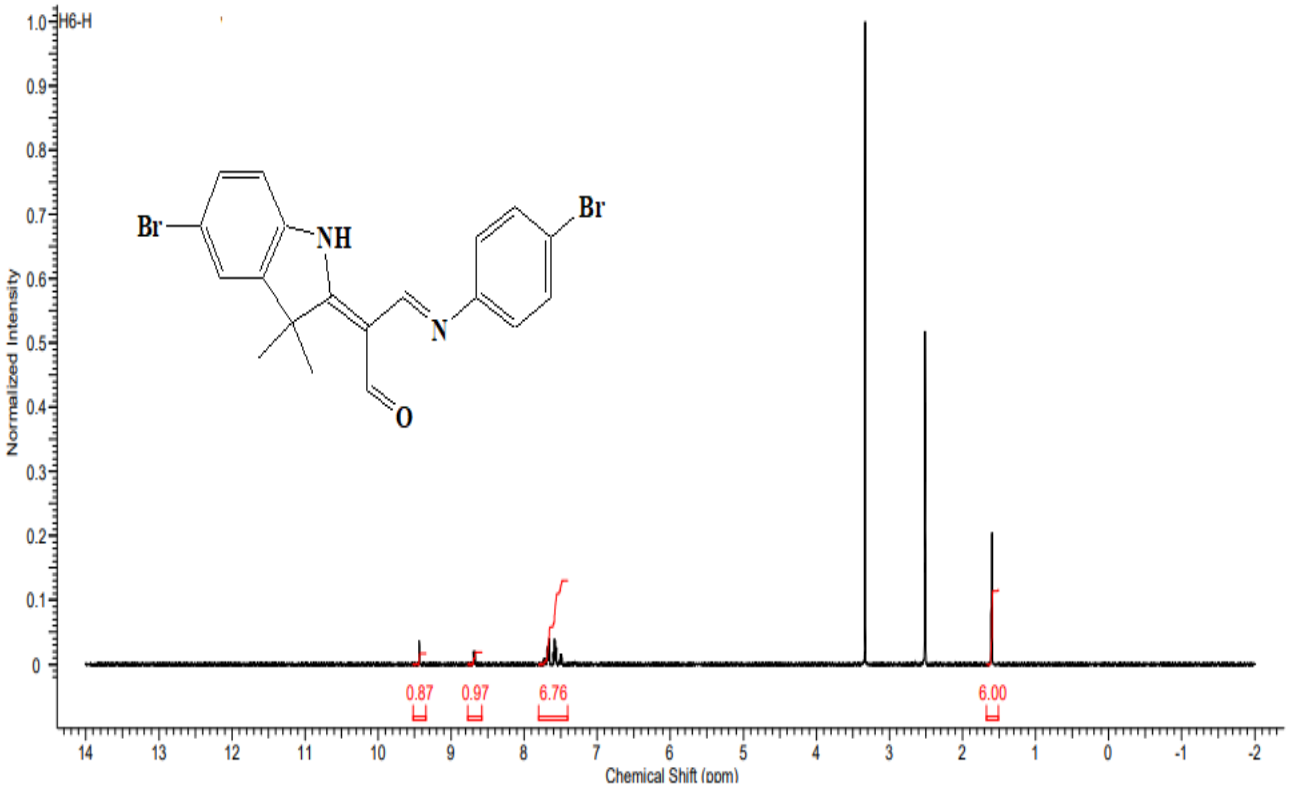

Figure (4.15): The ^{1}H-NMR spectra of the compound (7).

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The ^{1}H-NMR spectrum of the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal (8)

Figure (4.16) shows chemical shifts at 7.69 (s, 1H, NH), 9.43 (s, 1H -CH=O), 8.69 (s, 1H HC=N), 7.56 _7.10 (6H Ar.-H), 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 1.62 (s, 6H 2x CH_3).

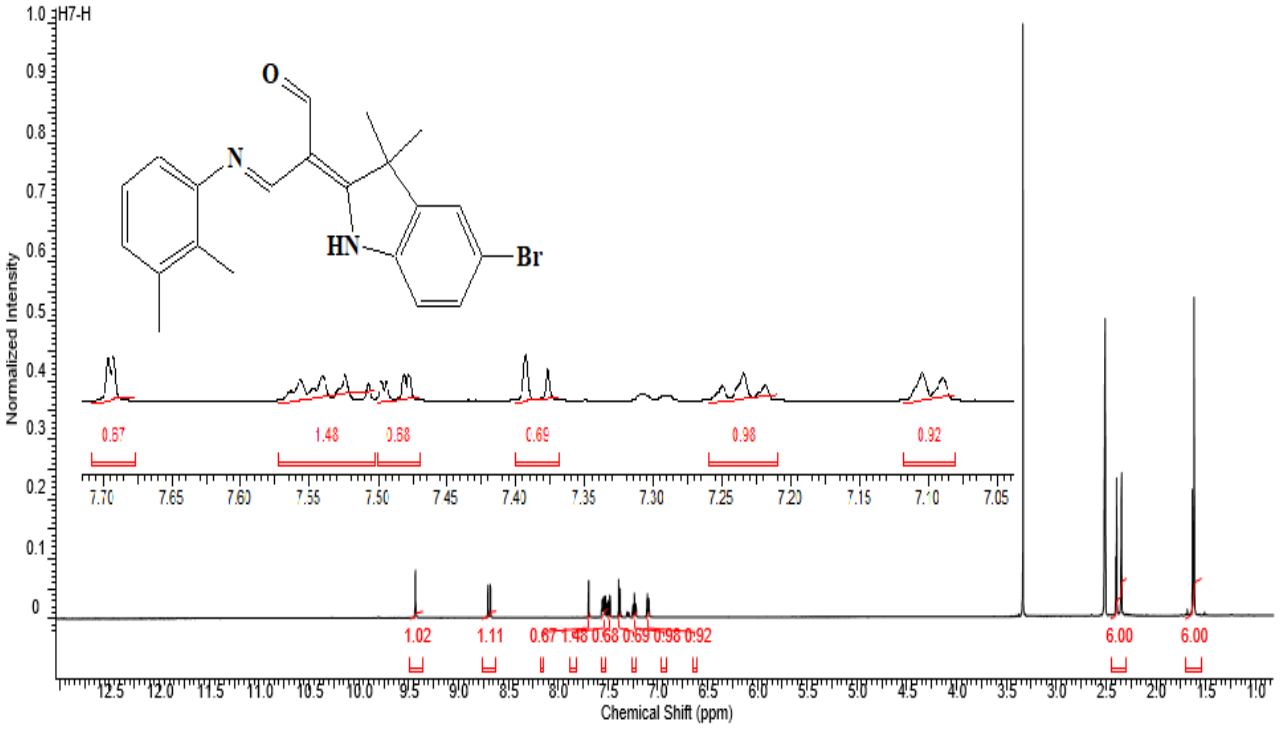

Figure (4.16): The ^{1}H-NMR spectra of the compound (8).

The ^{1}H-NMR spectrum of the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-chlorophenyl)imino)propanal (9)

Figure (4.17) shows chemical shifts at 7.69 (s, 1H, NH), 9.42 (s, 1H -CH=O), 8.67 (s, 1H HC=N), 7.62 _7.50 (7H Ar.-H), 1.60 (s, 6H 2x CH_3).

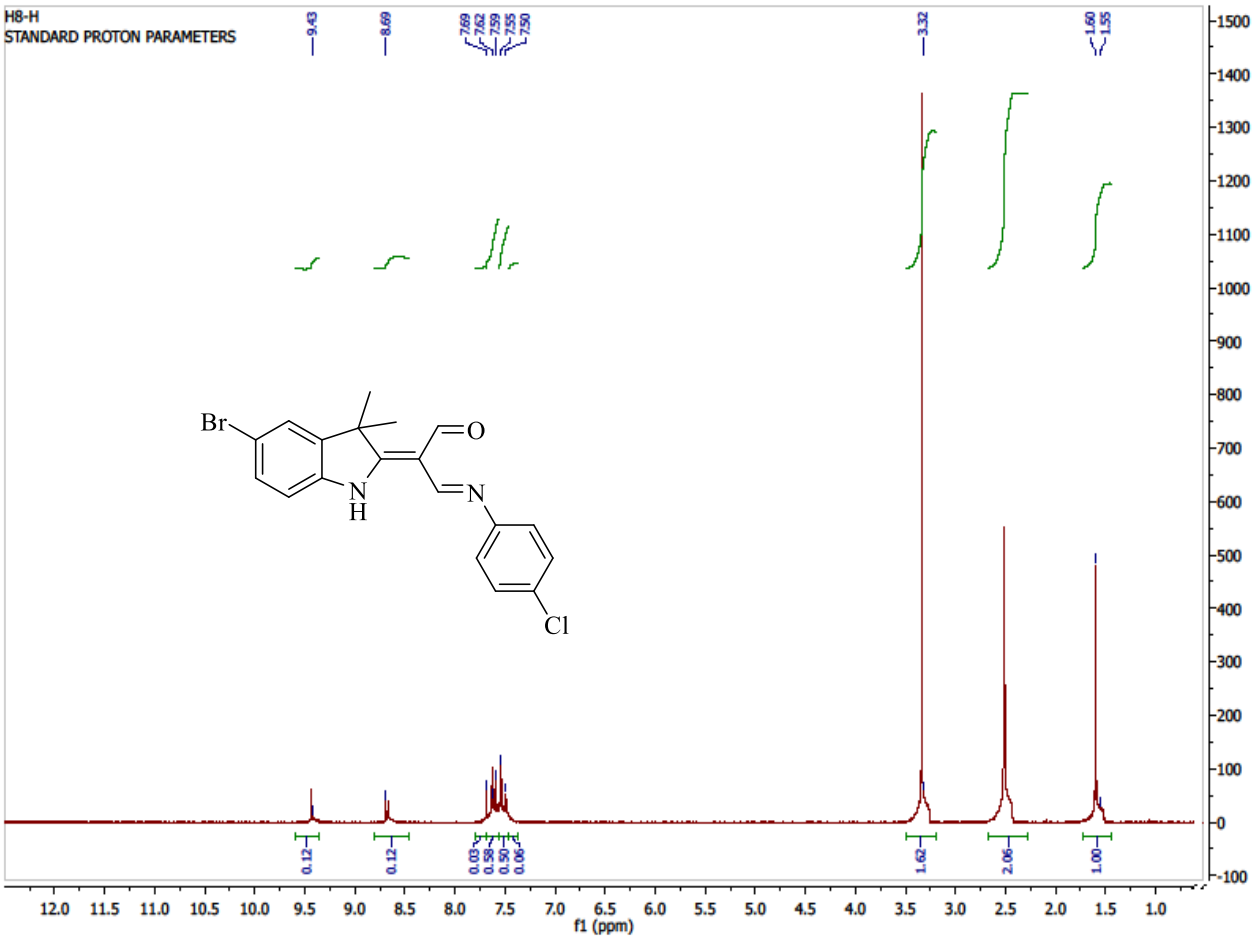

Figure (4.17): The ^{1}H-NMR spectra of the compound (9).

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The ^{1}H-NMR spectrum of the compound 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,4-dichlorophenyl)imino)propanal (10)

Figure (4.18) shows chemical shifts at 7.68 (s, 1H, NH), 9.44 (s, 1H -CH=O), 8.68 (s, 1H HC=N), 7.62 _7.31 (7H Ar.-H), 1.60 (s, 6H 2x CH_3).

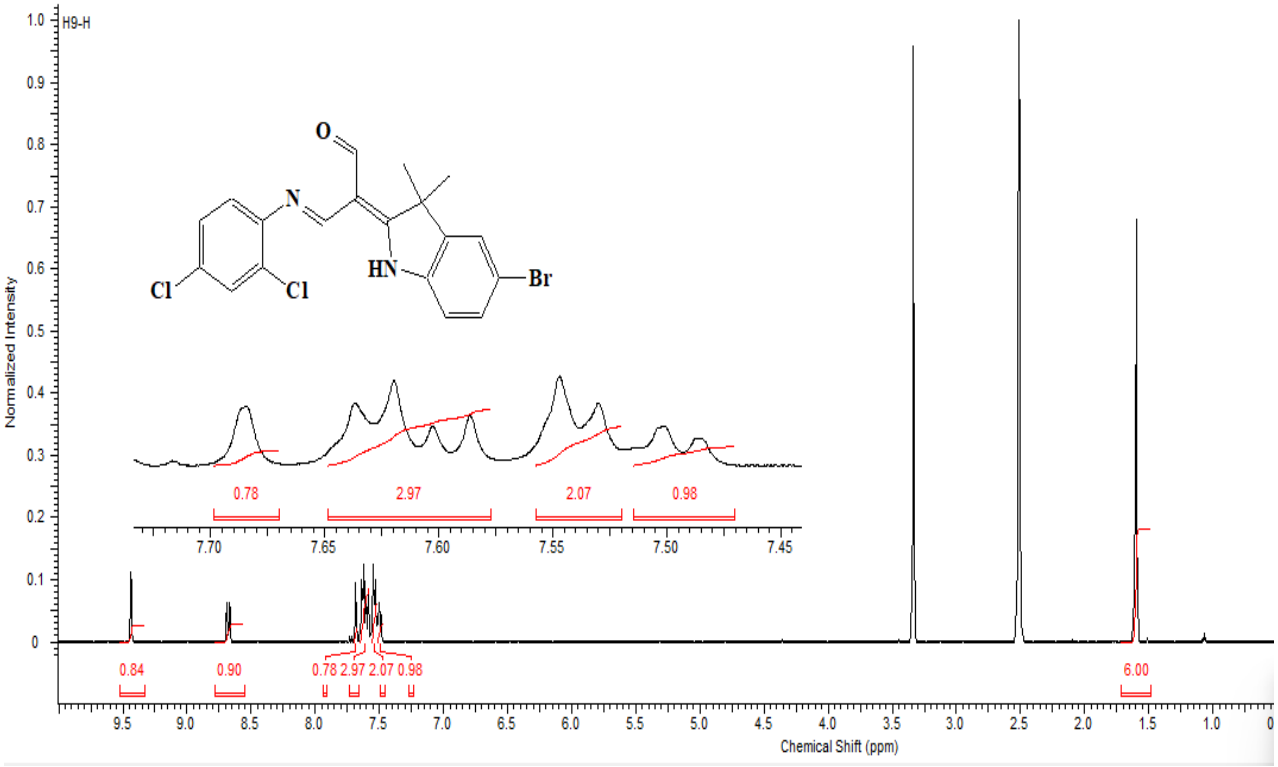

Figure (4.18): The ^{1}H-NMR spectra of the compound (10).

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4.2. Biological part

The antibacterial activity of prepared compounds was examined by using the agar well diffusion method using Muller Hinton agar medium with MacFarland turbidity as a standard solution. The zones of inhibition exhibited by the tested compounds were measured in (mm), as shown in Figure 9. The results are reported in Table 5. According to the screening results, the compound (**6**) have no inhibitory action against both *E. coli* and *S. aureus* bacteria, whereas the compound **(4)** showes moderate inhibition activity.

Table (4.4): Antibacterial activity of compounds (4,6).

Microorganism / Tested materials	*S. aureus*				*E. coli*			
	25%	50%	75%	100%	25%	50%	75%	100%
Comp. 4	10mm	13mm	14mm	15mm	-	-	-	12mm
Comp. 6	-	-	-	-	-	-	-	-

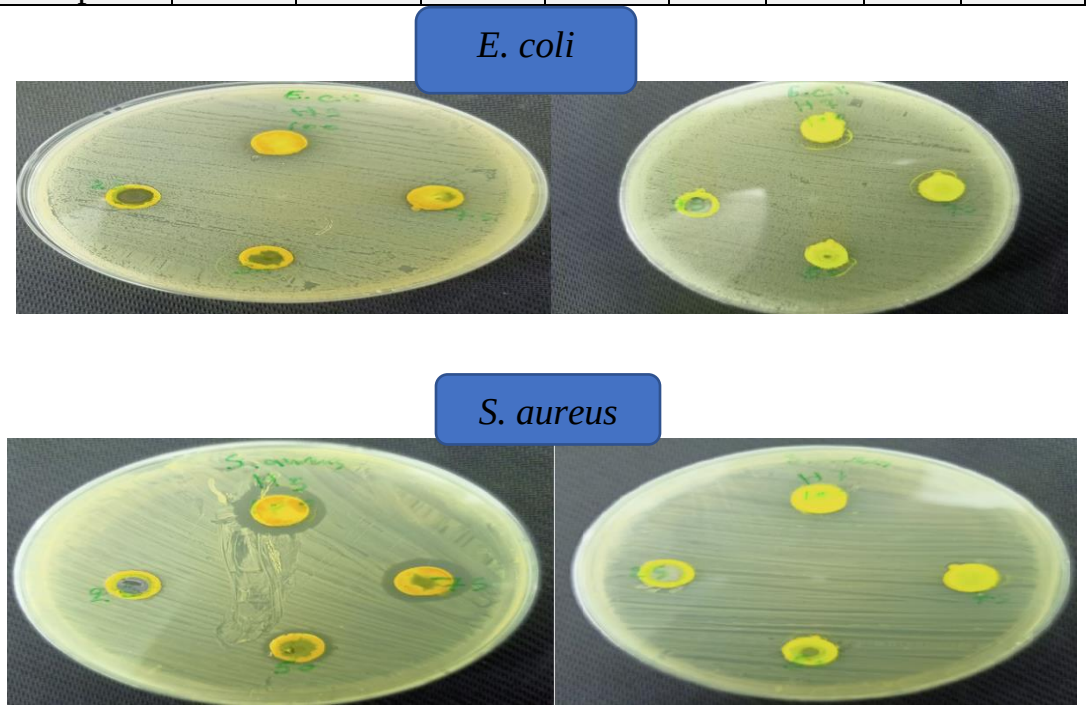

Figure (4.19): Effects of the tested compounds (4,6) against S. aureus and E. coli.

Conclusion.

1. The synthesis of indole Schiff base has been successfully achieved.
2. Characterization and identification of the target compounds were conformed by determination their physical properties like melting points, and spectral properties like FT-IR and ^{1}H-NMR spectra
3. The evaluation of the anti-bacterial activity against two bacterial strains, including gram-negative *E. coli* and gram-positive *S. aureus* indicate that compound **4** can be further explored as an activity agent.

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Suggestions for future work.

Our plan will be

1. Synthesis of new complexes from the synthesized indole Schiff bases (3-10) with various transition metal ions and evaluation of their biological activities.
2. Evaluating of different biological activities on new synthesized compounds, such as anti-inflammatory, antifungal, antiviral, and anti-cancer.
3. Study the use of the new syntheszed compounds in the industrial field.
4. Study the liqnid crystilline properties of the new syntheszed compounds.
5. Synthesized of new compounds using microwave method.
6. Study and explain the mass spectrum of the new syntheszed compounds.
7. Study of nanotechnology and its applications on syntheszed compounds.

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الخلاصة

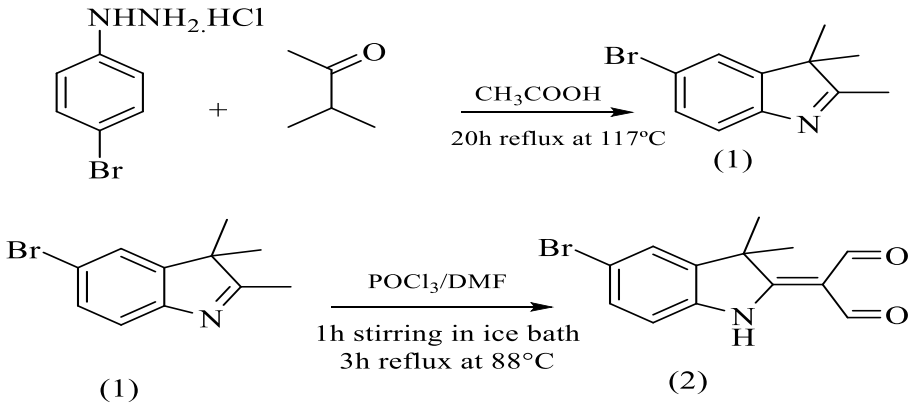
في هذه الرسالة ، تم تحضير سلسلة من قواعد شيف الجديدة بنجاح ، وتم تأكيد نقاوتها بواسطة كروماتوغرافيا الطبقة الرقيقة ، والتراكيب الكيميائية للمركبات المحضرة تم تحديدها بواسطة بعض التقنيات الطيفية مثل ، FT-IR ^{1}H-NMR، وكذلك تم تحديد الخصائص الفيزيائية للمركبات. تم تقسيم المركبات المحضرة إلى قسمين:

القسم الأول.

يتضمن تحضير المادة الاولية الجديدة ، 5-برومو 2 ,3,3 -ثلاثي ميثيل –*H* 3 -إندول **(1)** و 2- (5-برومو-3،3- ثنائي ميثيل-3,1-ثنائي هيدرو-إندول-2-يليدين)-مالون ألدهيد **(2)**.

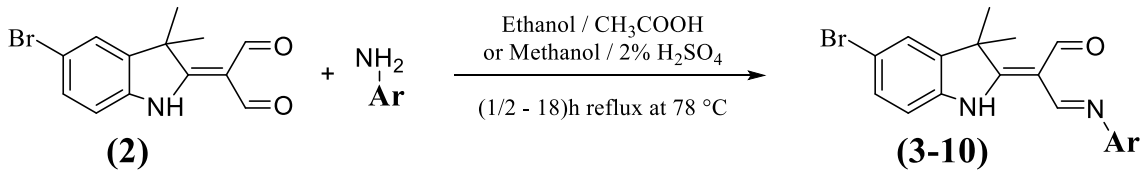
تم تحضير المركب الأول ، 5-برومو 2 ,3,3 -ثلاثي ميثيل –*H* 3 -إندول (**1**) عن طريق تفاعل 4-بروموفينيل هيدرازين هيدروكلوريد مع ميثيل أيزوبروبيل كيتون في وجود حامض الخليك الثلجي كمحفز(تفاعل فيشر إندول).

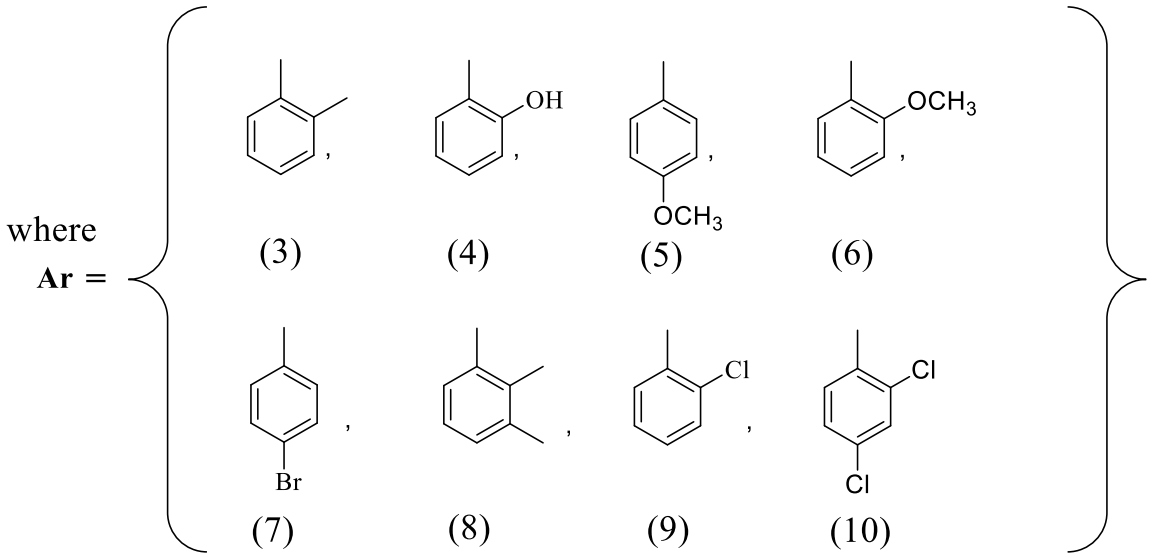
المركب الثاني ، 2- (5-برومو-3،3- ثنائي ميثيل-3,1 -ثنائي هيدرو-إندول-2-يليدين) -مالون ألدهيد (**2**) تم تحضيره عن طريق تفاعل 5-برومو- 3،3،2- ثلاثي ميثيل -H 3 -إندول (**1**) مع كلوريد الفوسفوريل ($POCl_3$) في وجود *N*، *N*- ثنائي ميثيل فورماميد (DMF) (تفاعل فليسمير هاك)



القسم الثاني.

يتضمن تحضير عدد من قواعد شيف الجديدة الناتجة عن تفاعل 2- (5-برومو -3 3-ثنائي ميثيل - 3,1- ثنائي هيدروإندول-2-يليدين) -مالون ألدهيد (**2**) مع مشتقات الانلين ، في إيثانول أو الميثانول كمذيب كما هو موضح في المخطط أدناه:





تم تقييم الفعالية البايولوجية للمركبين المحضرين الجديدين 4و6 ضد نوعين من البكتريا سالبة لصفة جرام *E. coli* و موجبة لصفة جرام *S. aureus* حيث اضهر المركب 4 تأثير مثبط لنشاط البكتريا.

وزارة التعليم العالي والبحث العلمي
جامعة ديالى
كلية العلوم
قسم الكيمياء

تحضير مشتقات قواعد شف جديدة من الإندول وتقييم فعاليتها البيولوجية

رسالة مقدمة إلى
مجلس كلية العلوم / جامعة ديالى
وهي جزء من متطلبات الحصول على شهادة الماجستير في علوم الكيمياء

من قبل
حوراء حسين خضير
بكالوريوس علوم الكيمياء / جامعة ديالى (2017)

بإشراف
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2021م 1443هـ