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Synthesis and biological evaluation of some quinoxaline derivatives and their metal complexes

A Thesis Submitted to the

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by

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

﴿ فَتَعَٰلَى ٱللَّهُ ٱلْمَلِكُ ٱلْحَقُّ ۗ وَلَا تَعْجَلْ بِٱلْقُرْءَانِ مِن قَبْلِ أَن يُقْضَىٰٓ إِلَيْكَ وَحْيُهُۥ ۖ وَقُل رَّبِّ زِدْنِى عِلْمًا ﴿١١٤﴾ ﴾

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Dedication

This humble effort is dedicated to the Holy Prophet Muhammad (peace be upon him and his people), as well as my mother, brothers and sisters, and husband.

ZAHRAA...

2022

ACKNOWLEDGMENT

First and foremost, I'd like to express my gratitude to Allah for providing me with the strength and courage to pursue my goals.

Thanks to God for all that you grant, I have the energy to do this task. I'd like to thank my supervisors, Dr. Wassan Baqir Ali and Dr. Areej Ali Jaraullah, for their encouragement, direction, and particular counsel during this project.

I am grateful to all of my good friends and especially to the employees of the chemistry department.

Finally, many thanks to my husband, my family and my girlfriend(Mariam).

Abstract

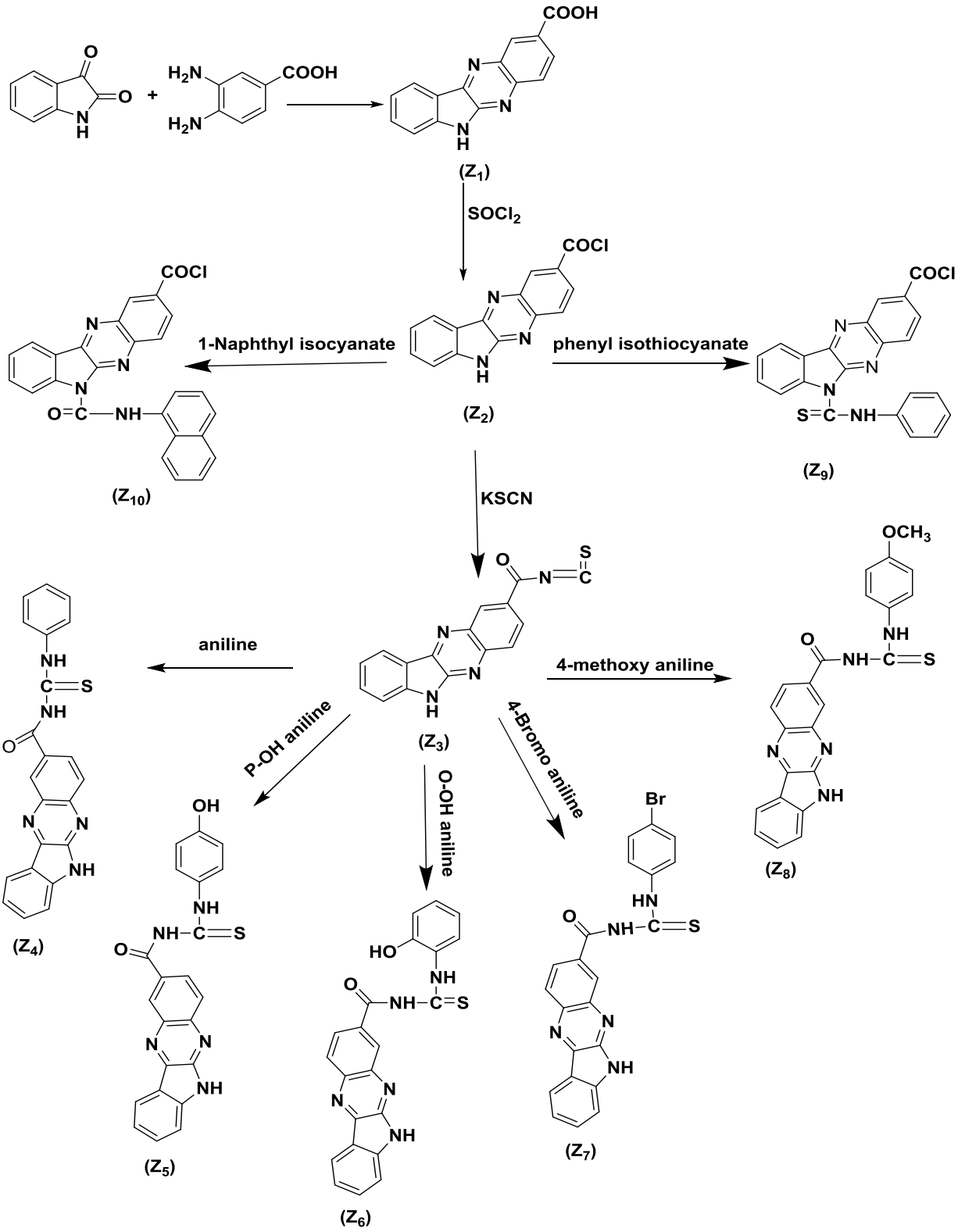
New compounds were synthesized from isatin and 1H-indene 1,2,3-trione in this thesis, and their purity was validated using thin layer chromatography(TLC) . Using spectroscopy techniques such as [FT-IR,^{1}H-NMR and^{13}C-NMR], the chemical structures of the produced compounds (Z_1-Z_{11}) were determined.

Compound Z_{11} was utilized as a ligand in the creation of new complexes by reacting with transition metal salts like($NiCl_2.6H_2O$,$CuCl_2.2H_2O$, $CdCl_2.H_2O$ and $ZnCl_2$). UV-Vis, FT-IR, atomic absorption spectroscopy, magnetic susceptibility, conductivity and studies were used to distinguish the novel complexes.

Melting points measurements using to characterize of prepared complexes. The following steps were included in the current research:

1. Synthesis of 6-H indolo[2,3-b]quinoxaline-2-carboxylic acide [Z_1], from the reaction of Isatin with 3,4-diamino benzoic acid.
2. Synthesis of 6H-indolo [2,3-b] quinoxaline-2-carbonyl chloride [Z_2] by the reaction of [Z_1] compound with thionyl chioride.Then allowed the second compound to react with potassium thiocyanate to synthesis 6H-indolo[2,3-b]quinoxaline-2-carbonyl iso thio**c**yanate[Z_3]**.**
3. Synthesis of thiourea derivitives [Z_4-Z_8] by the reaction of [Z_3] compound with aniline and substituted aniline.
4. Synthesis 6-(Phenyl carbamo thioyl)- 6H- indolo [2,3-b] quinoxaline- 2-carbonyl chloride[Z_9] by the reaction of Z_2 compound with isothiocyanate benzene to get new and effective replacement reaction compound**.**

5. Synthesis 6-(naphthalene-1-ylcarbamoyl)-6H-indolo[2,3-b]quinoxaline-2-carbonyl chloride (Z_{10}) by the reaction of Z_2 compound with 1-naphthyl isocyanate to get new and effective replacement reaction compound.
6. Reaction of 1H-indene 1,2,3-trione with 4-methyl benzene-1,2-diamine to produce a new compound 7-methyl-11H-indene[1,2-b]quinoxaline-11-one [Z_{11}]**,** and its complexes $[Ni(Z_{11})_2Cl_2].6H_2O$,$[Cu(Z_{11})_2Cl_2].6H_2O$, $[Cd(Z_{11})_2Cl_2].6H_2O$ and $[Zn(Z_{11})_2Cl_2].6H_2O$.
7. Finally, the biological activity of several produced compounds was tested against two species of bacteria (*E.Colias* and *S. Aureus*). When tested against two strains of bacteria, the majority of these compounds showed good to acceptable antibacterial activity.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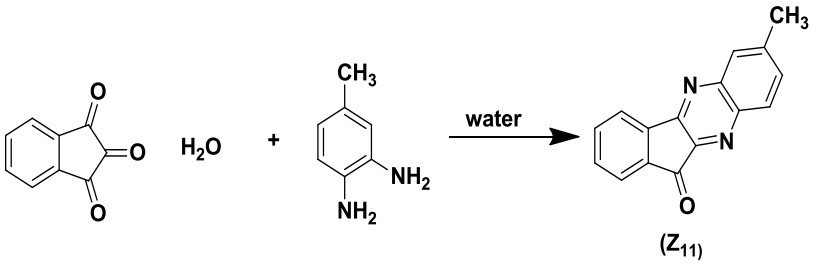
SOCl2
COCl
(Z2)
1-Naphthyl isocyanate
phenyl isothiocyanate
(Z10)
(Z9)
KSCN
aniline
4-methoxy aniline
P-OH aniline
O-OH aniline
4-Bromo aniline
(Z3)
(Z4)
(Z8)
(Z5)
(Z6)
(Z7)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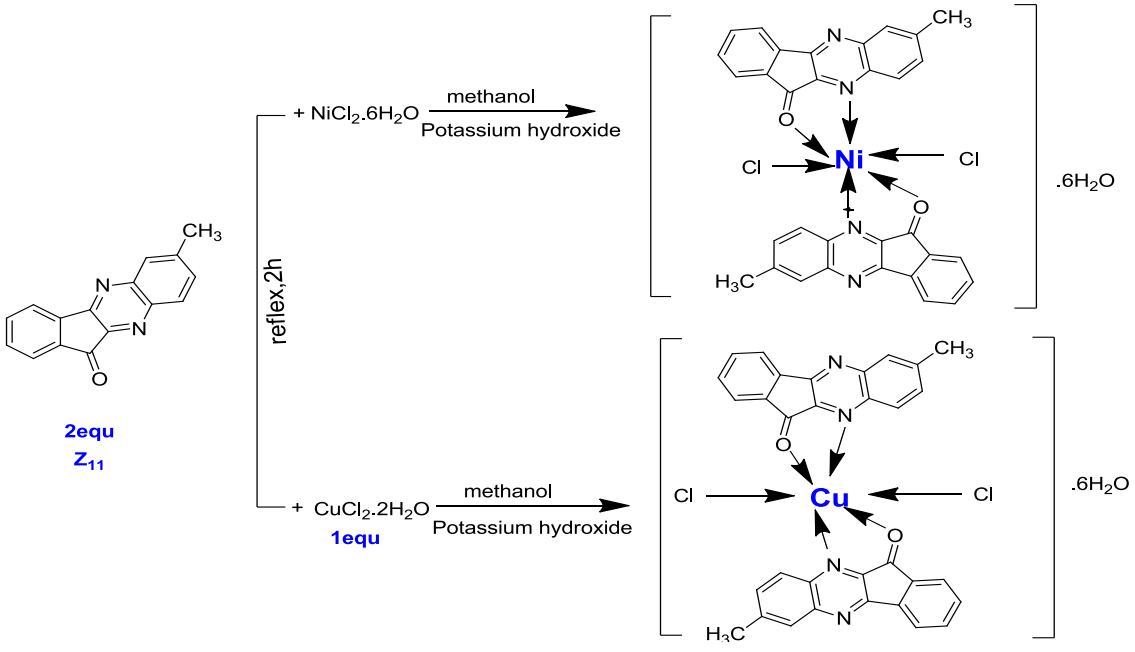
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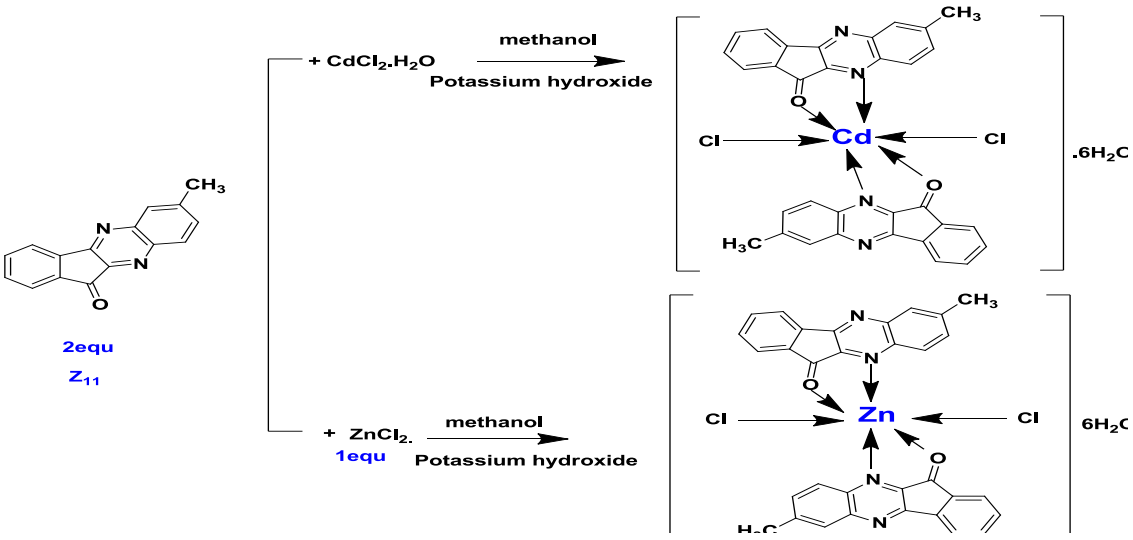
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Potassium hydroxide
Cd
Cl
Cl
H3C
.6H2C
+ ZnCl2.
1equ
methanol
Potassium hydroxide
Zn
Cl
Cl
6H2C

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List of Abberviations

Abbreviatin	Meaning
^{1}H-NMR	Proton Nuclear Magnetic Resonance
FT-IR	Fourier-transform infrared
UV-Vis	Ultraviolet-Visible
DMSO	Dimethyl sulfoxide
M.P.	Melting point
M.Wt	Molecular weight
TLC	Thin layer chromatography
S.aureus	*Staphylococcus aureus*
&	And
Ar	Aromatic ring
E.coli	*Escherichia coli*
Cm	Centimeter
G	Gram
µm	Micrometer
%	Percent (per cent)
H	Hour(s)
Min	Minute
MHz	Megahertz
Ppm	Parts per million
S	Singlet
Cal	Calculated
Λ	Wave length
Cond.	Conductivity
Oh	Octahedral

C.T.	Charge Transfer
^{0}C	Degree Celsius
$\bar{\upsilon}$	Wave number
μeff	Magnetic torque
Mmol	Millimol
B.M	Bohr Magneton
Mm	Millimeter
L: M	Ratio Ligand:Metal
DNA	Deoxy ribonucleic acid
RNA	Ribonucleic acid
r.t	room .temperature
I.L.	Intra ligand
PEG	Poly ethylene glycol
δ	Chemical Shift

Chapter One
(Perface & Literature review)

1.1. Preface

Heterocyclic chemistry is an essential field in the chemical sciences, and it accounts for a significant portion of current global research **[1]**. Heterocyclic compounds are cyclic organic compounds with at least one heteroatom; the most common heteroatoms are (N, O, S), but heterocyclic rings containing additional heteroatoms are also well-known**[2,3]**. Because of their usefulness in treating a variety of diseases, these chemicals are crucial and widely used in a variety of biological processes. The heterocyclic ring can be found in biological compounds such as RNA and DNA, chlorophyll, vitamins, and hemoglobin. Triazine derivatives, which are utilized as herbicides, antimicrobials, urinary antiseptics, and anti-inflammatory medicines, are examples of heterocyclic chemicals employed in a variety of diseases. **[4,5]**.

Indole has a bicyclic structure and is an aromatic heterocyclic molecule. Many important biological molecules contain indoles. Melatonin and Serotonin are biochemically active indole compounds, whereas tryptophan is a significant indole derivative. In nature, there are several indole alkaloid derivatives. Indigo-3-acetic acid is present in the plant hormone Auxin. In addition, a variety of important indole derivatives are used in treatment. Indole derivatives include the anti-inflammatory medicine indomethacin, the betablocker pindolol, and the hallucinogen dimethyltryptamine **[6]**.

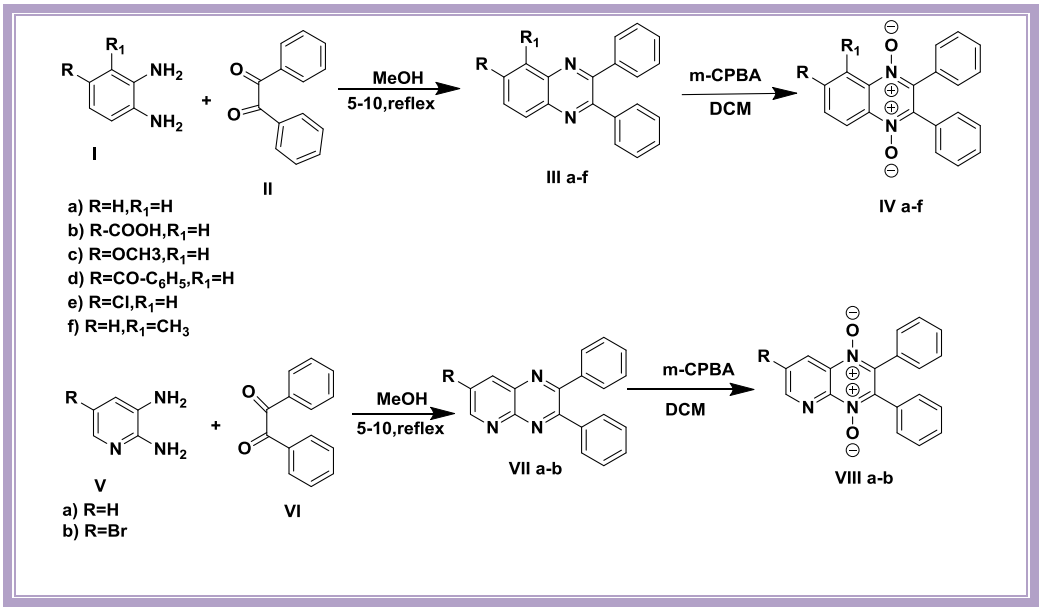
Quinoxaline and their derivatives are a significant class of heterocyclic compounds that have attracted a lot of attention over the years because of their intriguing biological properties and pharmaceutical like anticancer, insecticidal, anthelmintic, antifungal, antibacterial, and antiviral properties. Apart from their therapeutic uses, they also have a wide range of other uses. These compounds have found widespread use as dyes, electroluminescent materials, photoinitiators, and organic semiconductors. Recently, there has been a lot more

focus on developing sustainable and efficient methods for synthesis of quinoxaline derivatives**[7]**.

Thiourea (NH_2CSNH_2),a sulfur-containing compound,is of high industrial potential. Thiourea and its derivatives are used as corrosion inhibitors**[8]**. In industrial equipment such as boilers, which develop scales due to corrosion**[9]**. Thioureas are useful compounds as precursors for the synthesis of different classes of a cyclic and heterocyclic compounds **[10]**.

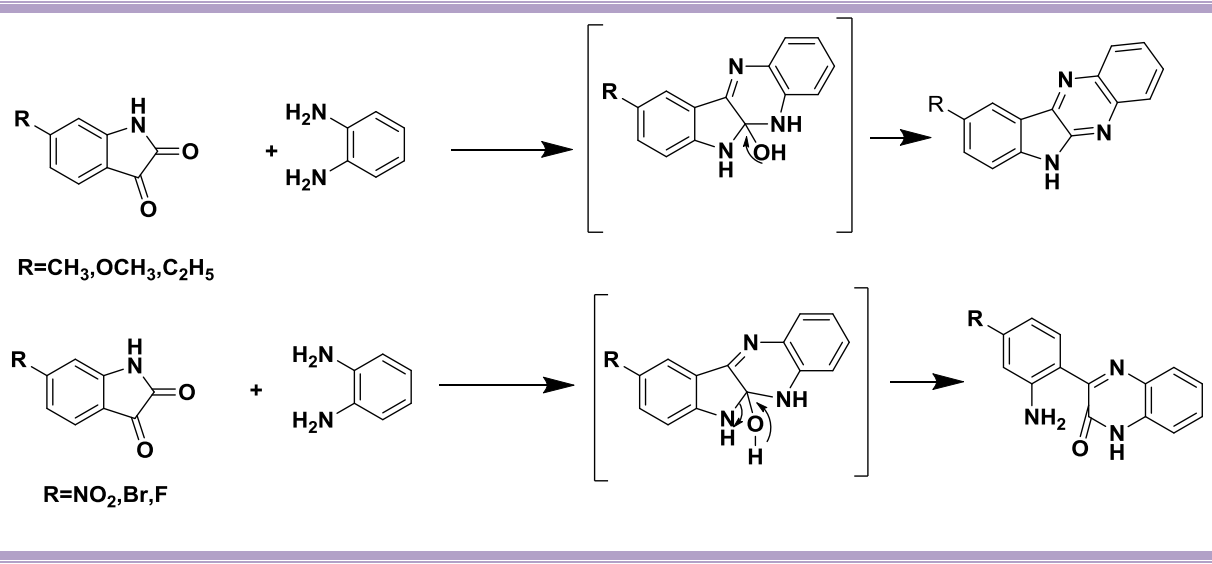
1.2. Literature review

Murthy Y. L. N. *et al*.(2011) synthesized and characterized of six compounds 6-sub, 2,3-diphenyl quinoxalines by the condensation of substituted *o-phenylene diamines* with *benzyl*. Further these compounds were reacted with *m-chloro per benzoic acid (m- CPBA)/dichloro methylene (DCM)* to form their corresponding 1,4-di-N-oxides. Antimicrobial activity of these compounds were screened in vitro. According to the findings, antimicrobial data for synthesized compounds have significant activity**[11]**. scheme(1.1) illustrate equation for synthesis of derivatives [2,3-diphenyl quinoxaline 1,4-di-Noxide].



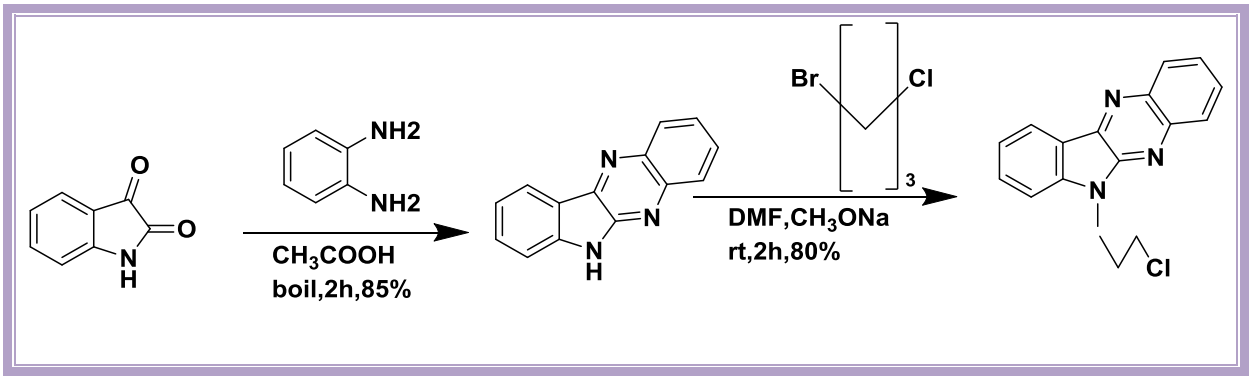
Scheme(1.1): Synthesis of [2,3-diphenyl quinoxaline 1,4-di-N-oxide derivatives]

Dowlatabadi R. *et al*.(2011) Studied the reaction of *orthophenylene diamine* with several substituted *isatin* in *acetic acid*. While electron-donor substituents on isatin shifting the reaction toward classical *6H-indolo[2,3-b] quinoxaline* ring closure and electron-withdrawing groups favor the formation of *3.(2'-amino-5'-substituted)- quinoxaline-2(1h)ones***[12]**. As shown in scheme (1.2)



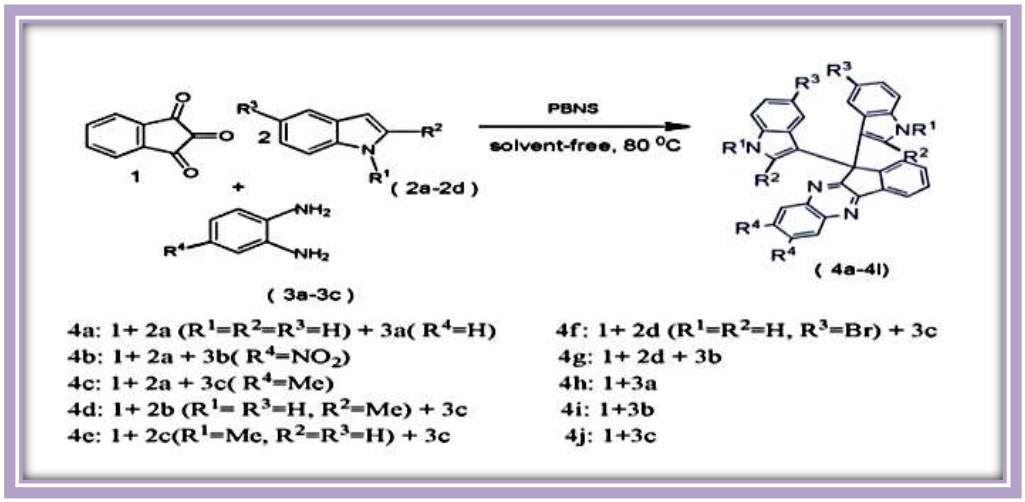
Scheme(1.2): reaction of ortho-phenylenediamine with substituted isatin

Shibinskaya M. O. *et al*. (2012) synthesized *6-(3-chloropropyl)- 6H-indolo-[2,3-b]quinoxaline* with 80% yield via indolo quinoxaline alkylation by *1-bromo-3- chloro propane*. Alkylation of *6H-indolo-[2,3-b] quinoxaline* was carried out in *DMF* when *sodium methylate* is present in an equimolar amount at room temperature**[13]**. As shown in scheme(1.3)



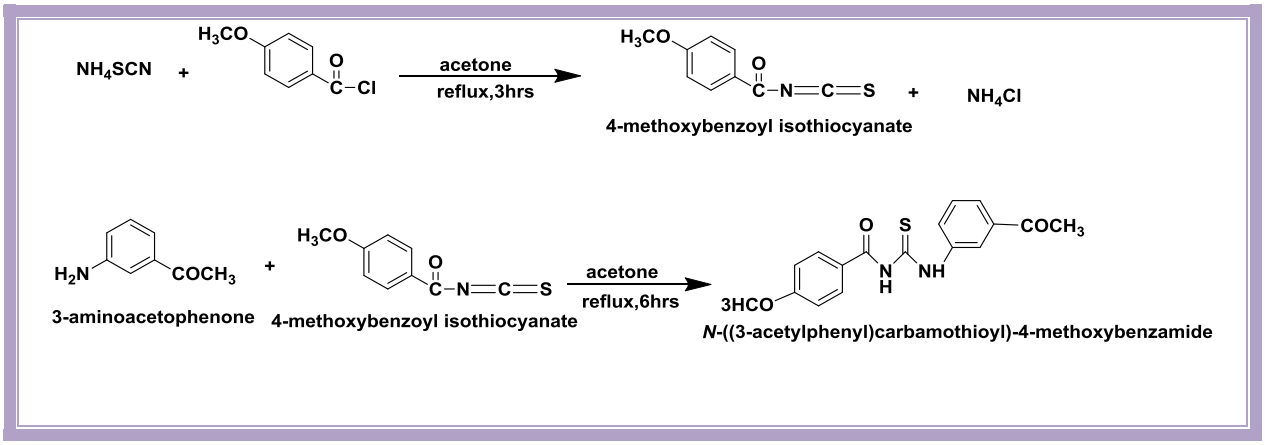
Scheme(1.3): synthesis of 6-(3-chloropropyl)-6H-indolo[2,3-b]quinoxalines

Khazaei A. *et al*. (2014) synthesized *bisindolylindeno[1,2-b] quinoxaline* derivatives from condensation reaction of *indole, indane1,2,3-trione,* and *diamine aromatic compounds* by *PBNS= Poly(N,N-dibromo-N-ethylnaphthyl-2,7-disulfonamide)* under solvent-free conditions at 80^{o}C in a simple procedure, short reaction times, good to excellent yields for new derivatives **[14].**As shown in Scheme(1.4)

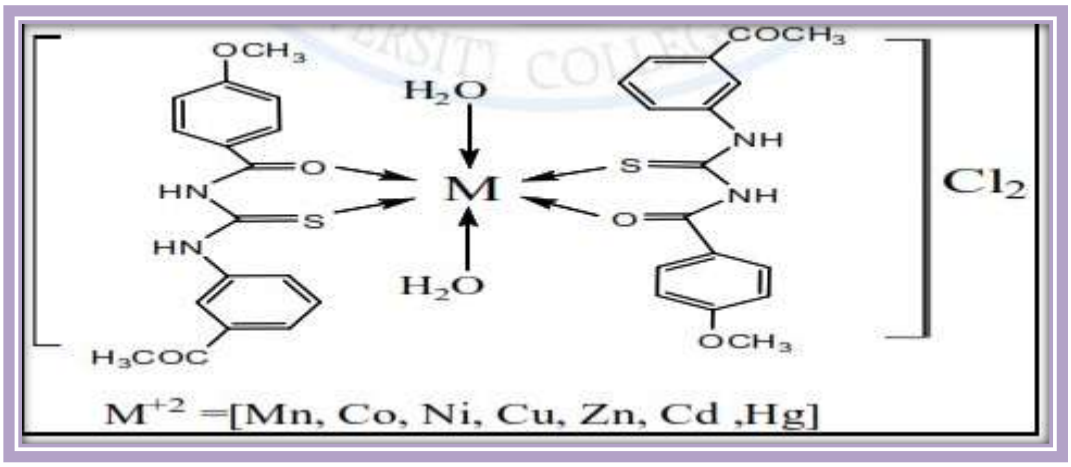


Schem Scheme (1.4):Synthesis of bisindolylindeno[1,2-b] quinoxaline derivatives

Sarhan B. M. *et al.* (2016) synthesized a new ligand *[N-(3-acetylphenylcarbamothioyl)-4-methoxybenzamide]* via the reaction of *4-methoxybenzoylisothiocyanate* with *3-aminoacetophenone* as illustrated in the Scheme (1.5). The results indicated that the proposed structure for all complexes was octahedral**[15]**.As illustrated in the Figure(1.1)



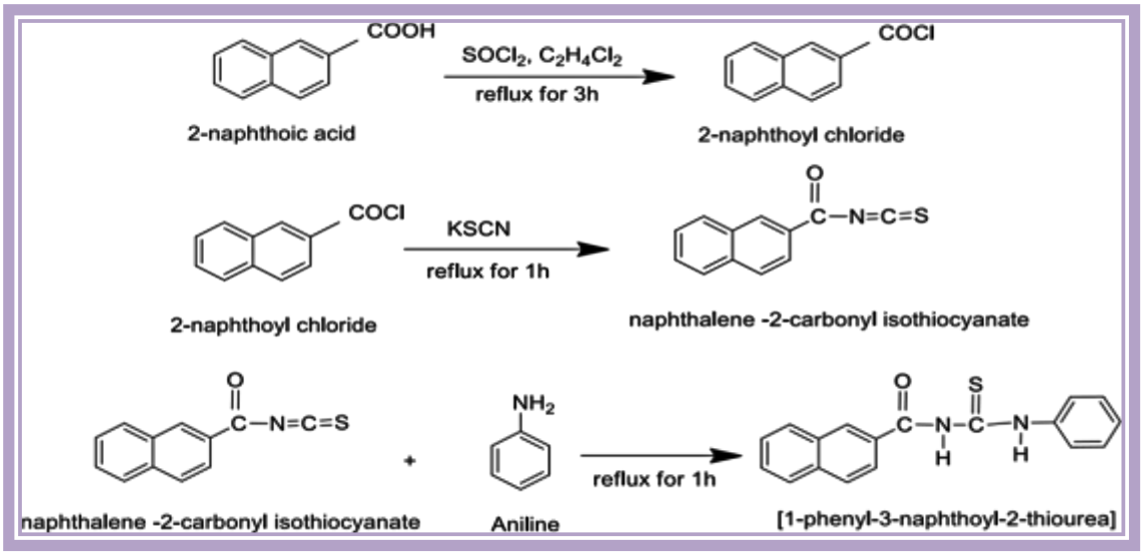
Scheme(1.5): synthesis [N-(3-acetylphenylcarbamothioyl)-4-methoxy benzamide]



Figure(1.1): The proposed structure formula of the complexes

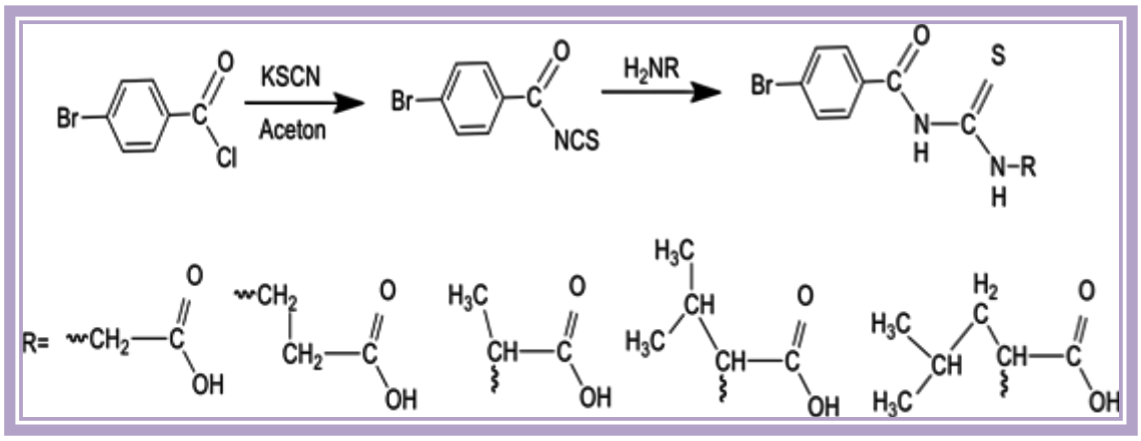
Ahmed N. K. *et al*. (2016) prepared the ligand [*1-phenyl-3naphthoyl-2-thiourea*] by three steps, the first steep preparation of *2naphthoyl chloride*, the second step preparation of *naphthalene -2carbonyl isothiocyanate* and the third step including reaction of *naphthalene -2-carbonyl isothiocyanate* with *aniline*.The suggested geometry of all complexes was octahedral.The

antibacterial activity *in-vitro* was scrutinized for the compounds against three types of pathogenic bacteria: ***Bacillus*** and ***Staphylococcusaureus*** as gram-positive and ***Escherichia Coli***as gramnegative. The synthesized compounds were active against ***Bacillus*** as gram-positive only**[16]**.As illustrated in the Scheme (1.6)



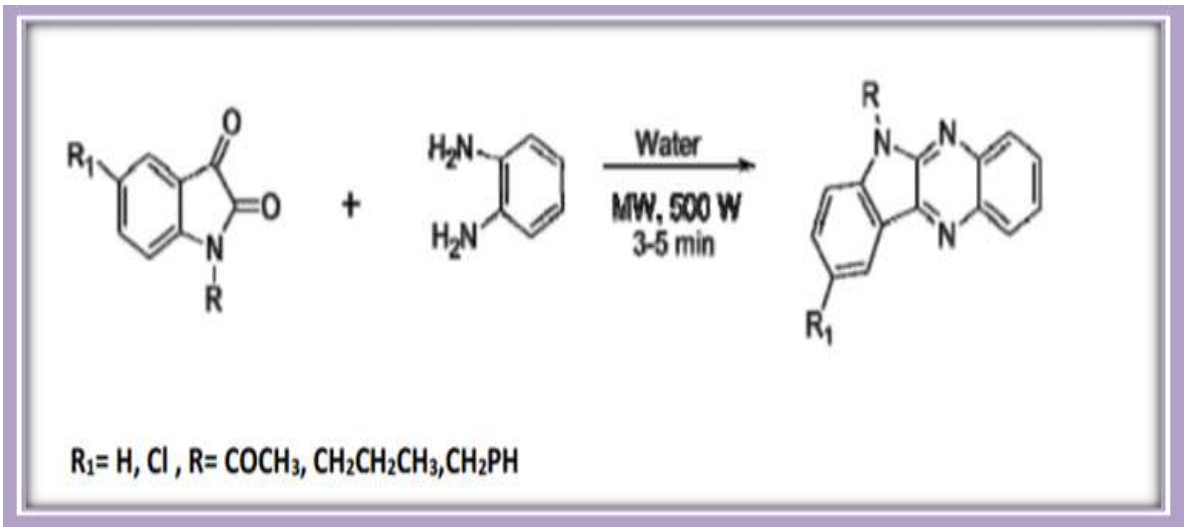
Scheme(1.6): synthesis [1-phenyl-3-naphthoyl-2-thiourea]

Raheel A. *et al*. (2016) Synthesized five new *bromobenzoyl thiourea* derivatives attached with *unlike amino acids* through the reaction of *bromobenzoyl chloride* with *potassium thiocyanide* and the corresponding amines .These compounds were tested for antibacterial and antifungal activity against different types of bacteria and fungi **[17]**. As illustrated in the Scheme (1.7)



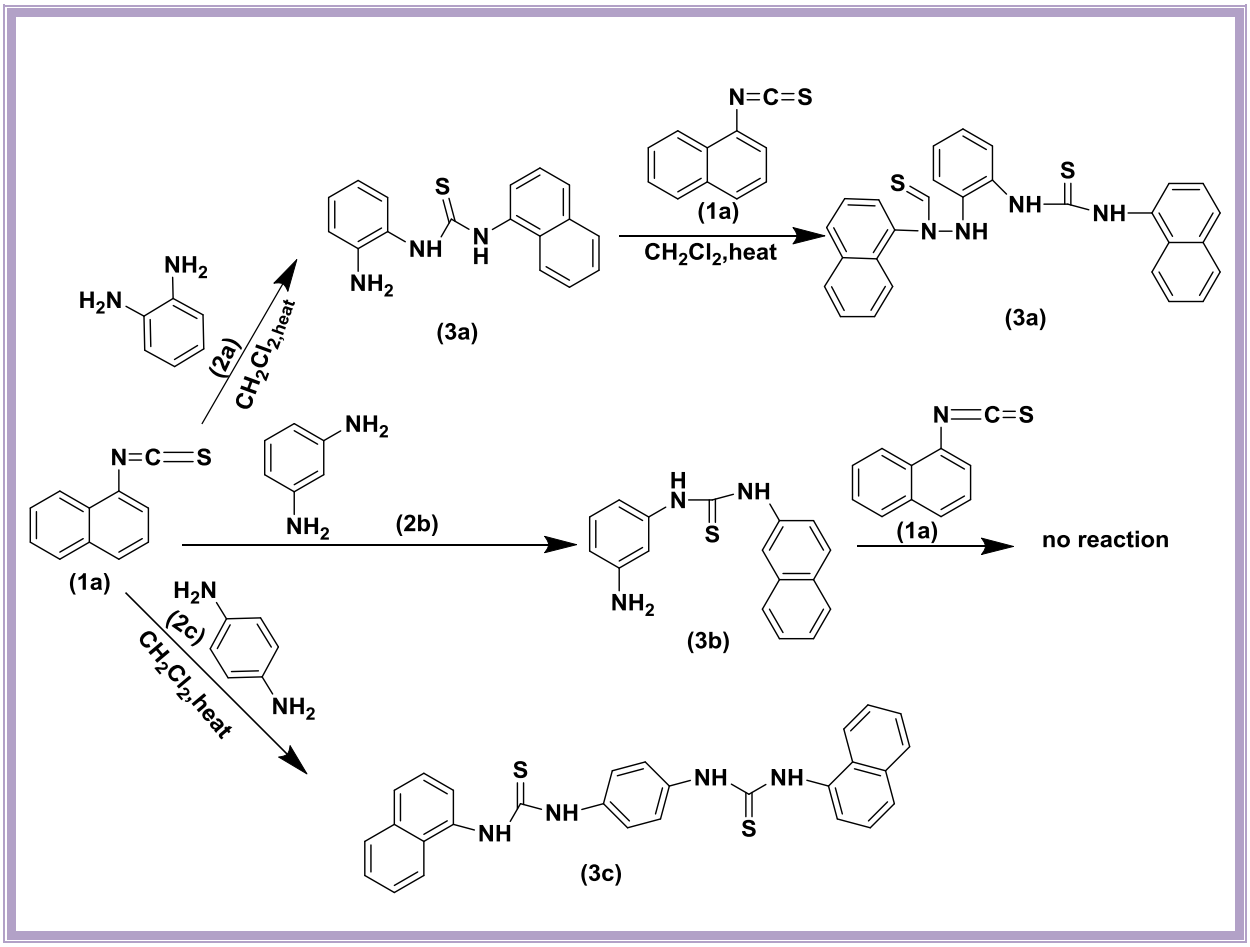
Scheme(1.7): synthesis bromobenzoyl thiourea and amino acids derivatives

Bajpai S. *et al*.(2017) used *isatin* derivatives with *o-phenylene diamine* for the synthesis of *quinoxaline* derivatives under microwave irradiation in xylene. The method given is mild, environmentally friendly, inexpensive and highly effective to give the products in good to excellent yields **[18].** As illustrate in Scheme(1.8)



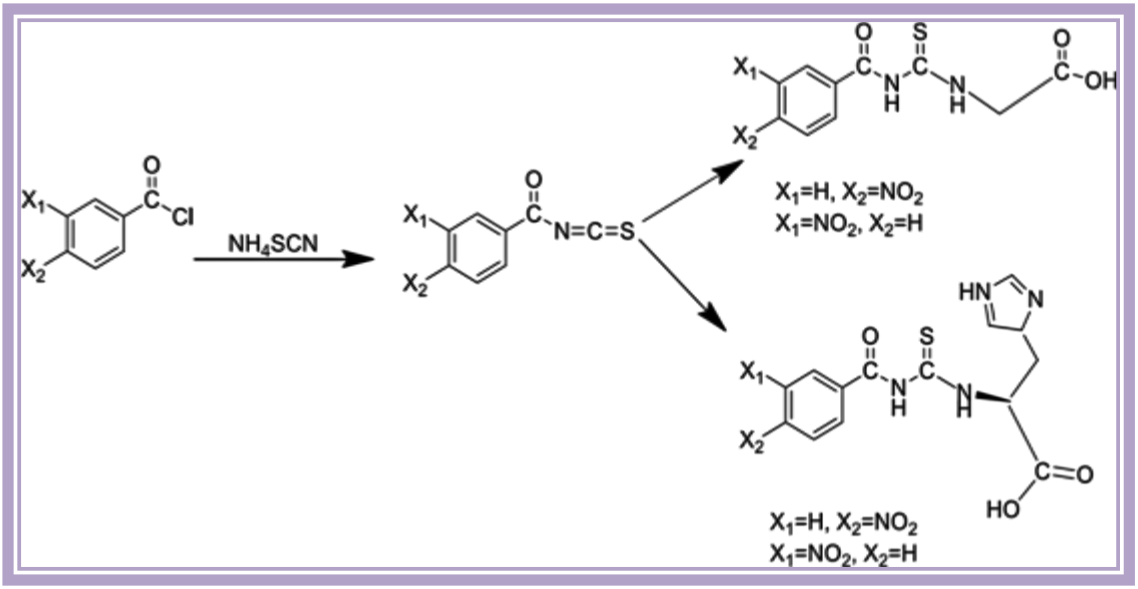
Scheme(1.8): Synthesis of quinoxaline derivatives under controlled microwave irradiation

Ngah F. A. A. *et al.* (2017) synthesized *a new thiourea derivatives 1-(2-aminophenyl)-3-(naphthlene-1-yl)thiourea,N-(2-aminophenyl)-N-(1-naphthalenyl)thiourea,1-(3-aminophenyl)-3-(naphthalene-1yl)thiourea, and 1,4-phenylene-bis[3-(α-naphthyl) thiourea]* by the reaction of *1-naphthyl isothiocyanate* with *1,2-phenylenediamine,1,3- phenylenediamine and 1,4-phenylenediamine***[19]**. As illustrated in the Scheme (1.9)



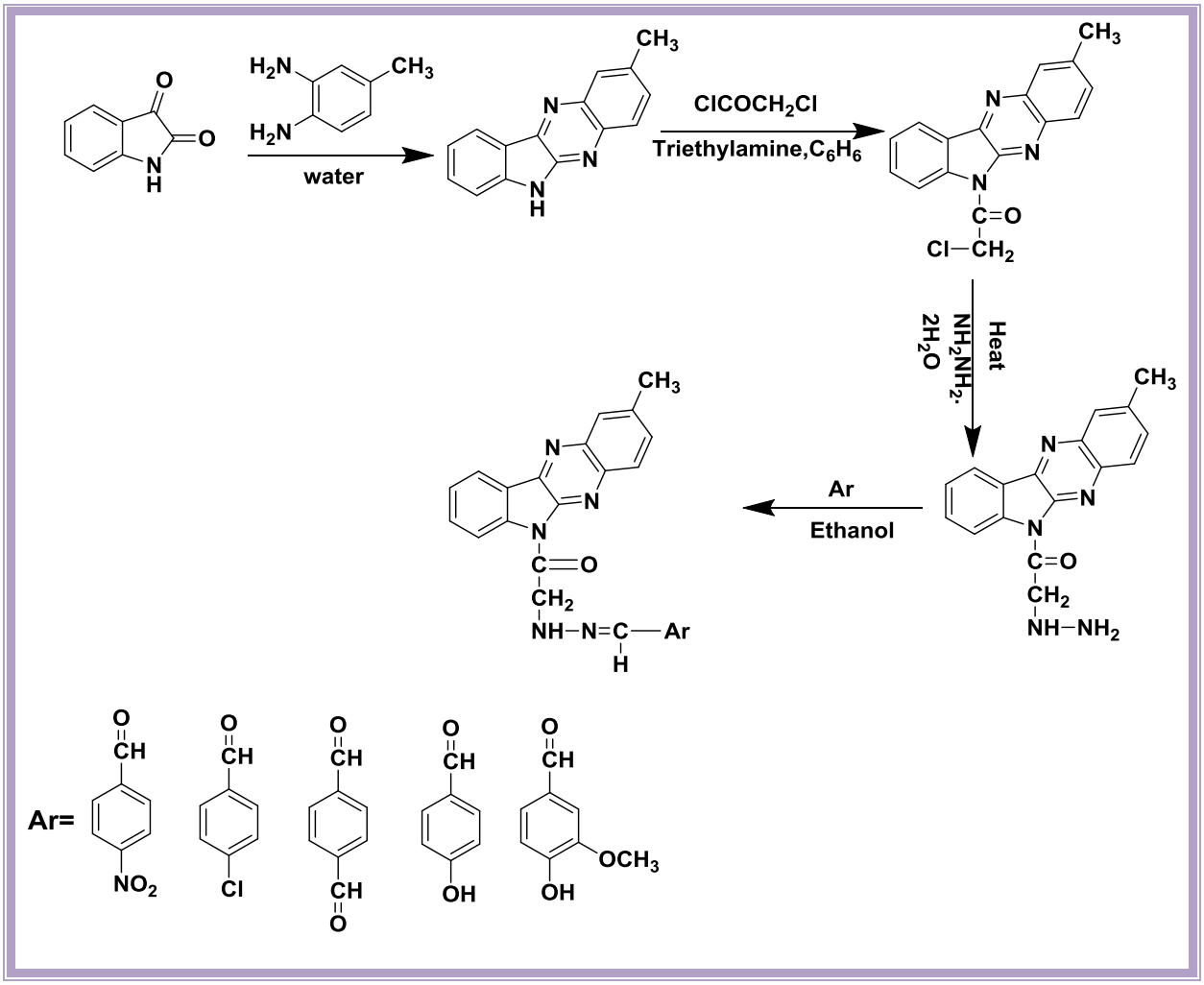
Scheme(1.9): synthesis of thiourea derivatives

Fayomi O. M. *et al.* (2018) synthesized a series of *nitrosubstituted N-(benzoylcarbamothioyl)-amino acids* by condensing *3-* or *4-nitro-benzoyl isothiocyanate* with *amino acids* (*glycine and histidine*). N-(3-nitro-benzoylcarbamothioyl)-glycine.The precursor antibacterial experiments of the compounds have good activity**[20]**. As illustrated in the Scheme(1.10)



Scheme(1.10):synthesis a series of nitro-substitutedN- (benzoylcarbamothioyl)amino acids

Ismail K. A. *et al*.(2020) prepared *2-methyl-6H-indolo [2,3-b] quinoxaline* through the reaction of *isatin* with *4-methyl-o-phenylene diamine*, and the product was reacted with *chloroacetyl chloride* to produce *2-chloro-1-(2-methyl- indolo [2,3-b] quinoxalin-6-yl)ethanone*, which was treated with *hydrazine hydrate* to give *2hydrazino-1-(2-methyl-indolo[2,3-b]quinoxalin-6-yl)-ethanone*. The Schiff bases were synthesized by the condensation of compounds *2hydrazino-1-(2-methyl-indolo[2,3-b]quinoxalin-6-yl)-ethanone* with *many aromatic aldehydes* .Antifungal activity of prepared compounds was studied**[21].** As illustrated in the Scheme(1.11)



Scheme(1.11) : synthesis of indolo [2,3-b] quinoxaline derivatives

1.3. The aim of the study

The major objectives of the present study are :

1. Synthesize a new chain of quinoxaline derivatives and quinoxaline complexes.
2. Characterization of the synthesized quinoxaline derivatives by was a chived by (FT-IR and ^{1}H- NMR^{13}C-NMR) spectroscopy.
3. Characterization of the quinoxaline complexes by using FT-IR, UV-Vis spectroscopy, metal analysis, magnetic susceptibility, and conductivity measurements.
4. Finally,measure the biological activity of some of the prepared compounds and determine their efficacy against bacteria of both positive and negative gram kinds.

Chapter Two

(Theoretical Part)

2.1. Heterocyclic compounds.

Heterocyclic compounds in which one or more of the ring atoms are different atom other than carbon are called heterocyclic compounds. The heteroatom is a Greek word which means different **[22-25]**. Common rings of five-membered heterocyclic compounds containing a single heteroatom are 1H-pyrrole, thiophene, and furan. As shown in Figure (2.1)

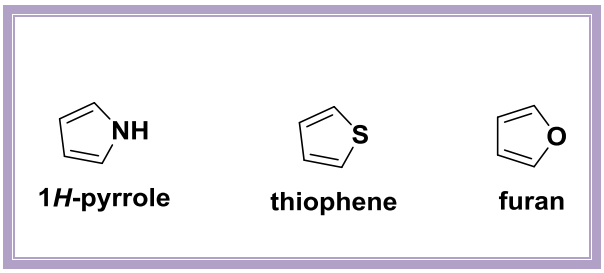


Figure (2.1): The chemical structures of 1H-pyrrole, thiophene, and furan.

While five-membered rings containing two heteroatoms (same kind of atoms) are pyrazoline and pyrazole Figure (2.2).

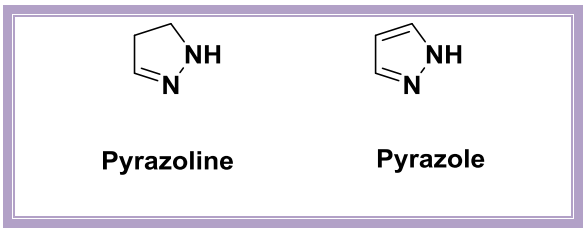


Figure (2. 2): The chemical structures of pyrazoline and pyrazole

Five-membered rings contain two or three heteroatoms (different kind of atoms) such as oxazole, thiazole, isoxazole and isothiazole, etc**[26-29]**. Figure (2.3)

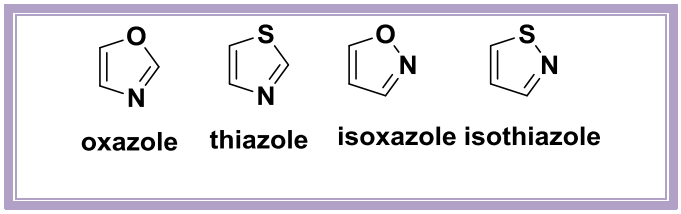


Figure (2.3): The chemical structures of oxazole, thiazole, isoxazole, and isothiazole.

Most of medications and physiologically active agrochemicals are heterocyclic, as are several additives and modifiers used in industrial applications such as cosmetics, reprography, plastics and data storage **[30-31]**. The ability of heterocycles to express substituents around a core scaffold in defined three-dimensional representations is a striking structural property intrinsic to heterocycles that the pharma industry continues to exploit to great effect. Throughout the decades of historical development of organic synthesis, nitrogen and sulfur-containing heterocyclic molecules have piqued chemists' curiosity **[32]**.

Five and six-membered heterocyclic are abundant in nature and great significance to life because of many natural products contains many subunits in their structure such as hormones, vitamins, and antibiotics. Therefore, they have attracted significant attention in the composition of many important biological molecules. Synthetic organic chemistry is a very interesting in finding a feasible way for making these molecules. Among the all heterocyclic, pyrazole and pyrazoline are a class of compounds with biological activities, such as antioxidant, antitumor, antipyretic , antimicrobial, and calcium channel modulators **[33]**. Heterocyclic compounds include more than one nitrogen atom have great biological activity that have piqued the interest of many researchers over time. Because of their anti-cancer**[34]**, cardiotonic, and anti-inflammatory characteristics**[35]**, these chemicals, like those from the benzodiazepine family, have been widely used as therapeutic agents **[36]**.

2.2. Indole.

Indole is an example of an aromatic heterocyclic organic compound **[37-38]**. A six-membered benzene ring is fused to a five-membered nitrogen-containing pyrrole ring Figure (2. 4), Knop and Baeyer published their work in

1866**[39]**. In the course of a study of the structure of indigo, reduced isatin and obtained two products, C_8H_7NO and $C_8H_7NO_2$ (oxindole and dioxindole), which they considered as hydroxyl derivatives of C_8H_7N; they named the latter indole. Baeyer and Emmerling continued the work, proposing the formula that is now widely recognized in 1869**[40]**.

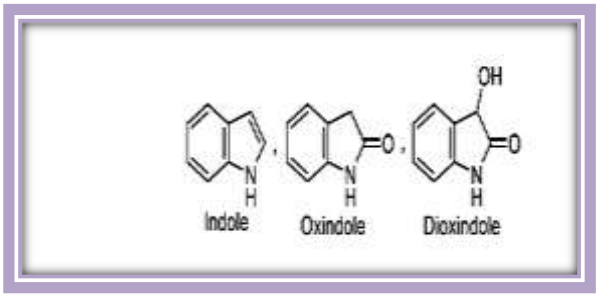


Figure (2. 4): The chemical structure of indole, oxindole, and dioxindole.

Indole chemistry began to develop with the study of the dye indigo. Indigo, a blue dye imported from India, is the source of the word indole. Indigo can be turned to isatin and then to oxindole. In 1866, Adolf von Baeyer used zinc dust to convert oxindole to indole. In 1869, he proposed an indole formula. **[41]**. The indole alkaloids are a class of chemical compounds with an indole or dihydroindole (Indoline) nucleus that exist naturally. Approximately 800 indole alkaloids have been isolated to date, with the majority of their structures known. This amount number to nearly one-fifth of all the known nitrogen containing plant bases (alkaloids). The first discoveries of indole alkaloids were the results of chemical studies on folk medicines or crude drugs used in various parts of the world, such as, Europe countries, India, and Japan. This approach proved to be a very effective one for natural product chemists. They includes such physiologically active compounds as strychnine**[42]**.

2.3.Isatin

Isatin, also known as indoline-2,3-dione **[43]** or indole-1H-2,3-dione **[44]**, is an indole derivative with keto (C=O) groups at positions 2 and 3 of the ring **[45-46]**. As shown in Figure (1.3). Isatin ring system consists of pyrrole ring fused with benzene ring **[47]**. which can be found in a variety of plants **[48]**. It was found 150 years ago [49] and is currently referred to as oxindole and Endogenous polyfunctional heterocyclic compounds **[50]**. Erdman **[51]** and Laurent **[52]** discovered the chemical in 1841 as a byproduct of the oxidation of indigo dye with nitric acid and chromic acide **[53-54]**.

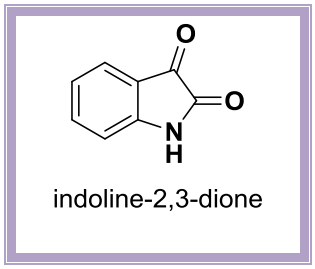


Figure (2.5): 1H-Indole-2,3-dione

Isatins are synthetically versatile substrates that may be utilized to make a variety of heterocyclic compounds like indoles and quinolines **[55]**. Previously, the study of isatin derivatives was linked to dye synthesis, but more recently, these heterocycles have been shown to have antiprotozoal **[56]**, antifungal **[57-58]**, antiviral **[59-60]**, anticonvulsant **[61]**, anti-inflammatory **[62-63]**, anti-tubercular **[64-65]**, antitumor **[66-67]**, antimicrobial **[68]**, antimalarial **[69]**, antihelminthic **[70]** and anti-Furthermore, they have an impact on neurological illnesses, participate in metabolism, act as acetylcholinesterase inhibitors, and encourage plant development **[71]**.Drugs containing the isatin skeleton are used to treat diseases such as eplilepsy , and bulimia . Therefore the need to create novel isatin derivatives for emerging drug targets is apromising area in medical chemistry **[72]**. Isatin is an endogenous compound identified in humans that possesses a wide range of biological activities **[73-74]**. Isatin has anticonvulsant activities and acts as a potent antagonist on a trial natriuretic peptide receptors in vitro Recently, a number of researchers have been studying the use of isatin in the fight against phytopathogens and as potential herbicides **[75]** .

2.3.1 Study of the reactivity of isatin

Isatin will mainly react at three different sites, N-alkylation, namely aromatic substitution at C-5, and carbonyl reactions at C-3. If the system carry electron-withdrawing groups in the benzene ring or at the nitrogen attack at C-2 can also occur**[76]**. As illustrate in Figure(1.4)

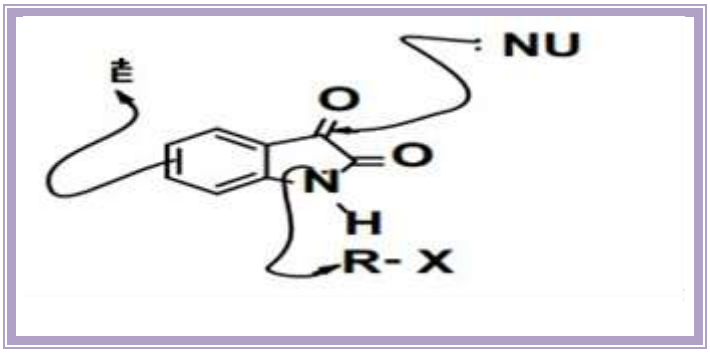


Figure (2.6): Reactivity of isatin

2.3.2 Application of Isatins in Organic Synthesis

Many synthetic **[77]** methodologies have been described for the conversion of isatins to other heterocyclic systems. This type of chemistry can be generalized as one of the following strategies:

-Partial or total reduction of the heterocyclic ring, leading to indoles and derivatives.

-Oxydation reaction .

-Nucleophilic addition at position C-3, which may be further followed by a cyclization process.

-Nucleophilic substitution at position C-2, leading to the opening of the heterocyclic.

2.4. Quinoxaline.

Quinoxaline 1 is a nitrogen-containing benzoheterocycle with antitumor, antibacterial, antiviral, anticonvulsant, antifungal, antimicrobial, anticancer, antitubercular, antimalarial, and anti-inflammatory properties **[78]**.Quinoxaline derivatives are used in Pesticides, fungicides, herbicides, anthelmintics, and other applications include dyes, fluorescent materials, semiconductors in organic photovoltaic (OPV) cells, pesticides, fungicides, herbicides, and anthelmintics. **[79]**. Quinoxaline, also known as benzopyazine, is a fused heterocyclic molecule with benzene and pyrazine rings fused together. Phthalazines 2, quinoazoline 3, and cinnolenes are isomeric with quinoxline. The fusion of the diazine 5 and benzene 6 rings produces quinoxaline **[80]**. Figure(2.9) explain structures of quinoxaline and related heterocycles compounds.

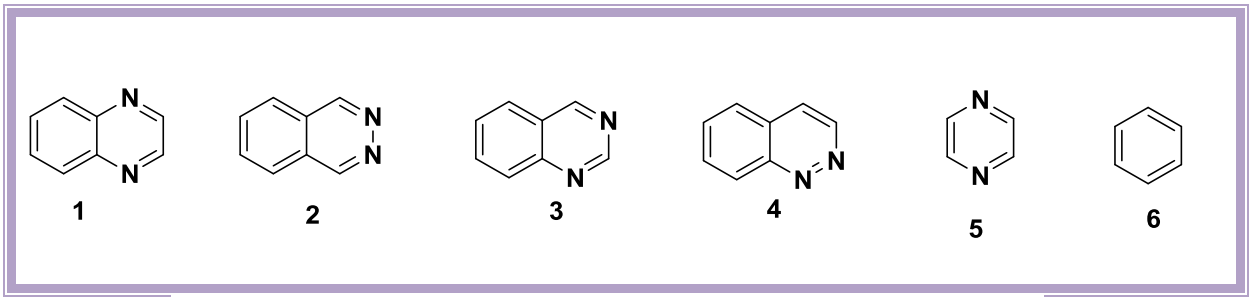


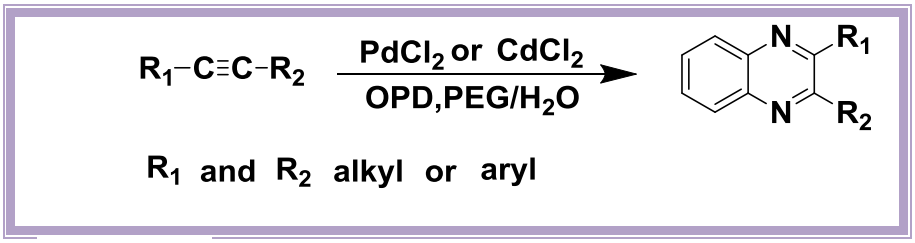
Figure (2.7): Structures of quinoxaline and related heterocycles.

Quinnoxaline is also known as benzopyrazine and diazanaphthalene.The number of resonance structures of quinoxaline are increased by the fusion of one or more benzene rings to quinoxaline and phenazine rings and the dipole moment of quinoxaline is zero**[81]** .

2.4.1. Synthesis of quinoxaline derivatives

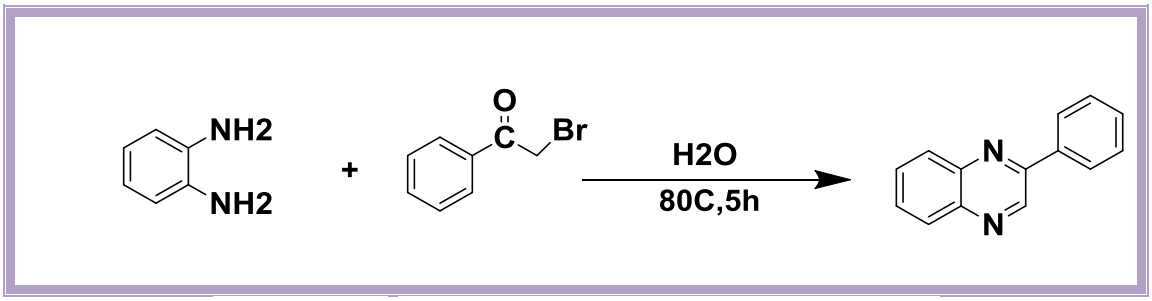
2.4.1.1. Synthesis of quinoxaline derivatives by catalytic strategies

Alkynes can be oxidized with *O-phenylene diamine (OPD)* in the presence of a catalyst to produce substituted *quinoxaline di-ketones* **[82]** . As illustrated in Scheme (2.1)



Scheme (2.1): Synthesis of substituted quinoxaline di-ketones.

On the other hand, *OPD* can react with *2-bromo acetophenone* in *an aqueous medium* for 5 h at 80°C to give quinoxaline derivatives**[83]**. As shown in Scheme (2.2)

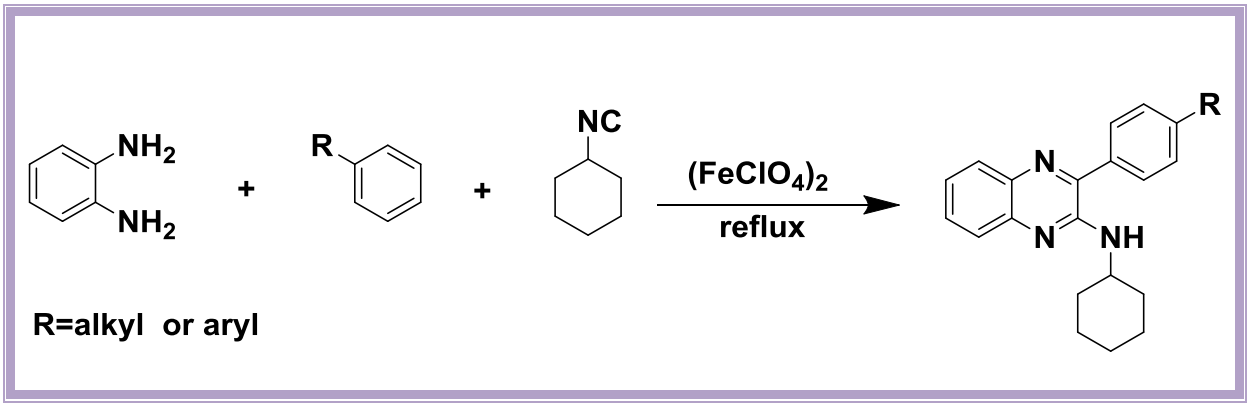


Scheme (2.2): Preparation of quinoxaline derivatives.

Another method to acquire substituted quinoxaline derivatives. This method was to react substituted *OPD* with *di-ketone* with the existence of *dimethyl sulfoxide (DMSO)* as a solvent and catalyst at room temperature**[84].** As illustrated in Scheme (2.3)

Scheme (2.3): Preparation of substituted quinoxaline derivatives from di-ketone.

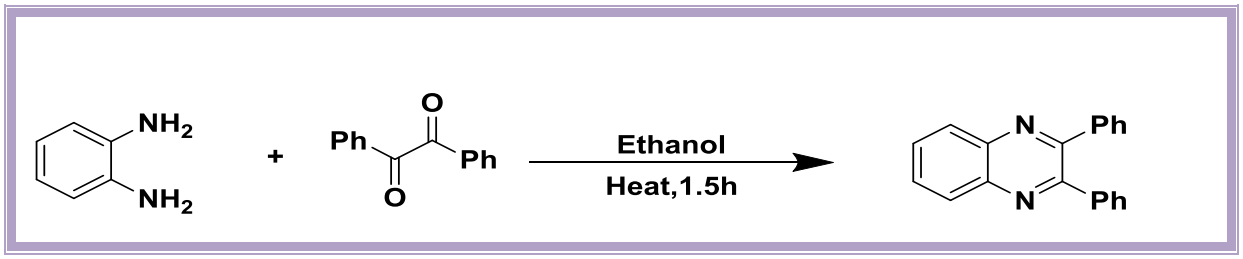
Also can be synthesized *N-Cyclohexyl-3-aryl-quinoxaline-2-amines* in good yields via the condensation reaction of *o-phenylene diamine* , *aldehyde* and *cyclohexyl isocyanide* **[85]**. As shown in Scheme (2.4)



Scheme (2.4): Synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines.

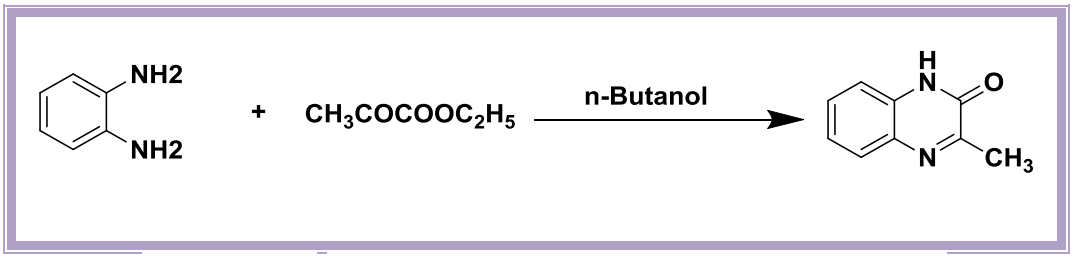
2.4.1.2. Synthesis of quinoxaline derivatives by non-catalytic strategies

The reaction of *O-phenylene diamine* with *benzil* in *ethanol* and heating for 1.5 hours can produce *2,3-diphenyl quinoxaline (DPQ)* **[86]**. As illustrated in the Scheme (2.5)



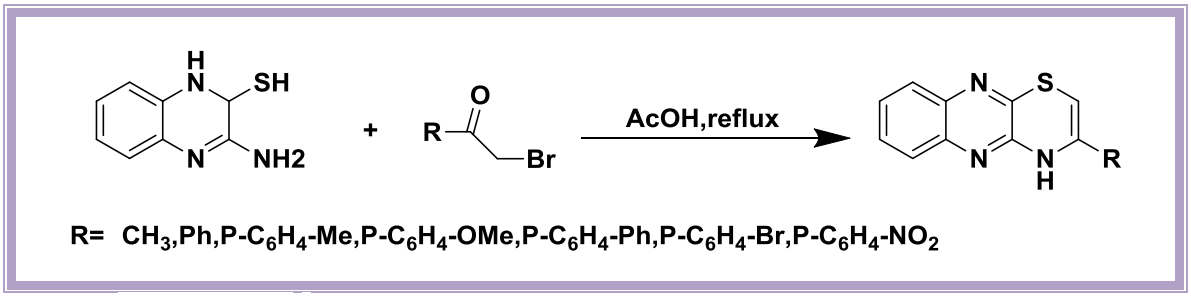
Scheme (2.5): Synthesis of (DPQ)

Also *O-phenylene diamine* can be reacted with *ethyl pyruvate* to produced *2-Hydroxy-3-methylquinoxaline* in *n-butanol***[87]**. As illustrated in the Scheme (2.6)



Scheme (2.6): Synthesis of 2-hydroxy-3-methylquinoxaline.

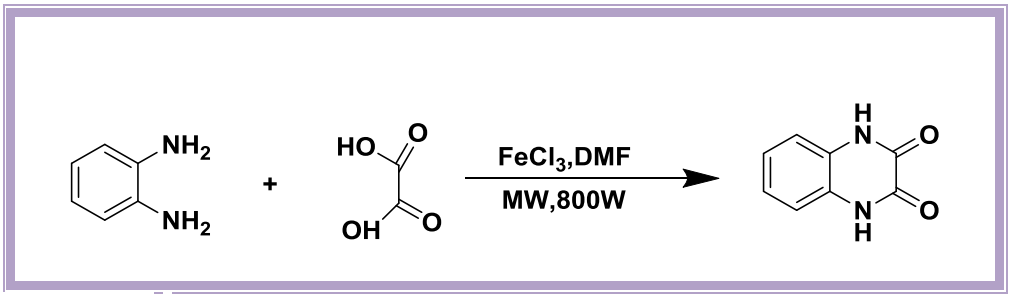
As well as that, quinoxaline derivatives can be synthesized from the reaction *α-haloketones* with *2-amino-3-quinoxalinethiol* in *glacial acetic acid* .The reaction mixture was heated to reflux and product was acquired after recrystallization in ethanol **[88]**. As shown in Scheme(2.7)



Scheme (2.7): Reaction of 2-amino-3-quinoxalinethiol with α-haloketones

2.4.1.3. Synthesis of quinoxaline derivatives using microwave radiation

Quinoxaline derivative can be synthesized by the reaction of *OPD* with *oxalic acid* in the existence of (*DMF*) and *iron(III) chloride* . The reaction mixture was heated in the microwave **[89]**. And Scheme (2.8) shown that



Scheme (2.8): Synthesis derivatives of quinoxaline using the microwave method

2.5. Thiourea and its derivatives .

Thiourea (TU) is the analogue compound to urea with replacement of oxygen atom in urea by sulphur atom, the properties of urea and thiourea differ significantly because of the difference in electronegativity between sulfur and oxygen atoms**[90]**. The name thiourea according to IUPAC system is 2-thiourea; also known as thiocarbamide or sulfaurea. Thiourea (CH_4N_2S) is a white crystalline solid and occurs in two tautomeric forms as shown in Figure (2.10).

Figure (2.10): The tautomeric forms of thiourea

Therefor it has three functional groups: amino, imino, and thiol**[91]** . Due to its wide range of applications in sectors such as medicine, agriculture, coordination, and analytical chemistry. Thiourea and its derivatives are a well-known important category of organic compounds**[92]**. Thioureas are useful compounds as precursors for the synthesis of different classes of a cyclic and heterocyclic compounds**[93]**. Thiourea and urea derivatives have been used to purify organic and inorganic effluents, industrial, agricultural, and mining wastes, spinning mixtures, paper, and paints, as well as wrinkle proofing agents for cotton and cotton polyester fabrics, where these compounds could also be used to detoxify super antigens from body fluids**[94]**.

Chapter Three

(Experimental Part)

3.1. Chemicals

As mentioned in Table (3.1), the chemicals, solvents utilized in this research and their supplies are listed. These materials have not been purified or modified in any way.

Table 3.1: Chemicals and solvents used

No.	Chemicals	Chemical formula	Supplied from	Purity %
1	Aceton	$(CH_3)_2CO$	Alpha	99.9
2	1,2-dichloro ethane	$C_2H_4Cl_2$	Alpha	99
3	1-Isocyanatonaphthalene	$C_{11}H_7NO$	Aldrich	98
4	Isothiocyanatobenzene	C_7H_5NO	Merck	97
5	Cobalt chloride hexahydrate	$CoCl_2.6H_2O$	Aldrich	96
6	Cupric chloride dehydrate	$CuCl_2.2H_2O$	ACS	99
7	3,4-Diaminobenzoic acid	$C_7H_8N_2O_2$	Aldrich	97
8	Thionyl chloride	$SOCl_2$	BDH	95
9	Aniline	C_6H_7N	Thomas Baker	98
10	Dimethyl sulfoxide (DMSO)	$C_2H_6SO.$	BDH	98
11	Ethanol	C_2H_6O	Scharlu	99.9
12	Ethylacetate	$C_4H_8O_2$	Aldrich	99
13	Potassium hydroxide	KOH	BDH	99.9
14	Hexane	C_6H_{14}	BDH	99
15	Isatin	$C_8H_5NO_2$	Aldrich	99
16	Potassium thiocyanate	KSCN	Alpha	98
17	Nickel chloride hexahydrate	$NiCl_2.6H2O$	CDH	99
18	2-Amino phenol	C_6H_7NO	Aldrich	98
19	Potassium carbonate	K_2CO_3	BDH	96
20	Sodium bicarbonate	$NaHCO_3$	BDH	96
21	Cdmium chloride monohydrate	$CdCl_2.H_2O$	Merck	98
22	Zinc chloride anhydrous	$ZnCl_2$	SCRC	99.9
23	Methanol	CH_3OH	Scharlu	98
24	4-amino phenol	C_6H_7NO	Alpha	95
25	1H-indene-1,2,3-trion .H_2O	$C_9H_4O_3.H_2O$	BDH	99
26	4-Methyl benzene-1,2-diamine	$C_7H_{10}N_2$	Merck	97
27	4-Methoxyaniline	C_7H_9NO	Hopkin &willia	95
28	4-Bromo aniline	C_6H_6NBr	Merck	96

3. 2. Instruments

-FT-IR Spectra: Infrared spectra of the prepared compounds were recorded in (KBr) disc by using PERKIN ELMER SPEACTRUM-65 / Germany at Chemistry Department, College of Science, Diyala University and FT-IR Spectra: Infrared spectra of the prepared complexes were recorded in (CsI) disc by using Shimadzu FT-IR spectrophotometer at the Chemistry department / College of education for pure science/ University of Diyala.

-Ultraviolet Cabinet: Thin Layer Chromatography (TLC) 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

-Melting Points: The melting points of the compounds and the metal-complexes was determined by open capillary tube in the Stuartsmplo electronic apparatus, at the Department of Chemistry, College of Science, University of Diyala.

-Antibacterial Activity: The antibacterial activity of compound was evaluated in the laboratory of General Baquba Hospital .

-Nuclear Magnetic Resonance Spectrometer (NMR): ^{1}H NMR the spectra were recorded on a Bruke 400 MHz spectrometer in Jordan, University of Science and Technology, College of Science, Tehran, Iran.

-Electronic Spectra (UV-Vis): The electronic spectra of the ligand and its complexes were obtained by using UV-Vis (V-650) JAPAN spectrophotometer type Cary 100 at range (800-200) nm, with quartz cell of (1.0 cm) length and the concentration of (1×10^{-3} M), at Department of Chemistry, College of Science, University of Diyala.

-Atomic Absorption: The metals percentage of the complexes was measured using atomic absorption technique by Shimadzu Atomic Absorption 680 Flam Spectrophotometer for the determination of (Ni^{2+}, Cu^{2+}, Zn^{2+}, and Cd^{2+}) metal ions.

- Conductivity measurements: Electrical measurements conductivity (Λm) of the complexes were registered at (25ºC) for (0.001 Molar) solution of the samples in **Ethanol** by using (conductivity meter, inolab / Germany) at Chemistry Department ,College of Science , University of Diyala and the determination of cell constant was made using the following relationship:

$$[\Lambda_m = 1000k/c]$$

Where, (Λm) =molar conductance (Ω^{-1} cm^2 mol^{-1}), (C)= concentration (mol^{-1}) and (K)= specific conductance (Ω cm^{-1}).

-Magnetic Susceptibility: The magnetic susceptibility in the complexes was measured by using (Balance Johnson Mattey). The μeff was determined in the solid state by Faraday's method at Department of Chemistry , College of Science , Mustansiriyah University. Using only spin magnetic moment according to the following equation.

$$\mu eff = 2.82 \sqrt{\mathbf{X_{A.}\,T}}\ \text{B.M}$$

XA = X M-(-D)

XM = Xg *M.Wt

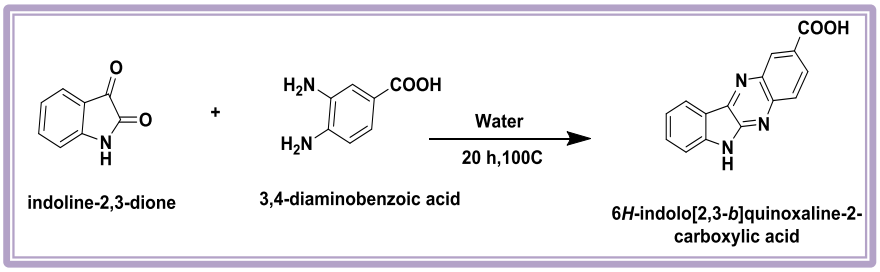
Where, T= Room temperature in degree K, XA= Atomic susceptibility,

XM = Molar susceptibility, Xg = Gramic susceptibility, D = Diamagnetic correction factor.

3. 3. Synthetic methods of the compounds[95-97]

3. 3. 1. Synthesis of 6H-indolo[2,3-b]quinoxaline-2-carboxylic acid (Z_1)

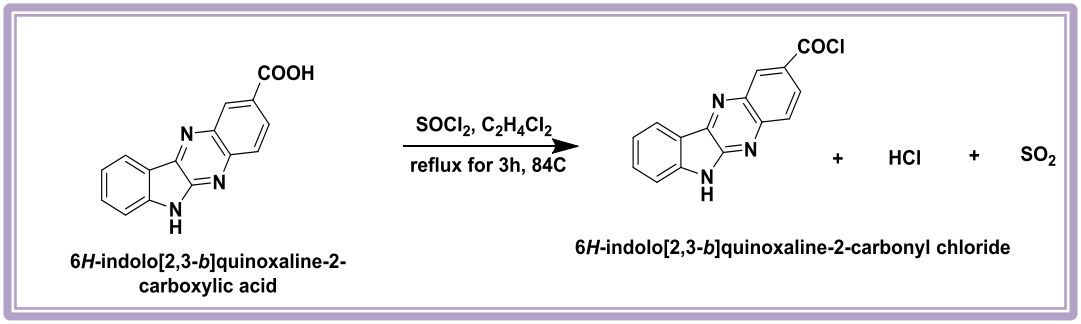
Indoline-2,3-dione (1.70 gm , 11.6 m mol) was dissolved in aqueous sodium bicarbonate solution (3.32 gm, 39.5mmol in 160 ml water), 3,4-diamino benzoic acid (2.20 gm , 13.2 mmol) was added and the mixture was refluxed for (20 h) . The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3). After cooling down to the room temperature the solutions was acidified with acetic acid and left to stay overnight .The precipitate was filter, washed with water and dried in air .The physical properties of compound are listed in Table (4.3). Scheme (3.1) demonstrate the synthetic path way of (Z_1)



Scheme (3.1): The synthetic pathway of (Z_1).

3. 3. 2. Synthesis of 6H-indolo[2,3-b]quinoxaline-2-carbonyl chloride (Z_2)

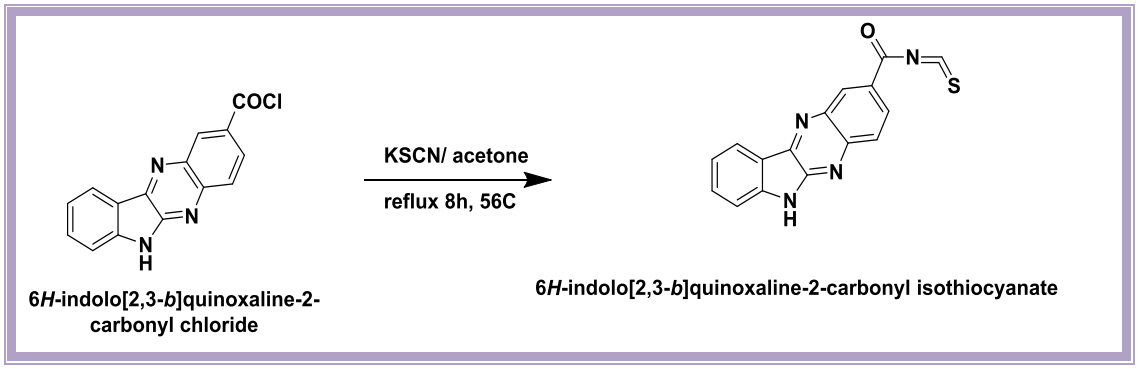
A thionyl chloride (0.7 ml,10 mmol) was added to the solution of 6H-indol[1,3-b] quinoxaline - 2 carboxylic acid (1.316 gm, 4.99 mmol) in anhydride 1.2-dichloroethane (11 ml). In around bottom flask equipped with condense -and-drying tube the mixture is refluxed for (3h). The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3). The solvent and the excess thionyl chloride are removed under vacuum distillation**.** The reaction was shown in Scheme (3.2) and the physical properties of compound are registered in Table (4.3).



Scheme (3.2): The synthetic pathway of (Z_2)

3.3.3. Synthesis of 6H-indolo[2,3-b]quinoxaline-2-carbonyl isothiocyanate (Z_3).

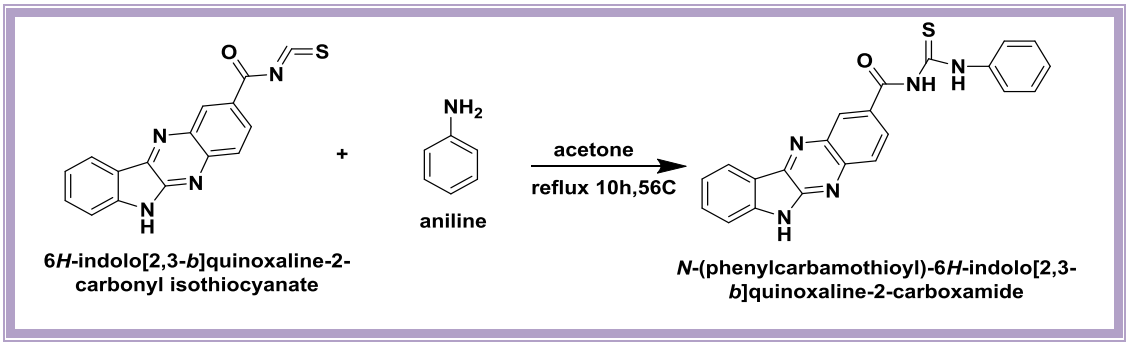
6Hindolo [2,3-b] quinaxaline-2- carbonyl chloride (0.6 gm, 2.129 mmole) was dissolved in acetone (15 ml) which added to a solution of potassium thiocyanate (0.2 gm, 2.05 mmole) in dry acetone (10 ml). The reaction mixture was refluxed for (8h) around bottom flask equipped with condenser and drying tube. The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3). The product was filtered washed in the acetone and left over night in the desiccator that contain silica gel. The reaction was shown in Scheme (3.3) and the physical properties of compound are registered in Table (4.3).



Scheme (3.3): The synthetic pathway of (Z_3)

3. 3. 4. Synthesis of N-(phenylcarbamothioyl)-6H-indolo[2,3-b] quinoxaline-2-carboxamide (Z_4).

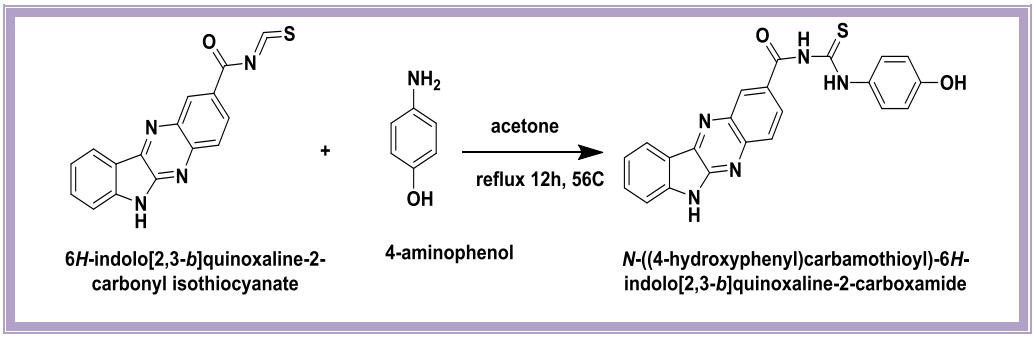
A solution of aniline (0.5 ml ,6 mmole) was dissolved in acetone (10 ml) which was added with stirring to 6H-indolo [2,3-b]quinoxaline - 2-carbonyl isothiocyanate solution (1.825 gm, 5.996 mmole) in (15 ml) of acetone the mixture was heated under reflux for (10 h). The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3) and after wards-foured into (5ml) of cold water. The product was washed in ethanol . The reaction was shown in Scheme(3.4) and Table (4.3) explain the physical properties of this compound.



Scheme (3.4): The synthetic pathway of (Z_4)

3. 3. 5. Synthesis of N-(4-hydroxy phenyl)carbamothioyl-6H-indolo [2,3-b]quinoxaline-2-carboxamide(Z_5).

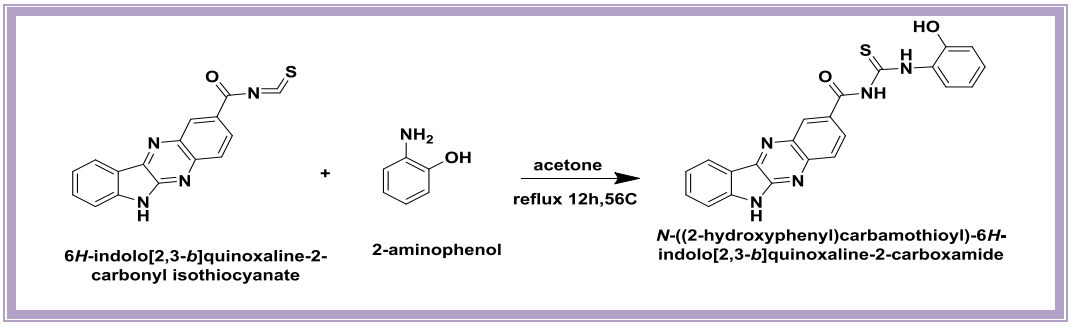
A solution of the 4-aminophenol (0.65gm, 6mmole) was dissolved in acetone (10 ml) which was added with stirring to 6H-indolo[2,3-b]quinoxaline-2-carbonyl isothiocyanate solution (1.826 gm , 6mmole) in (15 ml) of acetone. The mixture was reflux for (12h). The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3) , after wards poured into (5ml) of cold water. The product was washed in ethanol. The reaction was shown in Scheme (3.5) and Table (4.3) explain the physical properties of this compound.



Scheme (3.5): The synthetic pathway of (Z_5)

3. 3. 6. Synthesis of N-(2-hydroxy phenyl)carbamothioyl-6H-indolo [2,3-b]quinoxaline-2-carboxamide (Z_6).

A solution of the 2-aminophenol (0.65 gm, 6 mmol) was dissolve in acetone (10 ml) which was added with stirring to 6H-indolo[2,3-b]quinoxaline-2-carbonyt isothiocyanate solution (1.826 gm, 6mmol) in (15ml) of acetone. The mixture was reflux for (12h) .The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3) and after wards poured into (5ml)of cold water. The product was washed in ethanol . The reaction was shown in Scheme(3.6) and the physical properties of compound are registered in Table (4.3).

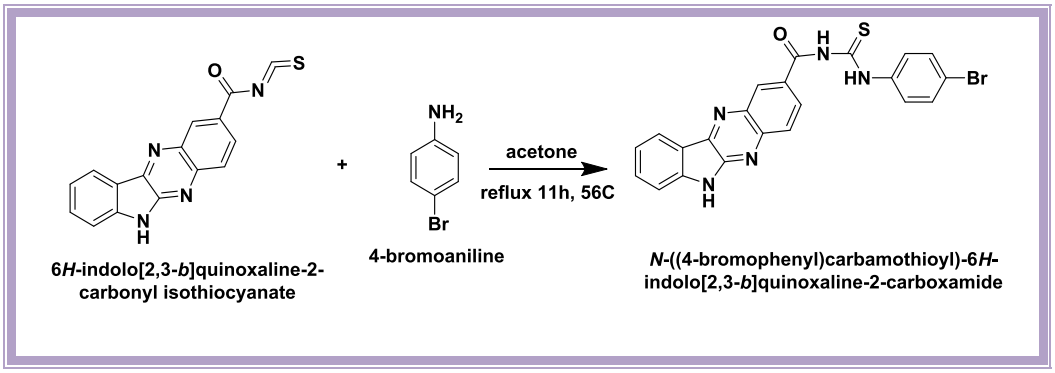


Scheme (3.6): The synthetic pathway of (Z_6)

3. 3. 7. synthesis of N-(4- bromo phenyl) carbamo thioyl-6H-indolo[2,3-b] quinoxaline-2-carboxamide(Z_7).

A solution of 4-bromo aniline (1.03 gm, 6 mmol) was dissolved in acetone (10 ml) which was added with stirring to 6H-indolo[2,3-b]quinoxaline -2-carbonyl isothiocyanate solution (1.826 gm, 6 mmol) in (15 ml) of acetone.

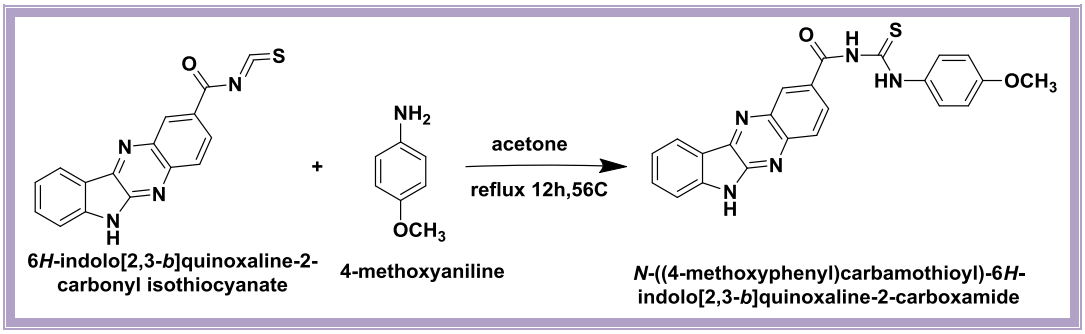
The mixture was reflux for (11 h). The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3) , after words poured into (5ml) of cold water. The product was washed in ethanol. The reaction was shown in Scheme (3.7) and the physical properties of compound are listed in Table (4.3).



Scheme (3.7): The synthetic pathway of (Z_7)

3. 3. 8. Synthesis of N - (4-methoxy Phenyl)carbamo thioyl- 6H- indolo [2,3-b]quinoxaline-2-carboxamide (Z_8).

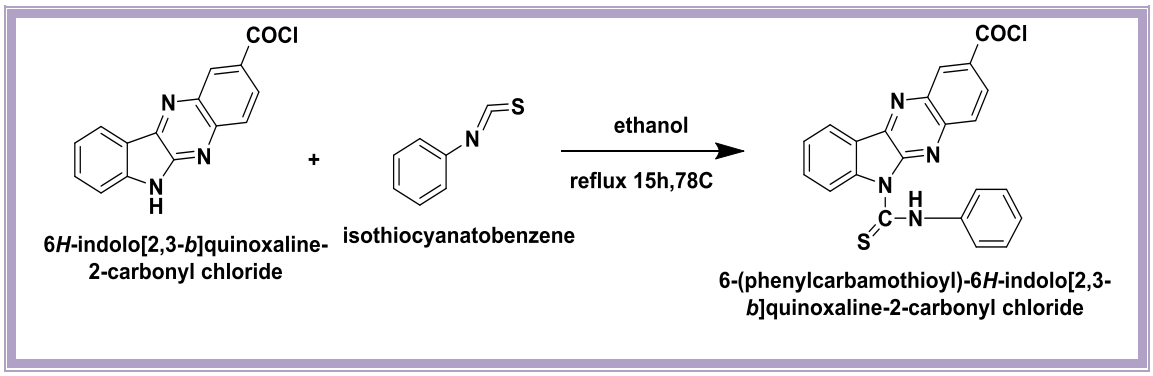
A solution of the 4-methoxy aniline (0.74 gm, 6mmol) in (10 ml) of acetone, was added to solution of 6H-indolo[2,3-b]quinoxaline -2-carbonyl isothiocyanate (1.826 gm, 6mmol) in(15 ml) of acetone .The mixture was reflux for (12 h). The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3). The product was filtered and washed in ethanol. The reaction was shown in Scheme(3.8) and the physical properties of compound are listed in Table (4.3).



Scheme (3.8): The synthetic pathway of (Z_8)

3. 3. 9. Synthesis of 6-(phenyl carbamo thioyl)- 6H- indolo [2,3-b] quinoxaline-2- carbonyl chloride(Z_9).

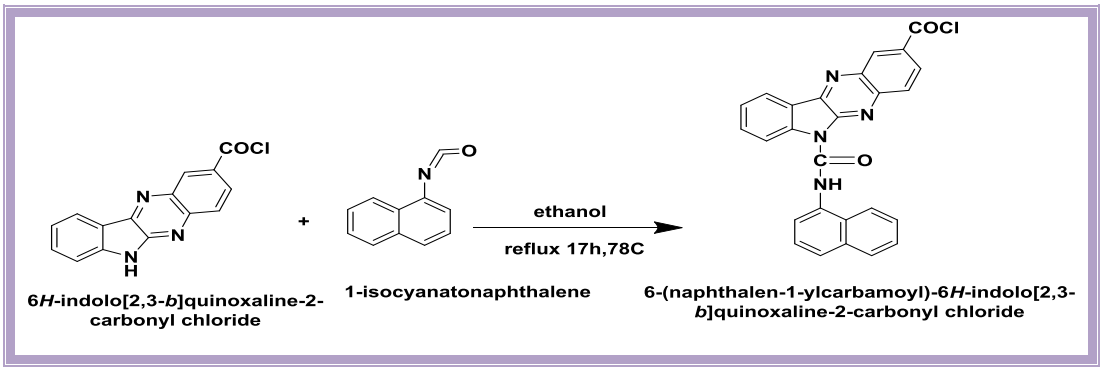
A solution of (0.2817 gm, 1mmol) of 6H-indolo[2,3-b] quinoxaline-2-carbonyl chloride in (20ml) ethanol, was added to isothiocyanatobenzene (0.13519 gm,1mmol). The mixture is refluxed with stirring for (15 h) in water bath.The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3). The precipitate was filtered, washed with hexane and dried . The reaction was shown in Scheme(3.9) and the physical properties of compound are illustrate in Table (4.3).



Scheme (3.9): The synthetic pathway of (Z_9)

3. 3.10. Synthesis of 6-(naphthalene-1-ylcarbamoyl)-6H-indolo[2,3-b] quinoxaline-2-carbonyl chloride (Z_{10}).

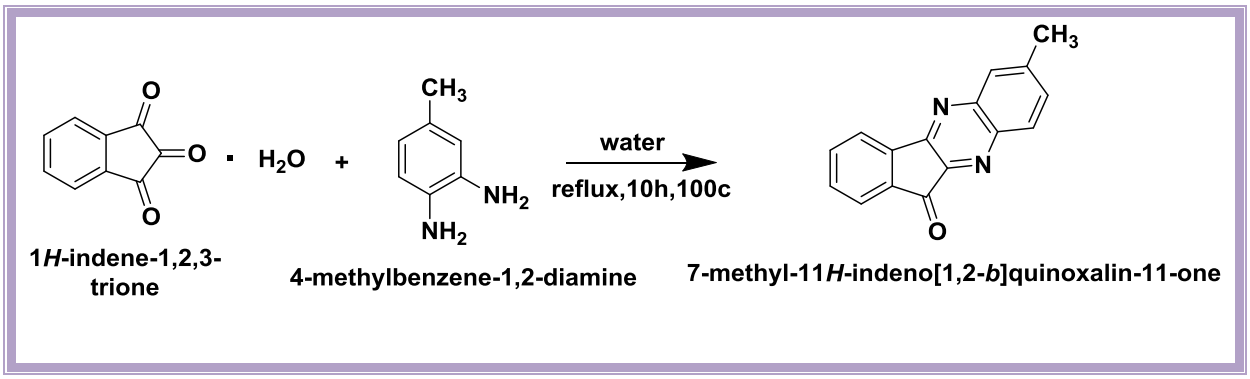
A solution of (0.28 gm ,1mmol) of 6H-indolo[2,3-b]quinoxaline-2-carbonyl chloride in (20 ml) ethanol was added to 1-isocyanatonaphthalene (0.169gm,1mmol). The mixture is refluxed with stirring for (17 h) in water bath. The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3). The products was filtered, washed with ethanol, and dried. The reaction was shown in Scheme (3.10) and the physical properties of compound are illustrate in Table (4.3).



Scheme (3.10): The synthetic pathway of (Z_{10})

3. 3.11. Synthesis of 7-methyl-11indeno[1,2-b]quinoxalin-11-one(Z_{11}).

1H-indene-1,2,3-trione (2gm , 11.6 mmol) was dissolved in aqueous sodium bicarbonate solution (3.32 gm, 39.5mmol in 160 ml water), 4-methylbenzene-1,2-diamine (1.6 gm , 13.2 mmol) was added and the mixture was refluxed for (10 h) . The completion of the reaction was checked by using T.L.C, mobile phase (ethyl acetate : hexane 1:3). The precipitate was filtered, washed with water and dried in the air. The reaction was shown in Scheme (3.11) and the physical properties of compound are illustrate in Table (4.3).

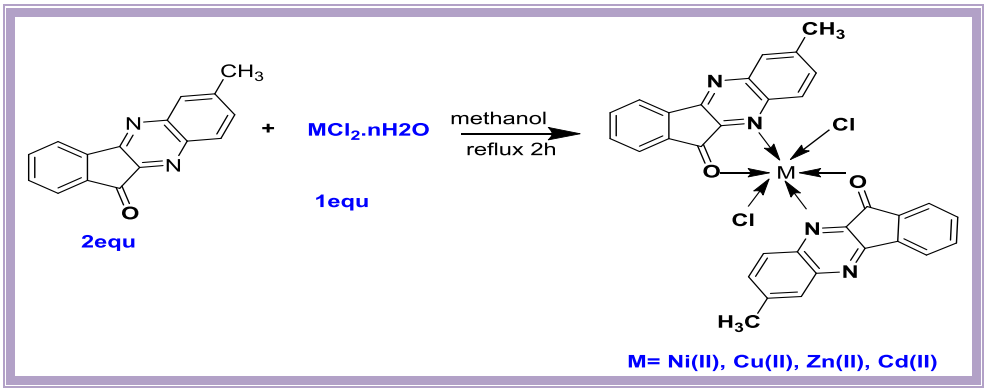


Scheme (3.11): The synthetic pathway of (Z_{11})

3. 3. 12. Synthesis of complexes $[M(C_{16}H_{10}N_2O)_2Cl_2]$

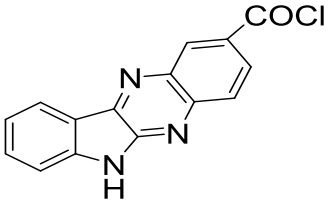
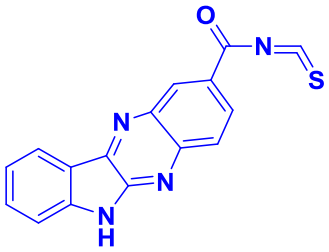
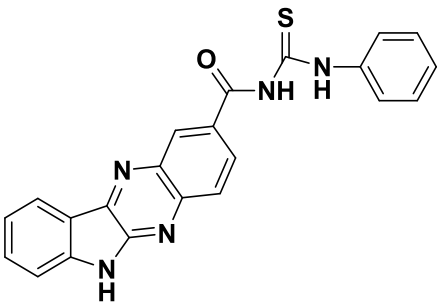
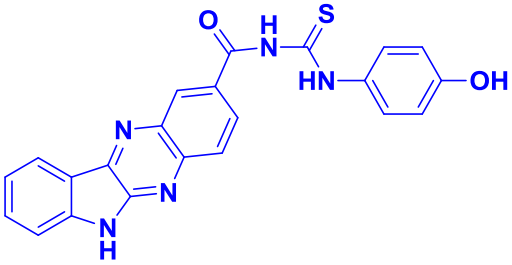
(0.4 mmol) of metal chloride such as ($NiCl_2.6H_2O$, $CuCl_2.2H_2O$, $ZnCl_2$ and $CdCl_2.H_2O$) was dissolved in (25 ml) of methanol. Then the solution added into a solution of ligand (Z_{11}) (0.2 gm, 0.81 mmol) in the same solvent (25ml). The mixture was placed in (100 ml) round bottom flask, and a few drops of

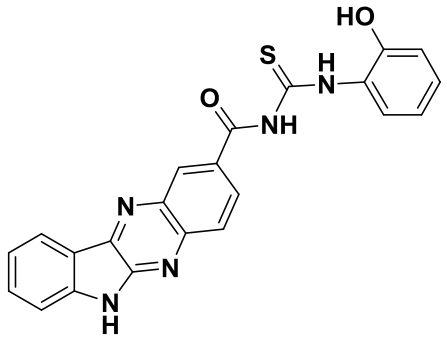
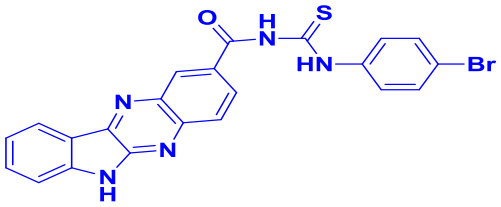
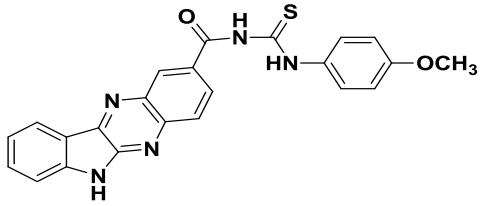
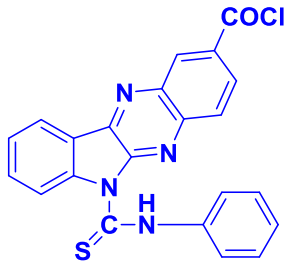
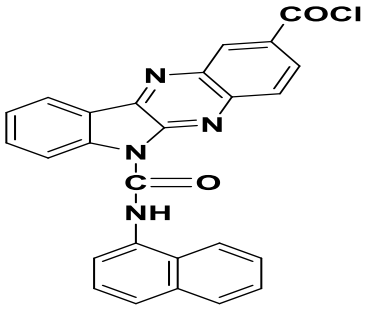
potassium hydroxide were added and the mixture was refluxed on a water bath at 64°C. The refluxing was continued for (2h), then cooled at room teperature. The solid precipitate was filtered, washed with water, and dried in an oven at 50°C. Scheme (3.12) demonstrates the synthetic pathway of (Z_{11}) and the physical properties of compound are illustrate in Table (4.3).

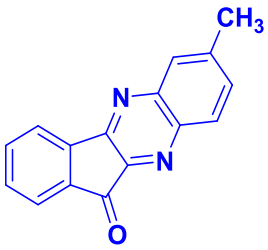
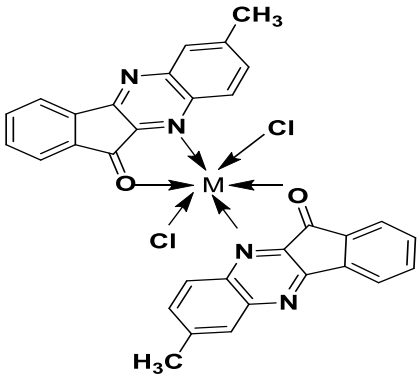


Scheme (3.12): The synthetic pathway of complexes with Z_{11} ligand.

Table 3.2: The structures and nomenclatures of the synthesized compounds

Comp. No.	Comp. Structure	Molecular Formula	Comp. name
Z_1		$C_{15}H_9N_3O_2$	6H-indolo[2,3-b]quinoxaline -2-carboxylic acid
Z_2		$C_{15}H_8N_3OCl$	6H-indolo[2,3-b]quinoxaline-2-carbonyl chloride
Z_3		$C_{16}H_8N_4OS$	6H-indolo[2,3-b]quinoxaline-2-carbonyl isothiocyanate
Z_4		$C_{22}H_{15}N_5OS$	N-(phenylcarbamothioyl) -6H-indolo[2.3-b]quinoxaline-2-carboxamide
Z_5		$C_{22}H_{15}N_5O_2S$	N-(4-hydroxyphenyl) carbamothioyl-6H-indolo [2,3-b] quinoxaline-2-carboxamide

Z_6		$C_{22}H_{15}N_5O_2S$	N-(2-hydroxyphenyl) carbamothioyl-6H-indolo[2,3-b] quinoxaline-2-carboxamide
Z_7		$C_{22}H_{14}N_5OSBr$	N-(4-bromophenyl) carbamothioyl-6H-indolo[2,3-b] quinoxaline-2-carboxamide
Z_8		$C_{23}H_{17}N_5O_2S$	N-(4-methoxyphenyl) carbamothioyl-6H-indolo[2,3-b] quinoxaline-2-carboxamide
Z_9		$C_{22}H_{13}N_4OSCl$	6-(phenylcarbamothioyl) -6H-indolo[2,3-b]quinoxaline-2-carbonyl chloride
Z_{10}		$C_{26}H_{15}N_4O_2Cl$	6-(naphthalene-1-ylcarbamoyl)-6H-indolo[2,3-b]quinoxaline-2-carbonylchloride

Z_{11}		$C_{16}H_{10}N_2O$	7-methyl-11H-indeno[1,2-b]quinoxalin-11-one
$[M(Z11)_2\ Cl_2].6H_2O$	 M= Ni(II), Cu(II), Zn(II), Cd(II)	$[M(C_{16}H_{10}N_2O)_2\ Cl_2].6H_2O$	Di chloro bis (7-methyl -11H-indeno[1,2-b] quinoxalin-11-one) metal(II) hexa hydrate

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.

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 108 cells/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 dishes and kept in the refrigerator until use.

Determination of the antimicrobial activity of synthesized compounds by the 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 108) 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.

Chapter Four

(Results and discussion)

4.1.Introduction

A new series of quinoxaline derivatives has been synthesized by the reaction of isatin with 3,4-diaminobenzoic acid, 1H-indene1,2,3-trion with 4-methyl benzene-1,2-diamine and the complexes prepared from it, which exhibited biological activity against two type of bacteria(*E.coli* and *S.aureus*).

4.2. Synthesis and identification of 6H-indolo [2,3-b] quinoxaline-2-carboxylic acid [Z_1].

Isatin was combined with 3,4-di aminobenzoic acid to produce compound (Z_1), which had the structure shown in Figure (4. 1).

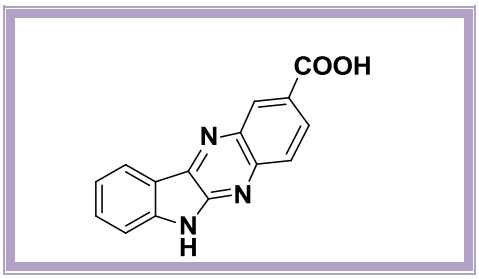
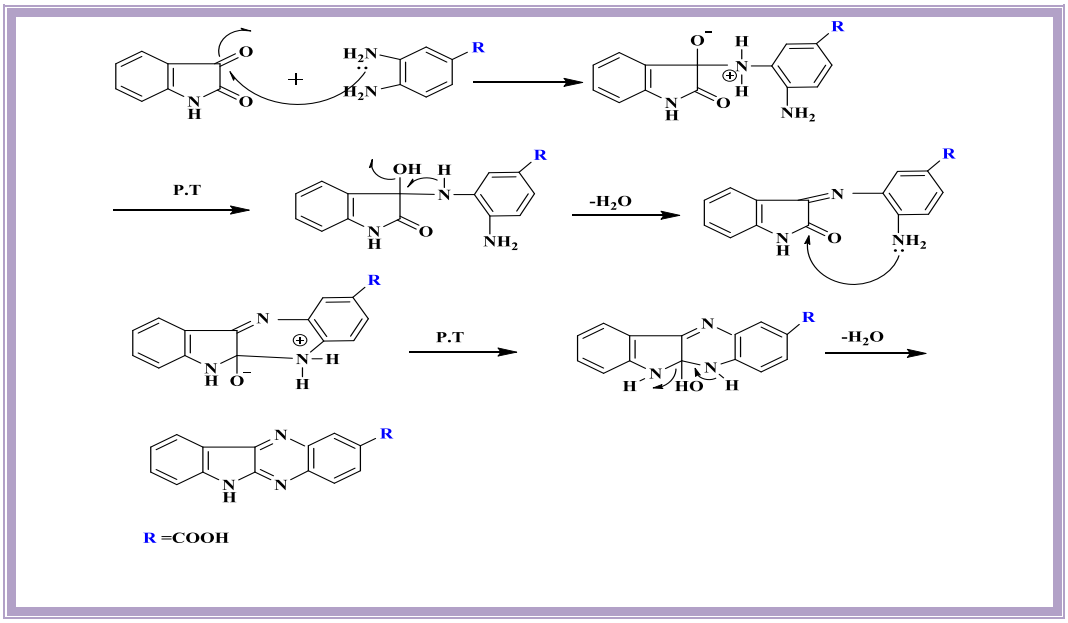


Figure (4. 1): The chemical structure of compound[Z_1].

The suggested mechanism of the closure ring reaction is explains in the scheme(4.1).



Scheme (4. 1): The mechanism for the synthesis of (Z_1) compound.

The structure of the compound Z_1 was confirmed by FT-IR and ^{1}HNMR spectroscopy. A peak at (3476 cm^{-1}) is accounted to O-H group**[98-100]**. The stretching vibration of C=O caused an absorption band at 1640 cm^{-1}. Also, the absorption band at 3352cm^{-1}due to N-H group. C=N stretching vibrations produced a new distinct absorption band at 1614 cm^{-1} **[101]** as shown in Figure (4.2) and Table (4.1).

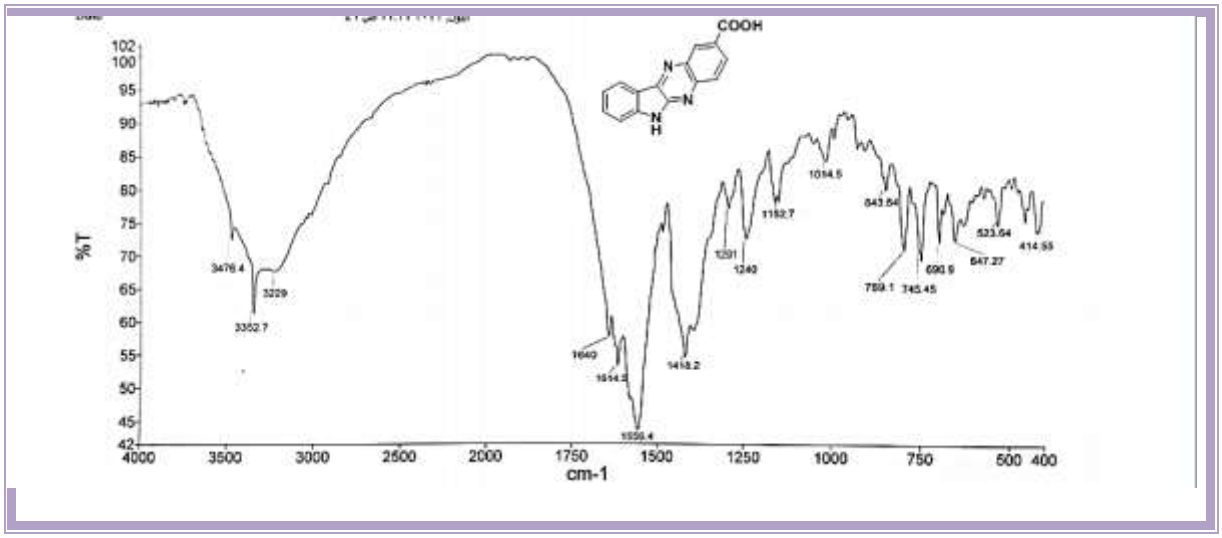


Figure (4. 2): FT-IR spectrum in of (Z_1) compound

The ^{1}H-NMR spectra of the compound (Z_1), Figure (4.3) shows the following chemical shifts (DMSO-d6, ppm): 12.69 (s,1H, COOH), 12.38 (s,1H,NH), 7.75 - 6.47 (m.7H,Ar-H)**[102]**.

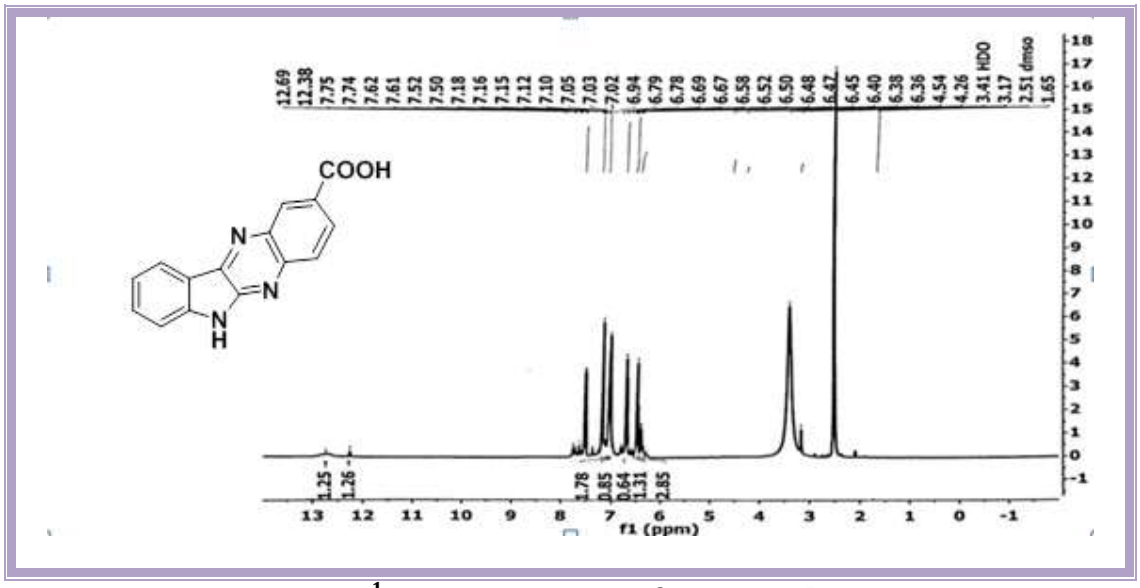


Figure (4. 3): ^{1}H NMR spectrum of compound (Z_1).

4.3. Synthesis and identification of (6H-indolo[2,3-b]quinoxaline-2-carbonylchloride[Z_2].

The Compound (Z_2) was synthesized through the reaction of 6H-indolo [2,3-b]quinoxaline-2-carboxylic acid (Z_1) with thionylchlorid, a structure appears in Figure (4.4).

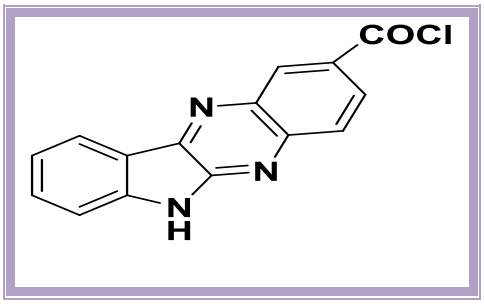
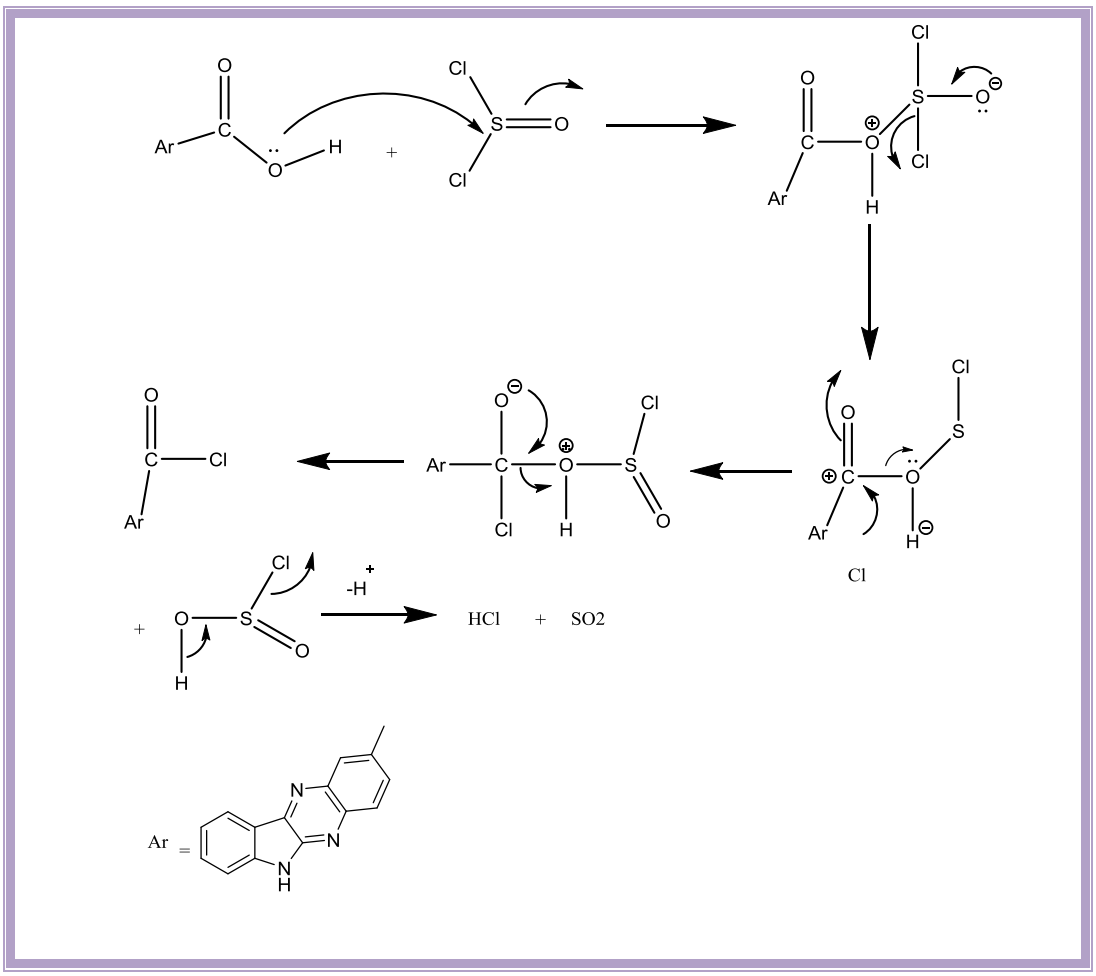


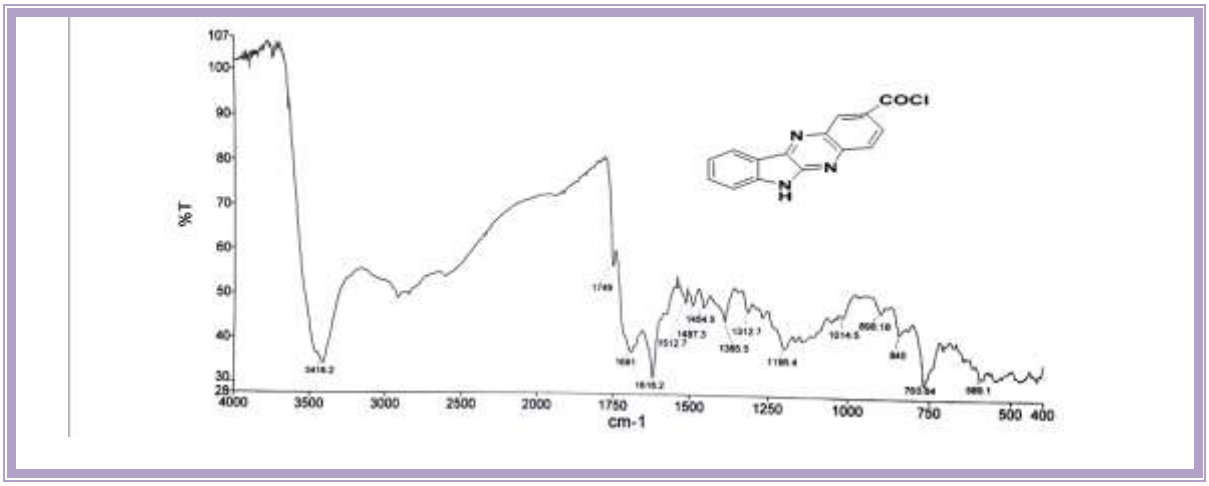
Figure (4. 4): The chemical structure of compound Z_2

The suggested mechanism for the formation of(Z_2) as shown in Scheme(4.2)



Scheme (4. 2): The mechanism for the synthesis of (Z_2) compound.

The FT-IR spectrum of compound Z_2, Figure (4. 5) and Table (4. 1) was indicated the absorption band at 3418 cm^{-1} was attributed to stretching vibration of N-H**[103]**. A peak at (1749 cm^{-1}) is accounted to the (C=O) group**[104]**. Whereas absorption band at 1691cm^{-1}and1618cm^{-1} was due to C=N stretching vibration. The bands at 1512 cm^{-1} and 1487cm^{-1} were due to the C=C aromatic**[105]**.



Figure(4. 5): FT-IR spectrum in of (Z_2) compound

The ^{1}H-NMR spectra of the compound (Z_2), Figure (4.6) shows the following chemical shifts (DMSO-d6, ppm):12.38 (s,1H, N-H), 8.33-6.50 (m,7H, Ar-H).

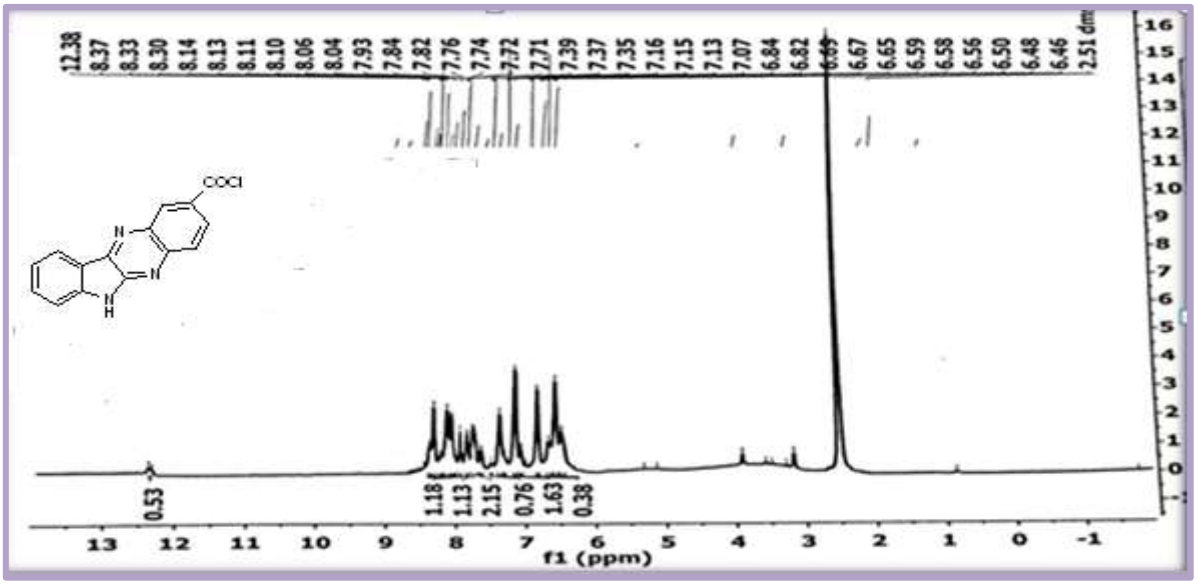


Figure (4. 6): ^{1}H NMR spectrum of compound (Z_2).

4.4. Synthesis and identification of (6H-indolo[2,3-b]quinoxaline-2-carbonylisothiocyanate[Z_3].

The compound (Z_3) was synthesized through the reaction of 6H-indolo [2,3-b] quinoxaline-2-carbonyl chloride (Z_2) with potassium thiocyanate, with a structure appears in Figure (4.7).

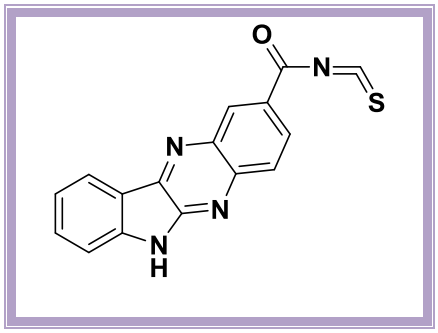


Figure (4. 7): The chemical structure of compound (Z_3)

The FT-IR spectrum of compound Z_3 Figure (4. 8) and Table (4. 1) shows absorption band at 3200 cm^{-1} was attributed to stretching vibration of N-H. Also, the absorption band at 1701 cm^{-1} was due to C=O. Whereas absorption band at 1618cm^{-1} was due to C=N stretching vibration. Absorption band at 1232 cm^{-1} was due to C=S**[106-107].** The C=C aromatic is responsible for the bands at 1516 cm^{-1} and 1443 cm^{-1}.

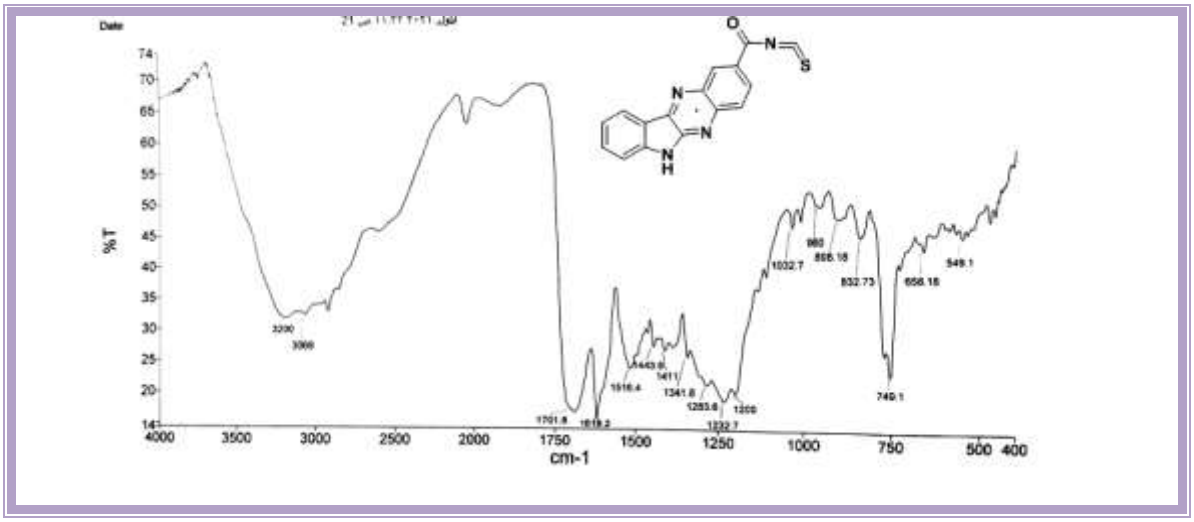


Figure (4. 8): FT-IR spectrum in of (Z_3) compound

The Figure (4.9) shows ^{1}H-NMR spectrum of compound (Z_3) and the chemical shifts (DMSO-d6, ppm): 12.82 (s,1H, N-H), 8.62-6.84 (m,7H, Ar-H).

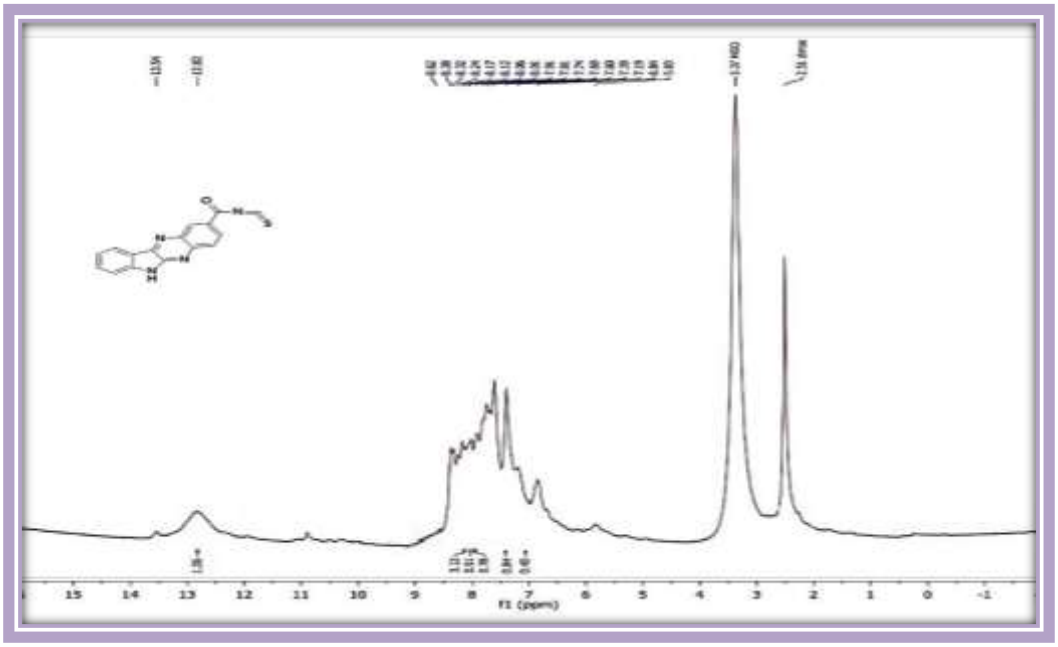


Figure (4. 9): ^{1}H NMR spectrum of compound (Z_3).

4.5. Synthesis and identification of N-(phenyl carbamothioyl)-6H-indolo [2,3-b] quinoxaline-2- carboxamide[Z_4].

Compound (Z_4) was synthesized through the reaction of compound (Z_3) with aniline, with a structure appears in Figure (4.10).

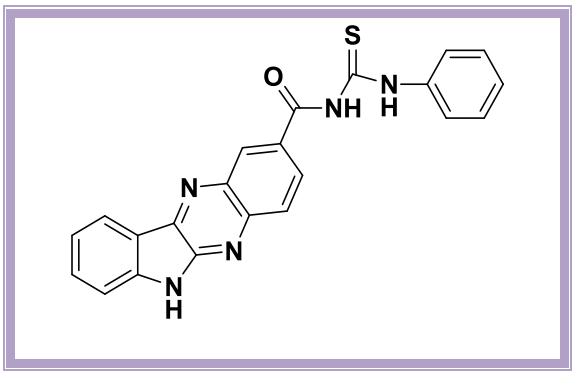
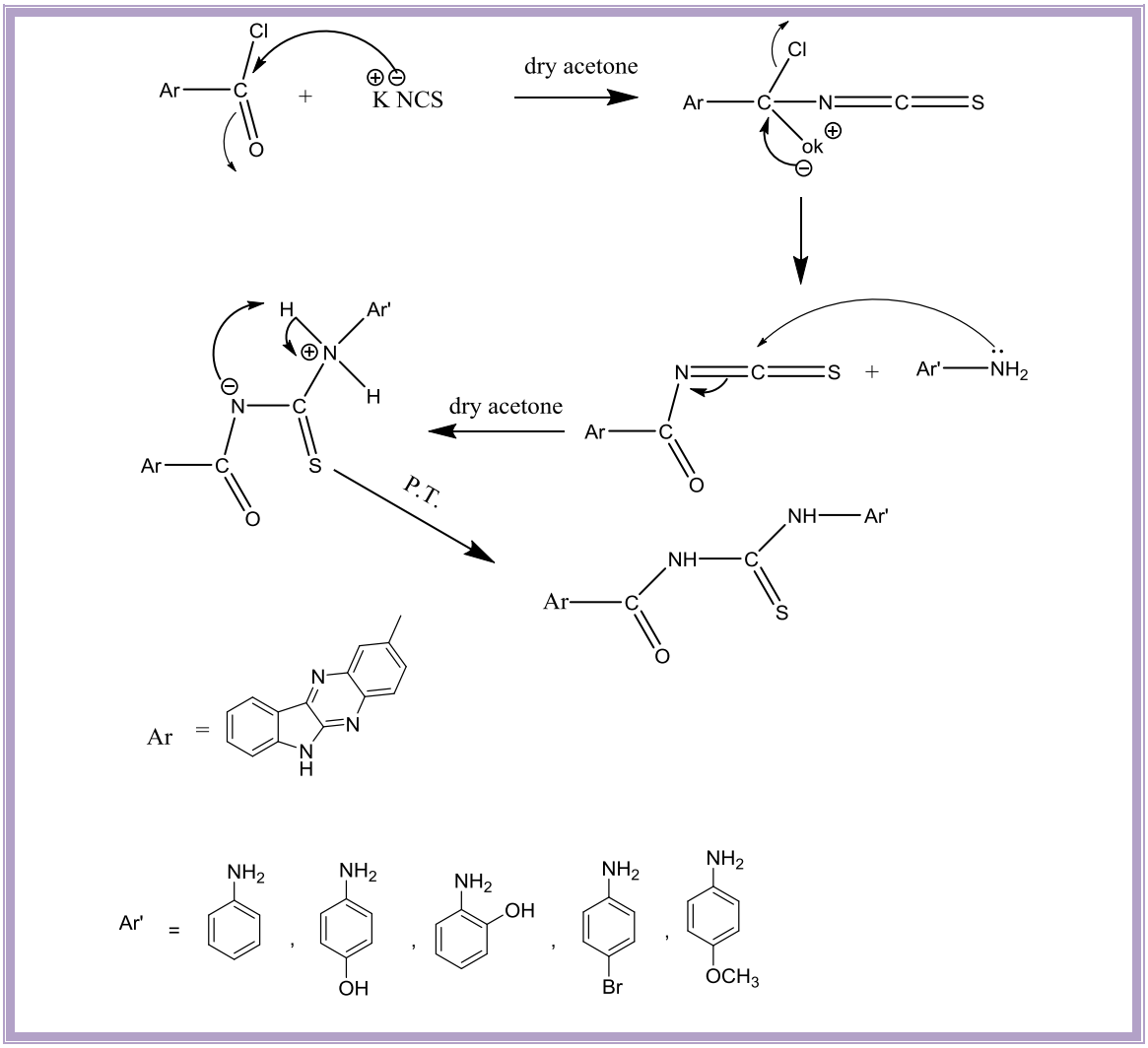


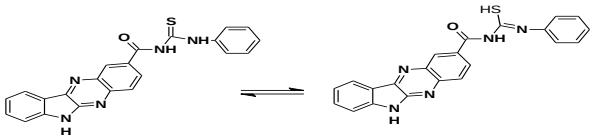
Figure (4. 10): The chemical structure of compound(Z_4)

The mechanisms for the formation of(Z_3-Z_8) is proposed by **[108]** as shown in Scheme (4.3).



Scheme (4. 3): The mechanism for the synthesis of (Z_3- Z_8) compound.

The FT-IR spectrum of compound (Z_4), Figure (4.11) and Table (4.1) shows bond absorption at 3345 cm^{-1} was due to N-H**[109]** and 1618cm^{-1} for the C=N group. Absorption at 1651 cm^{-1} was due to C=O**[110]**.The new compounds (Z_4- Z_8) showed absorption bands at 2200 $cm^{-1}$was attributed to (SH) group. As well known, organic compounds containing thiourea group of -NH-C=S-NH- can exist in two tautomeric forms thione and thiol,-NH (SH)-N=C-.



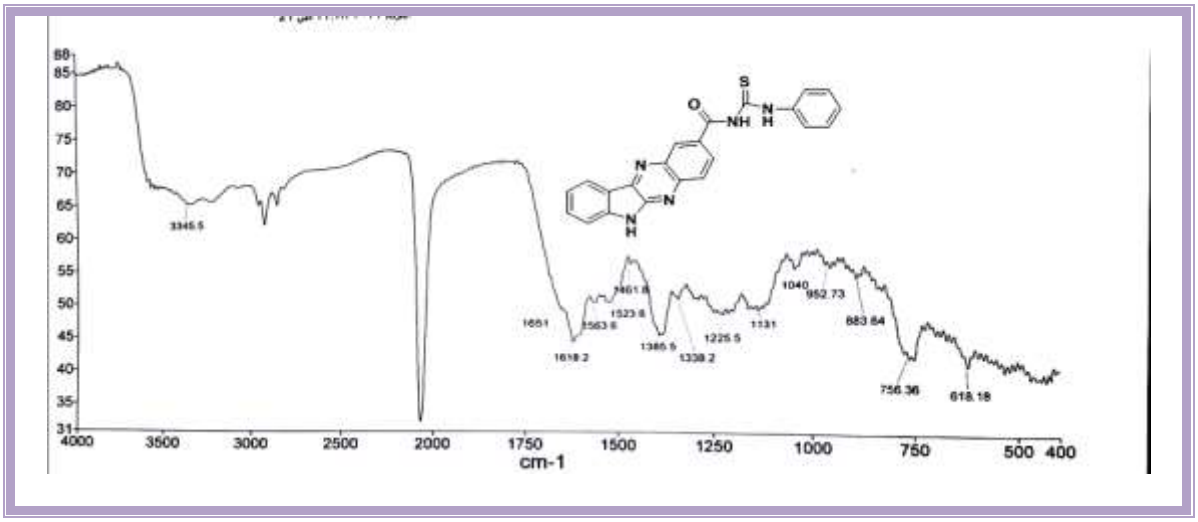


Figure (4. 11): FT-IR spectrum in of (Z_4) compound

The Figure (4.12) pointing to ^{1}H-NMR spectrum of compound (Z_4) and the chemical shifts (DMSO-d6, ppm): 12.10 (s,1H, SH), 10.13 (s,1H, N-H), 8.17(s,1H,CONH), 8.06 -6.82 (m,12H, Ar-H)and 5.84(s,1H,CSNH)**[111]**.

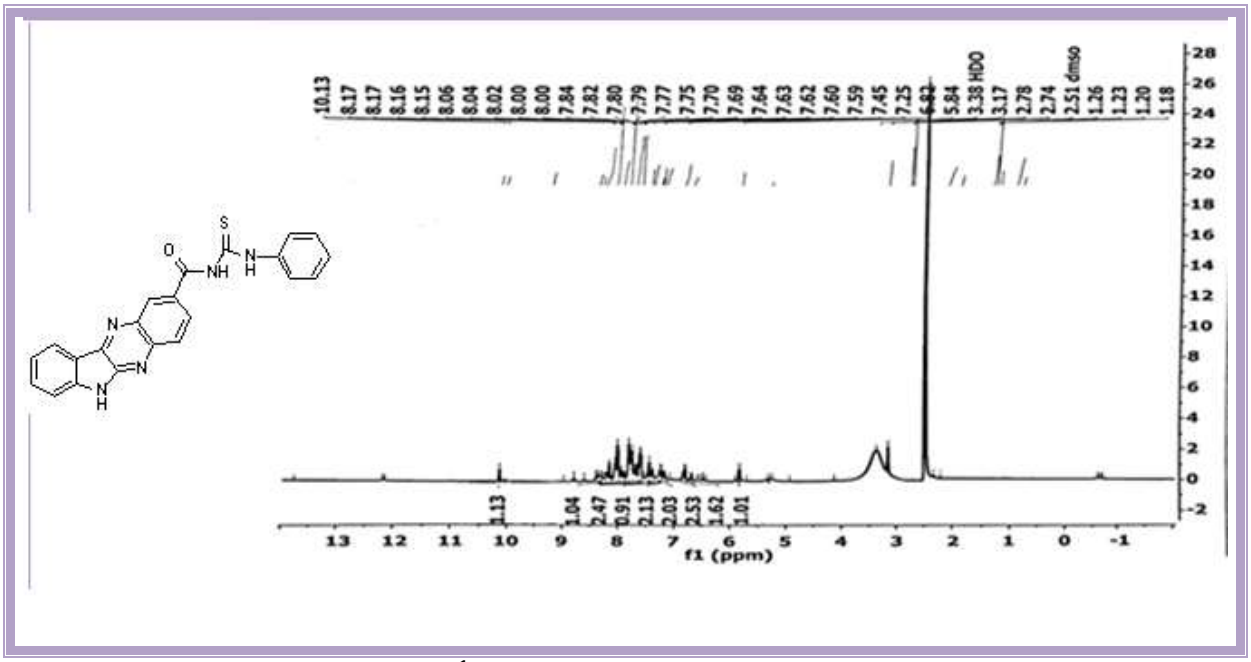


Figure (4. 12): ^{1}H NMR spectrum of compound (Z_4).

4.6. Synthesis and identification of N-((4-hydroxy phenyl)carbamothioyl)-6H-indolo[2,3-b]quinoxaline-2-carboxamide[Z_5].

The structure of compound (Z_5) was obtained by reacting compound (Z_3) with 4-aminophenol, as shown in Figure (4. 13).

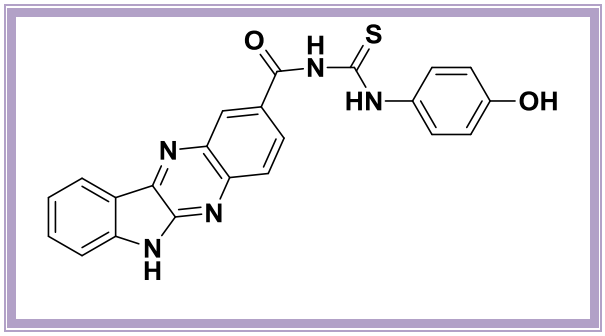


Figure (4. 13): The chemical structure of compound(Z_5).

The FT-IR spectrum of compound (Z_5), Figure (4. 14) indicated the appearance peak at (3425 cm^{-1}) is accounted to OH group. Also, (1774 cm^{-1}) for the (C=O) group. Absorption band at 3061cm^{-1}due to C-H aromatic**[112]**. Bond absorption at 1632 cm^{-1} was due to C=N stretching vibration as listed in Table (4. 1).

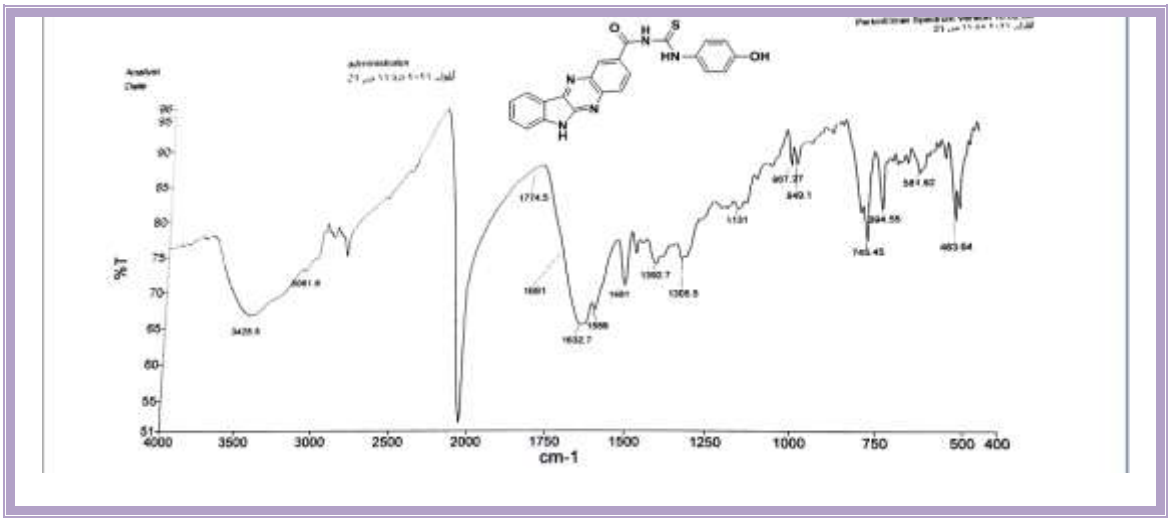


Figure (4. 14): FT-IR spectrum in of (Z_5) compound

The ^{1}H-NMR spectra of the compound (Z_5), Figure (4. 15) shows the following chemical shifts.(DMSO-d6, ppm): 12.29 (s,1H, SH), 12.25 (s,1H, N-H),8.96(s,1H,CONH), 8.17 -6.41 (m,11H, Ar-H)and 5.84(s,1H,CSNH)

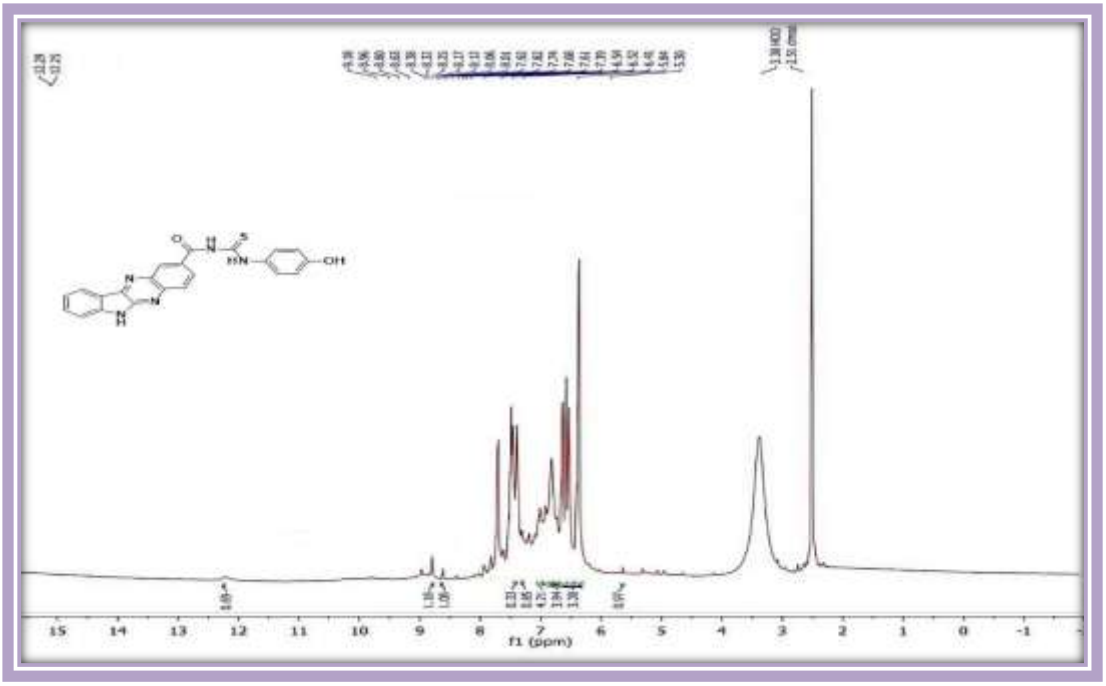


Figure (4. 15): ^{1}H NMR spectrum of compound (Z_5).

4.7 Synthesis7 and identification of N-((2-hydroxy phenyl) carbamothioyl) -6H-indolo[2,3-b] quinoxaline-2-carboxamide [Z_6].

The compound (Z_6) was made by reacting compound (Z_3) with 2-aminophenol, and its structure is shown in Figure (4. 16).

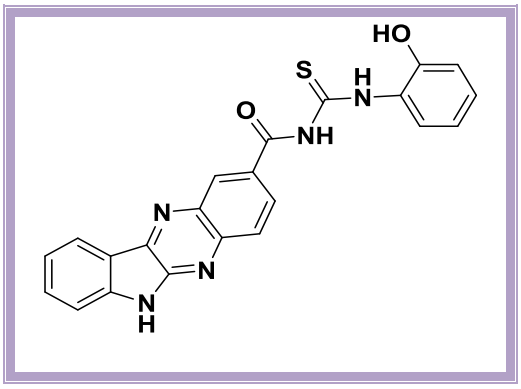


Figure (4. 16): The chemical structure of compound(Z_6).

The FT-IR spectrum of compound (Z_6) Figure (4. 17) and Table (4. 1) shows absorption band at 3303 cm^{-1} was due to N-H aromatic. Bond absorption at 3373 cm^{-1} was due to OH stretching vibration . Bond absorption at 1699cm^{-1} was due to C=O. Absorption band at 1598cm^{-1}due to C=N. The bands at 1511 cm^{-1} and 1461cm^{-1} were due to the C=C aromatic.

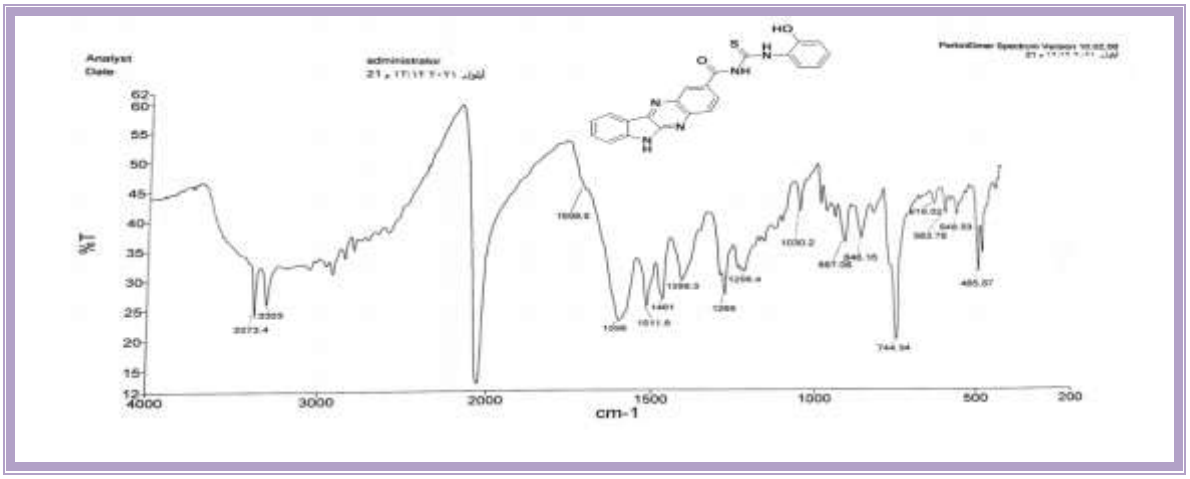


Figure (4. 17): FT-IR spectrum in of (Z_6) compound

4.8 Synthesis and identification of N-((4-bromo phenyl) carbamothioyl) -6H-indolo[2,3-b] quinoxaline-2-carboxamide [Z_7].

Compound (Z_7) was synthesized through the reaction of compound (Z_3) with 4-bromo aniline, with a structure appears in Figure (4. 18).

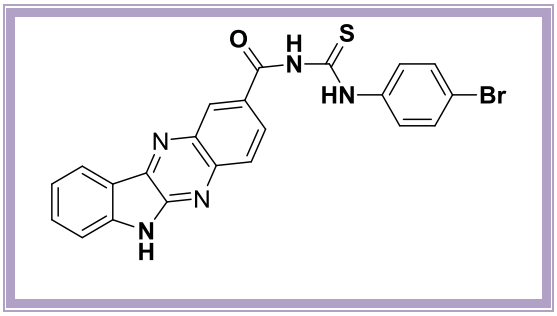


Figure (4. 18): The chemical structure of compound(Z_7).

The structure of the compound (Z_7) was confirmed by FT-IR spectrum as illustrated in Figure (4.19). The FT-IR spectrum shows an absorption band at (3447 cm^{-1}) which referred to N-H group. Absorption band at 1676 cm^{-1} was due to C=O group. Also, (3076 cm^{-1}) for the (C-H) aromatic. A peak at(1618 cm^{-1}) is accounted to the C=N stretching vibration. Also, the absorption band at (618 cm^{-1}) is assigned to C-Br. As listed in Table (4. 1).

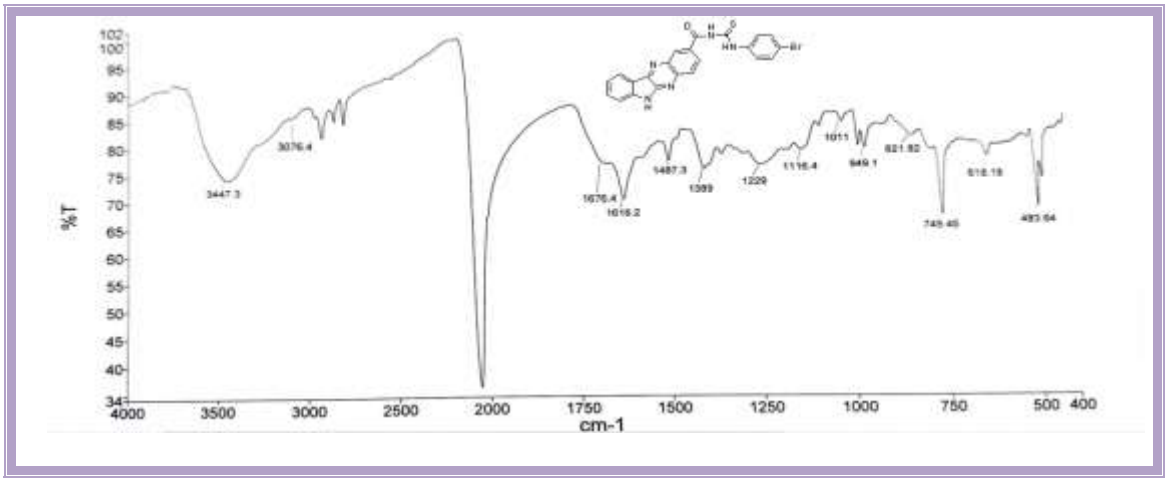


Figure (4. 19): FT-IR spectrum in of (Z_7) compound

4.9 Synthesis and identification of N-((4-methoxy phenyl) carbamothioyl) -6H-indolo[2,3-b] quinoxaline-2-carboxamide [Z_8].

The interaction of compound (Z_3) with 4-methoxy aniline yielded compound (Z_8), which has the structure shown in Figure (4. 20).

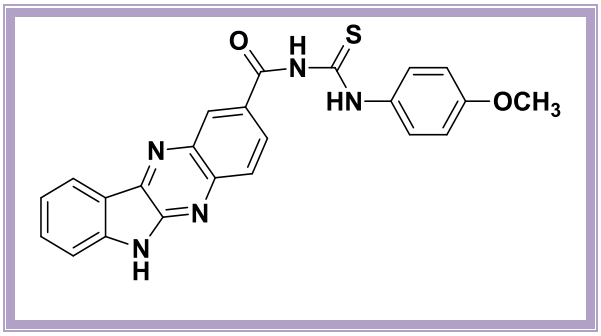


Figure (4. 20): The chemical structure of compound(Z_8).

The FT-IR spectrum of compound (Z_8) Figure (4. 21) and Table (4. 1) shows absorption band at 3236 cm^{-1} was due to N-H. Also, (1614 cm^{-1}) for the (C=N) group. Absorption band at 1672 cm^{-1} was due to C=O. The C=C aromatic was responsible for the bands at 1512 cm-1 and 1458 cm^{-1}.

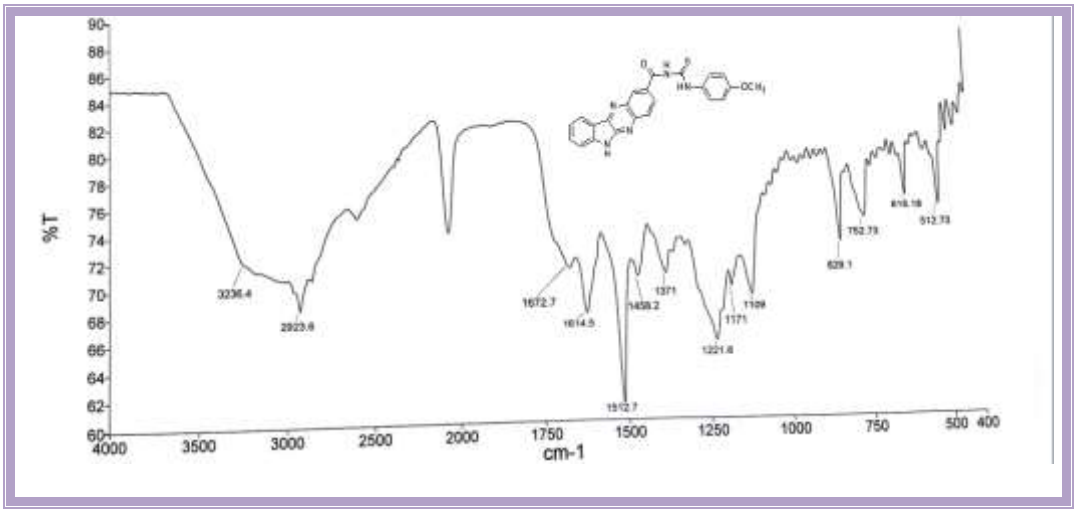


Figure (4. 21): FT-IR spectrum in of (Z_8) compound

The ^{1}H-NMR spectra of the compound (Z_8), shows the following chemical shifts.(DMSO-d6, ppm): 12.20 (s,1H, SH),9.95 (s,1H, N-H), 8.86(s,1H,CONH), 8.33 -6.65 (m,11H, Ar-H), 5.82(s,1H,CSNH) and 3.83 (s,3H, OCH_3)

4.10 Synthesis and identification of 6-(Phenyl carbamo thioyl)- 6H- indole [2,3-b] quinoxaline- 2- Carbonyl chloride [Z_9].

Compound (Z_9) was synthesized through the reaction of compound (Z_2) with isothiocyanatobenzene, with a structure appears in Figure (4.22).

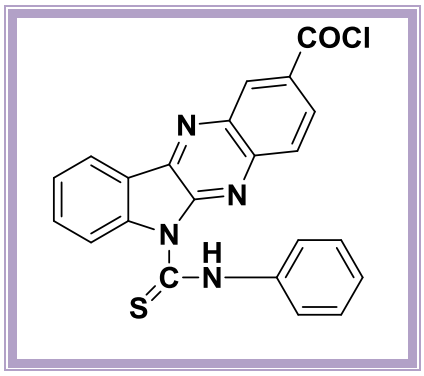


Figure (4. 22): The chemical structure of compound(Z_9).

The FT-IR spectrum of compound (Z_9) Figure (4. 23) indicated the appearance a peak at(3214 cm^{-1}) is accounted to the N-H group. Absorption bands at 1683 cm^{-1} and 1618 cm^{-1} were due to C=O and C=N stretching

vibration, respectively. Absorption band at 3061cm^{-1}due to C-H aromatic as listed in Table (4. 1).

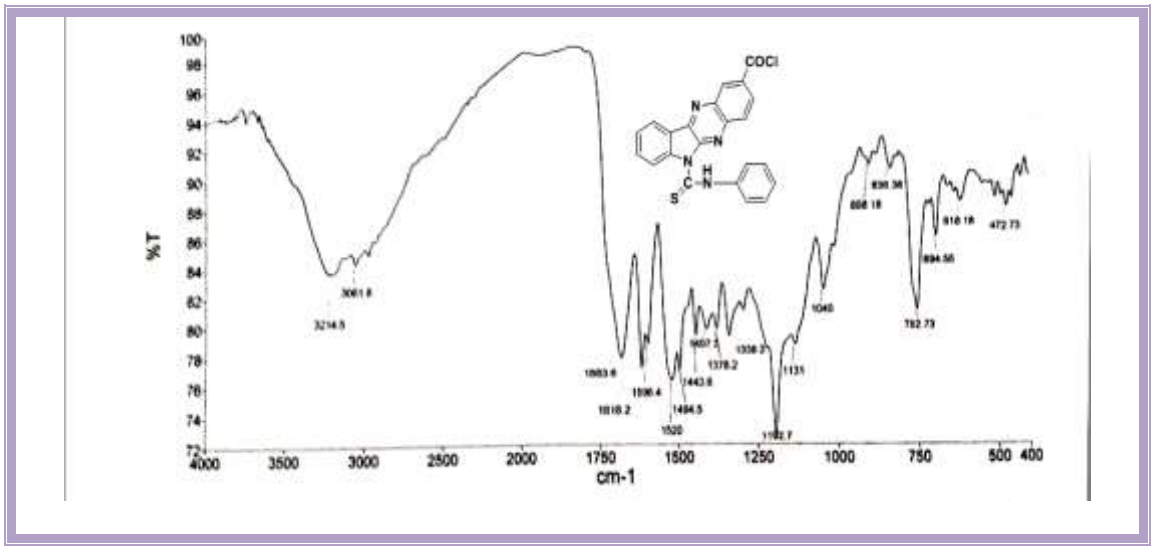


Figure (4. 23): FT-IR spectrum in of (Z_9) compound

Figure (4. 24) shows the chemical shifts in the ^{1}H-NMR spectra of the compound (Z_9),(DMSO-d6, ppm): 9.21 (s,1H,CSNH), and 8.45 -6.82 (m,12H, Ar-H).

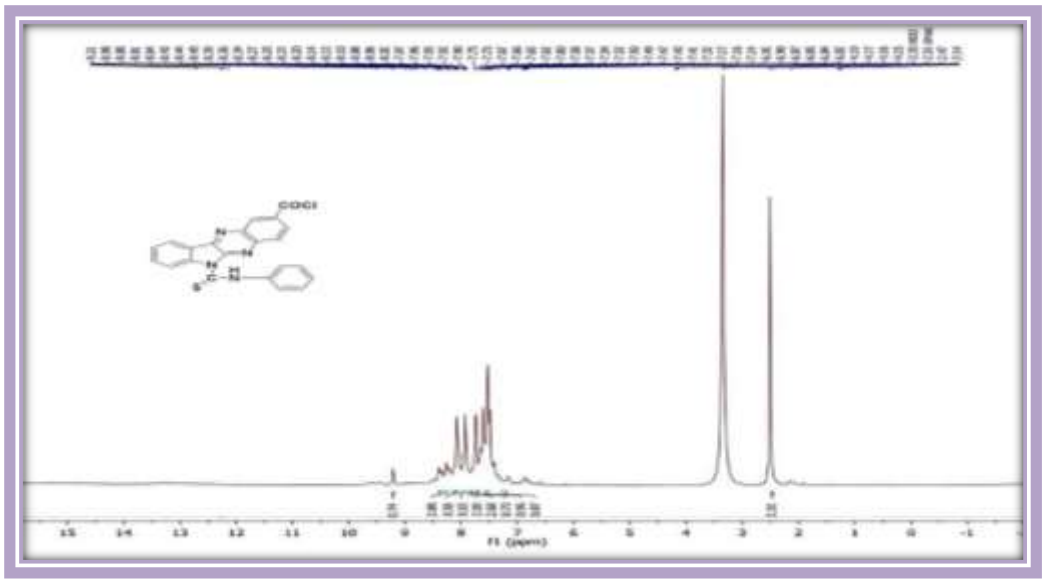


Figure (4. 24): ^{1}H NMR spectrum of compound (Z_9).

4.11 Synthesis and identification of 6-(naphthalene-1-ylcarbamoyl)-6H-indolo[2,3-b]quinoxaline-2-carbonyl chloride[Z_{10}].

Compound (Z_{10}) was synthesized through the reaction of compound (Z_2) with1-isocyanatonaphthalene, with a structure appears in Figure (4.25).

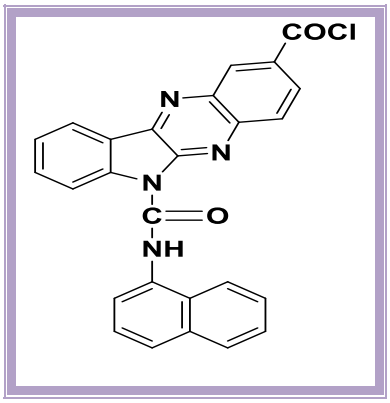


Figure (4. 25): The chemical structure of compound(Z_{10}).

The structure of the compound (Z_{10}) was confirmed by FT-IR spectrum as illustrated in Figure (4.26). The FT-IR spectrum shows an absorption band at (3287cm^{-1}) which referred to N-H group. Absorption band at 1694cm^{-1} was due to C=O group. Also, (3054cm^{-1}) for the (C-H) aromatic. Bond absorption at 1621 cm^{-1} was due to C=N stretching vibration. Also, the absorption bands at (1541cm^{-1} ,1443cm^{-1}) are assigned to C=C aromatic. as listed in Table (4. 1).

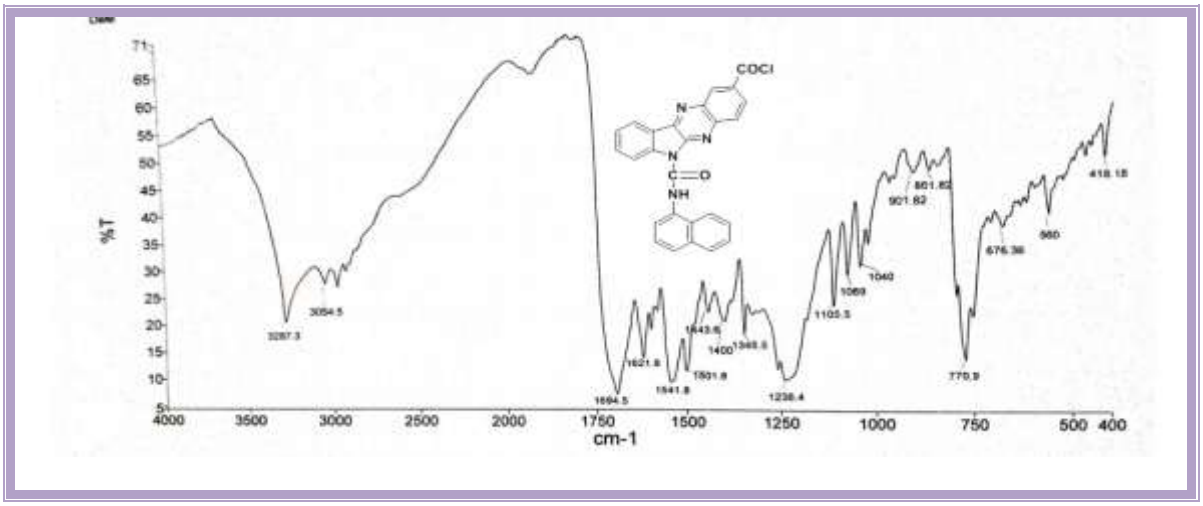


Figure (4. 26): FT-IR spectrum in of (Z_{10}) compound

The ^{1}H-NMR spectra of the compound (Z_{10}), Figure (4. 27) shows the following chemical shifts.(DMSO-d6, ppm): 11.08 (s,1H,CONH), and 8.80 - 6.95(m,14H, Ar-H).

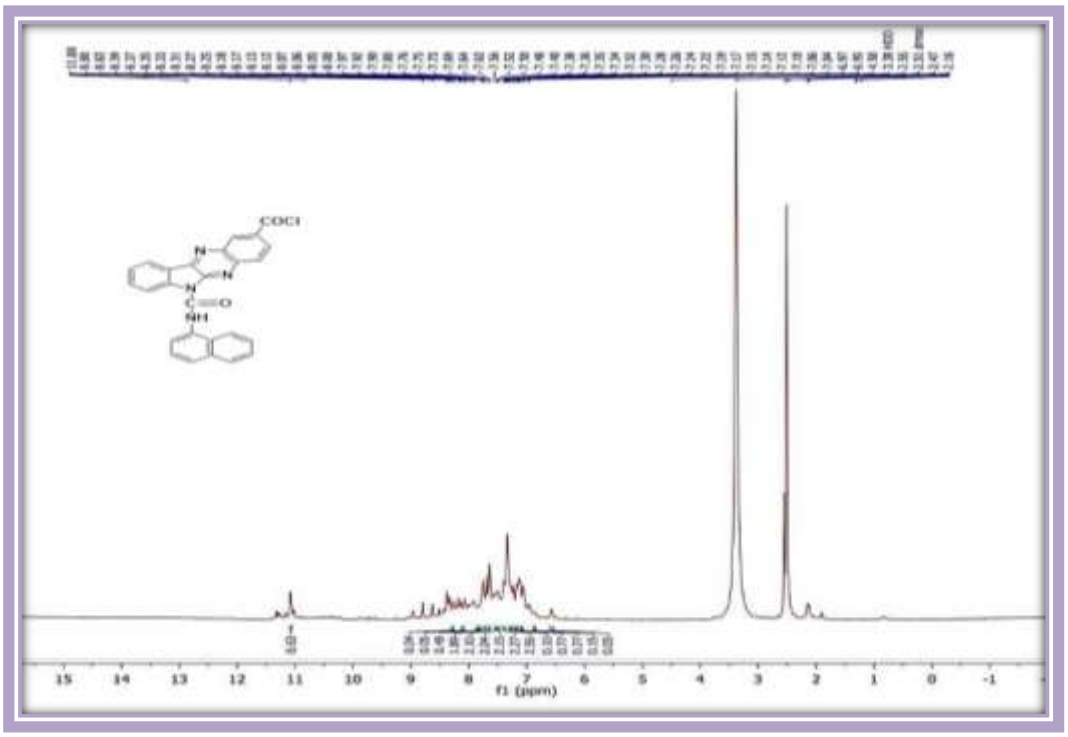


Figure (4. 27): ^{1}H NMR spectrum of compound (Z_{10}).

4.12. Synthesis and identification of compound 7-methyl-11H-indeno[1,2-b]quinoxaline-11-one [Z_{11}] and its complexes .

Compound (Z_{11}) synthesized through the reaction of (1H-indene-1,2,3-trionemonohydrate) with 4-methylbenzene1,2-diamine, and Figure (4.28) appears structure of this compound.

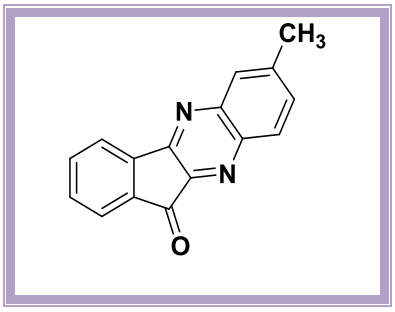
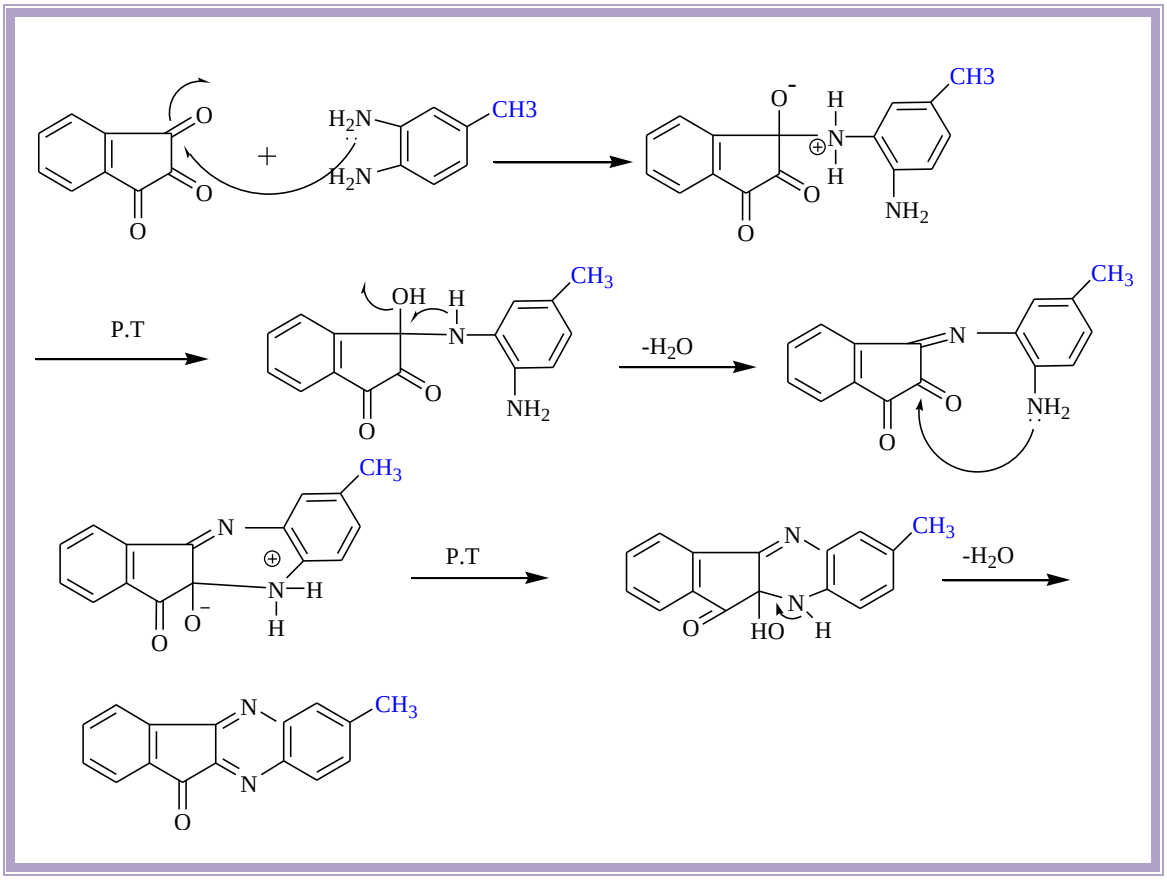


Figure (4. 28): The chemical structure of compound(Z_{11}).

The suggested mechanism for the compound Z_{11} appears in Scheme (4. 4).



Scheme (4. 4): The mechanism for the synthesis of (Z_{11}) compound.

Then, this compound was used as a ligand to synthesize complexes from the reaction of the ligand with salts of metals chlorides such as nickel chloride hexahydrate, copper chloride dihydrate, cadmium chloride monohydrate and anhydrous zinc chloride, the Figure (4. 29) appears structure of the complexes.

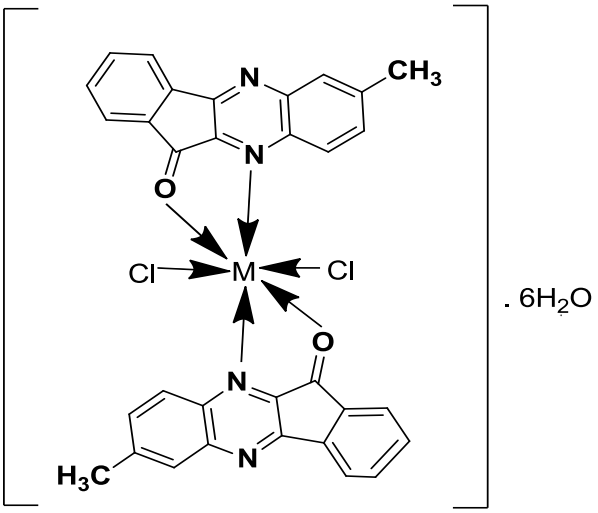


Figure (4. 29): The chemical structure of $[M(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$ complexes.

4.13. Identification of $[Z_{11}]$ and its complexes.

4.13.1. ^{1}H-NMR spectrum of compound (Z_{11})

The ^{1}H-NMR spectrum of compound 7-methyl-11H-indeno[1,2-b]quinoxaline-11-one (Z_{11}) Figure (4. 30) shows the chemical shifts (DMSO-d6, ppm): 7.64-8.02 (m,7H, Ar-H), 2.55(S,3H,CH_3)**[113-114]**.

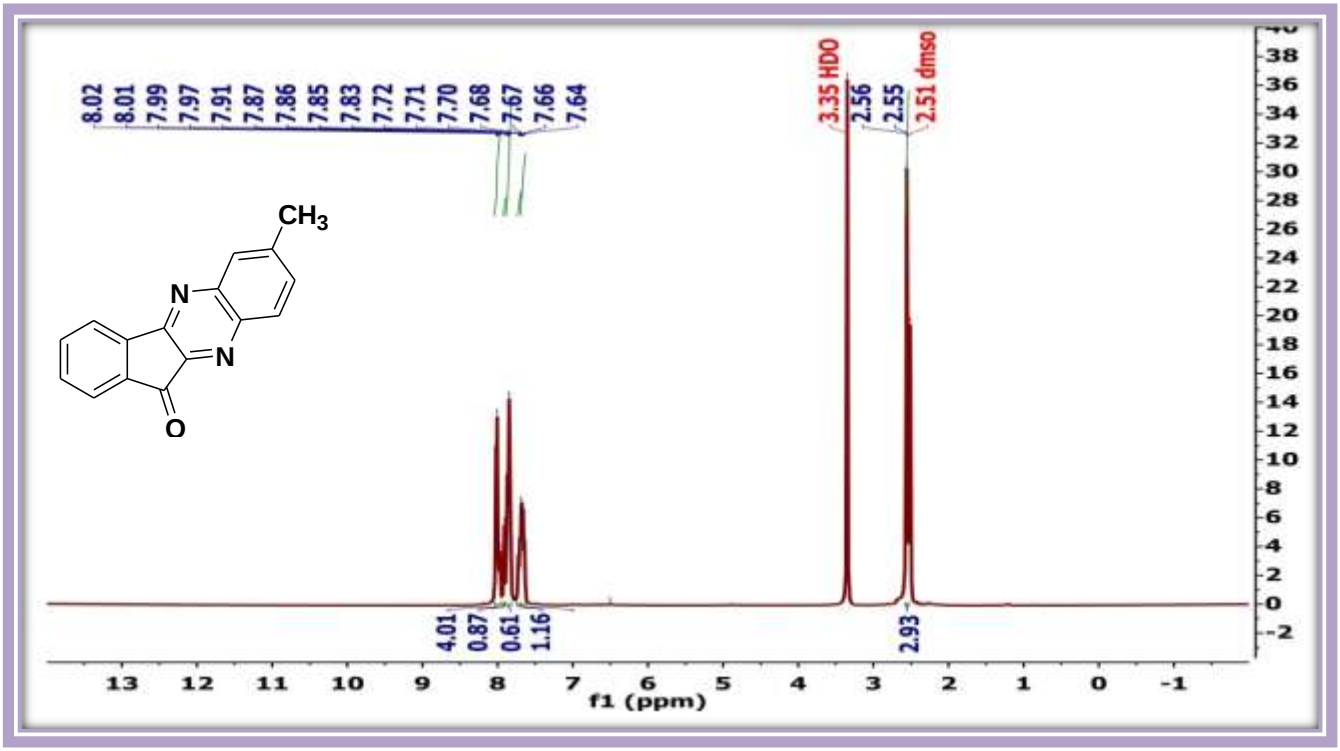


Figure (4. 30): ^{1}H NMR spectrum of compound(Z_{11}).

^{13}C-NMR spectra of the same compound (Z_{11}),(Figure 4.31) showed the following signals (DMSO-d6, ppm): 21.87 (C_{19}), 122.47-143.67(C_3,C_4,C_5,C_6,C_{10},C_{11},C_{12},C_{13},C_{14},C_{15}), 149.94-149.15(C_1,C_{17}), 156.13-156.92(C_8,C_9), 189.84(C_7).

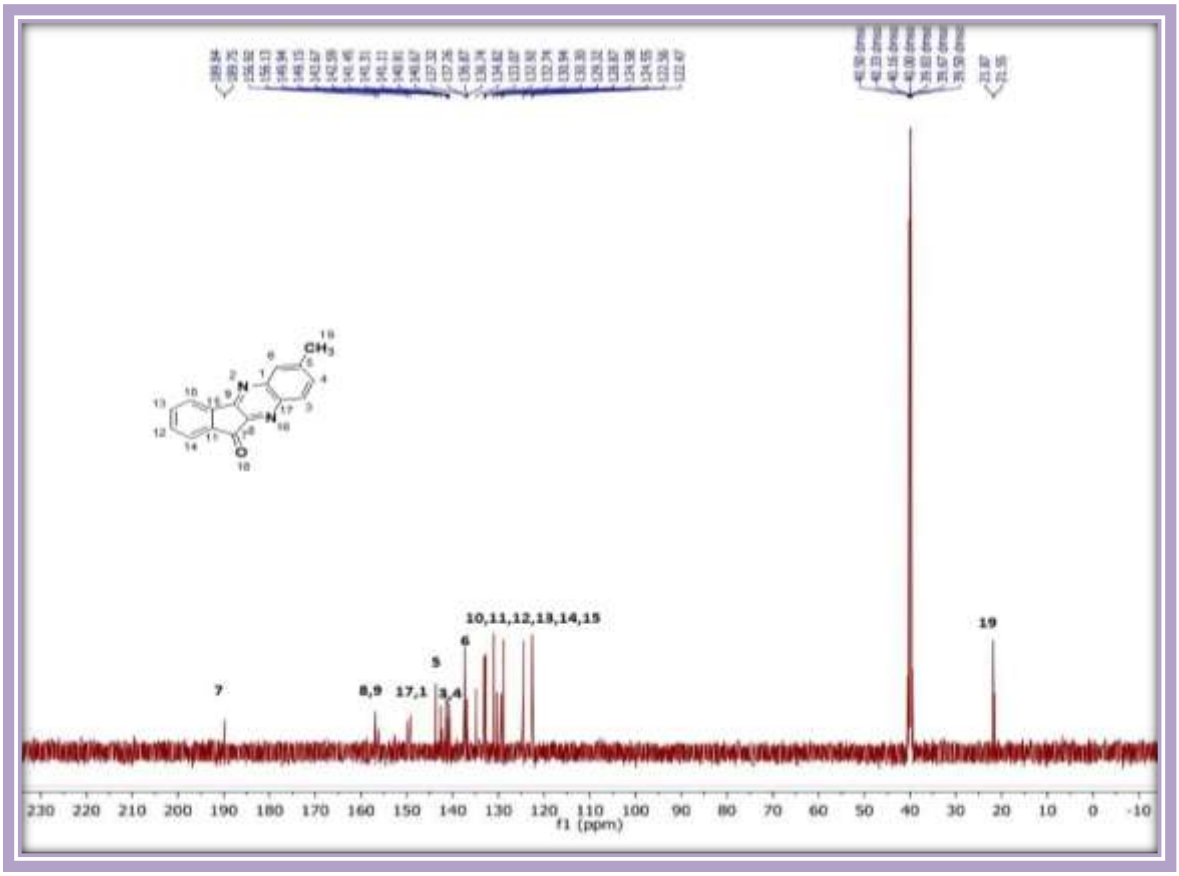


Figure (4.31): The ^{13}C-NMR spectra of the compound (Z_{11})

4.13.2 FT-IR of compound (Z_{11}) and its Complexes.

The FT-IR spectra of compound (Z_{11}) Figure (4. 32) show absorption bands at 3061 cm^{-1} and 3037 cm^{-1} were due to C-H aromatic ring. Bond absorption at 1729 cm^{-1} was due to C=O group .Absorption bands at 1625 cm^{-1} and 1607 cm^{-1} were due to C=N groups**[115-117]**. All these absorption bands an evidence to the formation of this compound (Z_{11}). Table (4. 1)explain the FT-IR spectra data of compound (Z_{11}).

The FT-IR spectrum of nickel, copper , zinc and cadmium complexes Figures (4.33) – (4.36) exhibited occurrence shifting in stretching vibration of the carbonyl C=O and C=N groups values with respect to free ligand, was good evidence of the coordination through the nitrogen atoms of quinoxaline ring, oxygen atoms of carbonyl groups of (Z_{11}) compound to the metal ion. In the other hand appeared new bands of weak intensity at (320, 317, 322, and 338) cm^{-1} which indicates vibration of M-Cl. for, Ni(II), Cu(II), Zn(II) and Cd(II) complexes respectively. In complexes appeared bands at (3432, 3491, 3381and 3469) cm^{-1} which referred to stretching band of H_2O uncoordination or out of sphere **[118]**. The FT-IR spectra data of ligand and its complexes were listed in Table (4.1).

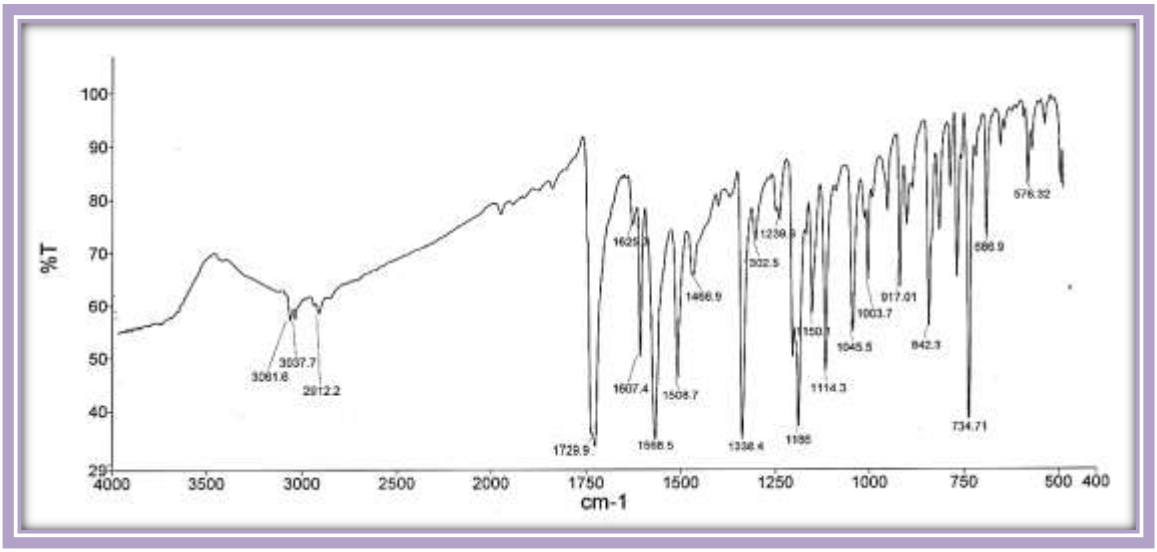


Figure (4. 32): FT-IR spectrum of compound(Z_{11})

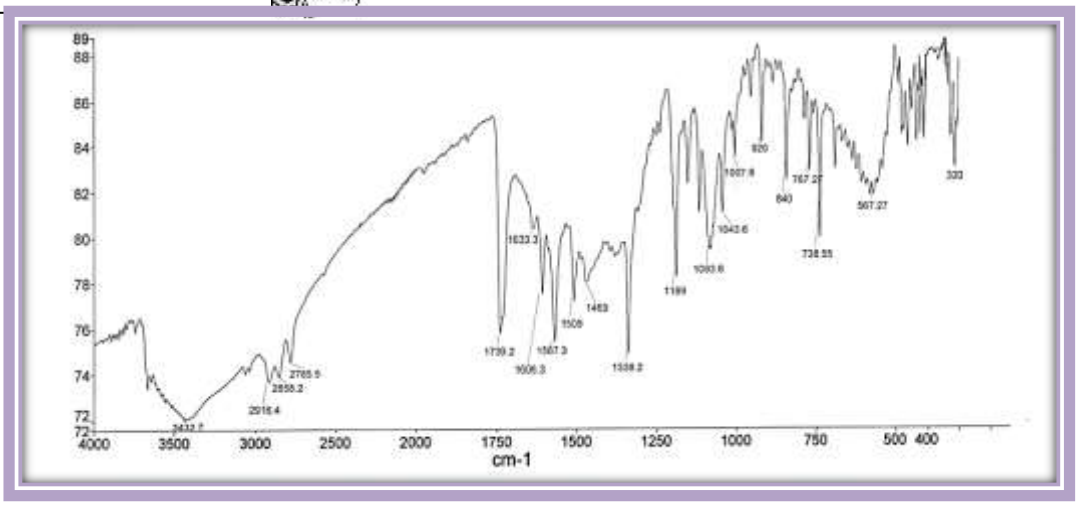


Figure (4.33): FT-IR spectrum of $[Ni(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

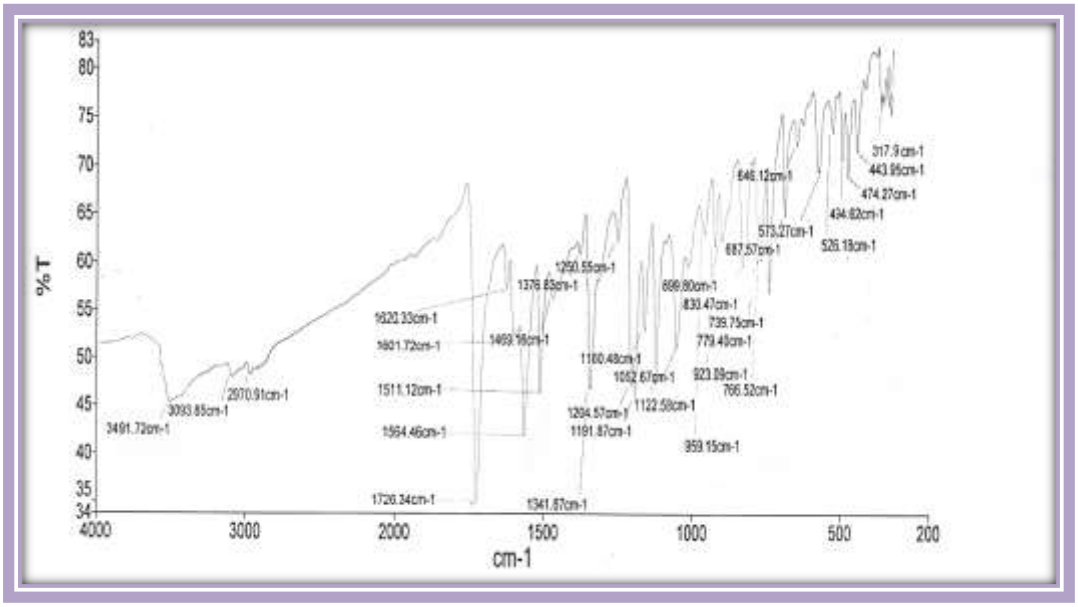


Figure (4.34): FT-IR spectrum of $[Cu(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

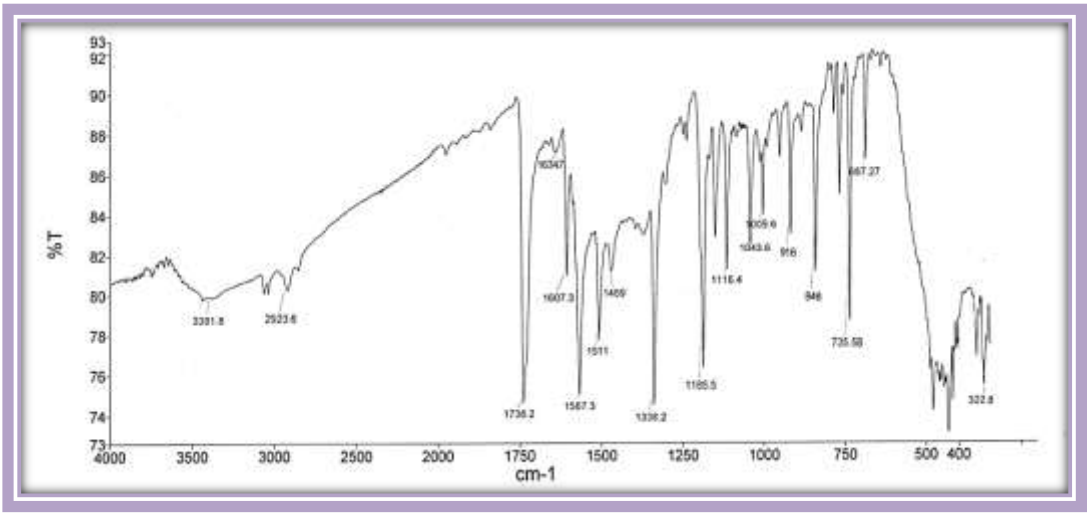


Figure (4.35): FT-IR spectrum of $[Zn(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

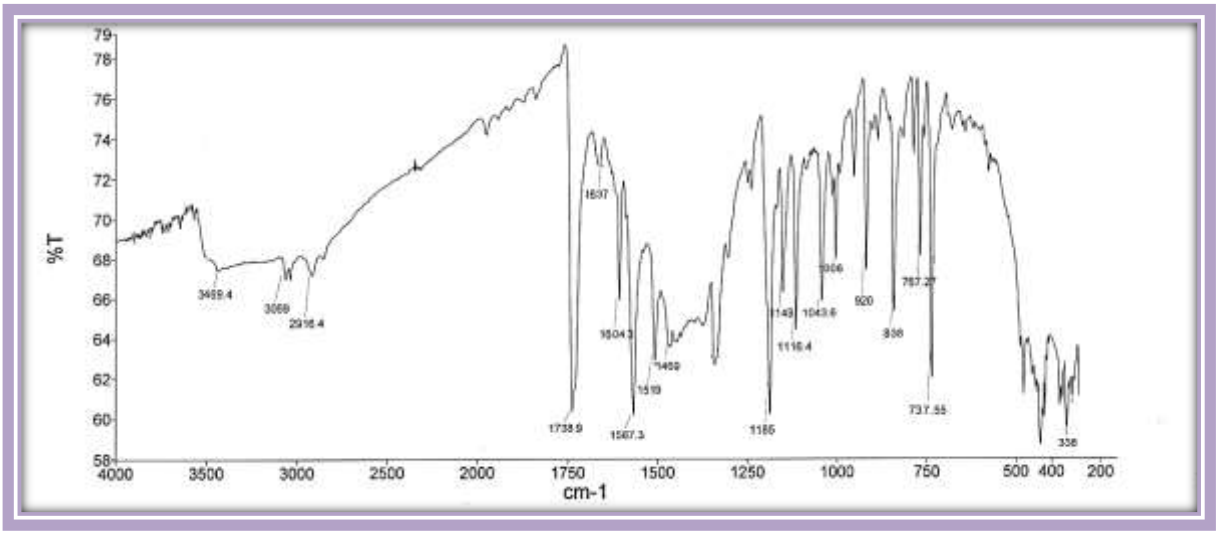


Figure (4.36): FT-IR spectrum of $[Cd(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

4.13.3. The electronic spectrum and magnetic susceptibility of complexes.

The electronic spectrum of compound $C_{16}H_{10}N_2O$ (Z_{11})in (UV-Vis) region in dimethyl sulfoxide solvent exhibited two bands as shown in Figure (4.37) and Table (4.3). The first absorption band attributed to $\pi \rightarrow \pi^*$ electronic transition which appeared at (311.4 nm, 32113 cm^{-1}), and second absorption band at (393.4 nm, 25419 cm^{-1}) assigned to $n \rightarrow \pi^*$ transition. **[119- 120]**.

The electronic spectrum of $[Ni(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$ complex Figure (4.38) was appeared two absorption bands at (304.4 nm, 32851 cm^{-1}) and (389.2 nm, 25693 cm^{-1}) were refers to intra ligand transitions, also the low intensity band was showed at (735.8 nm, 13590 cm^{-1}) assigned to d-d transitions $^3A2g_{(F)} \rightarrow {}^3T1g_{(F)}$. The observed magnetic moment value for this complex was (μ_{eff}= 3.1 B.M), indicating paramagnetic nature and octahedral geometry.

In the present work, the electronic spectrum of $[Cu(C_{16}H_{10}N_2O)_2Cl_2]. 6H_2O$ complex Figure (4.39) gave two bands at (304.2 nm, 32873 cm^{-1}) and (402.8 nm, 24826 cm^{-1}) were assigned to intra ligand transitions and new peak at (349.2 nm, 28636 cm^{-1}) and(371.6 nm, 26910 cm^{-})

refers to charge transfer (C.T) transition. As well as the complex shows one broad band at (685.2 nm, 14594 cm^{-1} attributed to electronic transition $^2Eg_{(D)} \rightarrow {}^2T_2g_{(D),}$ which is in conformity with the octahedral configuration around the copper ion**[121- 122]**. The value of (μ_{eff}) that measured for this complex is (1.7 B.M), indicating paramagnetic nature and octahedral geometry **[123]**.

The ultra violet-visible spectra of $[Zn(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$ and $[Cd(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$ complexes in Figure (4.40) and Figure (4.41) show no absorption band at (400-900) nm. That indicates no (d-d) electronic transition happened d^{10} system in the visible region and relative change in the bands position compared to that of the free ligand due to charge transfer between Zn, Cd ions and ligand. The prepared complex was diamagnetic which was expected for d^{10} ion**[124 -125]**.

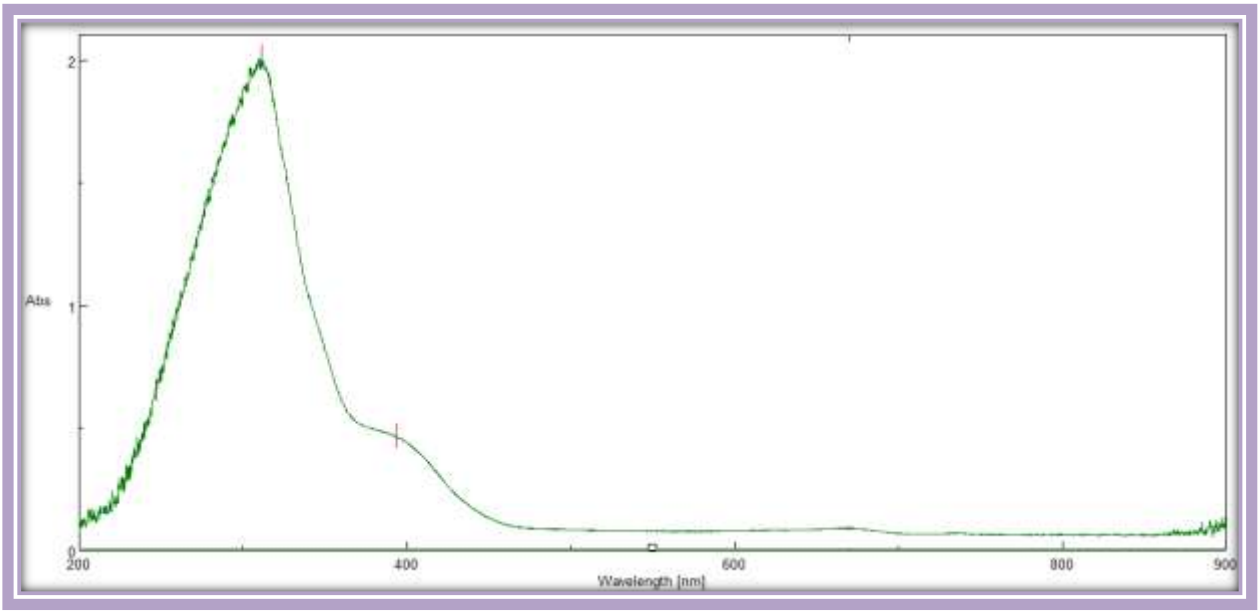


Figure (4.37): Electronic Spectrum of compound (Z_{11})

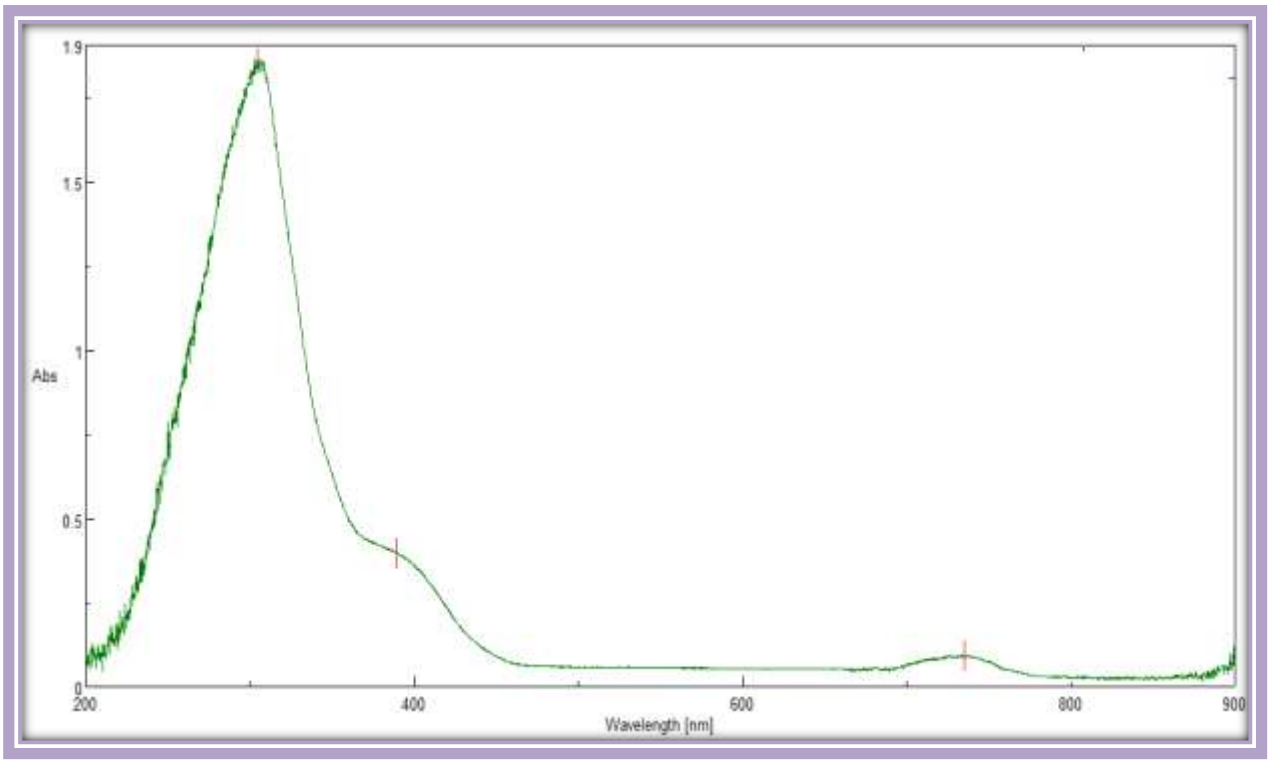


Figure (4.38): Electronic Spectrum of $[Ni(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

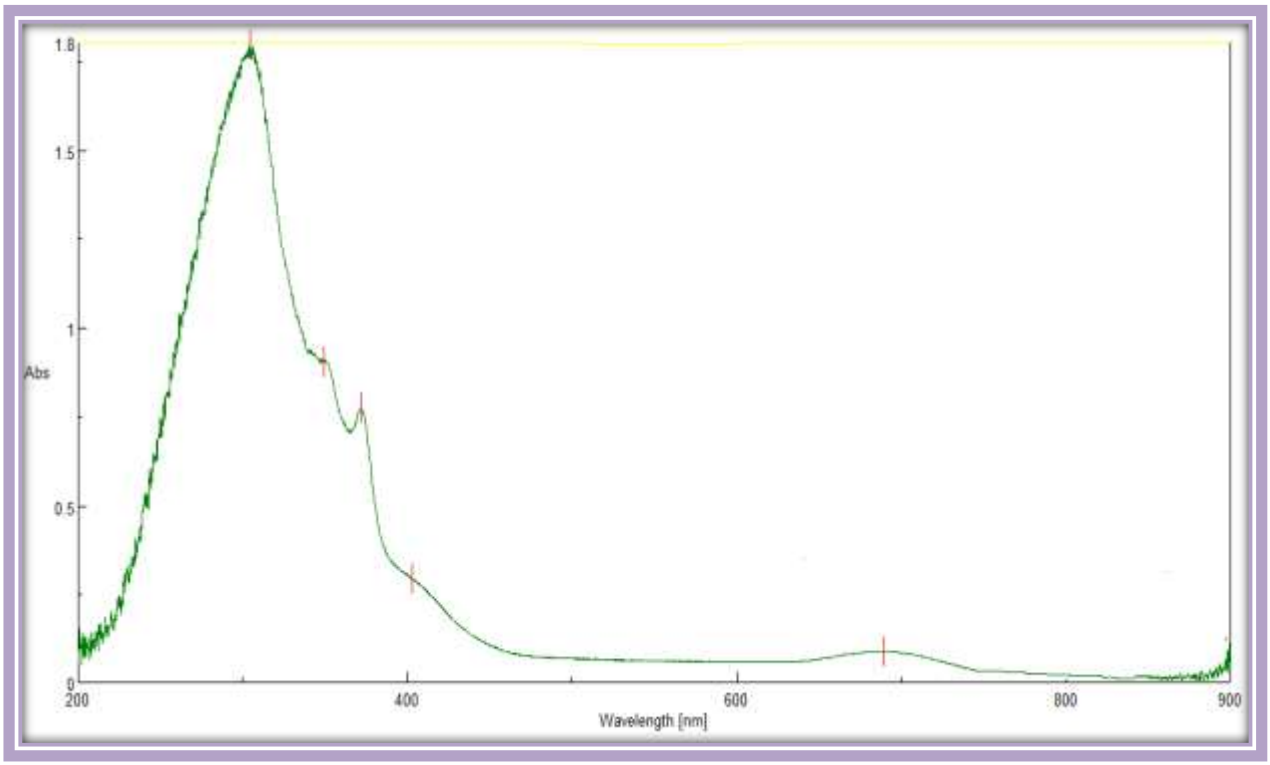


Figure (4.39): Electronic Spectrum of $[Cu(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

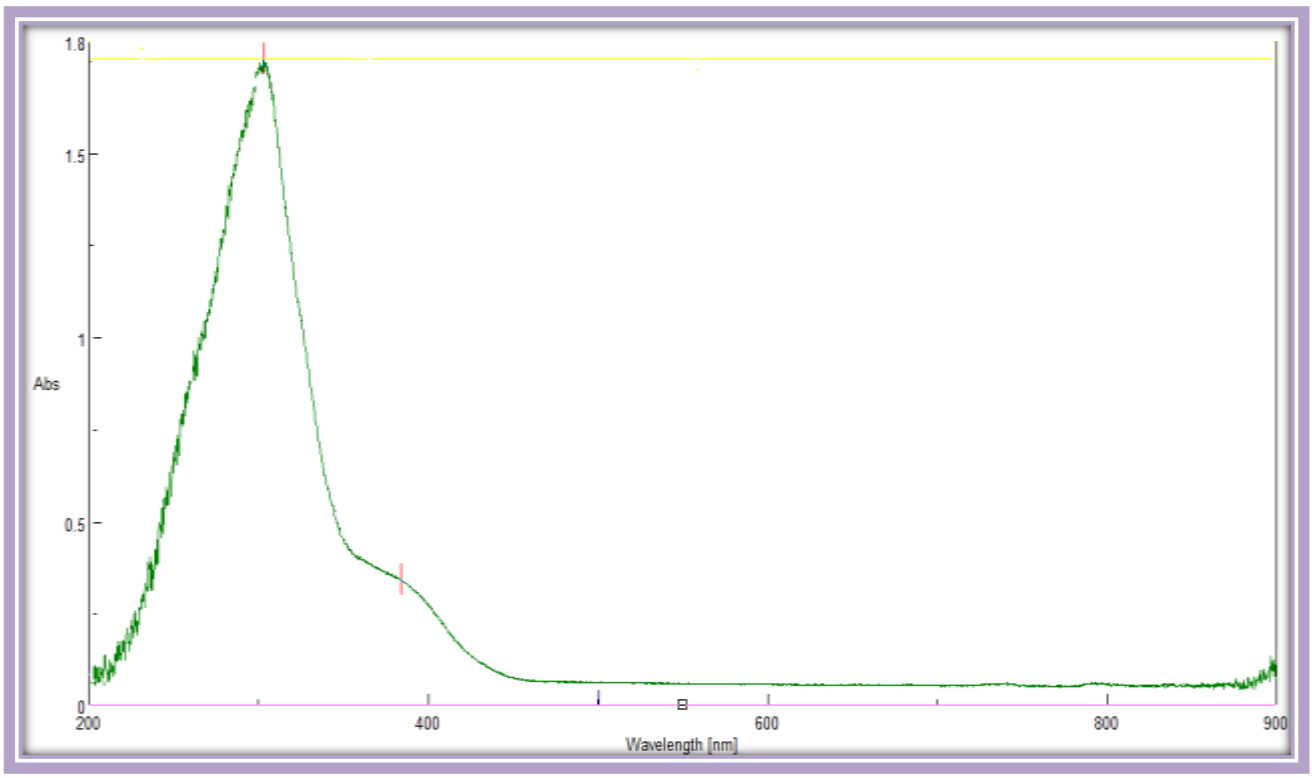


Figure (4.40): Electronic Spectrum of $[Zn(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

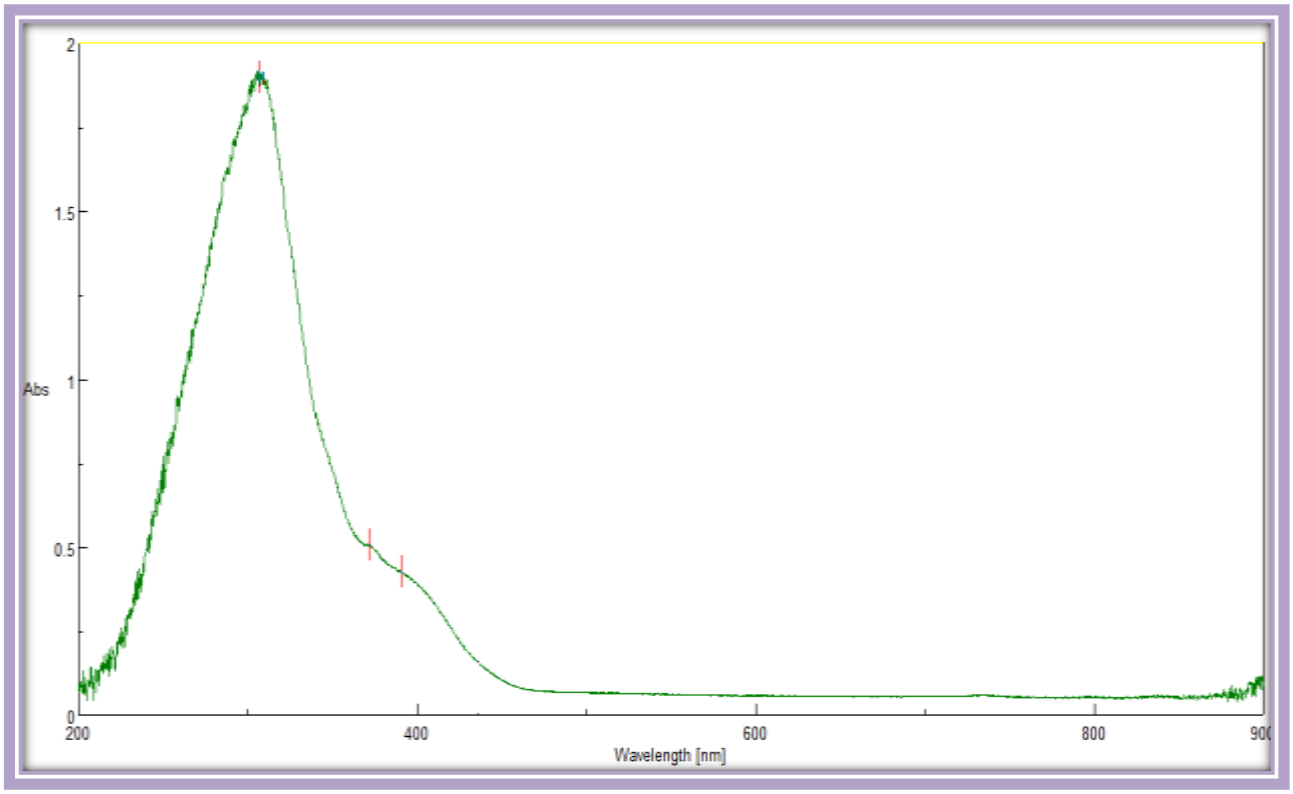


Figure (4.41): Electronic Spectrum of $[Cd(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

4.13.4.Physical properties and atomic absorption of the synthesized compound and the complexes.

The metal percentage of prepared complexes showed the calculated and found percentage values of metal was good agreement and was consistent with the structure of the synthesized complexes as shown in Table (4.3). In addition that, the physical properties of synthesized compounds and complexes were illustrated in Table (4.3).

4.13.5. Molar conductance of complexes$[M(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$

The molar conductance of all synthesized complexes was measured in EtOH at room temperature. The values obtained in the range (1.83 -18.53) $Cm^2.ohm^{-1}.\ mol^{-1}$, evidence that the complexes were non-ionic as illustrated in Table (3.2).

Table (4. 1):The most diagnostic FT-IR bands of the compounds (Z_1- Z_{11}) and the complexes in (cm^{-1}).

Comp.No.	ν C-H aromatic	ν C=O	ν C=C aromatic	ν C=N	Others
Z_1	------	1640	1556-1418	1614	ν (NH) 3352 ν (OH)3476
Z_2	-----	1749	1512-1487	1691-1619	ν (NH) 3418
Z_3	3069	1701	1516-1443	1618	ν (NH) 3200 ν (S=C)1232
Z_4	------	1651	1563-1461	1618	ν (NH)3345
Z_5	3061	1691	1589-1491	1632	ν (NH)3425
Z_6	----	1699	1511-1461	1598	ν (NH)3303 ν (OH)3373
Z_7	3076	1676	1500-1487	1618	ν (NH)3447 ν (C-Br)618
Z_8	------	1672	1512-1458	1614	ν (N-H) 3236 ν(C-H)aliphatic 2923
Z_9	3061	1683	1596-1444	1618	ν (N-H) 3214
Z_{10}	3054	1694	1541-1443	1621	ν (N-H) 3287
Z_{11}	3061-3037	1729	1558-1466	1625-1607	ν(C-H)aliphatic 2912

$[Ni(Z_{11})_2Cl_2].6H_2O$	3050 3033	1739	1567-1469	1633- 1606	M-Cl=320 Broad band (H_2O hydrate) M-N=511 M-O=603
$[Cu(Z_{11})_2Cl_2].6H_2O$	3093	1726	1564-1469	1620-1601	M-Cl=317 Broad band (H_2O hydrate) M-N=434 M-O=526
$[Zn(Z_{11})_2Cl_2].6H_2O$	3048 3060	1738	1567-1469	1634-1607	M-Cl=322 Broad band (H_2O hydrate) M-N=460 M-O=520
$[Cd(Z_{11})_2Cl_2].6H_2O$	3069	1738	1567-1469	1637-1604	M-Cl=338 Broad band (H_2O hydrate) M-N=450 M-O=501

Table(4.2): Electronic spectra ,conductance in ethanol solvent and magnetic moment for compound Z_{11} and its metal complexes.

Compounds	Absorption bands nm	Absorption bands Cm^{-1}	Assignments	M_{eff} B.M	Mol. Cond. $Cm^2.ohm^{-1}.Mol$	Suggested Geometry
$C_{16}H_{10}N_2O$	311.4 393.4	32113 25419	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$	-----	--------	-----
$[Ni(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$	304.4 389.2 735.8	32851 25693 13590	IL IL $^3A_2g_{(F)}\rightarrow{}^3T_1g_{(F')}$	3.1	1.83	Oh
$[Cu(C_{16}H_{10}N_2O)_2Cl_2].H_2O$	304.2 402.8 349.2 371.6 685.2	32873 24826 28636 26910 14594	IL IL CT CT $^2Eg_{(D)}\rightarrow{}^2T_2g_{(D)}$	1.7	18.53	Oh
$[Zn(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$	301.3 389.5	33189 25673	IL IL	0.00	1.91	Oh
$[Cd(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$	306.4 390.6 371.1	32637 26948 25601	IL IL CT	0.00	4.35	Oh

Table(4.3): Physical Properties for-new compounds Z_1 to Z_{11}, complexes and atomic absorption data for new prepared metal complexes

Comp. Symbol	Molecular Formula	M.Wt ($g.mol^{-1}$)	Color	M.P. ° C	Yield %	M % Found (Calc.)
Z_1	$C_{15}H_9N_3O_2$	263.26	Black	299-298	92	----
Z_2	$C_{15}H_8N_3OCl$	281.70	dark-Brown	281-280	72	----
Z_3	$C_{16}H_8N_4OS$	304.33	Light brown	288-287	81	----
Z_4	$C_{22}H_{15}N_5OS$	397.46	Brown – black	291-290	90	----
Z_5	$C_{22}H_{15}N_5O_2S$	413.46	Brown	297-296	62	----
Z_6	$C_{22}H_{15}N_5O_2S$	413.46	Light Green	290-289	64	----
Z_7	$C_{22}H_{14}BrN_5OS$	476.35	Brown	298-297	60	----
Z_8	$C_{23}H_{17}N_5O_2S$	427.48	Green	294-293	69	----
Z_9	$C_{22}H_{13}ClN_4OS$	416.88	Green	291-292	78	----
Z_{10}	$C_{26}H_{15}ClN_4O_2$	450.88	Light green	296-297	60	----
Z_{11}	$C_{16}H_{10}N_2O$	246.27	Brown yellow	176-177	90	----
Ni-complex	$[Ni(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$	730.189	Green	190-191 Dec	66	7.761 (8.038)
Cu-complex	$[Cu(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$	735.042	Dark green	185-186 Dec	71	8.198 (8.645)
Zn-complex	$[Zn(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$	736.906	Orange	220-221 Dec	59	7.453 (6.876)
Cd-complex	$[Cd(C_{16}H_{10}N_2O)_2Cl_2].6H_2O$	783.906	Brown	200-201 Dec	80	13.89 (14.339)

4. 14 Biological activity

The disk diffusion method was used to test the antibacterial activity of most of the target 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 Figure (4. 42). Table (4. 4) lists the antibacterial activity data of the

produced compounds. The test chemicals' antibacterial properties are briefly displayed here. The compounds $[Cu(Z_{11})_2Cl_2]$,$[Zn(Z_{11})_2Cl_2]$and $[Cd(Z_{11})_2Cl_2]$ showed high activity against *E. coli* bacteria while the compounds (Z_{11}), (Z_5) and $[Ni(Z_{11})_2Cl_2]$ showed moderate activity against *E. coli* bacteria, but compound (Z_3) don't appear any activity against *E. coli* bacteria. The compounds (Z_3), $[Ni(Z_{11})_2Cl_2]$, $[Zn(Z_{11})_2Cl_2]$and $[Cd(Z_{11})_2C_{l2}]$ showed moderate activity against *S. aureus* bacteria whereas the compounds (Z_5),(Z_{11}) and $[Cu(Z_{11})_2Cl_2]$ showed no any activity against the same type of bacteria.

Table 4. 4 : The inhibition zones of the compounds

Microorganism / Tested materials	*E. coli*				*S. aureus*			
	100	75	50	25	100	75	50	25
Z_3	R	R	R	R	15	15	14	14
Z_5	14	13	13	13	R	R	R	R
Z_{11}	15	14	12	11	R	R	R	R
$[Zn(Z_{11})_2Cl_2]$.$6H_2O$	21	20	20	20	13	12	14	16
$[Cd(Z_{11})_2\ Cl_2]$.$6H_2O$	21	20	21	20	16	13	12	13
$[Cu(Z_{11})_2\ Cl_2]$.$6H_2O$	23	23	22	20	R	R	R	R
$[Ni(Z_{11})_2\ Cl_2]$.$6H_2O$	16	11	10	10	14	14	12	12

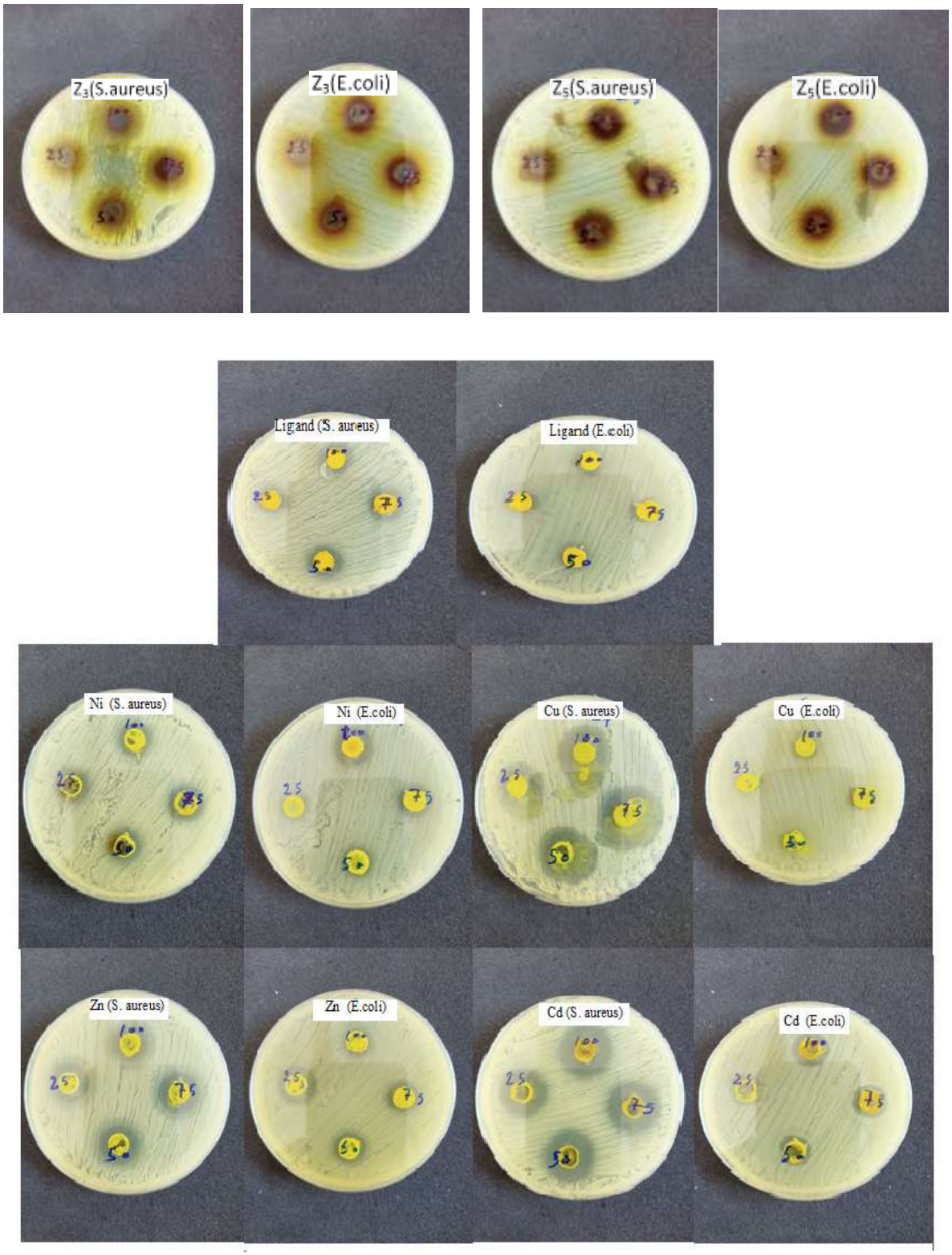


Figure (4. 42): Effects of the tested compounds (Z_3,Z_5,Z_{11} and it complexes) against *S. aureus and E. coil.*

Conclusion

According to the findings of this study:

1. Synthesis of ten new indole derivatives (Z_1-Z_{10}) from the reaction of isatin, they identified by FT-IR, ^{1}HNMR and ^{13}C-NMR spectroscopy techniques.

2. Synthesis of a new compound (Z_{11}) from 1H-indene-1,2,3-trione and its complexes and characterize them by using conventional techniques (FT-IR, UV-Vis, metal analysis, magnetic susceptibility and molar conductivity).

3. The ligand (Z_{11}) act like a bidentate ligand through coordination with nitrogen atom of a quinoxaline ring, oxygen atom of carbonyl group with Ni(II), Cu (II), Zn (II),and Cd(II)) ions.

4. Conductivity measurements showed that all the synthesized complexes were non-ionic.

5. According to the data obtained the proposal structures for complexes were octahedral geometry.

6. Some of the synthesized compounds were examined for their antibacterial activities toward two strains of bacteria (*E.colias*) and (*S. Aureus*). The result indicated that the activity against(*E.colias*) bacteria was high for $[Zn(Z_{11})_2Cl_2]$, $[Cd(Z_{11})_2Cl_2]$and $[Cu(Z_{11})_2Cl_2]$ moderate for (Z_{11}), [Ni $(Z_{11})_2Cl_2$], and (Z_5) and no apparent activity for (Z_3), Also the data proved the activity against (*S. aureus*) bacteria for compounds [Ni $(Z_{11})_2Cl_2$], [Cd $(Z_{11})_2Cl_2$], [Zn $(Z_{11})_2Cl_2$]and(Z_3) was moderate, whereas compounds $[Cu(Z_{11})_2Cl_2]$,(Z_{11})and(Z_5) showed no activity against this type of bacteria.

Suggestions for future work:

1. Synthesis a new chain of quinoxaline derivatives and determined their biological activities and industrial applications.
2. Synthesis a new chain of thiourea derivatives and determined their biological activities and industrial applications.
3. Synthesis a series of a new complexes for synthesized thiourea derivatives with different transition metal ions and evaluate their biological activities.

References

1. Ahmed S. K., Ali W. B., and Khadom A . A.(2019). Synthesis and characterization of 1،2،4triazol derivatives and study their activities as corrosion inhibitors of low carbon steel in acidic media. ***M.Sc. thesis,*** College of Science, University of Diyala, Iraq.

2. Mane V. D., Azeem S., Pande P. S., Malpani M. O., and Kharat H.J. (2018). Synthesis of some flavone and pyrazoline derivative and their antimicrobial and physicochemical study. ***International Journal of Current Engineering and Scientific Research***, 5(1): 489- 493.

3. Ahmed S. H.(2015). Transition Metal Catalyzed Synthesis of Biologically Active Heterocycles. ***European Academic Research***, 3(3): 3299–3314.

4. Mandour A. A., Nabil N., Zaazaa H. E., and Abdelkawy M. (2020). Review on analytical studies of some pharmaceutical compounds containing heterocyclic rings: brinzolamide, timolol maleate, flumethasone pivalate, and clioquinol. ***Future Journal of Pharmaceutical Sciences***, 6(52): 1-10.

5. Hossain M. and Nanda A. K. (2018). A review on heterocyclic: synthesis and their application in medicinal chemistry of imidazole moiety. ***Science Journal of Chemistry***, 6(5):83–94.

6. Karaaslan C. and Suzen S. (2011). Electrochemical Behavior of Biologically Important Indole Derivatives**.** ***International Journal of Electrochemistry***, 1-10.

7. Dânoun K., Essamlali Y., Amadine O., Mahi H. and Zahouily M. (2020).Eco-friendly approach to access of quinoxaline derivatives using nanostructured pyrophosphate $Na_2PdP_2O_7$as a new, efficient and reusable heterogeneous catalyst. ***BMC Chemistry*** ,14(6):1-13.

8. Sahu, S., Rani Sahoo, P., Patel, S., & Mishra, B. K. (2011). Oxidation of thiourea and substituted thioureas: a review. ***Journal of Sulfur Chemistry***, *32*(2), 171-197.

9. Katla, R. V., Syed, R., Golla, M., Shaik, A., & Chamarthi, R. N. (2014). Synthesis and biological evaluation of novel urea and thiourea derivatives of valacyclovir. ***Journal of the Serbian Chemical Society***, 79(3), 283-289.

10. Alan R. K., Xiaohong C. and Boris V. R. ,2002, "Solid phase synthesis and application of trisubstituted thioureas",Center for Heterocyclic Compounds, 392-399.

11. Murthya Y. L. N., Manib P., Govindha B., Diwakara B. S., Karthikeyana N., Raoc T. R. and Rao K. V. R.(2011). Synthesis and characterization of 2,3-diphenyl quinoxaline 1,4-di-N-oxide derivatives and study of their antimicrobial activities.***Research Journalof Pharmaceutical, Biological and ChemicalSciences***,2(1) :553- 560.

12. Dowlatabadi R., Khalaj A., Rahimian S., Montazeri M., Amini M., Shahverdi, A., and Mahjub E. (2011). Impact of substituents on the isatin ring on the reaction between isatin with ortho-phenylene diamine. ***Synthetic Communications***, 41(11): 1650-1658.

13. Shibinskaya M. O., Kutuzova N. A., Mazepa A. V., Lyakhov S. A., Andronati S. A., Zubritsky M. J., Galat V. F., Lipkowski J., and Kravtsov V. C. (2012). Synthesis of 6-Aminopropyl-6H-indolo [2, 3-b] quinoxaline Derivatives. ***Journal of Heterocyclic Chemistry***, 49(3): 678-682.

14. Khazaei A., Massoudi A. and Chegeni M. (2014). synthesis of bisindolylindeno[1,2-b]-quinoxaline and bisindolylindeno[3,4-b]- pyrazine

with poly (N,N'-dibromo-N-ethylnaphthyl-2,7disulfonamide.***Synthetic Communications***, (44): 633–639.

15. Sarhan B. M., Lateef S. M., Waheed E. J. (2016). Synthesis and characterization of some new eetals complexes of [N-(3-acetyl phenylcarbamothioyl)-4-methoxybenzamide]. ***Diyala Journal for Pure Science***, 12(1): 28-42.

16. Ahmed N. K. and Al-Abdaly B. I. M. (2016). Synthesis, characterization and study of antibacterial activities of ligands type (OS and ONS) and their metal complexes with some divalent metal ions, ***M.Sc., Thesis***, University of Baghdad.

17. Raheel A., Din I., Badshah A., Rauf M. K., Tahir M. N., Khan K. M., Hameed A. and Andleeb S.(2016).Amino acid linked bromobenzoyl thiourea derivatives: syntheses, characterization and antimicrobial activities.***J.Chem.Soc.Pak***., 38(5):959-965.

18. Bajpai S., Gajaganti S., Srivastava V., and Singh S. (2017). Development of greener approach: microwave assisted synthesis of quinoxaline derivatives in water. ***Journal of Scientific Research***, (61): 173-177.

19. Ngah F. A. A., Zakariah E. I., Hassan N. I., Yamin B., Sapari S. and Hasbullah S. A.(2017).Synthesis of thiourea derivatives and binding behavior towards the mercury ion. ***Malaysian Journal Of Analytical Sciences***,21(6): 1226-1234.

20. Fayomia O. M., Sha'Atob R., Wuanab R. A., Igolib J. O., Moodleya V. and Van Zyla W. E.(2018).Spectroscopic and antibacterial studies of some nitro-substituted n-(benzoyl carbamothioyl)amino acids: the crystal structure of n-

(3-nitrobenzoylcarbamothioyl)-glycine.***J. Chem Soc. Nigeria***, 43(2): 119-132.

21. Ismail K. A., Ali W. B. and Jarullah A. A. (2020). Synthesis, characterization and antifungal activity of some indolo [2-3-b] quinoxaline derivatives. ***Journal of Global Pharma Technology***, 12(2): 727-736.

22. Mane, D., Azeem, S., Pande, S., Malpani, O., and Kharat, J . (2018) . Synthesis of some flavone and pyrazoline derivative and their antimicrobial and physicochemical study. ***Current Engineering and Scientific Research,*** (5): 489- 493.

23. Mohammed, I. (2017). Synthesis of New Heterocyclic Polymers from Chalcone. ***Iraqi National Journal of Chemistry***, 17(1).

24. Patneedi, C. B., Prasadu, K., & Sharma, R. S. K. (2015). Synthesis of the heterocyclic chalconoid derivatives. ***Der Pharma Chemica***, 7(8), 10-16.

25. Shukla, P. K., Verma, A., & Mishra, P. (2017). Significance of nitrogen heterocyclic nuclei in the search of pharmacological active compounds. ***New Perspective in Agricultural and Human Health***, 2(1): 100-126.

26. Joule, J. A., and Mills, K. (2012). Heterocyclic chemistry at a glance. 2nd ed. John Wiley and Sons. ***USA***, 354-357.

27. Gandhi, D., Kalal, P., & Gupta, S. (2017). Synthetic aspects and Biological Studies of some Heterocycles. chemistry & biology interface, 7(2), 79-101.

28. Gupta, R. R., Kumar, M., & Gupta, V. (1999a). Benzo-Fused Five-Membered Heterocycles with One Heteroatom. In R. R. Gupta, M. Kumar, & V. Gupta (Eds.), Heterocyclic Chemistry: Volume II: Five-Membered Heterocycles, 181-355. Berlin, Heidelberg: Springer Berlin Heidelberg.

29. Rakesh, K., Mohd, S. Y., Saurabh, C., and Atul, S. (2013). Triazole as Pharmaceuticals Potentials. ***Int. J. Pharm Tech Res***, 5(4), 1844-1869.

30. Zaki R. M., Kamal El-Dean A. M., Radwan S. M., and Abdul-Malik M. A., (2018). A convenient synthesis, reactions and biological activities of some novel thieno [3,2-e] pyrazolo [3, 4-b] pyrazine compounds as anti-microbial and anti-inflammatory agents. ***Current Organic Synthesis***, 15(6): 863-871.

31. Mohammed , A. M. (2018) . Synthesis and characterization of some new benzimidazole derivatives and their biological activity study. ***M.Sc. thesis,*** College of Science, University of Diyala, Iraq.

32. Ali I. Nadeem Lone M., A Al-Othman Z., Al-Warthan A., and Marsin Sanagi M. (2015). Heterocyclic scaffolds: centrality in anticancer drug development**.** ***Current drug targets***, 16(7): 711-734.

33. Santosh R., Selvam M. K., Kanekar S. U., and Nagaraja G. K. (2018). synthesis, characterization, antibacterial and antioxidant studies of some heterocyclic compounds from triazole-Linked chalcone derivatives. ***Chemistry Select,*** 3(23): 6338-6343.

34. Sourav, D. E., Babu, N. M., Babu, S. T., Dree, B. R., Kiran, S. A., & Reddy, S. K. (2016). A review article on importance of heterocyclic compounds. ***Mintage J Pharma Med Sci, (5***): 18-27.

35. Khan ,S.A., Asiri ,A. M. (2012). "Synthesis , Characterization , and In Vitro Antibacterial Activities of Macromolecules Derived from Bis-Chalcone," ***J. Heterocycl. Chem, v***(49): 1434–1439.

36. Dubal, G. G. (2009). Studies on some novel bioactive synthetic compounds (Doctoral dissertation, Saurashtra University).

37. Kgokong, J. L., Smith, P. P., & Matsabisa, G. M. (2005). 1,2,4- Triazino-[5,6b]indole derivatives: effects of the trifluoromethyl group on in vitro antimalarial activity. ***Bioorganic & Medicinal Chemistry***, 13(8): 2935-2942.

38. Jalandra, R., & Jadon, G. (2014). A review article on Indole. ***International Journal of Advanced Research in Pharmaceutical & Bio Sciences***, 4(1), A1-A1.

39. Kerzarea, D. R., and Khedekar, P. B. (2016). Indole derivatives acting on central nervous system–review. *J.* ***Pharm Sci Bioscientific,*** *6*(1):144-156 .

40. Naim, M. J., Alam, O., Alam, J., Bano, F., Alam, P., and Shrivastava,N. (2016). Recent review on indole: a privileged structure scaffold. ***Int. J. Pharm. Sci. Res***, (7): 51-62.

41. Srivastava A., and Pandeya S. N. (2011). Indole a versatile nucleuse in pharmaceutical field. ***Int. J. Curr. Pharm. Rev. Res***, (*4)*: 5-8.

42.AL-Saggaf, A. T. (2008). Study the chemical structure of indole alkaloides from Aspidosperma excelsum A and Ambolania occidentales.

43. Kobelev, A. I., Stepanova, E. E., Dmitriev, M. V., and Maslivets, A. N. (2019). Annulation of 1H-pyrrole-2, 3-diones by thioacetamide: an approach to 5-azaisatins. *Beilstein* ***Journal of Organic Chemistry***, *15*(1): 364-370.

44. Guksu, Z., Palabıyık, O., Karaca, A., Süt, N., and Vardar, S. A. (2019). Effect of isatin on ischemia and reperfusion injury: an experimental study in the isolated rat heart. ***Koşuyolu Heart Journal***, *22*(1): 57-62.

45. Alkam, H. H. (2017). Synthesis and characterization of new bidentate schiff base ligand type (NO) donor atoms derived from isatin and 3-amino benzoic acid and its complexes with Co (II), Cu (II), Cd (II) and Hg (II) ions. ***Ibn AL-***

Haitham Journal For Pure and Applied Science, *30*(3): 158-169.

46. Vandana, K., Marathakam, A., Thushara, B. S., and Rajitha, K. (2017). A review on isatin derivatives with diverse biologigal activities. ***World Journal of Pharmaceutical Researc***, *6(16):* 318-332 .

47. Grewal, A. S. (2014). Isatin derivatives with several biological activities. ***International Journal of Pharmaceutical Research***, *6*(1): 1-7.

48. Baluja, S., Bhalodia, R., Bhatt, M., Vekariya, N., and Gajera, R. (2013). Solubility of a pharmacological intermediate drug isatin in different solvents at various temperatures. ***International Letters of Chemistry***, *Physics and Astronomy*, *12*: 36-46 .

49. Mathur, G., and Nain, S. (2014). Recent advancement in synthesis of isatin as anticonvulsant agents: a review. ***Med. Chem***, *4*(4): 417-427.

50. Chandra, P. M., and Venkateshwar, J. (2014). Biological evaluation of Schiff bases of new isatin derivatives for anti alzheimer's activity. ***Asian J . Pharm Clin Res***, *7*(2): 114-7.

51. Moradi, R., Ziarani, G. M., and Lashgari, N. (2017). Recent applications of isatin in the synthesis of organic compounds. ***Arkivoc***, *2017*(1): 148-201.

52. Khan, F. A., and Maalik, A. (2015). Advances in pharmacology of isatin and its derivatives: A review. ***Tropical Journal of Pharmaceutical Research,*** *14(10):* 1937-1942.

53. Birolli, W. G., Ferrreira, I. M., Jimenez, D. E., Silva, B. N., Silva, B. V., Pinto, A. C., and Porto, A. L. (2017). First asymmetric reduction of isatin by

marine-derived fungi. ***Journal of the Brazilian Chemical Society***, *28*(6): 1023-1029.

54. Asif, M. (2017). A mini review on synthesis and biological activities of isatin derivatives. ***Universal Journal of Chemistry,*** *1*(1): 17-26.

55. Chittethu, A. B., Asha, J., Balasubramanian, R., Saranya, T. S., and Manakadan, A. A. (2017). Utility of isatin semicarbazones in mammary carcinoma cells-A proof of concept study. ***Journal of Young Pharmacists***, *9*(2): 218

56. Banerjee, B. (2017). Recent developments on ultrasound-assisted one-pot multicomponent synthesis of biologically relevant heterocycles. ***Ultrasonics sonochemistry***, *35*: 15-35 .

57. Xie, Z., Wang, G., Wang, J., Chen, M., Peng, Y., Li, L., and Li, W. (2017). Synthesis, biological evaluation, and molecular docking studies of novel isatin-thiazole derivatives as α-glucosidase inhibitors. ***Molecules***, *22*(4): 659 .

58. Dogan , İ. S., Bolek, G. G., and Kahveci, B. (2019) . Synthesis of Some New Isatin Derivatives and Identification of Their Structures. ***Süleyman Demirel Üniversitesi Fen Bilimleri Enstitüsü Dergisi***, *23*: 67-70.

59. Yurttaş, L., Ertaş, M., Cankılıç, M. Y., and Demirayak, Ş. (2017). Synthesis and antimycobacterial activity evaluation of isatin-derived 3- [(4-aryl-2-thiazolyl]) hydrazone]-1H-indol-2,3-diones. ***Acta Pharmaceutica Sciencia***, *55(1):* 1307-2080 .

60. Jayabalakrishnan, C., and Natarajan, K. (2001). Synthesis, characterization,

and biological activities of ruthenium (II) carbonyl complexes containing bifunctional tridentate Schiff bases. *Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry*, *31*(6): 983-995.

61. Fernandes, I. P., Silva, B. V., Silva, B. N., Pinto, A. C., Oliveira, S. C. B., and Oliveira-Brett, A. M. (2018). Isatin 1-morpholinomethyl, 1-hydroxymethyl, 1-methyl, and their halogenated derivatives, redox behaviour. ***Journal of Electroanalytical Chemistry***, *812*: 143-152.

62. Meenakshi, K., Gopal, N., and Sarangapani, M. (2014). Synthesis, characterization and antimicrobial activity of some novel Schiff and Mannich bases of isatin. ***Int. J. pharm sci***., *6*(6): 318-322.

63. Haghighi, M., and Nikoofar, K. (2016). Nano TiO2/SiO2: an efficient and reusable catalyst for the synthesis of oxindole derivatives. ***Journal of Saudi Chemical Society***, *20*(1): 101-106.

64. Mishra, K. N., Sengupta, S. K., Pandey, O. P., and Goswami, S. (2017). Synthesis, physicoanalytical characterization and biological activity of Isatin Thiosemicarbazones derivatives of Dichloro bis (cyclopentadienyl) hafnium (IV)(Cp_2HfCl_2). ***Research Journal of Pharmaceutical Biolgical and Chemical Sciences***, *8*(3): 1779-1785 .

65. Birolli, W. G., Ferrreira, I. M., Jimenez, D. E., Silva, B. N., Silva, B. V., Pinto, A. C., and Porto, A. L. (2017). First asymmetric reduction of isatin by marine-derived fungi. ***Journal of the Brazilian Chemical Society***, *28(6):* 1023-1029.

66. Tisovský, P., Šandrik, R., Horváth, M., Donovalová, J., Jakusová, K., Cigáň,

M., and Filo, J. (2017). Effect of structure on charge distribution in the isatin Anions in aprotic environment: Spectral study. ***Molecules***, *22(11):* 1961.

67. Divar, M., Khalafi-Nezhad, A., Zomorodian, K., Sabet, R., Faghih, Z., Jamali, M., and Khabnadideh, S. (2017). Synthesis of some novel semicarbazone and thiosemicarbazone derivatives of isatin as possible biologically active agents. ***British Journal of Pharmaceutical Research***, *17*(6):1-13 .

68. Ziarani, G. M., Moradi, R., and Lashgari, N. (2016). Synthesis of spiro-fused heterocyclic scaffolds through multicomponent reactions involving isatin. ***ARKIVOC: Online Journal of Organic Chemistry***, (i): 1- 81.

69. Makarem, S., Mirza, B., Mohammad Darvish, Z., Amiri Notash, N., & Ashrafi, S. (2019). Organic electrosynthesis: apromising alternative methodology for the synthesis of nanosized particles of pyrans. ***analytical and bioanalytical Chemistry Research***, *6*(1): 231-240.

70. Kumar, R., and Kumar, M. (2018). Synthesis of 3-[4-(2-Amino-6 (substituted phenyl)-pyrimidin-4-yl)-phenylimino]-5-chloro-1, 3-dihydro- indol-2-one derivatives of 5-chloroisatin as potential antimicrobial agents. ***Journal of Pharmaceutical, Chemical and Biological Sciences***, *5*(4): 399-404 .

71. Da Silva, J. F., Garden, S. J., and Pinto, A. C. (2001). The chemistry of isatins: a review from 1975 to 1999. ***Journal of the Brazilian Chemical Society***, *12*(3): 273-324.

72. Aboul-Fadl, T., Bin-Jubair, F. A., and Aboul-Wafa, O. (2010). Schiff bases

of indoline-2, 3-dione (isatin) derivatives and nalidixic acid carbohydrazide, synthesis, antitubercular activity and pharmacophoric model building. ***European journal of medicinal chemistry***, *45*(10): 4578- 4586.

73. Zlatković, M. Z., Troter, D. Z., Stanojević, J. S., Todorović, Z. B., Cakić, V. S., and Konstantinović, S. S. (2018). Antibacterial activity and photolytic stability of synthesized 5-chloroisatin-3-hydrazone. ***Advanced Technologies***, *7*(1): 41-46.

74. Yılmaz, F., Karaali, N., and Şaşmaz, S. (2017). Microwave-assisted synthesis of some nitro-benzimidazoles and their salicyl and isatin Schiff bases. ***Bulletin of the Chemical Society of Ethiopia***, *31*(2): 351- 359.

75. Meeran, M. N., and Hussain, A. Z. (2017). Synthesis, Characterization and DPPH scavenging assay of isatin related spiroheterocyclic compounds. ***Indian Journal of Pharmaceutical Sciences***, *79*(4): 641-645.

76. Khaleel, A. M. (2008). Synthesis and characterization of new schiff bases and amides derived from N(1) substituted isatin with 2- aminobenzothiazole, 2-aminopyrimidine and dithiooxamide and some of their metal complexes. (Doctoral thesis , College of Science, University of Baghdad , Iraq) .

77. Al Maamari, K. A. (2013). Isatin drivatives: synthesis, reactivity and anti corrosion properties. (Doctoral thesis , College of Rabat faculty , University of mohammed V) .

78. Irfan, A., Sabeeh, I., Umer, M., Naqvi, A. Z., Fatima, H., Yousaf, S., & Fatima, Z. (2017). A review on the therapeutic potential of quinoxaline derivatives. ***World J. Pharm. Res,* (*6*)**: 47-68.

79. Bahekar, R. H., Jain, M. R., Gupta, A. A., Goel, A., Jadav, P. A., Patel, D. N., ... & Patel, P. R. (2007). Synthesis and Antidiabetic Activity of 3, 6, 7-Trisubstituted-2-(1H-imidazol-2-ylsulfanyl) quinoxalines and Quinoxalin-2-yl isothioureas. ***Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry, 340***(7): 359-366.

80. Noorulla S. &Sreenivasulu N.(2011). Antibacterial activity of novel substituted quinoxaline heterocycles with isoniazide. ***International Journal of Research in Pharmaceutical andBiomedical Sciences***, (2): 1100-1106.

81. Potey CL, Marathe R, Nikhade RR, Sarode SR.(2014). Quinoxaline as attractive target of research. Indo American of Pharmaceutical Research, (04): 1063-1066.

82. Chandrasekhar, S., Reddy, N. K., & Kumar, V. P. (2010). Oxidation of alkynes using $PdCl_2/CuCl_2$ in PEG as a recyclable catalytic system: one-pot synthesis of quinoxalines. ***Tetrahedron Letters, 51***(28): 3623-3625.

83. Kumar, K., Mudshinge, S. R., Goyal, S., Gangar, M., & Nair, V. A. (2015). A catalyst free, one pot approach for the synthesis of quinoxaline derivatives via oxidative cyclisation of 1, 2-diamines and phenacyl bromides. ***Tetrahedron letters***, 56(10), 1266-1271.

84. Dong, F., Kai, G., Zhenghao, F., Xinli, Z., & Zuliang, L. (2008). A practical and efficient synthesis of quinoxaline derivatives catalyzed by task-specific ionic liquid. ***Catalysis Communications,*** *9*(2): 317-320.

85. Heravi MM, Baghernejad B, Oskooie HA. (2009). A novel three-component reaction for thesynthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines. ***Tetrahedron Letters***, (50):767-769.

86. Potey CL, Kosalge BS, Hadke AM.(2013). Synthesis and antimicrobial activity of quinoxaline sulfonamide. ***International Journal of Advancements in Research &Technology,*** (2):126-133.

87. Dharmchand PS, Sanjay KD, Syed RH. Ram GS.(2010). Synthesis and antimicrobial activity of some new quinoxaline derivatives. ***Pharmaceuticals***,(3): 2416-2425.

88. Bakavolia M, Hossein E, Hamid A, Sattar S., Faezeh B.(2014). One-pot procedure for thepreparation of some thiazino[2,3-b]quinoxaline derivatives. ***Journal of ChemicalResearch***, (38): 189–191.

89. More M.P., Shradha R.J., Sandip S.K., Rajesh J.O.(2012). To study the effect of solvent on the synthesis of novel quinoxaline derivatives. ***Open Access Scientific Reports,(*** 1): 1-3.

90. Abdulfattah M. A., Zaineb I. L. and Ahmed E.Z. (2011). "Synthesis and use of thiourea derivative (1-phenyl-3-benzoyl-2-thiourea) for extraction of cadmium ion", ***International Journal of Chemical, Nuclear, Metallurgical and Materials Engineering***,(8):118-120.

91. Ziegler K. S., Kielhorn J., Könnecker G., Koppenhöfer J. and Mangelsdorf I.(2003). "Thiourea",Concise ***International Chemical Assessment Document***, 49, and reference there in.

92. Gun B., Bülent Z., Esma K., Nevzat K. and Hakan A.(2012). "Determination of the ionization constants of some benzoyl thiourea derivatives in dioxane-water mixture", ***Journal of Chemistry***, 1-7.

93. Alan R. K., Xiaohong C. and Boris V. R. (2002). "Solid phase synthesis and application of tri substituted thioureas",Center for Heterocyclic Compounds, 392-399.

94. Venkata R. K., Rasheed S., Madhava G., Adam S. and Naga R.C.(2014). "Synthesis and biological evaluation of novel urea and thiourea derivatives of valaciclovir" ***Journal Serbian Chemical Society***,79(3) :283–289.

95. Abdel-Sayed N. I. (2009). Novel routes to triazino [5, 6-b] indole and indolo [2, 3-b] quinoxaline derivatives. ***Bulgarian Chem,***41(4): 362-367.

96. Saeed, A., Abbas, N., Rafique, H., Rashid, S., & Hameed, A. (2009). Synthesis, characterization and antibacterial ctivity of some 1-aroyl-3-aryl thioureas. ***chemistry***, *18*(5): 152-158.

97. George M. N., Constantin D., Mariana C. C. and Alexandru V. M. (2009). "Synthesis of isomeric N-(1-methyl-1-hpyrazole-4-carbonyl)-N'-(XYLYL)-thiourea and their antimicrobial evaluation", Farmacia,57(5):527-533.

98. George,M., Joseph, L., and Thomas, A. (**2017**). Synthesischaracterization and biological screening of novel indole derivatives for certain pharmacological activities. ***Synthesis***, *2*(4).

99. Saleem L.M.N. and Sultan R.H.(2014). "Keto-enol tautomerism of Schiff-bases derived from 2-hydroxy naphthaldehyde and substituted aniline with LSR Pr(fod)3", ***International Journal of Enhanced Research in Science Technology and Engineering,*** *(3)*:167-172.

100. Robina A., Garima M., Manju L.U. and Tripti G. (2013). "Triorganotin (IV) complexes of Schiff base derived from glycine: synthesis, characteristic spectral studies and antifungal activity", ***Chemical Science Transactions,****2(2)*:389-394.

101. Zangade S. B., (2017). Irradiation of tungsten light: A useful energy source for synthesis of 4, 5-dihydro-pyrazole-1-carbaldehyde derivatives. orbital: ***The electronic Journal of Chemistry,*** 9(4): 315-317.

102. Zaranappa, H. M. Vagdevi, M. R. Lokesh, and B. C. Gowdarshivannanavar.(2012). "Synthesis and antioxidant activity of 3-substituted Schiff bases of quinazoline-2,4-diones," ***Int. J. ChemTech Res.,*** 4(4): 1527–1533.

103. Vartale, S. P., Halikar, N. K., Sirsat, S. B., & Pawar, Y. D. (2013). An Efficient Synthesis of Some Novel 3-Cyano-4-imino-2-(methylthio) 4H-pyrido [1, 2-a] pyrimidine and Their Derivatives. ***Journal of Heterocyclic Chemistry***, *50*(2): 351-354.

104. Dasharath P. P., Shailesh P. P. and Pankaj S. P.(2012).Studies of schiff basederived from sulphadiazine and 2-hydroxy,1-naphthaldehyde/benzoil acetone for gravimetric determination of the Cu (II), ***International journal of research in pharmaceutical and biomedical sciences,*** 3(3):1256-1261.

105. Ngan, N. K., Lo, K. M., & Wong, C. S. R. (2011). Synthesis,structure studies and electrochemistry of molybdenum(VI) Schiffbase complexes in the presence of different donor solvent molecules. ***Polyhedron***, 30(17): 2922-2932.

106. George M. N., Constantin D., Mariana C. C. and Alexandru V. M. (2009). "Synthesis of isomeric N-(1-methyl-1-hpyrazole-4-carbonyl)-N'-(XYLYL)-thiourea and their antimicrobial evaluation", ***armacia,****57(5)*:527-533.

107. Shakir M. A.(2012). "Synthesis and preliminary antimicrobial activities of new arylideneamino-1,3,4-thiadiazole-(thio/ dithio)- acetamido ephalosporanic . acids" ,***Molecules,*** *(17*):1025-1038.

108. Solomons .T.W.G and Fryhle. C. B .(2007). "Organic chemistry", 4th Edition, john wiley and Sons,Inc.,U.S.A, 792-794.

109. Revathi V. and Rajendran V. (2013). "Growth and characterization of semi-organic nickel bis thiourea nitrate single crystal", ***Der Pharma Chemica***,5(4):105-111.

110. Aamer S., Naeem A., Hummera R., Sadaf R. and Hameed A.(2009). "Synthesis characterization and antibacterial activity of some 1-aroyl-3- aryl thioureas", ***Chemistry***,*(18)*:152-158.

111. Mohammad B. and Nasir I.(2012). "Green synthesis of N-substituted -N′-aryl carbonyl bifunctional thioureas under solvent-free conditions", Iranian ***Journal of Organic Chemistry*** ,(4): 837-840.

112. Ali ,T .E., Ibrahim ,M .A., El-amin ,E. M. and El-gendy, Z. M.(2012)."4,6- Diacetylresorcinol in Heterocyclic Synthesis Part I: Vilsmeier-Haack Reactions of 4,6-Diacetylresorcinol and Its Schiff Bases and Hydrazones to Construct of New Linearly and Angularly Substituted Pyrano[3,2-g]chromenes Tarik," ***Int. Electron. Conf. Synth. Org. Chem***, v (16): 1–15.

113. Nafia R. A. and Faraj F. L.(2019). Synthesis and characterization of new indole Schiff bases and study effect of the compounds on Lymphatic cell in metaphase in human blood. ***Journal of pharmaceutical Sciences and Research***, 11(4): 1319-1326.

114. Faraj F. L., Khaledi, H., Morimoto Y. A., Itoh S., Olmstead M. M. and Ali H. M. (2014). A tetradentate β-diiminato ligand containing phenolate substituents: flexivalent coordination to MnIII, CoIII, NiII, and CuII. ***European Journal of Inorganic Chemistry***, (33): 5752-5759.

115. Silverstein R. M., Webster F. X. and Kiemle D.J. (2005). Spectrometric Identification of Organic Compounds. 7th ed., John wiley and Sons Inc., New York.

116. Faraj F. L., Ali W. B. , Jassim S. A. and Ali T. R. (2017). Synthesis, characterization and theoretical study of Zn(II) complex with new Schiff base. ***Diyala Journal for Pure Sciences***, 13(2):262-277.

117. Ismail K. A., Ali W. B. and . Jarullah A. A. (2020). Synthesis, characterization and antifungal activity of some indolo [2-3-b] quinoxaline derivatives. ***Journal of Global Pharma Technology***, 12(2):727-736.

118. Hashim C. S. and. Alias M. F. (2012). Synthesis and studying new complexes of some transition metals ions on RD cell line. ***M.Sc. thesis***, College of Science for Women,University of Baghdad, Iraq.

119. Al-Shaalan N. H. (2011). Synthesis, characterization and biological activities of Cu(II), Co(II), Mn(II), Fe(II), and UO2(VI) complexes with a new Schiff base hydrazone: O-Hydroxyacetophenone-7-chloro-4- quinoline hydrazine. ***Molecules***, (16): 8629-8645.

120. Lateef H. S., Jarullah A. A. and F. L. Faraj. (2019). Cytotoxicity effecting of new ligand (LCl) and it's complexes on a breast cancer. ***International Journal of Pharmaceutical Research***, 11(4): 1-10.

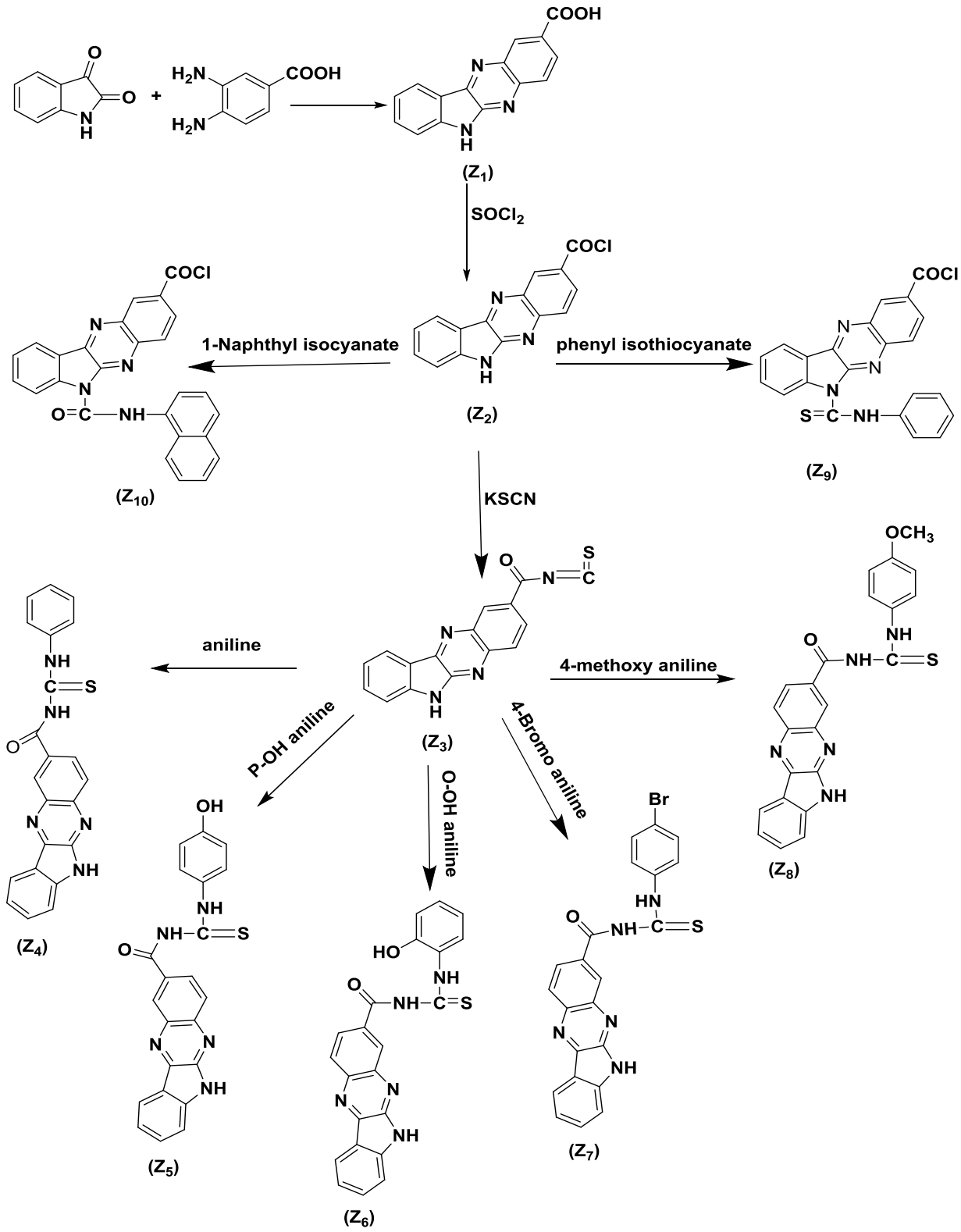
121. Lever A. B. P. (1968). Inorganic Electronic spectroscopy. Elsevier publishing Company, New York, London.

122. Figgis B.N. and Hitchman M.A. (2000). Ligand field theory and its application, 1St ed., WILEY-VCH, Printed in the United State of America, New York.

123. Housecroft C.E. and Sharpe A.G. (2008). Inorganic Chemistry, 3rd ed., Printic Hall, Printed and bound by Rotolito Lombarda, Italy.

124. Alias M.F. and Seewan A.N. (2013). Synthesis, spectral study, theoretical treatment and biological activity of some transition metal complexes with 2-amino acetic acid-6-chloro benzothiazole, ***Diyala Journal for Pure Sciences***, 9(4): 93-103.

125. Kette S. F. A. (1975). Coordination compounds, Thomas nelson and sons , Londone.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phenyl isothiocyanate
(Z2)
(Z10)
(Z9)
KSCN
aniline
4-methoxy aniline
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(Z3)
(Z4)
(Z8)
(Z5)
(Z6)
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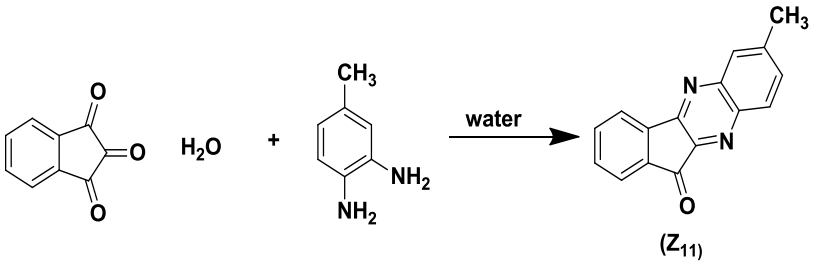
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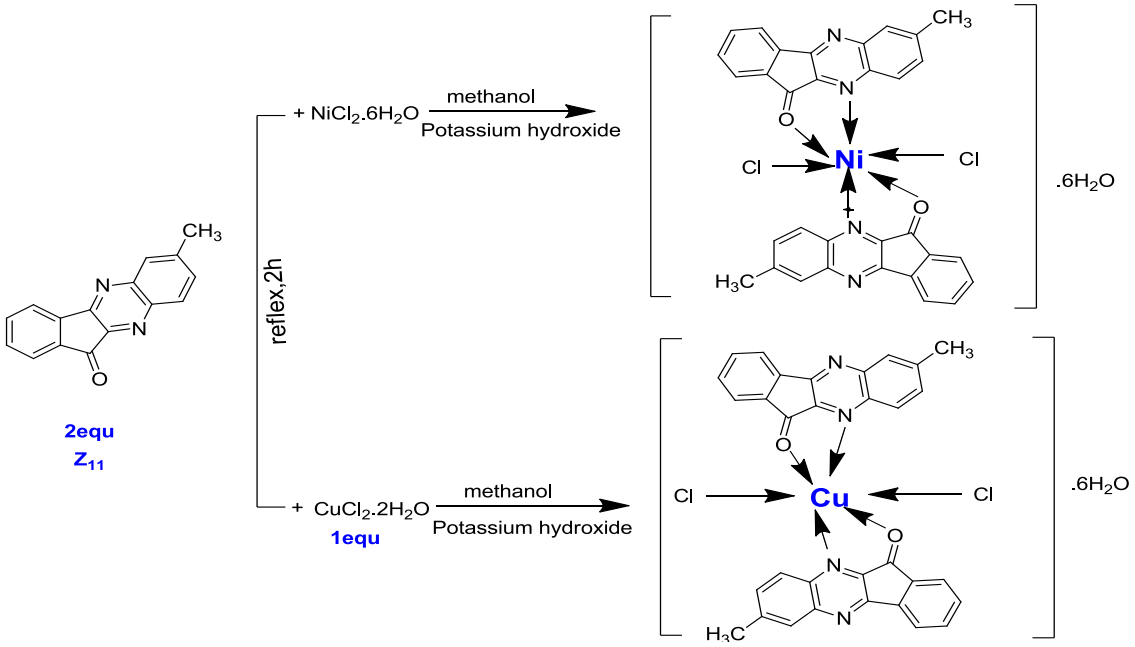
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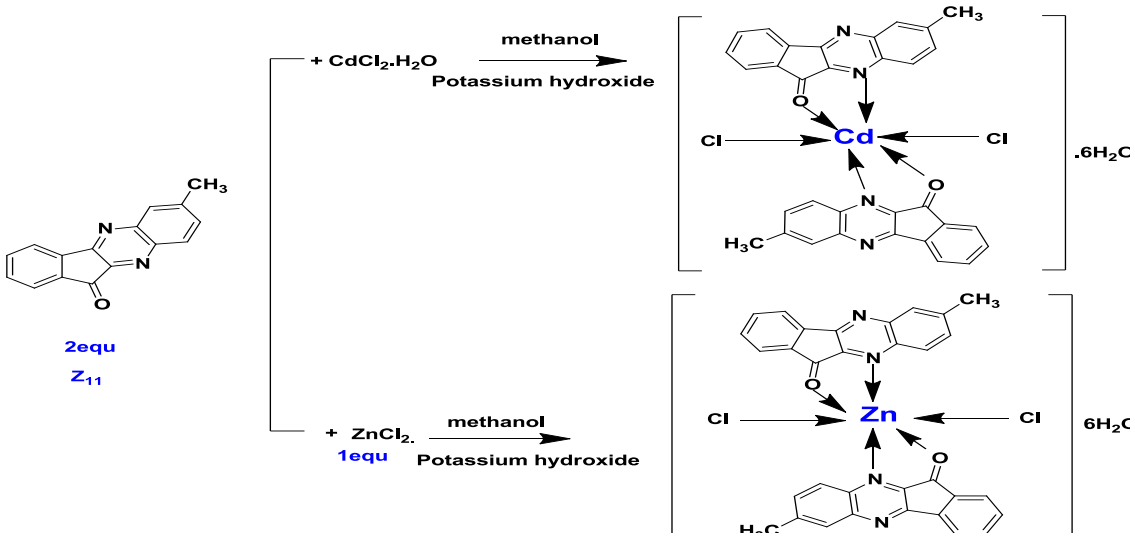
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الخلاصة

في هذه الرسالة تم تشخيص مركبات جديدة من isatin و(1H-indene 1,2,3-trione) ، وتم التحقق من صحتها باستخدام كروماتوجرافيا الطبقة الرقيقة(TLC) وباستخدام تقنيات التحليل الطيفي مثل [FT-IR و ^{1}H-NMR,^{13}C-NMR] وتم تحديد التركيب الكيميائي للمركبات الناتجة (Z_1-Z_{11}).

تم استخدام المركب Z_{11} كليكاند في تحضير معقدات جديدة من خلال تفاعله مع أملاح العناصر الانتقالية مثل ($NiCl_2.6H_2O$ و $CuCl_2.2H_2O$ و $CdCl_2.H_2O$ و $ZnCl_2$). تم تشخيص المعقدات المحضرة بواسطة اطياف الأشعة فوق البنفسجية-المرئية(uv-vis) و FT-IR ، والتحليل الطيفي للامتصاص الذري ، والحساسية المغناطيسية ، ودراسات التوصيلة للتمييز بين المعقدات الجديدة فضلا عن قياس درجات الانصهار.

- يتضمن البحث الخطوات التالية ..

١. تحضير مركب [Z_1] 6H-indolo [2,3-b] quinoxaline-2-carboxylic acid عن طريق تفاعل isatin مع ٣،٤-داي امينو حمض البنزويك.

٢. تحضير مركب [Z_2] 6H-indolo [2,3-b] quinoxiline-2-carbonyl chloride عن طريق تفاعل مركب (Z_1) مع ثايونيل كلورايد ، كما أن المركب(Z_2) يتفاعل مع ثايوسيانات البوتاسيوم لتحضير مركب (6H-indolo[2,3-b]quinoxaline-2-carbonyl iso thiocyanate)

٣. تحضير مشتقات الثايوريا [Z_4-Z_8] من تفاعل مركب[Z_3] مع الأنيلين ومشتقات الانيلين.

٤. تحضير مركب [Z_9] (6-Phenyl carbamo thioyl- 6H- indole [2,3-b] quinoxaline- 2- carbonyl chloride) عن طريق تفاعل مركب Z_2 مع بنزين إيزوثيوسيانات للحصول على مركب معوض جديد وفعال.

٥. تحضير مركب [Z_{10}] 6-naphthalene-1-ylcarbamoyl-6H-indolo[2,3-b] quinoxaline-2-carbonyl chloride عن طريق تفاعل مركب Z_2 مع ١-نفثيل أيزوسيانات للحصول على مركب معوض جديد وفعال.

٦.تحضير مركب [Z_{11}] 7-methyl-11H-indene[1,2-b]quinoxaline-11-one من تفاعل(1H-indene 1,2,3-trione) مع ٤-ميثيل بنزين-١،٢-داي امين ، ومعقداته مع املاح الايونات الفلزية [Ni (Z_{11}) $_2Cl_2$] .$6H_2O$، [Cu (Z_{11}) $_2Cl_2$] .$6H_2O$، [Cd (Z_{11}) $_2Cl_2$] .$6H_2O$ و [Zn (Z_{11}) $_2Cl_2$] .$6H_2O$

٧. أخيرًا ، تم اختبار الفعالية الحيوية للعديد من المركبات المنتجة ضد نوعين من البكتيريا (*E.Colias* و *S. Aureus*). وقد أظهرت غالبية المركبات المحضرة نشاطًا مضادًا للبكتيريا جيدًا إلى معتدل ضد هذه الانواع من البكتريا.

وزارة التعليم العالي والبحث العلمي

جامعة ديالى

كلية العلوم

قسم الكيمياء

تحضير والتقييم البايلوجي لبعض مشتقات الكوينوزايلين ومعقداتها الفلزية

رسالة مقدمة إلى

مجلس كلية العلوم - جامعة ديالى

وهي جزء من متطلبات نيل شهادة ماجستير في علوم الكيمياء

من قبل الطالبة

زهراء ابراهيم احمد

(بكالوريوس في علوم كيمياء- عام ٢٠١٢ كلية العلوم جامعة ديالى)

بإشراف:

أ.م.د. وسن باقر علي

أ.م.د. اريج علي جارالله

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