وزارة التعليم العالي والبحث العلمي

جامعـــــة ديـــــــالـى

كليـــــة العلـــــوم

قســـــــم الكيميـــاء

# تحضير ليكاندين جديدين لقواعد شف من مشتقات الأندول ومعقداتها مع بعض الأيونات الفلزية وتقييم فعاليتها البايولوجية

رســـالة مقدمـــة الى

مجلس كلية العلوم /جامعة ديالى

وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

من قبل الطالبة

**هدى صكبان لطيف**

**بكالوريوس في علوم الكيمياء 2011**

**كليـــــة العلـــوم – جامعـــة ديالـــى**

**بأشراف**

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## *1.Introduction*

### *1.1. Heterocyclic Compounds*

Heterocyclic compounds are the cyclic organic compounds which contain at least one hetero atom ,the most common heteroatoms are the nitrogen, oxygen and sulphur but heterocyclic rings containing other hetero atoms are also widely known.The chemical structures of heterocyclic rings in ***Figure (1.1)*** include simple aromatic and nonaromatic rings [1].Usually they are indicated as counter parts of carbocyclic compounds [2].

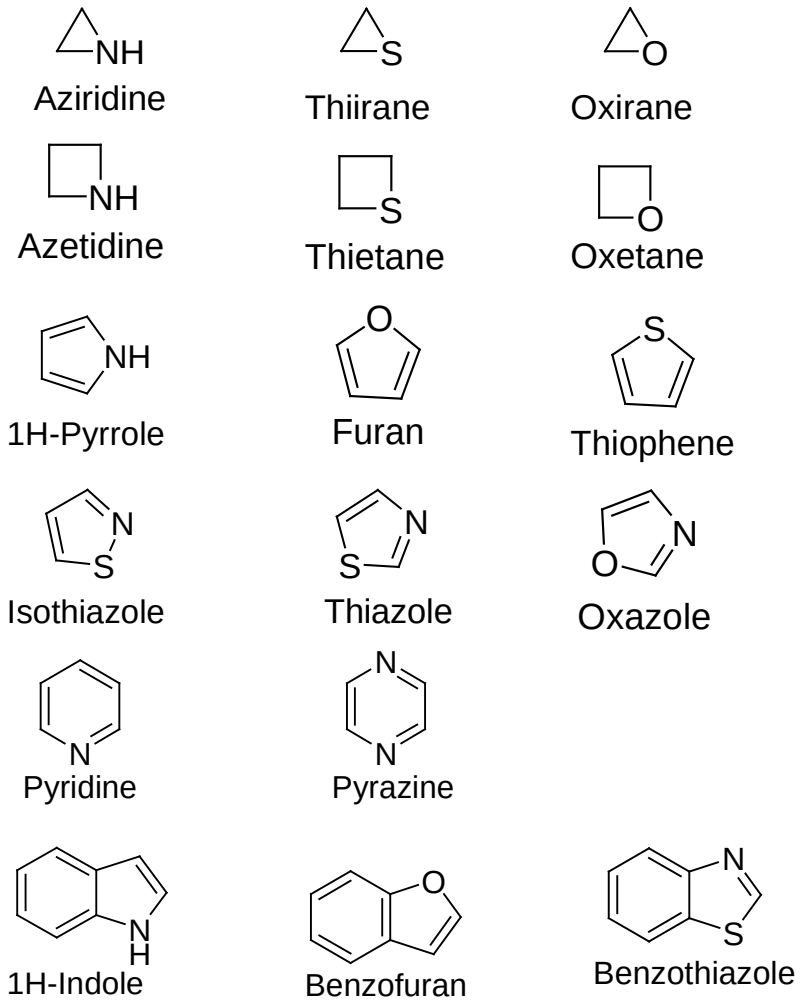


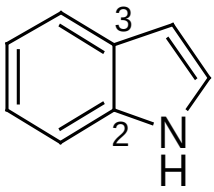

***Figure (1.1): Simple Aromatic Rings and Nonaromatic Rings***

Heterocyclic compounds considered as one of the vital classes of organic compounds ,which are used in many biological fields ,due to its activity in manifold illnesses .Biological particles for example DNA and RNA ,chlorophyll ,hemoglobin ,vitamins contains heterocyclic ring in their major skeleton [3].

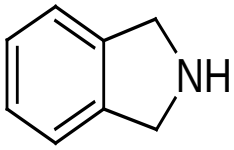
Heterocyclic compounds are occupying a prime place-in heterocyclic chemistry owing to their valuable properties as therapeutic agents, drugs, dyestuffs etc. These compounds are reported to possess antimicrobial, anti-inflammatory, anti-diabetic, blood platelet aggregation inhibiting property and the pesticide properties. It is also reported in various journals that these compounds are showing very good antibiotic activities. The heterocyclic compounds are very widely dispersed in nature and are essential to living organisms. They play a vital role in the metabolism of all the living cells. Among large number of heterocycles found, in nature, especially those containing nitrogend, oxygen and sulphur due to their inclusive distribution in nucleic acid design and their participation in plurality each physiological procedure of plants and animals [4].

### *1. 2. Indole Ring*

Indole ring is an aromatic heterocyclic compound, and it is a white solid compound at room temperature. The indole chemical formula is $C_8H_7N$. It has an aromatic bicyclic structure involving of a five-membered pyrrole ring fused together with a benzene ring to form two isomeric benzo-pyrroles [5].***Figure (1.2) and Figure (1.3).***




***Figure(1.2): The Chemical Structure of 1H-indole***




***Figure(1.3): The Structural Formula of 2,3-dihydro-1H-isoindole***

Indole is an important scaffold in the field of medicinal chemistry. Indole derivatives have been reported to possess significant pharmacological activities.Derivatives of indole have been used as anti–inflammatory, analgesic and antipyretic agents [6-8].

Hajiaghaalipoura and his colleague prepared a new indole Schiff base derived from benzo indole, as illustrated in ***Figure (1.4).*** They studied their effectiveness against the growth of colon cancer HCT 116 Cell line and concluded at the end of their study that this compound was cytotoxic against cancer cells and safe toward the normal cells [9].

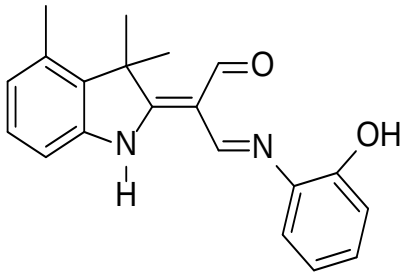



***Figure (1.4): The Chemical Structure of Schiff Bases Derived From Benzo Indole***

Indole and its derivatives are presented in most plants such as unripe bananas broccoli ,clove ,almost all flower oils (e.g .,jasmine and orange blossoms) and coal tar .In the pharmaceutical field it has been discovered that it acts as an antimicrobial and anti –inflammatory [10].

### *1. 3. Schiff Bases*

Schiff bases are compounds formed by the condensation reaction of primary amines with carbonyl compounds (aldehydes and ketones) in which the carbonyl group (C=O) of aldehydes or ketones has been swapped by an imine or azomethine group (–RC=N-) as synonymous to Schiff base ***Figure (1.5).***A Schiff base is a type of chemical compounds containing a carbon-nitrogen double bond as functional group, where the nitrogen atom connected to aryl group or alkyl group ( R ) but not hydrogen, and they were first discovered in 1864 by German chemist noble prize winner Huggo Schiff [11-13].

Schiff bases are a significant group of organic compounds that have biological activities and they have attracted the attention of chemists due to the case of preparation and complexation [14].

Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized ,while those which contain alkyl substituent’s are relatively unstable Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable [15]. While those of aromatic aldehydes having effective conjugation are more stable [16-18]. The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis [19].

The reactivity of aldehydes are usually quicker than those of the ketones in condensation reaction ,in that way resulting in the formation of Schiff bases with a centre that are less steric than the ketones relatively unstable and freely polymerizable, Schiff bases bonding ability depending on the nature of atoms that act as coordination site, such as N, O, and S, the electronegativity and steric factors. Schiff base acts as active ligands due to the presence of low-slung electronegativity of nitrogen N of the azomethine group (>C=N), lone pair of electrons on the nitrogen atom electron donating character of the double bond [20] , and thus bring about stability in metals several oxidation states, regulating metal activities for variety of useful biological, catalytic conversions [21]. The general formula for Schiff base is $R^1CR^2=NR^3$ ***.Figure (1.5)***, where $R^3$ is an aryl or an alkyl group, $R^1$ is an organic side chain and $R^2$ is hydrogen atom or an organic side [22].

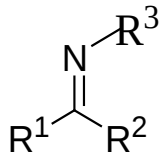
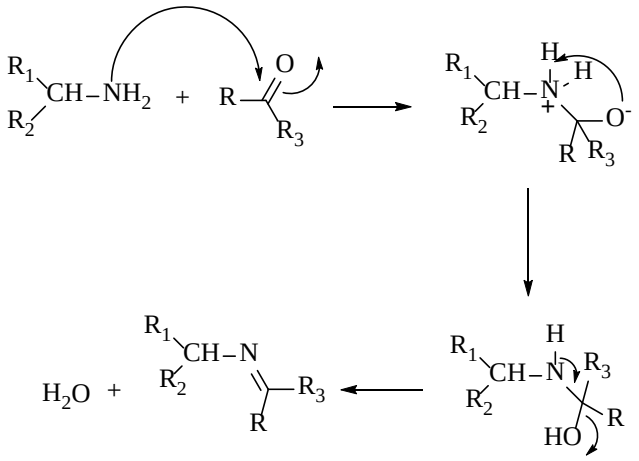



***Figure (1.5): The General Structure of Azomethines***

### *1.4. The Reaction Mechanism of Schiff Base*

The mechanism of Schiff base formation is another variation on the theme of neucleophilic addition to the carbonyl group .In this case, the nucleophile is the amine .In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine . The carbinolamine loses water by either acid or base

catalyzed pathways . Since the carbinolamine is an alcohol ,it undergoes acid catalyzed dehydration .Typically the dehydration of the carbinolamine is the rate determining step of Schiff base formation. The mechanism of Schiff base formation consists of two types of reactions: the addition and the removal as reported by [23].



R1= alkyl, aryl, cyclo alkyl or heterocyclic groups

R2= Aliphatic,aromatic compounds: or H

***Scheme (1.1): General Mechanism of Schiff Bases Formation***

### *1.5. Coordination Complexes*

A coordination compounds or metal complex might be defined as central metal atom attached with the sheath of ions or molecules .One of the more interesting aspects of transition metal is their ability to form coordination compounds. Such compounds are formed between a metal ion and a molecule with one or more unshared electron pairs called a ligand. A number of catalysts used in the chemical industry make use of coordination compounds [24].

The coordination compounds are of considerable interest because metal ions are found in the active sites of a large number of metalloproteins such as hemocyanin, and also in metalloenzymes like in ureases, tyrosinase, lactase and ascorbate oxidase . These proteins are involved in various biological process such as biological electron-transfer reaction oxygen atom insertion into substrates dioxygen reduction to hydrogen peroxide or water and hydrolytic reactions [25].

A study of coordination chemistry of transition metal ions with various types of ligands has been enhanced by the current advancements in the fields of bioinorganic chemistry and medicine. Through the years, Schiff bases have played a special role as chelating ligands in main group and transition metal coordination chemistry, due to their stability under a variety of oxidative and reductive conditions , and to the fact that imine ligands are borderline between hard and soft Lewis bases [26].

### *1.6. Indole Schiff Base Metal Complexes*

Schiff bases have been play, an important roles chelating ligands in, transition metal coordination chemistry because of their stability under,a variety of redox conditions. Tetradetate indole Schiff base complexes are increasingly significant for designing, metal complexes related to synthetic and natural oxygen carriers like nickel, copper and cobalt complexes ***Figures (1.6)- (1.9)*** [27 and 28].

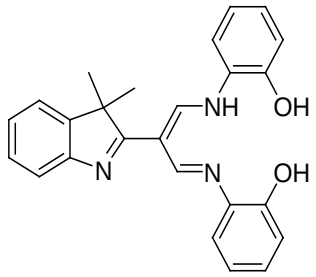



***Figure (1.6):: The Chemical Structure of $LH_3$ Compound***

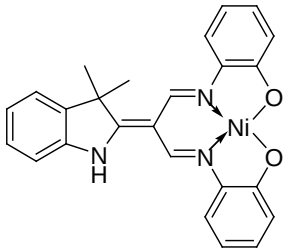



***Figure (1.7): The Chemical Structure of [Ni(LH)] Complex***

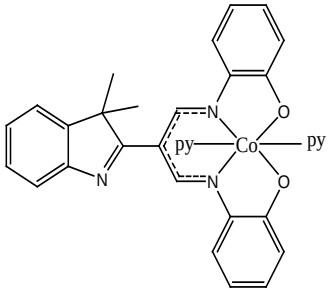



***Figure (1.8): The Chemical Structure of $[Co(L)(py)_2]$ Complex.***

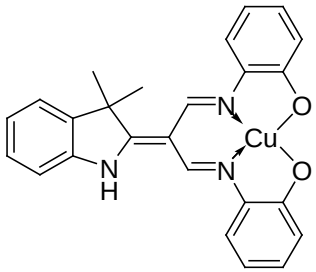



***Figure (1.9): The Chemical Structure of [Cu(LH)] Complex***

The indole Schiff bases are a very interesting class of heterocyclic compounds and consisting of an azomethine group coordinating to a number of metal ions in particular transition metal ions such as Ni, Co, Zn, Cu, Mn to form a number of metal complexes ***Figure (1.10)*** [29].

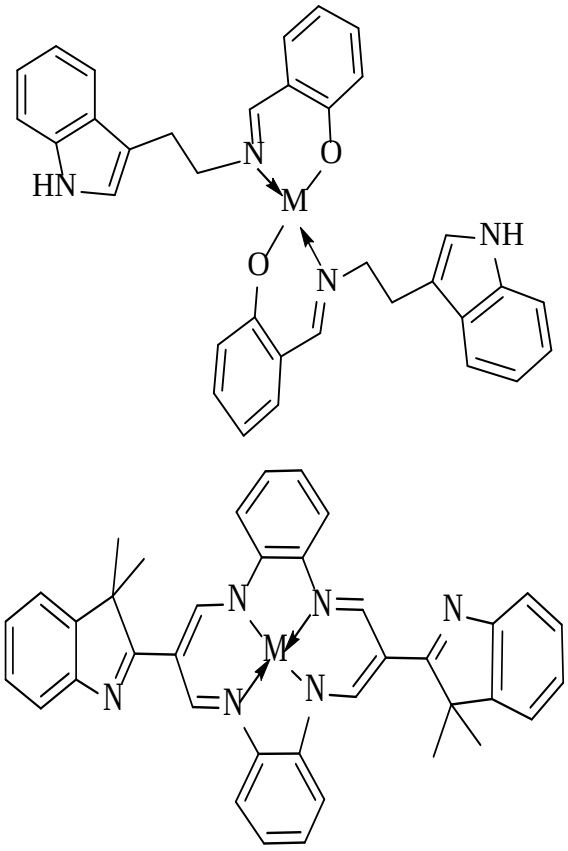



***Figure ( 1.10 ): The Chemical Structure of Some Indole Complexes***

Metal complexes of Schiff –base have played a central role in the development of coordination chemistry .They have been receiving the considerable research attention because of their use in biological and medicinal applications [30].

The complexes make these compounds effective and stereospecific catalyst for oxidation , reduction and hydrolysis ,and they show biological activity and other transformation of organic and inorganic chemistry. It is well known that some drugs have higher activity when administered as metal complexes than as free ligand. In addition, there is potential application in many fields such as antibacterial, anticancer drugs, antiviral, electrochemistry [31-34].

Metal Schiff base complexes have been known since the mid nineteenth century and even before the report of general preparation of the Schiff base ligands. Schiff base and their complexes were recently found to have significant biological activity like antitumour. The, azomethine group has good donar properties and can from stable complexes with transition metal ion. Oxygen, nitrogen etc. are the donor's centers in Schiff base chelation for the synthesis of their metal complexes, which have potential biological activities [35].

Indole Schiff bases represent one of the most used classes of ligands in the coordination chemistry to form metal complexes with a number of metal ions. The transition metals have a number of vacant *d*-orbital and can gain considerable stability by accepting electrons from the ligands in the form of dative bonds with the resultant formation of a metal-ligand complex. The tendency of the transition metals to form complex compounds is particularly known with cobalt, copper, zinc and nickel ion salts. Indole shiff base complexes also have versatile applications in a number of fields such as bioinorganics and catalysis. In addition, many natural products like haemoglobin (coloring matter in blood) and green pigment of plants (chlorophyll) are coordination compounds [36].

The coordination chemistry of the chelating agents with nitrogen donor atoms, for examples, indole derivatives have been an area of interest for a long time. These types of compounds include Schiff base complexes and have given attention due to their biological activities for example 1H-indole-3-ethylene-5-nitrosalicylaldimine TNS and its nickel complex which exhibited acute toxicity and gastro protective activity[37].***Figure (1.11)***

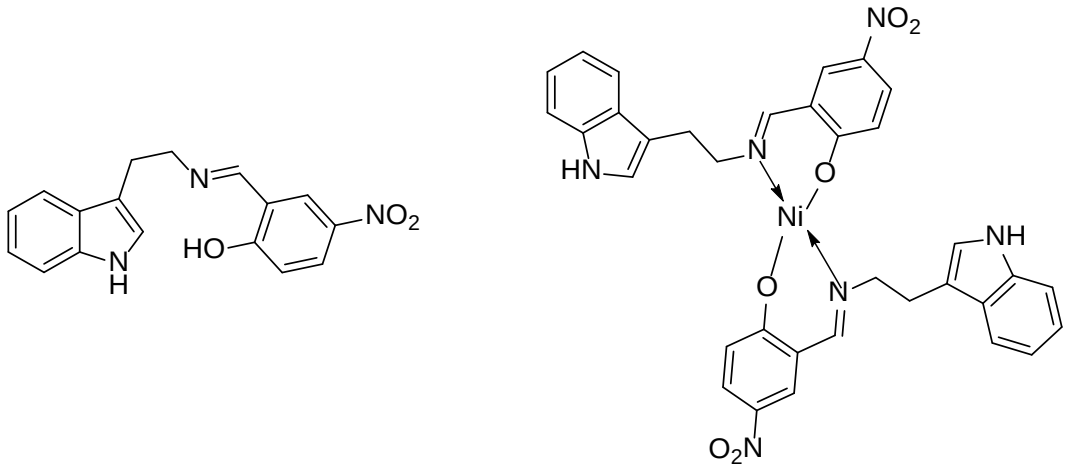



***Figure (1.11): 1H-indole-3-ethylene-5-Nitrosalicylaldimine and its Nickel Complex***

Also a S-benzyldithiocarbazate Schiff base derived from indole-carbaldehyde has been used to coordinate to diphenyltin(IV), and are antibacterial and antifungal activity ***Figure( 1.12)*** [38].

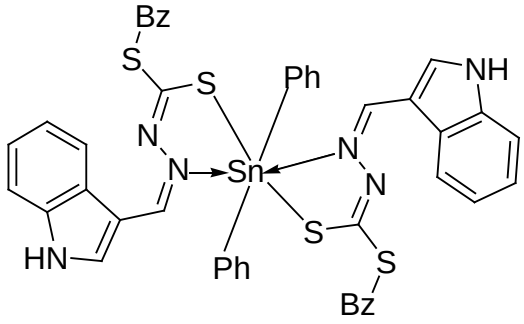



***Figure (1.12) :Anti-bacterially and Anti-fungally Active Sn-Complex***

The Ni (II),Co (II) and Pd (II) complexes ***Figure (1.13)*** derived from Azo-Schiff base were studies as well as evaluation of anti-ulcerogenic [39].

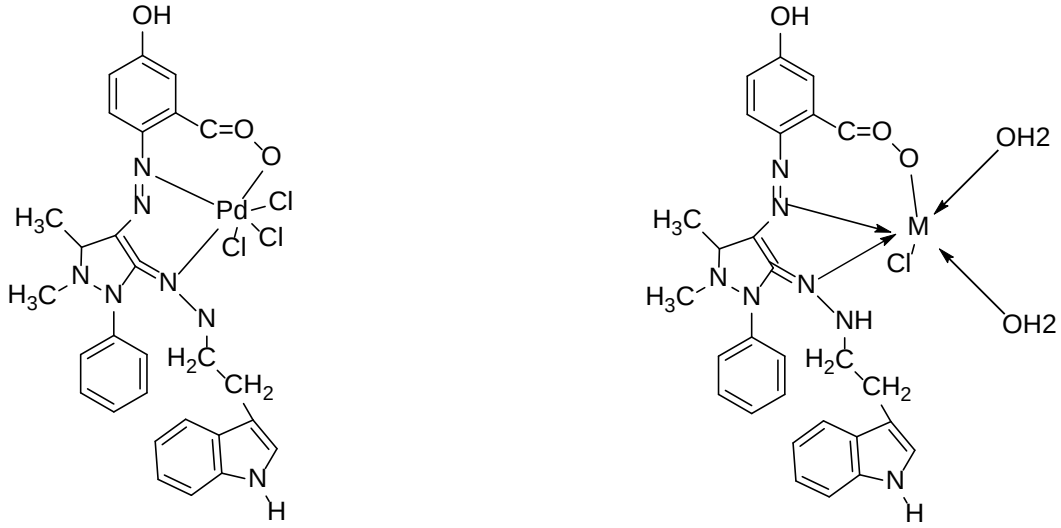



***Figure (1.13):The Ni(II), Co (II) and Pd (II) complexes derived from Azo-Schiff base***

The Co (II) , Ni(II), and Cu(II) complexes as well as ligand AEQT (3-amino 2-ethylquinazoline 4( 3H) thiosemicarbazone) ***Figure (1.14)*** were synthesized and tested against Gram positive and Gram negative bacteria. The results indicate that all the complexes were active agaainst Gram positive bacteria while less active against E. Coli which is Gram negative. The complexes were more active than the Schiff base which indicates that metallation increases theactivity [40] .

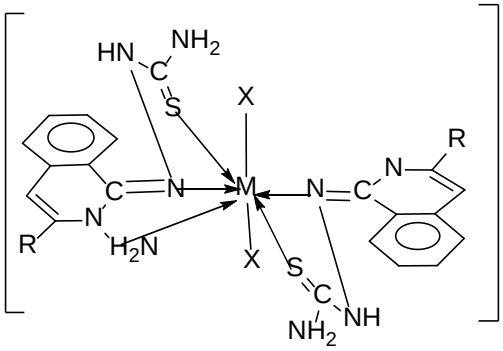



***Figure (1.14): The $[M(AEQT)_2]X_2$ Complexes***

***M= Co(II) and Ni(II), X= $Cl^-$, $Br^-$ and $I^-$; M= Cu(II) , X= $Cl^-$ and $Br^-$ ; R= Ethyl***

The complexation reaction of indole derivatives with a number of metal ions has produced a number of compounds which are now being used to treat anti-inflammatory [41and42] ,anti-hypertensive[43] ,anti-viral, antifungal and antibacterial activities [44,45] and anti ulcerogenic [46]. For these reasons, a series of metal complexes have been synthesized from the LOH and LCl ligands contains (*N , N, O)* atoms,and derived from 5-methoxy -2,3,3trimethyl-3H-indol and 6-chloro-2,3,3-dimethyl-3H-indole with nickel, cobalt, zinc, copper and manganese ions.

## *1.7. Medicinal Inorganic Chemistry*

Most of metal ions are fundamental components to preserve human homeostasis and play important roles in many biological processes by involving as cofactors in the biological function of proteins, and operating many regulation, stabilization, completion courses of cellular functions. Due to the important tasks of metals through continuity of many cellular events, a sophisticated and sensitive system has been developed by the human body for their transportation and distribution [47]. Medicinal inorganic chemistry is therefore the most attractive research area with the field of knowledge concerned with

implementation of metal –based complexes to therapy or diagnosis of disease[48]. Although the historically proven use of metal based remedies and drugs traces back to very ancient times, medicinal inorganic chemistry seems to be considered as a young discipline among the medicinal chemistry fields of biological drugs or small organic molecules. Silver, for instance, was used to treat wounds and ulcers by Greek physician Hippocrates, and gold was used to treat diseases thousands of years ago in China [49]. However, the modern era of metal–based complexes was heralded with the serendipitous discovery of cisplatin, a square planar platinum (II) complex, by Rosenberg and Vancamp (1965), and its clinical success against various types of cancer such as ovarian, head and neck, lung, testicular and bladder cancers, opened up the way of second and third generation platinum drugs such as carboplatin, oxaliplatin, satraplatin, nedaplatin, lobaplatin etc.[50 and51]. Despite the market for platinum-based drugs had showed rapidly global spread, classical platinum chemotherapy was limited due to the serious side effects such as vomiting, myelosuppression, nephrotoxicity and nephropathy, and drug resistance phenomenon after recurrent treatment[52]. To improve pharmacological profiles of metal-based complexes, scientists are taking a growing interest in the development of non-platinum metal compounds such as ruthenium, titanium, indium, gallium, gold, etc.[53].In **1991**,Peter Sadler noted that most elements of the periodic table, up to and including bismuth with an atomic number of (83), have potential uses as drugs or diagnostic agents. Inorganic compounds have found usage in chemotherapeutic agents such as [54]:

1. Anticancer agents like Cis-$[Pt(NH_3)_2Cl_2]$.
2. The gold-containing antiarthritic drug Auranofin.
3. Metal-mediated antibiotics like bleomycin, which requires iron or other metals for activity.

4. Technetium-99 mand other short-lived isotopes use radiopharmaceuticals in disease diagnosis and treatment.
5. Magnetic resonance imaging (MRI)-enhancing Gadolinium compounds.
6. Antibacterial , antiviral, antiparasitic and radio sensitizing agents.

***Objectives of The Study***

1. Synthesizing new Indole Schiff base ligands LOH, LCl and their complexes with some heavy metal ions.
2. Characterizing the chemical structures of the new synthesized Schiff bases ligand and their complexes by using FT-IR spectroscopy,$^{1}$H,$^{13}$C NMR, APT $^{13}$C NMR spectroscopy, U.V-Visible spectroscopy, elemental analysis (C.H.N). metal analysis, magnetic susceptibility and conductivity measurements
3. Estimating the biological activities of the new synthesized indole Schiff bases ligand LCl and its complexes against the MCF7 cancer cell line (breast cancer cell line)