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Analytical Study on Historical Milestone and Biological Implications of Potential Drugs Bearing Schiff Base Ligands And Their Metal Complexes

Rajendra Moryani Ph.D. Scholar
Department of Chemistry , Sarvepalli Radhakrishhan University, Bhopal, MP,India.
Email id:- rajahuja94@gmail.com (Correspondence Author)
Dr. Namrata Jain
Department of Chemistry , Sarvepalli Radhakrishhan University, Bhopal, MP,India.

There is an increase in activity in the synthesis of the Schiff base compounds as a reef of the future and biological activity is carried out with perfection. It is not only a biologic subject, but also a true multidisciplinary field in the many fields of chemistry and technology. The resultant compounds containing the azomethane groups (imine) have chemical and biological effects and are regarded to be 'privileged ligands' produced by condensing carbonyl molecules (aldehyde/ketones) with primary amino derivatives (Hine & Yeh 1967). These nitrogen-containing ligands and their structures played an essential part in the development of coordination chemistry owing to their synthesization, selectiveness, sensitivity, stability and unique magnetic characteristics towards the central metals atom (Garnovskii et al. 1993). Furthermore, Maillard reaction of different amino acids and reducing sugars such as glucose and ribose may be used to create Schiff base. The development of advanced glycemic end products (AGEs) is stabilised by the rearrangement of Amadori. Maillard reaction products may function as antioxidants, bactericidal compounds, anti-allergic and antimicrobial molecules, etc. and can be regulated via changes in dietary values and circumstances of processing and storage of various foods and drinks (Zhang et al. 2009). Moreover, the Schiff base and its metal complexes derive amino acids contain a broad spectrum of biological activities such as anti-inflammatory (Sondhi et al. 2006 and Chinnasamy et al. 2010, analgesic (Gyanakumari et al. 2010), anti-convulsant (Ali et al. 2012), anti-TB (Wei et al.) 2006, anti-oxidant (Avaji et al. 2009), antimicrobial and antitumor. The ship's base ligands are nevertheless not stable and susceptible to hydration and disintegrate when exposed to air (Sari et al. 2004). Schiffbases also have the capacity to kinetically stabilise because of their 'chelate effect,' and a wide range of effective catalytic reactions are used to controll various

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metals with varied oxidation states. In recent years, Schiff's transition metal complexes have been widely investigated in coordination chemistry primarily because of their excellent solubility in common solvents, extraordinary magnet and electronic characteristics, unique structural characteristics and significance to biological systems. The study of the vast number of ship bases and their metal complexes has garnered increasing attention owing to their enormous potential uses (Xie et al. 2010). The shipbases are usually categorised as bident, trident, tetradentate or polydentate, which with transition metal ions may form very stable complexes. Much more special attention has recently been paid to the multi-dented basemetal complexes in the area of optical materials, catalytic materials, the drug design, biological samples and chemical sensors etc. There has recently also been considerable interest in designing metal transition complexes as medicines and diagnostic agents in the area of medical chemistry.

Due to their structural versatility, ease of formation and stability in various oxidative and reductional conditions, transitional metallic complexes for shipbase ligands have been particularly important to chemists worldwide for the last four decades (Devi et al. 2018), playing a crucial role in the development of chemistry coordination due to these factors. Ship bases have shown potential biological action including, for example, anticancer, antibacterial, antifungal, herbicidal, medical imaging and model copper, cobalt, nickel and zinc complexes. Moreover, a large number, according to their stereoscopic, electro-chemical, biochemical and photochemical properties, perform nucleolytic cleavage/binding (Kavitha et al. 2013; Raman et al. 2012 and Li et al. 2010). A wide range of mixed ligand transition (II) complexes, including N, S or O donor sites, have been recently extensively examined, based on their unusual electronic characteristics, diverse chemical reactivities, and special structure, including 2.2'-bipyridine/1.10-phenanthroline coligands. However, in the case of nuclear acid chemistry, transition metal complexes are efficiently linked to DNA via noncovalent interactions and split DNA under physiological conditions, as foot printing and sequence specific binding agents for modelling, limiting enzymes in genomical research and as new structural samples in diagnostic medicinal applications in transmission (Dhar et al. 2005). Many study studies show that N-FPMs disclose various pharmacological actions and are utilised in the treatment of cancer, inflammatory disorders, pain, migraines, asthma, microbial and viral illnesses, etc (Thanusu et al. 2010). The metal-transition complexes can generally interact with DNA in a non-covalent manner through intercalation, groove binding or

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electrostatic external binding, and further reveal that the ligand changes can lead to a slight or dramatic change in binding modes, location, affinity and hydrogen binding capacity (Erkkila et al. 1999; Xiong et al. 1999 and Ji et al. 2001).

Currently, the vision and impact on cancer in underdeveloped nations is widespread. Because cancer is the general expression for a wide range of illnesses caused by complicated multi-target disorders that may affect any place of the body as abnormal cells develop rapidly and can enter neighbouring normal tissue or organ parts through the lymph / vascular system or bloodstream. Genetically unstable cancer cells contribute to their uncontrolled cell growth. Globally, the most current statistics reveal that cancer is the world's second largest cause of death, with more than 9.6 million deaths from 18.1 million cancer cases worldwide reported in 2018. According to WHO projections, this figure is projected to rise to more than 14,5 million fatalities by 2035 from the estimated 24 million diseases linked to cancer (Liu et al. 2018). Metal-based chemicals such as cisplatin, carboplatin, oxaliplatin, nedaplatin and iproplatin have recently been utilized in chemotherapy as effective anti-cancer drugs. But significant restrictions, such as nephrotoxicity, tissue toxicity, ototoxicity and myelosuppression, are related to covalent interaction with DNA. Rather, the complexes Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) of the bioactive metal transition may be utilized as therapeutic agents for non-covalent DNA interactions. Researchers are struggling to develop innovative strategies to synthesize lower-toxic, more efficient, target-specific and preferably not-covalently bound putative anticancer drugs in a critical situation with high stress and strain in order to face the challenges of cancer-related diseases (Arnésano & Natile 2009).

Antioxidants are compounds that block oxidation and prevent the formation of reactive free radical species through many mechanisms and free radicals are produced continually by cells during normal metabolism, which trigger chain reactions that might cause radical species further damage to macromolecular components such as DNA, carbihydrates, lipids, pr In homoostasis, dietary antioxidant (nonenzymatic antioxidants) and enzyme antioxidant systems continue to maintain levels of antioxidants and oxidants in the body. Accumulation of the oxidative harm results in oxidative stress that is linked to the pathogenesis of several ageing chronic diseases and human pathologies including diabetes mellitus, cancer, cardiovascular and alzheimer's disease, Parkinson's (Galli et al. 2005) disease, coronary cardiovascular disease etc (Valko et al. 2007). Many Schiff base ligand antioxidants may function as an agent to decrease the impact and strength of hazardous oxidants from

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damaging molecules by binding them together and to repair cell damage.

However, a number of clinical situations including atherosclerotics, cardiovascular dysfunctions, carcinogenesis, inflammation, medication toxicity, reperfusion damage and neurodegenerotic disorders are contributing to the pathophysiology of oxidative stress. Some of the enzyme endogenous and nonenzymatic exogenous antioxidants are most essential biocatalysts and play a protective role in body cell components from the oxidative stress/damage generated by reactive oxide (ROS) and reactive oxygen (RNS) species in normal and different conditions (Karami et al. 2017). There are two main classes of enzyme-superoxide detoxification (SOD) such as the enzyme Superoxide Dismutase (SOR), one of which is a radical oxygen enzyme and also two kinds of SOD enzyme are present in human cells such as CU/ZnSOD (cytoplasmic/nuclear) and MnSOD (mitochondrial). In addition, a variety of Streptomycin bacteria and cyanobacterias have been effectively isolated and recently identified as the nickel superoxide dismutase enzyme (NiSOD). However, several other enzyme-endogenous antioxidants such as Catalase (CAT), Glutathione, GPx, Coenzyme Q10 (CoQ10) and Alpha-Lipoic Acid (ALA) etc. Moreover, glutathione peroxidizes and coenzyme Q10 (CoQ10) may also repair the DNA damage produced by free radicals in the cellular system and enable the immune system to maintain and enhance mitochondria and delay ageing function. The endogenous antioxidant alpha lipoic acid (ALA) can replenish and recycle exogenous antioxidants. Some non-enzymatic exogenous antioxidants such as vitamin C, vitamin E (tocopherol), carotenoids or polyphenols are the most essential biocatalysts and are defence against the oxidative stress / damage caused in our body cell components of 1O2, O2−•, oooh, rooh and roofluid; h2O2, looh and RNS, and are constantly required to sustain normal and/or various pathological conditions (Katekhaye & Kale 2012). Endogenous antioxidants are more potent free radical combatants than exogenous antioxidants, though.

The ROS and RNS species produced following SOD activity is further converted into harmless and water molecules by donating hydrogen or electron to free radicals via catalases and peroxidis (Karami et al. 2017). While production of highly reactive free radicals and oxygen species exceeds the endogenous system's scavenging ability in normal/different pathologies during respiration and cell-mediating immune process functions, free radicals can assault specific biomolecules such as nucleic acids (DNA/RNA), carbohydrates, protein or stabium lipids Paired with biomolecules, free radicals can lead to lipid peroxidation and prolonged oxidative stress, which may eventually lead to many chronic diseases such as

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cancer, atherosclerosis, diabetes mellitus, ageing, cirrhosis, neurodegenerative stress, ischemia, arteriosclerosis, x-rays, inflammation, stroke and coronary heart disease, etc (Boora et al. 2014). Dismutation of radicals of the superoxide anion is essential to prevent severe harm to living organisms. Therefore the different DPPH, hydroxyl, superoxide and nitric oxide radicals antioxidant research have recently been established to conquer such illnesses (Divya et al. 2018). Research has been expanded due to the more stable and soluble produced complexes in common solvents such as methanol, ethanol, chloroform, and water. The powerful biological activities were also demonstrated. In consequence, it may be a prominent anti-cancer agent in future studies.

1.1 Synthesis and General Mechanism of Schiff Base and Their Metal Complexes / Mixed Ligand Complexes

Solvent based synthesis of Schiff bases involves three steps, which are shown in the Figure. 1.1.

1. Attack of proton on the carbonyl group leading to the formation of carbocation.
2. Attack of nucleophile on carbocation.

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3. Removal of water.

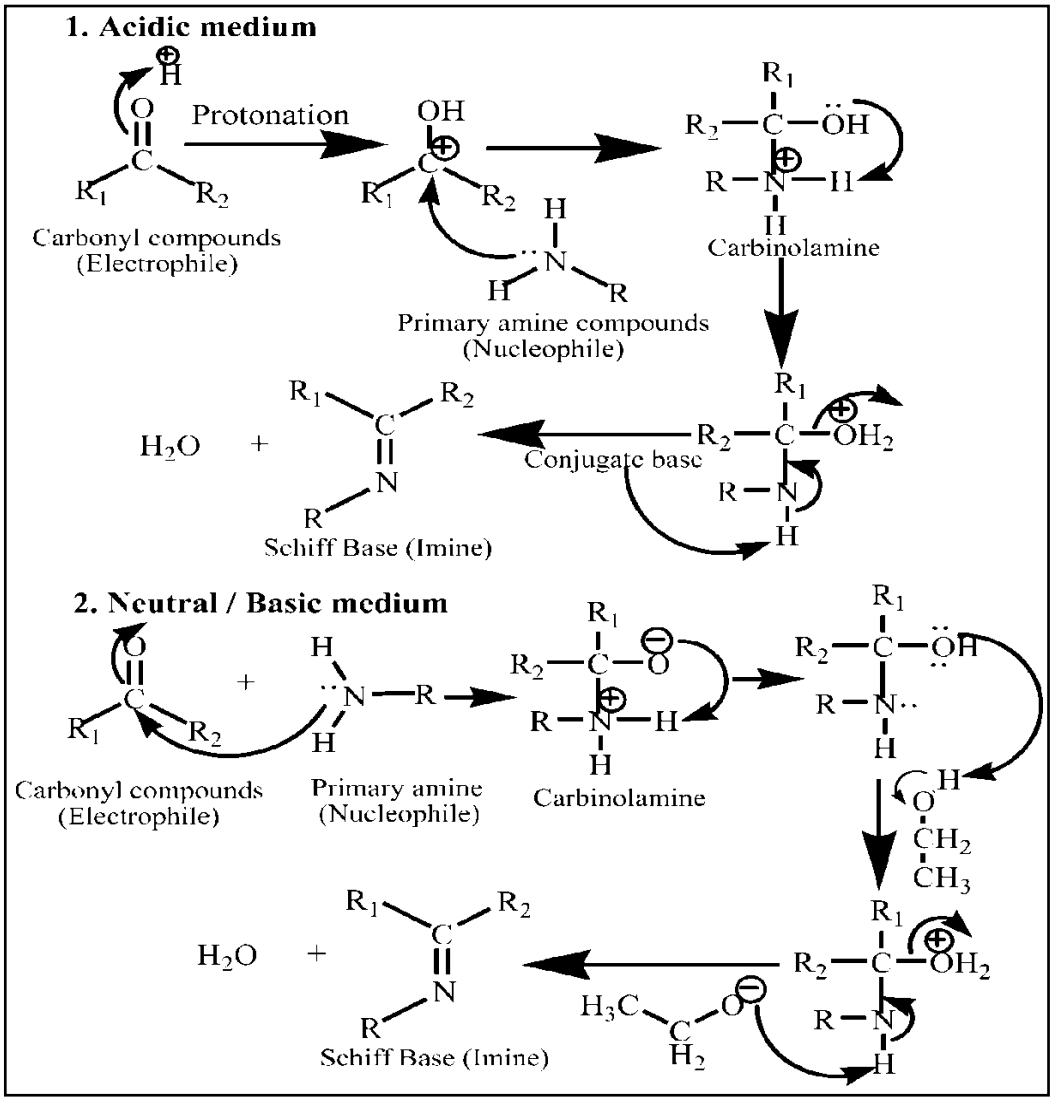

Figure 1.1 Mechanistic explanation of the formation of schiff base ligand

The mechanism of the ship base creation will be identical to that of the neutral medium and the response rate relies on its fundamental nature. The increased fundamentals of amines in the basic medium accelerate the nuclear assault, which leads to fast shipbase construction. In addition, shipbases may accept numerous metal centres including Cu(II), Co(II), Mn(II), Ni(II) and Zn(II), with diverse coordination modes, which enable effective synthesis of homo and hetero-metallic compounds. {(HL1) Methyl (-(2- morpholinoethyl) C13H18N2O2, (HL2) 2-(4-morpholinobenzolideneamino)phenol/C17H18N2O2, -4-bromophenol/C13H17N2BrO2), (HL2) (HL3) Phenol /C13H18N2O2} and integrated with 2,2'-bipyridine / 1,10-

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phenanthroline colegands (-(2-Morpholinoethylimino)methyl). Schiff base ligand Iminic nitrogen and 2,2-bipyridine/1,10-phenanthroline nitrogen atoms are associated with complexity via the donation of a lone pair electron to a metal centre because of coordination band formation. While ship's basic Ligand (primary Liagnd) [[(R1)(R2)>C=N-R]) and [MII(CH3COO)2(h2o)n] react with metal acetate n-hydrated salts [MII(CH3COO)2(H2O)n] The following potential Metal(II) complexes/mixed ligand complexes are produced by refluent in the presence of methanol, via elimination of acetic / water [(R1)(R2)>C=N-MII(H2O)-OOCCH3] (or) [[(R1)(R2)>C=N-MII-OOCCH3] . [(R1)(R2)>C=N-MII(bpy/phen)-OOCCH3] N. H2O n.H2O.

1.2 Choice of Schiff Base Ligands

Based on their stability under different oxidative and reductive circumstances, Schiff Basis plays an important role as a chelating ligand in metal coordination chemistry (Omar et al. 2017). They are borderlines between Lewis bases, hard and soft. Many literatures also indicate that imine ligand linkage is responsible for a variety of biological activities, such as antifungal, antibacterial, anti-cancer and anti-malarial properties, etc (Raman et al. 2001 and Du et al. 2010). A wide variety of Schiff base ligands transition metal complexes have a vast interest in a homogeneous and heterogeneous catalysis. They also have important characteristics including the capacity to bind oxygen reversibly (Jones et al. 1979), photochromic capabilities and complications in relation to certain hazardous metals, etc. However, 2-(-(2-morpholinoethylimino) methyl) is based on a produced bio-sensitive and physiologically active morpholine based vessel base ligans. Bioefficacy potential has been found in all instances to be -4-bromophenol (HL1), 2-(4-morpholinobenzylideneamino) phenol(HL2)and 2-(-(2-morpholinoethylimino)mehyl)phenol(HL3), metal complexes(1-10), /mixed ligand complexes(1a/1b-15a/15b). Furthermore, ship-based bases are the major co-ordinating class of ligands. They have been widely investigated because of heterocyclic compounds containers in certain donor functional groups such as sulphur, oxygen, amino nitrogen, azomethine nitrogen, alcoholic oxygen or phenolic oxygen (Tarafder et al. 2001). In recent years, Schiff Bases have been considerably more interested in different possible ligand groups owing to their delocalised − orbitals, flexible behaviour, multifunctional linkage sites etc. The clouds of μ-electron in the aromatic rings may be strongly polarised and thus these systems play an essential role in intermolecular interactions, such as μ-hydrogen bonding and α-positive contact (Desiraju & Steiner 2001). The Schiff base complexes also have significant

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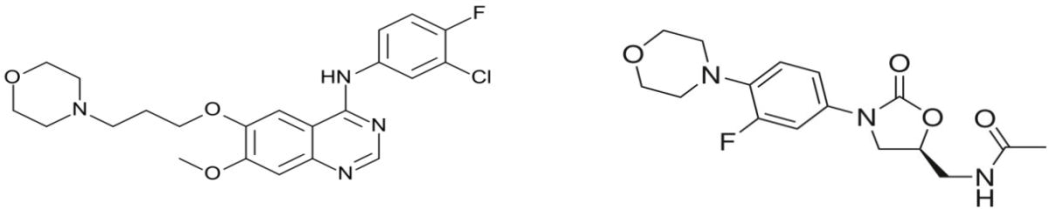
biological significance, in particular in model compound investigations. Most chemotherapy medications are effective, but regrettably they have a substantial toxicity profile. Treatment of cancer cells takes place elsewhere in the body at the cost of harming healthy cells, which leads to dose-restrictive toxicity. They may be obtained by designing cancer medicines in a manner that maintain effectiveness and to minimize adverse effects by targeting the tumour by the active ingredient specifically.

Currently, the following 4-(2-aminoethyl) morpholine-based gefitinib (Iressa-ZD1839) for certain breast, lung and other malignancies is utilized as selective chemotherapy agent (Figure 1.2a). It efficiently inhibits epidermal growth factor receptor (EGFR) tyrosine kinase by binding the enzyme's target cell binding site to adenosine triphosphate (ATP) (Sordella 2004). Derivatives' suppress tumour cells and have much lower impacts on normal cells, particularly by reducing the proliferation of cancer cells at low concentrations. Linezolid is an inhibitor of oxazolidinone (Figure 1.2b), acetamide-derived anti-bacterial mediator and protein synthesis inhibitor for the treatment of bacterial graph-positive strains in people's skin and respiratory tract infections. They are resistant to various drugs, including streptococcal, vancomycin-resistant enterococci (VRE) and Staphylococcus aureus (MRSA) resistant to methicillin (Roger et al. 2017). Phenylcarbonyl 1-[4-(2-aminoethoxy)] -3,5-bis(benzylidene) -4-piperidones is a novel kind of powerful MDR-reverser with an 11-43-fold greater power than verapamil-drug (Das et al. 2008), showing significant lethal potential towards leukemic HL-60 human cells (Das et al. 2010). These compounds usually impede the development of tumour cells and have much lesser effects on normal cells. The greatest selective toxicity was seen when morpholine is the terminal base (Figure 1.3).



(a) (b)

Figure 1.2 Chemotherapeutic agents: (a) Gefitinib and (b) Linezolid derived from 4-(2-amino ethyl) morpholine

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Figure 1.3 4-(2-amino ethyl)morpholine derivative anticancer agents

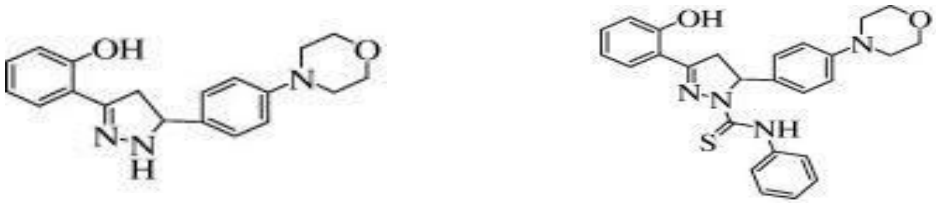

Figure 1.4Analgesic and anti-inflammatory agents derived from 2-(4-morpholinobenzylideneamino) derivatives

In addition, Ratnadeep S Joshi et al. have reported on a number of synthesized morphilinophhenyl derivatives having strong analgesic and anti-inflammatory properties (Joshi et al. 2010), and their in vivo analgesic and anti-inflammatory activities have been tested for the above synthesised compounds (Figure 1.4). Due to their strong biological characteristics, study has been done in additional research on the design and synthesis of morpholine derivatives such as 2-(-(2-morpholinoethylimine)methyl)phenol (HL1), 2-(-(2-morpholineethyl)-4-bromophenol (HL2) and 2-(4-morpholinobenzylideneamino)phenol shipping base (HL3). Furthermore, it is shown that Schiff base-ligands and their derivatives are responsible for enhanced biological properties and are listed in many fields of biological engineering, biotechnology and biochemistry (Kelley et al. 1996; Sarathi Mukherjee et al. 2001; Durmus et al. 2004; Guillonneau et al. 2003; Burli et al. 2004; Chattopadhyay et al. 2005; Panneerselvam et al. 2009; Han 2009; Sang & Lin 2010; Wang 2010; Gwaram et al. 2012; Dub et al. 2015; Bhattacharjee et al. 2017 and Dhahagani et al. 2018).

1.3 Choice of Coligands

In the biological sector, mixed ligand complexes of ship bases integrated by 2,2'-

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bipyridine/1,10-phenanthroline play an important function. Due to its high redox stability and easy operation, 2,2' bipyridine and 1,10 phenanthrolline coligands were widely employed in the complexation of metal ions (Kaes et al. 2000). The following chosen 2,2'- and 1,10-phenanthroline coligands for mixed ligand complex preparations. Because increased biological activity was promoted by the Co-Ligands as monomeric metal complexes and free ligands (1:1) and (1:2) in all instances. Selvaganapathy et al. 2016 have revealed that in in vivo and in vitro investigations of a range of tumour cells, certain mixed chelated metal-based medicines had more powerful action in antifungals than cisplatin (Selvaganapathy et al. 2016). Human cancer cell lines are an important model for the evaluation of the suppression by natural / newly produced chemicals of cancer cell growth. Furthermore, Hirohama and Palaniandavar have been reported to strongly bond DNA and split the DNA base pair oxydating non-covalent interactions with high sequential/structional selectivity with the mixed ligand copper(II) complexes with 2,2'-bipyridine/1,10- phenanthroline and showed an excellent anticancer effectiveness than cisplatin (Hirohama et al. 2005). Nagaraj et al. (2014) investigated the intercalative interaction of surfactant Cu(II) DNA with bespoke phenanthroline (Nagaraj et al. 2014). In recent times, numerous studies have shown that mixed ligand complexes have biological power than parent ligands (Manoussakis & Bolos 1985; Eshaghi Malekshah et al. 2017; De Souza et al. 2019 and Lu et al. 2011).

1.4 Choice of Metals

For synthesization (1:1), (1:2) molar ratio complexes and combination ligand complexes, the following transition metals were selected Cu(II), Co(II), Mn(II), Ni(II) and Zn(II). Because transition metals naturally abound in biotechnology and they play a key part in the regular operation of all living creatures and their coordination complexes are of considerable importance as possible medicines. The metal ions help to speed up the effect of drugs. Recently, interaction investigations of DNA/protein transitional metal ions have had a major effect on medication development and chemotherapy (Kohn et al. 2005). A lot of study has shown that in most instances metal complexes of medicines are more biological than their free medicines/parent organic substances (Hodnett & Mooney 1970 and Hodnett & Dunn 1972). Moreover, ligands and their transition metal complexes are based on morpholine heterocyclic ships with high antibacterial properties because of the presence of multifunctional groups. Most of these include N, O, Br and S groups which create strain-free 5 or 6 members and provide 1:1 chelate with physiologically active significant metal ions

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including Cu(II), Co(II), Mn(II), Ni(II) and Zn Metal ions (II). They are mostly restricted to square and octahedral geometry. The metal complexes with oxygen and nitrogen donor ligands have a unique shape, structural lability and a molecular environment. The metal centre environment plays an important influence in the metal coordination at the active heating place of many metal biomolecules (Golcu et al. 2005). Schiff-based compounds formed from 4-hydroxysalicylaldehyde and primary amines have been shown to exhibit significant anti-cancer action against Ehrlich Ascites Carcinoma (EAC) (Zishen et al. 1993). In 2000, the co(II), Ni(II) and Cu(II) complexes were synthesised using a ship base produced by condensing 2-amino pyridine with Furfuraldehyde, Ethylmethyl Ketone and Salicylaldehyde (Ejidike & Ajibade 2015). In 2003, a trident Schiff base with an ONN donor sequence was synthesised from condensing 1,6-diamino hexane to salicylaldehyde with its synthesised Cu(II), Pd(II), Ti(II), V(IV) complexes. Elements, conductivity, measurements, magnetic measures, and other spectral studies are also structurally characterised and are shown to convey poten-biological activities (Fahmi et al. 2004). In 2004, Feichang discovered that the 2-hydroxyl napthaldehyde produced ship base with 2-Amino pyridine and their metal complexes had a high level of catalytic action for norborene vinyle polymerisation (Feichang et al. 2004). Temel et al. 2001 reported new compounds of 1,2-bis(p- amino-phenoxy)ethanes, cobald(II), copper(II), and zinc(II), and Salicylaldehyde (Temel & Sekerci 2001). Also, Raman and coll. 2001, Jian-ning Liu et al. 2006 and Ahmed et al. 2011 reported on transitional biologically active metal complexes from base ship ligands (Temel et al. 2002; Raman et al. 2001 and El-Sherif et al. 2011).

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