WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 12, 100-127. Review Article ISSN 2277– 7105

A REVIEW ON PHARMACOLOGICAL ACTIVITY OF SOME SELECTED TRANSITION METAL COMPLEXES WITH HETEROCYCLIC LIGANDS

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Article Received on
13 August 2020,

Revised on 03 Sept. 2020,
Accepted on 24 Sept. 2020,

DOI: 10.20959/wjpr202012-18836

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ABSTRACT

Transition metal complexes play an important role in medicinal inorganic chemistry. Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. Due to the metal chelation, these compounds have attracted much attention in the development of new drug discovery. The heterocyclic ligands and their metal complexes can be used as antimicrobial, antitumor, antihistaminic, antioxidative, antiinflammatory, analgesic and neuroprotective properties. In this review, the anti-microbial, anti-inflammatory and anti-tumor activity of some selected heterocyclic ligands and their metal complexes are discussed. This survey encourages further research in this field for future applications.

KEYWORDS: Transition metal complexes, heterocyclic ligands, anti-microbial, anti-inflammatory, anti-tumor.

INTRODUCTION

The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance. Monographs and major reviews, as well as dedicated volumes, testify to the growing importance of the discipline.[1–11] Relevant reviews are to be found throughout annual series, for example Metal Ions in Biological Systems[12] and Coordination Chemistry Reviews[13] The field of inorganic chemistry in medicine may usefully be divided into two main categories: firstly, ligands as drugs which target metal ions in some form, whether free or protein-bound; and secondly, metal-based drugs and imaging agents where the central metal ion is usually the key feature of the mechanism of action.[14]

Metal ions play important roles in biological processes and the field of knowledge concerned with the application of inorganic chemistry to therapy or diagnosis of disease is medicinal inorganic chemistry.[15] Among the natural sciences, medicinal inorganic chemistry is still considered a rather young discipline by many, but this is contrary to the historically proven use of metals in pharmaceutical potions, which traces back to the ancient civilizations of Mesopotamia, Egypt, India, and China.[16-18] The introduction of metal ions or metal ion binding components into a biological system for the treatment of diseases is one of the main subdivisions in the field of bioinorganic chemistry.[19]

Nowadays, the bioinorganic chemists target the heterocyclic ligands and their metal complexes to study their pharmacology as the main focus of research.[20] A wide range of biological activities[21-23] such as antibacterial, antifungal, antitumor and antiviral activities are exhibited by the nitrogen-containing organic compounds and their metal complexes. Transition metal complexes offer two distinct advantages as DNA-binding agents.[24] First and foremost, transition metal centers are particularly attractive moieties for reversible recognition of nucleic acids research because they exhibit well-defined coordination geometries. Besides, they often show distinct electrochemical or photophysical properties, thereby increasing the functionality of the binding agent.[25] In fact, these smart features have fuelled the complexes to be used in a broad spectrum of applications, from fluorescent markers to DNA footprinting agents, to electrochemical probes.[26]

The literature survey reveals that numerous review articles and books have been published on medicinal inorganic chemistry[27, 28] in the field of metallodrugs[29-34] and especially on anticancer treatments.[35-37] We present an overview of the field today and explore a few pharmacological effects of the above transition metal complexes *viz.*, *in vivo* anti-inflammatory response and convulsive response as well as anti-tumor and microbial activity.

1.1. Biological Significance of Metal Complexes

Transition metal complexes have attracted considerable attention owing to their fascinating chemical and physical properties, and their wide-ranging applications in medicine.[38] The integration of metal with organic compound can produce well diversified structures with pronounced biological activities due to chelation.[39,40] The presence of heteroaryl ring systems have numerous benefits due to their unique properties as pH-sensitive, photochromic, redox responsive, stabilizes low valent metal oxidation states. Several reports also showed that metal complexes show higher activity than the parent ligands.[41,42] The

metal complexes prepared from heterocyclic ligands can be used as antifungal, antiinflammatory, anti-HIV, anticancer, diuretic, hypoglycemic, antithyroids, and antimalarials etc.[43,44] In view of this; the present review aims to summarize the recent progress in the biological activity of some selected transition metal complexes bearing heterocyclic ligands.

The use of metals and metal-containing compounds in medicine dates back to millennia which provide an empirical evidence for the effectiveness of such metal-based therapeutics. Transition metal chelates that play a key role in bio-inorganic chemistry and redox enzyme systems serve as the basis of models for active sites in biologically important compounds. They have varied coordination geometry, versatile redox, spectral and magnetic properties which are appropriate for designing non-porphyrinic metal-based PDT agents that could photocleave DNA in visible light.

The relationship between active metals and cancer is a multifaceted issue which combines the expertise of bioinorganic chemists, pathologists, pharmacologists and oncologists. Redox-active metals generally form reactive oxygen species (ROS) and this ROS can be used to induce DNA cleavage. The earliest report of the medicinal use of metals or metal complexes dates back to the sixteenth century.[45] The main application is the anti-tumour action of certain heavy metals which bind to DNA and distorting DNA causing cell death. For example, today the cis-platin is one of the most potent and widely used anticancer drugs in use. However, it cures only limited spectrum of cancers and acquired resistance.[46] To defeat these limitations of cis-platin, less toxic and more effective metallodrugs have been developed like oxaliplatin and carboplatin.

1.2. Heterocyclic compounds

In nature, the chemical compounds play a major role in various organisms from living cells to nonliving materials. These are widely categorized and are accordingly to the composition of chemical elements. For more than a century, heterocycles have been one of the largest areas of research in organic chemistry. Heterocyclic chemistry is an integral part of organic chemistry and deals with the heterocyclic compounds which constitute about sixty-five percent of organic chemistry literature. Heterocycles are abundantly distributed in nature and they play a vital role in the metabolism of living cells. They have contributed immensely in understanding the quality of life processes and to improve the quality of life. Presently, majority of the published work in crystallography involves at least one heterocyclic ring.[47-51]

A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound. If at least one atom other than carbon forms a part of the ring system then it is designated as a heterocyclic compound. Nitrogen, oxygen and sulfur are the most common heteroatoms but heterocyclic rings containing other heteroatoms are also widely known. A mountainous number of heterocyclic compounds are known and this number is increasing rapidly. Accordingly, the literature on the subject is very vast. A heterocyclic ring may comprise of three or more atoms which may be aliphatic or aromatic (which may be saturated or unsaturated). Also the ring may contain more than one heteroatom which may be similar or dissimilar. The chemistry of heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. Their study is of great interest both from the theoretical as well as practical standpoint.[52-56]

The aliphatic heterocyclics are the cyclic analogues of amines, ethers, thioethers and amides. Generally these compounds consist of small (3 and 4 membered) and common (5 to 7 membered) ring systems. In contrast, the aromatic heterocyclic compounds have a heteroatom in the ring and behave in a manner similar to benzene in some of their properties. These compounds comply with the general rule proposed by Hückel, which states that aromaticity is obtained in cyclic conjugated and planar systems containing (4n+2) π electrons. The conjugated cyclic rings contain six π electrons as in benzene and this forms a conjugated molecular orbital system which is thermodynamically more stable than the non-cyclically conjugated system. This extra stabilization results in a diminished tendency of the molecule to react by addition but a larger tendency to react by substitution in which the aromatic ring remains intact.[57-61]

Recent literature has explored a wide range of biological and pharmacological activities of various structural derivatives of heterocyclic compounds. Since 1886,[62] Schiff bases have become increasingly important mainly due to their stability, ease of preparation, structural variability and variety of applications. On the other hand Schiff bases, the condensed products of aromatic amines with aromatic aldehydes, have been known to possess a wide variety of biological applications like antibacterial, antifungal, antitumor, analgesic and anti-inflammatory activities[63,64] It has been observed that several Schiff bases show antifungal,[65,66] anti-inflammatory,[67] antibacterial,[68,69] antiviral,[70] antioxidant,[71] and anticancer activities.[72]

Heterocyclic chemistry is enormously expanding because of the immense amount of research work being done in this area. Majority of the known molecules are heterocyclics. Heterocyclic compounds dominate the field of biochemistry, medicinal chemistry, dyestuff and are of increasing importance in many other areas including polymers, adhesives and molecular engineering.

1.3. Need of New Drugs

The entire pharmaceutical industry today is faced with the challenge of increasing resistance of pathogen against existing drugs as well as its toxicity and side effects. To overcome these problems, its need of the hour to develop a new drug with higher activity and lesser toxicity or side effects. Various factors play a role while targeting a moiety as a possible new drugs, the most crucial being a base moiety i.e. skeleton of the molecule. As already stated earlier researcher has time and again remained dependent on nature to take clues for developing new drugs, moieties structurally similar to compounds exists in metabolic system are preferred and then engineered for desired pharmacophore. Taking the same path study carried out in this research also mainly based on compounds existing in nature, i.e. Heterocyclic compounds. Various natural medicine like as theobromine, theophylline, papaverine, emetine, procaine, quinine, reserpine codeine, morphine, &atropine are heteroatom containing system. Most of all the medicines we familiar as synthetic medicine like as ionized, chlorpromazine, diazepam, metronidazole, barbiturates, azidothymidine, captopril methotrexate, and antipyrine are also heteroatom containing system. Among the various hetercyclic compounds, Nitrogen heterocyclic compounds are the most prevalent. In addition to this Sulphur heterocycle is also a significant member of metabolic system.

1.4. Biological Activity of Some Selected Transition Metal Complexes

1.4.1. Antimicrobial activity of some transition metal complexes

Coordination compounds are of great importance in biological systems. For example, chlorophyll is a coordination compound of magnesium, haemoglobin is a coordination compound of iron and vitamin B_{12} is a coordination compound of cobalt. Coordination compounds, with bonds between a central metal atom and surrounding ligands, play critical roles in biology, biochemistry and medicine, controlling the structure and function of many enzymes and their metabolism. They play similarly vital roles in many industrial processes and in the development of new materials with specifically designed properties. Thus synthesis and study of such complexes is very important. Many studies concerning the

relationship between metal ions and the bioability of drugs have been a subject of great interest.[73] A number of known biochemical reactions which are catalysed by enzymes contain metal ions such as Zn, Co, Mo etc. Many metal chelates which have been proved to be more carcinostatic than the unchelated drugs and similarly, many antibacterial drugs when are complexed/ chelated, their bioability is effectively altered.

Ability of inert chiral transition metal complexes in binding DNA has also attracted considerable interest. Variety of transition metal complexes has significant potential as probes for sequence and structure-specific DNA binding. Significant attention has centered upon metal complexes capable of binding DNA by intercalation, and, in particular, due to their luminescent properties and strong DNA binding affinity. Replacement of the hydrogen-bonded base pairing of natural DNA by alternative base pairing modes is expected to lead not only to expansion of the genetic alphabet but to novel DNA structures and functions based on the controlled and periodic spacing of the building blocks along the helix axis. Nickel macrocyclic complexes that possess vacant or labile coordination sites are known to ligate to DNA bases, and effect site-specific reactions with DNA.[74]

Semicarbazones are among the most relevant nitrogen-oxygen donor ligands. A good deal of work has been reported on the preparation and structural investigation of semicarbazones and their complexes. This is due partially to their capability of acting as multidentate, NO, NNO and ONNO donors with the formation of either mono- or bi- or polynuclear complexes. In addition thio- and semicarbazones possess a wide range of bioactivities, and their chemistry and pharmacological applications have been extensively investigated. Polymer complexes have also been given a great deal of attention in recent years. Polyvinyl alcohol (ethanol homopolymer) which considered as moderate adhesive is a water soluble resin. PVA is a polymer with exceptional properties such as water solubility, biodegradability, biocompatibility, non-toxicity and non-carcinogenity that possesses the capability to form hydrogels by chemical or physical methods. Its fields of applicability were widely broadened during the later years due to the development of medicine.[75]

The PVA ligand is biologically active and its activity may arise from the hydroxyl groups which may play an important role in the antibacterial activity. The synthesized compounds were found to be more toxic compared with their parent PVA ligand against the same micro-organism and under the identical experimental conditions. The increase in biological activity of the metal chelates may be due to the effect of the metal ion on the normal cell process. A

possible mode of toxicity increase may be considered in the light of Tweedy's chelation theory. Chelation considerably reduce the polarity of the metal ion because of partial sharing of its positive charge with the donor group and possible p-electron delocalization within the whole chelate ring system that is formed during coordination. Such chelation could enhance the lipophilic character of the central metal atom and hence increasing the hydrophobic character and lipo solubility of the complex favoring its permeation through the lipid layers of the cell membrane. This enhances the rate of uptake/entrance and thus the antimicrobial activity of the testing compounds.[76]

Accordingly, they reported that antimicrobial activity of the complexes can be referred to the increase of their lipophilic character which in turn deactivates enzymes responsible for respiration processes and probably other cellular enzymes, which play a vital role in various metabolic pathways of the tested microorganisms.[77]

It is well known that the derivatives of thiosemicarbazones possess the antibacterial activity. In addition, there are many studies that show the antimicrobial activity of copper (II) complexes with these ligands. Common anti-bacterial agents have been also used as ligands to complex with copper ions. It was noticed that the antimicrobial activity against M. Smegmatis of a metal ion complex in comparison to free ciprofloxacin, a bacterial gyrase inhibitor, increased three times. It may result from facilitated diffusion of the drug through the cell membranes, presumably by an increase in the lipophilicity of the drug. The activity against Streptococcus can also be influenced by the slow release of the ligands inside the bacterial cell. This was noticed with the copper complex of isoniazide and ethambutol. It seems that intercellular reduction of Cu (II) into Cu (I) can acitivate the oxygen which is toxic for bacteria. Moreover, a copper (II) complex of sulfacetamide, (N-[4-(amino-fenil)sulfonil]acetamide), has been intensively used in treatment of ophthalmic and dermatologic infections. Further studies of the copper (II) complexes of sulfacetamide and sulfanilamide and sulfisoxazole have showed promising results.[78]

In general, sulfonamide copper(II) complexes show antimicrobial activity against both types, Gramm(+) (*Staphylococcus aureus, Bacillus subtilis*) and Gramm(-) (*Escherichia coli, Pseudom onas euruginosa*). More often it shows slightly higher activity against Gram(-) bacteria. The copper(II) complexes of benzimidazoles have not only shown antibacterial activity against S. epidermidis but also some strong activity was found against fungi. In addition, complexes of thiabendazole appeared to be active. Moreover, antifungal activity

against Aspergillus sp. and Penicillium sp. Was also found for a copper(II) complex of p-amino acetophenone benzoylhydra zone.[79]

Various Co (III) complexes have been reported with antimicrobial activities. For instance, a Co (III) complex of the known untiulcer drug famotidine turned out to have greater antimicrobial activity against E. coli and M. lysodeikticus than the metal free drug. The pyrazine-2,3-dicarboxylate complexes of 1,10-phenanthroline and alkyl diamines have recently shown activity against Gram(+) and Gram(-) bacterial strains and fungi C. albicans. The cobalt (II) complexes of hinikitiol, 4-isopropyltropolone, appeared to be active, in comparison to copper (II) complexes. Interesting biological properties have been found in the series of metal (II) oxinates of the derivative of sulfonohydrazide, belonging to the group of sulfonamides. The octahedral cobalt complex possessed good activity against both Gram (+) and Gram (-) bacterial strains but not higher than the free ligand alone. Cobalt (II) complexes not only show antimicrobial but also antifungal activities. The complex of the imidazole-2-carbaldehyde semicarbazone turned out to be active against the yeasts S. cerevisiae and C. tropicalis. Activity was most noticeable against such phytopathogenic fungi as Alternaria or Sclerotinia.[80]

Zinc (II) complexes of carboxylates appeared to have good antibacterial activity; e.g., a strong inhibitive effect was noticed towards E. coli and S. aureus[81] In the search for zinc (II) complexes of known antimicrobial drugs strong antibacterial activity has been achieved; e.g. the interaction between zinc and the gyrase inhibitor ciprofloxacin and various nitrogen-donor ligands have been studied and the complexes were found more potent than the drugs alone. The investigation of complexes of thiosemicarbazones gave promising results as well. A noticeable selective activity was seen by zinc (II) complexes of picolinaldehyde-S-methyl- and -S-benzylthiosemicarbazones which were active in comparison to their metal free ligands. Moreover, there zinc(II) complexes of salicylaldimine were found active against *S. aureus*.[82]

Zinc (II) complexes of sulfa drugs, such as sulfadiazine and sulfamerazine also proved to be effective antifungal agents against Aspergillus and Candida spp. Moreover, the activities of the complexes were higher than the free ligands, but lower than the drug ketoconazole. Zinc (II) complexes with amino acids have been developed with antimicrobial activity. The antibacterial activity of zinc (II) complex with S-phenylalaninato ligand was 10-fold greater

than the simple metal salt. A very good inhibitory activity was also found by the yeast Candida albicans.[82]

In general, when the antimicrobial activity of metal complexes is concerned, the following five principal factors may be considered:

i. The chelate effect, i.e. bidentate ligands, such as the quinolones, show higher antimicrobial efficiency towards complexes with monodentate ligands

ii. The nature of the ligands

iii. The total charge of the complex; generally the antimicrobial efficiency decreases in the order cationic > neutral > anionic complex

iv. The nature of the counter ion in the case of the ionic complexes

v. The nuclearity of the metal center in the complex; binuclear centers are more active than mononuclear ones.

The antimicrobial activities of metal complexes depends more on the metal center itself than on the geometry around the metal ion.[83]

1.4.2. Anti-tumor activity of some selected transition metal complexes

Although there were multiple reports in recently published papers about the ternary copper(II) complexes, that are synthesized by the combination of a bidentate N-donor heterocyclic ligand (phen, bpy or their substituted derivatives) and other synthetic co-ligands (i.e., salicylic acid[84], tetracycline derivatives[85], terpyridine[86], or imidazolidine-2-thione[87]), with remarkable *in vitro* cytotoxicity towards the human cancer cell lines, none of these dealt with the directed synthesis of mixed ligand copper(II) coordination compounds containing flavonoid-inspired co-ligands.

Lately, Reedijk et al. have found that efficient self-activated DNA cleavage and cytotoxic effects toward L1210 murine leukemia and A2780 human ovarian carcinoma cell lines can be brought out by the complex [Cu(pyrimol)Cl], synthesized by them.[88] Sadler and his co-workers have observed[89] that cytotoxic and antiviral activities are exhibited by their synthesized mixed ligand bis(salicylato) copper(II) complexes with diimines as co-ligands. Palaniandavar and his co-workers reported[90-92] the role of hydrophobicity of ligands in many ternary copper (II) complexes which exhibited strong DNA binding and cleavage and induced apoptosis in cancer cells. Kumbhar and his co-workers have investigated the cytotoxicity of certain mixed ligand Cu (II) complexes against HeLa (cervical) cancer cell lines.[93]

Generally, the molecules that are approved for clinical use are those which damage DNA, inhibit nucleic acid precursor biosynthesis thereby blocking DNA synthesis indirectly, or disrupt hormonal stimulation of cell growth as anticancer agents.[94] Sigman et al. reported[95] a facile approach for investigating the interaction of nucleic acids and oligonucleotides with proteins that is provided by the oxidation of DNA and RNA. Burstyn and his coworker have found that copper (II) complexes of macrocyclic triamines promote the hydrolytic cleavage of plasmid DNA.[96] So, the copper (II) complexes possessing high nucleobase affinity and biologically accessible redox potentials are considered as potential reagents for cleavage of DNA both oxidatively[97] and hydrolytically.[98] Such metal complexes would permit targeting of specific DNA sites by matching the shape, symmetry and functionality of the complexes to those of the DNA target. Marin- Hernandez et al.[99] indicated that some mixed chelate transition metal-based drugs had more potent antitumor activity than cisplatin in *in vivo* and *in vitro* studies of a variety of tumor cells. However, human cancer cell lines are a useful model to study cell growth inhibition of tumor cells by natural compounds or newly synthesized compounds. Sinha group have synthesized a monoanionic tetradentate- N_2O_2 Schiff base 2-[{[2-(dimethylamino)ethyl]imino}methyl]-6- methoxyphenol [100-103] and two of its analogous are mononuclear Co(II) derivatives, $[Co(LH)_2(NCS)]NO_3$ and $[Co(LH)_2(N_3)]NO_3$. Interestingly, the tetradentate ligand LH behaves either in a bidentate-NO or terdentate-N_2O fashion to coordinate the metal ions. The anticancer efficiency (*in vitro*) of these Co(II) derivatives has been investigated using various human cancer cells like human colorectal carcinoma cells (COLO 205 cells), human hepatocellular carcinoma cells (PLC5 cells), human lung carcinoma cells (A549 cells) and human fibroblasts cells (NIH 3T3). The biological effects of both Co(II) derivatives on the viability on NIH 3T3 cells indicate that these complexes induce a decrease in cell-population of human fibroblast cells with apoptosis. The human fibroblasts cells (NIH 3T3) are treated with $[Co(LH)_2(N_3)]NO_3$ and the investigations reveal the apoptotic properties of the Co(II) complex and also suggest that a mitochondriamediated pathway is induced by this compound.

Recently, Stanojkovic et al. have reported[104] that the antiproliferative activity of zinc(II) complexes of 2-acetylpyridine1-(4- fluorophenyl)-piperazinylthiosemicarbazone is found to be noticeably stronger than that of cis-platin. The IC50 values range from 26-90 μM, against all cell lines tested, while for cis-platin the IC50 values range from 2-17 μM and for the zinc salt, ZnCl2, the IC50 values range from 81-93 μM. The highest activity is exhibited by [Zn(HAcPipPheF)(OAc)] complex against all four cancer cell lines whereas the highest

selectivity is against K562 and MDA-MB-453 cancer cell lines. The tumor cell proliferation is achieved by arresting the cell cycle progression at the S phase by the compounds.

El-Asmy et al. have synthesized metal complexes having OO, ON, NS and ONS-donors and evaluated for anticancer activity against either Ehrlich ascites tumor cells (EACs)[105-108] or human cancer cell lines.[109-111] Recently, Pascu and his co-workers document that acenaphthenequinone based zinc bis(thiosemicarbazone) complexes (Figure 1) exhibit comparable cytotoxicity to cisplatin in the MCF-7 cell line and emit fluorescence as well.[112]

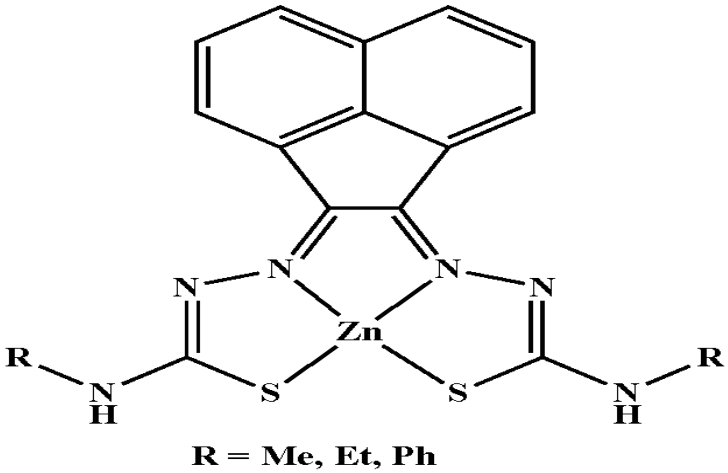


Figure 1: Structure of acenaphthenequinone based zinc bis(thiosemicarbazone) complexes.

Harding and his co-worker have synthesized bis(η5-(3,4- dimethoxybenzyl) cyclopentadienyl)-vanadium(IV) dichloride complex. Further *in vitro* and *in vivo* work reveal that V (IV) organometallic compounds exhibit significant anti-tumor properties[113] with vanadocene dichloride being one of the most promising among metallocenes.[114] These results encourage further preclinical studies[115,116] and have since been extended[117] with the study of the cytotoxic properties of vanadocene (Figure 2) and various derivatives.

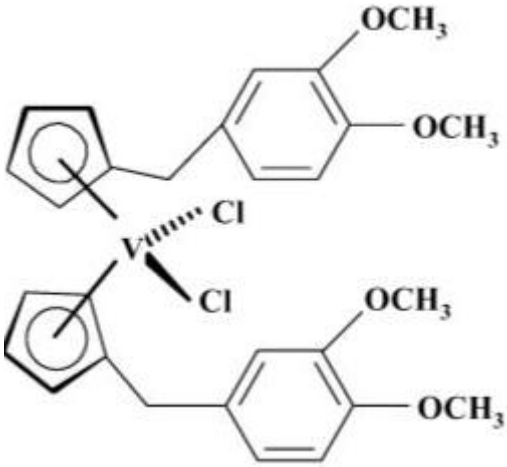


Figure 2: Structure of bis(η5-(3,4-dimethoxybenzyl)cyclopentadienyl)-vanadium(IV).

Manikandan et al.[118] have newly synthesized Co(II) complexes of 2-acetylpyridine N-substituted thiosemicarbazone with $(PPh_3)_2$ (Figure 3). The higher cytotoxic activity for the complex substituted benzene may be due to terminal phenyl substitution of the coordinated ligand. By comparing the cytotoxicity with that of the conventional standard cisplatin, they found that the complexes exhibited excellent activity in both the cancer cell lines. However, the cytotoxic activity of complexes against human breast cancer cell line (MCF-7) stood higher than that of skin carcinoma cell line (A431).

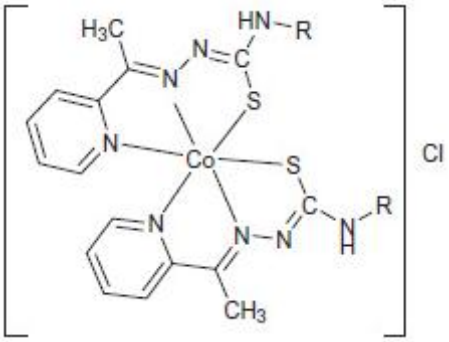


Figure 3: Structure of Co (III) complex of 2-acetylpyridine N-substituted thiosemicarbazone.

1.4.3. Anti-inflammatory activity of some selected transition metal complexes

The protective response of an organism, when treated by a noxious stimulus is known as inflammation. Such inflammatory conditions lead to rheumatic diseases that cause major disability. It is a part of the complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells and irritants.

Recently, Odisitse and Jackson reveal that 3,5-diaminodiamido- 4-oxahexacyclododecane (cageL) (Figure 4) can survive *in vivo* through a demonstration by speciation calculations using blood plasma model and animal bio-distribution experiments, which is because they are stable in lipophilic conditions.[119] In pursuit of developing better copper(II)-based anti-inflammatory drugs which can be administered orally, intravenously or even transdermally, they have designed and synthesized two ligands, N,NO-di(aminoethylene)- 2,6-pyridinedicarbonylamine (L1) and bis-(N,Ndimethylethyl)-2,6- pyridinedicarboxamide (L2). L1 and L2 both have pyridyl groups which are found in most of the non-steroidal anti-inflammatory drugs (NSAIDs).[120]

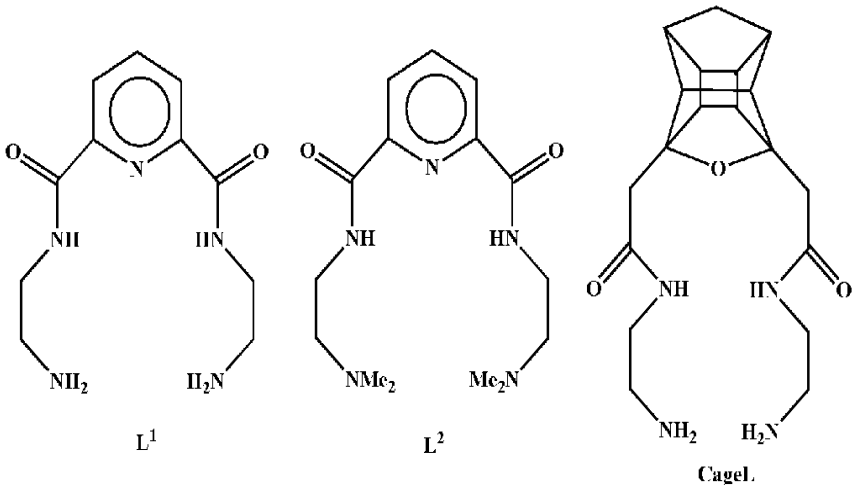


Figure 4: Schematic structures of ligands.

Pyridine derivatives are of high interest in several areas of medicinal chemistry, specifically, aminopyridinylmethanols and aminopyridinamines[121] have been considered as an analgesic as well as anti-inflammatory agents and for treating Alzheimer's disease.[122] The pyridine ring characterizes niflumic acid and flunixin[123], two standard NSAIDs belonging to the class of fenamates (Scheme5). These drugs are derived from N-aryl substituted anthranilic acid (2-amino-3-pyridinecarboxylic acid), and they are commonly used as analgesic, anti-inflammatory and anti-pyretic agents, like salicylates. Flunixin meglumine[124,125] is a substituted derivative of nicotinic acid (3-pyridinecarboxylic acid) which is structurally unique when compared to other NSAIDs (Figure 5).

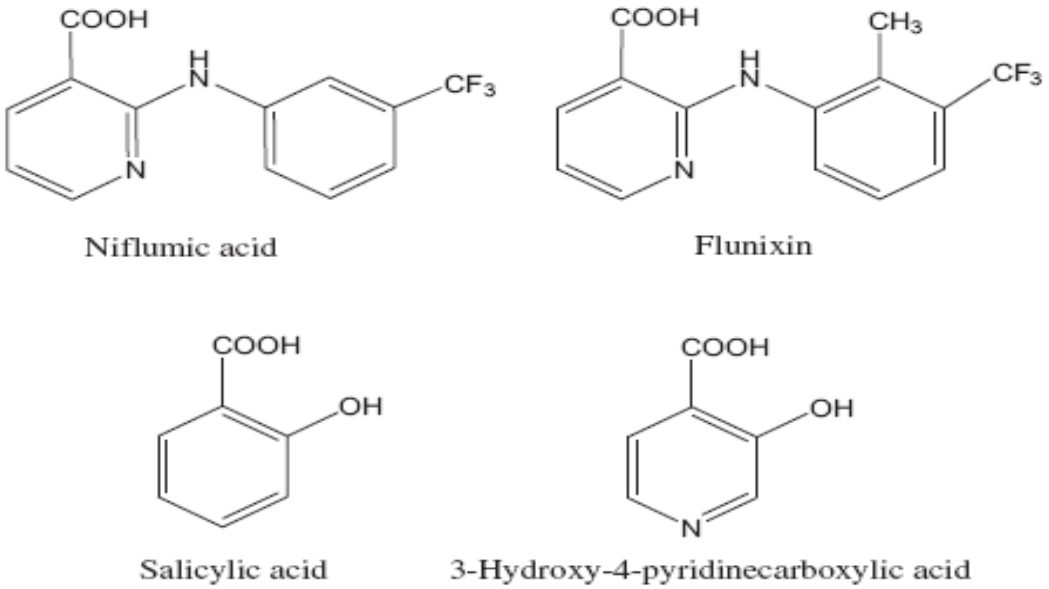


Figure 5: Structures of few known anti-inflammatory drugs and of 3-hydroxy- 4-pyridinecarboxylic acid.

Hoonur group has studied about the 1,2-dihydroquinazolin- 4(3H)-ones based metal complexes along with their structure and biological activity[126-131] with a view to explore structure-activity relationships. Study of the reactivity of this free amino group with aromatic aldehydes resulted in the formation of biologically active 1,2-dihydroquinazolinone. Compounds have demonstrated dose dependent activity which is better even at lower dose level (3 mg/kg) while the reported analogous compounds have shown activity at higher dose level (such as 10, 20 and 50 mg/kg). The anti-inflammatory activity of these metal complexes is higher than their parent ligand perhaps due to their enhanced lipophilicities (Figure 6).

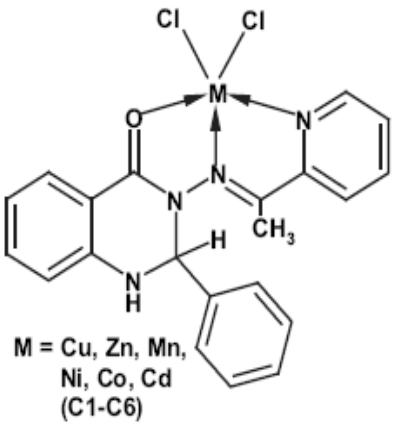


Figure 6: Structure of metal complexes of 1,2-dihydroquinazolin-4(3H)-ones.

A class of quinoline based compounds has been explored and found to have the ability to inhibit platelet-activating factor (PAF) synthesis which also contributes to anti-inflammatory properties.[132] The role of copper in the pathology of inflammation emphasizes a lot of evidence.[133] The thorough investigation of copper complexes with different ligands together with anti-inflammatory drugs and of the copper containing enzyme super oxide dismutase (SOD) brought to light the various therapeutic value of copper which is concluded to be an exogenous anti-inflammatory agent.[133]

Naik and his coworkers have explored a series of Schiff bases derived from 2-mercapto-3-formyl quinoline/2-hydroxy-3-formyl quinoline with 2,6-diaminopyridine (DAP) and their corresponding Co(II), Ni(II), Cu(II) and Zn(II) complexes (Figure 7) for their anti-inflammatory activity.[134] The rats challenged by carrageenan when treated with the complexes significantly reduced the inflammatory edema. The complexes did not induce sedation, ataxia, tremors, convulsions, lacrimation or changes in motor activity in mice and caused no significant toxicity to the stomach, intestines and liver of mice. The Cu (II) complexes showed the highest biological activities amongst the compounds tested.

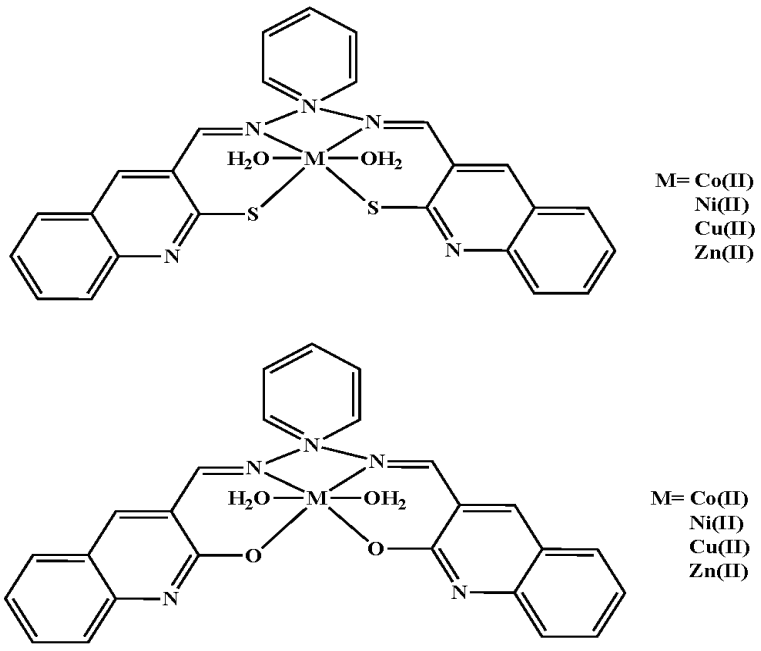
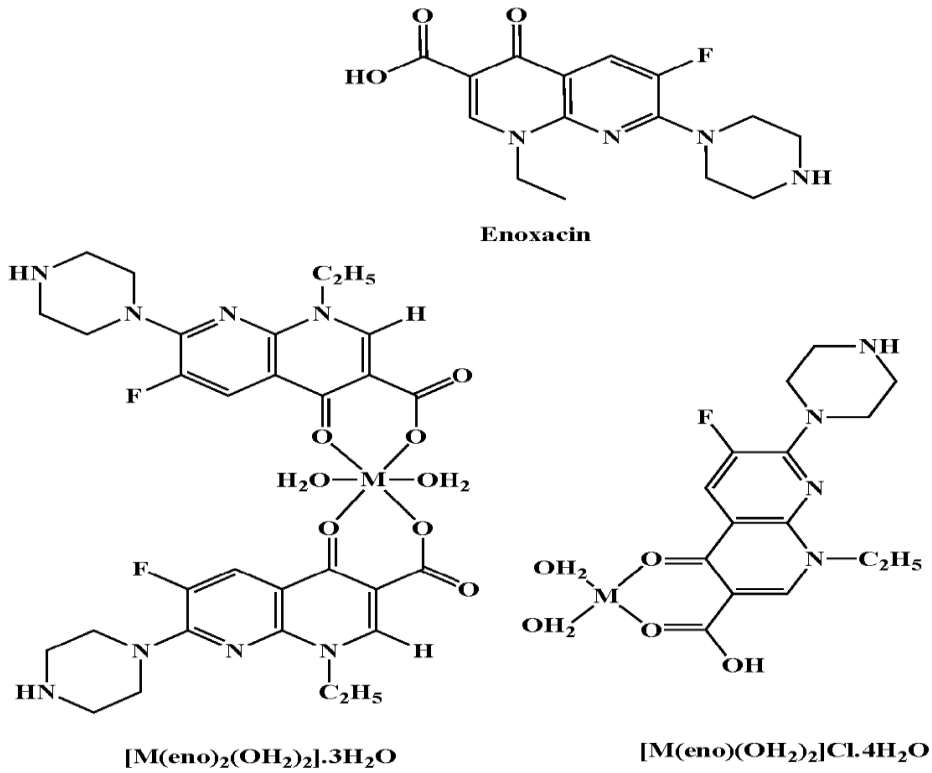


Figure 7: Chemical structures of the Co (II), Ni (II), Cu (II) and Zn (II) complexes with Schiff bases derived from 2-mercapto-3-formylquinoline or 2-hydroxy-3-formyl quinoline with 2,6-diaminopyridine (DAP).

In 2009, Arayne and his group studied the anti-inflammatory properties of enoxacin and their Cu (II) and Ni (II) complexes (Figure 8).[135] When enoxacin 36 is subjected to infrared spectroscopicanalysis, it is inferred that the compound acts as a monoanionic bidentate ligand and is coordinated to the metal ions *via* its carboxyl and carbonyl groups. The levels of reactive free radicals released by activated phagocytic cells are measured for evaluating the anti-inflammatory properties of the enoxacin complexes. The IC50 values of 15.3 and 18.7 μg.mL−1 of Cu(II) enoxacin complexes are found to be the most active against free radical release whereas enoxacin and its Ni(II) complexes are less effective (IC50>50 μg.mL−1). Nevertheless, the immunomodulatory effect of the enoxacin complexes that is governed by the molecular mechanism is not determined.



M= Co (II), Ni (II), Cu (II) and Zn (II)

Figure 8: Chemical structures of the complexes having enoxacin derivatives.

A series of potential anti-inflammatory agents that are Co (II) complexes and bearing the NSAID mefenamic acid ligand have also been investigated (Figure 9).[136-138] Mefenamic acid is found to act as a deprotonated monodentate ligand. It is coordinated to the Co(II) ion through its carboxylato oxygen atom, forming octahedral [Co(mef)2(MeOH)4] or $[Co(mef)_2(MeOH)_2(N\text{^}N)]$ (where mef = mefenamic acid and N^N = 2,2′-bipyridine, 1,10-

phenanthroline or (pyridine)2) complexes which is in accordance with the physicochemical and spectroscopic data. In later studies, Cu(II) complexes of mefenamic acid, naproxen, diclofenac, diflunisal and flufenamic acid, Co(II) complexes of naproxen and tolfenamic acid, and Mn(II) complexes of tolfenamic acid have been reported by the research groups that showed anti-inflammatory activity.

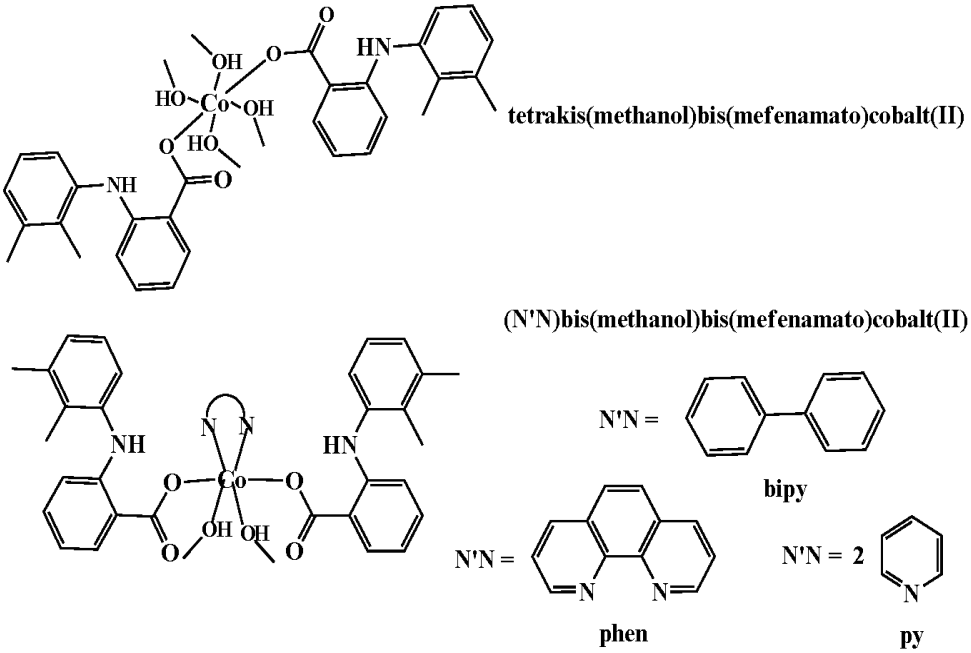


Figure 9: Co (II) complexes of NSAID mefenamic acid having anti-inflammatory responses.

CONCLUSION

In this work, the pharmacological effects of some selected transition metal complexes with heterocyclic ligands have been reviewed. The application of bioinorganic chemistry to medicine is a rapidly developing field. Novel therapeutic and diagnostic metal complexes are now having an impact on medical practice. Advances in bioinorganic chemistry are important for improving the design of compounds to reduce toxic side-effects and understand their mechanisms of action. This review will create new ideas in the field of medicine which helps the scientist to produce more new drugs which are specific in action. In spite of various syntheses in the drug analysis there is still a need to explore new drugs which are useful for future generation.

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