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APPLICATION OF TRANSITION METAL COMPLEX IN MEDICINE

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ABSTRACT

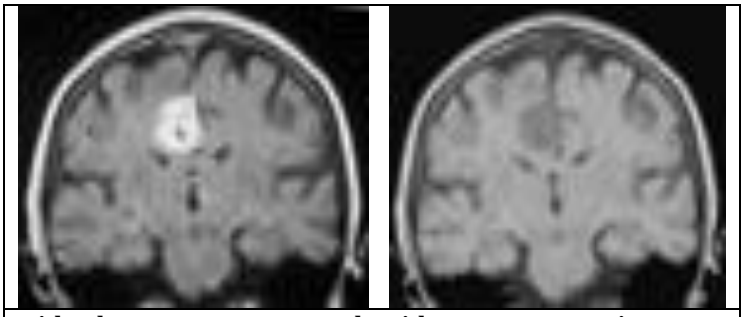
The transition metals are compounds where the compound has an incomplete d sub shell i.e. Mn (II), Fe (II),Fe (III) etc and due to their instability in structure it has variable oxidation number as well as unstable electronic configuration which modulate the variable redox system present inside the biological system and it exhibit different oxidation states and can interact with a number of negatively charged molecules. This aactivity of transition metals has started the development of metal based drugs with promising pharmacological application and may offer unique therapeutic opportunities and show remarkable therapeutic success of ***anticancer drugs such as cisplatin, carboplatin and oxaliplatin, metallodrugs have*** also shown promising results in the treatment of diseases other than cancer also. They have been developed to treat/cure a variety of ailments viz***. diabetes, ulcer, rheumatoid arthritis, inflammatory and cardiovascular diseases etc. Phytoconstituent like Curcumin has keto-enol*** form transformation property and utilising that property in the open chain configuration of enolic form metal ion will attach and its gives a structure of chelates where curcumin will act as ligand. This chelate can be synthesized in different proportion depending on the chemical nature of metal central cation as well also.

KEYWORDS: *cisplatin, carboplatin and oxaliplatin.*

Metals have an esteemed place in medicinal chemistry. Transition metals represent the d block element which includes groups 3 - 12 on the periodic table. Their d shells are in process of filling. This property of transition metals resulted in the foundation of coordination complexes. Metal complex or coordination compound is a structure consisting of a central metal atom, bonded to a surrounding array of molecules or anions. ***Sophus Jorgensen in Denmar*** synthesized metal conjugates for the first time in the mid 1870's. In 1893 the major breakthrough in this field was occurred when Alfred Werner investigated a series of compounds, which contained cobalt, chlorine and ammonia.

He awarded the Noble prizein 1913 for his work. work. The example of transition metals are where the compound has an incomplete d subshell i.e. Mn (II), Fe (II), Fe (III) etc and due to their instability in structure it has variable oxidation number as well as unstable electronic configuration which modulate the variable redox system present inside the biological system and show the antioxidant activity as well as anticancer activity. Curcumin has keto-enol form transformation property and utilising that property in the open chain configuration of enolic form metal ion will attach and its gives a structure of chelates where curcumin will act as ligand. These chelates can be synthesized in different proportion depending on the chemical nature of metal central cation. The 1, 3-diketone moiety of curcumin can transform automatically to a keto–enol tautomeric form, and the later is more table and can readily chelate the metal to form the complexes and scavenge the active free-radicals which is the main cause of the disease.[1-7] The earliest reports on the therapeutic use of transition metal complexes in cancer and leukemia date from the sixteenth century. ***In 1960 the anti-tumor activity of an inorganic complex cis-diammine-dichloroplatinum (II) (cisplatin)*** was discovered. Cisplatin has developed into one of the most frequently used and most effective cytostatic drug for treatment of solid carcinomas.Other metal like gallium, germanium, tin, bismuth, titanium, ruthenium, rhodium, iridium, molybdenum, copper,gold were shown effective against tumors in man and animals. The metal based drugs are also being used for the treatment of a variety of ailments viz.diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases as well as diagnostic agents.[8-10] In medicinal chemistry, metal complexes have received limited attention as compared to organic compounds. In fact, many organic compounds used in medicine do not have a purely organic mode of action and require traces of metal ions directly or indirectly for activation or biotransformation. Our health, aging, physiological disorders and diseases are related to the state of the metal

ions and their complexes with biomolecules in the body. Traces of metals are essential for the biological processes as about 30 - 40 % of all known proteins including metalloenzymes require metal cofactors (e.g., Fe, Cu, Zn, Ni, Mn) for their proper folding into an active three dimensional (3-D) structure.[11-12] Ligands having electron donor atoms like N, O, S, and P etc. may form coordination bond with metal ion. Chelation causes drastic changes in biological properties of ligands as well as metal moiety and in many cases it causes synergistic effect of metal ion and ligand both (13-14). A few well known metallopharmaceuticals include platinum (Pt) anticancer agents cisplatin, carboplatin and oxaplatin, arsenic (As) anticancer agent arsenic trioxide, orally active gold (Au) anti-rheumatoid agent auranofin, selenium (Se) anti-inflammatory agent ebselen, lithium (Li) anti-manic depressive agent lithium carbonate, aluminum (Al) and zinc (Zn) anti-ulcer agents scralfate and polaprezinc.



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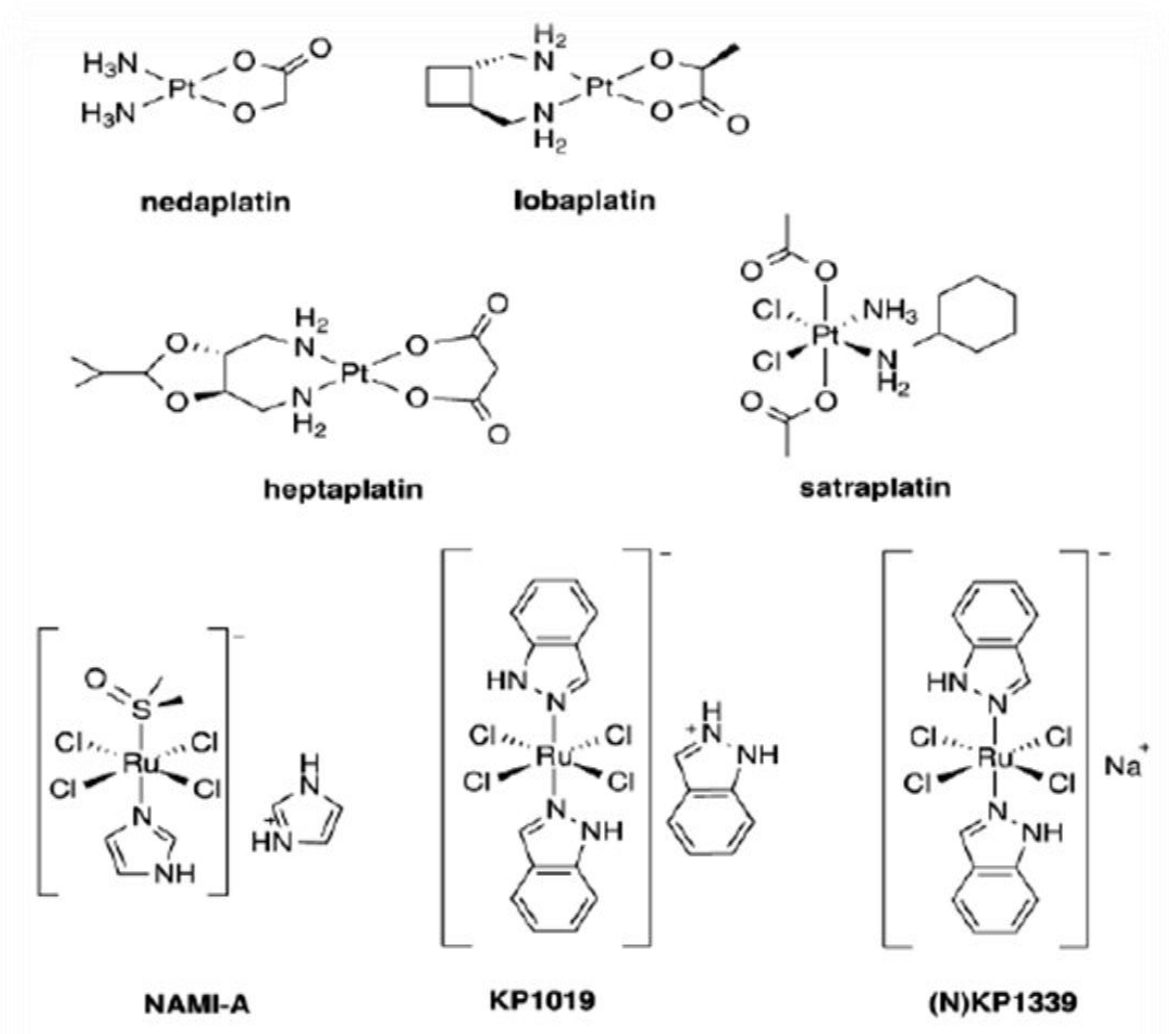
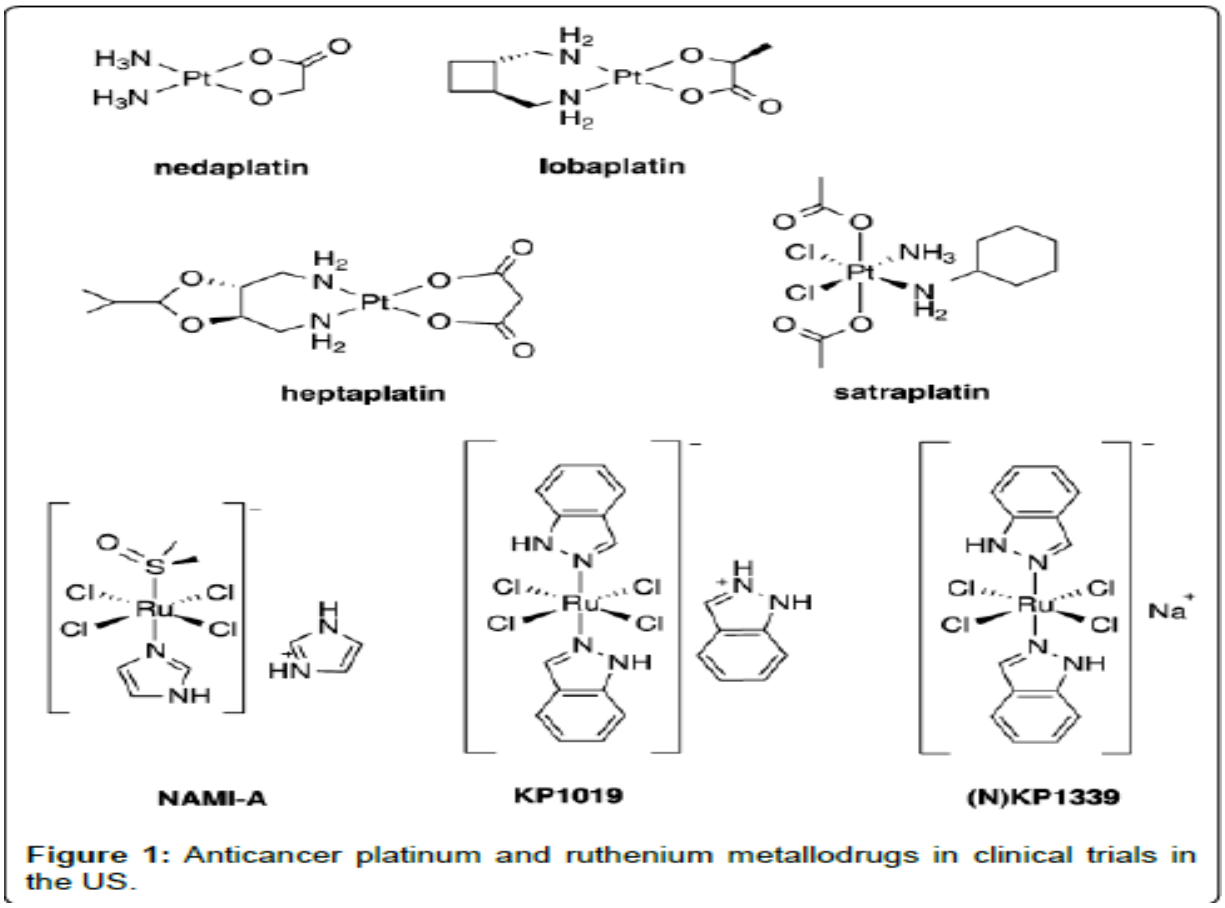


Figure 1: Anticancer platinum and ruthenium metallodrugs in clinical trials in the US.



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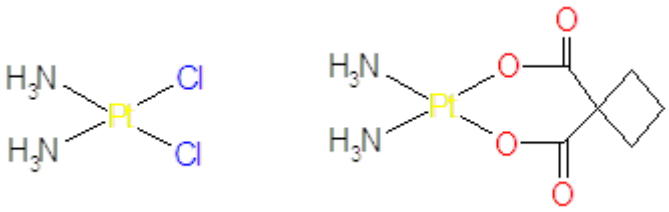

Properties Of The Transition Metals

The transition metals are the group of metals in the middle section of the periodic table. They are divided into three groups - the first row transition vided into three groups - the first row transition metals, the second row transition metals and, guess what, the third row transition metals. The most hey called the transition metals because they are the metals which make the transition to ***using the d-orbitals for their bonding***. Hence they are sometimes called the ***d-block elements.*** .These elements are very hard, with high melting points and boiling points. Moving from left to right across the periodic table, the five d orbitals become more filled. The d electrons are loosely bound, which contributes to the high electrical conductivity and malleability of the transition elements. The transition elements have low ionization energies. They exhibit a wide range of oxidation states or positively charged forms. The positive oxidation states allow transition elements to form many different ionic and partially ionic compounds. The formation of complexes causes the d orbitals to split into two energy sublevels, which enables many of the complexes to absorb specific frequencies of light. Thus, the complexes form characteristic coloured solutions and compounds. Complexation reactions sometimes enhance the relatively low solubility of some compounds.

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 Nowadays, the bioinorganic chemists target the heterocyclic ligands and their metal complexes to study their pharmacology as the main focus of research . A wide range of biological activities 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 . 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]. 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 electrochemicalprobes. Among the metal ions regarded as coordination centers of potential anticancer agents, platinum and ruthenium ions (Figure 1) are commonly explore]. However, there is an emerging curiosity in the synthesis of cheaper first-row coordination compounds as efficient DNA binders with potential cytotoxic activity]. Hence, herein the attention is focused primarily on the research concerning with a few pharmacological activities of the cheaper and easily available first-row transition metal coordination compounds V(IV), Co(II), Ni(II), Cu(II) and Zn(II) complexes. Moreover, these metal ions are the essential elements present in the biological intracellular environment of living organisms. They are most abundantly found trace elements present in biological systems together with iron and most of the metalloproteins have these elements. These metal ions are nowadays present in several inorganic pharmaceuticals.

Transion metals are ranging from antibacterial and antifungal to anticancer application]. Another fact for targeting these particular metal ions is their less toxic nature which can be further decreased when coordinated with the ligands. Though there are innumerable ligands available, the chosen ***amino acids, N-heterocycles (1,10 Phenanthroline, Bipyridine) and pyrazolones*** each have an added benefit to their properties which is a major advantage in designing Among metal ions regarded as coordination centers of potential anticancer agents, platinum and the ruthenium ions (**Figure 1**) are commonly explored]. However, there is an emerging curiosity in the synthesis of cheaper first-row coordination compounds as efficient ***DNA binders with potential cytotoxic activity***. Hence, herein the attention is focused primarily on the research concerning with a few pharmacological activities of the cheaper and easily available first-***row transition metal coordination compounds V(IV), Co(II), Ni(II), Cu(II) and Zn(II) complexes***. Moreover, these metal ions are the essential elements present in the biological intracellular environment of living organisms]. They are most abundantly found trace elements present in biological systems together with iron and most of the metalloproteins have these elements. These metal ions are nowadays present in several inorganic pharmaceuticals used as drugs against a variety of diseases, ranging from antibacterial and antifungal to anticancer applications . Another fact for targeting these particular metal ions is their less toxic nature which can be further decreased when coordinated with the ligands. Though there are innumerable ligands available, the chosen amino acids, N-heterocycles (1,10 Phenanthroline, Bipyridine) and pyrazolones each have an added benefit to their properties which is a major advantage in designing an ideal drug. The amino acids are the building blocks of the human body and when the environment of the drug is similar to that of the functions carried out inside the body, the chance of succeeding in designing a less toxic and cheap drug with high activity is more. In addition to that, the N-heterocycles and pyrazolones as ligands affect the environment of the complex in such a way that their lipophilicity increases which is a major factor in designing a drug.

21	22	23	24	25	26	27	28	29	30
Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
44.9559	47.867	50.9415	51.9961	54.938	55.845	58.9332	58.6934	63.546	65.4089
Scandium	Titanium	Vanadium	Chromium	Manganese	Iron	Cobalt	Nickel	Copper	Zinc
39	40	41	42	43	44	45	46	47	48
Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd
88.9058	91.224	92.9064	85.94	98	101.07	102.9055	106.42	107.8682	112.411
Yitrium	Zirconium	Niobium	Molybdenum	Technetium	Ruthenium	Rbodium	Palladium	Silver	Cadmium
71	72	73	74	75	76	77	78	79	80
Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg
174.967	178.49	180.9497	183.84	186.207	190.23	192.217	195.084	196.9666	200.59
Lutetium	Hafnium	Tantalum	Tungsten	Rhenium	Osmium	Iridium	Platinum	Gold	Mercury

Fig. Transition metal series.

Pharmalogical activity of transition metal

Bological Significance of Metal Complexes

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. 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. To defeat these limitations of cis-platin, less toxic and more effective metallodrugs have been developed like oxaliplatin and carboplatin.

DNA-metal Complex Interactions

DNA is the storage site of cellular information that is accessed continuously for storing and dispensing information required for existence. Thus, it acts as the main intracellular target for those who thrive to develop a new drug for innumerable diseases, especially cancer. Added to the fact, small molecules that can bind and react with specific DNA sites provide a means to access and manipulate this cellular information creating the desired results. There are many binding modes by which the small molecules bind to the DNA which are covalent and non-covalent binding. Cisplatin binds covalently with the DNA thereby restricting its replication. Among the non-covalent binding modes, intercalation, groove binding and external electrostatic binding, intercalation is the most important one because it invariably leads to cellular degradation. Humungous reports are available throughout the literature regarding the interactions of V(IV), Ni(II), Co(II), Cu(II) and Zn(II) complexes with DNA and still now many research groups have actively involved in this field . Among the research groups, most of them are concentrating only copper Schiff-base complexes. For, copper is found in all living organisms and is a vital trace element in redox chemistry, growth and development. It is significant for the function of several enzymes and proteins involved in energy metabolism, respiration and DNA synthesis, particularly cytochrome oxidase, superoxide dismutase (SOD), ascorbate oxidase and tyrosinase. Copper is found to bind DNA with high affinity than any other divalent cation, thus promoting DNA oxidation.

Acquaye et al. synthesized two new copper Schiff-base complexes and carried out DNA interactions with CT-DNA. The resultant Kb values are 1.52 × 105 M−1 and 5.00 × 105 M−1 respectively for the complexes]. Yang and his colleagues have synthesized and characterised two novel Schiff base copper(II) complexes derived from kaempferol and polyamines such as ethylenediamine and diethylenetriamine. They evaluated the DNA interactions with CT DNA and predicted the mode of interactions to be intercalation. An extensive DNA-metal complex interaction has been carried out by Lin and his colleagues by synthesizing two new benzimidazole based copper complexes. The studies showed that the complexes exhibited partial intercalation towards the DNA. The novel copper complexes synthesized by Gup and Gokce are found to bind significantly to calf thymus DNA by both groove binding and intercalation modes and effectively cleave pBR322 DNA. Xu et al. synthesized three novel structurally associated copper(II) complexes which displayed enhanced intercalation into CT DNA.

Pharmacological Actions

Chemotherapy using chemical agents is one of the effective methods for the treatment of various cancers. With the increasing number of compounds synthesized as potential anticancer drugs, effective screening methods are needed for classification of these compounds according to their anticancer activities. For preliminary screening, the *in vivo* methods are usually more accurate but rather expensive and time-consuming whereas the *in vitro* methods are simpler and more rapid but with lower accuracy. In general, for large scale preliminary screening, the *in vitro* methods are more effective for refined screening on a smaller scale, naturally, the *in vivo* methods with test animals must be used and the clinical experimental tests are also required. The key advances in the cancer chemotherapy.

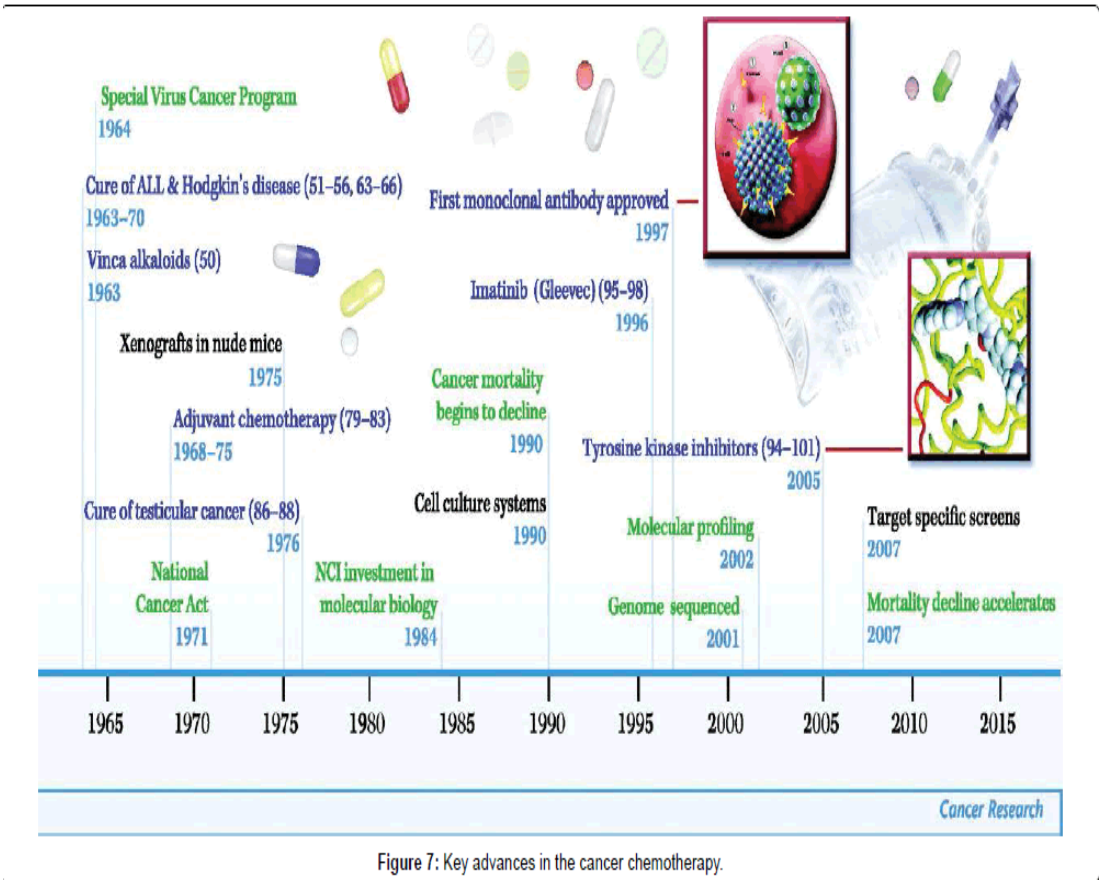

Figure 7: Key advances in the cancer chemotherapy.

Fig. Yearwise metal use in cancer chemotherapy.

Medicinal inorganic chemistry presents additional opportunities for the design of therapeutic agents, not accessible to organic compounds. The broad range of coordination numbers and geometries, available redox states, thermodynamic and kinetic characteristics and intrinsic properties of the cationic metal ion and ligand itself offer the medicinal chemist a large variety of reactivities to be exploited.

The increasing number of multi-drug resistant microbial pathogens hardened the treatment of infectious diseases that posed as an important and challenging problem. Despite the availability of a large number of antibiotics and chemotherapeutics, a substantial need for the development of new class of potent antimicrobial agents arose on account of the emergence of old and new antibiotic resistant bacterial strains. Thus, the heterocyclic compounds play a significant role in designing a new class of structural entities of medicinal importance with new mechanisms of action. The diverse pharmacological properties possessed by heterocyclic compounds are the well known antimalarial, antimicrobial, anti-inflammatory, anticancer, analgesic and anticonvulsant.

The search for novel antimicrobial and analgesic agents devoid of side effects continues to be an active area of research in medicinal chemistry. Although new and more expensive drugs have been developed, their cost is beyond the common man′s reach. Accordingly, the pressing need for new, more effective, cheaper and safe antimicrobial agents arose and has been emphasized.

Antioxidants are molecules capable of inhibiting the oxidation of other molecules and thereby preventing the cell death that occurs due to the release of free radicals. Free radicals such as DPPH•, NO• O_2 •-, OH•, hydrogen peroxide and lipid peroxide radicals have been implicated in a variety of diseases such as asthma, cancer, cardiovascular, diabetes, gastrointestinal inflammation, periodontal disease and other inflammatory processes . Hydroxyl is one of the key groups to enhance the antioxidant activity due to its easy conversion to phenoxy radical through hydrogen transfer mechanis].

The ***superoxide dismutases (SODs)*** known ***as metalloenzymes*** are able to keep the concentration of superoxide radicals in controllable low limits and thus, they can protect cells against an oxidative damage. Only recently, it has been found that reactive oxygen species, such as the superoxide radical or hydrogen peroxide, are important regulators of cell death. Particularly, H_2O_2 is implicated as a mediator of the apoptosis in cells. The cellular damage caused by H_2O_2 is due to the hydroxyl radical production that results from the reaction of H_2O_2 with transition metal ions.

Anti-microbial agents

A review by Turel focuses on the crisis of decrease in ***quinolone drug*** absorption when consumed simultaneously ***with magnesium or aluminium antacids***. He reviewed selected crystal structures of ***quinolone-metal compounds and their anti-microbial activities***. The reason for such behaviour is proposed to be the chelate bonding of the quinolone to the metal. The ***complex [Cu (cx)$_2$]. 2H$_2$O*** (where cx = cinoxacin) was screened for activity against several bacteria [minimal inhibitory concentration (MIC) values] showing the same antimicrobial activity as the free ligand].

Using a series of ***Gram positive and Gram negative bacterial strains, Scozzafava*** and his co-workers tested ***zinc and copper ciprofloxacin*** complexes which showed moderated antimicrobial effects. Very recently, Psomas research group synthesized few quinolone cobalt(II) complexes and tested their antimicrobial activity using oxolinic acid (Hoxo) in the absence or presence of the Lewis bases 2,2′-bipyridine (bipy), 2,2′-bipyridylamine (bipyam), 1,10-phenanthroline (phen), pyridine (py) or 4-benzylpyridine (4bzpy). Their antimicrobial activity showed that the activity was similar to the free Hoxo.

Kumar et al. synthesized copper(II) complexes with isoxazole Schiff bases, [Cu(L1)$_2$], [Cu(L2)$_2$] and [Cu(L3)$_2$] where, L1=[(1-((E)-(3,5-dimethylisoxazol-4-ylimino)methyl)naphthalen-2-ol,$C_{16}H_{14}N_2O_2$), L2= [2-((E)-(3,5-dimethylisoxazol-4-ylimino) methyl)-4-methoxyphenol, $C_{13}H_{14}N_2O_3$ and L3 = (2-((E)-(3,5-dimethylisoxazol-4- ylimino) methyl)-4-bromophenol, $C_{12}H_{11}BrN_2O_2$]. Their antimicrobial activities were screened and the results were favourable for Cu(II) complex of ligand L1 which possessed good anti-microbial activity against the other ligands and standard.

Devi et al. have synthesized a series of mixed ligand complexes of Co(II), Ni(II), Cu(II) and Zn(II) using various uninegative tridentate ligands derived from isatin monohydrazone with 2-hydroxynapthaldehyde /substituted salicylaldehyde and heterocyclic nitrogen base 8-hydroxyquinoline and characterized them by elemental analysis, conductometric studies, magnetic susceptibility and spectroscopic techniques (**Figure 9**). They tested *in vitro* antimicrobial activity against various pathogenic Gram positive bacteria, Gram negative bacteria and fungi using different concentrations (25, 50, 100, 200 µg/mL) of ligands and their complexes. The results indicate that complexes exhibited enhanced activity as compared to free ligands and copper(II) complex was found to be the most potent antimicrobial agent.

A new Co(II), Ni(II), Cu(II) and Zn(II) mixed ligand complexes (**Figure 10**) from N2, N3-bis(4-nitrophenyl) quinoxaline-2,3-diamine and 1,10-phenanthroline have been synthesized by Dhanaraj et al. The compounds have been characterized by elemental analyses, magnetic susceptibility, molar conductance, UV–Vis., IR, ^{1}H NMR, mass and ESR spectra. The complexes were screened for antimicrobial activity against various bacterial and fungal species viz., *E. coli, K. pneumoniae, P. aeruginosa, S. aureus, A. niger and C. albicans* by disc diffusion method. The Cu (II) complex exhibited the highest zone of inhibition against.

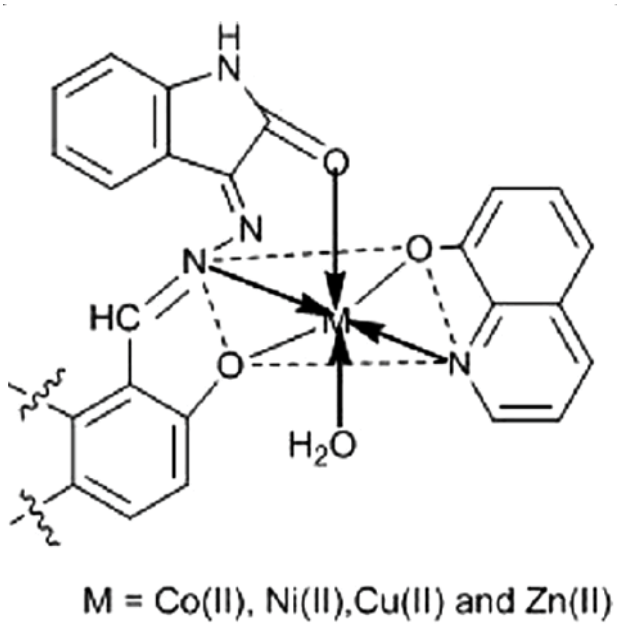

Figure 9: Structure of potent antimicrobial agents.

The bacterial species *K. pneumoniae* (12 mm) and *P. aeruginosa* (11 mm). The Ni(II) mixed ligand complex exhibited a higher zone of inhibition against E. coli (12 mm) and Zn(II) complex exhibited a higher zone of inhibition against *S. aureus* (12 mm). From the above, it was concluded that among the four mixed ligand metal complexes, Cu(II) mixed ligand metal complex showed higher antibacterial activity. In the case of antifungal activity, Co(II) complex showed the higher zone of inhibition against the fungal species *C. albicans* (13 mm) and Ni(II) complex showed higher activity against *A. niger* (8 mm). Overall, the antimicrobial activity of the complexes is in the following order: Cu (II)>Co(II)>Ni(II)>Zn(II). The superior activity of the metal complexes may possibly be as a result of increased lipophilic nature of the complexes attributed to chelation and heteroatoms present in against the fungal species *C. albicans* (13 mm) and Ni(II) complex showed higher activity against *A. niger* (8 mm). Overall, the ***antimicrobial activity of the complexes is in the following order: Cu (II)>Co(II)>Ni(II)>Zn(II).*** The superior activity of the metal complexes may possibly be as a result of increased lipophilic nature of the complexes attributed to chelation and heteroatoms present in ligand moiety.Anti-microbial assay Biological activity of the ligand and a series of its metal complexes [Cu(II), Ni(II), Co(II) and Mn(II)] were screened for antibacterial activity against S.sureus as gram positive bacteria and E.coli as Gram-negative and the fungi A. fumigatus by Jayaseelan, et al, (2010) using broth micro dilution procedures. From Table1, the Gram positive bacteria on

all metal complexes were found to inhibit all tested bacteria at different rates and the activity as following order Co > Ni >Cu > Mn. In Gram negative bacteria also follows the same order and all complexes havehigher bacterial activity than ligand. In fungal activity, the ligand showed activity against Aspergillus fumigatus and metal complexes show activity in the following order Cu > Co > Ni >Mn. It is known that chelation tends to make the ligand to act as more powerful and potent bacterial agent. A possible explanation.

Anti-tumor agents

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], tetracycline derivatives, terpyridine], or imidazolidine-2-thione]), 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 . Sadler and his co-workers have observed [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 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.

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 . Sigman et al. reported 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]. So, the copper(II) complexes possessing high nucleobase affinity and biologically accessible redox potentials are considered as potential reagents for cleavage of DNA both oxidative and hydrolytically . 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. [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 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 [182] 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.

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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) or human cancer cell lines Recently, Pascu and his co-workers document that acenaphthenequinone based zinc bis(thiosemicarbazone) complexes (**Figure 11**) exhibit comparable cytotoxicity to cisplatin in the MCF-7 cell line and emit fluorescence as well.

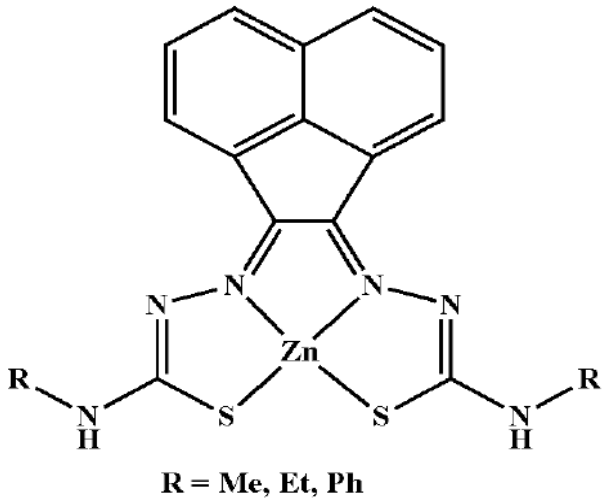

Figure 11: Structure of acenaphthenequinone based zinc bis(thiosemicarbazone) complexes.

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 with vanadocene dichloride being one of the most promising among metallocenes]. These results encourage further preclinical studies and have since been extended with the study of the cytotoxic properties of vanadocene (**Figure 12**) and various derivatives.

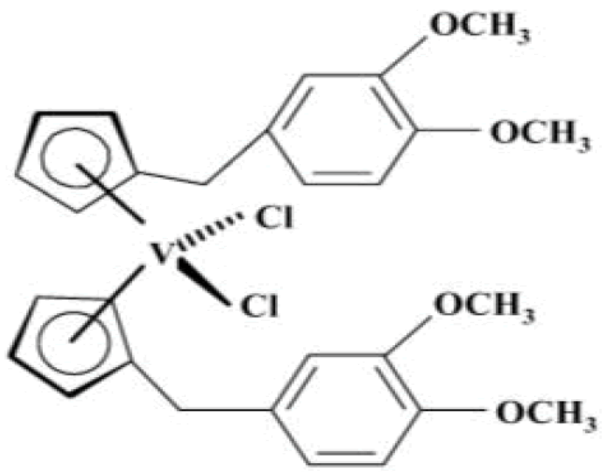

Figure 12: Structure of bis(η5-(3,4-dimethoxybenzyl)cyclopentadienyl)-vanadium(IV)

A new Co(II), Ni(II), Cu(II) and Zn(II) mixed ligand complexes (**Figure 10**) from N2, N3-bis(4-nitrophenyl) quinoxaline-2,3-diamine and 1,10-phenanthroline have been synthesized by Dhanaraj et al. The compounds have been characterized by elemental analyses, magnetic susceptibility, molar conductance, UV–Vis., IR, ^{1}H NMR, mass and ESR spectra [160]. The complexes were screened for antimicrobial activity against various bacterial and fungal species viz., *E. coli, K. pneumoniae, P. aeruginosa, S. aureus, A. niger and C. albicans* by disc diffusion method. The Cu(II) complex exhibited the highest zone of inhibition against the bacterial species *K. pneumoniae* (12 mm) and *P. aeruginosa* (11 mm). The Ni(II) mixed ligand complex exhibited a higher zone of inhibition against E. coli (12 mm) and Zn(II) complex exhibited a higher zone of inhibition against *S. aureus* (12 mm). From the above, it was concluded that among the four mixed ligand metal complexes, Cu(II) mixed ligand metal complex showed higher antibacterial activity. In the case of antifungal activity, Co(II) complex showed the higher zone of inhibition against the fungal species *C. albicans* (13 mm) and Ni(II) complex showed higher activity against *A. niger* (8 mm). Overall, the ***antimicrobial activity of the complexes*** is in the following order: ***Cu (II)>Co(II)>Ni(II)>Zn(II)***. The superior activity of the metal complexes may possibly be as a result of increased lipophilic nature of the complexes attributed to chelation and heteroatoms present in the ligand moiety [161].

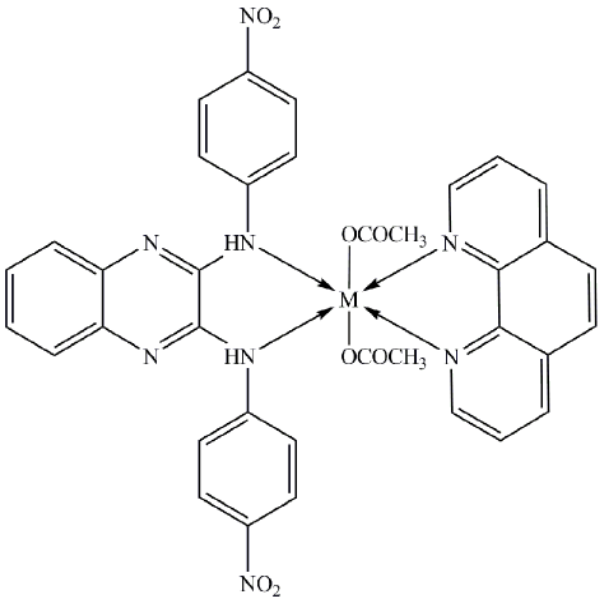

Figure 10: Structure of N2, N3-bis(4-nitrophenyl)quinoxaline-2,3-diamine based mixed ligand complexes.

Structure of N2, N3-bis(4-nitrophenyl)quinoxaline-2,3-diamine based mixed ligand comple Sinha group have synthesized a monoanionic tetradentate- N_2O_2 Schiff base 2-[{[2-(dimethylamino) ethyl] imino} methyl]-6-methoxyphenol 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 [182] 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.

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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) or human cancer cell lines]. Recently, Pascu and his co-workers document that acenaphthenequinone based zinc bis(thiosemicarbazone) complexes (**Figure 11**) exhibit comparable cytotoxicity to cisplatin in the MCF-7cell.

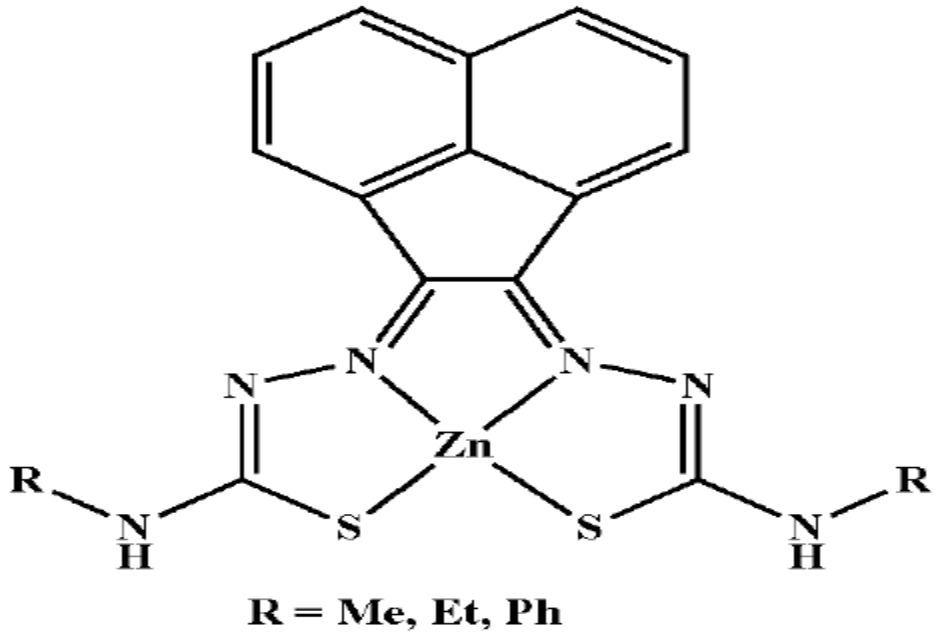


Figure 11: Structure of acenaphthenequinone based zinc bis(thiosemicarbazone) complexes.

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 with vanadocene dichloride being one of the most promising among metallocenes. These results encourage further preclinical studies and have since been extended with the study of the cytotoxic properties of vanadocene (**Figure 12**) and various derivatives.

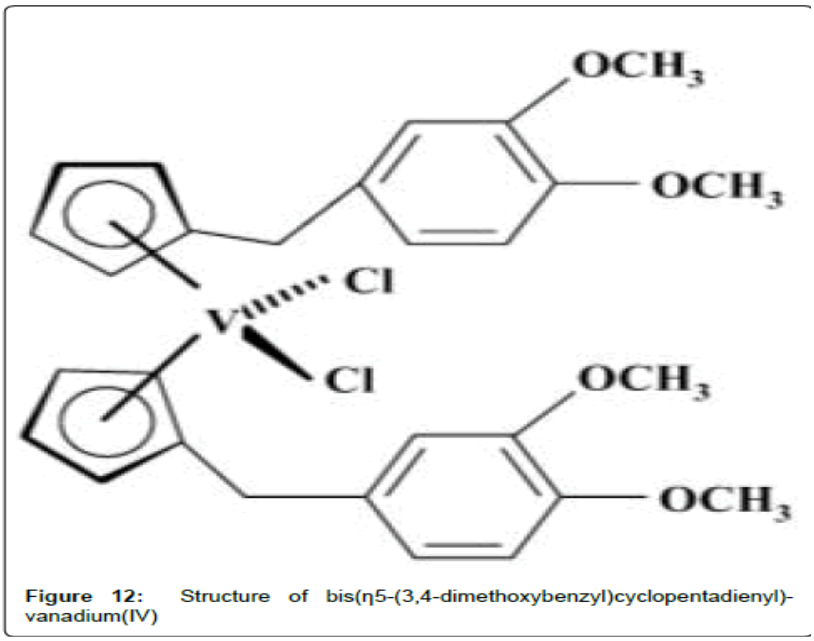


Figure 12: Structure of bis(η5-(3,4-dimethoxybenzyl)cyclopentadienyl)-vanadium(IV)

Figure 12: Structure of bis(η5-(3,4-dimethoxybenzyl)cyclopentadienyl)- vanadium(IV).

Manikandan et al. [196] have newly synthesized Co(II) complexes of 2-acetylpyridine N-substituted thiosemicarbazone with $(PPh_3)_2$ (Figure 13). 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).

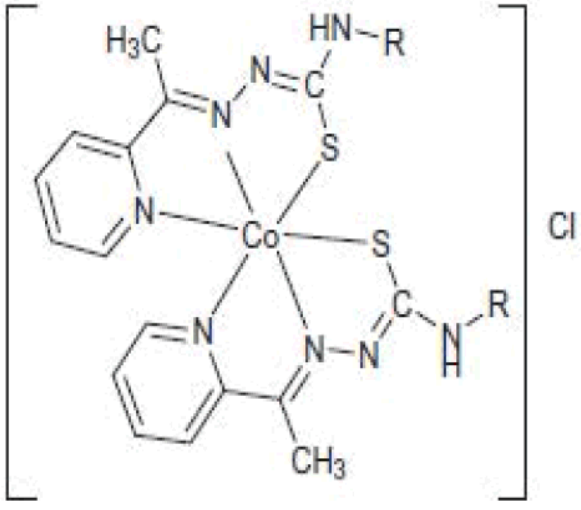


Figure 13: Structure of Co(III) complex of 2-acetylpyridine N-substituted thiosemicarbazone.

Figure 13: Structure of Co (III) complex of 2-acetylpyridine N-substituted thiosemicarbazone.

Anti-inflammatory agents

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 14**) 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. 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)].

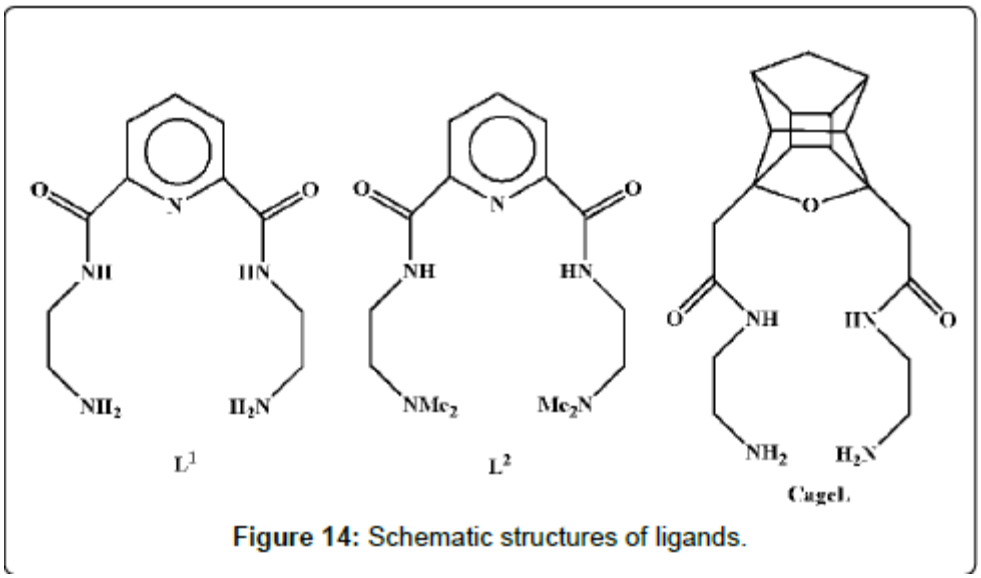


Figure 14: Schematic structures of ligands.

Figure 14: Schematic structures of ligands.

Pyridine derivatives are of high interest in several areas of medicinal chemistry, specifically, ***aminopyridinylmethanols and aminopyridinamines*** have been considered as an analgesic as well as anti-inflammatory agents and for treating ***Alzheimer's disease***. The pyridine ring characterizes ***niflumic acid and flunixin***, two standard NSAIDs belonging to the class of ***fenamates*** (**Scheme 15**). 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 is a substituted derivative of nicotinic acid (3-pyridinecarboxylic acid) which is structurally unique when compared to other NSAIDs (**Figure 15**).

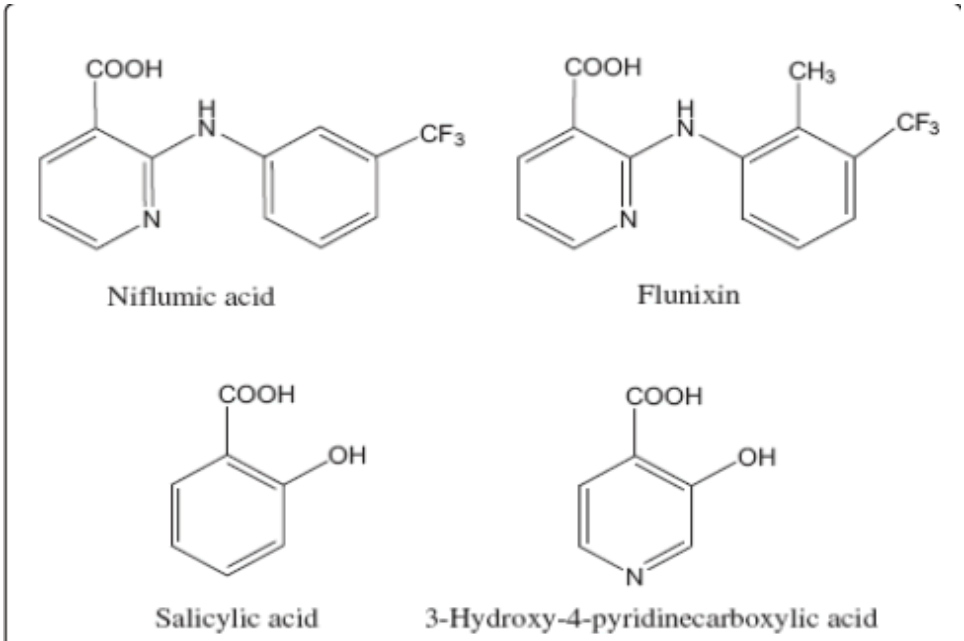


Figure 15: Structures of few known anti-inflammatory drugs and of 3-hydroxy-4-pyridinecarboxylic acid.

Hoonur group has studied about the ***1, 2-dihydroquinazolin- 4(3H)-ones*** based metal complexes along with their structure and biological activity 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.

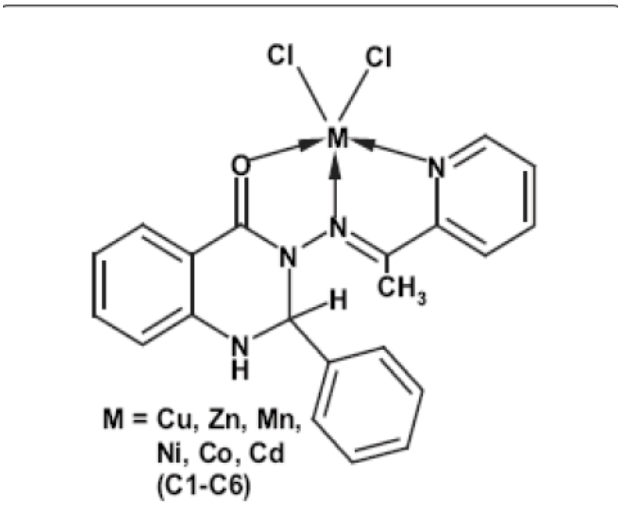


Figure 16: Structure of metal complexes of 1,2-dihydroquinazolin-4(3H)-ones.

Figure 16: 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 [210]. The role of copper in the pathology of inflammation emphasizes a lot of evidence [211]. 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 [211].

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 17**) for their anti-inflammatory activity [212]. 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.

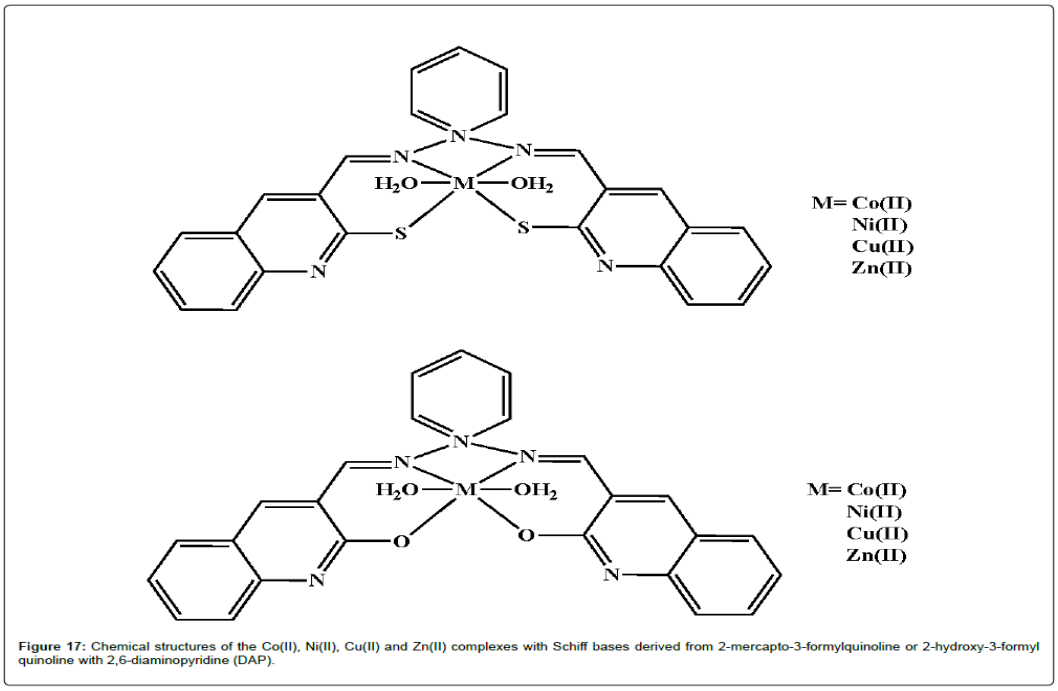


Figure 17: Chemical structures of the Co(II), Ni(II), Cu(II) and Zn(II) complexes with Schiff bases derived from 2-mercapto-3-formylquinoline or 2-hydroxy-3-formyl quinoline with 2,6-diaminopyridine (DAP).

Figure 17: 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 18**) . When enoxacin 36 is subjected to infrared spectroscopic analysis, 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 antiinflammatory properties of the enoxacin complexes. The IC_{50} values of 15.3 and 18.7 $\mu g.mL^{-1}$ 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 $\mu g.mL^{-1}$). Nevertheless, the immunomodulatory effect of the enoxacin complexes that is governed by the molecular mechanism is not determined.

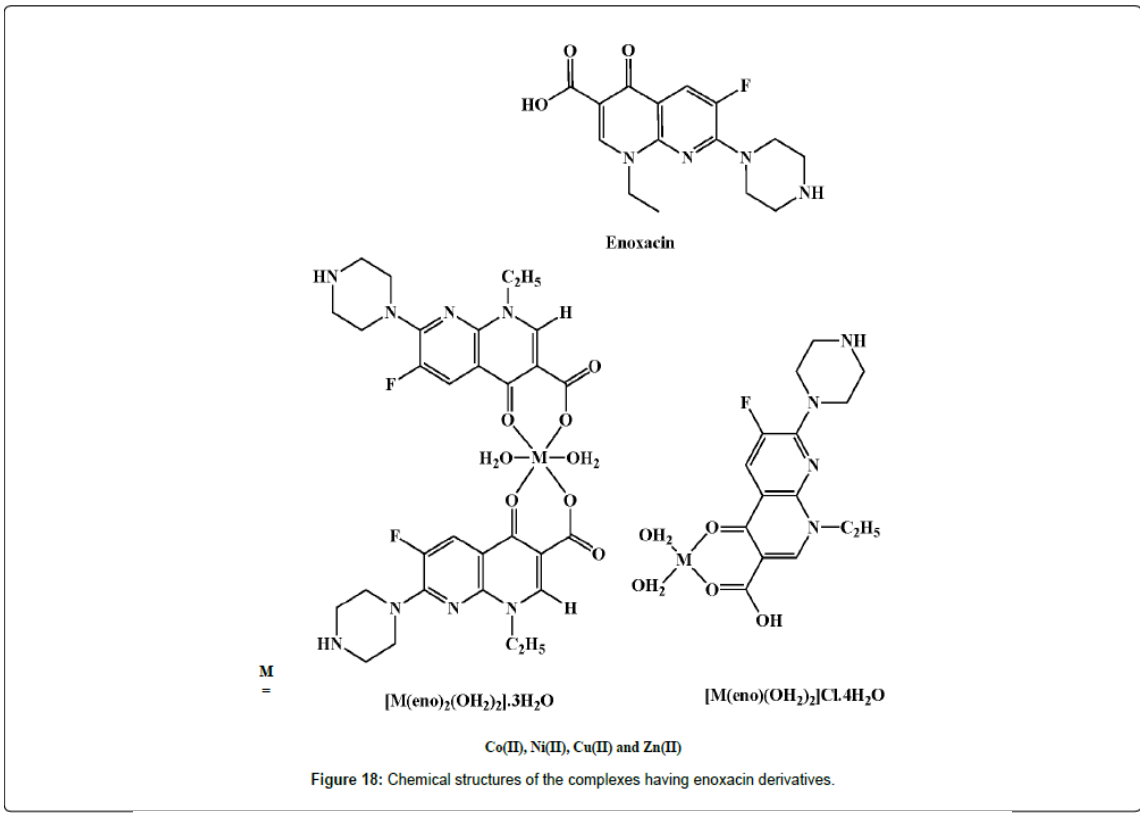


Figure 18: Chemical structures of the complexes having enoxacin derivatives.

A series of potential anti-inflammatory agents that are Co(II) complexes and bearing the NSAID mefenamic acid ligand have also been investigated (**Figure 19**) . 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^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.

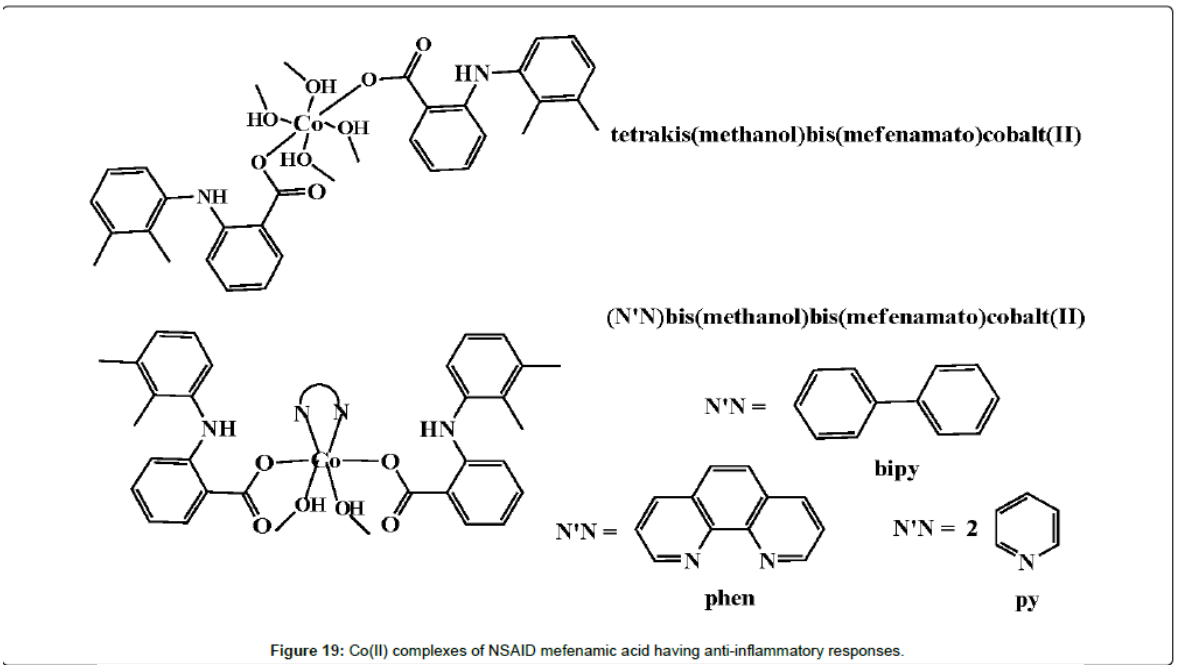
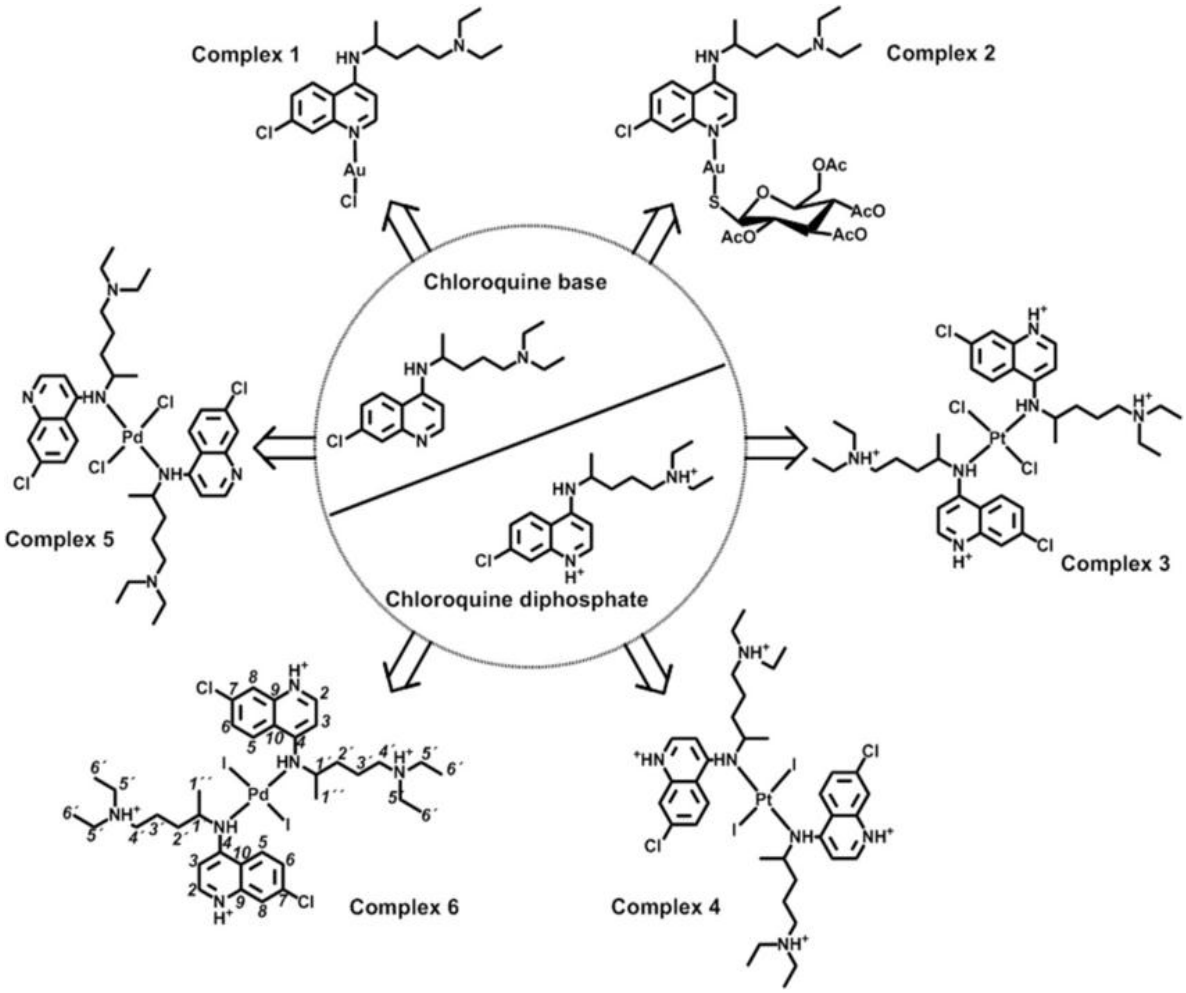


Figure 19: Co(II) complexes of NSAID mefenamic acid having anti-inflammatory resp.

Antiparasitic Agents

Metal complexes ***of gold (Au), platinum (Pt), iridium (Ir), palladium (Pd), rhodium (Rh) and Osmium (Os)*** have been reported to have activity against a variety of ***trypanosomatids.*** The enzymes, cysteine proteases have been found to play an important role in parasitic life cycles including Schistosoma***, Plasmodium, T. brucei, T. cruzi and Leishmania in nutrition, host invasion***, protein processing and evasion of the host immune response (. Arsenic and bismuth have been reported to be effective against trypanosomiasis and leishmaniasis, respectively. Salversane and neosalversane are well known for their antisyphilitic activity. The existing antimalarial drugs are now becoming less effective against Plasmodium. The emergence of resistance to chloroquine (an antimalarial drug) is one of reasons for an urgent need for new effective antiparasitic agents. In the search of better therapeutic results, gold and ruthenium complexes of chloroquine and clotrimazole have also been prepared and evaluated against Plasmodium . ***Chloroquine*** complex of transition metal ruthenium has been found to be 2-5 times more active ***than.***



Action of different chloroqiune based drug

In in-vitro test ***against chloroqiune–resistant strain of P. falciparum*** without any sign of acute toxicity. The incorporation of the metal produced an enhancement of the efficacy of chloroquine (101). Some of these complexes have shown improved therapeutic results even in chloroquine resistant cases. Another example where metal complexes have shown promising results include antimony compounds are used to treat leishmaniasis.

Anticancer drug: action and their mechanism (cisplatin)

Many metal-containing compounds have been utilized throughout history to treat a wide variety of disorders. In medicinal chemistry —traditionally dominated by organic chemistry— metal complexes have gained favor as diagnostic tools and anticancer agents. Cancer is the second most frequent cause of death in the world. The discovery of ***antitumor activity of cisplatin*** began a search for other metal complexes with ***cytotoxic properties*** against cancer cells. Organo-metallic compounds have been used in medicine for centuries. Metal complexes play essential role in pharmaceutical industry and in agriculture. The metallo-elements present

in trace quantities play vital roles at the molecular level in living system. The transition metal ions are responsible for proper functioning of different enzymes. Transition metals represent the D block element which includes groups 3 - 12 on the periodic table. Their d shells are in process of filling. The partially filled d orbital in transition metals impart interesting electronic properties that can act as suitable probes in the design of anticancer agents. This property of transition metals resulted in the foundation of coordination complexes. In ***1960*** the anti-tumor activity of an inorganic complex ***cis-diammine-dichloroplatinum (II)*** (cisplatin) was discovered. Cisplatin has developed into one of the most frequently used and most effective drug for treatment of ***solid carcinomas***. This review focuses ***on recent advances in development of platinum, gold, copper and ruthenium complexes as anticancer agents.***

Metal-containing compounds offer many advantages over conventional carbon-based compounds in the development of new medicinal compounds. These advantages are due to their ability to coordinate ligands in a three dimensional configuration, thus allowing functionalization of groups that can be tailored to defined molecular targets. The partially filled d orbitals in transition metals impart interesting electronic properties that can act as suitable probes in the design of anticancer agents. The oxidation state of a metal is also an important consideration in the design of coordination compounds, given that it allows the participation in biological redox chemistry and plays an influential role in optimal dose and bioavailability of the agent administered. Furthermore, the ability to undergo ligand exchanged reactions offers a myriad of opportunities for metals to interact and coordinate to biological molecules, as demonstrated by the widely used drug cisplatin Furthermore, when designing metal-based therapeutics, one is not restricted solely by metals selected by nature and can take advantage of the unique properties of nonessential metals, including other 1st and 2nd row transition metals and metals that can impart additional utility not found naturally.[6] This review focuses on recent advances in developing platinum, ruthenium, copper and gold anticancer agents.

Anticancer Platinum Complex

Platinum (II) complexes has been used as anti cancer drugs since long, among them cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers.[1] This prototypical anticancer drug remains one of the most effective chemotherapeutic agents in clinical use. Cisplatin, (cis-[PtCl2 (NH3)2], also known as cis-DDP), (Fig. 1) is perhaps the best known example of a small molecule metalcontaining drug.[2] Cisplatin enters cells by passive diffusion and also, as recently discovered, by active transport mediated by the copper transporter Ctr1p in yeast and mammals. The cytotoxicity of cisplatin originates from its binding to DNA and the formation of covalent cross-links. Binding of cisplatin to DNA causes significant distortion of helical structure and results in inhibition of DNA replication and transcription. Inside the cell it interacts with a number of other negatively charged biomolecules besides DNA such as proteins, ***sulphur-containing compounds like metallothioneins and glutathione*** that sequester heavy metals like Pt and remove it from the cell.[7] DNA damage and subsequent induction of apoptosis may be the primary cytotoxic mechanism of cisplatin and other DNAbinding antitumor drugs.[8] Cisplatin is used for the treatment of ***testicular cancer, epithelial ovarian cancer, gestational trophoblastic tumors, and small cell lung cancer as well as for cervical, nasopharyngeal, esophageal, and head and neck cancer***s. Despite this success, the clinical use of cisplatin against this and other malignancies is severely limited by doselimiting side-effects such as neuro-, hepatiand nephrotoxicity. In addition to the high systemic toxicity, inherent or acquired resistance is a second problem often associated with platinum-based drugs, which further limits their clinical use.[4] In an effort to address these shortcomings, 2nd and 3rd generation platinum analogs, namely carboplatin and oxaliplatin (Fig. 1), have been designed and clinically.

In designing a new platinum anticancer agent, several structural features can be strategically modified. As shown in Figure 1, three different ligand types generally comprise a platinum anticancer complex. The ligands L are typically nitrogen donors. They are referred to as "non-leaving group" ligands because they form thermodynamically stable bonds with platinum and are retained in the final ***platinum-DNA adduct***. Modifications of these ligands directly affect the nature of the resulting platinum-DNA adducts and therefore the manner by which cellular repair pathways.

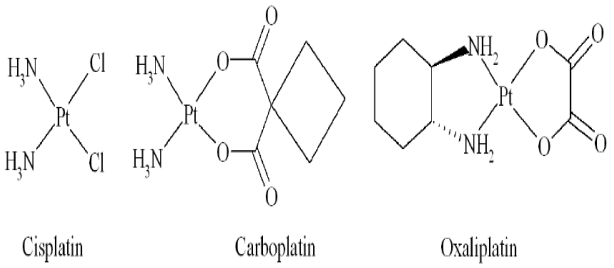


Fig. 1: Chemical structure of cisplatin, carboplatin and oxaliplatin, as drugs in clinical use for treatment of tumour diseases.

Respond to those adducts. Complexes that contain amine ligands different from the ammines in cisplatin usually exhibit a different spectrum of activity in cancer cell lines and are usually not cross-resistant with cisplatin.***Oxaliplatin,*** with its chelating and ***chiral 1,2-diaminocyclohexane ligand, trans-1R,2R-DACH (DACH),*** falls into this category. Modifications of the leaving group ligands X, so named because they are lost upon DNA-binding, can alter the overall reaction stoichiometry and aquation kinetics for a platinum anticancer complex. Complexes that react quickly, such as those with labile nitrate ligands, are generally more

toxic because of indiscriminate binding to off-target biological nucleophiles. Carboplatin, on the other hand, contains a relatively stable chelating ***CBDCA (CBDCA = 1,1-cyclobutane–dicarboxylato)*** ligand as its leaving group. By comparison to cisplatin, carboplatin can be administered at higher doses because of its lower toxicity profile. Although less toxic, carboplatin has a similar spectrum of activity and exhibits cross-resistance to cisplatin, which is a result of the same non-leaving group ammine ligands. The axial ligands R comprise the third category. Axial ligands are present only in higher-valent platinum complexes, such as those of platinum (III) and platinum(IV). These ligands can ultimately dissociate after biological reduction of the platinum complex, although there is no guarantee that reduction will lead to their specific departure from the coordination sphere. They provide convenient points for installation of tumor-targeting moieties or attachment to ***nanoparticles***. Any of the three ligand types can be modified in order to alter the ***lipophilicity*** and water solubility of the resulting platinum complex. Both of these properties are important in the design of an effective drug. The stereochemistry and the number of each respective ligand type can be altered as well.

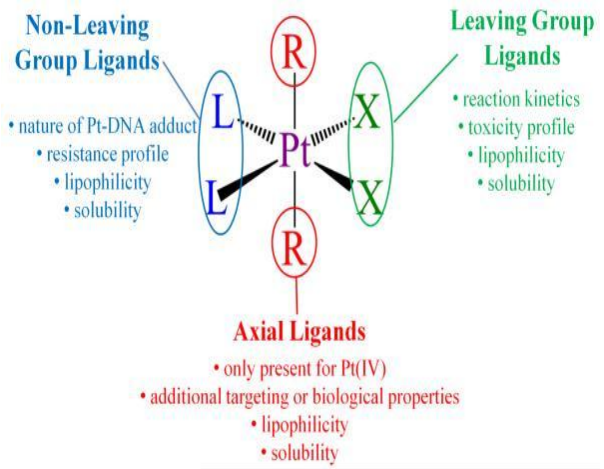


Figure 1: Different components of platinum anticancer agents. Additional factors that can be varied are the stereochemistry and the respective number of non-leaving and leaving group ligands.

In this review, we present an overview of known synthetic strategies for the synthesis of platinum anticancer complexes. Previous review articles have focused on the mechanistic details of platinum-based drugs at the cellular level, the chemistry of platinum under biological conditions, and new trends for the rational design of platinum anticancer agents. The present article provides synthetic inorganic chemists with practical advice on the synthesis and purification of potential platinum anticancer agents. The coordination chemistry principles employed for the preparation of such compounds are emphasized and are therefore useful to a broader readership. There are two major sections, which describe the synthesis of ***platinum (II) and platinum (IV) complexes***. These sections are further divided based on the nature and ***stereochemistry of the target complexes***. In each section, a short overview is provided of the anticancer properties of the target complexes. Multinuclear platinum complexes, some of which are excellent drug candidates, have been omitted from this review to maintain the focus on single-site reactivity. The reaction schemes do not display fully balanced chemical reactions, but instead illustrate only the major platinum-containing products. This choice stems from the complexity of many seemingly simple reactions of platinum compounds, the chemistry of which can be deceptively complicated. Two generic ligand types, L and X, are utilized (Figure 1), with ligands symbolized by "L" representing either an amine or *N*-heterocyclic unit. When "(L_2)" is used, the ligand is bidentate. Ligands designated with an "X" are monoanionic, like halides or carboxylates.

2. Synthesis of Platinum (II) Complexes

All clinically used platinum drugs (Chart 1) contain the element in the +2 oxidation state having almost exclusively square-planar coordination geometries. The major reaction pathways involved in the synthesis of platinum (II) and other ***square-planar d^8 complexes*** involve associative ligand substitution. These reactions proceed through five-coordinate ***trigonal-bipyramidal intermediates***. The stereochemistry of the resulting products is dictated by the relative trans effect of the ligands within the complex. Synthetic strategies discussed in the following sections therefore rely heavily on ***the trans effect principle***. For more detailed summaries of substitution reactions of platinum (II) and other d^8 complexes, as well as the trans effect, the reader is referred elsewhere. An early review on the synthesis of monodentate amine complexes of platinum (II) is also available.

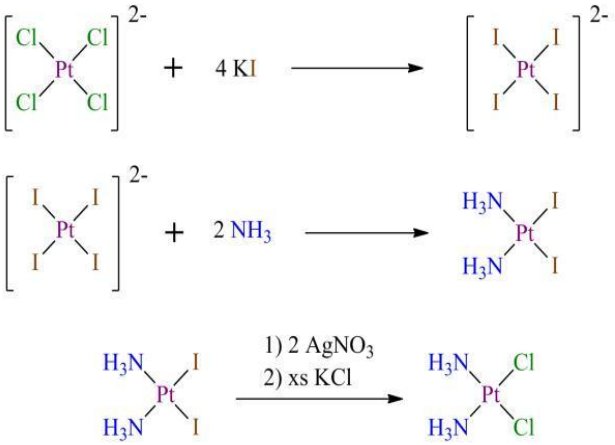
2.1. Synthesis of *cis*- and *trans*-$[PtL_2X_2]$ Complexes

cis- and *trans*-Diamminedichloro–platinum(II), are stereoisomers, representative members of the class of complexes having the general formula $[PtL_2X_2]$, where L is an am(m)ine or *N*-heterocycle and X is a halide or other labile ligand. Both cisplatin and its trans isomer were first prepared over 100 years ago by Peyrone and Reiset, respectively, and were commonly known as Peyrone's chloride and Reiset's second chloride. Cisplatin and the trans isomer, both yellow solids, were recognized to be isomers of Magnus' green salt, $[Pt(NH_3)_4][PtCl_4]$. Structural differences between these three compounds helped validate Werner's theory of coordination chemistry.

Following Peyrone's initial preparation of cisplatin, several different synthetic routes have been described. The common starting material for these procedures is ***$K_2[PtCl_4]$, a water-soluble salt***, which can be prepared directly from platinum metal in two steps. As with Peyrone's initial synthesis, several protocols for the synthesis of cisplatin involve the direct action of aqueous ammonia on the ***tetrachloroplatinate ion.*** This reaction

inevitably results in the formation of Magnus' green salt and the trans isomer as undesired byproducts, both of which must be removed by additional purification steps. Recently, the use of microwave irradiation for the synthesis of cisplatin directly from K_2PtCl_4 and NH_4OAc was reported. The adaptation of this method with flow chemistry techniques enables cisplatin to be synthesized on the gram scale in one step with no contaminating impurities from Magnus' green salt or the trans isomer.

The most widely used method for preparing cisplatin is that reported by Dhara in 1970. For this multistep reaction (Scheme 1), aqueous $[PtCl_4]^{2-}$ is first converted to $[PtI_4]^{2-}$ upon treatment with 4 equiv of KI. The addition of ammonium hydroxide to the dark brown solution of $[PtI_4]^{2-}$ yields the yellow precipitate, *cis*-$[Pt(NH_3)_2I_2]$. Removal of the iodide ligands from this complex with 2 equiv of $AgNO_3$ in water gives the diaqua cation, *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$, from which isomerically pure cisplatin can be isolated as a yellow solid following treatment with excess chloride ion. The absence of the trans isomer is attributed to the much higher trans effect of the iodide compared to that of the chloride ligand. The key intermediate in the formation of cisplatin from the tetrahaloplatinate anions is the monosubstituted complex, $[Pt(NH_3)X_3]^-$. When X is I, the large trans effect ensures that the next NH_3 ligand departs from a position trans to an iodide to give the desired cis isomer. When X is Cl, the lower trans effect of the latter renders substitution trans to NH_3kinetically competitive with substitution trans to the halide, thus yielding a small proportion of the trans isomer. Dhara's method has been adapted to prepare cis complexes with other amine or *N*-heterocyclic ligands, cisplatin *with* ^{15}N*-labeled ammines, and radiolabeled* ^{195m}Pt-cisplatin. When chelating diamines are used, this method is preferred as well. In cases where the desired amine or *N*-heterocyclic ligands are not water-soluble, an alternative synthetic route is employed, involving the addition of 2 equiv of the amine ligand to K_2PtCl_4 *i*n a solvent mixture of water and an alcohol at elevated temperatures. The use of DMF instead of ethanol or methanol as a cosolvent for this reaction has also been reported.

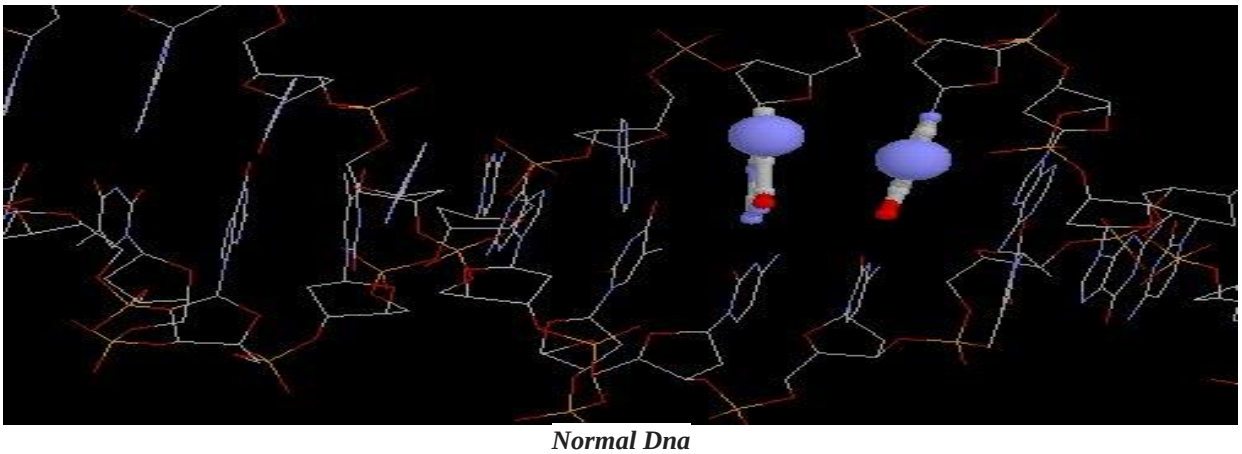


Scheme 1; ***Synthesis of cisplatin using the method of Dhara.[60] All reactions steps are carried out in aqueous solution.***

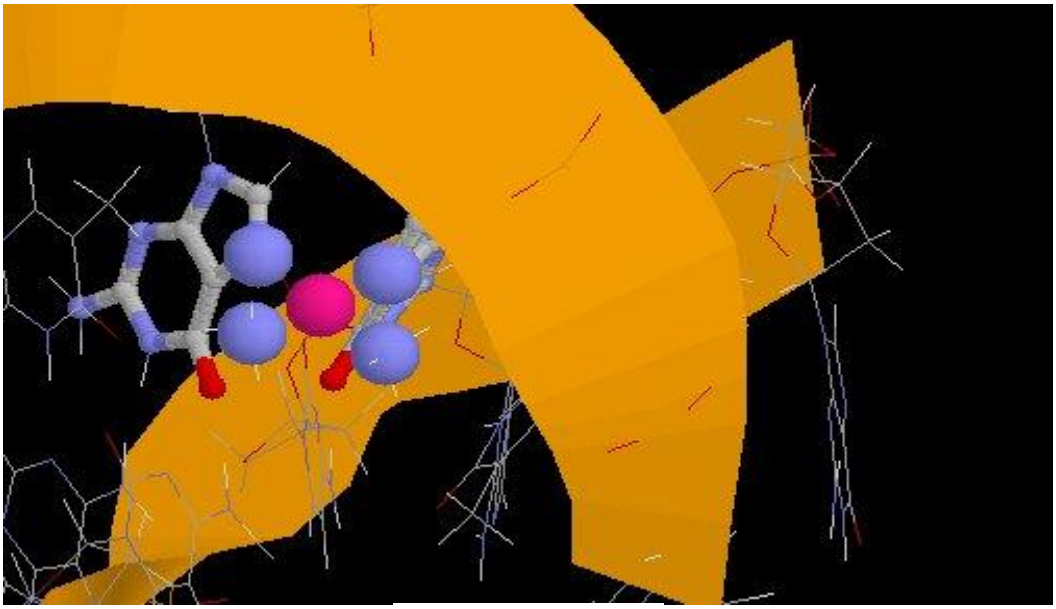
Mechanism of Action

Cisplatin is believed to kill cancer cells by binding to DNA and interfering with its repair mechanism, eventually leading to cell death. The first step in the process (after the cisplatin molecule penetrates the cell membrane intact) is for a molecule of water to replace one of the chloride ions. The resulting structure can then bind to a single nitrogen on a ***DNA nucleotide***. Then, the ***second chloride is replaced by another H_2O*** and the platinum binds to a ***second nucleotide***. Binding studies of cisplatin with DNA have indicated a preference for nitrogen 7 on two adjacent guanines on the same strand. It also binds to adenine and across strands to a lesser extent. The cisplatin-DNA complex attracts the attention of ***HMG (high mobility group)-1*** and other DNA repair proteins which become irreversibly bound. The resulting distortion to the shape of the DNA prevents effective repair. (The trans isomer of cisplatin is unable to form 1,2 intrastrand links and lacks antineoplastic activity.).

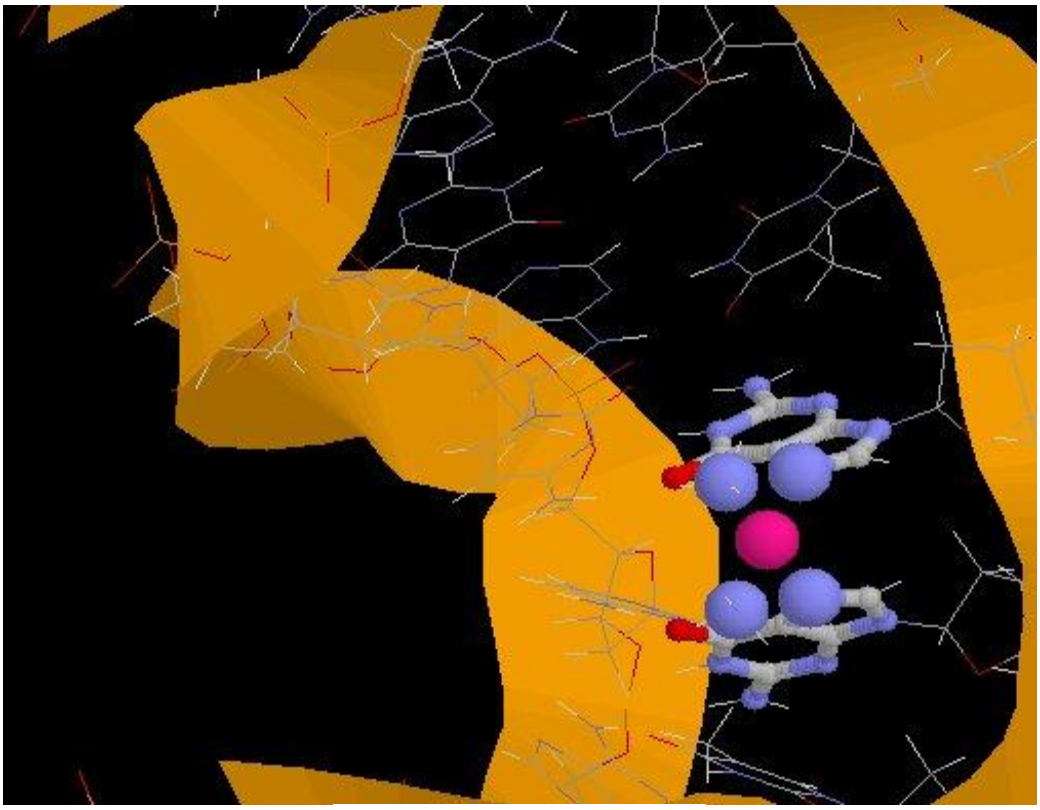
Other antineoplastic agents, such as ***etoposide,*** contribute to ***the platinum-DNA-protein complex*** and thus synergistically reinforce the activity of cisplatin. s**ome interactive structures of cisplatin and DNA are available:**



Normal Dna



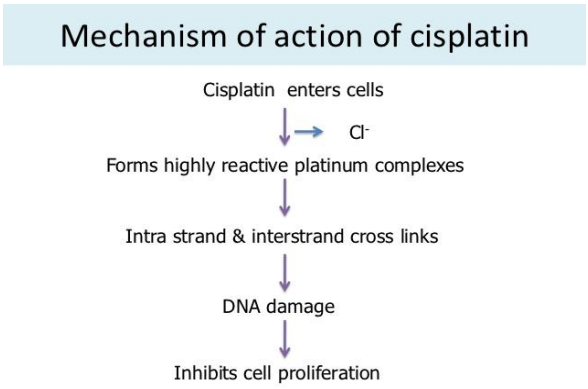
Cisplatin Bound To Dna



Cisplatin Bound To Dna Segment

- ***Diamminedichloroplatinum(I***I)) and its derivatives mostly act on adjacent guanines at their N^7 positions. The planar compound links to nucleobases through water displacement of one or both of its chloride groups, allowing cisplatin to form ***monoadducts to DNA or RNA, intrastrand DNA crosslinks, interstrand DNA crosslinks, and DNA-protein crosslink***s.[1] When cisplatin generates DNA crosslinks, it more frequently forms 1,2-intrastrand crosslinks (5'-GG), but also forms 1,3-intrastrand crosslinks (5-GNG) at lower percentages.[When cisplatin forms interstrand crosslinks (5'-GC), there is a severe distortion to the DNA helix due to a shortened distance between guanines on opposite strands and a cytosine that is flipped out of the helix as a consequence of the GG interaction.[Similar to nitrogen mustards, cisplatin is used frequently in chemotherapy treatment - especially for testicular and ovarian cancers.
- Chloro ethyl nitroso urea (CENU), specifically carmustine (BCNU), are crosslinking agents that are widely used in chemotherapy, particularly for brain

tumors. These agents differ from other crosslinkers as they alkylate O^6 of guanine to form an O^6-ethanoguanine. This intermediate compound then leads to an interstrand crosslink between a GC basepair. These crosslinking agents only result in small distortions to the DNA helix due to the molecules' smaller size.



Spectroscopic Characterization Of Some Medicine

Significant progresses have been made in the inorganic and organic chemistry up to the present concerning the synthesis, characterization, and application of the metal complexes of pharmaceutical substances. From the wide range of fields in which these coordination compounds find their application, many efforts were focused on the study of their importance in the biological processes. The coordination complexes of many pharmaceutical substances having different pharmacological effects e.g**.,** ***pyrazinamide (PZA), nicotinamide (NAM), nicotinic acid (NIC), theophylline (TEO), captopril (CPL), tolbutamide (TBA), clonidine (CLN), guanfacine (GUAF),*** etc. with transition metals were synthesized and used in order to improve their pharmacological and pharmacotechnical properties and also for the drug analysis and control. Several techniques such as ***Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy, surface-enhanced Raman spectroscopy (SERS), X-ray spectroscopy, mass spectrometry, ultraviolet-visible (UV-Vis) spectrophotometry, electron paramagnetic resonance (EPR) spectroscopy, X-ray diffraction, elemental analysis, electrochemical methods, thermal methods, and scanning electron microscopy*** were used for the physicochemical characterization of the complex composition. A significant interest in the development of metal complex-based drugs with unique research and therapeutic and diagnostic opportunities is currently observed in the medicinal inorganic chemistry area.

2.1. Metal complexes of pyrazinamide

Pyrazinamide (PZA) (pyrazine carboxamide) is a nicotinamide analogue used as a first-line drug to treat tuberculosis. The complexes of ***PZA with Cu(II)*** were assessed by different techniques such as elemental analysis, spectral methods [Fourier transform infrared spectroscopy (FTIR), FT-Raman spectrometry, mass spectrometry], and scanning electron microscopy (SEM) coupled with X-ray spectroscopy [energy-dispersive spectroscopy (EDS)]].

The elemental analysis indicated that the combination ratio of metal:ligand (Me:L) is 1:2 for ***[Cu(PZA)$_2$]Cl$_2$ and [Cu(PZA)$_2$](C$_6$H$_5$COO)$_2$ complexes. The mass spectra of the complex of PZA with Co(II)*** benzoate revealed the identity and the purity of PZA and of the complex fragments confirming its structure (Figure 1).

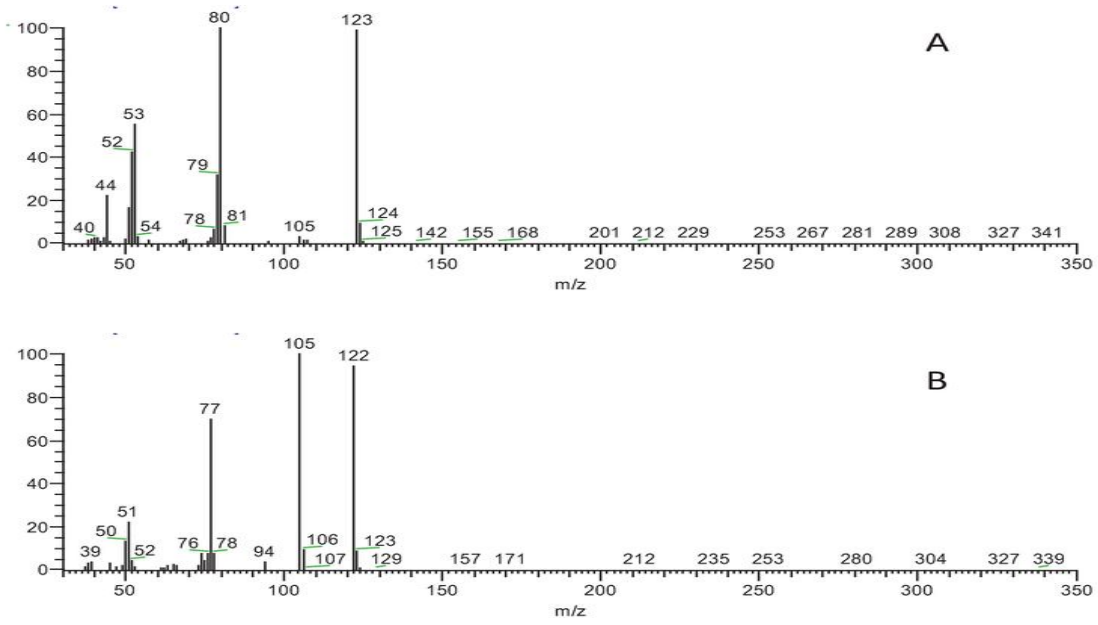


Figure 1: ***The mass spectra of PZA (A) and [Cu(PZA)2](C6H5COO)2 (B) [1, 10]. Reprinted with permission of Revista de Chimie and of Editura Universităţii din Oradea.***

The FTIR spectra of the complexes highlighted that –C═O groups and nitrogen from the pyrazine ring are implied in the coordination process (Table 1). Comparing the Raman spectra of PZA and of $[Cu(PZA)_2]Cl_2$, another analytical evidence for the complex formation is obtained. The appearance of new band characteristic for the Me:L bonds can be observed analyzing in detail the spectral region of low values of wave number (Figure 2.

PZA	$[Cu(PZA)_2](C_6H_5COO)_2$	$[Cu(PZA)_2]Cl_2$	Assignment
3410s	3610w	3430s	ν_{as} NH_2
3140m	3170m	3110m	ν_s NH_2
3080	3065m	3070m	νCH
1705s	1915w	1700s	νC═O(1)
1600m	1590m	1590m	δNH_2(2)
1570	1585m	1585m	ν ring
1530	1545s	1510w	ν ring
1375s	1380s	1385s	νCN(III)
1150w	1180w	1170m	δCH
1090m	1085w	1080w	ρ NH_2
870w	850w	870m	δ ring
665w	680m	670w	ρ NH_2
TABLE1			

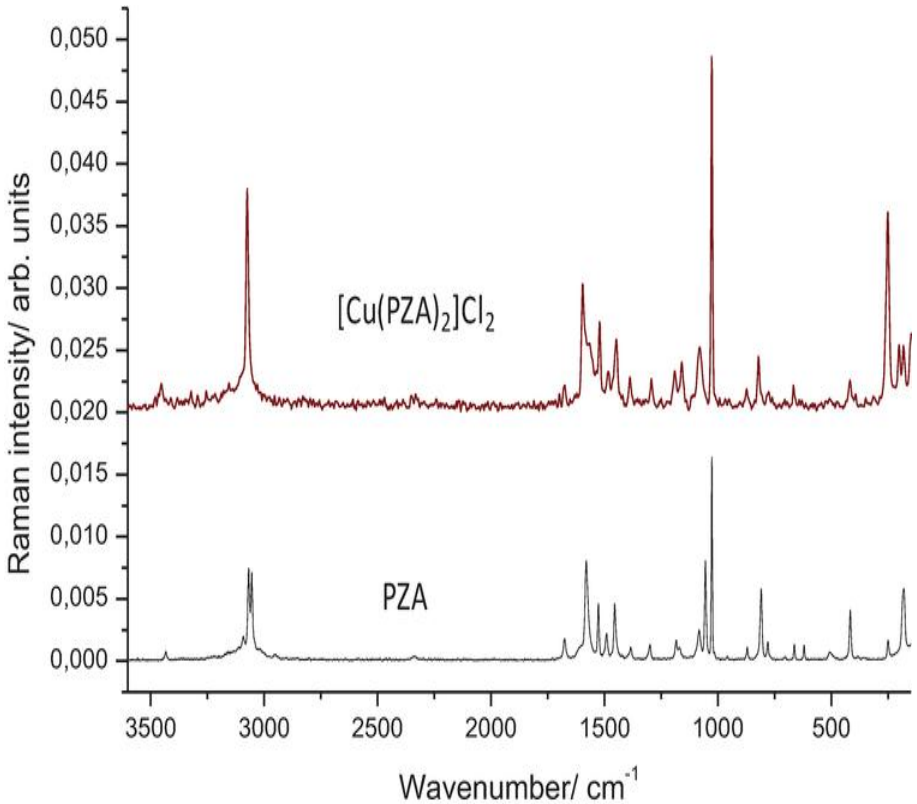


Figure 2. ***Raman spectra of PZA and of [Cu(PZA)2]Cl2 [1, 12]. Reprinted with permission of Studia Universitatis Babes-Bolyai and of Editura Universităţii din Oradea*.**

The morphology and the crystal structure of the two complexes were revealed by the SEM images and EDS spectra (Figures 3 and 4). The first complex, $[Cu(PZA)_2](C_6H_5COO)_2$, presented irregular conglomeration with different shapes and dimensions (Figure 3A); meanwhile, the second one, $Cu(PZA)_2]Cl_2$, presented acicular and elongated particles with an average size of about 1.5 microns (Figure 4A).

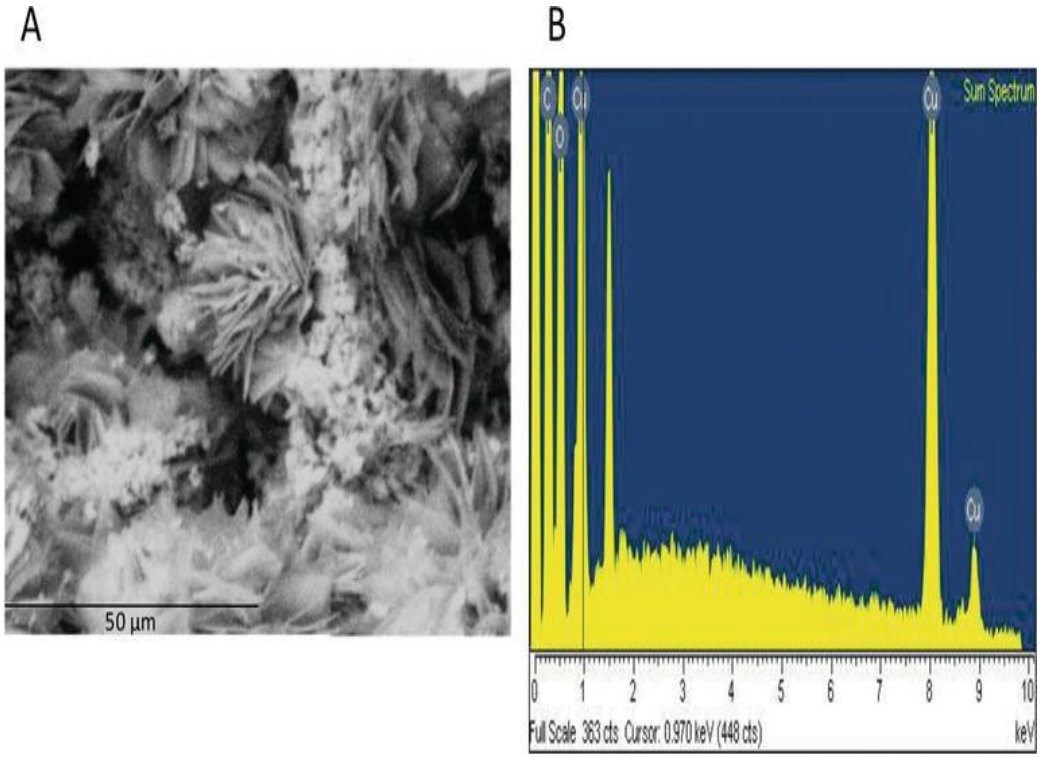


Figure 3: SEM image (A) and EDS spectrum (B) of [Cu(PZA)2](C6H5COO)2 [1, 14]. Reprinted with permission of Farmacia and of Editura Universităţii din Oradea.

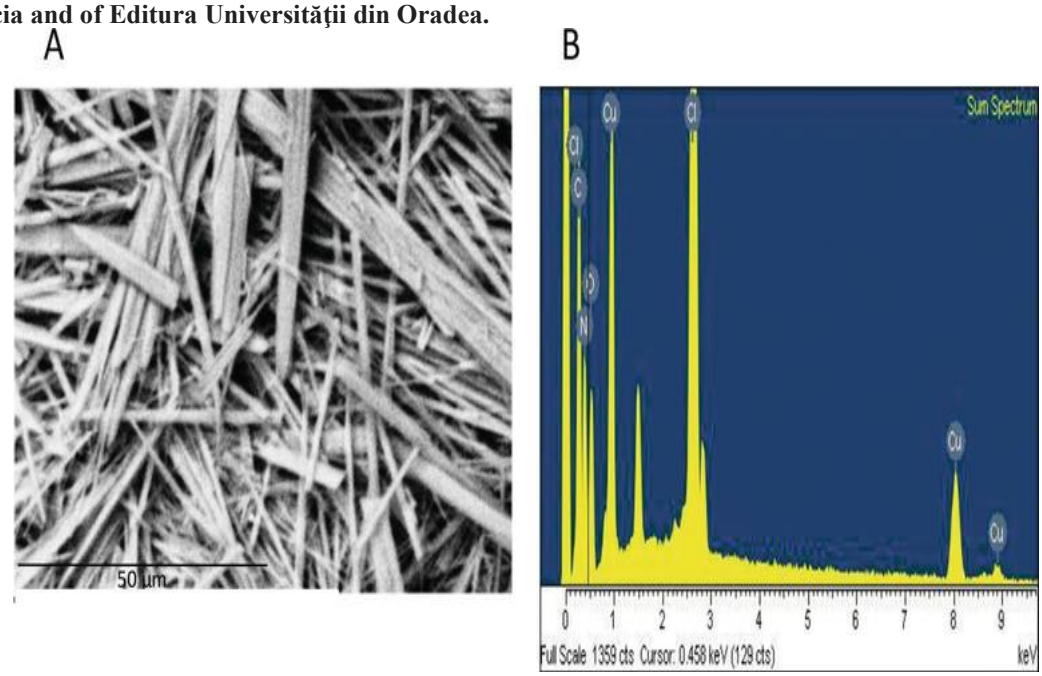


Figure 4: SEM image (A) and EDS spectrum (B) of [Cu(PZA)2]Cl2 [1, 14]. Reprinted with permission of Farmacia and of Editura Universităţii din Oradea.

Metal complexes of nicotinamide

Nicotinamide (NAM) (3-pyridine carboxylic acid amide) is the amide of nicotinic acid playing an important role in the biosynthesis of pyridine nucleotides. The NAM complexes with transition metals [Cu(II), Cd(II), Hg(II)] were synthesized and characterized by using elemental analysis, UV-Vis, and FTIR spectroscopy , The spectral data confirmed tetradentate coordination of NAM with Hg(II), Cd(II), and hexadentate coordination with Cu(II). In the FTIR spectra of these complexes, it can be observed that the characteristic bands of NAM are slightly shifted after coordination (Table 2). The slight shifting of the bands from NAM complexes with Hg may be explained by the stereochemistry of $HgCl_2$, which is less bulky than $Cu(C_6H_5COO)_2$ and $Cd(SCN)_2$.

Table 2: ***Assignment of the characteristic IR bands of the metal complexes of NAM .***

NAM	$[Hg(NAM)_2]Cl_2$	$[Cu(NAM)_2]$ $(C_6H_5COO)_2 2H_2O$	$[Cd(NAM)_2](SCN)_2$	Assignment
			3531w	(OH)
3364vs	3363s	3369s	3479s	$\nu_{as}(NH_2)$
3167s	3171s	3207vs	3176m	$\nu_s(NH_2)$
3065sh	3071sh	3071sh	3072w	ν(CH)
1654s	1654vs	1668vs	1667vs	ν(CO)
1622ws	1623ws	1632ws	1618m	$\delta(NH_2)$
1577ws	1577vs	1596s	1577s	ν(CN) + ν(CC)
1449m	1449m	1490s	1485m	β(CH)
1395ws	1400m	1377vs	1400s	ν(CN) amide
1297m	1296m	1301w	1331m	ν(CC)
1178m	1179m	1193w	1204s	ν(ring) NAM
1141m	1142s	1153sh	1153m	ν (CN)
1120m	1119s	1116m	1112m	$\rho(NH_2)$
1022m	1024w	1025m	1040m	υ(CNS)
–	919m	928w	937w	γ(CH) ring
–	844s	853m	840m	$\nu_{as}(C{-}CH_3)$
771m	786s	775w	770s	γ(CH) ring
698m	700ws	719w	719w	$\omega(NH_2)$
684m	686ws	687s	687ws	δ(ring)NAM
633s	641s	655w	657ws	γ(NH)

2.3. Metal complexes of nicotinic acid

Nicotinic acid ***(NIC) (pyridine-3-carboxylic acid) known as vitamin B_3, niacin***, has two important pharmacological properties: ***peripheral vasodilator and hypocholesterolemic drug.*** Its complexes with Co(II) and Cu(II) were synthesized and characterized by elemental analysis and spectral methods [FTIR spectroscopy, Raman spectroscopy, and surface-enhanced Raman spectroscopy (SERS)] (Figure 5). The significant differences observed from the spectral data of the metal complexes can be attributed to the coordination process with the metal ions: the stretching vibrations ν(C─C) from the pyridine ring (1500–1600 cm^{-1}) and ν(ring) of NIC (1037 cm^{-1}) are shifted; meanwhile, the vibration band γ(CH) of the ring at 811 cm^{-1} is shifted and also splitted indicating the ring deformation during the coordination process. There appear new bands corresponding to the Me:L bonds (at about 500 cm^{-1}) (Table 3). The spectral results confirmed the monodentate coordination of NIC with Cu(II) and Co(II).[17]

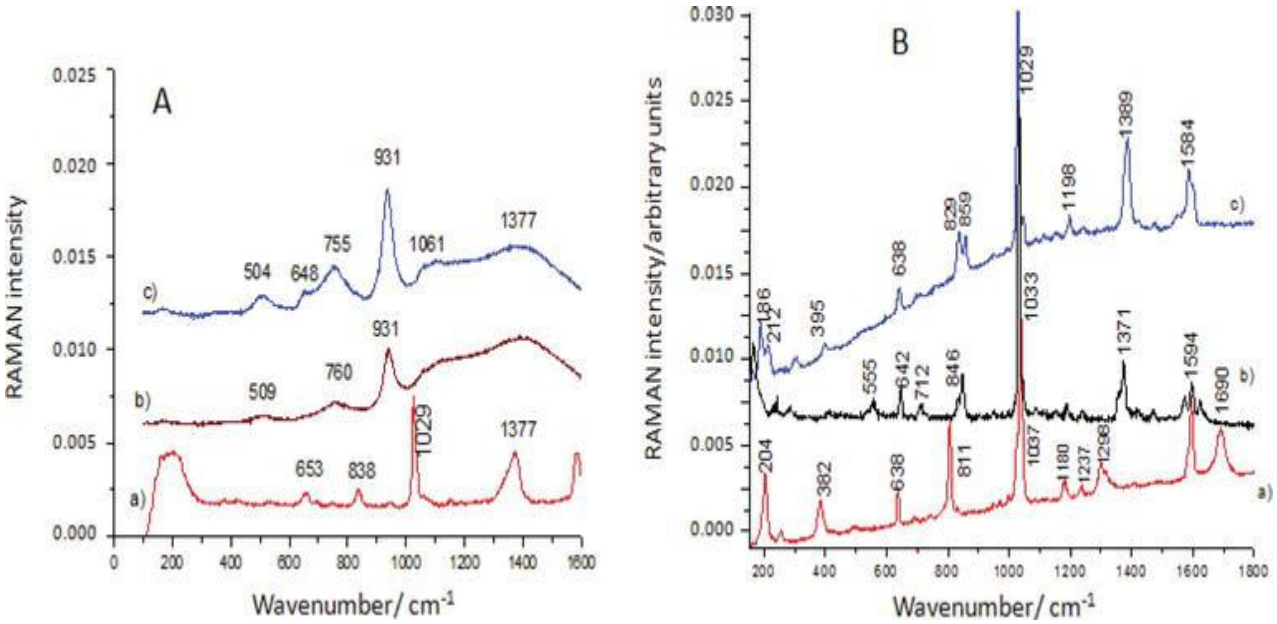


Figure 5: Raman (A) and SERS (B) spectra of NIC (a) and its complex with Cu(II) (b) and Co(II) (c) [17]. Reprinted with permission of Revista de Chimie.

Table 3: ***Assignment of the characteristic Raman and SERS bands of the metal complexes of NIC.***

Assignment (cm^{-1})	NIC Raman (cm^{-1})	NIC SERS (cm^{-1})	$Cu(NIC)_2(CH_3COO)_2$Raman (cm^{-1})	$Cu(NIC)_2(CH_3COO)_2$SERS (cm^{-1})	$Co(NIC)_2(CH_3COO)_2$Raman (cm^{-1})	$Co(NIC)_2(CH_3CO)_2$ SERS (cm^{-1})
ν(OH) acid	–	–	–	–	–	–
ν(CH)	–	–	–	–	–	–
*ν*C═O	1690m	–	–	–	–	–
ν(ring) NIC	1594m	1594m	1594m	–	1584m	–
ν(CN)	–	–	–	–	–	–
	–	1377m	1371m	1377wv	1389s	1377wv
ν(CC)	1298m	–	–	–	–	–
δ(CN)	1180m	–	–	–	1198m	–
ν(ring)NIC	1037vs	1029s	1033vs	1060wv	1029vs	1061wv
δ(OH)acid	–	–	–	931m	–	931m
γ(CH) ring	811m	838wv	846m	760wv	829m	755wv
δ(CH) ring	638m	653wv	642m	–	638m	648wv
*ν*Me-O	–	–	555wv	509wv	–	504wv

2.4. Metal complexes of guanfacine

Guanfacine (GUAF) (N-(diaminomethylidene)-2-(2,6-dichlorophenyl)acetamide), used as antihypertensive drug, is able to form colored complexes (combination ratio Me:L 1:2) with Mn(II) and Cd(II) having different spectral characteristics. These complexes were analyzed by using spectral techniques such as FTIR and Raman spectroscopy. The imine group vibration from ***the FTIR data of GUAF ($\nu_{C=N}$ at 1700 cm^{-1}) was shifted (Δ = 10–60 cm^{-1}) in the spectra of GUAF complexes with Mn(II) ($\nu_{C=N}$ at 1710 cm^{-1}) and Cd(II) ($\nu_{C=N}$ at 1760 cm^{-1}) s***howing the imine group involvement in the complex formation. The formation of new bonds Me:L was observed at around 500 cm^{-1} in the case of the two mentioned complexes. Significant differences appeared in the Raman spectra of the complexes in the region 1100–1250 cm^{-1} due to the electronic delocalization from NH═C─NH_2(Figure 6). After coordination, in the case of both complexes, two distinct bands were revealed at 1212 cm^{-1} for NH─C─NH_2 and at 1174 cm^{-1} for NH═C─NH_2. The spectral data indicated that GUAF is coordinated by nitrogen atoms, and the results confirmed a tetradentate coordination of Cd (II) complexes.[18]

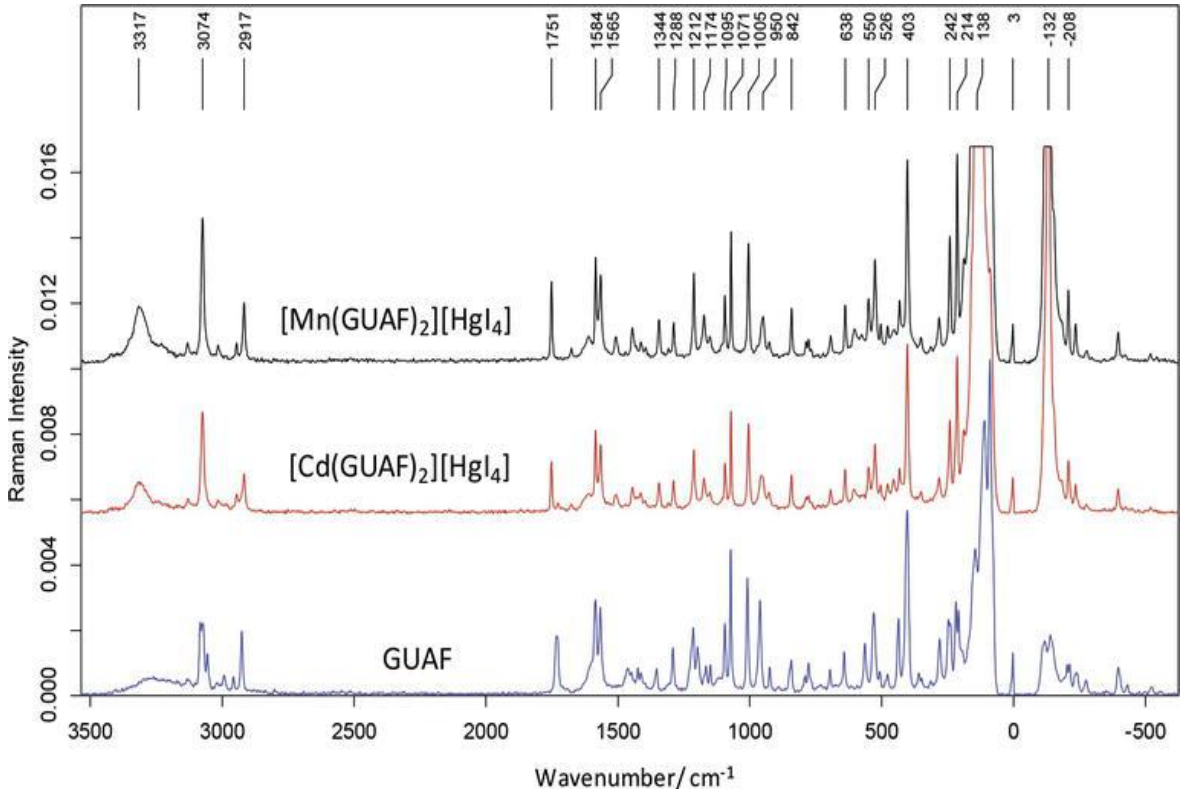


Figure 6: ***Raman spectra of GUAF and of its metal complexes.***

Metal complexes of theophylline

Theophylline (TEO) (3,7-dihydro-1,3-dimethyl,1H-purine-2,6-dione) also known as 1,3-dimethyl-xanthine belongs to the class of peripheral and cerebral vasodilator drugs. Metal complexes of TEO were synthesized having the general formula: $[Me_n(TEO)_x]A_m \cdot yH_2O$, where Me = Cu(II), Co(II), Cd(II), Zn(II), and Ni(II) and A = CH_3COO^-, $C_6H_5COO^-$; n = 1, x = 1 or 2, m = 2, and y = 2 or 4. The combination ratio was determined by using elemental analysis and conductometric titration; meanwhile, the number of water molecules was determined by using thermal analysis.[2,19–22]

The combination ratio Me:TEO is 1:2 for the complexes having the acetate anion. The complex $[Cu(TEO)_2](CH_3COO)_2$ has a high thermal instability even at 40°C, its thermal decomposition being already started. On the thermal curves, eight stages of decomposition, all scarcely separable, can be observed. The first five were weakly endothermic, and three were strongly exothermic. The X-ray diffractogram revealed that this complex crystallizes in the monoclinic system. The microscopic analysis showed a mixture of particles with different shapes: acicular, flake, irregular, and lamellar (Figure 7).

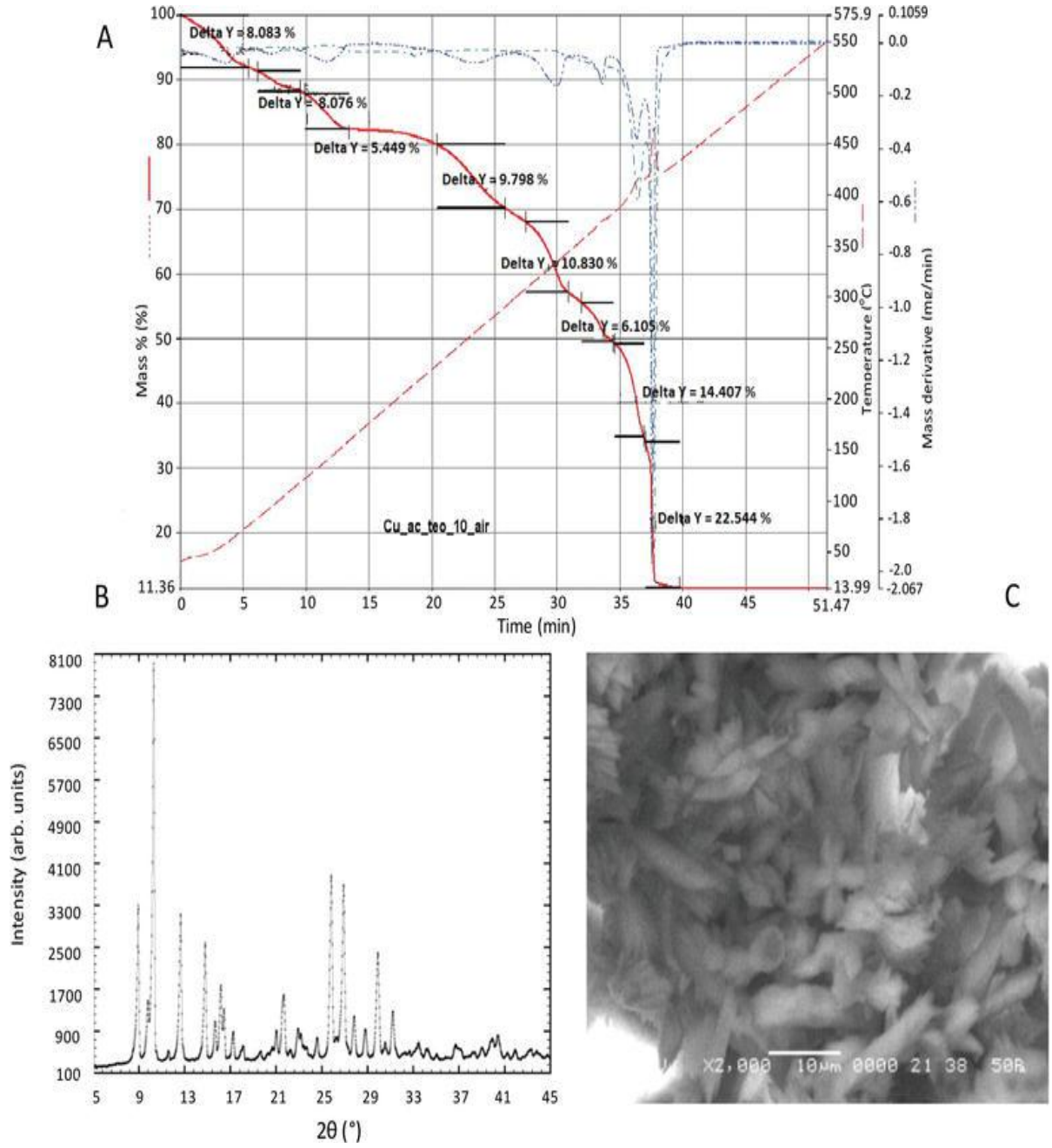


Figure 7: ***Thermogramms TG, DTG, and DTA (A); X-ray diffractogram; (B) and SEM images (C) of [Cu(TEO)2](CH3COO)2 [2, 19, 21, 22]. Reprinted with permission of Revista de Chimie, Farmacia and of Editura Politehnica Timişoara.***

In the case of ***[Cd(TEO)$_2$](CH$_3$COO)$_2$,*** the last stage of thermal decomposition was not achieved in the investigated temperature range; therefore, heating was required up to a higher temperature (850°C) when constant weight was reached corresponding to the cadmium oxide. The complex crystallizes in the monoclinic system, and it presents microcrystals with parallelepiped shape.

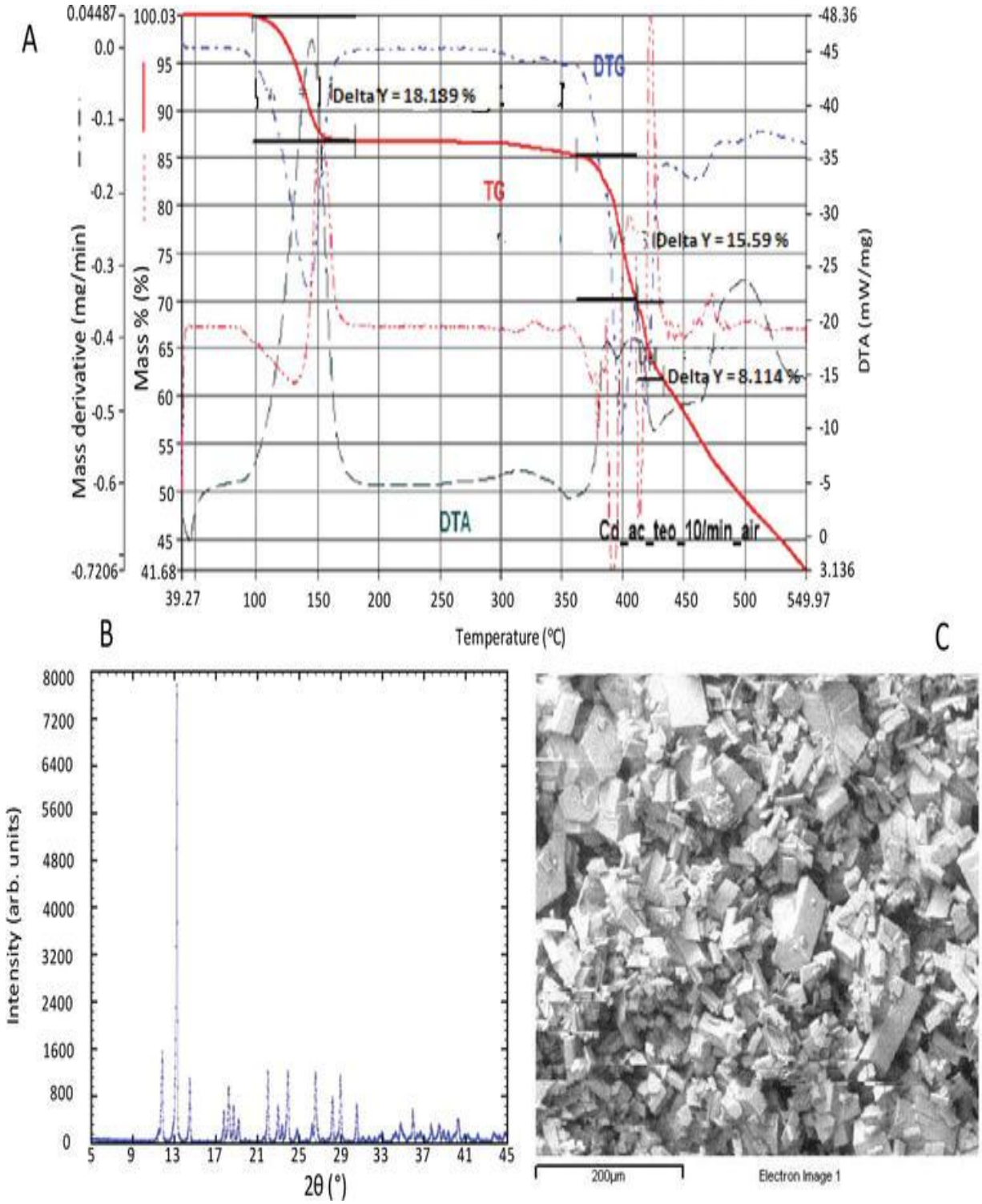


Figure 8: ***Thermogramms TG, DTG, and DTA (A); X-ray diffractogram; (B) and SEM images (C) of [Cd(TEO)2](CH3COO)2 [2, 19, 21, 22]. Reprinted with permission of Revista de Chimie, Farmacia and of Editura Politehnica Timişoara.***

The thermal decomposition of [Co(TEO)$_2$] (CH$_3$COO)$_2$ takes place in four stages: one endothermic and three exothermic. It presents monoclinic crystal system, and the microcrystals have a tabular form (Figure 9). The complex [Zn(TEO)$_2$] (CH$_3$COO)$_2$ presented similar properties as [Cd(TEO)$_2$] (CH$_3$COO)$_2$ complex.

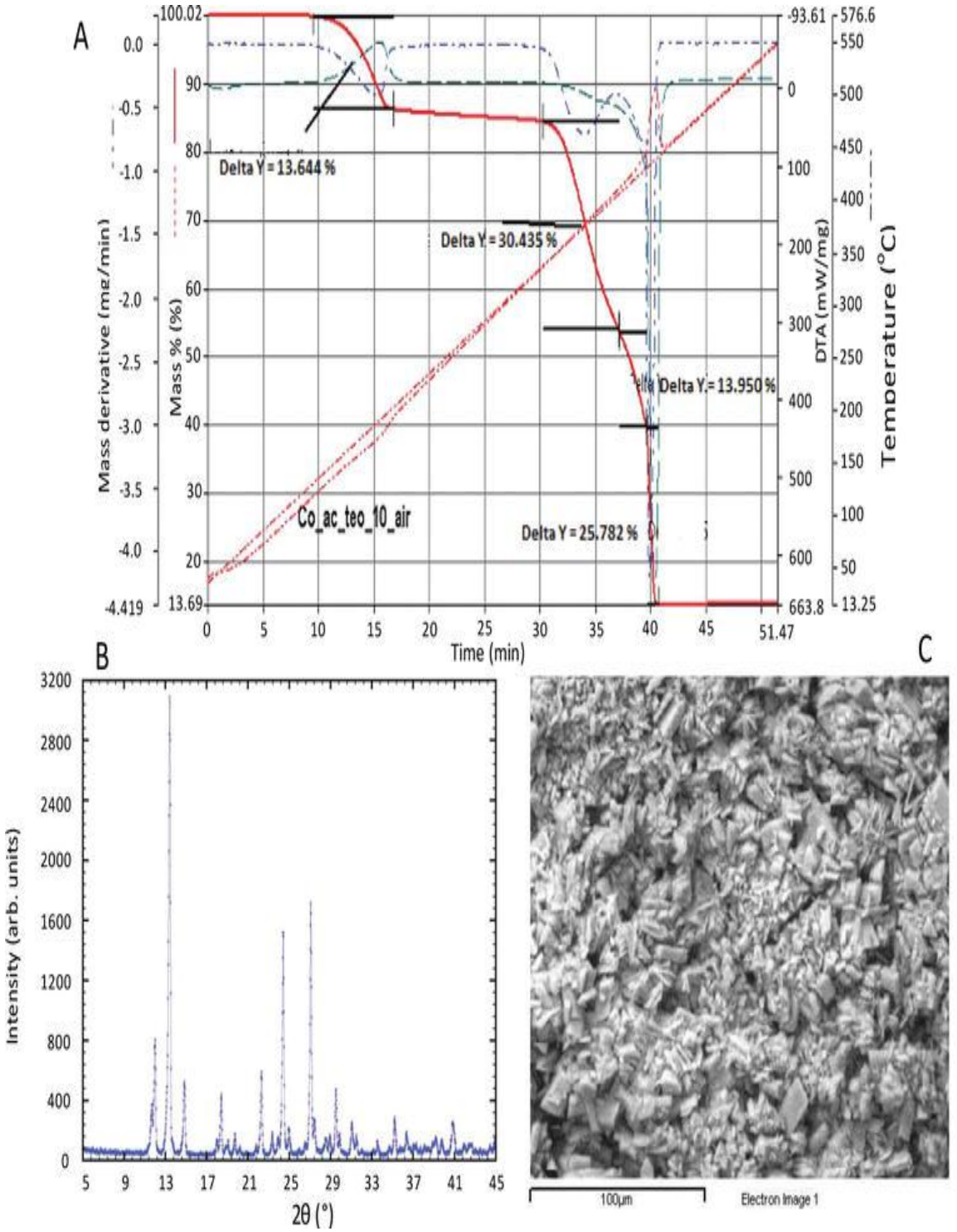


Figure 9: ***Thermogramms TG, DTG, and DTA (A); X-ray diffractogram; (B) and SEM images (C) of [Co (TEO) 2](CH3COO)2.***[2,19,21,22] ***Reprinted with permission of Revista de Chimie, Farmacia and of Editura Politehnica Timişoara.***

The endothermic peak at 272°C, which is characteristic for TEO decomposition, is not found in the differential scanning calorimetry (DSC) curves of the complexes, being a credible argument for the complex synthesis and not as a simple mechanical mixture (Figure 10)

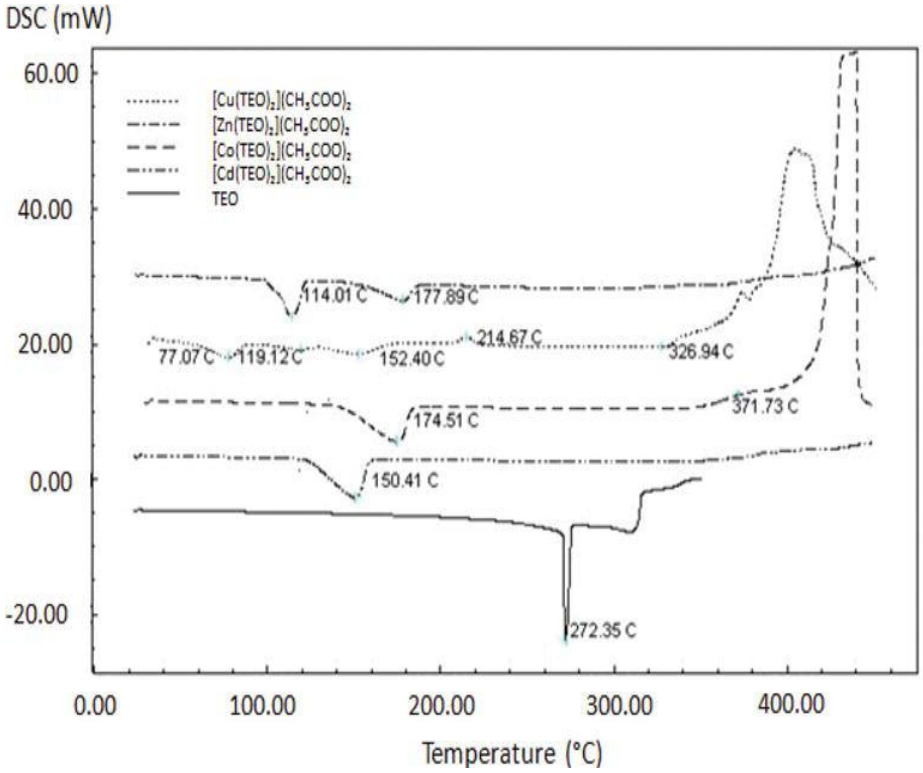


Figure 10: ***DSC thermogramms of metal complexes of TEO [2, 19]. Reprinted with permission of Revista de Chimie and of Editura Politehnica Timişoara*.**

The FTIR data also indicated the complex formation: the disappearance of the symmetric vibration band of ─C═O from TEO at 1717 cm^{-1} in the complexes spectra indicating that this bond is involved in the formation of Me:TEO coordinative bond; the deformation vibration of Me:N bond found at 570–685 cm^{-1}, the appearance of symmetric and asymmetric stretching vibrations of the ─COOH group (1260–1250 and 1535–1530 cm^{-1}), and the possibility of coordinating also the water of crystallization (appearance of large bands at 3050–3500 cm^{-1}) (Figure 11)

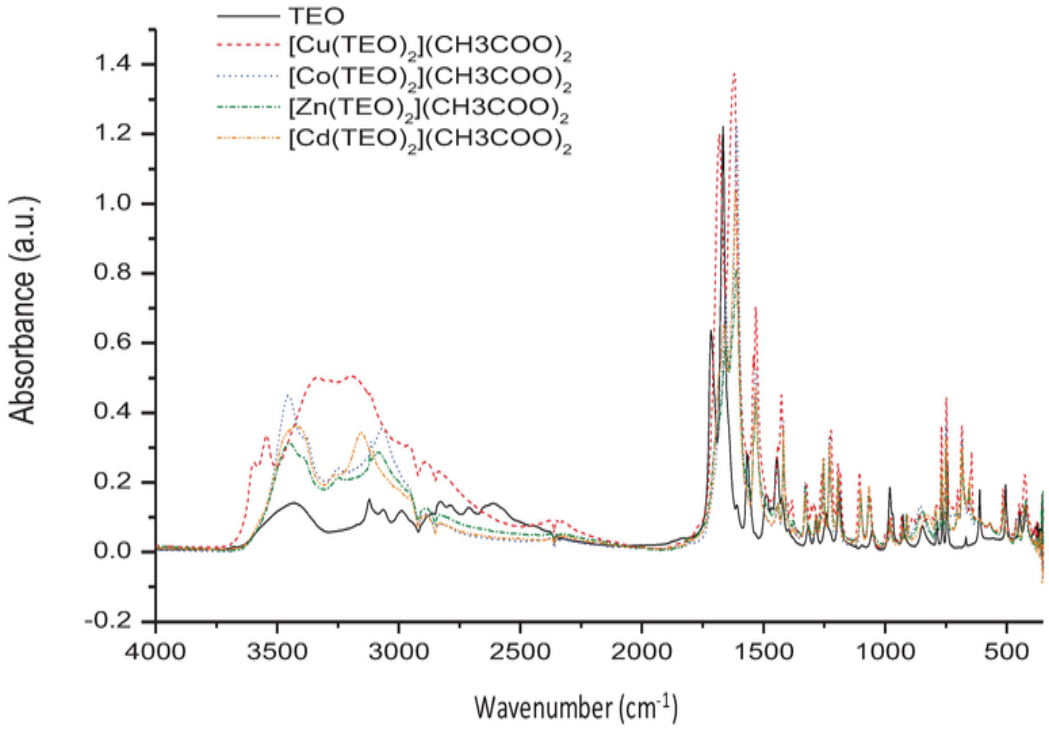


Figure 11: ***FTIR spectra of TEO and of its metal complexes (acetate anion).***

The combination ratio ***Me:TEO is 1:1 for the complexes having the benzoate anion: [Co(TEO)] $(C_6H_5COO)_2 \cdot 2H_2O$, [Ni(TEO)]$(C_6H_5COO)_2 \cdot 2H_2O$, [Cu(TEO)] $(C_6H_5COO)_2 \cdot 2H_2O$***. Their thermal decomposition takes place in four stages, the first one being the stage of loss of water of crystallization (Figure 12A). The FTIR data are similar with those of the complexes mentioned above (having the acetate group as anion); in addition, the specific vibration band of the aromatic ring (1438, 1442, 1440 cm^{-1}) appears. The microscopic image of $[Co(TEO)](C_6H_5COO)_2$ showed the acicular shape of the particles (Figure 12B).[2,20]

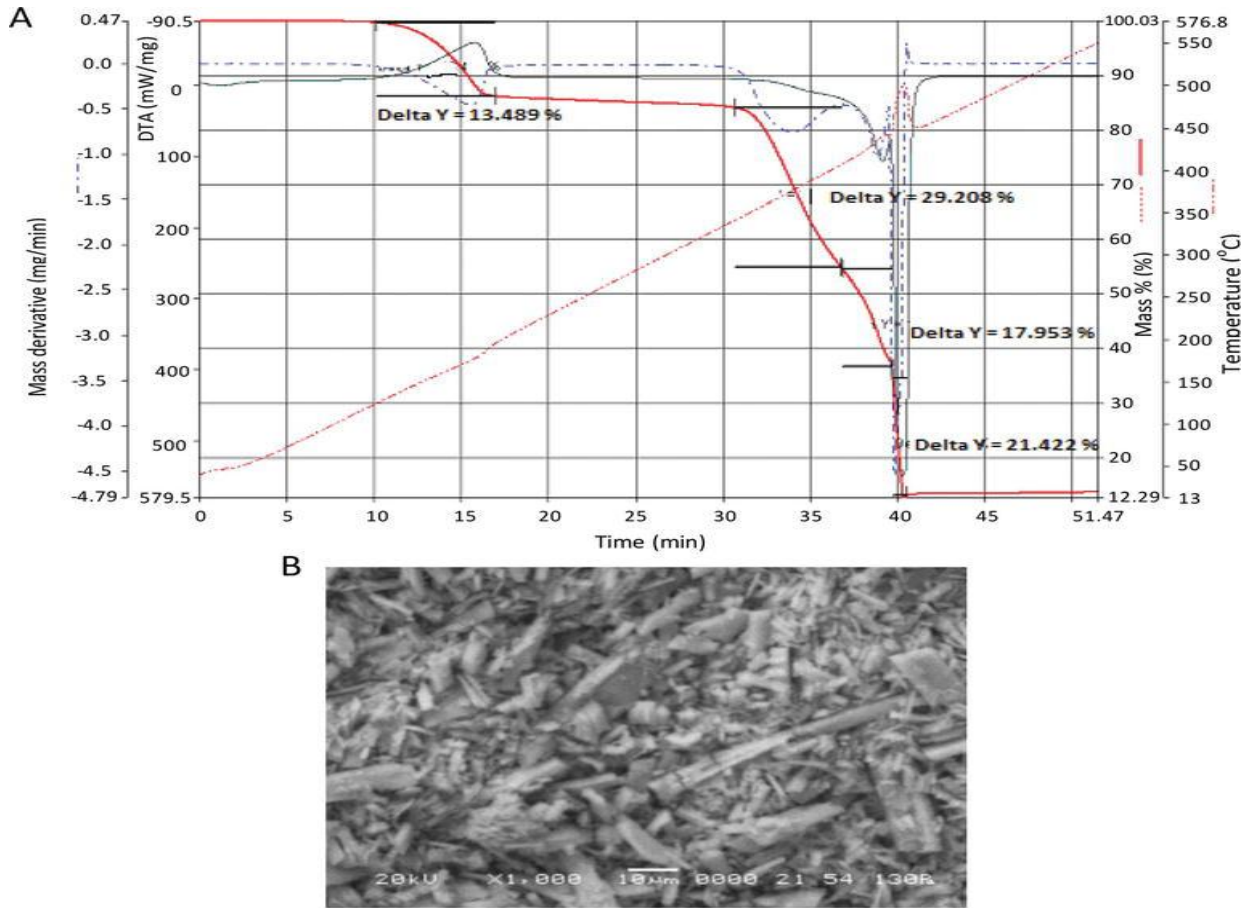


Figure 12: ***Thermogramms TG, DTG, and DTA (A) and SEM images (B) of [Co(TEO)](C6H5COO)2 [2, 20]. Reprinted with permission of Revista de Chimie and of Editura Politehnica Timişoara.***

Metal complexes of captopril

The chemical structure of captopril ***(CPL), a dipeptide derivative of L-alanine-L-proline with antihypertensive effect***, contains bonds such as ─C═O and ─N(─CH_2)$_2$ with donor atoms capable of forming Me:L bonds. The interaction between the metal ions such as Mn(II), Co(II), Zn(II), Ni(II), and Cd(II) with N and O atoms from the peptide (which act as donors) leads to the formation of stable chelate cycles. These complexes were characterized by elemental analysis obtaining the results presented in Table 4.

Table 4: Physicochemical characterization of the metal complexes of CPL

The molecular formula and weight	Color	Melting point (°C)	C% Found/calculate	H% Found/calculated	N% Found/calculated	S% Found/calculated
$[Cd(CPL)_2][HgI_4]$ M = 1255.18	White	210	17.09/17.21	2.56/2.39	1.881/2.23	5.579/5.099
$[Zn(CPL)_2][HgI_4]$ M = 1244.18	White	165	16.94/17.8	3.019/2.48	1.866/2.31	5.547/5.29
$[Ni(CPL)_2][HgI_4]$ M = 1199.48	Greenish yellow	170	18.07/18.01	3.022/2.5	1.955/2.33	6.083/5.33
$[Co(CPL)_2][HgI_4]$ M = 1199.68	Light pink	180	17.84/18.01	2.866/2.51	1.938/2.31	6.148/5.43
$[Mn(CPL)_2][HgI_4]$ M = 1195.68	White crystals	182	18.04/18.06	2.648/2.50	1.946/2.34	5.85/5.35

CPL forms complexes with transition metals mentioned above in the presence of ***tetraiodomercurate anion, $[HgI_4]^{2-}$***. The formation and the structure of these complexes are observed in the data of the elemental analysis and in the UV and IR spectra of the complexes with changes of the wavelength values and of absorbance due to the presence of Me:CPL bonds. In the IR spectra of the complexes, a diminution of the band at 1748 cm^{-1} of ─C═O from the carboxyl group, in comparison with the IR spectrum of CPL, was observed. A wider band appeared at 1600 cm^{-1} due to the overlapping of the bands corresponding to ─C═O from the amide group. In addition, a new band is observed at 1450 cm^{-1} due to ─C═O from the carboxyl group (─COO^-). In the IR spectra of the Zn:CPL complex, the band corresponding to ─C═O from carboxyl group decreased. It is possible that the reaction with some metals was not completely performed or some degradation products of CPL may be involved in the complexation reaction. In the case of the complex $Cu_2^{II}CPL_2(H_2O)_2$, the IR spectra have indicated the participation of ─COOH, ─C═O, and ─SH groups in coordination along with H_2O included in the inner coordination sphere.

The ***UV spectra*** of the complexes were compared to the UV spectrum of CPL in ***dimethylformamide*** establishing the parameters presented in Table 5 ($A^{\%}_{1\ cm} = 190$ for 2.5 µg% CPL).

Table 5: The parameters of the metal complexes of CPL from UV spectra.[23]

Complex	λ (nm)	$A^{\%}_{1\ cm}$	Concentration (µg %)
CPL–Cd	300	270	5
CPL–Zn	300	400	5
CPL–Ni	300	475	4
CPL–Co	300	250	8
CPL–Mn	321	520	4.5

Biomedical significance of metal complexes with pharmaceuticals

The study of the complexes structure and of their biological importance represented the major research interest toward the use of organic drugs as ligands in coordination chemistry for their application in the biomedical field.

The molecules of the pharmaceutical substances have one or more ***unshared electron pairs*** that can function as ligands. In fact, many of the ***basic components of living organisms*** (amino acids, peptides, proteins, hormones, lipids, carbohydrates, etc.) may function as ***ligands because they contain donor atoms*** in their molecules such as nitrogen, oxygen, sulfur, and phosphorus. It is well known that many molecules of drug substances act as ligands both in vitro and in vivo conditions. It is noteworthy to mention that in vivo these ligands will compete for a particular metal ion with a variety of other ligands determining that the extrapolation of this in vitro behavior should be done with moderation. It should always be taken into consideration that the therapeutic effect will be mainly influenced by the ***conformation of the drug ligands molecules*** and by their ability to combine with receptors.

Thus, the use of these metal complexes in the biomedical field can be realized by various purposes such as the introduction in the ***body of deficient metal ions, the use of the ligands as antidotes in various intoxications with metals, and the acquirement of pharmacotherapy effects by blocking metal ions essential for some enzymatic systems.*** Metal ions are of great importance not only in the vital functions of living organisms, but also they can be intensively used in analysis and control methods for pharmaceutical substances by forming complexes that can be detected by using ***different physicochemical methods such as spectroscopy, chromatography, microscopy,*** etc

CONCLUSIONS

Transition metal complexes find their application in ***catalysis, material synthesis, photochemistry, therapy, and diagnostics***. Various chemical, optical, and magnetic properties of the metal complexes of some pharmaceutical substances (pyrazinamide, nicotinamide, nicotinic acid, tolbutamide, theophylline, captopril, clonidine, and guanfacine) have been studied by using a wide range of techniques. The spectral methods such as Fourier transform infrared spectroscopy, Raman spectroscopy, surface-enhanced Raman spectroscopy, X-ray spectroscopy, mass spectrometry, ultraviolet-visible spectrophotometry, electron paramagnetic resonance spectroscopy, and X-ray diffraction provided information about the complexes and ligand structure. Other techniques such as elemental analysis, electrochemical, and thermal methods were also employed for the assessment of the complexation ratio. The scanning electron microscopy images revealed the morphology of the metal complexes underlying their crystalline or amorphous character. Many studies were conducted concerning the synthesis and the investigation of metal complexes in which the pharmaceutical substances play the role of ligand highlighting their increasing clinical and commercial importance.

In future many more complexes will formed with reduce side effect and more theraputeic advancement. That is why transition metal regared as "future weapon of pharmacuetical chemistry".....

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