Chapter 1

Introduction
1. Introduction

1.1 Medicinal inorganic chemistry

Metals have played an important role in medicine for years, ever since humans have walked the planet. The use and significance of inorganic compounds had been invaluable to the medical field. Medicinal inorganic chemistry includes the study of both non-essential and essential elements with applications to diagnosis and therapies. The use of metals in medicine involves (i) non-invasive radiopharmaceuticals, (ii) Magnetic Resonance Imaging, (iii) metal based drugs and (iv) mineral supplements [1,2].

Medicinal inorganic chemistry can be divided into two main categories, (i) metal-based drugs where the central metal ion is usually the key feature of the mechanism of action and (ii) drugs that target metal ions (free or protein-bound) [3–5]. For designing of inorganic drugs, metal-binding and metal-based agents are used. Three widely used inorganic pharmaceuticals are included in the area of metallotherapeutics, (i) Platinum anticancer drugs (cisplatin and carboplatin), (ii) Radiodiagnostic and radiopharmaceutical drugs (Cardiolyte – a heart imaging agent, a positively charged $^{99m}$Tc complex and (iii) Gold antiarthritic drugs (Auranofin) [6].

The functional roles of selected biological inorganic elements include: structure and templating (Ca, Zn, Si, S); energy storage (H, P, S, Na, K, Fe); group transfer such as CH$_3$, O, S(V, Fe, Co, Ni, Cu, Mo, W); charge balance and electrolytic conductivity (Na, K, Cl); signaling (Ca, B); Bronstead acid-base buffering (P, Si, Co; Lewis acid-base catalysis (Zn, Fe, Ni, Mn); electron transfer (Fe, Cu); biomineralization (Ca, Mg, Fe, Si, Sr, Cu, P) and redox catalysis (V, Mn, Fe, Co, Ni, Cu, W, S, Se).

1.2 Transition metals and their complexes

Transition metals have an important place within medicinal inorganic chemistry. Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. This activity of transition metals has started the development of metal-based drugs with promising pharmacological applications and may offer unique therapeutic opportunities [7,8].
The single coordination compound administration can have a series of beneficial effects that come from the metal ion alone, and from the metal and the ligand(s) after the coordinate bond(s) dissociate in the target tissue. The metal ion and the ligand(s) can have a synergic effect, the metal can stabilize the ligand against possible enzymatic degradation before reaching the target, the coordinated molecule can have a better hydrophilicity/hydrophobicity ratio than the free ligand, etc. Metal based drugs have been developed to treat/cure a variety of ailments viz. diabetes, ulcer, rheumatoid arthritis, inflammatory, cardiovascular diseases, neurological disorders, anti-inflammatory, carcinomas, infection control, lymphomas etc [9–11].

Metals can play an important role in modifying the pharmacological properties of known drugs after coordinating to a metal. Chelation causes drastic change in biological properties of ligands as well as metal moiety and in many cases it causes synergistic effect of metal ion and ligand both [12,13]. For example, complexation of nonsteroidal anti-inflammatory drugs to copper overcomes some of the gastric side effects of these drugs [14]. Metal complexes are supposed to exert their effect by inhibition of enzymes, interaction with intracellular biomolecules, enhanced lipophilicity, alteration of cell membrane functions and arrest of cell cycle etc. Metal compounds as anti-diabetic, anti-inflammatory, antimanic, antimicrobial, antiparasitic, antiulcer, antihypertensive agents were reported [15,16].

A wide variety of metal compounds are already in clinical use [17–23]. These include mineral supplements containing metals which are essential for mammalian life, e.g. Fe, Zn, Mn, Cu, Mo, Ca, Mg. Cobalt comes in the form vitamin B12, which is the physiologically effective complex. Widely used are antacids, many of which are simple inorganic salts of Group 1, 2 or 13 metals (sodium bicarbonate, magnesium oxide, trisilicate or carbonate, aluminum hydroxide).
Table 1.2.1 Transition metals and their roles in human body

<table>
<thead>
<tr>
<th>Transition metal</th>
<th>Function in human body</th>
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<tbody>
<tr>
<td>Copper</td>
<td>Thyroid and immune system, to synthesize enzymes which convert progesterone into estrogen, copper gluconate helps to reduce high cholesterol levels in humans, osteoporosis, wound healing, cardiac arrhythmia, hypoglycemia, peripheral vascular disease, osteoarthritis and rheumatoid arthritis</td>
</tr>
<tr>
<td>Chromium</td>
<td>Regulates sugar levels by interacting with insulin, lowers cholesterol or improves the body’s use of glucose</td>
</tr>
<tr>
<td>Manganese</td>
<td>Bone formation, present in the processing of cholesterol, carbohydrates and protein</td>
</tr>
<tr>
<td>Iron</td>
<td>Used to treat anemia, act as bactricides or bacteriostatic agents, haemoglobin, myoglobin</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Vitamin B$_{12}$ in protein formation and DNA regulation, cyanide Antidote</td>
</tr>
<tr>
<td>Zinc</td>
<td>Need for the growth and repair of tissues throughout our bodies, help in the formation of enzyme which convert progesterone into testosterone</td>
</tr>
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1.2.1 Therapeutic applications of metal complexes

**Antibiotic agents:** Antibiotic like bleomycin causes DNA strand scission through formation of an intermediate metal complex requiring a metal ion cofactor such as copper or iron [24,25] for the activity in the treatment of cancer. Antibiotic drugs of the tetracycline family are chelators of Ca$^{2+}$ and Hg$^{2+}$ ions.

**Antiviral agents:** It is recently discovered that ruthenium polyaminocarboxylate (Ru-pac complexes) possess cysteine protease inhibition activity. The ability of Ru-pac complexes to inhibit cysteine protease activity was attributed to the high affinity of the ruthenium complexes towards binding the SH group in the cysteine residue of the enzymes via a rapid aqua substitution reaction. The discovery of the protease inhibition activity of Ru-pac complexes may be of significance in developing antiviral agents in which Ru-pac complexes could act as metallo-inhibitor agents for disease progression [26].
**Anticancer agents:** Cisplatin, carboplatin are the first and second generation platinum drugs respectively, which are widely used in the treatment of cancer [27]. Many of the properties of the ruthenium agents tested are similar to that of platinum compounds that is, they bind to DNA.

Octahedral Ru(II) and Ru(III) complexes containing ligands, such as amines, N-heterocycle and dimethyl sulfoxides exhibited various degree of biological activity including antitumor action *in vivo* [28].

**Antiarthritic agents:** Auranofin and other gold(I) complexes are well known as antiarthritic drugs, but they also inhibit the growth of cultured tumor cells *in vitro* and many have antimitochondrial activity [29]. Auranofin has recently become known as a potent and specific inhibitor of thioredoxin reductase [30], an enzyme that may play an important role in the redox control of the permeability of mitochondrial membranes.

1.3 **Ligand**

1.3.1 **Definitions**

1) **In coordination chemistry**, an ion or molecule which binds to a central metal atom to form a coordination complex is known as a ligand.

2) **In biochemistry and pharmacology**, a ligand (*Latin* ligare = to bind) is a substance that is able to bind and form a complex with a biomolecule to serve a biological purpose. In a narrower sense, it is a signal triggering molecule, binding to a site on a target protein.

The bond between metal and ligand is formed due to formal donation of one or more of the ligand's electron deficient pairs. The nature of metal-ligand bonding can range from covalent to ionic. Ligands are classified in many ways: their charge, their size (bulk), the identity of the coordinating atom(s) and the number of electrons donated to the metal (denticity or hapticity).

Supramolecular chemistry has become a famous concept and a leading field in today's research community, when D.J. Cram, J.M. Lehn and C.J. Pedersen were honored with the Nobel prize for their results in selective host-guest chemistry in the year 1987 [31–33]. Supramolecular chemistry may be defined as ‘chemistry beyond the molecule’, bearing on the organized entities of higher
complexity that result from the association of two or more chemical species held together by intermolecular forces.

Metal-ligand coordination is one of the most important interactions used in supramolecular chemistry. In this field, chelates derived from N-heteroaromatic ligands, largely based on 2,2′-bipyridine, 1,10-phenanthroline and 2,2′:6′,2″-terpyridine, have become an ever-expanding synthetic and structural frontier. The chemistry of 2,2′:6′,2″-terpyridines is much younger than those of 2,2′-bipyridines. In 1932, terpyridine was isolated for the first time by two scientists namely Morgan and Burstall [34,35]. They heated (340 °C) pyridine with anhydrous FeCl₃ in an autoclave (50 atm) for 36 h; the parent terpyridine was isolated along with a myriad of other N-containing products. The terpyridine ligand contains three nitrogen atoms and can therefore act as a tridentate ligand [36,37]. Two adjacent 5-membered MN₂C₂ type chelate rings are formed in case of 2,2′:6′,2″-terpyridine [38]. It has been comprehensively studied as an excellent complexing ligand for a variety of transition metal ions. Advances in the design and synthesis of tailored terpyridine derivatives are the main reason for continuously increasing potential applications. Considerable research has been dedicated to better understand and utilize terpyridine metal complexes with a wide variety of transition metals and lanthanides, in order to use their unique photophysical, electrochemical, magnetic, optical properties, biological activities and can stabilize metals in lower oxidation states as they are π-acceptors. Due to these characteristics, terpyridine–metal complexes have potential applications, such as dendrimers [39], micelles [40], metallo-supramolecular polymers [41], dyesensitized solar cells [42], photosensitizers [43], photocatalysis [44], luminescent chemosensors [45], light-emitting diodes [46], homogeneous assays [47], DNA-binding [48], antigen [49], anti-tumor [50], anti-microbial agents [51] and magnetic resonance imaging contrast agents [52]. Self-assembly of terpyridine–metal complexes on different surfaces [53] have promising roles in nanomolecular devices [54]. A remarkable application regarding novel supramolecular architectures is the creation of “mixed complexes”, where two differently functionalized terpyridine ligands are coordinated to a single transition metal ion [55,56]. The immobilization of terpyridines onto polymer
resins could prove to be of importance in fields such as catalysis [57]. In particular, the use of $2,2':6',2''$-terpyridines functionalized in the $4'$-position is of great interest in the above described fields [58,59].

1.3.2 Fluoroquinolone as antimicrobial agents

*History and classification*

Unlike some of the first antibiotics discovered during the past century, the quinolone class of antimicrobial agents was not isolated from living organisms but, rather, was synthesized by scientists. The prolific development of the quinolones began in 1962, when George Lesher and coworkers [60] made the accidental discovery of nalidixic acid as a by-product of the synthesis of the antimalarial compound, chloroquine. This discovery led to the development of a library of quinolone compounds. The majority of quinolones in clinical use belong to the subset fluoroquinolones, which have a fluorine atom attached to the central ring system, typically at the 6-position.

Out of more than 10000 analogues of fluoroquinolones synthesized [61–64] bearing variety of ring systems, only a few analogues have been established in the market. Such a tremendous growth of compounds in case of this group occurred mainly due to three factors;

1) Their unique mode of action depending on inhibition ability of susceptible micro-organisms to shape their DNA for storage or replication.
2) Their potency and antimicrobial spectrum being equally comparative to the desired fermentation based semi-synthetic antibiotics.
3) Their chemical structure being simple, a large number of analogues could be prepared by simple synthetic steps in a cheaper way from readily available intermediates or chemicals.

Quinolones include two main groups of drugs that differ in structure, activity, pharmacokinetics and spectrum of indications for use: 1) non-fluorinated quinolones (as 1st generation) and 2) fluoroquinolones (2nd, 3rd and 4th). The earlier-generation agents are, in general, more narrow-spectrum than the later ones. Researchers divide the quinolones into generations based on their antibacterial spectrum [65,66]. Differences in the *in vitro* activity of the
fluoroquinolones primarily form the basis of their classification, as shown in the Table 1.3.1.

**Table 1.3.1 Classification of fluoroquinolones**

<table>
<thead>
<tr>
<th>Generations</th>
<th>Veterinary</th>
</tr>
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<tbody>
<tr>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td>Cinoxacin</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>Rosoxacin</td>
<td>Enoxacin</td>
</tr>
<tr>
<td>Flumequine</td>
<td>Pefloxacin</td>
</tr>
<tr>
<td>Oxolinic acid</td>
<td>Fleroxacin</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Rufloxacin</td>
</tr>
<tr>
<td>Pipemidic acid</td>
<td>Norfloxacin</td>
</tr>
<tr>
<td>Piromidic acid</td>
<td>Nadifloxacin</td>
</tr>
<tr>
<td></td>
<td>Ciproflaxcin</td>
</tr>
</tbody>
</table>

**Structure-activity relationship [67,68]**

![Structure of the quinolone molecule](image)

**Figure 1.3.1:** Structure of the quinolone molecule using the accepted numbering scheme for positions on the molecule. R indicates possible sites for structural modification.

**Position 1:**
- This position is part of the enzyme–DNA binding complex and has a hydrophobic interaction with the major groove of DNA [69].
- A cyclopropyl substituent is considered as the most potent modification here.
Introduction of a t-butyl group at N-1 produced quinolones with enhanced activity against Gram positive bacteria with minor reduction of activity against Gram negative bacteria.

**Position 2:**
- This location is very close to the site for DNA gyrase (or topoisomerase IV) binding. The addition of bulky substituent inhibits access and results in a lower level of microbiological activity [70, 71]

**Positions 3 and 4:**
- These two positions on the quinolone nucleus are considered critical for binding to DNA which is cleaved or perturbed. Therefore, the 3-carboxylate and 4-carbonyl groups are essential for antimicrobial activity [70].

**Position 5:**
- Substituents at this position of the basic quinolone nucleus appear to have the capacity to alter overall steric configuration (planar structure) of the molecule, which is how changes here are thought to affect activity [69].
- Modestly size additions, such as an amino, hydroxyl or methyl group can markedly increase *in vitro* activity against Gram positive bacteria [71, 72].

**Position 6:**
- The addition of a fluorine atom at this position markedly improved antimicrobial activity compared to the original quinolones and gave rise to the widely used and clinically successful fluoroquinolones.
- Another group of agents with novel substituents are the 6-amino, 8-methyl quinolones, which have expanded activity against Gram positive cocci [73].

**Position 7:**
- This position is considered to be one that directly interacts with DNA gyrase [74] or topoisomerase IV. The optimal substituents at this position have been found to be groups that contain a 5- or 6-membered nitrogen heterocycle. The most common of these are aminopyrrolidines and piperazines.
- Placement of a piperazine generally enhances potency against Gram negative bacteria whereas, an aminopyrrolidine improves Gram positive activity. Alkylation (-CH$_3$) of the 5-membered or 6-membered heterocycle (pyrrolidine
and piperazines, respectively) also enhances activity against Gram positive bacteria [75, 76].

**Position 8:**
- This position is considered to affect overall molecular steric configuration, similar to position 5 [69]. Therefore, changes made at this position affect target affinity, probably by altering drug access to the enzyme or DNA binding sites.
- A free halogen (F or Cl) may improve activity against anaerobes [71]. A methyl or methoxy substituents also increase the *in vitro* activity against Gram positive cocci, even in those bacteria resistant to older fluoroquinolones [77].

**Mechanism of action**

Fluoroquinolones inhibit the replication and transcription of bacterial DNA, which eventually culminate in cell death [78, 79]. They either inhibit the activity of DNA gyrase, an essential adenosine triphosphate-hydrolyzing topoisomerase II enzyme or/and prevent the detachment of gyrase from DNA. The topoisomerases exert their bactericidal activity by interacting with the DNA [80].

![Figure 1.3.2: Mechanism of action of fluoroquinolone](image)

During the processes of replication and transcription, enzymes called helicases unwind/uncoil the DNA double helix leading to excess supercoiling of
the remaining DNA double helix. A tension is created in this remaining double helix which must be relieved in order to continue the process. The topoisomerase II enzyme allows the relaxation of supercoiled DNA by breaking both strands of DNA chain, crossing them over, and then resealing them.

Fluoroquinolones have also been found to inhibit the in vitro activities of topoisomerase IV, having structure similar to DNA gyrase [81]. This enzyme has an important role in partitioning of chromosomal DNA during bacterial cell division and may be the primary target of fluoroquinolone activity in Gram positive bacteria. The quinolones are used for the treatment of urinary tract infections, soft tissue infections, respiratory infections, bone-joint infections, typhoid fever, sexually transmitted diseases, prostatitis, community acquired pneumonia, acute bronchitis and sinusitis.

1.4 Copper

The Egyptians used the Ankh symbol to denote copper in their system of hieroglyphs. The Ankh was also the symbol of Eternal Life, which is appropriate for copper since it has been used continuously by people for 10,000 years. Homer, following the Greek practice of around 1000 B.C., called the metal Chalkos. This is why the Copper Age is also known as the Chalcolithic Era. A thousand years later during the Early Christian Era, the words "aes Cyprium" appeared in Roman writings about copper, because much of the metal at the time came from Cyprus. The word "copper" is an Anglicized term of this Latin phrase.

1.4.1 Biochemistry of copper

Copper is an essential trace element that is vital to the health of all living things (humans, plants, animals, and microorganisms). The human body contains copper at a level of about 1.4 to 2.1 mg per kg of body mass [82]. In humans, copper is essential to the proper functioning of organs and metabolic processes. The human body has complex homeostatic mechanisms, which try to ensure a continuous supply of available copper, while eliminating excess copper whenever this occurs. Being a transition metal, copper gets biologically converted between different redox states namely oxidized Cu(II) and reduced...
Cu(I). This unique attribute has made copper metal to get manifested as an important catalytic co-factor for a variety of metabolic reactions in biological systems. Copper is involved in various important processes like 1) the formation of red blood cells, 2) the absorption and utilization of iron, 3) the metabolism of cholesterol and glucose and 4) the synthesis and release of life-sustaining proteins and enzymes. These enzymes in turn produce cellular energy and regulate nerve transmission, blood clotting and oxygen transport. Copper is an essential trace element (i.e. micronutrient) that is required for plant, animal and human health. It is also required for the normal functioning of aerobic (oxygen-requiring) microorganisms. Copper is incorporated into a variety of proteins and metalloenzymes which perform essential metabolic functions; the micronutrient is necessary for the proper growth, development and maintenance of bone, connective tissue, brain, heart and many other body organs. Copper's essentiality was first discovered in 1928, when it was demonstrated that rats fed a copper-deficient milk diet were unable to produce sufficient red blood cells [83]. The anemia was corrected by the addition of copper-containing ash from vegetable or animal sources. Copper(II) ions are water-soluble, where they function at low concentration as bacteriostatic substances, fungicides and wood preservatives. Copper doorknobs are used by hospitals to reduce the transfer of disease and Legionnaires' disease is suppressed by copper tubing in plumbing systems [84]. Copper in the body normally undergoes enterohepatic circulation (about 5 mg a day, vs. about 1 mg per day absorbed in the diet and excreted from the body), and the body is able to excrete some excess copper, if needed, via bile, which carries some copper out of the liver that is not then reabsorbed by the intestine [85,86].

In normal mammalian cells, reactive oxygen species (ROS) are

![Figure 1.4.2: Metal SODs](image)
produced through metabolic reactions resulting from aerobic respiration. Low levels of ROS are essential for proper cell function and a fine balance exists between the level of ROS produced during normal cellular metabolism and the amount of endogenous antioxidants (such as ROS scavengers and enzymes) present in the cells which protect tissues from oxidative damage. If this balance is disrupted a condition referred to as oxidative stress develops which is implicated in numerous pathophysiological processes such as rheumatoid arthritis, aging, inflammation and carcinogenesis [87]. It has been found that ROS such as the superoxide radical ($O_2^{-}$) or hydrogen peroxide ($H_2O_2$) are important regulators of cell death [88]. Particularly, $H_2O_2$ is implicated as a mediator of apoptosis in cells [89]. The cellular damage caused by $H_2O_2$ is likely produced in part through OH$^-$ radical production. Enzymatic antioxidants regulate superoxide concentration by dismutation of $O_2^{-}$ to hydrogen peroxide (SOD activity) which is then converted to water (peroxidase activity) or dismutated to water and dioxygen (catalase activity).

Copper deficiency leads to osteoporosis, osteoarthritis, rheumatoid arthritis, cardiovascular disease, colon cancer, chronic conditions involving bone, connective tissue, heart, and blood vessels [90–92]. Copper deficiency plays an important role in diseases in which oxidant stress is elevated [93,94].

### 1.4.2 Copper diseases in heredity

Improper utilization of copper in the body leads to several genetic diseases like Wilson disease, Menkes disease.

**Wilson's disease:** The basic characteristic of Wilson's disease was first described in 1912 [95]. There is a massive accumulation of copper in the liver and brain due to the inability of Wilson's disease patients to transport copper out of the affected tissues via the blood protein ceruloplasmin or via biliary excretion [96]. The accumulation of the copper leads to pathological lesions especially in the liver and to nervous disorders (mild tremors).

**Menkes' disease:** Menkes’ disease was described first in 1962 [97]. It causes retarded growth with progressive neurological and vascular disturbances, pallid skin and brittle hair, often referred to as steely or kinky. Cerebral function is grossly affected and there is progressive brain degeneration [98].
1.4.3 Copper in medicine

The first recorded medical use of copper is found in the Smith Papyrus, one of the oldest books known. The Papyrus is an Egyptian medical text, written between 2600 and 2200 B.C., which records the use of copper to sterilize chest wounds and to sterilize drinking water. Other early reports of copper’s medicinal uses are found in the Ebers Papyrus, written around 1500 B.C. Copper bracelets were thought to be beneficial in treating arthritic conditions around 1000 B.C. [99]. During 460 to 380 B.C., copper is recommended for the treatment of leg ulcers associated with varicose veins. To prevent infection of fresh wounds, the Greeks sprinkled a dry powder composed of copper oxide and copper sulfate on the wound. Aztecs prescribed gargling with a mixture of ingredients containing copper for the treatment of "Faucium Calor" (sore throat) around 100 A.D. The first observation of copper’s role in the immune system was published in 1867 when it was reported that, during the cholera epidemics in Paris of 1832, 1849 and 1852, copper workers were immune to the disease. Copper arsenate had been used to treat acute and chronic diarrhea as well as dysentery and cholera.

1.4.4 Copper complexes in medicine

The first modern research on the subject of copper medicinal substances was by John R. J. Sorenson, who, in 1966, demonstrated that copper complexes have therapeutic efficacy in the treatment of inflammatory diseases using doses that are nontoxic [100]. Since then, copper metallo-organic complexes have been used successfully to treat patients with arthritic and other chronic degenerative diseases. Copper(II) complexes of non-steroidal anti-inflammatory agents (aspirin and ibuprofen, for example) have been shown to be more active than their parent compounds [101]. Copper aspirinate has been shown not only to be more effective in the treatment of rheumatoid arthritis than aspirin alone, but it has been shown to prevent or even cure the ulceration of the stomach often associated with aspirin therapy. Current interest in copper(II) complexes is stemming from their potential uses as antimicrobial, antiviral, anti-inflammatory, antitumor agents, enzyme inhibitors, or chemical nucleases. The biochemical action of copper(II) complexes with non-steroidal anti-inflammatory drugs (NSAIDs) has been studied [102]. Numerous copper(II)
complexes of NSAIDs showing enhanced anti-inflammatory and anti-ulcerogenic activity, as well as reduced gastrointestinal toxicity compared to the uncomplexed drug, have been prepared and structurally characterized [102]. The copper complexes are thought to operate either as transporters of copper to copper dependent enzymes at the site of inflammation, e.g. lysyl oxidase or superoxide dismutase or as biochemical agents in their own right [103]. Several studies have concentrated on the potential chemotherapeutic properties of copper-based compounds [104,105]. Much of the research interest has centered on the finding that many copper complexes demonstrate superoxide dismutase (SOD) activity. Because of this reason, lots of compounds have been designated as SOD-mimic compounds [106]. The antifungal and antibacterial properties of a range of copper(II) complexes have been evaluated against several pathogenic fungi and bacteria [106–109]. Copper(II) complexes with drugs are much more active in the presence of a nitrogen donor heterocyclic ligand, such as 2,2'-bipyridine (bipy), 1,10-phenanthroline (phen), 2,2'-dipyridylamine (bipyam) [110–112].

1.4.5 Copper toxicity

An excess of copper in the body leads to toxicity. Free copper causes toxicity, as it generates ROS such as superoxide, hydrogen peroxide, the hydroxyl radical. These damage proteins, lipids and DNA [113]. Vomiting, hematemesis (vomiting of blood), hypotension (low blood pressure), melena (black "tarry" feces), coma, jaundice (yellowish pigmentation of the skin), and gastrointestinal distress are the symptoms are copper poisoning [114]. The liver and kidneys can be damaged due to long term exposure of copper. Some of the effects of aging may be associated with excess copper [115]. Copper and Zinc are known to bind to amyloid beta proteins in Alzheimer's disease [116]. This bound form is thought to mediate the production of ROS in the brain [117].
1.5 Ruthenium

Sniadecki discovered element 44 in 1808 while working with platinum ores from South America. After he published his results, other chemists tried to find the element as well. They were unsuccessful. Sniadecki became discouraged, dropped his claims of discovery and did no further research on the element. About twenty years later, the discovery of element 44 was announced again. This time, the discoverer was Russian chemist Gottfried W. Osann. Once more, other chemists could not repeat Osann’s results. There was disagreement as to whether the element had been found. Finally, in 1844, Russian chemist Carl Ernst Claus (also known in Russian as Karl Karlovich Klaus; 1796–1864) gave positive proof of a new element in platinum ores.

1.5.1 Properties of ruthenium suited to biological applications

There are three main properties that make ruthenium compounds well suited to medicinal applications:

1) Rate of ligand exchange: Many ruthenium complexes have been evaluated for clinical applications, particularly in the treatment of cancer, due in part, to Ru(II) and Ru(III) complexes having similar ligand exchange kinetics to those of Pt(II) complexes. Ligand exchange is an important determinant of biological activity, as very few metal drugs reach the biological target without being modified.

2) The range of accessible oxidation states: Two main oxidation states are accessible for ruthenium species in physiological solution: Ru(II) (d^6, diamagnetic) and Ru(III) (d^5, paramagnetic). In both oxidation states, the Ru ion is six-coordinate with octahedral geometry (while Pt(II) is square planar) and, like Pt(II), has good affinity for nitrogen and sulfur ligands. In biological systems glutathione, ascorbate and single electron transfer proteins are able to reduce Ru(III) and Ru(IV), while molecular oxygen and cytochrome oxidase readily oxidise Ru(II).

3) The ability of ruthenium to mimic iron in binding to certain biological molecules: The low toxicity of ruthenium complexes is also believed to be due to
the ability of ruthenium to mimic iron in binding to many biomolecules, including serum transferrin and albumin. These two proteins are used by mammals to solubilise and transport iron, thereby reducing its toxicity.

1.5.2 Ruthenium complexes as anticancer agents

Although platinum complexes are now widely used for the treatment of cancer, the development of drug resistance, the toxic side-effects of cisplatin and the lack of activity of platinum compounds against several types of cancer are problems, which need to be overcome [118]. This provides the impetus for the search for anticancer activity amongst complexes of other metals such as ruthenium. Ruthenium complexes are very promising, especially from the viewpoint of overcoming cisplatin resistance with a low general toxicity.

The first ruthenium complexes to be investigated for their anticancer activity were chloro-ammine-Ru(III) compounds that can be thought as Ru analogs of chloro-ammine-Pt compounds. In 1980, Clarke and co-workers reported anticancer activity for fac-[RuCl₃(NH₃)₃] in murine models. This compound was not pursued much further since its poor solubility precludes it from adequate formulation as a drug [119,120]. Mestroni et al., studied the anticancer activity of a well-known cis-[RuCl₂(dmso)₄] in comparison with that of cisplatin in 1980 [121,122]. In 1988, the Ru(II) complex trans-[RuCl₂(dmso)₄] was shown to be more active than the cis-[RuCl₂(dmso)₄] against Lewis lung carcinoma, a metastasizing murine tumor. Even though cisplatin was more active in reducing the primary tumor, trans-[RuCl₂(dmso)₄] demonstrated a more selective activity against metastases.

The group of Keppler demonstrated that two isostructural Ru(III) complexes [ImH]trans-[RuCl₄(Im)₂] (Im = imidazole) and [IndH]trans-[RuCl₄(Ind)₂](Ind = indazole) were active against a number of tumor models and, in particular, showed excellent activity against platinum-resistant colorectal autochthonous tumors [123]. These results clearly supported the basic premise of this field, i.e. non-platinum active complexes can be effective against platinum resistant tumors. [Na]trans-[RuCl₄(Im)(dmso-S)] (NAMI) is specifically active against solid metastasizing tumors in mice [124–126]. After some time, NAMI was replaced in pre-clinical experimentation by its imidazolium salt,
[ImH]trans-[RuCl₄(Im)(dmso-S)], called NAMI-A. It is capable of effectively inhibiting the development and growth of pulmonary metastases in all experimental models of solid tumors tested in vivo, including the non-small cell lung cancer human tumor xenografted in the nude mouse.

1.6 Deoxyribonucleic acid (DNA)

1.6.1 Structure of DNA

The structure of DNA is a double-helix polymer, a spiral consisting of two DNA strands wound around each other (Figure 1.6.1). Each strand is composed of a long chain of monomer nucleotides. DNA molecule is made up of 2 polynucleotide chains arranged on the double helix (the backbone). These nucleotides are composed of three parts: a phosphate, a sugar (deoxyribose) and a type of compound base. The DNA double helix is stabilized primarily by two forces: hydrogen bonds between nucleotides and base-stacking interactions among the aromatic nucleobases [127].

Figure 1.6.1: Simplified view of how the DNA organized in the chromosome.

Figure 1.6.2: Nucleotide composed of phosphate, a sugar molecule and base.
The information in DNA is made up of four bases which combine to form chains. These bases include two purines (Adenine and Guanine) and two pyrimidines (Cytosine and Thymine). These are commonly referred to as A, G, C and T respectively. Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people. It is the order, or sequence, of these bases which determines genetic characteristics.

Each base is attached to a sugar (S) molecule and a phosphate (P) molecule. The structure of double helix is somewhat like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming vertical side pieces of the ladder.

The number of purine bases in DNA is equal to the number of pyrimidines. This is due to the law of complimentary base pairing; which is thymine (T) can only pair with adenine (A) and guanine (G) can only pair with cytosine (C). Knowing this rule, we could predict the base sequence of one DNA strand if we knew the sequence of bases in the complimentary strand.

The backbone of the DNA strand is made from alternating phosphate and sugar residues. The sugar in DNA is 2-deoxyribose, which is a pentose (five-carbon) sugar. The sugars are joined together by phosphate groups that form phosphodiester bonds between the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean a strand of DNA has a direction.
double helix, the direction of the nucleotides in one strand is opposite to their 
direction in the other strand: the strands are antiparallel. The asymmetric ends 
of DNA strands are called the 5′ (five prime) and 3′ (three prime) ends, with the 5′ 
end having a terminal phosphate group and the 3′ end having a terminal 
hydroxyl group. One major difference between DNA and RNA is the sugar, with 
the 2-deoxyribose in DNA being replaced by the alternative pentose sugar ribose 
in RNA. The DNA double helix is stabilized primarily by two forces: hydrogen 
bonds between nucleotides and base-stacking interactions among the aromatic 
nucleobases. The structure of DNA of all species comprises two helical chains 
each coiled round the same axis, and each with a pitch of 34 Ångstroms 
(3.4 nanometres) and a radius of 10 Ångstroms (1.0 nanometres).

Twin helical strands form the backbone of DNA. Another double helix may 
be found due to the spaces or grooves formed between the strands. These spaces 
are adjacent to the base pairs and may provide a binding site. The grooves are 
unequally sized because the strands are not directly opposite to each other. The 
major groove is 22 Å wide and the minor groove is 12 Å wide [128]. The 
narrowness of the minor groove means that the edges of the bases are more 
accessible in the major groove.

![Diagram of DNA helix with major and minor grooves](image)

**Figure 1.6.5:** Structure of major groove and minor groove.
The minor groove occurs where the backbones are close together while the major groove occurs where the backbones are far apart. In case of major groove, the nitrogen and oxygen atoms of the base pairs pointing inward to the helical axis. In case of the minor groove, the nitrogen and oxygen atoms point outwards from the helical axis. The minor groove is narrow and shallow whereas the major groove is deep and wide. DNA-protein interactions are major/essential processes in the cell life (transcription activation or repression, DNA replication and repair). Proteins bind at the floor of the DNA grooves, using specific binding: hydrogen bonds, and non specific binding: van der Waals interactions, generalized electrostatic interactions. Some proteins bind DNA in its major groove, some other in the minor groove, and some need to bind to both.

1.6.2 Binding modes

There are various ways by which molecules can interact with DNA. Molecules may interact with DNA by various modes like covalent binding, groove binding, electrostatic binding and intercalation [129].

1) Covalent binding: The labile ligands such as aqua, halides etc. are replaced by covalent bond with nitrogen base of the DNA. Covalent binding in DNA is irreversible and invariably leads to complete inhibition of DNA processes and subsequent cell death. Cis-platin (cis-diamminedichloroplatinum) is a famous covalent binder used as an anticancer drug, and makes an intra/interstrand cross-link via the chloro groups with the nitrogens on the DNA bases.

2) Groove binding: There are two types of groove binding:

a) Minor groove binding: Minor groove binders are typically long elongated structures with a curvature that fits the curvature of the minor groove. The ligand is fitted between the narrow walls of the groove and stabilized via hydrogen bonds and van der waals interactions. The minor groove also has a certain flexibility to accommodate the ligands that do not have a perfect fit.

b) Major groove binding: Major groove binders utilize the numerous possibilities for specific hydrogen bonds with donors and acceptors on the nucleic bases providing the basis for both complex stabilization and sequence specificity [130]. Many proteins bind to DNA in the major groove.
3) **Electrostatic binding:** External or electrostatic binding occurs when cationic molecules or cations are attracted to the anionic surface of DNA. Charged metal complexes and ions such as Na\(^+\) can bind electrostatically with DNA by forming hydrogen bonds or ionic bonds along the outer surface of DNA double helix [131].

4) **Intercalation:** Intercalation occurs when ligands of an appropriate size and chemical nature fit themselves in between the base pairs of DNA. These ligands are mostly polycyclic, aromatic and planar. These properties allow intercalators to insert and stack in between base pairs in the hydrophobic interior of helical double stranded DNA. There are two types of intercalative modes: 1) Classical intercalation and 2) Partial intercalation.

1.7 **Literature survey**

1.7.1 **Literature survey of copper-fluoroquinolone complexes**

Metal ions play a crucial role in the actions of natural and a number of synthetic antibiotics. Metal ions are engaged in specific interactions of the antibiotics with proteins, nucleic acids and other bio-molecules [132]. It seems that the role of metal ions is vital for the way of function of fluoroquinolones. It was suggested that the reactions of metal ions with fluoroquinolones were necessary for the activity of the antimicrobial agents, and the metal ions (magnesium, copper, and iron) may bridge the binding of the quinolone to DNA gyrase or of bacterial DNA directly [133,134]. Shen et al., proposed a cooperative quinolone–DNA binding model mediated by Cu\(^{2+}\) for the inhibition of DNA gyrase [135]. Ming classified quinolones as “metalloantibiotics” because of the facts that some of metal–quinolone complexes interact with DNA and impair its function [136]. Yukinori et al., Turel et al., and Lee et al., have reported that quinolones can bind several divalent metal ions, including Mg\(^{2+}\), Ca\(^{2+}\), Mn\(^{2+}\), Fe\(^{2+/3+}\), Co\(^{2+}\), Ni\(^{2+}\), Cu\(^{2+}\), Zn\(^{2+}\), Cd\(^{2+}\) and Al\(^{2+}\), which may result in changes in their activity [137–139]. Okhamafe et al., reported that the antibacterial activities of fluoroquinolones were altered in the presence of divalent cations [140]. Mixed ligand complexes of copper with nalidixic acid and cinoxacin have been synthesized and characterised by Mendoza-Diaz et al., [141,142]. Turel et al., synthesized and characterized copper(II)–ciprofloxacin complexes i.e. [Cu(cf)(H\(_2\)O)\(_3\)]SO\(_4\)•2H\(_2\)O
and $[\text{Cu(CF)}_2\text{Cl}_2\cdot6\text{H}_2\text{O}]$ [143,144]. The interaction of cobalt(II), nickel(II), copper(II) and zinc(II) with cinoxacin has been studied by Ruiz et al. [145,146]. Mixed ligand complexes of Cu(I) with norfloxacin and triphenyl phosphine have been synthesized and characterized by Chen et al. [147]. Macias et al., reported a crystal structure of a new Cu(II)–ofloxacin complex [148]. Drevensek et al., synthesized the first known mixed-valance Cu(II)–Cu(I) complex with Cf[Cu^{II}[\text{Cf}]_2(Cu^{I}\text{Cl}_2)] [149]. Wallis et al., determined protonation constants of norfloxacin and ciprofloxacin and the formation constants with copper(II) by potentiometric titrations at 25°C [150]. Kokot and Urbaniak analyzed the factors which significantly influence the stability of fluoroquinolone–metal complexes [151]. Spectroscopic and X-ray absorption characterization of Cu(II) and Zn(II) complexes with a fluoroquinolone antibiotic (flumequine) have been reported by Perez-Guaita et al., [152]. Tabassum et al., investigated the binding of the bisciprofloxacin borate copper(II) complex with CT DNA and proposed intercalative binding with DNA [153]. Sousa et al., showed that the ternary copper(II)–levofloxacin complex has an antimicrobial effect comparable to that of the free levofloxacin [154]. Ftouni et al., carried out the structural study of the copper(II)–enrofloxacin metallo-antibiotic [155]. Hernández-Gil et al., reported that ternary complexes of copper(II) with ciprofloxacin and 1,10 phenanthroline behave as efficient chemical nucleases in the presence of ascorbate [156]. P. Ruiz et al., synthesized binary and ternary complexes of copper(II) with norfloxacin and 1,10 phenanthroline and also studied the ability of compounds to cleave DNA [157]. The $[\text{Cu(Nor)}_2(\text{H}_2\text{O})_2]\text{SO}_4\cdot5\text{H}_2\text{O}$ complex has been synthesized by Refat and during biological investigation, he found that complexes showed moderate activity against the Gram positive and Gram negative bacteria as well as against fungi [158]. Efthimiadou et al., studied the interaction of the copper–enrofloxacin complexes with CT DNA with diverse spectroscopic techniques and showed that all complexes are bound to DNA by the intercalative mode [159]. Saha et al., reported that $[\text{Cu(BF}_4)_2]\cdot6\text{H}_2\text{O}$ exhibited a significant enhancement in the antitubercular activity which is detrimental to the mycobacteria [160]. Wang et al., synthesized novel quaternary copper(II) complex with ciprofloxacin i.e. $[\text{Cu}_2[\text{cip}]_4(\text{bpy})_2(\text{pip})]\cdot6\text{H}_2\text{O}$ and reported that complex showed the same minimal inhibitory concentration (MIC) against $S.\text{Aureus}$ and $E.\text{Coli}$ bacteria as
the corresponding ligand [161]. Mendoza-Diaz et al., reported crystal structure of Cu(II) mixed compound with histamine and nalidixic acid [162]. Cu(II) complexes with enoxacin and ciprofloxacin were synthesized and the crystal structures were reported by Yu et al. [163]. Solution behavior of enrofloxacin complexes with Cu(II), Ni(II), Co(II) and Zn(II) in the presence and absence of 1,10-phenanthroline in aqueous solution has been studied by Saraiva et al. [164]. Biological evaluation of Co(II), Mn(II) and Cu(II) complexes of fluoroquinolones against T. cruzi was carried out by Batista et al. [165]. Valtierra et al., reported that Cu²⁺ ion play a significant role in the mode of action of fluoroquinolones [166]. Ferreira et al., studied the interaction of moxifloxacin with Cu(II) ion using square-wave voltammetry and also reported its application in the determination in tablets [167]. The influence of Cu(II) and Mg(II) on the binding of ciprofloxacin to DNA have been studied by Ulrich et al. [168]. They found that the Mg²⁺ ions were directly involved in ciprofloxacin binding to DNA via phosphate oxygen, and the Cu(II) interaction with the N(7) position of purine bases has been proposed. An experimental charge density study of a complex between copper(II) and ciprofloxacin i.e. [Cu(cfx)(H₂O)₃]SO₄•2H₂O using single crystal X-ray diffraction data has been performed by Overgaard et al. [169]. The mononuclear copper(II) complex with the quinolone antibacterial drug, N-propyl-protected norfloxacin (Hpr-norfloxacin) and 2,2'-bipyridine has been synthesized and characterized by Efthimiadou et al. [170]. They found that complex was bound with CT DNA by the intercalative mode.

1.7.2 Literature survey of ruthenium complexes

In the past two decades ruthenium coordination compounds have attracted considerable interest as potential anticancer agents because of their low toxicity and their efficacy against platinum-drug-resistant tumors, reflected in promising results in various stages of preclinical to early clinical studies. [171–176] First ruthenium organometallic complex of antibacterial agent ofloxacin has been synthesized and characterized by Turel et al. [177]. Thermal analysis of ruthenium– nalidixic acid complexes has been carried out by Sekhon et al. [178]. M. Cui et al., proposed a direct chemiluminescence method for the determination of prulifloxacin using tris-(4,7-diphenyl-1,10-
phenanthroline disulfonic acid) ruthenium(II)–cerium(IV) system [179]. Turel et al., synthesized ruthenium η⁶-p-cymene complexes with quinolones and also studied their tumor inhibiting potential in a cancer cell line panel [180]. Thermal degradation behavior of ruthenium complexes with enrofloxacin, ciprofloxacin and norfloxacin has been studied by Badea et al. [181]. McDonnell et al., proposed that dinuclear complexes comprising ruthenium polypyridyl centres linked by a bis(pyridylimine) bound to DNA via external electrostatic interactions [182]. Ratanaphan et al., concluded from their study that the influence of the polypyridyl intercalative ligands plays an important role in the DNA-binding affinity of ruthenium(II) complexes [183]. Thermal study of ruthenium(III) complexes with oxolinic acid, pipemidic acid, enoxacin and levofloxacin has been performed by Badea et al. [184]. Thermodynamics of binding of the two isomers to CT DNA has been studied by Xu et al., using isothermal titration calorimetry [185]. Two new ligands APIP, HAPIP and their relative ruthenium(II) complexes i.e. [Ru(bpy)₂(APIP)][ClO₄]₂ and [Ru(bpy)₂(HAPIP)][ClO₄]₂ have been synthesized and characterized by Liu et al. [186]. They suggested that ruthenium complexes intercalate between the base pairs of DNA. Kuwabara et al., demonstrated that the DNA-binding mode of the drug can be evaluated easily by utilizing the electrochemiluminescence of [Ru(phen)₂]⁺³ [187]. Huang et al., explored antioxidant activity of the DNPIP, DAPIP and relative ruthenium complexes and concluded that complexes may behave as potential drugs due to their high antioxidant activity [188]. Marian et al., reported that heterocyclic complexes of ruthenium(III) induce apoptosis in colorectal carcinoma cells [189]. Natarajan et al., screened antifungal activity of the ligand and their ruthenium(III) complexes against the pathogenic fungi A. niger, F. oxysporium and R. solani by the disc diffusion technique. From the studies, they concluded that the complexes possess more toxicity than their parent ligands [190]. Beckford et al., studied the biophysical characteristics of the ruthenium–thiosemicarbazone complexes by investigating their anti-oxidant ability as well as their ability to disrupt the function of the human topoisomerase II enzyme [191]. Snelders et al., observed that despite of forming strong interactions with DNA, ruthenium(II) arene complexes exhibit only modest cytotoxicities on the human ovarian cancer cell lines A2780 and A2780cisR
Jiang investigated binding behaviors of the mono- and dinuclear ruthenium–bipyridine complexes with CT DNA by absorption spectra, viscosity measurements and equilibrium dialysis experiments. The results indicated that either of the complexes bound to DNA via a non-intercalating mode [193]. Satyanarayana et al., concluded from the inhibitor studies that singlet oxygen plays a significant role in the cleavage mechanism for the polypyrindyl ruthenium(II) complexes [194]. Interaction of ruthenium–bisterpyridine complexes i.e. [Ru(tpy)2](PF6)2 and [Ru(Bitpy)2](PF6)2 with CT DNA have been studied by Sathyaraj et al., using absorption and CD spectra [195]. Vagg and Barnard observed that some of the ruthenium(II) complexes demonstrate an ability to bind to DNA, that is consistent with intercalation of the bidentate molecular component between the base pairs of the DNA molecule [196]. Huang et al., demonstrate that superoxide anion radical (O2•−) and singlet oxygen (1O2) may play an important role in the photocleavage of DNA [197]. Experimental results obtained by Bai et al., indicated that the two complexes bound to CT DNA through an intercalative mode and [Ru(bpy)2(HCIP)]2+ intercalates into DNA more deeply than [Ru(bpy)2(CAIP)]2+ does [198]. The oxidation of DNA by complexes of trans-dioxoruthenium(VI) has been investigated by Thorp And Goll [199]. Musatkina et al., synthesized and characterized mono- and dicarboxylic polypyridylic–Ru complexes as potential transfection agents [200]. pH- and DNA-induced dual molecular light switches based on a novel ruthenium(II) complex has been synthesized by Chen et al.[201]. Srivastava et al., showed that the radiophysical properties of 97Ru can be applied to radio diagnostic imaging [202,203]. Armitage concluded that compounds such as polyazaaromatic ruthenium(II) complexes are good candidates as photosensitizers, with properties that can be modulated by introducing changes in the ligands [204]. Han et al., performed molecular modeling study on the binding mode of polypyridydl ruthenium complexes with B-DNA [205]. Oliveira et al., developed a new nitrosyl ruthenium complex [Ru(NH•NHq)(terpy)NO]3+, which has been considered as a potential drug candidate due to its excellent vasodilator activity [206]. Tan et al., observed that [Ru(phen)2(NMIP)]2+ has also been found to promote cleavage of plasmid pBR 322 DNA from the supercoiled Form I to the open circular Form II upon irradiation [207]. Gaur et al., revealed
that upon molecular docking of the complex with DNA sequence d(ACCGACGTCGGT)_2, complex is stabilized by additional electrostatic and hydrogen bonding interaction with DNA besides probable displacement of a labile DMSO by the N7 of guanine [208].

1.8 Rational

The interaction and reaction of metal complexes with DNA has long been the subject of intense investigation in relation to the development of new reagents for biotechnology and medicine. Studies of small molecules, which react at specific sites along a DNA strand as reactive models for protein–nucleic acid interactions, provide routes toward rational drug design as well as means to develop sensitive chemical probes for DNA. A number of metal chelates have been used as probes of DNA structure in solution, as agents for mediation of strand scission of duplex DNA and as chemotherapeutic agents. Over the past decade, there has been substantial interest in the design and study of DNA binding properties of potential redox and spectroscopically active Cu(II/I) and Ru(II/III) complexes as new chemical nucleases.

It is well known that trace amounts of copper are essential for life and that an excess of this element has toxic effects (Wilson disease). Therefore it is necessary to know the specific mechanisms for copper to be available in order to prevent its accumulation or deficiency. In living organisms, copper forms complex compounds, involving either small molecules or proteins, which behave as carrier-transport molecules. The studies of the binding properties and the nature of the binding site have become an area of research interest. In addition, some copper(II) complexes containing similar ligands where found to have a variety of pharmacological and biological activities which encompass antiarthritis and antimicrobial, among others.

The compounds of transition elements of the platinum group hold promise in the design of new anti-cancer agents. However, in common with many other cytotoxic drugs, cis-platin induces normal tissue toxicity particularly to the kidney. Therefore, alternative metal compounds are presently being evaluated in clinical trials. One of the most promising metal is ruthenium. Ruthenium compounds are regarded as promising alternatives to platinum
compounds and offer many approaches to innovative metalopharmaceuticals. The compounds are known to be stable and to have predictable structures both in the solid state and in solution: tuning of ligand affinities accompanied by a steadily increasing knowledge of the biological effects of ruthenium compounds.

Because of the above importance, we have planned to synthesis drug based Cu(II), Ru(II) and Ru(III) complexes and performed their diverse biological activities like antimicrobial, DNA interaction, cytotoxic and SOD-like activity.

1.9 Objectives of research work:

- Synthesis of 4’–substituted–2,2′:6′,2″–terpyridines and their characterization using analytical and spectroscopic methods.
- Synthesis of mononuclear octahedral drug based copper(II) complexes with tridentate ligands, and their characterization using analytical and spectroscopic methods.
- Synthesis of mononuclear octahedral drug based ruthenium(II) and ruthenium(III) complexes, and their characterization using analytical and spectroscopic methods.
- Determination of in vitro antimicrobial activity of copper(II), ruthenium(II) and ruthenium(III) complexes in terms of MIC and CFU/mL.
- To check binding behaviour of copper(II), ruthenium(II) and ruthenium(III) complexes with Herring Sperm (HS) DNA.
- To determine DNA cleavage ability of copper(II), ruthenium(II) and ruthenium(III) complexes.
- Cytotoxic study of the copper(II), ruthenium(II) and ruthenium(III) complexes to find out LC50 values.
- SOD mimic activity study of copper(II) complexes in terms of IC50 values.
1.10 Outline of the thesis

Synthesis, characterization and biological studies of Cu(II), Ru(II) and Ru(III) complexes

Norfloxacin/Sparfloxacin
Terpyridines (L1–L14)
CuCl₂•2H₂O

Fluoroquinolones
PPh₃
RuCl₃•3H₂O

Cu(II) complexes
Ru(II) & Ru(III) complexes

Elemental analysis
Magnetic measurement
UV-Vis., IR and LC-MS

Nature: Neutral
Geometry: Octahedral

Applications

Antibacterial
DNA binding
DNA cleavage
Cytotoxicity
SOD mimic

MIC = 0.2-5.1 μM
CFU=30-300 Colonies

Intercalation
K₅ₐ = 3.68 × 10³ – 9.60 × 10⁴ M⁻¹

% Cleavage
55.68-83.14%

LC₅₀
4.01-11.96 μM

IC₅₀
0.552-1.848 μM

Antibacterial
DNA binding
DNA cleavage
Cytotoxicity

MIC = 0.6-5.7 μM
CFU=30-300 Colonies

Partial Intercalation
K₅ₐ = 7.78 × 10³ – 2.70 × 10⁵ M⁻¹

% Cleavage
54.65-73.56%

LC₅₀
6.27-16.05 μM
1.11 References


