histones, transcription factors and HMG-domain proteins[3-5]. The binding of HMG protein to cisplatin-DNA adduct has been suggested to enhance anticancer effect of the drug[6, 7]. Besides the effectiveness of cisplatin against cancer, it has encountered many side effects. Drugs like cisplatin does not specifically affect cancer cells but it also affect the rapidly dividing cells of certain normal tissues, such as those found in hair follicles, bone marrow and the lining of the gastrointestinal tract. Inside the cell it interacts with a number of other negatively charged bio molecules besides DNA such as proteins, sulphur-containing compounds like metallothioneins and glutathiones that sequester heavy metals like Pt and remove it from the cell. Pt(II) and Pt(IV) complexes are photo reactive. Irradiation of cis-platin modified DNA with UV light can induce cross-links with the protein HMG,which can inhibit RNA transcription[8-10]. Like many other anticancer drugs, cisplatin also faces the same problem called "Drug Resistance". It is a major complication in cancer chemotherapy since due to a decrease in intercellular accumulation of cisplatin, it cannot form adduct with DNA[11-13]. Organometallic compounds like Iron (III)-salophene with selective cytotoxic and antiproliferative properties have been used in platinum resistant ovarian cancer cells[14]. Different strategies have been used to improve efficacy of cisplatin like use of nanotechnology to specify the effect of the drug in the target cells[15]. Pt(II) complexes have been conjugated to molecules like porphyrin ring. The porphyrin enhances the tumor tissue specificity of the Pt(II) complexes. Porphyrins are used as photodynamic therapeutic agents and can offer additional antitumor activity by photo-induced mechanism[16]. The clinical use of cisplatin is limited because of the toxicity to the normal cells and drug resistance, therefore, new platinum based anticancer drugs has also been synthesized such as carboplatin, oxaplatin, nedaplatin *etc.*, Other drugs being developed that have slower hydrolysis rate than cisplatin, are longer acting and require more infrequent doses. One such drug is 2- pincoline Pt complex, which is active by injection and oral administration. Platinum complexes with distinctively different DNA binding modes from cisplatin may provide higher antitumor activity against cisplatin resistant cells. The trans isomer of diamminedichloroPt(II) has also been studied and trans DDP offers a different attachment mode with DNA and is used as anticancer drug for cisplatin resistant cancer cells. A series of trans piperazine compounds were reported to have significant cytotoxicity against cisplatin resistant cells[17]. Pt(II) complexes with thiourea have showed anti-cancer activity against leukemia cell lines[18]. Pt(II) has also been complexed with estrogen hormone and used

as anticancer agent for the treatment of hormone dependent cancer like breast cancer[19].

1.1.2. Non-platinum anticancer agents

Platinum is not the only transition metal used in the treatment of cancer, various other transition metals have been used in anticancer drugs[20]. Titanium complexes such as titanocene dichloride has been recognized as active anticancer drug against breast and gastrointestinal carcinomas. Gold complexes also show anti-cancer activity, these complexes act through a different mechanism as compared to cisplatin. The target site of Au complexes is mitochondria not DNA. Certain gold complexes with aromatic bipyridyl ligands have shown cytotoxicity against cancer cells[21]. The 2-[(dimethylamino) methyl] phenyl gold(III) complex has also proven to be anti-tumor agent against human cancers[22]. Gold nanoparticles when used in combination with radio therapy or chemotherapy enhance DNA damage and make the treatment target specific[23]. Lanthanum has also been used to treat various forms of cancer[24]. **Ansari *et al.,*** in 2009 reported on some complexes of Mn(III) to induce tumor selective apoptosis of human cells. Many ruthenium complexes were studied which showed anti-proliferative effects in human ovarian cancers. Ruthenium complexes with oxidation state +2 or +3 show antitumor activity against metastasis cancers. Ruthenocene derivatives act as an anti estrogen. The relative binding of ruthenocene derivatives were very high and even better than hydroxyl tamoxifen which is a novel antagonist for estrogen[25]. Ruthenocene complexes with aromatic ligands represent a relatively new group of compounds with antitumor activity. Ru(III) imidazole and Ru (III) indazole exhibit anti cancer properties. **Galanski *et al.,*** studied the anticancer properties of Ru(III) arene complexes[26]. Ruthenocene-cymene complexes have shown to damage DNA by forming monofunctional adducts selectively with guanine bases[27]. Ruthenocene complexes show antiproliferative effect on the MCF-7 (ER-positive) breast cancer cell lines. Many ruthenium complexes exhibit anti-estrogen properties similar to that observed for novel anti-estrogen tamoxifen[28]. Complexes of transition metals like iron have shown remarkable anti-proliferative properties[29]. The ferrocene derivatives with hydroxyl group in phenyl ring have high affinity for estrogen receptor. Many organometallic analogues of tamoxifen are used as a vehicle for introducing other cytotoxic agents to the cancer cells[30]. Normally, cancers are diagnosed at a stage of the disease, when some anatomical changes occur in the body in the form of well defined tumors. These

masses can be removed by surgery however this therapy is not suitable for treatment of small or hidden tumors. Nanotechnology offers potential solutions to this problem for the treatment of various types of cancers. **Hirsch *et al.,*** used silica gold nanoshell technology for thermal ablative therapy of cancer. Metal nanoshells are a class of nanoparticles with tunable optical resonances that has highly favorable optical and chemical properties for biomedical imaging and therapeutic applications. Nanoshells absorb light in the near infrared which can be used to deliver a therapeutic dose of heat by using moderately low exposures of extra corporeally applied near-infrared (NIR) light. It has been reported by **Asharani *et al.,*** that silver nanoparticles exhibit anti- proliferative activity. **Loo *et al.,*** described several examples of nanoshell-based diagnostic and therapeutic approaches including the development of nanoshell bioconjugates for molecular imaging. Mercaptopurines are well known anti-leukemic drugs but their use has been hampered by their short half life. This problem has been overcome by the use of gold nanoparticles in combination with mercaptopurines. Conjugation therapy of 6-mercaptopurine with gold nano particles not only enhanced its anti-leukemic and anti-inflammatory activity but also reduced the quantity of dose and side effects of the drug[31].

1.2. Transition metal complexes in other therapeutic uses

Transition metals like silver have been used for years as antimicrobial agents. Silver has low toxicity as compared to other transition metals. Silver nitrate is still given to the infants to prevent the development of opthalmia neonatorum. One of the most commonly used compounds of silver is silver(I) sulfazine; it is used to treat severe burns to prevent them from bacterial infections. Chlorohexidine-silver sulfadiazine is an anti infective metal complex against catheter infections *in vivo*[32]. Organometallic complexes of Pt, Rh, Ir, Pd, and Os with active organic molecules have been reported to exhibit trypanocidal activity[33]. An increasing amount of data showing the beneficial use of zinc in treating diarrhea continues to emerge from epidemiological and clinical trials. **Fukushima *et al.,*** also studied the role of zinc in the maintenance of hemodialysis patients. Nitrogen containing macrocyclic complexes of manganese(II) have shown antimicrobial activity. An octahedral geometry for these complexes has been confirmed by spectroscopic analysis. Many manganese complexes have been screened against a number of pathogenic fungi and bacteria to evaluate their growth and potential[34]. Metal complexes of Pt(II) and Ru(II) with o-Vanillin-(4-methylthiosemicarbazone) and o-Vanillin-(4-phenylthiosemi

carbazone) have been prepared, characterized by chemical methods and evaluated for anti-bacterial, anti-fungal, anti-amoebidal activity and have been proven more efficient anti-infective agents[35]. Transition metals have also been proved useful in the treatment of malaria. One strain plasmodium falciparum has become resistant to major antimalarial drugs such as quinolines. Metal complexes of Ga(III), Al(III) and Fe(III) were found to be active against malaria. Metal complexes of o-Vanillin-(4-methyl thiosemicarbazone) and o-Vanillin-(4-phenylthiosemicarbazone) exhibited anti-malarial activity in mice infected with plasmodium berghei indicating that cures were attainable at dose levels upto 60 mg/kg but with toxic death prevalence at higher doses.

1.3. Transition metal complexes as anti-inflammatory agents and free radical quenchers

Transition metals have also been used as anti-inflammatory and anti-arthritic agents. Several injectable transition gold complexes like sodium aurothiomalate, aurothioglucose and sodium aurothiopropanol are used clinically in the treatment of severe cases of rheumatoid arthritis. Gold and silver nanoparticles conjugated with heparin derivative possess antiangiogenesis properties. Silver nanoparticles are used in the development of an antimicrobial gel formulation for topical use. Gold has been used in the treatment of peripheral psoriatic arthropathy[36]. As a product of oxygen metabolism, superoxide anion can trigger oxidative injury to tissues. This activity has been suggested to be associated with riper fusion and inflammatory diseases as well as neurological disorders such as Parkinson disease and Alzheimer disease. In living systems, a natural defense system against superoxide mediated oxidative damages involves SODs, enzymes that catalysis the conversion of superoxide into oxygen and hydrogen peroxide. Metallic gold treatment reduces proliferation of inflammatory cells in brain injury. There are some side effects of anti-arthritic therapy using Au(I), mostly when it is oxidized to Au(III) by some of the potentially strong oxidants such as H_2O_2 available in inflammatory situations. Excessive use of gold complexes for the treatment of juvenile rheumatoid arthritis and osteoarthritis causes pain and fever. Among cutaneous symptoms intolerance was measured at low frequency, wider use of gold salts like gold salicylates and gold pyrazolone derivatives cause urticaria and angioedema. Tolfenamic acid and its metal complexes has been studied as anti-inflammatory, anti-proliferative and radical-scavenging agents. Among transition metals, complexes of copper and iron are capable of catalyzing dismutation of the

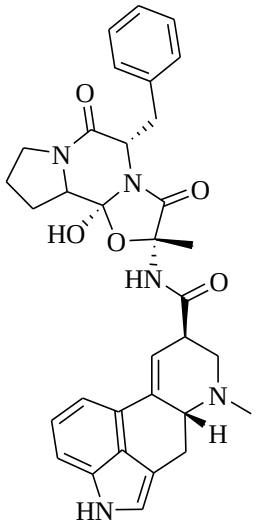
superoxide anion. In addition, Mn(II) complexes does not bind to NO and react slowly with H_2O_2, demonstrating specificity towards superoxide anion. Interaction of SOD mimics with NO and H_2O_2 levels, both of which can cause high blood pressure and weaken the immune system. NO are an excellent ligand for transition metal ions and these metal nitrosyls having therapeutic values. Sodium nitroprusside is used clinically to treat cardiovascular diseases by releasing NO but CN^- toxicity limits its application, however, discovery of new ruthenium nitrosyl complexes offer promising biological applications[37]. Over production of NO contributes to various diseases like sepsis, arthiritis, diabetes and epilepsy. Ruthenium polyaminocarboxylate complexes are efficient NO scavengers.

Many human diseases are associated with the over production of oxygen free radicals that inflict cell damage. Mn(II) complex with bis(cyclohexylpyridine) substituted macrocyclic ligand has been designed as a functional mimic of the superoxide dismutase (SOD) enzymes that normally remove these radicals. Manganese complexes have also been used to treat cell and tissue oxidative injuries by acting as superoxide anion scavenger. Magnesium is used for the treatment of asthema in children. Some Cu complexes are also active against inflammation but their use is limited. Cu(II) complexes tend to dissociate and bind to natural ligands such as albumins[38]. Zinc has been proved to be involved in the inhibition of pro inflammatory cytokines.

1.4. Biological importance of heterocyclic compounds

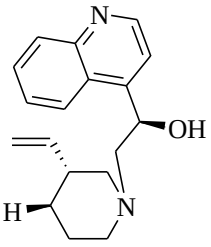
Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements. The non-carbon atoms in such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur and oxygen. The heterocyclic compounds having lesser common atoms such phosphorus, tin, boron, silicon, bromine, *etc.*, have been a subject of much investigation in recent years. The heterocyclic compounds having three to six carbons in the ring are numerous, but only those having five or six atoms in the ring are by far the most important. Heterocycles are an important class of compounds, making up more than half of all known organic compounds. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal and insecticidal agents. Also, they have been frequently found

as a key structural unit in synthetic pharmaceuticals and agrochemicals. Some of these compounds exhibit a significant solvatochromic, photochromic and biochemi-luminescence properties. Most of the heterocycles possess important applications in materials science such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics and analytical reagents. In addition, they have applications in supra molecular and polymer chemistry especially in conjugated polymers. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells and organic light-emitting diodes (OLEDs), light harvesting systems, optical data carriers, chemically controllable switches and liquid crystalline compounds[39]. Heterocycles are also of considerable interest because of their synthetic utility as synthetic intermediates, protecting groups, chiral auxiliaries and is asymmetric catalysts in inorganic synthesis. Therefore substantial attention has been paid to develop efficient new methods to synthesize heterocycles. The alkaloids form a major group of naturally occurring heterocyclic compounds having varied biological activity. Most alkaloids contain basic nitrogen atoms. Ergotamine (**1**), the indole based alkaloid exhibits antimigraine activity[40]**.**



ergotamine

1



cinchonine

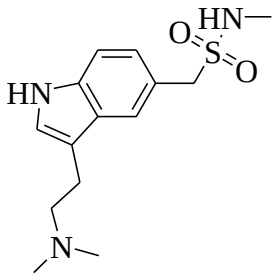
2

Cinchonine (**2**), a quinolone class of alkaloid shows antimalarial activity[41]. Posaconazole is a triazole antifungal drug[42]. It is active against the following microorganism *candida, aspergillus and Zygomycetes.*

Anastrozole is an aromatase-inhibiting drug approved for the treatment of breast cancer after surgery, as well as for metastasis in both pre and postmenopausal

women. The severity of breast cancer is increased by estrogen, as sex harmones cause hyperplasia and differentiation at estrogen receptor sites[43, 44]**.** Anastrozole works by inhibiting the synthesis of estrogen. Three out of twenty natural amino acids are heterocyclic, as are many essential vitamins. The range of application of heterocyclic compounds is very wide. They are of specific importance as they are associated with a wide variety of physiological activities. Significant number of compounds synthesized in the industrial sector is heterocyclic in nature. A large number of synthetic heterocyclic compounds are predominant among all types of pharmaceuticals, agrochemicals and veterinary products. Some of the synthetic heterocyclics are used in photography and as rocket propellants.

Heterocyclics are able to get involved in an extraordinarily wide range of reaction types. Depending upon pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, other with nucleophiles, yet others with both. Some are readily oxidized, but resist reduction, while others can be readily hydrogenated but are stable towards the action of oxidizing agents. The ability of many heterocyclics to produce stable complexes with metal ions has great biochemical significance. Sumatriptan, a heterocyclic compound is the first antimigrain drug[45], replacement of sulfonamide moiety in sumatriptan with 1, 2,4-triazole, a potent 5-HT1D receptor agonist(**3**)[46].



sumatriptan

3

The practical application of indole and pyrroles are heavily centered in the pharmaceutical area. Many analogues of indole derivatives have been synthesized in an effort to find substances with useful central nervous system (CNS) activity[47]. The furan ring is common in many naturally occurring terpenoid compounds. The cardiac active steroidal lactones are important class of naturally occurring 2(5H)- furanones and because of their pharmaceutical importance, many synthetic routes for the 2(5H)-furanones have been developed[48]. A number of relatively simple pyridines is used in

the treatment of muscular rheumatism[49]. Compounds which have unsaturated ∂-lactone rings are reported to have carcinogenic and antitumor activity as well as other biological property[50]. The fusion of five membered rings with six membered heterocyclic rings are interesting and pharmacologically active. The rich activity of heterocyclic compounds in biological systems is important for pharmaceuticals, agricultural, and natural products.

Heterocyclic compounds have provided a platform for the rapid exchange of research in the areas of organic, pharmaceutical, analytical and medicinal chemistry. In the pharmaceutical industry over 75% of the top two hundred branded drugs have heterocyclic fragments in their structures.

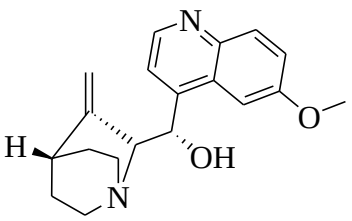
Isoxazole is an azole with an oxygen atom next to nitrogen. Isoxazolyl is the univalent radical derived from isoxazole. Isoxazole derivatives have served as versatile building blocks in organic synthesis[51]. The isoxazole nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with vital medicinal value[52]. Also, isoxazoles have applications in functional materials[53], such as liquid crystalline compounds[54] and exhibit GABAA antagonist[55], analgesic[56], anti-bacterial[57], anti-inflammatory[58], hypoglycemic[59],COX-2 inhibitory[60],anti-nociceptive[61] and anticancer activity[62]. Isoxazole rings are found in some natural products, such as ibotenic acid and also form the basis for a number of drugs, including the COX-2 inhibitor *viz.*, veldecoxib(Bextra). A derivative, furoxan, is a nitric oxide donor. An isoxazolyl group is found in many betalactamase-resistant antibiotics, such as cloxacillin, dicloxacillin and flucloxacillin. The synthetic androgenic steroid danazol also possess an isoxazole ring[63.]

1.4.1.Quinoxaline 1-4-di-N-Oxide derivatives

Quinoxalines display a broad spectrum of biological[64] and pharmacological[65] activities such as insecticides, fungicides, herbcides, anthelmintics, antibacterial[66,] antimycobacterial, antiprotozoal, anticancer and antibiotic properties[67.] Quinoxaline derivatives have found applications in dyes[68] electron luminescent materials[69] and chemically controllable switches[70]as building blocks for the synthesis of anion receptors[71], cavitands[72], dehydro annulenes[73] and organic semiconductors[74] and as electron transport materials in multilayer OLEDs[75]**.** A number of synthetic strategies have been developed for the preparation of substituted quinoxalines, including condensation of aryl-1,2- diamines with α-functionalized ketones, usually dicarbonyl compounds or their equivalents[76, 77].

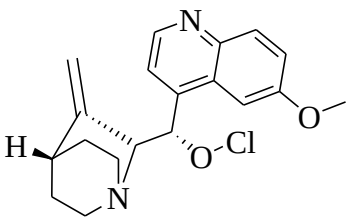
1.4.2.Heterocyclic compounds as antimalarial agents

Malaria is one of the most serious, complex and refractory health problems faced in this century. Some 300-500 million of world's population are infected by the disease, presenting 120 million clinical cases annually. Quinine (**4**) may be claimed, without exaggeration, as the drug to have relieved more human suffering than any other inhibitors. Chloroquinine (**5**), the main drug among the 4-aminoquinoline class, is one of the most successful antimalarial agents ever produced. Primaquinine is the drug of 8-aminoquinoline class, which is connected to amino acids by forming peptide bond to the amino group. These amino acid derivatives are known for higher activity and lower toxicity[78].



quinine

4

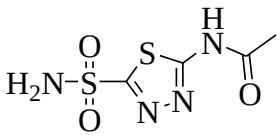


chloroquinine

5

1.4.3. Heterocyclic compounds as diuretic agents

Diuretics are medicines that help reduce the amount of water in the body. Acetazolamide, a potent carbonic anhydrase inhibitor,controls fluid secretion in the treatment of certain convulsive disorders and in the promotion of diuresis in instances of abnormal fluid retention. Acetazolamide (**6**) is not a mercurial diuretic, it is rather non-bacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides. The anticonvulsant activity of acetazolamide may depend on a direct inhibition of carbonic anhydrase in the CNS, which decreases carbon dioxide tension in the pulmonary alveoli, thus increasing arterial oxygen tension. The diuretic effect depends on the inhibition of carbonic anhydrase, causing a reduction in the availability of hydrogen ions for active transport in the renal tubule lumen[79-81]**.** This leads to alkaline urine and increase in the excretion of bicarbonate, sodium, potassium and water.



acetazolamide

6

1.4.4. Heterocyclic compounds as anthelmintic agents

Helminthes are parasitic worms, which infect an estimated two billion people worldwide, nearly all in poor developing tropical or semitropical countries. Helminthic infections contribute to malnutrition, anemia, stunted growth, cognitive impairment and increased susceptibility to other diseases. Benzimidazole, pyrazine, isoquinoline, tetrahydropyrimidine, tetrahydroquinolone, piperidine, piperazine, triazoles, indoleisoxazole derivatives are the different types of heterocyclics used as anthelmintics. Albendazole is the most active benzamidazole anthelminitic drug[82]**.**

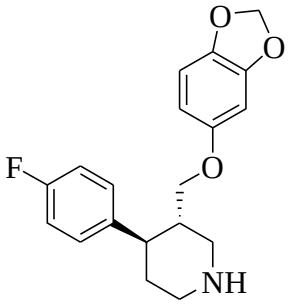
1.4.5. Heterocyclic compounds as antineoplastic agents

Cancer is a major human health problem worldwide and is the second leading cause of death in United States[83]. Systematic chemotherapy began in the 1940's and 1950's with nitrogen mustards developed from war gases and with antimetabolites developed from early knowledge of DNA metabolism. Compounds that alkylated DNA have long been of interest as anticancer drugs. Different types of antineoplastic agents are developed, which include nitrogen mustards (Bendamustine), tyrosine kinase inhibitors, 26S proteasome inhibitors *etc.,* Quinozoline and pyrimidine derivatives are used as tyrosine kinase inhibitors. A series of substituted 2-(aminopyridyl)-and 2-(aminopyrimidinyl)thiazole-5-carboxamides were identified as potent Src/Abl kinase inhibitors with excellent antiproliferative activity against hematological and solid tumor cell lines[84]**.** Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder that is characterized by hyper proliferation of stem cells, followed by their subsequent differentiation into peripheral white blood cells. Imatinib, is the block buster drug used for the treatment of Chronic Myelogenous Leukemial (CML). Imatinibmysilate is marketed under brand name Gleevec. The quinazoline derivative drugs like erlotinib and lapatinib are also important tyrosine kinase inhibitors.

1.4.6. Heterocyclic compounds as antidepressants

An antidepressant is a psychiatric medication used to alleviate mood disorders, such as major depression and dysthymia. Drugs including the monoamine oxidase inhibitors (MAOIS), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are most commonly associated with them. Paroxetine (**7**), reboxetine, are some of the most useful antidepressants containing heterocyclic

moiety in their structure. Some piperidine and pyrimidine derivatives also possess antidepressant activity. A variety of small molecule nano-peptide antagonist heterocyclics have been discovered and shown to possess antidepressant activity in animal behavioral tests[85, 86].



paroxetine

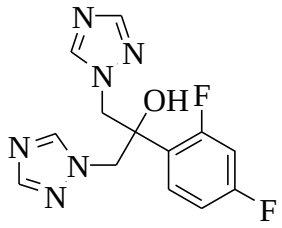
7

1.4.7. Heterocyclic compounds as antiulcer agents

Pyridine ring plays an important role in human metabolism due to its interaction with amino acids. Many of the active drugs in the market contain pyridine moiety[87, 88]. Benzamidazoles also are well known for their pharmacological properties in particular, they are widely used as anthelmintic agents[89]. Later several omprazole analogues like lanoprazole[90], pantoprazole[91] have been introduced in the market successfully.

1.4.8. Heterocyclic compounds as antipsychotic agents

Antipsychotic agents constitute a diverse class of heterocyclic drugs that are effective in the treatment of major psychosis, including those associated with schizophrenia which is a severe, life-long, idiopathic psychiatric disorder with a polygenic component. Schizophrenia is a disorder afflicting approximately 1% of human of most population. Benzisoxazole derivatives are found to have antipsychotic properties and are more potent. 3-(piperidin-4-yl)-1,2-benzisoxazole possess anti-psychotic properties and helpful in the treatment of variety of disorders in which serotonin release is of predominant importance[92]. Apart from the above significant classes of heterocyclic compounds useful as therapeutic agents, some indole derivatives are used as antimigraines and as antiosteoporotic agents[93]. Triazole compounds (fluconazole, Isavuconazole, Hexaconazole, epoxiconazole, difenoconazole, tebuconazole etc.,) are used as fungicides[94]. Quinoline/Isoquinoline drugs are used as antimalarial[95].



fluconazole

8

1.5. Schiff bases and its complexes

Schiff bases continue to occupy an important position as ligands in metal co-ordination chemistry even almost a century since their discovery. In recent years there has been enhanced interest in the synthesis and characterization of transition metal complexes containing Schiff bases as ligands due to their importance as catalysts in many reactions and their biological activities. Schiff bases named after Hugo Schiff described the condensation between an aldehyde and an amine.

$$R\text{-}NH_2 + R^{I}CHO \longrightarrow RN{=}CHR^{I} + H_2O$$

where 'R' may be aliphatic or aromatic group. Schiff base ligands are able to coordinate to metals through imine nitrogen and another group usually linked to aldehyde. Schiff bases are straight forward to prepare, monodentate electron donors with easily-tunable electronic and steric effect thus being versatile[96, 97]. Schiff bases are able to stabilize many different metals in various oxidation states, controlling the performance of metals in a large variety of useful applications in biological, clinical, analytical and industrial in addition to their important roles in catalysis and organic synthesis[98, 99]

A considerable number of Schiff base complexes are of biological interest being used as more or less successful models of biological compounds[100, 101]. Schiff base complexes incorporating phenolic group as chelating moieties in ligand are considered as models for executing important biological reactions and mimic the catalytic activities of metalloenzymes[102]. Furthermore macro cyclic derivatives of these Schiff bases have many fundamental functions such as photosynthesis and transport of oxygen in mammalian and other respiratory system[103, 104]. Schiff base ligands containing various donor atoms like N, O, S *etc.*, show broad biological activity and are of special interest because of the variety of ways in which they are bonded to metal ions. They not only play an important role in biological system but

also represent models for metalloenzymes, which efficiently catalyze the reduction of dinitrogen and dioxygen[105].

1.5.1. Transition metal complexes of Schiff bases

Organometallic complexes containing Schiff bases have played an important role in coordination chemistry of transition metals, mainly due to their stability, ease of preparation, structural variability and variety of applications. Salen-type ligands with 'N' and 'O' donor atoms are important since their metal complexes find widespread applications as homogeneous and heterogeneous catalyst in various organic transformations. Tetradentate Schiff base complexes are increasingly important for designing metal complexes related to synthetic and natural oxygen carriers. Transition metal complexes of Schiff bases are found to be of importance as biochemical, analytical and antimicrobial agents[107].

1.5.2. Applications of Schiff base transition metal complexes

Schiff bases have wide applications in food industry, dye industry, analytical chemistry, catalysis, fungicidal, agrochemical and biological activities[108]. Some of the applications are

As electroluminescent materials

Organic electroluminescent (EL) devices are useful in novel-type flat panel displays. Schiff base complexes, especially those of Zn (II) are nowadays used as electroluminescent materials[109, 110].

In non-linear optical devices

Non-linear optics (NLO) deals with the interaction of applied electromagnetic fields with various materials to generate new electromagnetic fields, altered in frequency, phase or other physical properties. Such materials that are able to manipulate photonic signals efficiently are of importance in optical communication, optical computing and dynamic image processing[111]. **Di-Bella** and co-workers have reported that bis(salicylaldiminato) metal Schiff base complexes exhibit good NLO properties[112].

In electrochemical sensors

Schiff bases have been used as carriers in the preparation of potentiometric sensors for determining cations and anions[113]. For example a ruthenium (III) Schiff base complex was used in the fabrication of chloride PVC-based membrane sensor[114].

In medicinal chemistry

Many Schiff bases are known to be medicinally important and used to design medicinal compounds[115]. The biological activity of Schiff bases either increase or decrease upon chelation with metal ions[116]. For example,

- Cobalt(II),Nickel(II) and Copper(II) complexes of Schiff bases derived from 3-substituted-4-amino-5-mercapto-1,2,4-triazole and 8-formyl-7-hydroxy-4-methyl coumarin showed potential antibacterial activity against *Escherichia coli, Staphylococcus aureus, Streptococcus pyogenes, pseudomonas aeruginosa* and *Salmonella typhi* and anti fungal activity against *Aspergillius niger, Aspergillus flavus and Cladosporium*[117].

- Ru(II)-PPh_3/$AsPh_3$ complexes containing hydrazone oxime ligands, show considerable activity against selected bacterial species and are capable of binding to Herring sperm DNA in mixed modes[118].

- Metal complexes of Schiff base derived from 2-thiophenecarboxaldehyde and 2-aminobenzoicacid exhibited antitumor effect[119].

- Tridentate Schiff base derived from the condensation of s-benzyldithiocarbazate with salicylaldehyde and its Zn, Sb, Cu complexes showed cytotoxic properties[120].

- Schiff bases of gossypol showed high antiviral activity[121].

- Schiff base derived from thiadiazole and salicylaldehyde and their complexes with Mo(II) showed insecticidal activities against bollworm.

- Schiff base of thiadiazole exhibited good plant growth regulatory activity towards auxin and cytopine. Several Schiff bases possess anti-inflammatory, analgesic, antioxidative and anthelmintic activities[122].

In catalysis

Schiff base complexes play a central role in various homogeneous catalytic reactions and the activity of these complexes varies with type of ligands, co-ordination sites and metal ions. For example, **Vchida** and **Katsuki** have reported the activity of cationic Cobalt(III) salen complexes in Baeyer-Villiger oxidation of 3-phenyl cyclobutanone with H_2O_2 or urea hydrogen peroxide adduct[123]. **Kureshy *et al.,*** have reported the catalytic activity of Ni(II) Schiff base complexes of N,N$^{'}$-bis(2-

hydroxyphenyl)ethylenediamine and N,N'-bis(2-hydroxy phenyl)acetamide in the epoxidation of olefins such as cyclohexene -1- hexane, cis and trans stilbenes with sodium hypochlorite[124]. Similarly Schiff base complexes of transition metals are efficient catalysts in hydrogenation and polymerization reactions[125, 126].

In DNA cleavage

Schiff bases are capable of forming complexes with transition metals that interact with DNA. The interchelation of transition metal complexes with nucleic acids is the major area of research due to the utility of these complexes in the design and development of synthetic restriction enzymes, chemotherapeutic agents, and food printing agents, site specific cleavers and molecular photo switches[127].

1.6. Ruthenium Schiff base complexes

There is much current interest in the chemistry of ruthenium[128] most of which is due to the fascinating electron-transfer and energy –transfer properties displayed by complexes of this metal. Octahedral ruthenium(III) complexes are the object of great attention in the field of medicinal inorganic chemistry owing to the favorable pharmacological properties of potential anti-tumour activities manifested by some members of this family of metallodrugs[129]. Transition metal phosphine/arsine complexes of ruthenium show a wide range of applications in catalytic processes such as hydrogenation, isomerization, decarboxylation, reductive elimination, oxidative addition and in C-C coupling reactions[130].

In continuation of our interest to synthesise heterocyclic compounds and their transition metal complexes, the present work is focused on the synthesis of some novel quinoxaline, pyrimidine and benzothiazole derivatives and their metal complexes and to evaluate their antimicrobial, anticancer, antioxidant, antitubercular activities. The DNA binding and cleavage ability of the synthesized complexes is to be studied exclusively using absorption and emission spectral measurements. Molecular docking studies of the ligands and the chemosensor ability are to be studied.

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Chapter 1

Introduction

1. Introduction

Transition metals have an important place within medicinal biochemistry. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases like carcinomas, lymphomas, infection control, anti-inflammatory, diabetes and neurological disorders. 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.

Medicinal inorganic chemistry is taking a growing interest in the development of metal complexes for the use as drugs or diagnostic agents. Based on their wide spectrum of co-ordination numbers and geometries as well as their kinetic properties, metal compounds offer mechanisms of drug action that cannot be realized by organic agents.

1.1. Transition metal complexes as anticancer agents

The development of metal complexes with platinum such as cisplatin or carboplatin had an enormous impact on current cancer chemotherapy. Nephrotoxicity is one of the major side effects of cisplatin but still cisplatin combination chemotherapy is the cornerstone in treatment of many cancers. Initial platinum responsiveness is high but the majority of cancer patients eventually relapse with cisplatin-resistant disease. Preclinical and clinical investigations show that the development of new metal agents other than platinum is also possible.

1.1.1. Platinum based anticancer drugs

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]. Cisplatin moves into the cell through diffusion and active transport. Inside the cell it causes platination of DNA, which involves interstrand and intrastrand cross-linking as well as formation of adducts, usually through guanine, as it is the most electron rich site and hence, easily oxidized. Formation of cisplatin DNA adducts causes distortion and results in inhibition of DNA replication[2]. Cisplatin DNA adducts also serve as binding site for cellular proteins such as repair enzymes,

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Chapter - II

Review of Literature

2. 1. Quinoxalines

Quinoxaline is nitrogen containing six membered heterocyclic in which two nitrogen atoms are based on pyrazine so called as benzopyrazine. α-dicarbonyl compounds react with aromatic ortho-diamine by consecutive addition-elimination mechanism to give quinoxaline. Quinoxalines have become an attractive target of extensive research due to its inherent properties and therapeutic uses. Quinoxaline finds many pharmacological activities like antibacterial, antifungal, antitubercular, antiinflammatory, antihyperglycemic, antitumor *etc.*,

2.1.1. Review on quinoxaline derivatives and its transition metal complexes

Quinoxaline-based Schiff bases were synthesized and characterized by several workers. The review of the previous work is presented below.