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Biologically Important Schiff Bases and Their Transition Metal Complexes

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Abstract:

Transition metal complexes with different ligand systems have been developed. Majority of them are derived from heteroaromatic cycles and Schiff bases of variety of aromatic aldehydes, diketones with amino acids, polyamines, N-aromatic cycles and ethylenediamines. Metal complexes of Schiff bases are used as polymers, dyes and in various biological systems. They show antimicrobial activity and can be used as suitable drug to treat bacterial and fungal infections. Most of the Cu, Ni and Co complexes are also capable of binding and cleaving DNA.

Keywords: Transition metals, amino acids, Schiff bases, antimicrobial activity, DNA cleavage

1. Introduction

Metal complexes have always intrigued chemists since their inception. Though they would have questioned elementary bonding theory in their infancy, today their applications are

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multifarious. A paradigm shift was experienced in medicinal chemistry, which is based on organic compounds, due to serendipitous discovery of cis-platin's antitumor property. Since then, chemists are engrossed in discovering novel metal complexes with medicinal properties to tackle diseases which always battle with human beings to gain an upper hand. Metal coordinated ligand's 3-dimensional orientation helps in specific molecule recognition. Thus the interaction of metal complexes with biomolecules is different when compared to that of classic drugs. Today gold and platinum complexes are already in the market serving as antiarthritic and antitumor drugs respectively, yet in-depth structure activity relationship (SAR) investigations are needed, to develop metal based drugs with improved pharmacological properties. Ligands can also be tailored for enhanced specificity. Diversity of transition metal complexes with medicinal properties are being reported, among which many are centered at metal complexes derived from Schiff bases. This is because of their easy synthesis, good donor abilities and established medicinal properties. Schiff base compounds find application as antibacterial, antifungal and antitumor drugs.

1.1 History of metallodrugs

Barnett Rosenberg, a biophysicist in Michigan State University, accidently discovered cis-platin. He was studying the effect of applied electric field on the growth of E.Coli cells, in order to prove that spindle fiber formation gets perturbed during cell division. Instead he observed cell elongation without cell division. Later he diagnosed that platinum from the electrodes, which he used to apply electric field, had dissolved in the buffer containing ammonium chloride forming $[Pt(NH_3)_2Cl_2]$ complex, which caused cell elongation.

The in vivo studies of the compound showed necrosis of tumor in rats. This initiated cis-platin, a metal complex to be used as a drug in the treatment of cancer and the search for new complexes with better pharmacological properties began and is continuing [1].

1.2 Theory of metal complex toxicity

Ab initio studies on drugs have proved that, lipophilic character of drugs plays an important role in its medicinal property, as phospholipid bilayered cell membrane is selectively permeable. One has to consider this property while developing metal complex based drugs. According to overtone's concept of cell permeability, the lipophilic cell membrane permits the passage of only lipid soluble materials, which makes liposolubility as an important factor for controlling the microbial activity. This has been emphasized in Tweedy's chelation theory [2].

1.3 Chelation theory

On chelation of ligand to the metal, the polarity of the metal ion is reduced to a great extent due to the overlap of the ligand orbital with the metal orbital and there is partial sharing of the positive charge of the metal ion with donor atom and increases the delocalization of pi-electrons over the chelate ring. Thus chelation enhances the lipophilic character of the central metal atom, which subsequently favors its permeation through the lipid layers of the cell membrane and enhances the penetration of the complexes into the lipid membrane, thereby blocking the metal binding sites in the enzymes of the microorganism. Many in vitro studies have shown the inhibition of enzyme activities in the presence of transition metal complexes [3], [4].

Inhibition of enzymes can disturb the respiration process, cell homeostasis and thus block the synthesis of proteins which restricts the further growth of the organisms. Moreover metal complexes easily undergo redox reactions and ligand substitutions, which allow them to participate in biological redox chemistry and interact with bio-molecules [5], [6].

Many transition metal complexes with different ligand systems have been developed, which show antimicrobial, antitumor (DNA binding and cleavage) properties, majority of them being derived from heteroaromatic cycles and Schiff bases of variety of aromatic aldehydes and amines.

2. Schiff Bases

The biological activity of chelating ligands having N, S and O as donor atoms have been studied due to their different metal binding modes. The metal ions alter or enhance the activity of the biologically active compounds on complexation [7]. Copper complexes of iminodiacetic acid and diimines have the ability of cleaving double–stranded DNA, by both oxidative and hydrolytic cleavage mechanisms [8].

3. Schiff base with Heterocyclic Group

Many synthetic compounds with quinoline derivatives were found to have pharmacological properties [9]. Drugs containing quinoline are known to act as antimalarials [10] [11]. Co(II) and Ni(II) complexes of Quinolino Schiff bases were also found to have antimicrobial properties[12].

Schiff base and their complexes have showed appreciable antibacterial and antifungal activity. Tumor growth is also found to be inhibited by some Schiff base complexes. Cobalt complexes of reduced N,N′-o-Phenylene bis (salicylideneimine) have showed significant growth inhibition of yeasts and fungi of the genus Scedosporium[13].

Cu(II), Ni(II) and VO(II) complexes of Schiff base ligands derived from indole derivatives have showed significant antimicrobial activity against pathogens in comparison to the ligands which showed no activity prior complexation to metals[14]. Co(II), Ni(II), Cu(II), Mn(II), Fe(II) complexes of isatin derivatives have been screened for their in-vitro antibacterial activities[15]. Complexes of various Schiff base ligands derived from aminoantipyrine had high antimicrobial activities and were found to cleave DNA [16-19].

4. Schiff Base Analogues of Amino Acids

Schiff bases behave as chelating ligands in coordination chemistry [20]. They are also used in catalysis, anti-oxidative activity and as

medicines [21]. Amino acid Schiff bases are very effective metal ligands and their metal complexes act as models for numerous biological systems [22]. These are also involved in numerous biochemical reactions which are catalyzed by enzymes [23]. Many of them serve as models for the study of pyridoxal (PLP)-amino acid Schiff bases which are involved in many metabolic pathways. [25].

Amino acid Schiff bases and their first row transition metal complexes exhibit antifungal, antibacterial, antiviral and antitubercular activity [24]. Most of these complexes interact with DNA through intercalative binding modes [26].

2-nitrobenzaldehyde-glycine and 2-nitrobenzaldehyde methionine Schiff base was coordinated with Co(II), Ni(II) and Cu(II) [27]. The metal chelates possessed reasonable antimicrobial potential.

Indole derivatives are known to show variety of biological activities such as CNS depressant, anticancerous, antibiotic, antihistamine, anticonvulsants, etc [28]. Antimicrobial activity of unsymmetrical Schiff bases of indole 3-carboxaldehyde with different amino acids like histidine, glutamic acid, aspartic acid, valine and leucine and amino acid analogues such as 2-aminophenol, 2-aminophenol-4-sulphonic acid, 1-amino-2-naphthol-4 sulphonic acid have been studied[29]. Co(II), Ni(II) and Cu(II) complexes of Schiff base ligand formed from glycylglycine and indole-3-carboxaldehyde were also investigated[30]. The Cu(II) complexes were found to possess higher bacterial and fungal properties than the other metal complexes and ligands.

5. DNA–metal Complex Interactions

It is now well established that DNA is the master molecule behind cell homeostasis and regulation. In tumor cells, cell division is uncontrolled leading to cancer. Various biological experiments suggest that DNA is the primary intracellular target of an anticancer drug because the interaction between this molecule and DNA can cause DNA damage in cancer cells blocking the irregular division of cancer cells and resulting in apoptosis [31], [32].

Cis-platin suffers from the major draw backs of nephrotoxicity, neurotoxicity and intravenous administration [33]. These drawbacks have stimulated an extensive search for other tumor-inhibiting complexes of bioessential transition metals like copper and iron with improved pharmacological properties. Investigations are going on for molecularly targeted metal-based anticancer drugs with high specificity versus cytotoxic and broad-spectrum agents.

The interaction of metal complexes with DNA is the most studied aspect of antitumor metal drugs because only then a chemist will be able to develop better drugs with enhanced medicinal properties. So the SAR is of first importance. The possible metal complex-DNA interactions are DNA binding and DNA cleavage.

5.1 DNA binding

Metal complexes can bind to DNA in the following ways:

a. Coordination of the DNA bases to the metal atom
   Purines and pyrimidines are the building blocks of DNA. The nitrogen atom in these compounds is a good donor towards transition metals. This type of interaction can happen through the major or the minor groove of DNA [34-36].

b. Intercalation between the stacked base pairs of DNA from the major groove side.
   Metal complexes with ligands such as fused ring organic heterocycles or polyaromatic planar hydrocarbons can efficiently lodge themselves in between the stacked base pairs [37].

c. Electrostatic interaction with DNA
   DNA is a negatively charged molecule due to the presence of phosphate groups. This inherent property of DNA is utilized in electrophoresis - a separation technique. The chances of electrostatic interaction of ligands with oxygen of phosphate groups or with nitrogen of the bases are high. Hydrogen bonding between the coordinated ligand and the

oxygen of the sugar phosphate back bone is also possible [38-40].

The two modes of binding (a&b) largely depend on the nature of conformation of DNA and structural properties, orientation of the ligands of metal complexes [25] [41] [42].

Some complexes show high avidity towards DNA. This may be due to synergistic contribution of all of the three(a,b&c) mentioned above and the best illustration in this case is $Ru(phen)_3$ complex, as it has high affinity towards DNA and binds by all the above said modes. One planar heterocyclic ring can intercalate with DNA, while the other can enter into a hydrophobic interaction with the minor groove and also involve in H-bonding with phosphate moieties of the sugar back bone. Such complexes are robust models, to design and develop metal complexes with desired properties [43].

Binding of the complexes can cause physical alterations like conversion of the super coiled form of DNA to the relaxed form. Many investigators have proposed that, on binding DNA, many metal complexes are found to inhibit the enzymes involved in DNA duplication, like topoisomerases (invitro), which may stall the DNA duplication in tumor cells. [44-47].

5.2. DNA cleavage

The second type of DNA-metal complex interaction is cleavage of DNA. DNA cleavage is an important property of transition metal complex based antitumor drugs. As these complexes exhibit slicing of DNA analogous to biological DNA cleavers – Nucleases, they are called Artificial Nucleases.

5.2.1 Types of cleavage

5.2.1.1 Redox cleavage

Metal complexes of copper can easily undergo redox reactions and generate reactive oxygen species (ROS) like superoxides, hydroxyl radicals or singlet oxygen. These oxidizing intermediates can cleave DNA. However generation of these reactive intermediates can be assisted chemically or in presence of light.

In chemically assisted DNA cleavage, oxidants like hydrogen peroxide can interact with copper complexes to generate hydroxyl radicals which in turn oxidize nucleotides of DNA [48 - 50].

In photo chemically assisted DNA cleavage, metal complexes are photo chemically excited to their higher energy states, which suffers an energy transfer to the triplet state, which can activate oxygen from its stable triplet state $^3\sum_g$ to its toxic singlet state $^1\Delta_g$ [51].

Various metal complexes are investigated for their DNA binding and cleaving properties. Copper complexes of different amino acids like alanine [52], threonine [53], l-leucine/isoleucine 54], phenylalanine [55], proline [56], methycystein [57], glutamine [58] have been synthesized and DNA cleavage properties are studied. It is proposed that DNA is cleaved by the reactive oxygen species - OH•, generated in the presence of H_2O_2 [44], [59], [60].

Transition metal complexes of Schiff bases of different aromatic, heteroaromatic aldehydes like, salicylaldehyde [61], pyridine carboxaldehyde [62], indole carboxaldehyde [63], oxo-quinoline-3-carbaldehyde [64] and amines like 2-aminobenzothiazole [65], aminomethylthiophene [66] and antipyrine [16], [18] were synthesized and their DNA binding cleavage abilities have been studied.

5.2.1.2. Hydrolytic cleavage

Coordination of metal complex to sugar phosphate backbone can cause hydrolysis of phosphodiester bond by polarizing P-O bond. Coordinated nucleophile can also react with phosphate groups leading to DNA cleavage [75] [76]. The effect of extended fused cycles [37], functional group substitution of ligands [70], planarity of cycles [77], [78], chirality [79] and orientation of ligands on metal assisted DNA binding have been investigated[24].

6. Schiff Bases of Different Amino Acids

Schiff bases of different amino acids like valine have been synthesized and their DNA binding and cleavage abilities have

been investigated [24], [44] ,[67-73], prioritizing selective DNA binding and site specific DNA cleavage [74].

Fused planar aromatic cycles are studied for DNA cleavage abilities worldwide because planar aromatic cycles show good DNA binding ability. Copper is a good lewis acid and can take part in redox chemistry and efficient in generating ROS like O_2^-, $OH^\bullet$, O_2 which can cleave DNA [48-58].

7. Conclusion

Metal complexes are next generation drugs. Intense and dedicated research is required for deciphering the metal complex's mechanism behind pharmacological properties and interactions with biological systems. Toxicity, metabolism and excretion of metallodrugs have to be studied thoroughly. Novel metal complexes may find place in DNA finger printing and in spectroscopic probing of biomolecules in future. A ray of hope is that these metal complex drugs may tackle the issue of multi drug resistance of pathogens and can be an efficient antitumor drug.

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