Some Divalent Metal(II) Complexes of Salicylaldehyde-Derived Schiff Bases: Synthesis, Spectroscopic Characterization, Antimicrobial and In Vitro Anticancer Studies

Dr. Rakesh Ranjan[1], Dr. Kumar Mukesh Ranjan[2]
[1,2]*Assistant Professor, Department of Chemistry DBSD Degree College, Kadana, Garkha,Jai Prakash University, Chapra*

Abstract-The huge research on Schiff base coordination complexes in the past few decades has given rise to several new molecules that have been of biological importance. The ease with which the Schiff base ligands are designed and prepared and their pattern is elucidated have made them to be referred to as "fortunate ligands" possessing azomethine derivatives, the C=N linkage that is essential for biological activity, including antibacterial, antifungal, antioxidant, anticancer, and diuretic activities. A variety of Schiff base and its complexes have been studied as model molecules for biological oxygen carrier systems. The uses of Schiff bases as DNA- cleaving agents and its mode of interaction and free-radical scavenging properties are described. The review encapsulates the applications of Schiff bases and their complexes.

Keywords: antimicrobial; antioxidant; antitumor; metal complexes; prospects; Schiff bases.

INTRODUCTION

Schiff bases and their complexes remain as the interests of many researchers due to their enormous application in the food industry, dye industry, analytical chemistry, catalysis, antimicrobial activity, and pharmacological application, such as antitumor, antifungal, antibacterial, and, usually obtained from the condensation reaction of diamine with various aldehydes, can coordinate either one metal center or several metal centers depending on the binding sites available or the structural arrangement of two amino groups in the precursor (Kondo et al. 2007, Kumari et al. 2008, Yamada et al. 2015). Many symmetrical and unsymmetrical tetradentate bis-type Schiff bases of both aliphatic and aromatic 1,2-diamines and different aldehydes/ketones have been investigated (Tan and Ang 1988, Phan et al. 2004, Lashanizadegan and Jamshidbeigi 2011). Also, the significant biological and physical proper- ties of Schiff bases are linked to the intermolecular hydrogen bonding and proton transfer equilibrium (Przybylski et al. 2002).

POTENTIAL APPLICATION OF SCHIFF BASES AS BIOLOGICALLY ACTIVE AGENTS

Schiff bases are widely studied ligands that coordinate to metal ions via azomethine nitrogen. In azomethine derivatives, the C = N linkage is essential for biological activity, and the presence of this group have made its complexes to be considered as important stereochemical models in the main group and transition metal coordination chemistry dueto ease in preparation and variety in structure (Prakash and Adhikari 2011). The interaction of metal ions with N, O, and S atoms from Schiff base organic compounds has gained much attention in recent years and provided an enthusiastic series of ligands possessing properties that can be modified by inserting different organic substituents, which bring about the variation in the fundamental donor properties (Kostova and Sasa 2013). The use of Schiff bases in biological or therapeutic applications as promising drug agents or biological probes and analytical tools has been reported by several researchers.

Also, the bioactivity of Schiff base compounds as anti- bacterial (Ronad et al. 2010, Saravanan et al. 2010, Lashanizadegan and Jamshidbeigi 2011, Abdel Aziz et al. 2012), antiradical (Vukovic et al. 2010, Wu et al. 2011, Bala et al. 2012), anticancer (Desai et al. 2001, De Souza et al. 2007, Creaven et al. 2010), antifungal (Rathelot et al. 1995, Domb etal. 1996), and antiviral (Wang et al. 1990, Sriram et al.

2006, Jarrahpour et al. 2007) agents has been reported. There has been an increasing focus on the binding of small molecules such as Schiff base compounds to DNA (Raman et al. 2011c, Annapoorani and Krishnan 2013). Their use in birth control and food packaging and as an O2 detector has been reported (Prakash and Adhikari 2011).

Furthermore, Schiff bases are found in diverse natural, semisynthetic, and synthetic compounds (Figure 1) and have been established to be significant for their biological activities (De Souza et al. 2007). In the past few decades, Schiff bases and their metal complexes have been among the most widely examined coordination compounds, and this can be attributed to their increasing importance as biochemical and analytical reagents. Schiff base complexes have been reported to offer ease and flexibility in their synthesis technique, diverse properties, and use as biologically active compounds (Kostova and Sasa 2013).

SCHIFF BASES AND THEIR METAL COMPLEXES AS ANTIBACTERIAL AND ANTIFUNGAL AGENTS

Infectious diseases that are directly related to bacteria exhibiting multiple resistance to antibiotics have increased the world's mortality rate. Therefore, the need to develop novelantibacterial drugs with excellent mechanisms of action and structural-activity relationship has become an urgent biomedical necessity (Rice 2006, Brodowska and Lodyga-Chruscinska 2014). Schiff base ligands and their biologically active complexes providing potential sites for biochemically active compounds have been studied extensively over the past few decades (Alias et al. 2014) for their antimicrobial (Kamalakannan and Venkappayya 2002) and anticancer (Aderoju et al. 2012) properties. Schiff base-transition and inner-transition metal complexes are one of such adaptable and thoroughly studied systems used as model molecules for biological oxygen carrier systems (Hester and Nour 1981, Fakhr et al. 2004, Malik)

SCHIFF BASES AND THEIR BIOLOGICAL ACTIVITIES

Chandrasekaran et al. (2014) synthesized a series of novel Schiff bases known as 6- bromo-2-[2-(2,6-dichlorophenyl) amino]benzyl-3-(substituted benzylideneamino)- quinazo- lin-4(3*H*)-one (**1**). These compounds were subjected to *in vitro antimicrobial activity using the cup plate method, and Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Candida albicans* strains were employed. Penicillin G and amphotericin B were set as standard drugs. The obtained results revealed that all compounds possess moderate to poor antifungal activity and good antibacterial activity (Chandrasekaran et al. 2014) and *Salmonella typhimurium*, was assessed, and all com- pounds were found to be moderate to strongly active (Essaet al. 2012).

MISCELLANEOUS APPLICATION OF ASYMMETRICAL SCHIFF BASES AND THEIR COMPLEXES

Cu(II), Co(II), Ni(II), Mn(II), and Cr(III) complexes have been prepared from three Schiff base ligands (H_2L^1-H_2L^3). The preconcentration of Cd(II), Cu(II), Zn(II), and Ni(II) using a minicolumn filled with silica gel modified with Schiff base has been proposed (Shemirani et al. 2004). The proposed method has been applied to the analysis ofthe metal ions in natural water samples and to a standard reference aluminum alloy with N_2O_2 donor sites obtained from the condensation of 1,5-diaminonapthalene with derivatives of benzaldehyde (Ceyhan et al. 2012). The electrochemical, thermal, and alkane oxidation activities of the ligands and their corresponding metal complexes were evaluated. It was observed that Cu(II) and Cr(III) complexes showed good catalytic activity in the oxidation of cyclohexane and cyclooctane to the desired oxidized products (Ceyhan et al. 2012). Zhang and Zhu (2008) have reported the synthesis and characterization of square-planar Ni(II) complex with tridentate ONO-donor 4-[(2-hydroxyphenyl)

The authors revealed a 1D assembly of the [Ni(H_2AC)(Hidz)] molecules through intermolecular hydrogen bonds between the imidazole N-H groups and the coordinated hydroxyphenyl-O atoms in the solid state (Zhang and Zhu 2008). Mixed-ligand dinuclear Cu(II)

complexes of the type $[Cu_2L(aminoantipy)_2]Cl_2$ have been reported.

A new oxovanadium(IV) Schiff base complex, $V_{IV}OD_2$, has been prepared from the reaction of a bidentate Schiff base ligand D and $VO(acac)_2$ The catalytic activity ofthe oxovanadium(IV) complex was tested in the epoxidation of cyclooctene. The results showed that the complex was a highly active and selective catalyst in optimized conditions in the epoxidation of cyclooctene (Grivani et al. 2012). Three dissymmetrical Schiff bases, viz., (*o*-hydroxybenzaldehyde) (2-hydroxy- acetophenone) ethylenediamine (L_1), (benzaldehyde) (2-hydroxyacetophenone) ethylenediamine (L_2), and (*p*-hydroxybenzaldehyde) (2-hydroxyacetophenone) eth- ylenediamine (L_3), have been obtained from the condensation of 2-hydroxyacetophenone, ethylenediamine, and several aldehydes leading to bibasic tetradentate (ONNO) and monobasic tridentate (NNO) ligands, with transition metals Co(II), Ni(II), Cu(II), and Zn(II) (Rabie et al. 2008).

The physicochemical studies of Ni(II) and Cu(II) complexes of 2-substituted-1- phenyl-1,3-butanedione (2-R-bzacH, R Cl, NO_2) and their 2,2 -bipyridine (bipy) and 1,10-phenanthroline (phen) adducts have been synthesized and characterized (Omoregie and Woods 2011). Six-coordinate octahedral geometry was suggested for all Ni(II) compounds, whereas a probable five-coordinate square-pyramidal geometry was suggested for Cu(II) compounds (Omoregie and Woods 2011). X-ray crystal- lography of tridentate ONN Schiff base complexes of [NiL(PR3)] [where L salicylidene-2-amino-4-nitrobenzene (L1), 5-BrSalicylidene-2-amino-4- nitrobenzene (L_2), 5-NO_2Salicylidene-2-amino-4-nitrobenzene (L_3), 5-MeO- Salicylidene-2-amino-4-nitrobenzene (L_4), and 3-MeOSali- cylidene-2-amino-4- nitrobenzene (L_5), R Bu and Ph (with L_1)] has been reported (Kianfar and Ebrahimi 2013). Aazam et al. (2012) have reported the preparation of mononuclear Zn(II), Cd(II), Cu(II), Ni(II), and Pd(II) metal complexes of Schiff base ligand (**52**) derived from 8- acetyl-7-hydroxy- coumarin and *p*-phenylenediamine. Metal-mediated enhancement was reported to be observed upon the complexation of the ligand with Zn(II) and Cd(II), whereas metal-mediated fluorescence quenching occurs in Cu(II), Ni(II), and Pd(II) complexes.

CONCLUSIONS AND FUTURE PROSPECTS

Despite many accomplishments of clinical research in the development of therapeutic agents, cancer is still the second most frequent cause of death. Infectious diseases that are directly related to bacteria and fungi exhibiting multiple resistance to antibiotics have increased the world's mortality rate. Free radicals have been implicated in the causation of several oxidative damage diseases, such as liver cirrhosis, atherosclerosis, cancer, diabetes, and aging. Hence, there is a need for a further investigation of coordination compounds with a wide spectrum of activity and structural-activity relationship than the readily available chemotherapeutic drugs. The applications of Schiff bases and their transition metal complexes have shown a broad biological activity in the areas of DNA-binding studies, bacterial and fungal inhibition, herbicides, insecticides, nematocides, rodenticides, free- radical chain termination, antileishmanial agents, radiotracers in nuclear medicine, anti-inflammation, plant growth hormone regulator/booster, and cytotoxic activity. The use of Schiff bases in biological or therapeutic applications as promising drug agents or biological probes and analytical tools and in pharmaceutical and chemical sciences have been reported by several researchers.

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