Original Research Article

Recent developments in anticancer applications of the Schiff bases and their metal complexes

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Abstract

Metal complexes of Schiff base signify a class of compounds that have become a field of huge interest for chemists all over the world because of their immense therapeutic applications. They show versatile bonding behaviour because of easy variation in steric and electronic structure of Schiff bases by taking appropriate aldehydes/ ketones and amines. This review highlights the up-to-date research on transition metal complexes of Schiff bases emphasizing mainly on their anticancer applications. We present a complete study of structural factors that are responsible for their activity against particular cancer cell lines and the methods used for such study that includes both experimental and theoretical approach. Contemporary strategies will be helpful to the development of new drugs based on the moiety and interactions with various cancer cell lines which lead to the apoptosis.

Key Words: Schiff Base; Metal Complexes; Cancer; Anticancer activity.

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INTRODUCTION

An extensive research has been carried out on Schiff base and its metal complexes due to their vast applications in the field of medicine, food, clinical, pharmaceutical, biochemistry, agricultural, and in photo-responsive biomaterials industry[1-3]. A variety of applications of the Schiff base may be counted due to the presence of intermolecular H-bonding and proton transfer equilibrium[4]. Schiff bases, named by the chemist Hugo Schiff, are the structurally diverse compounds in which imine group (-CH=N-) are formed by the condensation of the carbonyl and the primary amine group (**Fig. 1**) [5, 6].

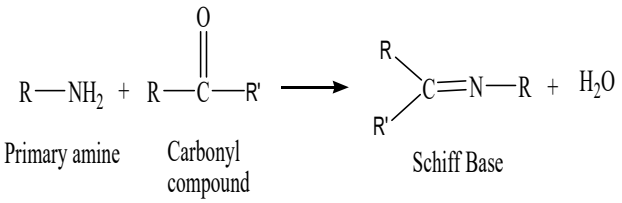

Figure 1: General scheme for the synthesis of Schiff base (R or R'= alkyl or aryl).

The lone pair of sp^2 hybridized N-atom of imine group is responsible for the biological activity of Schiff bases. Schiff bases are flexidentate ligands which can stabilize the metal ions in various oxidation states by coordinating them through the lone pair of azomethine group[7-9]. Schiff base metal complexes are used as a catalyst in both homogenous reactions as well as heterogeneous reactions although their activity depends upon the ligand binding sites and the metal ion present. They have been used in various catalytic reactions such as aldol reactions, oxidation of alkenes, alcohols, cycloalkanes and benzenoids, ring-opening polymerization of lactide, Diels-Alder reactions, alkene epoxidation, Baeyer-Villiger oxidation of aryl cyclobutanone[10,11]. They have been used in ion transport through membranes, phase transfer reactions, biomimic of metalloenzymes like hemoglobin and hemerythrin, isotope separation and ion

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selective electrodes[12-15]. Schiff base metal complexes have shown electrochemical, catalytic, and biological properties like antibacterial, anticancer, antifungal, antioxidant, anti-convulsant, anti-inflammatory, antiviral, antifertility, anti-HIV, antiproliferative, diuretic activities, herbicidal activities, analgesic and lipid-lowering properties, and enzyme inhibitory[16-19]. Cancer is the serious issue nowadays so that a great attention has been paid to the finding of novel drugs with improved efficacy, and lesser toxicity[20]. Cell growth is a normal biological process required for life, but there are various factors which leads to abnormal cell growth, is known as cancer. Cancer is a hereditary disease but it is caused by a number of factors like physical inactivity, obesity, exposure to ultraviolet radiations, chemical carcinogens, tobacco, and alcohol and many more[21,22]. There are numerous factors which can be considered for the advancement of drugs such as drug resistance, adverse effects, expensive and non selective in nature towards cancerous cells[23]. Cancerous cell has potential to resist the drug action; known as drug resistance. When particular cancerous cells treated with a combination of cytotoxic drug and antibodies, helps in targeting the cancerous cell and kill them as we have elucidated in **Fig. 2**[24]. Nanoparticles drug delivery is modern approach for the treatment of various types of cancer. It is found to be helpful in overcoming to drug resistance as well it allows the liberation of drugs at the site by biodegradation and self-regulation of nanoparticles *in vivo* and *in vitro*[25,26]. CdO-NPs are widely used in drug delivery, recognition and elimination of the cancer cells. CdO-NPs pass the cell wall and damage the DNA and protein of the cancerous cell[27].

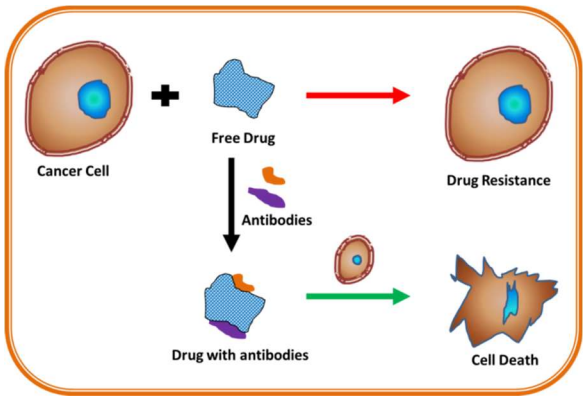


Figure 2: Figure showing Chemoresistance with drug and cell death due to conjugate drug and antibodies

Cisplatin, a well-established drug is used in the treatment of various cancers[28]. It is a platinum complex which can bind to nuclear DNA and shows carcinostatic activity. The study of interaction of DNA with the metal based drug makes the way easy for the synthesis of drugs which are target specific. The binding of DNA with the metal complexes can result in DNA damage which inhibits the growth of cancerous cells[29]. A number of research revealed that cancer therapy can be done by blocking the protein tyrosine kinase activity. Protein tyrosine kinase, which has been categorized into two types: receptor kinase and non-receptor kinase, catalyses many cellular processes such as metabolism, survival, cell mutation and apoptosis by the phosphorylation of tyrosine, serine and threonine residue of protein[30]. The uncontrolled cell division is due to the over-expression of these protein kinases which result in the mutation[31]. Epidermal growth factor receptor (EGFR) is one of the types of protein tyrosine kinase. The over-expression of EGFR is mainly responsible for the lung, head, neck, breast, ovarian and prostate cancer[32,33]. It has been reported that proteasome is more active in cancerous cells; its inhibition is responsible for the cell death of the cancerous cell. A number of Schiff Base and their metal complexes have been designed and used in the treatment of cancer either by binding with the DNA molecules or by the inhibition of EGFR and proteasome inhibitors[34,35]. Great attention has been received by Schiff base metal complexes in the treatment of cancer due to the higher toxicity, low chemical stability, and drug resistance of cisplatin [36]. A large number of metal-based Schiff base complexes have been synthesized which have shown potential anticancer properties but their mechanism of action is still a topic of research.

APPLICATIONS OF SCHIFF BASE METAL COMPLEXES TO CURE VARIOUS TYPES OF CANCERS

Prostate Cancer: Prostate cancer (PCa) is a common type of tumor found in males, and its prevalence is increasing with the time[37]. Prostate cancer is the most common cancer found among US male residents[38]. The treatment of prostate cancer can be achieved by the active surveillance, surgery, radiotherapy, hormone therapy, cryotherapy etc. The peptide-drug conjugation is an innovative method for the delivery of chemotherapeutic drugs specifically used in the treatment of prostate cancer[39]. Nano-medicines have also reached a remarkable milestone in the diagnosis and treatment of Prostate cancer[40]. The role of Schiff bases in the treatment of Prostate cancer cannot be ignored. Amino acid-Schiff base copper complexes can effectively inhibit proliferation and induce apoptosis in prostate cancer cells[41]. In another study, a novel hetero dinuclear Cu (II) and Mn(II) Schiff base complex in combination with P85 are utilized for the treatment of prostate *in vivo*[42]. Zhang *et al*. have introduced L-ornithine Schiff base copper and

cadmium complexes as an apoptosis inducer in the prostate cancer in human[43]. Adsule *et al*. have synthesized proteasome inhibitors for Human Prostate cancer cells. The proposed structure of the copper complex of novel Schiff base of quinoline-2-carboxyaldehyde has been given in **Fig. 3**. The copper complex of the Schiff base of quinoline-2-carboxyaldehyde has high antiproliferative activity against prostate cancer cell line PC-3 and LNCaP *in vitro*. It has been seen that cytotoxicity nature of the ligand has been affected by the functional groups attached to the side chains at the C_2 position of quinoline ligand[44].

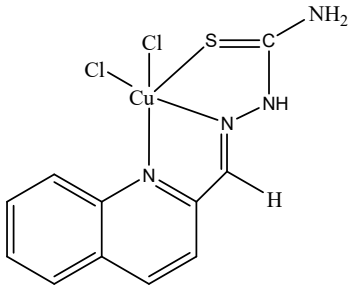


Figure 3: Copper (II) complex of Schiff base of quinoline-2-carboxyaldehyde which shows activity against prostate cancer cell [44].

Breast Cancer: Breast cancer is the second main cause of death in women of all ages. Some of the cytotoxic drugs available in the market for the treatment of breast cancer are carboplatin, doxorubicin, epirubicin, paclitaxel, furtulon[45]. Among all the breast cancer cell lines, the MCF-7 cell line has been successfully used to examine the anticancer activity *in vitro*. The MCF-7 cell line is an estrogen receptor (ER) positive control cell line because of the presence of estrogen in the form of estradiol in the cell cytoplasm[46]. The hybrid pharmacophore approach has been used to synthesize the anti-breast cancer drug as the available drugs in the market, are often limited due to undesirable side effects[47]. The breast pre-malignant and cancer cells are enriched with copper which has been used in the inhibition of proteasome as clioquinol and pyrrolidine dithiocarbamate spontaneously binds with endogenous copper. Both CQ and PDTC show non-toxic effect alone but when they bind with endogenous copper, they become toxic in nature towards cancer cells[48]. The magnetic material like iron oxide has also been used for the treatment of breast cancer. It eliminates the tumor cell by magnetically induced heating which increases the temperature by 5°C[49]. Arafath *et al*. have synthesized metal complexes of nickel, palladium, and platinum with carbothioamide NSO tridentate Schiff base ligand. They have shown apoptotic features such as membrane blebbing and DNA condensation which led to new strategies to treat human cervical, breast, and colon cancer cell[50]. Xin Li *et al*. has put forward additional considerations that fluorine-containing Schiff base copper (II) complexes exhibit strong proteasome inhibitor activity followed by apoptosis against the breast cancer cell line[51]. Some of the ligands have been summarized in Fig. 4 which upon complexation with metals used in the treatment of breast cancer cell line.

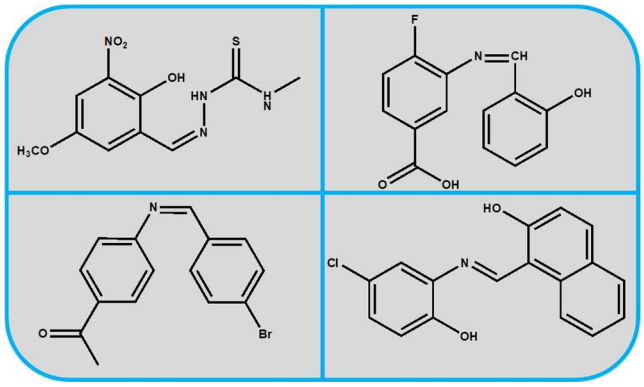


Figure 4: Different types of Schiff base ligands which upon complexation with metal ion, used in treatment of breast cancer [50-53].

The oxide-vanadium complexes have shown anticancer activity against MCF-7 cell lines using MTT assay. These complexes have shown the dose dependence anticancer activity as higher doses may cause undesirable side effects[52]. Ramadan *et al*. reported that Zn (II) complex of the synthesized Schiff base ligand (E)-1-(4-((4-bromobenzlidene)-amino)phenyl)ethanoate has better activity against breast cancer cell lines than the cisplatin. Activity of the reported aqua complex of Zn (II) has been attributed to the covalent cross-linking interaction with DNA as illustrated in **Fig. 5**[53].

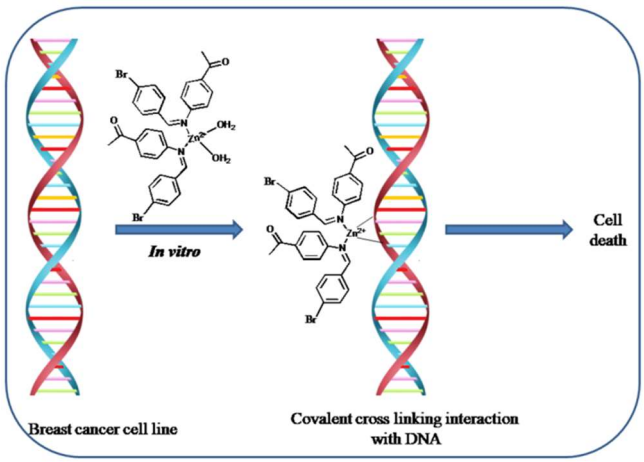


Figure 5: Covalent cross linking of Zinc complex with breast cancer cell line *in vitro*[53].

Liver cancer

Hepatocellular carcinoma is one of the deadly and common cancer in the world. Treatments usually used have low response rate, high recurrence rate with severe toxicity. Chemotherapeutic agents such as doxorubicin can be used in order to treat liver cancer but it has also adverse side effects[54]. The transcatheter arterial chemoembolization (TACE) method is used so that the liver tumor receives maximum effect otherwise nearly 60% of drugs have been excreted by the liver[55]. The method has been introduced by direct intra-arterial delivery of agents like 3-BrPA to liver tissue which arresting the growth of ATP production that induces the cell death[56]. *In vitro,* result revealed that the Schiff base copper complexes of nano-chitosan show higher inhibition rate against liver cancer cell lines SMMC-7721 than nano-chitosan[57]. The hybrid drug of podophyllotoxin-nor cantharidin has higher IC_{50} values than podophyllotoxin and lower toxicity against non-cancerous cell lines 293T by MTT assay[58]. Schiff base ligand derived from 4-(4-aminophenyl)morpholine derivatives and its Cu(II), Co(II), Zn(II) and VO(IV) metal complexes show cytotoxicity against HepG2 cell lines. Zn(II) complexes show better activity as compared with free Schiff base ligand due to increase in the conjugation upon complexation[59]. Ni(II) and Zn (II) complexes of Schiff base derived from 2-aminobenzamide and thiophene-2-carbaldehyde have been synthesized and was characterised by Tyagi and coworkers. Their anticancer activity has been studied against the cell line HepG2 from which Ni(II) complexes have shown 48% inhibition of cell proliferation[60]. Quinolinone is the important class of heterocyclic quinoline compound. They are well known for their diverse biological and therapeutical activities due to their physical and pharmacological properties such as conformational rigidity, charge density, lipophilicity, metabolic stability, and oral bioavailability. Some novel quinolinones have inhibitory activity against human immunodeficiency virus type-1 and they are also non-nucleoside reverse transcriptase inhibitors[61]. They are most effective target molecule for EGFR inhibitor and anticancer activity. Makawana *et al*. reported anticancer activity of quinoline derived Schiff base and also shows the EGFR inhibitor activity. They have synthesized Schiff base by the reaction of substituted 2-phenoxyquinoline-3-carbaldehydes and substituted 2-(2-methyl-5-nitro-1H-imadazoyl-1-yl)aceto-hydrazide. These compounds bind to the active site of EGFR receptor by hydrogen bonding, π-cation, and π-sigma interactions. They bind to the receptor by minimum binding energy by different substitution and spatial arrangement[62]. Anticancer activity of Cu(II) complexes has been reported by Creaven *et al*., derived from the condensation of 7-amino-4-methyl-quinolin-2(1H)-one and the substituted aromatic aldehydes. These Cu (II) complexes synthesized from Schiff bases show antimicrobial activity against the gram-positive and gram-negative species. Copper complexes of (7E)-7-(3-ethoxy-2-hydroxybenzylideneamino)-4-methylquinolin-2(1H)-one has the maximum anticancer potential using the human hepatic carcinoma cell line, Hep-G2 *in vitro* which is comparable to cisplatin as shown in Fig. 6 [63].

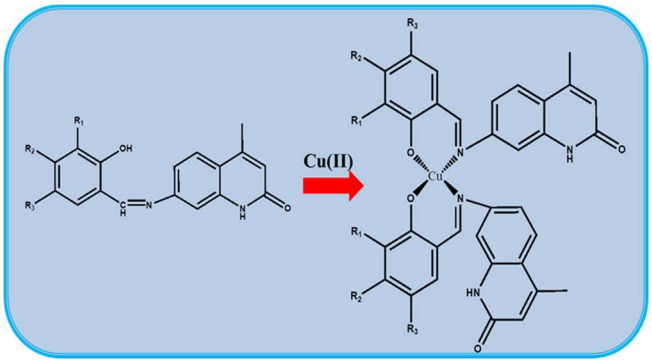
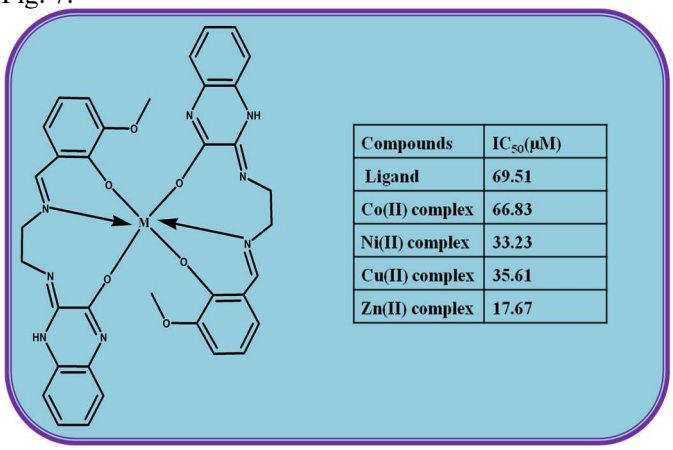


Figure 6: Copper complexes of (7E)-7-(3-ethoxy-2-hydroxybenzylideneamino)-4-methylquinolin-2(1H)-one which shows anticancer activity comparable to cisplatin (R is variable)[63].

Cervical Cancer: Cervical cancer is the most common cancer in women in the developing countries. The human papillomavirus (HPV) is a sexually transmitted infection and responsible for the cause of cervical cancer[64,65]. It has been observed that women with HIV-positive are more prone towards the HPV infection than HIV-negative women[66,67]. Cervical cancer can be treated with a combination of proteasome and histone deacetylases inhibitors, radiotherapy, surgery, and chemotherapy[68-71]. The design of anticancer drugs is based on the different labile group present on the ligand which interacts with duplex DNA and breakdown the DNA molecules[72,73]. The Schiff base ligand derived from indole-3-carboxaldehyde and 2-amino-3-carboxyethyl-4,5-dimethyl-thiophene and their Co (II), N i(II), Cu (II), Zn (II) complexes has been synthesized. Result of MTT assay revealed that Schiff base ligand show the least activity while Ni(II) complexes show the maximum activity when they were investigated against the human cervical carcinoma cell line (HeLa). The reason behind the higher anticancer activity of metal complexes rather than ligand is the enhancement of the lipophilicity upon chelation[74]. Chellaian and Johnson reported that tridentate ONO donor quinoxaline Schiff base ligand and their Co(II), Ni(II), Cu(II)and Zn(II) complexes have shown the antimicrobial activity. Their complexes have ability to bind with calf thymus DNA and possess anticancer activities *in vitro*. The anticancer activity of synthesized ligand and its complexes were

investigated by MTT cell proliferation assay. The IC_{50} values of MTT assay on human cervical carcinoma cells of these complexes are in the range of 17.67 to 69.59mM[75]. The proposed structure of metal complexes and IC_{50} values of the ligand and its complexes is given in Fig. 7.



Compounds	IC_{50}(μM)
Ligand	69.51
Co(II) complex	66.83
Ni(II) complex	33.23
Cu(II) complex	35.61
Zn(II) complex	17.67

Figure 7: The proposed structure of metal complexes of tridentate quinoxaline Schiff base ligand and their IC_{50} values of MTT assay on human cervical carcinoma cells (M= Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) [75].

Lung Cancer: Lung cancer is the leading etiologic of death in the United States and other developing countries after skin cancer. Chemotherapy, radiotherapy, and surgery or the combined radiotherapy-chemotherapy is generally used for the treatment of the lung cancer. The EGFR inhibitors are used as targets for treatment of the lung cancer[76]. Nanoparticle albumin-bound paclitaxel in combination with carboplatin is used in the first-line treatment of the NSCLC and has been achieved the objective response rate (ORR)[77]. The Sn (IV) complex of sulfonated Schiff base 2-[(2,3-dihydroxyphenyl) methylideneamino] benzenesulphonic acid has been synthesized. Non-convalent interactions have been shown by the ligand as well as $[Sn(n\text{-}Bu)_2(HL)(H_2O)]_2$ complexes such as hydrogen bonding and π-stacking which results in the formation of 3D network **(Fig. 8).** The antiproliferative activity has been studied and it has been found that Sn (IV) complex show effective cytotoxic agents on A-549 cell line *in vitro* and action pathway followed has also been studied using reactive oxygen species (ROS) generation and fluorescence-activated cell sorting (FACS)[78].

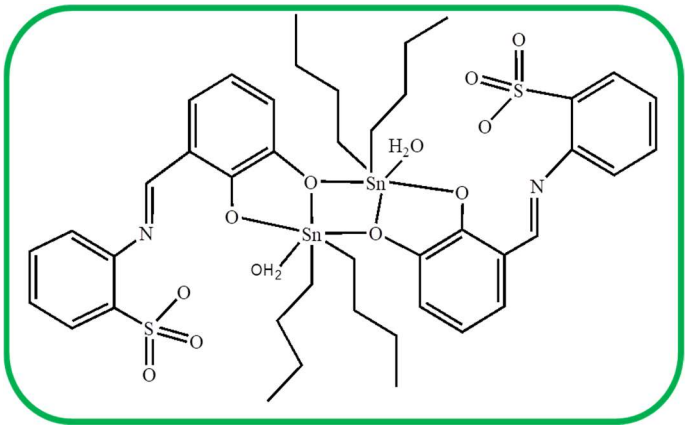


Figure 8: The proposed structure of $[Sn(n\text{-}Bu)_2(HL)(H_2O)]_2$ complex which is highly effective anticancer agents [78].

Future Directions: Schiff bases represent an important class of compounds that have been investigated in a large number of applications due to their versatile bonding behaviour and excellent therapeutic applications. Metal complexes of Schiff base also have enormous potential to bind to the cancerous cell lines. Although lots of research has been done in this area, still there is scope for the development of new molecules that serve as potential anticancer drug, relatively cheap and solve the problem of drug resistance. A variety of Schiff bases have been investigated for the anticancer activities which includes the variation in aldehyde/amine moiety and also in metal ions, which may further facilitate the discovery of novel drugs for various challenging diseases. We hope this review will help in designing new and more efficient anticancer drugs.

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