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Abstract:

Schiff bases are very important compounds synthesized from the condensation reaction of primary amines and carbonyl compounds having a wide application in industrial area and also have biological activities i.e., antibacterial, anti-inflammatory, antifungal, antimalarial, antiviral, anticancer properties. There are a lot of journals published the various applications of these compounds in past few decades. The various spectroscopical and elemental studies have done to show the binding of their metal complexes with DNA and various clinical applications and found some unbelievable results of these complexes in clinical field, i.e., cis platin and their derivatives like carbo platin have many side-effects with their anti-cancer treatment but metal complexes of Schiff bases reduce theseside-effects and also increase their activity.

Keywords: Schiff bases, DNA-binding, Intercalation, Spectroscopic, Biological activity, Transition metal complexes, Chemotherapeutic.

Introduction:

The Transition metal complexes and DNA interaction, has been the topic of research over the last several years. The binding of complex with DNA can be classified according to the type of association of complex with DNA, these are groove-binding, intercalation, coordinative binding, phosphodiester backbone-binding [1]. In the early twentieth century nitrogen mustard was discovered to have chemotherapeutic properties [2], and since then, progress has been made in the development of Transition metal complexes. cisplatin, was the first clinically successful platinum anticancer drug; Cisplatin is a widely used anticancer drug and has a very high curative effect on testicular cancer. Some functions of DNA, such as replication, Transcription and regulation through specific protein interactions after in-depth investigation [3-5]. The main focus of a scientist is on the drug development targeting DNA, because DNA is a genetic material which transfer genetic information from one living organism to another

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living organism.During the drug design from Schiff bases or from its metal complexes computational is also play a very important role like with the help of docking we can first find the idea of hotspot oractive site where the drug can bind. Molecular dynamics can also use to minimize the geometry. The experimental technique like elemental analysis, the spectroscopic techniques like IR, UV- vis are also very important to identify the geometry and binding with DNA.

DNA (Deoxyribonucleic acid): DNA Memory card of our genetic information. It is a genetic material which carries genetic information's in all living organism. DNA can store a huge data in 1 gm of it, so it may be a big achievement in future to store maximum amount of Data in small amount of DNA. It is the hot subject of research now and in future also. DNA is the finger print of the genetic information of each living organism. The Structure of DNA molecule consists of two strands that wind around one another to form double helix[6]. Each and every Strand contains a backbone which is made up of sugar and phosphate groups. The sugar which is present in the structure of DNA is deoxy ribose (Pentosesugar). The 1[°] carbon of deoxyribose is attached to the one of the four nitrogenous bases A, T,G, C. The two complementary strands of double helix DNA are held together by hydrogen bonds between the bases i.e. A and T attached by two hydrogen bonds whereas G and C attached by three hydrogen bonding and forms a base pair. The sequence of the bases along the backbone plays a quite important role to serve as information's for assembling protein and RNA molecules. When a drug molecule comes to bind with DNA it gets intercalate between two base pairs[7]. DNA has a major and a minor groove in its rigid double helix structure, out of these two grooves the major groove is deep and wide and the minor groove is narrower and shallow. The Complex can bound to the major or minor groove that is depends on its size and interaction. These are generally non covalent interaction. I found that in most of the research work they have used CT (Calf thymus) DNA, because it is easy and less costly to extracts DNA from calf. It resembles with mammalian DNA that's why peoples generally use it. Sometimes we use herring sperm DNA also for binding studies [8-9]. In this review properties and important applications of these ligands and their complexes by using the data which has been published already is presented. There are various properties which play a very important role in public service. The Schiff base also has a lot of applications in synthesis, as catalyst or many more. So, my complete focus in this paper is on the drug development targeting

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DNA.

Schiff Bases: Schiff bases are the nitrogen analogues of aldehyde or ketone in which the oxygen of carbonyl has been replaced by nitrogen of imine or azo-methylamino group. The formation of a Schiff base takes place when a primary amine reacts with a carbonyl compound (aldehyde or ketone) under some specific conditions. It is the N analogous of carbonyl compounds when one hydrogen got replaced by an alkyl group then the formation of primary amine takes place. When it reacts with aldehyde or some time ketones it forms Schiff base, which having N on the place of carbonyl oxygen attached bydouble bond and also attached to the alkyl group. This form of imine is very important in various organic reaction like ring opening, polymerization, dyes and many more[11].

Schiff base is the most favorite ligand due to the existence of the donor N atom and the stable imine function, which also stabilize the metal ion in various oxidation states. Schiff bases are widely used in medicinal Chemistry as in Alzheimer's disease, Cancer etc. Alzheimer's disease is a progressive neurological disease that can cause brain atrophy and brain cell death. It will be a great achievement if we will able to control on this disease in future. Alzheimer's disease is the most common cause of dementiacontinuous reduction in thinking, behavior and social skills can affect a person's ability to function independently[12-15]. And the Schiff bases which are chiral have more importance in organic synthesis. Schiff bases also play a very important role in the polymerization and Dyes which are very useful now a days in daily life. Most of the things we use in daily life contains polymer and the dyes are also equally important. Most of the catalytic reactions of Schiff bases are temperature dependent means it is depending on temperature that at which temperature it works well. In various reactions Schiff base enhance the rate and yield and also increase the selectivity. The chiral ligands exhibit stereoselectivity hence the formation of such Schiff bases becomes an important area of research now a days[16-19]. Many Schiff base complexes of metal ions show high catalytic activity. Chiral Schiff base complexes are more selective in various reactions such as oxidation, hydroxylation, aldol condensation and epoxidation[20-22]. The catalytic activity of metal complexes of binaphthyl, binaphthol and their combinations with salen Schiff base is presented in this review[17]. The pyridyl bis(imide) and pyridine bis(imine) complexes of cobalt(II), iron(II) ions have been used as catalysts in the polymerization of ethylene and

propylene[23-25]. The phenoxy-imine (FI) complexes of zirconium, titanium and vanadium and Schiff base complexes of nickel(II) and palladium(II) were also used as catalysts in the polymerization of ethylene. Schiff base complexes of metal ions were catalytic in ring opening polymerization processes at low temperature[26-28]. Schiff base complexes also catalyzed the oxidation of sulfides, thioanisoles, aldehydes, phenol and styrene. Schiff base complexes in super critical carbon dioxide (ScCO2) and in the presence of polar solvents were active catalysts. Schiff base complexes showed significant activity in catalyzing allylic alkylations, hydrosilation, the decomposition of hydrogen peroxide, isomerization, and annulation and carbonylation reactions[29]. The high thermal and moisture stabilities of many Schiff base complexes were useful attributes for their application as catalysts in reactions involving at high temperature. Schiff base ligands are easily synthesized and form complexes with almost all metal ions[30-32]. Many Schiff base complexes show excellent catalytic activity in various reactions at high temperature (>100 °C) and in the presence of moisture. Over the past few years, there have been many reports on their applications in homogeneous and heterogeneous catalysis, hence the need for a review article highlighting the catalytic activity of Schiff base complexes realized[33]. The interest in polymerization of olefins has increased recently due to the observed catalytic activity of Schiff base complexes in synthesis of commercially important branched and linear polyethylene[34]. The ring opening polymerization of cycloalkenes with transition metals such as tungsten, molybdenum and ruthenium in the presence of alkylating agents such as R4Sn or RAICl2 is possible at high temperature without any control on molecular weight of polymers. But Schiff base complex catalyzed ring opening polymerization of cycloalkenes at low temperature provided a control on the molecular weight of the polymers without any side reaction[35]. The oxidation of hydrocarbons using Schiff base complexes has been a field of academic and industrial interest to analyze the catalytic activity of various metal complexes. The ring opening of large cycloalkanes is usually a difficult process but Schiff base complexes of cobalt(II) and chromium(III) were effective in these reactions with significant enantioselectivity[36]. Phosphine substitution in N-heterocyclic carbene Schiff base ligand has enhanced ring closing metathesis reaction to synthesize functionalized olefins[37]. Schiff base complexes showed significant applications in reduction of

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ketones to alcohols and alkylation of allylic substrates. The phosphine Schiff base complexes also showed improved enantioselectivity inhydrosilation reactions[38]. The chiral Schiff base complexes of salen and binaphthyl were used as efficient catalysts in Michael addition reaction. Although the heteroannulation reaction is reported using transition metal complexes a new catalytic route for annulation reaction using Schiff base complexes has been an area of current research. Schiff base complexes showed catalytic activity in carbonylation of alcohols and alkenes at low pressure to produce -arylpropionic acid and their esters, which are used as non-steroidal anti-inflammatory drugs[39]. In addition to monometallic, the bimetallic Schiff base complexes also showed catalytic activity in carbonylation reactions[40]. The Heck reaction, an industrially useful process to synthesize fine chemicals and pharmaceutical, was successfully catalyzed using Schiff base complexes. The complexes of nickel(II) and copper(II) ions have increased enantioselectivity in alkylation of enolates. The enantiomeric synthesis of aziridines and amides with chiral metalloporphyrin was moderate but improved in the presence of Schiff base complexes of copper(II) and manganese(III)[41]. The isomerization of norbornadiene to quadricyclane was significantly catalyzed using diimine complexes of rhodium. These interconversions were useful for the storage of solar energy. The aluminium-salen Schiff base complexes were also used in catalyzing the addition of hydrogen cyanide to N-allylbenzaldimine, which showed significant enantiomeric excess. The enantioselectivity in the cyclopropanation reactions was modest; hence, attempts were also made to improve enantioselectivity in the cyclopropanation reactions using Schiff base complexes as catalysts[42]. The optically active cyanohydrins are widely used in the synthesis of drugs and pesticide. These synthesized successfully reacting trimethyl silylcyanide cyanohydrins were (TMSCN) with aldehydes in the presence of Schiff base complexes of transition metal ions. Schiff base complexes also played significant role in а desymmetrization of meso compounds with significant yield and enantiomeric excess^[43]. The homogeneous chiral lanthanum(III) Schiff base complexes showed catalytic activity in asymmetric Diels-Alder reactions and product yield and enantioselectivity were influenced by the nature of catalysts[44]. These studies are indicative that Schiff base complexes are potential catalysts to influence the yield and selectivity in chemical transformations; hence in this review, an attempt has

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been made to critically analyze and discuss the role of Schiff base complexes in various reactions. In Schiff base metal complexes, the environment at the coordination center can be modified by attaching different substituents to the ligand and a useful range of steric and electronic properties essential for the fine-tuning of structure and reactivity can thus be provided. The Schiff bases form metal complexes with p-block and d-block metals and these complexes have been known to act as highly efficient catalysts in various syntheses and other useful reactions. Many Schiff base complexes of ruthenium and palladium are used as catalyst in the syntheses of quality polymers. Unique asymmetric catalysis f metal complexes of salen and the related Schiff-base ligands has been reviewed by Katsuki. The review summarizes the generation of cis metallo-salen and its related complexes, their structural features, and their application to asymmetric syntheses. Wang et. al.[45] in 1999 reported the effective oxidation of olefins using Mn(II) amino acid Schiff base complexes. Gupta and Sutar reviewed the catalytic activities of transition metal complexes-both simple and polymer anchored. They have highlighted the potential of Schiff base complex as catalyst towards oxidations, hydrogenations, polymerizations, various coupling reactions and ring closures. Heterogenous and homogeneous catalysts have recently attracted the attention of chemists due to better selectivity and recyclability of the catalysts. In recent years there is an exponential increase in the number of publications in catalysis by supported Schiff base complexes. However, homogeneous catalysis is more relevant as the mechanism of the reaction can be arrived. BINAP ligands (BINAP is the abbreviation for the organophosphorus compound 2,2'- bis (diphenylphosphino)-1,1'binaphthyl) are famous for their stereoselective transformations. Cheand Huang has reviewed the catalytic activity of chiral BINAP Schiff base complexes in stereoselective organic transformations. Their studies reveal that these types of chiral metal complexes are active catalysts for stereoselective organic transformations including hydroxylation of styrene, aldol reactions, alkene epoxidation, trimethylsilyl cyanation of aldehydes, desymmetrization of meso-N-sulfonylaziridine, Baeyer-Villiger oxidation of aryl cyclobutanone, Diels-Alder reactions of 1,2-dihydropyridine, and ring-opening polymerization of lactide[46].

Classification of Schiff Bases: The classification of Schiff bases are as follows, firstly they are classified as on the basis of number of donor atoms in a ligand. 4-

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aminobenzenesulfonamide-1,3-benzodioxole-5-carbaldehyde Schiff base is a monodentate ligand with transition metal³¹. Monobasic bidentate Schiff bases of 2-((2,4- dichlorophenylimino)- methyl)-5-(diethylamino) phenol, 5-(diethylamino)-2-((3,5-dimethyl phenylimino)methyl)phenol. 2-((2-chloro-4-methyl phenylimino)methyl)-5-(diethyl amino)phenol, and 5-(diethylamino)-2-((2,6diethylphenyl imino)methyl)phenol[46]

K. Subin Kumar et. al[47]. Synthesized a novel tetradentate Schiff base ligand, (E)-3- ((2- ((E)- (1- (2- hydroxyphenyl)ethylidene)amino)-N-phenyl)ethylidene)amino) ethyl) imino)-N- phenylbutanamide (HEAc) Fig.1 and its VO(IV), Cr(III), Mn(II), Fe(III), Co(II), Ni(II) and Cu(II)complexes. To characterizing ligand, they have used analytical and spectroscopicallytechniques and elemental analysis, magnetic susceptibility, IR, UV-vis to characterized thecomplex. They also have evaluated the cytotoxic activities of ligand and its metal complexes.For the anti-tumor activities of its Cu(II) complex they have used Dalton Lymphoma Ascitescell persuaded tumour. For the treatment of tumour growth they have been used 15, 10 and 5three different concentrations (mg/kg body weight) of Cu(II) complex.



Fig. 1 Structure of the Schiff base ligand, HEAc. K. Subin Kumar et. al.

The magnetic moment (Table1) gives an idea about the geometry of the transition metal complexes have calculated with the support of Gouy balance at room temperature. At high temperature Schiffbase enhance the rate and yield of the reaction.

Si. No.	Complexes	Magnetic moment (BM)	Geometry
1.	[(VO)L]	1.71	Tetragonal Pyramid
2.	[Cr L(H2O)Cl]	3.88	Octahedral
3.	[Mn L(H2O)2]	5.91	Octahedral
4.	[Fe L(H2O)Cl]	5.88	Octahedral

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	5.	[COL]	4.78	Tetrahedral
(6.	[NiL]	3.40	Tetrahedral
	7.	[CuL]	2.01	Tetrahedral

Table. 1. Magnetic moment data and geometry of complexes.

Out of all complexes Cu(II) complex exhibited peak action and the concentration required for 50% death (IC50) was originate to be 47μ g/ml. Fig.2



Fig. 2. Variation of cytotoxity with concentration or cytotoxic act of ligand and its complexes. The concentration is taken in μg/ml. K. Subin Kumar et. al.

They found that the survival period of animal in the control group is 15.2 days. And the survival for standard id around 25.7 days. The survival for the copper complex with the concentration of 5, 10, 15 mg/kd18.7, 19.7 and 21.9 days correspondingly as shown in the Fig.3. Thus the Cu(II) complex suggests extra efficiency to growing the average existence span of the animal at 5, 10 and 15 mg/kg by the percentage of 44.8, 29 and 22 correspondingly. So the Cu(II) complex could be very powerful to continue to exist by growing the common existence span of rats.

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They all observe the tumour development by measuring thr diameter of tumour from 10^{th} day to 32^{th} day by using a digital Vernier caliper. The formula $V_1 = \frac{4}{3} \pi r^2 r_2$, is used to calculate the average value of the volume of tumour. In the formula the symbols have their usual indication i.e., r_1 , r_2 are indicating the minor and major diameter of tumour respectably Fig 4. The observation shows that on 32^{th} day the tumour of animal in control group varies by 3.001 cm^3 , But after the treatment with Cu(II) complex they found that there is a significant decrease in tumour volume. The volume observed 1.429 cm³ when treatment does with the concentration of 5mg/kg. whereas the volume was found to be 1.742 and 1.845 cm³ at the higher concentration 10 and 15 mg/kg. correspondingly.



Fig. 4 Effect of copper Copper complex of ligand on the solid tumour. K.

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Maria R, Martin J, B.S. Parajon-Costa et al[48]. Synthesized and characterized Schiff base ligand 2methoxy-6-{(E)-[(thiophen-2-ylmethyl)imino]methyl} phenol (HL), and its Cu(II), Zn(II) and VO(IV) complexes. Fig.5



Fig.5. Structure of the Schiff base ligand (HL). Maria R, Martin J, B.S. Parajon-Costa et al

They studied the binding with DNA with the help of agarose gel electrophoresis, UV Visible spectroscopy and computational studies like DFT, molecular Docking, molecular dynamics simulations, found that the ligand and its Cu(II) complex located in the minor groove while Zn(II) and oxovanadium (IV) complexes binds with the major groove of DNA. They found with the help of binding and cytotoxic studies that the Cu(II) complex caused double strand DNA cleavage, and having higher cytotoxic activities for tumor cell lines. Alaghaz, Abdel-Nasser MA, et al have Studied binding of metal complexes of Schiff base H2BHBDAP. They Synthesized and characterized the series of complexes of Schiff base H2BHBDAP by the help of Spectroscopical techniques.

Raman, N.S. Sobha, and A. Thamaraichelvan[49] have studied on binding of Schiff base which derived from tyramine and its complexes with DNA. Their structural characteristics and other properties are derived from elemental analysis, magnetic susceptibility, molar conductivity and mass, IR, UV-vis, 1H NMR and EPR spectroscopy.

Sobha, S., R. Mahalakshmi, and N. Raman[50] synthesized o-acetoacetotoluidide derived Schiff base ligands having good binding sites for metal ions. They form tetradentate ligand through an azomethine Nitrogen, a phenolic oxygen atom, enol carbonyl and complex of square planes Contains copper (II), nickel (II) and zinc (II)

ions.

Measurements and cyclic voltammetry indicate six metals The complex can interact with CT-DNA through insertion and binding Mode respectively.

The activity data show that equated with the parental Schiff base ligand, the platinum(II) complex has a stronger antibacterial effect on one or more microorganisms¹³. Synthesis of metal complexes Cu(II), Co(II), Ni(II) and Mn(II) with Schiff bases of glycine L-alanine and L-phenylalanine derived from o-phthalaldehyde and amino acids , And then tested against three fungi. Apparently, Cu(II) and Ni(II) complexes exhibited inhibitory effects on all the deliberated microorganisms, but Co(II) and Mn(II) complexes exhibited less inhibitory effects, while VO(II) complexes exhibited less inhibitory effects. The substance has no activity againstmicroorganisms¹⁴ Mustapha et. al[51]. synthesized, A Novel Schiff base bidentate ligand (3-{(E)-[(4-iodophenyl)imino]methyl}quinolin-2-ol) and characterized by 1H NMR and Mass spectroscopy. Its transition metal complexes with Cu (II), Zn(II), Ni(II) and La(III) having squire planer geometry.

A arrangement of Benzothiazole based ligand 2-((E)-(6-ethoxybenzo[d]thiazol-2ylimino) methyl)-4-nitrophenol and their Cu(II), Co(II), Ni(II), Zn(II) and Cd(II) complexes were synthesized and characterized by N.N. Rao, E. Kishan and K. Gopichand et.al[52]. The characterization performed by utilizing physical, explanatory and ghostly information such as essential examination. They found the square planer geometry for all these metal complexes by utilizing spectroscopic test information. The cytotoxicity rate decreases when we treated it with the metal complexes of Schiff bases. The living thing survive more time when it treated with the ligand and a more survival rate when it treated with the metal complexes. The DNA

binding studies of these metal complexes is also much important because DNA plays a very important role, it transfers genetic material from one organism to another.

Vincent, Sharow Geeth et.al[53] synthesized a bidentate flavone-Schiff base ligand and their Co(II), Cu(II) and Ni(II) complexes, and performed various experiments for binding properties with CT-DNA like electronic absorption spectra, viscosity measurement, Fluorescence quenching study.. All the above results suggest that the reactivity of Cu(II) complex is high then other metal complexes and the ligand shows lesser activity then metal complexes. By the viscosity measurement studies they have seen that order of interaction of the transition metal complexes to the CT-DNA is > Cu

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> Co > Ni. During viscosity measurement they found that increase in viscosity which suggest that the complex can bind to DNA by the intercalation binding mode which are consist with fluorescence and electronic data.

Savas Kaya et.al.[54] has synthesized two Schiff bases and studied their binding by computationalas well as experimental techniques as molecular docking and NMR, FTIR, UV-vis respectively. They also synthesized Pd, Fe, Cu metal complexes of these Schiff bases. They found that the ligand and the metal complexes bind in the minor groove of the DNA. The Auto Dock study shows the interaction energy and the hydrogen bonding with DNA. They also have showed thechanges in the geometry of DNA during ligand or complex binding with DNA by spectroscopic methods. The Cu(II) and Fe(II) complexes of Schiff base were found to have octahedral geometry.

In this study [1-(4-{[(3-hydroxynaphthalen-2-yl)methylidene]amino}phenyl)ethan-1one (B1 ligand) were synthesized from the reaction of 2-hydroxy-1-naphthaldehyde with 4- amino-acetophenone. Following that 1-(N-{4-[(1)-1-({6-[(Z)-[1-(4-{[(3hydroxynaphthalen-2-yl) methylidene]amino}phenyl) ethylidene]amino]pyridine2- yl} imino)ethyl]phenyl}carboximidoyl)naphthalen-2-ol (L1 ligand) were synthesized from the reaction of 2,6-diamino pyridine with B1 ligand. Using this Schiff base ligand Cu(II), Fe(II) and Pd(II) complexes were prepared. The structure of the ligand and its complexes were determined by ¹H NMR, FT IR, UV-Vis, elemental analysis, thermal analyses and magnetic susceptibility spectral data. Further, DNA binding properties of the ligand and its metal complexes were investigated and docking studies were carried out. As a result, ligands and copper complex showed DNA binding activity and an increase with H2O2. According to these results it can be suggested that these compounds are very suitable drug candidates. Molecular docking studies were performed to elucidate binding mode of the compounds with DNA. Auto Dock 4.2 and MGL Tools 1.5.6 were used for docking analyses. Since it was previously reported that the best scores were obtained by the Lamarckian algorithm this algorithm was employed in the docking process. For that purpose, crystal structure of the DNA file was retrieved from RCSB Protein Data Bank with PDB ID: 1BNA (https://www. rcsb.org), then water molecules were removed and hydrogens were added. The grid box was constructed with 62 56 110 Å dimensions and 0.375 Å grid spacing. As there were no parameters for copper and palladium in auto dock default parameter

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file, these parameters were retrieved from the United ForceField (UFF) for Cu and Pd atoms as radii 3.50 and 2.89 Å and well depth 0.015 and 0.048 kcal/mol, respectively. For iron atom, auto dock's default parameters were used. Since Gasteiger charges cannot be calculated for metals in MGL Tools, these charges taken from literature. As a result, charges for copper, iron and palladium wereset as b0.38, b1.35 and b 0.37 in the same order. Then, these charges and parameters were used for docking process as shown in previous studies. For all the remaining autodock parameters, default values were used and results were analyzed with Discovery Studio Visualizer software. According to the docking results, all complexes and ligands bound to DNA only via the minor groove. Between the L1 ligand and DNA, 4 hydrogen bonds. Similarly, B1 ligand forms only one hydrogen bond as shown. The DNA binding rankings for the complexes were L1 [Cu] > L1 [Fe]> L1 [Pd] in both hydrogen peroxide free experimental environment and the docking studies whereas the ligands showed less DNA binding activity than Cu complex in contrast to the docking result. The reason may be attributed to the fact that the solvents in the experimental ambience alter the DNA-binding activity of the compounds, but docking is performed in a vacuum. The changes in the DNA-binding activities of all compounds in the hydrogen peroxide environment also supports this suggestion.

Conclusion:

Schiff bases and their metal complexes are one of the most important chemical classes of compounds having a common integral feature of a variety structural diversity and of active medicinal agents. This review reflects the contribution of Schiff bases to the design and development of novel lead having potential biological activities. This bioactive core has maintained the interest of researchers in gaining the most suggestive and conclusive access in the field of various Schiff bases of medicinal importance from last decades. The present review is an attempt to present the chemistry of Schiff bases and their metal complexes along with their catalytic and Ribonucleotide Reductase activity. Moreover, Schiff bases and their metal complexes plays very important role in medicines, catalyst, dyes and many more. These are also very easy to synthesize. The binding of the metal complexes with DNA can takes place by various methods i.e., intercalation, groove binding, coordinatively, bi phosphor ester linkage. The binding of complex with DNA is depends on the shape

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and size of the components present in the complex whether it is planer or not. The

antitumor, anticancer, antibacterial compounds works well when they bind with DNA

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