

Review Article

Selected Pharmacological Applications of 1st Row Transition Metal Complexes: A review

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To cite this article:

Md. Saddam Hossain, Pijush Kanti Roy, Roushown Ali, C. M. Zakaria Md. Kudrat-E-Zahan. Selected Pharmacological Applications of 1st Row Transition Metal Complexes: A review. *Clinical Medicine Research*. Vol. 6, No. 6, 2017, pp. 177-191. doi: 10.11648/j.cmcr.20170606.13

Received: August 1, 2017; **Accepted:** August 7, 2017; **Published:** November 27, 2017

Abstract: Ninety elements occur naturally on earth. Out of these, nine are radioactive and among the remaining eighty one that could support life, sixty one are metals. Our bodies have approximately 3% metal. Researchers have been established that some of metal complexes were biologically active. A significantly rising interest in the design of metal complexes as drugs and diagnostic agents is currently observed in the area of scientific inquiry, specifically termed medicinal inorganic chemistry. Investigations in this area focus mostly on the speciation of metal species in biological media based on possible interactions of these metal ions with diverse biomolecules. In an effort to contribute to future development of new therapeutics or diagnostic agents metallo pharmaceuticals used as anticancer agents, anti-HIV, metal-mediated antibiotics, antibacterials, antivirals, antiparasitics, antiarthritics, antidiabetics and radio-sensitizing agents appear in therapeutic medicinal inorganic chemistry. The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance.

Keywords: Transition Metal Complexes, Antibacterial Activity, Antifungal Activity, Cytotoxicity, DNA-Interaction

1. Introduction

Metal ions play important roles in biological processes and the field of knowledge concerned with the application of inorganic chemistry to therapy or diagnosis of disease is medicinal inorganic chemistry [1]. The introduction of metal ions or metal ion binding components into a biological system for the treatment of diseases is one of the main subdivisions in the field of bioinorganic chemistry [2-5]. A characteristic of metals is that they easily lose electrons to form positively charged ions which tend to be soluble in biological fluids. It is in this cationic form that metals play their role in biology. Metal ions are electron deficient, whereas most biological molecules such as proteins and DNA are electron rich. The attraction of these opposing charges leads to a general tendency for metal ions to bind and interact with biological molecules [6-7]. This same principle applies to the affinity of metal ions for many small molecules and ions

crucial to life, such as oxygen. Given this wide scope for the interaction of metals in biology, it is not surprising that natural evolution has incorporated many metals into essential biological functions. Metals perform a wide variety of tasks such as carrying oxygen throughout the body and shuttling electrons. Hemoglobin, an iron-containing protein that binds to oxygen by which it carries this vital molecule to body tissues. Similarly, calcium-containing minerals are the basis of bones, the structural framework of the human body. Metals such as copper, zinc, iron and manganese are incorporated into catalytic proteins, the metalloenzymes, which facilitate a multitude of chemical reactions needed for life. Metal complexes are already in clinical use, and encourage further studies for new metallo drugs such as metal mediated antibiotics, antibacterials, antivirals, antiparasitics, anti-HIV [8], anti-diabetes, radio-sensitizing agents and anticancer compounds. However, their mechanisms of action are often still unknown. Nowadays, the bioinorganic chemists target

the heterocyclic ligands and their metal complexes to study their pharmacology as the main focus of research [9-10]. A wide range of biological activities [11-30] such as antibacterial, antifungal, antitumor, anti-HIV [31] and antiviral activities are exhibited by the nitrogen-containing organic compounds and their metal complexes. Transition metal complexes offer two distinct advantages as DNA-binding agents [32]. First and foremost, transition metal centers are particularly attractive moieties for reversible recognition of nucleic acids research because they exhibit well-defined coordination geometries. Besides, they often show distinct electrochemical or photophysical properties, thereby increasing the functionality of the binding agent [33]. In fact, these smart features have fuelled the complexes to be used in a broad spectrum of applications, from fluorescent markers to DNA footprinting agents, to electrochemical probes [34]. Among the metal ions regarded as coordination centers of potential anticancer agents, platinum and ruthenium ions are commonly explored [35-37]. However, there is an emerging curiosity in the synthesis of cheaper first-row coordination compounds as efficient DNA binders with potential cytotoxic activity [38-42]. Hence, herein the attention is focused primarily on the research concerning with a few pharmacological activities of the cheaper and easily available first-row transition metal coordination compounds V(IV), V(II), Cr(III), Mn(II), Fe(II) and Co(II) complexes. Moreover, these metal ions are the essential elements present in the biological intracellular environment of living organisms. They are most abundantly found trace elements present in biological systems together with iron and most of the metalloproteins have these elements [43-46]. These metal ions are nowadays present in several inorganic pharmaceuticals used as drugs against a variety of diseases, ranging from antibacterial and antifungal to anticancer applications [48-52]. In addition to that, the N-heterocycles and pyrazolones as ligands affect the environment of the complex in such a way that their lipophilicity increases which is a major factor in designing a drug. The chosen ligands and their characteristic are discussed in detail in the further sections. The literature survey reveals that numerous review articles and books have been published on medicinal inorganic chemistry [53-54] in the field of metallodrugs [55-59] and especially on anticancer treatments [60-61]. We present an overview of the field today and explore a selected pharmacological V(IV), V(II), Cr(III), Mn(II), Fe(II) and Co(II) complexes.

2. Bioactive Complexing Agent

Schiff bases, the condensation products of carbonyl compounds and primary amines were first discovered by German chemist noble prize winere Hugo Schiff [62]. The Schiff base compounds containing the azomethine group having the general formula $RHC=N-R'$, where R and R'=Alkyl, cyclo alkyl, aryl, or heterocyclic groups may be

differently substituted (Figure 1, 2). The Schiff bases are considered as 'privileged ligands' because of their capability to stabilize different metals in various oxidation states and their metal chelates are widely studied owing to the synthetic flexibility, sensitivity and selectivity toward various metal ions [63-69]. In azomethine derivative, the C=N linkage is essential for biological activity. Several azomethines were reported to possess important biological activities [70-71]. In many cases, beside the N-donor atoms, there are several other donor atoms such as O and S in the backbones of the ligands such that they can be coordinated to transition metal ions in the various modes to form the stable metal complexes [72-85]. These ligands are not only used in the development of coordination chemistry but also find applications in catalysis, optical and bioinorganic chemistry [86]. Aliphatic Schiff bases are relatively unstable [87, 88] and easily polymerizable compared to aromatic Schiff bases because the latter possesses effective conjugation and hence they are more stable. Generally, in condensation reactions, aldehydes react faster than ketones leading to the formation of Schiff bases because the reaction centres of aldehydes are sterically less hindered than ketones. Moreover, the additional carbon of ketone contributes electron density to the azomethine carbon and makes the ketone less electrophilic compared to the aldehyde. Generally, Schiff bases are classified into bidentate, tridentate, tridentate, tetradentate, hexadentate (figure 3) which are capable of to form very stable complexes with transition metal ions. If they contain additional functional groups like -OH, -NH₂ or -SH, the resulting Schiff bases can serve as mixed-donor ligands which can participate in bi-, tri-, tetra- and higher coordination modes. Therefore, the suitable choice of metals in a pharmacologically active organic scaffold changes the pharmacological activity. The literature survey indicates that the pharmacological activity depends on the nature of metal ion, organic scaffold and specific DNA binding site [89, 90]. The mechanism involved in the formation of metal complexes through monodentate and bidentate ligands is represented in a schematic diagram (Figure 4).

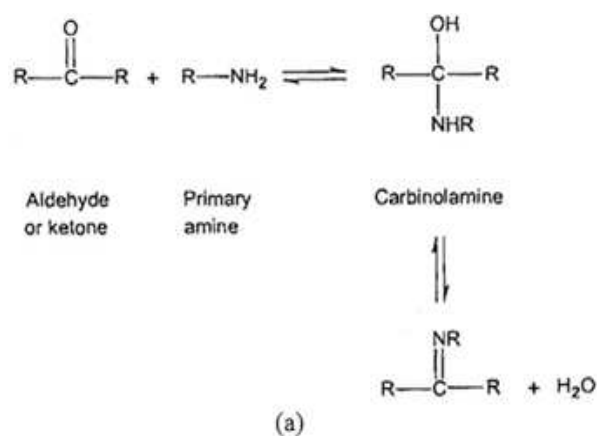


Figure 1. Reversible reaction of a Schiff base formed from an aldehydes or ketones.

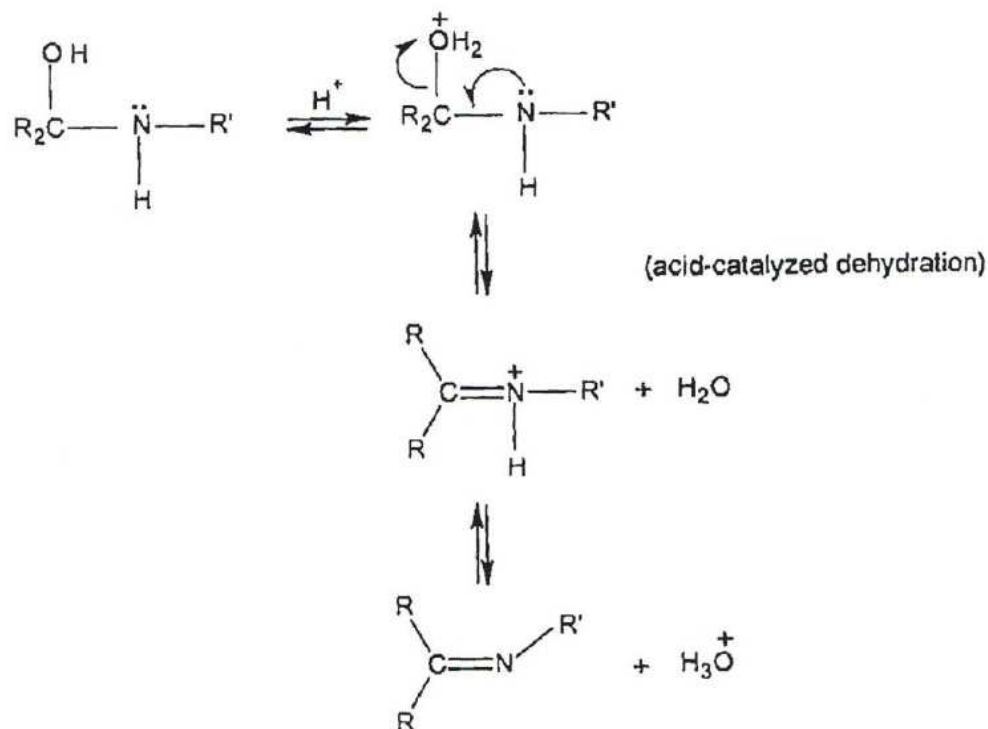


Figure 2. Mechanism of formation Schiff base.

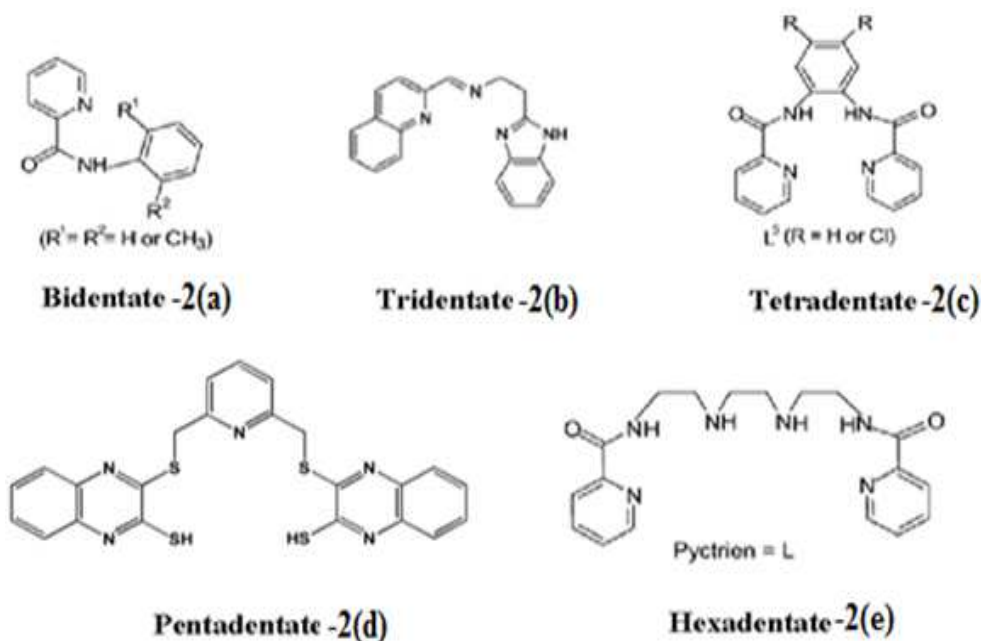


Figure 3. Few classes of Schiff base ligands.

Schiff base complexes with different transition metals can act as catalysts for various reactions [91, 92]. The metal complexes of thiosemicarbazone dramatically increase the biological activities such as antibacterial, antifungal, anti HIV, and anti-inflammatory [93]. Thiosemicarbazones and their metal complexes are also applicable in the field of material sciences such as nonlinear optical (NLO) [94],

electrochemical sensing [95], and Langmuir film [96]. Schiff bases derived from isatin exhibit many neurophysiological and neuropharmacological effects like antimicrobial, antiviral, anticonvulsant, anticancer, antimycobacterial, antimalarial, cysticidal, herbicidal and anti-inflammatory activity. They also exhibit anti-HIV, antiprotozoal and antihelminthic activities [97–98].

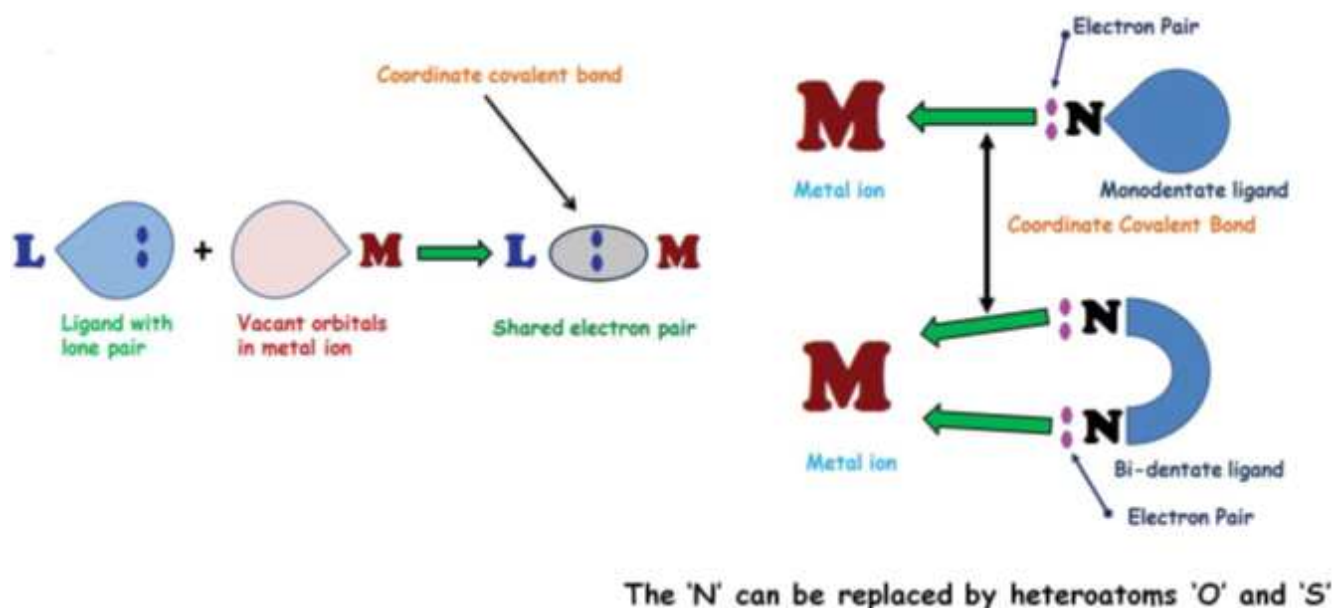


Figure 4. Schematic representation behind the formation metal complexes.

3. Pharmacological Activity of Metal Complexes

3.1. Antimicrobial Activity

Antibiotics, also called antibacterials, are a type of antimicrobial drug used in the treatment and prevention of bacterial infections. They may either kill or inhibit the growth of bacteria. 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 novel antibacterial 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 (Kamalakkannan 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 et al. 2011). Transition metals involved in various biological processes are essential to life processes; hence, they can coordinate with O- or N-terminals from proteins in a variety of models, play an important part in the conformation and utility of living macromolecules (Colacio et al. 2000, Karaliota et al. 2001), and act as an antimicrobial agent (Scozzafava et al. 2001). The phosphate Schiff base ligands of four- and six-coordinate metal chelate complexes have been reported to possess remarkable bacterial properties; however, this interesting biological activity could be enhanced upon the complexation with the metal ions (Abd EI-Wahab and

EI-Sarrag 2004). Garima Vatsa, O. P. Pandey and S. K. Sengupta were synthesized Titanocene Chelates of Isatin-3-Thiosemicarbazones and shown their toxicity property [99]. Ahmed M. Naglah, Hassan M. Awad and et al. synthesized novel isatin Schiff bases linked to nicotinic acid via certain amino acid bridge and described their antibacterial activity [100]. S. N. Pandeya, S. Smitha and et al were prepared some isatin derivatives and shown their biological activities [101]. W. Chu, J. Zhang, C. Zeng et al were synthesized N-benzylisatin sulfonamide analogues and shown as potent caspase-3 inhibitors [102]. W. Chu, J. Rothfuss, Y. Chu and et al were synthesized and determined in vitro evaluation of sulfonamide isatin Michael acceptors as small molecule inhibitors of caspase-6 [103]. Z. H. Chohan, H. Pervez and et al. prepared isatin based transition metal complexes and shown their antibacterial and antifungal property [104]. B. R. Nathani, K. S. Pandya and et al. synthesized some isatin derivatives and shown their antimicrobial activity [105]. T. Aboul-Fadl, H. A. Abdel-Aziz and et al. shown Schiff bases of indoline-2,3-dione as potential novel inhibitors of mycobacterium tuberculosis (Mtb) DNA gyrase [106]. Ahlam J. Abdul-Ghani and Asmaa M. N. Khaleel were synthesized new Schiff base ligand derived from N (1)-Substituted Isatin with Dithiooxamide and their Co(II), Ni(II), Cu(II), Pd(II), and Pt(IV) Complexes [107]. G. Cerhiaro and A. M. D. Ferreira were synthesized Oxindoles and copper complexes with oxindole-derivatives as potential pharmacological agents [108]. V. K. Sharma, S. Srivastava, and A. Srivastava were synthesized novel coordination complexes of the trivalent ruthenium, rhodium and iridium with hydrazones derived from isatin hydrazide and various aldehydes and investigate their biological activity [109]. R. M. Abdel Rahman and et al. synthesized of some new substituted 1,2,4-triazino-indole derivatives and related compounds and determine them as potential antifungal agent [110]. S. N. Pandeya, A. S. Raja, and J. P. Stables were synthesized isatin

semicarbazones as novel anticonvulsants-role of hydrogen bonding [111]. T. R. Bal, B. Anand, P. Yogeewari, and D. Sriram were prepared isatin β -thiosemicarbazone derivatives and evaluated as anti HIV active agent [112]. N. M. A. Al-Abidy was synthesized new Mannich- Schiff bases and some metal complexes derived from isatin, 3-amino-1,2,4-triazol and dithiooxamide [113]. Ahlam J. Abdulghani and Nada M. Abbas were synthesized some new Schiff and Mannich bases and some metal complexes derived from isatin and dithiooxamide and evaluated their biological activity [114]. S. N. Pandeya, D. Sriram, G. Nath, and E. De Clercq were synthesized some Schiff and mannich bases of isatin and its derivatives antiprimidine also evaluated their antimicrobial activity [115]. D. Maysinger and et al. synthesized some isatin analogue and determine their antimicrobial activity [116]. Ayman El-Faham and et al were synthesized some novel isatin derivatives and shown their biological activity [117]. M. C. Pirrung, S. V. Pansare and et al. shown isatin- β -thiosemicarbazones as anti-poxvirus agents [118]. A. Jarrahpour, D. Khalili were synthesized some new bis-Schiff bases of isatin and their derivatives and evaluated their antimicrobial, antifungal and antiviral activity [119]. M. Verma, S. N. Pandeya and et al were shown the anticonvulsant activity of isatin derivatives [120]. Sonika Jain, Anamika Sharma were synthesized Some Novel Trisubstituted s-Triazine Derivatives Based on Isatinimino, Sulphonamido, and Azacarbazole and evaluated their antimicrobial activity [121]. G. S. Singh, T. Singh and et al were synthesized new isatin-based spiroazetidiones and investigate their anticonvulsant activity [122]. Ronald Sluyter and Kara L. Vine and et al were shown N-Alkyl-Substituted Isatins Enhance P2X7 Receptor-Induced Interleukin-1 β Release from Murine Macrophages [123]. Ravi Jarapula and Kiran Gangarapu were prepared some isatin derivatives and shown their in vitro antiviral activity and molecular docking study [124]. K. Han, Y. Zhou, F. Liu et al. were designed, synthesised and in vitro cytotoxicity evaluation of 5-(2-carboxyethenyl)isatin derivatives as anticancer agents [125]. Mohd Abdul Fatah Abdul Manan and et al were shown crystal structure and cytotoxicity of centrosymmetric copper(II) complex derived from S-methyldithiocarbazate with isatin [126]. Patitungkho S, Adsule S, Dandawate P and et al were shown anticancer property of Cu(II) complexes of isatin[127]. Mohd Abdul Fatah Abdul Manan and et al were synthesized S-Benzylidithiocarbazate Schiff Bases Derived from 5-Fluoroisatin, 5-Chloroisatin, 5-Bromoisatin and evaluated their crystal structure and cytotoxicity effect [128]. G. Valarmathy and R. Subbalakshmi synthesized some Schiff base metal complexes and investigated their biological

activity [129]. Walcourt. A, Loyevsky and et al. synthesized Novel aroylhydrazone and thiosemicarbazone iron chelators with antimalarial activity against chloroquine resistant and sensitive parasites [130]. Gomathi. V and Selvameena. R prepared 3d transition metals and with Schiff Base derived from Sulfadiazine and 2- acetylnaphthalene and found their biological activity [131]. Shivakumar K, Shashidhar P, Vithalreddy, Halli M B investigated biological activity of benzofuran Schiff bases with Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) Complexes [132]. Rajesh D.

Hunashal and D. Satyanarayana prepared Schiff base metal complexes and determine their antimicrobial activity [133]. M. T. H Tarafder and et al. synthesized metal complexes with N, O and S containing Schiff base ligand and shown their biological activity [134]. Rajendran Jayalakshmi and Rangappan Rajavel synthesized some novel Schiff base metal complexes and determine their biological properties [135]. SumanMalik and et al. synthesized some 3d transition metal complexes containing Schiff base ligand and determine biological activity [136]. S. Z. Bootwala and et al. prepared binuclear oxovanadium (IV) complexes also investigated their biological application [137]. M. Revanasiddappa and et al. prepared first row transition metal complexes with Schiff base ligand and shown their biological properties [138]. P. Subbaraj et al. synthesized some Schiff base metal complexes and determined their DNA interaction and pharmacological activity [139].

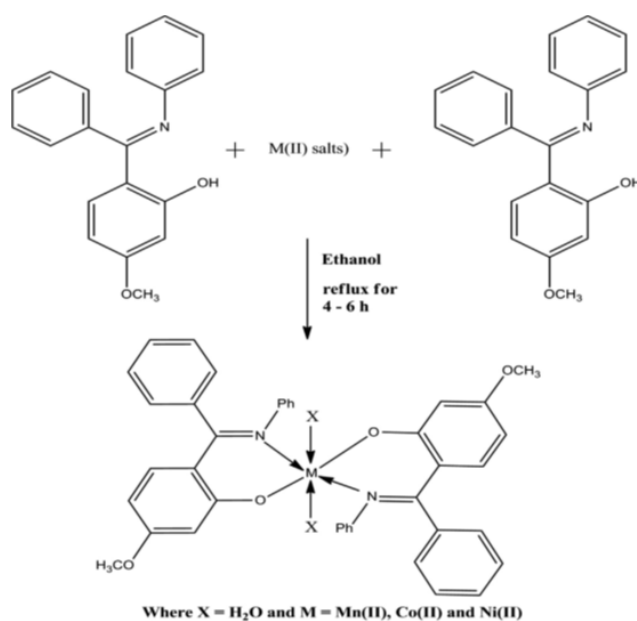


Figure 5. General outline for the synthesis of Schiff base metal(II) complexes.

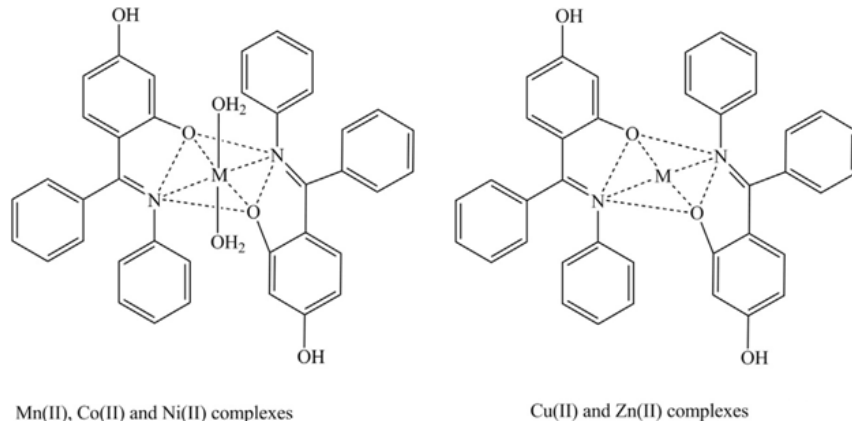


Figure 6. Proposed structures of the Schiff base metal complex Chung-Hang Leung and et al. shown metal complexes as potential modulators of inflammatory and autoimmune responses [140].

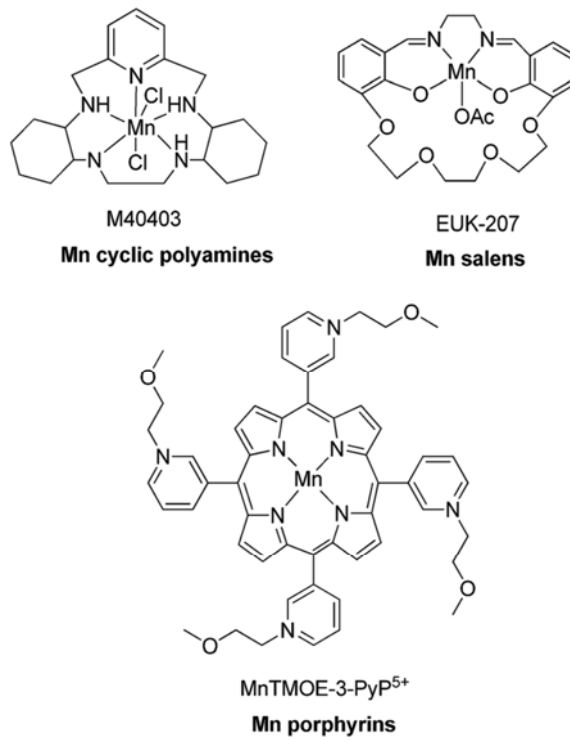


Figure 7. Chemical structures of Mn porphyrins, Mn cyclic polyamines and Mn salen derivatives.

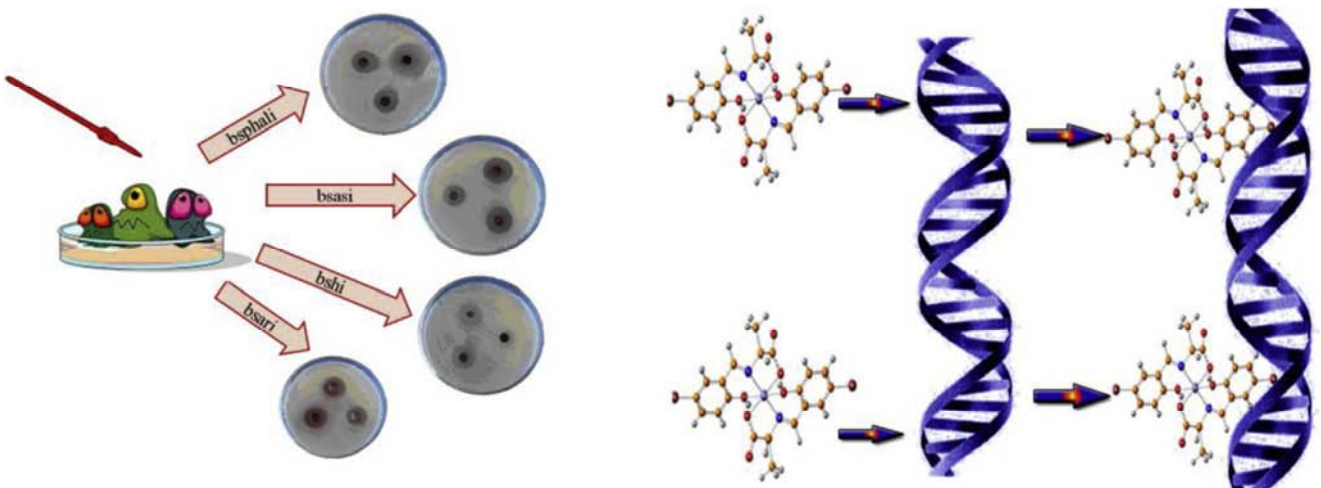


Figure 8. Schematic diagram for antibacterial activity and DNA interaction of the investigated complexes.

3.2. DNA-Metal Complexes Interactions

DNA is the storage site of cellular information that is accessed continuously for storing and dispensing information required for existence. Thus, it acts as the main intracellular target for those who thrive to develop a new drug for innumerable diseases, especially cancer. Added to the fact, small molecules that can bind and react with specific DNA sites provide a means to access and manipulate this cellular information creating the desired results. There are many binding modes by which the small molecules bind to the DNA which are covalent and non-covalent binding. Cisplatin binds covalently with the DNA thereby restricting its replication. Among the non-covalent binding modes, intercalation, groove binding and external electrostatic binding, intercalation is the most important one because it invariably leads to cellular degradation. Humungous reports are available throughout the literature regarding the interactions of V(IV), Ni(II), Co(II), Cu(II) and Zn(II) complexes with DNA and still now many research groups have actively involved in this field [141-143]. Among the research groups, most of them are concentrating only copper Schiff-base complexes. For, copper is found in all living organisms and is a vital trace element in redox chemistry, growth and development. It is significant for the function of

several enzymes and proteins involved in energy metabolism, respiration and DNA synthesis, particularly cytochrome oxidase, superoxide dismutase (SOD), ascorbate oxidase and tyrosinase. Copper is found to bind DNA with high affinity than any other divalent cation, thus promoting DNA oxidation. Acquaye *et al.* synthesized two new copper Schiff-base complexes and carried out DNA interactions with CT-DNA [144]. Yang and his colleagues have synthesized and characterized two novel Schiff base copper(II) complexes derived from kaempferol and polyamines such as ethylenediamine and diethylenetriamine. They evaluated the DNA interactions with CT DNA and predicted the mode of interactions to be intercalation [145]. An extensive DNA-metal complex interaction has been carried out by Lin and his colleagues by synthesizing two new benzimidazole based copper complexes. The studies showed that the complexes exhibited partial intercalation towards the DNA [146]. The novel copper complexes synthesized by Gup and Gokce are found to bind significantly to calf thymus DNA by both groove binding and intercalation modes and effectively cleave pBR322 DNA [147]. Xu *et al.* synthesized three novel structurally associated copper(II) complexes which displayed enhanced intercalation into CT DNA [148].

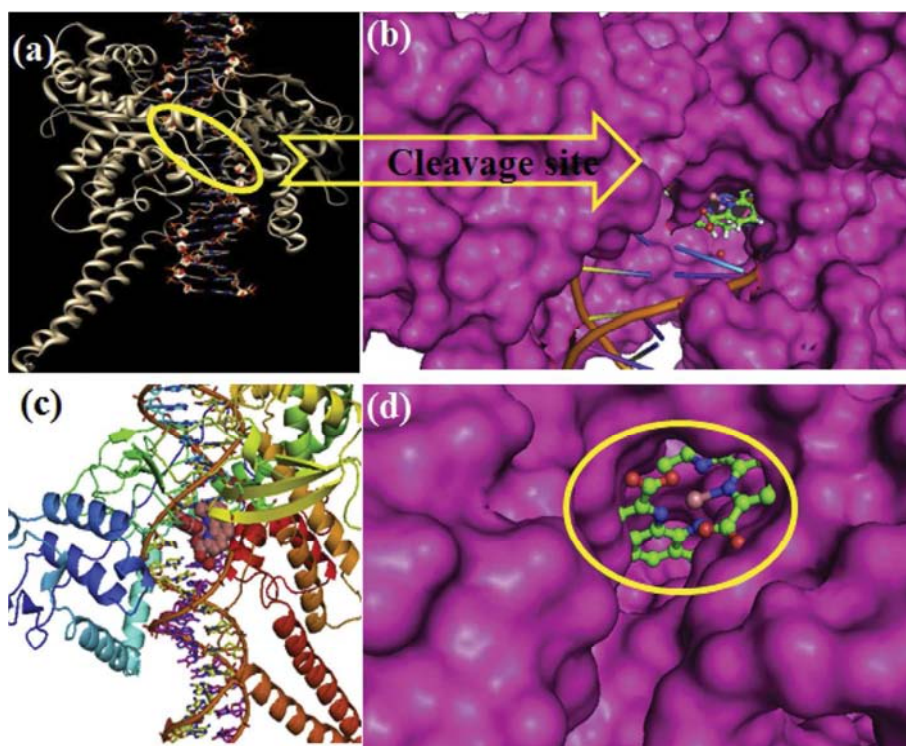


Figure 9. Diagram showing in (a) human-DNA-Topo-I (70 kDa) (PDB ID: 1SC7), (b) docked model of $\{[Co(mpca)_2].H_2O\}$ occupying cleavage active site of Topo-I, DNA is represented by the structure shown as stick representation, (c) docked model $\{[Co(mpca)_2].H_2O\}$ (surface representation) towards the cleavage site of Topo-I (cartoon representation) and (d) binding of $\{[Co(mpca)_2].H_2O\}$ in the Topo-I pocket, preventing the building of the topoisomerase I-DNA complex represented via surface presentation.

Natarajan Raman, Sivasangu Sobha, Liviu Mitu *et al.* synthesized isatin-derived tyramine bidentate Schiff base and its metal complexes also evaluated their structural elucidation,

DNA interaction, Biological property and molecular docking model [149] as shown (figure 10-14) respectively.

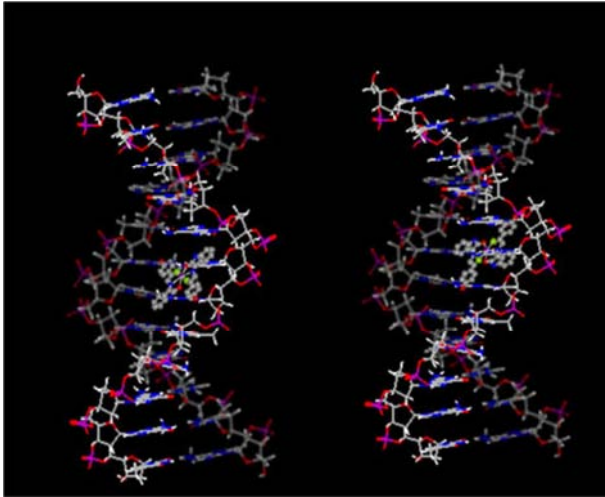


Figure 10. Interaction of the complexes $[CuL_2Cl_2]$ and $[ZnL_2Cl_2]$ with $d(CGCGAATTCGCG)$ strands of DNA by the minor groove binding approach.

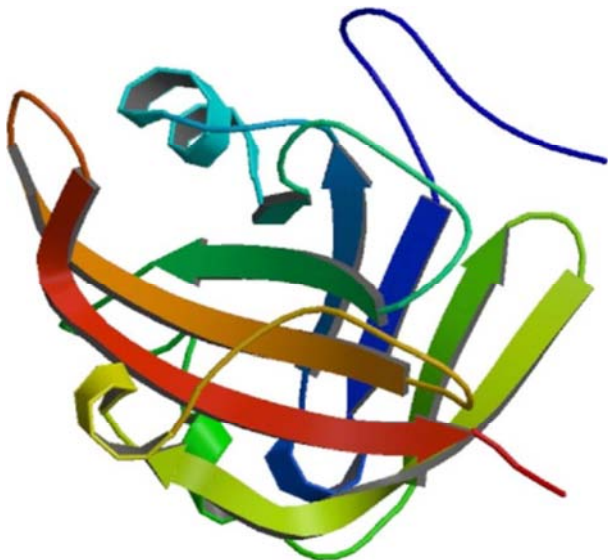


Figure 11. Crystal structure of *Staphylococcus aureus* sortase-A (PDB ID1T2).

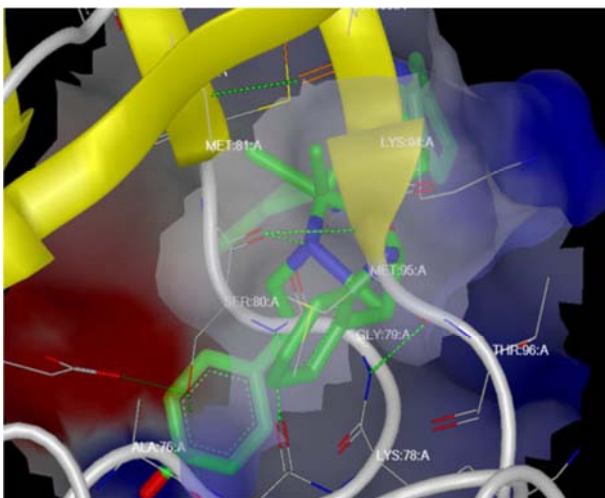


Figure 12. The binding model of the Schiff base complex $[ZnL_2 CL_2]$ in the enzyme active site of *Staphylococcus aureus* sortase-A.

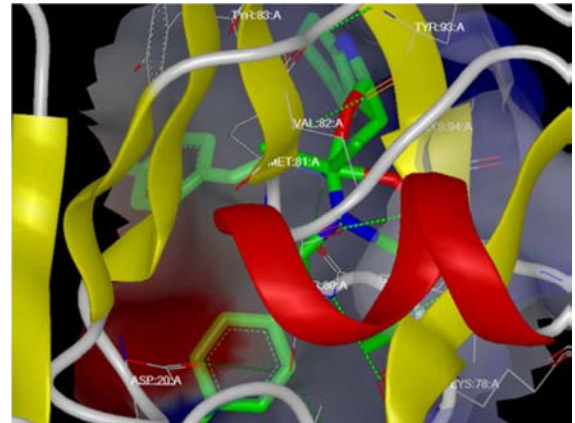


Figure 13. The binding model of the Schiff base complex $[CuL_2Cl_2]$ in the enzyme active site of *Staphylococcus aureus* sortase-A.

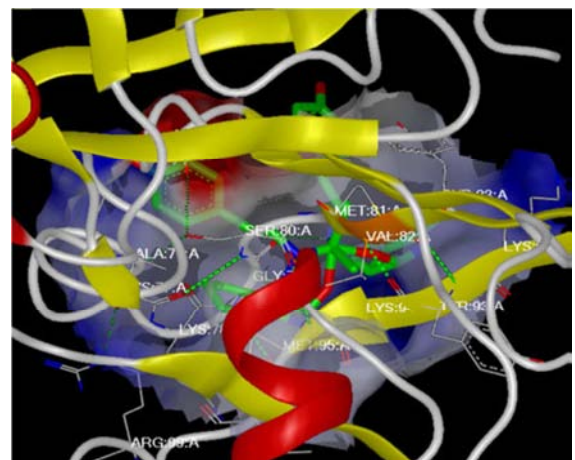


Figure 14. The binding model of the Schiff base complex $[NiL_2Cl_2]$ in the enzyme active site of *Staphylococcus aureus* sortase-A.

Mostafa K. Rabia, Ahmad Desoky M et al. synthesized Some Ni(II) Complexes with Isatin-Hydrazones and determined their physicochemical property [150]. V. Violet Dhayabaran and et al. synthesized Novel Bioactive Co(II), Cu(II), Ni(II) and Zn(II) Complexes with Schiff Base Ligand Derived from Histidine and 1, 3 Indandione and investigated the effect on molecular docking system [151] (figure 15, 16).

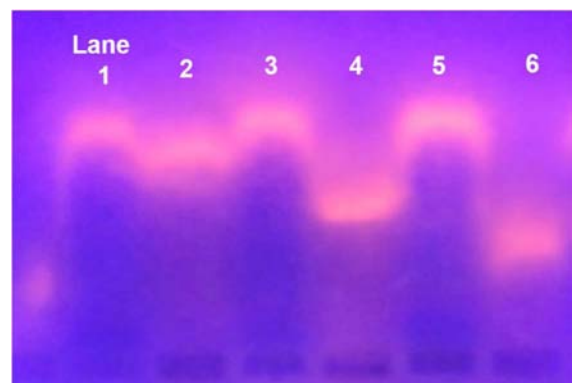


Figure 15. Changes in the Agarose gel electrophoretic pattern of pUC19 plasmid DNA, induced by H_2O_2 and metal complexes. Lane 1: Blank\DNA (Control); lane 2: DNA+ ligand + H_2O_2 ; lane 3: DNA+ $[Co(L)_2]$ + H_2O_2 ; lane 4: DNA+ $[Cu(L)_2]$ + H_2O_2 ; lane 5: DNA+ $[Ni(L)_2]$ + H_2O_2 ; lane 6: DNA + $[Zn(L)_2]$ + H_2O_2 .

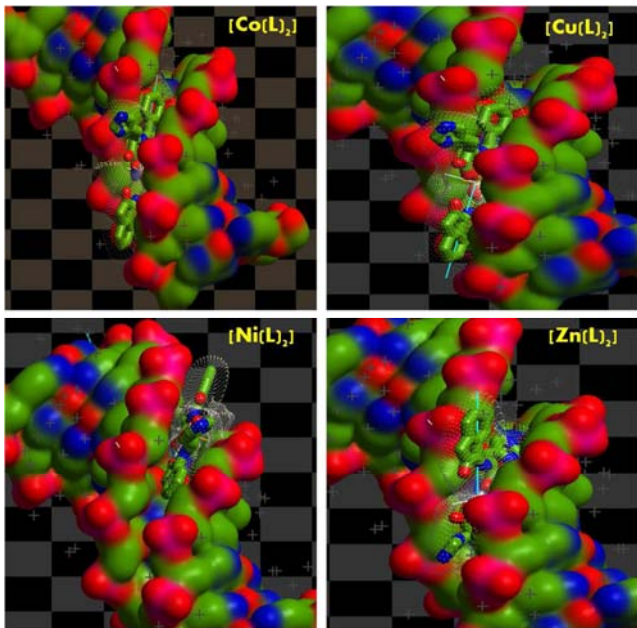


Figure 16. Molecular docked model of (a) Ligand (b) $[Co(L)_2]$ (c) $[Cu(L)_2]$ (d) $[Ni(L)_2]$ (e) $[Zn(L)_2]$ with BDNA.

N. Ramana, R. Jeyamurugana, B. Raj Kapoor and L. Mitu synthesized Copper(II) and Zinc(II) Complexes with Schiff base

ligand and investigated the DNA binding and cleavage properties [152]. Mohan N. Patel & Chintan R. Patel & Hardik N. Joshi synthesized metal based drug and investigated DNA Interaction, Antibacterial, Cytotoxic and SOD Mimic Activities [153]. Xin Li Cai-Feng Bi Yu-Hua Fan prepared Novel Three-Nuclear Cobalt(II) Complex with Schiff Base Derived from 4-Chloroanthranilic Acid and 2,4-Dihydroxybenzaldehyde and investigated the DNA interaction property [154]. Yong Li & Zheng-Yin Yang & Ming-Fang Wang synthesized some Transition Metal Complexes with Hesperetin-2-hydroxy Benzoyl Hydrazone and investigated the cytotoxicity and DNA interaction activity [155]. Mahadevan S *et al.* synthesized copper(II) complexes of bis(pyrid-2-yl)- di/trithia ligands bound to calf thymus DNA [156]. Xu H, Zheng KC and *et al.* shown ruthenium(II) complexes on the DNA-binding behaviors [157]. Mozaffar A and *et al.* investigated study on the binding of cationic Zn(II) and Co(II) tetrapyridinoporphyrazines to calf thymus DNA [158]. H Walaa and *et al.* synthesized some Schiff base metal complexes and shown their molecular docking effect [159]. Binding models of a *o*-benzoyl benzoic acid, b 4-aminoantipyrine and c HL to the *E coli* bacterial RNA was shown in (figure 17).

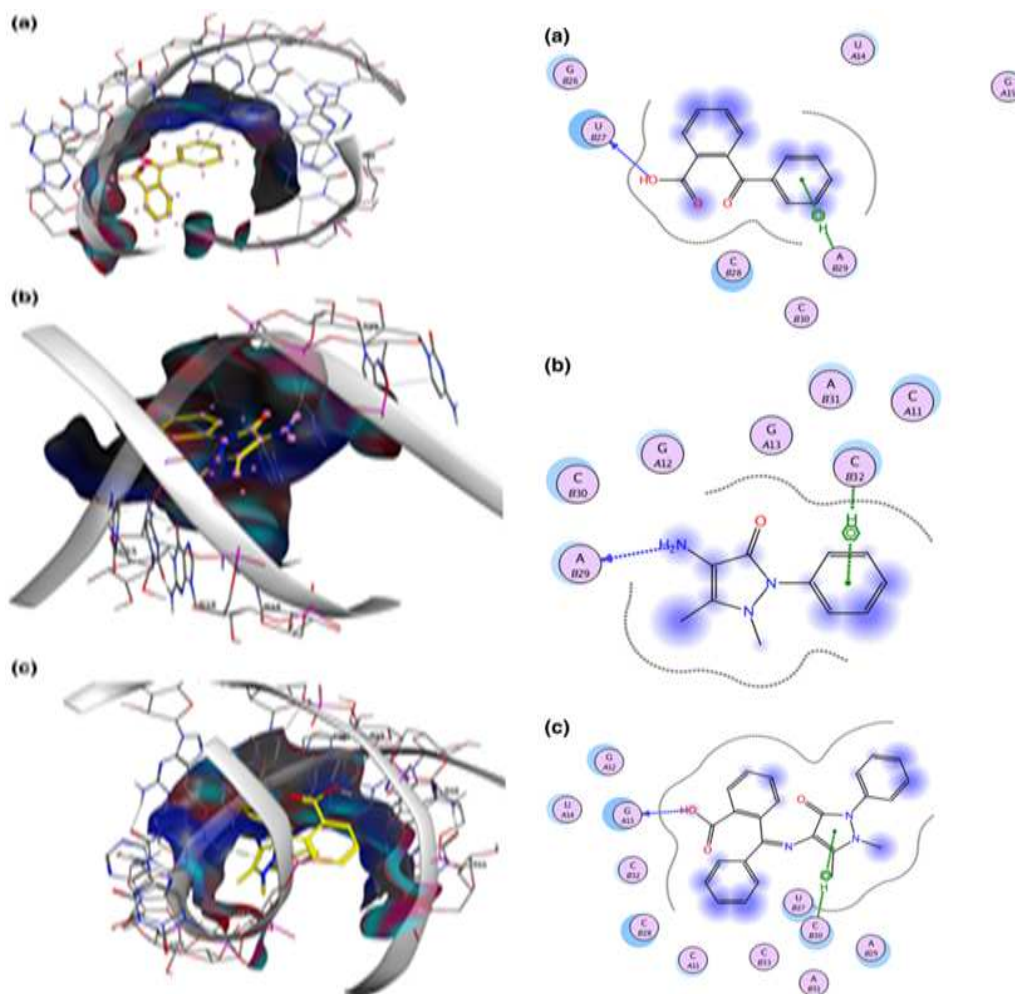


Figure 17. Binding models of a *o*-benzoyl benzoic acid, b 4-aminoantipyrine and c HL to the *E coli* bacterial RNA.

4. Conclusion

In this work, the pharmacological effects of a selected transition metal complexes have been reviewed. With the development in the field of medicinal chemistry, the role of transition metal complexes as therapeutic compounds is becoming increasingly significant. Recent advances in medicinal chemistry have made possible formation of number of transition metal complexes with organic ligand of interest, which can be used as therapeutic agent. Significant progress in the synthesis of platinum based anti-cancer drugs like cisplatin has been made. These drugs have proven to be highly effective chemotherapeutic agents for treating various types of cancers. The use of transition metal complexes as therapeutic compounds has become more and more pronounced. These complexes offer a great diversity in their action; they do not only have anti-cancer properties but have also been used as anti-inflammatory, anti-infective and anti-diabetic compounds. Development of transition metal complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Besides all these limitations and side effects, transition metal complexes are still the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics in a way that was unimaginable few decades back.

Acknowledgements

The authors are thankful to the Chairman, Department of Chemistry, Rajshahi University, Bangladesh for providing the laboratory facilities.

Conflict of Interest

The authors have no conflict of interest to publish the article.

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