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DNA Cleavage by Transition Metal Complexes and it's Applications - A Review

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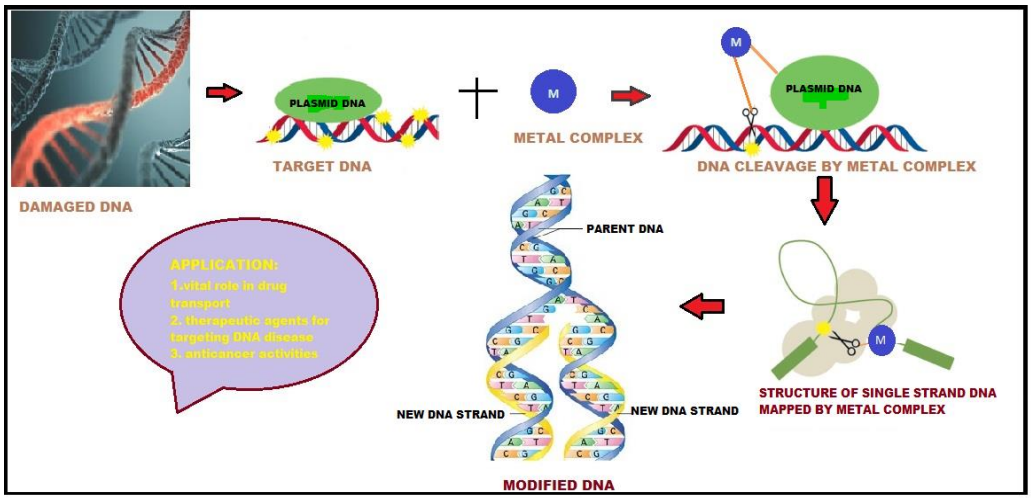
Abstract

In this review, we briefly summarize recent works done in designing metal complexes that show DNA cleavage activities, via hydrolytic or oxidative mechanisms. Transition metal complexes capable of cleaving DNA can also be used as therapeutic agents. We have focused here mainly on transition metal complexes of Cu^{+2}, Ni^{+2}, Co^{+2}, Mn^{+2}, Fe^{+2}, Zn^{+2} and Pt^{+2} that show DNA cleavage activity either in hydrolytic or oxidative pathways. We have also tried to summarise few applications of the transition metal complexes based on DNA cleavage phenomenon. Our future aim is to prepare Cr (III)-BLM complex as like as the other metallo-BLM complexes, that should play a vital role in drug transport, and/or DNA cleavage.

GRAPHICAL ABSTRACT



Keywords
Ascorbate, Bleomycin, DNAzymes, Nicked circular, Plasmid DNA, Super coiled.

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INTRODUCTION:

Nucleic acids are responsible for genetic information transfer, which require metal ions in all the steps. The fashion of interaction with the nucleic acids may vary for different metal ions. Some metal ions stabilize the DNA helix, whereas, the other may destabilize it. Metal ions (e.g. Cu^{+2}) that bind to the bases destroy the hydrogen bonds between the

complimentary bases; thereby destabilize the DNA double helix **[1]**.

The rate of DNA cleavage activity of the metal ions depends on the Lewis acidity and the ability to bind the metal with hydroxide of the nucleophile **[2]**. DNA cleavage via hydrolytic or oxidative mechanisms [**Figure :1**] can deactivate the DNA damage response signalling pathway in cells, while unrepaired DNA damage further activates the apoptotic pathway resulting cell death. Metal complexes that can be employed as therapeutic agents for targeting DNA disease, deserves a promising future. It is hoped that current study will open the new approaches for the development of efficient pharmaceutical systems in cancer treatment with low cytotoxic effects **[3]**.

Effect of metal ion addition to DNA:

Most of the metals play a vital role in biology in their cationic form. While almost every biological molecules (e.g.-proteins and DNA) are electron rich, metals are electron deficient. This deficiency helps metal ions to interact with biological molecules **[4]**. The metal ions, bind only to the phosphate groups, at lower concentration, resulting stabilization of the double helix. At higher concentration of the metal ions, H-bond breaking owing to metal-base binding outweighs the initial stabilization of the double helix at lower metal ion concentrations. The relative affinity of these metal ions towards phosphate to base binding falls in the order: **[5]**

$Mg^{+2} > Co^{+2} > Ni^{+2} > Mn^{+2} > Zn^{+2} > Cd^{+2} > Cu^{+2}$

Mg^{+2} and Ca^{+2} ions bind only to the phosphate groups, while Co^{+2}, Cu^{+2}, Mn^{+2} and Ni^{+2} ions bind to the phosphate as well as to the base sites of nucleotides.

Reason for cleaving DNA:

Cancer, which is the leading cause of mortality globally, is caused by abnormal and uncontrolled cell division. It can be cured by preventing the rapid growth of cancer cells for which the replication of the affected DNA is to be arrested. Many molecules inhibit the growth of tumour cells by binding with DNA and altering DNA replication. Thus they show anticancer activities. In the cell replication, DNA topology is controlled by an enzyme, namely topoisomerases. The enzyme basically breaks and repairs the polyphosphate backbone of the DNA by passing through the transient gaps to other strands of DNA **[6]**. Numerous systems have been evolved for the detection of DNA damage, and resolve it. Genome instability causes heritable human diseases. More or less 40 diseases are known causing due to unstable DNA repeat sequences. Such as Fragile X syndromes, Friedrich's ataxia, spinocerebellar ataxias, diabetes mellitus type 2, Creutzfeldt–Jakob disease, myotonic dystrophy and Huntington's Disease **[7]**.

Now a day's drug designing related to DNA cleavage is an area of serious consideration and offers enormous applications in the medicinal field **[8]**. The overall process of DNA cleavage includes various stapes like inflammation, mutagenesis, carcinogenesis and aging. Various efforts have been made to identify and characterize transition metal complexes (e.g.- metallo bleomycine) capable of cleaving DNA, because these species may serve as lead structures for the development of novel anti-cancer drugs **[9]**.

RESULT AND DISCUSSION:

DNA cleavage by Cu complexes:

- Sigma et al. at first reported a copper complex that shows DNA cleavage activity, namely bis (1, 10-phenanthroline) copper (I) that in the presence of H_2O_2 efficiently nick DNA **[10]**. It is unveiled that in presence of active oxo-species copper-based pseudo nucleases cleaves the DNA-strand by abstracting the proton of C-4′ or C-1′ positions from deoxyribose **[11, 12]**. The strand scission proceeds via two mechanistic pathways. One is either by binding the copper (I) complex to DNA followed by H_2O_2. The other is by binding the copper (II) complex to DNA leading to the reduction of the metal centre on the DNA surface so that it cannot react further with the H_2O_2 produced in the catalytic cycle.
  BKS et al. have recently reported the synthesis, crystal structure and properties of **[13]** [Cu $(dpq)_2(H_2O)](ClO_4)_2$. H_2O, that in the presence of ascorbic acid efficiently performs DNA cleavage. This redox active copper complex having a planar dpq ligand efficiently converted SC pUC19 DNA to its (NC) nicked circular form.
- Yan Jin and J. A. Cowan observed two [peptide-Cu] complexes ($[GGH\text{-}Cu]^-$ and $[KGHK\text{-}Cu]^+$) [**Figure: 2**]. These two complexes were found to show DNA cleavage activity in presence of dioxygen and ascorbate that acts as a mild reducing agent. The ATCUN (amino terminal Cu^{2+} and Ni^{2+} binding) peptide sequence was found to kill Ehrlich ascites tumour cells in a [GGHCu]/ascorbate system and was shown to cleave DNA under certain conditions [**1**]. Linearization of plasmid DNA is also observed in the case of $[KGHK\text{-}Cu]^+$. Comprehensive kinetic and product analyses of the DNA cleavage reactions by both $[GGH\text{-}Cu]^-$ and $[KGHK\text{-}Cu]^+$ complexes suggest C-4′ H abstraction to initiate the DNA cleavage pathway**[2]**.

[GGH-Cu]$^{-}$ [GGH-GlyGlyHis] in the presence of ascorbate, was found to perform rapid degradation of SC (form I) plasmid DNA in to NC (form II) plasmid DNA **(Figure 3 (A), (B))**, at lower concentrations (10 μM). Linear DNA was formed in the [KGHKCu]$^{+}$ [KGHK –LysGlyHisLys] cleavage samples requiring two breaks on opposing strands within 10 bp of each other, whereas linear DNA was not found in case of [GGH-Cu]$^{-}$.

- Lately Eric L. Hegg and Judith N. Burstyn reported, that Cu ([9] aneN$_3$)Cl$_2$, copper (II) 1,4,7-triazacyclononane dichloride, shows DNA cleavage activity towards both SS and DS DNA. Another complex, [Cu (*i*-Pr$_3$ [9] aneN$_3$) (OH$_2$) (CF$_3$-SO$_3$)] CF$_3$SO$_3$, **(Figure:4)** relative to the Cu ([9]aneN$_3$) Cl$_2$ complex was found to show a rapid increase in DNA cleavage activity.

  One of the most interesting and remarkable aspects of the Cu ([9] aneN$_3$) Cl$_2$-promoted cleavage of DNA is that approximately 70% of the cleavage activity is retained when the reactions are performed under rigorously anaerobic conditions. Cu ([9]-aneN$_3$) Cl$_2$ is one of only a few metal complexes shown to cleave DNA in the absence of O$_2$ or some other oxidants **[14]**.

DNA cleavage by Zn Complexes

Zn^{2+} is found to be one of the favourite metal centres present in phosphatases and nucleases **[15]**. In comparison to other metal ions used in certain artificial systems (like Cu or Co), it does not exhibit a redox chemistry, and hence, it catalyzes only a hydrolytic cleavage process. Furthermore, the aquo ion is not hydrolytically active at pH values close to neutrality, comprising to other high-valence metal ions (like Ce^{4+} and Zr^{4+}) **[16]**.

- Zhen Yu and JA Cowan studied that oxidative cleavage of nucleic acids by redox active metals, often approach an alternative pathway involving the formation of reactive oxygen species (ROS). The formation of the intermediate causes electron transfers from the metal centre to molecular oxygen or peroxide. Ascorbate or DTT now can reduce the metal and thereby abstracting proton from the deoxyribose /ribose ring results spontaneous cleavage of C–C and C–O bonds and continuing the formation of ROS **[17]**. They also studied the amphiphilic Zn–cyclen complexes conjugated to phosphocholine derivatives. They further allow the formation of Zn–cyclen surface modified micelles **[18]**. These Zn-containing micelle/vehicles exhibit~ 10^3–10^6-fold increase in catalytic activity for DNA hydrolysis, comparative to the isolated Zn–cyclen. A Zn complex of a diaza-crown ether was reported to exhibit vigorous DNA hydrolysis comparative to its copper analogues, since Zn(II) is more Lewis acidic than Cu(II) for oxidative cleavage **[19,20]**.
- Sartaj Tabassum et al. described the synthesis, characterization and DNA binding ability of Cu (II) and Zn(II) complexes of ligand L **(Figure: 5a)**, which was synthesised from barbituric acid and pyrazole scaffold **(Figure: 5b)**. Complex 1 was found to act as chemotherapeutic agent when examined over a panel of human cancer cell.

  Cu (II) and Zn (II) induced complexes (1 and 2) were synthesized by the reaction of ligand L with phenanthroline and metal nitrates (1:1:1 molar ratio) **(Figure: 5c)**.

The DNA cleavage activity of L and 1were determined by gel electrophoresis, upon SC pBR322 DNA, incubated with increasing concentration of L and 1 in specific condition [5 mM TriseHCl/ 50 mM NaCl buffer (pH 7.3)]. 1 was found to exhibit the cleavage of PBR322 plasmid DNA from SC Form I to NC Form II **(Figure: 5d) [6]**.

- Claudia Sissi et al. reported that dinuclear **Zn^{2+}** complexes of ligand **1 (Figure: 6(A))** remarkably show hydrolytic cleavage activity on plasmid DNA with clear evidence of cooperatively between the two Zn^{2+} centres. The plasmid DNA pBR322 was incubated (12 μM in base pairs) at 37 °C for 24 h in 20 mM HEPES at pH 7.0. In the presence of **1a**-2Zn^{2+} the plasmid DNA was converted from SC (form **I**) to both NC (form **II**) and linear (form **III**) **(Figure 6(B))**. From figure **6(B)** it may also be concluded that the relative amount of linear versus nicked plasmid increases upon increasing complex concentration. This suggests that DNA cleavage does not occur simultaneously on both strands. In conclusion, they have shown the ability of dinuclear Zn^{2+} complex of a tailored 3$_{10}$- helical hepta peptide to act as a powerful catalyst for the hydrolytic cleavage of plasmid DNA **[21]**. Figure **6(B)** also suggests that at very low concentration 1b-2Zn^{2+} appears to be slightly more active than **1a**.

Potassium Monopersulfate and a Water-Soluble Manganese Porphyrin Complex, [Mn (TMPyP)](OAc)$_5$, as an efficient reagent for the oxidative cleavage of DNA

Jean Bernadou et. Al reported that, [Mn(TMPyP)](OAc)$_5$, where TMPyP=meso-tetrakis(4N-methylpyridiniumyl)-porphyrin; TMPyP, can act as a DNA cleavage agent, in presence of KHSO$_5$.It is found that the number of SSBs varies linearly **(Figure:7)** with the concentration of the

water-soluble manganese porphyrin complex, and potassium monopersulfate is more efficient as oxygen source than H_2O_2. Within 1 min of incubation time and Mn-TMPyP concentrations above 60-80 nM, form I of ΦX174 DNA is fully converted to form II and form III. The number of DNA breaks per molecule of manganese porphyrin (=S'[DNA] [Mn-TMPyP]$^{-1}$) is close to 0.5Nm **[22]**.

Oxidative Cleavage of DNA by Fe(EDTA)$^{2-}$/DTT/O_2.

- Fe (EDTA) $^{2-}$, the most commonly used reagent **[23-25]** in oxidative cleavage mechanism, efficiently cleaves both SS and DS DNA in the presence of H_2O_2 or O_2 and a reducing agent. In this mechanism hydroxyl radicals are formed via the Fenton reaction, in which a hydrogen atom from the deoxyribose ring is abstracted; resulting rearrangement of the sugar ring and strand scission along with free base release. Bleomycin (BLM) is known to be an antitumor antibiotic, which is a second cleavage agent that requires Fe^{2+} and H_2O_2 or O_2 plus a reducing agent for activity, however, BLM does not produce free hydroxyl radicals **[26-28]**.

In this case SC pBluescript II ks(-) DNA (0.05 mg/mL) or SS M13 DNA (0.05 mg/mL) was incubated with 10 mM DTT and 0.1 mM Fe(EDTA)$^{2-}$ for 60 min at 50 °C. Ethanol was used as a reaction quencher and the above reactions were analyzed by agarose gel electrophoresis **[14]**.

- Another case is known where bleomycin, a glycopeptide antibiotic, binds to and cleaves DNA **(Figure: 8(A))** in a reaction that depends on ferrous ion and molecular oxygen **[29-31]**. This example explains the conception behind using a DNA as a binding molecule to deliver a metal ion to the site of the DNA helix where molecular oxygen is activated, resulting the DNA cleavage. **[32]**

Robert P. Hertzberg and Peter B. Dervan reported the synthesis of methidium propyl-EDTA (MPE) **(Figure: 8(B)) [33]**. This reagent having a short hydrocarbon tether covalently linked to the EDTA performs well in the presence of ferrous ion and oxygen for both SSB and some DSB in double helical DNA **[34]**.

The DNA cleavage function was monitored on the SC (form I) pBR-322 plasmid DNA [10^{-5} M in (bp)], which was converted in to open circular and linear forms respectively (forms II and III). Plasmid DNA will be cleaved for EDTA-Fe^{II} at >10^{-4} M concentrations; however, at concentrations ≤ 10^{-4} M little or no cleavage takes place. The addition of intercalator ethidium bromide (EB) to Fe (II) or EDTA-Fe^{II} fails to promote the cleavage reaction. From **Table–I**, we find that MPE-Fe^{II} even at lower concentration (10^{-6} M) cleaves plasmid DNA, Whereas, MPE alone or MPE-Fe^{III} is not at all active in these concentrations. **Table II** shows that in the presence of dithiothreitol (DTT), MPE-Fe^{II} (10^{-8} M concentration) cleaves plasmid DNA more efficiently compared to bleomycin **[35]**. Presumably, DTT plays the role of a reducing agent, regenerating Fe (II) from Fe (III) as a continuous source of active metal ion.

The reactions of plasmid DNA and MPE-Fe^{II} with and without DTT were performed in the anaerobic condition, but no strand scission was observed. So we can conclude that, MPE cleaves plasmid DNA at lower concentrations than EDTA-Fe^{II}, in a reaction that needs Fe (II) and O_2.

- Sethu Ramakrishnan et. Al reported the synthesis and characterization of the four complexes **(Figure:9(A))** *rac*-[Fe(diimine)$_3$](ClO_4)$_2$, **[**diimine = 2,2'-bipyridine (bpy) **1**,1,10-phenanthroline (phen) **2**, 5,6-dimethyl-1,10-phenanthroline (5,6-dmp) **3** and dipyrido[3,2-*d*:2',3'-f] quinoxaline (dpq) **4]**.They also studied their interaction with CT DNA. The DNA cleavage activities of all the four complexes have been performed at 10 mM concentration in the presence of 100 mM H_2O_2.Their DNA cleavage efficiency (> 90%) follow the order **3** > **1** > **2** > **4**. Their anticancer activity has also been studied against human breast cancer cell line (MCF-7).

The oxidative DNA cleavage efficiency of all the iron (II) complexes and Fe (ClO_4)$_2$.6H_2O (10 mM) were studied **(Figure. 9(B))** in the presence of an activator H_2O_2 (100 mM) using pUC19 SC DNA. All the complexes were shown to convert SC DNA (form I) into nicked circular (NC) DNA (form II) with prominent DNA cleavage (**1**, 94%; **2**, 86%; **3**, 97%; **4**, 73%, Table 3). **[43]**

DNA cleavage by Co complexes

- According to the proposal of James G. Muller et. Al $CoCl_2$ should be given serious attention as it induces base-specific and conformation-specific cleavage of DNA under a much flexible experimental conditions. Cobalt complexes have found to show DNA cleavage activity in the form of a cobalt bleomycin analog **[44]**, Co(NH_3)$_6^{3+}$**[45-47]** , cobalt(III) polypyridines **[48-50]**, [CoIII-(cyclam)(H_2O)Me]$^{2+}$**[51]**, Cobalt(III) desferal **[52,53]** and a cobalt(III) porphyrin **[54]** using photochemical activation or an oxidant such as iodosylbenzene, H_2O_2 or O_2.

Our current investigation reveals that cobalt (II) complexes, used in presence of $KHSO_5$, lead to guanine specific reaction under many vigorous conditions (high temperature and catalytic metal concentrations). The mechanism revealed that

guanines were indiscriminately modified when [Co $(H_2O)_6]^{2+}$ was used to elevate a DNA reaction with sulfite and O_2, and Gs, Cs, and Ts were susceptible to reaction in presence of an oxidant H_2O_2 **[55]**.

For initial DNA modification studies, the SS oligodeoxynucleotide [5'-^{32}P]-d(ATAGTCTAGATCTGA TAT), **1**, was used. The reaction at 20°C of **1** (3 μM), $CoCl_2$ (3 μM) and $KHSO_5$ (50 μM) for 10min followed by treatment with piperidine revealed strand scission corresponding to reactions occurring at all guanine residues. The higher reactivity of $CoCl_2$ allows its application to wider conditions (high temperature or low reagent concentration). For example, reactions conducted using 3 μM $CoCl_2$ and only 10 μM $KHSO_5$ revealed an overall DNA cleavage activity of 15% **[56]**.

When $KHSO_5$ remained at 50 μM, it was found that cobalt-mediated DNA cleavage was very active (26% cleavage) even at concentrations of $CoCl_2$ as low as 100 nM.

- Currently, the most efficient nonenzymic method of cleaving DNA is by an oxidative procedure **[57-59]**. In contrast, enzymes cleave DNA by catalyzing the hydrolysis of the phosphodiester bond. Metal ions are used as DNases activator by, which rapidly improve the rate of hydrolysis of DNA. Jik Chin and Xiang Zou recently showed that [Co (trien) (OH_2) $(OH)]^{2+}$ gives a much greater rate acceleration (10^8 fold) for the hydrolysis of cyclic AMP, a phosphodiester, than for the hydrolysis of methyl phosphate (10^2 fold), a phospho monoester. The rate of hydrolysis of BNPP increases linearly with increase in the concentration of $[Co(trien)(OH)(OH_2)]^{2+}$ (0.001-0.1 M), **(Figure: 10)** suggesting that there is only one cobalt complex involved in the hydrolysis of BNPP. Interestingly Scheme I shows that the rate of hydrolysis of the phosphodiester bond (k_2) is significantly affected by the structure of the amine ligand $[[Co(trien)(OH)(OH_2)]^{2+}$ > $[Co(en)_2(OH)(OH_2)]^{2+}$ > $[Co(dien)(OH)(OH_2)_2]^{2+}]$ [**Table IV**]. The reactivity pattern of the cobalt complex promoted hydrolysis of BDNPP closely resembles the reactivity pattern of the cobalt complex anation reaction $[[Co(dien)(OH)(OH_2)_2]^{2+}$ > $[Co(trien)(OH)(OH_2)]^{2+}$ > $[Co(en)_2(OH)(OH_2)]^{2+}$ >$[Co(en)_2(OH)(NH_3)]^{2+}]$ **[60]**.

DNA cleavage studies of isomeric pyridyl-tetrazole ligands and their Ni (II) and Zn (II) complexes

M.S. Surendra Babu et. Al have synthesized a new series of Ni(II) and Zn(II) complexes from bidentate isomeric pyridyl tetrazole ligands such as 2-(1-vinyl-1H-tetrazol-5-yl) pyridine (L^1); N,N-dimethyl-3-(5-(pyridin-2-yl)-1H-tetrazol-1-yl)propan-1-amine (L^2); 2-(2-vinyl-2H-tetrazol-5-yl)pyridine (L^3); N,N-dimethyl-3-(5-(pyridin-2-yl)-2H-tetrazol-2-yl)propan-1-amine (L^4) (**Figure: 11 (A)**). All the metal complexes of Ni (II) and Zn (II) were shown to cleave SC pBR322 plasmid DNA in presence of H_2O_2. All the Ni (II) complexes were coloured, stable, and nonhygroscopic in nature **[61]**. The elemental analysis showed that the complexes have 1:2 stoichiometry of the type $[M (L^{1-4})_2] Cl_2$, where L stands for singly deprotonated ligands **(Figure: 11 (B))**.

DNA cleavage was monitored by the gel electrophoresis for naturally occurring, covalently closed circular form transition to the nicked circular and linear forms. When circular plasmid DNA is subjected to electrophoresis, relatively fast migration will be observed for the super coil form, slower migration will be observed for nicked circular form and linear form occurred between the super coiled and nicked circular forms.

DNA cleavage by Pt complex

Methylglycine or sarcosine, is used as anticancer drug molecules, while its metal complexes exhibit efficient DNA cleavage ability. Fatemeh Safa Shams Abyaneh et. Al have studied the biological approach of methylglycine ligand on two platinum (II) complexes viz; cis-$[Pt(NH_3)_2(CH_3\text{-}gly)]NO_3$ and cis-$[Pt(NH_2\text{-}CH_3)_2(CH_3\text{-}gly)]NO_3$ (where CH_3-gly is methylglycine) **(Figure: 12 (A), (B))**.

The synthesized **(Figure: 13)** water soluble complexes were found to show anticancer activity upon human breast adenocarcinoma cell line of MCF7.The experimental spectroscopic results displayed that two complexes interact cooperatively with highly polymerized CT DNA and denature at micro molar concentrations and at pH 7.4**[62]**. Overall, experimental results indicate that the cis-$[Pt(NH_2\text{-}CH_3)_2(CH_3\text{-}gly)]NO_3$ interacts more efficiently than that of cis-$[Pt(NH_3)_2(CH_3\text{-}gly)]NO_3$ **(Figure: 14 (A) (B))**.

Application:

- DNA was first shown to participate in catalytic functions in 1994 **[63]**, and thus it was considered as DNAzymes, a member of enzyme family after proteins and RNA **[64]**. Yi Lu has reported that transition metal dependent DNAzymes have displayed high activity toward DNA cleavage. DNAzymes can also show the endonuclease activity, i.e. they can be used in biochemical studies to cut process and map RNA molecules **[65].** The endonuclease activity of DNAzymes, similar to that of RNAzymes **[66]**,

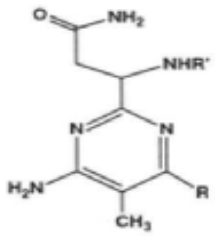
thus deserves a promising future as anti-viral pharmaceutical agents, against diseases such as AIDS and leukemia **(Figure: 15) [67-72].** Divalent metal ions e.g. Mg (II), Mn (II), or Ca (II) are essential for the catalytic function of the majority of DNA/ RNAzymes under physiological conditions**[73-76]**.

Transition metal ion dependent DNAzymes can also act as better metal biosensors for simultaneous detection of metal ions. The other advantages for choosing DNAzymes are – (1) They can be subjected for in vitro selection and requires short time and are cost effective compared to other organic moieties, (2) the synthesis of DNA is easier, cost friendly than that of synthesis of RNA. Not only that, physiological conditions, DNA is more stable to hydrolysis than proteins and RNA **[77]**.

- Formative research works by Sen et al. developed a new three-way junction-based DNA nano machine. This machine works mainly by binding of Hg^{2+} ions to T–T mismatches present in one of the three-way junction stems, that exhibits reversible, mechanical and electrical switching **(Figure: 16)**. Surprisingly, this type of switching can be subjected to couple mechanical motion with changes in hole transport efficiency, a feature which could facilitate electrical monitoring of structural changes in DNA **[78]**.
- Mercury (Hg), in its +2 state is highly water soluble, which is toxic [**79]** for both environment and our health. All the well-known methods for Hg^{2+} detection [absorption/emission spectroscopy, inductively coupled plasma mass spectrometry (ICPMS) etc] needs complicated sample preparation and sophisticated instruments [**80–82]**. Obviously it is of great necessity now to obtain new, cost effective, rapid, sensitive and selective Hg^{2+} detection methods. A fluorescent sensor was prepared for determination of Hg^{2+}.This method is ultrasensitive and can detect Hg^{2+} in tap water and lake water samples **[83]**. When Hg^{2+} was induced in a thymine rich SS DNA, it revealed that Hg^{2+} mediated T−Hg^{2+}−T pair is even more stable than the Watson−Crick A−T pair **[84]**. Due to the smaller the vander Waals radius of Hg^{2+}(≈1.44 Å) than that of the base pair spacing of DNA duplex (≈3.4 Å) **[85]**, Hg^{2+} can be easily induced into DNA duplex without hampering the double-helical structure of DNA.

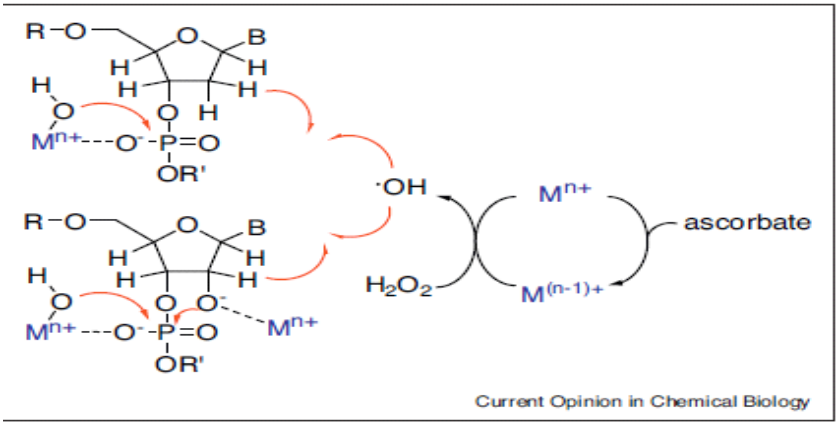
Future directions:

The bleomycins, a group of natural products derived from glycopeptides and isolated from *Streptomyces verticillus* **[86, 87]**, are clinically employed in the treatment of several neoplastic diseases **[88]** including squamous cell carcinomas **[89]**, non-Hodgkin's lymphomas **[90]**, testicular carcinomas **[91]** and ovarian cancer **[92]**. During the last decade enormous research works have been done for the isolation and evaluation of naturally occurring DNA cleaving agents. Bleomycin can be thought of as a naturally occurring metallo peptide in its active form; while Fe (II/III) has been the most extensively studied metal ion cofactor with regard to the cleavage of nucleic acids, other transition metals **[93]** including Cu, Co, Mn, Ni, Ru, V, and Zn bind to bleomycin and, in some instances, promote DNA strand scission **[94]**. While Ali Parand et. Al attempted to prepare a site selective DNA cleavage reagent, a tri nuclear Cr (III) complexes $[Cr_3(O_2CCH_3)_6(H_2O)_3]^+$ **[95]**. The complex was shown to nick DS, SC DNA in concentration and time domain in presence of H_2O_2. Now if we can prepare Cr (III)-BLM complex in future as like as the other metallo-BLM complexs, that should play a vital role in drug transport and/or DNA cleavage.



Structure of bleomycin

Figure: 1 Hydrolytic and Oxidative cleavage pathways for nucleic acids promoted by metal complexes. [1]



Summary of hydrolytic and oxidative cleavage pathways for nucleic acids, promoted by metal complexes.

Figure: 2 Structural representations of $[GGH\text{-}Cu]^-$ and $[KGHK\text{-}Cu]^+$ [2]

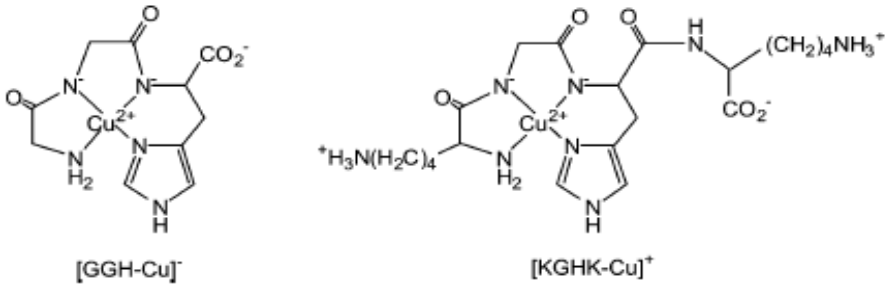
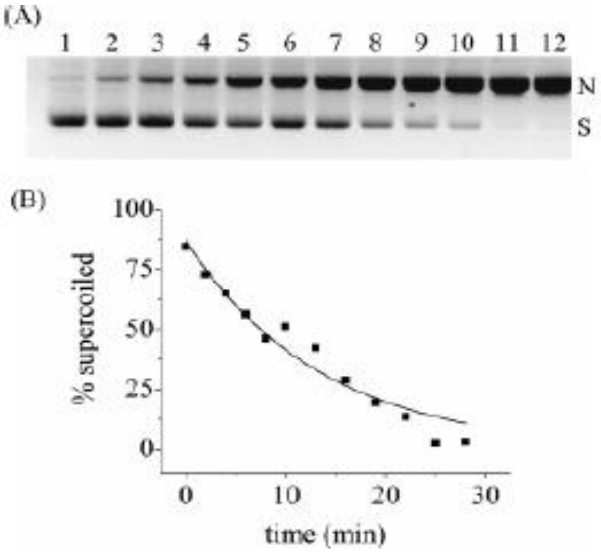


Figure: 3 Cleavage activity of $[KGHK\text{-}Cu]^+$ monitored 0.8% agarose gel electrophoresis, where [DNA]= 50 µM and $[GGH\text{-}Cu]^-$ =25 µM and [Ascorbate] = 250 µM. Time course measured in 10Mm Tris buffer, Ph = 7.4, 37 ° C [2]

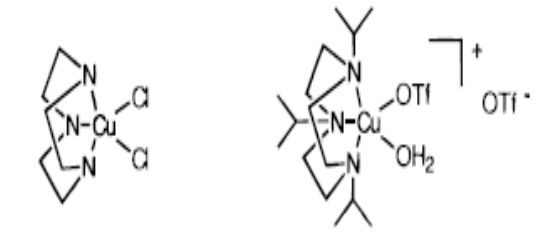


Showing the disappearance of DNA (S) at (1) 0 min, (2) 2 min, (3) 4 min, (4) 6 min, (5) 8 min, (6) 10 min and (12) 28 min.

(A) Gel image showing nicked (N) and (S) super coiled DNA

(B) Reaction curve showing a pseudo-first order kinetic profile (R^2 = 0.952), K_{obs}~ 0.07 min^{-1}

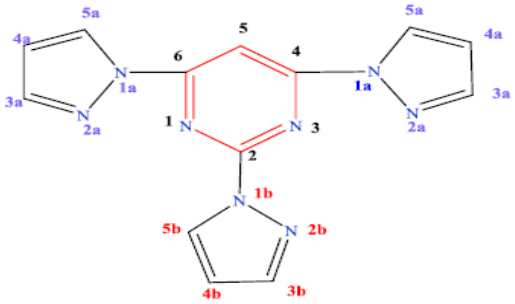
Figure: 4 Structures of Cu ([9] aneN$_3$)Cl$_2$ and [Cu(*i*-Pr$_3$[9]aneN$_3$)(OH$_2$)(CF$_3$-SO$_3$)]CF$_3$SO$_3$ [14]



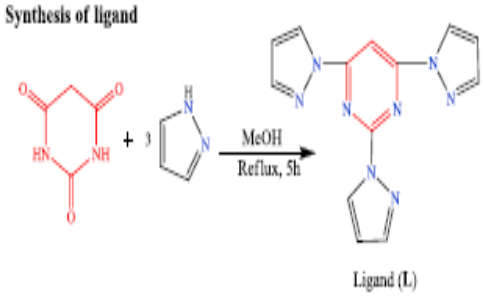
Cu([9]aneN$_3$)Cl$_2$ [Cu(*i*-Pr$_3$[9]aneN$_3$)(OH$_2$)(OTf)]OTf

[(OTf) CF$_3$SO$_3^-$]

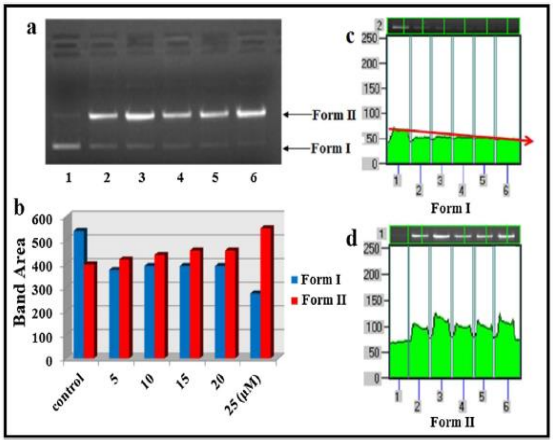
Figure: 5 (A) Structure of ligand L



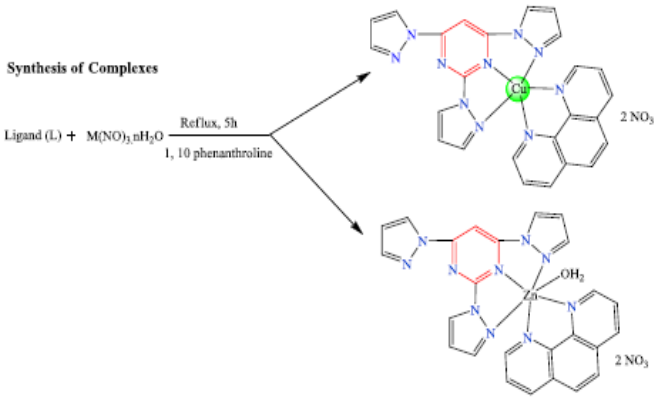
(B) Synthesis of ligand L



(C) Synthesis of Cu (II) and Zn (II)induced complexes (1 and 2) were by the reaction of ligand L with phenanthroline and metal nitrates (1:1:1 molar ratio)

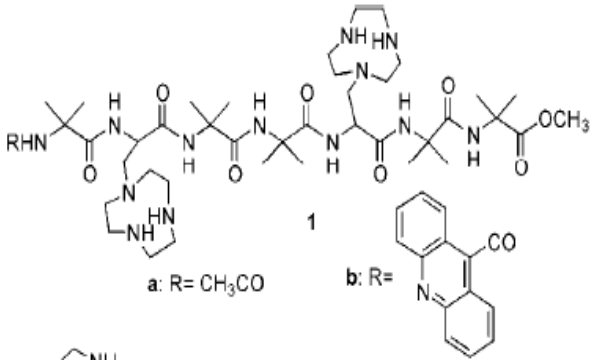


(D) Agarose gel electrophoresis pattern for the cleavage of pBR3222 plasmid DNA (300ng) by 1 at 37° C after incubation for 45 min at different concentration.



a. lane 1: DNA control; lane 2: 5 µM complex 1+ DNA; lane 3: 10 µM complex 1+ DNA; lane 4: 15 µM complex 1+ DNA; lane 5: 20 µM complex 1+ DNA; lane 6: 25 µM complex 1+ DNA;
b. quantification of band area in gel electrophoresis originating from Form I and Form II pBR322 plasmid DNA by complex 1 at different concentration. 2D projection of gel images for the cleavage of pBR322 plasmid DNA at different concentration of complex 1 for
c. From I bands and
d. From II bands. Arrow including decrease in relative intensity of from I band **[6]**.

Figure 6: (A) Structure of ligands 1(a and b) with two different substituents [21]



(B) DNA cleavage activity of two dinuclear Zn^{+2} complexes; 1b-2Zn^{2+} and 1a-2Zn^{2+} respectively [21].

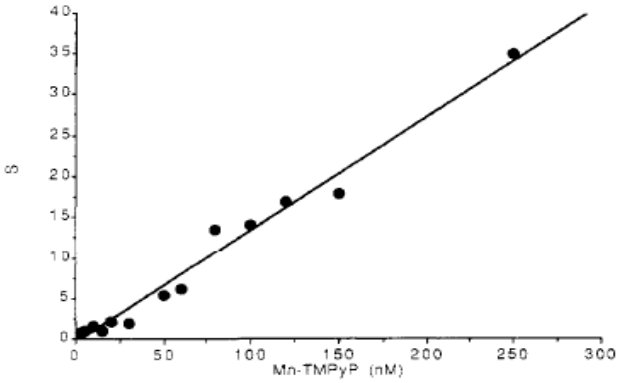


Fig: Cleavage of pBR 322 DNA (12 µM bp) in 20 mM HEPES, pH 7.0, 37 °C after 24 h incubation with the indicated concentration of Zn complexes. Lane C is DNA treated in the absence of ligands.

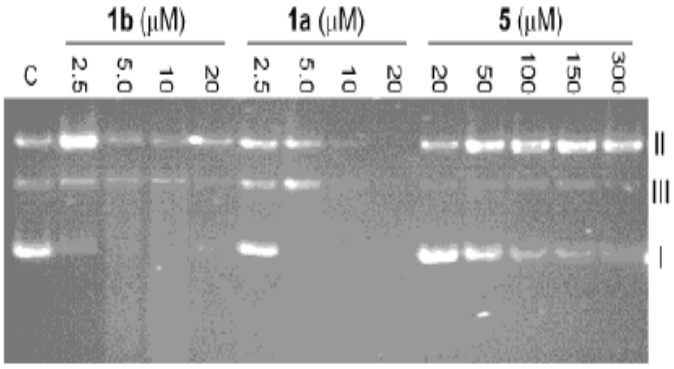
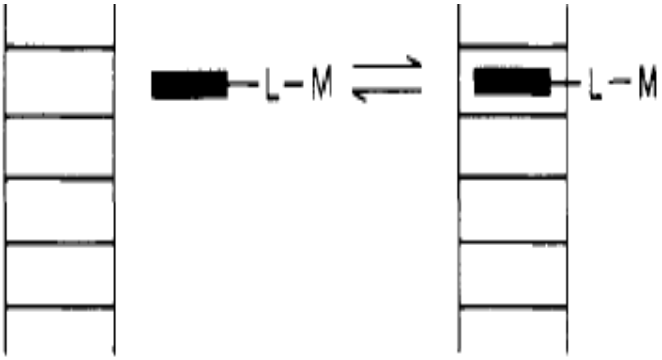


Figure: 7 Influence of Mn-TMPyP concentration on the cleavage of ΦX174 DNA in the presence of potassium monopersulfate. ΦX174 DNA (18.7 µM bp) is incubated 1 min at ambient temperature with the indicated concentrations of Mn-TMPyP and 10 µM KHS05 in the presence of 100 mM NaCl.[22]

Figure: 8 (A) Bleomycin binding to DNA [33]



(B) Structure of methidiumpropyl-EDTA (MPE) [33].

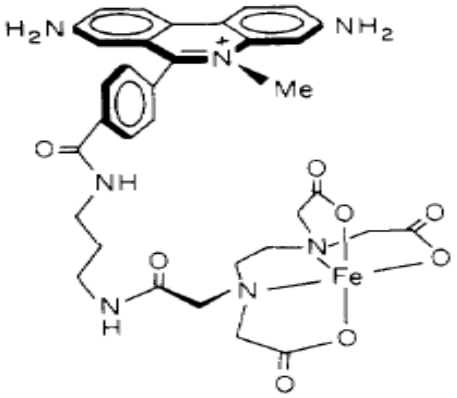
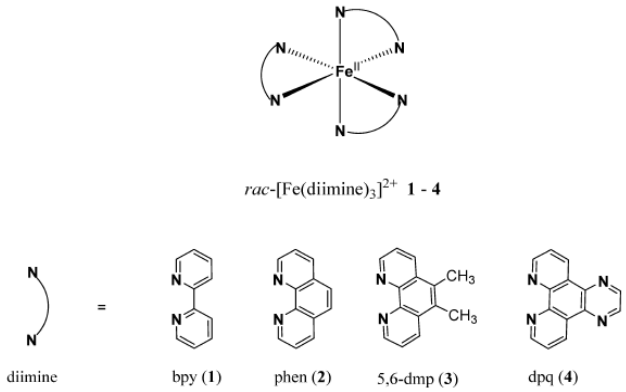
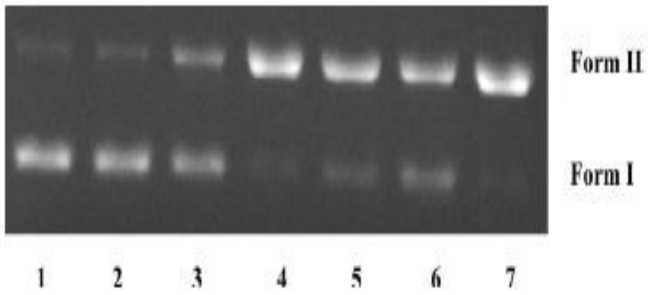


Figure: 9 (A) Structures of tris(diimine)iron (II) complexes 1–4 [43]



Here diimine is 2,2′-bipyridine (bpy) 1, 1,10-phenanthroline (phen) 2, 5,6-dimethyl-1,10-phenanthroline (5,6-dmp) 3 and dipyrido[3,2-d: 2′,3′-f]quinoxaline (dpq) 4

(B)



Cleavage of super coiled pUC19 DNA (40 mM) by 10 mM complex (**1–4**) in 5 mM Tris-HCl/50 mM NaCl at pH = 7.1 and 37 ◦C in the presence of H_2O_2 (100 mM) at 37 ◦C. Lane 1, DNA; lane 2, DNA + H_2O_2; lane 3, DNA + H_2O_2 + $[Fe(H_2O)_6] (ClO_4)_2$; lane 4, DNA + H_2O_2 + **1**; lane 5, DNA + H_2O_2 + **2**; lane 6, DNA + H_2O_2 + **4**; lane 7, DNA + H_2O_2 + **3**. Forms I and II are super coiled and nicked circular forms of DNA respectively. **[43]**

Figure: 10 Cis- $[Co(en)_2(OH)(OH_2)]^{2+}$ promoted hydrolysis of BNPP. [60]

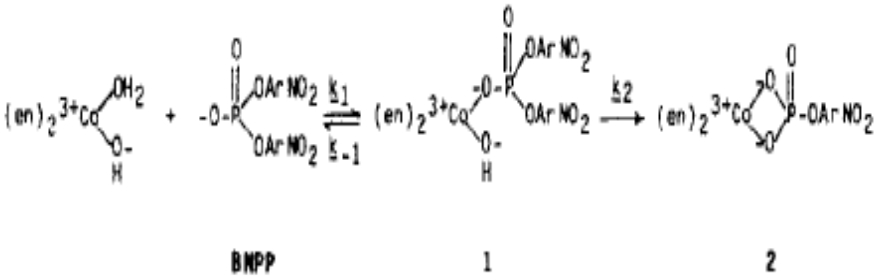
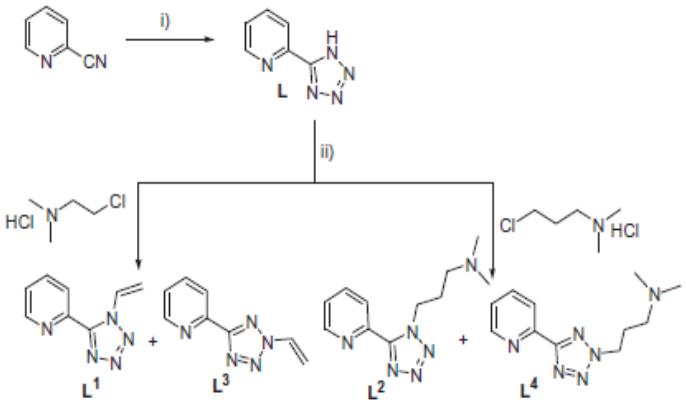


Figure: 11

(A)



Synthetic route for ligands L1–L4, reaction conditions
(i) NaN_3, LiCl, NH_4Cl, DMF, reflux 10 h; (ii) K_2CO_3, DMF, 70 °C 24 h. **[61]**

(B) Synthesis of Ni and Zn complexes with pyridyl-tetrazole ligands (L^1–L^4). [61]

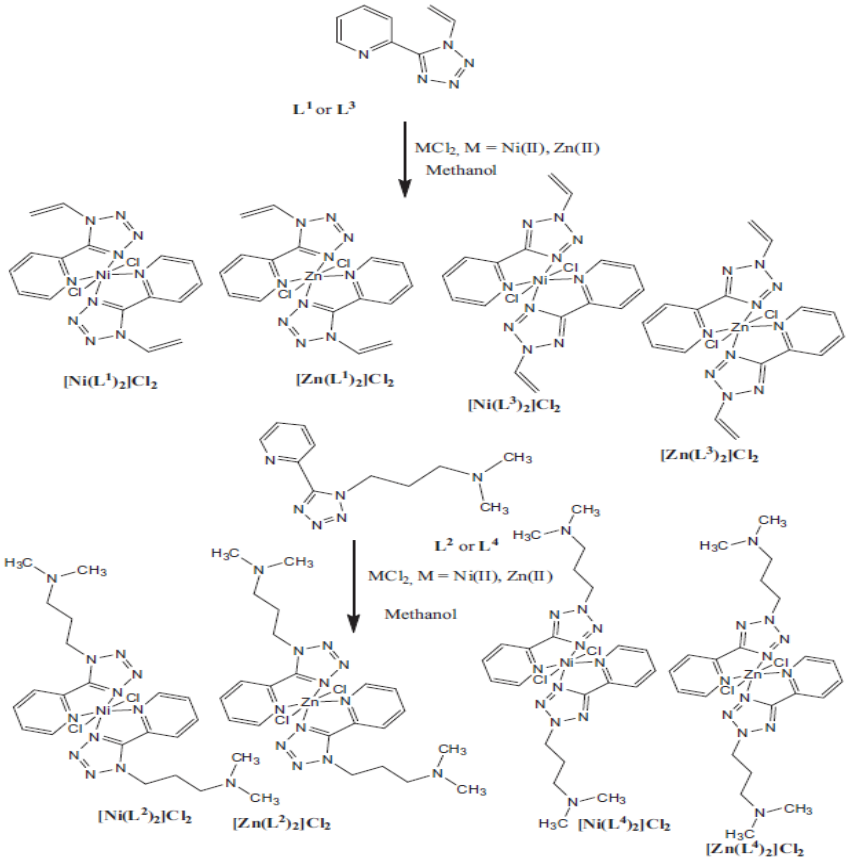
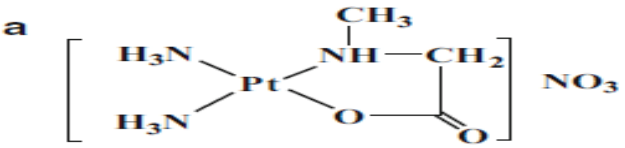


Figure: 12 Proposed structures of a. cis-[Pt(NH$_3$)$_2$(CH$_3$-gly)]NO$_3$ and b. cis-[Pt(NH$_2$-CH$_3$)$_2$(CH$_3$-gly)]NO$_3$ [62]

$$\text{Cis}-[\text{Pt}(\text{NH}_3)_2(\text{CH}_3-\text{gly})]\text{NO}_3 : (\text{M.W} = 381.9\ \text{g/mol})$$

$$\text{Cis}-[\text{Pt}(\text{NH}_2-\text{CH}_3)_2(\text{CH}_3-\text{gly})]\text{NO}_3 : (\text{M.W.} = 406.08\ \text{g/mol})$$

a



b

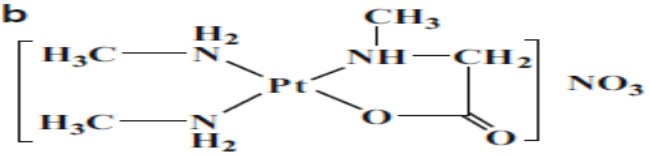


Figure: 13

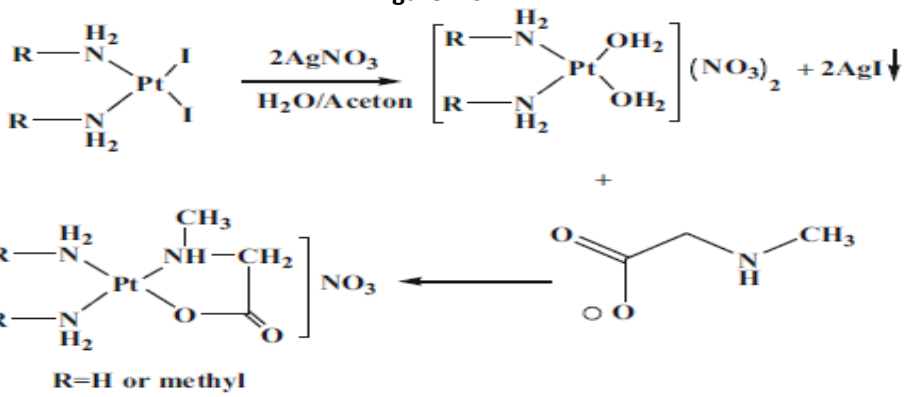
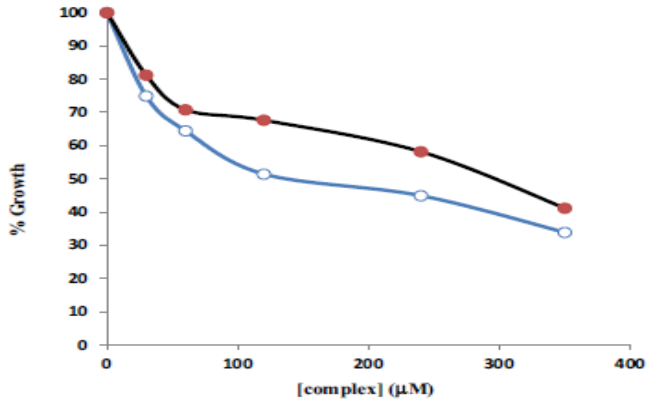


Fig: Schematic reaction of synthesis of two Pt complexes: cis-[Pt(NH$_3$)$_2$(CH$_3$-gly)]NO$_3$ and cis-[Pt(NH$_2$-CH$_3$)$_2$(CH$_3$-gly)]NO$_3$ [62]

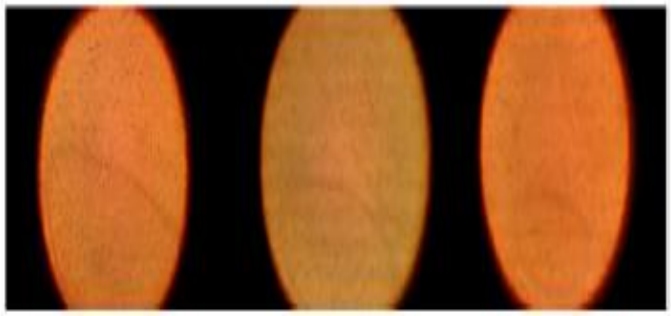
Figure: 14

(A)



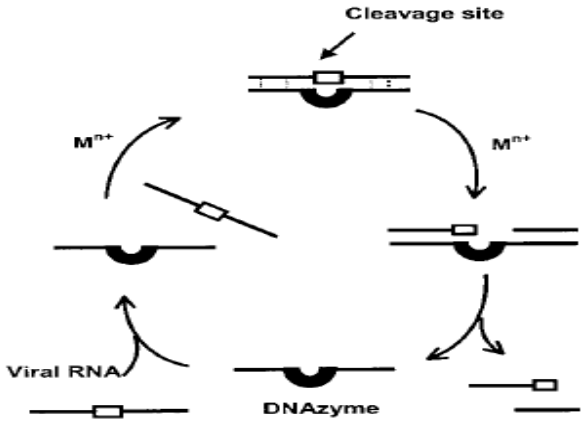
The growth inhibitory activity of the complexes of cis-[Pt (NH$_3$)$_2$(CH$_3$-gly)]NO$_3$ and cis-[Pt(NH$_2$-CH$_3$)$_2$(CH$_3$-gly)]NO$_3$ on the breast cancer line of MCF7, incubated with varying concentrations of the complexes for 24 h using MTT assay. **[62]**

(B)



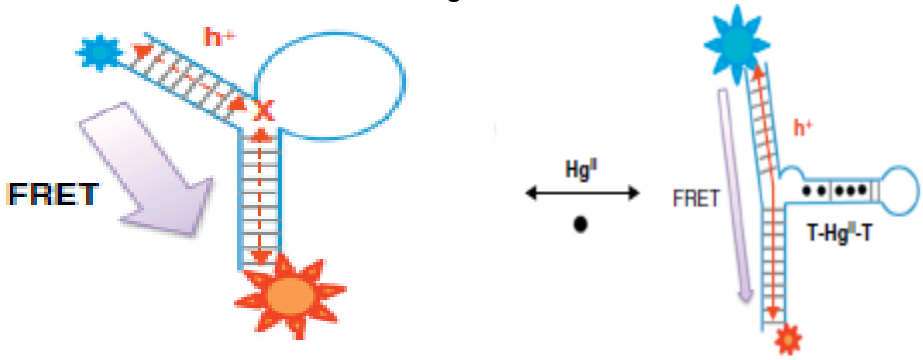
Phase- contrast microscopy of the effects of synthesised Pt (II) complexes on the morphological features of human cancer cell line MCF7 (from left to right, incubated in the absence of complex or control, in the presence of cis-[Pt $(NH_3)_2(CH_3\text{-gly})]NO_3$ and cis-$[Pt(NH_2\text{-}CH_3)_2(CH_3\text{-gly})]NO_3$.**[62]**

Figure: 15



Concept of DNA/RNAzymes as endonucleases to target viral RNA. DNA/RNAzymes can be designed to bind specifically to the target viral RNA through Watson-Crick base pairs, form a unique three-dimensional structure, and perform catalytic function by cleaving the viral RNA. After the RNA cleavage, the DNA/RNAzymes can, in principle, diffuse away, bind to another viral RNA, and perform another catalytic cycle. Metal ions may play essential roles in at least two steps, the folding and formation of active structure and the viral RNA cleavage steps **[66].**

Figure: 16



Three-way junction-based DNA nano machine that exhibits reversible, mechanical and electrical switching fuelled by binding of Hg^{2+} ions to T–T mismatches present in one of the three-way junction stems **[78].**

Table I. Cleavage of pBR-322 Plasmid[a]

reagent	concn, M	% form I	% form II	% form III	S[b]
Fe(II)	10^{-4}	92	8	0	0.08
EDTA-Fe^{II} [c]	10^{-4}	94	6	0	0.06
EDTA-Fe^{II} [c]	5×10^{-4}	38	62	0	0.97
MPE-Fe^{II}	10^{-6}	72	28	0	0.33
MPE-Fe^{II}	5×10^{-6}	40	60	0	0.92
bleomycin-Fe^{II}	10^{-7}	65	29	6	
bleomycin-Fe^{II}	10^{-6}	0	49	51	

[a] Form I pBR-322 (10^{-5} M bp), reagent and buffer (40 mM Tris-HC1, 5 mM NaOAc, pH 7.8) were allowed to react at 37 °C for 60 min. Forms I, II and III were analyzed with agarose gel electrophoresis and quantitated by ethidium bromide staining and densitometry **[36]**. [b]Calculated average number of strand scissions per DNA molecule **[39]**. These values cannot be calculated for bleomycin because of a nonrandom accumulation of single-strand breaks. [c] Values are the same for EDTA-Fe^{II} in the presence of 10^{-5} M EB.

Table II. Cleavage of pBR-322 Plasmid in the Presence of DTT[a]

reagent	concn, M	% form I	% form II	% form III	S
MPE-Fe^{II}	10^{-8}	82	18	0	0.20
	10^{-7}	43	57	0	0.84
	10^{-6}	0	85	15	9.2
bleomycin-Fe^{II}	10^{-8}	67	29	4	
	10^{-7}	0	79	21	
	10^{-6}	0	54	46	
Fe(II)	10^{-6}	90	10	0	0.11

[a] All reactions contain 1 mM DTT. Reaction conditions and analyses are as in Table I.

Table III. Oxidative cleavage data for SC pUC19 DNA (40 µM, in base pair) by complexes 1–4 (10 µM) in the presence of H_2O_2 (100 µM). [43]

Serial No	Reaction conditions	Form (%) SC	Form (%) NC
1	DNA control	93.0	7.0
2	DNA + H_2O_2	94.8	5.2
3	DNA + H_2O_2 + $[Fe(H_2O)_6](ClO_4)_3$	80.0	20.0
4	DNA + H_2O_2 + **1**	6.4	93.6
5	DNA + H_2O_2 + **2**	13.8	86.2
6	DNA + H_2O_2 + **4**	27.3	72.7
7	DNA + H_2O_2 + **3**	2.6	97.4

Table IV: Observed First-Order Rate Constants (k_{obsd}, s^{-1}) for Cobalt Complex (0.01 M) Promoted Hydrolysis of Phosphate Esters at 50°C, pH 7.0. [60]

cobalt complex	BNPP	BDNPP	NPP
$[Co(en)_2(OH)(NH_3)]^{2+}$	$<10^{-6}$	2.4×10^{-4}	$<10^{-6}$
$[Co(en)_2(OH)(OH_2)]^{2+}$	2.7×10^{-5}	4.2×10^{-4}	3.0×10^{-4}
$[Co(trien)(OH)(OH_2)]^{2+}$	4.8×10^{-4}	5.2×10^{-3}	5.6×10^{-3}
$[Co(dien)(OH)(OH_2)_2]^{2+}$	$<10^{-6}$	8.6×10^{-2}	$<10^{-6}$
none	$3.0 \times 10^{-10\,a}$	$2.1 \times 10^{-6\,b}$	$6.0 \times 10^{-8\,c}$

CONCLUSION:

In this review we have tried to focus on several transition metal complexes that show DNA cleavage activities either through hydrolytic or oxidative pathway, i.e. in presence of reducing agents like ascorbic acid or in presence of oxidant like H_2O_2. All the above complexes are mostly applied on plasmid DNA and CT DNA. We have also tried to mention few applications related to the DNA cleavage activities of the transition metal complexes. At the end we have tried to discuss a future prospect based on Cr (III) Induced bleomycine complex that can be used for cleaving DNA or Drug transport.

CONFLICTS OF INTEREST:

Authors declare that there is no potential conflict of interest.

ACKNOWLEDGEMENT:

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Abbreviations

CT- calf thymus
Dpq dipyrido - [3,2-d:2',3'-f]-quinoxaline
Bp – Base pair
SS- Single strand
DS- Double strand
BNPP - bis(p-nitrophenyl) phosphate
BDNPP – Bis (2,4-dinitrophenyl) phosphate

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[36] pBR-322 plasmid was 95% form I and 5% form II. The data in Tables I, II are corrected for the 5% form II and the decreased stainability of form I. [37]

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