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# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL APPLICATIONS OF OSMIUM(IV) COMPLEXES

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## ABSTRACT

***A series of osmium(IV) complexes of types [Os($L^{1-5}$)$(Br)_4$] (where $L^1$=2-benzoyl pyridine , $L^2$=di-pyridyl amine, $L^3$=2, 9-dimethyl-4,7-diphenyl-1,10-phenanthroline, $L^4$=o-phenylenediamine, $L^5$= di-pyridyl ketone) have been synthesized and characterized by electronic spectra, conductance measurements, magnetic measurement, LC-MS and FT-IR spectroscopy. An octahedral geometry around osmium(IV) has been assigned for all complexes. All complexes have been investigated for their interaction with Herring Sperm (HS) DNA utilizing the absorption titration and viscosity measurement study. The DNA-binding property of the osmium(IV) complexes have been also investigated theoretically using molecular docking study. The cleavage study on pUC19 DNA has been monitored by agarose gel electrophoresis. The results indicate that the osmium(IV) complexes can effectively promote the cleavage of plasmid DNA. The complexes have also been screened for their in vitro antibacterial and cytotoxicity activities. All complexes exhibited good antibacterial and cytotoxic activities.***

***Keywords: Osmium(IV), DNA-binding, Agarose gel electrophoresis, Cytotoxicity.***

## INTRODUCTION

Osmium metal have tendency to exhibit varying oxidation states, and due to such characteristics, it has been widely used in solar applications [1]. Attachment of heterocyclic moieties to the osmium metal brings up drastic changes in its applications to biological world. The heterocyclic environment around osmium metal could vary its reactivity as well as stability [2]. Osmium tetroxide is being used in hydroxylation of olefins [3]. But its salts bring ups a new look towards development of efficient and active complexes which could be important for biological studies. Complexes of different N-donor and O-donor ligands are of particular importance. Chemistry of osmium complexes is of keen importance. Osmium binding with P- and O- donor ligands has been studied widely. But, there is a thrust to study osmium metal with ligands having N-donor atoms.

There is a great potential of osmium in cancer treatment due to its unique chemical properties. So far, great promise has been shown in treating different types of cancer cells including colon and ovarian cancers that have developed and tested in the labs [4]. Complexes of osmium with phosphorus donor atoms have also been reported earlier [5]. Osmium complexes with phosphorous and arsenic donor atoms have been synthesized earlier and their spectral and electrochemical studies have been carried out [6]. Osmium metal binding with tris derivatives of bipyridyl ligands have been reported earlier [7].

Platinum compounds has been studied from decades. There is a need to explore chemistry of other metals. So we have synthesized Os(IV) complex of ligands with different donor atoms and have been characterized by mass spectroscopy, IR spectroscopy, electronic spectra, and magnetic measurement and conductance measurements. Biological studies of synthesized complexes i.e. DNA interaction activities, hydrodynamic volume measurement, absorption titration and molecular docking studies. Moreover antibacterial activity, cytotoxic activities if Os(IV) complex have been evaluated.

## EXPERIMENTAL

### Material and reagents

All chemicals used were of high purity were borrowed from Sigma Aldrich (Osmium tetroxide, ammonium bromide, hydrobromic acid, orthophenylene diamine, 2-benzoyl pyridine, dipyridyl amine, dipyridyl ketone, 2,9-dimethyl-4,7-diphenyl-1,10-phehanthroline) were procured from Sigma Chemical Co.(India) (EtBr )and Lurea broath), from MTCC, India.

### Physical measurements

FT-IR ABB Bomen MB 3000 spectrophotometer was used for taking IR spectra in; ῡ in $cm^{-1}$; range 4000–400 $cm^{-1}$. LC-MS spectra were taken using spectrophotometer which works thermally (United States of America). Electronic spectroscopy results were taken using Ultra Viloet-160A photometer operating on Shimadzu software (Japan). Gel electrophoresis was carried out using AlphaDigiDoc™ software.

## SYNTHESIS

### Synthesis and characterization of $(NH_4)_2OsBr_6$ salt

In round bottom flask, $OsO_4$ (0.001mmol) was mixed with 47% HBr and was refluxed for 2 hrs. The solution was decanted into 50 mL beaker and flask was rinsed with 9 mL HBr solution. To the hot beaker, 0.75gm $NH_4Br$ (0.075mol) was added. After solid gets dissolved, the mixture was cooled at room temperature followed by addition of ethanol (12.5mL) with stirring. The solution was allowed to settle until dense black solid was obtained. Residue was transferred to sintered glass filter and was washed with ethanol till free from bromide. The product was kept in deep freezer at 2-4°C and successive filtrate were collected after each day. The salt was collected and again was evaporated to some level and kept under same condition again [8-9].

### Synthesis and characterization of tetrabromido(2-benzoylpyridine)osmium(IV) (1)

$(NH_4)_2OsBr_6$ **(**0.2gm,0.46mmol) and 2-benzoylpyridine ligand (0.17gm,0.92mol) were dissolved and added in 10 mL methanol and refluxed for 45min.The reaction mass was cooled at RT followed by extraction with help of ethyl ethanoate. The compound was soluble in ethyl acetate and was collected by evaporating the solvent and excess salt left as residue was recovered and collected. The brownish precipitate formed were dried and washed with excess solvent.. Yield: 50%; M.p: (>300°c); Mol.Wt. : 693.06gm $mol^{-1}$; Magnetic Moment: 2.74 B.M ; ESI-MS (70eV) : m/z : 692.08($M^+$), 614.5, 539.06, 458.06, 377.05, 183.2 (Base Peak); IR (KBr, $cm^{-1}$): 3070 ν(C-H); 1597 ν(C=O); 1450 ν(C=C), 1087,ν(C-N); 524 ν(Os-Br), 578 ν(Os-N). Conductance: 24 Ʊ $mol^{-1}$ $cm^2$. UV-Vis (DMSO, $c$ = $10^{-4}$ mol $dm^{-3}$): $\lambda_{max}$ ($\varepsilon$) = 276 nm (15,750 $mol^{-1}dm^3$ $cm^{-1}$).

### Synthesis and characterization of tetrabromido(dipyridylamine)osmium(IV) (2)

It was synthesized using dipyridylamine by above procedure mentioned in *2.3.2*. Yield: 66.66%; M.p: (>300°c); Mol.Wt. : 681.05gm $mol^{-1}$; Magnetic Moment: 2.74 B.M ; IR (KBr, $cm^{-1}$): 3379 ν(C-H); 1365 ν(C=C); 1080 ν(C-N); 532.35 ν(Os-N); 354.90 ν(Os-Br). Conductance: 24 Ʊ $mol^{-1}$ $cm^2$. UV-Vis (DMSO, $c$ = $10^{-4}$ mol $dm^{-3}$): $\lambda_{max}$ ($\varepsilon$ = 432 nm (75,550 $mol^{-1}dm^3$ $cm^{-1}$).

### Synthesis and characterization of tetrabromido(2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline)osmium(IV) (3)

It was synthesized using 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline by procedure mentioned in the section 2.3.2. Yield: 75%; M.p: (>300°c); Mol.Wt. : 694.04gm $mol^{-1}$; Magnetic Moment: 2.74 B.M; ESI-MS (70eV): m/z: 870.31($M^+$), 795.60, 714.40, 636.40, 554.40, 360.60 (Base Peak), 78.40($C_6H_5^+$); IR (KBr, $cm^{-}$

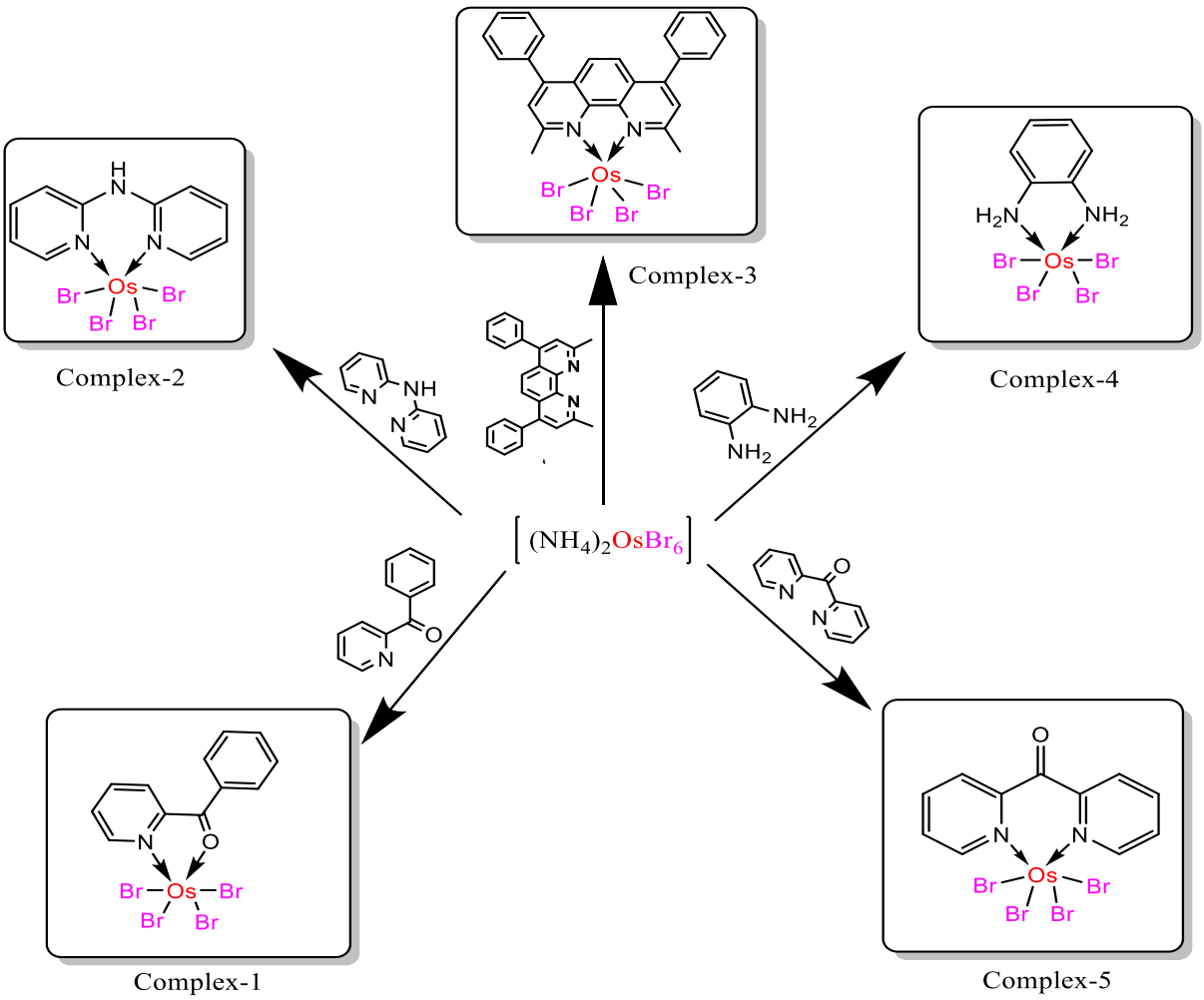
$^{1}$): 3055 ν(C-H)$_{ar.stretching}$; 1404 ν(C=C); 1033 ν(C-N); 393 ν(Os-Br); 540.07 ν(Os-N). Conductance: 24 Ʊ mol$^{-1}$ cm$^{2}$. UV-Vis (DMSO, $c$ = 10$^{-4}$ mol dm$^{-3}$): $\lambda_{max}$ ($\varepsilon$) = 272 nm (25,800 mol$^{-1}$dm$^{3}$ cm$^{-1}$).

**Synthesis and characterization of tetrabromido(orthophenylenediamine)osmium(IV) (4)**

It was synthesized using orthophenylenediamine by above procedure mentioned in *2.3.2*. Yield: 33.33%; M.p: (>300°c); Mol.Wt. : 617.99gm mol$^{-1}$; Magnetic Moment: 2.74 B.M; IR (KBr, cm$^{-1}$): 3055.24 ν(C-H); 1450.77 ν(C=C); 1010 ν(C-N); 570 ν(Os-N); 378.05 ν(Os-Br). Conductance: 24 Ʊ mol$^{-1}$ cm$^{2}$. UV-Vis (DMSO, $c$ = 10$^{-4}$ mol dm$^{-3}$): $\lambda_{max}$ ($\varepsilon$) = 432 nm (16,000 mol$^{-1}$dm$^{3}$ cm$^{-1}$).

**Synthesis and characterization of tetrabromido(dipyridylketone)osmium(IV) (5)**

It was synthesized using one mole of dipyridylketone by above procedure mentioned in *2.3.2*.Yield: 50%; M.p: (>300°c); Mol.Wt. : 694.04gm mol$^{-1}$; Magnetic Moment: 2.74 B.M; IR (KBr, cm$^{-1}$): 3078 ν(C-H); 1604,ν(C=O); 1033 ν(C-N); 1442 ν(C=C) ; 686.66 ν(Os-N); 362 ν(Os-Br). Conductance: 24 Ʊ mol$^{-1}$ cm$^{2}$. UV-Vis (DMSO, $c$ = 10$^{-4}$ mol dm$^{-3}$): $\lambda_{max}$ ($\varepsilon$) =270.50 nm (22,900 mol$^{-1}$dm$^{3}$ cm$^{-1}$).



## BIOLOGICAL STUDY

### *In-vitro* bacteriostatic activity

MIC study was carried out on Gram$^{+}$ and Gram$^{-}$ microorganisms [10].

### Absorption titration study of complex to HS DNA

This experiment was carried out using constant complex concentration in DMSO and varying HS-DNA concentration. [12-13].

### Hydrodynamic volume measurement for complex to HS-DNA interaction

Hydrodynamic measurements were carried out by calculating time elapsed for complex-DNA solution to flow [14].

### Brine shrimp toxicity screening

The activity was performed as described in literature method [11].

### Molecular docking with B-DNA

HEX 8.0.0 software used to study docking interaction with B-DNA. [15-16].

### Interaction of Os(IV) complexes with plasmid (pUC19) DNA by electrophoresis

Experiment was carried out using pUC19 DNA [17].

### *In-vivo* cytotoxicity

*Schizosaccharomyces pombe* cells were used for *in-vivo* cytotoxicity study [18-19].

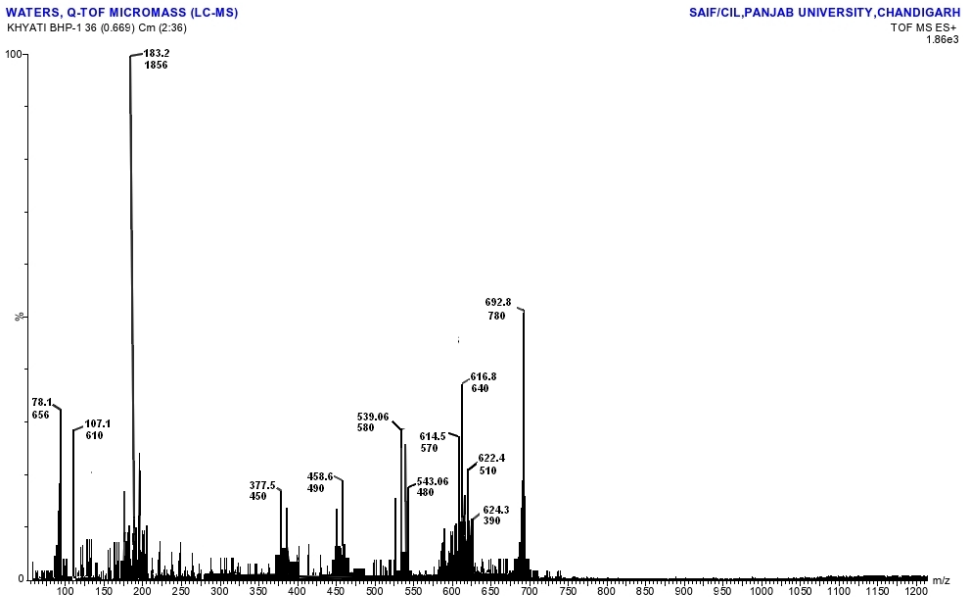



Figure 1. Mass spectra of *tetrabromido(2-benzoylpyridine)osmium(IV)* (1)

## RESULTS AND DISCUSSION

### Synthesis and characterization

Synthesized complexes have 2.74 BM magnetic moment value which is equivalent to theoretical spin value of octahedral complexes indicating paramagnetic behavior. Infrared spectra of complex 1 shows ν(C-H) at 3070 cm$^{-1}$, ν(C-O) at 1597 cm$^{-1}$, ν(C-C) at 1450 cm$^{-1}$, ν(Os-O) at 918 cm$^{-1}$, ν(Os-N) at 578 cm$^{-1}$ and ν(Os-Br) at 524 cm$^{-1}$ shown in supplementary material 1.

Further there is peak at frequency 655.80 which is of N-Os-Br linkage showing comparatively higher value than ν(Os-N) [20-22]. MS of compound 1 exhibits [$M^+$] at 692.08 m/z, $Ph^+$ at 78.10 m/z, [$C_6H_5CO^+$] at 107.10 m/z justifying the structure of synthesized complexes shown in figure 1. Electronic spectra of Os(IV) have been recorded in DMSO solvent. The general spectral range of all the complexes fall between 271-432 nm which depict "metal-to-ligand charge-transfer" MLCT. All the complexes show non electrolytic behavior having conductance value of 24 $\Omega^{-1}$ $mol^{-1}$ $cm^2$.

### *In-vitro* bacteriostatic activity

Broth dilution technique was used for carrying out to study activity of synthesized osmium(IV) complexes. It was performed against three $Gram^{-ve}$ and two $Gram^{+ve}$ bacteria.The values are effective in case of all the complexes as shown in Figure 2.

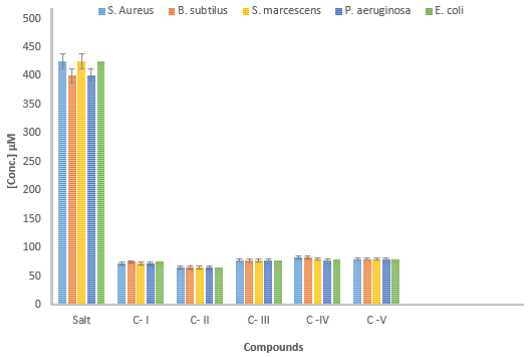



Figure 2. Minimum inhibitory concentration of Os(IV) complexes: The Os(IV) complexes are exposed at different concentrations overnight and the minimum inhibitory concentration of each complex is given by considering control sets gave null values

### Brine shrimp toxicity screening

Brine shrimp lethality bioassay is used to study pharmacological activities and cytotoxicity by screening procedure of compounds having active biological moieties. Procedure deals with screening the synthesized compounds and calculating $LC_{50}$ values (µg/ml). It is concluded that compound having least $LC_{50}$ value is considered to be more potent. The values of different synthesized osmium(IV) complexes i.e. complexes 1, 2, 3, 4 and 5 are 15.62, 15.77, 6.58, 12.99, 15.92 µg/ml respectively. It could be concluded that complexes with ketonic group or carbonyl moiety which comprise electron withdrawing tendency bears more potent value compare to one with amine functionality.

### Absorption titration study of complex to HS DNA interaction

Absorption titration study was carried out in presence of DMSO as a solvent and varying concentration of *HS DNA*. Complexes bind to DNA base pairs which shows Hypochromism shift as depicted in figure. The affinity of binding is calculated by following equation.

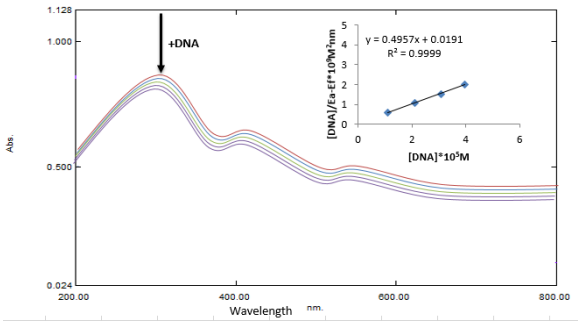



Figure 3**.** Absorption spectral changes on addition of HS DNA to the solution of complex III (after incubating it for 10 min. at room temperature in phosphate buffer. Graph: plot of [DNA]/($\varepsilon_a$–$\varepsilon_f$) vs. [DNA]. (Arrow shows the change in absorption with increase in concentration of DNA) amount of complexes and EtBr at 27±0.1 $^oC$ in phosphate buffer (pH 7.2)

$$[DNA]/(\varepsilon_a - \varepsilon_f) = [DNA]/(\varepsilon_b - \varepsilon_f) + 1/K_b(\varepsilon_b - \varepsilon_f)$$

where [DNA], $\varepsilon_a$, $\varepsilon_f$ and $\varepsilon_b$ are concentration of Deoxy ribonucleic acid, apparent absorption coefficient with respect to compound concentration, extinction coefficient and molar extinction coefficient respectively. From the graph of [DNA]/($\varepsilon_a$ – $\varepsilon_f$) versus [DNA], intrinsic

binding constant $K_b$ is calculated from the slope. The Kb values of complexes 1, 2, 3, 4 and 5 are $0.23 \times 10^5\,M^{-1}$, $0.43 \times 10^5\,M^{-1}$, $0.22 \times 10^5\,M^{-1}$, $0.48 \times 10^5\,M^{-1}$ and $0.16 \times 10^5\,M^{-1}$, respectively. The successive order of values is 4 > 2 > 1 > 3 >5. Figure 3 Shows absorption spectral changes on addition of increasing amount of complex concentration.

**Hydrodynamic volume measurement for complex to HS DNA interaction**

*Viscosity* data gives the information about mode of complexes to DNA interaction. The graph shows that the relative viscosity of the HS-DNA increases upon the addition of varying concentration of complexes suggesting partial intercalative mode of binding. Complexes 1, 2, 5 shows partial intercalative mode of binding whereas complexes 3 and 4 shows groove mode of binding that could be attributed due to planarity of phenyl ring in phenathrolene moiety in complex 3 and orthophenylenediamine ligand in complex 5 as shown in Figure 4. Due to planarity that could easily insert into binding site and show decrease in viscosity values hence showing groove mode of binding with the HS-DNA.

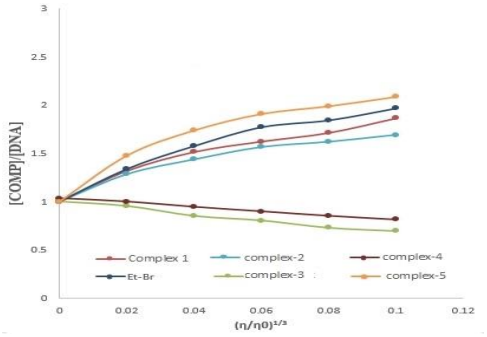



Figure 4. Plot of effect on relative viscosity of HS- DNA under the influence of increasing

**Molecular docking with B-DNA**

Molecular docking energy levels of complexes (1-5) are -301.07, -232.99, -287.73, -192.41 and -261.55 $kJmol^{-1}$ respectively. The energy values clearly reflect interaction of complexes with DNA indicating effective binding. This also indicate effectiveness of presence of osmium as metal in complexes which shows binding ability. Again here we conclude that complex bearing phenyl moiety has more effective energy value compare to other complexes due to planarity and ease of insertion inside the groove. The figure 5 shows docked structure of complex 3 bearing phenanthrolene moiety. Due to planarity of phenyl rings it can easily insert inside the DNA showing effective docking energy value.

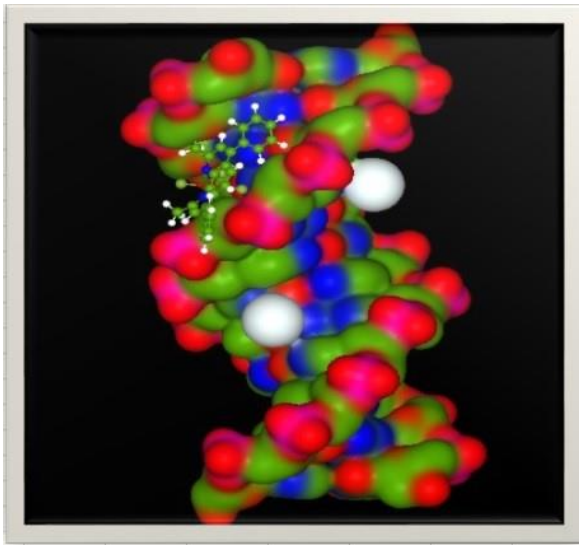


Figure 5. Docked structure of complex IV with B DNA

Table 1: Data of DNA cleavage by compounds during electrophoresis experiment.

| | Name | Form I | Form II | Form III | % Cleavage |
|---|---|---|---|---|---|
| **1** | DNA Control | 83.3 | 16.7 | | |
| **2** | Salt | 43.5 | 56.5 | | 47.77 |
| **3** | Complex 1 | 10.6 | 61.4 | 28 | 87.27 |
| **4** | Complex 2 | 3.8 | 59.7 | 36.5 | 95.43 |
| **5** | Complex 3 | 18.2 | 70.7 | 11.1 | 83.03 |
| **6** | Complex 4 | 29.8 | 38.3 | 31.9 | 64.22 |
| **7** | Complex 5 | 8.2 | 79.9 | 10.5 | 90.15 |

**Interaction of Os(IV) complexes with plasmid (pUC19) DNA by electrophoresis**

Gel electrophoresis property of ligands varies according to environment of surrounding ligands and complexes. Since our work consists of some planner and non-planner ligands surrounding metal salts, the cleavage properties varies accordingly. Complex having bipyridyl ketone moiety shows highest percentage of cleavage whereas complex with 2-benzoyl pyridine ring shows least. The successive order of cleavage of complexes is 2> 4 >3 > 5 >1.

In other words, high percentage of metal containing complex has good cleavage property to other. Photographed image figure 6 shows the cleavage of plasmid DNA in complexes and metal salt. The data are presented in Table 1.

***In-vivo* cytotoxicity**

For studying cell biology and cytotoxic effect, DNA of Schizosaccharomyces pombe cells is used. This are eukaryotic cells of big size. The selective activity of synthesized complexes is in order 3 >1 >4 >5 >2.. The complex with

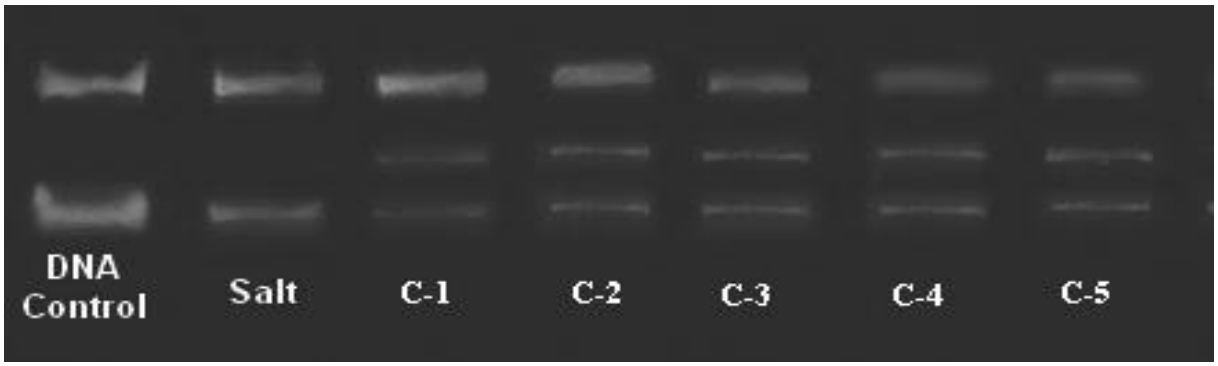



Figure 6. Photogenic view of cleavage of pUC19 DNA (50μM) with series of Os (IV) complexes (200 μ M) using 1% agarose gel containing 0.5 μgcm$^{-3}$ ethidium bromide. All reactions were incubated in TAE buffer (pH 8) in a final volume of 15 mm$^3$, for 3 h. at 37 $^o$

phenathrolene ring is more potent compare to others which could be attributed due to more planner structure of phenanthrolene ring to site into DNA of cells effectively

## CONCLUSION

A series of heterocyclic ligand based osmium(IV) are studied. Biological activities of synthesized complexes have been studied. Spectral studies reveal that complexes exhibit Octahedral geometry.With comparison to osmium salt, complexes showed higher antibacterial activity. From absorption titration and viscosity data we conclude that complexes 1, 4 and 5 shows partial intercalative mode of binding whereas complexes 2 and 3 show groove mode of binding. Docking studies lead to conclusion of binding mode between osmium compounds and base pairs of DNA which shows intercalation. Further, cleavage tendency of complexes were good compared to osmium salt.

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