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Review Article; Biological Applications of Schiff Base and Their Metal Complexes

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1. INTRODUCTION

The potential of Schiff bases and their metal complexes as drugs has been explored in a number of research papers. Several researches have demonstrated the biological diversity of Schiff bases and their metal complexes which include their antibacterial, antifungal, antitumor, anticancer, antitubercular, antioxidant, anticonvulsant, antiviral, cytotoxicity, antidiabetic, antileukaemia, analgesic and anti-inflammatory properties. The capacity of Schiff bases to bind metal ions has also facilitated their development as possible medicinal agents. Furthermore, Schiff bases are easily synthesized from simple starting materials, making them a potential building block for drug development. Overall, in-depth research on Schiff bases and their metal complexes has revealed encouraging possibilities for their use in creating new therapies with a variety of biological functions.

2. BIOLOGICAL APPLICATIONS

Kumari *et al.*¹ reported that the Schiff bases and their metal complexes have numerous applications in various biomedical pharmaceuticals such as antimicrobial, anti-malarial, anticancer, antiviral, anti-inflammatory, antioxidant, anticonvulsant, anti-anthelmintic, bioprinting, tissue regenerating, enzyme inhibition and drug delivery. In biological systems, the azomethine nitrogen of Schiff bases serves as a binding site for metal ions to attach to

diverse biomolecules such as proteins and amino acids for anti-germ activity. Our bodies' Schiff bases catalyzed many metabolic events in the form of enzymes that are active against certain bacteria. Several studies have been conducted to improve the bio-functions of Schiff bases and their metal complexes. Schiff bases can fight cancer, fungus, germs, ulcers, and viruses, depending on which transition metal ions they contain.

2.1 Antibacterial Activity

Patelet *al.*² synthesized some Schiff bases and tested against various bacteria. Schiff base derivatives 6-Bromo-3-(2-chlorobenzylideneamino)-2-[2-(2,6-dichlorophenyl)amino]benzylquinazolin-4(3H)-one (1), 6-Bromo-3-(4-chlorobenzylideneamino)-2-[2-(2,6-dichlorophenyl)amino]benzylquinazolin-4(3H)-one (2), 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(4-methoxybenzylideneamino)-quinazolin-4(3H)-one (3) and 2-azetidinone derivatives 6-Bromo-3-[3-chloro-4-(4-methoxyphenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzylquinazolin-4(3H)-one (4) and 6-Bromo-3-[3-chloro-4-(3,4,5-trimethoxyphenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzylquinazolin-4(3H)-one (5) exhibited good activities (50.88–52.88%) against gram positive bacteria *S. aureus* while compounds (3) and (4) displayed good activity (60%) against gram positive bacteria *B. subtilis*.

El-Sherif *et al.*³ prepared a Schiff base namely 2-aminomethylthiophenyl-4-bromosalicylaldehyde(ATS)(4-bromo-2-(thiophen-2-yl-imino)methylphenol) and its complexes with Ni(II), Zn(II) and Cu(II) ions. The ligand and metal complexes were tested against microbes. The results of antimicrobial activity show that the metal complexes exhibit antimicrobial properties and it is important to note that they show enhanced inhibitory activity compared to the parent ligand under identical experimental conditions.

Kumar *et al.*⁴ reported that the Schiff base, its metal complexes and standard drug Imipenem ($C_{12}H_{17}N_3O_4S$) were screened separately for their antibacterial activity against the bacteria *S. aureus* and *B. subtilis* (as gram +ve bacteria) and *P. aeruginosa*, *E. coli* and *S. typhi* (as gram -ve bacteria). The complexes are 1=[Cr($C_{34}H_{24}N_8O_6$)Cl]Cl₂, 2=[Cr($C_{34}H_{24}N_8O_6$)NO₃](NO₃)₂, 3=[Cr($C_{34}H_{24}N_8O_6$)OAc](OAc)₂, 4=[Mn($C_{34}H_{24}N_8O_6$)Cl]Cl₂, 5=[Mn($C_{34}H_{24}N_8O_6$)NO₃](NO₃)₂, 6=[Mn($C_{34}H_{24}N_8O_6$)OAc](OAc)₂, 7=[Fe($C_{34}H_{24}N_8O_6$)Cl]Cl₂, 8=[Fe($C_{34}H_{24}N_8O_6$)NO₃](NO₃)₂, 9=[Fe($C_{34}H_{24}N_8O_6$)OAc](OAc)₂, Imipenem= standard drug. Complex 3 shows excellent antibacterial activity against *S. aureus* and *B. subtilis* and other show moderate antibacterial activity against all bacteria.

Malladi and co-workers⁵ prepared many Schiff bases. All the newly synthesized compounds were screened for their antibacterial activity. For this, *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* microorganisms were employed and found better antibacterial activity against all above bacteria compare to Ceftriaxone. Antimicrobial study was assessed by Minimum Inhibitory concentration (MIC) by serial dilution method.

Uddinet *al.*⁶ prepared Salicylaldehyde-benzoylhydrazine, its derivative Schiff base and their complexes with Lead metal. Antibacterial activity of the prepared lead(II) evaluated against the five selective human pathogenic bacteria. All the tested complexes are quite effective against *Bacillus cereus*, *Salmonella typhi* and *Staphylococcus aureus*. On the other hand, they were not effective against *Escherichia coli* and *Bacillus megaterium*.

Shukla *et al.*⁷ synthesized a symmetrical tetradentate Schiff base, o-HACPHENEN. The Schiff base ligand and 1,10-phenanthroline were used for the tailored synthesis of four mixed-ligand complexes, [Mn(o-HACPHENEN)(1,10-phen)] (1), [Fe(o-HACPHENEN)(1,10-phen)]Cl (2), [Co(o-HACPHENEN)(1,10-phen)] (3) and [Ni(o-HACPHENEN)(1,10-phen)] (4). The antibacterial activity of the Schiff base ligand o-HACPHENEN, 1,10-phen and its 1-4 complexes were tested against *E. coli*. Complex 1 displayed the highest bactericidal activity. However, other complexes exhibit less antibacterial activity. The activity order of the synthesized compounds was 1 > 4 > 2 > 3 > o-HACPHENEN. It was observed that 1-4 have exhibited MIC in between 39-48 µg/mL, which was higher than standard drug Chloramphenicol but lower than Amoxicillin. MIC of the complexes follows trend as 1 > 4 > 2 > 3.

Anaconda *et al.*⁸ prepared 1,2-benzenidene-phenoxyethylpenicillin Schiff base and its complexes with metal Fe, Co, Ni, Cu, Zn. Schiff base ligand and the metal complexes were tested against G(+) bacteria. The results indicate that the complexes exhibited much better bactericidal activity than ligand.

Poormohammadi *et al.*⁹ synthesized two new Cu(II) Schiff base complexes. Antibacterial potential of these ligands and complexes were tested against four bacteria, both gram positive and gram negative. The ligands almost showed higher antibacterial activity than the corresponding complexes.

Esfahani¹⁰ and Behzad synthesized a new Cu(II) Schiff base complex namely bis{µ-[2-([3-(amino)propyl]imino)methyl]-4-bromophenolato]}-diaqua-(µ-perchlorato)-di-copper(II) perchlorate. These compounds tested against *E. coli*, *Salmonella*, *K. pneumonia*,

Proteus, *S. aureus* and show almost equivalent antibacterial activity to Gentamicin and Tetracycline.

Aziz *et al.*¹¹ prepared a Schiff base ligand 2-(benzo[d] [1,3] dioxol-5-ylmethyleneamino) benzoic acid and its complexes with metal Cu, Ni, Pb, Sn, Mn. The synthesized Schiff base and its metal complexes were screened for their antibacterial activity against gram positive (*Staphylococcus aureus*) and gram negative (*Escherichia coli*) bacterial strains. These compounds exhibit comparable antibacterial activity to Vancomycin.

Khoret *al.*¹² synthesized three novel Schiff base ligands namely N`-((1E,2E)-3-phenylallylidene)benzohy-drazide, N`-((1E,2E)-3-phenylallylidene)isonicotino-hydrazide, (E)-N-phenyl-2-((E)-3-phenylallyli-dene)hydrazidecarboxamide and their complexes with copper metal. These Schiff base ligands and its metal complexes exhibit good antibacterial activity against *S. aureus*, *A. baumannii*, *E. coli*, and *P. aeruginosa*.

2.2 Antifungal Activity

Chandra *et al.*¹³ prepared a Schiff base ligand 3,3'-Thiodipropionic acid bis(4-amino-5-ethylimino-2,3-dimethyl-1-phenyl-3-pyrazoline) and its complexes with metal Co, Ni, and Cu. The screening of antifungal activity of ligand and its complexes against the fungi *Alternariabrassicae*, *Aspergillusniger* and *Fusariumoxysporum* indicates that the complexes show the enhanced activity in comparison to free ligand.

Singh *et al.*¹⁴ synthesized Zn(II) complex of 3-[substituted phenyl]-4-amino-5-hydrazino-1, 2, 4-triazole Schiff base. The Schiff base and its metal complex screened and found very good antifungal activity against *Colletotrichumfalcatum*, *Aspergillusniger*, *Fusariumoxysporium* and *Carvulariapallescence* by petriplates methods.

Chohan¹⁵ and Sumrra synthesized five Schiff base ligands and their Oxovanadium(IV) complexes. In vitro antifungal screening of all the synthesized compounds was carried out against *Trichophytonlongifucus*, *Candida albican*, *Aspergillusflavus*, *Microscopumcanis*, *Fusariumsolani* and *Candida glabrata* fungal strains and results of inhibition were compared with the standard drugs, miconazole and amphotericin B. The ligands and their metal complexes exhibit good antifungal activity andIt was generally observed that the activity of ligands was increased upon coordination with the vanadium metal.

Palanimuruganet *al.*¹⁶ prepared Salicylidene-4-iminoantipyrinyl-2-imino-3-(1H-imidazol-4-yl)-propanoic acid Schiff base and its complexes with metal Co, Ni, Cu, Zn and

VO. These compounds show better antifungal activities against *C. albicans*, *R. bataticola*, *A. flavus*, *A. niger*, *R. stolonifer* than Nystatin.

Khan *et al.*¹⁷ prepared two Schiff base ligands namely 1-pentanoyl-3-methyl-3-(4-chlorophenyl) thiourea (HL₁), 1-(3-fluorobenzoyl)-3,3-diphenyl thiourea (HL₂) and their complexes 1 and 2 with nickel respectively. All the prepared compounds subjected for antifungal assay against three fungal strains including *A. fumigatus*, *F. soloni*, and *Mucor sp.* Terbinafine has been used as a standard drug in this test. HL₁ and HL₂ have shown low to good activity against fungal strains. Complex 1 exhibits good efficacy against the *A. fumigatus* fungal strain only.

2.3 Anticancer Activity

Initially the cytotoxicity of Cu(BrHAP)₂ was tested by Hajrezaie *et al.*¹⁸ on HT-29 and CCD 841 cell lines. For HT-29 the IC₅₀ values of the Schiff base compound were found 2.87 ± 0.21, (24h) 1.93 ± 0.37 (48h) and 1.44 ± 0.26 (72h) (μg/mL) for colon cancer cells from three independent MTT experiments respectively and for CCD 841 the IC₅₀ values of the Schiff base compound were found 50 < (μg/mL)(24h,48h,72h) for normal colon cells. Cu(BrHAP)₂ elicited a significant cytotoxicity and cell inhibitory effect after 24, 48, and 72 h of treatment on HT-29 cell.

Emamet *et al.*¹⁹ synthesized three Schiff base ligands as 1 -(5-methyl-5H-indolo[2,3-b]quinolin-11-yl)benzene-1,2-diamine (L₁), 2-((2-(5-methyl-5H-indolo[2,3-b]quinolin-11-ylamino)phenylimino)methyl)phenol (HL₂), 2-((3-(5-Methyl-5H-indolo[2,3-b]quinolin-11-ylamino)propylimino)methyl)phenol (HL₃) and their metal complexes with Co(II), Ni(II), Cu(II) and Pd(II) metals. Both ligands and their metal complexes were screened for anticancer activity against human colon carcinoma (HT-29) cell line using MTT assay. The anticancer activity of L₁ showed a percent of cell inhibition of 7.4 (weak activity). However, when this ligand chelates with metal ions such as Co(II), Ni(II), Cu(II) and Pd(II). The inhibition of the cancer cells depends on metal type. The best activity was observed in Co complex with L₁ with 86.10 % inhibition which is significantly higher.

Kahrovic *et al.*²⁰ synthesized ruthenium complex as [Ru₂L₂Cl₂(Et₂NH)(H₂O)]·H₂O, where L = N-2-pyridyl-5-Cl-salicylideneimine, hereinafter 1 and the homologous complexes with Schiff bases L = N-2-pyridyl-5-X-salicylideneimine, where X = H for 2, Br for 3 and NO₂ for 4. Anticancer activity corresponds to the order 2 > 1 ~ 3 > 4, indicating an effect of substituent on aldehyde ring of Schiff base.

Andiappanet *al.*²¹ reported that the SBL-based metal complexes (SBLPr and SBLEr) are to be useful as anticancer drugs because of their stability, cytocompatibility, and flexible binding with biomolecules. The antiproliferative actions of SBLPr and SBLEr were examined in three different cancer cell lines (i.e., Vero, HeLa, and MCF7 cells) and evaluated by MTT assay. Observations of the effect of synthesized SBLPr and SBLEr at different concentrations (i.e., 5, 10, 25, 50, 75, and 100 µg/ml complexes) on cell viability of Vero, MCF7, and HeLa cells were made at 24h. The observed results explicated the cells viability at 85–90% for the concentrations up to 5 µg/ml. The SBLPr-tested Vero cells displayed a good biocompatibility compared to the complex of SBLEr.

2.4 Antitumor Activity

Sunil *et al.*²² reported that SB-3, at a dose of 100 mg/kg, optimally inhibits the growth of EAC cells in vivo. This is evident from the reduced tumor weight and enhanced life span of that study group. The treatment with SB-3 (100mg/kg) restored the deviated hematological and biochemical parameters to the normal range. It is an effective antineoplastic agent with comparatively less toxic effects.

Uddinet *al.*²³ reported that the cytotoxic potential of all synthesized compounds were found very good against human breast adenocarcinoma cells MCF-7, human cervical adenocarcinoma cells HeLa and baby hamster kidney cells (BHK–21).

To study the antitumor effect, the ligand, DBAPB, and its Cu(II) complex prepared by El-ghamryet *al.*²⁴ in EtOH, in addition of its some more Cu(II) complexes prepared in CTAB/EtOH, SO/EtOH, MP/EtOH and their residues produced after heating at 200 °C for 1 h, have been tested against Hepatocellular carcinoma cell line (HepG-2 cells). The common drug cis-platin was utilized for comparison (IC₅₀=3.27 µg/mL against HepG-2 cell line). The IC₅₀ value, which refers to the compound concentration that suppresses tumor cell growth by 50%, was used to specify the antitumor activity.

Hosnyet *al.*²⁵ described that the ligand H₂L and its Cr and Cu nano-complexes prepared in CS/EtOH media before and after heating the nanodomain complexes at 200 °C were measured against a cell line (HepG-2) to establish in vitro antitumor efficiency and compared with the cis-platin anticancer drug (IC₅₀~1.714 µg/ml).

2.5 Antioxidant Activity

Vhanaleet *al.*²⁶ synthesized four Schiff bases 2,2'-((propane-1,3-diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(naphthalen-1-ol) (I) and 2,2'-((propane-1,3-diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-chloronaphthalen-1-ol) (II) 2,2'-

((pentane-1,3-diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(naphthalen-1-ol) (III) and 2,2'- ((pentane-1,3-diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-bromonaphthalen-1-ol)(IV) and tested their antioxidant activity. Schiff bases (I-IV) were evaluated for their radical scavenging capacity (antioxidant activity) by DPPH and hydroxyl radical scavenging assay using Ascorbic acid and α -Tocopherol as internal standard respectively. In both methods the compounds I and IV are exhibiting higher activity than II and III. It may be due to compound I is with free hydroxyl group in position 4 and presence of 1,3 propane diamine group also compound IV is with halogenated hydroxyl group in position 4 and 1,3 pentane diamines. Comparative study also revealed that the halogen substituent with extended carbon chain has good antioxidant activity.

Nawazet *al.*²⁷ synthesized twobidentate Schiff base ligands and their metal complexes with nickel metal. Antioxidant activity of the synthesised Ni(II) Schiff base complexes was tested by DPPH assay, in which there was a decrease in DPPH free radical with increasing concentration of complex. The results suggest that the Ni(II) complexes are good scavengers of free radical species.

Boraseet *al.*²⁸ were synthesized a heterocyclic Schiff bases ligand [DH-4M] 4-((E)-(4-methylpyridin-2-ylimino)methyl) benzene-1,3-diol and their metal complexes with Fe(III), Co(III), Ni(II), and Cu(II) metal ions. The antioxidant activity of metal complexes such as [DH-4M] with Fe(III), Co(III), Ni(II), and Cu(II) is tested against different concentration and inhibition increases with increasing concentration of complex.

2.6 Cytotoxicity

Shi *et al.*²⁹ synthesized a Schiff base (E)-4-chloro-2-[(2- morpholinoethylimino)-methyl]phenol and its Zn complex. Cytotoxicities of the compounds against KB, K562 and Hep-G2 cells were evaluated. The cytotoxicity of Zn complex found more than ligand.

Jiang *et al.*³⁰ synthesized three Schiff base ligands and their metal complexes with copper as $[\text{Cu}_2(\text{HL}_1)_2(\text{CH}_3\text{OH})(\text{NO}_3)] \cdot \text{NO}_3$ (1), $[\text{Cu}_2(\text{HL}_2)_2(\text{CH}_3\text{OH})_2] \cdot 2\text{NO}_3$ (2) and $[\text{Cu}_2(\text{HL}_3)_2(\text{C}_2\text{H}_5\text{OH})_2] \cdot 2\text{NO}_3$ (3). To determine the anti-proliferative efficacy of complexes 1–3, we performed MTT assays using four cancer cell lines (Bel-7402, HeLa, MCF-7, and MGC-803) and one normal lung fibroblast cell line (WI38). The widely used metallodrugs cisplatin was included as a control. The values of in vitro cytotoxicity measured for complexes 1-3 exceed those measured for the Schiff-base ligands by themselves, indicating that these ligands coordination to Cu(II) significantly increased their cytotoxicity. The IC_{50} values of complexes 1-3 were significantly lower than that of the cisplatin

Jayendran *et al.*³¹ synthesized a Schiff base ligand 4-bromo-2-(((3-(methylamino)propyl)imino) methyl)phenol (HL) and its metal complex 1 and 2 with Cu and Zn respectively. In vitro cytotoxic activity of complexes 1 and 2 were evaluated against Dalton's lymphoma ascites cells. While analyzing the results, it can be seen that although both the complexes showed significant cytotoxic activity against DLA cells, copper complex is having higher activity. The complex 1 is having 36 µg/ml as IC₅₀ value and for complex 2 it is 42 µg/ml.

Qiet *et al.*³² synthesized a Schiff base metal complexes [2-[1-(2-pyridinyl)ethylidene]hydrazinecarbothioamide-N,N,S-copper(II)] chloride (C₁), [N-methyl-2-[1-(2-pyridinyl)ethylidene]hydrazinecarbothioamide-N,N,S-copper(II)] chloride (C₂) and [N,N-dimethyl-2-[1-(2-pyridinyl)ethylidene]hydrazinecarbothioamide-N,N,S-copper(II)] chloride (C₃). The antiproliferative properties of the thiosemicarbazone ligands and Cu(II) complexes on two malignant cancer cell lines (human lung cancer cell lines A549, human colon cancer cell lines Caco-2) were evaluated. The antiproliferative activity of the Cu(II) complexes was significantly higher than that of the corresponding individual ligands, and the antitumor proliferative activity of C₁ was similar to C₃.

2.7 Antiproliferative Activity

Ejidike *et al.*³³ reported that the ruthenium(III) compounds and standard drug (parthenolide) IC₅₀ values revealed that the test samples showed significant inhibition against the tested cell lines. The cell viability percentages of ruthenium(III)-Schiff base complexes and parthenolide drug against TK-10, UACC-62, and MCF-7 cell lines, at different concentrations of ruthenium(III) compounds or parthenolide. The obtained results revealed that treatment of cell lines with different concentrations of Ru(III)-Schiff base complexes efficiently affected cell viability towards MCF-7 cells. [Ru(DAE)Cl₂(H₂O)], [Ru(HME)Cl₂(H₂O)], and [Ru(DEE)Cl₂(H₂O)] induced more efficient cell death with IC₅₀ values of 3.57±1.09, 4.88±1.28, and 3.43±1.48 µM, respectively, towards human breast cancer cell (MCF-7) cells than other investigated cell lines, compared with IC₅₀ values of 0.44 ± 2.02 µM MCF-7, for the standard cytotoxin drug parthenolide. The order of activity of the complexes against human melanoma cancer cell (UACC-62) is as follows: [Ru(DEE)Cl₂(H₂O)] > [Ru(HME)Cl₂(H₂O)] > [Ru(DAE)Cl₂(H₂O)].

Das *et al.*³⁴ prepared two ligands L₁, L₂ and two complexes [ZnL₁(N₃)₂] (1) and [ZnL₂(N₃)₂] (2). The antiproliferative activities of only azido complexes 1 and 2 were studied against breast cancer cell MCF 7. SRB assay is applied to get the results in terms of GI₅₀, TGI

and LC₅₀ where these notations indicate the conventional meaning. For positive control, a chemotherapeutic drug named Adriamycin was used. Both the compounds have shown significant growth inhibition of MCF-7 cell line. Interestingly complex 2 has shown a high antiproliferative activity. The GI₅₀ values for complex 1 and 2 are found to be 33.6 µg/mL and 24.4 µg/mL respectively.

Elsamraet *al.*³⁵ synthesized five BenzenesulfonamideSchiff base ligands and their nickel complexes. The concentration of synthesized compounds as anticancer candidates to inhibit the growth of the proliferative cells by 50% (IC₅₀) in µM was evaluated against MCF-7 (human breast cancer cell line). All ligands and some of their nickel complexes showed appreciable cytotoxicity against MCF-7 compared to cisplatin as a chemotherapy standard drug for breast cancer.

2.8 Anti-inflammatory and Analgesic Activity

Bhandariet *al.*³⁶ synthesized some Schiff bases using oxadiazole-2-thiol base structure. Anti-inflammatory activity of the synthesized Schiff bases investigated and found very good.

Alamet *al.*³⁷ prepared many Schiff bases compounds. Anti-inflammatory activity of 4-(3,4-Dihydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (1) and 4-(2, 4, 6-Trihydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (2) investigated. Both compounds demonstrated a potent antioxidant activity of < 1.0 µM at IC₅₀. However, one another compound could be evaluated in terms of inhibition of the production of inflammatory modulators associated with NO because the most active antioxidant compound, (2) was difficult to solubilize, even in DMSO.

Karthiket *al.*³⁸ synthesized a Schiff base ligand (E)-2,6-dimethoxy-4-((quinoline-3-ylimino)methyl)phenol (HL) and its complexes with Co (II), Ni (II), Cu (II), Zn (II) metal ions. The Anti-inflammatory activity of the ligand and metal complexes has been done by using the HRBC stabilization method. Diclofenac sodium was used as standard and distilled water was used as control. The percentage of membrane stabilization for synthesized ligand, complexes and standard were done at 20, 40, 60, 80 and 100 µg/mL. The percentage of hemolysis by diclofenac sodium, ligand and its metal complexes by HRBC membrane stabilization method increases with increase in concentration.

2.9 DNA Interaction

Abdel-Rahmanet *al.*³⁹ synthesized some Schiff base ligand as nal, nphal, nas, nh, nar and their complexes with iron nali, nphali, nasi, nhi, nari respectively. The interaction between CT-DNA and the investigated complexes were followed by spectrophotometric and viscosity

measurements. It was found that, the prepared complexes bind to DNA via classical intercalative mode and showed a different DNA activity with the sequence nhi>nari>nali>nasi>nphali.

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