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Enhanced superior activity of imines-based metal(II) coordination complexes for vaccines perspectives

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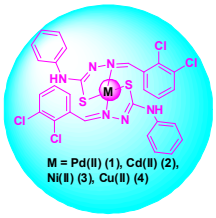
Abstract: We report enhanced superior activity of imines-based metal(II) coordination complexes of the general type $[Pd(L)_2]$ [where, HL = synthesized bidentate ligand, M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**)] for vaccines perspectives. They exhibit a distorted square planar geometry around the metal(II) ions coordinated through the NS donor atoms from their respective two deprotonated ligands HL. DFT calculations were performed to validate the experimental geometries and confirm the electronic structures. In addition, the superior biological activity (anticancer efficacy) were conducted against human cell lines while molecular docking calculations were employed to explore the antiviral potentials.

(Keywords : Superior biological activity, metal(II) complexes, imine-based ligand, DFT.).

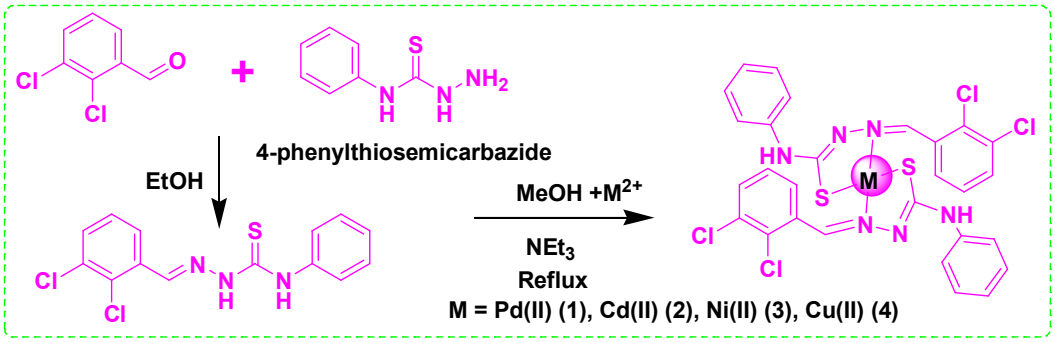


Introduction

Schiff base ligands known for their structural versatility and strong coordinating ability *via* N, S donor atoms, have long been recognized as important in stabilizing metal complexes, and make them well-suited ligands in coordination chemistry of biological palladium and copper ions [1,2]. Sulphur-ligated complexes may mimic the ligation of particular biomolecules in proteins [3] and are biologically potent [4]. Metal chelates with Schiff base ligands having N and S donor atoms are extensively studied due to their significant biological activities [5-7]. Metal complexes based on Schiff bases can have several applications with antiviral properties[8]. Metal(II) coordination complexes have attracted considerable attention due to their promising application in medicinal chemistry [9]. These metal-based compounds exhibit a wide spectrum of biological activities including antiviral, anti-inflammatory, anti-tubercular, anti-malarial, antibacterial, anti-proliferative, antioxidant and antitumor activities and some of these complexes have demonstrated enhance biological efficacy in both *in-vivo* and *in-vitro*[10]. Herein, this work report enhanced superior activity of imines-based metal(II) coordination complexes of the general type $[Pd(L)_2]$ [where, HL = (*E*)-2-(2,3-dichlorobenzylidene)-N-phenylhydrazine-1-carbothioamide; M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**)] for vaccines perspectives.

1. Results and Discussion

In this work, enhanced superior activity of imines-based metal(II) coordination complexes of the general type $[Pd(L)_2]$ [where, HL = (*E*)-2-(2,3-dichlorobenzylidene)-N-phenylhydrazine-1-carbothioamide; M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) for vaccines perspectives are described. The new bidentate-N, S ligand was synthesized and prepared by a single-step condensation reaction by ethanolic solution of 2,3-dichlorobenzaldehyde with 4-phenylthiosemicarbazide as shown in Scheme 1.



Scheme 1. Synthetic route leading to metal(II) complexes (1)-(4).

Spectroscopic data of HL: Yield: 86%; M.p.: > 195°C. ^{1}H-NMR (500 MHz, DMSO d6): ´ 12.04 (1H, s, -SH), ´ 10.22 (1H, s, -NH-), ´ 8.56 (1H, s, Ar -CH=N-), ´ 8.40- 8.42 (2H, d, Ar-H), ´ 7.63- 7.64 (1H, t, Ar-H), ´ 7.48- 7.50 (2H, t, Ar-H), ´ 7.32- 7.37 (1H, t, Ar-H), ´ 8.40- 8.42 (2H, d, Ar-H), ^{13}C{H} NMR (500 MHz, DMSO d6): 176.92, 139.43, 139.0, 134.33, 132.71, 131.95, 131.59, 128.69, 128.66, 126.88, 126.71 and 126.17 ppm. FT-IR data (KBr/cm^{-1}): 1589 (5ØÎÞC=N), 1307 (5ØÎÞC=S), 3568 (5ØÎÞN-H). UV-Vis 5ØÌÞ (nm): 338 (in DMSO). Fluorescence data (5ØÌÞ$_{nm}$): 373, 412, 435 (DMSO). Elemental analyses: Anal. Calc. for $C_{14}H_{11}Cl_2N_3S$, (%): C, 51.86, H, 3.42; N, 12.96. Found (%): C, 52.09; H, 3.61; N, 12.01. Spectroscopic data of complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**): Yield:80-90%. FT-IR (KBr/cm^{-1}): 3541-3552 (5ØÎÞN-H), 2939-2942 (5ØÎÞC-H), 1373-1376 (>C=N); 1666-1670(5ØÎÞArC=C), 1261-1264 (5ØÎÞC=S), 1087-1090 (5ØÎÞM-S), 651 (5ØÎÞM-N). UV-Vis 5ØÌÞ (nm): 338-354. Fluorescence data (5ØÌÞ$_{nm}$): 374-570. The quantum computational calculations were explored for structure-property relationship. The electronic properties such as HOMO and LUMO energies of the Frontier molecular orbitals (FMOs) (”E =E_{LUMO}-E_{HOMO}) were derived for the tructures of M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**). Frontier molecular orbital analysis shows that the HOMO-LUMO energy gap (”E_g) were found to be lower, which means that M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) have higher reactivity but lower kinetic stability. The energy gaps (”E_g) of HOMOs and LUMOs was found to be 0.50021 eV to 0.87003 eV for Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**), indicating main contributors of HOMO and LUMO in all complexes. The highest value of energy gap (”E_g) revealed that the Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) have high chemical stability and low reactivity [11].

Further, the in-silico antiviral efficacy analysis is new and shows the potential structures of M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) as antiviral drugs, which can inhibit viral proteins effectively. They bind to the active positions of viral proteins and shows good inhibition performance with the viral proteins [12-15]. The binding free energies computed by molecular docking approach were analyzed in details and the importance of specific interactions outlined. A stronger binding was predicted between the M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) and the SARS-CoV-2 3-CL protease protein (PDB ID:8K67) through the negative values of binding affinity (”G). The binding energies (”G) and respective K_i (inhibition constants) correlation values are found to be -10.7 (1.124) and -10.4 kcal/mol (2.163 µM), 8.8 (2.316) and -8.6 kcal/mol (2.049 µM) for M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**), respectively based on the molecular docking calculations study.

The complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) and the SARS-CoV-2 3-CL protease protein (PDB ID:8K67) shows several interactions

and some of them are highlighted here. There is observed two À-hydrogen bonds with a distance of 3.664 and 5.771 Å between NH_2 of GLN-110 and HIS-246 residues of 3-CL protease; two À-anionic electrostatic interactions with a distance of 3.410 and 4.756 Å between the (COO^-) group of anionic ASP-245 and ASP-295 residues of 3-CL protease protein; three hydrophobic interactions, which is between the À-electrons of PHE-294, PRO-108 and PHE-294 residues of 3-CL protease protein with the complex (1). Similar observations were found for remaining complexes M = Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) with the SARS-CoV-2 3-CL protease protein (PDB ID:8K67). The highest binding affinities (”G) of the docked for M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) were predicted that they might serve as better inhibitors for the development of new anti-SARS-CoV-2 drugs [16-18]. The complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) have ability to stabilized with target viral proteins, may have the potency to be evolved as anti-virus drug candidates for the inhibition of SARS-CoV-2 viral proteins for further experimental and/or clinical scientific validation.

To further evaluate the biological efficacy of the synthesized metal complexes, *in-vitro* cytotoxicity assays were conducted to assess the anticancer potential of complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**). The i*n-vitro* cytotoxicity effects were tested against various human cancer cell lines, including breast carcinoma (MCF-7), cervical carcinoma (HeLa) and lung carcinoma (A549) using the MTT assay with normal kidney epithelial (NKE) cells serving as the control to determine selective toxicity, which is interesting for bioinorganic and metal-based drug communities. The complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) exhibited superior cytotoxic activity particularly against MCF-7 (IC_{50} = 31.46 ± 1.14 ¼M) and HeLa (IC_{50} = 32.34 ± 0.07 ¼M) cells and suggests time dependent differences in cellular sensitivity. It is noticeable that the anticancer activity order of compounds found to be M = Pd(II) (**1**) > Cd(II) (**2**) >Ni(II) (**3**) > Cu(II) (**4**). The enhanced cytotoxicity for M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) may be attributed to its stronger coordination, strength and higher lipophilicity, which likely facilitates greater permeability through the lipid bilayer of cancer cell membranes [19,20]. A decrease in the net charge on the metal ion upon complexation might also contribute to improved membrane diffusion and cellular uptake. This comparison helps to clarify the degree of cytotoxicity and the potential specificity of the complexes for M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) toward cancer cells.

Further, with increasing the dose of the positive control, there was significant decrease in the haemolysis as expected ($P < 0.001$). All results were presented as mean ± SEM. So, the significance of the difference was determined using one-way ANOVA technique. The statistical significance was defined as a value of $P < 0.001$. The PBMCs were not cytotoxic in presence of 30% DMSO. The complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) demonstrate better cytotoxicity against the tested cancer cell line in comparison to the reported transition metal complexes [19,20], and may be considered a promising chemotherapeutic agent due to its lower toxicity and better cytotoxic efficiency. Thus, the tabular data results indicate that for M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) are with the lower cytotoxicity and may be suitable for biomedical applications. They exhibited good selectivity as obvious for their inactivity on normal cells. The complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**), represent good candidates for further research and testing to proof their potential superior activity of lead compounds for promising chemotherapeutic agents, which may propose the mechanism of action towards cancer therapy. Therefore, from these results, it is recommended to further test the cell cycle analysis. The complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) represent good candidates for further research and testing

to proof their potential superior activity of lead compounds as promising chemotherapeutic agents, which may have proposed the mechanism of action towards cancer therapy.

Conclusion

In conclusion, four metal complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**), which exhibits superior biological characteristics are described. Complexes Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) demonstrated good selectivity for cancerous cells, with limited toxicity suggesting their potential as chemotherapeutic agents. They show good inhibition performance with the intended drug targets of the viral proteins and may be used as potential inhibitors for the development of new antiviral drugs. Overall, this work reports enhanced superior activity of imines-based metal(II) coordination complexes M = Pd(II) (**1**), Cd(II) (**2**), Ni(II) (**3**) and Cu(II) (**4**) for vaccines perspectives

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