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Screening the efficient biological prospects of triazole allied mixed ligand metal complexes

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Triazole appended mixed ligand complexes (**1–8**) of the general formula [ML (bpy/phen)$_2$]Cl$_2$, where M = Cu(II), Co(II), Ni(II) and Zn(II), L = triazole appended Schiff base (E)–N-(4-nitrobenzylidene)-1H-1,2,4-triazol-3-amine and bpy/phen = 2,2′-bipyridine/1,10-phenanthroline, have been synthesized. The design and synthesis of this elaborate ligand has been performed with the aim of increasing stability and conjugation of 1,2,4 triazole, whose Schiff base derivatives are known as biologically active compounds thereby exploring their DNA binding affinity and other biological applications. The compounds have been comprehensively characterized by elemental analysis, spectroscopic methods (IR, UV–Vis, EPR, ^{1}H and ^{13}C NMR spectroscopy), ESI mass spectrometry and magnetic susceptibility measurements. The complexes were found to exhibit octahedral geometry. The complexes **1–8** were subjected to DNA binding techniques evaluated using UV–Vis absorption, CV, CD, Fluorescence spectroscopy and hydrodynamic measurements. Complex **5** showed a K_b value of 3.9×10^5 M^{-1}. The DNA damaging efficacy for the complexes was observed to be high compared to the ligand. The antimicrobial screening of the compounds against bacterial and fungal strains indicates that the complexes possess excellent antimicrobial activity than the ligand. The overall biological activity of the complexes with phen as a co-ligand possessed superior potential than the ligand.

1. Introduction

Designing of compounds that can easily form interactions with the DNA has lately become the prime target of research in the hunt for effective therapeutic agents [1]. Exploring DNA and manipulating it to serve the purpose of desired pharmacological aspects is essential owing to the vital role played by DNA in the biological systems [2]. J.K.Barton, in her article [3] quotes "*DNA is the library of the cell, simultaneously storing and dispensing the information required for life. Molecules that can bind and react with specific DNA sites provide a means to access this cellular information*". Indeed, DNA is the most sought after intracellular target that is believed to possess the ability to diagnose or treat a disease through its interactions with smaller compounds, especially metal complexes [4,5]. In this regard, Schiff base metal complexes are extensively studied and reported in literature [6]. On the other hand, many moieties based on their biological activity were chosen as a ligand for the synthesis of Schiff base with desired properties, one such moiety is the heterocyclic triazole moiety. The triazoles are a class of ligands which showed broad spectrum of activities in diverse applications [7–9]. Very recently, triazole analogues were reported to possess analgesic, antioxidant and anticancer properties [10,11].

Considering the above facts, we have chosen to design and synthesize few triazole based Schiff base metal (II) complexes, where M(II) = Cu(II), Co(II), Ni(II), Zn(II). Planar ligands 1,10-phenanthroline and 2,2′-bipyridine were incorporated into the metal ligand system to provide additional conjugating and planarity [12]. The complexes were subjected to various investigations like DNA binding with UV, CV, Viscosity, Fluorescence, CD and antimicrobial screening. The obtained results showed promise in designing and developing newer and effective antimicrobial agents as well as novel DNA probes.

2. Experimental protocols

The materials and methods, DNA binding, cleavage and antimicrobial procedures are included in the Supplementary file (S1).

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2.1. *Synthesis of Schiff base ligand (**L**)*

To a magnetically stirred ethanolic solution of 3-amino-1,2,4-triazole (5 mmol), *p*-nitrobenzaldehyde dissolved in ethanol was added dropwise and stirred vigorously for 3 h. The obtained pale yellow solid was washed with ethanol and dried *in vacuo*. This obtained solid is the Schiff base ligand **L**.

[**L**] Yield: 79%, Anal. Calc. for $C_9H_7N_5O_2$: C, 49.77; H, 3.25; N, 32.25%; Found C, 49.64; H, 3.21; N, 32.05%. IR data (KBr, cm^{-1}); 1638 ν(C=N); 3196 (−NH of triazole). MS *m*/*z* (%):217 [M^+]. ^1H NMR (δ, ppm): 7.4–8.3 (aromatic) (m); 8.6 (−CH=N, 1H) (d), 8.2 (−CH−, 1H) (d), 13.5 (−NH of triazole, 1H) (d). ^{13}C NMR (δ, ppm): 146.6 (C_1), 158.1 (C_2), 156.3 (C_3), 124.0–150.2 (C_4 to C_7). λ_{max} (cm^{-1}) in DMF, 36,764, 31,847.

2.2. *Synthesis of mixed ligand complexes*

A general procedure was followed in the preparation of the mixed ligand complexes **1**–**8**, in which the Schiff base **L** (5 mmol) was dissolved in ethanol and to this solution, a solution of M(II) chloride (5 mmol) (M = Cu, Co, Ni, Zn) in ethanol was added dropwise while stirring continuously. The temperature was maintained at 60 °C. After a reaction time of 2 h, ethanolic solution of the co-ligand 2,2′-bipyridine/1,10-phenanthroline (10 mmol) was added slowly. The obtained solution was then refluxed for 3 h in a rota mantle while constantly maintaining the temperature at 60 °C. After 3 h, the resultant mixture was set aside to cool to an ambient temperature. On cooling the acquired solid was filtered, washed with diethyl ether and dried *in vacuo*.

[CuL $(bpy)_2$]Cl_2 (**1**) Yield: 78%, Anal. Calc. for $C_{29}H_{23}CuN_9O_2$: C, 58.73; H, 3.91; Cu, 10.71; N, 21.25%; Found: C, 58.64; H, 3.84; Cu, 10.53; N, 21.11%. IR data (KBr, cm^{-1}); 1623 ν (C=N), 3196 (−NH of triazole), 462 ν (M − N). Λ_M 10^{-3} (ohm^{-1} cm^2 mol^{-1}) = 84.6. λ_{max} (DMF, cm^{-1}), 34,602, 32,154,13,586. μ_{eff} (BM): 1.85.

[CoL $(bpy)_2$]Cl_2 (**2**) Yield: 76%, Anal. Calc. for $C_{29}H_{23}CoN_9O_2$: C, 59.19; H, 3.94; Co, 10.01; N, 21.42; %; Found C, 59.07; H, 3.76; Co, 9.93; N, 21.27; %. IR data (KBr, cm^{-1}); 1629 (C=N); 3196 (−NH of triazole), 454 ν(M − N). Λ_M 10^{-3} (ohm^{-1} cm^2 mol^{-1}) = 79.3. λ_{max} (DMF, cm^{-1}), 35,587, 31,446, 14,084. μ_{eff} (BM): 4.86.

[NiL $(bpy)_2$]Cl_2 (**3**) Yield: 72%, Anal. Calc. for $C_{29}H_{23}N_9NiO_2$: C, 59.21; H, 3.94; N, 21.43; Ni, 9.98%; Found C, 59.14; H, 3.89; N, 21.35; Ni, 9.85%. IR data (KBr, cm^{-1}); 1613 ν(C=N); 3196 (−NH of triazole), 438 ν(M − N). Λ_M 10^{-3} (ohm^{-1} cm^2 mol^{-1}) = 68.5. λ_{max} (DMF, cm^{-1}), 35,211, 31,055, 15,197. μ_{eff} (BM):3.15.

[ZnL $(bpy)_2$]Cl_2 (**4**) Yield: 77%, Anal. Calc. for $C_{29}H_{23}N_9O_2Zn$: C, 58.55; H, 3.90; N, 21.19; Zn, 10.99%; Found C, 58.42; H, 3.86; N, 21.05; Zn, 10.82%. IR data (KBr, cm^{-1}); 1627 ν(C=N); 3196 (−NH of triazole), 427 ν(M − N). ^1H NMR (δ, ppm): 8.0–8.9 (aromatic) (m); 9.2 (−CH=N, 1H) (d), 8.3 (−CH−, 1H) (d), 13.5 (−NH of triazole, 1H) (d). ^{13}C NMR (δ, ppm): 146.6 (C_1), 158.0 (C_2), 160.0 (C_3), 122.9–150.2 (C_4 to C_7). Λ_M 10^{-3} (ohm^{-1} cm^2 mol^{-1}) = 75.2. λ_{max} (DMF, cm^{-1}), 35,842, 32,573. μ_{eff} (BM): diamagnetic.

[CuL $(phen)_2$]Cl_2 (**5**), Yield: 71%, Anal. Calc. for $C_{33}H_{23}CuN_9O_2$: C, 61.82; H, 3.62; Cu, 9.91; N, 19.66%; Found C, 61.53; H, 3.54; Cu, 9.76; N, 19.42%. IR data (KBr, cm^{-1}); 1609 ν(C=N); 3196 (−NH of triazole), 441 ν(M − N). Λ_M 10^{-3} (ohm^{-1} cm^2 mol^{-1}) = 80.3. λ_{max} (DMF, cm^{-1}), 34,129, 32,467, 13,192. μ_{eff} (BM): 1.87.

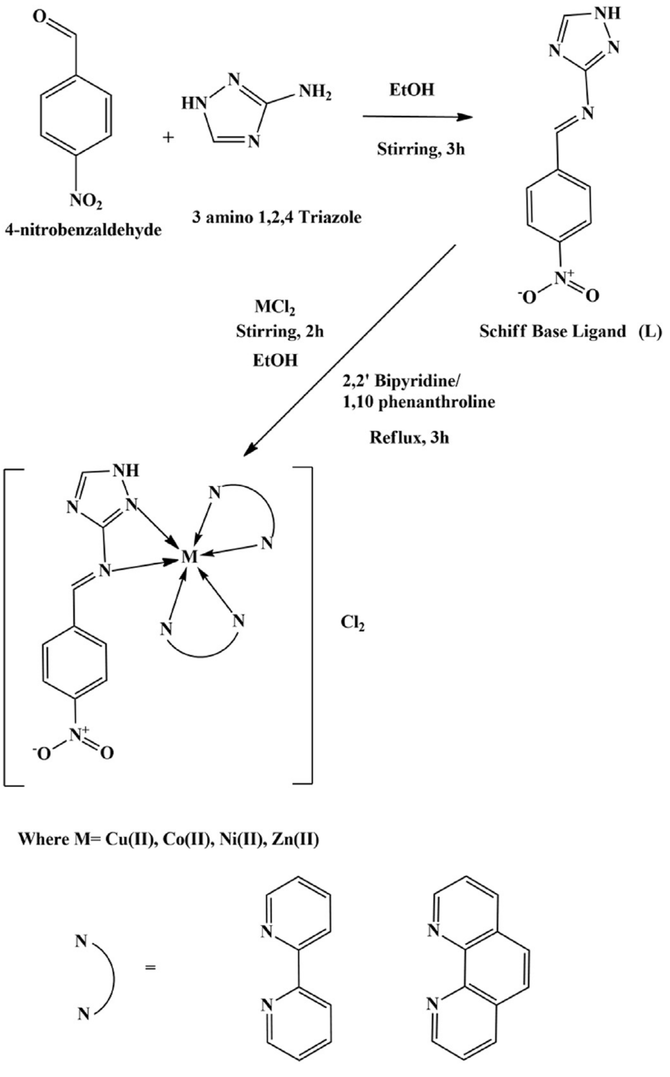
[CoL $(phen)_2$]Cl_2 (**6**) Yield: 73%, Anal. Calc. for $C_{33}H_{23}CoN_9O_2$: C, 62.27; H, 3.64; Co, 9.26; N, 19.80%; Found C, 62.14; H, 3.51; Co, 9.13; N, 19.68%. IR data (KBr, cm^{-1}); 1604 ν(C=N); 3196 (−NH of triazole), 437 ν(M − N). Λ_M 10^{-3} (ohm^{-1} cm^2 mol^{-1}) = 67.6. λ_{max} (DMF, cm^{-1}), 34,722, 31,645, 13,812. μ_{eff} (BM): 4.84.

[NiL $(phen)_2$]Cl_2 (**7**)Yield: 76%, Anal. Calc. for $C_{33}H_{23}N_9NiO_2$: C, 62.29; H, 3.64; N, 19.81; Ni, 9.22%; Found C, 62.14; H, 3.58; N, 19.65; Ni, 9.13%. IR data (KBr, cm^{-1}); 1598 ν(C=N); 3196 (−NH of triazole), 421 ν(M − N). Λ_M 10^{-3} (ohm^{-1} cm^2 mol^{-1}) = 71.9. λ_{max} (DMF, cm^{-1}), 34,482, 30,769, 14,577. μ_{eff} (BM): 3.13.

[ZnL $(phen)_2$]Cl_2 (**8**) Yield: 73%, Anal. Calc. for $C_{33}H_{23}N_9O_2Zn$: C, 61.64; H, 3.61; N, 19.61; Zn, 10.17%; Found C, 61.48; H, 3.54; N, 19.53; Zn, 10.03%. IR data (KBr, cm^{-1}); 1591 ν(C=N); 3196 (−NH of triazole), 432 ν(M − N). ^1H NMR (δ, ppm): 8.0–9.1 (aromatic) (m); 9.5 (−CH=N, 1H) (d), 8.2 (−CH−, 1H) (d), 13.5 (−NH of triazole, 1H) (d). ^{13}C NMR (δ, ppm): 146.6 (C_1), 157.6 (C_2), 161.5 (C_3), 124.0–146.7 (C_4 to C_7). Λ_M 10^{-3} (ohm^{-1} cm^2 mol^{-1}) = 74.8. λ_{max} (DMF, cm^{-1}), 33,898, 31,251. μ_{eff} (BM): diamagnetic.

3. Results and discussion

The complexes were soluble in DMSO and DMF but moderately soluble in ethanol whereas the ligand L is soluble in common organic solvents. The compounds are found to be stable in air. The stepwise synthetic pathway involved in the formation of Schiff base ligand L and its metal complexes are represented in Scheme 1. The compounds were characterized by elemental analyses, NMR, FTIR, EPR and mass spectrometry.



Scheme 1. Synthesis of Schiff base ligand (L) and its metal (II) complexes.