Structural Characterization, DFT Geometry Optimization, Cyclic Voltammetry and Biological Assay of (Tellurite-pyridine) Mixed Ligand complexes of Cd(II)

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Research Article

Keywords: Structural characterization, DFT computational simulation, cyclic voltammetry, biological activities

Posted Date: January 3rd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1203068/v1>

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Abstract

This research work presents spectral characterizations (IR, ^1H NMR and ^{13}C NMR) of anionic tellurite Cd(II) complexes that prepared using cyanopyridine derivatives as a polydentate ligands. Also, X-ray based techniques involving (EDX and XRD) are applied for cadmium complexes to realize elemental composition and average crystallographic coherence. Moreover, the electrochemical studies represented on cyclic voltammetry are determined for Cd(II) in (absence/presence) of ligands to detect the role of complexation in solution measurements. All the previous experimental investigations are supported with molecular modeling of the geometric optimized structures based on density function theory (DFT) for all compounds accompanied by the calculations of different energetic parameters such as E_{HOMO} and E_{LUMO} . Finally, anti-microbial (antibacterial and antifungal), anti-oxidant and Bleomycin dependent DNA damage are screened for all samples to predict the influence of metal complex formation on the biological activity of pyridyl ligands besides their priority.

1. Introduction

Transitional metals can exhibit a wide range of coordination and reactivity features that can be employed with pyridyl ligands to prepare complexes. Transition metal complexes display unique and impressive characteristics such as changing oxidation states and the ability to produce particular reactions with different biomolecules [1, 2]. Therefore, the coordination between transition metals with pyridyl ligand would prevent the resistance by microbes and enhance the antimicrobial activity of the pyridine derivative through new mechanisms of inhibition [3]. It was noticed that some metal-drug complexes are more effective than their pure drug [4, 5].

Various studies have been reported concerning the biological activities of pyridyl ligands metal complexes, involving their anticancer [6–8], antibacterial [9–11], antifungal [12], anticonvulsant [13] and antiviral properties [14–18]. On the parallel side, inorganic anions like selenite ion, SeO_3^{2-} and sulfite ion, SO_3^{2-} were used as ligands in transition metal complexes. Herein, we are reporting to the preparation and characterization mixed ligand (TeO_3^{2-} -pyridine) Cd(II) complexes accompanied by theoretical, electrochemical and biological applications.

2. Experimental

The used potassium chloride, cadmium chloride, absolute ethanol, DMF and diethyl ether were provided from Sigma Aldrich Co. Sodium sulphate was provided from (ADWIC), 2-amino pyridine and phenyl isothiocyanate were from Alfa Aesar Co. Sodium tellurite (Na_2TeO_3) was from BDH Chemicals Ltd Poole England. All of the chemicals were used without any purification processes.

2.1. Preparation of ligands

2.1.1. Preparation of 2-cyano-N-(pyridin-2-yl)acetamide (HCPA)

2-cyano-N-(pyridin-2-yl) acetamide (HCPA) (Scheme 1) was prepared by addition of 3-(3, 5-dimethylpyrazol-1-yl)-3-oxopropionitrile (0.01 mol) to a solution of 1.0 equiv. of 2-aminopyridine in toluene (10-15 ml), then the mixture was refluxed for 15 min and stirred at room temperature. The formed 2-cyano-N-(pyridin-2-yl) acetamide was filtered, washed with diethyl ether and dried (m.p 155 °C) [19-23].

2.1.2. Preparation of 2-cyano-3-mercapto-3-(phenylamino)-N-(pyridin-2-yl)acrylamide (HCMPPA)

A mixture of 2-cyano-N-(pyridin-2-yl) acetamide (0.01 mol) and solid KOH (0.01 mol) in DMF (20 mL) were stirred for 5 min at room temperature then phenyl isothiocyanate (0.01 mol) was added dropwisely. The mixture was stirred for 12 h and then poured over crushed ice containing HCl. The ppt formed was filtered off, washed with water, dried and finally, recrystallized from EtOH/DMF to get 2-cyano-3-mercapto-3-(phenyl amino)-N-(pyridin-2-yl) acrylamide (m.p 187°C) as explained in Scheme 2 [24-26].

2.2. Preparation of mixed ligand complexes

To a hot solution of ligands (HCPA and HCMPPA) in ethanol and sodium tellurite (Na_2TeO_3) in distilled deionized water, a solution of cadmium chloride in distilled water was added slowly as shown in Scheme 3, 4. The mixture was heated in reflux for (3-4) hr. The isolated solid complexes were filtered off, washed many times with hot distilled H_2O and/or EtOH and finally dried in a vacuum desiccator over anhydrous CaCl_2 .

2.3. Analysis of complexes

Carbon, hydrogen and nitrogen percentage for ligands and their complexes were performed in Microanalytical Unit, Azhar University, Egypt. Complexometric analysis was utilized to predict the contents of Cd(II) in the prepared complexes. While, the gravimetric analysis was employed to calculate the content of Cl⁻ which was determined as AgCl.

2.4. Instrumentation

All the spectroscopic techniques (IR, ^1H NMR, ^{13}C NMR, EDX and XRD) utilized to illustrate the structure of the solid compounds are collected and clarified in Scheme (1S).

2.5. Cyclic Voltammetry

The electrochemical cell consists of three electrodes: (i) a reference electrode represented on Ag/ AgCl / $\text{KCl}_{\text{saturated}}$, (ii) GCWE (glassy carbon working electrode) as a working electrode and (iii) an auxiliary electrode which is a platinum wire. These electrodes immersed in 30 ml from 0.1 M KCl supporting

electrolyte and connect with potentiostat of the type DY 2100 where the US convention is used to report CV data.

2.6. Molecular modeling

Density functional theory (DFT) modeling of the molecular structure and frontier molecular orbitals (HOMO/LUMO) is accomplished by using the Beck's three parameter exchange functional along with the Lee-Yang-Parr non local correlation functional (B3LYP) [27]. We used two different basis sets. We used 6-311+g (d, p) basis set for ligands and the Los Alamos National Laboratory basis set of double-zeta quality (LANL2DZ) for Cd complexes [28] in Gaussian 09 package in order to find the structural and electronic parameters [29].

2.7. Biological activities

2.7.1. Antifungal and antibacterial activities

MIC (the minimum inhibitory concentration of the substance) was determined using the disc diffusion method as explained in Scheme (2S).

2.7.2. Antioxidant activity

The advantage of ABTS method is that possessing an extra free radical more than other techniques. Where, a stable color was produced over (1hr) in this reaction. The procedures of this method are explained in Scheme (3S).

2.7.3. Colorimetric assay of BMC-dependent DNA damage

The colorimetric assay for the prepared compounds and the ligands against DNA damage was illustrated in Scheme (4S) [30].

2.8. Molecular docking

Molecular docking calculations were carried out using docking server [31]. Gasteiger partial charges were added to the atoms of ligand. Non-polar hydrogen atoms were conjoined and rotatable bonds were identified. With the help of AutoDock tools [32], essential hydrogen atoms, Kollman united atom type charges and solvation parameters were added. Affinity grid points and spacing of 0.375 Å were created using the Autogrid program [33]. Auto Dock parameter set- and distance-dependent dielectric functions were used to calculate the van der Waals and the electrostatic terms, respectively. Docking simulations were done by the use of the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method [34]. Orientation, initial position and torsions of the molecules of ligand were set randomly. All rotatable torsions were liberated during docking. Every docking experiment was derived from 10 different runs that were set to end after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å and quaternion and torsion steps of 5 were applied.

3. Results And Discussion

3.1. Chemical composition and Physical properties

The practical elemental analysis results of the investigated compounds refer to great resemblances with the calculated chemical compositions as shown in Tables (1 & 2) in addition to some of characteristic physical properties.

3.2. FT-IR

3.2.1. IR spectra of 2-cyano-N-(pyridin-2-yl)acetamide (HCPA) and its Cd(II) complex

The most characteristic infrared bands of HCPA and its Cd (II) complex were listed in Table 3 and represented graphically in (Figure 1S). There were six distinct absorption bands in the IR spectrum of HCPA at (3038 medium, 2257 medium-sharp, 1672 strong-sharp, 3345 medium-sharp, 1635 strong and 776 medium-sharp) cm^{-1} which represented stretching frequencies of methylene $\nu_{\text{as}}(\text{CH}_2)$ [35], cyano $\nu(\text{C}\equiv\text{N})$ [36], amide carbonyl $\nu(\text{NH}-\text{C}=\text{O})$ [37], secondary amine $\nu(\text{NH})$ [38], aromatic azomethine $\nu(\text{C}=\text{N})_{\text{pyridine}}$ [39] and pyridine ring breathing vibrational mode, respectively.

While IR spectrum of $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex revealed that HCPA ligand behaved as mononegative bidentate chelating agent *via* enolized carbonyl $\nu(\text{C}=\text{O})_{\text{enolic}}$ and heterocyclic azomethine $\nu(\text{C}=\text{N})_{\text{pyridine}}$. This mode of complexation was supported by the following observations:

1. Shift in band position of $\nu(\text{C}=\text{N})_{\text{pyridine}}$ to lower wave number 1624 cm^{-1} while $\nu(\text{NH})$ and $\nu(\text{C}\equiv\text{N})$ remained nearly at the same positions without change.
2. Disappearance of $\nu(\text{N}-\text{C}=\text{O})$ and $\nu(\text{CH}_2)$ as a result of enolization process with simultaneous appearance of new $\nu(\text{C}=\text{C})_{\text{aliphatic}}$ at 1633 cm^{-1} and $\nu(\text{C}=\text{O})_{\text{enolic}}$ at 1265 cm^{-1} [40].
3. Appearance of new bands at $525, 422$ and 677 cm^{-1} which referred to $\nu(\text{Cd}-\text{O})$, $\nu(\text{Cd}-\text{N})$ [41] and $\nu(\text{Te}-\text{O})$ [42], respectively.

3.2.2. IR spectra of 2-cyano-3-mercapto-3-(phenyl amino)-N-(pyridin-2-yl)acrylamide (HCMPPA) and its Cd(II) complex

The most characteristic infrared bands of HCMPPA and its Cd (II) complex were listed in Table 4 and represented graphically in (Figure 2S). The IR spectrum of HCMPPA displayed eight essential bands at $3221, 3103, 2929, 2193, 1644, 1549, 1598$ and 840 cm^{-1} which were referred to $\nu(\text{NH})_{\text{Phenyl}}$, $\nu(\text{NH})_{\text{Pyridyl}}$ [38], thiol $\nu(\text{SH})$ [43], cyano $\nu(\text{C}\equiv\text{N})$ [36], amide carbonyl $\nu(\text{NH}-\text{C}=\text{O})$ [37], aliphatic $\nu(\text{C}=\text{C})$ [44], $\nu(\text{C}=\text{N})_{\text{Pyridine}}$ and pyridine ring breathing vibrational mode [39], respectively.

While IR spectrum of $\text{Na}_2[\text{Cd}(\text{CMPPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex revealed that HCMPPA acted as mononegative bidentate ligand according to the following variations:

1. Disappearance of $\nu(\text{NH})_{\text{pyridyl}}$ and $\nu(\text{C}=\text{O})$ as a result of enolization process with simultaneous appearance of new $\nu(\text{C}=\text{N})$ at 1626 cm^{-1} and $\nu(\text{C}-\text{O})_{\text{enolic}}$ at 1150 cm^{-1} [43].
2. Shift in band position of $\nu(\text{C}=\text{N})_{\text{pyridine}}$ to lower wave number 1601 cm^{-1} While the other groups remained nearly at the same positions.
3. Appearance of new bands at $520, 470$ and 681 cm^{-1} which referred to $\nu(\text{Cd}-\text{O})$, $\nu(\text{Cd}-\text{N})$ [41] and $\nu(\text{Te}-\text{O})$ [42], respectively.

3.3. ^1H NMR and ^{13}C NMR spectra

3.3.1. ^1H NMR and ^{13}C NMR spectra of 2-cyano-N-(pyridin-2-yl)acetamide (HCPA) and its Cd(II) complex

The ^1H NMR spectrum of HCPA in DMSO (Figure 1) detected two singlet signals at 10.81 and 3.58 ppm characteristic for secondary imide proton ($-\text{NH}$) and methylene protons ($-\text{CH}_2$), respectively. Also, signals at 6.55- 8.31 ppm were assigned to aromatic protons of pyridine ring.

The ^{13}C NMR spectrum of HCPA in DMSO (Figure 2 A) showed sharp peaks at 25.74, 116.82 and 166.87 ppm characteristic for methylene carbon ($-\text{CH}_2$), cyano carbon ($\text{C}\equiv\text{N}$) and carbonyl carbon ($\text{C}=\text{O}$), respectively. The signals at 118.23, 138.96, 148.61, 113.96 and 153.44 ppm were assigned to carbons of pyridine ring.

While, the ^{13}C NMR spectrum of $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex in DMSO (Figure 2B) detected singlet signals at 116.24 ppm characteristic for cyano carbon ($\text{C}\equiv\text{N}$). It also showed signal at 160.20 ppm that belonged to enolic carbon ($\text{C}-\text{O}$) rather than carbonyl group in ligand and signal at 88.97 ppm referral to ethylene carbon ($-\text{CH}=\text{C}$). The signals at 150.12, 112.25, 148.15, 127.36 and 137.43 ppm indicated carbons of pyridine ring.

3.3.2. ^1H NMR and ^{13}C NMR spectra of 2-cyano-3-mercapto-3-(phenyl amino)-N-(pyridin-2-yl)acrylamide (HCMPPA) and its Cd(II) complex

The ^1H NMR spectrum of HCMPPA in DMSO (Figure 3) detected singlet signals at 13.865 ppm characteristic for thiol proton ($-\text{SH}$). It also showed two singlet signals at 9.804 and 10.915 ppm that belonged to the two imide protons ($-\text{NH}$)_{py} and ($-\text{NH}$)_{phenyl}. The signals at 7.135-8.343 ppm indicated aromatic protons.

The ^{13}C NMR spectrum of HCMPPA in DMSO (Figure 4 A) detected two signals at 116.38 and 168.35 ppm characteristic for cyano carbon ($\text{C}\equiv\text{N}$) and carbonyl carbon ($\text{C}=\text{O}$), respectively. In addition, two signals appeared at 88.97 and 180.06 ppm assigned to ($\text{C}=\text{C}$) and ($=\text{C}-\text{SH}$), respectively. The signals at 118.40 – 140.88 ppm indicated aromatic carbons.

While, the ^{13}C NMR spectrum of $\text{Na}_2[\text{Cd}(\text{CMPPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex in DMSO (Figure 4 B) detected two signals at 116.24 and 162.49 ppm characteristic for cyano carbon ($\text{C}\equiv\text{N}$) and enolic carbon ($=\text{C}-\text{O}$), respectively. In addition, two signals appeared at 77.13 and 166.87 ppm assigned to ($\text{C}=\text{C}$) and ($=\text{C}-\text{SH}$), respectively. The signals at 120.49 – 151.78 ppm indicated aromatic carbons.

3.4. EDX and XRD examinations

EDX analysis data showed peaks corresponding to the elements (C, N, O, S, Cl, Cd, Na and Te) making up the composition of the samples being analyzed as shown in (Figures 5 & 6).

X-ray diffraction was carried out at room temperature using (Cu, K_α) radiation. The diffraction pattern (Figure 7) was measured in the range of $10^\circ < 2\theta < 80^\circ$ [45] and displayed sharp peaks indicating that the formation of a well-defined crystalline structure. The crystallite size is measured by Debye–Scherrer equation (4) through applying FWHM of the characteristic peaks:

$$\beta = 0.94 \lambda / (S \cos \theta) \quad (1)$$

Where, " $\text{Cu}/K_\alpha (\lambda) = 1.5406 \text{ \AA}$ ", (θ) is the diffraction angle, (S) is the crystallite size and (β) is the line thickness at half highest height". Bragg equation (5) can be used to measure the inner crystal plane d-spacing value as follow:

$$n\lambda = 2d \sin(\theta) \quad \text{at } n = 1 \quad (2)$$

The magnitudes of Lattice parameters and the particle size were listed in Table 5.

3.5. Molecular chemical parameters

DFT (Density function theory) is adjusted to calculate quantum energies, the most important of which are E_{HOMO} (Energy of the highest occupied molecular orbital) and E_{LUMO} (Energy of the lowest unoccupied molecular orbital), because E_{gap} (the difference between them) shows the stability of the compounds under study. The molecular structures with atom numbering of ligands and their complexes are shown in (Figures 8 & 9). After the computational modeling simulation process, the following significant remarks can be recorded:

- E_{HOMO} and E_{LUMO} as shown in (Figures 10 & 11) are (- ve) values indicating the constancy of ligands and their complexes.
- Bond lengths as shown in (Figures 3S & 4S) and Tables (1S-4S) are correlated with the frequencies of the experimental Infra-Red bond expansion.

- Bond angles of the compounds shown in (Figures. 5S & 6S) and Tables (5S-8S) reveal that $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ as well as $\text{Na}_2[\text{Cd}(\text{CMPPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complexes had octahedral geometry.
- The energies of (FMO) frontier molecular orbitals ($E_{\text{HOMO}}/E_{\text{LUMO}}$) can be employed to derive number of quantum parameters like energy (E_{gap} : band gap), (ω : global electrophilicity index), (η : hardness), (μ : chemical potential), (χ : electronegativity) and (σ : Softness) [46] as shown in (Tables 6 & 7).

$$E_{\text{gab}} = E_{\text{HOMO}} - E_{\text{LUMO}} \quad (3)$$

$$\eta = 1/2(E_{\text{LUMO}} - E_{\text{HOMO}}) \quad (4)$$

$$\mu = \omega^2/2 \quad (5)$$

$$\mu = -\chi = 1/2 (E_{\text{LUMO}} + E_{\text{HOMO}}) \quad (6)$$

$$\chi = -1/2 (E_{\text{LUMO}} + E_{\text{HOMO}}) \quad (7)$$

$$\sigma = 1/\eta \quad (8)$$

3.6. Molecular Electrostatic Potential mapping

MEP of all compounds as presented in (Figures 12 & 13) are characterized by three colored zones [47] as follow: **(i)** the first zone has a red color which denotes to the high electron density region which responsible for the electrophilic attack reactions, **(ii)** the second green zone elucidates to the neutral electrostatic potential region and **(iii)** the blue colored are as with low electron density corresponding to the nucleophilic attack region.

3.7. Cyclic Voltammetry studies of CdCl_2

3.7.1. Electrochemical behavior of Cd(II) in absence of HCPA with the suggested mechanism at 301.15K

The redox behavior of CdCl_2 in 0.1M KCl as supporting electrolyte was examined by using cyclic voltammetry technique. Glassy carbon electrode (GCE) was used as working electrode within potential window (1V to -1.2V) and scan rate 0.1 V/s at 301.15K. Cd (II) solution was electroactive as it gave one cathodic peak and one anodic peak in cyclic voltammogram as shown in (Figure 14).

In the forward scan, (Cd^{2+}/Cd) cathodic potential was at -0.9235V while in the reverse scan, the (Cd/Cd^{2+}) anodic potential was at -0.6507V. Thus, the Cd^{2+} system was reversible and involved the transfer of two electrons. The redox mechanism can be represented by (Eqns. 9 and 10)

3.7.2. Cyclic Voltammetry theoretical approach

Applying the Randles-Sevcik equation (11), the analyte diffusion coefficient (D) in $\text{cm}^2\cdot\text{s}^{-1}$ was given as follow [48, 49]:

$$I_p = (2.69 \times 10^5) n^{3/2} A C v^{1/2} D^{1/2} \quad (11)$$

Where " I_p " is the current in Ampere, (n) is the number of electrons involved in the reaction (A) is surface area of the working electrode in cm^2 , (C) is metal cation concentration in $\text{mol}\cdot\text{cm}^{-3}$ and (v) is scan rate in $\text{volts}\cdot\text{sec}^{-1}$. Also, (ΔE_{peak}) the difference potential and (a) the charge transfer coefficient of electrons are calculated using equations (12) and (13) [50, 51].

$$\Delta E_p = E_{p,a} - E_{p,c} \quad (12)$$

$$an = 1.857 RT / (E_{pc} - E_{pc/2}) \quad (13)$$

where, " $E_{pc/2}$ " is the half-wave potential of the cathodic peak, ($R = 8.314 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$) is the universal gas constant, (T) is the temperature in kelvin. The heterogeneous charge transfer rate constant (k_s) in cm/sec can be calculated by the following equation (14) [52].

$$k_s = 2.18 [D an F v / RT]^{1/2} \exp [a^2 n F \Delta E_p / RT] \quad (14)$$

Where, " $F = 96485.33 \text{ coulombs}$ " is Faraday constant". The cyclic voltammetric parameters for an anodic and cathodic peak are calculated and listed in Table (8). The surface coverage (Γ : the number of adsorbed species on a surface divided by the number of species in a filled monolayer on that surface) in $\text{mol}\cdot\text{cm}^{-2}$ as well as (Q) the quantity of charge that consumed during the reduction reaction or the quantity of charge that produced as a result of the oxidation can be evaluated from equations (15) and (16), respectively [53, 54]. As CdCl_2 concentration increases, most of the cyclic voltammetric parameters (I_p , ΔE_p , Γ and Q) increase leading to more diffusion processes takes place between the bulk of solution and GCWE surface.

$$\Gamma = i_p 4RT / n^2 F^2 A v \quad (15)$$

$$Q = n F A \Gamma \quad (16)$$

3.7.3. Cyclic voltammetry response of Cd(II) in presence of HCPA

On adding HCPA to CdCl₂ solution in 0.1 M KCl solution at GCE within potential range from 1V to -1.2V and scan rate 0.1V/s as shown in (Figure 15), it was observed that there was shift in potential for both reduction and oxidation peaks. Cathodic current and anodic current also decreased with increasing concentration of HCPA. The voltammogram demonstrates the effect of complexation between HCPA and Cd(II) ions. The diffusion of species (D), the redox reaction rates (an) and the cyclic voltammetry parameters (Γ and Q) decrease as a result of complex formation in solution and weakness of GCWE role (less an), the change in the results shown in Table (9).

3.7.4. The stability constant and Gibbs free energies for the (Cd²⁺/HCPA) complex

The stability constants (β_{ML}) and Gibbs free energies (ΔG) increase by further addition of HCPA to the Cd(II) ions indicating the sequential and progressive construction to form a stable complex in the solution system as illustrated in Table (10). The following equations (17), (18) and (19) are used to calculate β_{ML} and ΔG:

$$E^{\circ} = (E_{pa} + E_{pc})/2 \quad (17)$$

$$\Delta E^{\circ} = E^{\circ}_C - E^{\circ}_M = 2.303 (RT/nF) \times (\log \beta_{ML} + j \log C_L) \quad (18)$$

$$\Delta G = -2.303 RT \log \beta_{MX} \quad (19)$$

Where, (E_M^o) is the formal peak potential of metal ion at zero ligand addition, (E_{ML}^o) is the formal peak potential of complex at each ligand addition, (j = [L]/[M]) is the molar ratio and (C_L) is molar ligand concentration. We can observe that as the ligand concentration increased as (β_{ML} and ΔG) increased.

8. Biological activities

3.8.1. Antimicrobial studies

The activity index percent (%Activity Index) of ligands (HCPA and HCMPPA) and their chelates against "*Staphylococcus aureus*" as a gram-positive bacteria, "*Escherichia coli*" as a gram-negative bacteria and "*Candida albicans*" as a pathogenic fungus was calculated by equation (20) [55, 56] and listed in the Tables (9S & 10S).

$$\% \text{ Activity Index} = \frac{\text{inhibition zone of test compound (diameter)}}{\text{inhibition zone of standard (diameter)}} \times 100 \quad (20)$$

In light of the results of biological study charts as shown in (Figures 16 & 17), we can notice the following:

- According to the activity index data, it has been found that HCPA and its Cd (II) complex showed low antibacterial activity toward *E. coli* and moderate values toward *S. aureus*. For antifungal activity, HCPA and Na₂[Cd(CPA)(TeO₃)(H₂O)Cl].2H₂O complex exhibited moderate values against *C. albicans*.
- While, HCMPPA and its Cd (II) complex had high antimicrobial activity. A glance of data indicated that:
- HCMPPA revealed the most potent antimicrobial activity against all organisms.
- HCMPPA and its Cd (II) complex were more effective against *S. aureus* than *E. coli*.

3.8.2 Antioxidant studies

ABTS (2, 2'-azino-bis [3-ethylbenzthiazoline]-6-sulfonic acid) method was applied to the compounds to evaluate their antioxidant ranking [57]. The standard antioxidant (+ve control) is L-ascorbic acid [58]. All compounds as in (Figures 18 & 19) and Tables (11S & 12S) show that:

- HCPA and its complexes exhibited moderate antioxidant activity, HCPA (30%) and Na₂[Cd(CPA)(TeO₃)(H₂O)Cl].2H₂O complex (31.6%).
- HCMPPA and its complexes had high antioxidant activity in comparison with standard ascorbic acid. HCMPPA showed the highest antioxidant activity (67.2%) then Na₂[Cd(CMPPA)(TeO₃)(H₂O)Cl].2H₂O complex (50.4%).

3.8.3. BMC-dependent DNA damage

The bleomycin (BMC) is a member from glycopeptides antibiotics which is utilized as antitumor agents. The bleomycin assay was certified as a specific method to estimate the pro-oxidant activity of drugs and food antioxidants. BMC binds iron ions and DNA. If the compounds are able to reduce the bleomycin-Fe(III) into bleomycin-Fe(II), DNA degradation in this system would be stimulated, resulting in a (+ve) pro-oxidant activity test [59]. The protective activity against DNA damage induced by the (BMC – iron) complex was screened for ligands (HCPA and HCMPPA) and their chelates. The results obtained were included in Tables (13S & 14S) and offered in (Figures 20 & 21) with a schematic representation in Figure (7S) where it was observed that HCPA and its complexes had low protective activity against DNA damage induced by the bleomycin iron complex compared to the results of ascorbic acid as a standard compound. While, HCMPPA and its complexes had high protection against DNA damage induced by the bleomycin iron complex.

3.9. Molecular docking

Molecular docking is an effective tool in computer drug design. Molecular docking of 2-cyano-N-(pyridin-2-yl) acetamide (HCPA) and 2-cyano-3-mercapto-3-(phenyl amino)-N-(pyridin-2-yl) acrylamide (HCMPPA) was carried out with receptors of *Escherichia coli* (PDB code: 1xk6), *Staphylococcus aureus* (PDB code:

6gyw), *Candida albicans* (PDB code: 3ppc) and *Covid 19* (PDB code: 7jpy). The docking studies showed an interaction between ligands and receptors as cleared in (Figures 22-25). The calculated bending energies of ligands as well as some parameters with the selected receptors were collected in Tables 11-14. The 2D plots of binding for ligands with the receptors were shown in (Figures 26-29), showing binding interaction sites of ligands with protein active sites of receptors. The HB plots that explained these interactions of ligands were shown in (Figures 30-33). Both estimated free energy of binding and interaction surface area revealed the most favored binding. The ligand which had more negative value of estimated free energy of binding represented more efficient binding. Based on data obtained from docking studies, it has been found that:

1. HCMPPA was the most efficient binding as it has the most negative value of estimated free energy of binding.
2. The order of best binding of ligands with antibacterial receptors (1xk6 and 6gyw) was found to be: HCMPPA > HCPA and this was congruent with experimental results.
3. A favorable interaction was shown between ligands and antibacterial receptors (1xk6 and 6gyw) than antifungal receptor (3ppc).
4. There was great interaction between ligands and receptor of *Covid 19* (PDB code: 7jpy) so it is possible to use ligands for *Covid 19* treatment.

4. Conclusion

Tellurite-pyridine Cd(II) complexes were synthesized and characterized by several advanced spectroscopic techniques. The data show the mononegative bidentate behavior of ligand giving anionic tellurite complex with octahedral configuration around Cd(II). Also, the molecular modeling of all compounds accompanied by theoretical calculations were performed using DFT where, the outcome data showed a great compatibility with the experimental investigations. Cyclic voltammetry studies explained the influence of the ligands on the electrochemical behavior of Cd(II) in solution which observed in the change in values of different cyclic voltammetry characteristics (D , i_p , E_{pc} , E_{pa} , α , k_s , Γ and Q). The biological studies were screened and emphasized Cd(II) complexes exhibit higher protection against DNA damage, lower antimicrobial and higher antioxidant features than the parent pyridyl ligands.

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Tables

Table 1: Analytical and physical data of HCPA and its Cd(II) complex

Compound	Empirical Formula (M.Wt.)	Color	M.P. (°C)	%Found (Calculated)				
				%C	%H	%N	%Cd	%Cl ⁻
HCPA	C ₈ H ₇ N ₃ O (161.1641)	Yellow	150	59.45 (59.62)	4.31 (4.38)	25.96 (26.07)	-	-
Na ₂ [Cd(CPA)(TeO ₃)(H ₂ O)Cl].2H ₂ O	Na ₂ CdTeC ₈ H ₁₂ N ₃ O ₇ Cl (583.6477)	White	>300	16.39 (16.46)	2.05 (2.07)	7.13 (7.2)	19.21 (19.26)	6.01 (6.07)

Table 2: Analytical and physical data of HCMPPA and its Cd(II) complex

Compound	Empirical Formula (M.Wt.)	Color	M.P. (°C)	%Found (Calculated)				
				%C	%H	%N	%Cd	%Cl ⁻
HCMPPA	C ₁₅ H ₁₂ N ₄ OS (296.3528)	Orange	180-185	60.72 (60.79)	4.05 (4.08)	18.85 (18.91)	-	-
Na ₂ [Cd(CMPPA)(TeO ₃)(H ₂ O)Cl].2H ₂ O	Na ₂ CdTeC ₁₅ H ₁₇ N ₄ O ₇ SCl (718.8364)	Dark green	>300	24.97 (25.06)	2.35 (2.38)	7.71 (7.79)	15.58 (15.64)	4.86 (4.93)

Table 3: Most important IR spectral bands of HCPA and its Cd(II) complex

Compound	ν(C=N) _{py}	ν(C=O)	ν(C≡N)	ν(C-O)	ν(C=C)	ν(Cd-O)	ν(Cd-N)	ν(Te-O)
HCPA	1635	1672	2257	-	-	-	-	-
Na ₂ [Cd(CPA)(TeO ₃)(H ₂ O)Cl].2H ₂ O	1624	diss	2260	1265	1633	525	422	677

Table 4: Most important IR spectral bands of HCMPPA and its Cd(II) complex

Compound	ν(C=N)	ν(C=O)	ν(C≡N)	ν(C=C)	ν(NH) _{py}	ν(C-O)	ν(C=N)*	ν(Cd-O)	ν(Cd-N)	ν(Te-O)
HCMPPA	1598	1644	2193	1549	3103	-	-	-	-	-
Na ₂ [Cd(CMPPA)(TeO ₃)(H ₂ O)Cl].2H ₂ O	1601	diss	2190	1527	diss	1150	1626	520	470	681

Table 5: The magnitudes of Lattice parameters and the particle size of $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex

Compound	θ (deg)	d (Å)	β (deg)	I (Counts)	S (nm)
$\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$	18.82	2.39	0.199	76	0.769

Table 6: Calculated quantum chemical parameters for HCPA and its $\text{Cd}(\text{II})$ complex

Theoretical data		
	HCPA	$\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$
E_{HOMO} (eV)	-7.1835	-6.7941
E_{LUMO} (eV)	-1.7954	-2.5747
E_{gap} (eV)	-5.3881	-4.2194
I (eV)	7.1835	6.7941
A (eV)	1.7954	2.5747
χ (eV)	4.4895	4.6844
μ (eV)	-4.4895	-4.6844
η (eV)	2.6941	2.1097
S (eV^{-1})	0.1856	0.237
ω (eV)	3.7407	5.2007
Total energy (eV)	-14930.62	-25063.76
Dipole moment (Debye)	8.8105	7.4188

Table 7: Calculated quantum chemical parameters for HCMPPA and its $\text{Cd}(\text{II})$ complex

Theoretical data		
	HCMPPA	$\text{Na}_2[\text{Cd}(\text{CMPPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$
E_{HOMO} (eV)	-6.4543	-6.0145
E_{LUMO} (eV)	-2.1288	-4.8654
E_{gap} (eV)	-4.3255	-1.1491
I (eV)	6.4543	6.0145
A (eV)	2.1288	4.8654
χ (eV)	4.2916	5.4399
μ (eV)	-4.2916	-5.4399
η (eV)	2.1628	0.5746
S (eV^{-1})	0.2312	0.8703
ω (eV)	4.2579	25.7528
Total energy (eV)	-34599.02	-34163.64
Dipole moment (Debye)	9.0048	7.7125

Table 8: Solvation and cyclic voltammetric parameters of CdCl_2 in the absence of HCPA at 301.15K and scan rate 0.1 V/s

$M \times 10^6$ (mol/cm ³)	E_{pa} (volt)	E_{pc} (volt)	ΔE_p (volt)	$-I_{pax} \times 10^4$ (Amp)	$I_{pcx} \times 10^4$ (Amp)	I_{pa}/I_{pc} (Amp)	E°	$D_a \times 10^4$ (cm ² /s)	$D_c \times 10^4$ (cm ² /s)	αn_a	K_s (cm/s)	$\Gamma_c \times 10^8$ (mol/cm ²)	(+) $Q_c \times 10^4$	Γ_x
0.99	-0.6507	-0.9235	0.2728	1.19	1.82	0.656	-0.7871	2.574	5.99	0.6964	16.8	1.5578	0.944	1
1.32	-0.6362	-0.9257	0.2895	1.77	2.34	0.757	-0.7809	3.212	5.60	0.6374	21.4	2.003	1.21	1
1.64	-0.5826	-0.8698	0.2872	4.46	2.76	1.618	-0.7262	13.145	5.02	0.8239	22.0	2.3617	1.43	3

Table 9: Solvation and cyclic voltammetric parameters of CdCl₂ in the presence of HCPA at 301.15K and scan rate 0.1 V/s

$M \times 10^6$ (mol/cm ³)	E_{pa} (volt)	E_{pc} (volt)	ΔE_p (volt)	$-I_{pax} \times 10^4$ (Amp)	$I_{pcx} \times 10^4$ (Amp)	I_{pa}/I_{pc} (Amp)	E°	$D_a \times 10^4$ (cm ² /s)	$D_c \times 10^4$ (cm ² /s)	αn_a	K_s (cm/s)	$\Gamma_c \times 10^8$ (mol/cm ²)	(+) $Q_c \times 10^4$	Γ_x
0.327	-0.5776	-0.8725	0.2949	4.42	2.98	1.4852	-0.7251	13.0	5.89	0.814	27.5	2.5509	1.55	3.
0.651	-0.5783	-0.8746	0.2963	4.10	2.91	1.4105	-0.7265	11.3	5.65	0.8746	28.7	2.4904	1.51	3.
0.974	-0.5738	-0.8844	0.3106	4.38	2.84	1.5432	-0.7291	12.9	5.43	0.8850	37.3	2.4319	1.47	3.
1.29	-0.5714	-0.8956	0.3242	3.95	2.76	1.4309	-0.7335	10.6	5.17	0.8366	45.9	2.3649	1.43	3.
1.61	-0.5696	-0.9038	0.3342	2.61	2.61	0.998	-0.7367	4.64	4.66	0.8168	52.2	2.2378	1.36	2.

Table 10: The stability constant for the (Cd²⁺/HCPA) complex at 301.15K

$[M] \times 10^6$ (mol/cm ³)	$[L] \times 10^6$ (mol/cm ³)	$(E^\circ)_M$ (volt)	$(E^\circ)_C$ (volt)	ΔE (volt)	Log[L]	Log β_{MX}	ΔG (kJ/mol)
1.63	0.327	-0.7262	-0.7251	-0.00115	-6.4857	1.2587	-7.2576
1.63	0.651	-0.7262	-0.7265	0.00025	-6.1861	2.4828	-14.3163
1.62	0.974	-0.7262	-0.7291	0.0029	-6.0114	3.7059	-20.9409
1.62	1.29	-0.7262	-0.7335	0.0073	-5.8879	4.9546	-28.5692
1.61	1.61	-0.7262	-0.7367	0.0105	-5.7924	6.1438	-35.4261

Table 11: Energy values obtained in docking calculations of ligands (HCPA and HCMPPA) with receptor of *Escherichia coli* (PDB code: 1xk6).

Ligand	Est. Free Energy of Binding (kcal/mol)	Est. Inhibition Constant (K_i) (μ M)	vdW+ Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total Intermolec. Energy	Interact. Surface
HCPA	-5.33	123.09	-6.06	-0.19	-6.25	500.934
HCMPPA	-8.9	299.09	-8.67	-1.19	-9.86	809.322

Table 12: Energy values obtained in docking calculations of ligands (HCPA and HCMPPA) with receptor of *Staphylococcus aureus* (PDB code: 6gyw).

Ligand	Est. Free Energy of Binding (kcal/mol)	Est. Inhibition Constant (K_i) (μ M)	vdW+ Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total Intermolec. Energy	Interact. Surface
HCPA	-4.45	548.77	-5.20	-0.17	-5.37	421.064
HCMPPA	-6.75	11.36	-6.19	-1.12	-7.32	564.898

Table 13: Energy values obtained in docking calculations of ligands (HCPA and HCMPPA) with receptor of *Candida albicans* (PDB code: 3ppc).

Ligand	Est. Free Energy of Binding (kcal/mol)	Est. Inhibition Constant (K_i) (μ M)	vdW+ Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total Intermolec. Energy	Interact. Surface
HCPA	-5.25	141.10	-6.11	-0.04	-6.14	451.566
HCMPPA	-4.45	103.10	-5.10	+0.42	-4.68	613.116

Table 14: Energy values obtained in docking calculations of ligands (HCPA and HCMPPA) with receptor of *Covid 19*(PDB code: 7jpy).

Ligand	Est. Free Energy of Binding (kcal/mol)	Est. Inhibition Constant (K_i) (μ M)	vdW+ Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total Intermolec. Energy	Interact. Surface
HCPA	-4.61	418.43	-5.31	-0.19	-5.50	479.486
HCMPPA	-6.33	24.87	-6.21	-0.73	-6.94	597.305

Scheme

Please see the Supplementary Files for the Scheme 1, 2, 3 and 4.

Figures

Chemical structure of 10b is shown in the top right corner. The spectrum displays peaks corresponding to the structure, with integration values provided for each major signal.

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¹³C NMR spectra of (A) HCPA and (B) Na₂[Cd(CPA)(TeO₃)(H₂O)Cl]·2H₂O complex

Figure 3

¹H NMR spectra of HCMPPA ligand

13C NMR spectrum of compound 10. The x-axis represents chemical shift in ppm, ranging from 200 to 0. The spectrum shows several peaks: a small peak at ~185 ppm, a small peak at ~175 ppm, a small peak at ~140 ppm, a large peak at ~130 ppm, a small peak at ~125 ppm, a small peak at ~120 ppm, a small peak at ~115 ppm, a small peak at ~110 ppm, a small peak at ~105 ppm, a small peak at ~100 ppm, a small peak at ~95 ppm, a small peak at ~90 ppm, a small peak at ~85 ppm, a small peak at ~80 ppm, a small peak at ~75 ppm, a small peak at ~70 ppm, a small peak at ~65 ppm, a small peak at ~60 ppm, a small peak at ~55 ppm, a small peak at ~50 ppm, a small peak at ~45 ppm, a small peak at ~40 ppm, a small peak at ~35 ppm, a small peak at ~30 ppm, a small peak at ~25 ppm, a small peak at ~20 ppm, a small peak at ~15 ppm, a small peak at ~10 ppm, a small peak at ~5 ppm, a small peak at ~0 ppm. The spectrum is labeled with '13C NMR' and '10'.

¹³C NMR spectra of (A) HCMPPA and (B) Na₂[Cd(CMPPA)(TeO₃)(H₂O)Cl]·2H₂O complex

Figure 5

EDX analysis of $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex

Figure 6

EDX analysis of $\text{Na}_2[\text{Cd}(\text{CMPPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex

Figure 7

XRD of $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex

(A)

(B)

Figure 8

Molecular modeling of (A) HCPA and (B) $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex

Molecular modeling of (A) HCMPPA and (B) $\text{Na}_2[\text{Cd}(\text{CMPPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}] \cdot 2\text{H}_2\text{O}$ complex

Figure 10

The frontier molecular orbitals (FMOs) of (A) HCPA and (B) $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex

Figure 11

The frontier molecular orbitals (FMOs) of (A) HCMPPA and (B) $\text{Na}_2[\text{Cd}(\text{CMPPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex

(A)

(B)

Figure 12

Molecular electrostatic potential map of (A) HCPA and (B) $\text{Na}_2[\text{Cd}(\text{CPA})(\text{TeO}_3)(\text{H}_2\text{O})\text{Cl}]\cdot 2\text{H}_2\text{O}$ complex

(A)

(B)

Figure 13

Molecular electrostatic potential map of (A) HCMPPA and (B) Na₂[Cd(CMPPA)(TeO₃)(H₂O)Cl].2H₂O complex

Figure 14

Cyclic voltammograms of CdCl₂ in 0.1M KCl at scan rate 0.1 V/s and at 301.15 K

Figure 15

Cyclic voltammograms of $1.64 \times 10^{-3} \text{ M CdCl}_2$ in 0.1 M KCl in presence of different concentrations of HCPA at scan rate 0.1 V/s and at 301.15 K

(A)

(B)

(C)

Figure 16

Effect of HCPA and its Cd(II) complex toward (A) *E. Coli*, (B) *S. aureus* and

(C) *C. Albicans*

Figure 17
 Effect of HCMPPA and its Cd(II) complex toward (A) *E. Coli*, (B) *S. aureus* and
 (C) *C. Albicans*

Figure 18

The antioxidant activity assay ABTS method for HCPA and its Cd(II) complex

Figure 19

The antioxidant activity assay ABTS method for HCMPPA and its Cd(II) complex

Figure 20

Bleomycin-dependent DNA damage assay of HCPA and its Cd(II) complex

Figure 21

Bleomycin-dependent DNA damage assay of HCMPPA and its Cd(II) complex

(A)

(B)

Figure 22

Ligands (A) HCPA and (B) HCMPPA (green in (a) and gray in (b)) in interaction with receptor of *Escherichia coli* (PDB code: 1xk6).

(A)

(B)

Figure 23

Ligands (A) HCPA and (B) HCMPPA (green in (a) and gray in (b)) in interaction with receptor of *Staphylococcus aureus* (PDB code: 6gyw).

Ligands **(A)** HCPA and **(B)** HCMPPA (green in (a) and gray in (b)) in interaction with receptor of *Candida albicans* (PDB code: 3ppc).

(A)

(B)

Figure 25

Ligands (A) HCPA and (B) HCMPPA (green in (a) and gray in (b)) in interaction with receptor of *Covid 19*(PDB code: 7jpy).

(A)

(B)

Figure 26

2D plot of interaction between ligands (A) HCPA and (B) HCMPPA and receptor of *Escherichia coli* (PDB code: 1xk6).

(A)

(B)

Figure 27

2D plot of interaction between ligands (A) HCPA and (B) HCMPPA and receptor of *Staphylococcus aureus* (PDB code: 6gyw).

(A)

(B)

Figure 28

2D plot of interaction between ligands (A) HCPA and (B) HCMPPA and receptor of *Candida albicans*(PDB code: 3ppc).

(A)

(B)

Figure 29

2D plot of interaction between ligands (A) HCPA and (B) HCMPPA and receptor of *Covid 19*(PDB code: 7jpy).

Figure 30

HB plot of interaction between ligands (A) HCPA and (B) HCMPPA and receptor of *Escherichia coli* (PDB code: 1xk6)

Figure 31

HB plot of interaction between ligands (A) HCPA and (B) HCMPPA and receptor of *Staphylococcus aureus* (PDB code: 6gyw)

Figure 32

HB plot of interaction between ligands (A) HCPA and (B) HCMPPA and receptor of *Candida albicans*(PDB code: 3ppc)

Figure 33

HB plot of interaction between ligand (A) HCPA and (B) HCMPPA and receptor of *Covid 19* (PDB code: 7jpy)

Supplementary Files

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