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Electroanalytical and spectroscopic studies of new metal-based drugs

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Abstract Cefaclor (CEF), a second generation cephalosporin antibiotic drug, reacts with transition metal ions to give the new generation drug candidate molecules [Cd(CEF)(H_2O)(Cl)](**1**), [Fe(CEF)(H_2O)$_2$(Cl)$_2$](**2**), [Pd(CEF)(H_2O)(AcO)](**3**), [Pt(CEF)(H_2O)(Cl)](**4**), [Ru(CEF)(H_2O)$_2$(Cl)$_2$](**5**), [Zn(CEF)(H_2O)(Cl)](**6**). These compounds have been then characterized by spectroscopic techniques involving UV-Vis, IR, ^{1}H-HMR, C, H, N elemental analysis, electrochemical and thermal behavior of compounds investigated. The electrochemical properties of all compounds have been investigated by cyclic voltammetry (CV) using glassy carbon electrode. The dependence of intensities of currents and potentials on pH, concentration, scan rate, nature of the buffer has been investigated. The oxidation/reduction mechanism has been proposed and discussed. The cyclic voltammograms of the compounds have been recorded in buffer solution different pH (pH= 2-12, phosphate) and the corresponding redox potentials have been estimated. The compounds have been screened for antibacterial activity against *Pseudomonas aeruginosa*, *Kluvyeromyces fragilis*, *Saccharomyces cerevisiae*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Bacillus megaterium*, *Candida albicans*, *Mycobacterium smegmatis*, *Bacillus cereus*, *Enterococcus cloacae* and *Micrococcus leteus*. The compound (**1**) has been found to be more potent against some bacterial species than the free CEF.

Keywords Drug-Metal compounds, Electrochemical properties, Antibacterial activity

Introduction

Cephalosporins are the second major group of β-lactam antibiotics, they are classified into four generations. β-lactam antibiotics, such as penicillin, cephalosporins and oxacephalosporins, represent the most important class of drugs against infectious diseases caused by bacteria [1]. The biological activity of these antibiotics is the β-lactam ring [2].

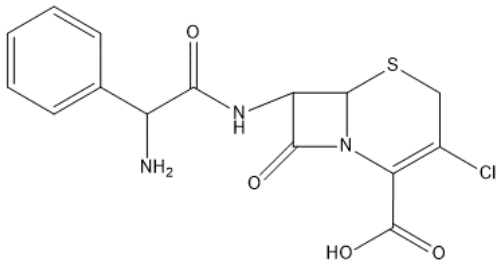

Figure 1: The chemical structure of CEF

Cefaclor is similar to the first-generation cephalosporin cephalexin, but with substitution of a chlorine atom for the methyl group in the 3 position of the dihydrothiazine ring (Fig. 1). This substitution gives Cefaclor substantially greater antibacterial activity, especially against *H influenzae*. Cefaclor has a highly stable zwitter ionic molecule (*i.e.*, a molecule with a positive and a negative charge). As a zwitter ionic compound, Cefaclor diffuses into external membranes more rapidly than does a monoanionic compound such as cefuroxime or a dianionic compound such as cefonicid. This characteristic contributes to its excellent penetration rate [3].

The design of drug based metal complexes is particular interest in pharmacological research. Metal combinations with pharmaceutical agents are known to improve drug activity and to decrease their toxicity [4].

Transition-metal ions play a number of critical roles in biological and pharmaceutical sciences. The interactions of drug and metal ions have been thoroughly studied especially due to the interesting biological and chemical properties. Based on their wide spectrum of coordination numbers and geometries as well as kinetic properties, metal compounds offer mechanisms of drug action, that cannot be realized by organic agents. It is supposed that metal ions are involved in the mechanism of action of antibacterial agents. Many drugs possess modified toxicological and pharmacological properties in the form of metal compounds [5].

Several metal complexes of CEF have been synthesized and characterized so far. Firstly, the Co(II) and Ni(II) complexes have been synthesized and characterized by Chohan [6] and antibacterial activities have been tested against several bacteria. Similarly, copper complex of CEF has been prepared in pH range from 5.60-11.05, and to find molar ratio of the metal: ligand, job method was used [7].

In our previous report, we prepared and characterized the mononuclear Cu(II), Co(II) and Ni(II) compounds of CEF as similarly [5,8-15]. As a part of our continuous work, in this text, we report the electroanalytical properties and spectroscopic characterization of new generation drug candidate molecules of CEF.

Materials and Methods

CEF was kindly provided by Eczacıbaşı Pharm. Comp. (Istanbul, Turkey). Metal salts ($FeCl_3{\cdot}6H_2O$, $RuCl_3{\cdot}6H_2O$, $CdCI_2$, $ZnCI_2.2H_2O$, $Pd(CH_3COOH)_2$ and $PtCI_2$) were purchased from Merck and were used without further purification. Dimethyl sulfoxide (DMSO) and methanol were purchased from Aldrich Chem. Co. All chemicals for preparation of buffers and supporting electrolytes such as H_2SO_4, H_3PO_4, NaH_2PO_4, Na_2HPO_4, H_3BO_3, CH_3COOH, NaOH were reagent grade (Merck or Sigma).

Elemental analyses (C, H, N) were performed using a LECO CHNS 932 elemental analyzer. IR spectra were obtained using ATR (4000-400 cm^{-1}) on a Perkin Elmer spectrum 400 FT-IR/FT-FIR spectrophotometer. The electronic spectra in the 200-900 nm range were obtained on a Perkin Elmer Lambda 45 spectrophotometer.

Magnetic measurements were carried out by the Gouy method using Hg[Co(SCN)] as calibrant. Molar conductance of the metal compound was determined in DMF (~10^{-3} M) at room temperature using a Jenway Model 4070 conductivity meter. Mass spectra of the compounds were recorded on a LC/MS APCI Agilent 1100 MSD spectrophotometer. The metal contents of the compounds were determined by an Ati Unicam 929 Model AA Spectrometer in solutions prepared by decomposing the compounds in aqua regia and then subsequently digesting in concentrated HCl. The thermal analyses studies of the compounds were performed on a Perkin Elmer Pyris Diamond DTA/TG Thermal System under nitrogen atmosphere at a heating rate of 10 ^oC/min.

All voltammetric measurement at a glassy carbon electrode was performed using a BAS 100W (Bioanalytical System, USA) electrochemical analyzer. A glassy carbon working electrode (BAS; Φ: 3mm diameter), an Ag/AgCl reference electrode (BAS; 3M KCl) and platinum wire counter electrode and a standard one-compartment three electrode cell of 10mL capacity were used in all experiments. The glassy carbon electrode was polished manually with aqueous slurry of alumina powder (Φ: 0.01 μm) on a damp smooth polishing cloth (BAS velvet polishing pad), before each measurement. All measurements were realized at room temperature.

Mettler Toledo MP 220 pH meters was used for the pH measurements using a combined electrode (glass electrode reference electrode) with an accuracy of ±0.05 pH.

Synthesis of iron(III), ruthenium(III), zinc(II), platinum(II) and cadmium(II) compounds (M:L=1:1)

(**1**), (**3**), (**4**), (**5**) and (**6**) compounds were obtained according to a general procedure: A solution of the metal salt (1 mmol) in absolute MeOH (25 mL) was added to a solution of the CEF drug material (1 mmol) in absolute

MeOH (20 mL) and the mixture was boiled under reflux for 6–7 h. At the end of the reaction, determined by TLC, the precipitate was filtered, washed with distilled water and then EtOH, and dried in vacuum.

Synthesis of palladium(II) compound

(**3**) compounds were obtained according to a general procedure: A solution of a metal salt (1 mmol) dissolved in 20 ml of 1M CH_3COOH was added to a solution of CEF (1mmol) in 5 ml of distilled water and finally 15 ml of MeOH was added to mixture and the mixture was heated under reflux for 1 day. At the end of the reaction, determined by TLC, the precipitate was filtered off, washed with distilled water, EtOH and dried under vacuum.

The analytical data and physical properties of the prepared compounds are given below.

(**1**): Formula weight (g mol^{-1}): 532.68, Yield: 65%, color: cream, m.p: 210 °C. Elemental analysis, found (calcd. %): C:33.82(33.87); H:2.84 (2.85); N:7.89 (7.94); M:21.10(21.16). FT-IR: (ATR, cm^{-1}) 3446; υ(OH), 3250,3110; $\upsilon(NH_2)$, 1764; $\upsilon(C{=}O)_{amid}$, 1539; $\upsilon(M\text{-}OOC)_{acid}$, 554; υ(M-O), 513; υ(M-N). UV-vis: λ_{max} (nm) (ε m^{-1} cm^{-1}) DMSO as solvent: 325, Conductivity: 12 $\Lambda(\Omega^{-1}cm^2\,mol^{-1})$, Diamagnetic.

(**2**): Formula weight (g mol^{-1}): 529.58, Yield: 75%, color: black, m.p: 224 °C. Elemental analysis, found (calcd. %): C:34.02(34.07); H:3.24 (3.21); N:7.93 (7.90); M:10.55 (10.50). FT-IR: (ATR, cm^{-1}) 3433; υ(OH), 3260,3097; $\upsilon(NH_2)$, 1772; $\upsilon(C{=}O)_{amid}$, 1637; $\upsilon(M\text{-}OOC)_{acid}$, 513; υ(M-O), 486; υ(M-N). UV-vis: λ_{max} (nm) (ε m^{-1} cm^{-1}) DMSO as solvent: 457, Conductivity: 27 $\Lambda(\Omega^{-1}cm^2\,mol^{-1})$, μ_{eff} (B.M.): 1.75.

(**3**): Formula weight (g mol^{-1}): 550.29, Yield: 70%, color: brown, m.p: 225 °C. Elemental analysis, found (calcd. %): C:37.11(37.16); H:3.30 (3.32); N:7.64 (7.61); M:19.34 (19.31). FT-IR: (ATR, cm^{-1}) 3437; υ(OH), 3234,3111; $\upsilon(NH_2)$, 1774; $\upsilon(C{=}O)_{amid}$, 1598; $\upsilon(M\text{-}OOC)_{acid}$, 584; υ(M-O), 496; υ(M-N). UV-vis: λ_{max} (nm) (ε m^{-1} cm^{-1}) DMSO as solvent: 416, Conductivity: 1 $\Lambda(\Omega^{-1}cm^2\,mol^{-1})$, Diamagnetic.

(**4**): Formula weight (g mol^{-1}): 615.35, Yield: 65%, color: brown, m.p: 321 °C. Elemental analysis, found (calcd. %): C:29.28(29.35); H:2.46 (2.48); N:6.83 (6.80); M:31.70 (31.72). FT-IR: (ATR, cm^{-1}) 3436; υ(OH), 3234,3107; $\upsilon(NH_2)$, 1754; $\upsilon(C{=}O)_{amid}$, 1591; $\upsilon(M\text{-}OOC)_{acid}$, 543; υ(M-O), 483; υ(M-N). UV-vis: λ_{max} (nm) (ε m^{-1} cm^{-1}) DMSO as solvent: 403, Conductivity: 7 $\Lambda(\Omega^{-1}cm^2\,mol^{-1})$, Diamagnetic.

(**5**): Formula weight (g mol^{-1}): 574.81, Yield: 63%, color: black, m.p: 128 °C. Elemental analysis, found (calcd. %): C:31.34(31.37); H:2.98 (2.95); N:7.31 (7.36); M:17.58 (17.63). FT-IR: (ATR, cm^{-1}) 3433; υ(OH), 3250,3058; $\upsilon(NH_2)$, 1751; $\upsilon(C{=}O)_{amid}$, 1590; $\upsilon(M\text{-}OOC)_{acid}$, 518; υ(M-O), 486; υ(M-N). UV-vis: λ_{max} (nm) (ε m^{-1} cm^{-1}) DMSO as solvent: 630, Conductivity: 25 $\Lambda(\Omega^{-1}cm^2\,mol^{-1})$, μ_{eff} (B.M.): 1.92.

(**6**): Formula weight (g mol^{-1}): 485.68, Yield: 70%, color: black, m.p: 212 °C. Elemental analysis, found (calcd. %): C:37.09 (37.13); H:3.11 (3.12); N:8.65 (8.61); M:13.47 (13.48). FT-IR: (ATR, cm^{-1}) 3446; υ(OH), 3310,3158; $\upsilon(NH_2)$, 1754; $\upsilon(C{=}O)_{amid}$, 1637; $\upsilon(M\text{-}OOC)_{acid}$, 543; υ(M-O), 513; υ(M-N). UV-vis: λ_{max} (nm) (ε m^{-1} cm^{-1}) DMSO as solvent: 362, Conductivity: 7 $\Lambda(\Omega^{-1}cm^2\,mol^{-1})$ μ_{eff} (B.M.): Diamagnetic.

Biological activity

The antibacterial activities of CEF and metal-based drugs were screened in vitro using the disc diffusion method. The chosen strains, *Pseudomonas aeruginosa, Kluvyeromyces fragilis, Saccharomyces cerevisiae, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Bacillus megaterium, Candida albicans, Mycobacterium smegmatis, Bacillus cereus, Enterococcus cloacae* and *Micrococcus leteus*were obtained from Microbiology Laboratory, Department of Biology, Faculty of Science and Arts, Kahramanmaras, Turkey. Test solutions of CEF and its Cd(II), Zn(II), Pt(II), Pd(II), Fe(III) and Ru(III) compounds were prepared in DMSO. The bacteria were cultured for 24 h at 37 ^oC in an incubator. Muller Hinton broth was used for preparing basal media for the bioassay of the organisms. Nutrient agar was poured onto a plate and allowed to solidity. The test compounds solutions (DMSO) were added drop wise to a 10 mm diameter filter paper disc plates at the center of

each agar plate. The plates were then kept at 5 ^{o}C for 1 h and transferred to an incubator maintained at 37 ^{o}C. The width of the growth inhibition zone around the disc was measured after 24 h incubation.

Results and Discussion

In this research Cd(II), Zn(II), Pt(II), Pd(II), Fe(III) and Ru(III) compound of CEF were synthesized as the new generation drug candidate molecules. The molar ratio for all compounds synthesized is CEF:M=1:1 for Cd(II), Zn(II), Pt(II), Pd(II), Fe(III) and Ru(III).

The found and the calculated percentages of C, H, and N data agree well with each other and these prove the suggested molecular structure. Diverse crystallization techniques were employed in order to obtain a crystal suitable for the structure determination with X-ray crystallography. Nevertheless, the compounds were collected as microcrystalline products [12,16].

The spectra of the free CEF showed absorption bands at the 3295 and 3050 cm^{-1} corresponding to the $\nu(NH_2)$ and ν(NH) stretching frequencies, respectively. These bands have seemed in the spectra of all compounds almost same wave number. This type of weak showed that $–NH_2$ and –NH groups did not participate to coordination with metal. The β-lactam ν(C=O) band appears at 1749 cm^{-1}; the compounds having a molar ratio of metal: CEF as 1:1 exhibit unchanged amide and β-lactam bands. These observations suggest that CEF is not coordinated to the metal ions through amide or β-lactam oxygen. The carboxylate ligand can bind to a metal atom as a mono-dentate ligand, causing changes in the relative positions of the asymmetric and symmetric vibrations[17]. In the IR spectrum of metal-based drugs, the ν(OH) vibration peaks between 3433-3446 cm^{-1} can be attributed to coordinated water molecules. The spectrum of CEF exhibits a band at 1500 cm^{-1} belongs to carboxylate group. A new band at 1539-1637 cm^{-1} observed in the IR spectra of compounds furthermore, suggested[18] bonding of the carboxylate the ν(M-OOC) group. The presence of the strong ν(M-N) and ν(M-O) stretching vibration at 483-513 cm^{-1} and 513-584 cm^{-1} for the metal-based drugs, support coordination of CEF through nitrogen of β-lactam ring and carboxylate. Moreover, the β-lactam band at 1749 cm^{-1} moved to lower frequency by 12-25 cm^{-1} indicating involvement /coordinating of the β-lactam oxygen to the metal ion. In the present studies, the CEF molecule has several potential donor atoms but, due to steric constrains, the molecule can provide a maximum two donor sites to the metal atom. The assumption that the CEF molecule coordinates through the carboxylate and β-lactam nitrogen seems likely from molecular model studies.

The electronic spectra of metal-based drugs were measured in DMSO in order to obviate the effect of the solvent. The UV-Vis spectra of CEF and metal-based drugs present two absorption maxima at 264 and 305 nm assigned to π-π* and n-π* transitions within the drug material. The spectra of the compounds contain same absorption bands in the range 565-416 nm (relatively weak, low-energy bands), which may be assigned to the d-d* transition in a tetrahedral, square planar and octahedral configuration. This data is in accordance with the assumption for the formation of M-N and M-O bands [19, 20].

The magnetic moments (as B.M.) of the compounds were measured at room temperature. The (**3**), (**4**) and (**5**) compounds are found in diamagnetic character and square planar geometry, (**1**) compound is found tetrahedral geometry around the metal ion, the observed magnetic moment of (**2**) compound is 1.75 B.M. Thus, the compound formed has the octahedral geometry. Magnetic susceptibility measurement of the (**5**) compound at 298 K showed a value of e.m.u.g^{-1} with an effective magnetic moment μ_{eff} of 1.92 B.M. and the compound formed has the octahedral geometry. The molar conductivity measurements were done on all compounds in DMSO (~1.10^{-3} M solutions). The conductivity data of the compounds are very low and can be regarded as nonelectrolytes [8].

When we compare the ^{1}H NMR spectra of CEF and metal-based drugs, there are some differences because of the complexation. The ^{1}H NMR spectra of CEF molecule in DMSO showed quartet at δ: 3.76 ppm corresponding to $–CH_2$; doublet at δ:5.1 ppm for H; singlet at δ: 5.4 ppm for –CH-CO-; a doublet at at δ: 5.72 ppm for H belong to the C of β-lactam ring. The peak at δ: 7.55 ppm in the spectrum of CEF can be assigned to the proton of phenyl. The ^{1}H NMR spectrum for diamagnetic (**3**) compound in the same solvent (DMSO-d_6) exhibited the new peak from δ:1.92 to 3.36 ppm, due to the presence of water molecules in the compound. The peak at 11.44 ppm in the NMR spectrum of CEF can corresponding to OH (-COOH) group. When the (**3**) compound occurred, this peak is disappeared. This situation supported that the (**3**) compound is occurred via the

carboxylic –OH. Also on comparing main peaks of CEF withmetal-based drugs, it is observed that all the peaks of the drug material are present in the NMR spectra of the compounds with chemical shift upon binding of the carboxylate oxygen and nitrogen of β-lactam ring to the metal ion.

In this study, the thermal behavior of the metal-based drugs was characterized using DTA and TGA/DTG methods. The DTA/TG measurements of the compounds were carried out in the 55-1250 ^{o}C range. The compounds contain the coordinated chloride ion, acetate ion and water molecules. There is one route in removal of the coordinated water molecules in the 116-219 ^{o}C temperature range from the compounds. Moreover, the coordinated chloride ion losses from compounds in the 286-316 ^{o}C temperature range. At the higher temperatures (400-1200 ^{o}C), all compounds decompose to give the approximate metal oxide.

The ratios of the metal present compounds were determined by atomic absorption spectroscopy. The compounds were decomposed in HNO_3/H_2O_2 (1/1) and then dissolved in 1.5 N HNO_3. The amounts of the metals were determined. They support the structures given in the Fig. 2- 4.

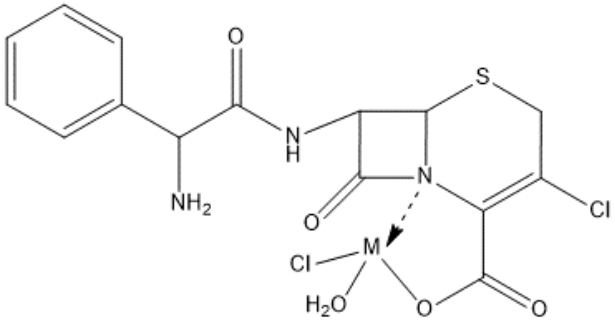

Figure 2: The proposed chemical structure of [Cd(CEF)(H$_2$O)(Cl)], [Pt(CEF)(H$_2$O)(Cl)] and [Zn(CEF)(H$_2$O)(Cl)]

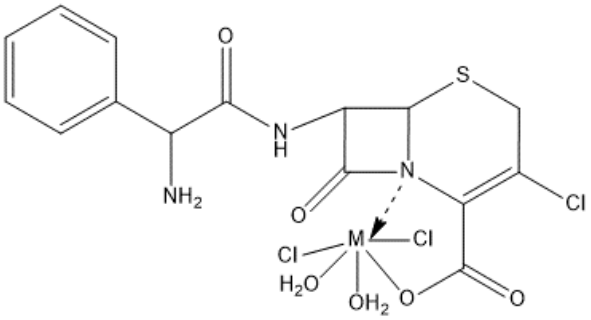

Figure 3: The proposed chemical structure of [Fe(CEF)(H$_2$O)$_2$(Cl)$_2$] and [Ru(CEF)(H$_2$O)$_2$(Cl)$_2$]

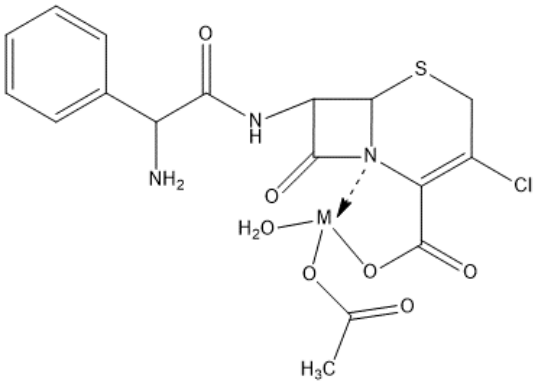

Figure 4: The proposed chemical structure of [Pd(CEF)(H$_2$O)(AcO)]

In order to give more detail about the structure of compounds, the mass spectra of the metal-based drugs were investigated. The mass spectra of chelates a well-defined parent peak at m/z= 548.0 (M^+, RI= 5%) for (**3**) compound. The mass spectra, also, show the base peak molecular ion with a (RI= 100%) at m/z 413

($C_{10}H_{11}ClN_2O_5PdS$). The other molecular ion peaks appeared in the mass spectra (abundance range from 5% to 100%) are attributed to the fragmentation of compound obtained from the rupture of different bonds inside the molecule. The different molecular ion peaks can be attributed to the loss of water, anions and different ions resulted from compound decomposition.

In this research, CEF and (**1-5**) compounds were subjected to a cyclic voltammetric study with the aim of the detailed characterizing compounds electrochemical behavior, on the glassy carbon electrode. Therefore, the electrochemical behaviors of compounds were studied over a wide pH range (2.0-12.0) with a glassy carbon electrode in buffered aqueous media. In CV studies the scanning was started at -2.0 V in the anodic direction at pH 2.0 phosphate buffer, the anodic oxidation of CEF did not occur until about 1.4 V for GCE. By reversing at high potentials the oxidation wave (E_{pa}= 1.485 V) to the anodic peak was observed on the anodic branch for GCE.

Figure 5 shows comparative CV of CEF in the presence of cadmium(II) ions at anodic directions for: (a) blank, (b) CEF alone, (c) (**3**). The anodic peak at -0.721 V shows the oxidation of the Cd(II) ion. This process is:

$$Cd^{+2} \longrightarrow Cd^{+3} + e^-$$

In addition, the cathodic peak at -1.186 V is the reduction peak of the (**3**) compound. This is

$$Cd^{+3} + e^- \longrightarrow Cd^{+2}.$$

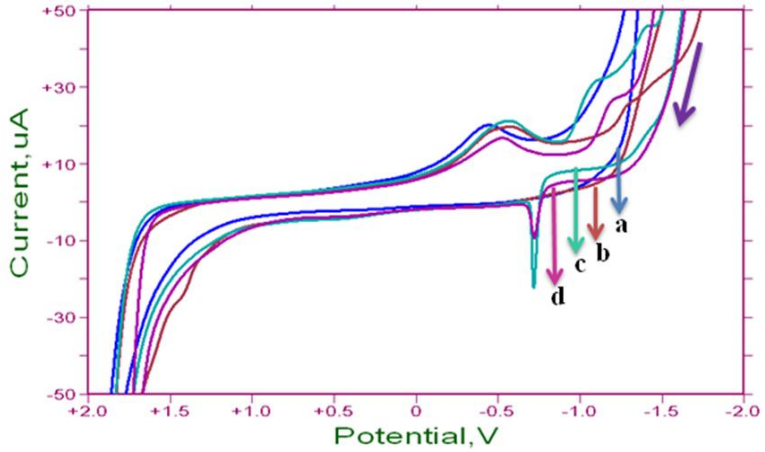

Figure 5: Cyclic voltamograms for (a) blank; (b) 1x10^{-4} M CEF; (c) 1x10^{-4} M $CdCI_2$; (d) 1x10^{-4} M (1) on the anodic direction

The oxidation and reduction process are irreversible because of $I_{pa}/I_{pc} \approx 0.52$ and ΔE=465 mV. The pH of the supporting electrolyte has a significant effect on the electro reduction of the compound at the GCE. CV voltamograms of solid synthesized compounds exhibited one or two well-defined peaks and the peaks developed best became sharper in phosphate buffer at pH 2. Plots of pH vs. E_p and I_p were investigated using CV techniques. The peak potential (E_p) at the redox process moved to less negative potential values by raising the pH. The plot of the peak potential vs. pH showed one straight line between pH 2.0-12.0, which can be expressed by the following equations in phosphate buffer;

E_p(mV)= -703.75 – 15.31 pH ; R^2 = 0,9385 for (**1**)
E_p(mV)= -879.67 – 21.28 pH ; R^2 = 0,9204 for (**2**)
E_p(mV)= -675.45 – 40.20 pH ; R^2 = 0,9243 for (**3**)
E_p(mV)= -789.46 – 20.52 pH ; R^2 = 0,9250 for (**4**)
E_p(mV)= -780.62 – 41.61 pH ; R^2 = 0,8978 for (**5**)
E_p(mV)= -820.10 – 39.52 pH ; R^2 = 0,9157 for (**6**)

The effect of pH on peak current of all compounds in the range of pH 2.0-12.0 were also evaluated. The best and sharpest peak and reproducible results were obtained in pH 2.0 phosphate buffer. Therefore, this media was chosen in this study as the supporting electrolyte for the electroanalytical investigations.

Scan rate studies were carried out to investigate whether the process at the GCE was under diffusion or adsorption control. The effect of the potential scan rate between 5 mV/s -1000 mV/s on the peak current and

potential of all compounds were evaluated in pH 2 phosphate buffer. The typical current-potential curve of scan rate studies of (**1**)compound was given in Figure 6.

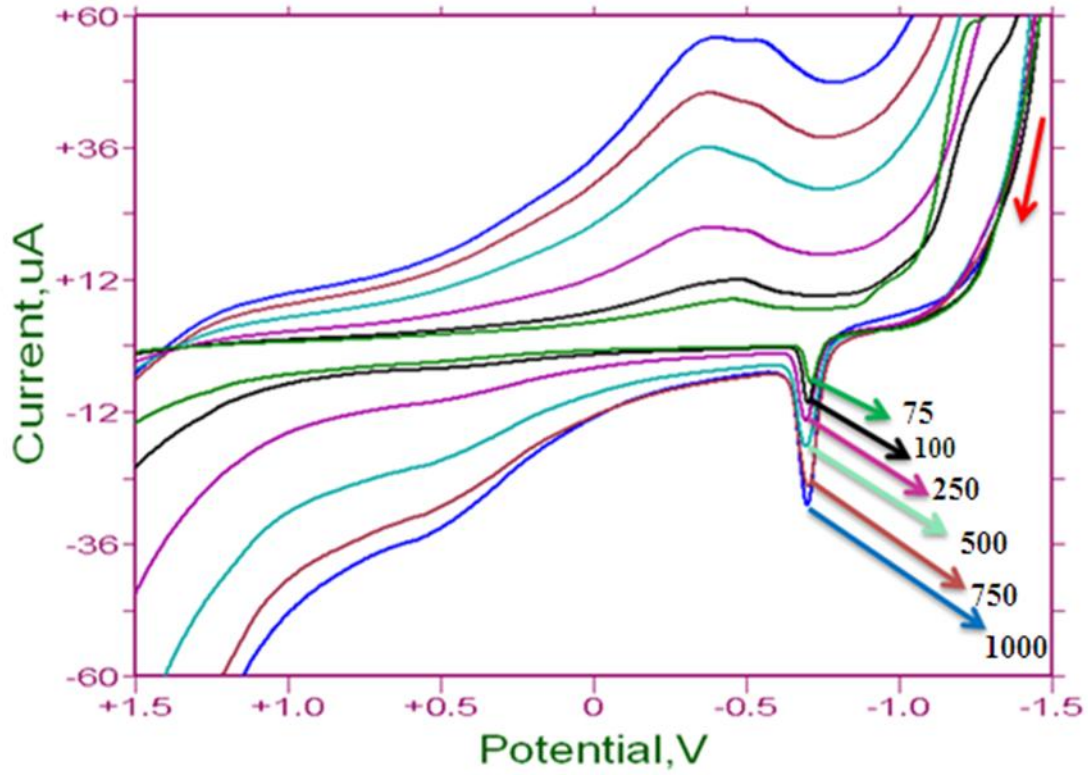

Figure 6: Cyclic voltammograms for (1) compound at different scan rates

When the scan rate was varied from 5-1000 mV/s in $1x10^{-4}$M compound solutions, a linear dependence of the peak current I_p(μA) upon the square root of the scan rate $v^{1/2}$(mVs^{-1}) was found by GCE, demonstrating a diffusional behavior. The equations are noted below in pH 2.0 phosphate buffer (n=10 in all studies);

I_p(μA) = 0.8391$v^{1/2}$ (mVs^{-1}) + 0.8391, r^2: 0.9919 for (**1**)
I_p (μA) = 0.5734$v^{1/2}$ (mVs^{-1}) + 0.7562, r^2: 0.9929 for (**2**)
I_p (μA) = 0.6439$v^{1/2}$ (mVs^{-1}) + 0.6782,r^2: 0.9948 for (**3**)
I_p (μA) = 0.7928$v^{1/2}$ (mVs^{-1}) + 0.8514, r^2: 0.9897 for (**4**)
I_p (μA) = 0.7285$v^{1/2}$ (mVs^{-1}) + 0.8575, r^2: 0.9915 for (**5**)
I_p (μA) = 0.8139 $v^{1/2}$ (mVs^{-1}) + 0.7249,r^2: 0.9854 for (**6**)

The effect of scan rate on peak current was also examined under the above conditions with a plot of logarithm of peak current vs. logarithm of scan rate giving a straight line within the same scan rate range. These linear relationships were obtained as follow (n=10 in all studies);

logI_p (μA) = 0.3464 log$v$ (mVs^{-1}) + 0.3794 (r^2: 0.9654) for (**1**)
logI_p (μA) = 0.4289 log$v$ (mVs^{-1}) + 0.4257 (r^2: 0.9964) for (**2**)
logI_p (μA) = 0.3417 log$v$ (mVs^{-1}) + 0.5807 (r^2: 0.9972) for (**3**)
logI_p (μA) = 0.4569 log$v$ (mVs^{-1}) + 0.3798 (r^2: 0.9957) for (**4**)
logI_p (μA) = 0.4828 log$v$ (mVs^{-1}) + 0.3629 (r^2: 0.9912) for (**5**)
logI_p (μA) = 0.3669 log$v$ (mVs^{-1}) + 0.4798 (r^2: 0.9921) for (**6**)

The slopes (between 0.34-0.48) of the relationship are close to the theoretically expected (0.5) for an ideal reaction of solution species, so in this case the process had a diffusive component [8,21].

The susceptibility of certain strains of bacterium towards CEF and metal-based drugs was judged by measuring the size of inhibition diameter. Antibacterial activities of the CEF and the metal-based drugs have been carried out six gram positive [*Staphylococcus aureus, Bacillus megaterium, Mycobacterium smegmatis, Bacillus cereus, Enterococcus cloacae and Micrococcus leteus*] and six gram negative [*Pseudomonas aeruginosa,*

Kluvyeromyces fragilis, Saccharomyces cerevisiae, Escherichia coli, Klebsiella pneumoniae, Candida albicans] bacteria. The test solutions were prepared in DMSO. The results of the antibacterial activities are summarized in Table 1 and Figure 7.

Table 1 Antimicrobial and antifungal activity of CEF and metal compounds.

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Cefaclor (CEF)	46	35	45	-	-	34	30	38	46	45	45	42
[Cd(CEF)(H_2O)(Cl)]	14	32	21	31	34	36	30	35	34	33	30	28
[Fe(CEF)(H_2O)$_2$($Cl)_2$]	13	17	20	9	20	12	-		15	-	27	26
[Pd(CEF)(H_2O)(AcO)]	23	15	14	15	20	8	16	14	19	8	13	21
[Pt(CEF)(H_2O)(Cl)]	22	9	15	22	9	32	13	10	18	-	-	23
[Ru(CEF)(H_2O)$_2$($Cl)_2$]	29	12	25	31	18	46	24	22	20	18	16	19
[Zn(CEF)(H_2O)(Cl)]	22	-	-	-	22	7	-	22	-	22	20	10

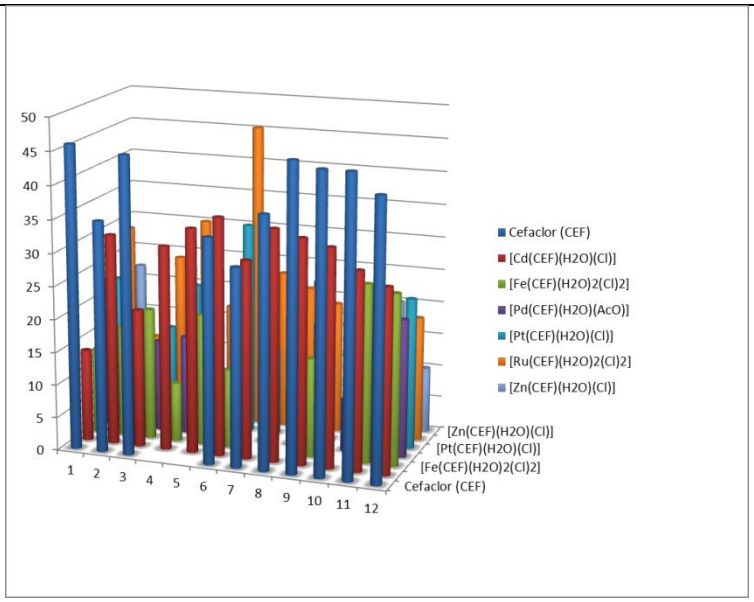

Figure 7: Biological diagram of CEF and metal compounds (1:Candida albicans, 2: Staphylococcus aureus, 3: Escherichia coli, 4: Klebsiella pneumoniae, 5: Bacillus cereus, 6: Kluvyeromyces fragilis, 7: Mycobacterium smegmatis, 8: Bacillus megaterium, 9: Pseudomonas aeruginosa, 10: Enterococcus cloacae, 11: Micrococcus leteus, 12: Saccharomyces cerevisiae).

The synthesized compounds were found to have remarkable bacterial and fungicidal properties: it is however interesting that the biological activity gets enhanced on undergoing complexation with the metal ion. From the structure point of view of the prepared compounds with their effects on microbial tested, it is clear that formation of the chelate derivatives in the 1:1 molar ratio (M:L) sometimes increase the biological activity as appeared from the (**I**) compound. Especially, while the CEF did not show any antibacterial effect against the *Klebsiella pneumoniae* and *Bacillus megaterium* bacteria, all compounds (expect (**6**) compound) have antibacterial effects these bacteria. Inhibition zones are 31 and 34 for *Klebsiella pneumoniae* and *Bacillus megaterium*, respectively. Moreover, enhanced activities of the metal-based drugs derivatives compared to the free drug material may be due to the chloride ion around the central metal ion arising from chelation in 1:1 molar ratio (M:L). Such an increased activity for the metal chelates as compared to the CEF can be explained on the basis of chelation theory[22].Chelation considerably reduces the polarity of the metal ion because of the partial sharing of its positive charge with the donor groups and possible p-electron delocalization over the chelate ring. Such chelation could increase the lipophilic character of the central metal atom, which subsequently favors the permeation through the lipid layer of cell membrane. The mode of action of the compounds may involve the formation of the hydrogen bond through the primer and secondary amines, thiol, β-lactam oxygen and free carbonyl oxygen groups with the active centers of the cell constituents resulting in the interference with normal cell process.

Conclusion

The synthesis and characterization of six new CEF to compound with Cd(II), Pt(II), Pd(II), Zn(II), Fe(III), and Ru(III) have been synthesized. In all these compounds, CEF is on deprotonated mode and acts as bidentate drug material bound to the metal ion through the carboxylate oxygen and nitrogen of β-lactam ring. A comprehensive electrochemical and spectrophotometric study has been presented and the compound formation conditions for obtaining the synthesized compounds have been demonstrated. The spectral results revealed complexation sites. The redox behavior of (**I**), and the pH, scan rate and solvent mixture effects of the compound have also been presented. The possible complex formation reaction that may occur between metal ions and CEF under investigation may indicate a possible effect of administrating this antibiotic with multivitamins that included trace elements. Possible interactions between metal and CEF as a metal-based drug have explained with the help of UV-Vis, IR, mass and electrochemical techniques.

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References

[1]. Gringauz A (1997). Introduction to medicinal chemistry 216: 552-557.
[2]. Abo El-Maali N, Osman AH, Aly AAM, Al-Hazmi GAA (2005). Bioelectrochemistry65: 95-104.
[3]. Meyers BR (2000). Clin Ther. MD, Clinical Therapeuticsv22:154-166.
[4]. Patel MN, Chhasatia MR, Dosi PA, Bariya HS, Thakkar VR. (2010) Polyhedron 29: 1918-1924.
[5]. Golcu A (2014). Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry 44: 1509–1520.
[6]. Chohan ZH (1991). Chemical and Pharmaceutical Bulletin 39: 1578-1580.
[7]. Dimitrovska A, Andonovski B, Stojanoski K (1996). International Journal of Pharmaceutics 134: 213-221.
[8]. Demirezen N, Tarinc D, Polat D, Cesme M, Golcu A, Tumer M (2012). Spectrochim Acta Part A, 94: 243-255.
[9]. Muslu H, Golcu A, Tumer M, Ozsoz M (2011). Journal of Coordination Chemistry 64: 3393-3407.
[10]. Muslu H, Golcu A, Ozkan SA (2010). Current Analytical Chemistry 6: 299-309.
[11]. Cesme M, Golcu A, Dolaz M, Tumer M, Zengin H, Ozkan SA (2012). Letters in Organic Chemistry 9: 35-44.
[12]. Golcu A (2006). Transition Metal Chemistry 31: 405-412.
[13]. Golcu A, Yucesoy C, Serin S (2004). Synthesis and reactivity in inorganic and metal-organic chemistry 34: 1259-1275.
[14]. Çesme M, Golcu A, Demirtas I (2015). Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 135: 887–906.
[15]. Avcıoglu VM, Golcu A (2015). Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry45: 581–590.
[16]. Efthimiadou EK, Karaliota A, Psomas G (2007). Inorganica Chimica Acta 360:4093.
[17]. Tarushi A, Efthimiadou EK, Christofis P, Psomas G (2007). Inorganica Chimica Acta 360: 3978-3986.
[18]. Nakamoto K. (1970). 2nd Edn. Wiley Interscience New York, 48: 419.
[19]. Bellamy L (1971). The infrared spectra of complexes molecules 3rd Edn. Jhon wiley New York.
[20]. Golcu A, Tumer M, Demirelli H, Wheatley, RA (2005). Inorg Chim Acta 358: 1785-1797.
[21]. Kemlo JA, Sheperd TM (1977). Chem Phys Lett 47: 158-162.
[22]. Ozkan SA, Uslu B, Zuman P (2004). Analytica Chimica Acta 501: 227-233.