Bulletin of Faculty of Science, Zagazig University (BFSZU)
e-ISSN: 1110-1555
Volume-2023, Issue-3, pp-151-161 http
Research Paper DOI: **10.21608/bfszu.2023.190224.1243**

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Biological investigations and spectroscopic studies of some new pregabalin and 2,2'-bipyridine metal complexes

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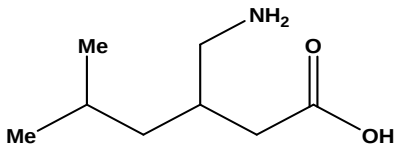
***ABSTRACT*: In this study the mononuclear complexes of Cu(II), Zn(II), Zr(IV) and Cd(II) were synthesized by the reaction of antiepileptic pregabalin (Preg) in the presence of 2,2'-bipyridine (Bipy) with molar ratio 1:1:1. The coordination of the two ligands toward metal ions was informed by using elemental analysis, FT-IR, UV-Vis., ^{1}H NMR, XRD, thermal analyses (TG-DTG), molar conductance and magnetic moment. FT-IR and UV-Vis. spectra proved that Preg acts as a bidentate ligand chelated to the metal ions via the oxygen atom of the carboxylic group and nitrogen atom of the amino group and Bipy chelated through the two nitrogen atoms forming octahedral complexes. The thermodynamic parameters (Ea, ΔH*, ΔS* and ΔG*) were calculated by using Coats-Redfern and Horowitze-Metzger method from TG-DTG curves. The antimicrobial activity for all compounds against various species of bacteria and fungi was assayed. Results showed that some metal complexes showed more biological efficiency than the parent ligands.**

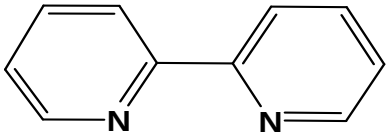
KEYWORDS: pregabalin ; 2,2'-bipyridine ; metal complexes

Date of Submission: 21-02-20232 Date of acceptance: 15-03-2023

I. INTRODUCTION

Pregabalin (Preg), is a pharmaceutical compound (lyrica) known as (S)-3-(aminomethyl)-5-methylhexanoic acid, the chemical structure is shown (Scheme 1A), it's regarded highly soluble since it dissolves in water, basic or acidic aqueous solutions, and it's also extremely permeable (**Lauria-Horner et al., 2003)**. Preg was recently approved and marketed as an antiepileptic medication, it's also been recognized to treat a variety of central nervous system disorders, painful diabetic peripheral neuropathy, lately for anxiety disorders and become more often used in clinical studies due to the greater frequency with which cancer pain is treated (**Taylor et al., 2007 and Hamandi et al., 2006)**. In a chemical sense, it is binds to an alpha-2-delta (α2–δ) ligand, which is responsible for its analgesic and anticonvulsant effects (**Ragavendran et al., 2007**; **Rose and Kam, 2002)**. Preg is rapidly absorbed and exhibits linear pharmacokinetics after oral administration with a relatively short half-life (approximately 6 hours) and in humans, it undergoes insignificant metabolism since, the major metabolite component for it is one of its derivative (N-methylated), approximately 90% of a dose is recovered in the urine as unchanged drug with regular renal function (**Bockbrader et al., 2010; Randinitis et al., 2003**). Literature is included in the survey supported that, Preg coordinated as monodentate or bidentate through one or two the oxygen atom of -COOH (**Shahabadi et al., 2019; Mahmoud et al., 2020**), or by one O atom of -COOH and N atom of -NH_2 (**Mahmoud et al., 2020)**. Bipy (Scheme 1B) continues to be utilised as a scaffold in a hetero organic compound through the two N atoms, creating compounds with a variety of metals (**Chen, 2008; Walsh, 2006)**. Now, our purpose to examine the empact of Cu(II), Zn(II), Zr(IV) and Cd(II) on the efficiency of prepared new complexes of Preg and Bipy and to characterize their structures we executed elemental analyses, IR, molar conductivity, UV-Vis., magnetic susceptibility measurements, ^{1}H NMR, XRD and thermal analyses and finally, we assessed the biological activity.





(A) (B)

Scheme 1: (A) Preg and (B) Bipy.

II. MATERIALS AND METHODS

2.1. Materials

The chemical reagents were chosen with no additional purifying procedures. Preg was gained from DBK pharmaceutical company whereas the solvents, Bipy, $Cu(NO_3)_2.3H_2O$, $ZnCl_2$, $ZrO(NO_3)_2$, $Cd(CH_3COO)_2.2H_2O$, KOH, $AgNO_3$, $FeSO_4$ were obtained from Aldrich and Fluka Chemical Co.

2.2. Synthesis of metal complexes

The dark green solid complex $[Cu(Preg)(Bipy)(H_2O)_2]NO_3.H_2O$ (1) was obtained by mixing 1 mmol (0.159 g) of Preg with 1 mmol (0.055 g) of KOH and 1mmol (0.155 g) of Bipy and 1 mmol (0.241 g) of $Cu(NO_3)_2.3H_2O$ by using the ethanol as a solvent. For 6 hours, the mixture was refluxed, filtered and the obtained solid washed and dried under vacuum over $CaCl_2$. White $[Zn(Preg)(Bipy)(H_2O)_2]Cl.2H_2O$ (2), off-white $[ZrO(Preg)(Bipy)(H_2O)]NO_3.2H_2O$ (3) and white $[Cd(Preg)(Bipy)(H_2O)_2]CH_3COO$ (4) complexes were gained in the same manner using $ZnCl_2$, $ZrO(NO_3)_2$ and $Cd(CH_3COO)_2.2H_2O$, respectively, with a molar ratio of 1:1:1:1Preg:KOH:Bipy:M.

2.3. Physical techniques

The IR spectra were estimated with IR-FT spectrophotometer (460 Plus) in the 4000-400 cm^{-1} range. By using a Perkin Elmer 2400 elemental analyzer was made for the C, H, and N analyses. Thermogravimetry and complexometric titration methods were used to evaluate the metal percent (**El-Shwiniy and Sadeek, 2018**). GBC Savantaa atomic absorption analysis was employed to obtain the assay of each metal. A CONSORT K410 was utilized to detect the conductivity of all compounds at 10^{-3} M. The melting points were obtained by a Buchi device. The Agilent Cary was employed to record electronic spectra, while Varian Mercury VX300 NMR spectrometer needed to analyze ^1H NMR spectra. On a Sherwood scientific magnetic equilibrium, the effective magnetic susceptibilities were assessed. TG and DTG values were represented using a Shimadzu TG-50H with N_2 atmosphere at ambient temperature.

2.4. Biological activity

Through the filter paper disc method, the biological activity of the compounds was examined against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis and Salmonella typhi* and against *Aspergillums niger* and *Aspergillums terreus* (**Beecher and Wong, 1994**). The nutrient agar media for antibacterial (20 gm agar, 3 gm beef extract, 5 gm peptone) and for antifungal (0.1% K_2HPO_4, 001% $FeSO_4$, 2% Agar) were prepared, cooled, seeded with 5 mm diameter holes of the desired microorganisms in 0.1 ml petri-dishes (**Fallik et al., 1993**). The compounds dissolved in DMF 10^{-3} M. These plates were cultured at 37 °C - 20 h for bacteria and 30 °C - 7 days for fungi. The activity was determined by measuring the inhibition zone diameter (mm) for the compounds and also for ampicillin, gentamicin and colitrimazole as standard. The activity index was getting using

$$\text{Activity Index \%} = \frac{\text{diameter zone for test compound}}{\text{diameter zone for standard compound}} \times 100$$

III. RESULTS

Preg interacts with Cu(II), Zn(II), Zr(IV) and Cd(II) in presence of Bipy forming monomeric complexes which were isolated as stable solids, characterized according to their elemental analysis, vibrational and electronic spectra, hydrogen proton, X-ray diffraction and their thermal analysis. According to the obtained data, the chelation of metal ions with Preg and Bipy ligands were proposed. Preg attached with the metal ions through O and N atoms of their carboxylic and amino groups, respectively, but Bipy coordinated through the two N atoms. The metal ions have been completed the coordination number by two H_2O molecules for Cu(II), Zn(II) and Cd(II) complexes and one H_2O molecule for Zr-complex.

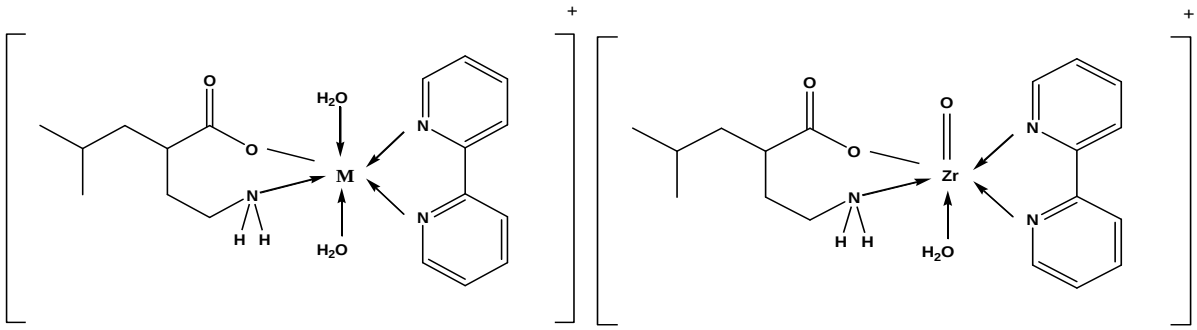
Table 1: Elemental analysis and physico-analytical data for Preg, Bipy and their metal complexes.

Compounds Formula and M.Wt.	Color Yield (%)	M.P.(°C)	Calc. (Found) (%)					Λ Ω cm^2 mol^{-1}
			C	H	N	M	Cl	
(**Preg**), ($C_8H_{17}NO_2$), 159.00	White	183	60.38 (60.21)	10.69 (10.61)	8.81 (8.77)	-	-	4.10
(**Bipy**), ($C_{10}H_8N_2$), 156.20	White	70	76.82 (76.38)	5.12 (5.01)	17.92 (17.39)	-	-	4.12
(1), ($CuC_{18}H_{30}N_4O_8$), 493.76	Dark green 91.23	310	43.79 (43.70)	6.08 (6.01)	11.35 (11.28)	12.87 (12.81)	-	65.41
(2), ($ZnC_{18}H_{32}N_3O_6Cl$), 487.06	White 87.79	295	44.39 (44.32)	6.57 (6.51)	8.63 (8.57)	13.43 (13.38)	7.28 (7.22)	70.84
(3), ($ZrC_{18}H_{30}N_4O_9$), 537.41	Off-white 89.44	340	40.23 (40.17)	5.58 (5.51)	10.42 (10.39)	16.97 (16.91)	-	63.13
(4), ($CdC_{20}H_{31}N_3O_6$), 521.65	White 85.55	260	46.05 (45.97)	5.94 (5.90)	8.06 (7.98)	21.55 (21.45)	-	84.26

Some physical properties of these complexes (color, melting points and molar conductivities) were shown in Table 1. The conductance measurements in 10^{-3} DMF solution were observed in 63.13-84.26 Ω cm^2 mol^{-1} range, proving that the complexes are electrolytes (**Geary, 1971**; **Sadeek et al., 2016; Vogel, 1987)**. These results were supported with the microanalysis data, which referred to that chloride, acetate and nitrate identified as counter ions. The copper complex was suggested that has a paramagnetic nature at room temperature, with magnetic moment 1.7 B.M in agreement with these reported for one unpaired electron d^9-systems.

3.1. FT-IR spectra

The infrared spectra of free Preg, Bipy and their metal complexes are given in Figure S1 and the assignments of the well-defined characteristics bands in Table 2. The spectra of the studied compounds characterized by vibrational peaks due to υ(O-H), υ(N-H), υ(NH_3^+), $\upsilon_{as}(COO^-)$, $\upsilon_s(COO^-)$, δ(N-H) and υ(C=N). All these bands undergo shift in their absorption due to the changes in the electronic density distribution among the aromatic ring, aliphatic chains and the attached function groups as a consequence of the proposed chelation in the metal complexes **(Mahmoud et al., 2020**). Preg is recognized to occur in the free state in the form of zwitterion, which contributes to extended hydrogen bonding between (NH_2) and (COOH). The spectrum of Preg has stretching bands at 3456 and 2954 cm^{-1}, assigned to υ_{as}(N-H), υ_s(N-H), respectively of NH_2, while its bending band δ(N-H) was observed at 1550 cm^{-1}. The stretching vibration of υ(N-H) characteristic for the cationic amino group NH_3^+ in free Preg observed at 2206 cm^{-1} , this band appeared when amino group was converted to ammonium structure, disappeared in the spectra of all complexes (**Cao and Fischer, 2000)**. The deprotonation of NH_3 and subsequent binding to the metal as neutral group NH_2, must cause an increase in the ν(NH_2) of free amino acids therefore, the existence of split bands in the complexes spectra at 3348-3070 cm^{-1} and what confirms the nitrogen of the amino group is participated in coordination we observe medium to strong deformation bands appeared in the 1550-1573 cm^{-1} range (**Bukietyńska et al., 2003; Zidan et al., 2000)**. $\upsilon_{as}(COO^-)$ and $\upsilon_s(COO^-)$ stretching vibrations are observed in the spectrum of Preg at 1643 and 1388 cm^{-1} , respectively (**Harikrishnan and Bhoopathy, 2014; Sinha et al., 2013)**. The complexes spectra exhibit these bands at different frequencies and intensities, $\upsilon_{as}(COO^-)$ obtained at 1658-1610 cm^{-1} and $\upsilon_s(COO^-)$ at 1419-1381 cm^{-1}, with $\Delta\nu = \nu_{as}(COO^-)-\nu_s(COO^-)$ >200 cm^{-1} (Table 2), which is an evidence of the monodentate character of the carboxylate (**Abdel-Rahman et al., 2016; Abdel-Rahman et al., 2017)** . Bipy band ν(C=N) at 1578 cm^{-1} observed shifts in 1587-1503 cm^{-1} range showing that the two N atoms were chelated (**Abd-El-Hamid et al., 2017)**. The new bands with different strengths for all complexes were observed for ν(M-O) and ν(M-N) at 660 and 501cm^{-1} for Cu-complex , at 640 and 516 cm^{-1} for Zn-complex, at 655 and 432 cm^{-1} for Zr-complex and for Cd-complex were 648 and 468 cm^{-1}, respectively.



M= Cu(II), Zn(II) and Cd (II)

Scheme 2: The coordination mode of Preg, Bipy with Cu(II), Zn(II), Zr(IV) and Cd (II) ion metals.

Table 2: Selected infrared transmitence, wavenumber and tentative assignments for Preg, Bipy and their metal complexes.

Compounds	ν(O-H); H_2O ν(NH_2)	ν(NH_3^+) ν(NH)	$\nu_{as}(COO^-)$	δ(NH)	ν(C=N)	$\nu_s(COO^-)$	Δ $\nu(\nu_{as}-\nu_s)_{COO^-}$	ν(Zr=O)	ν(M-O) and *ν*(M-N)
Preg	3456mbr	2206m 2954w	1643m	1550m	-	1388m	-	-	-
Bipy	3440mbr	-	-		1578ms	-	-	-	-
(1)	3387mbr	3263m 3181w 3104w 3070w	1610w	1566s	1511w	1381vs	229	-	660w, 501m
(2)	3464mbr	3325w 3255w 3170sh	1623w	1573s	1542w	1404m	219		640m,516w
(3)	3471mbr	3348m 3264m	1658m	1558m	1503w	1381s	277	825w	655m,432w
(4)	3471mbr	3294w 3248w 3163sh	1628w	1550m	1587sh	1419m	209		648m, 486w

Keys: s=strong, w=weak, m=medium, br=broad, *ν*=stretching, sh=shoulder.

3.2. UV-Vis. spectra

The electronic spectra of the ligands and their complexes at 200-800 nm were measured (Figure S2) using DMSO-d_6 as a solvent to gain data on all assumptions of ligand structure. The results showed that Preg and Bipy were absorbed at (295, 320, and 340) nm and (284 and 347) nm, respectively, that can be assigned to transitions π-π* and n-π* (Table 3) (**Gamil et al., 2020; Appleton et al., 1985)**. The complexes spectra displayed additional bands in the region 422-552 nm that can associated to the ligand-to-metal charge transfer have been revealed by the all complexes (**Sadeek, 2005)**, illustrating that the ligands coordinate to the metal ions. The band for Cu(II) complex refered to $^2B_{1g} \longrightarrow {}^2E_g$ transition seen at 623 nm (**Sadeek and El-Shwiniy, 2010)** with magnetic moment (1.70 B. M.) which is very similar to the predicted spin value (1.73 B. M.) for single electron. In Zn(II) and Cd(II) complexes, the transitions d-d could not be noticed in the visible zone, as predicted (**Yadav and Singh 2011; Das et al., 2006)**.

Table 3: UV-Vis. spectra for Preg, Bipy and their metal complexes

Compounds	π-π*and n-π* transitions, λmax (nm)	ν (cm^{-1})	Ligand-metal charge transfer λmax (nm)	ν (cm^{-1})
Preg	295, 320, 340	33898, 31250, 29411	-	-
Biby	284, 347	41152, 28571	-	-
(1)	236, 253, 271, 303	42372, 39525, 36900, 33003	455, 530	21978, 18867
(2)	242, 251, 272,301	41322, 39840, 36764, 33222	424	23584
(3)	260, 275	38461, 36363	537	18621
(4)	242, 262, 271	, 3690041322, 38167	422,552	23696, 18115

3.3. ^{1}H MNR studies

^{1}H NMR spectra of the examined compounds were recorded in Figure S3 and listed in Table 4. The peak for COOH at approximately 11–12 ppm could not be seen in the spectrum of Preg, but a band for $–NH_3^+$ group was noticed at 7.4 ppm which on deutration this signal is exchanged with D_2O, indicating the presence of Preg in zwitterion state **(Mahmoud et al., 2020**). In Bipy's ^{1}H NMR spectrum, the aromatic ring proton displayed peaks from 7.12 to 8.79 ppm (**Abd El-Hamid et al., 2019)**. The ^{1}H NMR spectra of all complexes documented that the peak responsible for $–NH_3^+$ group was disappeared. A major movement in the location of the proton of amine group ($-NH_2$) to 1.69-1.79 ppm implies that Preg is coordinated through its N atom of amino group and carboxylate oxygen atom (**El-Shwiniy and Sadeek, 2018)**. Complexes spectra illustrate additional peaks in the 3.10-3.82 ppm range can be confirming the existence of water molecules (**El-Shwiniy and Sadeek, 2018)**.

Table 4: ^{1}H NMR values (ppm) and tentative assignments for Preg, Bipy and their metal complexes.

Preg	Bipy	(1)	(2)	(3)	(4)	Assignments
2.23	-	1.69	1.79	1.77	1.78	**δH, $-NH_2$**
2.77-3.40	-	2.78	2.8	2.97	3.11	**δH, $-CH_2$ aliphatic**
-	-	3.82	3.30	3.31	3.32	**δH, H_2O**
7.42	-	-	-	-	-	**δH,$-NH_3$**
-	7.12-8.79	7.42-8.41	7.42-8.71	7.13-8.05	7.46-8.70	**δH, -CH aromatic**
-	-	-	-	-	-	**δH, -COOH**

3.4. Thermal analysis

The thermal degradation pathway of metal complexes is described by the TG curves, which are displayed in Figure S4 and summarized in Table 5. Preg decomposes in a single step at temperature 211 ^{o}C with weight loss 99.12% referred to $4C_2H_2+NH_3+2H_2O+H_2$. The degradation of Bipy was occurred in one step at temperature 164 °C with weight loss 99.64% (**Dendrinou-Samara et al., 2001; Elshafie et al., 2020**). TG thermograms of the four complexes exhibit two main steps. The first one occurs at 90, 85, (89,153) and 193 ^{o}C with a weight loss of 3.61, 7.33, 9.97 and 29.87 %, corresponding to loss of H_2O, $2H_2O$, $3H_2O$ and $4C_2H_2+C_2N_2$, respectively. The second occurs at (204,268), (215,295), (318) and (295,374) ^{o}C with a weight loss of 77.95, 76.86, 73.11 and 45.55 %, corresponding to the loss of $8C_2H_2+CO_2+3NH_3+2NO_2+3H_2$, $8C_2H_2+NO_2+CO_2+HCl+2NH_3+2.5H_2$, $8C_2H_2+2CO+2NO_2+2NH_3+H_2$ and $5C_2H_2+NH_3+5H_2O$ and the final thermal products obtained are CuO+C, Zn+C, Zr and CdO, respectively.

Table 5: The maximum temperature T_{max} (^{o}C) and weight loss values of the decomposition stages for Preg, Bipy and their metal complexes.

Compounds	Decomposition	T_{max}(^{o}C)	Weight loss (%)		Lost species
			Calc.	Found	
Preg	First step Total loss	211	99.34 99.34	99.12 99.12	$4C_2H_2+NH_3+2H_2O+H_2$
Bipy	First step Total loss	164	100 100	99.64 99.64	$4C_2H_2+C_2N_2$
(1)	First step Second step Total loss Residue	90 204, 268	3.65 77.81 81.46 18.54	3.61 77.95 81.56 18.44	H_2O $8C_2H_2+CO_2+2NH_3+2NO_2+3H_2$ CuO+C
(2)	First step Second step Total loss Residue	85 215, 295	7.39 76.72 84.11 15.89	7.33 76.86 84.19 15.81	$2H_2O$ $8C_2H_2+NO_2+CO_2+HCl+2NH_3+2.5H_2$ Zn+C
(3)	First step Second step Total loss Residue	89, 153 318	10.05 72.98 83.03 16.97	9.97 73.11 83.08 16.92	$3H_2O$ $8C_2H_2+2CO+2NO_2+2NH_3+H_2$ Zr
(4)	First step Second step Total loss Residue	193 295, 374	29.94 45.44 75.38 24.62	29.87 45.55 75.42 24.58	$4C_2H_2+C_2N_2$ $5C_2H_2+NH_3+5H_2O$ CdO

To evaluate how the complexes' structural features affect their thermal behavior, the heat activation of the decomposition stages were estimated from the TG and DTG thermo grams by using Coats-Redfern (**Coats and Redfern, 1964)** and Horowitz-Metzeger methods (**Horowitz and Metzger, 1963)**. Thermodynamic parameters of the decomposition stages for the complexes are given in Table 6 and Figure S5. The activation energies high values of the complexes which found from 39.40 to 167.44 kJ/mol, demonstrate their thermal stability (**Omar, 2009)**.

Table 6: Thermal behavior and kinetic parameters for Preg, Bipy and their metal complexes.

Compounds	Decomposition range (K)	T_s (K)	Method	Parameter					R^a	SD^b
				E^* (kJ/mol)	A (s^{-1})	ΔS^* (kJ/mol.K)	ΔH^* (kJ/mol)	ΔG^* (kJ/mol)		
Preg	451-574	484	CR HM	72.87 70.30	2.18×10^{5} 2.32×10^{5}	-0.1467 -0.1462	68.84 66.28	139.86 137.05	0.992 0.987	0.1342 0.1703
Bipy	315-554	437	CR HM	75.70 95.74	6.53×10^{6} 2.79×10^{9}	-0.1176 -0.0672	72.06 92.11	123.46 121.49	0.998 0.998	0.094 0.106
(1)	422-646	541	CR HM	75.49 112.32	1.34×10^{6} 5.36×10^{8}	-0.1325 -0.0827	70.99 107.82	142.70 152.58	0.987 0.982	0.1377 0.1595
(2)	450-516	488	CR HM	39.40 81.87	6.07×10^{2} 3.98×10^{6}	-0.1957 -0.1226	35.34 77.81	130.85 137.66	0.983 0.976	0.1417 0.1675
(3)	318-512	426	CR HM	39.40 62.38	6.07×10^{2} 3.06×10^{5}	-0.1945 -0.1428	35.86 58.84	118.75 119.69	0.983 0.976	0.1417 0.1675
	512-643	591	CR HM	131.27 167.44	9.35×10^{9} 6.03×10^{12}	-0.0597 -0.0059	126.35 162.52	161.64 166.03	0.991 0.989	0.1079 0.1169
(4)	369-504	466	CR HM	65.27 93.97	9.58×10^{5} 2.95×10^{8}	-0.1341 -0.0864	61.40 90.09	123.89 130.39	0.989 0.985	0.1222 0.1409
	504-668	569	CR HM	146.21 152.81	2.61×10^{12} 1.00×10^{12}	-0.01257 -0.02050	141.48 148.07	148.63 159.74	0.994 0.993	0.0967 0.1073

a=correlation coefficients of the Arrhenius plots and b=standard deviation

3.5. X-ray diffraction

The XRD patterns of Preg, Bipy and their metal complexes were stated over 2θ at scale (0-60) as shown in Figure 1 and Table 7. The diffraction of Preg shows peaks at 2θ = 9.89, 19.43, 25.02, 35.99 and 39.01 and Bipy reveals peaks at 2θ= 16.99, 20.63, 26.66 and 34.4. Cu-complex indicated peaks at 5.42, 11.89, 13.14, 19.82, 23.76, 26.11, 27.73 and 45.78. The patterns of Zn-complex exhibited peaks at 4.33, 6.06, 15.87, 18.33, 19.08, 22.35 and 28.66. Zr-complex forms peaks at 5.98, 11.63, 16.43, 17.56, 18.95 and 22.17, and for Cd-complex gives peaks at 6.03, 11.71, 16.48, 17.64, 19.05, 21.32, 22.37 and 22.79. Using Scherer equation (1), the crystalline sizes values of the synthesized compounds demonstrate the nano sized structures except Zr-complex.

$$d = \frac{k.\lambda}{\beta.\cos\theta} \qquad (1)$$

Where d is the particle diameter, k is the Scherer constant, λ is the X-ray wavelength, θ is the angle and β is FWHM of the diffracted peak.

Table 7: The average crystallite size of Preg, Bipy and their metal complexes estimated from XRD pattern.

Compounds	2θ (°)	d value (A°)	Full width at half maximum (FWHM)	Average crystallite size (nm)
Preg	9.89	8.94	0.0787	101.31
Bipy	16.99	5.22	0.1181	68.01
(1)	11.89	7.45	0.0984	81.17
(2)	6.06	14.59	0.0984	80.84
(3)	5.98	14.79	0.0787	101.08
(4)	6.03	14.66	0.1378	1.01

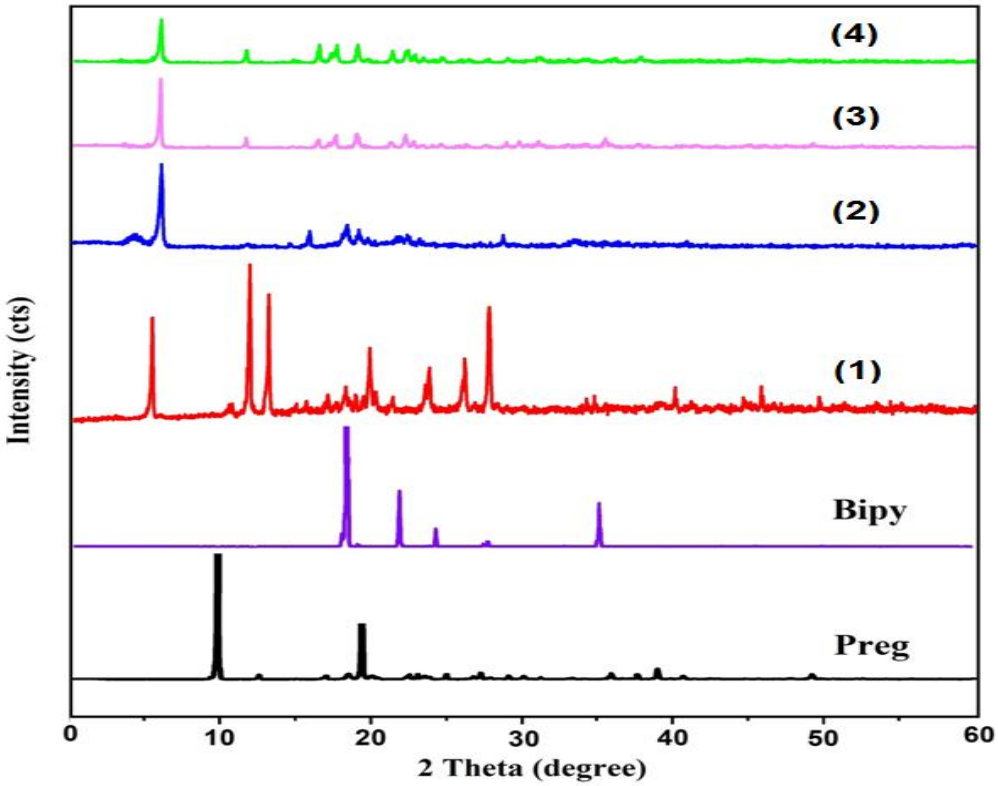


Figure 1: XRD pattern for Preg, Bipy and their metal complexes.

3.6. Antimicrobial efficiency

Against gram-positive and negative bacteria and two fungal forms, the ligands and the investigated complexes were assessed for their antibacterial properties with data shown in Table S1 Figure 2 (**Rehman et al., 2008)**. Although the tested compounds have no noticeable antifungal activity, they were implied to have outstanding bactericidal characteristics. For Cu-complex, it was very highly significant against *S. typhi* and highly significant against *B. subtillis*. Zn-Complex, showed very highly significant against *S. typhi*, while Zr-complex has very highly significant against it and the two complexes were significant against the other bacterial species. Cd-complex showed very highly significant against *B. subtillis* and was highly significant against *S. aureus* and *E. coli*, and also is more effective than all other compounds as shown in Figure 3. The order of compounds in case of *S. aureus*: Cd(II)>Zn(II)>Zr(IV)>Cu(II)>Bipy>Preg, order of *B. subtillis*: Cd(II)>Cu(II)>Zr(IV)>Zn(II)>Bipy>Preg, order of *E.coli*: Cd(II)>Zn(II)>Cu(II)>Bipy>Zr(IV)-Preg, order of *Salm. typhi*: Zn(II)>Cu(II) >Zr(IV)> Cd(II)>Bipy>Preg.

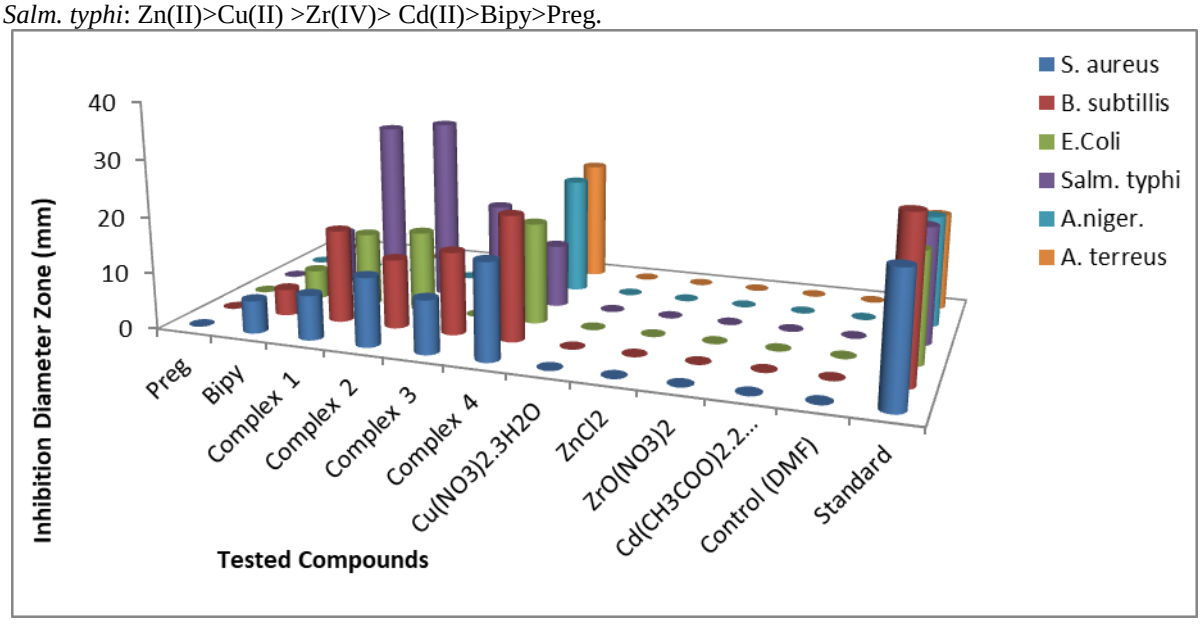


Figure 2: Statistical representation for biological activity for Preg, Bipy and their metal complexes.

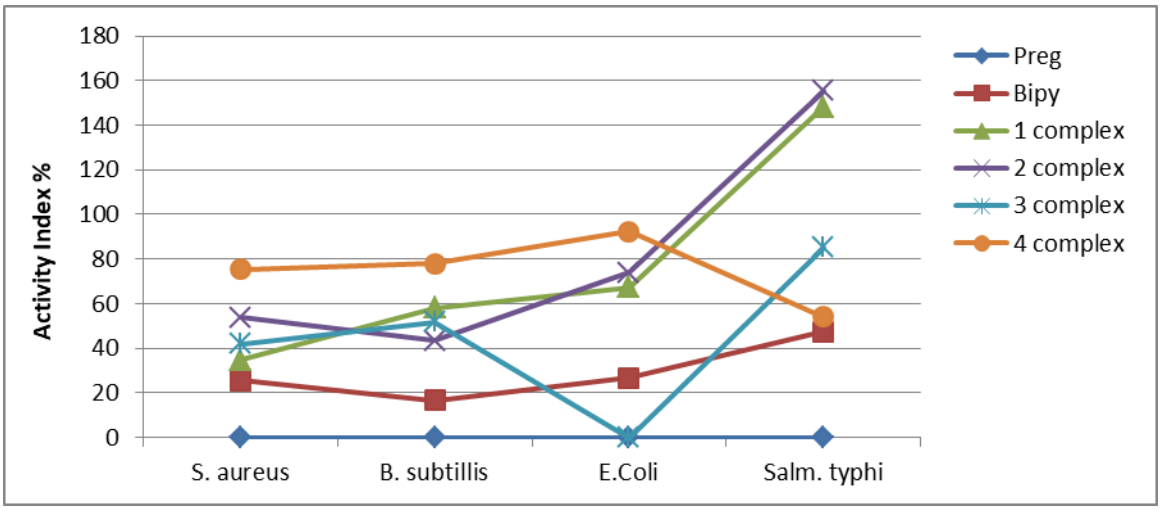


Figure 3: Activity index % for Preg, Bipy and their metal complexes.

4. Conclusions

Preg serves as bidentate chelate with two donating center O of -COOH and N atom of $–NH_2$, while Bipy chelates through pyridyl nitrogen atoms to synthesize the four complexes. Various spectroscopic techniques were applied to further recognise the metal complexes' structure; this investigation supports coordination number of all complexes is 6 and identifies the molecular arrangement. The Coats-Redfern and Horowitz-Metzeger techniques were utilized to assess the kinetic properties of the complexes' thermal degradation phases. At inhibiting microbial growth, Cd-complex compared to other complexes is considered more effective.

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