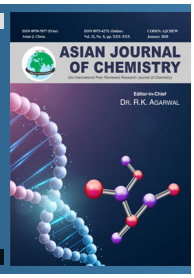
Asian Journal of Chemistry; Vol. 32, No. 6 (2020), 1266-1272

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22472



Novel Mixed Complexes Derived from Benzoimidazolphenylethanamine and 4-(Benzoimidazol-2-yl)aniline: Synthesis, Characterization, Antibacterial Evaluation and Theoretical Prediction of Toxicity

LOTFI M. AROUA[1,2,*]

[1]Department of Chemistry, College of Science, Qassim University, Campus University, King Abdulaziz Road, P.O.Box: 6644, Buraydah, Qassim, Kingdom of Saudi Arabia
[2]Laboratory of Organic Structural Chemistry & Macromolecules, Department of Chemistry, Faculty of Sciences of Tunis, Tunis El-Manar University, El Manar I 2092, Tunis, Tunisia

*Corresponding author: E-mail: aroua.lotfi@yahoo.com

Received: 30 September 2019; *Accepted*: 13 November 2019; *Published online*: 30 May 2020; AJC-19868

Benzoimidazolphenylethanamine (BPE) has been synthesized using condensation reaction from *o*-phenyldiamine and L-phenylalanine. Some metal complexes have been synthesized from 4-(benzoimidazol-2-yl)aniline, benzoimidazolylphenylethanamine and cadmium(II), tin(II), copper(II) and nickel(II) metal in a molar ratio (1:1:1). All new metal complexes were characterized by spectroscopic data of FTIR, UV-visible electronic absorption, X-ray powder diffraction and thermal analysis. Spectra analysis of the mixed metal complexes showed the coordination of ligands to the metal ions *via* nitrogen atoms. The XRD powder showed that metal complexes have a monoclinic system. The preliminary tested *in vitro* antibacterial activities of Sn(II) complex was assayed against four bacterial isolates namely *Micrococcus luteus, Staphylococcus aureus* as Gram-positive, *Pseudomonas aerugmosa* and *Escherichia coli*.

Keywords: Benzoimidazolylphenylethanamine, Mixed complexes, Thermal stability, Antimicrobial agents.

INTRODUCTION

The heterocyclic contain a nitrogen atom in general and benzimidazole, in particular, has a broad spectrum of biologically active natural products and presents a considerable therapeutic potential [1-6]. Benzimidazole derivatives are an important scaffold that possesses much application especially in pharmaceutical, veterinary and agrochemical fields [7].

Benzimidazole scaffold was especially employed for the treatment of diverse disease including antibacterial, antifungal, antituberculous [8], antimalarial [9], anti-inflammatory, analgesic, antiamoebic [10], antihistamine [11], antiulcer, antioxidant [12,13], antiproliferative [14], antihypertensive [15], antiallergic [16], antikinase and anti-HIV-1 [17]. Some benzimidazoles were evaluated as cholinesterase inhibitors [18,19] and pest medications [20,21]. Many candidates of this family were applied as antitumor and showed activity against several tumor cell lines such as breast cancer, human cells and human lung cancer cells [22-34].

In recent years, benzimidazole and some of its derivatives have emerged to become approved structures in medicinal chemistry with a multitude of drug introduced in the market including antiparasitics (albendazole, mebendazole), antiulcer (omeprazole) and antihypertensives (candesartan & telmisartan), antihistamines (bilastine), anticancer (bendamustine), antiemetics/antipsychotics (droperidol) [35-37].

On the other hand, benzimidazole derived from amino acids was considered as a good intermediate to lead the formation of biologically compounds for the discovery of future drugs. In particular, benzoimidazol phenylethanamine, prepared from L-phenylalanine, are the member of benzimidazole family and have found to be significantly effective against the three Gram-positive bacteria (*Staphylococcus aureus*, *Proteus vulgaris* and *Streptococcus faecalis*) and three strains pneumonia, (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli*) and considered as the most effective antibacterial agents more active than standard gentamycin [35-38].

This is an open access journal, and articles are distributed under the terms of the Attribution 4.0 International (CC BY 4.0) License. This license lets others distribute, remix, tweak, and build upon your work, even commercially, as long as they credit the author for the original creation. You must give appropriate credit, provide a link to the license, and indicate if changes were made.

In addition, 4-(benzoimidazol-2-yl) aniline [39,40] is an efficient intermediates to synthesized a target that have a many biological activities and have been described as heparanase inhibitors [41], suppress key markers of allergy [42]. The insertion of metals into molecular architectures to develop new complexes containing benzimidazole nucleus has been widely described in the literature [43-47]. It has been reported that the presence of metal ions in the complexes manifests generally a better therapeutic efficacy [48,49], similarly affecting their physico-chemical properties [50,51].

In present work, our intention was take account of previously mentioned properties of antibacterial ligands, by grouping the two motifs in one molecule and combining their properties. Here, we present a new way to increase the effectiveness of biologically active molecules. Herein, the synthesis and characterization of some complexes of cadmium(II), copper(II), tin(II) and nickel(II) from 4-(benzimidazole-2-yl)aniline (PBA) and benzoimidazolphenylethanamine (BPE), which could prove be efficacious antibacterial agents.

EXPERIMENTAL

FT-IR spectroscopy was recorded using Thermo-Nicolet-6700 FT-IR spectrometer by the KBr disc technique in the wavenumber range of 4000-400 cm^{-1}. Electronic absorption spectral were carried out in DMSO on a UV-2102 PC Shimadzu spectrophotometer using 1 cm matched quartz cell in the wavelength range 200-900 nm. The ^{1}H & ^{13}C-NMR were recorded on Bruker NMR at 400 MHz and 100 MHz, respectively. The chemical shifts were measured with reference to TMS as internal standard in deuteriated DMSO as the solvent. Simultaneous TGA and DTA analyses were performed employing a Shimadzu DTG-60 instrument using a heating rate of 10 ºC/min in air atmosphere. The average samples weight was 10 mg α-Al_2O_3 was used as a reference material in the DTA measurements. The X-ray powder diffraction patterns of the compounds were recorded an XRD diffractometer Model PW 1710 control unit the (Philips). The anode material was Cu*K*α (λ = 1.54180 Å), 40 K.V 30 M.A Optics: Automatic divergence slit. All reagents employed in the synthesis of different complexes were commercially available amd used without further purification.

Synthesis of 4-benzoimidazolaniline (PBA) L1: A mixture of *o*-phenylenediamine (0.54 g, 5 mmol) and 4-aminobenzoic acid (0.95 g, 7 mmol) was added to 10 mL of toluene. The reaction mixture was gradually heated and the temperature was maintained at 85 ºC for 9 h under magnetic stirring to obtain a solution, which was allowed to cool overnight. The mixture was filtered and washed with ether and then dried to afford 4-benzoimidazolaniline (PBA) in 82 % yield. m.p.: 235-237 ºC, IR (KBr, ν_{max}, cm^{-1}): 3430 (NH benzim); 3350, 3217 (NH_2 aniline); 3061 (CH=C); 1629 (C=N); 1605 (C=C). λ_{max} (nm) = 300. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 5.58 (s, NH_2), 6.63 (d, 2H, aniline), 7.08 (m, 2H, benzim), 7.46 (m, 2H, benzim), 7.79 (d, 2H, aniline), 12.46 (br, NH benzim). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 113.05, 114.14, 123.50, 129.32, 135.78, 151.59, 152.68.

Synthesis of benzoimidazolphenylethanamine (BPE) L2: A mixture of *o*-phenylenediamine (0.54 g, 5mmol) and L-phenylalanine (1.16 g, 7mmol) was added to 10 mL toluene. The reacting mixture was gradually heated and the temperature was maintained at 85 ºC for 9 h under magnetic stirring to obtain a solution which was allowed to cool overnight. The mixture was filtered and washed with ethanol and then dried to afford benzoimidazol phenylethanamine (BPE) in 97% yield. ^{1}H NMR (400 MHz, DMSO-d_6, 400 MHz) δ: 8.23 (s, 1H, NH), 7.63-7.61 (d, 2H, Ar-H), 7.57-7.55 (m, 2H, Ar-H), 7.24-7.21 (m, 5H, Ar-H benzyl), 5.14-5.12 (d, 1H, N*H*$_2$-CH), 4.22-4.17 (m, 1H, CH), 3.12-3.08 (dd, 1H), 3.03-2.98 (dd, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 143.9, 136.6, 134.9, 129.8 (2CH arom), 129.6 (2CH arom), 128.8 (2CH arom), 127.5, 127.2 (2CH arom), 119.5, 56.5, 39.0, 21.7. δ_{max} (nm) = 260, 274, 305. IR (KBr, ν_{max}, cm^{-1}): 3459, 3361 (N-H of NH_2), 3209 (N-H), 3022 (C-H), 1615 (C=N), 1575 (C=C), 749 (Ar-H).

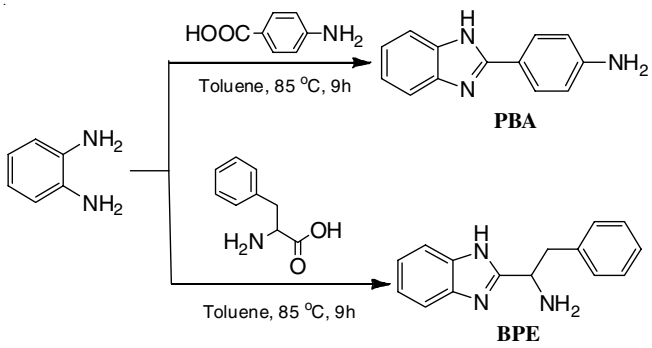
Synthesis of cadmium complex [Cd(PBA)(BPE)I_2] (1): To a solution of cadmium iodide 3.08 g, (8.4 mmol) in 30 mL ethanol was added 1.75 g (8.4 mmol) of PBA in 30 mL ethanol. The reaction mixture was stirred at room temperature for 30 min and then a solution of BPE (2 g, 8.4 mmL in 30 mL water) was added to mixture and heated at 100 ºC for 13 h. The progress of reaction was controlled with TLC (DMF/water: 50/50). At the end of reaction, the reaction mixture was cooled, filtered and the residue washed with ethanol followed by DMF to obtain a beige precipitate. Yield: 80%, m.p.: 265 ºC, m.f.: $C_{28}H_{26}N_6CdI_2$, UV-vis (DMSO); λ_{max} [nm]: 274 . IR (KBr, ν_{max}, cm^{-1}): 3408 (m), 3322 (m), 3243 (m), 3028 (m), 1608 (s), 1581 (s), 1495 (s), 1454 (m), 1384 (s), 1321 (m), 1102 (m), 1074 (m), 1002 (m), 997 (m), 847 (s), 776 (m), 745 (m), 698 (m), 604 (m), 556 (m), 524 (m), 504 (m), 468 (m).

Synthesis of tin complex [Sn(PBA)(BPE)Cl_2] (2): To a solution of stannous chloride 1.6 g, (8.4 mmol) in 30 mL water was added 1.75g (8.4 mmol) of PBA in 30mL ethanol. The reaction mixture was stirred at room temperature for 30 min and then a solution of BPE (2 g, 8.4 mmol in 30 mL water) was added to mixture and heated at 100 ºC for 14 h. The progress of reaction was controlled with TLC (DMF/water: 50/50). At the end of reaction, the reaction mixture was cooled, diluted with ethanol (40 mL), filtered and washed with ethanol and then with DMF to obtain a red precipitate. Yield: 85%, m.p.: 230 ºC; m.f.: $C_{28}H_{26}N_6SnCl_2$. UV-vis (DMSO); λ_{max} (nm): 280, 310, 430. IR (KBr, ν_{max}, cm^{-1}): 3443 (m), 3338 (m), 3224(m), 1601 (s), 1567 (s), 1497 (s), 1411 (m), 1320 (s), 1236 (s), 1168 (s), 1110 (s), 1069 (s), 849 (s), 744 (m), 607 (m) 498 (m), 434 (m).

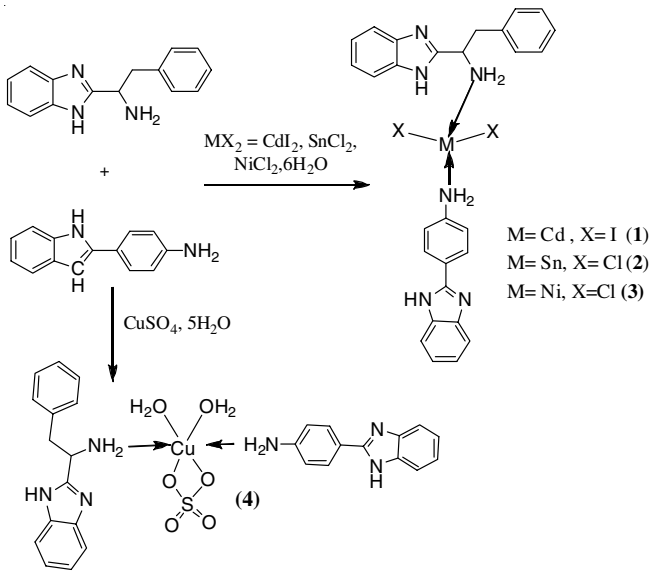
Synthesis of nickel complex [Ni(PBA)(BPE)Cl_2] (3): To a solution of nickel chloride hexahydrate 2 g, (8.4 mmol) in 30 mL water was added 1.75g (8.4 mmol) of PBA in 30 mL of ethanol. The reaction mixture was stirred at room temperature for 30 min and then a solution of BPE (2 g, 8.4 mml in 30 mL water) was added to mixture and heated at 100 ºC for 15 h. The progress of reaction was controlled with TLC (DMF/water: 50/50). At the end of reaction, the reaction mixture was cooled, filtered and the residue washed with ethanol and then with DMF to obtain a grey precipitate. Yield: 82%, m.p.: 345 ºC; m.f. $C_{28}H_{26}N_6NiCl_2$; UV-vis (DMSO); λ_{max} (nm): 272. IR (KBr, ν_{max}, cm^{-1}): 3390 (m), 3351 (m), 3218 (m), 3050 (m), 1589 (m), 1496 (s), 1452 (s), 1396 (s), 1336 (s), 1140 (m), 1060 (s), 817 (s), 765 (s), 747 (m), 725 (m), 655 (s), 597 (m), 544 (m), 479 (s).

Synthesis of copper complex [Cu(PBA)(BPE)SO_4] (4): To a solution of copper sulfate pentahydrate 2.1 g, (8.4 mmol) in 30 mL water was added 1.76g (8.4 mmol) of PBA in 30 mL ethanol. The reaction mixture was stirred at room temperature for 30 min and then a solution of BPE (2 g, 8.4 mmL in 30 mL water) was added to mixture and heated at 100 ºC for 17 h. The progress of reaction was controlled with TLC (DMF/water: 50/50). At the end of reaction, the reaction mixture was cooled, filtered and the residue washed with ethanol and then with DMF to obtain a grey precipitate. Yield: 89%, m.p.: 258 ºC; m.f.: $C_{28}H_{30}N_6O_6CuS$. UV-vis (DMSO); λ_{max} (nm): 272. IR (KBr, ν_{max}, cm^{-1}): 3343 (m), 3243 (m), 3028 (m), 1610 (s), 1535 (m), 1495 (s), 1455 (s), 1382 (m), 1322 (s), 1224 (m), 1113 (m),1102 (m), 1075 (m), 966 (m), 923 (m), 754 (m), 773 (m), 754 (m), 718 (m), 696 (s), 685(m), 673(m), 586 (m), 578 (m), (514), 467 (m), 421 (m).

***in vitro* Antibacterial bioassay:** The preliminary tested *in vitro* antibacterial activities of Sn(II) complex were screened for their antibacterial activity against two Gram-negative (*Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 33787) and two Gram-positive (*Micrococcus luteus* NCIMB 8166 and *Staphylococcus aureus* ATCC 25923) bacterial strains using agar spot method [52]. Aliquots of 20 µL of each samples were spotted on Mueller-Hinton agar plates, which were previously seeded with one of the pathogenic bacteria at a final concentration of 10^6 CFU mL^{-1}. All the assays were carried out in triplicates. The plates were held at 4 ºC for 2 h, so that the tested sample could diffuse into agar and then incubated at 37 ºC for 24 h. After incubation, the plates were examined for measuring the clear inhibition zone around the spot.



Scheme-I: Synthesis of ligands PBA and BPE



Scheme-II: Synthesis of mixed metal complexes

RESULTS AND DISCUSSION

Present approach started with the synthesis of two benzimidazole derivatives *viz*. 4-benzoimidazolaniline (PBA) and benzoimidazolphenylethanamine (BPE) ligands [38] from commercially available *o*-phenylenediamine and respectively 4-aminobenzoic acid and L-phenylalanine using toluene as solvent and the temperature was maintained at 85 ºC for 9 h according to **Scheme-I**. The reaction leads the expected product at 82-97% yields after recrystallization. Advantages associated with this novel, efficient, and simple protocol include, satisfactory product yields and a simple workup procedure.

The mixed metal complexes were synthesized by reacting one equivalent ethanolic solution of PBA, one equivalent of metal(II) salt in the appropriate solvent (ethanol or water) and one equivalent of BPE dissolved in water. All the metal complexes (**Scheme-II**) were characterized by spectroscopic data of FT-IR, UV-visible electronic absorption, thermal analysis and X-ray powder diffraction studies. The reaction started by reacting at room temperature 8.4 mmol of metal halides solution and 8.4 mmol of PBA solution for 30 min and then a solution of 8.4 mmol of PBE solution was added. The mixture was heated gradually and left at 100 ºC for 12-16 h.

The key infrared bands of ligands and their metal complexes were analyzed and examined. The infrared data of both free ligands PBA, BPE and their mixed complexes are given in Table-1. From the IR results, it has been revealed that the ligands PBA and BPE have a principle peak of absorption respectively at ν = 3457 and 3459 cm^{-1} attributed to $\nu(NH_2)$, which is in good agreement with the value of the literature [39-41].

The cadmium and tin mixed complexes showed the presence of this band but it is shifted towards the low frequencies and displays a broad spectrum respectively at 3408 and 3443 cm^{-1}

TABLE-1
VIBRATIONAL ASSIGNMENT WAVENUMBERS (cm^{-1}) OF LIGANDS (PBA), (BPE) AND THEIR MIXED COMPLEXES

Complex	$\nu(NH_2)$		$\nu(N\text{-}H)_{benzim}$ (ligands)	$\nu(N\text{-}H)_{benzim}$ (complex)	ν(C=N)	ν(M-N) (complex)
PBA	3457	3359	3227	–	1660	–
BPE	3459	3361	3229	–	1656	–
[Cd(PBA)(BPE)I_2]	3408	3325	–	3243	1608	468
[Sn(PBA)(BPE)Cl_2]	3443	3338	–	3224	1601	434
[Ni(PBA)(BPE)Cl_2]	–	3351	–	3218	1589	479
[Cu(PBA)(BPE)SO_4·2H_2O]	–	3343	–	3243	1610	436

indicating the implication of amino group of each ligands in the coordination sphere. The same band is not observed in the infrared spectra of both complexes Ni(II) and Cu(II) which indicates the establishment of M-N band with the ligands PBA, BPE and respectively Ni(II) and Cu(II) metal and confirmed the formation of coordination complexes.

In addition, C=N stretching frequencies of azomethine unit appeared at 1660 cm^{-1} for PBA ligand and 1656 cm^{-1} for BPE, which deviates in the metal complexes and reduces at lower frequencies (1608, 1589, 1601, 1610 cm^{-1}) respectively for metal complexes of Cd(II), Sn(II), Ni(II) and Cd(II), this is in good agreement with a previously reported data [53,54]. The appearance of new bands at 468, 434, 479 and 436 cm^{-1}, respectively for Cd(II), Sn(II), Ni(II) and Cu(II) is a further sign of the coordination of ligands with metal ions complex and assigned respectively to metal-nitrogen M-N bond [55]. These bands were absent in ligands spectra, thus confirmed the participation of the nitrogen atoms in the coordination. A new band at 415-402 was appeared and assigned to (M-Cl) for the Sn(II) and Ni(II) complexes [56].

The electronic absorption of the ligands and their metal complexes was recorded in DMSO at room temperature and the results are summarized in Table-2. Free ligand PBA shows a single transition at 300 nm relatively to $\pi\rightarrow\pi^*$ band. Moreover, the ligand BPE presents three bands, two of them appeared at 260 and 274 nm assigned to $\pi\rightarrow\pi^*$ transition and a third band located at 305 nm attributed to $n\rightarrow\pi^*$ transition. The cadmium complex revealed the presence of a transition at 276 nm corresponding to $\pi\rightarrow\pi^*$ band different than those of free ligands PBA and BPE, which indicate the coordination of ligands PBA and BPE to cadmium.

TABLE-2
ELECTRONIC DATA OF FREE LIGANDS AND THEIR MIXED COMPLEXES

Compound	λ_{max} (nm)	ν (cm^{-1})	Assignment
PBA	300	33333	$\pi\rightarrow\pi^*$
BPE	260	38461	$\pi\rightarrow\pi^*$
	274	36496	$\pi\rightarrow\pi^*$
	305	32786	$n\rightarrow\pi^*$
$[Cd(PBA)(BPE)I_2]$	276	36231	$\pi\rightarrow\pi^*$
$[Sn(PBA)(BPE)Cl_2]$	298	33557	$\pi\rightarrow\pi^*$
	434	23041	$(\nu_2)\ ^3A_2g(F)\rightarrow{}^3T_1g(F)$
$[Ni(PBA)(BPE)Cl_2]$	274	36496	$\pi\rightarrow\pi^*$
	430	23255	$(\nu_2)\ ^3A_2g(F)\rightarrow{}^3T_1g(F)$
$[Cu(PBA)(BPE)SO_4{\cdot}2H_2O]$	278	35971	$\pi\rightarrow\pi^*$
	432	23148	$(\nu_2)\ ^3A_2g(F)\rightarrow{}^3T_1g(F)$

Moreover, tin complex spectrum represent two transitions, one at 298 nm assumed to $\pi\rightarrow\pi^*$ in UV domain and at 434 nm appeared a second transition assigned to $\pi(N)\rightarrow d$ band confirmed the formation of complex *via* coordination of ligands to metal. Furthermore, organonickel manifest two electronic transitions. First band at 274 nm assigned to $\pi\rightarrow\pi^*$ transition. The second band at 430 nm band assumed to $\pi(N)\rightarrow d$ transition also confirmed the coordination of ligands to the metal ion. Copper(II) complex showed a principle two transitions, one of them located at 278 nm and associated to $\pi\rightarrow\pi^*$, the second band was observed at 432 nm corresponding to $\pi(N)\rightarrow d$ transition also confirmed the coordination of ligands to metal.

Thermal analysis: Thermal analysis of synthesized metal complexes was carried out in a dynamic air from room temperature to 650 °C. The thermograph degradation of cadmium complex revealed the two endothermic decomposition stages. The first endothermic stage at 204-285 ºC is responsible for desorption of ligands PBA and BPE with mass loss amounting 56.35% (calcd. 54.94%). The second exothermic step in the range of 279-410 ºC is assigned to the elimination of diiodine molecule with a mass loss amounting to34.59% (calcd. 31.22%).

The thermal decomposition of Sn(II) complex makes it possible to observe two stages of endothermic mass loss at 52-284 and 311-482 ºC. The first step is attributed to the exclusion of chloride atom and benzimidazole group of PBA ligand (PBA 0.56%) with a mass loss of 25.39% (calcd. 24.14%). These indicate that PBA ligand was in coordination with tin metal exclusively from the amino group. The second step is attributed to the removal of the BPE ligand with a mass loss of 37.43% (calcd. 37.30%).

Nickel complex thermogram showed an endothermic stage at 82-157 ºC correspond to the detachment of three molecules of water. The second endothermic step in the range 295-468 ºC associated to desorption of ligands PBA and BPE with a mass loss amounting to 72.05 (calcd. 72.94%). In addition, organocuprate mixed complex Cu(II) revealed the presence of two endothermic degradation stages. The first endothermic stage was accomplished at 183-291 ºC and attributed to the decomposition of BPE ligand with mass loss amounting to 37.39% (calcd. 36.95%). The second endothermic stage at 301-465 ºC assigned to the detachment of sulfate moiety and two water molecules with a mass loss amounting to 19.52% (calcd. 20.56%). The desorption of these water molecules at relatively high temperature indicates the involvement of these molecules through hydrogen bonding [57].

XRD analysis: Single crystal formation of the mixed metal complexes by different solvents (dichloromethane, ethanol, acetone) were failed. They were characterized by powder X-ray diffraction to provide the crystalline system type, lattice parameters, inter axial angles, cell volume, crystallinity size and density. The elementary cell parameters were also calculated and listed in Table-3. The X-ray powder diffraction patterns affirmed that Ni(II), Cd(II) and Cu(II) complexes have a monoclinic structure. Crystalline structures of a similar type of sample have been described as monoclinic and orthorhombic [58,59].

Moreover, using the diffraction data, the average crystallite sizes of the complexes, D, were calculated according to the Scherrer's equation ($D = K\lambda/\beta\cos\theta$), where K is the form factor and λ is the X-ray waveform length (1.5406 Å), θ is the Bragg diffraction angle and β is the total mid-height width of diffraction peak [60,61]. The average crystallite sizes of all the samples were found to be 152-185 nm.

Antibacterial activity: The complex of Sn(II) prepared herein were screened for their potential biological activities and the preliminary test of screening results is summarized in Table-4. The antibacterial screening revealed that the tested organotin complex showed a moderate inhibition towards all bacterial strains.

TABLE-3
X-RAY POWDER DIFFRACTION CRYSTAL DATA OF COMPLEXES: LATTICE CONSTANT, INTERAXIAL ANGLE, CRYSTAL SYSTEM, UNIT CELL VOLUME, 2θ RANGE, CRYSTALLINITY SIZE AND DENSITY

Parameters		[Cd (PBA)(BPE)I_2]	[Ni(PBA)(BPE)Cl_2]	[Cu(PBA)(BPE)SO_4·$2H_2O$]
Empirical formula		$C_{28}H_{26}N_6CdI_2$	$C_{28}H_{30}Cl_2N_6NiO_2$	$C_{28}H_{30}N_6O_6CuS$
Lattice constant	a (Å)	8.65	16.76	5
	b (Å)	6.27	9.48	6
	c (Å)	7.99	20.23	18
Inter axial angle	α (°)	90.00	90.00	90.00
	β (°)	115.12	98.22	86
	γ (°)	90.00	90.00	90.00
Crystal system		a ≠ b ≠ c, α= γ = 90, β ≠ 90 Monoclinic	a ≠ b ≠ c, α= γ = 90, β ≠ 90 Monoclinic	a ≠ b ≠ c, α = γ = 90, β ≠ 90 Monoclinic
Unit cell Volume (Å^3)		393.6	3185.61	538
2θ range		5.57-55.33	5.30-75.06	5.28-39-28
Crystallinity Size		154	152	185
Density (g cm^{-3})		4.541	1.325	2.547

TABLE-4
ZONE OF INHIBITION OF NEW SYNTHESIZED MIXED COMPLEX OF Sn(II) AGAINST DIFFERENT BACTERIA

Compound (1000 µg/mL)	Zone of inhibition (mm)			
	Gram-positive bacteria		Gram-negative bacteria	
	S. aureas	*M. Luteus*	*P. aerugmosa*	*E. coli*
[Sn(PBA)(BPE)Cl_2]	12	15	10	12

Bioactivity score evaluation: The prediction of bioactivity scores of Ni(II), Cu(II), Sn(II) and Cd(II) complexes were obtained by analyzing their bioactivity scores of GPCR (G-protein coupled receptors ligand), KI (kinase inhibitor), PI (protease inhibitor), EI (enzyme inhibitor), ICM (ion channel modulator) and NRL (nuclear receptor ligand). This study was performed with molinspiration software [62]. From the results depicted in Table-5, Ni(II), Cu(II), Sn(II) and Cd(II) complexes exhibited

TABLE-5
PREDICTION OF THE BIOACTIVITY SCORES OF Ni(II), Cu(II), Sn(II) AND Cd(II) COMPLEXES

Complex	GPCR ligand	Enzyme inhibitor	Nuclear receptor ligand	Protease inhibitor	Ion channel modulator	Kinase inhibitor
Ni(II)	0.19	0.13	-0.10	0.04	0.03	0.12
Cu(II)	0.19	0.06	-0.27	0.14	-0.32	-0.07
Sn(II)	0.19	0.13	-0.10	0.04	0.03	0.12
Cd(II)	0.19	0.13	-0.10	0.04	0.04	0.12
Aspirin [40]	-0.76	-0.28	-0.44	-0.82	-0.32	-1.06

TABLE-6
ORAL TOXICITY PREDICTION RESULTS OF Cu(II) MIXED COMPLEX

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.51
Toxicity end points	Carcinogenicity	carcino	Inactive	0.55
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Inactive	0.57
Toxicity end points	Cytotoxicity	cyto	Inactive	0.66
Tox 21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.81
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.94
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.89
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.80
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.80
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER – LBD)	nr_er_lbd	Inactive	0.91
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.95
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2 / antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.84
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.84
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.74
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.85
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.89

good bioactivity given by GPCR ligand, moderately nuclear receptor ligand, ion channel modulator and kinase inhibitor. The tested compounds possess similar bioactivity score as compared to aspirin for all drug targets.

Prediction toxicity of mixed complexes: The theoretical toxicity study of different new complexes has been achieved based on program protox-II-prediction toxicity of chemicals [63]. The results of this study revealed that all target compounds exhibited no significant toxicity to all human cells. The results obtained from the prediction toxicity of the copper II mixed complex in Table-6.

Conclusion

The ligands 4-benzoimidazolaniline (PBA) and benzoimidazolphenylethanamine (BPE) was successfully synthesized, characterized and reacted with various metal ions salts to produce the corresponding mixed complexes of Cd(II), Sn(II), Ni(II) and Cu(II). According to UV-Vis and IR data of mixed complexes, it is concluded that the ligands were coordinated through amino groups to metal atom leading to the formation of coordination complexes. The XRD results affirmed that the Ni(II), Cd(II) and Cu(II) complexes have monoclinic structures. Theoretical study of toxicity was revealed that several complexes exhibited no significant toxicity to all human cells. The different compounds presented good bioactivity scores and the antibacterial screening revealed that the Sn(II) complex showed moderate activity towards all bacterial strains.

ACKNOWLEDGEMENTS

The author thanks the Department of Chemistry, College of Sciences, Qassim University, Al-Qassim, Saudi Arabia. Thanks are also due to Dr. Fahd M. Elmenderej for DTA-DTG, IR and UV-vis spectral analysis of the synthesized compounds.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. M. Boiani and M. Gonzalez, *Mini Rev. Med. Chem.*, **5**, 409 (2005); https://doi.org/10.2174/1389557053544047
2. Salahuddin, M. Shaharyar and A. Mazumder, *Arab. J. Chem.*, **10(S1)**, S157 (2017); https://doi.org/10.1016/J.ARABJC.2012.07.017
3. L.K. Labanauskas, A.B. Brukstus, P.G. Gaidelis, V.A. Buchinskaite, É.B. Udrenaite and V.K. Dauksas, *Pharm. Chem. J.*, **34**, 353 (2000); https://doi.org/10.1023/A:1005213306544
4. Y. Bansal and O. Silakari, *Bioorg. Med. Chem.*, **20**, 6208 (2012); https://doi.org/10.1016/j.bmc.2012.09.013
5. B. Can-Eke, M. Orhan Puskullu, E. Buyukbingol and M. Iscan, *Chem. Biol. Interact.*, **113**, 65 (1998); https://doi.org/10.1016/S0009-2797(98)00020-9
6. R. Sevak, A. Paul, S. Goswami and D. Santani, *Pharmacol. Res.*, **46**, 351 (2002); https://doi.org/10.1016/S1043661802001500
7. S.I. Alaqeel, *J. Saudi Chem. Soc.*, **21**, 229 (2017); https://doi.org/10.1016/j.jscs.2016.08.001
8. P.K. Ranjith, P. Rajeesh, K.R. Haridas, N.K. Susanta, T.N. Guru Row, R. Rishikesan and N. Suchetha Kumari, *Bioorg. Med. Chem. Lett.*, **23**, 5228 (2013); https://doi.org/10.1016/j.bmcl.2013.06.072
9. J. Camacho, A. Barazarte, N. Gamboa, J. Rodrigues, R. Rojas, A. Vaisberg, R. Gilman and J. Charris, *Bioorg. Med. Chem.*, **19**, 2023 (2011); https://doi.org/10.1016/j.bmc.2011.01.050
10. S.M. Sondhi, S. Rajvanshi, M. Johar, N. Bharti, A. Azam and A.K. Singh, *Eur. J. Med. Chem.*, **37**, 835 (2002); https://doi.org/10.1016/S0223-5234(02)01403-4
11. S. Grassmann, B. Sadek, X. Ligneau, S. Elz, C.R. Ganellin, J.M. Arrang, J.C. Schwartz, H. Stark and W. Schunack, *Eur. J. Pharm. Sci.*, **15**, 367 (2002); https://doi.org/10.1016/S0928-0987(02)00024-6
12. R.A. Haque, M.A. Iqbal, P. Asekunowo, A.M.S.A. Majid, M.B. Khadeer Ahamed, M.I. Umar, S.S. Al-Rawi and F.S.R. Al-Suede, *Med. Chem. Res.*, **22**, 4663 (2013); https://doi.org/10.1007/s00044-012-0461-8
13. S.H. Nile, B. Kumar and S.W. Park, *Chem. Biol. Drug Des.*, **82**, 290 (2013); https://doi.org/10.1111/cbdd.12141
14. V. Kralova, V. Hanusova, P. Stankova, K. Knoppova, K. Canova and L. Skalova, *Anticancer Drugs*, **24**, 911 (2013); https://doi.org/10.1097/CAD.0b013e3283648c69
15. A. Jain, R. Sharma and S.C. Chaturvedi, *Med. Chem. Res.*, **22**, 4622 (2013); https://doi.org/10.1007/s00044-012-0462-7
16. C. Beaulieu, Z.Y. Wang, D. Denis, G. Greig, S. Lamontagne, G. O'Neill, D. Slipetz and J. Wang, *Bioorg. Med. Chem. Lett.*, **14**, 3195 (2004); https://doi.org/10.1016/j.bmcl.2004.04.005
17. T.M. Evans, J.M. Gardiner, N. Mahmood and M. Smis, *Bioorg. Med. Chem. Lett.*, **7**, 409 (1997); https://doi.org/10.1016/S0960-894X(97)00022-X
18. Y.K. Yoon, M.A. Ali, A.C. Wei, T.S. Choon, K.-Y. Khaw, V. Murugaiyah, H. Osman and V.H. Masand, *Bioorg. Chem.*, **49**, 33 (2013); https://doi.org/10.1016/j.bioorg.2013.06.008
19. J. Zhu, C.-F. Wu, X. Li, G.-S. Wu, S. Xie, Q.-N. Hu, Z. Deng, M.X. Zhu, H.-R. Luo and X. Hong, *Bioorg. Med. Chem.*, **21**, 4218 (2013); https://doi.org/10.1016/j.bmc.2013.05.001
20. L. Ceballos, G. Virkel, C. Elissondo, C. Canton, J. Canevari, G. Murno, G. Denegri, C. Lanusse and L. Alvarez, *Acta Trop.*, **127**, 216 (2013); https://doi.org/10.1016/j.actatropica.2013.05.004
21. J. Perez-Villanueva, A. Hernandez-Campos, L. Yepez-Mulia, C. Mendez-Cuesta, O. Mendez-Lucio, F. Hernandez-Luis and R. Castillo, *Bioorg. Med. Chem. Lett.*, **23**, 4221 (2013); https://doi.org/10.1016/j.bmcl.2013.05.012
22. A. Hori, Y. Imaeda, K. Kubo and M. Kusaka, *Cancer Lett.*, **183**, 53 (2002); https://doi.org/10.1016/S0304-3835(02)00110-6
23. H.T. Abdel-Mohsen, F.A.F. Ragab, M.M. Ramla and H.I. El Diwani, *Eur. J. Med. Chem.*, **45**, 2336 (2010); https://doi.org/10.1016/j.ejmech.2010.02.011
24. U. Velaparthi, P. Liu, B. Balasubramanian, J. Carboni, R. Attar, M. Gottardis, A. Li, A. Greer, M. Zoeckler, M.D. Wittman and D. Vyas, *Bioorg. Med. Chem. Lett.*, **17**, 3072 (2007); https://doi.org/10.1016/j.bmcl.2007.03.048
25. M.A. Pagano, M. Andrzejewska, M. Ruzzene, S. Sarno, L. Cesaro, J. Bain, M. Elliott, F. Meggio, Z. Kazimierczuk and L.A. Pinna, *J. Med. Chem.*, **47**, 6239 (2004); https://doi.org/10.1021/jm049854a
26. M.A. Pagano, F. Meggio, M. Ruzzene, M. Andrzejewska, Z. Kazimierczuk and L.A. Pinna, *Biochem. Biophys. Res. Commun.*, **321**, 1040 (2004); https://doi.org/10.1016/j.bbrc.2004.07.067
27. D.K. Neff, A. LeeDutra, J.M. Blevitt, F.U. Axe, M.D. Hack, J.C. Buma, R. Rynberg, A. Brunmark, L. Karlsson and G. Breitenbucher, *Bioorg. Med. Chem. Lett.*, **17**, 6467 (2007); https://doi.org/10.1016/j.bmcl.2007.09.098
28. K.L. Arienti, A. Brunmark, F.U. Axe, K. McClure, A. Lee, J. Blevitt, D.K. Neff, L. Huang, S. Crawford, C.R. Pandit, L. Karlsson and J.G. Breitenbucher, *J. Med. Chem.*, **48**, 1873 (2005); https://doi.org/10.1021/jm0495935
29. J.P. Hajduk, S. Boyd, D. Nettesheim, V. Nienaber, J. Severin, R. Smith, D. Davidson, T. Rockway and S.W. Fesik, *J. Med. Chem.*, **43**, 3862 (2000); https://doi.org/10.1021/jm0002228
30. D. Kumar, M.R. Jacob, M.B. Reynolds and S.M. Kerwin, *Bioorg. Med. Chem. Lett.*, **10**, 3997 (2002); https://doi.org/10.1016/S0968-0896(02)00327-9

31. A.S. Aboraia, H.M. AbdelRahman, N.M. Mahfouz and M.A. EL-Gendy, *Bioorg. Med. Chem. Lett.*, **14**, 1236 (2006); https://doi.org/10.1016/j.bmc.2005.09.053
32. Sh.I. El-Naem, A.O. El Nzhawy, H.I. El Diwani and A.O. Abdel Hamid, *Arch. Pharm.*, **336**, 7 (2003); https://doi.org/10.1002/ardp.200390005
33. M.M. Ramla, M.A. Omar, H. Tokuda and H.I. ElDiwani, *Bioorg. Med. Chem. Lett.*, **15**, 6489 (2007); https://doi.org/10.1016/j.bmc.2007.04.010
34. M.M. Ramla, M.A. Omar, A.-M.M. El-Khamry and H.I. El-Diwani, *Bioorg. Med. Chem. Lett.*, **14**, 7324 (2006); https://doi.org/10.1016/j.bmc.2006.06.033
35. A.A. Spasov, I.N. Yozhitsa, L.I. Bugaeva and V.A. Anisimova, *Pharm. Chem. J.*, **33**, 232 (1999); https://doi.org/10.1007/BF02510042
36. S.L. Khokra and D. Choudhary, *Asian J. Biochem. Pharm. Res.*, **3**, 476 (2011).
37. V.K. Vyas and M. Ghate, *Mini Rev. Med. Chem.*, **10**, 1366 (2010); https://doi.org/10.2174/138955710793564151
38. O. Ajani, D. Aderohunmu, S. Olorunshola, C. Ikpo and I. Olanrewaju, *Orient. J. Chem.*, **32**, 109 (2016); https://doi.org/10.13005/ojc/320111
39. K.P. Barot, K.S. Manna and M.D. Ghate, *J. Saudi Chem. Soc.*, **21**, 35 (2017); https://doi.org/10.1016/j.jscs.2013.09.010
40. M. Khattab, A.S. Galal, F.A.F. Ragab and H.I. El Diwani, *Res. Chem. Intermed.*, **39**, 2917 (2013); https://doi.org/10.1007/s11164-012-0843-z
41. Y.-J. Xu, H.-Q. Miao, W. Pan, E.C. Navarro, J.R. Tonra, S. Mitelman, M.M. Camara, D.S. Deevi, A.S. Kiselyov, P. Kussie, W.C. Wong and H. Liu, *Bioorg. Med. Chem. Lett.*, **16**, 404 (2006); https://doi.org/10.1016/j.bmcl.2005.09.070
42. M.L. Richards, S.C. Lio, A. Sinha, H. Banie, R.J. Thomas, M. Major, M. Tanji and J.C. Sircar, *Eur. J. Med. Chem.*, **41**, 950 (2006); https://doi.org/10.1016/j.ejmech.2006.03.014
43. F. Arjmand, S. Parveen, M. Afzal and M. Shahid, *J. Photochem. Photobiol. B*, **114**, 15 (2012); https://doi.org/10.1016/j.jphotobiol.2012.05.003
44. Z. Chen, X. Wang, Y. Li and Z. Guo, *Inorg. Chem. Commun.*, **11**, 1392 (2008); https://doi.org/10.1016/j.inoche.2008.09.014
45. S. Günal, N. Kaloglu, I. Özdemir, S. Demir and I. Özdemir, *Inorg. Chem. Commun.*, **21**, 142 (2012); https://doi.org/10.1016/j.inoche.2012.04.033
46. P. Toro, A.H. Klahn, B. Pradines, F. Lahoz, A. Pascual, C. Biot and R. Arancibia, *Inorg. Chem. Commun.*, **35**, 126 (2013); https://doi.org/10.1016/j.inoche.2013.06.019
47. X. Qu, H. Feng, C. Ma, Y. Yang and X. Yu, *Inorg. Chem. Commun.*, **81**, 22 (2017); https://doi.org/10.1016/j.inoche.2017.04.023
48. Z.A. Siddiqi, M. Khalid, S. Kumar, M. Shahid and S. Noor, *Eur. J. Med. Chem.*, **45**, 264 (2010); https://doi.org/10.1016/j.ejmech.2009.10.005
49. N.M. Agh-Atabay, B. Dulger and F. Gucin, *Eur. J. Med. Chem.*, **40**, 1096 (2005); https://doi.org/10.1016/j.ejmech.2005.05.006
50. S.A. Nikolaevskii, Y.V. Koshchienko, A.V. Chernyshev, A.S. Burlov, A.S. Cheprasov, G.G. Aleksandrov, M.A. Kiskin and A.V. Metelitsa, *Russ. J. Coord. Chem.*, **40**, 468 (2014); https://doi.org/10.1134/S1070328414070070
51. A. Tavman and A. Çinarli, *Inorg. Chim. Acta*, **421**, 481 (2014); https://doi.org/10.1016/j.ica.2014.07.036
52. U. Schillinger and F.K. Lücke, *Appl. Environ. Microbiol.*, **55**, 1901 (1989); https://doi.org/10.1128/AEM.55.8.1901-1906.1989
53. S. Mohan, N. Sundaraganesan and J. Mink, *Spectrochim. Acta A Mol. Biomol. Spectrosc.*, **47**, 1111 (1991); https://doi.org/10.1016/0584-8539(91)80042-H
54. N. Sundaraganesan, S. Ilakiamani, P. Subramani and B.D. Joshua, *Spectrochim. Acta A Mol. Biomol. Spectrosc.*, **67**, 628 (2007); https://doi.org/10.1016/j.saa.2006.08.020
55. D.G. Hill and A.F. Rosenberg, *J. Chem. Phys.*, **24**, 1219 (1956); https://doi.org/10.1063/1.1742744
56. A.S. El-Tabl, F.A. El-Saied and A.N. AL-Hakimi, *Transition Met. Chem.*, **32**, 689 (2007); https://doi.org/10.1007/s11243-007-0228-0
57. N.T. Abdel Ghani and A.M. Mansour, *Inorg. Chim. Acta*, **373**, 249 (2011); https://doi.org/10.1016/j.ica.2011.04.036
58. Y. Kara, B. Avar, A. Kayraldiz, B. Guzel and M. Kurtoglu, *Heteroatom Chem.*, **22**, 119 (2011); https://doi.org/10.1002/hc.20665.
59. J. Joseph and B.H. Mehta, *J. Coord. Chem.*, **33**, 124 (2007); https://doi.org/10.1134/S1070328407020091
60. B.P. Baranwal, T. Fatma and A. Varma, *J. Mol. Struct.*, **920**, 472 (2009); https://doi.org/10.1016/j.molstruc.2008.12.029
61. J. Kolmas, A. Jaklewicz, A. Zima, M. Buæko, Z. Paszkiewicz, J. Lis, A. Slósarczyk and W. Kolodziejski, *J. Mol. Struct.*, **987**, 40 (2011); https://doi.org/10.1016/j.molstruc.2010.11.058
62. P. Thangarasu, S. Thamarai Selvi and A. Manikandan, *Bioorg. Chem.*, **81**, 468 (2018); https://doi.org/10.1016/j.bioorg.2018.09.011
63. P. Banerjee, A.O. Eckert, A.K. Schrey and R. Preissner, *Nucleic Acids Res.*, **46**, W257 (2018); https://doi.org/10.1093/nar/gky318