World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers © All Rights Reserved
Available online at: http://www.wjpsonline.org/
Original Article

Eco-friendly preparation and bio-potential evaluation of Co(II), Ni(II) and Cu(II) complexes with phenylacetylurea and benzoate ion ligands

Arunachalam A [1]*, Ramachandramoorthy T [1], Padmavathy S [1], and Narendran R [2]

[1]PG & Research Department of Chemistry, Bishop Heber College (Autonomous), Tiruchirappalli – 620 017.
[2]CARISM, SASTRA University, Thanjavur – 613 402

Received: 28-07-2015 / Revised: 14-08-2015 / Accepted: 25-08-2015

ABSTRACT

The biological activities of Phenylacetylurea (PAU), a bidendate, neutral ligand get enhanced when complexed with transition metal ions. The current study deals with the microwave assisted preparation, physico-chemical, spectral and biological characterization of Co(II), Ni(II) and Cu(II) complexes with PAU and benzoate ion (ben) ligands. The molecular formulae of the complexes were arrived at from the estimation of metals and their electrical conductivity and effective magnetic moment (μ_{eff}) values. The electronic spectral data indicate the probable geometry of the complexes. The antibacterial and antifungal screening of the above three complexes against the bacteria, *viz., Lactobacillus sp., Micrococcus luteus, Raoultella planticola, Shigella flexneri and Vibrio cholerae* and fungi, viz., *Aspergillus flavus, Aspergillus niger, Aspergillus oryzae, Aspergillus sojae* and *Candida albicans* were carried out. The results indicate that the complexes exhibit enhanced biological activities when compared to pure ligands. The antibacterial and antifungal activities of the three complexes are higher than PAU, but lower than the reference compounds, *viz.* streptomycin and ketokonazole respectively. The diphenylpicrylhydrazyl (DPPH) free radical scavenging activity (antioxidantal activity) of the above three complexes are higher than PAU and benzoate ion ligands, but lower than the standard compound, vitamin-C.

Key words: Co(II), Ni(II) and Cu(II) complexes, Phenylacetylurea, Antibacterial, Antifungal, Antioxidantal.

◆

INTRODUCTION

Metal ions are the key factors in the structural organization of biochemical molecules and the functional processes operating in the genetic and metabolic systems[1]. Transition metal ions and their complexes are the essential components found in all living organisms[2]. Metals of groups 1 and 2 of the periodic table, namely, sodium, potassium, magnesium and calcium tend to be present in the biological systems in fairly large quantities. Transition metals are found to be present in relatively small quantities and are sometimes called in biochemistry as trace metals. The interaction of these ions with biologically active ligands, for example in drugs, is a subject of considerable interest. Some of the biologically active compounds act via chelation , but for most of them little is known about how metal binding influences their activity. Therefore, studying the biological activities of a few complexes and their ligands[3] has acquired greater interest.

Studies on simple metal complexes of biologically active ligands are important since they can, sometimes be considered as models of the more complex biological systems[4]. They assist in enhancing the biochemical activity by stabilizing various bio-molecules. They also serve as active sites and cofactor in many enzymes. Metal ions and their complexes find their use in drugs for many diseases. These metal ions in the complexes are usually present in the coordination sphere, bound with ligands by coordinate bond. The ligands involved in such metal complexes usually have the donor atoms like oxygen, nitrogen, sulphur and occasionally carbon.

Phenylacetylurea, called as phenacemide[5] is a urea based anticonvulsant administered for controlling severe epilepsy, particularly mixed forms of complex but partial (psychomotor or temporal lobe) seizures, which are refractory to other anticonvulsants. Phenylacetylurea based drugs accelerate the threshold for minimal electroshock convulsions and prevent the tonic

---

***Corresponding Author Address:** *Arunachalam.A, PG & Research Department of Chemistry, Bishop Heber College (Autonomous), Tiruchirappalli – 620 017, India*

phase of maximal electroshock seizures. It also prevents or modifies seizures induced by pentylenetetrazol or other convulsants. Microwave assisted preparation[6,7] of chemical compounds has become popular and gained much attention in this decade. The microwave irradiation is a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules. The application of microwave irradiation provides enhanced reaction rate and improved product yield[8,9]. It is pollution free, eco-friendly, cheap, less time consuming, effluent free and doesn’t require special vessels.

The present work aims at the preparation of Co(II), Ni(II) and Cu(II) complexes with phenylacetylurea and benzoate ion as ligands by microwave irradiation and characterization by physico-chemical, spectral and biological methods.

MATERIALS AND METHODS

Preparation of complexes: All the chemicals viz. cobalt(II) nitrate, nickel(II) nitrate, copper(II) nitrate, phenylacetylurea and sodium benzoate were of Analytical reagent grade. The solvents acetonitrile, DMF, DMSO, ethanol and methanol were of AnalaR grade and used as such.

All the three metal complexes were prepared by the addition of required mole ratios of phenylacetylurea (1.23 g, 6.91 mmol; 1.23 g, 6.91 mmol and 0.74 g, 4.16 mmol) in methanol and sodium benzoate (1.00g, 6.94 mmol; 1.00g, 6.94 mmol and 1.20 g, 8.33 mmol) in ethanol to the Co(II) nitrate, Ni(II) nitrate and Cu(II) nitrate solutions (1.00g, 3.44 mmol; 1.0g, 3.44 mmol and 1.00g, 4.14 mmol) respectively followed by microwave irradiation for about 10 seconds after each addition of ligands. Microwave oven IFB 25PG1S model was used for the preparation of complexes. The precipitated complexes were filtered, washed with ethanol and dried.

Characterization: The estimation of cobalt and copper in the complexes was carried out by volumetric method by titration with EDTA and sodium thiosulphate respectively and nickel by colorimetric method using dimethylglyoxime[10]. The molar conductance measurements of the 10^{-3} M complex solutions were carried out in acetonitrile using Systronic 304 Conductivity meter at 30°C. The effective magnetic moment (μ_{eff}) values of the complexes were determined by VSM technique. Solid state UV-visible absorbance spectra of all the complexes were recorded by using Varian CARY-5000 model UV-vis Spectrophotometer. The IR spectra of complexes and ligands were recorded in Shimadzu, FT-IR 8400 Spectrometer at 4000-400 cm^{-1} range by KBr pellet technique. The antibacterial and antifungal [11-13] activities of the individual ligands and complexes were carried out by agar well diffusion method. Antioxidantal activities of the complexes and ligands were carried out by DPPH free radical scavenging method[14-16].

RESULTS AND DISCUSSION

Physico-chemical properties: The Co(II) complex was pale pink in color, Ni(II) and Cu(II) complexes were yellowish green colored precipitates. The yield of Co(II), Ni(II) and Cu(II) complexes were 60.9%, 61.9% and 79.5% respectively. The cobalt, nickel and copper contents in the respective complexes were 8.86%, 8.80% and 13.05% as against the theoretical values of 8.97%, 8.94% and 13.14% respectively. The electrical conductivity of Co(II), Ni(II) and Cu(II) complexes were 69.90, 70.80 and 85.30 $ohm^{-1}cm^{2}mol^{-1}$ respectively (Table 1).

From the metal percentage, the molecular formulae of the three complexes have been arrived at as $[Co(PAU)_2(ben)_2]$, $[Ni(PAU)_2(ben)_2]$ and $[Cu(PAU)(ben)_2]$. The low electrical conductance values indicate that the complexes are non-electrolytes in nature and of 1:0 type.

Electronic spectra and magnetic moments: In the electronic spectra, absorption frequencies obtained at ~265 nm in the UV region for all the three Co(II), Ni(II) and Cu(II) complexes indicate that there is charge transfer transition (Fig.1).

The effective magnetic moment of Co(II) complex is 4.42 BM, which indicates its distorted octahedral geometry. The λ_{max} values observed in the electronic spectrum at 619 nm (Table 2) corresponding to ${}^4T_{1g}(P) \leftarrow {}^4T_{1g}(F)$ transition indicate distorted octahedral geometry of the complex. For Ni(II) complex, the effective magnetic moment 3.08 BM and the electronic transition ${}^3T_{1g}(F) \leftarrow {}^3A_{2g}$ corresponding to the λ_{max} value 642 nm respectively (Table 2) suggest a distorted octahedral geometry. The effective magnetic moment 1.85 BM for Cu(II) complex and the λ_{max} values observed at 710 nm (Table 2) corresponding to ${}^2E_g \leftarrow {}^2B_{1g}$, ${}^2B_{2g} \leftarrow {}^2B_{1g}$ and ${}^2A_{1g} \leftarrow {}^2B_{1g}$ transitions indicate the tetragonally distorted octahedral geometry of the complex.

IR Spectra: In the IR spectrum, the PAU ligand exhibited frequencies (Fig.1) at 712 cm^{-1}, 1092 cm^{-1}, 1672 $cm^{-1}$and 3389 cm^{-1} and they are assignable[17,18] to the ν(C-H) bending (aromatic), ν(C-N) stretching (alkyl), ν(C=O) stretching (amide) and ν(N-H) stretching(amide) vibrations respectively. These vibrations are found almost in the same region in all the three complexes with broadening of the peaks (Table 3 and Fig.3). In the case of the benzoate ion (another ligand), the IR frequencies recorded at 706 cm^{-1} (assignable to **ν**(C-H) bending vibration - aromatic), 1414cm^{-1} (assignable to ν (C=C) stretching- aromatic) and 3412 cm^{-1} assignable to ν(O-H) stretching-carboxylic acid) are shifted to 712 cm^{-1}, 1393 cm^{-1}, 3391 cm^{-1} in Co(II)complex and the same are shifted almost to the same position in the other two complexes (Table4 and Fig.3). Thus, the IR spectral data confirm the entry of both PAU and benzoate ion ligands into the coordination sphere of the metals.

Biological activities

Antibacterial activity: All the three complexes exhibit higher antibacterial activity than the pure PAU ligand (Table 5 and Fig.4). The antibacterial activities of Co(II) complex against *Micrococcus lutius*, Ni(II) complex against *Micrococcus lutius* and *Vibrio cholerae* and Cu(II) complex against *Lactobacillus sp.* are higher than those of pure PAU and benzoate ion ligands. $[Co(PAU)_2(ben)_2]$, $[Ni(PAU)_2(ben)_2]$ and $[Cu(PAU)(ben)_2]$ exhibit highest antibacterial activity against *Micrococcus luteus*, *Vibrio cholerae* and *Lactobacillus sp.* *r*espectively when compared to the activities against other bacteria. All the three complexes show lower activity against *Raoultella planticola* and *Shigella flexneri* than benzoate ion ligand. Pure benzoate ion ligand exhibits higher antibacterial activities than pure PAU ligand. However, the antibacterial activities of all the three complexes are low when compared to the standard, streptomycin.

Antifungal activity: All these complexes exhibit higher antifungal activity than PAU ligand. Ni(II) and Cu(II) complexes show higher antifungal activity against A*spergillus sojae* and *Aspergillus flavus* respectively than pure PAU and benzoate ion ligands (Table-6 and Fig.5). The antifungal activities of Ni(II) and Cu(II) complexes are very low against *Aspergillus flavus* and *Aspergillus sojae* respectively. Benzoate ion ligand shows higher antifungal activity than the other ligand, PAU. However, the antifungal activities of all the three complexes are very low when compared to the standard, ketokonazole.

Antioxidantal activity: All the three complexes show higher inhibition of DPPH free radical scavenging activities at a concentration of 500 μgml^{-1} than pure PAU and benzoate ion ligands. Co(II) complex exhibits higher antioxidantal activity than Ni(II) and Cu(II) complexes. The antioxidantal activities of the three complexes increase with increase in concentration of the respective complexes (Table 7 and Fig.6). However, the antioxidantal activities of all the three complexes are low when compared to the standard, vitamin-C.

CONCLUSION

From the analytical data and UV-visible spectral studies, the molecular formulae and their probable geometries were arrived at for the complexes. In general all the three complexes exhibit enhanced biological activities than pure ligands as expected. All the three complexes exhibit enhanced antibacterial activities when compared to pure PAU ligand. $[Co(PAU)_2(ben)_2]$, $[Ni(PAU)_2(ben)_2]$ and $[Cu(PAU)(ben)_2]$ exhibit higher antibacterial activities against *Micrococcus luteus, Vibrio cholerae*, and *Lactobacillus sp.* respectively than pure ligands. All these complexes show higher antifungal activities than pure PAU ligand. Ni(II) and Cu(II) complexes exhibit higher antifungal activities against A*spergillus sojae* and *Aspergillus flavus* respectively than pure PAU and benzoate ion ligands. All the three complexes exhibit higher antioxidantal activities than PAU and benzoate ion ligands.

ACKNOWLEDGEMENTS

The authors are thankful to the Principal and Management, Bishop Heber College, Tiruchirappalli and CARISM, SASTRA University, Thanjavur for providing necessary laboratory facilities. They also thank the Management of Tamilnadu Newsprint and Papers Limited (TNPL), Kagithapuram, Karur for encouragement and support.

TABLE 1. PHYSICO-CHEMICAL PROPERTIES OF Co(II), Ni(II) AND Cu(II) COMPLEXES

S. No.	**Complex**	**Colour**	**Yield %**	**Metal %***	**Electrical conductivity $ohm^{-1}cm^2mol^{-1}$**
1	$[Co(PAU)_2(ben)_2]$	Pale pink	60.9	8.86 (8.97)	69.90
2	$[Ni(PAU)_2(ben)_2]$	Yellowish green	61.9	8.80 (8.94)	70.80
3	$[Cu(PAU)(ben)_2]$	Yellowish green	79.5	13.05 (13.14)	85.30

(*-Theoritical metal content of the complexes is given in parenthesis)

TABLE 2. MAGNETIC MOMENT, SPECTRAL DATA AND GEOMETRY OF Co(II), Ni(II) and Cu(II) COMPLEXES

S.No.	**Complex**	**μ_{eff}, BM**	**λ_{max}, BM**	**Assignments**	**Probable geometry**
1	$[Co(PAU)_2(ben)_2]$	4.42	619	$^4T_{1g}(P) \leftarrow {}^4T_{1g}(F)$	Distorted octahedral
2	$[Ni(PAU)_2(ben)_2]$	3.08	642	$^3T_{1g}(F) \leftarrow {}^3A_{2g}$	Distorted octahedral
3	$[Cu(PAU)(ben)_2]$	1.85	710	$^2E_g \leftarrow {}^2B_{1g}$ $^2B_{2g} \leftarrow {}^2B_{1g}$ $^2A_{1g} \leftarrow {}^2B_{1g}$	Tetragonally distorted octahedral

TABLE 3. IR SPECTRAL DATA OF PAU (LIGAND), Co(II), Ni(II) AND Cu(II) COMPLEXES

S.No.	**Ligand/Complex**	**ν(C-H) bending (aromatic)**	**ν(C-N) stretching (alkyl)**	**ν(C=O) stretching (amide)**	**ν(N-H) stretching (amide)**
1	PAU	712	1092	1672	3389
2	$[Co(PAU)_2(ben)_2]$	712	1090	1670	3391
3	$[Ni(PAU)_2(ben)_2]$	710	1090	1672	3391
4	$[Cu(PAU)(ben)_2]$	712	1091	1670	3389

TABLE 4. IR SPECTRAL DATA OF BENZOATE ION (LIGAND), Co(II), Ni(II) AND Cu(II) COMPLEXES

S. No.	**Ligand/Complex**	**ν(C-H) bending (aromatic)**	**ν(C=C) stretching (aromatic)**	**ν(O-H) stretching (carboxylic acid)**
1	benzoate	706	1414	3412
2	$[Co(PAU)_2(ben)_2]$	712	1393	3391
3	$[Ni(PAU)_2(ben)_2]$	712	1400	3391
4	$[Cu(PAU)(ben)_2]$	712	1388	3389

TABLE 5. ANTIBACTERIAL ACTIVITIES OF Co(II), Ni(II) AND Cu(II) COMPLEXES, PAU AND BENZOATE ION LIGANDS AND STREPTOMYCIN (STANDARD) (DIAMETER INHIBITION AT 100µgml^{-1} CONCENTRATION)

S.No.	**Complex/ligand**	***Lactobacillus sp.***	***Micrococcus luteus***	***Raoultella planticola***	***Shigella flexneri***	***Vibrio cholerae***
1	$[Co(PAU)_2(ben)_2]$	10	23	14	14	12
2	$[Ni(PAU)_2(ben)_2]$	18	18	13	13	22
3	$[Cu(PAU)(ben)_2]$	26	16	18	15	13
4	PAU	7	10	6	13	13
5	ben	19	16	23	16	17
6	Streptomycin (standard)	27	36	48	47	52

TABLE 6. ANTIFUNGAL ACTIVITIES OF Co(II), Ni(II) AND Cu(II) COMPLEXES, PAU AND BENZOATE ION LIGANDS AND KETOKONAZOLE (STANDARD) (DIAMETER INHIBITION AT 400µgml^{-1} CONCENTRATION

S.No.	**Complex/Ligand**	***Aspergillus flavus***	***Aspergillus niger***	***Aspergillus oryzae***	***Aspergillus sojae***	***Candida albicans***
1	[Co(PAU)$_2$(ben)$_2$]	15	14	13	12	17
2	[Ni(PAU)$_2$ (ben)$_2$]	10	14	13	15	15
3	[Cu(PAU)(ben)$_2$]	20	16	11	10	16
4	PAU	12	11	7	10	4
5	ben	16	24	22	13	22
6	Ketokonazole (standard)	89	94	91	92	86

TABLE 7. DPPH FREE RADICALSCAVENGING ACTIVITIES OF Co(II), Ni(II) AND Cu(II) COMPLEXES, PAU AND BENZOATE ION LIGANDS AND VITAMIN-C (STANDARD) (PERCENTAGE INHIBITION)

S.No.	**Concentrationµg ml^{-1}**	**Co(II) complex**	**Ni(II) complex**	**Cu(II) complex**	**PAU**	**ben**	**Vitamin-C**
1	1000	-	-	-	12.09	7.66	-
2	500	60.24	38.46	53.65	10.01	5.20	90.23
3	250	52.02	27.31	34.16	7.14	2.98	92.03
4	125	38.40	19.43	25.36	6.01	3.03	93.22
5	62.5	30.18	15.45	22.82	4.96	2.88	93.09
6	31.3	16.82	10.95	18.06	4.47	3.03	88.92
7	15.6	12.78	9.26	16.56	4.11	2.93	75.23
8	7.81	9.71	6.71	13.63	4.06	3.03	38.72
9	3.90	9.71	2.54	4.76	4.06	3.03	25.68
10	1.95	9.19	0.59	3.52	3.91	2.31	11.99
11	0.98	9.58	-0.261	3.33	-	-	-

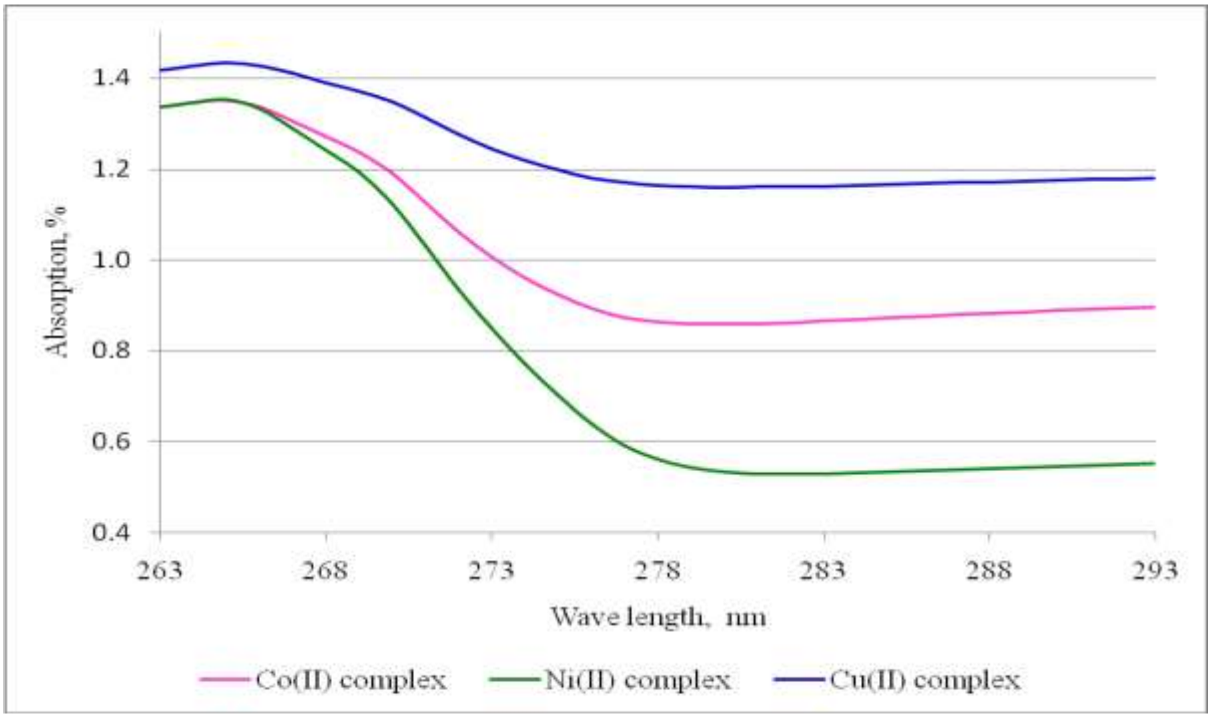

FIG. 1 UV SPECTRA OF Co(II), Ni(II) AND Cu(II) COMPLEXES

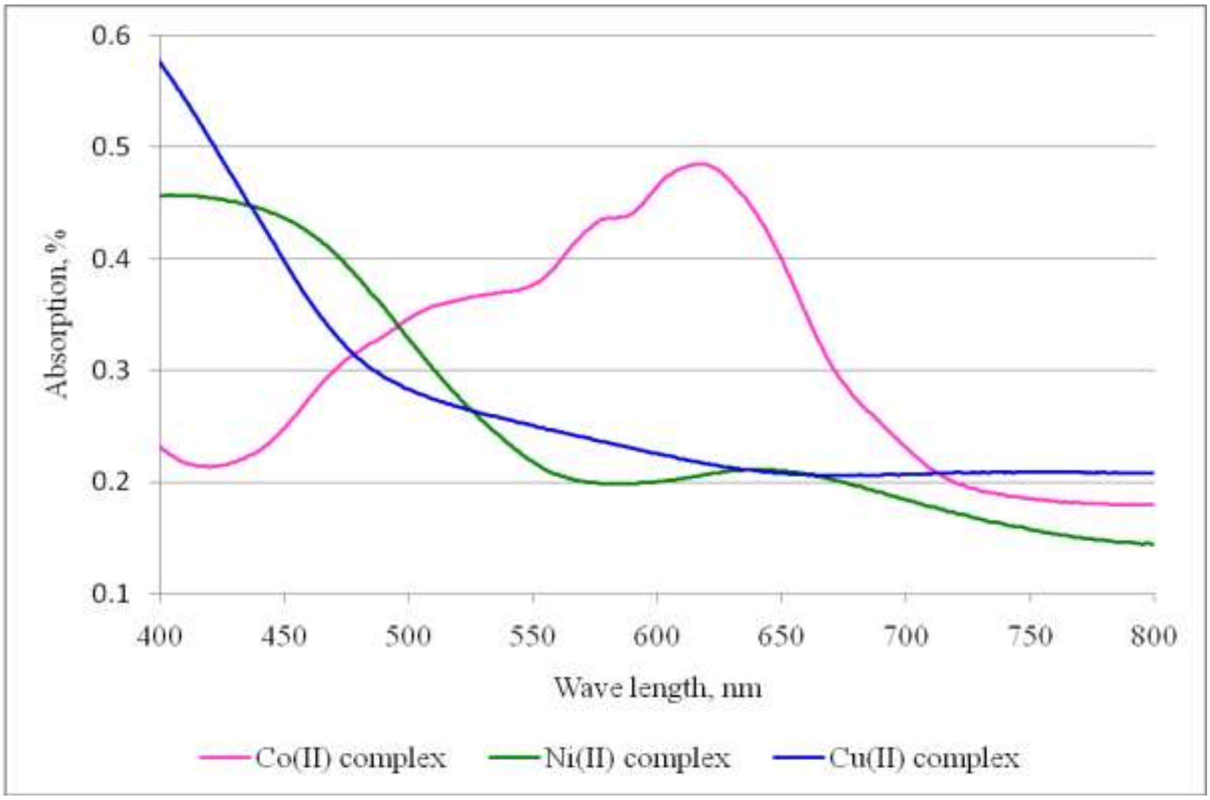

FIG. 2 VISIBLE SPECTRA OF Co(II), Ni(II) AND Cu(II) COMPLEXES

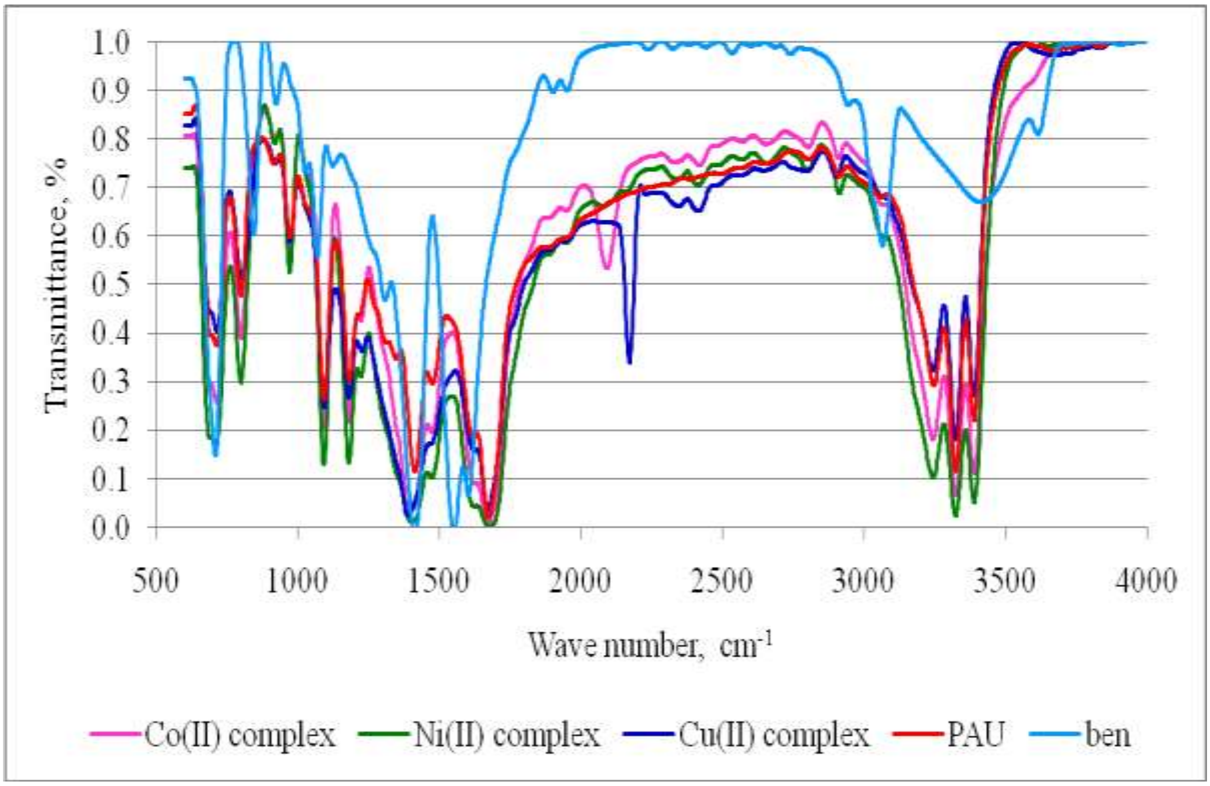

FIG. 3IR SPECTRA OF Co(II), Ni(II) AND Cu(II) COMPLEXES, PAU AND BENZOATE ION LIGANDS

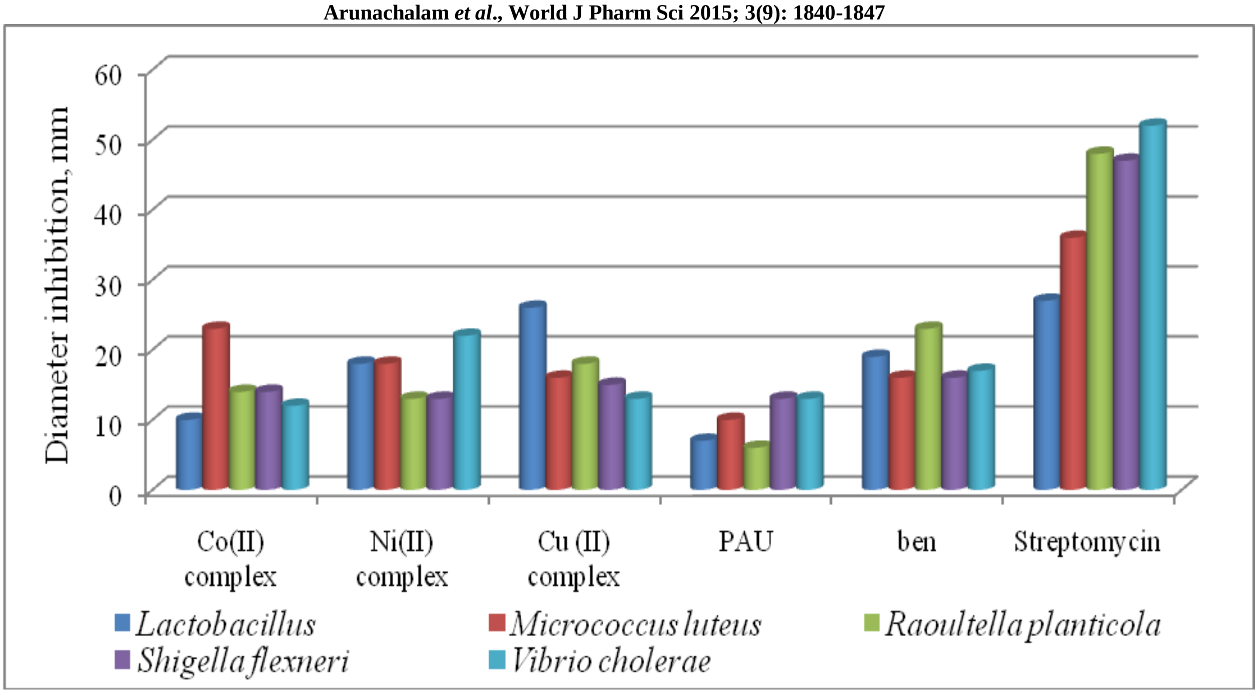

FIG. 4 COMPARISONOF ANTIBACTERIAL ACTIVITIES OF Co(II), Ni(II) AND Cu(II) COMPLEXES, PAU AND BENZOATE ION LIGANDS AND STREPTOMYCIN(STANDARD) (DIAMETER INHIBITION IN mm AT 100µgml^{-1} CONCENTRATION

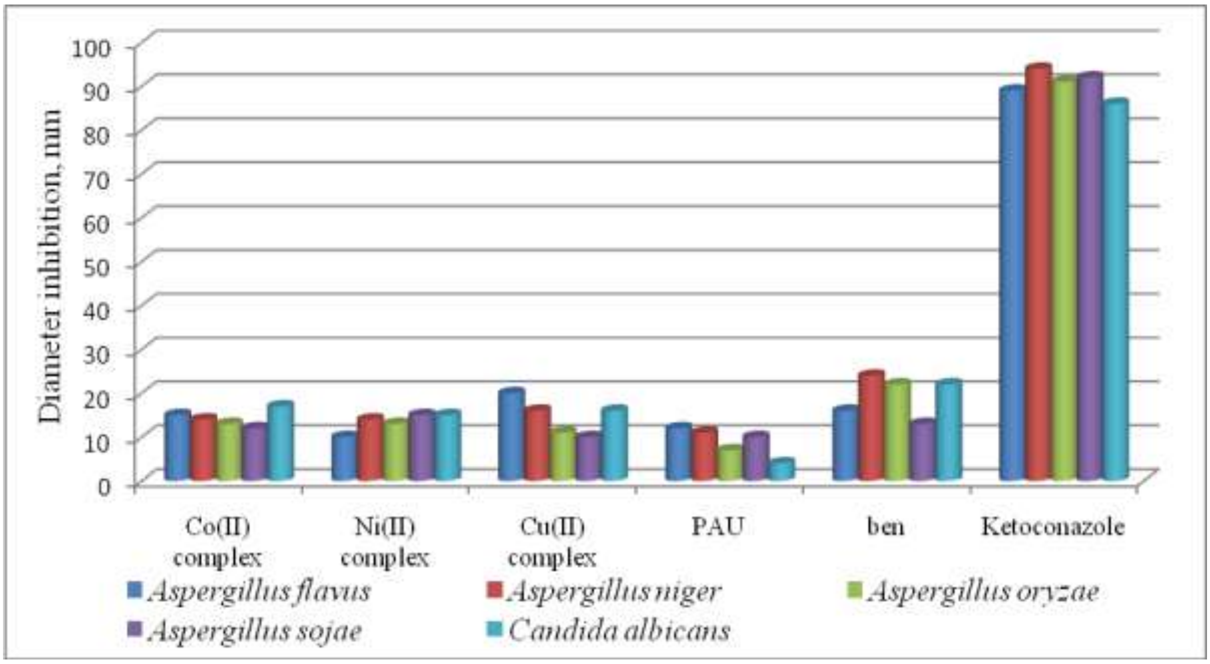

FIG. 5 COMPARISON OF ANTIFUNGAL ACTIVITIES OF Co(II), Ni(II) AND Cu(II) COMPLEXES, PAU AND BENZOATE ION LIGANDS ANDKETOKONAZOLE (STANDARD) (DIAMETER INHIBITION IN mm AT 400µgml^{-1} CONCENTRATION**)**

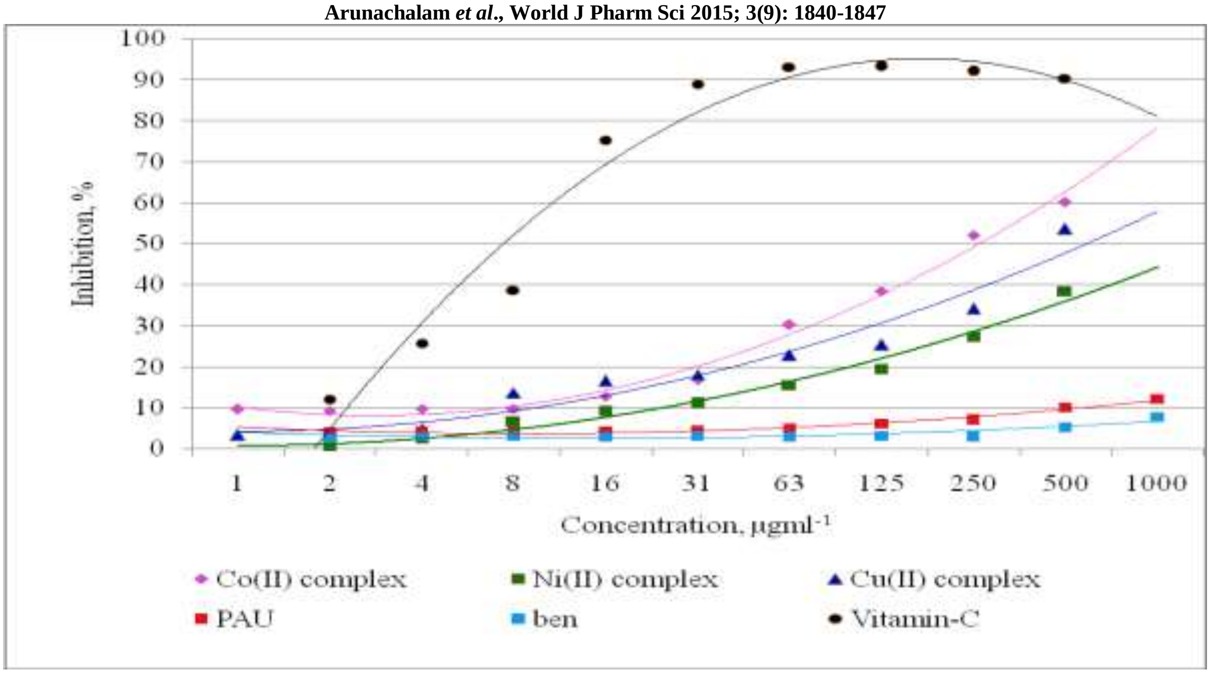

FIG. 6 DPPH FREE RADICAL SCAVENGING ACTIVITIES OF Co(II), Ni(II) AND Cu(II) COMPLEXES, PAU AND BENZOATE ION LIGANDS ANDVITAMIN-C (STANDARD) (PERCENTAGE INHIBITION AT VARIOUS CONCENTRATIONS OF METALCOMPLEXES)

REFERENCES

1. Jenney P.Glusker et al. Metal ions in biological systems. Rigaku J.1999; 16(2): 8-16.
2. Prafulla M Sabale et al. Metal complexes: Current trends and future potential. J Pharm Chem Biol Sci 2012; 2(3): 251-265.
3. Silvia E. Castillo-Blum, Norah Barba-Behrens. Coordination chemistry of some biologically active ligands. Coord. Chem. Rev. 2000; 196: 3–30.
4. Navneet Kumar, Prasad A.V.G.S. Synthesis, characterization and biological activity of metal complex of furoic acid. Int. J. Basic Appl. Chem. Sci. 2015; 5 (1): 52-57.
5. Rockville. Drug Information for the Health Care Professional. In: USP Convention USPDI, 17th ed. Volume I. MD Convention, Inc., 1997: 2315
6. Shangzhao Shi, Jiann-Yang Hwang. Microwave-assisted wet chemical synthesis: advantages, significance, and steps to industrialization. J. Miner. Mater. Charact. Eng. 2003; 2(2): 101-110.
7. Brittany L. Hayes. Recent advances in microwave assisted synthesis. Aldrichimica ACTA 2004: 31(2); 66-76.
8. Madhvi A. Surati et al. A brief review: Microwave assisted organic reaction. Scholars Research Library Archives of Applied Science Research 2012: 4 (1): 645-661.
9. Ravichandran S, Karthikeyan E. Microwave synthesis - A potential tool for green chemistry. Int. J. ChemTech Res. 2013; 3(1): 466-470.
10. Jeffery GH, Bassett J, Mendham J, Denney RC Vogel's The Text Book of Quantitative Chemical Analysis, 5th ed, Longman Scientific & Technical, Longman Group UK Limited, Longman House, Burnt Mill, Harlow Essex CM20 2JE, **1989**; pp. 329, 693, 393.
11. Dhaveethu K et al. Microwave-assisted synthesis of mixed ligand complexes of Zn(II), Cd(II) and Hg(II) derived from 4-aminopyridine and nitrite ion: Spectral, thermal and biological investigations. J. Korean Chem. Soc. 2013; 57 (3): 341-351.
12. Gunasekaran P. Laboratory manual in Microbiology, New Age International (P) Limited; New Delhi, **2000**; pp.75-77.
13. Singh AK et al. Synthesis, spectral and antimicrobial activity of Zn(II) complexes with schiff bases derived from 2-hydrazino-5-[substituted phenyl]-1,3,4-thiadiazole and benzaldehyde/2-hydroxyacetophenone/indoline-2,3-dione. Spectrochim. Acta, Part A 2013;113: 393-399.
14. Gunars Tirzitis, Grzegorz Bartosz. Determination of antiradical and antioxidant activity: basic principles and new insights. Acta Biochim. Pol. 2010; 57(1): 139–142
15. Molyneux P. The use of the stable free radical diphenylpicrylhydrazyl (DPPH) for estimating antioxidant activity. Songklanakarin J. Sci. Technol. 2004; 26(2) : 211-219.
16. Rawat S et al. Evaluation of antioxidant effect of artocarpus heterophyllus leaves extract. World J. Pharm. Pharm. Sci. 2015; 4(7): 626-631.
17. Typical Infrared Absorption Frequencies. Stretching Vibrations. Bending Vibrations. Functional Class. Range (nm). Intensity. Assignment. Range (nm) Intensity. http://staff.aub.edu.lb/~tg02/IR.pdf.
18. Packialakshmi N, Nilofer Nisha HM. Screening of antibacterial activity in polar and non polar flower and stem extract of anisomeles malabarica plant. World J. Pharm. Res. 2014; 3(6): 846-857.