Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(2):1301-1307

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

One pot template synthesis, characterization and antimicrobial studies of macrocyclic complexes of transition metal ions of bioinorganic relevance

Devendra Kumar*, Rubeena Akhtar, Neelam and Shivani Singh

Department of Chemistry, Institute of Basic Sciences, Dr. B. R. Ambedkar University, Khandari Campus, Agra

---

ABSTRACT

A novel series of mononuclear macrocyclic metal complexes of the type [M($C_{28}H_{20}N_4O_4$) X_2] using the metal (II) salts { M= Co(II), Ni (II) and Cu (II) and X= OAc^- } were synthesized by the reaction of diethylphthalate with O-phenylenediamine by adopting template method. The complexes have been characterized on the basis of microanalytical, IR, UV-Vis spectral and magnetic measurement studies. Spectral studies suggested a distorted octahedral geometry around the copper ion in copper complex where as octahedral geometry around the cobalt and nickel ions in their complexes. The antimicrobial activity of the complexes have been screened in vitro against two bacteria Pseudomonas aeruginosa and Staphylococcus aureus and two fungi Rhizopus stolonifer and Penicillium notatum to access their inhibiting potential. Metal complexes exhibited enhanced antimicrobial activity in comparison to their fragments.

Key words: Template, Macrocyclic complexes, Antimicrobial, Bioinorganic.

INTRODUCTION

The significance of macrocyclic compounds extends from large number of life composing and naturally occurring complexes with enormous biological functions to vast numbers of synthetically made ones for diverse biological and non biological functions [1-3]**.** These compounds have been explored for their antibacterial [4-6] ,fungicidal [7-8], antitumour , anticonvulsant[9]and catalytic [10] activities. The available literature has also evidenced about their anti oxidant [11] and anti HIV activities [12]**.** They are also used as MRI contrast agents [13-15], NMR shifts reagents, [16] sensitizers in dye sensitized solar cells, for heavy metal removal from aqueous solution, diet supplementation[17] and catalytic cleavage of RNA and DNA [18]**.** The thermodynamic and kinetic inertness of transition metal complexes of poly azamacrocyclic ligands have significant industrial application [19]. In view of immense pharmacological and analytical significance of macrocyclic complexes, it has been created an interest to synthesize some new macrocyclic complexes which may represent a novel class of metal-based antimicrobial agents and can provide opportunities for a large number of synthetic variations for modulation of the activities.

EXPERIMENTAL SECTION

Physical and analytical measurements

All chemicals used were of A.R. Grade. All the solvents used were of high purity and distilled in laboratory before use according to standard procedures. All the complexes were prepared by one pot template synthesis in order to

produce high yield without side reaction due to polymerization. The microanalysis of C, H, N and O were carried out at SAIF CDRI, Lucknow using Carlo Ebra 1108 Elemental analyser. The metal contents were determined by standard pyridine complex formation method [20]. The IR spectra were recorded in the range 4000-200 cm^{-1} on Perkin Elmer spectrophotometer (model RXI) using KBr pellets. The electronic spectra of the complexes in DMF were recorded on Shimadzu UV 1800 spectrophotometer. The magnetic susceptibilities were measured at room temperature on a Gouy balance using $CuSO_4.5H_2O$ as calibrant.

Synthesis of 5, 16, 25, 32- tetraoxo-1, 8, 17, 24-tetraaza- cyclodo-triacontane Co (II) complex: An ethanolic solution (20 ml) of diethyl phthalate (1.98 ml, 0.01M) was mixed with 15 ml ethanolic solution of o-phenylenediamine (1.082 g, 0.01M) in a round bottom flask with constant shaking. To this solution, 15 ml aqueous solution of cobalt acetate tetra hydrate (2.499 g, 0.01M) was mixed and contents were refluxed for 6 h. On cooling the solution a brownish precipitate was obtained. It was filtered washed with alcohol, followed by diethyl ether. Finally, it was dried in vacuum desiccator over anhydrous $CaCl_2$. . Yield = 72 %, and m.p 245 ºC; Elem. anal. calcd. **C** 54.31, **H** 3.67, **N** 7.92, **O** 9.05 % Found **C** 55.65, **H** 4.89, N 8.83, **O** 10.18 %.

Synthesis of 5, 16, 25, 32- tetraoxo-1, 8, 17, 24-tetraaza- cyclodo-triacontane Ni (II) complex: In a 250 ml round bottom flask, 0.396 ml (0.002 M) diethyl phthalate dissolved in 20 ml ethanol, was mixed with 0.216 gm (0.002 M) o-phenylenediamine, dissolved in 15 ml ethanol. To this, 15 ml aqueous solution of (0.49 g, 0.002 M) nickel acetate tetra hydrate was added. The resulting solution was refluxed for 7 h and allowed to cool. A dark green precipitate was obtained which was filtered, washed with alcohol and followed by diethyl ether. The drying of precipitate was done in vaccum desiccator over anhydrous $CaCl_2$. Yield = 68% and m.p 275ºC. Elem.anal. Calcd **C** 54.33,**H** 3.67,**N** 7.92, **O** 9.05 Found **C** 55.89, **H** 4.97, **N** 6.65, **O** 11.06 % .

Synthesis of 5, 16, 25, 32- tetraoxo-1, 8, 17, 24-tetraaza- cyclodo-triacontane Cu(II) complex: 0.99 ml (0.005 M) diethyl phthalate was dissolved in 20 ml ethyl alcohol and 0.54 gm (0.005 M) o-phenylenediamine was dissolved in 15 ml ethyl alcohol separately. Both solutions were transferred to a round bottomed flask and then 15 ml aqueous solution of (0.99 g, 0.005 M) copper acetate monohydrate was added. The mixture was refluxed for 5 h and allowed to cool at room temperature. A black product was obtained which was filtered and washed with alcohol followed by diethyl ether. The obtained product was dried in vacuum desiccator over anhydrous $CaCl_2$. Yield = 53 % and m.p 280ºC. Elem. Anal. Calcd **C** 53.96,**H** 3.65,**N** 7.87, **O** 8.99 Found **C** 54.45, **H** 4.66, N 6.54, **O** 10.02%.

Antimicrobial Studies

The macrocyclic complexes and their individual ligand constituents were screened for antimicrobial activity in *vitro* by determining zone of inhibition using disc diffusion method [21] against two bacterial strains ***Pseudomonas aeruginosa*** and ***Staphylococcus aureus*** and two fungi ***R.stolonifer*** and ***Penicillium notatum*** at different concentrations (100,50 and 25 µg/ml). The complexes were dissolved in 10% DMF which was found to be biologically inactive. All the bacterial and fungal strains used in this study were obtained from **All India Institute of Medical Sciences, New Delhi**. The results were expressed as the mean of zone of inhibition (in mm) of the repeated experiments with standard deviation (± SD). The obtained results were compared with standard drugs **Gentamycin** in case of bacteria and **Flucanazole** in case of fungi.

RESULTS AND DISCUSSION

The elemental analysis and spectroscopic data of the complexes support their mononuclear nature with the molecular formula $[M (C_{28}H_{20}N_4O_4) X_2]$ {where M= Co (II), Ni (II) and Cu (II) and X= OAc^- }.

IR Spectra

The IR spectra of all complexes exhibited an absorption band in the region 1661.7-1659.7 cm^{-1} due to >C=O stretching vibrations. A medium intensity absorption band obtained in the region 3470.3-3400.2 cm^{-1} may be assigned to >N-H stretching vibrations. This value is higher as compared to normal value for >N-H stretching vibrations, which suggested that >N-H moiety is involved in the coordination with metal ion. The involvement of N-H moiety in coordination is further confirmed by the appearance of a band in the region 493.3-483.5 cm^{-1} which may be attributed due to M-N stretching vibrations. Appearance of a band in the region 1081.7-1076.6 cm^{-1} may be attributed due to C-N stretching vibrations. The sharp intensity band in the region 1724.7-1721.9 and 1367.5-1359.8 cm^{-1} may be assigned to asymmetric and symmetric stretching vibrations of coordinated acetate ions respectively for the complexes. The complexes also exhibited absorption signals for C-H and C=C stretching vibrations in the region

3021.9-3021.3 and 1590.2-1586.4 cm^{-1} respectively. All complexes exhibited a weak band in the region 530-510 cm^{-1} due to M-O stretching vibrations.

Electronic spectra

Cobalt (II) Complex The electronic spectra of Co (II) complex displayed three bands at 13450, 15,815 and 19676 cm^{-1} corresponding to transitions from $^4T_{1g}$ (F) → $^4T_{2g}$(F), $^4T_{1g}$ → $^4A_{2g}$ and $^4T_{1g}$ (F) → $^4T_{1g}$(P) respectively. These transitions as well as the measured value of magnetic moment 4.78 BM suggested the octahedral geometry [22] for this complex.

Nickel (II) Complex

Ni (II) complex exhibited three spin allowed transitions from $^3A_{2g}$→ $^2T_{2g}$, $^3A_{2g}$ → $^3T_{1g}$ and $^3A_{2g}$ → $^3T_{1g}$(P) [12] which fall at 12,656, 18,210 and 26,107 cm^{-1} respectively which are in good agreement with the octahedral geometry. The magnetic moment value of this complex was found 3.16 BM which further indicated the octahedral environment around the metal ion.

Copper (II) Complex

The electronic spectra of Cu (II) complex displayed three bands at 13,105, 16,135 and 25,997cm^{-1} corresponding to the transitions $^2B_{1g}$ → $^2A_{1g}$, $^2B_{1g}$→ $^2B_{2g}$ and $^2B_{1g}$ → $^2E_{1g}$ respectively [23], which are in good agreement with the distorted octahedral geometry for this complex. The magnetic moment of this complex was found 1.83 BM which confirmed the distorted octahedral geometry.

On the basis of elemental analyses, IR, electronic spectral data and magnetic moment values the probable structure of complexes have been given in Fig. 1.

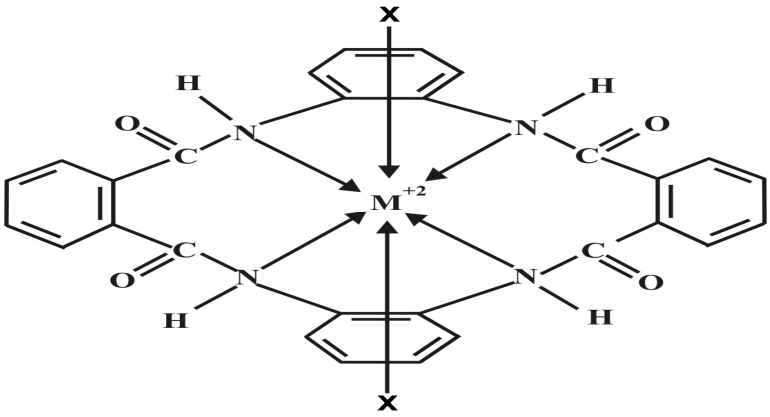

Fig.1: Where M= Co (II), Ni (II) and Cu (II) and X= OAc^-

Antimicrobial results and discussion

The cobalt complex exhibited maximum zone of inhibition 26.0 mm at the concentration 100 µg/ml against ***Staphylococcus aureus*** where as at lower concentration (25**µg/ml)** the maximum zone of inhibition was found 7.5 mm against ***Pseudomonas aeruginosa.*** The Nickel complex exhibited maximum zone of inhibition equal to 12.5 mm and 17 mm at lower concentration (25**µg/ml)** against ***Staphylococcus aureus*** and ***Rhizopus stolonifer*** respectively**.** The copper complex exhibited maximum zone of inhibition at higher and lower concentrations against the same fungus named ***Penicillium notatum*** which were found to be 21 and 14 mm respectively. The solvent used (10% DMF) was found to be biologically inactive so we can effectively conclude that the whole of the antimicrobial effect is due to the different concentrations of metal complexes and ligand constituents. The comparison of antimicrobial results of complexes with standard antibacterial and antifungal drugs showed significant and matching biological properties. The mean inhibition diameter zones with standard deviation of the complexes along with their ligand fragments are shown in the Tables 1,2 & 3.

TABLE 1: The mean inhibition diameter zone values with standard deviation (in mm) for *5, 16, 25, 32-tetraoxo-1, 8, 17, 24-tetraaza- cyclodo-triacontane Co(II) complex* against tested microorganisms.

Conc in µg/ml		100	50	25	$C_{o\,(100)}$	$C_{d\,(100)}$	Gentamycin/ Flucanazole (100)
Bacteria	*P. aeruginosa*	12.5 ± 0.71	8.0 ± 1.41	**7.5 ± 0.71**	6.5 ±0.71	6.5 ± 0.71	19.0 ± 0
	S. aureus	**26.0 ± 1.41**	20.0 ± 0	12.0 ± 0.71	11.5 ± 0.71	6.0 ± 0	21 ± 0
Fungi	*R. stolonifer*	14.5 ± 0.71	10.0 ± 1.41	7.0 ± 1.41	6.0 ± 0	8.0 ± 1.41	15.0 ± 0
	P. notatum	20.0 ± 0	15.5 ± 0.71	13.0 ± 1.41	11.5 ± 0.71	6.0 ± 0	15.5 ± 1.41

C_o = Orthophenylenediamine C_d = Diethylphthalate S = Gentamycin (Antibiotic drug), Flucanazole (Anti-fungal drug)

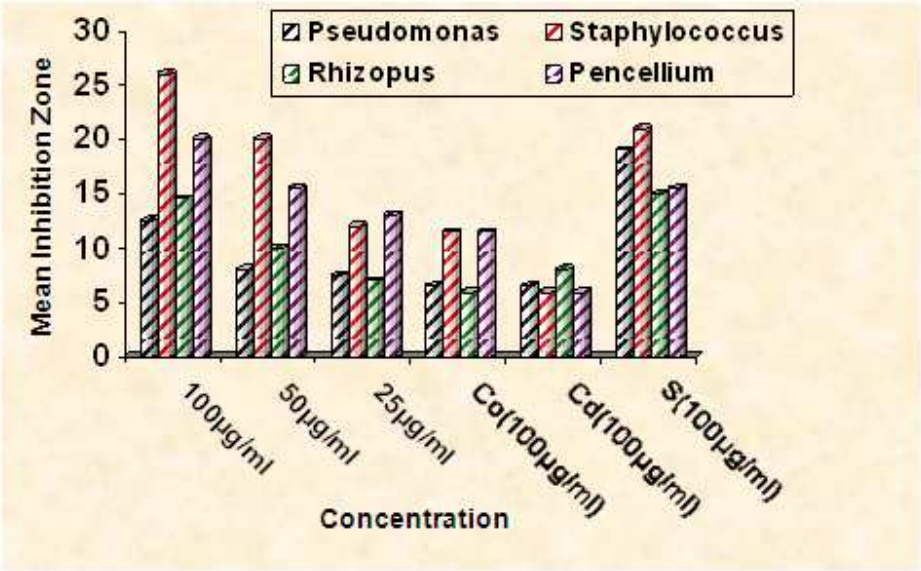

Fig (a): Mean inhibition zone at different concentrations of complex, fragments and standards against tested pathogens

TABLE.2: The mean inhibition diameter zone values with standard deviation (mm) for *5, 16, 25, 32- tetraoxo-1, 8 17, 24-tetraaza- cyclodo-triacontane Ni (II) complex* against tested microorganisms

Conc in µg/ml		100	50	25	$C_{o\,(100)}$	$C_{d\,(100)}$	Gentamycin/ Flucanazole (100)
Bacteria	*P.aeruginosa*	15.0 ±1.41	7.5 ± 0.71	6.0 ± 0	10.0±1.41	6.0 ±0	19.1 ± 0.71
	S. aureus	19.5 ± 0.71	14 .0 ± 1.41	**12.5 ± 0.71**	10.0±1.41	6.5 ± 0.71	20.9±0.71
Fungi	*R. stolonifer*	24.0 ± 1.41	20.5 ±0.71	**17.0 ± 1.41**	10.5±0.71	9.0 ± 1.41	14.9±1.41
	P. notatum	15.0 ± 0	11.0±1.41	9 .0± 1.41	12±0	6.0 ± 1.41	15.4±1.41

C_o = Orthophenylenediamine C_d = Diethylphthalate S = Gentamycin (Antibiotic drug), Flucanazole (Anti-fungal drug)

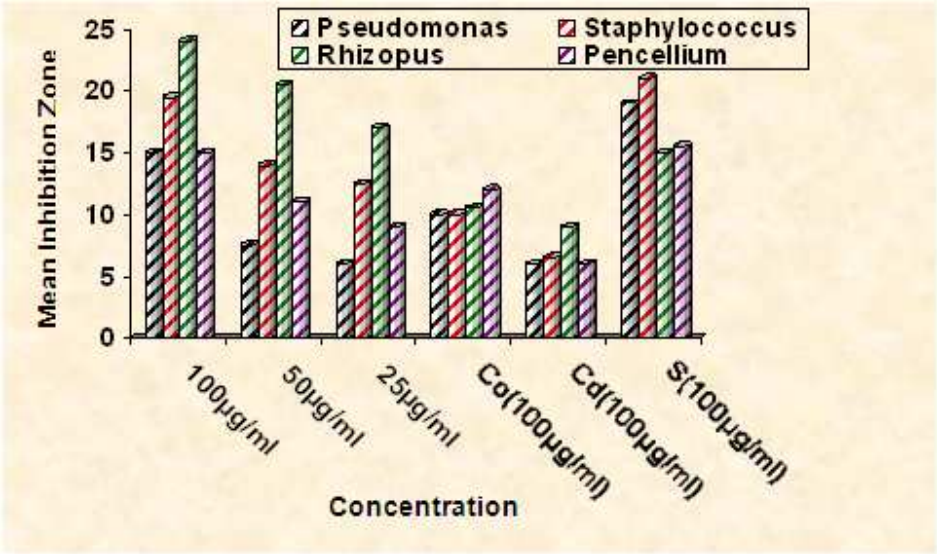

Fig.(b) : Mean inhibition zone at different concentrations of complex, fragments and standards against tested pathogens

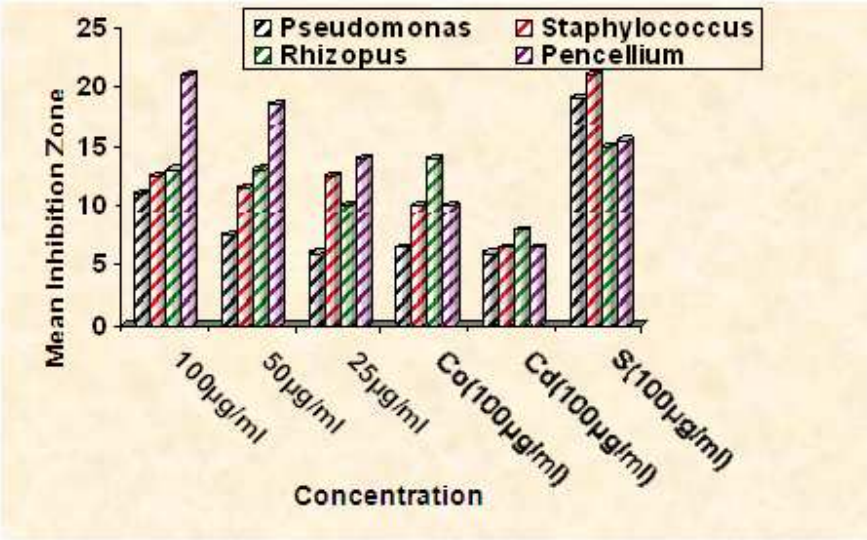

Fig.(c) : Mean inhibition zone at different concentrations of complex, fragments and standard against tested pathogens

CONCLUSION

In the present work the macrocyclic complexes were synthesized by adopting template method. The structures of the complexes were confirmed by elemental analyses, spectral data and magnetic measurement values. In these studies it was noticed that Co (II) and Ni (II) complexes have octahedral geometry while Cu(II) complex has distorted octahedral geometry. The antimicrobial activity of the complexes and ligand fragments was determined by evaluating minimum zone of inhibition by disc diffusion method.

A comparative study indicated that the complexes exhibited enhanced antimicrobial activity than their individual ligand fragments. Such enhanced activity of metal complexes may be because of increased lipophilicity due to chelation which in turn enhances penetration of complexes in to lipid membrane and blocks metal binding sites in enzymes of microorganisms. Other factor for enhancement of activity may be due to the presence of uncoordinated carboxylic moieties which bonds to trace metals in microorganisms. [24-30]**.**

TABLE 3: The mean inhibition diameter zone values with standard deviation (mm) for *5, 16 , 25, 32-tetraoxo-1, 8, 17, 24-tetraaza- cyclodo-triacontane Cu(II) complex* against tested microorganisms.

Conc in µg/ml		100	50	25	$C_{o\,(100)}$	$C_{d\,(100)}$	Gentamycin/ Flucanazole (100)
Bacteria	*P. aeruginosa*	11.0 ±1.41	7.5 ± 0.71	6.0 ±1.41	6.5±0.71	6.0 ±0	18.9±1.41
	S. aureus	12.5 ± 0.71	11.5 ± 0.71	12.5 ± 0.71	10.0±1.41	6.5 ± 0.71	21.1±0.71
Fungi	*R. stolonifer*	13.0 ± 1.41	13.0 ±0	10.0 ± 0	14.0±1.41	8.0 ± 1.41	15.1±1.41
	P. notatum	**21.0 ± 0**	18.5±0.71	**14.0± 1.41**	10.0±1.41	6.5 ± 0.71	15.4±1.41

C_o = Orthophenylenediamine C_d = Diethylphthalate S = Gentamycin (Antibiotic drug), Flucanazole (Anti-fungal drug)

Acknowledgements
Authors are thankful to Head of Department for providing necessary facilities for conducting the experimental work. The authors would like to thank the Head, Department of Microbiology School of Life Science, Dr. BR. Ambedkar University Agra for providing facility to screen antimicrobial activity of the complexes.

REFERENCES

[1] R Huszank; G Lendvay; O Horvath .*J. Biol. Inorg. Chem*. **2007,** 12, 681-690.
[2] JD Hobbs; JA Shelnutt . *J. Protein Chem*. **1995,** 14, 19-25.
[3] W Jentzen; X.Z Song; JA Shelnutt.. *J. Phy. Chem*. **1997,** 101(B), 1684-1699.
[4] S Srinivasan; P Athappan. Trans. Met. Chem. **2001**, 26 (4), 588-593.
[5] D P Singh; R Kumar; V Malik; P Tyagi. *J. Enz. Inhib. Med. Chem*. **2007,** 22**,** 177-182.
[6] M B Deshmukh; K N Alasundkar; D K Salunkhe; S A Sankpal**.** *J.Chem.Pharm.Res.***2010**, 2(4), 437-441.
[7] M Gielen; ERT Tiekink; A. Bouhdid; Dde Vos M Biesemans; I Verbruggen; R William. *Appl.Organo Met. Chem*. **1995**, 9(7), 639-648.
[8] M Tyagi ; S Chandra ; S K Choudhary. *J. Chem. Pharm. Res.*, **2011**, 3(1), 56-63.
[9] CP Bhasin; KV Goswami; M Gongiwala. *J. Indian Council Chem.*, **2009,** 26(1), 12-22.
[10] RM Chopra; D.P Singh. *Rasayan J. Chem.,* **2008,** 1(1), 93-98.
[11] V Uma; S Joshi; V Pawar. *J. Chem. Pharm. Res.* **2011**, 3 (1), 169-175.
[12] D Kumar; S Sharma; RC Sharma. *J. Indian Chem. Soc*. **2010**, 87, 1547-1550.
[13] K Kumar; MF Tweedle. *Pure and Appl. Chem*. **1993**, 65, 515-520.
[14] AD Watson; S M Rockladge. *Magetic Resonance Imaging of the Body*.2nd Edition, Raven Press, New York, **1992,** 1257-1287**.**
[15] A Bianchi; L Calabi; F Corana; S Fontan; P Iosi; A Maiocchi; L Paleari ; B Valtancoli. *Coord. Chem. Rev*., **2000**, 204, 309-93.
[16] D P Singh; R Kumar.*Trans. Met. Chem*., **2006**, 31, 970-973.
[17] JA Shelnutt; CJ Medforth; M D Berber; KM Barkigia; KM Smith. *J. Am. Chem. Soc.* **1991**, 113, 4077-4087.
[18] DP Singh ; R Kumar ; V Malik; K Kumar. *Rasayan J. Chem.*, **2008**, 1(2), 349-354.
[19] S Chandra; D Jain; B Ratnam. *J. Chem. Pharm. Res.*, **2010,** 2(1), 533-538.
[20] A.I. Vogel, 'A text book of Quantitative Inorganic Analysis' 3rd Edition .Longmann's London **1968**
[21] SA Sadeek; WH Shiwiniy; WA Zordok; AM Didamony. *J. Argen. Chem. Soc*. **2009**, 97 (2), 128-148.
[22] AA Hashmi; RA Sheikh; S Shreaz; LA Khan. *J. Chem. Pharm. Res*., **2010**, 2(2), 172-185.
[23] ABP Lever. *Inorganic Electronic Spectroscopy*, 2ndEdition Elsevier, Armsterdam, New York, **1984,** 553-571.
[24] R Sellappan; S Prasad; P Jayseelan; R Rajavel. *Rasayan J. Chem*. **2010**, 3 (3), 556-562.
[25] M Padmaja; J Pragathi; C Gayana Kumari. **2011**, 3(4), 602-613.
[26] R Sharma; Prabhat; R Singh; S Pawar; A Chauhan. *J. Am.Sci*., **2010**, 6(9) 559-564.
[27] S Shukla; A P Mishra. *Der. Pharma. Chemica*., **2010,** 2 (5), 410-418.
[28] S Rehaman; M Ikram; A Faiz; Shanawaz. *Bull. Chem. Soc*. Ethiop., **2010**, 24 (2), 201-207.
[29] N Raman; J Joseph; A Sakthivel; R Jeyamurugan. *J.Chil.Chem. Soc*. **2009**, 54 (4)**,** 354-357.
[30] SI. Habib; MA Baseer; PA Kulkarni. *Der Chemica Sinica***. 2011**, 2(1), 27-32.