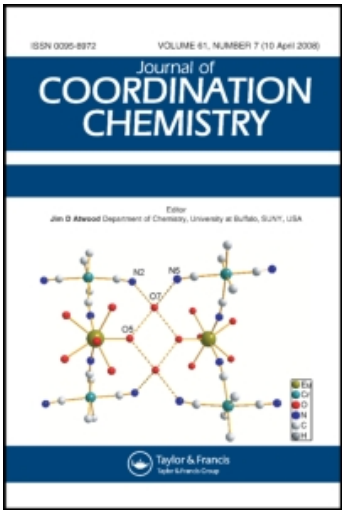

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Synthesis, spectral, and antibacterial studies of 16-membered tetraazamacrocyclic complexes

D. P. Singh[a]; Ramesh Kumar[a]; Monika Kamboj[a]; Kiran Jain[b]
[a] Department of Chemistry, National Institute of Technology, Haryana, India [b] Department of Chemistry, M.L.N. College, Haryana, India

To cite this Article Singh, D. P. , Kumar, Ramesh , Kamboj, Monika and Jain, Kiran(2009) 'Synthesis, spectral, and antibacterial studies of 16-membered tetraazamacrocyclic complexes', Journal of Coordination Chemistry, 62: 18, 2995 — 3002
To link to this Article: DOI: 10.1080/00958970903006191
URL: http://dx.doi.org/10.1080/00958970903006191

Journal of Coordination Chemistry
Vol. 62, No. 18, 20 September 2009, 2995–3002

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Synthesis, spectral, and antibacterial studies of 16-membered tetraazamacrocyclic complexes

D.P. SINGH*†, RAMESH KUMAR†, MONIKA KAMBOJ† and KIRAN JAIN‡

†Department of Chemistry, National Institute of Technology, Kurukshetra – 136 119, Haryana, India
‡Department of Chemistry, M.L.N. College, Yamunanagar, Haryana, India

(*Received 25 November 2008; in final form 2 March 2009*)

A new series of macrocyclic complexes $[M(C_{24}H_{28}N_4)X_2]$, where M = Co(II), Ni(II), Cu(II), or Zn(II) and $X = Cl^-$, NO_3^-, or CH_3COO^-, has been synthesized by [2+2] condensation of *o*-phenylenediamine with acetonylacetone (diacetonyl) in the presence of divalent metal ions. The complexes have been characterized by elemental analyses, conductance measurements, electronic, NMR, and infrared spectral studies. On the basis of these studies, a distorted octahedral geometry has been proposed for all of these complexes. The complexes were tested for *in vitro* antibacterial activity. Some show remarkable antibacterial activity against selected bacterial strains.

Keywords: Antibacterial activity; Minimum inhibitory concentration; Macrocyclic complexes; Infrared spectra

1. Introduction

Macrocyclic compounds have attracted the attention of both inorganic and bio-inorganic chemists. Condensation between diketones and primary diamines in the presence of metal ion has played a vital role in the development of tetraazamacrocyclic complexes. The metal directs the steric course of reaction toward cyclic entities rather than polymeric structures. Transition metal ions are templates for the preparation of Schiff-base macrocyclic complexes. Macrocyclic complexes are thermodynamically more stable and more selective ion binders than open chain analogs. Naturally occurring macrocycles have many roles in biological systems. Synthetic macrocyclic complexes are also important as dyes and pigments, MRI contrast agents, and models for naturally occurring macrocycles [1–4]. Macrocyclic nickel complexes find use in DNA recognition and oxidation [5], while macrocyclic copper complexes find use in DNA binding and cleavage [6]. Some macrocyclic complexes show antibacterial, antifungal, and anti-inflammatory activities [7–9]. Macrocyclic metal chelating agents are useful to detect tumor lesions [10]. In this article, a new series of macrocyclic complexes of Co(II), Ni(II), Cu(II), and Zn(II) obtained by template condensation of

*Corresponding author. Email: dpsinghchem@yahoo.co.in

ISSN 0095-8972 print/ISSN 1029-0389 online © 2009 Taylor & Francis
DOI: 10.1080/00958970903006191

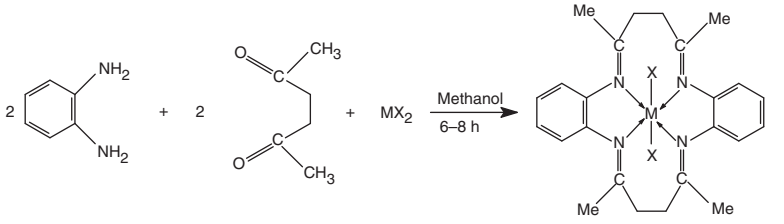
o-phenylenediamine and acetonylacetone has been reported and characterized by elemental analyses, IR, NMR, magnetic susceptibilities, electronic spectra, and molar conductance. These macrocyclic complexes were also screened for *in vitro* antibacterial activity.

2.. Experimental

2.1. *Chemistry*

All the reported macrocyclic complexes were prepared by metal ion template method. To a stirring methanolic solution (~50 cm^3) of *o*-phenylenediamine (10 mmol), divalent cobalt, nickel, copper, or zinc (5 mmol) dissolved in a minimum of methanol (~20 cm^3) was added. The resulting solution was refluxed for 0.5 h. After that acetonylacetone (10 mmol) dissolved in ~20 cm^3 methanol was added to the refluxing mixture and again refluxed for 6–8 h. Dark complexes formed by overnight cooling were filtered; washed with methanol, acetone, and ether; and dried *in vacuo* (yield 45%–50%). The complexes were soluble in DMF and DMSO, but insoluble in common organic solvents and water. They were thermally stable up to ~250°C and then decomposed.

The template syntheses of the complexes may be represented by the following scheme:



where M = Co(II), Ni(II), Cu(II), Zn(II) and
X = Cl^-, NO_3^-, CH_3COO^-

2.2. *Biological assay (*in vitro *antibacterial activity*)

The macrocyclic complexes were tested for their *in vitro* antibacterial activity against some bacterial strains using spot-on-lawn on Muller Hinton Agar [11].

2.2.1. Test pathogens. Four test pathogenic bacterial strains, namely *Bacillus cereus* (MTCC 1272), *Salmonella typhi* (MTCC 733), *Escherichia coli* (MTCC 739), and *Staphylococcus aureus* (MTCC 1144) were considered for determination of minimum inhibitory concentration (MIC) of synthesized complexes.

2.2.2. Culture conditions. The test pathogens were subcultured aerobically using Brain Heart Infusion (BHI) Agar (HiMedia, Mumbai, India) at 37°C per 24 h. Working cultures were stored at 4°C in BHI broth (HiMedia, Mumbai, India), while stock cultures were maintained at −70°C in BHI broth containing 15% (v/v) glycerol

(Qualigens, Mumbai, India). Organism was grown overnight in 10 mL BHI broth, centrifuged at 5000 × *g* for 10 min and the pellet was suspended in 10 mL of phosphate buffer saline (PBS, pH 7.2). Optical density at 545 nm (OD-545) was adjusted to obtain 10^8 cfu mL^{-1} followed by plating serial dilution onto plate count agar (HiMedia, Mumbai, India).

2.2.3. Determination of MIC. Minimum inhibitory concentration is the lowest concentration of the antimicrobial agent that prevents viable growth after overnight incubation. The antimicrobial activity of compounds was evaluated using spot-on-lawn on Muller Hinton Agar (MHA, HiMedia, Mumbai, India). Soft agar was prepared by adding 0.75% agar in Muller Hinton Broth (HiMedia, Mumbai, India). Soft agar was inoculated with 1% of 10^8 cfu mL^{-1} of the test pathogen and 10 mL was overlaid on MHA. From 1000X solution of compound (1 mg mL^{-1} in DMSO) 1, 2, 4, 8, 16, 32, 64, and 128X solutions were prepared. Dilutions of standard antibiotics (Linezolid and Cefaclor) were also prepared in the same manner. Five microliters of the appropriate dilution was spotted on the soft agar and incubated at 37C for 24 h. Pure DMSO with no compound was considered as negative control and the zone of inhibition for the compounds under investigation was measured after subtraction of the zone observed with negative control.

2.3. *Analyses*

The microanalyses of C, H, and N were recorded on an Elementar Vario EL III (Carlo Erba 1108) at CDRI, Lucknow. Melting points were determined using capillaries in electrical melting point apparatus. The metal contents were estimated using standard methods.

2.4. *Physical measurements*

Electronic spectra of metal complexes were recorded in the region 1100–200 nm on a Hitachi U-2000 spectrophotometer. IR spectra were recorded on a Beckman IR-20 spectrophotometer in KBr per Nujol mull in the range 4000–200 cm^{-1}. Proton NMR spectra were recorded in DMSO (d_6) on a Bruker ACF 300 spectrometer at 300 MHz reference to Me_4Si (0.0 ppm). Magnetic moment studies were carried out at SAIF, IIT, Roorkee, on a Vibrating Sample Magnetometer (Model PAR 155). The conductivity was measured on a digital conductivity meter (HPG System, G-3001).

3.. Results and discussion

3.1. *Chemistry*

Analytical data suggest formulas $[M(C_{24}H_{28}N_4)X_2]$, where M = Co(II), Ni(II), Cu(II), or Zn(II) and $X = Cl^-$, NO_3^-, or CH_3COO^-. The test for anion is positive only after decomposing the complexes with conc. HNO_3, indicating their presence inside the coordination sphere. Conductivity measurements in DMSO indicate nonelectrolytes

(10–20 Ω^{-1} cm^2 mol^{-1}) [12]. All compounds give satisfactory elemental analyses results as shown in table 1.

Several attempts were unsuccessful to grow crystals of complexes in different solvents or mixture of solvents for X-ray crystallography.

3.1.1. Infrared spectra. A pair of bands at ~3200 and ~3250 cm^{-1} observed in the spectrum of *o*-phenylenediamine corresponding to $\nu(NH_2)$ were absent in spectra of the complexes. A strong peak at ~1700 cm^{-1} in the spectrum of acetonylacetone from >C=O group was absent in the spectra of the complexes. This indicates the absence of >C=O of acetonylacetone in all complexes, confirming condensation of carbonyl groups of acetonylacetone and amino groups of *o*-phenylenediamine [13, 14]. This is also supported by the appearance of a new strong absorption band in the region ~1590–1610 cm^{-1} attributed to ν(C=N) [15–17]. The lower values of ν(C=N) indicate coordination of azomethine nitrogen [18]. Bands at ~1350–1000 cm^{-1} may be assigned to ν(**C**–N) and bands at ~2900–3130 cm^{-1} may be assigned to ν(C–H).

3.1.2. Far infrared spectra. Far infrared spectra show bands at ~420–450 cm^{-1} corresponding to ν(M–N) in the complexes [19–21]. Bands in the region ~420–450 cm^{-1} from ν(M–N) azomethine give information on the coordination of azomethine [22]. Bands at ~300–320 cm^{-1} may be assigned to ν(M–Cl) [19, 21]. Bands at ~210–240 cm^{-1} in all nitrato complexes are assignable to ν(M–O) of nitrato [19].

3.1.3. NMR spectra. In the ^{1}H NMR spectrum of the zinc complex, multiplets in the region 7.1–8.0 ppm may be assigned due to aromatic protons, while the –CH_2 protons (8H) are at 2.6 ppm and CH_3 protons (12H) are at 2.45 ppm [23].

3.1.4. Magnetic measurements and electronic spectra. *Cobalt complexes*. The magnetic moments of cobalt complexes at room temperature were in the range 4.82–4.90 B.M., corresponding to three unpaired electrons. The electronic spectra of cobalt complexes show bands at ~8110–9200 (ν_1), 12,400–15,550 (ν_2), and 18,750–20,210 cm^{-1} (ν_3) typical for octahedral [24], assigned as $^4T_{1g} \rightarrow {}^4T_{2g}$ (F), (ν_1), $^4T_{1g} \rightarrow {}^4A_{2g}$ (F), (ν_2), $^4T_{1g} \rightarrow {}^4T_{1g}$ (P), (ν_3). The assignment of the first spin-allowed band seems plausible since the first band appears at approximately half the energy of the visible band [25].

Nickel complexes: Nickel complexes show magnetic moments from 2.81 to 2.85 B.M. at room temperature, consistent with an octahedral environment around the divalent nickel. The solution spectra of nickel complexes exhibit a band with a shoulder on the low energy side. The other two bands observed at ~16,700–17,030 cm^{-1} (ν_2) and 26,850–28,000 cm^{-1} (ν_3) are assigned to $^3A_{2g} \rightarrow {}^3T_{1g}$ (F) (ν_2) and $^3A_{2g} \rightarrow {}^3T_{1g}$ (P) (ν_3), respectively. The first two bands result from the splitting of ν_1 and are in the range ~9710–10,500 and 11,850–12,500 cm^{-1}, which can be assigned to $^3B_{1g} \rightarrow {}^3E_g$ and $^3B_{1g} \rightarrow {}^3B_{2g}$, assuming the effective symmetry to be D_{4h} (component of $^3T_{2g}$ in O_h symmetry) [25]. The intense higher energy band at ~34,550 cm^{-1} may be due to a Π–Π* transition of the (C=N). Some bands do not follow a regular pattern and seem to be anion independent. The spectra are consistent with distorted octahedral complexes.

Copper complexes: Magnetic moments of copper complexes lie in the range 1.77–1.79 B.M. Electronic spectra of the copper complexes exhibit bands in the

Table 1. Analytical data of divalent cobalt, nickel, copper, and zinc complexes derived from and *o*-phenylenediamine and acetonylacetone.

		(Found/Calcd) %						
No.	Complexes	M	C	H	N	Color	Mol. wt.	Yield (%)
1	$[Co(C_{24}H_{28}N_4)Cl_2]$	11.90(11.75)	56.98(57.37)	5.19(5.57)	10.72(11.15)	Dark brown	502	45
2	$[Co(C_{24}H_{28}N_4)(NO_3)_2]$	10.61(10.63)	51.77(51.89)	5.00(5.04)	15.12(15.13)	Brown	555	48
3	$[Co(C_{24}H_{28}N_4)(CH_3COO)_2]$	10.50(10.74)	61.01(61.20)	5.89(6.19)	9.69(10.20)	Dark brown	549	49
4	$[Ni(C_{24}H_{28}N_4)Cl_2]$	11.22(11.57)	57.03(57.48)	5.14(5.58)	11.08(11.17)	Dark brown	501	50
5	$[Ni(C_{24}H_{28}N_4)(NO_3)_2]$	10.31(10.46)	51.29(51.90)	4.89(5.05)	15.01(15.16)	Light purple	554	42
6	$[Ni(C_{24}H_{28}N_4)(CH_3COO)_2]$	10.15(10.58)	61.21(61.31)	5.99(6.20)	9.98(10.21)	Dark green	548	44
7	$[Cu(C_{24}H_{28}N_4)Cl_2]$	11.89(12.45)	56.49(56.91)	5.28(5.53)	10.58(11.06)	Dark brown	506	50
8	$[Cu(C_{24}H_{28}N_4)(NO_3)_2]$	10.90(11.27)	51.40(51.52)	4.65(5.00)	15.1(15.02)	Brown	559	42
9	$[Cu(C_{24}H_{28}N_4)(CH_3COO)_2]$	11.02(11.39)	60.3(60.75)	6.0(6.14)	10.03(10.12)	Dark brown	553	50
10	$[Zn(C_{24}H_{28}N_4)(CH_3COO)_2]$	14.82(14.94)	60.29(60.54)	6.19(6.12)	10.07(10.09)	Light brown	555	49

region 17,500–19,550 cm^{-1} with a shoulder on the low energy side at ~14,550–16,100 cm^{-1}, and show that these complexes are distorted octahedral [24, 25]. Assuming tetragonal distortion in the molecule, the d-orbital energies may be $x^2 - y^2 > z^2 > xy > xz > yz$; the shoulder can be assigned to $z^2 \rightarrow x^2 - y^2$ ($^2B_{1g} \rightarrow {}^2B_{2g}$) and the broad band contains both $xy \rightarrow x^2 - y^2$ ($^2B_{1g} \rightarrow {}^2E_g$) and xz, $yz \rightarrow x^2 - y^2$ ($^2B_{1g} \rightarrow {}^2A_{2g}$) transitions [26]. The band separation is in the order of 2500 cm^{-1}, consistent with the proposed geometry of the complexes [26].

3.2. *Biological assay*

The synthesized macrocyclic complexes were tested for *in vitro* antibacterial activity against *B. cereus* (MTCC 1272), *S. typhi* (MTCC 733), *E. coli* (MTCC 739), and *S. aureus* (MTCC 1144). The MIC shown by the complexes against these bacterial strains was compared with MIC shown by standard antibiotics "Linezolid" and "Cefaclor" (table 2, figure 1).

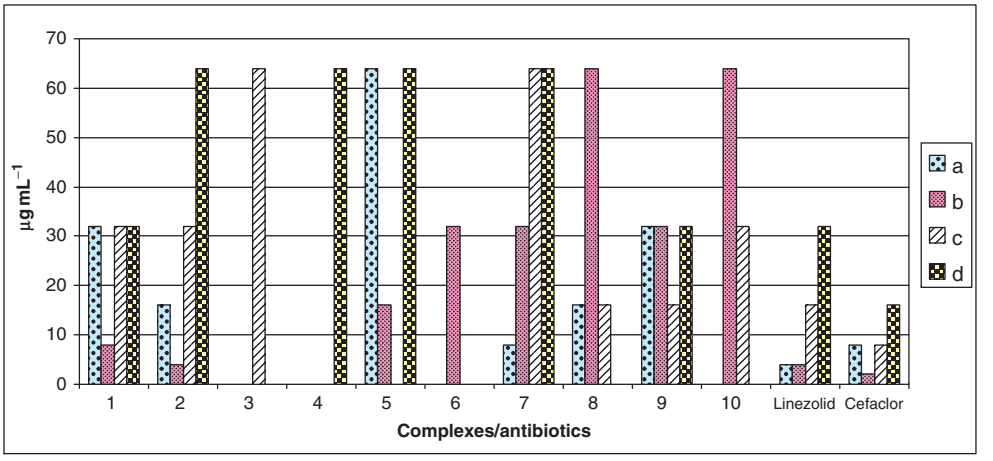
Complex **1** showed MIC ranging from 8 to 32 $\mu g\,mL^{-1}$; 32 $\mu g\,mL^{-1}$ against *S. typhi* (MTCC 733) is equal to MIC shown by standard antibiotic Linezolid against the same bacterial strain. Complex **2** showed a MIC of 4 $\mu g\,mL^{-1}$ against *S. aureus* (MTCC 1144) which is equal to MIC of Linezolid. Complex **7** showed MIC of 8 $\mu g\,mL^{-1}$ against *B. cereus* (MTCC 1272), equal to MIC shown by Cefaclor against the same bacterial strain. Complexes **8** and **9** showed MIC of 16 $\mu g\,mL^{-1}$ against *E. coli* (MTCC 739), which is equal to that of Linezolid. Further, MIC of **9** against *S. typhi* (MTCC 733) is registered as 32 $\mu g\,mL^{-1}$, equal to that of Linezolid against the same bacterial strain.

Complexes **3**–**6** and **10** showed poor antibacterial activity against all bacterial strains and **9** was most potent. Complexes **1**, **2**, **7**, and **8** showed satisfactory antibacterial activity (table 2).

Table 2. Minimum inhibitory concentration shown by complexes against test bacteria by using agar dilution assay.

	MIC ($\mu g\,mL^{-1}$)			
No.	a	b	c	d
1	32	8	32	32
2	16	4	32	64
3	128	>128	64	128
4	–	–	128	64
5	64	16	128	64
6	>128	32	–	128
7	8	32	64	64
8	16	64	16	128
9	32	32	16	32
10	128	64	32	>128
Cefaclor	8	2	8	16
Linezolid	4	4	16	32

(–) No activity; a – *B. cereus* (MTCC 1272); b – *S. aureus* (MTCC 1144); c – *E. coli* (MTCC 739); d – *S. typhi* (MTCC 733). Cefaclor and Linezolid are standard antibiotics.



a – *B. cereus* (MTCC 1272).
b – *S. aureus* (MTCC 1144).
c – *E. coli* (MTCC 739).
d – *S. typhi* (MTCC 733).
Cefaclor and Linezolid are standard antibiotics.

Figure 1. Comparison of MIC of complexes with standard antibiotics up to 64 µg mL^{-1}.

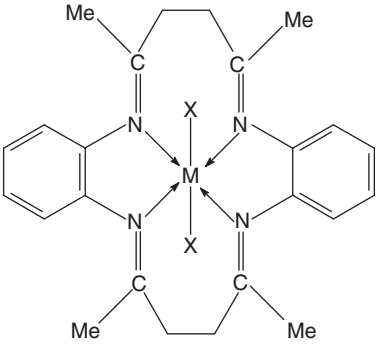


Figure 2. Proposed structures, M = Co(II), Ni(II), Cu(II), or Zn(II) and X = Cl^-, NO_3^-, or CH_3COO^-.

4.. Conclusions

4.1. *Chemistry*

Based on elemental analyses, conductivity, magnetic, electronic, NMR, and IR spectral studies, the structure shown in figure 2 may be proposed for these complexes.

4.2. *Biological activity*

Chelation, solubility, dipole moment, and conductivity influenced by metal ion may be reasons for the remarkable antibacterial activities of these complexes [27–29]. Moieties such as azomethine linkage or heteroaromatic nucleus exhibit extensive biological activities that may be responsible for the increase in hydrophobic character and

liposolubility of the molecules in crossing the cell membrane of the microorganism and enhancing biological utilization ratio and activity of complexes [30–33].

Acknowledgements

D.P. Singh thanks the University Grants Commission, New Delhi, for financial support in the form of Major Research Project. Thanks are also due to authorities of NIT Kurukshetra for providing necessary facilities. We are highly thankful to Jitender Singh for carrying out biological activities of synthesized macrocyclic complexes.

References

[1] L.F. Lindoy. *The Chemistry of Macrocyclic Ligand Complexes*, Cambridge University Press, Cambridge (1989).
[2] E.C. Constable. *Coordination Chemistry of Macrocyclic Compounds*, Oxford University Press, Oxford (1999).
[3] D.P. Singh, R. Kumar, V. Malik, P. Tyagi. *Trans. Met. Chem.*, **32**, 1051 (2007).
[4] A.D. Watson, S.M. Rockladge. In *Magnetic Resonance Imaging of the Body*, C.B. Higgins (Ed.), Raven Press, New York (1992).
[5] J.G. Muller, X. Chen, A.C. Dadiz, S.E. Rokita, C.J. Burrows. *Pure Appl. Chem.*, **65**, 545 (1993).
[6] J. Liu, T.B. Lu, H. Deng, L.N. Ji, L.H. Qu, H. Zhou. *Trans. Met. Chem.*, **28**, 116 (2003).
[7] H. Keypour, H. Khanmohammadi, K.P. Wainwright, M.R. Taylor. *Inorg. Chim. Acta*, **357**, 1283 (2004).
[8] D.P. Singh, R. Kumar, V. Malik, P. Tyagi. *J. Enz. Inhib. Med. Chem.*, **22**, 177 (2007).
[9] R.V. Singh, A. Chaudhary. *J. Inorg. Biochem.*, **98**, 1712 (2004).
[10] C. Kosmos, D. Snook, C.S. Gooden, N.S. Courtenay-Luck, M.J. McCall, C.F. Meares, A.A. Epenetos. *Cancer Res.*, **52**, 904 (1992).
[11] D.P. Singh, R. Kumar, J. Singh. *Eur. J. Med. Chem.*, **44**, 1731 (2009).
[12] S. Chandra, S.D. Sharma. *Trans. Met. Chem.*, **27**, 732 (2002).
[13] R.N. Prasad, M. Mathur. *J. Indian Chem. Soc.*, **83**, 1208 (2006).
[14] Q. Zeng, J. Sun, S. Gou, K. Zhou, J. Fang, H. Chen. *Trans. Met. Chem.*, **23**, 371 (1998).
[15] A.K. Singh, R. Singh, P. Saxena. *Trans. Met. Chem.*, **29**, 867 (2004).
[16] L.K. Gupta, S. Chandra. *Trans. Met. Chem.*, **31**, 368 (2006).
[17] A.K. Mohamed, K.S. Islam, S.S. Hasan, M. Shakir. *Trans. Met. Chem.*, **24**, 198 (1999).
[18] C. Lodeiro, R. Basitida, E. Bertolo, A. Macias, R. Rodriguez. *Trans. Met. Chem.*, **28**, 388 (2003).
[19] M. Shakir, K.S. Islam, A.K. Mohamed, M. Shagufta, S.S. Hasan. *Trans. Met. Chem.*, **24**, 577 (1999).
[20] F.M.A.M. Aqra. *Trans. Met. Chem.*, **24**, 337 (1999).
[21] S. Chandra, R. Kumar. *Trans. Met. Chem.*, **29**, 269 (2004).
[22] V.B. Rana, D.P. Singh, P. Singh, M.P. Teotia. *Trans. Met. Chem.*, **7**, 174 (1982).
[23] V.P. Krzyminiewska, H. Litkowska, W.R. Paryzek. *Monatsh. Chem.*, **130**, 243 (1999).
[24] V.B. Rana, D.P. Singh, P. Singh, M.P. Teotia. *Trans. Met. Chem.*, **6**, 36 (1981).
[25] A.B.P. Lever. *Inorganic Electronic Spectroscopy*, Elsevier, Amsterdam (1984).
[26] A.B.P. Lever, E. Mantovani. *Inorg. Chem.*, **10**, 40 (1971).
[27] Z.H. Chohan, C.T. Supuran, A. Scozzafava. *J. Enzyme Inhib. Med. Chem.*, **20**, 303 (2005).
[28] Z.H. Chohan, A. Scozzafava, C.T. Supuran. *J. Enzyme Inhib. Med. Chem.*, **17**, 261 (2002).
[29] Z.H. Chohan, M.U. Hassan, K.M. Khan, C.T. Supuran. *J. Enzyme Inhib. Med. Chem.*, **20**, 183 (2005).
[30] Z.H. Chohan, A.U. Shaikh, A. Rauf, C.T. Supuran. *J. Enzyme Inhib. Med. Chem.*, **21**, 741 (2006).
[31] Z.H. Chohan, A.U. Shaikh, M.M. Naseer, C.T. Supuran. *J. Enzyme Inhib. Med. Chem.*, **21**, 771 (2006).
[32] K. Singh, D.P. Singh, M.S. Barwa, P. Tyagi, Y. Mirza. *J. Enzyme Inhib. Med. Chem.*, **21**, 749 (2006).
[33] K. Singh, D.P. Singh, M.S. Barwa, P. Tyagi, Y. Mirza. *J. Enzyme Inhib. Med. Chem.*, **21**, 557 (2006).