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Copper(II), Nickel(II), Cobalt(II), Lithium(I) Complexes of thiosemicarbazide derivatives and Antibacterial activity

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ABSTRACT

A new series of Copper(II), Nickel(II), Cobalt(II) and Lithium(I) complexes of 2-(phenylaminoactetyl-N-phenyl hydrazine carbothioamide(H_2L) were prepared and characterized by IR, elemental analysis, H NMR spectroscopy, magnetic susceptibilities, electronic spectra and antibacterial activity . The ligand behaves as a neutral bidentate in coordination. This coordination takes place via the carbonyl oxygen of (C=O) and nitrogen atom of the N(2)H group in all complexes. Results showed that these medicaly important complexes had positive effects against some pathogenic bacteria including gram positive bacteria and gram negative bacteria that are pathogenic to human and animals

Key words: Metal complexes, IR, Conductance, Electronic spectra,TGA, Antibacterial activity.

INTRODUCTION

Thiosemicarbazones are a unique and versatile type of ligand amongest the sulfur family not only because they possess a variety of flexible donor sets but also due to the fact that they exhibit diverse biological, structural and electrochemical properties[1]. It is now well established that their transition metal complexes are more potent antimarial, antibacterial, antileprotic and antitumor agents than parent thiosemicarbazones[2]. Such a feature stems from the fact than these metal complexes inhibit DNA biosynthesis at molecular level through blocking the activity of ribonucleotide diphosphate reductase, a key enzyme involved in the transformation of DNA to RNA[3]. Another possible mode of action involves binding of complex molecules at the minor groove of the DNA helical structure through intercalation thus preventing the unwinding of

DNA[4]. Reactions of 2-thiosemicarbazido-1,4-naphthoquinone with iron(II), iron(III), cobalt(II) and copper(II) chloride yield different complexes depending on the synthetic conditions[5].The complexes of 2-hydroxy-1-napthaldehyde thiosemicarbazone with the transition metals copper(II), palladium(II) and ruthium(III) were prepared and the physical, analytical and biological data of these complexes are reported[6]. The synthesis, structure, electrochemistry and biological studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes of thiocarbohydrazone ligand are described[7] . New series of UO_2(VI), Ti(IV), Sn(IV), Zr(IV) and Th(IV) complexes were prepared, characterized and were measured, investigated for biological activity[8]. Recently complexes of copper(II), nickel(II), cobalt(II) and Lithium(I) were prepared, characterized and antirbacterial activity were study.

EXPERIMENTAL SECTION

2.1: Materials

Reagent grade chemicals were used without further purification.

2.2: Preparation of the ligand

The ligand of 2-phenylaminoacetyl-N-phenylhydrazine carbthioamide(H_2L) was prepared by mixing equimolar amount of desired hydrazide (0.01mol) in 10ml the phenyl isothiocyanate (0.01mol) in 10 ml of absolute ethanol[9, 10] . The reaction mixture was refluxed for 3 hrs. The reaction mixture was recrystalized several times from ethanol.

2.3: Preparation of the metal complexes

Complexes of copper(II), nickel(II), cobalt(II) chloride and lithium(I) chlorate of the ligand were prepared by adding stoichiometric amount of the different salts in EtOH to 2-phenylaminoacetyl-N-phenyl hydrazine carbthioamide(H_2L) in EtOH in a 1:1 molar ratio. The reaction solution was stirred magnetically at 60°C for certain about 2-6hrs. The resulting solids were filtered off, washed several times with EtOH and dried under vacuum over $P_4O_{10.}$ Elemental analyses (C, H and Cl) were performed by Microanalytical unit of the Cairo Univerisity, Egypt. Metal analysis were estimated using standard methods. IR absorption spectra were recorded using KBr discs and a Perkin-Elmer 1430 recording specrtrophotometer. ^1H NMR spectra were recorded in d^6-DMSO using 300 MHz Varian NMR spectrometer. The electronic spectra were carried out as solution (10^{-3}M) in DMF using a Perkin- Elmer Lambada 4B spectrophotometer. The molar conductivity measurements were made in DMF solution (10^{-3}M) using a Tacussel conductometer type CD6N. Magentic susceptibilities were measured at 27°C using a modified Gouy method with Johnson Mattey balance. Thermogravimetric analysis(TGA) were carried out in air using a Schimadzu(Japan) thermal analyzer at a heating rate of 10 $^oC min^{-1}$ in the temperature range 25-600 using platinum crucibles.

3.4 : Biological procedure:

The antibacterial activities of thiosemicarbazide (H_2L) and metal complexes were studied by the usual cup-plate-agar-diffusion method[24, 25] . The compounds were screened for their antibacterial activity against the following microorganisms: (a) gram positive Staphylococcus aureus and gram negative pseudomonas aeurginosa. The cup-plate-agar- diffusion method comprises of the following steps:

(1) Preparation of media, sterilization, and tubing.
(2) Sterilization of the cleaned glass apparatus.

(3) Pouring of the seeded medium into sterilized Petri dishes and cutting of the cups.
(4) Pouring of the dilute solution of the compounds into the tubs.
(5) Incubation at a particular
(6) Determination of the `zones of inhibition`

The composition of the test media is the factor, which often exerts the greatest effect upon the drug activity. This is particularly true for thiosemicarbazide, since inhibitors of these compounds appear to be present in the common bacteriological culture medium. Efficient media of known chemical composition are available for many species such as Staphylococcus aureus. and pseudomonas aeurginosa. In addition to the composition of the test media, its pH is a factor which may directly or indirectly influence the activity of a drug. The pH of the test media taken for Staphylococcus aureus and pseudomonas aeurginosa was adjusted in the range 7.6.

The composition of the basal media used in the experiments was (i) sodium chloride = 6.0 gm, (ii), peptone = 10.0gm, (iii) beef extract = 3.0 gm, (iv) yeast extract = 2.0gm, (v)
Sucrose = 1.5 gm, (vi) agar-agar = 3.0%, and (vii) distilled water = 1.0 litre.

Procedure

The measured quantity of the culture of the test organism (0.5 mL) was added to each heated (nearly 55◦C) agar media tubes. The tubes were shaken well, and the inoculated media were poured on to the sterilized Petri dishes and then allowed to set in a refrigerator maintained at 4-8◦C. The test solutions of 100, 200 and 500 ppm dilutions of the respective thiosemicarbazide were prepared in a solution of DMF. Five cups of 5mm diameter were cut in the culture media on the pert dishes. A compound solution of particular dilution (100,200 and 500 ppm) was put in the outer four cups of one of the Petri dishes, and the second solution was put in the four cups of other Petri dishes. The central cups of all the Petri dishes were filled with the controlled solution, and all the Petri dishes were allowed to remain in the refrigerator maintained at 10◦C for 1hr. to allow diffusion of the solution. The Petri dishes were then transferred to an incubator maintained at 35◦C and kept for nearly 30 hrs. The zones of inhibition formed were measured with calipers. The control of DMF, showed no activity. The activity of the compounds is represented by size of the diameter in mm.

RESULTS AND DISCUSSION

3.1: ^{1}H NMR Spectra

The ligand 2-[phenyl amino acetyl-N-phenyl hydrazine carbothio amide(H_2L) was confirmed by elemental analysis Table(1), infrared Table(2) and ^{1}HNMR spectroscopy.

The ^{1}H NMR spectrum of H_2L in chloroform, which would produce more information concerning intra molecular hydrogen bonding[11] , was not possible due to their low solubility, so they have recorded as d^6-DMSO solution. The resonance for the amido N(4)H attached to phenyl group is located in the 9.7 ppm spectral region, including that hydrogen bonding with d^6-DMSO does not occur, in agreement with previous results[12, 13] . The 1H signals due to the hydrazido group for N(1)H occurs at at 10.0 ppm indicating the involvement of these hydrogens through intramolecular hydrogen bonding with the carbonyl oxygen of – C-NH group. The other hydrazido group N(2)H appears at 9.5 ppm . A singlet at.3.8 ppm and multiplet at 7.6 ppm are attributed to the protons CH_2 and aryl groups respectively. The reaction of the ligand with Co(II), Ni(II), Co(II) chloride and Li(I) chlorate produce complexes of the general formulae $Cu(H_2L)_2Cl_2.2H_2O$, $Ni(H_2L)\ Cl_2.3H_2O$, $Co(H_2L)_2Cl_2$ and $Li(H_2L)_2.ClO_4$ are shown in Table (1). These air stable complexes are non-hygroscopic, partially soluble in most organic solvents, but freely soluble in DMF and DMSO. Values of molar conductivities in DMF (10^{-3}M) solution (Table1) show that the complexes are non-electrolytes, indicating coordination of the ligand anions[14].

Table: 1 Elemental analyses, molar conductivities and magnetic susceptibilities of ligand (H_2L, $C_{15}H_{16}N_4OS$) and their metal complexes.

No.	Complex	Colour	Found (Calc .) %					μ_{eff} (B.M)
			C	H	Cl	M	^M	
	H_2L	Pale brown	60.2(60.1)	5.6(5.3)	-	-	__	__
1	$Cu(H_2L)_2Cl_2.2H_2O$	Green	46.4(46.7)	4.4(4.7)	9.2(9.4)	8.3(8.1)	22	1.7
2	$Ni(H_2L)\ Cl_2.3H_2O$	Brown	36.9(37.2	4.7(4.5)	14.7(14.5)	12.1(12.2)	29	2.4
3	$Co(H_2L)_2Cl_2$	Dark brown	49.2(49.3)	4.7(4.4)	9.73(9.9)	8.1(8.4)	32	4.8
4	$Li(H_2L)_2ClO_4$	*Brown*	51.3(51.0)	4.4(4.5)	10.0(10.2)	1.0(1.3)	20	-

M=molar conductivity ohm^{-1} cm^2 mol^{-1} in 10^{-3}M DMF solution

3.2: The infrared spectra of the ligand and complexes

A study and comparison of the IR spectra of the ligand(H_2L) and their metal complexes Table 2. imply that the ligand is bidentate in nature. The IR spectrum of the free ligand shows five bands at 3340, 3290, 3250, 1677 and 747 cm^{-1} are assigned to ν(N4-H), ν(N2-H), ν(N1-H), ν(C=O) and ν(C=S) vibrations.

The IR spectra of the complexes $Cu(H_2L)_2Cl_2.2H_2O$,$Ni(H_2L)\ Cl_2.3H_2O$, $Co(H_2L)_2Cl_2$ and $Li(H_2L)_2.ClO_4$ show that the ligand(H_2L) behaves as neutral bidentate in nature, coordinating occur in all complexes via the carbonyl oxygen (C=O) and nitrogen atom of the(N-2H) group. The mode of complexation is suggested by shifted of both ν(C=O) and ν(N-2H) to lower frequencies compared to that of free ligand . The new bands appeared at 390-445 cm^{-1} and 480-495 cm^{-1} assigned to ν(M-O) and ν(M-N) [15, 16]respectively. The chloro complexes[17] show bands at 315 -325 cm^{-1}. While in complex $Li(H_2L)_2ClO_4$ appeared two bands at 1120 and 630cm^{-1} indicates that the T_d of Clo_4 is maintained[18]. The absence of coordinated water molecules from the hydrated complexes $Cu(H_2L)_2Cl_2.2H_2O$,$Ni(H_2L)\ Cl_2.3H_2O$ are confirmed by the absence of rocking , twisting and wagging vibrational modes which are normally activated at 910-930 cm^{-1} and 660-600 cm^{-1} , as well as the presence of medium and broad band at 3440-3450 cm^{-1} indicating that the water in these complexes are lattice rather than coordinated[19].

Table: 2 Infrared spectral bands (cm^{-1}) for ligand (H_2L) and their metal complexes

No.	Compound	ν(N4-H)	ν (N2-H)	ν (N1-H)	ν (C=O)	ν C=S)	ν (M-N)	ν (M-O)	ν (M-Cl)
	H_2L	3340(m)	3290(w)	3250(w)	1677(s)	747(s)	-	-	-
1	$Cu(H_2L)_2Cl_2.2H_2O$	3325(br)	3240(w)	3185 (w)	1605(s)	750(s)	480(m)	390(m)	325(w)
2	$Ni(H_2L)\ Cl_2.3H_2O$	3290(w)	3230(w)	3170 (w)	1640(s)	755(s)	490(m)	420(w)	330(w)
3	$Co(H_2L)_2Cl_2$	3285(m)	3245(w)	3185 (w)	1605(s)	760(s)	495w)	445(w)	315(w)
4	$Li(H_2L)_2ClO_4$	3430(w)	3285(m)	3180 (m)	1610(m)	755(s)	475(m)	432(m)	320(m)

3.3: Magnetic susceptibilities and electronic absorption spectroscopy

The magnetic moment value of the copper(II) complex Table (1), lie in the range observed for the copper(II) complex with one unpaired spin(1.73B.M) [20].While the magnetic moment value of nickel(II) complex(2.4B.M), corresponding to two unpaired electrons[21] . Also the value of magnetic moment of cobalt(II) complex (4.8B.M), with three unpaired electrons is in good agreement with those reported for octahedral structure[22]. The electronic spectral bands of the copper(II) complex as well as the spectra of the ligand in solution DMF are shown in Table (3). The π - π^* transition band is observed at 33000 cm^{-1} for H_2L. Compared to the free ligand, in the copper(II) complexes. This band is shifted to longer wave length (Red shift) which is consistent with an increase in the degree of Pi- cloud conjugation. The electronic spectra of copper(II) complex display one broad band at the 15560 cm^{-1} range due to the $^2B_{2g} \rightarrow {}^2A_{2g}$ transition with a square planar geometry.The band at 15760 cm^{-1}, assigned to charge transfer band.

The electronic spectra of nickel (II) complex was found to be paramagnetic , which excluded a square planar configuration. The possible geometry for the complex had been assigned from the electronic spectral studies[21] .

The electronic spectra of cobalt(II) complex lie in range reported for an octahedral geometry around the Co(II) ion[23] . The electronic spectrum of an octahedral cobalt(II) complex is expected to involve three allowed transitions[22] .$^1T_{1g} \rightarrow {}^4T_{2g}$ (ν_1), $^1T_{1g} \rightarrow {}^4A_{2g}$ (ν_2) and $^4T_{1g} \rightarrow {}^4T_{2g}(F)$ (ν_3) . The values of the nepheloauxetic parameters ß indicate that the covalent character of the metal ligand)σ –bond is low.

Table: 3 Solution DMF electronic spectra (cm^{-1}) of H_2L and their metal complexes

Compounds	Intraligand and charge transfer			d-d bands
H_2L	33000			
$Cu(H_2L)_2Cl_2.2H_2O$	31875	30300	26210	15760
$Ni(H_2L)\ Cl_2.3H_2O$	31755	30215	25635	147 20
$Co(H_2L)_2Cl_2$		28325	-	17245 14915

3.4: Themogravimetric analysis

Thermogravimetric analysis of the solid complexes have been studied. $Cu(H_2L)_2Cl_2.2H_2O$ displays initial weight loss within the temperature range 25-90 °C, corresponding to loss of two mole of water crystallization (Found 3.5%,Calc. 3.0%). complex $Ni(H_2L)\ Cl_2.3H_2O$ show that the loss of lattice water overlap with thermal decomposition of the complex. The TGA curves of the two complexes exhibit a thermal stability up to 270 °C. The complexes start to decompose up temperature.

3.5 : Antimicrobial activity

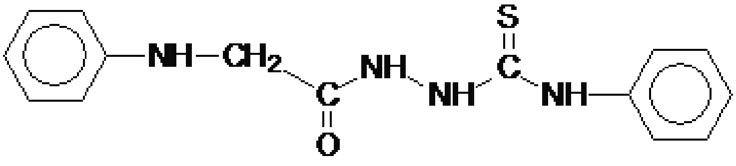
A number of authors[26- 30] were interested to investigate the biological and medicinal properties of transition metal complexes of thiosemicarbazides. Thomas and Parmeswaran[27] studied the antitumor activities of Mn2+, Co2+, Ni2+, and Cu2+ chelates of anthracene-9-carboxaldehyde thiosemicarbazone. Murthy and Dharmaraja[28] reported the cytotoxic activity of phenylglyoxal bis (thiosemicarbazone) against Ehrlich ascites carcinoma cells. These compounds were also screened for antimicrobial activity on Staphylococcus aureus and pseudomonas aeruginosa. They inhibited the bacterial growth considerably. Recently, Singh[31] published a review article on metal complexes of glutathione and their biological properties. In the present studies the anti-bacterial activities of the Copper(II), Nickel (II), Cobalt(II) and Lithium(I) complexes of thiosemicarbazide by the agar plate method. In DMF solvent at a concentration of 100, 200 and 500 ppm were tested against Gram positive bacteria Staphylococcus aureus and Gram negative bacteria pseudomonas aeruginosa Table (4). Diameter of inhibition zone (in mm) against Gram positive and Gram negative bacteria were indicated the effect of complexes on the bacterial growth.under the same conditions. Table (4) show that all complexes of thiosemicarbazide have moderate antibacterial activities against these bacteria.

Table: 4 Bactericidal activities of different concentrations of metal complexes on the growth of Staphylococcus aureus and Pseudomonas aeruginosa. Data are expressed as indicated of growth inhibition G mm

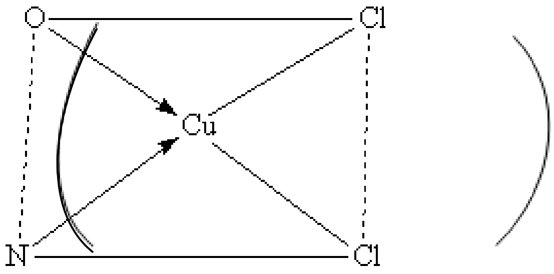
No.	Compound	*Staphylococcus aureus*			*Pseudomonas aeruginosa*		
		100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm
	H_2L	7	9	11	8	10	13
1	$Cu(H_2L)_2Cl_2.2H_2O$	15	18	22	13	16	20
2	$Ni(H_2L)\ Cl_2.3H_2O$	11	15	19	10	13	16
3	$Co(H_2L)_2Cl_2$	13	17	21	12	14	18
4	$Li(H_2L)_2ClO_4$	10	13	18	9	12	15

CONCLUSION

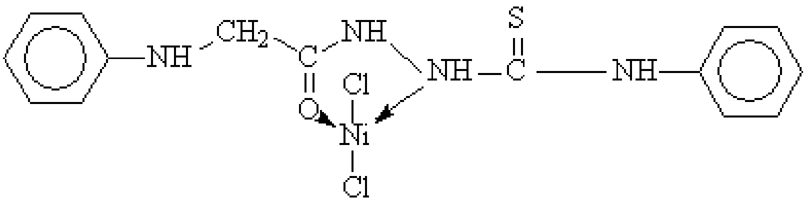
We have synthesized and structurally characterized copper(II),nickel(II),cobalt(II)and lithium(I) complexes with 2-[phenyl amino acetyl-N-phenyl hydrazine carbothioamide(H_2L). It should be pointed out that the ligand act as neutral bidentate , coordinating to the metal ion through the carbonyl oxygen ν(C=O), and nitrogen atom of the(N(2)H) group. The study revealed that these complexes had antibacterial activities against Gram positive and Gram negative bacteria, these type of bacteria are pathogenic to human and animals, so these complexes have medical importance.



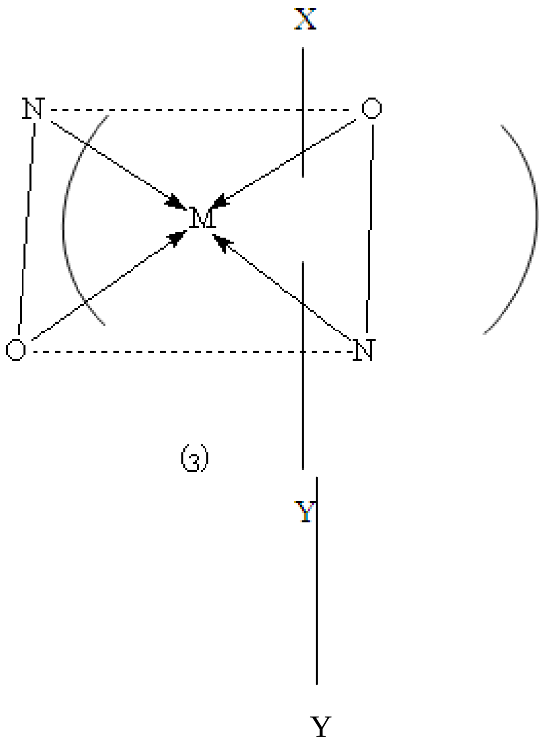
H_2L



(1)



(2)



(3)

M	*X*	*Y*	*Complexes no.*
Co	*Cl*	*Cl*	*3*
Li	*0*	ClO_4	*4*

Fig(1): The chemical structure of the ligand and its metal complexes

REFERENCES

[1] MV Angelusiu; Gal Almajan; TRosu; M Negoiu; ER Almajan; J Roy. *Europan J. M.Chem.*, **2009**, 44, 3323-3329.
[2] AG Quiroga; CN Ranniger. *Coord. Chem. Rev.*, **2004**, 248, 1-9 .
[3] J Easmon; G Purstinger; G Heinisch; T Roth; H H Fiebig; W Holzer; W Jager; M Menny; J Hoffimann. *J. Med.Chem*., **2001**,44, 2164-2175.
[4] G Nocentini; Grit Rev. *Oncol.Hematol*, **1996**, 22, 89-101 .
[5] R C Chikate; S B Padhyde. *Polyhedron*, **2005**, 24, 1689-1697.
[6] S H Abo El-Fetoh; A E Eid; A I Abd El-Kareem; M A Wassel. *Synth.React. Inorg. Met.Org. Chem*., **2000**, 30(3), 513-523 .
[7] M P Sathisha; V K Revankar; K S Pai. *Metal-Based Drugs*, **2008**, ID362105, 1.
[8] S A Aly; T I Kasher; M A El-Mogy. *Egypt, J. Chem*., **2007**, 50(1)), 87-95.
[9] A M Aal; W A El-Sayed; A H A Aleem; E S H El-Ashry. *Pharamazie*, **2003**, 58(11), 788-799.
[10] S P Hirmath; J S Biradar ; S M Kudari. *J. Indian, Chem., Soc*., **1984,** 61(1), 746-756.
[11] D X West; AM Stark; G A Bain; A E Liberate. *Transition Met.*, **1996**, 21, 2
[12] S A Aly , *The World Journal of Chemistry*, **2008**, 4 (1), 1-8.
[13] D X West; Y H Yang; T L Klein; K I Goldbery; A E Liberate; J Valdez Martinez; S Hemdrdez. *Polyhedron*, **1995**, 14, 305-316.
[14] H Youhong; I Zienglu; Z Yulan; W Shozu. *Syn. React. Inorg. Met. Org. Chem*., **1995**, 25, 349-360.
[15] N T Akinchan; D X West; Y H Yang; M M Salberg; T L Kelin. *Transition Met. Chem.*, **1995**, 70, 48-54.
[16] A K El-Sawaf; D X West; F A El-Saied; R M El-Bahnasawy. *Transition Met., Chem*., **1998**, 23, 565-655.
[17] G M Abou; El-Reash; K M Ibrahim; R E El-Shadily; M M Bekheit. *Acta, Chem., Hung*, **1990**, 127, 21-32.
[18] R Raina; T S Srivastava. *Inorg.Chim. Acta*, **1982**, 67, 83-97.
[19] S V Tatwawadi; A P Sing; K K Narang. *J. Sci., Res*., Banners Hindu Univ., 1980, 3, 143-155 .
[20] M Pulauniandavar; C Natajon. *Aust. J.Chem.*, **1985**, 1985,37, 237-248 .
[21] F A El-Saied; M I Ayad; R M Issa; S A Aly. *Polish. J.* **2001**,75, 773-783.
[22] S Yamada. *Coord.Chem. Rev*., **1966**, 1, 415-423.
[23] E K Barefeid; D H Busch; S M Nelson. *Quart. Rev*., **1968**, 22, 457-469.
[24] W C Kaska; C Carrans; J Michalowski; J Jackson; W Levinson. *Bioinorg. Chem*., **1978**, 8, 245-258.
[25] D L Klayman; J E Bartosevich; T S Griffith; C J Mason; J P Scovill. *J. Med. Chem*., **1979**, 22, 855-868 .
[26] S B Padhye; G B Kauffman; *Coordination Chemistry Reviews*, **1985**, 63,127-138.
[27] J Thomas; G Parameswaran. *Asian Journal of Chemistry*, **2002**, 14(3), 1354-1360 .
[28] N Murthy; T S Dharmarajan. *Asian Journal of Chemistry*, **2002**, 14(3), 1325-1335.
[29] M R Taylor; J P Glusker; E J Grabe; J A Minkin. *Bioinorganic Chemistry*, **1974**, 3(3), 189-198.

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[30] M Bellaci Ferrari; G Gasparri Fava; E Leporati. *Journal of Inorganic Biochemistry*, **1998**, 70(2),145-156 .
[31] B K Singh. *Asian Journal of Chemistry*, **2005**, 17(1),1-12.