



Synthesis, Characterization and Biological Screening of Novel Metal(II) Complexes of 2-[[2-(5-Benzoyl-1H-benzotriazol-1-yl)-2-oxoethyl]amino]-5-bromobenzoic Acid

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Received: 18 November 2020;

Accepted: 8 January 2021;

Published online: 20 March 2021;

AJC-20276

In this work, 5-bromoanthranilic acid was condensed with 1-(5-benzoyl-1H-1,2,3-benzotriazole-1-yl)-2-chloro-ethanone to form 2-[[2-(5-benzoyl-1H-benzotriazol-1-yl)-2-oxoethyl]amino]-5-bromobenzoic acid. The newly synthesized ligand and its metal(II) complexes with first transition metal series (Cu(II), Ni(II), Co(II), Zn(II) and Mn(II)) have been synthesized and characterized by using elemental analysis, infrared and electronic spectra. The IR spectra, NMR spectra and atomic absorption analysis show that the benzotriazole ligand formed chelates with metal in a 2:1 (ligand:metal) stoichiometry. All the metal(II) complexes were screened for their antibacterial activity against Gram-positive and Gram-negative bacteria. Among the synthesized metal(II) complexes, Cu(II) complex showed the highest antibacterial activity.

Keywords: Antifungal, Antibacterial, Benzotriazole, Triazole, 5-Bromo anthranilic acid.

INTRODUCTION

Synthetic organic chemist made significant progresses in discovering and developing wide range of heterocyclic compounds for the benefit of mankind [1]. One remarkable structural feature and characteristic to heterocycles, which continue to be exploited, is their capability to accommodate the substituent's around central frame. Ever since their initial use in agriculture which began a century ago, the chemistry of nitrogen and sulfur containing heterocycles has made remarkable advances [2]. A number of nitrogen containing heterocyclic derivatives are known to be good ligands. Some of them are crown ethers, calixarenes, cucurbiturils and porphyrins [3] are also able to used as ligands to prepare complexes with different metal ions due to the presence of electron donor groups. Benzotriazole is continuing prompt growth in the synthesis of heterocycles since it can be used as a shape to construct novel biologically active molecules [4-6].

Compounds containing triazole moiety have attracted much interest because of their biological applications [7-9]. Triazole containing compounds shows in several metabolic products of fungi and primitive marine animals. The coordination chemistry of triazole and benzotriazole derivatives was

studied due to their importance in industry, agriculture and their biological activities [10-13]. Benzotriazole derivatives functions as an agonist for a number of proteins. As vorozole and alizapride have valuable inhibitory properties in contrast to distinct proteins and benzotriazole esters have been started to perform as mechanism based fascinator for many respiratory syndrome 3CL proteases [14]. Benzo-fused azole consists of three heteroatoms, which are benzoxazole, benzothiazole and benzotriazole have been widely investigated for their biological activities [15,16].

Benzotriazole is continuing prompt growth in the synthesis of heterocycles since it can be used a shape to construct novel biologically active molecules. Nitrogen atom containing organic compounds are some of the leading complexing agents used in the industries. Many researchers synthesized several ligands containing 5-benzoyl benzotriazole moiety and prepared their metal complexes and also evaluated their antimicrobial activity [17-20]. The present work comprises the synthesis and characterization of few transition metal(II) complexes of the novel ligand containing benzotriazole moieties, 2-[[2-(5-benzoyl-1H-benzotriazol-1-yl)-2-oxoethyl]amino]-5-bromobenzoic acid with first transition series elements Zn^{2+} , Cu^{2+} , Ni^{2+} , Mn^{2+} , Co^{2+} and evaluated their antimicrobial an antifungal activity.

EXPERIMENTAL

The chemicals and solvents used of analytical grade and procured from the commercial sources. The melting points of all the metal(II) complexes were determined by open capillary methods and are uncorrected. 1*H*-benzoyl benzotriazole (1) [21] and *N*-(1-chloroacetyl)-5-benzoyl benzotriazole (2) [22] were synthesized by the reported procedures.

Synthesis of 2-{[2-(5-benzoyl-1*H*-benzotriazol-1-yl)-2-oxoethyl]amino}-5-bromobenzoic acid (ligand): *N*-(1-Chloroacetyl)-5-benzoyl benzotriazole, (2.99 g, 0.01 mol) and 5-bromo anthranilic acid (2.16 g, 0.01 mol) in ethanol were suspended. To this suspension, sodium bicarbonate (0.84 g, 0.01 mol) was added and the mixture content was warmed on the steam bath for about 6 h. On cooling, the solid crystals were separated out by filtration and washed with little alcohol and dried (**Scheme-I**). Yield 68%; m.p.: 240 °C, m.f.: C₂₂H₁₅N₄O₄Br, m.w.: 479 g/mol.

Synthesis of metal complexes: Metal(II) complexes were synthesized by the following common methods. The ligand (0.01 mol) dissolved in ethanol was mixed with the corresponding metal(II) salt (0.005 mol) dissolved in minimum quantity of ethanol. Both the solutions were mixed together with continuous stirring and raised pH (4-5 for Cu²⁺, 6 for Ni²⁺ and Co²⁺, 5.6 for Mn²⁺ and Zn²⁺) by addition of sodium acetate solution. The resulting mixture was refluxed for 4 h. The solid coloured complexes were filtered, washed and dried and recrystallized. The yield of complexes was in the range of 64-68%.

Measurements: The elemental analysis for C, H and N elements of metal chelates were carried out on elemental analyzer Thermofinigan 1101 Flash EA (Italy). The metal contents were estimated using standard methods [23]. The halogen content was determined by Carius methods [24]. The infrared spectra (KBr) were examined in the range 4000-600 cm⁻¹ with Nicolet 760 FTIR spectrophotometer. A diffused reflectance spectrum of solid metal complexes was recorded on a Beckman DK2A spectrophotometer using MgO as reference. Magnetic susceptibility measurement of the entire metal complex was carried out at room temperature (303K) by the Gouy method [25] using mercury tetrathiocyanatocobaltate (II) as calibrant [26]. The values of effective magnetic moment μ_{eff} were calculated by the using eqn. 1 and diamagnetic corrections were made by using Pascal's constant [27].

$$\mu_{\text{eff}} = 2.84\sqrt{X_m \times T} \quad (1)$$

¹H NMR spectrum were recorded on Bruker WM 400FT MHz NMR instrument using CDCl₃ or DMSO-*d*₆ as solvent and TMS as internal reference.

Biological activities: The ligand and their metal(II) complexes were screened at 1000 ppm concentration *in vitro* for their antifungal activity against three fungi *viz.* *Penicillium expansum*, *Nigrospora* sp. and *Aspeginus niger*. The antifungal activity of the compounds was measured by cup-plate method [28]. Five days old cultures were suspended in potato dextrose agar medium and autoclaved at 1200 °C for 15 min at 15 atmospheric pressure. The percentage of inhibition of fungi was calculated after 5 days using eqn. 2:

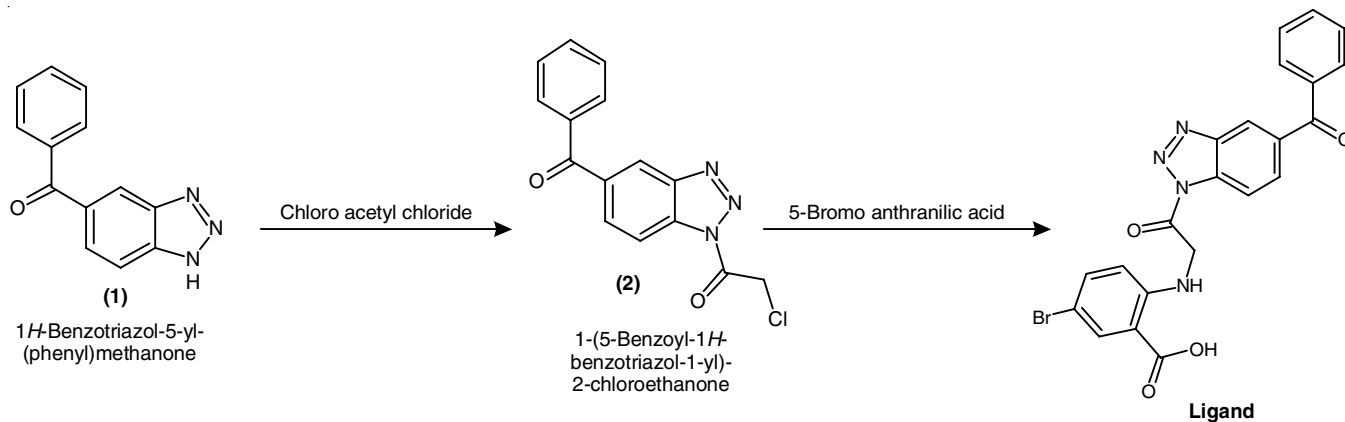
$$\text{Inhibition (\%)} = \frac{100(A - B)}{A} \quad (2)$$

where, 'A' is area of colony in control plate and 'B' is area of colony in test plate.

RESULTS AND DISCUSSION

1-(5-Benzoyl-1*H*-1,2,3-benzotriazol-1-yl)-2-chloroethanone condensed with 5-bromo anthranilic acid to form 2-{[2-(5-benzoyl-1*H*-benzotriazol-1-yl)-2-oxoethyl]amino}-5-bromobenzoic acid. The synthesized novel ligand was further utilized for the synthesis of Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) complexes. The synthesized ligand and its metal(II) complexes were characterized by ¹H NMR, IR, mass and elemental analysis. The ligand was soluble in CH₃OH, C₂H₅OH, DMSO and DMF where as metal(II) complexes were soluble in DMSO/DMF. The physical properties of ligands and its metal complexes are shown in Table-1.

The structure of ligand and its metal(II) complexes were confirmed from the IR and NMR spectral data. The anticipated IR spectral, inflections around 1450 and 1480 cm⁻¹ attributed to symmetric and asymmetric stretching vibrations frequencies of CH₂ presence in COCH₂NH linkage. The bands around 1500 cm⁻¹, 1600 cm⁻¹ and 3030 cm⁻¹ in the region of double bond are appeared. The strong band around 1690 ± 10 cm⁻¹ largely responsible to C=O of COOH group of aromatic acid. The other bands in the fingerprint region are appeared at their respective positions. The bands around 1020 and 1220 cm⁻¹ are mainly



Scheme-I: Synthetic route of 2-{[2-(5-benzoyl-1*H*-benzotriazol-1-yl)-2-oxoethyl]amino}-5-bromobenzoic acid (Ligand)

TABLE-1
MICROANALYTICAL DATA OF THE SYNTHESIZED LIGAND AND ITS METAL(II) COMPLEXES

Compound	m.w. (g/mol)	Yield (%)	Elemental analysis (%): Calcd. (found)				
			C	H	N	Br	M
C ₂₂ H ₁₅ N ₄ O ₄ Br	479.00	68	55.11 (55.10)	3.13 (3.11)	11.69 (11.66)	16.70 (16.68)	–
C ₄₄ H ₂₆ N ₈ O ₈ Br ₂ Cu·2H ₂ O	1053.54	66	50.11 (50.09)	2.46 (2.45)	10.63 (10.61)	15.18 (15.17)	6.03 (6.01)
C ₄₄ H ₂₆ N ₈ O ₈ Br ₂ Ni·2H ₂ O	1048.69	70	50.34 (50.32)	2.47 (2.46v)	10.67 (10.66)	15.25 (15.23)	5.59 (5.57)
C ₄₄ H ₂₆ N ₈ O ₈ Br ₂ Co·2H ₂ O	1055.38	67	50.02 (50.01)	2.46 (2.44)	10.61 (10.60)	15.16 (15.15)	6.19 (6.17)
C ₄₄ H ₂₆ N ₈ O ₈ Br ₂ Mn·2H ₂ O	1048.93	72	50.33 (50.31)	2.47 (2.45)	10.67 (10.65)	15.25 (15.24)	5.61 (5.60)
C ₄₄ H ₂₆ N ₈ O ₈ Br ₂ Zn·2H ₂ O	1044.93	65	50.52 (50.51)	2.48 (2.45)	10.71 (10.70)	15.31 (15.30)	5.25 (5.24)

due to C-N bending vibrations, while the C-N stretching vibration appeared around 1690 cm⁻¹. The weak bands due to out of plane deformation of 1,3,5-substituted benzene ring systems appeared at near 896 cm⁻¹. The bands appears at 2341, 1558 and 1488 cm⁻¹ due to benzotriazole structure and the band around at 723 cm⁻¹ may be arise from 1,2,3-triazole system.

Most of the bands appeared in the spectra of corresponding metal complexes were observed at the similar position in the IR spectra region for their metal ligands. The band due to C=O of COOH group appeared in the spectra of ligand is almost vanished in the spectra of metal complex. The new strong band around 1600 cm⁻¹ appeared and this might be responsible for COO⁻ anion. This is expected as COOH group of ligand participated in the metal chelate bond formation. A new band at 1077 cm⁻¹ had appeared in the spectra of metal complexes. This may be assigned to ν(C-O) of C-O-metal bond formation.

In this present work, the magnetic moment of Cu(II) complexes was found to be 2.10 B.M., indicating the distorted octahedral geometry for metal complex. These findings are in agreement with data reported by several researcher [29,30]. The two absorption bands are observed in the region 15513 cm⁻¹ and 24515 cm⁻¹ for ligand. In electronic spectra of Cu(II) metal complexes may be assigned to ²B_{1g}→²A_{1g} and charge transfer transition respectively. These results revealed that the distorted octahedral geometry for these complexes.

The magnetic moment of Ni(II) complex was 3.4 B.M., indicating the octahedral distorted structure of Ni(II) complex and further the high magnetic moment value may be due to orbital contribution. Such remarks are also supported by many researchers [31,32]. Further, the diffuse reflectance spectrum of Ni(II) shows two bands at 15780 and 23131 cm⁻¹ which can be assigned to transitions ³A_{2g}(F)→³T_{1g}(F) and ³A_{2g}(F)→³T_{1g}(P), respectively suggesting octahedral geometry for the Ni(II) complex. The data are presented in Table-2.

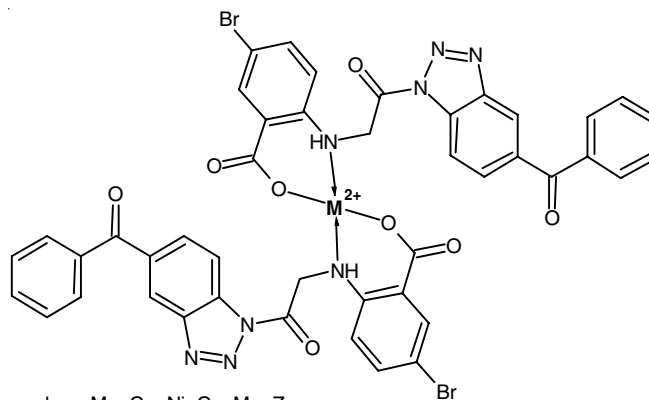
The data assessment of electronic spectra of Co(II) reflected in Table-2, indicates that transitions observed near the range of 8900 cm⁻¹ are assigned to ⁴T_{1g}(F)→⁴T_{2g}(F) and another bands around the 19000 cm⁻¹ and 24900 cm⁻¹ may be attributed to ⁴T_{1g}(F)→⁴A_{2g} and ⁴T_{1g}(F)→⁴T_{2g}(P) transition, respectively [33,34]. Magnetic moment values of some Mn(II) complexes give the coordination value of three unpaired electrons instead of five unpaired electrons and thus thereby show low magnetic moment (5.24 B.M.) [35]. This may be due to aerial oxidation of Mn²⁺→Mn³⁺ in the solid state [36,37] and/or due to spin exchange in the solid state. Mn(II) complex compounds show two bands in the region 18000-20000 cm⁻¹ and weak

TABLE-2
MAGNETIC MOMENT AND ELECTRONIC SPECTRAL DATA OF THE SYNTHESIZED METAL(II) COMPLEXES

Complex	Absorption band	Transitions	μ _{eff} (B.M.)
Cu(II) complex	24515, 15513	CT, ² B _{1g} → ² A _{1g}	2.10
Ni(II) complex	23131,	³ A _{2g} → ³ T _{1g} (P),	3.15
	15780	³ A _{2g} → ³ T _{1g} (F)	
Co(II) complex	24974,	⁴ T _{1g} (F)→ ⁴ T _{2g} (P),	4.52
	19116,	⁴ T _{1g} (F)→ ⁴ A _{2g} ,	
	8874	⁴ T _{1g} (F)→ ⁴ T _{2g} (F)	
Mn(II) complex	23994,	⁶ A _{1g} → ⁴ A _{1g} (4Eg),	5.24
	18780,	⁶ A _{1g} → ⁴ T _{2g} (4G),	
	16533	⁶ A _{1g} → ⁴ T _{1g} (4G)	

band in the region 23600-24350 cm⁻¹ for octahedral geometry [38]. These three bands can be allocated as ⁶A_{1g}→⁴T_{1g}(G), ⁶A_{1g}→⁴E_{1g}(G) and ⁶A_{1g}→⁴A_{1g}(G) transitions [35]. The absorption spectrum of Zn(II) complexes was not properly resolved and not interpreted. The values of μ_{eff} indicates its diamagnetic nature as expected [38,39].

The tentative structure of the synthesized metal(II) complexes are as follows:



Biological studies: The antibacterial activities of all the synthesized metal(II) complexes were screened against two Gram-positive bacteria (*Bacillus subtilis* and *S. aureus*) and two Gram-negative bacteria (*Escherichia coli* and *Salmonella typhi*). Antifungal activities were screened against three fungal species (*Penicillium expangum*, *Nigraspora* sp. and *A. niger*). The minimal inhibitory concentration (MIC) of all the synthesized metal(II) complexes were determined by the borth micro-dilution method according to National Commitee for Clinical

TABLE-3
BIOLOGICAL ACTIVITY DATA OF THE SYNTHESIZED LIGAND AND ITS METAL(II) COMPLEXES

Complex	Zone of inhibition (mm)						
	Antibacterial activity				Antifungal activity		
	Gram-positive		Gram-negative		<i>Penicillium expansum</i>	<i>A. niger</i>	<i>Nigrospora</i> Sp.
	<i>B. subtilis</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>E. coli</i>			
Ligand	16	19	17	18	16	18	15
Cu(II) complex	22	20	16	22	25	24	22
Mn(II) complex	10	14	10	12	18	10	12
Co(II) complex	12	11	10	11	20	19	18
Zn(II) complex	15	16	15	09	19	14	17
Ni(II) complex	18	16	15	14	22	21	23

Laboratory Standards (NCCLS) [40]. The results are presented in Table-3. It has been observed that the majority of the metal(II) complexes showed good efficiency against Gram-positive bacteria. Copper(II) complex showed a highest potency than the synthesized all the metal(II) complexes.

The antifungal activity of all the synthesized metal(II) complexes measured for various plant pathogens. Results (Table-3) clearly indicated that all the synthesized complexes have good inhibition efficiency in contrast to the synthesized ligand. Among all the synthesized metal(II) complexes, Cu(II) complex was found to be more toxic than the other.

Conclusion

A novel ligand 2-[[2-(5-benzoyl-1*H*-benzotriazol-1-yl)-2-oxoethyl]amino]-5-bromobenzoic acid was synthesized by the condensing 5-bromoanthranilic acid with 1-(5-benzoyl-1*H*-1,2,3-benzotriazole-1-yl)-2-chloroethanone. This ligand was chelated with some metal ions of 3*d*-series. All the synthesized metal(II) complexes were characterized and were found to be in full compliance with suggested structure. The novel ligand and its metal(II) complexes were found to exhibit an enhanced antibacterial and antifungal activities.

CONFLICT OF INTEREST

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

REFERENCES

- S. Maddila, R. Pagadala and S.B. Jonnalagadda, *Lett. Org. Chem.*, **10**, 693 (2013); <https://doi.org/10.2174/157017861010131126115448>
- P.K. Sharma, A. Amin and M. Kumar, *Open Med. Chem. J.*, **14**, 49 (2020); <https://doi.org/10.2174/1874104502014010049>
- I. Briguglio, S. Piras, P. Corona, E. Gavini, M. Nieddu, G. Boatto and A. Carta, *Eur. J. Med. Chem.*, **97**, 612 (2015); <https://doi.org/10.1016/j.ejmech.2014.09.089>
- R.R. Kale, V. Prasad, P.P. Mohapatra and V.K. Tiwari, *Monatsh. Chem.*, **141**, 1159 (2010); <https://doi.org/10.1007/s00706-010-0378-1>
- M. Vinodh, F.H. Alipour, A.A. Mohamad and T.F. Al-Azemi, *Molecules*, **17**, 11763 (2012); <https://doi.org/10.3390/molecules171011763>
- I. Briguglio, S. Piras, P. Corona, E. Gavini, M. Nieddu, G. Boatto and A. Carta, *Eur. J. Med. Chem.*, **97**, 612 (2015); <https://doi.org/10.1016/j.ejmech.2014.09.089>
- L. Tian, Y. Sun, H. Li, X. Zheng, Y. Cheng, X. Liu and B. Qian, *J. Inorg. Biochem.*, **99**, 1646 (2005); <https://doi.org/10.1016/j.jinorgbio.2005.05.006>
- B. Modzelewska-Banachiewicz, J. Banachiewicz, A. Chodkowska, E. Jagiello-Wójtowicz and L. Mazur, *Eur. J. Med. Chem.*, **39**, 873 (2004); <https://doi.org/10.1016/j.ejmech.2004.07.002>
- D.-K. Kim, J. Kim and H.J. Park, *Bioorg. Med. Chem. Lett.*, **14**, 2401 (2004); <https://doi.org/10.1016/j.bmcl.2004.03.024>
- Z. El-Sonbati, A.A. El-Bindary, A. El-Dissouky, T.M. El-Gogary and A.S. Hilali, *Spectrochim. Acta A, Mol. Biomol. Spectrosc.*, **58**, 1623 (2002); [https://doi.org/10.1016/S1386-1425\(01\)00627-8](https://doi.org/10.1016/S1386-1425(01)00627-8)
- A. El-Dissouky, O. Al-Fulij and S.S. Kandil, *J. Coord. Chem.*, **57**, 605 (2004); <https://doi.org/10.1080/00958970410001701026>
- A. El-Dissouky, O. Al-Fulij and S.S. Kandil, *J. Coord. Chem.*, **57**, 605 (2004); <https://doi.org/10.1080/00958970410001701026>
- N.M. Shuaib, N.A. Al-Awadi, A. El-Dissouky and A.-G. Shoaib, *J. Coord. Chem.*, **59**, 743 (2006); <https://doi.org/10.1080/00958970500402736>
- A.R. Katritzky, J. Jiang and L. Urogdi, *Tetrahedron Lett.*, **30**, 3303 (1989); [https://doi.org/10.1016/S0040-4039\(00\)99227-X](https://doi.org/10.1016/S0040-4039(00)99227-X)
- A. Palumbo Piccionello and A. Guarcello, *Curr. Bioact. Compd.*, **6**, 266 (2010); <https://doi.org/10.2174/157340710793237308>
- B.V. Suma and N.N. Natesh, *J. Chem. Pharm. Res.*, **3**, 375 (2011).
- K.M. Pandya, P.S. Desai, N.B. Patel and B.P. Dave, *Chem. Biol. Interact.*, **8**, 314 (2018).
- P.S. Desai and D.V. Parekh, *Der Chem. Sinica*, **3**, 722 (2012).
- P.S. Desai and D.V. Parekh, *Adv. Appl. Sci. Res.*, **3**, 1992 (2012).
- K.M. Pandya and P.S. Desai, *World J. Pharm. Res.*, **10**, 465 (2018); <https://doi.org/10.20959/wjpr201810-12240>
- A.I. Vogel, *A Organic Practical Book*, Longmans: London, ed 6, p. 1274 (1989).
- S. Guru, R. Yadav, S. Srivastava, S.K. Srivastava and S.D. Srivastava, *J. Indian Chem. Soc.*, **83**, 1236 (2006).
- A.I. Vogel, *A Text Book of Quantitative Inorganic Analysis*, ELBS: London, ed 3 (1978).
- S. Bance, *Hand Bbook of Practical Microanalysis*, John Wiley & Sons: New York (1988).
- J. Lewis and R.G. Wilkins, *Modern Coordination Chemistry*, Interscience: New York (1964).
- B.N. Figgis and J. Lewis, *The Magneto Chemistry of Chelates in Modern Coordination Chemistry*, Interscience: New York (1960).
- J.O. Williams, *Adv. Phys. Org. Chem.*, **16**, 159 (1978); [https://doi.org/10.1016/S0065-3160\(08\)60088-X](https://doi.org/10.1016/S0065-3160(08)60088-X)
- W.R. Bailly and E.G. Scott, *Diagnostic Microbiology*, The C V Mosby Cost Lovis, p. 257 (1996).
- C. Furlani and G. Morpurgo, *Theor. Chim. Acta*, **1**, 102 (1963); <https://doi.org/10.1007/BF00529392>
- C.K. Jørgensen, L.H. Smith, G. Hanshoff and H. Prydz, *Acta Chem. Scand.*, **9**, 1362 (1955); <https://doi.org/10.3891/acta.chem.scand.09-1362>
- R. Pappalardo, *J. Chem. Phys.*, **33**, 613 (1960); <https://doi.org/10.1063/1.1731199>
- J. Lewis and R.S. Wilkins, *Modern Coordination Chemistry*, Interscience: New York, p. 290 (1960).

33. S. Satpathi, H.C. Rai and B.S. Sahoo, *J. Indian Chem. Soc.*, **52**, 701 (1975).
34. R.H. Holm, G.W. Everett and A. Chakravorty, *Prog. Inorg. Chem.*, **7**, 83 (1966).
35. S.N. Poddar, K. Dey, J. Haldar and S.C. Nathasarkar, *J. Indian Chem. Soc.*, **47**, 743 (1970).
36. L. Sacconi, P. Paoletti and M. Ciampolini, *J. Am. Chem. Soc.*, **85**, 441 (1963); <https://doi.org/10.1021/ja00887a009>
37. L.E. Lempert, V.A. Kogan, O.A. Osipov and G.V. Nemirov, *Russ. J. Inorg. Chem.*, **11**, 506 (1966).
38. B. Singh and R. Singh, *J. Inorg. Nucl. Chem.*, **34**, 3449 (1972); [https://doi.org/10.1016/0022-1902\(72\)80240-9](https://doi.org/10.1016/0022-1902(72)80240-9)
39. L.N. Mulay, *Magnetic Susceptibility*, John Wiley & Sons: New York, (1972).
40. A. Rattan, *Antimicrobials in Laboratory Medicine*, B.I. Churchill, Livingstone, pp 85-108 (2001).