Synthetic, structural and biochemical approach of the macro cyclic complexes of manganese (II) and tin (II)

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Abstract

This study presents a brief account of the synthesis, spectroscopic and biochemical aspects of tetraazamacrocyclic complexes of managenese (II) and tin (II). The complexes of manganese (II) and tin (II) were prepared by the template condensation of metal salts with phthalic acid and diamines (1,3-diaminobutane and 1,4- diaminobutane) in 1:2:2 molar ratio. All the complexes are soluble in polar solvent.

The structures were investigated using elemental analyses, molecular weight determinations, conductivity measurements, electronic, infrared and X-Ray diffraction spectral studies. The elemental analyses are consistent with the formation of complexes of the type $[M(Mac^n)Cl_2]$ *(where, n=1-2, M=Mn(II), Sn (II)). An octahedral geometry around the metal ion is suggested for these complexes. All the complexes were screened against several fungi and bacteria to assess its biological properties and results are discussed.The importance of this method includes shorter reaction time and high yield.*

Keywords: Tetraazamacrocyclic complexes, diamines, template condensation.

Introduction

Macro cyclic species based on transition metal compounds and multi dentate ligands is an interesting field in chemistry and has been the subject of extensive research due to its potential applications in building block macro cyclic-based chemistry [16, 4]and environmental chemistry[3].A number of nitrogen donor macro cyclic derivatives have long been used in analytical, industrial and medical applications.[17] Macro cyclic compounds and their derivatives are interesting ligands system because they are good hosts for metal anions, neutral molecules and organic cation guests.[5]

In situ, one pot template condensation reaction lies at the heart of macro cyclic chemistry.[8] Therefore, template reactions have been widely used for the synthesis of macro cyclic complexes[22] where generally transition metal ions are used as the templating agent.[19] A number of important macro cyclic molecules which show biological activities including antibacterial, antifungal, anti diabetic, antitumor, anti proliferative, anticancer, herbicidal and anti-inflammatory activities, have been reported[11]. Due to their capability to form complexes with different transition metals, macro cyclic metal complexes can act as catalysts for different reactions.[14,20] Synthetic macro cycles are emerging class of compounds with varying chemistry, different molecular topologies and sets of donor atoms.

It is known fact that N atom plays a key role in the coordination of metals at the active sites of numerous metallobiomolecules.[2] Due to the demand of new metal based antibacterial and antifungal compounds, metallo-organic chemistry is becoming an emerging area of research.[21,23] Important characteristics that can be correlated with good antimicrobial activities are the lipophilicity and penetration of complexes through the lipid membrane.

Nevertheless, the development of new synthetic methods for the efficient preparation of macro cycles containing N_4 donor ligands is an interesting challenge. Therefore, it has been well thought out to prepare macro cyclic compounds of Sn and Mn. Here, we report one-pot three component reaction for title compounds in neutral medium.

Material and Methods

Chemicals Used: The chemicals used include phthalic acid (fluka), 1,3-diaminobutane and 1,4- diaminobutane (E.Merck), $SnCl_2$ and $MnCl_2.4H_2O$ (BDH). All solvents used were of high purity and distilled in laboratory before use. Moisture was excluded from the glass apparatus using $CaCl_2$ guard tubes.

Preparation of the complexes: Weighed amount of $MnCl_2.4H_2O$ or $SnCl_2$ was added to the calculated amounts of diammine and phthalic acid in 1:2:2 molar ratios using dry MeOH as the reaction medium. The resulting mixture was stirred for 10 – 12 hrs. The contents were kept at room temperature for 12 hrs resulting in the formation of crystalline compounds. The products were repeatedly washed with methanol so as to assure their purity and then dried. These compounds were recrystallised from benzene and dried again in vacuum.

Molecular weights were determined by the Rast camphor method.[27] Conductivity measurements were carried out in 10^{-3} M dimethylformamide solutions at 20ºC using a digital conductivity meter model CC 601 century. Electronic spectra were recorded on Cary 14 spectrophotometer. I.R. spectra were recorded as KBr discs, using a Nicolet-Magna FTIR - 550 spectrophotometer. X-Ray powder diffraction measurements were performed on a Philips X-Ray diffractometer (Model PW 1840) with Fe($K\propto$) target and operated at 30 KV and 40 *m*A.

Table 1
Physical properties and analytical data of manganese (II) and tin (II) macro cycles

S.N.	Reactants (g)			Complex Empirical Formula	M.P. (°C)	Colour	Analyses Found (Calcd.)%					Mol. Wt. Found (Calcd.)
	Metal Salt (g)	Diammine	Phthalic Acid				C	H	N	Cl	Metal	
1.	$MnCl_2.4H_2O$ 0.78	.69 1,3-Diaminobutane	1.30	$C_{24}H_{28}N_4O_4Cl_2$ Mn	225	Red	51.42 (51.26)	5.26 (5.02)	9.84 (9.96)	12.42 (12.61)	9.56 (9.77)	571 (562.35)
2.	$MnCl_2.4H_2O$ 0.89	.79 1,4-Diaminobutane	1.49	$C_{24}H_{28}N_4O_4Cl_2$ Mn	209	Brown	51.74 (51.26)	5.46 (5.02)	10.04 (9.96)	12.41 (12.61)	9.46 (9.75)	570 (562.35)
3.	$SnCl_2$ 0.84	.78 1,3-Diaminobutane	1.47	$C_{24}H_{28}N_4O_4Cl_2$ Sn	208	Off-White	46.26 (46.04)	4.94 (4.51)	8.84 (8.95)	11.46 (11.52)	18.78 (18.96)	634 (626.10)
4.	$SnCl_2$ 0.88	.82 1,4-Diaminobutane	1.54	$C_{24}H_{28}N_4O_4Cl_2$ Sn	210	Cream	46.42 (46.04)	4.69 (4.51)	8.84 (8.95)	11.41 (11.52)	18.90 (18.96)	632 (626.10)

Nitrogen and chlorine were determined by Kjeldahl's and Volhard's methods respectively.[28] Manganese and tin[28] were estimated complexometrically. Carbon and hydrogen analyses were performed at CDRI Lucknow. Magnetic measurements and ESR spectra of powdered samples at the room temperature were recorded on a vibrating sample magnetometer model 155 and X band varian spectrometer respectively at the RSIC, IIT, Madras.

Results and Discussion

Elemental Analysis: The elemental analyses and analytical data of the prepared complexes are given in table 1. All the complexes are stable at room temperature and non-hygroscopic. They are soluble in most organic solvents such as methanol, benzene, dichloromethane, tetrahydrofuran and carbon tetrachloride. The low values of their molar conductivities (25-45 $\Omega^{-1}cm^2Mol^{-1}$) in anhydrous dimethylformamide show them to be non-electrolyte.[18] Molecular weights of the complexes indicated the monomeric nature of the complexes.

Infrared Spectra: The IR spectra of the starting materials and their metal complexes were recorded and their comparative studies confirmed the formation of macro cyclic complexes with the proposed coordination pattern. The bands observed in the regions 3309 - 3273 cm^{-1} and 3000 - 2500 cm^{-1} are attributed to the $-NH_2$ of amino[9] and -OH of dicarboxylic acid respectively. Both of these bands ($-NH_2$ and -OH) disappeared in the spectra of all the complexes confirming the cyclization.

The appearance of four amide bands in the regions 1705 - 1650, 1576 - 1460, 1270 - 1230 and 685 - 630 cm^{-1} in the plane deformation vibrations also suggests the proposed cyclization.[3] A single sharp absorption band in the region 3294 - 3180 cm^{-1} is attributed to ν(N-H) of an amide group. The absorption bands appearing in the regions 3080 - 2880 and 1465 - 1410 cm^{-1} in the spectra of all the complexes may reasonably be assigned to the C-H stretching and C-H bending vibrational modes.[6]

The bands in the region 460 - 420 cm^{-1} in the spectra of the complexes may be attributed to ν(M-N) vibration[9].

The (M-Cl) stretching vibrations of the complexes have been assigned at 420- 320 cm^{-1}. Moreover, the bands due to Mn-N and Mn-Cl are obtained at 420-460 cm^{-1} and 250-300 cm^{-1} respectively. The bands corresponding to phenyl group vibrations appeared in the 3090-3070 cm^{1}.

Electronic Spectra: The electronic spectra of the manganese complexes gave two bands around 16740 , 21000 and 25400 cm^{-1} which may be assigned to $^6A_{1g} \rightarrow {}^4T_{1g}$, $^6A_{1g} \rightarrow {}^4T_{2g}$ and $^6A_{1g} \rightarrow {}^4T_{eg}$ transitions respectively suggesting on octahedral environment around the Mn^{+2} ion.[13]

The magnetic moments for the compounds $[Mn(Mac)^n Cl_2]$ and $[Sn(Mac)^nCl_2]$ were observed at 5.67-5.82 B.M. and 4.85-4.98 B.M respectively suggesting a high spin state for these complexes with central metal atoms being hexacoordinated.[1,15]

^{1}H NMR Spectra: The bonding pattern in the Sn complexes has been further confirmed by ^{1}H NMR spectra of the complexes and their starting material in DMSO-d6 using tetra methyl silane (TMS) is the internal standard. In the spectra of the precursor, the proton resonance signals due to $–NH_2$ and – OH were observed which are absent in the respective metal complexes, suggesting that the proposed macro cyclic skeleton has been formed through condensation reactions.

In the spectra of the complexes, a broad signal observed in the region δ 7.80 – 8.56 ppm may be assigned to the amide (CO – NH) proton.[24] A multiplet appearing in the region δ 3.12 – 3.65 ppm may be ascribed to the methylene proton. In the complexes, a multiplet was observed that δ 1.93 – 2.15 ppm is due to middle methylene proton of 1, 3-diaminobutane and 1, 4 - diaminobutane.

The complexes showed in additional multiplet in the region δ 6.98 – 7.26 ppm attributed to phenyl ring proton. A sharp singlet at δ 1.04 – 1.60 ppm in the spectra of the complex of 1, 3 – diaminobutane is due to - CH_3 proton. The absence of carboxylic proton (–COOH) of the carboxylic acid and $–NH_2$ proton of the diammine moiety supports the proposed macro cyclic framework. The conclusions drawn from IR and ^1H NMR spectra are parallel with the ^{13}C spectral data regarding the authenticity of the proposed structure. The ^{119}Sn NMR of these complexes gives signal at around δ -568.96 ppm indicating coordination number six in these complexes around the Sn atom.[29]

ESR spectra: The electronic spin resonance spectra of Mn complexes were recorded at the room temperature. These consist of a single broad peak in each case and from which the Lande splitting factor (g' value) has been calculated. For the present complexes, the g value lies in the range 2.001-2.052 indicating a hexa-coordinated state for these complexes.

X-ray spectral studies: The X-Ray powder diffraction studies of the compound $C_{24}H_{28}N_4O_4Cl_2Sn$ have been carried out to determine its lattice dynamics. The observed inter planar spacing values, d (°A) and the miller indices h, k and l are given in table 2. The data confirm the orthorhombic lattice to this derivative having unit cell dimensions a = 10.7246, b = 24.1426 and C = 29.8423. The structures shown in figure 1 may be assigned to the complexes based on the preceding spectral studies.

Biochemical Studies

Antifungal Activity: The starting materials and their metal complexes have been screened for their antifungal activities by the radial growth method[10] using potato dextrose agar medium. The pathogenic fungi used during the investigations are *Fusarium oxysporum* and *Aspergillus niger*. The compounds were directly mixed with the medium in 50, 100 and 200 ppm concentrations. Controls were also run and three replicate were used in each case. Bavistin was used as standard. The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after four days. The percent growth inhibition was calculated by using the following formula:

$$\% \text{ Growth inhibition} = \frac{dc - dt}{dc} \times 100$$

where dc = diameter of the fungal colony in the control plate and dt = diameter of the fungal colony in the test plate.

The experimental results show that there is an increase in the toxicity of the complexes as compared to the starting materials. The evaluation of antifungal studies further revealed that the fungitoxicity of the complexes also depends on the nature of the metal ion. In general, the activity of these metal complexes increases as their concentration is increased in the test solution. Tin (II) complexes have more fungitoxic activity than the manganese (II) complexes.

Antibacterial Activity: The starting materials and their complexes were screened for their antimicrobial activity against gram negative as well as gram positive microorganisms such as *E.coli* and *S.aureus*. For antibacterial activity, inhibition zone technique[7] was used.

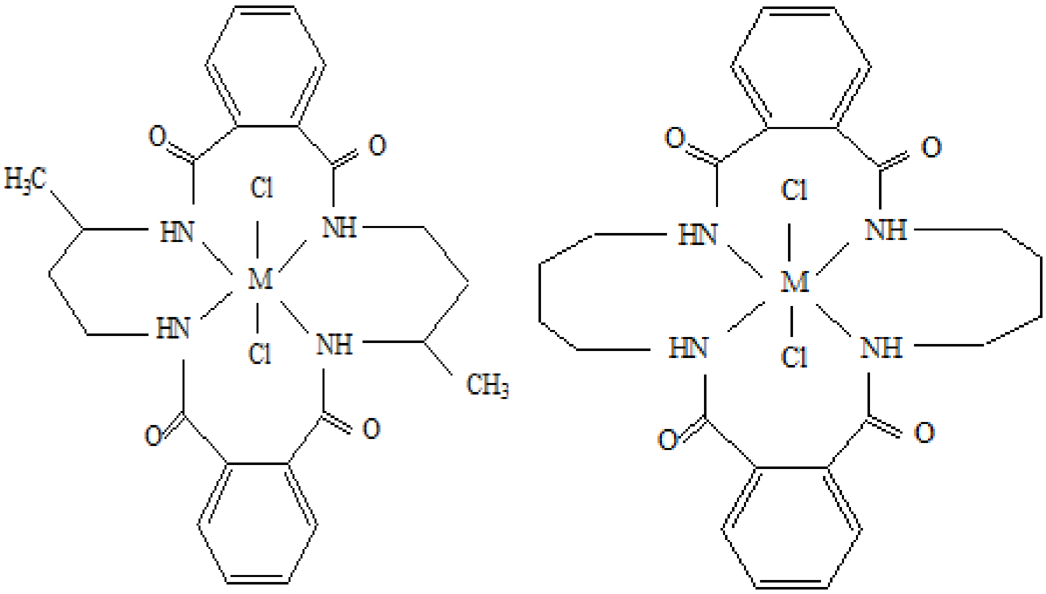
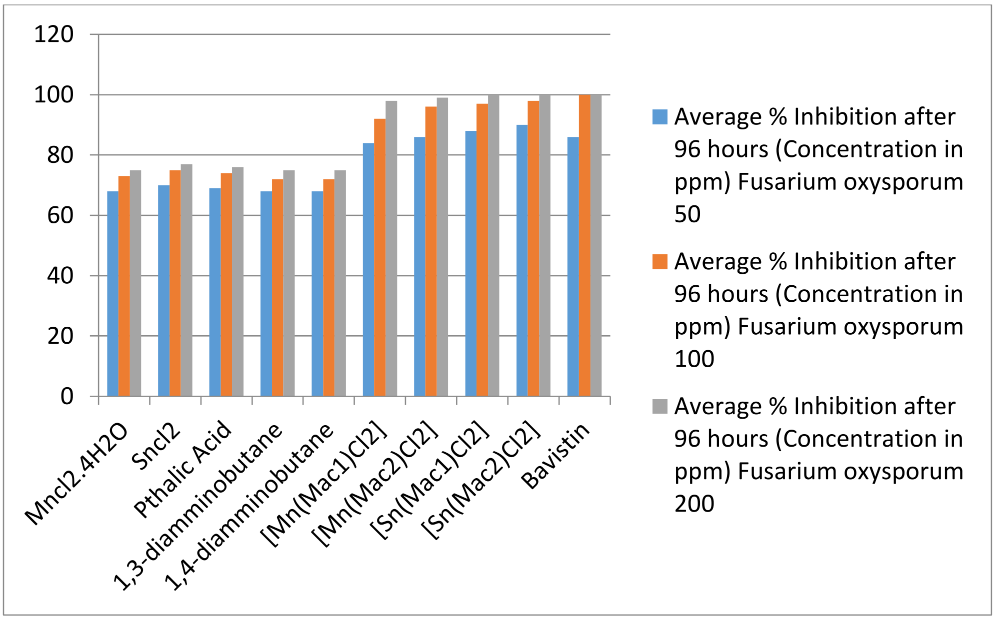


Figure 1: Macrocyclic Complexes of 1,3-diaminobutane and 1,4- diaminobutane
where M = Sn or Mn

Table 2
X-ray powder diffraction data of the compound $[Sn(Mac_1)Cl_2]$

Peak No.	2θ (obs.)	2θ (Calcd.)	d-spacing	h	K	l
1	17.95	17.98	6.284	0	2	4
2	18.50	18.56	6.142	1	2	4
3.	19.25	29.28	5.846	1	2	3
4.	21.24	21.26	5.244	2	1	0
5.	23.42	23.52	4.811	2	1	1
6.	23.86	23.94	4.684	2	2	1
7.	25.63	25.58	4.394	2	3	0
8.	25.89	25.92	4.286	2	3	1
9.	26.10	26.18	4.214	1	3	4
10.	26.94	26.98	4.198	1	3	5
11.	27.42	27.40	4.120	0	3	6
12.	29.48	29.56	3.546	1	0	5
13.	32.44	32.52	3.642	3	2	0
14.	36.36	36.38	3.042	3	4	0
15.	37.30	37.42	3.012	3	4	2
16.	38.50	38.44	2.984	0	8	1
17.	48.64	38.74	2.842	1	1	4
18	42.46	42.55	2.742	3	2	6
19	43.50	43.80	2.614	0	4	8

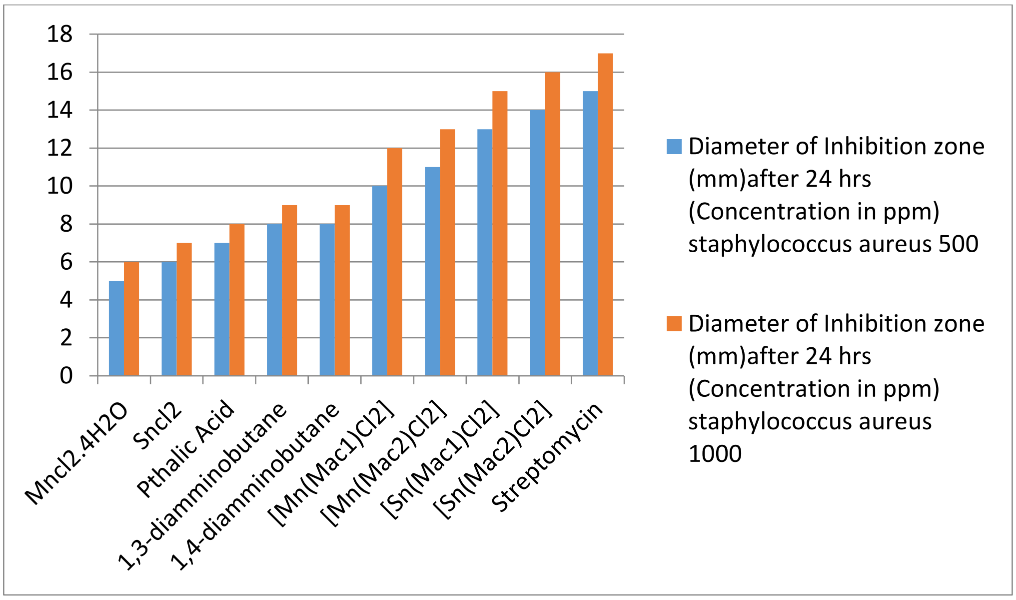
Refined Values, a = 10.7246, b = 24.1426, C = 29.8423 and $\alpha=\beta=\gamma=90^\circ$



Graph I: Antifungal screening data of manganese (II) and tin (II) macro cyclic complexes

Solution of the test compounds in methanol in 500 and 1000 ppm concentrations were prepared in which discs were dipped in solution of the test sample and then placed on seeded plates. The Petri-plates having these discs on the seeded agar are placed at low temperature for 2 - 4 hours to allow for the diffusion of chemicals before being incubated at suitable optimum temperature 28 ± 2°C for 24 - 30 hours. After the expiry of their incubation period, the zone of inhibition associated with the treated disc was measured in mm. Streptomycin was used as standard and three replicates were used in each case.

Chelation may enhance the biochemical potential of the bioactive species. Because on chelation, the polarity of the metal ion will be reduced due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups.



Graph 2: Antibacterial screening data of manganese (II) and Tin (II) macrocyclic complexes.

Hence macrocyclic complexes become very stable due to delocalisation of π-electrons. It enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms[12]. These complexes also disturb the respiration process of the cell thus blocking the synthesis of the proteins which restricts further growth of organisms.[30]

Conclusion

Macro cyclic complexes of Mn(II), Sn(II) with phthalic acid and 1,3-diaminobutane,1,4-diaminobutane were synthesized and characterized by analytical and spectral techniques. Spectroscopic investigations revealed the formation and purity of compounds. These compounds were tested against different bacterial and fungal strains and exhibited promising activity against all the tested microorganisms.

References

1. Anacona J.R. and Gomez J., Transition Metal bis(2-bromophenyl)disulfide Complexes, *Journal of the Chilean Chemical Society*, **53(4),** 1694 **(2008)**

2. Bagihalli G.B., Avaji P.G., Patil S.A. and Badami P.S., Synthesis, spectral characterization, in vitro antibacterial, antifungal and cytotoxic activities of Co(II), Ni(II) and Cu(II) complexes with 1,2,4-triazole Schiff bases, *Eur. J. Med. Chem.*, **43(12),** 2639 **(2008)**

3. Bansal N. and Dave S., Synthesis, spectral, antimicrobial and antifertility studies of tetraaza macrocyclic complexes of tin (II), *Main Group Metal Chemistry*, **36(3-4)** ,101 **(2013)**

4. Belghoul B., Weiterlich I., Maier A., Toutianoush A., Rabindranath A.R. and Tieke B., Supramolecular sequential assembly of polymer thin films based on dimeric, dendrimeric and polymeric schiff-base ligands and metal ions, *Langmuir*, **23(9),** 5062 **(2007)**

5. Chandra S., Gautam A. and Tyagi M., Synthesis and spectroscopic characterization of transition metal complexes of a 12-membered tetraaza [N 4] macrocyclic ligand and their biological activity, *Transition Metal Chemistry*, **32(8),** 1079 **(2007)**

6. Chaudhary A. and Singh R.V., Pharmaceutically important organotin(II) macrocyclic complexes: synthetic, spectral and antimicrobial approach, *Rasayan*, **2(1)**, 191 **(2009)**

7. Chaudhary A., Swaroop R. and Singh R., Tetraazamacrocyclic complexes of tin (II): synthesis spectroscopy and biological screening, *Boletín de la Sociedad Chilena de Química*, **47(3)**, 203 **(2002)**

8. Curtis N.F., Macrocyclic coordination compounds formed by condensation of metal-amine complexes with aliphatic carbonyl compounds, *Coordination Chemistry Reviews*, **3(1),** 3 **(1968)**

9. Fahmi N., Sharma S., Kumar R. and Singh R.V., New Class of Macrocyclic Complexes of Bivalent Manganese: Template Synthesis, Spectroscopic, Electrochemical and Biological Studies, *Chem Sci. Rev. Lett*., **3(11),** 488 **(2014)**

10. Ghani S.S., Synthesis, characterization and biological activity of tin (IV) macrocyclic complexes derived from 1, 2-diphenylethane-1, 2-dione dihydrazone, *Main Group Metal Chemistry*, **40(5-6)**, 113 **(2017)**

11. Gull P. and Hashmi A.A., Biological Activity Studies on Metal Complexes of Macrocyclic Schiff Base Ligand: Synthesis and Spectroscopic Characterization, *J. Braz. Chem. Soc.*, **26(7)**, DOI:10.5935/0103-5053.20150099 **(2015)**

12. Hazra M., Dolai T., Pandey A., Dey S.K. and Patra A., Synthesis and Characterisation of Copper(II) Complexes with Tridentate NNO Functionalized Ligand: Density Function Theory Study, DNA Binding Mechanism, Optical Properties and Biological Application, *Bioinorganic Chemistry and Applications*, DOI:10.1155/2014/104046 **(2014)**

13. Khan T.A., Rathore A.M., Mohamed K.A., Islam S.K. and Jahan N., Synthesis and Physico-chemical studies of manganese(II), nickel(II), cobalt(II), copper(II) and zinc(II)

complexes of new 13-membered pentaazamacrocycles with N_4 donor sets, *Indian J. Chem*., **41(A),** 1424 **(2002)**

14. Kumar G., Devi S. and Johari R., Synthesis and Spectral Characterization of Schiff Base Cr(III), Mn(III) and Fe(III) Novel Macrocyclic Complexes Derived from Thiocarbohydrazide and Dicarbonyl Compound, *E-Journal of Chemistry*, **9(4),** 2255-2260 **(2012)**

15. Lal R.A., Kumar A. and Chakravorty J., Synthesis and characterization of manganese(IV) and manganese(II) complexes with bis(2-hydroxy-1-naphthaldehydehyde)malonoyl dihydrazone, *Indian J Chem*, **40(A),** 4222 **(2001)**

16. Lehn J.M., Supramolecular Chemistry Concepts and Perspectives, Wiley-VCH, Weinheim, Germany, 1st edition **(1995)**

17. Ma W., Tian Y.P., Zhang S.Y., Wu J.Y., Fun H.K. and Chantrapromma S., Synthesis and characterization of 1, 8-bis (ferrocenylmethyl)-5, 5, 12, 12, 14-hexamethyl-1, 4, 8, 11-tetraazacyclotetradecane, a macro cyclic ligand and its complexes, *Transition Metal Chemistry*, **31(1),** 97 **(2006)**

18. Mounika K., Anupama B., Pragathi J. and Gyanakumari C., Synthesis¸ Characterization and Biological Activity of a Schiff Base Derived from 3-Ethoxy Salicylaldehyde and 2- Amino Benzoic acid and its Transition Metal Complexes, *J. Sci. Res.*, **2(3),** 513 **(2010)**

19. Prasad R.N., Gupta S. and Jangir S., Synthesis and characterization of Mg (II), Ca (II), Sr (II) and Ba (II) complexes of 2, 13-dimethyl-3, 14-diethyl/propyl/phenyl-1, 4, 12, 15-tetraazacyclodocosa-1, 3, 12, 14-tetraene, *Journal of the Indian Chemical Society*, **84(12),** 1191 **(2007)**

20. Rayati S., Torabi N., Ghaemi A., Mohebbi S., Wojtczak A. and Kozakiewicz A., Vanadyl tetradentate Schiff base complexes as catalyst for C–H bond activation of olefins with tert-butylhydroperoxide: Synthesis, characterization and structure, *Inorg. Chimica. Acta*, **361(5),** 1239 **(2008)**

21. Rice S.A., Givskov M., Steinberg P. and Kjelleberg S., Bacterial signals and antagonists: the interaction between bacteria and higher organisms, *J Mol Microbiol Biotechnol.*, **1(1)**, 23 **(1999)**

22. Salavati-Niasari M. and Davar F., In situ one-pot template synthesis (IOPTS) and characterization of copper (II) complexes of 14-membered hexaaza macrocyclic ligand “3, 10-dialkyl-dibenzo-1, 3, 5, 8, 10, 12-hexaazacyclotetradecan, *Inorganic Chemistry Communications*, **9(2),** 175 **(2006)**

23. Scozzafava A. and Supuran C.T., Carbonic anhydrase and matrix metalloproteinase inhibitors: sulfonylated amino acid hydroxamates with MMP inhibitory properties act as efficient inhibitors of CA isozymes I, II and IV and N-hydroxysulfonamides inhibit both these zinc enzymes, *J Med Chem*., **43(20),** 3677 **(2000)**

24. Shakir M. and Varshney S.P., A new synthetic route for the preparation of a new series of 14-22 membered tetraoxomacrocyclic tetraamines and their transition metal complexes, *Polyhedron*, **14**, 1117 **(1995)**

25. Tripuramallu B.K., Kishore R. and Das S.K., Synthesis, structural characterization and properties of one-dimensional coordination polymers of cobalt(II)- and nickel(II)-phosphonate complexes with 2,2′-bipyridine as a secondary ligand component: observation of both cis and trans conformations of a diphosphonic acid, *Polyhedron.*, **29(15),** 2985 **(2010)**

26. Tušek-Božić L., Marotta E. and Traldi P., Efficient solid-state microwave-promoted complexation of a mixed dioxa-diaza macrocycle with an alkali salt, Synthesis of a sodium ethyl 4-benzeneazophosphonate complex, *Polyhedron*, **26(8)**, 1663 **(2007)**

27. Vogel A.I., A Text Book of Practical Organic Chemistry, 4th Edition, Zongmans, ELBS, London, 232 **(1978)**

28. Vogel A.I., A Text Book of Quantitative Inorganic Analysis, Longmans Green, ELBS, London, 302 **(1991)**

29. Winter C.A., Risley E.A. and Nuss G.W., Carrageenan-induced edema in hind paw of the rat as an assay for anti-inflammatory drugs, *Proc. Soc. Exp. Biol. Med*., **162**, 544 **(1963)**

30. Yusoff S.F.M., Huddin A.A.S., Yusoff L.M., Yamin B.M. and Leng O.W., Synthesis, Characterization and Antibacterial Activity of Cu (II), Ni (II) and Zn (II) Complexes of 14-Membered Macrocyclic Tetraaza Ligand, *Oriental Journal of Chemistry*, **31(3),** 1751 **(2015)**.

(Received 04th May 2020, accepted 06th July 2020)