ISSN 0975-6299 Vol 2/Issue 1/ Jan-Mar 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

MEDICINAL CHEMISTRY

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF SCHIFF BASES METAL COMPLEXES CO (II), ZN (II), NI (II), AND MN (II) DERIVED FROM AMOXICILLIN TRIHYDRATE WITH VARIOUS ALDEHYDES.

Corresponding Author

SUNIL JOSHI

Synthetic Lab, P. G. Department of Chemistry, Faculty of Science, Government College, Ajmer, Rajasthan (INDIA).

Co Authors

VATSALA PAWAR , AND V.UMA

Synthetic Lab, P. G. Department of Chemistry, Faculty of Science, Government College, Ajmer, Rajasthan (INDIA).

ABSTRACT

In the present investigation some new Schiff bases derived from Amoxicillin trihydrate with Cinnamaldehyde and p-Chlorobenzaldehyde and their complexes with bivalent transition metal ions viz. Co(II), Zn(II), Ni(II), and Mn(II), have been synthesized. The ligand and their metal complexes were characterized on the basis of elemental analysis and micro analytical datas. Shift in the characteristic spectral frequency of the metal complexes, confirms the coordination through metal ion with azomethine group. They were screened for antibacterial activity against several bacterial strains namely *E. coli*(-), *S. aureus*(+) *M. luteus*(+) and *B. lichenformis*(+) (ATCC), the metal complexes showed enhanced antibacterial activity compared to uncomplexed ligand.

KEY WORD

Antibacterial activity, Amoxicillin trihydrate.

INTRODUCTION

Compound containing imines bases have not only found extensive application in organic synthesis,[1-2] but several of these molecules display significant biological activity. In the last decade Schiff base ligands [3-6] have received more attention mainly because of their wide application in the field of catalysis and due to their antimicrobia, [11-12] anti-tuberculosis[7] and anti-tumor activity. They easily form stable complexes with most transition metal ion.[13-14] The development of the field of bioinorganic chemistry has increased the interest in Schiff base complexes, since it has been recognized that many of these complexes may serve as models for biologically important species.[8] Co-ordination compound have been reported to act as enzyme inhibitor[9] and are useful due to their pharmacological application.[10] In view of the importance of such imines, we describe here the synthesis and characterization of Co(II), Zn(II), Ni(II) and Mn(II) complexes of cinnemaldehyde and p-chlorobenzaldehyde with amoxicillin trihydrate.

MATERIAL AND METHOD

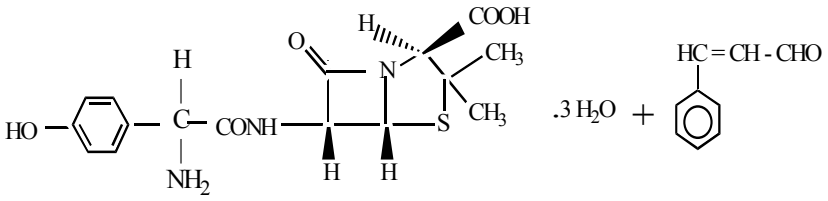
All chemicals and solvent used were of analytical grade. All metal (II) salts were used as chloride.UV-VIS spectra were obtained on digital spectrophotometer in the range 300-900nm in DMF.

IR spectra were recorded using KBR disc on a FT-IR spectrophotometer, Shimadzu 8201PC in the range of 4000-400cm^{-1}. ^{1}HNMR spectra were recorded in MeOD at room temperature. Elemental analysis was carried out on Elementar Vario ELIII . Conductance measurement of 10^{-3} M solution of the complexes in DMF was carried out on an Equiptronic model no. Eq-660A. Melting point of the ligands and their metal complexes were determined by open capillary method using sunsim electric melting point apparatus and are uncorrected. Molecular weight of ligands and their metal complexes were determined by Rast camphor method.

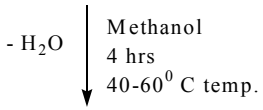
Synthesis of the organic ligand (CmA, PbA)

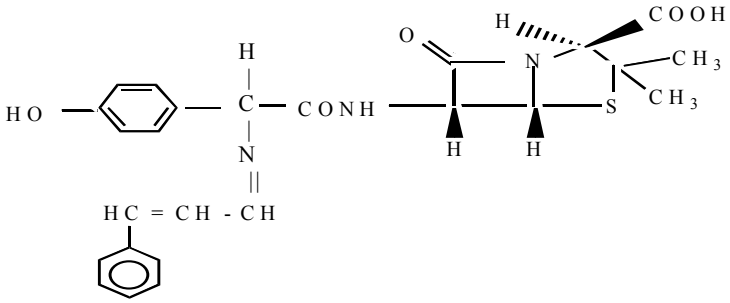
The aldehyde cinnamaldehyde (1 mol, 1.321gm), *p*-chlorobenzaldehyde (1 mol, 1.521gm.) were dissolved in methanol (10 ml) and added to the amoxicillin trihydrate (1 mol, 4.194 gm) dissolved in methanol (10 ml). To this KOH (0.1 % in methanol) was added to adjust the pH of the solution between 7-8 and then the mixture respectively was refluxed for 4 hrs. After complete refluxation Schiff base was separated out on removal of the solvent at room temp. A light yellowish and brown colored crystalline solid obtained and then dried over anhydrous $CaCl_2$ in vacuum.

Figure of ligands and their metal Complexes

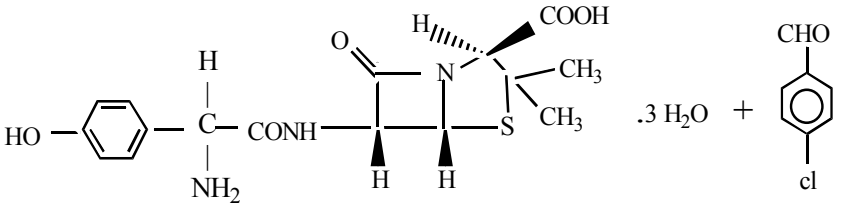


Amoxycillin trihydrate Cinnamaldehyde

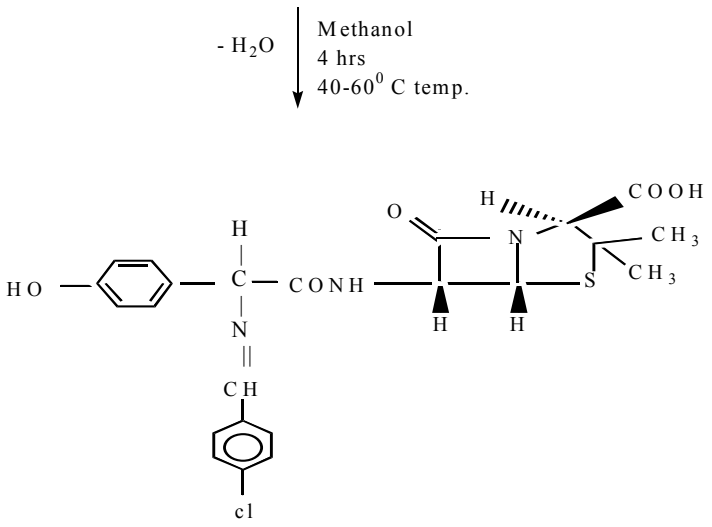




Scheme I of Synthesis of ligand CmA



Amoxicillin trihydrate p- chlorobenzaldehyde



Scheme II of Synthesis of ligand PbA

Synthesis of metal complex (CmAM, PbAM)

Amoxicillin trihydrate (0.2 mol, 0.838 gm.) cinnamaldehyde (0.2 mol, 0.264 gm.), *p*-chlorobenzaldehyde (0.2 mol, 0.838 gm) and (0.1 mol.) metal M= Zn (II) (0.199 gm.), Ni (II) (0.136 gm.), Mn (II) (0.197 gm), and Co (II) (0.237gm), were dissolved in methanol (10 ml) separately. To this KOH (0.1 % in methanol) was added to adjust the pH of the solution between 7-8 and the mixture was refluxed for 6 hrs. A dark colored product was isolated after reduction of solvent volume by evaporation, which was then filtered, washed with methanol and then dried over vacuum.

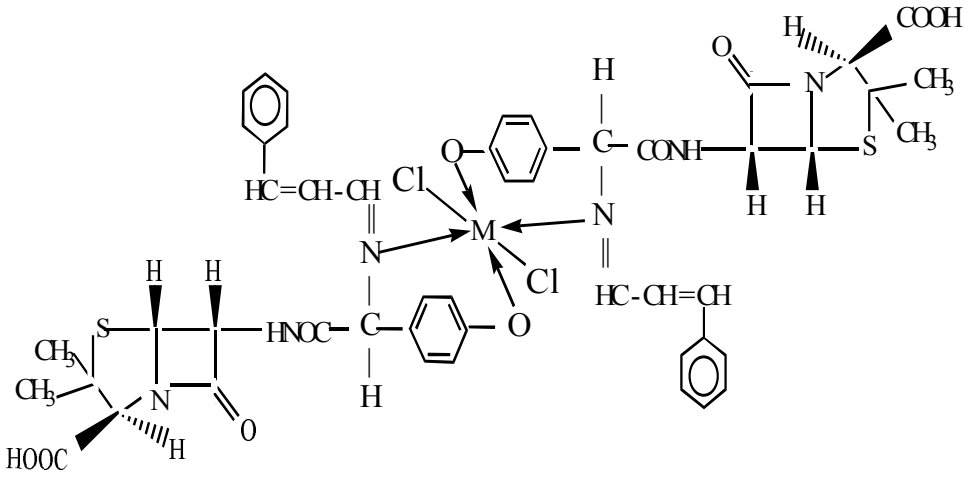
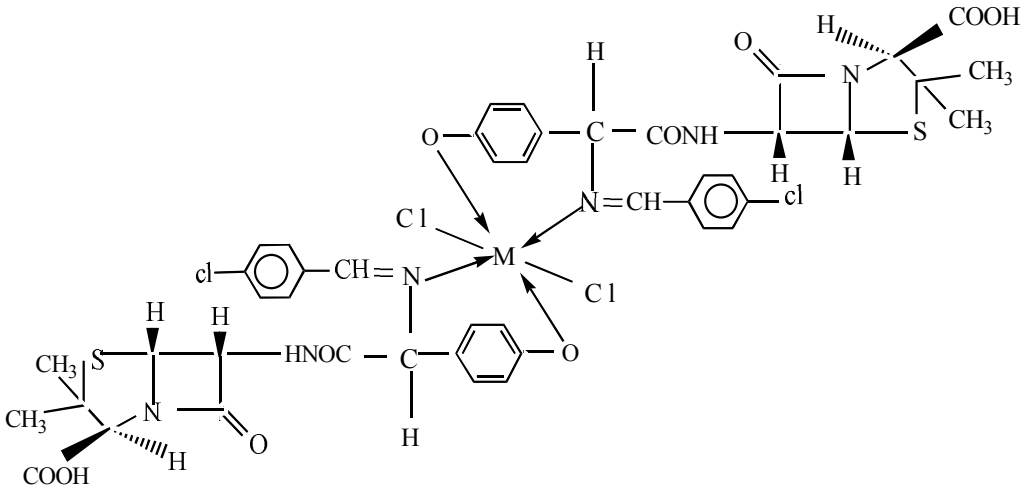


Fig 1
Metal Complex (CmAM)



.

Fig 2
Metal Complex (PbAM)

RESULT AND DISCUSSION

Physical Properties

These complexes are air and moisture stable, intensely colored amorphous solid which decomposes above 200^{0}C. They are insoluble in common organic solvent like chloroform, acetone, ether, ethanol and carbon tetra chloride but soluble in DMF and DMSO. Molecular weight determined by Rast Camphor method and were found in accordance with calculated value the range of ligands (533-542) and metal complexes (1142-1176) confirming the monomeric nature of the compounds. The yield of compounds was found in the range of (60-80 %)

The molar conductance of all the compounds using DMF as a solvent, have been found to be in the range 0.12 to 0.45 ohm^{-1}cm^{2}mol^{-1} indicating their non electrolyte nature. values are also shown in **table 1.**

Table 1
Micro analytical datas of ligand and their metal complexes

S. No.	Name of compound	C% Found (Calc.)	H% Found (Calc.)	O% Found (Calc.)	N% Found (Calc.)	Conductivity	M.P. (°C)	M.W. found (calc.)	Colour	Yield in %
1.	CmA	62.55 (62.23)	5.21 (5.20)	16.68 (16.50)	8.75 (8.65)	0.30	210	479.61 (479.25)	yellow	68
2.	CmA -Zn^{+2}	54.91 (54.62)	4.39 (4.31)	14.64 (14.56)	7.68 (7.60)	0.20	320	1092.5 (1085.3)	black	72
3.	CmA -Co^{+2}	55.25 (55.20)	4.42 (4.40)	14.73 (14.60)	7.73 (7.58)	0.19	340	1085.8 (1069.3)	black	75
4.	CmA -Mn^{+2}	55.50 (55.48)	4.44 (4.32)	14.80 (14.72)	7.77 (7.62)	0.12	308	1080.9 (1074.2)	brown	74
5.	CmA -Ni^{+2}	55.26 (55.18)	4.42 (4.30)	14.73 (14.62)	7.73 (7.63)	0.20	342	1085.6 (1077.2)	brown	69
6.	PbA	59.03 (59.01)	4.50 (4.35)	16.39 (16.30)	8.60 (8.55)	0.45	240	487.82 (479.9)	light brown	78
7.	PbA -Co^{+2}	52.20 (52.12)	3.80 (3.74)	14.50 (14.38)	7.61 (7.59)	0.28	304	1103.44 (1099.6)	brown	72
8.	PbA -Zn^{+2}	51.89 (51.80)	3.78 (3.72)	14.41 (14.34)	7.56 (7.50)	0.26	308	1110.04 (1103.2)	black	74
9.	PbA -Mn^{+2}	52.43 (52.43)	3.82 (3.80)	14.56 (14.50)	7.64 (7.52)	0.30	338	1098.54 (1080.3)	brown	69
10.	PbA - Ni^{+2}	52.20 (52.16)	3.80 (3.74)	14.50 (14.40)	7.61 (7.50)	0.35	342	1103.24 (1100.6)	yellow	76

All the spectral data was consistent with the assigned structure of the compounds. In The band IR spectraum, the (Ar-OH) observed at 3428, 3389 cm^{-1} in the ligands and disapiared in metal complexes showing the participation of the O-M group in coordnation. The ligands show strong band in the regin1650-1661 cm-1 due to C=N which is assignable to the Schiff bases, which appeared in both synthesized ligands. This band gets shifted to lower frequency in the complexes, indicating the coordination through azomethine nitrogen. It is found from the IR spectra of the complexes that there are wide and strong band at 564 – 670 cm^{-1} for (M-N) bonding and 460-490 cm^{-1} for (M-O) which are assigned to metal stretching vibration. The ^{1}HNMR spectral data of ligands (CmA) and **(**PbA) shows signal between δ7.45-7.60 and δ7.48-7.57 respectively due to aromatic ring which gets shifted downfield in their metal complexes. The VU-VIS spectra of ligands (CmA and PbA) showed two bands between 300-350 nm and 310-365 nm. The first band may be due to Π – Π* transition within the arometic ring. The second band would be due to n- Π * transition within –C=N group. Shown in **table 2.**

Table 2
Characteristic IR and ^{1}HNMR spectral datas of the ligands and their metal complexes

		IR spectra cm^{-1}				^{1}HNMR ppm Spectra			U.V.	
S. No.	Nameof Comp.	(M-O)	(N-M)	(C=N)	(ArOH)	δ(CH=CH)	δ(Ar-H)	(N=H)	(C=C)	(C=N)
1.	CmA	-	-	1659	3389	4.91	6.77-7.2	7.49	300	350
2.	CmA - Zn^{+2}	462	670	1603	--	4.39	6.15-7.1	7.29	300	320
3.	CmA -Co^{+2}	468	617	1635	--	4.87	6.44-7.1	7.32	300	318
4.	CmA -Mn^{+2}	488	616	1605	--	4.85	6.16-6.83	7.36	300	340
5.	CmA -Ni^{+2}	482	613	1604	--	4.87	6.30-7.02	7.24	300	320
6.	PbA	-	-	1661	3428	5.19	6.79-7.18	7.53	310	365
7.	PbA -Co^{+2}	472	669	1639	--	5.10	6.45-7.02	7.40	340	355
8.	PbA -Zn^{+2}	468	670	1630	--	4.86	6.23-7.16	7.38	320	346
9.	PbA -Mn^{+2}	469	564	1644	--	4.20	6.77-6.79	7.35	320	326
10.	PbA - Ni^{+2}	474	570	1640	--	4.40	6.42-7.28	7.28	320	342

Antibacterial Studies

Evaluation of antimicrobial activity of all compounds *in vitro* was carried out by paper disc method against bacteria including *E. coli, S. aureus, M. luteus, and B. lichenformis.* Streptomycin was additionally tested as positive control. Significance level of all compounds (P<.001), (*P<.01). The datas represent the values of three replicates and are evaluated as mean ± SEM values were determined and are shown in **table 3,** also their MIC values in the **table 4**.

Table 3
Antimicrobial activity of ligands and their metal complexes.

S. No.	*E. Coli* (-)				*S. aureus* (+)			
	100 ppm	500 ppm	1000 ppm		100 ppm	500 ppm	1000 ppm	
CmA	19(±.528)	27(±.578)	36(±.305)		19(±.728)*	27(±.420)	35(±.378)	
CmA_{-Zn}^{+2}	22(±.305)	34(±.305)	37(±.503)		23(±.435)	22(±.264)	38(±.305)	
CmA_{-Co}^{+2}	21(±.416)	31(±.586)	37(±.493)		21(±.152)	32(±.676)	40(±.305)	
CmA_{-Ni}^{+2}	21(±.305)	32(±.297)	38(±.378)		22(±.493)	31(±.350)	37(±1.07)	
CmA_{-Mn}^{+2}	22(±.200)	32(±.305)	35(±.755)		20(±.251)	32(±.586)	39(±.152)	
PbA	18(±.200)	27(±.551)	36(±.321)		18(±.952)*	28(±.379)	36(±.264)	
PbA_{-Zn}^{+2}	20(±.305)	29(±.264)	37(±.200)		21(±.400)	30(±.400)	37(±.152)	
PbA_{-Ni}^{+2}	21(±.231)	30(±.200)	38(±.462)		20(±.091)	30(±.208)	38(±.173)	
PbA_{-Co}^{+2}	20(±.115)	30(±.231)	35(±.208)		20(±.057)	30(±.379)	40(±.208)	
PbA_{-Mn}^{+2}	19(±.416)	29(±.346)	36(±.397)		21(±.993)*	29(±.208)	38(±.264)	
Streptomycin	24±.235	29±.513	33±.350		25±.598	30±.265	34±.365	

M. luteus (+)			*B. lichenformis* (+)		
100 ppm	500 ppm	1000 ppm	100 ppm	500 ppm	1000 ppm
18(±.557)	26(±.096)	30(±.305)	17(±.503)	25(±.305)	28(±.152)
22(±.305)	31(±.305)	36(±.099)	20(±.264)	28(±.557)	38(±.305)
21(±.611)	29(±.712)	34(±.493)	20(±.305)	28(±.465)	36(±.305)
19(±.208)	29(±.712)	32(±.053)	18(±.100)	28(±.152)	37(±.305)
20(±.400)	30(±.416)	36(±.200)	19(±.305)	26(±.305)	35(±.200)
18(±.231)	26(±.251)	30(±.057)	17(±.100)	25(±.305)	28(±.264)
19(±.586)	29(±.416)	32(±.152)	18(±.305)	27(±.200)	36(±.305)
20(±.115)	30(±.416)	38(±.208)	19(±.231)	26(±.100)	34(±.379)
21(±.493)	30(±.208)	37(±.503)	18(±.231)	27(±.493)	36(±.469)
21(±.551)	29(±.379)	34(±.264)	19(±.436)	27(±.346)	34(±.611)
24±.256	28±.248	32±.542	20±.254	25±.695	30±365

*Significance level (P<.001), (*P<.01).*

Table 4
MIC of the ligand and their metal complexes

Name of Compound	*E. Coli (-)*	*S. Aureus (+)*	*M. Luteus(+)*	*B. Lichenformis(+)*
	mg/ml	mg/ml	mg/ml	mg/ml
CmA	0.48	0.50	0.50	0.48
CmA -Zn^{+2}	0.21	0.21	0.24	0.26
CmA -Co^{+2}	0.28	0.38	0.31	0.26
CmA -Mn^{+2}	0.24	0.35	0.32	0.39
CmA -Ni^{+2}	0.26	0.28	0.37	0.34
PbA	0.48	0.45	0.50	0.48
PbA -Co^{+2}	0.36	0.36	0.30	0.36
PbA -Zn^{+2}	0.37	0.34	0.37	0.36
PbA -Mn^{+2}	0.39	0.38	0.31	0.34
PbA - Ni^{+2}	0.30	0.36	0.32	0.39

CONCLUSION

The result of this investigation supports the suggested structure of the metal complexes. A square planner structure was suggested for all the complexes, the Schiff base ligands were found to be biologically active and their metal complexes display enhanced antimicrobial activity against one or more strains, chelation tends to make the ligands act as more powerful and potent bactericidal agent.

ACKNOWLEDGMENT

We are thankful to The Principal and Head chemistry department, Govt. College Ajmer for providing research facilities. SAIF , Central Drug Research Institute , Lucknow, for spectral studies.

REFERENCES

1. Pekhnyo V I, Orysyk S P, Bon V V and Orysyk V V, *Polish J. Chem.,* 80, 1789, (2006).
2. Dobrzynska D, Jerzykiewicz L B, Jerzierska J and Sloniec, *E. Polish J. Chem.,* 80, 1789, (2006).
3. Chohan Z H, Mohammad M A and Akhtar A*, Bio- Inorganic Chem. and Application,* 83**,** 131, (2006).
4. Chohan Z H, *Applied Organometalic Chemistry,* 20 (2): 112, (2006).
5. Chavan A A and Pai N R, *Molecules*, 12, 2467-77, (2007).
6. Chohan Z H, Hassan M, Khan K M and Supuran C T, *J. Enz. Inhib. Med. Chem.,* 20, 183-88, (2005).
7. Muthukumaran, *Spectrochim Acta A Mol Biomol Spectrosc*, 71, 628-35, (2008).

8. Neelakantan M A, Rusalraj F, Dharmaraja J, Johnsonraja S, Jeyakumar T and Pillai M S,*Spectrochim Acta A Mol. Biomol. Spectrosc.*, **7**, 1599-609, (2008).
9. Mehata P D, *Indian J. Pharm. Sci.*, 68, 101-103, (2006).
10. Wadher S J, *Int. J. PharmTech Res.*, 1 (1): 33, (2009).
11. Mittal P and Uma V, *Int. J. Chem. Sci.*, 6 (2): 1050-1060, (2008).
12. Mittal P and Uma V, *Asian Journal of Chemistry*, 21 (2): 1230-1238, (2009).
13. Mittal P and Uma V, *Oriental Journal of Chemistry*, 24 (3): 935-942, (2008).
14. Mittal P, Joshi S, Pawar V and Uma V, *International Journal of ChemTech Research,* 1 (2): 225 - 232, (2009).