



SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF MIXED LIGAND COMPLEXES DERIVED FROM OXIMES OF 2-ACETYLFURAN AND 2-ACETHYLTHIOPHENE USING TRANSITION METALS

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ABSTRACT: Present work deals with synthesis, characterization and biological screening of some mixed ligand transition metal complexes derived from 2-Acetylfuran and 2-Acetylthiophene using transition metals viz. Zn(II), Cu(II), Co(II), Ni(II) and Mn(II). The synthesized complexes have been analyzed, characterized on the basis of spectral techniques such as ¹H-NMR, IR and elemental analysis. The biological screening performed on derived complexes reflected that all these complexes show quite appreciable activity against the pathogens *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas diminuta*, *Staphylococcus aureus* and *Candida albicans*.

KEYWORDS: Mixed ligand complexes; Oximes; 2-Acetylfuran; 2-Acetylthiophene; Antimicrobial activity.

INTRODUCTION:

Mixed ligand metal complexes have always attracted the researchers as they differ from the traditional concept of metal complexes. Mixed ligand complexes have been defined and known to include a minimum of two different types of donor ligands linked to the same Metal ion.^{i-vii} Such a mixed ligand metal complex may in fact vary in their expected characteristics and properties owing to the presence of more than one type of donor ligand. Various results, findings have been reported; accounted for the synthesis, characterization and biological significance of metal complexes derived from ligands involving donor O, S and/or N donor atoms.^{viii-xi} Oximes as potential ligands have been predominant in varied fields of chemistry.^{xii-xv} It is evident that metal ions are significant for variety of bio-chemical reactions. For instance, enzymes perform their role only when such metal ions are present. Interaction of transition metal complexes with DNA,^{xvi, xvii} diagnostic-therapeutic properties of such complexes have led to their importance and applicability in different aspects of modern medicine.

In progression to our recent research work based on some transition metal complexes;^{xviii, xix} herein we report and highlight the synthesis, characterization, biological significance of some mixed ligand transition metal complexes derived from 2-Acetylfuran and 2-Acetylthiophene using transition metals viz. Zn(II), Cu(II), Co(II), Ni(II) and Mn(II).

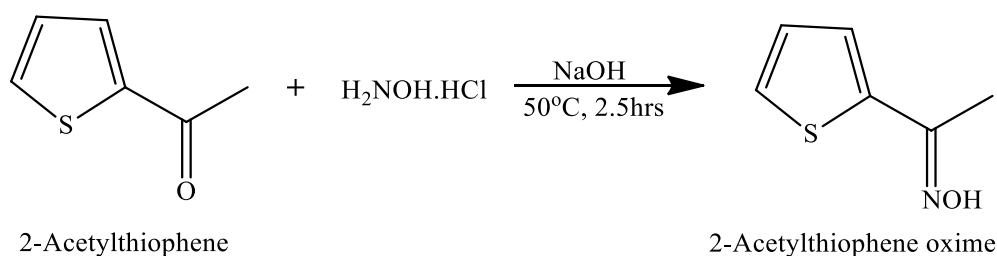
EXPERIMENTAL:

All the chemicals and reagents (purchased from Merck/Sigma) were used as such without further purification. Oximes were prepared by reported green method.^{xviii} Hydrogen, Nitrogen and Carbon were analyzed on a Perkin-Elmer C, H, N and S II series 2400 analyzer. Chlorine and metals were estimated by standard methods.^{xx} KBr pellets were used for recording IR spectra on a Perkin Elmer spectrophotometer (Spectrum Version: 10.4.00) in the standard range of 4000-400cm⁻¹. ¹H-NMR spectra for the synthesized compounds were recorded using TMS as an internal reference on a Bruker Ascend 300 MHz system in d₆-DMSO as solvent. Melting points were observed using an electric melting point apparatus and were uncorrected. The IR & ¹H-NMR studies were carried out at *MNIT, Jaipur*. Biological activities were carried out at *Seminal Applied Sciences Pvt. Ltd., Jaipur* and *Dr. B. Lal Clinical Laboratory Pvt. Ltd. - CIRD, Jaipur*.

Synthesis of 2-Acetylthiophene oxime

An equimolar mixture of 2-Acetylthiophene(4.0 g, 31.701 mmol) and hydroxylamine hydrochloride (2.203 g, 31.701 mmol) in 20 ml water was stirred for around 30 minutes at 50 °C. Sodium hydroxide (1.27 g, 31.701 mmol) was then added in portions and stirring was continued at room temperature for another 1.5-2 hours (Scheme 1). Contents were filtered off under reduced pressure and the crystalline solid product HON=C(CH₃)C₄H₃S was obtained as precipitate; washed twice with cold water and dried.

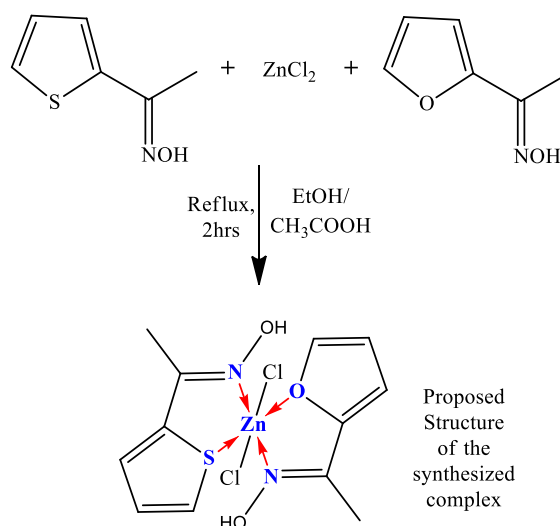
A similar procedure resulted in synthesis of HON=C(CH₃)C₄H₃O.



Scheme 1. Synthesis of 2-Acetylthiophene oxime

Synthesis of Mixed ligand complexes^{xxi}

A warm ethanolic solution of anhydrous Zincchloride (2.85 g, 20.912 mmol) was mixed with equimolar amounts of 2-Acetylthiophene oxime (2.95 g) and 2-Acetylfuran oxime (2.62 g). 2-3 drops of glacial acetic acid were added to this mixture and the contents were allowed to reflux for 2 hours (Scheme 2). Contents were precipitated out on cooling; filtered, washed twice with cold ethanol to obtain [Zn(C₁₂H₁₄N₂O₃S)Cl₂].



Scheme 2. Synthesis of [Zn(C₁₂H₁₄N₂O₃S)Cl₂]

A similar procedure resulted in synthesis of [Cu(C₁₂H₁₄N₂O₃S)Cl₂], [Co(C₁₂H₁₄N₂O₃S)Cl₂], [Ni(C₁₂H₁₄N₂O₃S)Cl₂] and [Mn(C₁₂H₁₄N₂O₃S)Cl₂].

RESULT AND DISCUSSION

General Chemical Composition of Complexes

The general chemical composition of all the synthesized complexes can be represented as [M(C₁₂H₁₄N₂O₃S)Cl₂] (where M = Zn, Cu, Co, Ni and Mn). All these colored mixed ligand complexes were found to be thermally stable and were obtained in 72-83% yield. Physical and analytical observations are listed in Table 1 and 2.

Table 1

Physical and Analytical data of the synthesized mixed ligand Metal complexes

S. N.	Complex	Color, % Yield	M.p. (°C)	Elemental Analysis % Found (% calcd.)				
				C	H	Cl	N	Metal
1	[Zn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	Creamy White, 83%	196	35.76 (35.80)	3.58 (3.50)	17.53 (17.61)	7.08 (6.96)	16.27 (16.24)
2	[Cu(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	Blue, 80%	224	35.82 (35.96)	3.44 (3.52)	14.77 (17.69)	6.89 (6.99)	15.91 (15.86)
3	[Co(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	Dark Pink, 76%	204	36.25 (36.38)	3.63 (3.56)	17.82 (17.90)	7.16 (7.07)	14.79 (14.88)
4	[Ni(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	Green, 72%	212	36.34 (36.40)	3.64 (3.56)	17.90 (17.91)	7.04 (7.08)	14.89 (14.82)
5	[Mn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	Brown, 78%	220	36.81 (36.75)	3.56 (3.60)	18.17 (18.08)	7.11 (7.14)	14.08 (14.01)

IR Spectra

Some significant IR peaks are mentioned in Table 2.

IR Spectra of the mixed ligand metal complexes were observed in the standard region of 4000-400 cm^{-1} . All these spectra were studied based on some key peaks as observed. The signals in the region 3391-3212 cm^{-1} in spectra of mixed ligand metal complexes are accounted for $\nu(\text{O}-\text{H})$; which depicted that there was no deprotonation of O-H bond during interaction of metal ions with ligands, since similar signals were obtained in the region 3320-3280 cm^{-1} in the spectra of parent ligands.^{xviii,xxii} The peaks observed in the spectra of mixed ligand complexes in the region 1628-1593 cm^{-1} attributed to $\nu(>\text{C}=\text{N})$ i.e.; azomethine group of oxime moiety, were lower in position with respect to similar signals observed in the spectra of the parent oximato ligands in the region 1665-1655 cm^{-1} . This shift towards lower frequency region suggested bonding of metal ions with ligands via N-atom of the C=N-OH group present in both the ligands. In a similar pattern; peaks observed in the spectra of mixed ligand complexes in the region 1395-1294 cm^{-1} attributed to $\nu(\text{C}=\text{X}, \text{aromatic ring where X = O, S})$, were lower in position with respect to similar signals observed in the spectra of the parent oximato ligands in the region 1430-1405 cm^{-1} .^{xviii} Furthermore, peaks observed in the spectra of these complexes in the regions 1022-1000 cm^{-1} and 634-452 cm^{-1} can be attributed to $\nu(\text{N}-\text{O})$ and $\nu(\text{Metal}-\text{N})$, respectively.

Table 2

IR spectral readings of the synthesized mixed ligand Metal complexes

S. N.	Complex	$\nu(\text{O}-\text{H})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}-\text{X}; \text{aromatic ring})$	$\nu(\text{Metal}-\text{N})$	$\nu(\text{N}-\text{O})$
1	[Zn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	3384	1618	1395	535	1006
2	[Cu(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	3391	1605	1344	452	1002
3	[Co(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	3288	1617	1368	590	1003
4	[Ni(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	3212	1628	1349	634	1000
5	[Mn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	3382	1593	1294	521	1022

¹H-NMR Spectra

The persistence of O-H signals in 11.18-11.13 ppm region as observed in the proton spectra of all the synthesized complexes revealed that no deprotonation of O-H bond occurred during formation of complexes. Further, it was noticed that the synthesized complexes exhibited high field shifting of signals as compared to their position in parent ligand systems;^{xviii, xxiii} suggesting the formation of M←L coordinate bond.

Table 3

¹H-NMR spectral readings of the synthesized mixed ligand Metal complexes

S. N.	Complex	¹ H-NMR in δ p.p.m.
1	[Zn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	11.16 (s, 1H), 7.68 (s, 1H), 6.72 (d, J = 3.4 Hz, 1H), 6.56-6.49 (m, 1H), 2.04 (s, 3H).
2	[Cu(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	11.13 (s, 1H), 7.52 (d, J = 1.7 Hz, 1H), 6.78 (d, J = 3.4 Hz, 1H), 6.59 (dd, J = 3.4, 1.8 Hz, 1H), 2.01 (s, 3H)
3	[Co(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	11.14 (s, 1H), 7.45 (d, J = 5.1 Hz, 1H), 7.32 (d, J = 3.6 Hz, 1H), 7.09 (dt, J = 23.7, 4.5 Hz, 1H), 2.15 (s, 3H).
4	[Ni(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	11.17 (s, 1H), 7.70 (d, J = 1.7 Hz, 1H), 6.74 (d, J = 3.4 Hz, 1H), 6.54 (dd, J = 3.4, 1.8 Hz, 1H), 2.06 (s, 3H)

5	[Mn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	11.18 (s, 1H), 7.31 (s, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 2.20 (s, 3H).
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Antibacterial Activity

In-vitro antibacterial activity of these mixed ligand metal complexes in methanol solution was studied against different bacteria and MIC (Minimal Inhibitory Concentration) was evaluated by means of Kirby-Bauer well diffusion method,^{xxiv} using Mueller Hinton agar No. 2 (Hi Media, India). Bacterial discs were kept in incubation overnight at 37°C. Standard laboratory culture strains of *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas diminuta* and *Staphylococcus aureus* were used. The extracts were diluted in 100 % dimethyl sulfoxide at the concentrations of 5mg/ml and 100µl of the test compound was used in the well, sized 6mm. Ciprofloxacin was used as a standard for comparing zone of inhibition produced by the test compounds. The antibacterial results (Table 4) reflect that all the metal complexes have a significant effect on bacterostatic potency (Figure 1).

Table 4

Antibacterial activity resultsof mixed ligand metal complexes

S. N.	Complex	log MIC values (in µg/ml)			
		<i>B. subtilis</i>	<i>E. coli</i>	<i>P. diminuta</i>	<i>S. aureus</i>
1	[Zn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	4.325	4.109	4.256	4.198
2	[Cu(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	4.566	4.246	4.200	4.345
3	[Co(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	4.815	4.483	4.653	4.450
4	[Ni(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	4.522	4.213	4.147	4.250
5	[Mn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	4.333	4.317	4.267	4.214

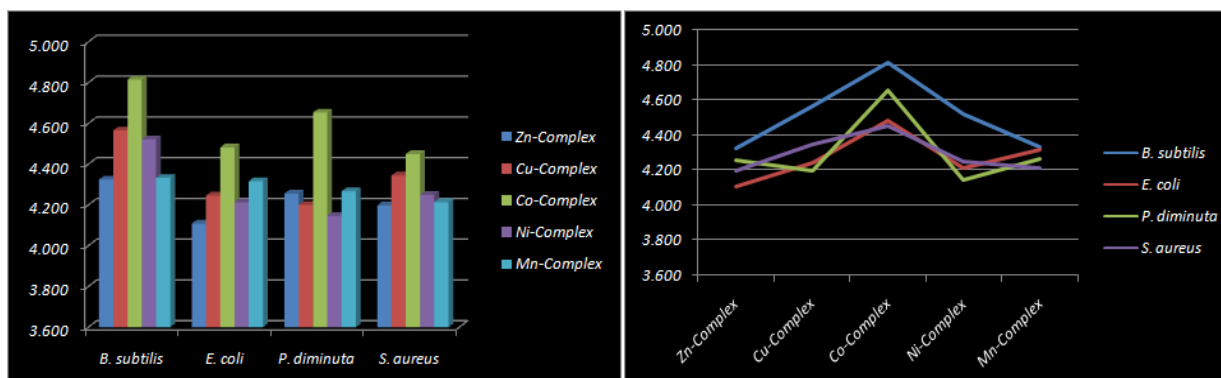


Figure 1(a & b). Antibacterial activity of Mixed Ligand metal complexes (Y-axis stands for log MIC data in µg/ml)

Anticandidal Activity

The preliminary *in-vitro* anticandidal activity of the synthesized mixed ligand metal complexes suggested that they are remarkably effective against *Candida albicans* (Table 5).

Table 5

Anticandidal activity resultsof mixed ligand metal complexes

S. N.	Complex	Organism	PC	NC	At conc. 5 mg/ml	At conc. 10 mg/ml
1	[Zn(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]	<i>Candida albicans</i>	18mm	10mm	23mm	29mm
2	[Cu(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]				26mm	31mm
3	[Co(C ₁₂ H ₁₄ N ₂ O ₃ S)Cl ₂]				21mm	28mm

4	$[\text{Ni}(\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3\text{S})\text{Cl}_2]$				26mm	31mm
5	$[\text{Mn}(\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3\text{S})\text{Cl}_2]$				13mm	15mm

The in-vitro analysis was performed by means of Kirby-Bauer well diffusion method using Sabouraud's Dextrose Agar.^{xxiv} Discs were kept in incubation for 48 hours at 28°C. Compounds were dissolved in DMSO. Two test concentrations 10mg/ml, 5mg/ml were prepared from respective stock solution of each synthesized metal complex and 100µl of both concentrations were used in separate wells (Figure 2). Itraconazole was used as PC (positive control) at 5mg/ml concentration and DMSO was used as NC (negative control). The observed order of activity exhibited by complexes can be arranged in the order:

Cu-Complex = Ni-Complex > Zn-Complex > Co-Complex > Mn-complex



Figure 2. Anticandidal activity of $[\text{Ni}(\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3\text{S})\text{Cl}_2]$
(PC: Positive Control; NC: Negative Control; Conc. 0.5X: 5mg/ml; Conc. 1X: 10mg/ml)

CONCLUSION

In the present research paper, we have reported mixed ligand metal complexes prepared by interaction of 2-Acetylfuran oxime and 2-Acetylthiophene oxime with transition metal chlorides viz. ZnCl_2 , CuCl_2 , CoCl_2 , NiCl_2 and MnCl_2 . All the synthesized metal complexes were characterized by spectral techniques such as $^1\text{H-NMR}$, IR. In general; a coordination environment depicting octahedral geometry can be proposed for all these complexes. The biological screening of all the mixed ligand complexes illustrates their significant biological activity against a variety of pathogens.

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