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SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF THIOSEMICARBAZONE BASED METAL COMPLEXES

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Abstract: Synthesis of cyanuric chloride based various chalcones **A1-A5** by condensation reaction of Cyanuric chloride with 1-(5-hydroxynaphthalen-1-yl) Ethenone to yields product which upon condensation with various aromatic Aldehyde**a-e**. This chalcones on further condensation with Thiosemicarbazide to produced heterocyclic compounds **B1-B5** which were used as the ligands. Two moles of this prepared ligand were reacted with three different metal chloride such as $MnCl_2$, $CuCl_2$ and $ZnCl_2$ to produced Complexes **C1-C15.** Characterizations of all synthesized complexes were done using ^{1}HNMR and IR. Biological evaluation of all prepared complexes was done using against two-gram positive bacteria such as *Staphylococcus aureus*, *Bacillus megaterium* and two-gram negative bacteria *Escherichia coli*, *Proteus vulgaris*. Most of the synthesized products exhibited moderate to good potency against bacteria as compared to standard drugs.

Keywords: Cyanuric Chloride, Chalcone, Metal complexes, Antimicrobial activity, Thiosemicarbazone, Spectroscopy.

1. Introduction: Transition metal complexes are a fascinating class of molecules that can be found in almost every branch of science and technology. Modifications to the central metal atom or the ligand sphere can be used to adjust them to a certain function. These complexes can be encapsulated in chemical or biological matrices and employed in a variety of settings. The interaction between transition or inner transition metal ions and other heterocyclic ligand molecules has received greater study in recent years. Transition metal complexes open up a world of possibilities for designing and developing new biological active chemicals that outperform the present metal salts in terms of biological efficacy. By changing the geometry of metal complexes with different heterocyclic ligands, they can be made more reactive and physiologically active. Heterocyclic ligands often

contain a functional group such as OH, $-NH_2$, -SH, -C=N (Schiff base), etc., which forms five or six membered chelating rings when complexes with metal ions.

Thi Bao Yen Nguyen et al. Have synthesized thiosemicarbazone based metal complexes of [M(L)] (M = Ni, Pd, Pt) and [Re(OMe)(L)]·H2L and carried out antimicrobial activity[1].

Şaban Uysal et al. Have synthesized an d characterize a novel tetra-directional ligand and prepared its metal complexes with transition metal such as Cr and Fe and tested prepared compounds for their biological evaluation[2].

M. Lavanya et al. Synthesized have metal complexes of substituted thiophene thiosemicarbazones derivatives prepared and characterised and tested prepared compound for their anticancer activity[3].

Kritika Bajaj et al. Have examined the development of thiosemicarbazones, bis(thiosemicarbazones) and their metal complexes as potential antifungal agents against more than 65 different fungal strains[4].

Fathy A.El-Saied et al. Have studied on Pd^{2+}, Pt^{2+}, Ni^{2+} and Cu^{2+} complexes of N-ethyl-2-(2-hydroxybenzylidene) hydrazine-1-carbothioamide (H2L) and characterised by SCXRD, FTIR, CHNS, UV–Vis, GC-MS, TGA and NMR. Ni^{2+}, Pd^{2+} and Pt^{2+} complexes were used as novel single precursors for the preparation of noble metal/metal oxide nanoparticles via solid state thermal decomposition method based on their thermal characteristics[5].

GabrieliL Parrilha et al. Have examined Mono(thiosemicarbazones) and bis(thiosemicarbazones) give wide pharmacological profile and ability to chelate metals forming stable complexes and behaviors of different radio metal complexes with mono(thiosemicarbazones) and bis(thiosemicarbazones) as diagnostic and therapeutic radiopharmaceutical drug[6].

Ahmed Ezzat et al. Have Synthesized new Cu (II), Zn (II) thiosemicarbazone based on sulfonyl isatin and its spectral characterization and antimicrobial evaluation and molecular docking[7].

Raquel Alcaraz et al. have synthesized Thiosemicarbazone-metal complexes exhibiting cytotoxicity in colon cancer cell lines through oxidative stress and thiosemicarbazone based metal complexes cause changes in oxidative stress levels in several metabolic points leading to cell death[8].

Lincoln Dkhar et al. have synthesized thiosemicarbazone based containing salicylaldehyde platinum complexes and biological evolution like antibacterial and antioxidant studies[9].

DharmenderSharma et al. have synthesized substituted benzaldehyde thiosemicarbazone and used nickel and silver metal and its metal complexes also examine their antitubercular activity[10].

K. Jayakumar et al. Have synthesized mono- and binuclear copper(II) complexes derived from 2-benzoylpyridine-N4-methyl-3-thiosemicarbazone and characterised

molecular structure of sulfur bridged Cu(II) box-dimer and EPR studies indicate dimeric nature of one of the complexes[11].

Priya P. Netalkar et al. Have synthesized thiosemicarbazone based transition metal complexes used of Cu, Zn and Co transition metal and characterised by various spectro-analytical techniques.and examined its biological activity[12].

David G.Calatayud et al. Have synthesized Zinc and mercury complexes of benzil bis(4-methyl-3-thiosemicarbazone). Complexes containing a neutral or a doubly deprotonated ligand, depending on the reaction conditions. The complexes have been thoroughly characterized by elemental analysis, mass spectrometry, FTIR and ^{1}H, ^{13}C and ^{199}Hg NMR spectroscopy[13].

Nandhagopal Raj put et al. Have synthesized Pyrenyl-based thiosemicarbazone half-sandwich complexes and characterized. The cytotoxicity of all complexes has been established using cancerous and noncancerous cell lines[14].

Franco Bisceglie et al. Have synthesized Quinoline-2-carboxaldehyde thiosemicarbazones and their Cu(II) and Ni(II) complexes and complexes were tested for their antiproliferative properties on histiocytic lymphoma cell line U937. Copper(II) derivatives are systematically more active than the ligands and the nickel complexes[15].

In continuation to metal complexes, the present paper described synthesis of metal complexes from cyanuric chloride based ligand and its complexation with transition metal such as Mn, Cu and Zn.

2. MaterialsandMethods

2.1 Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification. Various aldehydes, pyridine, Cyanuric chloride, 1-(5-hydroxynaphthalen-1-yl) ethenone,Thiosemicarbazide, NH_4OH, KOH, $CuCl_2$, $MnCl_2$, $ZnCl_2$ and ethanol were used as received from Merck, Mumbai, India

2.2 Experimental

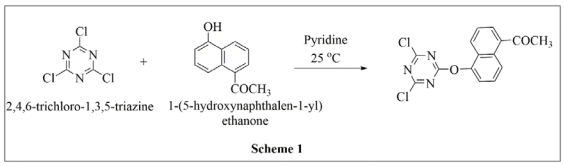
Bruker Avance-400 instrument was used for Proton NMR study and 100MHZ frequency instrument was used for ^{13}C NMR. Parts per million unit was used to expressed chemical shift value. ABB Bomem Inc. FT-IR 3000 Spectrophotometer was used for Infrared Spectral study. Data obtained was expressed in cm^{-1} unit. Shimadzu LCMS-2010 was used for MASS spectral analysis. Perkin Elmer-2400 Series II CHNS/O Elemental Analyzer was used for Composition measurement.

2.3 Method of Synthesis

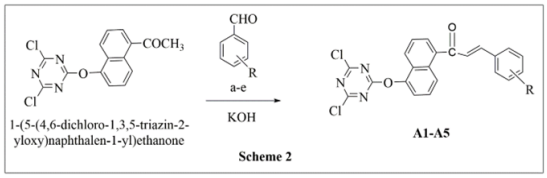
2.3.1 Synthesis of Chalcones A1-A5

In a 250 ml round bottom flask, Cyanuric Chloride (0.1 mole) and1-(5-hydroxynaphthalen-1-yl)ethenol nedissolved in pyridine (50 ml) with constant shaking maintaining the temperature below 25°C. After the completion of dissolution, the mixture was refluxed for 1.5 hour. then it was

cooled and poured into crushed ice. Solid was separated by filtration and crystalline from ethanol. Prepared product was treated with aldehyde thiosemicarbazide a-e(0.1 mole) to produced chalcones A1-A5 (Scheme 1 & 2).



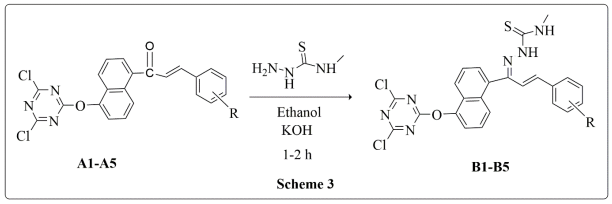
Scheme 1



Scheme 2

2.3.2 Synthesis of Ligands B1-B5

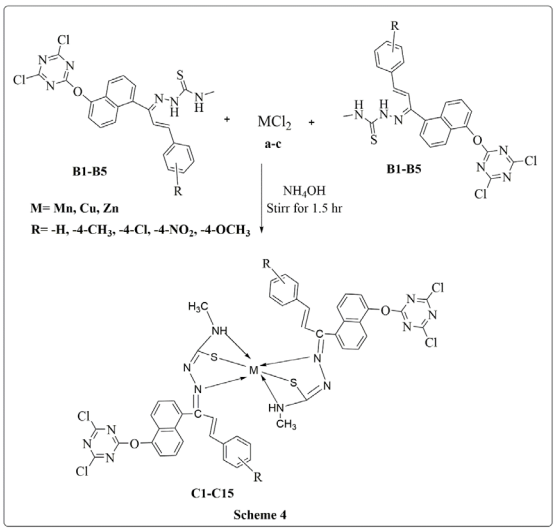
To a well stirred solution of chalcones (0.01 mole)in 250 ml Round bottom flask add 0.01 molThiosemicarbazide, 40 ml ethanol and 40 ml 40% KOH to this mixture solution. Reflux the entire mixture for 30-50 minutes to produced B1-B5. Completion of reaction was monitored by TLC (Scheme 3).



Scheme 3

2.3.3 Synthesis of Metal Complexes C1-C15

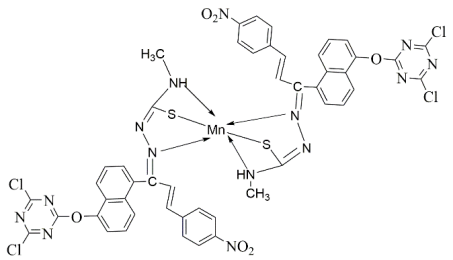
To a well stirred solution of ligands B1-B5in 250 ml Round bottom flask add 0.01 mole MCl_2 (M=Cu, Zn and Mn), 40 ml ethanol. Reflux the mixture in the presence of HCl for 1-2 hour to produced metal complexes C1-C15. Completion of reaction was monitored by TLC (Scheme 4).

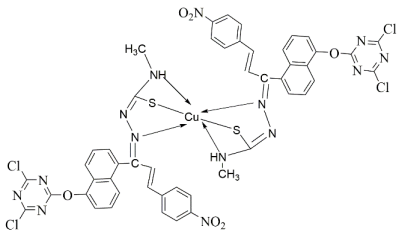


Scheme 4

3. Characterization

C4 & C9 compounds of the series is taken as the representative compound. In the ^1H, NMR spectrum the characteristic signals due to each proton and functional groups with protons are well described on the basis of shielding and deshieldingeffect. From the 1HNMR spectra it shows that the aromatic protons are comes in the region of 6-8.5 δppm in downfield region where as the methyl protons attached to nitrogen atoms is appear at 2.3 δppm. Vinylic protons are comes at 4-5.5 δppm and -NH protons comes in more down field region at chemical shift value around 11.3 δppm. From IR spectroscopy it clearly confirms the presence of the NH group in the structure. It also confirms the S-C and O-C linkage in the metal complexes.

Compound code: C4	
Molecular formula: $C_{48}H_{32}Cl_4MnN_{14}O_6S_2$	
M. P. (°C): >300	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	11.4 (2H, NH, s), 6.8-7.8 (20H, Ar-H, complex), 5.2 (2H, -CH= Vinylic Protons), 4.4 (2H, Vinylic -CH= Protons), 2.3 (6H, 2-CH_3, s).
IR cm^{-1} (KBr):	3425 (-NH stretching), 3010 (Aromatic C-H stretch.), 2940 (Aliphatic C-H Stretch.), 1660 (C=C stretching), 1330 (C-S stretching), 1110 (C-O stretching), 740 (C-H bending in substituted ring).
Mass (M+1):	1161.0
Elemental analysis:	**Calculated (%):** C: 49.63; H: 2.78; N: 16.88. **Found (%):** C: 49.35; H: 2.74; N: 16.72

Compound code: C9	
Molecular formula: $C_{48}H_{32}Cl_4CuN_{14}O_6S_2$	
M. P. (°C): >300	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	11.3 (2H, NH, s), 6.8-7.7 (20H, Ar-H, complex), 5.6 (2H, -CH= Vinylic Protons), 4.3 (2H, Vinylic -CH= Protons), 2.3 (6H, 2-CH_3, s).
IR cm^{-1} (KBr):	3420 (-NH stretching), 3020 (Aromatic C-H stretch.), 2960 (Aliphatic C-H Stretch.), 1660 (C=C stretching), 1345 (C-S stretching), 1100 (C-O stretching), 744 (C-H bending in substituted ring).
Mass (M+1):	1170.0
Elemental analysis:	**Calculated (%):** C: 49.26; H: 2.76; N:16.76. **Found (%):** C: 49.32; H: 2.88; N:16.62

4. Result and Discussion

Table 1 Data showing synthesis of Complexes C1-C15.

Sr. No.	Compounds Code	M	R[c]	Reaction Time[a] (hr)	% Yiled[b]
1	**C1**	Mn	H	4	81
2	**C2**	Mn	4-CH_3	4.5	78
3	**C3**	Mn	4-Cl	3.5	85
4	**C4**	Mn	4-NO_2	3.5	85
5	**C5**	Mn	4-OCH_3	5	75
6	**C6**	Cu	H	4	81
7	**C7**	Cu	4-CH_3	4.5	78
8	**C8**	Cu	4-Cl	3.5	85
9	**C9**	Cu	4-NO_2	3.5	85
10	**C10**	Cu	4-OCH_3	5	75
11	**C11**	Zn	H	4	81
12	**C12**	Zn	4-CH_3	4.5	78
13	**C13**	Zn	4-Cl	3.5	85
14	**C14**	Zn	4-NO_2	3.5	85
15	**C15**	Zn	4-OCH_3	5	75

[a]Reaction is monitored by TLC, [b]Isolated yield and [c]Names of aldehyde groups

From the Table 1 show the various complex prepared by reaction between chalcone based ligands which having thiosemicarbazone moiety with transition metal such as Mn, Cu and Zn chlorides in the presence of ammoniumhydroxide as the basic reagent by stirring the mixture for further 1-2 hr to produced various metal complexes C1-C15. Results shows that the metal complexes bearing electron withdrawing groups are synthesized in the shorter reaction time with good yields of the product (C3, C4, C8, C9, C13 and C14) as compare to the metal complexes bearing electron releasing group such as complexes C2, C5, C6, C7, C10, C12 and C15.

5. Antimicrobial Activity

5.1 Preparation of Media:

For bacterial activity nutrient agar is used. Nutrient agar is prepared as follows:

5gm Peptone, 3gm Metal Extract, 5gm NaCl and 15gm Agar-Agar Peptone were mixed in one liter distilled water and heated to dissolve all the ingredients. The medium was stabilized in autoclave at 15 pound pressure at 125°C for 20 minutes. The medium was cooled down to 45°C and 20 ml poured in sterilized Petri-dish. The pH of the medium was adjusted between 7.0 to 7.5. The culture of the above organism was prepared in nutrient broth dissolved in distilled water. The content of nutrient broth is:

1) Beef extract : 10 gm
2) Peptone : 10 gm
3) Sodium chloride : 5 gm

After sterilizing the above media, it was used for the culture purpose. The culture was ground at 37°C in incubator. With the help of swab, the culture was spread over the agar plates, under specific condition 5 mm diameter paper discs were prepared and were sterilized in autoclave. The solution of the test compound was kept over these paper discs with the help of micropipette. These discs were dried to remove the solvent. Sterile test compound coated by discs were kept in Petri dish containing culture media. The discus was pressed to sterile on media and Petri dishes were incubated for 24 hours at 37°C. After the incubations the zone of inhibition was measured.

5.2 Experimental Data of Antimicrobial Study.

Table 2 Antibacterial Activities of complexes C1-C15

Samples	S.aureus (+Ve)	B.megaterium (+Ve)	E.coli(-Ve)	P.vulgaris(-Ve)

C1	6	4	5	6
C2	9	5	7	6
C3	11	11	10	11
C4	4	5	3	11
C5	5	7	5	6
C6	9	8	7	7
C7	8	8	5	8
C8	9	12	10	11
C9	11	8	6	11
C10	9	3	3	7
C11	9	9	4	6
C12	11	7	9	10
C13	10	12	11	4
C14	8	7	8	10
C15	8	8	6	10
Ampicillin	15	14	17	19
Gentamycin	16	15	14	16

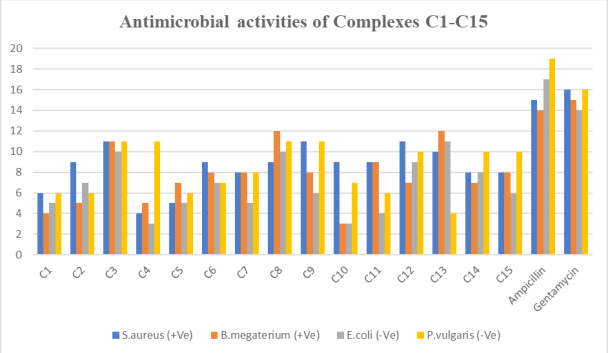


Figure 1 Antimicrobial activities of Complexes C1-C15

(I) Against Staphylococcus aureus:

Maximum activity were found in compounds (C3, C9, andC12) zone of inhibition 11.0 m.m whereas minimum activity were found in compound (C4) zone of inhibition 4.0 m.m.

(II) Against Bacillus megaterium:

Maximum activity was found in compounds (C3, C8 and C13) zone of inhibition-11-12.0 m.m. and minimum activity were found in compounds (C10) zone of inhibition -3.0 m.m

(III) Against Escherichia coli:

Maximum activity were found in compound (C3, C8 and C13) zone of inhibition -10-11.0 m.m (near to standard drug) and minimum activity were found in compounds (C4, C10 and C11) zone of inhibition 3 4.0 m.m

(IV) Against Proteus vulgaris:

Maximum activity were found in compounds (C3, C4, C8, C9, and C14) zone of inhibition 10-11m.m and minimum activity were found in compounds (C13) zone of inhibition 4.0 m.m

6. Conclusion

In conclusion the highly functionalized ligand-based metal complexes C1-C15 were synthesized from various thiosemicarbazide based chalcones and transition metal chloride in the presence of basic condition. All the prepared complexes were characterized by different ^{1}HNMR and IR spectroscopic techniques and screened for antimicrobial activity against gram positive and gram negative bacteria. Satisfactory results of antimicrobial activity were obtained with most of the compounds.

7. Acknowledgements

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