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SYNTHESIS, SPECTRAL AND ANTIMICROBIAL ACTIVITIES OF METAL COMPLEXES WITH PHENYL THIOUREA AND ACID HYDRAZIDE

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Abstract:

Several substituted arylamines were prepared, which were then converted into β-benzoyl-α-arylthioureas by reacting their acetonic solutions with benzoyl chloride and ammonium thiocyanate. The product thus obtained, was then hydrolysed with 10% NaOH to afford the desired arylthiourea which were then treated with adipic acid dihyrazide along with metal salt which than produces the neutral monobasic bidentate complexes. Thus a series of new metal complexes have been prepared. These complexes are coloured solids having sharp melting points and are soluble in DMSO and ethanol. These compounds are characterized by their elemental analysis and on the basis of their spectral (IR, ^{1}HNMR and FAB Mass) studies.Some representative Iigands and their corresponding complexes of this series were screened for their antibacterial activity against pathogenic bacteria *E.coli, S.aureus* and fungi *A.niger A. flavus.* Complexes of Cu(II), Ni(II), Fe(llI) and Eu(III) with o-chlorophenylthiourea with adipic acid dihydrazide exhibited pronounced efficacy against bacteria species *E.coli*.

Keywords: *Phenyl thiourea ,Metal Complex, di hydrazides and Antibacterial activity*

Introduction:

Antimicrobial resistance have become a global problem that ultimately affects human ability to prevent and treat the spread of infectious diseases, viruses, bacteria and fungi as well the success of surgery and cancer chemotherapy. It happens naturally over time, usually genetically viral mutations when exposed to antibiotics. One of the causes of the emergence of the problem is the overuse and misuse of existing antimicrobials, which fueled the emergence of germs resistance to the current library of antimicrobial agents [1,2]. As a result, available medicines become inactive, diseases persist in the body, which increases the risk to patients' health, spread and health maintenance costs. Bacteria resistance to many drugs, such as Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acetinobacter baumanii, Pseudomonas aeruginosa, and Enterobacteriaceae species (“ESKAPE”), are a major problem for the World Health Organization (WHO) and health authorities. These are germs causing a large number of victims worldwide [3]example, methicillin-resistant Staphylococcus aureus (MRSA) is one of the most serious causes of health-related or community-related diseases, due to the high resistance of antibiotics and the toxicity produced. So, it is obvious that there is an urgent need for the development of new and more effective antimicrobial agents methods of action [1].

Researchers discovered that metal complexes of urea and thiourea, as well as their alkyl and aryl derivatives, are monodentate and are linked to the central metal ion through oxygen and sulfur donor atoms, respectively. However, it is well known that the metal ions Cu(lI), Au(II) and Pt(II) are bound through the nitrogen of these Ligands [4,5]. Many researchers created various Pt(II)-urea complexes with strong anti-tumour and other biological properties with hydrazide ligands [6,7]. Lanthanide(III) complexes of the general formula, $(LnX_3m(Ptu)n]\ Xm.2H_2O$ and La(III)the complexes of general formula, $[LnX_3$-m (*o* / *m* / *p*-Totu) n] $Xm.2H_2O$ [where Ln = Pr (III), Nd (III), Sm (III), Eu (III), Dy(III) , Ho (III), Er (III), Yb (III), Y (III); X = NO_3-, Ptu = N-Phenylthiourea, Totu = tolyl thiourea; m = 0,1 and n = 3,4] were divided into Kalyani et al. Thiourea extracts such as 4- methyl phenyl thiourea, 2-hydroxyphenyl thiourea etc [8,9]. Complexes are formed with other flexible metals such as Mn (II), Co (lI) and Ni (II) [10].

The ligand arylureas, N-acyl thioureas and its combination of Co (II) and Ni (lI) of the common formula $ML_2X_2.nH_2O$ [M = Ni (II) or Co (II), L = N-acyl ureas or N-acyl thiourea, X = Cl and n = 6] prepared.

The tetrahedral structure was elevated in these complexes and the antimicrobial activity of the ligands and complexes was tested against Candida albicans and Penicillium tritaphora species. Researchers also assembled and isolated bivalent metal components such as Co (II), Ni (II), Cu (II), Zn (II), Cd (II) and Hg (II) in 1- (N,N-dicyclohexylamine) methylthiourea (OCMT), [(CeHII) 2-N-CH_2-NH-CS-NH_2]maintaining this recognition through and as part of our strategic plans to develop new structures containing -HN-CO-NH- moiety[11,12]. We have compiled and classified the components of this type and tested other compounds.

Experimental:

All compounds have been characterized on the basis of spectral (IR, ^{1}HNMR) studies and elemental analysis. IR spectra (4000-400cm^{-1}) were recorded using PerkinElemer model-557 and Nicolet magna model-750 spectrophotometer in KBr pellets at Central Drug Research Institute (CDRI), Lucknow and Department of Chemistry, University of Rajasthan, Jaipur. ^{1}HNMR spectra were recorded on Brucker spectrometer (300MHz) at CDRI, Lucknow using $CDCI_3$ / DMSO as solvent TMS was taken as internal standard. Mass spectra were recorded on kratos 30 and 50 mass spectrometer at CDRI Lucknow, C, H, N and S analysis of these compounds have been done using Coleman C and H analyzer. Melting points were determined in open glass capillaries and are uncorrected. In all reactions and preparations of starting material, reagents were purified either by distillation or by recrystallization. The purity of compounds was checked by TLC using silica gel-G as adsorbent, visualization was accomplished by UV light or iodine absorption. The middle fractions boiling within +/- 0.5^{o}C of 'the standard boiling points were collected in each case.

Materials and methods :

All the chemicals used were of A.R. grade and the reactionwere carried out under strictly anhydrous conditions. All the solvents and reagents were dried and distilled before use.

Synthesis of ligands and their metal complexes:

(i) *o*-chlorophenylthiourea (CPT)

o-chlorophenylthiourea was synthesized by reacting benzoyl chloride with ammonium thiocyanate followed by treatment of acetonic solution of appropriate substituted phenylamine. This o-chlorophenyl thiourea was then converted into metal complexes by treating it with aqueous/ethanolic solution of metal salts.

(ii) Adipic acid dihydrazide (AHZ)

Adipic acid dihyrazide was synthesized from reaction of ice cooled solution of adipic acid in chloroform by dropwise addition of thionyl chloride with constant stirring. The adipoyl chloride obtained was then treated with ethanolic solution of hydrazine hydrate to obtain adipic acid dihydrazide.

(iii) Tris-(o-chlorophenylthiourea) Nickel(II) complexes

An ethanolic solution of o-chlorophenylthiourea was usedfor the synthesis of Nickel(II) metal complexes.To this anaqueous solution of metal salt $Ni(OCOCH_3)_2.H_2O$ was added in 1: 1 molar-ratio slowly with stirring.

(iv) Tris-(Adipic acid dihydrazide) Nickel(II) complexes

An ethanolic solution of adipic acid dihydrazide was usedfor the synthesis of Nickel(II) metal complexes.To this anaqueous solution of metal salt $Ni(OCOCH_3)_2.H_2O$ was added in 1: 1 molar-ratio slowly with stirring.

(v) Tetrakis-(o-chlorophenylthiourea) Samarium (III) complexes

An ethanolic solution of o-chlorophenylthiourea was used for the synthesis of Sm(III) metal complexes. To this anaqueous solution of metal salt $SmCl_3.H_2O$was added in 1: 1 molar-ratio slowly with stirring.

(vi) Tetrakis-(Adipic acid dihydrazide) Samarium (III) complexes

An ethanolic solution of adipic acid dihydrazide was used for the synthesis of Sm(III) metal complexes. To this anaqueous solution of metal salt $SmCl_3.H_2O$was added in 1: 1 molar-ratio slowly with stirring.

(vii) Tris-(o-chlorophenylthiourea and Adipic acid dihydrazide) Nickel(II) complexes

An ethanolic solution of o-chlorophenylthiourea and adipic acid dihydrazide mixture was usedfor the synthesis of Nickel(II) metal complexes.To this anaqueous solution of metal salt $Ni(OCOCH_3)_2.H_2O$ was added in 1: 1 molar-ratio slowly with stirring.

(viii) Tetrakis-(o-chlorophenylthiourea and Adipic acid dihydrazide) Samarium (III) complexes

An ethanolic solution of o-chlorophenylthiourea and adipic acid dihydrazide mixture was used for the synthesis of Nickel(II) metal complexes. To this anaqueous solution of metal salt $SmCl_3.H_2O$was added in 1: 1 molar-ratio slowly with stirring.

Bio-efficacy studies:

The efficacy of synthesized ligands (o-chlorophenylthiourea and adipic acid hydrazide) and their metal complexes (Nickel (II) and Samarium (III) complexes) were assessed antibacterial and antifungal activities. The streptomycin and micostatine were taken as the standards for antibacterial and antifungal activities, respectively.

Micro-organisms and culture:

Thegram positive bacteria*S.aureus* and gram negative bacteria *E.coli* was used for antibacterial activities. While for antifungal activity *A.flavus and A.niger were used. The seven days old cultures of* these organisms grown on potato-dextrose-agar(PDA) medium were used. All the glassware's and water sterilized in an autoclave.

Zone Inhibition Technique:

The bio-efficacy of metal complexes of o-chlorophenylthiourea and adipic acid hydrazide was estimated by employing zone inhibition technique. The agar plates were prepared in a standard manner and bacterial culture were seeded uniformly on the agar surface. The disc containing sample was placed in petri plate to see the antimicrobial inhibition area of sample and compared with the standard bio-efficacy of standard drugs. One petri plate was also without the disc as a control to check the actual growth of micro-organisms. The plates were incubated for 24 h for testing bactericidal efficacy and for 72 h for testing fungicidal efficacy at $37^{o}C$.

Results and discussion:

All compounds have high melting points and low solubility in common organic solvents. This might be due to the high molecular weight associated with them. The analytical data of the complexes indicate that they have 2:1:1 metal ligand stoichiometry. The analytical and physical data of ligands, i.e., o-chlorophenylthiourea and adipic acid hydrazide and complexes of mixture of these ligands with metal ions Ni (II) and Sm (III) have been summarized in Table 1 and Table 2, respectively.

Table 1. Analytical and physical data of ligands

Ligand	Molecular formula	Colour	Mol.wt.	M.P(C)	Yield (%)	Elemental Analysis % Calculated (Observed)			
						C	H	N	S
CPT	$ClC_6H_4NHCSNH_2$	White	186	146	74	45.16 (45.09)	3.76 (3.52)	15.45 (16.16)	17.20 (16.98)
AHZ	$C_6H_4N_4O_2$	White	174	184	89.4	4.14 (40.68)	8.05 (7.97)	32.18 (32.02)	– _

Table 2. Analytical and physical data of metal complexes

Metal ion	Molecular formula	Colour	Mol. wt.	M.P(C)	Yield (%)	Elemental Analysis % Calculated (Observed)				
						C	H	N	S	M
Ni (II)	$C_{20}H_{26}N_8S_3O_2Cl_2Ni$	Cream	603.69	237	82	2.52 (2.51)	23.21 (23.10)	5.39 (5.30)	9.43 (9.32)	10.28 (10.12)
Sm (III)	$C_{27}H_{32}N_{10}S_3O_2Cl_3Sm$	Cream	880.86	297	82	36.18 (36.71)	3.63 (3.62)	15.86 (15.82)	10.89 (10.28)	17.07 (16.09)

IR and NMR spectral studies :

The IR and NMR spectroscopic studies have been employed for the characterization of ligands, i.e., o-chlorophenylthiourea and adipic acid hydrazide and complexes of mixture of these ligands with metal ions Ni (II) and Sm (III).

o-Chlorophenylthiourea: In the IR spectra of o-chlorophenylthiourea, a signature band at 3380 cm^{-1} and 3420cm^{-1} is observed due to the $–NH_2$ stretching (sym. and asym.) vibration (Table 3). The appearance of absorption band at 3282cm^{-1} and 1242cm-^{1} which are attributed to –NH[11,12] and >C=S stretching vibrations, respectively confirms it's formation. Similarly in the ^{1}HNMR spectra, singlet at δ 3.55ppm due to –NH protons and δ 9.35 ppm due to $–NH_2$ protons confirms the formation of o-Chlorophenyl thiourea (Table 4).

Adipic acid dihydrazide: A sharp band is seen in the region 1665-1660 cm^{-1} in the spectra of hydrazides indicating the presence of amide-I band [v(C=O)] (Table 3). Further, two additional bands observed at 1515-1505(w) and 1330-1320 (Sh) cm^{-1} in the hydrazides may be assigned as amide-II and amide-III bands respectively[13]. In the ^{1}HNMR spectra, singlet at δ 3.55 ppm due to –NH protons and δ 9.35 ppm due to $–NH_2$ protons confirms the formation of adipic acid dihydrazide (Table 4). Signal at δ 1.99 ppm and δ 1.44 ppm depicting the methylene protons.

Table 3. Characteristic IR spectral data of o-chlorophenylthiourea and adipic acid dihydrazide ligands

IR (KBr : *v* max cm^{-1})									
Ligand	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
	$-NH_2$	**>NH Hydrazide**	**(Ar) C-H**	**(Al)C-H**	**>C=O Hydrazide**	***v*(>NH)**	***v* (C=C)**	***v*(C=S)**	***v*(C-Cl)**
CPT	3380, 3420(s)	---	2995(m)	---	---	3282(s)	1502(m)	1242(m)	770(w)
AHZ	3390(s)	3472(b)	---	2880(w)	1665(s)	---	---	---	---

Table 4. Characteristic ^{1}HNMR spectral data of o-chlorophenylthiourea and adipic acid dihydrazide ligands

Ligand	**1HMNR Spectral data (d, ppm)**			
	-CH$_2$ (methylene)	**Ar-H(m)**	**-NH2 (s)**	**-NH (s)**
CPT	---	7.53 – 7.56	9.35	3.55
AHZ	1.99 and 1.44	---	4.15	8.93

Metal complexes of o-chlorophenylthiourea and Adipic acid di hydrazide mixture: In the IR spectra of the ligands and complexes only selected absorption peaks are discussed which are important for ascertaining the donor sites of Iigands (Table 5).

Table 5. Characteristic IR spectral data of o-chlorophenylthiourea and adipic acid dihydrazide metal complexes

IR (KBr : *v* max cm^{-1})										
Metal complex	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
	-NH$_2$	**>NH Hydrazide**	**(Ar) C-H**	**(Al)C-H**	**>C=O Hydrazide**	***v*(>NH)**	***v* (C=C)**	***v*(C=S)**	***v*(C-Cl)**	***v*(M-N)**
Ni-CPT	3380, 3420 (s)	---	2990 (m)	---	---	3250(s)	1498(m)	1190 (m)	768(w)	490(w)
Ni-AHZ	3376 (s)	3422(b)	---	2880(m)	1655(s)	---	---	---	---	498(w)
Ni-MIX	3350 (s)	3420(b)	2992 (m)	29882 (m)	1655(s)	3272(s)	1496(m)	1190 (m)	772(w)	495(w)
Sm-CPT	3380, 3420 (s)	---	3020 (m)	---	---	3250(s)	1498(m)	1090 (w)	822(w)	487(w)
Sm-AHZ	3346 (s)	3422(b)	---	2876(w)	1620(s)	---	---	---	---	497(w)
Sm-MIX	3378 (s)	3420(b)	3018 (m)	2876(w)	1620(s)	3272(s)	1496(m)	1090 (w)	820(w)	492(w)

In IR spectra of metal complexes of Ni-(o-chlorophenylthiourea)presence of absorption bands at 3380cm^{-1} and 3435 cm$\cdot^{1}$ due to –NH$_2$ (sym.) and –NH$_2$ (asym.) modes respectively, remains almost unaltered which clearly indicates the non-involvement of this group on complexation reaction. But slight displacement of >NH frequencies is due to increased positive charge on nitrogen atom arising due to donation of electron pair to metal ion. Sulphur-metal bond formation is expected to increase the contribution of the highly polar structure $H_2N^0 = CS^0NH_2$ to the thiourea molecule. This will result in the greater double bond characters for N-C bond while at the same time C-S bond will attain greater single bond character. In adipic acid dihydrazide Ni complexes the presence of absorption bands at 3422 cm^{-1}due to >NH stretching vibrationsshifted from 3478 cm^{-1} indicative of the involvement of this group in complexation.

Similarly, in IR spectra of Sm-(o-chlorophenylthiourea) complexes the presence of unaltered absorption bands at 3380cm^{-1} and 3435 cm$\cdot^{1}$ due to –NH$_2$ (sym.) and –NH$_2$ (asym.) modes clearly indicates the non-involvement of this group on complexation reaction. The shifting of >NH band indicated the formation of Sm-N bond. In adipic acid dihydrazide Sm complexes also the presence of absorption bands at 3422 cm^{-1} due to >NH stretching vibrations shifted from 3478 cm^{-1} indicative of the involvement of this group in complexation.

In metal complexes of mixture of both ligands the signature bands of all groups appeared. The bands of both groups indicates the complexation of both ligands with the respective metal ions.

In ^{1}H-NMR spectra of the metal complexes also support the IR data. In ^{1}H-NMR spectra of metal complexes of o-chlorophenylthiourea singlet at δ 9.35 ppm for –NH$_2$ and δ 3.92 ppm for >NH indicative of the non-involvement of the NH$_2$ group in complexation. While in metal complexes of adipic acid dihydrazide the deshielded chemicalshift value of >NH at δ 9.48-9.42 ppm singlet indicative of metal-N bond formation.

Table 6. Characteristic ^{1}HNMR spectral data of o-chlorophenylthiourea and adipic acid dihydrazide metal complexes

Metal complex	**1HMNR Spectral data (d, ppm)**					
	-CH$_2$ (methylene)	**Ar-H(m)**	**-NH2 (s)**	**-NH2 (s) hydrazide**	**-NH (s)**	**-NH (s) hydrazide**
Ni-CPT	---	7.67 – 7.71	9.35	---	3.92	---
Ni-AHZ	2.21 and 1.50	---	---	4.92	---	9.48
Ni-MIX	2.21 and 1.50	7.58 – 7.61	9.35	4.91	3.92	9.48
Sm-CPT	---	7.67 - 7.70	9.35	---	3.90	---
Sm-AHZ	2.21 and 1.50	---	---	4.92	---	9.42
Sm-MIX	2.21 and 1.50	7.59 - 7.62	9.35	4.90	3.90	9.43

Antibacterial and antifungal studies:

The antibacterial and antifungal efficacy bio-efficacy results revealed that ligandsexhibited less efficacy in comparison to their metal complexes. This might be due to the high mobility of metal complexes to cross the cell membrane. The mobility of metal complexes across the cell membrane can be explained by chelation theory. The chelation effect in complexes reduce the polarity of metal ions which increase the lipophilicity of metal complexes and ultimately facilitating them to cross the cell membranes easily. The results of antibacterial activity and antifungal activities are summarized in Table 7 and Table 8, respectively.

Table 7. Antibacterial activity data of ligand and their metal complexes

Metal ion	**Ligand**	**Bacterial Species**	**Mean value of area of inhibition in mm ZI (El)**			
			1000ppm	**500ppm**	**200ppm**	**100ppm**
Ni (II)	CPT	*S. aureus*	9.7 (1.0)	9.0 (0.9)	7.4 (0.6)	8.5 (0.7)
		E. coli	12.0 (1.6)	10.7 (0.9)	9.0 (0.8)	7.0 (0.8)
Ni (II)	AHZ	*S. aureus*	9.7 (0.8)	9.6 (0.8)	7.2 (0.6)	8.4 (0.7)
		E. coli	12.2 (1.8)	10.5 (1.0)	8.9 (0.8)	6.6 (0.8)
Ni (II)	Mixture	*S. aureus*	9.8 (0.9)	9.2 (0.9)	7.6 (0.7)	8.6 (0.8)
		E. coli	12.4 (1.9)	10.6 (0.9)	9.2 (0.9)	6.9 (0.7)
Sm (III)	CPT	*S. aureus*	11.4 (0.9)	9.7 (0.8)	9.2 (0.9)	9.0 (1.0)
		E. coli	12.7 (1.7)	11.3 (1.1)	11.0 (1.1)	8.4 (0.8)
Sm (III)	AHZ	*S. aureus*	11.8 (1.2)	9.9 (1.0)	9.0(1.0)	9.1 (0.9)
		E. coli	12.8 (1.8)	11.5 (1.2)	11.1 (1.1)	8.5 (0.8)
Sm (III)	Mixture	*S. aureus*	11.7 (1.0)	9.8 (0.9)	9.2 (0.9)	9.2 (0.9)
		E. coli	12.6 (1.9)	11.6 (1.3)	11.2 (1.2)	8.6 (0.9)

ZI = Zone of Inhibition area excluding diameter of disc.
El (Efficacy Index) = zone of Inhibition area of sample/zone of inhibition area of standard.

Table 8. Antifungal activity data of ligand and their metal complexes

Metal ion	**Ligand**	**Fungal Species**	**Mean value of area of inhibition in mm ZI (El)**			
			1000ppm	**500ppm**	**200ppm**	**100ppm**
Ni (II)	CPT	*A. niger*	11.1 (0.9)	8.1 (0.9)	7.2 (0.8)	6.8 (0.8)
		A. flavus	11.0 (1.0)	10.1 (1.1)	6.4 (1.5)	6.1 (0.8)
Ni (II)	AHZ	*A. niger*	11.1 (1.1)	0.9 (0.8)	7.1 (0.8)	7.0 (.9)
		A. flavus	10.9 (1.0)	10.2 (1.1)	6.6 (1.6)	5.9 (0.8)
Ni (II)	Mixture	*A. niger*	11.6 (1.2)	8.2 (1.0)	7.6 (1.0)	7.2 (1.0)
		A. flavus	11.5 (1.2)	10.6 (1.2)	6.9 (1.8)	6.4 (0.9)

Sm (III)	CPT	*A. niger*	12.9 (1.6)	12.5 (1.2)	11.0 (1.1)	10.4 (1.2)
		A. flavus	12.2 (1.0)	11.0 (1.1)	10.7 (1.1)	9.7 (1.0)
Sm (III)	AHZ	*A. niger*	12.8 (1.4)	12.4 (1.0)	11.1 (1.2)	10.8 (1.4)
		A. flavus	12.6 (1.2)	11.1 (1.1)	10.7 (1.0)	9.8 (1.0)
Sm (III)	Mixture	*A. niger*	13.2 (1.8)	12.9 (1.4)	11.2 (1.3)	10.2 (1.1)
		A. flavus	12.8 (1.3)	11.4 (1.3)	10.9 (1.2)	9.8 (1.1)

ZI = Zone of Inhibition area excluding diameter of disc.
El (Efficacy Index) = zone of Inhibition area of sample/zone of inhibition area of standard.

Conclusions:

Significant results were obtained with adipic acid hydrazide ligand. It was found that o-chlorophenylthiourea exhibited less efficacy against bacteria and fungi but adipic acid dihydrazide exhibited more efficacy against both *bacteria* and fungi.

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