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Nagendra Singh
Research Scholar, Department of Chemistry, Narain (P.G.) College, Dr. Bhimrao Ambedkar University, Agra, Uttar Pradesh, India

Arvind Kumar
Associate Professor, Department of Chemistry, Narain (P.G.) College, Dr. Bhimrao Ambedkar University, Agra, Uttar Pradesh, India

Corresponding Author:
Arvind Kumar
Associate Professor, Department of Chemistry, Narain (P.G.) College, Dr. Bhimrao Ambedkar University, Agra, Uttar Pradesh, India

Mixed ligand complexes of nickel (ii): Synthesis and bio medicinal studies

Nagendra Singh and Arvind Kumar

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Abstract
Mixed ligand nickel (II), complexes of 2, 2 bipridyle and thioamides of 2-aminopyridine, 2-aminoadinine, 2-aminoguanine and 2-aminocytocine were prepared. The success of synthesis was confirmed through physical and spectral characterization on the basis of IR and NMR spectroscopy, antimicrobial and antitumour studies. The synthesized compounds were found to be active against the tested three bacterial strains (*Pseudomanas auruginosa*, *Klebseila pneumonia* and *Staphylococcus aureus*), two fungal strains (*Aspergillus flavus* and *Aspergillus nigar*) and antitumour activity against MCF-7 (Human breast adenocarcinoma) cell line.

Keywords: Thioamide, 2, 2 bypridyle, antimicrobial antitumour etc.

Introduction
Transition metal ions are involved in many biological processes in the body [1, 2]. Nickel (II), copper (II), and zinc (II) ions, for example, are the most abundant transition metal ions in humans. They're found in a lot of enzymes, either at the active sites or as structural components [3, 4]. One of the most recent advancements in the field of bioinorganic chemistry has been the study of the coordination chemistry of physiologically relevant metal ions with mixed ligands. Pyridine derivatives are found in a wide range of biological systems, including vitamins, nucleic acids, enzymes, and proteins [5]. However, there are little research on the antibacterial properties of their metal complexes in the literature. Metal complexes having nitrogen and sulphur donors have been shown to be antibacterial and fungicidal agents [6], as well as components of various vitamins and medicines [7, 8]. Metal ion binding to nicotinanilide groups has sparked renewed interest, as many of these reactions serve as simple models for far more complicated metal peptide systems and enzymes. The transition metal ions, Zn, Co, Pe, etc. are known to persist in biological systems by coordination with numerous enzymes containing the heme, and related structures such as catalases, peroxidases and cytochromes. The iron containing proteins, ferritin, transferrin and hemosiderin are known to predominate in biological systems [9-12]. Zinc complex as sine insulin and Beryllium salt or complex, as lymphocyte activator are- known for their- importance. The present manuscript contains the details of the synthesis of some mixed ligand complexes of Ni and their biomedicinal studies.

Experimental
All the chemicals used were of analytical grade and were procured from Sigma-Aldrich and Fluka. Metal salts were purchased from Merck. All the employed solvents were of standard spectroscopic grade. The Infrared absorption spectra of complexes under investigation have been obtained in KBr pallet using Perkin-Elmer model-577 IR absorption spectrophotometer. ^{1}H NMR spectra of the mixed ligand complexes was recorded in $CDCl_3$ using TMS as an internal reference at 25 °C.The molecular weights of all mixed-ligand complexes were determined using the cryoscopy method. The method given by Sen has been used for the estimation of SH group present in the mixed-ligand complexes. Antibacterial activity of these compounds was determined by disc-diffusion method [13-14]. Against the three human pathogenic bacterial strains *Pseudomanas auruginosa*, *Klebseila pneumonia* and *Staphylococcus aureus*. The antifungal activity of these compounds was determined by agar plate method; (23) using four concentrations *viz*; 50 and 100 µg/ml of test compounds against human pathogenic fungal strains, *Aspergillus flavus* and *Aspergillus nigar*. The human Breast Cancer cell line (MCF-7) was co-incubated with the test compounds at 1 µg/ml doses for 96 hrs and the cell growth count was measured by MTT assay as described below (25). Here 17β estradiol as positive control and culture medium as negative control was used.

Primary ligands i.e. 2,2'-bipyridyl will be taken as such BDH-(AR) and will be used while preparing the mixed ligand complexes Zn(II) salts. All chemicals will be of analytical grade.

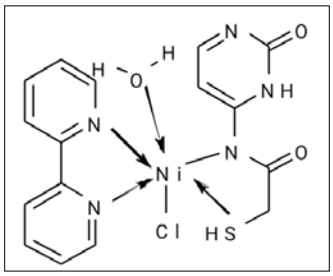
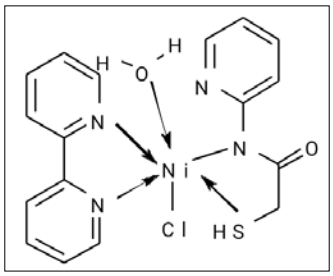
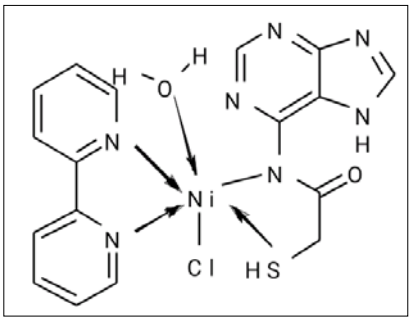
Secondary Ligands (Amides) will be synthesized by taking 1:1 molar ratio of thio-glycolic acid and 2-aminopyridine, 2-amino- adinine, 2-amino – guanine and 2- amino cytosine by refluxing the components for appropriate periods and the resultant product will be crystallized.

Mixed ligand complexes of Zn(II), Cd(II), Co(II), Ni(II) and Cu(II) will be synthesized by taking 1:1:1 molar ratio of metal ion, 2,2'- Bipyridyl / 1,10- phenanthroline, secondary ligand (thio amide).

The content in 1:1:1 molar ration will be refluxed for suitable period and crystallized using suitable procedures. Finally the mixed ligand complexes of Zn(II) will characterized by elemental analysis, molecular weight determination, IR and NMR.

Ni(II)-Bipridyl-Thioamide

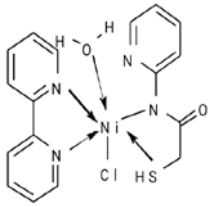
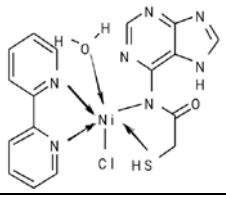
Calculated amount of $NiCl_2$ (0.005 mole) and bipridyl (0.005 mole) were dissolved separately in 25 ml double distilled water and in 25 ml ethanol (95%) respectively. The solutions were warmed and mixed, in a 250 ml round bottomed flask. 30 ml of ethanolic solution of thioamide (0.005 mole) was added to the contents in round bottomed flask and a requisite amount of 10/6 sodium acetate solution was added so as to adjust pH of the contents between 4.0 and. 5.0. The contents in round bottomed flask were refluxed for 1-2 hours. This resulted in separation of granular white precipitate. The contents ware cooled to room temperature and filtered under vacuum suction. The residue was washed with water and then 3-4 times with ethanol to remove the unreacted metal ion and ligands if any, and finally it was washed with ether and dried in an oven.

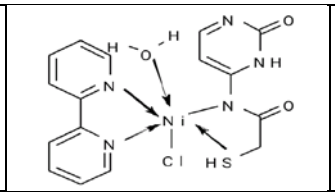




Results and Discussion

The mixed-ligand complexes of Zn(II), Cd(II), Cr(II) and Ni(II) ions are appreciably soluble in ethanol and slightly soluble in nitrobenzene, acetone etc. These complexes dissolve readily in acetic acid. All these complexes do not melt sharply but decomposes above 150°C. Their conductance measurements in glacial acetic acid indicate that these mixed ligand complexes are non-electrolyte. Molecular weight determinations of these complexes correspond to their monomeric nature in solution. The mixed-ligand complexes of Co(II) ion are insoluble in common organic solvents and do not, melt up to 250 °C. This may be indicative of their polymeric nature. The complexes show proper ratios of elements as in their data of elemental analysis.

Table 1: Physical and spectral data of the synthesized compounds (1-4)

S. No	Formula of Compounds	Thioamide used	M.W	M.P	I.R(V:CM^{-1})	NMR (δ:ppm)
1.	$C_{17}H_{17}ClN_4O_2SNi$ 	2-amino pyridine	435.55	155	3294 ν (NH), 1669 ν (C=O), 1598 ν (C=N), 2083 ν (CN), 700 ν (CS), 583 ν (M-N),	8.59-7.12 (12H, m, 2-pyridine CH) 3.33 (2H, s, methylene)
2.	$C_{17}H_{16}ClN_7O_2SNi$ 	2-amino adinine	476.56	178	3294 (NH), 1669 ν (C=O), 1598 ν (C=N), 2083 ν (CN), 700 ν (CS), 583 ν (M-N),	δ 8.55-7.14 (12H, m, 2-pyridine CH), 7.50 (2H, s, CH, aldimine) 3.4 (2H, s, methylene)
3.	$C_{17}H_{18}ClN_7O_2SNi$	2-amino guanine	478.78	176	3294 ν (NH), 1669 ν (C=O), 1598 ν (C=N), 2083 ν (CN), 700 ν (CS), 583 ν (M-N),	8.59-7.12 (12H, m, 2-pyridine CH), 7.50 (2H, s, CH, aldimine), 3.33 (2H, s, methylene) 1.5 (1H, s, methine)
4.	$C_{16}H_{16}ClN_5O_3SNi$	2-amino cytosine	452.54	180	3294 ν (NH), 1669 ν (C=O), 1598 ν (C=N), 2083 ν (CN), 700 ν (CS), 583 ν (M-N), 454 ν (SCN)	8.0 (1H, s, NH sec. amide) 7.50 (2H, CH, aldimine) 8.59-7.12 (12H, m, 2-pyridine CH) 3.33 (2H, s, methylene)

(a)Anti-microbial activity: The antibacterial activity of these mixed ligand complexes were tested against the three human pathogenic bacterial strains which are basically human pathogens, *Pseudomanas auruginosa*, *Klebseila pneumonia* and *Staphylococcus aureus*. In case of *pseudomonas auruginosa*, compounds, 1 and 2, shows highest activity and the rest of compounds shows moderate activity. In *Klebsiella pneumonia*, activity of the compounds **3** found highest in comparison to other complexes. All compounds are morderate active agaist *Staphylococcus aureus*.the results are given in the table 2.

Table 2: Antibacterial Activity of Mixed Ligand complexes of Ni

S. N.	Compounds	Control	*Pseudomonas aeruginosa*	*Staphylococcus aurius*	*Klebsiela pneumonia*
1.	$C_{17}H_{17}ClN_4O_2SNi$	–	+++	++	++
2.	$C_{17}H_{16}ClN_7O_2SNi$	–	+++	++	++
3.	$C_{17}H_{18}ClN_7O_2SNi$	–	++	++	+++
4.	$C_{16}H_{16}ClN_5O_3SNi$	–	++	+	++

The Fungicidal activity of mixed ligand complexes of Ni was carried out by using four concentrations 50 and 100 µg/ml conc. of test compound in two fungal strains *Aspergillus flavus* and *Aspergillus nigar*. At 50 µg/ml concentration, compounds 1 and 2 shows highest percentage inhibition against *Aspergillus flavus* while all compounds shows mordarate percentage inhibition against *Aspergillus nigar*. At 100 µg/ml conc. compound shows high value of percentage inhibition against the fungal stains *Aspergillus flavus* and *Aspergillus nigar* respectively. The variation in fungicidal activity is due to variation in ligands molecules attached. The results are given in tables-3and 4.

Table 3: Anti-Fungal Activity of Mixed Ligand complexes of Ni

(A)	Activity at 50 µg/ml of conc. of test compounds				
S. N.	Compounds	*Aspergillus nigar*		*Aspergillus flavus*	
		Colony dia (mm)	% Inhibition A. nigar	Colony dia (mm)	% Inhibition A. flavus
1.	$C_{17}H_{17}ClN_4O_2SNi$	0.5	83.3	1.0	50.0
2.	$C_{17}H_{16}ClN_7O_2SNi$	0.5	83.3	0.8	60.0
3.	$C_{17}H_{18}ClN_7O_2SNi$	0.8	73.3	0.8	60.0
4.	$C_{16}H_{16}ClN_5O_3SNi$	0.8	73.3	1.0	50.0

(B)	Activity at 100 µg/ml of conc. of test compounds				
S. N.	Compounds	*Aspergillus nigar*		*Aspergillus flavus*	
		Colony dia (mm)	% Inhibition A. nigar	Colony dia (mm)	% Inhibition A. flavus
1.	$C_{17}H_{17}ClN_4O_2SNi$	0.1	96.7	0.4	80.0
2.	$C_{17}H_{16}ClN_7O_2SNi$	0.2	93.3	0.2	90.0
3.	$C_{17}H_{18}ClN_7O_2SNi$	0.5	83.3	0.5	75.0
4.	$C_{16}H_{16}ClN_5O_3SNi$	0.2	93.3	0.5	75.0

(B) In-vitro Antitumour activity

The mixed ligand complexes of Ni were tested for their *in-vitro* antitumor activity against MCF-7 (Human breast adenocarcinoma) cell line. The results of the activity are quite surprising. The complex 2 and 3 exhibit higher antitumor activity while the rest of the compounds were ineffective against cancerous cell line. These compounds show about 40% to 45% of inhibition against MCF-7 cell line.

Table 4: *In-vitro* antitumor activity of Mixed Ligand complexes of Ni

S. N.	Compounds	Cell No. x 10^4	Activity
1.	$C_{17}H_{17}ClN_4O_2SNi$	12.36±1.06	–
2.	$C_{17}H_{16}ClN_7O_2SNi$	9.12±0.92	+
3.	$C_{17}H_{18}ClN_7O_2SNi$	8.93±0.65	+
4.	$C_{16}H_{16}ClN_5O_3SNi$	11.79±1.06	–

Conclusion

All the newly synthesized mixed ligand complexes for their antibacterial activity against three pathogenic bacterial strains *viz. Pseudomonas aeruginosa*, *Staphylococcus aereus* and *Klebsiela pneumoniae* by disc diffusion method; antifungal studies against two pathogenic strains, *Aspergillus flavus* and *Aspergillus nigar* at concentrations of 50 and 100 µg/ml; anti-tumor activity against human breast adenocarcinoma (MCF-7) *in-vitro* using MTT bioassay method. The results of these screening clearly indicates that these compounds can be potentially used in the treatment of infectious and acute diseases.

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