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Synthesis, Characterisation & Antimicrobial Studies of Some Metal Complexes of Norfloxacin

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Abstract

The synthesis of some copper (II), cobalt (II), nickel (II) and iron (II).Complexes of norfloxacin (Nor) are studied & reported. Their structures were elucidated by elemental analysis, UV and IR Spectroscopy. It was observed from the study that norfloxacin molecule coordinated to metals through the two oxygen of the 3-carboxylate and 4-keto groups. Antimicrobial and toxicological studies carried out on some of the products showed a level of antimicrobial activity and toxicity comparable with their respective parent drug.

Key words: metal complexes, norfloxacin, antibacterial studies.

1. Introduction

Many drugs have shown modified pharmacological and toxicological properties, when administered in the form of metal complexes. Complexes of fluoro-quinolones had been synthesized and their structures are studied. Depending on the medium of preparation different products can be obtained[1-4]. Fluoro-quinolones are very attractive agents for treating numerous infectious diseases[5]. In this study, some copper (II), cobalt (II), nickel (II) and iron (II) complexes of norfloxacin were synthesized. The antimicrobial and toxicological properties of some of the complexes were investigated.

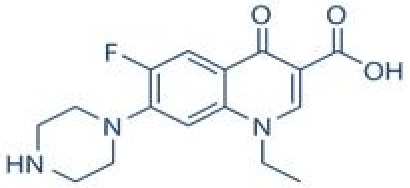

Fig. 1. Norfloxacin - The structure of Norfloxacin

2. Experimental

2.1 Materials and Methods

The pH was measured on μpH System 361. Elemental analysis (for C, H, and N) was carried out with the help of elemental analyzer at the laboratory of

CDRI Lucknow. The metal concentration was determined complexometrically by EDTA titration method[6]. The UV-Vis Spectra between 190-800nm were obtained on IR/UV Spectrophotometer (Perkin-Elmer) 397.The sample solutions were prepared in distilled water. The I.R. spectra were recorded using KBr pellets.

2.2 Synthesis of complexes :

Solutions of the ligands (norfloxacin) were prepared in distilled water, basic medium (in NaOH or NH4OH) and acid medium (HCl). A mixture of aqueous solutions of the metal salts ($CuCl_2.2H_2O$, $CoCl_2.6H_2O$, $NiCl_2.6H_2O$ and $FeCl_3.6H_2O$) with the ligands in 1:2 metals: ligand molar ratios were prepared and stirred with a magnetic stirrer (1-2hrs). Similar synthetic procedures had been reported elsewhere[2,3]. The products were obtained by filtration, washed and dried over $CaCl_2$ in desiccators.

2.3 Antimicrobial Studies :

The Minimum Inhibitory Concentration and Minimum Bactericidal concentration were determined using method described elsewhere. The clinical cultures of ***Staphylococcus aureus, Klebsiella specie, Pseudomonas aeruginosa, Neissera gonorrhea, Salmonella typhi*** and ***Shigella dysentria*** were used. The test organisms were individually grown overnight on nutrient agar slant at 35°C. The suspension was then prepared by washing the growth off with the normal saline solution and further serially diluting with sterile 20mM phosphate buffer to give counts of factor of 1x 106. The test sample stock solution for each metal complex and ligand were prepared by placing 0.05g in an amber colored bottle and the appropriate solvent (either sterile 0.01M HCl or distilled water) was added to get a solution of 100ug/ml.

3. Results and Discussion

3.1 Synthesis and Physico-analytical data :

The different conditions used in the synthesis have been reported to lead to differences in bonding or complex formation of fluoro-quinolones complexes[7-10]. Differences were observed in the amount of water molecules, anions present in or outside the coordination sphere, protonation of piperazinyl or carboxylic groups etc. The ratio of metal to ligands of the complexes was 1:2 for single ligand metal complexes. The chloride ions from the metal salts

Table1. Elemental Analysis of prepared complexes-

Formula of complex	colour	Elemental Analysis of complexes prepared						Solubility
$[Co (Nor)_2Cl_2]2H_2O$	Pink		C	H	N	F	Metal	Poorly soluble in H_2O, CH_3OH & C_2H_5OH
		found	48.91	5.40	10.68	4.17	7.19	
$[C_{32}H_{32}N_6F_2O_6CoCl_2]2H_2O$	N 1	Calc.	48.0	4.50	10.5	4.75	7.35	
$[Ni (Nor)_2Cl_2]4H_2O$	Light green N2	found	45.75	4.89	10.19	4.64	7.09	Poorly soluble in H_2O, CH_3OH & C_2H_5OH
$[C_{32}H_{32}N_6F_2O_6NiCl_2]4H_2O$		Calc.	45.93	4.78	10.04	4.54	7.02	
$[Cu (Nor)_2Cl_2]$	Light yellow N3	found	49.89	4.09	10.78	4.76	8.19	soluble in H_2O, CH_3OH & C_2H_5OH
$[C_{32}H_{32}N_6F_2O_6CuCl_2]$		Calc.	50	4.16	10.93	4.94	8.26	
$[Fe(Nor)_2Cl_2]6H_2O$	Orange N4	found	48.26	5.68	10.75	4.69	6.98	soluble in H_2O, CH_3OH & C_2H_5OH
$[C_{32}H_{32}N_6F_2O_6FeCl_2]6H_2O$		Calc.	48.12	5.51	10.5	4.76	7.00	

appear in the complexes within the coordination spheres as shown by the elemental analysis and test with silver nitrate. The terminal nitrogen on the 7-piperazinyl group may be protonated where chloride ions are present to balance the charge on the complex.[1]. Cobalt and Nickel complexes of norfloxacin showed poor solubility in most solvents. All the ionic compounds (that is complexes with protonated fluoro-quinolones) and some iron complexes were soluble in water due to their strong ionic nature.

3.2 Ultraviolet-visible Spectra :

The metal complexes of norfloxacin showed intense UV bands at 260- 340nm were assigned to intra ligands π- π^* transitions. The strong absorption peak corresponds to the chromophore involving the nitrogen atom at position 1 to carboxyl group. The weak absorption peak at the long Wave length side corresponds to the chromophore involving the nitrogen of the piperazinyl group attached to the 7-carbon to the keto group[11]. No absorption bands are seen in the visible region even at high sample concentration. This is attributed to the low intensity of the d-d transitions. From past work, no d-d transitions in the visible region have been reported for norfloxacin and ciprofloxacin metal complexes.

3.3 Infrared Spectra :

Norfloxacin Metal Complexes **:**

In the infrared spectrum of Norfloxacin, the ligand exists as a zwitter ion since no band exists for *V*(C=O)c (stretching vibration frequency of carbonyl in carboxyl group) at 1720cm^{-1} as reported for H-Nor[6,9]. However, peaks appear for *V*as(OCO) and *V*s(OCO). A strong peak also appears around 1490cm^{-1} assigned to vibrations for C-C, and C-N, which appears at a lower frequency on complexation. The infrared spectrum of Norfloxacin showed an unexpected broad band between 3600-3000cm^{-1}, which was assigned to absorbed moisture and not OH *str* since the carboxylic group is de protonated. The *V*(C=O) c vibration was absent in the IR spectra of the compounds [Co (Nor)$_2$ Cl$_2$].2H2O- **N1,** [Ni (Nor)$_2$Cl$_2$].4H$_2$O-**N2,** [Cu (Nor)$_2$Cl$_2$] – **N3** and [Fe(Nor) 2Cl$_2$]6H$_2$O- **N4** as present in the free ligand, indicating that the carboxyl group is deprotonated and complexed to the metal. The *V*(C=O) p (stretching vibration frequency of pyridone group) absorption appears strong for the compounds. However, the IR spectrum of [Fe(Nor)$_2$Cl$_2$]6H$_2$O- **N4** shows bands at 1738.2 cm^{-1} and 1684 .9cm^{-1} which is similar to that reported for ionic norfloxacin complexes[6]. Strong bands assigned to *V*(C=O)c were also seen in the IR spectra of [Ni (Nor)$_2$Cl$_2$].4H$_2$O-**N2** indicating the ligand directly Co-ordinate to the metal ion. The IR spectra of **N1**, **N2**, **N3** and **N4** showed absorptions for *V*as (OCO) and *V*s (OCO) at 1390-1410 cm^{-1} and 1580-1610cm^{-1} of resonance stabilized carboxylate anion indicating that coordination is through the carboxyl group.

Table 2. Spectral Analysis of prepared complexes-

Formula of complex	IR spectra of prepared complex *V*max (cm^{-1})					UV spectra
	-OH	(C=O)$_p$	(OCO)$_{as}$	(C-C & C-N)	(OCO)s.	λ (nm)
[Co (Nor) $_2$Cl$_2$]2H$_2$O	3424-3376	1623	1588	1493	1378	281.5 & 328.0
[Ni (Nor) $_2$Cl$_2$]4H$_2$O	3500-3300	1614	1580	1484	1392	276.0 & 329.5
[Cu (Nor) $_2$Cl$_2$]	3392	1704	1632	1470	1372	276.5. & 329.5
[Fe(Nor) $_2$Cl$_2$]6H$_2$O	3500-3300	1684	1636	1475	1375	276.5. & 329.5

Table 3. Minimum Inhibitory Concentration (ug/ml) of some norfloxacin metal complexes.

Bacteria	Minimum Inhibitory conc.(ug/ml)				
	Norfloxacin	N1	N2	N3	N4
S.Typhi	200	150	300	300	250
Shigella spp	100	100	100	200	200
Klebsiella spp	500	450	400	500	550
S.aureus	500	500	400	600	600
Pseudomonas spp.	100	500	500	200	600
N.gonorrhoea	200	300	300	300	400

On the basis of above discussion the mode of coordination can assigned as shown in fig. 2.

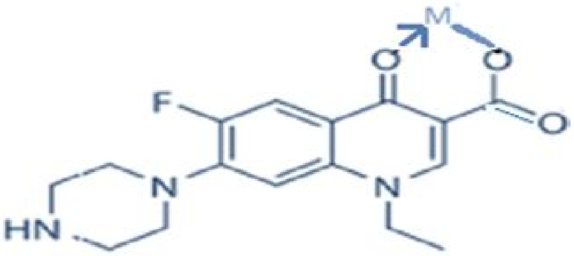

Fig. 2. Mode of coordination in NORFIOXACIN

3.4 Results on Biological Studies

Antimicrobial Studies

The results of the Minimum Inhibitory Concentration (MIC) determinations of the fluoroquinolones and their metal complexes are presented in Tables3.The ligands and metal complexes also showed antimicrobial activity against the tested organisms except against the molds of *Penicillin* and *Aspergillus* as has been earlier reported[2]. Some of the metal complexes showed comparable activity or greater activity against some of the microorganisms in comparison to the parent compounds. The MIC of the samples against the various isolates ranged from 50ug/ml to 600ug/ml of the antimicrobial dilutions. These concentrations in comparison to reported MIC90 of the ligands are seemingly high[5,10,12]. Increasing the concentrations of the samples led initially to increased bactericidal effect to a certain point, after which the reverse effect occurred, that is increasing concentration leading to decreasing sensitivity.

4. Conclusion

The nature of bonding of the ligands and the structure of the isolated metal complexes were elucidated on the basis of their physical and spectroscopic studies {elemental analysis, ultraviolet-visible spectroscopy and infrared spectroscopy}. The infrared spectra suggest that these compounds were obtained as *molecular complexes* in which the ligands were bi-dentately bonded to the metal through the ring carbonyl oxygen and one of the oxygen of the carboxylate group as can be seen in figure **2** for products **N1**, **N2**, **N3 and N4.**[13,14].

The complex shows more activity as compared with the standard ligand indicating that metal complexation enhances the activity of the parent ligand; this may be explained by chelation theory[15,16] according to which chelation reduces the polarity of the ligand and the central metal atom because of the delocalization of electrons over the whole chelate ring increases, which favours permeation of the complexes through the lipid layer of the cell membrane

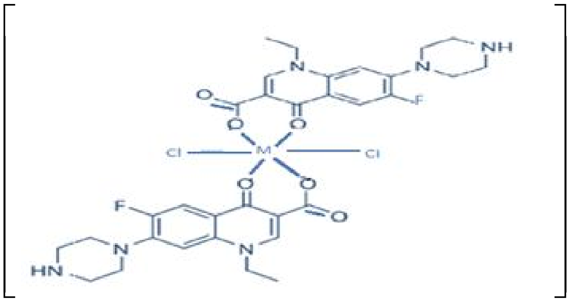

Fig. 3: The structure of Di (norfloxacin) complex with metal ions-Cu (II), Co (II), Ni (II) & Fe (II)

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