

Synthesis, Characterization and Antimicrobial Study Of Mixed Isoniazid-Trimethoprim Metal Drug Complexes

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ABSTRACT

The Mn²⁺, Fe²⁺, Cu²⁺, Co²⁺, Zn²⁺, Cd²⁺ complexes of mixed of Trimethoprim- Isoniazid were synthesized. The complexes were characterized using solubility, melting point, conductivity measurement and infrared spectroscopy. Trimethoprim complexes of coordination of the metal to the ligands is through the nitrogen of the pyrimidine group and coordination through the nitrogen of the amine group. The antimicrobial activity of the complexes were carried out against Staphylococcus aureus, Pseudomonas aureginosa, Klebsiella pneumonia, Escherichia coli. The results show that the complexes were more active than their ligands.

Keywords: Trimethoprim, Isoniazid, synthesis, complexes, characterized, antimicrobial ligands metal.

1. INTRODUCTION

Antibiotic is a compounds or substance which inhibit the growth of bacteria⁽¹⁾.

Tuberculosis is a disease caused by Mycobacterium tuberculae, a bacteria that is passed from people to people through the air. Combinations of the drugs are used to treat tuberculosis (TB) which are normal for effective treatment^(2,3).

Antituberculosis drugs are drugs which are used to treat tuberculosis that are available only in tablets, capsules, liquid and injectable forms⁽⁴⁾. This work is aimed as:

1. To synthesize more new alternative effective drugs.
2. To carry out some analysis on the metal drug complexes such as solubility, melting point, conductivity measurements and infrared spectrometry .
3. To carry out anti-microbial analysis on the synthesized metal complexes against the organisms.

2. MATERIALS AND METHODS

Trimethoprim was obtained from Jostade pharmaceuticals Ilesa, Osun State, while Isoniazid was obtained from SIGMA-ALDRICH. Physico-chemical analysis such as Solubility, Melting point and Conductivity measurement were carried out in Chemistry Department, University of Ilorin with the use of HANNA instrument conductivity meter at cell constant 1.34.

The infrared spectra were also carried out in REDEEMERS University in Lagos, Lagos state using FT-IR spectrophotometry. Antimicrobial activity of the synthesized complexes were done by screening the complexes against the tested organisms. Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia, and Pseudonoma aureginosa which were obtained from Microbiology Department, University of Ilorin Teaching Hospital.

2.1 METHODOLOGY

SYNTHESIS OF THE COMPLEXES.

2.1.1 SYNTHESIS OF [Co (TMP)(ISO)Cl₂] [Zn (TMP)(ISO)SO₄] and [Fe (TMP)(ISO)Cl₂] COMPLEXES.

Procedure described by Obaleye et al 1993⁽⁵⁾ was used to synthesized this complexes. 5mmol of the solution of the metal salts used were dissolved in a beaker containing 20ml of their suitable solvents and solution of 5mmol of the ligands were also dissolved in a beaker containing 20ml of their suitable solvents. The solutions were

mixed together. Immediately there was formation of precipitate. The results obtained were washed and dried. They were kept in a sample bottle for analysis.

2.1.2 SYNTHESIS OF [Mn(TMP)(ISO)Cl₂] [Cd(TMP)(ISO)SO₄] [Co(Py)(Iso)Cl₂] COMPLEXES.

Procedure described by Tella et al 1993⁽⁶⁾ 5mmol of the metal salts used were dissolved in a beaker containing 20ml of their suitable solvents and 5mmol of the ligands were also dissolved in a beaker containing 20ml of their suitable solvents. The solutions were mixed together and refluxed for 5 hours but no precipitate were formed. The refluxed solution were and left for 5 weeks. A dried precipitate obtained were washed and dried. They were kept in a sample bottle for analysis.

3. ANTIMICROBIAL SCREENING PROCEDURE

Method used by Matangi S. et al ⁽⁷⁾ was adopted in studying the antimicrobial activity. 7 gram of nutrient agar was weighed in to a 250ml conical flask, 250ml distilled water (sterilized for 24hrs) was mixed with the agar and it was cover properly with cotton wool and foil paper so as to avoid contamination. The solution was then heated for 15mins so as to dissolve the nutrient agar. it was sterilized for 24hours in an autoclave.

The nutrient agar was then introduce into the Petri dish and was allowed to set properly to solidified. 1cm hole was bored at the center of the plate with the aid of a hole borer and was allowed to remove the cracked hole so as to view the bottom of the Petri dish. The antibacterial activity of the ligands and complexes were determined at various concentrations: 20ppm, 40ppm, 50ppm and 100ppm. This various concentrations of complexes and ligands solutions were poured gently into the hole bored in the Petri dish and left covered. This was left in the incubator for 24hrs to allow the out growth of the micro organism. The zone inhibitory of the complexes and ligands were determined.

4. RESULTS AND DISCUSSIONS

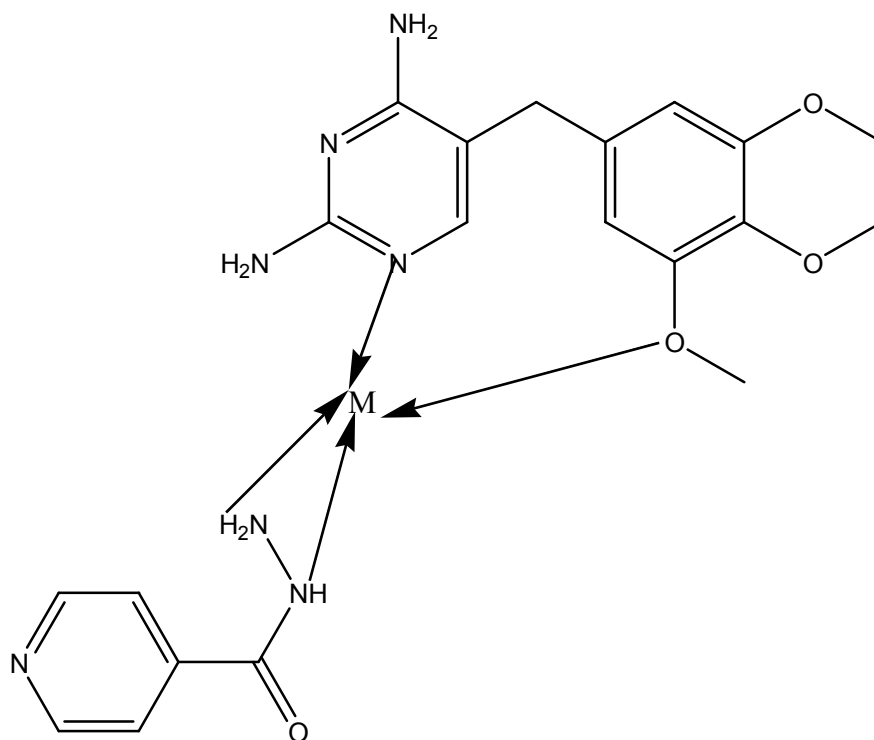
The complexes were synthesized by the reaction of Isoniazid and Trimethoprim with metals in the ratio 1:1:1. The melting point obtained for each of the complexes is higher than the melting point of the ligands ranging from 180-260°C. This shows that there is co-ordination between the ligands and their metal salts, thereby resulting to complexation⁽⁸⁾.

The IR spectra of the ligands and the complexes are shown in table 2. In Isoniazid, the band at 1725cm⁻¹ was assigned to $\nu(C=O)$. The bands at 3325cm⁻¹ was assigned to $\nu(N-H)$ which is shifted to higher frequency (3300-3400cm⁻¹). This indicates that coordination of the Isoniazid occurs through the nitrogen of the amine group⁽¹⁰⁾. Isoniazid acts as a tetradentate ligand.

In the infrared spectra of Trimethoprim, the band at 1083cm⁻¹ was assigned to $\nu(C-O)$. The reaction of Isoniazid and Trimethoprim with the metal salts was evidenced by the shifting of the band 3300 cm⁻¹ which is assigned to $\nu(O-H)$ to lower frequency in the complexes. From the results obtained in conductivity measurements, it was observed that the complexes are non-electrolyte⁽⁹⁾. The molar conductance values were measured in DMSO solution.

The antimicrobial activities of the ligands and their complexes were screened on Staphylococcus aureus, Pseudomonas aureginosa, Klebsiella pneumonia, Esherichia coli. The results shows that the micro organisms are active over the synthesized metal complexes.

Proposed structure for metal complexes of TMP and ISO



WHERE M is Cd, Fe, Zn, Cu, Mn or Co

5.CONCLUSION

The transition metal of Co^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , Fe^{2+} and Mn^{2+} complexes of mixed ligands have been synthesized. The complexes undergo various characterization using solubility, electric conductivity, melting point, Thin Layer Chromatography and infrared Spectroscopy.

The ligands form a chelating complex. The new alternative drugs obtained, confirmed that they are more effective than their parent ligands. From the results obtained in infrared spectra, it was revealed that the complexes are tetrahedral in nature.

Also, the complexes were subjected into antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aureginosa*, *Klebsiella pneumonia*, and *Esherichia coli*. The result of this shows that the complexes were active on the micro organism than the original corresponding ligands. The combined result of the physical and spectroscopic studies confirmed formation of complexes.

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Table 1: ANALYTICAL DATA OF MIXED ISONIAZID-TRIMETHOPRIM METAL DRUG COMPLEXES.

Complexes/ ligand	Melting point (°C)	Conductivity $\Omega^{-1}\text{cm}^2 \text{mol}^{-1}$	TLC (Rf)
Mn[TMP][ISO]Cl ₂	195-197	5.67	4.90
Fe[TMP][ISO]Cl ₂	215-218	5.05	3.20
Cu[TMP][ISO]SO ₄	190-192	5.25	3.80
Co[TMP][ISO]Cl ₂	260-262	5.06	5.70
Cd[TMP][ISO]SO ₄	224-226	5.21	4.65
Zn[TMP][ISO]SO ₄	180-182	5.66	5.97
TRIMETHOPRIM	140-143	-	6.10
ISONIAZID	168-170	-	6.00

Table 2: INFRARED SPECTRAL OF MIXED ISONIAZID-TRIMETHOPRIM METAL DRUG COMPLEXES.

Complexes/ Ligand	ν N-H	ν C=C	ν C-	ν C-N	ν C=O	ν C-H	ν M-L
Mn[TMP][ISO]Cl ₂	3466	1640	1279	1233	1738	3075	748
Fe[TMP][ISO]Cl ₂	3325	1669	1086	1228	1743	3060	737
Cu[TMP][ISO]SO ₄	3270	1658	1279	1329	1750	3055	751
Co[TMP][ISO]Cl ₂	3232 3325 5673 187.80	1660	1149	1190	1748	3040	763
Cd[TMP][ISO]SO ₄	3299	1657	1084	1200	1735	3064	781 776.37
Zn[TMP][ISO]SO ₄	3346	1669	1085	1186	1745	3060	778
TRIMETHOPRIM	3300	1647	1083	1293	-	3038	-
ISONIAZID	3304	1635	-	1062	1725	3032	-

Table 3: Antimicrobial study of some mixed isoniazid-trimethoprim metal drug complexes:

Complexes/ Ligands	Escherichia Coli (mm) (+ve)					Staphylococcus aureus (mm) (-ve)					Klebsiella pneumonia (mm) (-ve)
	20	40	50	100	200	20	40	50	100	200	20
Concentration (ppm)	20	40	50	100	200	20	40	50	100	200	20
Isoniazid	0	0	0	0	0	0	0	10	0	5	
Trimethoprim	0	1	4	0	0	0	5	3	3	0	
Mn(Iso)(Tm)Cl ₂	0	3	51	45	60	22	0	30	23		
Co(Iso)(Tm)Cl ₂	50	25	0	34	42	27	0	0	0		
Cu(Iso)(Tm)(SO ₄)	0	24	38	0	43	9	10	65	8		
Zn(Iso)(Tm)(SO ₄)	43	25	12	18	44	15	20	6	17		
Cd(Iso)(Tm)(SO ₄)	35	55	12	10	14	45	0	45	0		
Fe(Iso)(Tm)Cl ₂	60	15	22	25	18	23	35	16	33		

							<i>Pseudomonas aureginosa</i> (mm) (-ve)						
40	50	100	20	40	50	100							
0	2	0	0	0	0	0							
0	1	0	0	0	0	0							
20	45	60	24	54	0	0							
2	8	8	1	1	0	0							
36	45	9	12	18	46	39							
5	8	30	6	31	36	42							
0	19	43	12	24	27	12							
0	0	47	24	10	53	18							

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