



Abstract

Metal (II) complexes of mixed-ligand trimethoprim (TMP) and 2,2'-bipyridine (bipy) with the formular [M(TMP)(bipy)X].nH₂O, where M = Mn(II), Co(II), Ni(II), Cu(II), Fe(II), Zn(II) and X= Cl/SO₄, were synthesized and characterized by percentage metal, infrared, electronic spectroscopies, room temperature magnetic moments, melting points, conductance measurements and elemental analysis. The infrared spectral data showed TMP as a bidentate ligand bonding to the metals via the N atom of the pyrimidine amino group (3412-3300 cm⁻¹) and nitrogen atom of the azomethine moiety (1666-1639 cm⁻¹) while the bipy bonded through the diimine nitrogen atoms (1593-1404 cm⁻¹). The electronic spectral data and magnetic moments indicated that the metal (II) complexes have octahedral geometries and were monomeric. The molar conductance of the complexes in the range 24-40 Ω·1cm² mol⁻¹ confirmed their non-electrolytic and covalent nature. The antimicrobial studies showed that the complexes were inactive towards the tested fungus *Candida albicans*, but possessed good antibacterial activities. The observed trend for the antibacterial activities displayed by the complexes was in the order Mn > Zn > Cu > Fe > Co ~ Ni thus making [Mn(TMP)(bipy)Cl₂].2H₂O the most biologically active among them. It was also observed that antibacterial activities exhibited varied directly with concentration as the highest activities were observed at the highest concentration of 40 mg/mL.

Keywords: Trimethoprim, 2,2'-bipyridine, Mixed- ligands, Antimicrobial, Metal Complexes, Heterocycle.

Introduction

Trimethoprim (TMP) (Fig. 1), chemically known as 5-(3,4,5-trimethoxybenzy l)pyrimidine-2,4-diamine and a chemical analogue of a broad-spectrum antimicrobial agent used in prophylaxis treatment and urinary tract infections¹.

Most gram-negative and gram-positive microorganisms are sensitive to trimethoprim, but resistance can develop when the drug is used as a single therapy².

Thus, it is normally used as combination therapy with sulfamethoxazole in 1 to 5 ratios to give sequential and synergistic inhibition of bacterial folate metabolism³⁻⁴.

The clinical conquest of this combination is due mainly to the efficacy of TMP³. However, the emergence of resistance disease pathogens and serious side effects of sulfamethoxazole has led to the recent decline in the clinical importance of TMP-SMZ combination as a first line therapy for several infections⁵⁻⁶.

Heterocycles and their derivatives have been reported to have remarkable broad spectrum of biological activities⁷. Nitrogen heterocycles are one of the most important classes of ligands in coordination chemistry⁸.

Metal(II) Complexes of Mixed Ligands Trimethoprim and 2,2' Bipyridine Heterocycle: Synthesis, Characterisation and Antimicrobial Studies

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Among the nitrogen heterocycles, 2,2'-bipyridine (bipy) (Fig. 2) have been widely used as a chelating donor site due to its robust redox stability and relative ease of fuctionality⁹.

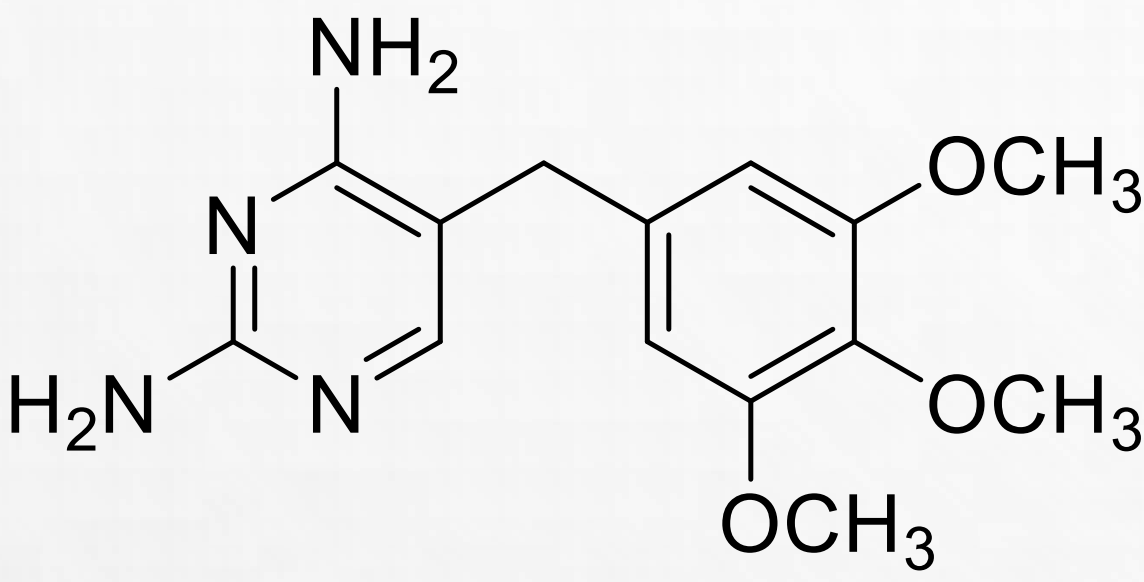


Fig. 1: Trimethoprim

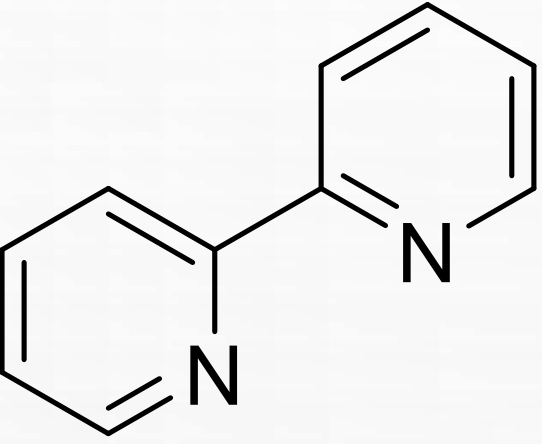


Fig.2: 2,2'-bipyridine)

Biological applications, thermal stability, antitumor effect and bactericidal effect of mixed-ligand complexes involving heterocyclic bases such as pyridine, 2,2'-bipyridine, o-phenanthroline, have been reported¹⁰⁻¹¹.

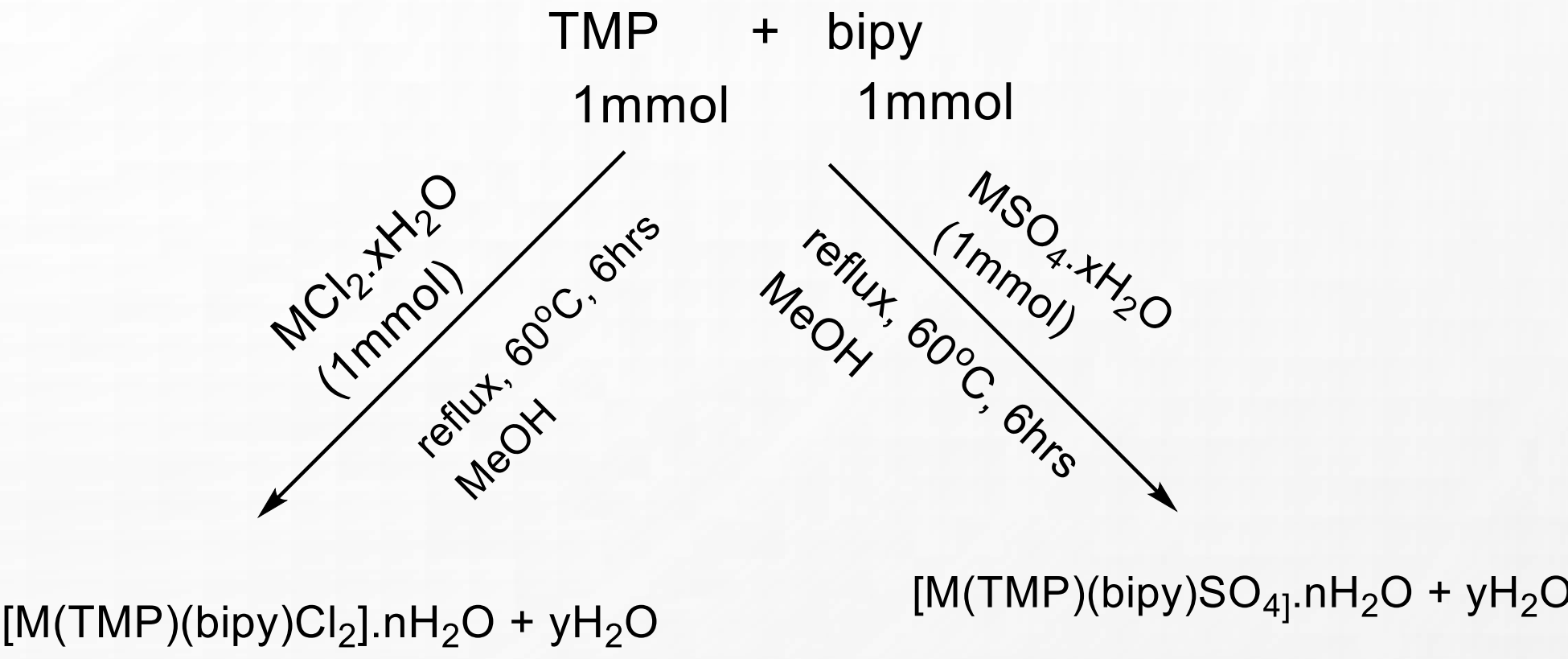
Here we present , mixed-ligand complexes of trimethoprim and 2,2'-bipyridine, their synthesis, characterisation and antimicrobial activities against some selected microorganisms

Materials and methods: Trimethoprim was a gift from Bond pharmaceutical Companies, Awe, Oyo State Nigeria. While other chemicals and reagents were obtained from Sigma Aldrich.

Physical measurements: The electronic spectra of the complexes in DMSO were recorded on a Perkin-Elmer Lambda 25 Spectrophotometer and infrared spectra were recorded as KBr disc on a Perkin-Elmer BX II FT-IR spectrometer 4000–370 cm⁻¹. The room temperature magnetic susceptibilities at 303K were measured on Sherwood Susceptibility Balance MSB Mark 1, melting points were determined with Stuart SMP10 melting point apparatus and conductivity measurement was obtained using a Labtech Digital conductivity device in 1 x 10⁻³ M nitromethane. Metal analysis by complexometric titration and CHN analysis using Flash 2000 elemental Analyser.. Antimicrobial study on the synthesized compounds was carried out in Department of Pharmaceutical Microbiology, University of Ibadan .

Antimicrobial studies: Antimicrobial screening in vitro by Agar diffusion method against identified clinical strains *Staphylococcus aureus*, *Enterotoxigenic E. coli*, *Enteropathogenic E. coli*, *Klebsiella pneumonia* *Leclercia adecarboxylata*, *Morganella morganii*, *Salmonella typhi* and a fungus *Candida albicans*

Synthesis of Metal Complexes of [M(TMP)(bipy)X].nH₂O, where X= Cl /SO₄ ; M = Ni, Cu, Co, Mn, Fe, Zn



Results and discussions

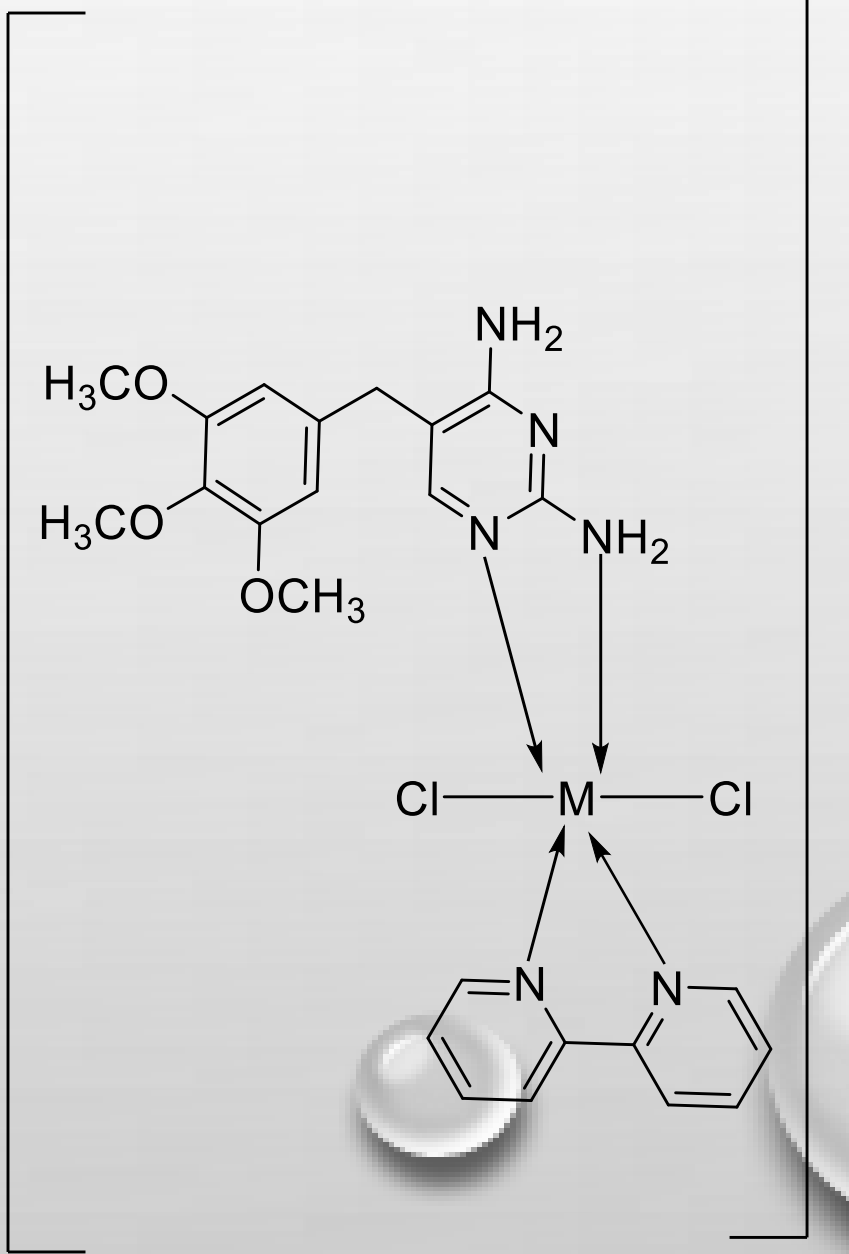
The complexes Figures 3 and 4 exhibit variety of colours with their percentage yields ranging from 36 – 98% . The complexes are soluble mainly in DMF and DMSO and are non-electrolytes with low values of the molar conductivity in the range 24-38Ω⁻¹cm²mol⁻¹

IR studies

From the infrared spectral data, TMP and bipy behaved as bidentate ligands with TMP bonding to the metals via the N atom of the pyrimidine amino group (3412-3300 cm⁻¹) and nitrogen atom of the azomethine moiety (1666-1639 cm⁻¹) while the bipy coordinated through the diimine nitrogen atoms (1593-1404 cm⁻¹).

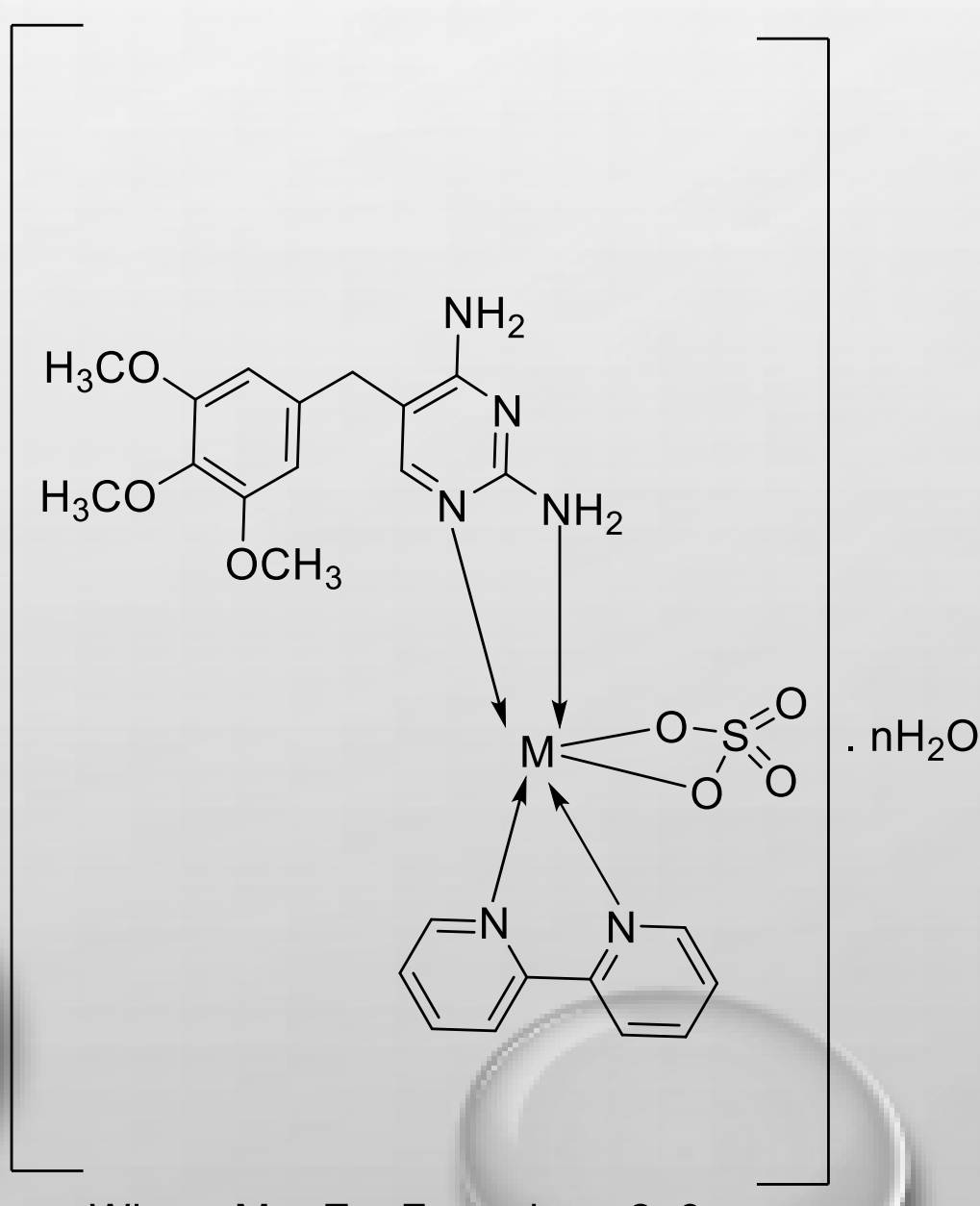
Electronic spectra, magnetic moment studies and conductivity .

Electronic spectra and the magnetic momenta data indicated that all the metal (II) complexes were monomeric and octahedral. The molar conductance measurements in the range 24-38Ω⁻¹cm²mol⁻¹ confirmed their non-electrolytic and covalent nature.



Where M = Co, Cu, Mn, Ni and n = 0, 2

Fig. 3 metal complex



Where M = Zn, Fe and n = 2, 3

Fig. 4 metal complex



Antimicrobial studies :

The antimicrobial studies showed that the complexes were inactive towards the tested fungus but possessed good antibacterial activities. The observed trend for the antibacterial activities was in the order Mn > Zn > Cu > Fe > Co ~ Ni thus making [Mn(TMP)(bipy)Cl₂].2H₂O the most biologically active. It was also observed that antibacterial activities exhibited varied directly with concentration as the highest activities was at the highest concentration of 40 mg/mL.

Conclusion

Mixed-ligands complexes of trimethoprim (TMP) and 2,2'-bipyridine (bipy) of Co(II), Cu(II), Fe(II), Mn(II), Ni(II) and Zn(II) were synthesised and characterised spectroscopically. The infrared spectra data, showed TMP and bipy as bidentate ligands with TMP bonding to the metals via the N atom of the pyrimidine amino group and nitrogen atom of the azomethine moiety while the bipy coordinated through the diimine nitrogen atoms. The electronic spectra data indicated that monomeric and octahedral geometries for all complexes and their low conductivity measurements showed they are non-electrolyte. were monomeric and octahedral and the conductivity. The complexes and their ligands did not show antifungal activity but the observed antibacterial trend was in the order Mn > Zn > Cu > Fe > Co ~ Ni thus making [Mn(TMP)(bipy)Cl₂].2H₂O the most biologically active among them.

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