SYNTHESIS, CHARACTERIZATION AND INVESTIGATION OF CHELATING AND ANTIMICROBIAL ACTIVITIES OF 4-((-1H-BENZO(D)IMIDAZOL-L-YL)METHYLAMINO)-2-HYDROXYLBENZOIC ACID AND ITS 2- SUBSTITUTED DERIVATIVES

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CERTIFICATION

This is to certify that this work was carried out by Mr. FASASI, Abimbola Semiudeen under my supervision and approved in accordance with the requirement for the award of Master of Science (M.Sc) degree in Chemistry in the Department of Chemistry, Obafemi Awolowo University, Ile-Ife.

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DEDICATION

This work is dedicated to Allah for his mercy and guidance. To my close relations who have joined the saint triumphants, you have gotten my dedication.

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ABSTRACT

This study involved the synthesis, characterization and investigation of the chelating and antimicrobial properties of 4-((-1H-benzo(d)imidazole-l-yl)methylamino)_2-hydroxylbenzoic acid and its 2 substituted derivatives. It was carried out with a view to exploring the wide spectrum of biological properties associated with Benzimidazole nucleus, its derivatives and transition metal complexes.

Infrared and Nuclear Magnetic Resonance spectroscopic methods were used to characterize the synthesized ligands. Manganese (II), Copper(II) and Zinc(II) complexes of these ligands were synthesized and characterized by the same methods. The percentage metal composition was determined through complexometric titration. The antimicrobial activities of all the ligands and their transition metal complexes of Mn(II), Cu(II) and Zn(II) were measured for bacteria and fungi pathogens using the agar well diffusion method.

The Mannich reaction between 2-Aminobenzimidazole, Methanal and 4-Aminosalicylic acid yielded 4-((2-Amino-1H-benzo(d)imidazol-1-yl)methylamino)-2-hydroxylbenzoic acid (2-Amino BISA). All the compounds and their transition metal complexes were found to be more toxic to fungi than bacteria. Copper complexes had greatest toxicity against the fungi. Toxicity of biocide increased with concentration and Cu(II) complex of 2-AminoBISA was found to be more toxic against *Trichophyta Tonsuras, Aspergillus flavus* and *Candidas albican* than the referenced ketofung standard. Conductivities of all complexes were measured in acetonitrile as solvent. They were found to be electrolytes. All the metal complexes were high melting solids and stable in air. All the ligands and their transition metal complexes were soluble in dimethylsulfoxide but insoluble in water.

The study concluded that 4-((2-Amino-1H-benzo(d)imidazol-1-yl)methylamino)-2-hydroxylbenzoic acid (2-Amino BISA) could be successfully prepared through the Mannich reaction between 2-Aminobenzimidazole, Methanal and 4-Aminosalicylic acid.

CHAPTER ONE

INTRODUCTION

1.1 Background to the Study

Benzimidazole derivatives are important class of nitrogen containing heterocycles and have been reported to possess wide spectrum of biological properties such as antitubercular, anticancer, antihelminthic and antimicrobial (Gowda et al., 2009). Benzimidazoles are classified under several classes of drugs based on the possible substitutions at different positions of the benzimidazole nucleus. Many reports have revealed that the influence of the substitution at positions 1, 2 and 5 of the benzimidazole ring is very important for their pharmacological effects. Introduction of a small substituent into the 2- and 5- position is characteristic of benzimidazole antihelminthics property. It has been observed that benzimidazole derivatives, as well as their complexes with transition metal ions, have shown considerable biological activity and have been of wide interest because of their diverse clinical applications. Furthermore, heterocyclic benzimidazoles, their derivatives and transition metal complexes have received considerable attention in coordination chemistry because it was found that such complexes showed larger antimicrobial activities than the free ligands (Gumus et al., 2003). Therefore, incorporation of the benzimidazole nucleus is an important synthetic strategy in drug discovery. Furthermore, resistance against antibiotics by pathogenic bacteria has been a major concern in the anti-infective therapy of both humans and animals. Bacteria are able to adapt rapidly to new environmental conditions such as the presence of antimicrobial molecules and, as a consequence, resistance increases with the antimicrobial use (Falagas et al., 2007; Jansen et al., 2006).

These concerns have made the drive for the synthesis of more potent antimicrobial drugs that will inactivate various resistance mechanisms.

The enormous therapeutic values of these benzimidazole and its derivatives motivated this research work, which involved mannich reactions of benzimidazole, 2-aminobenzimidazole and 2-chloromethylbenzimidazole each with formaldehyde and 4-aminosalicylic acid to produce BISA, 2-aminoBISA and 2-chloromethylBISA respectively. These synthesized ligands expectedly to possess potential antimicrobial properties and also serve as good chelating ligands for some specific transition metals of biological significance.

The choices of formaldehyde and 4-aminosalicylic acid as reactants in the mannich reactions were not by accident but were based on the wide spectrum of useful antimicrobial properties associated with them. According to Di Stefanol et al., 1999, uses of formaldehyde are not limited to its disinfectant properties in pathology laboratories for tissue fixation in hospitals but also extend to cold sterilization of endoscopes and other medical instruments, while 4-aminosalicylic acid (para-aminosalicylic acid (PAS)) has found application as antibiotics for the treatment of multidrug-resistant tuberculosis (Fox et al., 1999)

The present work therefore focused on the synthesis, characterization and investigation of the chelating and antimicrobial properties of 4-((-1H-benzo(D)imidazol-1-yl)methylamino)-2-hydroxylbenzoic acid and its 2-substituted derivatives.

1.0.1 Objectives of the Study

The objectives of this study are to:

1. synthesize 4-((-IH benzo(d)imidazol-1-yl)methylamino)-2-hydroxylbenzoic acid. (BISA), 4-((2-Amino-IH benzo(d)imidazol-1-yl)methylamino)-2-hydroxylbenzoic acid. (2-Amino BISA), 4-((2-Chloro methyl-IH benzo(d)imidazol-1-yl)methylamino)-2-hydroxylbenzoic acid. (2-Chloromethyl BISA).
2. characterize BISA, (2- Amino) BISA and (2-chloromethyl) BISA.
3. investigate the chelating properties of the BISA, (2-Amino) BISA and (2-chloromethyl) BISA.
4. compare the microbial activities of BISA and its complexes with (2-Amino) BISA , (2-chloromethyl) BISA and their complexes
5. compare the microbial activities of benzimidazole with (2-Amino) BISA and (2-chloromethyl) BISA.

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