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# Antibacterial activity of new benzylbenzimidazole complexes against Gram-positive ($+v^{e)}$ and-negative ($-v^{e)}$ bacterial species isolated from surgical wounds of Iraqi patients

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***Abstract***

*Antibiotics or antibacterial are a type of antimicrobial drug. Used to treat infections caused by germs (bacteria and certain parasites).They may either kill or inhibit the growth of those organism. Several types of antibiotics also possess antiprotozoal activity. In each year all over the world, millions of patients become infected with bacteria that are resistant to antibiotics and thousands of people die each year as a direct result of these infections. Prompting the researchers to find new antibiotics to confrontation like this challenge. So for the first time in this project we evaluate the effect of New complexes of $VO^{+2}$, $Co^{+2}$, $Ni^{+2}$, $Cu^{+2}$ and $Ag^{+}$ with 1-benzylbenzimidazole (Bbz) were synthesized by reaction of the ligand with suitable metal sources against several selected human pathogenic bacterial species for both Gram-positive ($^{+}v^{e)}$ and negative ($^{-}v^{e)}$ bacteria isolated from surgical wounds. By using of disk diffusion technique our findings demonstrated that New complexes of $VO^{+2}$, $Co^{+2}$, $Ni^{+2}$, $Cu^{+2}$ and $Ag^{+}$ with 1-benzylbenzimidazole (Bbz) showed inhibition for both Gram-positive ($^{+}v^{e)}$ and negative ($^{-}v^{e)}$ bacteria but varying effects of each compound.*

***Keywords:*** *Benzylbenzimidazole, Antibacterial, Gram-positive and negative bacteria, Iraqi, patients*

## 1. Introduction

Benzimidazole is aheterocyclic aromatic organic compound, it has been three modes (figure.1), they have been often bioactive. Many anthelmintic drugs like albendazole, mebendazole, and triclabendazole belong to the benzimidazole class of compounds. They act by binding to the fungal microtubules and stopping hyphal growth. It also binds to the spindle microtubules and blocks nuclear division of many microorganism.(1). This bicyclic compound consists of the fusion of benzene and imidazole. The most prominent benzimidazole compound in nature is Nribosyl- dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. Both Benzimidazole and imidazole act as good ligands to transition metal ions (2) (Sundberg *et al*., 1974), and they exhibit different coordination modes as shown in Chart 1. Benzimidazole and imidazole ligands were used in the synthesis of different model complexes of metallo-enzymes such as hemocyanin, superoxide dismutase, and plastocyanin for copper and haemerythrin, methane monooxygenase, and ribonucleotide reductase for iron (3,4). (Adams *et al*., 1990; Crane and Fenton, 1990).

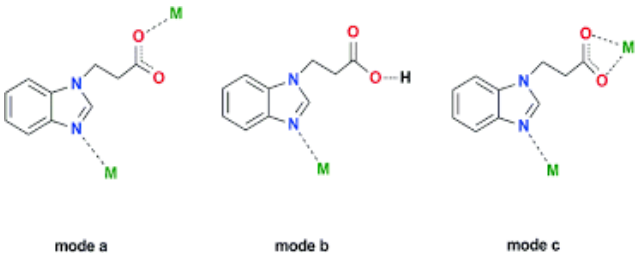


**Figure 1**: Coordination modes in benzimidazole

Most of azoles including benzimidazole, in an extension of the well-elaborated imidazole system, have been used as carbon skeletons for N- heterocyclic carbons (NHC), that are usually used as ligands for transition metal complexes. Benzimidazoles are involved in a great variety of biological processes. Some of their poly-functional derivatives have been proved to possess antibacterial, fungicide and anti-helminthic activity (5.6,7) (Pawar *et al*., 2004; Mothilal *et al*., 2004; Özden *et al*., 2005). Therefore, substituted benzimidazoles have attracted the interest of various research groups. This interest was increased since it has been reported that the influence of the substitution at the 1, 2 and 5 positions of the benzimidazole ring is very important for their pharmacological effects (Ayhan-Kilcigil and Altanlar, 2006). Nevertheless, the biological

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studies of coordination compounds containing benzimidazole derivatives have been limited. In 2015 Abbas Washeel Salman Synthesized new complexes of $VO^{+2}$, $Co^{+2}$, $Ni^{+2}$, $Cu^{+2}$ and $Ag^{+}$ with 1-benzylbenzimidazole (Bbz) (8). So in this study we evaluated the effect of new 1- benzylbenzimidazole coordination complexes with $VO^{+2}$, $Co^{+2}$, $Ni^{+2}$, $Cu^{+2}$ and $Ag^{+}$ on growth of Gram-positive (+ve) and-negative (-ve) bacterial species isolated from surgical wounds of Iraqi patients .

**Martial and Methods**

*Mueller-Hinton Agar plate*

In this study we used disk diffusion method; is performed by using of Mueller-Hinton Agar (MHA) media, which is the best medium for routine susceptibility tests because it has good reproducibility, and gives satisfactory growth of most bacterial pathogens. Preparation of MHA dishes accomplished according to the manufacturer's instructions.

*Microorganisms*

The antimicrobial activities of new complexes of $VO^{+2}$, $Co^{+2}$, $Ni^{+2}$, $Cu^{+2}$ and $Ag^{+}$ with 1-benzylbenzimidazole were purchased from Wasit University, Department of Chemistry, College of Science, Kut, Wasit, Iraq. It were evaluated against gram (+) (Staphylococcus aureus, (-) (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis bacteria. Most of all bacterial strains were provided from AL-Hashimiah and Al-Qasim General hospitals. All the conducting laboratory diagnosis of each species were performed.

*Antimicrobial disks*

Anti-bacterial disks were prepared to the detection of the antibacterial effect of the new complexes of 1-benzylbenzimidazole described above. Disks filter papers (Whatman No: 1) 6 mm in diameter were autoclaved and dried at 37 ◦ C overnight. Each complex of of 1-benzylbenzimidazole was dissolved in Dimethyl sulfoxide (DMSO), and all disks impregnated with 9% w/v of each complex. Then all disks were placed onto the agar surface and incubated at 37 ◦ C for 24 h. Growth inhibition zones were used for quantitative antibacterial evaluations.

*Inoculation of plates*

Dip a sterile cotton swab into the standardized bacterial suspension then Inoculating of the Mueller-Hinton Agar surface by streaking with the swab containing the inoculum. Same producer repeated of all samples.

**Results**

The antibacterial activity of new complexes $VO^{+2}$, $Co^{+2}$, $Ni^{+2}$, $Cu^{+2}$ and $Ag^{+}$ with 1-benzylbenzimidazole against several selected human pathogenic bacterial species for both Gram-positive and negative bacteria are presented in Table 1. Our findings demonstrated that all bacterial strains demonstrated variable sensitivity of all complexes of 1-benzylbenzimidazole with 9% w/v concentration. As well as this results revealed that staphylococcus was the most effected among all species whereas Klebsiella Pneumonia it was the least affected among of all tested bacterial species. On other hand no inhibition of growth of all bacterial species with all complex for 4.5% w/v concentration was observed.

**Table 1**: Zones of Inhibition of new 1-benzylbenzimidazole complexes (mm) with 0.9 w/v concentration

| Microorganisms | Inhibition Zones of New **Benzylbenzimidazole Complexes** (mm) | | | | |
|---|---|---|---|---|---|
| **Gram $^{+ve}$ bacteria** | **VO+2,** | **Co+2,** | **Ni+2,** | **Fe+2** | **Ag+** |
| Staphylococcus. aureus | 11 | 12 | 13 | 14 | 10 |
| Streptococcus. Pneumonia | 10 | 9 | 10 | 9 | 11 |
| **Gram$^{-ve}$ bacteria** | | | | | |
| Escherichia Coli | 7 | 8 | 8 | 4 | 8 |
| Klebsiella Pneumonia | 3 | 6 | 4 | 8 | 10 |
| Pseudomonas Aeruginosa | 8 | 9 | 5 | 8 | 9 |
| Proteus Mirabilis | 9 | 11 | 7 | 8 | 5 |

**Discussion**

The expansion of antimicrobial drugs to treat infectious disease has been one of the most notable medical achievements of the past century. Most of azoles including benzimidazole, are an important class of nitrogen heterocycles with electron-rich property. This special structure endows azole-based derivatives easily bind with the enzymes and receptors in organisms through noncovalent interactions such as hydrogen bonds, coordination bonds, ion-dipole, and hydrophobic effect as well as van der Waals force ( 9 ,10). Previously described the design and synthesis of some benzimidazole derivatives in both imidazole and triazole groups in 4 different categories (imidazoles (1), benzimidazoles (2), triazoles (3) and benztriazoles (4)) and investigated their antibacterial activity against different species of gram positive and gram negative microorganisms. By using of Disc plate method and serial dilution assay which showed antibacterial activity on both gram positive and gram negative species. Compounds 1-trityl-1H-benzo (d) imidazole (2a) and 1-octyl-1H-1,2,4-triazole (3b) had higher effect for gram positive and gram negative bacteria respectively. Compounds 2-methyl-1-nonyl-1H-imidazole (1f) and 1-butyl-2-methyl-;4-nitro-1H-imidazole (1l) had moderate activity for gram negative bacteria.( 11).

In our study, most of the new synthesized compounds of 1-benzylbenzimidazole previously described by (Abbas 2015) have shown good to moderate activity inhibition against growth of Gram-positive (+ve) and-negative (-ve)

bacterial species. Since the inhibition of bacterial growth area ranged from 9-14 mm against Gram-positive (+ve) (Staphylococcus Aureus and Streptococcus Pneumonia) , whereas ranged from 4 – 11 mm with Escherichia Coli, Klebsiella Pneumonia, Pseudomonas Aeruginosa, and Proteus Mirabilis.

From previous studies (9,10,11) and interpretation results of present study demonstrated that the activity of 1-benzylbenzimidazole compounds against growth of microorganism like bacteria it can be concluded that presence of substituents such as fluoro, chloro and nitro in the aryl ring of pyrazole moiety of compounds that enhanced antibacterial activity for such compounds. Also in the results of this study, it seems there is a difference to the effectiveness of the Gram-positive (+ve) and ) and-negative (-ve) bacteria that may because that the cell wall of Gram-negative bacteria consists of a thin layer of peptidoglycan in the periplasmic space between the inner and outer lipid membranes (12,13,14) . The outer membrane contains lipopolysaccharides on its outer leaflet and facilitates non-vesicle-mediated transport through channels such as porins or specialized transporters. It is thought that vesicles from these organisms are produced by the pinching off of the outer membrane, resulting in outer-membrane vesicles and the final effect of such cell wall structure may protect like microorganisms from the acute effect of most anti-bacterial agents . (15,16). So future studies to determine the effect of these new complexes on the cell cycle of the organism will be very necessary, because it would open a new outlook for the manufacture of a new generation of new antibiotics.

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