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# Synthesis, Characterization And Biological Studies of Carbamoylbenzene-1,5-dicarboxylic Acid Analogues

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## Abstract

### 1. Introduction

Development of novel bioactive drugs in chemical warfare against bacteria, fungi, and other infectious diseases has become an important and challenging task for the synthetic and medicinal chemists. Many research programs are tailored towards the design and synthesis of new drugs, for their chemotherapeutic application. The emergence of antimicrobial resistance threatens the effective prevention and treatment of an ever increasing range of infections caused by bacteria, parasites, virus, and fungi. New resistance mechanisms are emerging and spreading globally; the appearance and widespread use of fake and substandard drugs have further compounded the problem. The HIV epidemic around the world has led to an increase in the number of immunocompromised patients, which in turn has led to an increase in the number of systemic bacterial and fungal infections. Compounds containing carboxylic acid functional groups are playing a major role in the field of medicine. Generally, they play an active and critical role in the biochemistry of human or animal physiology. They have been involved in studies as antibacterial, anti-inflammatory, antiplatelet, antimicrobial, anticancer, antifungal, and analgesic and antiseptic.

Currently, there are more than 450 clinically approved drugs containing a free carboxylic acid group. To the best of our knowledge no biological studies and syntheses of these compounds have been reported. We present here the syntheses of different substituted carboxylic and dicarboxylic acid analogues, with electron withdrawing and donating groups (OH, OCH3, CH3, NO2, and F) and explored their potentials as antibacterial and antifungal drugs.

### 2. Materials and Methods

#### 2.1. General Experimental Details

All chemicals and solvents were purchased from Sigma-Aldrich (Germany) and used as purchased without further purification. Thin-layer chromatography was performed using precoated silica gel 60 (F254) from MERCK (Germany). Spots on the TLC plates were visualized under UV light (254 nm and 366 nm) and by heating with 10% sulphuric acid in MeOH. The melting point was recorded using a Gallenkamp melting point apparatus. The UV-VIS analysis was carried out on a Perkin Elmer Lambda 35 UV/VIS Spectrometer, scanning from 200 to 400 nm. Absorbance was measured with a 1 cm quartz cell. The infrared spectra of the solid products were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer using ATR sampling accessory. 1H and 13C-NMR spectra were recorded using Bruker 400 MHz Spectrometer at room temperature (400 MHz for 1H and 100 MHz for 13C), using TMS as reference. Chemical shift values (δ) were reported in parts per million (ppm) relative to TMS and coupling constants are given in Hz. The solvent used for these measurements was deuterated DMSO. Multiplicities are given as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), and multiplet (m).

#### 2.2. General Procedure for the Synthesis of Z1–3,5,7–12

A solution of 1,3-dioxo-2-benzofuran-5-carbonyl chloride (5 g, 23.8 mmol) was weighed into a round bottom flask containing 100 mL of (5%) and then stirred for 30 min; the solid product (1,3-dioxo-2-benzofuran-5-carboxylic acid) formed was then filtered under suction. The products were pure enough for further reaction without further purification; this acid (0.3 g, 1.56 mmol) was further transferred to a 10 mL round bottom flask containing dichloromethane (7 mL) and a magnetic stirrer and 1.5 equiv. of different classes of amine were each added individually to the respective flasks and the mixture refluxed for at least two hours. The heat was then removed and the reaction stirred for a further 30 min. The reaction mixtures were allowed to stand at room temperature for a further 30 min; the solid precipitates formed were then filtered under suction and washed thoroughly with dichloromethane to remove any excess amines (Scheme 1). After drying, they were recrystallized from dichloromethane to give the purified products.

### 3. Biological Assay

#### 3.1. Clinical Isolate

The test compounds (Z1–3,5,7–12) were evaluated on the following isolates, obtained from the Department of Medical Microbiology, Ahmadu Bello University Teaching Hospital Zaria, Nigeria (ABUTH): Candida stellatoidea, Candida tropicalis, Candida krusei, Candida albicans, Shigella dysenteriae, Salmonella typhi, Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus vulgaris, Escherichia coli, Corynebacterium ulcerans, Streptococcus pyogenes, Staphylococcus aureus,

Vancomycin Resistant Enterococci (VRE), and Methicillin Resistant Staphylococcus aureus (MRSA).

**3.2. Antimicrobial Susceptibility Test**

Pure cultures of the organism were inoculated on to Mueller Hinton Agar (MERCK) and incubated for 24 h at 38°C for bacteria and 48 h at 34°C for fungi. About 5 discrete colonies were aseptically transferred using sterile wire loops into tubes containing sterile normal saline (0.85% NaCl) and were adjusted to a turbidity of 0.5 McFarland Standard. The suspensions were then inoculated on the surface of sterile Mueller-Hinton Agar plates using sterile cotton swabs. A sterile 6 mm diameter Cork borer was used to make holes (wells) into the set of inoculated Mueller-Hinton Agar. The wells were filled with different concentration of the test compounds. The plates were then incubated; all the tests were performed in triplicate and the antimicrobial activities were determined as mean diameter of inhibition zone (mm) produced by the test compounds.