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Synthesis, antimicrobial activity and molecular docking studies of novel hydantoin derivatives as potential phospholipase A2 inhibitors

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ABSTRACT

This work presents the synthesis, characterization and evaluation of a series of new multifunctional *N*-substituted hydantoin derivatives for their antibacterial and antifungal activity. Elemental analysis, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy were used to confirm the newly synthesized compounds' structure. The antibacterial and antifungal properties of each synthesized molecule were examined. The examined compounds showed significant to moderate antimicrobial activity against the tested Gram-positive, Gram-negative, and fungal strains with MIC values ranging from 10.3 to 84.2 μM. Compounds 22 (MIC: 11.7–13.5 μM) and 25 (MIC: 10.2–11.9 μM) demonstrated an impressive MIC value against the tested bacterial and fungal strains when compared to the reference medications fluconazole (MIC: 11.7–14.5 μM) and streptomycin (MIC: 14.5 μM), which are broad-spectrum antibiotics and antifungal agents, respectively. Additionally, all of the compounds were tested for their ability to inhibit the phospholipase A2 (PLA2) enzyme, with the IC_{50} values ranging from 8.53 to 65.14 μM. When compared to the reference drug ursolic acid (IC_{50}: 12.58 μM), compounds 22 (IC_{50}: 10.27 μM) and 25 (IC_{50}: 8.53 μM) were shown to be the most potent PLA2 inhibiting compounds in this series. The findings of the Molecule description with Drug-Likeness Prediction demonstrated that all the compounds are in a linear correlation with Lipinski's rule of five, demonstrating good drug-likeness qualities. The inhibitory effects of the most potent compounds (18, 19, 22 and 25) against the target PLA2 protein (PDB ID: 2H4C) were explained by molecular docking studies. The molecular docking results were in good accord with the experimental findings, and as these compounds had superior binding affinities within the active pocket, they may be classified as potent inhibitors of specific targets.

Introduction

The hydantoin is a significant heterocyclic moiety that contains nitrogen and has two nitrogen atoms arranged in a five-membered ring. Over more than 140 years, researchers have studied the chemistry and characteristics of hydantoins and their derivatives. The hydantoin moiety, which may be found in many physiologically active substances, has medicinal significance [1]. Hydantoin derivatives are a significant family of heterocyclic compounds, and their synthesis and characterization have attracted a lot of attention [2]. Derivatives of hydantoin that have intriguing effects on a variety of biological targets have been discovered [3,4]. Due to their numerous medical and commercial uses as essential pharmacophoric moieties or skeletal components, hydantoins have been well studied. Hydantoin offers four derivatizable regions as well as four hydrogen donors and acceptors, despite its modest size. The position and type of substitution of hydantoin rings affect the activity of hydantoin derivatives. The characteristics of the molecule are altered by changing the hydantoin core at *N*-1 or *N*-3 [5]. The effects of different alkyl and aryl groups on these places on the hydantoin ring in various conditions were examined by Edward and Nielsen [6]. Hydantoins are also crucial building blocks in the chemical synthesis of both natural and artificial amino acids. Hydantoin derivatives have been employed

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