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Ultrasonic-promoted green synthesis of new 1, 3, 4-oxadiazoles: Anti-esophageal cancer evaluation, apoptosis morphology, DFT-calculations, *in silico* ADME, and molecular docking study

Ahmed Majeed Jassem *, Sabreen Mahdi Hassan, Kawkab Ali Hussein, Sadiq M.H. Ismael, Faeza Abdulkareem Almashal, Hadi A.S. Jabir

Department of Chemistry, College of Education for Pure Sciences, University of Basrah, Basrah, 61001, Iraq

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ABSTRACT

A new series of 3-acetyl-2, 3-dihydro-1, 3, 4-oxadiazole derivatives (8a-j) was synthesized under ultrasonic technique to explore their antiproliferative efficacy towards esophageal cancer. The chemical structures of the target derivatives were authenticated by different spectroscopic tools including ^{1}H and ^{13}C NMR, FTIR, and Mass spectra. Using ultrasonic technique offers a simple operation, high scalable yields solvent-free, saving energy, and being agreement with green chemistry. The potential enantiomers found in the target derivatives were separated by an enantioselective HPLC technique. The HPLC analysis confirmed these derivatives are a racemic mixture. The target derivatives were tested against three esophageal cell lines (KYSE-150, EC9706, and SLMT-1). Interestingly, the separated (R)-(+) enantiomers are found to show high antiproliferative activity than their racemic and corresponding (S)-(−) forms. Among the (R)-(+) enantiomers, (R)-(+) 8a, (R)-(+) 8b, (R)-(+) 8c and (R)-(+) 8j showed high potency with a range of IC_{50} values (1.68 ± 0.01 to 2.89 ± 0.11 μM) compared to cisplatin (IC_{50} = 1.32 ± 0.01 to 2.63 ± 0.21 μM). By using a dual staining assay (annexin V-FITC and PI), the morphological data demonstrated that the most potent (R)-(+) enantiomers are able to trigger the apoptotic process of the aforementioned cells in a characteristic pathway compared with their effects in the NE-3 and HET-1A (normal cells). In DFT calculations, the findings revealed that the major (R)-(+) enantiomers found in the target derivatives (8a-j) were more stable compared to their corresponding (S)-(−) enantiomers. The ADME predictions of the most potent derivatives (8a, 8b, 8c, and 8j) displayed no Lipinski's violation as they have favorable oral drug-likeness criteria. The docking scores of the above derivatives with some targeting proteins (PDB ID: 2LEO, 5HZN, and 6DUK), confirmed favorable binding interactions with the aforementioned proteins. Overall, the most potent derivatives emerge as a promising candidate for esophageal cancer diseases.

1. Introduction

Cancer disease is becoming a serious human health problem and the foremost causes of death on a global scale [1,2]. According to WHO, the reported cancer cases were 8.8 and 19.3 million deaths in the years 2015 and 2020, respectively and approximately 30 million cases are expected by the year 2040 [3–5]. Peoples both females and males are primarily affected by various kinds of cancer such as breast, colorectal, cervix, lung, thyroid, prostrate, liver, prostrate, rectum, stomach, and colon [6–8]. Esophageal cancer is the sixth leading cause of mortality among all the cancer types in the worldwide [9]. According to the statistics, 450,000 deaths were caused by esophageal cancer over in 2005 globally [10]. In 2013, the statistical report by National Cancer Institute (NCI) declared that the death cases by esophageal cancer were 15,210 in United States and this type of cancer is expected to become a global problem, influencing almost half million people across the world [11]. By looking at the recent statistics, a range of 456,000–500,000 esophageal cancer cases has been reported each year [12]. There are two characterized types of esophageal cancer, the first one is esophageal adenocarcinoma cell (EAC) and the other is esophageal squamous cell carcinoma (ESCC). It is reported that the risk of ESCC combines with several factors that include achalasia symptoms, advanced age, tobacco smoking, exposure to polluted food, and excessive drinking of alcohol [13]. Generally, the present cancer remedies include using different

* Corresponding author.
E-mail address: ahmed.majedd@uobasrah.edu.iq (A.M. Jassem).

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