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An alternative technique for cyclization synthesis, *in vitro* anti-esophageal cancer evaluation, and molecular docking of novel thiazolidin-4-one derivatives

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ABSTRACT

In this work, two novel series of thiazolidin-4-one derivatives (**9a–e** and **10a–e**) constituting ten compounds were synthesized under batch and ultrasound irradiation. It is found that the use of sonochemical methodology in the thiazolidin-4-ones synthesis offers several ecological advantages such as an effective, inexpensive, easy applicable, eco-friendly, and waste-free chemicals than the batch method. Different techniques including NMR (^{1}H and ^{13}C), mass spectra, and infrared radiation (FTIR) were employed to characterize the chemical structures of all the synthesized thiazolidin-4-one derivatives. The purified derivatives were tested for their anti-esophageal cancer activity against a panel of human esophageal cancer cell line (SKGT-4). The *in vitro* cytotoxic and apoptotic activities of these derivatives were evaluated by MTT and AO/EB assays, respectively. Among these derivatives, thiazolidin-4-one derivatives **9e** and **10b** were found to have the most potency toward SKGT-4 human esophageal cells. When compared to the reference standard (cisplatin, IC_{50} 5.21±0.41 μg/mL), the values (IC_{50}) of the derivatives **9e** and **10b** were found as 17.6 ± 0.06 and 18.5 ± 0.01 μg/mL, respectively. The collected data from AO/EB assay revealed these derivatives are able to stimulate the apoptotic effect in the SKGT-4 cells with a selective pathway compared to their behaviors in the normal Vero cells. Moreover, DFT-assisted calculations with theoretical level: B3LYP/6–31G(d,p) were adopted to optimize the geometrical structures of the derivatives **9e** and **10b**. To elucidate the possible binding mechanisms of these derivatives **9e** and **10b** with the active sites of human esophageal proteins (PDB ID: 6DUK, 2LEO, and 5HZN), the docking study was accomplished. According to the docking analysis, the derivatives **9e** and **10b** showed efficient interactions with the target receptors with low values of binding affinity. Thus, the biological tests and docking scores suggested that the synthesized thiazolidin-4-one derivatives **9e** and **10b** may be considered as a potential candidate for esophageal cancers treatments.

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1. Introduction

Cancer is a seriously health problem characterized by an uncontrolled division of cells, resulting in proliferation of cells, and often proliferates from organ to other by metastasis in the body [1,2]. According to the statistics declared by the World Cancer Report, 8.2 million deaths in 2012 and 19.3 million diagnostic cases in 2020 caused by cancer diseases as well as these cases are expected to be 28.4 million in 2040 [3,4]. Among the various kinds of cancer, esophageal cancer is being considered to rank as the sixth mortality cancer type in the worldwide [5]. By looking at the declared incidences of esophageal cancer, this type of cancer caused over 450,000 deaths in 2005 and these incidences were expected to increase rapidly [6]. In 2013, the National Cancer Institute reported that the real number of esophageal cancer incidences in the United States was 15,210 deaths and the percentage of these incidences are estimated to reach 140% by 2025 [7,8]. In this type of cancer, a malignant tumor occurs in the inner layers of the mucosa (linings) of the esophagus cells. The esophagus cancer cells act to spread the tumor from organ to other organs of human body [9]. Two common types of esophageal cancer are diagnosed, the first one is adenocarcinoma and the other is squamous cell carcinoma. It is highly expected that the squamous cell carcinoma associate with several reasons which include advanced age, achalasia, excessive drinking of alcohol, and tobacco smoking [10]. Therefore, the design of new anti-cancer agents with desirable properties involving efficient potency, significant cytotoxicity, and reducing the side effects is highly needed [11]. This concern addresses

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