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Synthesis, molecular docking of new amide thiazolidine derived from isoniazid and studying their biological activity against cancer cells

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ABSTRACT

BCL2, an antiapoptotic protein, is overexpressed in many cancers, making it a good cancer treatment target. In 30 years, few BCL2 targeting agents have shown clinical significance. This work designed new amide thiazolidine derived from isoniazid targeting BCL2 and tested them on cancer cell lines, for binding affinities, the novel candidates were docked to the BCL2 target receptor. IC50 of compound A8 46.67 ± 0.9 and 57.14 ± 0.88 µg/ml against PC3 and HEPG2 respectively with docking score −7.6 Kcal/mol with 6GL8 make it the best compound in this series. Melting point, FT-IR, elemental microanalysis (CHN), ^{1}HNMR, and ^{13}CNMR confirmed chemical structures.

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BCL2l; thiazolidine penicillamine; isoniazid; molecular docking

1. Introduction

Cancer cells indicate the rapid and uncontrollable expansion and proliferation of cells. It is the second leading cause of mortality in countries, after atherosclerotic disease. According to the WHO (World Health Organization), cancer mortality reached 7.9 million individuals in 2007, and the number keeps rising and exceeding the threshold annually (Alghamdi & Nazreen, 2020; Sak et al., 2005; Sun et al., 2019). Therefore, to get rid of this disease a different set of treatments is applied depending on the nature of the tumor and the condition of the cells. The proteins of the Bcl-2 family are important regulators of cell death pathways, working to either block or enhance programmable cell death or apoptosis. It is triggered by a wide range of stimuli and results in the removal of cells without the release of hazardous compounds into the surrounding environment (Wang et al., 2019). Bcl-2 family proteins are classified into two types based on their apoptotic function: antiapoptotic proteins that protect cells from apoptosis and proapoptotic proteins that actively kill cells (Schirrmacher, 2019). A misalignment of antiapoptotic and proapoptotic components may influence tumor formation (Ion et al., 2020). Bcl-2 is an interior mitochondria protein found in the membrane that controls apoptosis, giving cell that produces this oncoprotein an edge in survival (Alici et al., 2021). Cancer development in overall, and prostatic cancer development in specific, are influenced by proliferation of cells and programmed death of cells (apoptosis). Bcl-2 protein amplification has been found often et al., 2021). Chemoinformatic (in silico approaches) has been employed as an efficient way in drug discovery, conserving both time and money especially in cancer research. This involves approaches such as docking of molecules, ADMET evaluation, and MD simulations (Shirasu et al., 2013). Thiazolidine compounds are one of the heterocyclic containing Nitrogen and Sulfur, it has been used increasingly recently (Naim et al., 2017). Previous studies indicate that thiazolidine derivatives have affected active antibacterial, antiviruses, anti-cancer cells, heart disease (Ahmed & Dawood, 2021) and as well in the treatment of diabetes (Venkata et al., 2019) in addition, the thiazolidine-4-carboxylic acid derivatives were known by its structure similarity (symmetry) to proline, which is an essential amino acid for living cells (Alessia et al., 2013; Vivek et al., 2014). Thiazolidine-4-carboxylic acid derivative is used in the treatment of many diseases, including atherosclerosis, viruses, antioxidant, fungi, influenza, bacterial and cancer disease, especially prostate cancer (Trotsko et al., 2018; Song et al. 2015; Tiago et al., 2015). Thiazolidine- (TZs) are an especially significant class of heterocyclic molecules that have received a lot of research interest in the scientific community. TZs have a wide range of biological effects, including lowering blood sugar, anti-infective agent, anti-inflammatory, painkilling, an antioxidant, immunomodulatory effect, and hyperactive bladder inhibitory properties (Osmaniye et al., 2018; Seyed et al., 2021; Guy et al., 2019).

In addition, it has been shown that TZs influenced can-