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Design, synthesis, anticancer activity and molecular docking of novel 1H-benzo[*d*]imidazole derivatives as potential EGFR inhibitors

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ABSTRACT

Here, we present the design, synthesis, and evaluation of a new series of 1H-benzo[*d*]imidazole derivatives (10a–j) to determine their anticancer efficacy. The MCF-7 and HCT116 cancer cell lines were used to test the synthesized compounds anticancer effects. Most of the newly synthesized benzimidazole compounds had a cytotoxic impact, in some cases much more potent than the reference medication. When compared to the reference drug erlotinib, compounds 10g, 10i, and 10j in particular shown strong anticancer efficacy against the tested cancer cell lines with good safety and selectivity indices. All newly synthesized compounds relative inhibitory potency against EGFR wild type (WT) and mutant EGFR L858R/T790M was evaluated in comparison to erlotinib, a standard drug. Comparing compound 10i to other members of the series, it showed the most inhibitory effect against EGFR WT and L858R/T790M with IC_{50} values of 4.38 and 5.69 nM, respectively. Synthetic compounds revealed substantial EGFR WT and L858R/T790M inhibition with selectivity of over 3.09 and 13.29-folds greater activity than reference medication erlotinib. One such example is compound 10i. The mode of action mechanisms between the potent molecules and the matching EGFR kinase protein were explained by molecular docking investigations. Additionally, predicting the drug-likeness of molecules were promising, indicating the compounds' drug-like characteristics. Compounds 10g, 10i, and 10j have been shown to be good candidates and deserving further exploration.

1. Introduction

Cancer has brought about a significant burden for society and families because it is one of the illnesses that gravely endangers human life and health. Despite the enormous efforts made by experts around the world, cancer continues to be one of the leading causes of mortality [1]. By 2030, it is projected to have increased to over 21 million, accounting for over 10.0 million deaths [2]. The majority of cancers have uncontrolled cell division, uncontrolled development, and defective proliferation. The main cause of this is the dysregulation of essential proteins and enzymes that control the cell cycle [3]. The variety of the disease, as well as the inevitable emergence of resistance and the potentially fatal metastasis, are grounds for the availability of several therapeutic alternatives and the pursuit of new ones [4]. The effectiveness of the currently used cancer medicines is hampered by all those difficulties. Additionally, scientists are working to create novel molecules that can block or limit the growth of cancer cells by preventing the development of metastatic cancer cells from normal cells and by avoiding the need of cytotoxic chemotherapy, which frequently kills both healthy and cancerous cells [5,6]. It is urgently necessary to look for new and selective anticancer drugs due to the unfavorable side effects that are displayed by the majority of the present anticancer treatments, such as diminished bioavailability, toxicity, and drug resistance.

With more than 500 enzymes, protein kinases are the biggest family of enzymes. The phosphorylation of proteins, which is their primary activity, causes them to be important in a variety of cellular functions, including proliferation, differentiation, and survival in particular [7]. As a result, a key therapeutic approach for the treatment of cancer is the

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