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Design, synthesis, molecular docking and biological evaluation of novel pyrazole derivatives bearing quinoxalinone moiety as multi-targeted anticancer agents

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ABSTRACT

Based on a multitarget-directed drug design technique, a series of new quinoxalinone-based pyrazole derivatives (**4a-h**) were designed and synthesized. The potency of newly synthesized molecules to inhibit the anti-proliferation of the human cancer cell lines MCF-7 (breast), HCT-116 (colon), and A549 (lung) was examined. The most effective compounds against the examined cancer cell lines were **4e, 4f**, 4 g, and 4 h. Among these, compounds **4e** and 4 h had a strong anticancer activity that was equivalent to sorafenib. The capacity of the potent compounds (**4e, 4f**, 4 g, and 4 h) to inhibit the *in vitro* activity of the thymidylate synthase (TS) enzyme, BRaf, and EGFR kinases was also tested. With IC_{50} values for the TS enzyme, BRaf kinase, and EGFR kinase ranging from 1.16 to 2.97 μM, 1.28 to 3.69 μM, and 1.93 to 4.28 μM, respectively, all the investigated compounds showed a noticeable inhibitory action. Among the synthesized hybrids, compound 4 h showed IC_{50} value of 2.04, 2.69 and 1.93 μM against MCF-7, HCT-116, and A549 cell line, respectively, and 1.16, 1.28 and 1.93 nM against TS, BRaf and EGFR kinase enzyme, respectively. All of the synthesized hybrids adhered to Lipinski's guidelines, which suggested that they would have favorable oral drug-like qualities. To determine the probable interaction between the potent compounds and the TS active site, molecular docking study was conducted.

1. Introduction

The primary worldwide health issue and one of the leading causes of mortality is cancer, which is caused by the abnormal division and spread of cells [1]. To hasten tumor growth, proliferation, and motility, cancer is characterized by an increase in several complicated signaling pathways. To fulfill its anticancer goals, targeted chemotherapy slows the proliferation of cancer cells, making it a key tool in the fight against the disease [2]. As of right now, there are no fully effective and practical medications or methods to stop this disease's unrelenting progression [3]. Apoptosis, which effectively stops tumor cell growth, can be induced by decreasing the DNA synthesis of tumor cells since the level of DNA synthesis in tumor cells is considerably higher than that in normal cells [4]. As a result, the creation of medications designed to operate against a specific target with high potency and selectivity has received considerable attention in the discovery of chemotherapeutic treatments [5].

Because of their crucial function in DNA manufacture, thymidylate synthase (TS) has attracted attention in cancer treatment [6]. Deoxythymidine monophosphate (dTMP), a direct precursor for DNA synthesis, is created by TS from deoxyuridine monophosphate (dUMP), which is then further phosphorylated to generate the triphosphate group (dTTP) [7]. The absence of thymine that arises from TS inhibition is fatal to the majority of actively dividing cells. Through DNA damage and thymidylate depletion, inhibition of TS eventually results in cell death [8]. TS is consequently viewed as a prime candidate for cancer

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