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Development of penipanoid C-inspired 2-benzoyl-1-methyl-2,3-dihydroquinazolin-4(1H)-one derivatives as potential EGFR inhibitors: Synthesis, anticancer evaluation and molecular docking study

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ABSTRACT

A novel class of penipanoid C-inspired 2-benzoyl-1-methyl-2,3-dihydroquinazolin-4(1H)-ones (3a-3f) and 1-methyl-2-(3,4,5-trihydroxybenzoyl)-2,3-dihydroquinazolin-4(1H)-one derivatives (10–15) was successfully synthesized using the I_2/DMSO method. The newly synthesized compounds were characterized and tested for cytotoxicity against three cancer cell lines: HepG2 (human liver), MCF7 (human breast), and HCT116 (human colorectal). The majority of the tested molecules had a considerable cytotoxic impact, in some cases larger than doxorubicin. Furthermore, the inhibitory effect of six compounds (10–15) against epidermal growth factor receptor (EGFR) kinases were investigated, with three compounds (10, 11 and 12) showing good IC_{50} values. The IC_{50} values for compounds 10 and 12 against wildtype EGFR were 0.222 and 0.172 µM, respectively. Compound 12 had good enzyme inhibitory efficacy with 71.30 and 421.53 µM for the EGFR L858R and T790M mutants, respectively, which is more effective than the positive control, erlotinib, and close to lapatinib. The results of the biological screening were also confirmed by docking studies, which predicted the potential binding interactions of the target compounds with the EGFR active sites. Compounds 10 and 12 appear to be interesting lead compounds with the potential to be developed as anticancer agents, based on the findings.

1. Introduction

Cancer is currently regarded as a global threat to public health [1,2]. Cancer is the second most deadly illness, accounting for 21% of all yearly deaths and the greatest significant impediment to increasing global life expectancy [3]. Cancer rates rise annually, and it is predicted that over the next 20 years, cancer rates will rise by around 60%. According to the WHO, there are 600 different forms of cancer, each of which has its diagnosis and treatment procedure [4]. Chemotherapy is the most widely used treatment for this purpose all over the world. However, chemotherapy's efficacy is hampered by several severe adverse effects, poor selectivity, and drug resistance [5]. As a result, one of the most ardently pursued goals of modern medicinal chemistry is the creation of strong and efficient new anticancer drugs [6]. One of the variables that have been linked to the development of cancer is protein kinases. Protein kinases play a crucial part in signal transduction pathways that mediate a variety of cellular processes. As among the protein kinases, the tyrosine kinase (TK) of the EGFR is vital for cancer cell proliferation, survival, adhesion, migration, and differentiation [7]. Overexpression of some EGFR kinases is closely linked to cancer [8]. Therefore, protein kinase inhibitors have gained a lot of attention in recent decades because of their continued importance in cancer treatment [9]. Cancer cell survival, invasiveness, and treatment resistance have all been linked to kinase activity in several cell signaling pathways [10]. As a result, anticancer drugs that target kinases like EGFR have been among the broadly used [11,12]. As a result, tumor growth inhibition by directly targeting EGFR tyrosine

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