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Synthesis, anticancer activity and molecular docking of new pyrazolo [1,5-*a*]pyrimidine derivatives as EGFR/HER2 dual kinase inhibitors

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ABSTRACT

The pyrazolo[1,5-*a*]pyrimidine core framework is a good starting point for the synthesis of drug-like molecules since the biological activity is determined by the kind and position of the substituents on the heterocyclic center. To develop safer and more effective anticancer medications, pyrazolopyrimidine derivatives (6a-o) were designed and developed. The structure and purity of the resulting molecules were confirmed by elemental analysis and various spectroscopic techniques. The human cancer cell lines, including HepG2 (liver), MCF-7 (breast), and HCT116 (colorectal), have been used to test the synthetic compounds' anticancer properties. The most of pyrazolopyrimidine derivatives demonstrated a cytotoxic impact, few compounds exhibit much more potent than doxorubicin and sorafenib. For HepG2, MCF7, and HCT116, respectively, the IC_{50} values of compound 6b were 3.26, 3.19, and 5.01μM. To determine their selectivity indices, the potent molecules were assessed for cytotoxicity on the WI-38 cell line, a normal healthy cell line. Inhibition studies for the human epidermal growth factor receptor 2 (HER2) and the epidermal growth factor receptor (EGFR) were also carried out in an effort to determine their mode of cytotoxicity. With IC_{50} values of 0.163 (EGFR), 0.116 (HER2) for compound 6a and 0.126 (EGFR), 0.083 (HER2) for compound 6b were the most effective dual EGFR/HER2 kinase inhibitors. Finally, molecular docking research showed that compounds 6a and 6b firmly binds to EGFR and HER2 *via* hydrogen bonding interactions, leading to irreversible dual kinase inhibition. The substances displayed favorable characteristics of drugs and might be applied as prototypes for further improvement.

1. Introduction

In today's medical era, cancer ranks second only to cardiovascular illnesses in terms of morbidity and mortality, and it is predicted to surpass as the leading killer throughout globally in the near future [1]. In light of this, the WHO predicted that 13 million people will die from cancer by the year 2030 [2]. Uncontrolled cell division, growth, and flawed proliferation are features of most malignancies. This is mostly attributable to the dysregulation of crucial proteins and enzymes that govern cell cycle [3]. Drug resistance has become increasingly prevalent a major concern on a global scale [4], despite several advances in cancer therapy such as chemotherapy, surgery, radiation, and biotherapy. As a result of this, developing novel anticancer drugs that are both effective and safe is of paramount importance [5]. The receptor tyrosine kinase superfamily's subclass 1 includes the EGFR. Since EGFR and HER2 are frequently overexpressed in breast tumours and are members of the EGFR family, they have been identified as the most crucial molecular targets in cancer treatment. Angiogenesis, metastasis, impaired apoptosis, and cell proliferation are only a few of the unfavorable tumor features and tumor development associated with overexpression of EGFR in cancer [6,7]. Early in the anticancer drug discovery process, it is a potential target. Additionally, HER2 is a significant cancer biomarker, yet HER2 has not been linked to any known ligands. As a result, HER2 activation requires dimerization, and HER2 heterodimers comprising additional members of the ERBB group have garnered considerable attention because to their enhanced stability and solid signaling

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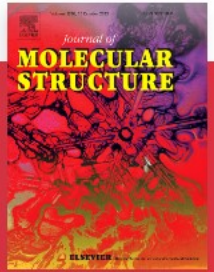

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