Design, Synthesis and Biological Evaluation of Novel Pyrazolotriazolopyrimidine Derivatives as Potential Anticancer Agents

Ihab M. Almasri

Department of Pharmaceutical Chemistry and Pharmacognosy, Faculty of Pharmacy,
Al Azhar University-Gaza, Palestine.

DOI: https://doi.org/10.35516/jjps.v16i2.1485

ABSTRACT

Three novel pyrazolo-[4,3-e][1,2,4]triazolopyrimidine derivatives (**1**, **2**, and **3**) were designed, synthesized, and evaluated for their in vitro biological activity. All three compounds exhibited different levels of cytotoxicity against cervical and breast cancer cell lines. However, compound **1** showed the best antiproliferative activity against all tested tumor cell lines, including HCC1937 and HeLa cells, which express high levels of wild-type epidermal growth factor receptor (EGFR). Western blot analyses demonstrated that compound **1** inhibited the activation of EGFR, protein kinase B (Akt), and extracellular signal-regulated kinase (Erk)1/2 in breast and cervical cancer cells at concentrations of 7 and 11 μM, respectively. The results from docking experiments with EGFR suggested the binding of compound **1** at the ATP binding site of EGFR. Furthermore, the crystal structure of compound 3 (7-(4-bromophenyl)-9-(pyridin-4-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine) was determined by single crystal X-ray analysis. Our work represents a promising starting point for the development of a new series of compounds targeting EGFR.

Keywords: Pyrazolo[1,2,4]triazolopyrimidine, EGF-receptor inhibitor, breast cancer, cervical cancer, molecular modeling, crystal X-ray analysis.