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Design, synthesis and anti-inflammatory activity of pyrimidine scaffold benzamide derivatives as epidermal growth factor receptor tyrosine kinase inhibitors

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ABSTRACT

Novel serious of pyrimidine scaffold benzamide derivatives (**9 a-k**) were synthesized and characterized by IR, HRMS, and NMR. Docking study of compounds 9 g, 9 h exhibited H-bonding interacts with Met769 into ATP binding site of EGFR-TK which showed similar binding mode to Lapitinib (PDB code: 1M17). Results indicated the ability to potent and selective inhibitors of the Epidermal Growth Factor Receptor tyrosine kinase (EGFR-TK). The molecular electrostatic potential (MEP), frontier molecular orbitals (FMOs) and HOMO-LUMO energy gap of the title compounds were investigated by using the B3LYP/6-31G method. The synthesized compounds were screened for *in vitro* anti-inflammatory activity.

1. Introduction

Cancer is continuing to be a major health problem in developed as well as undeveloped countries [1]. The great cancer incidence worldwide increases the search for new, safer and efficient anti-cancer agents, aiming the prevention or the cure of this illness. Generally, curing of cancer is difficult because of the side effect of drugs on the normal cells and makes some other abnormalities in our body. Lung cancers are malignant tumors with poor prognoses and ranked as the top cause of cancer-related deaths [2,3]. Inhibitors of the EGFR PTK are therefore expected to have great therapeutic potential in the treatment of malignant and nonmalignant epithelial diseases [4,5]. One of the most prominent protein kinases is the endothelial growth factor receptor (EGFR) because that kinase is known to be involved in the various cancer-associated processes of uncontrolled cell growth [6,7]. EGFR inhibitors are well-known active targets and to be efficient in the drug development for the treatment of cancer [8–10]. EGFR-TK inhibitors are the second most essential drug targets have been approved for the therapy of non-small cell lung cancer and this motivated inhibition of EGFR signaling may not only active in anti-proliferative effects and have also been increased sensitivity to cytotoxic therapies [11]. In recent days, various approaches have been developed to small molecule inhibitors of the intrinsic tyrosine kinase domain-like Lapitinib **(a)**, Erlotinib **(b)**, Gefitinib **(c),** Fig. 1 which has been approved for the chemotherapeutic treatment of patients with advanced non-small lung cancer [12] and also Lapatinib (**a**) is a potent dual EGFR/ErbB2 inhibitor, recently approved by US Food and Drug Administration (FDA) for the breast cancer therapy [13]. The epidermal growth factor receptor (EGFR) is cellular transmembrane tyrosine kinases that are over-expressed in a significant number of human tumors (e.g., Colon, breast, ovarian and NSC lung cancer) [14]. Therefore, EGFR inhibitors represent a sensible approach for the development of novel anticancer therapies which would act by competing with ATP for binding at the catalytic domain of their target enzyme [15–17].

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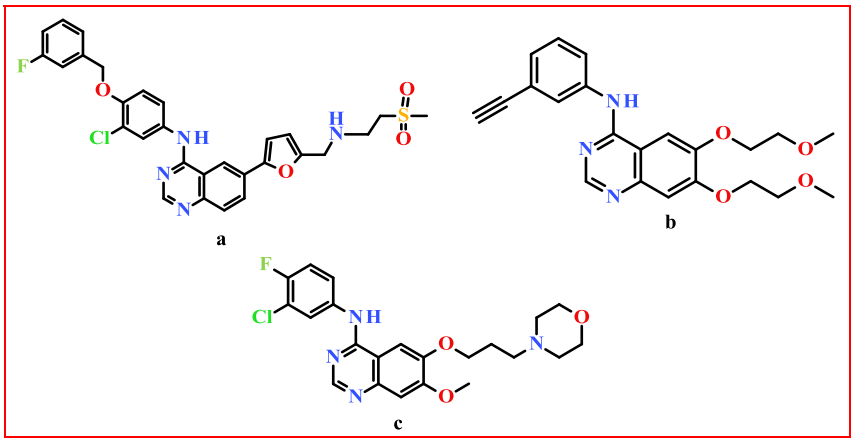

Fig. 1. 4-Anilinoquinazolines EGFR-TK inhibitors, Lapitinib **(a)**, Erlotinib **(b)**, Gefitinib **(c)**.

In recent years, various nitrogen heterocyclic rings are known to exhibit interesting biological activities. Pyrimidine is an important class of heterocyclic ring is found in vitamins like thiamine, riboflavin and folic acid. During the last two decades, several pyrimidine derivatives have been developed as chemotherapy of AIDS [18]. The previously reported literature presented that different structured fused pyrimidine ring systems are highly active in numerous chemotherapeutic activities such as anti-cancer [19,20], antibacterial [21,22], antifungal [23,24], and anti-viral [25,26] applications. The substituted pyrimidine ring systems were also reported to possess excellent antitumor activity [27–29]. Literature evaluations have pointed out the inherited antitumor potency of compounds containing pyrimidine and fused quinazoline moieties [30–32]. FDA has been approved for several quinazoline derivatives as anticancer drugs (e.g., Gefitinib, Erlotinib, Lapatinib and Vandetanib). Nowadays, the bio-medicinal activity of quinazoline derivatives and drug development of novel quinazoline derivatives for the anticancer therapy is a promising field [33–35].

The present work, we have carried out the chemical modifications on the general features of quinazoline-containing compounds. These modifications involve a replacement of the furan moiety in the quinazoline skeleton by pyrimidine scaffold benzamide moiety to develop more effective target molecules utilizing a fragment-based drug design approach and biologically evaluated their anti-inflammatory activity Fig. 2.

2. Experimental

2.1. Materials and methods

All the solvents and chemicals were used analytical grade from SRL and Merck Ltd. Microwave reactions were performed with a Biotage®. Initiator with a continuous focused microwave power delivery system in a pressure glass vessel (10 mL) sealed with a septum under magnetic stirring. TLC was performed on commercial Merck silica gel 60 F 254. Column chromatography was carried out using silica gel 60–120 mesh. ^{1}HNMR spectra were recorded in $CDCl_3$ and DMSO-d6 using TMS an internal standard with Bruker 300 MHz NMR spectrometer. High-resolution mass spectra (HRMS) were measured on a Finnigan spectrometer.

2.2. 3-(Dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (3)

The mixture of *N*, *N*-dimethylformamide dimethylacetal (0.02 mol), acetylpyridine (0.01 mol), and toluene (3.5 mL) in a 10 mL glass vial well equipped. The reaction mixture was irradiated in the microwave synthesizer at 120 °C for 15 min. After completion of the reaction (indicated by TLC), the mixture was cooled down to room temperature. Petroleum ether (2 mL) was added to the reaction mixture and kept stirring for 20 min. The resultant solid was collected by filtration and washed with hexane to get compound

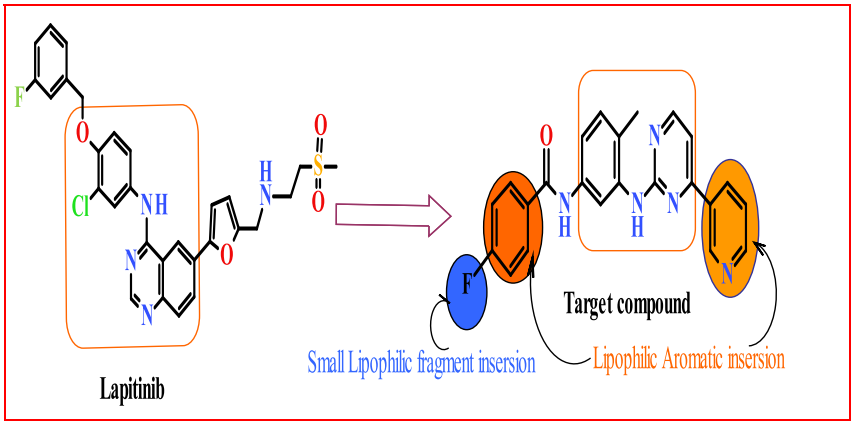

Fig. 2. Design of target pyrimidine scaffolds benzamide compounds.