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Synthesis and in vitro biological evaluation of novel quinazoline derivatives

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Abstract: A series of novel 4-arylamino-6-(5-substituted furan-2-yl)quinazoline derivatives were designed, synthesized and evaluated on biological activities in vitro. Compound **2a**, **3a** and **3c** exhibited highly anti-proliferation activities on all tested tumor cell lines including SW480, A549, A431 and NCI-H1975 cells. Especially, compound **2a** not only exhibited strong anti-proliferation activities against the tumor cell lines which expressed wild type or mutant $EGFR^{L858R/T790M}$, but also showed the most potent inhibitory activity toward wild type EGFR (IC_{50} = 5.06 nM). The result of docking with EGFR suggested the binding mode of **2a** was similar to that of lapatinib. While Western-blot analyses showed **2a** obviously inhibited the activation of EGFR, Akt and Erk1/2 in lung cancer cells at indicated concentration. It is believed that this work would be very useful for developing a new series of TKIs targeting EGFR.

Keywords: 4-arylamino-6-(5-substituted furan-2-yl)quinazoline, EGFR, tyrosine kinase inhibitors, anti-proliferation

Several quinazoline derivatives as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), for example gefitinib, erlotinib and lapatinib, have been approved for the cancer treatment by the US Food and Drug Administration (FDA).[1-4] Gefitinib and erlotinib as the first-generation EGFR inhibitors were highly effective in the treatment of lung-cancer patients with activated EGFR mutations, which occurred in the kinase domain of the *EGFR* gene with deletions in exon 19 or point mutation of L858R in exon 21.[5-7] Unfortunately, patients harboring the *mut*EGFR (T790M) were reported to develop resistance to these drugs.[5, 8, 9] Replacement of the threonine with methionine leads to steric repulsion of the first- and second-generation inhibitors (afatinib and dacomitinib) and results in a slightly different binding geometry, which accounts for the loss of inhibitory activity both in vitro and in vivo.[10] Lapatinib, a dual inhibitor of the EGFR and human epidermal growth factor receptor 2 (HER2), was approved in 2007 for the treatment of breast cancer.[4, 11-14] However, a mandatory black-box warning was released in 2008 because of lapatinib-related hepatotoxicity in clinical trials and post-marketing surveillance.[15]

Nazartinib, osimertinib and rociletinib as the third-generation EGFR inhibitors were designed to avoid the steric interference caused by Met790. These inhibitors bind with EGFR in a covalent form through the alkylation of EGFR at Cys797 at the lip of the ATP-binding site.[10] However, the effective treatment of patients that harbor the EGFR-T790M drug resistance mutation is limited by the emergence of new drug resistances.[16] C797S is a recently discovered resistance mutation in the kinase domain of EGFR.[9] This mutation prevents the covalent bond formation with third-generation inhibitors and reduces their efficacy.[17] Thus there is an urgent demand for new EGFR inhibitors that effectively treats various cancers.

Herein, we report the design, synthesis, and biological evaluation of some novel quinazoline