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Facile and efficient synthesis and biological evaluation of 4-anilinoquinazoline derivatives as EGFR inhibitors

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ABSTRACT

Series of 4-anilinoquinazoline derivatives were conveniently and efficiently synthesized and their antitumor activities were evaluated by MTT assay in three human cancer cell lines: H1975, HepG2 and SMMC-7721. New compounds **19a-19h** were designed and synthesized to seek for powerful EGFR inhibitors and to explore whether methyl group at C-2 position of quinazoline ring has a positive effect on EGFR inhibition. All the compounds of **19a-19h** were found potent against all three cell lines and five compounds (**19c**, **19d**, and **19f-19h**) were found more potent against H1975 than gefitinib. SAR studies revealed that methyl group at C-2 position of quinazoline ring could significantly improve the antitumor potency of 4-anilinoquinazolines. The same conclusion was also drawn according to the results of Western blotting analysis. Among all the tested compounds, **19g** exhibited extremely potent against H1975 with an IC_{50} value of 0.11μM, remarkably lower than that of gefitinib (1.23μM). The results of western blotting analysis showed that compounds **19c** and **19g** could notably inhibit the expression of phosphorylated EGFR, especially **19g**, almost inhibited completely.

[1]The epidermal growth factor receptor (EGFR, erbB1) is a member of the erbB family of receptors including erbB2/HER2, erbB3/HER3, and erbB4/HER4.[1, 2] It is over-expressed in a large number of human solid tumors, and is associated with cancer cell proliferation, apoptosis, angiogenesis, and metastasis.[3,4] Therefore, EGFR as a target of anticancer drugs has received much attention in the past decade. A series of EGFR inhibitors with different molecular scaffolds have been discovered. Among them, 4-anilinoquinazolines play a key role and have been extensively studied. As shown in **Figure 1**, PD153035, named 6, 7-dimethoxy-4-anilinoquinazoline, was the first EGFR inhibitor reported in 1994.[5] Though finally it was abandoned due to the depressing water solubility, the chemical structure of PD153035 was reserved to do structure modification. Gefitinib and erlotinib have been used to treat non-small-cell lung cancer (NSCLC).[6-11] Canertinib is the first irreversible kinase inhibitor to enter clinical trial. [12]

These agents all belong to the 4-anilinoquinazoline class of inhibitors and the key features between the receptor and this template have been revealed as follows [13,14], (1) the quinazoline moiety fits into the ATP binding pocket of the kinase domain, (2) the N-1 of the quinazoline ring interacts with the backbone NH of Met-769 via a hydrogen bond, and water mediated hydrogen bonding is observed between the N-3 of the quinazoline ring and the Thr-766 side chain, (3) the aniline moiety lies in a deep and hydrophobic pocket, and (4) the substitution at C-6 or C-7 of the quinazoline ring conveys a more favorable pharmacokinetic profile and improves the physical properties.

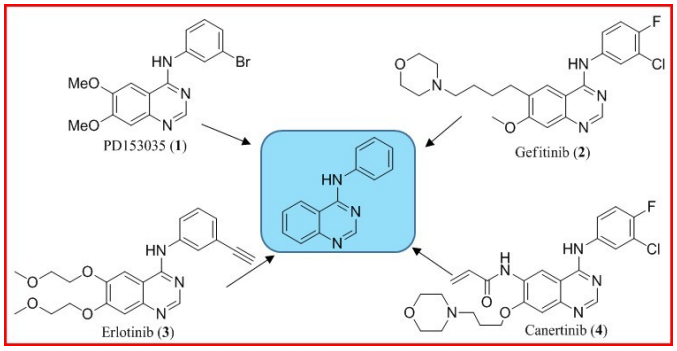

Figure1. Chemical structure of tyrosine kinase inhibitors

It was reported that 4-substitution was assumed to be optimal as aniline, with other linkers being less effective. However, the structure activity relationship (SAR) of 4-arylamino was reported barely. Therefore, nine 4-anilinoquinazolines with different anilines substituted at 4-position were synthesized and the SAR was discussed. In our ongoing to seek for more potential substituent to enhance the antitumor activity of 4-

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