SYNTHESIS AND BIOEVALUATION OF NOVEL QUINAZOLINE DERIVATIVES TARGETING EPIDERMAL GROWTH TARGET RECEPTOR (EGFR)

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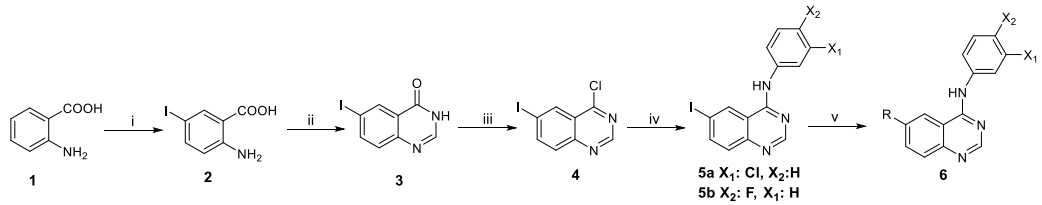
The epidermal growth factor receptor (EGFR) has been extensively studied as an attractive target for the development of anticancer agents, due to its regulative role in important cellular processes as survival and proliferation. Many types of human cancers, including lung, breast, head and neck, and brain cancers are frequently associated with overexpression or mutations of EGFR. Extensive research efforts for the discovery of EGFR inhibitors, led to the development of three generations of inhibitors, exemplified by the approved drugs Gefitinib and Erlotinib, Afatinib, and Osimertinib, all sharing a central 4-anilinoquinazoline core.

Herein, we report the synthesis of novel quinazoline derivatives, bearing various alkynyl substituents at position 6 of the essential pharmacophore quinazoline. These derivatives are expected to bind to the hinge Met793 residue of EGFR, through its N-1 atom, while the quinazoline aromatic ring will occupy the lipophilic region I within the kinase active site, in analogy with the known binding of Gefitinib. Our goal is to explore extensively, through structure to activity (SAR) studies, these aromatic substituents, aiming at a favorable methylthio-aryl interaction that will enhance binding affinity. Such methionine-aromatic interactions play significant roles in stabilizing protein conformations and in ligand-protein interactions. Additionally, the selection of appropriate substituents for each position has been facilitated by computer-aided prediction of the binding mode and affinity of each target compound.



6a X_1 = Cl, X_2 = H, R = 4-ethynyltoluene
6b X_1 = Cl, X_2 = H, R = 1-ethynyl-2,4-dimethylbenzene
6c X_1 = Cl, X_2 = H, R = 4-ethynylanisole
6d X_1 = Cl, X_2 = H, R = 3-chloro-1-ethynylbenzene
6e X_1 = H, X_2 = F, R = 1-ethynyl-4-pentylbenzene

Scheme 1: i) KI, H_2O_2, CH_3COOH, ii) $HCONH_2$, 130-140 ^oC, iii) $SOCl_2$, DMF, reflux, iv) 3-chloro or 4-fluoro anilines, i-PrOH, v) DMF, $Pd(PPh_3)_4$, CuI, Et_3N, alkynes