Discovery of novel EGFR inhibitor targeting wild-type and mutant forms of EGFR: *in silico* and *in vitro* studies

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Targeting L858R/T790M and L858R/T790M/C797S mutant EGFR is a critical challenge in developing EGFR tyrosine kinase inhibitors for overcoming drug resistance in non-small cell lung cancer (NSCLC). Herein, the discovery of a next-generation EGFR tyrosine kinase inhibitor (TKI) is necessary. A series of furopyridine derivatives were elucidated by a computational combined biological approach for their EGFR-based inhibition and antiproliferative activities. We found that several compounds derived from virtual screening based on molecular docking and solvated interaction energy (SIE) method showed the potential to suppress wild-type and mutant EGFR. The most promising PD13 displayed strong inhibitory activity against wild-type (IC_{50} of 11.64±1.30 nM), L858R/T790M (IC_{50} of 10.51±0.71 nM), which are more significant than known drugs. In addition, PD13 revealed the potent cytotoxic effect on A549 and H1975 cell lines with IC_{50} values of 18.09±1.57 and 33.87±0.86 μM, respectively. The 500-ns MD simulations indicated that PD13 formed a hydrogen bond with Met793 at the hinge region, which involved creating excellent EGFR inhibitory activity. Moreover, the binding of PD13 toward EGFRs was a major factor in stabilizing via hydrogen bonds and van der Waals (vdW) interactions. Altogether, PD13 is a promising novel EGFR inhibitor that could develop for fourth-generation EGFR-TKIs