Design, Synthesis and Biological Evaluation of Novel Anthranilic Acid Derivatives as Anticancer Agents Targeting Tyrosine Kinases

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Abstract

Tyrosine kinases (TKs) are well-known molecular targets in anticancer drug design. TKs are involved in cell apoptosis, proliferation, differentiation, migration, and cell cycle. The abnormal expression of TKs has been identified as a key factor in cancer initiation and progression. Therefore, several TK inhibitors with different chemical scaffolds, such as quinazolines and quinazolinones, are available and clinically used as anticancer agents. Nevertheless, many factors have limited the clinical efficacy of these molecules, including low potency, reduced efficiency and developed resistance. Therefore, targeting TKs by developing new compounds to overcome the treatment limitations, is needed. In this project, novel molecules with an anthranilic acid (the precursor of quinazolinones) scaffold were designed, synthesized and evaluated for their antitumor activity using the *in-vitro* SRB assay against seven cancer cell lines (MCF-7, MDA-MB-231, MDA-MB-468, SKBR-3, HCT-116, K562 and HepG-2). Two compounds (**12** and **13**) showed significant anti-proliferative

chemo-sensitivity against all tested cell lines, with IC_{50} values ranging from 0.69 ± 0.15 to 1.78± 0.15 µM and 0.39 ± 0.08 to 1.24 ± 0.38 for compounds **12** and **13**, respectively. To understand the compounds' binding mode with the enzymes' active sites, molecular docking simulation was performed. Despite the close IC_{50} values between compounds **12** and **13**, different binding modes to EGFR-TK crystal structures was observed, which was hypothesized for compound **13** to have an extra binding with Cys772 residue that suggested its higher activity, when compared with compound **12**. In conclusion, two novel compounds were developed as potential EGFR-TK inhibitors with promising anticancer activity. All synthesized compounds should be further kinetically assayed on different tyrosine kinases to investigate their affinity and selectivity. In addition, more analogues are worth making for lead optimization and concluding a comprehensive structure-activity relationship.