Thesis summary

Design, Synthesis and Biological Evaluation of Novel Quinoline Based Small Molecules as Anticancer Agents Targeting Topoisomerase I

(トポイソメラーゼI阻害薬を目指したキノリン誘導体の設計、合成、生物活性)

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Cancer is considered as a major health obstacle threating the life of millions of people annually. The incidence and mortality of cancer are increasing rapidly worldwide. Consequently, enormous efforts are being implemented to develop potential anticancer agents.

Quinoline is considered as one of the most privileged motifs in drug discovery and exerts a crucial and prominent role in anticancer drug discovery. So far, sets of quinoline derivatives have been developed for cancer treatment. Interestingly, various quinolines provoked their anticancer influences through inhibition of enzymes essential for proliferation of cancer cell as Epidermal Growth Factor Receptor (EGFR) and topoisomerase I.

Topoisomerase I (TOP1) is ubiquitous nuclear enzyme and is crucial in vital cellular events as transcription and replication. For cancer cells, it was revealed that they displayed overexpressed levels of TOP1. Therefore, TOP1 is emerged as a validated target for cancer therapy. Moreover, the medicinal use of TOP1 poisons (topotecan and irinotecan) for cancer therapy has been hindered owing to several problems like metabolic instability and clinical resistance.

Herein adopting fragment-based drug design, novel two series of 4-alkoxy-2-arylquinolines were synthesized as anticancer agents targeting TOP1 enzyme. The anticancer potential of all compounds have been evaluated. Interestingly, the propoxy-2-phenyl analogs showed good anticancer activity. Additionally, two morpholinopropoxy-2-phenyl derivatives moderately stabilized TOP1ccs as the first 4-alkoxy-2-arylquinolines TOP1 poisons lead compounds.

Pursuing of our endeavor to develop quinolines as TOP1 poisons endowed with potential anticancer activity, we exploited structural modification strategy of our reported TOP1 poison to design six series of 4-propoxy-2-arylquinolines and 4-propoxy-2,6-diarylquinolines. Despite of the good anticancer activity of most compounds, they exhibited no or weak TOP1 poisoning

activity. Based on literature review, the compounds were evaluated against nine kinases to detect the plausible mechanism of anticancer action. The potent anticancer compounds showed EGFR/FAK potent dual inhibition. The binding interactions of the tested compounds and EGFR/FAK active sites have been rationalized by molecular docking, likewise the stability of complexes of the potent compounds with EGFR/FAK has been investigated by molecular dynamics simulation. As a result, this study reported the first 2-aryquinolines as EGFR/FAK dual inhibitors with potential anticancer effects.

Furthermore, two novel series of 11-aminopropoxybenzofuro[3,2-*b*]quinolines and 11-aminobenzofuro[3,2-*b*]quinolines have been designed applying ring fusion and bioisosterism strategies of our reported TOP1 poison to afford quinoline-benzofuran hybrids merging both of their characteristics aiming to improve the anticancer and TOP1 poisoning actions of the lead compound. Anticancer activity, TOP1 and TDP1,2 inhibitory actions have been tested for the synthesized compounds. Some of the investigated compounds exerted good anticancer activity, but none of them possessed TOP1 inhibitory action. Remarkably, 3,7-dichloro hydroxypiperidine analog emerged as the first reported benzofuroquinoline with TDP1 selective inhibition can be used to enhance the anticancer impact of some drugs as TOP1 poisons.