Abstract

Glioblastoma (GBM) is an aggressive brain tumor with limited treatments, characterized by drug resistance, high recurrence rates, and low survival rates. Amplification of the epidermal growth factor receptor (EGFR) in GBM contributes to tumor resistance by activating critical signaling pathways, making it a potential therapeutic target. Efforts to inhibit EGFR with small molecule inhibitors have largely failed due to tumor heterogeneity and the blood-brain barrier. Therefore, developing potent EGFR inhibitors for halting GBM cell proliferation and migration is a crucial necessity. Recently, we found that hydrazones and indole analogs can bind and block the EGFR signaling pathway in GBM. To find more effective ligands, we developed a library of hydrazones and indole compounds and evaluated their interactions with the EGFR protein using both structure-based and ligand-based virtual screening. The cytotoxicity of 40 synthesized molecules were evaluated on GBM cell lines using *in vitro* studies, and the top-lead compounds were chosen for further exploration into their inhibitory kinetics and anti-migratory effect. Data indicates that novel indole compounds are more cytotoxic than hydrazones, with lower micromolar half-maximal inhibitory concentrations in GBM cells. In time-dependent analysis, indole derivatives considerably reduced GBM cell proliferation and were more efficient in halting cell migration than hydrazone-treated cells. Overall, our findings revealed that novel indole compounds are more effective against GBM cell proliferation and migration than hydrazones, indicating their potential as therapeutic agents targeting the EGFR signaling pathways.