

**Abstract**

Glioblastoma (GBM) presents a significant clinical challenge due to its resistance to treatment and frequent recurrence. 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. Therefore, developing potent EGFR inhibitors for halting GBM cell proliferation and migration is a crucial necessity. The newly synthesized hydrazone and indole analogs, identified as small molecules, investigated in this study are hypothesized to induce apoptosis in GBM cells by inhibiting EGFR-mediated survival signaling and promoting caspase activation.

Molecular docking and dynamics simulations were used to explore interactions of 21 novel hydrazone and indole derivatives with EGFR. Cytotoxicity of all compounds was assessed in LN229 and SNB19 glioblastoma cells, and  $IC_{50}$  values were determined. Lead compounds were further tested for effects on cell migration and apoptosis by measuring Caspase-3/7 activation in both cell lines.

Novel indole compounds demonstrate significant cytotoxicity compared to hydrazones, significantly reducing cell survival and proliferation. They are also more effective at halting cell migration than hydrazones. Treatment with top lead indole compound led to a significant increase in caspase 3/7 activity in both cell lines, indicating the induction of apoptosis.

The newly synthesized indole-based derivative exhibited superior activity against GBM cell proliferation and migration compared to the hydrazone compound. The observed cytotoxicity appears to be mediated through apoptosis, as evidenced by enhanced caspase activation, highlighting its potential as a therapeutic candidate targeting EGFR signaling pathways.