قطاع الدراسات الصيدلية (٩٤)
اللجنة العلمية للكيمياء الصيدلية والحيوية
الدورة الثالثة عشر (٢٠١٩-٢٠٢٢)

باللغة الانجليزية: (٦)

New Multi-Targeted Antiproliferative Agents: Design and Synthesis of IC261-Based Oxindoles as Potential Tubulin, CK1 and EGFR Inhibitors

A series of 3-benzylideneindolin-2-one compounds was designed and synthesized based on combretastatin A-4 and compound IC261, a dual casein kinase (CK1)/tubulin polymerization inhibitor, taking into consideration the pharmacophore required for EGFR-tyrosine kinase inhibition. The new molecular entities provoked significant growth inhibition against PC-3, MCF-7 and COLO-205 at a 10 μM dose. Compounds 6-chloro-3-(2,4,6-trimethoxybenzylidene) indolin-2-one, 4b, and 5-methoxy-3-(2,4,6-trimethoxybenzylidene)indolin-2-one, 4e, showed potent activity against the colon cancer COLO-205 cell line with an IC50 value of 0.2 and 0.3 μM. A mechanistic study demonstrated 4b's efficacy in inhibiting microtubule assembly (IC50 = 1.66 ± 0.08 μM) with potential binding to the colchicine binding site (docking study). With an IC50 of 1.92 ± 0.09 μg/mL, 4b inhibited CK1 almost as well as IC261. Additionally, 4b and 4e were effective inhibitors of EGFR-TK with IC50s of 0.19 μg/mL and 0.40 μg/mL compared to Gifitinib (IC50 = 0.05 μg/mL). Apoptosis was induced in COLO-205 cells treated with 4b, with apoptotic markers dysregulated. Caspase 3 levels were elevated to more than three-fold, while Cytochrome C levels were doubled. The cell cycle was arrested in the pre-G1 phase with extensive cellular accumulation in the pre-G1 phase, confirming apoptosis induction. Levels of cell cycle regulating proteins BAX and Bcl-2 were also defective. The binding interaction patterns of these compounds at the colchicine binding site of tubulin and the Gifitinib binding site of EGFR were verified by molecular docking, which adequately matched the reported experimental result. Hence, 4b and 4e are considered promising potent multitarget agents against colon cancer that require optimization.