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Entitled

THE ANTICANCER ACTIVITY OF NOVEL 8-HYDROXYQUINOLINE DERIVATIVES AGAINST 5-FLUOROURACIL RESISTANT COLORECTAL CANCER CELLS

by

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Abstract

Cancer is a global health crisis for which 20 million new cases were diagnosed in 2022 alone, with 9.3 million cancer-related deaths. Nearly 900,000 deaths were due to colorectal cancer (CRC), which is the third leading cause of cancer related mortality. In the United Arab Emirates, 550 new cases of CRC were reported in 2022. A major clinical challenge with CRC treatment is the development of resistance to 5-fluorouracil (5FU)-based chemotherapy regimens, which are the standard treatment for CRC. In the present study, the anticancer activity of two novel 8-hydroxyquinoline (8-HQ) derivatives AS45 and AS47 was examined against 5FU-sensitive (HCT116) and 5FU-resistant (5FU-R-HCT116) human CRC cell lines. Both 8-HQ derivatives were found to inhibit the viability as well as the colony formation ability of HCT116 and 5FU-R-HCT116 cells. Based on the results of both viability and colony formation assay, AS47 was selected as the candidate 8HQ derivative with potent activity. Further analysis revealed AS47 induced senescence in HCT116 cells, as confirmed by positive staining for senescence-associated β-galactosidase and downregulation of cell cycle associated protein cyclin D1 and the upregulation of p21 and p27. In contrast, AS47 induced autophagy in 5FU-R-HCT116 cells, which was confirmed by accumulation of LC3B-II on western blotting. Lastly, AS47 could inhibit the migratory capacity of both cell lines, demonstrated its ability to prevent wound closure in wound healing assay. Our collective data suggest that the novel 8-HQ derivative AS47 is a promising anticancer agent for both 5FU-sensitive and 5FU-resistant CRC and should be studied further.

Keywords: Colorectal Cancer; 5-Fluorouracil-Resistant Colorectal Cancer, 8-Hydroxyquinoline; Senescence; Autophagy