IN VITRO ANTICANCER ACTIVITY OF HYDRAZONE DERIVATIVES IN PANCREATIC CANCER CELLS UNDER NORMOXIA AND HYPOXIA

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Pancreatic adenocarcinoma is one of the deadliest gastrointestinal cancers, accounting for over 90% of pancreatic malignancies and being frequently diagnosed at advanced stages due to late-onset symptoms and the lack of specific biomarkers [1,2]. Hypoxia within the tumor microenvironment plays a crucial role in pancreatic cancer progression by promoting aggressiveness and resistance to therapy [3].

This study aimed to evaluate the cytotoxic activity and selectivity of hydrazone derivatives synthesized at Kaunas University of Technology in human pancreatic cancer cells in vitro under normoxic and hypoxic conditions. The effects of 22 hydrazone derivatives were assessed in MIA PaCa-2 and PANC-1 cell lines using the MTT assay.

Several compounds significantly reduced cell viability, and IT199, IT206, IT207, and IT227 were selected for further analysis. Their EC_{50} values were determined in pancreatic cancer cells and human fibroblasts, with dasatinib used as a reference compound. Compared to dasatinib, the activity of the investigated hydrazone derivatives was 3–146-fold lower, depending on the cell line and oxygen conditions. Under normoxia, IT227 was the most active compound in MIA PaCa-2 (EC_{50}= 1.7 µM) and PANC-1 (EC_{50} = 4.3 µM) cells, whereas under hypoxia, IT207 (EC_{50}= 27.3 µM) and IT199 (EC_{50} = 21.7 µM) showed the highest activity. Under normoxic conditions, the compounds were largely non-selective toward cancer cells (SI ≤ 1), whereas under hypoxia, both potency and selectivity increased. Notably, IT227 demonstrated very high selectivity under hypoxia in both PANC-1 (SI = 15.9) and MIA PaCa-2 (SI = 30.3) cells, while IT207 (SI = 3.1) and IT199 (SI = 2.3) showed moderate hypoxia-associated selectivity.

In conclusion, the hydrazone derivatives exhibited differential cytotoxic effects against pancreatic cancer cell lines, with compounds containing a double hydrazone fragment showing higher activity. The most active compounds (IT199, IT206, IT207, and IT227) were 3–146-fold less potent than dasatinib. IT206, bearing a double hydrazone fragment with methyl and naphthalene substituents, demonstrated increased cytotoxic activity under hypoxic conditions but limited selectivity toward cancer cells (SI ≈ 1). Further studies are required to elucidate the mechanisms of action and therapeutic potential of the investigated compounds

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