ACTIVITY OF NOVEL HYDRAZONE DERIVATIVES IN 3D TUMOR SPHEROIDS AND SINGLE-CELL MIGRATION IN HUMAN BRAIN, TRIPLE-NEGATIVE BREAST, AND SKIN CANCER CELL LINES

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Triple-negative breast cancer accounts for less than 15% of all new cases of breast cancer, but due to its biologically aggressive and highly proliferative nature, it has a poor prognosis [1]. Melanoma is the most aggressive and severe form of skin cancer, which accounts for less than 2% of global cancer diagnoses and is the fifth most common cancer in the US [2]. The global incidence of glioblastoma is considered rare but one of the most aggressive and lethal brain tumors in adults and children, with a poor prognosis and a survival rate of 14-15 months [3]. Targeted drugs have led to major breakthroughs in cancer treatment. Therefore, hydrazone derivatives as potential kinase inhibitors are anticipated to contribute to cancer treatment. Our research aimed to evaluate the anticancer activity of hydrazone derivatives synthesized at Kaunas University of Technology (Lithuania) in human triple-negative breast, melanoma, and glioblastoma cell lines.

In our previous study, we investigated the activity of 22 hydrazone derivatives bearing substituted aromatic and different heterocyclic moieties on triple-negative breast cancer cell line MDA-MB-231, melanoma cell line IGR39, and glioblastoma cell line U87. Compounds IT199, IT207, and IT227 showed selectivity and a significant reduction of cell viability by MTT assay. In this study, we determined the compound effect on cell spheroid growth and viability at 5 μM concentration after 10 days of incubation, compared with anticancer drug dasatinib. We also investigated the impact on cell migration using a single-cell migration method in the presence of 5 μM of the tested compound during 8 hour period.

Compounds showed a lower viability-reducing effect on cancer cell 3D spheroids compared to their activity in a cell monolayer. Compound IT227 significantly reduced spheroid growth by up to 47% and viability by up to 86%, while another compound, IT207, inhibited only spheroid growth by up to 9%. IT199 reduced spheroid cell viability by up to 44% and showed little to no effect on spheroid growth. Dasatinib reduced MDA-MB-231 and U87 cell spheroid viability by approximately 49%, and IGR39 spheroid viability by less than 40%. Based on preliminary results from single-cell migration analysis, the average speed of cell migration was slightly reduced by compound IT227 on MDA-MB-231 cell line, while IT199 and IT207 had no significant effect on migration. A similar effect was observed with IGR39 and U87 cell lines.

In conclusion, compounds IT199, IT207, and IT227 showed generally weaker inhibition of spheroid formation compared to 2D monolayers. Among the tested compounds, IT227 exhibited the most pronounced anticancer activity, significantly reducing both spheroid growth and cell viability, as well as inhibiting cell migration in multiple cancer cell lines, thus indicating the compound as a promising candidate for further investigation.

Keywords: hydrazone; cell viability; tumor spheroids; cell migration

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