Identification and characterization of anticancer potential of a novel small molecule, Mortaparib^{mild}

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Background. The development of new anticancer drugs and treatment modalities form a priority research field. The tumor suppressor protein p53 is frequently mutated or functionally inactivated in a large variety of cancers. Its inactivation by mortalin, a member of the heat shock 70 protein family, has been shown to contribute to carcinogenesis. The small molecule inhibitors of mortalin-p53 interactions have been shown to reactivate p53 yielding apoptosis/growth arrest in cancer cells. Therefore, abrogators of mortalin-p53 interaction have emerged as possible new therapeutic anticancer reagents.
Methods. We performed chemical library screening based on the imaging of mortalin-p53 interaction, leading to the identification of a novel triazole derivative 4-[(4-amino-5-thiophen-2-yl-1,2,4-triazol-3-yl)sulfanylmethyl]-N-(4-methoxyphenyl)-1,3-thiazol-2-amine.
Bioinformatics and experimental analyses were conducted to assess the anti-cancer potency of this molecule, named Mortaparib^{mild}.
Results. Mortaparib^{mild} could bind to mortalin and p53 on their interaction sites. It caused downregulation of mortalin and PARP1 expression. However, a higher dose of Mortaparib^{mild} was required for inducing apoptosis/growth arrest in cancer cells as compared to Mortaparib and Mortaparib^{Plus}, the previously reported molecules with similar properties [*Elwakeel et. al. (2021) Cancers 13:3043; Sari et.al. (2021) Cancers 13:835 and Putri, et.al. (2019) J Exp Clin Cancer Res 38:1*]. It was also effective for triggering apoptosis/growth arrest in p53^{null} cancer cells suggesting its p53-independent activities. Molecular characterization of p53-dependent and independent Mortaparib^{mild} activity and their relevance to cancer therapy will be discussed.
Conclusion. Mortaparib^{mild} is a new small molecule capable of inhibiting mortalin and PARP1 and inducing apoptosis in cancer cells.

Keywords: anticancer molecule, cancer, mortalin-p53 interaction