DESIGN AND INVESTIGATION OF 1,2,4-TRIAZOLE-3-YL THIOACETOHYDRAZIDES BEARINGALDIMINE MOIETY AS BIOLOGICALLY ACTIVE AGENTS

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Tumors are abnormal tissue masses resulting from uncontrolled cell growth, a characteristic of cancer. This widespread condition affects various organs, posing challenges for healthcare [1]. While cytotoxic drugs play a crucial role in cancer treatment, their limitations prompt the search for selective anticancer drugs. This study aims to enhance patient quality of life and revolutionize cancer therapy by developing substances targeting cancer cell vulnerabilities, such as immunotherapeutic strategies and specific drugs. Aldimine derivatives have shown promising efficacy against diverse tumor cells like those found in colon, leukemia, breast, and kidney cancers [2].

This work's objective is to synthesize variously substituted 1,2,4-triazole-3-yl thioacetohydrazides, and evaluate their anticancer properties.

1,2,4-Triazole-5-thione [3] reacted with ethyl chloroacetate in DMF, facilitated by triethylamine at ambient temperature, yielded ethyl 2-[[4-phenyl-5-[(phenylamino)ethyl]-4*H*-1,2,4-triazol-3-yl]thio]acetate in 80% yield. Subsequent reaction with hydrazine monohydrate in propane-2-ol at 60 °C produced 1,2,4-triazol-3-ylthioacetohydrazide in 94% yield. Further reaction of 1,2,4-triazol-3-ylthioacetohydrazide with corresponding aldehydes in methanol under reflux yielded target aldimines in the yield range of 29–98% [4, 5]. Structural confirmation of the novel compounds relied on ^{1}H and ^{13}C NMR, IR, and MS spectroscopy.

Newly synthesized compounds were assessed for anticancer activity against melanoma IGR39, triple-negative breast cancer MDA-MB-231, and pancreatic carcinoma Panc-1 cell lines. Aldimines featuring 2-hydroxybenzene or 2-hydroxy-5-nitrobenzene moieties proved to be most effective against all tested cancer cells among the synthesized 1,2,4-triazole-3-thiol derivatives. Notably, derivatives with pyrrole and 4-(methylthio)benzene moieties, initially less active against IGR39, exhibited increased efficacy against triple-negative breast cancer cells. The substituents in these compounds may play a crucial role in achieving specificity against the typically more resistant MDA-MB-231 cell line. Testing on tumor spheroids simplified 3D cell models with hypoxia in their core, revealed that the most active compounds were 1,2,4-triazol-3-ylthioacetohydrazides containing pyrrole, 2-hydroxybenzene, and 2-hydroxy-5-nitrobenzene fragments.

Overall, from a range of 1,2,4-triazole-3-thiol derivatives, the chosen aldimines emerged as particularly promising anticancer agent-candidates, exhibiting significant cytotoxicity against the various tested cancer cell lines. Due to their encouraging initial results, these newly synthesized compounds have been earmarked for further studies and investigations.

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