DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF ANTICANCER AND NEUROPROTECTIVE DRUGS

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In the present study, four new series of compounds were synthesized and screened for three new molecular targets, namely sirtuin-2 (SIRT2), heat shock protein 70 (Hsp70) and 4-Hydroxy-2-nonenal (HNE), aiming at the discovery of new anticancer or neuroprotective agents.

Five novel histidine-pyridine-histidine (HPH) analogues were synthesized and examined for their antiproliferative activity against human pancreatic adenocarcinoma AsPC-1 cells and two brain cancer cell lines, namely U87 and U251. The results showed that HPH-1Trt derivative was the most active anticancer compound among the new derivatives, but quite less active than HPH-2Trt. *In vitro* DNA cleavage assay revealed that both HPH-2Trt and HPH-1Trt completely disintegrated DNA at 30 μM by generating activated oxygen species.

Hsp70 plays a crucial role in the protein homeostasis (Proteostasis), thus pharmacological activation of Hsp70 is a promising strategy for treatment of many neurodegenerative diseases that caused mainly due to protein misfolding or aggregation such as Alzheimer and Parkinson’s disease. Consequently, these several compounds were scanned whether they induce Hsp70. A new compound showed high Hsp70 induction with low toxicity.

SIRT2 expression in acute myeloid leukemia cells is higher in comparison to normal bone marrow cells, and SIRT2 inhibition by SIRT2 inhibitors causes apoptosis of the acute myeloid leukemia cells. Likewise, high SIRT2 levels is proved to be a biomarker to poor prognosis in acute myeloid leukemia patients. So, a new series of compounds were synthesized and evaluated for their SIRT2 inhibition ability as well as their anticancer activity against three cell lines. A compound was found to be highly potent and selective inhibitor.

HNE is a secondary product generated during lipids peroxidation which produce protein cross-linking and low-density lipoprotein aggregation. Recently, it was proved that intracerebral injection of HNE produces neurodegeneration. Additionally, persistent higher levels of HNE were
detected in the plasma of ischemic stroke patients for at least 6 months after stroke. Then, HNE is considered a new molecular target for treatment of ischemic-induced neuronal death. A new compound showed good activity in HNE-quenching activity.