

Improving therapeutic activity and selectivity is the main goal of developing a strategy for anticancer therapy. Particularly, drugs that are targeted on induction of oxidative stress appears to be an attractive and promising approach, due to genetic differences between normal and cancer cells. Cancer cells have increased level of reactive oxygen species (ROS), associated with oncogenic transformations and glycolytic metabolic adaptations for accelerated metabolism. Thus, the high level of ROS in tumor cells renders them more susceptible to the harmful effects of the increased oxidative stress that is induced by specific drugs. The aforementioned effects promote the generation of ROS and/or debilitates the antioxidant system defenses in a cell. This approach may be an effective strategy to eliminate cells, including colon, pancreatic, and breast cancers, which are characterized by elevated basal ROS levels.

The main purpose of this work was searching novel thiosemicarbazone derivatives (TSC), that exhibited potent antiproliferative activities. Moreover, one of the important aspects a clarification of the molecular mechanism of action for selected highly active TSC in cancer cells and their application in anticancer therapy targeted on induction of oxidative stress. The scope of the this work included analysis of cytotoxicity of novel derivatives on panel of various cancer cell lines, such as colon, breast and brain cancers. For those compounds that appeared active the cytotoxicity against normal human cells was determined. Similar cytotoxicity tests for highly active TSC derivatives in the presence of copper and iron ions were performed against human colon and breast cancers. Evaluation of involvement of selected TSC derivatives in the induction of oxidative stress included determination of level ROS generation, changes in glutathione concentration, and expression of genes involved in antioxidant defense system. In addition, impact of TSC derivatives on the expression of proteins involved in cell cycle arrest and apoptosis induction was determined. These results were also confirmed by flow cytometry. Moreover, selected active TSC derivatives have been tested for their utility in combination therapy with other chemotherapeutics, or photosensitizers in photodynamic therapy (PDT).