

Cancer is one of the leading causes of morbidity and mortality worldwide. The search for novel drug candidates is a priority goal for cancer therapy. Natural products and their derivatives or analogs represent over 50% of all drugs in clinical use and continue to be viewed as major sources for the development of new anticancer drugs showing high biological activity.

A very special group of natural and synthetic products are heterocyclic rings in which a carbonyl group is conjugated with an *exo*-cyclic methylene group. Compounds with such motif are abundant in plants of the *Compositae* family and show promising biological activities, including cytotoxic activity. It is generally accepted that compounds with such structural motif react with cysteine mercapto groups (-SH) of enzymes, other functional proteins and free intracellular glutathione, leading to the formation of covalent adducts which disturb many important processes, leading to cell death. Investigations of anticancer activity of such compounds are currently being performed in many laboratories in the world.

Another important group of compounds that are already used as anticancer drugs are derivatives of uracil, a pyrimidine base present in RNA. Uracil analogs, such as 5-fluorouracil, are antimetabolites, because they block synthesis of thymidine necessary for DNA replication, which also leads to cell death.

Anticancer activity of both mentioned above groups of compounds is based on the fact that quickly dividing cancer cells are much more susceptible to their action than normal cells. Nevertheless, serious side-effects always accompany such therapy and the search for better drug candidates is still going on.

Another major problem facing chemotherapy is the multidrug resistance of cancer cells. Various mechanisms, such as activation of DNA repair pathways, anti-apoptotic events or the efflux of intracellular drugs by the ATP-dependent transmembrane transporters (ATP-binding cassette transporters, ABC transporters) are involved in the multidrug resistance effect. ABC transporters is a large family of proteins that transport various structurally unrelated and potentially dangerous substances out of the cells. These transporters have evolved as a complex cellular defence system, for the recognition and removal of toxic agents entering the cells from their environment. The development of synthetic small molecule compounds or the identification of natural products that block ABC transporter-mediated efflux is an approach used to combat multidrug resistance.

On the other hand, a new promising paradigm for anticancer therapy is combination chemotherapy, involving at least two drugs that work by different mechanisms, thereby decreasing the likelihood that resistant cancer cells will develop.

Recently, a new approach is the possibility of the use of hybrid molecules that combine two structural elements with different mode of action in one molecule. Such strategy may result in increasing activity and selectivity of new drug candidates and combating multidrug resistance.

The goal of this project is to evaluate the anticancer activity of new hybrid molecules, in which an *exo*-cyclic methylene group is introduced into the uracil ring. The tests will be performed on two cancer cell lines (MCF-7 and HL-60), as well as on two normal cell lines (HUVEC and MCF-10A) and should enable to select analogs that are highly cytotoxic and selective for cancer cells. Then, the molecular mechanisms of action of these hybrid compounds will be elucidated.

This is a basic science study with possibly high significance of outcomes. The obtained results will increase our understanding of the molecular mechanisms by which compounds containing uracil skeleton with an *exo*-cyclic methylene group can exert their anticancer activity and combat multidrug resistance.