Anticancer activity of novel tubulin polymerization inhibitors obtained by the chemical modification of colchicine

The successful battle against cancer is one of the most important topics and the biggest challenges that scientists are facing nowadays. According to the World Health Organization (WHO) cancer is a leading cause of death worldwide (around 13% of all deaths).

Over the last few decades, natural products have played a very important role as established cancer chemotherapeutic agents, either in their unmodified (naturally occurring) or synthetically modified forms (about 40% of all used chemotherapeutics). The identification and development of natural compounds and their derivatives have greatly contributed to this progress and many of these compounds are now being used in clinical studies.

Colchicine, as a major alkaloid isolated from *Colchicum autumnale*, is of particular interest as a starting compound. Colchicine shows very strong anticancer effects on a number of cancer cell lines. Biological activity of colchicine is strictly connected with its ability to bind to tubulin, which blocks mitosis and reduces cell motility in different types of cancer cells. Tubulin dynamics is a promising target for new chemotherapeutic agents. Colchicine binding site is one of the most important pockets for potential tubulin polymerization destabilizers. Colchicine binding site inhibitors (CBSI) exert their biological effects by inhibiting tubulin assembly and suppressing microtubule formation. A large number of molecules interacting with the colchicine binding site have been designed and synthesized with significant structural diversity.

The aim of this interdisciplinary project is to synthetize new colchicine derivatives and study their *in vitro* anticancer activity. Synthetic and biological studies will be connected with additional structural studies of the obtained compounds with *in vitro* evaluation of the interaction of colchicine derivatives with tubulin. Additionally, docking simulations will be carried out to estimate how the colchicine derivatives are bound by tubulin at the molecular level and possible binding conformations will be explored to explain mechanism of action of these compounds.

Colchicine derivatives will be evaluated for their *in vitro* antiproliferative effect against several human cancer cell lines. The cytotoxic effect will be also studied on the normal cells in order to estimate the toxicity and selectivity of the studied compounds.

The results of this project should be useful in development of new and effective chemical methods of modification of colchicine. Moreover, these studies should help to find the correlation between structure of colchicine derivatives and their anticancer activity (*structure–activity relationship* - *SAR*). The currently observed scientific interest in microtubule targeting drugs and colchicine binding site inhibitors, especially their unusual anticancer activity, make this project innovative and its scientific results can help in rational drug design in near future.