ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmaceutical Chemistry and Drug Control

Student: Vendula Králová

Supervisor: Prof. PharmDr. Martin Doležal, Ph.D

Specialized supervisor: Kristiina Huttunen, Ph.D

Title of diploma thesis: Prodrug structures to improve the drug delivery of anti-cancer agents

Cancer belongs to the most widespread diseases in the world, and we can expect that it will remain among the deadliest illnesses in the future. For this reason, scientists have put enormous efforts into researching new drugs, which would stop this growing trend. Nowadays, pharmaceutical research is focused mainly on the development of targeted treatment of oncological diseases, which aims at specific structures on the surface or in the core of the tumorous cells. This treatment is limited only to a precisely targeted group of tumors, and it usually leaves healthy cells unharmed. Through clinical studies, many new medications have been developed, and they show high efficiency in the treatment of various types of cancer. However, their success is constrained by drug resistance, which has become a significant obstacle to their use.

The topic of this thesis is the synthesis of new anticancer drugs and their prodrugs. These prodrugs were prepared in such a way that they would increase the cellular uptake of the anticancer drugs, via transporters that are over-expressed in cancer cells.

One of the presented ideas is the preparation of an analogue of verapamil, where I used thieno[2,3-b]pyridine as the linker and the methoxyphenyl group as the necessary part of the potential anti-resistance effect. Its impact, which had already been tested, shows promising results for further drug development. My goal was to prepare a prodrug from this compound, which would be transported selectively via transporter into the cancer cells.

The second part of this thesis examines the nuclear factor-Kβ, which is associated with the development of cancerous growth and autoimmune disease. My plan was to prepare a new inhibitor of IKKβ (subunit of NF-Kβ), and its transporter-targeted prodrug, which would introduce new therapeutic possibilities in the treatment of cancer. For the lack of time, I was not able to finish the preparation of this prodrug. However, the synthesis still continues at the University of Eastern Finland, Kuopio.

The third part of the thesis is focused on Ganciclovir - a potential medication for the gene therapy of the malignant glioma. My plan was to perform the synthesis of new prodrugs for ganciclovir, which could, due to their higher lipophilicity, penetrate to the tumorous cells in higher quantity than the ganciclovir, and thus reach higher concentration and better effect.

The main contribution of this thesis is in the experimental part. However, the field of the synthesis of new anticancer drugs with better pharmacological properties is very extensive, and thus still open to more research.