Synthesis of fluorinated analogues of nucleoside dimers containing a 1,2,3-triazole linker of potential use in molecular biology and medicine

Gliomas are the most frequent tumors occurring in the central nervous system. Despite decades of advancement in both the understanding of their molecular pathogenesis and the clinical protocols available (the combination of surgical treatment with radio- and chemotherapy), it is possible to achieve only a limited therapeutic successes, which is expressed by several months of survival. It is necessary to search for new forms of treatment for these cancers, because none of the current state-of-the-art therapies could be regarded as sufficiently effective. The synthesis of biologically active substances, potential medicines, is an important research area in the medicinal chemistry. Among drugs used in the treatment of cancer the modified nucleosides and nucleotides occupy the leading position.

The presented research project concerns the coupling of naturally occurring nucleosides and modified derivatives using the ”*click*” reaction, i.e. a copper(I) or ruthenium(II)-catalyzed 1,3-dipolar Huisgen cycloaddition. Using the ”*click*” chemistry it is possible to obtain nucleoside conjugates which can exhibit interesting biological activity, so it is planned to carry out the synthesis of analogues of dimers of natural nucleosides and especially their fluorinated derivatives of known pharmacological activity (e.g. floxuridine, gemcitabine, clofarabine). A 1,2,3-triazole subunit, which does not occur in nature and replaces the phosphodiester bond, is formed as a result of the catalyzed Huisgen reaction. In addition, it constitutes an additional pharmacophore with attractive properties beeing resistant to hydrolysis and other reactions at physiological pH, it exhibits biological activity (i.e. antibacterial, antitumor and antiviral properties) and can be considered as a rigid analogue of amide linkage. Such modifications of internucleotide linkages are also designed to increase the hybridization binding affinity toward native DNA/RNA, to enhance resistance to nucleases, to improve ability to penetrate cell membranes, and above all, to allow for the transport of masked nucleoside drugs across cell membranes. The innovation of this project lies in the possibility in exploitation of the ”*click*” approach in nucleoside chemistry, which allows for additional modifications of nucleosides and which rapidly developes the fluorinated nucleoside chemistry, both in the synthesis and the use of. Presented examples comply with the current concept of designing new drugs that are sufficiently lipophilic, able to penetrate cell membranes and cross the blood/brain barrier, but also contain more than one active fragment. Thus, their potential use as nucleoside drugs, which are inhibitors of enzymes involved in the DNA biosynthesis or terminators of the biosynthesis due to the lack of the 3'-hydroxyl group.

Hereby, the presented project describes and provides synthetic protocols with biological assay of novel molecular tools for cancer treatment.