WYDZIAŁ CHEMICZNY
KATEDRA CHEMII ORGANICZNEJ,
BIOORGANICZNEJ I BIOTECHNOLOGII

mgr inż. Monika Domińska

ROZPRAWA DOKTORSKA

Glikokoniugacja *N*-heterocyklicznych związków biologicznie aktywnych oraz ocena ich aktywności przeciwnowotworowej

Przewodnik po monotematycznym cyklu publikacji

Promotor: dr hab. inż. Gabriela Pastuch-Gawołek, prof. PŚ

Gliwice 2023

SUMMARY OF THE DOCTORAL DISSERTATION

Glycoconjugation of *N*-heterocyclic biologically active compounds
and assessment of their anticancer activity

mgr inż. Monika Domińska

Supervisor: dr hab. inż. Gabriela Pastuch-Gawołek, prof. PŚ

Glycoconjugation of biologically active compounds consists in attaching a sugar fragment to a biologically active molecule by forming a covalent bond. This treatment is aimed at directing the molecule to interact with GLUT membrane proteins, which are responsible for the transport of sugars into intracellular spaces. Glycoconjugation improves the pharmacokinetic properties of potential anticancer drugs, especially their selectivity, as sugar transporters are overexpressed in rapidly proliferating cancer cells.

The research presented in the doctoral dissertation concerns the synthesis and assessment of the biological activity of glycoconjugates of *N*-heterocyclic biologically active compounds. The structure of the designed glycoconjugates consists of three basic building blocks: a sugar unit, a biologically active compound (8-hydroxyquinoline or methotrexate), and a various types of linkers containing a 1,2,3-triazole ring. In the synthetic part of the work, appropriately designed building blocks were connected together as a result of a copper(I) catalyzed reaction of 1,3-dipolar azido-alkyl cycloaddition belonging to the innovative *click chemistry* concept. The structures of all obtained compounds were confirmed by spectroscopic methods (NMR and HRMS). The biological activity of the obtained glycoconjugates was evaluated in terms of their ability to inhibit the proliferation of selected cancer cell lines and healthy cells (MTT cytotoxicity test), as well as the ability to inhibit the model enzyme from the group of transferases on the example of β-1,4-galactosyltransferase I, which overexpression is associated with the growth of some types of cancer. For the most active compounds, additional studies were conducted to approximate the possible mechanism of their action.

As part of the work, the influence of structural modifications of 8-hydroxyquinoline derivatives on their biological activity was determined. Their activity depends on the type of sugar attached, the position by which the sugar is attached, the presence of protecting groups in the sugar moiety, and the presence of a linker between the sugar and the quinoline aglycone. Sugar improves the bioavailability of the preparation and its solubility, while the presence of the 1,2,3-triazole fragment in the linker structure improves the ability to chelate divalent metal ions necessary for the growth of cancer cells. Glycoconjugates formed using the C-6 position of D-glucose have been shown to be more cytotoxic and selective compared to analogous glycoconjugates formed by the anomeric position. Such designed glycoconjugates show increased affinity for GLUT, thanks to which they can be transported directly to cancer cells, avoiding systemic toxicity. An important aspect of the next research was the use of polymeric nanocarriers for the targeted transport of selected glycoconjugates, which were released as a result of chemical degradation of the carrier in the reduced pH of the cancer microenvironment. In the following part of the paper, research on the sugar derivative of methotrexate was presented. This glycoconjugate is selectively taken up by a range of cancer cells and inhibits their growth in the *in vitro* environment. Its activity has also been confirmed by *in vivo* toxicity studies in a mouse model of breast cancer.