Politechnika Śląska

WYDZIAŁ CHEMICZNY
KATEDRA CHEMII ORGANICZNEJ, BIOORGANICZNEJ I BIOTECHNOLOGII

ROZPRAWA DOKTORSKA

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Przewodnik po monotematycznym cyklu publikacji pt.

Synteza i właściwości biologiczne modyfikowanych interkalatorów i makrocykli

Gliwice 2023

ABSTRACT OF THE DOCTORAL THESIS

"Synthesis and biological properties of modified intercalators and macrocycles"

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Chemical structure modifications of organic compounds are one of the most effective strategies for creating new compounds with biological activity. This strategy often involves introducing small modifications to the investigated molecule and analyzing their impact on various biological properties, such as antiproliferative activity, selectivity towards cancer cells, changes in cellular uptake, and intracellular localization. The results of such studies are crucial for the development of new and more effective anticancer drugs, gene therapies, and imaging methods for disease detection.

The research presented in this doctoral thesis focuses on the synthesis and evaluation of selected physicochemical and biological properties of small molecule derivatives of 1,8-naphthalimide, thioxanthone, cyclen, and 1-aza-12-crown-4, as well as their conjugates with oligonucleotides. All obtained derivatives are characterized by the introduction of alkyl linkers terminated with an azide or propargyl group, which were utilized in the click chemistry strategy enabling the connection of building blocks and biomolecules through copper(I)-catalyzed 1,3-dipolar azido-alkyne cycloaddition reaction. The structures and physicochemical properties of the obtained compounds were characterized using various techniques, including HRMS spectrometry, NMR, IR, UV-Vis and emission spectroscopy. The basic biological properties of the obtained compounds were also assessed, including their antiproliferative activity against cancer and normal cell lines (considering the photodynamic effect), as well as their ability to inhibit topoisomerase II, induce DNA damage, interact with DNA, and stabilize the double helix.

The results of the conducted research provided an understanding of the impact of specific chemical modifications on the biological activity of the investigated compound groups. It was determined which modifications contribute to an increase, decrease, or have no significant effect on antiproliferative activity. Furthermore, the effectiveness of conjugating derivatives of 1,8-naphthalimide and thioxanthone with appropriate macrocycles as a strategy to modify their biological properties, particularly cellular uptake, was demonstrated. Improved cellular uptake was observed in the case of conjugation with 1-aza-12-crown-4, while conjugation with cyclen led to a decrease in cellular uptake, affecting the antiproliferative activity of the obtained conjugates. The studies also allowed for determining the influence of conjugation on the complementarity and stabilization of the DNA double helix. The results of this doctoral thesis can find practical applications in the field of medicinal chemistry for the design of new biologically active substances with potential applications in anticancer and genetic therapies.