Abstract

Synthesis of New Steroid Conjugates with Potential Antimicrobial Properties

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This doctoral dissertation focuses on the design, synthesis, and spectroscopic characterization of new steroid conjugates obtained through „click" reactions. The aim of the research was to develop and investigate the biological properties of bile acid and sterol derivatives linked *via* a 1,2,3-triazole ring, representing potential antimicrobial compounds. The thesis consists of a literature section, discussing the theoretical background and current state of research on chemical modifications of steroids, and an experimental section devoted to the synthesis and analysis of new steroid conjugates.

The literature part presents the structural and stereochemical characteristics of steroids and their diverse biological functions. The biological significance of sterols and bile acids is discussed in detail, particularly their roles in lipid metabolism and cell membrane function. Various directions of chemical modification of the steroid framework are reviewed, including transformations involving individual rings of the cyclopentanoperhydrophenanthrene system and the use of protecting groups in their functionalization. Special attention is given to „click" chemistry and the Huisgen cycloaddition reaction, which due to their simplicity, high efficiency, and selectivity, enable the formation of stable conjugates containing a 1,2,3-triazole ring. The importance of such linkages in the design of bio-conjugates with therapeutic potential is analyzed, along with examples of known steroid conjugates.

The experimental section describes the development of a synthetic strategy and structural analysis of new steroid conjugates, including twenty-seven mixed and dimeric derivatives. The compounds were obtained via the Cu(I)-catalyzed Huisgen reaction, leading to the formation of triazole linkages. The structures of the resulting products were confirmed by NMR, FT-IR, and ESI-MS spectroscopy. Quantum-mechanical calculations (PM5), as well as *in silico* studies using PASS prediction and molecular docking, allowed for the evaluation of their stability and predicted biological properties.

Within the scope of this work, a series of conjugates with diverse structures and properties was synthesized. The triazole-linked steroid derivatives exhibited reduced hemolytic activity compared to their parent substrates, while selected compounds demonstrated high affinity for HMG–CoA reductase, indicating potential as cholesterol biosynthesis inhibitors. Dimeric bile acid conjugates displayed greater energetic stability and lower cytotoxicity, and docking studies confirmed their ability to interact with DNA gyrase and Lipid II transglycosylase. Additionally, a series of formylated bile acid and sterol

conjugates was developed, several of which exhibited notable antifungal activity against *Fusarium culmorum* and *Botrytis cinerea*. Molecular docking analysis revealed their affinity for the TRI5 enzyme, which participates in mycotoxin biosynthesis.

The obtained results demonstrate that the conjugation of steroidal fragments through a triazole bridge enables the formation of stable and bioactive structures with a broad spectrum of predicted biological activities, including antibacterial, antifungal, hypolipidemic, and anticancer effects. The conducted studies provided valuable insights into structure–activity relationships within steroid derivatives, representing a meaningful contribution to the development of bioorganic and medicinal chemistry.

This work significantly advances the methods for the synthesis and design of steroid conjugates, confirming that the application of „click" chemistry is an efficient tool for obtaining new compounds with controlled structures and potential therapeutic relevance.