Abstract

This bachelor thesis explores various methods for neurosteroid prodrugs synthesis. The thesis aims to optimize the physicochemical and metabolic properties of neurosteroids to facilitate their transport across membranes, in particular the permeability of the blood-brain barrier. Neurosteroids are endogenous compounds that are synthesized in the brain from cholesterol. Their characteristic functional group is the hydroxyl substituent at the C-3 position. This substituent is a significant structural feature for biological activity (e.g., allosteric modulation of γ-aminobutyric acid receptors). However, the C-3 hydroxyl group can be easily metabolized. Moreover, the free hydroxyl group in the neurosteroid molecule increases its hydrophilicity which can limit the transport across the membrane. Therefore, within this thesis: 1) neurosteroids with different skeletons and 2) analogs of neurosteroids with ester group in C-3 position, will be prepared. The C-3 substituents have been selected based on literature research identifying ester prodrugs targeting improved blood-brain barrier permeability. For newly prepared substances, their metabolic and physicochemical properties, such as solubility, permeability, and metabolic stability will be determined within the collaboration at the Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences.

Key words*: neurosteroids, prodrugs, permeability, stability*