Unnatural serine derivatives as precursors of morpholine and piperazine heterocyclic pharmacophores bearing a quaternary stereogenic center

The main goal of this proposal is to develop an approach for the preparation of α-alkyl- and α-aryl-substituted serine derivatives bearing a quaternary stereogenic center which will serve as precursors of selected heterocyclic scaffolds. Particularly, the proposal is focused on morpholine, thiomorpholine, and piperazine scaffolds, which have been classified as privileged structural motifs in drug discovery and continue to have increasing appearance in life-saving medication pharmacophores. The current research proposal is concerned with three challenges: 1) the development of an efficient method for the preparation of non-racemic allyl alcohols bearing an additional hydroxymethyl group in high enantio- and *E*/*Z* selectivity, 2) their transformation to the corresponding allylic carbamates and studies on their rearrangement into hydroxy-allylamines with a quaternary stereogenic center, and 3) the development of a cyclization strategy for the resulting allylamines and derivatives (e.g. amino esters, amino alcohols, or amino nitriles) into selected heterocyclic scaffolds (e.g. morpholines, thiomorpholines, and piperazines).

The proposed synthetic pathway for the conversion of allyl alcohols into quaternary allylamines will be based on allyl cyanate-to-isocyanate rearrangement and result in the generation of allyl isocyanate intermediates. Advantageously, these compounds can be directly functionalized by the reaction with various nucleophiles. An essential advantage of such a strategy is its intramolecular course, which is crucial for the preparation of sterically demanding allylamines, which in many cases cannot be achieved efficiently by intermolecular processes. Moreover, in comparison with other sigmatropic rearrangements, this reaction proceeds under mild conditions and does not require a transition metal catalyst.

The compounds obtained during the project are not only important building blocks in organic synthesis, but also constitute structural elements of biologically active substances. Therefore, the developed methodology could be used in the pharmaceutical or chemical industry for the synthesis of essential compounds with biological or pharmacological activity in the future.