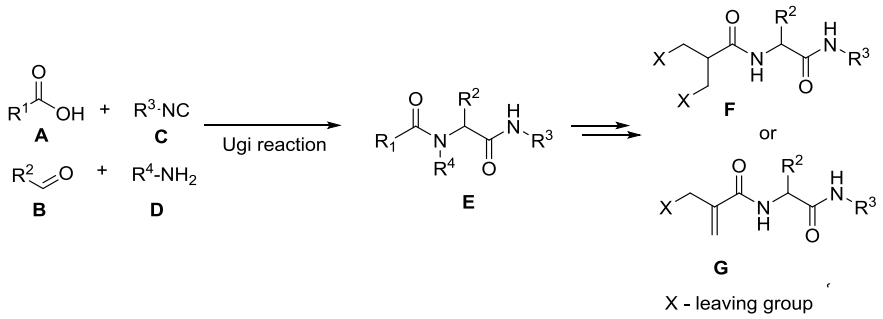
The synthesis of the novel thioredoxin – thioredoxin reductase system inhibitors

Abstract

Author: *Szymon Kłossowski*

Promoter: *Prof. Ryszard Ostaszewski*

The aim of the presented studies was the synthesis of a novel inhibitors of the thioredoxin – thioredoxin reductase system. Considering the possible mechanism of the inhibition, the peptidomimetics containing an electrophilic fragment were designed as a leading structure. The multicomponent Ugi reaction with acid **A**, aldehyde **B**, isocyanide **C** and amine **D** was proposed as a key step for the synthesis of peptidomimetic scaffolds. The products of the Ugi reaction **E** were then modified towards peptidomimetics **F** and **G** possessing various electrophilic fragments.



In the thesis, the studies on the synthesis of various peptidomimetics with electrophilic fragment were presented and results of their biological activity were shown. This studies lead to a development of the *β*-acyloxyacrylamides **G** (X = ArCOO-), which are efficient inhibitors towards thioredoxin – thioredoxin reductase system. For the synthesis of non-racemic peptidomimetics, a synthetic strategy based on a novel chiral auxiliary for Ugi reaction was proposed. Applying the enzymatic kinetic resolution of amines, the methodology for the synthesis optically pure (*R*) and (*S*)-*α*–2,4-(dimethoxyphenyl)ethylamine was developed. The (*S*) enantiomer was then used in diastereoselective Ugi reaction (amine **D**) for the synthesis of non-racemic inhibitors **G.**

Furthermore, in order to perform structure – activity relationship studies, the series of the *β*-acyloxyacrylamides **G** was synthesized using the developed methodology, what consequently allowed the optimization of the lead compound.

In addition, the novel enzymatic multicomponent reaction was developed. The reaction catalyze by the lipase from *Candida antarctica* can be applied for one pot synthesis of α-aminoamides from aldehyde, amine and ethyl isocyanoacetate. The presented reaction is the first example of the Ugi reaction catalyzed by an enzyme.