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Biocatalytic Synthesis of Pharmaceutically Relevant Amides and Amino Acids

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Biocatalytic Synthesis

of

*Pharmaceutically Relevant Amides and
Amino Acids*

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The research described on this thesis was carried out in the Department of Chemical and Pharmaceutical Biology (Groningen Research Institute of Pharmacy, University of Groningen, The Netherlands) and was financially support by Indonesia Endowment Fund by Education (LPDP).

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Biocatalytic Synthesis of Pharmaceutically Relevant Amides and Amino Acids

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Be patient

Some things
take times.

Paranymphs

Ali Syaria'ti

Michele Crotti

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AIM AND OUTLINE

Biocatalysis is the use of native or redesigned natural catalysts (enzymes or whole cells) to accelerate chemical reactions. Over the past decades, enzymes have been used as powerful tools for the synthesis of optically pure compounds, including pharmaceuticals, food additives, and versatile chiral synthons. Enzymes have superior properties compared to conventional chemical catalysts, often showing high catalytic efficiency and high stereo-, regio-, and chemo-selectivity, which are very desirable features for chemical synthesis. Other advantages such as biodegradability and the ability to work under relatively mild reaction conditions are also preferred properties, leading to the increased use of enzymes as catalysts in various industrial processes, ranging from chemical and pharmaceutical synthesis to food processing.

The work described in this thesis aimed to exploit the biocatalytic potential of ethylenediamine-*N,N'*-disuccinic acid lyases (EDDS lyase) and pantothenate synthetase (PS) for the preparation of amino acid and amide precursors to important biologically active molecules. We also intended to design artificial multienzymatic cascades for the selective and step-economic synthesis of vitamin B₅ and its derivatives, starting from simple building blocks, by combining the PS enzyme with other enzymes, such as 3-methylaspartate ammonia lyase (MAL), aspartate α -decarboxylase (ADC), β -methylaspartate- α -decarboxylase (CrpG) and glutamate decarboxylase (GAD), in one pot.

In **Chapter 1**, we review recent studies on the application of native and engineered C-N lyases in enantioselective synthesis of important synthetic precursors to pharmaceuticals and food additives. In addition, biochemical, structural, and mechanistic features of MAL and EDDS lyase are briefly discussed.

In the work described in **Chapter 2**, we demonstrate the biocatalytic application of EDDS lyase for the enantioselective synthesis of *N*-arylalkyl-substituted L-aspartic acids. The enzyme was found capable of catalyzing the addition of arylalkyl amines to fumarate, achieving good conversions and producing highly enantiopure products with >99% e.e.

In the study reported in **Chapter 3**, we combined the C-N lyase MAL with an appropriate decarboxylase (ADC, CrpG, and GAD) and pantothenate synthetase (PS) in a one-pot system to prepare a precursor for a promising antimicrobial compound against *Plasmodium falciparum* and multidrug-resistant *Staphylococcus aureus*. This

novel modular enzymatic cascade synthesis approach could be further tailored and used for the biocatalytic production of diverse vitamin B₅ derivatives by modifying the pantoyl or β -alanine moiety.

In the study described in **Chapter 4**, we investigated the biocatalytic potential of the PS enzyme for the synthesis of pharmaceutically-relevant amides, including known vitamin B₅ antimetabolites. We show that besides the natural amine substrate β -alanine, the enzyme accepts a wide range of structurally diverse amines for coupling to the native carboxylic acid substrate (*R*)-pantoic acid to give amide products with up to >99% conversion. This enzymatic synthesis strategy may prove to be useful in the quest for new antimicrobials that target coenzyme A biosynthesis and utilisation.