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New applications of dynamic combinatorial chemistry to medicinal chemistry

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DOI:
[10.33612/diss.102259269](https://doi.org/10.33612/diss.102259269)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Hartman, A. (2019). *New applications of dynamic combinatorial chemistry to medicinal chemistry*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen.
<https://doi.org/10.33612/diss.102259269>

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New applications of dynamic combinatorial chemistry to medicinal chemistry

Alwin Mathijs Hartman

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Institut für Pharmazeutische Forschung Saarland

New applications of dynamic combinatorial chemistry to medicinal chemistry

Alwin Mathijs Hartman

Ph.D. Thesis

University of Groningen, The Netherlands

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The research described in this thesis was carried out at the Stratingh Institute for Chemistry, University of Groningen, The Netherlands, at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Germany and at the Faculty of Natural Sciences and Technology of Saarland University, Germany.

In compliance with the requirements of the Graduate School of Science and Engineering of the Faculty of Science and Engineering, University of Groningen, The Netherlands, as well as with requirements of the Faculty of Natural Sciences and Technology of Saarland University.

This work was financially supported by the University of Groningen and the Netherlands Organization for Scientific Research (VIDI grant: 723.014.008).

Netherlands Organisation for Scientific Research

Cover was designed by Lysette Hartman.

Printing of this thesis was generously supported by the University of Groningen and the Graduate School of Science and Engineering.

Printed by Ipskamp Drukkers BV, Enschede, The Netherlands.

ISBN: 978-94-034-1970-1 (printed)
978-94-034-1969-5 (digital)

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New applications of dynamic combinatorial chemistry to medicinal chemistry

PhD thesis

to obtain the degree of PhD of the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.

and

to obtain the degree of PhD at the
Faculty of Natural Sciences and Technology of
Saarland University

Double PhD degree

This thesis will be defended in public on
Thursday 28 November 2019 at 11.00 hours

by

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***“Luck is what happens when preparation meets
opportunity.”***

Seneca, roman philosopher 5 b.c.

***“Man ist nie fertig mit der Wissenschaft, höchstens ist
die Wissenschaft fertig mit einem.”***

Martin Empting

Aan mijn ouders

Summary

Applying dynamic combinatorial chemistry (DCC) to medicinal chemistry projects can be a helpful strategy for finding starting points in the drug-discovery process. As relevant drug target, 14-3-3 proteins play a role in several diseases and many biological processes. Proteins of this family engage in protein-protein interactions (PPIs), and can up-or down-regulate their binding partner's activity. Another family of relevant targets are glucansucrases, which are important enzymes in the initiation and development of cariogenic dental biofilms, commonly known as dental plaque. In the last two chapters, endothiapepsin was used for protein-templated DCC (ptDCC). Endothiapepsin belongs to the family of the aspartic proteases, which are involved in for example the maturation of the HIV virus particle.

Throughout this thesis, we focus on applying DCC to various projects. The main achievements are: 1) the description of the in-house protocol of DCC, in which aspects like solubility of building blocks and products, protein stability and more need to be taken in to account, 2) the application of acylhydrazide-based DCC to two targets, a (PPI)-target and a glucansucrase, 3) the identification of small-molecules, which stabilise PPIs of 14-3-3/ synaptopodin, 4) expanding the reaction toolbox of ptDCC by two additional reactions: nitron and thiazolidine formation.

Zusammenfassung

Die Verwendung dynamisch kombinatorischer Chemie (DCC) in medizinisch-chemischen Projekten kann eine sehr hilfreiche Strategie sein, um Anknüpfungspunkte für die Wirkstoffentdeckung zu finden. 14-3-3 Proteine spielen eine Rolle in verschiedenen Krankheiten und vielen biologischen Prozessen. Proteine dieser Familie beteiligen sich an Protein-Protein-Interaktionen (PPIs) und können die Aktivität der Bindungspartner sowohl hoch- als auch herabregulieren. Eine andere Familie relevanter Targets sind die Glukansucrasen, welche wichtige Enzyme in der Initiierung und Entwicklung von kariogenen dentalen Biofilmen, allgemein bekannt als Plaque, sind. In den letzten beiden Kapiteln wurde Endothiapepsin für Protein-vermittelte DCC (ptDCC) verwendet. Endothiapepsin gehört zur Familie der Aspartylproteasen, welche zum Beispiel an der Reifung des HIV Viruspartikels beteiligt sind.

Im Verlauf dieser Arbeit fokussieren wir uns auf die Anwendung von DCC in verschiedenen Projekten. Die Hauptleistungen sind: 1) die Beschreibung des hausinternen DCC-Protokolls, in welchem Aspekte wie Löslichkeit von Bausteinen und Produkten, Proteinstabilität und weiteres wichtige zu beachten sind, 2) die Anwendung von Acylhydrazon-basierter DCC auf zwei Targets, eine Glukansucrase und ein PPI-Target, 3) die Identifikation kleiner Moleküle, die PPIs von 14-3-3/ Synaptopodin stabilisieren, 4) die Erweiterung des Reaktionsspielraums der ptDCC durch zwei zusätzliche Reaktionen: Nitron- und Thiazolidinbildung.

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