Design Strategies for New Drugs Targeting Multicomponent Systems

Focusing on Class II MHC Proteins and Acetylcholinesterase

Cecilia Lindgren

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar vid Kemiska Institutionen, Umeå Universitet, KBC-huset, KB.E3.03, fredagen den 8 september, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Professor, Antti Poso,
University of Eastern Finland, School of Pharmacy, Kuopio, Finland

Kemiska institutionen/Department of Chemistry
Umeå universitet/Umeå University
Umeå 2017

Organization
Umeå University
Department of Chemistry

Document type
Doctoral thesis

Date of publication
18 August 2017

Author
Cecilia Lindgren

Title
Design Strategies for New Drugs Targeting Multicomponent Systems — Focusing on Class II MHC Proteins and Acetylcholinesterase

Abstract
The field of medicinal chemistry is constantly evolving. Aided by advances within techniques as well as knowledge of biological systems, increasingly complex targets and drugs can be considered. This thesis includes two projects focusing on the design of drugs targeting multicomponent systems, referring to systems for which multiple components must be considered during the drug design process.

In the first project, the long-term goal is to develop a vaccine against the autoimmune disease rheumatoid arthritis (RA). The cause of RA is unknown, but it is genetically linked to expression of class II MHC proteins that present antigens to T-cell receptors (TCRs), responsible for initiating an immune response. A glycopeptide fragment, CII259–273, from type II collagen has shown promising results as a vaccine against arthritis resembling RA in mice. CII259–273 binds to the class II MHC protein followed by presentation to the TCR, forming a multicomponent system.

We have used molecular dynamics (MD) simulations to study the effect that modifications of CII259–273 have on the multicomponent system. Non-native amino acids and amide bond isosteres have been introduced. This has demonstrated the importance of retaining the backbone conformation of CII259–273, as well as the hydrogen bonds formed to the backbone. The ability to introduce such modifications would be of value to affect the potency towards the MHC protein, and prevent degradation of the glycopeptide. The studies have revealed a multicomponent system that is highly sensitive to even small modifications that can affect the dynamics of the entire complex.

In the second project, the long-term goal is to develop a broad-spectrum antidote against nerve agents. Nerve agents are extremely toxic compounds that act by covalently inhibiting the enzyme acetylcholinesterase (AChE), which is essential for termination of nerve signalling. A major limitation of current antidotes is that their efficiency is dependent on the type of nerve agent. A broad-spectrum antidote must be able to bind to the multicomponent system consisting of AChE covalently inhibited by different nerve agents. It will then act by performing a nucleophilic attack on the nerve agent adduct, thus breaking the covalent bond to AChE.

We have used statistical molecular design (SMD) and quantitative structure-activity relationship (QSAR) modelling to identify a fragment with a potency for AChE inhibited by different nerve agents. A nucleophilic component able to restore the enzyme to the active form was thereafter introduced. This resulted in a functional reactivator, efficient for multiple nerve agents. Furthermore, the mechanism of reactivation has been investigated through structural studies, enabled by a combination of X-ray crystallography and molecular modelling. A high flexibility of the reactivator, as well as the ability to bind to AChE in multiple conformations, are defined as important properties for a broad-spectrum antidote.

Keywords
Acetylcholinesterase, class II MHC protein, drug design, molecular dynamics simulation, multicomponent system, nerve agent, oxime, (quantitative) structure-activity relationship, reactivator, rheumatoid arthritis, statistical molecular design, T-cell receptor.

Language
English

ISBN
978-91-7601-737-1

Number of pages
92 + 4 papers