The Solution Conformations of Macrocycles

Applications in the exploration of weak interactions and in drug development

EMMA DANELIUS

GÖTEBORGS UNIVERSITET

Institutionen för kemi och molekylärbiologi
Naturvetenskapliga fakulteten
2017

AKADEMISK AVHANDLING

för filosofie doktorsexamen i Naturvetenskap, inriktning kemi, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredag den 20 oktober 2017 kl. 09:15 i KC, institutionen för kemi och molekylärbiologi, Kemigården 4, Göteborg. Fakultetsopponent är Professor Alethea B. Tabor, UCL, London, UK. Avhandlingen kommer att försvaras på engelska.

ISBN: 978-91-629-0274-2 (Print)
ISBN: 978-91-629-0275-9 (PDF)
Tillgänglig via http://hdl.handle.net/2077/52335

Abstract

Understanding the solution conformation and dynamics of molecules with biological relevance, as well as the impact of their conformation stabilizing weak interactions, is for example important for drug design. Macrocycles have attractive pharmaceutical properties, and are of special interest as drug leads for targets with large, flat and featureless binding sites like protein-protein interfaces. As they are usually flexible and adopt a variety of solution geometries, the description of their ensembles is of high value. Most macrocyclic drugs are peptides or macrolides. Peptides, and in particular β-hairpin peptides, are suitable model systems for studying weak interactions. Due to their resemblance to proteins, studying peptides by solution state experiments provides knowledge gained in a biologically relevant environment. In this thesis, nuclear magnetic resonance (NMR) spectroscopy has been used for investigation of the solution ensembles of various macrocycles. Using a cyclic β-hairpin model system and NMR analysis of molecular flexibility in solution (NAMFIS), a single interstrand hydrogen bond was shown to provide significant stabilization of the folded conformation. In addition, it was shown that a chlorine-centered halogen bond stabilizes the β-hairpin to a comparable extent. Further, the solution ensembles of four cyclic β-hairpin inhibitors of the MDM2/p53 protein-protein interaction were described, and a higher conformational flexibility was found to correlate with an increased inhibitory activity. In contrast, for cyclic azapeptide inhibitors of the cluster of differentiation 36 (CD36) receptor, higher flexibility correlated to decreased inhibitory activity. An increased population of one of the conformational families in solution was found to be beneficial for the CD36 inhibitory activity. Lastly, roxithromycin, a macrolide antibacterial agent, was described to convert from a more open conformation in polar media to a more closed and less flexible conformation in non-polar media. This thesis demonstrates that macrocycles are applicable as model systems for the study of weak interaction forces, which have a large influence on their conformational behavior. Furthermore, the obtained results show that the conformational stability of macrocycles vastly influences their bioactivity.

Keywords: Macrocycles, cyclic peptides, NMR, solution conformational analysis, NAMFIS, β-hairpin, weak interactions, halogen bonding, protein-protein interaction, bioactive conformation, macrolides, cell permeable conformation.