Chiral recognition mechanism of cellobiohydrolase Cel7A for ligands based on the ?-blocker propranolol. The effect of explicit water molecules on binding and selectivities.

Alexandra Fagerström[1], Mats Sandgren[2], Roland Isaksson[3], Tommy Liljefors[4], Jerry Ståhlberg[5], and Ulf Berg[1]

[1]Lund University
[2]Swedish University of Agricultural Sciences
[3]Linnaeus University
[4]University of Copenhagen
[5]Swedish University of Agricultural Sciences Faculty of Natural Resources and Agricultural Sciences

January 10, 2023

Abstract

: Proteins are useful chiral selectors. In order to understand the recognition mechanism and the chiral discrimination, binding of the (R)- and (S)-enantiomers of a series of designed amino alcohol inhibitors based on propranolol to cellobiohydrolase Cel7A (Trichoderma reesei) has been studied more closely. X-ray crystal structures were determined of the protein complex with the (R)- and (S)-enantiomers of the strongest binding propranolol analog. The combination of the structural data, thermodynamic data from capillary electrophoresis and microcalorimetry experiments and computational modeling give a clearer insight into the origin of the enantioselectivity and its opposite thermodynamic signature. The new crystal structures were used in computational molecular flexible dockings of the propranolol analogues using the program Glide. The results indicated that several water molecules in the active site were essential for the docking of the (R)-enantiomers, but not for the (S)-enantiomers. The results are discussed in relation to the enantiomeric discrimination of the enzyme. Both dissociation constants (Kd-values) and thermodynamical data are included to show the effects of the structural modifications in the ligand on enthalpy and entropy in relation to the enantioselectivity.

Hosted file

`MS_subm-ulf.docx` available at https://authorea.com/users/574846/articles/618390-chiral-recognition-mechanism-of-cellobiohydrolase-cel7a-for-ligands-based-on-the-blocker-propranolol-the-effect-of-explicit-water-molecules-on-binding-and-selectivities