Popular Summary

When researchers design new drug molecules, it is easy to imagine binding as a lock-and-key problem: the drug molecule should fit as well as possible into the binding site of the protein. However, reality is much more complex. Proteins are not rigid structures, they are in constant motion, and these motions can influence how favorably a molecule can bind.

In this thesis, galectin-3C was studied. Galectin-3C is part of the protein galectin-3, which has been proven to be involved in cancer and cardiovascular diseases. The protein has been investigated as a possible target for future drug development. The work focused on two small "keys", also known as ligands, denoted as FS435 and FS471. These ligands are structurally similar but differ in how they interact with galectin-3C.

One of the ligands (FS435) is more preorganized. This means that it already resembles the shape it adopts when bound to the protein and therefore does not need to rearrange as much during binding. The other ligand, FS471, is more open and flexible and can adopt several conformations. A common idea in ligand design is that a preorganized ligand should bind more favorably than a flexible, because the former ligand does not lose as much conformational freedom as the latter upon binding. However, previous data suggests the opposite trend for these two ligands. One possible explanation is that the preorganized ligand causes the protein to be more rigid in the bound state, whereas the flexible ligand may enable the protein to maintain its flexibility.

To investigate this paradox, nuclear magnetic resonance (NMR) was used. NMR can examine the movement of molecules. In this thesis, NMR relaxation experiments were used to examine the motions of the backbone of galectin-3C when bound to FS435 and FS471.

The observable differences between the two ligands were observed in how the two ligands affected the local dynamics of the amino acid residues in the binding site differently. These differences suggest that Galectin-3C retains more backbone motional freedom when bound to the flexible ligand FS471 than when bound to the preorganized ligand FS435.

This means that a more preorganized ligand is not necessarily more favorable for the entire binding process, because FS435 may lose less flexibility itself, it appears to restrict the protein backbone more than FS471.

In conclusion, protein motions can help to explain why two similar structural molecules exhibit different binding properties. For drug design, this means that researchers should not only ask how well a molecule fits into a protein structure, but also how the molecule affects the movements of the protein.