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Galectin-3: studying role of fluorines in the protein-ligand interaction to achieve high affinity and selectivity

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Galectin-3 belongs to the galectin family that recognizes carbohydrates. It has a highly conserved carbohydrate recognition domain (CRD) of 130 residues, which is responsible for binding to beta-galactosides. Galectin-3 has been shown to be involved in cancer, angiogenesis and stroke. Its involvement in these important diseases makes it a wonderful drug target. Our previous work[1] showed the mode of binding of lactose and role of structured water molecules in carbohydrate binding site. These results prompted us to explore the molecular recognition and role of water molecules in designing high affinity inhibitors. Natural ligands of galectin-3 almost always have a galactose residue.

Selective small molecule galectin-3 inhibitors are valuable both as research tools to study protein-ligand interactions and as lead compounds in drug discovery. These compounds usually involve galactose-based derivatives, 1- and 3-substitutions of galactose. We have solved numerous protein-ligand crystal structures to study the effect of various substitutions. Fluorines are known to have diverse effects on physicochemical and conformational properties of ligands. Introduction of Fluorines at key positions in ligands has been proven to be promising strategy in lead optimization. Position and amount of fluorination has strong effect on the protein ligand interactions. Fluorines enhance ligand affinity by interacting with both the polar electropositive and hydrophobic groups in protein. Orthogonal multipolar C-F…C=O interactions with both peptide backbone and side chain carbonyls have been found important for Fluorines[2]. Distinct fluorophilic environments in proteins are the ubiquitous peptide bonds, which undergo multipolar C-F ⋯ H-N, C-F ⋯C=O, and C-F ⋯ H-CR interactions. Here we report several structures of galectin-3 CRD with mono-galactose based compounds having fluorines in different positions and numbers.

References:

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MS06- Molecular machines and big complexes

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MS06-P01

Crystal structure of new [3]rotaxane

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Discovery and development of mechanically interlocked molecular architectures (MIMAs) has opened up a completely new area of research. Such systems are used in construction of numerous artificial molecular devices (i.e. molecular switches, motors or shuttles). They could be applied in molecular electronics, materials chemistry, sensors, photonics or photoactive catalysis [1,2]. In the year 2016, Sauvage, Stoddart and Feringa were awarded the Nobel Prize in Chemistry for their pioneering work in this field, and there is still a great interest of chemists in design, synthesis and properties of new compounds belonging to this fascinating family of chemicals. Among the mechanically interlocked compounds, one of the most important place is occupied by the rotaxanes [3]. Compounds of this type are built from “dumbbell shaped molecule” threaded through a macrocycle or macrocycles. Here, we present the crystal structure of new [3]rotaxane (see schematic representation). It consists of two dibenzo-24-crown-8 ether wheels and axle containing tetraazamacrocyclic complex coordinating the nickel ion. The identity of investigated compound was confirmed by the single-crystal X-ray diffraction analysis. Interestingly, in the case of (DB24C8)2/TAM system, the TAM unit is a π-acceptor and a hydrogen bond donor, which is reflected in the formation of specific molecular interactions between individual [3]rotaxane components, and influences its topology. The results of our study could be helpful to understand properties of the mechanically interlocked molecular compounds, especially polyrotaxanes.

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