MONO- AND MULTIVALENT GLYCOMIMETICS TARGETING DENDRITIC CELLS AS NOVEL TOOLS FOR MEDICINAL CHEMISTRY

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The recognition of complex carbohydrate epitopes on the surface of pathogens or aberrant cells is a hallmark of the innate immune system. Dendritic cells (DCs) are equipped with a variety of lectin receptors that bind and internalize glycosylated cells in a context dependent manner.[1] This event is often coupled with the induction of specific immune responses tailored to the encountered stimuli. Carbohydrate-based drugs that mimic the structure of certain glycan epitopes represent an underappreciated tool for the modulation of innate immune functions in a disease-related context. In this context, the C-type lectin receptor dendritic cell-specific intermolecular adhesion molecule 3 grabbing non-integrin (DC-SIGN) represents a particularly attractive target. DC-SIGN acts as a pathological host factor in viral infections, enabling either direct infection of DCs, or virus dissemination through the lymphatic system.[2] In addition, DC-SIGN is highly expressed on competent antigen-presenting immature DCs, as well as on tumor associated DCs and macrophages, thus making it a prime target for immune modulation and targeted delivery.
Here, the development of DC-SIGN-targeting glycomimetics and carbohydrate-based multivalent compounds is presented. A thermodynamics-guided ligand optimization campaign is described that resulted in the discovery of a potent mannose-mimetic compound.[3,4] Key insights about the formation of a cooperative interaction network in the DC-SIGN binding site were obtained by X-ray crystallography combined with a thorough analysis of the interaction thermodynamics. The combination of a stereospecific hydrogen bond and an electrostatic polarization of the interaction network was identified as the origin for a non-additive enhancement of binding enthalpy. In addition, it is shown how the complex interplay of design choices for multivalent DC-SIGN ligands gave rise to compounds with unexpected supramolecular properties that successfully interacted with DC-SIGN-expressing cells and efficiently enabled cell-specific intracellular delivery.
These insights pave the way for a further development of DC-SIGN-targeting mono- and multivalent compounds as multi-purpose tools in the context of infectious diseases and cancer.

References:

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