

THE PREORGANIZATION OF THE TRISACCHARIDE CORE OF SIALYL LEWIS^x IS ESSENTIAL FOR BINDING TO E-SELECTIN

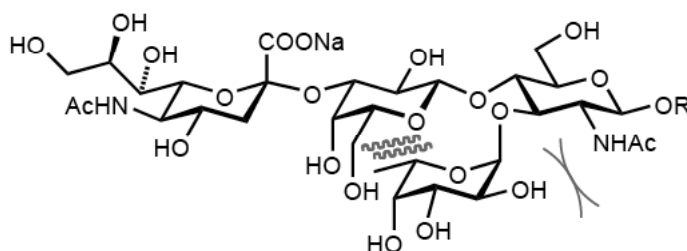
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The selectins play a key role in the inflammatory process, i.e. the recruitment of leukocytes from blood vessels into inflamed tissue. Excessive infiltration of leukocytes can cause acute or chronic reactions, as observed in reperfusion injuries, stroke or rheumatoid arthritis. Therefore, the antagonism of selectins is a valuable pharmaceutical goal.

Since the physiological ligands of the selectins all contain the tetrasaccharide epitope sialyl Lewis^x (sLe^x), this epitope served as lead structure in the search for E-selectin antagonists. The bioactive conformation of sLe^x has been elucidated [1]. It has been shown that the preorganization of the core in the bioactive conformation contributes substantially to the affinity of E-selectin antagonists [2].

In addition to the exoanomeric effects, there are two factors that stabilize the core conformation of sLe^x: (i) by steric compression with sterically demanding substituents of the GlcNAc moiety and (ii) by lipophilic interaction between the alpha-face of fucose with the beta-face of galactose.



Stabilizing interactions of the bioactive conformation of sLe^x

In order to verify the above considerations, a series of E-selectin antagonists were synthesized and biologically evaluated.

- [1] Scheffler, L.; Ernst, B.; Katopodis, A.; Magnani, J. L.; Wang, W. T.; Weisemann, R.; Peters, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1841-1844. Rinnbauer, M.; Ernst, B.; Wagner, B.; Magnani, J.; Benie, A. J.; Peters, T. *Glycobiology* **2003**, *13*, 435-443.
- [2] Kolb, H. C.; Ernst, B. *Chem. Eur. J.* **1997**, *3*, 1571-1578. Thoma, G.; Magnani, J. L.; Patton, J. T.; Ernst, B.; Jahnke, W. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1941-1945.