CHIMIA 1999, *53*, No. 5

Carbohydrate-Protein Interactions

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Abstract. To improve the understanding of the biological role of oligosaccharides and glycoconjugates, the interactions of carbohydrates with their receptor proteins are studied. For this purpose, the natural carbohydrate ligands are prepared by chemical and enzymatic synthesis, and structure-activity relationships are established. The conformational analysis of such ligands in solution and bound to receptor proteins, in conjunction with docking studies, reveals major aspects of the carbohydrate-protein recognition process at a molecular level. This knowledge is of practical importance for the rational design of carbohydrate mimics.

Beat Ernst was born in 1946 in Stäfa, Switzerland. He studied chemistry at the ETH in Zürich where he completed his dissertation entitled 'Novel Tricyclic C_{10}-, C_{11}- and C_{12}-Hydrocarbons' under the guidance of *O. Jeger* and *C. Ganter*. Afterwards, he went as a postdoctoral fellow to the California Institute of Technology in Pasadena to work with *R.E. Ireland* on the total synthesis of tirandamycic acid. In 1981, he joined the Central Research Laboratories of *Ciba-Geigy Ltd.* in Basel, where he was head of the Section Carbohydrate Chemistry. On the basis of this research, he was awarded the *Werner*-Prize of the *New Swiss Chemical Society* and became *CIBA-Fellow* in 1993. After the merger of *CIBA* and *SANDOZ* in 1996, he moved to the therapeutic area 'Transplantation', where he headed the Selectin Antagonist project. In October 1998, he accepted the position as Professor of Molecular Pharmacy at the University of Basel.

Introduction

Defining the biological role of oligosaccharides and glycoconjugates has challenged scientists for decades. In theory, oligosaccharides have the potential to store an enormous amount of information. Cells can readily decode this information through specific protein receptors. To capitalize on knowledge about recognition of carbohydrates by their receptors, *e.g.*, for drug design, the intimate details of the recognition process must be delineated.

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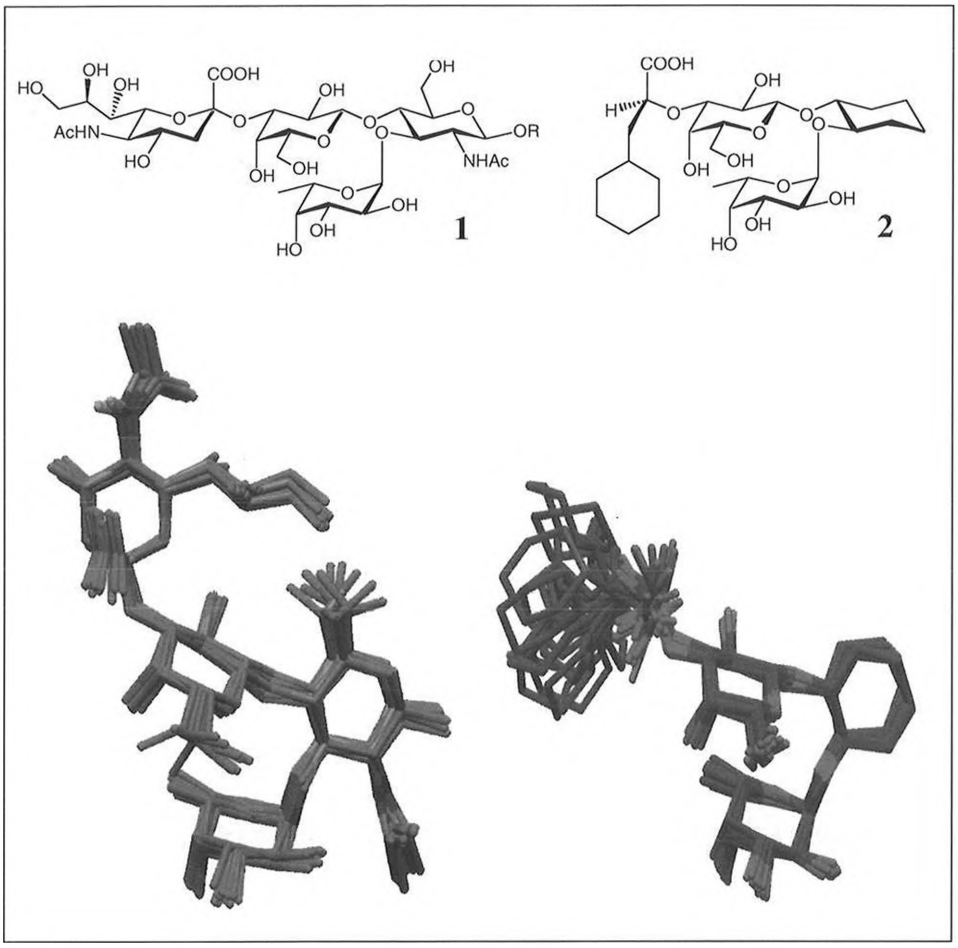

Figure. *Structure and bioactive conformation of sialyl* Lewis^x (**1**) *and the mimic* **2**

To achieve this goal, we have initiated (in collaboration with German and US research partners) activities in the following areas:

- chemical and enzymatic synthesis of oligosaccharides and glycoconjugates;
- conformational analysis of carbohydrate ligands in solution and bound to the receptor proteins;
- rational design of carbohydrate mimics;
- carbohydrate-lectin binding assays.

Our activities in the selectin field exemplify this approach.

Carbohydrate-Selectin Interactions

Numerous diseases and pathological situations are related to excessive influx of leukocytes into tissues. Although this influx normally represents an essential defense mechanism against infection, excessive or inappropriate leukocyte accumulation results in injury to host tissues as observed in ischemia-reperfusion injury, respiratory disease, dermatitis or gastrointestinal inflammation.

Early in the inflammatory response, leukocytes adhere to and roll along endothelial cells on the inner surface of blood vessels. It has been clearly shown that an inducible set of calcium-dependent adhesion molecules, the selectins, mediates this initial event. Since leukocyte rolling is a prerequisite for later inflammatory events, inhibition of selectins offers a valuable strategy for preventing the deleterious consequences of excessive leukocyte influx.

It was shown that all selectin ligands contain the common carbohydrate epitope sialyl *Lewis*^{x} (**1**). This tetrasaccharide has, therefore, served as a lead structure in our search for selectin antagonists with increased biological activity, simplified structure, and improved bioavailability. Our recent findings are summarized below:

- Elucidation of the structure/activity relationship for the lead structure (SAR study).
- Determination of the bioactive conformation (conformation of the ligand bound to E-selectin) of sialyl *Lewis*^{x} (**1**) [1] and mimics (*e.g.*, **2**) [2] thereof by transfer-NOE NMR spectroscopic techniques.
- Development of molecular modeling tools [Monte Carlo (jumping between wells)/stochastic dynamic simulation] for the rational design of potential antagonists [3].
- Preparation of potential selectin antagonists by chemical and chemo-enzymatic synthesis (glycosyl transferases are expressed from CHO cells or baculovirus-transfected insect cells) [3][4].
- Comparison of the biological activity of sialyl *Lewis*^{x}, **1**, with mimics [5].

Following this approach, several selectin antagonists more potent than the lead tetrasaccharide sialyl *Lewis*^{x} have been identified, demonstrating an improved understanding of the carbohydrate-protein recognition process. Extensions to a variety of pharmaceutically important carbohydrate-protein interactions are currently studied in our laboratory.

Received: February 26, 1999

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