Computational analysis of oligosaccharide conformations

- methodological development, applied studies, and design of glycomimetics

AKADEMISK AVANDLING

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av

Francesco Strino

Fakultetsopponent:
Dr. Alfred D. French
US Department of Agriculture, New Orleans, USA

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I. A. Nahmany, F. Strino, J. Rosén, G. J. L. Kemp and P.-G. Nyholm. The use of a genetic algorithm search for molecular mechanics (MM3)-based conformational analysis of oligosaccharides. Carbohydr Res, 2005. 340: 1059-64.

II. F. Strino, A. Nahmany, J. Rosén, G. J. L. Kemp, I. Sá-correia and P.-G. Nyholm. Conformation of the exopolysaccharide of Burkholderia cepacia predicted with molecular mechanics (MM3) using genetic algorithm search. Carbohydr Res, 2005. 340: 1019-24.

III. C.A.K. Koppisetty, W. Nasir, F. Strino, G.E. Rydell, G. Larson, P.-G. Nyholm. Computational studies on the interaction of ABO-active saccharides with the norovirus VA387 capsid protein can explain experimental binding data. J Comput Aided Mol Des, 2010. Doi:10.1007/s10822 010 9353-5.

IV. F. Strino, J.-H. Lii, H.-J. Gabius and P.-G. Nyholm. Conformational analysis of thioglycoside derivatives of histo-blood group ABH antigens using an ab initio-derived reparameterization of MM4: implications for design of non-hydrolysable mimetics. J Comput Aided Mol Des, 2009. 23: 845-852.

V. F. Strino, J.-H. Lii, C.A.K. Koppisetty, P.-G. Nyholm and H.-J. Gabius. Selenoglycosides in silico: ab initio-derived reparameterization of MM4, conformational analysis using histo-blood group ABH antigens and lectin docking as indication for bioactivity. J Comput Aided Mol Des, *under revision*.

UNIVERSITY OF GOTHENBURG

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Francesco Strino

Department of Medical Biochemistry and Cell Biology, Institute of Biomedicine at Sahlgrenska Academy, University of Gothenburg

Carbohydrates are the most abundant class of biomolecules. Besides their roles as structural elements and energy storage, they are involved in signaling and recognition processes. Their functions and activities depend on their preferred conformations. The software GLYGAL was developed to perform conformational studies of oligosaccharides using a genetic algorithm tailored for carbohydrates. The new method was applied to the highly branched exopolysaccharide of *Burkholderia cepacia*. The results show that its heptasaccharide repeating units assume a well defined conformation, stabilized by steric interactions between consecutive units. Furthermore, GLYGAL was used to calculate favorable conformations of histo-blood group antigens. The compounds were then fitted in the binding site of the surface protein of the norovirus VA387 strain and their binding affinity was estimated by molecular dynamics and Glide scoring, giving insights into the interaction patterns involved in norovirus infection. Finally, the mimetic properties of thioglycosidic and selenoglycosidic derivatives of the ABH antigens were studied by conformational and dockings studies, indicating potentially bioactive derivatives with increased resistance to hydrolysis.

In conclusion, the computational methodologies developed during this study were successfully used, together with existing methods, for the investigation of natural carbohydrates and the rational design of glycomimetics.

Keywords: *Burkholderia cepacia, histo-blood group antigens, saccharide conformations, genetic algorithms, norovirus, thioglycoside, selenoglycoside*

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