Synthesis of *C*-Linked Neuraminic Acid Oligomers as Potential Immunogen for Meningococcal Meningitis and Carcinomas

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ABSTRACT

Oligosaccharides and oligosaccharide glycocojugates are involved in a multitude of biological processes including cell recognition, cell differentiation and cell adhesion. A considerable amount of research has focused on the synthesis of *C*-glycosides, stable mimics of the naturally occurring *O*-saccharides.

Sialic acids are one of the most important molecules of life. Polysialic acids (PSAs) are naturally occurring linear homopolymers with a helical secondary structure, composed entirely of negatively-charged sialic acid residues joined by α(2,8), α(2,9) or α(2,8)/α(2,9) alternating ketosidic linkages. PSAs play a number of important functions during developmental biology. The poor immunogenicity of the group B meningococcal polysialic acid has made it difficult to formulate a comprehensive polysaccharide-based vaccine to protect against meningococcal meningitis. The dimmer Neu5Acα(2,8)Neu5Ac is an important constituent of gangliosides GD_2 and GD_3.

The importance of PSAs in developmental biology, their reappearance in tumors, the lability of interglycosidic linkages, make their C-glycoside analogs ideal research targets for biological and pathogenesis evaluation and potential pharmaceutical application. We have synthesized first *C*-linked α(2,8) Neu5Ac disaccharide, wherein C-9 of one residue is used as a hydroxymethylene bridge. This synthesis relies on samarium mediated *C*-glycosylation.This is a versatile precursor of more complex oligosialic acid *C*-analogs. It is also a common *C*-glycoside precursor of GD2 and GD3. After installation of a short

PEG-linker terminated by a thiol group failed, hydrolyzed product of *C*-disaccharide was fully deprotected for conformation analysis next.

Bacterial polysaccharides have been considered classic T cell-independent antigens (TI-2). However, zwitterionic polysaccharides (ZPSs) elicit T-cell mediated immune response. Although mAbs, directed against α(2,8) PSAs require a minimum of nine to ten residues for binding, MHCII dependent T-cell proliferation may require a lower number of residues in zwitterionic oligosialic acids. A dual-functionalized monomer, which has an aldehyde group (as glycosyl acceptor) at C-8 and a pyridyl sulfide group (as glycosyl donor) at anomeirc postion, was prepared. *C*-Oligomerization of the monomer afforded polydisperse mixture of *C*-oligosialic analogs. Deallylation and removal of acetyl group of 5-acetomido and saponification should finally afford *C*-oligosialic ZPSs.

As a minor sialic acid, KDN occurs in all types of sialo-glycocojugates including glycolipids, glycoproteins, and bacterial polysaccharides. In almost all of these KDN-linked structures, one can find counterparts where KDN replaces Neu5Ac. *C*-Glycoside analogs of KDN were prepared and tested along with Neu5Ac *C*-glycosides for anti-influenza virus activity.