Design Synthesis of Sialyl Triazoles with the 2-Naphthylsulfonyl C-9 Substituent as Siglec-8 Ligands

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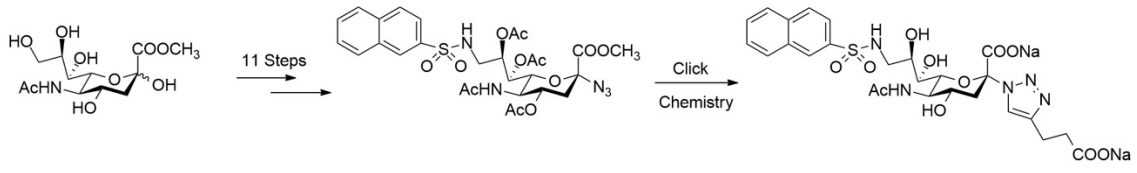
Siglecs are sialic acid-binding immunoglobulin [Ig]-like lectins, a family of single-pass transmembrane cell surface proteins in humans [1]. Siglec-8 is a human immune-inhibitory receptor is expressed by human eosinophils, basophils and mast cells [2]. Siglec-8 upon binding with antibodies or glycan ligands results in apoptosis in human eosinophils and inhibits the release of mediators from human mast cells without affecting their stability. Thus, potential glycan ligands may be ideally used as inhibitors for treatment of eosinophil and mast cell-related diseases, such as asthma, chronic rhinosinusitis, chronic urticaria, hypereosinophilic syndromes, mast cell and eosinophil malignancies and eosinophilic gastrointestinal disorders by targeting Siglec-8.[3].

In a previous study, mimetics of 6'-sulfo-sLe^x, a specific glycan ligand for siglec-8, were identified. Keeping the neuraminic acid (sialic acid), while replacing the galactopyranose with a cyclohexyl derivative led to a higher affinity ligand[4] with significantly reduced carbohydrate character. Here, we will present the design and synthesis of 2-naphthyl sulfonyl C-9 based sialic acid ligands with a triazole ring having carboxylate and sulphate group as a replacement for the sulphated galactose residue. The triazole moiety has predicted additional interactions with siglec-8 based on glide-docking.



Scheme of Azide Intermediate

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