



Synthesis of a cluster-forming sialylthio-D-galactose fullerene conjugate and evaluation of its interaction with influenza virus hemagglutinin and neuraminidase



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ABSTRACT

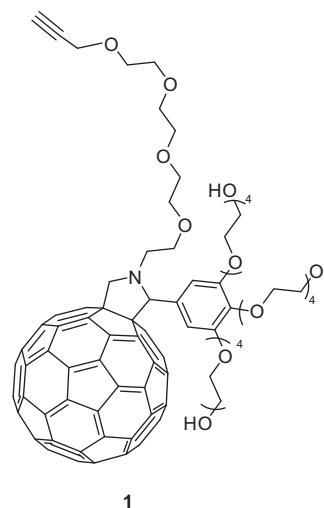
In order to obtain self assembling, multivalent ligand for influenza virus hemagglutinin α -N-acetylneuraminyl-(2-6)-D-galactopyranose has been synthesized and bonded to a water soluble fullerene derivative using 1,3-dipolar cycloaddition click reaction. The aggregating amphiphilic compound did not inhibit the influenza virus hemagglutinin, but it proved to be an inhibitor of its neuraminidase with a 50% inhibitory concentration of 81 μ M.

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Human influenza A and B viruses are highly contagious respiratory pathogens causing considerable morbidity and mortality, particularly in aged individuals.¹ Current influenza vaccines require annual updating and provide only partial protection in elderly people.² Currently available anti-influenza drugs include the M2 blockers amantadine and rimantadine, which nowadays are rarely used in clinical praxis because of widespread viral resistance to these agents, and the neuraminidase inhibitors oseltamivir and zanamivir.³ Influenza viruses carry two surface glycoproteins with a sialic acid recognition site: the hemagglutinin (HA), that is responsible for initial virus attachment to host cell receptors, and the neuraminidase (NA) which releases the newly formed virions at the end of the virus life cycle.

Due to its crucial role in viral entry, the influenza virus HA represents^{4,5} a suitable target for antiviral intervention. The HAs of human-adapted influenza viruses bind mainly to host cell surface glycans having sialyl- α (2-6)-galactosyl termini, while avian influenza viruses preferentially bind to glycans with sialyl- α (2-3)-galactosyl termini.^{6,7} Since sialic acid binding is similar in

all influenza virus (sub)types,⁴ interfering with the HA–sialic acid interaction is a relevant antiviral strategy. According to the



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Figure 1. Structure of the fullerene–pyrrolydine carrier 1.

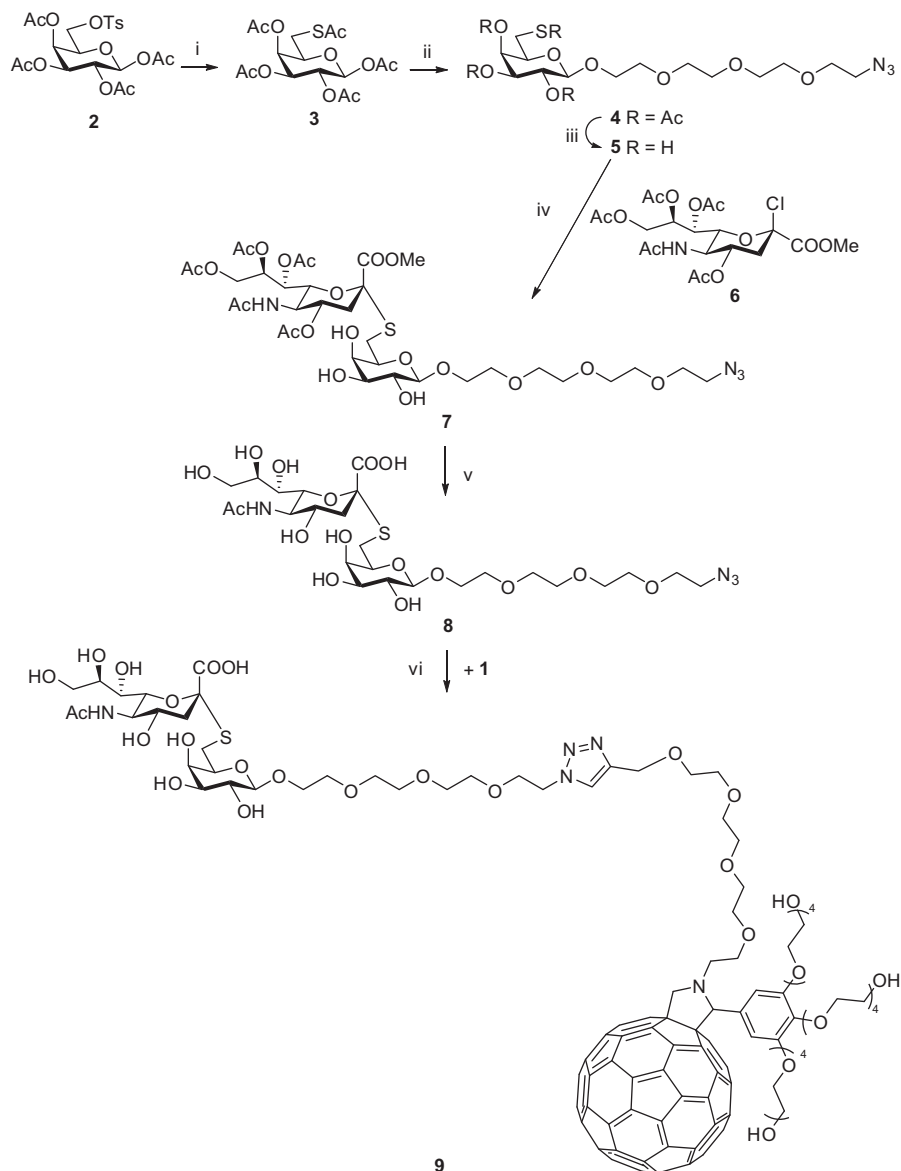
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estimations of Whitesides et al.,⁸ the association constant for interaction of a single sialic acid with monomeric HA is 10^3 M^{-1} . However, due to polyvalent virus–cell interactions, the binding affinity between multiple viral HA ligands and sialic acid receptors of an erythrocyte is estimated 10^{13} M^{-1} . This strong cooperative interaction inspired the pioneering works of the teams of Bovin,⁹ Roy¹⁰ and Whitesides¹¹ to synthesize multivalent sialic acid-containing polymers and study their effect on HA–sialic acid binding.

In the last decades, many sialoconjugates of polymer carrier molecules have been synthesized^{12,13} and evaluated for their anti-influenza virus activity. However, the polymer backbone of these sialosides can be immunogenic, insoluble, cytotoxic and inconsistent. These disadvantages initiated the research of monomeric sialosides that can form multivalent aggregates. One of the other approaches is the incorporation of monosialosides into liposomes.^{14–16} The Bovin's group elaborated an ingenious HA-decoy method: they conjugated sialosides to oligoglycine chains that can form self-assembled nano-sheets through hydrogen bonding.^{17–19}

In the framework of our systematic studies of glycopeptide antibiotic aglycons, we previously prepared a series of ristocetin and teicoplanin derivatives bearing lipophilic side-chains,²⁰ several of which exhibited high antibacterial and anti-influenza virus activity. We postulated that the unusual/serendipitous antiviral activity originates from their ability to form nano-aggregates. Since it is known that fullerene (C_{60}) derivatives can form self-assembled supramolecular nanostructures in water,²¹ we designed and prepared the fullerene derivative **1** as one of the lipophilic side-chains. Compound **1** was provided with tetraethyleneglycole chains for improving the water solubility and a propargyl ether residue allowing its functionalization with bioactive compounds via a 1,3-dipolar cycloaddition (click) reaction (Fig. 1).²²

We anticipated that conjugation of **1** with an appropriate sialodisaccharide ligand of the HA receptor would result in a sialo-cluster-forming fullerene derivative with HA-decoy properties. The thiosialoside analog of *N*-acetylneuraminy- α (2,6)-*D*-galactose has been chosen for the conjugation, because this is the terminal structure of human cell surface glycoproteins recognized by the



Scheme 1. Synthesis of the thiosialoside-functionalized fullerene **9**. Reagents and conditions: (i) KSAC, dry DMF, 90 °C, 2 h, 70%; (ii) HO-TEG-N₃, BF₃·Et₂O, dry CH₂Cl₂, rt, 4 h, 33%; (iii) (1) NaOMe, dry MeOH, (2) Serdolite Red (H⁺); (iv) Na₂CO₃, H₂O, Bu₄NHSO₄, EtOAc, 40% for **7** over two steps; (v) (1) NaOMe, dry MeOH, 2. Serdolite Red (H⁺), (3) KOH, H₂O, MeOH, (4) Amberlite IR 120 (H⁺), 51%; (vi) Et₃N, Cu(I), Ar, rt, 24 h, dry CH₂Cl₂, dry MeOH, 60%.

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