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Highly reactive "RIKEN click" probe for glycoconjugation on lysines

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ABSTRACT

One pot double click strategy containing strain-promoted click-reaction followed by 6π-azaelectrocyclization (RIKEN click reaction) has worked well in the synthesis of multivalent homogeneous and heterogeneous *N*-glycoalbumins. We have slightly changed the structure of linker unsaturated aldehyde used in this method. As a result it can be easily synthesized from commercially available material and furthermore, the enhancement of its reactivity towards both click-reactions was observed. The data described in this Communications facilitate the usage of the double click strategy as a general method for the synthesis of a variety of neo-*N*-glycoproteins.

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Introduction

Glycans play an important role in various functions of living organisms. For instance, asparagine-linked glycans (*N*-glycans) are involved in such important processes as polypeptide processing, catabolism, innate immune response and adhesion.[1] The basis of these processes is cell surface recognition through pattern recognition mechanisms which are strongly depending on the *N*-glycan structures.[2–5] However, a molecular basis of pattern recognition is still not clearly understood.

In order to study, control, interfere, or block carbohydrate–lectin interactions, accessing multivalent glycocluster systems, e.g., mimicking protein and/or cell surface glycoenvironment, with well-defined topologies is necessary. Various glycoconjugates reported on dendrimers, nanoparticles, polymers and proteins are widely used to mimic natural glycoproteins and cells.[6–10] In particular, conjugation on albumin has exclusively used as template for glycoconjugation thanks to several advantages, such as serum stability in circulation, less immunogenicity when applying to clinical applications and availability of the more than 30 lysine residues for glycan immobilization.[11]

Historically, a method of conjugation with lysine was covalently attachment via reductive amination.[12] However this method has some disadvantages such as necessity to use large excess of sugar, high concentration and long reaction time. Moreover, only carbohydrates containing free reducing end can be used in reductive amination and this reducing end is destroyed during the reaction.[12–14] Different methods for glycan conjugation to lysines were established later in order to find more general procedure without these limitations. Almost all of them are based on the linker-mediated processes.[14] These examples include diazonium coupling of aminophenyl[15,16] or phenylisothiocyanato glycosides[15] with lysines, ω-carboxyoctyl glycosides conjugation by acyl azide method.[17] The use of isothiocyanate[6] or carbodiimide-activated carboxylic acids[18] and S-methylglycosylthiourea[19] also constitute small part of lysine glycoconjugation methods.

One-pot double click strategy developed in our group as a combination of a strain-promoted click reaction of dibenzocyclooctyne (DIBO) (alkyne-azide click cycloaddition)[20] followed by 6π-azaelectrocyclization of unsaturated imines (RIKEN click reaction)[14,21–28] is one of the most efficient lysine glycoconjugation methods. Importantly, this method provides an efficient immobilization of up to dozen *N*-glycan molecules onto albumin. It was successfully used in the synthesis of various homogeneous and heterogeneous *N*-glycoalbumins (Scheme 1, Chemical *N*-glycan structures and corresponding symbols applied to this Communication are shown in

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