Synthesis and bioactivity of carbohydrate conjugates with Toll-like receptor 7 ligand 1V209

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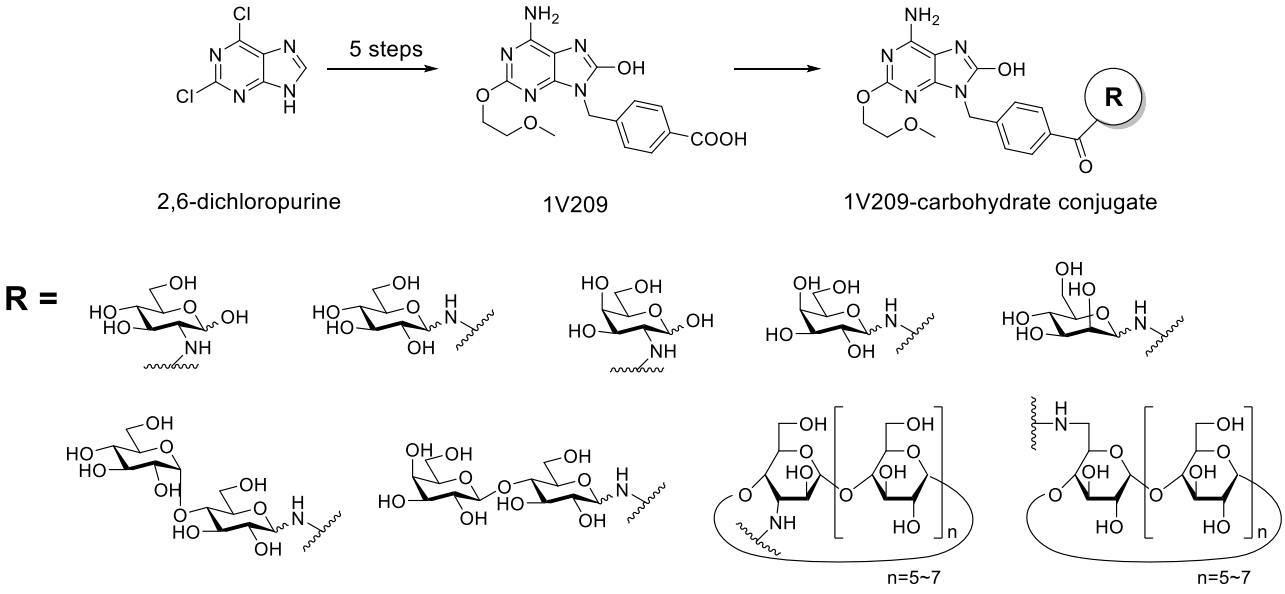
Abstract

Toll-like receptor 7 (TLR7) recognizes single strand RNA (ssRNA), which is one of pathogen-associated molecular patterns (PAMPs). TLR7 is mainly located in the endosomal compartment of immune cells. Signalling through TLR7 activates the innate immune system via the adaptor protein MyD88, and shapes adaptive immune responses. Therefore, TLR7 ligands are expected to be effective reagents for anti-viral or anti-tumor therapy. Several low molecular weight TLR7 ligands, such as imiquimod and resiquimod, have been clinically approved.[1] However, their therapeutic uses has been limited due to side effects associated with cytokine release syndrome. Conjugation of the ligand with macromolecules like proteins, polysaccharides, lipids, or polymers [2-4] is a promising method to reduce or eliminate unacceptable side effects and can improve the pharmacokinetics and pharmacodynamics of the ligand. In this study, we focused on our original low molecular weight TLR7 ligand named 1V209 and carbohydrates, which are often utilized as hydrophilic tags for drug delivery system, and prepared 13 conjugates and examined their immune-stimulating activity.

The conjugation of 1V209, 2-methoxyethoxy-8-oxo-9-(4-carboxybenzyl) adenine is shown in Scheme 1. 1V209 was prepared from 2,6-dichloropurine as previously reported.[2] The conjugation with carbohydrates was done via the 9-amino group in 1V209 by a simple condensation reaction using HATU. The immune-stimulating activity of synthesized compounds was investigated on the basis of the TNF-α and interleukin-6 (IL6) production from RAW264.7 cells and mouse born marrow-derived dendritic cells (mBMDC), respectively.



Scheme 1. Synthetic outline of TLR7 ligand-carbohydrate conjugates

References

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