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Screening and kinetic characterization of synthetic polyphenol derivatives as sialyltransferase inhibitors

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Sialyltransferases (ST) which transfer the sialic acid residue to acceptor carbohydrates biosynthesize sialyl-glycoconjugates possibly involved in many biological processes. To address their biological significance, ST inhibitors could be powerful tools. In the present study, we had discovered new class of inhibitors against ST from natural products by a method using artificial substrate. We first generated and purified a soluble and active form of recombinant human ST6Gal I in *Escherichia coli* which is involved in the biosynthesis of human influenza virus receptor, terminal Neu5Acalpha2-6Galbeta1-R residues. We also used STs commercially available, a rat ST6Gal I and ST3Gal I which catalyzes the biosynthesis of avian influenza virus receptor, terminal Neu5Acalpha2-3Galbeta1-R residues.

Thirty-seven synthetic polyphenols were screened by solid-phase enzyme assay using three STs. As a result, several compounds showed inhibitory activity against all enzymes examined regardless of either species or reaction types of ST. Experiments concerning structure-inhibitory activity relationship demonstrated two characteristic features of inhibitory compounds. One is, hydrophobic functions modified on hydroxy groups of the A ring enhances the activity. The other is that increase of hydrophilicity on the B ring remarkably augments the inhibitory activity. Finally we generated one compound which elicits inhibitory activity against rat ST6Gal I with about 1 micromolar of *Ki* value. This compound could be a useful reagent to both control cellular expression of sialic acid and prevent hosts from influenza virus infection. In conclusion, our screening assay is very effective and polyphenol derivatives with specific structures could be new types of ST inhibitors.