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 examined synthetic polyphenol compounds derived from natural products as ST inhibitors by a solid-phase enzyme assay. 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 as well as siglec ligands, terminal Neu5Acα2-6Galβ1-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 Neu5Acα2-3Galβ1-R residues.

Synthetic polyphenols were tested 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. We found two characteristic features of inhibitory compounds by structure-inhibitory activity relationship. First, hydrophobic functional group modified on hydroxy groups of the A-ring enhances the activity. Second, increase of hydrophilic property on the B-ring remarkably augments the inhibitory activity. Kinetic analysis using mutated ST6Gal I with single amino acid substitution demonstrated that the compounds reduced both *Ki* and *Vmax* values of the enzyme, strongly suggesting mixed inhibition mechanism of the compounds. Finally we generated one compound which elicits inhibitory activity against ST6Gal I with about 1 μM of *Ki* value. In conclusion, this compound could be a useful reagent to both control cellular expression of sialic acid and prevent hosts from influenza virus infection.