

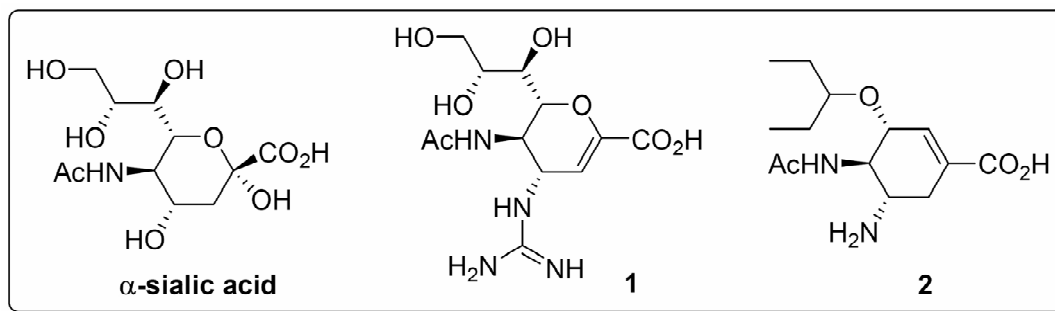
POTENTIAL ANTI-INFLUENZA AGENTS: SYNTHESIS AND EVALUATION OF SIALIDASE INHIBITORS

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The transition states of sialidase-catalyzed reactions are likely similar to those of other glycosidases with respect to charge distribution (oxacarbenium ion character) and geometry (non-chair pyranosyl ring conformation). We, therefore, postulate that a structural starting point for new sialidase inhibitors will include certain motifs found in other glycosidase inhibitors. Indeed, current sialidase inhibitors for the treatment of influenza infections, on the market or in development, include some of these transition state elements. Of more importance, these sialidase inhibitors incorporate distinctive structural features that occupy more space than the corresponding functional groups of the sialoside-based natural substrates. For example, Zanamivir **1** [1] contains a guanidino group rather than the alcohol functionality present at that position in sialic acid and Oseltamivir **2** [2] contains a 3-pentyl ether group in place of sialic acid's glycerol side chain. Such structural differences between sialidase inhibitors and natural substrates ultimately underlie the appearance of resistant viral strains. Mutation of a non-catalytic active site residue can affect the binding of the inhibitor without influencing the catalytic activity of the enzyme.

The focus of the work presented here is the synthesis of conformationally-constrained analogues of sialic acid that mimic the hydrolytic transition state structure in the sialidase-catalyzed process. Our designed structures are sterically homologous to sialic acid so that, in theory, these potential inhibitors will be less prone to causing influenza viral mutation.



[1] von Itzstein, M. *et al. Nature* **1993**, *363*, 418-423.

[2] Kim, C. U. *et al. J. Am. Chem. Soc.* **1997**, *119*, 681-690.