Selective Inhibitors of Human Neuraminidase 3

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Human neuraminidases (NEU) are associated with human diseases including cancer, atherosclerosis, and diabetes. To obtain small molecule inhibitors as research tools for the study of their biological functions, we designed a library of 2-deoxy-2,3-didehydro- N-acetylneuraminic acid (DANA) analogues with modifications at C4 and C9 positions. This library allowed us to discover selective inhibitors targeting the human NEU3 isoenzyme. Our most selective inhibitor for NEU3 has a K; i; of 320 ś 40 nM and a 15-fold selectivity over other human neuraminidase isoenzymes. This inhibitor blocks glycolipid processing by NEU3 in vitro. To improve their pharmacokinetic properties, various esters of the best inhibitors were synthesized and evaluated. Finally, we confirmed that our best compounds exhibited selective inhibition of NEU orthologues from murine brain.
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