

Atherosclerosis Treatment:

Potent and selective neuraminidase inhibitors

Human neuraminidases (hNEU) are a family of four isoenzymes, each of which has important roles in cancer, inflammation, heart disease, and infectious disease. GlycoNet researchers have developed a panel of small molecule NEU inhibitors (CG33301, CG22601, CG17701, CZ16601) with unprecedented selectivity and potency towards hNEU1, hNEU3, and hNEU4. In addition, inhibitors for hNEU3 demonstrate an ability to reduce the formation of fatty streaks in animal models of atherosclerosis, making NEU a novel druggable target and these compounds potential therapeutic agents to treat atherosclerosis.¹

Key Benefits

- High potencies across lead compounds (20 ~ 250 nM)
- Improved selectivity (50x ~ 500x) against other isoenzymes
- Activity in oncology and atherosclerosis targets

Global Impact

Atherosclerosis is the leading cause of morbidity and mortality in the US and in most developed countries. Over the age of 40, people in general good health have ~50% chance of developing serious atherosclerosis.

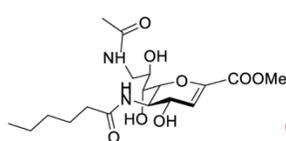
NEU were first studied clinically to develop anti-influenza drugs. Recently, several isoenzymes of the NEU family were identified as critical contributors to the progression of atherosclerosis. The isoenzymes, namely NEU1 and NEU3, initiate the removal of sialic acids from low-density lipoproteins. This triggers the formation of fatty streaks and eventually plaques in the arteries. As a result, effective NEU inhibitors are emerging as a prime interest for developing new drugs to treat or prevent atherosclerosis.

Current NEU Inhibitors

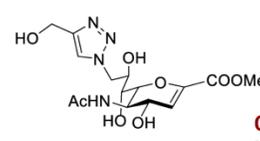
Four NEU inhibitors are currently on the market: oseltamivir (Tamiflu™), zanamivir (Relenza™), peramivir (Rabivab™), and laninamivir (Inavir™). These drugs are used to treat or prevent influenza infections, and they have poor activity and selectivity against hNEU.

GlycoNet's Lead Compounds and Applications

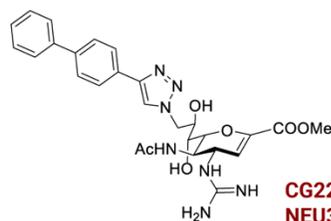
Several early hits for hNEU isoenzymes with high potency and selectivity have been developed and patented. Furthermore, the mechanism of action of NEU inhibitors in atherosclerosis has been established in murine models. These lead compounds have therapeutic potential in areas including cardiovascular disease, oncology, infection, and inflammation.



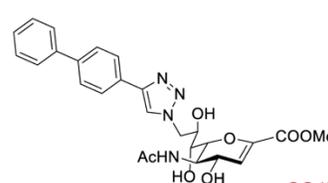
CG33301
NEU1: 50 nM



CY16601
NEU4: 30 nM



CG22601
NEU3: 230 nM



CG17701
NEU3/4: 250 nM

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Reference

1. Demina Ekaterina et al. (2021) Neuraminidases 1 and 3 Trigger Atherosclerosis by Desialylating Low-Density Lipoproteins and Increasing Their Uptake by Macrophages. *Journal of the American Heart Association*. **10**, e018756