ACS Medicinal Chemistry Letters

In This Issue

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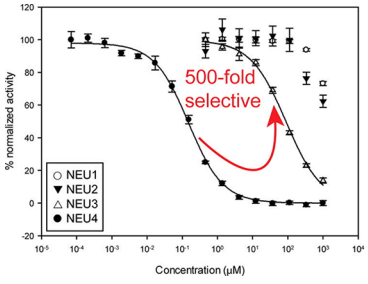
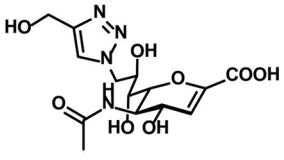
HIGHLY SELECTIVE HUMAN NEURAMINIDASE INHIBITOR

Neuraminidase inhibitors have been successfully used for treating influenza virus infection. While research efforts have been largely focused on inhibitors of viral neuraminidase enzymes, only a handful of investigations have been conducted to identify specific inhibitors of human neuraminidase. Current inhibitors of human neuraminidase, consisting of four human isoenzymes, have shown micromolar potency at best. Exploring human neuraminidase as a target would alleviate concerns for drug resistance and decrease off-target effects and could lead to new therapeutic strategies.

In this issue, Albohy et al. (DOI: 10.1021/ml400080t) identify the first compounds with nanomolar potency for one isoenzyme of human neuraminidase. The authors describe testing of a series of compounds against the full panel of human neuraminidase isoenzymes. The inhibitors exhibited between 50- to 500-fold selectivity for their targets over the other isoenzymes tested. Given the proposed roles of human neuraminidase isoenzymes in inflammation and cancer, these compounds could provide critical new research tools for understanding the role of these enzymes in human physiology.





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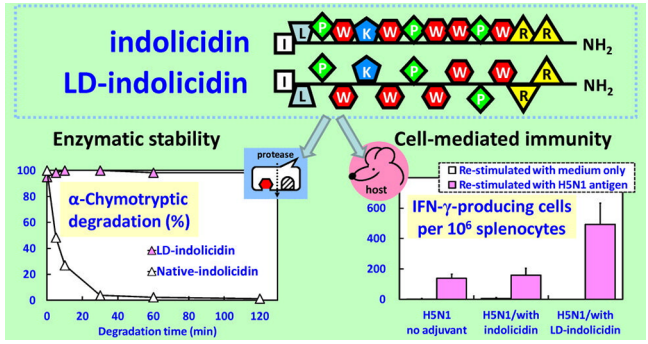
K_i = 30 ± 19 nM
(NEU4)

NOVEL PEPTIDE-BASED ADJUVANT

Vaccine adjuvant refers to the substance that helps to elicit a robust antigen-specific immune response. Alum and oil-in-water emulsions are two types of adjuvant with significant potential in the development of pandemic influenza vaccines. However, both of them are either a poor adjuvant for cell-mediated immunity or a vigorous adjuvant for hypersensitive autoimmunity.

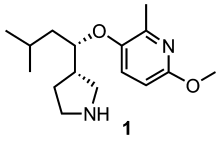
Here, Chang et al. (DOI: 10.1021/ml400081f) report the novel peptide-based adjuvants derived from the peptidomimetic stereoisomer of host defense peptides. Synthetic peptides provide an interesting vaccine adjuvant alternative as it allows identification of epitopes recognized by pathogen recognition receptors. This study is the first to evaluate a peptide sequence acting as an immunoregulatory agent after alternating D-amino acid substitution. Furthermore, this report serves as an example for the design of future vaccines against the emerging infectious diseases, as well as offers the potential in the immunotherapeutic treatment for cancers, chronic inflammation, and autoimmune diseases.



BALANCED SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITOR

Inhibition of serotonin transporter (SERT) and norepinephrine transporter (NET) has been a successful strategy in the treatment of several central nervous system disorders. Several inhibitory compounds are currently available on the market and are proven as safe and effective drugs for pain or mood disorders. While these compounds inhibit both SERT and NET, they do so with unbalanced potency.

Here, Dreyfus et al. (DOI: 10.1021/ml400049p) evaluate their hypothesis that a serotonin and norepinephrine reuptake inhibitor (SNRI) that inhibited both SERT and NET with comparable potency could lead to a compound with better efficacy and safety profile. The authors describe the discovery of a new potent and balanced serotonin norepinephrine reuptake inhibitor. One compound is shown to be a potent and selective SNRI in vitro and in vivo and retains pain inhibiting activity in a model of pain behavior. This balanced SNRI also exhibits good brain exposure, stability, and minimal drug−drug interaction.



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