MODULATING THE ACTIVITY OF GSK-3 TO TREAT MULTIPLE PATHOLOGIES

OU ID: #14006

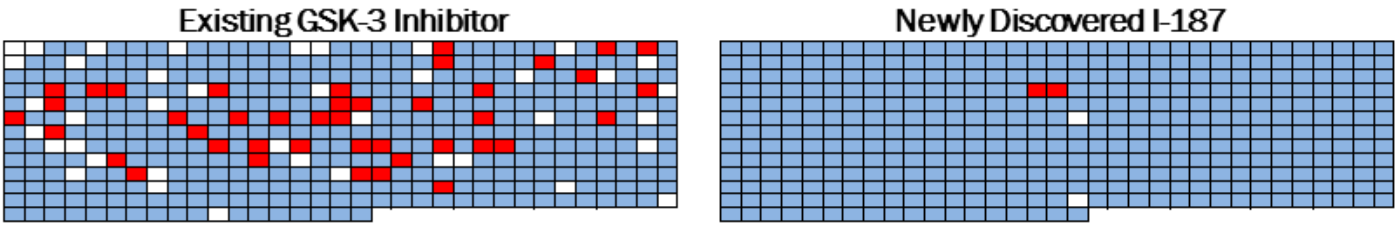
Overview

Glycogen synthase kinase-3 (GSK-3) is a protein kinase that has been implicated in a number of pathologies, including bipolar disorder, Alzheimer's disease, schizophrenia, pathological inflammation, and diabetes. Identifying selective inhibitors for GSK-3 to aid in the treatment of these pathologies, however, is difficult due to the similarities among the catalytic domains of kinases. Research at Ohio University has led to the development and testing of novel compounds that are highly specific for GSK-3. This group of small organic compounds, represented by the molecule known as I-187, inhibit both isozymes of GSK-3 (α and β) with IC_{50} values in the nanomolar range, and have a limited effect on other kinases. These data make compounds like I-187 attractive targets for further development and testing as potential treatments for GSK-3-mediated pathologies.

Benefits

A novel family of compounds that are:

- Structurally distinct from existing GSK-3 inhibitors
- Highly selective for GSK-3
- More potent than existing GSK-3 inhibitors



An existing GSK-3 kinase inhibitor and I-187 were screened in 414 kinase assays, representing 404 unique kinases. Each cell in the above tables represents the result of a particular kinase assay. Red cells indicate significant inhibition; white cells modest inhibition; and blue cells little to no inhibition. The existing GSK-3 inhibitor hits a multitude of off-target kinases, while I-187 is very specific (two red cells are GSK-3α/β) demonstrating a substantial improvement in specificity.

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Commercial Application

Several small organic compounds have been developed and tested as potential therapeutics for GSK-3-mediated disorders, but have failed to meet clinical trial end points. Researchers at Ohio University tested novel compounds like I-187 against one such inhibitor that had previously gone through clinical trials for central nervous system (CNS) disorders. The data indicate greater potency and selectivity, leading to the hypothesis that I-187 and similar compounds will perform better as treatments for CNS pathologies, including bipolar disorder, Alzheimer's disease and schizophrenia.

About the Inventors

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