Development of Glycogen Synthase Kinase-3β and Carbonic Anhydrase IX Inhibitors by Novel Encoded Library Technology

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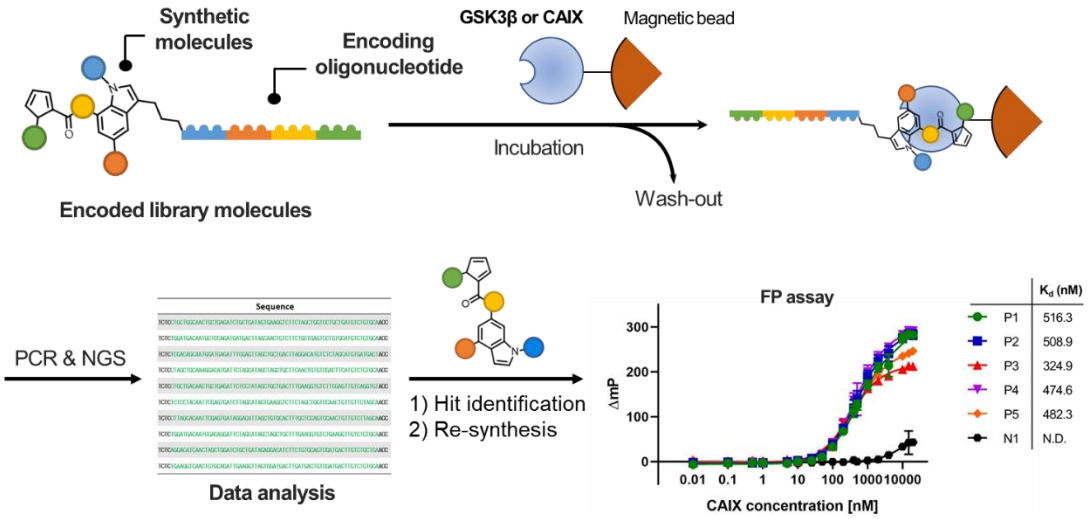
Glycogen synthase kinase-3β (GSK3β) is a serine/threonine kinase that plays a critical role in various biological pathways, particularly in the Wnt signaling pathway, which is involved in normal cell functions such as cell differentiation. Aberrant activation of the Wnt signaling can induce epithelial–mesenchymal transition (EMT) in human cancers, where Axin mediates EMT by modulating nuclear GSK3β activity, the key kinase responsible for the stability of Snail1 which is a potent EMT inducer. Therefore, inhibition of the GSK3β/Axin protein-protein interaction has emerged as a promising therapeutic strategy for cancer treatment. However, molecules that selectively target this protein-protein interaction have not yet been developed.
Here, we have developed inhibitors for targeting the GSK3β/Axin protein-protein interaction by novel encoded library technology. Our encoded library technology has multiple important advantages over the widely used DNA-encoded libraries (DELs) due to the enhanced chemical stability of the encoding material and compatibility with organic reations. We successfully developed potent peptidomimetic inhibitors of the GSK3β/Axin protein-protein interaction, which are the first synthetic inhibitors to disrupt this interaction. In addition, we have identified small-molecule inhibitors of carbonic anhydrase IX (CAIX), which is a promising therapeutic target involved in tumor acidosis.



References
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