Drug Discovery Seminar

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Design of improved sEH inhibitors through understanding the structure-kinetic-relationship

Soluble epoxide hydrolase (sEH) is a cytosolic enzyme that degrades epoxy-polyunsaturated fatty acids (PUFAs). Epoxy-PUFAs are key lipid signaling molecules in mammals. Stabilization of epoxy-PUFAs by inhibiting sEH is anti-inflammatory, anti-hypertensive, analgesic and anti-fibrotic. Recent studies also demonstrate that sEH inhibitors are neuroprotective against neurodegenerative diseases. Thus, sEH inhibitor is an important therapeutic target. In fact, two sEH inhibitors are currently in clinical trials. Therefore, designing sEH inhibitors with improved in vivo activity is highly desired for treating other diseases such as neurodegenerative diseases. Research suggests that drugs with long drug-target residence time have better in vivo efficacy and are desired properties for CNS drugs. However, the design principle for improving drug-target residence time of drug candidates remains elusive and Structure-Kinetics-Relationship (SKR) of sEH inhibitors are not known. To better understand the SKR of sEH inhibitors and the effect of drug-target residence time on in vivo activity of the sEH inhibitors, we will take a multidisciplinary approach by combining organic chemistry, high-throughput screening assay, new computational model, machine learning, PK modeling and novel in vivo assay. We will 1) screen a library of sEH inhibitors for their inhibition constant and drug- target residence time; 2) use computational model named WExplore to identify key inhibitor-sEH dissociation pathway; 3) implement a machine learning model based on the screening dataset to better predict drug-target residence time of new sEH inhibitor and 4) novel in vivo displacement assay which measures the target occupancy of testing sEH inhibitor at different post-dosing time by using a highly potent sEH inhibitor to displace sEH-bound testing inhibitor at specific time point.
In this presentation, we will present our screening data of a sEH library and the SKR of sEH inhibitor obtained from this screening dataset. We will also report newly designed sEH inhibitors based on the WExplore modeling results. We will discuss our preliminary machine learning model in predicting sEH inhibitor's drug-target residence time. Lastly, we will demonstrate how drug-target residence time affects in vivo activity of sEH inhibitors

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