Pharmacophore-based discovery of novel inhibitors of the innovative therapeutic target soluble epoxide hydrolase (sEH)

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As a key enzyme within the arachidonic acid cascade, the soluble epoxide hydrolase (sEH) plays an important role in the regulation of inflammation. While the cyclooxygenase (COX) and lipoxygenase (LO) enzymes produce largely pro-inflammatory metabolites, the cytochrome P450 epoxygenases metabolize arachidonic acid into anti-inflammatory epoxyeicosatrienoic acids (EETs). These endogenous compounds are rapidly oxidized to the corresponding dihydroxyeicosatrienoic acids (DHETs) by sEH. Inhibitors of sEH block this degradation and therefore stabilize EET levels, which leads to an enhancement or extension of the anti-inflammatory effect. Hence, there is an increasing interest in this potential therapeutic strategy for treating inflammatory disorders. [1-3]

This study aimed at the identification of novel potent sEH inhibitors. Therefore, several structure- as well as ligand-based pharmacophore models for sEH inhibitors were developed and theoretically validated using data from literature. The best eight models were used as a search query to virtually screen the chemical database supplied from the Specs. For each model, six virtual hits showing high fit values were selected for biological investigation in a fluorescence-based enzyme activity assay. At least one of the six virtual hits, respectively, displayed a sEH remaining activity of less than 35% of control at a concentration of 10 µM. In total, out of 48 compounds, eight compounds of different chemical scaffolds showed a sEH remaining activity of less than 60% of control at a concentration of 0.1 µM and IC_{50} values in the low nanomolar range. The most active compound exhibited an IC_{50} of 5.0 nM.

Within this study, pharmacophore modeling and virtual screening led to the identification of novel potent inhibitors of sEH, a promising anti-inflammatory target.

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[1] C. Morisseau, B.D. Hammock, *Annu Rev Pharmacol Toxicol*, **2013**, *53*, 37-58.
[2] H.C. Shen, B.D. Hammock, *J Med Chem*, **2012**, *55*, 1789-1808.
[3] S. Pillarisetti, I. Khanna, *Inflamm Allergy Drug Targets*, **2012**, *11*, 143-158.