Use of the SEE-Tx Drug Discovery Platform to Identify Pharmacological Chaperones for Glutaric Acidemia Type 1

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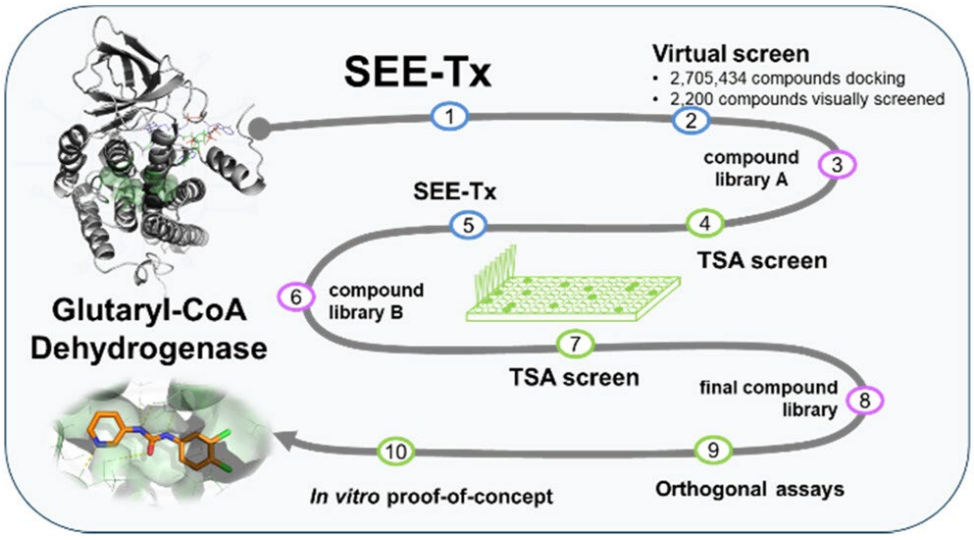
Allosteric regulators acting as pharmacological chaperones have the potential to facilitate innovative therapeutics as they target non-catalytic sites and stabilise folded proteins without competing with the natural substrate. This results in a net gain of function, which could have significant implications for the development of new treatments. Exogenous allosteric regulators are typically more selective than active site binders and can be more potent than competitive binders when the natural substrate levels are high.

In order to identify novel structure-targeted allosteric regulators (STARs) that bind to and stabilise the mitochondrial enzyme glutaryl-CoA dehydrogenase (GCDH), the computational SEE-Tx™ technology was employed. SEE-Tx™ is an innovative drug discovery platform with the potential to identify drugs that treat protein misfolding disorders, such as glutaric acidemia type 1 (GA1) disease, a rare metabolic disorder caused by deficiency of GCDH. Putative allosteric regulators were discovered using structure- and ligand-based virtual screening methods and validated using orthogonal biophysical and biochemical assays. The computational approach presented here could be used to discover allosteric regulators of other protein misfolding disorders.



J. Med. Chem. 2024, 67, 19, 17087-17100