Enabling Metabolic Disease Research with DNA-Encoded Library (DEL) Screening: Case Study on HAO1

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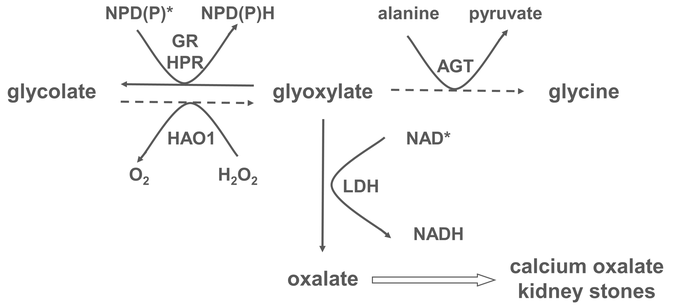
Abstract

For numerous rare diseases, the steep costs associated with drug discovery and limited patient populations pose significant obstacles to the advancement of treatments. The DNA-encoded discovery platform presents a swift and cost-effective approach to identifying promising candidates, thereby facilitating drug discovery efforts for complex targets, including those relevant to rare diseases. Primary hyperoxaluria type 1 (PH1) is a rare inherited liver disorder affecting glyoxylate metabolism. Targeting hydroxy acid oxidase 1 (HAO1) as a strategy can reduce the buildup of toxic oxalate, offering a potential cure for PH1. Leveraging the DNA-encoded discovery platform, our team successfully identified multiple new chemical series of potent HAO1 binders. Through medicinal chemistry optimization, we enhanced these compounds' potency and their absorption, distribution, metabolism, excretion (ADME), and pharmacokinetic (PK) profiles. This case study underscores the efficacy of this discovery approach in accelerating therapy development timelines and improving the success rate of identifying lead compounds for rare diseases, offering significant promise for entities focused on these challenging therapeutic areas.

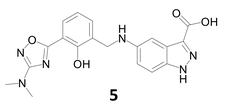
Primary Hyperoxaluria Type 1 (PH1) and HAO1



Primary hyperoxaluria type 1 (PH1) is a rare hereditary condition arising from mutations in the AGXT gene. Traditional PH1 management primarily involves liver and kidney transplants. However, RNAi and small molecule interventions are now improving PH1 treatments by effectively lowering urinary oxalate levels. Dysfunction of AGXT results in the buildup of harmful oxalate, leading to kidney stones and ultimately, kidney failure. Inhibiting hydroxyacid oxidase 1 (HAO1), involved in oxalate production, has shown promise in reducing oxalate levels. In our search for a small molecule HAO1 inhibitor, we utilized DEL technology, a proven approach for generating leads against varied targets. This method screens a vast library of compounds, leveraging significant structural diversity. We can also utilize known binders in DEL screenings to elucidate the binding modes of potential hits.

DEL-Driven Hit Identification for HAO1

DNA-Encoded Library (DEL) screening provided distinct hit series of potent HAO1 inhibitors. **Compound 5**, derived from X-Chem's proprietary oxadiazole library, was of high interest due to its high ligand efficiency (LE of 0.36), and outstanding physicochemical properties. Moreover, **Compound 5** demonstrated high potency in biochemical assays and was effective in the stringent CHO-GO cell assay. However, it exhibited low permeability, leading to less-than-optimal oral bioavailability and systemic exposure in mouse pharmacokinetic (PK) studies.



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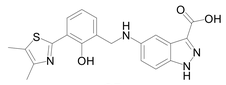

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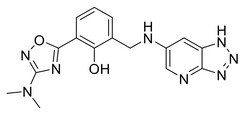
Category	Physicochemical Properties [a]				In Vitro Data		In Vivo Data (Pharmacokinetics [d])			
Compound	MW	clogP	clogD	tPSA	HAO1 IC_{50} (nM)[b]	Cell Rescue at 30μM (%)[c]	Cl_{obs} (mg/min/kg)	$T_{1/2}$(h)	AUC_{inf} (h*ng/m)	%F
5	394	2.2	1.0	131	37	82	2.1	2.5	4398	6
35	394	3.0	0.2	106	25	76	1.8	3.9	18180	19

[a]Calculated from ChemAxon. [b]Determined from at least two replicates. [c]Cell rescue values represent the average of at least n=3 separate assays (except for compound 35, n=1). [d]PK data on Compounds 5,35: Male CD1 mice were used for cassette iv (0.3 mg/kg) and po (10 mg/kg) PK studies. Pharmaokinetic parameters were calculated from plasma concentration time data and are reported as an average of 3 animals.

Structure-activity relationship (SAR) exploration methods were used to further optimize **Compound 5:** we developed **Compound 35** by replacing the dimethylamino oxadiazole with dimethyl thiazole, which maintained strong potency in the biochemical assay and exhibited improved permeability, leading to enhanced bioavailability and exposure upon oral administration. **Compound 35** represents a significant improvement over existing HAO1 inhibitors documented in current literature.

Drawing upon the crystal structure of **Compound 5** in complex with HAO1, we have identified a non-acidic HAO1 inhibitor, **Compound 37**, which aims to reduce risks related to poor permeability, significant protein binding, and the formation of potentially reactive glucuronide metabolites typical of acid-containing compounds.

A



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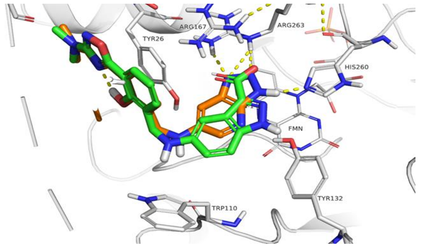
MW = 352, LE = 0.3
clogP = 1.8, tPSA = 119
HAO1 IC_{50} = 2.9 μM

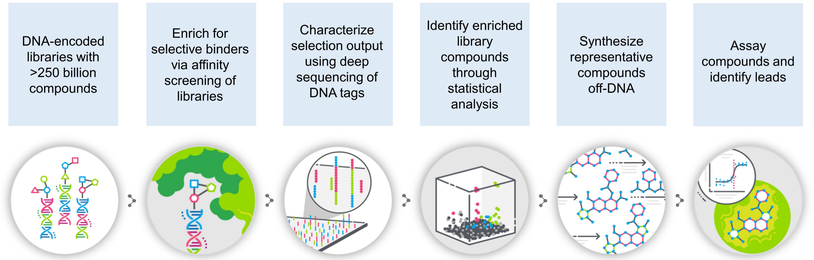
B



A. Compound 37. **B.** Docking mode of **Compound 37**, an azabenzotriazole designed as isosteric replacement to **Compound 5**, assumes a shifted orientation in the binding site. The docking pose was minimized with MM-GBSA.

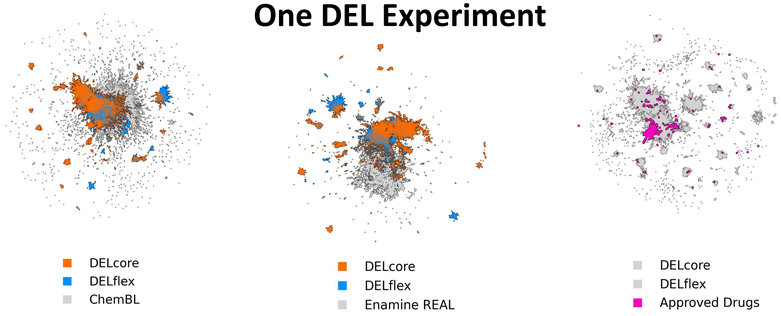
DEL to Accelerate Rare Disease Research

X-Chem DEL Platforms



Non-Covalent, Covalent, and Customized DNA Encoded Libraries

Unlock Large and Diverse Chemical Space With One DEL Experiment



DELcore and DELflex are X-Chem's DNA-Encoded Libraries.
Umap plots were generated using ECFP4 fingerprints.

For More Information

- Website: x-chemrx.com
- Contact us: info@x-chemrx.com
- Message me through LinkedIn: Jingyi (Zooey) Wang

References

[1] Lee, E.C.Y et al, 2021. Discovery of Novel, Potent Inhibitors of Hydroxy Acid Oxidase 1 (HAO1) Using DNA-Encoded Chemical Library Screening. Journal of Medicinal Chemistry, 64(10), 6730–6744. https://doi.org/10.1021/acs.jmedchem.0c02271