Lipoxygenase Library

Designed for identification of new lipoxigenases ligands
1,280 compounds

Lipoxygenases (LOXs) are enzymes that catalyze the formation of corresponding hydroperoxides from polyunsaturated fatty acids such as linoleic acid and arachidonic acid. LOX dioxygenases are widely expressed in immune, epithelial, and tumor cells. LOX activation induces structural and metabolic changes in the cell. Disregulation of LOX activity contributes to a number of pathophysiological conditions including inflammation, skin disorders and tumorogenesis.

The 1280 compound Enamine lipoxygenase library was created by taking two orthogonal approaches in the search for potentially active molecules:

- Docking-based *in silico* screening identified new chemical cores and scaffolds.
- Similarity searching discovered new points and vectors using 2D linear fingerprints and 3D pharamacophore features of reported lipoxygenases inhibitors

Molecular docking

Docking models were built from PDB reported protein structures 3O8Y, 4NRE and 3D3L. Prior to docking, all structures were optimized and reconstructed to correct gaps and missing side chains. Water molecules in coordination with Fe^{3+} ion (ionization state was assigned) were restrained to obtain suitable geometry.
Exhaustive filtering of Enamine's entire stock collection (2.6 million) resulted in a MedChem refined subset of ~2.0 million molecules that were then screened against the validated LOX protein models.

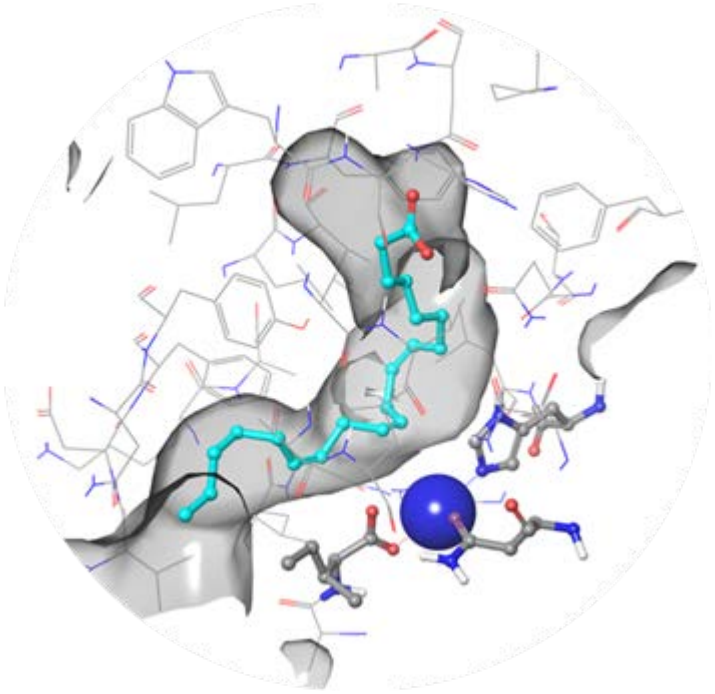

Figure 1. *h*LOX-5 binding site in surface volume representation (channel mode) with bound native substrate – arachidonic acid.

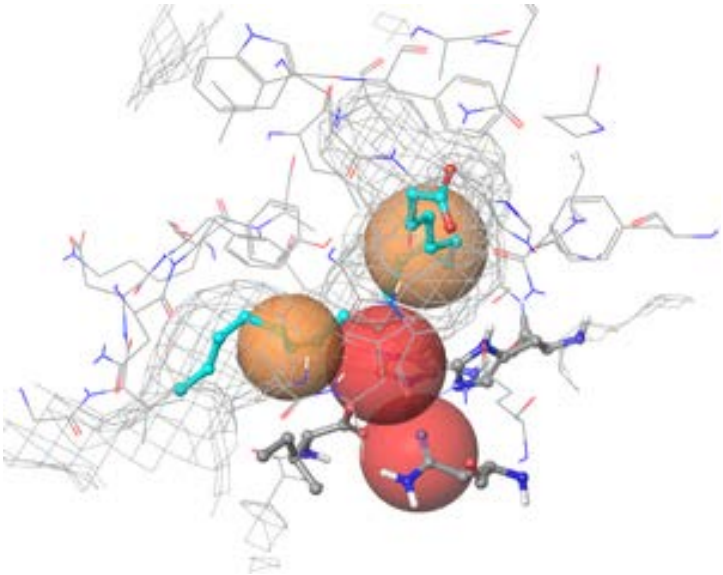

Figure 2. Binding site of *h*LOX-15-II (4NRE) in grid representation with indicated most important pharmacophore features: volume/shape, hydrophobic areas (colored in brown), H-bond acceptor and electron deficient fields colored in red.

Each docking model contained electrostatic descriptors of the binding site and three mandatory positional constraints. Hits were defined as possessing an obligatory alignment for two positional constraints - ***metal coordination*** (red) and ***hydrophobic center*** (orange), Fig.2. Docking results were evaluated through a comparison of docking scores and a follow up visual analysis of binding poses (presence of H-bonds, degree of exposure to water). The evaluation process of high scoring docking hits that passed manual inspection produced **950 molecules**.

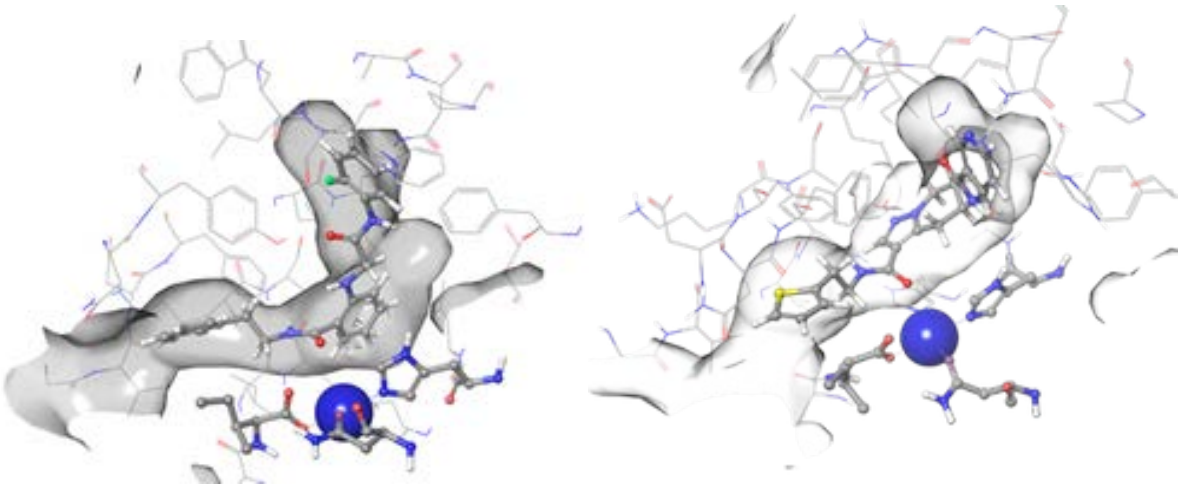

Figure 3. Examples of hit binding poses identified after docking calculation with high scoring functions – Z31004492 (left) and Z1849138647 (right). Both molecules form coordination bonds with iron and match two hydrophobic features in the binding pockets.

Similarity search

- A search of ChEMBLdb against the lipoxygenase targets name produced a reference set of 322 active molecules for three lipoxygenase types (A5, A12, A15). These compounds were then filtered by activity values (IC_{50}≤1μM) and against substructural MedChem filters to remove toxicophores.

- 2D similarity searching with a 0.85 threshold was performed using linear fingerprints and a Tanimoto algorithm (assumes more accurate assignment of atom types).
- Approximately **500 compounds** were selected from Enamine's screening collection and merged into the LOX library.

Representative examples of analogs included in the library with structures of reported active molecules