DESIGN OF XANTHORRHIZOL DERIVATIVES USING *IN SILICO* FRAGMENT-BASED DRUG DESIGN (FBDD) APPROACH AS LIPOXYGENASE INHIBITORS

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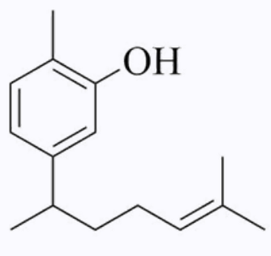
This study aimed to improve the activity of XNT towards sLOX by modifying its hydroxyl functionality using combination of *in silico* methods, which are molecular docking and fragment-based drug design (FBDD) approach. In this study, a total of 1887 new XNT derivatives were generated as sLOX inhibitors by using LigBuilder software. Then, only the top 50 derivatives which exhibit binding energies, ranging from –8.4 to –9.0 kcal/mol were screened to remove duplicates. Subsequently, these generated derivatives underwent further evaluation and modification based on their ADME (absorption, distribution, metabolism, and excretion) properties, druglikeness as well as synthetic accessibility of these derivatives, resulting in the generation identification of the final four structures of XNT derivatives.

INTRODUCTION



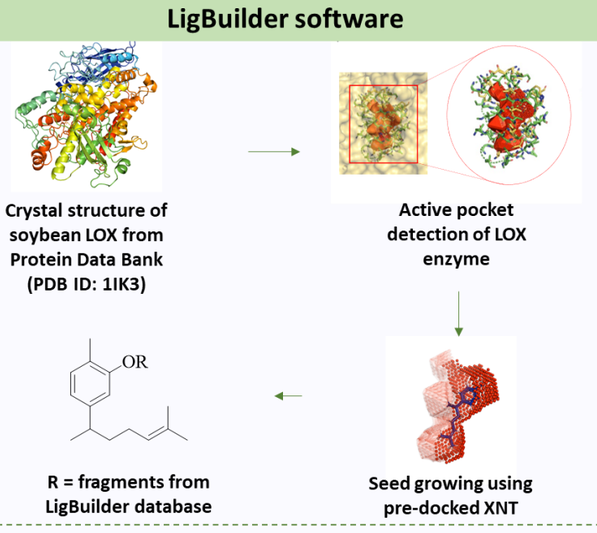
- Xanthorrhizol (XNT) is isolated from rhizome part of *Curcuma xanthorrhiza (*temulawak)[1]
- Small molecular weight (MW = 281.33 g/mol)
- A suitable candidate to be modified as potent drug compound.
- The traditional drug design approach has high cost and time-consuming with low success rate[2]

OBJECTIVES

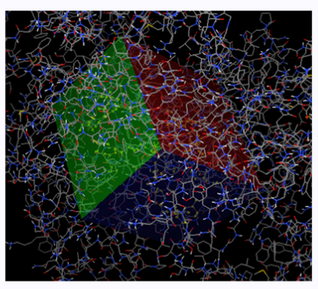
- To design novel xanthorrhizol derivatives as potential LOX inhibitors using *in silico* FBDD approach.
- To evaluate the ADME and druglikeness properties of xanthorrhizol derivatives using SwissADME tools.

METHODOLOGY

1. *In silico* FBDD using XNT as "seed" structure *via* LigBuilder software



2. Molecular docking of XNT derivatives against LOX enzyme using AutoDock Vina

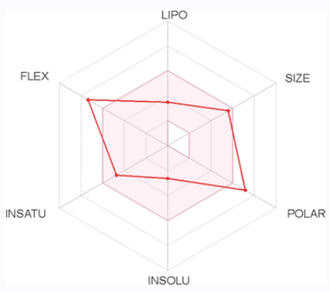


Center;
x= 20.950
y= 0.657
z= 18.863

No. of points;
x= 20
y= 26
z= 26

Site-targeted docking

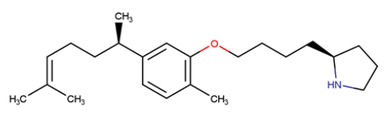
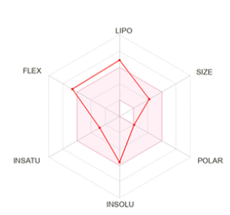
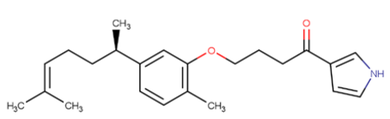
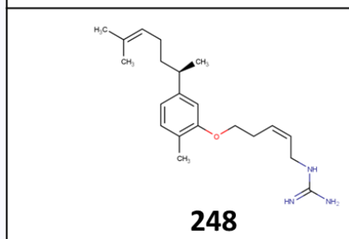
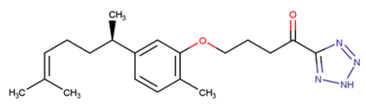
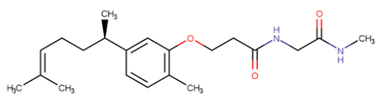
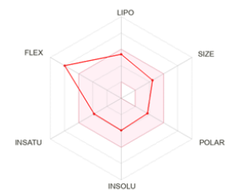
3. *In silico* ADME and druglikeness properties prediction using SwissADME tools



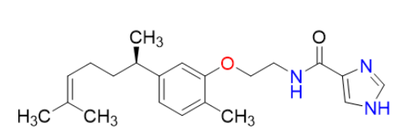
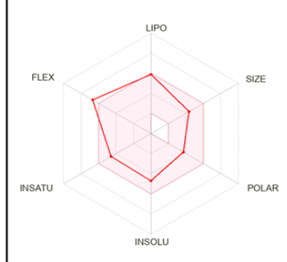
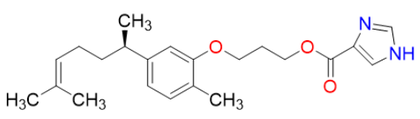
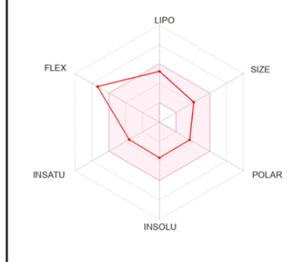
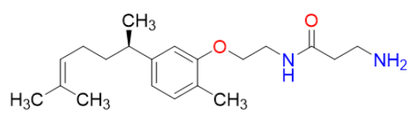
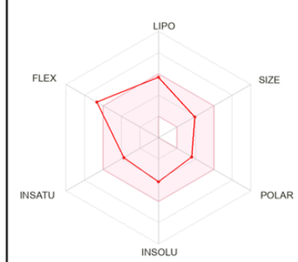
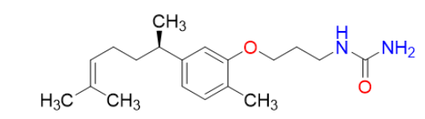
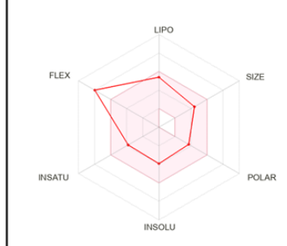
Bioavailability radar diagram

RESULTS AND DISCUSSIONS

- 1887 derivatives composed of long alkyl chain with heteroatoms were generated.
- Long alkyl chain moieties due to the long hydrophobic channel of sLOX binding pocket[3].
- Derivatives generated did not satisfy the parameters required to fulfil the criteria as drug-like compounds.
- Further modifications were needed to improve their ADME properties.

Derivative Binding energy, BE (kcal/mol)	Bioavailability radar diagram
 408 BE= -8.9	
 922 BE= -8.9	
 248 BE= -8.7	
 694 BE= -8.7	
 167 BE= -8.6	

Modification of side chain

Derivative Binding energy, BE (kcal/mol)	Bioavailabity radar diagram
 LOX-01 BE= -8.3	
 LOX-02 BE= -8.3	
 LOX-03 BE= -8.0	
 LOX-04 BE= -8.1	

✓ Good binding energy
✓ Improved ADME properties
✓ Feasible synthetic route

CONCLUSION

- 1887 derivatives with improved binding affinity were generated by modifying the -OH group of XNT using *in silico FBDD* approach.
- Further modification of the derivatives with consideration of its good BE, improved ADME properties as well synthetic accessibility successfully generated four final compounds to be synthesized.
- This work provides **more efficient approach in term of time and cost consumption** for drug modification towards more potent drug candidates through the incorporation of computational tools.

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