

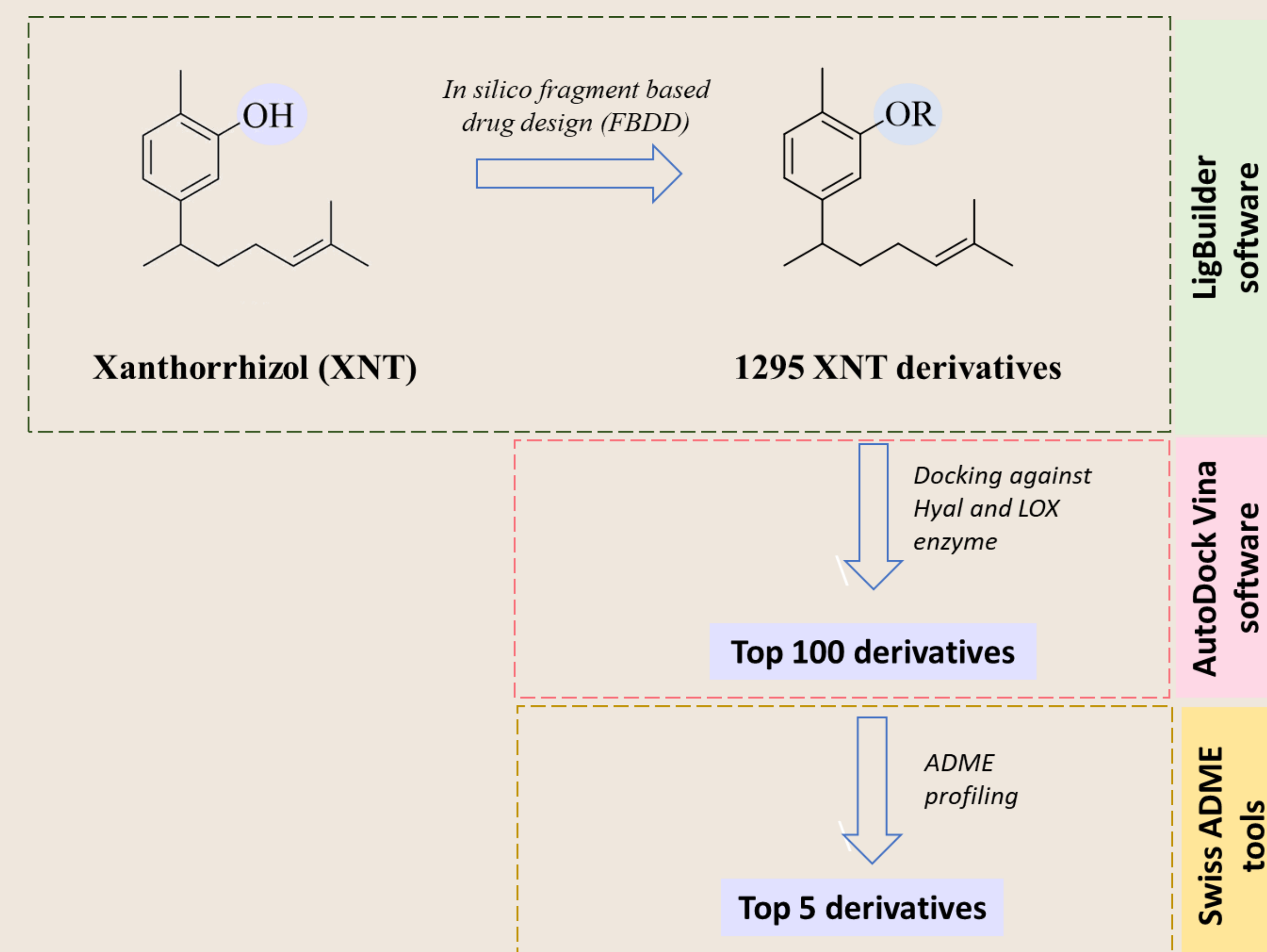
DESIGN OF XANTHORRHIZOL DERIVATIVES USING *IN SILICO* FRAGMENT-BASED DRUG DESIGN (FBDD) APPROACH AS HYALURONIDASE INHIBITORS

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GRAPHICAL ABSTRACT



INTRODUCTION

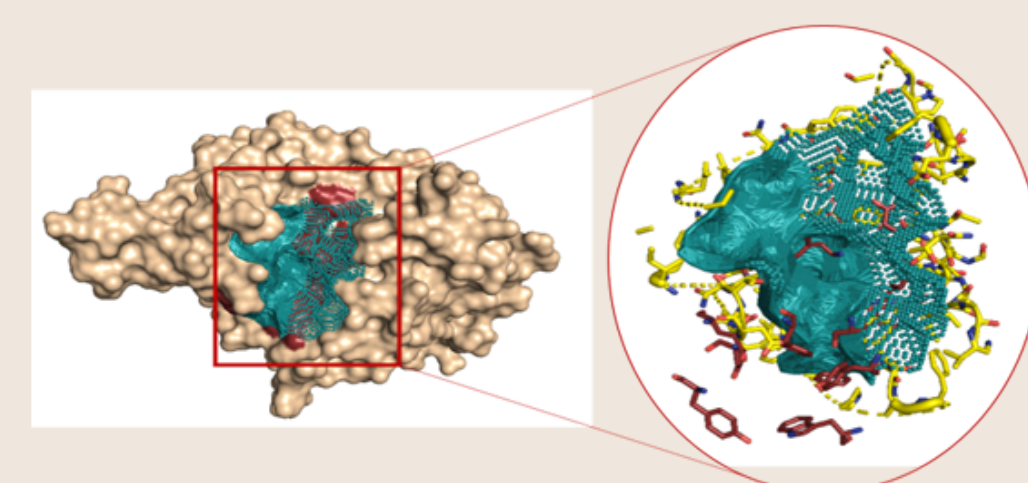
Xanthorrhizol (XNT) is a type of bisabolene sesquiterpenoids and can be isolated from rhizome part of *Curcuma xanthorrhiza* essential oil¹. Various biological activities of XNT were reported in literature, including anti-inflammatory properties through inhibition of pro-inflammatory enzymes, such as cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS)². Due to its small molecular weight (MW = 281.33 g/mol) and biological benefits, XNT is a suitable candidate to be further optimized as a more potent drug compound. Preliminary *in vitro* and *in silico* inhibitory studies showed that XNT exhibited low activity (8.79 % inhibition at concentration 100 µg/mL, binding energy = -6.5 kcal/mol) towards hyaluronidase (Hyal), an enzyme responsible for the degradation of hyaluronic acid (HA), resulting in the formation of small, low-molecular weight hyaluronic acid fragments that can induce inflammatory response towards human body³. In this study, *in silico* fragment-based drug design (FBDD) approach was utilized to optimize XNT by modifying the hydroxyl (-OH) group, generating new derivatives with stronger affinity towards Hyal enzyme, as well as better ADME and druglikeness properties, which are crucial for the drug absorption in human body.

METHODOLOGY

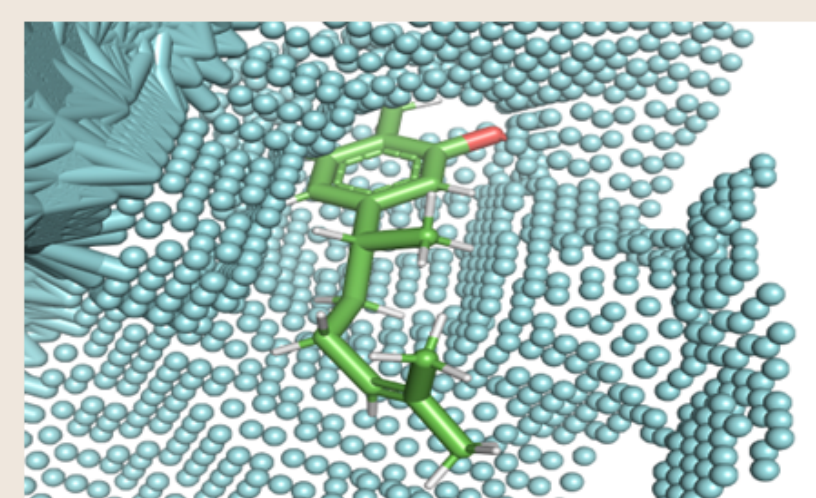
1. *In silico* FBDD using XNT as “seed” structure via LigBuilder software



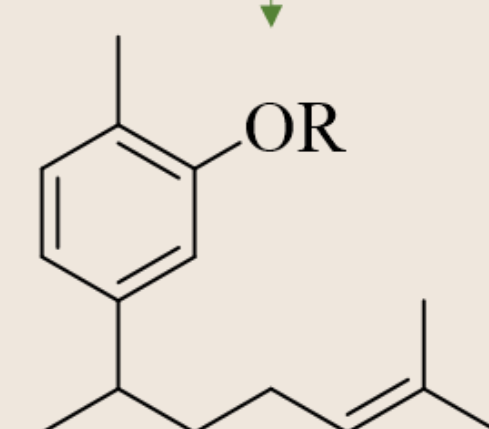
Crystal structure of human hyaluronidase-1 from Protein Data Bank (PDB ID: 2PE4)



Active pocket detection of Hyal enzyme

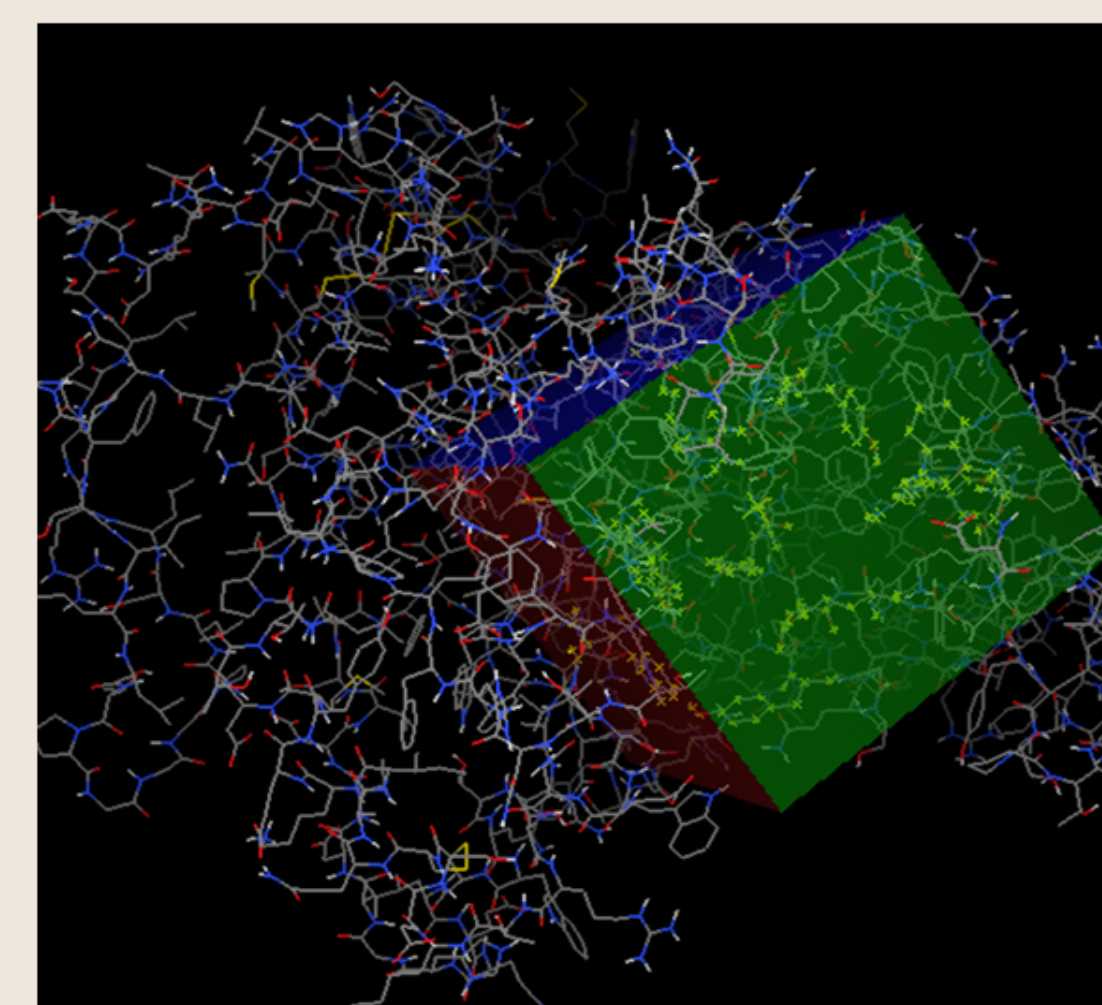


Seed growing using pre-docked XNT



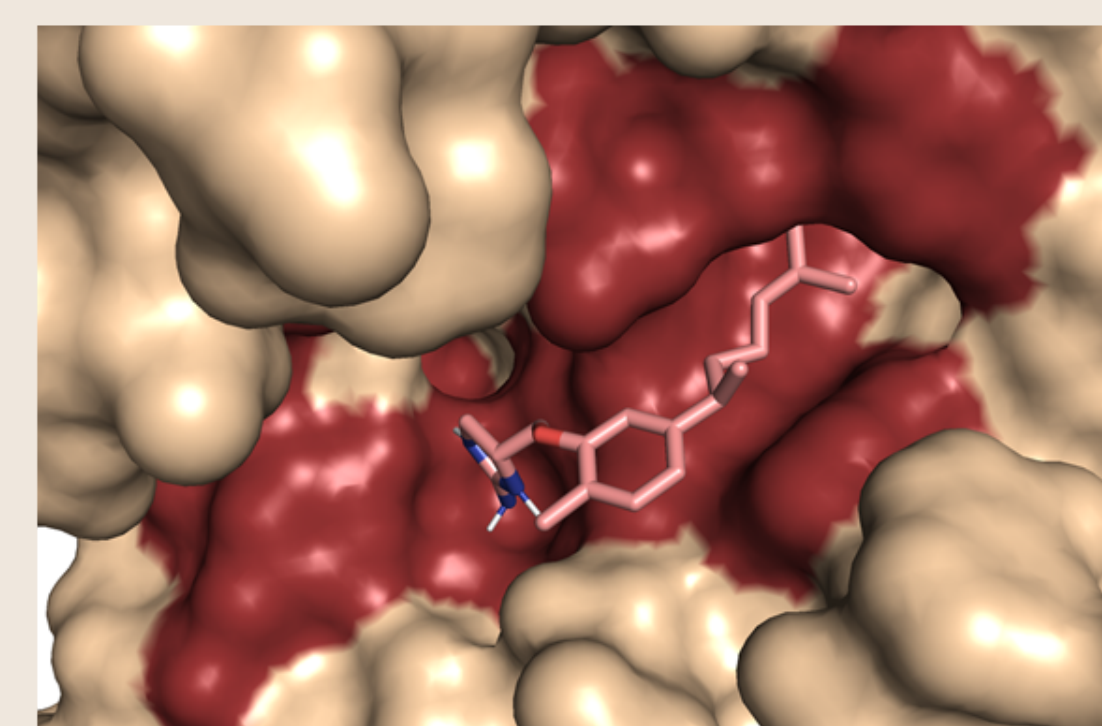
R = fragments from LigBuilder database

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



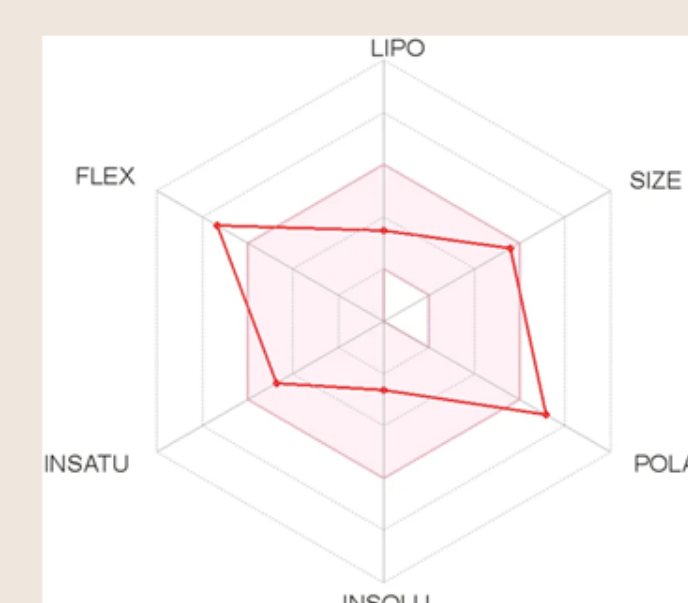
Grid box specification

Center; No. of points;
 x= 37.045 x= 62
 y= -17.292 y= 58
 z= -10.421 z= 58



Site-targeted docking

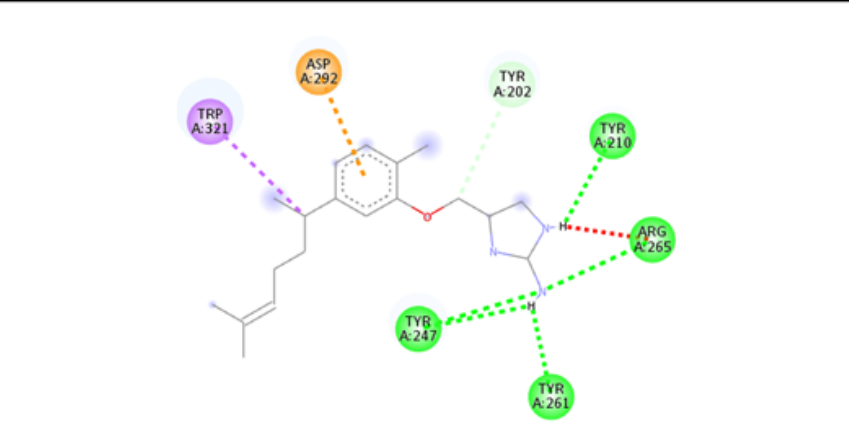
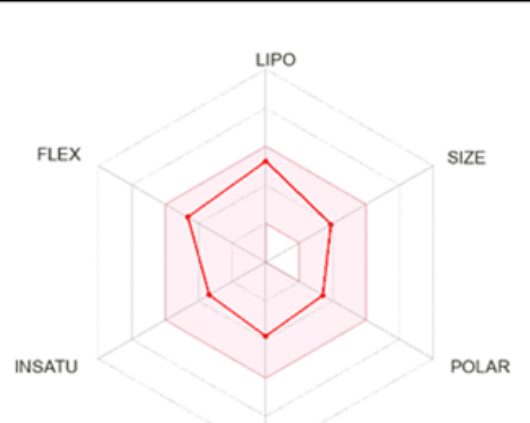
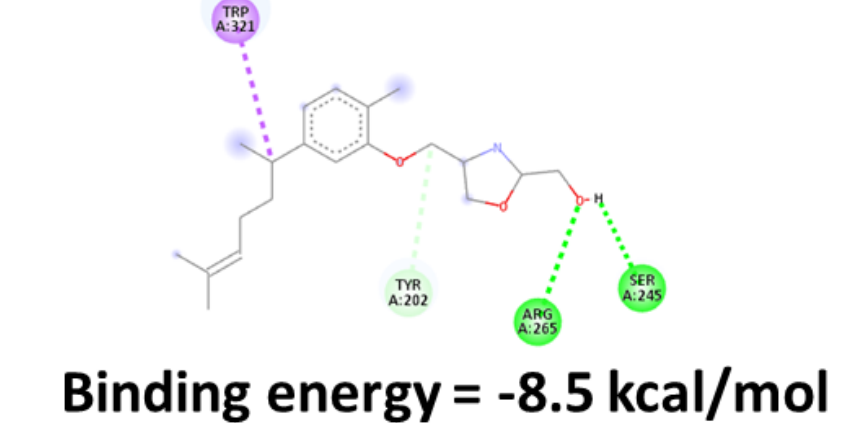
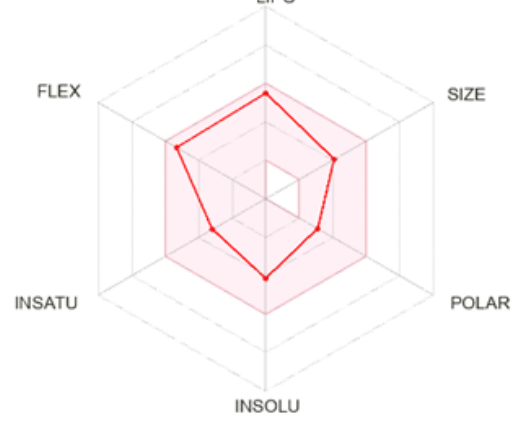
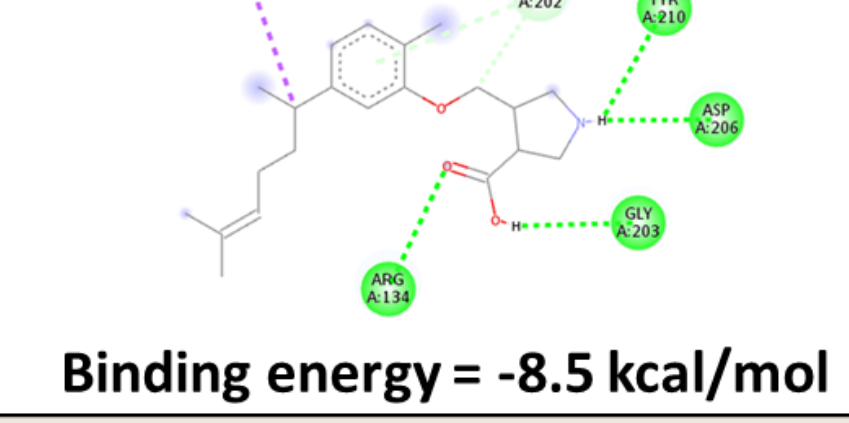
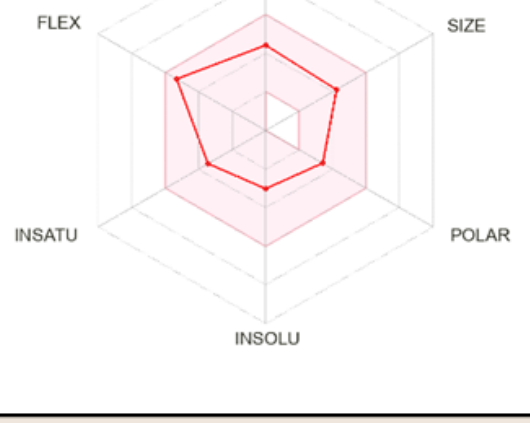
3. *In silico* ADME prediction using SwissADME tools

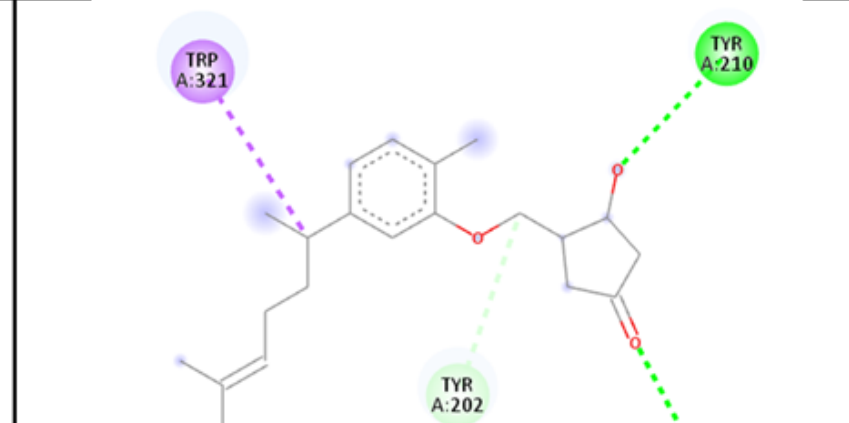
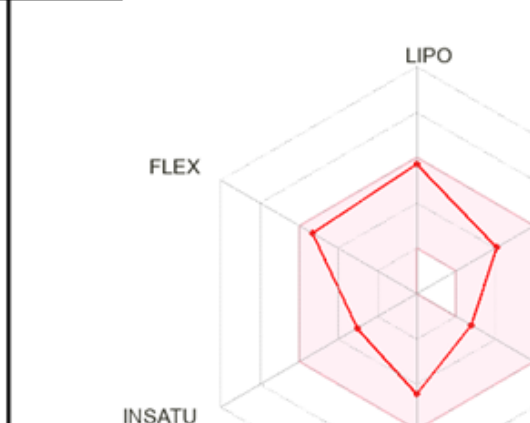
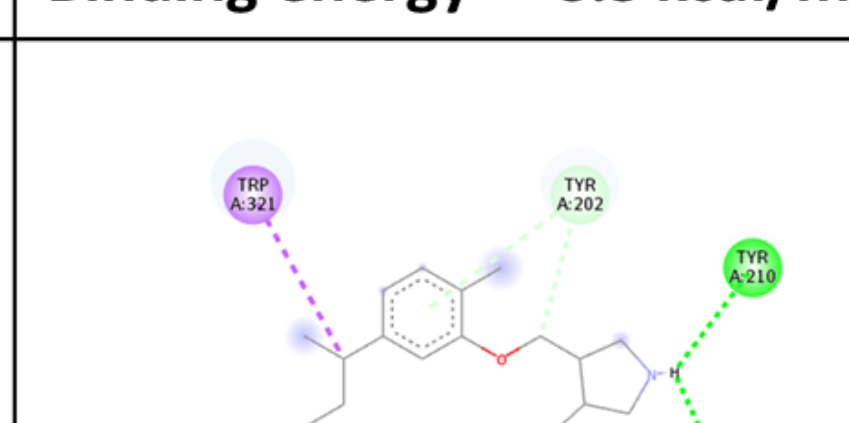
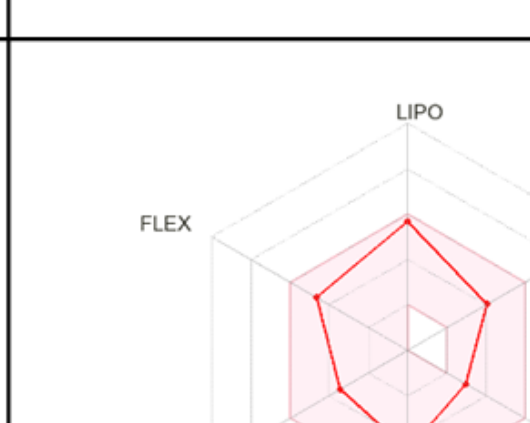


Bioavailability radar diagram

RESULTS AND ANALYSIS

1295 XNT derivatives were generated through *in silico* FBDD approach in LigBuilder, and molecular docking studies revealed that the derivatives were bound to Hyal enzyme with binding energies ranging from -8.5 kcal/mol to -6.2 kcal/mol. Then, top 100 derivatives with best binding energies were further screened to remove duplicates and predict their druglikeness properties using SwissADME tools. Five fragments, **013**, **515**, **552**, **885**, and **507** substituted to the -OH group of XNT showed improved binding affinity and drug likeness properties compared to XNT. From the 2D representation of the docking result, it can be observed that derivatives composed of pentacyclic rig fragment exhibited higher energy and favourable binding through hydrogen bonding and pi-interactions. Moreover, the presence of heteroatoms such as nitrogen and oxygen not only contributed to the protein-ligand interactions, but also towards optimized ADME properties.

Fragments	2D representations	Bioavailability radar
013	 Binding energy = -8.5 kcal/mol	
515	 Binding energy = -8.5 kcal/mol	
552	 Binding energy = -8.5 kcal/mol	

Fragments	2D representations	Bioavailability radar
885	 Binding energy = -8.3 kcal/mol	
507	 Binding energy = -8.2 kcal/mol	

CONCLUSION

- 1295 derivatives were successfully generated by modifying the -OH group of XNT using *in silico* FBDD approach
- Substitution to pentacyclic ring fragment** improved the binding affinity towards Hyal and were also predicted to **satisfy all the important parameters for drug absorption in human body**.
- Through the incorporation of computational tools, this work greatly helped in the **exploration of chemical space for site-targeted drug design** as well as providing a **more efficient approach in term of time and cost consumption** for drug modification towards more potent drug candidates.

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ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from the Fundamental Research Grant Scheme FRGS19-029-0637 (FRGS/1/2018/STG01/UIAM/03/3) by the Ministry of Higher Education, Malaysia, and the Kulliyyah of Science, International Islamic University Malaysia (IIUM), Kuantan for the research facilities