Binding Mode Analysis of Chaetomellic Acids (A and B) as Farnesyl Transferase Inhibitors

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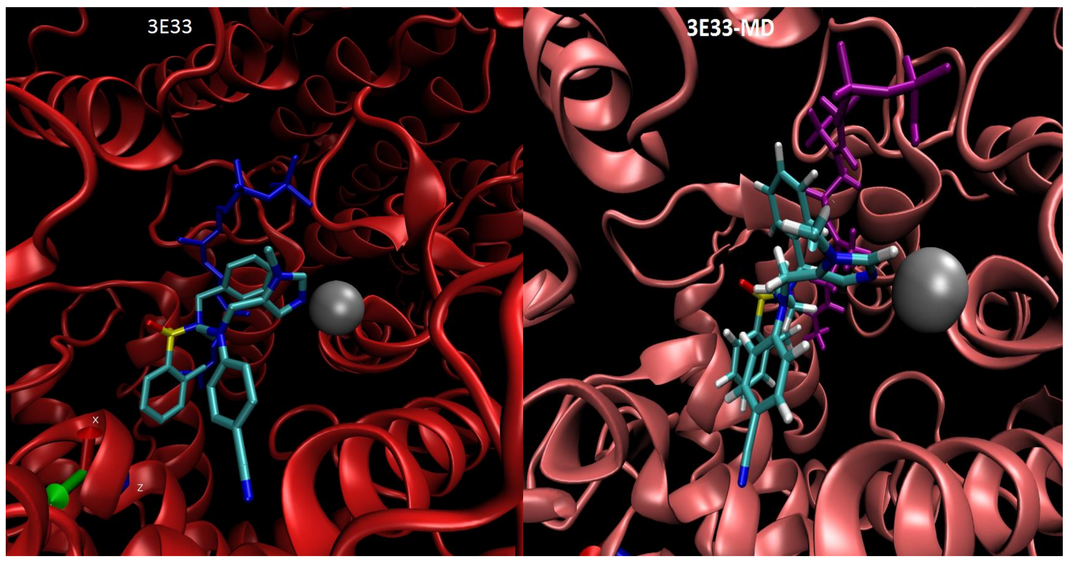
Farnesyltransferase (FTase) is one of three prenyltransferase enzymes has become a major target in the development of potential anticancer drugs. In the present investigation, we have predicted the binding mode of natural product compounds chaetomellic acid A (N1) and B (N2) on the FTase enzyme.

Figure 1: Binding of inhibitors present in pdb (3E33) in normal and after MD simulations



In the present investigation, we have performed docking and molecular dynamics (MD) simulation on different FTase enzymes (with and without the farnesyl pyrophosphate (FPP) substrate). In addition, protein ligand interaction fingerprint (PLIF) analysis was performed on different docked conformations of a data set of natural products.

Docking : vs-Lab with VMD plug in, Autodock,
Molecular Dynamics Simulation: Amber 9 and Amber12
PLIF Pharmacophore analyses : MOE
***In silico* Pharmacokinetic studies:** SwissADMET
Biological evaluation : Activity reported in literature

Table 1: *In silico* Predicted Properties of compounds

Properties	Predicted Value (N1)	Predicted Value (N2)
Water solubility (A)	-2.754	-2.97
Caco2 permeability (A)	0.335	0.321
Intestinal absorption (human) (A)	91.98	90.186
Skin Permeability (A)	-2.735	-2.735
P-glycoprotein substrate (A)	No	No
P-glycoprotein I inhibitor (A)	No	No
P-glycoprotein II inhibitor (A)	No	No
VDss (human) (D)	-1.012	-1.023
Fraction unbound (human) (D)	0.198	0.13
BBB permeability (D)	-0.393	-0.386
CNS permeability (D)	-2.817	-2.759
CYP2D6 substrate (M)	No	No
CYP3A4 substrate (M)	Yes	Yes
CYP1A2 inhibitor (M)	No	No
CYP2C19 inhibitor (M)	No	No
CYP2C9 inhibitor (M)	No	No
CYP2D6 inhibitor (M)	No	No
CYP3A4 inhibitor (M)	No	No
Total Clearance (E)	1.876	1.981
Renal OCT2 substrate (E)	No	No
AMES toxicity (T)	No	No
Max. tolerated dose (human) (T)	-0.427	-0.514
hERG I inhibitor (T)	No	No
hERG II inhibitor (T)	No	No
Oral Rat Acute Toxicity (LD50) (T)	2.285	2.335
Oral Rat Chronic Toxicity (LOAEL) (T)	3.058	3.112
Hepatotoxicity (T)	No	Yes
Skin Sensitisation (T)	No	No
T.Pyriformis toxicity (T)	0.281	0.285
Minnow toxicity (T)	-0.713	-1.101

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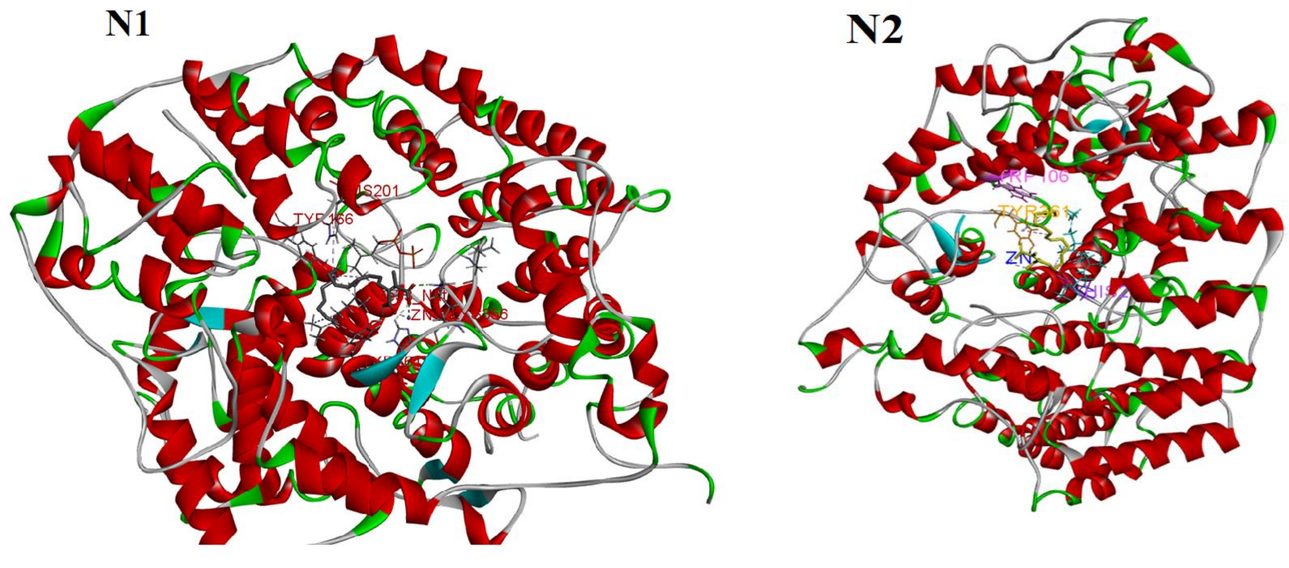
Figure 2: Binding mode of Chaetomellic acid A (N1) and Chaetomellic acid B (N2)



Figures 3: Fingerprint representations on natural product compounds Chaetomellic acid A (N1) and B (N2)

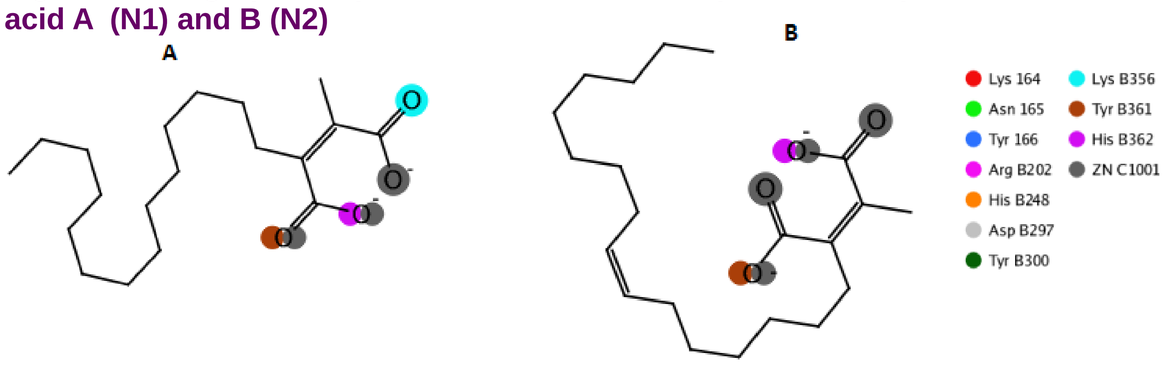
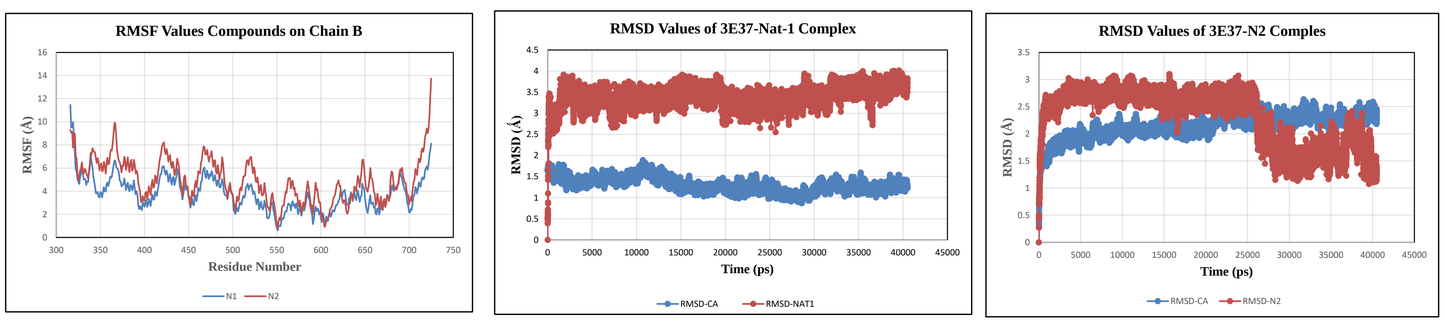


Figure 4: RMSD and RMSF values of Molecular Dynamic simulations



The natural compounds have same binding pose as the ligands in the PDB structures. The molecular dynamics simulations and in silico pharmacokinetic analysis reveled that these compounds can be used for the development of novel bioactive molecules.

Table 2: Fingerprint of Natural product compounds

Residue Number	Type of Interaction	% Abundance	
		N1	N2
164	Surf1	20.000	
B96	Surf1	20.000	
B300	ChAcc1	60.000	66.667
B356	ChAcc1	40.000	
B356	ChAcc2	40.000	
B356	Ionic1	40.000	
B356	Ionic2	40.000	
B361	ChAcc1	20.000	66.667
B361	ChAcc2	20.000	66.667
B362	ChAcc1		66.667
B362	ChAcc2		66.667
C1001	Ionic1	80.000	66.667
C1001	Ionic2	80.000	66.667

The docking, molecular dynamics simulations, protein ligand interaction fingerprint (PLIF) and *in silico* ADME prediction on these compounds were performed to analyse the binding mode interactions. The crystallographic structure (pdb id 3E33) was used for the docking and MD simulation studies and it provided the docking score of -8.5 and -7.55 for chaetomellic acid A and B respectively.

The chain B of the FTase has significant interactions with these compounds. The results showed that some important residues, such as LeuB96, ArgB202, TyrB300, AspB359, TyrB361 and His362 are predominantly present in the complexes for interactions. In all protein-ligand complexes, the LeuB96 interacts with chaetomallic acid via surface interaction (solvent exposed surface).

TyrB300 and TyrB361 are forming surface and side-chain acceptor interactions with the ligands. The later residue (TyrB361) also provided an interaction fingerprint on the backbone acceptor interactions. The Molecular Dynamics simulations of the complexes showed significant RMSD and RMSF values on stabilized complexes through interaction with TYR361, His362, Lys356, etc residues.

In silico pharmacokinetic prediction of the compounds revealed that these compounds have high logP values (>5.5). It showed that these compounds are not metabolized by the CYP enzymes except CYP3A4 and do not have any hERG blocking activity.

These compounds have reported FTse inhibitory activities of 55 nM and 185 nM for Chaetomellic acid A and B respectively. The binding interaction studies, *in silico* pharmacokinetic prediction and the reported biological activities of the compounds showed that it may be taken as lead compounds to develop novel FTase inhibitors.

References
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