Reduction of Anti-HER2 Resistance in Breast Cancer by Resolving Steric Clashes at the Orthosteric Site of HER2^{T798I} Mutant

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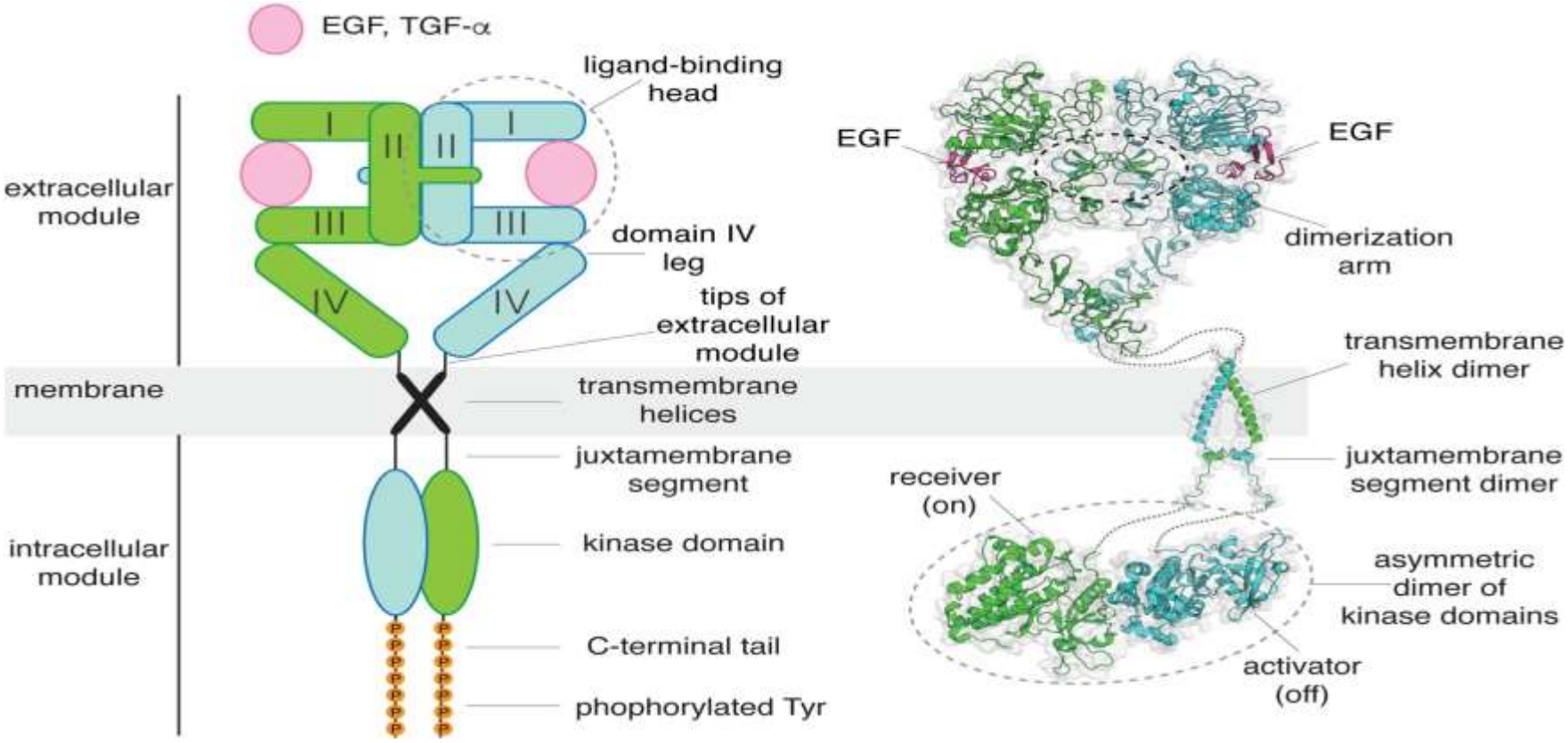
Introduction

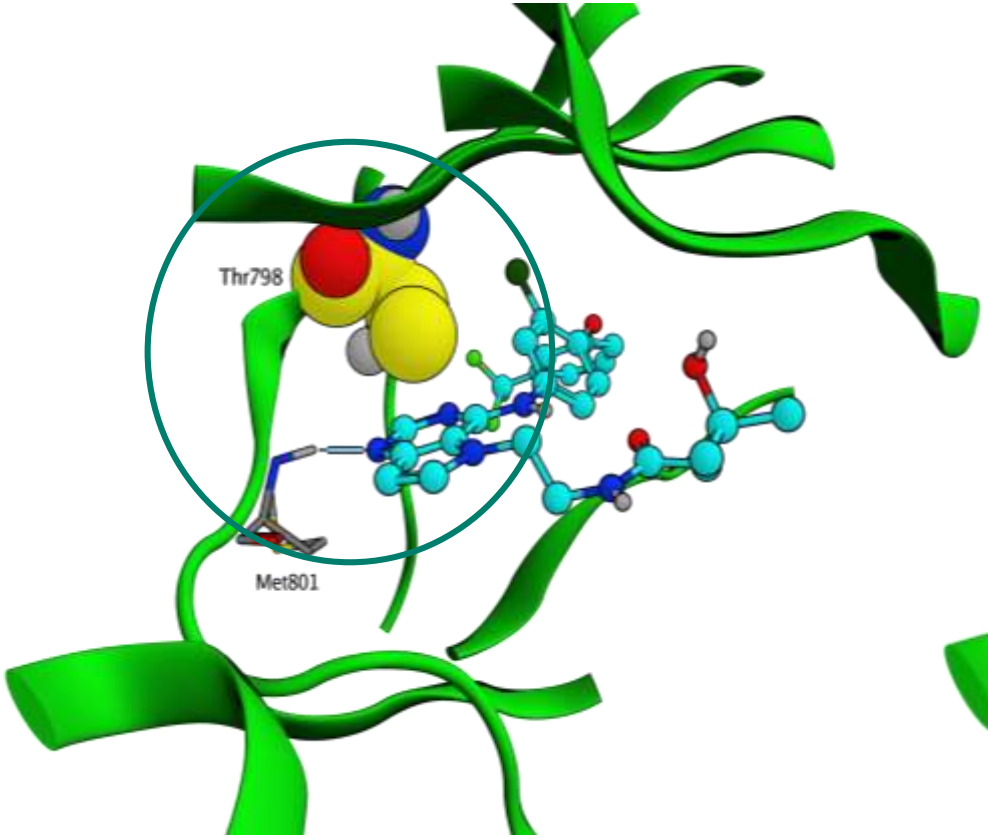
- Breast cancer develops from cells that grow uncontrollably.
- Classified into three subtypes or classes based on the presence or absence of specific proteins in the cancer cells.

Around 70% of BC cases are hormone receptor-positive, meaning they have either the progesterone receptor (PR) or estrogen receptor (ER) protein. Another 15 to 20% are HER2-positive, indicating high levels of the HER2 protein. The remaining 15% of cases are triple-negative, meaning the cancer cells lack all Three target proteins: ER, PR, and HER2.

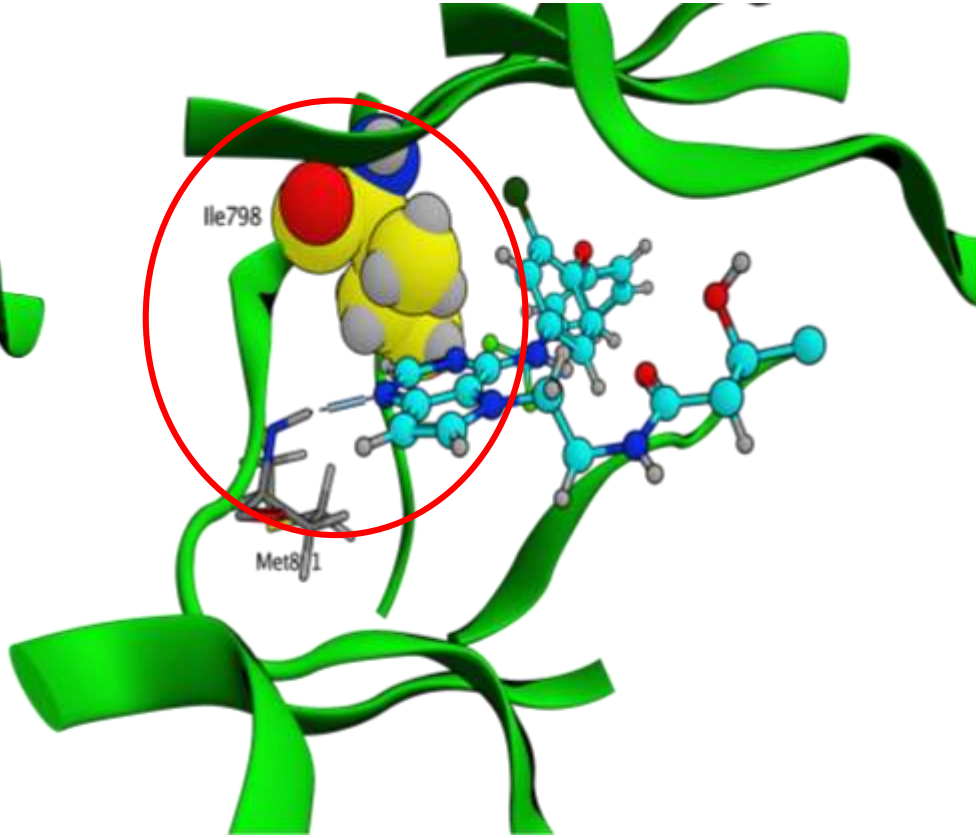
Human Epidermal Growth Factor Receptor 2 (HER2)



Mutated Receptor



Wild HER2 kinase (HER2^{T798})



Mutant HER2 kinase (HER2^{I798})

Aim of the Project

The study aims to reduce anti-HER2 resistance in breast cancer by eliminating steric clashes at the orthosteric site in mutant $HER2^{T798I}$, flexible lapatinib analogs will be designed to avoid these clashes.

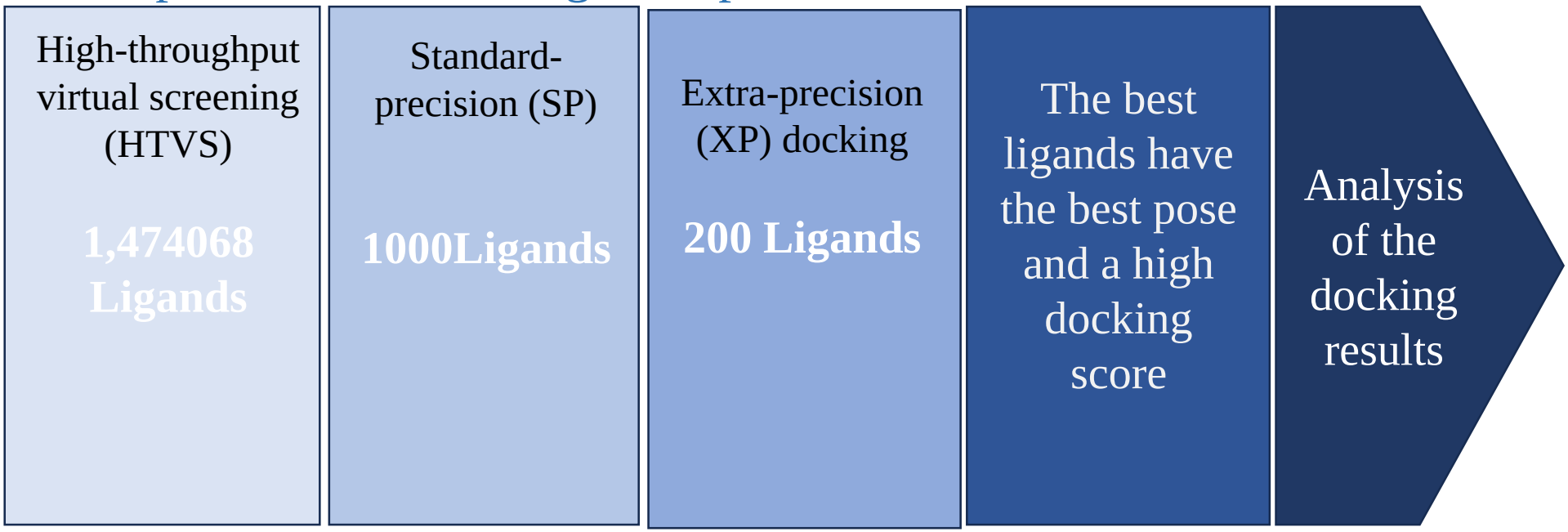
Methods & Material

We use computational methodologies and modeling software by using

- Maestro software to prepare and dock for ligand and protein.
- The next step is monitoring pharmacokinetics by Swiss ADME assign
- And pose ligand by Molecular Dynamics (MD) Simulations.

Methods & Material

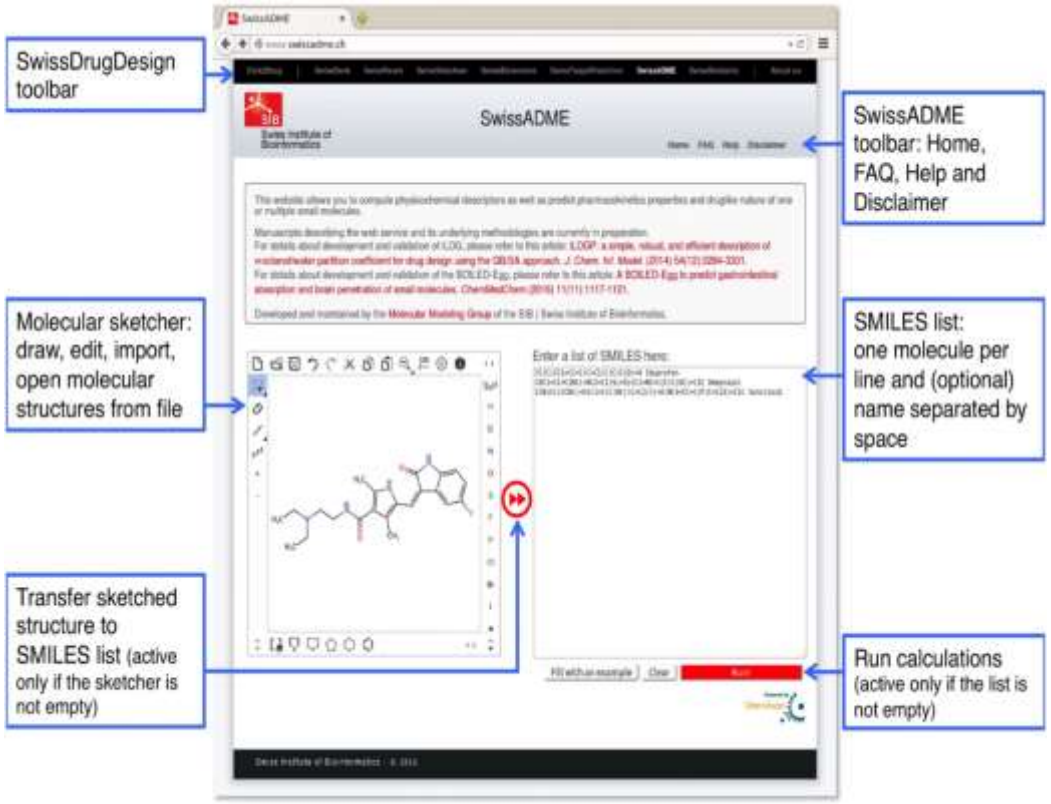
1. Prepare and dock for ligand _ protein



Methods & Material

2. Swiss ADME

- The Swiss ADME web tool presented here is freely accessible Pharmacokinetics examining absorption, distribution, metabolism, and excretion.
- Early estimation during discovery reduces pharmacokinetics-related failure in clinical phases.

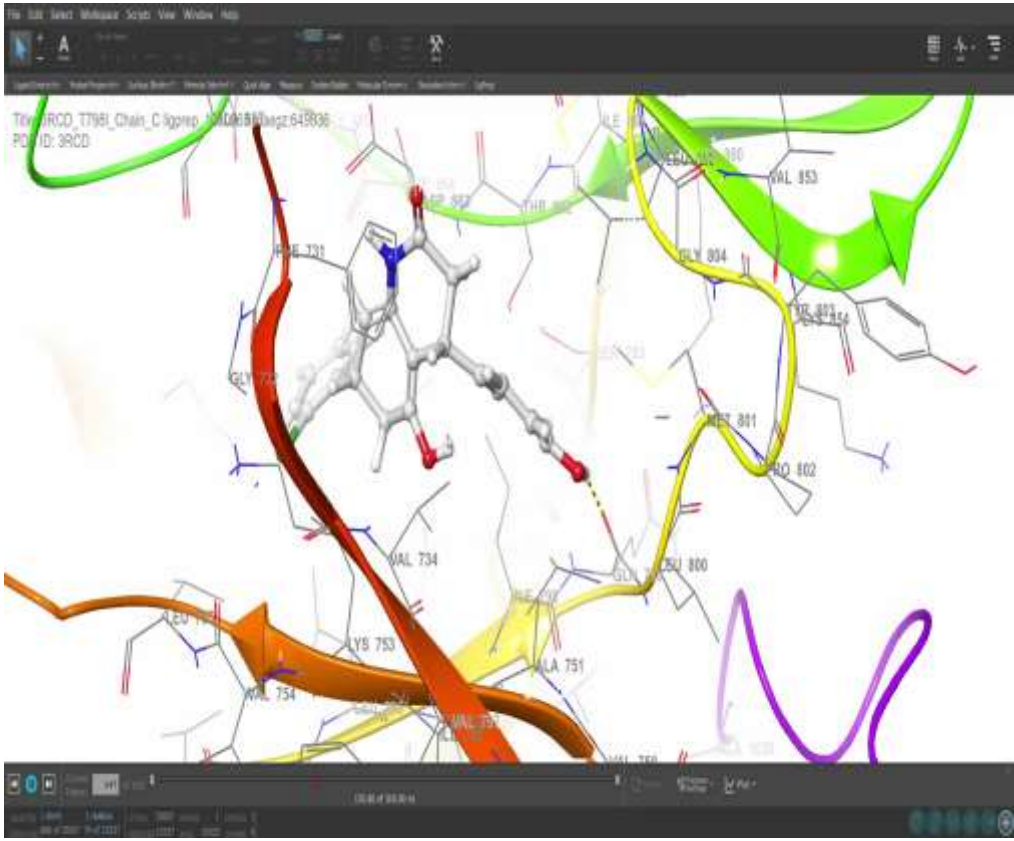


Methods & Material

3. Molecular dynamics analysis

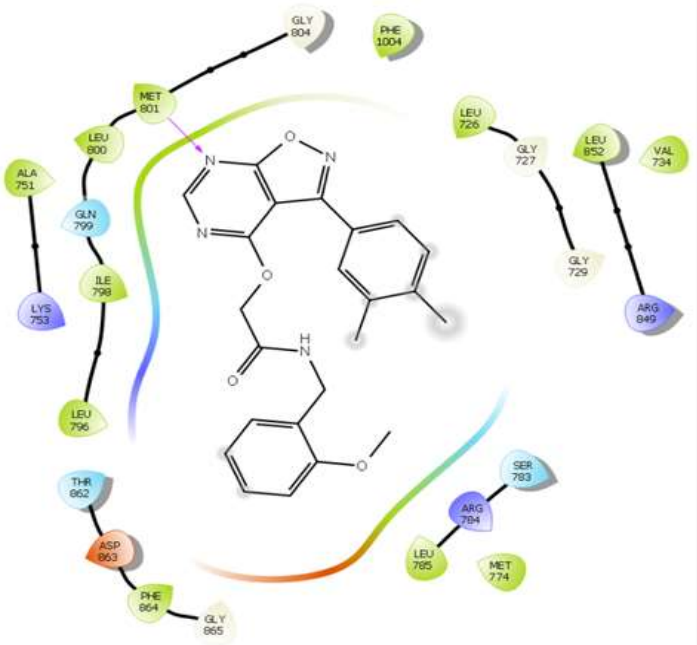
Molecular dynamics simulation is a method used to determine how atoms and molecules move over a certain time.

The timeline depicts protein interactions with ligands, including H-bonds, hydrophobic, ionic, and water bridges.



Results and discussion

1. Docking analysis: Compound have docking higher than Lapatinib.



Compound (C):856174
Docking score: -9.921

Results and discussion

2. Swiss ADME analysis

A. Physicochemical Properties

Compound	MW Daltons (Da)	TPSA Å	Rotatable bonds	HBA	HBD	ESOL Class	CLog P
856174 (C)	418.45	99.37	8	7	1	Moderately soluble	3.29

B. Pharmacokinetics Properties:

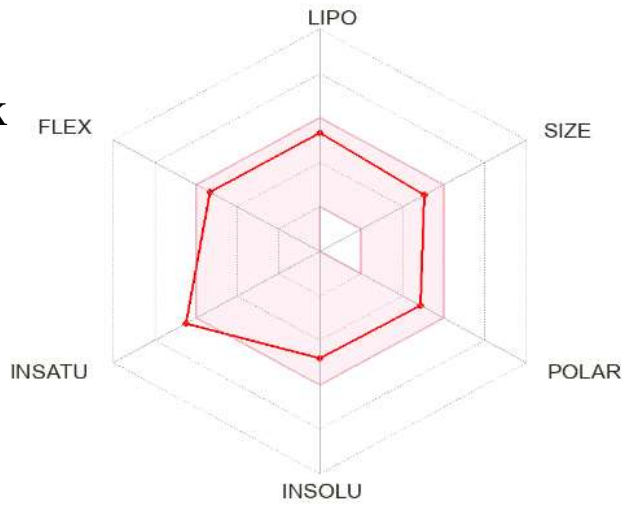
Compound	Predicted LD50: mg/kg	Predicted Toxicity Class	Hepato-toxicity	GI absorption	BBB permeant
856174 (C)	10000mg/kg	6	Inactive	High	No

Results and discussion

C. Bioavailability

Bioavailability radars for the most active compound: **C** The pink area represents the optimal range for each property:

- lipophilicity (LIPO) (XLOGP3 between −0.7 and +5.0)
- Molecular mass (SIZE) (between 150 and 500 g•mol -1) polarity (POLAR) (TPSA between 20 and 130 Å 2)
- Solubility (INSOLU) (log S not higher than 6)
- Saturation (INSATU) (fraction of carbons in the sp 3 hybridization not less than 0.25
- Flexibility (FLEX) (no more than nine rotatable bonds).



(C):856174

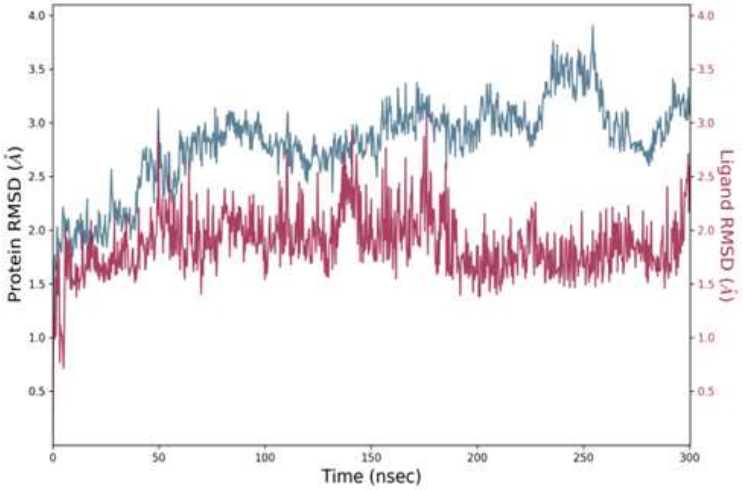
Ideal Drug likeness

Results and discussion

3. Molecular dynamics analysis

Shows the Cα protein backbone starts stable but at 235.5 ns of trajectory has significant fluctuations ranging between 3.4–3.6 Å indicating no large conformational changes to the protein.

(Lig)fit on the protein plot the protease complex's overall RMSD plot compound(C)856174, which displays ripples between 1.5-3 Å, indicates that the ligand is stably attached to the binding site of the protease and has not dispersed away from it

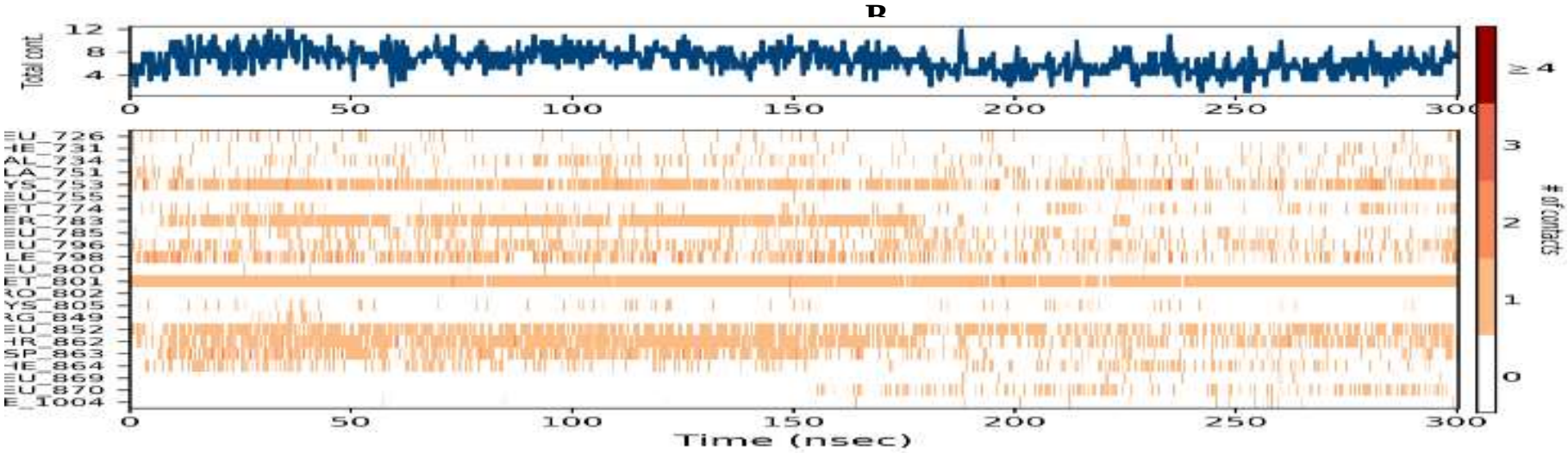


Compound(C): 856174

Results and discussion

A

Protein-ligand contacts analysis for 3RCD-compound 856174



. **Figure.** shows longer continued contact with MET801.

Conclusions and future scope:

The study screened compounds for anti-her2 resistance in breast cancer, with showing best docking scores. **Compound (C)856174**, with a docking score of -9.92 kcal/mol, formed H-bonds with receptor residues and showed moderate solubility, low hepatotoxicity, and high GI absorption.

Further studies will be conducted through:

a) Kinase profiling against HER2 protein kinase.

b) In vitro and in vivo screening of **Compound (C)856174** to validate its activity.

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Thank you