The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

In silico drug discovery of new anti-breast cancer inhibitors based on 3D-QSAR, molecular docking and ADMET investigation

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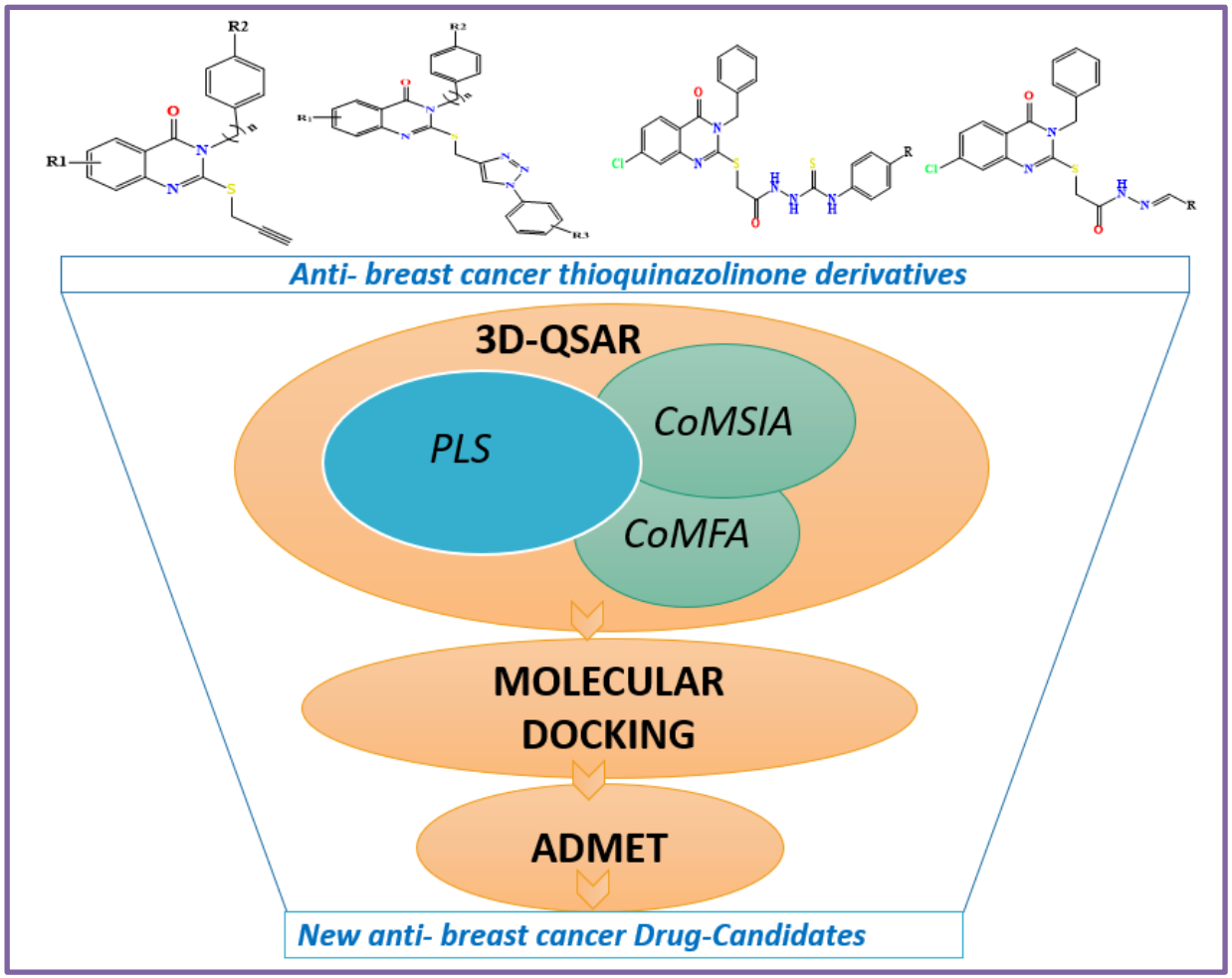
In silico drug discovery of new anti-breast cancer inhibitors based on 3D-QSAR, molecular docking and ADMET investigation



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Abstract:
Breast cancer is a common kind of cancer affecting women with a fatal outcome. Due to extensive treatment cycles, breast cancer resistance has now become a worldwide issue. Therefore, the only realistic treatment is the rapid development anti-breast cancer medications. To improve and propose new anti-breast cancer drugs, three-dimensional quantitative structure-activity relationships (3D-QSAR) and molecular docking studies on thioquinazolinone derivatives with aromatase enzyme (PDB: 3S7S) were attempted. Comparative Molecular Similarity Indices Analysis (CoMSIA) was utilized to develop the 3D-QSAR model in this study. The best CoMSIA model (with considerable values of Q^2, R^2 and R^2_{pred}) was also utilized in an effort to get the high predictability. External validation that uses a test set has been utilized to validate the predictive ability of the fitted model. According to the findings, the Electrostatic, Hydrophobic, Hydrogen Bond Donor and Acceptor fields had a serious influence on anti-breast cancer activities. Thus, we designed a variety of novel effective aromatase inhibitors based on prior findings and predicted their inhibitory activities using the best model. Moreover, ADMET investigations were employed to analyze the pharmacokinetic properties of drug-candidates.
abstract.

Keywords: Breast cancer; Thioquinazolinone derivatives; QSAR; Molecular docking; ADMET

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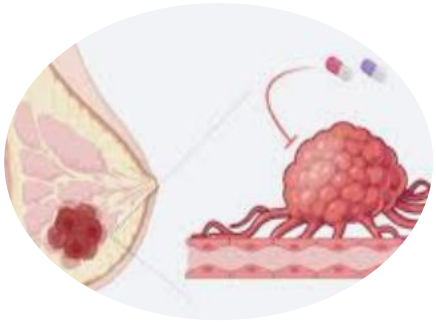
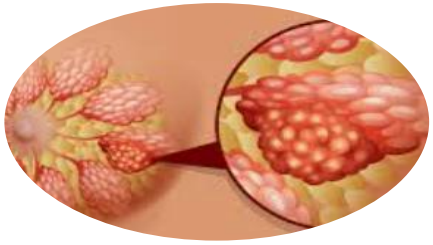
Plan

- Introduction
- Methodology
- Results and Discussion
- Conclusion

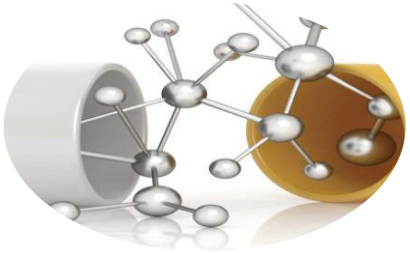
Introduction



According to WHO, Breast cancer is the second cause of cancer mortality among women ;



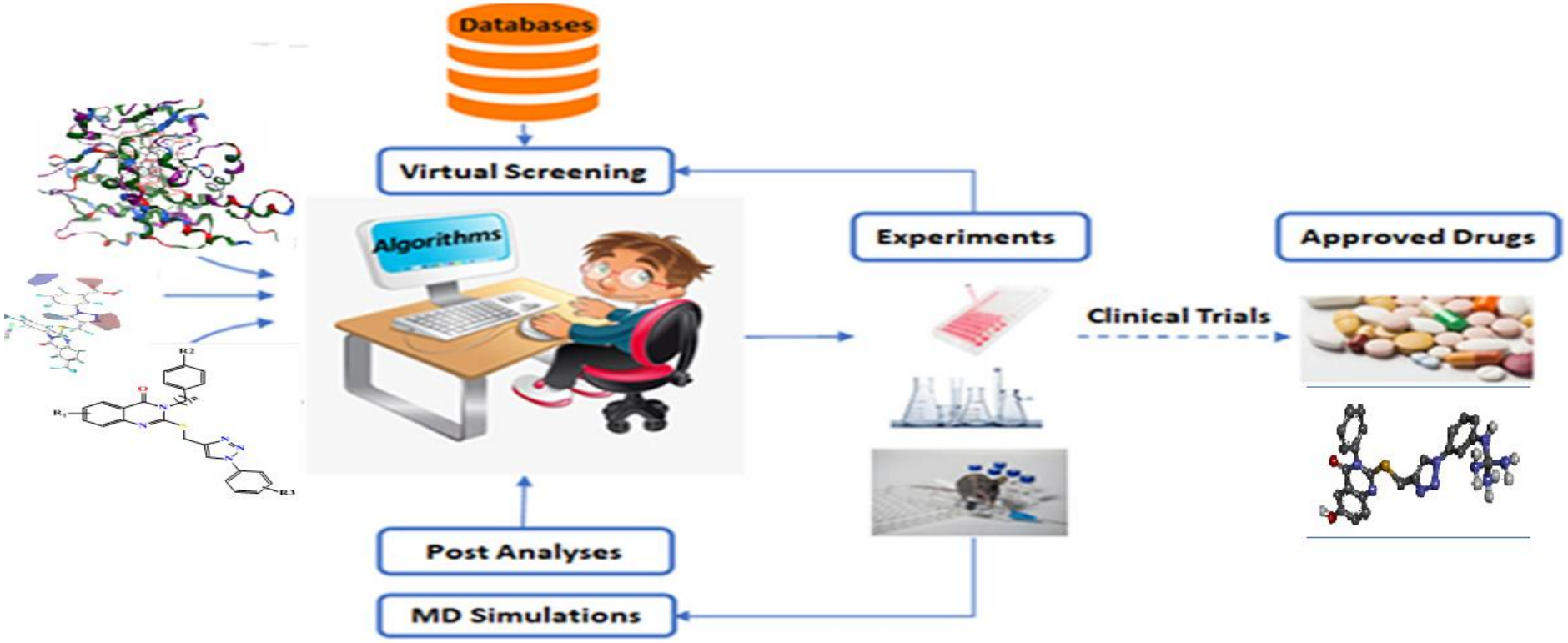
Cancer treatment is mainly complicated by drug resistance of cancer cells (Mutation);



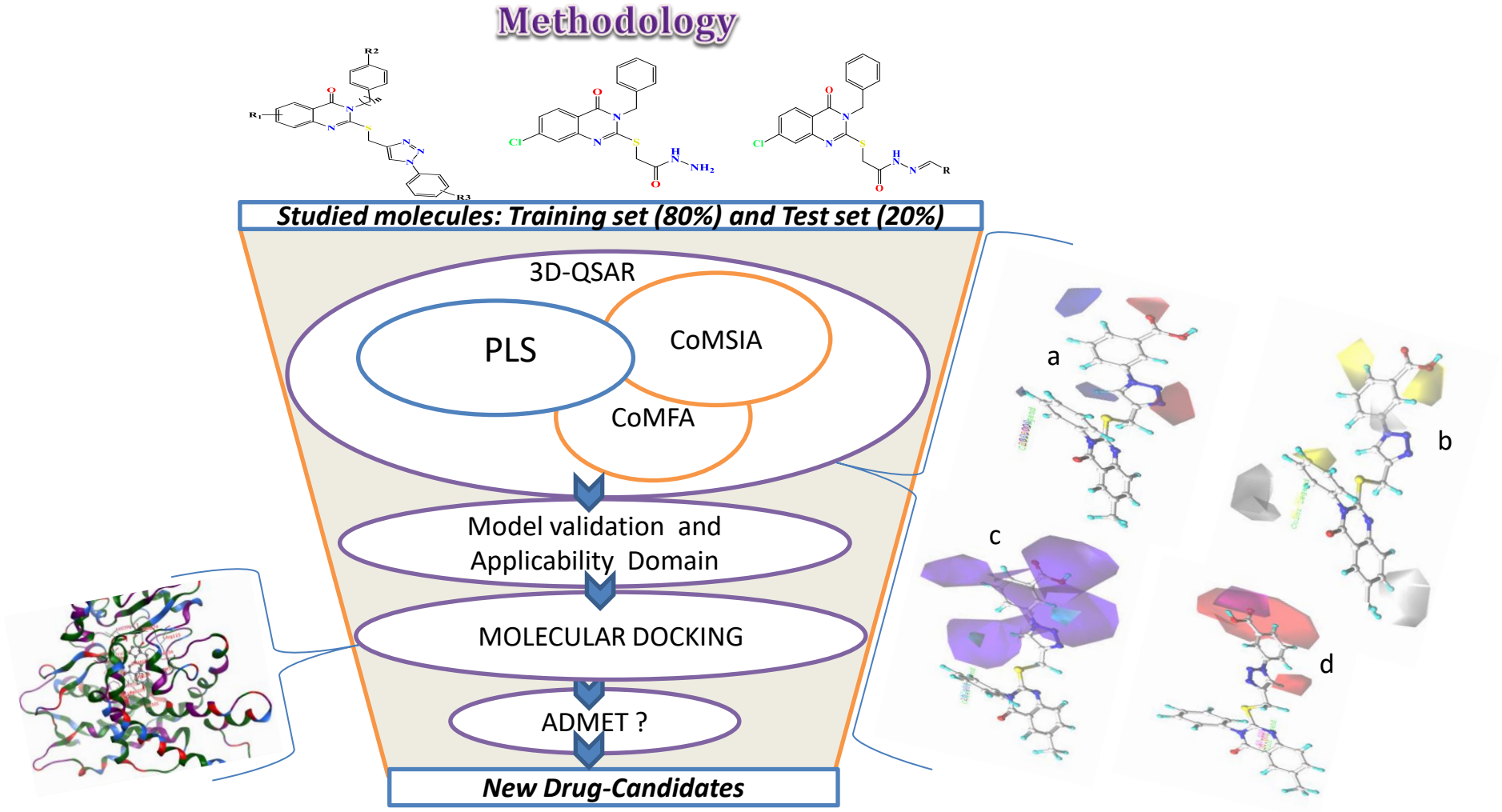
Rational drug design methods (QSAR modelling) minimize the time and cost needed for drug discovery

Introduction

Quantitative Structure Activity Relationship (QSAR)



Introduction

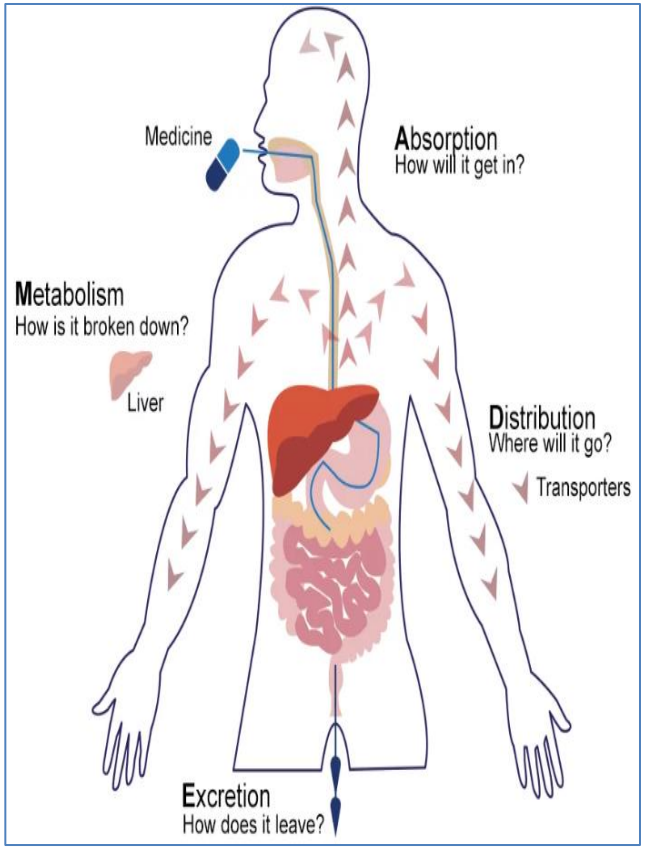


Introduction

Methodology

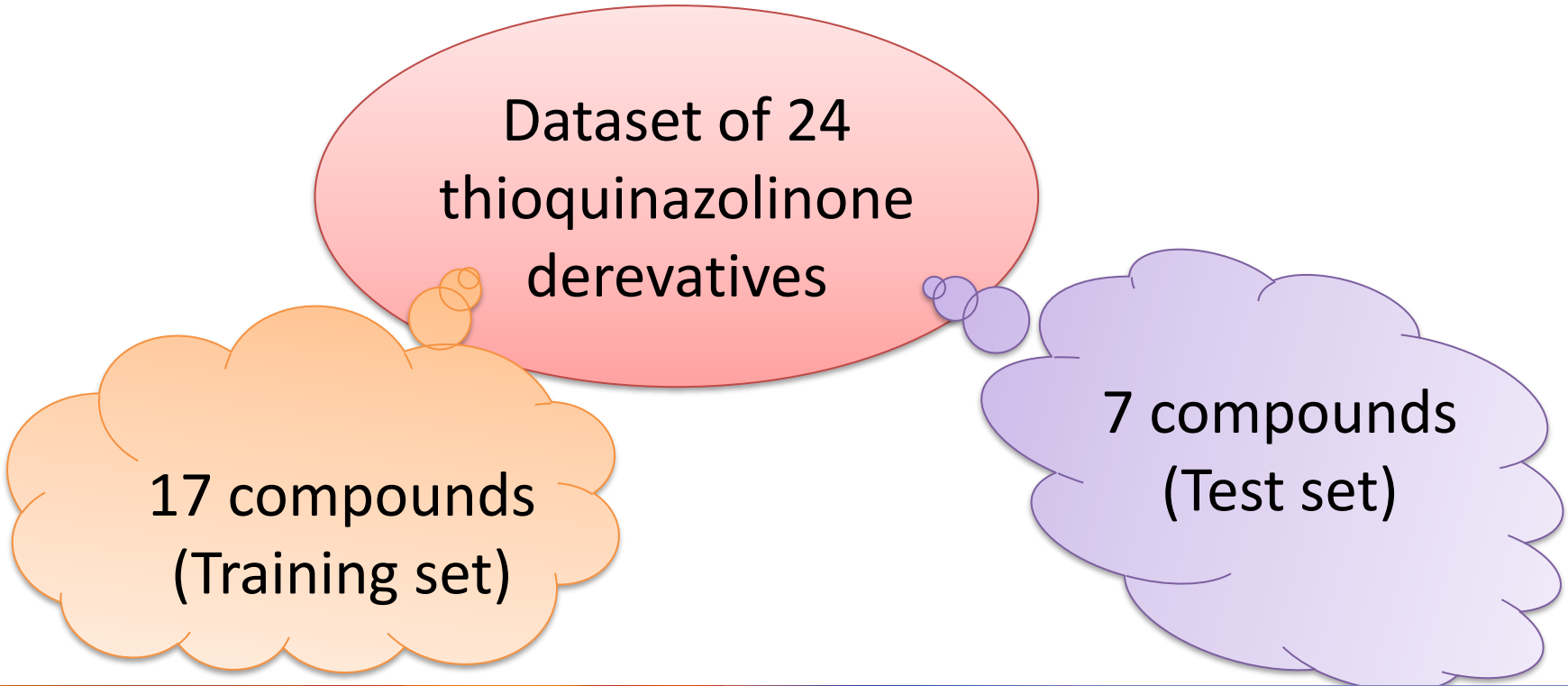
ADMET investigations :

- **A**bsorption ; How much of the drug is absorbed and how quickly?
- **Di**stribution; Where is the drug distributed within the body? What is the rate and extent of the distribution?
- **M**etabolism; How fast is the drug metabolized? What is the mechanism of action? What metabolite is formed and is it active or toxic?
- **E**limination; How is the drug excreted and how quickly?
- **T**oxicity; Does this drug have a toxic effect to body systems or organs?



Results and discussion

Dataset collection



Results and discussion

Molecular alignment and 3D-QSAR models generation

Alignment of molecules

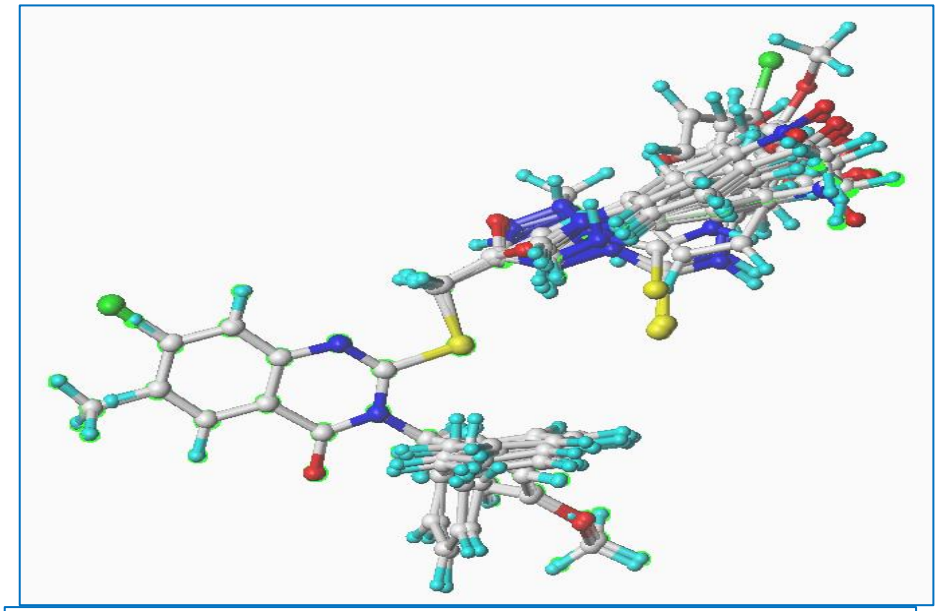


Figure 1. Superposition and alignment of the 24 studied compounds utilizing the most active molecule as a template

CoMSIA investigation

Statistical parameters of the best model (CoMSIA/EHDA):

- Q^2 = 0.589
- N= 2
- R^2 = 0.749; SEE = 0.242 ; F-test =20.872
- R^2_{pred}= 0.621

Table 1. Fields' fraction of CoMSIA analysis

COMSIA Fields	Norm.Coeff.	Fraction
COMSIA_ELECTROSTATIC	0.305	0.152
COMSIA_HYDROPHOBIC	0.182	0.091
COMSIA_ACCEPTOR	0.422	0.210
COMSIA_DONOR_AND_ACCEPTOR (Steric)	0.422	0.210
COMSIA_DONOR_AND_ACCEPTOR (Electrostatic)	0.674	0.336

Results and discussion

Visualization of CoMSIA :

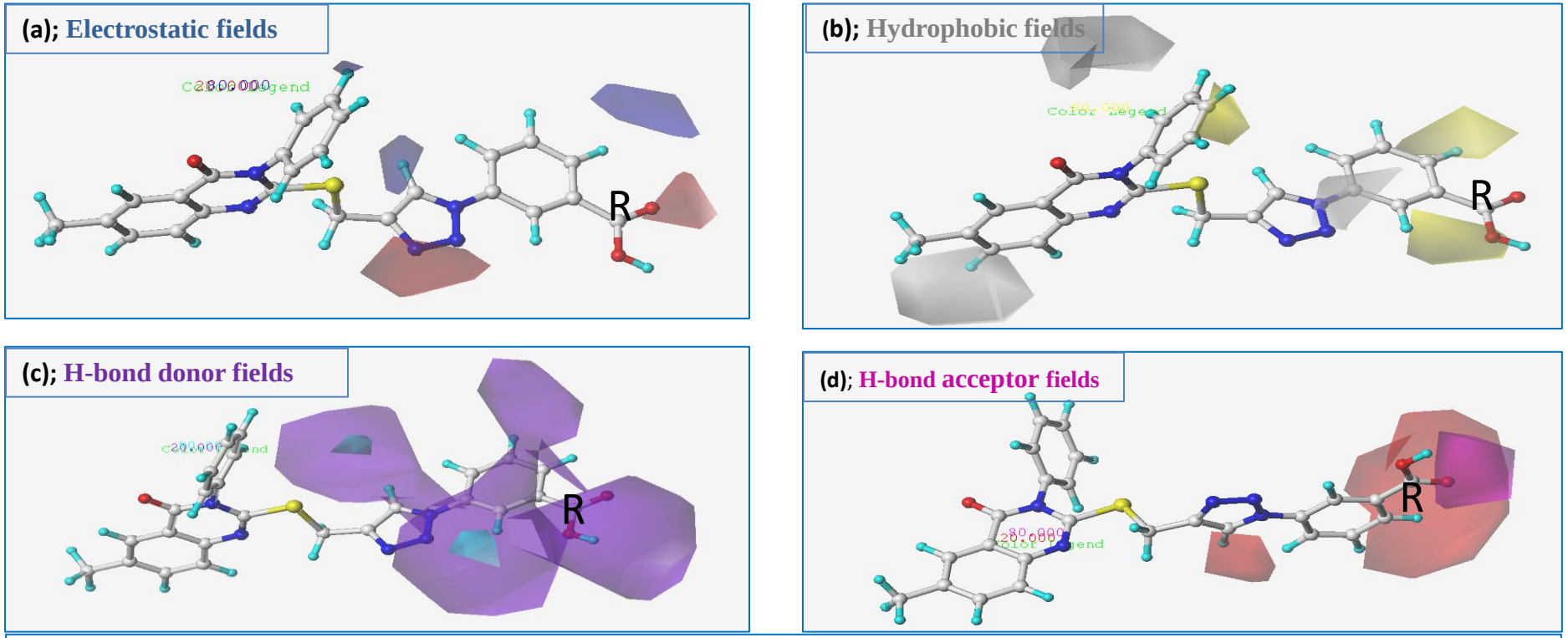


Figure 2. Contour maps of CoMSIA analysis with 2 Å grid spacing in combination with most active molecule

Results and discussion

The applicability domain :

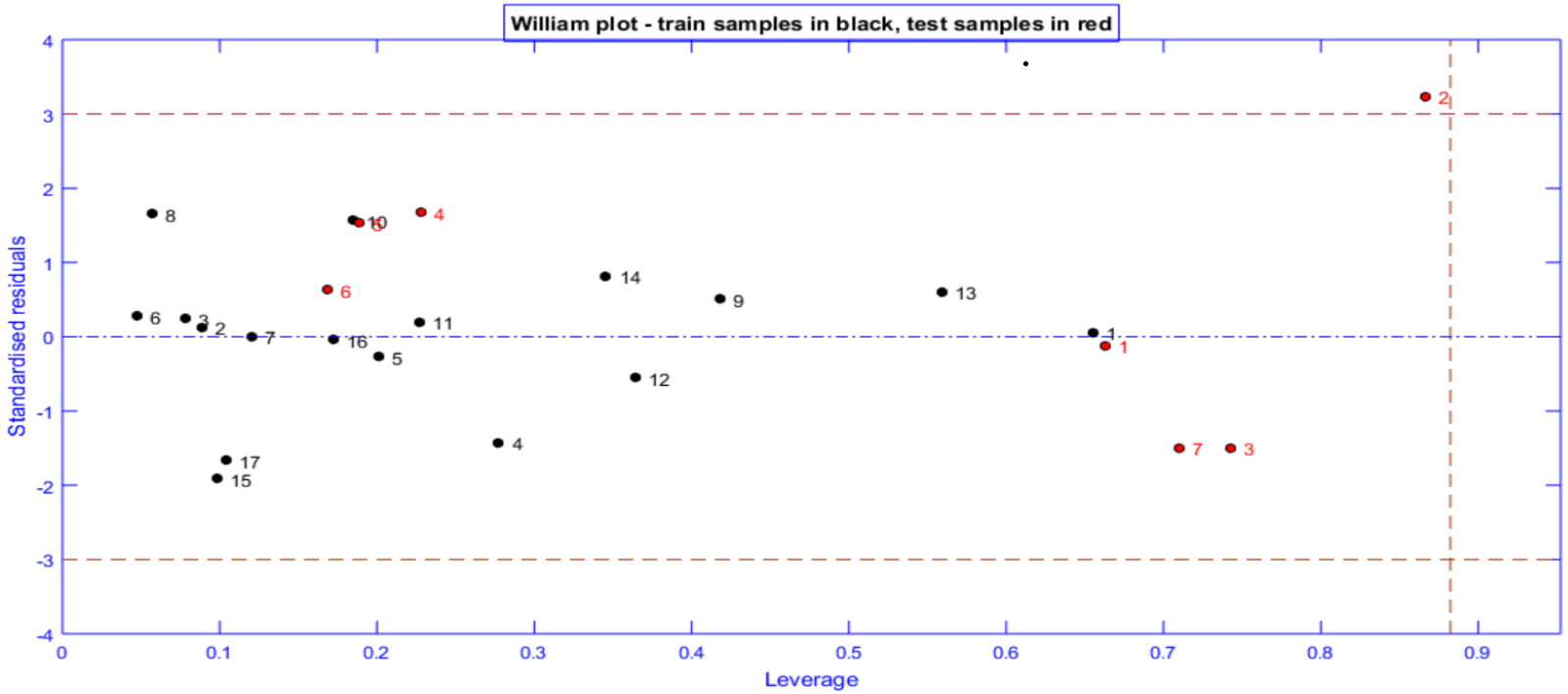


Figure 3. William's plot the CoMSIA (EHDA) model (h*= 0.882)

Results and discussion

Molecular docking process

Step 1 : Identification of active site

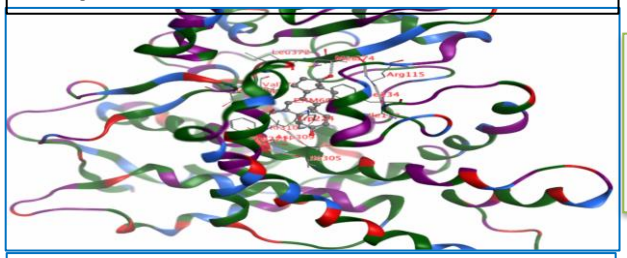


Figure 4. 3D interactions of complex 3S7S-exemestane (co-ligand)

proteine and ligands preparation

Step 2 : Docking validation

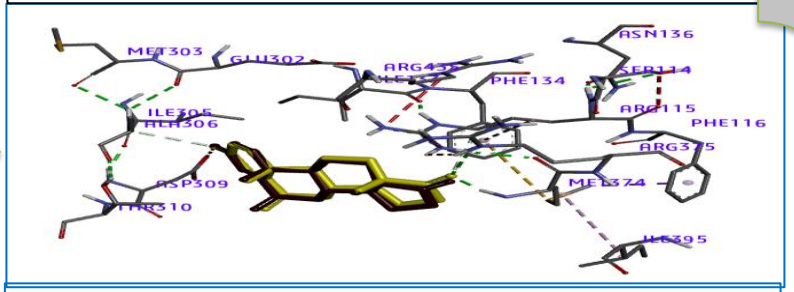
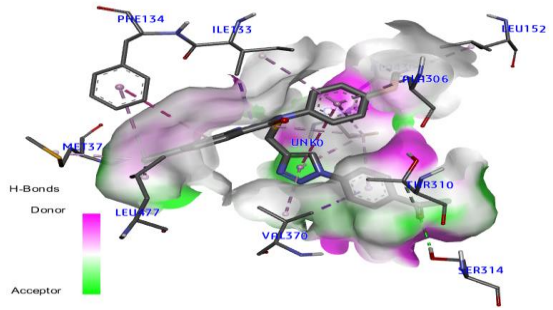
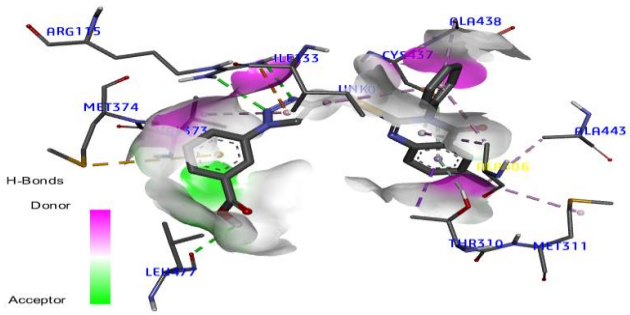


Figure 5. Re-docking results With RMSD=0.26 A°(co-crystallized ligand =brown and docked ligand=yellow)

Step 3 : Docking of the most and least active molecules



(b)



(a)

Docking

Figure 6. 3D interactions of most active molecule (a) and least active (b) molecule with aromatase enzyme.

Results and discussion

The predicted active site of target protein (PDB ID: 3S7S) :

The crucial amino acids ; MET374, ARG115, PHE134, ILE133, ALA306, LEU477, PHE221, VAL370, TRP224 and VAL373

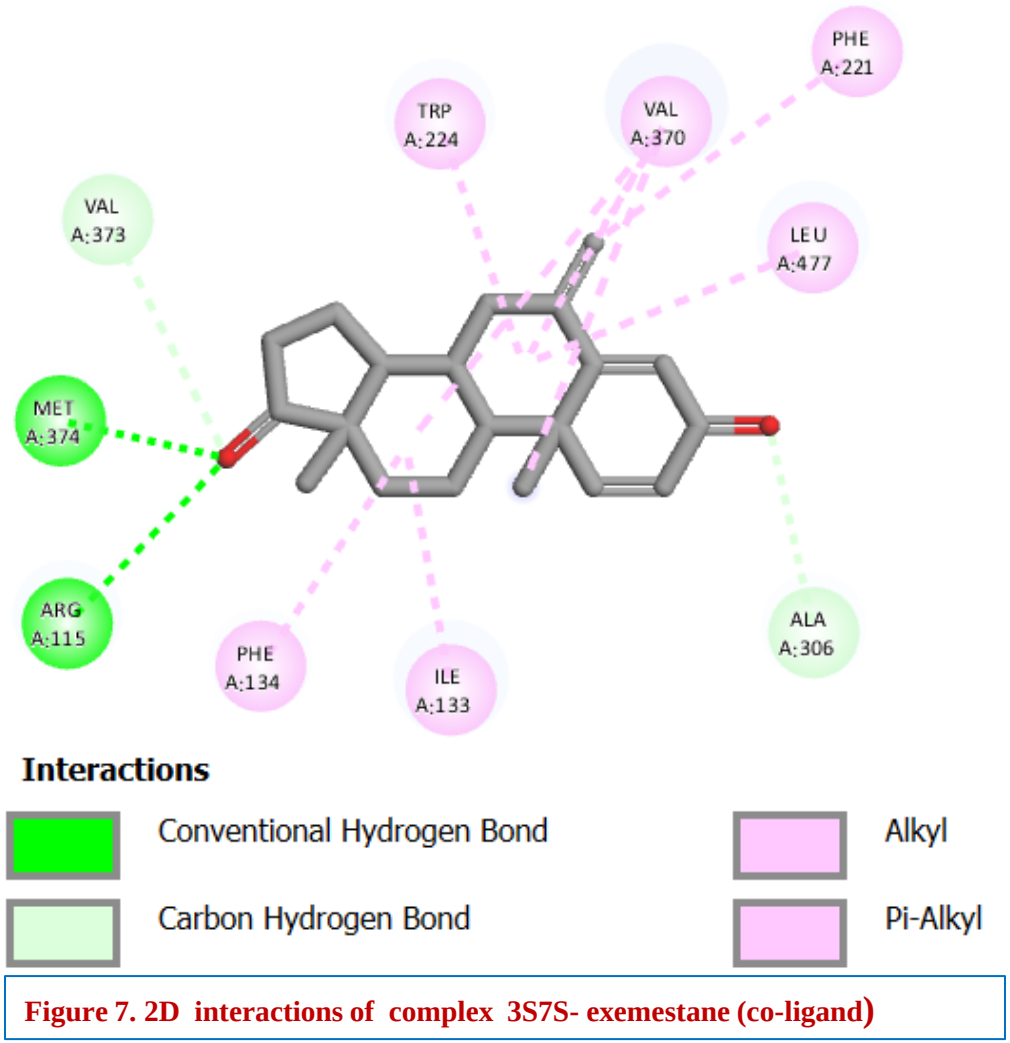


Figure 7. 2D interactions of complex 3S7S- exemestane (co-ligand)

Results and discussion

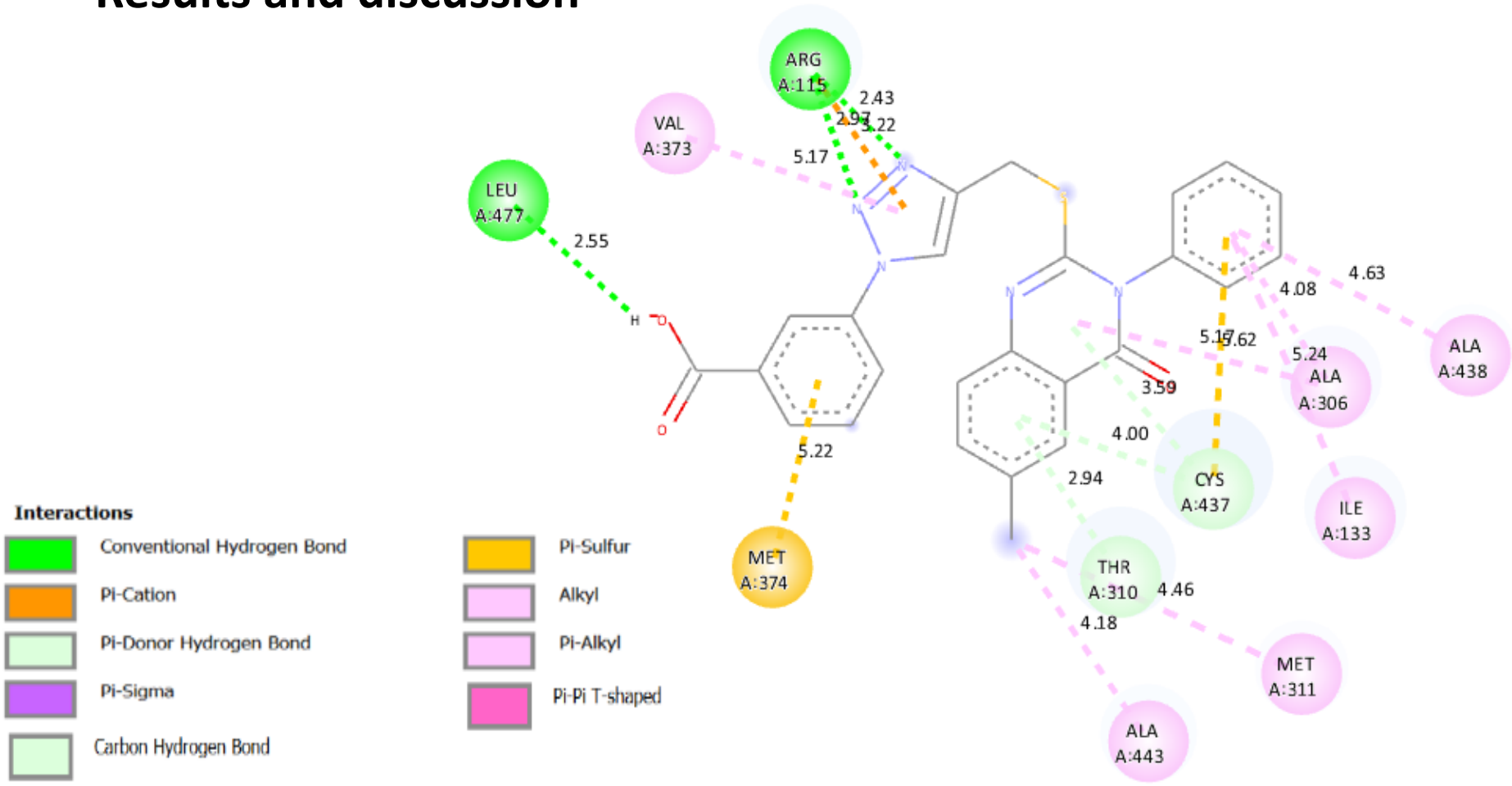
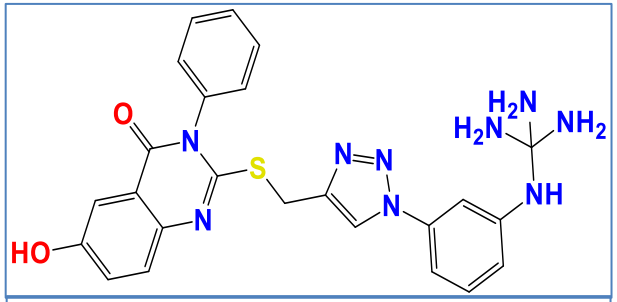


Figure 8. 2D interactions of most active molecule (a) with aromatase enzyme.

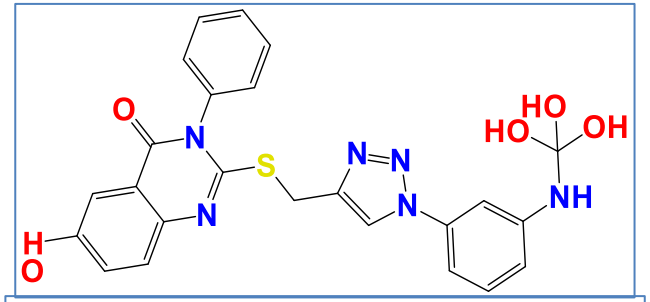
Results and discussion

Design of new compounds

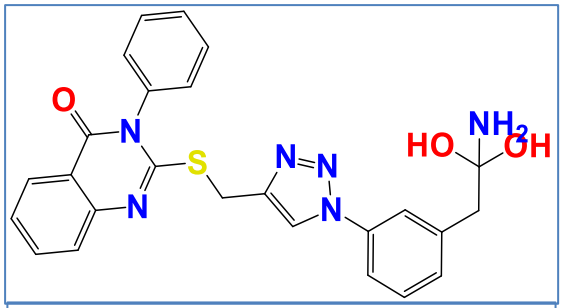
Based on visualization fields of CoMSIA/EHDA model and the interactions of docking studies, new molecules (Ligand1, Ligand 2 and Ligand 3) have been designed:



Ligand 1 (pIC_{50} =5.443) / No toxic



Ligand 2 (pIC_{50} = 5.427) / No toxic

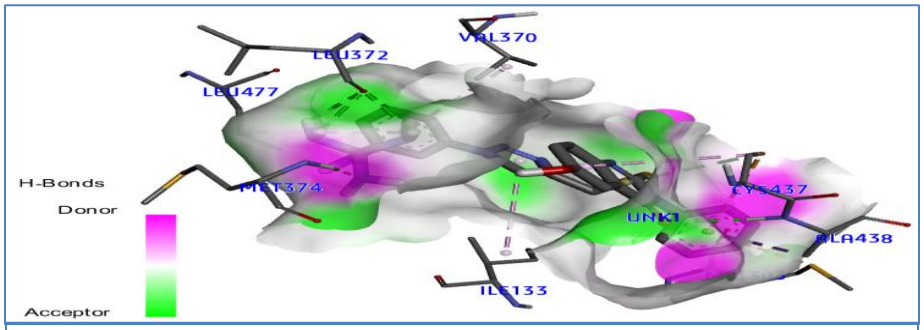


Ligand 3 (pIC_{50} =5.398) / No toxic

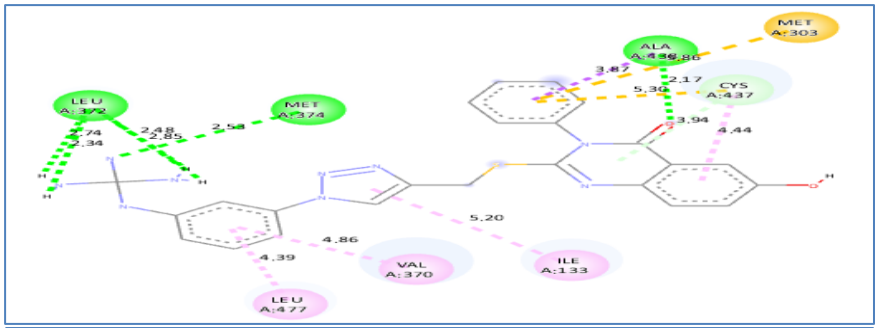
Figure 9. Chemical structures of newly designed molecules and their best pIC50 values (biological activities)

Results and discussion

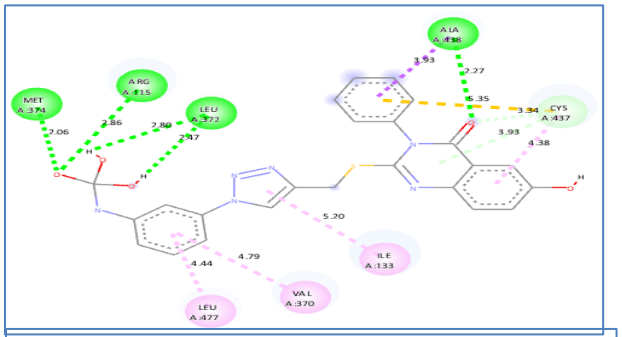
Molecular Docking of new compounds



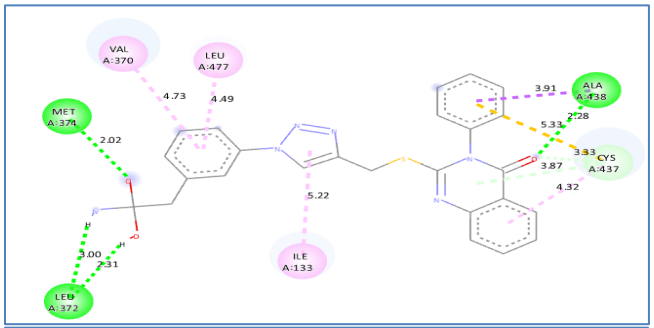
Ligand 1 -3D interactions (Affinity = -11.3 kcal/mol)/ pIC_{50} =5.443



Ligand 1 -2D interactions (Affinity = -11.3 kcal/mol)/ pIC_{50} =5.443



Ligand 2 (affinity = -11.1 kcal/mol) / pIC_{50} = 5.427



Ligand 3 (affinity = -9.910 Kcal/mol) / pIC_{50} =5.398

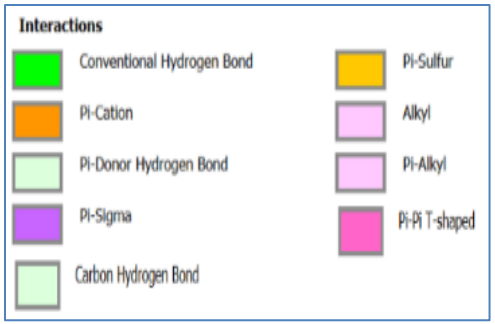


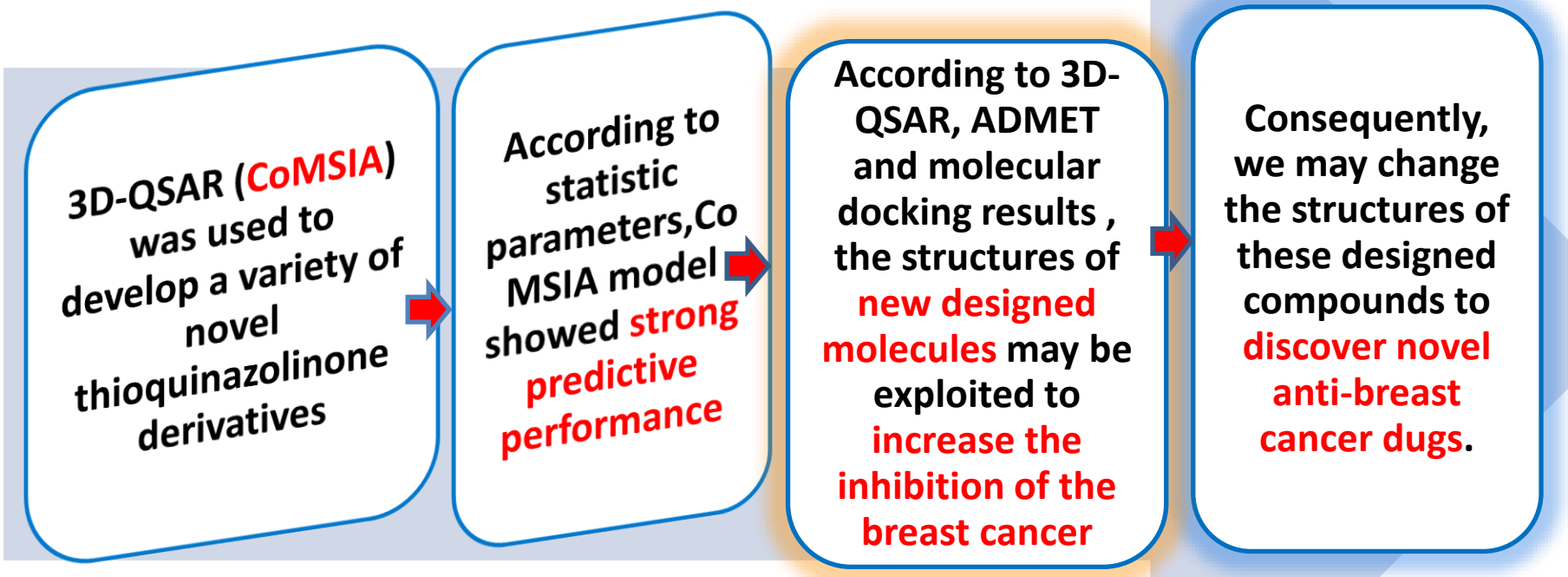
Figure 10. 2D and 3D interactions of the new designed Ligands with aromatase enzyme

Results and discussion

Table 2. Docking results of the designed ligands and the most active molecule as reference

Ligands	Complex	Binding energy (Kcal /mol)	Hydrogen-Binding interactions (HB)		Hydrophobic interactions	Electrostatic Interactions
			Acceptors HB	Donors HB	Pi / alkyl; pi; sigma	Cation/anion
Ligand 1	Ligand1 - 3S7S	*-11.300*	*MET 374-ALA 438*	*4 HB with LEU 372 / Pi; CYS 437*	*LEU 477-VAL 370- ILE 133- CYS 437-ALA 438*	*CYS437- MET 303*
Ligand 2	Ligand2 - 3S7S	*-11.100*	*MET 374-ALA 438 -ARG 115-CYS 437*	*2 HB with LEU 372 / Pi; CYS 437- ALA 438*	*LEU 477-VAL 370- ILE 133- CYS 437-ALA 438*	*CYS 437*
Ligand 3	Ligand 3 -3S7S	*-10.910*	*MET 374-ALA 438-CYS 437*	*2 HB with LEU 372 /Pi; CYS 437*	*LEU 477-VAL 370- ILE 133- CYS 437-ALA 438*	*CYS 437*
Active molecule	Active molecule - 3S7S	*-10.900*	*2 HB with ARG 115*	*LEU 477/ Pi; 2 HB with CYS 437-THR 310*	*ALA 438- ALA 306 (2 interactions) - ILE 133- MET 311-ALA443- VAL 373*	*MET 374- CYS 437*

Conclusions



Thank you for your attention