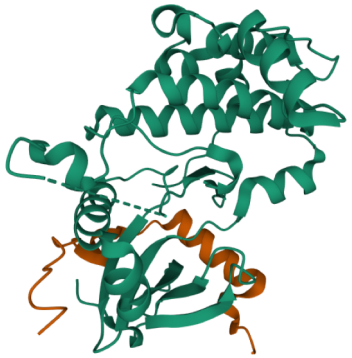
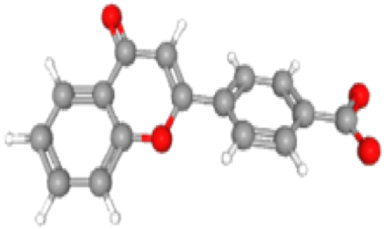
Development of novel Anticancer drugs using *in silico* studies on Aurora Kinase B using PubChem Database





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Introduction and Background

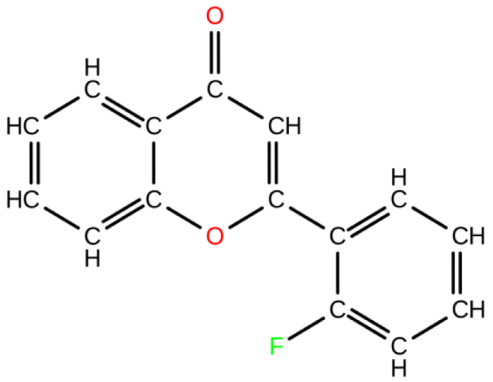
- **Aurora kinases**
  - Group of enzymes belong to the Serine- threonine protein kinase family.
  - It plays an important role in cell division and participates in several steps of mitosis and chromatid segregation .
  - Overexpression, polymorphism and splicing variants in the Aurora Kinase B leads to tumerogenesis and further it leads to cancer .

Location, function and tumor types in different Aurora kinases

Kinases	Localization	Function	Tumour type
Aurora Kinase B	Chromosome Kinetochore Midbody	Chromosome condensation; Microtubule-kinetochore attachment; Chromosomal alignment; Chromosomal segregation; Regulating Cytokinesis	Breast cancer, Ovarian cancer, Gastric/Gastrointestinal cancer, Colorectal cancer, Lung cancer, Cervical cancer, Prostate cancer, Glioma, Acute myeloid leukemia (AML), Oral cancer

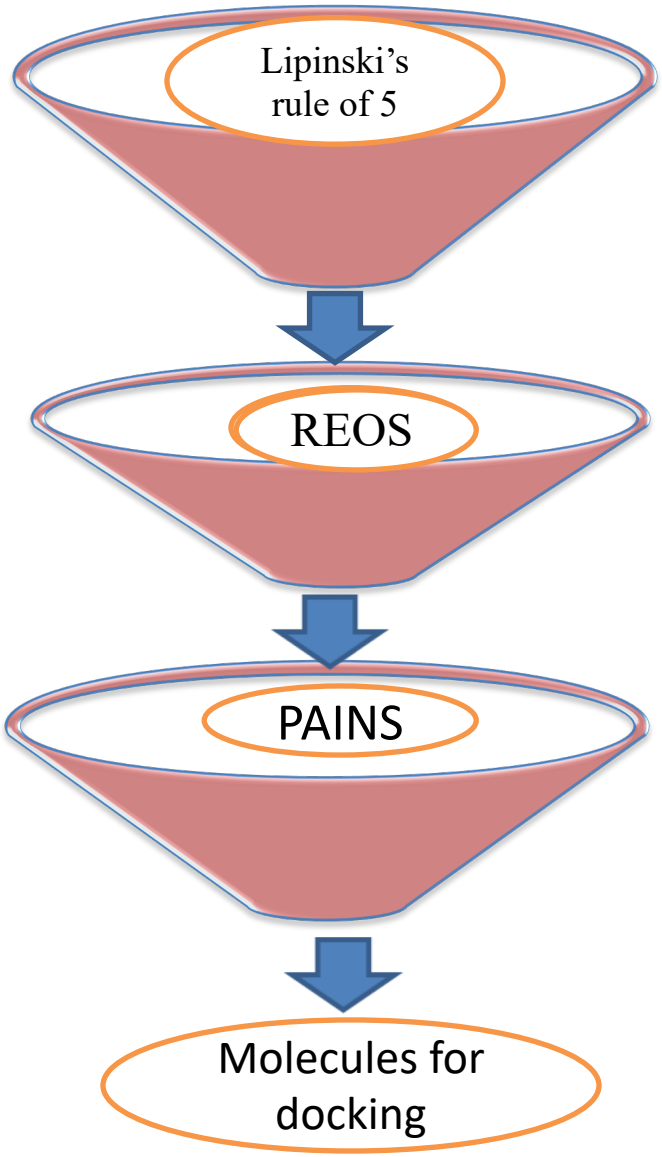
Flavones derivatives

- Flavones are a class of flavonoids.
- Common in fruits and many plant foods.
- Shows anticancer activity.
- Flavone derivatives containing fluoro groups are taken.
- These fluoro derivative flavones with Aurora Kinase B is used in docking experiments .



Filtration

Total number of analogs of Fluoro Flavones from Pubchem databases = 3882

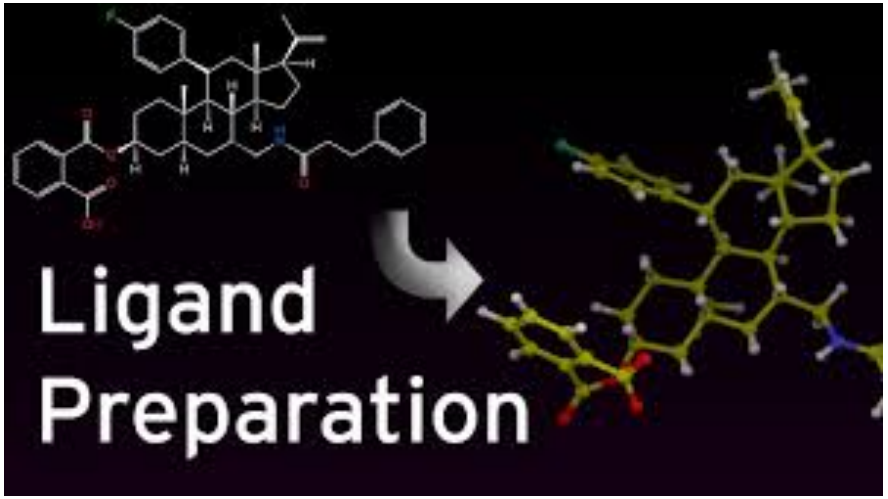


3882 compounds

3430 compounds

2449 compounds

2448 compounds



Using LigPrep

Flouro_flavones And its 2448 Analogs

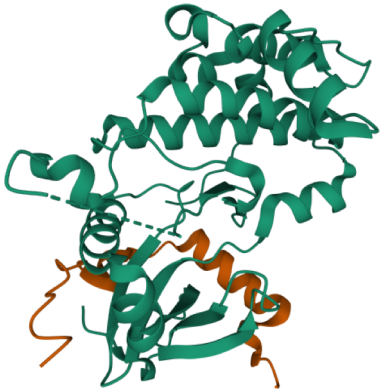
pH maintenance (7±1)

Energy minimization

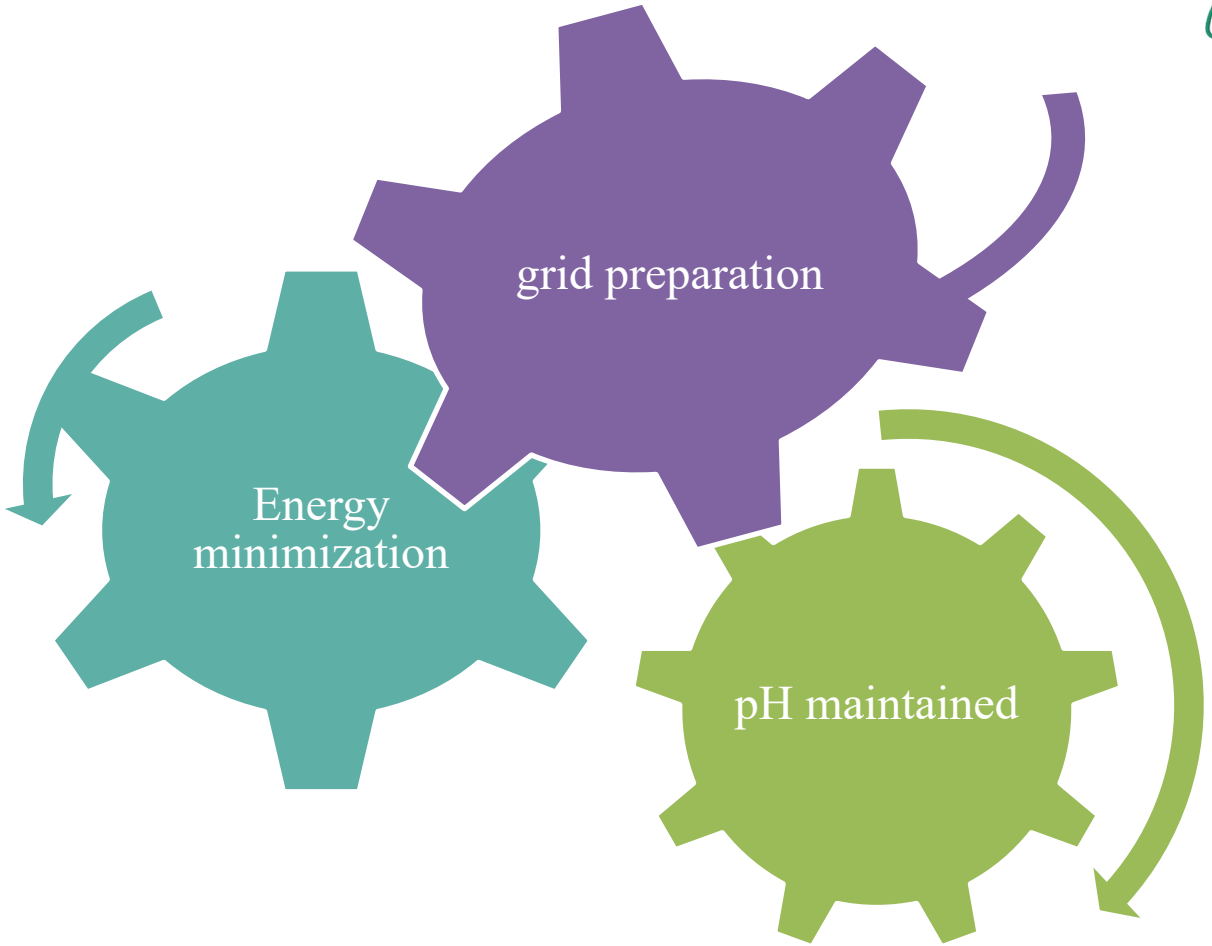
Ligands Prepared

Protein Preparation for docking

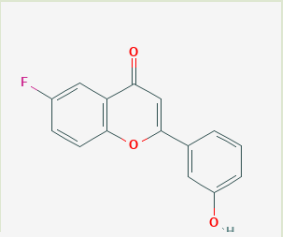
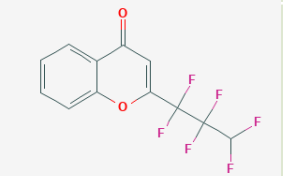
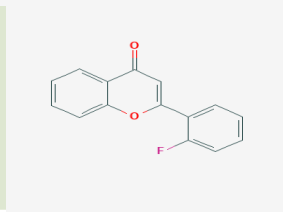
- Aurora Kinase B



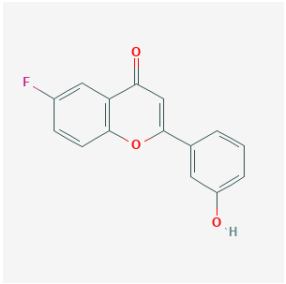
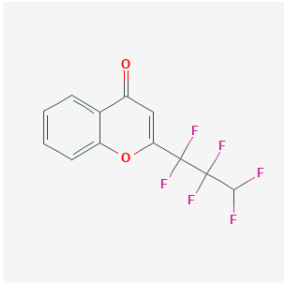
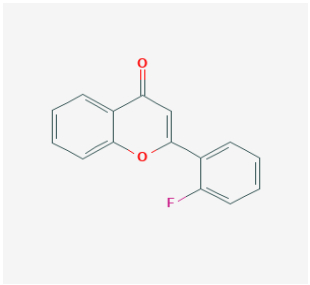
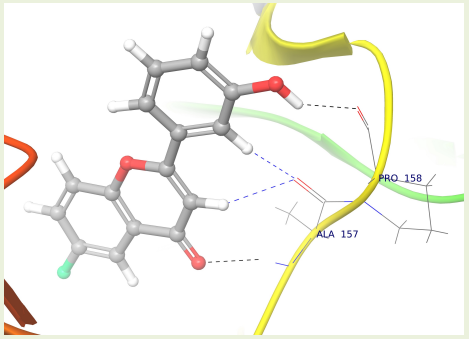
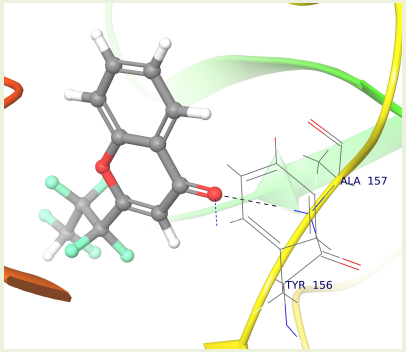
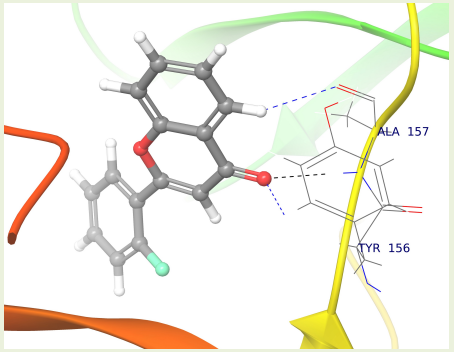
Aurora Kinase B
PDB ID: 4AF3



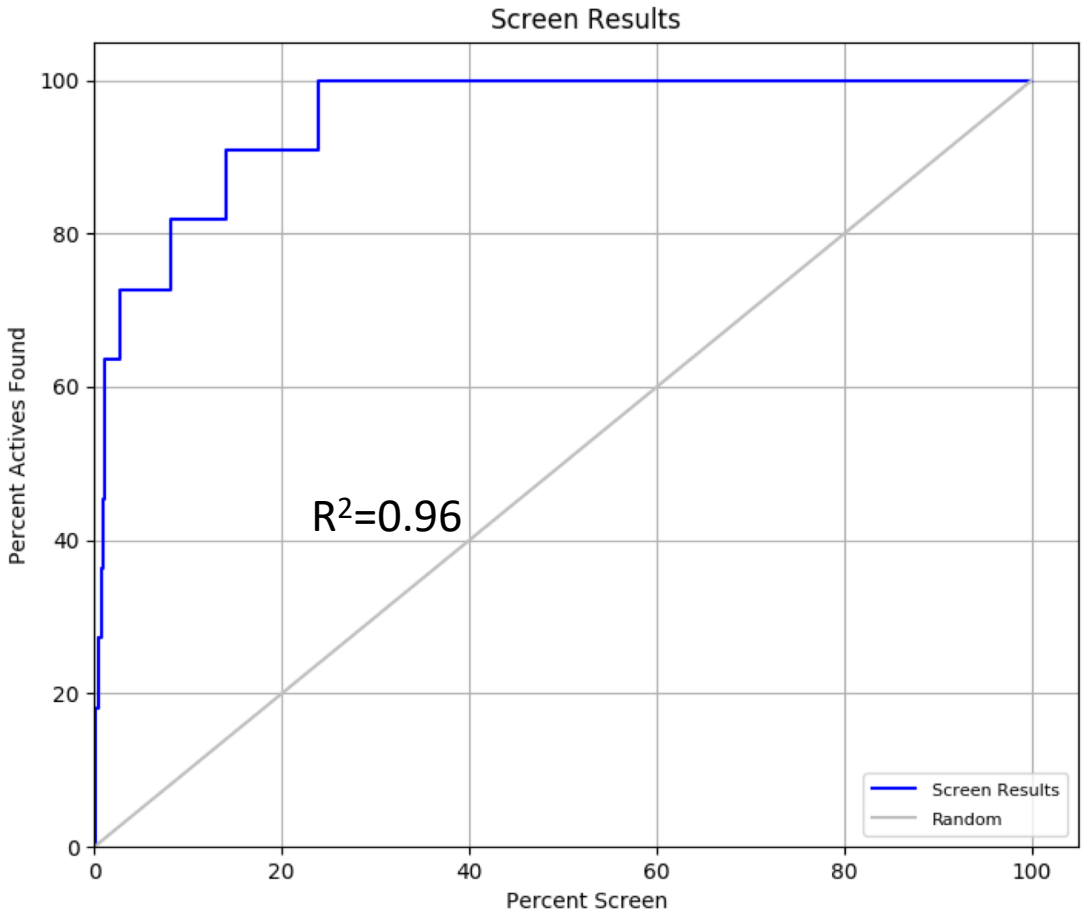
Docking results

Glide Docking	PubChem ID (structure)	2 D Structure	Binding Energy (kcal/mol)	Interaction	Bond Type	Bond length (Å)
SP	44298667		-9.153	Pro158	H-bond	1.87
				Ala157	H-bond	2.02
				Ala157	Aromatic H-bond	2.45
				Ala157	Aromatic H-bond	2.54
XP	101664315		-10.287	Ala157	H-bond	2.00
				Tyr156	Aromatic H-bond	3.20
Reference	261400		-8.907	Ala157	H-bond	2.00
				Tyr156	Aromatic H-bond	3.18
				Ala157	Aromatic H-bond	2.63

Interactions with Aurora Kinase A

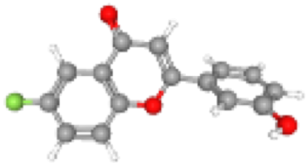
PubChem ID	**CID: 44298667 (SP Docking)**	**CID:101664315 (XP Docking)**	**CID: 261400**
Binding Energy (kcal/mol)	-9.153	-10.287	-8.907
2D Structure			
Interactions			

Enrichment calculations

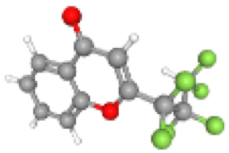


Molecular dynamic (MD) studies

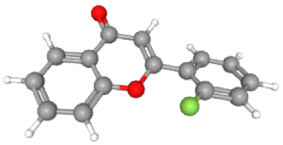
44298667

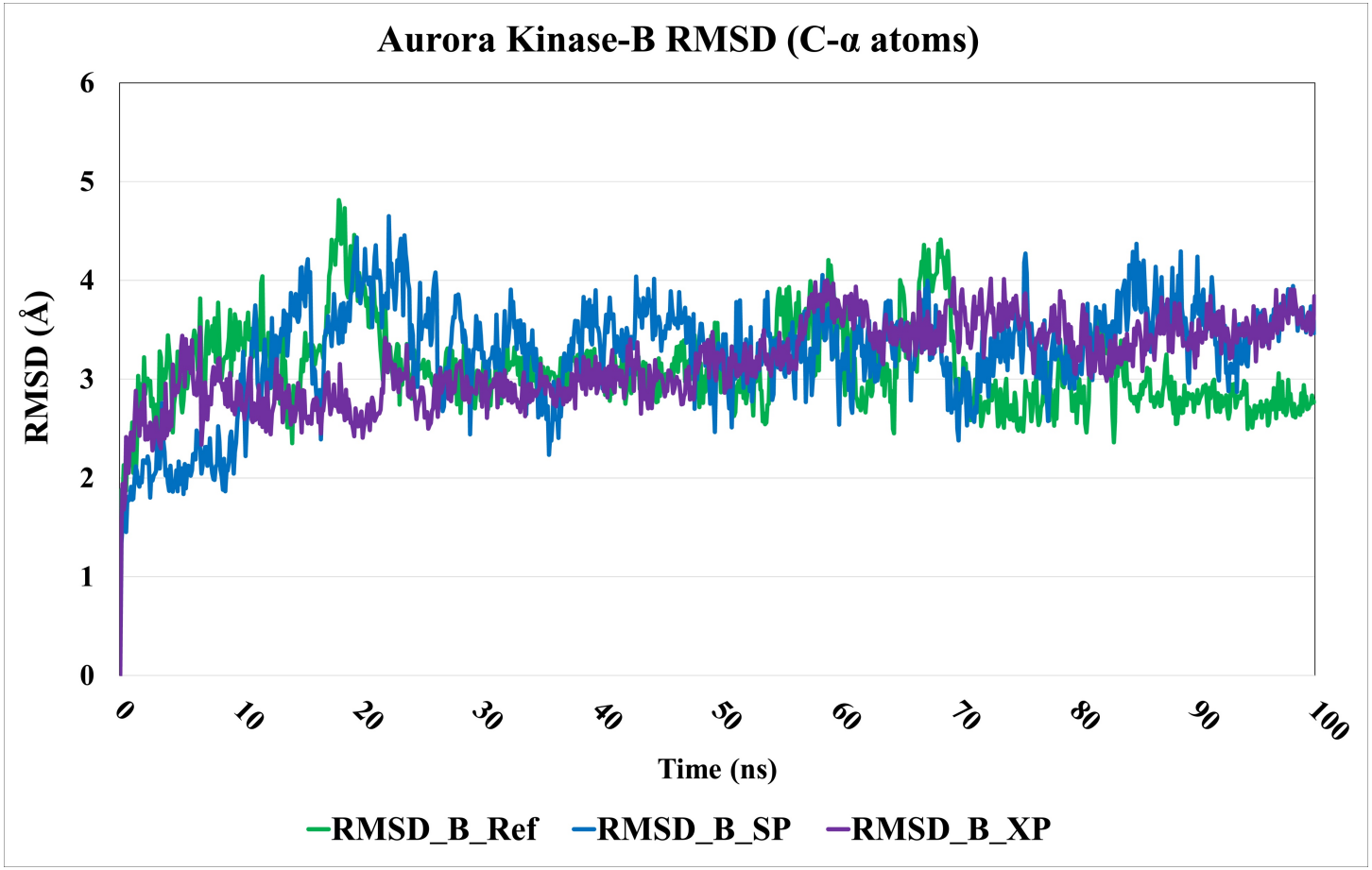


101664315



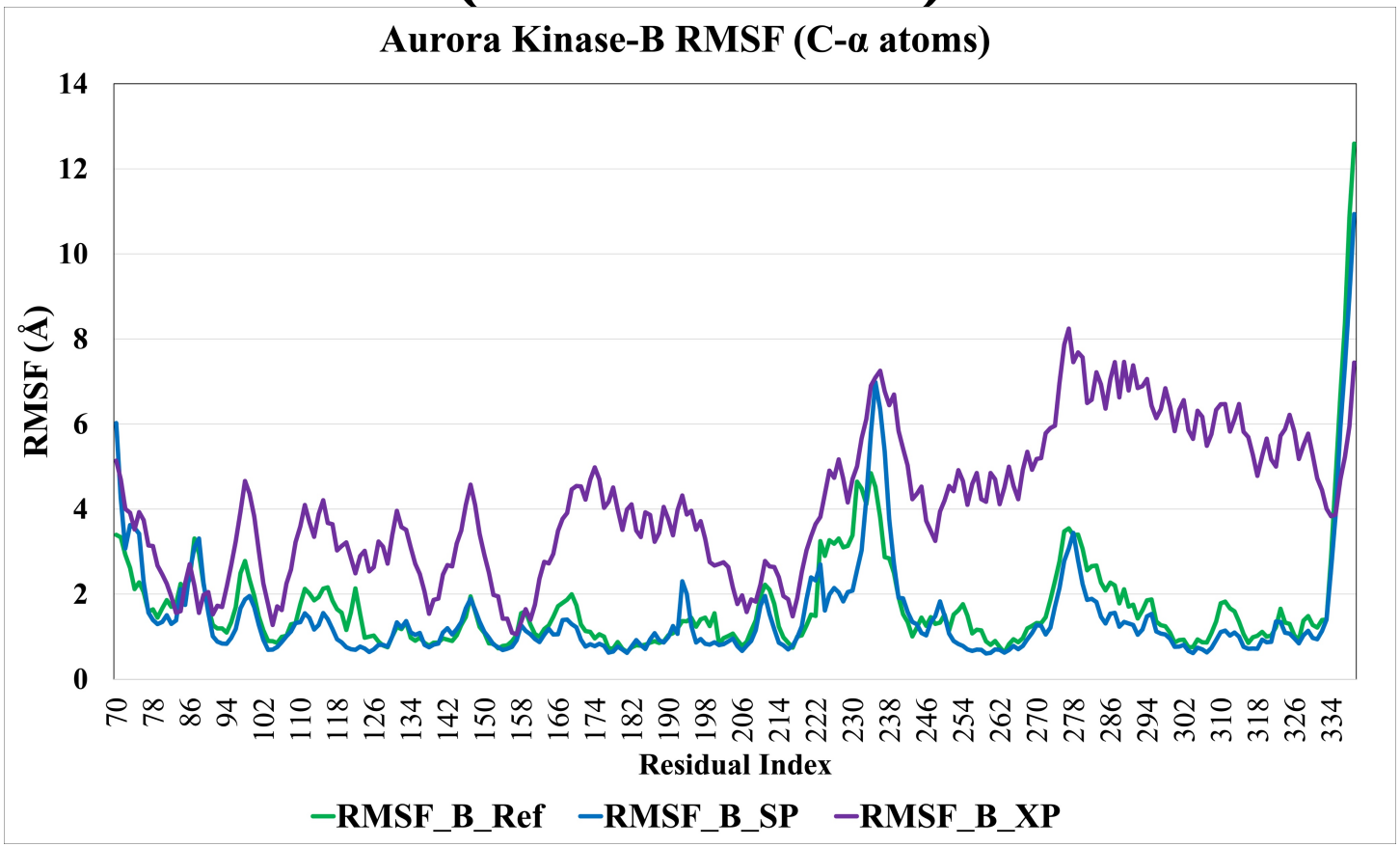
241400





Time dependence of root mean square deviations (RMSDs) of the C-α backbone of Aurora Kinase A after binding with flouro flavones and its 2 best analogs with viz. CID: 261400, 44298667, 101664315

Molecular dynamic (MD) studies (continued)



Time dependence of root mean square fluctuation (RMSFs) of the C-α backbone of Aurora Kinase A after binding with floro flavones and its 2 best analogs with viz. CID: 261400, 44298667, 101664315.

Prime MM/GBSA energies for the complexes of Aurora Kinase A protein

Flouro flavone derivatives (CID)	ΔG Bind[1] (kcal/mol)	ΔG Coulomb[2] (kcal/mol)	ΔG Bind vdW[3] (kcal/mol)	ΔG Solv GB[4] (kcal/mol)	Complex Energy[5] (kcal/mol)
261400	-56.051 ± 1.942	-2.622 ± 1.001	8.458 ± 1.554	-33.201± 1.294	-8114.447 ± 2.0628
101664315	-62.181 ± 1.270	-6.359 ± 0.397	7.384 ± 0.543	-31.059 ± 2.001	-8294.082 ± 1.174
44298667	-65.981 ± 1.995	-16.471 ± 0.644	10.203 ± 1.014	-32.771 ± 1.607	-8148.007 ± 2.074

[1] MM/GBSA binding free energy.

[2] Coulomb energy.

[3] Van der Waals energy.

[4] GB Generalized Born electrostatic solvation energy.

[5] Energy of protein-ligand complex

Conclusion

- The result obtained show that 2-(1,1,2,2,3,3-Hexafluoropropyl)-4H-1-benzopyran-4-one has best docking score of -10.287 kcal/mol among all the analogs docked with Aurora Kinase B
- MD simulations was carried out for of 100 ns for each of these three complexes of Aurora Kinase B and flouro flavones and its 2 best analogs, with the mean RMSD value of 2.56Å.
- The molecular dynamics results further confers the conformational stability of the protein-ligand complexes as the RMSF of the pocket residues after binding of the ligand and the protein is lower than 2.0 Å .
- The MM/GBSA free energy calculations reveal that the analogs of the compound forms a stable complex with Aurora Kinase B.
- Thus, the obtained 2 best analogs of flouro flavones can be further used *in vitro* and *in vivo* experiments and can probably serve as an novel drug for cancer treatment.

References

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