Pharmacophore-based Virtual Screening for designing PI3K/AKT/mTOR inhibitor for the treatment of Triple negative breast Cancer

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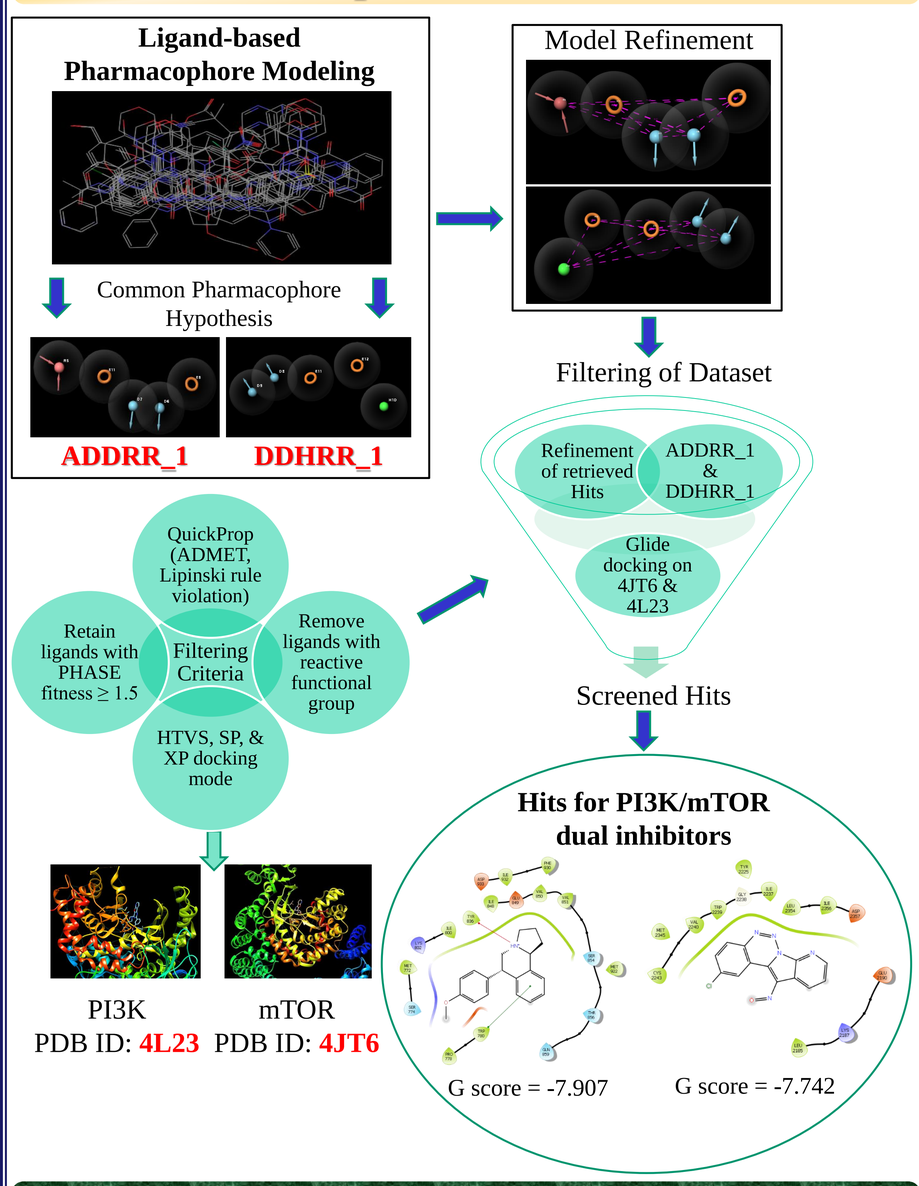
Graphical Abstract



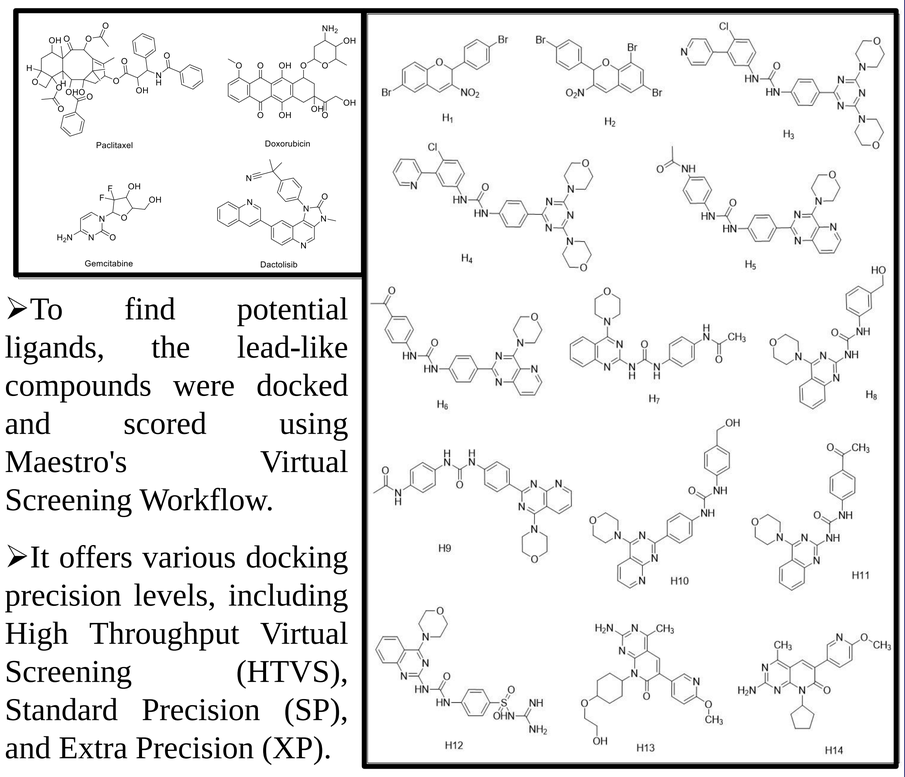
Rational

➢To utilize the virtual screening method for identifying and developing novel **PI3K/mTOR** dual inhibitors with improved selectivity when combined with pharmacophore modeling, molecular docking, and consensus scoring function.

Methodology

➢In the current study, we built pharmacophore models and performed virtual screening of datasets collected from the **ChEMBL** database in order to design novel and potent PI3K/mTOR dual inhibitors that specifically target triple-negative breast cancer.

➢The library for the pharmacophore model consists of a combination of 4 FDA-approved drugs: paclitaxel, doxorubicin, dactolisib, and gemcitabine, with 14 breast cancer, clinical trial candidates: H1to H14.



➢To find potential ligands, the lead-like compounds were docked and scored using Maestro's Virtual Screening Workflow.

➢It offers various docking precision levels, including High Throughput Virtual Screening (HTVS), Standard Precision (SP), and Extra Precision (XP).

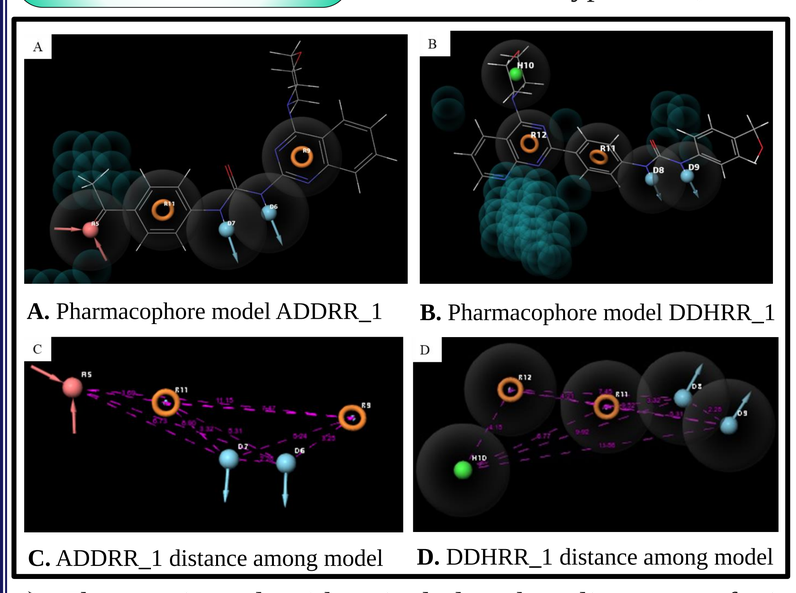
➢Prior to further refining a favorable ligand posture, we initially performed an HTVS calculation, followed by SP, and finally XP mode.

➢The screened substances were additionally filtered using Lipinski's rule of five (QikProp version 3.6). Additionally, XP docking was done for 116 of the ligands that will be used to create the 3D-QSAR model.

Result and Discussion

Pharmacophore modeling

➢ To find a common pharmacophore hypothesis (CPH), the collected dataset was divided into active (**pIC50>7.2**), inactive (**pIC50<5**), and moderately active (**pIC50** between **5** and **7**). In Phase, CPH is identified from a set of variants. The scoring procedure provides a ranking of the different hypotheses, allowing us to make a rational choice.



A. Pharmacophore model ADDRR_1 **B.** Pharmacophore model DDHRR_1

C. ADDRR_1 distance among model **D.** DDHRR_1 distance among model

Score of different hypotheses generated against PI3K inhibitor

HypoID	Survival	Site	Vector	Volume	Select	Matches	Inactive
ADDRR_1	**4.111**	**0.9147**	**0**	**0.6045**	**1.7467**	**7**	**1.192**
ADDRR_2	4.1016	0.9143	0	0.5919	1.7503	7	1.1739
AHRRR_1	3.8402	0.5888	0	0.6426	1.8307	6	0.8223
AHRRR_2	3.7766	0.5625	0	0.5975	1.8384	6	0.835
AADHR_1	3.4491	0.6505	0	0.4813	1.4723	7	0.7055
AAHRR_1	3.353	0.3712	0	0.4856	1.7181	6	0.7561

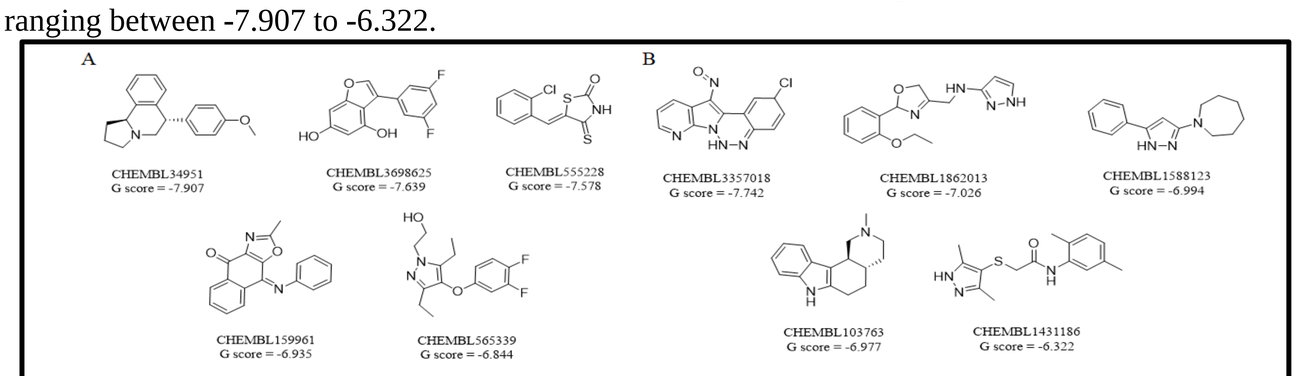
Score of different hypotheses generated against mTOR inhibitor

HypoID	Survival	Site	Vector	Volume	Select	Matches	Inactive
DDHRR_1	**4.5355**	**0.8689**	**0**	**0.7382**	**2.0834**	**7**	**0.5035**
ADDRR_1	4.3425	0.9506	0	0.6896	1.748	9	0.5462
ADDRR_2	4.3343	0.9548	0	0.6733	1.752	9	0.4774
ADDRR_3	4.3105	0.9479	0	0.6603	1.748	9	0.5215
ADDHR_1	4.2639	0.8659	0	0.7136	1.8393	7	0.5522
AADHR_1	4.1522	0.8769	0	0.7266	1.7037	7	0.6659
AADHR_2	4.121	0.8398	0	0.724	1.7121	7	0.6156
AAHRR_1	4.1176	0.831	0	0.7449	1.6967	7	0.6312
AAADR_1	4.0257	0.8396	0	0.7258	1.6152	7	0.7091
AAADR_2	3.9745	0.7934	0	0.7291	1.6069	7	0.6874

➢ The scoring algorithm includes the alignment of site points and vectors, volume overlap, number of ligands matched, selectivity, relative conformational energy, and activity. A total of 16 hypotheses survived the scoring processes which will be used to build an atom-based & field-based QSAR model.

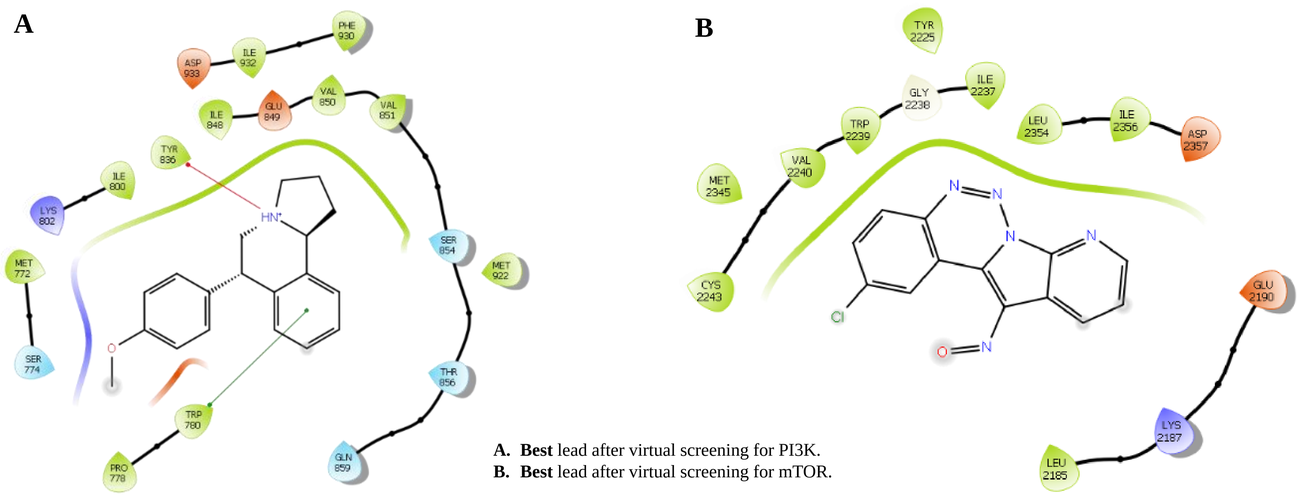
Virtual Screening

➢ Filtering the 3D database for structures that fit the pharmacophoric features of the model involved ADDRR_1 (PI3K) and DDHRR_1 (mTOR) as top-scored features. A virtual screening workflow was used to screen a total of 1,32,841 compounds that were retrieved as hits from ChEMBL. A total of 107 compounds were identified, with XP docking scores ranging between -7.907 to -6.322.



A. Structures of leads with GLIDE scores obtained after virtual screening for PI3K.

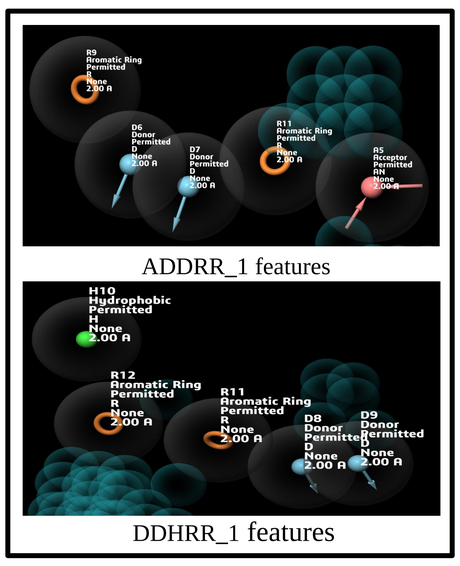
B. Structures of leads with GLIDE scores obtained after virtual screening for mTOR.



A. Best lead after virtual screening for PI3K.
B. Best lead after virtual screening for mTOR.

Conclusions

- The most frequent genetic abnormalities in breast cancer, affecting all subtypes, were those affecting the PI3K/AKT/mTOR pathway. Consequently, it was found to be the most recently discovered target in the therapy of triple-negative breast cancer.
- In this study, about 18 PI3K/mTOR dual inhibitors were collected from the literature and were used to build a five-point pharmacophore model using Phase (Schrodinger module).
- The statistically significant pharmacophore hypothesis of ADDRR_1 (PI3K) & DDHRR_1 (mTOR) with survival scores of 4.111 & 4.5355, respectively was used as a 3D query to search against a 3D database namely ChEMBL.
- A total of 1,32,841 compounds obtained as hit were subjected to high throughput virtual screening (HTVS module of Schrodinger). Among the hits, ten compounds with good G-score ranging from -7.907 to -6.322 with good binding energy to PI3K/mTOR dual inhibitor were identified.



ADDRR_1 features

DDHRR_1 features

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