196P-Targeting ESR1 in Breast Cancer Treatment: Repurposing of Statins

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BACKGROUND

- Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases according to GLOBOCAN, 2020.
- Management of breast cancer has significantly changed in the last few years, witnessing the advent of more and more therapeutic approaches.
- With the increase in the incidence of breast cancer, precisely targeted therapies are urgently needed for treatment.
- Aberrantly high levels of Estrogen Receptor alpha are found in more than 70% of all breast cancers.
- Estrogen Receptor alpha (ESR1/ERα) (Figure 1) has proven to be a crucial therapeutic target for treating ERα positive breast cancer.
- Most medications currently being used in breast cancer treatment are becoming resistant.
- Alternatives to the current treatment strategies are being explored.
- Statins, traditionally indicated in cardiovascular diseases to reduce lipid levels, have been found to also exhibit anti-cancer activities.
- This systematic *in silico* study identified a number of potential statin drug candidates that may be used in breast cancer treatment.

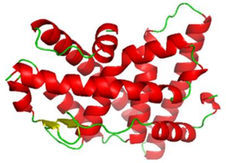

Figure 1. 3D structure of ESR1 visualized in PyMOL

METHODS

- Molecular docking of statins with ESR1 protein using AutoDock Vina.
- Superimposition with Brilanistrant (reference drug) using PyMOL.
- Interactions of reference inhibitor and candidate drugs with the protein (ESR1) using Discovery Studio Visualizer.
- Pharmacokinetic properties of the chosen drugs were evaluated using QikProp.

Table 1. List of Tools and Software

Sl. No.	Software and tools	Version
1	Open Babel	2.4.1
2	PyMOL	2.0.4
3	AutoDock Vina	1.5.6
4	Discovery Studio Visualizer	17.2.0.16349
5	QikProp	2020-3

RESULTS

Molecular Docking Results are shown in Table 2.

Table 2. Binding Affinity Values of the Reference Inhibitor and Statins with ESR1

Sl No	Drugs	Binding affinity (kcal/mol)
1	**Brilanestrant (Reference Inhibitor)**	-8.6
2	Rosuvastatin	-8.6
3	Simvastatin	-8.1
4	Lovastatin	-7.9
5	Cerivastatin	-8.0
6	Mevastatin	-7.8
7	Pitavastatin	-8.3
8	Pravastatin	-8.0

Superimposition Results

Rosuvastatin, simvastatin, lovastatin, cerivastatin, mevastatin, pitavastatin and pravastatin were found to superimpose with the reference drug, brilanistrant (Figure 2).

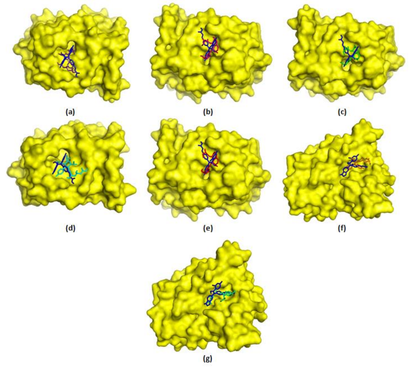

Figure 2(a) Superimposition of Brilanistrant (Blue) and Rosuvastatin (Dark violet); (b) Superimposition of Brilanistrant (Blue) and Simvastatin (Magenta); (c) Superimposition of Brilanistrant (Blue) and Lovastatin (Green);(d)Superimposition of Brilanistrant (Blue) and Cerivastatin (Sky blue); (e) Superimposition of Brilanistrant (Blue) and Mevastatin (Red); (f) Superimposition of Brilanistrant (Blue) and Pitavastatin (Orange); (g) Superimposition of Brilanistrant (Blue) and Pravastatin (Cyan)

The interactions of the superimposed drugs with ESR1 was visualized in Discovery Studio. The results are given in Table 3.

Table 3. Common amino acids involved in drug-ESR binding

Sl No	Drugs	Amino acids
1	**Brilanestrant (Reference Inhibitor)**	**GLU323, TRP393, ILE326, ARG394, LEU403**
2	Rosuvastatin	TRP393, ARG394, LEU403
3	Simvastatin	ARG394, ILE326, LEU403,, TRP393
4	Lovastatin	ARG394, LEU403, ILE326
5	Cerivastatin	ARG394, TRP393
6	Mevastatin	ARG394, LEU403, ILE326
7	Pitavastatin	GLU323, ILE326, TRP393,ARG394
8	Pravastatin	ARG394, GLU323, TRP393

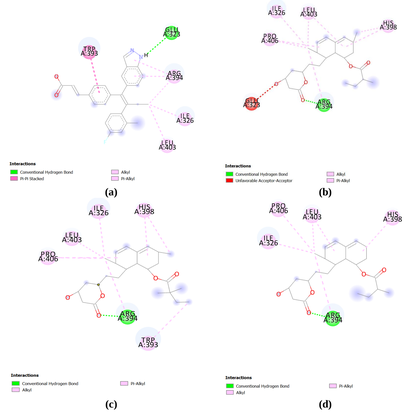

Figure 3. Interactions of (a) Brilanestrant (b) Lovastatin (c) Simvastatin and (d) Mevastatin with ESR1

Absorption, Distribution, Metabolism and Excretion (ADME)

- The pharmacokinetic properties of both the reference and selected candidates were assessed using QikProp.
- The predicted human oral absorption of the reference drugs, brilanestrant was 79.35%. All the candidates showed good oral absorption except rosuvastatin and pravastatin.
- Simvastatin, lovastatin and mevastatin showed excellent human oral absorption (100%).
- Brilanistrant showed moderate intestinal and renal permeability (45.897 nm/second and 69.755 nm/second respectively).

- Among the selected candidates, simvastatin, lovastatin and mevastatin:
  - Showed excellent intestinal permeability (784.019 nm/second, 718.894 nm/second and 625.056 nm/second respectively).
  - Showed moderate renal permeability.
  - QPlogKhsa values of these three drugs were within range.
  - Did not penetrate the CNS or the blood brain barrier as suggested by the CNS, logBB and PSA values.

CONCLUSION

The results of the study indicated that out of the eight candidate drugs taken, the three drugs - simvastatin, lovastatin and mevastatin - could be potential drugs in the treatment of breast cancer.

Further studies including *in vitro* and *in vivo* tests will be required to investigate and confirm their safety, efficacy and dosing profiles

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DECLARATION STATEMENT

The authors declare there is no conflict of interest