Repurposing of FDA-Drugs as Potential ERβ Agonists using Multicomplex-Based Pharmacophore Maps. A new approach in Breast Cancer Therapy

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Breast cancer: current scenario

2040

Mortality

42%

Efficacy and selectivity
Chemotherapy resistance
Endometrial cancer
Lack of FDA-approved drugs for TNBC

It is necessary to design strategies to identify drugs that target a particular activity

Selective activation of estrogenic receptors

DPN, selective agonist:
- Inhibits the proliferation in breast cancer cells
- Increases expression of ERβ in cells with a down-regulation
- Increased levels of ERβ result in a good prognosis and survival of patients with TNBC

Are there FDA-approved drugs that meet the structural agonist characteristics for ERβ activation?
Structural differences in binding site

PDB ID: 1X7B  Prinabere

PDB ID: 2QH6  Oxabicyclic diareylethylene

Multicomplex-based pharmacophore modeling of ERβ

- **Hydrophobic**
- **Hydrogen bond donor**
- **Hydrogen bond acceptor**

Ligandscout software

2.15 Å
2.57 Å
6.92 Å
9.04 Å
6.24 Å
6.72 Å
2.71 Å
5.87 Å
2.67 Å
3.03 Å

Hydrogen bond donor

Hydrogen bond acceptor
Workflow for pharmacophore-based virtual screening and selection of potential ERβ agonist drugs

Pharmacophore-based Cross virtual screening

No ERα agonist

ERβ map

ERβ/α Cross- docking

Potential ERβ agonists

Antiproliferative activity

Pharmacophore fit ERβ= 78.6
ERβ ΔG° = -9.51 Kcal/mol
ERα ΔG° = -8.85 Kcal/mol

LB36894-69-6

Potential ERβ agonists

Pharmacophore fit ERβ= 87.02
ERβ ΔG° = -9.7 Kcal/mol
ERα ΔG° = -8.44 Kcal/mol

SB211110-63-3

MCF-7 and MDA-MB-231
**In vitro** evaluation on breast cancer cell lines (ERβ+)

**SB211110-63-3**

**LB36894-69-6**

Effect of sobetirome and labetalol on cell proliferation in MCF-7 and MDA-MB-231. MTT assay was used to determine the % of cell proliferation. The data are presented as means S.E. ANOVA one way with poshoc dunnet, *p<0.05, *p<0.01 and ***p<0.001 Vs control.
Conclusions

- The application of multicomplex-based pharmacophoric modeling of ERβ allowed the identification of drugs with high affinity for the ERβ receptor and antiproliferative activity in breast cancer cell lines (MCF-7 and MDA-MB-231).

- This work contributes with a viable alternative for the possible repositioning of SB211110-63-3 and LB36894-69-6, to be used in the therapy against luminal breast cancer and aggressive triple negative.