XXVIII Symposium on Bioinformatics
and Computer-Aided Drug Discovery

INSTITUTO POLITÉCNICO NACIONAL
ESCUELA SUPERIOR DE MEDICINA
POSTGRADUATE STUDIES AND RESEARCH SECTION

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

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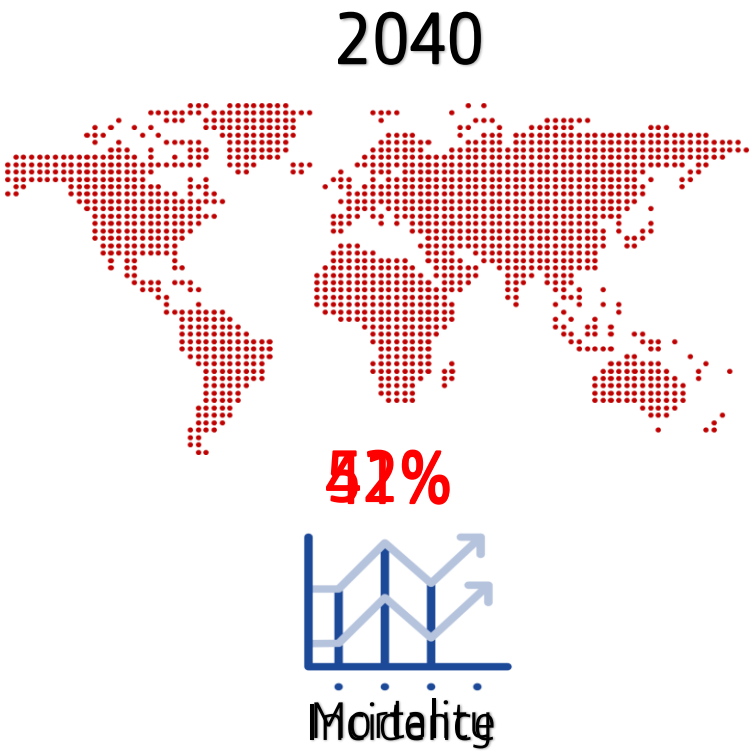
Breast cancer: current scenario

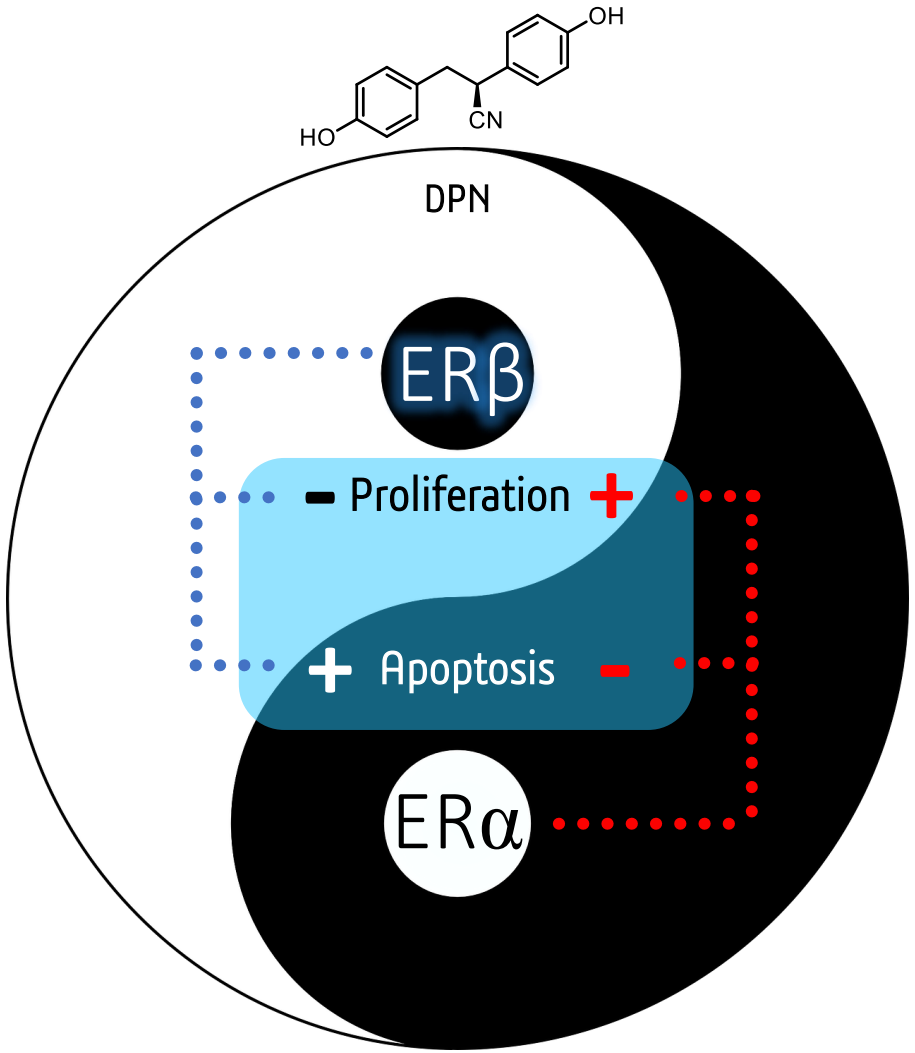


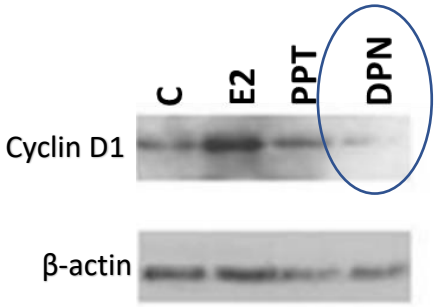
- Efficacy and selectivity
- Chemotherapy resistance
- Endometrial cancer
- Lack of FDA-approved drugs for TNBC

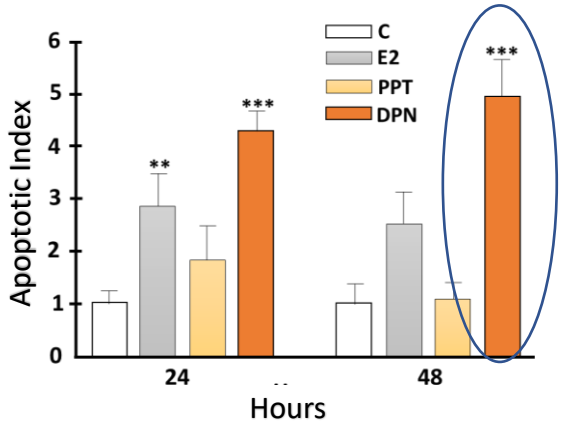
It is necessary to design strategies to identify drugs that target a particular activity

World Health Organization International Agency for Research on Cancer (IARC). GLOBOCAN 2020: estimated cancer incidence, mortality and prevalence worldwide in 2020.
Hu R, Hilakivi-Clarke L. Molecular mechanisms of tamoxifen-associated endometrial cancer (Review). ONCOLOGY LETTERS. 2015;9:1495-1501.

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
- <u>Increased levels of ERβ result in a good prognosis and survival of patients with TNBC</u>

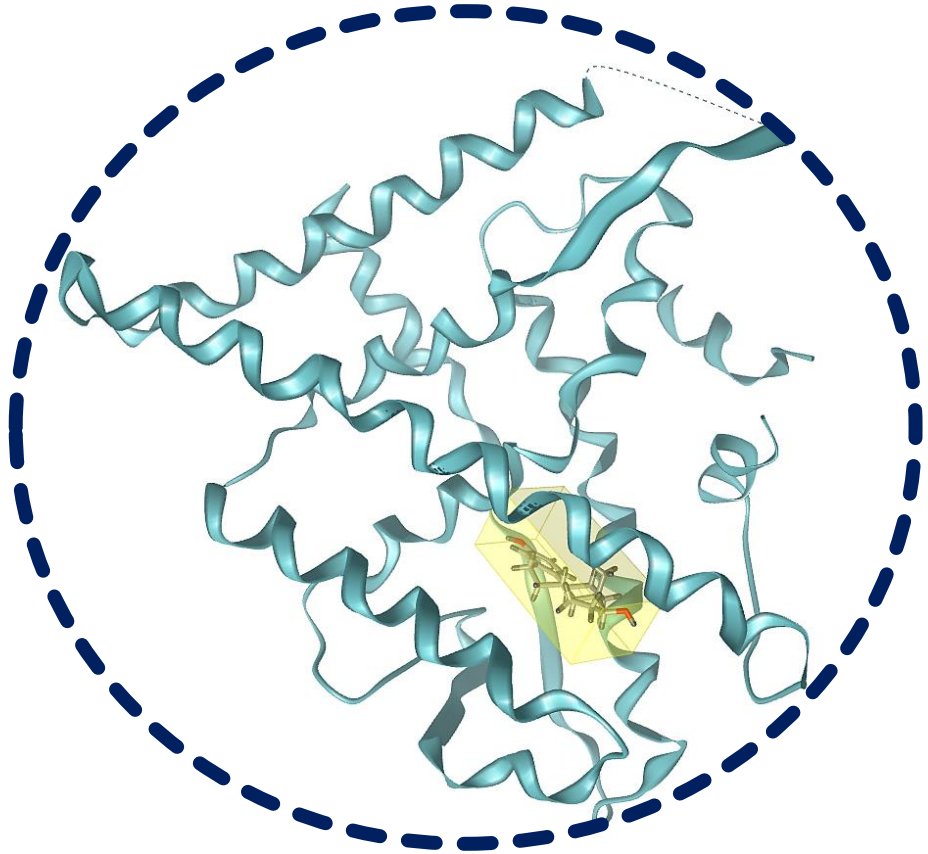
Warner M, Huang B, Gustafsson J. Estrogen Receptor beta as a Pharmaceutical Target. Trends in pharmacological sciences. 2017;38(1):92-99.

Suzuki H, Barros R, Sugiyama N, Krishnan V, Yaden B, Kim H, Warner M, Gustafsson J. Involvement of estrogen receptor beta in maintenance of serotonergic neurons of the dorsal raphe. Molecular psychiatry. 2013;18(6):674-80.

Are there FDA-approved drugs that meet the structural agonist characteristics for ERβ activation?

FDA Database

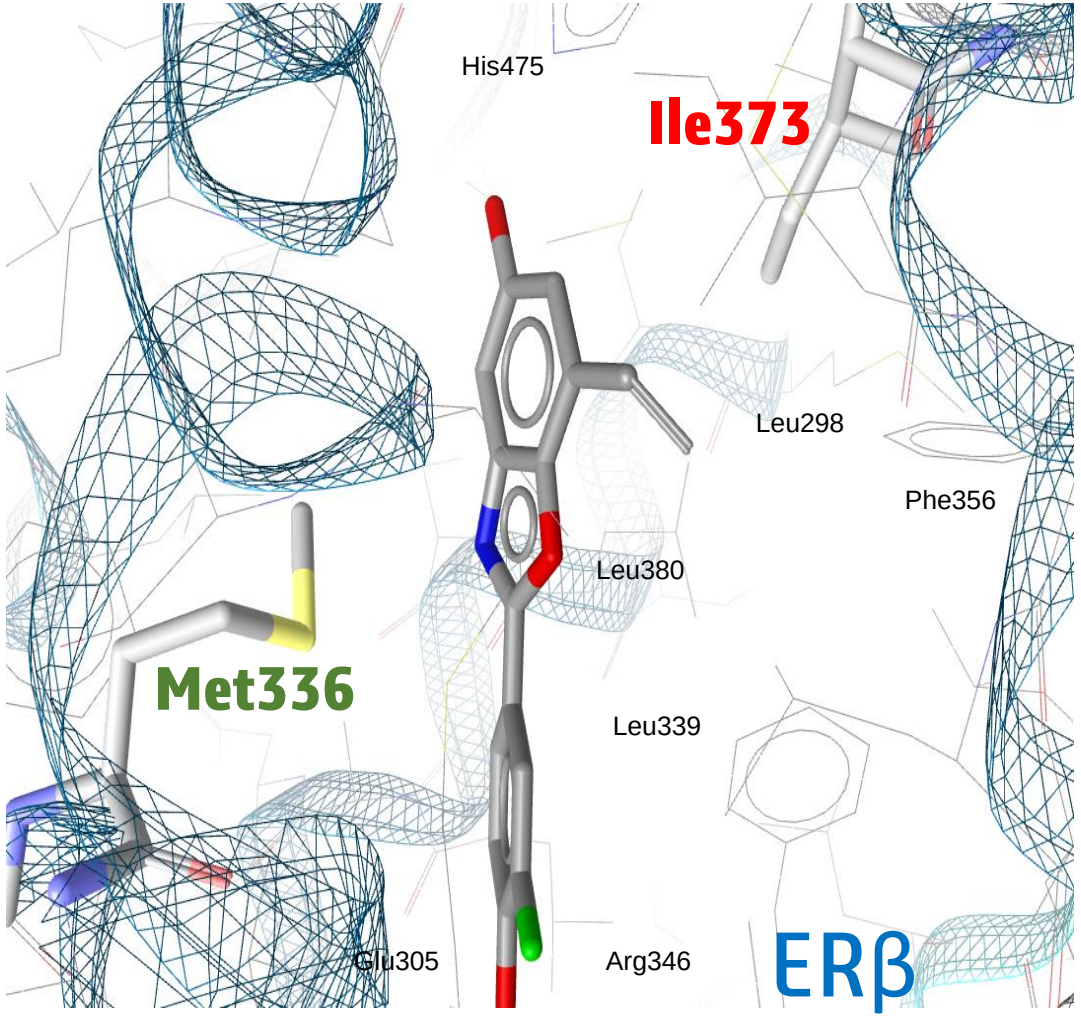
U.S. FOOD & DRUG ADMINISTRATION



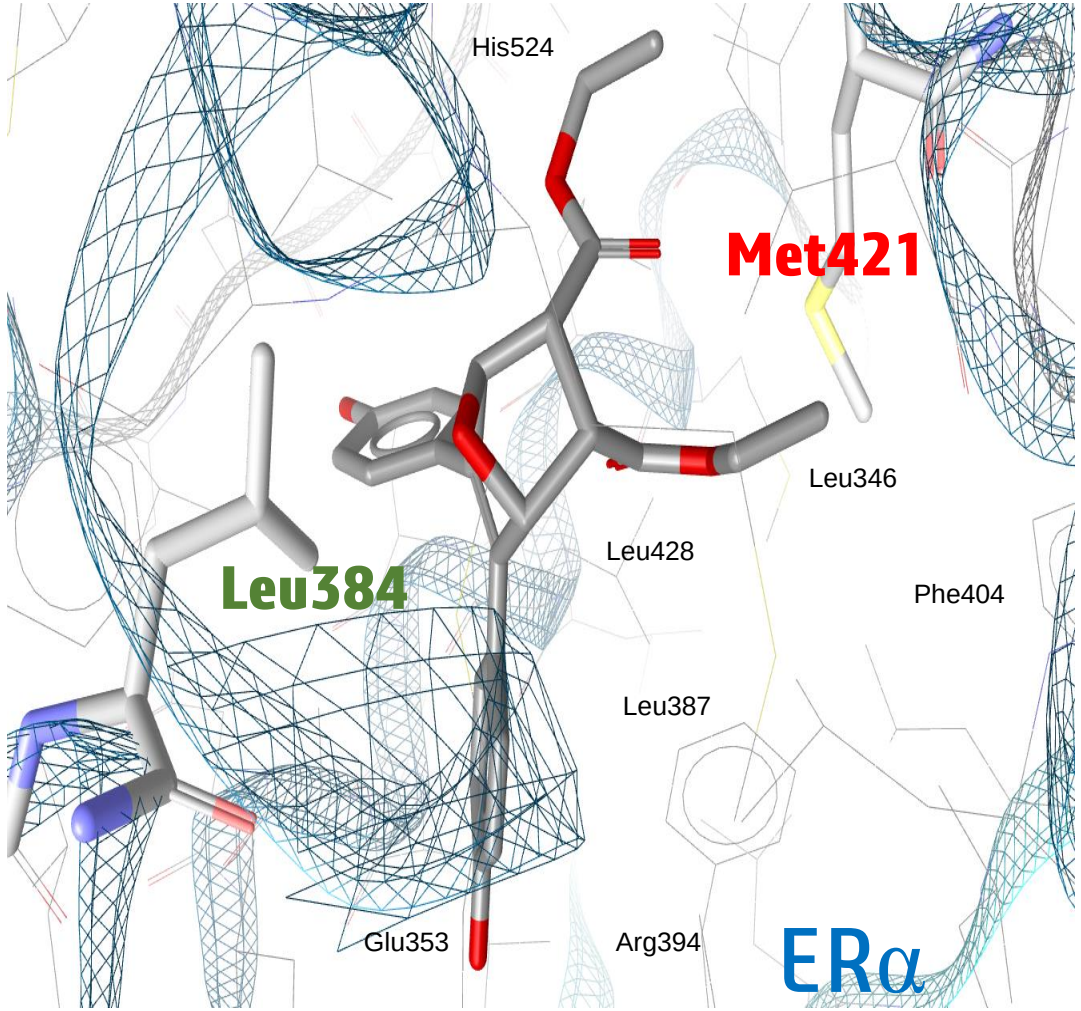
ERβ

Drug Repositioning

Structural differences in binding site



PDB ID: 1X7B Prinaberel



PDB ID: 2QH6 Oxabicyclic diarylethylene

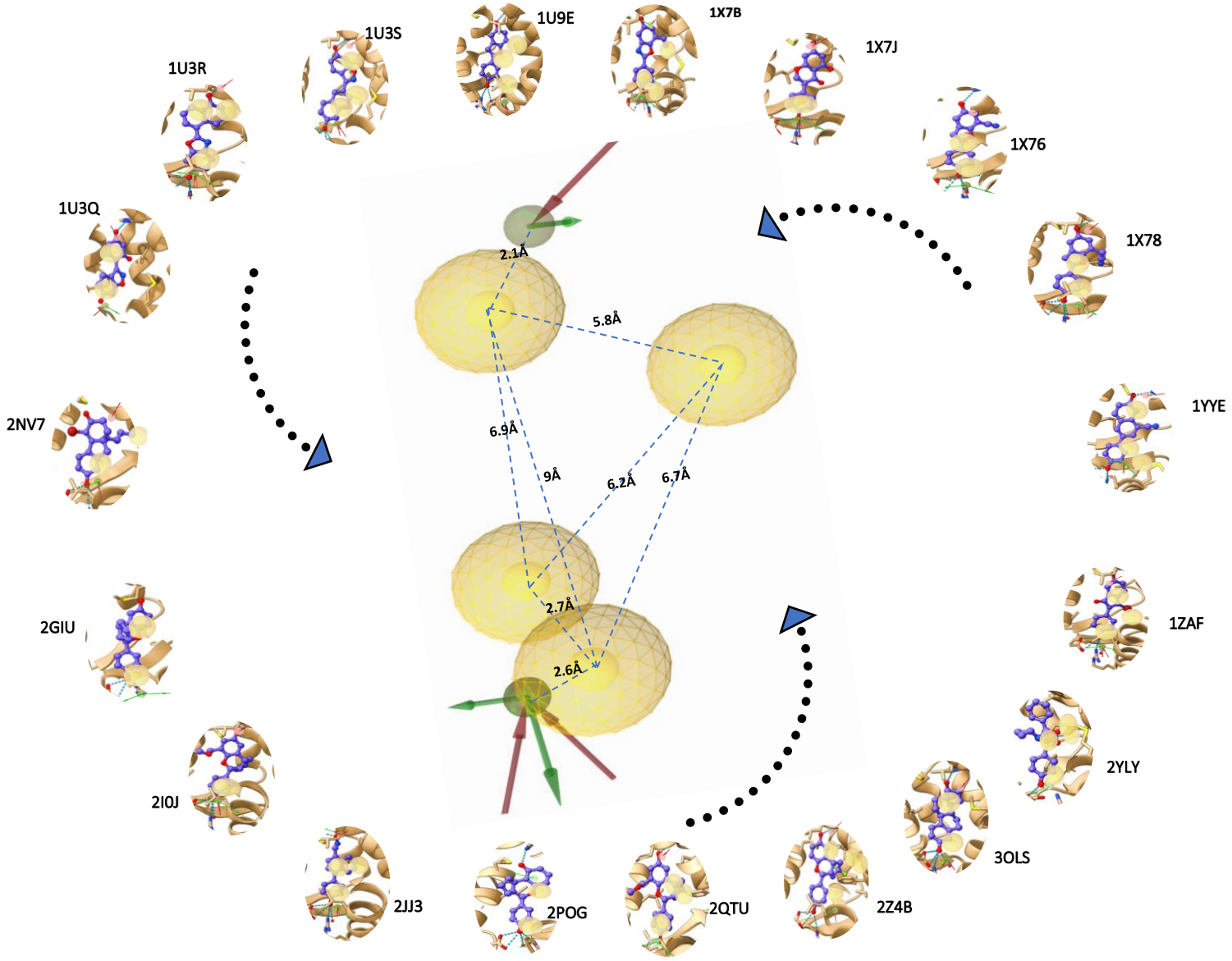
Kato, K., Fujii, K., Nakayoshi, T., Watanabe, Y., Fukuyoshi, S., Ohta, K., Oda, A. (2018). Structural differences between the ligand-binding pockets of estrogen receptors alpha and beta. Journal of Physics: Conference Series, 1136, 012021

Multicomplex-based pharmacophore modeling of ERβ

Hydrophobic

Hydrogen bond donor

Hydrogen bond acceptor



Ligandscout software

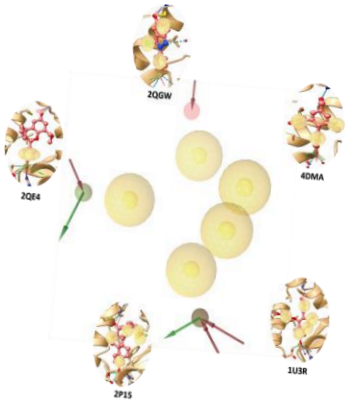
Workflow for pharmacophore-based virtual screening and selection of potential ERβ agonist drugs

Here the Poster

FDA DRUGBANK

Pharmacophore-based Cross virtual screening

⚠ No ERα agonist



ERα map

ERβ map

ERβ/α Cross- docking

Potential ERβ agonists

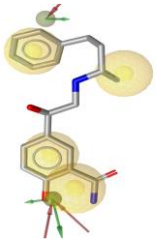
Antiproliferative activity

MCF-7 and MDA-MB-231

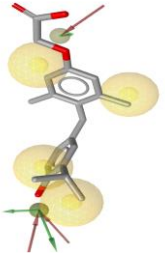
Pharmacophore fit ERβ= 78.6

ERβ ΔG°= **-9.51** Kcal/mol

ERα ΔG°= -8.85 Kcal/mol



LB36894-69-6



Pharmacophore fit ERβ= 87.02

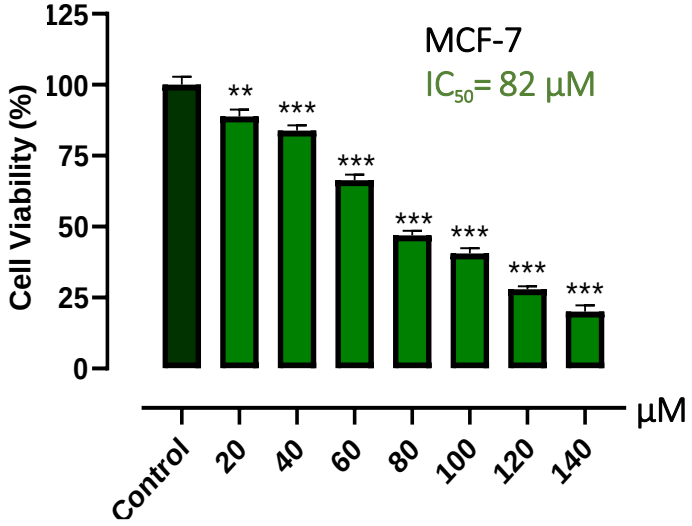
ERβ ΔG°= **-9.7** Kcal/mol

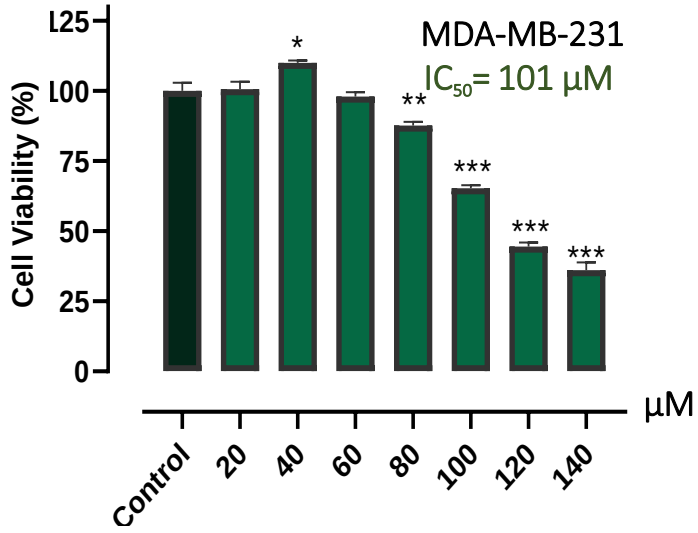
ERα ΔG°= -8.44 Kcal/mol

SB211110-63-3

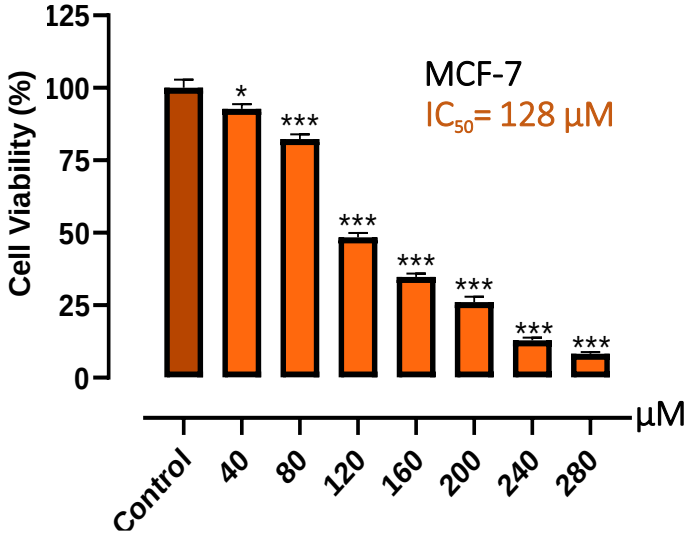
In vitro evaluation on breast cancer cell lines (ERβ+)

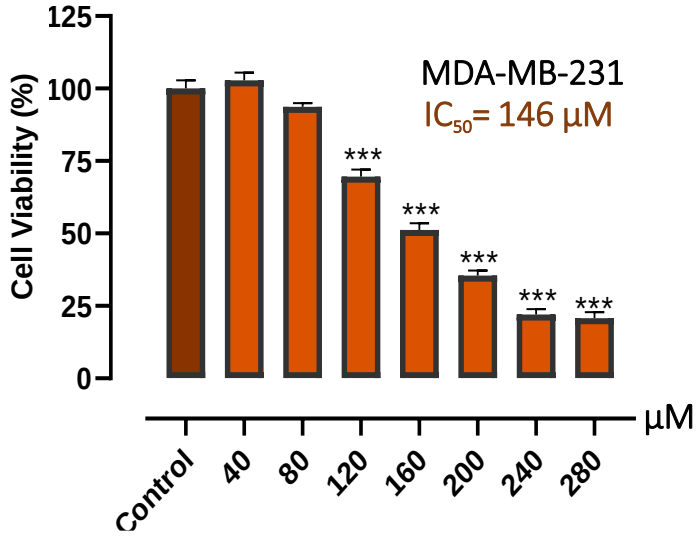
SB211110-63-3





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.