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BOOK OF PROCEEDINGS

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Computer-aided design of new drugs against breast cancer

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Abstract: Computational medicinal chemistry, if used properly and in accordance with the available experimental data, may provide significant support to rational drug design. Herein, an overview of the computational approaches that have been applied to an estrogen receptor α (ERα) and endowed in the rational design of pM ERα antagonists with profound anti-breast cancer activity either *in vitro* or *in vivo*, will be presented. ERα is a 17β-estradiol inducible transcriptional regulator that initiates the RNA polymerase II-dependent transcriptional machinery, pointed for breast cancer (BC) development *via* either genomic direct or genomic indirect (*i.e.*, tethered) pathway. To develop innovative ligands, structure-based (SB) 3-D QSAR, ComBinE, and 3-D Pharmacophore studies have been undertaken from experimentally resolved partial agonists, SERMs, and SERDs within either wild-type or mutated ERα receptors. SB and ligand-based (LB) alignments gave rules to align the untested compounds. The protocols led to the development of **3DQ**s, **CBE**s, and **3DPQ**s compounds, further synthesized and submitted to either *in vitro* or *in vivo* assessments, upon which new leads were revealed as candidates for clinical trials.

Keywords: ERα, 3-D QSAR, COMBINE, 3-D Pharmacophore, SB and LB alignment assessment, rational design of new SERMs, synthesis, pharmacological evaluation *in vitro* and *in vivo*

1. Introduction

Breast cancer is one of the leading causes of death in women worldwide. Its development is usually associated with the binding of estrogen receptor α (ERα), as nuclear receptor (NR), to human Estrogen Response Element (*h*ERE) sequence, as a promoter, initiated by the interaction of 17β-estradiol (**E2**), as a morphogen, which subsequently endows over-expression of breast proteins and cancer [1-3]. No full structure of ERα has been yet deposited at Protein Data Bank (https://www.rcsb.org/),

but only the crystal structures of DNA binding domain (DBD), complexed with *h*ERE sequence, and ligand-binding domain (LBD), co-crystallized with a series of partial agonists/antagonists (Figure 1), are available (Table 1) [1-3].

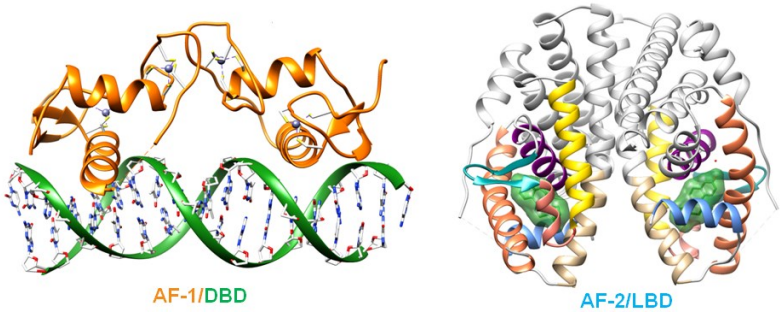


Figure 1. Left: The crystal structure of the ERα DBD domain in complex with human Estrogen Response Element (*h*ERE) (PDB ID: **1HCQ**). Right: The crystal structure of the ERα LBD domain E region in complex with 17β-estradiol (PDB ID: **1ERE**, resolution of 3.1 Å).

The LBD conveys either partial agonists', SERM's, or SERD's potency on the transcription (Table 1) and is considered a target for rational design. All the available data was used in herein-described case studies [1-3] to derive new anti-breast cancer drugs, by combining structure-based (SB) and ligand-based (LB) computational approaches with wet chemistry methods, *viz.* synthesis and pharmacological evaluation *in vitro* and *in vivo*.

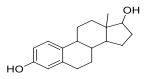
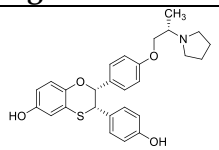
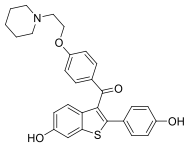
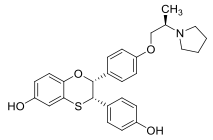
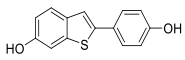
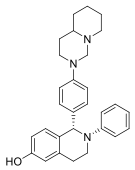
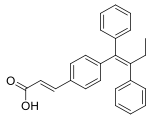
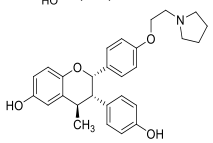
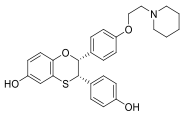
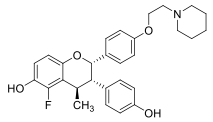
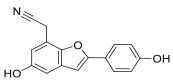
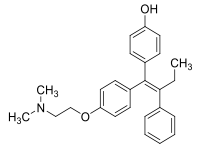
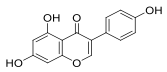
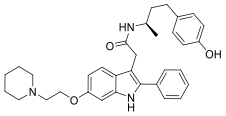
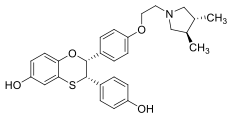
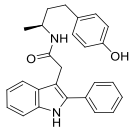
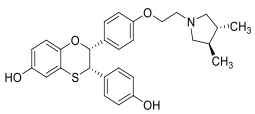
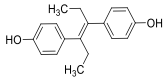
2. Materials and methods

All the experimental details regarding SB 3-D QSAR, SB ComBinE, and 3-D pharmacophore models, SB and LB alignment assessments, design, syntheses, and pharmacological protocols were reported elsewhere [1-3].

3. Results and Discussion

For designing the innovative SERMs, all the available ligand-ERα complexes have been retrieved from PDB (Table 1) and co-aligned. Upon extracting ligands, the pharmacodynamics profiles were obtained by means of generating either SB three-dimensional quantitative structure-relationships (3-D QSAR) (Figure 2), comparative molecular binding energies (ComBinE), or 3-D Pharmacophore models. The yielded molecular determinants further guided the rational design of new SERMs. Their bioactive conformations were generated by applying the consensus SB/LB alignment assessment on crystals, and upon being aligned into the active site of ERα, hits were potency predicted by means of the generated 3-D QSAR, ComBinE, and 3-D Pharmacophore models and prioritized for synthesis and pharmacological evaluation. The designed compounds were promptly synthesized and evaluated against ERα, breast cancer cell lines, and *in vivo* xenograft models, showing pM activity and optimal pharmacological profiles.

Table 1. PDB codes, ligand structures, and pharmacological profile of wild-type (WT) estrogen receptor α complexed with agonists, partial agonists, and antagonists.

PDB	Ligand structure	pIC_{50}	PDB	Ligand structure	pIC_{50}
1ERE PA[a] H12: CC[b]		9.24	**1XP9** SERM H12: OC		8.80
1ERR SERM[c] H12: OC[d]		9.52	**1XPC** SERM H12: OC		8.70
1GWQ PA H12: CC		5.85	**1XQC** SERM H12: OC		7.20
1R5K SERD[e] H12: OC		7.40	**1YIM** SERM H12: OC		8.80
1SJ0 SERM H12: OC		9.09	**1YIN** SERM H12: OC		8.80
1X7E PA H12: CC		5.90	**2BJ4** SERM H12: OC		8.60
1X7R PA H12: CC		8.01	**2IOG** SERM H12: OC		8.09
1XP1 SERM H12: OC		9.30	**2IOK** SERM H12: OC		9.00
1XP6 SERM H12: OC		9.30	**3ERD** PA H12: CC		9.48

[a]Partial agonist; [b]H12: closed conformation; [c]SERM – mixed agonist/antagonist; [d]H12: open conformation; [e]SERD – full antagonist.

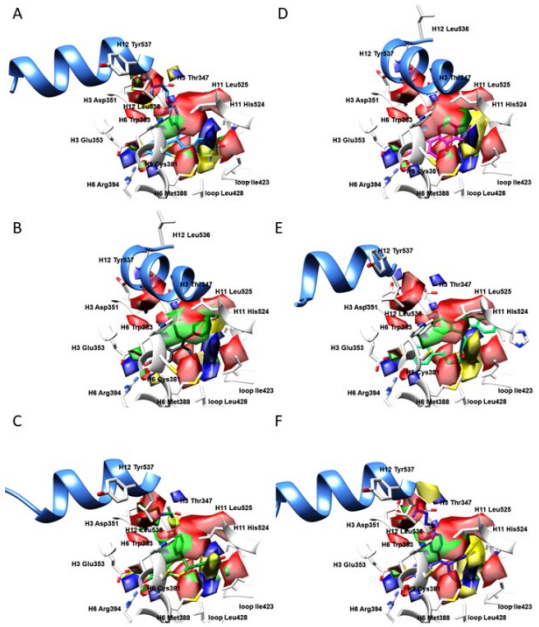


Figure 2. Representative N probe 3-D QSAR model *PLS-coefficients* contour maps (in red positive coefficients, in blue negative ones) and *Actual Activity Contribution* plots (L*ACC*, positive green, negative yellow) for **1ERR** (A); **3ERD** (B); **1XP1** (C); **1ERE** (D); **2IOK** (E); **2BJ4** (F).

4. Conclusions

The applied procedures led to the development of three series of compounds, 3**DQ**s, **CBE**s, and **3DPQ**s, characterized with pM potency either *in vitr*o or *in vivo*, proving that cheminformatics tools are very useful in the rational design of new anti-breast cancer agents.

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References

[1] N. Kurtanović, N. Tomašević, S. Matić, M.M. Mitrović, D.A. Kostić, M. Sabatino, Lorenzo Antonini, R. Ragno, M. Mladenović., *Human estrogen receptor α antagonists, part 1: 3-D QSAR driven rational design of innovative coumarin-related antiestrogens as breast cancer suppressants through structure-based and ligand-based studies*, Journal of Chemical Information and Modeling, 61 (2021) 5028-5053.

[2] N. Kurtanović, N. Tomašević, S. Matić, M.M. Mitrović, D.A. Kostić, M. Sabatino, Lorenzo Antonini, R. Ragno, M. Mladenović., *Human estrogen receptor α antagonists, part 2: synthesis driven by rational design, in vitro antiproliferative, and in vivo anticancer evaluation of innovative coumarin-related antiestrogens as breast cancer suppressants*, European Journal of Medicinal Chemistry, 227 (2022) 113869.

[3] N. Kurtanović, N. Tomašević, S. Matić, E. Proia, M. Sabatino, L. Antonini, M. Mladenović, R. Ragno., *Human estrogen receptor alpha antagonists, part 3: 3-D Pharmacophore and 3-D QSAR guided brefeldin a hit-to-lead optimization toward new breast cancer suppressants*, Molecules, 27 (2022) 2823.