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EXPLORING THE MOLECULAR BINDING MECHANISMS OF CLINICALLY-RELEVANT SELECTIVE ESTROGEN RECEPTOR MODULATORS THROUGH MOLECULAR DYNAMICS SIMULATIONS

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ABSTRACT

Estrogen receptor alpha (ERα), the representative of the nuclear hormone receptors class, is essential in different processes: maturation of female and male reproductive phenotype, maintenance of bone integrity, various aspects of central nervous system development, and cell proliferation in breast tissue-being the key player in the development and evolution of breast cancer (BC), the leading cause of mortality among female population worldwide [1]. Efficient treatment strategies against BC are known, but in some cases these therapies lead to drug resistance. Studies have shown that selective estrogen mimicking ligands therapy is effective in treating some patients with advanced BC resistant to TAM and AIs [2,3].
Here, we investigate the molecular mechanism of action for several selective estrogen mimicking modulators, in different stages of clinical development: BMI-135, TTC-352, BPTPE, through molecular docking [4] and molecular dynamics (MD) simulations [5]. The data show BMI-135 and TTC-352 binding to slightly distinct agonist conformations of ERα when compared with estradiol, explaining the partial agonist profile of this compounds [6,7].

METHODS

Ligand preparation. Ligands were prepared for docking using the LigPrep utility of Schrodinger 2019-02.
Protein preparation. ERα complexes were prepared for docking with the Protein Preparation Workflow implemented in Schrodinger 2019-02. A restrained minimization on the ligand-protein complexes was carried out with the OPLS_2001 force field (RMSD = 0.30Å for non-H atoms).
Docking description. Docking simulations were performed with Glide [4]. A degree of flexibility was allowed to the agonist conformation of ERα by scaling down the van der Waals radii of non-polar atoms (scale factor = 0.8) and allowing the free rotation of OH groups. The ligand poses were evaluated with Schrodinger's proprietary version of ChemScore empirical scoring function, GlideScore.

Molecular dynamics. The molecular dynamics (MD) simulations were performed with Desmond [5] in the NPT ensemble with periodic boundary conditions. Each structure was placed in a water box whose boundaries were set at 12 Å away from the nearest ERα atom. Then, each solvated system was minimized using the standard protocol implemented within Desmond 3.7 and simulated for 50ns. The particle mesh Ewald method (PME) was employed to treat electrostatic interactions with a cutoff distance of 10 Å while constant temperature (300K) and pressure (1atm) were used during the simulations. All simulations were carried out with a 2 fs time step and snapshots were recorded every 2.4 ps.

RESULTS

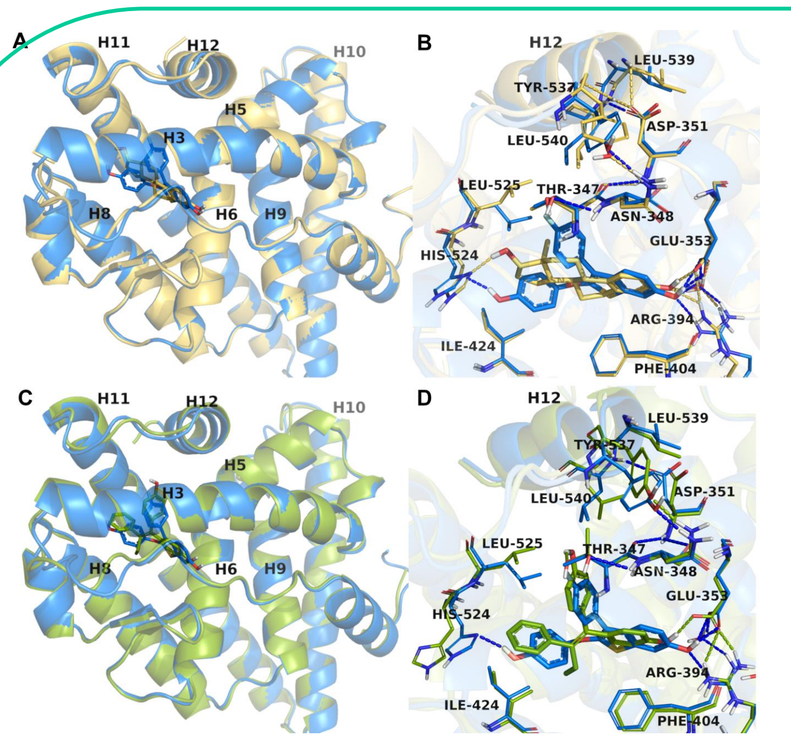

Fig. 2 - Comparison between TTC-352 (blue), E2 (yellow) and BPTPE (green).

DOCKING RESULTS

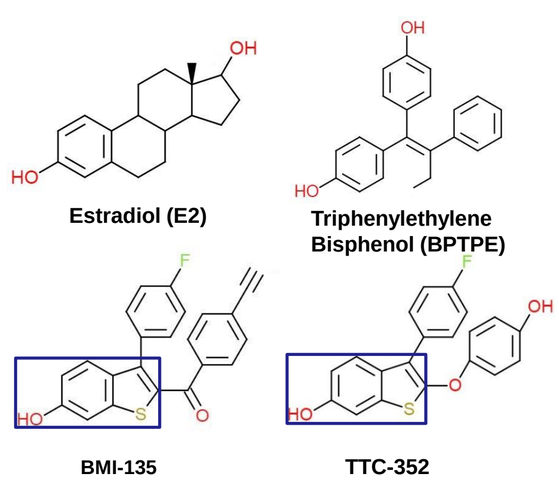

Fig. 1 – Chemical structures of the investigated ligands

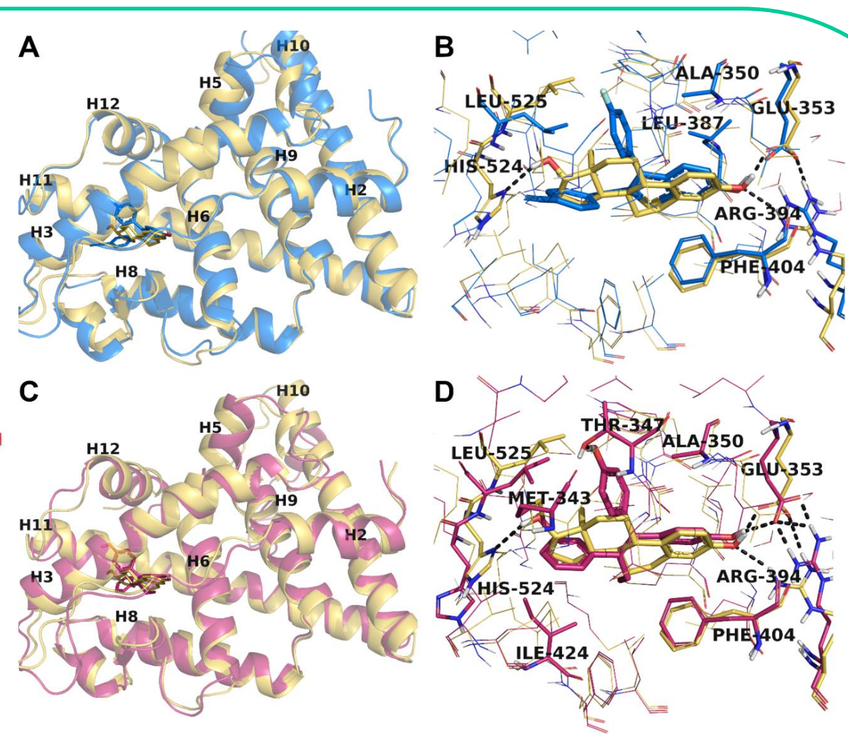

Fig. 3 - Comparison between BMI-135 (blue), E2 (yellow) and BPTPE (magenta).

MD SIMULATIONS ANALYSIS

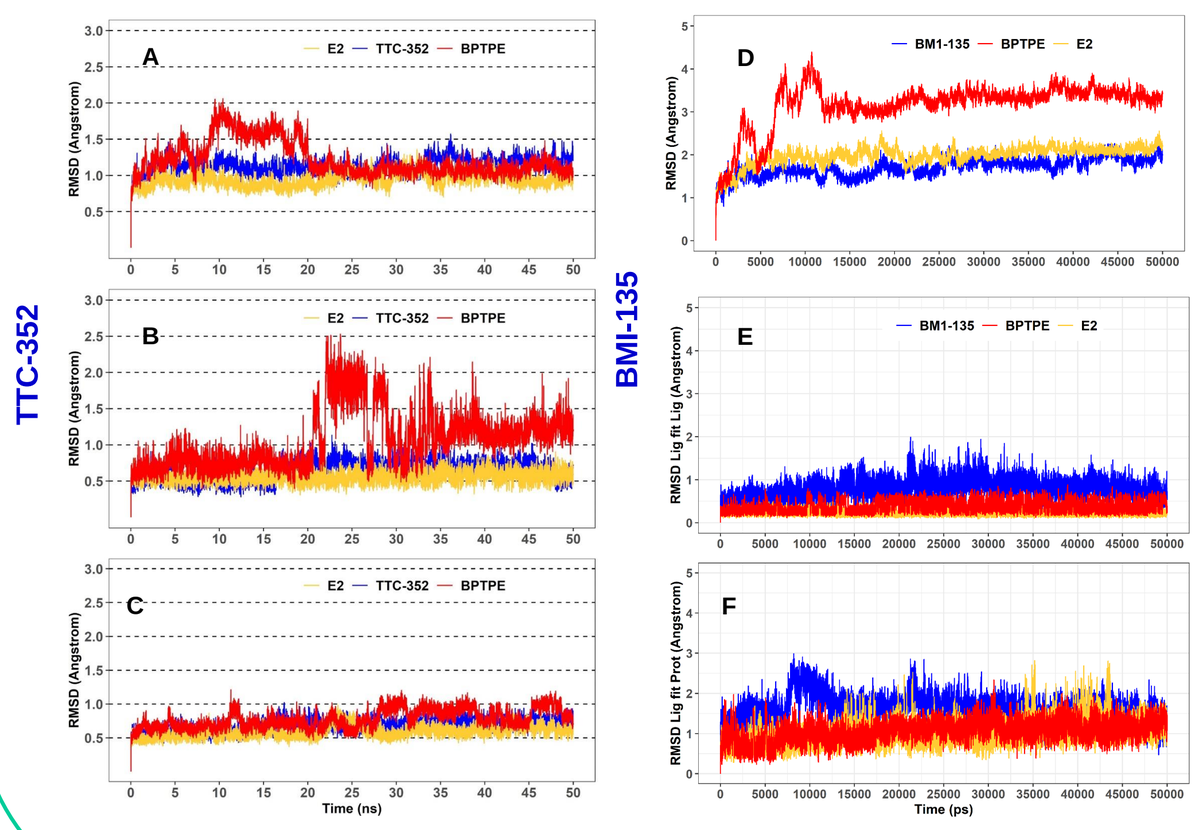

Fig. 4 - Structural analysis of trajectories. Comparison of the structural parameters RMSD for ERα:LBD WT bound to: E2 (yellow), TTC-352 (blue), and BPTPE (red). RMSD parameters were calculated for the backbone atoms of the whole proteins (A,D), helix 12 (B,E), and binding site amino acids (C,F).

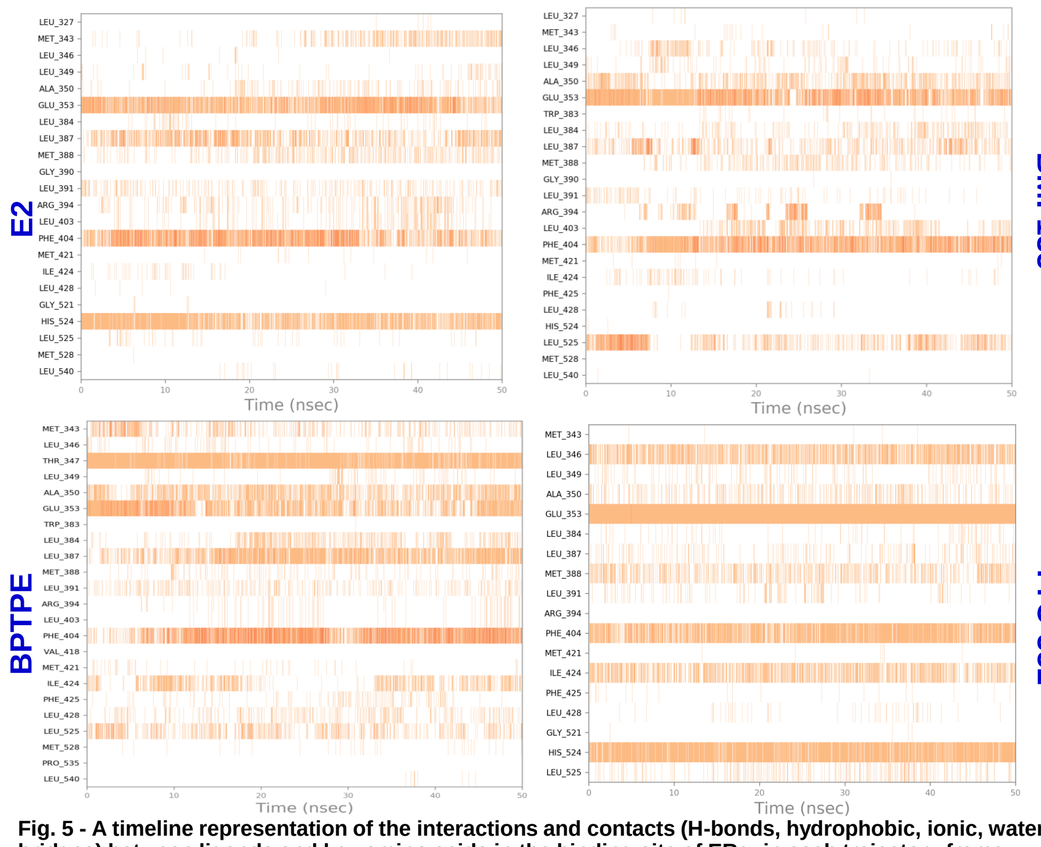

Fig. 5 - A timeline representation of the interactions and contacts (H-bonds, hydrophobic, ionic, water bridges) between ligands and key amino acids in the binding site of ERα, in each trajectory frame, during the 50ns simulation time. Residues involved in more than one specific contact with the ligand are represented in darker shades of orange.

REMARKS

- Two features specific for the estrogenic activity of E2, the H-bond to Glu353 followed by the H-bond to His524, are the most stable contacts to the binding mechanism of TTC-352. In contrast, in the binding mode of BPTPE the most stable interaction is the H-bond to Thr347, while the contact to Glu353 is weaker (Fig. 2, Fig. 5). This network of H-bonds is better kept in the structure of TTC-352, but to a lesser extent compared with the full-agonist structure of E2, explaining the altered functional profile of TTC-352:ERα (Fig. 5).
- Flexible docking and MD simulations performed for BMI-135:ERα complex show the dynamic profile of the system to be similar to E2 (Fig. 4D); with the ligand firmly bound to the active site (Fig. 4E, 4F).
- MD simulations showed that BPTPE forms a distinctive and robust interaction with Thr347 (Fig. 5), which induces stability to the ligand binding, but leads to increase mobility of H12 and the loop connecting H11 and H12, affecting the overall stability of the system, and thus, most likely, being responsible for the partial agonist profile of the ligand.
- These data support the molecular classification of TTC-352 and BMI-135 as full agonists that are weaker than E2, and further explain their observed biological behavior.

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