Docking of estrogen and genistein like molecular library on Estrogen Receptor alpha and beta

Chiappori F.(1), Ferrario M.G.(1), Gaiji N.(1), Fantucci P.(1)

(1)Department of Biotechnology and Bioscience University of Milano Bicocca, Milano

Motivation

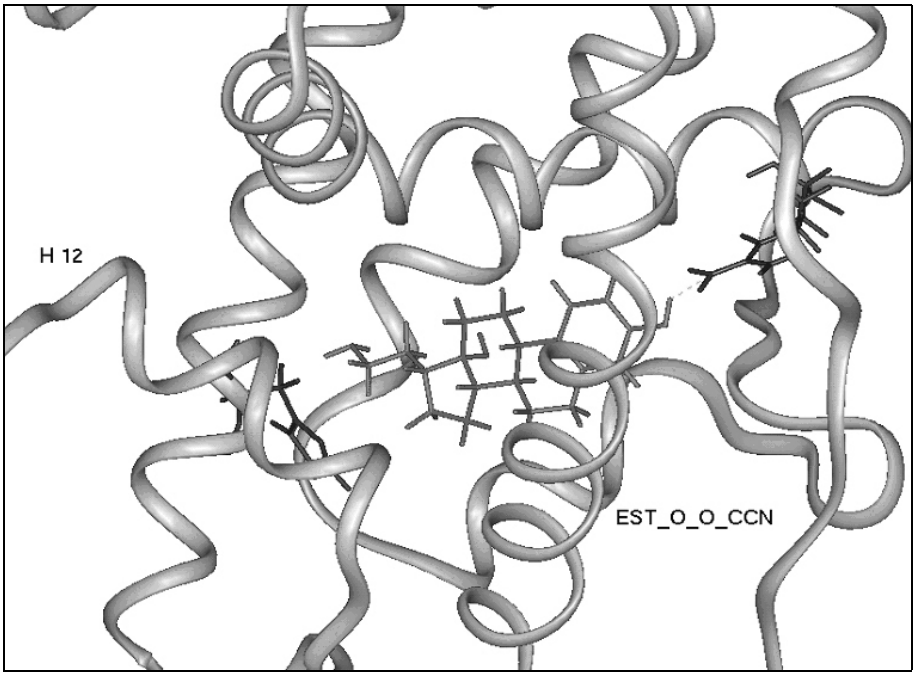
Estrogen replacement therapy is one of the most efficient treatment of menopausal symptoms. Unfortunately, despite the benefits of estrogenic therapy evidence exists of increasing number of cases of reproductive tissue cancer. This lead to a strong interest in discovering new compounds that display the benefits of estrogens avoiding such risks. We decided to apply a virtual high throughput screening, based on docking simulations, for the identification of new possible selective receptor compounds.

Methods

In this work, different compounds have been docked on the structures of Era and Erb in their apo forms. The X-ray structure of Era was downloaded from the Protein data Bank (code 1G50), the apo experimental Erb structure is missing, it was rebuilt by homology modelling techniques, using as a template Era due to the strong homology between sequences. Both structures where optimized by means of molecular mechanics (MM) in explicit solvent with the following protocol: MM on the side chains in vacuo, MM of the solvent with protein fixed, MM in solvent with only the backbone fixed and finally MM of the whole system. In the following step, a small estrogen-genistein virtual molecular library has been built, using 17bestrogen and genistein, deprived of the oxygen atoms, as scaffolds. We defined substitution points on which we clasped a small database of substituents (OH, CH3, CH2CH3, CH2OH, CH2CH2OH,CH2CH2NH2, OCH2CH2NH2). The structures of the molecules where optimized by means of molecular mechanics using MOE software and MMFF94 force field. Docking simulations where performed with Autodock version 3.0, AMBER charges were used for protein molecules, and Gasteiger for all ligands. The two docking partners where treated according to the rigid bodies approximation so no internal torsions were added to the ligand. For searching, we used genetic algorithm with a number of individuals in population equal to 100, maximum number of energy evaluations 300000 and maximum number of generations 30000

Results

We docked 40 different ligands on the two isoforms. In order to evaluate the reliability of the docking energies we also docked 17bestradiol and genistein. The results obtained with genistein reproduce well the experimental results indicating a selectivity for receptor b, in fact the docking energies are respectively -6,60kcal/mol for Erb and -5,35 for Era. The docking energies of the library compounds ranged from -5,38 to -10,78 kcal/mol, 25% of the compound displayed a selectivity for Erb, the docking energies for this isoform where 1,5kcal/mol greater than for the a one. In particular three estradiol derived compounds (reported in figure1) have a docking energy of 4kcal/mol higher (in modulus) for Erb. The interactions are overall of hydrophobic nature in agreement with the characteristic of the central groove, and with some hydrogen bonds with the residues of the active site (GLU ARG HIS).



Contact email: noura.gaiji@unimib.it