Abstract

This study performed *in silico* screening of a series of small molecules for endocrine disrupting capacity based on their interaction with the Human Estrogen Receptor alpha (hERα), a fundamental protein responsible for the detection of sex hormone estrogens and regulating downstream gene expression activated by the binding of a natural hormone. The hERα has flexibility to interact with and be activated by many synthetic and natural chemicals, so called endocrine disruptive chemicals (EDCs). Malfunctioned estrogen receptor pathways have been indicted for causing breast cancer. The force field polarization model, Moving Domain Quantum Mechanics/Molecular Mechanics (MoDQ3M), was used to describe the electric fields and electronic polarization effects inside the hERα protein. In depth analysis were carried out in order to understand the underlying molecular mechanism using techniques including force field polarization, molecular dynamics, ligand-protein residue interaction and free energy landscape analysis. These showed that the mutated residues changed the overall electrostatic environment of the system along with the ligand-protein interactions. Mutation on two important residues were carried out *in silico*, and the results were compared between the wild type and mutant for both the agonist (PDB ID: 2B1Z) and antagonist (PDB ID: 3ERT). The mutation of Y537C on the agonist and N532D on the antagonist within the ligand binding domain of the protein altered the interaction of the top ranked EDC compounds giving an MM-PBSA binding energy of –5.531 kcal/mol and –8.047 kcal/mol, better than that of the wild type for the antagonist. Glide docking studies gave top ranked EDCs as DES, Genistein, Nonylphenol-9, DDE, BPA with glide scores (kcal/mol) of -10.332, -11.127, -8.627, -8.735, -9.007 respectively on the agonist and -10.459, -10.119, -8.612, -8.507, -9.988 respectively on the antagonist. Similar EDCs ranks were also realized for the mutants. The insights from this study could be of great relevance while designing new drugs for the treatment of breast cancer and the effect of mutation on the overall binding mechanism of other compounds to the system.