Analysis of Raloxifene and its Derivatives Binding Affinities to the α Estrogen Receptor Ligand Binding Domain

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The drug molecule raloxifene has been shown to inhibit the growth of breast cancer cells due to its ability to competitively inhibit the α estrogen receptor (ER-α). Unfortunately, the molecule undergoes extensive glucoronidation in the human small intestine and liver, leaving only 2% of the dose bioavailable in its potent form. With this in mind, researchers have synthesized raloxifene derivatives and reported experimental binding affinities in the literature. Using these laboratory derived analogs as our probes, we have explored the binding dynamics of the αER to substrates that will inhibit its function. Due to the incompleteness of the αER in the ER-raloxifene crystal structure (1ERR), we used the high resolution (1.9Å)ER from the ER-tamoxifen crystal (3ERT) for our calculations. We used Gaussian to build each derivative and then optimized it using HF/6-31G* level of theory. The ligands were then assigned RESP charges in the antechamber module of AMBER8, followed by their docking into the crystal ER-α using the program AutoDock Tools. We then used sander to minimize the energy of the complex using Generalized Born implicit solvation. After we minimized the structure, we heated the complexes for 50 ps from 0 K to 300 K in MD and then let the system run for another 1950 ps. In an attempt to cut down on the expense of computations, we reduced the size of the system to 1400 atoms by cutting away all the residues of the ER that were further than 10Å away from the docking site and capped the end groups, and then restrained them. In addition, it is unclear whether or not the amine tail of the ligands should be protonated in the binding pocket, so both protonated and non-protonated ligands were used in our simulations. We report the RMS of the ligands in the whole systems compared to the cut system, as well as the difference between protonated and unprotonated ligands.