DOCKING AND ROTATIONAL BARRIER EFFECTS ON THE ACTIVITY OF VARIOUS SELECTIVE ESTROGEN RECEPTOR MODULATORS USED AS ANTI-TUMOR AGENTS

M. Buckles¹, J. S. Cooperwood², J. Ford-Green³, M. Cato³, T. D. McGee⁴, L. Mandela⁵, L. D. Thomas⁶, A. Turner¹, N. Wong², A. Roitberg⁴, J. Leszczynski³ and J. Edwards¹

¹Department Chemistry, Florida A&M University, Tallahassee, Florida 32307, USA
²College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, Florida 32307, USA
³Department of Chemistry, Jackson State University, Jackson, Mississippi 39217, USA
⁴Department of Chemistry/Quantum Theory Project, University of Florida, Gainesville, Florida 32608, USA
⁵Department Chemical Engineering, Florida A&M University/Florida State University College of Engineering, Tallahassee, Florida 32307, USA
⁶Department of Biology, Florida A&M University, Tallahassee, Florida 32307, USA

Abstract: Endocrine therapy has been proven to be effective treatment of estrogen receptor positive breast cancer through disruption of estrogen action. Selective estrogen receptor modulators (SERMs) are a group of compounds that bind to estrogen receptors and elicit an agonist or antagonist response based upon their chemical structure and target tissues. Tamoxifen is a well-known triphenylethylene SERM that is used as an adjuvant therapy in breast cancer. A series of glucocorticoid steroid derivatives have been synthesized by the J. Cooperwood et. al. with greater or comparable activity to Tamoxifen. Using the stiff steroid fused ring structure combined with the aminoalkyl portion of Tamoxifen Cooperwood et. al. synthesized this unique set of compounds. We use molecular mechanics to calculate the rotational barriers of the functionalized tails of these estrodiol derivatives compounds. The contours plots show qualitatively that the greater the flexibility of the compounds the more active the compound. In the case of the isopropyl derivative the barriers around the minimum energy structure are as low as 10 kcal/mol while 2 diehedral angles in the aminoalkyl-oxy tail are held constant and the other two are varied from 0-360 degrees. Further investigation of these contour plots will provide insight to the activity and potential mode of action of these compounds. We will report on several contours plots of several of these compounds. A comparison between docked structures to the active site and low energy conformations will also be made with particular interest in the rotational barriers of these conformations preventing them from achieving the docked structures.