Poster #30

Estrogenic Activity of Novel Synthetic Non-Steroidal Chemicals: Molecular Modeling and Fluorescence Polarization Studies.

Rajendram V Rajnarayanan, Matthewos Eshete, Georgi Nikov and William L. Alworth*

Department of Chemistry, Tulane University, New Orleans, LA 70118

Email: alworth@tulane.edu

Structurally diverse synthetic chemicals may affect the estrogenic signaling pathways through interactions with the estrogen receptors. Since the discovery of diethylstilbestrol (DES), a non-steroidal estrogen, many compounds have been synthesized and tested for estrogenic activity. Estrogenic activity of such a wide range of chemicals is a resultant of striking similarity in the bonding interactions of these molecules with the estrogen receptor.

The binding of 17-_-estradiol with the estrogen receptor is dictated by two factors : (I) Hydrogen bonding interactions between the hydroxyl groups of the ligand with Glu-353 and His-524 (II) Hydrophobic interactions. Modeling studies suggest that compounds having bulky adamantyl moiety and phenolic groups at appropriate positions, such as 4-(1-adamantyl) phenol (AdP) and 4,4′-(1,3-adamantanediyl) diphenol (AdDP) could bind to ER__ in a similar manner.

We used fluorescence polarization to compare the binding affinities of AdP, AdDP, and 2-(1-adamantyl)-4-methylphenol (AdMP) for human ER_ and ER_ with the binding affinities of the known ER ligands, DES and 4-hydroxytamoxifen. Competitive binding experiments show that AdDP has greater affinity for both ERs than AdP, while AdMP does not bind the receptor proteins. We also found that AdDP and AdP can cause conformational changes in ER_ and ER_, which result in altered affinities of the ERs for fluorescein-labeled EREs.

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