In Silico Search for Novel Estrogen Receptor Ligands

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The estrogen receptors (ERs) α and β are intracellular proteins responsible for controlling transcription of genes necessary for human development and reproduction. ER activity is normally modulated by the endogenous hormone 17β-estradiol which binds to the ERs resulting in recruitment of coregulatory complexes. Due to the important role the ER signaling networks play in developmental, reproductive, neural, skeletal, and cardiovascular processes, irregularities in ER activity can lead to a number of conditions including breast, ovarian, colon, prostate, and endometrial cancers. In around 70% of breast cancer cases, the estrogen receptors are overexpressed, a condition referred to as ER-positive breast cancer. Selective estrogen receptor modulators (SERMs) are compounds which can display both agonist and antagonist effects on ER activity dependent upon the specific cell type in which the estrogen receptor is present. For example, when tamoxifen, a leading drug for treating ER-positive breast cancer, is metabolized in the liver it becomes the SERM 4-hydroxytamoxifen which is an ER antagonist in breast cells, an ER agonist in bone, helping to prevent osteoporosis, and, unfortunately, a partial agonist in endometrium cells leading to an increased risk of uterine cancer.

The development of novel SERMs is important both for developing better drug treatments for ER-related disorders as well as for finding molecular tools to help further elucidate the details of ER signaling pathways. In order to discover new estrogen receptor ligands, libraries of compounds were assembled on the computer based around the common SERM substructure triphenylethylene. A triphenyltriazole scaffold was also investigated. Searches were performed on the ZINC database in order to identify available compounds with these substructures as well as available precursors which could yield compounds with our desired form. The resulting dataset of compounds was screened virtually against x-ray crystallographic structures of ERα found on the Protein Data Bank using the automated docking program eHiTS. Known estrogen receptor ligands included in the screening set were shown to perform well providing initial validation of the accuracy of the docking program. Compounds receiving scores in the docking program similar to or better than known SERMs were designated as “lead” compounds. These lead compounds are in the process of being obtained and/or synthesized in order to screen against ZR-75-1 breast cancer cells which will help determine if these compounds are indeed SERMs.