

# **“Quantitative Structure – Activity Relationships (QSAR) of Phytoestrogens, Mycoestrogens, and Diethylstilbestrol Derivatives with Estrogen Receptor- $\alpha$ Reveal Core Functional Centers for Estrogens”**

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## **Abstract:**

Three different types of Quantitative Structure-Activity Relationship (QSAR) models were constructed for the estrogen receptor (ER) binding activity of 58 myco, phyto and stilbene estrogens reported in the NCTR database (FANG, H., et al., 2001, Chemical Research in Toxicology, 14, 280-294). The purpose of this project was to develop QSAR models that can be used to predict the ER binding of untested compounds in these discrete structure classes. This data set was divided into 50 training set compounds used to build QSAR models and 8 test set compounds to evaluate the predictive capability of each model. A hologram QSAR (HQSAR) model was developed that defines two-dimensional fragments (4-7 atom fragments) responsible for ER activity ( $Q^2=0.758$ ,  $R^2=0.915$ ). Three dimensional structures were used to develop Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) QSAR models that define distinct structure features responsible for ER binding activity (Steric, Electrostatic, Hydrophobic). All relevant isomers and enantiomers were modeled to include the stereochemical nature of particular phytoestrogens in these 3D-QSAR models. The optimal CoMFA model displayed a predictive  $Q^2$  of 0.792 ( $R^2=0.983$ ) while the optimal CoMSIA model produced in a predictive  $Q^2$  of 0.831 ( $R^2=0.933$ ). This study has produced the most comprehensive QSAR models of ER binding activity for myco, phyto and stilbene estrogens to date. These three models have considerable potential to predict the ER binding activity of myco, phyto and stilbene compounds found through database screening or the analytical separation and identification of plant and fungal extract, as well as being able to develop pharmaceuticals.