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Hypothesis

# Novel aromatase inhibitors selection using induced fit docking and extra precision methods: Potential clinical use in ER-alpha-positive breast cancer

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**Abstract:**
Aromatase (*CYP19A1*) the key enzyme of estrogen biosynthesis, is often deregulated in breast cancer patients. It catalyzes the conversion of androgen to estrogen, thus responsible for production of estrogen in human body. However, it causes over-production of estrogen which eventually leads to proliferation of breast cancer cells. Identification of new small molecule inhibitors targeted against *CYP19A1* therefore, facilitates to increase drug sensitivity of cancer cells. In this scenario, the present study aims to identify new molecules which could block or suppress the activity of aromatase enzyme by molecular docking studies using Schrödinger-Maestro v9.3. In this study we used *in silico* approach by modeling *CYP19A1* protein the strcture was subjected to protein preparation wizard; to add hydrogen and optimize the protonation states of Thr310 and Ser478 and Asp309 residues. Active site of the *CYP19A1* protein was identified using SiteMap tool of Scchrodinger package. We further carried out docking studies by means of Glid, with various ligands. Based on glid score, potential ligands were screeened and their interaction with *CYP19A1* was identified. The best hits were further screened for Lipinski's rule for drug-likeliness and bioactivity scoring properties. Thus, we report two rubivivaxin and rhodethrin compounds that have successfully satisfied all *in silico* parameters, necessitating further *in vitro* and *in vivo* studies.

**Keywords:** aromatase inhibitors, anticancer drug, breast cancer, molecular docking

**Background:**
Breast cancer is the most prevailing malignancy among females, and the second most common cause of cancer-related deaths in women in the United States **[1].** An estimated 235,030 new cases of invasive breast cancer are diagnosed among both males and females in the US during 2014 withan estimated death of 40,430 people **[2].** Breast cancer is a complex and heterogeneous diseasewith varying clinical outcomes, disease progression, and responses to specific treatmentsattributed by a wide array of elements ranging from tumorintrinsic genetic factorstoextrinsic tumor micro-environmental factors **[3].** Gene expression studies using DNA microarrays have identified several distinct breast cancer subtypes based on an intrinsic gene list that includes 496 genes that differentiate breast cancers into separate groups based only on gene expression patterns **[4].** Estrogens are important players in breast cancer tumorio-genesis. The estrogen-bound Estrogen Receptor (ER) complex regulates the transcriptome of breast cancer cells by interaction with different transcription factors.Despite the plethora of physiological and pathophysiological functions of estrogen, a large number of