Identification of high affinity small molecules targeting ESR1 inhibitors for the treatment of Breast Cancer

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The estrogen receptor (ER) belongs to a family of nuclear hormone receptors that act as ligand-activated transcription factors. Breast cancer is the most prevalent cancer in women, and over two-thirds of cases express estrogen receptor-a (ER-a, encoded by ESR1). Two hypotheses have been proposed to explain why this causes tumorigenesis, and the available evidence suggests that both mechanisms contribute: First, binding of estrogen to the ER stimulates proliferation of mammary cells, with the resulting increase in cell division and DNA replication, leading to mutations. Second, estrogen metabolism produces genotoxic waste. The result of both processes is disruption of cell cycle, apoptosis and DNA repair, and, therefore, tumor formation. Estrogen therapy therefore forms an ideal therapeutic strategy in treatment of breast cancer, however, a subset of patients develop resistance to estrogen therapy owing to mutations in ER1 gene. In recent years massively parallel genome sequencing has revealed the common presence of point mutations on ESR1 are drivers for resistance, and promote the agonist conformation of ERα without the bound ligand. Such constitutive, estrogen-independent activity is driven by specific mutations promote cell proliferation and tumor progression without hormone stimulation. The issue of resistance has bolstered in discovering new therapeutic options which have been successful, however still raises concerns for efficacy, the progressive research may solve this setback in the future ahead. The present investigation is sought to identify a high affinity molecule targeting against *ESR1* for the treatment of Breast Cancer through Molecular Docking studies Molecular Docking studies was performed with 15 established inhibitors of ESR1 using Molegro Virtual Docker. Compound anastrozole was found to be the high affinity inhibitor which efficiently binds to ESR1. In the present investigation , Pharmacophore mappings are also discussed testifying the better interactions of anasrozole and Esr1 . The compound identified in the study can be subjected further for tested for *in vitro* and *in vivo* correlates for determining ADMET properties.

Keywords: ESR1, ESR1 inhibitors, Molecular Docking, Breast Cancer