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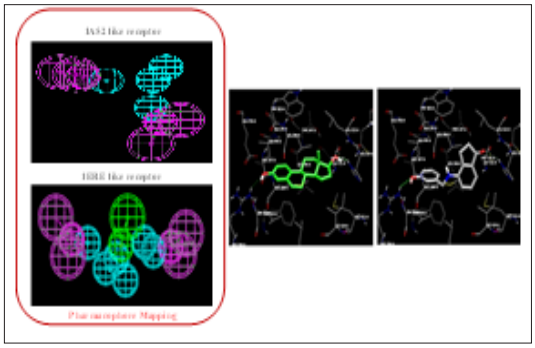
Structure based drug design of novel analogues targeting estrogen receptor-α



Human breast carcinoma is the second leading cause for death in women worldwide. According to the American Cancer Society, 231,840 new cases of breast cancer were diagnosed among women, with morbidity rate expectations up to 40,290 women in 2015. In Egypt, The National Cancer Program (NCP) reported that breast cancer patients represent 15.40% among other types of cancer cases with expectations of 3-fold increase by 2050. Estrogen receptor-α positive (ERα +) subtype is the principle subtype for breast cancer cases (60-80%) of breast cancer cases. Estrogen receptor has been investigated as potential molecular target targeting ER-α dependent breast cancer. Previous reports have investigated that inhibiting estradiol from binding to the ligand binding domain (LBD) of estrogen receptor (ER)-α can be a plausible approach to inhibit cell growth and induce apoptosis. Different chemotherapeutic agents were developed targeting ER, however, the main complication is the emerging resistance developed by malignant tumors. Therefore, generation of novel scaffolds targeting ER and breast cancer creates important necessity. Our initial efforts started with generating pharmacophore models; identifying the common structural features among ligands bound to the ligand binding domain of ER. A virtual library comprising 200 compounds was screened along with ER-α (PDB ID: 1 ERE and 1A52) to filter the synthesized analogs into 12 analogs. The whole synthetic route was executed via assembly of substituted protected amino-(indanone, indazolyl and indole) based derivatives via amide coupling along with 3-hydroxybenzoic acid. This was validated by in comprehensive *in vitro* biological evaluation against MCF-7 cell lines, where they show promising inhibitory activity ranging from 2 μM-12 μM. Our efforts were further extended to elucidate the inhibitory mechanistic pathway via monitoring ER expression levels as well as screening of the apoptotic parameters.

Recent Publications

1. Ahmed M S, El-Senduny F, Taylor J and Halaweish F T (2017) Biological screening of cucurbitacin inspired estrone analogs targeting mitogen-activated protein kinase (MAPK) pathway. *Chemical Biology and Drug Design;* 90(3): 478-484.
2. Hajer M Arjaibi, Mahmoud S Ahmed, Fathi T Halaweish (2017) Mechanistic investigation of hepato-protective potential for cucurbitacins. *Medicinal Chemistry Research*; 26(7): 1567-1573.

Biography

Mahmoud Salama Ahmed is a professional Medicinal Chemist with academic and research experience with over 10 years of experience in lead optimization, molecular modeling drug design, process chemistry, method development, chemistry of natural products, heterocyclic chemistry, structural elucidation, bioassay guided fractionation and *in vitro* biological screening. He has also been Visiting Scientist at South Dakota State University and University of Texas Southwestern Medical Center.

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