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Review Article

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SYNTHETIC HETEROCYCLIC CANDIDATES AS PROMISING ESTROGEN RECEPTOR ALPHA INHIBITORS; AN OVERVIEW

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ABSTRACT

There has been a lot of curiosity in estradiol's mode of action and potential therapeutic benefit ever since it was discovered and its chemical structure was elucidated. It is now widely accepted that estrogens serve a variety of purposes in numerous cell types. Controlling reproductive function, bone metabolism, cardiovascular diseases, as well as the prevention of mood swings, Alzheimer's disease, cancer, and hot flushes are all possible therapeutic uses for estrogens. For over a decade, it was thought that estrogens signal through a single estrogen receptor, now known as Estrogen receptor alpha (ER-α), which belongs to a family of ligand-activated transcription factors. Yet more recently, a second estrogen receptor called ER-β was discovered. In the present review we have covered the role of estrogen receptor α antagonists as anticancer agents.

KEYWORDS: Estrogen receptor alpha, Anticancer, Indole, Pyrimidine.

INTRODUCTION

Estrogen receptor (ER) is a nuclear receptor with known physiological functions such as controlling normal growth, development of reproductive organs, protecting the cardiovascular system and bone homeostasis.[1] The DNA binding domain (DBD) and ligand-binding domain (LBD), which are connected by a hinge region, as well as the N and C terminal domains make up the structural organisation of the ER.[2] ER is expressed in two isoforms, ER-α and ER-β, with up to 95% and 55% homology at the DBD and LBD, respectively. Normally, 17 β -estradiol is acting as agonist for induction favorable conformation for activation function-2 (AF2), coactivator binding surface of the LBD, where helix-12 (H-12) harbors across helix-11 and helix-3 (H-11 and H-3) leading to formation of one side of the AF2 surface, leading to promotion of ER-α gene expression.[3] Estrogen and estradiol are renowned for their promoter roles in cancer proliferation accompanied with increased tumor invasion. In the fight against ER dependent breast cancer, new chemical entities must be developed that prevent the estrone family from binding to ER.

While ER-β is mostly expressed in the prostate gland, bladder, ovary, colon, adipose tissue, and immune system, ER-α is expressed in the breast gland, uterus, ovary, bone, male reproductive organs (testis, prostate), liver, and adipose tissue.[4,5] By preventing the growth of interstitial cells with a male phenotype (which produce sex hormones) and preserving the integrity of female sex differentiation, ER-α is also essential for maintaining the female phenotype of the somatic cells in the ovary.

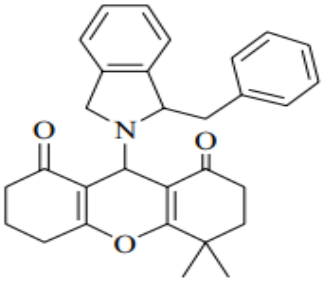
Cancer, which is the uncontrolled, fast, and pathological proliferation of abnormal cells, is a major problem in today's world. Breast cancer is one of the most common cancers, is often diagnosed, and accounts for over 15% of all cancer-related deaths in women.[6] In 2018, the World Health Organization (WHO) reported that 2.1 million women had breast cancer, with 627,000 deaths as a result. In India alone, there were 162,468 new instances of breast cancer in 2018 and 87,090 deaths from the disease. ER-α was discovered to be the prime culprit in 65% of breast cancer cases. In two possible ideas, ER-α is thought to play a role in the development of breast cancer mechanistically.[7]

The initial theory postulated that estrogen binding to the ER caused and promoted mammary cell growth, increasing the target cell density inside the tissue. Because of the increased rate of cell division and DNA synthesis, there was an increased chance of replication mistakes and harmful mutations, which might lead to abnormal cell death, DNA repair, or cellular proliferation.[7, 9] As a result, the second theory proposed that the metabolism of estrogen produced genotoxic by-products, which have the potential to directly damage DNA and cause mutations in it. Single-nucleotide polymorphisms or multiple sequence changes in the ER-α gene have been related to either an increased or decreased risk of breast cancer.[7,8] Moreover, two single-nucleotide polymorphisms in the ER-β gene have been linked to an increased risk of breast cancer in postmenopausal women.[9] This review study may be helpful to the several research teams working hard to

create effective molecular designs to fight against breast cancer.

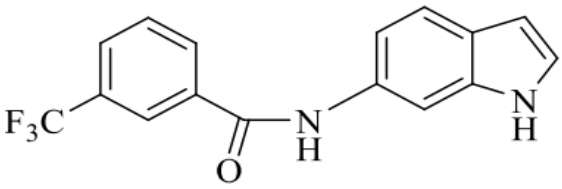
Compounds containing indole nucleus

Singla *et al.*, synthesized hybrids of indole-xanthendione and evaluated their antitumour activity. Compound 1 from the synthesised series was observed to be the most effective against T47D with good ER-α binding affinity, with IC_{50} values of 16.51±0.75 µM and 55±1.97 µM, respectively. Compound 1 interacted with different amino acids by H-bonds and van der Waal forces, and its docked score was recorded as being 12.51 kcal/mol.[10]



1

Hendy *et al.*, designed, synthesized and evaluated two non-steroidal indole-based templates as ER-α receptor antagonists by substituting various sulphonamide or carboxamide derivatives from the steroidal scafold using the ring-opening strategy. Compounds 2 and 3 were found to be effective anti-proliferatives, with Tamoxifen serving as the reference. Compound 2 had an IC_{50} of 30.63 µM against MCF and 28.23 µM against T47D. Compound 3 had an IC_{50} of 30.89 µM against MCF and 32.96 µM against T47D. All compounds were subjected to ER-α competitive binding assay utilising ER-α ELISA Kit to investigate synthetics' capability for competing with estrogen against ER-α.[11]



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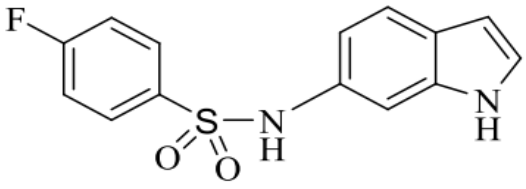
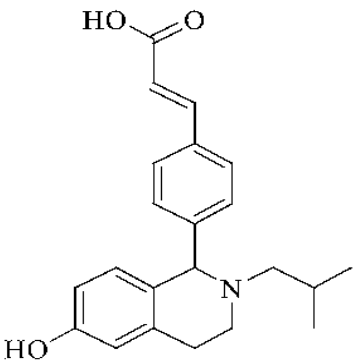


3

Compounds containing isoquinoline nucleus

Scott *et al.*, pre-synthesized tetrahydroisoquinoline (THIQ) derivatives in which compound 4 was the most effective. They hybridised compounds 4 and 5 and replaced the phenol group with a hydrogen bond donor group to create novel tricycle indazole derivatives that act as selective estrogen receptor degrader antagonists. Compound 6 stood out as the most effective of the bunch, with an IC_{50} value of 9.5 µM for ER-α degrader antagonist in vitro and no trapping of microsome-based GSH assay. Afterwards, the MCF-7 xenograft breast model was used to evaluate compound 6 pharmacologically, and the results of the ER-α downregulation assay, tamoxifen competition assay, and ER-α antagonism assay showed that the compound has the required profile of degrader and antagonist.[12]



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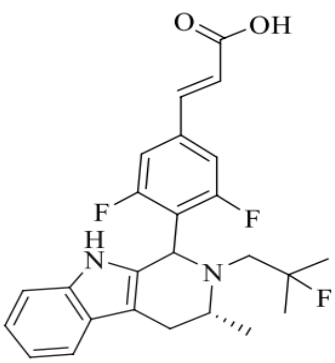

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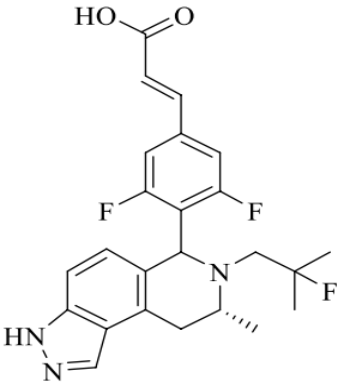
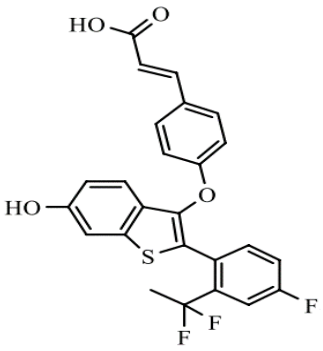


6

Compounds containing benzothiophene nucleus

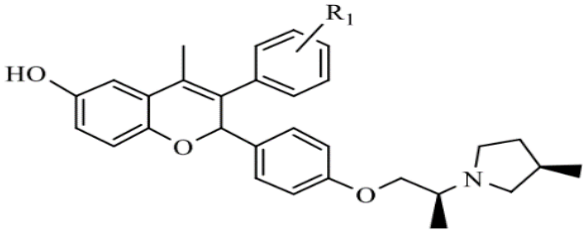
Tria *et al.*, designed and synthesized a series of selective estrogen receptor degraders, by coupling benzothiophene in aroxifene, with carboxylic acid side chain. Compound 7 was observed to be potent ER-α antagonist and degrader with an IC_{50} value of 0.2 nM, after successful evaluation of all prepared compounds by using an estrogen-responsive reporter gene in ER+ MCF-7 breast cancer cells and degradation of ER-α was measured using an in-cell western protocol. Initial research confirmed that compound 7 was well tolerated when taken orally. As a result, this candidate was selected and put to a Phase I/Ib trial for advanced or metastatic ER α+ breast cancer.[13]



7

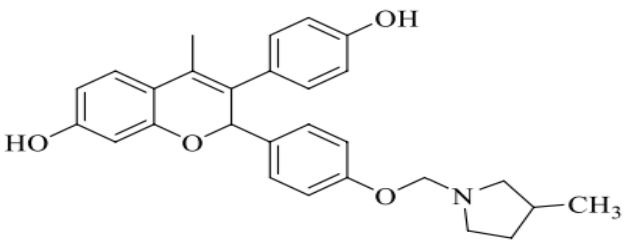
Compounds containing chromene nucleus

Nagasawa *et al.*, synthesized and examined a series of chromene derivatives to determine their ER-α degradation efficiency. When subcutaneous estradiol pellets were used to supply sufficient quantities of estradiol to stimulate tumour growth in a xenograft model of tamoxifen-resistant breast cancer, compound 8 was discovered to be the most effective SERD (selective estrogen receptor degraders). Compound 8 had a 91% ER-α degradation efficiency and showed high activity, but compound 9, which had a greater oral exposure and an ER-α degradation efficiency of 82%, was practically inactive.[14]



Compound	R_1
8	3-OH
9	4-F

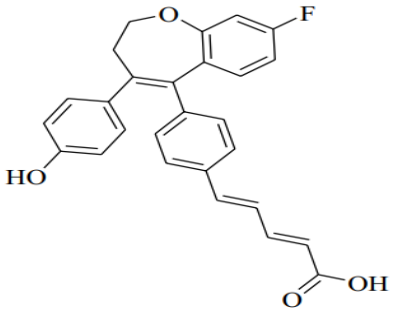
Fanning *et al.*, designed and synthesized unique line of pure anti-estrogen and SERD compounds with benzopyran nucleus and different substitution on pyrrolidine moiety to target ER-α. Using the immunoblotting assay with an ER-α specific antibody on the MCF-7 and CAMA-1 cell lines, all the substances were assessed for their ability to alter ER-α expression, and the results were compared to the SERD benchmark: Following a successful assessment of the compounds, compound 10 was shown to successfully reduce the expression of ER-α by 49% with an IC_{50} value of 7.20.9 nM. These outcomes were also found to be comparable with CAMA-1 cell lines.[15]



10

Compounds containing benzoxepine nucleus

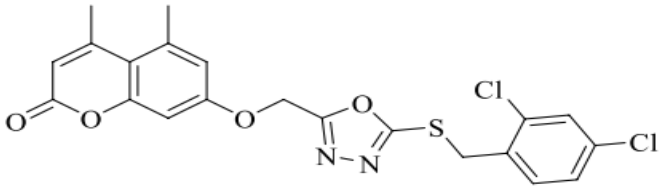
Three series (acrylic acid, acrylamide and saturated carboxylic acid) of ER-ligands based on benzoxepine moiety were synthesized by O'boyle *et al.*, with an aim to specifically target ER-α. Among them, it was discovered that compound from series 1 containing acrylic acid was more ER-α selective. In MCF-7 breast cancer cells, compound 11 containing phenylpenta-2,4-dienoic acid had antitumor action and decreased ER-α and ER-β expression. The existence of extra H-bonding between the carbonyl group and Leu 536 and Tyr 537 was the cause of the downregulation effect in ER-α.[16]



11

Compounds containing coumarin nucleus

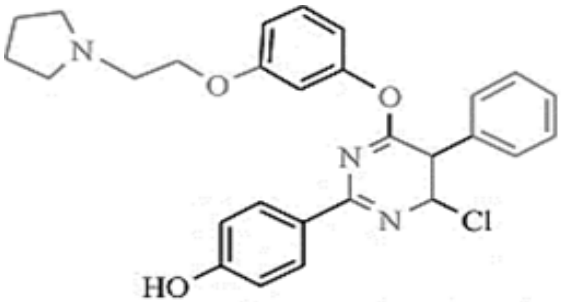
Dhawan *et al.*, designed and synthesized combinations of coumarin-1, 3. 4-oxadiazole (conjugates) and studied their anti-proliferative effects against MDA-MB-231 and MCF-7 breast cancer cell lines. Compound 12 of the synthetic compounds were discovered to have an IC_{50} value that made them the most powerful.[17]



12

Compounds containing pyrimidine nucleus

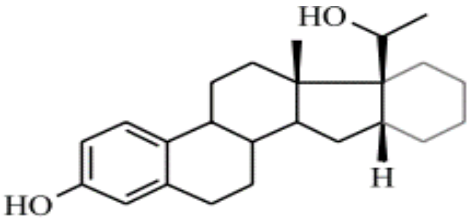
Luo *et. al.*, designed and synthesized 2,4-disubstituted pyrimidine analogues with a basic side chain to act as dual ER-α/ VEGFR-2 ligands. Initially, ER-α binding affinities of synthetic compounds were assessed using an ER-α competitor assay kit. In addition, the MTT assay was used to assess the anti-proliferative ability of the MCF-7 cell line using tamoxifen as a reference. Compound 13 from the series demonstrated the highest binding affinity, with a binding affinity value of 1.64 µM and also showed greatest cell growth inhibition against MCF-7 cells with IC_{50} of 0.81 µM.[18]



13

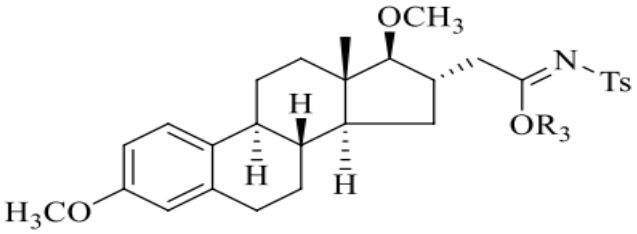
Compounds containing steroidal pharmacophore

Kuznetsov *et. al.*, synthesized 3,20-dihydroxy-19-norpregna1,3,5(10)-trienes containing an additional carbocyclic ring D′ as estrogen receptor antagonists. Compound 14 from the series demonstrated the highest ER-α antagonist potency, demonstrating 70% inhibition.[19]



14

Volkova *et. al.*, synthesized androstene and estrane series (in total twenty-five) steroidal based N-sulphonylimidate's derivatives as anti-proliferative agents derived from 17α-ethynyl steroids. These compounds were tested against MCF-7 breast cancer cell line by MTT assay using cisplatin as a standard. The most effective compound 25 was found to have an IC_{50} value of 4.3 µM. Using 17-estradiol as the reference medication (activity-100%), the ER-α mediated transcription activity of all derivatives was further tested by assessing luciferase activity. Hit compound 15 was used as a lead to investigate its other biological characteristics. Compound 15 showed anti-proliferative efficacy against triple-negative breast cancer cells when tested against the MDA-MB-231 breast cancer cell line.[20]



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CONCLUSION

In conclusion, estrogen, an agonist to ER-α, is essential for initiating and regulating various signalling pathways that are responsible for cell diferentiation and development of breast tissue or cells. Any change in these signalling pathways may result in unregulated cell growth, which could ultimately result in the creation of a tumour or breast cancer. Since ER-α is mostly expressed in breast tissue, researchers are curious about developing SERD or SERM to block this receptor and regulate mammary cell differentiation. The biochemistry of this enzyme disclosed numerous details about the active binding site and creating methods for producing substances that bind and inhibit the ligand-binding domain in a competitive manner. Also, a summary of recently published and peer-reviewed studies showed a variety of factors significant for the development of innovative SERD and SERM. A hypothesis that gives information regarding the choice and location of pharmacophores or substituents so that the compounds are highly specific towards ER-α was developed and described based on the articles.

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