

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Review Paper

A Walk around Clinically used Selective Estrogen Receptor Modulators (SERMs) in Breast Cancer Management

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Received 9 January 2013; Accepted 20 February 2013

Keywords: Estrogen Receptor, Selective Estrogen Receptor Modulators (SERMs), Tamoxifen, Raloxifene, Breast Cancer.

Abstract: Despite of many beneficial effects of estrogen in women health, estrogen has been identified to play a significant role in the development of breast cancer. The estrogenic response is mediated by estrogen receptors (ER), either by ER- α or ER- β . Selective Estrogen Receptor Modulators (SERMs) acts on estrogen receptors as either agonist or antagonist depending on the tissue involved and their tissue distribution. SERMs are clinically used for the treatment of all stages of ER-positive breast cancer. Various studies have shown the molecular mechanism for selective action of SERMs and concluded that different ER ligands induce different conformational changes in the estrogen receptors leading to change in its ability to interact with co-regulatory proteins (co-activators and co-repressors). This review summarizes the therapeutic action of the clinically used SERMs, particularly in the management of breast cancer along with their pharmacokinetics and side effects.

Introduction

Cancer is a clinical state of uncontrolled growth of the cells and the cells divide too quickly.[1] Cancer is of many types such as lung, colon, breast, skin, bones, or nerve cancer depending on the tissue involved in uncontrolled growth.[2] The most commonly death causing cancer is lung

cancer [3], while the breast cancer is the second most prevailing cancer, mainly in women. In India 226,870 women were diagnosed with cancer and 39,510 women were died because of breast cancer in 2012.[4]

Tumor start as microscopic clumps of cell mass, but later on it grows, often as lump, large enough to be felt. Breast cancer starts in breast tissue as one or more accumulations of abnormal cells and is

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known as solid tumor. As the disease develops, these cells can spread from the original tumor (through the blood or lymph systems) to other parts of the body [5], where they may damage other organs and may form new tumors. Several factors raise breast cancer risk such as older age (especially above the age of 60); breast cancer history and genetic changes in BRCA1 and BRCA2 genes.[6,7] Other factors include the child birth at older age, first menstruation before the age of twelve years or menopause after the age of fifty five and infertility. Obesity after menopause or physical inactivity is also considered as major risk factors.[8]

Types of breast cancer:

There are various types of breast cancer such as Ductal Carcinoma In Situ (DCIS) which is a non-invasive breast cancer and Invasive Ductal Carcinoma (IDC).[9] In DCIS, the abnormal cells have been contained in the lining of the breast milk duct. In IDC abnormal cells originated in the lining of the breast milk duct but invades to the surrounding tissues.[10] Inflammatory breast cancer is a less common type that may not develop into a tumor and frequently affects the skin. In Metastatic breast cancer, the cancer cells spread away from the breast tissue sometimes into the lung, bones, or brain. The other less common types of breast cancer include Medullary Carcinoma, Tubular Carcinoma, and Mucinous Carcinoma.[11]

Symptoms of breast cancer:

Breast cancer symptoms includes swelling of all or parts of the breast, skin irritation or pitting, breast pain, pain in nipples, redness, scaliness, change in shape and size of the breast [12] or thickening of the nipple or breast skin. In addition, an unusual nipple

discharge and lumps in the underarm area are some of the noticeable symptoms.

Estrogen Non-Responsive and Responsive Cancer:

Breast cancer may be widely divided into two types depending on their sensitivity to estrogen hormone: 1) Estrogen Non-Responsive cancer, also known as triple-negative breast cancer: about 15% of the total breast cancer are of this type and 2) Estrogen Responsive breast cancer.[10] Triple-negative breast cancer is characterized by tumors that do not propagate through the estrogen receptor (ER), progesterone receptor (PR), or HER-2 genes. This type of cancer represents an important clinical challenge because these cancers do not respond to endocrine therapy. The metastatic potential in triple-negative breast cancer is similar to that of other breast cancer subtypes, but these tumors are associated with a shorter median time to relapse and death.[13] Current treatment strategies for triple-negative cancer include chemotherapy with anthracyclines, taxanes, ixabepilone, platinum agents, and biologic agents. More recently, EGFR inhibition has been proposed as a therapeutic mechanism in triple-negative breast cancer. Agents that target poly ADP-ribose polymerase and androgen receptors have also been proposed useful. Ongoing clinical trials on these agents should result in definite guidance with respect to the value of these agents in triple-negative cancer.[14]

Hormone responsive breast cancer is sensitive to the female hormone estrogen. The sensitive cancer cells need estrogen to stay alive and propagate. Estrogen hormone is essential for normal growth and development of the breast and other tissues important for reproduction. It also helps in regulation of normal menstrual cycles and to

maintain healthy bones and heart. Distribution of estrogen receptors in various tissues and organs are illustrated in Table-1. Studies have shown that patient with breast cancer have higher level of circulating estrogen in the blood than the normal one.[16] Another recent study showed that a higher level of estrogen after treatment leads to relapse cancer very soon.[17] These evidences, suggests that life-long exposure to estrogen, and other ovary hormones, plays an important role in determining breast cancer risk. This also supports the theory that the number of menstrual cycles a woman have, longer the exposure to estrogen during lifetime and long exposure time increases the risk for breast cancer.[18]

Normal Physiological Role of Estrogen:

Estrogen acts as a messenger in each menstrual cycle. Estrogen together with other ovarian hormones stimulates the cells in the breast and uterus to divide. Estrogen is recognized by the cells through estrogen receptors.[19] Estrogen binds to estrogen receptor to form a complex that enters the nucleus of the cell. The estrogen-receptor complex binds to specific regulatory sites on the cell DNA, and starts a series of events that turns on the estrogen-responsive genes. These specialized genes instruct the cell to synthesize new proteins that signal the cell to carry out important activities. Some of these signaling proteins direct the cell to divide.[20]

Estrogen and breast cancer:

Since estrogen stimulates cell division, it can increase the chances of DNA copying error in a dividing breast cell. Estrogen can also make a spontaneous or chemically-induced mutation as permanent. About 85% of all breast tumors depend on the estrogen for growth. Anti-estrogenic drugs can block the

binding of estrogen to its receptors, and thereby preventing its signal to the breast tumor cells to divide and multiply.[21]

Estrogen Receptors:

Estrogen receptors are hormone responsive receptors.[22] ER have specific site for estrogen binding. Both types of ER are structurally as well as functionally different from each other, i.e. structurally they are different in ligand-binding pockets, and functionally they are different in transcription. (Figure-1) Estrogen activates the transcription through ER- α and inhibits transcription through ER- β . (ligand-bound ER- α was found to activate transcription, while ligand-bound ER- β inhibited transcription from the AP1 site). The agonists of ER- α includes estradiol **1**, diethylstilbestrol **2**, [23] and the agonist of ER- β is genistein **3** as shown in Figure-2. The crystal structure of ER (ER- α and ER- β) with their ligands is shown in Figure-1.

Management of estrogen responsive breast cancer:

In general, there are many strategies for the management of breast cancer such as surgery, radiotherapy and chemotherapy. Radiation therapy is highly targeted and effective way to destroy cancer cells. Radiation can reduce the risk of breast cancer relapse by about 70%. Radiation therapy is relatively easy to tolerate with limited side effects. Chemotherapy includes the use of cytotoxic agents to effectively destroy the cancer cells mainly by inhibiting the cell division. [26] Hormonal therapy includes, overall lowering of estrogen level in the body or blocking the action of estrogen on their receptors. The hormonal therapy mainly includes three category of drugs; 1) Aromatase Inhibitors, 2) Selective Estrogen Receptor Modulators (SERMs),

and 3) Estrogen Receptor Down regulators (ERDs). Biological therapy empowers the immunity of the patient to fight against the cancer cells or to reduce the side effects of other treatments. The first three biological agents to receive FDA approval for the treatment of breast cancer are herceptin, avastin and tykerb.[27]

Selective Estrogen Receptor Modulators (SERMs)

SERMs modulate the effect of estrogen by blocking the estrogen receptors and arrest its activity.[28] There are specific agents available for the breast cancer management. These SERMs mainly include tamoxifen **4**, raloxifene **5**, toremifene **6**, idoxifene **7**, arzoxifene **8** and acolbifene **9** as shown in Figure-3.

Mechanism of action SERMs:

SERMs bind with estrogen receptors (ER- α or ER- β) to form a complex and this complex activates the co-activator or co-repressor, the formed complex can be homo- or hetero-dimerize and alter the gene expression by two pathways:

- 1) Non-traditional pathway: through Activated Protein-1 (AP-1) and is activated by protein/protein interactions by means of binding with fos/jun.
- 2) Traditional pathway: through ER-DNA complex via an estrogen-response element. (Figure-4)

The pathway of SERM-receptor interaction results in biochemical or physiological responses. In breast cancer cells, tamoxifen binding antagonizes estrogen binding and the subsequent conformational changes which were necessary for co-activators. It may also prompt the recruitment of co-repressor. Genetic variations can cause

variation in the response of the organism to the drug.

Clinically used SERMs:

1) Tamoxifen and its analogues:

Tamoxifen **4** has triphenylethylene as a core structure and is a selective estrogen receptor modulator (SERM).[29] It is a drug of choice for women diagnosed with hormone-responsive breast tumour (both estrogen and progesterone positive).[13] Initially, it has been used as an anti-neoplastic agent in 1971.[30]

Tamoxifen **4** has been primarily recognized in the early 1960s in a programme planned to develop new contraceptives.[31] During 1970s, the clinical evaluation of tamoxifen for breast cancer treatment has been accepted by the clinical community, because it simply produced responses similar to the other endocrine approaches and with fewer side effects.[32-34]

Tamoxifen **4** is an antagonist of the estrogen receptor in breast tissue via its active metabolite i.e., hydroxyl tamoxifen. In other tissues (except breast tissue) for example the endometrium, it acts as an agonist, and thus may be considered as a mixed agonist and antagonist.[35] Tamoxifen has protective effects against heart diseases and osteoporosis because of its ability to decrease LDL cholesterol and increase bone mineralization.

Pharmacokinetics of Tamoxifen:

Tamoxifen is effective on oral administration and is largely metabolized by the liver. Some metabolites possess antagonistic activity while others have agonistic activity. Unchanged drug and its metabolites are excreted predominantly through the bile into feces. Tamoxifen is

administered as a single oral dose of 20 mg and is rapidly absorbed, reaching its peak plasma concentration in about 5 h. The elimination half-life is about 5-7 days. Steady state concentration in plasma reaches after about four weeks of tamoxifen therapy. Tamoxifen is extensively metabolized after oral administration; about 65% of the administered dose is excreted mainly as polar conjugates, which account for about 70% of the elimination products.[36] Tamoxifen is metabolized to either *N*-desmethyltamoxifen or 4-hydroxytamoxifen. *N*-desmethyltamoxifen is then converted to endoxifen by the action of enzyme CYP2D6, as shown in Figure-5.

Adverse effects:

The most common side effect of using tamoxifen **4** involves hot flashes, nausea, vomiting, skin rashes, vaginal bleeding and discharge.[37] Tamoxifen can also lead to increase in pain if the tumor has metabolized to bone. Tamoxifen has the potential to cause endometrial cancer.[38] Studies have indicated that the binding affinity of tamoxifen to the receptor is less than that of the binding affinity of estradiol.

Tamoxifen Analogues:

Large numbers of new analogues of tamoxifen were synthesized with the aim to develop new anti-estrogenic antitumor drugs. The biological properties of the new analogues are screened by 1) estrogen receptor (ER) binding assays, 2) toxic effect on MCF-7 cells, 3) uterotrophic effect, 4) inhibition of estradiol induced uterotrophic effect and 5) antitumor effect.

Among tamoxifen analogues, toremifene **6** exhibited competitive inhibition of estradiol binding to ER, inhibition of MCF-7 cell growth in a concentration-dependent manner

and cytotoxic effect at higher concentration. Minimal estrogenic dose of toremifene on rat uterus was about 40 times higher than that of tamoxifen.

Toremifene **6** has significant effect against dimethyl benzanthracene (DMBA)-induced rat mammary cancer. Toremifene **6** inhibits the growth of ER-negative, glucocorticoid sensitive, mouse uterine sarcoma in a dose-dependent manner. Pharmacokinetics and metabolism of toremifene resembles closely with tamoxifen, but since the chlorine atom of the toremifene is not metabolically cleaved, tamoxifen and toremifene did not have chemically similar metabolites. Toremifene is well tolerated in animal with minimum toxicity.[39]

Another analogue idoxifene **7** (Figure-3) is a novel SERM that has been evaluated for treatment of advanced breast cancer. [40] Idoxifene is 4-iodo-substituted analogue of tamoxifen, synthesized by using rational drug design to decrease the estrogen agonist activity and increase the estrogen antagonist activity of the parent compound. [41] Compared with tamoxifen, idoxifene has been found to be metabolically more stable and have a higher relative binding affinity for the ER. It has reduced agonistic activity on breast and uterine cells, greater *in vitro* activity than tamoxifen, and high anti-proliferative effect on tamoxifen-resistant breast cancer cells.[41]

The effects of another new antiestrogen derivative, droloxifene **11**, on human breast cancer cells *in vitro* and *in vivo* were studied. These results suggest that droloxifene has significant antitumor effects on ER-positive breast cancer, being less estrogenic and more antiestrogenic than tamoxifen.[42] Other derivatives such as nafoxidine **12**, clomifene **13** and trioxifene

14 are also evaluated for their antiestrogenic activity. (Figure-6)

2. Raloxifene and its analogues:

Raloxifene **5** is an oral selective estrogen receptor modulator that has estrogenic actions on bone and anti-estrogenic actions on the uterus and breast tissue. It is used in the prevention of osteoporosis in postmenopausal women. In 2006, the National Cancer Institute declared raloxifene as effective as tamoxifen in reducing the incidence of breast cancer in postmenopausal women. Raloxifene has lower incidence of causing uterine cancer than tamoxifen.[43]

In 2007, the U.S. Food and Drug Administration has approved raloxifene for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis. [44] Raloxifene has quick absorption, widespread first pass metabolism and enterohepatic cycling. About 60% of an oral dose is metabolized to a sequence of glucuronide compounds, all of which are highly protein bound (>95%) as shown in Figure-7.

Raloxifene is metabolized via UDP-glucuronosyl-transferases (UGTs) to give glucuronides (**15** and **16**); UGTs are membrane-bound proteins originated from the endoplasmic reticulum. Raloxifene glucuronides are expelled into the intestine via bile, reversibly transformed to raloxifene via intestinal β -glucuronidase, and reabsorbed or excreted in feces. Raloxifene plasma concentration time profiles show multiple peaks, consistent with significant enterohepatic recycling. Raloxifene and its metabolites have maximum plasma concentrations of about 6 h after oral administration with elimination half-life of 27.7 h. The greater part of raloxifene and its

glucuronide metabolites are excreted within 5 days through feces, whereas less than 6% is excreted in the urine.[45-49]

Adverse effects

Like estrogen and tamoxifen, raloxifene has also an increased risk of deep vein thrombosis. However, the benefits of raloxifene are believed to generally outweigh the risks. Raloxifene should be avoided in women with pregnancy and patient with past or active history of venous thromboembolic events. Cholestyramine can reduce the absorption of raloxifene by 60%. Raloxifene can cause a 10% drop in prothrombin time in patients taking warfarin.[44]

Raloxifene analogues:

Arzoxifene **8** is an analogue of raloxifene which acts as a potent estrogen antagonist in breast and uterine tissue while estrogen agonist on bones to maintain bone density and lower level of serum cholesterol. Arzoxifene is a highly effective agent for prevention of mammary cancer induced in the rat by the carcinogen nitroso-methylurea and is more potent than raloxifene. Arzoxifene is devoid of uterotrophic effects of tamoxifen. In contrast to tamoxifen, it is unlikely that the clinical use of arzoxifene will increase the risk of developing endometrial carcinoma.[50]

Another analogue of raloxifene, acolbifene **9** is used to inhibit the stimulatory effect of estrogens on the proliferation of human breast and uterine cancer cells. It practically causes disappearance of the estrogen receptor in the mammary gland and uterus. It acts by blocking access of estrogens by the estrogen receptors and preventing activation of the estrogen receptors by growth factor-stimulated kinases in the absence of estrogens.[51]

Conclusion:

The SERMs are unique class of drugs that bind to Estrogen Receptors and are distinguished from estrogen by their capacity to act as an antagonist or agonist in various tissues. The benefits of tamoxifen to lower the risk of relapse of breast cancer after surgery have already been established. Raloxifene is the only SERM approved for the prevention and treatment of postmenopausal osteoporosis, with the efficacy to prevent bone loss and fractures, and with the added benefit of preventing breast cancer. Clinical data of newer SERMs (in development) indicates that these compounds have a beneficial feature to represent an improvement relative to currently available SERMs. Other SERMs

are undergoing investigation for possible benefits for the prevention of breast cancer. Increase incidences of hot flushes are the common adverse effect associated with SERMs and this amplify eagerness for further study to determine the clinical relevance. It is clear that SERMS are efficient in their efficacy and safety profiles. The future of SERMs remains rich with possibilities, but their widespread application has been hampered by the fact that they affect many different tissues.

Acknowledgement:

Authors are thankful to Mr. Praveen Garg, Chairman, ISF College of Pharmacy, Moga, Punjab, for his continuous support and encouragement.

Table-1 Distribution of Estrogen Receptors in various tissues/organs [15]

| Estrogen Receptor (ER- α and ER- β) | Tissue Distribution |
|---------------------------------------------------|------------------------------------------------------------------------------|
| ER- α High | Epididymis, testis, ovary, pituitary gland, uterus, kidney and adrenal gland |
| ER- α Intermediate | Prostate gland, bladder, thymus, heart and liver |
| ER- β High | Prostate gland and ovary |
| ER- β Intermediate | Uterus, bladder, lungs and testis |

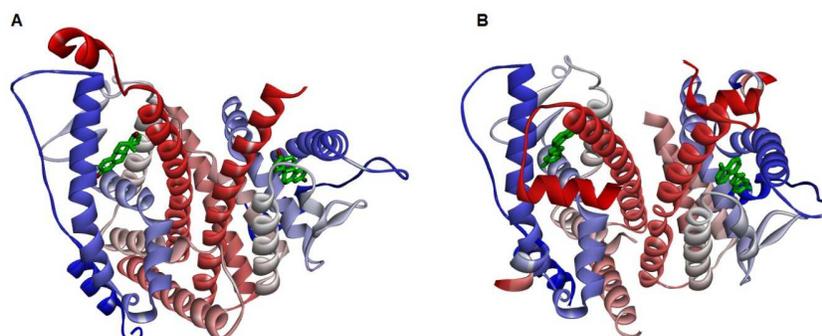


Figure: 1. Crystal structure of Estrogen receptors. A) Crystal structure of ER- α with estradiol and B) Crystal structure of ER- β with raloxifene [24, 25]

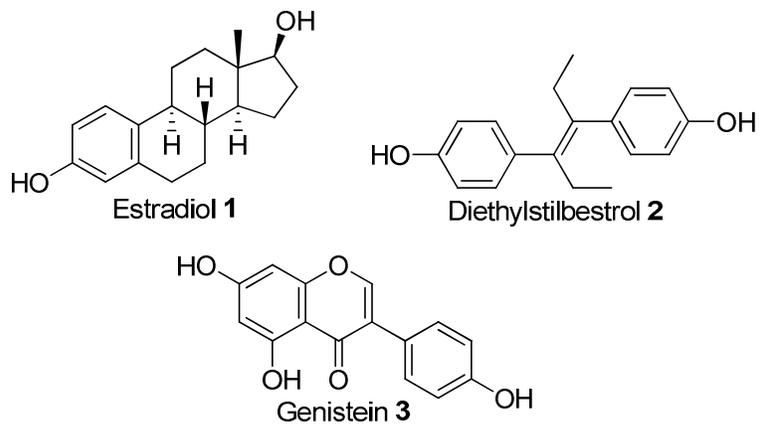
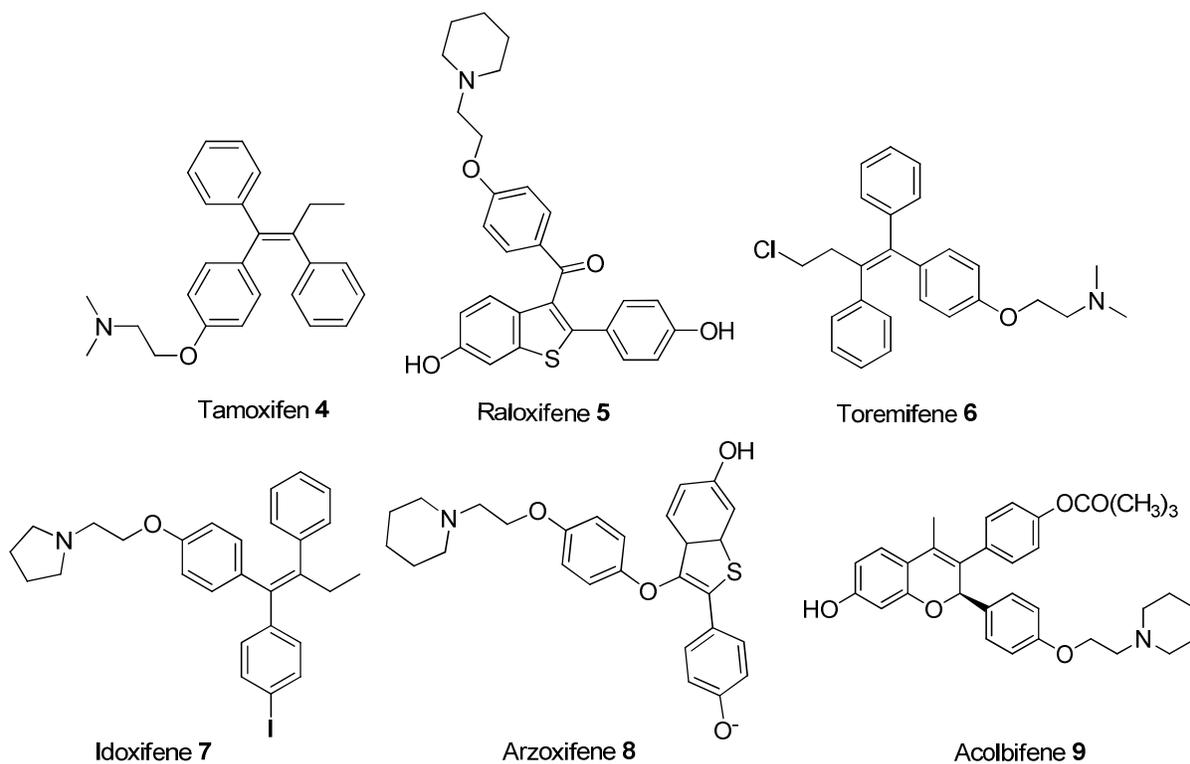
Figure-2 Agonist for ER- α and ER- β 

Figure:3- Clinically used SERMs

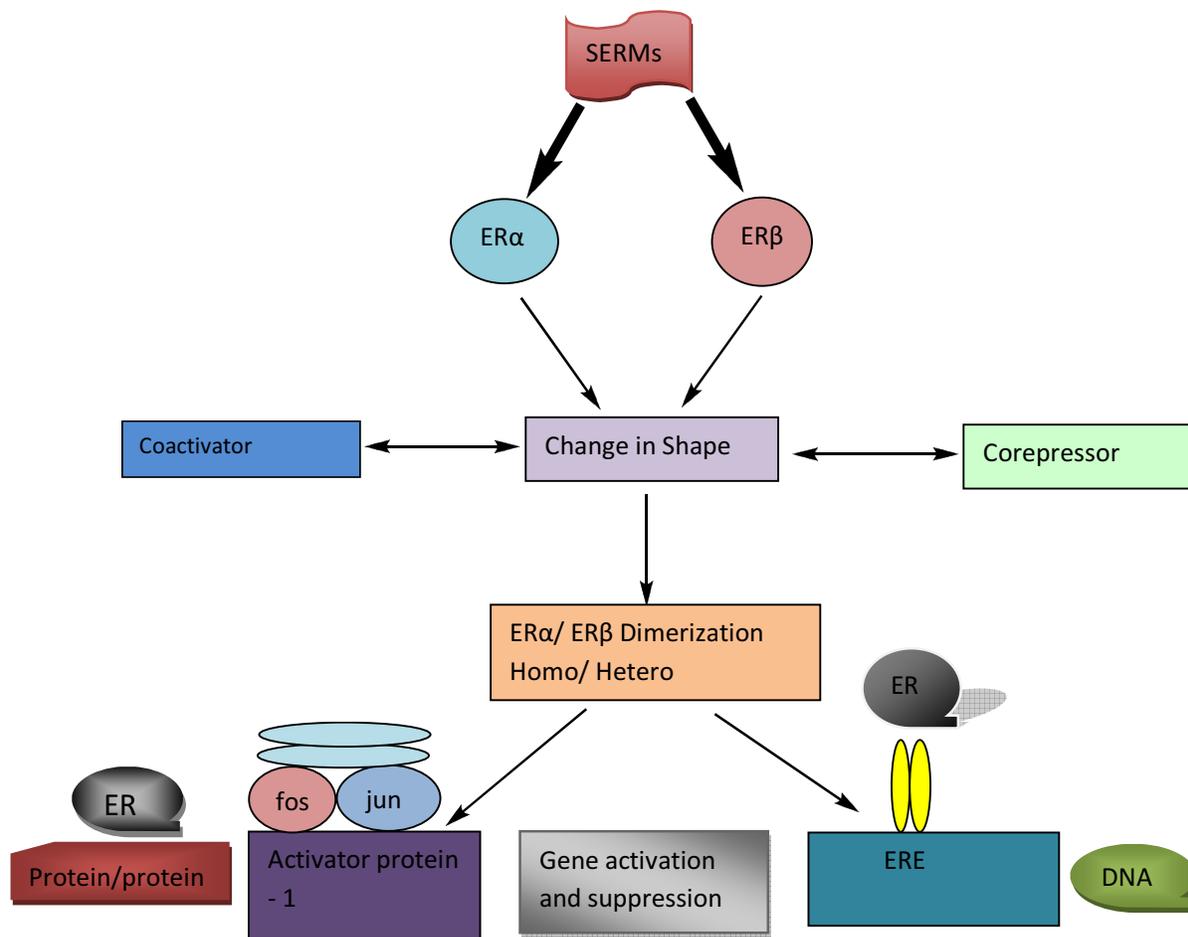


Figure-4 Molecular mechanism of SERMs, ER: estrogen receptor; ERE: estrogen responsive element.

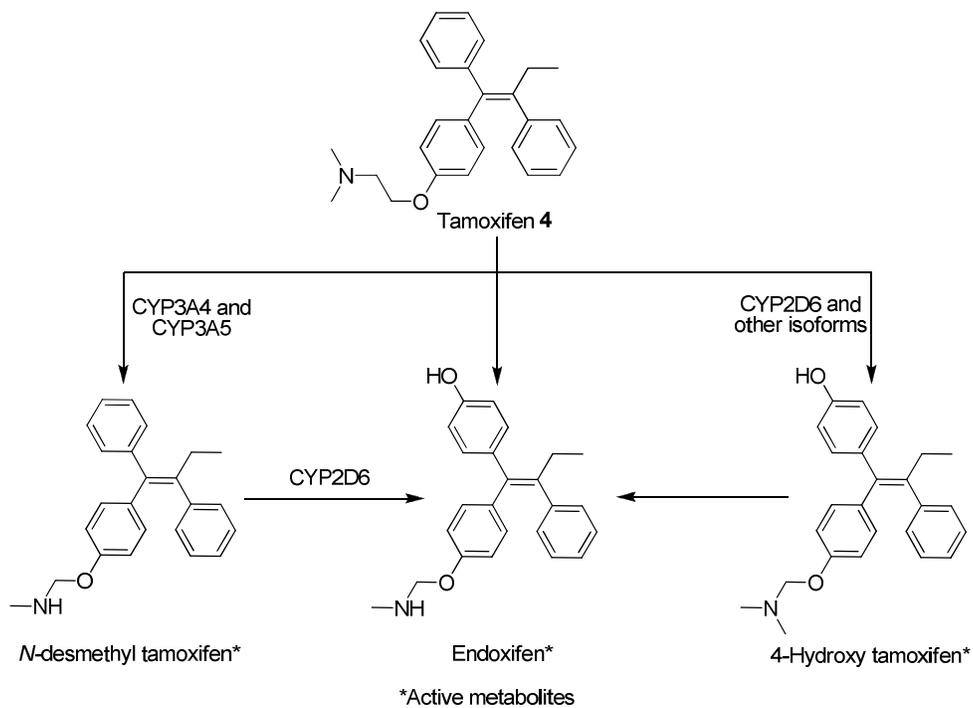


Figure-5. Metabolism of Tamoxifen; CYP2D6: Cytochrome P450 2D6 enzyme; CYP3A4: Cytochrome P450 3A4 enzyme; CYP3A5: Cytochrome P450, family 3, subfamily A, polypeptide 5.

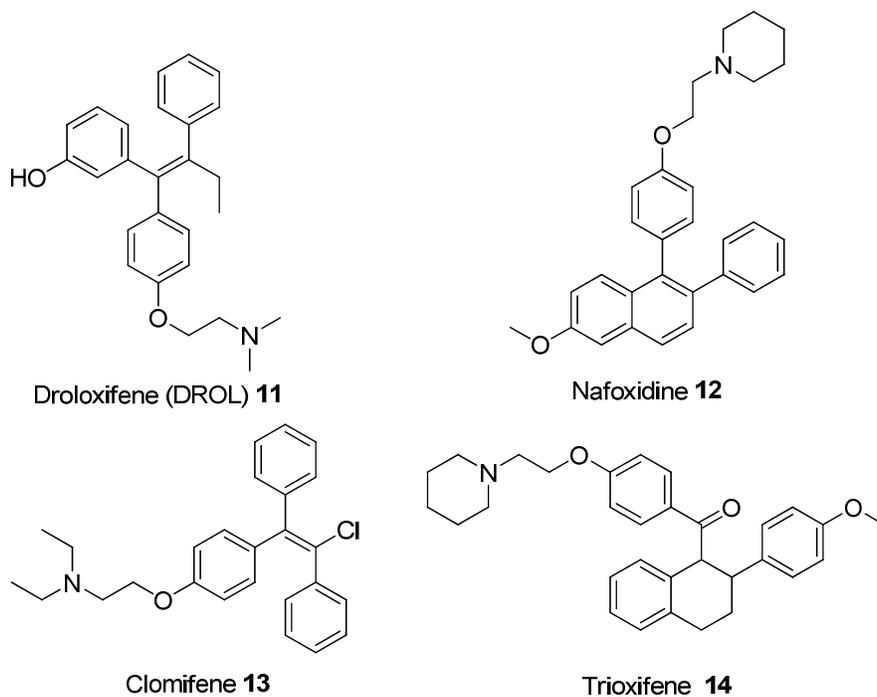


Figure-6 Derivatives of tamoxifen

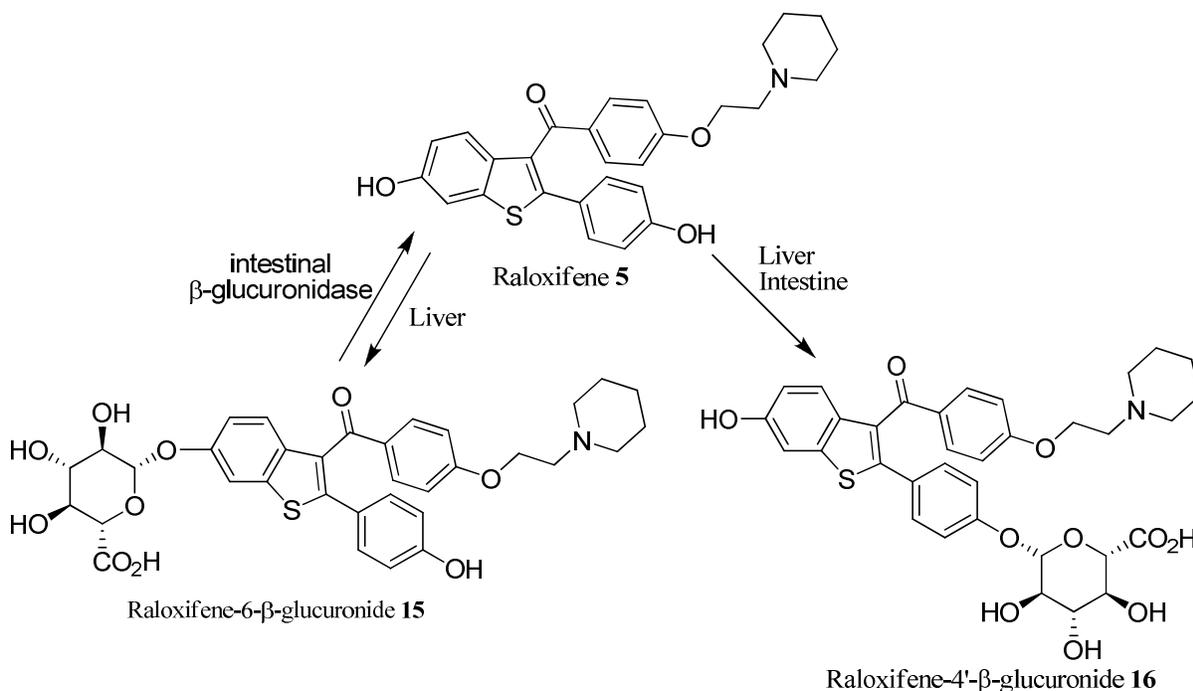


Figure-7 Raloxifene glucuronidation

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