ISSN: 0975-8232

IJPSR (2010), Vol. 1, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received 15 March, 2010; received in revised form 10 April, 2010; accepted 21 May, 2010

AROMATASE INHIBITORS: A NEW HOPE FOR BREAST CANCER PATIENTS

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Keywords:

Breast Cancer,
Endocrine Therapy,
Tamoxifen,
Aromatase Inhibitors

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ABSTRACT

Breast Cancer is the leading cause of mortality among the women of age 30 to 60. Endocrine therapy used for the treatment has shown promising results in which the anti-estrogen tamoxifen has been the standard first-line treatment used for more than 30 years. But its side effects like resistance, increase risk of thromboembolism, endometrial cancer and uterine sarcoma limits its use. The development of selective Aromatase Inhibitors has offered an alternative approach for postmenopausal patients failing anti-estrogen therapy alone or other hormonal therapies. These drugs are approved as first-line therapy for the treatment of postmenopausal women with metastatic estrogen-dependent breast cancer. They are proven superior to tamoxifen for disease free survival, especially in receptor positive patients and reducing the incidence of colorectal breast cancer.

INTRODUCTION: ***Estrogens***, female sex hormones are involved in development and maintenance of female sexual organs, reproductive cycle, reproduction, various neuroendocrine functions. Estrogens produce normal physiological effects by binding to specific nuclear proteins, estrogen receptor-α and estrogen receptor-β [1]. Following the binding of estrogen to its receptor, the estrogen-receptor complex forms homodimers and interact with sequence specific estrogen response elements in promoter region of responsive genes in the target cell chromatin and thus initiate the transcription of the relevant gene to produce mRNA which in result in increased protein synthesis in the endoplasmic reticulum. These proteins include enzymes, receptors and secreted factors that result in the steroid hormonal response regulating cell functions, growth and differentiation [2].

These hormones also play a crucial role in certain disease states, particularly in mammary and endometrial carcinomas. Estrogens enhance growth and proliferation of certain target cells, such as breast epithelial cells and estrogen-dependent mammary carcinoma cells. This has becoming one of major cause of death among women between the ages of 30 and 54, with breast and uterine cancers comprising 28% and 10% of all cancers in females per year. An estimated 217, 440 new cases of breast cancer will be diagnosed and 40, 580 women in the United States were projected to die from breast cancer in 2004 [3]. In the United States the risk of breast cancer is about 1 in 230 less than 39 years, 1 in 24 women of 40-59 years and 1in 13 for women 60-79 years.

HOW BREAST CANCER HAPPEN? For the formation of breast cancer, estradiol is responsible. Estradiol acts to stimulate cell proliferation with concomitant increase in the number of cell divisions. As cells divide, errors in DNA replication occurs [4]. As cell replicate more rapidly, the chances for errors increase mathematically and the time available for DNA repair during the cell cycle is reduced. In this way, estradiol causes propagation of cells bearing these mutations and promotes the tumor growth. These "initiating" and "promotional" events explain the ability of estradiol to induce breast and endometrial cancer [5].

Estradiol can be metabolized to 4- OH estradiol and then to 3, 4- estradiol quinone [6]. This highly reactive quinone metabolite of estradiol can bind covalently to adenine and guanine on the DNA helix. Through activation of a glycosidase, these adducts are removed to produce a depurinated segment of DNA. Error prone DNA repair can result in mutations which could provide the mechanism for the initiation of cancer as shown in Fig 1. An imbalance between the formation of reactive estradiol metabolites and their detoxification might result in breast cancer [7]. In vitro studies have also shown that estradiol can cause genetic mutations and transform cells which do not contain an estrogen receptor.

Successful therapy of breast cancer remains a challenge till now. Although the incidence of the disease shows significant geographical differences, it is the leading cause of morbidity and mortality among pre and postmenopausal women [8]. It is known for a long time that estrogen has an important role in the pathology of breast cancer. About 75% of the breast cancers are positive for the estrogen receptor(ER) and estrogen is the main stimulant in the development and growth of these tumors. So, deprivation of estrogenic signalling has been

the main form of hormonal therapy for patients with ER-positive, initially by surgical approaches (ovariectomy in premenopausal women and adrenalectomy or hypophysectomy for the postmenopausal women) but more recently with medicinal therapy [9].

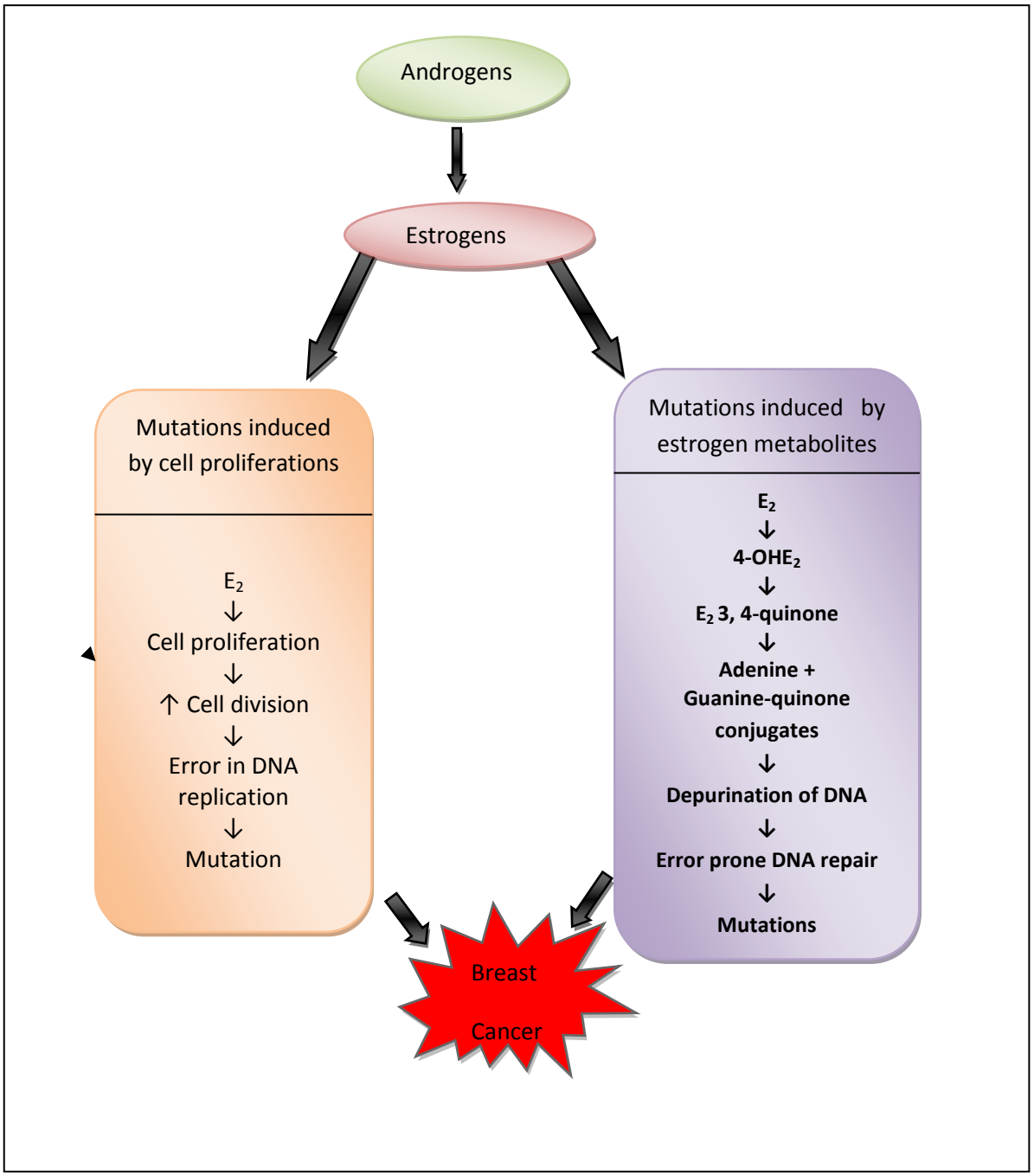


FIG.1. PATHOPHYSIOLOGICAL BACKGROUND OF BREAST CANCER

Endocrine therapy is the oldest, safe and best established systemic treatment for breast cancer, with utility in all stages of treatment. Initially used to treat metastatic disease, it later became a critical component of adjuvant and neo- adjuvant treatment [10]. Endocrine therapy removes the influence of estrogen on breast cancer cells, preventing the cancer cells from growing and spreading. All endocrine treatment is systemic or body-wide therapy, and is effective against cancer cells regardless of where they are located within the body (e.g., the breast, bones, liver, etc.).

Because endocrine therapy usually has fewer side effects than chemotherapy, it is often recommended as the initial treatment for women with ER-positive metastatic breast cancer [11]. Since the development of full therapeutic effect in hormonal therapy is slower than in chemotherapy, the hormonal therapy is used traditionally in patients whose progression of disease is moderate. It is very effective against bone metastases but good results can be achieved in metastases of other localizations. The response rate of the hormonal therapy is 60-75% when the patients are both estrogen and progesterone receptor positive; 40-45% in progesterone receptor positive cases; 25-30% in estrogen receptor positive cases and less than 10% when both estrogen and progesterone receptor are negative [12]. The mechanisms of action of endocrine therapies are threefold:

- Lower the estrogen level in the tumor(oophorectomy, aromatase inhibitors) [13]
- Modulate estrogen receptors, SERMS (tamoxifen) [14]
- Modulate estrogen receptor with pure agonist activity, ER down-regulator (fulvestrant) [15]

In spite of the numerous choices in endocrine therapies, tamoxifen has remained the **"gold standard"** of first-line hormonal therapy in patients who have tumors expressing hormone receptors. Tamoxifen prevents estrogen from binding to the ER, and also interacts with ER and thus decreases cancer growth in patients with established breast cancer. But it increases the risk of thromboembolism by two fold and the risk of endometrial cancer by about 2.5 fold. In addition, not all patients with advanced ER-positive disease respond to tamoxifen and nearly all of those that do respond eventually relapse with resistant disease [14.] The toxicities of tamoxifen have been well documented. These include hot flushes, vaginal discharge, and increased risk of thrombotic events, increased risk of endometrial cancer and uterine sarcoma and probable increased risk of cerebral vascular disease. These toxicities assume even greater importance for the treatment of metastatic disease. Some of these toxicities may be due to estrogenic properties of tamoxifen [16]. Although several benefits are offered by tamoxifen, still there is enough room for the improvement.

Aromatase Inhibitors are the new class of drugs which are used in the treatment of metastatic breast cancer in postmenopausal women. They inhibit the synthesis of estrogen by blocking the activity of aromatase enzyme. In postmenopausal women this enzyme is responsible for estrogen production [17]. Aromatase activity is present in the fat tissues, in muscles, in the breast, and in many cases within the breast carcinoma as well [18]. In premenopausal women the estrogen production is mainly in the ovaries. The aromatase inhibitors could potentially be used to treat a wide spectrum of disease processes. Several disorders in patients require estradiol to produce clinical manifestation and abrogation of the effects of this sex steroid ameliorates

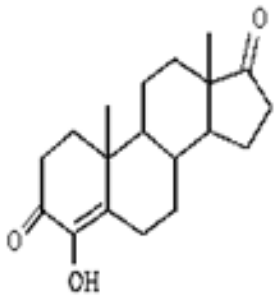
disease-related signs and symptoms. Included in this list are hyperplasia and neoplasia of the breast and endometrium as well as gynecomastia, premature thelarche, precocious and delayed puberty, mastodynia, oligo and anovulation, leiomyomata uteri and endometriosis.

Aromatase Inhitors for Postmenopausal Women: Before menopause, the ovaries produce most of a woman's estrogen, so reducing estrogen from other sources has little or no effect. But in post-menopausal women, most of the body's estrogen is made from another hormone, androgen. Aromatase inhibitors stop the enzyme called aromatase from turning androgen into estrogen, lowering the amount of estrogen produced outside the ovaries[19]. That means less estrogen in the bloodstream, less estrogen reaching estrogen receptors, and less cancer cell growth. Also, two-third of breast tumors demonstrates aromatase activity, making this enzyme a likely source of local estrogen for breast cancer cells.

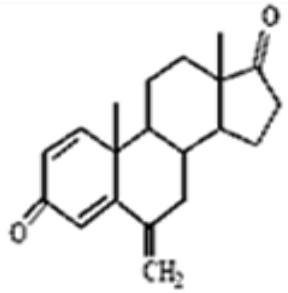
In premenopausal women, AIs cause an increase in gonadotropin secretion because of the reduced negative feedback of estrogen in the pituitary. This in turn leads to ovarian stimulation, an increase in ovarian size, which may result in cysts in premenopausal females [20]. For these reasons, AIs have been used in postmenopausal women and currently not recommended for patients with intact ovarian function. AIs should not be used in patients with chemotherapy-induced amenorrhea, unless it is clear that menstrual function will not return.

Aromatase Inhibitors: Aromatase Inhibitors are of two types differing in their chemical structure and mechanism of action: steroidal type and non-steroidal type inhibitors as shown in Fig 2. The steroidal inhibitors are analogues of androstenedione, a natural substrate of aromatase and act initially as competitive-substrate mimics. These agents become strongly bound to the binding site of the enzyme and then converted to reactive intermediates that bind covalently to the enzyme. As such, they are known as **aromatase inactivators** [21].eg, exemestane, formestane.

Steroidal Aromatase Inhibitors:



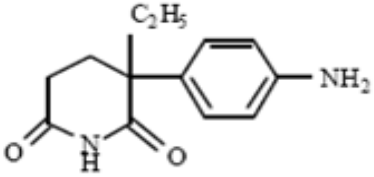
FORMESTANE



EXEMESTANE

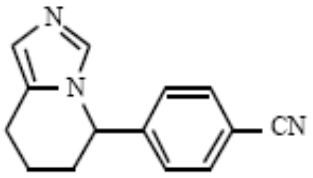
Non- steroidal Aromatase Inhibitors:

First Generation:



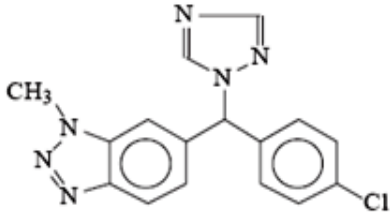
AMINOGLUTETHEMIDE

Second Generation:

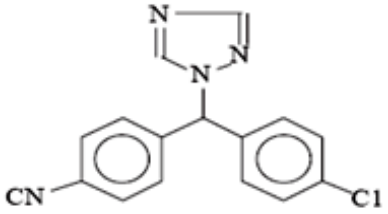


FADROZOLE

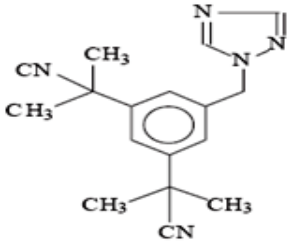
Third Generation:



VOROZOLE



LETROZOLE



ANASTROZOLE

FIG. 2: STRUCTURES OF AROMATASE INHIBITORS

Non-steroidal inhibitors include the prototypical agent aminoglutethimide and second-generation compound fadrozole, but the current used compounds are the triazole derivatives: vorozole, anastrozole, letrozole. All of these compounds act by binding through a basic nitrogen atom to the iron atom in the heme group of the enzyme [22].

AIs are divided in three generations (Table 1) based on the chronology of clinical trials:

a. **First generation:** aminoglutethmide and testalactone. Aminoglutethimide was initially developed as anticonvulsant but was withdrawn from use after reports of adrenal in sufficiency [23]. It was subsequently found to inhibit several cytochromes P_{450} enzymes involved in adrenal steroidogenesis and was then developed for use as "medical adrenalectomy" against breast cancer [24].

b. **Second generation:** fadrozole, formestane. These drugs were considerably more potent but they either had poor pharmacokinetics when given orally or affected other steroidogenic enzymes in addition to aromatase [25].

c. **Third generation:** anastrozole, letrozole, exemestane. These are extremely potent and specific in blocking aromatase at nanomolar concentrations [22].

Apart from these inhibitors there is a class of naturally occurring compounds, flavanoids which also shown activity towards aromatase inhibition, thus lowering the estrogen biosynthesis and circulating estrogen levels [26]. It has been seen that these natural products present in soy and in rye flour, are dietary factor that may be responsible for the lower incidence of breast cancer in certain regions of the world [27]. Generally, flavones and flavanones have higher aromatase inhibitory than isoflavones. Chrysin, 7- hydroxyflavone, the most potent flavones, inhibitor of aromatase [28]. But poor oral bioavailability is major limitation for the success of use of dietary flavanoids as chemopreventive agents.

TABLE 1: CURRENTLY AVAILABLE AROMATASE INHIBITORS

AROMATASE INHIBITORS	CLINICAL APPLICATIONS	COMMON SIDE EFFECTS
FIRST GENERATION:		
Aminoglutethmide: (3- (4- aminophenyl)- 3- ethyl- 2, 6-piperidinedione) **$C_{13}H_{16}N_2O_2$**	Medical adrenalectomy in breast cancer	Drug rash, fever and lethargy.
Testalactone: (13- hydroxy- 3- oxo- 13, 17- secoandrosta- 1, 4- dien- 17- oic acid δ- lactone) **$C_{19}H_{24}O_3$**	It is s used to treat advanced stage breast cancer in women who have been through menopause or whose ovaries no longer function.	Abnormal skin sensations, aches of the legs and arms, general body discomfort, hair loss ,loss of appetite, nausea, redness of the tongue, vomiting.
SECOND GENERATION:		
Fadrozole: (4- (5, 6, 7, 8- tetrahydroimidazo [1, 5- a] pyridin- 5- yl) benzonitrile) $C_{14}H_{13}N_3$	In the treatment of patients with post-menopausal breast cancer.	Nausea, vomiting, loss of appetite, abdominal pain and fatigue.
Formestane: (4- hydroxyandrostenedione) **$C_{19}H_{26}O_3$**	In postmenopausal women with breast cancer.	Pain and irritation at the injection site, rash, itching, hot flushes, nausea and vomiting, and rarely growth of facial hair, baldness, vaginal bleeding, pelvic and muscle cramps, joint pain, headache, dizziness, drowsiness and sore throat.
THIRD GENERATION:		
Anastrozol: (2- [3- (1- cyano- 1- methyl-ethyl)- 5- (1H- 1, 2, 4- triazol- 1-yl methyl) phenyl]- 2- methyl- propanenitrile) **$C_{17}H_{19}N_5$**	Post-menopausal women diagnosed with hormone-receptor-positive, early-stage breast cancer after surgery	Diarrhea, constipation, nausea, vomiting, loss of appetite, headache, hot flashes, dizziness, dry mouth, back pain, vaginal dryness and cough
Letrozole: (4- [(4- cyanophenyl) - (1, 2, 4- triazol- 1- yl) methyl] benzonitrile) **$C_{17}H_{11}N_5$**	To treat hormonally- responsive breast cancer & is effective only in post-menopausal women.	Fatigue, nausea, constipation, diarrhea, headache, drowsiness
Vorozole: (6- [(4- chlorophenyl) - (1, 2, 4- triazol- 1- yl) methyl]- 1- methyl- benzotriazole) **$C_{16}H_{13}ClN_6$**	To treat advanced postmenopausal breast cancer following Tamoxifen failure.	Malaise, anorexia, nausea, hot flashes, fluid retention, vaginal infection, alopecia, lightheadedness, and allergic reaction which causes lip swelling
Exemestane: (6- methylenandrosta- 1, 4- diene- 3, 17- dione) **$C_{20}H_{24}O_2$**	In the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following Tamoxifen therapy.	Hot flashes, nausea, fatigue, headache and undesirable weight gain

Aromatase: Aromatase is a cytochrome P_{450} enzyme that catalyses the conversion of androgens to estrogen. This enzyme was first reported in human placental tissues by K. J. Ryan in 1959 [29]. The enzyme is localized in the endoplasmic reticulum of estrogen producing cells with highest levels of the enzyme present in ovaries of premenopausal women, in the placenta of pregnant women and in the peripheral adipose tissues of the postmenopausal women [30, 31]. Aromatase activity has also been demonstrated at the breast tissue *in vitro*. Furthermore, expression of aromatase is highest in or near breast tumor sites [32]. Aromatase enzyme is comprised of two polypeptides [33]. The first is cytochrome $P_{450\ arom}$, a haemoprotein that converts C19 steroids (androgens) into C18 steroids (estrogens) containing a phenolic A ring [34]. The second is a flavoprotein, NADPH-cytochrome P_{450} reductase which transfer reducing equivalent to cytochrome $P_{450\ arom}$. Three moles of NADPH and three moles of oxygen are utilized in the conversion of one mole of substrate into one mole of estrogen product. Aromatization of androstenedione, the preferred substrate, proceeds via three successive oxidation steps as shown in Fig. 3, with the first two being hydroxylations of the angular C-19 methyl group.

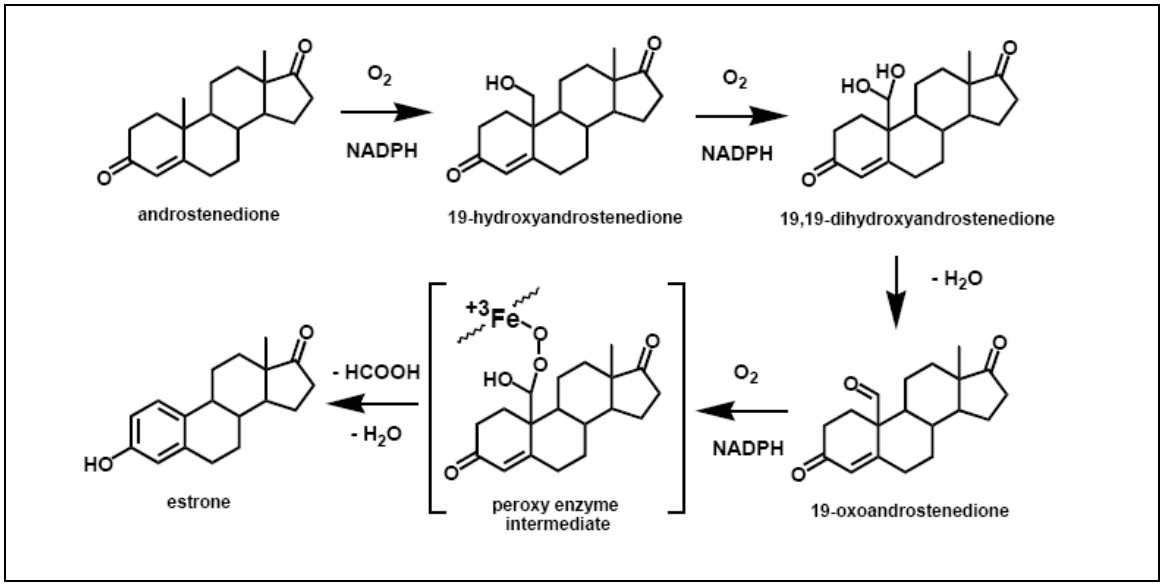


FIG. 3: REACTION MECHANISM FOR ESTROGEN BIOSYNTHESIS BY AROMATASE

The final oxidation step, whose mechanism remains for complete elucidation, proceeds with the aromatization of the A ring and loss of the C-19 carbon atom as formic acid [35]. This third and final step in aromatase reaction oxidatively cleaves the C_{10}-C_9 bond, although the mechanisms of this step yet to be explained. A number of mechanism have been proposed, and one mechanism for the oxidative deformylation step that has received significant favor involves nucleophilic attack of the 19-aldehyde by the reduced ferrous di- oxygen or peroxy intermediate as shown in fig 4. The resulting peroxo hemiacetal is suggested to decay via processes by which the proximal oxygen atom removes the 1β-hydrogen, resulting in aromatization of the steroid A ring and formic acid release [36].

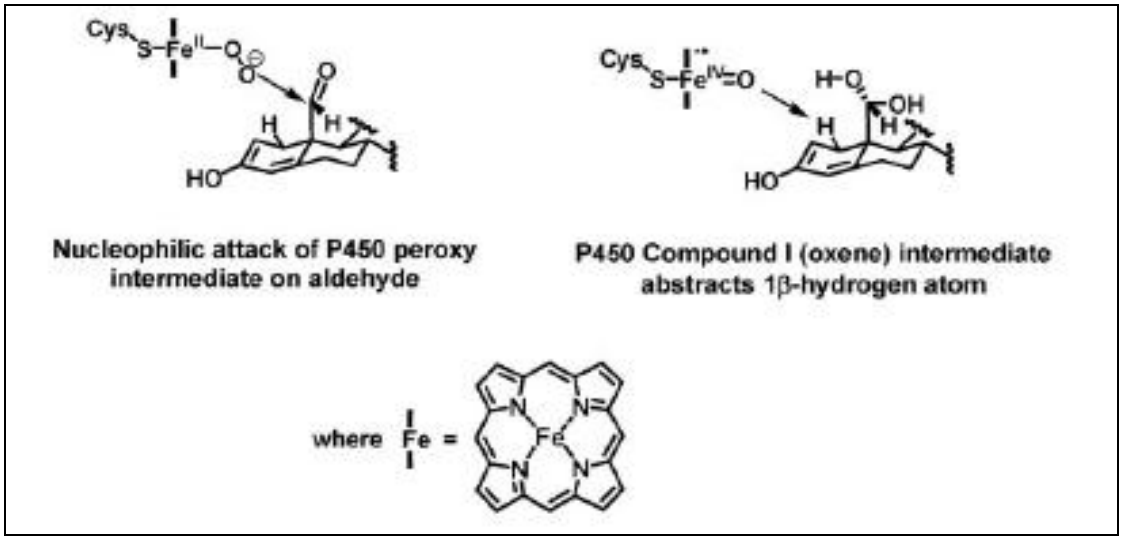


FIG. 4: MECHANISM FOR THE THIRD OXIDATION STEP OF AROMATASE REACTION

Gene Expression and Breast Cancer: The aromatase gene, designated CYP19 encodes the cytochrome P_{450}arom, and this gene is located on chromosome 15q21.1 [37]. The aromatase gene consists of 10 exons, and its full length cDNA of 3.4 kb encodes for protein of 503 amino acids. The regulation of aromatase is complex in various tissues, and several tissue specific promoter regions have been identified upstream from the CYP19 gene [37, 38]. These tissue specific promoters include promoter PI.1, PI.3, PI.4, PI.6, PI.7 and PII. The PII promoter is utilized in the ovary and in breast cancer tissues, and it contains a cAMP response element. Promoters P1.3, P1.4, PI.6 and PI.7 are the primary promoter used in extra glandular sites such as adipose tissue and are responsive to glucocorticoids and cytokines such as IL-1β, IL-6 and TNFα. Promoter P1.1 is the promoter used in placental tissues and its regulation is still under extensive investigations [39].

The increased expression of aromatase cytochrome P450arom observed in breast cancer tissues was recently associated with a switch in the major promoter region utilized in gene expression, and promoter II is the predominant promoter used in breast cancer tissues [40].

Genetic polymorphisms have been described in *CYP19* that are hypothesized to influence aromatase function and have been assessed for their association with breast cancer risk. A higher frequency of tetranucleotide (*TTTA*)n-repeat alleles in intron 4 have been reported among women with breast cancer in some studies [41]. Significant associations between the (*TTTA*)n polymorphism and bone mass, which is also dependent on estrogen, support the presence of functionally variant forms of aromatase [42]. Although this polymorphism will not affect the protein sequence, it might affect transcript elongation and/or it might have linkage to other polymorphisms that do have functional significance. Significantly higher plasma levels of oestradiol, oestrone and particularly oestradiol: testosterone and oestrone: androstenedione ratios have been found in postmenopausal women who carry the T allele at a single nucleotide polymorphism C/T site in the untranslated region of exon 10 of *CYP19*, but no significant association has been found

between this polymorphism and breast cancer risk [43]. These data indicate that variant forms of *CYP19* influence plasma estrogen exposure but that the influence on this and on breast cancer risk is modest.

Designing of Aromatase Inhibitors: Inhibitors for aromatase are designed by studying the active sites of the enzyme and through molecular modeling studies. Early studies focused on energy minimization calculations, conformational analysis, molecular volume calculations, pharmacophore mapping of aromatase inhibitors [44, 45]. Recently the comparative Molecular Field Analysis (COMFA) 3D-QSAR method was applied to the analysis of non-steroidal aromatase inhibitors, correlating the inhibitory activity with steric field value [46.] The major interaction for non-steroidal aromatase inhibitors is through the coordination bond of suitably placed heteroatoms with iron of the heme. The 3D-QSAR studies show the presence of two hydrophobic binding pockets in the C_6 region of the steroid. One of this is large and in the α-face while another is smaller and located in the β-face [47]. This hydrophobic pocket is constituted by highly hydrophobic aliphatic amino group I 305, A 306, T 310, V 369, V 370, L 477. The putative ligands are expected to have non-polar interaction with amino acids in the active site. The selective inhibition of aromatase can be attributed to the formation of hydrogen bond by acceptor group present in ligand along with the hydroxyl group of S 478 [22]. Thus a ligand should possess the following characteristic for selective inhibition of aromatase enzyme:

- Interact strongly with the iron atom of the heme group. Imidazole and triazole ring appear to be best suited for this purpose [48].
- Have a hydrophobic spacer group between heme coordinating groups and hydrogen bond acceptor moiety. This hydrophobic group is required to interact with aliphatic amino acid residues on active site [49].
- Have a chemical group that is able to accept H-bond from S-478 present in the active site. This particular serine residue plays a crucial role in the first and second hydroxylation reactions occurring in the reactive process catalyzed by aromatase [50].

Protein homology modeling analysis of aromatase has involved modeling the aromatase cytochrome P_{450} based upon sequence comparisons with bacterial cytochrome P_{450}'s that have been crystallized, particularly cytochrome P_{450cam}, cytochrome $P_{450terp}$, and cytochrome $P_{450BM-3}$, and site directed mutational studies [51, 52]. As such it is difficult to crystallize the human aromatase cytochrome P_{450}. These models have identified the active site of the enzyme located near the heme-binding region and the I-helix, with the carboxyl-terminal residues of helix F and the terminal residues of helix G contributing to the structure of the active site [53].

Clinical Applications of Aromatase Inhibitors:

1. **In Metastatic Breast Cancer:** Targeting aromatase in breast cancer as a therapeutic strategy was first conceptualized in the 1960s. Aminoglutethimide was the first aromatase inhibitor tested for this purpose. Although the first generation aromatase inhibitors was as efficacious as tamoxifen in the treatment of metastatic breast cancer but its side effect like lethargy, ataxia and morbilliform skin rash and development of more potent aromatase inhibitors resulted in cessation of its further development.

Second generation aromatase inhibitors were tested in Europe in 1980s and were found to be as efficacious as tamoxifen but its poor oral bioavailability limits its use [54].

The third generation aromatase inhibitors are approved for the treatment of postmenopausal women with metastatic estrogen dependent breast cancer. They are even proved superior to tamoxifen as first line treatment for advanced breast cancer. In the above mentioned clinical studies, the aromatase inhibitors demonstrated improved clinical efficacy and response rates (complete response, partial response, or disease stabilization), time to progression and time to treatment failure. Patients having estrogen receptor positive/ or progesterone receptors positive had better response rates when treated with aromatase inhibitors than tamoxifen [14, 55].

2. **In Neoadjuvant Therapy:** The rationale for the use of aromatase inhibitors for neoadjuvant therapy is to shrink hormone-responsive tumors before surgical resection, since early tumor shrinkage would reduce time for surgery [56]. Neoadjuvant hormonal treatment is being used increasingly and is emerging as an excellent method to downstage tumors and avoid mastectomy. Selected patients with hormone responsive tumors may be able to avoid cytotoxic chemotherapy [57]. Multiple Phase II trials have evaluated hormonal therapies in neoadjuvant setting. In such therapy tamoxifen showed short term control but poor long term control. Letrozole compared with tamoxifen showed significant differences in tumor response rates (letrozole 80%, tamoxifen 48%). Similar results were also obtained with anastrozole [58].
3. **In treatment of short stature:** The use of aromatase inhibitors has been shown to be effective in prolonging the length of the growth phase in children with idiopathic short stature, constitutional growth delay, delayed puberty, as well as in children with growth hormone deficiency, in which bone age advancement jeopardizes the result of hormonal replacement therapy with growth hormones [59].Estrogens are mainly responsible for bone maturation, promoting the complete ossification of the growth cartilage and limiting the linear growth.
4. **In Ovulation Induction:** The third generation aromatase inhibitors are successfully used for the induction of ovulation in WHO type II anovulatory patients. Promising pregnancy rates were associated with the use of aromatase inhibitors for induction of ovulation in these women [60]. As these inhibitors block estrogen production by inhibiting aromatization, would release the hypothalamic/pituitary glands from estrogenic negative feedback, thereby increasing gonadotropin secretion and resulting in ovarian follicle. A major advantage of using aromatase inhibitors is the ability to achieve restoration of monofollicular ovulation in anovulatory infertility as aromatase inhibition does not antagonize ERs in brain, the initiation of follicle growth results in increasing concentration of both estradiol and inhibin resulting in normal secondary feedback loop that limit FSH response to aromatase inhibition, thereby avoiding the risk of high multiple ovulation and ovarian hyperstimulation syndrome (OHSS) [61]. It also opens the possibility of using aromatase inhibitors to treat benign

conditions such as cyclic breast pain, fibroadenomata and recurrent cystic disease, which occur in women before the menopause.

5. **In Male breast carcinoma:** Male breast cancer is rare [62]. Less than 1% of breast carcinoma occurs in men. Leydig cell tumors are induced by aromatase over expression [63] and testicular tumors are the leading cancer in men between ages of 20-40 years. The pathology is similar to that of female breast cancer & infiltrating ductal cancer is the most common tumor type. Majority of breast cancer in male patients are hormone receptor positive. Preliminary data show effective suppression of estradiol level in male treated with Aromatase Inhibitors [64].

Side Effects: Most of the adverse effects with aromatase inhibitors therapy are due to their capacity to decrease estrogen levels which play a significant role in regulation of metabolism and maintenance of sexual organs.

Osteoporosis and fracture: The aromatase enzyme converts androgens to estrogens and is the principle source of endogenous estrogen in postmenopausal women. As a class effect, the aromatase inhibitors cause bone loss by lowering the levels of endogenous estrogen. In contrast, tamoxifen has tissue-specific estrogen agonist effects; in the bone of postmenopausal women, tamoxifen acts as a weak estrogen to preserve bone mineral density (BMD) and may decrease fracture [65, 66, 67]. However, Exemestane is a steroidal irreversible inhibitor, structurally related to androstenedione. The major metabolite of exemestane, 17-hydro-exemestane, is androgenic as well, and androgens have protective effects on bone. In contrast, letrozole and anastrazole are nonsteroidal reversible inhibitors devoid of androgenic activity [68].

Effect on Serum Plasma Lipids: Estrogen decreases the serum levels of LDL cholesterol, thus having a cardioprotective effect. Different aromatase inhibitors have shown different effects on serum lipid profile. In metastatic setting, anastrozole did not show any major effect on lipids [69] but led to increase in HDL cholesterol and decrease in triglyceride levels [70]. ATAC trail has also shown that patients receiving anastrozole had higher cholesterol level than tamoxifen [71]. In few studies, letrozole had no effect on serum lipid profile, while in one small study levels of both total and LDL cholesterol increased during letrozole administration [72]. In contrast, exemestane has shown no adverse effects on cholesterol levels and seems to decrease the serum triglycerides in patients with metastatic breast cancer [73].Other side effects include nausea, vomiting, headache, vaginal dryness. In some cases, hair thinning is also reported but this effect disappears with the discontinuation of the therapy.

CONCLUSION: The third generation aromatase inhibitors are now widely replacing tamoxifen for the treatment of breast cancer and perhaps also for its prevention. They are highly effective in postmenopausal women who experience failure of tamoxifen alone or tamoxifen plus other hormonal agents. Both steroidal and nonsteroidal inhibitors have been developed which are very potent and highly selective for aromatase. They all have good pharmacokinetic profile with lengthy half-lives allowing once daily administration without significant drug interaction & side effects.

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