International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 8, Issue 8, 2016

Review Article

# AROMATASE INHIBITORS - TYPES AND ADVANTAGES

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*Received: 29 Jan 2016 Revised and Accepted: 20 Jun 2016*

**ABSTRACT**

The role of aromatase inhibitors in the management of breast cancer has been promising as it markedly suppresses the production of estrogen. The inhibitors are very effective in postmenopausal women and used as the first line therapy for hormone-sensitive breast cancer. The third generation aromatase inhibitors are advantageous having less adverse effects over other breast cancer drugs and they have also been recommended for use with tamoxifen. The aromatase inhibitors are of two different types; steroidal and nonsteroidal. Steroidal inhibitors are mechanism based inhibitors that mimic the natural substrate and are irreversible, unlike non-steroidal inhibitors which are reversible. The expression of aromatase occurs in a tissue specific manner with a set of distinctive transcription factors. In tumorous breast tissue, the enzyme is overexpressed with the help of four different promoters, I.3, I.4, I.7 and II and in turn, the growth stimulatory effects of estrogen is magnified to very high levels. Aromatase inhibition approach is considered as the gold standard and hence, in this review, we have discussed different types of aromatase inhibitors with their advantages.

**Keywords:** Breast cancer, Aromatase inhibitor, Steroidal, Non-Steroidal, Natural inhibitors



## INTRODUCTION

Aromatase, being the key enzyme in the biosynthesis of estrogen, has acquired much attention as estrogen is the primary molecule that promotes the growth of normal and cancerous breast epithelial cells. Estrogen binds to estrogen receptors that get activated and bind to the promoters in the nucleus. Due to the activity of these estrogen receptors, cell division and blood vessel formation are enhanced. Moreover, binding of the estrogen receptors to the promoters also helps in inhibiting the cell death, thus promoting the tissue growth [1]. Aromatase is a cytochrome P450 enzyme catalyzing the critical rate limiting step (fig. 1), converts two different androgens; androstenedione and testosterone. It consists of a complex containing a cytochrome P450 protein and a flavoprotein NADPH cytochrome P450 reductase [2, 3]. The transcription of the enzyme is highly regulated and its gene coding for P450 protein has about 70kb which is the largest in its family. The polypeptide chain of the enzyme consists of 503 amino acids with a molecular weight of 55 kDa. It is placed in a separate CYP19 family as its overall homology to other members of the P450 superfamily is low [4, 5]. The region that encodes aromatase protein is about 30kb of the 3' end which contains nine exons (II-X) [6]. Tissue specific expression of a number of promoters regulates the expression of aromatase through alternate splicing. Under physiological conditions, in disease free women, the aromatase expression is controlled at very low levels through promoter I.4 that is present 73kb upstream of the common coding region. There are other two promoters I.3 and II which are used very minimally in normal breast tissue [7]. However, the expression of the promoters I.3 and II is markedly increased to a very high level in breast tumor fibroblasts [7-10]. Additionally, yet another promoter I.7 is also overexpressed in breast tumor tissue and thus in breast cancer, a total of four different promoters contribute to the overexpression the enzyme and in turn, increasing the total aromatase mRNA levels when using promoter I.4 in normal breast tissue [11]. Hence, the inhibition of the enzyme is currently preferred over other modes of treatment for breast cancer and the drugs have been classified as "Aromatase Inhibitors (AIs)". SERM (Selective Estrogen Receptor Modulator) and SERD (Selective Estrogen Receptor Down-regulated) are other class of drugs that impact a variety of pathways regulated by activated estrogen receptors. Depending on the site of action, the SERMs will have either estrogen antagonist or agonist effects by modifying the expression of multiple genes whose transcription is regulated by estrogen receptors [12-16]. New approaches for treating breast cancer in postmenopausal women have also been proposed recently. An orphan nuclear receptor, DAX1, which is activated by the ligand activated androgen receptor, has been found to inhibit aromatase activity in breast cancer cell lines [17]. With the advent of newer genomic and transcriptomic techniques, personalized medicine is not an unreachable target. Breast cancer diagnostics has come a long way with advanced techniques such as real-time PCR, microarrays, Next Generation Sequencing leading to the identification of new biomarkers which would eventually help in the personalized management of treatment [18]. The role of miRNAs is being closely examined in the progression of breast cancer as they have been identified to be essential for the growth of HER2 positive breast cancer cells and further investigation would pave the way to develop strategies for prevention and treatment of breast cancer [19]. In this review, we have discussed the various types of aromatase inhibitors and its contribution in the treatment of breast cancer.

### Aromatase inhibitors

Three generations of aromatase inhibitors have been in practice; each successive generation with higher specificity and less adverse effects. The list of aromatase inhibitors is tabulated in table 1. The third generation AIs are more specific with greater enzyme suppression [20-25]. These inhibitors can be pharmacologically divided into two different types as Type I and Type II; suicide inhibitors and competitive inhibitors respectively. The suicide inhibitors bind to the active site irreversibly and also leads to byproducts. They form covalent bonds in the active site or nearby the pocket inactivating the enzyme permanently and hence, they are of steroidal in nature. Type II, competitive inhibitors, on the other hand, prevent the product formation by binding reversibly to the active site. Once the inhibitor detaches, the active site becomes available to the substrate for binding. Unlike the suicide inhibitors, the competitive inhibitors could be steroidal or non-steroidal in nature [26]. As the aromatase inhibitors were more effective than the SERMs such as tamoxifen, the use of AIs increased drastically over the years. Moreover, the use of SERMs have a disadvantage of resistance in the women with ER+tumors that lack progesterone receptors. Overexpression of growth factors such as human epidermal growth factors also disrupted the effectiveness of the treatment [27, 28]. The most widely used SERM, tamoxifen was also found to increase late recurrence rates which might be due to its ability to act as estrogen agonists under differing conditions. Even

though this condition was attributed to prolonged use of tamoxifen, it urged the researchers to look for an alternate mode of treatment which resulted in the development of aromatase inhibitors that are effective regardless of progesterone receptor or growth factor receptors [27-31]. Metastasis is a major problem in any breast cancer as the tumorous cells spread to the distant sites such as lungs, liver, bone and brain. This stage is referred to as metastatic breast cancer, advanced breast cancer or secondary tumor. Aromatase inhibitors are more effective in the metastatic conditions when compared to tamoxifen by delaying the progression [32]. Aromatase inhibitors also have various adverse effects such as hot flashes, nausea, vomiting, fatigue, mood disturbances, musculoskeletal disorders, vaginal bleeding, vaginal discharge and vaginal dryness [33]. Moreover, recent studies have shown that the accumulation of p53 indicates recurrence in patients who were treated with aromatase inhibitors [34]. Amid such negative effects, aromatase inhibition is considered as Gold Standard for the treatment of early and advanced breast cancer as the advantages outweigh improving survival [35].

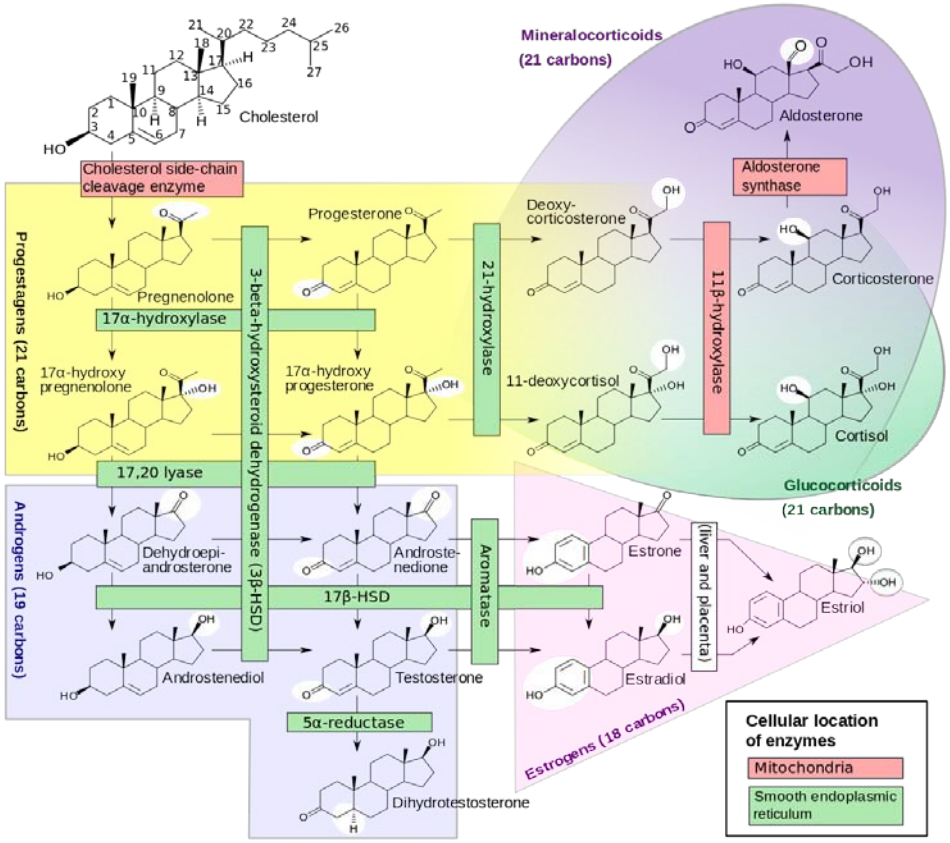


**Fig. 1: Biosynthesis of estrogen**

**Table 1: Aromatase inhibitors**

| | 1st generation | 2nd generation | 3rd generation |
|---|---|---|---|
| Steroidal AIs | Testololactone | Formestane | Exemestane |
| Nonsteroidal AIs | Aminoglutethimide | Fadrozole | Anastrozole, Letrozole, Vorozole |

**Steroidal aromatase inhibitors**

Testololactone was the first generation steroidal aromatase inhibitor, used widely more than aminoglutethimide, a non-steroidal inhibitor for treating advanced breast carcinoma. But, because of the misinterpretation of the mechanism of its action and the delay in determining its actual mechanism, i. e aromatase inhibition, the usage became obsolete soon [36]. Most of the clinical studies were conducted with testololactone were conducted prior to the time that its aromatase inhibition mechanism was unknown and this might have been a reason for its lower recognition [37]. It is a synthetic antineoplastic drug which is structurally similar to testosterone and its main action is the inhibition of conversion of androstenedione to estrone. Even though it is structurally similar to testosterone, it has never been found to be exerting androgenic activity. The drug can be easily produced from progesterone by microorganisms [38]. Testololactone was used in postmenopausal women as the main source of estrogen for them is estrone. The effect of the drug remains for a very long time even after the drug withdrawal. Due to its side effect and less potency as an inhibitor, industries came out with the second generation steroidal aromatase inhibitor, formestane (4-hydroxyandrostenedione) which is the first selective steroidal aromatase inhibitor and an analog to androstenedione. The performance of the drug, when compared with tamoxifen, had no significant difference except with time duration. Even then, since the drug was not active orally, the use was discontinued [39,40] which led to the development of third generation steroidal aromatase inhibitor, exemestane. Second and third generation inhibitors are more potent up to 1000 fold than the first generation drugs. As the half-life of the drugs is more, they are able to decrease the concentration of the circulating estrogen greatly [41]. Exemestane (6-methyleneandrosta-1,4-diene-3,17-dione) is structurally related to the natural substrate, androstenedione and hence, acting as a false substrate binding to the enzyme irreversibly. The drug has added the advantage of rapid absorption from the gut. It reaches high plasma concentration within about 1 hour in breast cancer patients; faster than healthy subjects where the absorption is about 3 h and mostly, the absorbed drug is bound to plasma proteins [42, 43]. The potent

activity of exemestane has been attributed to its different metabolites which eventually arises due to its complex metabolization. The four identified metabolites are tabulated in table 2.

**Table 2: Metabolites of exemestane**

| S. No. | Metabolites of exemestane |
|---|---|
| 1. | 17β-hydroxy-6-methylenandrosta-1,4-dien-3-one (17-βHE) |
| 2. | 6-(hydroxymethyl)androsta-1,4,6-triene-3,17-dione (6-HME) |
| 3. | 6β-Spirooxiranandrosta-1,4-diene-3,17-dione (6-SPE) |
| 4. | 1α,2α-epoxy-6-methylenandrost-4-ene-3,17-dione (1-EME) |

6-SPE was found to be more potent than the other metabolites resulting in an increase in the activity of MCF-7aro cells when compared to exemestane as the IC50 values were 0.25 μM and 0.90 μM respectively [44]. Moreover, recent studies have demonstrated that the mechanism of action of the exemestane metabolites is different from that of exemestane. The metabolites, through the mitochondrial pathway, induced cell cycle arrest and apoptosis involving caspase-8 activation. They also induced the physiological cell destruction, autophagy promoting apoptosis and consequently, the aromatase inhibitor-resistant breast cancer cells were also sensitized due to enhanced apoptosis indicating that the efficacy of the exemestane may be dependent on the activity of its metabolites and not just exemestane [45]. The drug has also been found to be effective with everolimus, a mammalian target of rapamycin (mTOR) pathway inhibitor, which is promising as the aberrations in Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway are common in breast cancer. The increased resistance to endocrine therapies have been correlated with the mTOR pathway aberrations and hence, therapy with everolimus in combination with exemestane has been approved for use based on the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study [46].

**Nonsteroidal aromatase inhibitors**

Aminoglutethimide was primarily introduced as an anticonvulsant in 1960. It was observed that the drug had side effects including dizziness, drowsiness and ataxia. Adrenal insufficiency was also observed later which led to the withdrawal of the drug by FDA and on the other hand, led to series of studies determining its aromatase inhibition mechanism. Aminoglutethimide was the first nonsteroidal aromatase inhibitor and it was widely used in the treatment of metastatic breast cancer in postmenopausal women [47-50]. The drug has many advantages such as decreasing plasma estrone and estradiol concentrations up to 80%, and acceleration of metabolism of estrogen sulphate [51]. It was also observed through isotopic kinetic studies that aminoglutethimide is able to inhibit aromatase activity up to 90-95% [47]. The non-selectivity of the drug for aromatase led to very serious side effects as it was found to inhibit other cytochrome P450 mediated steroid hydroxylations and this mandated that the drug be combined with hydrocortisone [36, 50, 51]. A fairly more potent second generation aromatase inhibitor, fadrozole replaced aminoglutethimide. Effective aromatase inhibition was observed even at lower concentrations [52]. The efficacy of the drug was compared with tamoxifen in trials and found that there was no significant difference in response rates and response duration [53, 54]. Considering the data generated out of various trials and experiments, it was demonstrated that fadrozole might be inferior to tamoxifen in efficacy. Even though the drug was approved for use in advanced breast cancer postmenopausal women in Japan, it was placed in third line therapy. Newer third generation drugs like anastrozole and letrozole were more potent and had more selectivity for the enzyme [41]. Anastrozole was the first nonsteroidal aromatase inhibitor to be approved in the US as it was able to inhibit the aromatase activity by 50% without having any effects on any molecules such as aldosterone, cortisol or thyroxine synthesis as that of previous versions. It was used at very low concentration of 0.1 mg/Kg orally for the management of breast cancer in postmenopausal women. The suppression of estradiol in patients was even up to levels approaching assay sensitivity. It was also found to be well tolerated than previous drugs and had less undesirable side effects such as weight gain, dyspnea, thromboembolic occurrences. The more attractive effect of anastrozole was that the survival advantage was higher up to 56% observed in a period of 2 y [55, 56]. Because of the superiority of the drug, it stays in the market to date even after the introduction of letrozole, yet another third generation nonsteroidal aromatase inhibitor. Letrozole has been approved for the management for metastatic breast cancer as it possesses considerable selectivity for aromatase [57]. The aromatase inhibition efficiency was detected using a highly sensitive DNA based estradiol assay and the results showed that the drug could decrease the plasma estradiol concentration up to 95% [58]. Letrozole administration over a wide dose range showed that it is highly selective for aromatase as there was no significant change in the levels of gonadotropins, ACTH, cortisol, aldosterone or TSH [59]. The toxicity was also tested with heavily treated postmenopausal breast cancer women and proved to be nontoxic with high clinical efficacy [60]. Vorozole is another highly potent and selective third generation nonsteroidal aromatase inhibitor. The efficacy of the drug is as similar as anastrozole and letrozole, but higher than aminoglutethimide [61]. Letrozole remains the preferred drug as it has also been found to be more advantageous when used with various small molecules such as dasatinib, palbociclib and buparlisib. Dasatinib, a Bcr-Abl tyrosine kinase inhibitor combined with letrozole improved the median progression free survival (PFS) from 11 mo to 22 mo in metastatic breast cancer (MBC) [62] and also, in combination with the cyclin dependent kinase inhibitor, palbociclib when tested with advanced estrogen receptor-positive and HER2-negative breast cancer women, significantly improved the PFS [63]. Apart from being used for treatment, aromatase inhibitors have been assessed for the prevention and reducing the recurrence in high risk postmenopausal women. In a study, it has been shown that anastrozole reduces the incidence of breast cancer in the women at high risk. The results are similar to the reduction in incidence due to exemestane in MAP.3 trial [64] and greater than the reduction in incidence due to tamoxifen [65]. The side effects due to the deprivation of estrogen were not attributed specifically to the treatment with anastrozole as they were also seen in the placebo group and most importantly, the risk of invasive estrogen receptor positive breast cancer was reduced to more than 50% [66]. A recent study reveals the advantage of using letrozole beyond 5 y in women with early breast cancer as it was beneficial in preventing recurrence. Moreover, the incidence of contralateral breast cancer was also reduced significantly by 34% with 10 y continuous treatment [67].

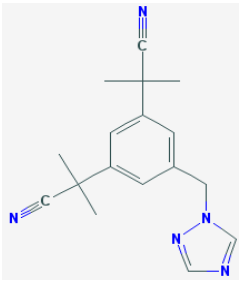

**Fig. 2: Anastrozole**

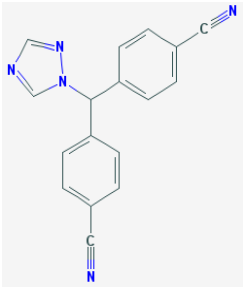

**Fig. 3: Letrozole**

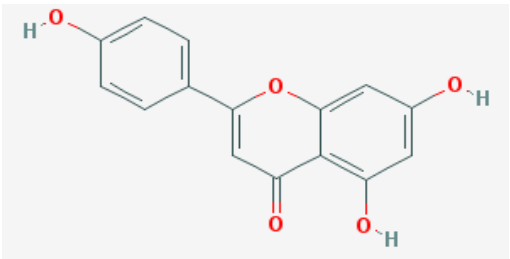

**Fig. 4: Apigenin**

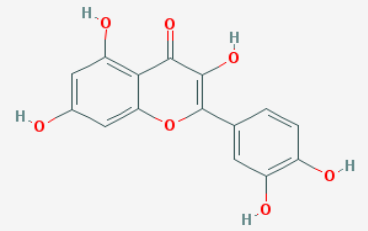

**Fig. 5: Quercetin**

**Natural aromatase inhibitors**

Various natural small molecules have been tested for aromatase inhibition activity. Most of the molecules are secondary metabolites and they have been assayed in both i*n vitro* and *in vivo*. Among the molecules investigated, flavonoids are being investigated to a greater extent. Apart from flavonoids, terpenoids, peptides, lignans, xanthones, fatty acids, alkaloids, and other miscellaneous compounds having been evaluated [68]. Chrysin (5,7,4'-trihydroxy-3',5'-dimethoxyflavone) was evaluated in microsomes, human preadipocyte cells, H295R adrenocortical carcinoma cells and in MCF-7 dual assay for its anti-aromatase activity [69-74]. Another common flavonoid tested in multiple studies is apigenin (5,7,4'-trihydroxyflavone, 8). It has been found to be highly active in microsomes, Arom+HEK293 cells and granulosa-luteal cells [70-72, 75, 76]. Apigenin is only moderately active in H295R adrenocortical carcinoma cells and not active in trout ovarian aromatase [74, 77]. Quercetin is natural dietary molecule that is present in many fruits and vegetables. It has been in use as a dietary supplement for a long time. The small molecule isolated from Epilobium capense and *Morinda citrifolia* L were found to have moderate inhibitory activity on aromatase [78]. Unsubstituted flavone, 7-Hydroxyflavone, Luteolin, 7,8-Dihydroxyflavone, 6-hydroxyflavone, 7-methoxy-flavone, isolicoflavonol, broussoflavonol F, galangin, kaempferol, 5,7,4'-trihydroxy-3'-methoxyflavone and rutin are other small molecules that have aromatase inhibition activity [68]. Apart from natural compounds, extracts have been shown to have anti-aromatase activity. The extracts tested range from plants, edible fungi, spices, cycads to dietary substances and they were mostly investigated in microsomal assays. The extracts that showed activity on aromatase were from *Dioon spinulosum*, *Encephalartos ferox*, *Riedelia Meisn. sp*, *Viscum album L*, *Cycas rumphii*, *Cycas revoluta*, *Alpinia purpurata* etc. [79, 80].

**Advantages over tamoxifen**

The efficacy of the aromatase inhibitors over tamoxifen have been studied in many studies, particularly, the third generation aromatase inhibitors [81-84]. The nonsteroidal aromatase inhibitors, anastrozole and letrozole had better efficacy when compared with tamoxifen in two different studies where the 80% subjects were tamoxifen naive [83]. Even though anastrozole did not give statistically significant difference in Objective Response Rate (ORR), clinical benefit and time to progression (TTP), letrozole demonstrated superiority in all of these parameters [84]. In a randomized phase trial conducted by European Organization for Research and Treatment of Cancer (EORTC), the steroidal aromatase inhibitor, exemestane was compared with tamoxifen. The results were promising as: Exemestane and tamoxifen produced an ORR of 40.9% and 13.6%; the clinical benefit of 55.7% and 42.4% respectively. Large trials were also conducted to prove the superiority of the third generation aromatase inhibitors over tamoxifen. Unlike other studies, the trial was involving multinational investigators and the results were confirming that the third generation aromatase inhibitors are superior in clinical efficacy with improved responses ranging from 2 to 13%. All the results were statistically significant except a trial in which the receptor status was unknown [85-87]. Toxicity was also compared between the use of tamoxifen and aromatase inhibitors in which the symptoms were comparable to some extents. Nausea, hot flashes and gastrointestinal distress were seen in both the treatments. Effects like deep venous thromboses and pulmonary emboli were significantly higher in tamoxifen than aromatase inhibitors. However, aromatase inhibitors associated side effects were also observed such as osteoporosis, osteopenia, arthralgias and myalgia [88,89]. Aromatase inhibitors have also been investigated in combination therapeutic approaches with tamoxifen. In ATAC (Anastrozole and Tamoxifen Alone and in Combination) trial, the effects like TTP, TTF and overall survival rates were compared [90]. After a 5 y follow up, in both the trials the aromatase inhibitors had superiority of about 3%. But the overall survival did not have much difference. Moreover, tamoxifen increased endometrial cancer and venothrombotic incidence whereas the aromatase inhibitors were associated with bone loss and urogenital atrophy symptoms [91-93]. A recent study, a meta-analysis that was conducted on 36889 postmenopausal women with ER-positive invasive breast cancers to determine if the continuous or sequential regime of aromatase inhibitors is more effective than sequential tamoxifen monotherapy for preventing recurrence. The outcome of the analysis clearly revealed that the reduction in recurrence (827/4,970 vs 964/4,915, $p<0.0001$) was seen more with aromatase inhibitors than tamoxifen [94]. In a similar study, determination of recurrence rates showed that there is 30% reduction when compared with tamoxifen and moreover, 10-year breast cancer mortality rates were reduced by 15% [95] indicating that the use of aromatase inhibitors in postmenopausal women is advantageous over tamoxifen having a better outcome and less toxicity.

**CONCLUSION**

Third generation inhibitors have gained an advantage over other endocrine therapies for the treatment of postmenopausal women in both early and metastatic breast cancers. They are effective not only alone but with other SERMs like tamoxifen. Additionally, they have also been helpful in adjuvant and neoadjuvant treatments [33,96-98]. Prevention is another regime for any disease in which aromatase inhibitors could also be effective. On the other hand, estrogen is a necessary endocrine molecule which is also involved in biological processes other than endocrine function such as the brain, bone metabolism, energy expenditure, cardiovascular physiology, testis and prostate physiology and regulation of gonadotropin secretion. Hence, developing more advanced therapeutic approaches that can act on intratumoral production of estrogen, targeting only the cancerous cells would be the near future.

**CONFLICT OF INTERESTS**

Declared none

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**How to cite this article**

- Benedict paul C, Sudandiradoss C. Aromatase inhibitors-types and advantages. Int J Pharm Pharm Sci 2016;8(8):1-7.