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REVIEW

Origination Progress and Utility of Selective Estrogen Receptor Modulators in Clinical Practice as an Efficient Substitute of Estrogen for Treating Hormone Dependent Issues

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ABSTRACT

The discovery, development and utility of selective estrogen receptor modulators (SERMs) are presented in this study. As per literature review SERMs used in the treatment of estrogen hormone responsive diseases like osteoporosis, Alzheimer, angiogenesis, hyperlipidemia, coronary heart disease, atherosclerosis, endometriosis, breast cancer, post-menopausal depression, dysfunctional uterine bleeding, gynaco-mastia, Albright syndrome, ovarian cancer, dyspareunia, cyclical mastalgia, hypogondism and induced ovulation in sub-fertile woman, *etc*. Basically world wide a large no. compounds available those function as SERMs successfully or under different phase clinical trials or discontinued because of unwanted side effects during clinical trials. This work describes the specific reference compounds which have created a substitute of estrogen for treating hormone dependent issues.

KEYWORDS

Estrogen receptor, Hyperlipidemia, Alzheimer, Hormone responsive disease, Atherosclerosis.

INTRODUCTION

Selective estrogen receptor modulators (SERMs) are the class of compounds which interact with estrogen receptors as agonist or antagonist. The activity of SERM depends on the type of tissues. Mainly these are non-steroidal drug molecules which can be efficiently used as an alternate of estrogen in hormone replacement therapy (HRT). Hormone replacement therapy is a medication which is needed when the level of female hormone (estrogen and progesterone) reduced due to ageing and cause menopause and many other ageing effects. SERMs modulate the activity of estrogen receptors selectively means wherever the cellular growth required it introduced agonistically and wherever cellular growth control needed it works antagonistically [1], so these SERMs are partially agonist and partially antagonist. As they named selective estrogen receptor modulators their activity is tissue selective. Here we will discuss the discovery, development and applications of SERMs. As per literature review SERMs used in the treatment of hormone responsive diseases like osteoporosis, Alzheimer, angiogenesis, hyperlipidemia, coronary heart disease, atherosclerosis, inflammation, endometriosis, breast cancer, post-menopausal depression *etc*. In some cases SERMs utility better than

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estrogen [2]. When scientist were trying to synthesize some antifertility drugs (contraceptive) accidently some different moieties had been synthesized which later on called as SERMs. Two strong moieties those were famous in that timeline were tamoxifen and clomifene. At initial stage when clomifene and tamoxifen both preventing conception in rat but respond oppositely in humans. Means somewhere these moieties were helping for sub-fertile women who wish to conceive. Clomifene depicted successfully, induced ovulation in sub-fertile women and on 1st Feb. 1967, it was approved in US as the medicine for ovulatory dysfunction in women [3]. Some serious side effect of clomifene prevented long term use of it and drug molecule again evaluated for other potential application such as hormone dependent problems [4]. After 10 years of research on the clomifene and tamoxifen, finally tamoxifen had approved for hormonal treatment to treat and prevent breast cancer in December 1977 [5]. Then a regular research on the same generic molecules discovered a new drug molecule raloxifene which was an antiosteoporotic drug. Earlier tamoxifen had exposes antiestrogenic effect in breast cells while raloxifene introduced estrogenic effect on bone cells in ovary ectomized rat. This experiment help to understand the function of estrogen receptor or nuclear receptor. Modulating behaviour of these drug molecules coined them as selective estrogen receptor modulators [6]. Toremifene another SERM had shown strong antiestrogenic activity on breast cells. In 1996 it has approved as a medicine of breast cancer in postmenopausal woman [7]. Ospemifene was the first SERM which has shown conjugated effect on estrogen receptors and can be used for prevention and treatment of osteoporosis and breast cancer both. In Feb. 2013, it has approved for the treatment of moderate to severe dyspareunia which is an effect of menopause and vaginal atrophy [8]. In Oct. 2013 bazedoxifene a new SERM with combination of conjugated estrogen had approved for the treatment of vasomotor symptoms. It also possessed anti-osteoporotic activity and used for osteoporosis treatment in postmenopausal women [9]. The search for a potential SERM with bone efficacy and better bioavailability then raloxifene lead to the discovery of lasofoxifene. This has approved in 2009 but due to some reasons had not marketed for 3 years [9]. Ormeloxifene another SERM has approved in 1991 as antifertility and also used in the treatment of dysfunctional uterine bleeding [10].

Classification: There is a large number of compounds that can be considered as SERMs. Some are still under different phase of clinical trials some are using as successful medicine [11]. Chemically, the classification of SERMs is given in Table-1.

These drug molecules are tissue selective, their functions depend on the type of tissue so their activity in different human cells, as shown in Table-2 [12]:

Beginning of selective estrogen receptor modulators: There are several compounds which possess activity with estrogen receptors and can be act as SERMs (Fig. 1). Some of the compounds successfully used as SERM's, some are under different phase of clinical trials and some are discontinued due to severe side effects during clinical trials. Here we have to introduce all the compounds which have been identified as SERM's worldwide.

Clomifene approved in 1967 for medicinal purpose in United States. It is on the world health organization essential medicine list. Clomifene is most effective and safe medicine needed in health system. It has been approved for the treatment of infertile women induces ovulation; those women suffering with polycystic ovary syndrome are including them [13-15].

Tamoxifene approved in 1977 in US for the treatment of breast cancer in pre and post-menopausal women. It is an essential, effective and safe medicine according to WHO, possess multiple biological activities and can be used in the treatment of osteoporosis, gynecomastia, Albright syndrome, endometrial cancer, cardiovascular and metabolic issues, infertility

TABLE-1
CLASSIFICATION OF SERMs

	Chemical name	SERMs
1	Triphenylethylenes	Tamoxifen, clomifene, toremifene, droloxifene, miproxifene (TAT-59), idoxifene, fispemifene, GW5638, MDL103323, broparestrol, ospemifene
2	Benzothiophenes	Raloxifene (keoxifene), arzoxifene, LY-117018
3	Naphthylenes	Lasofoxifene, nafoxidine, trioxifene
4	Indoles	Bazedoxifene, pipendoxifene
5	Benzopyran	EM-800 (SCH57050), acolbifene, SP-500263, ormeloxifene, levormeloxifene, NNC45-0781 & derivatives

TABLE-2
TISSUE SPECIFIC ESTROGENIC AND ANTI-ESTROGENIC ACTIVITY OF SERM's

Medication	Breast	Bone	Liver				Uterus	Vagina	Brain	
			Lipids	Coagulation	SHBG	IGF-1			Hot flashes	Gonadotropins
Estradiol	+	+	+	+	+	+	+	+	+	+
Ideal SERM	–	+	+	–	±	±	–	+	+	±
Bazedoxifene	–	+	+	+	+	+	–	±	–	?
Clomifene	–	?	?	?	+	+	?	?	–	±
Lasofoxifene	–	+	+	+	?	?	±	±	–	?
Ospemifene	–	+	+	+	+	+	±	±	–	±
Raloxifene	–	+	+	+	+	+	±	–	–	±
Tamoxifene	–	+	+	+	+	+	+	–	–	±
Toremifene	–	+	+	+	+	+	+	–	–	±

+ = Agonistic activity; – = Antagonistic activity; ± = Agonistic and antagonistic combined activity; ? = any activity not confirmed.

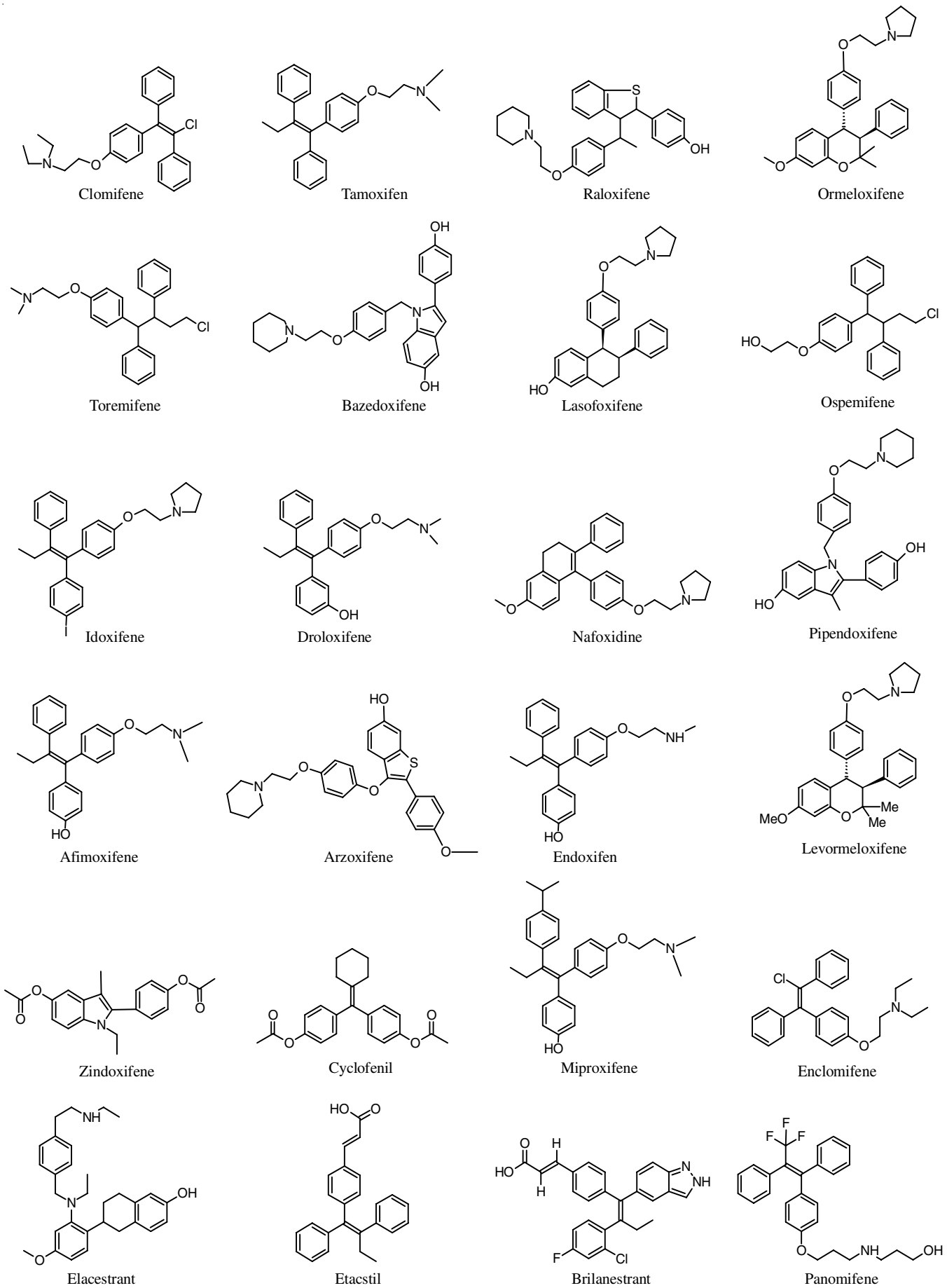

Fig. 1. Structure of selective estrogen receptor modulators

problems in male and female *etc*. its antiestrogenic activity made it perfect to use in the treatment of breast cancer [16-25].

Raloxifene was first introduced for the treatment osteoporosis in post-menopausal women in 1997. It has been approved in 1999 as antiosteoporotic medicine and in 2007 approved to reduce the risk of breast cancer in post-menopausal women. Estrogenic activity on the bone cells made it perfect for the treatment of osteoporosis. Majorly it is used in the treatment of osteoporosis. It is also studied for the treatment of prostate cancer and schizophrenia in post-menopausal women [26-35].

Ormeloxifene discovered by Central Drug Research Institute (CDRI) Lucknow and approved as antifertility drug in 1991 in India, marketed the brand name Saheli and Choice-7. Its major action as antiestrogen in uterus and breast and partially estrogen action on bone tissues.it causes asynchrony in menstrual cycle between ovulation and the development of the uterine lining. It has been tested and approved for birth control as well as for the treatment of dysfunctional uterine bleeding [36-45].

Toremifene introduced in 1997 and approved for the treatment of metastatic breast cancer in post-menopausal women in US only. It is a competitive ligand of estrogen receptor and has combined effects on different tissues. It exposes estrogenic activity of bone tissues partially estrogenic activity on liver and uterus and antiestrogen activity in breast cells. It is very similar to tamoxifen and shared most of its properties. In some studies it quit safer than tamoxifen such as it is not hepatocarcinogen in animals and may have less potential for gene toxicity. Overall there is no significant difference in clinical trials between tamoxifen and toremifene so this drug hadn't got much response from market [46-50].

Bazedoxifene approved by European Medicine Agency in European Union 2009. In 2013 it is in combination with premarin (conjugated estrogen) has approved for the treatment of menopausal osteoporosis and moderate to severe hot flushes. This was the first hormonal therapy product that contains combination of SERM and estrogen.it is in category of 2-phenyl indole [51-56].

Lasofoxifene has approved in 2009 for the treatment of metastatic breast cancer. It is under clinical trial for the treatment of metastatic breast cancer and dyspareunia associated with vaginal atrophy in US and Europe. It is also being studied for treatment ovarian cancer. Its phase III clinical trial for breast cancer and phase II clinical studies for dyspareunia has done in 2017. It is naphthalene derivative which is selectively binding ER-α and ER-β both similar to estradiol [57-61].

Ospemifene approved by FDA in 2013 for the treatment of dyspareunia. It is an estrogen agonist/antagonist which makes vaginal tissues thicker and less fragile for reduction of pain a female experience during sexual intercourse. Dyspareunia is commonly caused by vulvar vaginal atrophy. It is under phase III clinical trials [64-67].

Idoxifene is a non-steroidal SERM which is iodine derivative of tamoxifen. It has studied for the breast cancer and post-menopausal osteoporosis but never marketed because of side effect of generated in phase II for postmenopausal osteoporosis and Phase III clinical trials for breast cancer. It has discontinued 1999 due to ineffectiveness in both cases [67-71].

Droloxifene developed in Germany and later in Japan for the treatment of breast cancer and osteoporosis in man and women both. It is analogue of tamoxifen and found less effective than tamoxifen during clinical trials it has discontinued after phase II and phase III clinical trials in 2000 [72-74].

Nafoxidine is non-steroidal SERM which is partial antiestrogen of triphenylethylene group developed for the treatment of breast cancer in 1970 but never marketed. It has developed for fertility control program as post-coital contraceptive but afterward repurposed for the treatment of breast cancer.it is effectively works on breast cancer but dropped due to severe side effects such as ichthyosis, partial hair loss and photo toxicity of skin [75-77].

Pipendoxifene is non-steroidal SERM which has developed for the treatment of breast cancer. It is structurally related to zindoxifene & bazedoxifene. It has reached up to phase II clinical trials then development discontinued. Pipendoxifene was synthesized at the same time as bazedoxifene and projected as backup drug for bazedoxifene, its development planned to continue if bazedoxifene failed in clinical trials. In 2005, its development officially ended [78-81].

Afimoxifene is a hydroxy derivative of tamoxifene, this drug is under trials beneath the brand name Tamo Gel as ointment for treating hyperplasia of breast. It had completed phase II clinical trials for cyclical mastalgia, but further development required for next level of clinical trials. It exposes antiestrogenic activity with ER-β and ER-γ. It is externally used as ointment gel therefore expected to decrease some unpleasant side effect of tamoxifene. A study in France on 55 women showed that rubbing of afimoxifene on skin is more effective than tamoxifene at reducing breast cancer growth [82-85].

Arzoxifene is SERM of benzothiophene group which has never marketed due to the high risk of endometrial carcinoma. It has mixed agonist and antagonist activity on estrogen receptors. It is highly effective agent for prevention of mammary cancer induced in the rat by the carcinogen nitrosomethylurea more effective than reloxifene, it is potential estrogen antagonist in breast and uterine cells and agonist to bone cells. It is devoid the uterotrophic effect of tamoxifen. After phase III clinical trial it has discontinued in 2009 [86-89].

Endoxifen is orally active non-steroidal SERM of triphenylethylene group. It is under development for the treatment of ER+ breast cancer and also evaluated as an antipsychotic for treating mania and other psychotic disorder. It is an active metabolite of tamoxifen [69,90,91].

Levormeloxifene is a non-steroidal SERM which is benzopyran derivative developed as an substitute of estrogen replacement therapy for treating postmenopausal bone loss but during clinical trials proved incompetent due to high incidence of gynecological side effects. Structurally it is laevorotatory enantiomer of ormeloxifene [92-94].

Zindoxifene is a non-steroidal SERM which discovered in 1984 for the treatment of breast cancer but never marketed. It exposes antagonistic effect in preclinical trials but failed during clinical trials for treating breast cancer. Bazedoxifene an active SERM moiety was derived from the major active metabolite of zindoxifene [95-98].

Cyclofenil is first introduced in 1970 in France then announced in Japan, UK, Germany and Italy, Turkey *etc*. It is selective estrogen receptor modulator used as gonadotropin stimulant has been marketed in Europe, South Korea, Brazil and Mexico. In 1970 it had developed for the treatment of induced ovulation in sub-fertile, infertile women and further investigated for the treatment of scleroderma in 1980 but found inactive in both cases [99-101].

Miproxifene is non-steroidal selective estrogen receptor modulator which is derivative of afimoxifene in which 4-isopropyl group exists in the β-phenyl ring. It is 3-10 fold more active than tamoxifen for preventing breast cancer cell growth in *in vitro* studies. Miproxifene is active metabolite of miproxifene phosphate (TAT-59) a phosphate ester and pro-drug of miproxifene that has developed to improve its solubility in water. Its phosphate derivative studied in Japan for the treatment of breast cancer but discontinued before reaching phase III clinical trials and never marketed [102-105].

Enclomifene is a non-steroidal SERM which still under development treating male hypogondism. It is in pre-registration phase of development under reviewed by Food and Drug Administration (FDA) in US and European medicines agency (EMA) in the European Union. A committee of EMA declined for the marketing authorization of emclomifene for the treatment of secondary hypogoniodism in 2018. It is E-stereo-isomer of clomifene, which acts as antagonist on ER present pituitary gland. Functionally, enclomifene is more promising than clomifene as a progonadotropin for treating of male hypogonadism [23,106-108].

Elacestrant is a mixture of non-steroidal SERM and SERD. It has developed for treating menopausal vasomotor, endometrial cancer, breast cancer and kidney cancer. Its phase II clincical trial for treating vasomotor symptoms and breast cancer has been done in 2016. Now it is under development, it has dose dependent, tissue selective estrogenic and antiestrogenic activity [109-111].

Etacstil is also non-steroidal drug molecule which was combination of SERM and SERD for treating breast cancer. It has developed in early 1990s by Duke University, Glaxo Wellcome and later in 2001 developed by Dupont due to non-scientific corporate reason it has discontinued and so many years its modified form(structural analogue) generated which has known as brilanestrant [112-114].

Brilanestrant is combination of SERM and SERD (selective estrogen receptor modulator & selective estrogen receptor degrader) discovered for the treatment of breast cancer. It has discontinued in 2017 before reached phase II clinical trials because of some side effects such as diarrhea, nausea and fatigue mild to moderate severely. It is structural analogue of Etacstil [115,116].

Panomifene is non-steroidal SERM of triphenylethylene group. It has discovered in 1981 and developed as an antineoplastic agent discontinued before phase II clinical trials in 1990 [59,117,118].

Advantages and disadvantages of selective estrogen receptor modulators

Advantages: Postmenopausal women need an alternate of estrogen in hormone replacement therapy. Selective estrogen receptor modulators drugs act as partial estrogen receptors agonists for maintaining bone density for applications in osteoporosis treatment and at the same time act as estrogen receptor antagonists in breast tissues for applications in breast cancer prevention in women, along with effects on the uterus and vagina that depend on their interaction with the estrogen receptors in target tissues [119].

- SERMs are interacting with estrogen receptor α and β, their selective behaviour differentiate them from estradiol, these are used to prevent and cure osteoporosis because of their agonistic activity these are capable to develop BMD (bone mineral density) and prevent bone loss and decrease the incidences of fractures.
- These are also effective to prevent and cure cardiovascular disease because of capability to inhibit biosynthesis of cholesterol and able to reduce the label serum fibrinogen and serum cholesterol [primarily LDL-C (low density lipoprotein cholesterol)]. These are able to reduce aortic lipid amassing and carotid initial thickness in case of injury, inhibit lipid peroxidation, reduce membrane fluids and progress of coronary artery atherosclerosis.
- Due to their selective interaction with estrogen receptors these are also used to prevent and cure estrogen dependent cancers, few members of this class are successfully used as antibreast cancer, endometrial cancer and uterine cancer.
- These are expressed progress in cognitive function of brain and palliation and create probability to Alzhimer's disease and postmenopausal depression.

Disadvantages: Clinical usage of SERM medications can have several side effects. The previously mentioned estrogen receptor modulators, especially tamoxifen and toremifene, have been the preferred first-line hormonal therapy for estrogen-responsive postmenopausal breast cancer, but they have several disadvantages related to their partial estrogenic agonistic activity. These limitations stimulated the search for pure estrogen receptor antagonists [120,121].

- Representative side effects of raloxifene include hot flashes.
- Leg cramps are another side effect of SERM treatment.
- Higher frequency and extent of menopausal symptoms, including hot flashes and atrophic vaginitis, are the most commonly observed side effects.
- Raloxifene use has also been linked to rare, but serious side effects, such as venous thromboembolism, including deep vein thrombosis (DVT).
- SERMs also cause pulmonary embolism (PE).
- Retinal vein thrombosis is the problem with estrogen disorder treatments.
- Retinopathy has also been observed among women who use high-dose tamoxifen, but a less extensive retinal change can occur from time to time in cases of normal dose usage.
- Use of tamoxifen has also been linked to a higher occurrence of cataracts.
- The side effects include tumor stimulation in some patients at the initial stages of treatment and increased endometrial cancer.

Conclusion

This paper has demonstrated the discovery development and function of selective estrogen receptor modulators which

lie under the different stages of medical availability and can be better substitutes of estrogen for treating estrogen hormone dependent multiple issues generated in the different phase of life in female and male both. Clearly, this class of compounds shows promise for the treatment and prevention of a number of pathologies associated with estrogens, by which novel estrogen pharmaceuticals can be developed as tissue-selective drug in the new millennium.

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