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Importance of Selective Estrogen Receptor Modulators as Potential Multiple Therapeutic Agents

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Research Article

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ABSTRACT

Selective estrogen receptor modulators (SERMs) are a group of drugs with diverse structural chemical characteristics that are characterized as high-affinity ligandsto estrogenic receptors (ERs) but have the peculiarity of triggering estrogen-agonist or estrogen-antagonist actions, depending on the tissue in which they act. From a pharmacological perspective, SERMs should be segregated from pure antiestrogens, such as fulvestrant. Which are molecules chemically related to estradiol and exclusively exhibit estrogenic antagonist activity. SERMs also should be distinguished from the so-called “gonad mimetic” drugs, such as tibolone, that act by means of non-selective binding to different types of sex steroid receptors. A number of novel groups of synthetic compounds called Selective Estrogen Receptor Modulators (SERMs) have been discovered and are currently in use or under various stages of clinical evaluation, while several new compounds continue to appear in the patent literature. Although published clinical trial data are limited, these novel compounds are being evaluated for the prevention and treatment of hormone-responsive cancer, for prevention and treatment of post-menopausal osteoporosis and for prevention of cardiovascular disease and other estrogen deficiency-related indications.

INTRODUCTION

Control of gene expression by intracellular receptors (IRs) is regulated by small molecule naturally occurring hormones. The ability of certain small molecules to mimic (agonism) or inhibit (antagonism) effects of natural hormones provides as opportunity to influence cell growth, cell differentiation, and other cellular process. IRs, including sex steroid receptors (mainly estrogen) are therefore attractive targets for drug discovery.

The development of new pharmaceuticals as well as other biologically active compounds has historically relied on serendipitous discoveries. Once a "lead compound" has been successfully identified, large numbers of structural analogs are generally synthesized and then evaluated in numerous *in vitro* and *in vivo* models, with the goal of designing the ideal drug.

The development of compounds that can counteract the biological effects of estrogens has drawn a lot of attention over the last several decades. Such compounds, termed as estrogen antagonists industries as well as in academic research groups as potential therapeutic agents [1-3].

In the classical approach to be discovery of novel estrogen antagonists, a partnership between synthetic organic chemistry and *in-vivo* screening for biological activity has provided a wide variety of both steriodal as well as non-steroidal molecules with 'hormonal activity. While the pursuit of such compounds with such activity was initially prompted by the search for effective contraceptive agents for the human female, interest was refocused on these compounds because of their potential for controlling the growth of estrogen dependent neoplasm particularly tumors of the breast. Interestingly however, recent global studies all over has revealed that be scope for such compounds is confined not only to the primary and secondary reproductive tissue but also to various other parts of body such as skeletal, central nervous, cardiovascular and immune systems etc., further widening

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the scope of their therapeutically application in the privation and treatment of various disorders related to estrogen. A number of non-steroidal estrogen agonist/ antagonists are being evolved as drug for the prevention and treatment of osteoporosis in past-menopausal women several patents have been published claiming their use in various pathological conditions such as atherosclerosis, coronary artery diseases, Alzheimer's disease, hyperlipidemia, immune gynecological and dermatological disorders, uterine fibrosis, autoimmune diseases, post-menopausal depression, estrogen replacement therapy, endometriosis and premenopausal depression, estrogen replacement therapy, endometriosis and premenstrual and premenopausal syndromes etc. [4].

The subject of hormone antagonism at the cellular level has benefited from a great deal of research activity over a post few decades.

Classically, a hormone antagonist has been defined as a substance endogenous to be organism which in minute amounts capable of altering the rate of cellular process, attending or antagonizing to various degree, a hormone induced response, regardless of their mechanism or site of action innate to the target tissues. The unusual properties exhibited by some non-steroidal estrogen antagonist as tissue selective or target site-specific agents has aroused considerable research interest. While the 7α-substituted estradiol derivatives such as ICI-182790, ICI 164,385 etc. have been classified as 'pure' estrogen antagonists, most non-steroidal analogues such as triarylethylenes (TAES e.g., Tamoxifine 1,2 triarylpropenones (2-TAPs, e.g., trioxitene), benzopyrans, chromenes and chromans, etc. are also reported to be associated with some agonist character and exhibited mixed agonist-antagonist biological profile to varying degree [5].

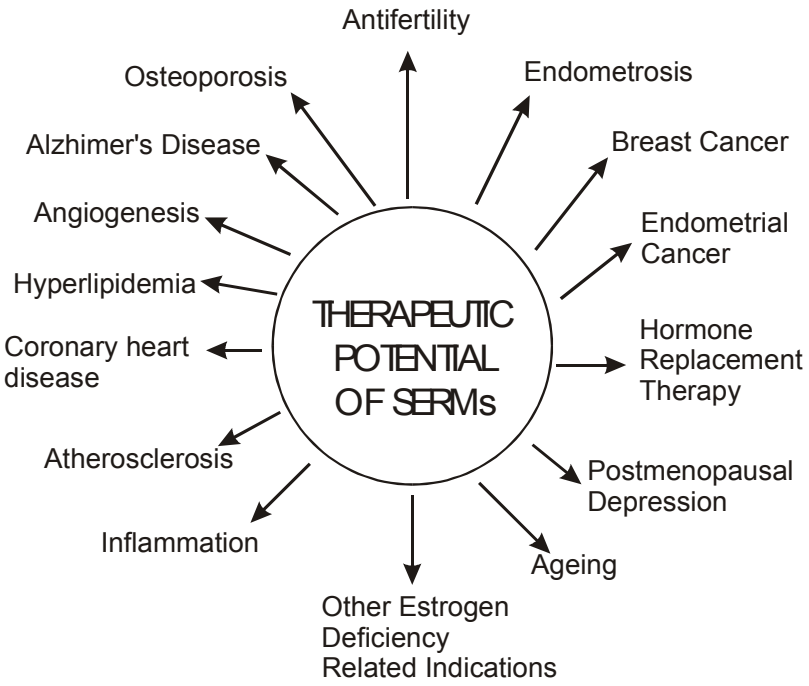

Figure 1. The concept of estrogen receptor modulation: Development of Selective Estrogen Receptor Modulators (SERMs).

Given the multiple potential target tissues and varying degree of physiological responses shown by the estrogenic ligands, the current approach in the development of tissue-selective drugs has necessitated the development of novel ligands that may confer tissue selective effects showing advantages of estrogen on non-traditional target tissues while mitigating some of disadvantages, particularly concerns over estrogen positive cancers. This had led to emergence of structurally diverse novel compounds that bind to estrogen receptors (ER) showing pronounced subtype (ER_αor ER_β) selective differences in binding affinity and transcriptional efficacy and elicit agonist or antagonist responses depending on the target tissue and hormonal milleu [6]. Such compounds on the target tissue and hormonal miller. Such compounds, which are capable to modulate the activity of estrogen receptor in cell-selective manner, tamed as selective estrogen receptor modulators (SERMs) are thus the archetype for a rich category of drug therapy based on single molecular target [7]. The SERMs are able to mimic the effects of estrogen in skeletal, cardiovascular and central nervous systems (agonist effect), yet produce almost complete antagonism in the breast and uterus **(Figure 1; Table 1)**. On the basis of the ability of a compound to exhibit agonist-antagonist response on a cell-selective manner the compounds may be classified as following:

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Table 1. Classification of estrogen receptor modulators.

Classification	Genitourinary and reproductive tissue	Skeletal, cardiovascular and central nervous system	Examples
Agonists	Yes	Yes	Di-ethyl stilbestrol, hexasterol
Partial agonist/ antagonists	Yes/No	Yes	Tamoxifen, Clomiphene
SERMs	No	Yes	Raloxifen, CP-336156
Antagonists	No	No	ICI-182, 790 ICI-164, 385

SALIENT FEATURES OF SERMs

1. They can be used in the prevention and treatment of Osteoporosis [8] as they have been shown to cause -

a) Substantial increase in bone mineral density (BMD).

b) Prevention of bone loss and decreases in fracture incidences.

2. Through their agonists effects they can also be used in the prevention and treatment of the cardiovascular diseases [9] as they have shown following effects -

a) Inhibit biosynthesis of cholesteron.

b) Reduce serum fibrogen and serum cholesterol [primarily low density lipoprotein - cholesterol (LDL-C)].

c) Reduce aortic lipid accumulation and carotid initial thickness in case of injury.

d) Inhibit lipid peroxidation and decreases membrane fluidity.

e) Inhibit progression of coronary artery atherosclerosis.

3. Through their antagonistic properties they can be used prevention and treatment of estrogen responsive cancers [10] and they have shown following properties.

a) Anti-breast cancer properties.

b) Antagonistic effect at uterus showing no stimulation of endometrial hyperplasia.

c) Reduction in the risk of lever carcinogenesis.

4. They have been shown to improve cognitive function of brain and palliation of Alzhimer's disease and postmenopausal depression [11] through agonist effect.

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.

CONCLUSION

The main pharmacodynamic characteristics of the SERMs that are currently available reflect their antineoplastic activity in estrogen-dependent breast cancer (tamoxifen and toremifene) and the beneficial effects on bone remodeling, bone mineral density, and reduction of osteoporotic fractures in postmenopausal women observed with raloxifene [12]. However, one major consequence of the Women's Health Initiative findings has been an increased interest in the full therapeutic potential of SERMs – still to be explored – because of their potential to retain some of the beneficial effects of estrogen while avoiding most of its adverse effects [13]. Given the extraordinary complexity of the different diseases that SERMs can impact, this exploration is contemplated as a major, long-term, costly task [14]. In this respect, clinical trials that are close to being finalized with raloxifene will clarify within the next few years the potential role of this SERM in primary prevention of breast cancer and cardiovascular disease in postmenopausal women [15]. Likewise, the encouraging preliminary results on new SERMs such as lasofoxifene, bazedoxifene, arzoxifene, ospemifene, etc. are still to be confirmed in large-scale clinical trials currently under way. With regard to our current knowledge of these drugs, it is tempting to speculate on the ideal pharmacological characteristics of a selective estrogen receptor modulator.

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REFERENCES

1. Hajela K, et al. Non-Steroidal Estrogen Antagonists; Present status and Future perspectives. Curr Med Chem Immunol Endocrinol Metabolic Agents 2001;1:235-256.
2. Pandey J. Significance of Synthetic SERMs in Women's Health. Editorial-Organic Chem Curr Res 2013;2:2.
3. Pandey J and Avidha K. Raloxifene: An Effective Selective Estrogen Receptor Modulator. Ecronicon Chemistry Journal 2015;2:92-96.
4. Jordan VC. The strategic use of antiestrogens to control the development and growth of breast cancer. Cancer 1992;70:977-982.
5. Jordan VC. Designer estrogens. Scientific American 1998;279:60-67.
6. Gustafsson JA. Therapeutic potential of selective estrogen receptor modulators. Curr Opin Chem Biol 1998;2:508-511.
7. Wakeling AE. Similarities and distinctions in the mode of action of different classes of antioestrogens. Endocrine-Related Cancer 2000;7:17-28.
8. Webb P, et al. Tamoxifen activation of the estrogen receptor/AP-1 pathway: potential origin for the cell-specific estrogen-like effects of antiestrogens. Mol Endocrinol 1995;9:443–456.
9. Webb P, et al. The estrogen receptor enhances AP-1 activity by two Distinct mechanisms with different requirements for receptor transactivation functions. Mol Endocrinol 1999;13:1672-1685.
10. Paech K, et al. Differential ligand activation of estrogen receptors ER alpha and ER beta at AP1 sites. Science 1997;277:1508–1510.
11. Montano MM and Katzenellenbogen BS. Identification of a novel cis-acting element in the promoter of an estrogen-responsive gene that modulates sensitivity to hormone and antihormone. Proc Natl Acad Sci USA 1997;94:2581–2585.
12. Hajela K, et al. Resolution, Molecular Structure and Biological Activities of the d- & l- enantiomers of potent anti-implatation agent, dl-2[2-piperidinoethoxy] phenyl-3-2H-1benzopyran. Bioorg Med Chem 1999;7:2083-2090.
13. Pandey J, et al. Synthesis of 2,4-dinitrophenylhydrazone derivatives of subs.1,2-diphenyl enthanones as possible anti-estrogenic and antibreast cancer agents. K Arzneimittel-Forsch 2002;52;39-44.
14. Pandey J, et al. Studies on the Synthesis and Biological Efficacy of Some New 6H-Dibenzo [b,d] pyran-6-one and 6,6-dimethyl dibenzopyrans as Estrogen Antagonists/Modulators. Bioorg Med Chem 2004;12:2239-2242.
15. Pandey J and Hajela K. Synthesis and biological activities of some substituted 6H-dibenzo [b,d] pyran-6-one and 6,6-dimethyl 6H-dibenzo [b,d] pyran derivatives. Global J Sci Front Res B Chemistry 2014;1:13-24.