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 steriodial 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
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 triarylethlenes (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$_α$ or ER$_β$) selective differences in binding affinity and transcriptional efficacy and elicit agonist or antagonist responses depending on the target tissue and hormonal milieu (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:
Table 1. Classification of estrogen receptor modulators.

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

**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 Alzheimer’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


