Other selective oestrogen receptor modulators (SERMs) in development

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Chemical modifications of the synthetic stilbene nucleus of diethylstilboestrol led to the non-toxic triphenylethylene, tamoxifen. This compound was developed in the 1960s and used in clinical practice in the early 1970s to inhibit oestrogen's proliferative actions on breast cancer. Surprisingly for an anti-oestrogen, tamoxifen behaves as an oestrogen-like compound in the skeleton, cardiovascular system and uterus explaining its profile as a selective oestrogen receptor modulator (SERMs). The beneficial effects of SERMs on breast, bone and serum cholesterol have stimulated the pharmaceutical industry to invest in other synthetic compounds that, with a high-affinity, interact with the oestrogen receptor (ER) leading to a similar or even better effect as tamoxifen without its uterine side-effects.

The requirement for a SERM is that it displays a good fit into the nuclear ER-space and that its minimised structure overlaps well with oestrogens. SERMs induce conformational changes in the ER sufficient to enable interactions with target gene DNA. It is the degree of conformational change, the subsequent presentation of the transcription activation function within the ligand-ER complex to the transcription apparatus and the cell type that determines the tissue selectivity of each SERM [1,2]. Any modification of the core structure of each compound may have powerful effects on the efficacy and tissue selectivity of the compound. Presumably, different conformational states of the ligand-ER complex are also likely to exist. Most such drugs under development have indications for postmenopausal breast cancer and osteoporosis, treatment and prevention. Synthetic non-steroidal SERMs which have as such been tested or are still in development include a wide variety of structural families, among others, triphenylethylenes like tamoxifen (toremifene, droloxifene, idoxifene, GW 5638), benzothiophenes (raloxifene, SERMIII — LY 353381), naphtalenes (nafoxidine, trioxifene, lasofoxifene-CP 336,156), benzopyran (chromans-levormeloxifene, SCH 57050) and indoles (zindoxifene).

The current state of the art regarding toremifene, idoxifene, raloxifene and SERMIII or LY 353381 has been covered in the previous chapters. Some of these compounds have similar effects in the endometrium as tamoxifen, have no breast cancer advantage over tamoxifen or have other unacceptable side-effects and are, therefore, no longer in clinical study (nafoxidene, trioxifene, zindoxifene, levormeloxifene). Nafoxidene and trioxifene have been tested in phase I and II breast cancer trials with similar objective results as tamoxifen but an unacceptable side-effect profile. Zindoxifene, a member of the indole derivatives, demonstrated only a marginal therapeutic activity in advanced breast cancer with a strong oestrogenic activity leading to an increase in sex hormone-binding globulin (SHBG) levels; it induced nausea which was a dose-limiting side-effect. In connection with long-term use of levormeloxifene (and others), an increased endometrial thickness, urinary incontinence and utero-vaginal prolapse has been reported [3]. Droloxifene, with its 20–60-fold higher affinity for the ER, its advantage over tamoxifen in preclinical breast and uterine studies has been compared with tamoxifen in women with advanced breast cancer. These studies have been prematurely stopped because no advantage was observed of droloxifene over tamoxifen. At this moment, there are no data published on droloxifene's effect on the human endometrium and studies with droloxifene for osteoporosis are ongoing.

Other new compounds in development are GW 5638 (a triphenylethylene) and lasofoxifene or CP-336,156, already referred to as SERM IV [4,5]. Both appear, at least in the rat model, to have a markedly reduced uterotrophic effect while maintaining tamoxifen's beneficial activities on bone, lipids and breast. The nafoxidene derivative CP-336,156 was shown to have improved oral bioavailability with similar beneficial effects at lower dose levels. SCH 57050, a benzopyran, has potent anti-oestrogenic characteristics in MCF-7 human breast cancer cells and it also prevents the development of dimethylbenz(a)anthracene (DMBA)-induced mammary tumours. This compound inhibits the growth of the human Ishikawa endometrial cancer cell line while being beneficial in bone, reducing serum cholesterol and triglyceride levels. As assessed by their activity in the human Ishikawa endometrial carcinoma cells, the SCH 57050 compound is the most potent known anti-oestrogen and most importantly, devoid of the oestrogenic activity observed with SERMs such as tamoxifen, toremifene, droloxifene andraloxifene [6]. A

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combination of radiotherapy and this compound showed a cytotoxic effect in 87% of an ER-sensitive human breast tumour in nude mice. Clinical studies with these new compounds will help to elucidate if these preclinical effects translate to the desired efficacy in postmenopausal women. The clinical success of currently available SERMs like tamoxifen, toremifene and raloxifene has set the stage for a variety of drug therapies based on the selective modulation of nuclear receptor activity [7].

References

1. McDonnell DP, Clem DL, Hermann T, *et al*. Analysis of ER function *in vitro* reveals three distinct classes of antiestrogens. *Mol Endocrinol* 1995, **9**, 659–669.
2. Mitlak BH, Cohen FJ. Selective estrogen receptor modulators. A look ahead. *Drugs* 1999, **57**, 653–663.
3. Novo Nordisk discontinues osteoporosis development programme of levormeloxifene. *Stock Exchange Announcements* 1998, **20**, 1.
4. He HZ, Paralkar M, Grasser WA, *et al*. Effects of CP-336,156, a new nonsteroidal estrogen agonist/antagonist on bone, serum cholesterol, uterus, and body composition in rat models. *Endocrinology* 1998, **139**, 2068–2076.
5. Sato M, Grese TA, Dodge JA, *et al*. Emerging therapies for the prevention or treatment of postmenopausal osteoporosis. *J Med Chem* 1999, **42**, 1–24.
6. Simard J, Sanchez R, Poirier D, *et al*. Blockade of the stimulatory effect of estrogens, OH-tamoxifen, OH-toremifene, droloxifene and raloxifene on alkaline phasphatase activity by the antiestrogen EM-800 in human endometrial adenocarcinoma Ishikawa cells. *Cancer Res* 1997, **57**, 3494–3497.
7. Couillard S, Gutman M, Labrie F, *et al*. Effect of combined treatment with the pure antiestrogen EM-800 and radiotherapy on the growth of human ZR-75-1 breast cancer xenografts in nude mice. *Cancer Res* 1999, **59**, 4857–4863.

The oestrogen receptor and its selective modulators in gynaecological oncology

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Oestrogens are clearly implicated in the pathogenesis of breast cancer. These hormones are known as potent mammary mitogen substances and are the major stimulus for the growth of hormone-dependent tumours. Endocrine therapy is an active treatment option and in contrast to chemotherapy is effective through selective mechanisms.

1. Receptor and mechanism

Oestrogens and progestins show their cellular effects through the binding and activation of specific nuclear receptors, the oestrogen-receptor (ER) and the progesterone-receptor (PR). Since the original cloning of cDNAs for these receptors, substantial data in the field of steroid hormone action has been obtained.

Molecular studies have shown two different binding sites of the ER protein. At the amino end (TAF1) and at the carboxyl end (TAF2) of the molecule there are independent domains of transcriptional activity. Depending on the relative strength of TAF1 and TAF2 selective oestrogen receptor modulators (SERMs) act as an agonist or as an antagonist. They typically bind to the ER and activate it by forming receptor dimers. The SERM-ER complex binds itself to the DNA binding sites. There are significantly different tissue distributions of the ER leading to different effects of SERMS in different organs.

2. SERMs

SERMs are a new category of therapeutic agents, which bind with high affinity to ERs and mimic the effect of oestrogens in some tissues, but act as oestrogen antagonists in others.

2.1. Tamoxifen

Tamoxifen is a triphenylethylene derivative. As a potent anti-oestrogen compound it has shown its benefit in the adjuvant setting as well as in the treatment of advanced breast cancer. It has oestrogen-like activity on bone metabolism, as well as cholesterol reduction and a reduction in myocardial morbidity. Analysis after 5 years supports the maintenance of decreased low-density lipoprotein (LDL) and total cholesterol. Furthermore, tamoxifen lowers the risk of contralateral breast cancer by 36%. Tamoxifen has been implicated in the development of endometrial tumours in patients.

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