Recent Advances in Selective Estrogen Receptor Modulators for Breast Cancer

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Abstract: Estrogen has important physiological effects on the growth and function of hormone-dependent tissues, and the link between estrogen and breast cancer has been deciphered at the end of the 20th century. Tamoxifen, one of the first generation selective estrogen receptor modulators (SERMs), has been the gold standard of first-line therapeutic drugs for all stages of estrogen-dependent breast cancer and has been found to reduce the incidence of breast cancer in high-risk pre- and postmenopausal women. Raloxifene, a second-generation SERM, was recently approved by FDA to decrease the risk of invasive breast cancer in postmenopausal women. During these years, many other novel types of SERAMs are being studied. This review highlights their recent advances. The discovery of selective estrogen receptor alpha modulators (SERAMs) and the latest information about their clinical and preclinical trials will be introduced intensively.

Key Words: Estrogen, breast cancer, selective estrogen receptor modulators.

1. INTRODUCTION

Estrogen plays an essential role in reproductive endocrinology and it is also important for supporting physiologic homeostasis in a woman's body as evidenced by the progressive changes that occur at menopause when ovarian estrogen synthesis stops around the age of 50 [1]. In addition, estrogen preserves bone mineral density and reduces the risk for osteoporosis, protects the cardiovascular system by reducing cholesterol levels, and modulates cognitive function and behavior [2]. Estrogen exerts these physiological effects through estrogen receptors (ERs), which are around a woman's body: hypothalamopituitary axis, liver, bones, vagina, uterus, ovary and breast [3].

The link between estrogen and breast cancer growth and development has been known for more than a century [4, 5]. Estrogen can stimulates the proliferation of breast epithelial cell, and both endogenous and exogenous estrogens have been implicated in the pathogenesis of breast cancer [6]. The finding of ERs in breast provided the rationale for the eventual development of antiestrogens as a safe and simple alternative to ablative surgery for the treatment of breast cancer.

Selective estrogen receptor modulators (SERMs) are structurally diverse compounds which have the potential to modulate selectivity of the different estrogen target tissues. SERMs, such as tamoxifen, have been used clinically for about 40 years, but the concept of SERMs emerged with the first published use of this term in 1994 [7]. The interaction between a SERM and the ER allows a selective response in a given tissue. In other words, SERMs induce "estrogen agonistic" activities in some tissues such as bones and vagin, and "estrogen antagonistic" activities in others such as uterus and breast. The definition of SERMs has been further modified, as the recent research data show that each SERM may have a unique functional response by interacting with the ER [8]. The molecular basis for this tissue-selective activity is not completely understood. Without being limited to any particular theory, the ability of the ligand to place the estrogen receptor into different conformational states and allowing for differential capabilities in recruiting coactivator and corepressor proteins, as well as other important proteins involved in transcriptional regulation, is believed to play a role.

Tamoxifen, the first FDA-approved non-steroidal SERM, is considered the gold standard for first-line treatment of all stages of breast cancer and for the reduction of breast cancer incidence in high-risk pre- and postmenopausal women [9]. Currently, five years of adjuvant tamoxifen is recommended to be optimal, since extending treatment beyond five years provides no further improvement [10, 11]. But a long-term tamoxifen application would increase the risk of endometrial cancer, although the risk has been perceived to be small in relation to the substantial benefit from reduction in breast cancer related events [12].

Raloxifene, one of the second generation SERMs, was approved by FDA in the December 1997 to prevent osteoporosis. Several large phase III trials, including the Multiple Outcomes of Raloxifene Evaluation (MORE) [13-15], Continuing Outcomes Relevant to Evista (CORE) [16, 17], and Raloxifene Use for the Heart (RUTH) [18], have shown practical and promising results. In addition, the Study of Tamoxifen and Raloxifene (STAR) [19, 20] trial further confirmed the efficacy of raloxifene in preventing breast cancer and showed it to be similar to tamoxifen. In these trials, raloxifene not only decreased the incidence of osteoporosis-associated complications, but also offered benefits for breast cancer prevention with a dramatic decrease in the incidence

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of all breast cancers. Raloxifene has been approved to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.

During recent years, many other novel types of SERMs have been designed and synthesized, and some of these SERMs are in clinical trials. This review highlights the research progress of SERMs, the structure-activity relationships (SARs) of different types of SERMs in up-to-date literatures.

2. ESTROGEN RECEPTORS AND THE BINDING MODE INVESTIGATIONS OF SERMS WITH ERS

2.1. ERs Subtypes and their Molecular Basis

The biological effects of estrogen are now known to be mediated by two ERs referred to as ERα and ERβ. As members of the nuclear receptor super-family, human ERα and ERβ are modular proteins sharing common regions (A-F) (Fig. **1**).

The A/B region of ERs, involved in protein-protein interactions and in transcriptional activation of target-gene expression, contains the activation function-1 (AF-1) domain and several phosphorylation sites. It is generally presumed that the AF-1 domain binds, directly or *via* coactivators/corepressors, to some parts of the primary transcription machinery. Moreover, the DNA binding domain (DBD) as well as the ligand binding domain (LBD) geometry may affect the functional state of the AF-1 domain. When the AF-1 domain is combined with the DBD, even in the absence of the LBD, it can act constitutively to activate transcription from genes containing the proper response element in the promoter. So the AF-1 domain is originally believed to be ligand-independent [3, 21]. The C-terminal E/F region of ERs encompasses the LBD, the AF-2 domain, and part of the nuclear localization region. The E/F region is also involved in the binding of chaperone proteins, such as heat shock protein (Hsp) 70 and 90. The LBD is folded into a three-layered anti-parallel α-helical sandwich comprising a central core layer of three α-helices (H5-6, H9, and H10) sandwiched between two additional layers of α-helices (H1-4, H7, H8, and H11). This helical arrangement creates a "wedge-shaped" molecular scaffold that maintains a sizeable ligand-binding cavity at the narrower end of the domain. The remaining secondary structural elements, a small two-stranded anti-parallel β-sheet (S1 and S2) and H12 are located at this ligand-binding portion of the molecule and flank the main three-layered motif [3, 22] (Fig. **2**). The C-terminal α-helix of ER LBD contains the sequence critical to the AF-2 transcription activating function, since it affects the LBD surface upon which much coactivator/corepressor binding depends in a ligand-dependent manner [23].

Human ERα and ERβ have two large highly conserved domains: the DBD and the LBD sharing 96% and 60% amino acids identities respectively, whereas the A/B region and F region are not well conserved [24] (Fig. **1**).

The A/B regions of ERβ and ERα are poorly conserved (about 20%). The AF-1 domains of ERα and ERβ are different in both length and amino acid sequence, suggesting that their AF-1 activities might be different and possibly that different coactivators interact with this region [25]. The AF-1 domain in ERα is very active in the stimulation of reporter-gene expression from a variety of estrogen response element (ERE)-reporter constructs in different cell lines, while the AF-1 of ERβ is negligible.

The LBDs of ERα and ERβ have very similar 3D structures, only two positions are different: Leu384/Met421 in ERα correspond to Met336/Ile373 in ERβ. Furthermore, the ligand-binding cavity of ERβ is significantly smaller (~20%) than that of ERα and this may have implications for the selective affinity and pharmacology of ligands [24].

Several types of splice variants of ERβ have been reported to date. Among them, ERβcx (also called ERβ2) is an important target in breast cancer biology. ERβcx is identical to wild-type ERβ in exons1-7, but exon8 is replaced by 26 unique amino acid residues [26] (Fig. **1**). Because of the difference in the last exon, ERβcx lacks the amino acid residues important for ligand binding and those that constitute the core of the AF-2 domain. Therefore, ERβcx does not bind estradiol and lacks the ability to activate transcription of an estrogen sensitive reporter gene. Moreover, ERβcx prefers to heterodimerize with ERα rather than with ERβ, inhibiting ERα DNA binding. Functionally, the heterodimeriza-

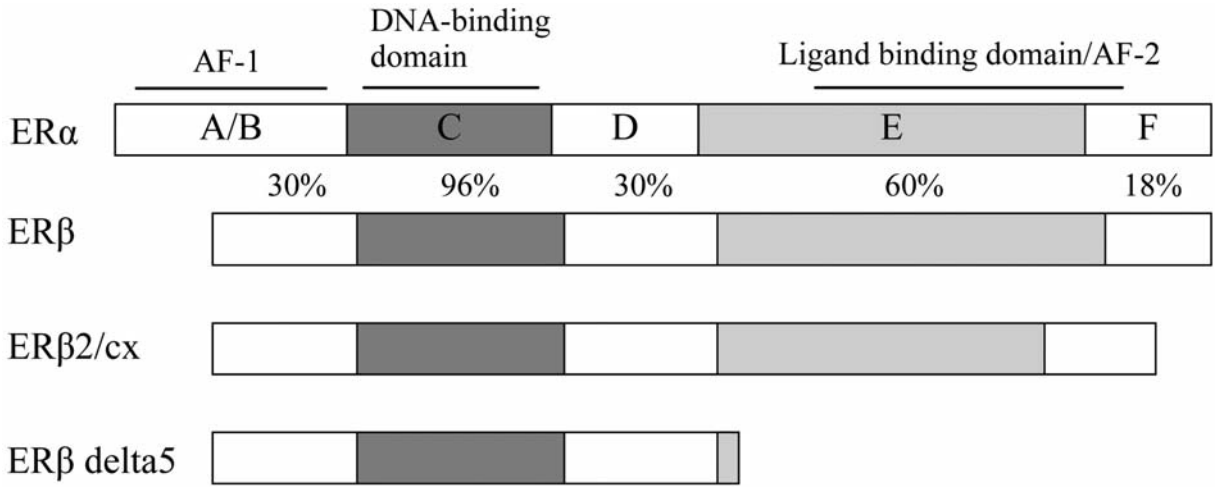


Fig. (1). Structures of hERα, hERβ and splice variants of ERβ.

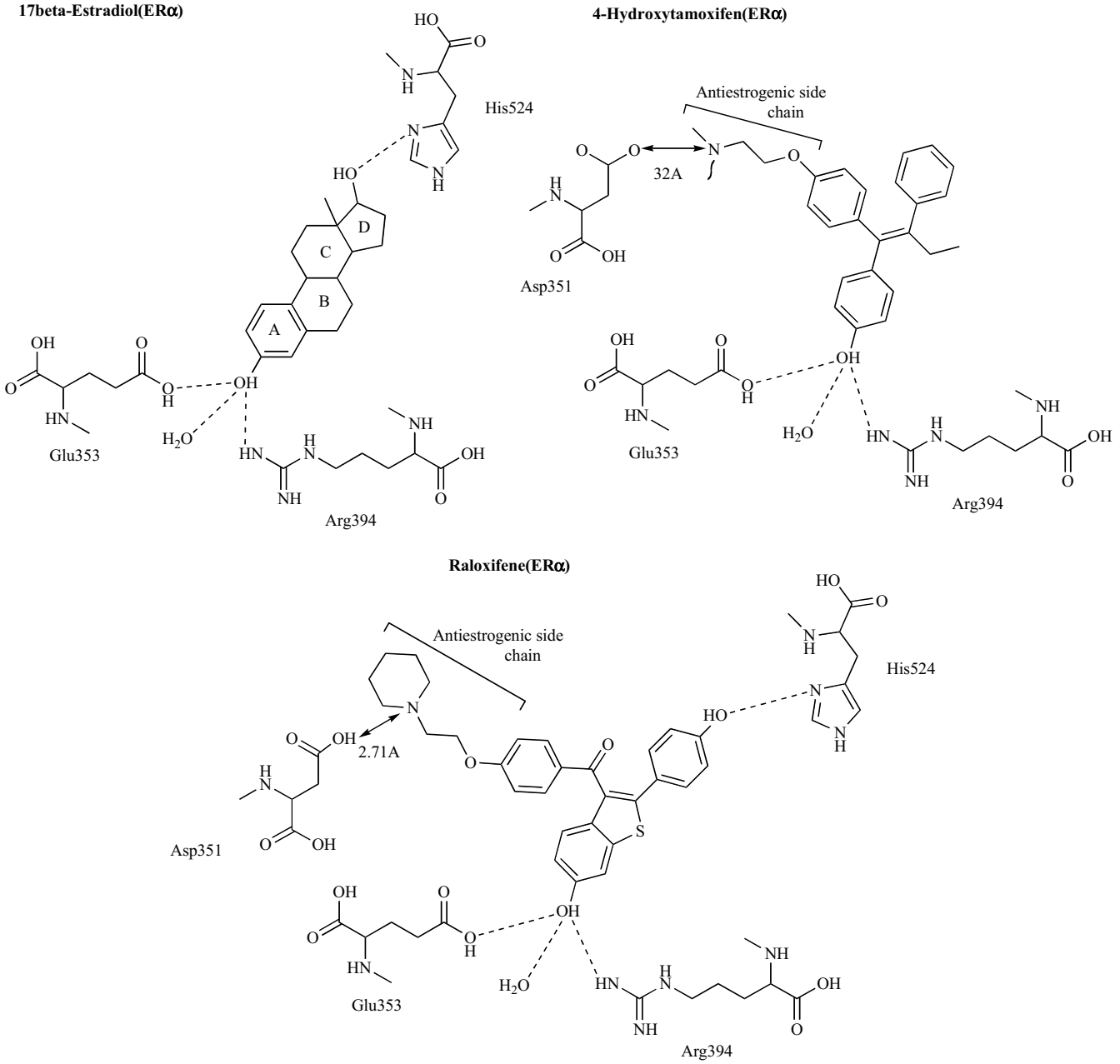


Fig. (2). Binding of estradiol, 4-hydroxytamoxifen and raloxifene in the hydrophobic pocket of the E region of human ERα.

tion of ERβcx with ERα has a dominant negative effect on the ligand-dependent transactivation function of ERα [26].

2.2. ERα and ERβ in ER Signaling

In classical ER signaling, estradiol binding to ER leads to the loss of the heat shock proteins, dimerization, phosphorylation of receptors, and conformational change of ER-estradiol complex. Then ER-estradiol complex binds to ERE in the regulatory regions of target genes, and activated AF-1 and AF-2 recruit coactivators of estrogen-regulated transcription, and ultimately stimulate the gene transcription. AF-1 is activated by growth factors acting through the mitogen-activated protein kinase (MAPK) pathway, while AF-2 is activated y estradiol. Full transcriptional activity required both AFs to be active [27].

For several years it was thought that the only mechanism through which estrogens affected transcription of E2-sensitive genes was by direct binding of activated ER to ERE. And now it is established that ERα and ERβ can also modulate the expression of genes without directly binding to DNA. One example is the interaction between ERα and the c-rel subunit of the NF-kB complex.

Another example of indirect action on DNA is the interaction of ERα with the stimulating protein 1 (SP1) transcription factor. Furthermore, ERs can interact with the fos/jun

transcription factor complex on activator protein1 (AP-1) sites to stimulate gene expression.

2.3. The Binding Mode Investigations

Estradiol, tamoxifen and raloxifene have been well investigated. Their binding modes with ERα will help us to understand the binding modes of SERMs and to develop new types of SERMs.

In the ERα-estradiol complex, H12 sits snugly over the ligand binding cavity and is packed against H3, H5-6, and H11. Although, H12 makes no direct contact with estradiol, it forms the lid of the binding cavity and projects its inner hydrophobic surface towards the bound hormone. The H12 charged surface is directed away from the body of the LBD on the side of the molecule lying perpendicular to the dimerization interface. This positioning of H12 seems to be a prerequisite for transcriptional activation as it generates a competent AF-2 region that is capable of interacting with coactivators.

However, the side chain, which is critical for antiestrogenic activity, interacts with Asp351 in the case of raloxifene and 4-hydroxytamoxifen. It is established that the charge distribution around Asp351 is part of the "antiestrogenic region" and the bulky side chain prevents the sealing of the ligand binding domain by helix 12. Accordingly prevent binding the coactivators to the complex and leading to inactivation of AF-2, which is critical of gene expression.

Comparing the crystal structure of the ERα with estradiol, 4-hydroxytamoxifen and raloxifene, we can find that the phenolic group interacts with Glu353 and Arg394 by a hydrogen bond to locate the ligand correctly in the binding domain, which the phenolic ring of 4-hydroxytamoxifen or raloxifene functions as estradiol A-ring mimic (Fig. **2**).

3. RECENT PROGRESS OF DIFFERENT TYPES OF SERMS

SERMs have been the subject of extensive medicinal chemistry efforts all over the world. During recent years, different types of SERMs are emerging and in this section, these types of SERMs will be introduced and the SARs will also be discussed as guidance in the future development of novel SERMs.

3.1. The Reported SERMs in Clinical Trials

Arzoxifene (LY353381, Eli Lilly & Co) (Fig. **3**) is currently being evaluated as a breast cancer therapy in advanced

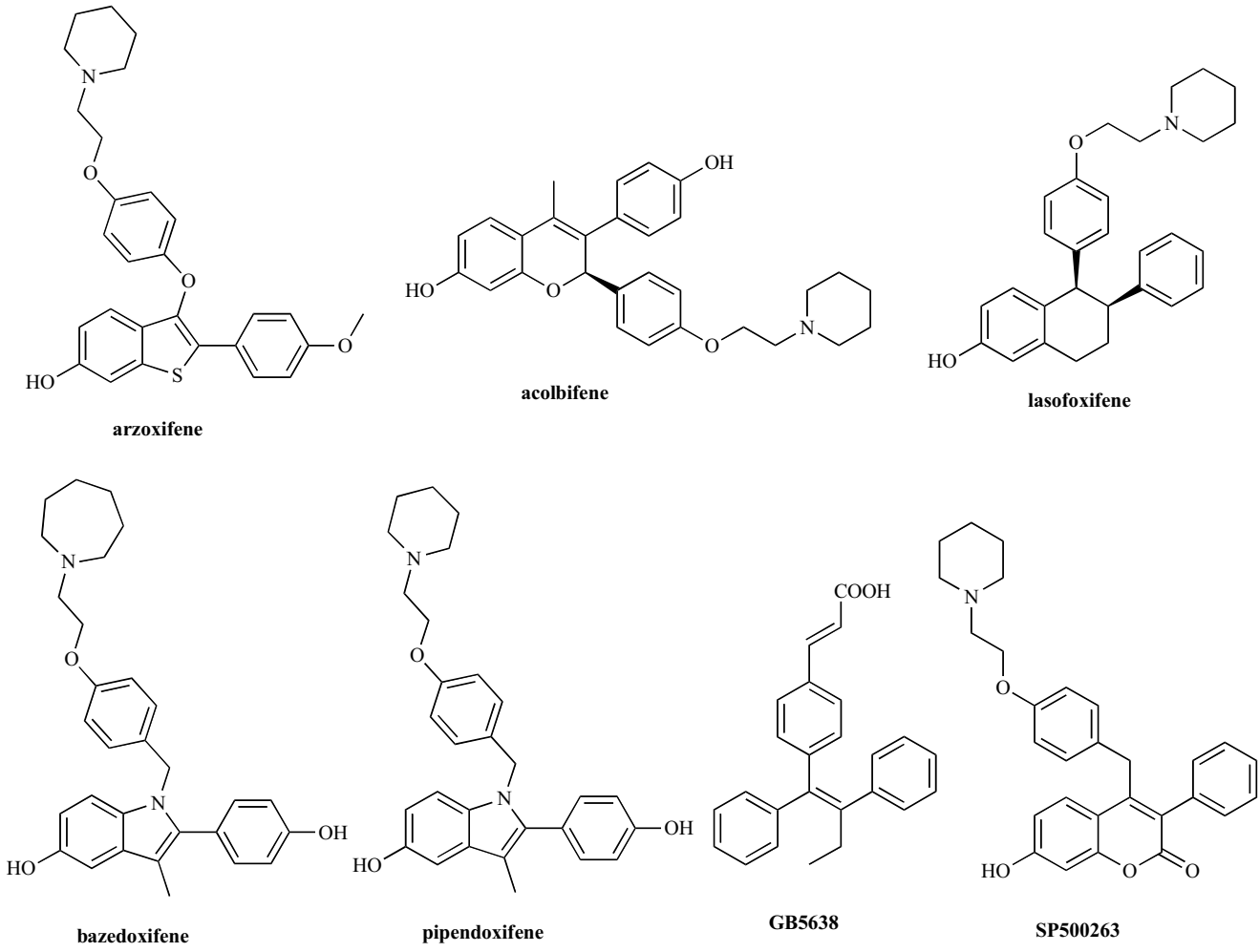


Fig. (3). The reported SERMs in clinical trials.

disease [28]. Replacement of the ketone group of raloxifene with an ether oxygen results in a 10-fold increase in anti-estrogen potency both *in vivo* and *in vitro* [29]. A methoxy substitution improved the bioavailability over Raloxifene [30].

Acolbifene (EM652, Universite Laval) (Fig. **3**), the active metabolite of EM800, is a potent SERM. It is orally active agents with virtually no uterotrophic activity. The early clinical studies, a small phase II study and a blinded, randomized phase III study indicated that EM800 has a promising results in breast cancer patients who had not responded to tamoxifen. Compared with the aromatase inhibitor anastrazole, anastrazole had substantially greater antitumor activity than EM-800, and the trial was terminated.

Pipendoxifene (ERA923, Wyeth) (Fig. **3**) is a potent SERM *in vivo* using mouse xenograft models [31] and is currently in phase Ⅱ clinical trials for the treatment of hormone-dependent breast cancer. Bazedoxifene (TSE4247, Wyeth), an analog of pipendoxifene, is effective at protecting bone loss and reducing total cholesterol in ovariectomized rats. It is being advanced to treat postmenopausal osteoporosis.

Lasofoxifene (CP336156, Pfizer) (Fig. **3**) has been reported to have high binding affinity for ERs and have potent activity in preserving bone density in the rat. A recent evaluation of lasofoxifene in the prevention and treatment of rat mammary tumors induced by N-nitroso-N-methylurea showed activity similar to that of tamoxifen [32].

GW5638 (GlaxoSmithKline) (Fig. **3**) is a tamoxifen analogue. It is currently being rigorously tested in new and established animal models of drug resistance to tamoxifen to establish a lack of cross-resistance to tamoxifen and low potential to enhance endometrial cancer growth. GW5638 is apparently non-cross-resistant with tamoxifen in the tamoxifen-stimulated MCF-7 model in athymic mice [33, 34].

SP500263 (Celgene Corporation) (Fig. **3**) is a potent benzopyranone SERM [35]. *In vitro*, SP500263 acted as an anti-estrogen and potently inhibited estrogen-dependent MCF-7 proliferation, and it also strongly inhibited MCF-7 proliferation in the absence of estrogen at all of the concentrations tested. *In vivo*, SP500263 was also as efficacious as tamoxifen and superior to raloxifene at the corresponding doses. Maximum efficacy was reached with the 30 mg/kg dose [36].

3.2. New Type of SERMs

3.2.1. Benzopyran

Galbiati *et al*. [37] have identified a new benzopyran derivative, CHF 4227 (Fig. **4**), with high affinity to the human ERα and ERβ with dissociation constant of 0.017 nM and 0.099 nM, respectively. The results of immature female rat assay showed that CHF 4227 administered orally before estrogen stimulus inhibited the uterotrophic action (ED_{50}= 0.016 mg/kg·day), while raloxifene was 25 times less potent as estrogen antagonist (ED_{50}=0.39 mg/kg·day).

3.2.2. Benzothiepin and Benzoxepin

Meegan *et al*. [38, 39] synthesized a series of novel benzothiepin and benzoxepin-derived compounds as potent SERMs. Among benzothiepin series, compound (**1**) (Fig. **4**) proved to be the most active compound with IC_{50} value of 18.5 nM in the MCF-7 breast cancer cell assay. And the 12-fold selectivity of compound (**1**) for ERβ was attributed to the presence of the F substituent at position 8 in aromatic ring of the molecular scaffold. Among benzoxepin series, compound (**2**) (Fig. **4**) had competitive ER binding and exhibited antiestrogenic potency through inhibition of proliferation of human MCF-7 breast cancer cells with IC_{50} value of 6.1 μM.

3.2.3. 5H-naphtho[1, 2-c]chromene

A novel series of highly potent SERMs based upon tetracyclic naphtha[1,2-c]chromene scaffolds were synthesized by Lilly laboratories [40]. Among these, LY357489 (Fig. **4**) showed potent antiestrogen activity with IC_{50} value of 0.4 nM in the MCF-7 breast cancer cell assay.

Furthermore, LSN2120310 (Fig. **4**), an optically pure isomer, was synthesized [41], and it potently had competitive ERα and ERβ binding and exhibited antiestrogenic potency through inhibition of human MCF-7 breast cancer cells with IC_{50} value of 1.4 nM and Ishikawa human uterine cells with IC_{50} value of 5.3 nM.

3.2.4. Spiroindene System

From X-ray crystal studies of the active conformation of raloxifene and tamoxifen, we can conclude that the side chain orientation may play an important role. The side chain of raloxifene was orthogonally to the benzothiophene ring rather than coplanar [42, 43]. The carbonyl "hinge" between the side chain and the benzothiophene ring induced a molecular conformation that was significantly different from that of tamoxifen. This altered molecular conformation may induce an unique conformation of the ER-ligand complex [40]. This strategy has been used for synthesizing a spiroindene system. Several spiroindenes were prepared [44] and compound (**3**) (Fig. **4**), the analog which most closely resembles raloxifene, was found to be a balanced ER ligand with excellent affinity for both ERs with IC_{50} value of 1.0 nM for ERα and 1.8 nM for ERβ, respectively. Then the carbonyl groups were introduced into the five-membered ring of compound (**3**) (Fig. **4**) to generate compound (**4**) [45]. It showed a substantially weaker binding affinity than compound (**3**) with IC_{50} value of 170 nM for ERα and 220 nM for ERβ, respectively.

3.2.5. N-arylbenzophenanthridine

A novel series of N- arylbenzophenanthridines scaffolds based upon tetracyclic naphtha [1,2-c]chromene scaffolds were synthesized by Lilly laboratories. The nitrogen for carbon replacement could provide a similar side chain orientation without the introduction of chirality. Among these, compound (**5**) (Fig. **4**) showed potent antiestrogen activity with IC_{50} value of 1 nM in the MCF-7 breast cancer cell assay [46].

3.2.6. Quinoline

GSK laboratories [47] have employed a peptide profiling assay to identify potential SERMs from a quinoline template that demonstrate low stimulation of uterine cell proliferation. Compound (**6**) (Fig. **5**) showed high affinity for both ERα

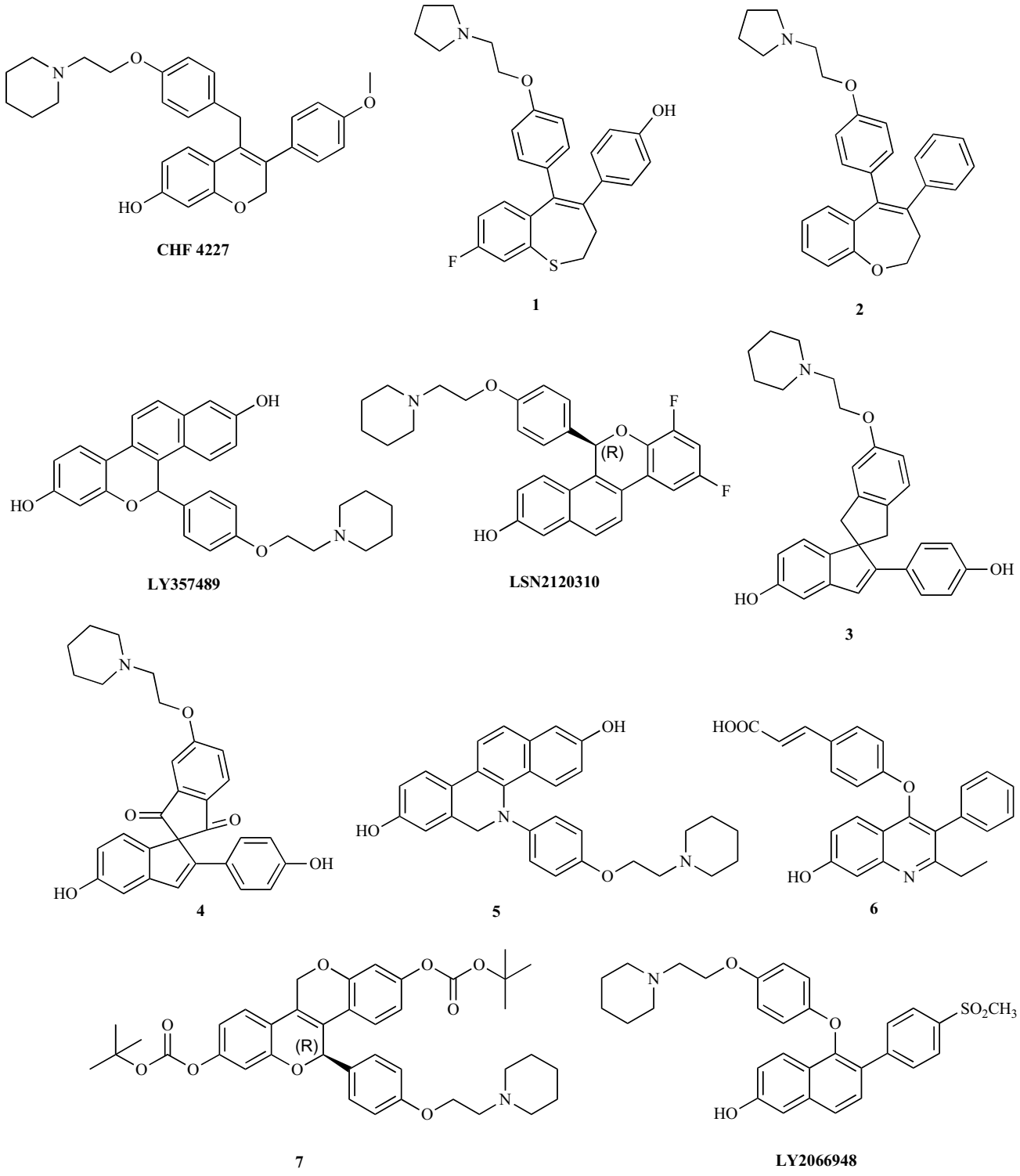


Fig. (4). Structures of new types of SERMs.

and ERβ without significant subtype selectivity and demonstrated the lowest induction of uterine cell activity.

3.2.7. Bisbenzopyran

A series of SERMs with bisbenzopyran as core structure was synthesized [48] and among these, compound (**7**) (Fig. **4**) possessed ideal SERM profile in animal studies. It not only exhibited estrogen agonistic effects on bone and lipid, and antagonistic effects on mammary glands and uterus, but also alleviated hot flushes and increased the amount of vaginal fluid.

3.2.8. Naphthalene

A novel series of SERMs based upon naphthalene scaffold were designed and synthesized [49]. Compound LY2066948 (Fig. **4**) showed high affinity to both ERs and

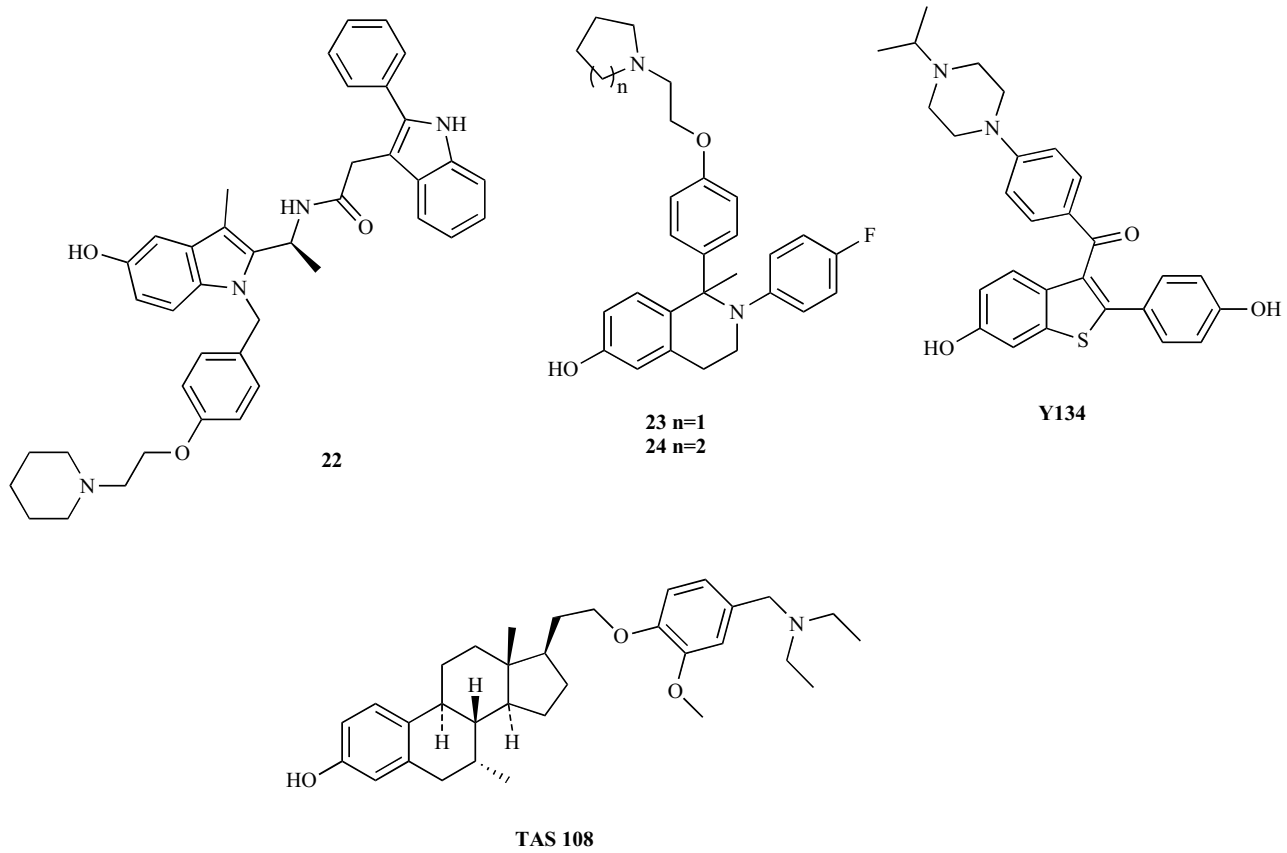


Fig. (5). Structures of some SERAMs.

was a potent inhibitor of MCF-7 breast cancer cell assay with IC_{50} of 0.86 nM. The effect on uterine tissue was assessed at the *in vitro* level in Ishikawa cells in the presence (antagonism) and absence (agonism) of estradiol. In the antagonist mode, LY2066948 (Fig. **4**) blocked the effects of 1nM estradiol by >90% with an IC_{50} of 10.7 nM. The agonist activity was significantly less than that of 4-hydroxytamoxifen. One interesting thing was that the methyl sulfone in LY2066948, replacing for the traditional hydroxyl group, also formed a hydrogen bond with His524 and thus represented a novel phenol mimic among ER ligands.

3.3 Selective Estrogen Receptor Alpha Modulators (SERAMs)

Merck laboratories have been engaged in the discovery of ERα selective antagonists since 1994, and have made a great breakthrough [50-62].

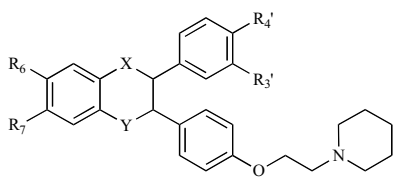
Initially, based on the four natural estrogen ligands: genistein, daidzein, coumestrol and WS-7528, researchers synthesized some flavanones as a mixture of cis and trans isomers [50]. Of these compounds, compound (**8**) (Table **1**) was the most active analog and was found to be 66-fold ERα selective. The cis-compound (**8**) (IC_{50}: ERα ~31 nM, ERβ ~2049 nM) and trans-compound (**8**) (IC_{50}: ERα ~49 nM, ERβ ~1947 nM) isomers had similar ligand binding affinities, but the cis isomer was clearly superior functional antagonist in a rat uterine weight gain assay. This phenomenon was also observed in other flavanones. Molecular modeling of compound (**8**) suggested that its ERα selectivity was due to an unfavorable interaction of the carbonyl oxygen with the Met354 residue of ERβ, which would be expected to be absent in ERα, where the corresponding residue is Leu384 [50].

A study of the SAR of the flavanone core was undertaken with the goal of improving binding affinity and *in vivo* potency. Several alternative platforms (see Table **1**), including dihydrobenzoxathiins (e.g. compound (**8-14**)) [51, 52, 63], dihydrobenzodithiins (e.g. compound (**15**)) [54], benzothiopyrans (e.g. compound (**16**)) [64] and isochromans/isothiochromans [59] were examined.

Then researchers were focused on the examination of various amine side chains. The compound (**17**) and the pyrrolidine analog, compound (**18**) (IC_{50}: ERα ~0.9 nM, ERβ ~37 nM), were superior to both the dimethyl piperidine analog and the morpholine analog. Compound (**18**) was selected for development as a treatment for osteoporosis based on its *in vitro* and *in vivo* activity and rat pharmacokinetic properties (F=40%, $t_{1/2}$=2.8 h).

Further study [57, 60] showed that methylation of both the pyrrolidine ring and the linker result in analogs with even better uterine activity. Compound (**19**) (IC_{50}: ERα ~1.3 nM, ERβ ~52 nM)and compound (**20**) (IC_{50}: ERα ~1.2 nM, ERβ ~69 nM)possessed potent uterine antagonists in the rat uterine weight gain assay and also exhibited high activity in an *in vitro* MCF-7 breast cancer cell activity.

Table 1



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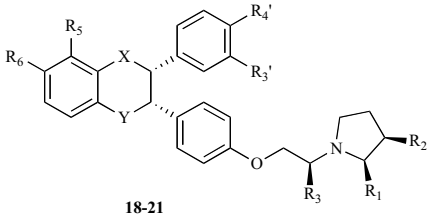

18-21

Compound[a]	2,3	X	Y	R_6	R_7	$R_{3'}$	$R_{4'}$	R_1	R_2	R_3	R_5	ERα[b] (nM)	ERβ[b] (nM)
8	cis	CO	O	H	OH	H	OH	-	-	-	-	31	2049
9	trans	CO	O	H	OH	H	OH	-	-	-	-	49	1947
10	cis	CH2	O	H	OH	H	OH	-	-	-	-	6.7	8.9
11	cis	S	O	H	OH	H	OH	-	-	-	-	1.6	45
12	cis	S	O	OH	H	H	OH	-	-	-		3.0	143
(+)-12	cis[d]	S	O	OH	H	H	OH	-	-	-	-	0.8	45
(−)-12	cis[f]	S	O	OH	H	H	OH	-	-	-	-	353	3876
13	cis	SO	O	OH	H	H	OH	-	-	-	-	>104	>104
14	cis	SO_2	O	OH	H	H	OH	-	-	-	-	1090	5950
15	cis	S	S	OH	H	H	OH	-	-	-	-	21	326
16	cis	S	CH_2	OH	H	H	OH	-	-	-	-	5.8	590
17	cis	S	O	OH	H	OH	H		-	-	-	3.0	250
18	cis	S	O	OH	-	OH	H	H	H	H	H	0.9	37
19	cis	S	O	OH	-	OH	H	H	CH_3	CH_3	H	1.3	52
20	cis	S	O	OH	-	H	OH	H	CH_3	CH_3	H	1.2	69
21	cis	$CHCH_3$	0	OH	-	H	OH	CH_3	H	CH_3	F	0.7	4.1

[a] all compounds racemic except (+)-**12** and (-)-**12**; b. human enzyme IC_{50} (nM).

The favorable results obtained with the dihydrobenzoxathiin platform prompted re-examination of the previously investigated chroman platform with structural modifications designed to mimic the critical sulfur atom of the dihydrobenzoxathiins. This effort led to the discovery of a series of ERα selective trans-methylated chromanes with uterine and MCF-7 activity comparable to the compound (**20**) [58]. Compound (**21**) (IC_{50}: ERα ~0.7 nM, ERβ ~4.1 nM) was the most active analog of chroman platform, with IC_{50} value of 0.07 nM in the MCF-7 breast cancer cell assay.

Compound (**22**) (Fig. **5**) as a novel class of indole ligands for ERα has been discovered by the Merck laboratories [62]. It demonstrated high affinity and selectivity for ERα (~130-fold) while showing moderately improved antagonism (76%) with IC_{50} value of 30 nM in the MCF-7 breast cancer cell assay.

A series of SERAMs based on tetrahydroisoquinoline scaffold were synthesized [65]. Compound (**23**) and (**24**) (Fig. **5**) showed high affinities and moderate selectivity for ERα while exhibited good antagonism with IC_{50} value of 3.5 nM and 6.0 nM in the MCF-7 breast cancer cell assay respectively.

Y134 (Fig. **5**), a raloxifene analog, was designed and synthesized [66]. It appeared to be more selective for ERα (120-fold) and suppressed estrogen-stimulated proliferation of ER-positive breast cancer MCF-1 and T47D cells. Furthermore, it was found that Y134 showed a better selectivity in the mammary gland than the uterus in comparison with raloxifene. This unique attribute would certainly be useful in the development of a novel treatment for breast cancer.

Besides, newly research data [67] show that TAS-108 (Fig. **5**), is a novel steroidal antiestrogen compound, has a strong binding affinity to the estrogen receptor and, in preclinical studies, has antitumor activity against tamoxifen-resistant breast cancer cell lines. Its molecular mechanism of

actions is different from those of tamoxifen. Phase I studies did not show any effects on the endometrium.

CONCLUSIONS

SERMs have currently been one of the most effective strategies for the treatment and prevention of breast cancer. The success of tamoxifen and raloxifene for the treatment of breast cancer promotes the research and development of other newer SERMs with ideal pharmacological profile. Many new platforms of SERMs such as indole, benzopyran, quinoline and naphthalene derivatives have been developed based upon the classic triphenylethylenes and benzothiophenes. Moreover, the researches of dihydrobenzoxathiin scaffolds as a series of SERAMs have been made by Merck and showed that the ERα selectivity will provide better therapeutic effects. As the molecular mechanism of ERα and ERβ in estrogen signaling is elucidating, more and more new SERMs with higher ER subtype selectivity will emerge.

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ABBREVIATIONS

ER	=	Estrogen receptor
SERMs	=	Selective estrogen receptor modulators
SERAM	=	Selective estrogen receptor alpha modulators
ERE	=	Estrogen receptor element
DBD	=	DNA binding domain
LBD	=	Ligand binding domain
AF	=	Activation function
AP-1	=	Activator protein1
Sp-1	=	Stimulating protein 1

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