Drugs of the Future 1999, 24(6): 599-604

CCC: 0377-8282/99

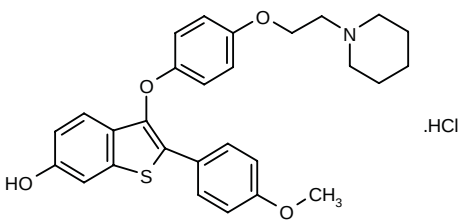
Arzoxifene Hydrochloride

Prop INNM

Estrogen Receptor Modulator
Treatment of Postmenopausal Syndrome
Antineoplastic

LY-353381.HCl

2-(4-Methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]phenoxy]benzo[*b*]thiophen-6-ol hydrochloride



$C_{28}H_{29}N_4S.HCl$ Mol wt: 512.0730

CAS: 182133-27-3
CAS: 182133-25-1 (as free base)

EN: 249850

Synthesis

The reaction of 6-methoxybenzo[*b*]thiophene (I) with triisopropyl borate by means of BuLi in THF gives the boronic acid (II), which is condensed with 4-(methanesulfonyloxy)phenyl bromide (III) by means of sodium carbonate in toluene, yielding the intermediate (IV). The demethylation of (IV) with boron tribromide in dichloromethane affords phenol (V), which is protected with benzyl chloride (VI) and cesium carbonate to afford the benzyl ether (VII). The reduction of (VII) with $LiAlH_4$ in THF provides the phenol (VIII), which is methylated with NaH and methyl iodide to the ether (IX). The bromination of (IX) with Br_2 and $NaHCO_3$ in $CHCl_3$ affords the 3-bromo derivative (X), which is oxidized with H_2O_2 in TFA/dichloromethane to the sulfoxide (XI). The condensation of (XI) with 4-[2-(1-piperidinyl)ethoxy]phenol (XII) in basic medium gives the expected condensation product (XIII), which is reduced at the sulfinyl group to yield the protected compound (XIV). Finally, this compound is debenzylated by hydrogenation by means of ammonium formate over Pd/C in ethanol/ethyl acetate and converted to its hydrochloride salt by treatment with ethyl ether/HCl in ethyl acetate (1). Scheme 1.

Description

Crystals, m.p. 156-60 °C; free base, m.p. 174-6 °C.

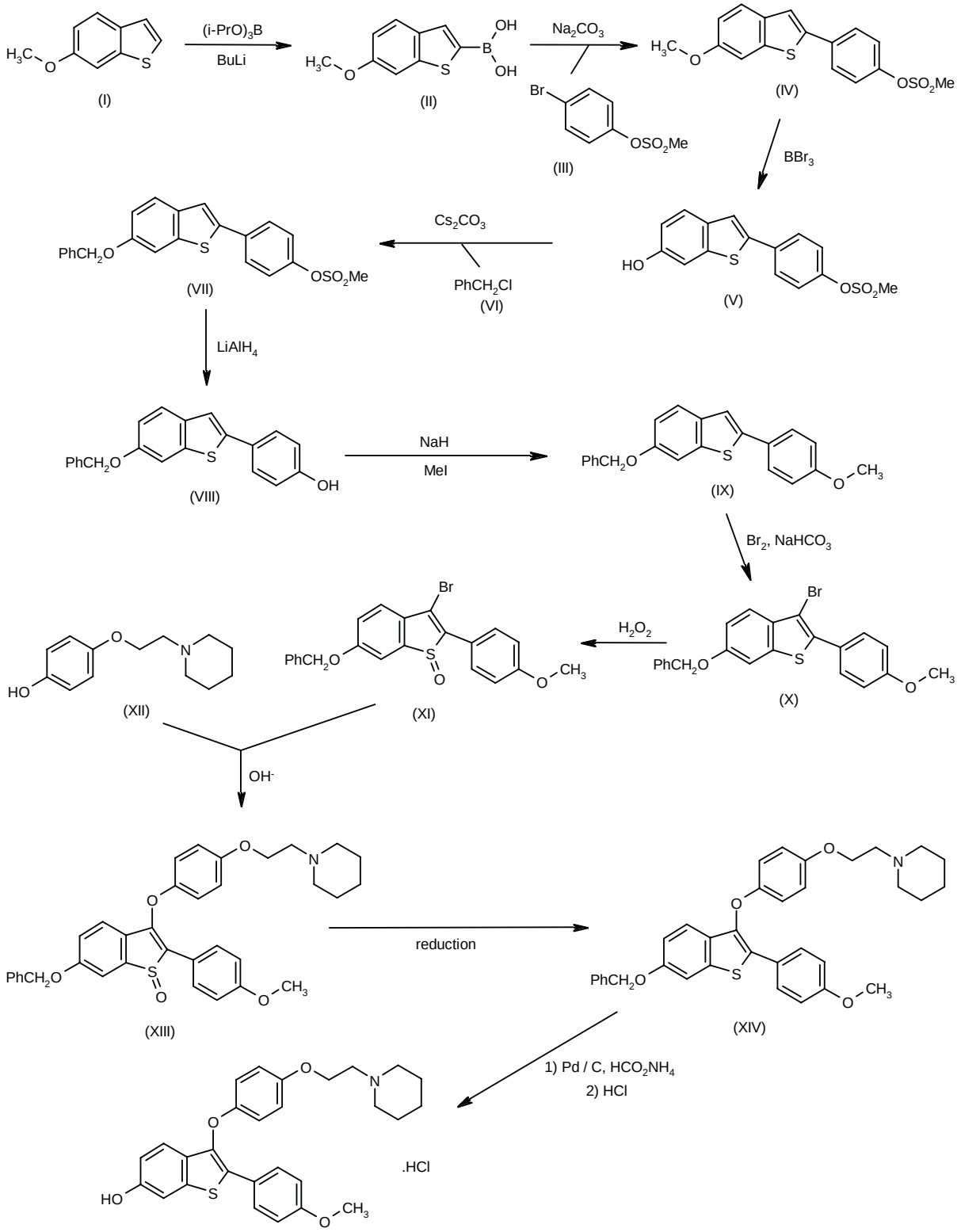
Introduction

Menopause, or the end of menstruation, develops at around 51 years of age in women in developed countries. It can be divided into four phases: premenopause, corresponding to the reproductive years from the first menstrual period to menopause; perimenopause, which is the time period (2-3 years) immediately before menstrual cessation during which some women begin to experience menopausal symptoms; menopause, which refers to the end of menstruation and is confirmed after 12 consecutive months without menstruation; and postmenopause, which are the years following menopause.The postmenopausal period accounts for approximately 28 years, thus representing a third of a woman's life. This period of time poses a health risk with regard to osteoporosis, heart disease and cancer (especially breast cancer).

Agents that bind with high affinity to estrogen receptors while showing tissue-selective agonist or antagonist activity are known as selective estrogen receptor modulators (SERMs). These drugs mimic the actions of estrogen on bone tissue and serum lipids but antagonize the stimulatory action of estrogens in the breast and uterus, thus they are putatively useful in estrogen-dependent conditions such as osteoporosis, breast cancer and gynecological disorders. Four main types of SERMs have been investigated: triphenylethylenes (including tamoxifen, toremifene, droloxifene and idoxifene), benzothiophenes (*e.g.*, raloxifene and arzoxifene), naphthalenes (the best characterized of which is nafoxidine) and benzopyrans (ormeloxifene and related derivatives). The classification, structures and indications of these and other SERMs are shown in Table I (2).

X. Rabasseda, P.A. Leeson, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona Spain.

Scheme 1: Synthesis of Arzoxifene Hydrochloride



Osteoporosis

Osteoporosis is a loss of bone mass that leads to bone fragility and an increased risk of fractures and is a major complication of menopause. Postmenopausal osteoporosis-related fractures involve primarily the vertebrae (47%), followed by the hip (20%) and the wrist (13%). Bone is not a "dead" tissue, but a living dynamic tissue that is continuously remodeled through the action of osteoblasts and osteoclasts. Based on studies in ovariectomized rats, therapeutic utility in postmenopausal osteoporosis has been predicted for estrogens, calcitonin and bisphosphonates, in addition to SERMs. These are especially important because of the diverse effects of estrogen on bone, the cardiovascular system, uterus, breast and other tissues and because of the tissue-selective effects of the SERMs.

Breast cancer

In developed countries, cancer is the second leading cause of mortality in women following heart disease. Breast cancer was the most common, with an estimated incidence of 178,700 new cases reported in the U.S. in 1998, followed by lung cancer (around 80,000 cases). Furthermore, the incidence of breast, lung and thyroid cancer has been increasing during the past 20 years, in parallel with a continuous increase in mortality from lung cancer. In contrast, mortality from breast cancer has shown a declining trend.

Each type of cancer has its own risk factors, screening procedures, treatments and outcomes. Education can increase the likelihood of preventing cancer or enhancing survival. Lifestyle choices (refraining from smoking, following a healthier diet) can help prevent some types of cancer and achieve longer survival. However, regular medical checkups, including cancer screening, continue to be the best means for early detection of cancer. This is exemplified in breast cancer, which can be divided into five stages: in situ carcinoma; cancer < 2 cm in diameter that has not spread outside the breast; cancer < 2 cm that has spread or > 2 cm that has not spread; cancer that has spread to local lymph nodes; and cancer that has spread to other organs or tissues. Early detection can be achieved by breast self-examination or by regular imaging explorations after 40 years of age. Early detection and prompt treatment have proven successful in saving lives (breast cancer is the most common, but is not the most deadly).

Recent findings suggest that drugs used in the treatment of osteoporosis also decrease the risk of breast cancer (3). Several agents are currently being clinically investigated alone or in combination as chemopreventive drugs for major cancer targets. Large-scale intervention trials have been performed with some of them (*e.g.*, tamoxifen and fenretinide in breast cancer), while others are in phase II trials to establish their chemopreventive efficacy and safety (*e.g.*, fenretinide, DFMO, oltipraz, some NSAIDs).

Tamoxifen is currently the most widely used endocrine therapy for early and advanced breast cancer. New SERMs with equal or higher potency and lower toxicity than tamoxifen are under investigation, including raloxifene and its more potent derivative arzoxifene (4).

Mechanism of Action

SERMs act by interaction with ERα and ERβ receptors in different tissues, thus regulating the transcription of genes. In ER binding assays, arzoxifene exhibited a relative binding affinity of 0.5 compared to 1.0 for 17β-ethynylestradiol. Arzoxifene has been shown to be more potent than raloxifene in both *in vitro* and *in vivo* assays (5, 6). Arzoxifene demonstrated potent inhibitory activity against estrogen-stimulated MCF-7 human breast cancer cell proliferation *in vitro*, with an IC_{50} of 0.3 nM; this was comparable to an IC_{50} of 0.37 nM reported previously for raloxifene (6, 7).

The chemopreventive activities of arzoxifene were evaluated in a *neu*-induced rat mammary carcinogenesis model. Two days following infusion of the *neu* retroviral vector, female rats were treated with arzoxifene (20 mg/kg) or tamoxifen (2 mg/kg), or were ovariectomized. When tumor development was measured at 13 weeks postinfusion, the untreated, intact control animals had an average of 13.9 carcinomas per rat as compared to 3.5, 8.4 and 4.5 carcinomas per rat for the arzoxifene, tamoxifen and ovariectomized rats, respectively. Arzoxifene had little or no effect on body weights, indicating a very low toxicity (8).

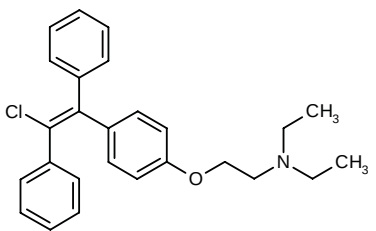
Pharmacological Actions

Body weight gain, uterus hypertrophy, hypercholesterolemia and bone mass loss indicate a decrease in circulating levels of estrogens similar to that observed in postmenopause. Experimental studies in rats have shown that arzoxifene effectively inhibits ovariectomy-induced body weight gain, hypercholesterolemia and bone mass loss, with respective ED_{50} values of 1, 20-30 and 10 μg/kg/day after oral treatment. The drug also prevented 17α-ethynylestradiol-induced uterus hypertrophy at a daily oral dose of 30 μg/kg, thus being less stimulatory to the uterus than most SERMs. In all these tests, arzoxifene was 30-100 times more potent than raloxifene, with similar or lower levels of estrogen antagonism in the uterus (6, 7, 9) (Table II).

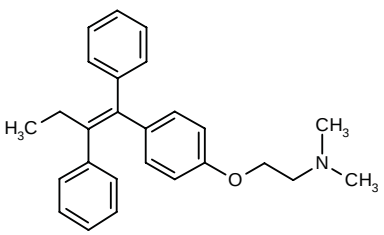
Arzoxifene, like raloxifene, produces antiresorptive effects very similar to those of estrogen (10). In ovariectomized rats, title compound prevented bone loss, with an ED_{50} of 10 μg/kg/day p.o. (6). In a very detailed analysis in an ovariectomized rat model of postmenopausal osteoporosis, arzoxifene prevented bone resorption to the same extent as 17α-ethynylestradiol but was less active

Table I: Classification, chemical structures and main indications of selective estrogen receptor modulators and antiestrogens acting at the ER receptor (from Prous Science Ensemble database).

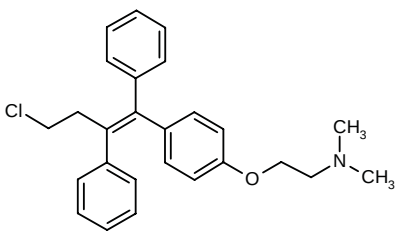
Phase	Drug (Source)	Main Indications
Triphenylethylenes		
1. Launched	Clomiphene (Serono)	Female infertility
2. Launched	Tamoxifen (Pharmacia Upjohn; AstraZeneca)	Breast cancer, female infertility
3. Launched	Toremifene (Orion Pharma)	Breast cancer
4. Phase III	Miproxifene phosphate (Taiho)	Breast cancer
5. Phase III	Droloxifene (Pfizer)	Breast cancer, atherosclerosis, osteoporosis
6. Phase II	Idoxifene (SmithKline Beecham)	Breast cancer
Benzothiophenes		
7. Launched	Raloxifene hydrochloride (Lilly)	Postmenopausal syndrome, osteoporosis
8. Phase II	Arzoxifene hydrochloride (Lilly)	Breast/ovary cancer, postmenopausal syndrome
Naphthalenes		
9. Phase III	CP-336156 (Pfizer)	Osteoporosis, atherosclerosis, breast cancer
Benzopyrans		
10. Launched	Ormeloxifene (Central Drug Res. Inst.)	Breast cancer, contraceptive
11. Phase III	EM-800 (Endorecherche; Schering Plough)	Breast cancer
Miscellaneous		
12. Phase III	Fulvestrant (Zeneca)	Breast/ovary cancer, gynecological disorders
13. Phase II	Tesmilifene HCl (Bristol-Myers Squibb)	Breast/ovary cancer
14. Phase I	A-007 (Dekk-Tek)	Breast/ovary cancer
15. Phase I	ERA-923* (Ligand; Wyeth-Ayerst)	Breast/ovary cancer



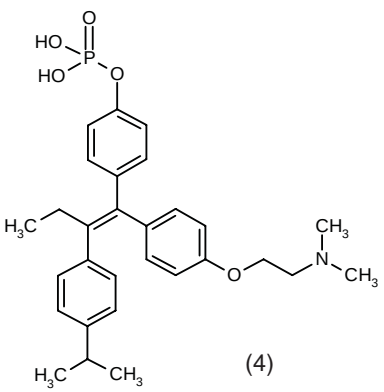
(1)



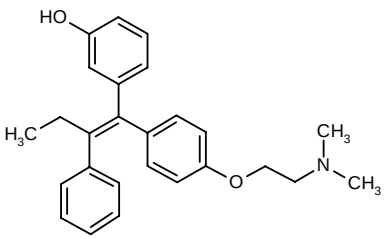
(2)



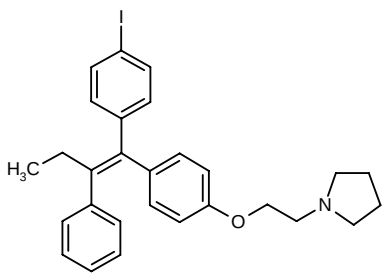
(3)



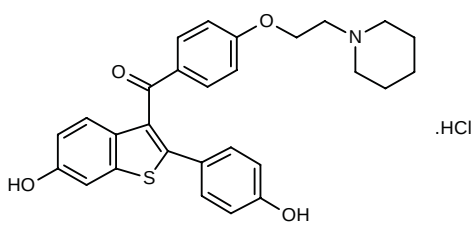
(4)



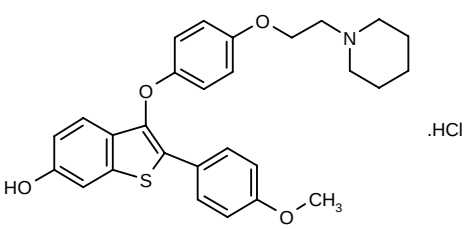
(5)



(6)



(7)



(8)

*Structure not yet detected

Continued

Table I: Continuation.

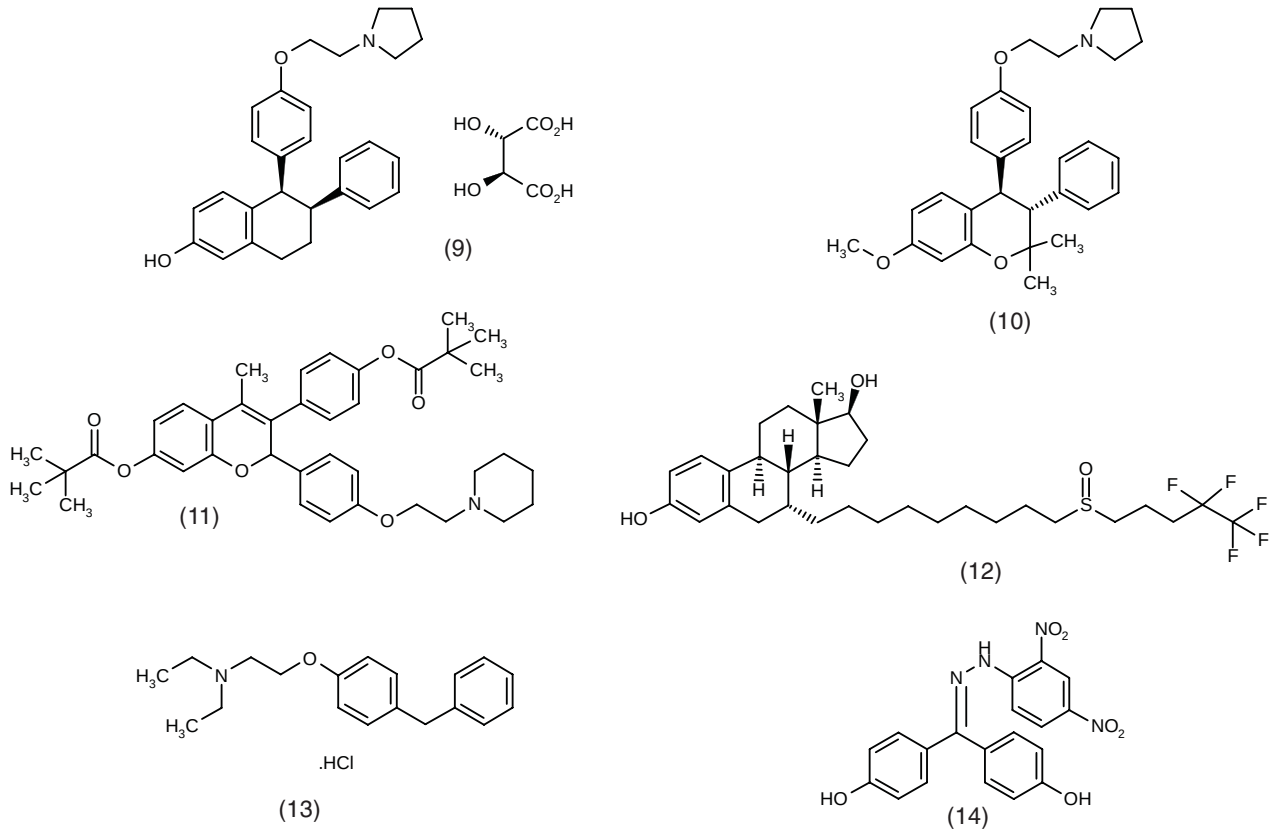


Table II: General pharmacological data on arzoxifene (6, 7, 9) [from Prous Science MFLine database].

Test	Result
In vitro	
Inhibition of estrogen-induced mitogenesis in MCF-7 cells	IC_{50} = 0.3 nM
In vivo	
Inhibition of ovariectomy-induced weight gain in rats	ED_{50} = 1 µg/kg/day p.o.
Inhibition of ovariectomy-induced hypercholesterolemia in rats	ED_{50} = 20-30 µg/kg/day p.o.
Inhibition of ovariectomy-induced bone mass loss in rats	ED_{50} = 10 µg/kg/day p.o.
Prevention of estrogen-induced uterus hypertrophy in rats	ED_{50} = 30 µg/kg/day p.o.

in inhibiting *de novo* bone formation. The combination of parathormone (PTH) plus arzoxifene increased bone mass at a faster rate and to a greater extent in comparison to PTH alone or PTH combined with estrogens or raloxifene. Furthermore, arzoxifene prevented the rapid bone loss observed upon discontinuation of PTH (11).

Arzoxifene has also been evaluated in experimental models of breast cancer. In a rat model of estradiol-promoted breast cancer induced by nitrosomethylurea, rats given 20 or 60 mg/kg arzoxifene in the diet presented an 8% incidence of cancer compared to 88% in control animals. Significant preventive activity was demonstrated at doses as low as 0.6 mg/kg, with potency similar to that of tamoxifen (7). The drug also inhibited human breast tumor progression in xenotransplanted nude mice with more potency than tamoxifen, raloxifene, droloxifene or idoxifene at equivalent doses. Furthermore, arzoxifene did not stimulate the endometrium or the uterus of ovariectomized rats, confirming the lack of deleterious effects of the drug on the uterus (12).

Pharmacokinetics

In female cynomolgus monkeys, arzoxifene was well absorbed after oral administration, reaching peak plasma levels by 3 h. The drug and its main metabolite (LY-335563) were excreted mainly in the feces, with < 2% of the dose being recovered in the urine and cage wash (13). Assays in female rats gave very similar results (14) (Table III).

Table III: Pharmacokinetic properties of arzoxifene and LY-335563 [in brackets] (13, 14) [from Prous Science PKLine database].

Species	Dose	C_{max} (µg/l)	t_{max} (h)	$AUC_{(0-\infty)}$ (µg.h/ml)	t½ (h)
Rats	5 mg/kg p.o.	34.5 [3.7]	4	519.1 [43.3]	5.7 [6.9]
Monkeys	4 mg/kg p.o.	9.12 [0.9]	3	213 [25]	14.2
	4 mg/kg i.v.	558 [45]		4193 [68]	17.7

Clinical Studies

A phase I trial has evaluated daily oral doses of arzoxifene (10, 20, 50 and 100 mg) in 32 patients with refractory, metastatic breast cancer, all of whom had failed prior tamoxifen and most of whom had had prior chemotherapy. Pharmacokinetics were similar following both single and multiple doses. No dose-limiting toxicity and no endometrial thickening were observed. The major side effect was mild to moderate hot flashes in 19 patients, which was observed at all doses. However, 1 patient on the 10-mg dose developed pulmonary embolism. All patients were evaluable for response: 1 patient achieved a minor response and 9 patients had stable disease with a median duration of 6 months. Based on the findings from this study, a phase II trial has commenced comparing doses of 20 and 50 mg (15, 16).

Arzoxifene is in phase II clinical testing for the treatment of breast, ovarian and endometrial cancers (17).

Manufacturer

Eli Lilly & Co. (US).

References

1. Palkowitz, A.D., Thrasher, K.J.(Eli Lilly and Company). *Benzothiophene cpds., intermediates, compsns. and methods.* EP 729956, JP 97183776, US 5488058, US 5492922, US 5510357, US 5856339.

2. Sato, M., Grese, T.A., Dodge, J.A., Bryant, H.U., Turner, C.H. *Emerging therapies for the prevention or treatment of postmenopausal osteoporosis.* J Med Chem 1999, 42: 1-24.

3. Cummings, S.R., Eckert, S., Krueger, K.A. et al. *The effect of raloxifene on risk of breast cancer in postmenopausal women. Results from the MORE randomized trial.* JAMA - J Am Med Assoc 1999, 281: 2189-97.

4. Kelloff, G.J. *Strategies in chemoprevention drug development.* 10th Int Cong Horm Steroids (June 17-21, Québec) 1998, 19.

5. Palkowitz, A.D., Glasebrook, A.L., Bryant, H.U. et al. *Design, synthesis, and pharmacological evaluation of a novel series of benzothiophene derived selective estrogen receptor modulators (SERMs).* 213th ACS Natl Meet (April 13-17, San Francisco) 1997, Abst MEDI 204.

6. Cole, H.W., Adrian, M.D., Shetler, P.K. et al. *Comparative pharmacology of high potency selective estrogen receptor modulators (SERMs): LY353381.HCl and CP336,156.* J Bone Miner Res 1997, 12(Suppl. 1): Abst F491.

7. Sporn, M., Suh, N., Peer, C. et al. *LY353381.HCl, a new benzothiophene for chemoprevention of breast cancer.* Proc Amer Assoc Cancer Res 1997, 38: Abst 3538.

8. Gould, M.N., Haag, J.D., Kennan, W.S., Watson, P.A. *Chemopreventive activities of the selective estrogen receptor modulator LY353381.HCl against neu-induced rat mammary carcinomas.* Proc Amer Assoc Cancer Res 1999, 40: Abst 2014.

9. Sato, M., Turner, C.H., Wang, T., Adrian, M.D., Rowley, E., Bryant, H.U. *LY353381.HCl: A novel raloxifene analog with improved SERM potency and efficacy in vivo.* J Pharmacol Exp Ther 1998, 287: 1-7.

10. Bryant, H.U. *Estrogen and raloxifene prevent bone loss via similar mechanistic pathways.* 10th Int Cong Horm Steroids (June 17-21, Québec) 1998, 27.

11. Sato, M., Zeng, G.Q., Rowley, E., Turner, C.H. *LY353381.HCl: An improved benzothiophene analog with bone efficacy complementary to parathyroid hormone-(1-34).* Endocrinology 1998, 139: 4642-51.

12. Fuchs-Young, R., Iversen, P., Shelton, P. et al. *Preclinical demonstration of specific and potent inhibition of mammary tumor growth by new selective estrogen receptor modulators (SERMs).* Proc Amer Assoc Cancer Res 1997, 38: Abst 3847.

13. Lantz, R., Knadler, M.P. *The disposition of a selective estrogen receptor modulator, LY353381, and its metabolites in female cynomolgus monkeys following single oral and intravenous doses of ^{14}C-LY353381.* Pharm Res 1997, 14(11, Suppl.): Abst 1222.

14. Rash, T., Knadler, M.P. *The disposition and biotransformation of the selective estrogen receptor modulator, LY353381, in female Fischer 344 rats following a single oral dose.* Pharm Res 1997, 14 (11, Suppl.): Abst 1223.

15. Münster, P., Buzdar, A., Booser, D., Theriault, R., Frye, D., Major, M., Dhingra, K., Ni, L., Norton, L., Hudis, C. *Pharmacodynamics and pharmacokinetics of LY353381.HCl, a selective estrogen receptor modulator (SERM), in women (pts) with refractory, metastatic breast cancer (MBC).* Proc Amer Soc Clin Oncol 1999, 18: Abst 414.

16. Hudis, C., Buzdar, A., Munster, P. et al. *Preliminary results of a phase I study of a third-generation selective estrogen receptor modulator (SERM3, LY353381.HCl) in refractory, metastatic breast cancer.* Cancer Invest 1999, 17(Suppl. 1): Abst 43.

17. *Second-generation SERM advances through the Lilly pipeline.* DailyDrugNews.com (Daily Essentials) May 7, 1999.