Drugs of the Future 2001, 26(9): 841-850

CCC: 0377-8282/2001

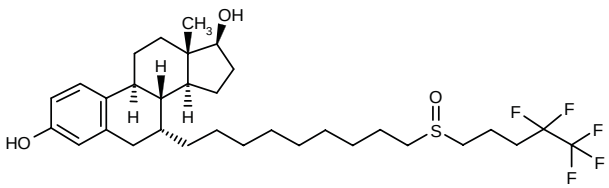
Fulvestrant

Prop INN; USAN

Treatment of Breast Cancer
Antiestrogen

ICI-182780
ZD-9238
Faslodex™

7α-[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol



$C_{32}H_{47}F_5O_3S$ Mol wt: 606.7860

CAS: 129453-61-8

EN: 177872

Synthesis*

Protection of 9-bromononan-1-ol (I) with *tert*-butyldimethylsilyl chloride and imidazole in THF gives the silyl ether (II), which reacts with Mg in the same solvent to yield the Grignard reagent (III). Reaction of compound (III) with CuI affords the corresponding organocuprate that condenses with 6,7-didehydro-19-nortestosterone (IV) to provide the adduct (V). Cleavage of the silyl ether group of (V) with AcOH/water in THF gives alcohol (VI), which is esterified with Ac_2O and pyridine, yielding the corresponding diacetate (VII). Aromatization of enone (VII) with $CuBr_2$ and LiBr in refluxing acetonitrile affords phenol (VIII), which is selectively hydrolyzed with NaOH in methanol to provide the primary alcohol (IX). The selective esterification of the phenolic OH group of (IX) with benzoyl chloride and NaOH in acetone/water furnishes the aryl benzoate (X), which by reaction of its primary OH group with mesyl chloride and TEA in dichloromethane gives the mesylate (XI). Compound (XI) is condensed with 4,4,5,5,5-pentafluoropentanethiol (XII) by means of NaH in THF to yield the thioether (XIII), which is submitted to basic hydrolysis of the ester groups by means of NaOH in MeOH/water to afford the corresponding dihydroxy compound (XIV). Finally, this compound is oxidized with sodium metaperiodate to provide fulvestrant (1). Scheme 1.

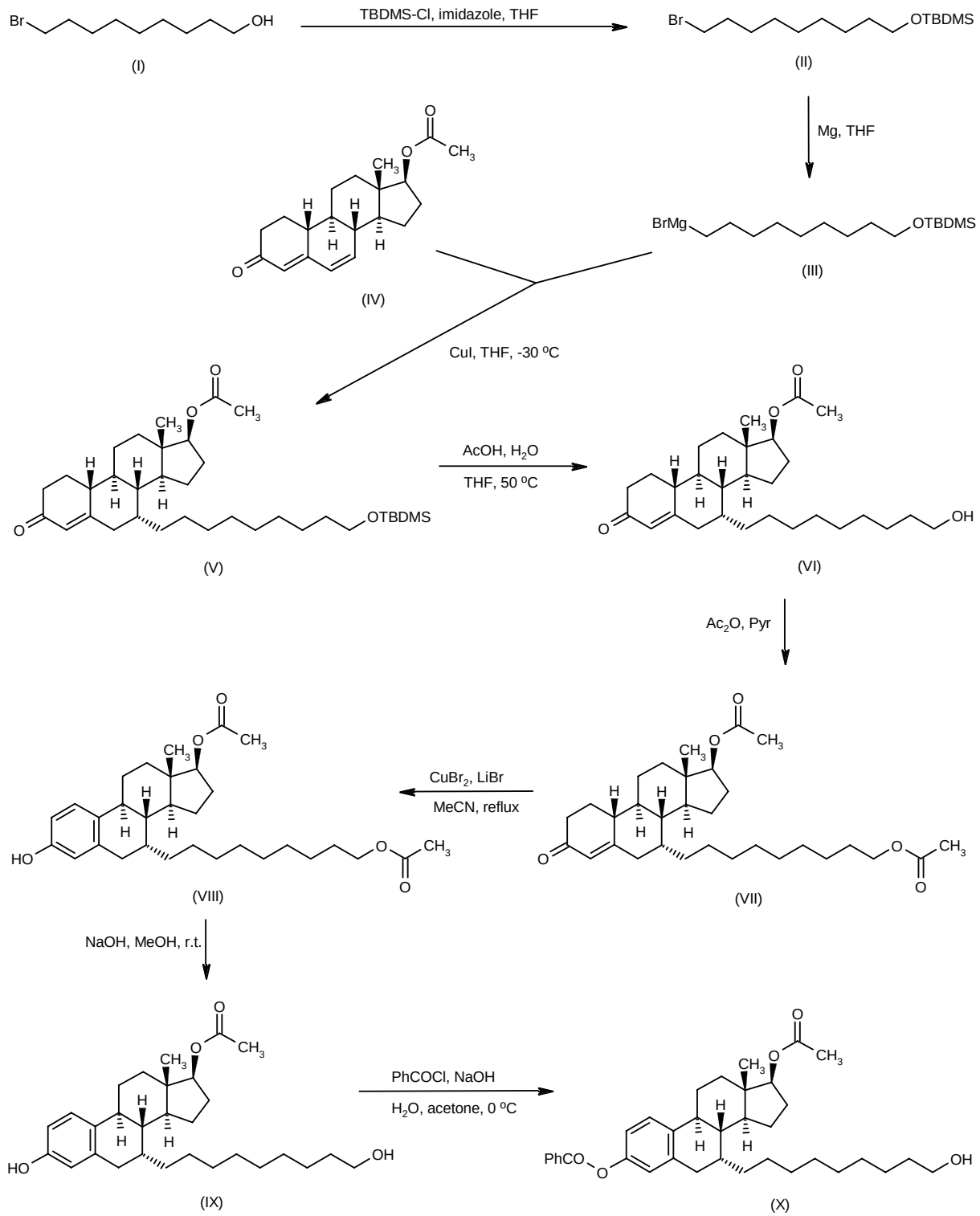
Introduction

Despite significant strides in the fields of cancer screening, detection and therapy, breast cancer still remains a serious public health concern and metastatic and locally advanced breast cancer continues to represent a significant problem. It was estimated that there would be 184,200 new cases of breast cancer in the U.S. in 2000 and 41,200 deaths (2). Surgery, radiation and adjuvant chemotherapy and hormonal therapy is recommended for early stage disease and chemotherapy and hormonal therapy are used for metastatic disease. Still, approximately half of breast cancer patients will die of their disease; this statistic has remained essentially unchanged since the 1930s (2). While surgery and radiotherapy are still the mainstay of treatment of primary breast cancer, there have been several advances in the last decade that have contributed to improving the quality of life of these patients, including breast-conserving surgery, effective reconstructive surgery and less toxic adjuvant chemotherapeutic and hormonal agents. Hormonal agents can produce an objective response rate of 60-75% when they are used in the neoadjuvant setting. Metastatic breast cancer, however, still remains a threat in 40-70% of patients who relapse after variable periods of disease-free survival.

Though chemotherapy has long been an established treatment modality, especially in the U.S., there is a

Mark Levin[1], Nina D'Souza[1], J. Castañer[2]*. [1]Comprehensive Cancer Center at Lincoln Medical and Mental Health Center, Bronx, New York; [2]Prous Science, P.O. Box 540, 08080 Barcelona, Spain. *Correspondence: Mark Levin, MD, 234 Eugenio Maria De Hostos Blvd., Bronx, NY 10451, New York, USA.

Scheme 1: Synthesis of Fulvestrant



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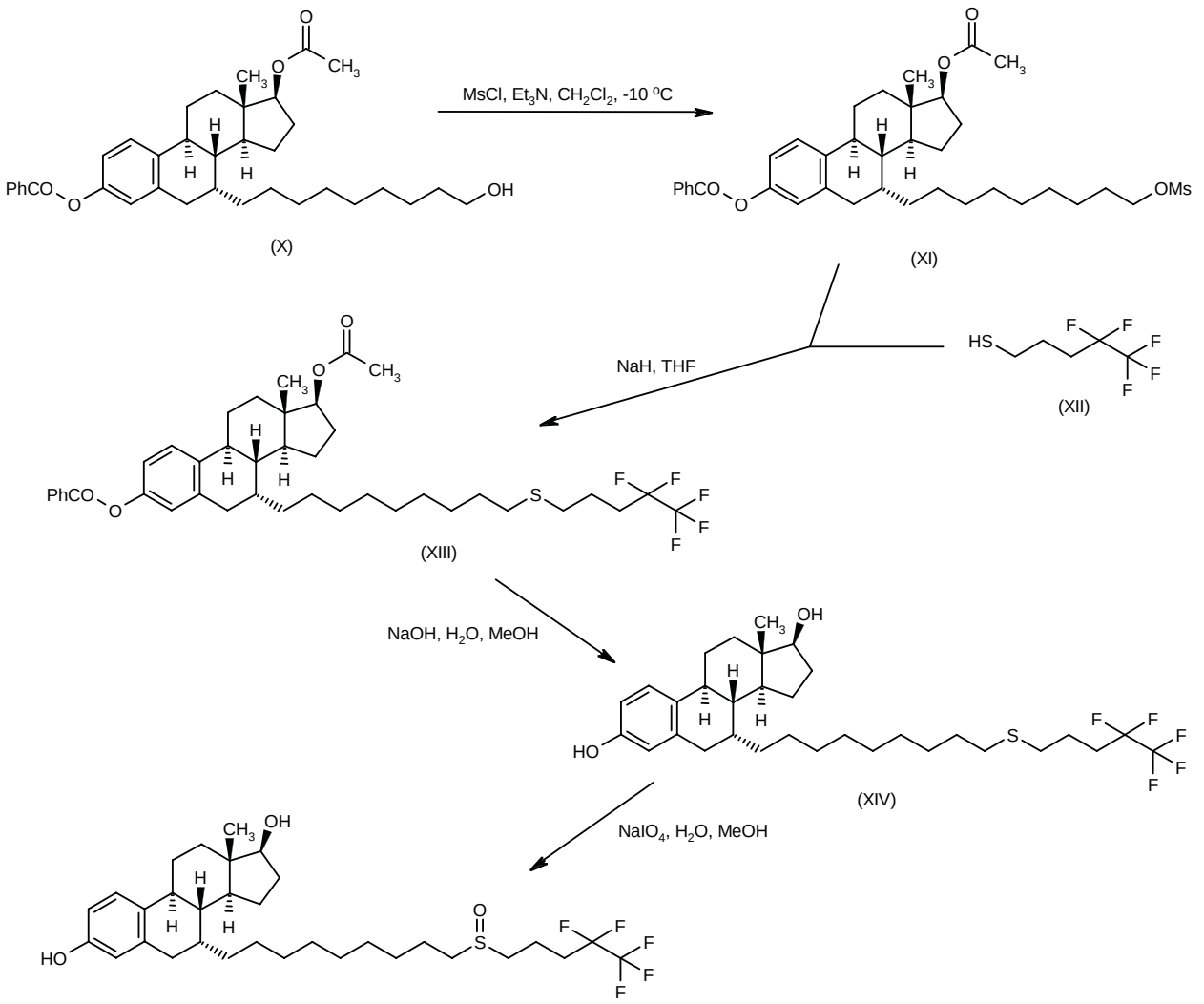
Scheme 1: Synthesis of Fulvestrant (Cont.)

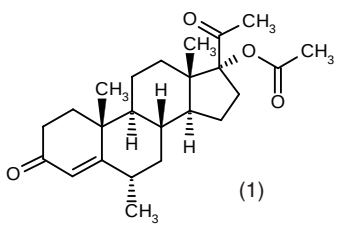


growing recognition of the need for less toxic but effective therapeutic strategies. Since the discovery of the hormonal dependency of many breast cancers in 1896 (4), when the response of metastatic breast cancer to bilateral oophorectomy was reported, endocrine therapy has been extensively investigated as a candidate for such a therapy. Tamoxifen, a partial estrogen agonist-antagonist and estrogen receptor (ER) modulator, is currently the most widely used endocrine therapy worldwide and has found a wide range of applications in the entire spectrum of breast cancer ranging from preventive and adjuvant therapy to treatment of metastatic disease. In the breast, tamoxifen functions as a competitive antagonist. In other organs, the agonistic effects of tamoxifen result in increasing bone density and a beneficial alteration of serum lipid profile; it also, however, produces deleterious effects such as the development of tumor flare, endometrial stimulation, overgrowth and cancer, and distressing vasomotor symptoms. Since droloxifene and idoxifene have been dropped from development for breast cancer therapies, the only triphenylethylene-type antiestrogens available are tamoxifen and the very similar drug toremifene. The second generation of antiestrogens include raloxifene, arzoxifene and EM-652. The FDA has recently approved anastrozole, an aromatase inhibitor, as first-line therapy for advanced or locally advanced postmenopausal hormone-receptive breast cancer (5). This family of drugs also includes letrozole, Aromasin™ and others (Tables I and II).

Fulvestrant (Faslodex™) is a pure antiestrogen that does not suffer from these disadvantages and, therefore, represents a significant breakthrough in the treatment of breast cancer. Studies have shown that bone cells

Table I: Hormonal agents marketed for the treatment of breast cancer (Prous Science R&D Backgrounders database).

Drug Name	Company	Year of First Launch
Progestins		
1. Medroxyprogesterone acetate (*Farlutal*)	Wyeth-Ayerst/Pharmacia	1958
2. Megestrol acetate (*Megace*)	Bristol-Myers Squibb	1963
Antiestrogens		
3. Tamoxifen citrate (*Nolvadex*)	AstraZeneca	1973
4. Toremifene (*Fareston*)	Orion Pharma	1988
LHRH agonists		
5. Leuprolide acetate (*Enantone*)/(*Lupron Depot*)	Takeda	1984/1989 (depot)
6. Triptorelin (*Decapeptyl*)	Beaufour-Ipsen	1986
7. Goserelin (*Zoladex*)	AstraZeneca	1987



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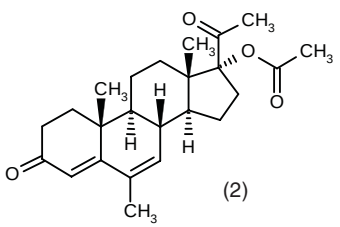

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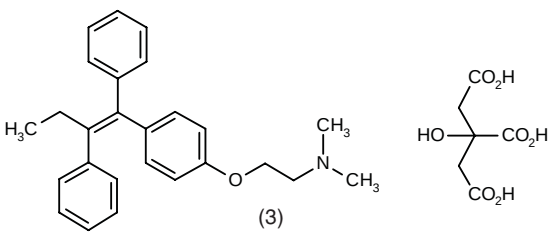

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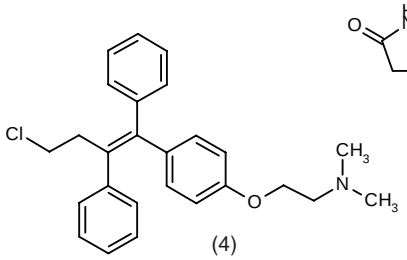

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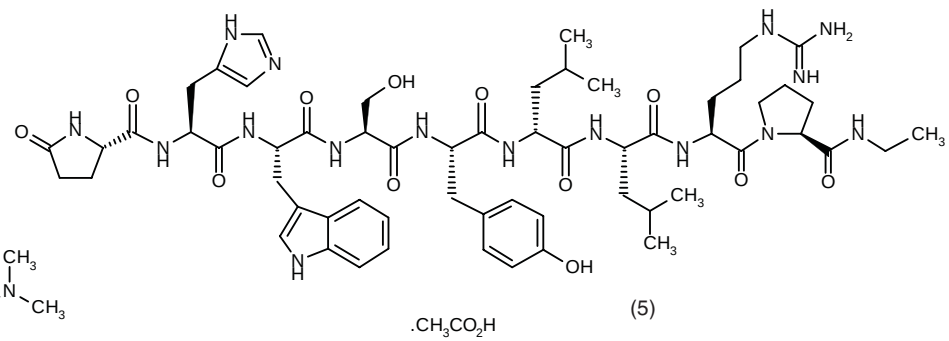
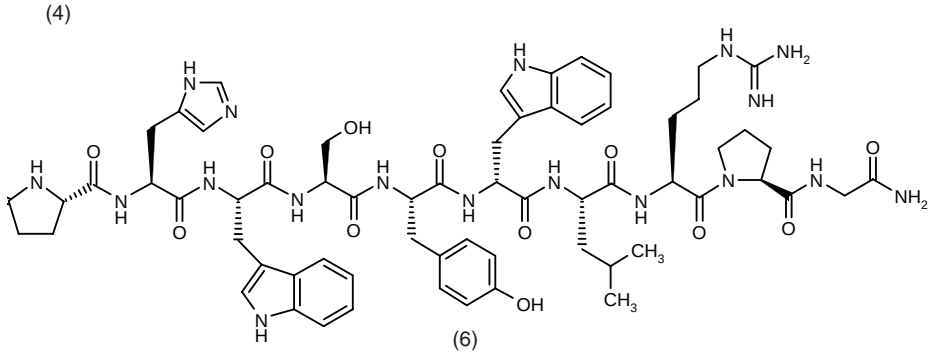


.CH_3CO_2H (5)



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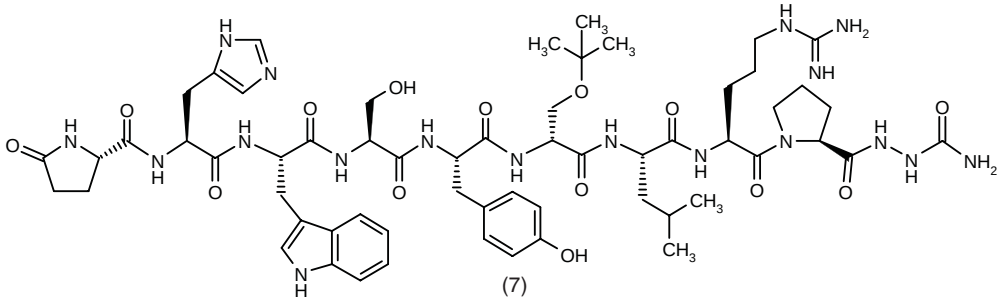

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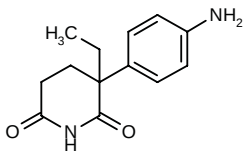
Table I (Cont.): Hormonal agents marketed for the treatment of breast cancer (Prous Science R&D Backgrounders database).

Drug Name	Company	Year of First Launch
Aromatase inhibitors		
8. Aminoglutethimide (*Orimeten*)	Novartis	1981
9. Formestane (*Lentaron*)	Novartis	1992
10. Anastrozole (*Arimidex*)	AstraZeneca	1995
11. Fadrozole HCl (*Afema*)	Novartis	1996
12. Exemestane (*Aromasin*)	Pharmacia	1999



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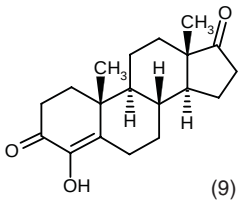

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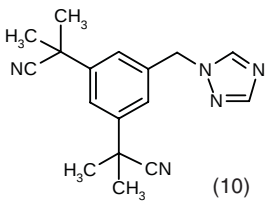

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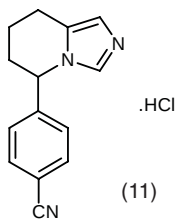

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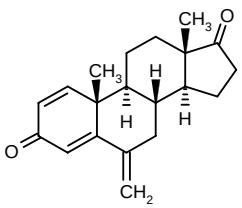


(12)

possess classic ERs and a hypoestrogenic state is associated with bone resorption and osteoporosis. Despite its pure antagonist activity, studies on ovariectomized rats have confirmed that fulvestrant, in contrast to tamoxifen which acts like estrogen to reduce periosteal bone formation, does not exert estrogen-like or antiestrogenic effects (6). Fulvestrant also has some distinct advantages on target organs other than breast tissue. In the endometrium, the partial agonist activity of tamoxifen is associated with an increased incidence of endometrial carcinoma, a finding which was absent in animal studies with fulvestrant, which not only showed a lack of uterotrotrophic activity but also blocked the mitogenic effects of tamoxifen in ovariectomized, estrogen-treated monkeys (7).

Biochemistry and Mechanism of Action

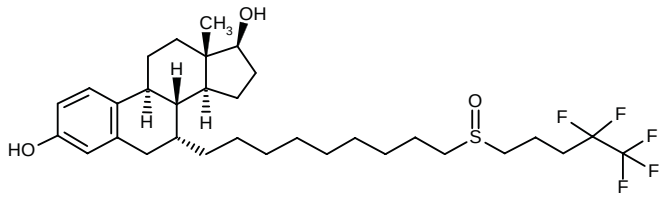
Fulvestrant is a steroidal pure antiestrogen with a chemical structure similar to that of estradiol. It is essentially an estradiol with an attached moiety at the 7α position. *In vitro* studies of ER function have demonstrated that estradiol binding to the ER initiates a sequence of events , including dimerization of the estrogen-ER complex, and binding of the dimer to estrogen-sensitive genes at the estrogen response element. The ER activates transcription via two transactivation factors located in the *N*-terminal (AF-1) and C-terminal (AF-2) ligand binding region (8). This increases the tumor cell growth fraction and the passage of tumor cells through the cell cycle (9).

Fulvestrant is a 7α-alkylamide analogue of 17β-estradiol, which antagonizes estrogen action by occupying the ER and preventing estrogen-stimulated gene activation, thus interfering with the estrogen-related processes essential for cell-cycle completion (10). It binds to the ER with affinity close to that of estradiol and 100-fold greater than that of tamoxifen. *In vitro* studies of the effect of fulvestrant on MCF-7 cells have shown that it promotes a highly effective restriction of the cell cycle about 5 h into the G_1 phase, resulting in arrest of cell-cycle progression, evidenced by the fall in estrogen-regulated proteins and their mRNA levels, as well as decreased immunostaining for pS2, an estrogen-induced protein of unknown function in breast tissue. Fulvestrant not only modifies ER function by reducing the rate of dimerization and nuclear localization but also blocks ER transactivation from both AF-1 and AF-2 domains and reduces cellular levels of ER by downregulation (7). It appears to downregulate the ER by 80-90%, often to nondetectable levels. This last effect has been observed *in vitro* and *in vivo*, earning this drug the appellation of ERD, or estrogen receptor downregulator. In fact, after several weeks of treatment with fulvestrant one finds virtually no estrogen receptor in breast tissue. Tamoxifen, on the other hand, activates AF-1 and inactivates AF-2, accounting for a proestrogenic effect on some tissues.

Apoptosis is essential in the maintenance of internal homeostasis and may be another major mechanism

Table II: Hormonal agents in development for treatment of breast cancer (Prous Science R&D Backgrounders database).

Drug Name	Source	Mechanism of Action	Status*
1. Fulvestrant (*Faslodex*)	AstraZeneca	Antiestrogen	Preregistered
2. Vorozole (*Rivizor*)	Janssen	Aromatase inhibitor	Preregistered
3. Arzoxifene HCl	Lilly	Selective estrogen receptor modulator	Phase III
4. Octreotide	Novartis	Somatostatin analogue	Phase III
5. Raloxifene HCl (*Evista*)	Lilly	Selective estrogen receptor modulator	Phase III
6. SCH-57050 (EM-800)	Endorecherche/Schering-Plough	Antiestrogen	Phase III
7. Tesmilifene HCl	Bristol-Myers Squibb/YM BioSciences	Antiestrogen	Phase III
8. Lasofoxifene tartrate	Pfizer/Ligand	Selective estrogen receptor modulator	Phase II/III
9. Biomed-777^{+}	Schering AG/BioMedicines	Aromatase inhibitor	Phase II
10. ERA-923	Wyeth-Ayerst/Ligand	Selective estrogen receptor modulator	Phase II
11. YM-511	Yamanouchi	Aromatase inhibitor	Phase II
12. Fluasterone	Aeson Therapeutics	Androgen, synthetic DHEA analogue	Phase I



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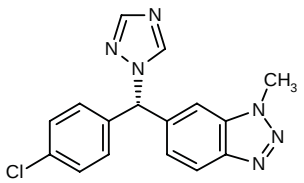

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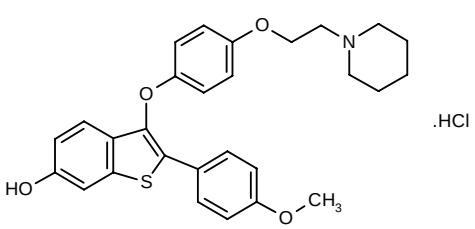

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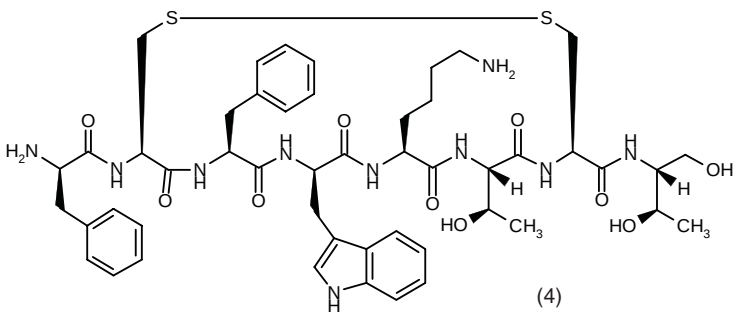

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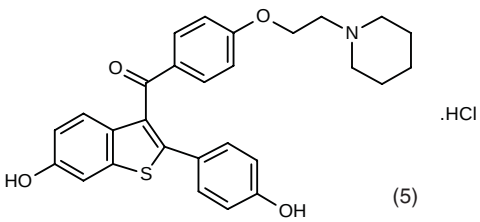

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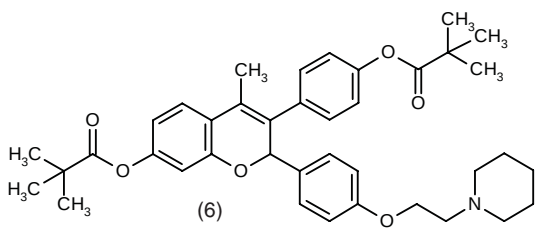

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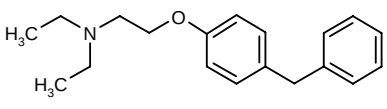

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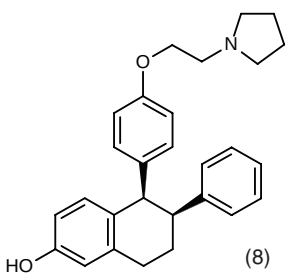

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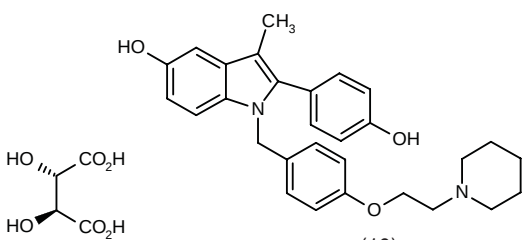

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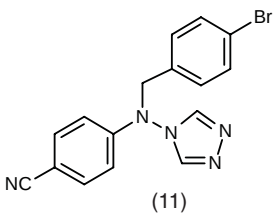

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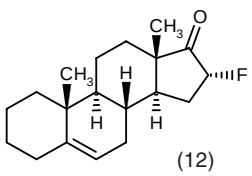

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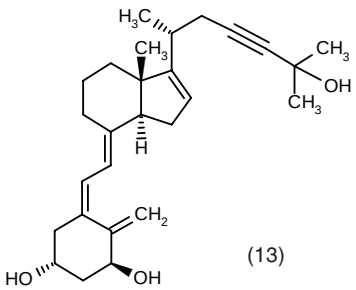
Table II (Cont.) Hormonal agents in development for treatment of breast cancer (Prous Science R&D Backgrounders database).

Drug Name	Source	Mechanism of Action	Status*
13. ILX-23-7553	Roche/Ilex Oncology	Vitamin D3 analogue	Phase I
14. SPC-8490+	Celgene	Selective estrogen receptor modulator	Phase I
15. 2-MeOEMATE	Univ. Bath/Imperial Coll. Sci. Technol. Med. (GB)	Steroid sulfatase inhibitor	Preclinical
16. 667COUMATE	Univ. Bath/Imperial Coll. Sci. Technol. Med. (GB)	Steroid sulfatase inhibitor	Preclinical
17. EM-652.HCl (Sch-57068.HCl)	Endorecherche/Schering-Plough	Selective estrogen receptor modulator	Preclinical
18. MEN-11066	Menarini	Aromatase inhibitor	Preclinical
19. MR-20492	University of Caen/CNRS	Aromatase inhibitor	Preclinical
20. NV-50+	Novogen	Selective estrogen receptor-α antagonist	Preclinical
21. SR-16234+	SRI/Taiho	Antiestrogen	Preclinical
22. ZK-191703+	Schering AG	Antiestrogen, selective estrogen receptor destabilizer	Preclinical
23. ZK-230211	Schering AG	Progesterone antagonist	Preclinical



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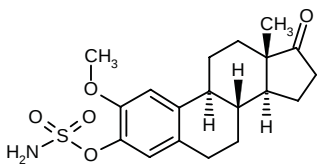

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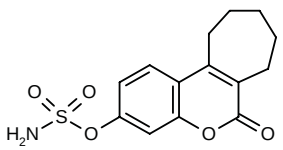

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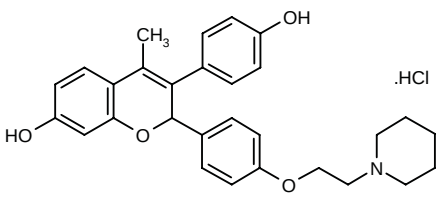

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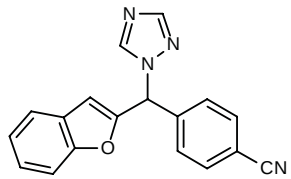

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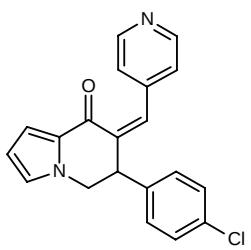

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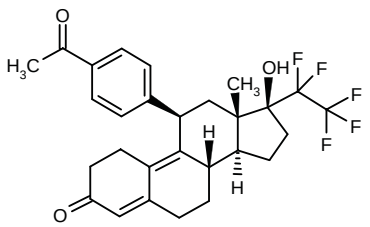

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*For this indication; +structure not yet detected

for the therapeutic effects of fulvestrant. In studies on MCF-7 cells, fulvestrant was far superior to tamoxifen in the modulation of apoptosis induction via BCL-2 and the TNF-1 associated signal transduction pathways (11, 12). In addition, fulvestrant in conjunction with docetaxel induces BCL-2 phosphorylation and massive apoptosis in MDR resistant cells (13).

In addition to its well-documented antiestrogenic properties, studies using reporter gene constructs have demonstrated that fulvestrant also has weak antiprogestin activity by virtue of inhibition of cross-talk between the ER and the progesterone receptor (PR) and of progestin-induced transcription (14, 15).

Comparison with tamoxifen

The unique properties of pure antiestrogens are the key to their superior antitumor activity over partial agonist-antagonists like tamoxifen. Tamoxifen binds to the

ER with an affinity 100 times less than fulvestrant and is only AF-1 active, in effect attenuating the ER functions but not completely blocking them (8).

Despite it currently being the most popular endocrine therapy of choice worldwide for ER-positive breast cancer, the clinical effectiveness of tamoxifen is ultimately attenuated by the development of resistance. The causes for development of resistance are multifactorial and are speculated to include loss of ER, mutations in ER resulting in cell proliferation independent of estrogen, and differential recruitment of ER co-regulator proteins into ER-driven transcription complexes resulting in selection of ER-positive disease that is tamoxifen-stimulated for growth or IRF-1-mediated activity (16). In contrast, being a pure agonist fulvestrant is totally devoid of estrogenic activity in the breast as well as in the uterus (17). It also reverses uterine mucosal hypertrophy induced by tamoxifen or estradiol. In fact, both *in vitro* studies on MCF-7/LCC9 cells as well as *in vivo* studies in ovariectomised female nude mice have shown that tamoxifen-resistant cell lines still remain sensitive to fulvestrant-mediated growth inhibition (18, 19). Though resistance to fulvestrant has been studied in MCF-7 cells, it is not associated with the loss of ER expression or estrogen responsiveness. In contrast to tamoxifen resistance, resistance to fulvestrant appears to arise through ER-independent mechanisms (20). As such, resistance to tamoxifen would not imply resistance to fulvestrant but not *vice versa* (21). These findings are consistent with another mechanism that has been proposed for the clinical superiority of fulvestrant over tamoxifen, namely, its binding to a high-affinity site distinct from the ER (22). Studies conducted using tamoxifen-resistant MCF5-23 cells and tamoxifen-sensitive MCF5-21 cells showed that both cell lines had a 2- to 4-fold greater affinity for fulvestrant than tamoxifen. Another proposed mechanism, the regulation of angiogenesis in tamoxifen-stimulated breast tumors by decreasing levels of VEGF, may also account for these findings (23).

Pharmacological Actions

Fulvestrant has relatively poor oral bioavailability and is administered in a lipid vehicle as intramuscular injection. No significant difference was noted in pharmacokinetics and adverse events when 250 mg of fulvestrant was administered as a single 5-ml injection or two 2.5-ml injections in an open, randomized, multicenter study in postmenopausal women with advanced breast cancer (24). The serum concentration is dose-dependent but shows variability between individuals. No significant changes in serum levels of LH, FSH or SBHG are seen over a 7-day treatment period and it does not cross the blood-brain barrier (25). Accordingly, it appears to not cause vasomotor side effects (26). Theoretically, estrogen inactivation may increase bone turnover and promote osteoporosis; however, this effect has not been seen in animal models and surrogate markers of bone turnover are not increased by fulvestrant. In rat tibia, it exhibited complete estrogen antagonism in cortical and cancellous bone, partial agonism in cancellous bone and no activity on tibial longitudinal growth rate (27).

Minor adverse effects can occur, such as transient bloodstained vaginal discharge, altered body odor and a “dream-like state”. There was no reported incidence of vaginal dryness, weight gain, altered coagulation, thrombogenicity or altered libido, nor was there any change in the symptoms of hot flushes or sweats if already present (28). In a small phase II trial, fulvestrant was shown to produce a 67% clinical benefit rate after tamoxifen failure in 19 women with metastatic breast cancer, with no major safety issues. Fulvestrant had to be administered by monthly injection but was well tolerated, with only minor injection site redness or soreness noted. There were no changes in hot flashes, endometrial thickness, sex hormone binding globulin levels, follicle-stimulating hormone levels or luteinizing hormone levels in those subsets of women studied for these variables (28). Trial 019 explored the safety of fulvestrant. It included premenopousal women treated with three different doses of fulvestrant versus goserelin and placebo. Fulvestrant was well tolerated in these women with no menopausal symptoms, no evidence of ovarian stimulation, no increase in bone catabolism as judged by surrogate markers and no difference in safety endpoints among the arms.

Clinical Studies

Since 1991, several phase I and II studies of fulvestrant demonstrated its ability to obtain a significant decline in ER and PR in primary breast tumors.

Studies in premenopousal women with benign gynecological disease showed that fulvestrant was well tolerated and there was no evidence of ovarian hyperstimulation, menopausal symptoms or safety endpoints at the end of 3 months. For that reason, two large randomized studies that compared fulvestrant to anastrozole as therapy for tamoxifen-refractory patients were conducted, one in Europe (29) and one in the U.S. and Canada (30). For both studies, patients were required to have ER-positive or PR-positive tumors; if the ER status was unknown, patients were required to have had a clinical response to prior hormonal therapy. All patients were postmenopausal and had tamoxifen-resistant advanced breast cancer. Originally, there were three arms: fulvestrant at 125 mg, fulvestrant at 250 mg and anastrozole at 1 mg. However, the lowest fulvestrant arm showed too few objective responses at interim analysis and accrual to that arm was suspended. There were no differences in response rate or time to progression between fulvestrant and anastrozole. The North American study was a double-blind, double-dummy trial with patients not randomized to fulvestrant receiving sham i.m. injections. The European trial was not double-blinded. One of trials administered fulvestrant as a single i.m. injection, whereas the other as 2 i.m. injections. Pharmacokinetic data presented

separately (24), however, do not suggest that this would result in a clinically significant difference.

These trials were recently presented at the San Antonio Breast Cancer Symposium in December of 2000 (32). It now appears that fulvestrant and anastrozole result in a similar time-to-progression and response, as well as comparable tolerability. One of the trials, however, appears to indicate that median duration of response may be significantly longer for fulvestrant. The North American trial had 206 patients in the fulvestrant arm and 194 patients in the anastrozole arm. At 16.8 months of follow-up, overall response rates to fulvestrant were 17.5%, identical to that for the anastrozole arm. Median time to progression was 5.4 months and 3.4 months, respectively. The most common side effects were similar in both groups, consisting primarily of gastrointestinal symptoms and hot flushes. There were no unexpected toxicities and the incidence of severe side effects was very low; 2.5% of patients from each arm withdrew from the study due to side effects. Median duration of response favored fulvestrant at 19.3 months versus 10.5 months for anastrozole.The European trial randomized 222 women to fulvestrant and 229 to anastrozole, and included 25% of patients with unknown or negative ER receptors. At 305 days, no statistically significant difference between arms had emerged. Objective response rate was 20.7% for fulvestrant and 15.7% for anastrozole, a nonsignificant difference. Both treatments were very well tolerated. Duration of response was likewise similar, 14.5 months for fulvestrant and 14 months for anastrozole. The North American and European studies differed in some important aspects. Women in the North American studies had received prior chemotherapy and were, in general, heavier than those in the European studies. They were also more likely to have ER-positive tumors as per study design.

It is important to realize that fulvestrant may have different activity on breast cancers that were previously exposed to tamoxifen than on hormone-naive cancers. A trial that compares tamoxifen and fulvestrant in metastatic disease is expected to be reported next year. An ongoing neoadjuvant placebo-controlled EORTC trial of fulvestrant versus tamoxifen in such patients may help clarify its role in prevention of metastases and spread in a preoperative setting. The NSABP is planning an adjuvant trial (B-35) that would randomize fulvestrant against tamoxifen in node-negative, receptor-positive women.

AstraZeneca has submitted an NDA with the FDA seeking priority review for fulvestrant for the treatment of locally advanced or metastatic breast cancer in postmenopausal women who have previously progressed following hormonal therapy (33).

Conclusions

Fulvestrant, a novel antiestrogen, represents a new class of hormonal agents in the treatment of breast cancer. As an estrogen receptor inactivator, it promises to have equivalent or superior activity to the competitive antiestrogens and aromatase inhibitors or inactivators currently in use. At the same time, its unique mechanism of action promises to avoid clinical disadvantages of these agents. Although disadvantaged by the need for parenteral administration, fulvestrant appears to be somewhat more potent, does not promote undesirable effects on other hormone-sensitive tissues and may not be vitiated by the development of resistance to the same extent. Ongoing studies will continue to provide new knowledge and experience that will enable effective application in the clinic.

Manufacturer

AstraZeneca plc (GB).

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