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Biochimica et Biophysica Acta 1587 (2002) 326–337

BIOCHIMICA ET BIOPHYSICA ACTA

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Review

Exemestane, a new steroidal aromatase inhibitor of clinical relevance☆

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Received 24 January 2002; accepted 24 January 2002

Abstract

Breast cancer is the leading cause of death among women and the contribution of circulating oestrogens to the growth of some mammary tumours has been recognized. Consequently, suppression of oestrogen action by inhibition of their biosynthesis at the androstenedione-oestrone aromatization step, by means of selective inhibitors of the enzyme aromatase, has become an effective therapeutic option for the treatment of hormone-dependent breast cancer. Exemestane (6-methylenandrosta-1,4-diene-3,17-dione) is a novel steroidal irreversible aromatase inhibitor recently approved and introduced into the global market under the name Aromasin®. The design, laboratory and viable syntheses of exemestane, starting from a variety of steroidal precursors, are presented and discussed. Data from biochemical and pharmacological studies as well as the clinical impact of the compound are briefly reviewed. The drug is an orally active and well-tolerated hormonal therapy for postmenopausal patients with advanced breast cancer that has become refractory to standard current hormonal therapies. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Exemestane; 6-Methylenandrosta-1,4-diene-3,17-dione; Aromasin; Aromatase inhibitor; Steroid chemistry; Breast/hormone-dependent cancer

1. Introduction

Breast cancer is the leading cause of deaths among women with 1 million new cases in the world each year and with a rate of over 56 per 100,000 population in Western Europe [1]. One-third of human breast tumours are hormone-dependent [2] and epidemiological and experimental evidence strongly supported that oestrogens are the most important hormones involved in the growth of these tumours [3]. The observation that administration or subtraction of hormones could interfere with the growth of some tumours was first made over a century ago when regression of metastatic breast carcinoma was achieved successfully by ovariectomy [4], and significant advances in the endocrine ablative therapy for breast cancer were obtained with the introduction of bilateral adrenalectomy in the fifties, and of hypophysectomy in the sixties, as a mean of depleting oestrogens biosynthesis.

The development of hormone receptor measurements [5], by allowing the identification of patients likely to respond to hormonal therapy (60% of postmenopausal women), provided an impetus for the search and development of anti-oestrogens, progestins, LH-RH antagonists and inhibitors of oestrogen biosynthesis, in order to counteract oestrogen action.

The agents used to block oestrogen biosynthesis as a mean to deplete circulating oestrogen levels, highlighted the importance of the enzyme aromatase as a rational target for the effective and selective treatment for some postmenopausal patients with hormone-dependent breast cancer [6,7].

Aromatase, a *P*-450-dependent enzyme, catalyses the ultimate step in oestrogen biosynthesis (Scheme 1) that converts androgens to oestrogens both in pre- and postmenopausal women [8]. While the main source of oestrogen (primarily oestradiol) is the ovary in premenopausal women, the principal source of circulating oestrogens in postmenopausal women is from the aromatization of adrenal and ovarian androgens (androstenedione and testosterone) to oestrogens (oestrone and oestradiol) by the enzyme aromatase in peripheral tissues (muscle, body fat).

Abbreviations: AcOH, acetic acid; *i*-AmOH, *iso*-amylic alcohol; DABCO, 1,4-diazabicyclo[2.2.2.]octane; DDQ, dichlorodicyanobenzoquinone; DMBA, 7,12-dimethylbenzanthracene; DMF, *N*,*N*-dimethylformamide; ED_{50}, median effective dose; IC_{50}, median inhibiting concentration; K_i, inhibition constant; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NaOAc, sodium acetate; PMSG, pregnant mares' serum gonadotropin; THF, tetrahydrofuran; *p*-TsOH, *para*-toluenesulfonic acid

☆ Text of oral presentation at the 8th International Symposium on Molecular Aspects of Chemotherapy, September, 2001, Gdansk, Poland.

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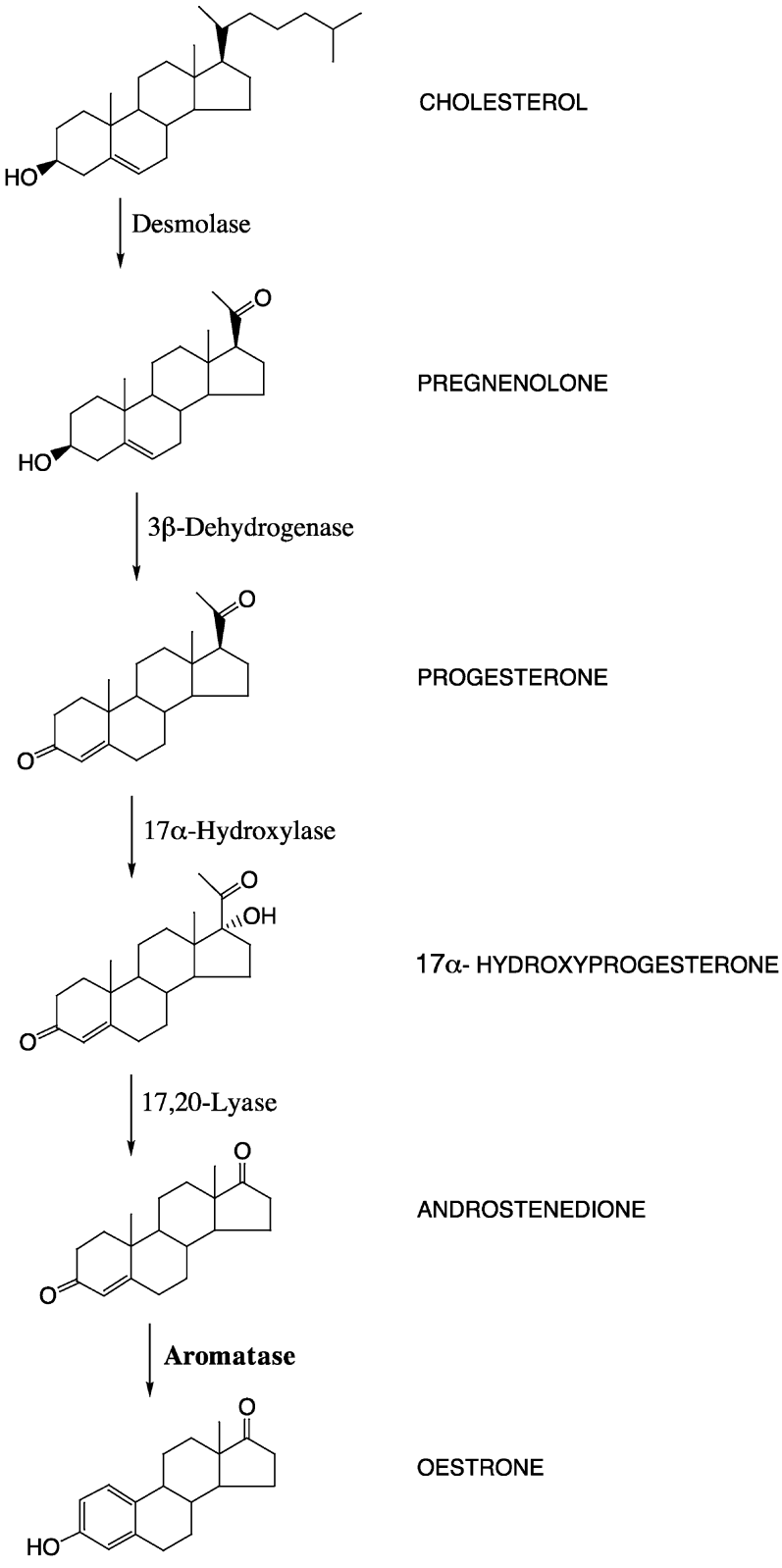
0925-4439/02/$ - see front matter
PII: S0925-4439(02)00096-0



Scheme 1. Biosynthesis of oestrogens.

Testololactone, marketed under the name TESLAC®, and aminoglutethimide, marketed under the name ORIMETEN®, may be regarded as the pioneer drugs of this type. The former has been used clinically in the treatment of postmenopausal breast cancer for 20 years with modest response rate, and later was discovered to be an

irreversible aromatase inhibitor of very low potency [9]. The latter, a nonsteroidal, nonspecific, reversible and competitive inhibitor of aromatase, serendipitously showed its endocrine properties after years of clinical use as an anticonvulsant [10].

Since these drugs have been of some benefit in postmenopausal breast cancer but of moderate efficacy or tolerability, the search and development of new, more potent, specific and safer aromatase inhibitors became an attractive, shared and well-founded option in the early 1980s. Efforts from numerous research groups worldwide eventually produced a selection of aromatase inhibitors, which are now in clinical use or in advanced clinical trials [11–15] (Fig. 1), positioning today these new agents in the mainstay of endocrine therapy for breast cancer treatment [16–19,20a,b,21].

2. The enzyme aromatase and aromatase inhibitors

The aromatization of C19-steroids (androgens) to obtain C18-steroids (oestrogens) is performed by the enzyme complex aromatase (oestrogen synthetase). The complex

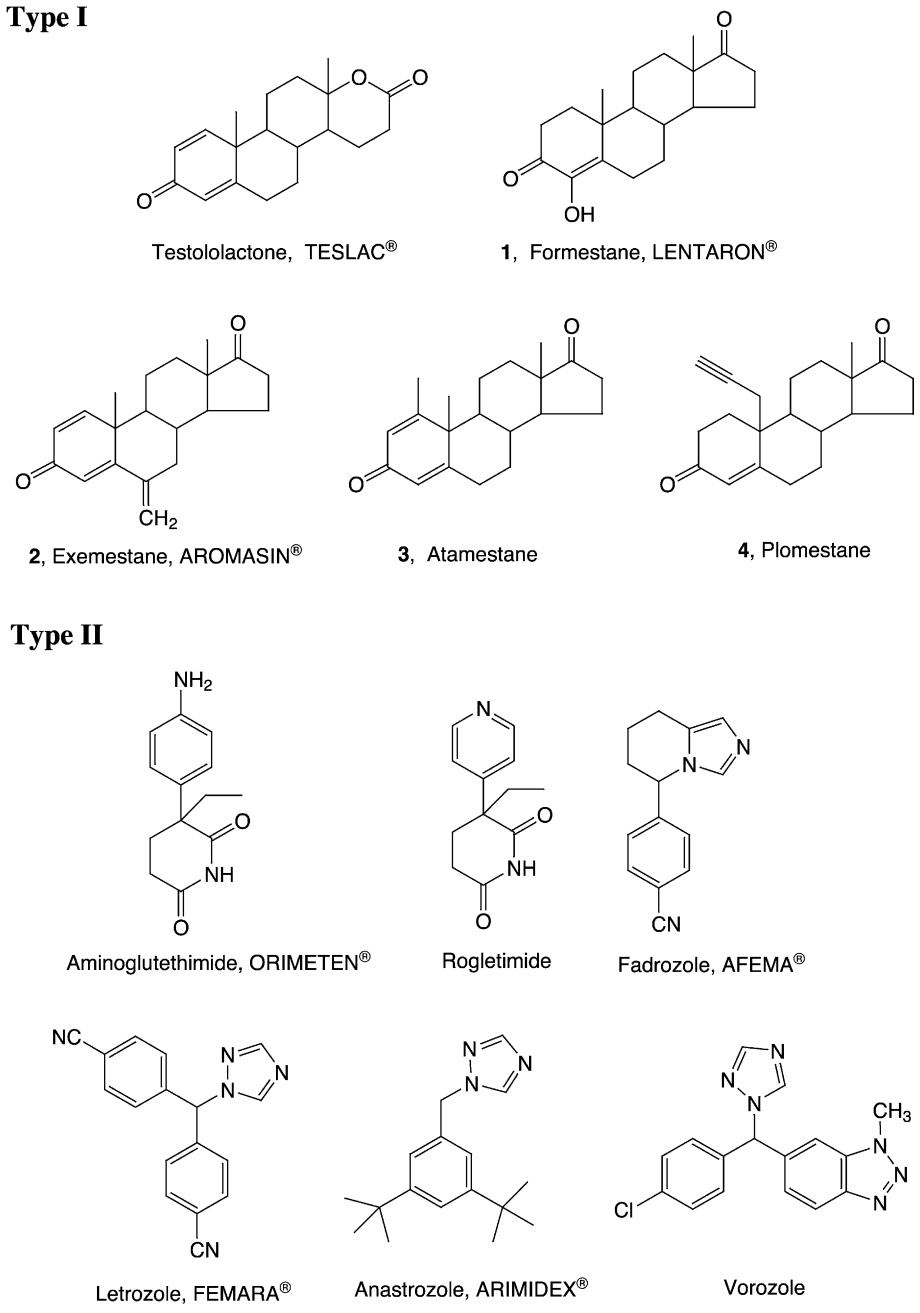


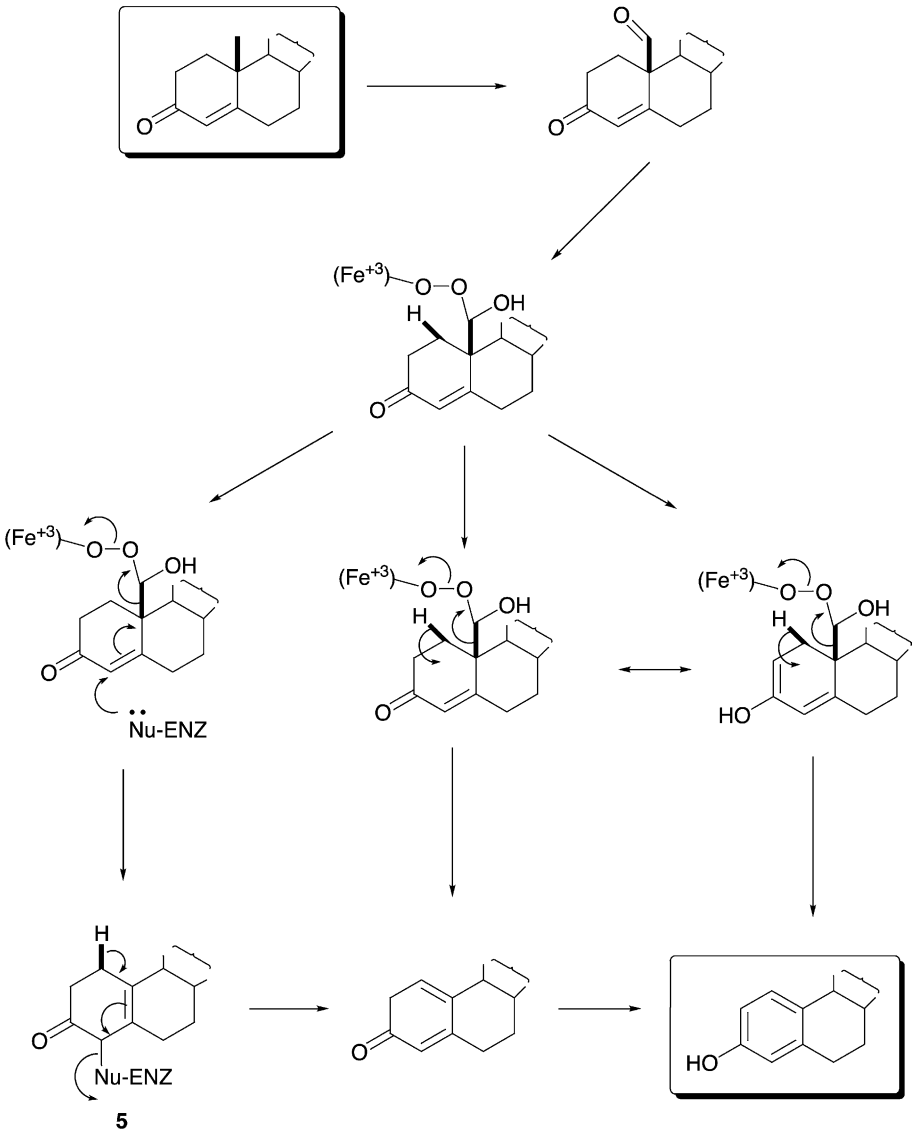
Fig. 1. Structure and classification of aromatase inhibitors in the clinical practice or in the clinical testing.

consists of a flavoprotein, reduced nicotinamide adenine dinucleotide phosphate (NADPH)–cytochrome *P*-450 reductase, that transfers electrons from NADPH to the terminal enzyme, and a specific form of the cytochrome *P*-450 enzyme system, known as aromatase cytochrome *P*-450, which is the protein involved in the specific recognition and binding of C19-steroid substrates. The protein catalyzes a three-step oxidative reaction sequence at C-19 culminating in the cleavage of the angular C-19 methyl group and in the aromatization of the ring A, releasing formic acid and water (Scheme 2) [22]. The process is allowed by the ability of the prosthetic group (haeme–iron porphyrin complex) of aromatase to activate dioxygen for insertion into C–H bonds. A number of postulated mechanisms have been considered over the years, and the rationalization of the third oxidative step as well as the stereochemical outcome of the elimination of the 1- and 2-hydrogens are still matters for debate. It is not a purpose of this paper to comment on various hypothesis, and authors active in this field are only referred [23–32].

Since aromatase has both an iron-containing and a steroid-binding site presenting two reasonable ways for inhibition, aromatase inhibitors have been traditionally divided into the two classes of Type I and Type II inhibitors.

2.1. Type II aromatase inhibitors

Type II aromatase inhibitors, such as aminoglutethimide, rogletimide, fadrozole, anastrozole, letrozole and vorozole, act by reversibly binding to the enzyme and by interfering with the haeme–iron group of the cytochrome *P*-450 moiety of the enzyme. A variety of enzymes possess cytochrome *P*-



Scheme 2. Conversion of androgens into oestrogens. A number of postulated mechanisms about the last oxidative step have been considered over the years.

450 prosthetic groups, therefore, candidate inhibitors should be carefully designed in order to be aromatase-specific. Because they are reversible, ongoing oestrogen deprivation depends upon the continued presence of the drug, thus posing potential toxicity issues [13–15].

2.2. Type I aromatase inhibitors

Type I, or irreversible inhibitors (also known as suicide or mechanism-based inactivators), such as testololactone, formestane (4-hydroxyandrost-4-ene-3,17-dione (**1**)), exemestane (6-methylenandrosta-1,4-diene-3,17-dione (**2**), FCE 24304, PNU 155971), atamestane (1-methylandrosta-1,4-diene-3,17-dione (**3**), SH 489) and plomestane (10β-(2-propynyl)estr-4-ene-3,17-dione (**4**), MDL 18692) interact with the substrate-binding site of the enzyme. They must have an androstenedione-like structure and should be designed in order to be transformed by the normal catalytic action of the target enzyme into reactive species. Covalent bond formation then occurs with a nucleophilic site of the enzyme, leading to the irreversible inactivation of the target enzyme by preventing enzyme catalysis from occurring [11]. Because the inhibition is irreversible, renewed oestrogen production requires biosynthesis of new enzyme aromatase [15]. This would result in reduced side effects when the inhibitor is used as a drug, since the inhibitor's effect can persist after its clearance from the system and the continuing presence of the drug to maintain inhibition is thus not necessary.

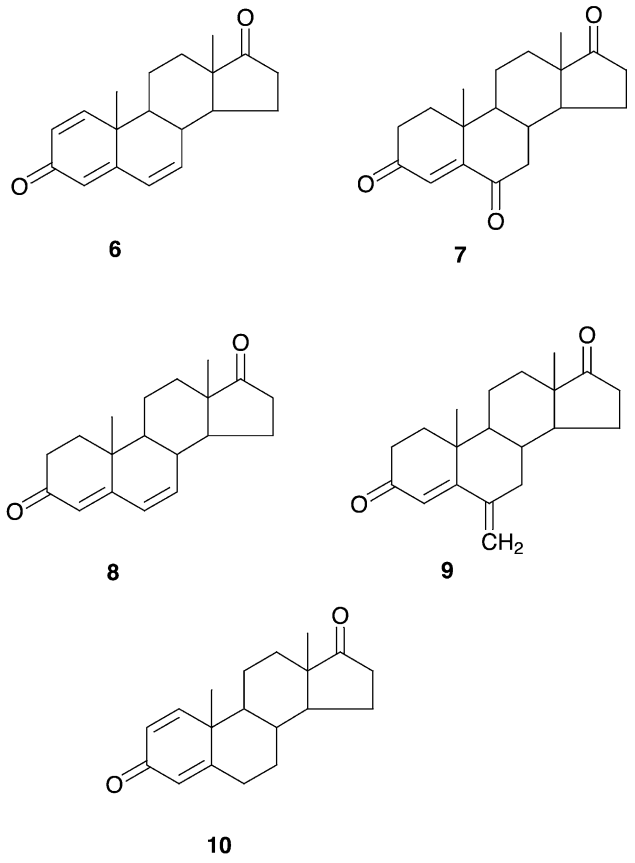


Fig. 2. Androstenedione-like structures tested as aromatase inhibitors.

2.3. Formestane

As early as 1973, over 100 steroids were studied by the group led by H. Brodie and A. Brodie for potential anti-aromatase activity [33,34]. Candidate inhibitors were evaluated in vitro by comparing the extent of aromatization of [1β,2β-^{3}H]androstenedione to oestrogen in incubations of microsomes from aromatase-containing tissues (human placenta or ovaries of rats stimulated with pregnant mares' serum gonadotropin, PMSG). The inhibitors with greatest activity were 1,4,6-androstatriene-3,17-dione (**6**) [34,35], 4-androstene-3,6,17-trione (*7*) [33] (Fig. 2), and **1** [36a]. All showed Lineweaver–Burk plots typical of competitive inhibition, which occurs rapidly in the presence of both substrate (androstenedione) and inhibitor, and also caused slower time-dependent loss of enzyme activity which follows pseudo first-order kinetics in microsomes preincubated in the absence of substrate, but in presence of the cofactor NADPH [36a]. No loss of activity occurred in the absence of the cofactor. These findings suggested that all three compounds caused long-term inactivation or irreversible inhibition of aromatase, and that they can be regarded as mechanism-based or suicide inhibitors.

The most interesting compound resulted to be **1**, a potential anabolizing agent previously synthesized in the laboratories of Farmitalia [36b], which was evaluated clinically in the 1980s under the name formestane [37] and introduced into the market in 1993 under the name LENTARON® (Ciba-Geigy, now Novartis) with the indication for the treatment of advanced breast cancer in postmenopausal women. In clinical trials, weekly deep intramuscular injections with 500 mg of formestane to unselected breast cancer patients resulted in a 60% suppression of plasma oestradiol levels and an overall response rate of almost 30%. Similar responses, obtained with a daily oral administration of 500 mg, were however indicative of a poor bioavailability by this route. A rapid metabolization of formestane also occurs primarily as the glucoronide conjugate.

3. Exemestane

In order to overcome the unfavourable metabolism and poor oral availability of 4-hydroxyandrostenedione, several groups were engaged in the synthesis and pharmacological evaluation of novel irreversible aromatase inhibitors with improved oral activity. The group led by E. di Salle and P. Lombardi at Farmitalia Carlo Erba (now Pharmacia) designed, synthesised and evaluated the novel steroid **2** (FCE 24304, exemestane). Despite impressive steroid chemistry conducted over the previous decades, the structure of exemestane resulted a new one. The design of the

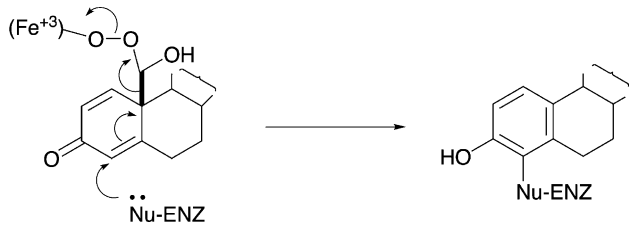
molecule was derived by early findings that effective aromatase inhibitors resemble the androst-4-ene-3,17-dione substrate sterically and electronically, and that better inhibition was found in derivatives containing the Δ^4-3,6-dione, $\Delta^{1,4,6}$-3-one or the $\Delta^{4,6}$-3-one moieties [33]. The 6-keto and Δ^6 groupings of these compounds extend linear conjugation of the parent Δ^4-3-one system and the enzyme system appeared to bind well to these longer, delocalised π bond systems. Exemestane was found to inhibit human placental aromatase with a potency similar to formestane (in comparative experiments, $IC_{50} = 42$ and 44 nM, respectively) and in preincubation studies exemestane caused time-dependent (irreversible) inactivation of the enzyme [38,39].

However, both androsta-4,6-diene-3,17-dione (**8**) [24] and 6-methylenandrost-4-ene-3,17-dione (**9**) [38] are not time-dependent inactivators, and irreversible aromatase inhibition exibited by exemestane as well as by ***6***, and 1,4-androstadiene-3,17-dione (**10**), may rely on the lack of the 1β-hydrogen. At the time these compounds were under characterization, a postulated mechanism for conversion of androgens into oestrogens hypothesised the formation of an enzyme-bound intermediate **5** [24]. This intermediate collapses to an aromatized product via elimination of the 1β-hydrogen and enolisation of the resulting keto-diene moiety, which releases the oestrogen and simultaneously regenerates the unaltered and active free enzyme (Scheme 2). In the presence of the 1,2-double bond, the enzyme-bound intermediate will aromatize without undergoing the final elimination reaction. Thus, the 1,2-unsaturation acts as a latent alkylating group (Scheme 3).

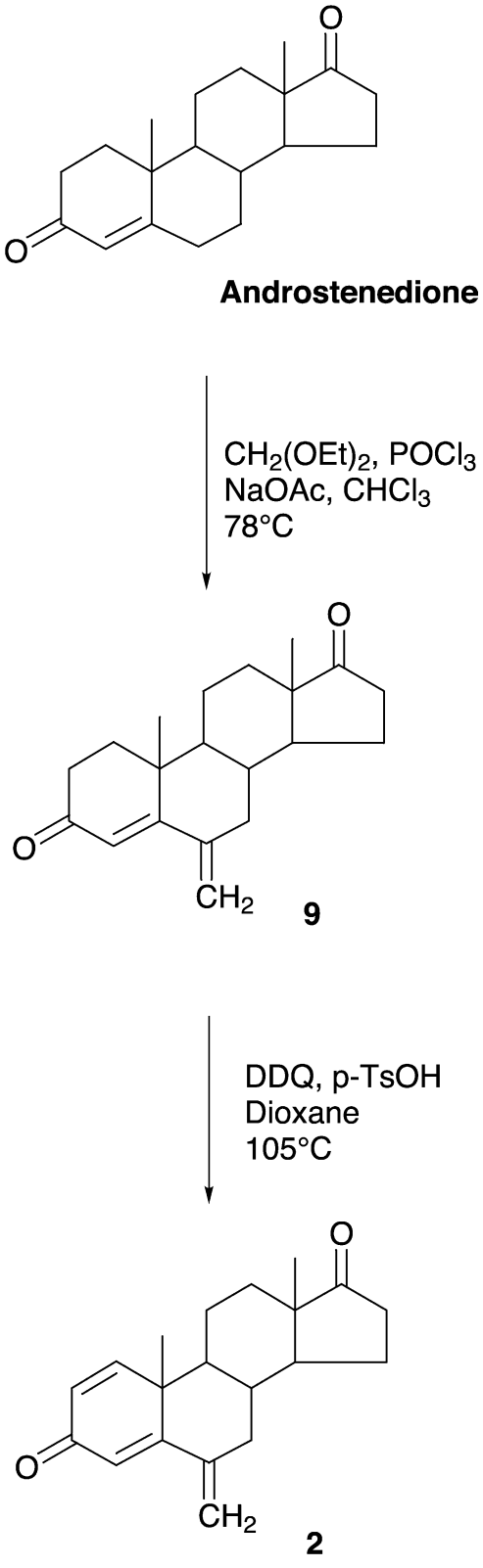
Exemestane entered preclinical development in 1986, and successfully performed clinical trials during the 1990s to receive FDA approval on October 21, 1999 for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen (antioestrogen) therapy. The compound, marketed under the name AROMASIN® (Pharmacia), is the first oral aromatase inactivator.

3.1. Chemistry

The direct introduction of a methylene group at 6-position of a 3-oxo-4-ene steroid is a known process. Therefore, the laboratory synthesis of exemestane, **2**, (Scheme 4) [40] exploited the 6-methylenation of androstenedione with



Scheme 3. Postulated aromatase inactivation mechanism by 1,4-androstadiene-like structures.



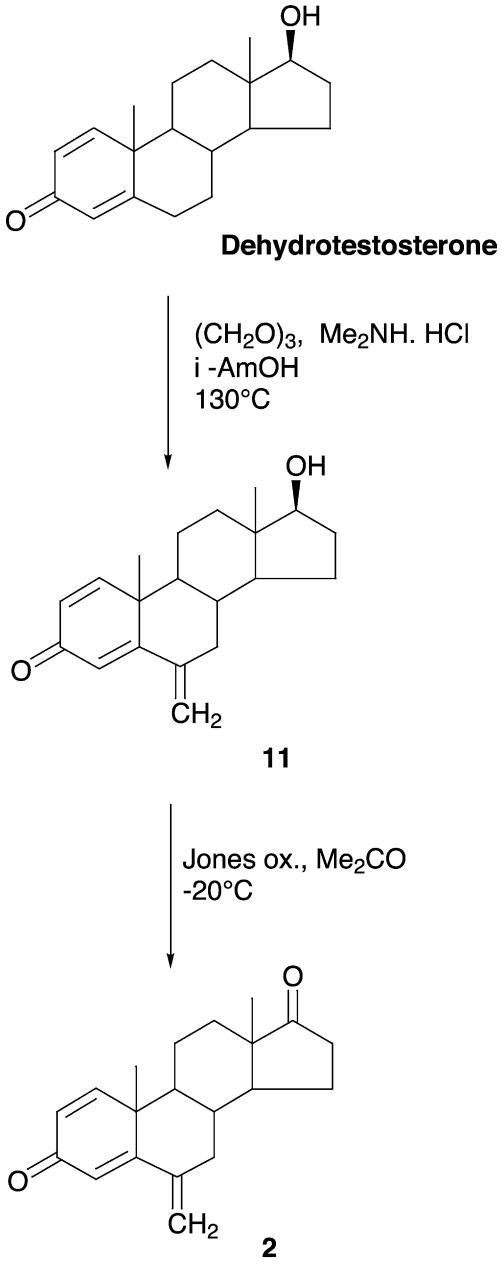
Scheme 4. Laboratory synthesis of exemestane (**2**).

formaldehyde acetal and $POCl_3$ to give **9**, according to the general method of Annen et al. [41]. The introduction of the required 1,2-double bond to obtain **2** was then per-

formed by dichlorodicyanobenzoquinone (DDQ) dehydrogenation.

In order to overcome the disadvantages and drawbacks of these methods, represented by low yields, high price of DDQ and chromatographic purifications, other processes amenable to be scaled up were developed at Farmitalia Carlo Erba.

A more original and practical synthetic approach, starting from commercially available dehydrotestosterone, disclosed an unusual and unprecedented Mannich reaction on a cross-conjugated dienone moiety by fetching the direct introduction of the methylene group at the 6-position of a 3-oxo-1,4-diene steroid, performed with paraformaldehyde and dimethylamine in *iso*-amylic alcohol (*i*-AmOH) at 130 °C (Scheme 5) [42]. The hydroxyl function at C-17 of the ring D of the starting steroid must be initially present to avoid a competitive Mannich reaction occurring preferentially at C-16 if the 17-oxo analogue would have been the synthetic precursor. The 6-methylene intermediate (**11**), obtained by precipitation from the above reaction mixture in 35% yield, gave exemestane, **2**, in 28% overall yield, after crystallisation of the solid residue resulting from the work-up of the Jones oxidation to introduce the 17-keto group.



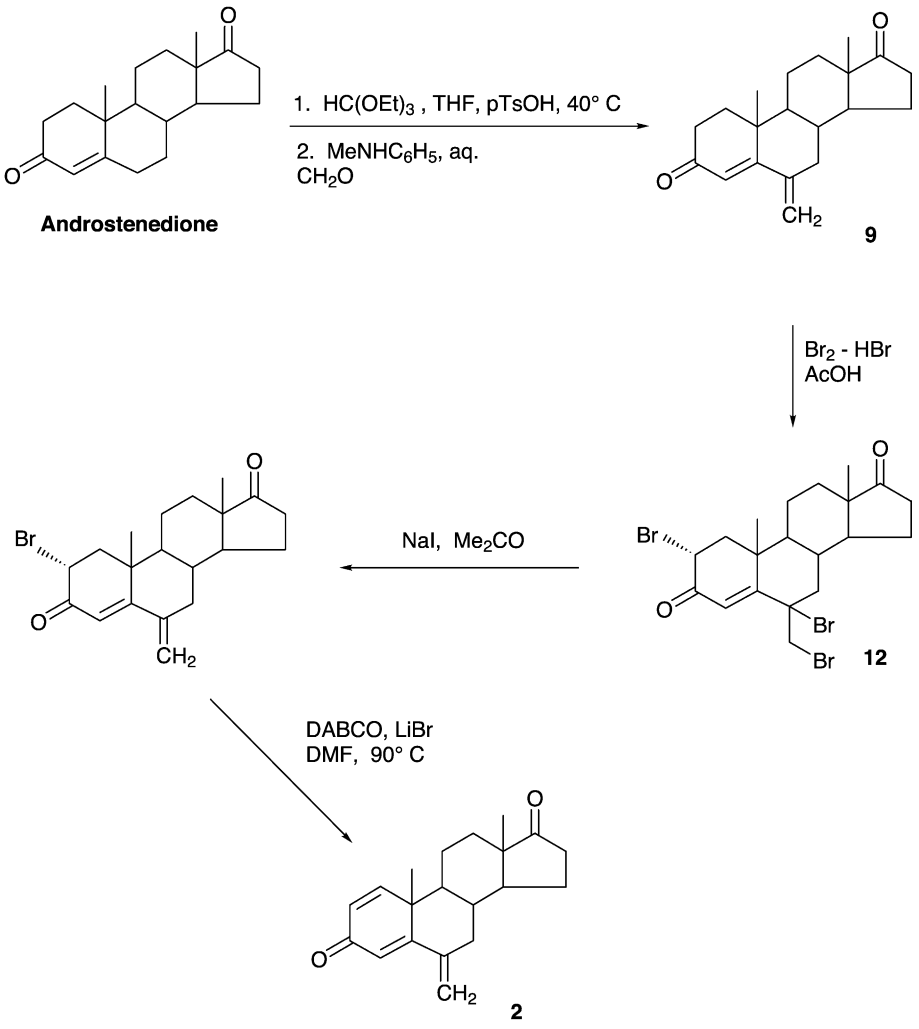
Scheme 5. Viable synthesis of exemestane (**2**) from dehydrotestosterone.

An alternative synthetic viable route of exemestane was also set up after having performed a remarkably efficient 6-methylenation of the less expensive and more readily available androstenedione with a corporate know-how used in the industrial synthesis of Farmitalia's medroxyprogesterone acetate (Scheme 6) [43,44]. Accordingly, androstenedione was first reacted with triethylorthoformate in tetrahydrofuran (THF)–EtOH at 40 °C in the presence of *para*-toluenesulfonic acid (*p*-TsOH). The resulting ethyl 3,5-dienolether without isolation was subjected to Mannich reaction with *N*-methylaniline and aqueous formaldehyde. The adduct intermediate was decomposed with concentrated HCl and the resulting 6-methylene intermediate **9** was obtained in 73% yield after simple precipitation. The introduction of the double bond at 1,2-position of the 3-oxo steroid skeleton can be also easily carried out by bromination–dehyrobromination. However, in the present case, bromination of **9** with bromine in THF–AcOH at 0 °C and a catalytic amount of HBr afforded the expected tribromide (**12**) in 84% yield and in almost pure form after precipitation. Partial debromination with sodium iodide in refluxing acetone provided the crude 2-bromointermediate, which was dehydrohalogenated with LiCl and $LiCO_3$ in *N*,*N*-dimethylformamide (DMF) at 120 °C to give exemestane, **2**, by precipitation with water in 47% yield based on androstenedione.

A recent Pharmacia process entailed the enzymatic 1,2-dehydrogenation of **9** (Scheme 7) [45]. Accordingly, the intermediate **9** and whole cells of *Arthrobacter simplex* were mixed and agitated during some days in toluene and water in the presence of menadione, as a radical scavenger, and phosphate buffer. Exemestane, **2**, was collected from the toluene phase after concentration and precipitation with octane.

3.2. Biology

The properties of exemestane were compared in vitro and in vivo with the structurally related compounds **9** and **10** [38]. In initial co-incubation studies with the substrate, all three steroids were found to inhibit human placental aromatase, being exemestane the more potent (Table 1). However, this experiment gives only a preliminary indication of the compounds' inhibitory potency, since the values could be the result of both competitive and time-dependent



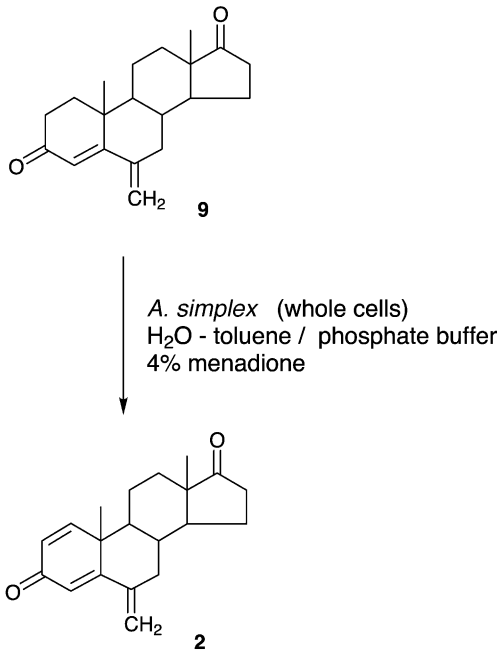
Scheme 6. Viable synthesis of exemestane (**2**) from androstenedione.

enzyme inhibition. In pre-incubation studies (0–32 min with human placental aromatase and in the presence of NADPH) both exemestane, **2**, and **10** induced time-dependent enzyme inactivation, whereas no time-related decrease in aromatase activity was observed with the 6-methylene derivative **9** (Table 2). Exemestane showed a higher aromatase affinity than **10** (K_i = 26 and 92 nM, respectively) and a faster enzyme inactivation ($t_{1/2}$ = 13.9 and 24.1 min, respectively).

For in vivo studies, female rats with PMSG-stimulated ovarian aromatase were used. Twenty-four hours after dosing (10 mg/kg subcutaneously), **9** was completely inactive, **10** lowered ovarian aromatase to 66% of the control value, whereas inhibition was far more pronounced with exemestane which reduced ovarian aromatase to 19% of control activity (Table 3). In further dose–response studies, exemestane was shown to reduce ovarian aromatase with an ED_{50} of 1.8 mg/kg (s.c.) and, much interestingly, the compound was also very potent when given orally, its ED_{50} being 3.7 mg/kg (p.o.) (Fig. 3).

The antitumour activity of exemestane was studied in rats with 7,12-dimethylbenzanthracene (DMBA)-induced tumours. Exemestane given s.c. induced 44% tumour regression at a dose of 3 mg/kg per day and, when the compound was given orally on the same treatment schedule, tumour regressions amounted to 50% at 100 mg/kg [46]. However, in the DMBA-induced mammary tumour in ovariectomized female rats treated with testosterone, a postmenopausal breast cancer model, exemestane was shown to be highly effective by both s.c. (88% and 96% tumour regression at 10 and 50 mg/kg daily, respectively), and oral routes (76% and 88% tumour regression at the same doses) [47].

The properties of exemestane were also compared with those of steroidal aromatase inhibitors developed by other research groups, namely formestane, **1**, atamestane, **3**, and plomestane, **4** [39]. In initial coincubation studies with the substrate, atamestane was found to be the most potent inhibitor, showing an IC_{50} of 20.3 nM, compared to 31.3 nM for plomestane, 42.5 nM for exemestane, and 43.7 nM



Scheme 7. Microbiological conversion of 6-methylenandrostenedione (**9**) to exemestane (***2***).

for formestane. In preincubation studies with the enzyme, formestane, atamestane and plomestane caused, like exemestane, time-dependent enzyme inhibition, and striking differences between them were observed. Formestane was the fastest aromatase inactivator, showing a $t_{1/2}$ of 2.1 min, whereas plomestane had a $t_{1/2}$ of 13.1 min, similar to exemesatne (13.9 min), and atamesatne was the slowest inactivator, with a $t_{1/2}$ of 45.3 min. Plomestane and atamestane showed very high affinity for the enzyme, having a K_i of 0.7 and 2.0 nM, respectively, compared to 26.0 nM for exemestane and 29.0 nM for formestane.

However, the most striking and significant differences were observed in vivo in the PMSG-pretreated rat experiment. Compared to formestane, plomestane and atamestane, exemestane was the most potent compound after both subcutaneous and oral admnistration, giving ED_{50} values of 1.8 and 3.7 mg/kg, respectively. Plomestane showed the same potency as exemestane only by the subcutaneous route (ED_{50} 1.4 mg/kg) and was less effective orally (ED_{50} 18 mg/kg). Formestane caused enzyme inactivation after subcutaneous dosing (ED_{50} 3.1 mg/kg), but had scant effect even at 100 mg/kg orally. Atamestane, despite its very high enzyme affinity, caused very low enzyme inactivation even subcutaneously (Table 4). In comparative DMBA-induced mammary tumour studies in rats, the antitumour efficacy of exemestane was much greater than that of atamestane, plomestane and formestane [48,49].

Table 1
In vitro inhibition of human placental aromatase

Compound	IC_{50} (nM)
Exemestane (**2**)	42.5
6-Methylenandrostenedione (**9**)	110.5
1,4-Androstadienedione (**10**)	81.1

The compounds were co-incubated for 15 min with substrate [1β,2β-^3H]androstenedione (50 nM).

Table 2
Time-dependent aromatase inhibition

Compound	K_i (nM)	$t_{1/2}$ (min)
Exemestane (**2**)	26	13.9
6-Methylenandrostenedione (**9**)	no time-dependent inhibition observed	
1,4-Androstadienedione (**10**)	92	24.1

The compounds were pre-incubated for 0–32 min with human placental aromatase in the presence of NADPH.

3.3. Clinical efficacy

In healthy postmenopausal volunteers, which were given single oral doses of exemestane ranging from 0.5 to 800 mg, the minimal effective dose in decreasing oestrogen levels was 5 mg and the minimal dose which produced the maximum suppression of plasma oestrogens, observed at day 3 and persisting on day 5, was 25 mg. The long-lasting inhibitory effect of exemestane on oestrogen synthesis is likely due to the irreversible nature of its enzyme inhibitory property, rather than to its pharmacokinetic properties. In fact, the drug was rapidly adsorbed and reached peak levels within 2 h after oral administration, rapidly disappearing thereafter [50, 51].

Exemestane was extensively metabolized in all species. The initial steps are the reduction of the 17-keto group to give the 17β-hydroxy steroid **11**, and the oxidation of the methylene group in position 6 with subsequent formation of many secondary metabolites, identified by comparison with synthetic reference compounds (Fig. 4) [52,53]. All metabolites were found to be either inactive in inhibiting aromatase or less potent than exemestane, thus excluding a possible contribution of any metabolite to the observed prolonged effect of the drug.

In earlier clinical studies with heavily pretreated, postmenopausal patients with advanced breast cancer failing multiple hormonal treatments, exemestane, at repeated daily oral doses ranging from 5 to 600 mg, caused a maximal

Table 3
Effect of subcutaneous dosing on ovarian aromatase activity in PMSG-stimulated rats

Compound	Dose (mg/kg, s.c.)	Ovarian aromatase (% controls)
Vehicle	–	100
Exemestane (**2**)	10	19
6-Methylenandrostenedione (**9**)	10	104
1,4-Androstadienedione (**10**)	10	66

Aromatase activity remaining was determined in the ovarian microsomal fraction obtained 24 h after inhibitor dosing.

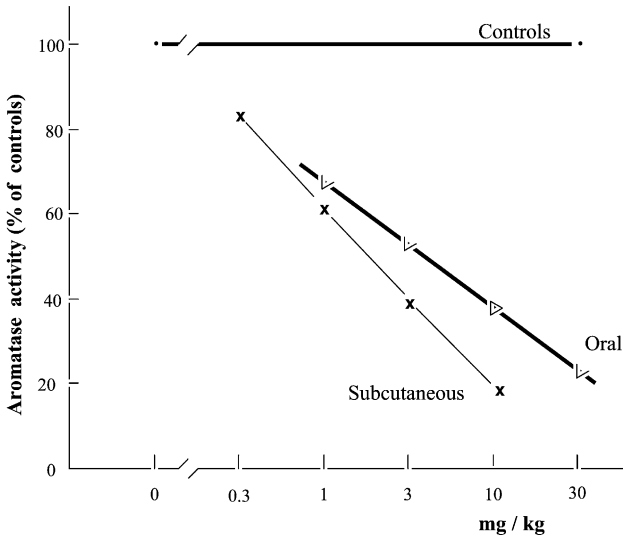


Fig. 3. Effect of subcutaneous and oral dosing of exemestane (**2**) on ovarian aromatase activity in PMSG-stimulated rats. Aromatase activity remaining was determined in the ovarian microsomal fraction obtained 24 h after inhibitor dosing and expressed as percentage (%) of controls.

inhibition (>90%) of plasma oestrogens starting from the lower doses. An objective positive response was observed in up to 33% of evaluable patients, which was promising considering that exemestane was administered as third- or fourth-line hormonal treatment in most cases [54–57].

The minimal effective exemestane oral dose for endocrine activity in advanced breast cancer patients was assessed at 0.5 mg/day, achieving oestrogen suppression of about 25–30% versus baseline starting from day 7 of treatment [58]. The most favourable effects, as maximal suppression of oestrogens, tolerability and antitumour activity, were observed at 25 mg daily oral dose and a large, safe therapeutic window of up to 600 mg was defined [59,60].

A study aimed at determining the effect of exemestane on in vivo aromatization in postmenopausal women with advanced breast cancer showed, that at 25 mg daily oral dose exemestane inactivated peripheral aromatase activity by approximately 98% and reduced basal plasma oestrone, oestradiol and oestrone sulfate levels by 85% to 95% after 6–8 weeks of therapy, with respect to values before treatment [61].

Table 4
Effect of oral dosing on ovarian aromatase activity in PMSG-stimulated rats

Compound	Dose (mg/kg, orally)	Ovarian aromatase (% controls)	ED_{50} (mg/kg, orally)
Exemestane (**2**)	1	67.8	3.7
	3	53.6	
	10	34.8	
	30	23.6	
Formestane (**1**)	10	79.9	>100
	30	75.7	
	100	71.6	
Plomestane (**4**)	3	71.6	18
	10	57.4	
	30	43.7	
Atamestane (**3**)	30	76.8	>100
	100	89.2	

Aromatase activity remaining was determined in the ovarian microsomal fraction obtained 24 h after inhibitor dosing.

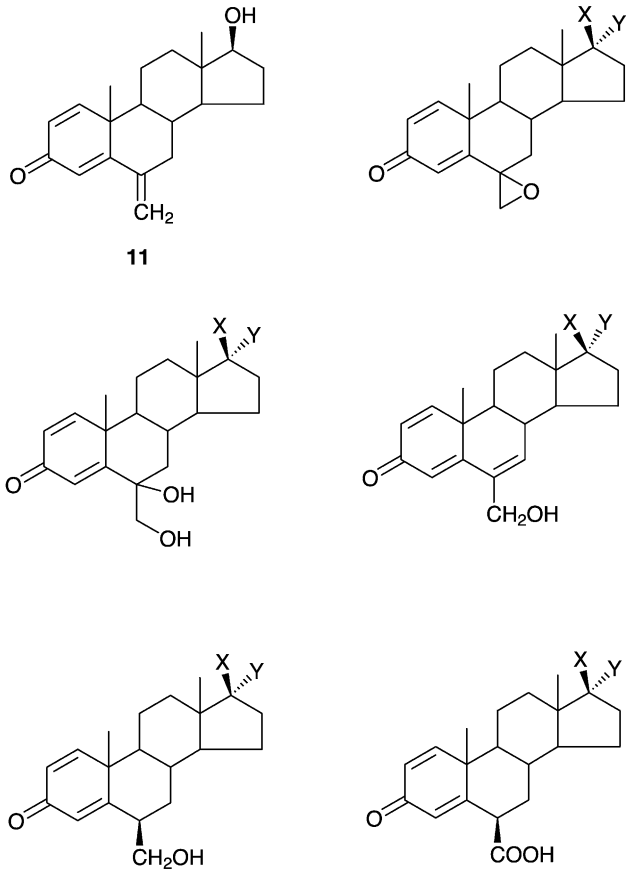


Fig. 4. Metabolites of exemestane (**2**). Exemestane is extensively metabolized to the 17β-hydroxy derivative (**11**) and to other compounds following oxidation of the 6-exomethylene group (X = OH, Y = H; X,Y = O).

In later clinical trials, exemestane improved survival time in postmenopausal patients with either advanced breast cancer or metastatic breast cancer, who had previously failed on the antioestrogen agent tamoxifen or on non-steroidal aromatase inhibitors treatment [62–66]. Ongoing clinical studies, aimed at comparing exemestane with tamoxifen as first-line therapy in metastatic breast cancer, already showed a preliminary, higher anti-tumour efficacy of 42–44% positive responses for exemestane versus 14–16% for tamoxifen [67,68].

4. Conclusions

Over the past decade, novel aromatase inhibitors have been discovered and introduced into the clinical practice, on the observation that the main mechanism of action of

aminoglutethimide was via inhibition of the enzyme aromatase, thereby reducing levels of circulating oestrogens in postmenopausal breast cancer patients.

The second generation drug was **1** (formestane), introduced into the market in 1993 under the name LENTARON®. Although its use was limited by its need to be given parenterally, it was found to be a well-tolerated form of endocrine therapy.

Third-generation inhibitors include anastrozole, letrozole, vorozole and exemestane, the former three being nonsteroidal competitive inhibitors, the latter being a steroidal irreversible inhibitor. All are capable of inhibiting aromatase action by >90% compared to 80% in the case of formestane.

Exemestane (AROMASIN®), a rationally designed, selective, orally active, long-lasting and safe hormonal drug, has demonstrated impressive pharmacologic and clinical properties in improving the treatment of breast cancer patients. It has also showed a great potential to be more effective as first-line treatment than other current drugs, comprising antioestrogens and nonsteroidal aromatase inhibitors.

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