Steroid Hormones

Steroid Hormones

- ✓ Steroid Hormones and related products represent one of the most widely used classes of therapeutic agents.

These drugs are used primarily in

1. Birth Control
2. Hormone-replacement Therapy HRT
3. Inflammatory Conditions
4. Cancer Treatment

- ✓ Most of these agents are chemically based on a common structural backbone, the steroid backbone.

Steroid Hormones

- ✓ There are Five general groups of Steroid Hormones :

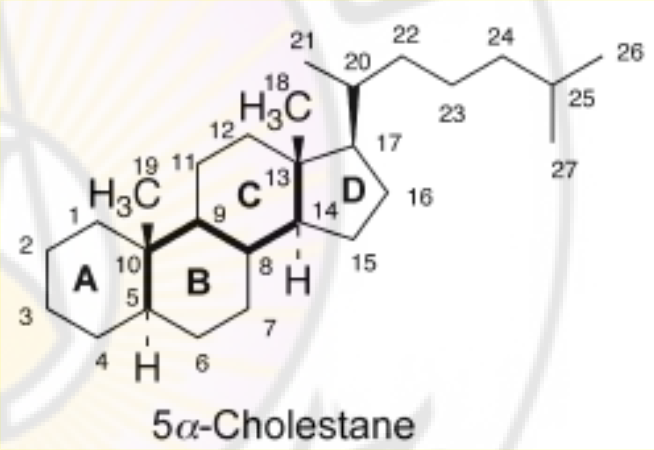
1. Estrogens
2. Progestins
3. Androgens
4. Glucocorticoids GCs
5. Mineralocorticoids MCs

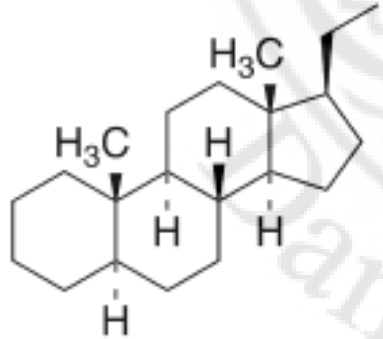
- ✓ Steroid Hormones in mammals are biosynthesized from Cholesterol.
- ✓ Although Steroid Hormones share a common structural foundation, the variations in the structures provide specificity for the unique molecular targets.

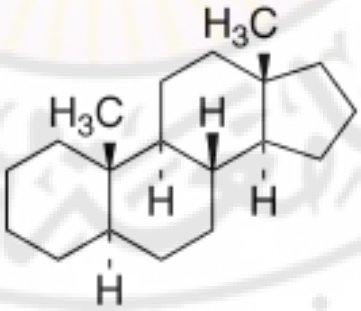
Steroid Hormones

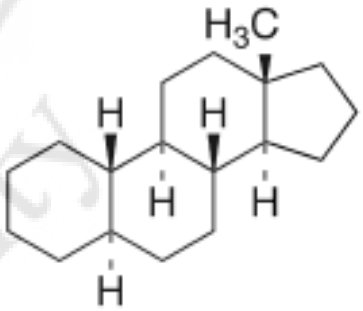
✓ nearly all steroids are named as derivatives of:

1. Cholestane
2. Pregnane
3. Androstane
4. Estrane



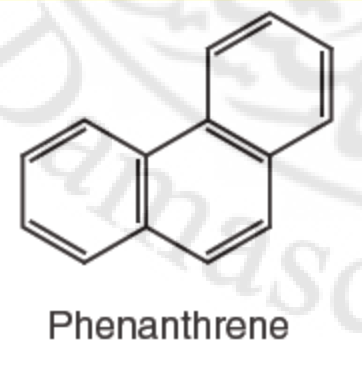


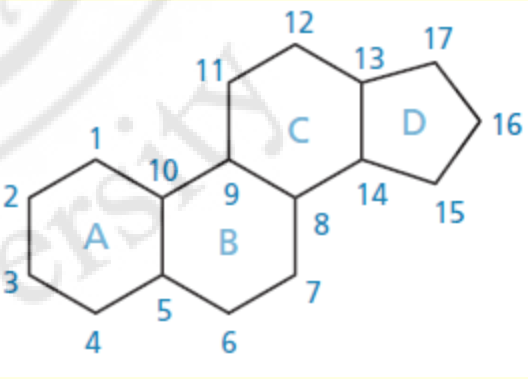




Steroid Hormones

- ✓ Steroids hormones consist of four fused rings (A, B, C, D).
- ✓ Chemically, these hydrocarbons are Cyclopentano perhydro phenenthrenes.
- ✓ They contain a five-membered cyclopentane (D) ring and the three rings of Phenanthrene.
- ✓ A perhydro phenanthrene (ring A, B, and C) is the saturated derivative of Phenanthrene.





Gonadotropins Hormone

- ✓ The gonadotropins are peptides that have a close functional relationship to estrogen, progesterone, testosterone.
- ✓ They are called *Gonadotropins* because of their actions on the gonads الغدد التناسلية.

- ✓ The gonadotropins include:

1. Luteinizing hormone LH
2. Follicle-stimulating hormone FSH
3. Chorionic gonadotropin CG

(hCG is human chorionic gonadotropin) a glycopeptide produced by the placenta; its pharmacological actions are essentially the same as those of LH

Gonadotropin Hormone

- ✓ They are called *gonadotropins* because of their actions on the gonads.

- ✓ Gonadotropins control:

1. Ovulation.
2. Spermatogenesis.
3. Development of Sex Organs.
4. Maintain Pregnancy.

Gonadotropin-Releasing Hormone GnRH

- ✓ The hypothalamus releases GnRH.
- ✓ GnRH is a peptide that stimulates the anterior pituitary to secrete LH and FSH in males and females.
- ✓ GnRH controls and regulates both male and female reproduction

Gonadotropin-Releasing Hormone GnRH

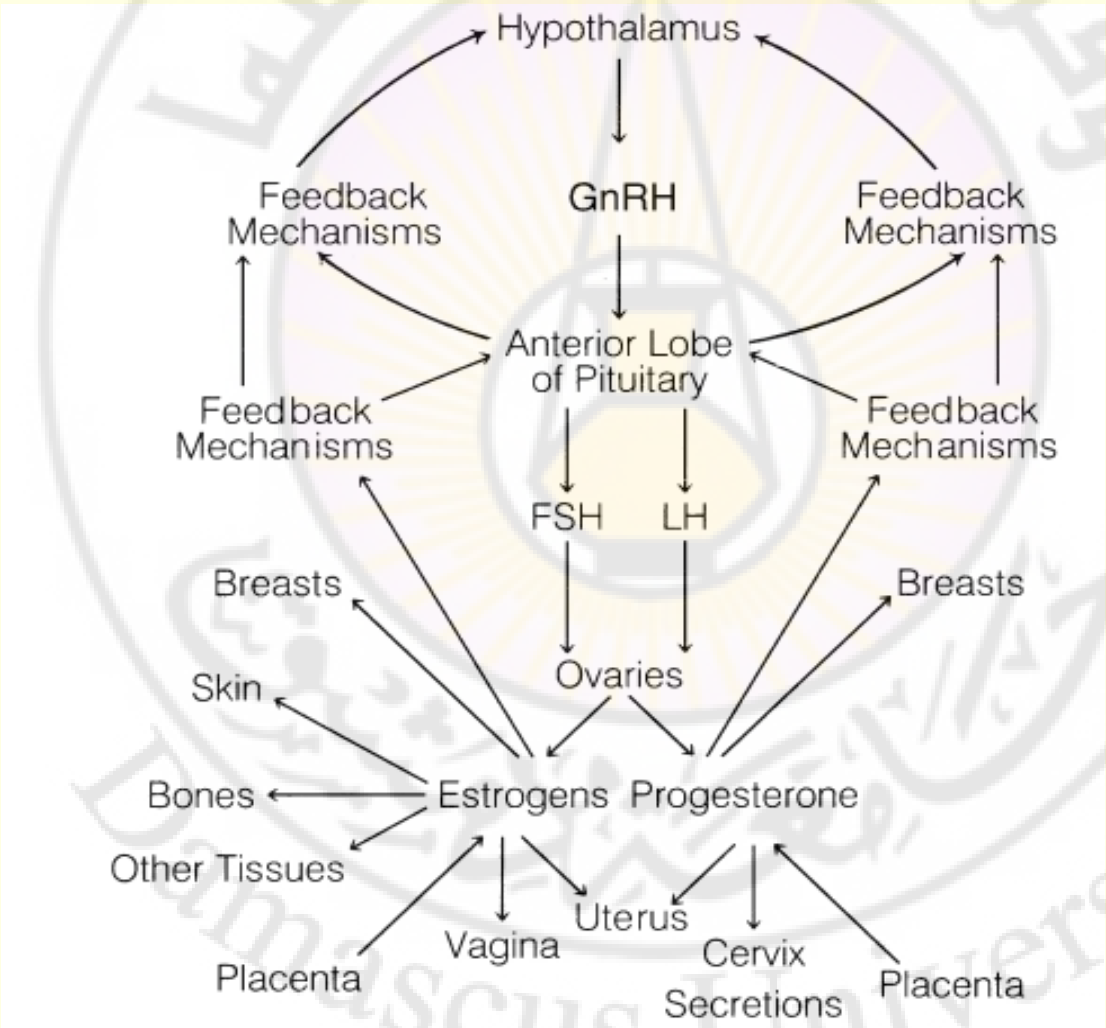


Figure 25.9 • Regulation of ovulation by GnRH.

Gonadotropin-Releasing Hormone GnRH

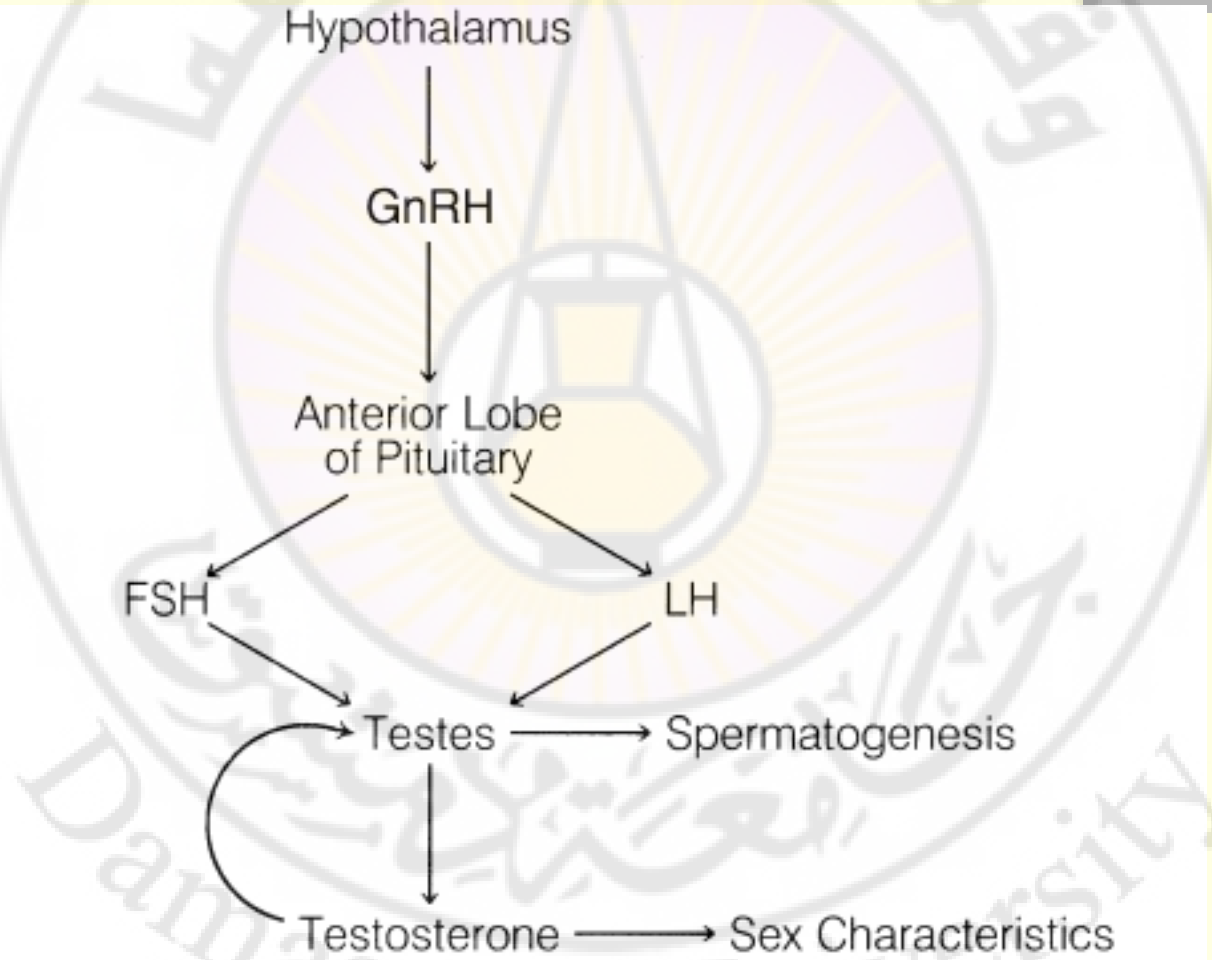


Figure 25.10 ● Regulation of spermatogenesis.

The pituitary gonadotropins: LH & FSH In Females

- ✓ In females, LH and FSH regulate the menstrual cycle.
- ✓ At the start of the cycle, plasma concentrations of estradiol and other estrogens and progesterone are low.
- ✓ FSH and LH stimulate several ovarian follicles to enlarge and begin developing more rapidly than others.
- ✓ After a few days, only one follicle continues developing to the release of a mature ovum.

The pituitary gonadotropins: LH & FSH In Females

- ✓ The granulosa cells of the maturing follicles begin secreting estrogens, which then cause the uterine endometrium to thicken and vaginal and cervical secretions increase.
- ✓ Gonadotropins and estrogen reach their maximum plasma concentrations at about day 14 of the cycle.
- ✓ The release in LH causes the follicle to break open, releasing a mature ovum.
- ✓ Under the stimulation of LH, the follicle changes into the corpus luteum, which begins secreting progesterone as well as estrogen.

The pituitary gonadotropins: LH & FSH In Females

- ✓ The increased concentrations of estrogens and progesterone regulate the hypothalamus and the anterior pituitary by a feedback inhibition process that decreases GnRH, LH, and FSH production.

- ✓ The result is that further ovulation is inhibited (this is the primary mechanism by which steroid birth control products inhibit ovulation).

- ✓ If fertilization does not occur by about day 25, the corpus luteum begins to degenerate, slowing down its production of hormones.

The pituitary gonadotropins
LH & FSH In Females

- ✓ The concentrations of estrogens and progesterone become too low to maintain the vascularization of the endometrium, and menstruation results.
- ✓ The pharmacological actions of hCG are essentially the same as those of LH.
- ✓ In females during pregnancy, the hCG secreted by the placenta maintains the corpus luteum to continue secretion of estrogen and progesterone, thus inhibiting ovulation and menstruation.

The pituitary gonadotropins
LH & FSH In Males

- ✓ LH stimulates testosterone synthesis by the testes.
- ✓ Testosterone and LH promote spermatogenesis (sperm production) and development of the testes.
- ✓ Testosterone is also essential for the development of secondary sex characteristics in males.
- ✓ FSH stimulates production of proteins and nutrients required for sperm maturation.

The pituitary gonadotropins
LH & FSH In Males

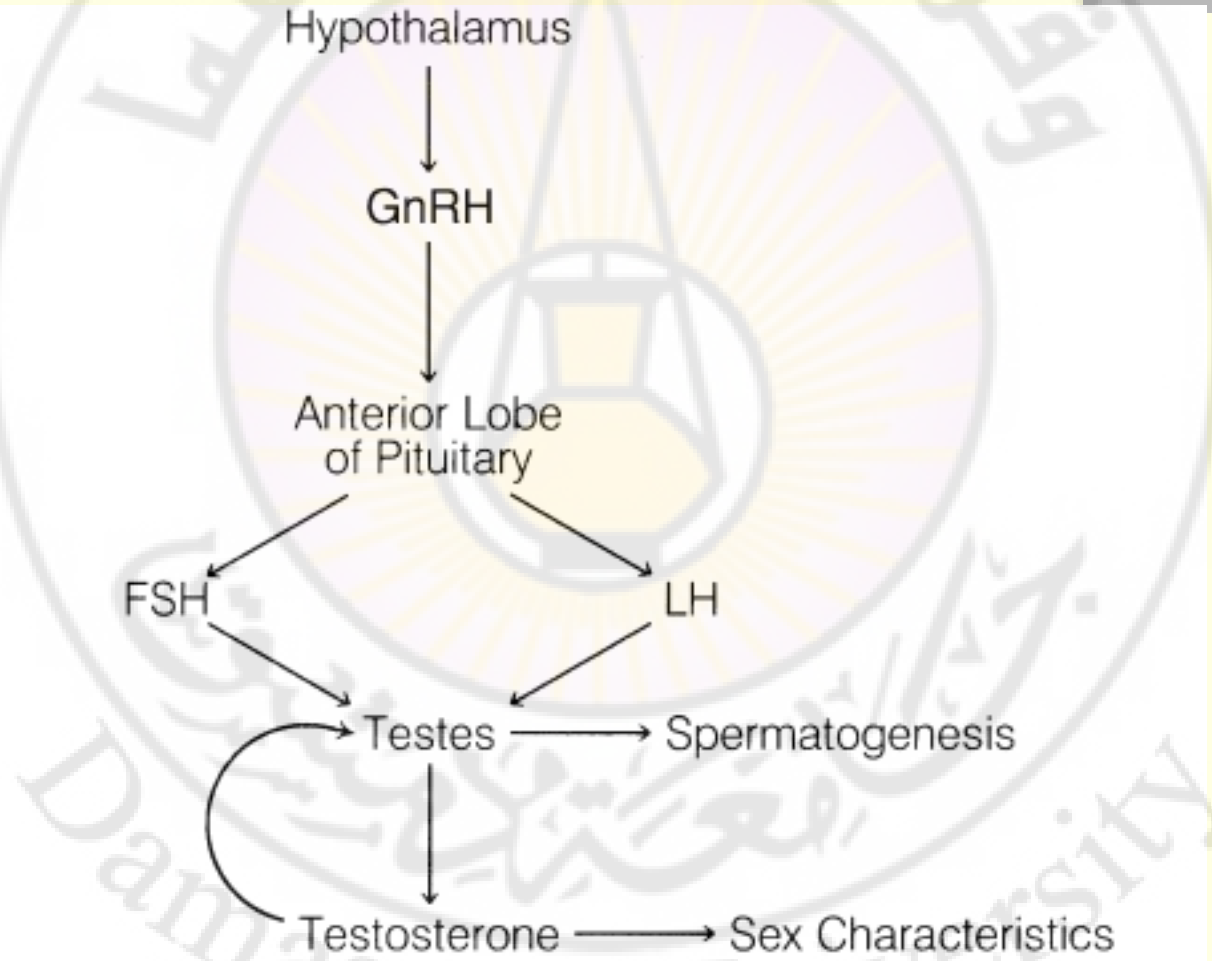


Figure 25.10 ● Regulation of spermatogenesis.

Sex Hermones

- ✓ Although estrogens and progesterone are usually called female sex hormones and testosterone is called a male sex hormone, all of these steroids are biosynthesized in both males and females.

- ✓ Estrogens and progesterone are produced in much larger amounts in females as is testosterone in males.

- ✓ These hormones play profound roles in reproduction, in the menstrual cycle, and in giving women and men their characteristic physical differences.

Sex Hermones

- ✓ Several modified steroidal compounds, as well as some nonsteroidal compounds, have estrogenic activity.
- ✓ A large number of synthetic or semisynthetic steroids with biological activities similar to those of progesterone have been made, and these are commonly called Progestins.
- ✓ Although the estrogens and progestins have had their most extensive use as chemical contraceptive agents for women and in HRT, their wide spectrum of activity has given them a diversity of therapeutic uses in women, as well as a few uses in men.

Sex Hermones

- ✓ Testosterone has two primary kinds of activities:

1. Androgenic Activity (promoting male physical characteristics).
2. Anabolic Activity (muscle building).

- ✓ Many synthetic and semisynthetic androgenic and anabolic steroids have been prepared.

- ✓ Despite efforts to prepare selective anabolic agents (e.g., for use in aiding recovery from debilitating illness or surgery), all “anabolic” steroids have androgenic effects.

Sex Hermones

- ✓ The Androgenic agents are mainly used in males, but they do have some therapeutic usefulness in women (e.g., in the palliation of certain sex organ cancers).
- ➢ In summary
- ✓ many sex hormone products have their greatest therapeutic uses in either women or men, nearly all have some uses in both sexes.

- ✓ the higher concentrations of estrogens and progesterone in women and of testosterone in men cause the development of the complementary reproductive systems and characteristic physical differences of women and men.

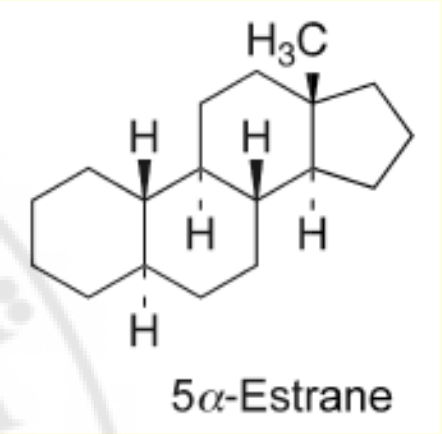
Sex Hermones – Estrogens

- ✓ The Endogenous Estrogens
- ✓ The active endogenous estrogens are

1. Estradiol
2. Estrone
3. Estriol

- ✓ Estradiol provides the greatest estrogenic activity, with less activity for estrone, and the least activity with estriol.

Sex Hermones – Estrogens



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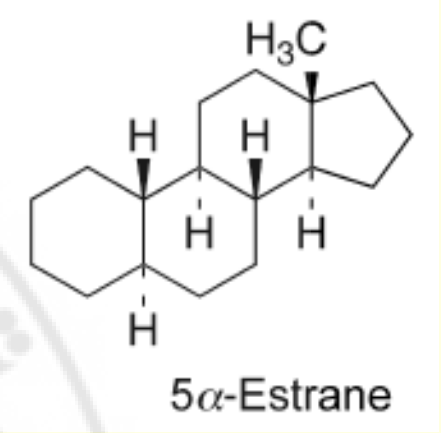
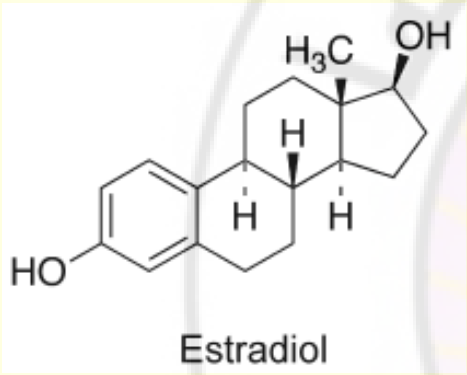
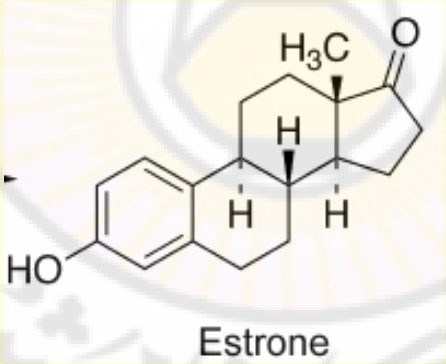
Sex Hermones – Estrogens



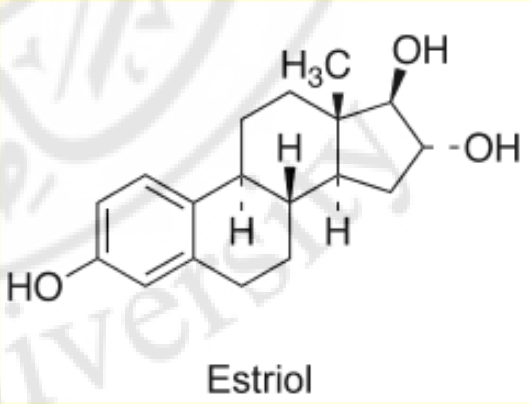
5α-Estrane



Estradiol

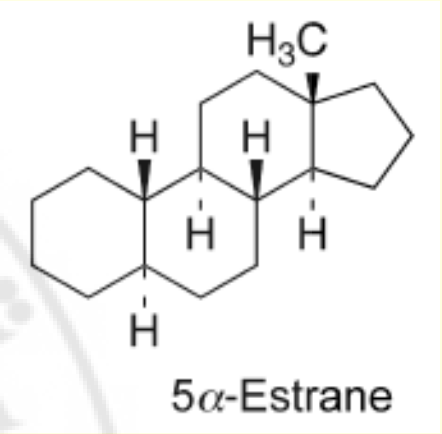


Estrone



Estriol

Sex Hermones – Estrogens

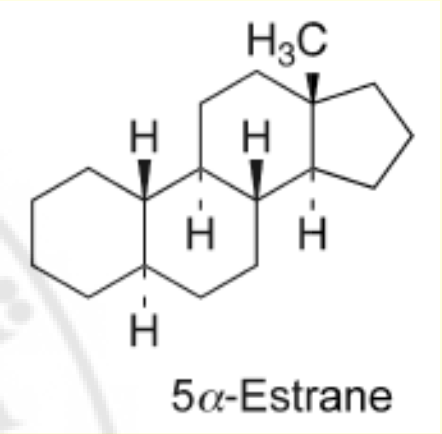


- ✓ Biosynthesis
- ✓ The estrogens are synthesized by the action of the enzyme aromatase on Androstenedione or Testosterone.
- ✓ estrogens are normally produced in

1. large quantities in the ovaries and the placenta
2. lower amounts in the adrenal glands
3. trace quantities in the testes.

- In postmenopausal women, most estrogens are synthesized in adipose tissue and other nonovarian sites.

Sex Hermones – Estrogens



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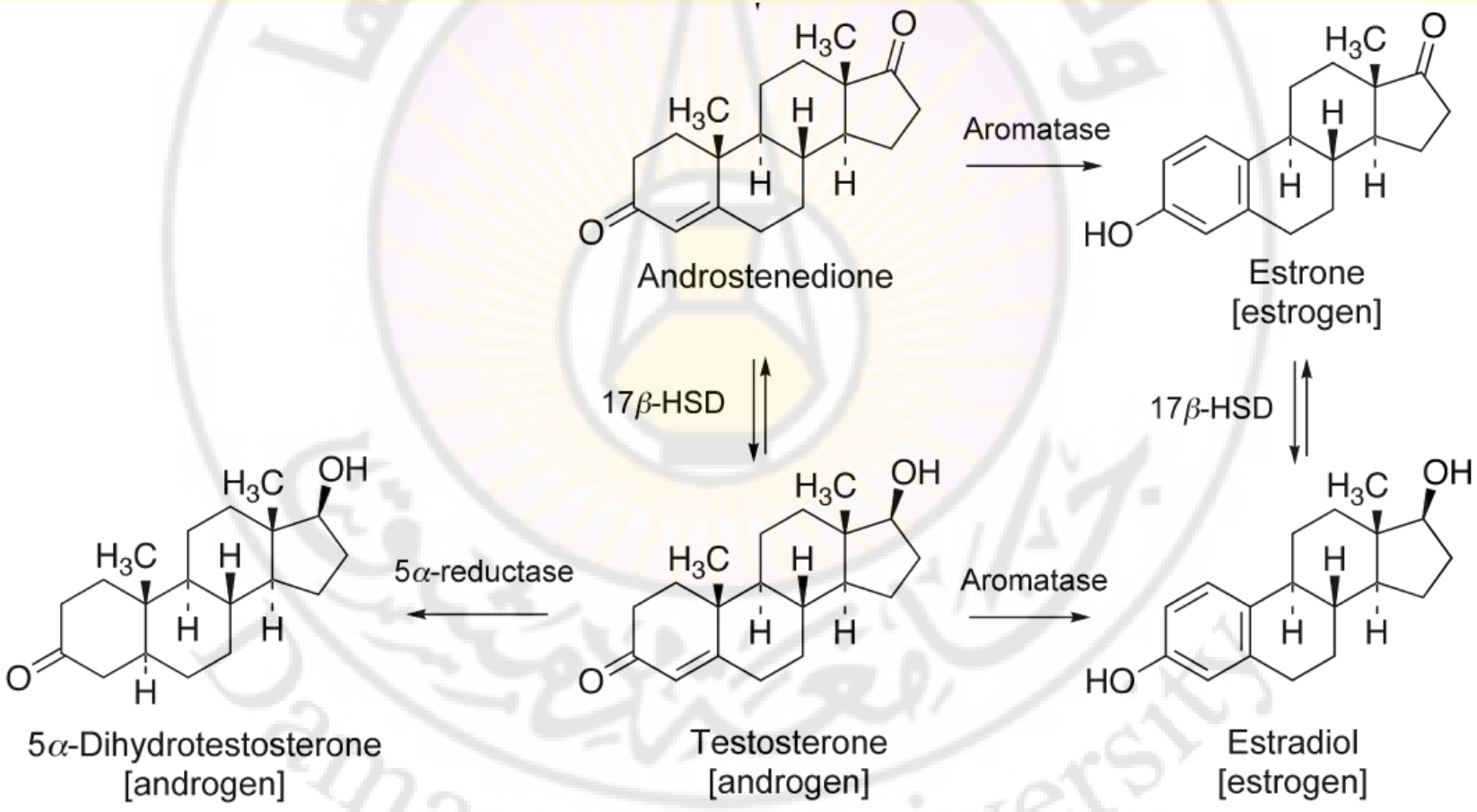
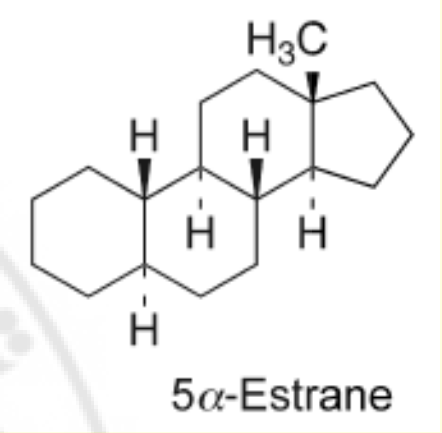
Sex Hermones – Estrogens



Sex Hermones – Estrogens



- ✓ Metabolism
- ✓ The three primary estrogens in women are
- ✓ Estradiol
- ✓ Estrone
- ✓ Estriol

- ➢ Although Estradiol is produced in the greatest amounts, it is quickly oxidized to Estrone, which is the estrogen that found in highest concentration in the plasma.
- ✓ Estrone, inturn, is converted to Estriol, the major estrogen found in human urine

Sex Hermones – Estrogens
Biological Activities of Estrogens

1. The estrogens have important roles in the menstrual cycle
2. the estrogens (and to a lesser extent,progesterone) are largely responsible for the development of secondary sex characteristics in women at puberty.
3. The estrogens cause a proliferation of the breast ductile system, and progesterone stimulates development of the alveolar system.
4. The estrogens also stimulate the development of lipid and other tissues that contribute to breast shape and function. Pituitary hormones and other hormones are also involved.
5. Fluid retention in the breasts during the later stages of the menstrual cycle is a common effect of the estrogens.

Sex Hermones – Estrogens
Structural Classes of Estrogens

- There are three structural classes of estrogens:

1. Steroidal Estrogens and derivatives
2. Diethylstilbestrol and other synthetic compounds
3. Phytoestrogens

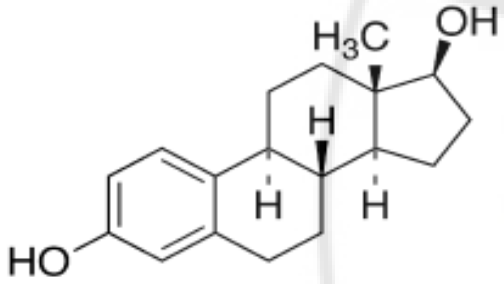
- The steroidal estrogens include

I. naturally occurring estrogens found in humans and other mammals
II. semisynthetic derivatives of these compounds.

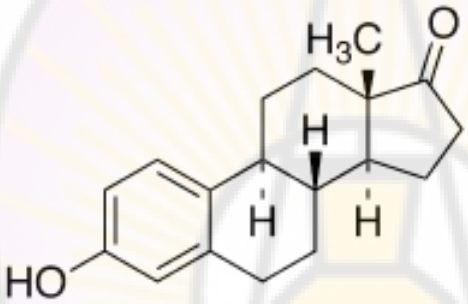
Sex Hermones – Estrogens

Structural Classes of Estrogens

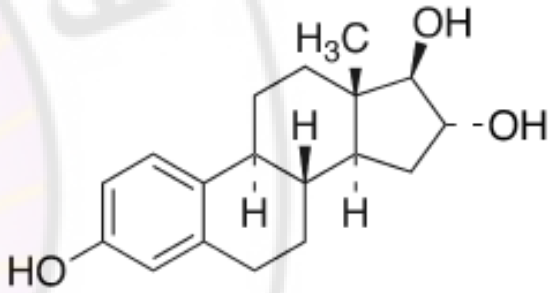
1. Steroidal Estrogens and derivatives



Estradiol
(Oral, transdermal, emulsion, gel, cream, vaginal ring)

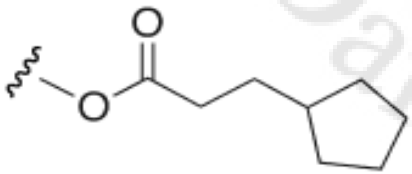


Estrone
(IM, topical)

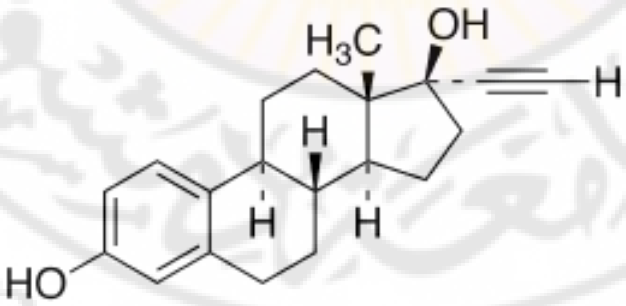


Estriol
(Topical)

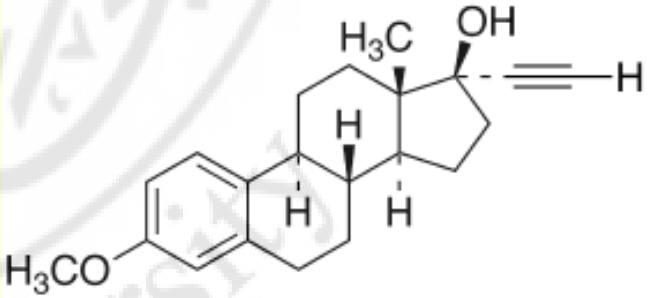
Esters
- Estradiol 3-acetate
- Estradiol 17-valerate
- Estradiol 17-cypionate



Cyclopentylpropionate
= cypionate



Ethinyl Estradiol
(Oral)



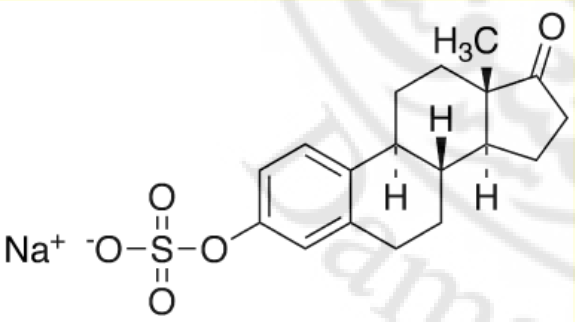
Ethinyl Estradiol 3-methylether;
Mestranol
(Oral)

Sex Hermones – Estrogens

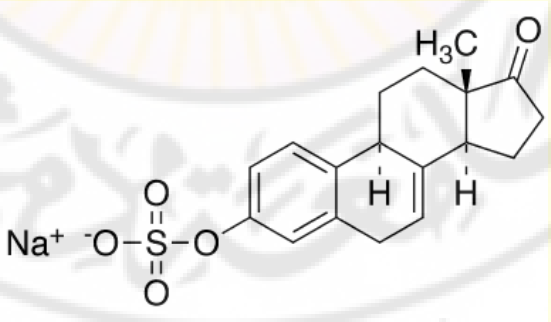
Structural Classes of Estrogens

1. Steroidal Estrogens and derivatives

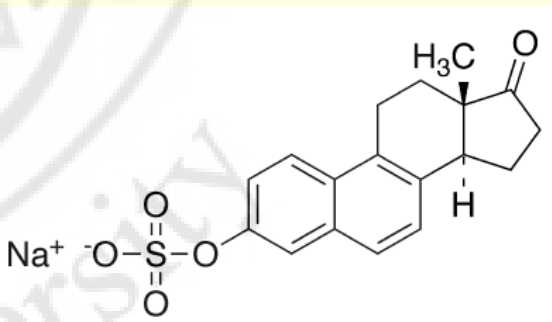
(a) Conjugated Estrogens: (Oral, IM, IV, vaginal cream)	50-65% Sodium Estrone Sulfate 20-35% Sodium Equilin Sulfate plus nonestrogenic compounds
(b) Esterified Estrogens: (Oral)	70-85% Sodium Estrone Sulfate 6.5-15% Sodium Equilin Sulfate plus nonestrogenic compounds



Sodium Estrone Sulfate



Equilin sodium sulfate



Sodium Equilenin Sulfate

Sex Hermones – Estrogens

Structural Classes of Estrogens

1. Steroidal Estrogens and derivatives

(a) Conjugated Estrogens: (Oral, IM, IV, vaginal cream)	50-65% Sodium Estrone Sulfate 20-35% Sodium Equilin Sulfate plus nonestrogenic compounds
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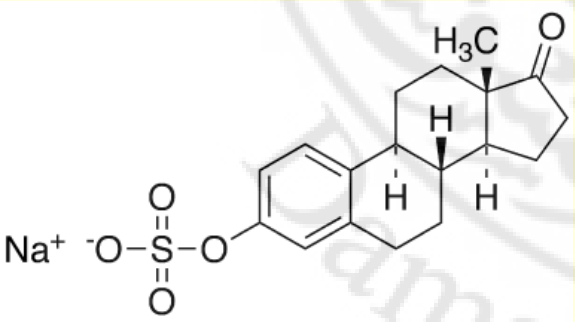
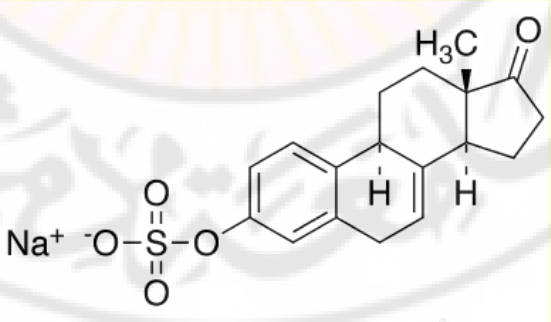
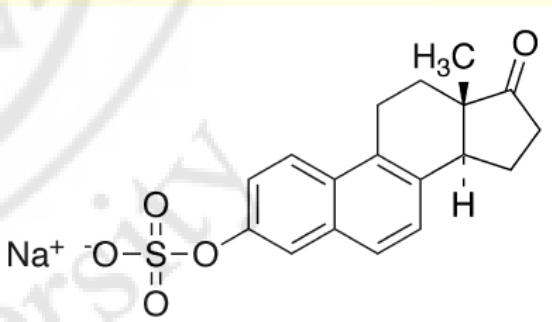


Sodium Estrone Sulfate



Equilin sodium sulfate

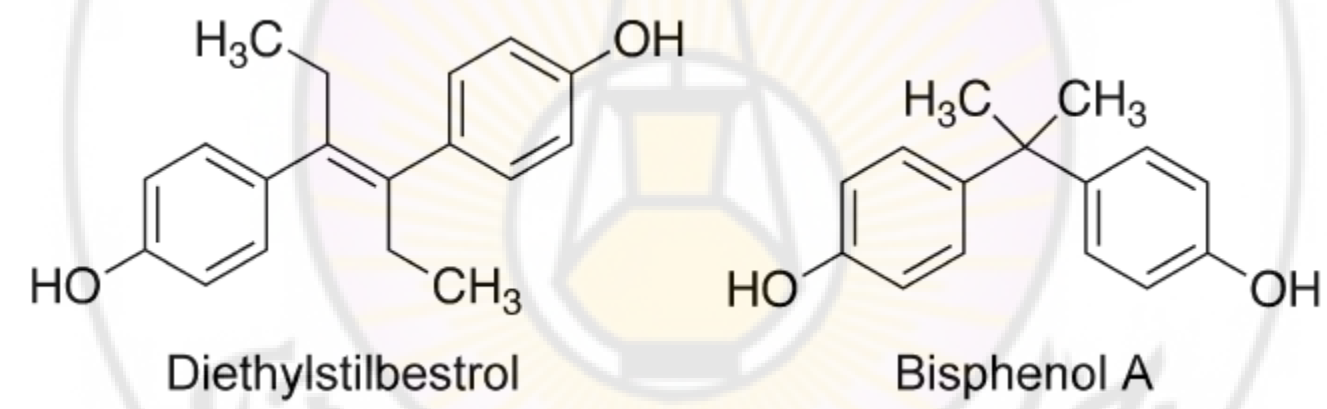


Sodium Equilenin Sulfate

Sex Hermones – Estrogens

Structural Classes of Estrogens

2. Diethylstilbestrol and other synthetic compounds



Sex Hermones – Estrogens

Structural Classes of Estrogens

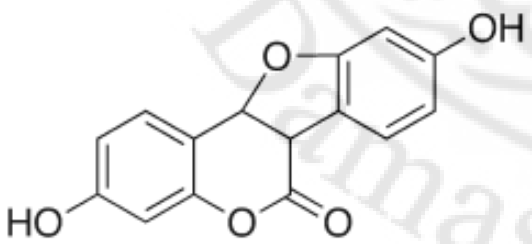
3. Phytoestrogens : Several natural plant substances that have general structural features similar to those of DES and estradiol also have estrogenic effects and have been termed *phytoestrogens*.

✓ Phytoestrogens include :

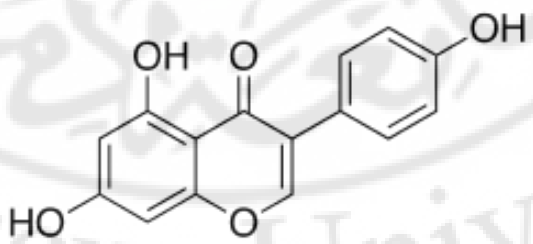
I. Genistein from soybeans and a species of clover.

II. Daidzein from soybeans.

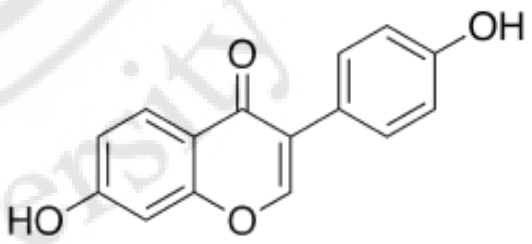
III. Coumestrol found in certain legumes.



Coumestrol



Genistein



Daidzein

Sex Hermones – Estrogens

Therapeutic Uses of Estrogens

I. Birth Control. تحديد النسل

II. Hormone Replacement Therapy HRT.

المعالجة الهرمونيةالمعاوضة

III. Treatment of Estrogen Deficiency from Ovarian Failure or after Oophorectomy.

علاج نقص الايستروجينات الناجم عن عجز المبيض أو بعد استئصال المبيض

IV. Treatment of Advanced, Inoperable Breast Cancer in Men and Postmenopausal Women and of Advanced, Inoperable Prostate Cancer in Men.

Sex Hermones – Estrogens

Therapeutic Uses of Estrogens

I. Birth Control. تحديد النسل

- ✓ A major use of estrogens is for inhibition of ovulation, in combination with progestins.

II. Hormone Replacement Therapy HRT.

المعالجة الهرمونيةالمعاوضة

- ✓ Another major use of estrogens is in HRT for postmenopausal women.
- ✓ For this use, a progestin is often included to oppose the effects of estrogens on endometrial tissue.

Sex Hermones – Estrogens
Therapeutic Uses of Estrogens

III. Treatment of Estrogen Deficiency from Ovarian Failure or after Oophorectomy.

علاج نقص الايستروجينات الناجم عن عجز المبيض أو بعد استئصال المبيض

- ✓ Estrogen therapy, usually with a progestin, is common in cases of ovarian failure and after an oophorectomy.

IV. Treatment of Advanced, Inoperable Breast Cancer in Men and Postmenopausal Women and of Advanced, Inoperable Prostate Cancer in Men.

Sex Hermones – Estrogens

Therapeutic Uses of Estrogens

IV. Treatment of Advanced, Inoperable Breast Cancer in Men and Postmenopausal Women and of Advanced, Inoperable Prostate Cancer in Men.

- ✓ Estrogens are used to treat inoperable breast cancer in men and in postmenopausal women, but estrogen therapy can actually stimulate existing breast cancers in premenopausal women.
- ✓ The selective ER modulator Tamoxifen is reported to have fewer side effects; hence, it is usually preferred.
- ✓ Estrogens have also been used to treat inoperable prostate cancer, but GnRH analogs are now generally preferred because of fewer unwanted side effects.

Sex Hermones – Estrogens
Estrogens and Cancer

- ✓ Many years of study have firmly established an association between Estrogen use and increased risk of breast cancer.

- ✓ Estrogens in HRT Hormone Replacement Therapy for postmenopausal women are also linked to an increased risk of endometrial carcinoma, which is the basis for inclusion of a progestin in many forms of HRT.

Sex Hermones – Estrogens Products Estradiol

- ✓ Estra-1,3,5(10)-triene-3,17-diol,
- ✓ Estradiol is the most active of the natural steroid estrogens.
- ✓ Although its 17-OH group is vulnerable to bacterial and enzymatic oxidation to Estrone.
- ✓ Estradiol can be protected

1. Temporarily بشكل مؤقت as an ester at C3 or C17.

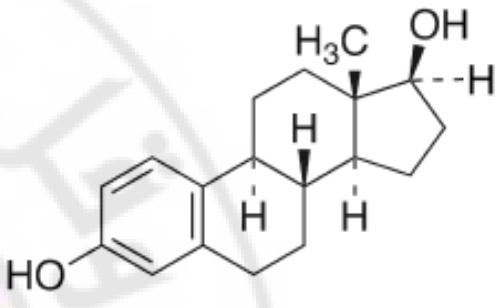
or

2. Permanently بشكل دائم by adding a 17-alkyl group (e.g., 17-ethinyl estradiol, the most commonly used estrogen in oral contraceptives).

Sex Hermones – Estrogens Products

Estradiol

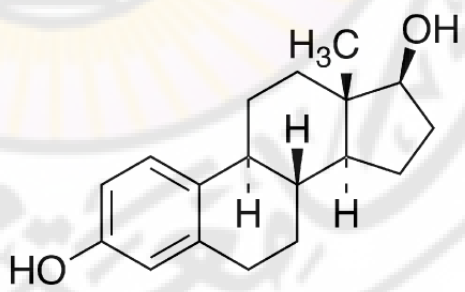
- ✓ Estra-1,3,5(10)-triene-3,17-diol.



17β-estradiol
(Estra-1,3,5(10)-triene-3,17β-diol)

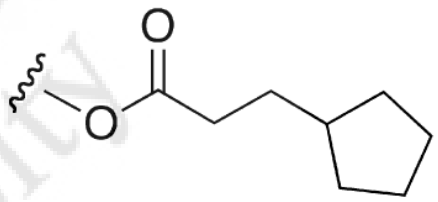
- ✓ Estradiol is commercially available in a wide variety of dosage forms:

1. Oral tablets
2. Vaginal creams, gel, cream and foams
3. Transdermal patches
4. Vaginal ring
5. IM dosage preparations.



Estradiol
(Oral, transdermal, emulsion, gel, cream, vaginal ring)

Esters
Estradiol 3-acetate
Estradiol 17-valerate
Estradiol 17-cypionate



Cyclopentylpropionate
= cypionate

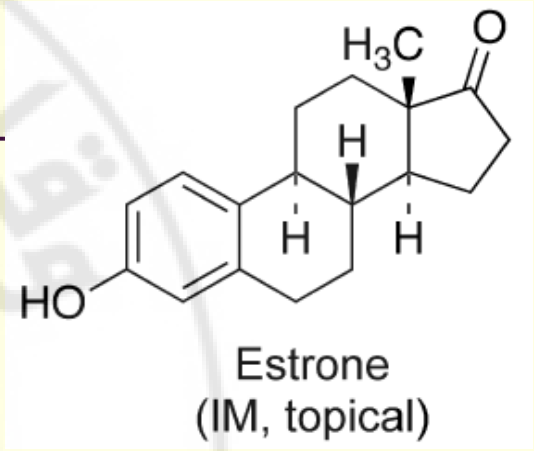
Sex Hermones – Estrogens Products
Estrone

- ✓ 3-hydroxyestra-1,3,5(10)-trien-17-one.
- ✓ Estrone is less active than estradiol but more active than its metabolite estriol.
- ✓ As the salt of its 3-sulfate ester, estrone is the primary ingredient in conjugated estrogens, USP, and esterified estrogens, USP.
- ✓ Estrone is originally obtained from the urine of pregnant mares
- ✓ Estrone is now prepared synthetically.
- ✓ Estrone itself is not available in commercial Oral Formulations, but can be obtained at compounding pharmacies as a Topical Formulation

Sex Hermones – Estrogens Products

Estrone

- 3-hydroxyestra-1,3,5(10)-trien-17-one.



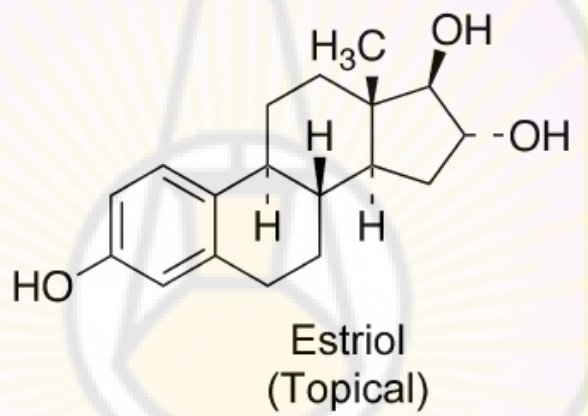
Estrone
(IM, topical)

- Oleoylestrone (the C3 ester of estrone with oleic acid) is in phase II clinical trials for the treatment of obesity.

- This acyl estrone derivative reduces fat stores by a mechanism not involving the ER

Sex Hermones – Estrogens Products
Estriol

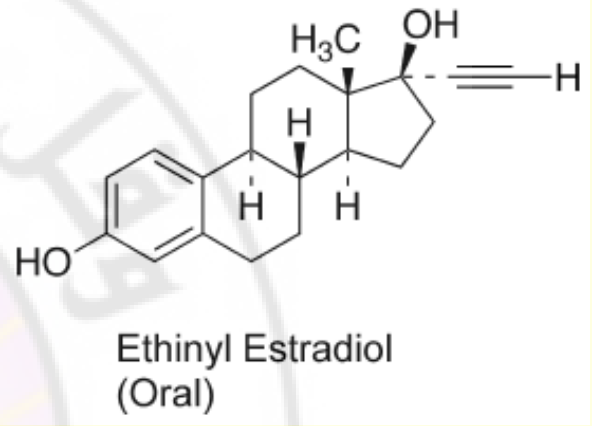
- ✓ estra-1,3,5(10)-triene-3,16,17- triol



- ✓ It is available for compounding into several different formulations for use in HRT.

- ✓ It can be used alone or in combinations with estradiol (Bi-Est) or with estradiol and estrone (Tri-Est).

Sex Hermones – Estrogens Products
Ethinyl Estradiol



- ✓ 17α-Ethinyl estradiol
- ✓ Ethinyl Estradiol

has the greatest advantage

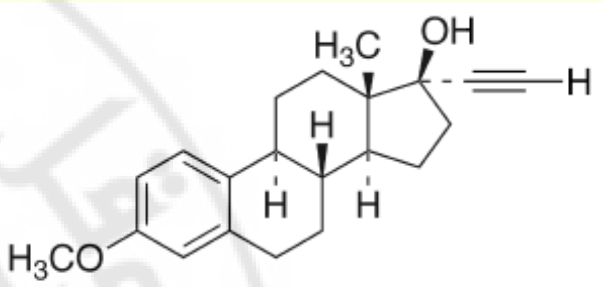
over other estradiol products of being orally active.

- ✓ It is equal to estradiol in potency by injection but is 15 to 20 times more orally active.

- ✓ The primary metabolic path for ethinyl estradiol is 2-hydroxylation by cytochrome P450 followed by conversion to the 2- and 3-methyl ethers by catechol-*O*-methyltransferase.

Sex Hermones – Estrogens Products

Mestranol



Ethinyl Estradiol 3-methylether;
Mestranol
(Oral)

- ✓ Mestranol is The 3-methyl ether of ethinyl estradiol
- ✓ It is used in oral contraceptives.

- ✓ Mestranol is a prodrug that is 3-O-demethylated to the active Ethinyl Estradiol.

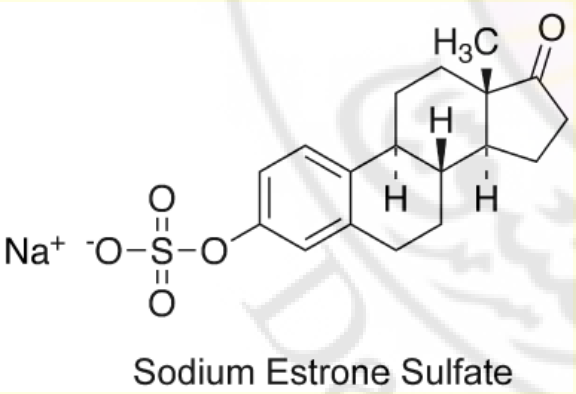
Sex Hermones – Estrogens Products conjugated Estrogens

- ✓ The term conjugated estrogens refers to the mix of sulfate conjugates of estrogenic components isolated from pregnant mare urine (Premarin).

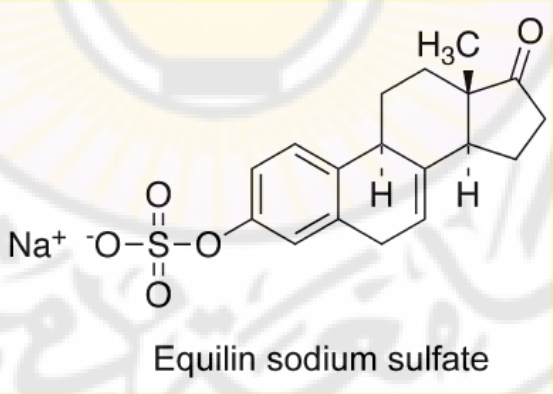
- ✓ These compounds are also referred to as CEE (conjugated equine estrogens).
- ✓ Conjugated estrogens contain :
- ✓ 50% to 65% sodium estrone sulfate and 20% to 35% sodium equilin sulfate.
- ✓ the sulfate esters of 17-estradiol, 17-dihydroequilin, and 17-dihydroequilin, in addition to other minor components.

Sex Hermones – Estrogens Products conjugated Estrogens

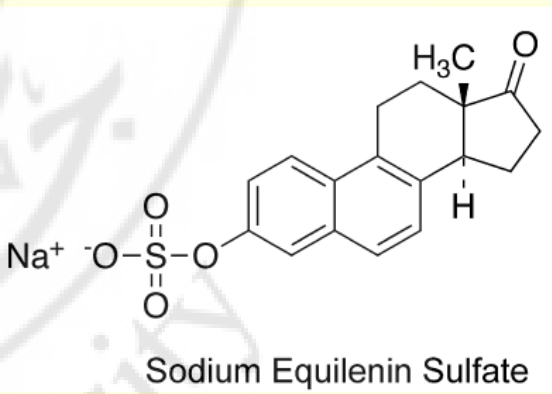
- ✓ conjugated estrogens are commonly used in HRT to treat postmenopausal symptoms.
- ✓ conjugated estrogens are used for the entire range of indications except birth control.



Sodium Estrone Sulfate



Equilin sodium sulfate



Sodium Equilenin Sulfate

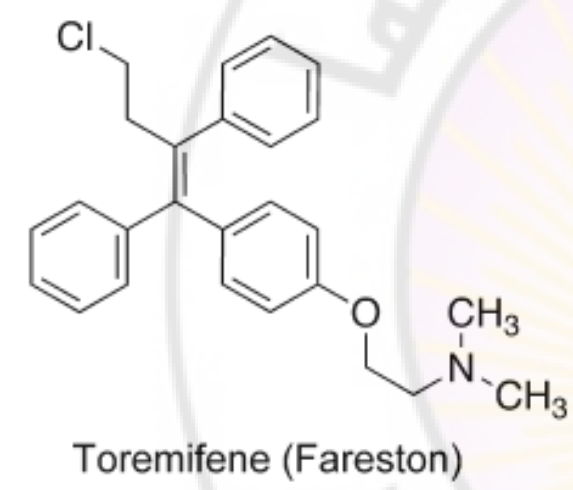
Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulators and antiestrogens SERM

- ✓ Whereas estrogens have been very important in chemical contraception and HRT.
- ✓ The compounds that can antagonize the ER have been of great interest for the treatment of estrogen dependent breast cancers.

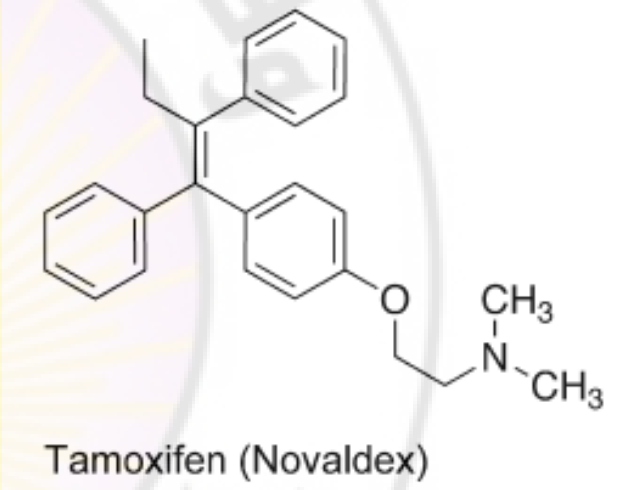
- ✓ Three compounds that are used clinically for estrogen antagonist action in the treatment of breast cancer are

1) Tamoxifen
2) Toremifene
3) Fulvestrant

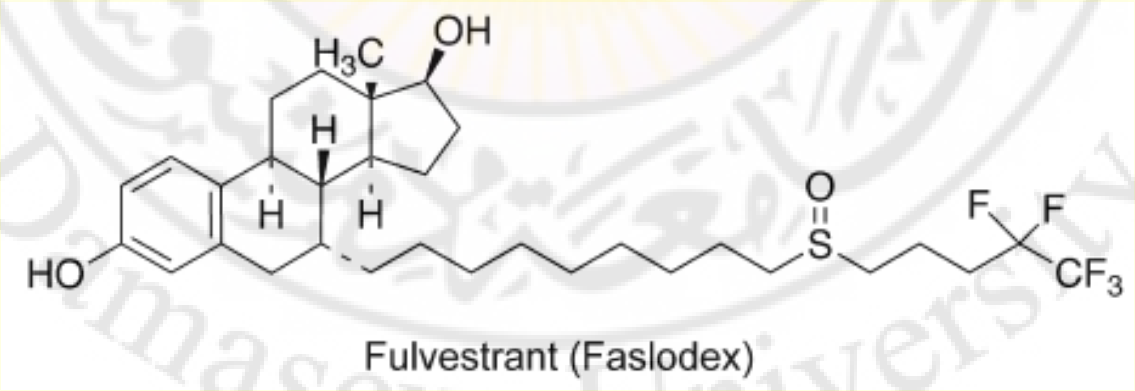
Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulators and antiestrogens SERM



Toremifene (Fareston)



Tamoxifen (Novaldex)



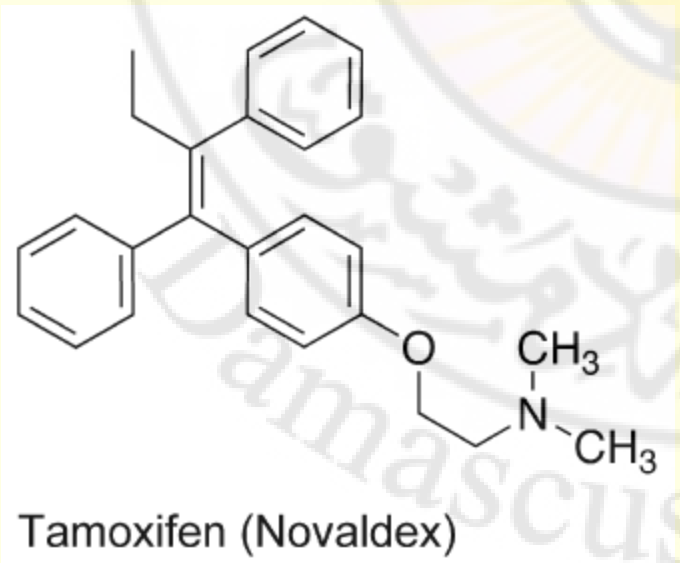
Fulvestrant (Faslodex)

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

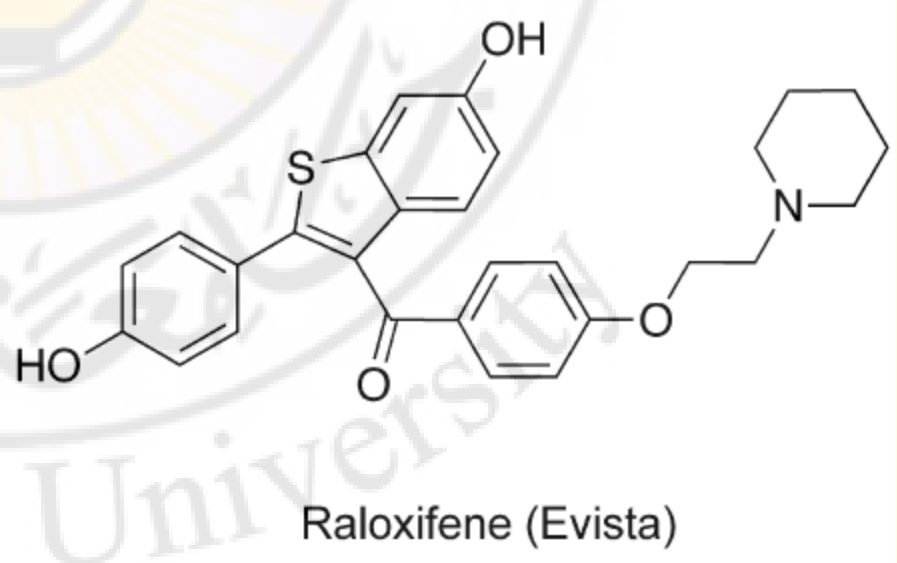
✓ Two additional agents that can antagonize ERs are:

1. Clomiphene, which is used as an ovulation stimulant.

2. Raloxifene, which is used for the prevention and treatment of osteoporosis.



Tamoxifen (Novaldex)



Raloxifene (Evista)

Sex Hermones – Estrogens Products Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ Tamoxifen and clomiphene were traditionally called ER antagonists or antiestrogens.
- ✓ Referring to these compounds as ER antagonists, however, does not accurately portray how these compounds work in vivo.
- ✓ Although tamoxifen is an ER antagonist in breast tissue, it has agonist actions on endometrium, liver, bone, and cardiovascular system.
- ✓ Because of the differential agonist and antagonist effects of these types of compounds on the ER, depending on the specific tissue, a new term was coined: selective estrogen receptor modulators (SERMs).

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ A SERM is a drug that has tissue-specific estrogenic activity.
- ✓ Although many compounds exhibit SERM activity, a few agents are antagonists in all tissues.

- ✓ SERM activity, a few agents are antagonists in all tissues.
- ✓ These compounds are termed antiestrogens, and Fulvestrant is one example.

- ✓ Tamoxifen and clomiphene are often referred to in older literature as antiestrogens.

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ Tamoxifen has seen extensive use in treating primary breast cancers that are ER dependent.

- ✓ For premenopausal women with metastatic disease.

- ✓ Tamoxifen is an alternative and adjuvant with:

I. Oophorectomy استئصال المبيض.
II. Ovarian irradiation.
III. Mastectomy استئصال الثدي.

Sex Hermones – Estrogens Products Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ Tamoxifen use, is not problem free.
- ✓ Tamoxifen increases the incidence of endometrial polyps, hyperplasia and carcinoma, and uterine sarcomas.
- ✓ The risk of endometrial cancer resulting from tamoxifen is, much lower than the “modest but highly significant reductions in morbidity and mortality of breast cancer
- ✓ Because of the increased risk of endometrial cancer with tamoxifen therapy, tamoxifen should be used to prevent breast cancer only in women at high risk.

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulators and antiestrogens SERM

- ✓ Raloxifene is another SERM, but its profile of activity differs from that of tamoxifen.
- ✓ Raloxifene is an ER antagonist in both breast and endometrial tissue, but
- ✓ It has agonist action on bone and acts as an estrogen agonist in lowering total cholesterol and low-density lipoprotein (LDL).
- ✓ The agonist action on bone tissue is the basis for the use of this drug for treating osteoporosis.

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulators and antiestrogens SERM

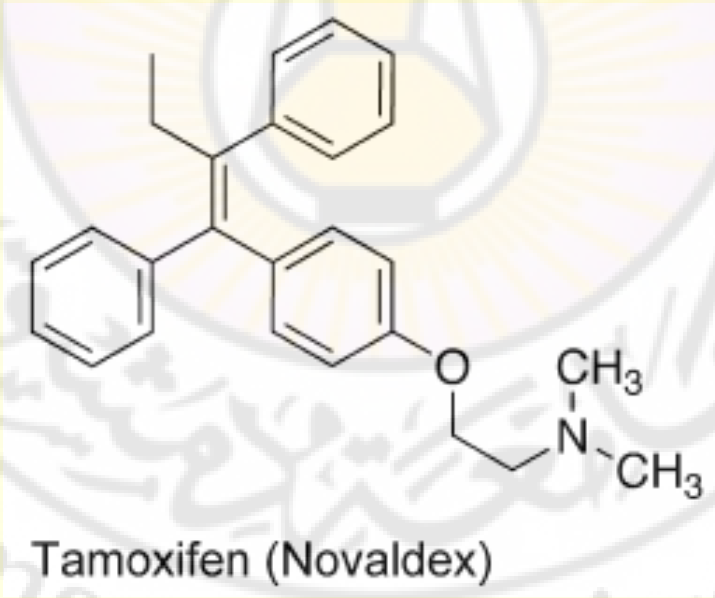
- ✓ Clomiphene is another drug that exhibits antiestrogen actions, but it is not used for treating breast cancer or osteoporosis.
- ✓ Clomiphene is used for increasing the odds of a successful pregnancy.
- ✓ Clomiphene's therapeutic application as an ovulation stimulant results from its ability to increase GnRH production by the hypothalamus.

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ The mechanism is presumably a blocking of feedback inhibition of ovary-produced estrogens (via ER antagonism).
- ✓ The hypothalamus and pituitary interpret the false signal that estrogen levels are low and respond by increasing the production of GnRH.
- ✓ The increased GnRH, in turn, leads to increased secretion of LH and FSH, maturation of the ovarian follicle, and ovulation

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ Tamoxifen
- ✓ 2-[4-(1,2- diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine (Nolvadex),



Tamoxifen (Novaldex)

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

✓ Tamoxifen is used

1) To treat early and advanced breast carcinoma in postmenopausal women.
2) as adjuvant treatment for breast cancer in women following mastectomy and breast irradiation.
3) To reduce the occurrence of contralateral breast cancer in patients receiving adjuvant tamoxifen therapy.
4) To treat metastatic breast cancer in both women and men.
5) To treat premenopausal women with metastatic breast cancer, tamoxifen is an
6) as alternative to oophorectomy or ovarian irradiation.
7) Preventatively to reduce the incidence of breast cancer in women at high risk.

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

✓ Tamoxifen

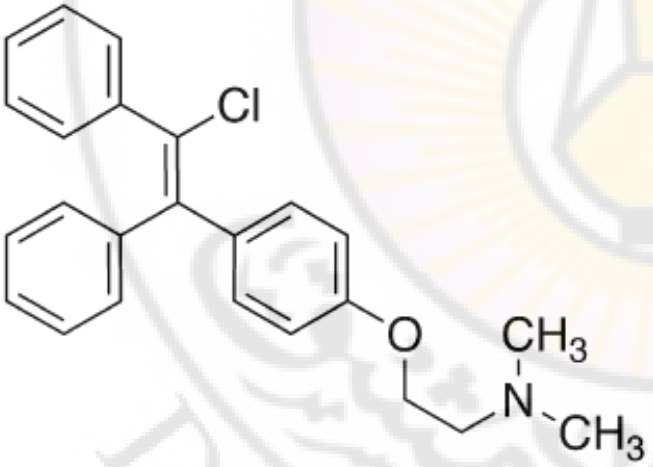
Antiestrogenic and estrogenic side effects can include

1. Hot Flashes.
2. Nausea, Vomiting.
3. Platelet Reduction.
4. Hypercalcemia in patients with bone metastases.

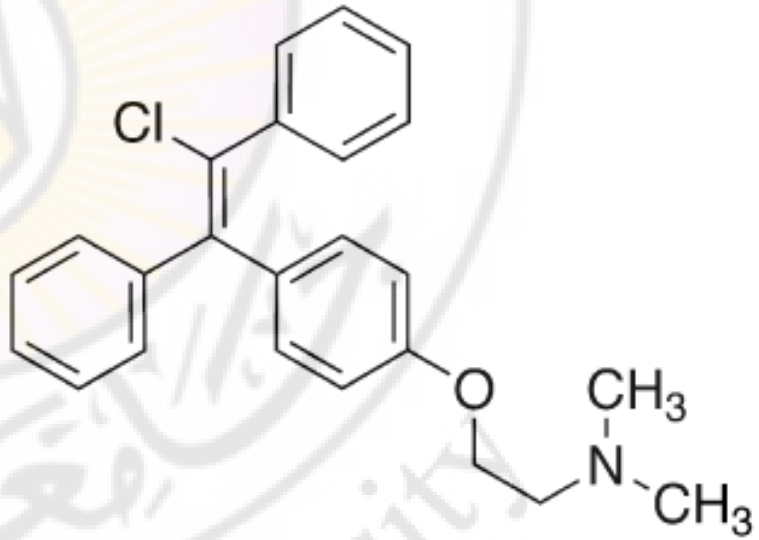
Like all triphenylethylene derivatives, it should be protected from light.

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ Clomiphene (Clomid)
- ✓ 2-[4(2- chloro-1,2-diphenylethenyl)phenoxy]-N,N-diethylethanamine



Zuclomiphene. [Clomiphene (Clomid) is a mixture of isomers, zuclomiphene and enclomiphene]



Enclomiphene

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ Clomiphene (Clomid)
- ✓ 2-[4(2- chloro-1,2-diphenylethenyl)phenoxy]-N,N-diethylethanamine
- ✓ It is used as an ovulation stimulant in women desiring pregnancy.
- ✓ Although early literature refers to clomiphene as an estrogen antagonist, it is more accurately a SERM.
- ✓ Clomiphene is chemically a mixture of two geometric isomers,

1. Zuclomiphene the cis-isomer
2. Enclomiphene the trans-isomer.

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

- ✓ these isomers have different estrogenic actions in different tissues.
- ✓ Zuclomiphene appears to have weak agonist actions on all
- ✓ tissues studied, Whereas
- ✓ Enclomiphene has antagonist actions on uterine tissue, but agonist action on bone tissue.

- ✓ The actions of clomiphene in humans are likely a composite of the actions of the two isomers.

Sex Hermones – Estrogens Products
Selective Estrogen Receptor Modulatorsand antiestrogens SERM

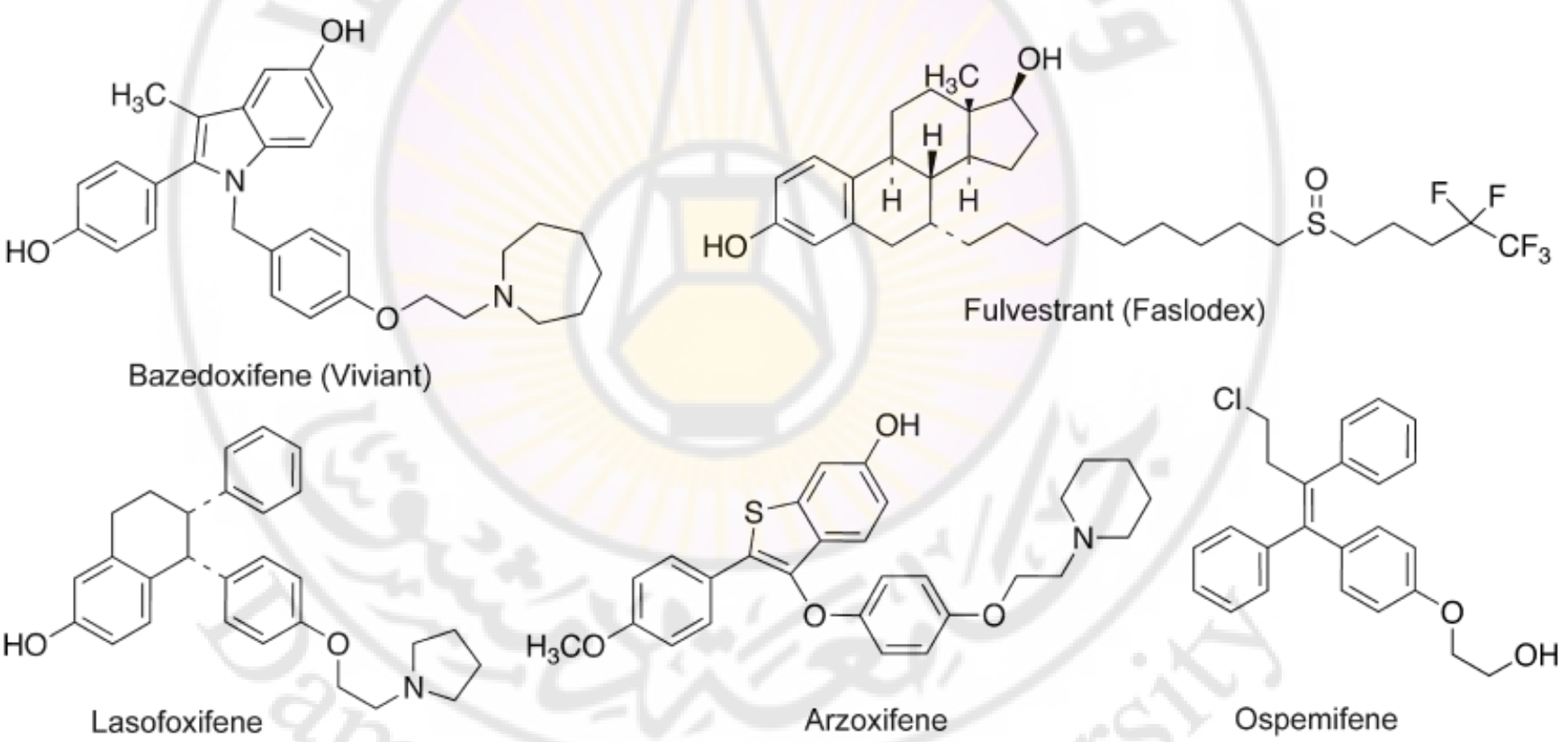


Figure 25.15 ● Selective estrogen receptor modulators (SERMs) and antiestrogens.

Sex Hermones – Estrogens Products Aromatase Inhibitors

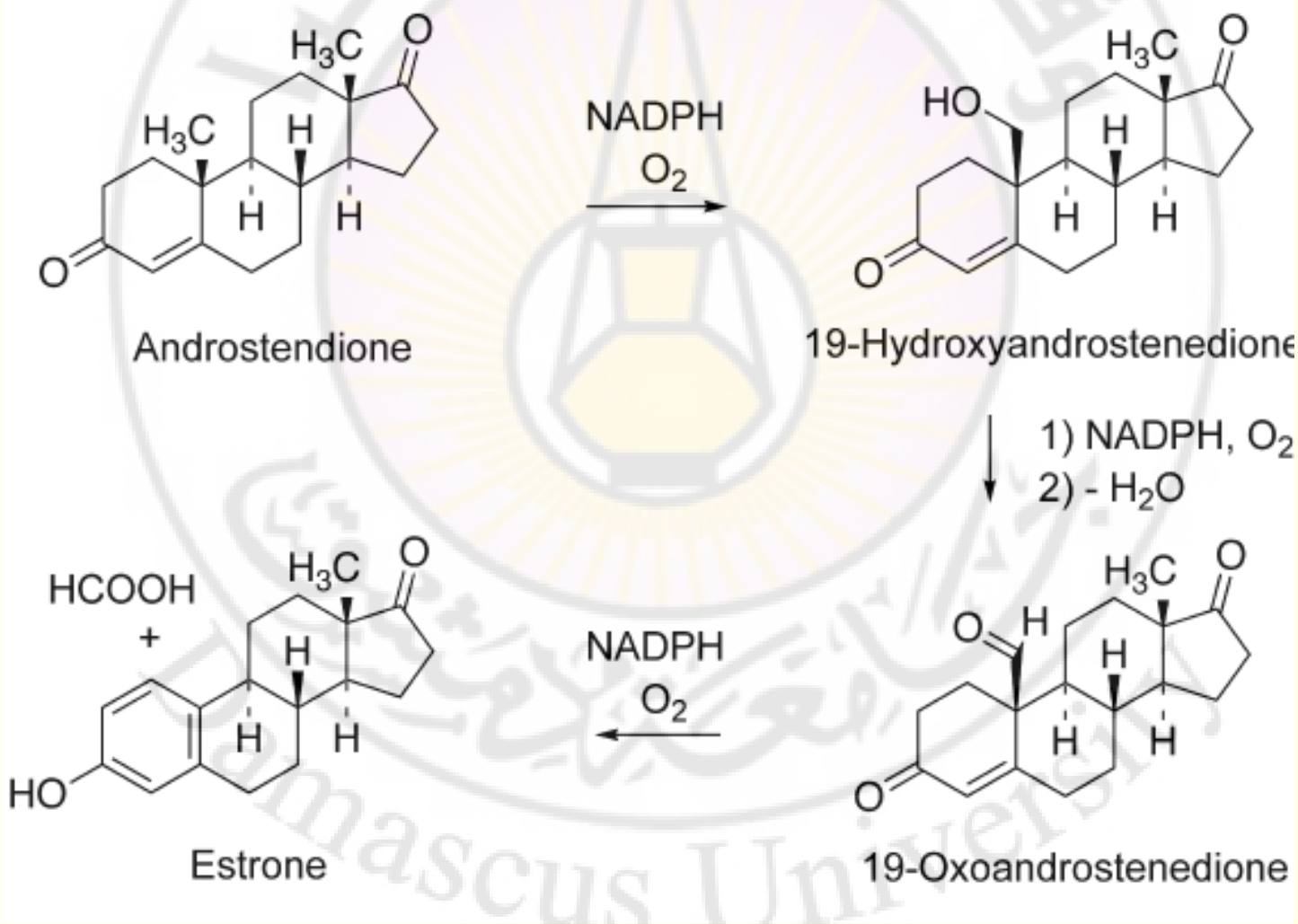
- ✓ Aromatase is a cytochrome P450 enzyme complex that catalyzes the conversion of

1. Androstenedione to Estrone
2. Testosterone to Estradiol

- ✓ Aromatase Inhibitors were used as second-line therapy in postmenopausal women who failed on tamoxifen therapy.

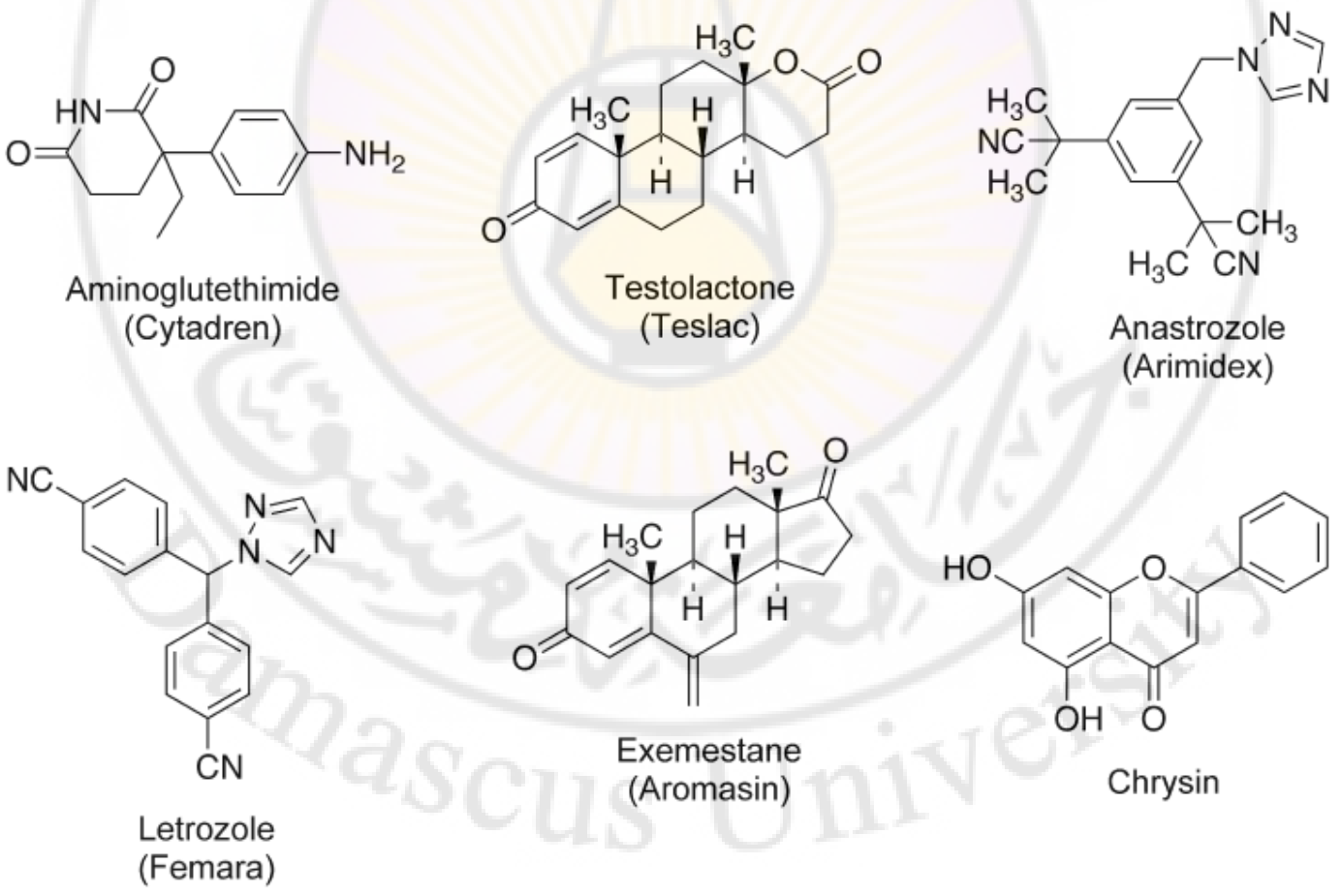
- ✓ Recent studies have indicated that the newer aromatase inhibitors can be used as first-line therapy and possibly for cancer prevention in patients at high risk

Sex Hermones – Estrogens Products Aromatase Inhibitors



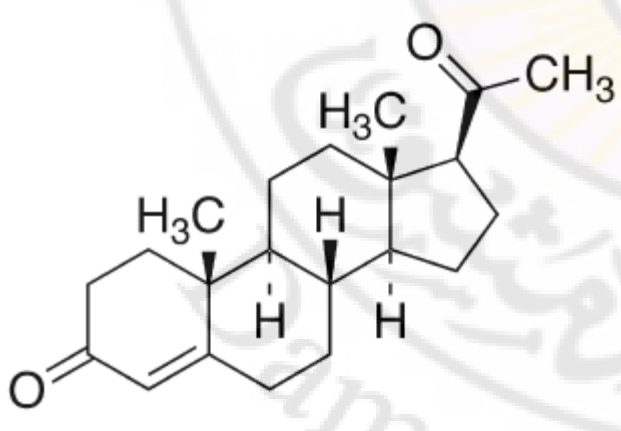
Sex Hermones – Estrogens Products Aromatase Inhibitors

- ✓ Aromatase inhibitors include both steroidal and nonsteroidal compounds.

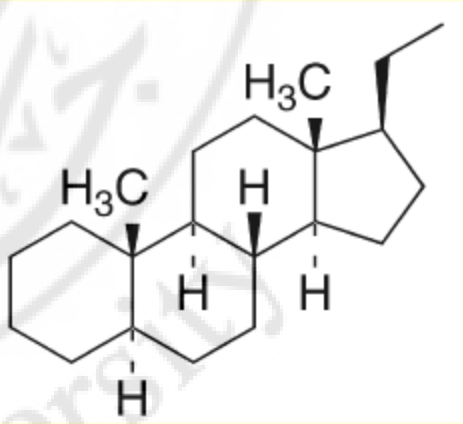


Sex Hermones
Progestins

- ✓ Endogenous Progestins
- ✓ Progesterone is the key endogenous steroid hormone that acts at the Progesterone Receptors PRs.
- ✓ All other endogenous steroids lack significant progestational action.



Progesterone:
pregn-4-en-3,20-dione



Pregnane

Sex Hermones

Progestins

- ✓ Biosynthesis
- ✓ Progesterone is produced in the Ovaries, Testes, and Adrenal Glands.
- ✓ Much of the progesterone that is synthesized from Pregnenolone is immediately converted to other hormonal intermediates and is not secreted.
- ✓ The corpus luteum secretes the most progesterone, 20 to 30 mg/day during the last stage of the menstrual cycle.
- ✓ Normal men secrete about 1 to 5 mg of progesterone daily

Sex Hermones

Progestins

- ✓ Metabolism of Progesterone
- ✓ Progesterone has a half-life of only about 5 minutes when taken orally, because of rapid metabolism.
- ✓ The principal excretory product of progesterone metabolism is 5β-pregnane-3α,20α-diol and its conjugates.
- ✓ Structural features that can block reduction at C4-5 double bound or C20 ketone have greatly increased the half-lives of progesterone derivatives

Sex Hermones

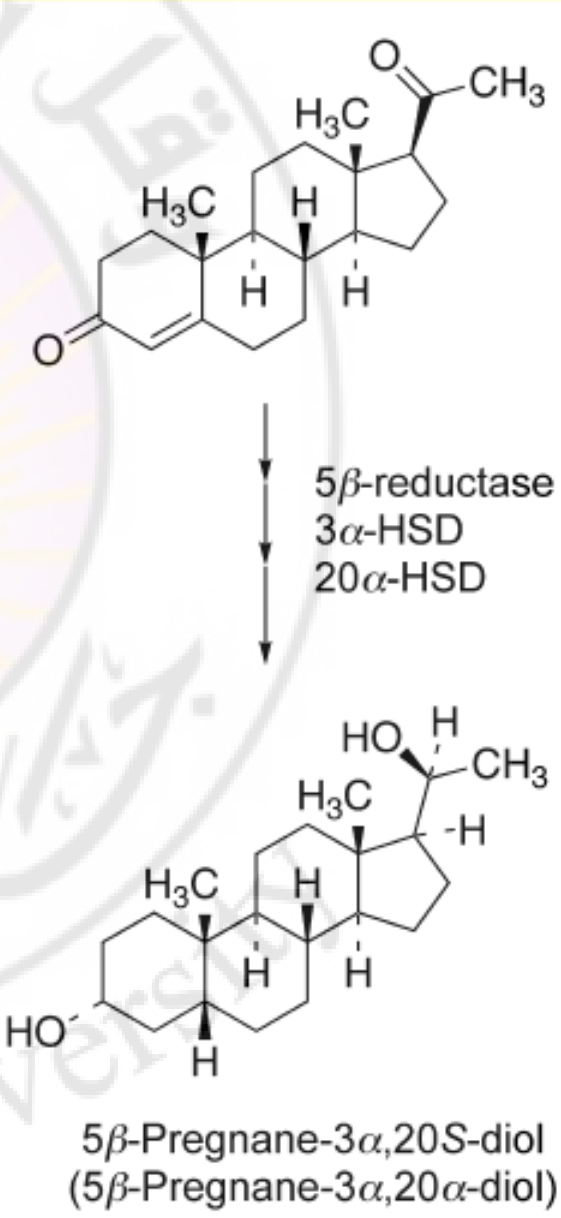
Progestins

The steps that are involved in the formation of
this metabolite are

1. reduction of the C4-5 double bond.

2. Reduction of the C3 ketone providing the 3-ol.

3. reduction of the C20 ketone providing 20-ol.



5β-Pregnane-3α,20S-diol
(5β-Pregnane-3α,20α-diol)

Sex Hermones – Progestins
Biological Activities of the Progestins

- ✓ Progesterone has various pharmacological actions, with the main target tissues being :

1. the Uterus
2. the Breast
3. the Brain

Sex Hermones – Progestins
Biological Activities of the Progestins

- ✓ The actions of progesterone include:

1. Development of the Endometrium.
2. Menstruation: The release of progesterone from the corpus luteum at the end of the menstrual cycle declines, menstruation begins.
3. Progesterone also acts to thicken cervical secretions, decreasing cervical penetration by sperm.
4. Thermogenic Action during the menstrual cycle: progesterone mediates a slight temperature increase near midcycle and maintains the increased temperature until the onset of menstruation.

Sex Hermones – Progestins
Biological Activities of the Progestins

5. Anti Ovulatory Activity:

Progesterone and Estrogen regulate the hypothalamus and the anterior pituitary by a feedback inhibition process that decreases GnRH, LH, and FSH production

6. Maintenance of Pregnancy:

Progesterone is critical for the maintenance of pregnancy by suppressing menstruation and decreasing uterine contractility.

7. Prepare for Lactation:

Progesterone has important actions in the breasts during pregnancy, acting in conjunction with estrogens to prepare for lactation.

Sex Hermones – Progestins
Structural Classes of the Progestins

- ✓ Progestins are compounds with biological activities similar to those of progesterone.

- ✓ They include three structural classes:

1. Progesterone and its Derivatives.

2. Testosterone and 19-nortestosterone derivatives.

3. miscellaneous Synthetic Progestins.

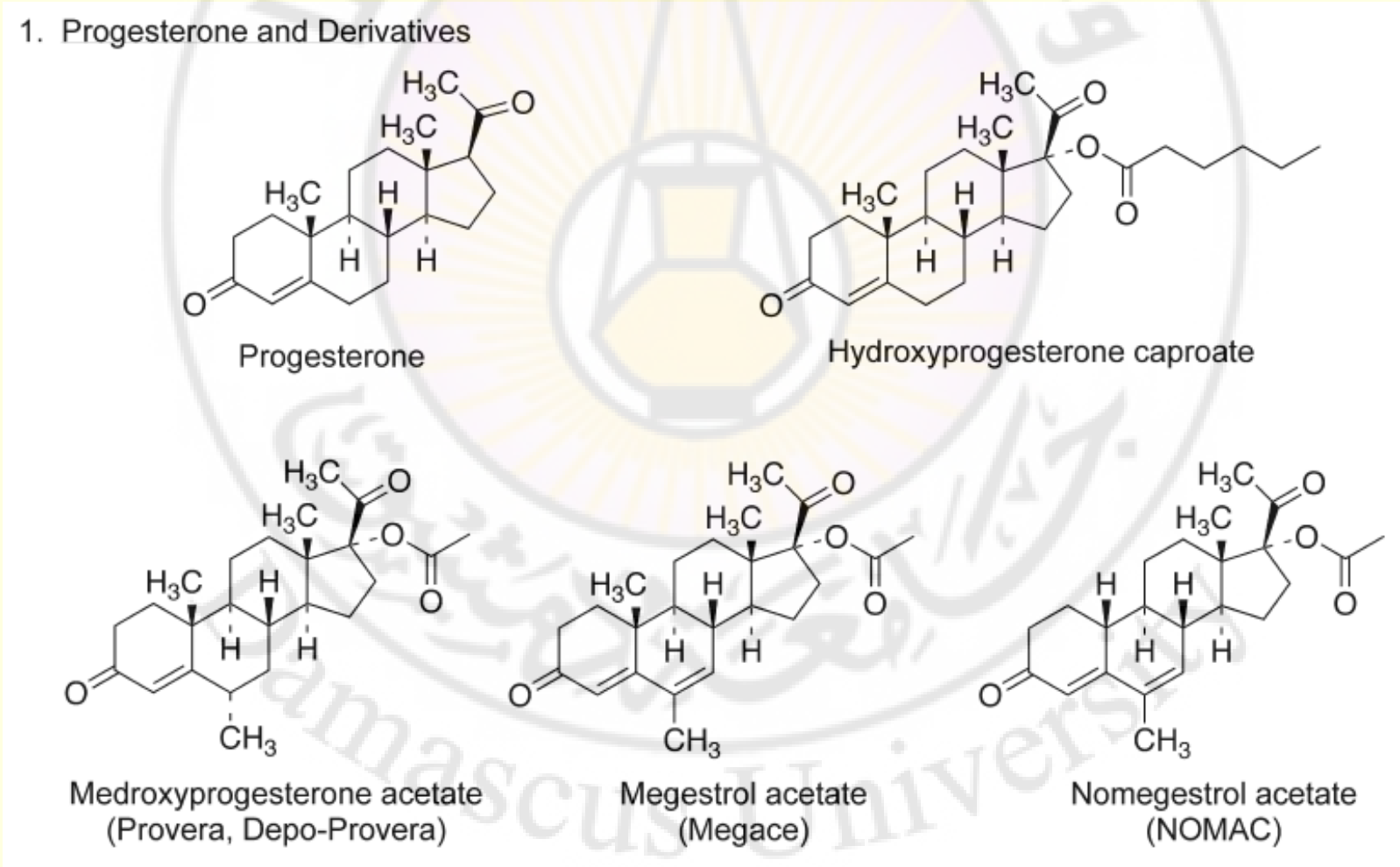
Sex Hermones – Progestins
Structural Classes of the Progestins

1. Progesterone and its Derivatives:

- ✓ Progesterone itself has low oral bioavailability because of poor absorption and almost complete metabolism in first passage through the liver.
- ✓ The progesterone 4-en-3-one ring A is a key to binding with Progesterone receptors PRs
- ✓ Adding 17α-acyl groups slows metabolism of the 20-one.
- ✓ Adding 6- methyl group enhances activity and reduces metabolism.

Sex Hermones – Progestins
Structural Classes of the Progestins

1. Progesterone and its Derivatives.



Sex Hermones – Progestins
Structural Classes of the Progestins

2. Testosterone and 19-nortestosterone derivatives.

Two important discoveries led to the development of the nortestosterone derivatives:

- ✓ One was that 19-norprogesterone still maintained significant progestational activity.
- ✓ Second was that 17α-alkynyl testosterone had greater progestational than androgenic activity.
- ✓ the 17α-alkynyl group also blocks metabolic or bacterial oxidation to the corresponding 17-ones.

Sex Hermones – Progestins
Structural Classes of the Progestins

2. Testosterone and 19-nortestosterone derivatives.

✓ Thus, by adding a 17α-ethinyl group to testosterone, one can simultaneously:

I. Decrease Androgenic Activity.

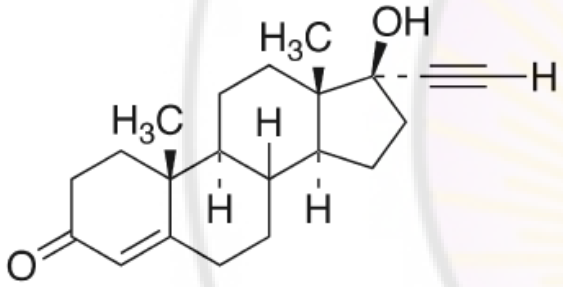
II. Increas Good Progestational Activity.

III. have an orally active compound as well.

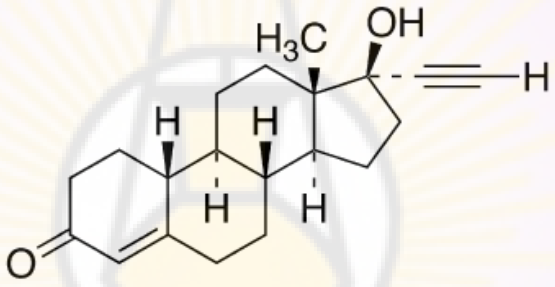
✓ Changing the alkyl group at C13 from a methyl to an ethyl group reduces the androgenic effects, while maintaining the progestational effects.

Sex Hermones – Progestins
Structural Classes of the Progestins

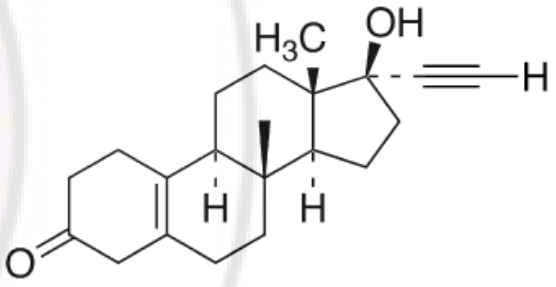
2. Testosterone and 19-Nortestosterone derivatives.



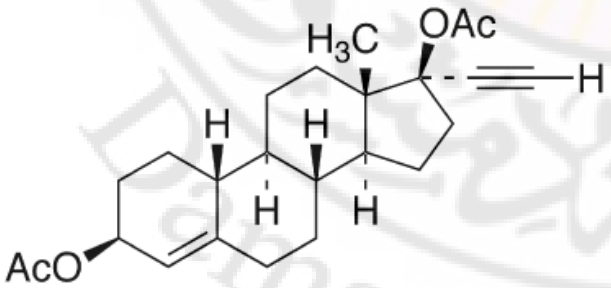
Ethisterone



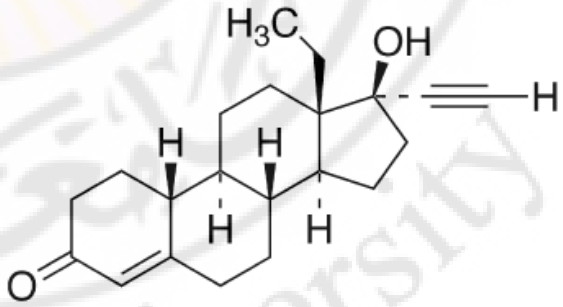
Norethindrone



Norethynodrel



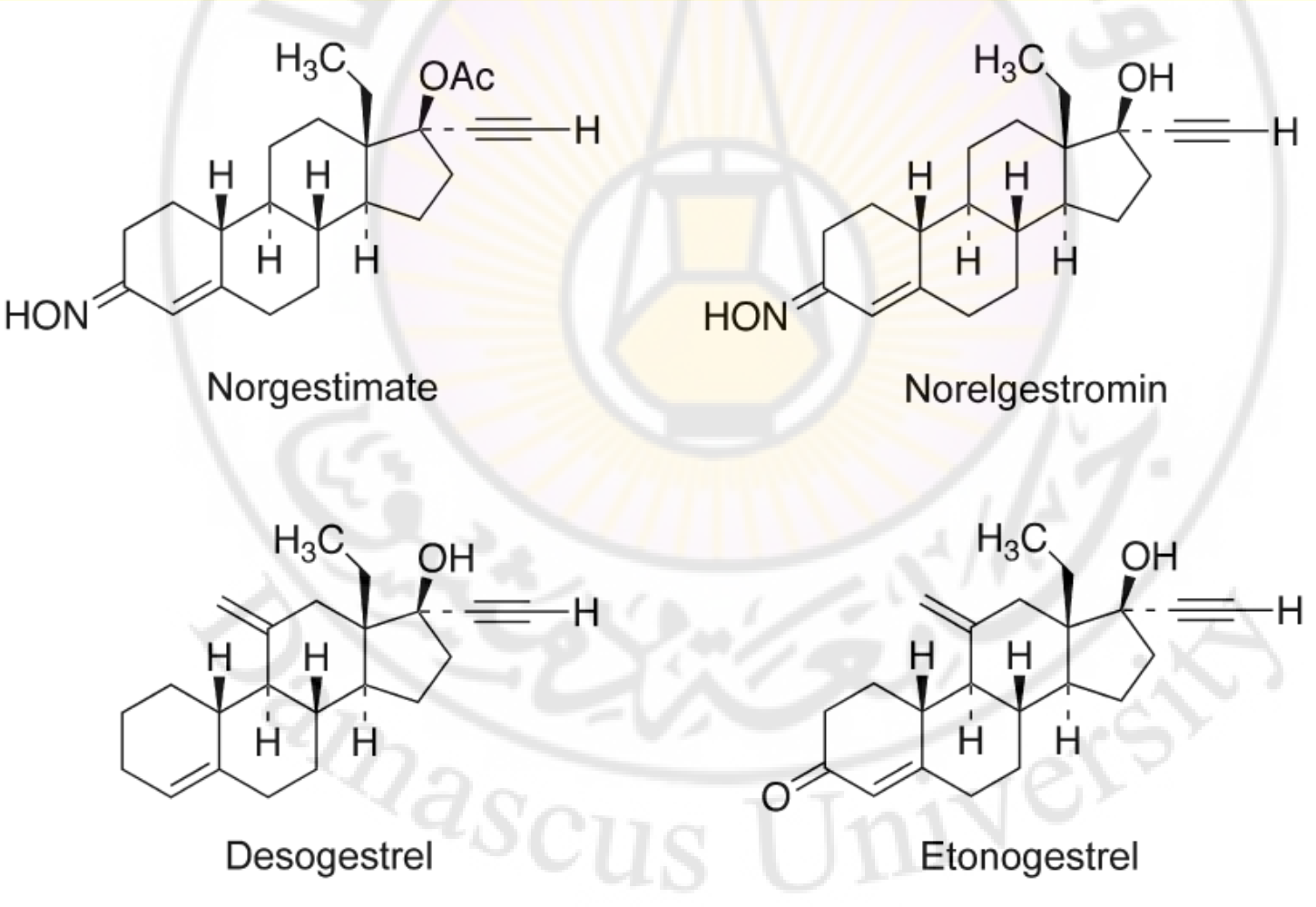
Ethynodiol diacetate



Norgestrel (Levonorgestrel)

Sex Hermones – Progestins
Structural Classes of the Progestins

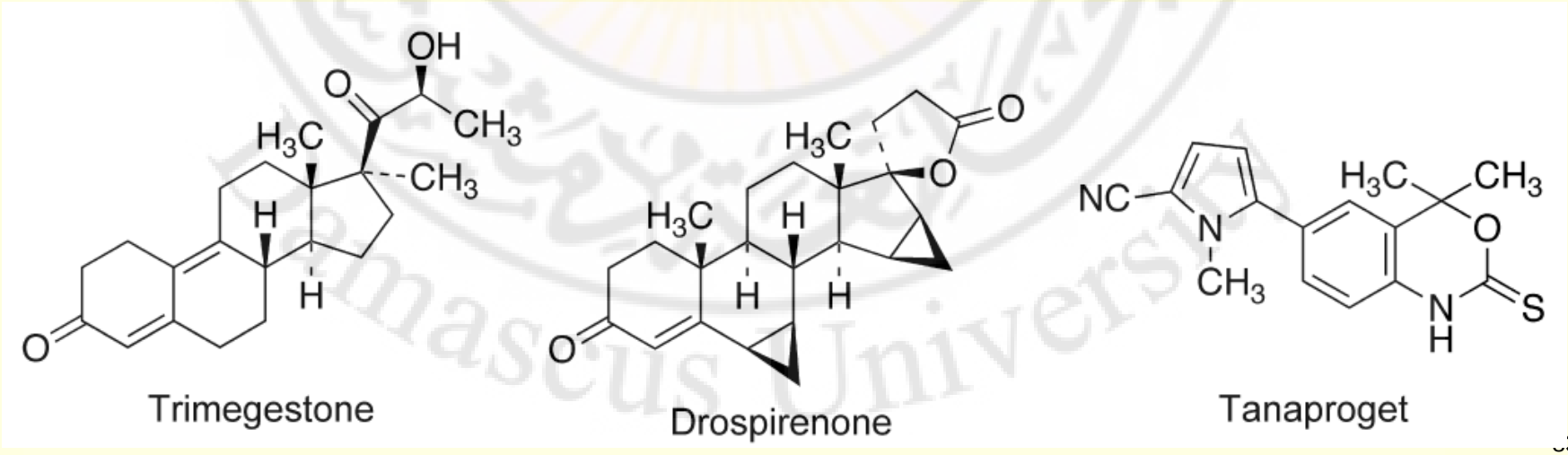
2. Testosterone and 19-Nortestosterone derivatives.



Sex Hermones – Progestins
Structural Classes of the Progestins

3. miscellaneous Synthetic Progestins.

- ✓ The most exciting new research area relating to progestins is the development of nonsteroidal PR agonists.
- ✓ Tanaproget is completely unrelated to progesterone, but it still has high affinity and selectivity for the PR



Sex Hermones – Progestins
Therapeutic Uses of the Progestins

1. Birth Control.

2. Reduction of the Risk of Endometrial Cancer from Postmenopausal Estrogens.

3. Breast or Endometrial Carcinoma.

4. Primary and Secondary Amenorrhea and Functional Uterine Bleeding Caused by Insufficient Progesterone Production or Estrogen–Progesterone Imbalance.

Sex Hermones – Progestins
Therapeutic Uses of the Progestins

1. Birth Control.

- ✓ A significant use of the Progestins, as of the estrogens, is inhibition of ovulation.

2. Reduction of the Risk of Endometrial Cancer from Postmenopausal Estrogens.

- ✓ the combination of a progestin with an estrogen may significantly reduce the risk of endometrial cancer in women taking postmenopausal estrogens.
- ✓ Because of this, a progestin is often included in HRT.

Sex Hermones – Progestins
Therapeutic Uses of the Progestins

3. Breast or Endometrial Carcinoma

- ✓ Progestins can be used for palliative treatment of advanced carcinoma of the breast or endometrium.
- ✓ These agents should not be used in place of surgery, radiation, or chemotherapy.

4. Primary and Secondary Amenorrhea and Functional Uterine Bleeding Caused by Insufficient Progesterone Production or Estrogen–Progesterone Imbalance.

- ✓ Progestins have been used very effectively to treat primary and secondary amenorrhea, functional uterine bleeding, and related menstrual disorders caused by hormonal deficiency or imbalance.

Sex Hermones – Progestins
Progestins Products

- ✓ The progestins are primarily used in oral contraceptive products and in hormone replacement regimens for women.

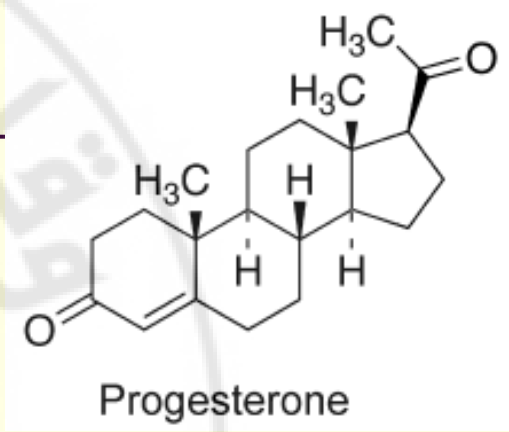
- ✓ They are also used to treat several gynecological disorders:

1) Dysmenorrhea
2) Endometriosis
3) Amenorrhea
4) Dysfunctional Uterine Bleeding.

- ✓ Estrogens are given simultaneously in most of these situations.

Sex Hermones – Progestins Products

Progesterone

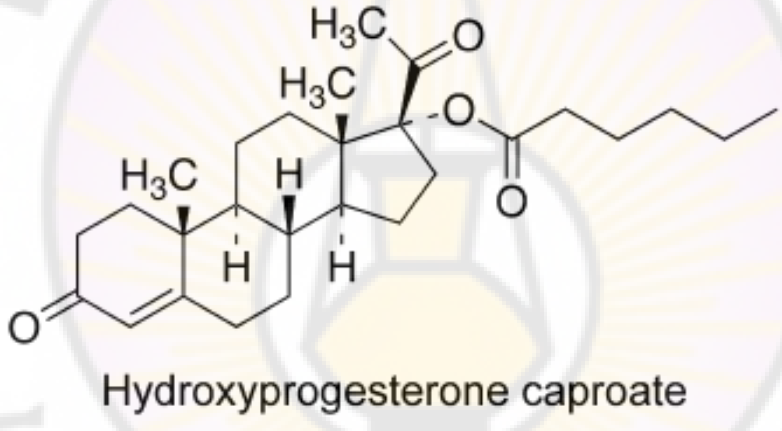


Progesterone

- ✓ Pregn-4-en-3,20- dione.
- ✓ Progesteron so rapidly metabolized that it is not particularly effective orally, being only one twelfth as active as intramuscularly.
- ✓ Progesterone given intramuscularly can be very irritating.
- ✓ A vaginal gel containing 4% or 8% progesterone offers an alternative dosage form.
- ✓ The discovery of 19-nortestosterones with progesterone activity made synthetically modified progestins of tremendous therapeutic importance.
- ✓ Progesterone (and all other steroid 4-ene-3-ones) is light sensitive and should be protected from light.

Sex Hermones – Progestins Products Hydroxyprogesterone Caproate

- ✓ 17-hydroxypregn-4-ene-3,20-dione hexanoate.

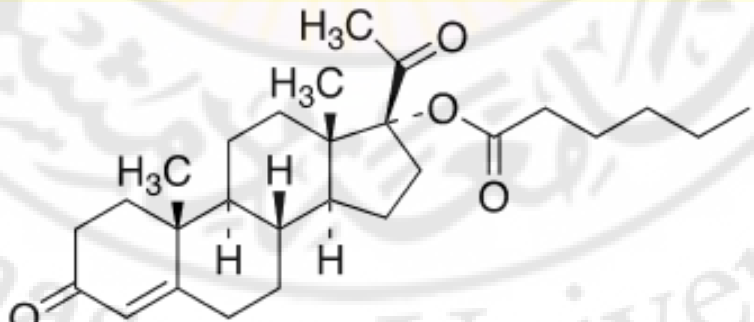


Hydroxyprogesterone caproate

- ✓ The 17-caproate group decreases reduction of the 20-one.
- ✓ Hydroxyprogesterone Caproate is much more active and longer acting than Progesterone because the 17 ester hinders reduction to the 20-ol.
- ✓ In contrast, Hydroxyprogesterone itself lacks progestational activity.

Sex Hermones – Progestins Products
Hydroxyprogesterone Caproate

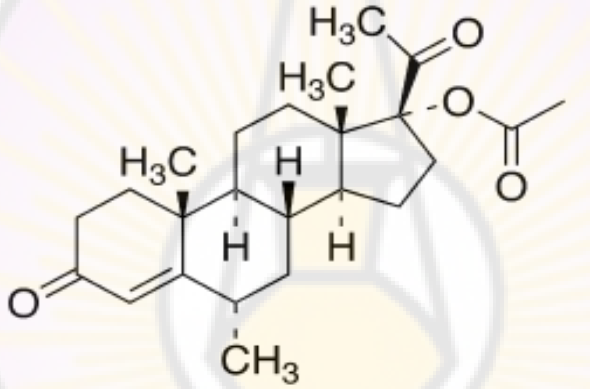
- ✓ The caproate ester is given only intramuscularly.
- ✓ The ester greatly increases oil solubility, allowing it to be slowly released from depot preparations
- ✓ a new formulation (Gestiva) was deemed approvable by the FDA in late 2006 for the prevention of preterm labor



Hydroxyprogesterone caproate

Sex Hermones – Progestins
Medroxyprogesterone Acetate MPA (Provera)

- ✓ 17-acetyloxy- 6-methylpregn-4-ene-3,20-dione.



Medroxyprogesterone acetate
(Provera, Depo-Provera)

- ✓ adding a 6-methyl group to the 17- hydroxyprogesterone structure greatly decrease the rate of reduction of the 4-ene-3-one system.
- ✓ The 17-acetate group also decreases reduction of the 20-one, similar to the 17-caproate.

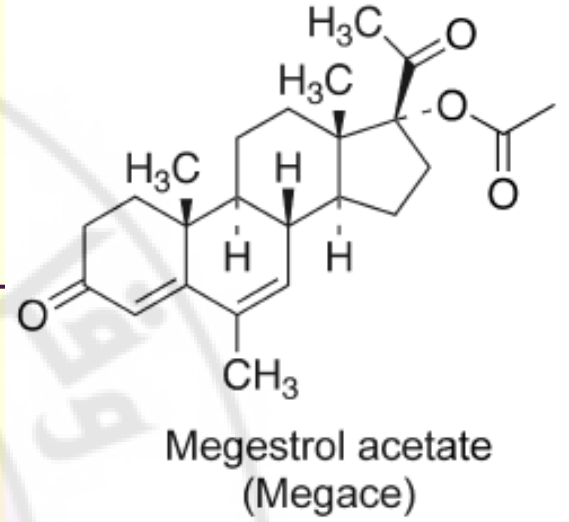
Sex Hermones – Progestins
Medroxyprogesterone Acetate (MPA)

- ✓ MPA is very active orally and has such a long duration of action intramuscularly that it cannot be routinely used intramuscularly for treating many menstrual disorders.

- ✓ The IM intramuscularl formulation of MPA is useful in the palliative treatment of advanced endometrial, breast carcinomas.

- ✓ MPA also has an important role in several birth control products (Depo- Provera, Depo-SubQ Provera 104).

Sex Hermones – Progestins
Megestrol Acetate (Megace)

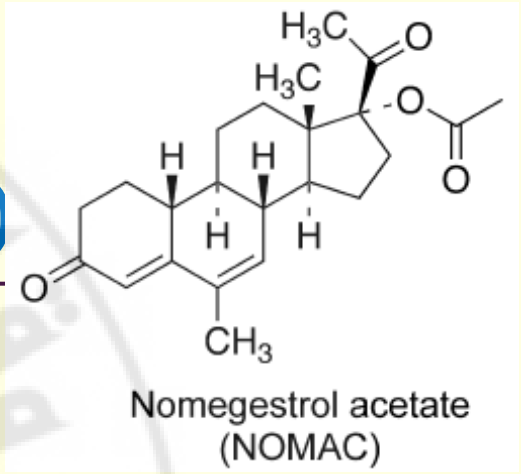


- ✓ 17- acetoxy-6-methylpregna -4,6-diene-3,20-dione .

- ✓ It is a progestin used primarily for the palliative management of recurrent, inoperable, or metastatic endometrial or breast carcinoma.

- ✓ Megestrol acetate has also been indicated for appetite enhancement in patients with AIDS.

Sex Hermones – Progestins
Nomegestrol Acetate (NOMAC)

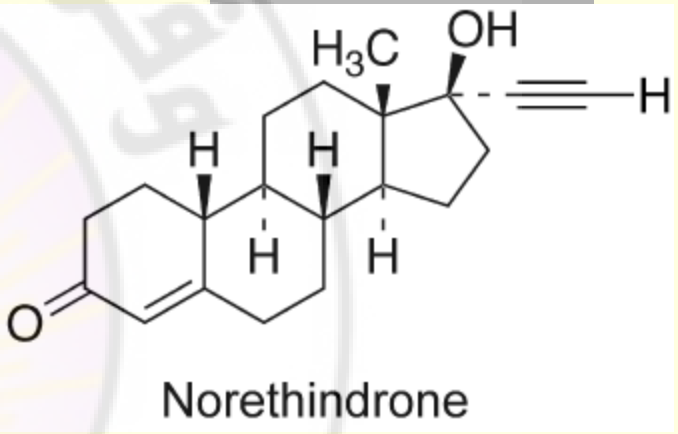


- ✓ 17- acetoxy-6-methyl-19-norpregna 4,6-diene-3,20-dione
- ✓ Nomegestrol Acetate is being investigated as the progestin component of a new oral contraceptive, in combination with the estrogen estradiol.
- ✓ This new combination, NOMAC/E2, is in phase.
- ✓ NOMAC is considered a nor-progesterone derivative that lacks the C19 methyl group in megestrol acetate.

Sex Hermones – Synthetic Progestins Norethindrone &Norethynodrel

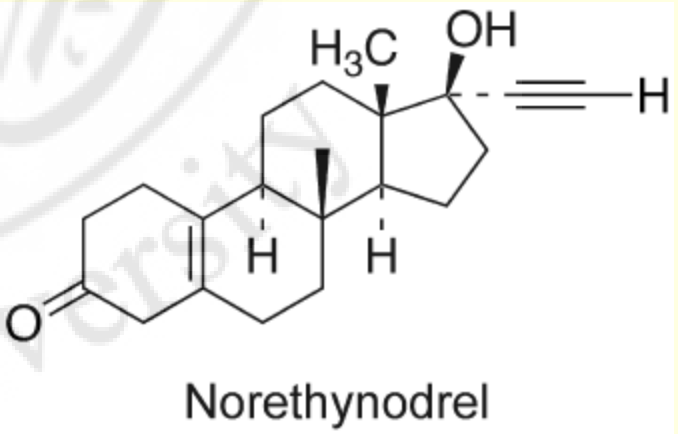
- ✓ Norethindrone

17-ethinyl-19-nortestosterone



Norethindrone

- ✓ its 5(10)-isomer,Norethynodrel
- ✓ One would predict that the 5(10)-double bond would isomerize in the stomach's acid to the 4-position
- ✓ In fact the that isomerization is not as facile in vivo as one might predict.



Norethynodrel

Sex Hermones – Synthetic Progestins Norethindrone &Norethynodrel

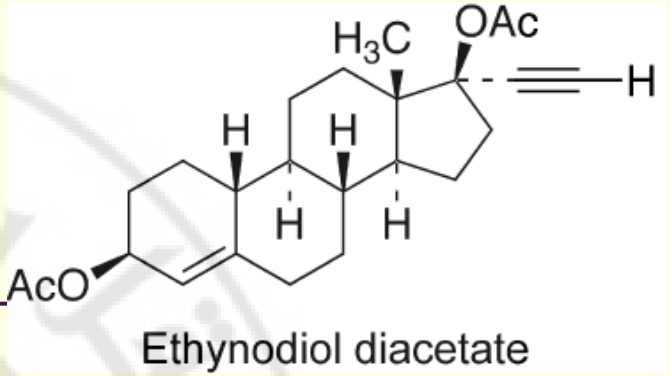
- ✓ It might appear at first glance to be subtle copies of each other. neither can be considered a copy of the other.
- ✓ Norethindrone is about 10 times more active than Norethynodrel.
- ✓ Although they are less active than progesterone when given subcutaneously, they have the important advantage of being orally active.

Sex Hermones – Synthetic Progestins Norethindrone &Norethynodrel

- ✓ Both are orally active, with the 17-ethinyl group blocking oxidation to the less active 17-one.
- ✓ The rich electron density of the ethinyl group and the absence of the 19-methyl group greatly enhance progestin activity.
- ✓ Both compounds were of great importance as progestin components of oral contraceptives.

- ✓ Because these compounds retain key features of the testosterone structure, including the 17β-OH, it is not surprising that they possess some androgenic side effects.

Sex Hermones – Progestins
Ethynodiol Diacetate

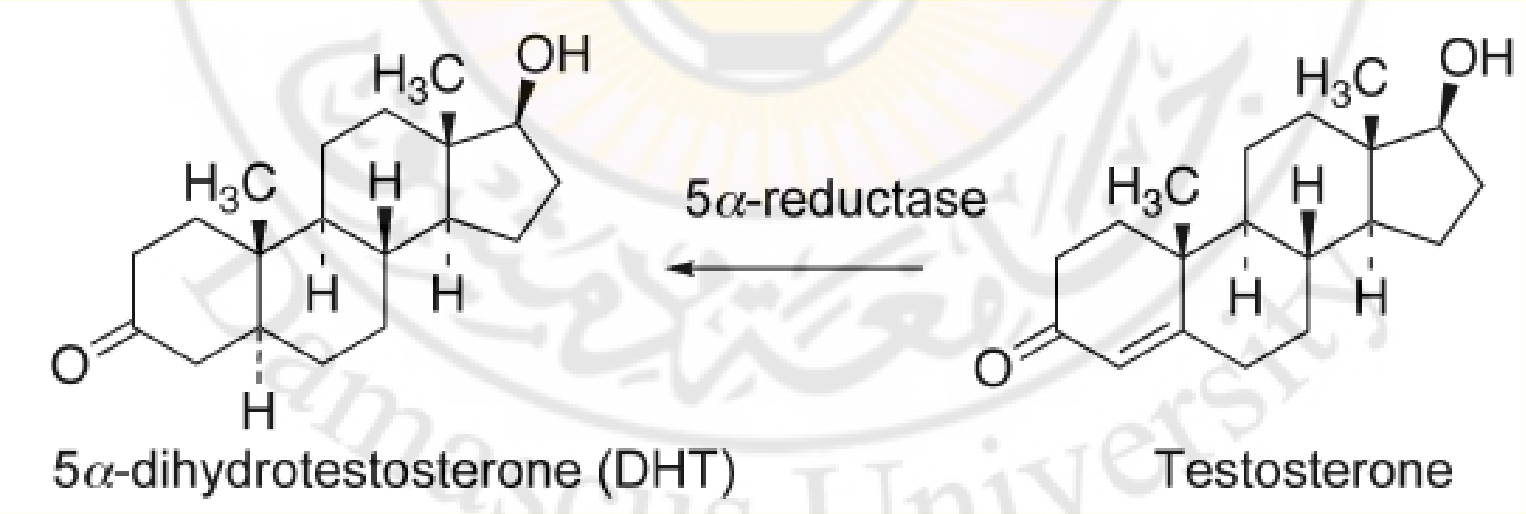


Ethynodiol diacetate

- ✓ 19- norpregn-4-en-20-yne-3,17-diol diacetate.
- ✓ Ethynodiol Diacetate is a prodrug of Norethindrone.
- ✓ A combination of hydrolysis of both esters and oxidation of the C3 alcohol to the ketone is necessary to provide the fully active progestin Norethindrone.

Sex Hermones – Androgens

- ✓ Endogenous Androgens
- ✓ Testosterone and its more potent reduction product 5α-DHT are produced in significantly greater amounts in males than in females, but females also produce low amounts of these “male” sex hormones.



5α-dihydrotestosterone (DHT) Testosterone

Sex Hermones – Androgens

✓ Endogenous Androgens

These endogenous compounds have two important activities:

1. Androgenic Activity (promoting male sex characteristics) and

2. Anabolic Activity (muscle building).

Sex Hermones – Androgens
Biological Activities of Androgens

- ✓ Biological Activities of Androgens
- ✓ They induce the development of the prostate, penis, and related sexual tissues.
- ✓ At puberty, the secretion of testosterone by the testes increasesgreatly, leading to an increase in facial and body hair, deepening of the voice, increased protein anabolic activity and muscle mass, rapid growth of long bones, and loss of some subcutaneous fat.
- ✓ Spermatogenesis begins, and the prostate and seminal vesicles increase in activity.

Sex Hermones – Androgens
Biological Activities of Androgens

- ✓ Biological Activities of Androgens
- ✓ Sexual organs increase in size.
- ✓ The skin becomes thicker, and sebaceous glands increase in number, leading to acne in many young people.
- ✓ The androgens also play important roles in male psychology and behavior.

- ✓ In women, testosterone plays a role in libido, mood, muscle mass and strength, as well as bone density

Sex Hermones – Androgens

Therapeutic Uses of Anabolic Androgenic Steroids

- The primary use of Anabolic Androgenic Steroids AAS is in androgen replacement therapy in men, either at maturity or in adolescence.
- The cause of testosterone deficiency may be either hypogonadism or hypopituitarism.
- The use of the AAS for their anabolic activity or for uses other than androgen replacement has been limited because of their masculinizing actions.
- This has greatly limited their use in women and children.
- Although anabolic activity is often needed clinically, especially in patients with AIDS, none of the products presently available is free of significant androgenic side effects.

Sex Hermones – Androgens

Therapeutic Uses of Anabolic Androgenic Steroids

- ✓ The masculinizing (androgenic) side effects in females include:

1. Hirsutism.
2. Acne
3. Deepening of the Voice
4. Clitoral Enlargement.
5. Depression of the Menstrual Cycle.

- ✓ Furthermore, AAS generally alter serum lipid levels and increase the probability of atherosclerosis, characteristically a disease of men and postmenopausal women.

Sex Hermones – Androgens

Therapeutic Uses of Anabolic Androgenic Steroids

- ✓ 17β-Esters and 17α-alkyl products are available for a complete range of therapeutic uses.
- ✓ These drugs are contraindicated in:

1. men with prostate cancer.
2. men or women with heart, kidney, or liver disease.
3. pregnancy.

- ✓ Diabetics using the androgens should be carefully monitored.
- ✓ Androgens potentiate the action of oral anticoagulants, causing bleeding in some patients.

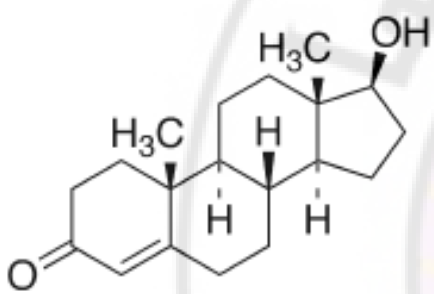
Sex Hermones – Androgens

Therapeutic Uses of Anabolic Androgenic Steroids

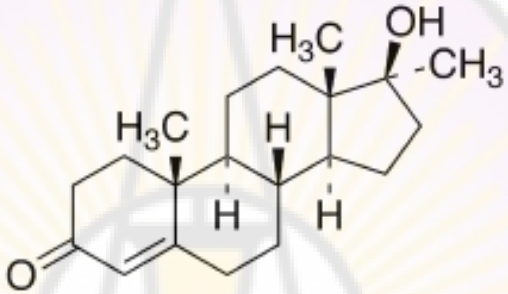
- ✓ Female patients may develop virilization side effects, and some of these effects may be irreversible (voice changes).
- ✓ All the anabolic agents currently commercially available (oxymetholone, oxandrolone, nandrolone decanoate) have significant androgenic activity; hence, virilization is a potential problem for all women patients.
- ✓ Many of the anabolic agents are orally active, as one would predict by noting a 17α-alkyl group in many of them.
- ✓ anabolic agents without the 17α-alkyl (nandrolone decanoate) are active only intramuscularly.
- ✓ The 17-alkyl products may induce liver toxicity in some patients.

Sex Hermones – Androgens

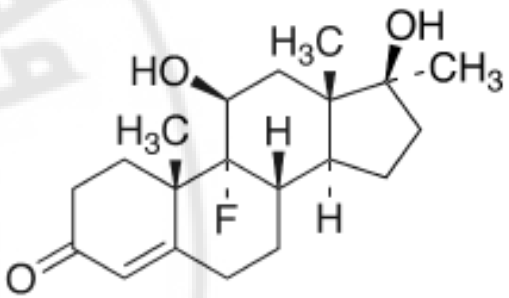
Therapeutic Uses of Anabolic Androgenic Steroids



Testosterone

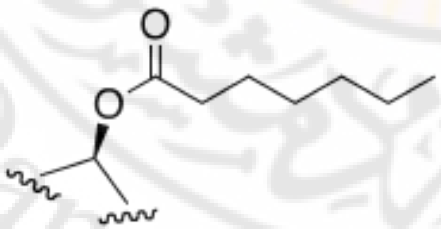


17α-methyltestosterone
(Testred)

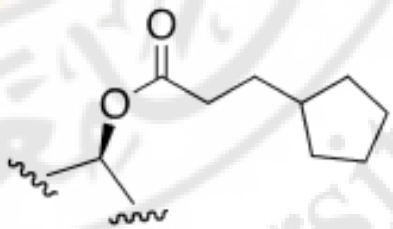


Fluoxymesterone
(Halotestin)

17β-Esters Commercially Available (for IM injection):
Also testosterone propionate (for compounding)



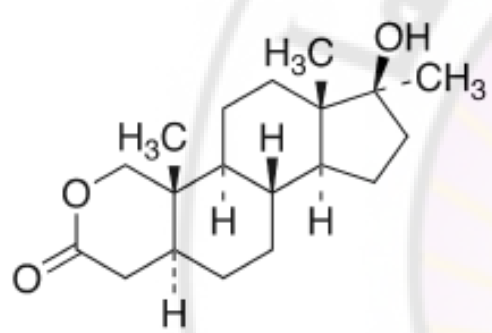
Testosterone enanthate



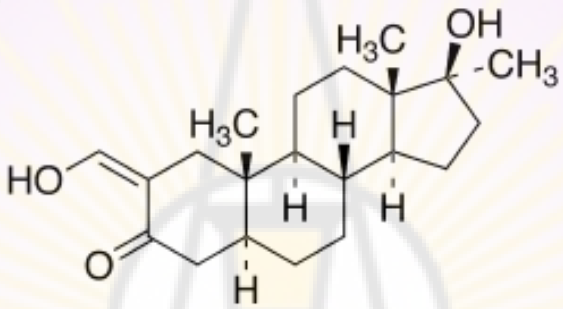
Testosterone cypionate

Sex Hermones – Androgens

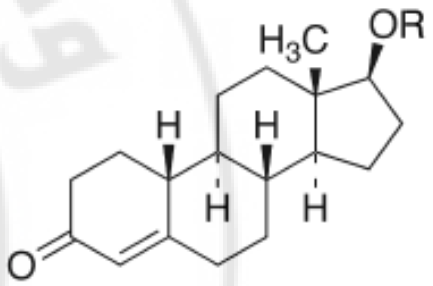
Therapeutic Uses of Anabolic Androgenic Steroids



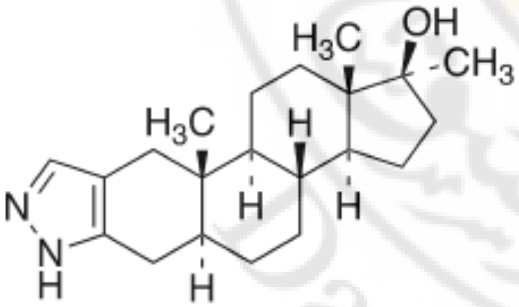
Oxandrolone (Oxandrin)



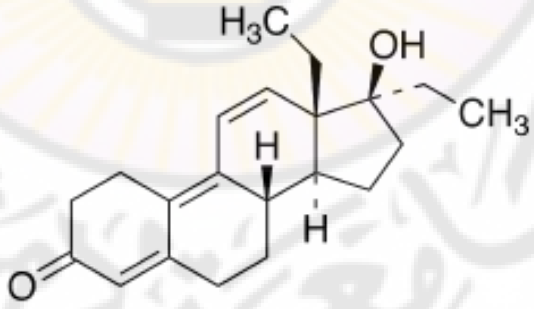
Oxymetholone (Anadrol-50)



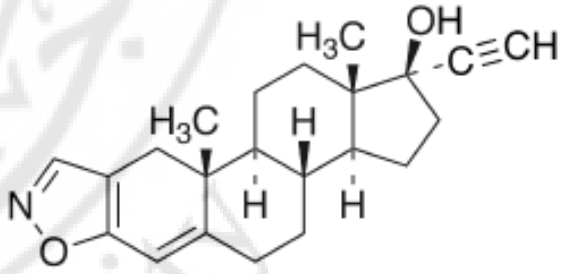
Nandrolone decanoate
R = decanoate



Stanozolol



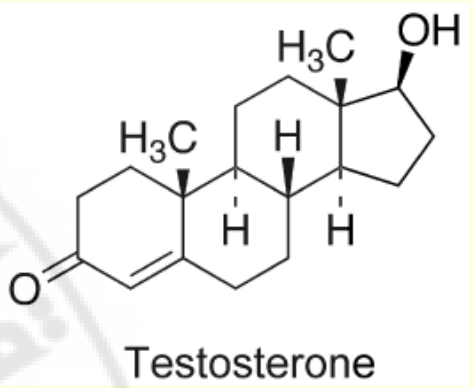
Tetrahydrogestrinone (THG)



Danazol

Sex Hermones – Androgens

Testosterone



Testosterone

- ✓ 17β-hydroxy androst- 4-en-3-one.
- ✓ Testosterone is a naturally occurring androgen in men.
- ✓ In women, it mainly serves as a biosynthetic precursor to estradiol but also has other hormonal effects.
- ✓ It is rapidly metabolized to relatively inactive 17-ones preventing significant oral activity.
- ✓ Testosterone is available in a

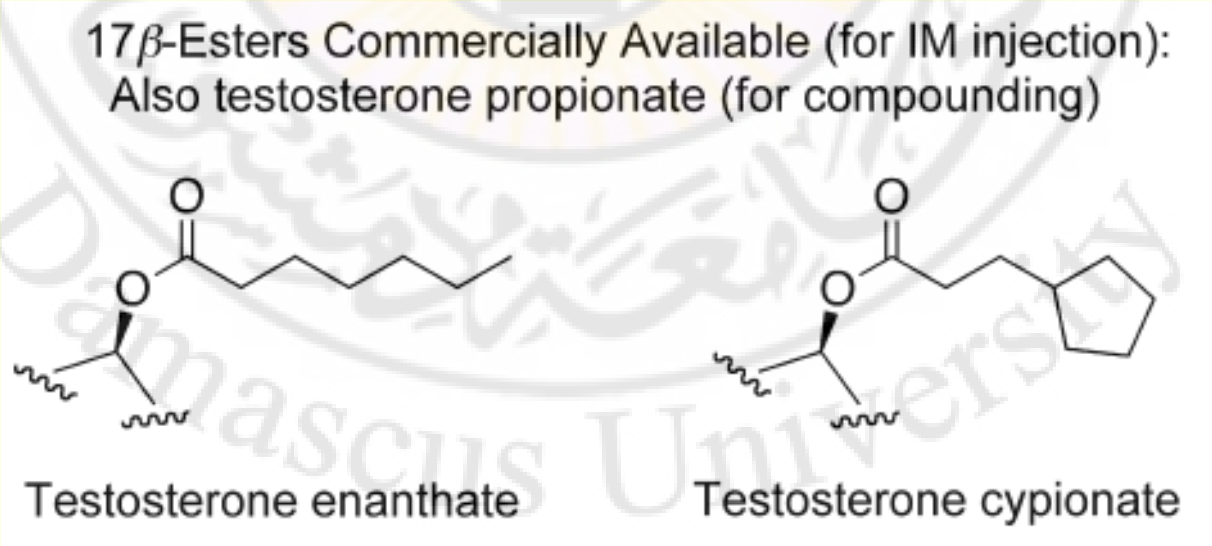
1. Transdermal Delivery System (Patch)
2. Gel Formulation
3. Buccal System
4. Implantable Pellets

Sex Hermones – Androgens

Testosterone

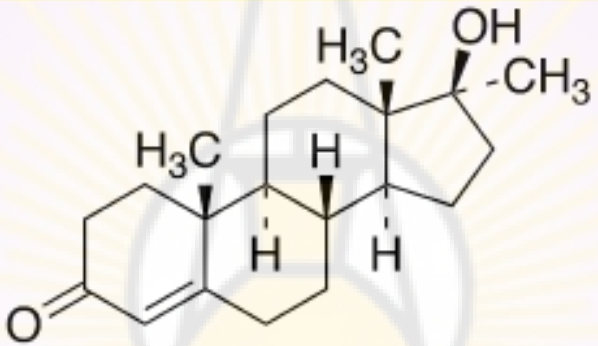
- ✓ Testosterone 17- esters are available in long-acting IM depot preparations including the following:

1. Testosterone cypionate, USP: Testosterone 17 cyclopentylpropionate
2. Testosterone enanthate, USP: Testosterone 17-heptanoate
3. Testosterone propionate, USP: Testosterone 17-propionate



Sex Hermones – Androgens
Methyltestosterone

- ✓ 17β-hydroxy-17-methylandrost-4-en-3-one.

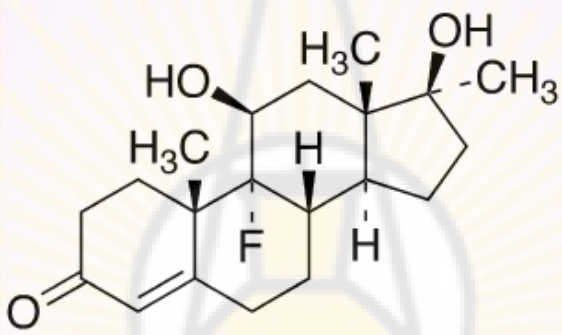


17α-methyltestosterone
(Testred)

- ✓ Methyltestosterone is only about half as active as testosterone (intramuscularly), but it has the great advantage of being orally active.

Sex Hermones – Androgens
Fluoxymesterone

- ✓ 9α-fluoro -11β,17 β-dihydroxy-17-methylandrost-4-en-3-one.

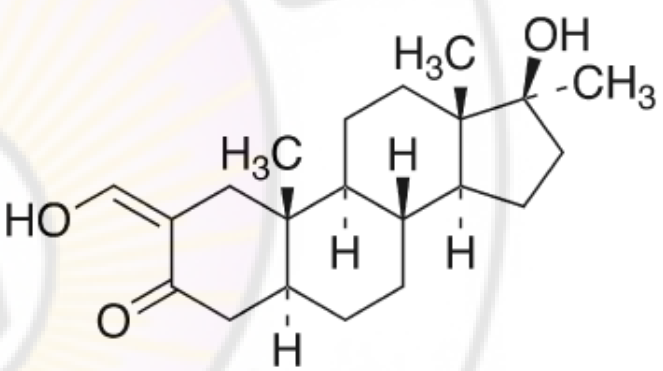


Fluoxymesterone
(Halotestin)

- ✓ It is a highly potent, orally active androgen, about 5 to 10 times more potent than testosterone.
- ✓ It can be used for all the indications discussed previously, but its great androgenic activity has made it useful primarily for treatment of the androgen-deficient male.

Sex Hermones – Androgens
Oxymetholone

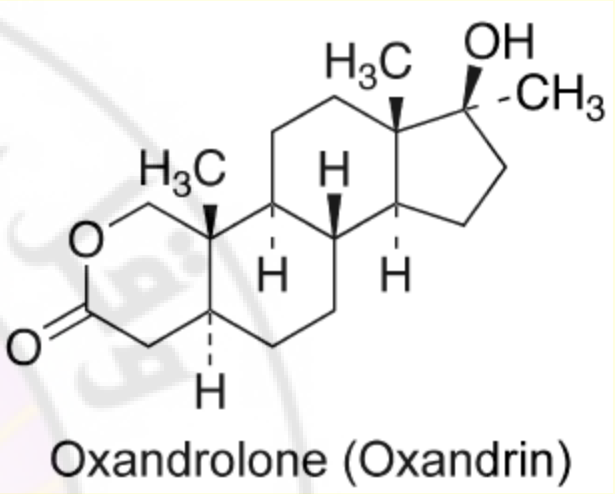
- ✓ 17 β -hydroxy-2- (hydroxymethylene)-17-methylandrostan-3-one.



Oxymetholone (Anadrol-50)

- ✓ It is approved for the treatment of various anemias.

Sex Hermones – Androgens
Oxandrolone

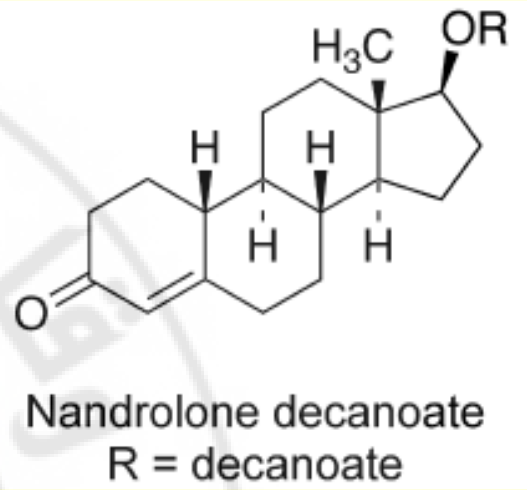


Oxandrolone (Oxandrin)

- ✓ 17 β -hydroxy-17-methyl-2-oxaandrostan-3-one.

- ✓ It is approved to aid in the promotion of weight gain after weight loss following surgery,chronic infections, or severe trauma and to offset protein catabolism associated with long-term corticosteroid use.
- ✓ Oxandrolone is also used to relieve bone pain accompanying osteoporosis.
- ✓ It has been used to treat alcoholic hepatitis and HIV wasting syndrome.

Sex Hermones – Androgens
Nandrolone decanoate



Nandrolone decanoate
R = decanoate

- ✓ 17β -hydroxyestr-4-en-3-one

17-decanoate.

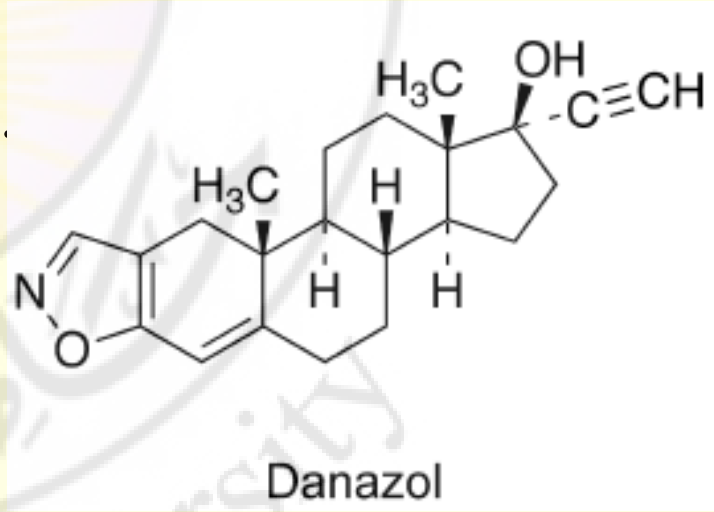
- ✓ It has been used in the management of certain anemias, but the availability of erythropoietin has greatly reduced this use.

Sex Hermones – Androgens
Danazol

- ✓ Danazol is a weak androgen that, in spite of the 17-ethinyl group, has little estrogenic or progestogenic activity.

- ✓ Danazol has been called a synthetic steroid with diverse biological effects
- ✓ It binds to PRs, GRs, ARs, and ERs.
- ✓ Danazol used to treat

1. Endometriosis
2. Hereditary Angioedema
3. Fibrocystic Breast Disease



Danazol

Sex Hermones – Antiandrogens

Antiandrogens are of therapeutic use in treating:

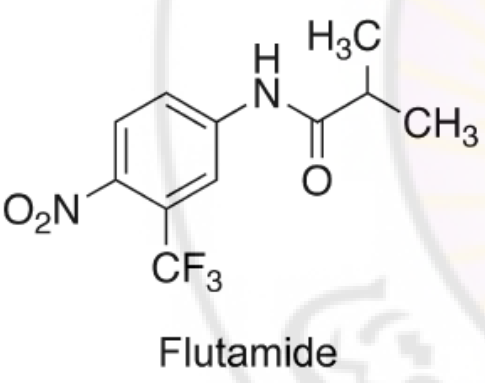
- ✓ conditions of Hyperandrogenism

1. Hirsutism.
2. Acute Acne.
3. Premature Baldness.

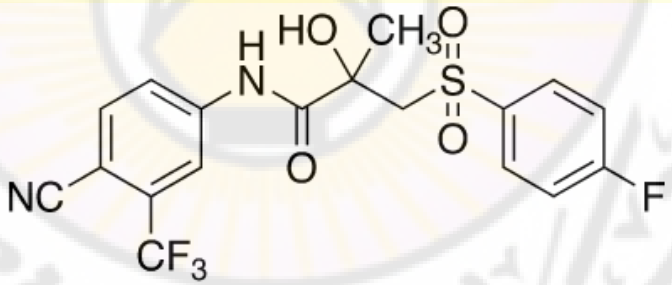
- ✓ Androgen-stimulated Cancers (prostatic carcinoma).
- ✓ The ideal antiandrogen would be nontoxic, highly active, and devoid of any hormonal activity.
- ✓ Both steroidal and nonsteroidal antiandrogens have been investigated.

Sex Hermones – Antiandrogens
Flutamide, Bicalutamide, and Nilutamide

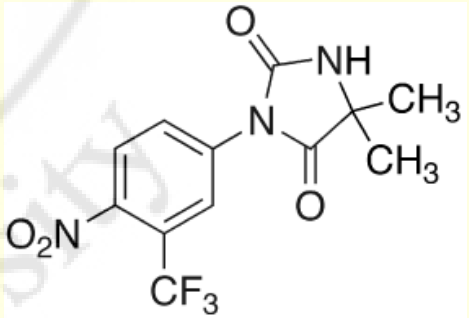
- ✓ Three nonsteroidal antiandrogens are in clinical use in the
- ✓ United States Flutamide, Bicalutamide, Nilutamide



Flutamide



Bicalutamide (Casodex)



Nilutamide (Nilandron)

Sex Hermones – Antiandrogens
Flutamide, Bicalutamide, and Nilutamide

- ✓ They are mainly used in the management of prostate cancer.
- ✓ Flutamide was the first of these compounds approved for use by the FDA, but liver toxicity and thrice daily dosing offered room for improvement.
- ✓ It was also determined that a metabolite of Flutamide, hydroxyflutamide, had greater antiandrogen action than the parent.
- ✓ Bicalutamide has greater potency than Flutamide, and it is dosed once a day and has less toxicity than Flutamide and Nilutamide, making it a preferred choice when initiating therapy.

Sex Hermones – Androgens
Inhibition of 5α-Reductase

- ✓ 5-DHT is important for maintaining prostate function in men.
- ✓ The formation of DHT is mediated by 5α-reductase, an enzyme that has two distinct forms, type I and type II.
- ✓ DHT also plays a major role in the pathogenesis of Benign Prostatic Hyperplasia (BPH).

- ✓ Finasteride (Proscar, Propecia) is a relatively selective inhibitor of type II 5α-reductase .
- ✓ Dutasteride (Avodart)is a newer drug for treating BPH, inhibits both isoforms of the enzyme

Sex Hermones – Androgens
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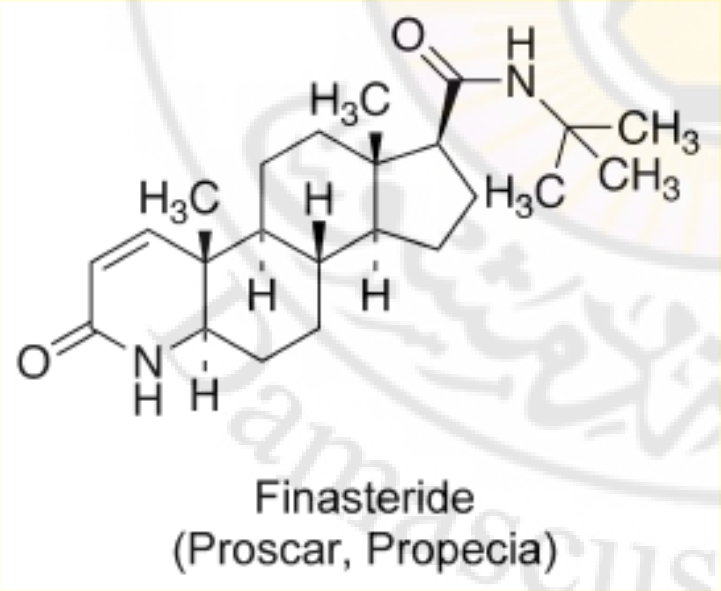
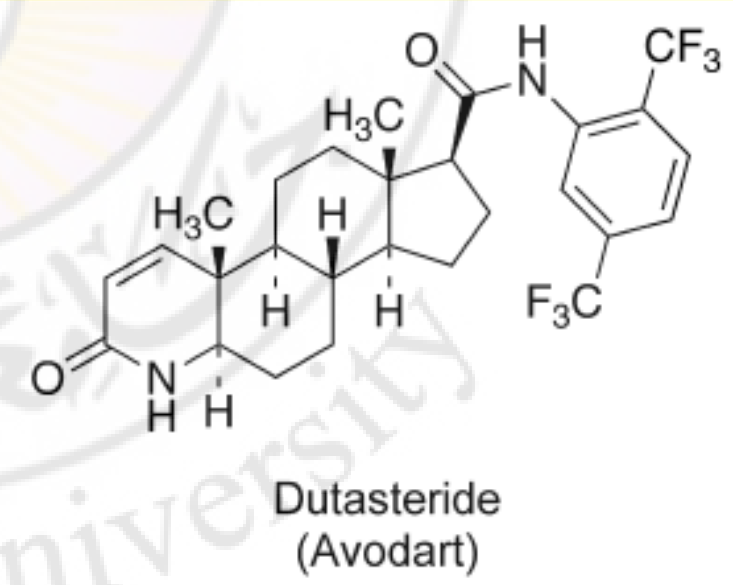


Finasteride
(Proscar, Propecia)



Dutasteride
(Avodart)

Sex Hermones – Androgens
Inhibition of 5α-Reductase

- ✓ Finasteride (Proscar, Propecia) is a relatively selective inhibitor of type II 5α-reductase .
- ✓ This enzyme is present in high levels in the prostate and at lower levels in other tissues.
- ✓ A second use of finasteride is in the treatment of male pattern baldness.
- ✓ The conversion of testosterone to DHT in advancing years leads to thinning of hair in men.
- ✓ Inhibition of this conversion was envisioned as a possible baldness treatment.