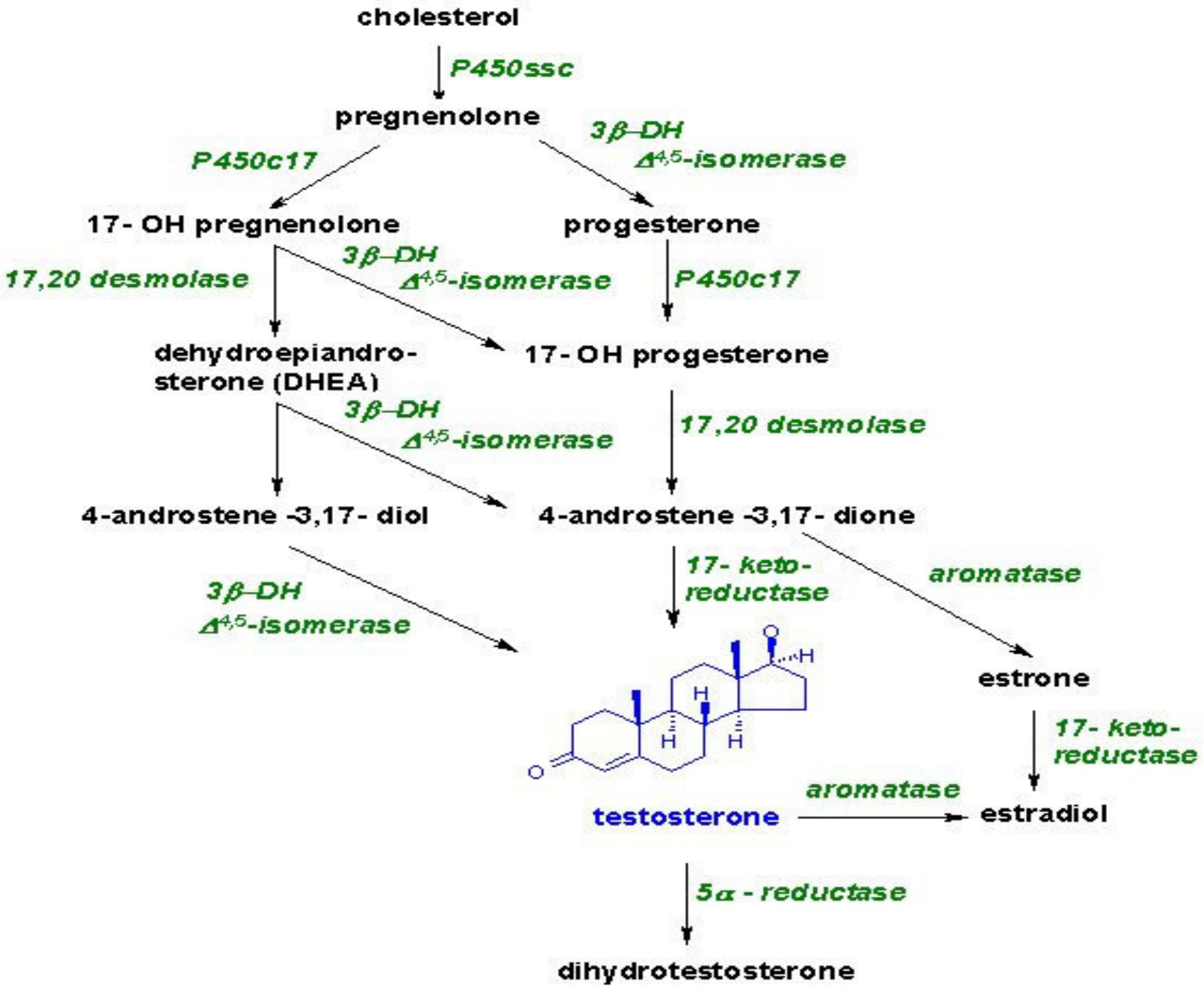
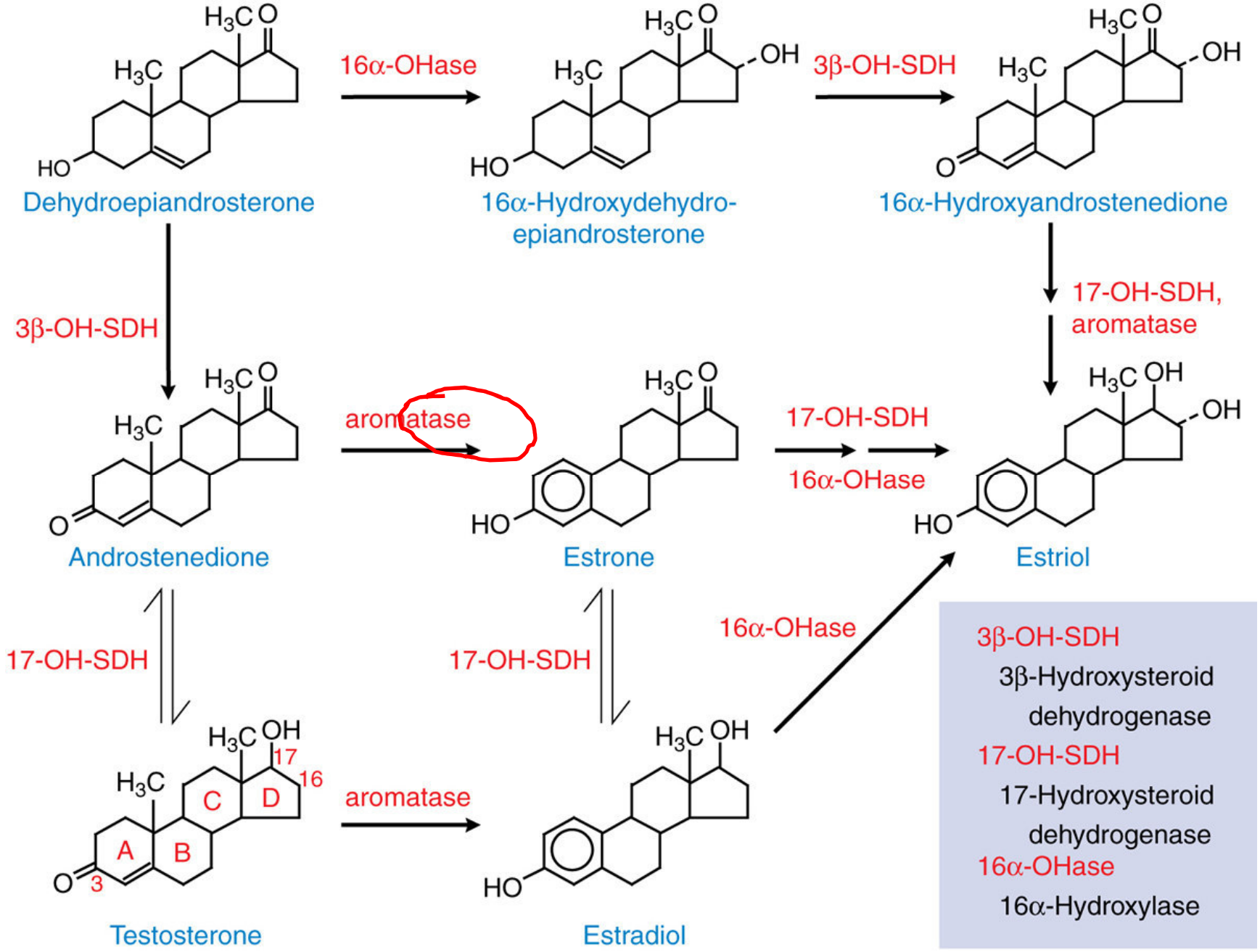
GONADAL HORMONES

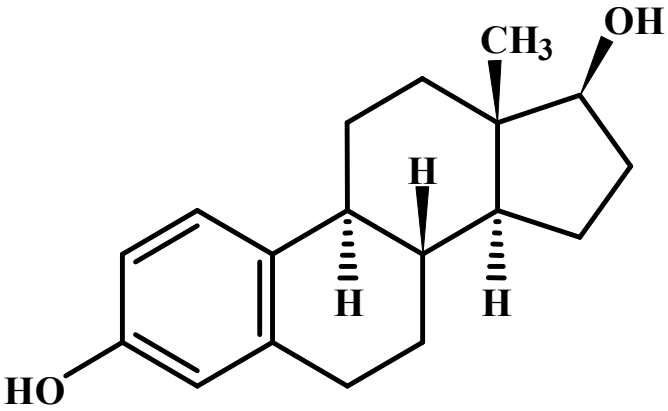
BIOSYNTHETIC PATHWAYS OF ESTROGENS



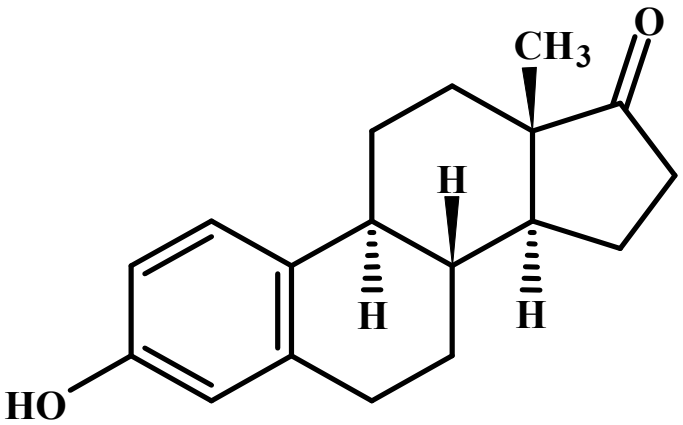
BIOSYNTHETIC PATHWAYS OF ESTROGENS



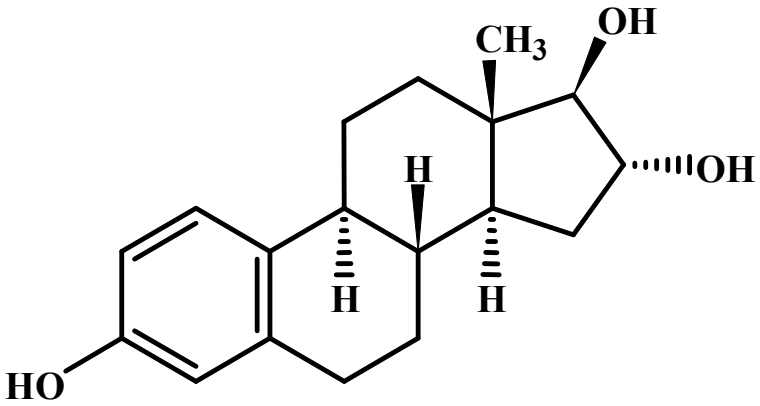
NATURAL ESTROGENS



ESTRADIOL



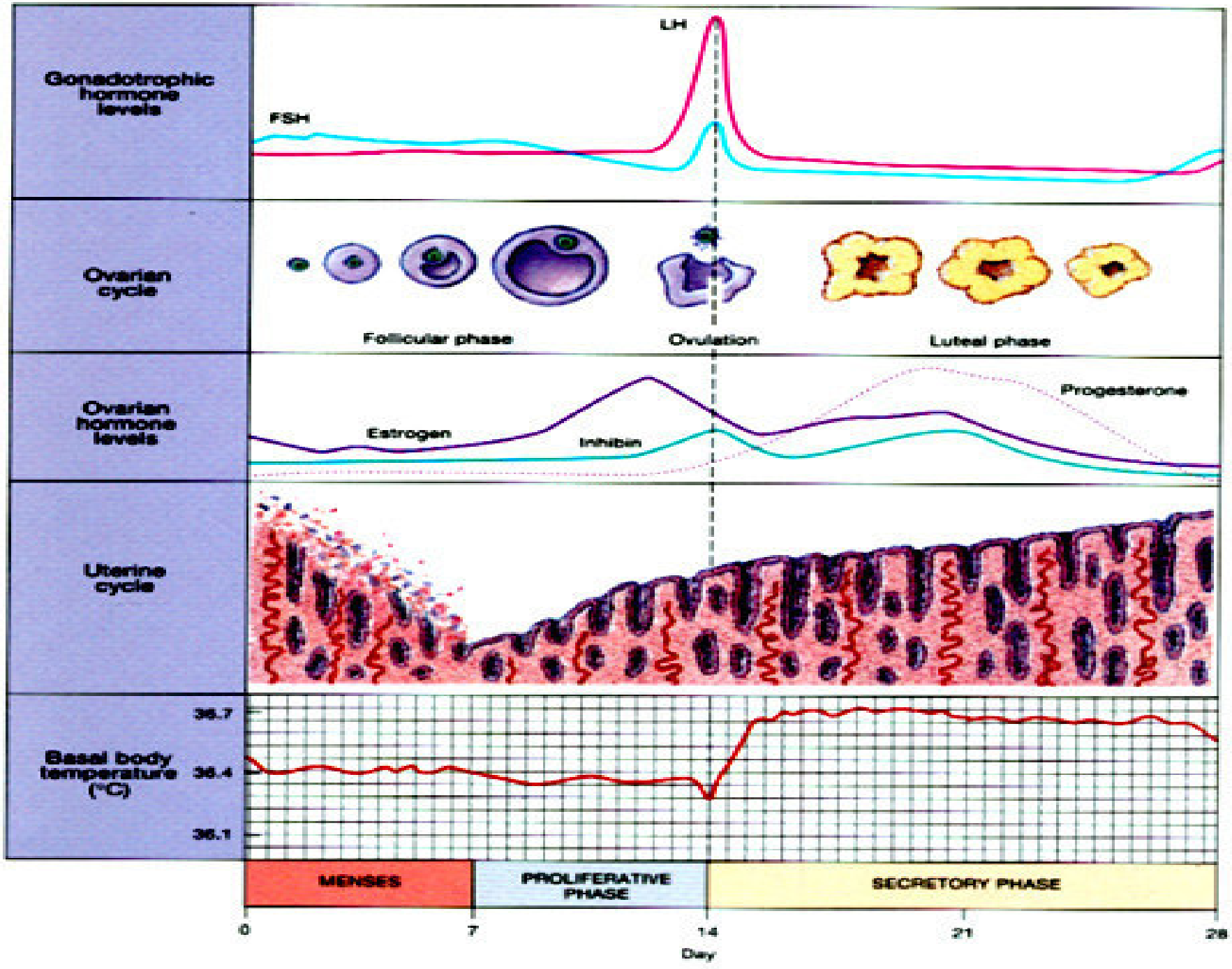
ESTRONE



ESTRIOL

ESTROGENS

- Estrogens include the natural hormones as well as semi-synthetic and synthetic (stilbene) agents
- Estrogens are used as hormone-replacement therapy (menopause), in oncology and as contraceptives
- Most estrogen in the female is produced in the ovaries by the theca interna and the granulosa cells of the follicles


Gonadotrophic hormone levels
LH
FSH
Ovarian cycle
Follicular phase
Ovulation
Luteal phase
Ovarian hormone levels
Progesterone
Estrogen
Inhibin
Uterine cycle
Basal body temperature (°C)
36.7
36.4
36.1
MENSES
PROLIFERATIVE PHASE
SECRETORY PHASE
0
7
14
21
28
Day

ACTIONS OF ESTROGENS

- on sexual organs (primary and secondary sexual characteristics)
  - ovaries: stimulate follicular growth; small doses cause an increase in weight of ovary; large doses cause atrophy
  - uterus: endometrial growth
  - vagina: cornification of epithelial cells with thickening and stratification of epithelium
  - cervix: increase of cervical mucous with a lowered viscosity (favoring sperm access)
  - breast: cause enlargement of the breasts, shaping the body contours and the skeleton
  - Induces the growth of axillary and pubic hair and pigmentation of the genital tract.

ACTIONS OF ESTROGENS

- Development and maintenance of internal (fallopian tubes, uterus, vagina), and external genitalia
- skin: increase in vascularization, development of soft, textured and smooth skin
- bone: increase osteoblastic activity
- electrolytes: retention of Na^+, Cl^- and water by the kidney
- cholesterol: hypocholesterolemic effect

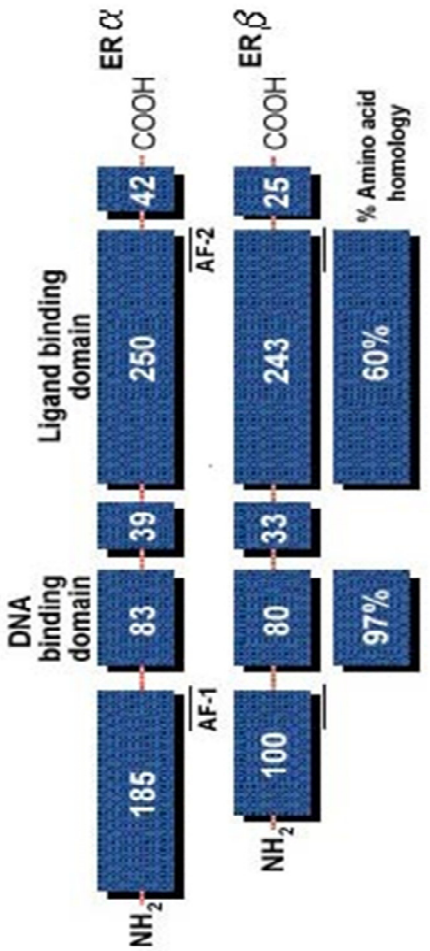
METABOLIC EFFECTS OF ESTROGENS

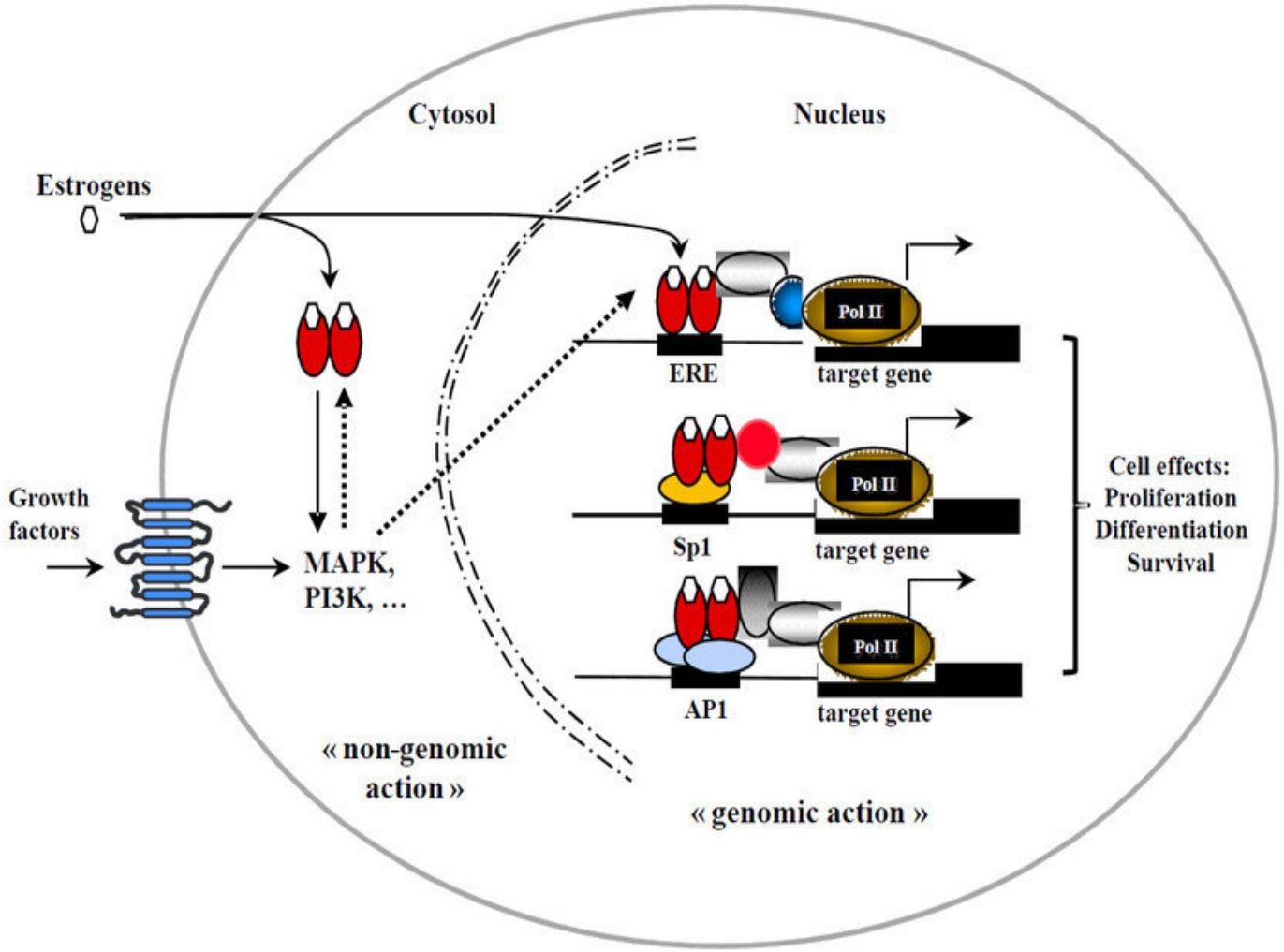
- Decrease stromal cell production of IL-1, IL-6, TNFalpha
- Increase the production of Insulin-like growth factor (IGF)-1, bone morphogenic protein (BMP)-6 and transforming growth factor (TGF)-beta which are antiresorptive.
- Increase osteoblast production of the cytokine osteoprotegrin (OPG). OPG antagonizes the binding of osteoprotegrin-ligand to its receptor (termed RANK, or **r**eceptor **a**ctivator of **N**F-**K**appa B) and prevents the differentiation of osteoclast precursors to mature osteoclasts.
- Estrogens increase the osteoclast apoptosis.
- Estrogen affects bone growth and epiphyseal closure in both sexes.

EFFECT ON LIPID METABOLISM AND COAGULATION

- Elevates HDL and decreases LDL and Lp(a)
- Alter bile composition by increasing cholesterol secretion and decreasing bile acid secretion. → Gallstone formation.
- Estrogens increase plasma levels of CBG, TBG, SSBG.
- Cause an increase in coagulation factor VII and XII. Decrease the anticoagulation factors protein C, protein S and antithrombin III. → Thrombosis
- Increase the fibrinolysis.
- In high concentration have antioxidant activity.
- Long-term administration of estrogens decrease the plasma renin, ACE, ET-1 production.
- Increase production of nitric oxide in the vascular wall.
- Increase melanin cc in the skin (chloasma gravidarum)

ESTROGEN RECEPTORS





NATURAL ESTROGENS

- Conjugated estrogenic substances:
  - an amorphous preparation containing water soluble conjugated forms of mixed estrogens from the urine of pregnant mares (Premarin, Cenestin - synthetic conjugated estrogens)
- estradiol :
  - oral : Estrace
  - transdermal: Climara, Alora, Vivelle, Vivelle-Dot, Estraderm, FemPatch

NATURAL ESTROGENS

- estrone:
  - Kestrone 5 (injectable only)
- esterified estrogen
  - (75-85% sodium estrone sulfate and 6- 15% sodium equilin sulfate)
  - Estratab; Menest
- estropipate (piperazine estrone sulfate)
  - Ogen; Ortho-Est

NATURAL ESTROGENS

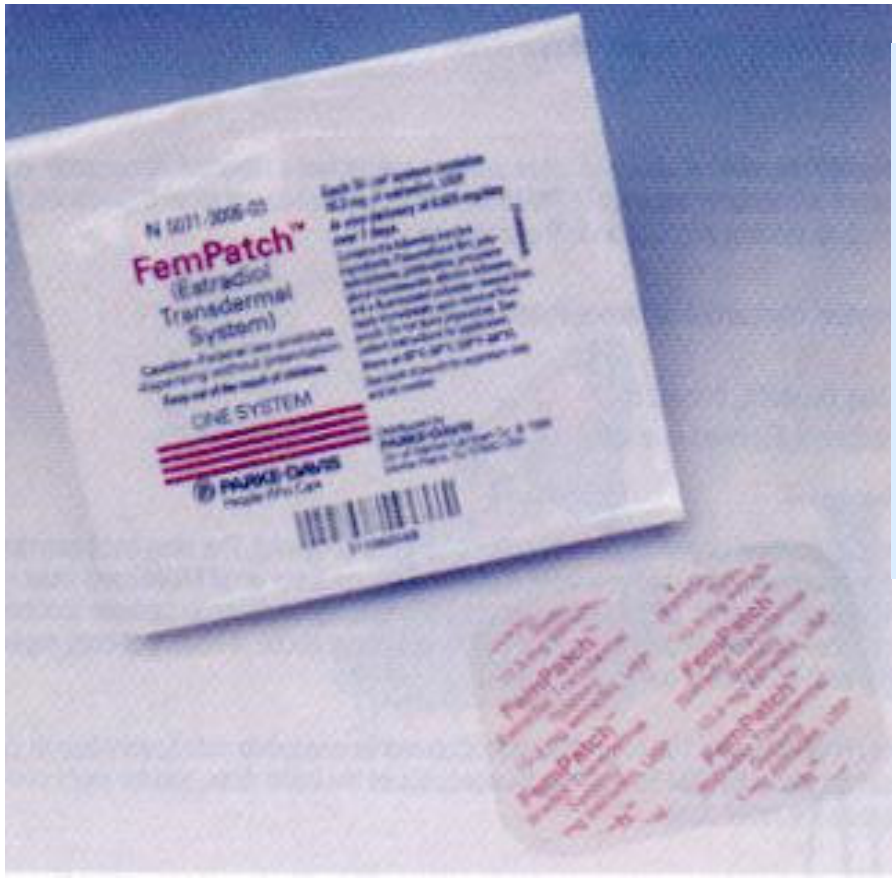
- Sustained-release injectables:
  - estradiol valerate in oil (Delestrogen; Valergen)
  - estradiol cypionate in oil (depGynogen; DepoGen)
  - duration of action from 3 to 8 weeks
  - esterified at C-17 hydroyl group

ESTROGEN PRODUCTS IN HUNGARY

- Estradiol
  - Dermestril
  - Divigel
  - Estrimax
  - Estrofem
  - Linoladiol
  - Vagifem
- Estriol
  - Estrokad
  - Ortho-Gynest D
  - Ovestin
- Tibolon
  - Livial

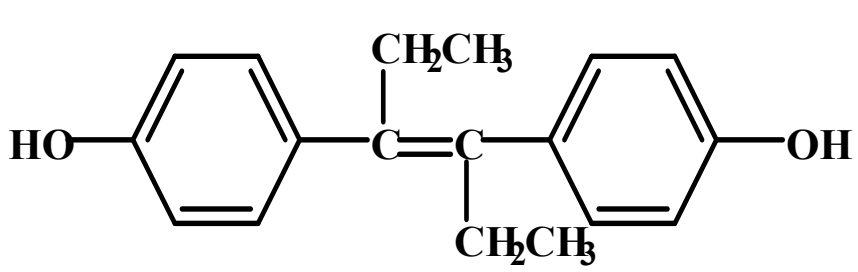
ESTROGEN PRODUCTS

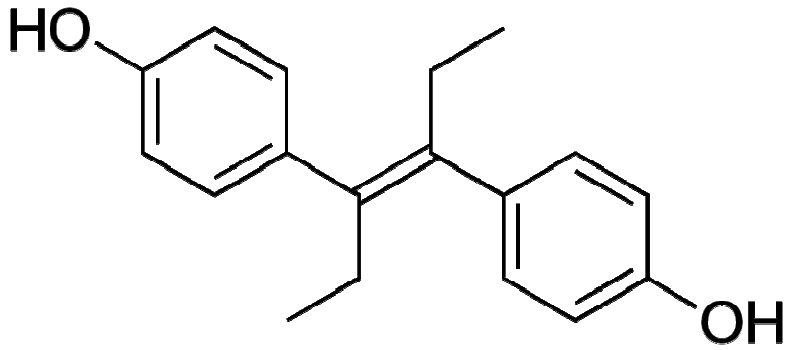
ESTROGEN PRODUCTS



25µg
VAGIFEM®
estradiol vaginal tablets
CONVENIENT, COMFORTABLE
RELIEF WITHOUT THE MESS

DIETHYLSTIBESTROL





DIETHYLSTILBESTROL (DES)

- Synthesized in 1938.
- From about 1940 to 1970, DES was given to pregnant women under the mistaken belief it would reduce the risk of pregnancy complications and losses.
- In 1971, DES was shown to cause a rare vaginal tumor (adenocarcinoma) in girls and women who had been exposed to this drug in utero.
- In male babies: testicular hypoplasia, cryptorchism, epididymal cysts.
- Breast cancer development in the mothers.

THERAPEUTIC USE OF ESTROGENS

1. Hormone replacement therapy: Conjugated estrogens: 0.625 mg/day for replacement (oral potency is lower than ethinyl estradiol. Means around 5-10 μg.)
2. Contraceptive: Ethinyl estradiol (EOD): 20-35 μg/day
3. Postmenopausal hormone-replacement therapy: prevention of bone loss and amelioration of vasomotor systems.
4. Vasomotor symptoms: hot flashes may alternate with chilly sensations, inappropriate sweating and paresthesias. Instead of estrogen medroxyprogesterone acetate can be administered.
5. Prevention of cardiovascular diseases, but thrombembolic disease and the incidence of gallstones are increased.
6. Neuroprotective effect: Delay the onset of Alzheimer's disease. The trial result is controversial.
7. Urogenital atrophy: dryness and itching of the vagina, pain during urination and intercourse, a need to urinate urgently and often, incontinence. Estrogen orally, vaginal cream, ring device.
8. Treatment of testosterone-dependent prostate carcinoma

SERMS – SELECTIVE ESTROGEN-RECEPTOR MODULATORS

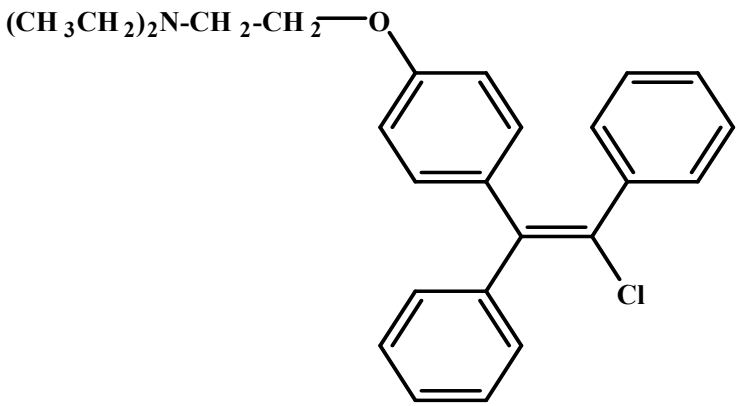
- Clomiphen (Clomid, Omiphin), exception!!
- Tamoxifen
- Toremifen (Fareston)
- Raloxifen (Evista)
- Centchroman/Ormeloxifene (Saheli, Novex-DS, Centron, Sevista)
- Under development
  - Droloxifen
  - Idoxifen
  - Nafoxiden
- Common feature: variable actions depending on target tissue:
  - Agonist in bone
  - Partial agonist in endometrium
  - Antagonist in breast

CLOMIPHENE CITRATE

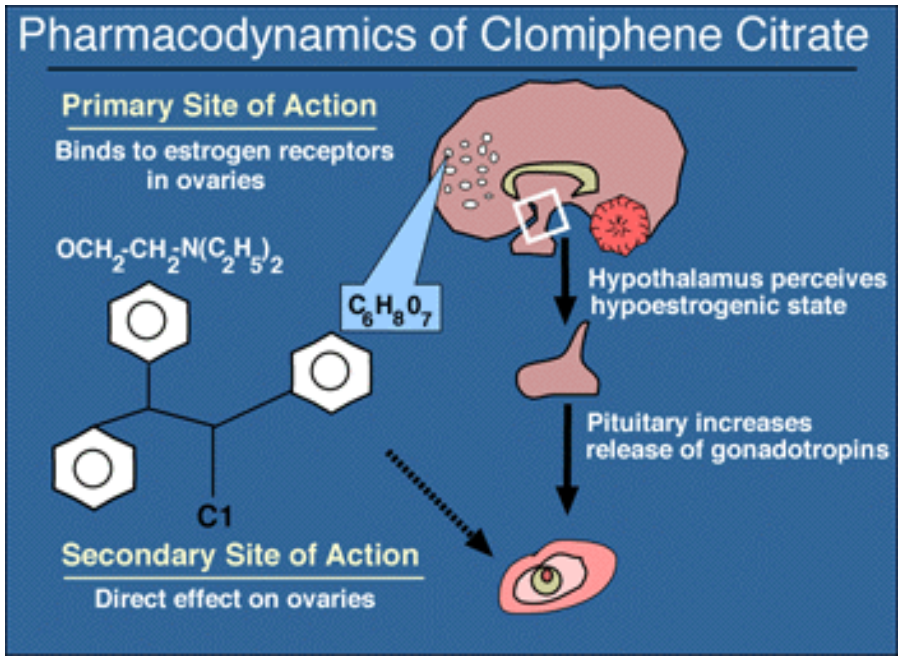
Adverse effects:

- vasomotor flushes (or hot flashes)
- abdominal discomfort
- visual blurring (dose-dependent)
- reversible ovarian enlargement and cyst formation
- twin formation!!!

Fertility pill!!!

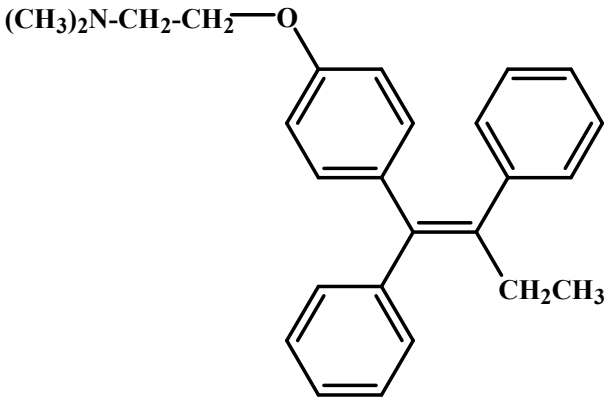


CLOMIPHENE (CLOMID)



TAMOXIFEN

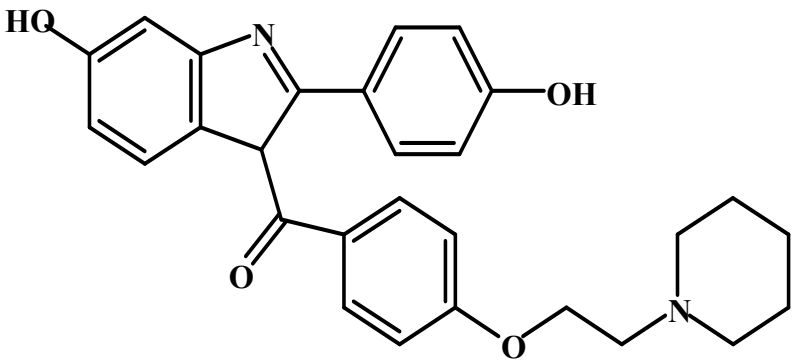
- Tamoxifen competitively binds to ER (on tumors)
- Nonsteroidal
- Causes cells to remain in the G0 and G1 phases
- Cytostatic rather than cytocidal
- Prodrug (2D6, 3A4)
- Side effects:
  - Bone
  - Cardiovascular and metabolic
  - CNS
  - Premature growth plate fusion
  - Agonist at bone
  - Partial agonist at uterus (cancer risk)
  - Antagonsit at breast



TAMOXIFEN (NOLVADEX)

RALOXIFENE (EVISTA)

- Agonist at bone
- Antagonist at breast and uterus
- no increased cancer risk
- Known as a SERM (selective estrogen receptor modulator)
- currently used to modify/ prevent postmenopausal osteoporosis

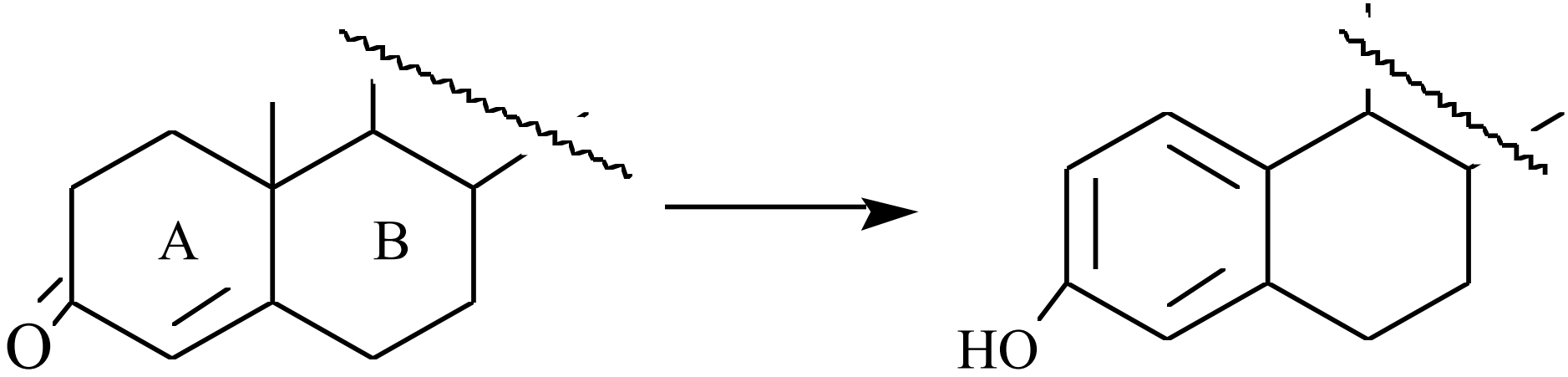


RALOXIFENE (EVISTA)

ESTROGEN RECEPTOR ANTAGONISTS

- Fulvestrant (Faslodex)
  - 30 x stronger than tamoxifen
  - Ind: breast cancer

STEROID AROMATASE

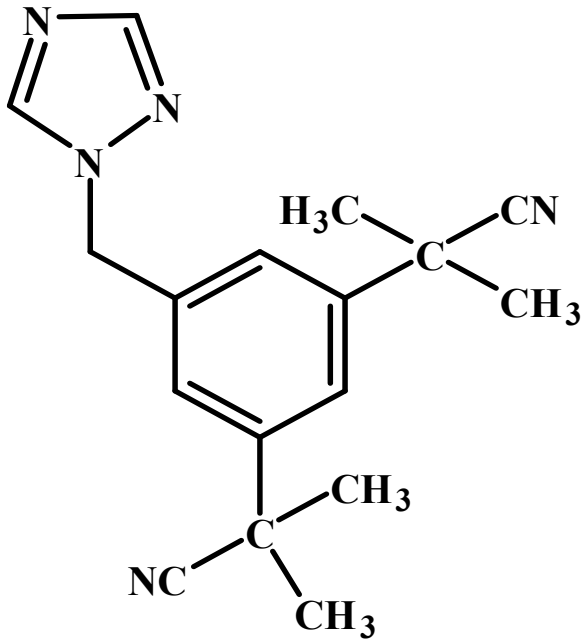


Estrogens

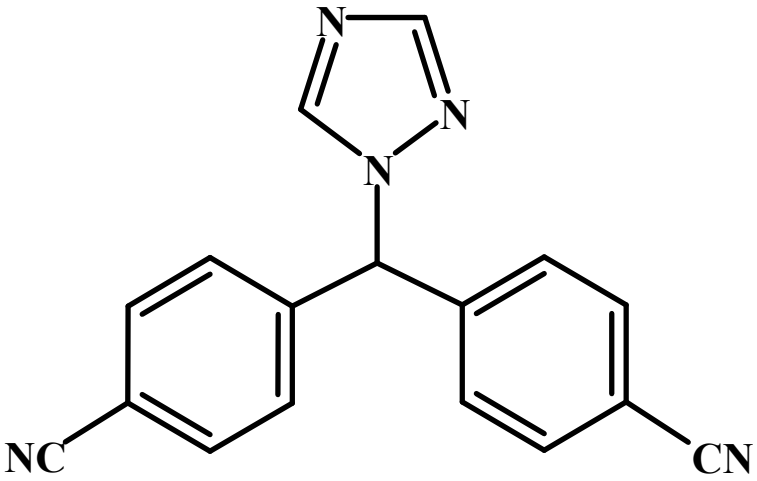
AROMATASE INHIBITORS

- Aromatase is a cytochrome P450 enzyme that catalyzes the conversion of adrenal androgen androstenedione to estrone in both pre- and post menopausal women
- Reaction occurs in the liver, muscle, adipose and breast tissue
- In post-menopausal women, aromatization is responsible for the majority of circulating estrogen
- Aminoglutethimide was used but has now been replaced by more selective drugs
- Drugs may be steroidal (formestan, exemestane) or non-steroidal (anastrozole, letrozole, vorozole)
- Estrogen deprivation through aromatase inhibition is an effective and selective treatment for some post-menopausal patients with hormone-dependent breast cancer
- Second line drugs in the treatment of breast cancer

AROMATASE INHIBITORS



ANASTROZOLE (ARIMIDEX)

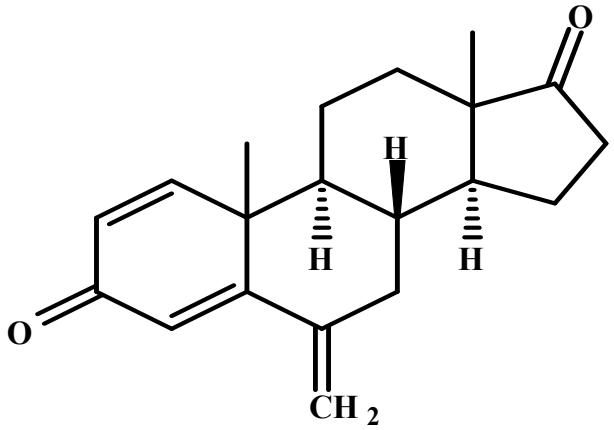


LETROZOLE (FEMARA)

- both of these drugs are used in the treatment of advanced
- breast cancer in post-menopausal women with disease
- progression following tamoxifen therapy

EXEMESTANE (AROMASIN)

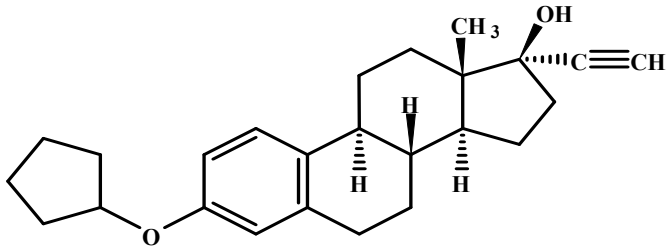
- 6-methylenandrosta-1,4-diene-3,17-dione
- structurally related to androstenedione
- acts as an irreversible (suicide) inhibitor of aromatase
- has no effect on other enzymes involved in steroidogenesis
- indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy



EMESTANE (AROMASIN)

QUINESTROL

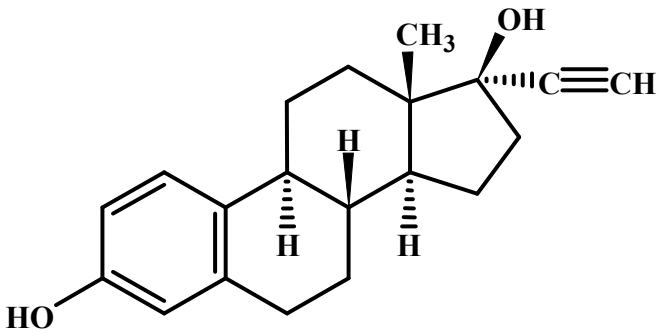
- is a prodrug of ethinylestradiol (EE), with no estrogenic activity of its own
- used in menopausal hormone therapy
- hormonal birth control
- to treat breast cancer and prostate cancer
- very long biological half-life of more than 120 hours (5 days)



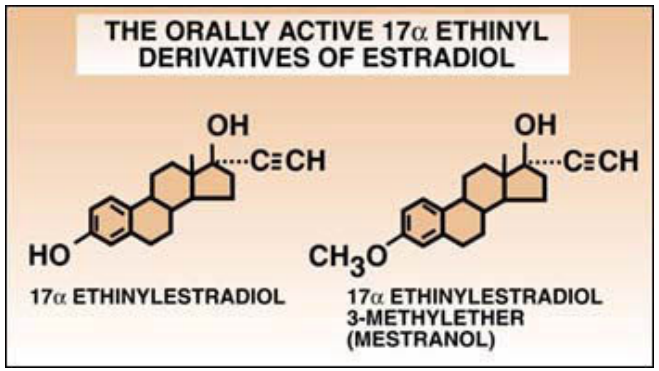
QUINESTROL

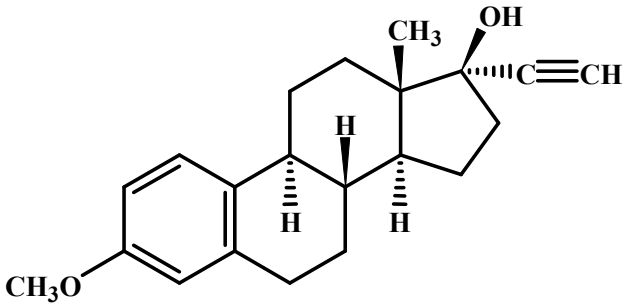
SEMI-SYNTHETIC ESTROGENS

- Very commonly utilized in oral contraceptive products
- ethinyl estradiol is more potent than mestranol



ETHINYL ESTRADIOL





MESTRANOL

PROGESTERONE AND PROGESTINS

- Drugs which mimic the action of progesterone
- complement the action of estrogen on primary and secondary sex characteristics
- many are used as oral contraceptives:
  - norgestrel, levonorgestrel, norethindrone, norethindrone acetate, norethynodrel, ethynodiol diacetate, desogestrel and norgestimate

EFFECTS OF PROGESTINS

Reproductive tract

- Decreases the frequency of the hypothalamic pulse generator.
- Endocervical glands: scant, viscid material, helps to block the penetration of sperms.
- Suppress menstruation and uterine contractility.
- Breakthrough bleeding can occur!

Mammary Gland

- With estrogen causes the proliferation of the acini of mammary gland.

CNS effects

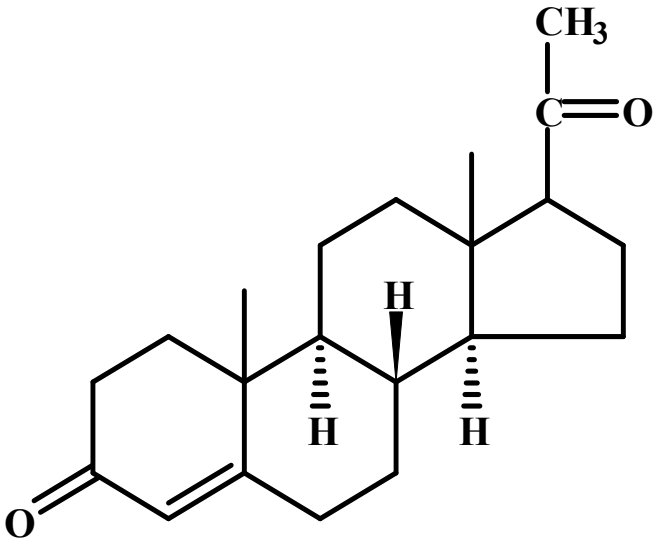
- At midcycle the body core temperature is elevated by 0.5 C°. → ovulation. Temperature increase is persists until the onset of menstruation.
- Depressant and hypnotic effect.

Metabolic effects

- Increase the basal insulin level. Long-term administration of potent progestins (norgestrel) **decrease glucose tolerance**.
- Increase LPL and fat deposition. Increase LDL level.
- **↓ HDL and ↑ LDL**
- **Hirsutism and acne (androgenic effect)**

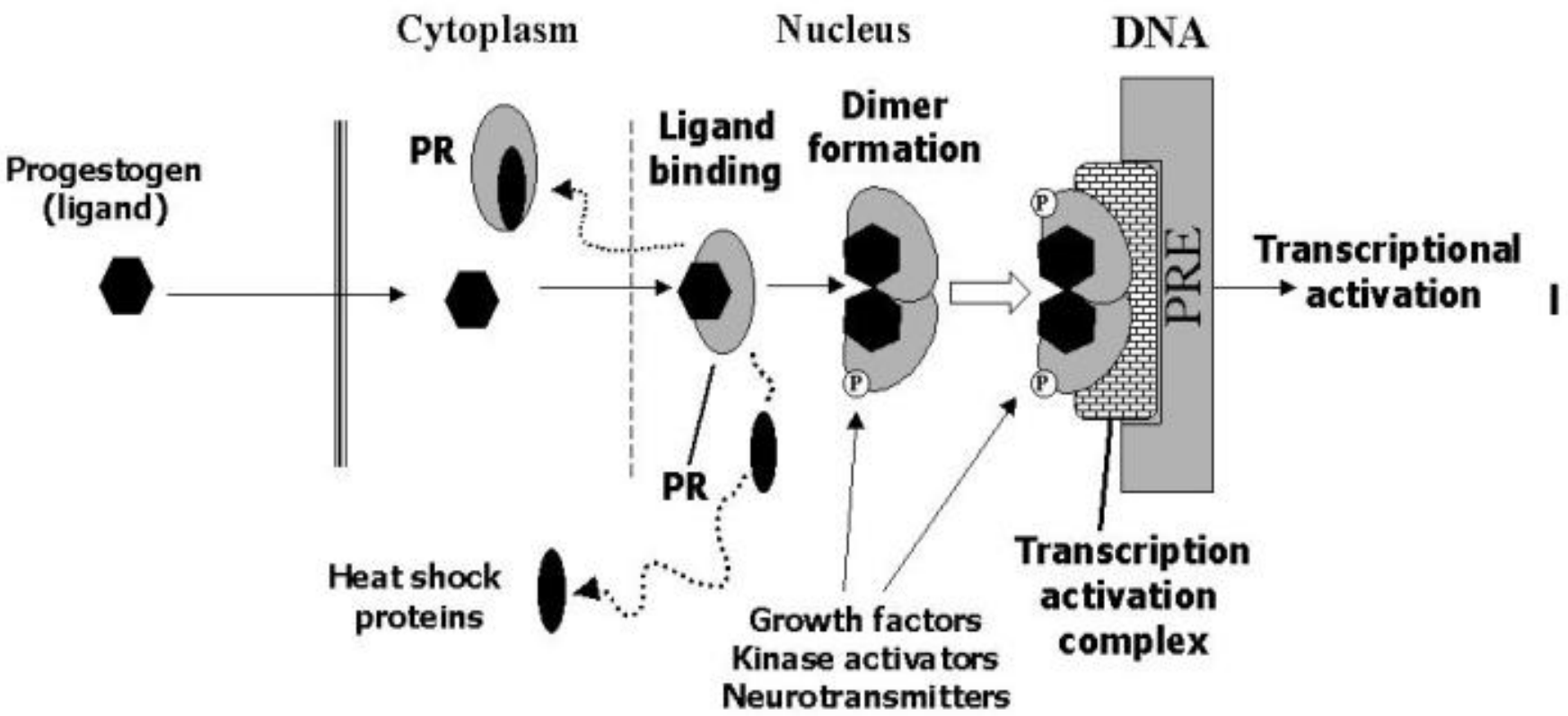
PROGESTERONE

- Natural hormone secreted
- by the corpus luteum and the
- placenta (a C-21 steroid).
- It is also an important intermediate in steroid biogenesis in all tissues that produce steroids (testes, adrenal cortex).
- Intestinal absorption is quite erratic; must be micronized for
- most effective absorption (Prometrium)



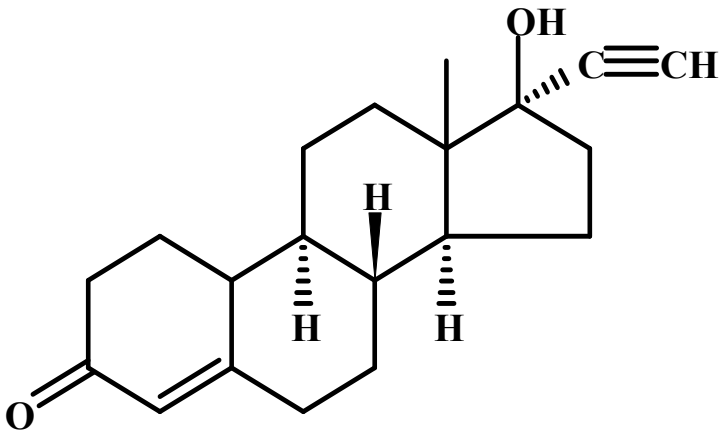
PROGESTERONE

Schematic representation of progesterone receptor binding and transactivation

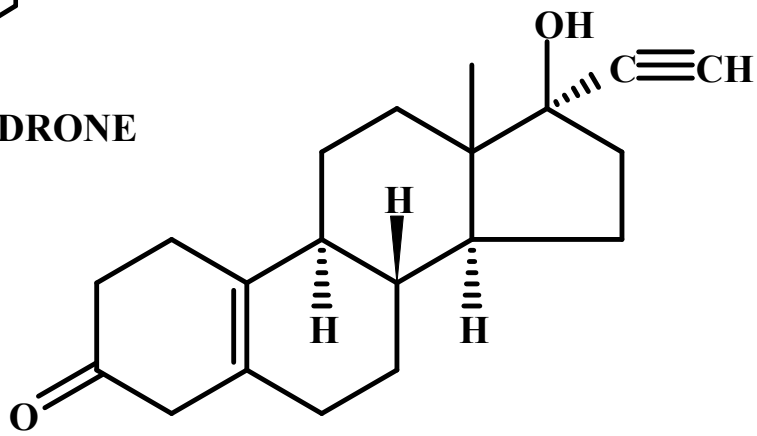


19-NOR STEROIDS

- Chemical analogues of testosterone - some retain some
- androgenic activity such as norethindrone

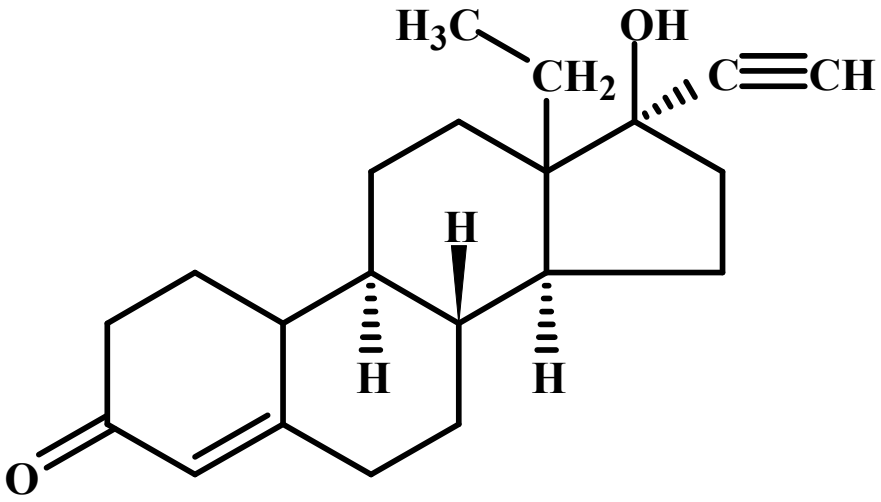


NORETHINDRONE

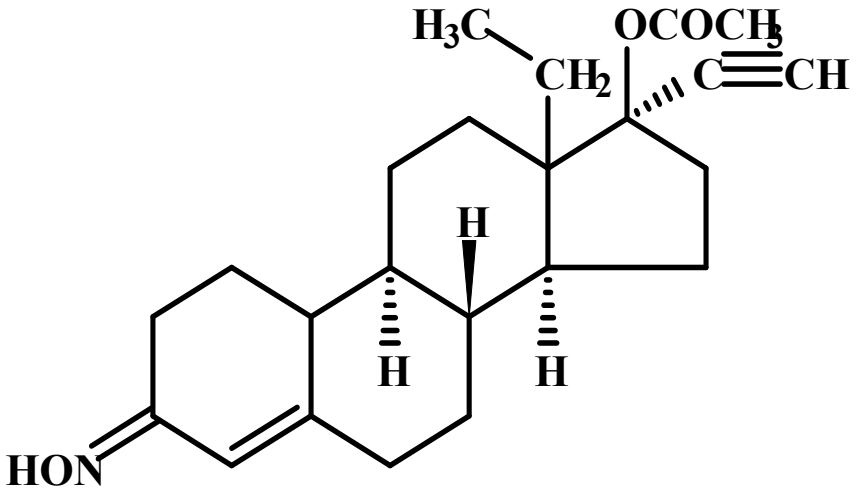


NORETHINODREL

19-NOR STEROIDS

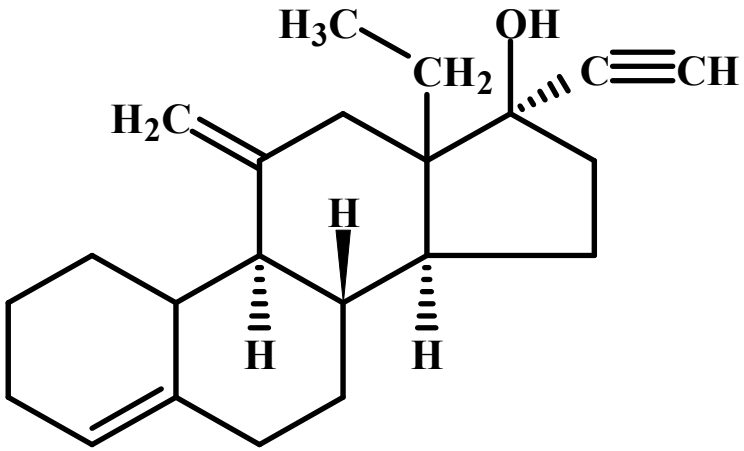


NORGESTREL

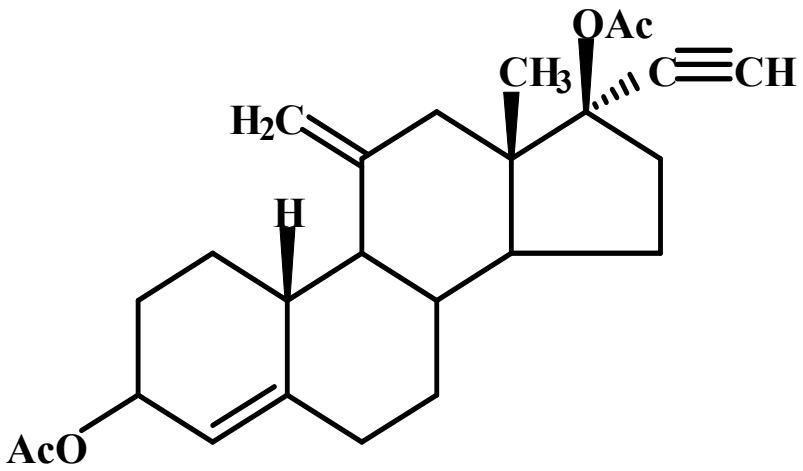


NORGESTIMATE

19-NOR STEROIDS



DESOGESTREL

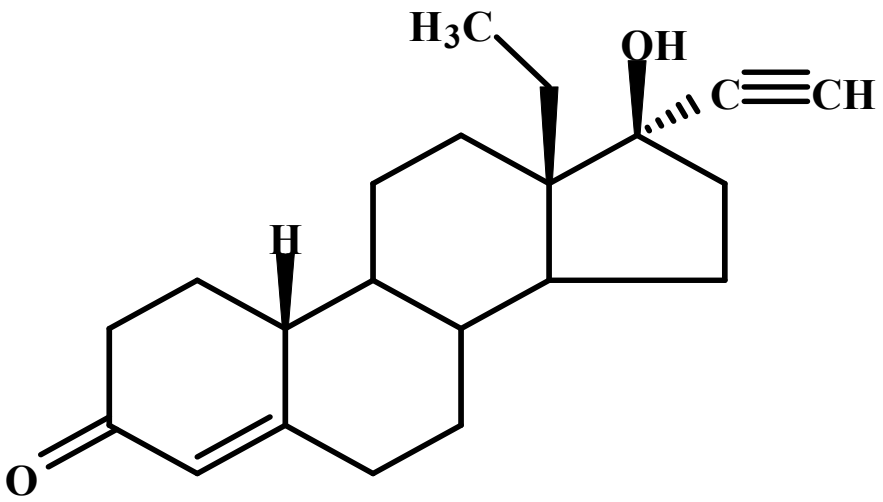


ETHYNODIOL DIACETATE

- Devoid of androgenic and anti-estrogenic activites!!!

19-NOR STEROIDS

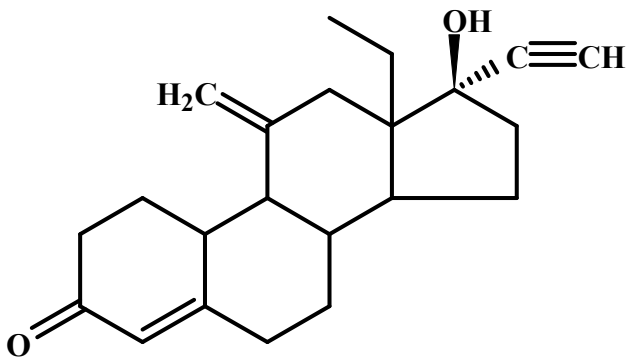
- Both the racemic and the optically pure (levonorgestrel) are used in oral contraceptive products



NORGESTREL

ETONORGESTREL

- Vaginal rings
- provide controlled release of drugs for intravaginal administration over extended periods of time.
- self-administered once a month
- leaving the ring in for three weeks
- slowly releases hormones into the body

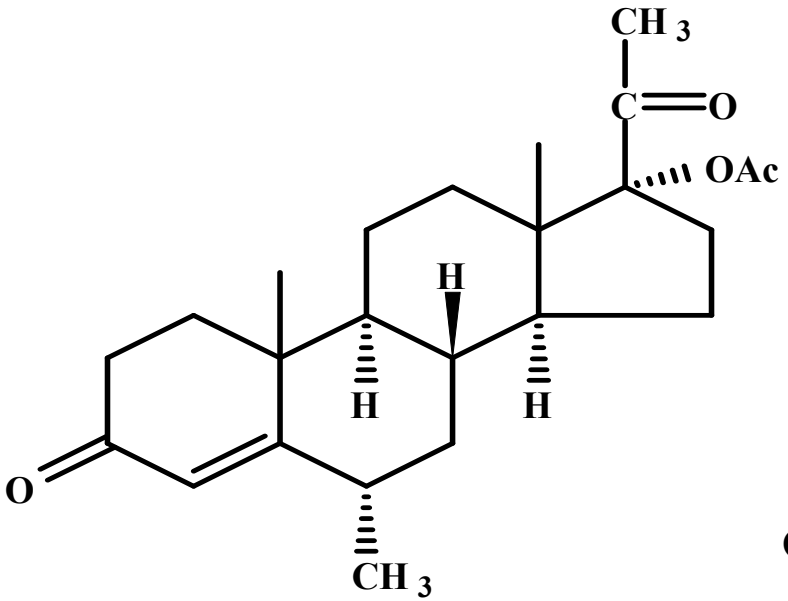


ETONORGESTREL (NUVARING)

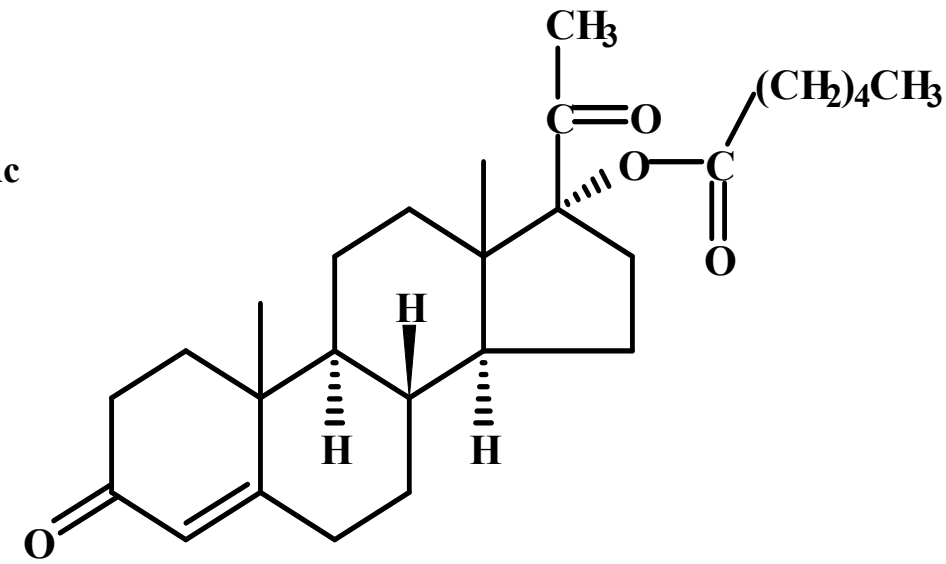
19-NOR STEROIDS

- Some 19-nor steroids can be metabolized to estrogenic compounds
- these progestins then exhibit estrogenic activity
  - norethynodrel and ethynodiol diacetate have estrogenic activity

17-HYDROXY ESTERIFIED PROGESTINS



MEDROXYPROGESTERONE ACETATE

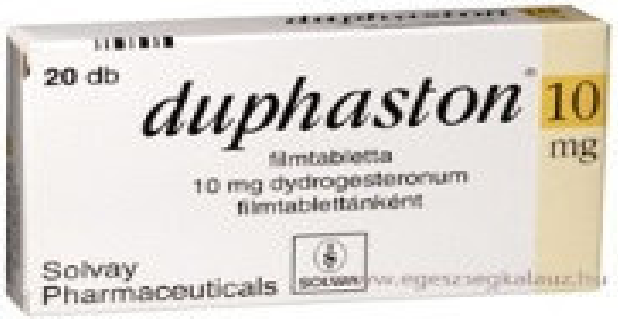


HYDROXYPROGESTERONE CAPROATE

- Medroxyprogesterone acetate is a very popular orally effective progestin (Provera)

PROGESTINS AVAILABLE IN HUNGARY

- Medroxyprogesterone (PROVERA)
- Progesterone (CRINONE, UTROGESTAN)
- Dydrogesterone (DUPHASTON)
- Norethisterone (NORCULUT)



COMBINED ESTROGENS AND PROGESTINS

- Currently very popular forms for HRT
- combine an estrogen (natural or semi-synthetic) with an orally effective progestin
  - Prempro and Premphase
  - FemHRT
  - Combipatch

GONADOTROPINS FOR OVULATION STIMULATION (DRUGS IN HUNGARY)

- Chorionic gonadotrophin (CHORAGON, PREGNYL)
- Human menopausal gonadotrophin (MENOPUR, MERIONAL)
- Urofollitropin (FOSTIMON)
- Follitropin alpha (GONAL)
- Follitropin beta (PUREGON)
- Lutropin (LUVERIS)
- Choriogonadotripin alpha (OVITRELLE)
- Corifollitropin alpha (ELONVA)

PROGESTIN ANTAGONIST

- **Mifepristone**
  - Glucocorticoid receptor antagonist as well
  - Abortifacient (used with PGs)