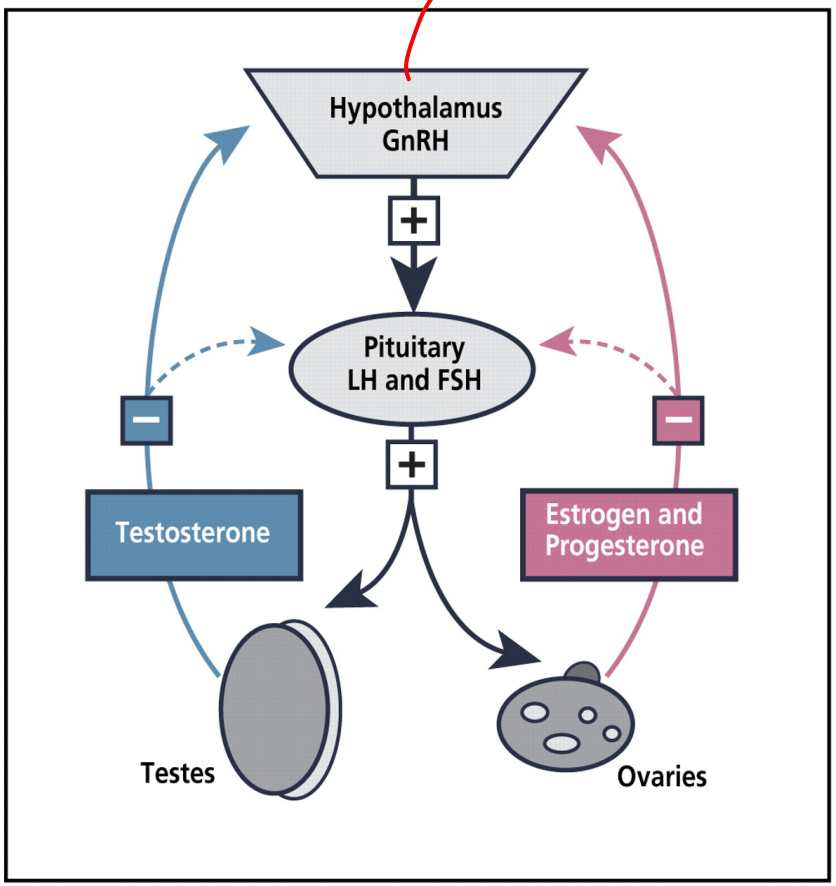
Sex Hormones

hypothalamus releases

gonadotropin releasing hormone (aka luteinizing hormone releasing hormone LnRH)



GnRH goes to pituitary

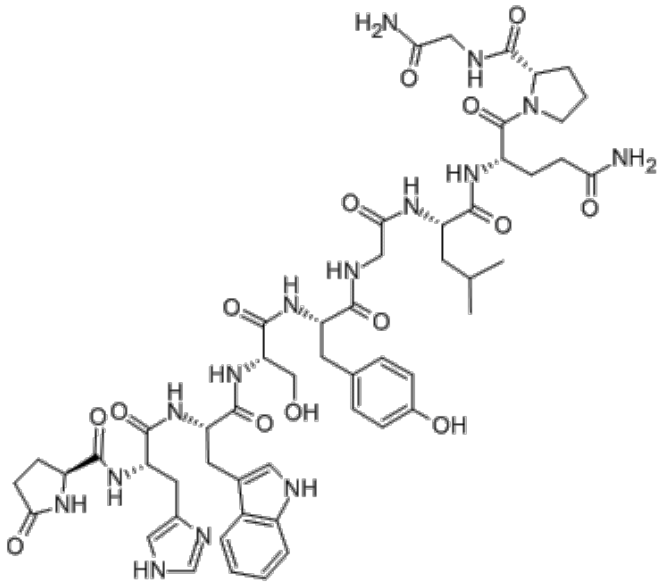
releases

gonadotropins

FSH — follicle stimulating hormone

LH — leutinizing hormone

gonatotropins cause release of steroid sex hormones from ovaries + testes



GnRH

LHRH

decapeptide

PYR-HIS-TRP-SER-TYR-GLY-LEU-GLN-PRO-GLY-NH2

↑ pyroglutamate

Leuprolide = analogue of ⇑

Gonadotropins

found in both males + females

Follicle Stimulating Hormone

promotes formation of follicle on ovary that releases an egg

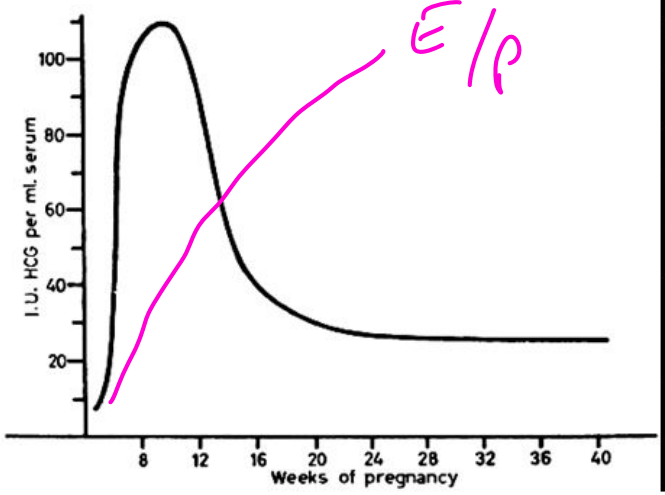
Luteininzing hormone

acts on matere follicle to cause ovulation

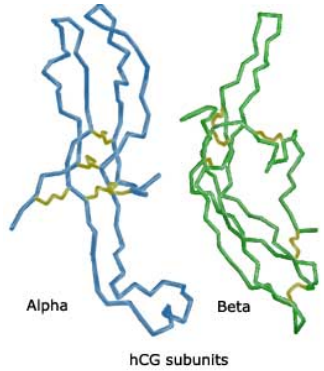
hCG human chorionic gonadotropin

produced by placenta to maintain pregnancy

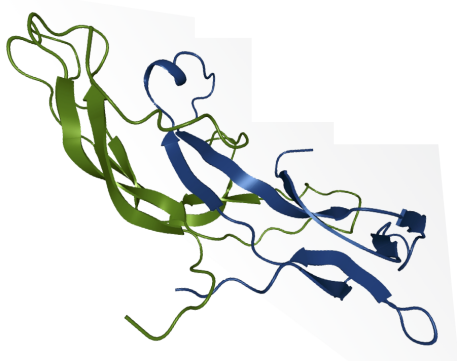
basis for pregnancy test



from conception	from LMP	(mIU/ML or IU/L)
7 days	3 weeks	0 to 5
14 days	28 days	3 to 426
21 days	35 days	18 to 7,340
28 days	42 days	1080 to 56,500
35 - 42 days	49 - 56 days	7,650 to 229,000
43 - 64 days	57 - 78 days	25,700 to 288,000
57 - 78 days	79 - 100 days	13,300 to 253,000
17 - 24 weeks	2nd trimester	4060 to 65,400
25 wks to term	3rd trimester	3640 to 117,000



hCG subunits



2 main classes of hormones released by ovaries

Estrogens

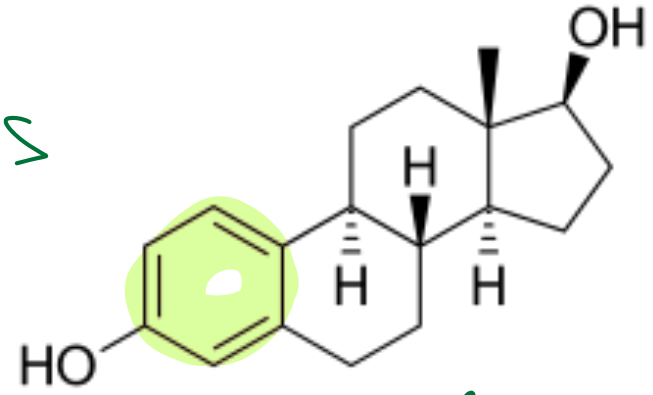
2° sexual characteristics

induce estrus

reduce bone resorption

to prevent osteoporosis

increase bone formation

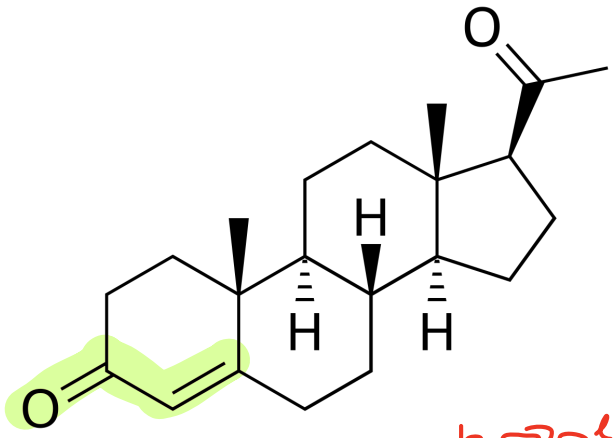


17 β estradiol

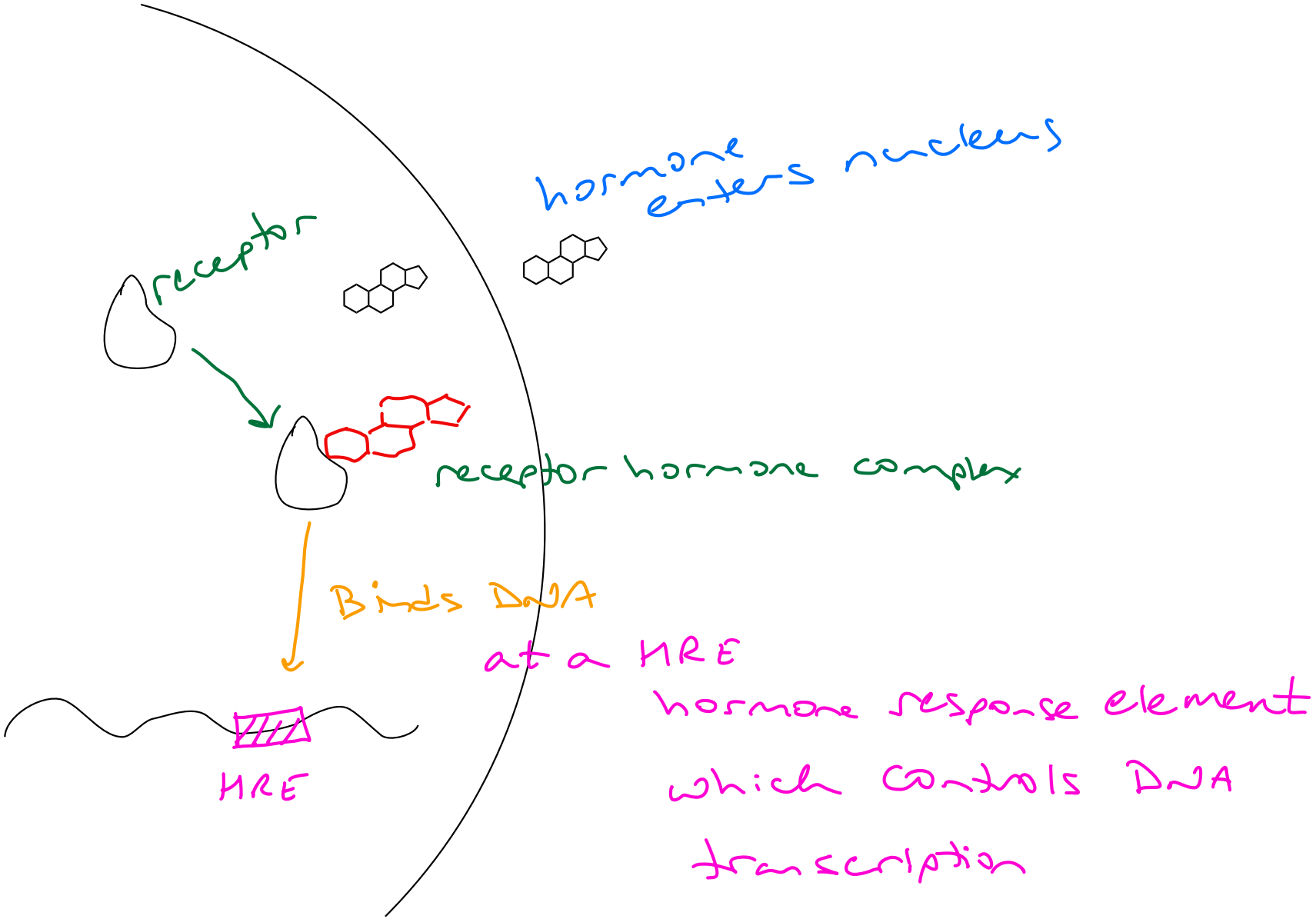
Progestins

maintain pregnancy

prevent ovulation



progesterone

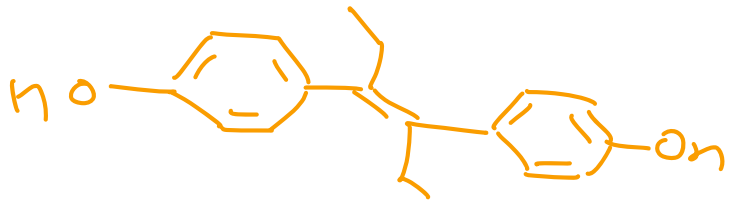

hormone enters nucleus
receptor
receptor hormone complex
Binds DNA at a HRE
HRE
hormone response element which controls DNA transcription

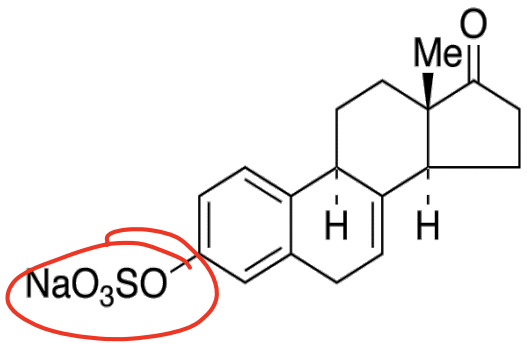
Three Structural Classes of Estrogens

Equine → estradiol metabolites obtained from pregnant mares

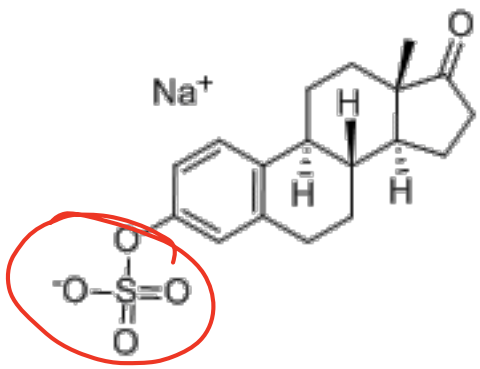
Human → estradiol

Diethylstilbestrol derivatives





Equilin sodium sulfate



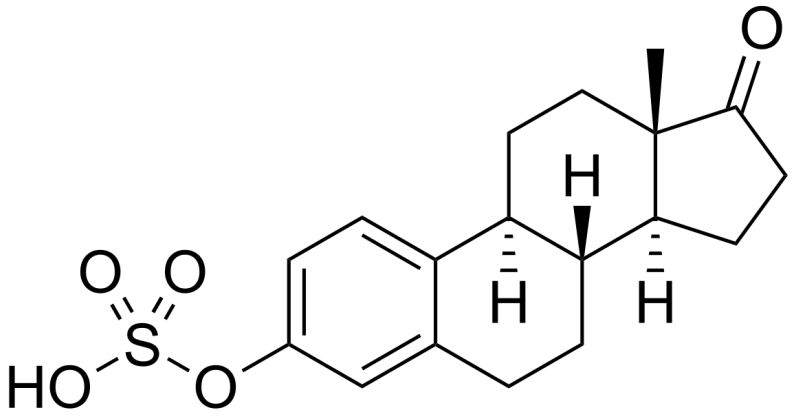
Estrone sodium sulfate

Both metabolites of estradiol

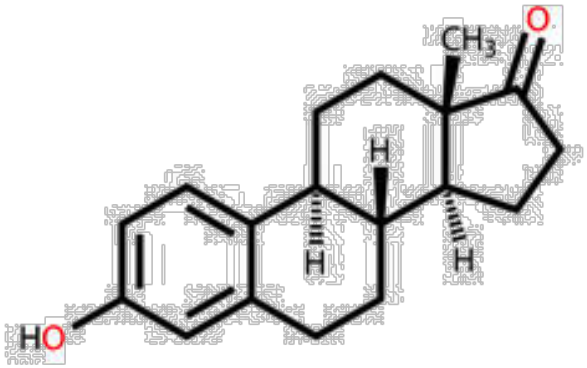
Premarin

- water soluble
- not found in humans
- now made semi-synthetically

Hormone Replacement Therapies : conjugated estrogens

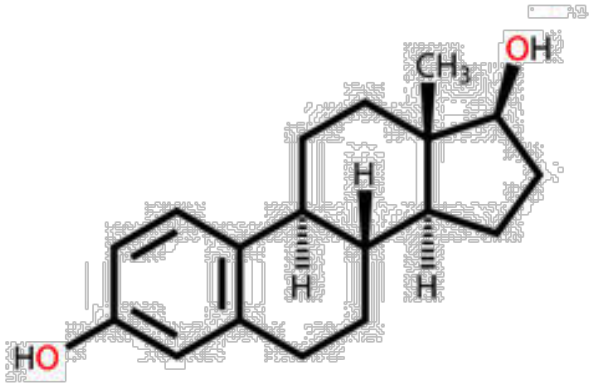


Human Estrogens



Estrone

$\frac{1}{3}$ activity



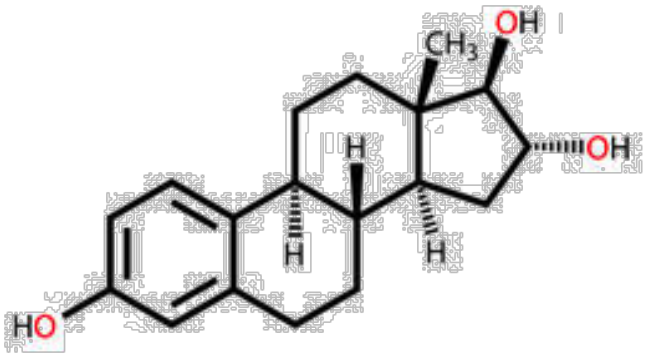
Estradiol

most active

↑

low oral activity

- broken down by bacteria in GI
- quickly metabolized by liver



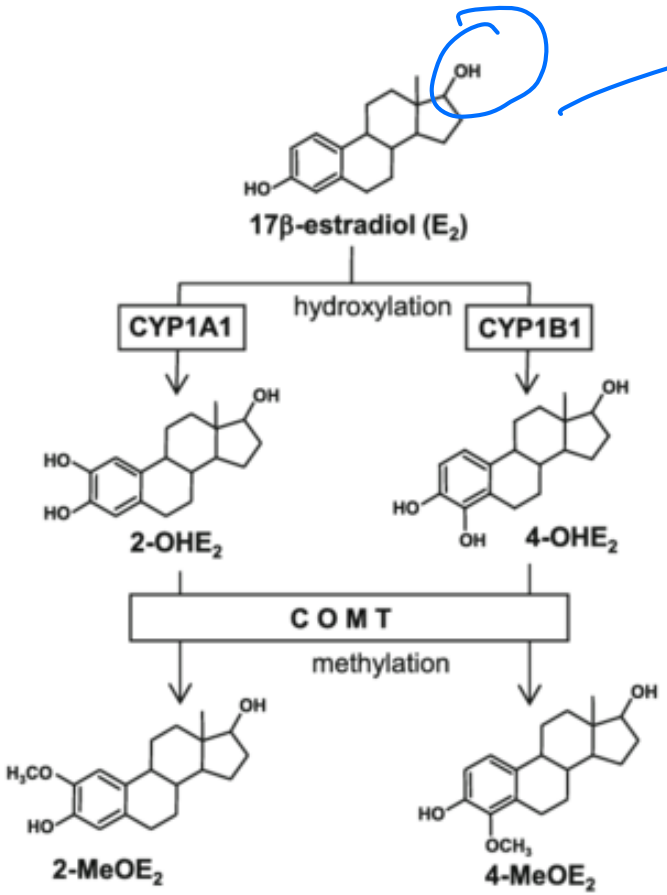
Estriol

$\frac{1}{60}$ activity

an impeded estrogen

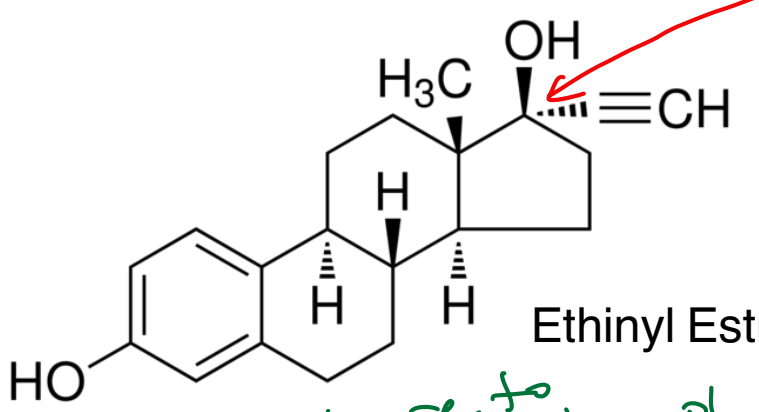
interacts with receptor but to briefly to get response

Estrogen Metabolism



also gets oxidized to estrone

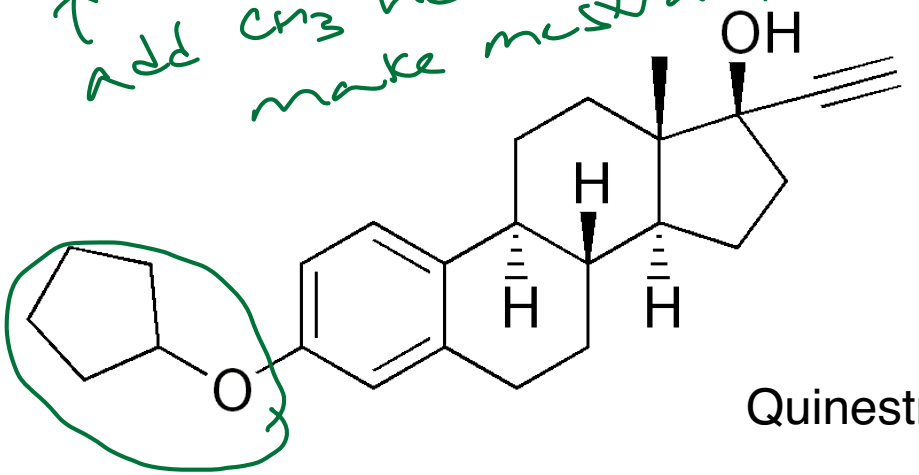
C-OH → C=O



Ethinyl Estradiol

3° ROH, can't be oxidized
stable for oral use

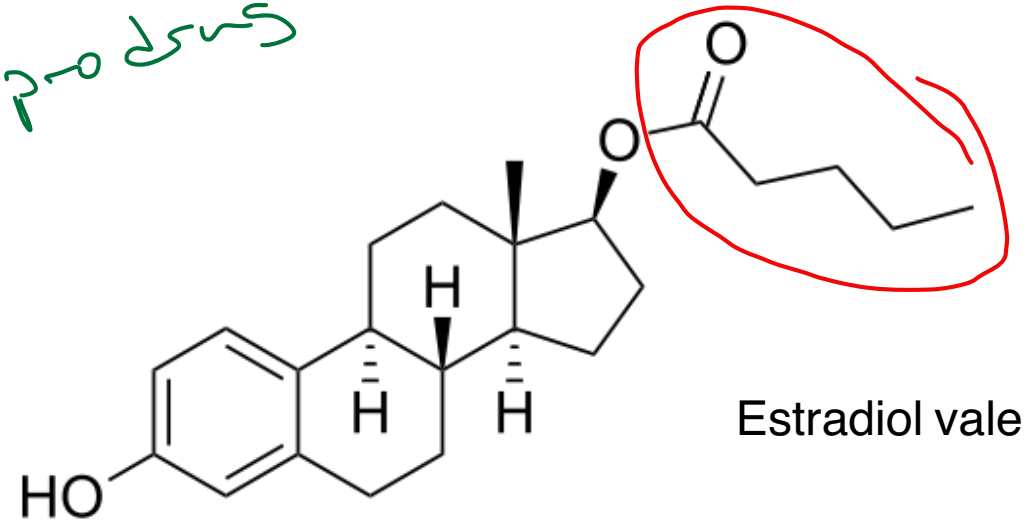
add CH_3 here to make mestranol



Quinestrol

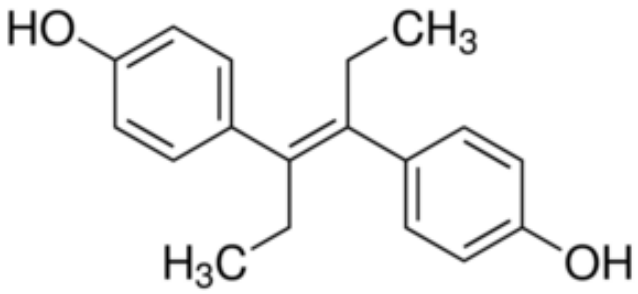
take 1x per week after a loading dose

pro-drugs

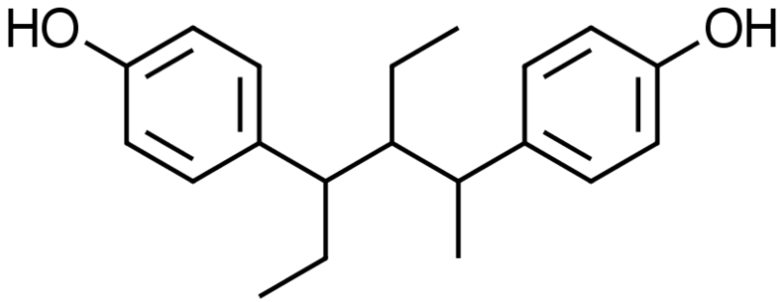


Estradiol valerate

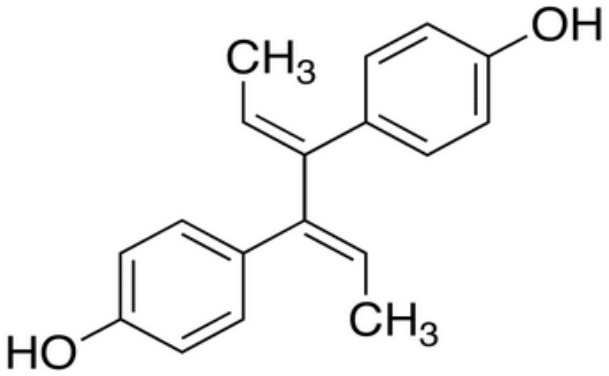
another pro-drug
can be given by IM
slow hydrolysis releases estradiol



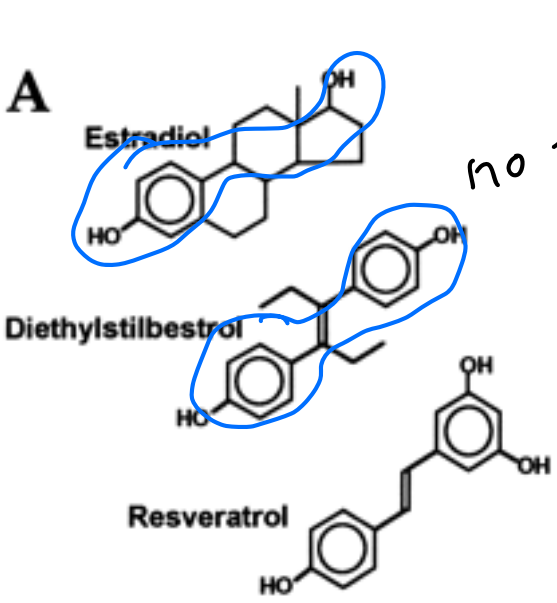
Diethyl stilbestrol

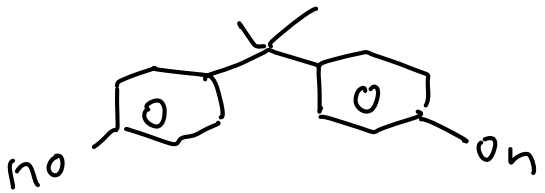


Benzestrol



Dienestrol

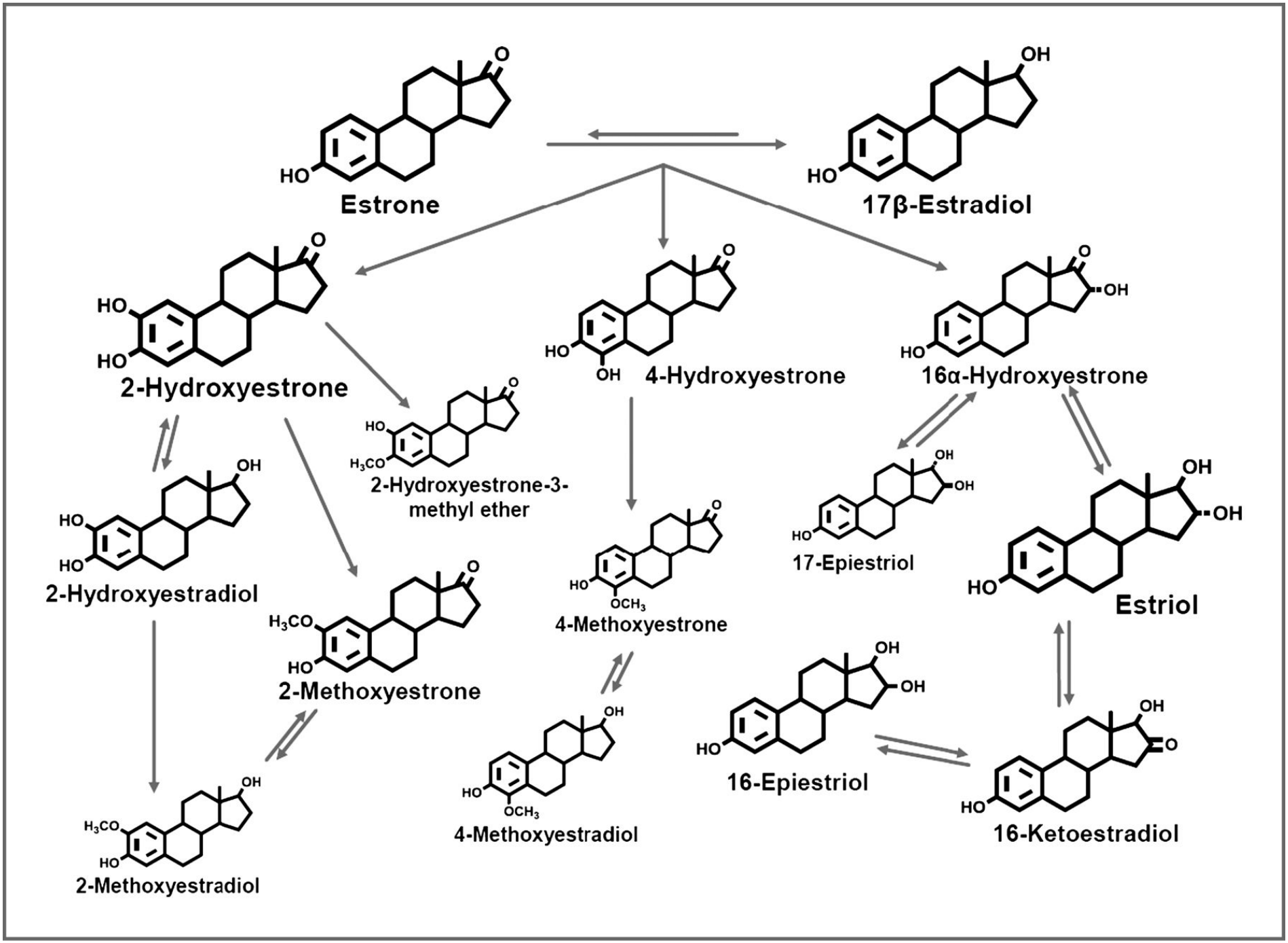


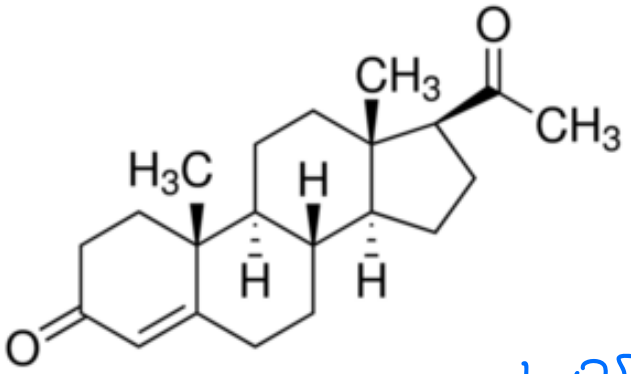


BPA

endocrine

disruptor

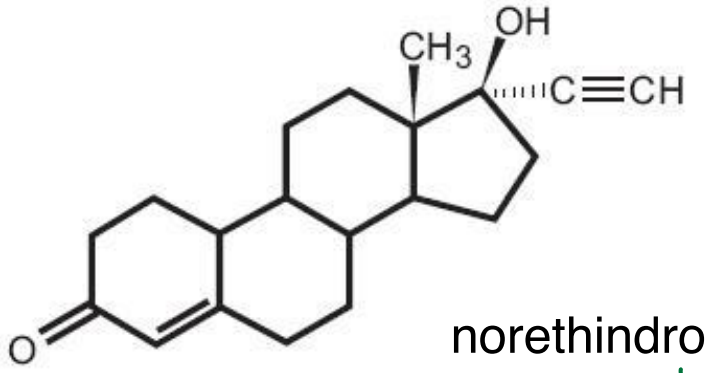

Estrone
17β-Estradiol
2-Hydroxyestrone
4-Hydroxyestrone
16α-Hydroxyestrone
2-Hydroxyestrone-3-methyl ether
2-Hydroxyestradiol
17-Epiestriol
Estriol
2-Methoxyestrone
4-Methoxyestrone
16-Epiestriol
16-Ketoestradiol
4-Methoxyestradiol
2-Methoxyestradiol



Progesterone

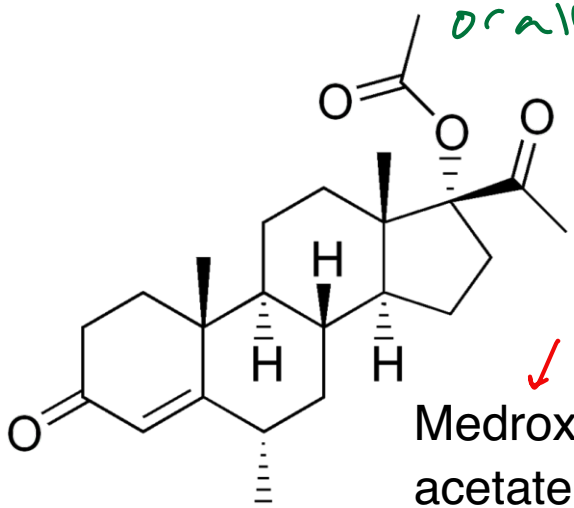
not orally active

metabolized by reduction + conjugation



norethindrone

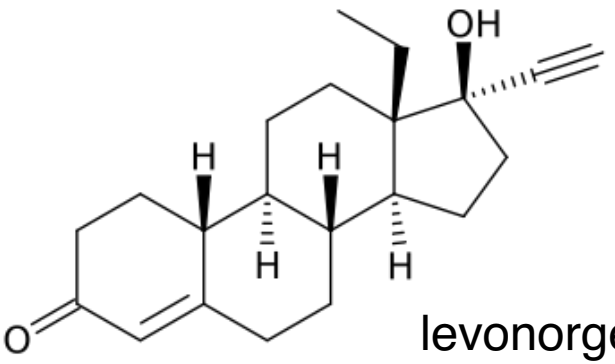
mini pills orally active



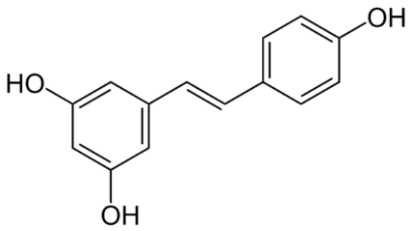
mini pill

Medroxyprogesterone acetate

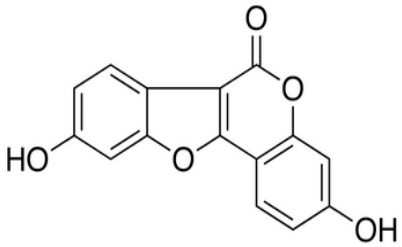
norplant + IUD's



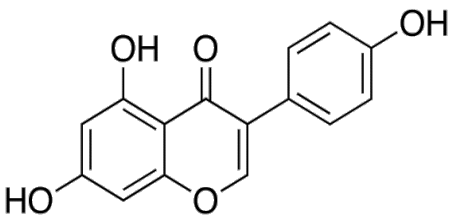
levonorgestrol



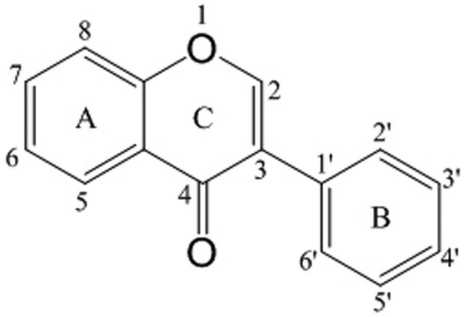
Resveratrol



Coumestrol



Genistein



Isoflavone backbone

	5	6	7	4'
Daidzein (**1**)	H	H	OH	OH
Daidzin (**2**)	H	H	O-Glc	OH
Genistein (**3**)	OH	H	OH	OH
Genistin (**4**)	OH	H	O-Glc	OH
Glycitein (**5**)	H	CH_3O	OH	OH
Glycitin (**6**)	H	CH_3O	O-Glc	OH

Structure of soy isoflavones. Daidzein (1), daidzin (2), genistein (3), genistin (4), glycitein (5), and glycitin (6). Glc: glucosyl.

Oral Contraceptives

1. Sequential

estrogen followed by progestin

first was Enovid in 1961

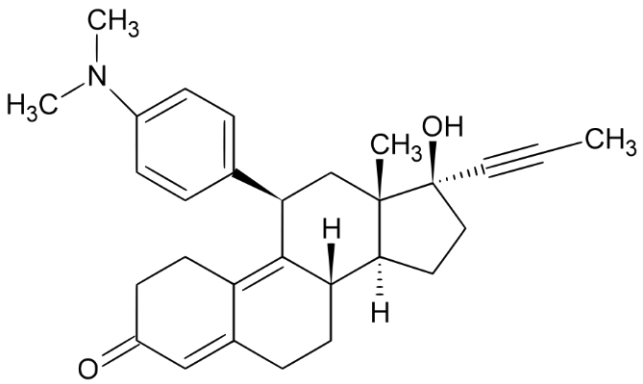
2. Combination

E+P mixed together 21 days

7 days nothing

3. Minipills

Continuous small dose of progestin



Mifepristone

Progesterone Antagonist

RU-486

Can be used to terminate pregancy

also for progesterone sensitive cancers + Cushing's Disease

Estrogen Antagonists estrogen dependent cancers

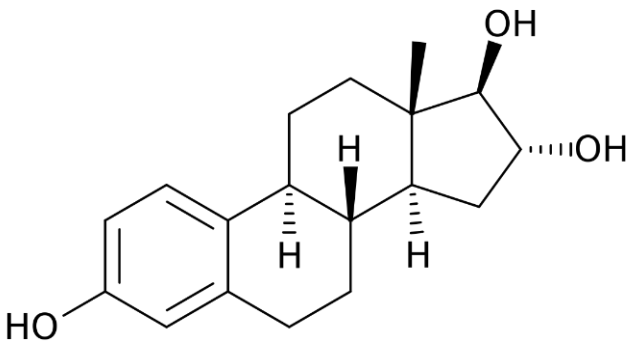
1. Impeded estrogens competitive antagonist

2. Triphenylethylenes

3. Aromatase Inhibitors

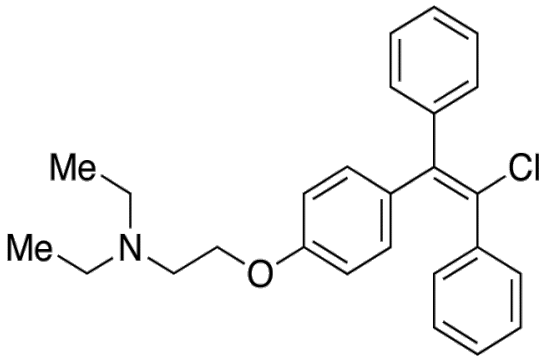
↑ makes the aromatic ring

Impeded Estrogens



Estriol

Triphenylethylenes



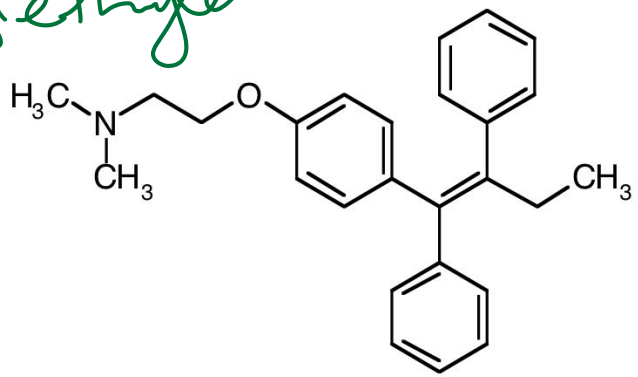
• HCl

Clomiphene

Clomid

used to induce ovulation

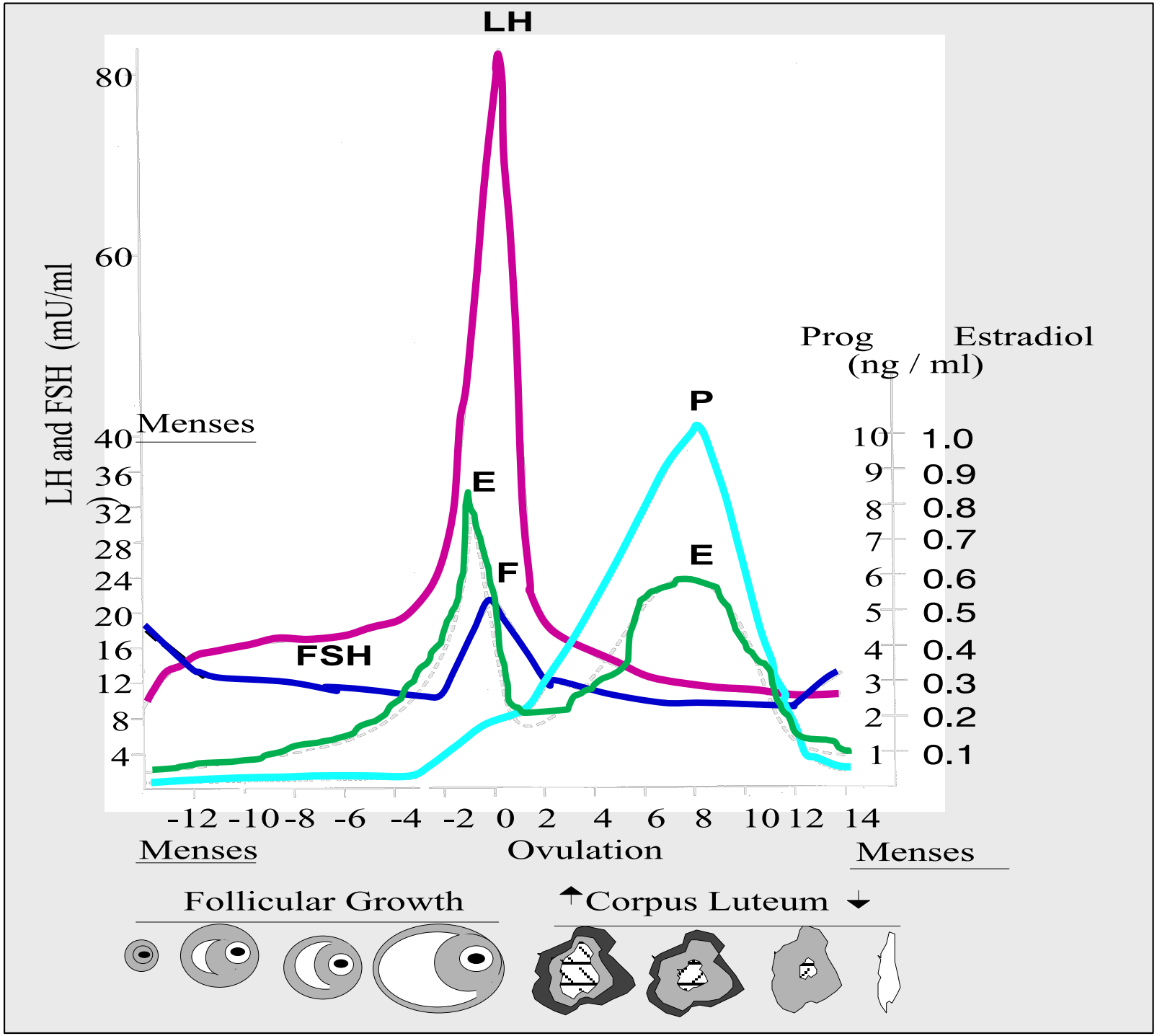
~10% of cases lead to multpl births

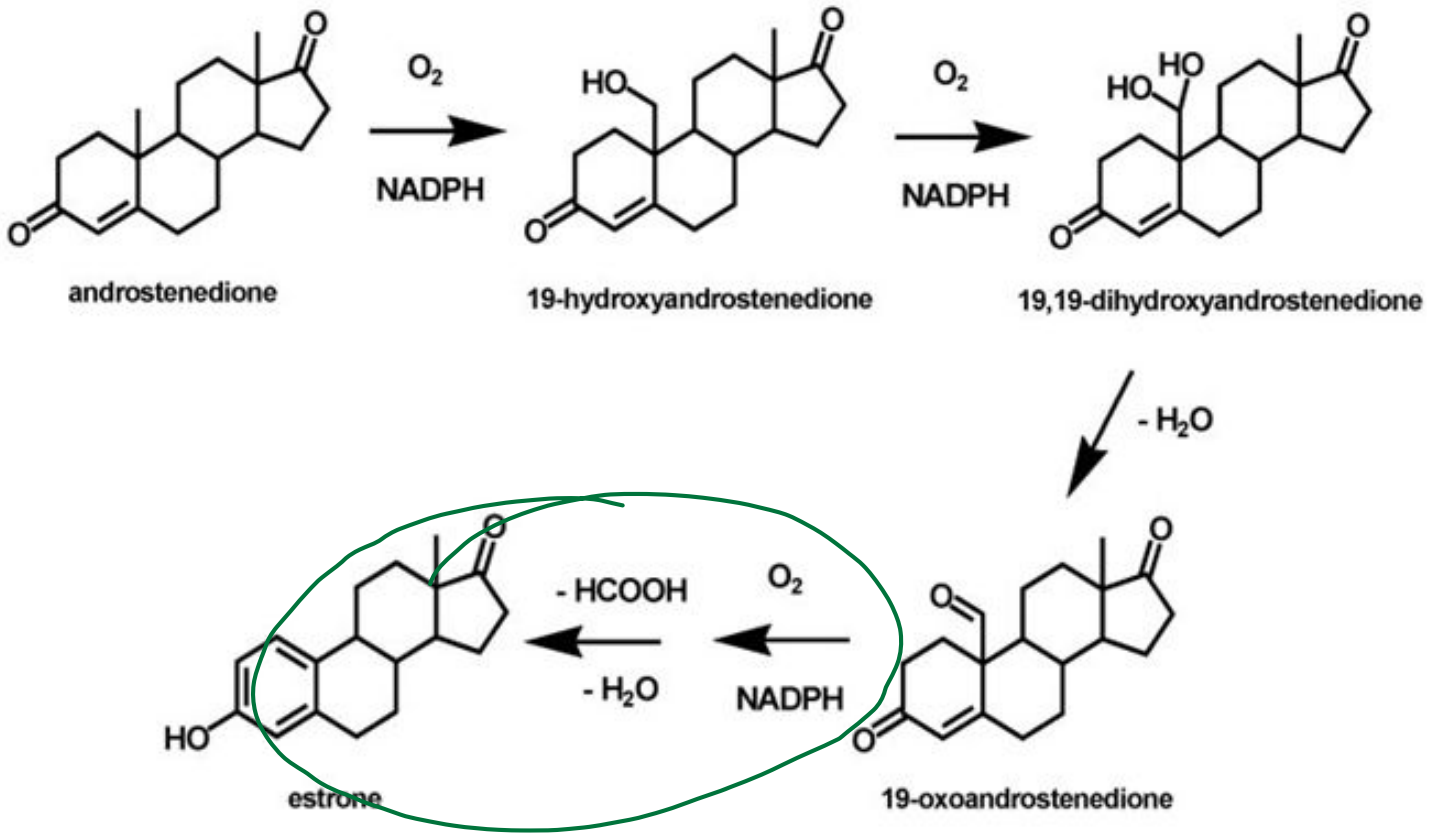


Tamoxifen

breast cancer

Regulation : Circulating Levels





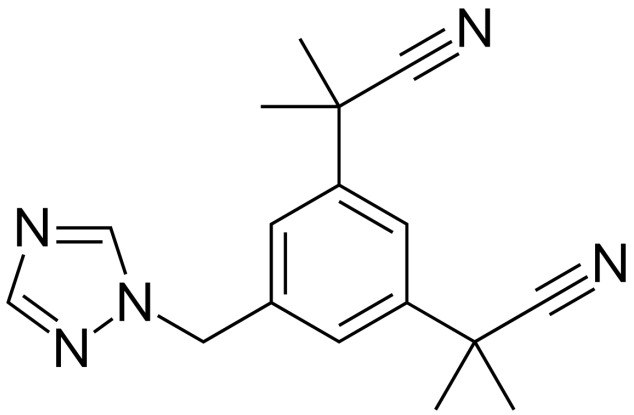
aromatase makes aromatic ring

inhibitors used for estrogen

dependent cancers

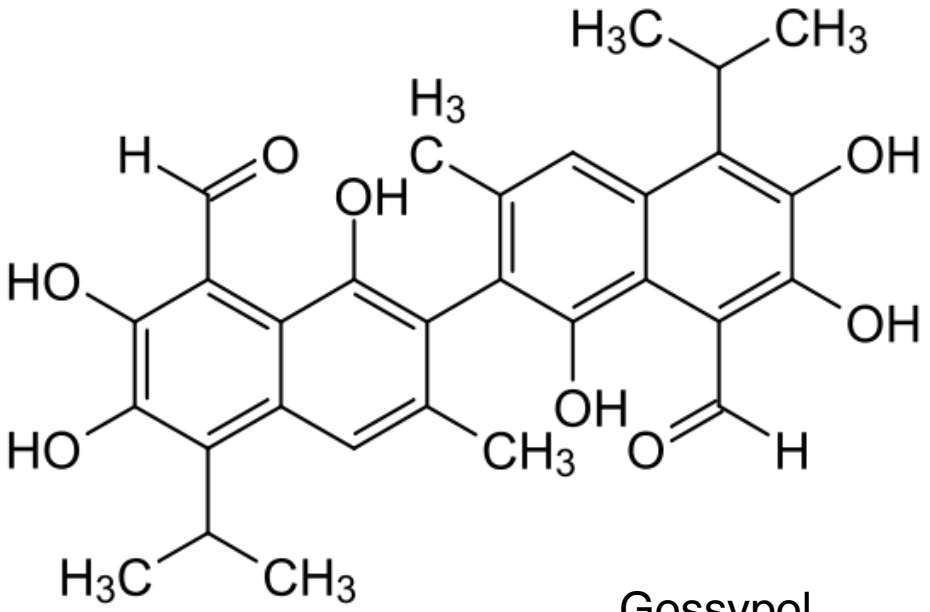
Cyp450 enzymes

Aromatase Inhibitors



Arimidex

Anastrazole



Gossypol

- investigated as male contraceptive
- isolated from Cottonseed oil (also found in okra)

Stops spermatogenesis

Cycle is 74 days

Irreversible in 20% of men

Can cause hypokalemia irreversible in 20%

Androgens

Hypothalamus releases GnRH

FSH: promotes sperm development

ICSH: aka LH stimulates secretion of androgens

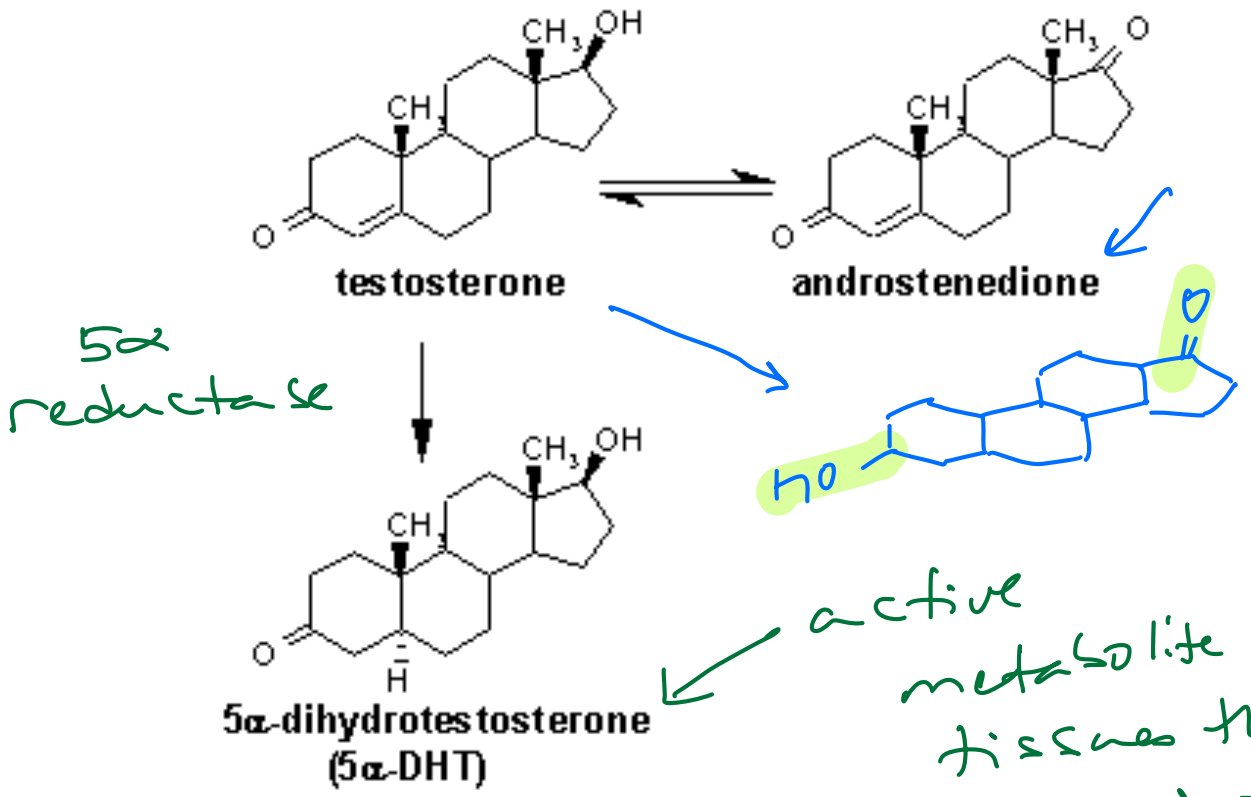
Interstitial cell stimulating hormone

Androsterone was first isolated

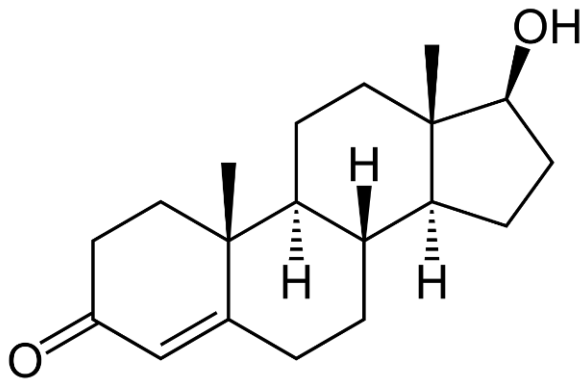
1931 15mg 15,000L male urine

1935 testosterone 270mg

1 ton of bull testes



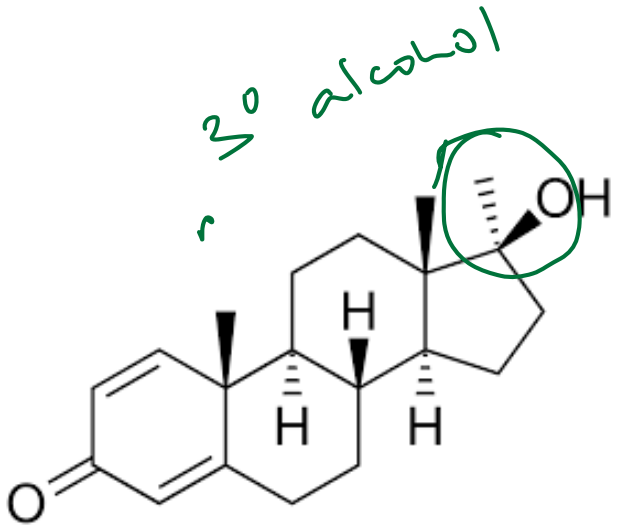
active metabolite in tissues that maintains prostate function



not orally active
has to be given by injection

androgenic - promotes 2° sexual characteristics

anabolic - muscle building



methandrostelone

Several times as anabolic

not very androgenic

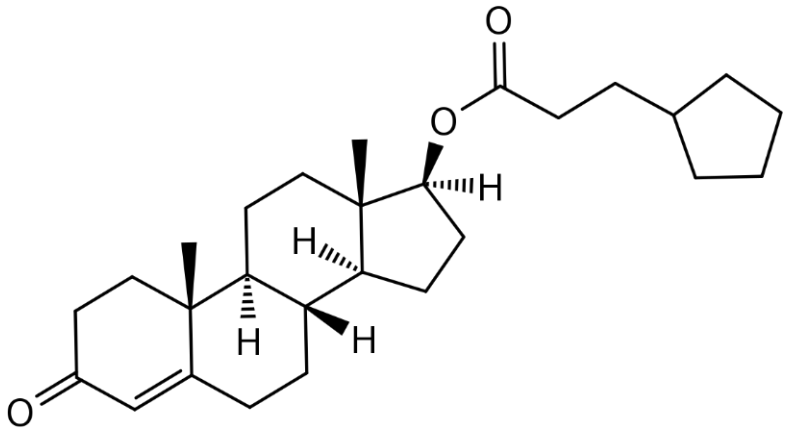
Can have mammogenic effects

used as androgen replacement

Nabolin

Dianabol

Aromatase probably converts to estrogen like stuff



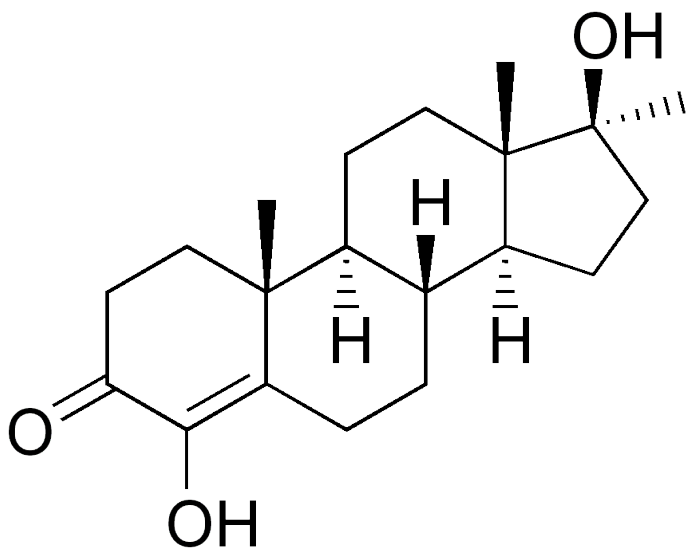
testosterone
cyclo pentyl
propionate

Depo- testosterone

Im 1x every 4 weeks

Androgen Replacement Therapy

- male climacteric
- testosterone deficiency
- anemics
- prevent wasting during immobilization
- serious injuries like burns



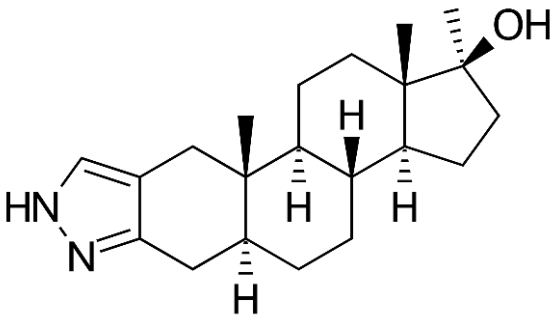
oxymesterone

3x anabolic

1/2 as androgenic

as testosterone

Androgens and Sports



Stanozolol

2mg 3x/day

5:1 anabolic:androgenic

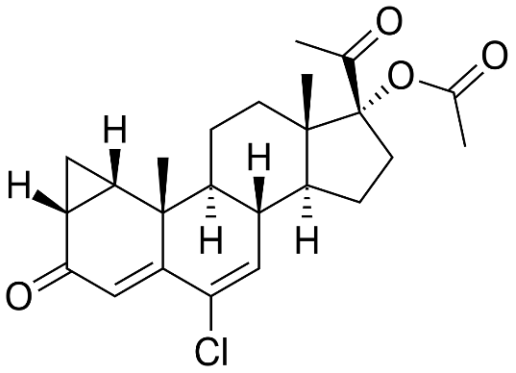
Androgen Antagonists

used for androgen dependent cancers

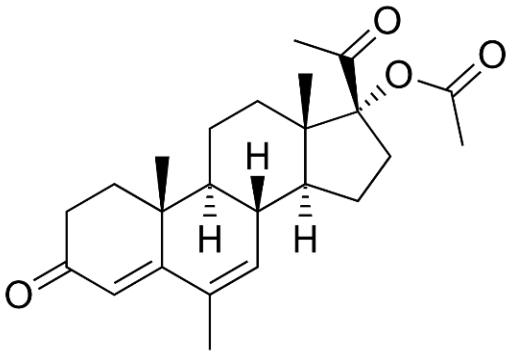
acute acne

premature baldness

Steroidal Antiandrogens



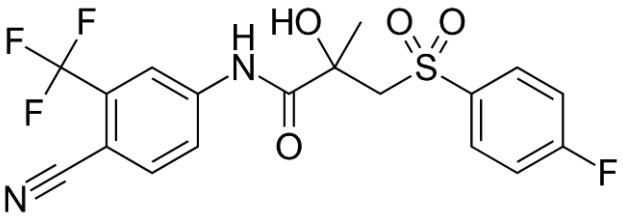
Cyproterone acetate



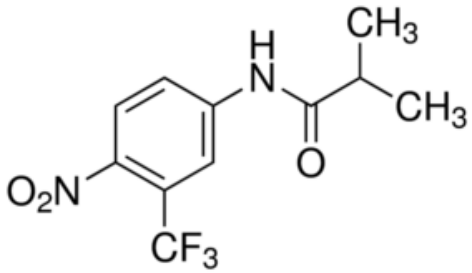
megestrol acetate

Nonsteroidal Antiandrogens

used for advanced prostate cancer



Casodex

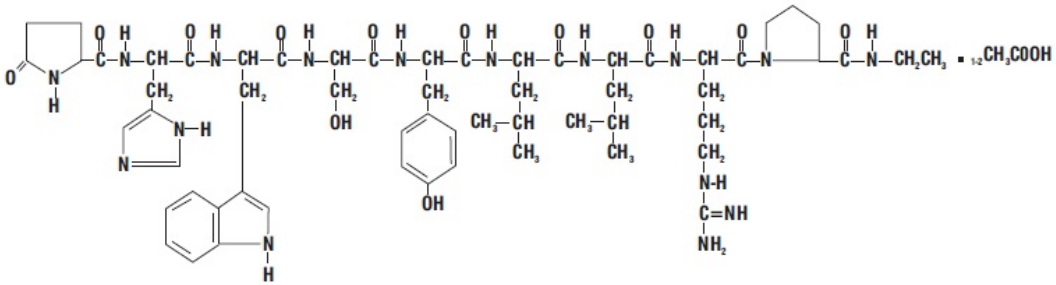


flutamide

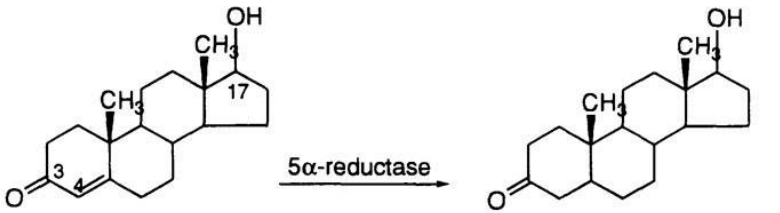
Inhibit Gonadotropin Secretion

Lupron

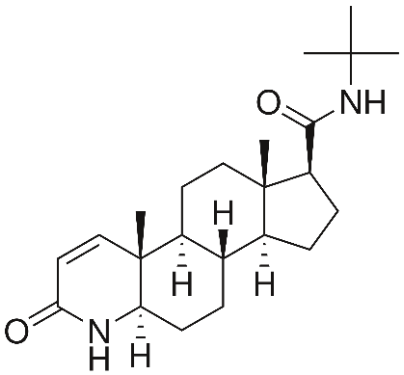
leuprolide acetate



Androgen Biosynthesis Inhibition



testosterone dihydrotestosterone

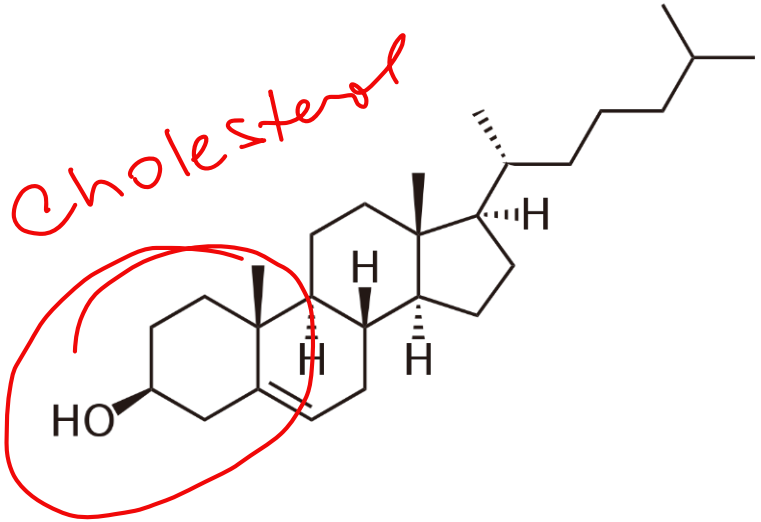


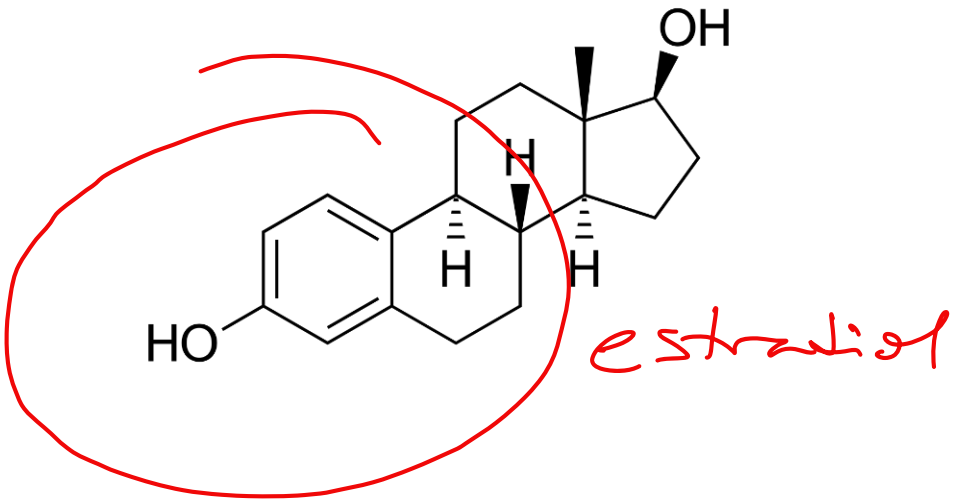
Propecia

used for androgenic alopecia

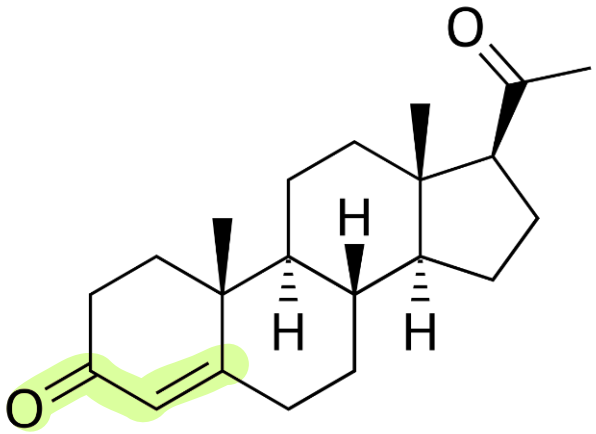
Inhibits DHT Synthesis

Cholesterol

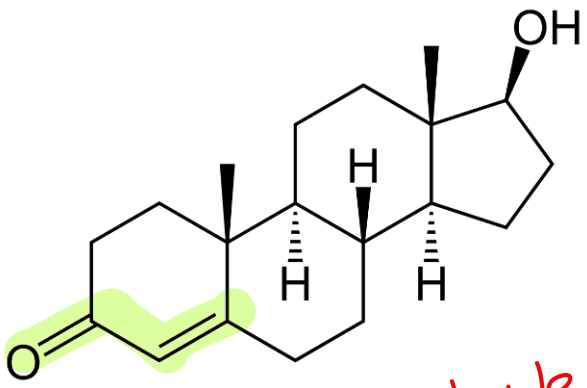




estradiol

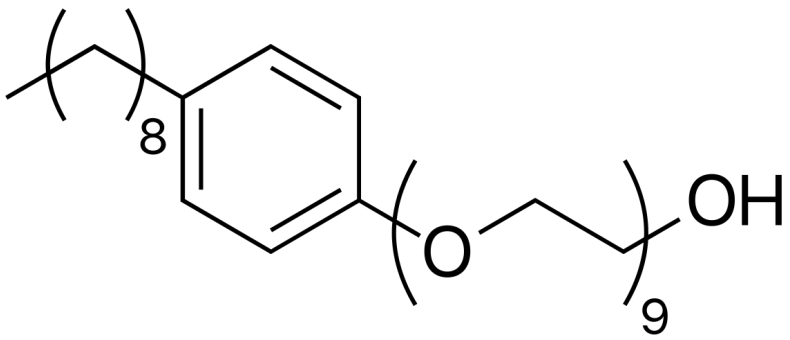


progesterone

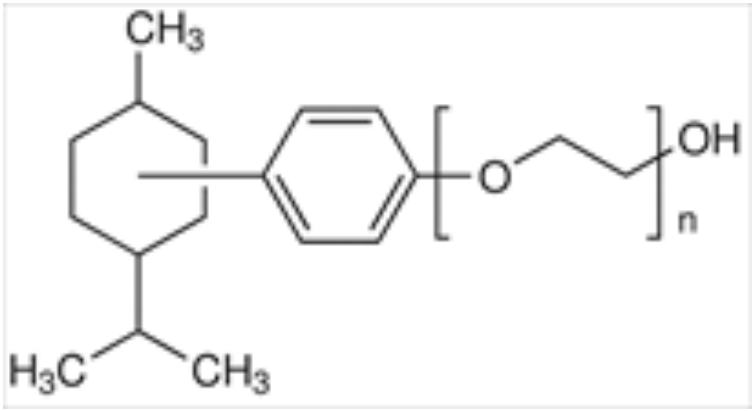


testosterone

Spemicides

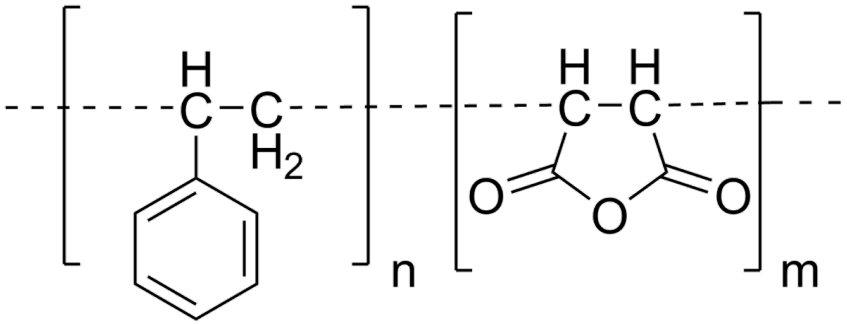


nonoxynol-9



menfegol

Vasalgel



Polymer injected into vas deferens to block sperm

RISING

Can reverse by injecting bicarbonate solution

oxandrolone

tri-abol

anadrol