Sex hormones

Sex hormones

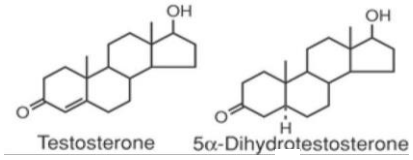
- The sex steroid hormones are steroid molecules that are necessary
  - for reproduction in females and males and that
  - affect the development of secondary sex characteristics in both sexes.
- The sex steroids are comprised of two classes:
  - Male sex hormones
    - androgens – testosterone and its metabolite DHT
  - Female sex hormones
    - estrogens - estradiol
    - progestins - progesterone
- All three classes of endogenous steroids are present in both males and females.
- The production and circulating plasma levels of estrogens and progestins are higher in females, however, and the production and circulating plasma levels of androgens are higher in males.

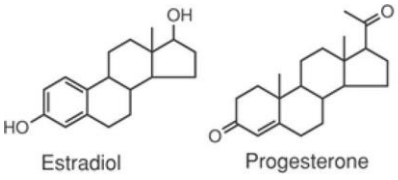
Sex hormones

The naturally occurring **androgens** are
- C-19 steroids
- **Androstane derivatives**
- oxygen atoms (as either hydroxyl or ketone groups) at both the C-3 and C-17 positions.

The naturally occurring **estrogens** are
- C-18 steroids
- **Estrane derivatives**
- a planar unsaturated A ring with a 3-phenolic group

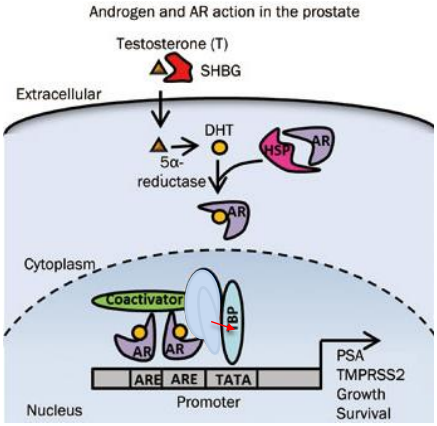
The naturally occurring **progestins** are
- C21 steroids
- **Pregnane derivatives**
- a 3-keto-4-ene structure in the A ring and a ketone at the C-21 position.





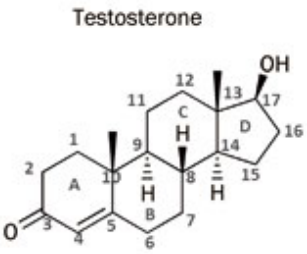
Androgens

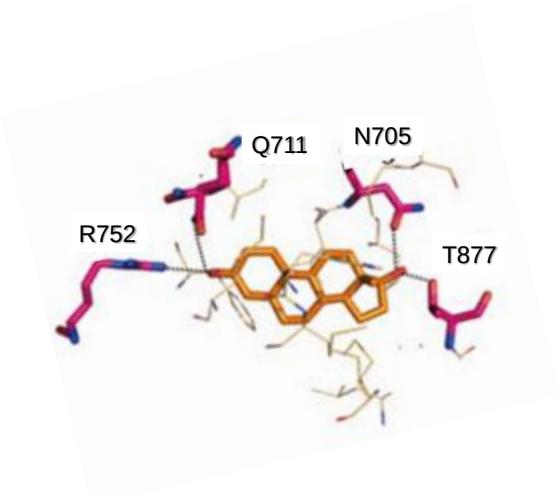
Androgen pathway in Prostate



- After testicular synthesis, testosterone is transported to target tissues such as the prostate
- Testosterone is converted to dihydrotestosterone (DHT) by 5-α-reductase.
- DHT binds to the ligand-binding pocket and promotes the dissociation of heat-shock proteins (HSPs) from the AR.
- The AR then translocates into the nucleus
- Dimerizes
- Recruits the coactivator
- Conformational opening of hinge
- DNA-binding domain binds to DNA
- Transcription
- Protein synthesis

Testosterone binding to AR



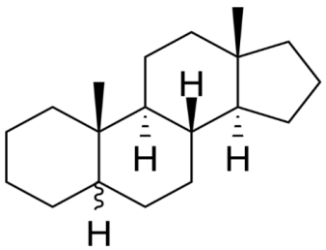


Uses

- Testosterone has two primary kinds of activities:
  - androgenic
    - promoting male physical characteristics
  - Anabolic
    - muscle building
    - aid recovery from debilitating illness or surgery

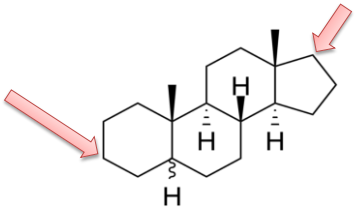
SAR of Androgens

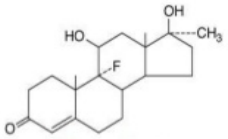
- For a substance to have androgenic activity, it must contain the androstane steroid skeleton.



SAR of Androgens

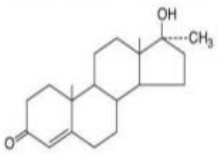
- Oxygen at C-3 and C-17 are not essential for the androgenic activity. However, introduction of 3α- -hydroxy group or 3-keto group and hydroxy group at C-17 position enhances the androgenic activity.
- 17β-OH can be esterified to give compounds with longer duration of action. Evidence indicates that the longer-acting esters of the 17β-OH compounds are hydrolyzed in vivo to the free alcohol , which is the active species.
- 17β-oxygen
  - It is thought that the 17β-oxygen atom is important for attachment to the receptor site and that
- 17α-alkyl
  - 17α-alkyl groups are important for preventing metabolic changes at this position. Such 17α-substituents render the compounds orally active.



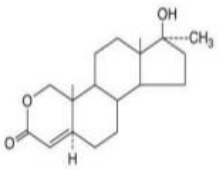


Fluoxymesterone

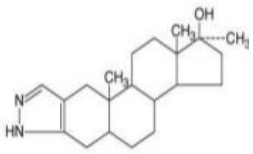
17α-Alkylated Androgens



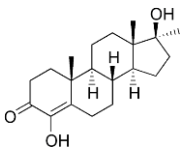
Methyltestosterone
(ORETIN METHYL, others)



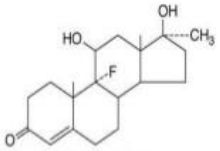
Oxandrolone
(OXANDRIN)



Stanozolol
(WINSTROL)



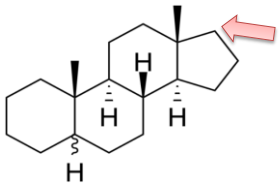
Oxymesterone
orally active anabolic-androgenic steroid



Fluoxymesterone
(HALOTESTIN)

SAR of Androgens

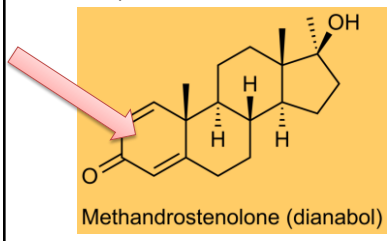
- Increasing the length of the alkyl side chain at the 17α-position, however, resulted in decreased activity, and the incorporation of other substituents, such as the 17α-ethynyl group, produced compounds with useful progestational activity (progestins)



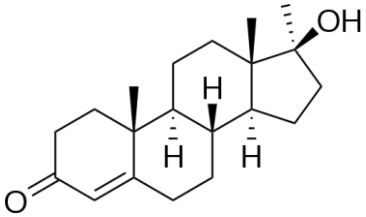
Fluoxymesterone

Danazol

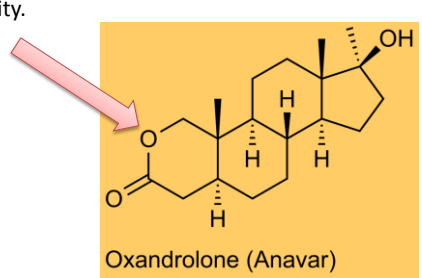
- Introduction of double bond at C-1 position increases the anabolic activity for example – methandrostenolone is more active than methyltestosterone



Methandrostenolone (dianabol)

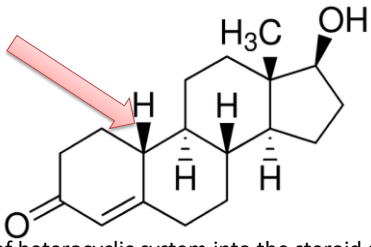


- 1- or 2-alkylation favors anabolic activity
- Replacement of carbon atom at C-2 position by oygen (e.g. oxandrolone) gives the oral anabolic activity.

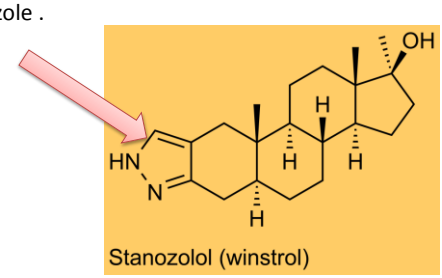


Oxandrolone (Anavar)

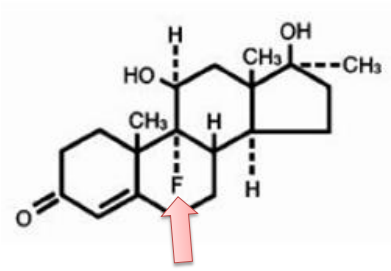
- Removal of CH3 group in testosterone gives 19-nor testosterone with more anabolic activity and less androgenic activity when compared with testosterone.



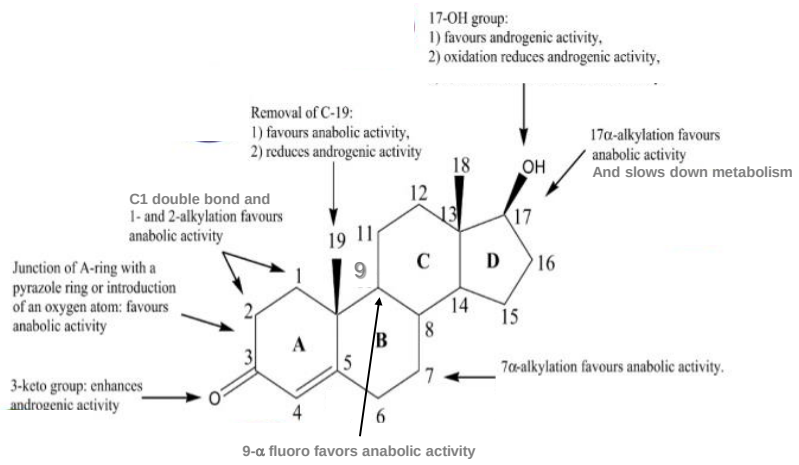
- The introduction of heterocyclic system into the steroid nucleus in ring A improve the anabolic activity . For example ,stanozolol are found to possess more anabolic activity, possessing pyrazole .



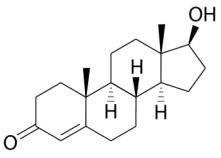
- Halogen substitution produces compounds with decreased activity except when placed at C-4 or C-9 position. For example ,
- 9-fluoro derivatives produces an anabolic effect 20 times that of 17 alpha-methyl testosterone



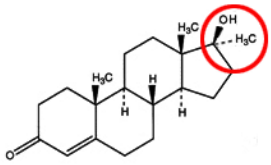
SAR - Androgen/Anabolic effect



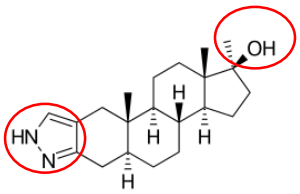
Testosterone and analogs



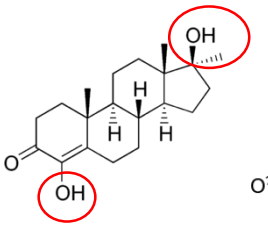
Testosterone



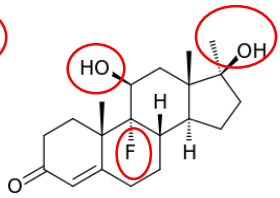
17-αMethyltestosterone



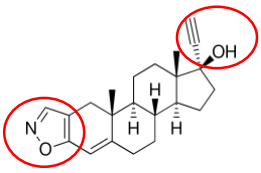
Stanazolol



Oxymesterone



Fluoxymesterone

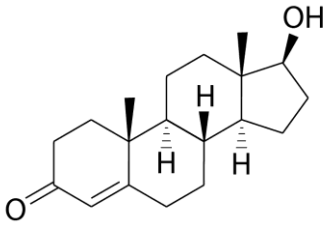


Danazolol

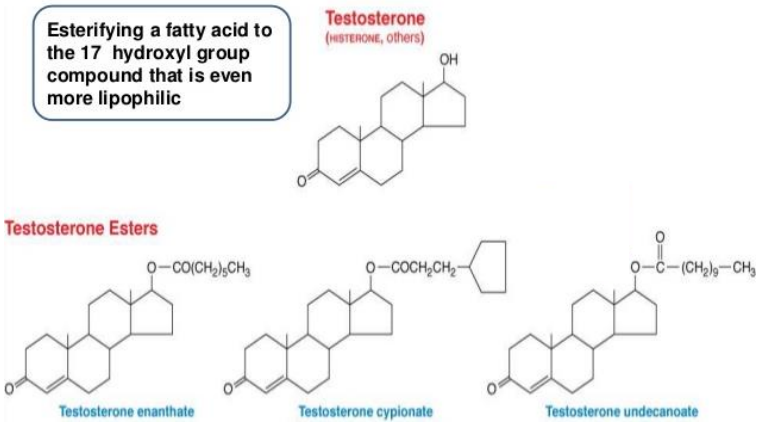
Testosterone

17-hydroxyandrost-4-en-3-one

- Naturally occurring androgen in men.
- It is rapidly metabolized to relatively inactive 17-ones which prevents significant oral activity.
- Testosterone 17-esters are available in long-acting IM depot preparations including Testosterone cypionate, Testosterone enanthate, Testosterone propionate, Testosterone undecanoate (long-acting preparation for the treatment of male hypogonadism)

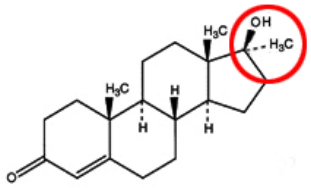


Therapeutic androgen preparations



17-α Methyltestosterone

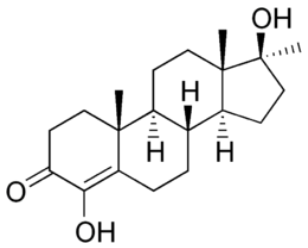
- The presence of a 17α alkyl group reduces susceptibility to hepatic oxidative metabolism, thereby increasing oral bioavailability by slowing metabolism.
- This drug has the androgenic activity of testosterone but higher anabolic activities than testosterone.
- Although orally active, it is more effective when administered sublingually.
- The alkylated oral androgens are potentially hepatotoxic and hence not be used.



(17β)-17-Hydroxy-17-methylandrost-4-en-3-one

Oxymesterone

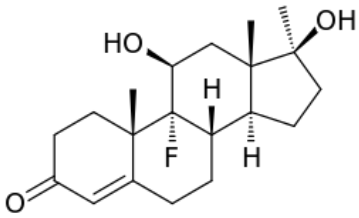
- An orally active anabolic-androgenic steroid
- 4-hydroxy-17α-methyltestosterone or 17α-methylandrost-4-en-4,17β-diol-3-one



(11β,17β)-9-Fluoro-11,17-dihydroxy-17-methylandrost-4-en-3-one

Fluoxymesterone,

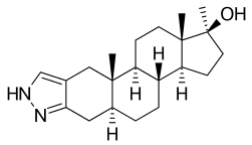
- Synthetic, orally active androgenic-anabolic steroid (AAS) and a 17α-alkylated derivative of testosterone
- 9α-fluoro group onto an analog of 17α-methyl testosterone gives fluoxymesterone which has 20 times the anabolic and 10 times the androgenic activity of 17α-methyl testosterone
- An adverse effect of fluoxymesterone is sodium and water retention that could lead to edema.



9α-Fluoro-11β-hydroxy-17α-methyltestosterone

Stanazolol

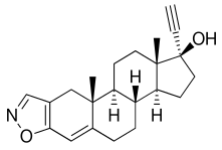
- Synthetic anabolic steroid derived from dihydrotestosterone
- Unlike most injectable anabolic steroids, stanozolol is not esterified and is sold as an aqueous suspension, or in oral tablet form.
- The drug has a high oral bioavailability, due to a C17 α-alkylation which allows the hormone to survive first-pass liver metabolism when ingested. It is because of this that stanozolol is also sold in tablet form.
- Stanozolol is one of the anabolic steroids commonly used as performance-enhancing drugs and is banned from use in sports competition under the auspices of the International Association of Athletics Federations (IAAF) and many other sporting bodies.



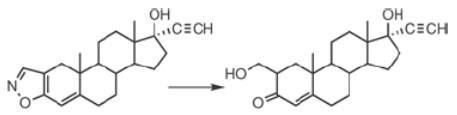
17β- Hydroxy-17α-methyl androstano[3,2-c]pyrazole

Danazol

- Isoxazole ring attached to ring A
- Exhibits potent antigonadotropic properties, weak androgen and anabolic properties, and no estrogen or progestin activity.
- As a gonadotropin inhibitor , danazol suppresses the surge of LH and FSH from the pituitary, thus suppressing ovarian steroidigenesis.
- Danazol is metabolized by CYP3A4 to its inactive metabolite, 2-hydroxymethylethisterone.



17α-Ethynyl-17β-hydroxy-4-androsteno[2,3-d]isoxazole

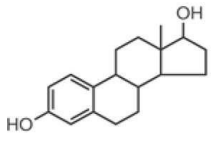


Danazol 2-Hydroxymethylethisterone

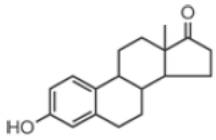
Estrogens

Estrogens

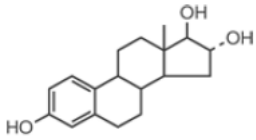
- The naturally occurring **estrogens** are
  - C-18 steroids
  - **Estrane derivatives**
  - a planar unsaturated A ring with a 3-phenolic group



Estradiol



Estrone

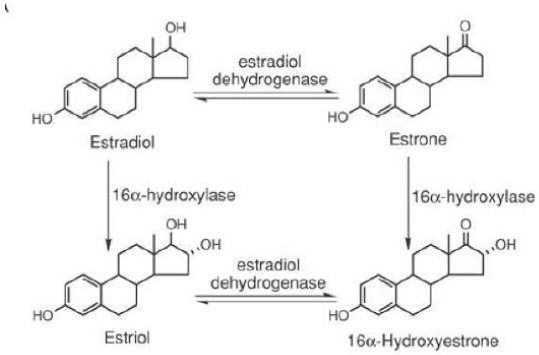


Estriol

- Estradiol, the most potent of the three, represents 10 to 20% of the circulating estrogen.
- Estrone is 10-fold less potent than estradiol. It accounts for 60 to 80% of the circulating estrogen.
- The remaining 10 to 20% is in the form of estriol, a very weak estrogen.

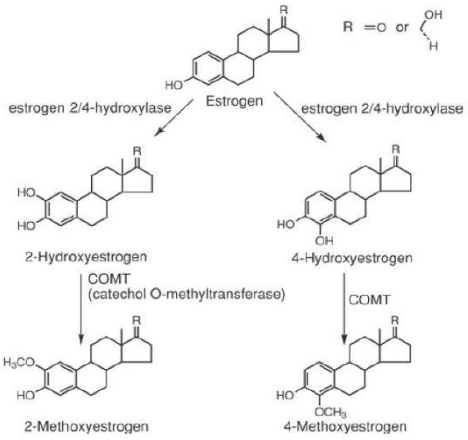
Biosynthesis

- In endocrine tissues, cholesterol is the steroid that is stored and converted to estrogen, progesterone, or androgen when the tissue is stimulated by a gonadotropic hormone.
- 17β-Estradiol is formed first which is then converted to estrone by the catalytic action of estradiol dehydrogenase and estriol by the action of 16α-hydroxylase.



Estrogen metabolism

- Estrogens are metabolized by estrogen 2/4-hydroxylase (CYP3A4) a positions ortho to the 3-phenolic group to form the 2-hydroxyl estrogens and the 4-hydroxyl estrogens
- The resulting catechol estrogens bind to estrogen receptors (ERs) and produce weak to moderate estrogenic effects.
- These metabolites are unstable in vivo, however, and are rapidly converted to their 2-methoxy and 4-methoxyestrogen metabolites as well as to their glucuronide, sulfate, and glutathione conjugates which are excreted in the urine

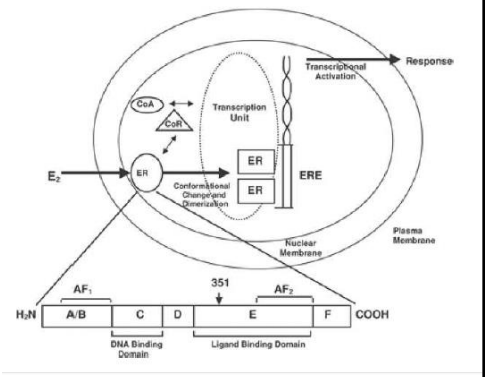


Estrogen Receptors

- Estradiol plays a key role in several physiological processes, including the development of secondary sex characteristics during puberty, stimulation of the mammary glands during pregnancy, and thermoregulatory capacity.
- Estradiol facilitates these processes via its biological target, the Estrogen receptor (ER), of which there are two subtypes
  - ER-α – expressed predominantly in the female reproductive tract and mammary glands
  - ER-β- found primarily in vascular endothelial cells, bone, and male prostate tissues.
- Estradiol has similar affinities for both ER-α and ER-β unlike certain non-steroidal estrogenic compounds and antiestrogens

Estrogen mechanism of action

- When estradiol binds either ER-α or ER-β, the receptor protein is phosphorylated
- The receptor protein as a result undergoes a conformational change to produce either homo- or heterodimers (ER-α/ER-α, ER-β/ER-β, or ER-α/ER-β)
- The dimeric ER complex then migrates from the cytosol to the cell nucleus, where it teams up with specific estrogen-response elements (ERE) found within an adaptor protein, typically a promoter, which aids in binding of the complex to estrogen activated genes
- This complex also enlists a coactivator (CoA) complex to this promoter, which regulates DNA transcription
- Transcriptional activation
- Response - Protein synthesis

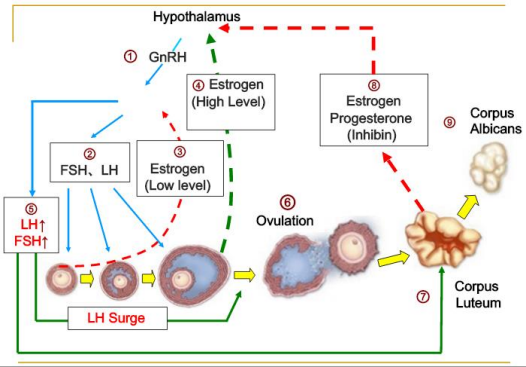


Therapeutic uses of estrogens

- Birth Control.
  - A major use of estrogens is for inhibition of ovulation, in combination with progestins.
- Hormone Replacement Therapy.
  - Another major use of estrogens is in HRT for postmenopausal women.
- Treatment of Estrogen Deficiency from Ovarian Failure or after Oophorectomy.

Interplay between FSH / LH and ovarian hormones

- Negative feedback:
  - occurs during follicular phases when estrogen levels are still low. GnRH is secreted which triggers release of FSH and LH which play a role in follicle development
- Postive feedback:
  - occurs at high concentrations near the end of the follicular phase, estrogen becomes a positive inducer of the anterior pituitary
  - positive feedback triggers the anterior pituitary to release more FSH and LH
  - the ensuing LH surge is responsible for ovulation

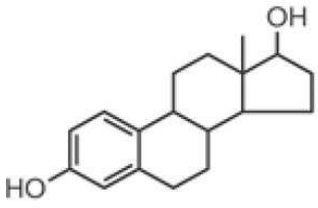


Estrogens

High levels of administered estrogens suppress the initial negative feedback axis and prevents release of FSH which is required for follicle growth and development - **Contraception**

Estradiol

- Estradiol is the most potent endogenous estrogen, exhibiting high affinity for the ER and high potency when administered parenterally.
- When administered orally, estradiol is promptly conjugated in the intestine and oxidatively metabolized by the liver, resulting in its low oral bioavailability and therapeutic effectiveness.



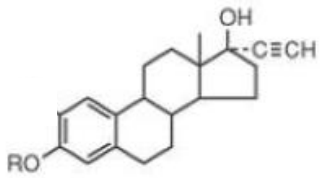
Estradiol

Estrogen

- 3 structural classes of estrogens:
  - steroidal estrogens,
  - Nonsteroidal estrogens eg.diethylstilbestrol
  - phytoestrogens
    - Most of the therapeutically useful steroidal estrogens are produced semisynthetically from natural precursors such as diosgenin, a plant sterol.

Estrogen steroidal analogs

- One method to increase the oral bioavailability of estradiol is to prevent metabolic oxidation of the estradiol C17 hydroxyl group to estrone.
- This is readily accomplished via alkylation of the C17 position with a chemically inert alkyne group e.g., ethynyl estradiol or administering a prodrug of EE such as mestranol (3-O-methyl ether of EE)
- Both EE and mestranol are used primarily in oral contraceptive formulations



Ethinyl estradiol: R = H

Mestranol: R = CH_3

Estrogen steroidal analogs

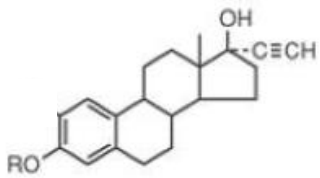
- Because of rapid metabolism, estradiol itself has poor oral bioavailability.
- The addition of a 17-alkyl group to the estradiol structure blocks oxidation to estrone.
- Ethinyl estradiol is therefore very effective orally, whereas estradiol itself is not.

Ethinyl estradiol

- This synthetic analogue is several hundred-fold more potent than estradiol
- Following oral administration, EE is rapidly and almost completely absorbed, with an oral bioavailability of approximately 40% and an elimination half-life of 26 hours
- Ethynyl estradiol undergoes extensive first-pass metabolism to its 3-O-glucuronide and 3-O-sulfate metabolites and, via aromatic hydroxylation, to 2–hydroxyethynylestradiol and its O-methyl metabolites.
- Ethynyl estradiol undergoes extensive enterohepatic recycling.
- The bacteria in the GI tract hydrolyze the glucuronide and sulfate conjugates, thereby permitting reabsorption of EE.
- It is for this reason that a number of antibacterial agents have an adverse effect on oral contraceptive (OC) efficacy.

Mestranol

- Semisynthetic estrogen
- The 3-O-methyl ether of Ethinyl estradiol
- Mestranol is a prodrug and, following oral administration, is rapidly metabolized to EE via hepatic O-demethylation.

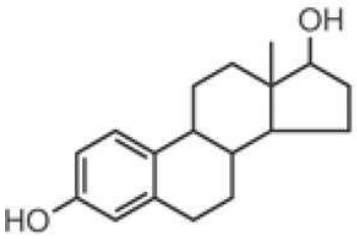


Ethinyl estradiol: R = H

Mestranol: R = CH_3

SAR

- The aromatic A ring and the C3 hydroxyl group are essential structural features essential for estrogenic activity.
- It is now generally accepted that the estrogens must have a phenolic moiety for binding,
- Moreover, Steroids with a phenolic A ring and related phenolic compounds lack high-affinity binding to the other steroid hormone receptors.

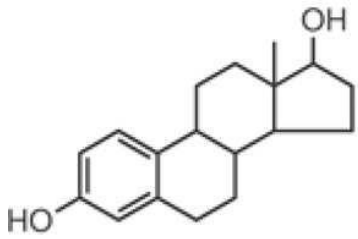


Estradiol

- Removal of the oxygen function from position 3 or 17, or epimerization of the 17β-hydroxyl group of estradiol to the α-configuration, results in an estrogenic analogue that is less active

SAR

- The steroid nucleus is not necessary for estrogenic activity.
  - The 17β-hydroxyl, the distance between the C3 and C17 hydroxyl groups, and the presence of planar hydrophobic scaffolding also are important structural contributors and help to optimize estrogenic activity.
  - Many constituents of plants like genstein, coumestrol do not contain steroid nucleus but possess estrogenic activity
  - Ideally, the distance between the oxygen atoms of the C3 and C17 hydroxyl groups should range from 10.3 to 12.1 A.

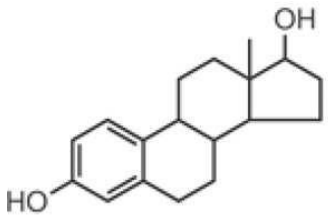


Estradiol

SAR

Substitution of the estrogen steroid nucleus can significantly modify estrogenic activity.

- Substitution at the C1 position greatly reduces activity, and only small groups can be accommodated at the 2 and 4 positions.
- Addition of hydroxyl groups at positions 6, 7, and 11 reduces activity.
- Other substituents at the 11β position are tolerated;
  - for example, 11β-methoxy or 11β-ethyl has significantly greater affinity for the ER as compared to estradiol.

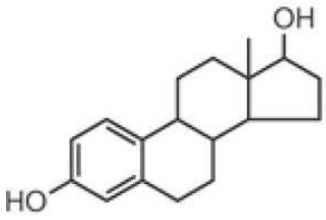


Estradiol

SAR

Substitution of the estrogen steroid nucleus can significantly modify estrogenic activity.

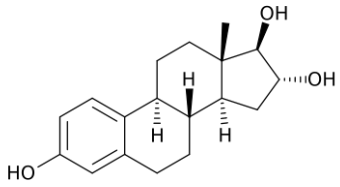
- Additional double bonds in the steroidal B ring substantially boosts the estrogenic potency of these estrogens.
- Enlargement of the D ring greatly reduces estrogenic activity.



Estradiol

- Certain modifications at the 17α and 16 positions can lead to enhanced activity.
  - For eg. The 17α-ethynyl or 17α-vinyl groups provide the greatest activity, whereas highly polar substituents at this position are poorly tolerated.
  - At the 16 position, moderate size and polarity are tolerated.

SAR

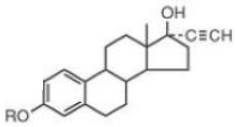


- The biological activity varies with the mode of administration of estrogens .
  - Subcutaneous administration of three naturally occuring steroids
    - The order of activity is estradiol > estrone > estriol.
  - Oral administration of three naturally occuring steroids
    - The order of activity changes to estriol > estradiol > estrone

SAR

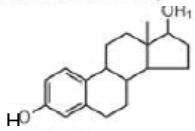
Estradiol modifications to enhance oral bioavailability

- Estradiol is not effective orally due to rapid metabolism in liver
- Approaches to enhance oral bioavailability
  1. Placement of ethinyl group at C-17 position increases the resistance to metabolic inactivation and makes the compound orally effective .
  2. Methylation of 3-OH group .e.g. mesteranol converts the drug to a prodrug and makes the compound orally effective
  3. Ester derivatives of the naturally occurring and synthetic estrogens have prolonged action.
  4. Labile ethers e.g., 3-(2-tetrahydropyranyl) and 17β-(2-tetrahydropyranyl) estradiol are 12- and 15-fold as active, respectively, as estradiol.

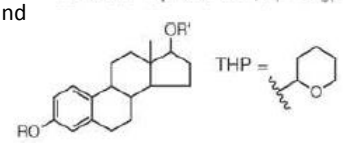


Ethinyl estradiol: R = H

Mestranol: R = CH_3



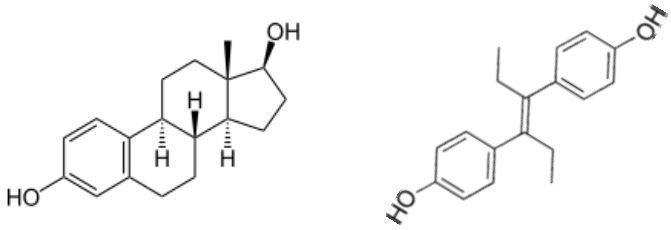
Estradiol 17β-valerate:; $R_1 = CH_3(CH_2)_3CO$



3-(2-Tetrahydropyranyl) derivative R = THP; R' = H

17β-(2-Tetrahydropyranyl) derivative R = H; R' = THP

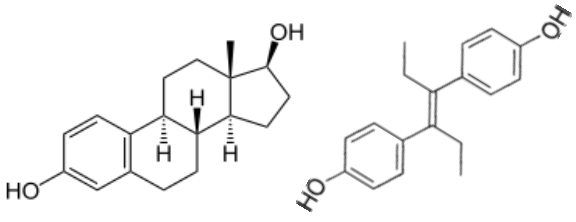
Nonsteroidal Estrogens



Nonsteroidal estrogens

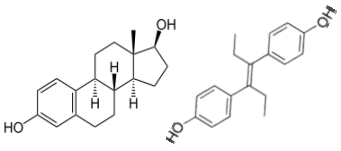
Common pharmacophore

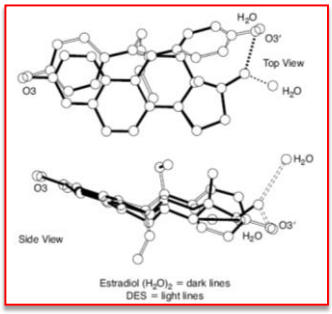
- Nonsteroidal diethylstilbestrol (DES) have the same activity as estradiol or other estrogens.
- DES can be viewed, however, as a form of estradiol with rings B and C open and a six-carbon ring D.



Nonsteroidal estrogens - Common pharmacophore

- DES can be viewed, as a form of estradiol with rings B and C open and a six-carbon ring D.
- It was proposed that the distance between the two DES phenol OH groups was the same as the 3-OH to 17-OH distance of estradiol; therefore, they could both fit the same receptor.
- Medicinal chemists have shown the OH-to-OH distance to be actually 12.1 Å in DES and 10.9 Å in estradiol.
- In aqueous solution, however, estradiol has two water molecules that are hydrogen bonded to the 17-OH.
- If one of the two water molecules is included in the distance measurement, there is a perfect fit with the two OH groups of DES
- This suggests that water may have an important role for estradiol in its receptor site.

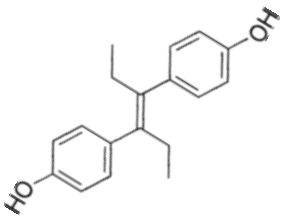




Nonsteroidal estrogens

Diethylstilbestrol (DES)

- Stilbene (diphenylethylene) derivative
- Therapeutically demonstrates potent estrogenic activity.
- A *trans* stilbene, DES has 10-fold the estrogenic potency of its *cis* isomer, largely because the *trans* isomer more closely resembles estradiol (20).
- Unfortunately, when DES was administered to relieve pregnancy-related symptoms, it was correlated with abnormal growth in the offspring.
- Although DES was used for many years, it was discovered that the daughters of women who had taken DES during pregnancy (DES babies) had a high risk of vaginal, cervical, and uterine abnormalities, along with a low risk of vaginal clear cell adenocarcinoma.
- Because of the safety concerns associated with DES, it was completely removed from the U.S. market in the late 1990s.
- DES is still available as an estrogen for use in veterinary medicine, however.



Anti-Estrogens

Anti-estrogens

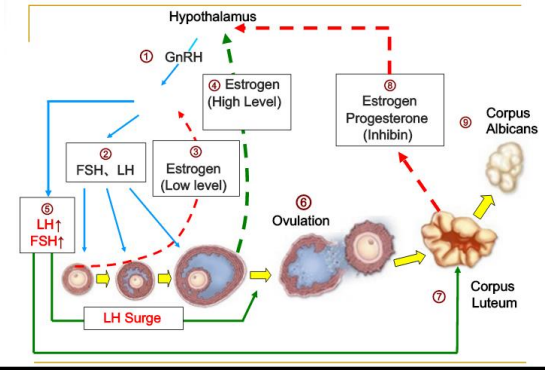
- Agents that antagonize the actions of estrogens
- **Therapeutic uses**
  - Estrogens are important in
    - chemical contraception and
    - hormone replacement therapy (HRT),
  - Anti-estrogens are used in the
    - **treatment of estrogen dependent breast cancers**
    - **Antifertility treatment**

Therapeutic uses

- Anti-estrogens are used in the **treatment of estrogen dependent breast cancers**
  - Some breast cancers require estrogen to grow. Those cancers have estrogen receptors (ERs), and are called ER-positive. Antiestrogens block the synthesis / action of estrogen. This lowers the estrogen level, and slows the growth of cancers.

Interplay between FSH / LH and ovarian hormones

- Negative feedback:
  - occurs during follicular phases when estrogen levels are still low. GnRH is secreted which triggers release of FSH and LH which play a role in follicle development
- Postive feedback:
  - occurs at high concentrations near the end of the follicular phase, estrogen becomes a positive inducer of the anterior pituitary
  - positive feedback triggers the anterior pituitary to release more FSH and LH
  - the ensuing LH surge is responsible for ovulation



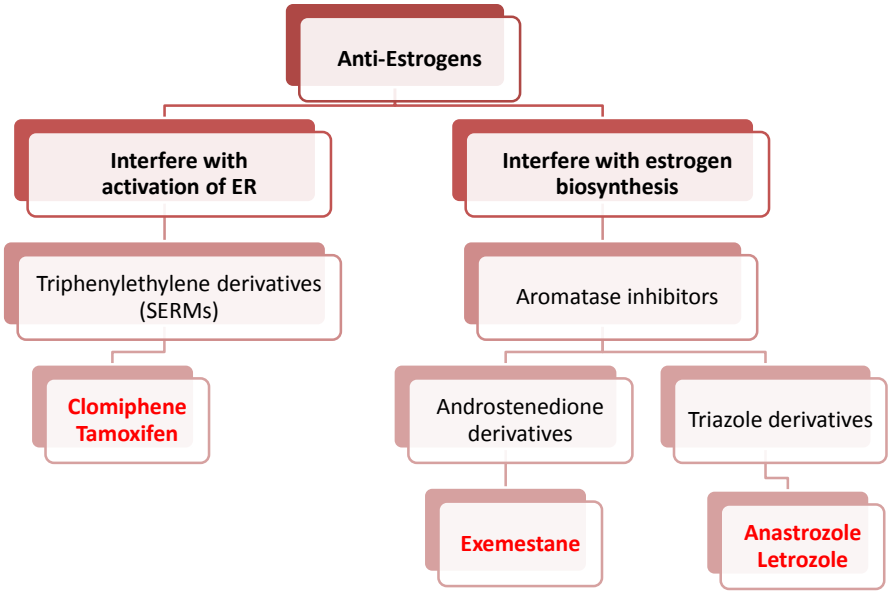
Estrogens

- Estrogens are used for **Contraception**
  - High levels of administered estrogens suppress the initial negative feedback axis and prevents release of FSH which is required for follicle growth and development
- Anti-estrogens are used for **Ovulation (antifertility treatment)**
  - Low levels of administered anti-estrogens activate the initial negative feedback axis and
  - cause release of LH and FSH and increase in circulating estrogens
  - Stimulation of positive feedback axis results in LH surge
  - Ovulation

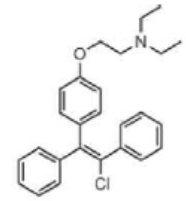
Mechanism of action

- Mechanism of action of antiestrogens-
  - interfere with estrogen activation of its receptor or
  - limit estrogen biosynthesis

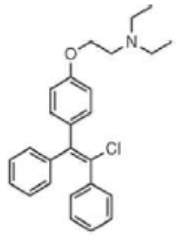
Classification



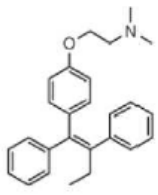
Agents that Interfere with activation of Estrogen receptor (ER)



Enclomiphene
(E-(*cis*) isomer of clomiphene)



Zuclomiphene
(Z-(*trans*) isomer of clomiphene)



Tamoxifen
(Z-diastereomer)

Triphenylethylene derivatives

Selective Estrogen Receptor Modulators

SERMs

SERMs

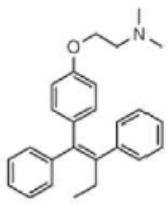
- These agents act as
  - Agonist at some tissues e.g. on endometrium, liver, bone, and cardiovascular system.
  - Antagonist at other tissues e.g. Breast
- Because of the differential agonist and antagonist effects of these types of compounds on the ER, depending on the specific tissue, a new term was coined:
- Selective estrogen receptor modulators (SERMs). A SERM is a drug that has tissue-specific estrogenic activity

Triphenylethylene derivatives (SERM)

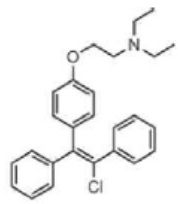
- Therapeutic uses
  - Treatment of estrogen-dependent breast cancer
  - Treatment of infertility in women

Triphenylethylene derivatives (SERM)

- The triphenylethylene antiestrogens are structurally related to the stilbene family of estrogens and exhibit high affinity for the ER.
- They prevent translocation of the estrogen–receptor complex into the nucleus of target cells and interfere with the binding of the receptor–hormone complex to the acceptor site of the chromatin



Tamoxifen
(Z-diastereomer)



Enclomiphene
(E-(*cis*) isomer of clomiphene)

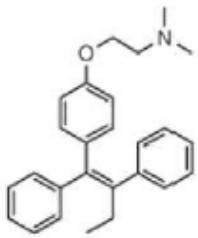
Mechanism of SERMs

- Tamoxifen (SERM) as well as estradiol (nonselective) both bind to the ER at the same site, but their binding modes are different.
- Each induces a distinct conformation in the trans-activation region of the ligand-binding domain.
- These unique conformations dictate how the receptor–ligand complex will interact with coregulator proteins (coactivators or corepressors).
  - Estradiol
    - In all tissues, the estradiol–ER complex recruits **coactivators**, so gene transcription is stimulated – **ER agonist**
  - Tamoxifen
    - In breast tissue, tamoxifen-bound receptors prevent the association with coactivators, but rather recruit **corepressors**, so antagonist action is observed - **ER antagonist**
    - In uterine tissue, however tamoxifen–ER complex recruits a **coactivator**, SRC-1, which leads to agonist action - **ER agonist**

Tamoxifen

- Tamoxifen itself is a prodrug, having relatively little affinity for its target protein, the estrogen receptor (ER).
- It is metabolized in the liver by the cytochrome P450 into active metabolites such as 4-hydroxyl tamoxifen (4-OHT) (afimoxifene) and N-desmethyl-4-hydroxyl tamoxifen (endoxifen) which have 30–100 times more affinity with the ER than tamoxifen itself
- These active metabolites compete with estrogen in the body for binding to the ER.
- In breast tissue, 4-OHT acts as an ER antagonist so that transcription of estrogen-responsive genes is inhibited

Z)-2-[4-(1,2-diphenylbut-1-enyl) phenoxy]-*N*,*N*-dimethylethanamine

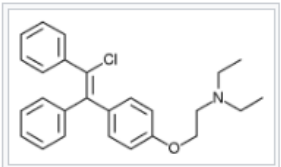


Tamoxifen
(Z-diastereomer)

Clomifene

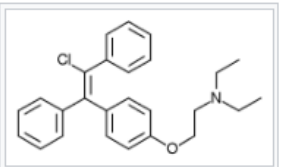
- Clomiphene citrate is by far the most frequently prescribed agent to stimulate ovulation.
- It is administered orally as a mixture of two geometric isomers.
- The Z (*cis*, zuclomiphene) - diastereomer displays estrogenic activity, and the E (*trans* , enclomiphene) -diastereomer exhibits antiestrogenic activity

Z-2-(4-(2-chloro-1,2-diphenylethenyl) phenoxy)-N,N-diethyl-ethanamine



Zuclomifene

E-2-(4-(2-chloro-1,2-diphenylethenyl) phenoxy)-N,N-diethyl-ethanamine



Enclomifene

Interplay between FSH / LH and ovarian hormones

- Negative feedback:
  - occurs during follicular phases when estrogen levels are still low. GnRH is secreted which triggers release of FSH and LH which play a role in follicle development
- Postive feedback:
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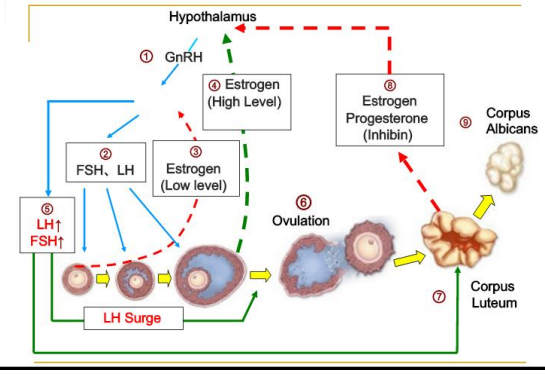
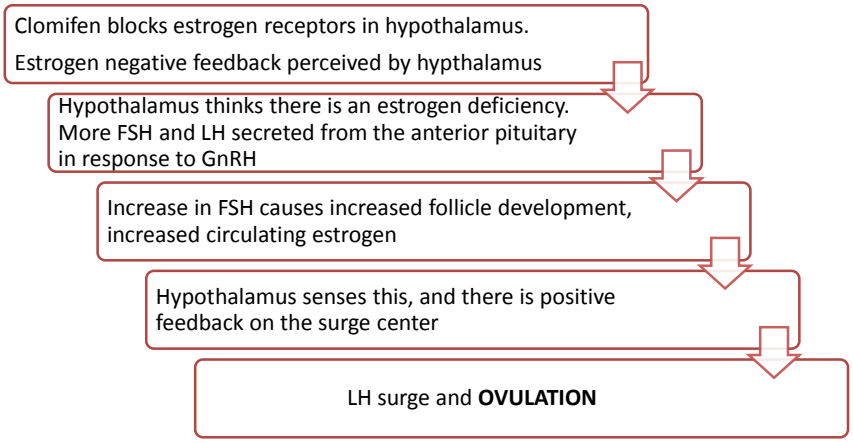


Clomifene

- Its ability to stimulate ovulation stems from its action at the hypothalamic ERs , where it serves to block these receptors and inhibits the natural feedback mechanism.
- When an estrogen deficiency is perceived by the hypothalamus , it responds by secreting GnRH.
- This peptide hormone signals the pituitary to release the gonadotropins FSH and LH. Elevated FSH levels promote follicular development, which in turn causes the maturing follicles to secrete estradiol which results in LH surge acting via positive feedback mechanism of the hypothalamus.
- This surge in LH causes the dominant follicle to rupture and release an egg, a process known as ovulation.
- Clomiphene is administered orally (50 or 100 mg) for 5 consecutive days , typically on days 5 to 9 of the menstrual cycle. Approximately 7 days after the last clomiphene tablet is taken, the hypothalamus finally is able to detect that circulating estradiol levels are elevated, and it then signals the pituitary to secrete LH.

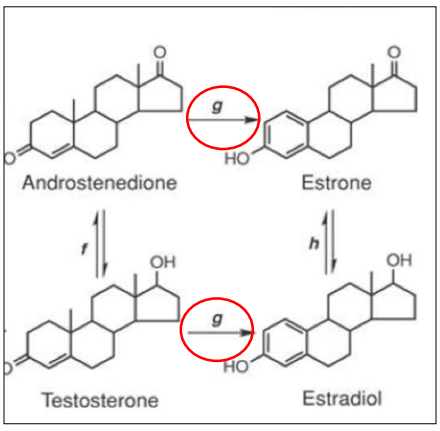
Clomifene Mechanism of action



Agents that Interfere with Estrogen synthesis

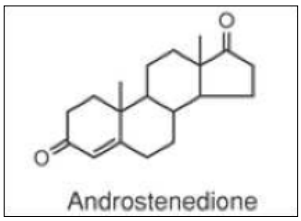
Aromatase Inhibitors

- Aromatase is a cytochrome P450 enzyme complex that catalyzes the conversion of androstenedione to estrone and testosterone to estradiol
- Aromatase inhibitors block the conversion of androgens to estrogens
- They have the therapeutic potential to control reproductive functions and aid in the treatment of estrogen-dependent cancers, such as breast cancer
- The aromatase reaction is unique in steroid biosynthetic pathways and aromatase inhibitors are very specific in their estrogen biosynthesis blockade.



Chemical classes

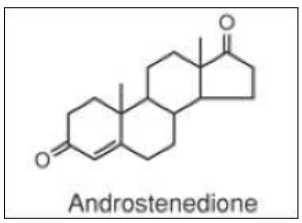
- Androstenedione derivatives

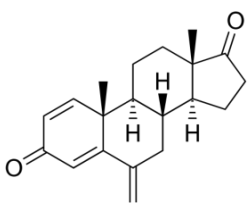


- Triazole derivatives

Androstenedione derivatives

- Inhibitors of aromatase block the conversion of androgens to estrogens and, therefore, have the therapeutic potential to control reproductive functions and aid in the treatment of estrogen-dependent cancers, such as breast cancer.
- These steroidal agents compete with androstenedione for the active site of the aromatase enzyme.

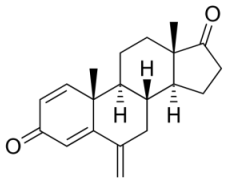


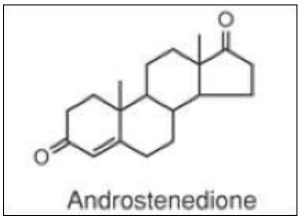


Exemestane

SAR - Androstenedione derivatives

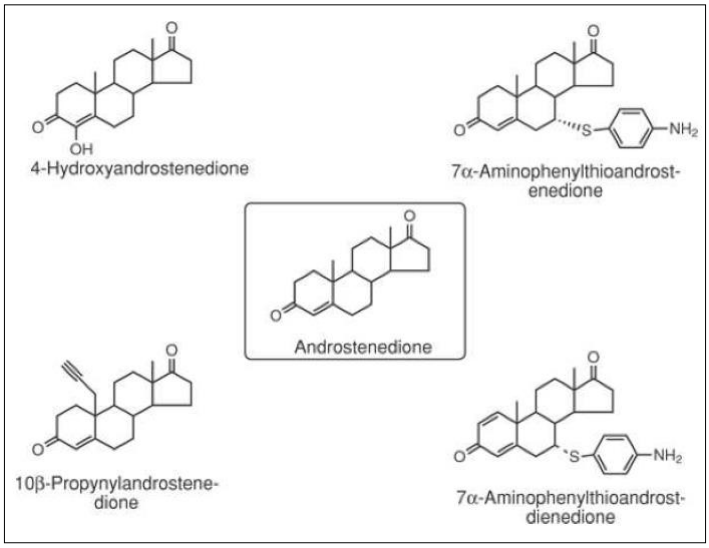
- Best agents are substrate analogues, with only small structural changes to the A ring and at C19 permitted
- Analogues that contain aryl functionalities at the 7α position have enhanced affinity for the enzyme
- Following substrates act as suicide substrates for this enzyme
  - 4-hydroxy-androstenedione
  - Several androsta-1,4-diene-3,17-diones





  - 10β-propynylestr-4-ene-3,17-dione

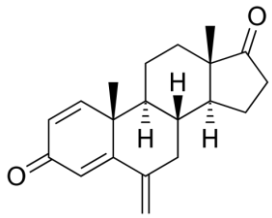
Androstenedione derivatives



Exemestane

- Example – Exemestane
- It is distinguished from the natural 4-androstenedione only by the methylidene group in position 6 and an additional double bond in position 1
- Drug used to treat breast cancer.
- It is a member of the class of drugs known as aromatase inhibitors.

6-Methylideneandrosta-1,4-diene-3,17-dione



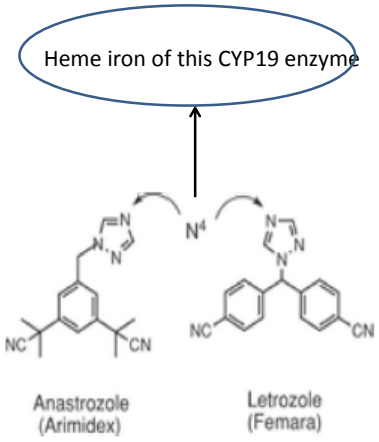
Mechanism –

Some breast cancers require estrogen to grow. Those cancers have estrogen receptors (ERs), and are called ER-positive. They may also be called estrogen-responsive, hormonally-responsive, or hormone-receptor-positive. Aromatase is an enzyme that synthesizes estrogen. Aromatase inhibitors block the synthesis of estrogen. This lowers the estrogen level, and slows the growth of cancers.

Triazole derivatives

- Were developed based on the aromatase inhibitor aminoglutethimide
- Competitive inhibitors of aromatase and selectively inhibit the conversion of testosterone to estrogens

Mechanism of Action

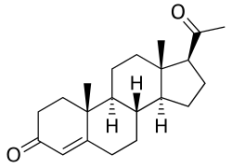


- The nonsteroidal aromatase inhibitors are competitive inhibitors that bind to the enzyme active site by coordinating the iron atom present in the heme group of the P450 protein.
- Aside from aminoglutethimide, the first selective aromatase inhibitor to be marketed in the United States was anastrozole (Arimidex).
- Anastrozole incorporates a triazole ring into its structure that can coordinate to the heme iron.
- Letrozole is another triazole-containing inhibitor that is also effective in the treatment of breast cancer.

Progesterone analogs and Progestins

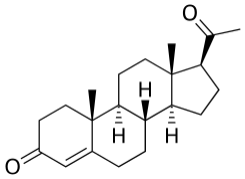
Progesterone derivatives

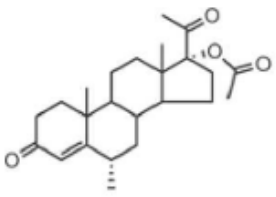
- Progesterone has a significant role in priming the uterine endometrium for implantation of a potential blastocyst.
- It also is involved in formation of the placenta post-implantation, the development of mammary glands, and by preventing contraction of the uterine musculature, pregnancy maintenance.
- Progesterone also has inhibitory roles, including ovulation prevention via an antigonadotropic effect



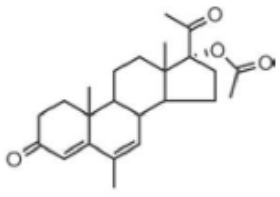
- However, the oral bioavailability of progesterone is low and oral progesterone analogs were developed as oral contraceptives.

Progesterone derivatives





Medroxyprogesterone acetate

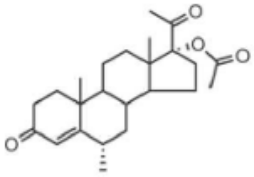


Megestrol acetate

Progesterone derivatives

Medroxyprogesterone acetate

- The initial structural modifications made to progesterone led to only weakly active or inactive analogues. For example, 17α-acetoxy progesterone had limited activity when administered orally
- Addition of a C6 substituent to 17α-acetoxyprogesterone with the aim of limiting metabolic hydroxylation at C6 gave medroxyprogesterone acetate with improved biological activity



Medroxyprogesterone acetate

Medroxyprogesterone acetate

- Synthetic hormone of the progestin type.
- It works by decreasing the body's release of gonadotropins.
- Therapeutic uses
  - Contraceptive
  - Part of hormone replacement therapy for menopausal symptoms.
  - Treatment of endometriosis, abnormal uterine bleeding,
  - Treatment of certain types of cancer.
- It is used by mouth or injection into a muscle or under the skin
- Side effects
  - no periods, abdominal pain, headaches, and anxiety. bone loss, blood clots, allergic reactions, depression, and liver problems.

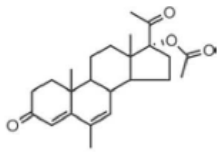
Mechanism

- The mechanism of action of progestogen-only contraceptives depends on the progestogen activity and dose.
- High-dose progestogen-only contraceptives inhibit follicular development and prevent ovulation as their primary mechanism of action.
- The progestogen decreases the pulse frequency of gonadotropin-releasing hormone (GnRH) release by the hypothalamus, which decreases the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary.
- Decreased levels of FSH inhibit follicular development, preventing an increase in estradiol levels.
- Progestogen negative feedback and the lack of estrogen positive feedback on LH release prevent a LH surge.
- Inhibition of follicular development and the absence of a LH surge prevent ovulation

Progesterone derivatives

Megesterol acetate

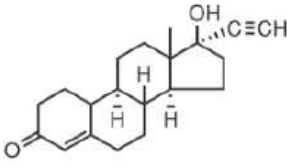
- Progestin activity is further enhanced when a double bond is introduced between positions 6 and 7, as is found in megestrol acetate.
- Megestrol is used primarily in the treatment of breast and endometrial carcinomas and in postmenopausal women with advanced hormone-dependent carcinoma.
- Less than 10% of an oral dose undergoes metabolism.
- Several major metabolites appear in the urine (e.g., 2-hydroxy and 6-hydroxymethyl megestrol and their glucuronide conjugates).



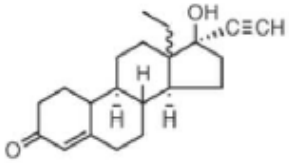
Megestrol acetate

Progestins

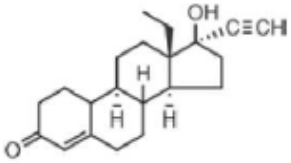
- Potent, orally active progesterones
- Synthetic 19-norsteroid
- Used clinically for progesterone- related disorders .
- When combined with estrogens , such as EE or mestranol, these agents are effective contraceptives .
- Although norethindrone is a weak androgen, it does not exhibit any glucocorticoid or antimineralocorticoid activity



Norethindrone



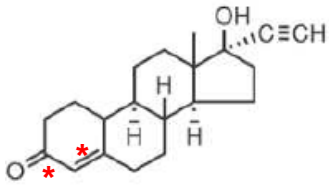
Norgestrel



Levonorgestrel

Norethindrone

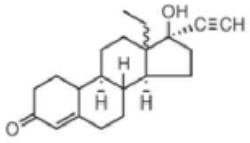
- Following oral administration, norethindrone acetate is completely and rapidly deacetylated by hepatic and intestinal first -pass metabolism to norethindrone, with an oral bioavailability of approximately 64%.
- Subsequent metabolism of norethindrone includes reduction of the Δ^4 double bond to both the 5α- and 5β-dihydronorethindrone products as well as reduction of the ketone.



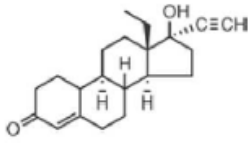
- Norethindrone acetate also can be administered transdermally along with estradiol when formulated as a patch. This combination of hormones can be utilized as part of either a continuous or a cyclic hormone replacement regimen.

Norgestrel

- Norgestrel is formulated as a racemic mixture despite the fact that only its levo isomer, levonorgestrel, is pharmacologically active
- Levonorgestrel exhibits some androgenic activity but no glucocorticoid or antimineralocorticoid action.
- Levonorgestrel can be administered orally, transdermally (combined with estradiol and formulated as a 7-day patch) , and for prolonged, continuous use, via an intrauterine device (IUD).



Norgestrel



Levonorgestrel