

Unit-4

Medicinal Chemistry- II

B.Pharma 5th Sem Notes

Unit: 4

Drugs acting on Endocrine system

- Nomenclature, Stereochemistry and metabolism of steroids
- **Sex hormones:** Testosterone, Nandralone, Progestrones, Oestriol, Oestradiol, Oestrione, Diethyl stilbestrol.
- **Drugs for erectile dysfunction:** Sildenafil, Tadalafil.
- **Oral contraceptives:** Mifepristone, Norgestril, Levonorgestrol
- **Corticosteroids:** Cortisone, Hydrocortisone, Prednisolone, Betamethasone, Dexamethasone
- **Thyroid and antithyroid drugs:** L-Thyroxine, L-Thyronine, Propylthiouracil, Methimazol

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Endocrine system:

- The endocrine system is a network of glands and organs that produce hormones to regulate and coordinate many functions of the body:

Hormones:

- The body's chemical messengers that carry information and instructions from one set of cells to another.

Glands

- Located throughout the body, including the hypothalamus, pineal gland, pituitary gland, thyroid gland, parathyroid glands, thymus, adrenal glands, pancreas, testes, and ovaries.

Receptors

- Located in various organs and tissues, these recognize and respond to the hormones.

The endocrine system controls many important functions in the body, including:

- Growth and development
- Metabolism
- Reproduction
- Energy level
- Response to injury, stress, and mood



Nomenclature, Stereochemistry and metabolism of steroids

Steroids:

- These are the class of naturally occurring organic compounds produced naturally in the body.
- The steroid core structure is composed of seventeen carbon atoms (C17), bonded in four "fused" rings.
- Three six-member cyclohexane rings (rings A, B and C in the first illustration) and one five-member cyclopentane ring (the D ring).
- Steroids vary by the functional groups attached to this four ring core and by the oxidation state of the rings.

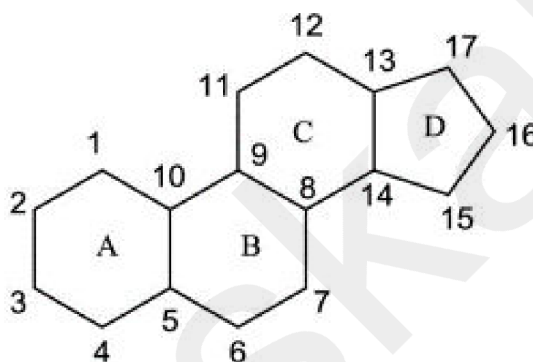


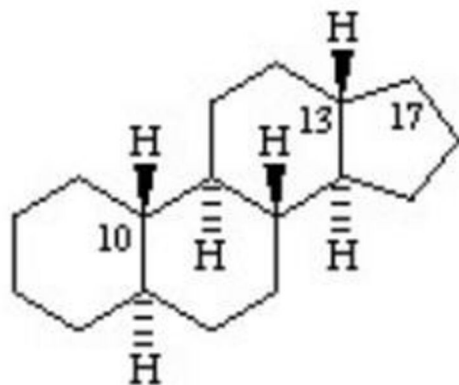
Fig. 2: Structure of Cyclopentanoperhydrophenanthrene ring.

Almost all steroids are named as derivatives of any one of the following basic steroidal ring.

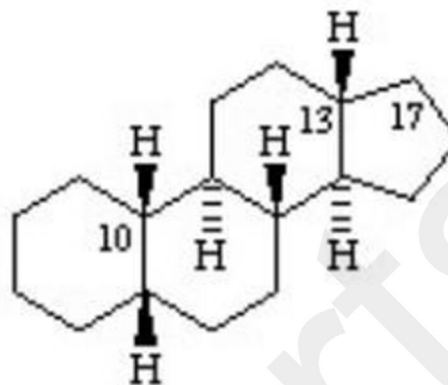
- Solid line indicates groups above the plane of the nucleus (β -configuration) and dotted line denote groups below the plane (α -configuration).
- The configuration of the hydrogen (-H) at C-5 position is always indicated in the name.
- Compounds with 5- α cholestane belong to the 'allo series' while compounds derived from the 5- β cholestane belongs to the 'normal series'.
- If the double bond is not between sequence numbered carbon, in that case both carbons are indicated in the name.
- The symbol Δ (delta) is used to indicate C=C bond in steroids.
- When a methyl group is missing from the side chain, these are not indicated by the prefix 'nor' with the number of the carbon atom which is disappear.

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Gonane: The parent tetracyclic hydrocarbon without methyl groups at C-10 and C-13 and without a side chain at C-17 is named gonane. E.g. 5 (α or β) gonane (C =17)



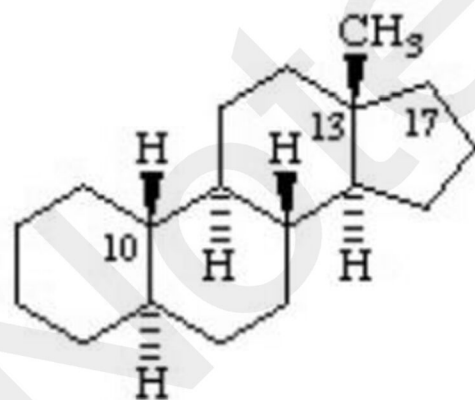
5 α -Gonane



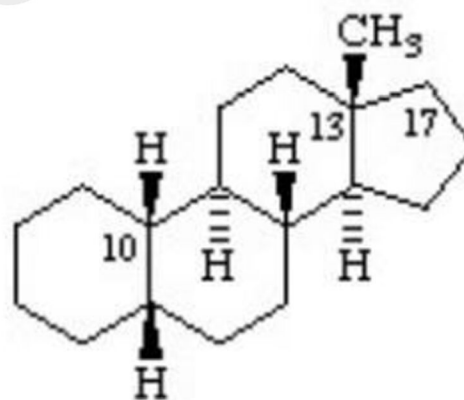
5 β -Gonane

Structure of Gonane (C17)

Estrane: The hydrocarbon with a methyl group at C-13 but without a methyl group at C-10 and without a side chain at C-17 is named as estrane. E.g. 5 (α or β) estrane (C =18)



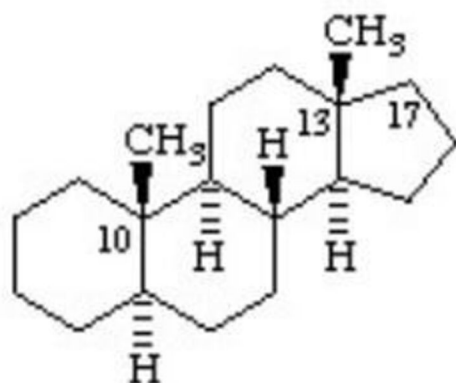
5 α -Estrane



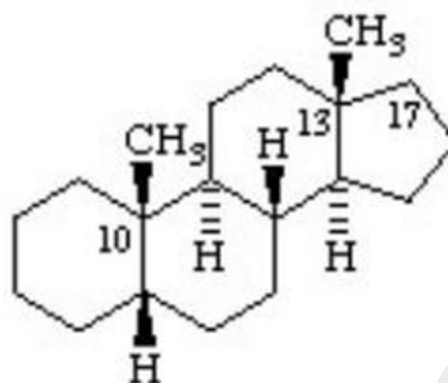
5 β -Estrane

Structure of Estrane

Androstane: The hydrocarbon with methyl groups at C-10 and C-13 but without a side chain at C-17 is named as androstane. E.g. 5 (α or β) androstane. (C =19)



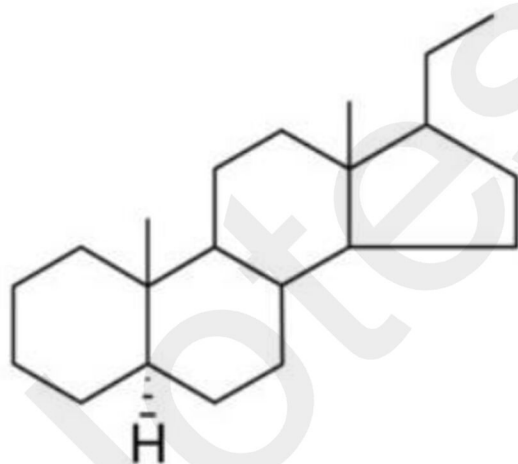
5 α -Androstane



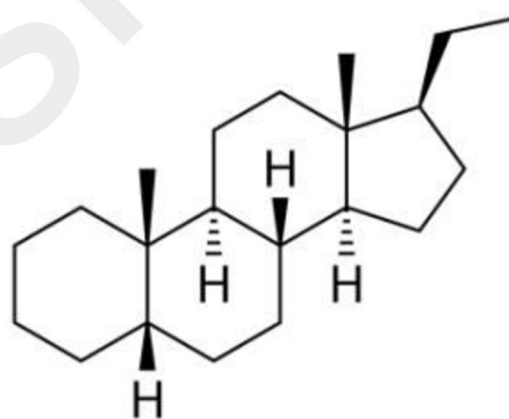
5 β -Androstane

Structure of Androstane

Pregnane: The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto C-21 containing is named Pregnane (Fig. 6). It is a parent hydrocarbon for two series of steroids stemming from 5 α -pregnane and 5 β -pregnane (C=21).



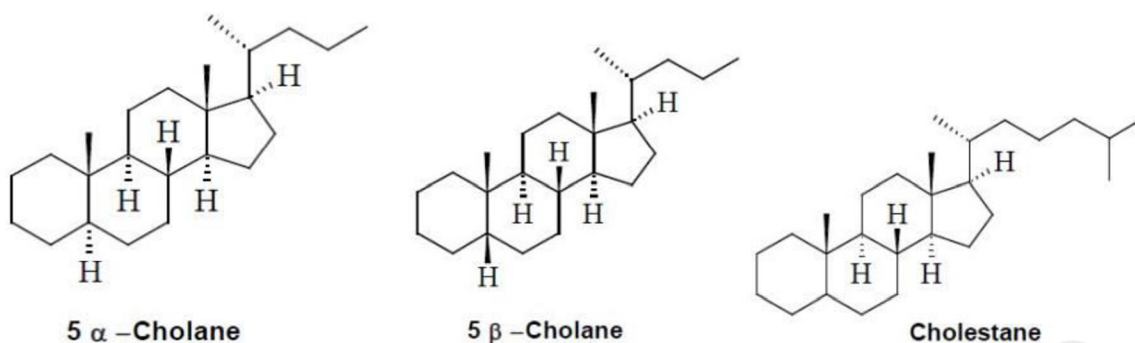
5 α -pregnane



5 β -pregnane

Structure of Pregnane

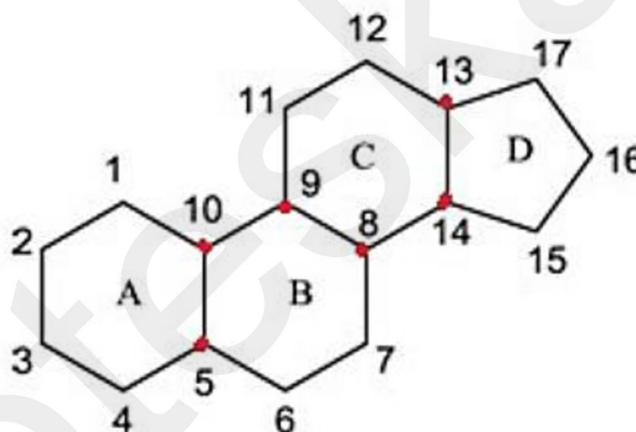
Cholane & Cholestane: The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto Carbon chain 24 is named Cholane and upto Carbon chain 27 named Cholestane.



Structure of Cholane & Cholestane.

Stereochemistry of steroids:

There are six asymmetric carbon atoms 5,8,9,10,13,14 in the nucleus, therefore 64 optically active forms are possible.

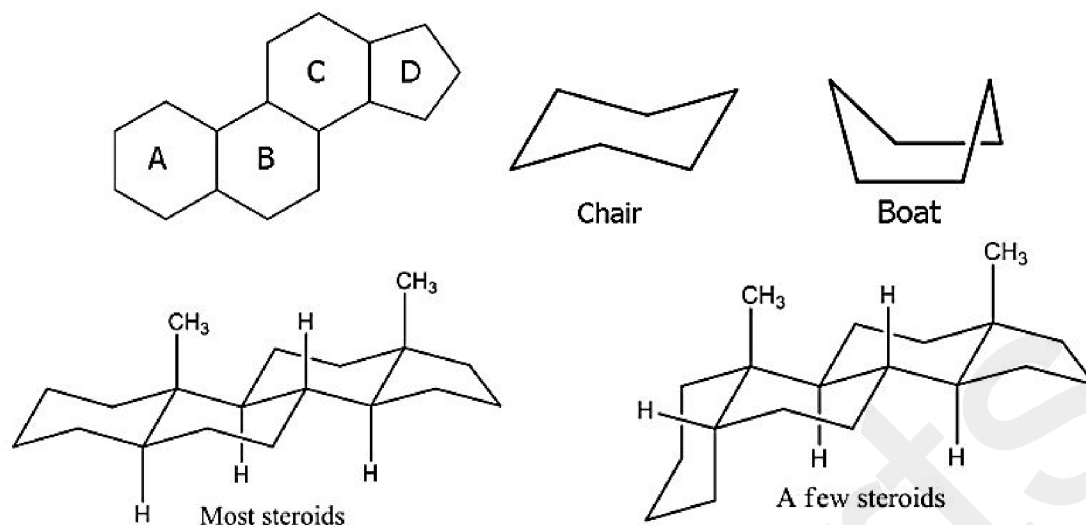


Skeleton of steroids with asymmetric centers.

Cholestane, androstane and pregnane exist in two conformations such as chair form and boat form. Chair form is more stable than boat form due to less angle strain, therefore all cyclohexane rings in steroid nucleus exist in the chair form.

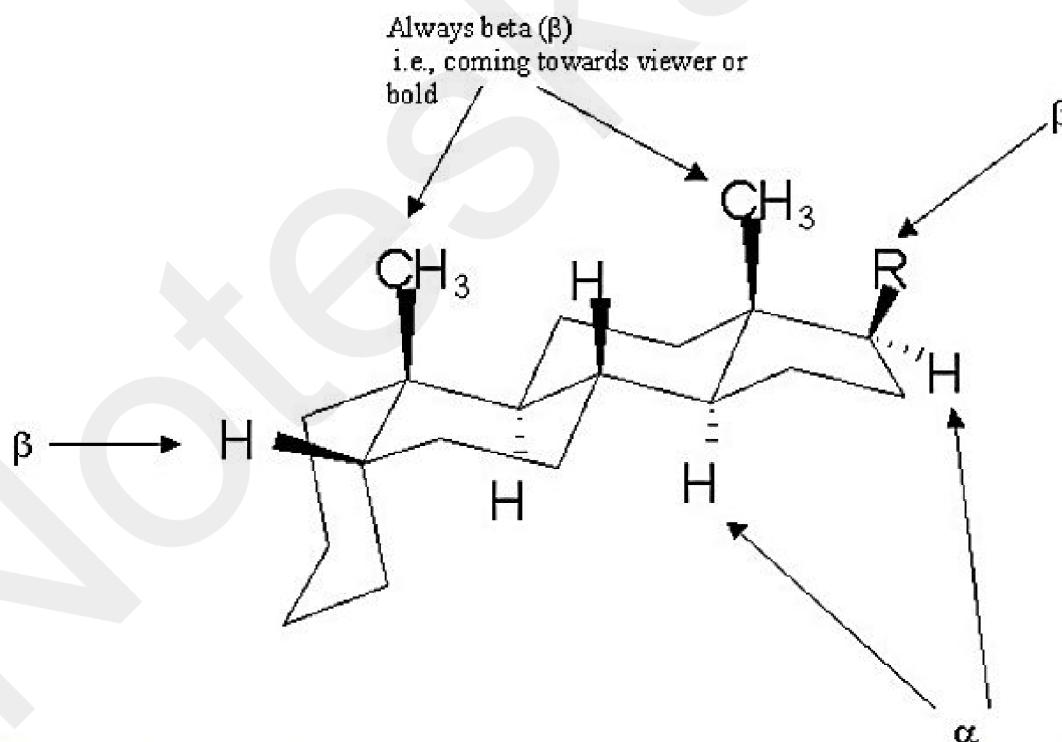


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Conformations of steroids.

The absolute stereochemistry of the molecule and any substituent is shown with solid bond (β -configuration) and dotted bond (α -configuration).



Configuration of steroids.

The aliphatic side chain at C-17 position is always assumed to be β -configuration. The term cis and trans are sometimes used to indicate the backbone stereochemistry between the rings.

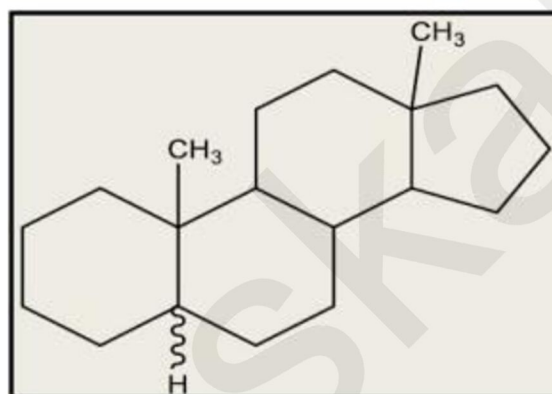
Example; 5- α - steroid are A/B Trans and 5- β - steroids are A/B Cis.

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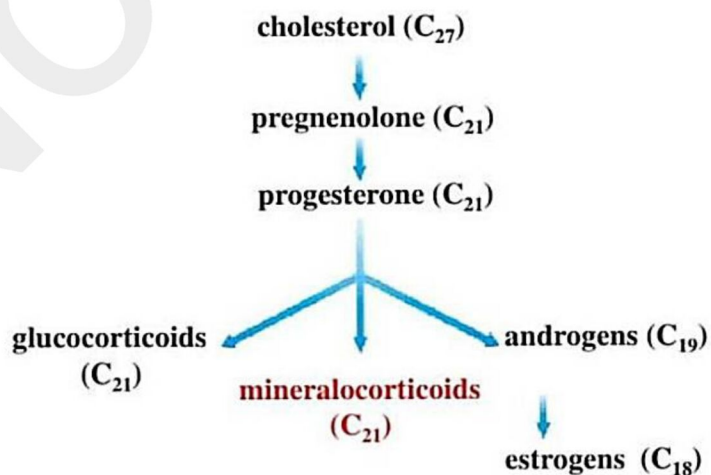
Structure of 5- α and 5- β steroid.

If A/B fusion cis and trans both position possible or position is unknown, it is indicated by waving lines/bonds



Structure of Trans/cis form of steroid.

Metabolism of steroids:



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- **Sex hormones:** Testosterone, Nandralone, Progesterones, Oestriol, Oestradiol, Oestrione, Diethyl stilbestrol.

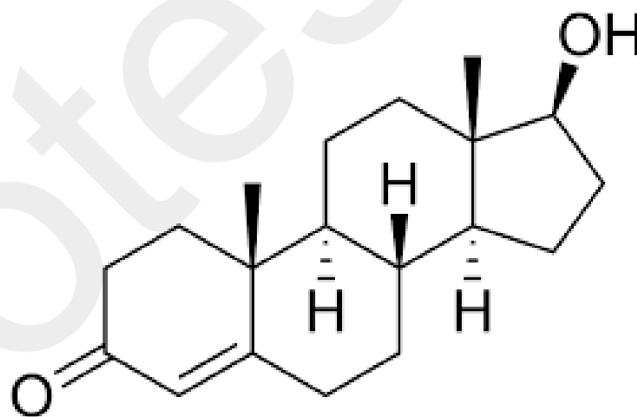
Sex hormones:

- Sex hormones are chemical messengers that are essential to the human body's growth and operation.
- They are responsible for the development of secondary sexual characteristics, the regulation of sexual behavior, and the maintenance of reproductive health.

Testosterone:

- **Testosterone** is a steroid hormone classified as an androgen, primarily produced in the testes in males and in smaller amounts by the ovaries in females and the adrenal glands in both sexes.
- It is the primary male sex hormone responsible for the development of male secondary sexual characteristics and the regulation of reproductive functions.

Structure of Testosterone:



Mechanism of action:

- Testosterone antagonizes the androgen receptor to induce gene expression that causes the growth and development of masculine sex organs and secondary sexual characteristics.

Structure activity relationship:

- It must contain the androstane skeleton for its biological activity.

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- Introduction of double bond at C1 position increases the anabolic activity. Example: methandrostenolone is more active than methyl testosterone.
- Replacement of carbon atom at C2 position by oxygen (e.g. oxandrolone) gives the oral anabolic activity.
- Presence of Oxygen at C3 and C17 are not essential for the androgenic activity.
- Presence of hydroxy group at C17 position has no androgenic or anabolic activity.

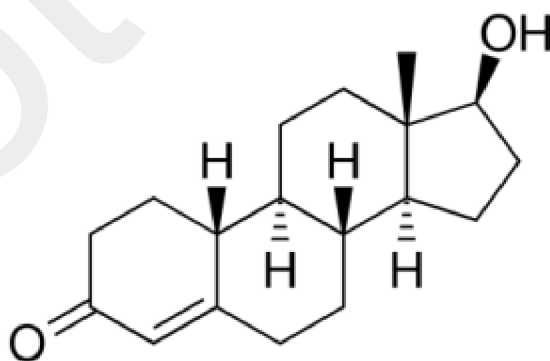
Uses:

Testosterone is used primarily to treat symptoms of sexual dysfunction in men. Its potential benefits include improved libido, increased bone mass, and increased sense of well-being.

Nandralone:

- Nandrolone is also known as 19-nortestosterone.
- It is an androgen and anabolic steroid (AAS) and is used in the form of esters such as nandrolone decanoate (brand name Deca-Durabolin) and nandrolone phenylpropionate (brand name Durabolin). Its IUPAC name is 19-norandrost-4-en-17 β -ol-3-one.

Structure of Nandralone:



Mechanism of action:

- Nandrolone binds to the androgen receptor to a greater degree than testosterone, but due to its inability to act on the muscle in ways unmediated by the receptor, has less overall effect on muscle growth.
- It is an androgen receptor agonist.

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Structure activity relationship:

- Steroidal skeleton is essential for activity.
- Saturation of ring A decreases the activity.
- Removal of the keto function removes androgenic activity.

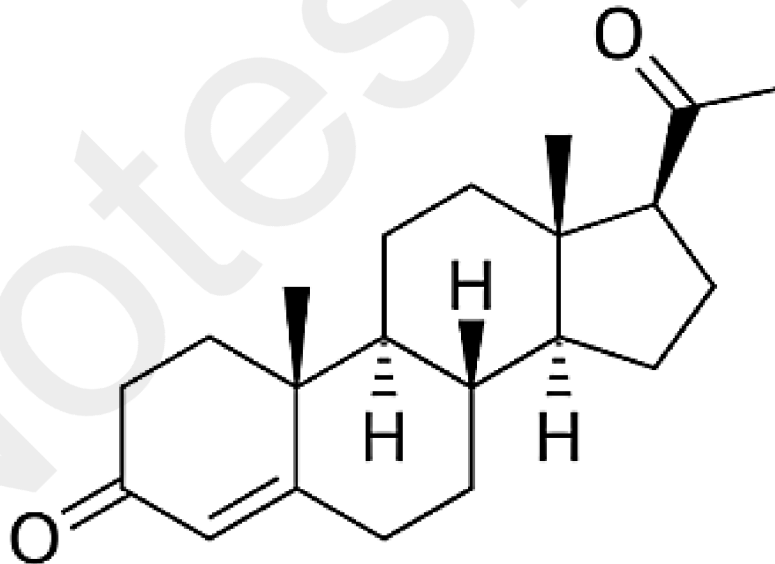
Uses:

- Nandrolone esters are used in the treatment of anemias, cachexia (wasting syndrome), osteoporosis, breast cancer.

Progesterones:

- Progesterones belong to a group of steroid hormones called the progestogens.
- **IUPAC Name:** (8S,9S,10R,13S,14S,17S)-17-acetyl-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta- [a] phenanthren-3-one

Structure of Progesterones:



Mechanism of action:

- Progesterone converts the endometrium to its secretory stage to prepare the uterus for implantation.
- At the same time progesterone affects the vaginal epithelium and cervical mucus, making it thick and impenetrable to sperm.

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Structure activity relationship:

- Steroidal skeleton is essential for activity.
- Saturation of ring-A decreases the activity.
- Removal of the keto function removes androgenic activity.
- Substitution at 17 α with ethynyl, methyl, ethyl group reduce the activity.

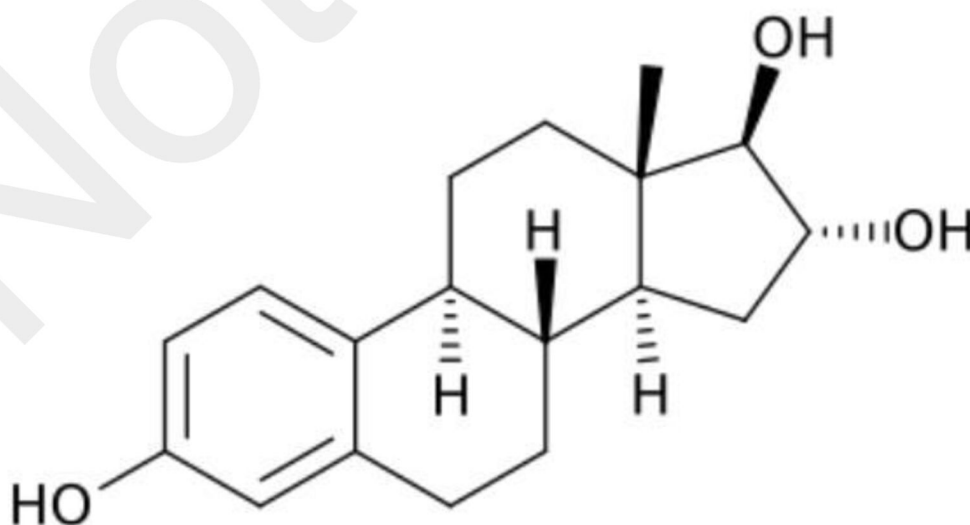
Uses:

- Progesterone is used in combination with estrogens mainly in hormone therapy for menopausal symptoms and low sex hormone levels in women.
- It is also used in women to support pregnancy and fertility and to treat gynecological disorders.

Oestriol:

- Estriol is the major estrogen involved in pregnancy and is produced naturally by the placenta and fetus.
- Estriol was first discovered in 1930.
- **IUPAC name:** 8R,9S,13S,14S,16R,17R)-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta [a]phenanthrene-3,16,17-triol.

Structure of Oestriol:



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Mechanism of action:

- Estriol acts as an antagonist of the G-protein-coupled estrogen receptor (GPER), a membrane estrogen receptor.
- Estriol has been found to inhibit estradiol-induced proliferation of triple-negative breast cancer cells through blockade of the GPER.

Structure activity relationship

- Aromatic ring with –OH at C-3 is essential for activity.
- Steroidal structure is essential for activity.
- Unsaturation of ring-B decreases the activity.

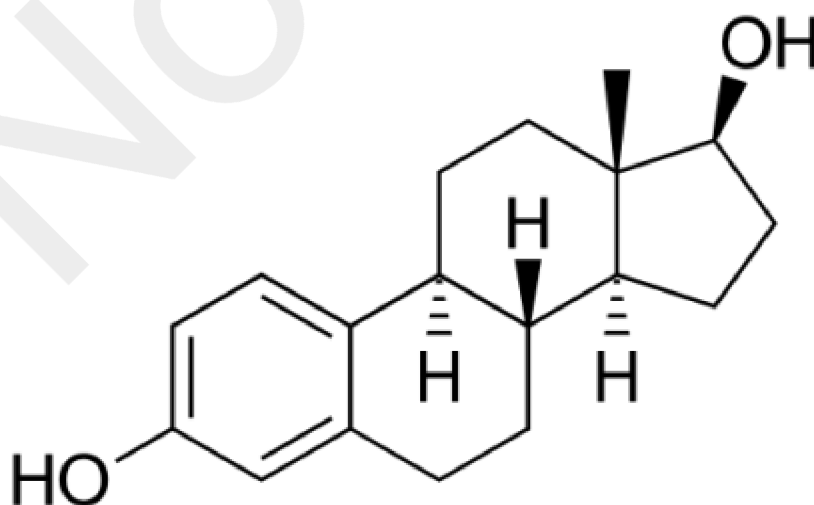
Uses:

- Estriol is used in menopausal hormone therapy to treat menopausal symptoms, such as hot flashes, vulvovaginal atrophy, and dyspareunia.

Oestradiol:

- Estradiol or oestradiol is an estrogen steroid hormone and the major female sex hormone.
- It is also used to treat low estrogen levels in women with ovarian failure.
- **IUPAC name:** (8R,9S,13S,14S,17S)-13-Methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]-phenanthrene-3,17-diol.

Structure of Oestradiol:



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Mechanism of action:

- Estradiol is a nuclear hormone as it acts on receptors present inside the cell that can activate or deactivate transcription in the nucleus.
- Estradiol interacts with a target cell receptor (E_{α} or E_{β}) within the cytoplasm of the cell.

Structure activity relationship:

- Aromatic ring with $-OH$ at C3 is essential for activity.
- Steroidal structure is essential for activity.
- Unsaturation of ring-B decreases the activity
- Methylation of $-OH$ at C3 make the compound orally active (e.g. Mesterolone).
- Insertion of $-OH$ group at C6, C7 and C11 position reduces estrogenic activity.

Uses:

- Estradiol is used to treat menopause symptoms such as hot flashes and vaginal changes, and to prevent osteoporosis (bone loss) in menopausal women.
- Estradiol is also used to treat low estrogen levels in women with ovarian failure.
- It is also indicated to treat certain types of breast cancer and prostate cancer.

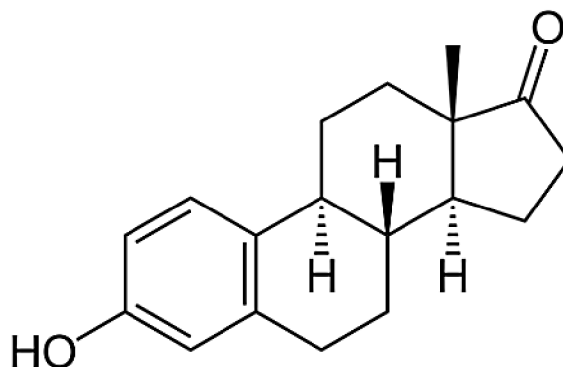
Oestrione:

- Oestrione is the major endogenous estrogens. It acts as both a precursor and metabolite of estradiol.
- It was discovered in 1929 independently by the American scientists Edward Doisy and Edgar Allen and the German biochemist Adolf Butenandt.

IUPAC name: (8R,9S,13S,14S)-3-hydroxy-13-methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]-phenanthren-17-one.

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Structure of Oestrone:



Mechanism of action:

- It is specifically act as an agonist of the estrogen receptors ER α and ER β .

Structure activity relationship

- Aromatic ring with -OH at C3 is essential for activity.
- Steroidal structure is essential for activity.
- Unsaturation of ring-B decreases the activity
- Insertion of -OH group at C6, C7 and C11 position reduces the estrogenic activity.

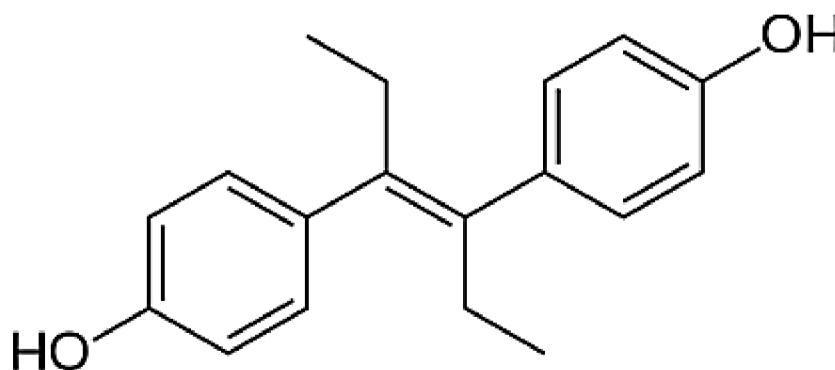
Uses:

- Estrone has been available as an injected estrogen for medical use in hormone therapy for menopausal symptoms.

Diethyl stilbestrol:

- Diethylstilbestrol is also known as stilbestrol or stilboestrol.

Structure of Diethyl stilbestrol:



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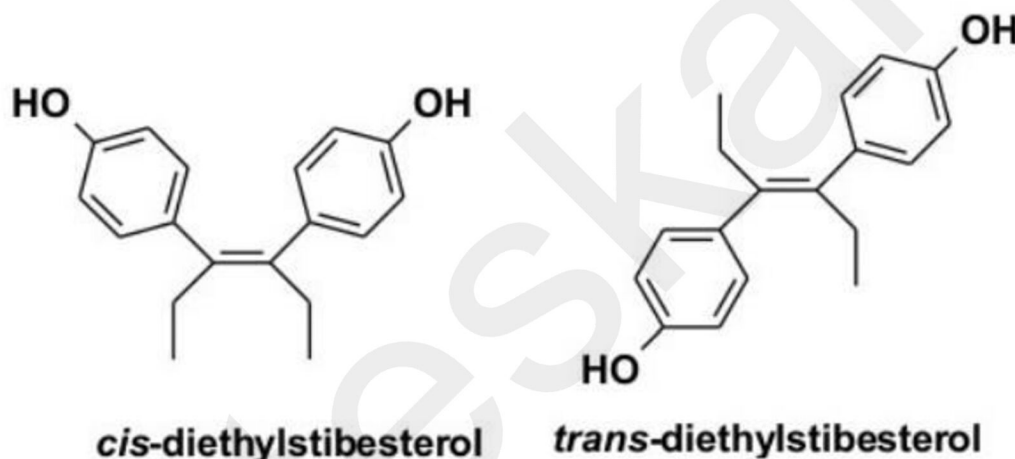
Mechanism of action:

Diethylstilbestrol inhibits the hypothalamic-pituitary-gonadal axis, thereby blocking the testicular synthesis of testosterone, lowering plasma testosterone, and inducing a chemical castration.

Structure activity relationship:

- Trans-diethylstilbestrol is more stable as compared to cis-diethylstilbestrol.
- Trans-diethylstilbestrol is more effective (estrogenic) as compared to cis-diethylstilbestrol due to steric factors.

Structure of Cis- and Trans-diethylstilbestrol:



Uses:

- Diethylstilbestrol is only used in the treatment of prostate cancer and less commonly breast cancer. It is also used in the treatment of prostate cancer in men.



Drugs for erectile dysfunction: Sildenafil, Tadalafil.

- Erectile dysfunction is defined as the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance.
- It is a common condition, particularly in men aged 40 and above, but it can affect men of all ages. While occasional difficulty with erections is normal, persistent ED may indicate underlying health issues or psychological concerns.

Causes:

- Stress
- Anxiety
- Depression
- Relationship problems
- Low self-esteem
- Unhealthy Life Style

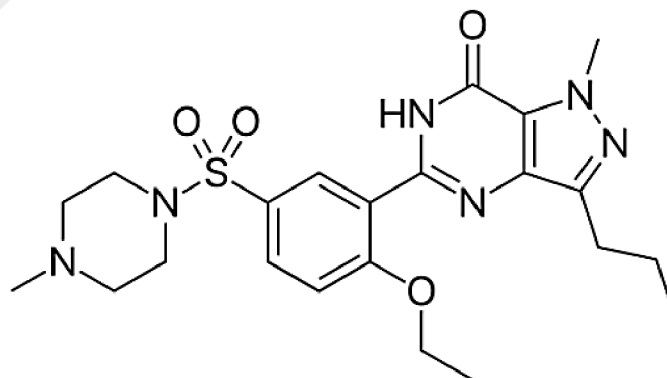
Drugs:

- Sildenafil,
- Tadalafil

Sildenafil:

- Sildenafil is sold under the brand name Viagra.
- This medication is most effective when taken on an empty stomach one hour before sex. It is taken by mouth or injection into a vein.
- **IUPAC Name:** 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

Structure of Sildenafil:



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Mechanism of action:

- Sildenafil acts by blocking phosphodiesterase-5 (PDE5), an enzyme that promotes breakdown of cyclic guanosine monophosphate (cGMP), which regulates blood flow in the penis.

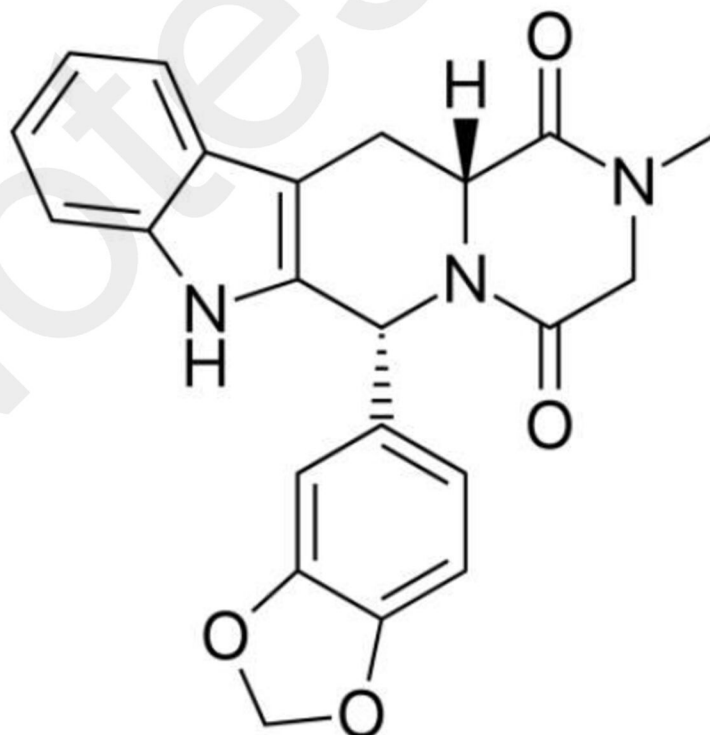
Uses:

- Sildenafil is used to treat male sexual function problems (impotence or erectile dysfunction-ED).

Tadalafil:

- Tadalafil is an orally administered drug used to treat male sexual function problems (impotence or erectile dysfunction-ED).
- Tadalafil is sold under the brand name Cialis. It is a pyrazinopyridoindole derivative.
- **IUPAC Name:** (2R,8R)-2-(2H-1,3-benzodioxol-5-yl)-6-methyl-3,6,17-triazatetracyclo[8.7.0.0³,⁸.0¹¹,¹⁶] heptadeca-1(10),11,13,15-tetraene-4,7-dione.

Structure:



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Mechanism of action:

- It is a phosphodiesterase-5 (PDE5) inhibitor. It works by increasing blood flow to the penis to help a man get and keep an erection.

Uses:

- It is used to treat erection problems (erectile dysfunction) and symptoms of an enlarged prostate (benign prostate enlargement).
- It's also sometimes used to treat pulmonary hypertension (high blood pressure in the blood vessels that supply the lungs).

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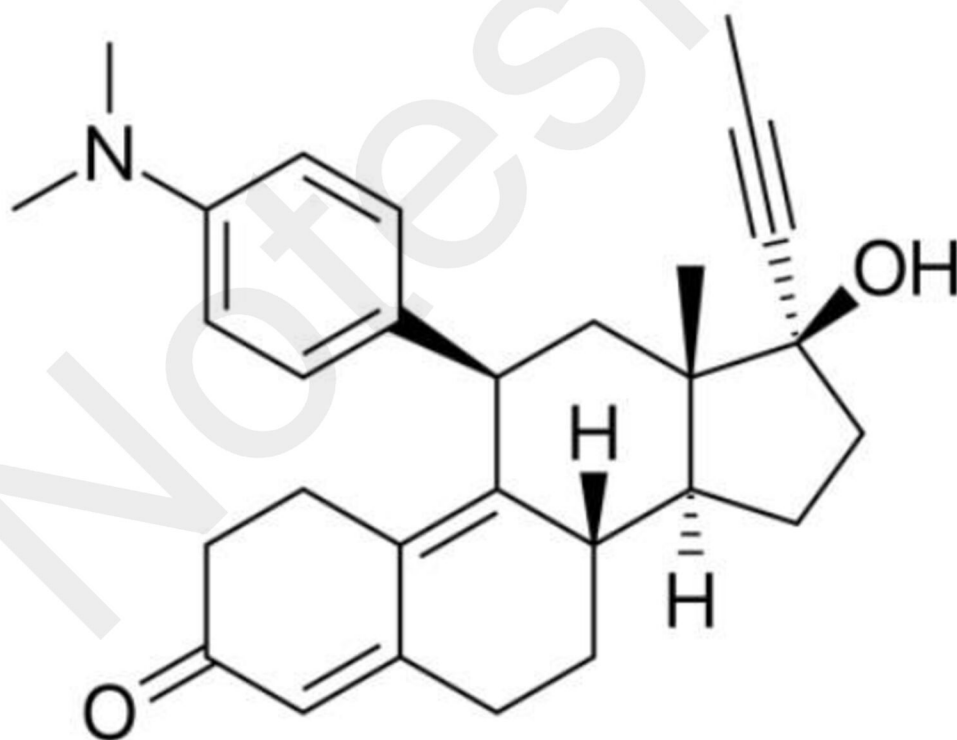
Oral contraceptives:

- Oral contraceptives (OCPs) are also known as birth control pills.
- These are medications taken by mouth for the purpose of birth control.
- There are various types of female oral contraceptive pill.
- Example: combined oral contraceptive pill contains estrogen and a progestin, progestogen-only pill and Ormeloxifene is a selective estrogen receptor modulator which offers the benefit of only having to be taken once a week.

Mifepristone:

- Mifepristone is a synthetic steroid and also known as RU-486.
- It is a medication mainly used in combination with misoprostol to bring about an abortion during pregnancy.
- **IUPAC Name:** 11 β --17 α -(1-propynyl)estra-4,9-dien-17 β -ol-3-one.

Structure:



Mechanism of action:

- Mifepristone is an anti-progestin that blocks the action of progesterone, a hormone necessary to maintain a pregnancy.

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- By blocking the action of progesterone, mifepristone alters the endometrium (the uterine lining), induces bleeding, and causes the uterine lining to shed.

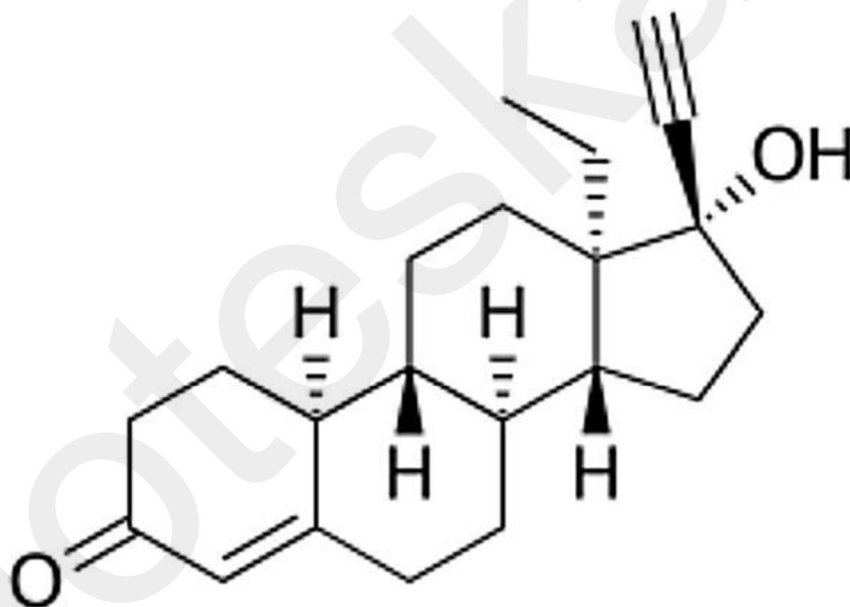
Uses:

- Mifepristone is used in combination with misoprostol (Cytotec) to end an early pregnancy.

Norgestrel:

- Norgestrel is a form of progestin hormone that prevents pregnancy.
- **IUPAC Name:** rac-13- ethyl-17 α -ethynyl-19-nortestosterone or rac-13-ethyl-17 α -ethynylestr-4-en-17 β -ol-3-one.

Structure:



Mechanism of action:

- It binds to the progesterone and estrogen receptors within the female reproductive tract and the mammary gland

Uses:

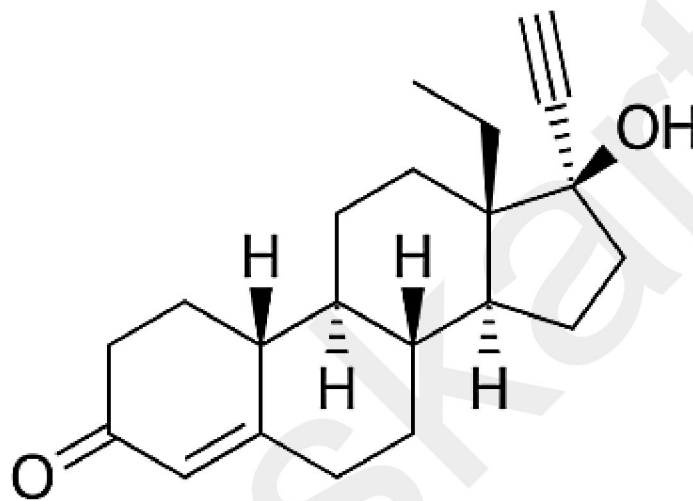
- It is a hormone that prevents pregnancy by making vaginal fluid thicker to help prevent sperm from reaching an egg (fertilization), and changing the lining of the uterus (womb) to prevent attachment of a fertilized egg.

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Levonorgestrol:

- Levonorgestrel (LNG) is a synthetic estrane steroid and a derivative of testosterone.
- It is used in contraception and hormone therapy.
- **IUPAC Name:** 17 α -ethynyl-18-methyl-19-nortestosterone or as 17 α ethynyl-18-methylestr-4-en-17 β -ol-3-one.

Structure:



Mechanism of action:

- It prevents fertilization by inhibiting the ovulation and thickening of cervical mucus.

Uses:

- Levonorgestrel is used to prevent pregnancy after unprotected sexual intercourse.



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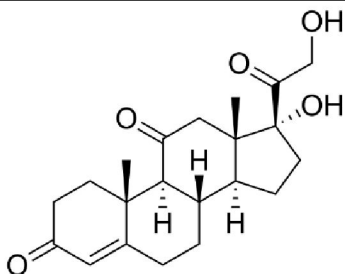
- **Corticosteroids:** Cortisone, Hydrocortisone, Prednisolone, Betamethasone, Dexamethasone

Corticosteroids:

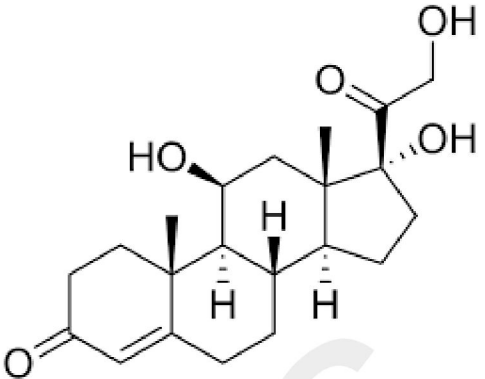
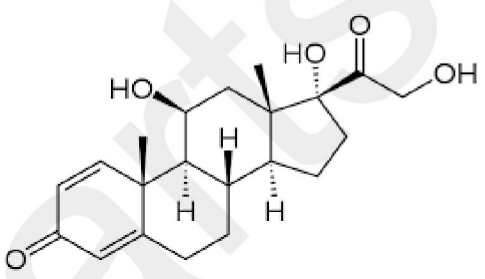
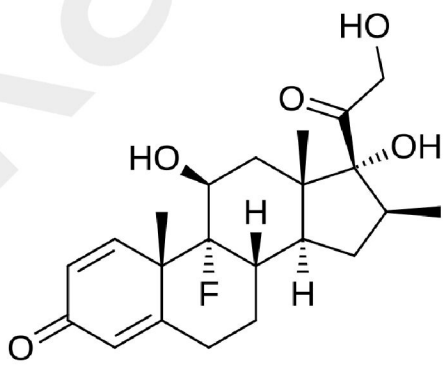
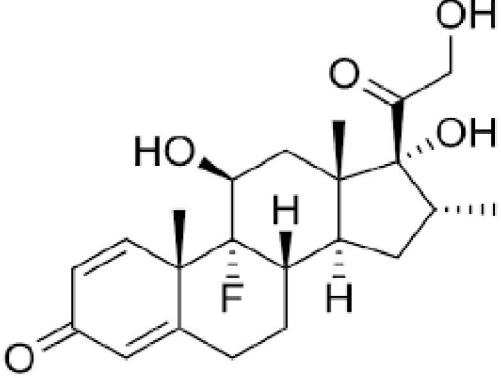
- Corticosteroids are the class of steroid hormones (C₂₁). These are produced in the adrenal cortex.
- These are the class of drugs that lower the inflammation in the body. They also reduce the activity of immune system.

Classification of Corticosteroids:

Corticosteroids			
Glucocorticoids		Mineralocorticoids	
Natural	Synthetic	Natural	Synthetic
Cortisone Hydrocortisone	Prednisone, Prednisolone, Triamcinolone, Betamethasone, Dexamethasone	Aldosterone, Deoxycorticosterone	Fludrocortisone

Drug	Mechanism of Action	Uses	Structure
Cortisone	Prodrug converted to hydrocortisone in the liver; binds glucocorticoid receptors to exert anti-inflammatory effects.	Adrenal insufficiency, rheumatoid arthritis, allergic conditions.	



Hydrocortisone	Directly active form; binds glucocorticoid receptors to modulate inflammatory pathways.	Inflammatory skin conditions, adrenal insufficiency, ulcerative colitis, asthma.	 <p>The chemical structure of Hydrocortisone is a steroid nucleus with a ketone group at C3, a double bond between C4 and C5, a hydroxyl group at C11, and a dihydroxyethyl side chain at C17.</p>
Prednisolone	Higher glucocorticoid activity; suppresses inflammatory response and cytokine production.	Severe allergies, autoimmune disorders, asthma, inflammatory bowel disease.	 <p>The chemical structure of Prednisolone is a steroid nucleus with a ketone group at C3, a double bond between C4 and C5, a hydroxyl group at C11, and a dihydroxyethyl side chain at C17. It differs from hydrocortisone by the absence of a hydroxyl group at C20.</p>
Betamethasone	Potent anti-inflammatory and immunosuppressive effects; longer duration of action.	Dermatitis, asthma, arthritis, prenatal lung maturation in preterm labor.	 <p>The chemical structure of Betamethasone is a steroid nucleus with a ketone group at C3, a double bond between C4 and C5, a hydroxyl group at C11, a methyl group at C13, a dihydroxyethyl side chain at C17, and a fluorine atom at C20.</p>
Dexamethasone	Very high anti-inflammatory potency; longer duration; suppresses ACTH production in feedback loops.	Brain edema, cancer-associated nausea, autoimmune diseases, COVID-19 severe inflammation.	 <p>The chemical structure of Dexamethasone is a steroid nucleus with a ketone group at C3, a double bond between C4 and C5, a hydroxyl group at C11, a methyl group at C13, a dihydroxyethyl side chain at C17, and a fluorine atom at C20. It differs from betamethasone by the absence of a hydroxyl group at C20.</p>

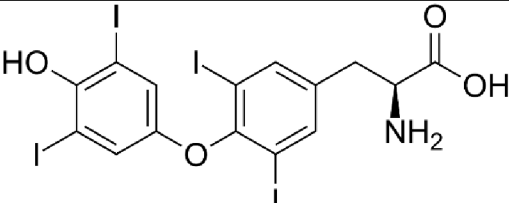
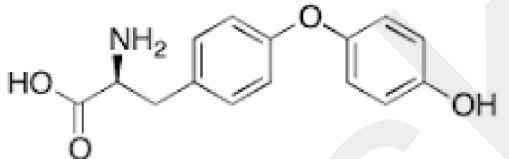
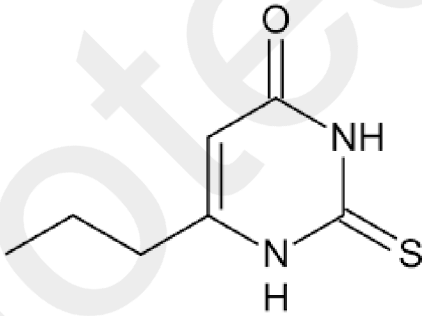
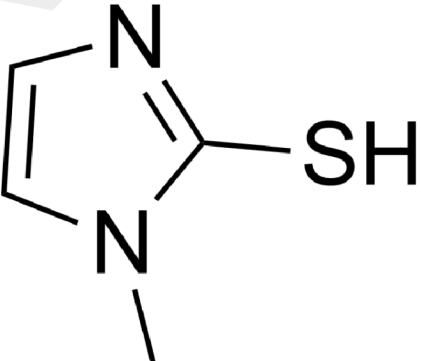


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- **Thyroid and antithyroid drugs:** L-Thyroxine, L-Thyronine, Propylthiouracil, Methimazol

Thyroid Drugs: L-Thyroxine, L-Thyronine.

Antithyroid drugs: Propylthiouracil, Methimazol

Drug	Structure	Mechanism of Action	Uses
L-Thyroxine		Synthetic T4; converted to active T3 in peripheral tissues, binds nuclear thyroid hormone receptors to regulate gene expression.	Hypothyroidism, thyroid hormone replacement therapy.
L-Thyronine		Synthetic T3; directly active form that modulates metabolism and protein synthesis via nuclear receptor binding.	Severe hypothyroidism (myxedema coma).
Propylthiouracil		Inhibits thyroid peroxidase enzyme, preventing iodination of tyrosine residues and synthesis of thyroid hormones; also inhibits T4 to T3 conversion.	Hyperthyroidism, Graves' disease.
Methimazole		Inhibits thyroid peroxidase enzyme, blocking hormone synthesis. More potent than propylthiouracil but lacks peripheral T4 to T3 inhibition.	Hyperthyroidism, Graves' disease.

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