Bachelor of Pharmacy (B. Pharm)

SEMESTER:5TH

Subject: MEDICINAL CHEMISTRY-II

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UNIT:IV

UNIT: IV

4. Drugs acting on Endocrine system

4.1. Introduction to steroids

4.1.1. Classification of Steroids

4.1.2. Nomenclature,

4.1.3. Stereochemistry

4.1.4. Metabolism of steroids

4.2. Sex hormones:

4.2.1. Testosterone,

4.2.2. Nandralone,

4.2.3. Progestrones,

4.2.4. Oestriol,

4.2.5. Oestradiol,

4.2.6. Oestrione,

4.2.7. Diethyl stilbestrol.

4.3. Drugs for erectile dysfunction

4.3.1. Sildenafil

4.3.2. Tadalafil

4.4. Oral contraceptives

4.4.1. Mifepristone

4.4.2. Norgestril

4.4.3. Levonorgestrol

4.5. Corticosteroids

4.5.1. Cortisone

4.5.2. Hydrocortisone

4.5.3. Prednisolone

4.5.4. Betamethasone

4.5.5. Dexamethasone

4.6. Thyroid and antithyroid drugs

4.6.1. L-Thyroxine

4.6.2. L-Thyronine

4.6.3. Propylthiouracil

4.6.4.Methimazole

4. Endocrine system

The endocrine system helps to maintain internal homeostasis through the use of endogenous chemicals known as hormones. A hormone is typically regarded as a chemical messenger that is released into the bloodstream to exert an effect on target cells located some distance from the hormonal release site. The endocrine system is a series of glands that produce hormones which regulate respiration, metabolism, growth and development, tissue function, sexual function, reproduction etc. Endocrine glands are ductless glands of the endocrine system that secrete their products, hormones, directly into the blood. The major glands of the endocrine system include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid gland, parathyroid gland, hypothalamus and adrenal glands (**Fig. 1)**.

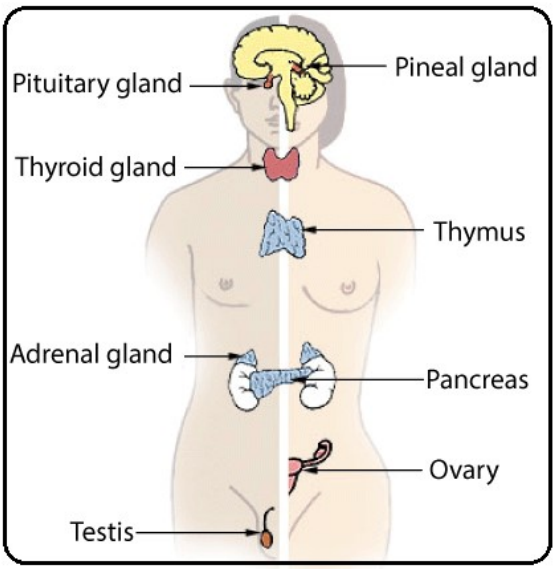


Fig. 1: Endocrine system.

4.1. Introduction to steroids

Steroids are the class of naturally occurring organic compounds with four rings arranged in a specific molecular configuration. Steroids exhibit two principal biological functions such as important components of cell membranes which alter membrane fluidity and as signaling molecules.

4.1.1. Classification of Steroids

Anabolic Steroids: Interact with androgen receptor and enhance muscle mass and male sex hormones

Glucocorticoids: Regulate metabolism and immune function and anti-inflammatory activity

Mineralocorticoids: Maintain blood volume and renal excretion

Progestins: Development of female sex organs

Phytosteroids: Plant steroids

Ergosteroids: Steroids of the fungi and vitamin D

4.1.2. Nomenclature of steroids

Beginning in the 1950s, nomenclature rules for steroids were being developed, and the most recent IUPAC-IUB Joint Commission rules for systematic steroid nomenclature were published in 1989. 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) (**Fig. 2**). Steroids vary by the functional groups attached to this four ring core and by the oxidation state of the rings.

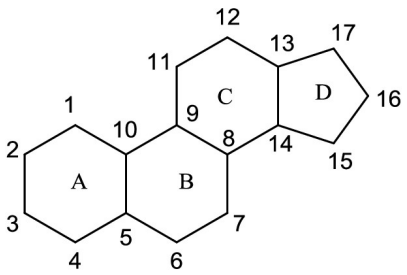


Fig. 2: Structure of Cyclopentanoperhydrophenanthrene ring.

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 indicate 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.

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) (**Fig. 3**).

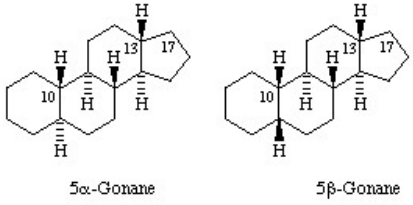


Fig. 3: Structure of Gonane.

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 (**Fig. 4**). E.g. 5 (α or β) estrane (C =18)

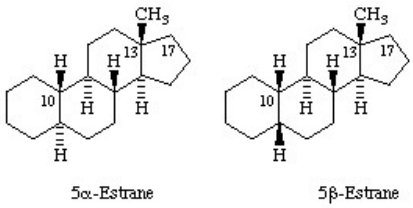


Fig. 4: Structure of Estrane.

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

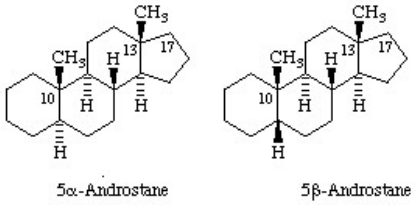


Fig. 5: Structure of Androstane.

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 5α-pregnane and 5β-pregnane (C=21).

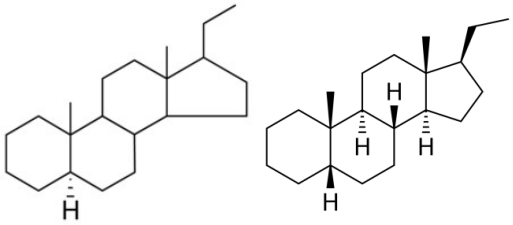


Fig. 6: Structure of Pregnane.

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 (**Fig. 7**).

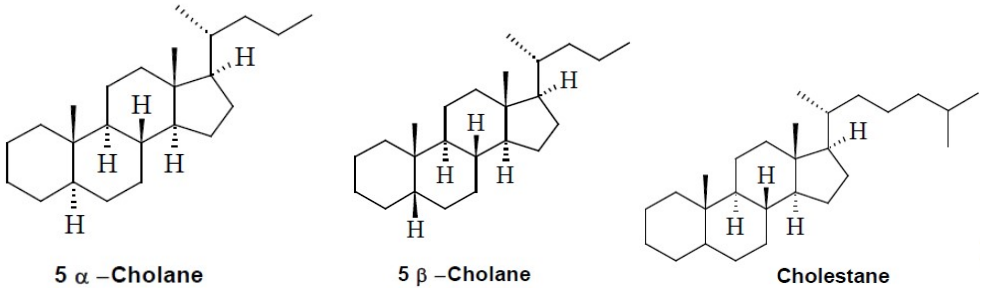


Fig. 7: Structure of Cholane & Cholestane.

4.1.3. 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 (**Fig. 8**).

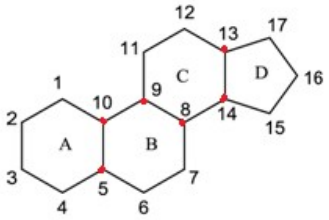


Fig. 8: Skeleton of steroids with asymmetric centers.

Cholestane , androstane and pregnane exist in two conformations such as chair form and boat form. Chair form is more stable then boat form due to less angle strength, therefore all cyclohexane ring in steroid nucleus exist in the chair form (**Fig. 9**).

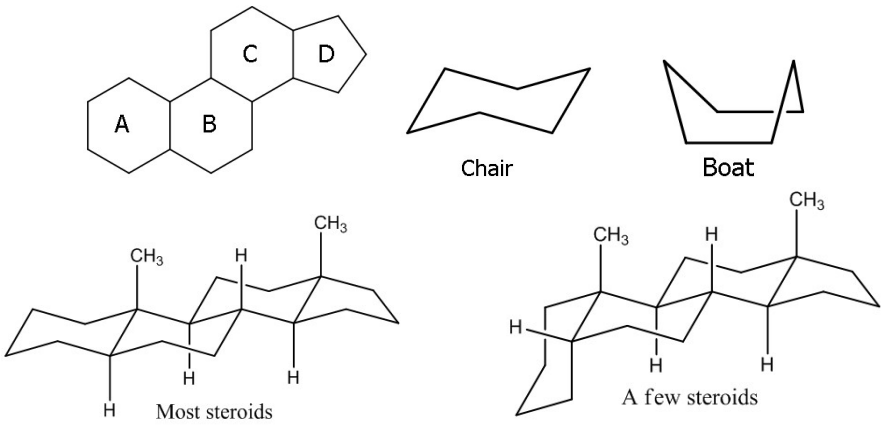


Fig. 9: Conformations of steroids.

The absolute stereochemistry of the molecule and any substituent is shown with solid bond (β-configuration) and dotted bond (α-configuration) (**Fig. 10**).

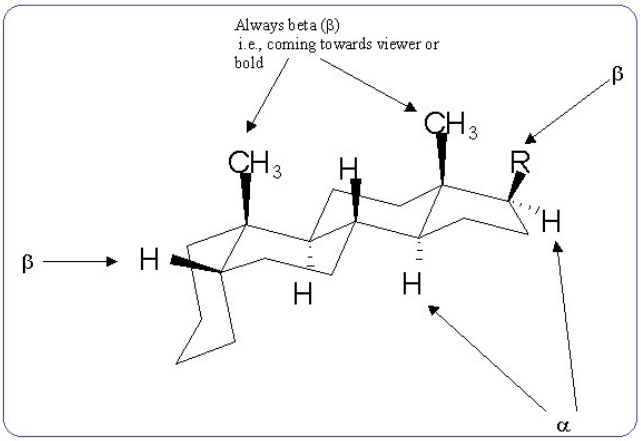


Fig. 10: Configuration of steroids.

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 (**Fig. 11**).

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

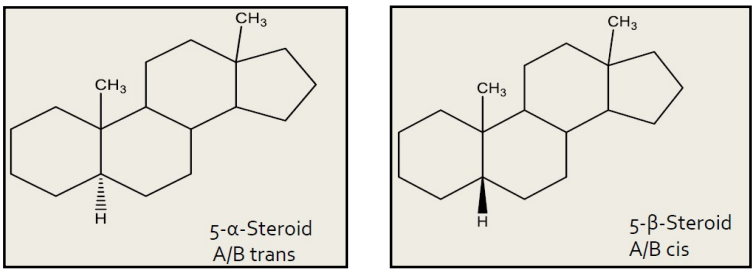


Fig. 11: Structure of 5-α and 5-β steroid.

If A/B fusion cis and trans both position possible or position is unknown, it is indicated by waving lines/bonds (**Fig. 12**).

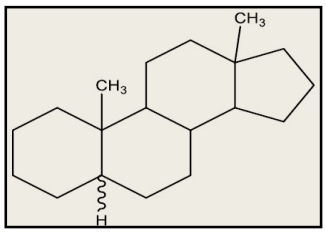


Fig. 12: Structure of Trans/cis form of steroid.

4.1.4. Metabolism of steroids

Steroids are primarily oxidized by cytochrome P450 oxidase enzymes, such as CYP3A4. These reactions introduce oxygen into the steroid ring, allowing the cholesterol to be broken up by other enzymes into bile acids. These acids can then be eliminated by secretion from the liver in bile. The liver catalyses extensive phase 1 and phase 2 metabolisms of steroids, thereby regulating their activity and clearance. Hepatic phase 1 metabolism of steroids includes the following types of reactions: (1) 5α/β reduction of the Δ^4-double bond followed by 3 α/β -reduction of the 3-ketone; (2) oxidations by a large set of hepatic P450 enzymes; (3) HSD reactions of 11b- and 17b-hydroxyls if available and of hydroxyls introduced by P450s (**Fig. 13**).

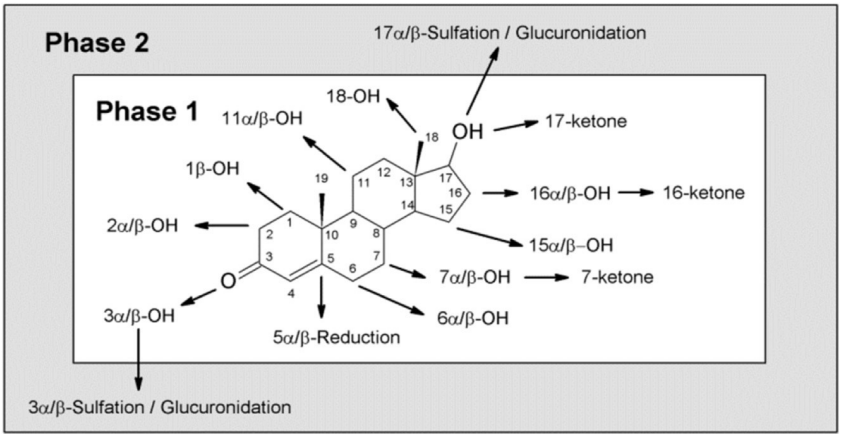


Fig. 13: Metabolism of steroids.

4.2. Sex hormones: Sex hormones are steroid hormone (such as estrogen or testosterone) which are produced especially by the ovaries, testes, or adrenal cortex and affects the growth or function of the reproductive organs or the development of secondary sex characteristics. Estrogens and progestins are female sex hormones and androgens are male sex hormones. These hormones are synthesized from cholesterol mainly in the gonads and adrenal cortex.

4.2.1. Testosterone

Testosterone is the primary male sex hormone and anabolic steroid. In male humans, testosterone plays a key role in the development of male reproductive tissues such as testes and prostate, as well as promoting secondary sexual characteristics such as increased muscle and bone mass, and the growth of body hair. Its IUPAC name is 17β-Hydroxyandrost-4-en-3-one (**Fig. 14**).

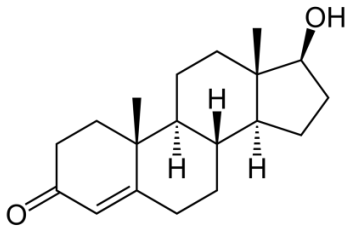


Fig. 14: Structure of Testosterone.

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 andostane skeleton for its biological activity.
- Introduction of double bond at C_1 position increases the anabolic activity. Example: methandrostenolone is more active than methyl testosterone.
- Replacement of carbon atom at C_2 position by oxygen (e.g. oxandrolone) gives the oral anabolic activity.
- Presence of Oxygen at C_3 and C_{17} are not essential for the androgenic activity.
- Presence of hydroxy group at C_{17} position has no androgenic or anabolic activity.

Metabolism

Testosterone is converted into dihydrotestosterone (active metabolite) and estradiol in presence of 5α-reductase and aromatase respectively (**Fig. 15**).

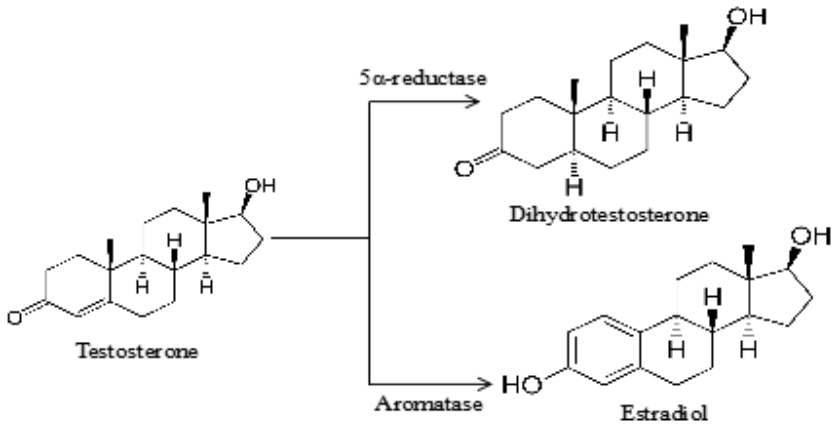


Fig. 15: Metabolism of Testosterone.

Adverse effect

Common side effects of testosterone include acne, swelling, and breast enlargement in men. Serious side effects may include liver toxicity, heart disease, and behavioral changes.

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

4.2.2. 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-17β-ol-3-one (**Fig. 16**).

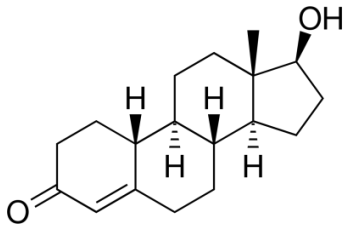


Fig. 16: Structure of Nandralone.

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.

Structure activity relationship

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

Metabolism

Nandrolone is metabolized by the enzyme 5α-reductase. It is less susceptible to metabolism by 5α-reductase and 17β-hydroxysteroid dehydrogenase than testosterone.

Adverse effect

Adverse effects of nandrolone esters include symptoms of masculinization like acne, increased hair growth, voice changes etc.

Uses

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

4.2.3. Progesterones

Progesterones belong to a group of steroid hormones called the progestogens. Its IUPAC name is (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 (**Fig. 17**).

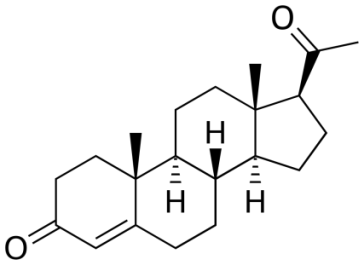


Fig. 17: Structure of Progesterones.

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.

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 17α with ethynyl, methyl, ethyl group reduce the activity.

Metabolism

The metabolism of progesterone is rapid and extensive and occurs mainly in the liver. The enzyme 5α reductase is responsible for transforming testosterone into the more potent androgen 5α-dihydrotestosterone (**Fig. 18**).

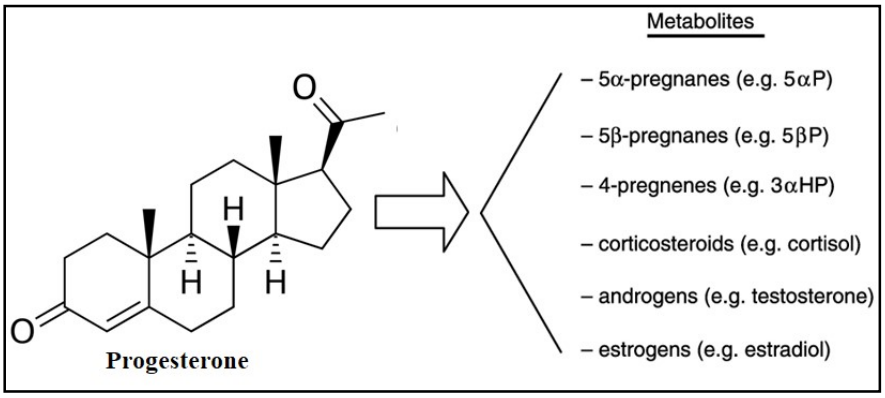


Fig. 18: Metabolism of progesterone.

Adverse effect

The commonly reported side effects of progesterone include abdominal cramps, depression, dizziness, and headache. Other side effects include anxiety, cough, diarrhea, fatigue, musculoskeletal pain, nausea, bloating, and irritability.

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.

4.2.4. Oestriol

Estriol is the major estrogen involved in pregnancy and is produced naturally by the placenta and fetus. Estriol was first discovered in 1930. Its IUPAC name is 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 (**Fig. 19**).

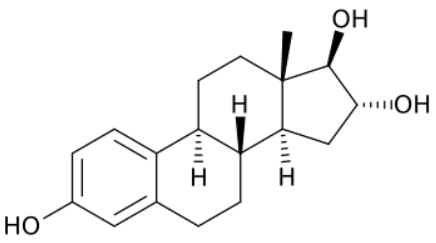


Fig. 19: Structure of Oestriol.

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

Metabolism

Estriol is extensively metabolized via conjugation, including glucuronidation and sulfation. Glucuronidation of estriol takes place mainly in the intestinal mucosa, while sulfation occurs in the liver.

Adverse effect

Estriol is well-tolerated and produces relatively few adverse effects. Side effects may include breast tenderness, vaginal discomfort and discharge, and endometrial hyperplasia.

Uses

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

4.2.5. 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. Its IUPAC name is (8R,9S,13S,14S,17S)-13-Methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]-phenanthrene-3,17-diol (**Fig. 20**).

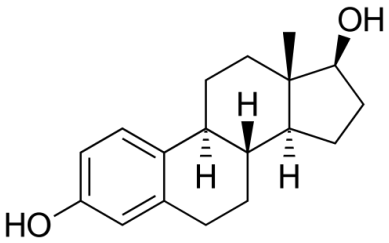


Fig. 20: Structure of Oestradiol

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 (Erα or Erβ) within the cytoplasm of the cell.

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
- Methylation of –OH at C_3 make the compound orally active (e.g. Mesterolone).
- Insertion of –OH group at C_6, C_7 and C_{11} position reduces estrogenic activity.

Metabolism

Estradiol undergoes metabolism via hydroxylation, sulfation, glucuronidation in Liver.

Adverse effect

Common side effects include headache, breast pain, irregular vaginal bleeding or spotting, stomach/abdominal cramps, bloating, nausea and vomiting, and hair loss.

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.

4.2.6. 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. Its IUPAC name is(8R,9S,13S,14S)-3-hydroxy-13-methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]-phenanthren-17-one (**Fig. 21**).

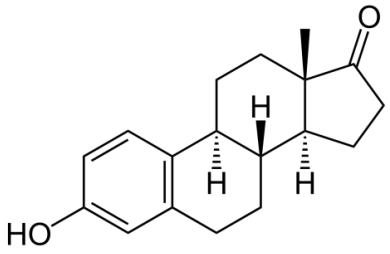


Fig. 21: Structure of Oestrione.

Mechanism of action

It is specifically act as an agonist of the estrogen receptors ERα and ERβ.

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
- Insertion of –OH group at C_6, C_7 and C_{11} position reduces the estrogenic activity.

Metabolism

Oestrione is metabolized into estradiol by 17β-HSD (Hydroxy steroid dehydrogenase) in the liver. Oestrione is conjugated into estrogen conjugates such as estrone sulfate and estrone glucuronide by sulfotransferases and glucuronidases. It can also be hydroxylated by cytochrome P450 enzymes into catechol estrogens such as 2-hydroxyestrone and 4-hydroxyestrone or into estriol. These transformations take place predominantly in the liver.

Adverse effect

Common side effects include spotting, changes in vaginal discharge, abdominal pain or cramps, bloating, nausea, vomiting and breast tenderness.

Uses

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

4.2.7. Diethyl stilbestrol

Diethylstilbestrol is also known as stilbestrol or stilboestrol (**Fig. 22**). It is a synthetic, nonsteroidal estrogen medication. It was first marketed for medical use in 1939. It was approved by the United States Food and Drug Administration (FDA) on September 19, 1941 in tablets formulation up to 5 mg for four indications such as gonorrheal vaginitis, atrophic vaginitis, menopausal symptoms, and postpartum lactation suppression to prevent breast engorgement.

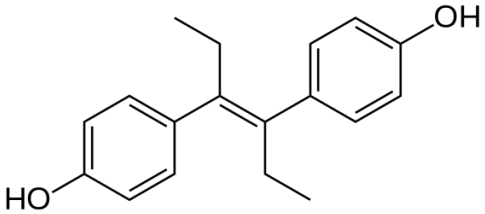


Fig. 22: Structure of Diethyl stilbestrol.

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 (**Fig. 23**).
- Trans-diethylstilbestrol is more effective (estrogenic) as compared to cis-diethylstilbestrol due to steric factors.

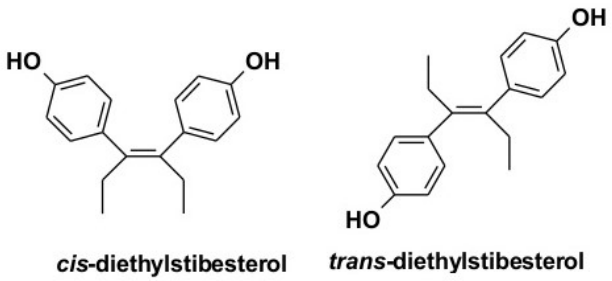


Fig. 23: Structure of Cis- and Trans-diethylstilbestrol.

Metabolism: Diethylstilbestrol is metabolized by hydroxylation, oxidation, glucuronidation in liver.

Adverse effect: It is associated with high rates of side effects including nausea, vomiting, abdominal discomfort, headache, and bloating.

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.

4.3. Drugs for erectile dysfunction

Erectile dysfunction (ED) is the inability to get or keep an erection firm enough to have sexual intercourse. It is sometimes referred as impotence. Many men experience it during the time of stress. Patients suffering from erectile dysfunction should first be evaluated for any underlying physical and psychological conditions.

4.3.1. 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. Its IUPAC name is 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (**Fig. 24**).

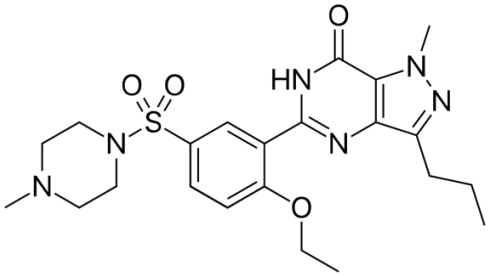


Fig. 24: Structure of Sildenafil.

Mechanism of action

Sildenafil acts by blocking phosphodiesterase-5 (PDE_5), an enzyme that promotes breakdown of cyclic guanosine monophosphate (cGMP), which regulates blood flow in the penis.

Metabolism

Sildenafil is broken down in the liver by hepatic metabolism using cytochrome p450 enzymes, mainly CYP450 3A4 (major route), but also by CYP2C9 (minor route) hepatic isoenzymes.

Adverse effect

Dizziness, headache, flushing, or stomach upset may occur. Vision changes such as increased sensitivity to light, blurred vision, or trouble telling blue and green colors apart may also occur.

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

4.3.2. 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. Its IUPAC name is (2R,8R)-2-(2H-1,3-benzodioxol-5-yl)-6-methyl-3,6,17-triazatetracyclo[8.7.0.0^{3},^{8}.0^{11},^{16}] heptadeca-1(10),11,13,15-tetraene-4,7-dione (**Fig. 25**).

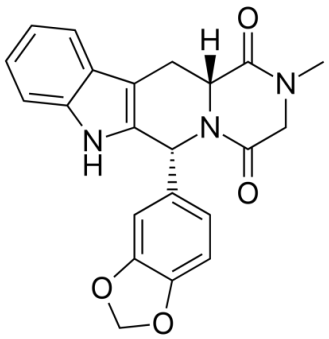


Fig. 25: Structure of Tadalafil.

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.

Metabolism

Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively.

Adverse effect: Headache, stomach upset, back pain, muscle pain, stuffy nose, flushing, or dizziness may occur.

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).

4.4. Oral contraceptives

Oral contraceptives (OCPs) are also known as birth control pills. Thease 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.

Sometimes, emergency contraception pills are taken at the time of intercourse, or within a few days afterwards. Example: Levonorgestrel, sold under the brand name Plan B, Ulipristal acetate, Mifepristone and misoprostol, when used in combination, are more than 95% effective during the first 50 days of pregnancy.

4.4.1. 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. Its IUPAC name is 11β--17α-(1-propynyl)estra-4,9-dien-17β-ol-3-one (**Fig. 26**).

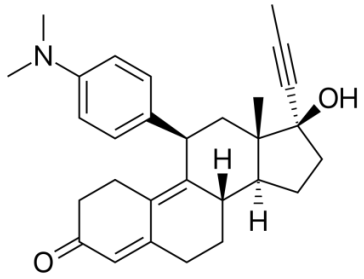


Fig. 26: Structure of Mifepristone .

Mechanism of action

Mifepristone is an anti-progestin that blocks the action of progesterone, a hormone necessary to maintain a pregnancy. By blocking the action of progesterone, mifepristone alters the endometrium (the uterine lining), induces bleeding, and causes the uterine lining to shed.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain.

Adverse effect: Nausea, vomiting, diarrhea, weakness, or dizziness may occur. Bleeding and cramping are expected during this treatment.

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

4.4.2. Norgestril

Norgestrel is a form of progestin hormone that prevents pregnancy. Chemically, it is also known as rac-13-ethyl-17α-ethynyl-19-nortestosterone or rac-13-ethyl-17α-ethynylestr-4-en-17β-ol-3-one (**Fig. 27**).

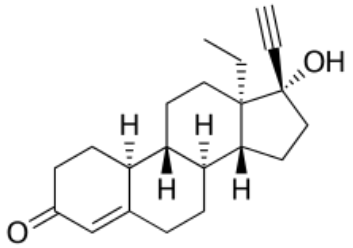


Fig. 27: Structure of Norgestril.

Mechanism of action

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

Metabolism: The metabolism of Norgestrel can be increased when combined with Estradiol dienanthate.

Adverse effect

Nausea, vomiting, stomach cramping/bloating, dizziness, headache, tiredness, breast tenderness, decrease in breast size, acne, oily scalp, hair loss, weight gain, and vaginal infections may occur.

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.

4.4.3. Levonorgestrol

Levonorgestrel (LNG) is a synthetic estrane steroid and a derivative of testosterone. It is used in contraception and hormone therapy. Chemically, it is 17α-ethynyl-18-methyl-19-nortestosterone or as 17α-ethynyl-18-methylestr-4-en-17β-ol-3-one (**Fig. 28**).

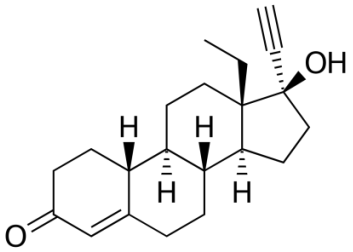


Fig. 28: Structure of Levonorgestrol.

Mechanism of action: It prevents fertilization by inhibiting the ovulation and thickening of cervical mucus.

Metabolism: Levonorgestrel is metabolized in the liver, via reduction, hydroxylation, and conjugation (specifically glucuronidation and sulfation). Oxidation occurs primarily at the C2α and C16β positions, while reduction occurs in the A ring.

Adverse effect

Nausea, vomiting, abdominal pain, tiredness, dizziness, changes in vaginal bleeding, breast tenderness, diarrhea, or headache may occur.

Uses: Levonorgestrel is used to prevent pregnancy after unprotected sexual intercourse.

4.5. 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.

Table 1. Classification of Corticosteroids.

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

4.5.1. Cortisone

Cortisone is corticosteroid hormone (glucocorticoid) of pregnane type. It is released by the adrenal gland. Its IUPAC Name is (8S,9S,10R,13S,14S,17R)-17-hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-1,2,6,7,8,9,12,14,15,16-decahydro-cyclopenta[a]phenanthrene-3,11-dione (**Fig. 29**).

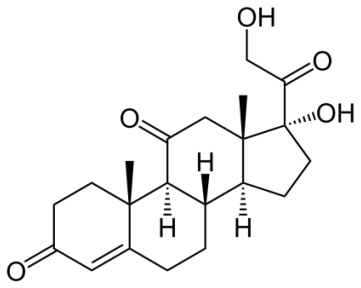


Fig. 29: Structure of Cortisone.

Mechanism of action

Cortisone acetate binds to the cytosolic glucocorticoid receptor. After binding the receptor the newly formed receptor-ligand complex translocates itself into the cell nucleus, where it binds to many glucocorticoid response elements (GRE) in the promoter region of the target genes.

Metabolism

Corticosteroids are metabolized through enzymatic transformations that diminish their physiologic activity and increase water solubility to enhance their urinary excretion. The majority of serum cortisol is reduced to dihydrocortisol and then to tetrahydrocortisol, which is then conjugated to glucuronic acid.

Adverse effect: Fluid retention, causing swelling in lower legs. Problems with mood swings, memory and behavior and other psychological effects, such as confusion or delirium.

Uses: Cortisone is used as an anti-inflammatory medication.

4.5.2. Hydrocortisone

Hydrocortisone is a class of corticosteroids. It is used topically to treat redness, swelling, itching, and discomfort of various skin conditions. Chemically, it is 11β,17α,21-Trihydroxypregn-4-ene-3,20-dione (**Fig. 30**).

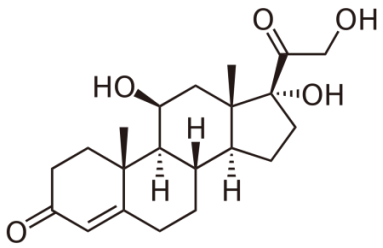


Fig. 30: Structure of Hydrocortisone.

Mechanism of action

Hydrocortisone binds to the glucocorticoid receptor leading to downstream effects such as inhibition of phospholipase A2, NF-kappa-B, other inflammatory transcription factors, and the promotion of anti-inflammatory genes.

Metabolism: It is metabolized in the liver to inactive glucuronide and sulfate metabolites.

Adverse effect: Nausea, heartburn, headache, dizziness, menstrual period changes, trouble sleeping, increased sweating, or acne may occur.

Uses: Hydrocortisone topical is used to treat redness, swelling, itching, and discomfort of various skin conditions.

4.5.3. Prednisolone

Prednisolone is a glucocorticoid. Chemically, it is 11,17-Dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydrocyclopenta[a] phenanthren-3-one (**Fig. 31**). It is a medication used to treat certain types of allergies, inflammatory conditions, autoimmune disorders, and cancers.

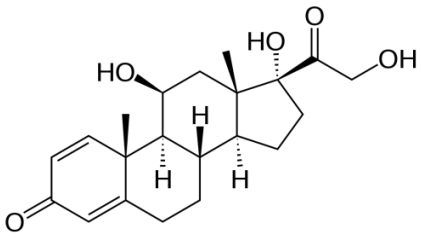


Fig. 31: Structure of Prednisolone.

Mechanism of action

It decreases the inflammation via suppression of the migration of polymorphonuclear leukocytes and reversing increased capillary permeability.

Metabolism

It is metabolized in liver to active metabolite prednisolone, which is then metabolized to inactive glucuronide and sulfate metabolites.

Adverse effect: Nausea, heartburn, headache, dizziness, menstrual period changes, trouble sleeping, increased sweating, or acne may occur.

Uses

- Prednisolone is used to treat allergies, blood disorders, skin diseases, infections, certain cancers.
- It is also used to prevent organ rejection after a transplant.
- It helps to reduce inflammation.

4.5.4. Betamethasone

Betamethasone is in a class of corticosteroids (**Fig. 32**). It is a steroid medication. It is used for a number of diseases such as rheumatoid arthritis, systemic lupus erythematosus and skin diseases like dermatitis.

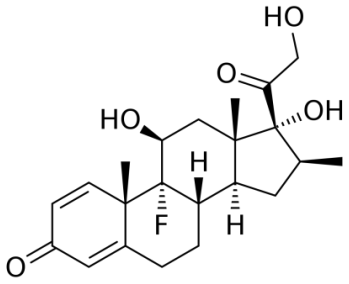


Fig. 32: Structure of Betamethasone.

Structure-activity relationship (SAR) Study

- Presence of keto (C=O) group and double bond between C_4 and C_5 is essential for both gluco and mineralo corticoid activities (**Fig. 33**).
- Presence of double bond between C_1 and C_2 is essential for glucocorticoid activity.

- Presence of 11β-hydroxy is essential for glucocorticoid activity.

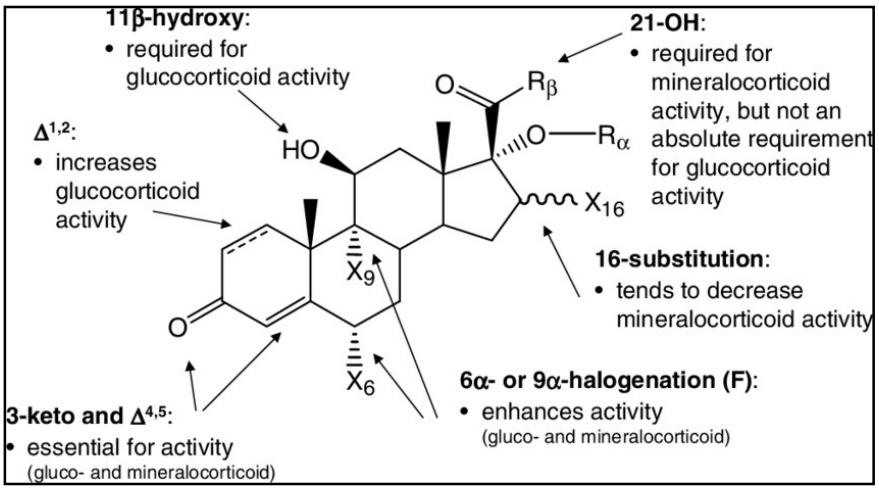


Fig. 33: SAR Study of Betamethasone.

Mechanism of action

Betamethasone binds to specific intracellular glucocorticoid receptors and subsequently binds to DNA to modify gene expression. The synthesis of certain anti-inflammatory proteins is induced while the synthesis of certain inflammatory mediators is inhibited.

Metabolism: It is metabolized in the liver to inactive glucuronide and sulfate metabolites.

Adverse effect: Common side effects of betamethasone include abdominal bloating, abdominal fat deposits, abnormal hair growth.

Uses: Betamethasone is used topically to treat itching, redness, dryness, crusting, scaling, inflammation, and discomfort of various skin conditions, including psoriasis and eczema.

4.5.5. Dexamethasone

Dexamethasone is a type of corticosteroid medication. It is used in the treatment of rheumatic problems, skin diseases, allergies, asthma, chronic obstructive lung disease etc. Its IUPAC Name is (1R,2R,3aS,3bS,9aS,9bR,10S,11aS)-9b-fluoro-1,10-dihydroxy-1-(2-hydroxyacetyl)-2,9a,11a-trimethyl-1H,2H,3H,3aH,3bH,4H,5H,7H,9aH,9bH,10H,11H,11aH-cyclopenta[a]phenanthren-7-one (**Fig. 34**).

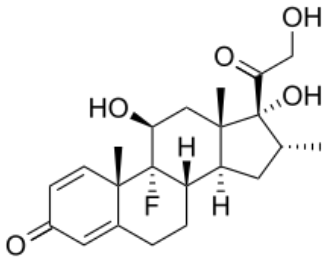


Fig. 34: Structure of Dexamethasone.

Mechanism of action

- It inhibits phospholipase A_2, which decreases the formation of arachidonic acid derivatives.
- It inhibits NF-Kappa B and other inflammatory transcription factors.
- It promotes anti-inflammatory genes like interleukin-10.

Metabolism

- Dexamethasone is 6-hydroxylated by CYP3A4 to 6α- and 6β-hydroxydexamethasone.
- Dexamethasone is reversibly metabolized to 11-dehydrodexamethasone by corticosteroid 11-beta-dehydrogenase isozyme-2 and can also be converted back to dexamethasone by Corticosteroid 11-beta-dehydrogenase isozyme 1.

Adverse effect: The following side effects are common for patients taking dexamethasone.

- Increased appetite.
- Irritability.
- Difficulty sleeping (insomnia)
- Swelling in your ankles and feet (fluid retention)
- Heartburn.
- Muscle weakness.
- Impaired wound healing.
- Increased blood sugar levels.

Uses: It relieves inflammation (swelling, heat, redness, and pain) and is used to treat certain forms of arthritis.

4.6. Thyroid and antithyroid drugs

The thyroid is a butterfly-shaped gland that sits low on the front of the neck. Thyroid has two side lobes, connected by a bridge (isthmus) in the middle (**Fig. 35**).

The thyroid gland consists of 2 types of cells.

- Follicular cells: These are more abundant, and the major secretory cells. They secrete Thyroid hormone.
- Parafollicular cells or C-cells: These are fewer in number & interspersed. They secrete Calcitonin.

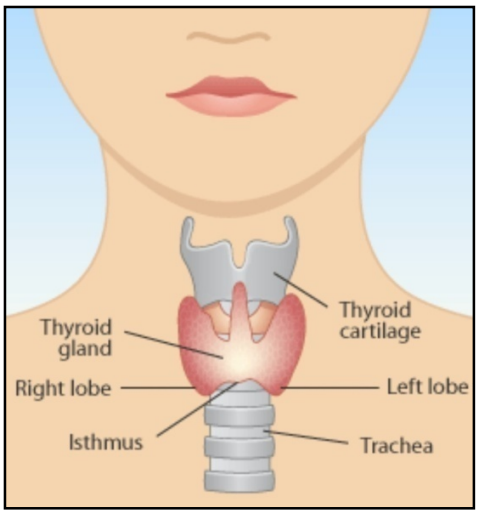
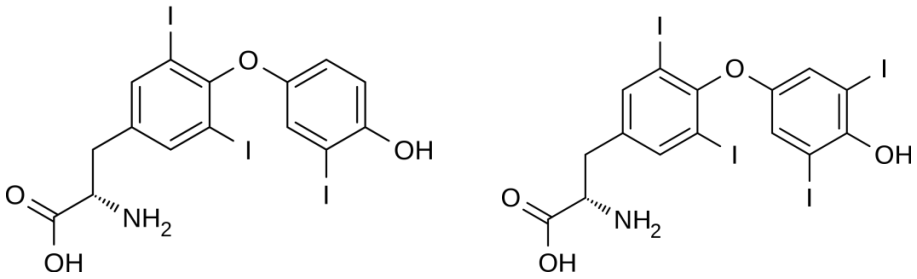


Fig. 35: Thyroid gland.

There are two types of thyroid hormones produced and released by the thyroid gland namely triiodothyronine (T_3) and thyroxine (T_4) (**Fig. 36**) There are presences of 3 and 4 atoms of iodine in T_3 and T_4 respectively. The deficiency of iodine leads to decreased production of T_3 and T_4 that enlarges the thyroid tissue and will cause the disease known as simple goitre. Both T_3 and T_4 are used to treat thyroid hormone deficiency (hypothyroidism).



(S)-triiodothyronine or T_3 (S)-thyroxine or (T4)

Fig. 36: Structure of triiodothyronine (T_3) and thyroxine (T_4).

4.6.1. L-Thyroxine

Levothyroxine is also known as L-thyroxine. Levothyroxine is a synthetic form of thyroxine (T_4) (**Fig. 37**). It is manufactured form of the thyroid hormone thyroxine. It is used to treat thyroid hormone deficiency including the severe form known as myxedema coma. It is also used to treat and prevent certain types of thyroid tumors.

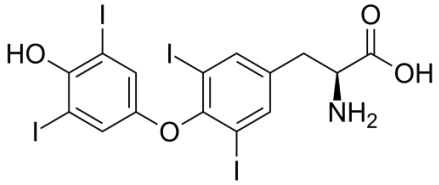


Fig. 37: Structure of L-Thyroxine.

Mechanism of action

Thyroxine stimulates oxygen utilization and heat production of body cells. It causes increased utilization of carbohydrates, increased protein catabolism, as indicated by a greater excretion of nitrogen, and greater oxidation of fats as suggested by loss in body weight.

Metabolism: Thyroxine is metabolized by different pathways such as glucuronidation, sulfation, and deiodination (**Fig. 38**).

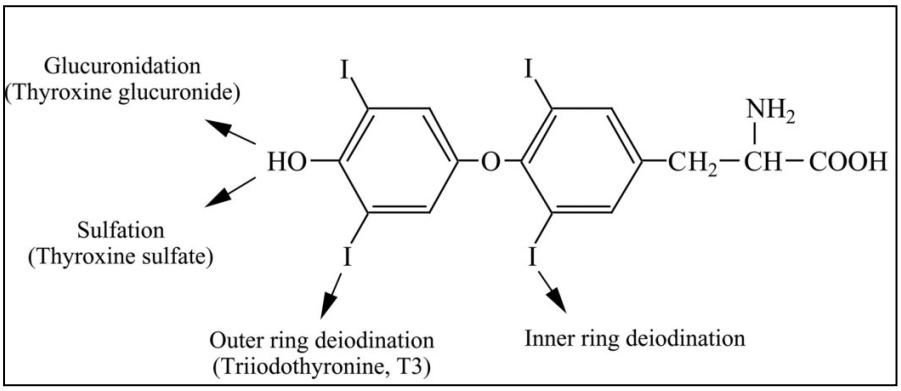


Fig. 38: Metabolism of Thyroxin.

Adverse effect

If the levothyroxine doses are too high that cause symptoms such as hyperthyroidism, tachycardia, dysrhythmias, tremor, nervousness, insomnia, diarrhea, weight loss, sweating, heat sensations, fever, decreased glucose tolerance.

Uses: Levothyroxine is used to treat an underactive thyroid (hypothyroidism).

4.6.2. L-Thyronine

Thyronine is a deiodinated form of thyroxine. Its IUPAC Name is (2S)-2-amino-3-[4-(4-hydroxyphenoxy)phenyl]propanoic acid (**Fig. 39**).

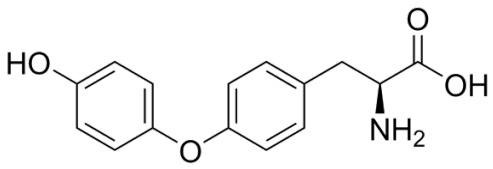


Fig. 39: Structure of L-Thyronine.

Uses: It is to treat thyroid hormone deficiency (hypothyroidism).

4.6.3. Propylthiouracil

Propylthiouracil is a medication used to treat hyperthyroidism (**Fig. 40**). This includes hyperthyroidism due to Graves' disease and toxic multinodular goiter.

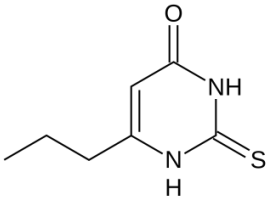


Fig. 40: Structure of Propylthiouracil.

Mechanism of action

Propylthiouracil binds to thyroid peroxidase and thereby inhibits the conversion of iodide to iodine. Thyroid peroxidase normally converts iodide to iodine (via hydrogen peroxide as a cofactor) and also catalyzes the incorporation of the resulting iodide molecule onto both the 3 and/or 5 positions of the phenol rings of tyrosines found in thyroglobulin. Thyroglobulin is degraded to produce thyroxine (T_4) and tri-iodothyronine (T_3), which are the main hormones produced by the thyroid gland. Therefore propylthiouracil effectively inhibits the production of new thyroid hormones.

Metabolism: It is metabolized rapidly in liver.

Uses: Propylthiouracil is used to treat overactive thyroid (hyperthyroidism). It works by stopping the thyroid gland from making too much thyroid hormone.

4.6.4. Methimazole

Methimazole is a thionamide antithyroid agent that inhibits the synthesis of thyroid hormones (**Fig. 41**). It was first introduced as an antithyroid agent in 1949 and is now commonly used in the management of hyperthyroidism.

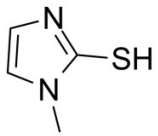


Fig. 41: Structure of Methimazole.

Mechanism of action

Methimazole prevents iodine and peroxidase from their normal interactions with thyroglobulin to form T_4 and T_3. This action decreases thyroid hormone production. Methimazole also interferes with the conversion of T_4 to T_3.

Metabolism: Methimazole is rapidly and extensively metabolized by the liver, mainly via the CYP450 and flavin-containing monooxygenase (FMO) enzyme systems.

Uses: Methimazole is used to treat hyperthyroidism (overactive thyroid). It is also used before thyroid surgery or radioactive iodine treatment.

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