Pharmaceutical Chemistry

Steroid Hormones and Therapeutically Related Compounds

Assist. Prof. Karima fadhil Ali

Al mustansiriyah university
College of pharmacy

Steroid Hormones and Therapeutically Related Compounds

Steroid hormones and related products represent one of the most widely used classes of therapeutic agents. These drugs are used primarily in birth control, hormone-replacement therapy (HRT), inflammatory conditions, and cancer treatment. Most of these agents are chemically based on a common structural backbone, the steroid backbone.

ADRENAL CORTEX HORMONES
Endogenous Corticosteroids

The adrenal glands (which lie just above the kidneys) secrete over 50 different steroids, including precursors for other steroid hormones. The most important hormonal steroids produced by the adrenal cortex, however, are aldosterone and hydrocortisone. Aldosterone is the primary MC in humans (i.e., it causes significant salt retention).

Hydrocortisone is the primary GC in humans (i.e., it has its primary effects on intermediary metabolism).

The GCs have become very important in modern medicine, specially for their anti-inflammatory effects. GCs inhibit the production and release of other mediators of inflammation, including prostaglandins, leukotrienes, and histamine.

In addition, GCs inhibit the expression of the gene encoding collagenase, an important enzyme involved with inflammation. The adrenocortical steroids are used primarily for their GC effects, including immunosuppression, anti-inflammatory activity, and antiallergic activity.

Biosynthesis

Aldosterone and hydrocortisone are biosynthesized from pregnenolone through a series of steps involving hydroxylations at C17, C11, and C21 that convert pregnenolone to hydrocortisone.

Deficiencies in any of the enzymes cause congenital adrenal hyperplasia. The 21-hydroxylase is important for the synthesis of both MCs and GCs.

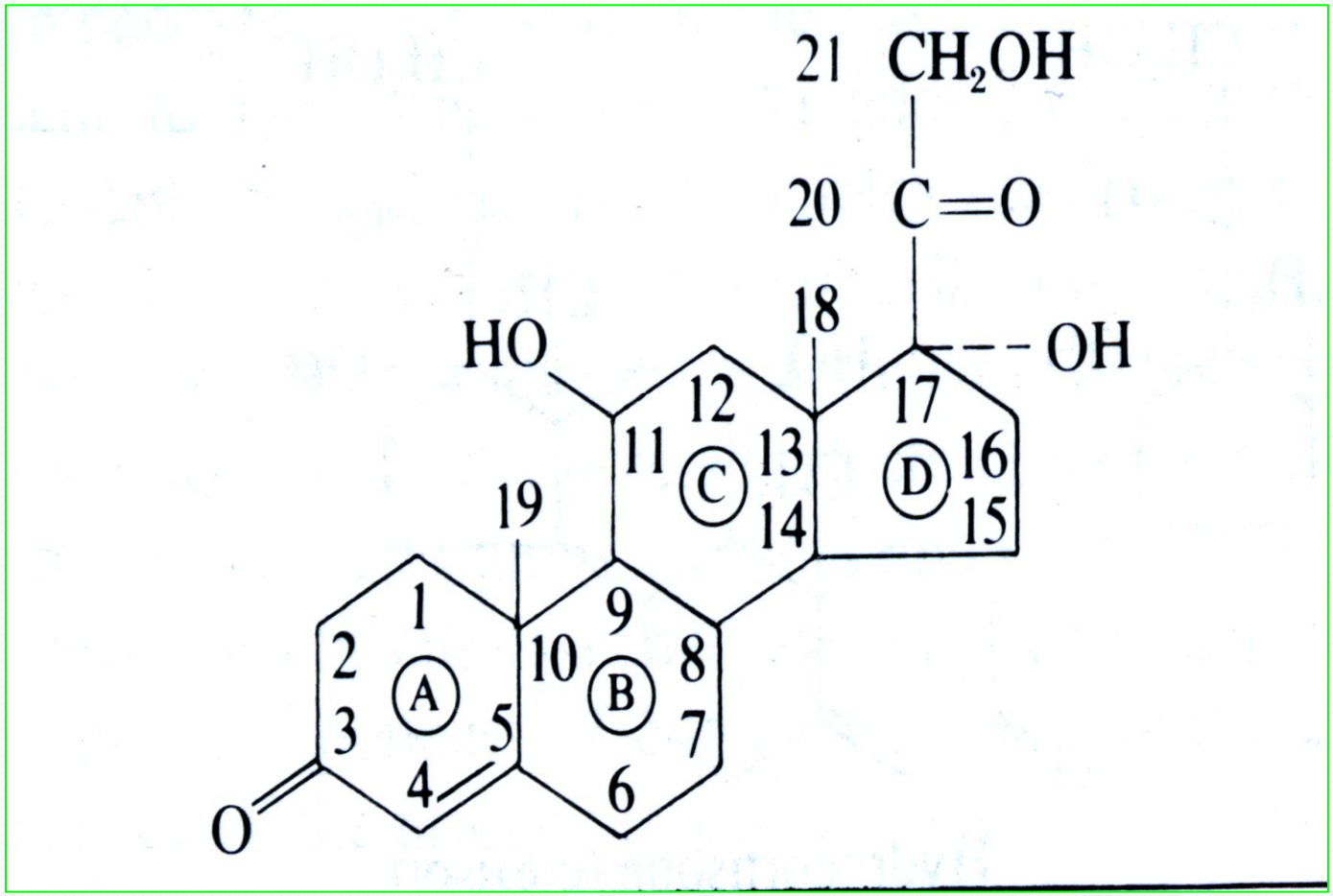
Biological Activities of Mineralocorticoids and Glucocorticoids

Aldosterone and, to a lesser extent, other MCs maintain a constant electrolyte balance and blood volume, and the GCs have key roles in controlling carbohydrate, protein, and lipid metabolism. In addition, GCs have anti-inflammatory and immunosuppressive actions that arise through complex mechanisms.

Steroids

Are modified triterpenes which derived also from squalene by cyclization, unsaturation and substitution. The nucleus of all steroids is the tetracyclic C17 hydrocarbon 1,2-cyclopentanoperhydrophenanthrene (gonane or sterane) substituted by methyl groups at C10 and C13, as well as an alkyl side-chain at C17.

Cyclopentano perhydro phenanthrene nucleus



The modifications include attack at the 11, 16, 17, 18, 19, 20, and 21 positions, conversion of the 3-hydroxyl to a ketone, and isomerization of the 5-6 double bond to the 4-5 position. A number of additional modifications, not shown here, occur during conversion of the steroid hormones to inactive metabolites. sites of unsaturation (i.e. double bonds) are often referred to using the Greek letter D.

Thus, steroids containing the 5-6 double bond, such as cholesterol, are designated D5 steroids; those with a 4-5 double bond are called D4 steroids.

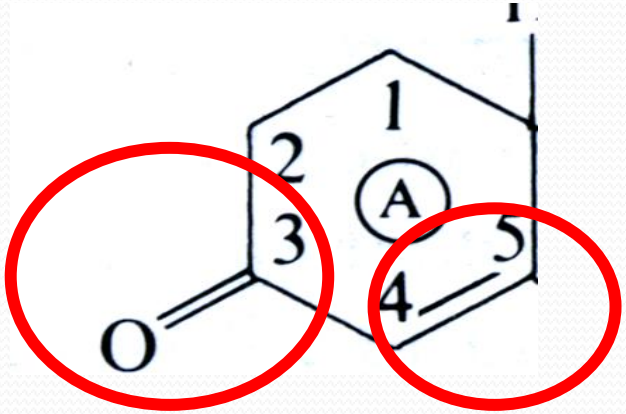
Cholesterol have a 3-β-hydroxyl, and the branched 8-carbon side-chain at the 17- β position).

However, there is a chemical nomenclature for each steroid that uniquely denotes the structure for that compound

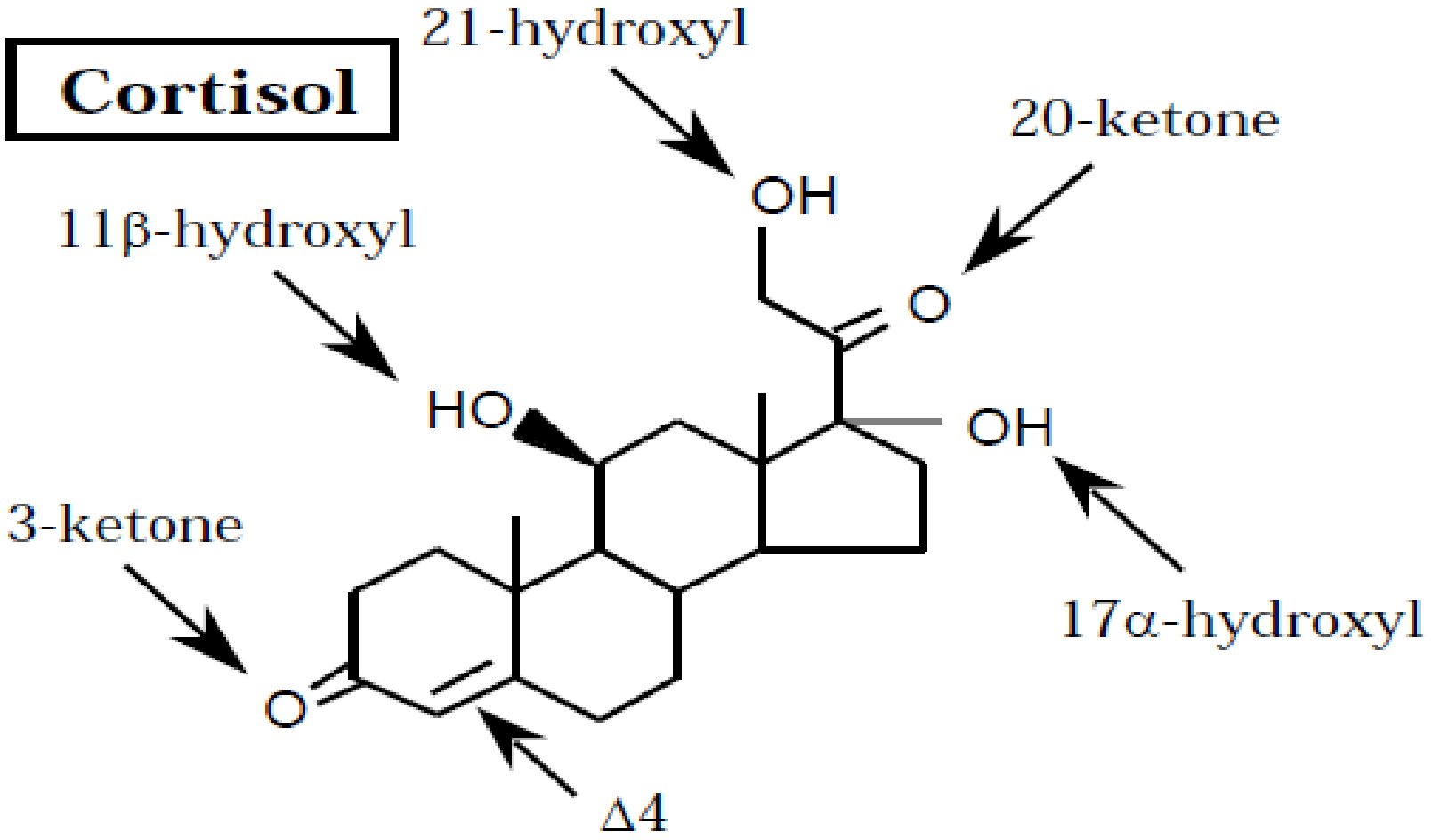
Steroid nucleus is the common structure;

The keto group in C3, carbonyl group in C20, and the double bond between C4 & C5 are essential for both glucocorticoids & mineralocorticoids

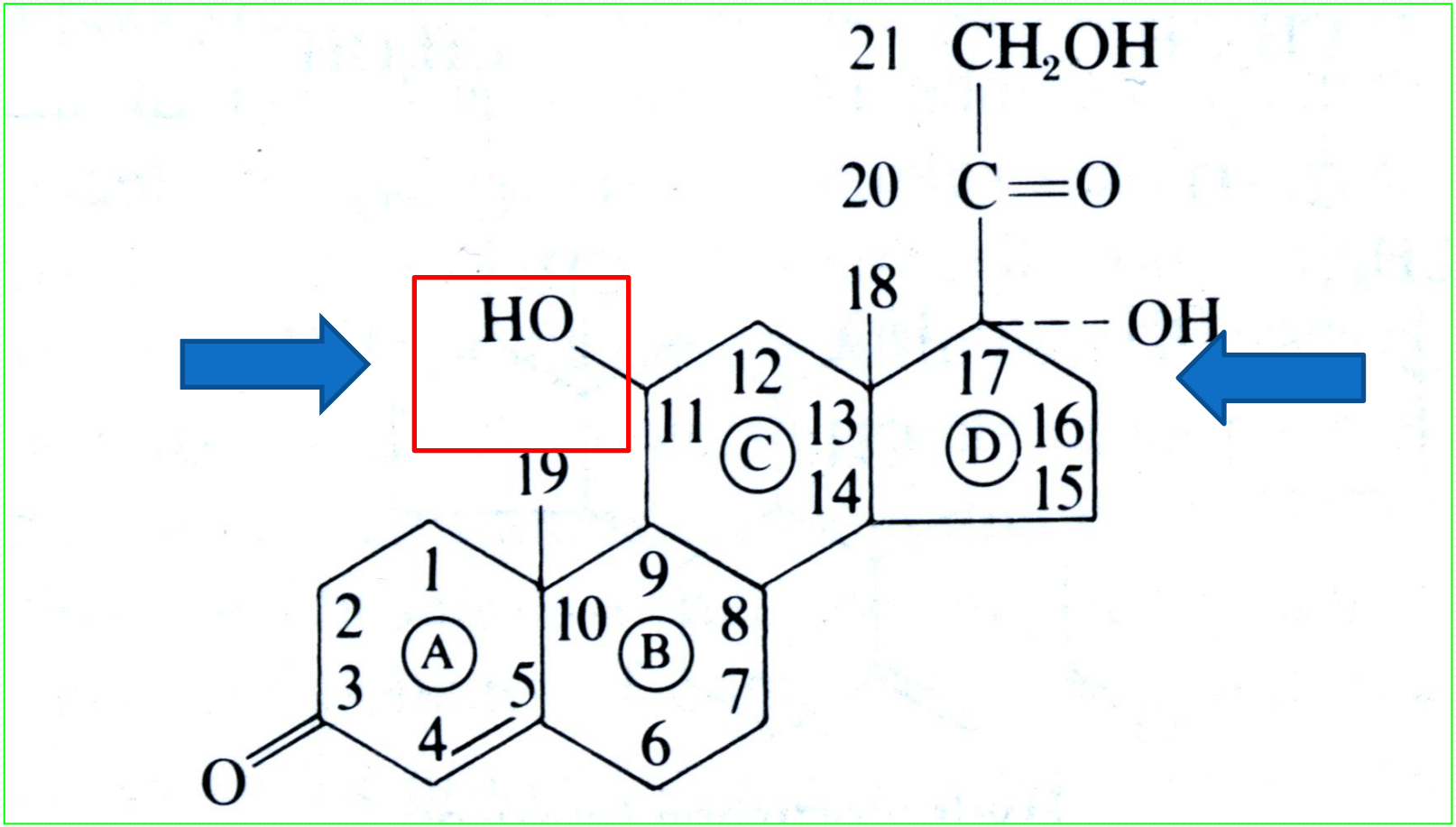
All require 3 keto group and
4,5 unsaturation, carbonyl group in C20



Cortisol is a 21-carbon steroid, a pregnane. conversion of the 11β-hydroxyl to a ketone yields cortisone, an inactive metabolite of cortisol. The steroid that lacks the 17α- hydroxyl, corticosterone, has 70% lower glucocorticoid activity in humans, although it is the major glucocorticoid in rats.


Cortisol
21-hydroxyl
20-ketone
11β-hydroxyl
OH
O
HO
OH
3-ketone
17α-hydroxyl
O
Δ4

Glucocorticoid activity requires 11 β hydroxyl(OH) group , an α-hydroxyl group linked to C17

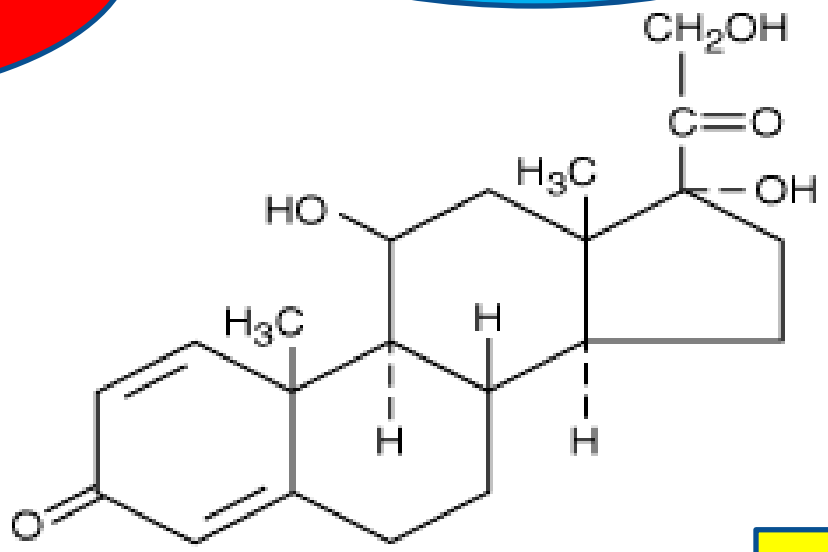


Additional unsaturation of Ring A

increase in GC activity

Slow metabolism

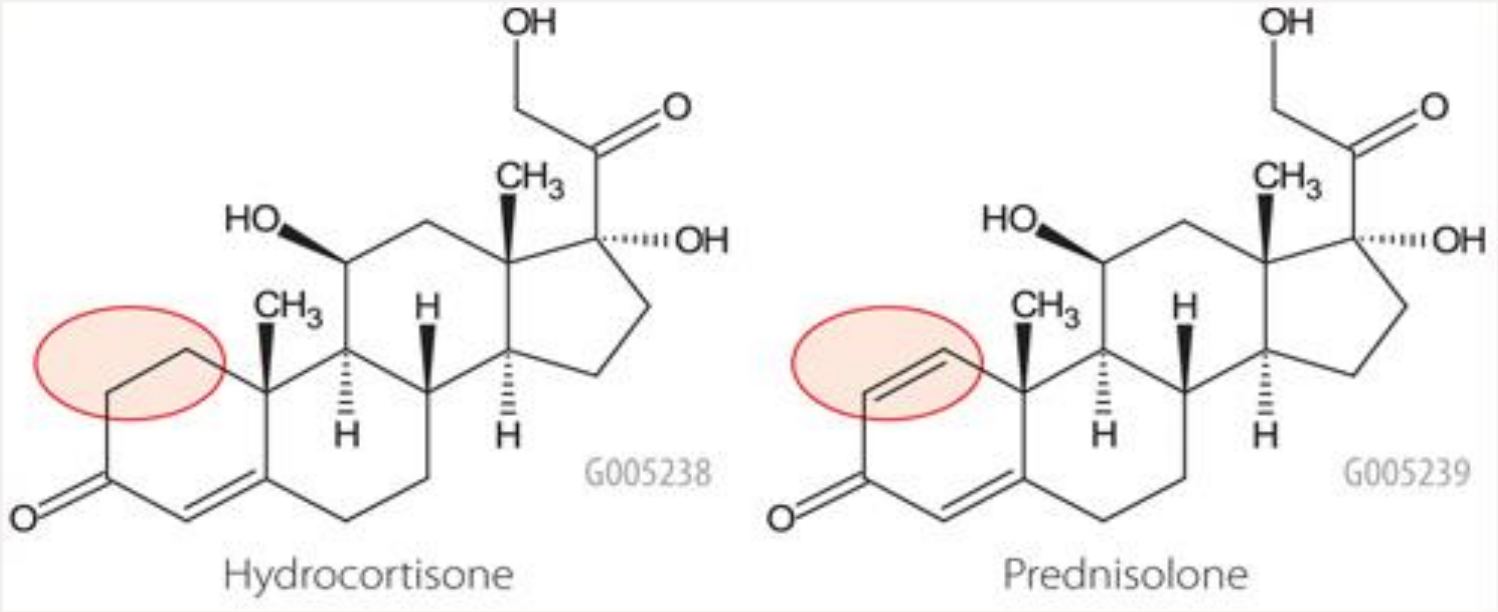
glucocorticoid/ mineralocorticoid potency ratio



Prednisolone

Salt retaining activity decreases

Enhance antiinflammatory effect



- Increases glucocorticoid activity,
- Enhanced glucocorticoid/ mineralocorticoid potency ratio.
- Metabolized more slowly than hydrocortisone

Some structural changes

Changing single bond between C1 & C2 into the double, the anti-inflammatory effect enhances and salt & water effects weakens;

Cortisone→ prednisone

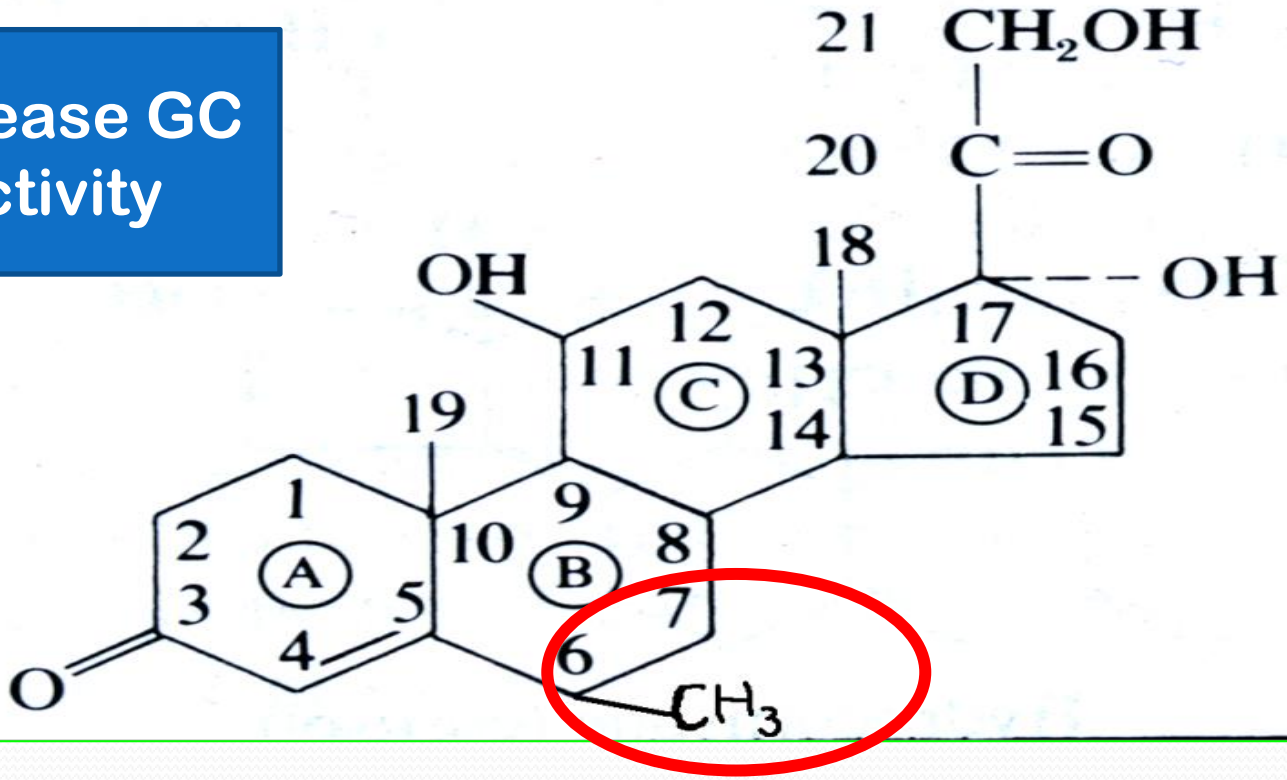
Hydrocortisone → prednisolone

Adding a -CH_3 **to C6, the** anti-inflammatory effect enhances more;

Prednisolone→ 6-methyl-prednisolone

6-Methylcortisol has increased glucocorticoid and mineralocorticoid activity, whereas 6-methylprednisolone has somewhat greater glucocorticoid activity and somewhat less mineralocorticoid activity than prednisolone

Increase GC activity



Unpredictable effects

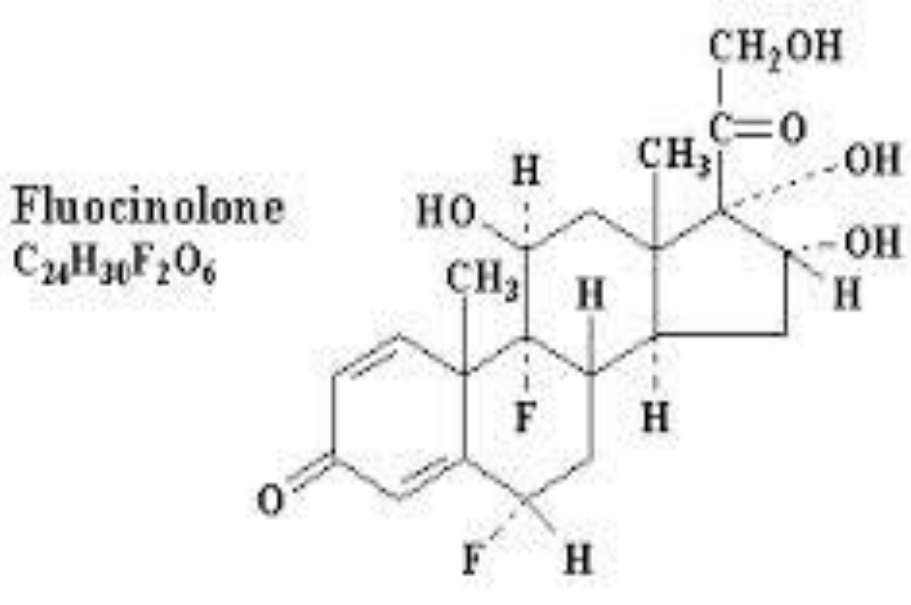
6 α methyl cortisol - ↑GC & ↑MC activity

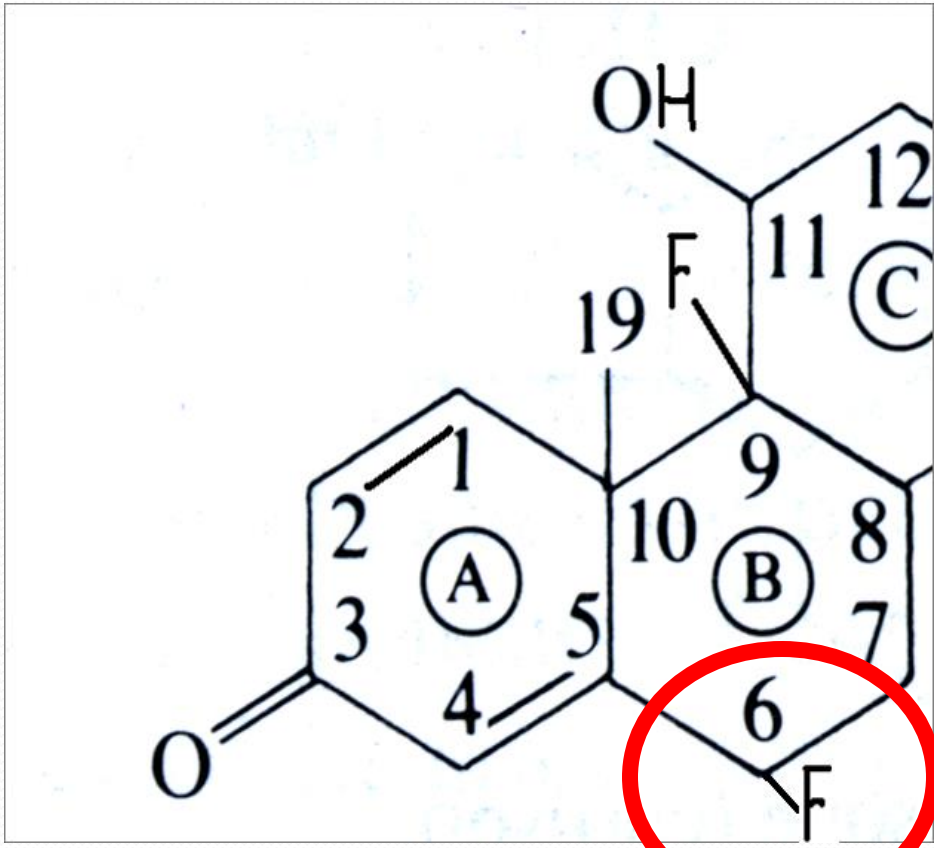
6 α methyl prednisolone - ↑GC & ↓ MC

6α-Fluorination

6α-fluoro has less salt retention properties than 9α-fluoro.

Fluocinolone

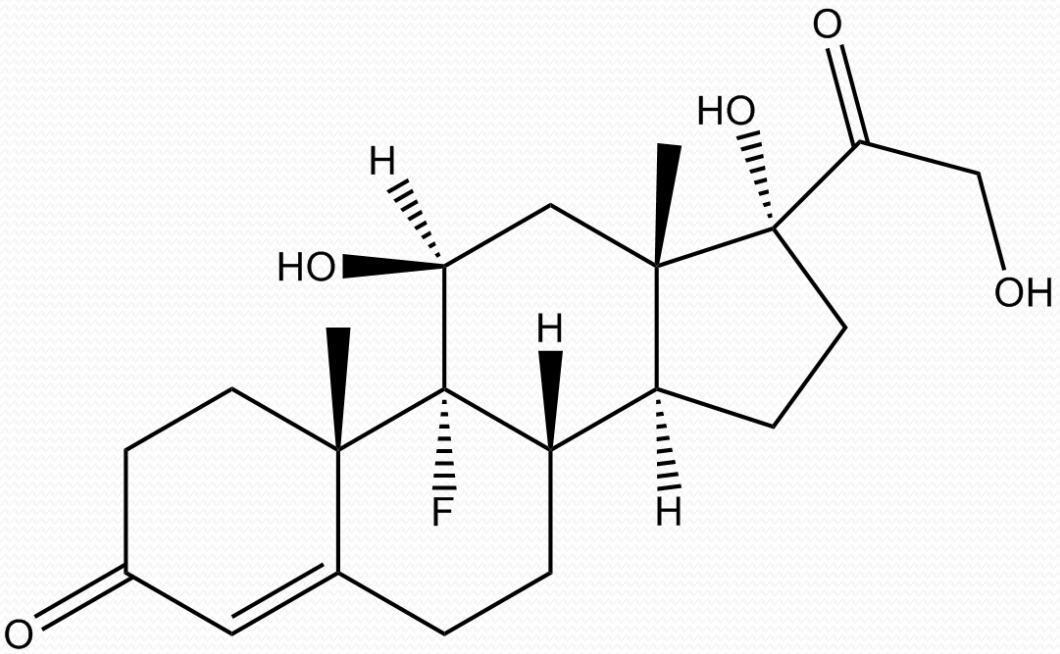




Fludrocortisone (9-fluorocortisol)

enhanced activity at the GR (10 times relative to cortisol)

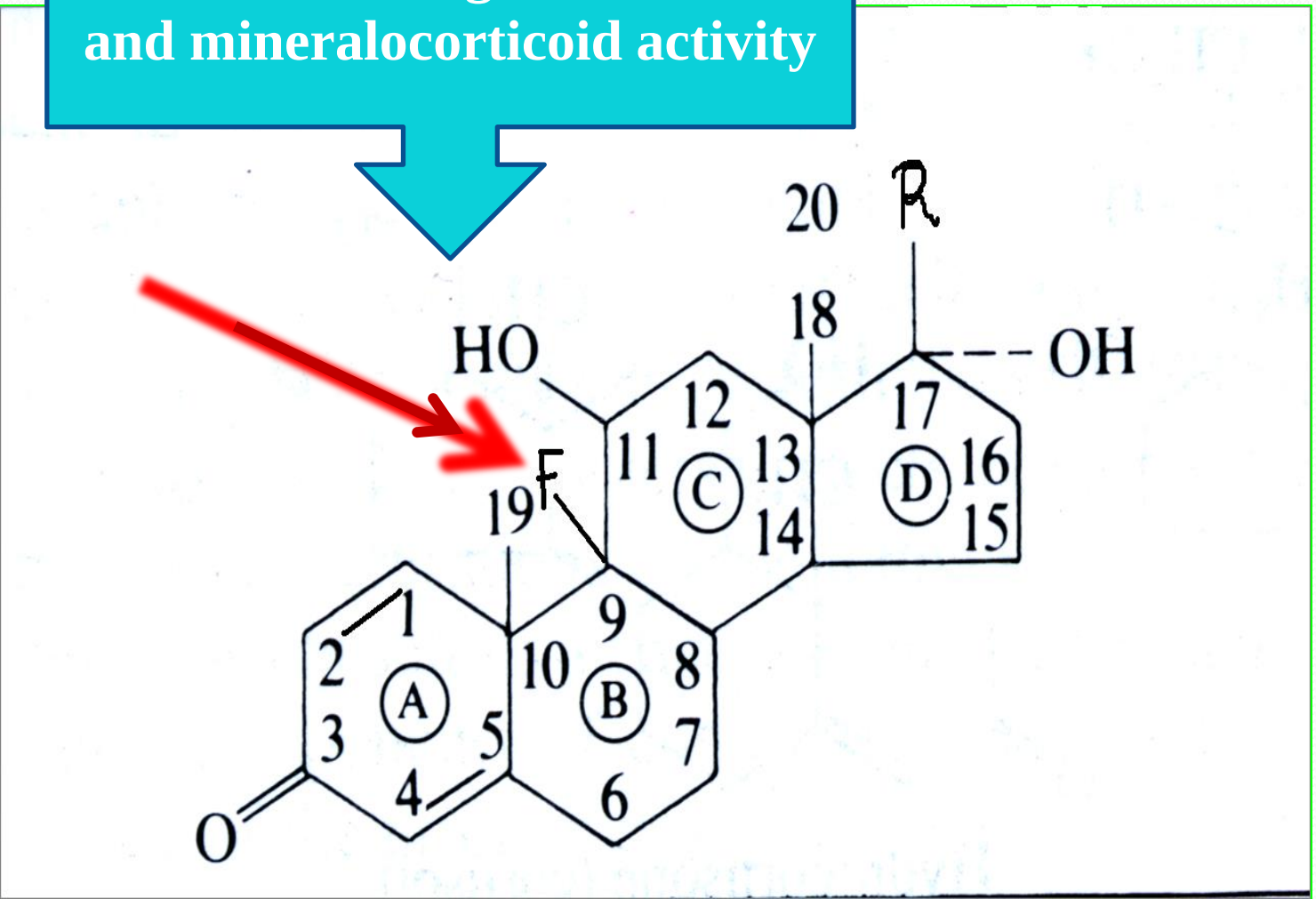
greater activity at the MR (125 times relative to cortisol).



Fluorination at the 9 position on ring B enhances both glucocorticoid and mineralocorticoid activity, possibly related to an electron-withdrawing effect on the nearby 11-hydroxyl group. It is used in mineralocorticoid replacement therapy and has no appreciable glucocorticoid effect at usual daily doses of 0.05-0.2 mg.

Fluorination at 9 alpha

Enhances both glucocorticoid and mineralocorticoid activity

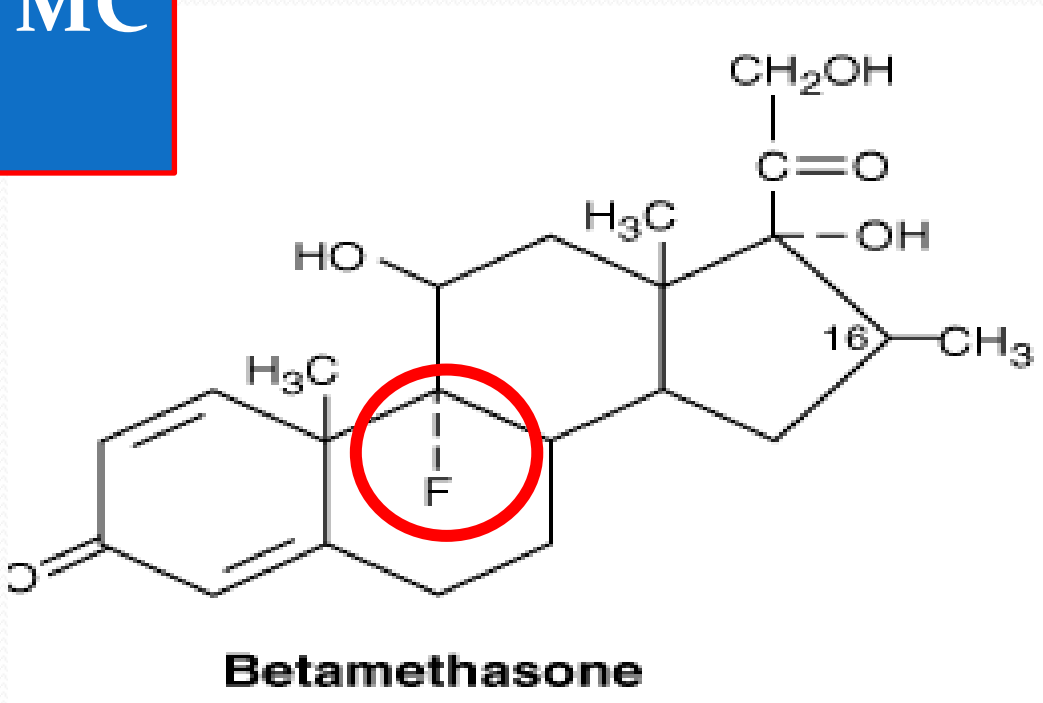


Resistant to local destruction

When combined with the 1,2 double bond in ring A plus other substitutions at C16 on ring D, the 9-fluoro derivatives formed (e.g., triamcinolone, dexamethasone, and betamethasone) have marked glucocorticoid activity—the substitutions at C16 virtually eliminate mineralocorticoid activity

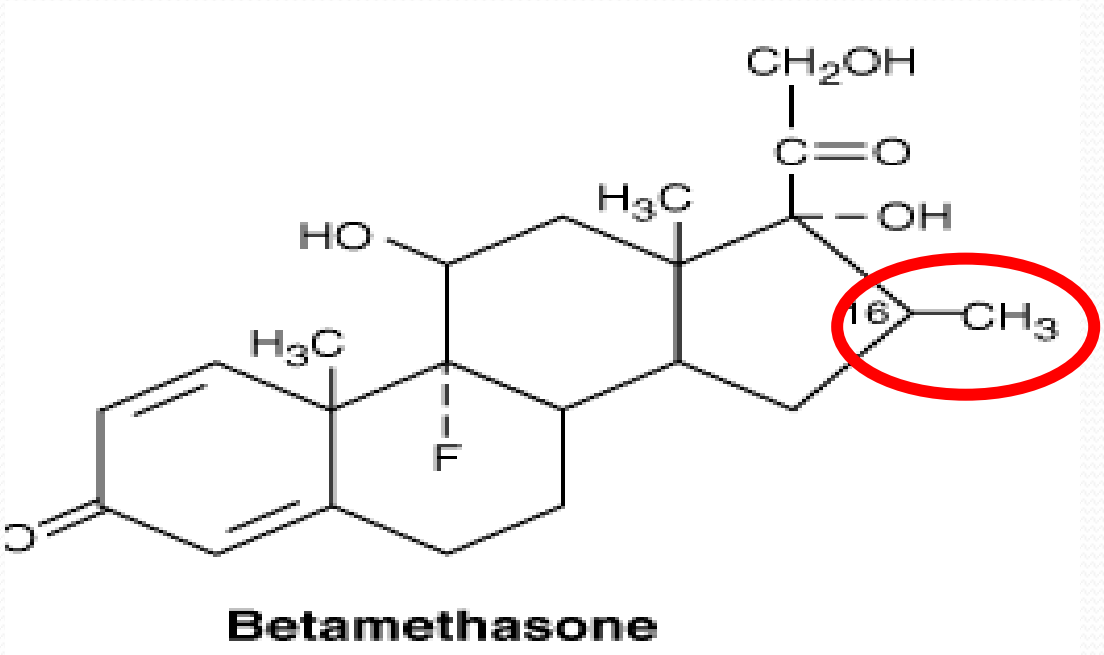
9 α fluorination of Ring B

Enhances GC & MC activity



Betamethasone

Substitution at C16 on ring D



Betamethasone

More GC activity & anti inflammatory activity

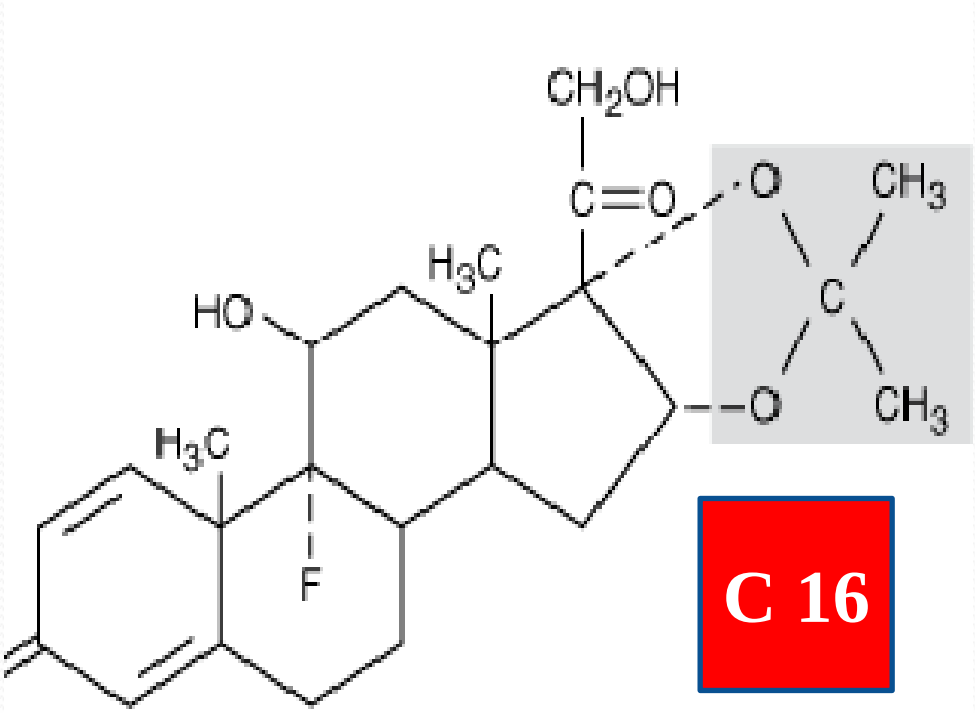
Eliminates MC activity

Hydrocortisone→fludrocortisone→dexamethasone & triamcinolone

1,2 double bond in ring A + other substitutions at C16 on ring D

the 9-fluoro derivatives

Anti-inflammatory effect enhances and salt- retaining effects weakens further.



Triamcinolone (acetonide moiety shaded)

Acetonide b/w OH groups at C16 & C17

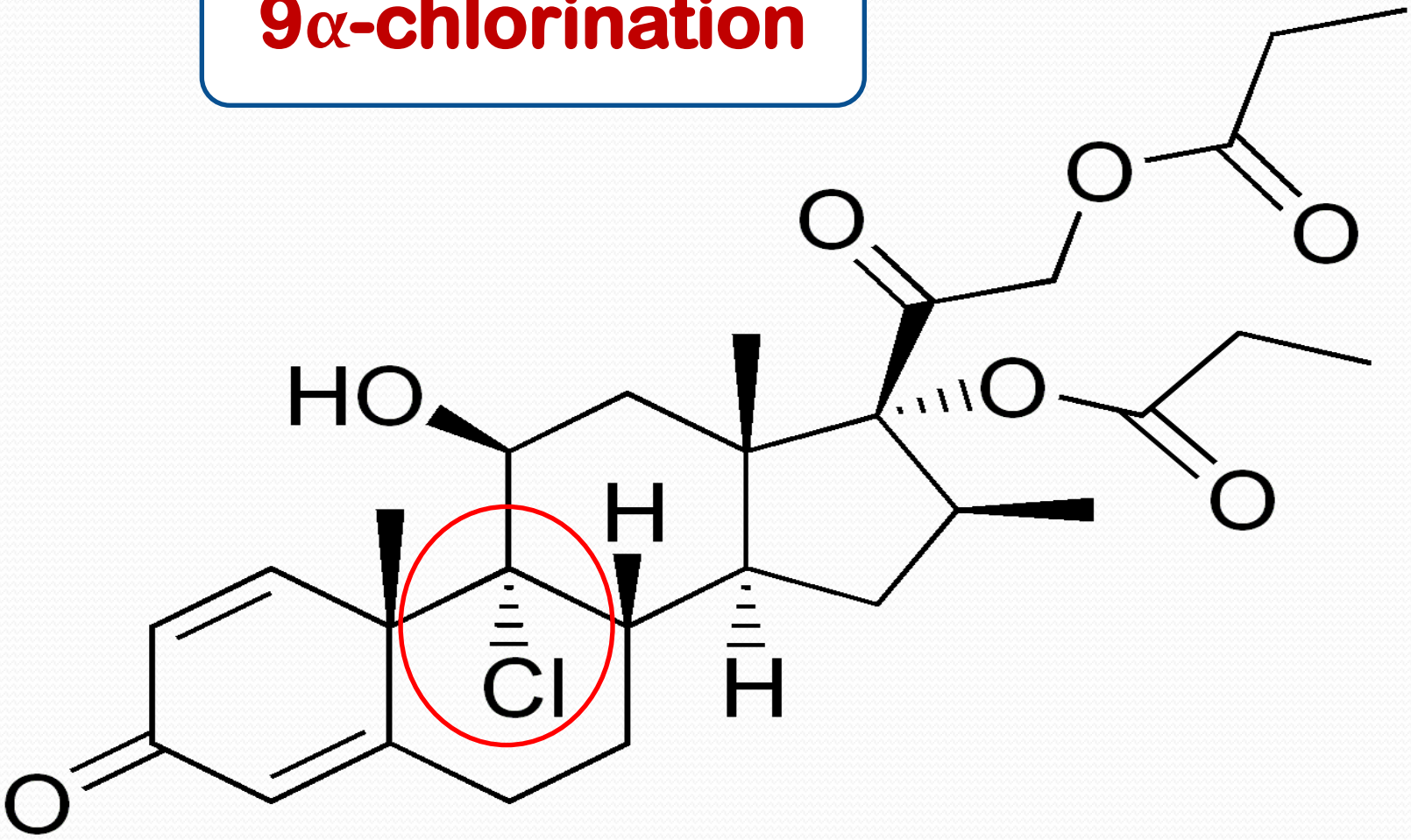
9α-chlorination

9α-chloro derivative of betamethasone

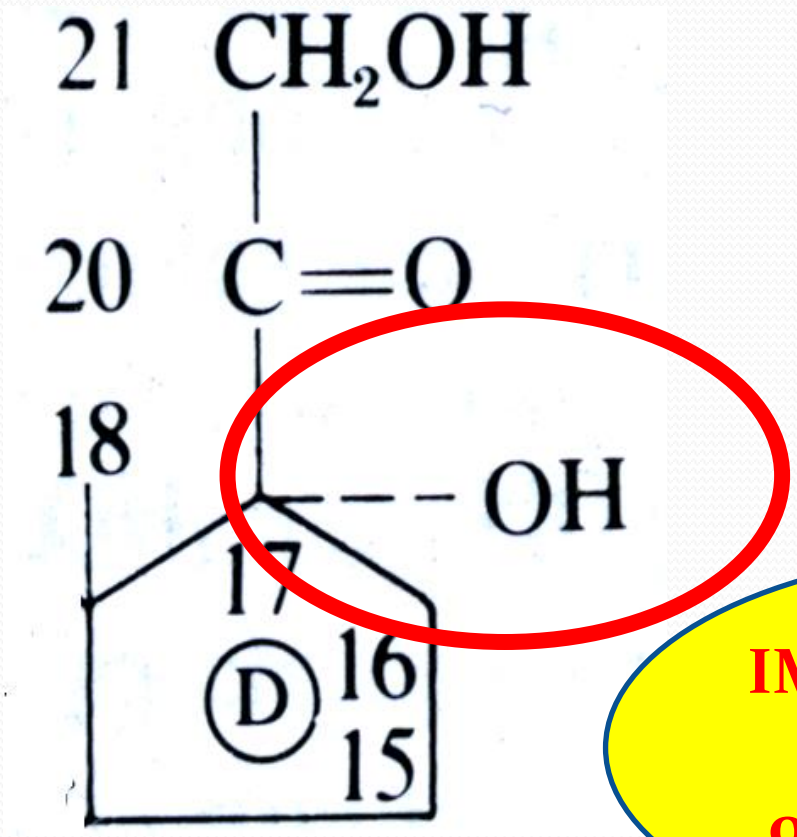
Beclomethasone dipropionate

- **Increase stabilization**
- **Increase lipophilicity**
- **Increase bronchial tissue absorption**
- **Increase duration of action**

9α-chlorination



17 α hydroxyl group on ring D- esterification of the hydroxyl group



Valerate at C17
Propionate at C17 and C21
Substitution group at C21 with chlorine

IMPORTANT FOR GC ACTIVITY- optimal potency

Lipophilicity & topical/systemic potency ratio

Acetonide b/w OH groups at C16 & C17

Esterification of OH groups with **Valerate** at C17

Esterification of OH groups with **propionate** at C17 & C21

Substitution of OH group at C21 with **Chlorine**

As a result of the great economic benefit of having a potent anti-inflammatory product on the market, pharmaceutical manufacturers have made numerous combinations of these various substituents.

The number of permutations and combinations has resulted in a redundant array of analogs with very low salt retention and high anti inflammatory activity.

A primary goal of these highly anti-inflammatory drugs has been to increase topical potency. some are as much as 100 times more active topically than hydrocortisone.

The steroids can be made more lipid soluble or more water soluble by making suitable ester derivatives of hydroxyl (OH) groups.

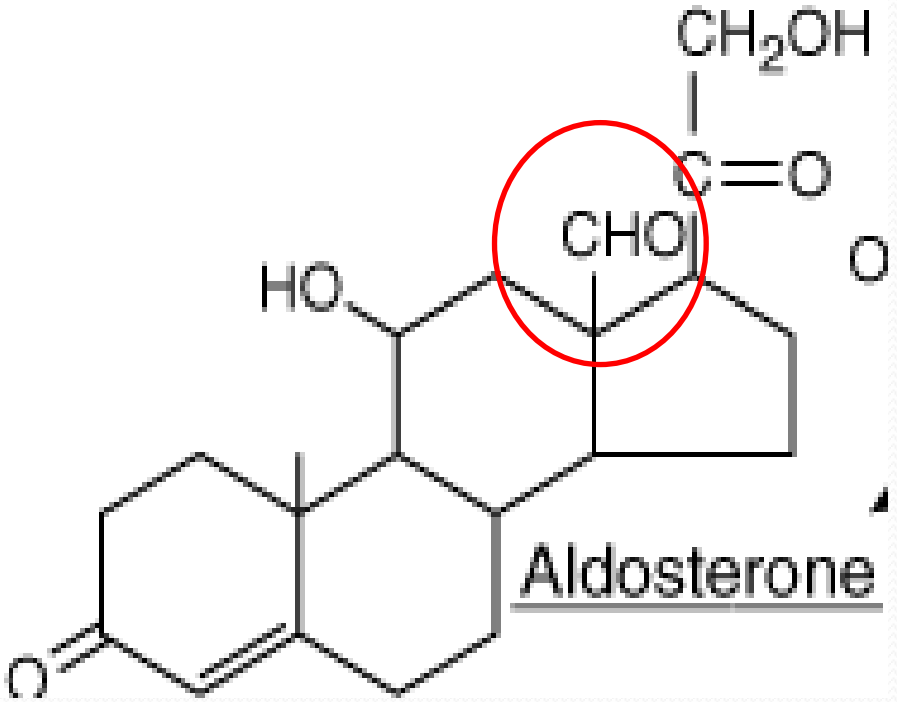
Derivatives with increased lipid solubility are often made to decrease the release rate of the drug from intramuscular (IM) injection sites (i.e., in depot preparations).

More lipid-soluble derivatives also have improved skin absorption properties and thus, are preferred for dermatological preparations.

Derivatives with increased water solubility are needed for intravenous preparations

Mineralocorticoid activity requires

Aldehyde group at C18 on ring



Mineralocorticoids

The MCs are adrenal cortex steroids and analogs with high salt-retaining activity. They are used mainly for treatment of Addison disease, or primary adrenal insufficiency. The naturally occurring hormone aldosterone has an 11-OH and an 18-CHO . Aldosterone is too expensive to produce commercially; therefore, other semisynthetic analogs have taken its place for treatment of Addison disease.

Adding a 9-fluoro group to hydrocortisone greatly increases both salt retention and anti-inflammatory activity.

Aldosterone structurally very similar to cortisol, except that it lacks the 17a-hydroxyl group, and has an aldehyde at the 18-methyl.

The 18-aldehyde is critical for mineralocorticoid activity; the sole difference between corticosterone and aldosterone is the 18-aldehyde, but aldosterone has 200 times higher mineralocorticoid activity than corticosterone.

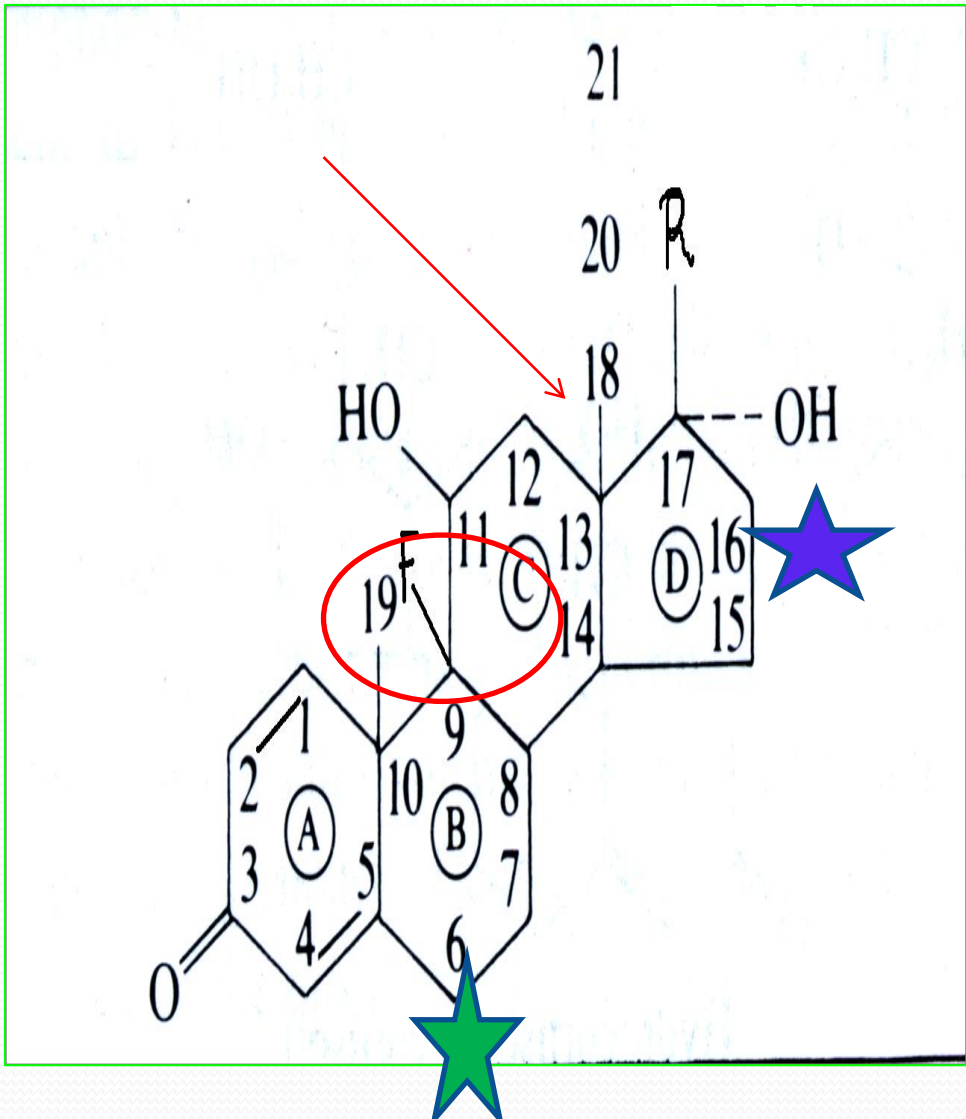
Changes that alters mineralocorticoid activity

Aldehyde group in the C18

Fluorination at the 9α position on ring B

6α substitution on ring B

Substitution at C16 on ring D



Changes that increase glucocorticoid activity

Additional double bond b/w 1 & 2 carbon atoms

Alpha methylation at 6^{th} position

Alpha fluorination at 9^{th} position

Substitution at 16^{th} position

Sex Hormones

Although estrogens and progesterone are usually called female sex hormones and testosterone is called a male sex hormone, all of these steroids are biosynthesized in both males and females.

Progesterone serves as a biosynthetic precursor to hydrocortisone and aldosterone and, to a lesser extent, to testosterone and estrogens. Testosterone is one of the precursors of estrogens.

Estrogens and progesterone are produced in much larger amounts in females, however, as is testosterone in males.

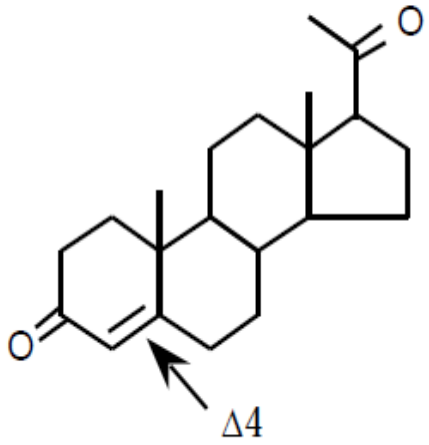
Sex Hormones

Estrogen, Progesterone, Androgen

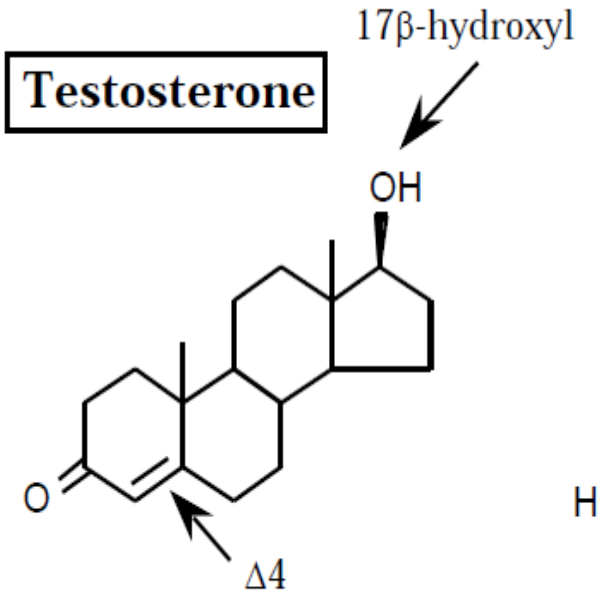
21-carbon3-keto D4

18-carbon

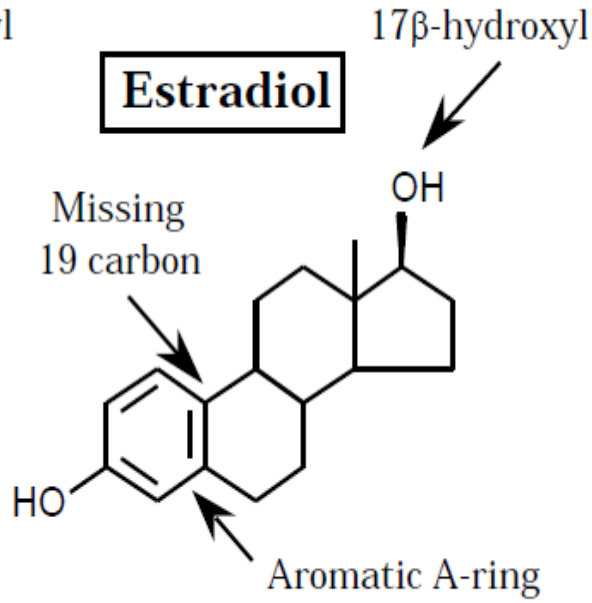
Progesterone



Testosterone



Estradiol



Testosterone,
it lacks the 2-carbon side-chain attached to the 17 position, making it a *19-carbon* steroid .

These hormones play profound roles in reproduction, in the menstrual cycle, and in giving women and men their characteristic physical differences.

Several modified steroidal compounds, as well as some nonsteroidal compounds, have estrogenic activity. A large number of synthetic or semisynthetic steroids with biological activities similar to those of progesterone have been made, and these are commonly called progestins. Although the estrogens and progestins have had their most extensive use as chemical contraceptive agents for women and in HRT, their wide spectrum of activity has given them a diversity of therapeutic uses in women, as well as a few uses in men.

Testosterone, like progesterone, aldosterone, and cortisol, is a D4 steroid. However, it lacks the 2-carbon side-chain attached to the 17 position, making it a 19-carbon steroid (an androstane). The side-chain has been replaced by a 17b-hydroxyl.

Testosterone has two primary kinds of activities: androgenic (promoting male physical characteristics) and anabolic (muscle building).

Natural and synthetic estrogens

The most potent naturally occurring estrogen in humans is 17-estradiol, followed by estrone and estriol .

Each contains a phenolic A ring with a hydroxyl group at carbon 3, and a -OH or ketone in position 17 of ring D.

Most alkyl substitutions on the A ring impair binding, but substitutions on ring C or D may be tolerated. Ethinyl substitutions at the C17 position greatly increase oral potency by inhibiting first-pass hepatic metabolism.

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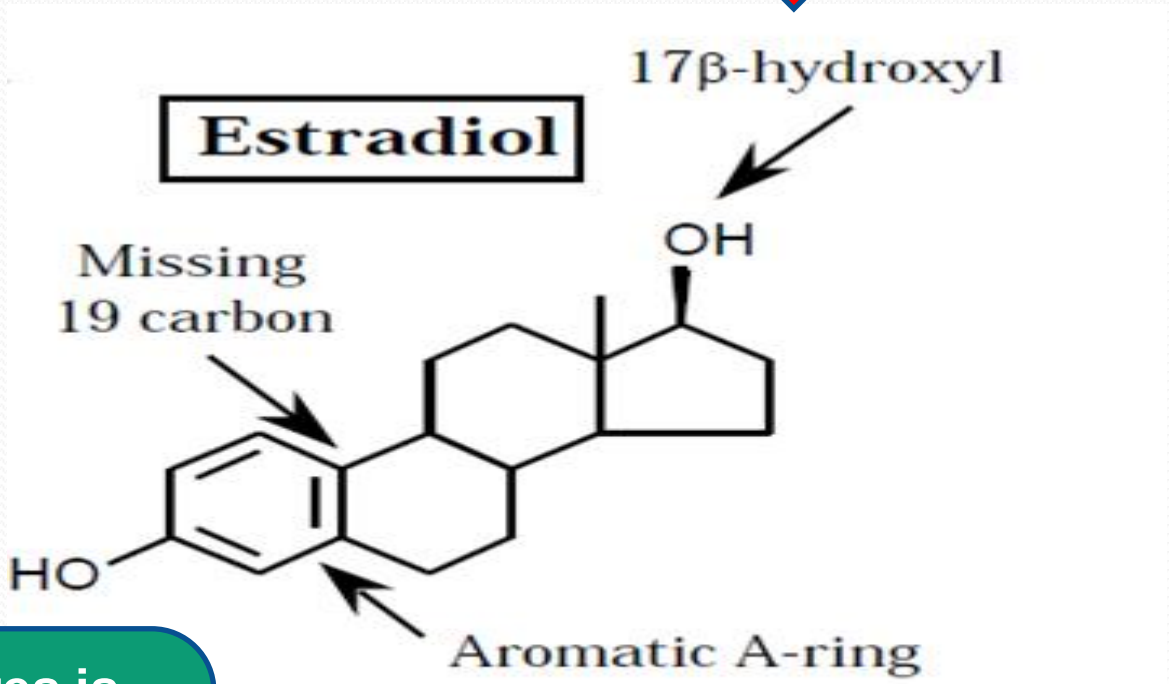
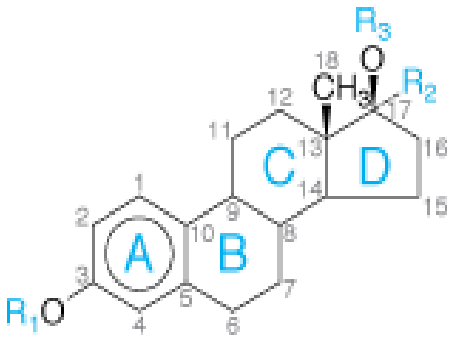


- **Steroidal structures is not essential for activity.**
- **Alkylation of the aromatic ring decrease the activity.**

High-affinity binding to both receptors

Diethylstilbestrol (DES),(synthetic nonsteroidal molecules which is structurally similar to estradiol when viewed in the trans conformation, binds with high affinity to both estrogen receptors and it is as potent as estradiol in most assays but has a much longer $t_{1/2}$. DES no longer has widespread use, but it was important historically as an inexpensive orally active estrogen

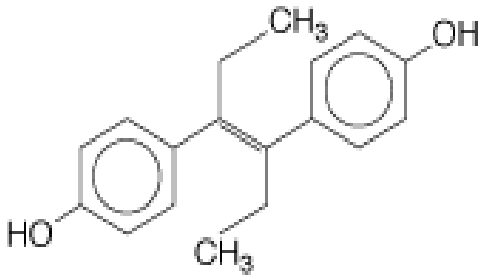
STEROIDAL ESTROGENS



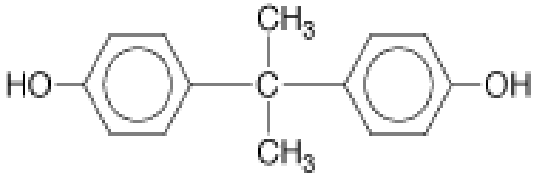
Derivative	R_1	R_2	R_3
Estradiol	—H	—H	—H
Estradiol valerate	—H	—H	—C(=O)(CH$_2$)$_3$CH$_3$
Ethinyl estradiol	—H	—Cæ CH	—H
Mestranol	—CH$_3$	—Cæ CH	—H
Estrone sulfate	—SO$_3$H	—[a]	Á O[a]
Equilin[b]	—H	—[a]	Á O[a]

NONSTEROIDAL COMPOUNDS WITH ESTROGENIC ACTIVITY

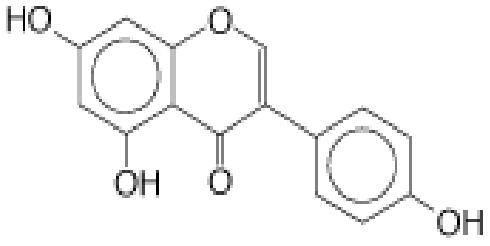
Diethylstilbestrol



Bisphenol A



Genistein



Therapeutic uses of estrogens

Birth Control.

Hormone Replacement Therapy

Treatment of Estrogen Deficiency from Ovarian Failure or after Oophorectomy

Treatment of Advanced, Inoperable Breast Cancer in Men and Postmenopausal Women and of Advanced, Inoperable Prostate Cancer in Men.

Estrogens and Cancer.

Many years of study have firmly established an association between estrogen use and increased risk of breast cancer. The risk is associated, however, with the timing of estrogen exposure, the estrogen dose, the length of use, and the type of estrogen used. A patient should discuss the potential risks of breast cancer with her doctor carefully before starting estrogen therapy. Unopposed estrogens in HRT for postmenopausal women are also linked to an increased risk of endometrial carcinoma, which is the basis for inclusion of a progestin in many forms of HRT.

Selective estrogen receptor modulators and anti estrogen

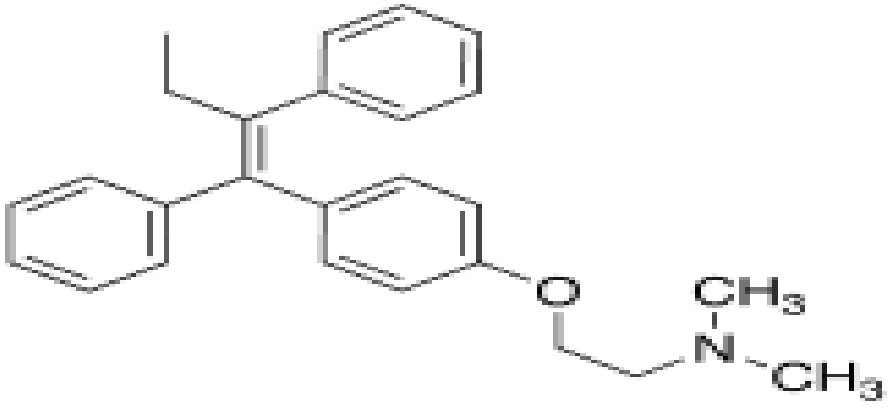
Tamoxifen is a tri phenyl ethylene with the same stilbene nucleus as DES; compounds of this class display a variety of estrogenic and anti-estrogenic activities. In general, the *trans* conformations have anti-estrogenic activity, whereas the *Cis* conformations display estrogenic activity. However, the pharmacological activity of the *trans* compound depends on the species, target tissue, and gene. Tamoxifen is marketed as the pure *trans*-isomer. Tamoxifen is used as adjuvant treatment for breast cancer in women following mastectomy and breast irradiation

Toremifene is a triphenylethylene with a chlorine substitution at the R2 positionToremifene is used in the treatment of metastatic breast cancer in postmenopausal women.

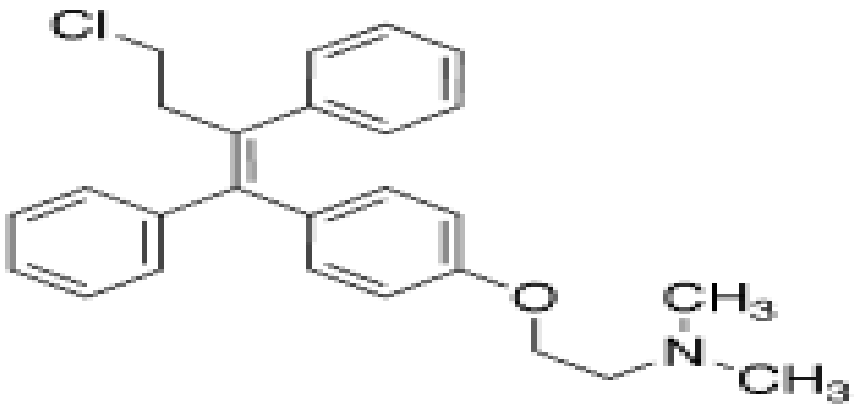
Raloxifene is a benzothiophene derivative that differs slightly from the triphenylethylene.

A key structural difference is the carbonyl “hinge” that connects the modified phenolic side chain to the benzothiophene ring system.

Raloxifene has similar effectiveness to tamoxifen, but has a preferable side effect profile

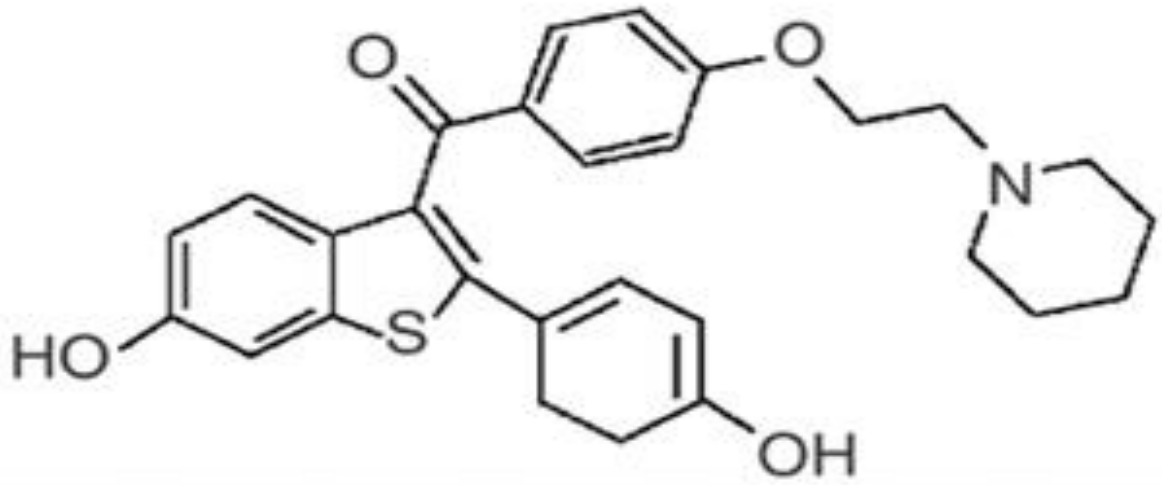


Tamoxifen (Novaldex)

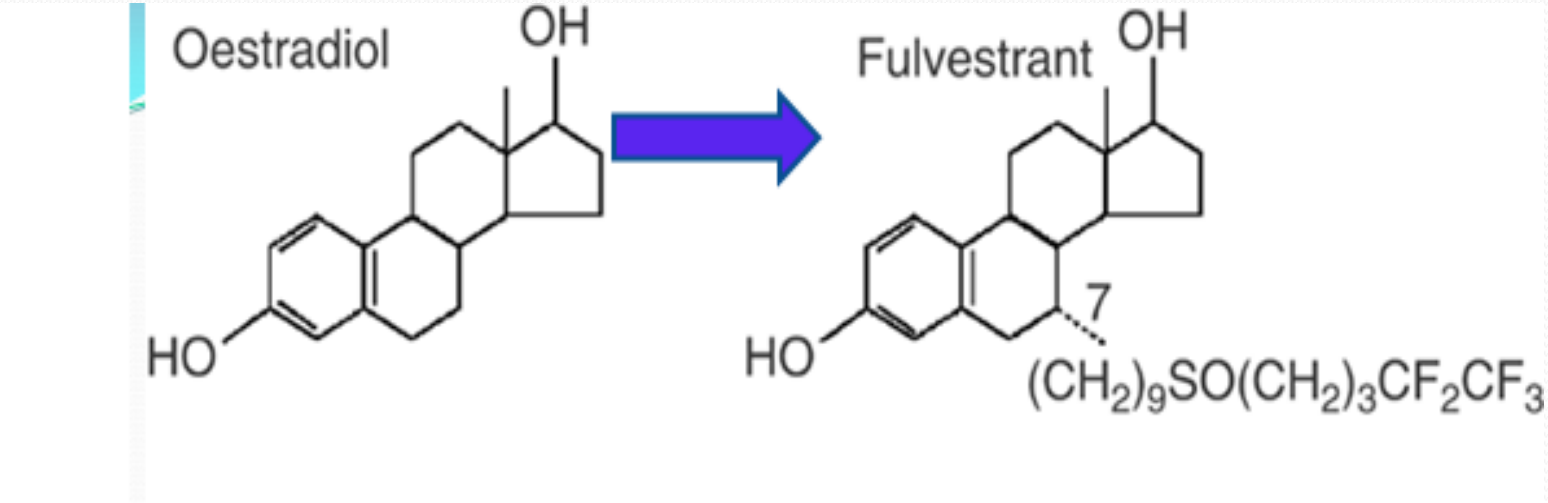


Toremifene (Fareston)

Raloxifene



Fulvestrant is an antagonist structurally based on the estradiol structure, with a long, substituted alkyl chain attached at the 7-position of the steroid skeleton. When bound to the ERs, this alkyl chain induces a conformation of the receptor distinctive from that formed upon estradiol or tamoxifen binding, preventing agonist action.



Points to remember(estrogens)

Aromatic ring with C-3-OH is essential for activity.

Steroidal structures is not essential for activity.

Alkylation of the aromatic ring decrease the activity.

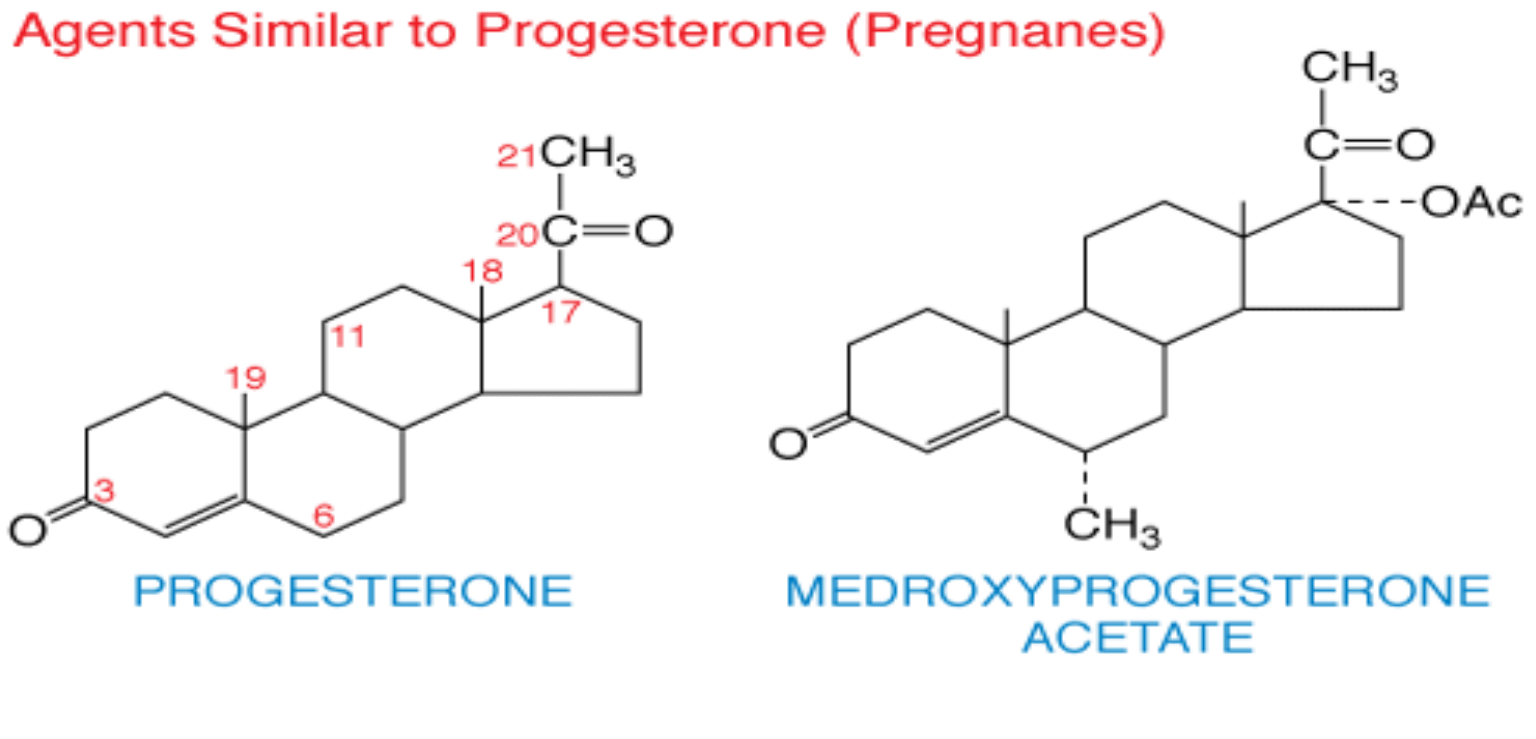
The 17b-hydroxyl with constant distance from 3-OH is essential for activity.

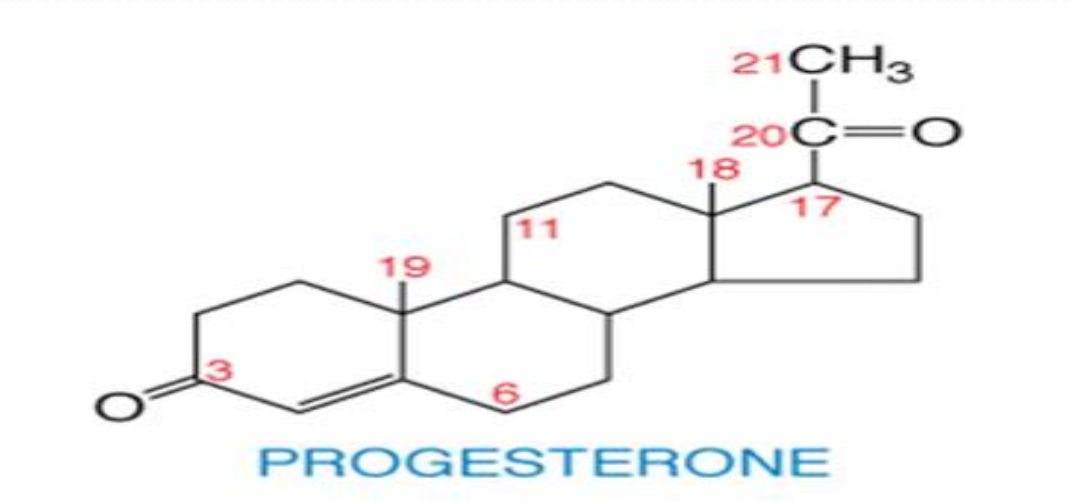
Unsaturation of ring B decreases the activity.

17alpha- and 16 position when modified enhance the activity.

PROGESTINS: (progesterone derivatives)

Compounds with biological activities similar to those of progesterone





Steroidal nucleus essential for activity.

Have some androgenic activity.

Removal of the 19 CH_3 increase activity.

Unsaturation of ring B or C increase the activity.

Removal of the keto function remove androgenic activity

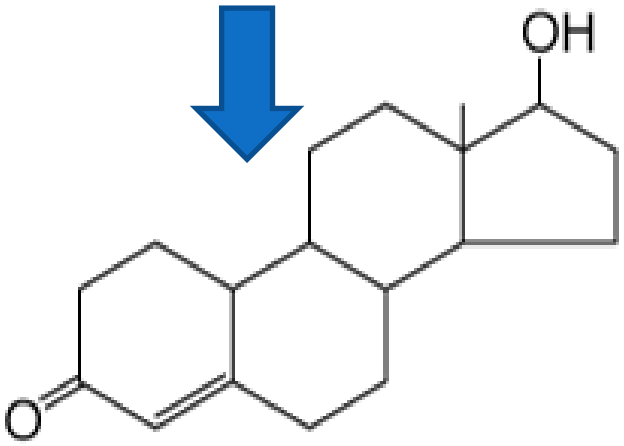
17-Hydroxyprogesterone /Hydroxyprogesterone caproate

Progestational activity .Used parenterally due to first-pass hepatic metabolism.

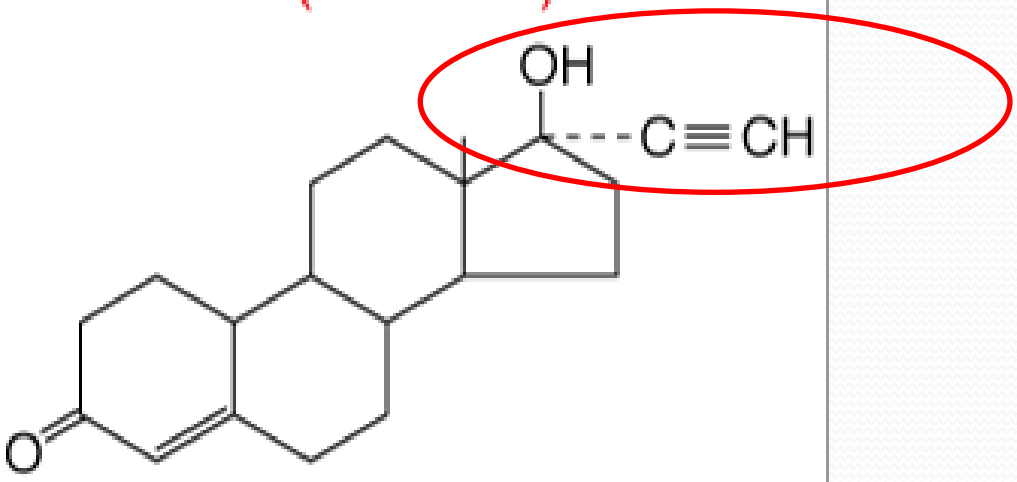
Substitutions at the 6-position of the B ring yield orally active **Medroxyprogesterone acetate**

Selective Progestational activity.

Agents Similar to 19-Nortestosterone (Estranes)



19-NORTESTOSTERONE

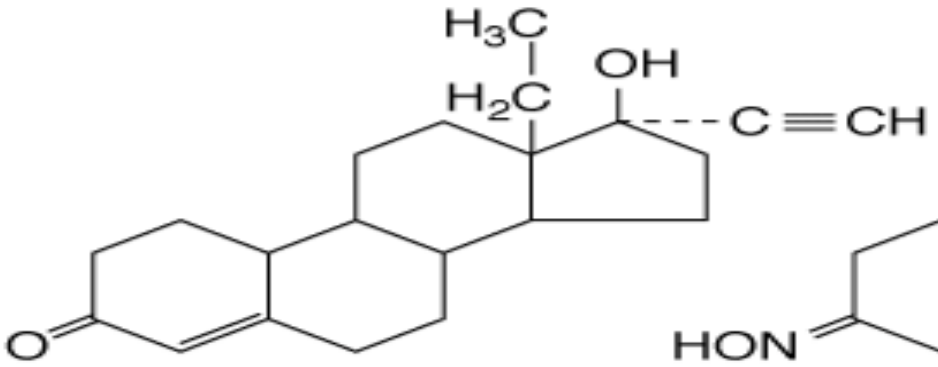


NORETHINDRONE

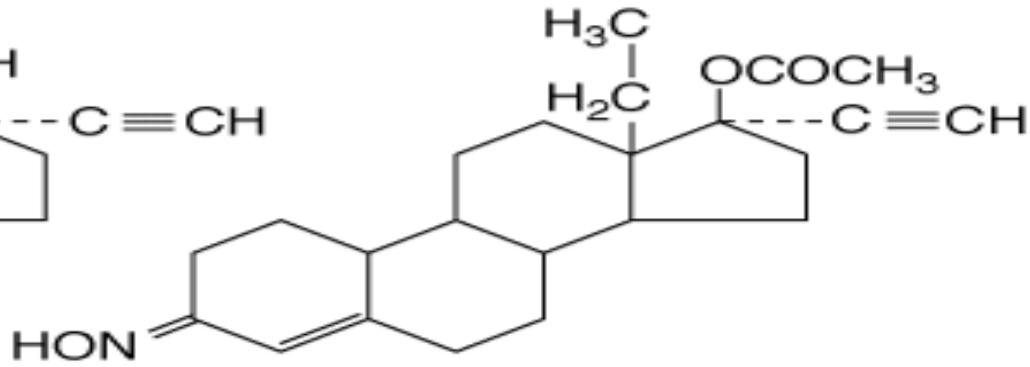
Lack the C19 methyl group

An Ethinyl substituent at C17 decreases hepatic metabolism and yields orally active

Agents Similar to 19-Norgestrel (Gonanes)



NORGESTREL



NORGESTIMATE

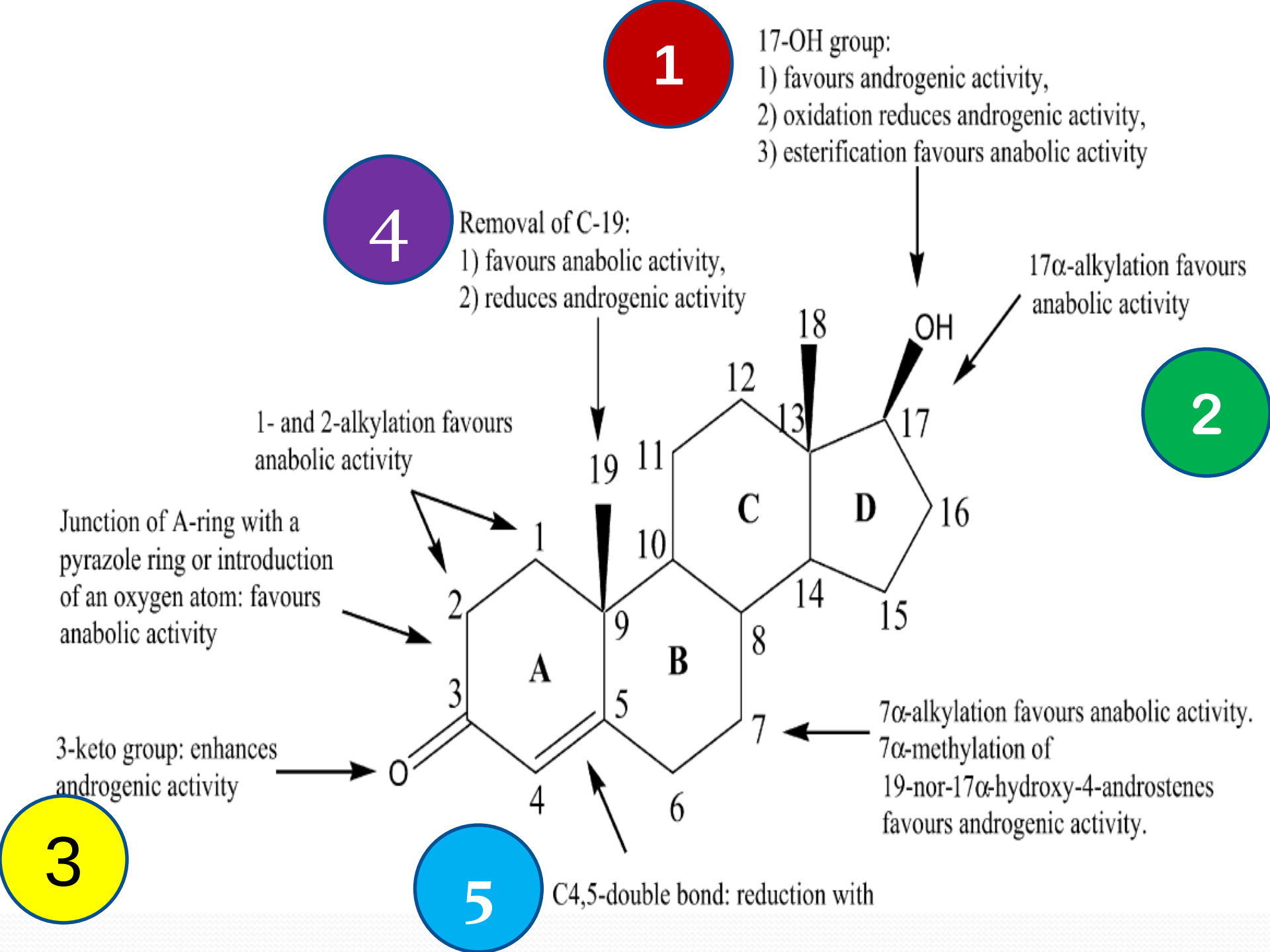
- **Replacement of the 13-methyl group of norethindrone with a 13-ethyl substituent**
- More potent progestin than the parent compound but has Less androgenic activity
- **Norgestimate, Desogestrel,Gestodene, Nomegestrol, Nestorone, Trimegestone**

ANDROGENS

Anabolic steroids, technically known as **anabolic-androgenic steroids** (**AAS**), are drugs that are structurally related to the cyclic steroid ring system and have similar effects to testosterone in the body.

In men, testosterone is the principal secreted androgen

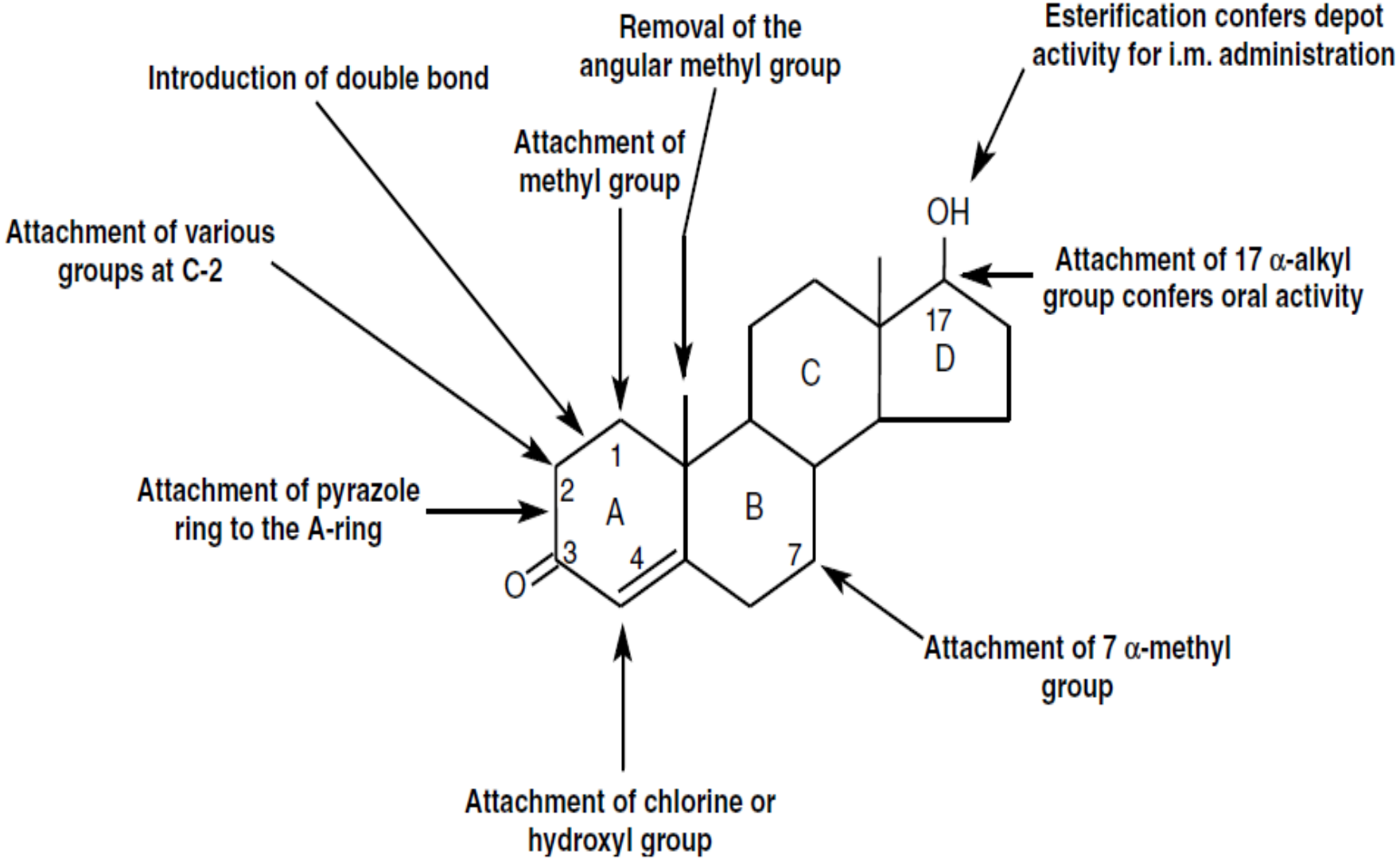
These endogenous compounds have two important activities: androgenic activity (promoting male sex characteristics) and anabolic activity (muscle building).


1
17-OH group:
1) favours androgenic activity,
2) oxidation reduces androgenic activity,
3) esterification favours anabolic activity
4
Removal of C-19:
1) favours anabolic activity,
2) reduces androgenic activity
17α-alkylation favours anabolic activity
2
1- and 2-alkylation favours anabolic activity
Junction of A-ring with a pyrazole ring or introduction of an oxygen atom: favours anabolic activity
3-keto group: enhances androgenic activity
3
7α-alkylation favours anabolic activity.
7α-methylation of 19-nor-17α-hydroxy-4-androstenes favours androgenic activity.
5
C4,5-double bond: reduction with
OH
O
A
B
C
D
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19

Known modifications of testosterone molecule include alkylation at the 17-position and/or modification of the ring structure.

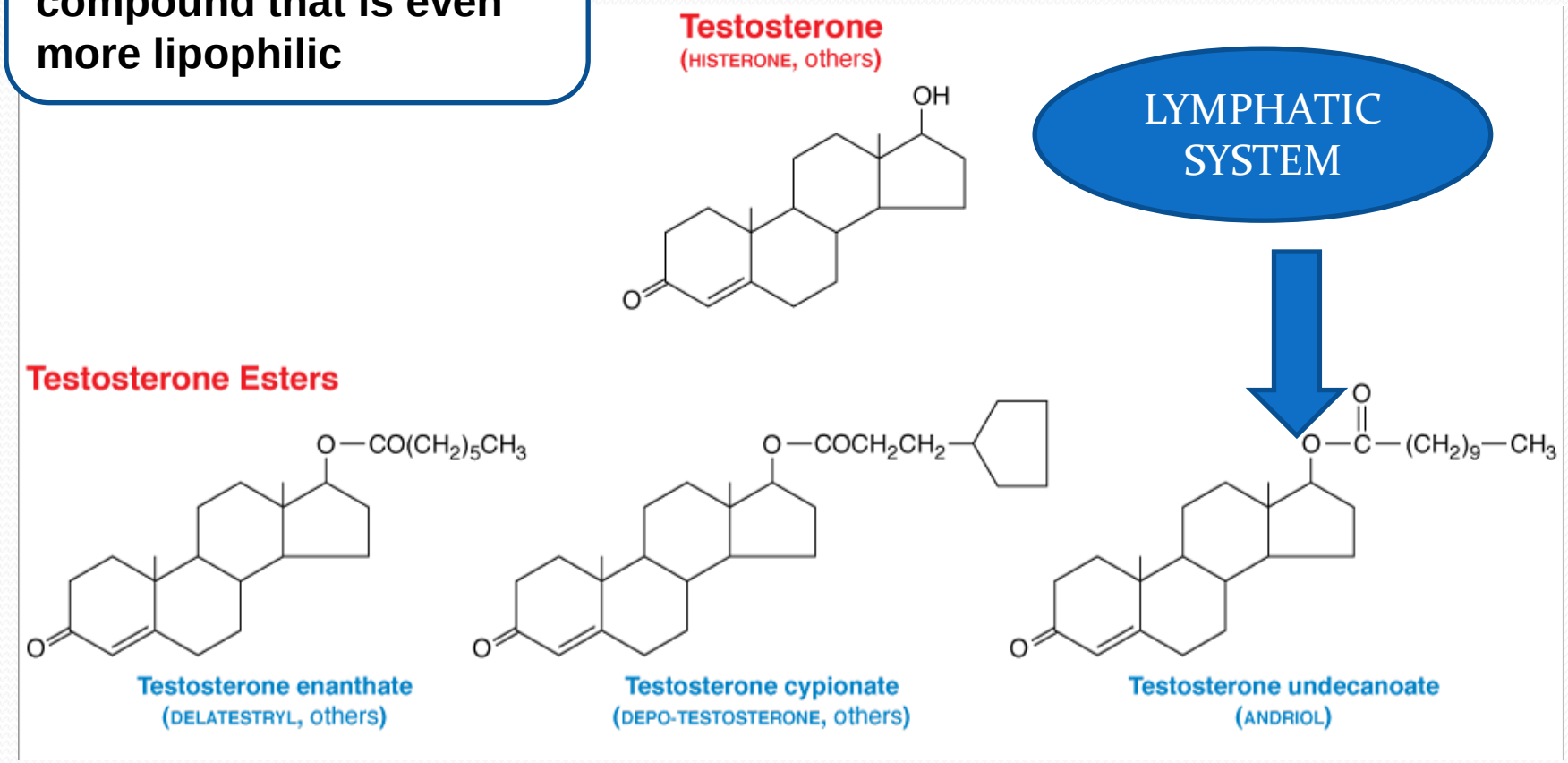
The goal of these modifications is the production of derivatives that are more anabolic and less androgenic than the parent molecule.

The esterification of the 17-hydroxyl group by carboxylic acids also increases the steroid activity due to the prolongation of the action, as the steroid gets lipophilic properties and the capability of retaining in fat tissue


Introduction of double bond
Removal of the angular methyl group
Esterification confers depot activity for i.m. administration
Attachment of methyl group
Attachment of various groups at C-2
OH
Attachment of 17 α-alkyl group confers oral activity
17
D
C
1
2
A
B
Attachment of pyrazole ring to the A-ring
3
4
7
O
Attachment of 7 α-methyl group
Attachment of chlorine or hydroxyl group

Therapeutic Androgen preparations

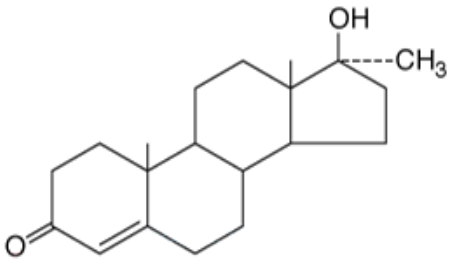
Esterifying a fatty acid to the 17 hydroxyl group compound that is even more lipophilic



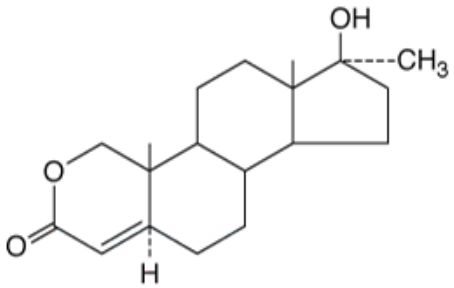
They are less androgenic than testosterone itself, they cause hepatotoxicity

Retarded its hepatic catabolism

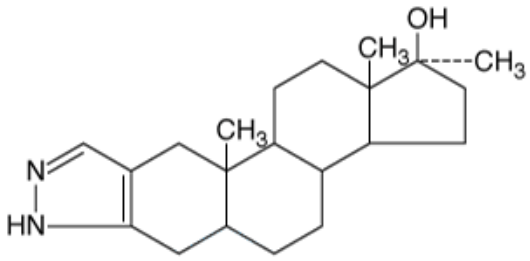
17α-Alkylated Androgens



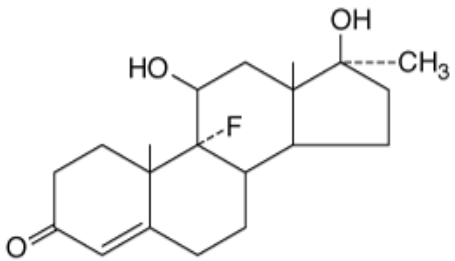
Methyltestosterone
(ORETIN METHYL, others)



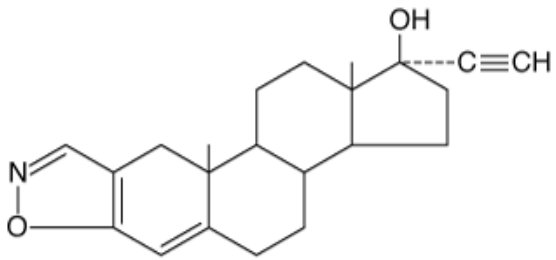
Oxandrolone
(OXANDRIN)



Stanozolol
(WINSTROL)



Fluoxymesterone
(HALOTESTIN)



Danazol
(DANOCRINE)


THANK
YOU!