Topic 10: Steroidal anti-inflammatory agents

❖ Introduction to steroids

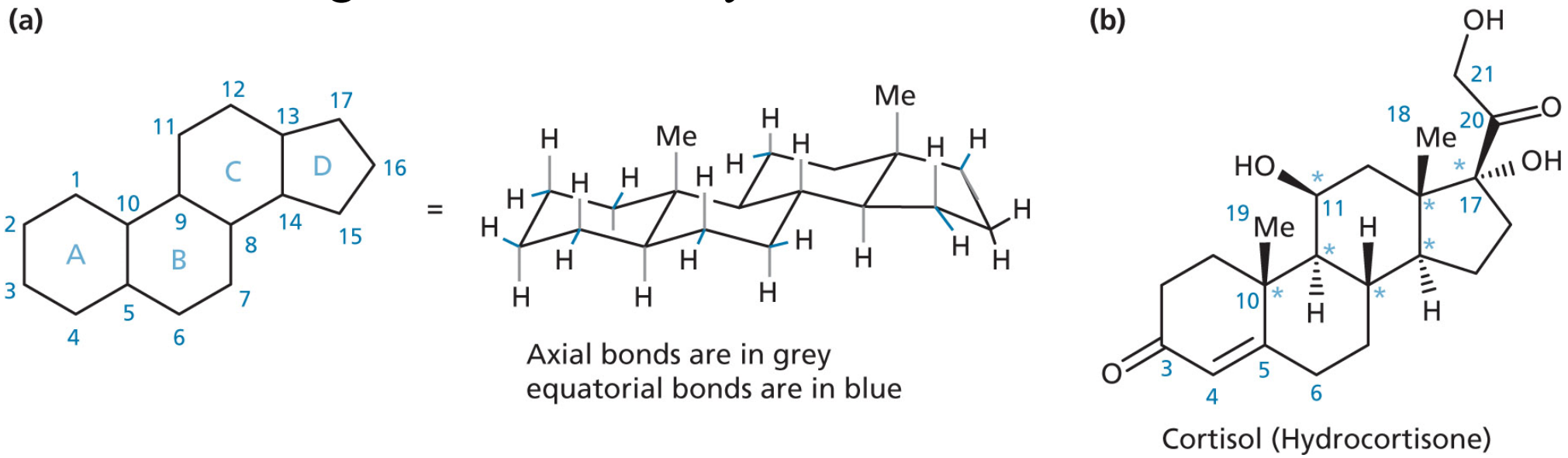
• Steroids are important endogenous hormones found in many life forms.

• They all share a common ***tetracyclic structure***, as shown in the figure, but they ***vary*** in the substituents and functional groups that are present.

• The stereochemistry of the rings in fully saturated steroids is identical in mammalian steroids, where the three 6-membered rings have chair conformations.

• There are several asymmetric centers present, but only one stereoisomer occurs naturally for any particular steroid.

• **Cortisol** has seven asymmetric centers, but only the stereoisomer shown in the figure exist naturally

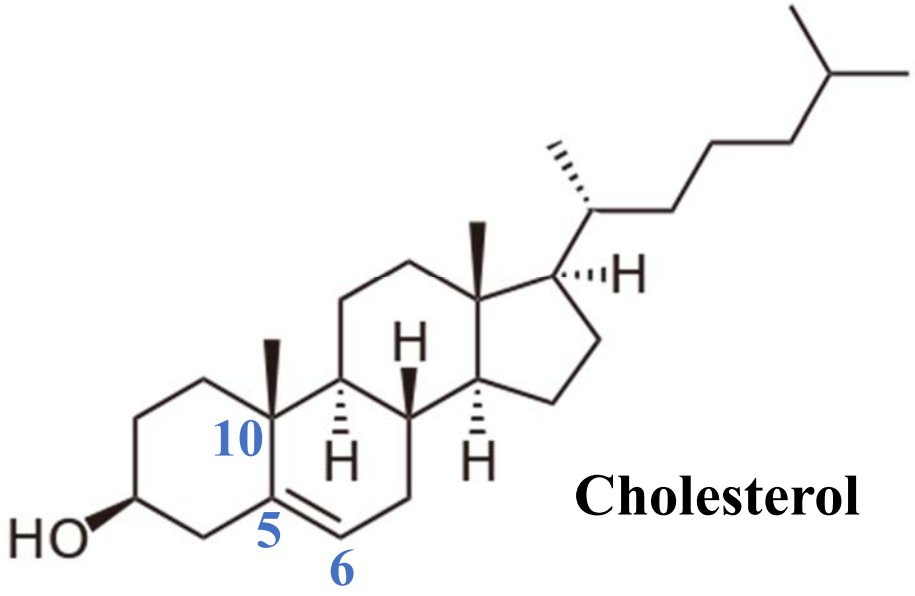


• One of the terminology used in the nomenclature of steroids is the substituents are often described as being alpha (α) or beta (β).

• α-substituents are below the general ***plane*** of the steroid and are presented by hatched wedges in two-dimensional diagrams (e.g. H9 & H14), whereas β-substituents are above the ***plane*** and are presented by solid wedges (e.g. C18 & C19).

• The position of double bonds in steroids is usually identified by the symbol delta (Δ); e.g. Δ^4 signifies the double bond between C4 & C5 in cortisol.

• If there is any doubts then numbers of both carbons are indicated, e.g. cholesterol has a double bond between C5 & C6, rather than C5 & C10, so this is indicated as $\Delta C^{5(6)}$



Cholesterol

• Steroids are **hydrophobic compounds** owing to their extensive hydrocarbon skeleton. This is an important character as the hormonal steroids have to cross cell membranes in order to interact with intracellular steroid receptors.

• All of the important endogenous steroids have **polar functional groups**, such as alcohols, phenols, and ketones. These play a crucial role in the binding steroids to their target receptors, but their presence does not alter the hydrophobic nature of the molecule as a whole.

• Because most steroids are **hormones**, they are present in very small quantities in the body. The exception is cholesterol which is present in much larger quantities and has a non-hormonal roles " in developing cholesterol-lowering drugs".

• Here, we will concentrating on those steroid released from the adrenal cortex of the adrenal gland- the **adrenocorticoids**.

• There are two types of adrenocorticoids- the **glucocorticoids** and the **mineralocorticoids**.

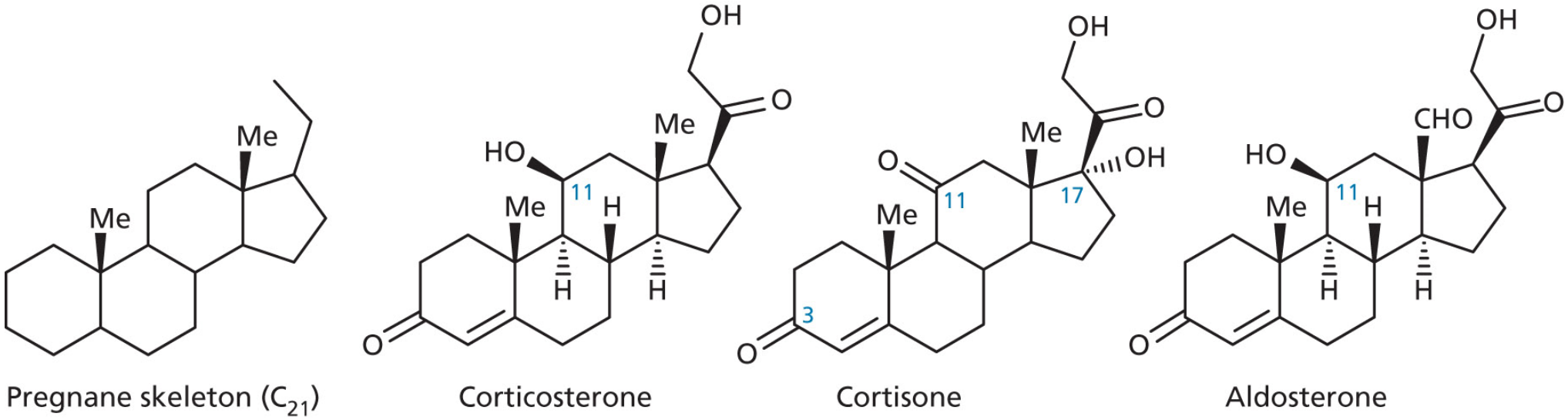
• **Glucocorticoids** act on carbohydrate, fat and protein metabolism mainly in liver, muscles, and brain cells. They have an important anti-inflammatory effect which is separated from their metabolic effects.

• **Mineralocorticoids** regulate electrolyte balance through sodium ion retention in kidney cells.

• The major endogenous glucocorticoids are **corticosterone**, **cortisone** and **cortisol** "also known as **hydrocortisone**".

• **Aldosterone** is the major endogenous mineralocorticoid.

• The adrenocorticoids are examples of steroids having **a pregnane** skeleton-steroids having a two carbon side chain at position 17 of the tetracyclic steroid skeleton.



Pregnane skeleton (C_{21}) Corticosterone Cortisone Aldosterone

• An imbalance of these steroids can lead to certain diseases. E.g. an excess of glucocorticoids causes **Cushing´s syndrome**, where as a deficit results in **Addison´s disease**. An excess of mineralocorticoids leads to **Conn´s syndrome**.

• The glucocorticoids have an important clinical role in replacement therapy for Addison´s disease.

• They have also been used as anti-inflammatories and immunosuppressants in the treatment of conditions such as asthma, hypersensitivity, rheumatoid arthritis, cancer and diseases which have an autoimmune or inflammatory effect.

• One of the most important applications of glucocorticoids in medicine is as anti-inflammatory agents.

• Unfortunately, the endogenous glucocorticoids suffer from the fact that they have **mineralocorticoid** and **immunosuppressant effects**, which can cause oedema and increase susceptibility to infection.

• Moreover, the endogenous glucocorticoids affect a large number of enzymes in different cell types.

❖ Orally active analogues of cortisol

• In 1947, it was found that cortisone could relive the symptoms of rhuematoid arthritis.

• Cortisone is readily converted in the liver to cortisol and it is now thought that the effects of cortisone are actually due to cortisol.

• A large number of analogues have been synthesized which have identified the features of cortisol that are important for corticosteroid activity.

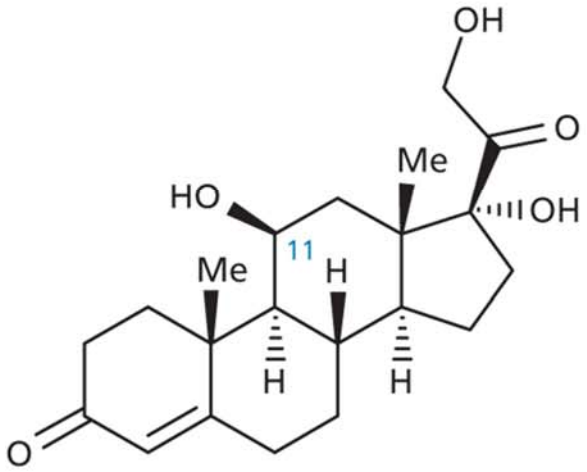
• In essence, all the functional groups **are important**, and the removal of any of these groups either reduces or eliminates activity.

• However, further studies have shown that the introduction of extra substituents can **increase** activity, which **allows the removal** of one of the original functional groups.

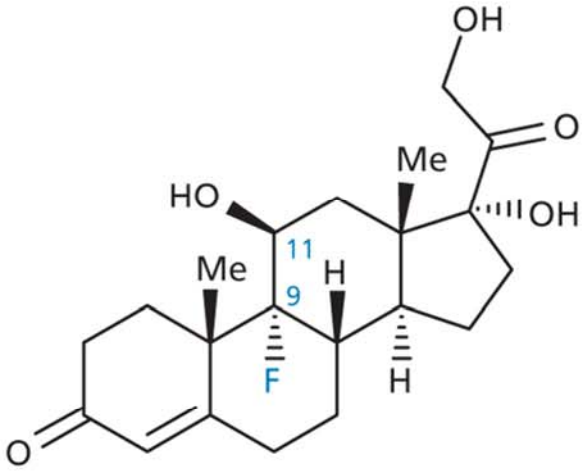
• Introducing a **9α-fluoro** substituent to give **fludrocortisone** increased activity 10-fold, but it also increased minieralocorticoid activity 300-600 times.

• the introduction of an extra double bond at the **Δ^1 position** increased activity 4-fold without increasing mineralocoticoid activity (**prednisolone and prednisone**).

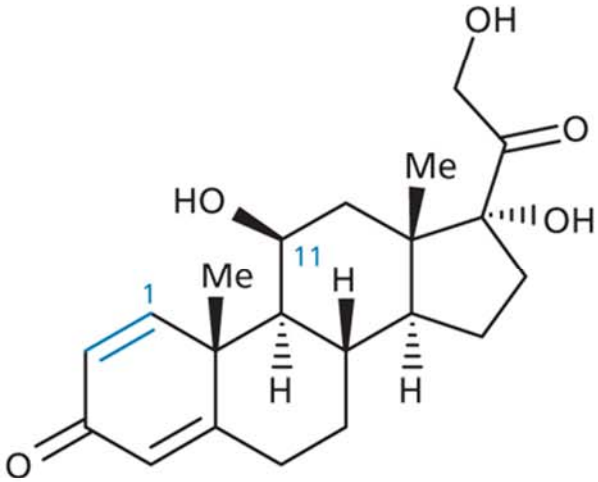
• Introducing substituents such as methyl or flourine at the **6α-position** has also been found to be beneficial because these groups serve to block metabolism at that position. E.g. **methylprednisolone** has a 6α-methyl group.



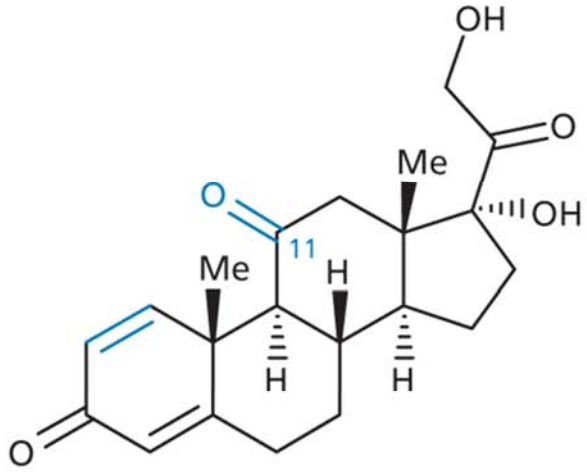
Cortisol



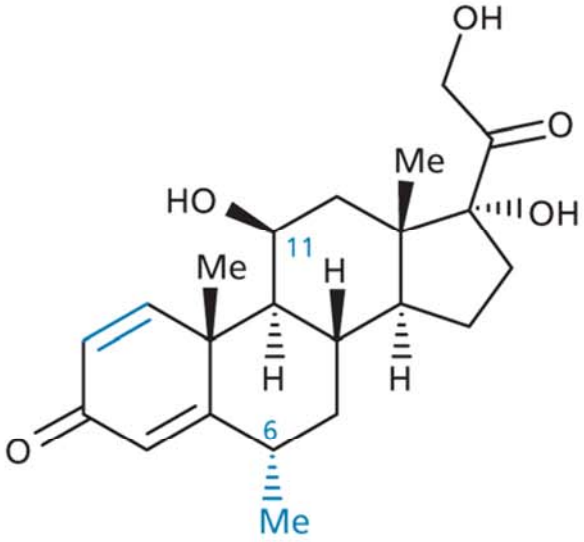
Fludrocortisone



Prednisolone



Prednisone

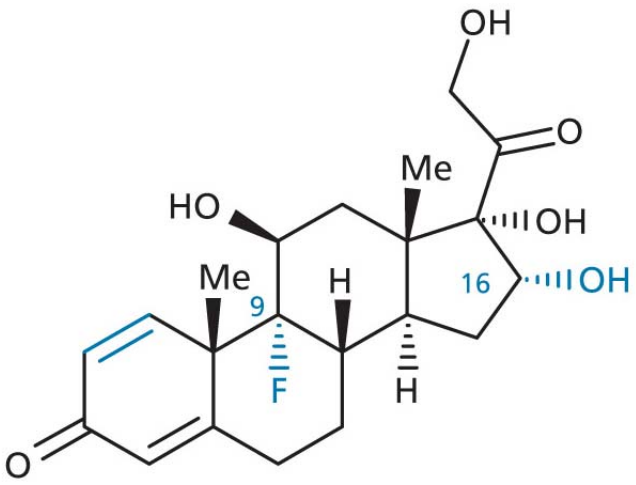


Methylprednisolone

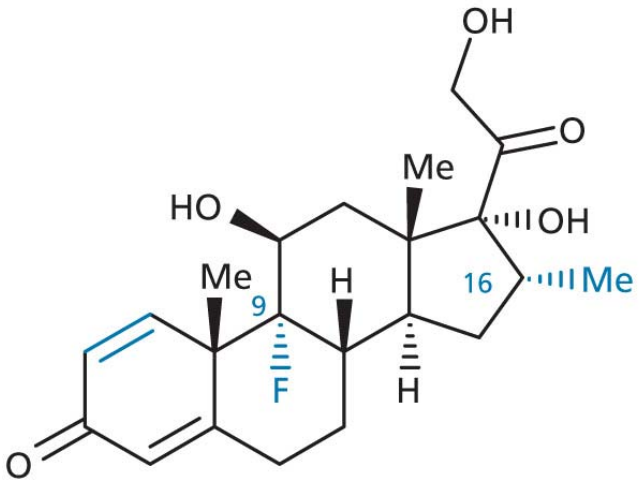
• A methyl group was introduced at **C-16** to see whether it would block the metabolic reduction of the C-20 keto group of hydrocortisone analogues- a reaction that is known to lead to inactive metabolites.

• Further research revealed that the introduction of C-16 substituents such as a methyl or hydroxyl group, **counteracted** the mineralocorticoid effect of a 9-fluoro substituent.

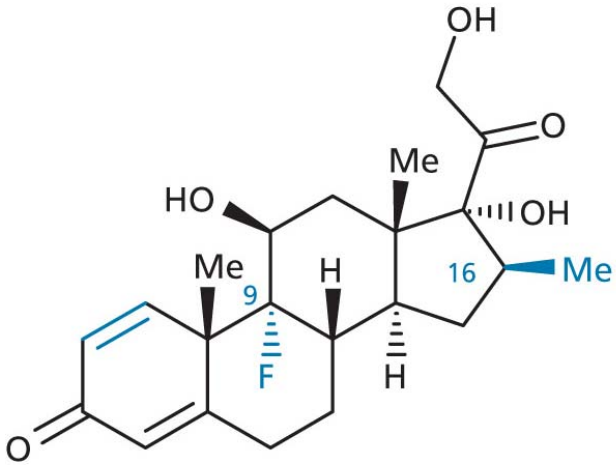
• This resulted in the development of **triamcinolone, dexamethasone, betamethasone, and flumetasone pivalate**, all of which have increased glucocorticoid activity and negligible mineralocorticoid side effects.



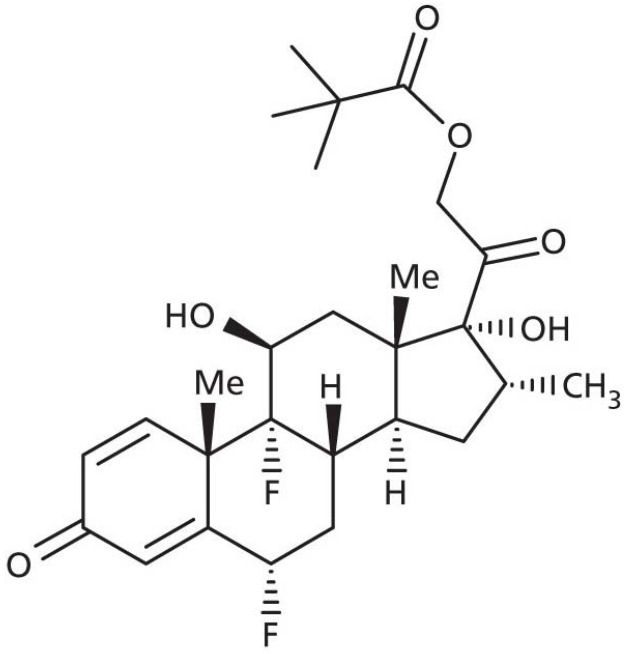
Triamcinolone



Dexamethasone



Betamethasone



Flumetasone pivalate

❖ Topical glucocorticoids as anti-inflammatory agents

❑ Cortisol analogues

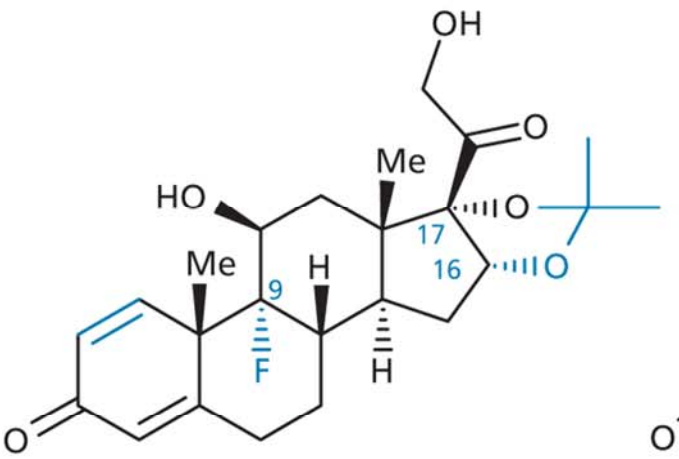
• Glucocorticoids are often applied topically to treat skin inflammation.

• **Triamcinolone acetonide** is one such agent; the **acetonide group** links the alcohol substituents at C16 & C17 of triamcinoline thus reducing the polarity of the molecule.

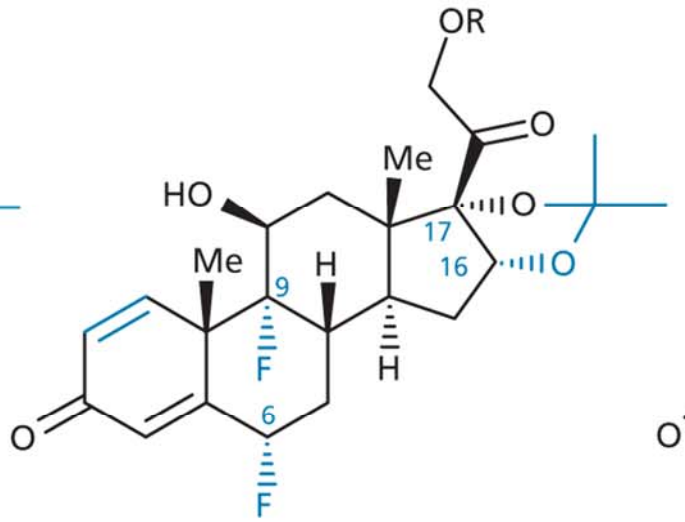
• This leads to better skin absorption and a 1000-fold increase in activity compared with triamcinolone itself.

• If the compounds are injected under the skin, they have equal activity.

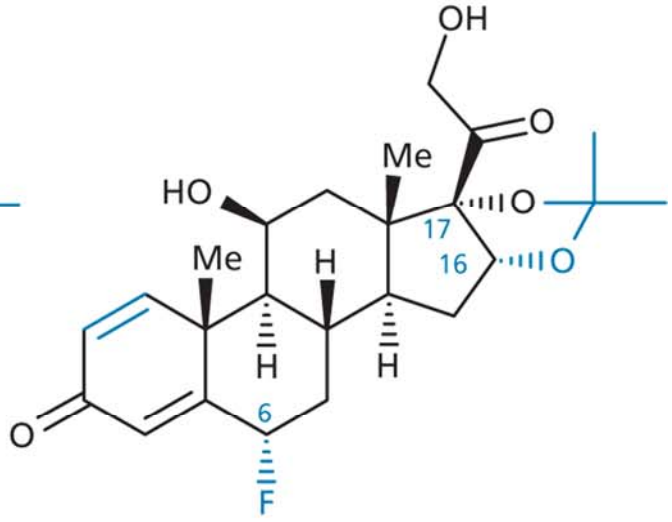
• **Fluocinolone acetonide**, **fluocinonide** and **flunisolide** are clinical agents that contain the same acetonide group.



Triamcinolone acetonide



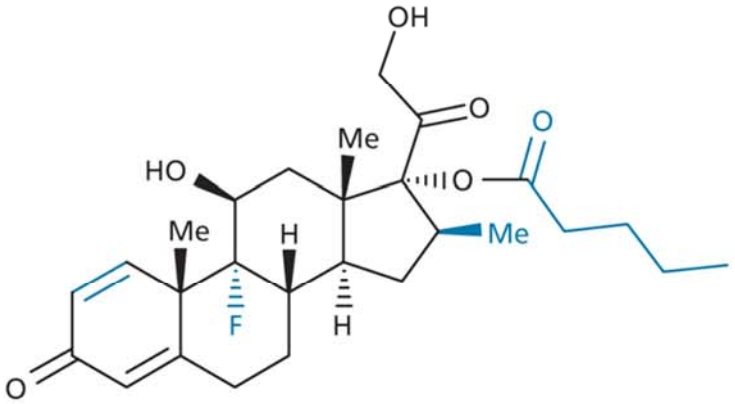
Fluocinolone acetonide; R = H
Fluocinonide; R = Ac



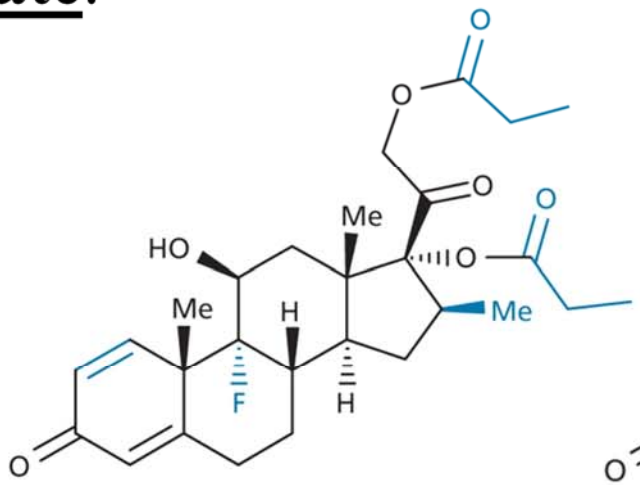
Flunisolide

• Good skin absorption can also be achieved by **esterifying** one or more alcohol groups. The corresponding phosphate esters were less active, providing further evidence that lipophilicity is important to the activity of topically applied anti inflammatories.

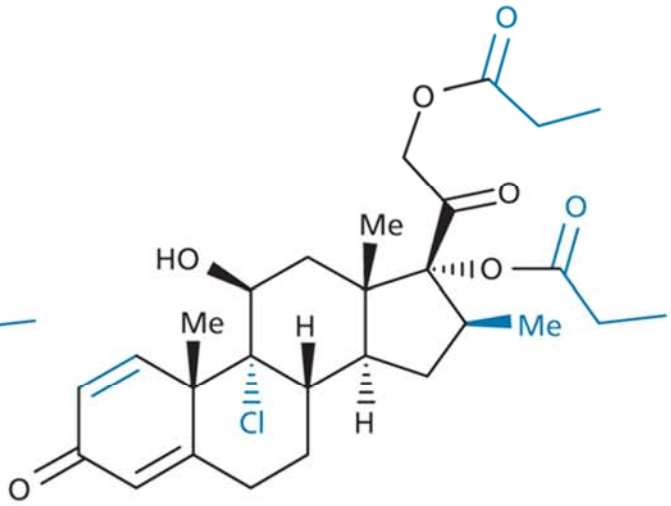
• Glaxo used this strategy to develop the clinically useful agents **betamethasone 17-valerate**, **betamethasone dipropionate** and **beclometasone dipropionate**.



Betamethasone 17-valerate



Betamethasone 17,21-dipropionate



Beclometasone 17,21-dipropionate

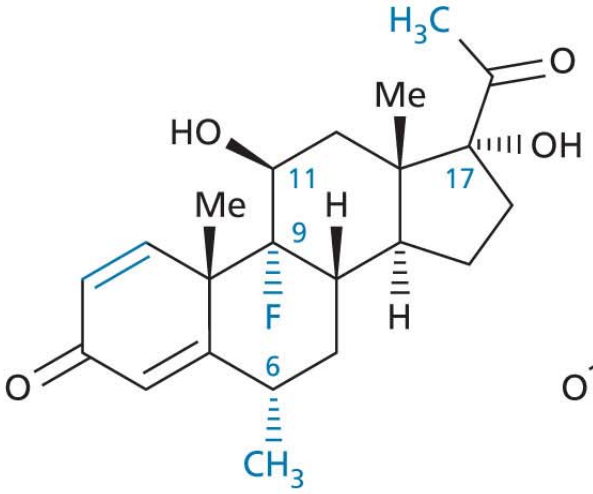
❑ 21-Deoxysteroids

• Removal of the 21-OH group from cortisol eliminates activity, but introducing an **extra double bond** in the A ring along with substituents at C6 and C9 restore the activity and results in **fluorometholone**.

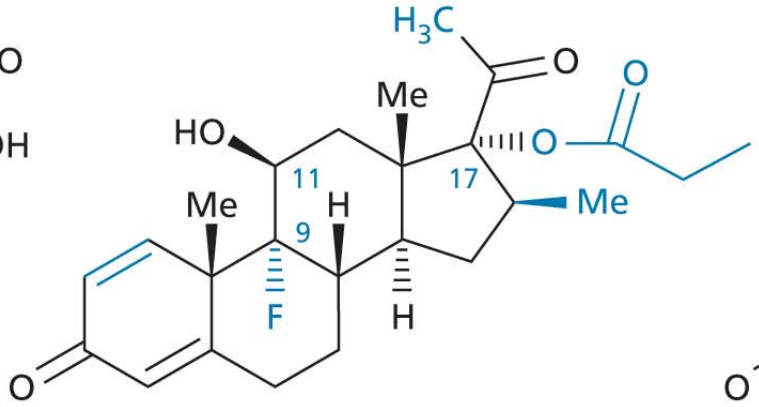
• **Esterification** of the 17-OH group results in better skin absorption and increased topical activity, e.g. **21-dexoybetamethasone 17-dipropionate**.

• **Introducing a halogen** at position 21 was particularly beneficial for the 17-esters. The best activity was obtained using F or Cl, with short chain esters at C-17.

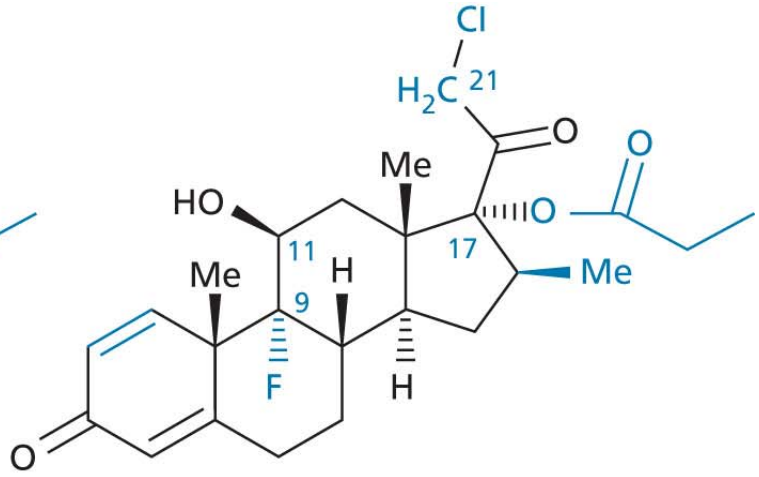
• The best compound arising from these studies was **clobetasol propionate**.



Fluorometholone



21-Deoxybetamethasone 17-propionate



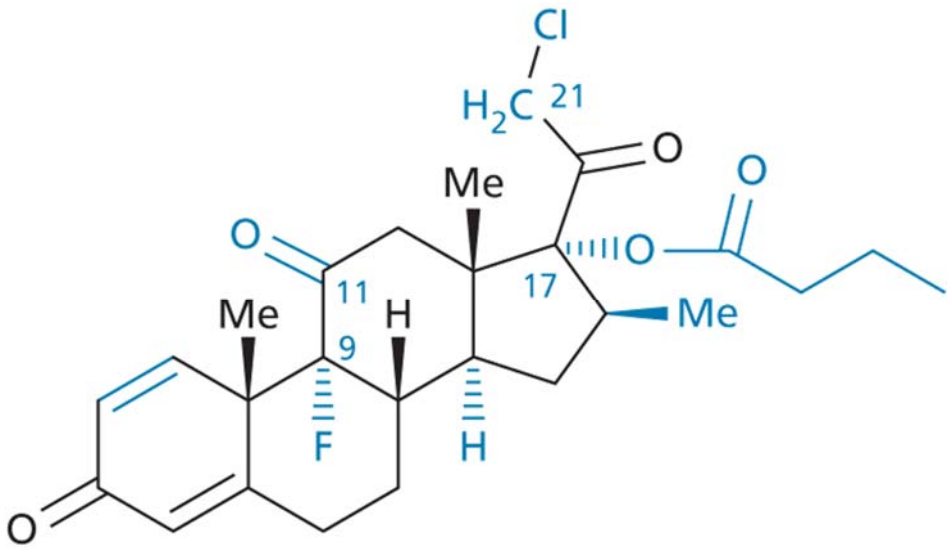
Clobetasol 17-propionate

❑ 11-Ketosteroids

• In general, **replacing the 11β-OH group** of cortisol with a keto group results in a drop in activity.

• However, activity can be **restored** by introducing suitable substituents elsewhere.

• **Halogens** at positions C-9 and C-21 are particularly important in this respect, e.g. **<u>clobetasone butyrate</u>**.



Clobetasone 17-butyrate

❑ Analogues with modified C-17 side chains

• The two carbon chain at C-17 is generally important for activity, but it was found that activity could be retained if the side chain was replaced with a **carboxylic acid** as long as both it and the 17-OH group **were esterified**.

• If only one was esterified then there was no activity.

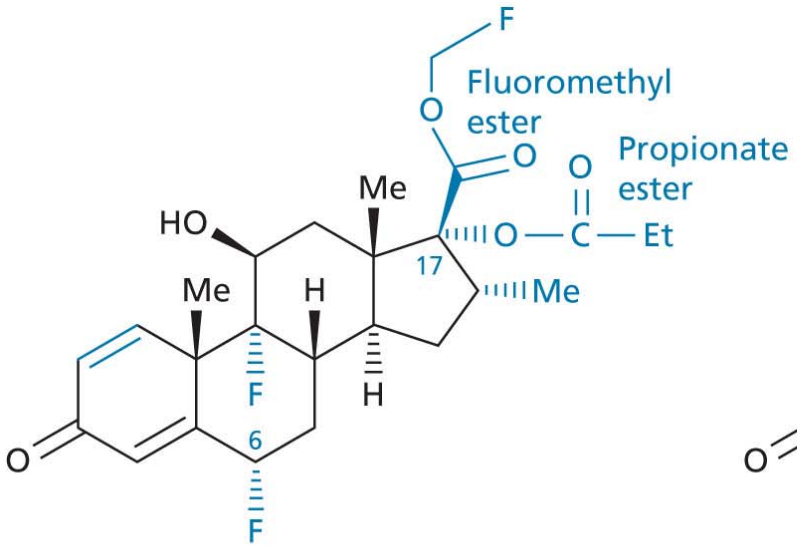
• This discovery is important that the di-esters would be active at the site of the administration but would be hydrolyzed to inactive compounds as soon as they reached the blood circulation.

• Thus reducing the chances of unwanted side effects elsewhere in the body.

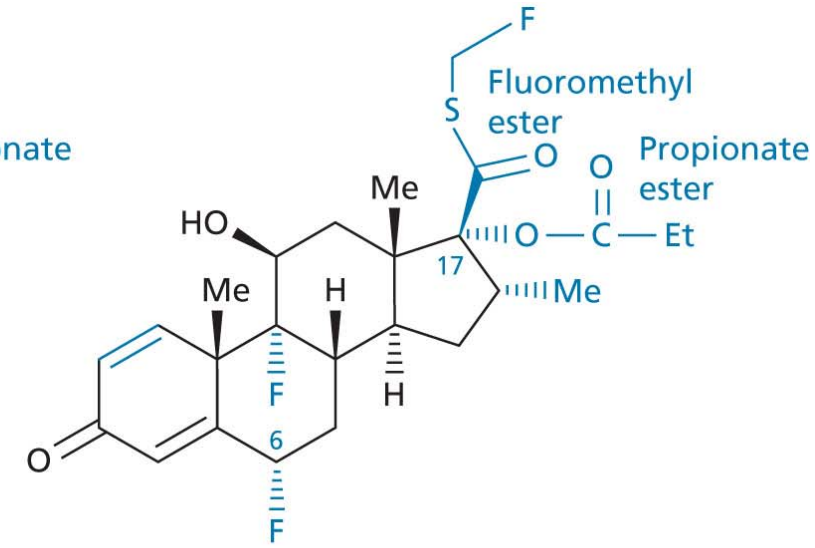
• A variety of esters were synthesized which demonstrated that the **17α-propionate and 17β-fluoromethyl** esters were ideal.

• Further variations led to the discovery that the **17β-fluoromethyl thioester** was also beneficial leading to the clinically important **fluticasone propionate**.

• This agent has a high affinity for target receptors, high potency, and low oral bioavailability (1%) because of low solubility and rapid metabolism in the liver.



Structure I



Fluticasone propionate

❑ Glucocorticoids used in asthma treatment

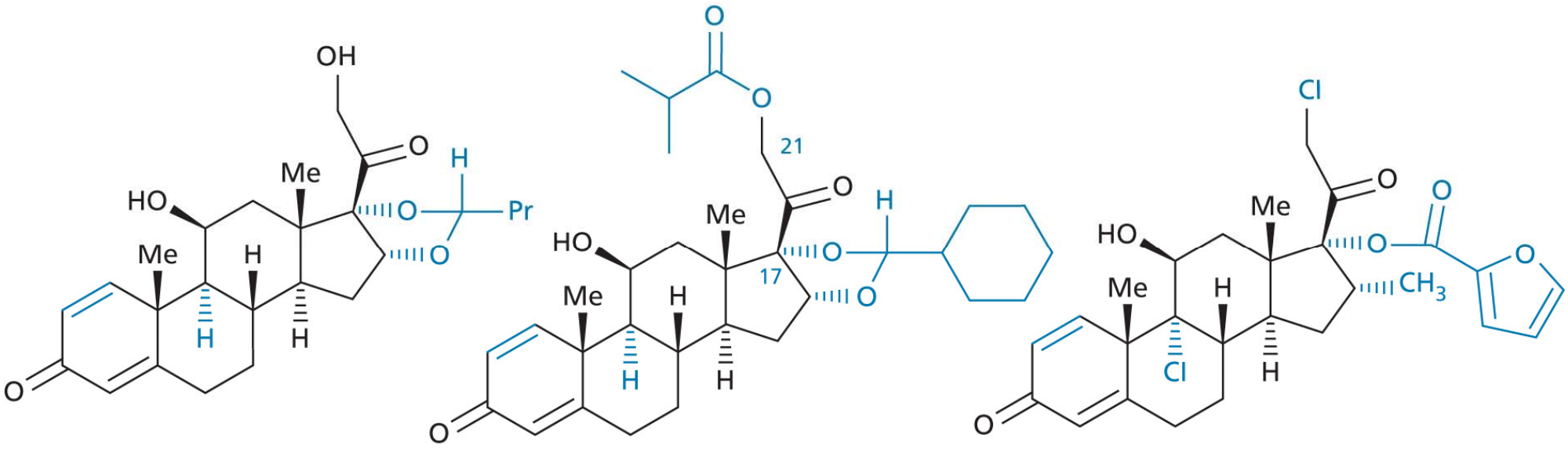
• Glucocorticoids are used as anti-inflammatory agents in the treatment of asthma and are administered by inhalation in order to reduce the risks of side effects caused by their presence in the blood supply.

• Most of the glucocorticoids used in asthma treatment are rapidly metabolized in the liver.

• Of more significance is the proportion of inhaled dose that gets absorbed into the blood supply through the lungs.

• Therefore, it is important that glucocorticoids used in asthma treatment are susceptible to metabolic deactivation in the blood; e.g. by esterase.

• **Beclometasone dipropionate** represented a breakthrough in asthma treatment and is currently used as an inhaler, as are **budesonide**, **ciclesonide**, **mometasone furoate**, and **fluticasone propionate**.



• Budesonide is an example of a new generation of non-halogenated glucocorticoids. May be expected a drop in activity as a result of a lack of halogen but the nature of **acetal** is key in providing high topical anti-inflammatory activity.

• The acetal group increases the hydrophobic nature of the compound leading to prolonged residence in lung tissue.

• Budesonide has been found to have high receptor affinity and a higher anti-inflammatory potency than fluticasone propionate.

• In contrast, its systematic glucocorticoid activity is 4-7 times lower owing to extensive first-pass metabolism in the liver by the cytochrome P450 enzyme (CYP3A4) to much less potent metabolite.

• **Ciclesonide** is the latest in this series and is an example of a soft steroid.

• The structure acts as prodrug and is activated by esterases in lung tissue which hydrolyze the C-21 ester to reveal a free alcohol group.

• This is the active compound and has a prolonged duration of action in lung tissue, and a negligible activity elsewhere in the body, despite it being able to reach the circulatory system. This is because it is rapidly metabolized by CYP450 enzymes to inactive metabolites.

• The use **of heterocyclic esters** at C-17 in **mometasone furoate** results in high topical anti-inflammatory activity.

❑ Glucocorticoids used in ophthalmology

• A number of steroids have been used as topical anti-inflammatory agents in ophthalmology such as **dexamethasone**, **fluorometholone**, **betamethasone sodium phosphate**, **hydrocortisone acetate**, **prednisolone acetate**, & **prednisolone sodium phosphate.**