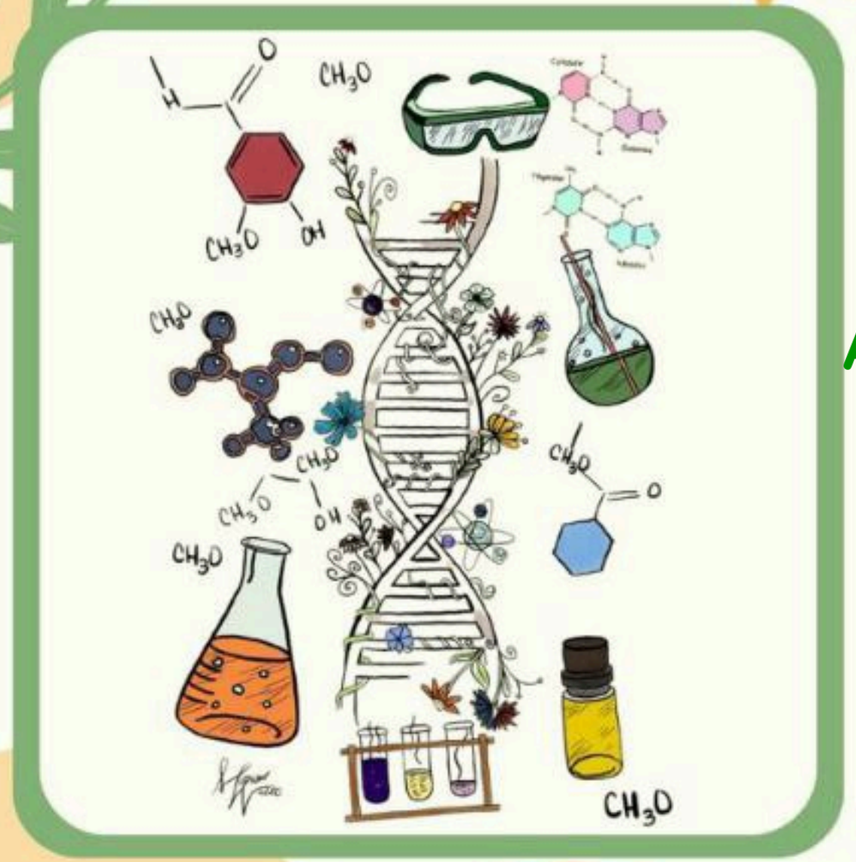
تفريغ عقاقير



اسم الموضوع: Acetate malonate pathway

إعداد الصيدلاني/ـة: *Alaa Otoum*

Soul Academy

لجان الدُّفعات

Chapter 6:
Acetate – Malonate Pathway

Acetate-derived Natural Products

Acetate formed from carbohydrate via pyruvic acid

Acetate is precursor for large no. of important natural products (flavonoids, anthraquinones, macrolides, terpenes & steroids)

2 main routes originate with acetate pathway:

1. **Acetate – Malonate Pathway** leading to FA & polyketides
2. Mevalonic acid pathway producing terpenes & steroids

Acetate malonate pathway

- The biogenesis of naturally occurring acetylenic substances is very closely related to the synthesis of unsaturated fatty acids.
- In the Plant Kingdome, fatty acids are used to form of triglycerides to produce oils.
- The natural sequence of the fatty acids (even-numbered fatty acids) starts with Palmatic acid (16 carbons), Stearic acid (18 carbons) and then Arachidonic acid (20 carbons). Palmatic acid and stearic acid are important in plants' oils,
- oils are composed of three fatty acids connected to glycerol.
- If glycerol is connected to 3 saturated fatty acids, the product is a solid substance called fat, and its found primarily in animal kingdom (mammals especially).
- When at least two of the hydroxyl groups in the glycerol are connected to unsaturated fatty acids, the product is termed as Oil, because of its liquid consistency.
- Oils are mainly found in plants, but there are some exceptions (like coconut oil, which is solid).

Lipids in plant kingdom include

- fatty acids and waxes
- essential oils
- many vitamins (vitamin "A" → hydrophobic (lipophilic vitamins))
- hormones (non-peptide)
- components of cell membranes (non-peptide) e.g.:- phospholipid.

Lipids are Hydrophobic (non-polar, soluble in organic solvent), typically of low molecular compound or organic origin

Share a common biosynthesis that ultimately derives their carbon source from glucose (glycolysis)

Glucose → pyruvate (3C) → acetate (2C)

glycolysis of glucose

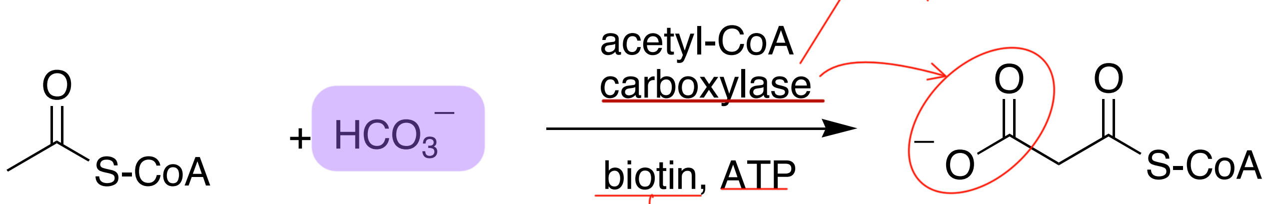
decarboxylation of pyruvate.

pyruvate

Acetate-malonate pathway and Mevalonic acid pathway start their biogenetic role with **acetyl CoA**.

Acetyl CoA is a very important building block of two carbons compound, it is needed in the **degradation** of carbohydrates and the **synthesis** of fatty acids, and appears in Krebs cycle and in the breakdown process of fatty acids.

Acetyl CoA + CO_2 ➔ Malonyl-CoA "3 carbons"

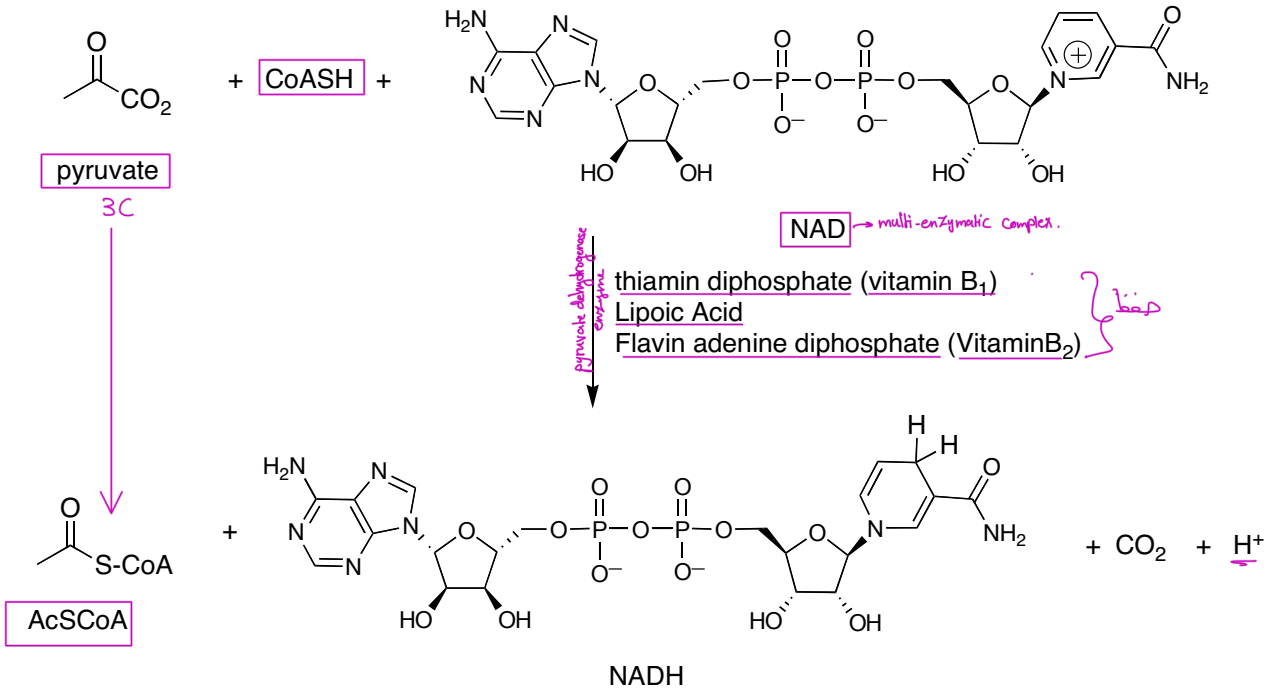


Malonyl CoA

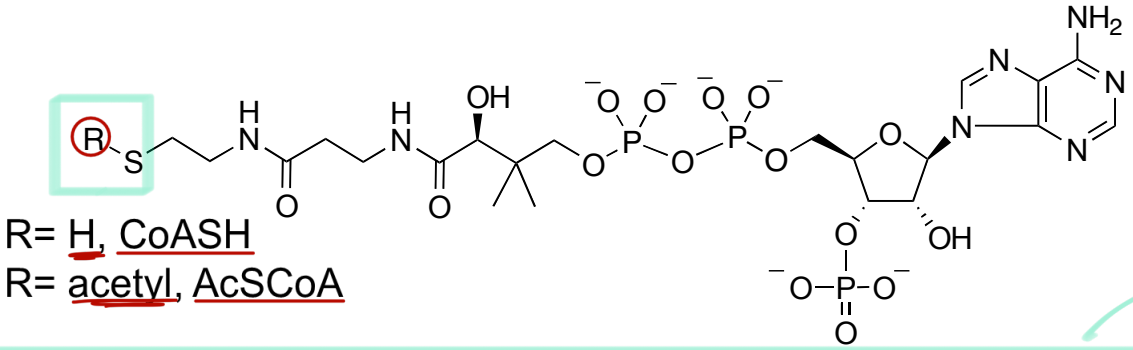
Now we will start with acetate-malonate pathway, and specifically with **non-aromatic (aliphatic) derivatives**.

None-aromatic derivatives in the acetate-malonate pathway polyacetylenic or polyynes , compounds having several unsaturated bonds.

Pyruvate dehydrogenase: Multi-enzyme complex that converts
pyruvate to AcSCoA (most important step in Acetate-malonate pathway).



Acetyl Coenzyme A. AcSCoA is a *thioester*.



R= H, CoASH
R= acetyl, AcSCoA

CoA enzyme

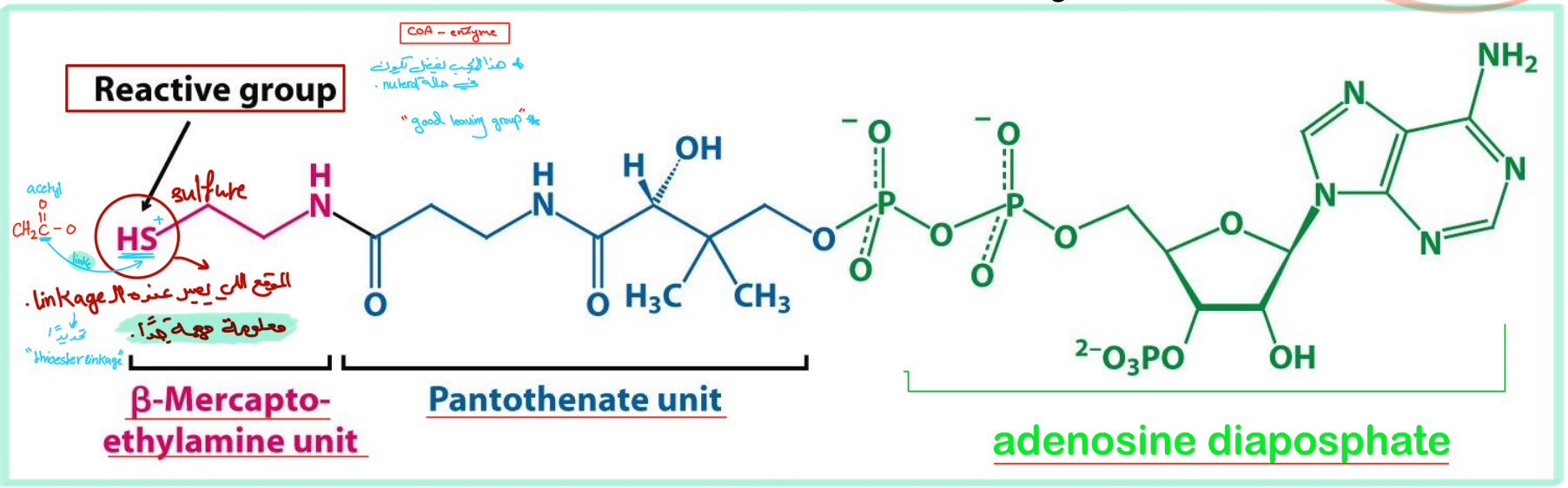
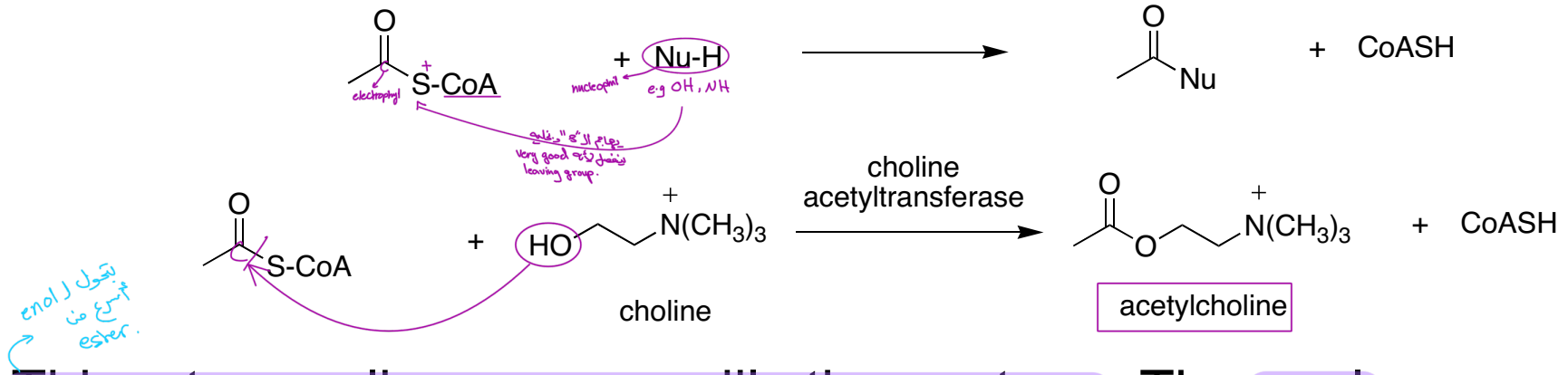
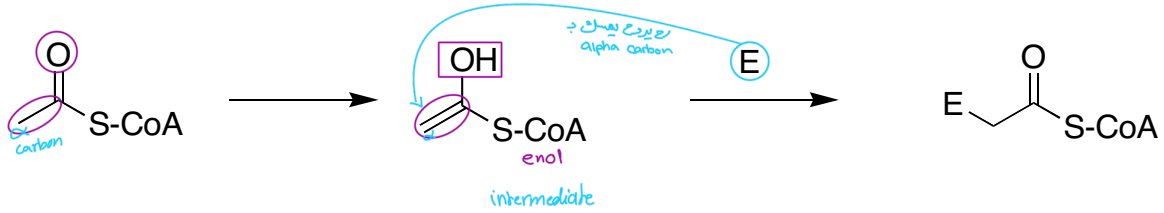


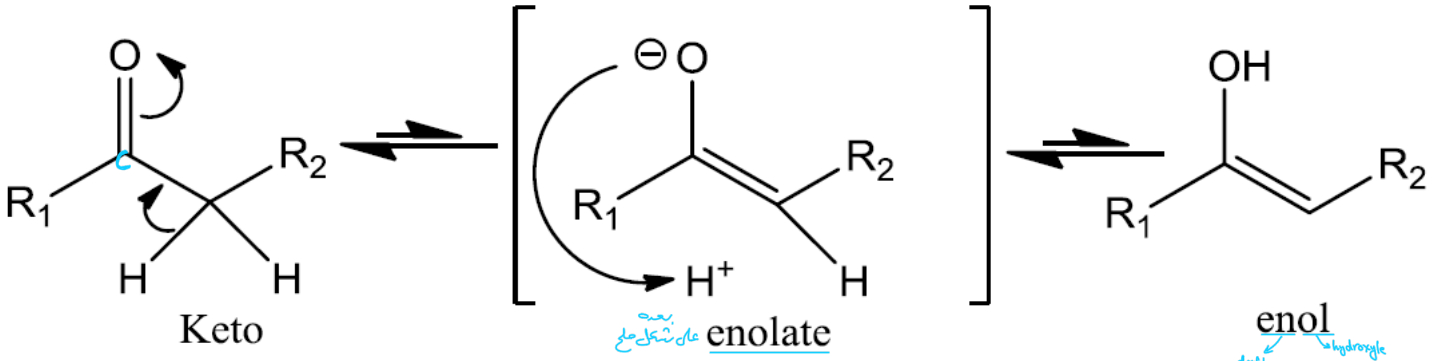
Figure 15.16
***Biochemistry*, Seventh Edition**

Acetyl CoA is a thioester. Thioesters are more reactive toward nucleophilic acyl substitution than esters, but considerably less reactive than acid chlorides and anhydrides.



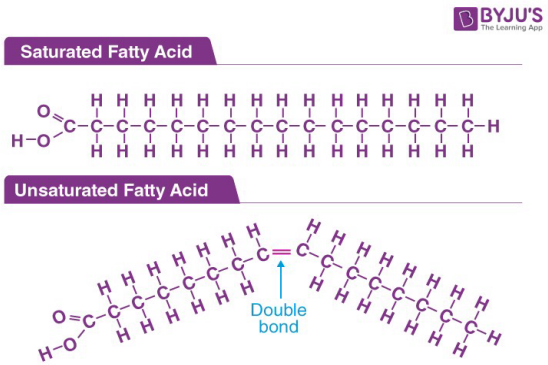
Thioester enolize more readily than esters. The enol can react with electrophile to afford α-substitution products





keto-enol tautomerism

Fatty acids (FA), fats, waxes



- FA: saturated or unsaturated
- Biosynthesis:

Saturated:

$AcetylCoA + CO_2 \rightarrow MalonylCoA$

$AcetylCoA + MalonylCoA - CO_2 \rightarrow FA\ (4C)$

Butyric (4C), Caproic (6C), Caprylic (8C), Capric (10C), Lauric (12C), Myristic (14C), Palmitic (16C), Stearic (18C), Arachidic (20C)

Unsaturated: by dehydrogenation of saturated FA

Oleic acid 18:1 (9c) (18C → one double bond at carbon "9") (in olive oil) Linoleic acid 18:2 (9c, 12c)

α-Linolenic acid 18:3 (9c, 12c, 15c)

γ- Linolenic acid 18:3 (6c, 12c, 15c)

Arachidonic acid 20:4 (5c, 8c, 11c, 14c) → eicosanoid derivative.

Eicosapentaeonic acid [EPA] 20:5 (5c, 8c, 11c, 14c, 17c)

→ omega 3

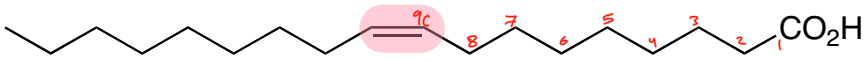
Fats, Oils, and Fatty Acids. *Fatty acids*: refers to long, straight-chain saturated and unsaturated acids, typically from C_{12} - C_{20} (Table 26.1, p. 1069).

saturated fatty acids:

$CH_3(CH_2)_nCO_2H$

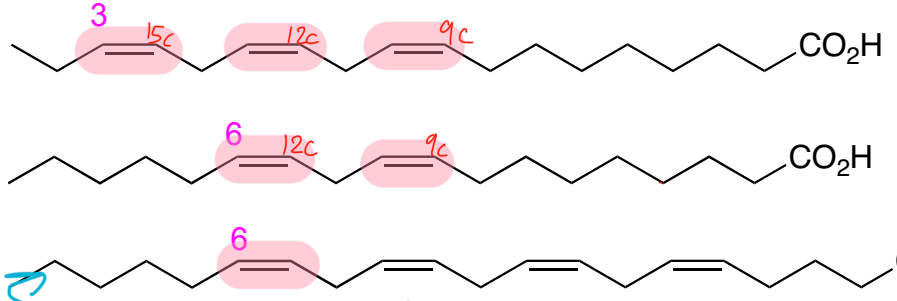
n=10, lauric acid (C_{12})
n=12, myristic acid (C_{14})
n=14, palmitic acid (C_{16})
n=16, stearic acid (C_{18})

unsaturated fatty acid



C_{18}, oleic acid

polyunsaturated fatty acids (PUFA)



C_{18}, linolenic acid (Omega 3)

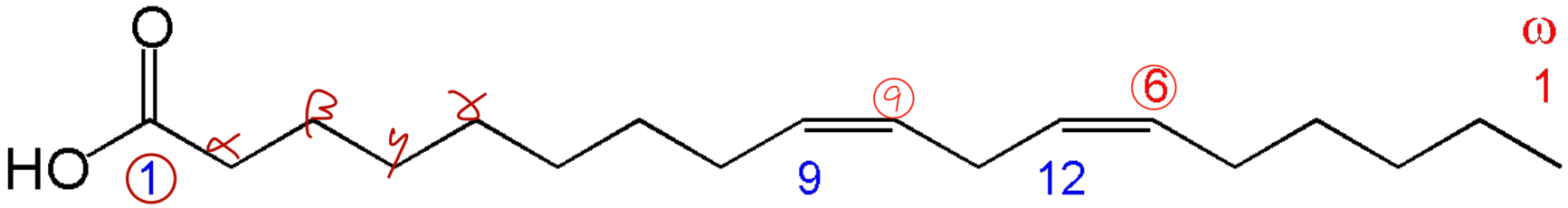
C_{18}, linoleic acid (Omega 6)

C_{20}, arachidonic acid (Omega 6)

في حالة تسمية omega يبدء بالعكس من السار بين من هون

Linoleic acid

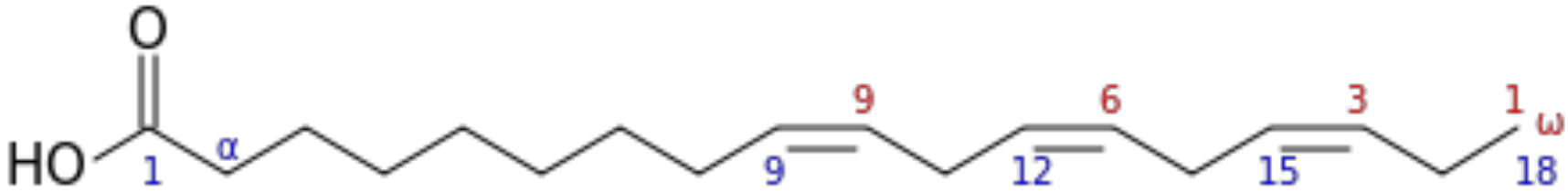
is a polyunsaturated omega-6 fatty acid



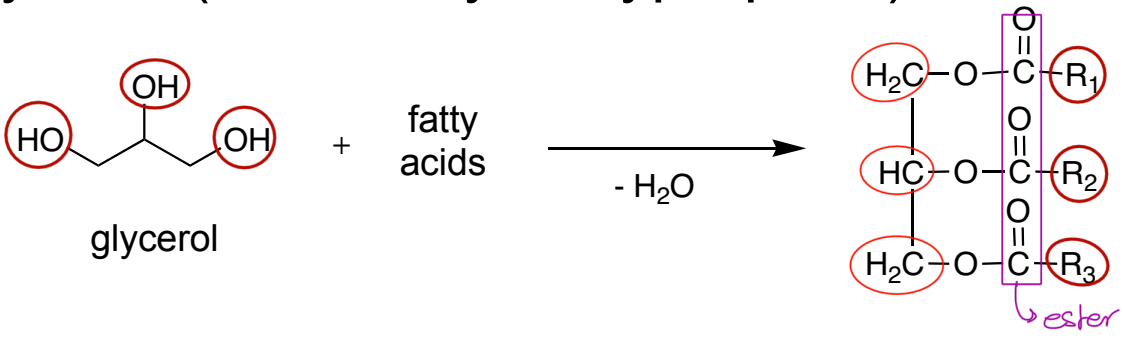
alpha-Linolenic acid

(ALA) is an *n*−3 fatty acid, it is one of two essential fatty acids (EFAs), so called because they are necessary for health, and they cannot be produced within the human body. They must be acquired through diet.

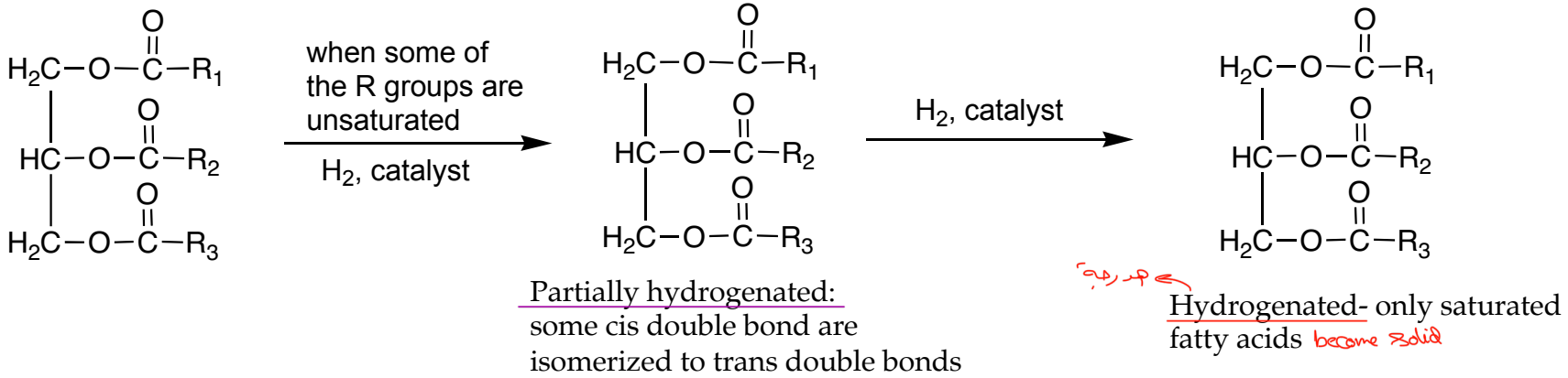
ALA is an omega-3 fatty acid(9c, 12c, 15c)



Fats and Oils: *Triglycerides* (triacylglycerols) are tri-esters of glycerol (1,2,3-trihydroxypropane) and fatty acids.



The R groups can be saturated or unsaturated, the same or different



Partially hydrogenated: some cis double bond are isomerized to trans double bonds

Hydrogenated- only saturated fatty acids become solid

Some important oils/fats/waxes

- Olive oil: Olea europea (Oleaceae)
- Arachis oil, peanut oil: Arachis hypogea (Fabaceae)
- Sesame oil: Sesamum indicum (Pedaliaceae)
- Almond oil: Prunus amygdalus (Rosaceae)
- Cottonseed oil: Gossypium herbaceum (Malvaceae)
- Soya bean oil: Glycine max (Fabaceae)
- Castor oil: Ricinus communis (Euphorbiacea)
- Cocoa butter: Theobroma cacao (Sterculiacea)
- Beeswax : Cera flava
- Spermaceti: Physeter macrocephalus

Spermaceti (from Latin *sperma* meaning "semen", and *ceti* meaning "whale") is a waxy substance found in the head cavities of the sperm whale

Castor Bean, Castor Oil Plant:
(بذور الخروع- زيت بذور الخروع)
•Ricinus communis L. Family: Euphorbiaceae

•Castor bean Oil:
•Oil from the castor bean seeds:
•The oil is obtained from the seeds by two principal methods - expression and decoction. The latter process is largely used in India, where the oil on account of its cheapness and abundance, is extensively employed for illuminating, as well as for other domestic and medicinal purposes.

Castor :
is a triglyceride, comprised of fatty acids, 90 % of which is ricinoleic acid, 7% oleic, 3% linoleic, 2% palmitic, 1% stearic, and trace amounts of dihydroxystearic.

Medicinal Uses

Where can I find Castor oil in the pharmacy?

1. Castor oil is used to traet Constipation it is Laxative (ملين) & purgative. (مسهل)
2. Castor oil can be used to treat Skin Problems such as sunburn, abrasions (تقرحات), acne, dry skin warts (ثآليل).
3. Castor oil is used in hair treatment: Castor oil protects the scalp and hair from microbial and fungal infections due to the presence ricinoleic acid which has germicidal, insecticidal and fungicidal properties
4. Castor oil is used in as anti-wrinkle Treatment

Contradictions: (تناقضات)

- Castor oil is contraindicated in intestinal obstruction and during pregnancy and nursing (رضاعة).
- The drug cant be administered to children under 12 years

Toxic Part in castor : The toxin Ricin
is found within the hard, water-impermeable coat of the seeds. The toxin is not released unless the seed coats are broken (e.g., chewed) and the contents digested.

Symptoms of Poisoning

Variations in the severity of toxicity may be related to the degree to which seeds are chewed. Effects begin as nausea, vomiting, abdominal cramping, diarrhea, and dehydration.

•One castor bean contains enough ricin to kill a child

Omega 3 fats

Omega-3 fats are a key family of polyunsaturated fats. There are three main omega-3s:

1. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) come mainly from fish, so they are sometimes called marine omega-3s.
2. Alpha-linolenic acid (ALA), the most common omega-3 fatty acid in most Western diets, is found in vegetable oils and nuts (especially walnuts), flax seeds and flaxseed oil, leafy vegetables, and some animal fat, especially in grass-fed animals. The human body generally uses ALA for energy, and conversion into EPA and DHA is very limited.

Why do we need Omega 3?

Alpha-linolenic acid (ALA), is found in vegetable oils and nuts (especially walnuts), flax seeds and flaxseed oil, leafy vegetables, and some animal fat, especially in grass-fed animals. The human body generally uses ALA for energy
The strongest evidence for a beneficial effect of omega-3 fats has to do with heart disease.
Omega-3 fats lower blood pressure and heart rate, improve blood vessel function, and, at higher doses, lower triglycerides and may ease inflammation, which plays a role in the development of atherosclerosis.

Several large trials have evaluated the effect of fish or fish oils on heart disease. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (known as the GISSI Prevention Trial), heart attack survivors who took a 1-gram capsule of omega-3 fats every day for three years were less likely to have a repeat heart attack, stroke, or die of sudden death than those who took a placebo.

There have also been promising results from studies looking at omega-3 for cancer, depression, and attention-deficit hyperactivity disorder (ADHD). Due to these potential health benefits, fish oil, which is rich in omega-3 fatty acids, has become a popular supplement.
There is evidence that recommended amounts of DHA and EPA, taken as fish or fish oil supplements, may lower triglycerides and reduce the risk of heart attack, abnormal heartbeat, and stroke in people who have heart disorders. DHA and EPA may also benefit people who have hardening of the arteries or high blood pressure. Similar effects have been found for ALA, but more evidence is needed to support its potential benefits.

Linseed- Flax seed بذر الكتان

- Linum usitatisimum L. Family: Linaceae.

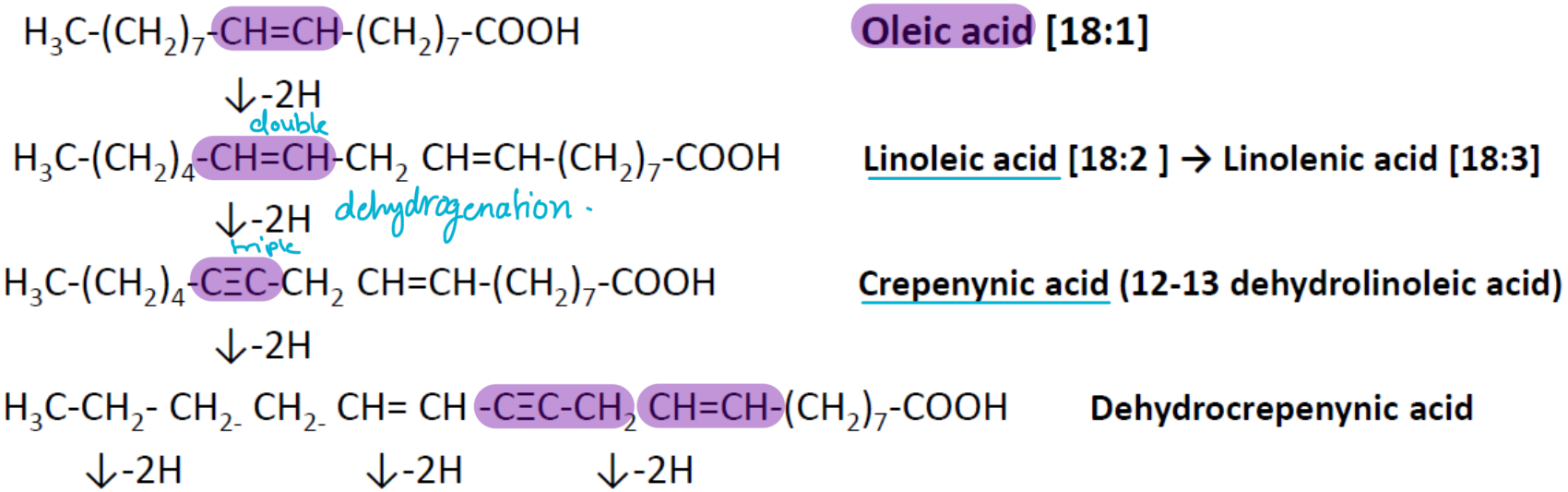
- They're the best plant source of omega-3 fatty acids.
- Flaxseeds are also a powerful source of fiber, protein, magnesium, iron, and potassium.
- Flaxseeds are also the leading source of a class of compounds called lignans, which are phyto-estrogens, or plant estrogens. Lignans influence the balance of estrogens in the body and help protect against breast cancer.
- **The seeds must be ground, as the nutrients are difficult to absorb from the whole seeds**. Since the oil in flaxseed spoils quickly, it's best to grind them as needed. Some people use a grinder dedicated to flaxseeds, grind them in small amounts, and keep the ground portion in the fridge in a small glass jar.
- Sprinkle ground flaxseeds on oat-meal, cereal, and yogurt, and use it in smoothies, pancakes, muffins, and quick breads. **One to two tablespoons of ground flaxseed a day is all you need.**

Linseed- Flax seed بذر الكتان

- **Active constituents:**
- **Mucilages:** including arabinoxylans, galactans, rhamnogalacturonans.
- **Cyanogenic glycosides:** Linamarin, linustatin, neolinustatin (yielding under optimal conditions 30-50 mg HCN per 100 gm).
- Linmarin (may play a role in cancer treatment)
- **Fatty oil** (30-45%): chief fatty acids linolenic acid , linoleic acid ,oleic acid.
- **Proteins**.
- **Gluten: Flax is gluten-free**.
- •**Lignans:** secoisolariciresinol-diglucoside
- **lignans**: Flax is a very rich source of a lignan called secoisolariciresinol diglucoside (SDG), which is found in amounts ranging from 1 mg/g of seed to nearly 26 mg/g of seed.
- **lignans** are natural antioxidants that may reduce the activity of cell-damaging free radicals, slow the aging process, and increase overall wellness.
- Besides acting as antioxidants, lignans are phytoestrogrens
- Lignans are especially important for women as studies have shown them to decrease the risk of breast cancer. In addition, lignans have been proven to reduce breast cancer symptoms and reduce the spread and growth of breast cancer after diagnosis.

Biogenesis of natural acetylenes

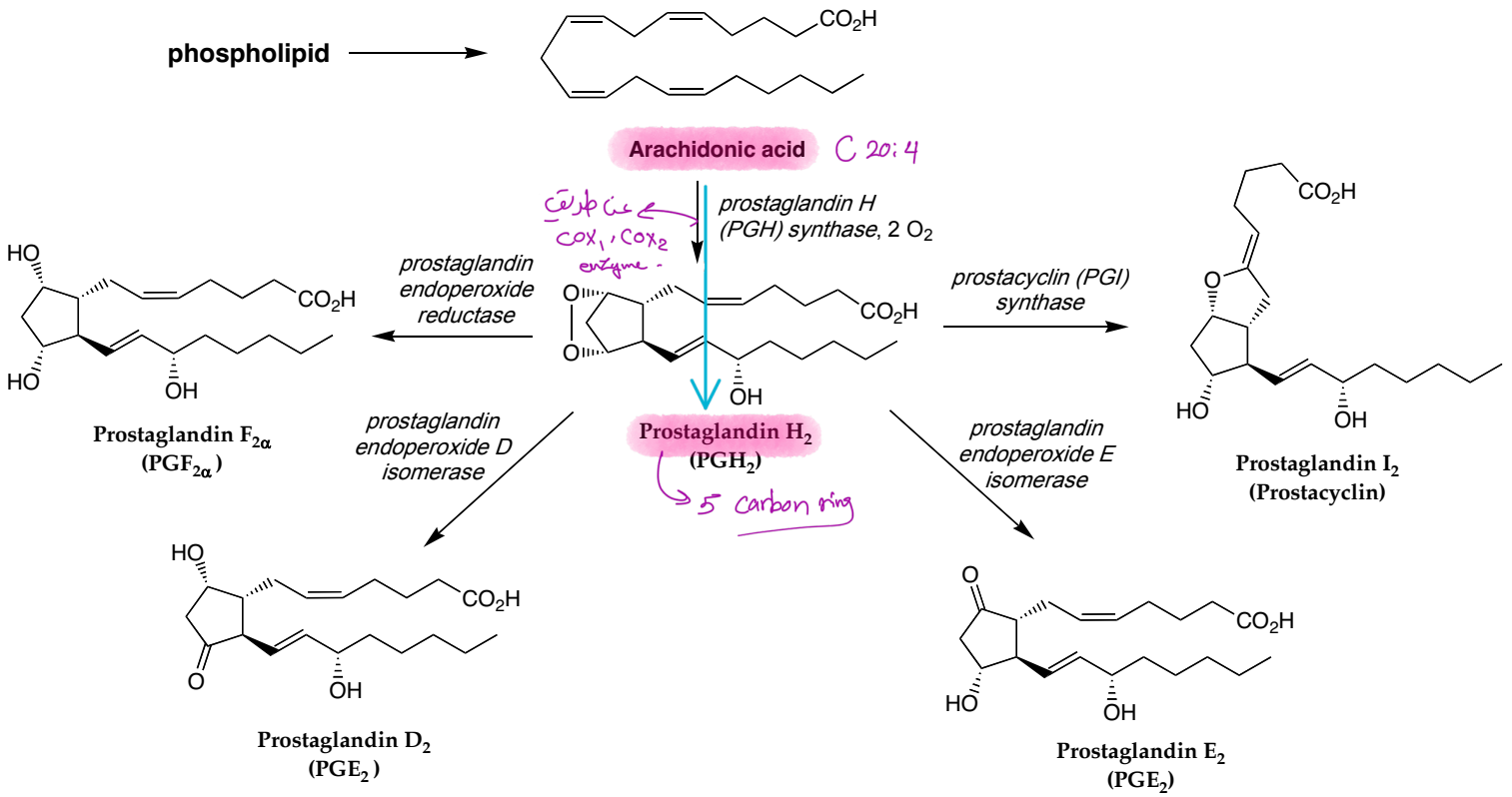
The precursor of the acetylenic substances is oleic acid



Ref.:
Prof. Sulaiman Khalil

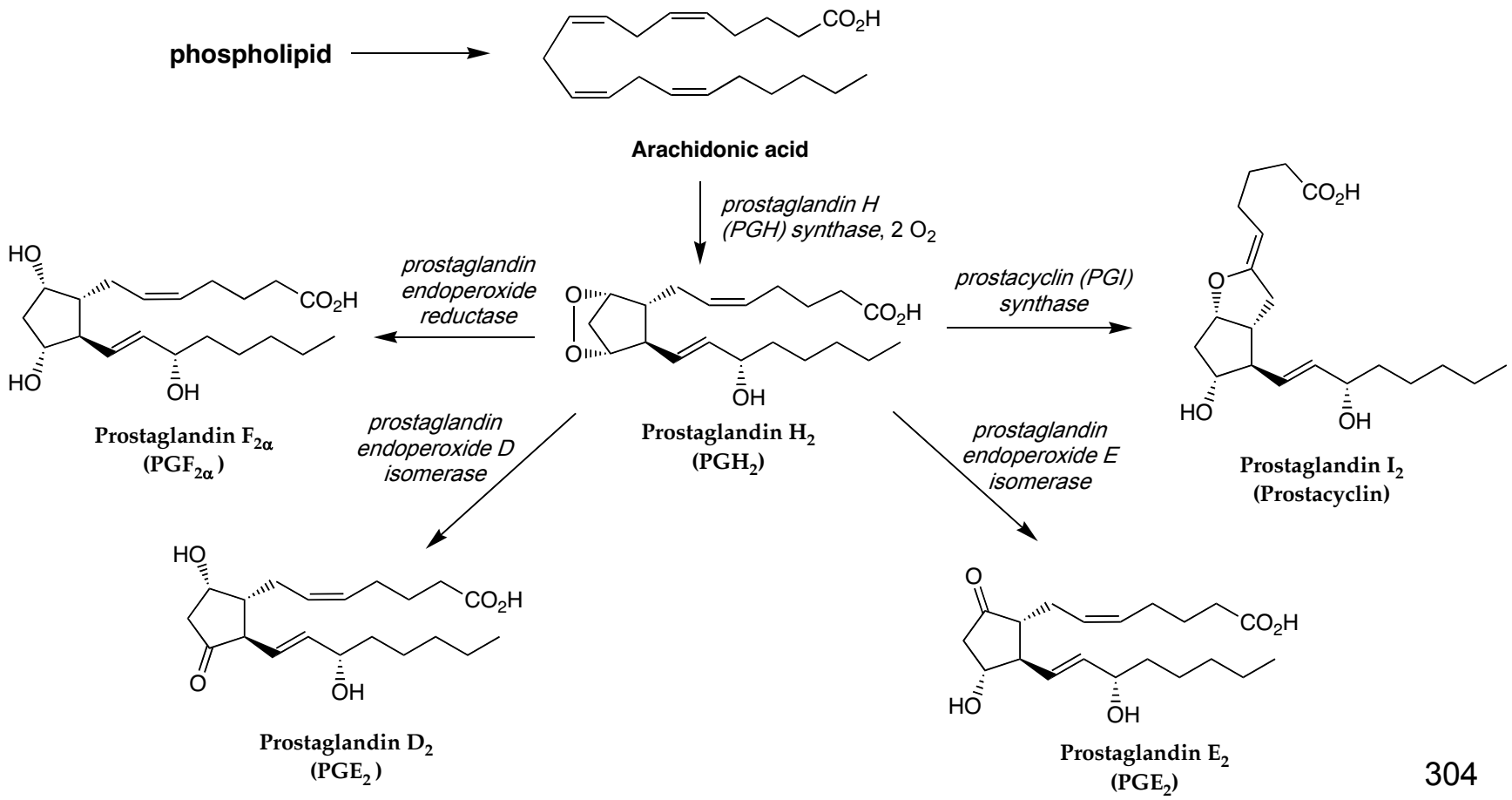
Prostaglandin

- The **prostaglandins** (PG) are a group of physiologically active lipid compounds having diverse hormone-like effects in animals.
- Prostaglandins have been found in almost every tissue in humans and other animals. They are derived enzymatically from fatty acid (Arachodonic acid). Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring

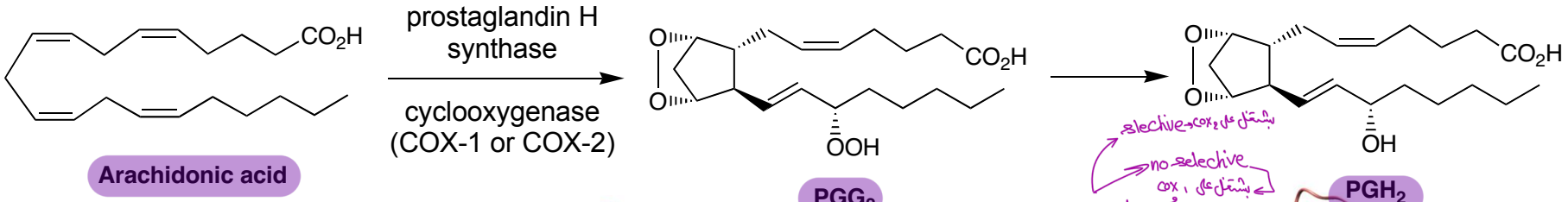


Prostaglandins. (eicosanoids) C_{20} compounds derived from arachidonic acid and related fatty acids

hormone: (Greek, *horman*, to set in motion) chemical messengers from one cell to another, that acts as a signal for a biochemical event.



Prostaglandin biosynthesis



Arachidonic acid

PGG_2

PGH_2

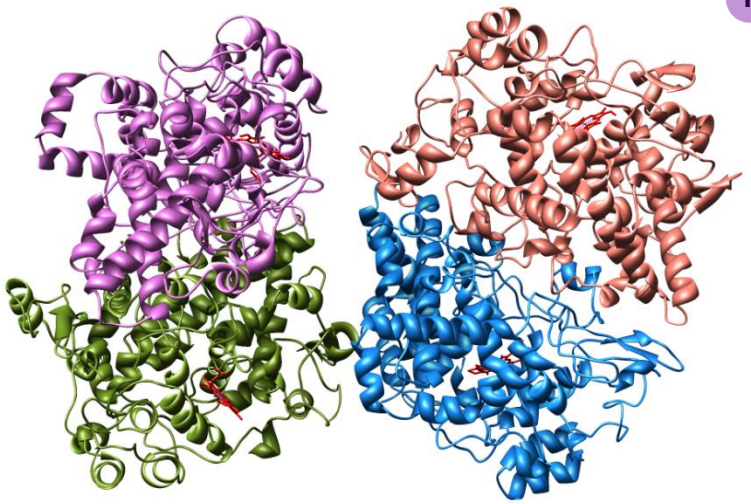
selective → cox_2 بشتغل على

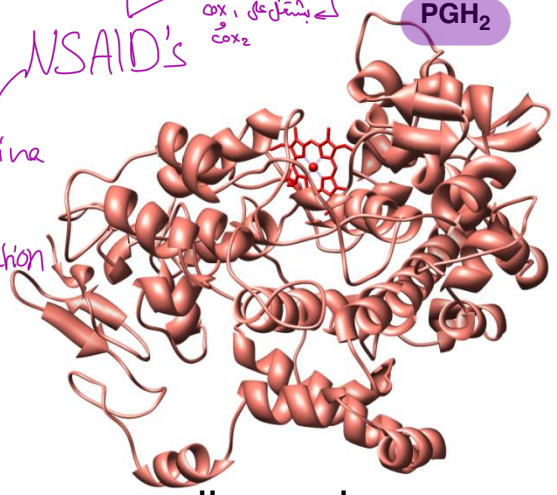
no selective بشتغل على cox_1 و cox_2

NSAID's

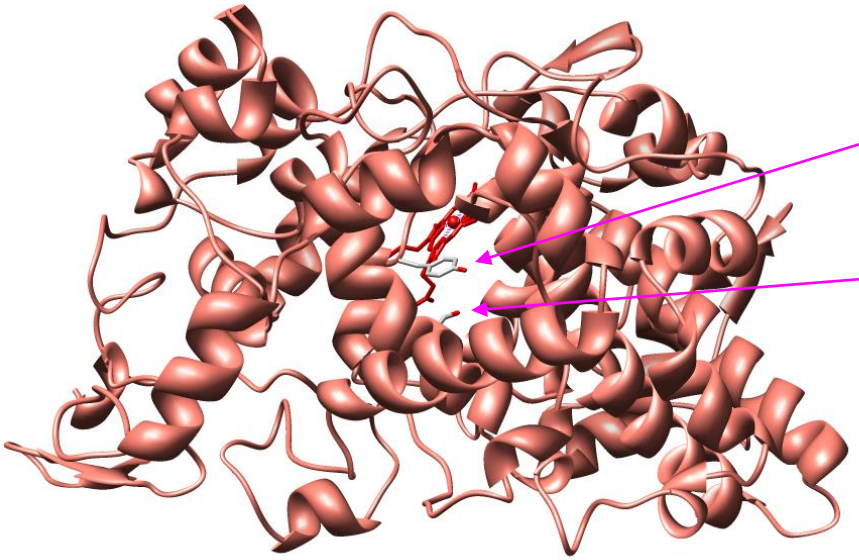
Aspirina
- pain
- inflamation

COX-2



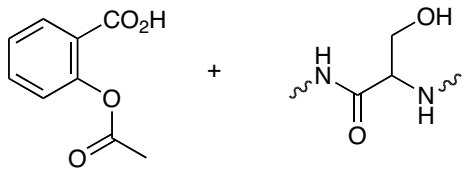


cell membrane



Tyr-385

Ser-385

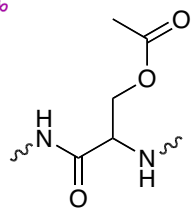


أسبرين

acetylsalicylic acid

Ser-530 COX

inhibitor of cox_1 & cox_2
طبخ الألم والحرارة



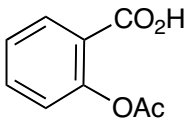
covalently modified enzyme

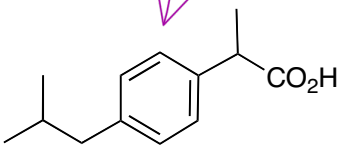
COX-1 is a constitutive enzyme that is expressed in virtually all mammalian cells

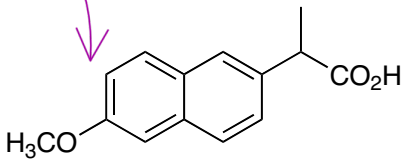
COX-2 is an inducible enzyme that is expressed as a results of a biochemical response; expressed in phagocytes (macrophages) as part of an inflammation response.

NSAIDs: non-steroidal anti-inflammatory drugs

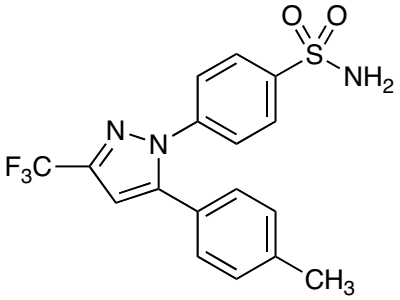
Aspirin, ibuprofren, and naproxen are non-selective inhibitors of COX

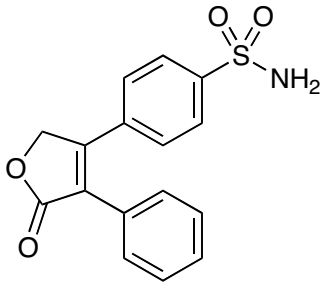


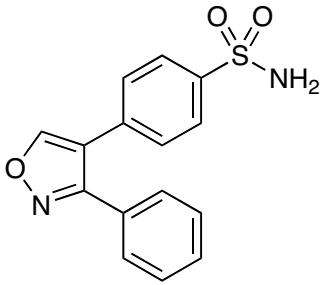




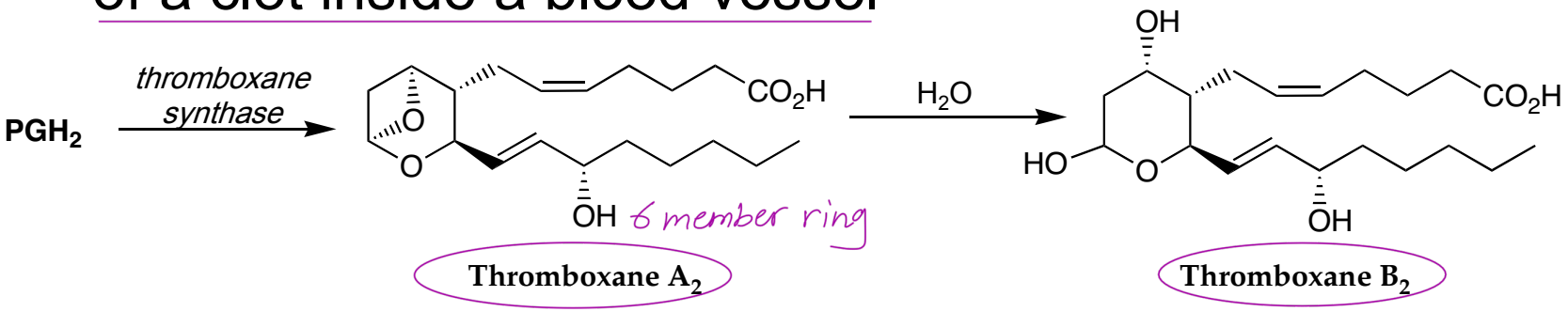
Celebrex, vioxx, and brextra are selective inhibitors of COX-2 (coxibs)





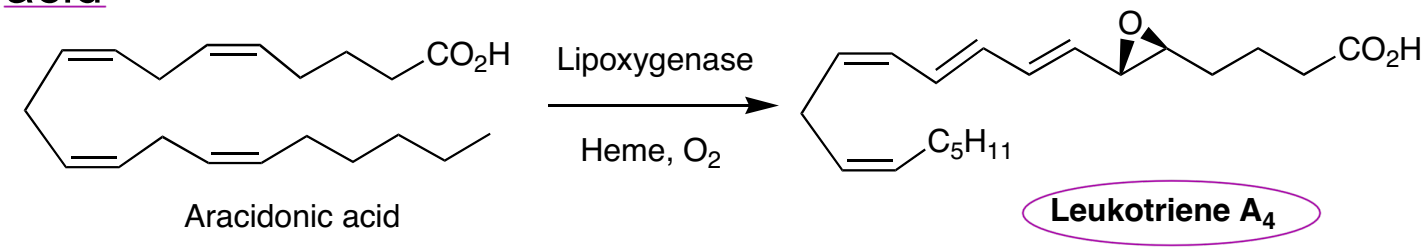


Thromboxanes: named for their role in thrombosis, the formation of a clot inside a blood vessel



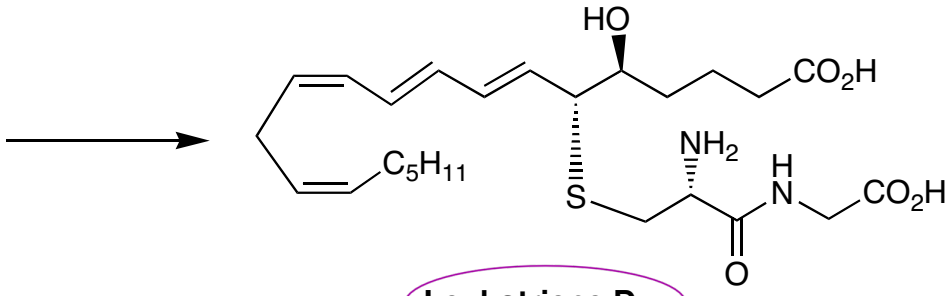
Thromboxane A_2 | Thromboxane B_2

Leukotrienes: a family of eicosanoid inflammatory mediators produced in leukocytes by the oxidation of the essential fatty acids arachidonic acid



Aracidonic acid

Leukotriene A_4



Leukotriene D_4

Antibiotics Derived from Acetate Malonate Pathway

Professor Suleiman OLIMAT

Antibiotics Derived from Acetate Malonate Pathway

Antibiotics derived from the acetate metabolism

1- Antibiotics with fused ring system:

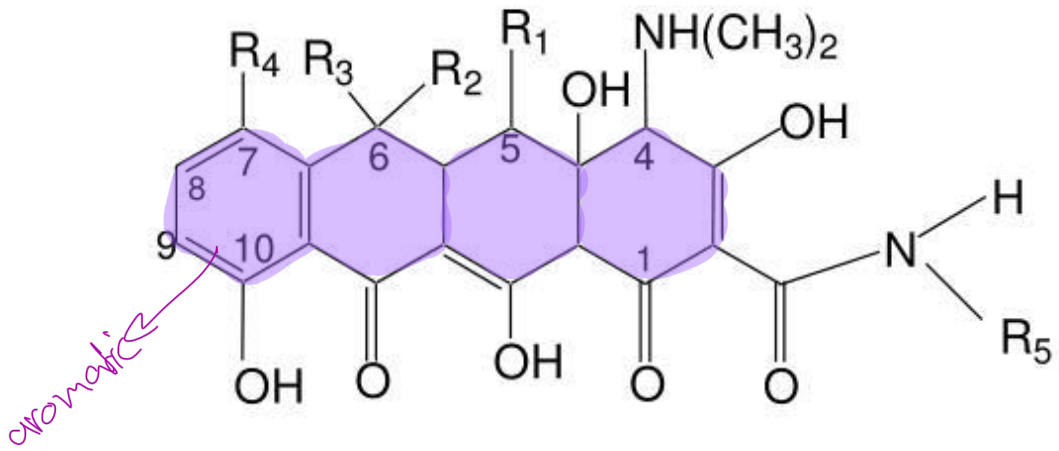
- Griseofulvin
- Tetracyclines
- Anthracyclines

2- Macrolide antibiotics

3- Polyene antibiotics

Tetracyclines

4 cycle



Tetracyclines

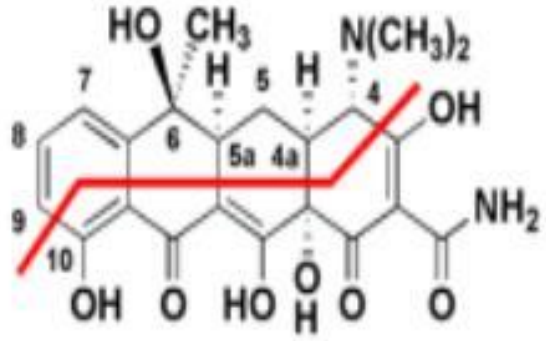
- **Biosynthesized from** **1 MalonamylCoA + 8 MalonylCoA** → 2C

  (1NH_2-CO-CH_2-CO-SCoA +8 HOOC-CH_2-CO-SCoA)→C-19 Polyketide → → →cyclisation →C-6 methylation →OH at C-4 →dearomatization → 4-keto derivative → Cl^- at C-7 → amination and stepwise methylation at C-4 → hydroxylation C-6 →reduction of double bond in ring B

- Biosynthesized in *Streptomyces* spp. (*S. aureofaciens, S. rimosus,…)*
- Broad spectrum activity
- Protein synthesis inhibitor
- Side effects! → chelating agent. يخلي لون الأسنان أصفر.

Tetracyclines

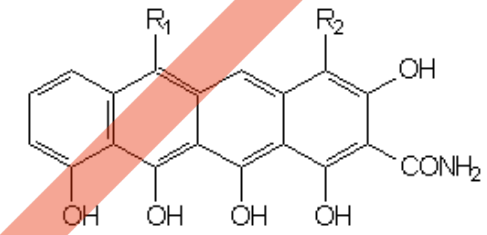
Positions amenable to modification



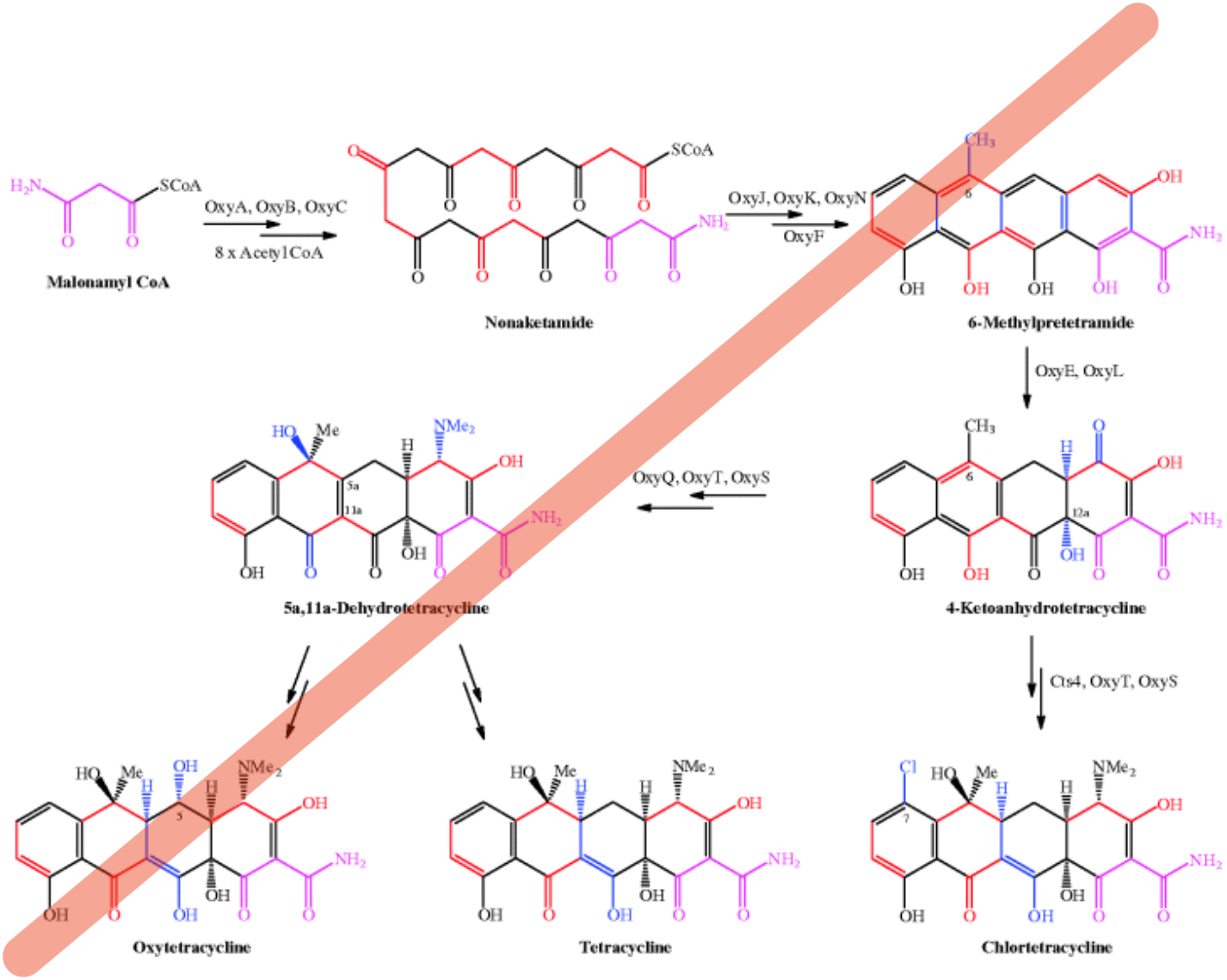
Positions believed to be key to ribosomal binding

Biosynthesis

- A biosynthesis of tetracycline, particularly in its latter stages, has been studied with the use of mutant cultures. It has been established that the so-called **pretetronids**:



- are intermediates, convertible by non-mutated *Streptomyces aureofaciens* into tetracyclines. Cosynthesis, by use of blocked mutants, has demonstrated that 4-hydroxy-6-methylpretetranid (R_1 = Me, R_2 = OH) is a transformable intermediate and the precursor to the 6-methyltetracyclines. The complete biosynthesis is as follows :

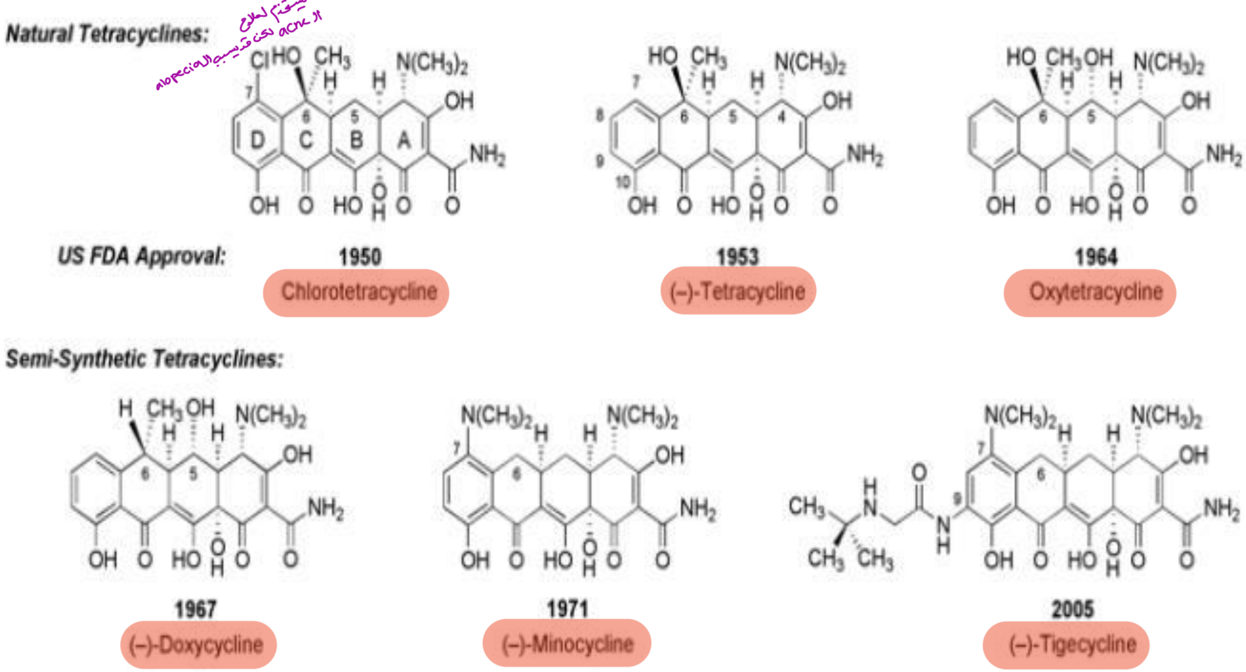

Malonamyl CoA
OxyA, OxyB, OxyC
8 x Acetyl CoA
Nonaketamide
OxyJ, OxyK, OxyN
OxyF
6-Methylpretetramide
OxyE, OxyL
4-Ketoanhydrotetracycline
OxyQ, OxyT, OxyS
5a,11a-Dehydrotetracycline
Cts4, OxyT, OxyS
Oxytetracycline
Tetracycline
Chlortetracycline

Naturally occurring: Tetracycline, Chlorotetracycline, Oxytetracycline, Demeclocycline

→ without any modification.

Semi-synthetic: Doxycycline, Meclocycline, Methacycline, Minocycline, Tigecycline,...

→ after chemical modification.



الـ structure مش مطلوب، أفرق بينهم.

Antineoplastic anthracycline derivatives

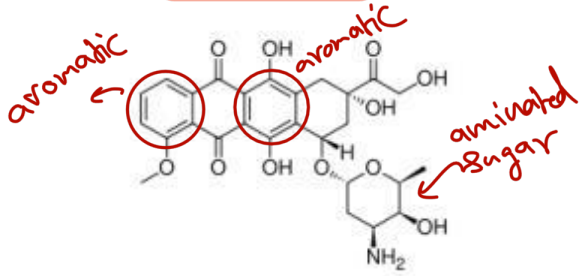
Produced by cultures of *Streptomyces* spp.; inhibit DNA dependent RNA synthesis (anticancer)

SE: nausea, bone marrow depression, hair loss, local tissue necrosis;

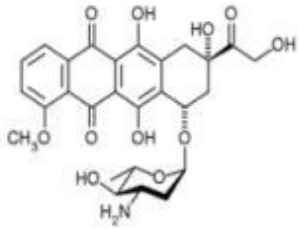
Biosynthesis: 1 PropionylCoA + 9 MalonylCoA

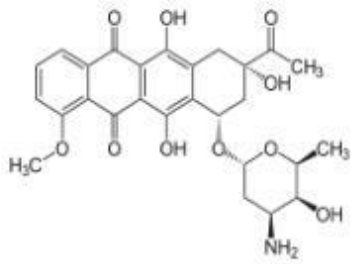
2c 18c

Doxorubicin

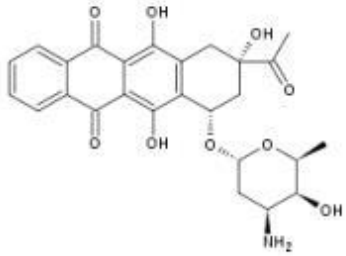


Epirubicin





Daunorubicin



Idarubicin

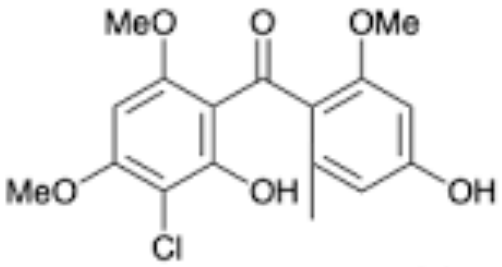
Griseofulvin:

Produced by *Penicillium* spp (*P. griseofulvum*, ….)

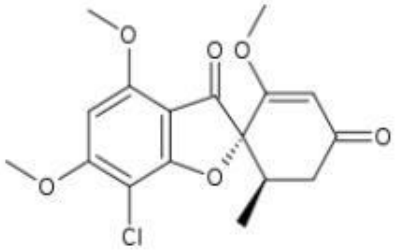
1 AcetylS-CoA + 6 MalonylS-CoA → Polyketide →

~~Griseophenone C →B →A →Dehydrogriseofulvin~~ →

Griseofulvin



griseophenone A (8)



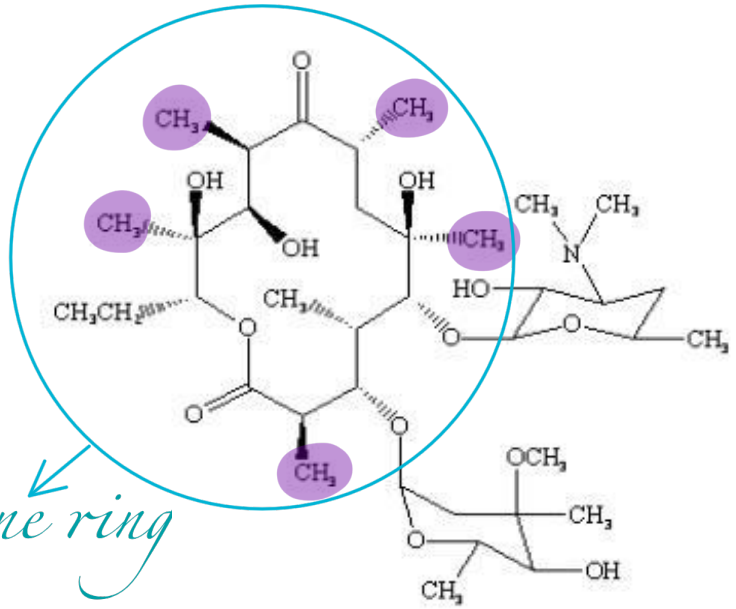
Griseofulvin

Macrolide antibiotics

- Synthesized from acetate units
- Produced by *Streptomyces* spp.
- Large lactone ring (12, 14, 16 or [illegible] atoms)
- Numerous CH_3 substituents in lactone ring
- 1-3 deoxy-sugar/sugar moieties attached to the ring
- Erythromycin A, B as examples
- Mainly active against Gram-positive bacteria and *Mycoplasma* spp.; useful in pat. with penicilline allergy
- Protein synthesis inhibitors
- SE: few, mainly GI symptoms

Erythromycin A: 1 [PropionylCoA] + 6 [2-MethylmalonylCoA] →Poly-keto-acid →condensation →Erythronolide ring (14 atoms)→glycosidation →Erytrhromycine (Azithromycine is its semi-synthetic analog)

[1 CH_3-CH_2-CO-SCoA + 6 HOOC-CH-(CH_3)-CO-SCoA]



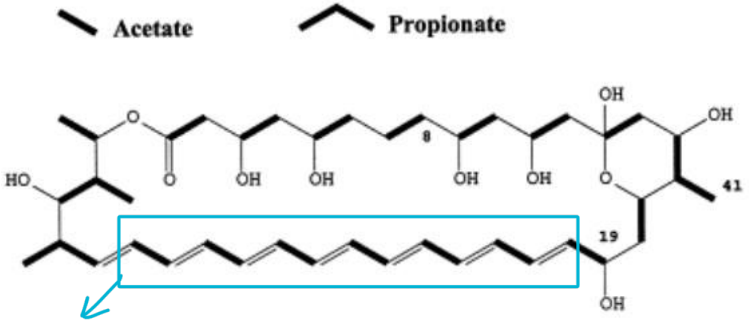
Polyenes

double bond

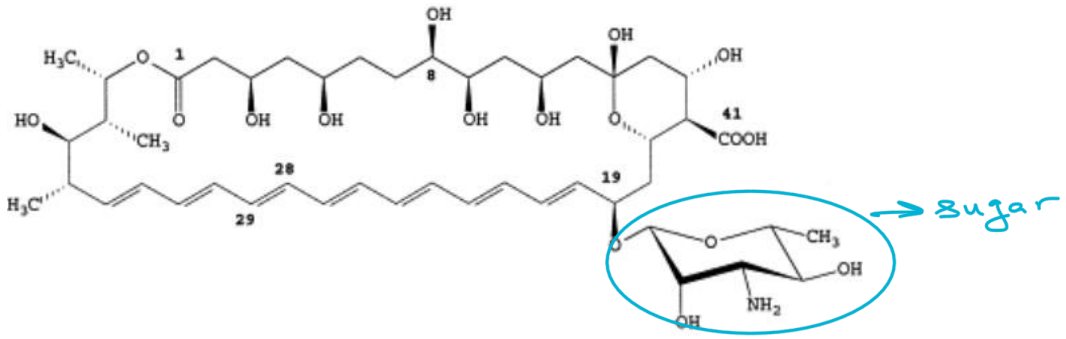
- The group of antibiotics known collectively as polyenes is characterized by a large lactone ring (20–44 membered) containing a series of conjugated double bonds.
- The macrolide ring is often linked via a hydroxyl group to an aminosugar unit
- The macrolide ring is probably derived from acetate and propionate.
- They are often mixtures of closely related compounds.
- *Streptomyces* are the usual producing organisms, and to date over *200* polyenes have been claimed
- *Candida albicans* is susceptible to the polyenes
- Cutaneous, intestinal and vaginal infections of *Candida*

antifungal

Amphotericin B: formed of 16 acetate units (1 AcetylCoA + 15 MalonylCoA + 3 MethylmalonylCoA); macrolactone ring followed by glycosidation withD-mycosamine via OH at C-19



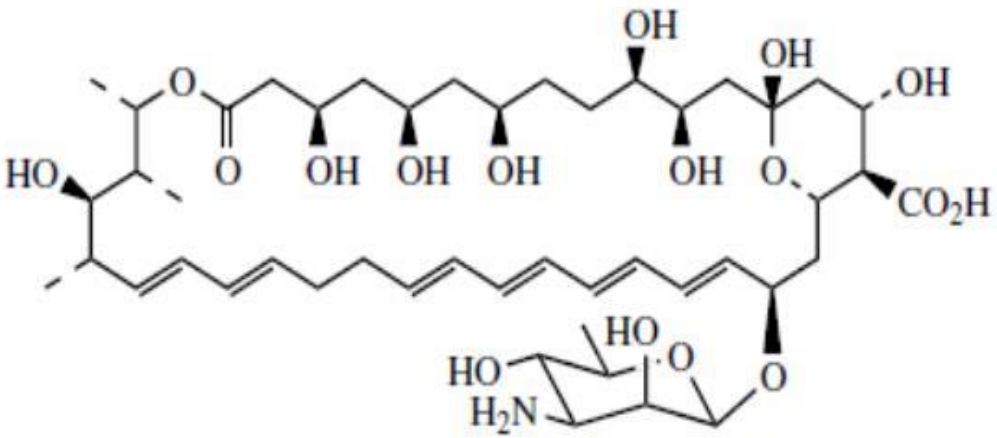
Large lactone ring.



sugar

Nystatin A_1

Antifungal



D-mycosamine

nystatin A_1