بسم ألله الرحمن الرحيم

Basic Principles and Perspectives in Medical Chemistry and Biochemistry

Chemistry of Lipids

Part-1- Fatty acids & Derivatives

Medical and Biochemistry (BIQC-101) Lecture
by
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10. Leukotrienes
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Chemistry of lipids

Learning objectives

1. Have general idea about lipid structure and properties
2. Classify lipids
3. List the major physiological functions of fatty acids •
4. Derive the structure of saturated or unsaturated fatty acids.
5. Study the relation between the structure and function of fatty acids
6. Be able to specify the omega or delta ends. Recognize the alpha, beta and gamma carbons of fatty acids
7. List and be able to identify the general features of the ecosanoids.
8. Know the biochemical functions of the eicosanoids

Introduction

- The lipids are a large and diverse group of naturally occurring organic compounds that are related by their solubility in nonpolar organic solvents (e.g. ether, chloroform, acetone & benzene) and general insolubility in water.
- Unlike other macromolecules (carbohydrates, proteins, and nucleic acids) lipids are not polymeric molecules.
- Scientists sometimes define lipids as hydrophobic or amphiphilic small molecules.
- Fats and oils are the most widely occurring types of lipids. Thick layers of fat help insulate polar bears against the effects of low temperatures.

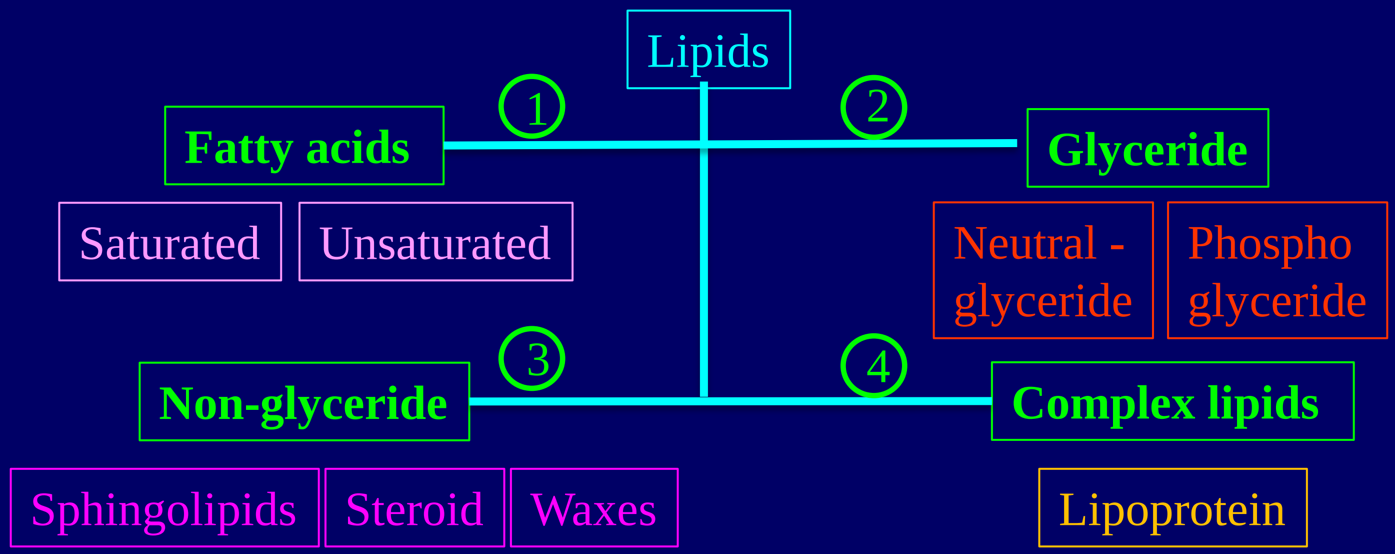
The Biological Functions of Lipids

1. As an energy source, lipids provide 9 kcal of energy per gram
2. Triglycerides provide energy storage in adipocytes
3. Phosphoglycerides, sphingolipids, and steroids are structural components of cell membranes
4. Steroid hormones are critical intercellular messengers
5. Lipid-soluble vitamins (A, E, D, K)
6. Dietary fat acts as a carrier of lipid-soluble vitamins into cells of small intestine
7. Provide shock absorption and insulation
8. Emulsification i.e. Bile acids

Classification of Lipids

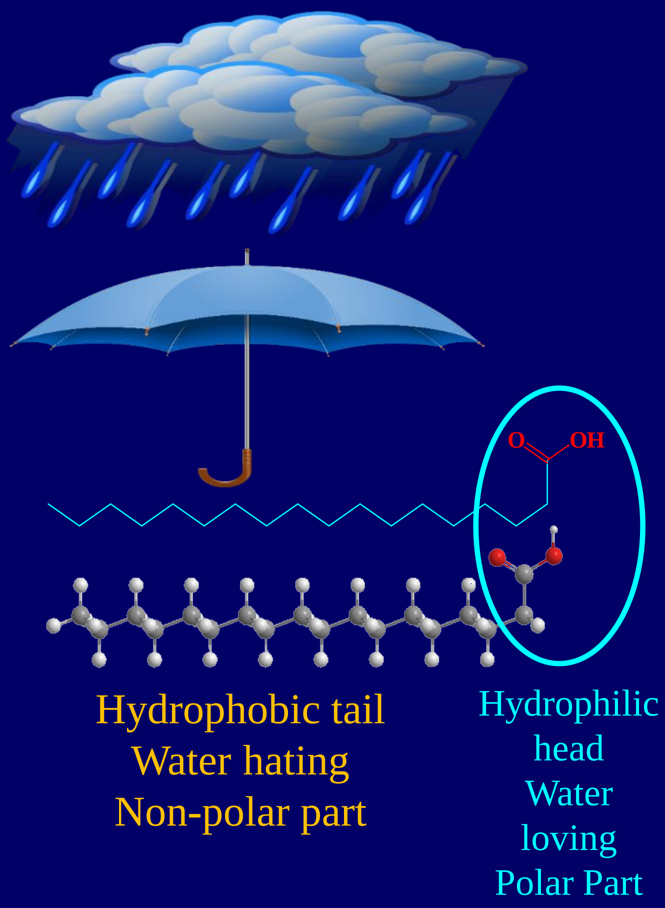
Lipids are subdivided to four mean groups:-

1. **Fatty acids** (saturated & unsaturated)
2. **Glyceride** (neutral glyceride, phosphoglyceride)
3. **Non-glyceride** (sphingolipids, steroid, waxes)
4. **Complex lipids** (lipoprotein)



Fatty acids

- A fatty acid is a carboxylic acid with a long aliphatic chain, which is either **saturated** or **unsaturated**.
- Most naturally occurring fatty acids have an unbranched chain of an even number of carbon atoms, from **5 to 28.**
- Fatty acids are usually not found in organisms in their standalone form, but instead exist as three main classes of esters: **triglycerides**, **phospholipids**, and **cholesteryl esters**.

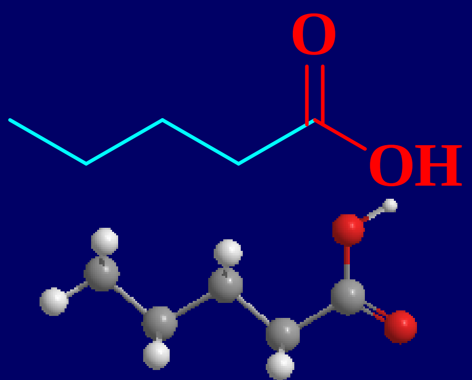


Amphiphilic structure of fatty acids

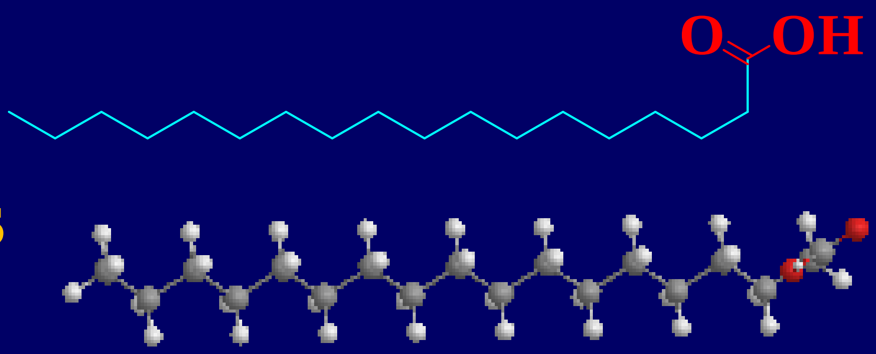
Types of fatty acids

Saturated fatty acids

1. **Short-chain fatty acids.** five or fewer carbons.
2. **Medium-chain fatty acids** C6 to C12. medium-chain triglycerides.
3. **Long-chain fatty acids** C13 to C21 carbons.
4. **Very long chain fatty acids** C22 or more carbons



Pentatonic acid C5

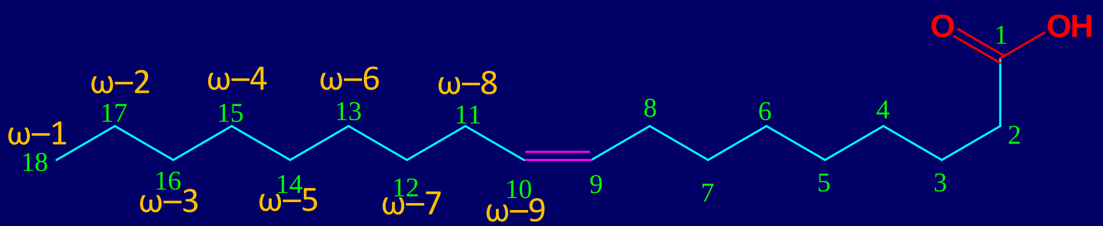


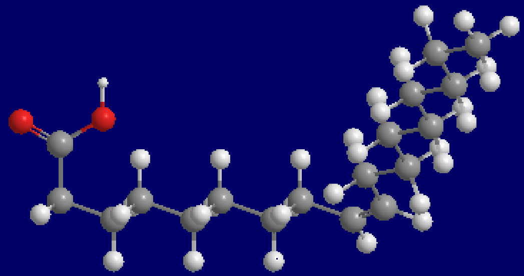
Stearic acid C18

Types of fatty acids

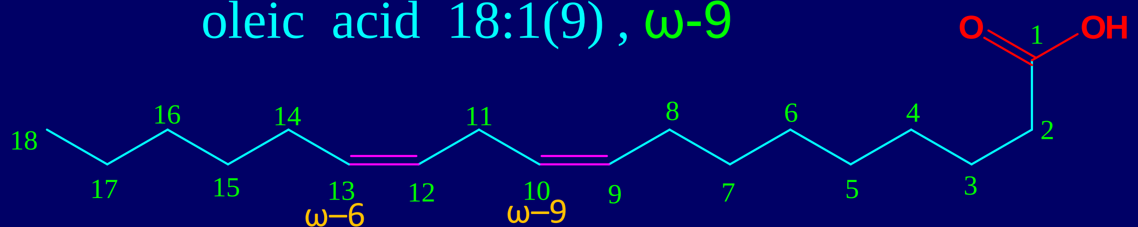
Unsaturated fatty acids

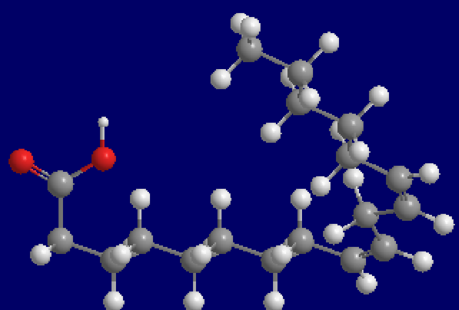
Fatty acids have one or more C=C double bonds. The C=C double bonds can give either **cis** or **trans** isomers.



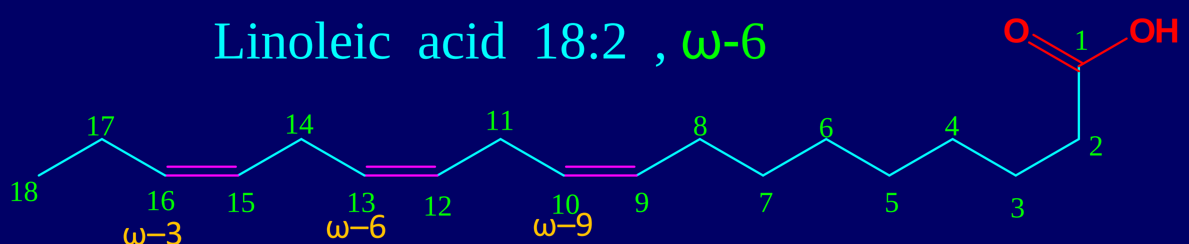


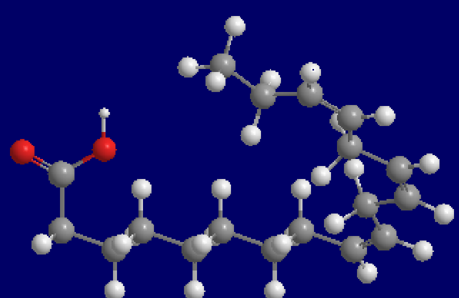
oleic acid 18:1(9) , ω-9





Linoleic acid 18:2 , ω-6

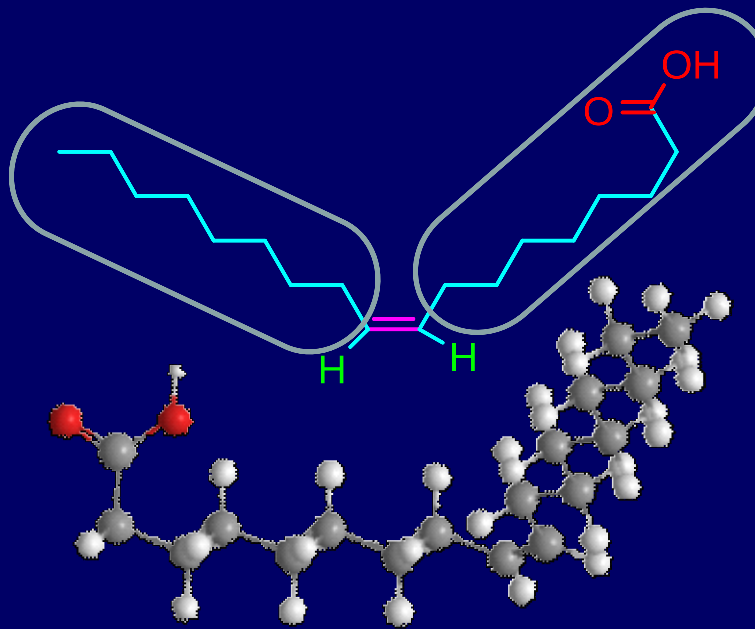




Alpha linoleic acid 18:3, ω-3

Cis fatty acid

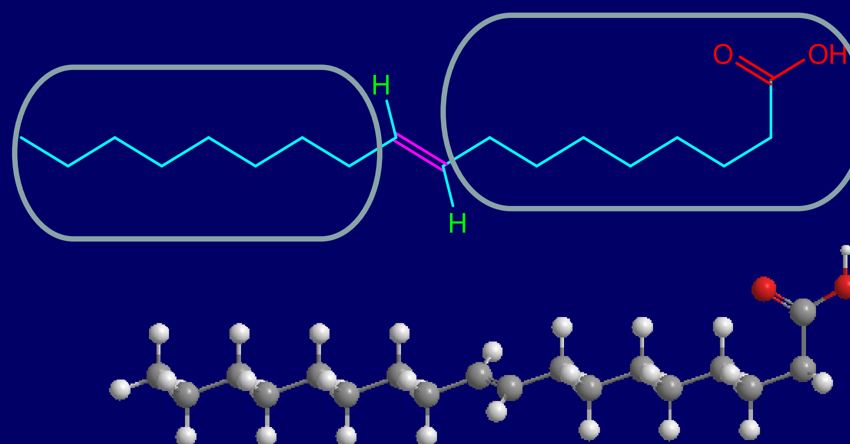
Cis configuration means that the two hydrogen atoms adjacent to the double bond stick out on the same side of the chain. The rigidity of the double bond freezes its conformation and, in the case of the cis isomer, causes the chain to bend and restricts the conformational freedom of the fatty acid.



oleic acid cis 18:1(9) , ω-9

Trans fatty acid

A trans configuration, by contrast, means that the adjacent two hydrogen atoms lie on opposite sides of the chain. As a result, they do not cause the chain to bend much, and their shape is similar to straight saturated fatty acids.



oleic acid trans 18:1(9) , ω-9

Fatty Acid Properties

1. Melting point increases with increasing carbon number.
2. Melting point of a saturated fatty acid is higher than an unsaturated fatty acid with the same number of carbons.
3. The double bond in naturally occurring fatty acids are normally in a cis configuration
4. Typical saturated fatty acids are tightly packed together.
5. Cis double bonds prevent good alignment of molecules in unsaturated fatty acids leading to poor packing
6. Double bonds lower melting point relative to saturated acid.

Some Common Fatty Acids Found in Natural Fats

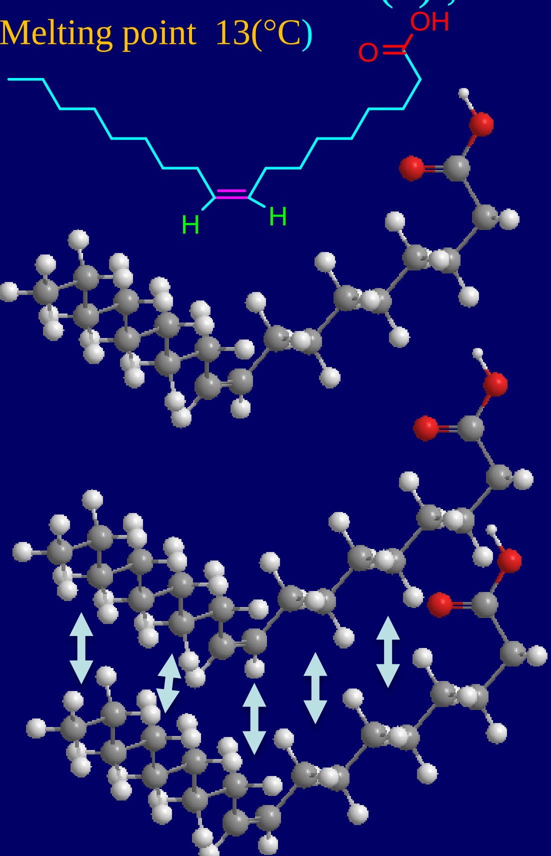
Name of fatty acid	Abbreviated Structural Formula	Condensed Structural Formula	Melting Point (°C)	Source
Lauric acid	$C_{11}H_{23}COOH$	$CH_3(CH_2)_{10}COOH$	44	palm kernel oil
Myristic acid	$C_{13}H_{27}COOH$	$CH_3(CH_2)_{12}COOH$	58	oil of nutmeg
Palmitic acid	$C_{15}H_{31}COOH$	$CH_3(CH_2)_{14}COOH$	63	palm oil
Palmitoleic acid	$C_{15}H_{29}COOH$	$CH_3(CH_2)_5CH=CH(CH_2)_7COOH$	0.5	macadamia oil
Ptearic acid	$C_{17}H_{35}COOH$	$CH_3(CH_2)_{16}COOH$	70	cocoa butter
Oleic acid	$C_{17}H_{33}COOH$	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	16	olive oil
Linoleic acid	$C_{17}H_{31}COOH$	$CH_3(CH_2)_3(CH_2CH=CH)_2(CH_2)_7COOH$	−5	canola oil
α-linolenic acid	$C_{17}H_{29}COOH$	$CH_3(CH_2CH=CH)_3(CH_2)_7COOH$	−11	flaxseed
Arachidonic acid	$C_{19}H_{31}COOH$	$CH_3(CH_2)_4(CH_2CH=CH)_4(CH_2)_2COOH$	−50	liver

Changes in the melting point of various *cis* – *trans* geometrical isomers of different fatty acids

Fatty acid	Isomerism	Melting point (°C)
C12:0	------	44.2
C16:0	------	62.7
C18:0	------	69.6
C18:1	Cis	13.2
C18:1	Trans	44.0
C18:2	cis, cis	-5.0
C18:2	trans, trans	18.5
C18:3	cis, cis, cis	11.0
C20:3	trans, trans, trans	29.5

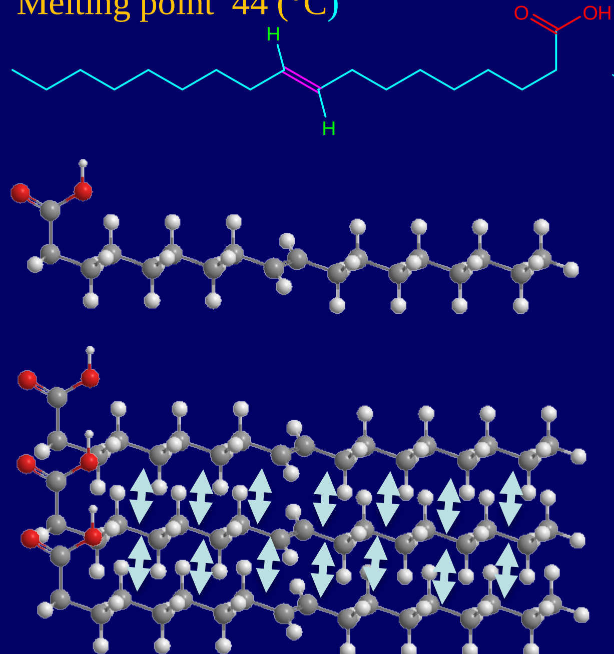
oleic acid cis 18:1(9) , ω-9

Melting point 13(°C)



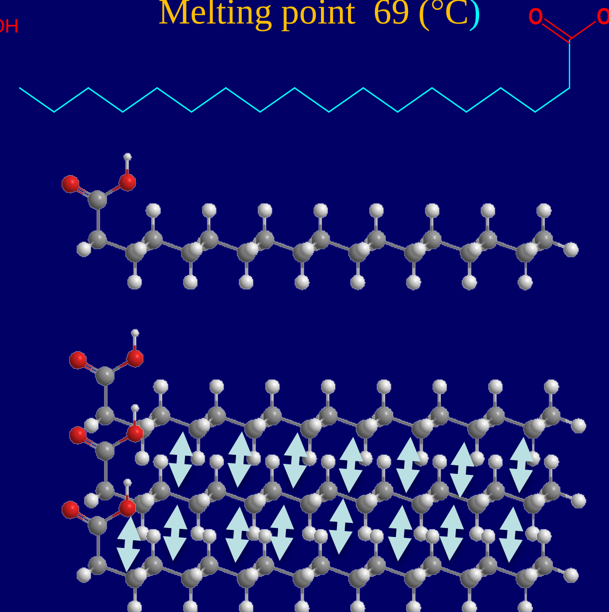
oleic acid trans 18:1(9) , ω-9

Melting point 44 (°C)



stearic acid C18(0)

Melting point 69 (°C)



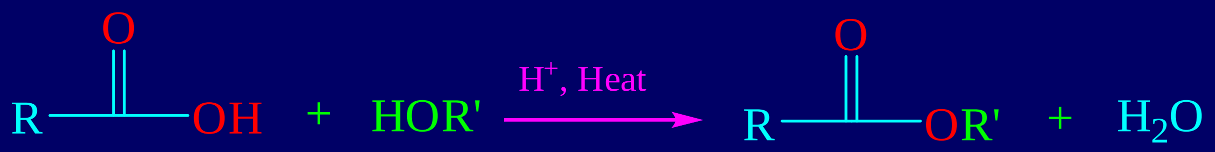
Molecules very difficult to liberate

Molecules easy to liberate

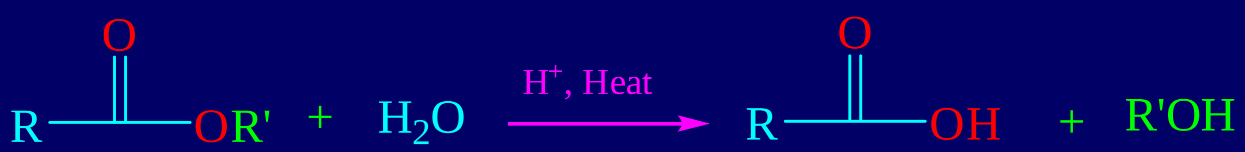
Less — **Van der Walls Forces Hydrophobic Interaction** — **More**

Chemical Reactions of Fatty Acids

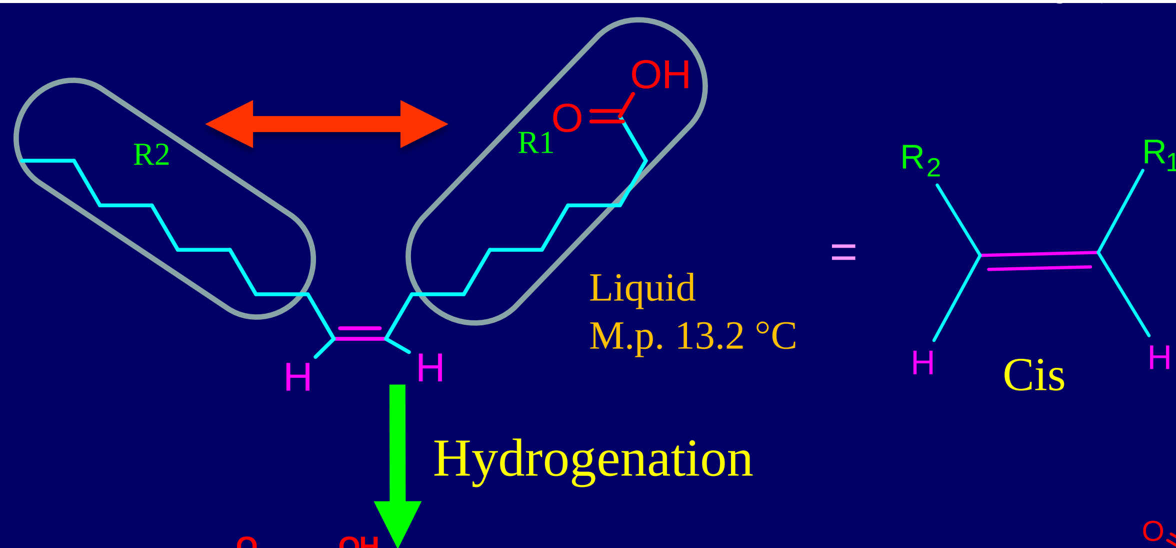
1. **Esterification is** the reaction of fatty acids with alcohols to form esters and water

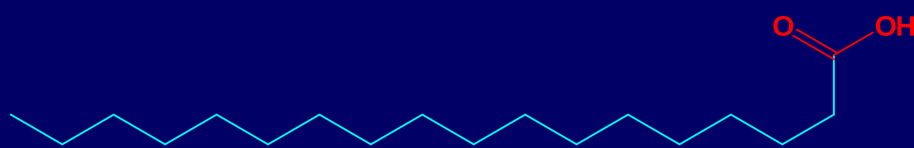


2. **Fatty Acid hydrolysis** hydrolysis reverses esterification fatty acids are produced from esters.



3. **Hydrogenation** is the addition hydrogen atom to the carbon–carbon double bond. Unsaturated fatty acids can be converted to saturated fatty acids, hydrogenation is used in the food industry

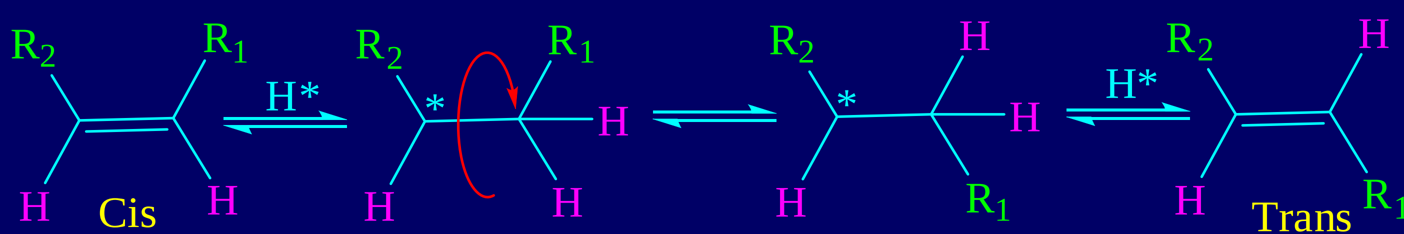




Saturated fatty acids- The target product
Solid M.p. 69.6 °C

Trans fatty acid -The side product
Semi Solid M.p. 44.0 °C

Because of the free rotation around the carbon-carbon single bond axis followed by dissociation of a hydrogen , the re-formed double-bond molecule can be in the *cis* or *trans* geometric configuration.



Fatty acid derivatives

Eicosanoids

- Fatty acids which can't be synthesized by the body are essential fatty acids.
- Linoleic acid is an essential fatty acid required to make arachadonic acid.
- Arachidonic acid (20 C) is the eicosanoid precursor.
- Arachidonic acid is a polyunsaturated fatty acid present in the phospholipids (especially phosphatidylethanolamine , phosphatidylcholine , and phosphatidylinositides) of membranes of the body's cells.

Dietary Linoleic Acid

(C18: $\Delta^{9,12}$) (from plant oils)

Elongase

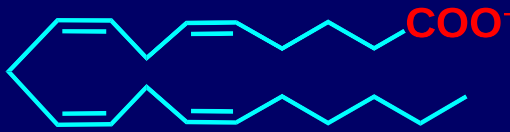
Desaturase

Arachidonic Acid

(C20: $\Delta^{5, 8, 11, 14}$)

Omega-6 fatty acid

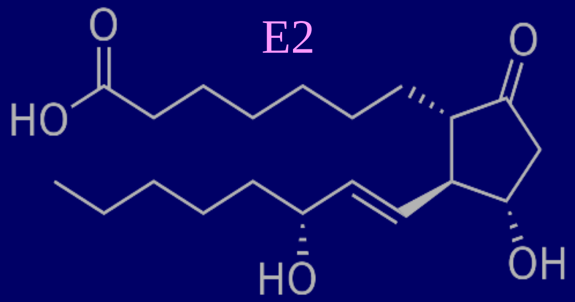
20:4(ω-6)



arachadonic acid

- Eicosanoids are three groups of structurally related compounds
  1. Prostaglandins
  2. Leukotrienes
  3. Thromboxanes

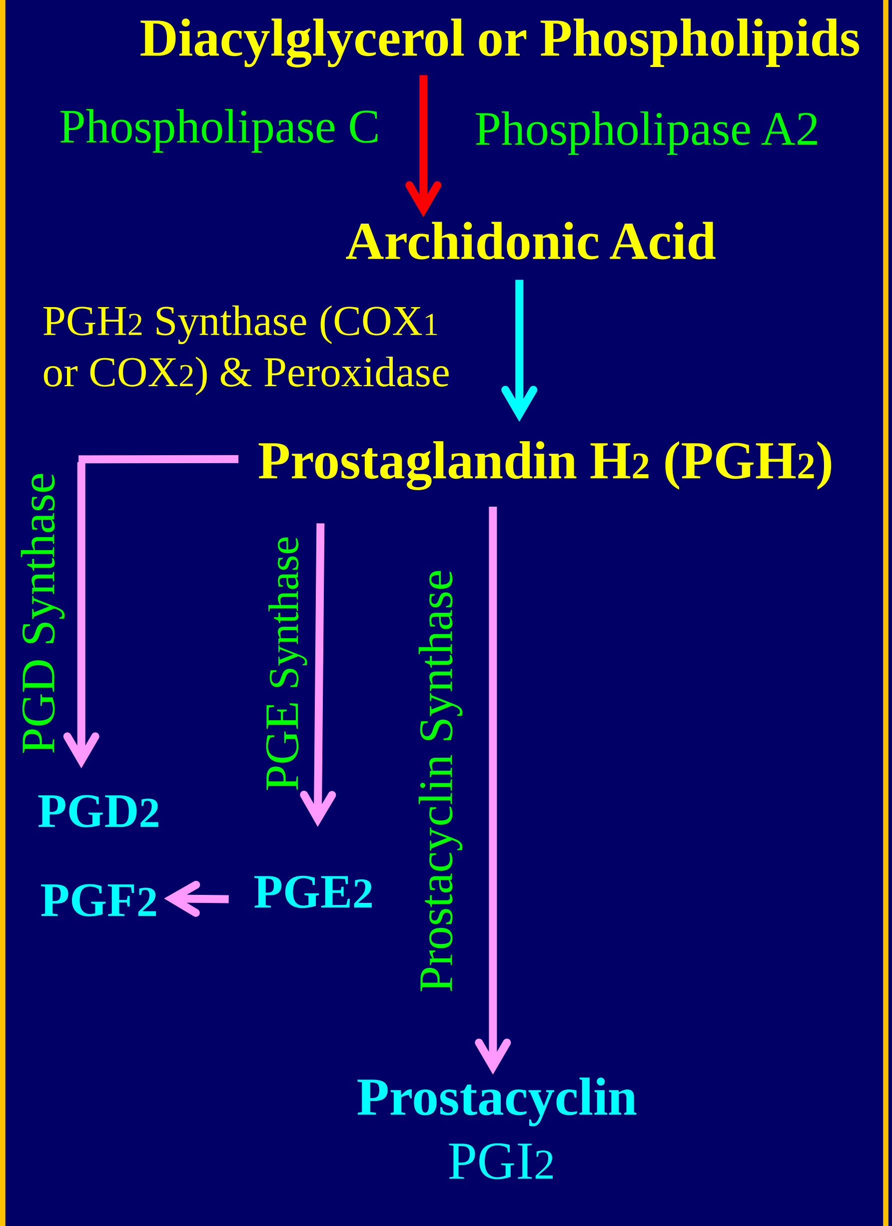
Prostaglandins



- Containing 5-carbon ring. Made at sites of tissue damage or infection that are involved in dealing with injury and illness.
- They control processes such as inflammation, blood flow, and blood clots
- Prostaglandins are also involved in regulating the contraction and relaxation of the muscles in the gut and the airways.
- Prostaglandins are known to regulate the female reproductive system, and are involved in the control of ovulation , the menstrual cycle and the induction of Laboure. prostaglandin E_2 - can be used to induce (kick-start) labour.
- Four types :-Prostaglandin D_2; E_2; F_2; and I_2 (which is also known as prostacyclin, has the opposite effect to thromboxane, reducing blood clotting and removing any clots that are no longer needed

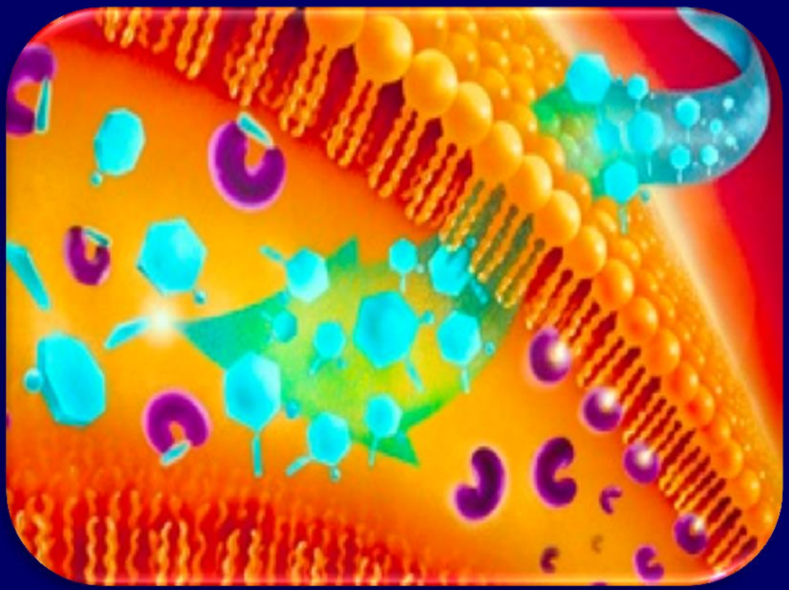
Synthesis

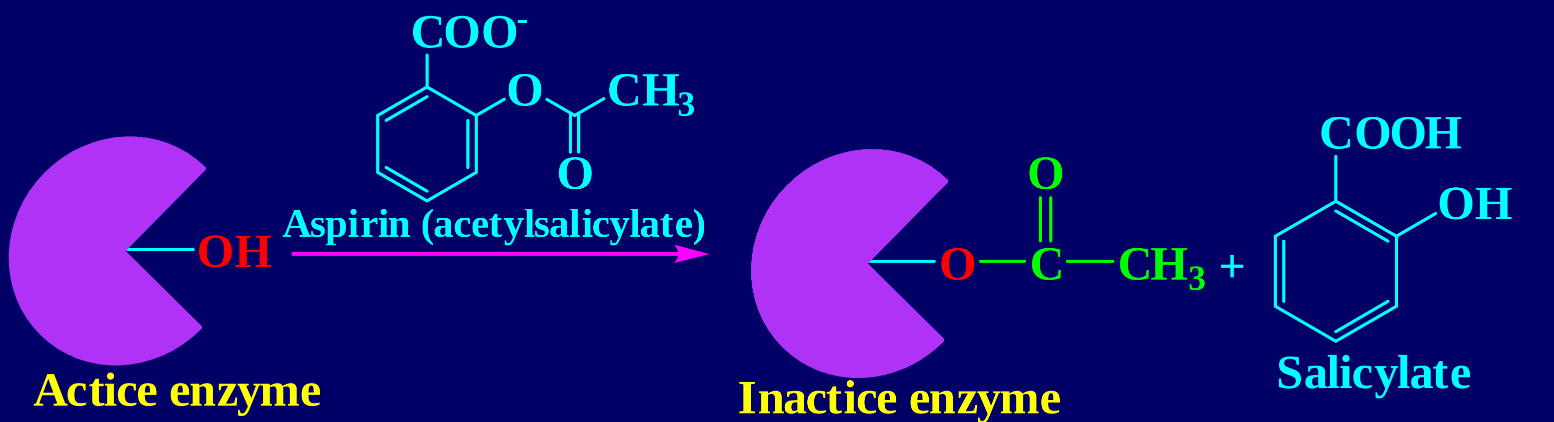
- The first step is carried out by an enzyme called cyclooxygenase.
- There are two main types of this enzyme: cyclooxygenase-1 and cyclooxygenase-2
- When the body is functioning normally, baseline levels of prostaglandins are produced by the action of cyclooxygenase-1.
- When the body is injured (or inflammation occurs in any area of the body), cyclooxygenase-2 is activated and produces extra prostaglandins, which help the body to respond to the injury.
- Prostaglandins are very short-lived and are broken down quickly by the body.



Mechanism of action of the drug aspirin.

Aspirin works by stopping prostaglandin being made: aspirin molecules (blue hexagons) enter the cell and chemically modify the cyclooxygenase enzyme (purple) to prevent prostaglandin being made.

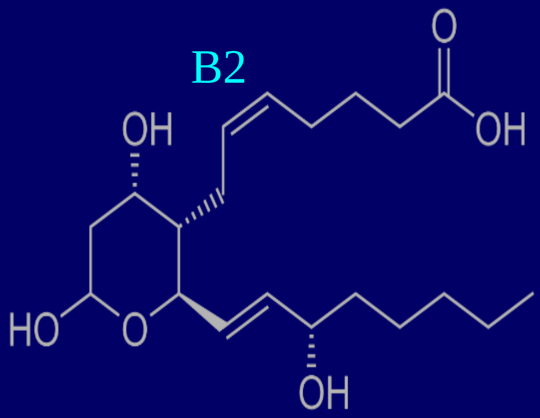




Thromboxane

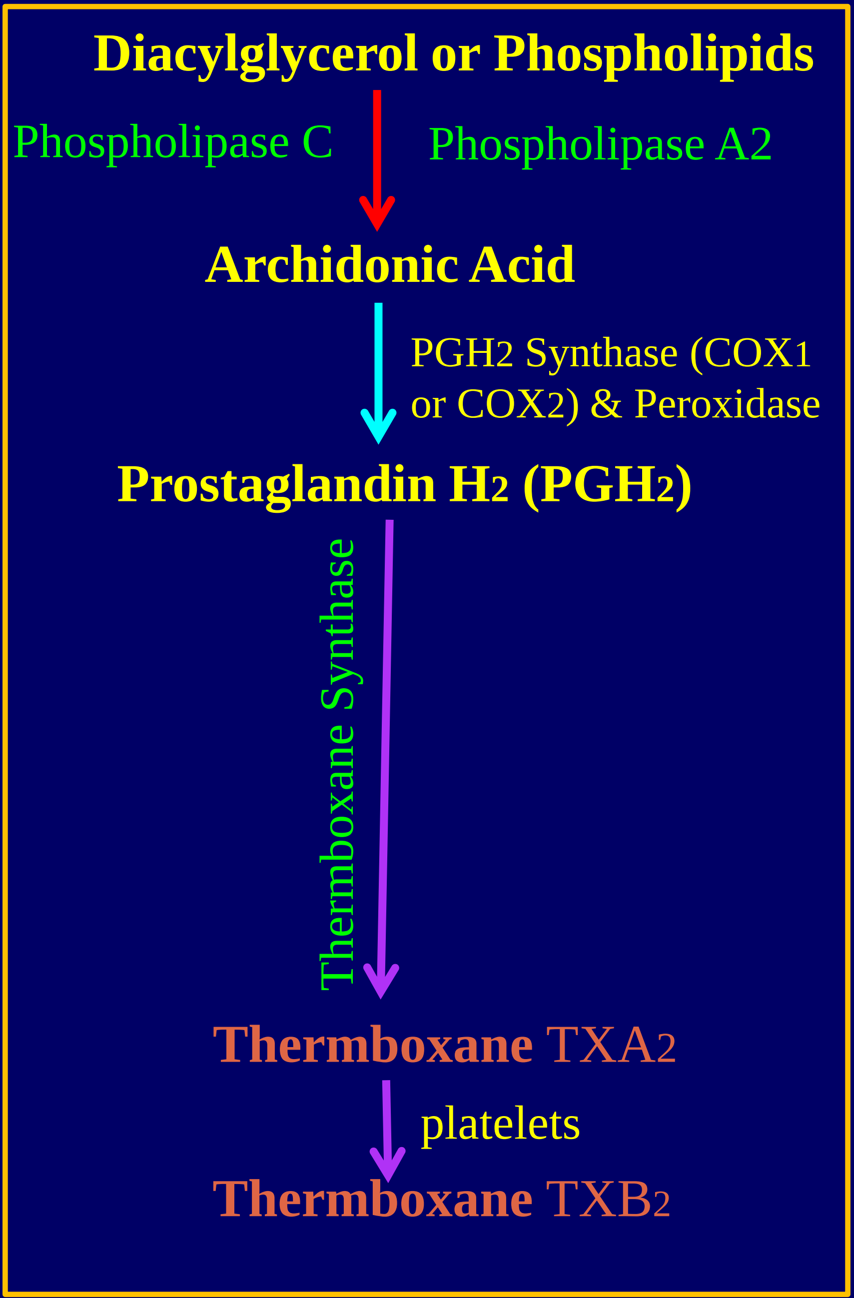
- The two major are thromboxane A_2 and thromboxane B_2.
- The distinguishing feature of thromboxanes is a 6-membered ether-containing ring.

B2



- Act in the formation of blood clots and reduce blood flow to the site of a clot.
- It is in homeostatic balance in the circulatory system with prostacyclin.
- If the cap of a vulnerable plaque erodes or ruptures, as in myocardial infarction, platelets stick to the damaged lining of the vessel and to each other within seconds and form a plug. These "Sticky platelets" secrete several chemicals, including thromboxane A_2 that stimulate vasoconstriction, reducing blood flow at the site.

- **Thromboxane-A synthase** an enzyme found in platelets, converts the arachidonic acid derivative prostaglandin H_2 to thromboxane.



Leukotriene

- Leukotrienes are eicosanoid produced in leukocytes by oxidation of arachidonic acid and the essential fatty acid Eicosapentaenoic acid (EPA) by the enzyme arachidonate 5-lipoxygenase.

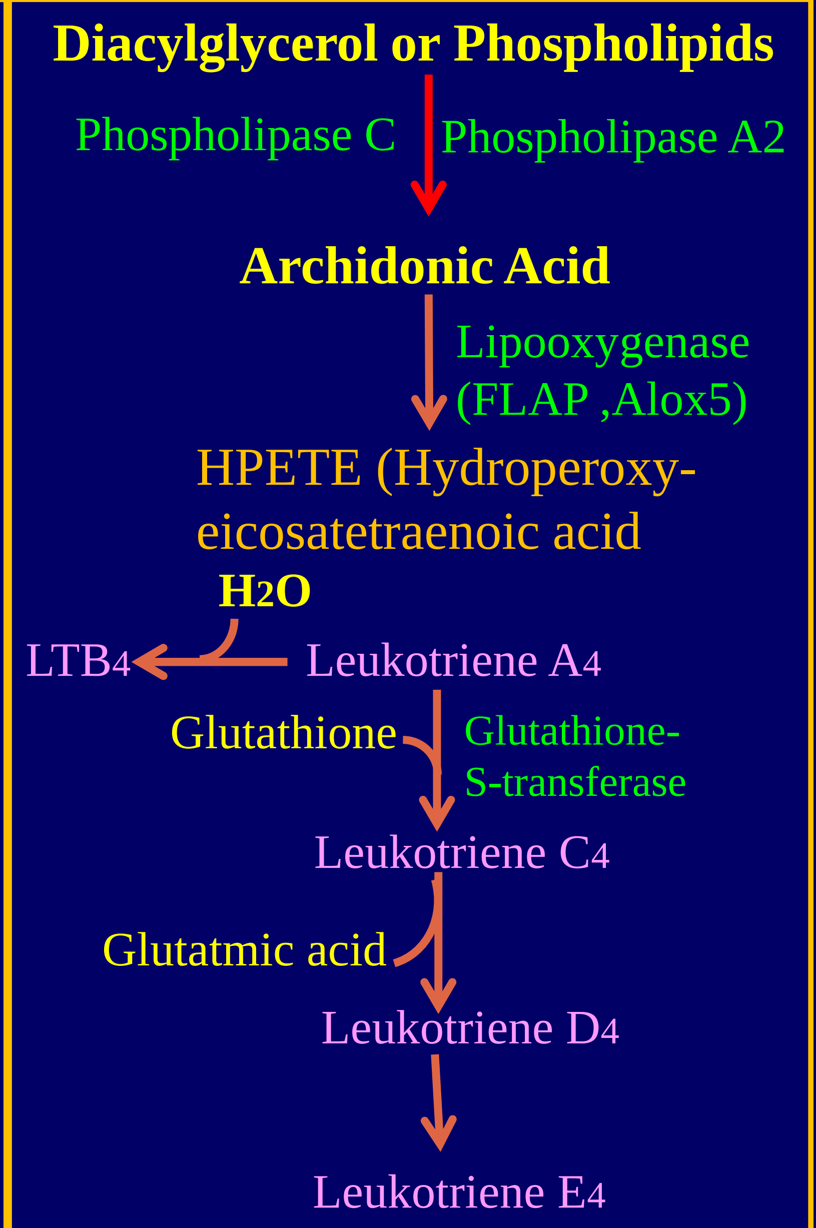
LTA4

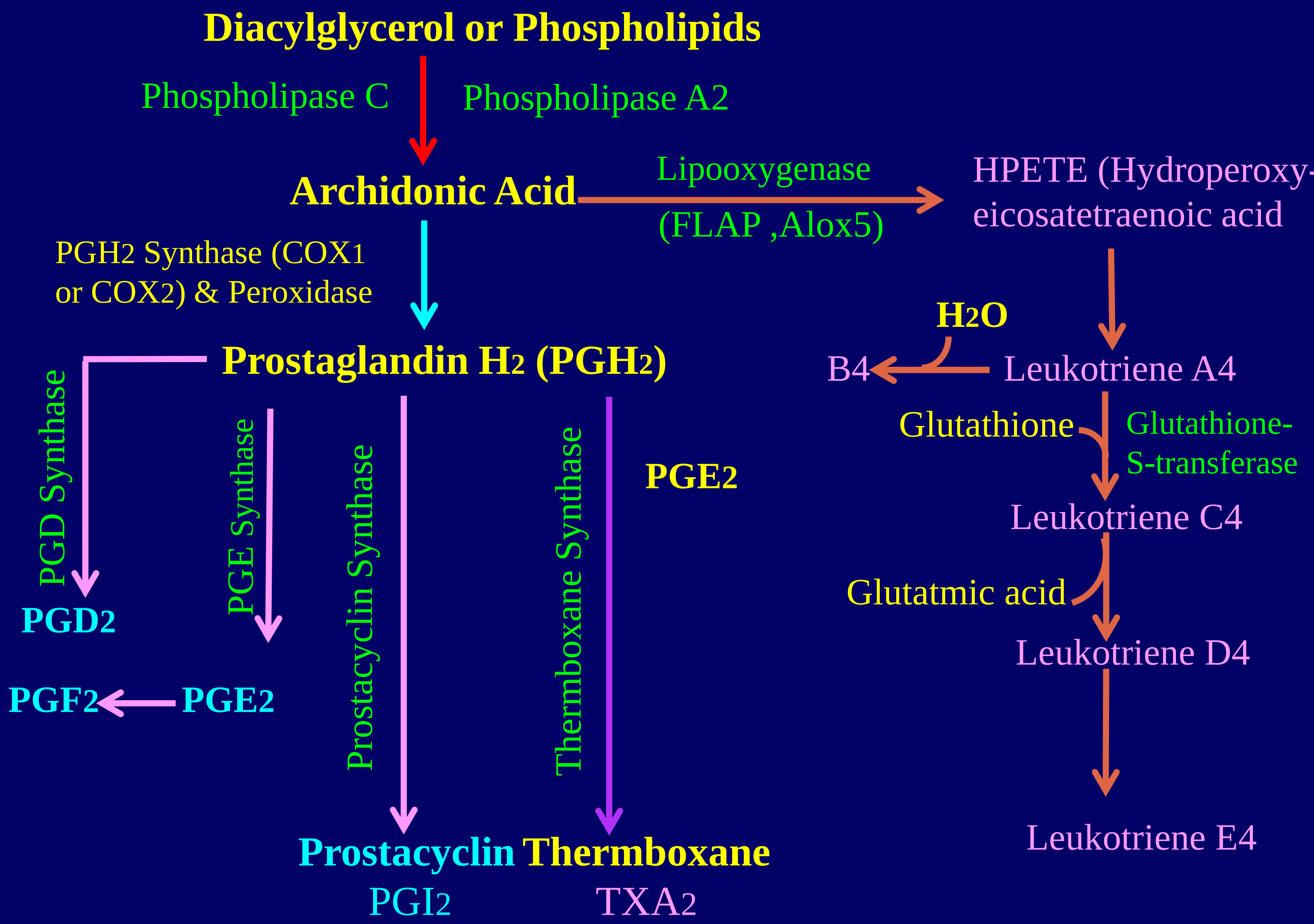
- They are important agents in the inflammatory response and a powerful effect in bronchoconstriction and increase vascular permeability.

Synthesis

- The lipoxygenase pathway is active in leukocytes and other immunocompetent cells.
- Arachidonic acid is liberated from cell membrane phospholipids by phospholipase A2, and donated by the 5-lipoxygenase-activating protein (FLAP) to 5-lipoxygenase

- 5-Lipoxygenase (5-LO) uses FLAP to convert arachidonic acid into 5-hydroperoxyeicosatetraenoic acid (5-HPETE).
- HPETE spontaneously reduces to 5-hydroxyeicosatetraenoic acid (5-HETE).
- The enzyme 5-LO acts again on 5-HETE to convert it into leukotriene A_4 (LTA_4).
- LTA_4 is converted to the dihydroxy acid leukotriene LTB_4
- LTC_4 synthase, LTA_4 is conjugated with the tripeptide glutathione to form the first of the cysteinyl-leukotrienes, LTC_4
- LTC_4 converted by enzymes to form successively LTD_4 and LTE_4,




Diacylglycerol or Phospholipids
Phospholipase C
Phospholipase A2
Archidonic Acid
Lipooxygenase
(FLAP ,Alox5)
HPETE (Hydroperoxy-eicosatetraenoic acid
PGH2 Synthase (COX1 or COX2) & Peroxidase
Prostaglandin H2 (PGH2)
H2O
B4
Leukotriene A4
Glutathione
Glutathione-S-transferase
Leukotriene C4
Glutatmic acid
Leukotriene D4
Leukotriene E4
PGD Synthase
PGD2
PGE Synthase
PGF2
PGE2
Prostacyclin Synthase
Thermboxane Synthase
PGE2
Prostacyclin
PGI2
Thermboxane
TXA2

thank you!