
بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ
IN THE NAME OF ALLAH,
THE MOST GRACIOUS, THE MOST MERCIFUL

LIPID METABOLISM

Synthesis of Eicosanoids

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KGMC-2022

BY THE END OF THIS LESSON THE STUDENT WILL BE ABLE TO….

Inform Learner of Objectives

Know

- Biological effects of Eicosanoids
- Synthesis of Eicosanoids

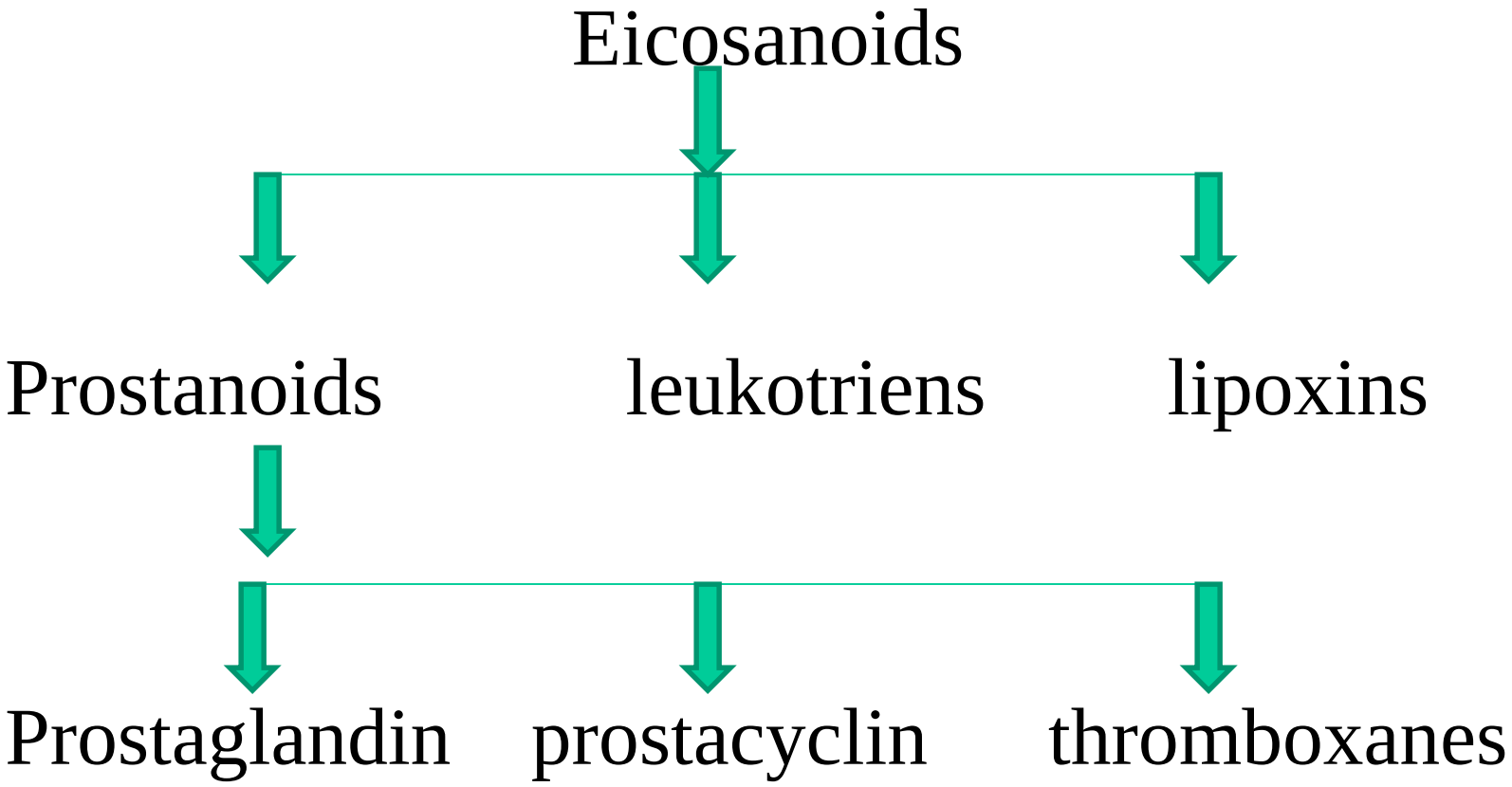

KEEP
CALM
AND
ACTIVATE PRIOR
KNOWLEDGE

- What are eicosanoids
- Classify eicosanoid.
- Functions of eicosanoids

Eicosanoids

- Eicosanoids are compounds derived from EFA linoleate or from dietary archidonate (C20) etc.
- Eicosanoids are paracrine hormones (substances that act only on cells near the point of hormone secreted instead of being transported in the blood to act on cells in distant tissues or organs).

Eicosanoids

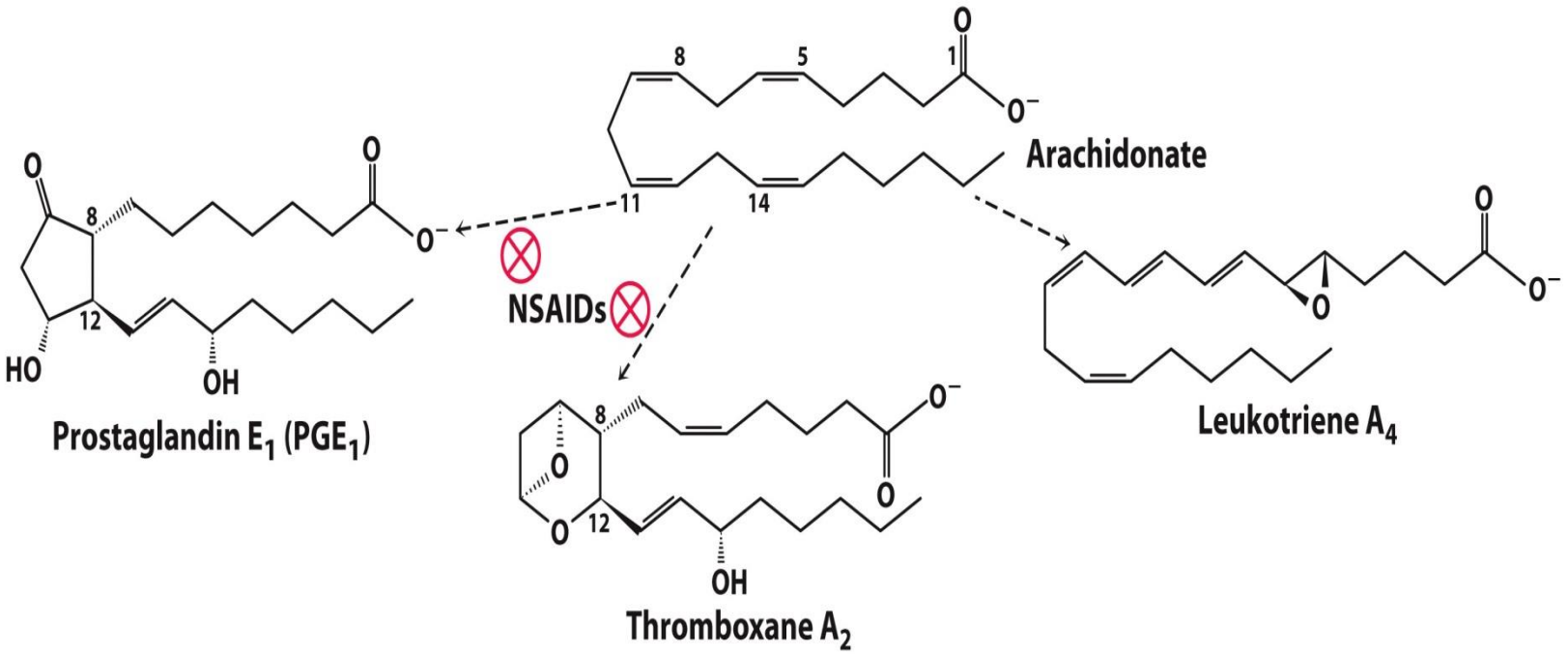


Eicosanoids classification

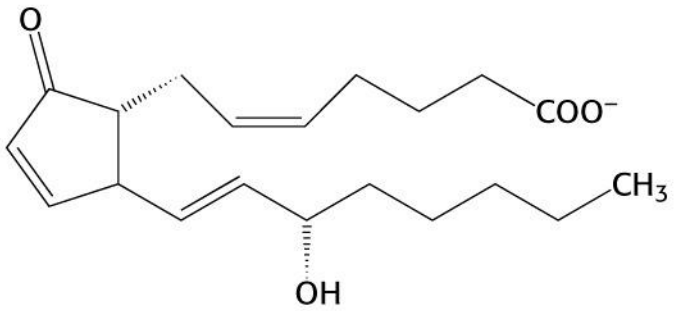
- Prostanoids (PG)

(prostaglandin PGs, prostacyclin PGIs,Thromboxanes TX)

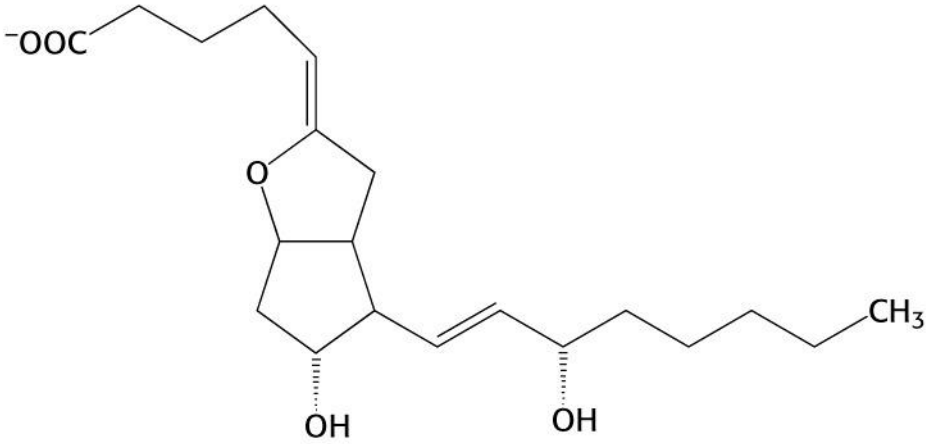
- Leukotrienes (LT)
- Lipoxins (LX)



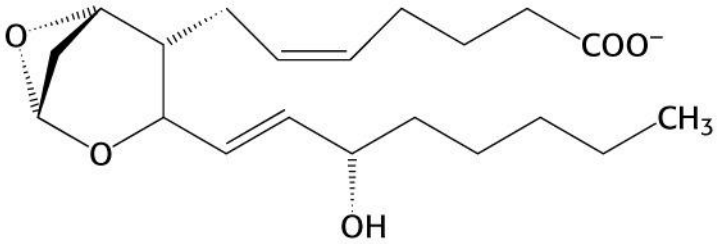
Eicosanoids



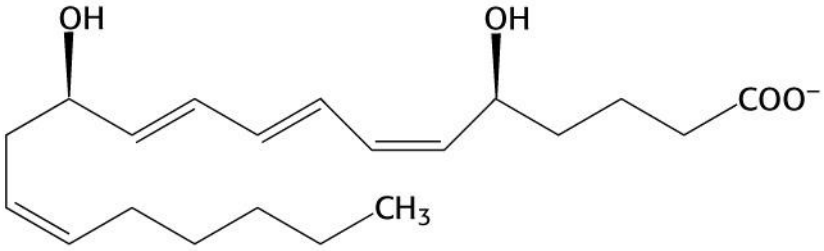
Prostaglandin A_2



Prostacylin (PGI_2)



Thromboxane A_2 (TXA_2)

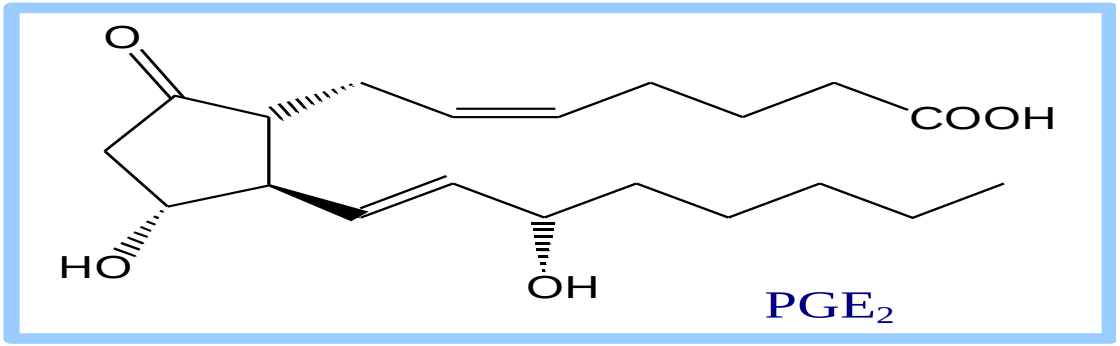


Leukotriene B_4

Prostanoids (PGs)

- Mostly isolated from prostate, derived from prostanoic acids.
- Most potent local hormone.
- 5-C cyclopentene ring

PGE_2
(prostaglandin E_2).

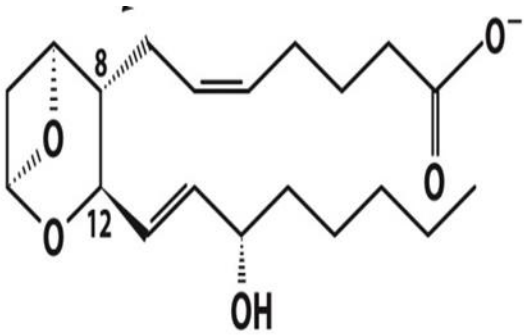


Prostaglandins have a **cyclopentane ring**.

- A **letter code** is based on ring modification A, B, E, F, I..
- A **subscript** refers to the number of double bonds in the two side-chains.
- 5 out of 19 naturally occurring PGs widely distributed in our body are PGD_2 ,PGE_2 , PGF_2 , PGI_2, TXA_2

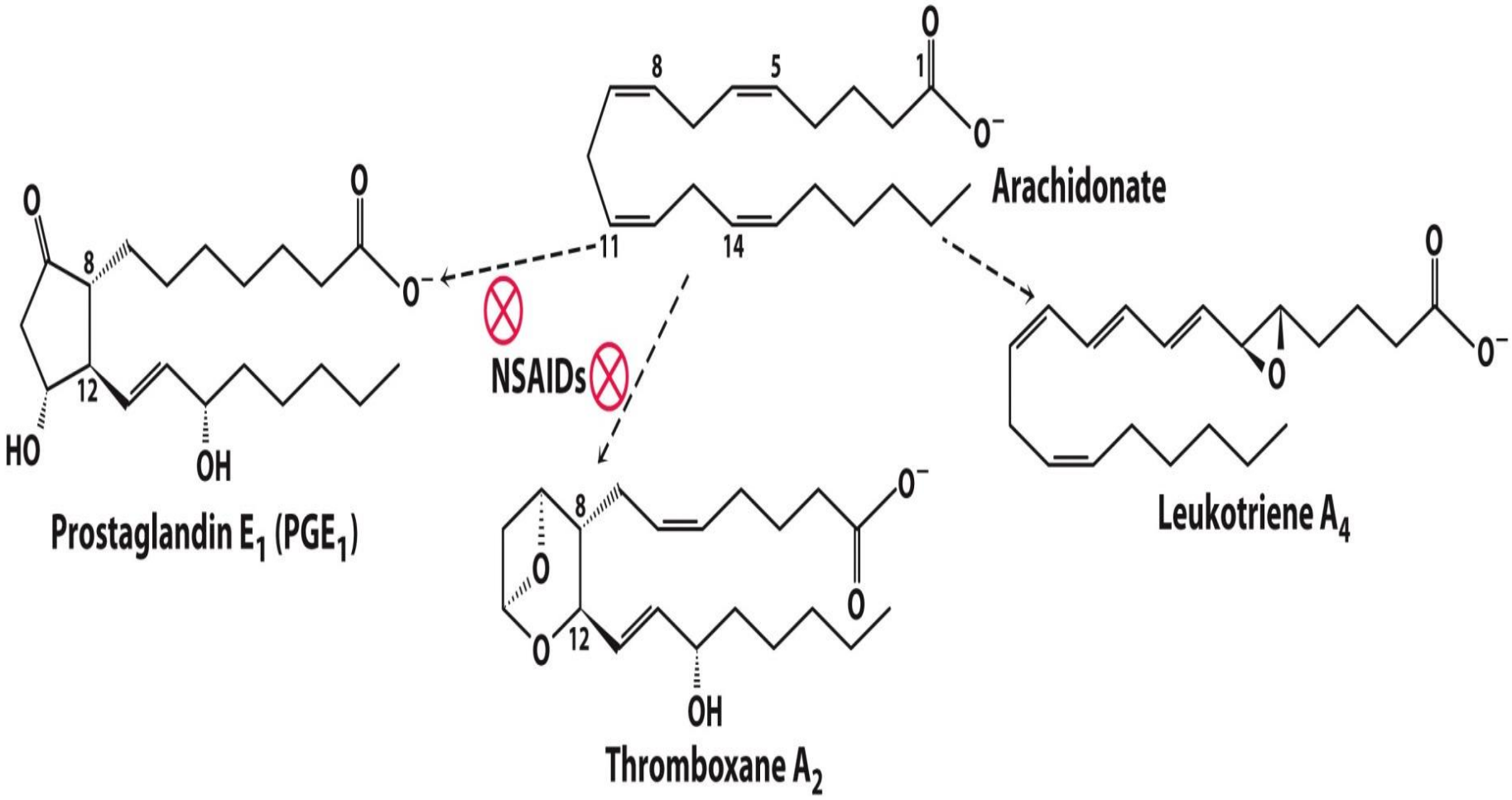
Thromboxans (Tx)

- Derived from prostanoic acid.
- 6-C oxane ring.
- They are produced by platelets (also called thrombocyte) and act in the formation of blood clots and the reduction of blood flow to the site of a clot. The non steroidal anti inflammatory drugs (NSAIDS), such as aspirin and ibuprofen, inhibit the enzyme, which catalyzes an early step in the pathway from arachidonate to prostaglandins and thromboxanes.



Thromboxane A_2

Effect of NSAIDs on Eicosanoids



Leukotrienes (LTs)

- Derived from arachidonic acid.
- Produced in neutrophil.
- Muscle contractors.
- Vasocontractors.
- Leukotrienes, found in leukocytes.

- They induces contraction of the smooth muscle lining the airways of the lung. Overproduction of leukotriene occurs in asthma and anaphylactic shock. The steroid drug inhibits the synthesis of prostaglandins, thromboxane, and leukotriene by blocking the release of arachidonic acid from membrane lipids by phospholipase A_2.

Biosynthesis

From PUFA

- Series 1 ..... Linoleic acids. 1ʌ 13-14
- Series 2.....Arachidenic acids. 2ʌ 13-14,5-6
- Series 3.....Eicoa pentaenoic acids. 3ʌ 13-14, 5-6, 17-18
- Precursor are stored in membrane phospholipids.
- phospholipase-A2, PGH synthase, cyclooxygenase, peroxidase etc are the enzymes.

Eicosanoids synthesis

Two pathways

- Cyclooxygenase pathway
  - Prostaglandin (PG)
  - Thromboxane (TX)
- Lipoxygenase pathway
  - Leucotriene (LT)
  - Lipoxin (LX)

Main sites of eicosanoids biosynthesis

- Endothelial cells
- Leukocytes
- Platelets
- Kidney

Eicosanoids are NOT synthesized in advance or stored in granules – when needed, they can be produced very quickly from arachidonate released from membranes Phospholipids in endoplasmic reticulum.

Main steps of eicosanoid biosynthesis

- 1) Activation of phospholipase A_2 (PLA_2)
- 2) Release of arachidonate from membrane phospholipids by PLA_2
- 3) Eicosanoid synthesis: Cyclooxygenase pathway

  or Lipoxygenase pathway + subsequent cell-specific modifications by synthases / isomerases.

Phospholipase

- Activated by Epineph, thrombin, angiotensin 11, bradykinine and vasopressin.

2) Eicosanoid biosynthesis

- In almost all cell types (except for red blood cells)

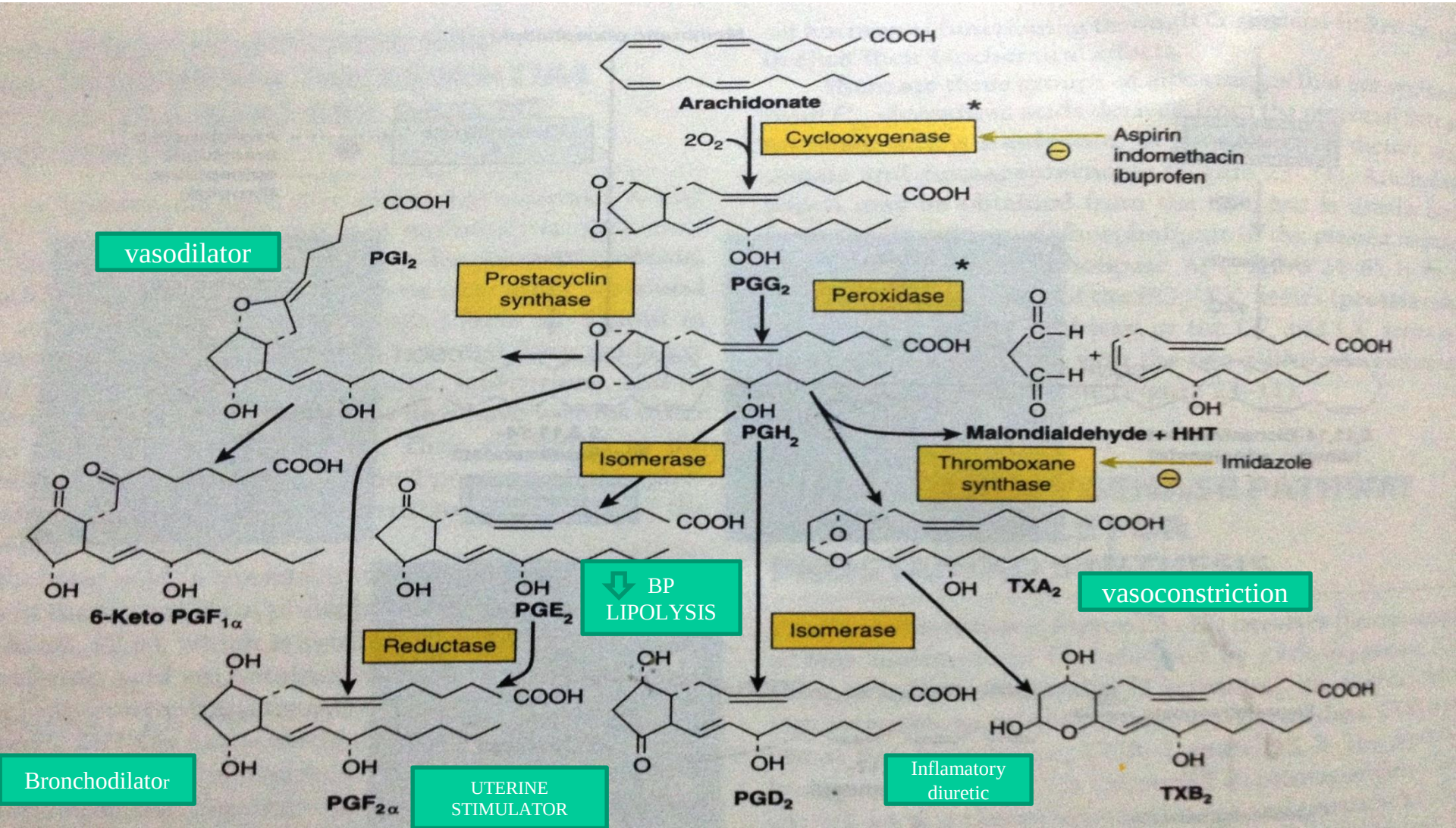
- 2 pathways:
  - A) cyclooxygenase (COX) – produces prostaglandins and thromboxane
  - B) lipoxygenase(LO) – produces leukotriene, lipoxin, 12- and 15-HPETEs (hydro-peroxy-eicosa-tetra-enoic acids)etc.

Cyclooxygenase

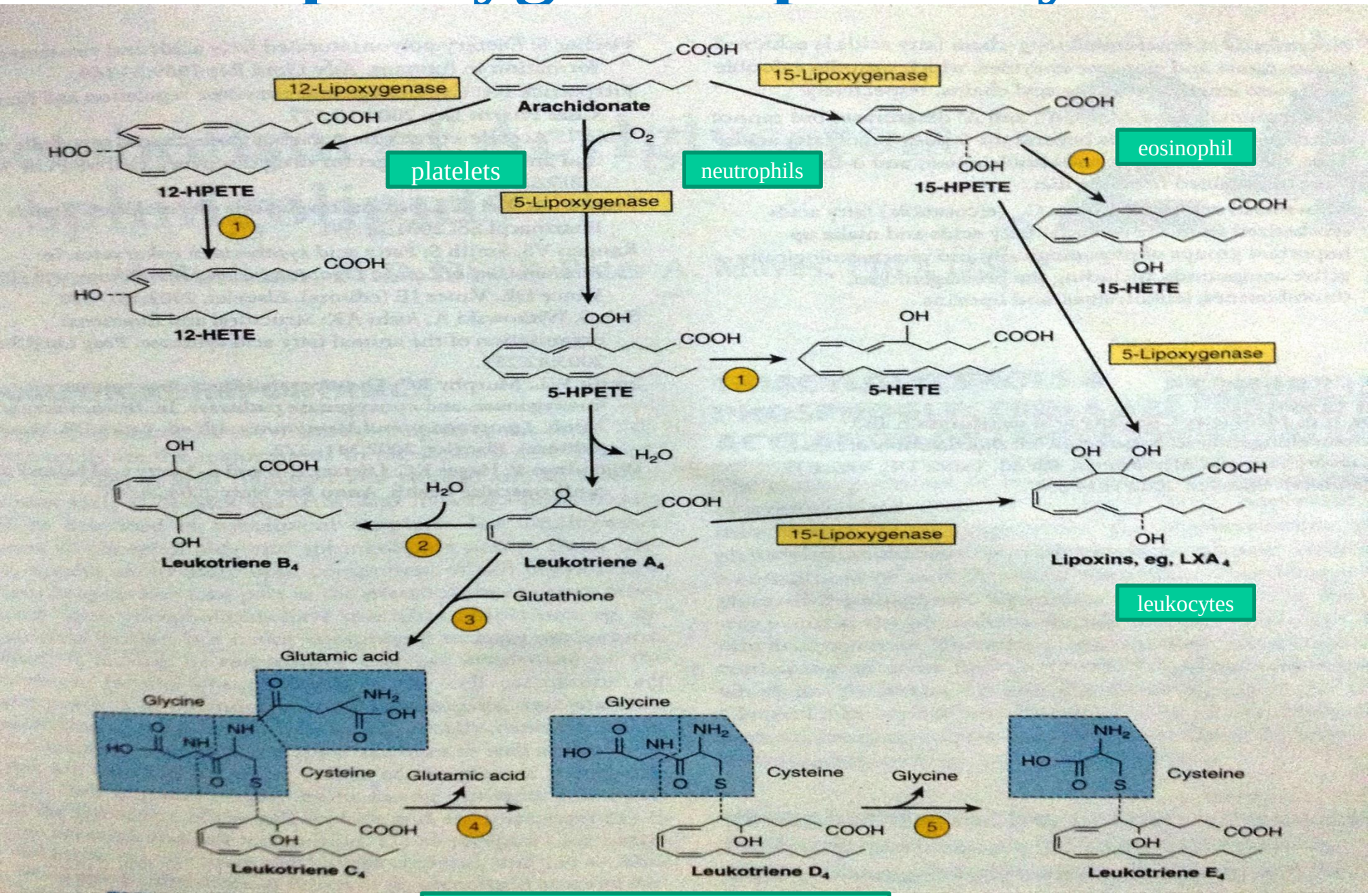
- Activated by catacholamin.
- Inhibited by NASIDs.
- Suicide enz b/c it itself catalyse them self and Prevent excessive production of PGs.
- PGs short life 30 sec.
- Inactivated by 15-OH-PG-dehydroxygenase .

Products of the Cyclooxygenase pathway

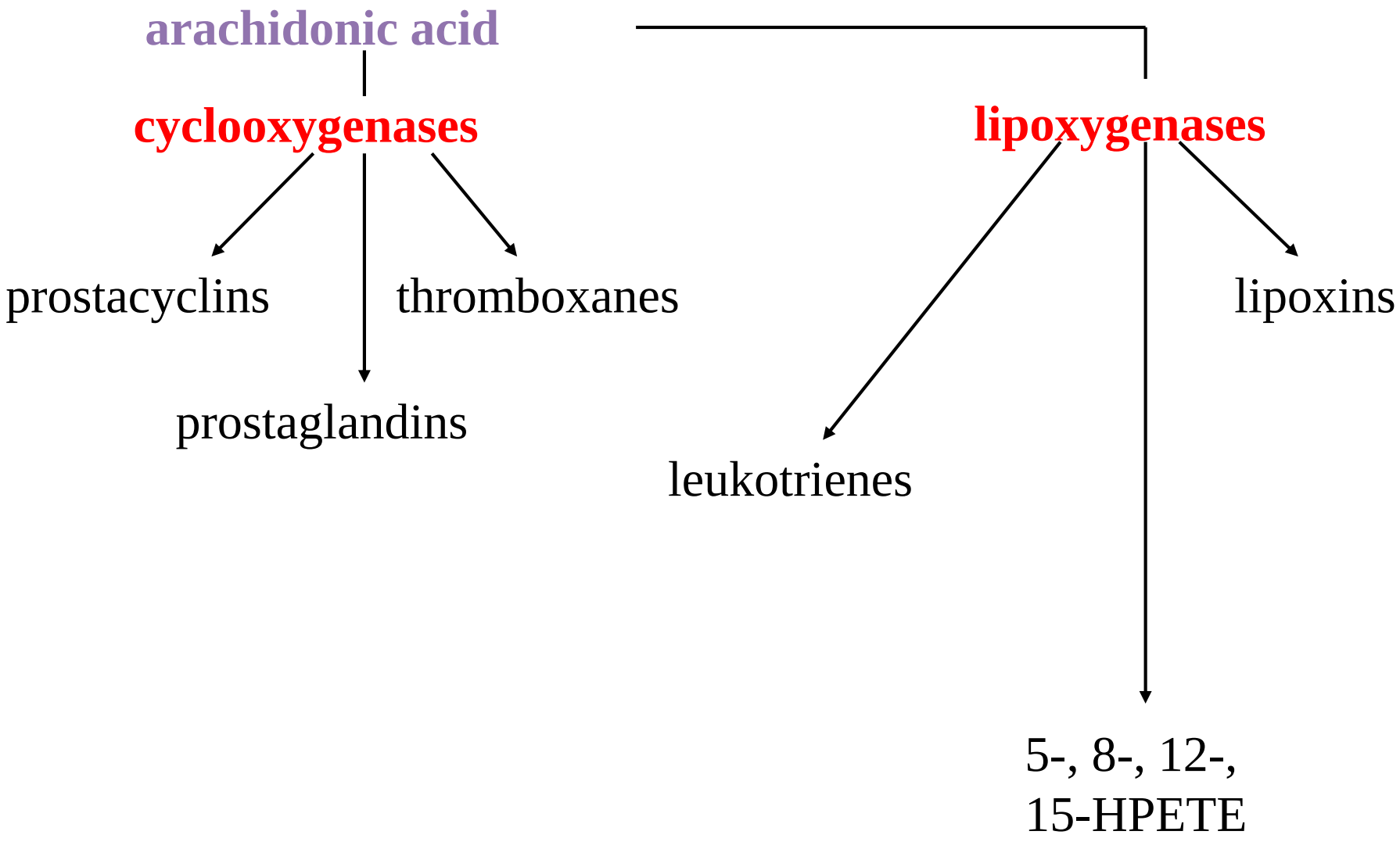
- Platelets contain thromboxane synthase producing **TXA_2,** TXB_2
- Vascular endothelial cells contain prostacyclin synthase which converts PGH_2 to prostacyclin PGI_2



Lipooxygenase pathway



Summary of the products



BIOLOGICAL EFFECTS OF EICOSANOIDS

- Eicosanoids, like hormones, display profound effects at extremely low concentrations

- They have a very short half-life; thus, they act in an autocrine or paracrine manner (unlike hormones)

- Biological effects depend not only on the particular eicosanoid but also on the local availability of receptors that it can bind to.

In general, eicosanoids mediate:

- Inflammatory response, notably as it involves the joints (rheumatoid arthritis), skin (psoriasis), and eyes.
- Production of pain and fever.
- Regulation of blood pressure.
- Regulation of blood clotting.
- Regulation of renal function.
- Control of several reproductive functions, such as the induction of labor and termination of pregnancy.

Effects of prostaglandins

- Mediate inflammation:
  - cause vasodilation $\Rightarrow$ redness, heat (PGE_1, PGE_2, PGD_2, PGI_2)
  - increase vascular permeability $\Rightarrow$ swelling (PGE_2, PGD_2, PGI_2)
- Regulate pain and fever (PGE_2)
- PGE_2, PGF_2 stimulate uterine muscle contractions during labor
- Prostaglandins of the PGE series inhibit gastric acid secretions (synthetic analogs are used to treat gastric ulcers)
- Regulate blood pressure: vasodilator prostaglandins PGE, PGA, and PGI_2 lower systemic arterial pressure
- Regulate platelet aggregation: PGI_2 = potent inhibitor of platelet aggregation
- PGE_2 inhibits reabsorption of Na^+ and water in the collecting duct.
  PGI_2: vasodilatation and regulation of glomerular filtration rate.

Biological role of thromboxanes

- Thromboxanes are synthesized by platelets and, in general, cause vasoconstriction and platelet aggregation
- TXA_2 is also produced in the kidney where it causes vasoconstriction
- Thus, both thromboxanes and prostaglandins (PGI_2) regulate coagulation
  - The higher intake of eicosapentaenoic acid and group 3 prostanoids may be responsible for low incidence of heart diseases and prolonged clotting times.

Biological role of leukotrienes

- LTs are produced mainly in leukocytes .
- Leukotrienes are very potent constrictors of the bronchial airway muscles.
- They increase vascular permeability
- They cause activation of leukocytes (primarily eosinophils and monocytes), enhance phagocytosis.
- They regulate vasoconstriction.
- They regulate inflammatory reactions, defense against infections as well as hyper-reactivity (asthma…)

- Overproduction of LTB_4 was demonstrated in:
  - Crohn's disease
  - rheumatoid arthritis
  - psoriasis
  - cystic fibrosis
- Leukotrienes are also suspected of participating in atherosclerosis development.
- Excessive bronchoconstriction can be found in some forms of asthma.

Lipoxins

- Lipoxins are produced mainly by leukocytes and platelets stimulated by cytokines
  - a) 5-lipoxygenase of neutrophils produces leukotriene LTA_4 which enters platelets.
  - b) The epithelial cells and monocytes forms 15-HPETE (hydro-peroxy-eicosa-tetra-enoic acids) which becomes a substrate for lipoxin biosynthesis.

Biological roles of lipoxins

- Unlike pro-inflammatory eicosanoids, lipoxins facilitate the resolution of the acute inflammatory response .

- Therefore, potential therapeutically used of LXs in the treatment of inflammatory diseases like glomerulonephritis, asthma.

Biological effects of HPETEs (hydro-peroxy-eicosa-tetra-enoic acids)

- 5-HPETE participates in defense against bacterial infection (chemotaxis and degranulation of neutrophils and eosinophils)

- 20-HPETE causes vasoconstriction (by its effect on the smooth muscle of vessels); in kidney, it regulates Na^+ excretion, diuresis, and blood pressure.

- 12-15-HPETE are produced in kidney and participate in the regulation of the renin-angiotensin system.

ANY QUESTION

- **CHATTERJEA BIOCHEMISTRY**
- **LIPPINCOTT BIOCHEMISTRY**
- **HARPERS BIOCHEMISTRY**
- **SATYANARAYANA BIOCHEMIST**
- **INTERNET**

Thank you