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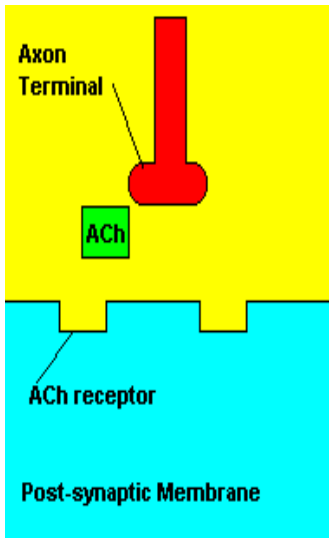
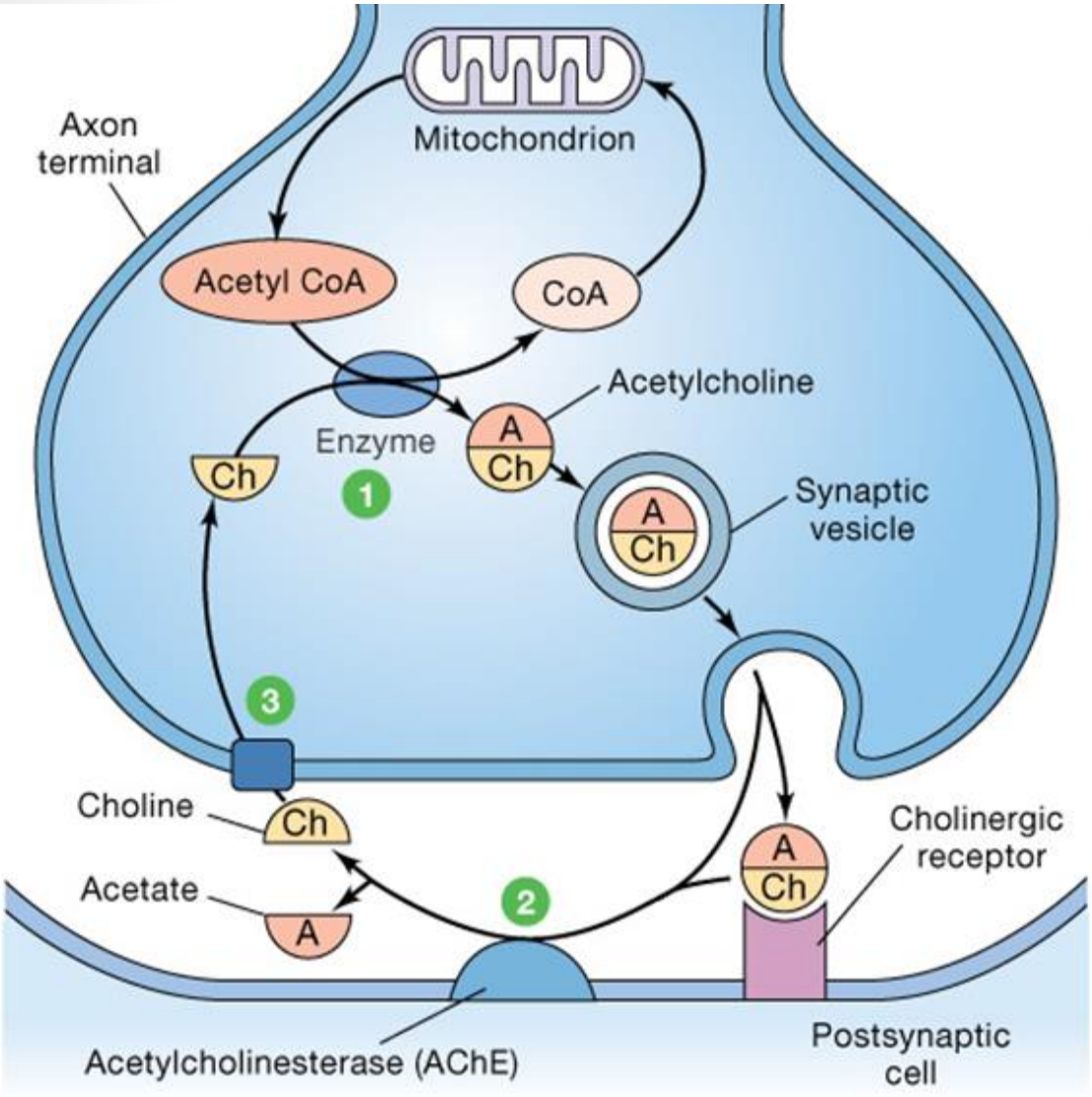
Atropa belladonna (*Solanaceae*)



Acetylcholine and transmission



1. **Acetylcholine** (ACh) is made from choline and acetyl CoA.

2. In the synaptic cleft ACh is rapidly broken down by the enzyme **acetylcholinesterase.**

3. Choline is transported back into the axon terminal and is used to make more ACh.

Dr. Yousef Abusamra

Pharmacological actions and uses:

The three alkaloids are anti-cholinergic agents i.e.:

1-Decrease saliva and GIT secretions so used preoperative.

2-Decrease motility of smooth muscles so used as antispasmodics.

3-Stimulate respiratory system.

4- Have a mydriatic effect (cause dilatation of the eye pupil).

5-An antidote to organophosphorus insecticides.

6-Hyoscine has a more central effect, so it is used as a sedative and hypnotic.

7-Hyoscine is mainly used as **antiemetic**.

Atropine is a **cholinergic-blocking agent**, it occupies the postsynaptic receptor site, and prevents the normal neurotransmitters (acetylcholine) from acting, so atropine has the following effects:

a- Antispasmodic: it relaxes the smooth muscles of intestine and bronchi.

b- Mydriatic: is used in ophthalmology during examinations of eye.

c- In **small doses** atropine is a smooth **stimulant to respiration and myocardium.**

d- Locally, **atropine ceases pain** (slight paralysis of nerve endings)

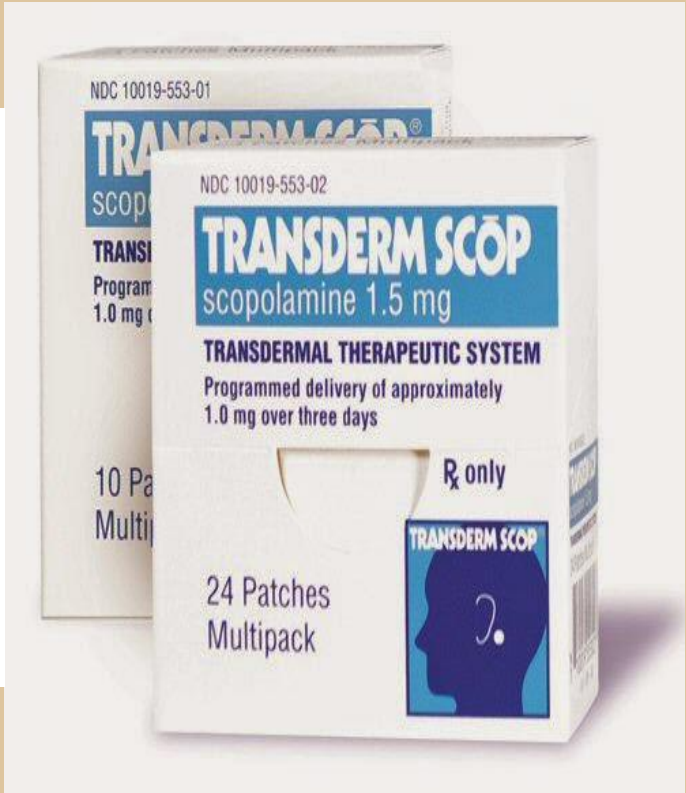
e- It is used **pre-operative to decrease the salivation, secretions of stomach and intestine.**

f- It is an **antidote** against the poisoning with the following agents:

Physostigmine, neostigmine, pilocarpine, organophosphorus insectisides and muscarine.

Scopolamine:

- Is selectively sedative to the CNS, and it quiets excitability especially in the insane patients.
- Is used in motion sickness **(nausea caused by motion, especially by travelling in a vehicle)**.



Side effects of tropane alkaloids:

Dry mouth, skin (decreased sweating) and eye, headache, nervousness, dizziness, drowsiness, palpitation, tachycardia, mydriasis, blurred vision, nausea, vomiting, urinary retention, fever, constipation, glaucoma.

Cocaine Alkaloids:

Obtained from the **leaves** of the shrub *Erythroxylum coca* (**Bolivian coca**, **1%**), or *E, truxillens* (**Peruvian coca, 2%**) (**Erythroxylaceae**).

- Coaine is quickly absorbed from the mucous membrances and is used only **topically as anesthetic** in ophthalmology (salt 1%).
- 50 mg of cocaine lead to euphoria and hallucinations. Larger doses lead to cerebral cramps, hyperirritability and paralysis.
- It is highly addictive.

Cocaine alkaloids

** Occurrence:

Coca leaves contain about 2% total alkaloids

** It is the major alkaloid in Coca leaves.
Cocaine is diester alkaloid.

** Heating at 160 C○ in conc. HCl leads to hydrolyses of cacaine to MeOH, benzoic acid and ecogonine base.

Main Alkaloids are:

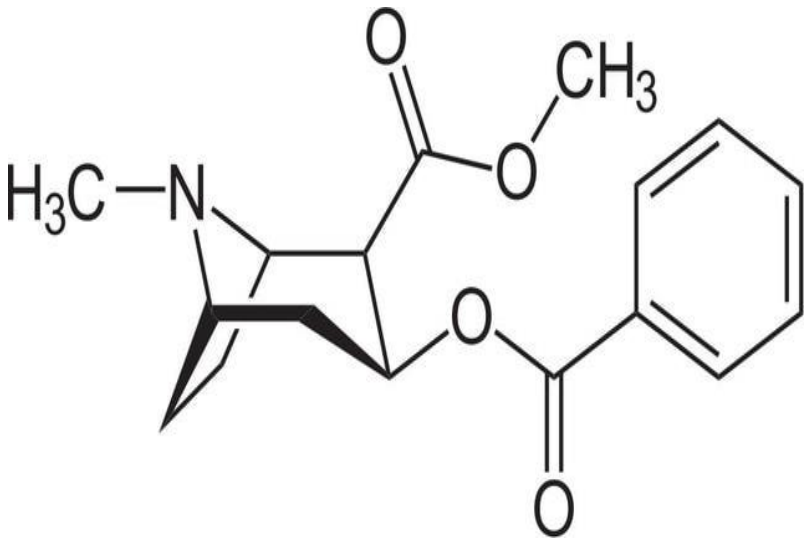
1- Cocaine.
2- Cinnamylcocaine.
3. Truxilline.

** The base for Coca Alkaloids is called “Ecogonine”

Uses:

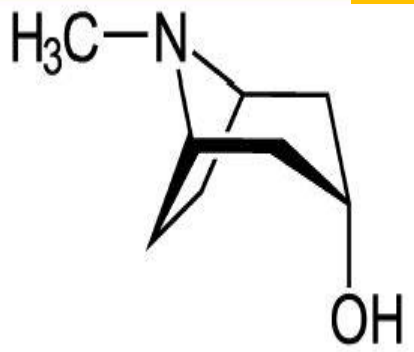
Cocaine was used as local anesthetic.

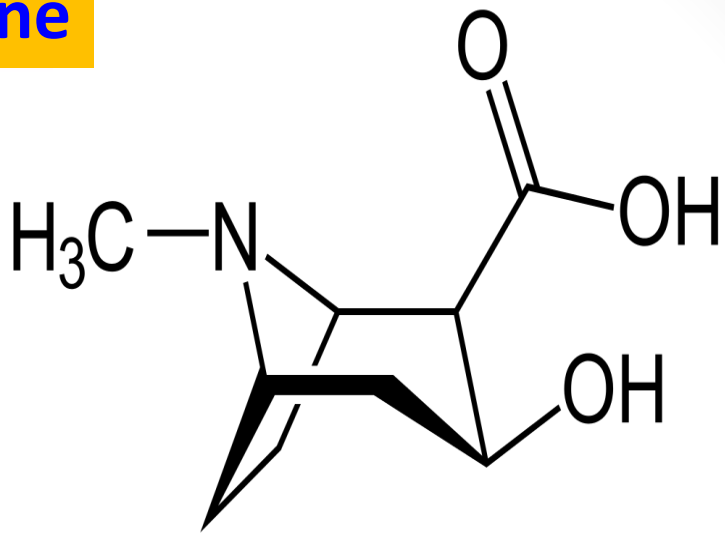
Cocaine has a CNS stimulant activity so it is one of the widely abused drugs.



Cocaine: benzoylmetheylecogonine

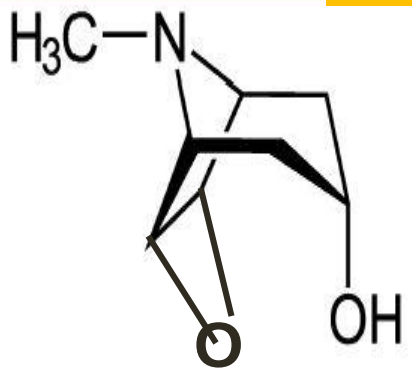
Tropine



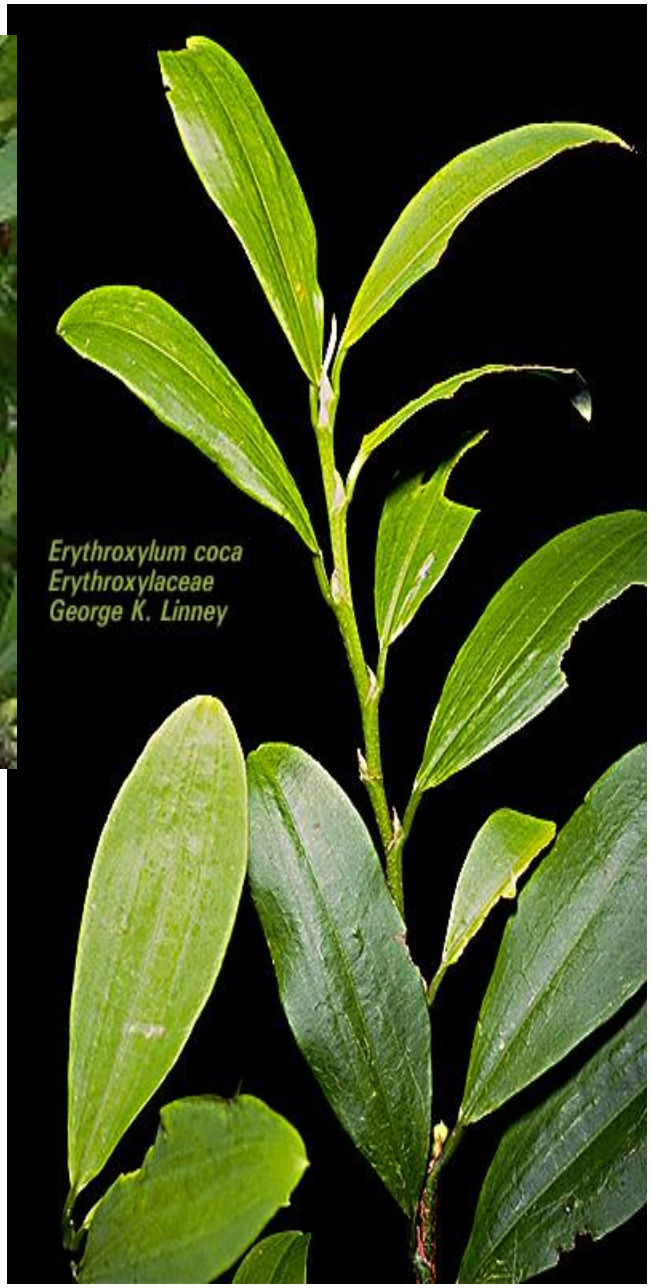


Ecogonine

Scopoline

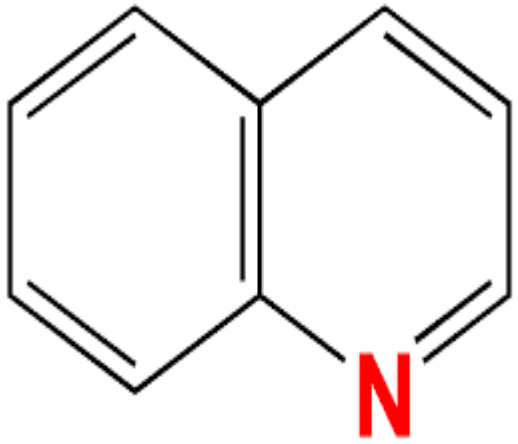


TROPANE TYPES



Erythroxylum coca - Erythroxylaceae

Quinoline Alkaloids



Dr. Yousef Abusamra

Biosynthetic origin:

- The alkaloids (> 25) of this group occur only in 2 genera
  1. Cinchona and 2. Remijia {Rubiaceae}
- They are obtained from the **bark** of different

Most famous species of Cinchona:

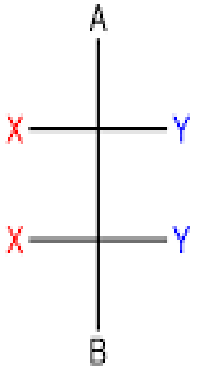
1. *Cinchona succirubra*
2. *C. ledgeriana*
3. *C. officinalis*
4. *C. calisaya*

- **Cinchona Alkaloids:**

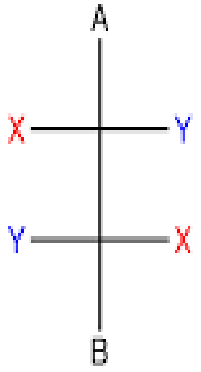
1-Quinine and its dihydroform and (+) quinidine and its dihydroform.

2-Cinchonidine and its dihydroform and (+) cinchonine and its dihydroform.

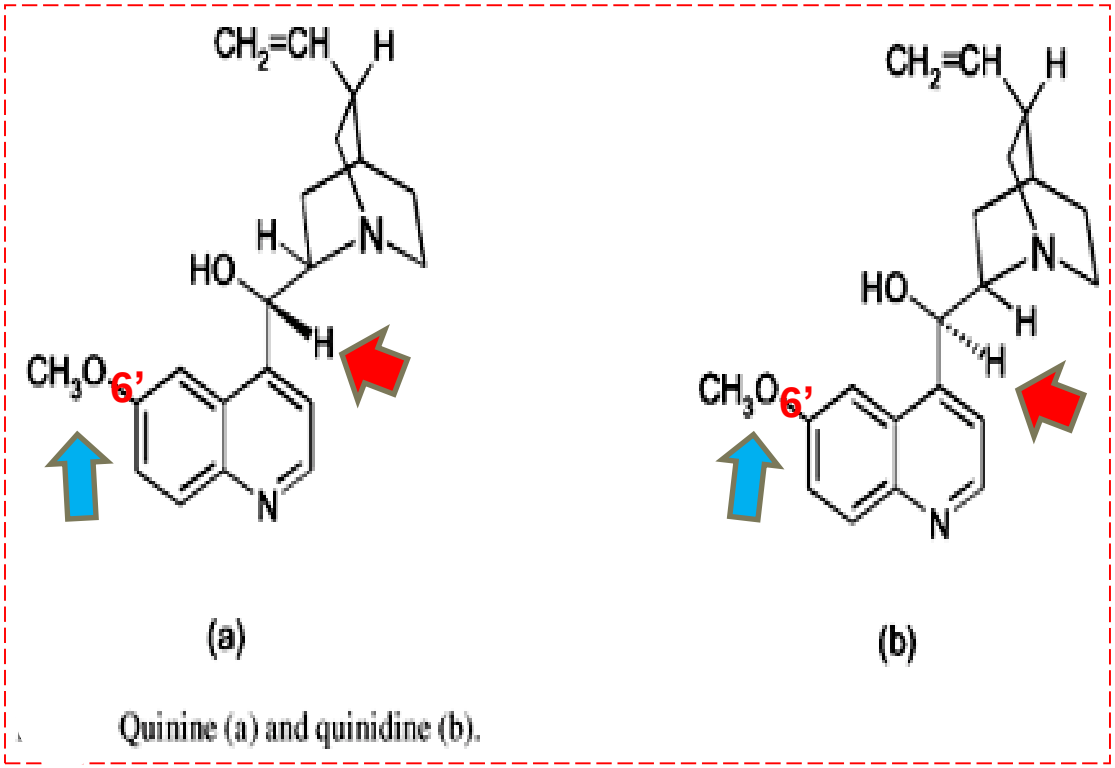
- They fall into <u>two configurational group</u>, quinine and cinchonidine have the **erythro** configuration while quinidine and cinchonine ,have the **threo** configuration.



erythro isomer

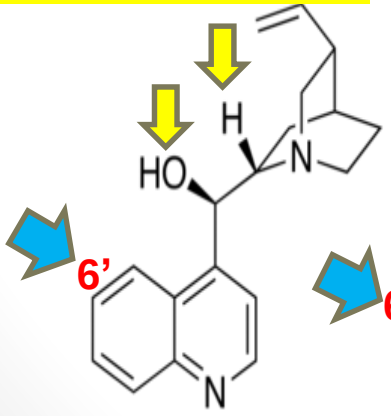


threo isomer

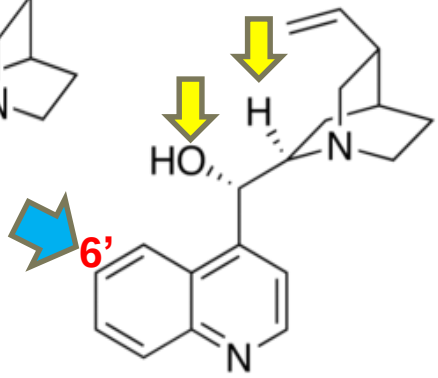


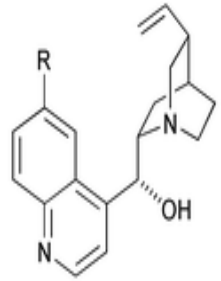
Quinine (a) and quinidine (b).

Cinchonidine

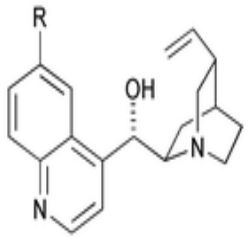


Cinchonine

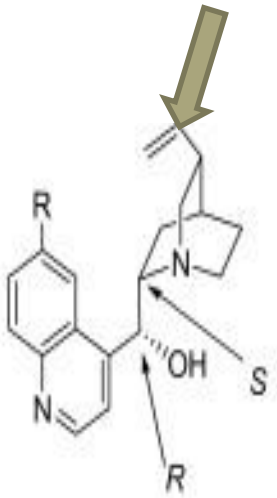




Quinine (R = OMe)
Cinchonidine (R = H)

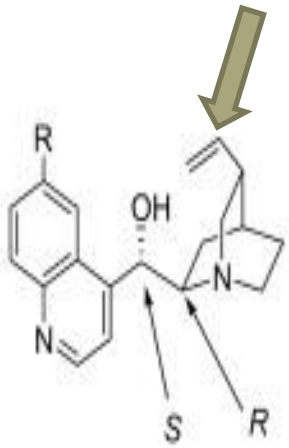


Quinidine (R = OMe)
Cinchonine (R = H)



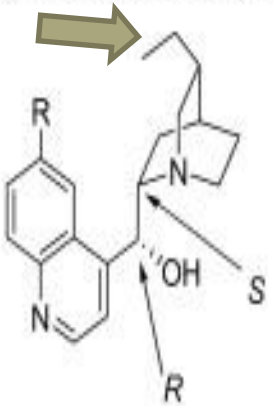
1 quinine (R = OMe) **Q**

3 cinchonidine (R = H) **CD**



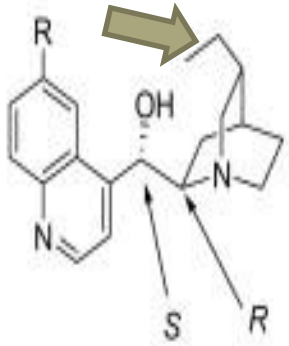
2 quinidine (R = OMe) **QD**

4 cinchonine (R = H) **CN**



5 dihydroquinine (R = OMe) **DHQ**

7 dihydrocinchonidine (R = H) **DHCD**

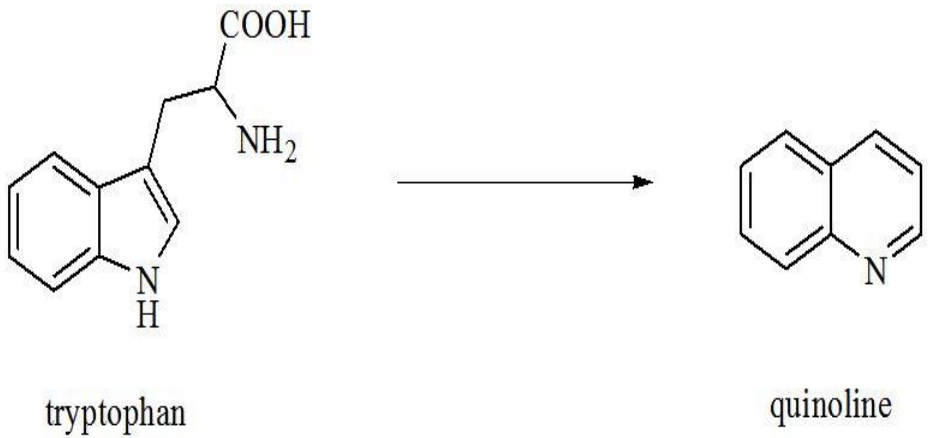


6 dihydroquinidine (R = OMe) **DHQD**

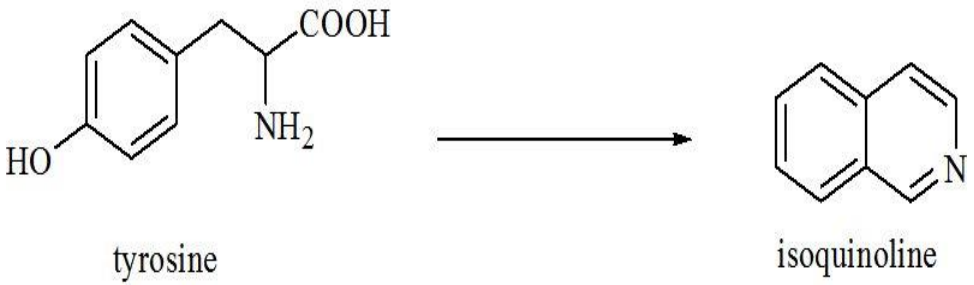
8 dihydrocinchonine (R = H) **DHCN**

Biosynthesis of cinchona alkaloids

- They are synthesized from the amino acid **tryptophan**.

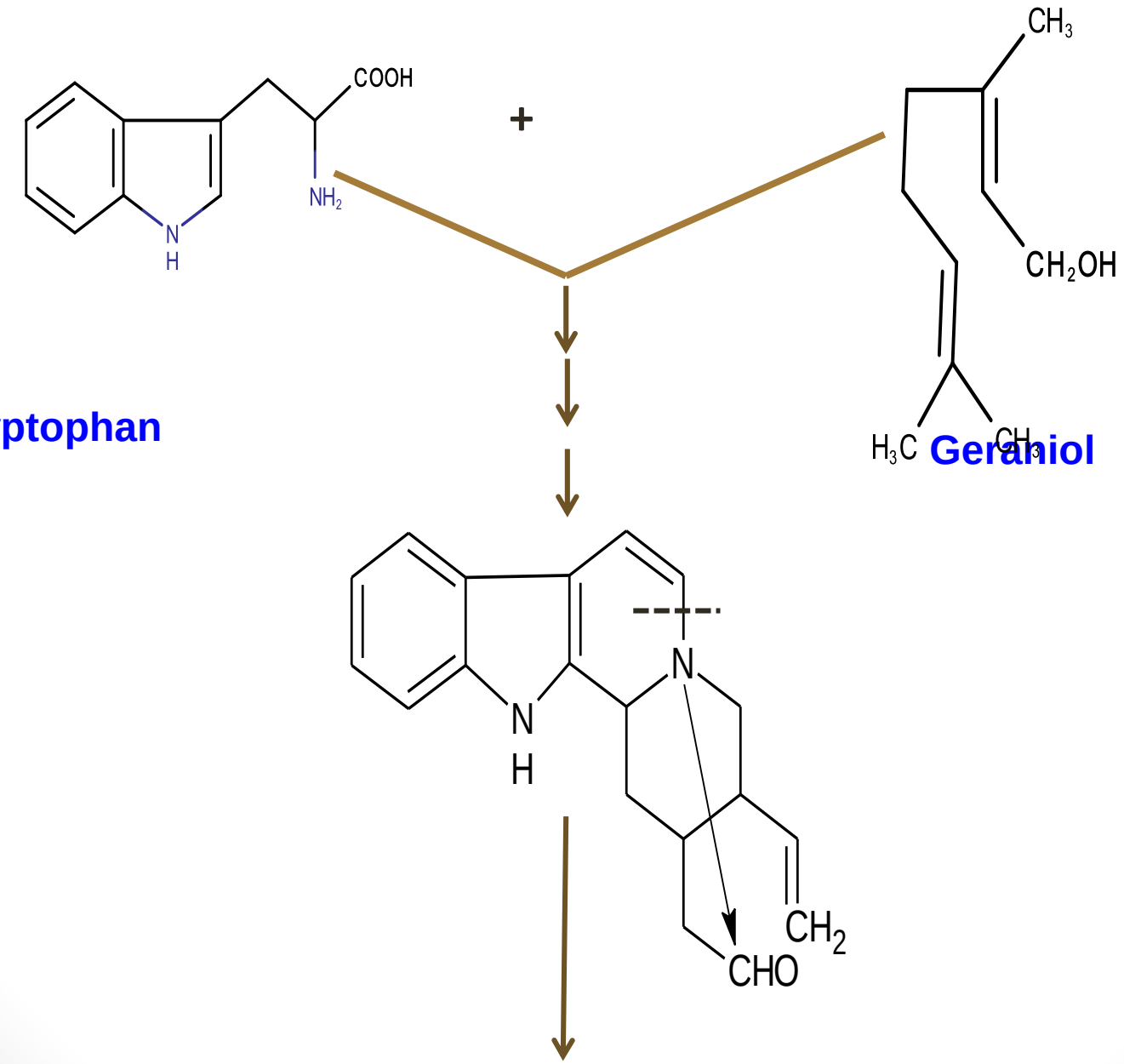


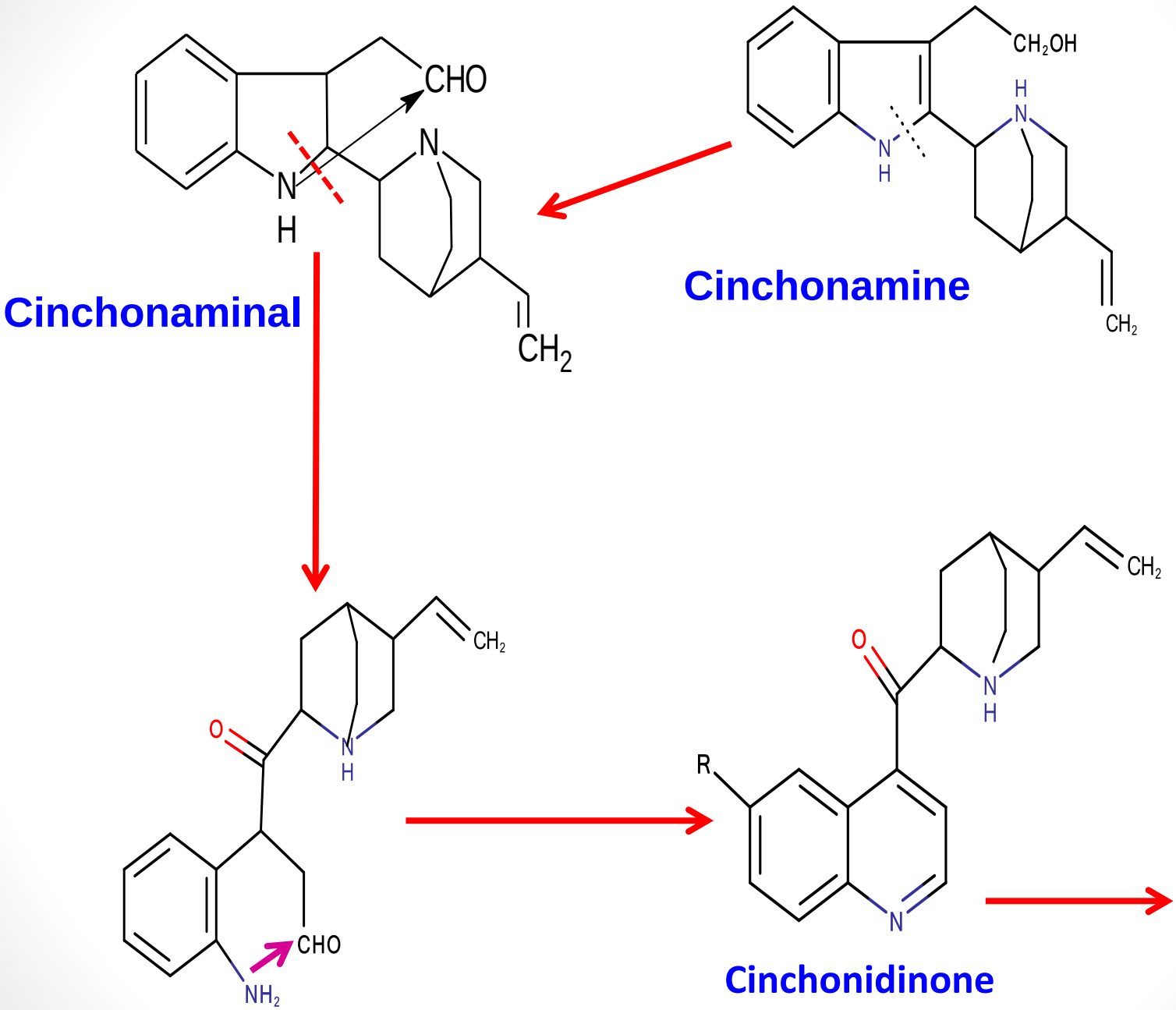
tryptophan quinoline

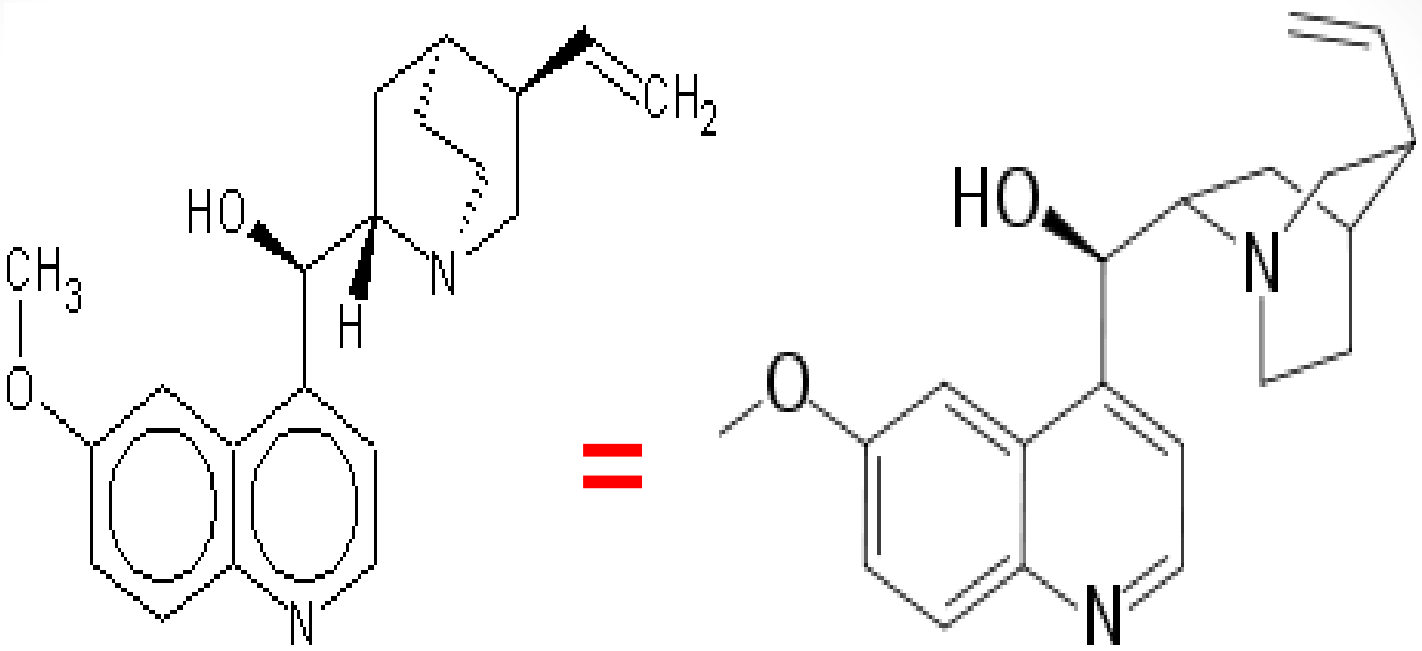


tyrosine isoquinoline

Biosynthesis of Cinchona Alkaloids




CHO
N
H
CH2
Cinchonaminal
CH2OH
H
N
N
H
Cinchonamine
CH2
O
N
H
CH2
CHO
NH2
R
O
N
H
CH2
N
Cinchonidinone

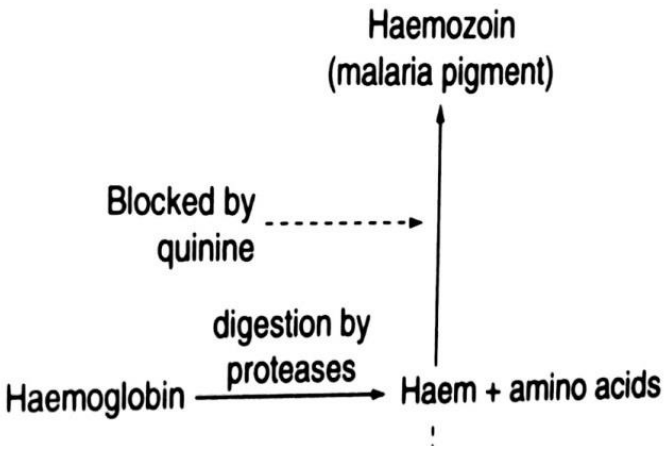


Quinine

- The biosynthesis involves **strictosidine** and **cornantheal** as intermediates

Pharmacology

Mechanism of action of quinine (as antimalarial):



The parasite detoxifies heme by converting it to malaria pigment, **haemozoin**.
This process is blocked by the drug.

- **TOXICITY:** it causes **tinnitus** and other side effects which are collectively called **CINCHONISM** {high-tone hearing loss, photophobia (an intolerance of light) and other visual disturbances, dysphoria, headache, nausea, vomiting, sweating, dizziness and postural hypotension}, **hypoglycemia** (from the drug's stimulatory effect on pancreatic β cells; most common in the treatment of severe malaria), **hypotension**.
- Has a **muscle relaxant effect**, so it can be used to treat **nocturnal leg cramp** تشنج عضلي ليلي.
- Since it is usually used for long time, the parasite can develop resistance to it.
- Accordingly, synthetic drugs (mefloquine, chloroquine and primaquine) have been manufactured to face the parasite resistance to the natural drugs.
- Again, the parasite managed to develop resistance even for the synthetic drugs.

- The strategy now depends on using **combinations** of members from both the **natural** and **synthetic** products.
- The extract of the bark of this tree is also **used** as **bitter tonic in beverages** and as **stomachic** {TONIC for the stomach: slows down the stomach and reinforces it}.

QUINIDINE USES:

- For **cardiac arrhythmia** such as **atrial fibrillation**: it decreases myocardial excitability, and thus it has an **interaction** with digoxin {Quinidine may increase the blood level of digoxin, i.e. pharmacokinetic effect}.

Quinidine-digoxin mechanism of interaction

- Patients who receive the combination almost always will have a significant elevation in their digoxin plasma concentrations and can suffer digoxin-induced toxicity, including arrhythmias, anorexia, altered color vision, and mental changes.

- A series of studies identified a mechanism that appears to underlie the digoxin interactions reported with a wide variety of precipitant drugs. It was first noted that quinidine reduced the renal tubular secretion of digoxin by inhibiting a renal transporter protein?P-glycoprotein (P-gp).

Quinidine-digoxin mechanism of interaction

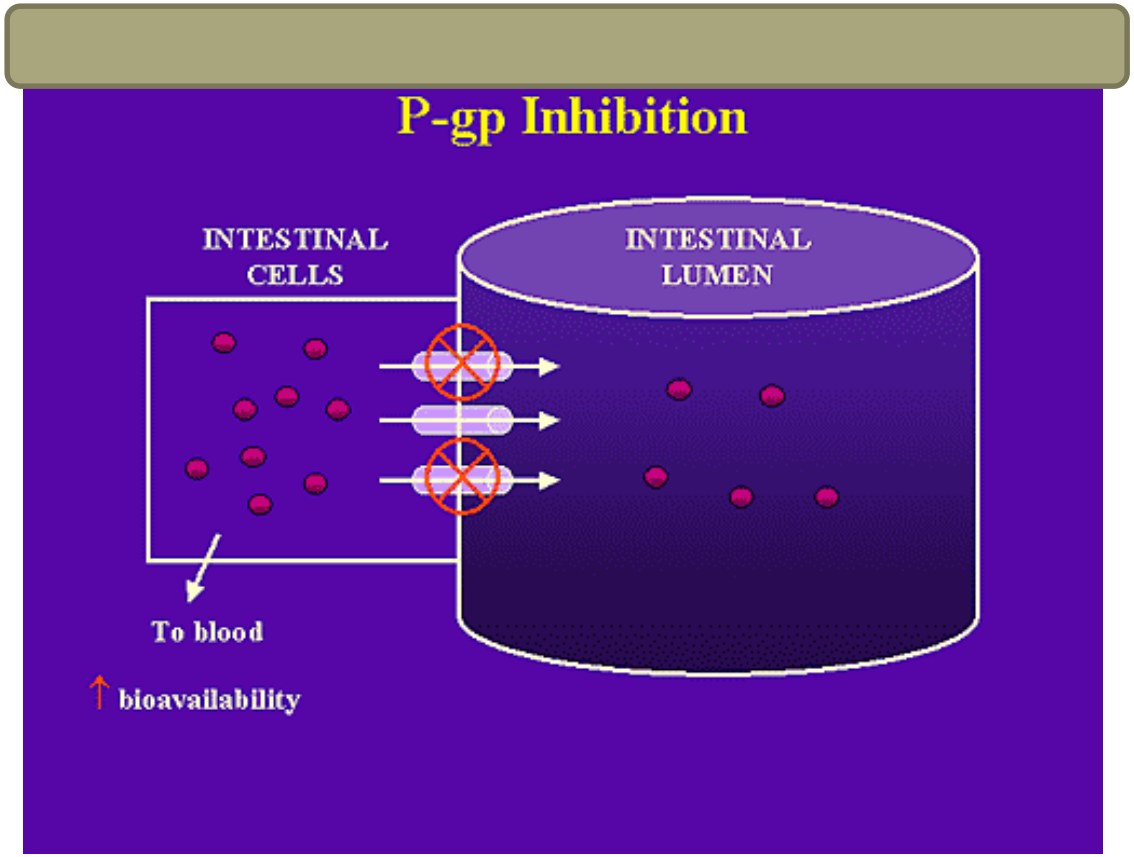
- In 1996, it was demonstrated that the effect of quinidine on plasma digoxin concentrations was the result of quinidine-induced **inhibition** of P-gp in the **intestine**, as well as at sites of digoxin elimination such as the **kidney**.
- P-glycoprotein is an energy-dependent **efflux** transporter. Simply stated, Pgp pumps drug molecules **out** of cells. P-gp is found in the epithelial cells of the intestine (enterocytes) along the apical (luminal) side of the cell. When a drug is taken orally, drug molecules have to pass through the enterocyte to enter the blood. As the molecules diffuse through the enterocyte, P-gp can pick up the molecules and carry them back to the luminal side of the cell, where they are (thrown) back into the lumen of the intestine.

Quinidine-digoxin mechanism of interaction

- Patients who receive the combination almost always will have a significant elevation in their digoxin plasma concentrations and can suffer digoxin-induced toxicity, including arrhythmias, anorexia, altered color vision, and mental changes.

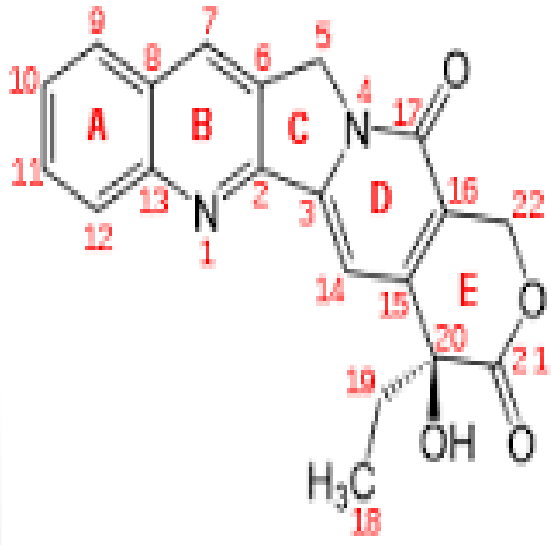
- A series of studies identified a mechanism that appears to underlie the digoxin interactions reported with a wide variety of precipitant drugs. It was first noted that cyclosporine reduced the renal tubular secretion of digoxin by inhibiting a renal transporter protein?P-glycoprotein (P-gp).

Quinidine-digoxin mechanism of interaction

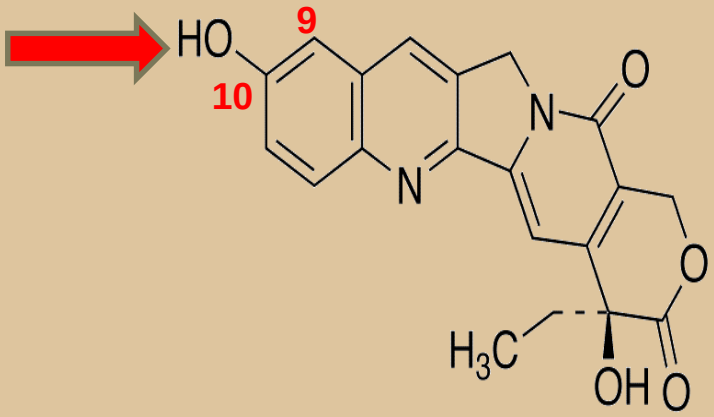


Camptothecin
Quinoline alkaloid

- Obtained from the **bark** and the **stems** of the Chinese tree *Camptotheca acuminata* (**Nyssaceae**).
- This alkaloid showed broad spectrum activity as **anticancer** but its toxicity is high.



- The natural 10-hydroxy camptothecin is more active and is used in China for **neck and head cancer**.



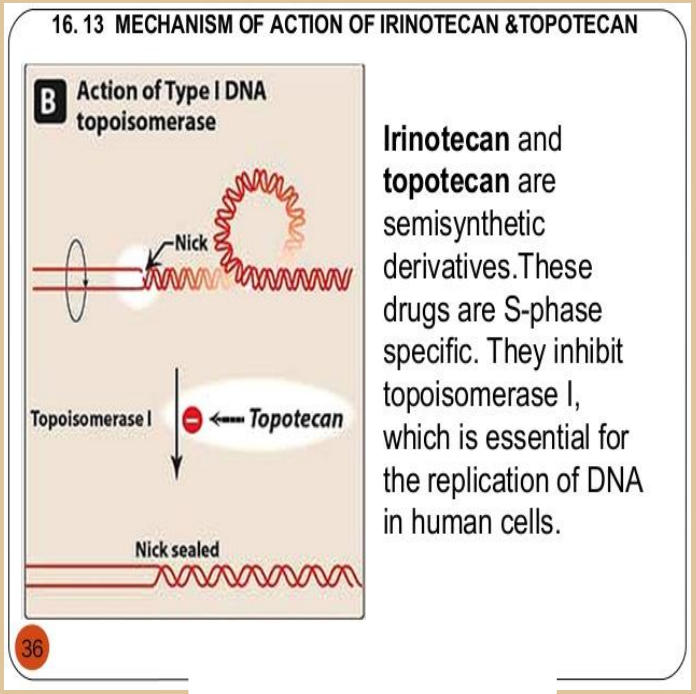
- Another derivative is **9-aminocamptothecin**, which is poorly water-soluble but more active than the camptothecine at much lower doses.
- The **water-soluble** derivatives **topotecan** and **irinotecan** showed good response in number of cancers.
- They are now available for treatment of ovarian cancer and colorectal cancer, while **belotecan** (Camtobell ®: available in USA) is used for small cell lung cancer and ovarian cancer.

Mechanism of action

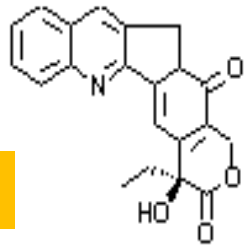
- Irinotecan is an **antineoplastic enzyme inhibitor** primarily used in the treatment of colorectal cancer.
- It is a derivative of camptothecin that inhibits the action of topoisomerase I.
- Irinotecan prevents unwinding of the DNA strand by binding to topoisomerase I-DNA complex, and causes double-strand DNA breakage and cell death.

Side effects of irinotecan:

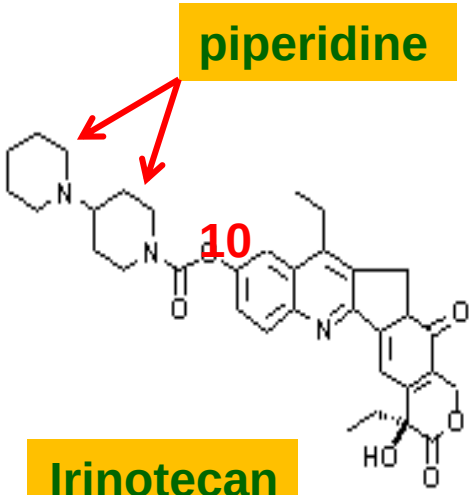
Diarrhea, anemia, hair loss, abdominal cramp, vomiting and nausea -------
(common almost to all chemotherapy).



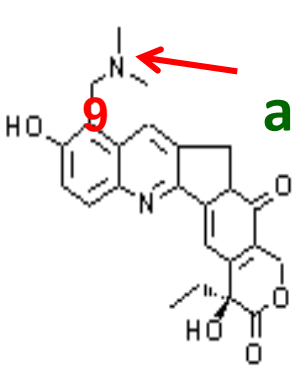
Camptothecin



piperidine

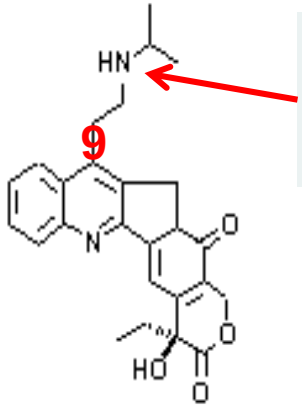


Irinotecan



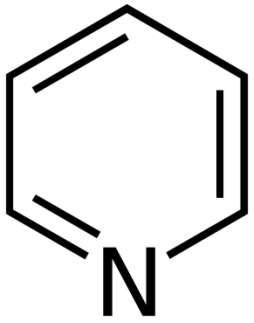
3° amine

Topotecan

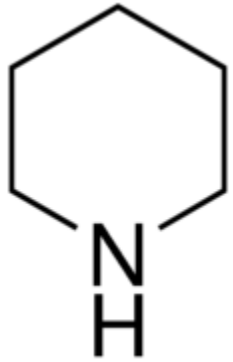


2° amine

Belotecan
= Camtobell®



Pyridine-piperidine Alkaloids



Dr. Yousef Abusamra

Pyridine alkaloids and Nicotinic acid derivatives:

- Biosynthetic (botanical) origin:
- **Nicotine:** very toxic compound
-Botanical source: leaves of *Nicotiana tobacum* - *Solanaceae*
-Pharmacological effect:
-It works on the nicotinic receptor (starts by stimulation then inhibition).
-Highly hydrophobic, so can cross blood brain barrier.

- **In low doses**, such as those inhaled in smoking, nicotine causes hypertension, respiratory stimulation, stimulation of secretion from several glands and stimulation of CNS.
- The lethal dose (50-100 mg) corrosponds to 5-cigarette content of nicotine, but it is destroyed by heat or distributed into the air.
- **Toxic doses** cause hypotension and death occurs as a result of respiratory arrest.

Uses:

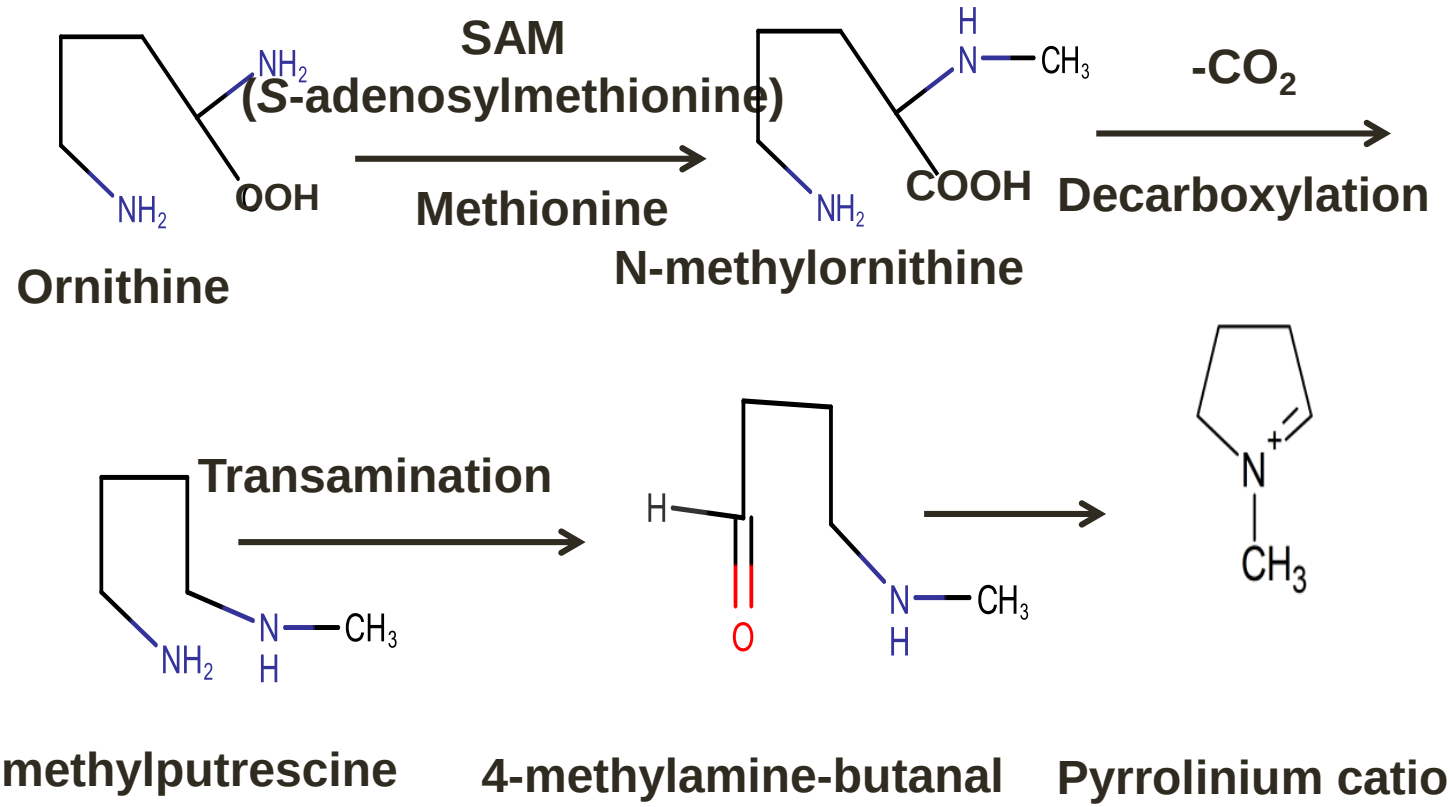
- Nicotine in medical products is used to aid in smoking cessation (available in form of **chewing gum**, **nasal spray** and **nicotine-impregnated patches**).
- Enhances hippocampal transmission and improves long-term memory.
- Potential evidence: in ulcerative colitis.
- Vehicle on CNS (stimulant), dental carries, in Alzheimer and Parkinson [is still **not** clear].
- Insecticide especially in gardening (and is prepared by isolation from tobacco waste).

- It's an oily liquid compound, yellowish in color.
- Oxidized by light to form a brown color.
- Toxicity: Cancer and atherosclerosis, as it yields nitrous amine (very nucleophilic), leads to change in DNA structure, pulmonary and cardiac disease, effect on hepatic system, it leads to increase metabolism.

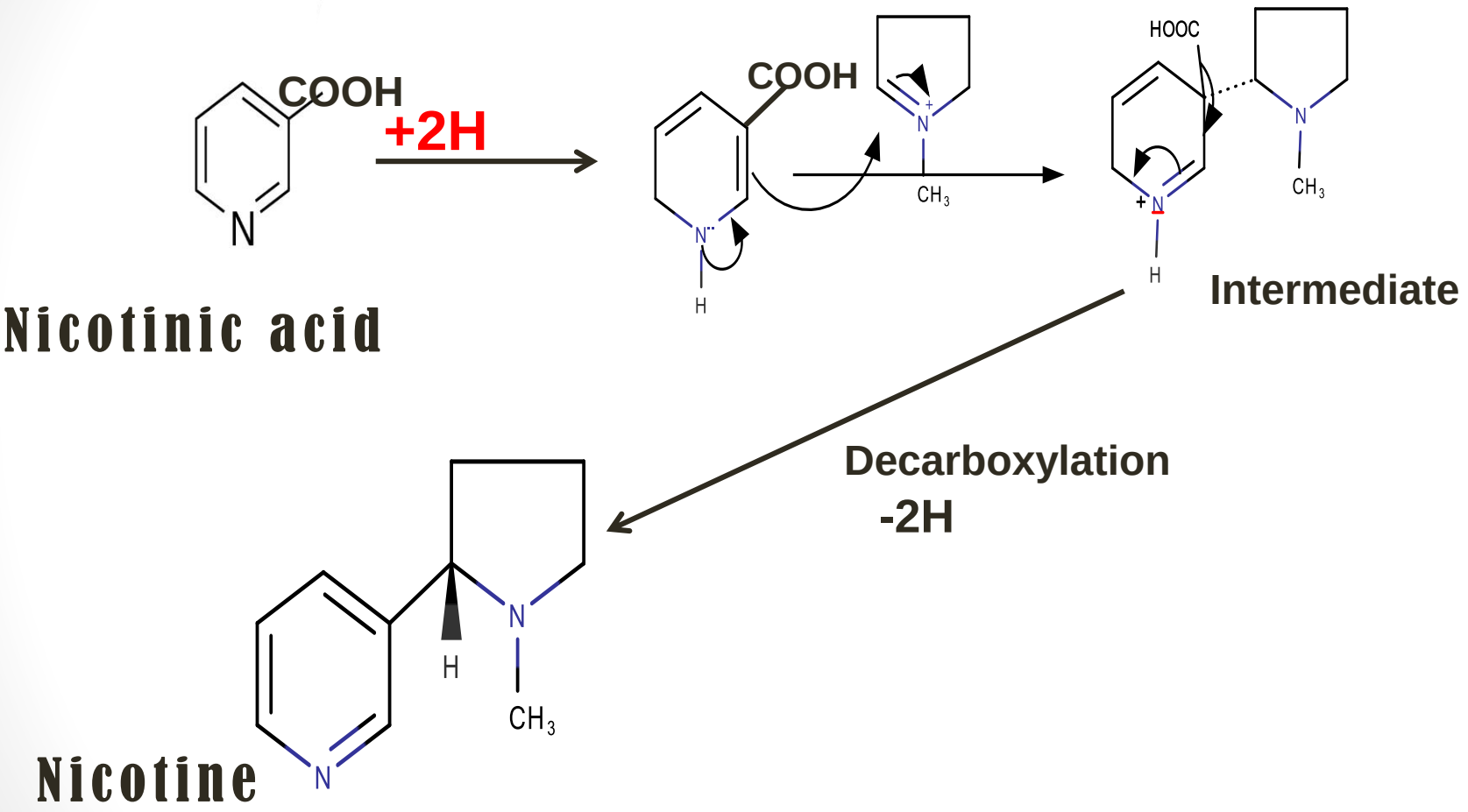
YouTube:https://www.youtube.com/watch?v=cKzBpkiOrZg&ab_channel=Pharmapedia

- Smoking tree, *Nicotiana*, cuases deaths more than any other plant.
- Smokings is responsible for causing one-third cancer cases.
- It is estimated that more than 3 million deaths occur annually (2004).
- The mortality is expected to jump to 10 million deaths by 2030.
- The leaf contains more than 4,000 chemicals, with nicotine coming on the top of the list.
- Nicotine is responisble for the addiction in smokers.

Biosynthesis of nicotine

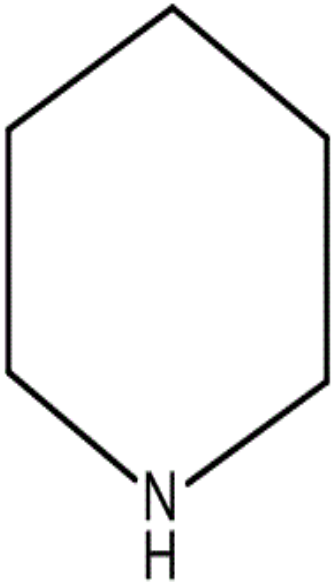


Biosynthesis of nicotine



It is a pyridine alkaloid yet it contains another heterocyclic ring, pyrrolidine.

Piperidne Alkaloids



1. Pelletierine:

- It is found in pomegranate tree bark, *Punica granatum*, الرمان(Punicaceae).
- The official drug is the tannate salt of this alkaloid.
- It is used as a **vermicidal** as it is toxic to tape worms and has been used as **anthelmintic**.