Pharmacognosy and Phytochemistry

Alkaloids-Part 5

B. Pharm. Semester-1

Course Code: 0510221; Session: 2022-2023

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Learning Outcomes

At the end of this lesson, students will be able to explain

Quinoline alkaloids: Chinchona alkaloids: Quinine, Quinidine, Chinchonine, Chinconidine and Camptothecin Derivatives

Quinolizidine alkaloids: Sparteine, Lupine, Anagyrine and Cytisine

Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the alkaloids as major phytoconstituents.

Quinoline alkaloids: Cinchona

- Cinchona bark consists of the various species and hybrids of Cinchona, such as

  Cinchona succirubra or ‘red’ bark (alkaloid content 5–7%)

  Cinchona calisaya or ‘yellow’ bark with an alkaloid content of 4–7%

  Cinchona ledgeriana or ‘brown’ bark (alkaloid content 5–14%)

- Family: Rubiaceae
- Cinchona is indigenous to Colombia Equador, Peru & Bolivia (South America)
- The Cinchona barks are harvested at 8-10 years old.

Quinoline alkaloids: Cinchona

Cinchona succirubra

Cinchona ledgeriana

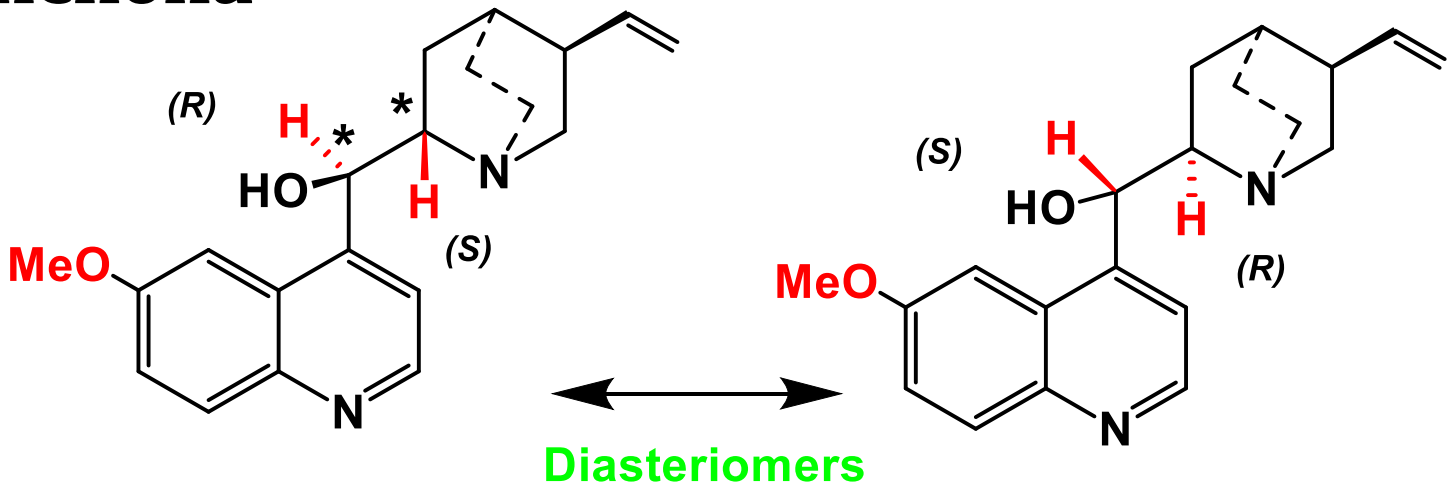
Cinchona calisaya

Bark

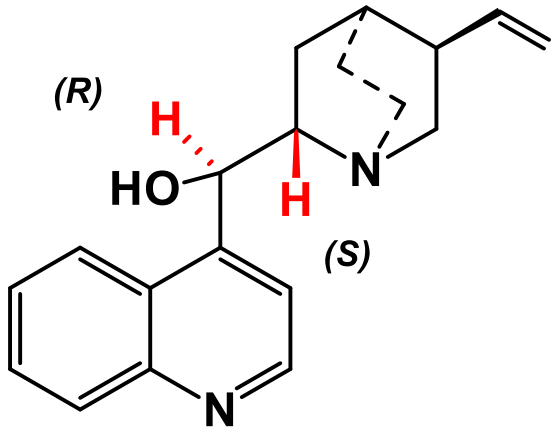
Quinoline alkaloids: Cinchona

Cinchona alkaloids consist of four important constituents:-

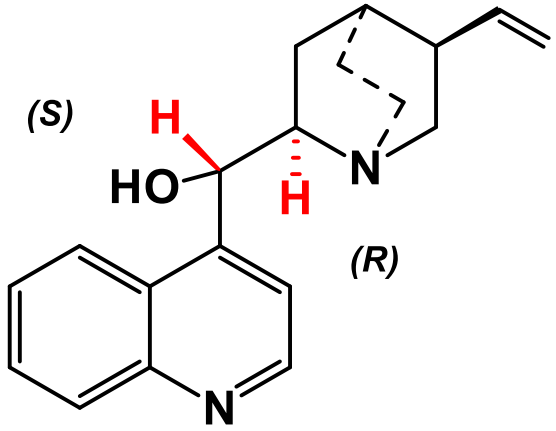
1. *Quinine*
2. *Quinidine*
3. *Cinchonine*
4. *Cinchonidine*



Quinine (RS) Quinidine(SR)



Cinchonidine

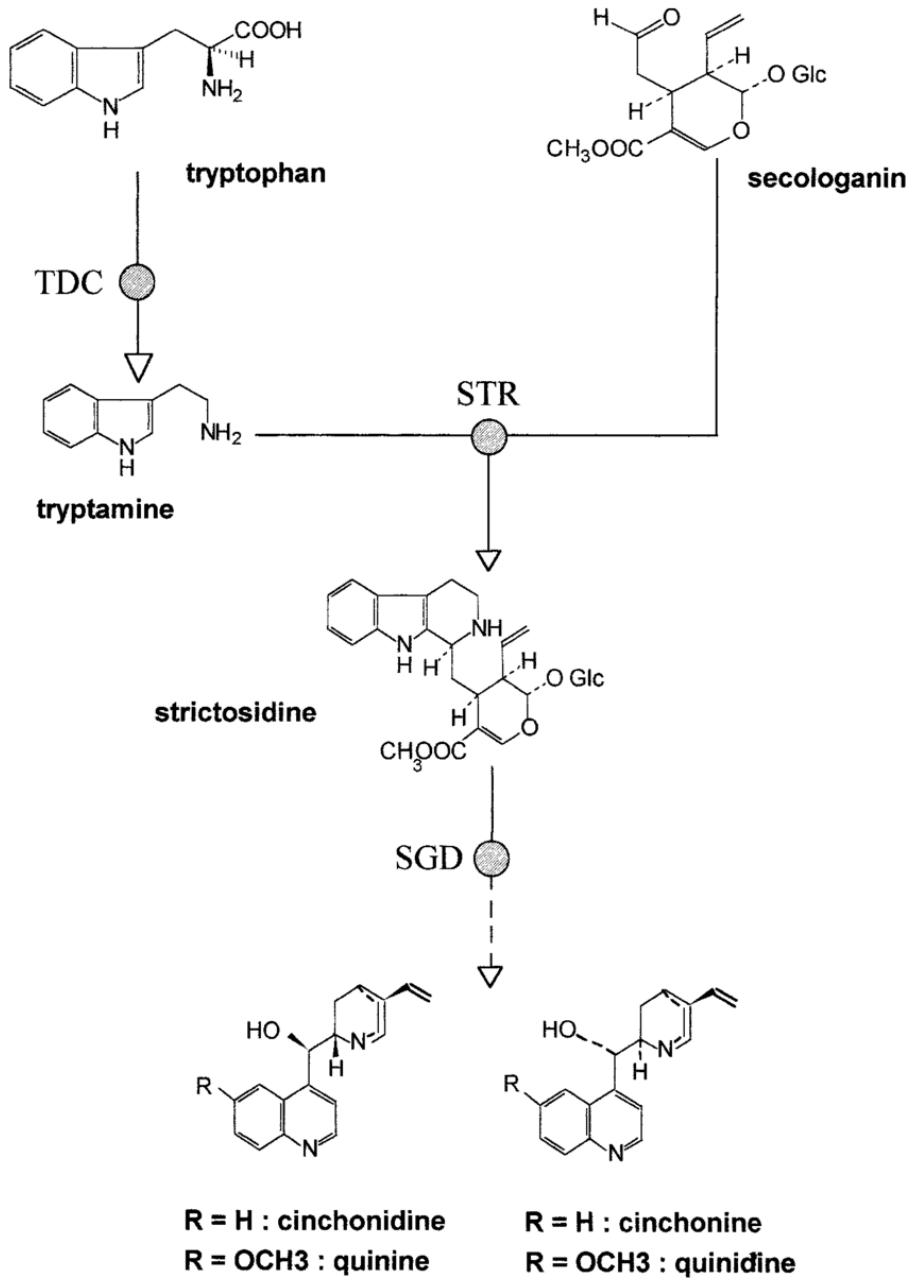


cinchonine

Quinine and Quinidine are diastereomers with opposite configurations at two stereogenic centers.

Quinoline alkaloids of Cinchona: Biosynthesis

Biosynthesis of quinoline alkaloids in Cinchona species. Dashed arrow indicates that the biosynthetic route(s) involved are not exactly known.
TDC: tryptophan decarboxylase,
STR: strictosidine synthase
SGD: strictosidine b-D-glucosidase)

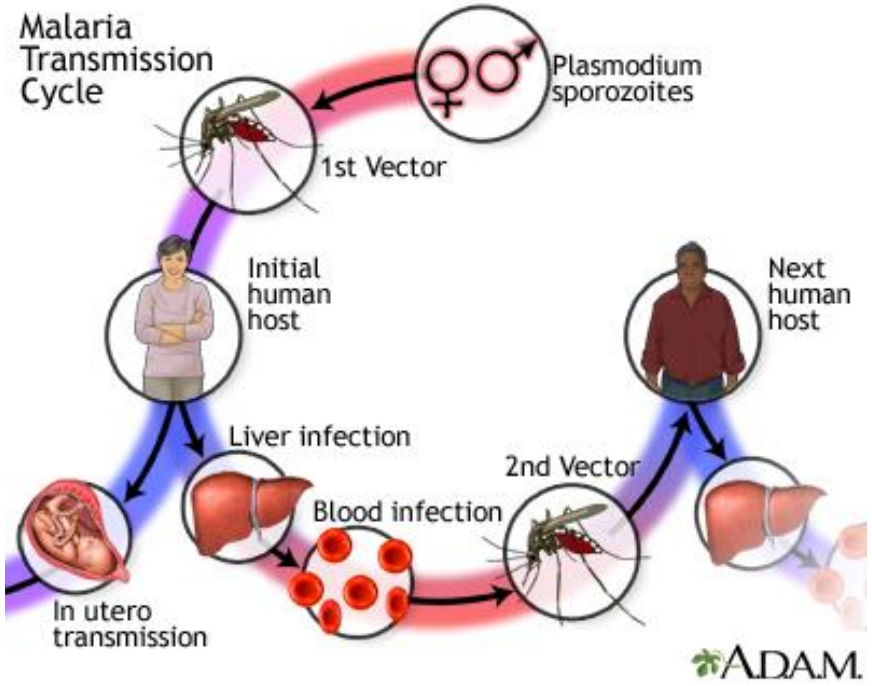


Quinoline alkaloids of Cinchona: Therapeutic uses

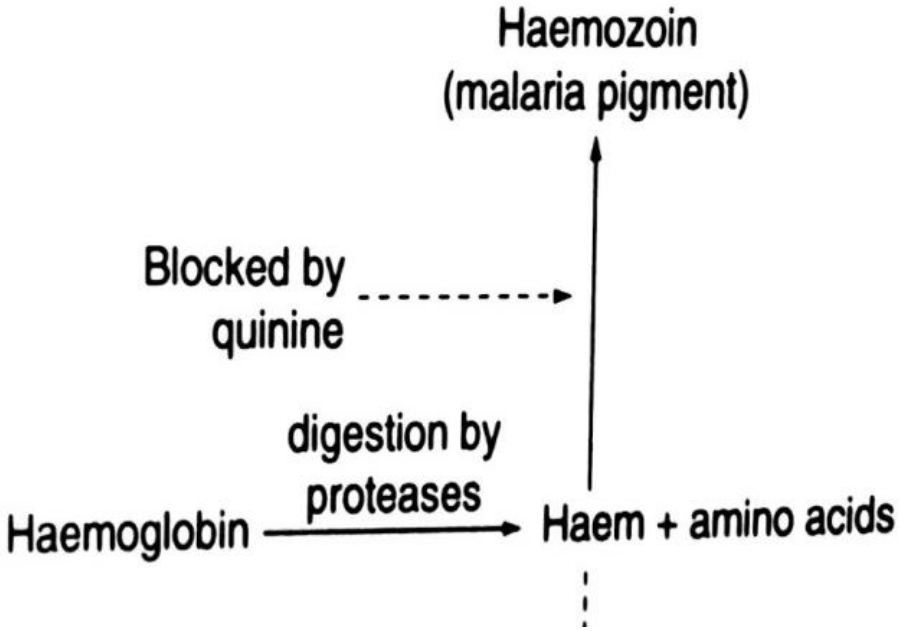
- Cinchona and its alkaloids, particularly **quinine**, have been used for many years in the treatment of malaria, a disease caused by protozoa, of which the most troublesome is *Plasmodium falciparum.*
- **Quinine** is a major active metabolite of Cinchona bark, used for many years as **antimalarial**.
- **Quinine** administered as free base or salts, continues to be used for treatment of **multidrug-resistant malaria**, it **is not** suitable for prophylaxis or prevention of Malaria. Toxicity of quinine is known as Cinchonism and symptoms are ringing of the ears (tinnitus), blurred vision, impaired hearing, confusion.

Mechanism of Action of Quinine

Malaria Transmission Cycle



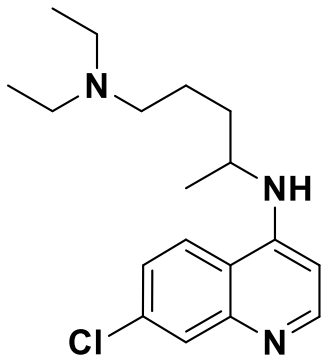
Mechanism of action of Quinine in treating Malaria



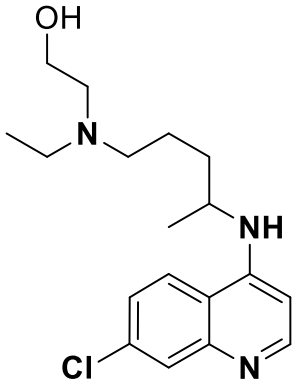
- The parasite detoxifies heme (toxic), by converting it to malaria pigment, **Haemozoin** (non-toxic).
- This process is blocked by the drug. Longer usage of this drug develops plasmodium species to be drug-resistant.

Synthetic Antimalarial drugs derived from cinchona alkaloids

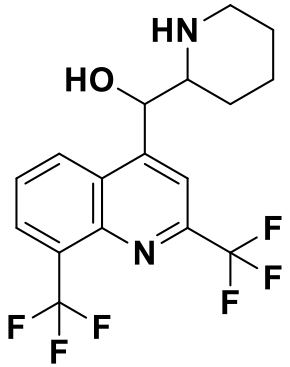
- **Mefloquine** is currently active against chloroquine-resistant strains, but, ten times as active as quinine, does produce gastrointestinal upsets and dizziness, and can trigger psychological problems such as depression, panic, or psychosis in some patients.
- **Chloroquine** and its derivative **hydroxychloroquine** although antimalarials, are also used to suppress the disease process in rheumatoid arthritis.



Chloroquine



Hydroxychloroquine



Mefloquine

Therapeutic uses of Quinidine

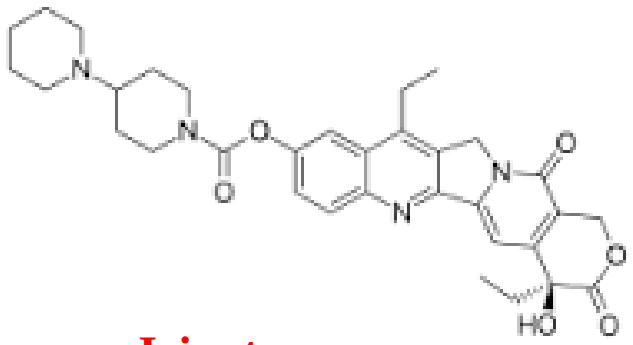
- For cardiac arrhythmia such as atrial fibrillation: it decreases myocardial excitability, and thus it has an interaction with digoxin {Quinidine may increase the blood level of digoxin, i.e. pharmacokinetic effect}.
- **Quinidine** is used to treat **cardiac arrythmias**.
- Quinidine-induced inhibition of P-gp in the intestine, as well as at sites of digoxin elimination such as the kidney is the basis of this interaction.

Camptothecin

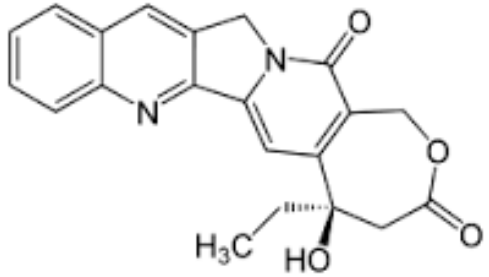
- It is obtained from the bark and the stems of the Chinese tree *Camptotheca acuminata* (Family: Nyssaceae).
- Seeds yield about 0.3% camptothecin, bark about 0.2%, and leaves up to 0.4%
- This alkaloid showed broad spectrum activity as **anticancer**.
- The natural 10-hydroxy camptothecin is more active and is used in China for neck and head cancer.
- The synthetic analogues are 9-aminocamptothecin.
- Particularly, water-soluble derivatives topotecan, irinotecan showed good for the treatment of ovarian cancer and colorectal cancer, while belotecan (camtobell ® available in USA) is available for small cell lung cancer and ovarian cancer.

Camptothecin Derivatives

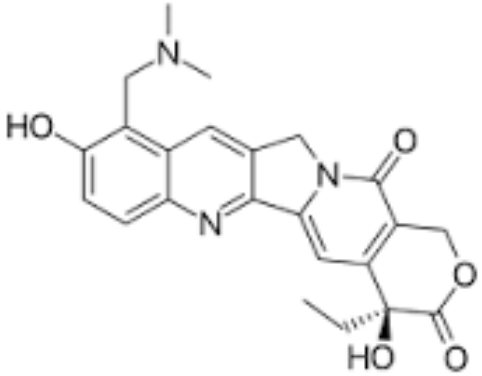
- **Irinotecan** inhibits the action of topoisomerase I (essential for the replication of DNA in the human cells) by binding to topoisomerase I-DNA complex, and causes double-strand DNA breakage and cell death.
- Side effect of Irinotecan: diarrhea, anemia, hair loss, abdominal cramps, vomiting and nausea (common almost to all chemotherapy).



Irinotecan



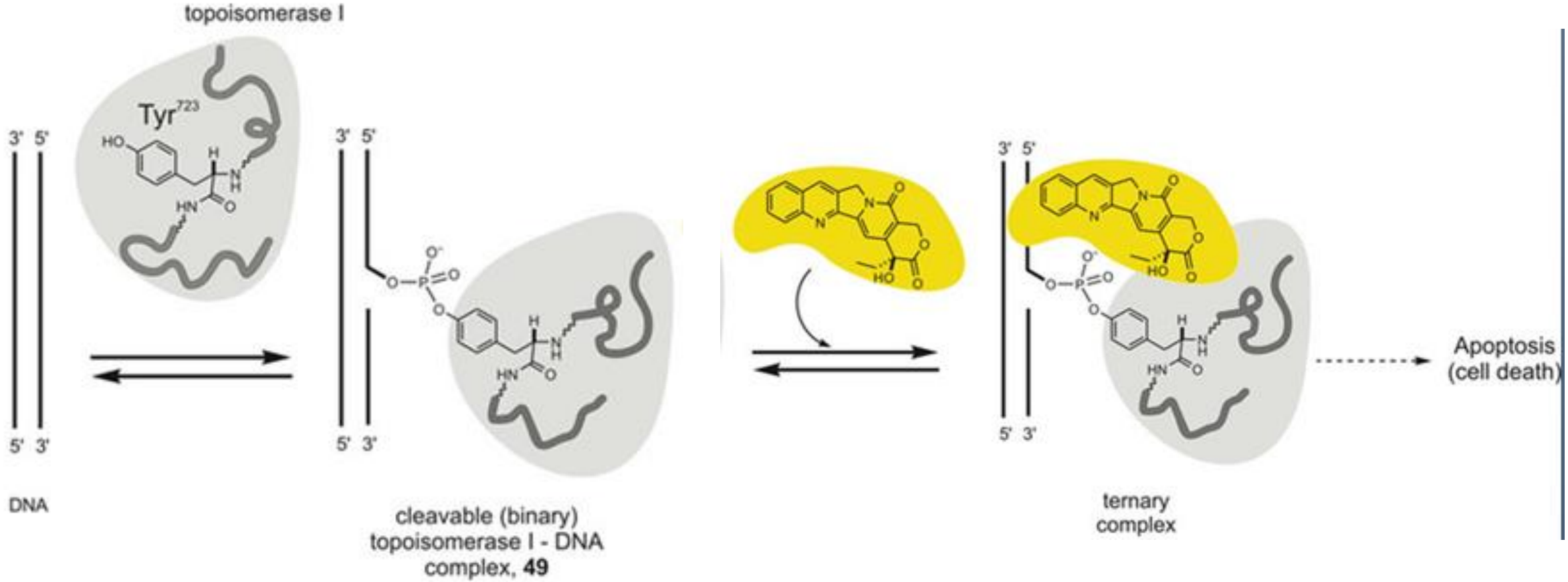
Campetothecine



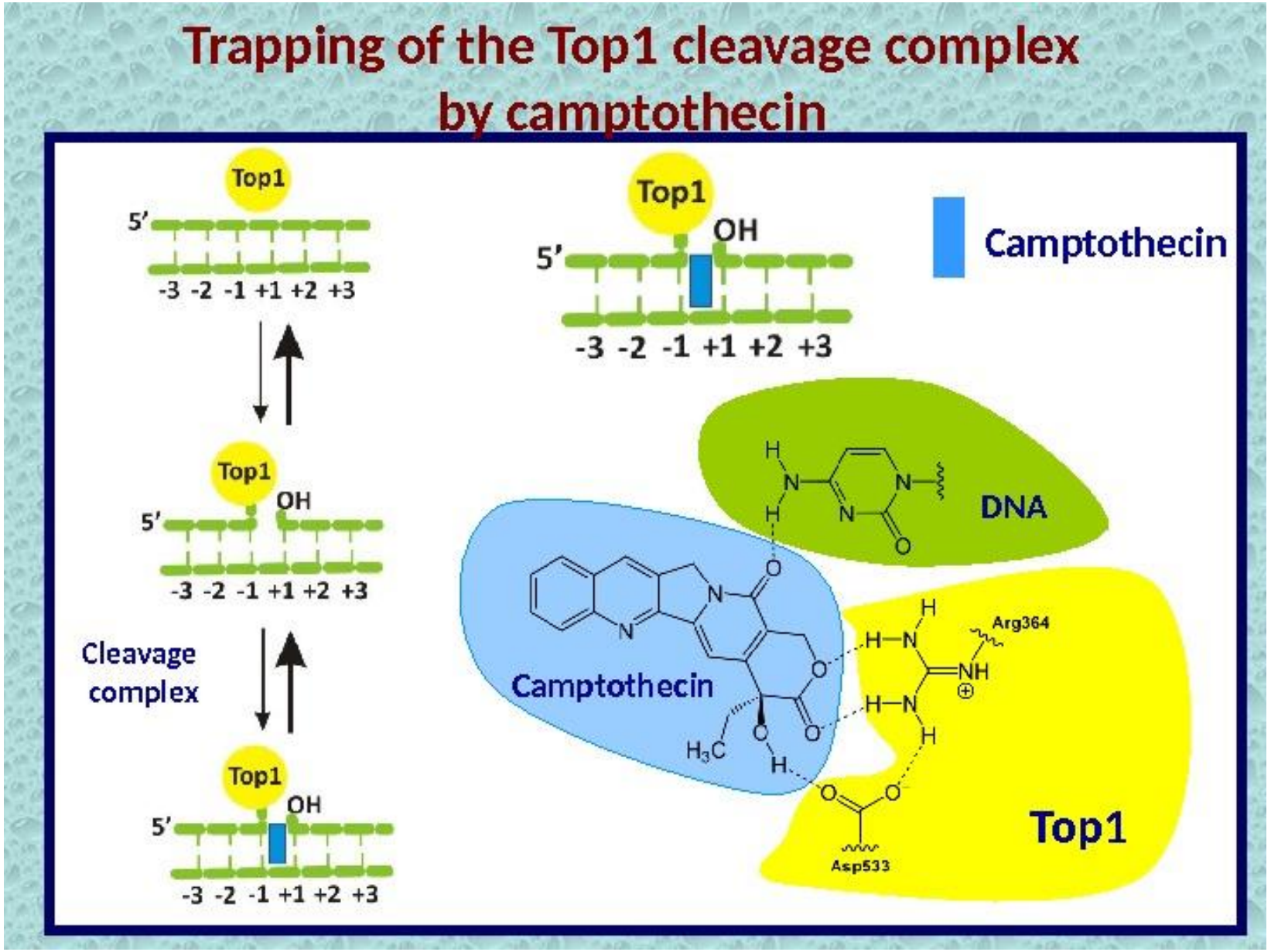
Topotecan

Mechanism of action of Irinotecan

Irinotecan prevents unwinding of the DNA strand by binding to topoisomerase I -DNA complex, and causes double-strand DNA breakage and cell death

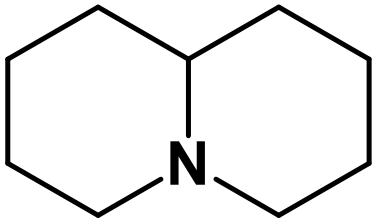


Mechanism of action of Irinotecan

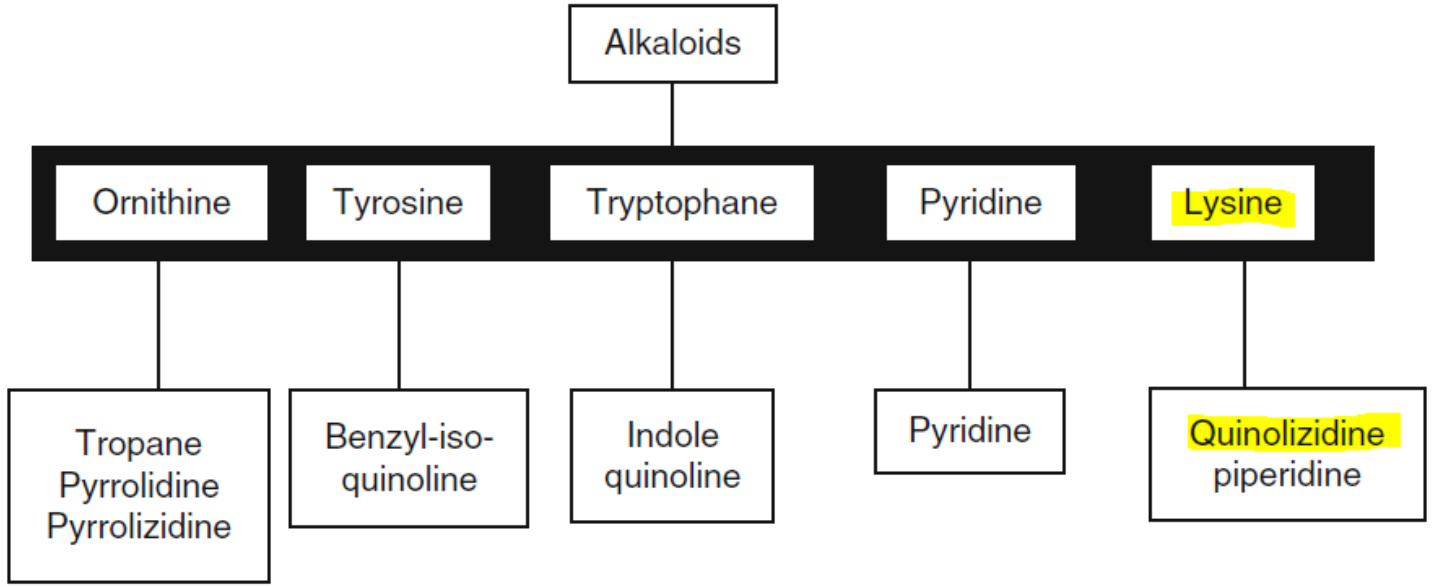


Quinolizidine alkaloids

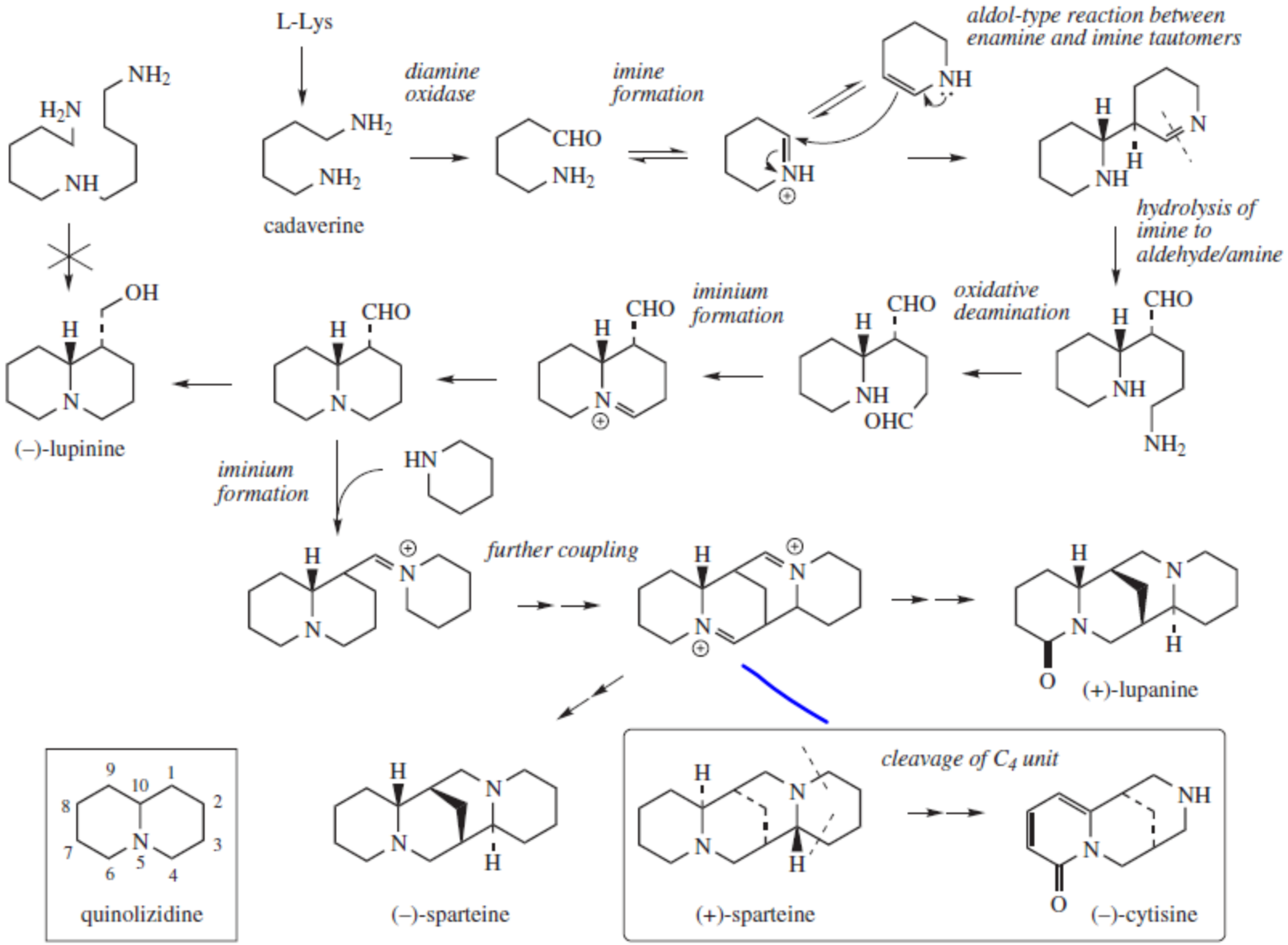
1. **Lupinine**
2. **Anagyrine**
3. **Sparteine**
4. **Cytisine**



Quinolizidine



Quinolizidine alkaloids: Biosynthesis



Quinolizidine alkaloids

- ✓Quinolizidine alkaloids are toxic and repel animals from feeding on the plants containing them, but there are certain strains with acceptable low alkaloid content and with a high protein content like Lupinus luteus (Fabaceae). الترمس الأصفر.
- ✓Quinolizidine alkaloids have:
  - Insecticidal activity (defense against insects pests)
  - Prevents herbivores predation
  - Allelopathic effect: inhibiting the growth of some agricultural weeds
- ❑Allelopathy is a biological phenomenon by which an organism produces one or more biochemicals that influence the germination, growth, survival, and reproduction of other organisms.
- ❑These biochemicals are known as allelochemicals and can have beneficial (positive allelopathy) or detrimental (negative allelopathy) effects on the target organisms and the community.

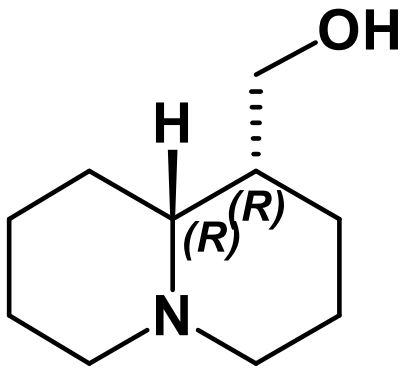
Quinolizidine alkaloids: Lupinine and Cytisine

1. **Lupinine** (Bicyclic lupin alkaloid):

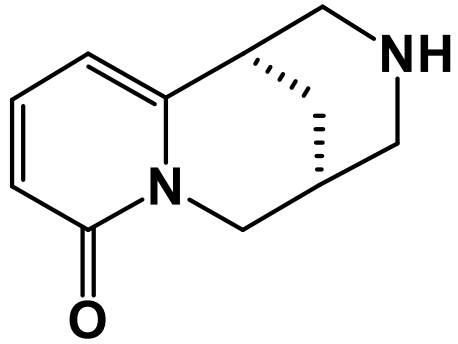
- ❖ It has been used medically to help with smoking cessation in Eastern Europe.
- ❖ Its molecular structure has some similarity to that of nicotine and it has similar pharmacological effects.

2. **Cytisine** (Tricyclic lupin alkaloid)

- ❖ Cytisine (**broom family, Fabaceae**) is a partial agonist of nicotinic acetylcholine receptors.



Lupinine



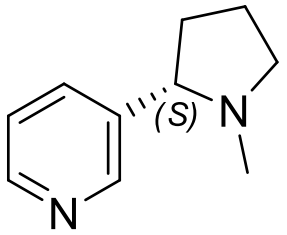
Cytisine

Quinolizidine alkaloids (QAs)

Generally QAs have the Blocking effect (partial agonist) on the **nACRs** and they are weak antagonists at the mACRs.

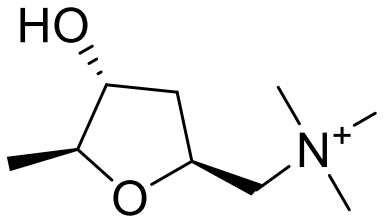
ACh Receptors (AChRs)

- Nicotinic Acetyl cholinergic (nAChR)
  - Ligand-gated Ion Channels
  - Identified by their subunit composition
    - e.g. $(\alpha_4)_3(\beta_2)_2$ (5 subunits)
  - Found in ganglia and neuromuscular junctions
    - And some other sites (such as the brain)
- Muscarinic Acetyl cholinergic (mAChR)
  - G-Protein Coupled Receptors (GPCRs)
  - Identified by their subtype (M_1 - M_5)
  - Parasympathetic, postganglionic
  - Also located in the CNS



nicotine

Muscarine is Isolated from *Amanita muscaria*

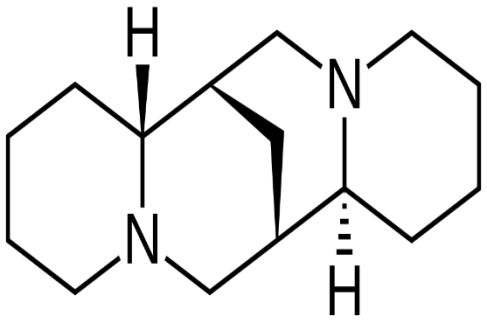


muscarine

Quinolizidine alkaloids: Sparteine

3. Sparteine (Tetracyclic lupin alkaloid):

- It has been obtained from *Cytisus scoparius* Scotsh broom (Family: Leguminosae).



Sparteine

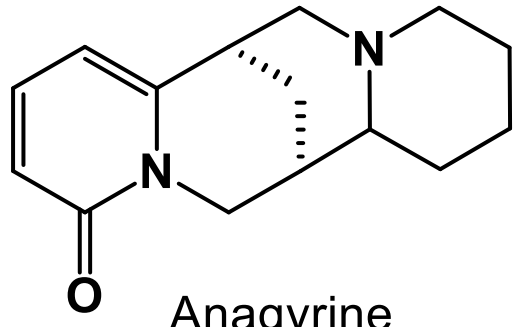
Therapeutic uses: Sparteine sulphate is used in Europe in the **treatment of cardiac insufficiency** .

It is also used as an **oxytocic,** and it acts by stimulation of uterus contraction.

Quinolizidine alkaloids: Anagyrine

4. Anagyrine : A Tetracyclic lupin alkaloid isolated from *Anagyris foetida.*

- Family: Fabaceae.
- It causes crooked (curved, bent) calf disease as it is teratogenic to cow fetus (causes paralysis of the fetus).



Anagyrine

(Teratogenic compound)

REFERENCES

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2. **Textbook of Pharmacognosy and Phytochemistry 2nd Edition, 2019, Authors: B. Shah, A. N. Kalia, Publisher: Elsevier, ISBN: 978-978-9386217738.**
3. **Medicinal Natural Products: A Biosynthetic Approach, 2nd Edition, 2002, Author: Paul M Dewick, Publisher: John Wiley and Sons Ltd, ISBN: 0471496405.**

Supplementary book:

Fundamentals of Pharmacognosy and Phytotherapy. A Guide for Health Care Professionals by Carol A. Newal, Linda A. Anderson and J. David Phillipson. (2010). the Pharmaceutical Press, London, UK; ISBN: 0 85369-474-5.