College of pharmacy /Al-Nahrain University

3rd stage/ 2nd coarse

Quinoline and Isoquinoline alkaloids

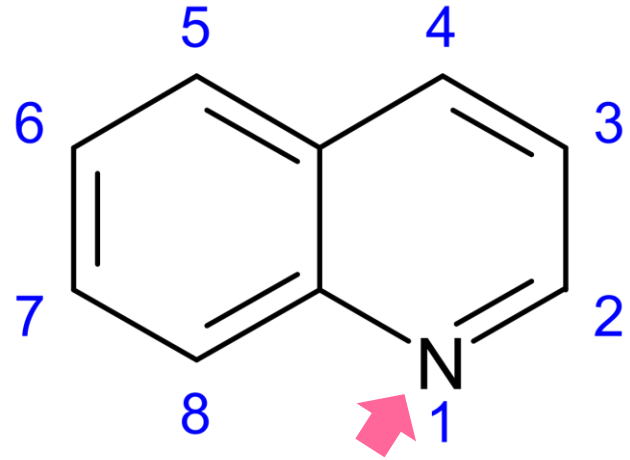
Pharmacognosy-Lecture 4

Lecturer Ayah Al-Qrimli/MSc pharmacognosy

Quinoline alkaloids

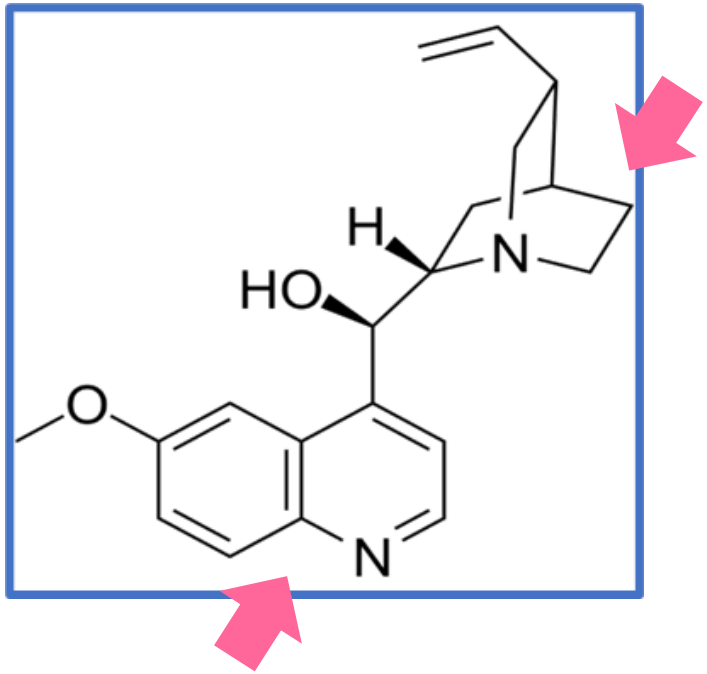


- Alkaloids containing the Quinoline basic nucleus (benzene + pyridine) include the alkaloids obtained exclusively from **Cinchona bark**, which is the bark of the stem and root of cinchona plant *cinchona succirubra* F: Rubiaceae.
- Quinoline alkaloids have potent pharmacological activities.
- The major alkaloids of Quinoline alkaloids :
- Quinine
- Quinidine
- Cinchonine
- Cinchonidine



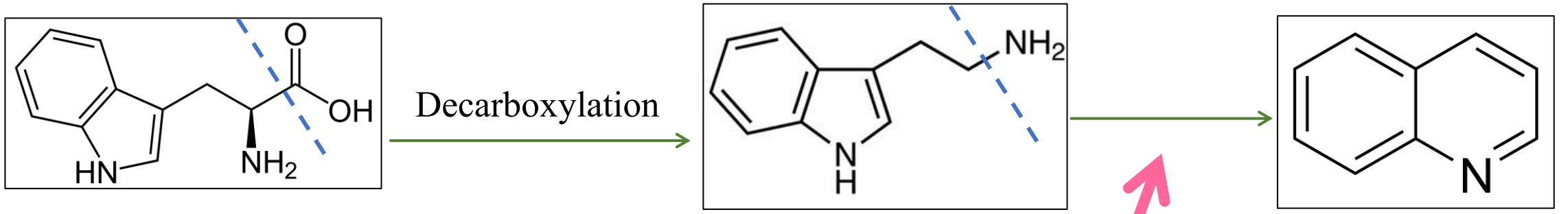
Quinoline alkaloids are True alkaloids

- Quinine alkaloid is composed of 2 heterocyclic systems:
- **Quinoline:** One part comes from an **amino acid**
- **Quinuclidine :** One part comes from a **terpenoid**
- They are joined through a **Schiff base–type condensation**



Quinoline alkaloids are True alkaloids

- Quinoline alkaloids are biosynthesized from aromatic amino acid **Tryptophan.**
- It undergoes **decarboxylation** and forms tryptamine (AMINE)



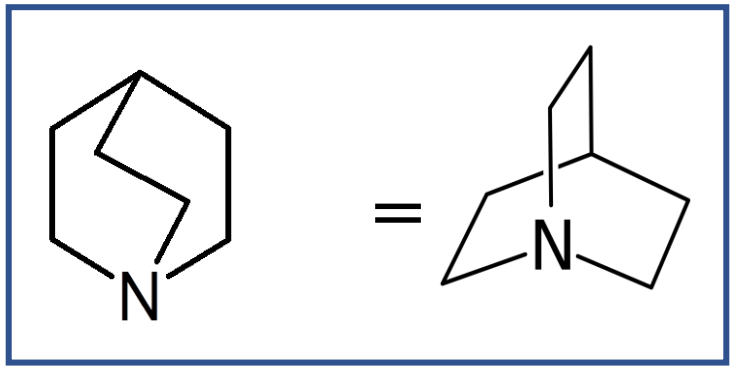
Tryptophan

Tryptamine
6 + 5 ring system

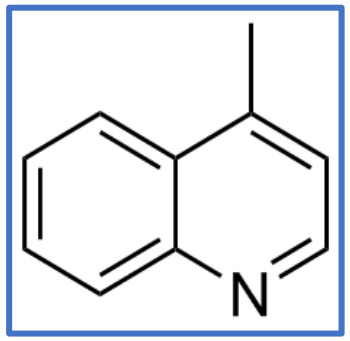
Quinoline
6 + 6 ring system

- **Amine gp. removal**
- **Ring opening and rearrangement**

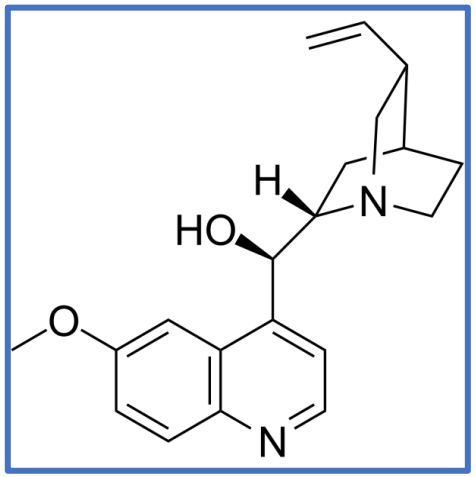
Biosynthesis



Quinuclidine



4- methyl Quinoline

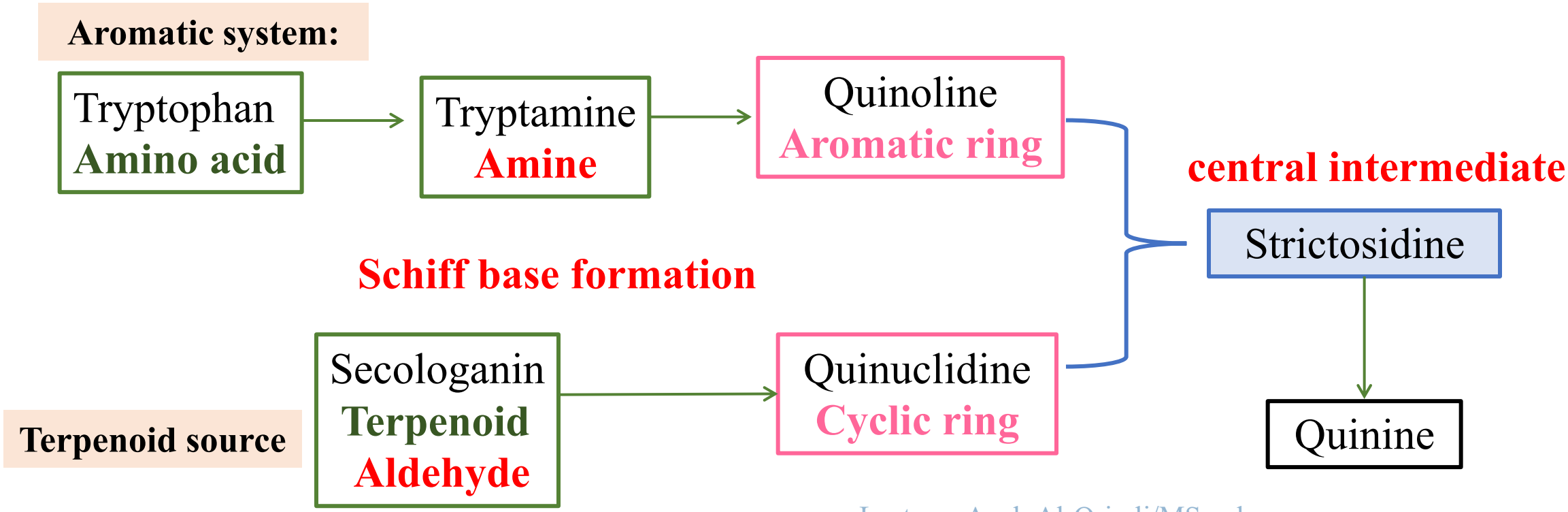


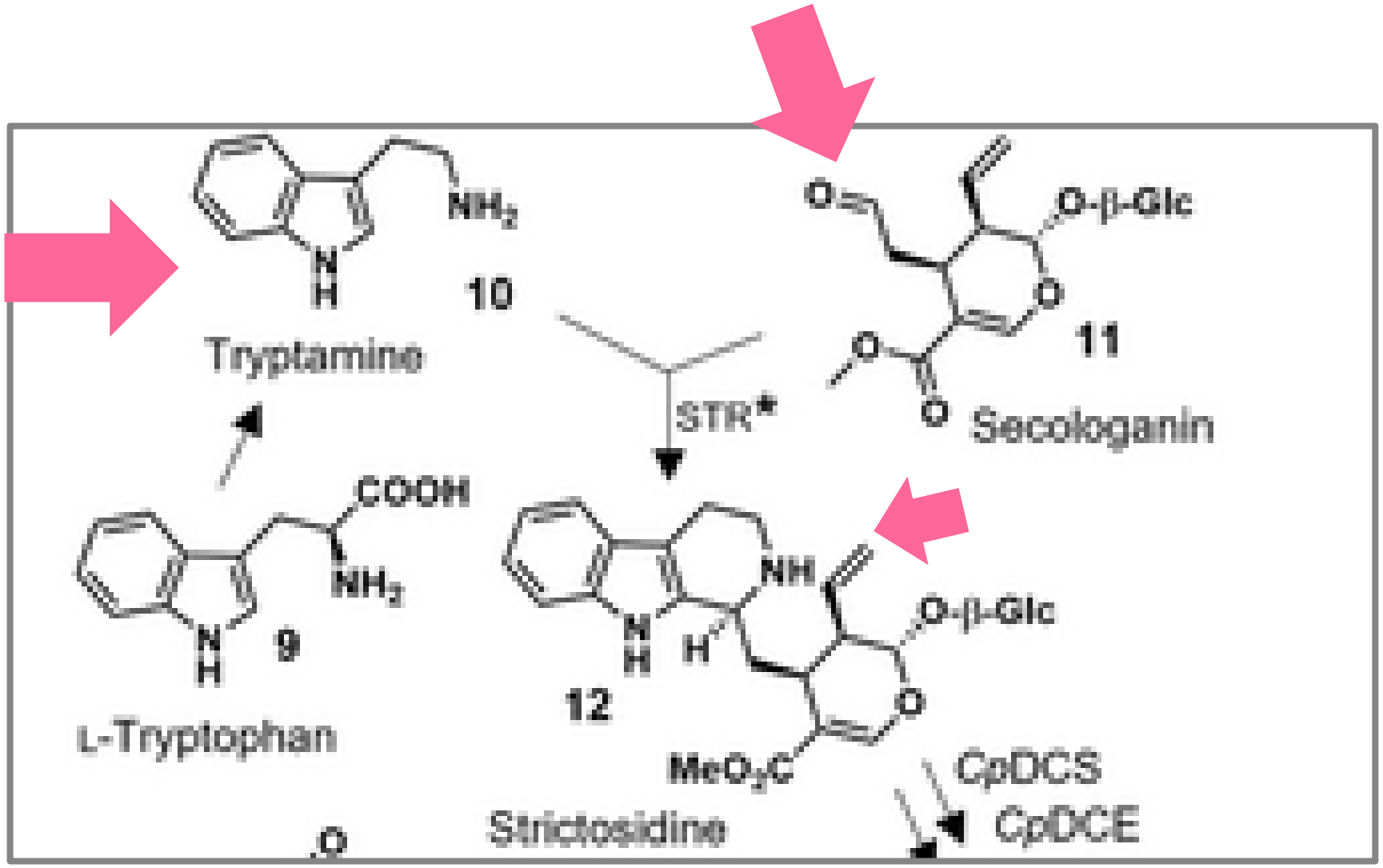
Quinin.

- In Quinoline alkaloids: the Quinoline basic ring system has **4- methyl group** attached to form the building block of Quinoline alkaloid's structure.
- **The quinoline ring** represents the **aromatic nitrogen-containing portion of quinine.**
- **Quinuclidine** is derived from a **terpenoid compound Secologanin** formed via the **mevalonate pathway**
- **Secologanin cyclizes to form quinuclidine, Quinuclidine = bicyclic aliphatic amine**
- The **4- methyl Quinoline** structure then binds to **a bicyclic ring Quinuclidine** to form Quinin.

Biosynthesis

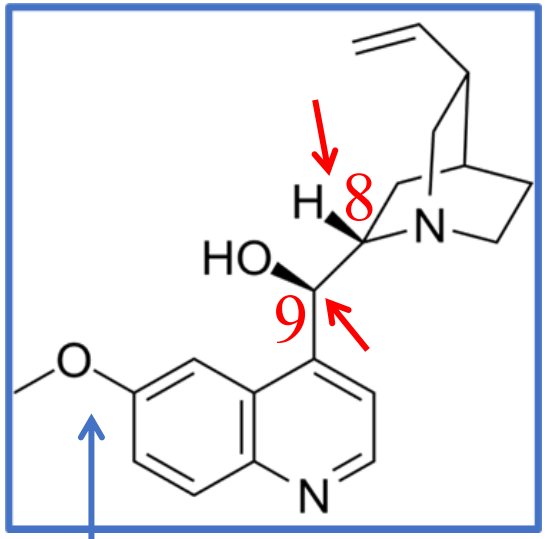
- Thus, Quinine forms by the condensation of 4-methyl Quinoline and Quinuclidine.
- **Strictosidine** is the universal intermediate linking **amino acid–derived alkaloids with terpenoid** units. **Strictosidine** contains the **Schiff base carbon–nitrogen linkage**
- Schiff bases in biosynthesis are **transient.**




NH2
10
Tryptamine
STR*
O-β-Glc
11
Secologanin
COOH
NH2
9
L-Tryptophan
NH
H
12
O-β-Glc
MeO2C
Strictosidine
CpDCS
CpDCE

Stereochemistry

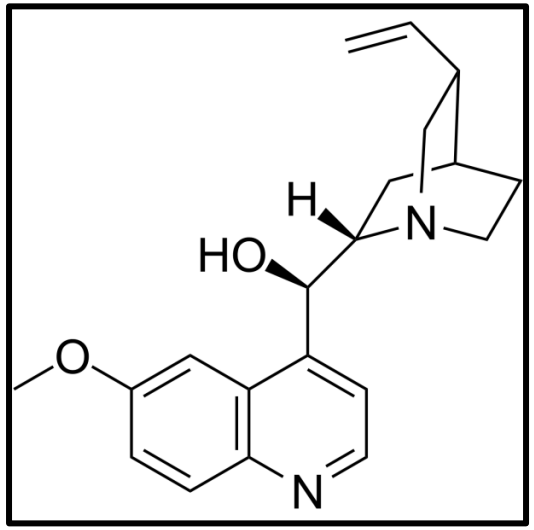
- In alkaloids like quinine, stereochemistry is important because biological systems are chiral (Receptors-Enzymes-Ion channels are all 3-dimensional and asymmetric)
- Quinine at position 8 and 9 has **TWO chiral centers** (Asymmetric centers) this results in **4 stereoisomers** **R and S**. (diastereomers)
- **Stereoisomers:** are molecules that have the **Same molecular formula** and **sequence of bonded atoms (constitution),** but that **differ only in the three-dimensional orientations of their atoms in space.**
- These stereoisomers give **two different compounds** which **show different pharmacological activities** (so, **configuration must be specified** by each drugs as it gives different effect).
- Same formula ≠ same drug effect
- The **R group substituted on the benzene ring** also produces two different compounds R : OCH3 / R : H



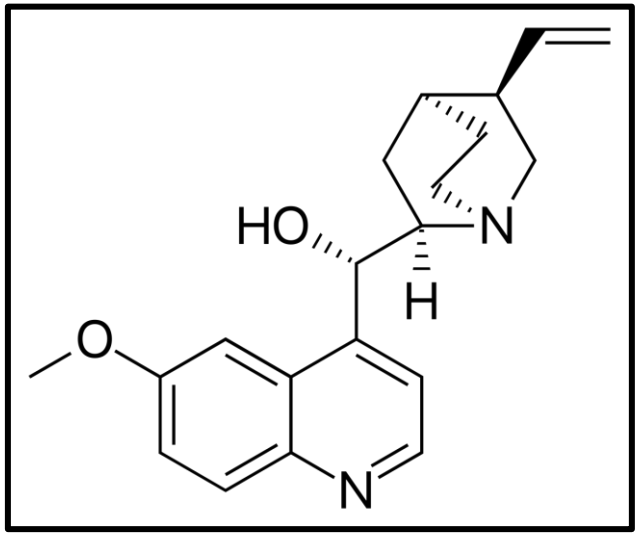
Stereoisomers :

Difference in optical rotation

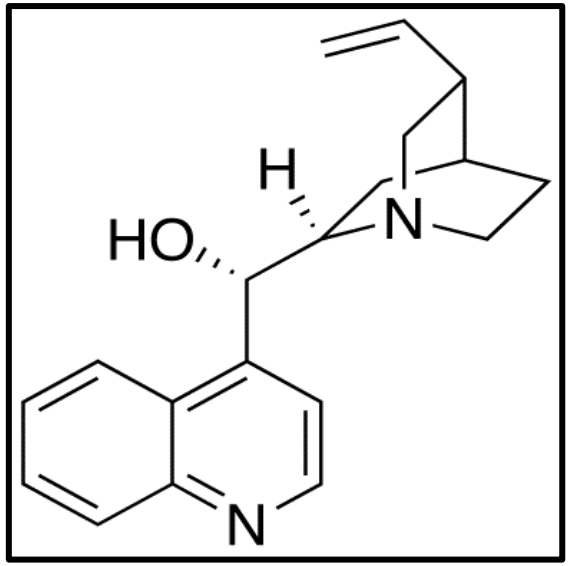
- **R: OCH3 :**
- **Quinine : Levorotatory 8S, 9R**
- **Quinidine: Dextrorotatory 8R, 9S**
- **R : H**
- **Cinchonine 8S, 9R**
- **Cinchonidine 8R, 9S**



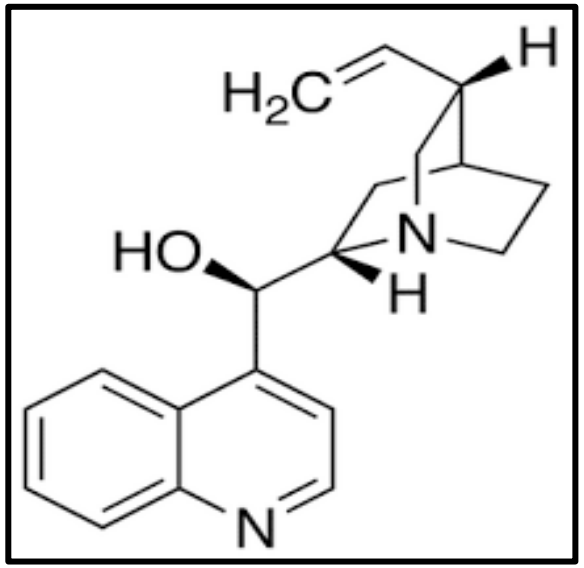
Quinine 8S, 9R



Quinidine 8R, 9S



Cinchonine 8S, 9R



Cinchonidine 8R, 9S

Stereoisomers :

-OCH_3 present → quinine / quinidine
-OCH_3 absent (H) → cinchonine -cinchonidine

- **OCH_3 group:** Is non-ionized **More lipophilic**
- **H atom:** Very small **Less lipophilic**
- **Result:**
- **Quinine / quinidine (OCH_3)**
- **cross membranes better,enhancing membrane penetration**
- **OCH_3-containing compounds have stronger and more specific receptor binding**
- **greater potency and longer duration**
- **Cinchonine / cinchonidine** are
- **less membrane-permeable**
- **H-substituted compounds bind more weakly or nonspecifically**

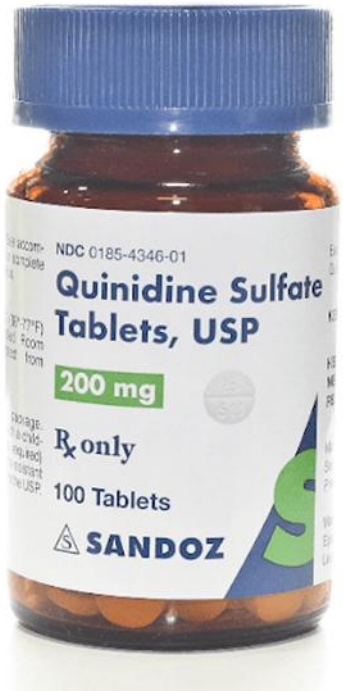
Pharmacological activity of Quinin

- Cinchona & its alkaloids have been used in the treatment of **malaria fever** for many years.
- **Quinine sulfate** continues to be used for malaria which is caused by the parasite **plasmodium** in many parts
- The mechanism is not well understood however the suggested mechanism is that : **Quinine intercalates between DNA bases resulting in the inhibition of DNA transcription and replication.**
- It has been used as an analgesic and in the treatment of cold.
- In covid-19, Quinin was used as an **antiviral** (binds to **Angiotensin Converting Enzyme -2 (ACE-2)** receptor to prevent binding between the Virus and ACE2 R thus, prevent viral Fusion to cells and reduce the virus capability to infect cells.)



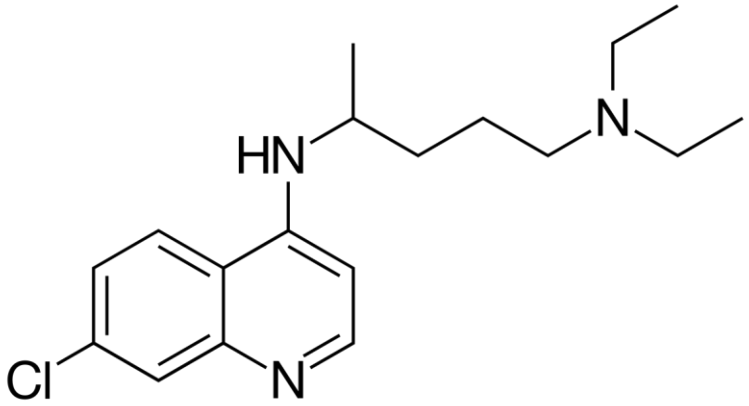
Pharmacological activity of Quinidine

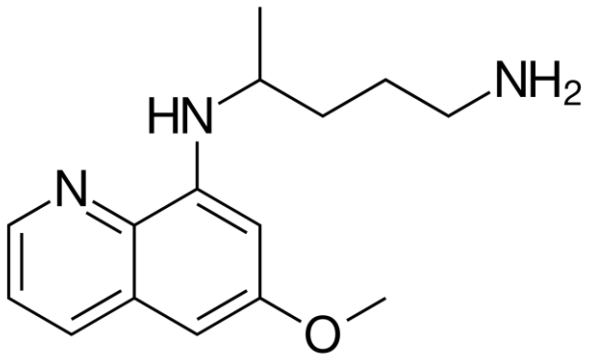
- Quinidine is an **antiarrhythmic agent** used in **treatment of arterial & ventricular tachycardia atrial fibrillation & ventricular contraction**.
- Quinidine is found as salts (sulfate & gluconate).
- It depresses myocardial excitability, conduction velocity & contractility by :
- Quinidine acts as a **Class IA antiarrhythmic** by **blocking fast sodium channels and potassium channels**, leading to **slowed conduction**, and **prolonged action potential duration** resulting in **decrease of myocardium excitability**.



Synthetic quinoline drugs

- Synthetic quinoline drugs were developed to **Retain antimalarial activity and Improve safety and availability**
- A range of synthetic antimalarial drugs was produced as an alternative to quinine due to the **resistance.**
- Of the wide range of compounds produced, **chloroquine, primaquine,** and **mefloquine** are important antimalarials.
- **Antimalarial activity** depends on the **quinoline nucleus**, not on the full quinine molecule. This ring is **responsible for interaction with the malaria parasite**









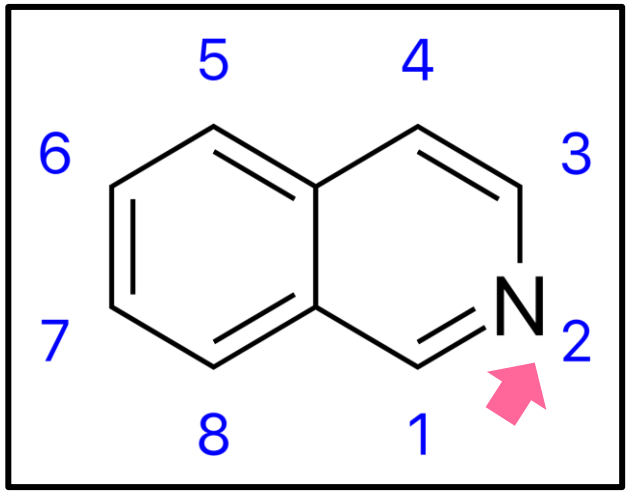
Cinchonism or quinism

- Treatment with cinchona products result in symptoms **of mild cinchonism which may occur from standard therapeutic doses of quinine** these include :
- Flushed and sweaty skin,
- Ringing of the ears (tinnitus),
- Blurred vision, impaired hearing,
- Confusion and headache.
- **Reversible** high-frequency hearing loss,,
- Abdominal pain, nausea, vomiting and diarrhea.
- Ringing in the ears is a symptom of toxicity.
- When these symptoms are produced as the result of continuous use of cinchona or of quinine the condition has been called cinchonism.



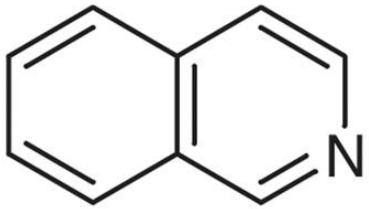
Isoquinoline Alkaloids

- Isoquinoline is a heterocyclic aromatic organic compound.
- It is the **structural isomer** of Quinoline (**having the same chemical formula but different constitution**)
- Isoquinoline and Quinoline are **benzo-pyridines**, which are composed of a benzene ring fused to a pyridine ring.
- Many drugs are Isoquinoline alkaloids including Morphine, Tubocurarine, papaverine and codeine.

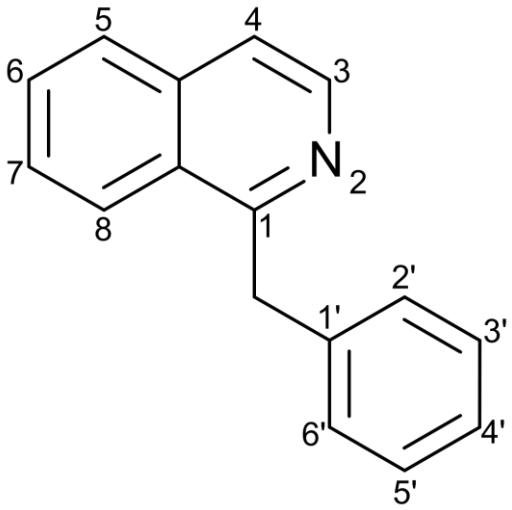


Isoquinoline Alkaloids

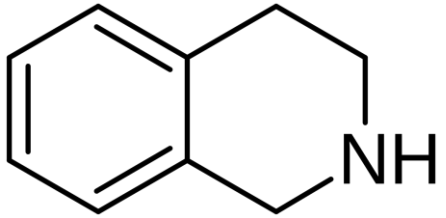
The Isoquinoline structure can be present in plants with some modifications.



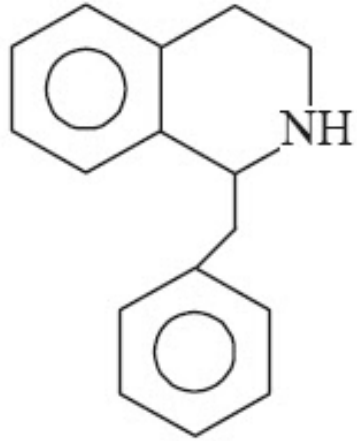
Isoquinoline



Benzyl-Isoquinoline



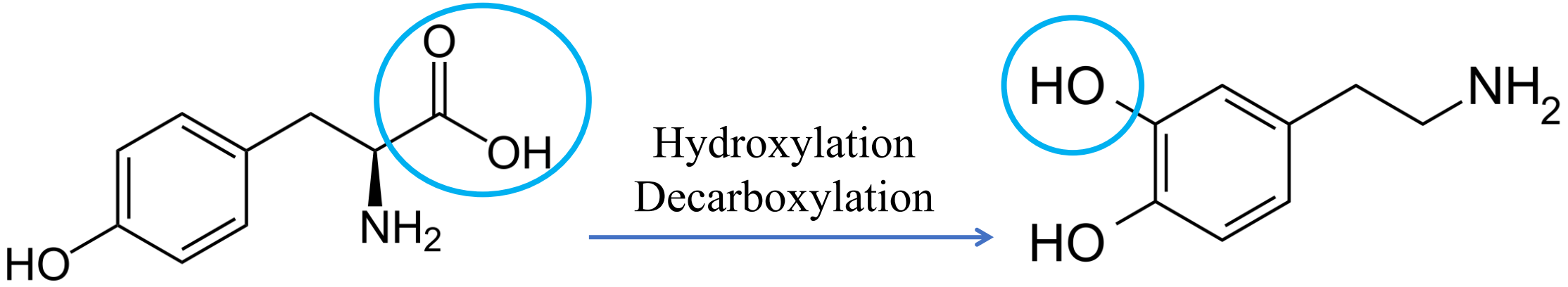
Tetrahydro-isoquinoline



Benzyl-Tetrahydro-Isoquinoline

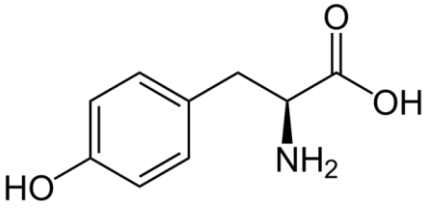
Isoquinoline alkaloids are True alkaloid

- Generally, In plants isoquinoline alkaloids are biosynthesized from the amino acid **Tyrosine** and some from **Phenylalanine .**
- Tyrosine undergoes **hydroxylation** and **decarboxylation** to form **Dopamine** which is a key compound in the biosynthesis of Isoquinoline alkaloids in plants.
- In plants, dopamine is used for alkaloid biosynthesis (unlike in humans, where it acts as a neurotransmitter). Dopamine acts as the **nitrogen-containing building block** for isoquinoline alkaloids in plants.



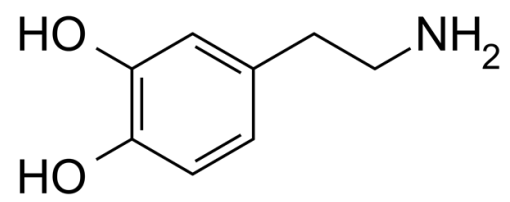
Tyrosine **Dopamine**

Isoquinoline forms in plant alkaloids

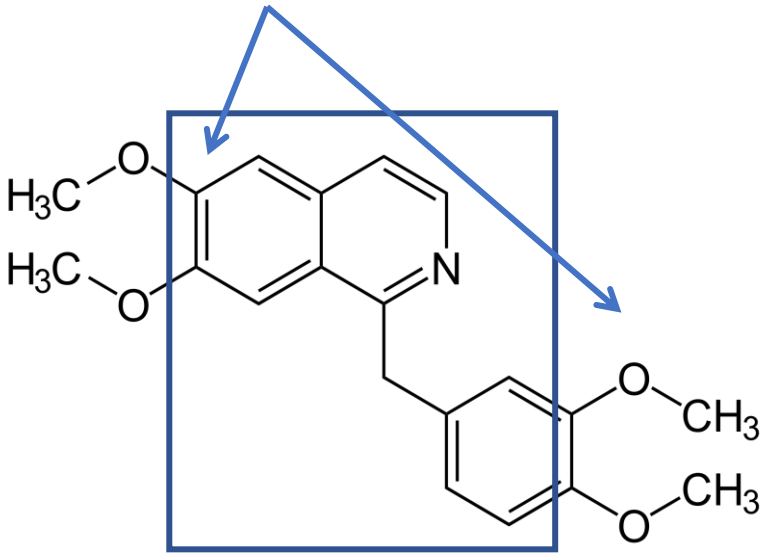


Tyrosine

- **Benzyl isoquinoline (BIQ): Papaverine**
- Alkaloid from the opium family which contains morphine alkaloids, though it is from the same plant, but it has **different structural features and physiological activity** being a **smooth muscle relaxant , vasodilator and bronchodilator** rather than an analgesic.
- Despite originating from the same plant, papaverine lacks the morphinan (phenanthrene) structure required for analgesic activity.
- **Two dopamine**-derived units condense to form a benzyl-isoquinoline skeleton **through Schiff base and Mannich-type reactions**.
- **Amine** from dopamine-**Aldehyde** from oxidized dopamine-derived unit, These two react to form **a Schiff base (C=N)**
- **Mannich-type cyclization** of dopamine-derived intermediates produces the isoquinoline ring system.

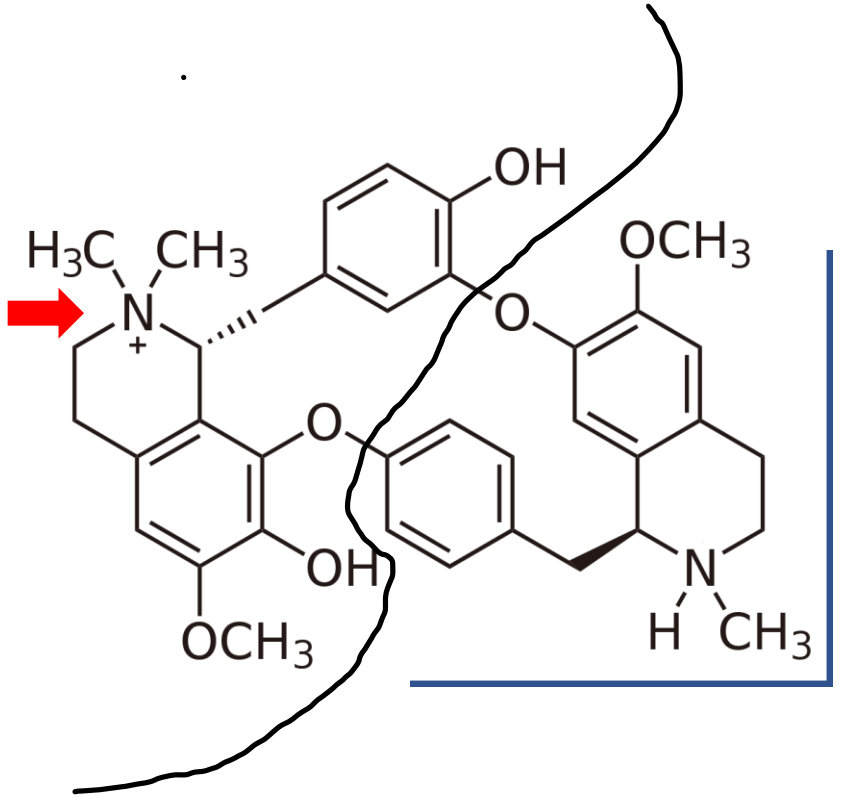


2 dopamine moieties



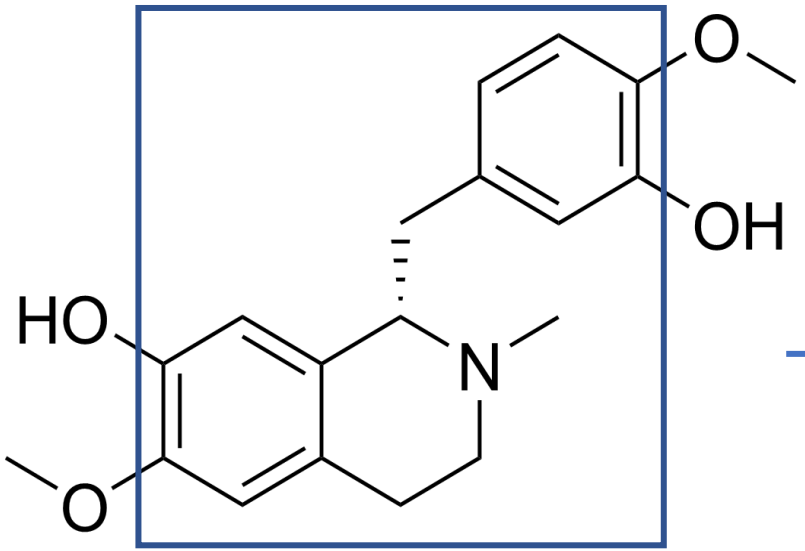
Bis- benzyl- tetrahydro-isoquinoline

- **Bis-benzyl-tetrahydro-isoquinoline: Tubocurarine**
- Bis: means **two benzyl- tetrahydro- isoquinoline** linked by an **ether linkage.**
- Tubocurarine is considered as a **quaternary alkaloid** ,thus **it can't cross the BBB producing only peripheral action.**
- Tubocurarine is a non- depolarizing neuromuscular blocker on nicotinic receptor (antagonist) causing **skeletal muscle relaxation.**
- The bis-benzyl structure gives tubocurarine **a rigid shape** that **blocks neuromuscular transmission without CNS penetration.**



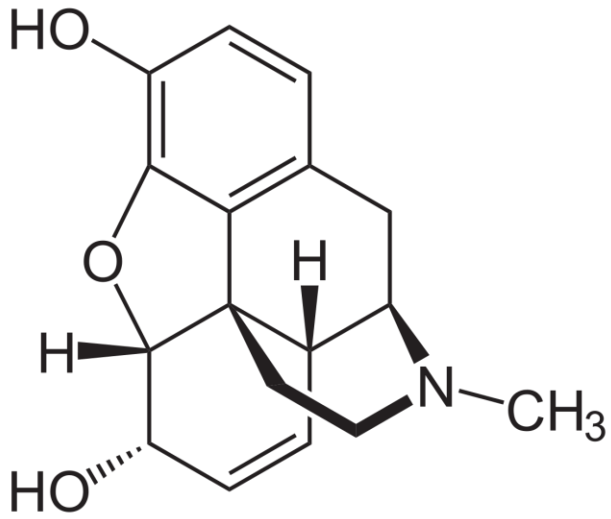
Benzyl tetra-hydro-isoquinoline (THBIQ)

- **Benzyl tetra-hydro-isoquinoline (THBIQ): R-reticulin (key biosynthetic intermediate for opium alkaloids).**
- Which gets modified and gives rise to the **opium alkaloid structure (morphine like structure) : phenanthrene basic structure.**



R-reticulin

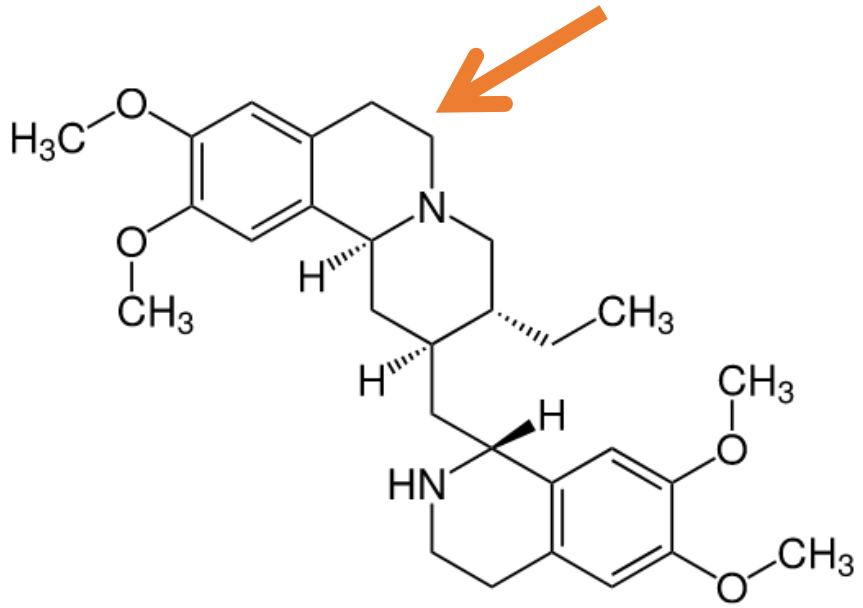
Ring closure

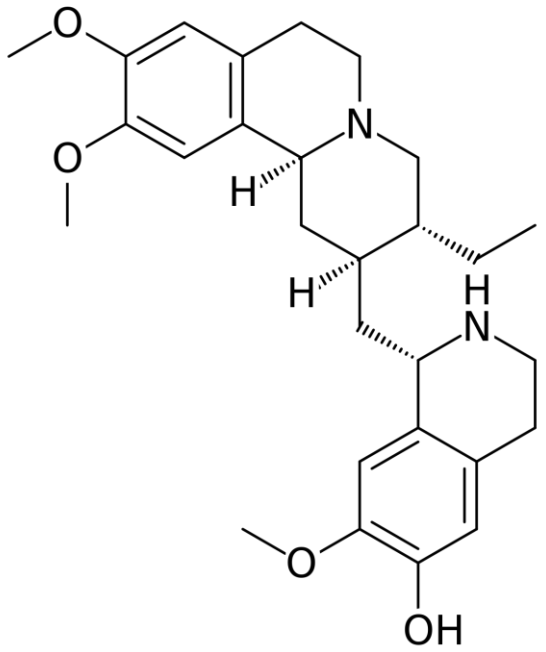


Morphine

Terpenoid -Tetrahydro -Isoquinoline

- **Phenyl alanine** amino acid (**dopamine like precursor**) and the **terpenoid structure secologanin** are involved in the biosynthesis of these alkaloids : **Emetine and Cephalin.**







The END

THANK YOU