Pharmacognosy and Phytochemistry

Alkaloids-Part 7

B. Pharm. Semester-1

Course Code: 0510221; Session: 2022-2023

Dr. BALAKUMAR CHANDRASEKARAN

Professor-Faculty of Pharmacy

Philadelphia University-Jordan

Learning Outcomes

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

Indole group of alkaloids.

Objective

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

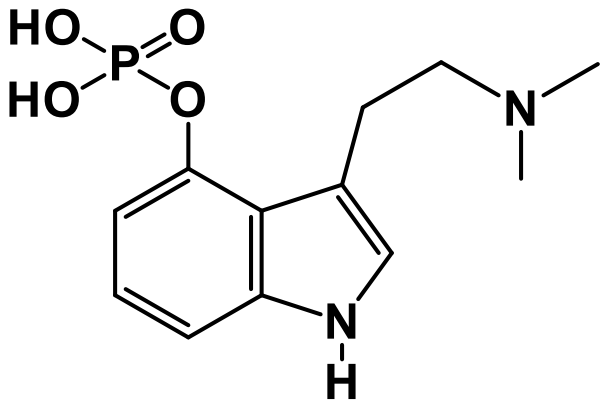
Indole group of alkaloids

1. **Simple tryptamines (psilocin and psilocybin)**
2. **Physostigma alkaloids (Physostigmine)**
3. **β-carbolines type of alkaloids**
   A. **Harmine and Harmaline**
   B. **Rauwolfia alkaloids (Reserpine and Rescinnamine)**
   C. **Ajmalicin**
4. **Ergot alkaloids (Ergometrine and Ergotamine)**
5. **Vinca alkaloids (Vincristine and Vinblastine)**
6. **Nux vomica alkaloids (Strychnine and brucine)**

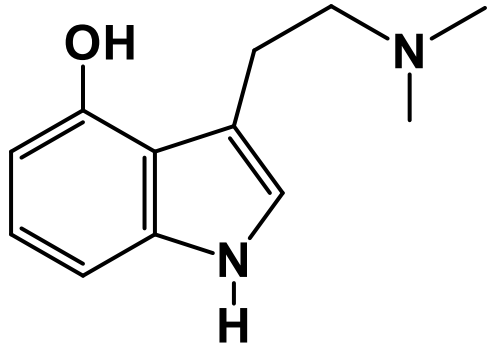
Alkaloids derived from tryptophan

Psilocybe mexicana

PSILOCYBIN



PSILOCIN

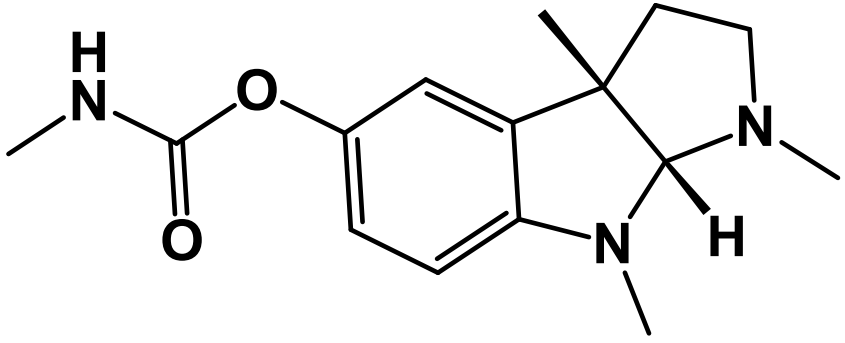


- **Ingestion of *Psilocybe*** mushrooms causes **visual hallucination**
- Psilocybin (6-20 mg) is required to produce hallucinations.
- Psilocin is about 10 times more active then psilocybin.
- Mushrooms have only traces of psilocin, but after ingestion psilocybin
- quickly metabolizes *in vivo* to highly active psilocin.

Physostigma alkaloids (Physostigmine)

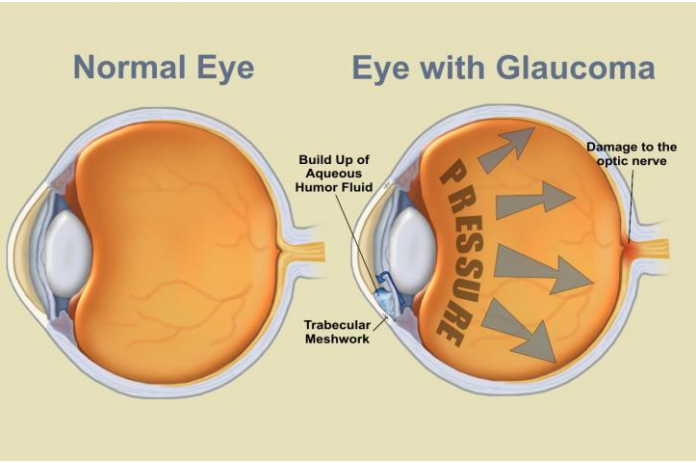
- Physostigmine is a major alkaloid found in the seeds of the *fabaceous* plant *Physostigma venenosum*.
- It is a powerful and **reversible acetylcholine esterase inhibitor** which effectively **increases the concentration of acetylcholine** at the sites of cholinergic transmission (parasympathomimetic).
- Common name: Calabar been.

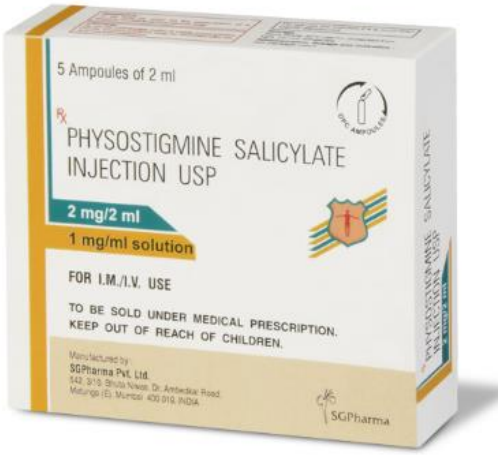
Physostigmine



Medicinal Uses of Physostigmine

- ❖Physostigmine is used in combination with pilocarpine for the treatment of acute open-angle glaucoma
- ❖ It increases the contraction of ciliary muscles
- ❖ It increases excretion of aqueous humor
- ❖Thus, it decreases intraocular pressure (IOP).
- ❖ It is given I.V or I.M route
- ❖ It is unstable compound as it is an ester and amide.
- ❖ It is also used as an Antidote against *Datura stramonium* poisoning.



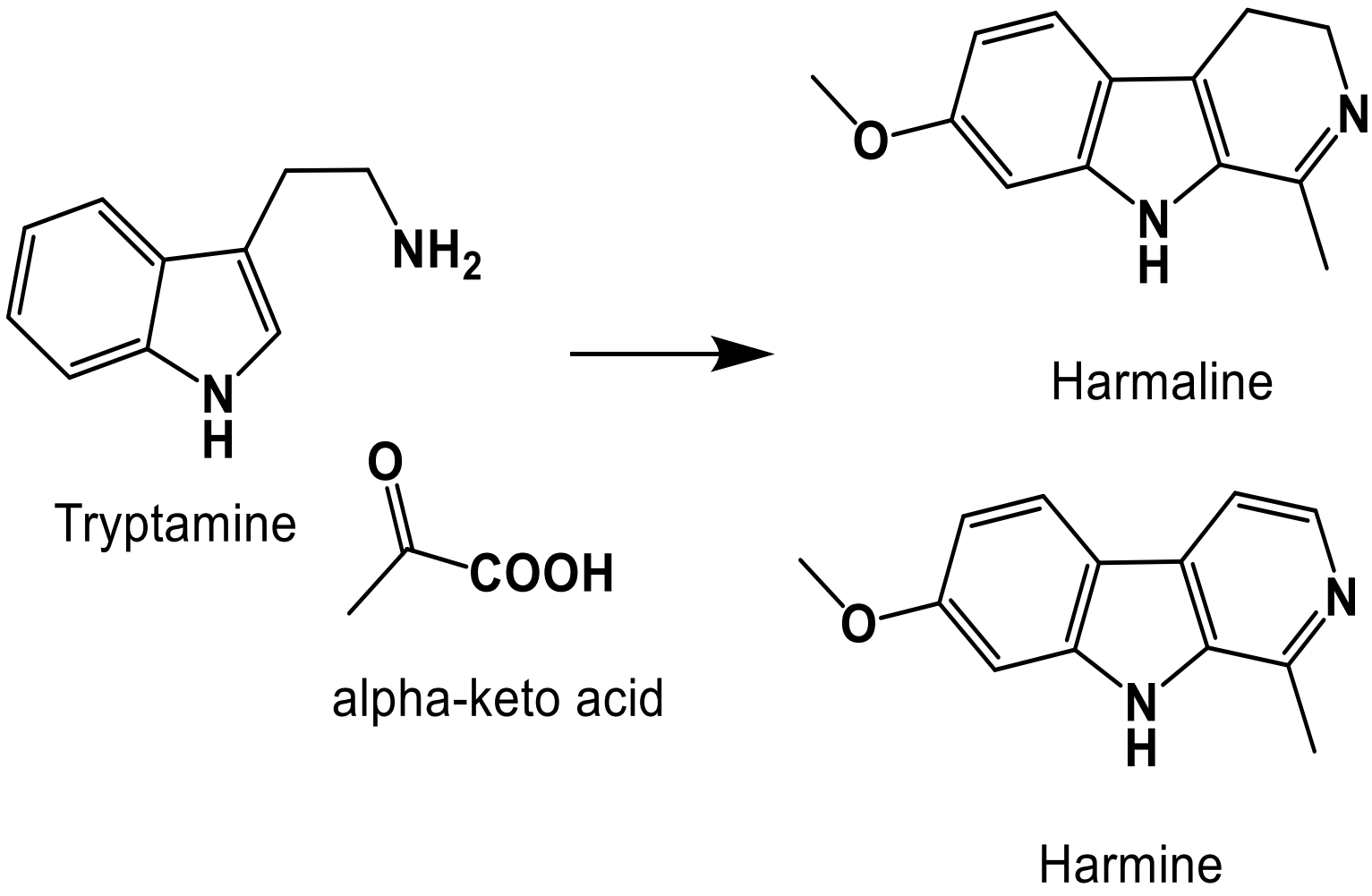


β-carbolines type of alkaloids

Harmine and **Harmaline** are the major alkaloids found in the plant *Peganum harmala* (Syrian rue).

Harmaline is used as a **sedative** and to treat **Mental depression**.

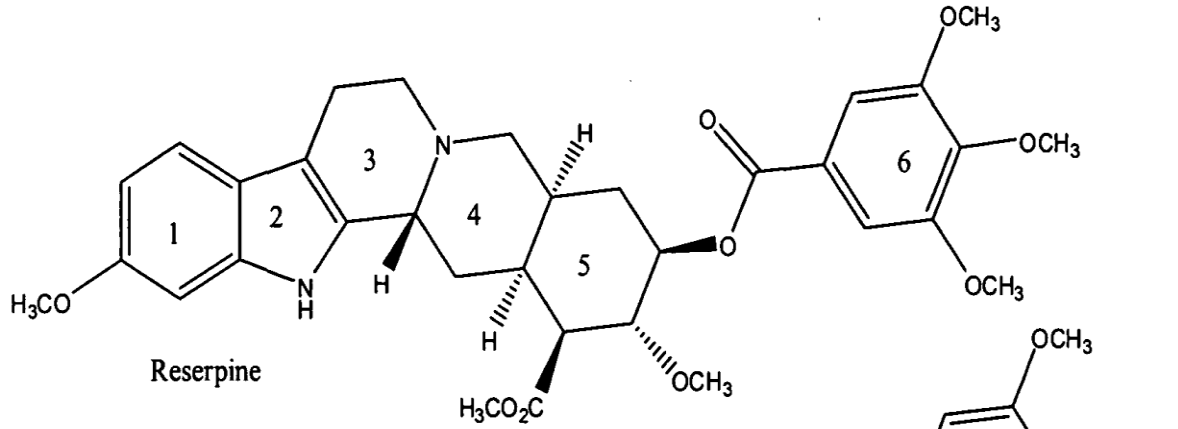
Mechanism of action: Harmaline inhibits **MAO-A** (Mono-amine oxidase type A), which leads to an increased availability of neurotransmitters like norepinephrine, serotonin.



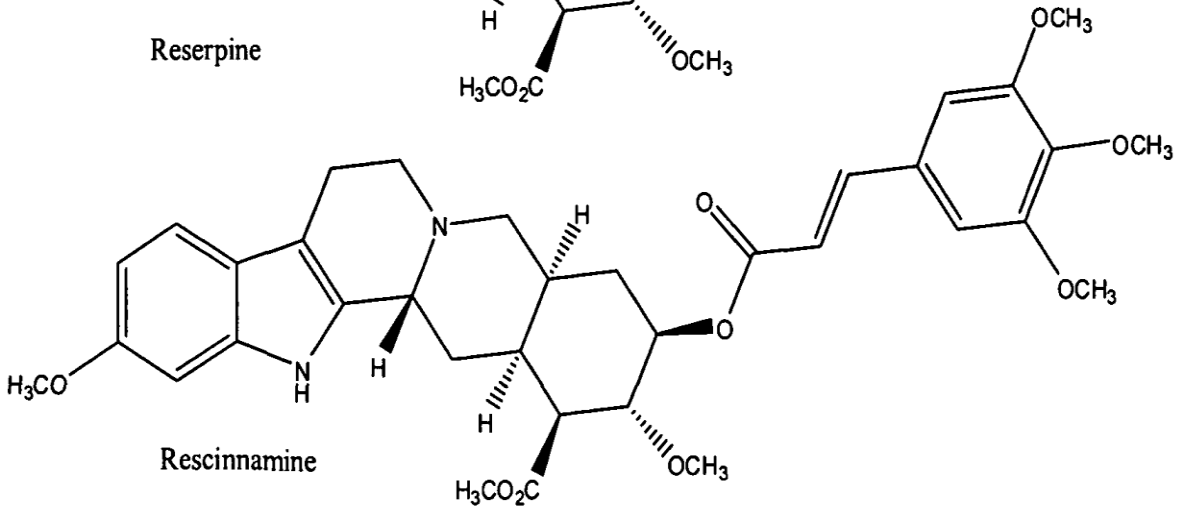
Rauwolfia alkaloids (Reserpine and Rescinnamine)

- Botanical source: Roots of *Rauwolfia serpentina* (Family: Apocyneceae) contains the alkaloids: Reserpine and Rescinnamine.
- Reserpine is a **antihypertensive** drug and also having tranquilizing effect.
- High doses of Reserpine causes mental fatigue and depression.

Snake root



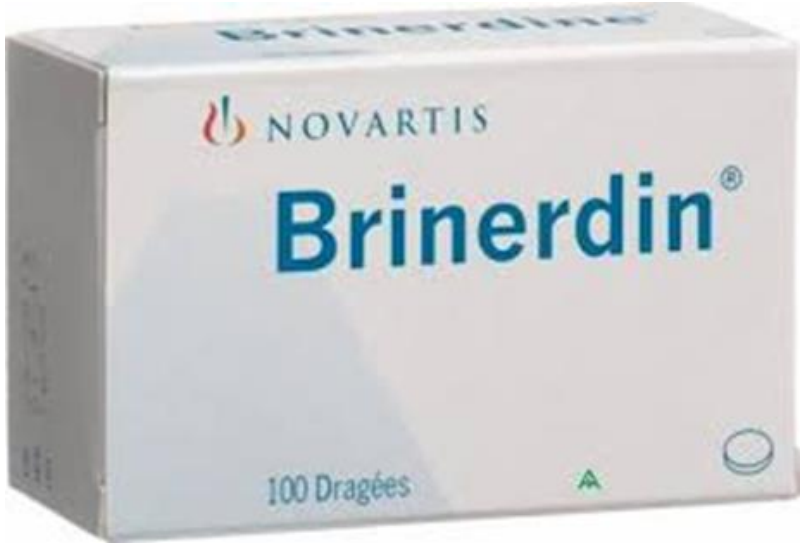
Reserpine



Rescinnamine

Mechanism of Action of Reserpine

- ❖Reserpine and Rescinnamine are anti-hypertensives by inhibiting the enzyme called angiotensin-converting enzyme (ACE).
- ❖ They decrease catecholamines peripherally (decrease in epinephrine and norepinephrine), depletion of central neurotransmitter (mainly serotonin and norepinepherine).
- ❖ Reserpine is an unstable compound due to the presence of an ester linkage.



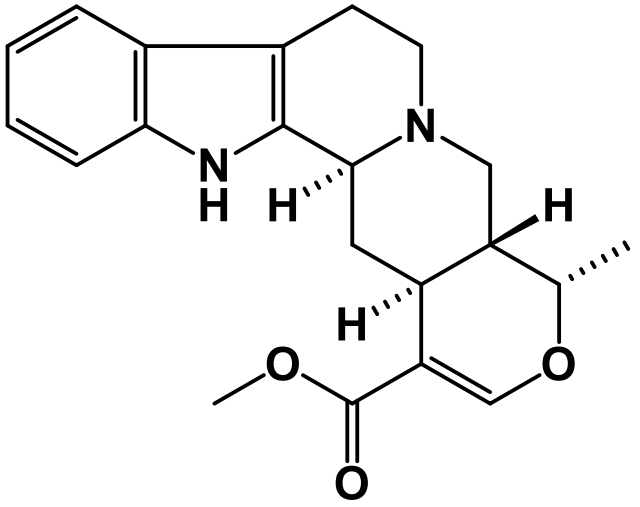
Brinerdin (Antihypertensive drug) consists of Reserpine, Clopamide, Dihydroergocristine

Side effect: Depression

Ajmalicine

❖ **Ajmalicine**: An **indole alkaloid** obtained from the roots of *Vinca rosea* (*Catharanthus roseus*) and the roots of *Rauwolfia serpentina*.

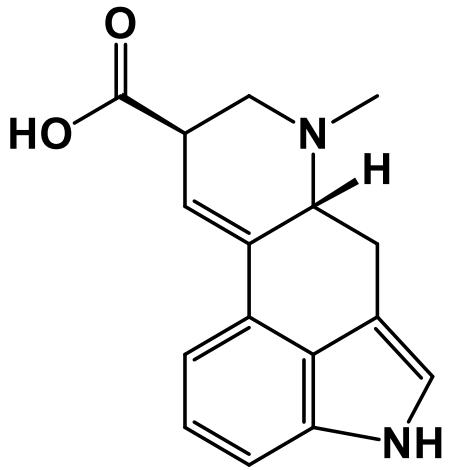
❖ It is an **antihypertensive** drug and also used to increase the blood flow in the brain and in the peripheral parts of the body.



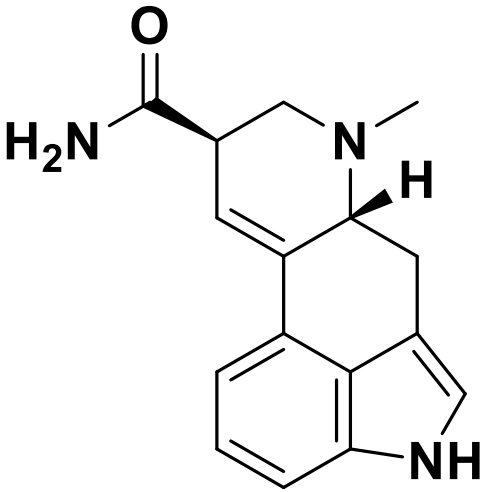
ajmalicin

Ergot alkaloids

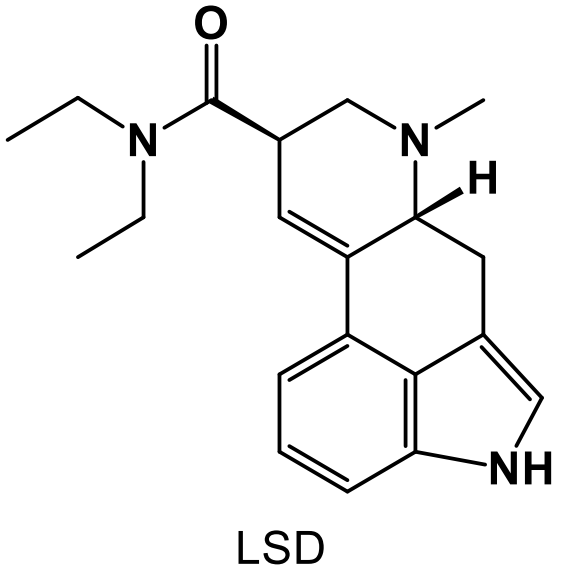
- Ergot is a fungal disease, found on wild and cultivated grasses.
- Ergot of rye is the dried sclerotium of a fungus, *Claviceps purpurea* grown on rye (Secale cereale) protruding from its seeds.
- The hallucinogenic alkaloid of ergot is called **Ergine** (+) **-** lysergic acid amide (LSA), better known as natural lysergic acid diethylamide (LSD).



LA



LSA or Ergine

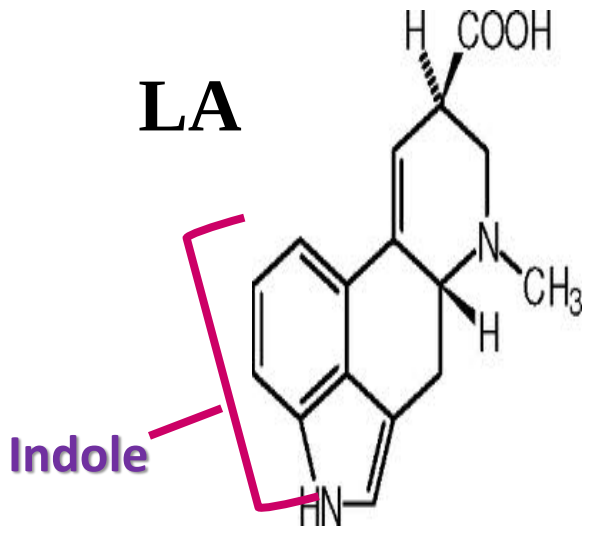


LSD

LSD

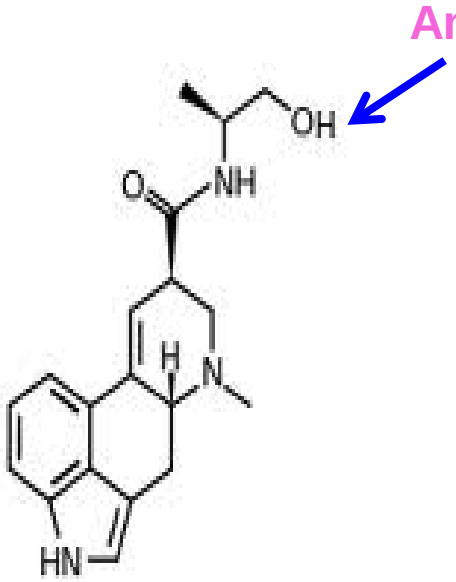
Ergot alkaloids: Chemistry

- The chemical structure of Ergot alkaloids are composed of lysergic acid and its isomer isolysergic acid, combined through an amide linkage with a peptide {tripeptide of 3 amino acids} (ergotamine group) or with an aminopropanol (ergometrine group).
- Ergotamine is a cyclic peptide containing the following amino acids: α-hydroxyalanine, proline, phenylalanine.
- Other cyclic peptide ergot alkaloids (like ergotamine): ergocristine, α-ergocryptine, β-ergocryptine, ergocornine.



Ergot alkaloids: Chemistry

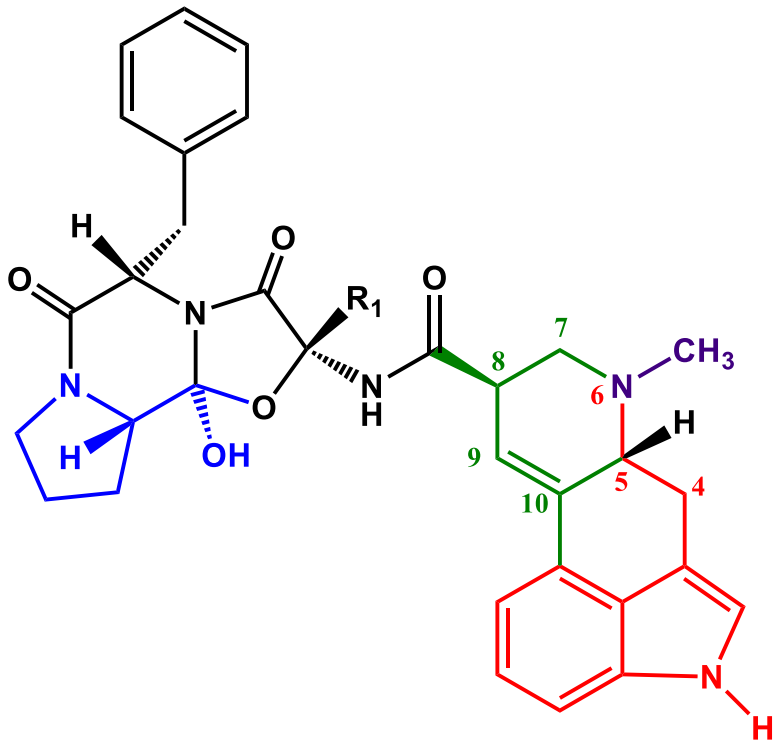
Ergometrine (ergonovine)



- **Ergometrine** causes prompt and vigorous contraction of the uterus (**oxytocic action**),
- It is used for prevention of hemorrhage after child birth.

Ergot alkaloids: Chemistry

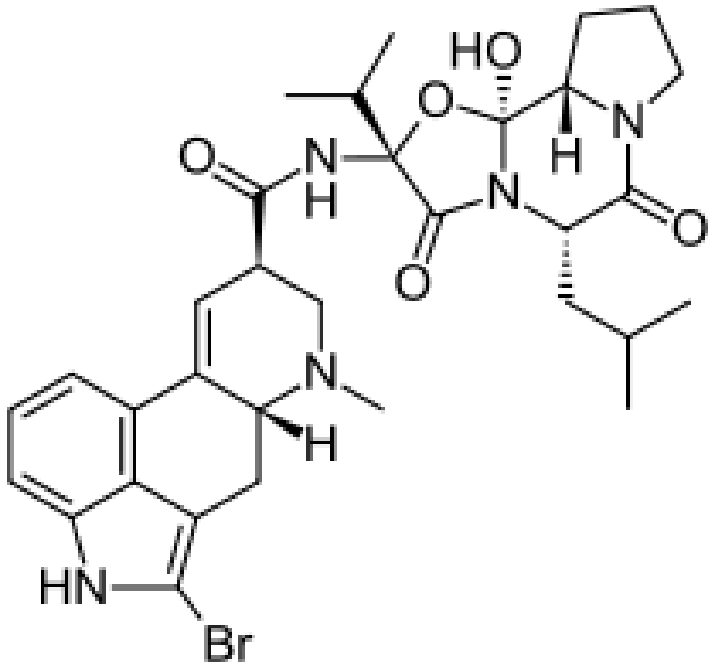
Ergotamine



- **Ergotamine**, the official salt is **ergotamine tartrate**.
- It is unstable, specially in aqueous solution and on exposure to light.
- On hydrogenation, **dihydroergotamine** is produced, which is used as **migraine analgesic** (Cafergot® tablets with caffeine).
- Ergotamine is a cyclic peptide containing following amino acids: α-hydroxy alanine, proline, and phenylalanine.

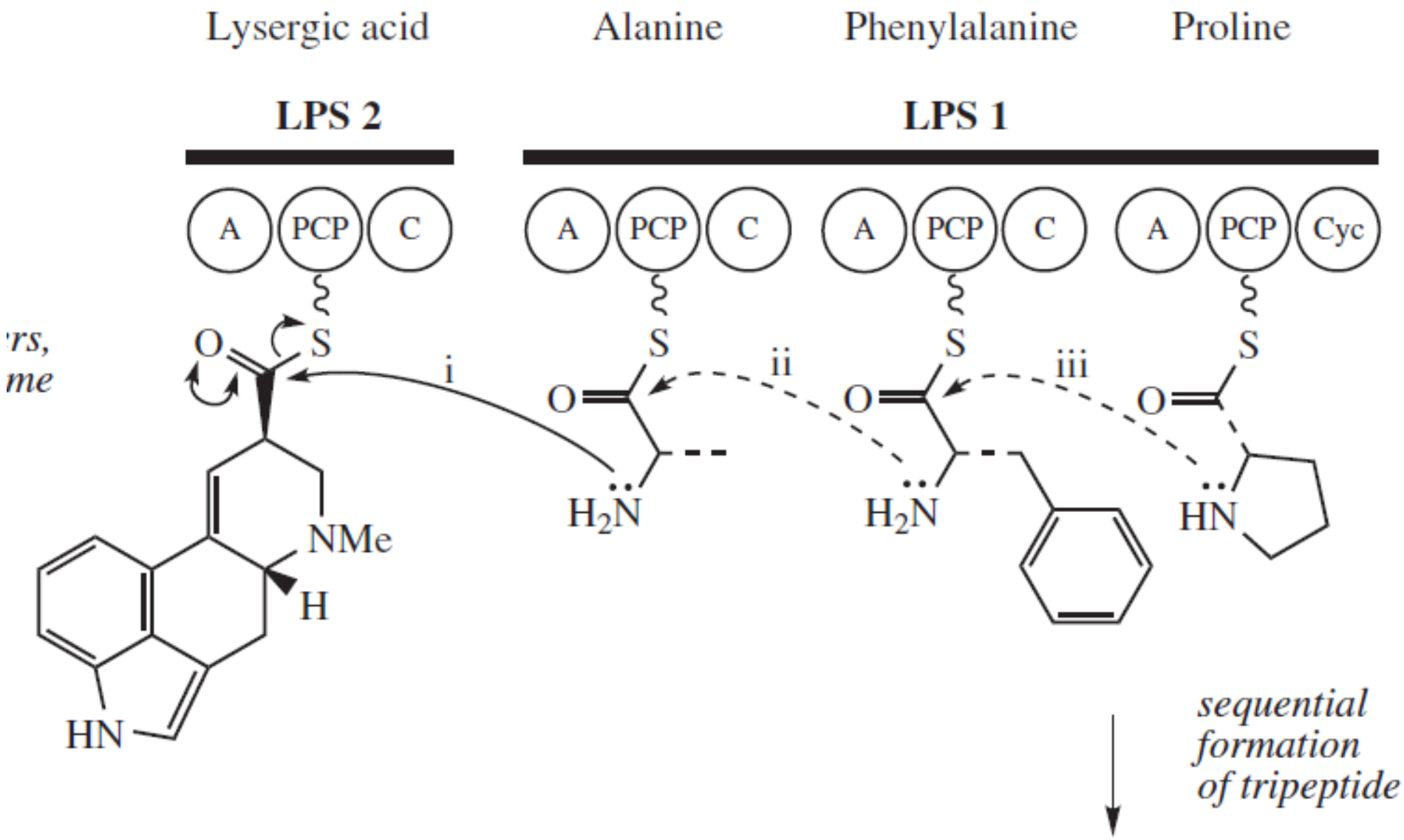
Ergot alkaloids: Chemistry

Bromocriptine



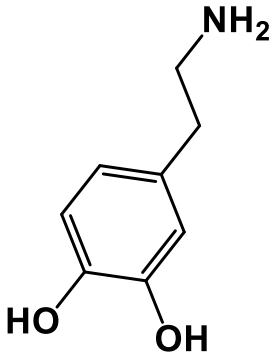
Bromocriptine: It is an ergoline derivative, work like a dopamine agonist, used in the treatment of **pituitary tumors**, **Parkinson's disease (PD)**, **hyperprolactinemia.**

Ergot alkaloids: Formation of Tripeptide

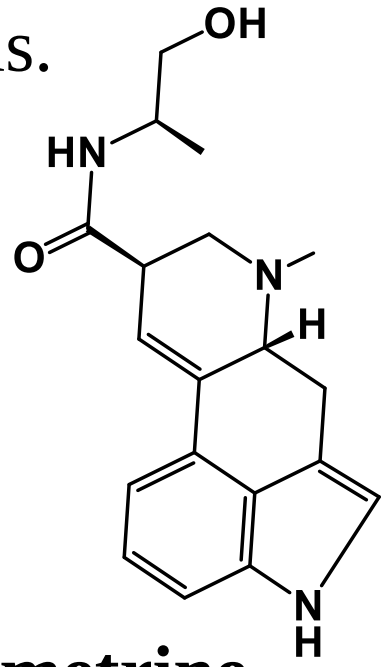


Ergot alkaloids: Pharmacology

- Ergot contains 0.15-0.5 % of alkaloids, more than 50 have been characterized.
- Medicinally useful ergot alkaloids are (+) lysergic acid derivatives.
- Ergot alkaloids act at α-adrenergic, dopaminergic and serotonin receptors.
- Ergot used initially to induce uterine contraction during a childbirth (**oxytocic** effect).
- The same effect is now achieved by isolated ergot alkaloid, **ergometrine**.
- Ergometrine also **reduce bleeding** after Caesarian operations.
- Other ergot alkaloids are used for vasoconstriction activity.

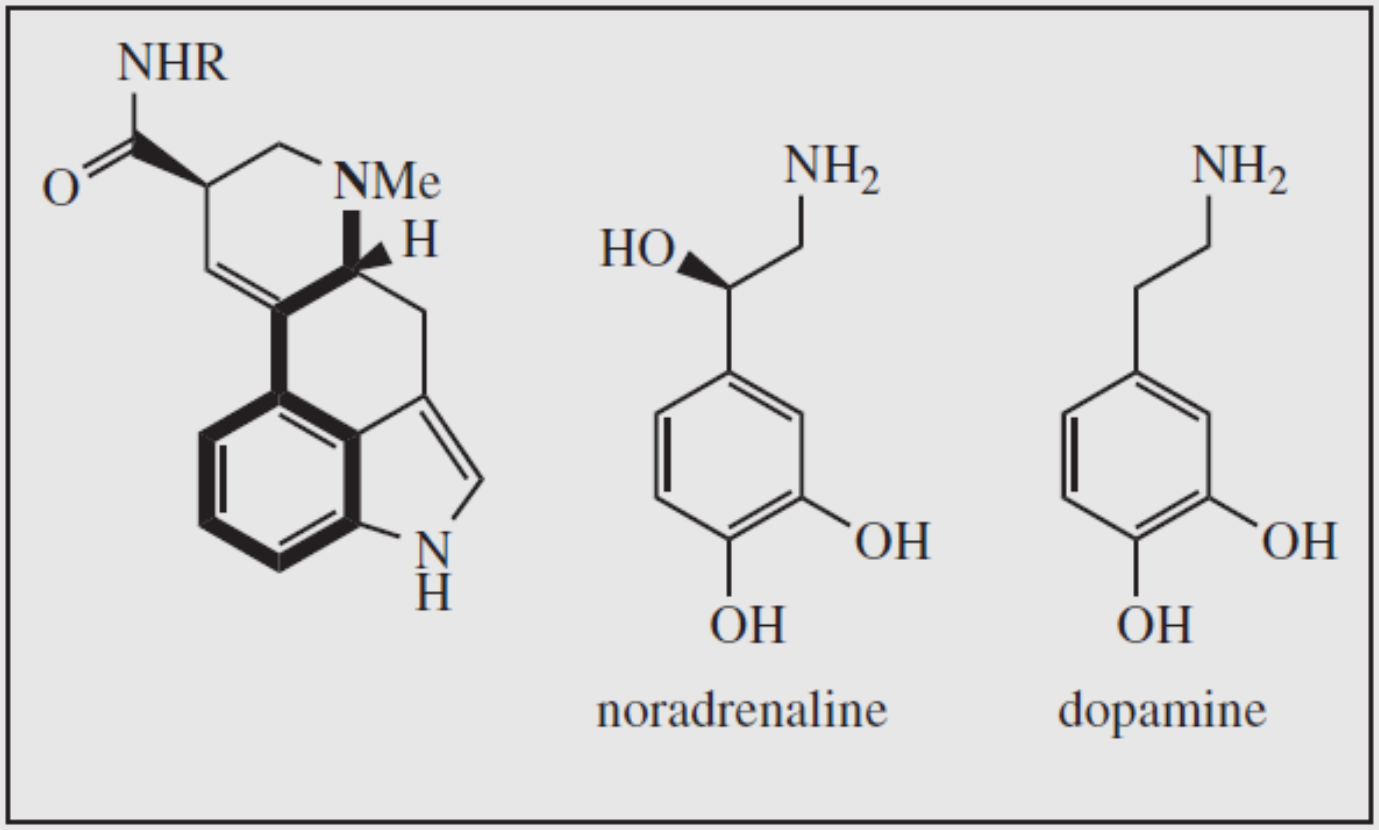


dopamine

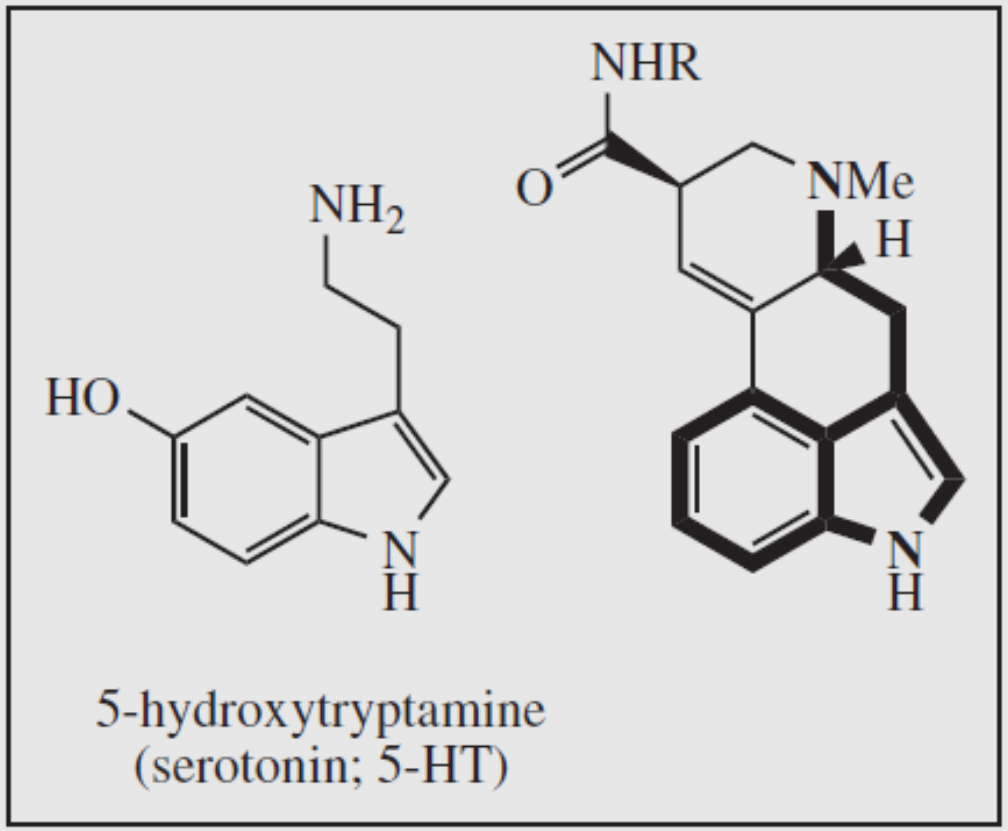


Ergometrine

Structural analogues of Ergot alkaloids with neurotransmitters



noradrenaline dopamine



5-hydroxytryptamine
(serotonin; 5-HT)

Lysergic acid Derivatives: Effects on CNS

- Most notorious of all lysergic acid derivatives is **LSD**, widely **abused drug** to produce hallucination.
- One of the most active **psychomimetic**, mixed agonist-antagonist of 5-hydroxy tryptamine (5-HT) receptors.
- Although not addictive, may lead to **schizophrenia** (a serious mental disorder in which people interpret reality abnormally).
- The psychic effects are very marked (marks of psychosis :(ذهان, اضطراب عقلي
- Perceptual changes (shapes, sounds, colors).
- Subjective time alteration (Living in the past or future; refers to a person's subjective impression of the speed at which time passes).
- A disintegration of the self.
- An increase in suggestibility, i.e. (a person will accept the suggestions of another person and acting accordingly).

Ergot Poisoning

Three broad clinical features of Ergot Poisoning:-

1. **Alimentary upsets**: Diarrhea, abdominal pains and vomiting.
2. **Circulatory changes**: Coldness of hands and feet, vasoconstriction effect.
3. **Neurological symptoms**: Headache, vertigo convulsions and hallucinations.

Ergotism: -

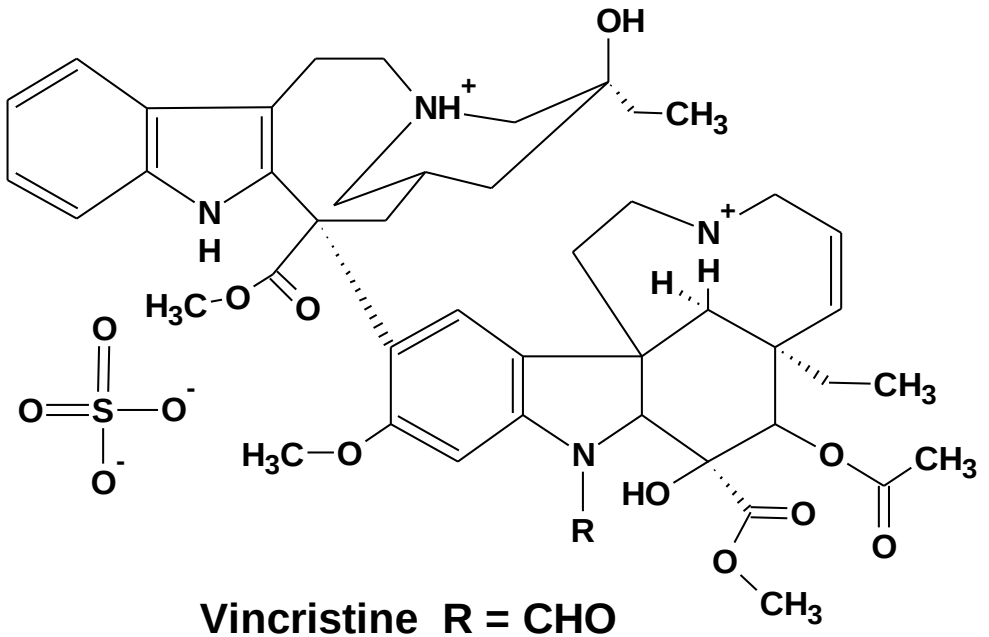
1. Ergotism is a disease caused by consumption of ergot-infected rye or wheat.
2. The history of ergotism is well documented since 1000 A.D.
3. Massive poisoning (pandemics) with continued ingestion of bread from infected flour.

1. Vasoconstriction effect leads to restricted blood flow in small termina arteries, death of the tissue, gangrene, and eventually losing entire hands, feet, or limbs
2. Ergot pandemic in the middle Age was known under the name of “St. Anthony’s fire”.

Vinca alkaloids (Vincristine and vinblastine)

- Vinca alkaloids like Vincristine and Vinblastine are obtained from *Catharanthus roseus* (Vinca rosea), Family: Apocynaceae.
- Now, it is widely cultivated and used as **anticancer drugs**.

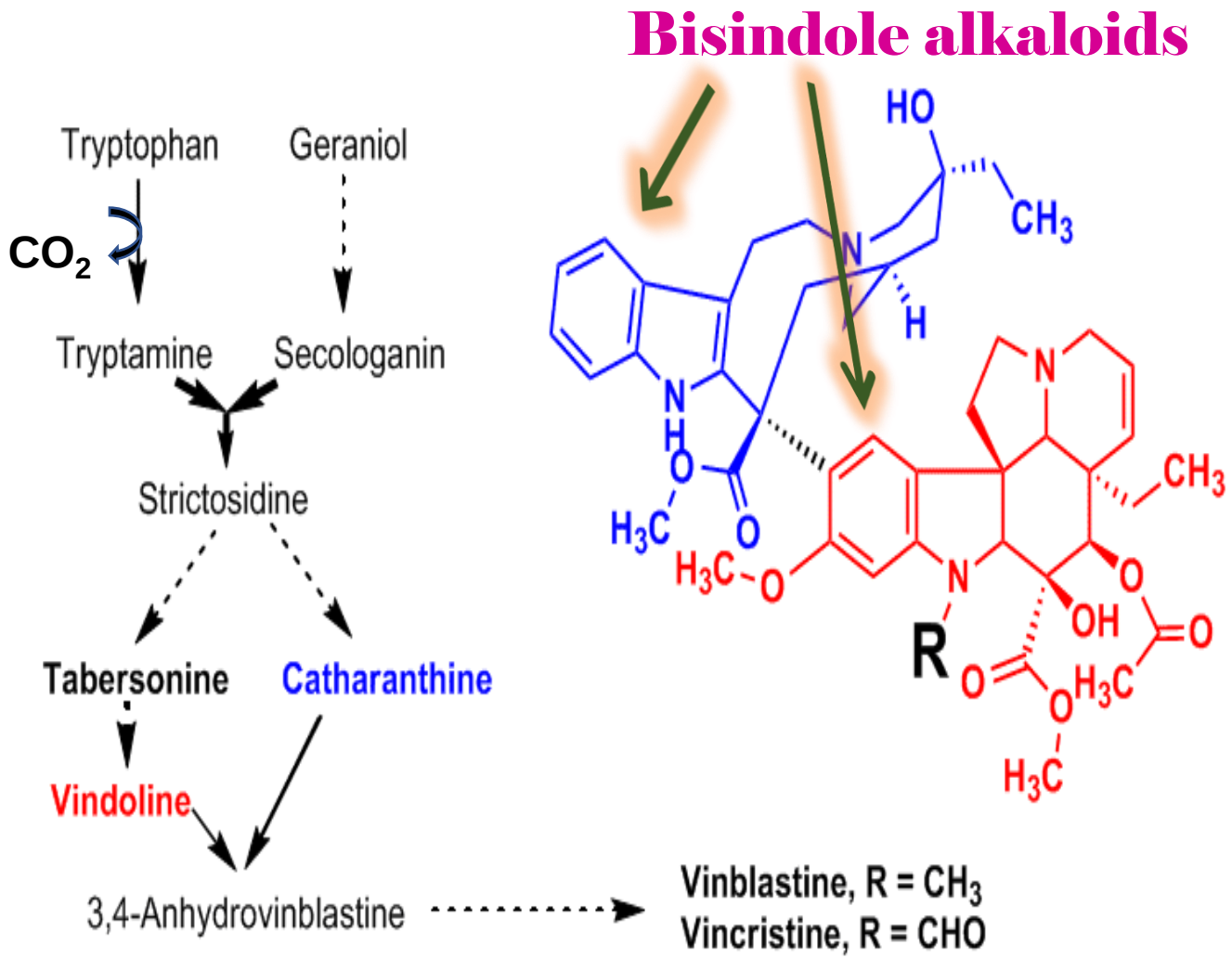
Catharanthus roseus



Vincristine R = CHO

Vinblastine R = CH_3

Vinca alkaloids: Biosynthesis



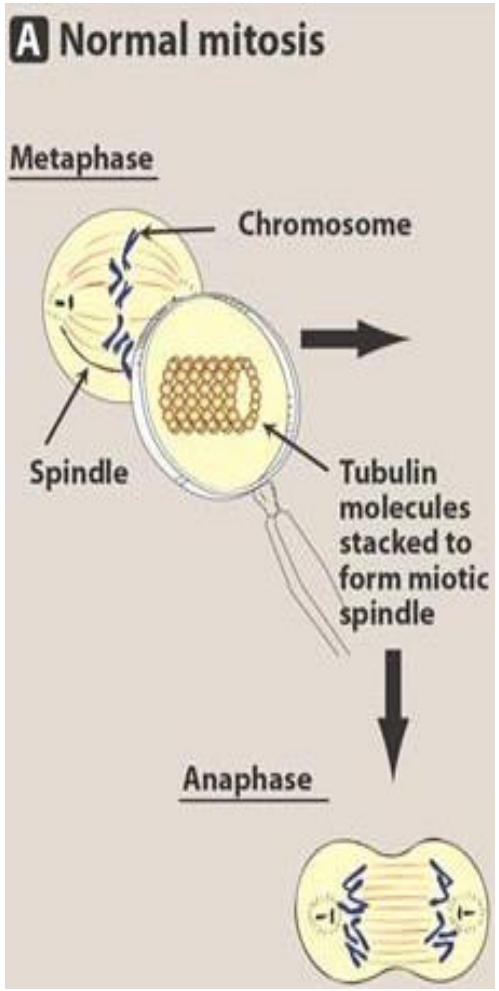
Overview of the pathway to the bisindole alkaloids Vinblastine and Vincristine.
Dotted lines: Two or more reactions

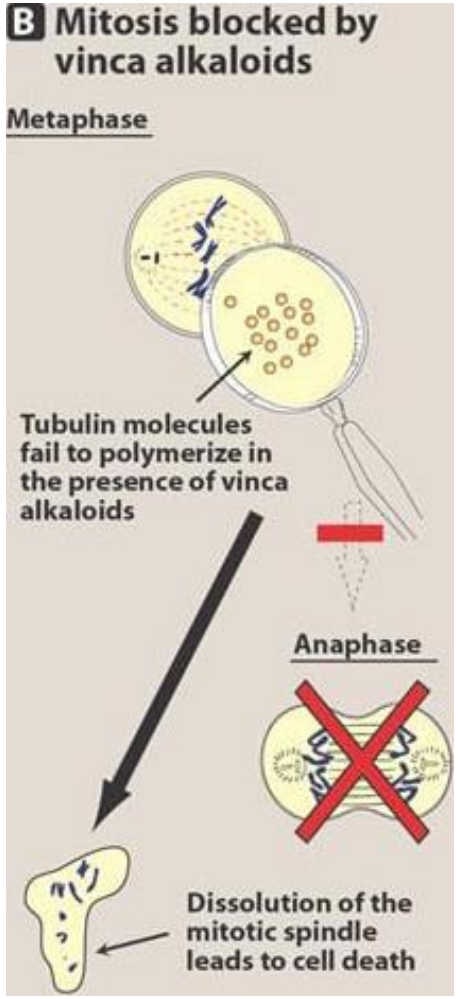
Vinka alkaloids (Vinblastine, Vincristine)

Mechanism of Action:

•These drugs **block the formation of mitotic spindle** by preventing the assembly of tubulin dimers into microtubules.

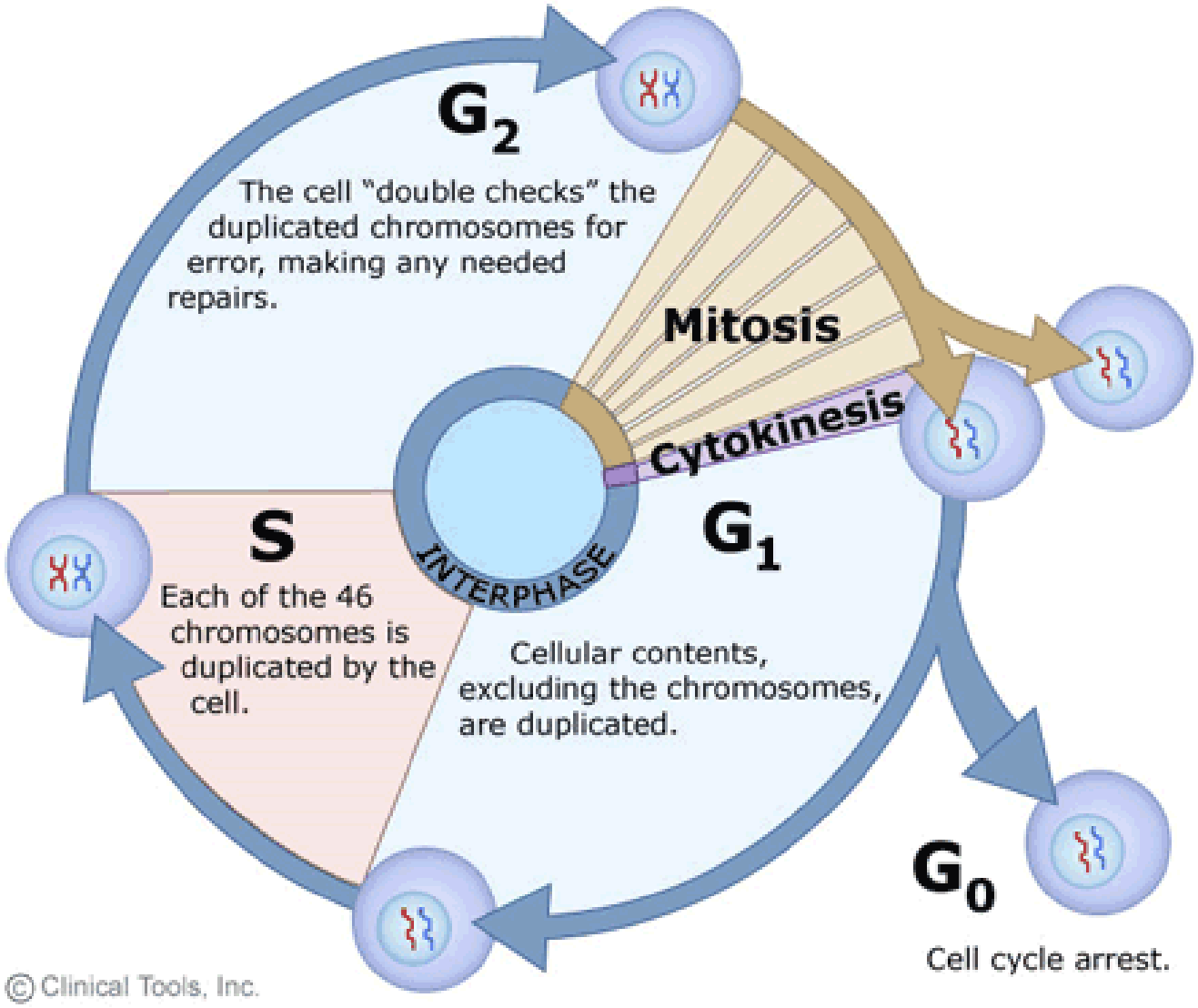
•prevention of microtubule assembly, causing cells to arrest in the late G2 phase by preventing formation of mitotic filaments for nuclear and cell division.

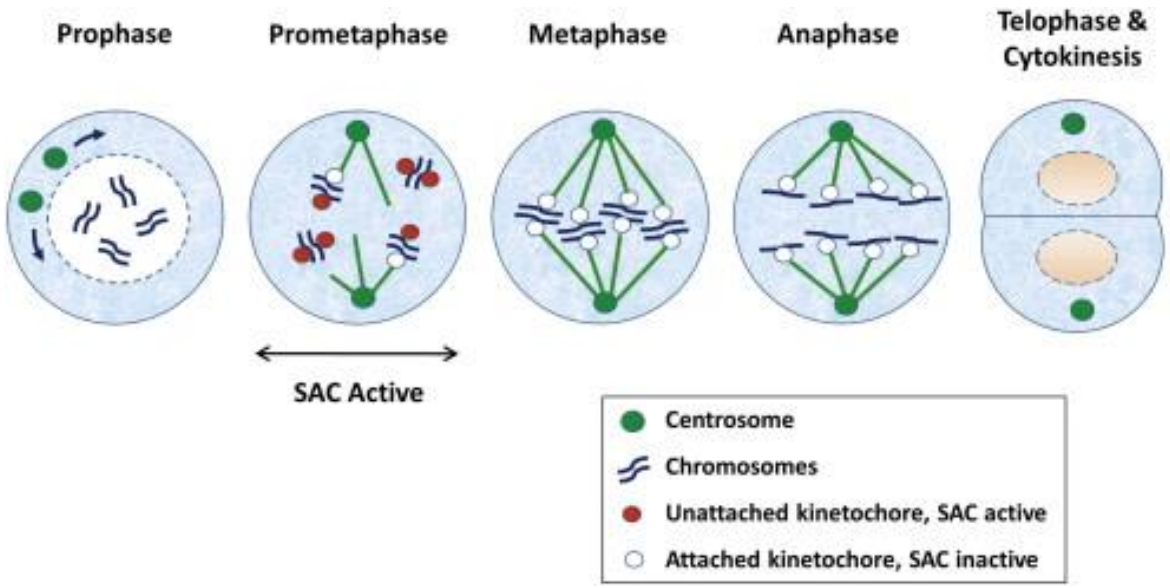




- They act primarily on the **M phase of cancer cell cycle**
- Resistance is due to increased efflux of drugs from tumor cells.

Cell Division Cycle





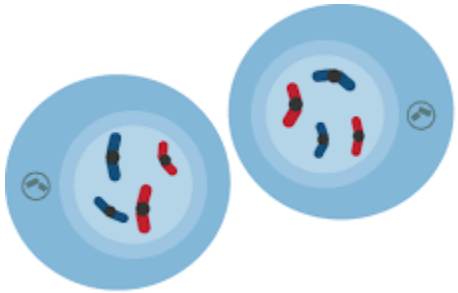
Vinca alkaloids

α–tubulin

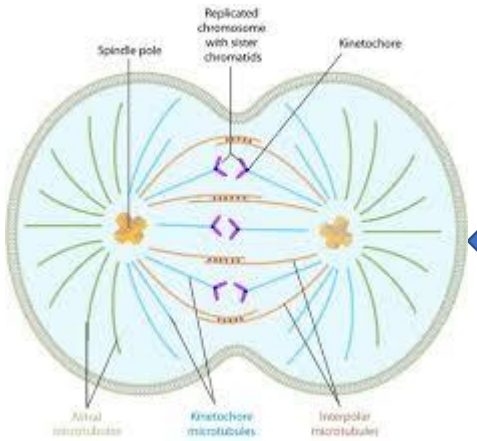
β–tubulin

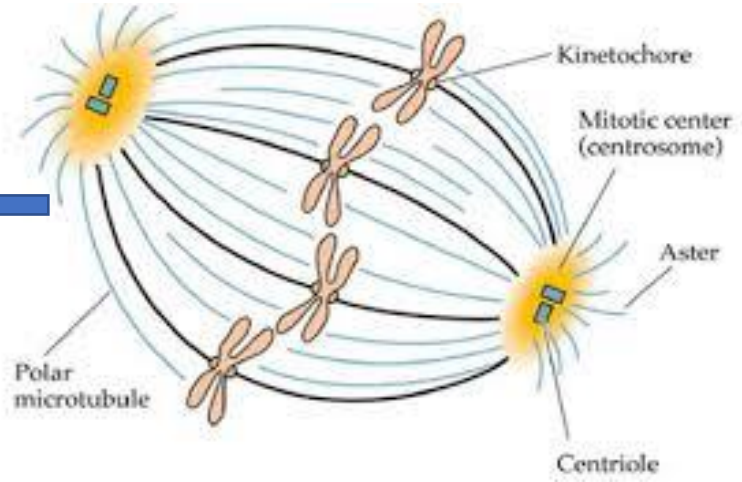
α and β tubulin heterodimers

Section of a Microtubule



α and β tubulin heterodimers





Vinca alkaloids (Vinblastine, Vincristine)

Vinca gives **low level of alkaloidal content** (500 kg to produce 1 g of vincristine, and the extraction, purification are too complicated).

•Content of vinblastine is higher, but vincristine is demanded more.

•**Vincristine sulfate** (Oncovin®):- Used for the treatment of leukemias, lymphomas, sarcomas, and some carcinomas.

•**Vinblastine sulfate** (Velban®): Vinblastine, the more active compound, used for the treatment of solid tumors, especially in combination with drugs such as cisplatin and BLM (bleomycin) for testicular tumor, advanced Hodgkin's disease, breast carcinoma.

Vinca alkaloids (Vinblastine, Vincristine): Formulations

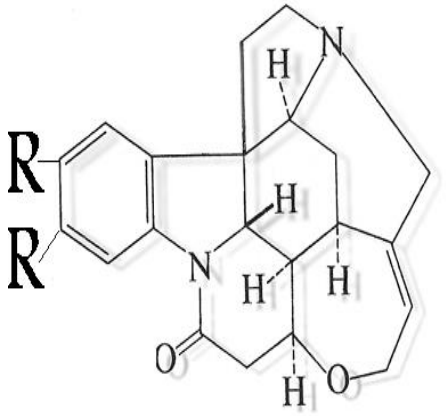
Nux Vomica alkaloids (Strychnine and brucine)

- ✓ The dried seeds of *Strychnos nux-vomica* (family: Loganiaceae) are commonly known as kuchla.
- ✓ Kuchla contain 2.6%–3% total alkaloids, out of which 1.25%–1.5% is **strychnine**, 1.7% is **brucine**, and the remaining are vomicine and igasurine.
- ✓ Strychnine is no longer used medicinally, it was used historically in small doses **to strengthen muscle** contractions, such as a heart and bowel stimulant and performance-enhancing drug.
- ✓ Brucine is having good **anti-cancer effects** on both hepatocellular carcinoma and breast cancer.
- ✓ Its **narrow therapeutic window** limited its use as a treatment for cancer.
- ✓ Brucine is also used in traditional Chinese medicine as an **anti-inflammatory** and **analgesic** agent.
- ✓ It is a biter tonic, increasing appetite; it stimulates peristalsis.

Nux Vomica alkaloids (Strychnine and brucine)

Seeds

Structure



R= H:
Strychnine

R= OCH_3
Brucine

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.