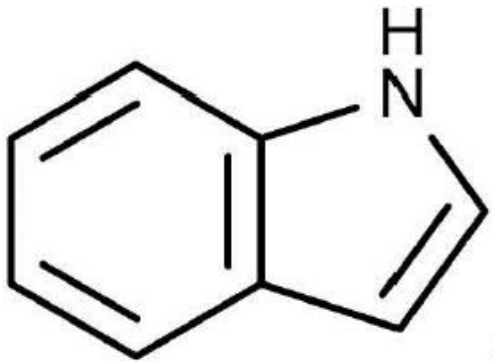
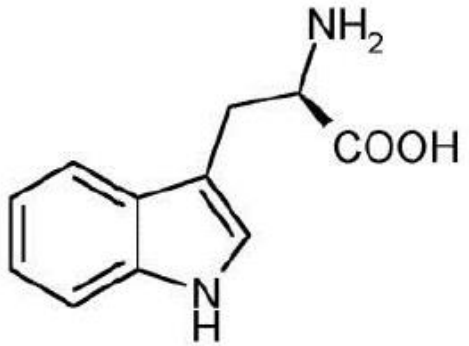
Indole alkaloids

Tryptophan derived alkaloids

- Indole and Quinolines alkaloids are derived from the same amino acid which is tryptophan.
- Indole alkaloids are widely distributed among the Apocynaceae, Loganiaceae and Rubiaceae families.

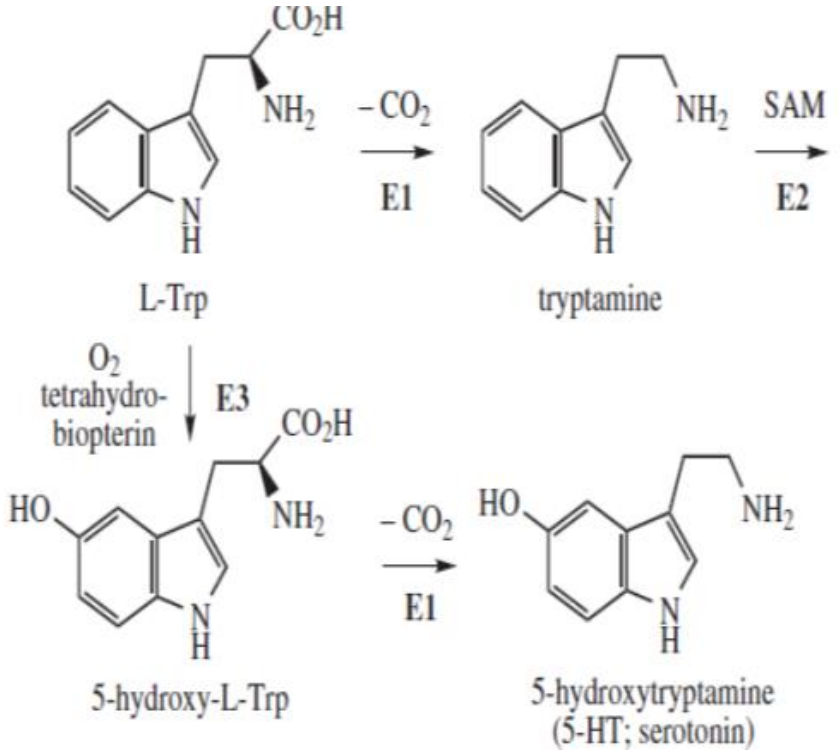


← indole



← tryptophan

- Tryptophan has 2 possible pathways to end up with the formation of our simple derivatives that we will discuss here,



Synthesis of Seratonin

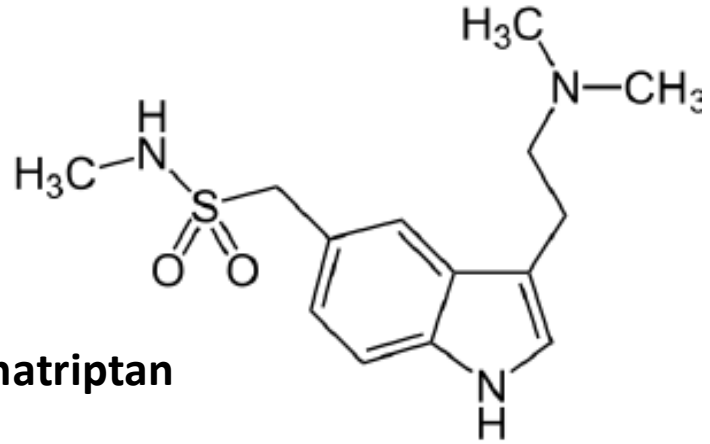
- first it can be decarboxylated to obtain tryptamine further reactions include oxidation will end up with 5-hydroxytryptamine (**serotonin** our first simple derivative)
- Or it can be first hyroxylated to 5-hydroxy tryptophan →further decaboxylation will also lead to serotonin.

5-Hydroxytryptamine
5-HT, Serotonin

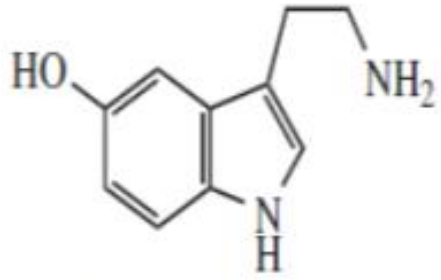
- 5-HT, serotonin is a monoamine neurotransmitter found in cardiovascular tissue, the peripheral nervous system, blood cells, and the central nervous system.
- **It** mediates many central and peripheral physiological functions, including contraction of smooth muscle, vasoconstriction, food intake, sleep, pain perception, and memory.
- **Although** 5-HT may be metabolized by monoamine oxidase, platelets and neurons possess a high affinity 5-HT reuptake mechanism.
- This mechanism may be **inhibited**, thereby increasing levels of 5-HT in the central nervous system, by widely prescribed **antidepressant** drugs termed **selective serotonin re-uptake inhibitors (SSRIs).**
- **PROZAC®** which contains **Fluoxetine** which is a **selective serotonin re-uptake inhibitors (SSRIs)** officially approved for treatment of depression

Serotonin derivatives

- **Migraine** headaches that do not respond to analgesics may be relieved by the use of an **agonist of the 5-HT1 receptor**, since these receptors are known to mediate vasoconstriction.
- **Sumatriptan** is used to treat migraine
- Sumatriptan is produced through methylation of 5-HT and turning the amino group into a tertiary one , and the hydroxyl group on carbon # 5 will be replaced by a sulphate group
- One of its benefits is that it is used for the treatment of acute migraine attacks



Sumatriptan



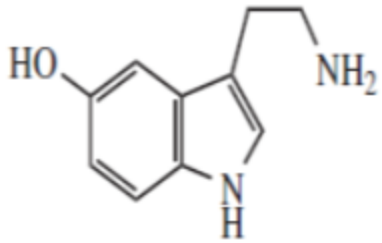
5-hydroxytryptamine
(5-HT; serotonin)

Serotonin

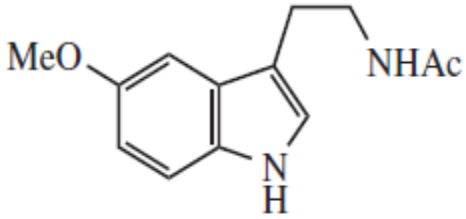
- Serotonin is one of the most important compounds found in the brain (or CNS) and plays an important role in controlling the secretion of several hormones, and other cellular functions in the body, as well as the contraction and relaxation of blood vessels
- 5-hydroxytryptamine (serotonin) plays an important role in the cardiovascular system (it controls blood vessels and their contraction and relaxation) it also controls the peripheral nervous system
- Its problem is that if an imbalance occurs; sleeping disorders would occur and depression as well
- Scientists have been trying to form compounds of good use in situations where there is a disorder like depression or so
- PROZAC which contains **fluoxetine** was officially approved for as a medicine

Melatonin
(the second simple derivative)

- In animals, **melatonin** is a hormone synthesized by the pineal gland in the brain.
- it can be synthesized by methylation of the 5-OH and acetylation of the amino group of the serotonin.



5-hydroxytryptamine
(5-HT; serotonin)



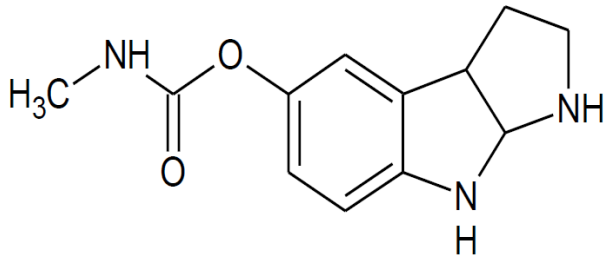
melatonin

Melatonin

- plays a key role in the **circadian rhythm**, sleep regulation, and seasonal photoperiodic regulation. The duration of elevated melatonin levels is usually proportional to night length in vertebrates. Melatonin concentration and its daily rhythm can thus inform the organism about the time of day and about the season. It is also found in invertebrates and plants, though less is known about its role
- Melatonin is claimed to be effective in helping to regulate disrupted circadian rhythms and **sleep disorders**. A slow-release formulation is available for treating insomnia in older patients; melatonin production is found to **decrease with age.**
- It is currently also popular to reduce the effects of **jet-lag** by resetting the internal body clock.

Physostigmine (eserine)

- Isolated from the seeds of the Physostigma venenosum ,this plant contain many alkaloids but the most important one is physostigmine.
- Physostigmine is a very unstable compound and should be kept in tightly closed containers because it oxidized easily, with luck we can detect the deterioration of this compound by the color change that occur due to oxidation therefore the oxidized derivative (rubreserine) can be easily recognized by its red color.

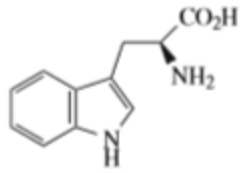


Physostigma venenosum:

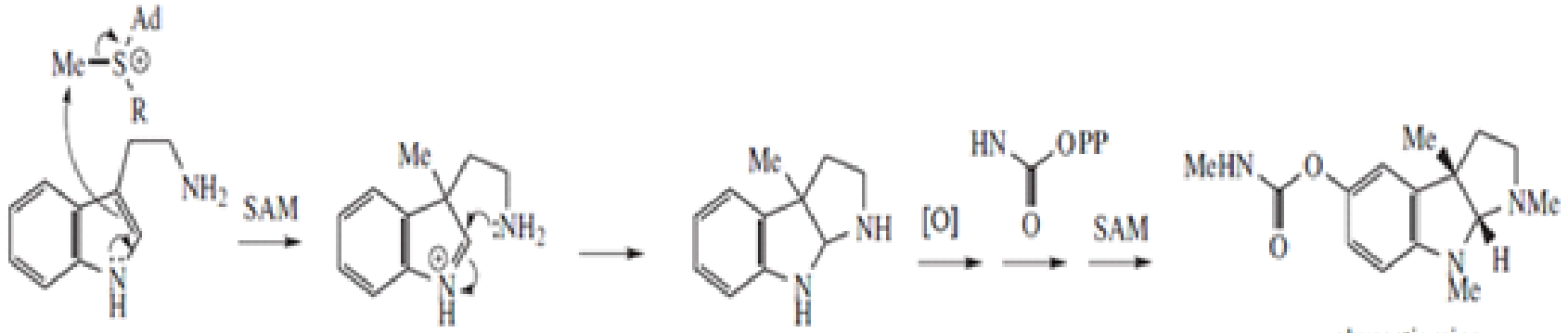
- From its name **venenosum**, it's **very toxic** plant, it comes from **seeds** of **calabar bean** (found in **Nigeria**), family: **Fabaceae**.
- This seeds are important as a source for **physostigmine**. It was used in **ordeal poison** by giving it to a person, if that person **vomiting** then he is **innocent**; if he **died** then he is guilty.
- The person who eat this plant die due to **progressive paralysis** followed by **cardiac, respiratory failure.** Nowadays it's used as **rodenticide** (the **most** important use).

Physostigmine (eserine) :

- In the structure of the amino acid tryptophan (or its derivative tryptamine), there are 2 adjacent carbons (the a & b carbons) of the NH group inside the indole ring, which are important nucleophilic centers because many of tryptophan



L-Trp



tryptamine

physostigmine (eserine)

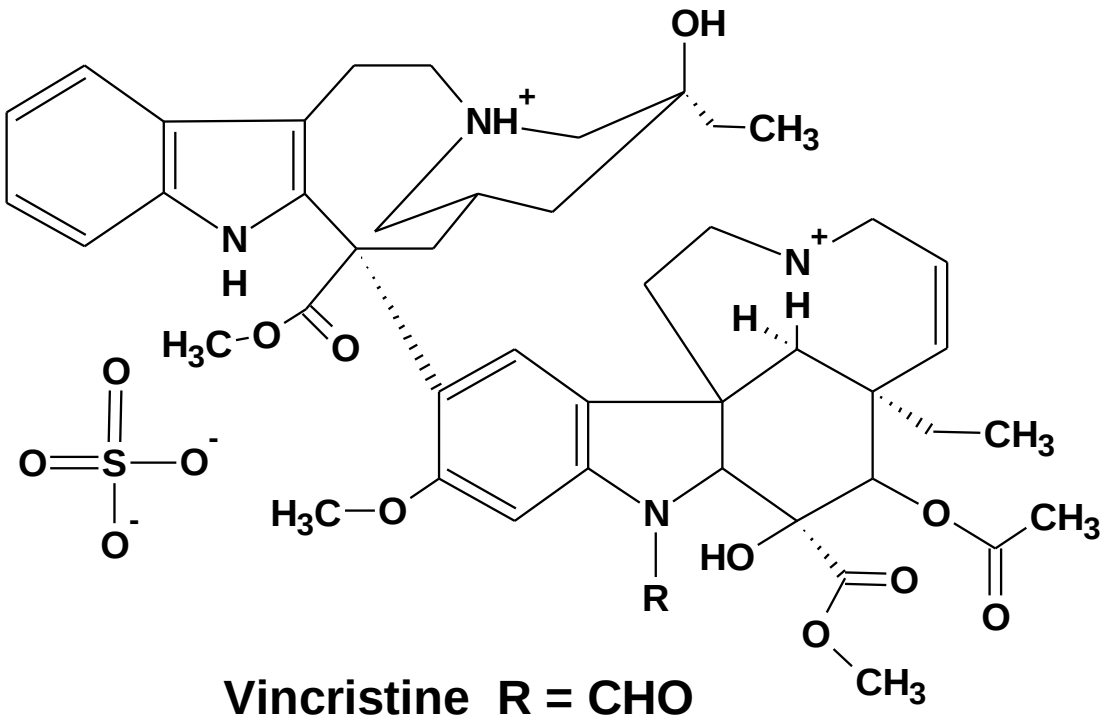
Physostigmine (eserine)
Acetylcholine esterase inhibitor

- Uses : physostigmine is the antidote for several anticholinergic compounds such as atropine hyoscyamine and related substances as well as it is an antidote for muscle relaxants like curare
- Moreover it is a **transient (reversible**) inhibitor of acetylcholinesterase, which mean that it will cause accumulation of Ach and this accumulation will enhance the memory & it is needed in the treatment of several disease like **Alzheimer's** disease
- This drug will not reverse the disease but it will delay it. It can be useful also for the treatment of glaucoma because of their capability of reducing intraocular pressure.
- With this discussion of melatonin, serotonin & physostigmine we complete the important representatives of simple derivatives of the amino acid tryptophan which are primarily obtained by decarboxylation of the amino acid tryptophan to obtain typtamine and then further modification especially oxidation at position 4 or at position 5.

Venca Alkaloids

- **Viniblastine** and **Vincristine** are anti-cancer compounds from *Catharanthus raserus* and ***Venca rosera*** . they are antimitotic agents , but they cause serious neurotoxicity .
- other disadvantage of them is their low concentration in nature (we need 5000 Kg of their leaves to produce 1 g of them !!)
- Venicristine has more pharmacological activity than Viniblastine.

The alkaloids of the periwinkle plant (*Vinca rosea*)

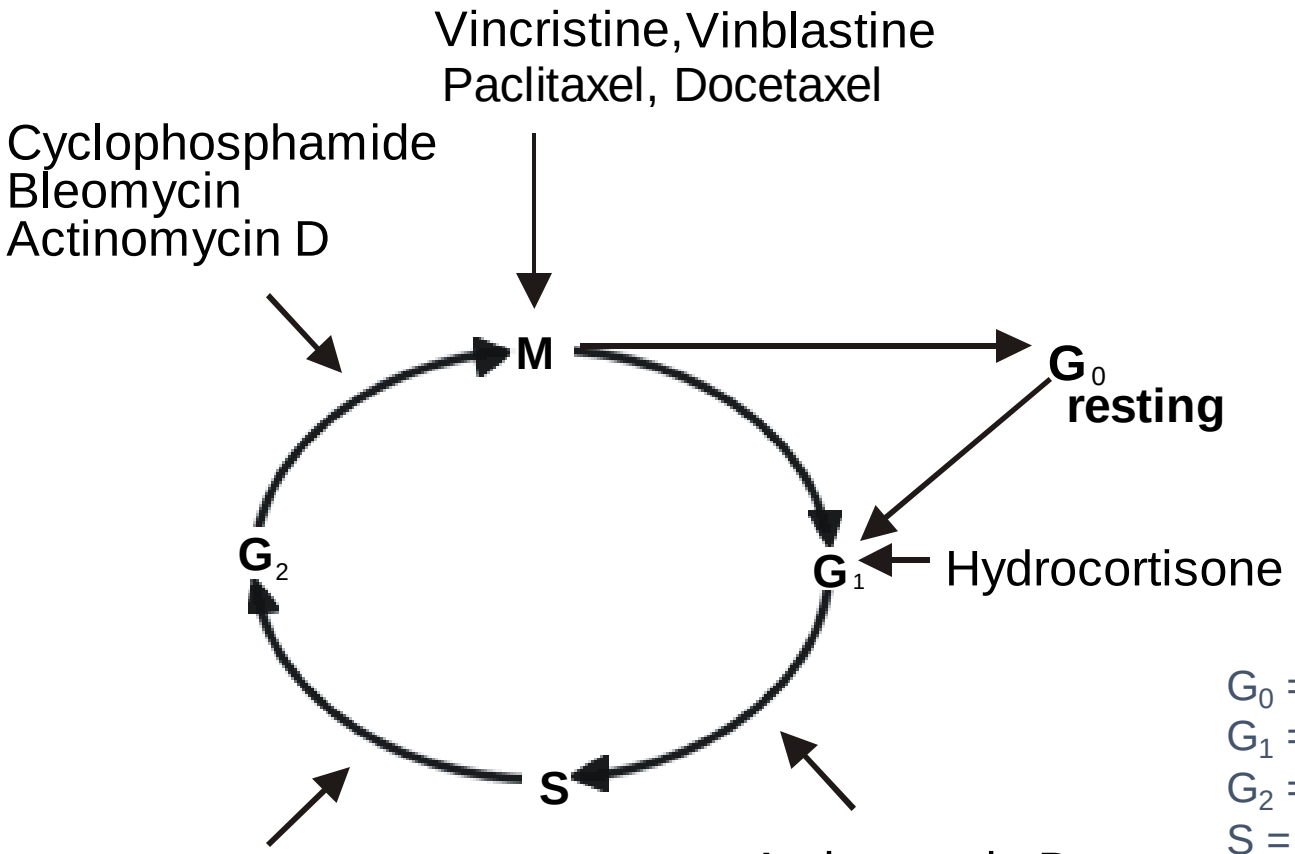


Vincristine R = CHO

Vinblastine R = CH_3

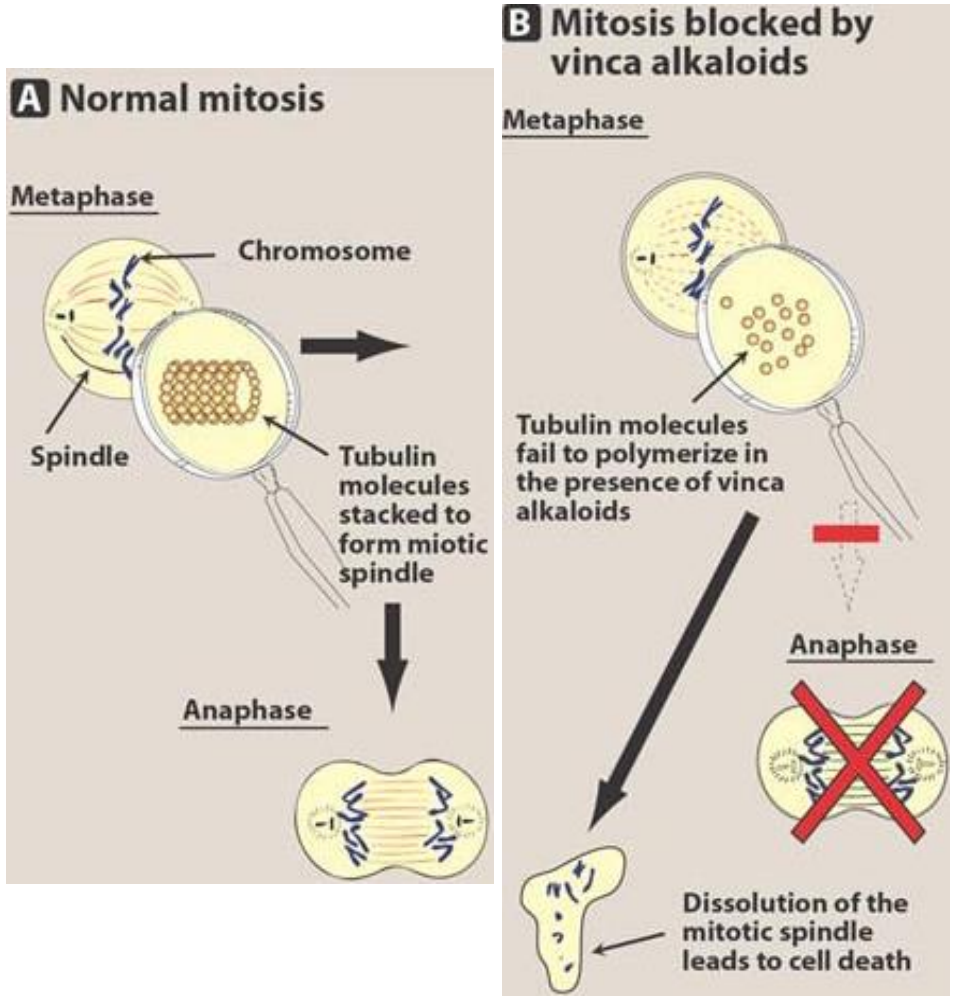
They are dimeric indole-dihydroindole derivatives

Cell cycle specificity of Anti-Neoplastic Agents



G_0 = resting phase
G_1 = pre-replicative phase
G_2 = post-replicative phase
S = DNA synthesis
M = mitosis or cell division

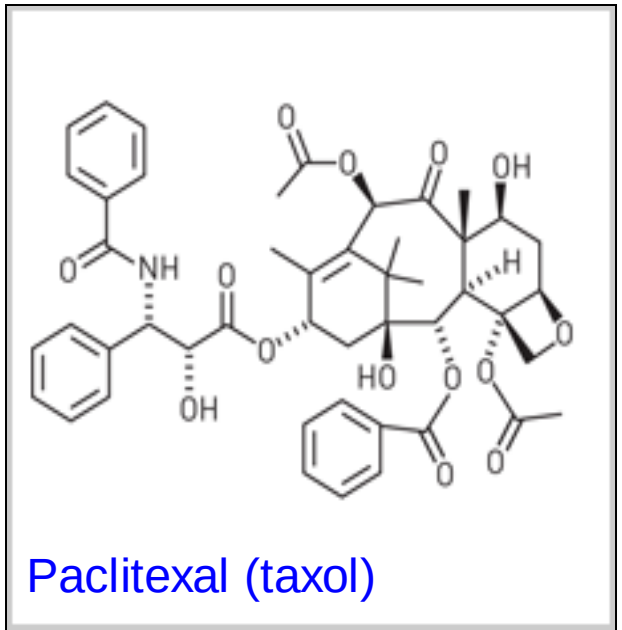
Vinka alkaloids (Vinblastine, vincristine)



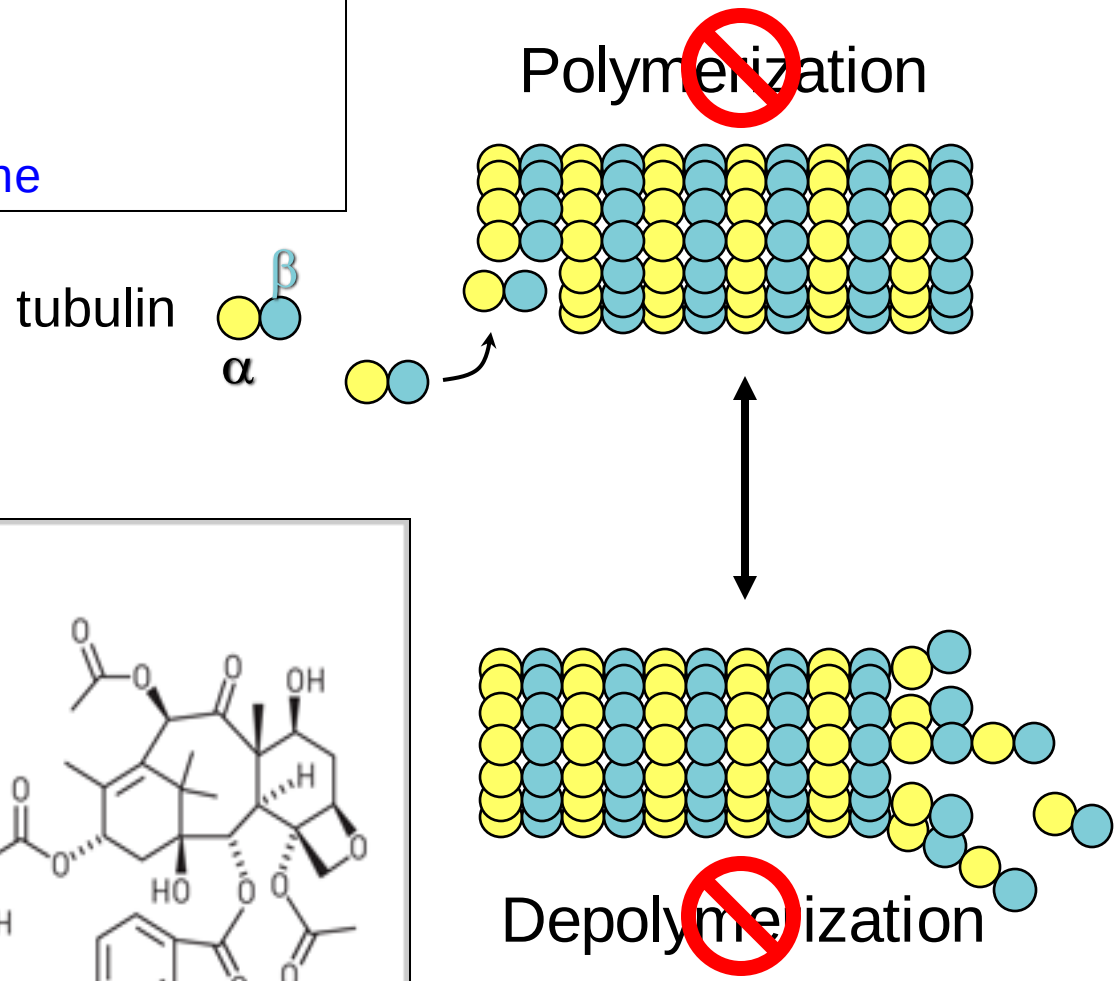
- These drugs block the formation of mitotic spindle by preventing the assembly of tubulin dimers into microtubules
- ***They act primarily on the M phase of cancer cell cycle

Tubulin Binding Agents

Vincristine



Paclitexal (taxol)



e.g., Vincristine, Vinblastine, Vindesine Vinorelbine: Inhibition of mitotic spindle formation by binding to tubulin.
M-phase of the cell cycle.

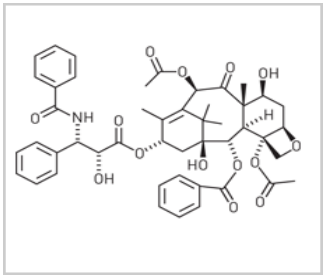
e.g., Paclitexal: binds to tubulin, promotes microtubule formation and retards disassembly; results in mitotic arrest.

1. Antimitotic Drugs

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Vincristine	Cytotoxic: Inhibition of mitotic spindle formation by binding to tubulin. M-phase of the cell cycle.	Metastatic testicular cancer, Hodgkins and non-Hodgkins lymphoma, Kaposi's sarcoma, breast carcinoma, chriocarcinoma, neuroblastoma	I.V.	Bone marrow depression, epithelial ulceration, GI disturbances, neurotoxicity
B. Vinblastine	Methylates DNA and inhibits DNA synthesis and function	Hodgkins and non-Hodgkins lymphoma, brain tumors, breast carcinoma, chriocarcinoma, neuroblastoma	I.V.	Nausea and vomiting, neurotoxicity, thrombocytosis, hyperuricemia.

2. Antimitotic Drugs

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
Paclitaxel (Taxol) 	Cytotoxic: binds to tubulin, promotes microtubule formation and retards disassembly; mitotic arrest results	Melanoma and carcinoma of ovary and breast	I.V.	Myelodepression and neuropathy



Ergot alkaloids ergoline

- Ergot alkaloids are isolated from infected plants (fungal infection).
- They are tryptophan derivatives

Ergot Alkaloids

Ergot is a fungal disease commonly found on many wild and cultivated grasses that is caused by species of *Claviceps* [Box 6.19]. The disease is eventually characterized by the formation of hard, seed-like 'ergots' instead of normal seeds; these structures, called sclerotia, are the resting stage of the fungus. The poisonous properties of ergots in grain, especially rye, for human or animal consumption have long been recognized, and the causative

Ergotism symptoms

- 1. Starts in **redness** of the skin.
- 2. **GI upset** include **diarrhea**, **abdominal pain**, and **vomiting**.
- 3. affect **CNS** and cause **convulsions**
- 4. In last stages we have **circulatory changes** that involved **coldness** of the hands and feet due to **vasoconstriction** which lead to **gangrene**.

Ergot alkaloids

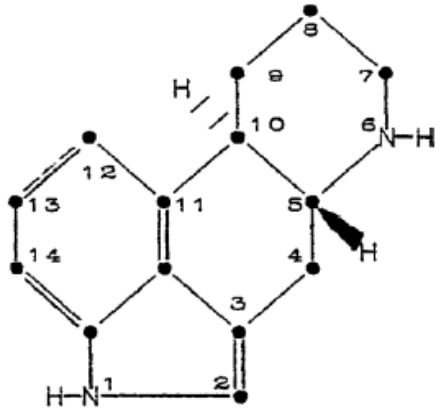
- Again, ergot alkaloids aren't naturally occurring; it's synthesis in response to infection by Claviceps purpurea fungus.

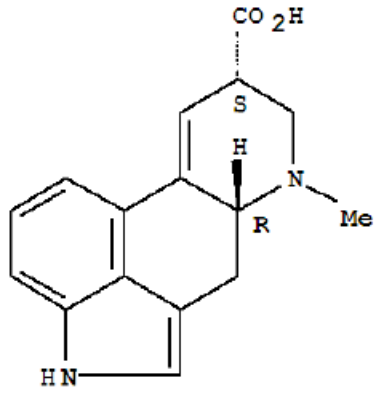
- **Ergot Alkaloids** in general are classified into **2** gp:

- 1. **water soluble gp** :due to presence of **amino alcohol** functional gp, it forms **20**% of total alkaloids, an example **ergometrin**, **alcohol** alkaloids contain what is called **lysergic acid**, this acid has **2** forms: **dextro**(+) which is the **active** form and **levo (-)** form is inactive

Lysergic acid

- **Lysergic** acid which is the **active** ingredient for **ergot** alkaloids may exposed to some changes which is **enolization** (**heat or alkaline effect**), this will convert it to **inactive** compound called **isolysergic** acid. The **only** difference
- The only difference between lysergic acid and isolysergic is stereochemistry of amide functional gp at C8.



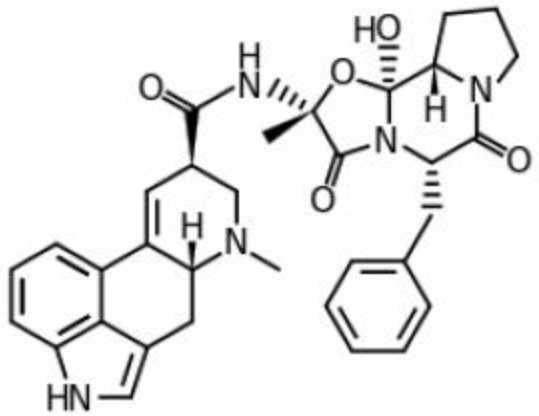


Isolysergic acid

Ergotamine:

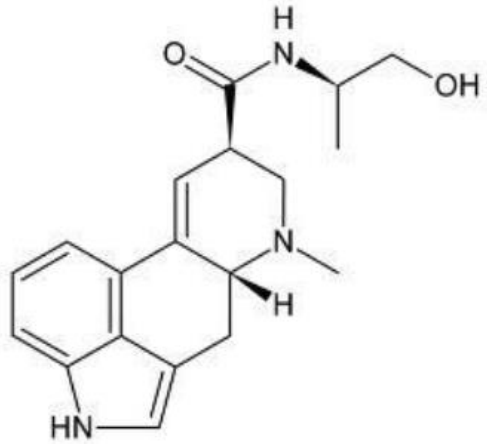
- 2. **Water insoluble gp**:It's a **peptide** derivative(contain an **amide** gp and parts of **protein** and **amino acid**).

- **Ergotamine:**
- It's a **peptide** derivative contain **tripeptide** fragments **bonded** to lysergic acid via **amid** link. It's used for migraine
- the **hydrolysis** of **peptide ergot** alkaloids will produce **lysergic acid** + **proline** +**phenylalanine** + **pyruvic acid** +**ammonia**



Ergometrine

- Ergometrine importance : it has been used since the
- 16th century to induce uterine contractions during childbirth and to reduce haemorrhage following the birth. This oxytocic effect is still medicinally valuable, but is now achieved through use of the isolated alkaloid ergometrine.
- Ergometrine is used during the final stages of labour and immediately following childbirth, especially if haemorrhage occurs. Bleeding is reduced because of its vasoconstrictor effects, and it is valuableafter Caesarian operations.
- Ergometrine is also orally active while oxitocine is only given parentrally. we have the semi-synthitic type of ergometrine that has a longer duration and orally active.

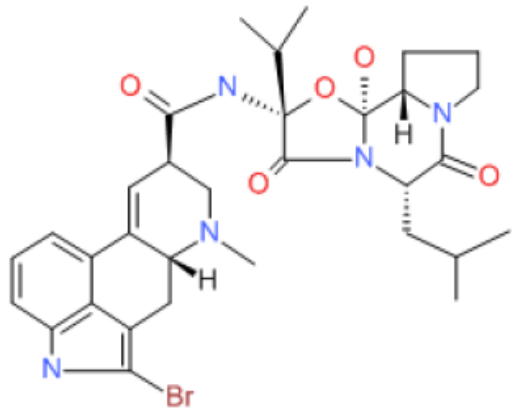


Ergometrine

Bromocriptine:

- It's very **cheap** compound, It's used to **inhibit prolactine** production, also useful in treatment of **Parkinson disease**
- trade names **Parlodel**, **Cycloset**, **Brotin (Pakistan)**),
- It is a dopamine agonist that is used in the treatment of pituitary tumors, Parkinson's disease (PD), hyperprolactinaemia, and type 2 diabetes.
- It has **bromine** (Br) at **C2**, **2 isopropyl** moiety at **peptide** compound..

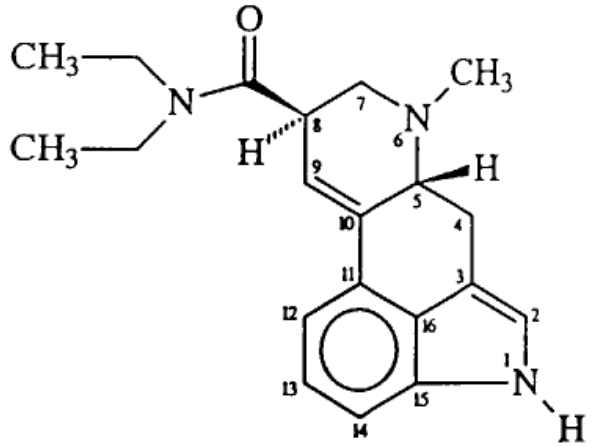
Bromocriptine is a semisynthetic derivative of a natural ergot alkaloid



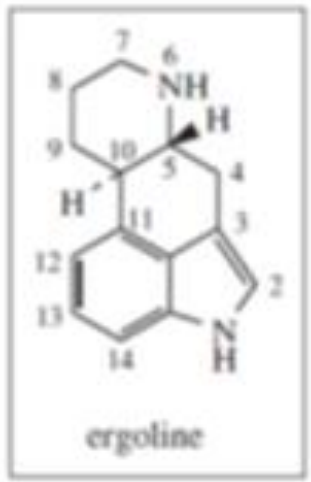
Bromocriptine

Lysergic Acid Diethyl amid (LSD),

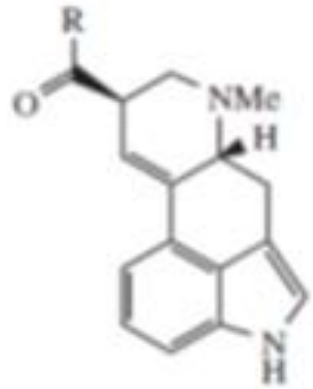
- It's **semisynthetic** derivative of **Lysergic Acid Diethyl amid** (LSD), **very cheap** to produce. It's widely **abused hallucination** and **most** active specific **psychotomimitic** know till now. It's very **potent** compound **30-50** microgram (**effective** dose), this compound is put it on **sugar cubes** or **gelatin**, and it **doesn't** cause **complete addiction** but can cause **neurological** disease, because it can act as **mixed agonist-antag**



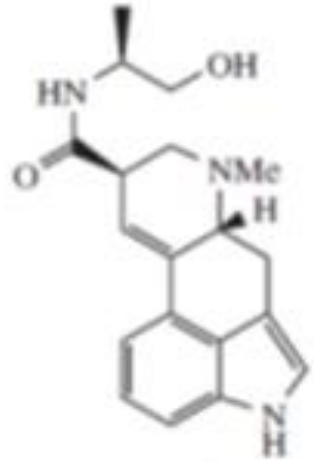
LSD



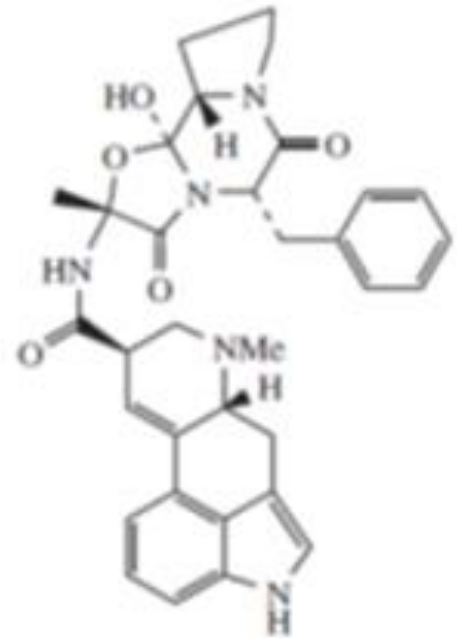
ergoline



R = OH, (+)-lysergic acid
R = NH_2, ergine



ergometrine



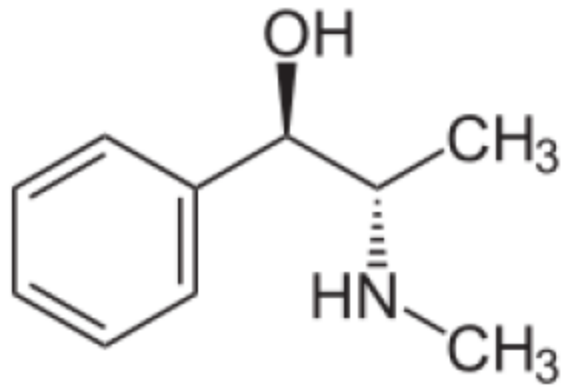
ergotamine

Phenylalanine derived alkaloids

- it's a **proto** alkaloids(means the **nitrogen** is **not part** of heterocyclic structure)
- **Ehpedra: (family: Asteracea)**
- It's very long plant, **leaves**, and **flowers** are considered as a **source** for **ephedrine**. We have many species of ephedra the **officially** one is **Ephedra sinica** and **Ephedra equisetina** used in **traditional Chinese medicine** for 5,000 years; also we have
- **ephedra intermedia**, and **ephedra geriardiea**.
- Now it's known as **herbal ecstasy** because it has **CNS stimulant** and **hallucination**.

Ephedrine (norephedrine)

- Synthesis from **phenylalanine** that provide **C6C3** structure, or **C6C2** (by **removing** of **carboxylate** gp), or **C6C1**. So **phenylalanine** goes **several steps**, the **first** is **removing of carboxylate** gp then we add **amino gp** or **alkyl** gp to produce **norephidrine** then we add **methyl** gp to produce ephedrine.
- **NOTE**: the **active** form of **ephedrine** is **levo** (-) form.

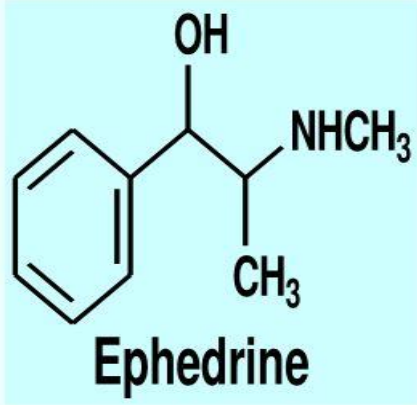


Ephedrine

Mixed-Action Adrenergic Agonists

- Mixed means Direct and Indirect actions.
- direct action on the adrenergic receptors.
- indirect effect on the release of NE from the storage site

- The prototype of this group is the natural alkaloid ephedrine.



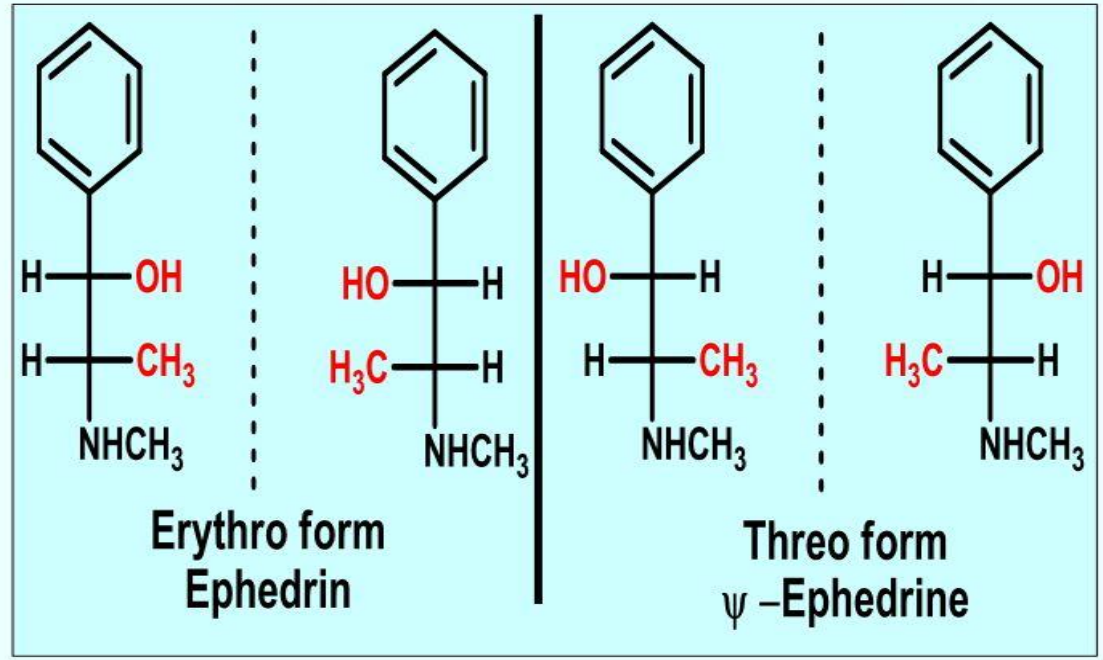
Ephedrine

What are the structural Features?

Ephedrine

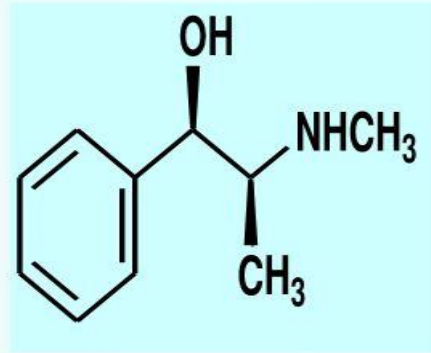
Ephedrine has two (asymmetric) chiral carbons: so four stereoisomers (4 optically active isomers that exist as two pairs of enantiomers.)

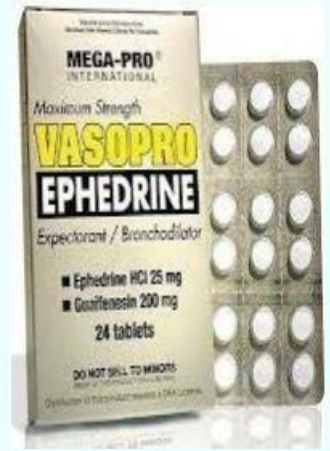
- The *erythro* pair is known as ephedrine.
- The *threo*- is known as pseudoephedrine (ψ-ephedrine).



See introductory part about stereochemistry of drug molecules

Ephedrine





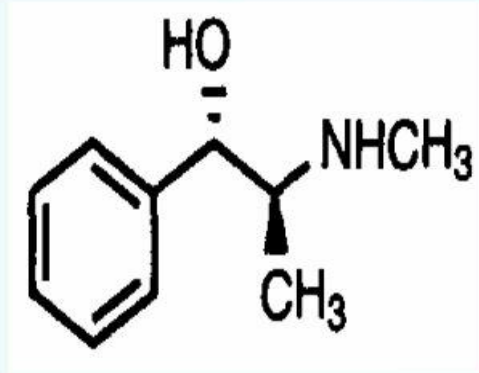
(-)-*Erythro*-2-(methylamino)-1-phenyl-1-propanol
(-)-*Erythro*- α-[(1-methylamino)ethyl] benzyl alcohol.

- It is available as HCl or as Sulphate. Can U draw ???
- Used by injection and orally.
- Used as adrenergic, as vasopressor, cardiac stimulant, nasal decongestant and bronchodilator and CNS stimulant activity .
- in hypotensive conditions
- In allergic disorders, colds, nasal congestion
- In asthma
- in narcolepsy

Catha edulis (celastraceae)

- A plant that causes physical and physiological addiction, known in the historical books as absenin tea , this word came from absenia (al-Yemen and Ethiopia) geographically they used to be one land then they separated from many different reasons . This plant is the reason of the retardation of these countries. In some countries like the UK, Khat is a plant that can legally used in small quantities

Pseudoephedrine



(+)-*Threo*-2-(methylamino)-1-phenyl-1-propanol

(+)-*Threo*-α-[(1-methylamino) ethyl] benzyl alcohol

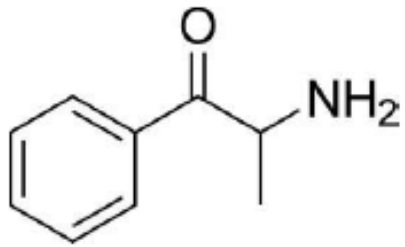
- Pseudoephedrine is the *threo*-diastereoisomer of ephedrine
- HCl and Sulphate salts
- has virtually no direct activity
- Mainly indirect action.
- widely used as nasal decongestant.

Catha edulis (celastraceae):

- A plant that causes physical and physiological addiction, known in the historical books as absenin tea , this word came from absenia (al-Yemen and Ethiopia) geographically they used to be one land then they separated from many different reasons . This plant is the reason of the retardation of these countries. In some
- countries like the UK, Khat is a plant that can legally used in small quantities.

The main compounds in this plant are

Cathinone: (ketonic) which is very similar to norepinephrine?



Cathine: (alcoholic or reduced) form of pseudoephedrine.