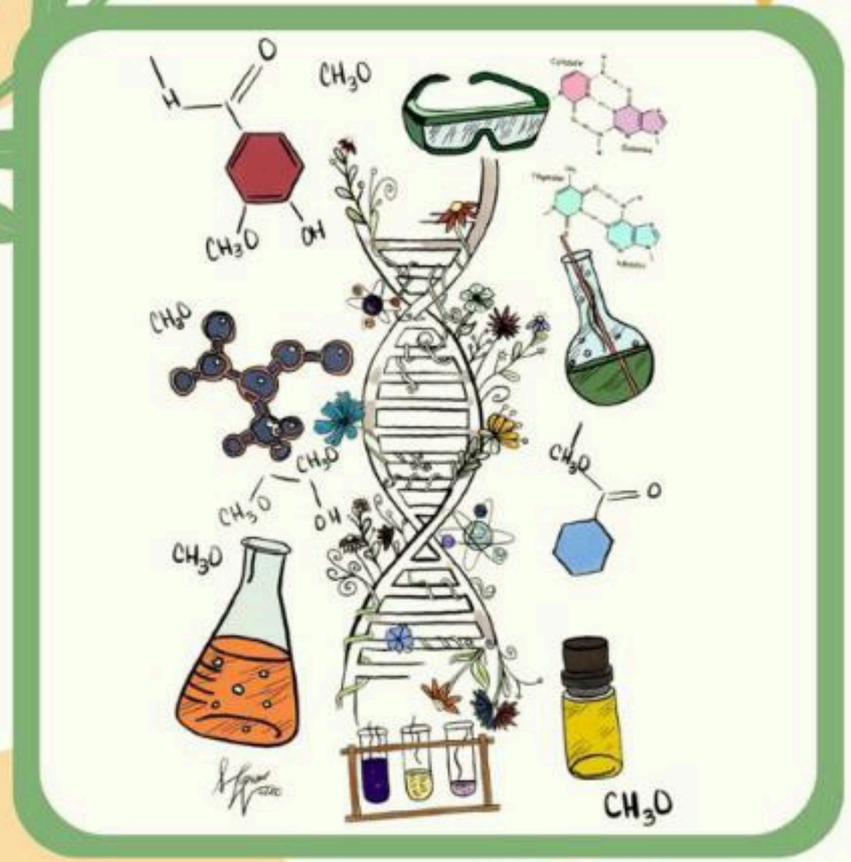
تفريغ عقاقير



اسم الموضوع: Indole and proto alkaloids

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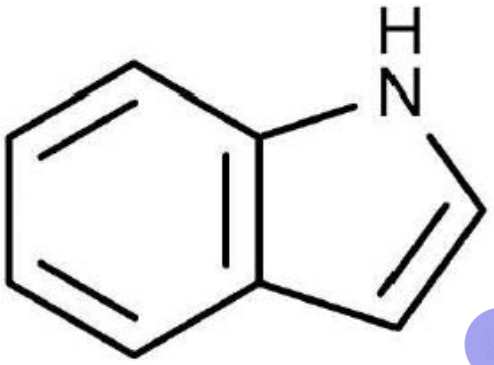
Soul Academy

لجان الدفعات

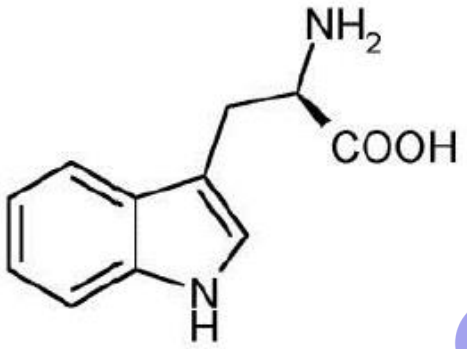
Indole and proto alkaloids

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.

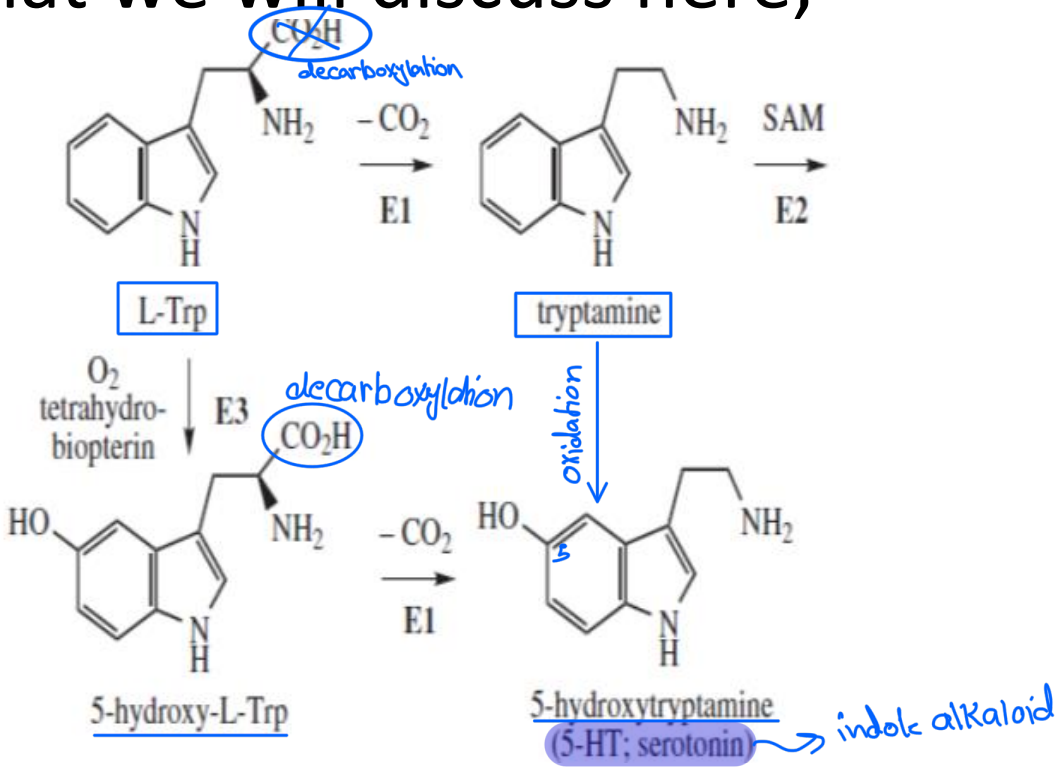


← indole



← 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.

- Indole alkaloids derivatives including melatonin, serotonin & physostigmine
- These are 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.

5-Hydroxytryptamine

5-HT, Serotonin

هرمون السعادة

5-Hydroxytryptamine

- 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).**

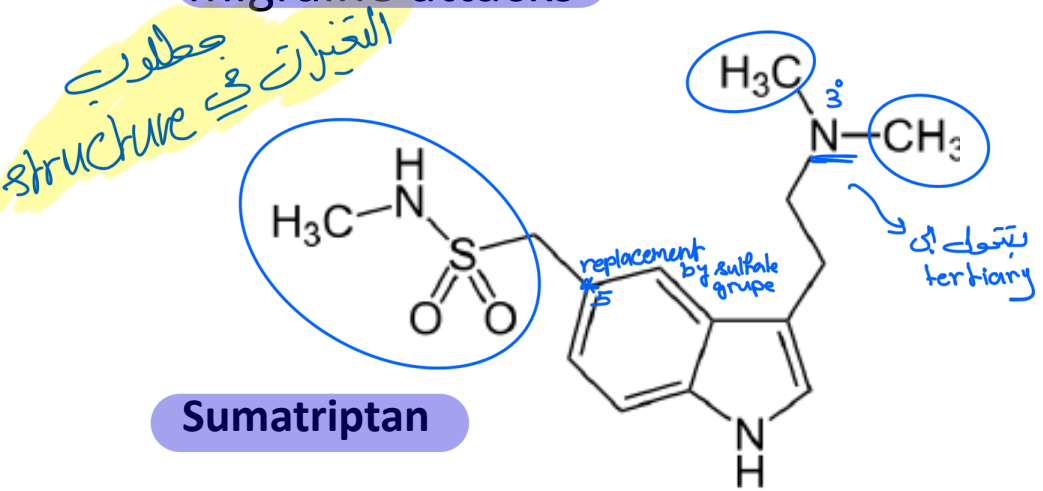
مضاد الكتئاب

- **PROZAC®** which contains **Fluoxetine** which is a **selective serotonin re-uptake inhibitors (SSRIs)** officially approved for treatment of depression

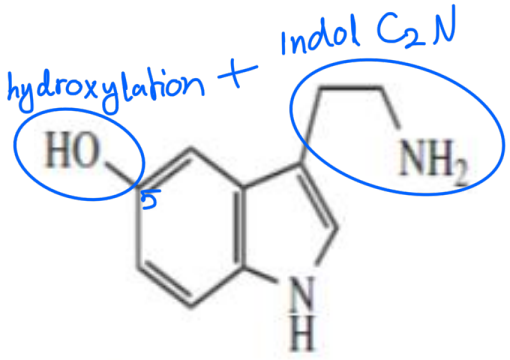
e.g. مثلاً

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



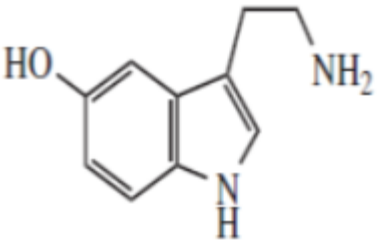
Sumatriptan



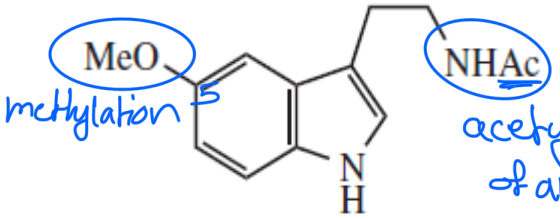
5-hydroxytryptamine
(5-HT; serotonin)

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

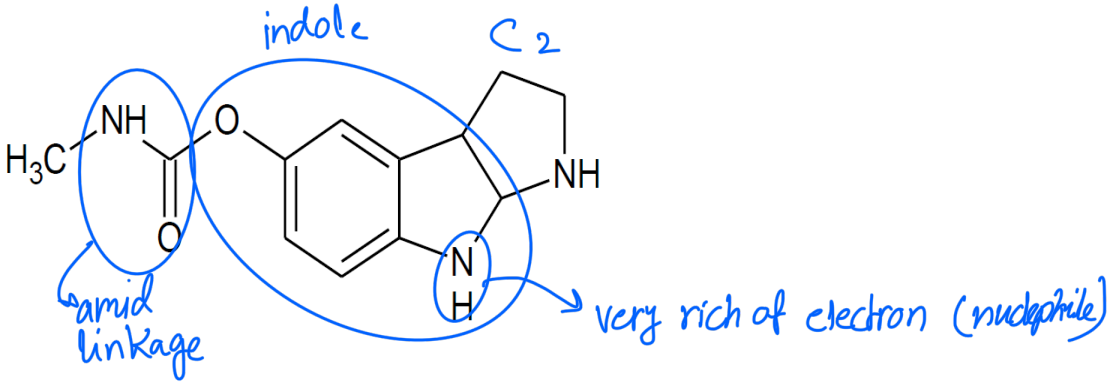
Melatonin

- 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.

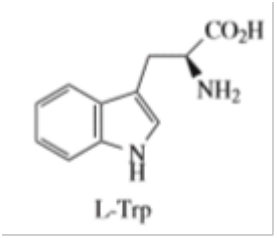
Physostigmine (eserine)

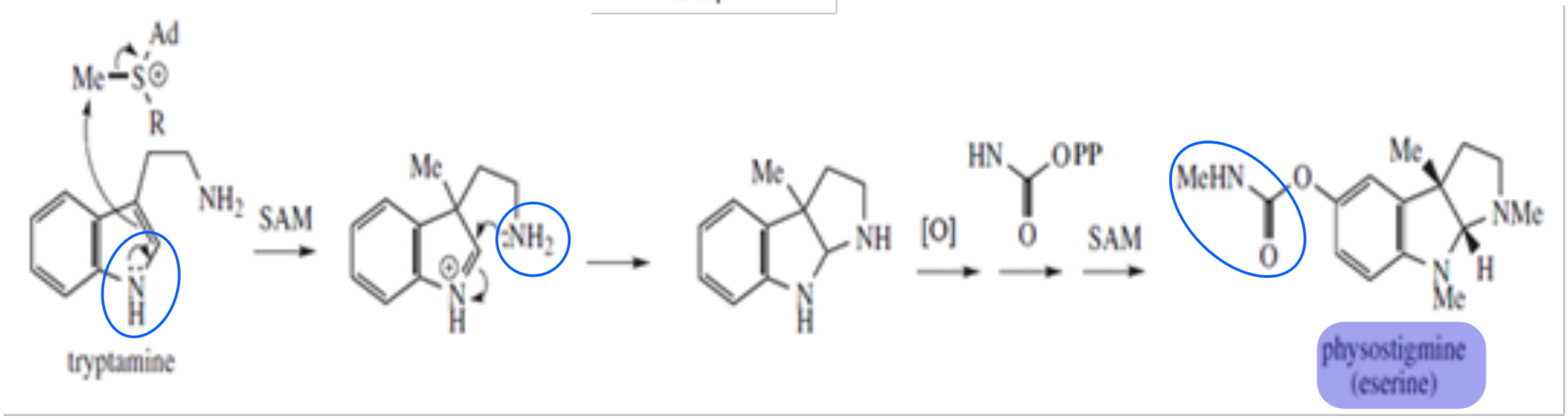
- Isolated from the seeds of the Physostigma venenosum ,this plant contain many alkaloids but the most important one is physostigmine.
- Physostigmine is a very unstable compound it oxidized easily,
- we can detect the deterioration of this compound by the color change that occur due to oxidation therefore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



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





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.

Physostigma venenosum:

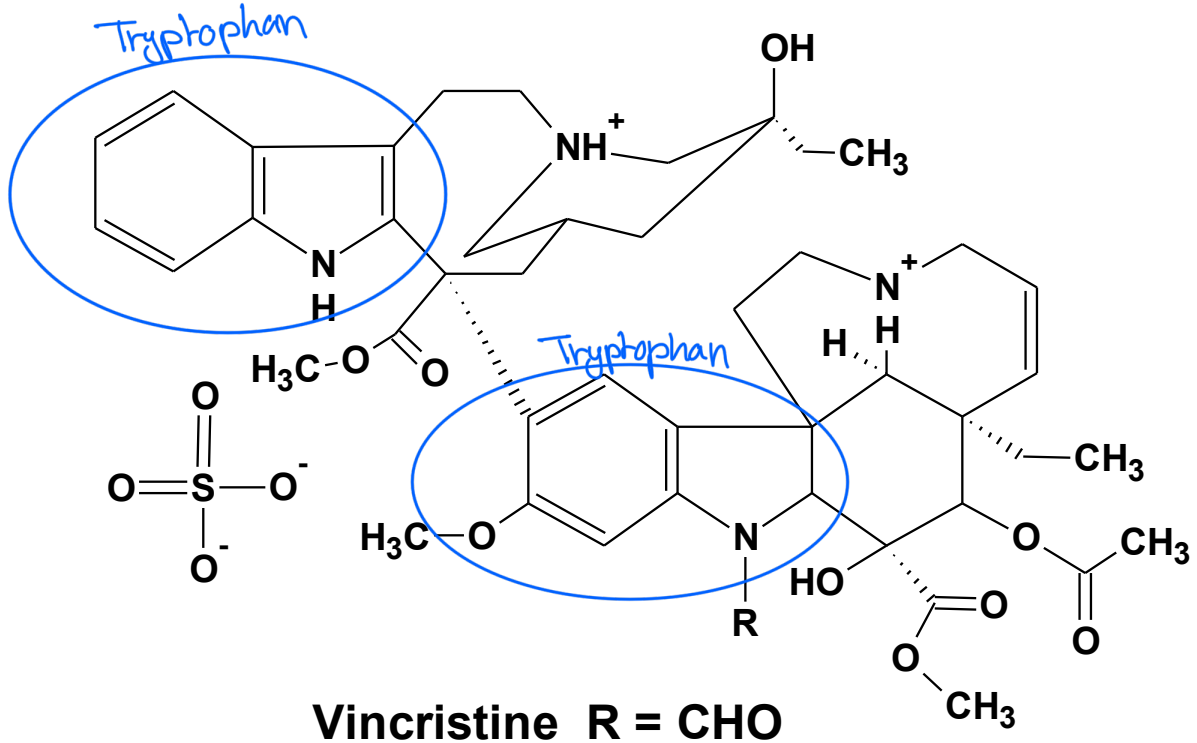
- From its name **venenosum**, it's **very toxic** plant, it comes from **seeds** of **calabar bean** (found in **Nigeria**), family: **Fabaceae**.

- 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).

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*)

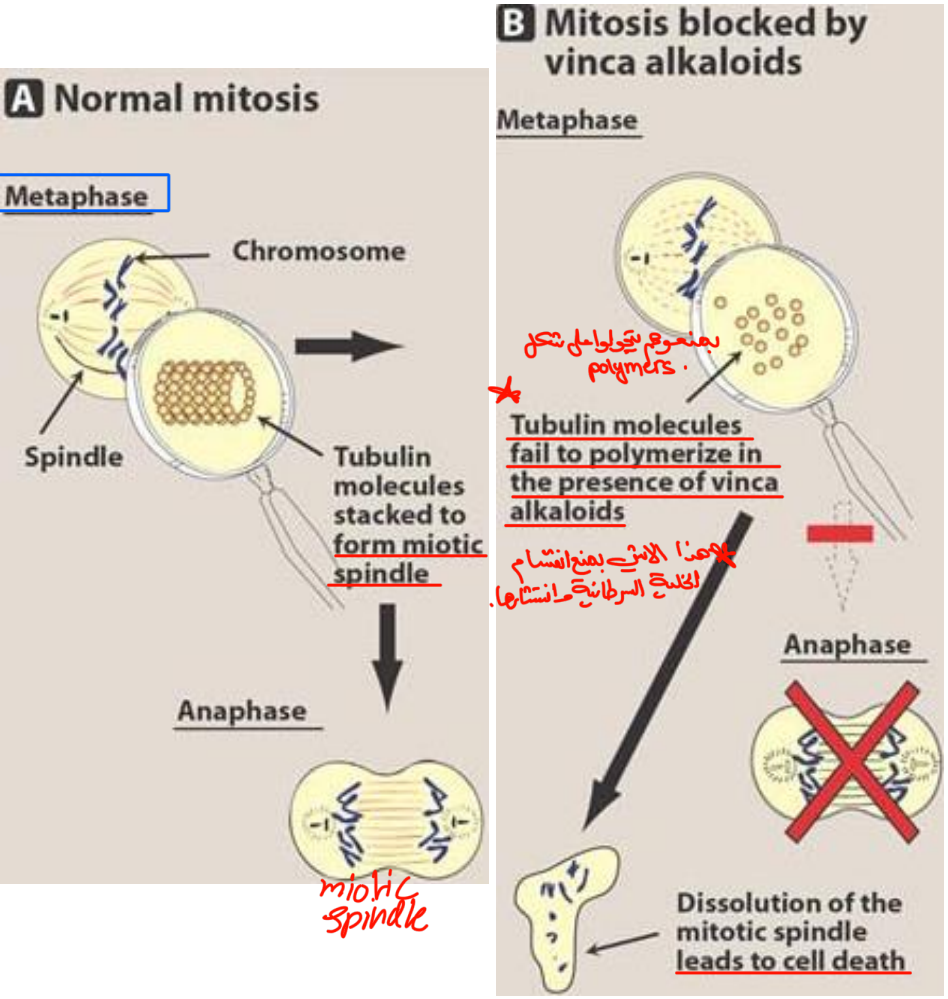


Vincristine R = CHO

Vinblastine R = CH_3

They are dimeric indole-dihydroindole derivatives

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

Ergot alkaloids ergoline

↘ fungal disease

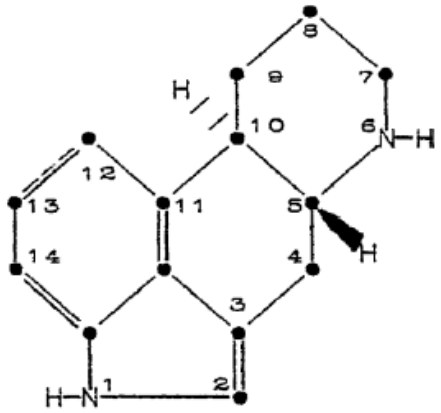
- Ergot alkaloids are isolated from infected plants (fungal infection).
- They are tryptophan derivatives

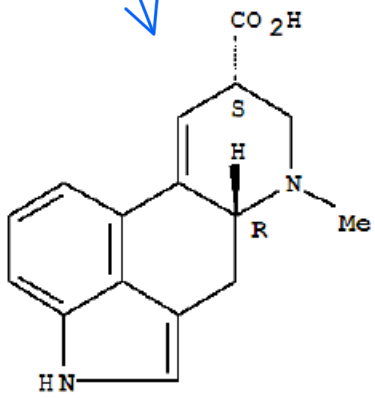
Ergot alkaloids

- 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.



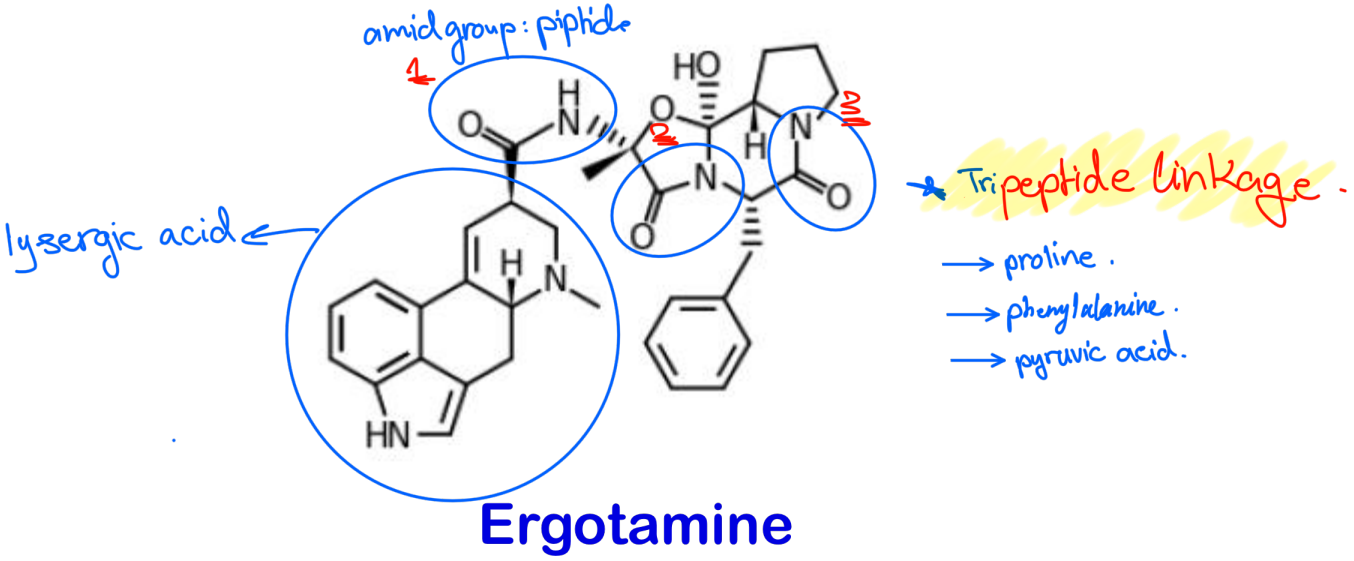


Isolysergic acid

Ergotamine:

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

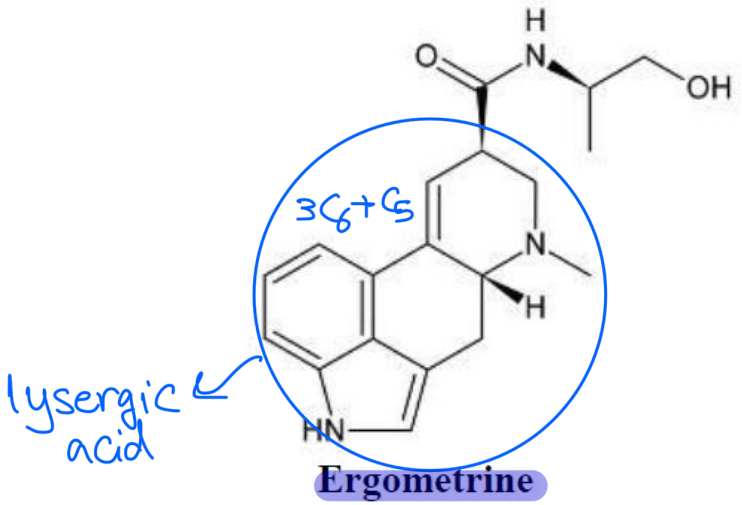
- **Ergotamine:**
- It's a **peptide** derivative contain **tripeptide** fragments **bonded** to lysergic acid via **amid** link. It's used for migraine
- the **hydrolysis** of **peptide ergot** alkaloids will produce **lysergic acid** + **proline** +**phenylalanine** + **pyruvic acid** +**ammonia**



Ergometrine

- Ergometrine 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.

عمليات الولادة القيصرية .

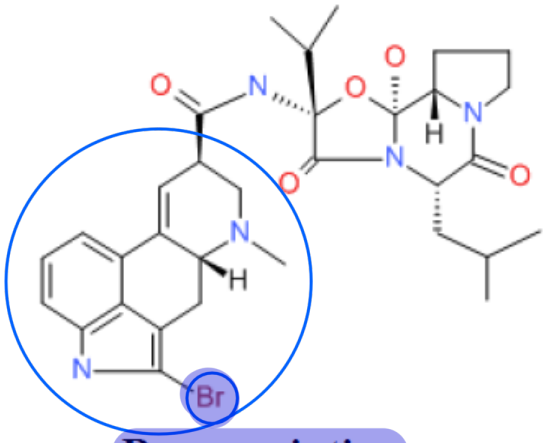


Bromocriptine:

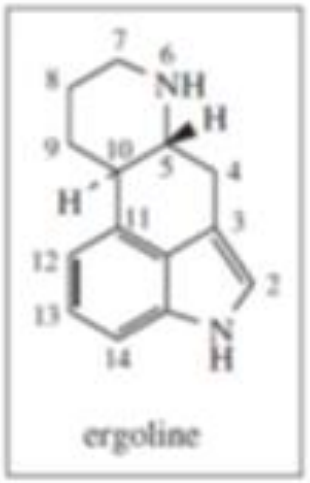
- It's very **cheap** compound, It's used to **inhibit prolactine** production, also useful in treatment of **Parkinson disease**
- It is a dopamine agonist that is used in the treatment of pituitary tumors, Parkinson's disease (PD), hyperprolactinaemia, and type 2 diabetes.
- It has **bromine** (Br)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

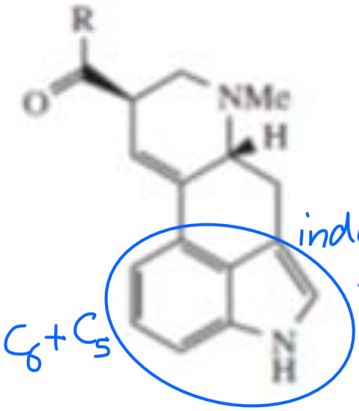
Bromocriptine is a semisynthetic derivative of a natural ergot alkaloid

Ergotamine
Ergometrine
Lysergic acid
Bromocriptine



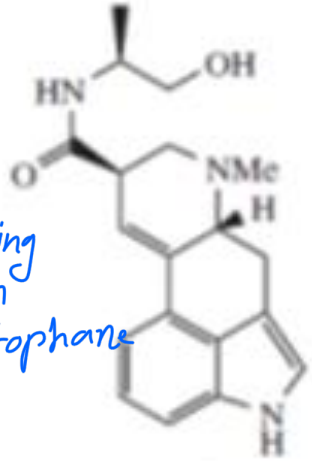
Bromocriptine



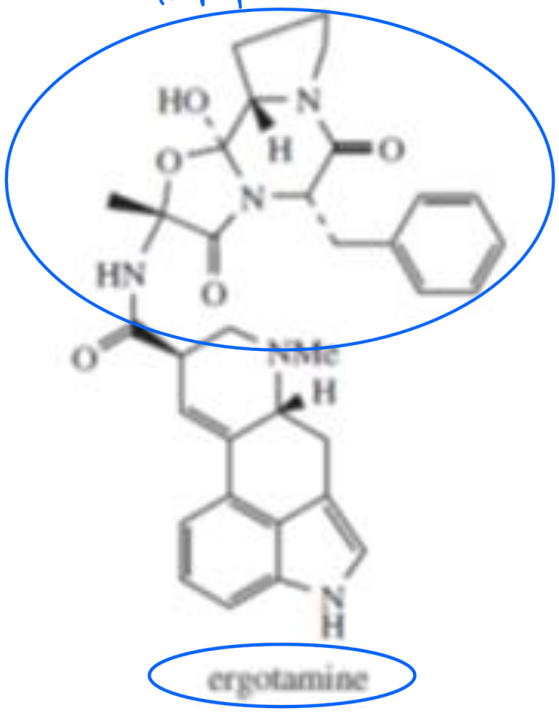


3 C6+C5

indole ring from tryptophane



Tripeptide



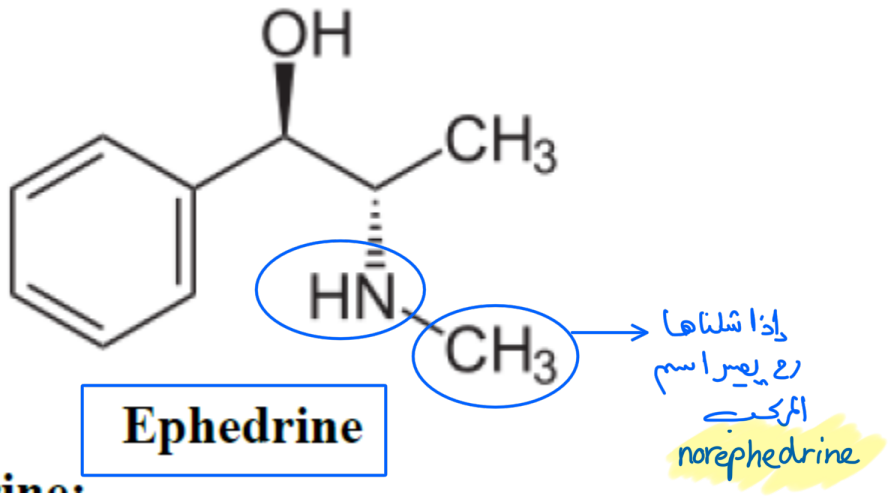
Proto alkaloids

- **proto** alkaloids(means the **nitrogen** is **not part** of heterocyclic structure) **derived from Phenylalanine**
- **Ehpedra: (family: Asteraceae)**
- It's very long plant, **leaves**, and **flowers** are considered as a **source** for **ephedrine**.
- Now it's known as **herbal ecstasy** because it has **CNS stimulant** and **hallucination**.

Ephedrine (norephedrine)

methyl group لاحظنا

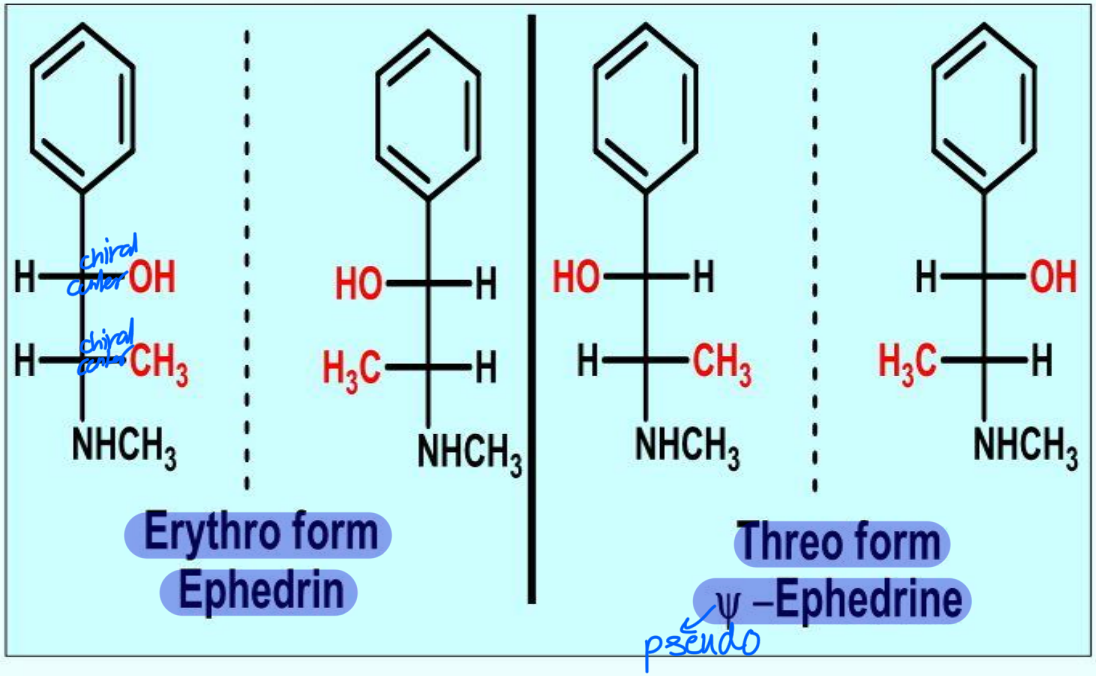
- Synthesis from **phenylalanine** that provide **C6C3** structure, or **C6C2** (by **removing** of **carboxylate** gp), or **C6C1**. So **phenylalanine** goes **several steps**, the **first** is **removing of carboxylate** gp then we add **amino gp** or **alkyl** gp to produce **norephidrine** then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



Ephedrine

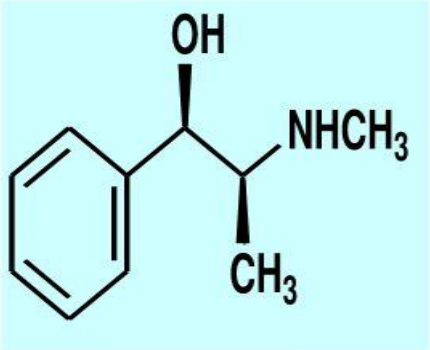
Ephedrine has two (asymmetric) chiral carbons: so four stereoisomers (4 optically active isomers that exist as two pairs of enantiomers.)

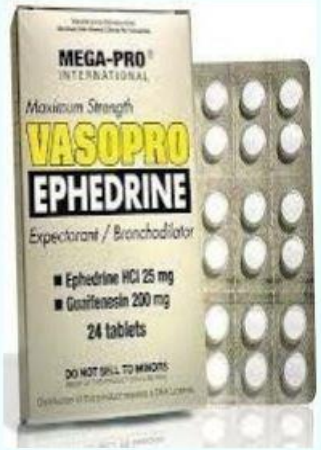
- The *erythro* pair is known as ephedrine.
- The *threo*- is known as pseudoephedrine (ψ-ephedrine).



See introductory part about stereochemistry of drug molecules

Ephedrine

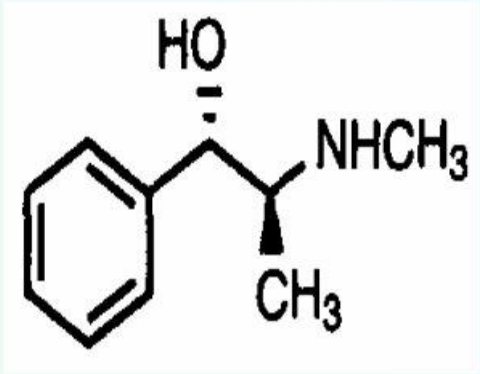




(-)-*Erythro*-2-(methylamino)-1-phenyl-1-propanol
(-)-*Erythro*- α-[(1-methylamino)ethyl] benzyl alcohol.

- 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

Pseudoephedrine



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

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

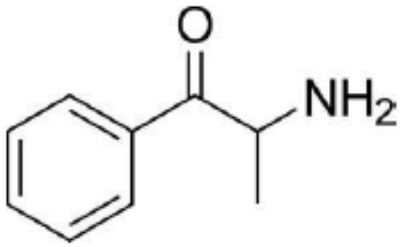
- Pseudoephedrine is the *threo*-diastereoisomer of ephedrine
- HCl and Sulphate salts
- has virtually no direct activity
- Mainly indirect action.
- widely used as nasal decongestant.

Catha edulis (celastraceae) قات

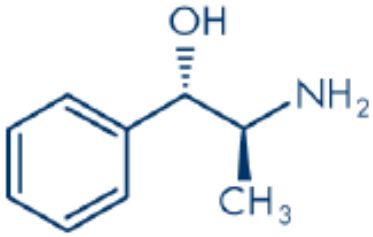
- A flowering plant contains alkaloid cathinone, a stimulant, which is said to cause excitement, loss of appetite, and euphoria

The main compounds in this plant are

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



Cathine: (alcoholic or reduced) form of pseudoephedrine.



- These two compounds have an effect on the brain barrier in the CNS, due to the similarity in structure with amphetamines (a compound already found on the nerve barriers); some people may take amphetamine supplements to have euphoria, restlessness and to stay awake for a long time. People can gain this effect by suckling the leaves of this plant.
- only fresh leaves contain cathinone and cathine, while the dried ones don't, and upon drying cathinone is converted to another derivative.

- **Mechanism of action :** when cathonine attacks the barrier in the CNS,this attack will lead to high secretion of catecholamines ,with time, as a result tolerance might happen and the person need to take higher amount than the previous one. So who usually take cathonine for a long periods of time, will need higher doses due to tolerance. To stop the effect of Khat, take a CNS depressant; like barbiturates or opioids (compounds from opium like morphine) that terminate the effect of

- Khat is not used for its pharmacological effect anymore. In the past they used to use khat in the treatment of addiction, now it's abused because of the psychological dependence and some people may die because of the tolerance.