Benha University **Faculty of Science** **Chemistry Department**	كلية العلوم	**Date : June, 10th 2019** **Time : 2 hrs.** **Natural products &applications** **Code (720 Ch)** **Ph.D Students**

الإجابة النموذجية لامتحان مادة المنتجات الطبيعية وتطبيقاتها

كود المادة: (720 ك)

(ورقة امتحانية كاملة)

المستوى : تمهيدى دكتوراه كيمياء عضوية

التاريخ : الاثنين 10 / 6 / 2019

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قسم : الكيمياء

كلية : العلوم

*Answer the following questions: (80 Marks)

1. Discuss the following (2 x 10 = 20 mark)

a. Features of the steroid receptor proteins

The receptor amino acid sequences are deduced from the sequence of the cloned receptor genes. By comparing the sequences of receptors for different hormones and the sequences of receptors for the same hormone from different species, and by experiments using the cloned receptors, it has been discovered that the receptor proteins contain three main regions (Figure 1).

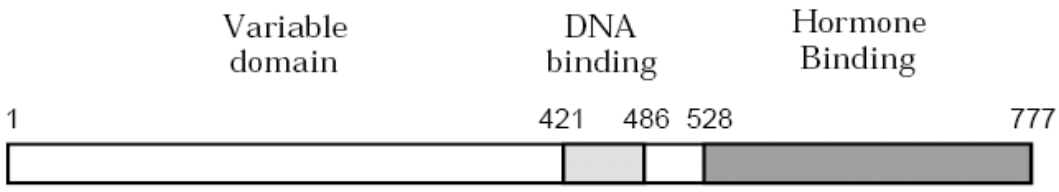


Figure 1. Schematic of the glucocorticoid receptor (GR Type II)

One region, a short segment of about 70 amino acids, is the part of the protein that specifically binds DNA, and is the most highly conserved part of the protein. An approximately 250 amino acid region at or near the C-terminus of the protein is the hormone binding domain. Finally, there is a third region at the (the variable domain) that is by far the least conserved, in either length or amino acid sequence. This last region is responsible for mediating some of the transcriptional effects of the protein. Table III shows the percent amino acid sequence identity of the different regions relative to the corresponding part of the glucocorticoid Type II receptor.

The receptors are divided into three sub-families by similarities of protein sequence and by some functional aspects: The GR Type I and II, progesterone, and androgen receptors form one family; the estrogen receptor forms a family of least two genes for the same ligand (as well as some closely related orphan receptors);

and the Vitamin D, thyroid hormone, and the two types of retinoic acid receptors comprise a third family.

b. Mechanism of steroid hormone receptor

It has not yet been possible to determine the three-dimensional structure of one of the steroid hormone receptors, and there are many gaps in our understanding of mechanism by which the interaction of the steroid hormone with its receptor elicits a biological effect. The following discussion presents a working model for steroid hormone action at the molecular level. The model is certainly incomplete, is somewhat simplified, and may be incorrect in some details, but represents a picture of the current consensus opinion.

The receptors for retinoic acid, thyroid hormone, and Vitamin D appear to be tightly associated with DNA in both the presence and absence of hormone. For the thyroid hormone receptor, in particular, the effect of hormone appears change the nature of the receptor activity from a negative effect to a positive effect.

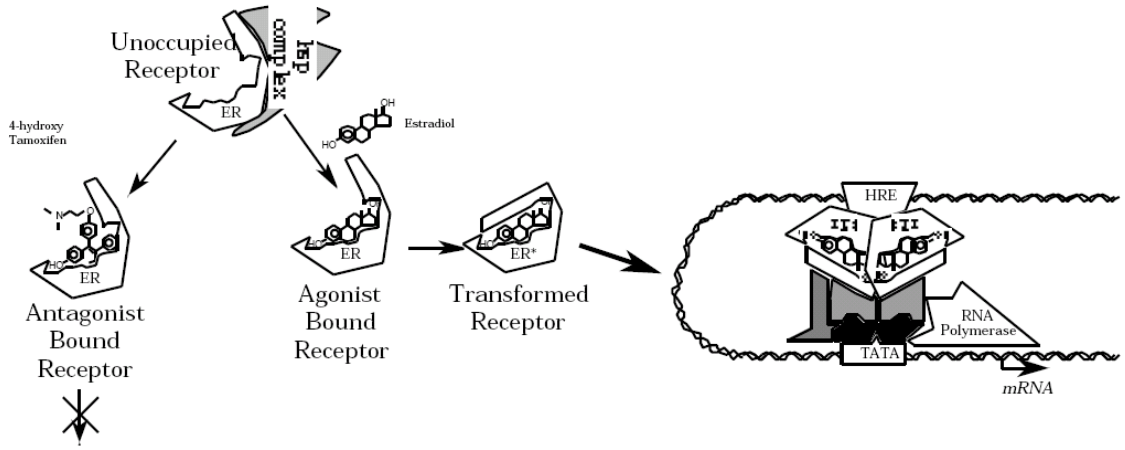
In contrast, the receptors for the steroid hormones are, at most, loosely associated with the DNA (or the chromatin) in the absence of hormone. In addition, ligand-free steroid receptors are probably bound to several other proteins, including hsp90 (hsp = heat shock protein, 90 refers to the fact that this particular heat shock protein has a molecular weight of 90,000) and hsp70. The hsp complex is

thought to both stabilize the receptor and prevent the unoccupied receptor from affecting gene transcription. The hsp complex proteins dissociate from the receptor upon ligand binding.

The receptors for retinoic acid, thyroid hormone, and Vitamin D are thought not to form these complexes.

The model shown in the foolwing figure uses the estrogen receptor as an example; all of the steroid hormone receptors are thought to work by similar mechanisms, although the ligands are different. If an antagonist (shown in Figure 11 as 4-hydroxy-tamoxifen, but the same principle applies to all steroid hormone antagonists) binds to the

receptor, nothing happens. This "nothing" can be profound therapeutically, because as long as an antagonist is bound to the receptor, the receptor cannot bind an agonist, and therefore a hormone, *even if present*, has no effect. On the other hand, if an agonist binds, the receptor undergoes an event called "activation" or "transformation". The nature of this event is not yet clear, but it probably involves a conformational change within the hormone binding domain. The activated receptor binds a specific type of enhancer DNA sequence called a hormone response element (HRE). (Note that an HRE is a region of DNA just like any other except for the specific sequence -- the real DNA double helix does not have a box labeled HRE!) The receptor dimer can also interact with other transcription factors (shown in the following figure as irregular polygons with various patterns). The transcription factors that comprise this complex are not yet fully characterized, and probably vary in different cell types and/or for different genes. It is thought that the presence of the activated receptor stabilizes the complex formed by the other transcription factors and stimulates the binding of RNA polymerase, and as a result, initiation of RNA synthesis.



2- Outline on the major classes of steroid hormones (20 Mark)

In human endocrine physiology, there are three major classes of steroid hormones: glucocorticoids, mineralocorticoids, and the sex steroids. The following discussion is intended only to point out a few of the structural differences among

these types; thefunction of some of these steroids (glucocorticoids and mineralocorticoids).

***1) Glucocorticoids*:** steroid hormones that affect energy metabolism (among a large variety of other actions). The primary glucocorticoid in humans is cortisol (Figure 1).

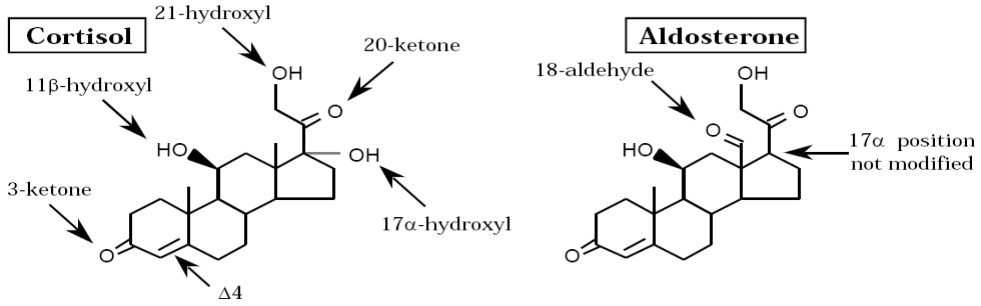


Figure 1. The structures of the primary human glucocorticoid steroid hormone, cortisol (4-pregnene-11β,17α,21-triol-3,20-dione), and of the primary human mineralocorticoid, aldosterone (4-pregnene-11β,21-diol-3,18,20-trione).

2) *Mineralocorticoids*: steroid hormones that affect electrolyte balance. The primary human mineralocorticoid, aldosterone, is also shown in Figure 2. Note that it is structurally very similar to cortisol, except that it lacks the 17α-hydroxyl group, and has an aldehyde at the 18-methyl. The 18-aldehyde is critical for mineralocorticoid activity; the sole difference between corticosterone and aldosterone is the 18-aldehyde, but aldosterone has 200 times higher mineralocorticoid activity than corticosterone.

3) *Sex steroids*: steroid hormones that affect sexual development and reproductive functioning. There are three types of sex steroids in humans: progestins, androgens, and estrogens. Representative structures of these hormones are shown in Figure 2.

The human *progestin* is progesterone, which is a *21-carbon* (pregnane) 3-keto Δ4 steroid like cortisol and aldosterone. In addition to its hormonal function, progesterone is also a precursor to the other hormonal steroids, and therefore it has fewer modifications from the basic steroid backbone.

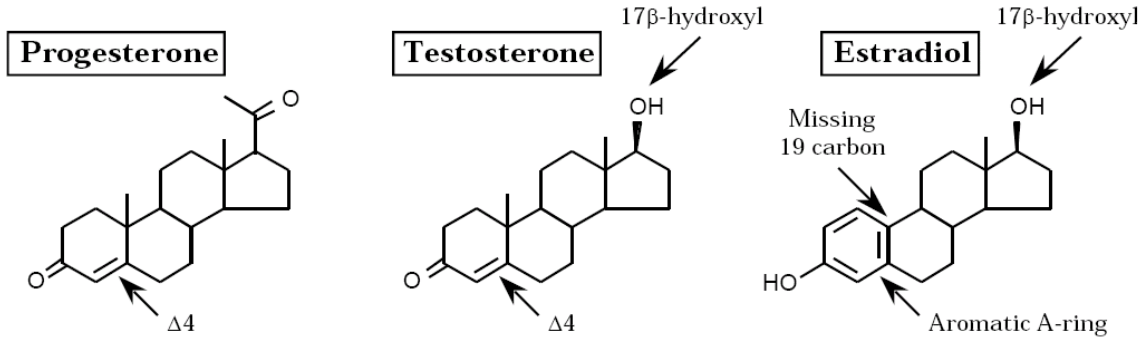


Figure 2. The structures of the sex steroids: the progestin progesterone (4-pregnene-3,20-dione), the androgen testosterone (4-androstene-17β-ol-3-one), and the estrogen estradiol (1,3,5(10)-estratriene-3,17β-diol).

3- Write on the chemistry of terpenoids? (20 Mark)

In general, **terpenoids**, may be defined as natural products whose structures are considered to be divided into several isoprene units; therefore, these compounds are invariably termed as **isoprenoids**. Besides, this particular group of compounds is sometimes collectively referred to as the **terpenes** in relatively older texts. Logically, the *–oid* suffix seems to be more acceptable and convincing, as it is in the same vein for steroids, alkaloids, flavonoids, etc., However, the-*ene* suffix must be solely confined to the unsaturated hydrocarbon belonging to this specific class of compounds. It has now been established experimentally that the **isoprene units** come into being through the biogenetic means starting from acetate *via* mevalonic acid. Each such unit essentially consists of five-carbons having two unsaturated bonds and possesses a branched chain. The **terpenoids** usually have a number of such **isoprene units** joined together *in a head to tail manner*, as exemplified below:

Terpenoids are broadly classified on the basis of the number of **isoprene units** incorporated into a **specific unsaturated hydrocarbon terpenoid molecule,** as

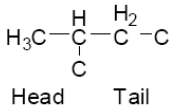
(*a*) **Monoterpenoids:** These are built up of *two* isoprene units and have the **molecularformula C10H16;**

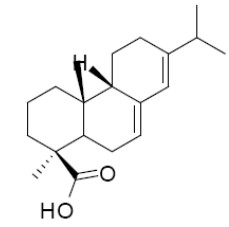
(*b*) **Sesquiterpenoids:** These are composed of *three* isoprene units and have the **molecular formula C15H24;**

(*c*) **Diterpenoids:** These are comprised of *four* isoprene units and have the **molecularformula C20H32;**

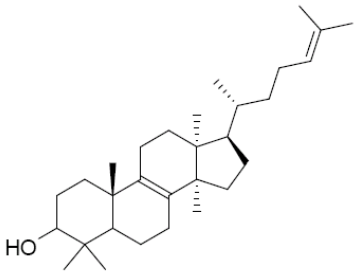
(*d*) **Triterpenoids:** These contain *six* isoprene units and have the **molecular formula C30H48;** and

(*e*) **Tetraterpenoids** These are made up of *eight* isoprene units and have the **molecular formula (Carotenoids): formula C40H64**





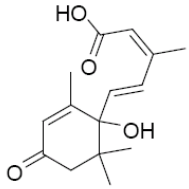
abietic acid diterpene



lanosterol triterpenoid

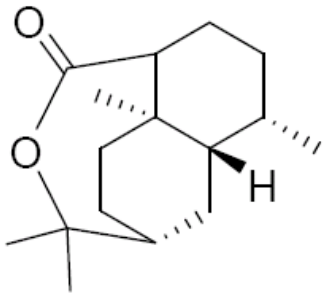
Sesisquiterpenoid

Consist of 3 isoprene units, could be mono, di or tri cyclic compounds, example abscicic acid.

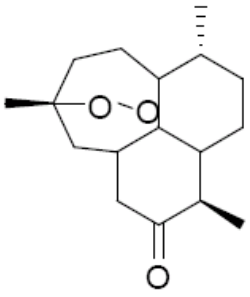


abscisic acid
monocyclic sesquiterpenoid

Sesquiterpenoid Lactones Interestingly, another class of compounds essentially bearing such characteristic features as a **methylene, lactone system; β-unsaturated carbonyls,** and **epoxides** and obiviously chemically distinct from the **sesquiterpenoids** are collectively termed as **sesquiterpenoid lactones**. The specific and vital **biological nucleophilies** *e.g.*; thiol and amino moieties present in the enzymes, help in the augmentation of faster and reactive approach to receptor sites by these **sesquiterpenoid lactones.** Thus, the overall effect is evidenced by marked and pronounced biological activities, for instance: modified antimicrobial activity, enhanced antitumour properties.



Eudesmanolide

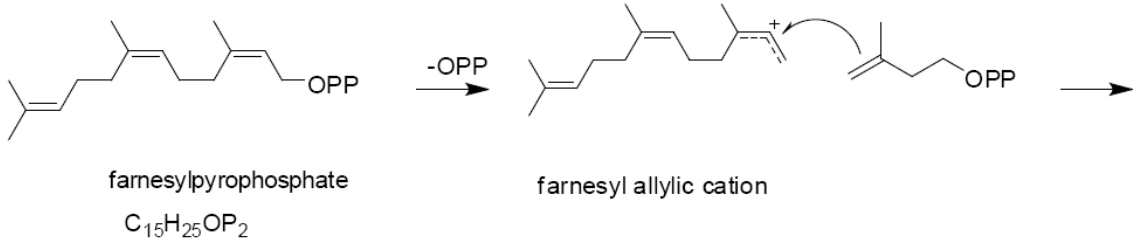


Artemisinin

Diterpenoids

Generally, **diterpenoid** represent a broad class of non-volatile C2O compounds that have been essentially obtained from **geranyl pyrophosphate.**

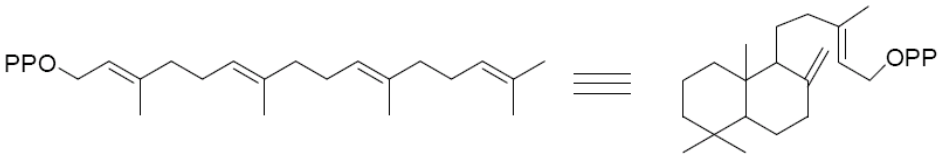
Biosynthesis of diterpenoid



farnesylpyrophosphate

$C_{15}H_{25}OP_2$

farnesyl allylic cation



geranylgeranylpyrophosphate

$C_{20}H_{33}OP_2$

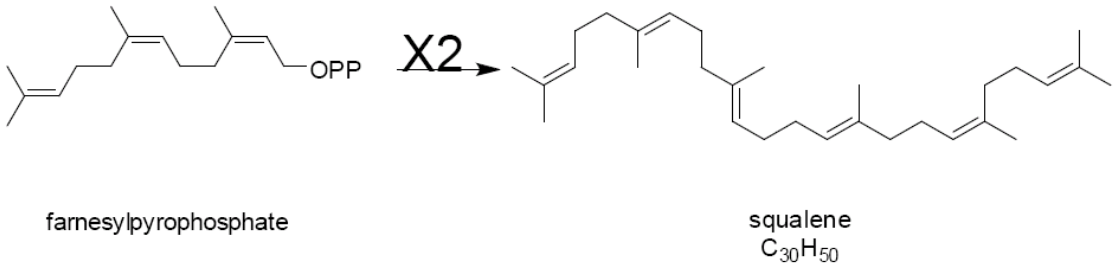
LDPP

Biosynthesis of diterpenoid

Triterpenoids

Generally are obtained by biogenesis from six isoprene units, They are found to share commonly the acyclic precursor **squalene** (C30). Based on the various possible modes, whereby ring closure in squalene takes place may ultimately give rise to a large number of triterpenoids having a variety of skeleton structures. In actual practice, more than 4000 naturally occurring triterpenoids have been isolated and identified, and over 40 varying skeleton types have been established.The **triperpenoids** may be categorized into two major groups, namely: the tetracyclic and the pentacyclic compounds: the former ones of the steroidal types with C-27

carbon atoms present in the skeleton while the latter are of the triterpenoid types with C-30 carbon atoms

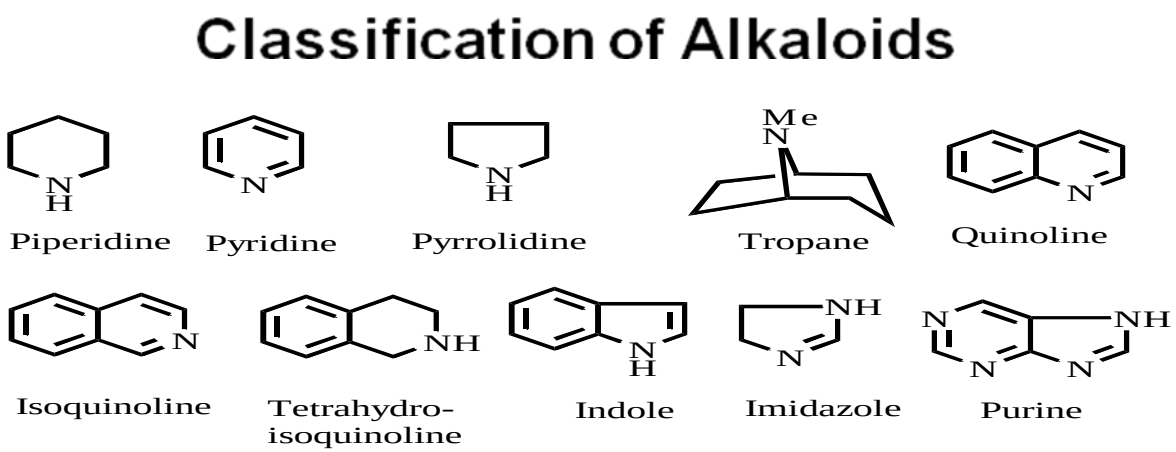


farnesylpyrophosphate

squalene
$C_{30}H_{50}$

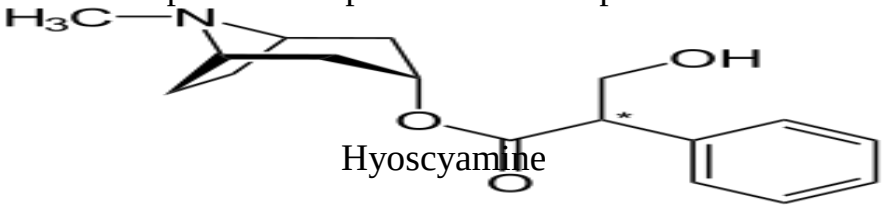
Biosynthesis of triterpene

4- Explain the application and classification of alkaloids ? (20 Mark)



Main Alkaloids are:

-Atropine.
- Hyoscyamine.
- Hyoscine (Scopolamine).
-Hyoscyamine is the major natural alkaloid with negative optical rotation (*l*-form).
-During extraction hyoscyamine racemizes to the optically inactive *dl* Atropine.
-Both alkaloids composed of tropine base and tropic acid.

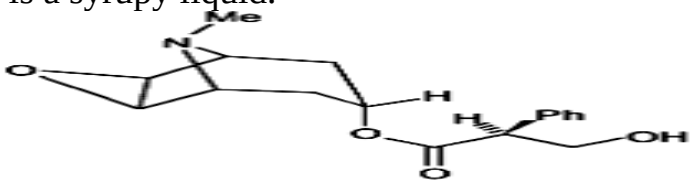


Hyoscyamine

Hyoscine (Scopolamine)

-Hyoscine is an ester of *l*-tropic acid with scopoline base.

-Hyoscine is a syrupy liquid.



Pharmacological actions and uses:

The three Alkaloids are anticholinergic agents:

-Decrease saliva and GIT secretions so used preoperative.

-Decrease motility of smooth muscles so used as antispasmodics.

-Stimulate respiratory system.

-A mydriatic (causes dilatation of the eye pupil).

-An antidote to organophosphorus insecticides.

-Hyoscine has more central effect so it is sedative and hypnotic.

-Hyoscine is mainly used as antiemetic.

Cocaine alkaloids Occurrence:

-Coca leaves contain about 2% total alkaloids

-It is the major Alkaloid in Coca leaves.

-Cocaine is diester Alkaloid.

-Heating at 160 0C in conc. HCl leads to hydrolyses of cacaine to MeOH, Benzoic acid and Ecogonine base.

Main Alkaloids are:

-Cocaine.

- Cinnamylcocaine.

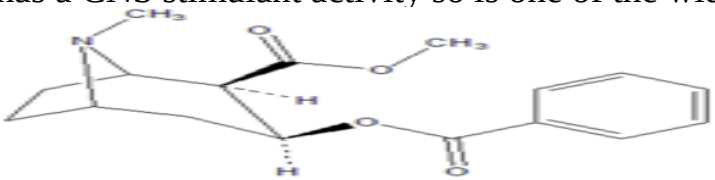
- truxilline.

The base for Coca Alakloid is called "Ecogonine"

Uses:

-Cocaine was used as local anesthetic

-Cocaine has a CNS stimulant activity so is one of the widely abused drugs.



Quinoline alkaloid:

Cinchona Alkaloid :

It diverting to 4 main compound:

-Quinine. -Cinchonine.

-Cinchonidine. - Quinidine

Biosynthetic origin:

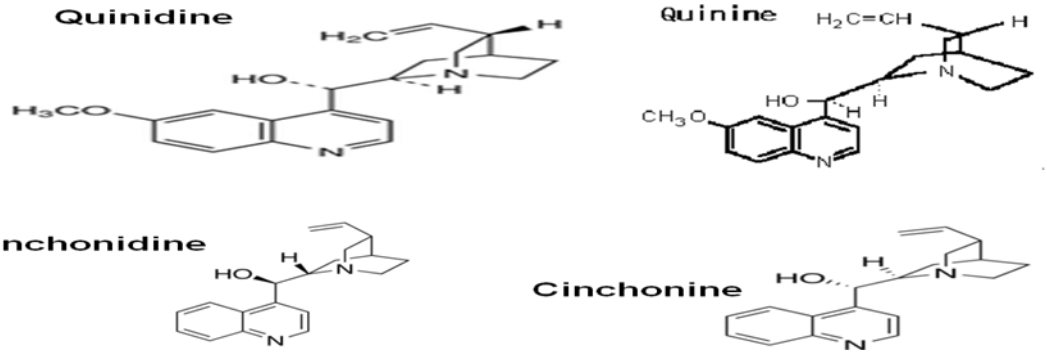
Botanical source: dried barks of (*Cinchona succirubra* Rubeaceae).

Pharmacological effect:

Antimalaria

Antiarhythmitic

Detection under U.V 366nm blue fluorescent with sulfuric acid.



Pyridine alkaloids and Nicotinic acid derivatives:

Biosynthetic origin:

- Nicotine: very toxic compound

-Botanical source: leaves *Nicotiana tobacum* Solanaceae

-Pharmacological effect:

-It works on nicotinic receptor (start by stimulation then inhibition.

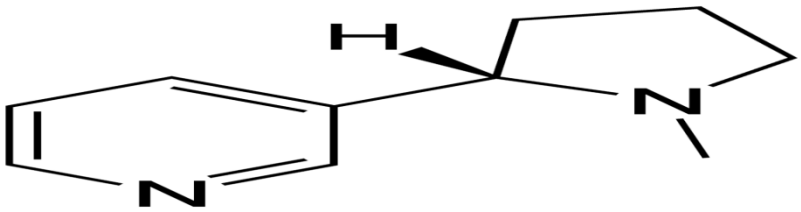
-Highly hydrophobic, so can cross blood brain barrier.

-**Uses as**: Vehicle on CNS (stimulant), dental carries, Alzheimer ????

-It's liquid compound, yellowish.

Oxidized by light and will form brown color.

Toxicity: Cancer which give nitrous amine (very nuclephilic) lead to change in DNA structure, Pulmonary and cardiac disease, Effect in hepatic system lead to increase metabolite



Piperdin

Biosynthetic origin:

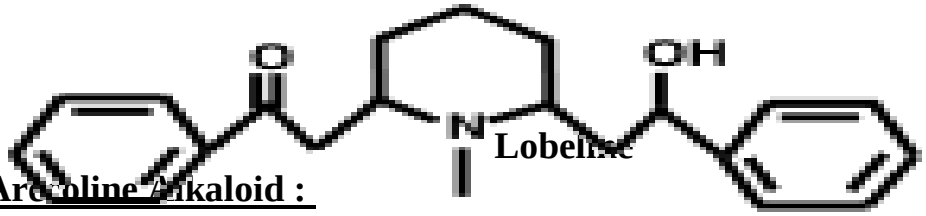
-Botanical sours form *Lobelia inflata* Lobeliaece.

Pharmacological effect:

-CNS Stimulant (cholinergic agonist).

-**Uses**: For premature babies (has Problem in respiration) so give cortisone to dilution lung.

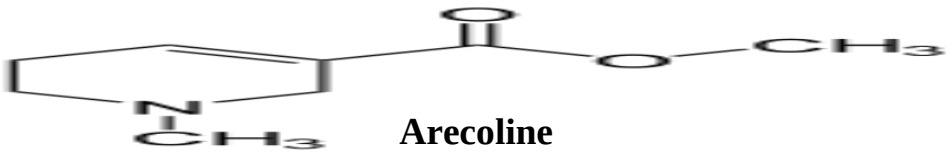
-High dose cause tonic spasm for skeletal and smooth muscle.



Lobeline

Arecoline Alkaloid :

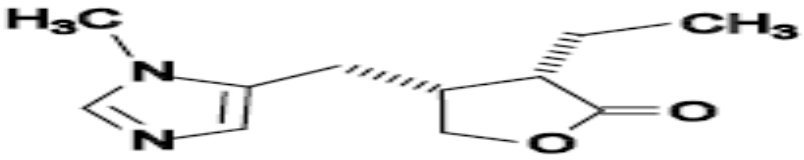
-Botanical sours are seed of *Areca catechu* Arecaceae.
-Pharmacological action: Parasympathomimetic work on messianic receptor and in high dose work on nicotinic receptor
-Uses:, Alzheimer disease, has Psychocyco active effect "Cigarette as cocaine in malaise".
-It causes redness of mouth, teeth an saliva, when use for long time cause buccal cancer.



Arecoline

Imidazole Alkaloid

Biosynthetic origin:
-**Examples**: Pilocarpine
-**Botanical sours** are *Pilocarpus jaborandi* Rutaceae.
-**Pharmacological effect**: Parasympathomimetic
-**Uses**: in Glaucoma (wide and narrow angle Glaucoma) and myosis of the eye.
-Keep away from light.
-**Side effect**: bronco contraction, brady cardiac, not first choice for glaucoma because headache and increase in lacrimation.



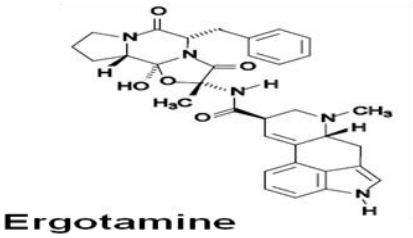
Indole alkaloid: (Periwincle, Rauwolfia, Nux-vomica, physostigma, Ergot)

-**Biosynthetic origin:** Ergot: fungus grow on Rye and Cereals.
- Botanical sours are fungus of *Claceveceps purpurea* Clavecpetaceae
-Sant antony fire→ inflammation → redness then vasoconstriction (cyanosis) → loss limbs and extremities the death.
-Convulsion and delirium.

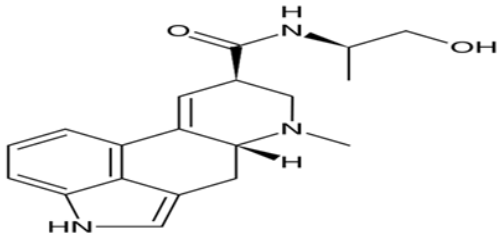
Erogtamine:
-It has low D.O.A, introduction of of double bound (9-10) lead to increase D.O.A.
Ergotamine and Ergometrine: & dopamine and Serotonin. & Lysergic acid (LSD)

Uses of Ergotamine:

-Migraine (at low dose has agonist adrenergic).
-Make vasoconstriction.
-Oxytocic (stimulate or induce labor).
- Postpartum hemorrhage (vasoconstriction).



Ergotamine



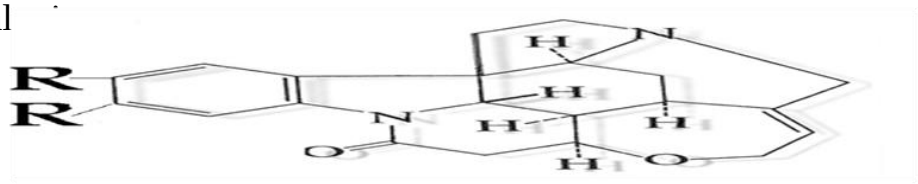
Ergometrine

–**Strychnine and Brucine:** Nux-vomica

-**Botanical source:** Seed of S*trychnus nux-vomica* Loganiaceae.
-Very toxic compound which block Neurotransmission from the spinal cord to the brain.
- Used only for study the sympathetic and parasympathetic action of drug.

Detection :

-Nitric acid: strychnine will give yellow PPT.
- Brucine will give red PPT.
-Chemical :



R= H: Strychnine
R= OCH3: Brucine

Physostigmine and Neostigmine Alkaloid :

Biosynthetic origin: Botanical source Botanical sours are seed of *Physostigma vensum* Fabaceae.

Common name (Calaber been).

:Pharmacological effect:

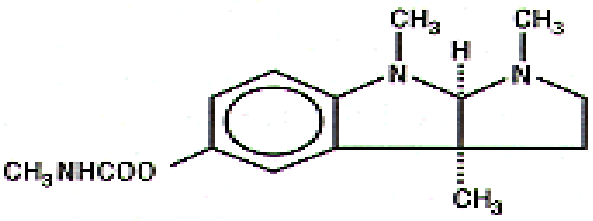
-Irreversible chorine esterase inhibitor (parasympathomimmtic).
-Used in acute open angle glaucoma will increase the contraction of ciliary's
- muscle and increase excretion of aqueous hummer and will decrease IOP.
-Give I.V or I.M for it toxicity, has unstable compound (ester and amide).
-Neostgmine: not indol alkaloid.

Action normalize contraction of striated muscle by facilities nerve imbuls.

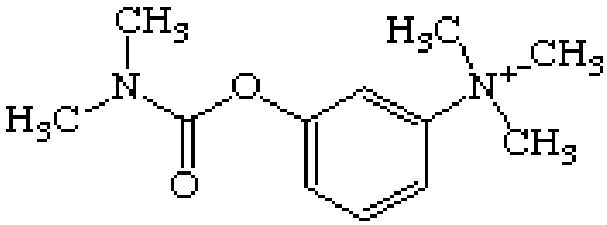
-Has positive charge (4° alkaloid).
-Soluble in water so can use be given S.C.

Used:

For diagnosis of myasthenia gravis.
Post operation Bladder surgery.
Side effect: Miosis, Convolution, Respiratory arrest, Brady cardiac.



Physostigmine 15



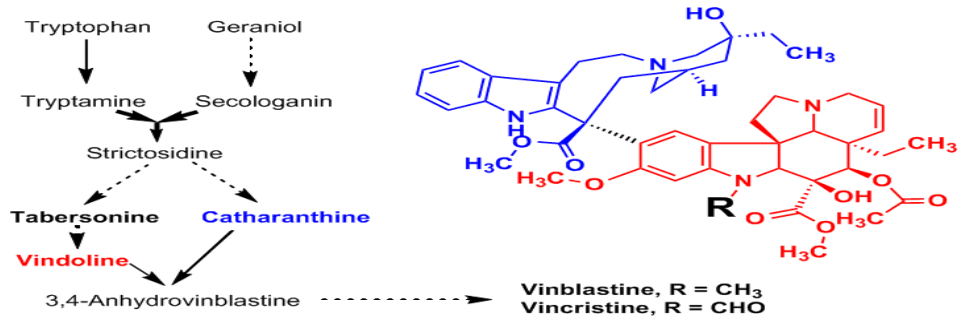
Neostigmine

Vicristine and vinblastine:

-**Biosynthetic origin**: -Botanical sours are Arial part of C*atharanthus roseus* (*Vinca rosa*) Apocynaceae.
-**Pharmacological effect**: It's cytotoxic used for hodgkins and non hodgkins disease.
-**Used**: Anticancer single or combination therapy.
M.O.A: bind to protein (tubulin) which inhibits mitosis in microtubules.
Side effect: Alopecia, Gastrointestinal (Nausea, vomiting, ulcer). Aspermia

Rauwlfia Alkaloid:

Botanical sours are Root of *Rauwlfia serpentine* Apocyneceae.
-Examples: Reserpine and Rescinnamine.
-M.O.A: anti hypertensive, depletion of catecholamine peripherally (decrease ephedrine and nor ephedrine), depletion of central neurotransmitter(mainly serotonin so neuroleptic)
-Unstable compound ester linkage
-Biosynthetic origin:
-Botanical source:
-Pharmacological effect:
-Hydrolytic product for both reserpine:
-Trimethoxybenzoic acid + Methanol and ressinamine + Reserpic acid
Trimethoxycinnamic acid + Methanol + reserpic acid.



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