Objective of the course (2 hours / week) 100/150

- Why we study alkaloids?
- Importance of alkaloids as medicine?
- The poppy plant, *Papaver somniferum*, is the source for non-synthetic narcotics.
- Tropane alkaloids (antispasmodic etc)
- Taxol the best anti-ovarian cancer
- CNS stimulant (caffeine, ephedrine etc)
- Identification of alkaloids, chemical test (specific).
- Isolation from natural origin
- Biosynthesis of certain alkaloids
- NEW (MARINE ALKALOIDS).
Alkaloids are a group of molecules distributed everywhere.

Alkaloids represent a group of natural products that had a great influence, all over history on the economic, medical, political and social affairs of humans.

Millions of people around the Globe use purine alkaloids every day whether starting the day with a cup of coffee or drinking a cup of tea in the afternoon.

Many have potent physiological effects and therefore, are considered as important therapeutic agents e.g. atropine, morphine, quinine etc. They are widely used to treat diseases ranging from malaria to cancer.
Alkaloids are biomolecules of secondary metabolites which are derived from amino acids or from the transamiation process and are classified according to the amino acids that provide their nitrogen atom and part of their skeleton.

Similar alkaloids have different biosynthetic pathways.

Alkaloids are derived from L-lysine, L-ornithine, L-tyrosine, L-tryptophane, L-histidine, L-phenylalanine, nicotinic acid, anthranilic acid or acetate.

Alkaloids also occur in the animal kingdom. Differently from plants, the source of these molecules in an animal’s body can be endogenous or exogenous.
General definition of alkaloid:

- Alkaloids (mean alkali-like substances), are basic nitrogenous compounds of plant or animal origin and generally possessing a marked physiological action on man or animals
All alkaloids are nitrogenous, but not all the nitrogenous compounds are alkaloids.

Plants are a rich source of alkaloids but some have been found in animals e.g. (muscoppyridine) of musk deer and fungi e.g. Ergot alkaloids and almost all alkaloids have been synthesized.

Most but not all possess basic properties due to the presence of an amino nitrogen but certain are amphoteric e.g. cephaline and psychotrine or even acidic e.g. colchicines and recinine.
Sources of alkaloids:

A) Plant sources

- The important alkaloid-bearing families are: Liliaceae, Amaryllidaceae, Asteraceae, Ranunculaceae, Papaveraceae, Leguminosae, Rutaceae, Loganiaceae, Apocynaceae, Solanaceae and Rubiaceae.

B) Animal sources

- Recently alkaloids were found in animals and insects e.g. Pyocyanine from the bacterium *Pseudomonas aeruginosa*.
- Ergot alkaloids; ergotamine and ergometrine from *Ergot fungus*.
- Lycopodine from Lycopodium spores, and muscopyridine from the Musk deer.
Distribution of alkaloids:

- In general, alkaloids occur in a salt form with organic or inorganic acids, or in combination with specific acids e.g. Opium alkaloids occur with meconic acid and Cinchona alkaloids with cinchotannic acid.
- Some occur in combination with sugars as glycosides e.g. solanine

Function of alkaloids in plants:
- They play the following functions in plants:
  1) Protective for the plant against insects
  2) As end products of metabolism.
  3) As waste products.
  4) Source for energy and reserve of nitrogen.
Nomenclature:
Alkaloids terminate with the suffix-ine, their names may be derived from:

<table>
<thead>
<tr>
<th>Genus name</th>
<th>e.g., Atropine from <em>Atropa</em>.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species name</td>
<td>e.g., Cocaine from <em>Coca</em>.</td>
</tr>
<tr>
<td>Common name</td>
<td>e.g., Ergotamine from Ergot.</td>
</tr>
<tr>
<td>Physiological activity</td>
<td>e.g., Emetine (emetic).</td>
</tr>
<tr>
<td>Discoverer</td>
<td>e.g., Pelletierine from Pelletier.</td>
</tr>
</tbody>
</table>
Classification of alkaloids:

**Different systems of classification based on:**
- The chemical structure (type of nitrogen, heterocyclic or non-heterocyclic).
- The pharmacological action (biological activity).
- The biochemical origin (biosynthetic pathway of production in the plant).
- The taxonomical origin (plant families rich in alkaloids).

According to chemical structure, two broad divisions may be recognized:

**Heterocyclic or typical alkaloids:**
They are sub-classified into different groups according to their ring structure.

**Non-heterocyclic or atypical alkaloids:**
They are sometimes called “protoalkaloids” or biological amines.
1. Proto-alkaloids

- They are simple amines, or biological, amines.
- The amino acid nitrogen atom is not in a heterocyclic ring.
- Protoalkaloids are compounds, in which the N atom derived from an amino acid is not a part of the heterocyclic.
- Such kinds of alkaloid include compounds derived from l-tyrosine and l-tryptophan, e.g. mescaline, ephedrine and N, N-dimethytryptamine, are certain examples of proto-alkaloids.

2. Pseudo-alkaloids

- These alkaloids derived from non-amino acid precursors.
- Alkaloids of this type are very weak in its basic characters.
- Examples of pseudoalkaloids include such compounds as solanidine, caffeine, theophylline and theobromine.
- The N atom is inserted into the molecule at a relatively late stage, for example, in case of steroidal or terpenoid skeletons. Certainly, the N atom can also be donated by an amino acid source across a transamination reaction, if there is a suitable aldehyde or ketone group.
3. True alkaloids

- True alkaloids derived from amino acid and they share a heterocyclic ring with nitrogen.
- These alkaloids are highly reactive substances with biological activity even in low doses.
- All true alkaloids have a bitter taste and appear as a white solid; with the exception of some are liquids.
- True alkaloids may occur in plants (a) free state, (b) as salts and (c) as N-oxides.
- Examples of true alkaloids include such biologically active alkaloids as cocaine, quinine, atropine and morphine.
Prefixes and suffixes:
These are, usually, added to the name of the parent alkaloid and are used to designate related alkaloids, generally present in the same plant.

**Prefixes:**
- "Nor-
  - Designates N-demethylation e.g. nor pseudoephedrine and nor nicotine
- "Apo-
  - Designates dehydration e.g. apomorphine.
- "Iso-, pseudo-, neo- and epi-
  - Indicate different types of isomers.

**Suffixes:**
- "-dine
  - Refer to isomerism as in the case of the Cinchona alkaloids, quinidine and cinchonidine are the optical isomers of quinine and cinchonine, respectively.
- "-inine
  - Indicates, in case of ergot alkaloids, a lower pharmacological activity e.g. ergotaminine is less potent than ergotamine.
**Amides:** made from **Amine + Carboxylic acid.** Amides are produced by reaction of a carboxylic acid with ammonia or an amine using heat.

- **Nitrogen in alkaloids:**
  - Number of nitrogen atoms: Alkaloids usually contain one nitrogen atom. Yet, certain alkaloids may contain more than one up to 5 nitrogen atoms in their molecule e.g. nicotine contains 2 N atoms and ergotamine.
  - Nitrogen in alkaloids exists in the form of amine as follow:
Amides: made from **Amine** + **Carboxylic acid**.

Amides are produced by reaction of a carboxylic acid with ammonia or an amine using heat.

\[
\text{CH}_3\text{COOH} + \text{NH}_3 \xrightarrow{\text{heat}} \text{CH}_3\text{CONH}_2 + \text{H}_2\text{O}
\]

\[
\text{CH}_3\text{COOH} + \text{CH}_3\text{NH}_2 \xrightarrow{\text{heat}} \text{CH}_3\text{CONHCH}_3 + \text{H}_2\text{O}
\]
Physicochemical Properties:
Physical characters:
1) Condition:
   Most alkaloids are crystalline solids. Some are liquids like:
   - Volatile e.g. nicotine and coniine, or
   - Non-volatile e.g. pilocarpine and hyoscine.
2) Color:
   The majority of alkaloids are colorless but some are colored e.g.:
   - Colchicine and berberine are yellow. Canadine is orange.
   - The salts of sanguinarine are copper-red. Betanine is red.
3) Solubility:
   The solubility of alkaloids and their salts is of considerable importance because:
   - They are often administered in solution (injection form).
   - The differences in solubility between alkaloids and their salts are used as a base for their isolation and purification from non-alkaloidal substances.
Due to the great variation in their structure, the solubility of different alkaloids and salts are variable.

Both alkaloidal bases and their salts are soluble in alcohol. **A general rule:** the bases are soluble in organic solvents and insoluble in water. **Exceptions:**

- **Bases soluble in water** Caffeine, ephedrine, codeine, colchicine, pilocarpine and quaternary ammonium bases. **Bases insoluble or sparingly soluble in certain organic solvents:** Morphine and psychotrine insoluble ether, theobromine and theophylline insoluble benzene.
A general rule:

- Alkaloidal salts and the quaternary alkaloid are soluble in H₂O, and, insoluble
- or sparingly soluble in organic solvents.

Exceptions:

- **Salts insoluble in water** Quinine monosulphate. **Salts soluble in organic solvents** Lobeline and apoatropine hydrochlorides are soluble in chloroform.

- **Generally**, salts of weak bases are easily hydrolyzed in solution without alkalinization and release the bases, which are extracted with organic solvents e.g. colchicine is soluble as a base or hydrochloride salt in H₂O and CHCl₃.
Optical activity: Many alkaloids are optically active due to the presence of one or more asymmetric carbon atoms in their molecule.

Generally, the levo (-) form is more active than the dextro (+).

(-) Ephedrine is 3.5 times more active than (+) isomer d-ephedrine (-) ergotamine is 3-4 times more active than (+) - isomer d-ergotamine.

Exceptions:

- d- Tubocurarine is more active than the corresponding l- form. Both quinine (l-form) and its d- isomer quinidine are active. The racemic dl- atropine is physiologically active.
II) Chemical characters:

- **A) Basicity of alkaloids:**
  - The basicity of alkaloids is due to the presence of a lone pair of electrons on the nitrogen atom. Amines and, consequently, alkaloids resemble ammonia \([\text{NH}_3]\) in chemical characters. They form salts with acids without liberation of water.
  - In plants, alkaloids occur as free bases, salts or N-oxides \((\text{N} \rightarrow \text{O})\). When the salt of an alkaloid is treated with hydroxyl ion, nitrogen gives up a hydrogen ion and the free amine is liberated.

\[
\begin{align*}
\text{N:} & \quad \text{+} \quad \text{H}^+\text{Cl}^- \\
\text{Amine} & \quad \rightarrow & \quad \text{[N\text{H}]^+Cl}^- \\
\text{Hydrochloric acid} & \quad \text{Amine hydrochloride} \\
\end{align*}
\]
In plants, alkaloids occur as free bases, salts or N-oxides (N→O). When the salt of an alkaloid is treated with hydroxyl ion, nitrogen gives up a hydrogen ion and the free amine is liberated.

Quaternary ammonium compounds (R₄N⁺X⁻), e.g. tubocurarine chloride and berberine chloride have four chemical groups covalently bonded to nitrogen. The positive charge of this ion is balanced by some negative ion. The quaternary ammonium ion, have no proton to give up. Thus; it is not affected by hydroxyl ion; so quaternary ammonium compounds have chemical properties quite different from those of the amines.
Factors influence the degree of basicity:

- Piperidine
- Pyridine
- Ricinine
The degree of basicity varies greatly depending on the structure of the molecule such as the degree of unsaturation of the heterocyclic ring. Unsaturation decreases the basicity e.g. piperidine alkaloids are more basic than pyridine alkaloids.

The presence and position of other substituents and functional groups e.g.: The electron donating groups, such as alkyl groups, increase the basicity. The electron withdrawal groups, such as the carbonyl groups, decrease the basicity. Adjacent groups to nitrogen decrease basicity as electron withdrawing so the availability of electrons on the nitrogen decreases and therefore, the alkaloid be neutral or slightly acidic e.g. recinine alkaloid in castor seeds.

Strong basic alkaloids can form salts even with very weak acids, while weak bases require more acidic medium. Some alkaloids are amphoteric due to the presence of acidic groups in their molecule.

Examples are: The phenolic alkaloids such as: morphine, psychotrine and cephaline. The alkaloids containing a carboxylic group such as: narceine.
Due to their basic character, alkaloids react with acids to form salts.

Weak bases require stronger acids. Dibasic alkaloids may form two series of salts. Very weak bases form unstable salts, e.g. piperine, papaverine, narcotine and caffeine. Amphoteric alkaloids (e.g. containing phenolic or carboxylic groups) can form salts with both acids and alkalis e.g. morphine.

Alkaloids showing acidic characters do not form salts with acids e.g. ricinine.
C) Stability:

- The influence of different factors such as exposure to light, heat, oxygen, acids and alkalis should be considered during preservation and manipulation of alkaloids. In general, alkaloids are less stable in solution than in the dry state.

- **Effect of heat**
  Alkaloids are decomposed by heat, except caffeine that sublimes without decomposition.

- **Effect of heat and light in presence of oxygen:**
  Most tertiary amine alkaloids are easily transformed to the N oxides when exposed to light and oxygen at elevated temperature. N-oxides are usually water-soluble, they are characterized by their delayed release properties, low toxicity and low addictive properties as compared to the parent tertiary alkaloids.

- **Effect of acids,**
  Hot, dilute acids and concentrated mineral acids may cause:
  - **Dehydration** to produce anhydro- or apo-alkaloids, e.g.: dehydration of morphine to produce apomorphine and that of atropine to yield apoatropine.
  - **O-demethylation** of certain alkaloids such as quinine, narcotine and codeine to produce phenolic alkaloids by treatment with HI, e.g. conversion of codeine to morphine.

- **Hydrolysis of ester alkaloids,** such as atropine and reserpine, and glycoalkaloids, such as solanine.

- **Effect of alkalis**
  - **Weak alkalis:** liberate most alkaloids from their salts e.g. NH₃. They also can form salts with alkaloids containing a carboxylic group e.g. narceine, when treated with NaHCO₃, yields the corresponding sodium salt.
  - **Strong alkalis:** such as aqueous NaOH and KOH form salts with phenolic alkaloids.
  - **Hot alkalis:** resulted in hydrolysis of ester alkaloids e.g. atropine, cocaine and physostigmine and cleavage of lactone ring, if present, to produce the corresponding acid e.g. pilocarpine is transformed to pilocarpic acid.
D) Tests for detection and identification:

- Chemical tests commonly performed for detection of alkaloids involve two types of reactions:
  - 1) Precipitation reactions:
    - Most alkaloids are precipitated from their neutral or acidic solutions by a number of reagents which contain certain heavy metals such as mercury (Hg), platinum (Pt), bismuth (Bi), and gold (Au), by forming double salts with them.
    - The composition of the most common alkaloidal precipitants
    - Care must be taken in the application of these tests as:
      - Certain alkaloids such as caffeine and some others do not react.
      - False positive response may be obtained in certain cases as most of the reagents used precipitate proteins, tannins, coumarins and certain flavonoids.
2) **Color reactions:**

- These reactions are usually performed by the addition of color reagents (Table 1) to the solid free bases not to their salts to produce characteristic colored solutions.
- The reagents used generally contain concentrated sulphuric acid and an oxidizing agent.
- They give colors with most alkaloids, or may be specific for one alkaloid or a group of related alkaloids.
## Composition of common reagents used for detection of alkaloids.

<table>
<thead>
<tr>
<th>Name of reagent</th>
<th>Composition</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer's</td>
<td>Potassium-mercuric iodide</td>
<td>Creamy white (positive with most alkaloids, except caffeine and dilute ephedrine).</td>
</tr>
<tr>
<td>Wagner's</td>
<td>Iodine in potassium iodide</td>
<td></td>
</tr>
<tr>
<td>Hager's</td>
<td>Saturated solution of picric acid</td>
<td></td>
</tr>
<tr>
<td>Dragendorffs</td>
<td>Potassium bismuth iodide</td>
<td></td>
</tr>
<tr>
<td>Marmé's</td>
<td>Potassium cadmium iodide</td>
<td></td>
</tr>
</tbody>
</table>

Yellow precipitate.
<table>
<thead>
<tr>
<th>Color reagents:</th>
<th>Ammonium molybdate / conc. H₂SO₄</th>
<th>The colors formed are characteristic.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Froehd's</td>
<td>Ammonium vanadate / conc. H₂SO₄</td>
<td>The tests are sensitive to micro amounts</td>
</tr>
<tr>
<td>Mandalin's</td>
<td>Formaldehyde / conc. H₂SO₄</td>
<td>and can be used for colorimetric assay</td>
</tr>
<tr>
<td>Marquis'</td>
<td>Conc. nitric acid / conc. H₂SO₄</td>
<td></td>
</tr>
<tr>
<td>Erdmann's</td>
<td>Selenious acid / conc. H₂SO₄</td>
<td></td>
</tr>
<tr>
<td>Mecke's</td>
<td>Hydrogen peroxide / conc. H₂SO₄</td>
<td></td>
</tr>
<tr>
<td>Shaer's</td>
<td>Potassium arsenate / conc. H₂SO₄</td>
<td></td>
</tr>
<tr>
<td>Rosenthaler's</td>
<td>Potassium bismuth iodide</td>
<td></td>
</tr>
<tr>
<td>Dragendorff's</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3) Special colour reagents:

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlich's reagent (Van-Urk reagent): Acidified ( p )-dimethylaminobenzaldehyde</td>
<td>It gives characteristic blue or grayish-green color with ergot alkaloids</td>
</tr>
<tr>
<td>Acidified ceric ammonium sulphate.</td>
<td>Characteristic for indole alkaloids, it gives a yellow or orange/red colour.</td>
</tr>
<tr>
<td>Vitali-Morin reagent.</td>
<td>Characteristic for Tropane alkaloids</td>
</tr>
<tr>
<td>Thaleoquine reaction.</td>
<td>Characteristic for Cinchona alkaloids.</td>
</tr>
<tr>
<td>Murexide reaction.</td>
<td>Characteristic for Purine bases</td>
</tr>
</tbody>
</table>