The design of medicinal substances of natural origin for modeling their biological activity.

Alkaloids

Medicinal products of plant origin

The fight against diseases has been conducted by humans for a long time. People discovered the first medicines by accident. Ancient people received them from the "natural pharmacy": plants (leaves, bark, flowers, fruits, roots, stems), animals and minerals.

Medicinal products of plant origin

For thousands of years, folk remedies have been successfully used in India and China, prepared from many natural sources (now this area of treatment is called, unlike official medicine, ethnomedicine and ethnopharmacology).

Medicinal products of plant origin

One of the modern medicines, ephedrine, introduced into official medicine in the 1920s to stop bleeding and as an antitussive agent, has been used in China for almost 5 thousand years in the form of an unrefined herbal medicine "ma huang".

Medicinal products of plant origin

In the works of Pliny there is a reference to the medicinal plant ephedron, which was used in ancient times for the same medicinal purposes. In India, there are 7,500 medicinal plants that are used in folk medicine, and, in particular, Rauwolfia serpentina, which contains the antihypertensive agent is the alkaloid reserpine.

Medicinal products of plant origin

Back in the old days in Russia, handwritten herbalists were compiled with descriptions of ways to prepare medicines from plants "for the treatment of the sick." Folk healers of many countries prepared medicines from bee propolis, mountain mummies, beaver jets, snake and scorpion poisons, mouse droppings, antlers of spotted deer, etc.

Medicinal products of plant origin

From the 17th to the beginning of the 20th century The modern arsenal of medicinal products was replenished mainly by accidental discoveries of herbal medicines. The first individual natural compounds with a therapeutic effect (the so-called "active principle") began to be isolated from plants only in the 19th century. So, in 1803 The year the alkaloid morphine was first isolated.

Medicinal products of plant origin

Plants are autotrophic organisms and serve as both a major and the ultimate source of food for animals and microorganisms. Plants cannot run away or fight back when attacked by a herbivore, nor do they have an immune system to protect them against pathogenic bacteria, fungi, viruses, or parasites.

Medicinal products of plant origin

Secondly, plants are masters of chemical defense, with a fascinating ability to produce a high diversity of chemical defense compounds, also known as secondary metabolites or allelochemicals.

Medicinal products of plant origin

Among the secondary metabolites that are produced by plants, alkaloids figure as a very prominent class of defense compounds. Over 21 000 alkaloids have been identified.

Alkaloids

Alkaloids are widely distributed in the plant kingdom, especially among angiosperms (more than 20 % of all species produce alkaloids). Alkaloids are less common but present in gymnosperms, club mosses (Lycopodium), horsetails (Equisetum), mosses, and algae.

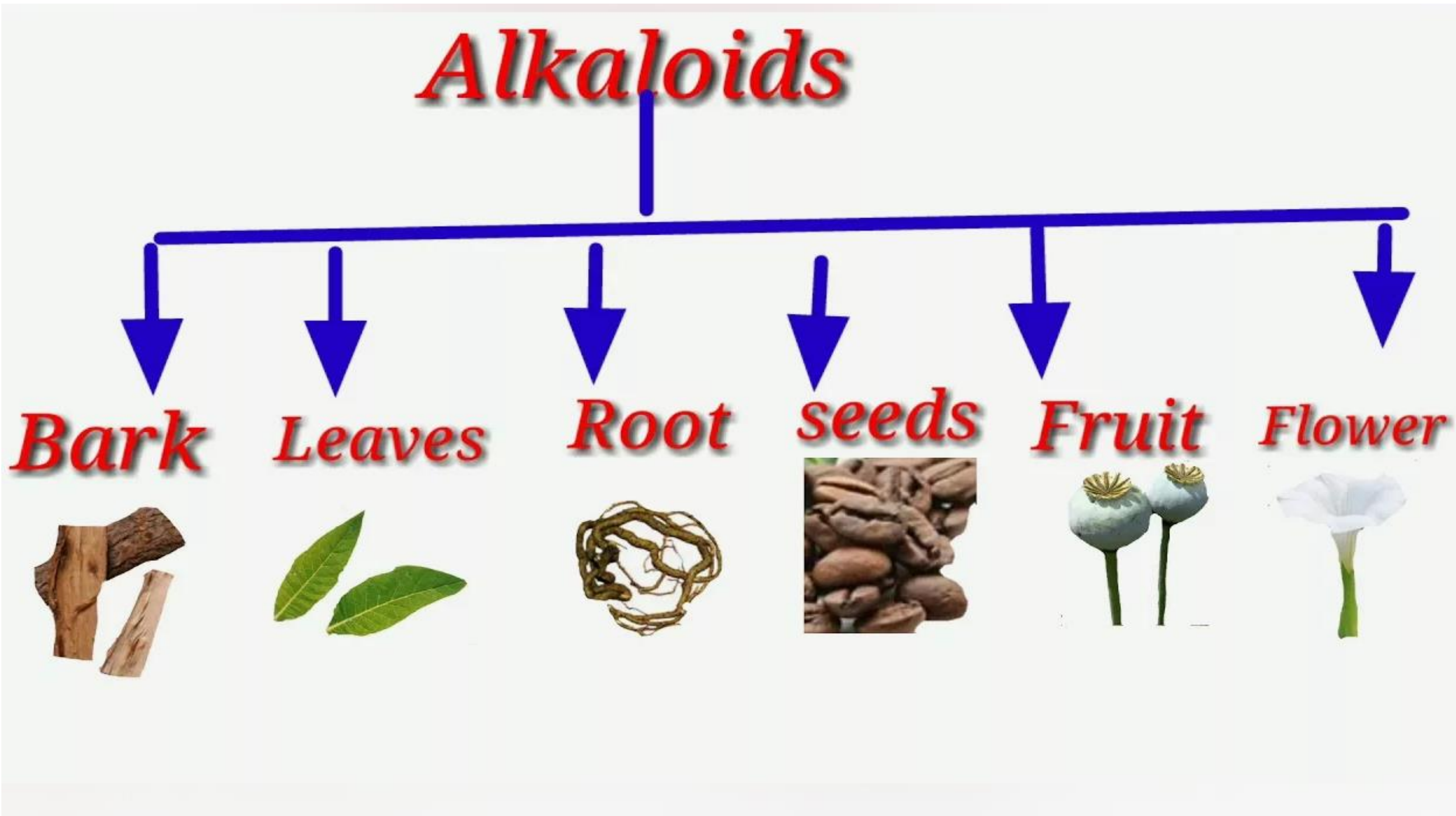
Alkaloids

Alkaloid, any of a class of naturally occurring organic nitrogen –containing bases. Alkaloids have divers and important physiological effects on humans and other animals.

Alkaloids

Alkaloids also occur in bacteria (often termed antibiotics), fungi, many marine animals (sponges, slugs, worms, bryozoa), arthropods, amphibians (toads, frogs, salamanders), and also in a few birds, and mammals

Alkaloids



Alkaloids

Alkaloids are apparently important for the well-being of the organism that produces them. One of the main functions is that of chemical defense against herbivores or predators.

Alkaloids

Some alkaloids are antibacterial, antifungal, and antiviral; and these properties may extend to toxicity towards animals. Alkaloids can also be used by plants as herbicides against competing plants.

Alkaloids

An alkaloid never occurs alone; alkaloids are usually present as a mixture of a few major and several minor alkaloids of a particular biosynthetic unit, which differ in functional groups.

Alkaloids

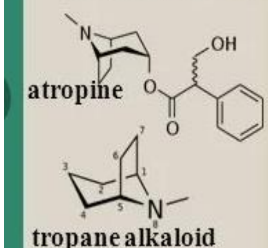
Furthermore, an alkaloid-producing plant often concomitantly accumulates mixtures of other secondary metabolites, mostly those without nitrogen, such as terpenoids and polyphenols, allowing them to interfere with even more targets in animals or microorganisms.

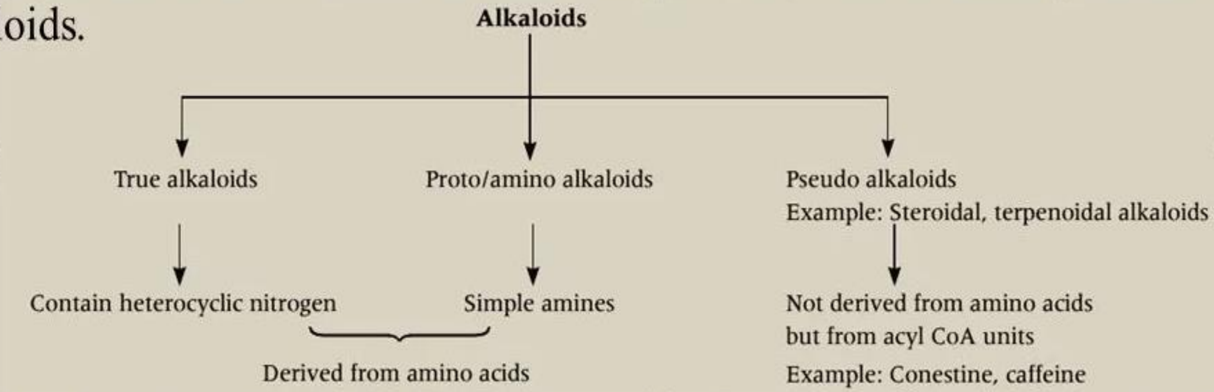
Alkaloids

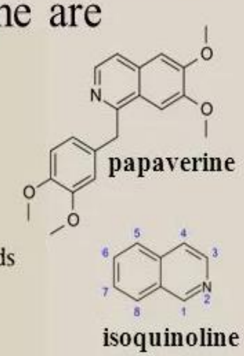
The multiple functions that alkaloids can exhibit concomitantly include a few physiological tasks: sometimes, alkaloids also serve as toxic nitrogen storage and nitrogen transport molecules.

Alkaloids

◦ **Chemical classification**: It is based on the chemical structure of the alkaloid. The chemical classification of alkaloids is universally adopted and depends on the basic ring structure present. For example, atropine is a tropane alkaloid; quinine is considered as a quinolinetype alkaloid; papaverine is an isoquinoline and reserpine, strychnine and ergometrine are indole alkaloids.







Based on the chemical nature, alkaloids are further classified into two major groups as mentioned below:

1. Heterocyclic or typical alkaloids
2. Nonheterocyclic or atypical alkaloids [protoalkaloids (or) biological amines]

They are further subdivided as follows:

Alkaloids

Modes of Action

In order to deter, repel, or inhibit the diverse set of potential enemies, ranging from arthropods and vertebrates to bacteria, fungi, viruses, and competing plants, alkaloids must be able to interfere with important cellular and molecular targets in these organisms.

Alkaloids

The modulation of a molecular target will negatively influence its communication with other components of the cellular network, especially proteins (cross-talk of proteins) or elements of signal transduction.

Alkaloids

As a consequence, the metabolism and function of cells, tissues, organs, and eventually the whole organism will be affected and an overall physiological or toxic effect achieved.

Alkaloids

Among broadly active alkaloids, a distinction can be made between those that are able to form covalent bonds with proteins and nucleic acids, and those that modulate the conformation of proteins and nucleic acids by noncovalent bonding.

Alkaloids

Covalent modifications are the result when the following functional groups interact with proteins:

- reaction of aldehyde groups with amino and sulfhydryl groups;
- reaction of exocyclic methylene groups with SH groups;
- reaction of epoxides with proteins and DNA;
- reaction of quinone structures with metal ions

Alkaloids

Noncovalent bonds are generated when the following groups interact with proteins:

- ionic bonds (alkaloids with phenolic hydroxyl groups, that can dissociate as phenolate ions);
- alkaloid bases that are present as protonated compounds under physiological conditions);
- hydrogen bonds (alkaloids with hydroxyl groups, carbonyl, or keto groups);
- Van der Waals and hydrophobic interactions (lipophilic compounds).

Alkaloids

Noncovalent bonds, especially hydrogen bonds, ionic bonds, hydrophobic interactions, and van der Waals forces are weak individually, but can be powerful if they work cooperatively. For example, alkaloids with phenolic properties (found in several isoquinoline and indole alkaloids) usually have two or more phenolic hydroxyl groups that can form hydrogen bonds with proteins and nucleic acids.

Alkaloids

Both the covalent and the noncovalent interactions will modulate the three-dimensional protein structure, that is, the conformation that is so important for the bioactivities of proteins (enzymes, receptors, transcription factors, transporters, ion channels, hormones, cytoskeleton).

Alkaloids

A conformational change is usually associated with a loss or reduction in the activity of a protein, leading to inhibition of enzyme or receptor activity or interference with the very important protein-protein interactions

Alkaloids

Lipophilic compounds, such as the various terpenoids, tend to associate with other hydrophobic molecules in a cell; these can be biomembranes or the hydrophobic core of many proteins and of the DNA double helix. In proteins, such hydrophobic and van der Waals interactions can also lead to conformational changes, and thus protein inactivation.

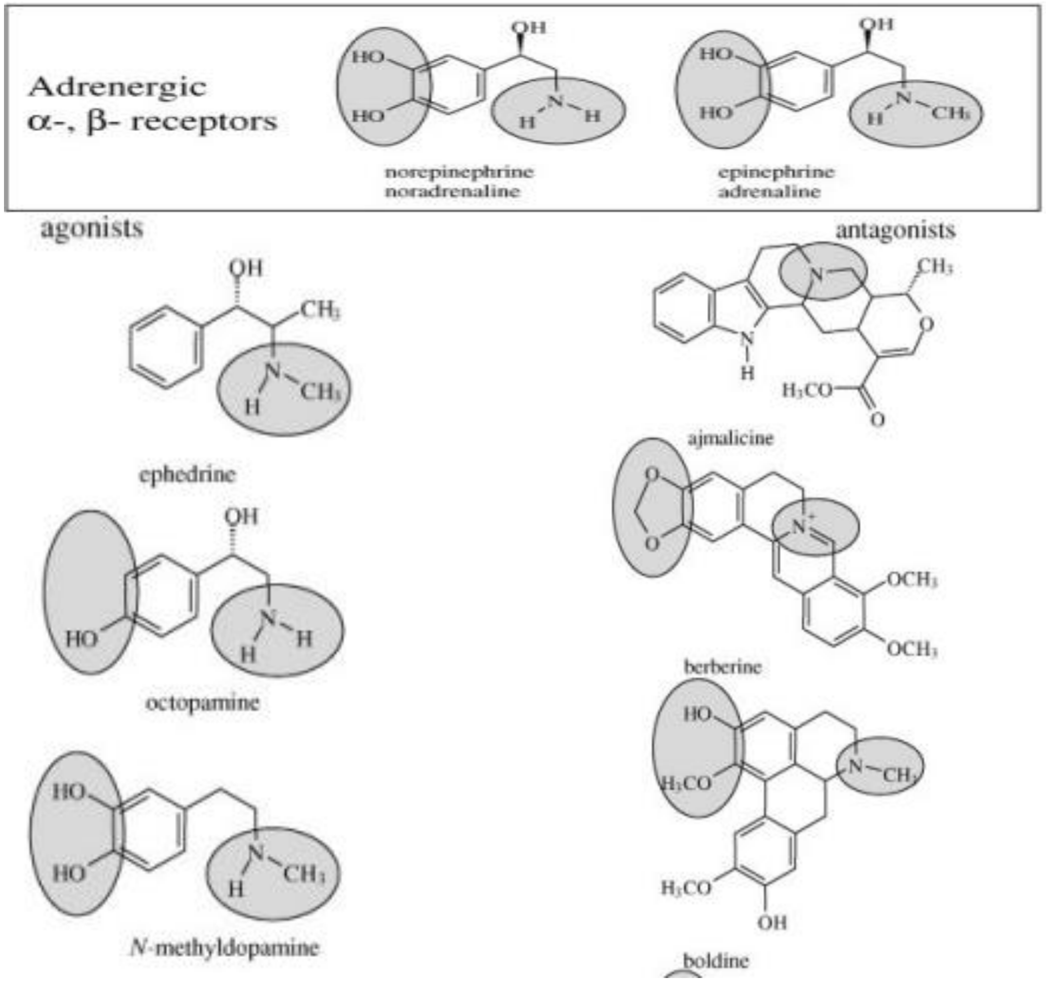
Alkaloids

Many alkaloids fall into the class of specific modulators and have been modified during evolution in such a way that they mimic endogenous ligands, hormones, or substrates. Many alkaloids are strong neurotoxins that were selected for defense against animals.

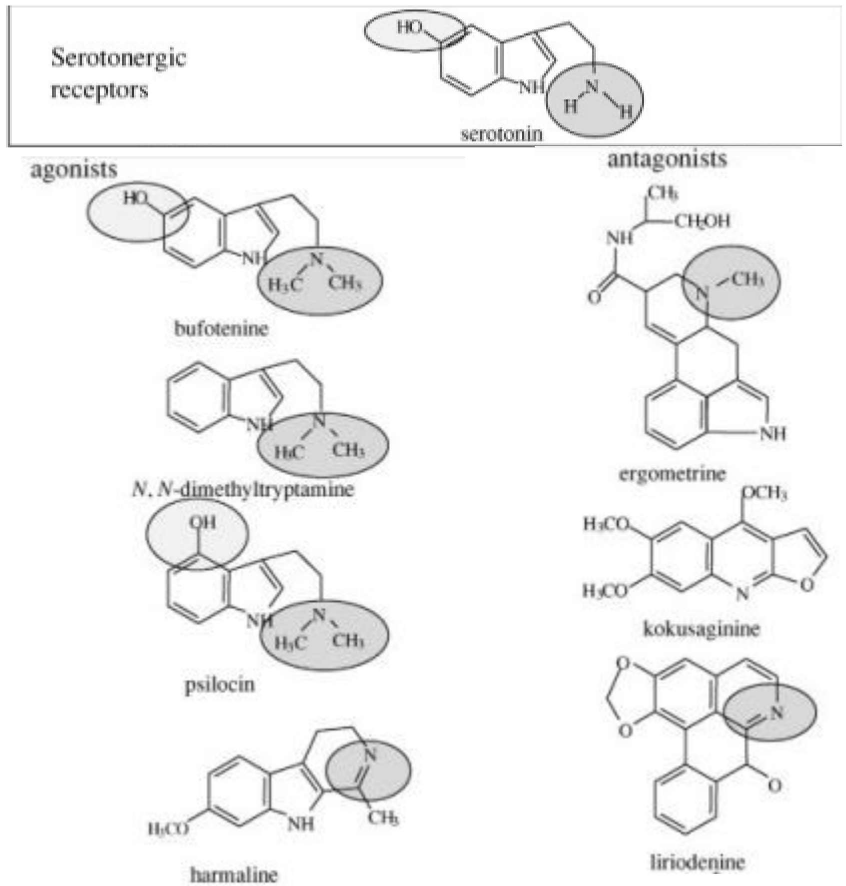
Alkaloids

Neurotransmitters derive from amino acids; most of them are amines that become protonated under physiological conditions. Since alkaloids also derive from amino acids (often the same ones as neurotransmitters) it is no surprise that several alkaloids have structural similarities to neurotransmitters. They can be considered as neurotransmitter analogs.

Alkaloids


Adrenergic
α-, β- receptors
norepinephrine
noradrenaline
epinephrine
adrenaline
agonists
antagonists
ephedrine
ajmalicine
octopamine
berberine
N-methyldopamine
boldine

Alkaloids



Serotonergic receptors
HO
NH
N
H
H
serotonin
agonists
antagonists
HO
NH
N
H3C
CH3
bufotenine
NH
N
H3C
CH3
N, N-dimethyltryptamine
OH
NH
N
H3C
CH3
psilocin
N
H3CO
NH
CH3
harmaline
CH3
CH2OH
NH
O
N
CH3
NH
ergometrine
OCH3
H3CO
H3CO
N
O
kokusaginine
O
O
N
O
liriodenine

Alkaloids

Alkaloids that structurally mimic neurotransmitters can bind to neuroreceptors and either activate (agonists) or inactivate (antagonists) them. Additional important targets are ion channels; several alkaloids are known that inhibit or activate these ion channels.

Alkaloids

Alkaloids do not only serve as poisons against herbivores and microorganisms; they can also be interesting and important in medicine as pharmaceutical agents. Given at a lower dose (than the plants use for defense) these alkaloids no longer work as poisons but can mediate useful pharmacological activities, such as reducing blood pressure, relieving pain and spasms, stimulating circulation and respiration, or killing tumor cells.