Ministry of Public Health of Ukraine
Poltava State Medical University
Department of biological and bioorganic chemistry

Heterocyclic compounds.

Assoc. Prof. Bilets M.V.

Lecture plan

- **Classification of heterocycles.**
- **Classification of five-membered heterocycles and their derivatives.**

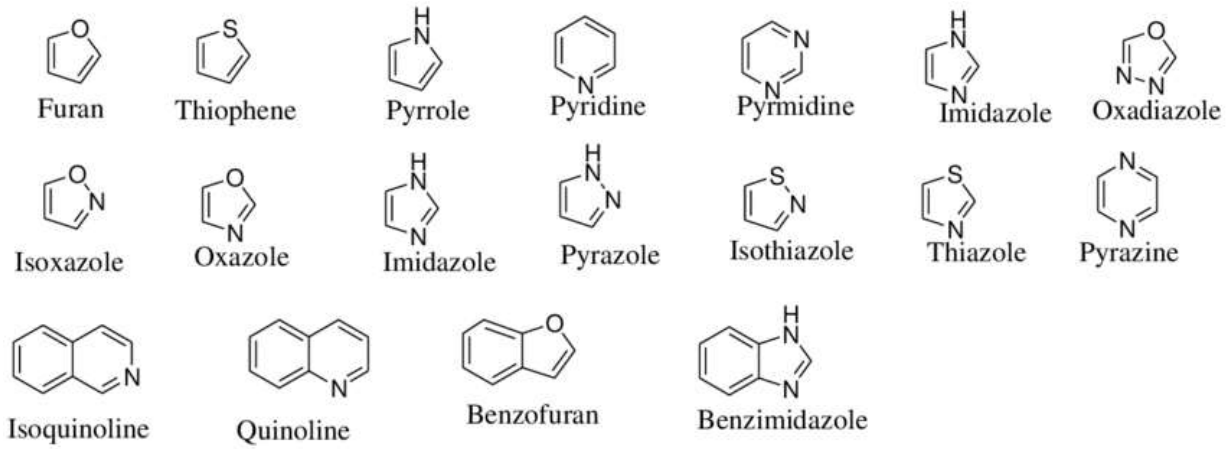
- Five-membered heterocycles with one heteroatom (pyrrole, furan, thiophene). Biomedical importance of tetrapyrrole compounds: porphins, porphyrins, heme.
- Indole and its derivatives: tryptophane and reactions of formation of tryptamine and serotonine; indoxyle, skatole, skatoxyle – role in the processes of protein decomposition in the intestine.
- Five-membered heterocycles with two nitrogen heteroatoms. Pyrazole, pyrazolone; derivatives of pyrazolone-5 as medicines (antipyrine, amidopyrine, analgin). Imidazole and its derivatives: histidine, histamine.
- Five-membered heterocycles with two different heteroatoms: thiazole, oxazole. Thiazole as a structure component of the thiamine molecule (vitamin B_1).

- **Characteristics of six-membered heterocycles and their derivatives.**

- Six-membered heterocycles with one nitrogen atom: pyridine. Nicotinamide (vitamin PP) as the component of reduction-oxidation pyridine coenzymes. Pyridoxine and molecular forms of vitamin B_6.
- Six-membered heterocycles with two nitrogen atoms. Diazines: pyrimidine, pyrazine, pyridazine. Nitrogenous compounds – derivatives of pyrimidine (uracil, cytosine, thymine).
- Derivatives of pyrimidine as medical preparations: 5-fluoruracil, potassium orotate. Barbituric acid; barbiturates as sedatives and antiepilepthic compounds (phenobarbital, veronal).
- Purine and its derivatives. Amino derivatives of purine (adenine, guanine), their tautomeric forms; their biochemical role in formation of nucleotides and coenzymes.
- Hydroxyderivatives of purine: hypoxantine, xantine, uric acid. Methylated derivatives of xantine (caffeine, theophylline, theobromine) as physiologically active compounds that act on the central nervous system and the cardiovascular system.

Heterocyclic compounds

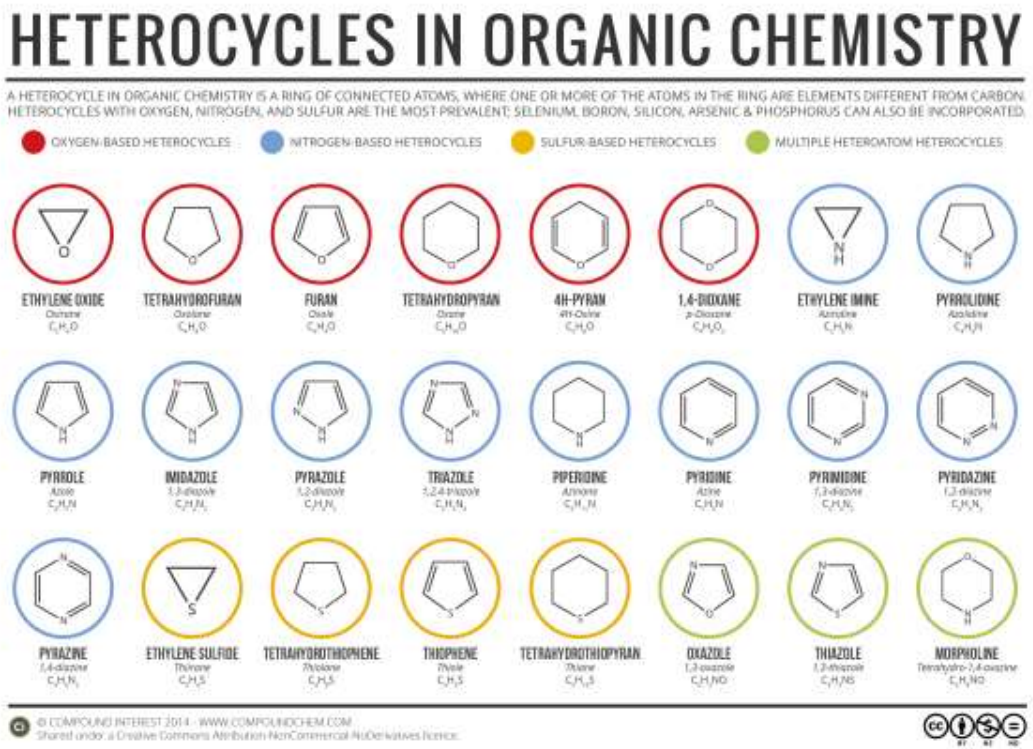
- are cyclic molecule with two or more different kinds **Heterocyclic compounds** of atoms in the ring.
- Heteroatom can be represented by N, O, S, B, Al, Si, P, Sn, As, Cu, but more often - by **N, O, or S**.



https://www.researchgate.net/figure/Chemical-structures-of-some-heterocyclic-compounds_fig2_260683286

Heterocyclic compounds classification

- There are two main ways of heterocyclic compounds classifying:
- By ring size
- Aromatic/non aromatic
- Type of heteroatom



https://www.compoundchem.com/2014/07/31/heterocycles/

Nomenclature of heterocyclic compounds

- The commonly used names for heterocyclic compounds are their trivial names (furan, pyrrole, thiphene).
- The Hantzsch-Widman naming system is used to name heterocycles. Firstly, a prefix is given for the element other than carbon which makes up the heterocycle:

ELEMENT	OXYGEN	SULFUR	SELENIUM	NITROGEN	PHOSPHORUS	SILICON	BORON	ARSENIC
PREFIX	oxa-	thia-	selena-	aza-	phospha-	sila-	bora-	arsa-

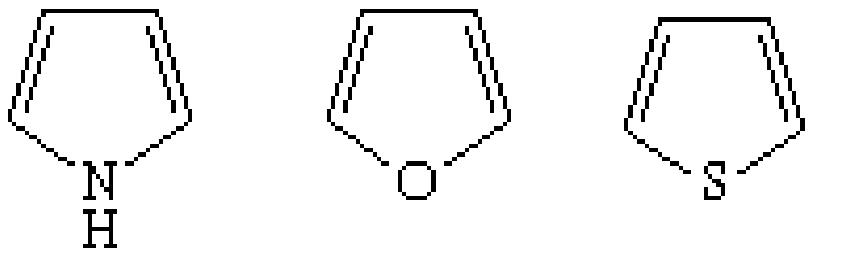
- Following this, the vowel at the end of the prefix is removed, and a suffix is added. This suffix is based on the number of atoms that make up the ring, and also depends on whether the heterocycle is saturated (contains only single bonds) or unsaturated (contains double bonds):

SIZE OF RING	3	4	5	6	7	8	9	10
UNSATURATED	-irene	-ete	-ole	-ine	-epine	-ocine	-onine	-ecine
SATURATED	-irane	-etane	-olane	-inane	-epane	-ocane	-onane	-ecane

- The examples of systematic and trivial names of some heterocyclic compounds with one heteroatom are given: furan(oxole), pyrrole (azole), thiphene (thiole).

Five-membered heterocycles with one heteroatom (pyrrole, furan, thiophene).

- Pyrrole, furan, and thiophene:



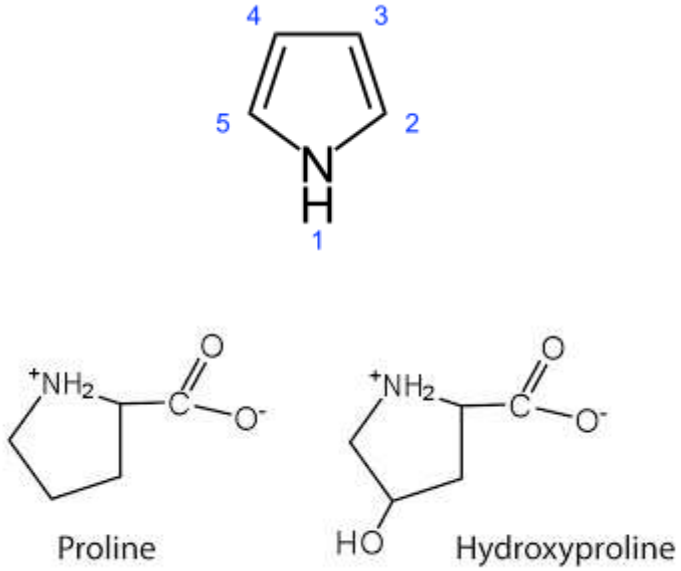
pyrrole furan thiophene

- The saturated derivatives are called **pyrrolidine, tetrahydrofuran, and thiophane**.
- The bicyclic compounds made of a pyrrole, furan, or thiophene ring fused to a benzene ring are called **indole** (or isoindole), benzofuran, and benzothiophene, respectively.

https://www.britannica.com/science/heterocyclic-compound/Five-membered-rings-with-one-heteroatom

Pyrrole derivatives

- Pyrrole rings are found in the amino acids proline and hydroxyproline, which are components of many proteins and which are present in particularly high concentrations in collagen, the structural protein of bones, tendons, ligaments, and skin.



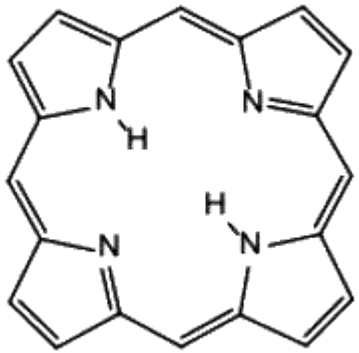
https://cbm.msoe.edu/crest/ePosters/a15collagen.html

- Pyrrole derivatives are widespread in the living world. Pyrrole compounds are found among the alkaloids, a large class of alkaline organic nitrogen compounds produced primarily by plants. Nicotine is the best-known pyrrole-containing alkaloid.

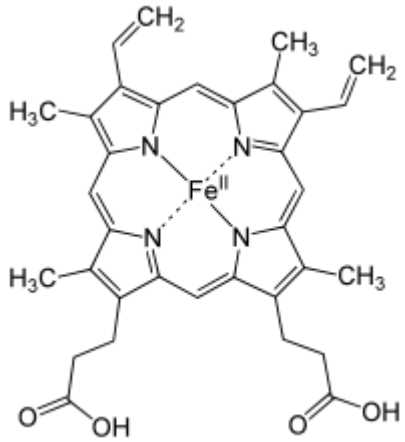
https://www.bigstockphoto.com/image-357748391/stock-vector-nicotine-formula-on-a-white-background-vector-illustration

Pyrrole derivatives

- The heme group of the oxygen-carrying protein hemoglobin and of related compounds such as myoglobin; and vitamin B12 are all formed from four pyrrole units joined in a larger ring system known as a porphyrin.

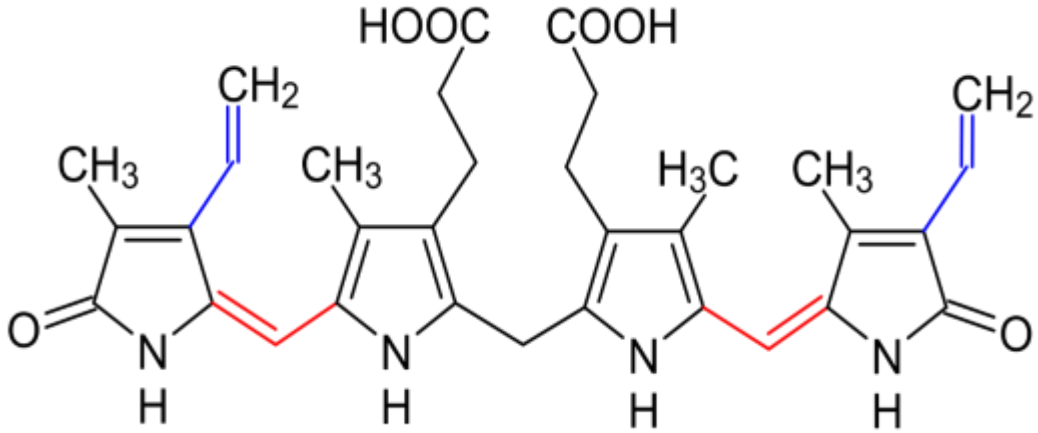


porphyrin.



heme

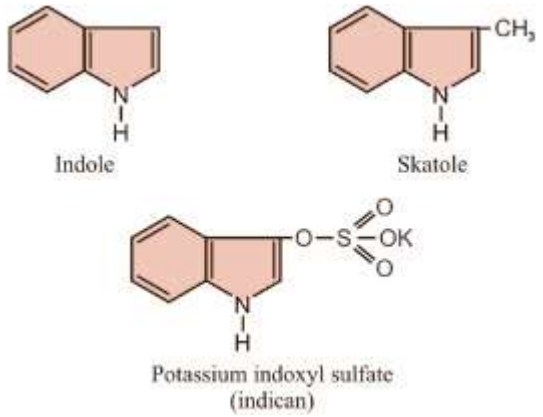
- The bile pigments are formed by decomposition of the porphyrin ring and contain a chain of four pyrrole rings. Bilirubin, for example, the brownish yellow pigment that gives feces its characteristic colour, is the end product of the breakdown of heme from destroyed red blood cells.



https://en.wikipedia.org/wiki/Heme

Indole

Indoles are compounds which consist of a pyrrole ring fused to benzene to form 2,3-benzopyrrole.
Indican is a substance occurring naturally in the urine of humans and mammals and also in blood plasma as a normal metabolite of tryptophan.
Tryptophan is first converted to indole by intestinal bacterias. Following absorption from the intestine, indole is converted to indican in the liver. It is then transported to the kidneys for excretion.

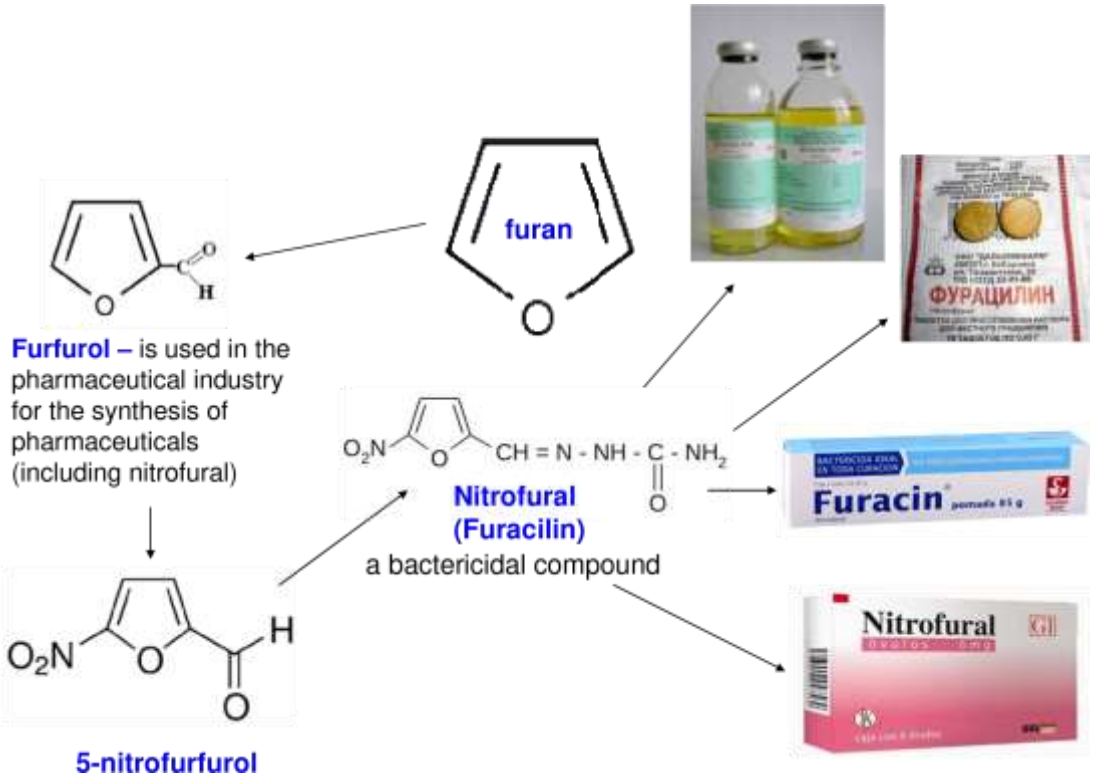


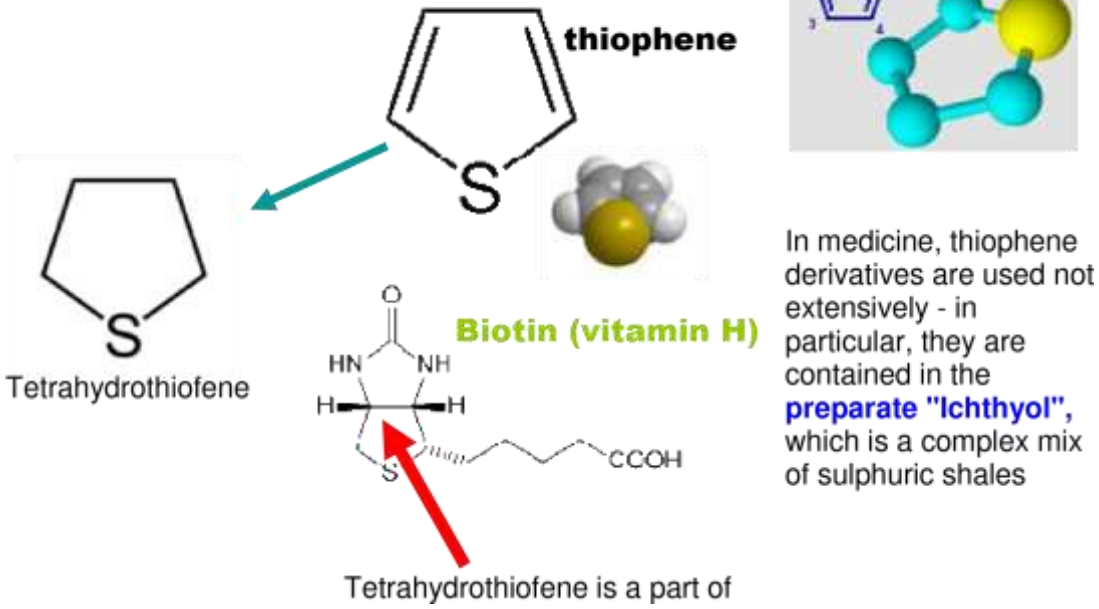
An increased urinary excretion of indican is seen in Hartnup disease from the bacterial degradation of unabsorbed tryptophan Hartnup disease is an autosomal recessive metabolic disorder affecting the absorption of nonpolar amino acids (particularly tryptophan), which leads to excessive bacterial fermentation of tryptophan (to indole) in the intestine.

The production of indole and, accordingly, indican increases with putrefaction of proteins in the intestine due to chronic constipation,
a diet rich in proteins or a tumor in the intestine

https://www.researchgate.net/figure/Metabolic-pathways-showing-role-of-indole-3-hydroxylation-in-vivo-A-and-in-vitro-B_fig1_11550227

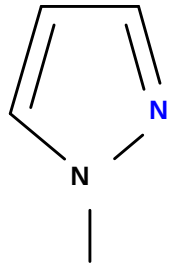
Furan and thiophene derivatives



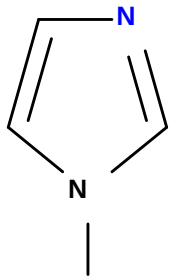


https://biology.univ.kiev.ua/images/stories/Napryamy_pidgotovky/Medicine_ENG/Bulletin_board/news/2018_05_21_Materials_for_Preparations/3_5_Heterocycles.pdf

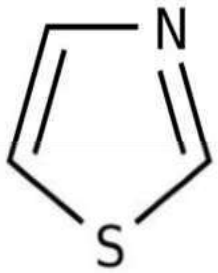
Five-membered heterocycles with two nitrogen heteroatoms.



Pyrazole



Imidazole

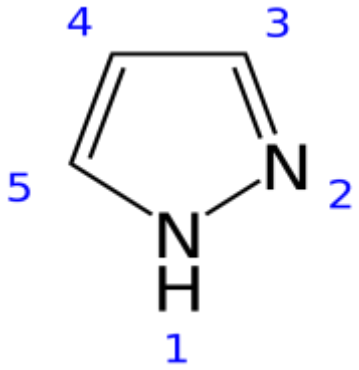


Thiazole

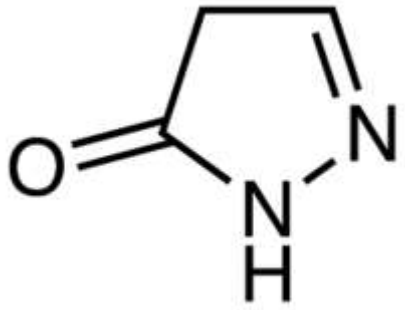
These compounds don’t occur in nature, but many drugs have been synthesized on the basis of pyrazole such as antipyrine, aminopyrine (or aminophenazone), analgine (or metamizole) and phenylbutazone (or butadion)

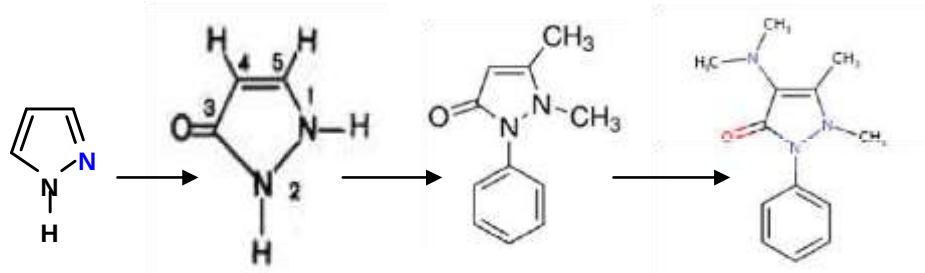
https://biology.univ.kiev.ua/images/stories/Napryamy_pidgotovky/Medicine_ENG/Bulletin_board/news/2018_05_21_Materials_for_Preparations/3_5_Heterocycles.pdf

Pyrazole, pyrazolone; derivatives of pyrazolone-5 as medicines (antipyrine, amidopyrine, analgin).

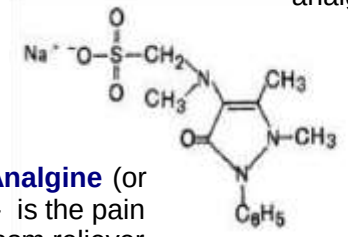


Pyrazolone, a five-membered-ring lactam, is a derivative of pyrazole that has an additional keto (=O) group.

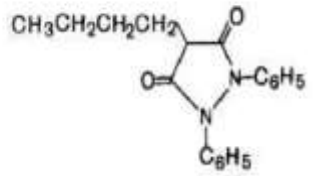




Pyrazole — **3-Pyrazolone** — **Antipyrine** - antipyretic and analgesic — **Aminopyrine** (or **Aminophenazone**) has analgesic, anti-inflammatory, and antipyretic properties



Analgine (or **Metamizole**) - is the pain and spasm reliever



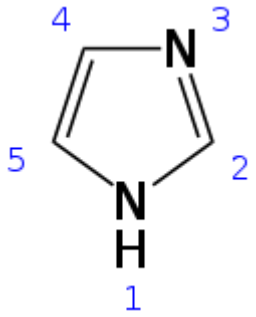
Phenylbutazone (**Butadion**) - Nonsteroidal anti inflammatory drug

https://www.tcichemicals.com/TH/en/p/P2563

https://ru.m.wikipedia.org/wiki/Файл:Pyrazole_2D_numbered.svg

https://biology.univ.kiev.ua/images/stories/Napryamy_pidgotovky/Medicine_ENG/Bulletin_board/news/2018_05_21_Materials_for_Preparations/3_5_Heterocycles.pdf

Imidazole and its derivatives: histidine, histamine.

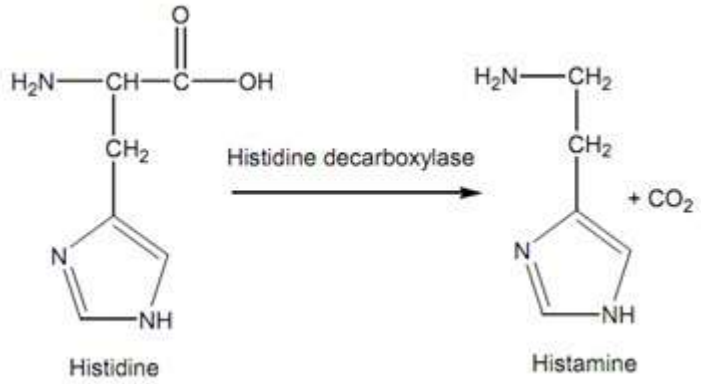


Imidazoles are well known heterocyclic compounds having important feature of a variety of medicinal agents. Imidazole is a planar 5-membered ring. It is highly soluble in water and also is soluble in other polar solvents. It exists in two equivalent tautomeric forms because the proton can be located on either of the two nitrogen atoms. Due to the presence of a sextet of π-electrons the compound is classified as aromatic. It consists of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Imidazole is amphoteric, i.e., it can function as both an acid and as a base.

The imidazole ring is a constituent of several important natural products, including purines, histamine, histidine and nucleic acids.
The most pervasive is the amino acid histidine, which has an imidazole side-chain.
Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin. Imidazole-based histidine compounds play a very **important** role in intracellular buffering.

https://ru.wikipedia.org/wiki/Имидазол

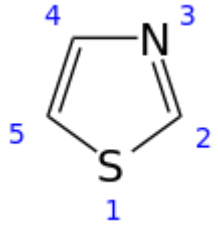
Histidine can be decarboxylated to histamine, which is also a common biological compound. Histamine can cause urticaria (hives) when it is produced during allergic reaction.



The derivatives shows various pharmacological activities such as anti viral, anti inflammatory and analgesic, anti depressant, anti fungal and anti-bacterial, anti cancer, anti tubercular and antileishmanial activity.

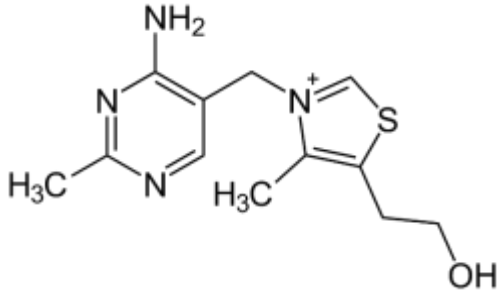
http://www.tutorsglobe.com/homework-help/biochemistry/decarboxylation-71923.aspx

Five-membered heterocycles with two different heteroatoms: thiazole, oxazole. Thiazole as a structure component of the thiamine molecule (vitamin B_1).



Thiazole, or 1,3-thiazole

The thiazole ring is notable as a component of the vitamin thiamine (B_1).



Coenzyme (nonprotein part of complex enzymes) of vitamin B1 - thiamine diphosphate (ThDP), also known as thiamine pyrophosphate (TPP) or cocarboxylase. ThDP is a coenzyme for several enzymes that catalyze the transfer of two-carbon units and in particular the dehydrogenation (decarboxylation and subsequent conjugation with coenzyme A) of 2-oxoacids (alpha-keto acids):

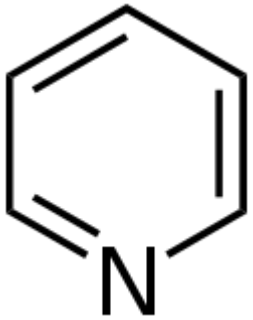
pyruvate dehydrogenase and α-ketoglutarate dehydrogenase
branched-chain α-keto acid dehydrogenase,
transketolase

https://ru.wikipedia.org/wiki/Тиамин

Oxazole and its derivatives have been incorporated into a large number of compounds of potential medicinal value. Aluminum salts of oxaprozin are have value as antiinflammatory agents. Other 4,5-diphenyl-2-oxazoyl derivatives showed activity as prostacyclin mimetics. The most potent compound of the series contained another oxazole ring, which locked an important double bond in the cis configuration and served as a hydrogen bond acceptor.
A series of triazolylmethyloxazolidine derivatives are inhibitors of the cytochrome P450.

https://en.wikipedia.org/wiki/Oxazole

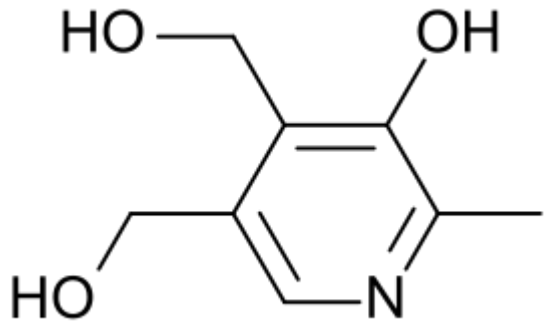
Six-membered heterocycles with one nitrogen atom: pyridine. Pyridoxine and molecular forms of vitamin B_6.



Pyridine is a basic heterocyclic organic compound. It is structurally related to benzene, with one methine group (=CH−) replaced by a nitrogen atom. It is a highly flammable, weakly alkaline, water-miscible liquid with a distinctive, unpleasant fish-like smell. Pyridine is colorless. The pyridine ring occurs in many important compounds, including pharmaceuticals, and vitamins.

https://ru.wikipedia.org/wiki/Пиридин

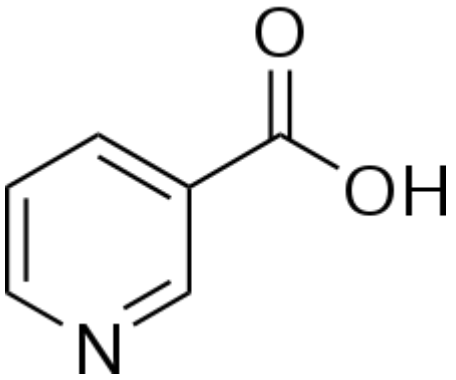
- **Pyridoxine**, also known as **vitamin B_6**



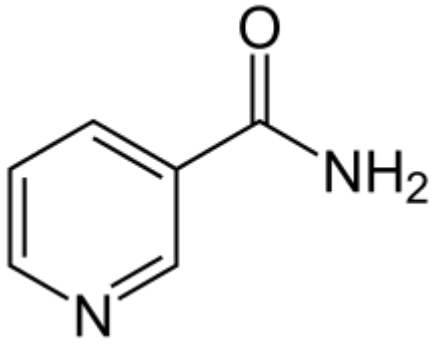
Coenzyme forms ov vitamin B6 are pyridoxal phosphate and pyridoxaminephosphate. There participate in transamination and decarboxylation of amino ocids, heme synthesise, niacin (vitamin PP) synthesise.

https://en.wikipedia.org/wiki/Pyridoxine

Nicotinamide (vitamin PP) as the component of reduction-oxidation pyridine coenzymes.



Nicotinic acid



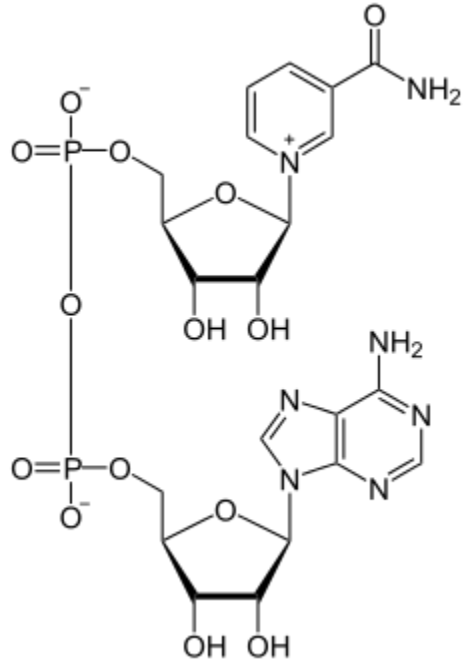
Nicotinamide

Niacin, also known as nicotinic acid, is an organic compound and a form of vitamin B3. It can be synthesized from the amino acid tryptophan. The niacin deficiency is pellagra. The classic symptoms of pellagra are diarrhea, dermatitis, dementia,

The amide derivative nicotinamide (niacinamide) is a component of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP+).

Nicotinamide adenine dinucleotide (NAD) is a cofactor central to metabolism. Found in all living cells, NAD is called a dinucleotide because it consists of two nucleotides joined through their phosphate groups. One nucleotide contains an adenine nucleobase and the other nicotinamide. NAD exists in two forms: an oxidized and reduced form, abbreviated as NAD+ and NADH (H for hydrogen) respectively.

In metabolism, nicotinamide adenine dinucleotide is involved in redox reactions, carrying electrons from one reaction to another. The cofactor is, therefore, found in two forms in cells: NAD+ is an oxidizing agent – it accepts electrons from other molecules and becomes reduced. This reaction forms NADH, which can then be used as a reducing agent to donate electrons. These electron transfer reactions are the main function of NAD.

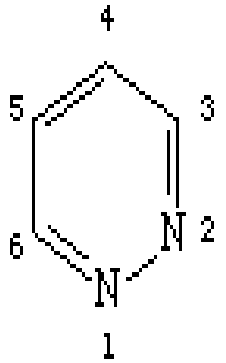


Nicotinamide adenine dinucleotide

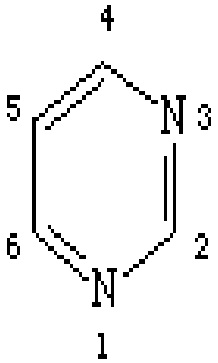
https://en.wikipedia.org/wiki/Nicotinamide_adenine_dinucleotide

Six-membered heterocycles with two nitrogen atoms. Diazines: pyrimidine, pyrazine, pyridazine. Nitrogenous compounds – derivatives of pyrimidine (uracil, cytosine, thymine).

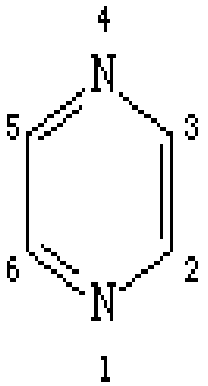
- The three monocyclic diazines—six-membered ring compounds with two nitrogen heteroatoms:



pyridazine

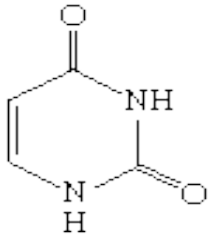


pyrimidine

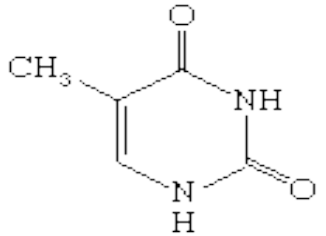


pyrazine

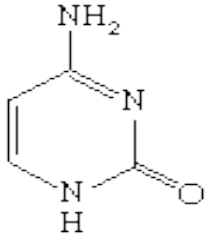
- The most important diazines are the pyrimidines. Uracil, thymine, and cytosine. This nitrogenouse bases are components of nucleotides.



uracil



thymine



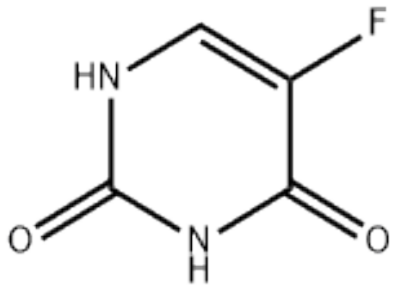
cytosine

- The vitamin thiamin contains a pyrimidine ring (in addition to the five-membered thiazole ring mentioned above), and synthetic barbiturates such as amobarbital (amylobarbitone) are widely used drugs.

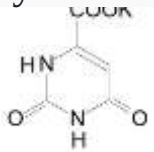
https://www.sciencedirect.com/science/article/abs/pii/S0277538714003052

Derivatives of pyrimidine as medical preparations: 5-fluoruracil, potassium orotate.

- **5-fluorouracil** is a nucleobase analogue that is uracil in which the hydrogen at position 5 is replaced by fluorine. It is an antineoplastic agent which acts as an antimetabolite - following conversion to the active deoxynucleotide, it inhibits DNA synthesis (by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase) and so slows tumour growth.

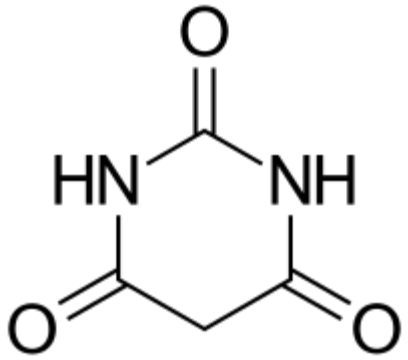


Potassium orotate. Pharmacological action - anabolic, regenerating. Provides the synthesis of pyrimidine nucleotides in the nucleic acids involved in the formation of protein molecules. It is used in the complex treatment of liver diseases (including intoxication), myocardial
dystrophy, extrasystoles and atrial fibrillation, malnutrition
in children (alimentary and alimentary-infectious);
with heavy and constant physical exertion.

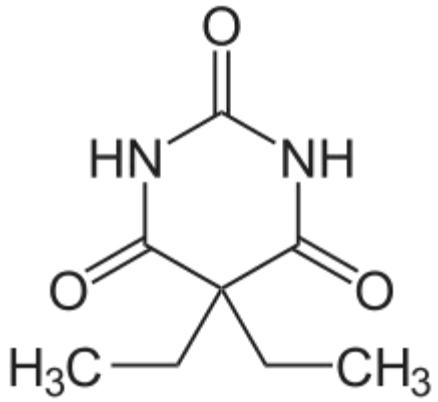


Barbiturates as sedatives and antiepilepthic compounds (phenobarbital, veronal).

- Barbital (or barbitone), marketed under the brand names Veronal for the pure acid and Medinal for the sodium salt, was the first commercially available barbiturate. It was used as a sleeping aid (hypnotic) from 1903 until the mid-1950s. The chemical names for barbital are diethylmalonyl urea or diethylbarbituric acid.



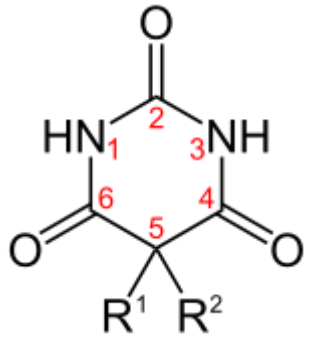
Barbituric acid, the parent structure of all barbiturates



Barbital (diethylbarbituric acid).

https://www.wikidata.org/wiki/Q412409

- Barbiturates are a group of sedative-hypnotic medications used for the treatment of seizure disorder, neonatal withdrawal, insomnia, preoperative anxiety, induction of coma for increased intracranial pressure. They are also useful for inducing anesthesia.

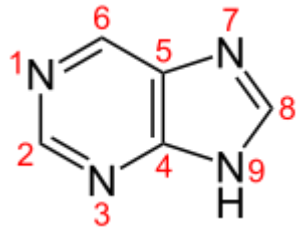


Short Name	R^1	R^2	IUPAC Name
amobarbital	CH_2CH_3	$(CH_2)_2CH(CH_3)_2$	5-ethyl-5-isopentyl-barbiturate
pentobarbital	CH_2CH_3	$CHCH_3(CH_2)_2CH_3$	5-ethyl-5-(1-methylbutyl)-barbiturate
phenobarbital	CH_2CH_3	C_6H_5	5-ethyl-5-phenylbarbiturate

Purine and its derivatives. Amino derivatives of purine (adenine, guanine), their tautomeric forms; their biochemical role in formation of nucleotides and coenzymes.

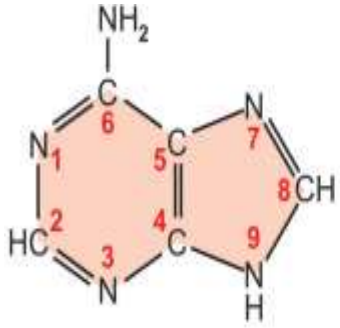
Purine is a heterocyclic aromatic organic compound that consists of two rings: pyrimidine and imidazole.

Purine also gives its name to the wider class of molecules, purines, which include substituted purines and their tautomers. They are the most widely occurring nitrogen-containing heterocycles in nature

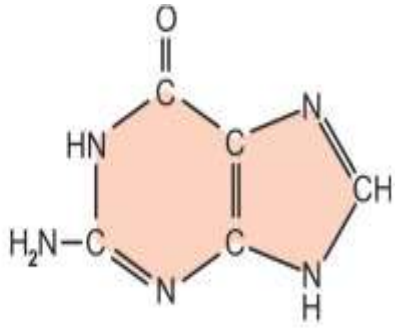


https://en.wikipedia.org/wiki/Purine

Purines and pyrimidines make up the two groups of nitrogenous bases, including the two groups of nucleotide bases. The purine nucleotide bases are guanine (G) and adenine (A) which distinguish their corresponding deoxyribonucleotides (deoxyadenosine and deoxyguanosine) and ribonucleotides (adenosine, guanosine). These nucleotides are two of the building blocks of DNA and RNA. Purines are also significant components in a number of other important biomolecules, such as ATP, GTP, cyclic AMP, NADH, and coenzyme A.



Adenine



Guanine

https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/nitrogenous-base

Tautomeric forms purines and pyrimidines

- The four bases of DNA can exist in at least two tautomeric forms as shown below. Adenine and cytosine (which are cyclic amidines) can exist in either
- Amino or imino forms, and guanine, thymine, and uracil (which are cyclic amides) can exist in either lactam (keto) or lactim (enol) forms.
- The tautomeric forms of each base exist in equilibrium but the amino and lactam tautomers are more stable and therefore predominate under the conditions found inside most cells. The rings remain unsaturated and planar in each tautomer.

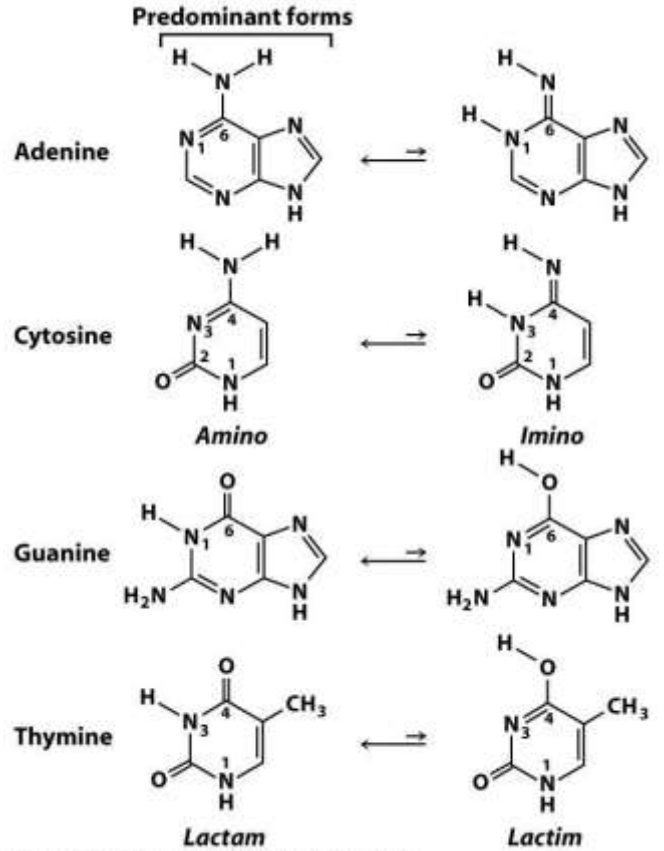


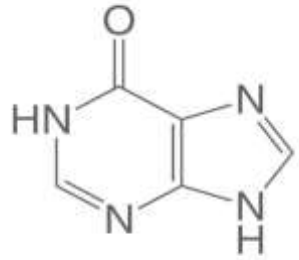
Figure 19-5 Principles of Biochemistry, 4/e

http://corneliabl.blogspot.com/2007/07/tautomers-of-adenine-cytosine-guanine.html

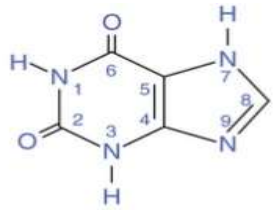
Hydroxyderivatives of purine: hypoxantine, xantine, uric acid.

- **The xanthine derivatives are caffeine, theobromine and methylxanthines.** These are plant alkaloids and components of coffee, tea and chocolate. The major pharmacologic actions of the xanthines are inhibition of tissue phosphodiesterases which increases cellular cyclic AMP levels by inhibition of its breakdown and metabolism. The xanthines also are adenosine receptor antagonists. Xanthines may have antiinflammatory effects, either via release of antiinflammatory cytokines or modulation of gene transcription or activation of histone dacetylase. All of these actions may be important in their effects of bronchial tree, resulting in relaxation of smooth muscle. The major use of xanthine derivatives are for relief of bronchospasm caused by asthma or chronic obstructive lung disease. The most widely used xanthine is theophylline.

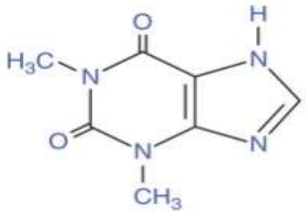
- The xanthines also have other activities mediated by their effects on different tissue phosphodiesterases including inhibition of platelet function and arterial vasodilation. These activities have potential use in preventing arterial thrombosis and thus prevention of myocardial infarction and stroke. The vasodilation caused by xanthines has been used to treat intermittent claudication (pentoxifylline). Xanthines also stimulate muscle and cardiac cells and neurons. Xanthines can cause a mild diuresis**.**



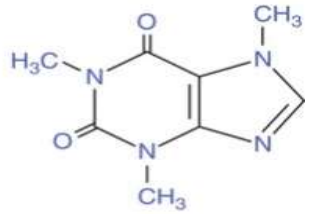
Hypoxanthine
(6-oxypurine)



Xanthine

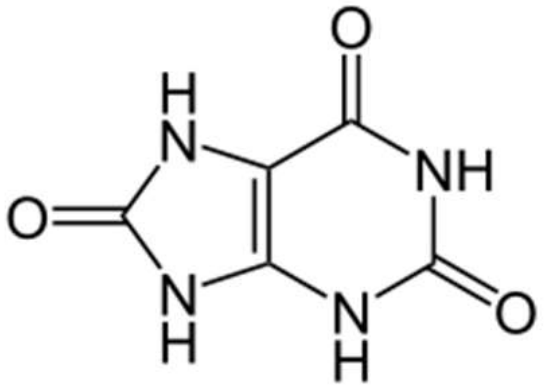


Theophylline



Caffeine

Uric acid



Uric acid (its keto form) is the final product of purine nucleotides catabolism and is characterized by low solubility in water.

It forms ions and salts known as **urates** and **acid urates**, its sodium salt is distinguished by its higher solubility.

The form in which uric acid is found in biological fluids (blood, urine, cerebrospinal fluid) depends on the pH of this liquid.

At normal pH - uric acid and its monosodium salt (sodium urate).At a higher pH, its dominant form is sodium uric acid.

At a lower value (especially if the pH is <5.75) – (in tissues, but more often in the renal tubules and urine),

the main molecular form is sparingly soluble urine acid in keto form.

- An increase in the concentration of uric acid in the blood – **hyperuricemia**.

Causes of hyperuricemia: hereditary purine metabolism defects, for example, (Lesh-Nyhan syndrome), a diet rich in purines (meat products, fish, liver), increased catabolism of nucleoproteins, blood, kidney diseases, lead poisoning and other conditions.

Hyperuricemia often leads to the development of **gout.**

This disease is characterized by the deposition of crystals of uric acid salts (urates) in the joints (mainly of the metatarsophalangeal thumb) and around them, in soft tissues,

places of attachment of ligaments, tendons.

https://www.researchgate.net/figure/Chemical-structure-of-uric-acid-1-7-9-dihydro-1H-purine-2-6-83H-trione_fig94_287602840

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