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Evolution of urea from prebiotic molecule to supramolecular architecture

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Abstract. The article shows that urea - as an archetypal prebiotic compound on the one hand, and reactive oxygen-containing compounds - on the other hand, serve as a basis for the formation of an extensive repertoire of chemical compounds, which are represented by various acyclic and heterocyclic carbamide-containing substances. Among the urea-containing substances, this paper pays special attention to using the prebiotic monomer urea as a starting building block in synthetic organic chemistry, including novel macrocyclic and supramolecular systems. Although most of the urea chemistry experiments performed have been conducted under conditions that are far from prebiotic-like states - some intermediate results of the studies performed open the way for the trajectory of the formation of complex nitrogen-containing organic molecules that may emerge from the iterative assembly of urea and reactive components. The proposed work draws considerable attention to various practical applications of acyclic and heterocyclic urea. Among the numerous valuable acyclic and heterocyclic ureas, the most important substances that have found useful applications in human life are highlighted separately. The summarised information on the chemistry and applications of urea indicates its continuous development by the convergence of knowledge in chemistry, physics, materials science and medicine.

Keywords: urea, prebiotics, evolution, acyclic and heterocyclic urea-containing substances, glycoluriles, cucurbituriles, bambusuriles, supramolecular systems.

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Introduction

The edge of the observable Universe is 46.5 billion light-years away. According to astrophysicists, this vast space includes, according to various estimates, from 200 billion to 2 trillion galaxies. And each galaxy contains, on average, about 100 billion stars. Because the birth of chemical elements is one of the main functions of stars, it is not easy to imagine the number

of these elements and their combinations due to nuclear reactions. Nuclear fusion of helium is considered the beginning of all natural reactions, the root cause of life, light, heat and meteorological phenomena on Earth. The original building blocks of the material world were hydrogen and helium, the lightest elements in the Mendeleev table. But today, our universe is a rich and diverse world, populated by countless atoms and molecules, diversified by their interaction through bizarre combinations that result in complex chemical compounds that define life on our planet.

The main question facing astrochemistry is: how far can the synthesis of complex molecules go in outer space? The answer to this question has direct relevance to the problem of the origin of life on Earth. A fundamental question in the research on the origin of life and astrochemistry concerns the actual processes that initiate the diversity of chemical compounds. Some answers to this problem are found in the most plausible description of the processes of transformations of substances compatible with environments probable to Earth during the origin of life, as well as in cosmic conditions. Many simple and complex organic compounds have been found in space objects. A few examples are hemolithin, a protein containing iron and lithium found in the meteorite Acfer 086. It's believed to be the first extraterrestrial protein discovered. A large number of organic inclusions were found in the Murchison meteorite-nucleic bases [1], amino acids, with L- enantiomers predominating [2].

In the Murchison meteorite and in meteorite NWA 801 (Morocco) it was possible to find about 10 carbohydrates [3]. These findings are interpreted by some scientists as evidence that organic compounds brought from space by meteorites could have been involved in the origin of life on Earth [4]. More than 50 stable organic molecules have been found in the interstellar medium, based on astronomical observations, in both the gas and solid phases [5]. There is a view that some of these organic substances eventually ended up on the early Earth under the influence of cosmic factors, which contributed to the origin of life on our planet.

On the other hand, there is an equally valid alternative path to the origin of life on Earth. Thus, chemists from Harvard University during experiments to simulate lightning strikes in the conditions of the "early Earth" found that during this process, carbon and nitrogen could be converted into important molecules, for example, carbon monoxide, nitrite, ammonium salts, formic acid and other compounds. It is believed that these compounds, formed through a series of chemical reactions, may have played a key role in the formation of life on Earth. Although, the reader may say - why invent mechanisms for synthesizing complex pre-organic compounds on Earth, since they were already present in our planetary system initially. But, such point of view leads the reader away from the scientific understanding of the problem of the origin of life on Earth. To test the hypothesis that the interaction of certain molecules triggers chemical reactions that lead to the formation of amino acids and other biotic compounds conducted scientific research using the program Allchemy. As it turned out, for the emergence of life was sufficient for the presence of molecules of water, nitrogen, hydrogen sulfide, ammonia and cyanide, which the researchers believe a priori at the time of the origin of life was present on Earth. The Allchemy program also identified new pathways for the prebiotic synthesis of organic compounds such as glycine, acetaldehyde, malic, fumaric, citric and uric acids. In 2024, Chinese scientists exposed glycine to gamma radiation to produce glycine from methane, oxygen, water and ammonia, molecules commonly found in space [6].

Based on the results of these studies, one can easily construct a chemical trajectory of urea formation from glycine, which in turn, with the participation of simple carbonyl compounds, is quite simply transformed into various nitrogen-containing acyclic and heterocyclic compounds, including urea or uric acid.

The most likely astronomical sources of urea and related compounds are photoprocesses occurring in outer space and bodies. Modeling of this kind of photochemistry using a condensed

methanol-ammonia ice mixture irradiated with UV light at 80 K revealed the formation of, among other things, urea, glycolic acid, and glycerol in a nonvolatile organic residue [7].

This paper shows that the reactions of urea - as an archetypal prebiotic substance - and reactive oxygen- containing compounds lead to an extensive range of chemical compounds, which are represented by various acyclic and heterocyclic nitrogen-containing compounds. The material outlined herein covers the application of urea, the first artificial prebiotic molecule, as a synthon to form an extensive molecular repertoire that can be composed of rather trivial condensation of urea and oxygen-containing substrates, probable astrochemical and prebiotic molecules. Although most of the urea chemistry experiments performed have been conducted under conditions that are far from prebiotic-like states - some interim research results shed light on the pathways for the formation of complex nitrogen-containing organic molecules that may emerge from the iterative assembly of urea and reactive components.

In view of the above, this work demonstrates the use of prebiotic urea monomer as a building block in synthetic organic chemistry, including novel supramolecular systems.

General characterization of urea. Urea is a colorless crystalline substance, odorless, cool to the taste. It dissolves well in polar solvents and poorly in non-polar organic solvents. The melting point of urea under standard conditions is 132.6°C and the density is 1.335g/cm^3. The bulk density is 0.52-0.62 kg/l. Urea, being a diamide of carbonic acid, although it shows typical properties of amides, but due to the peculiarities of its structure, it shows its own properties leading to the formation of a variety of acyclic and heterocyclic nitrogen-containing compounds. The chemical properties of urea are due to the presence of three reactive groups in its molecule - two amine groups and one carbonyl group. However, the C=O group has low reactivity and does not enter into reactions characteristic for C=O groups of ketones. This is explained by the fact that the C=O group of urea has a partial rather than a full double bond, due to the conjugation of its π-electrons with unshared pairs of nitrogen electrons occupying 2p-orbitals. Urea crystals belong to tetragonal syngony, space group P421m, Z=2, a=5.645 Å, b=5.645 Å, c=4.704 Å. The bond lengths of C-O, C-N and N-H are 1.26 Å, 1.34 Å and 0.77 Å, respectively, the valence angles of N-C-O and N-C-N are 121° and 133.1. The C=O bond length in urea is longer than in ketones, and the C-N bond length is shorter than in amines (Table 1) [8].

Table 1. Comparative lengths of carbon-oxygen and carbon-nitrogen bonds in organic compounds of different classes

Carbon- oxygen bonding	Length, Å	Carbon- nitrogen bonding	Length, Å
C=O	1.26 (urea)	C–N (urea)	1.34
C=O	1.21 (ketones)	C=N (imines)	1.27
C–O	1.43 (alcohols)	C–N (amines)	1.47

Currently, in industry, urea is synthesized from NH_3 and CO_2 according to a two-step process: through the exothermic formation of ammonium carbamate ([NH_4]+H_2 NCOO-) from liquid ammonia and carbon dioxide, followed by endothermic decomposition of ammonium carbamate, which produces urea and water (Figure 1).

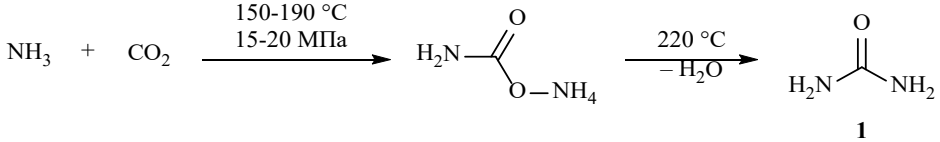


Figure 1. Urea production scheme

The current scale of urea production is approximately 100 million tons per year, with more than 90% of the production destined for use as fertiliser [9,10].

Literature review

Effect of urea on biochemical processes in the body.

The presence of the urea fragment in many drugs, in metabolic products of nitrogen-containing compounds and in many biologically important natural compounds (enzymes, nucleotides, vitamin B13) makes it a subject of increased interest in biochemistry.

Urea is the most important product of nitrogen metabolism, the end product of amino acid metabolism. Urea is synthesized from ammonia, which is constantly formed in the body during oxidative and non-oxidative deamination of amino acids, during hydrolysis of glutamic and asparagic acid amides, as well as during the breakdown of purine and pyrimidine nucleotides. Part of ammonia is formed in the intestine as a result of the action of bacteria on food proteins (protein putrefaction in the intestine) and enters the blood of the portal vein [11]. In mammals, the main pathway responsible for the removal of these products is the synthesis of urea in the liver in the so-called ornithine cycle. The largest amount of ammonia formed in the body is used for the synthesis of urea, which is excreted with urine as the main end product of protein metabolism in humans and animals. In the liver, its activity is strictly controlled to maintain the concentration of ammonia in the liver within strictly defined limits. This makes it possible to exclude the entry of ammonia into the systemic bloodstream, since an increase in its concentration in blood plasma leads to impaired function of the central nervous system [12]. In the process of evolution, living organisms have developed different types of nitrogenous metabolism. This is the ammoniotelic type, in which the main end product of nitrogen metabolism is ammonia; it is characteristic mainly of fish. In the ureotelic type of metabolism, the main end product of protein metabolism is urea; this type is characteristic of humans and animals. Uricotelic type is characteristic of birds and reptiles; the main end product of this type of metabolism is uric acid [13]. Nitrogen balance in the body is regulated by the production of urea [15].

One of the most important aspects of the manifestation of urea properties is its induced denaturation of proteins in aqueous solutions [15] and chiral recognition of amino acids by urea-based receptors [16].

Concentrated (6-8 M) aqueous solutions of urea are usually used in protein denaturation. The urea molecule mimics a peptide bond and is able to act both as a donor and an acceptor of hydrogen bonds, competing with peptide and other functional groups of the protein that form a developed system of hydrogen bonds in native form (Figure 2).

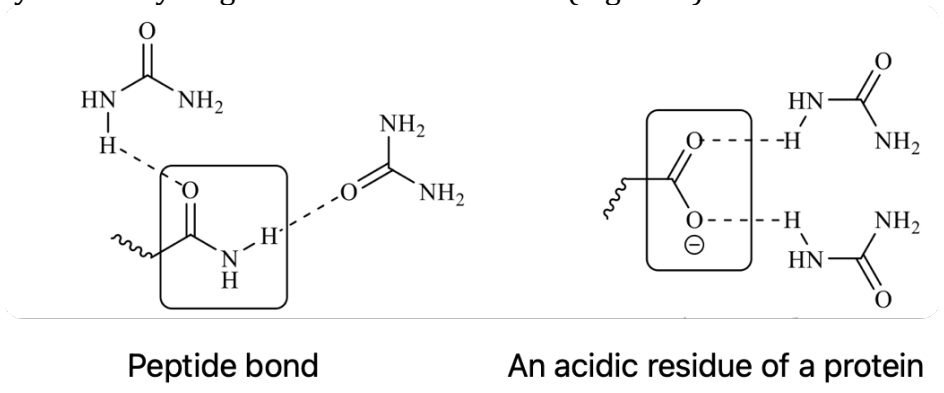


Figure 2. Schemes of formation of hydrogen bonds of urea with proteins

Protein denaturation is often accompanied by damage to covalent bonds. For example, prolonged urea action at elevated temperatures can lead to carbamoylation of the NH_2-group of lysine (Figure 3):

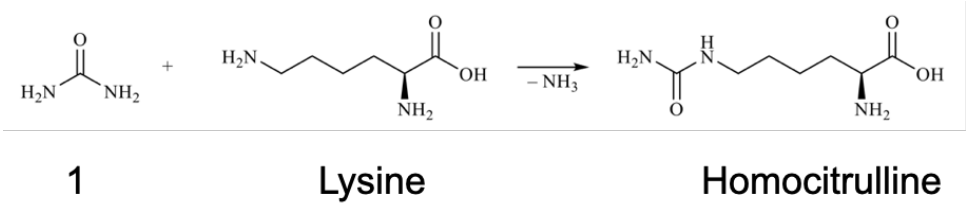


Figure 3. Scheme of carbamoylation of NH_2-group of lysine

Urea has low lipid solubility and consequently low permeability through artificial lipid bilayers (4×10^{-6} cm/s), which lack any transport proteins to facilitate its transport. In clinical practice, urea plays an important role in laboratory diagnosis and is of great renal importance. Blood urea nitrogen (BUN) analysis is commonly used to measure the amount of nitrogen from urea in the blood. It assesses kidney function and indicates kidney health [17]. Elevated blood AMK indicates impaired renal function and is associated with many factors: Urea plays an important role in neuropsychiatry, and AMK is considered a biochemical indicator of delirium in emergency and intermediate care units [18]. In humans, urea can be excreted with sweat, tears, saliva, and digestive fluid (faeces) [19].

Methods of urea synthesis. The existing methods for the preparation of urea, which have found practical and preparative applications, are overwhelmingly based on the transformation of amines under the action of nitrogen-containing (isocyanates, cyanates, urea) or carbonylating (phosgene, CO) reagents [20-27]. Comparatively rare are methods of direct transformation of urea with preservation of urea skeleton (alkylation, acylation, phosphorylation, *etc*.) or Hoffmann rearrangement from amides. The most common methods for the preparation of urea, depending on the substrates and reagents used, will be discussed below, and the pathways for the formation of the urea fragment of the molecule, which are rarely used in synthetic practice, will be shown.

Isocyanate method. Methods of synthesis of substituted urea by transformations of alkylisocyanates under the action of water are essentially the first examples, when 1,3-disubstituted alkylureas, the formation of which occurs according to the scheme in Figure 4, were obtained:

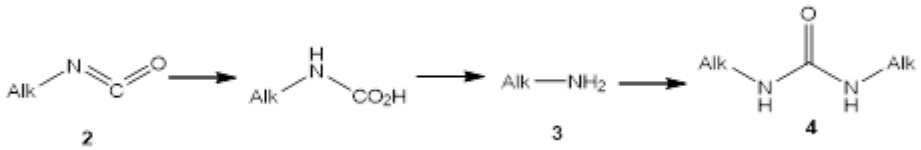


Figure 4. Scheme for production of substituted urea

Although urea synthesis from isocyanates was first carried out more than 160 years ago, this method is still relevant today. Due to its preparative simplicity and good yields, the reaction of organic isocyanates with amines remains the most popular method for the preparation of asymmetric urea, including their chiral derivatives. Over the last ten years, the isocyanate method has been used in the synthesis of aryl-ketarylureas, which are characterized by a variety of practically useful properties, di- and trisubstituted adamantylureas, triterpene ureas, macrolides, ureidopeptides, etc. At the same time, it is recognized that the main limitation of this method is the relative inaccessibility of starting organic isocyanates. Often, the direct synthesis of urea is preceded by a rather laborious multistep synthesis of the corresponding amines and/or organic isocyanates.

Phosgenation of amines. By interaction of phosgene with primary and secondary alkyl-, arylalkyl- and arylamines, only symmetrical 1,3-disubstituted ureas are obtained. The history of this method goes back to the 19th century, when in 1849 Hoffmann first synthesized 1,3-diphenylurea by passing phosgene through a saturated aqueous solution of aniline (Figure 5):

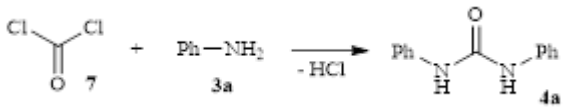


Figure 5. Scheme of diphenylurea synthesis

The process of phosgenation of amines is well enough investigated, details of the mechanism are revealed, its high efficiency for synthesising symmetric urea is shown. But, it should be noted, high toxicity and low selectivity of phosgene imposed its limitations on its application.

In recent years, the use of bis-electrophilic analogs of phosgene has become one of the methods of improving the methods of synthesis of 1,3-disubstituted urea. Thus, bis(trichloromethyl)carbonate proved to be excellent for realization of this kind of reaction, and the synthesis with its participation was carried out on a liquid-phase polymeric carrier. Sufficiently attractive synthetic analog of phosgene in the preparation of urea turned out to be low-toxic and fusible ethylene carbonate. The proposed method allows to obtain unsymmetrical urea as well. Another method of urea synthesis was proposed by the authors of the work, where the high synthetic potential of carbamoylimidazolium salts, which can be considered as urea derivatives, was used. The high ability to substitute the imidazolium fragment in reactions of secondary amines with the salts was used for the synthesis of a large number of tetrasubstituted urea, as well as carbamates and amides. It is important to emphasize the mechanistic and simplicity of the approach, which includes the possibility of diversifying the nucleophiles used and automating the isolation process. Considering the comparative simplicity of synthesis and availability of carbamoylimidazolium salts, to date, this method of urea synthesis can be considered as the most efficient and promising. Recently, 1,1'-carbonyldi(benzotriazole) was successfully used in the solid-phase synthesis of asymmetric ureidodicy acids containing two different amino acid residues. To purify the products from benzotriazole impurity, its extraction with borate buffer solution (pH 9.2) was proposed.

Reactions of amines with alkali metal cyanates. The first synthesis of substituted urea from alkylamine sulfate with potassium cyanide was carried out by Wurtz in 1851 (Figure 6):

Figure 6. Scheme of synthesis of monosubstituted urea

This cyanate method was further extended to a wide range of amines. A modification of the cyanate method for preparing substituted urea is the interaction of alkyl halides (chlorides, bromides) with alkali metal cyanate in aqueous solutions. Despite the ease of realization of carbamoylation reactions of amines when working with alkali metal cyanates, the main limiting condition for the process is the high toxic properties of these compounds.

Reactions of amines with urea. The interaction of urea with amines in melt or in solutions is one of the popular and convenient methods for the synthesis of a wide variety of urea (Figure 7). Both amines and their salts in the form of hydrochlorides, sulfates or phosphates are used as condensing reagents. The procedure for the preparation of substituted urea is usually the heating of a mixture of urea and amines at temperatures of 150-180°C, resulting in a mixture

of products consisting of mono- and 1, 3- disubstituted urea, the composition of which is regulated mainly by the molar ratio of the reagents and, to a lesser extent, by -other reaction conditions.

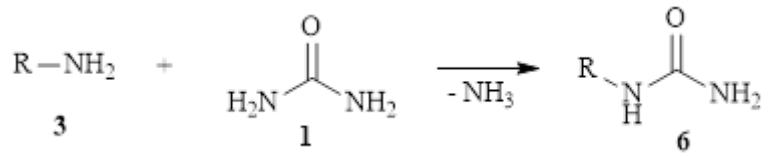


Figure 7. Scheme of reaction of urea with amines

By varying the ratio of amine and urea, this process can be directed either toward the preferential formation of monosubstituted urea or 1,3-disubstituted urea. Sometimes, to accelerate the process and increase the yield of target products, the interaction of urea with amines is carried out in high-boiling solvents -decalin, phenol, cyclohexanol. Modification of the above method by using nitrourea in aqueous or aqueous-alcoholic medium instead of urea allows to carry out reactions with amines under mild conditions. This process is convenient because the nitramide formed during the decomposition of nitrourea under the conditions of synthesis irreversibly decomposes into water and nitrous oxide, thereby shifting the equilibrium towards the formation of isocyanic acid, which of course determines the obtaining of the corresponding urea. This method has advantages over other methods given above in that it does not require working with highly toxic substances such as KCN, isocyanates, pyridine; it is characterized by simplicity of carrying out and apparatus design; yields of final products are not lower than in other methods.

Thus, aminolysis of urea with amines of various structures allows to synthesize symmetric and asymmetric ureas, and in some cases serve as a good method of identification of liquid and oil-like amines in the form of crystalline ureas. Reaction of urea with amines for identification of the latter is convenient because the resulting N-substituted ureas are well crystallized and easily analyzed by traditional methods

Other methods of urea synthesis. In addition to the above methods, there are other methods for the preparation of N-substituted urea, which are fundamentally different from those discussed earlier and rely on the chemical properties of urea. Among these methods the processes of condensation of urea with formaldehyde in aqueous alkaline, which lead to methylol- and dimethylolurea, which are the initial products for obtaining urea resins, stand out.

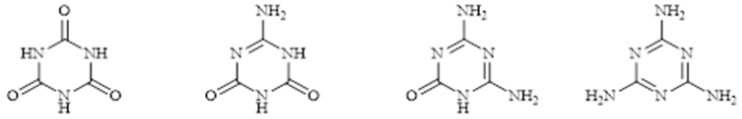
Aldehydes and ketones with urea under hydrogen pressure in the presence of nickel and cobalt catalysts give the corresponding N-alkyl- and N, N-dialkylureas in satisfactory yields (reaching 75-77%). The process is generally carried out at temperatures of 60-150°C, with monoalkylureas being formed at 60-100°C and dialkylureas at 100-155°C.

One of the attractive but poorly studied methods for the synthesis of N-substituted urea is the alkylation of urea with alcohols. In the preparative practice of N-substituted urea synthesis, there are few examples of direct interaction of alcohols with urea, and those are mainly related to reactions of aliphatic alcohols. There are single data on alkylation of urea with organic halides. The way to organometallic urea (Si, P, Se) passes through the traditional ways of urea preparation in which the corresponding element-containing reagents and substrates are used.

The above methods of urea synthesis have opened the way to the synthesis of a large number of nitrogen-containing acyclic and heterocyclic compounds.

The most important urea-containing heterocycles. Cyanuric acid, 1,3,5-triazine-2,4,6-trione A, is almost the main representative of azaheterocycles containing three nitrogen atoms and synthesized on the basis of urea (Figure 8). Due to its unique properties, it is widely used

in various industries. Cyanuric acid is obtained mainly by pyrolysis of urea in organic solvents, in a fluidized bed on the surface of metals. However, during pyrolysis of urea, along with cyanuric acid A, related triazines - ammelid B, ammelin C, melamine D-amination products of cyanuric acid are formed, which are of independent practical interest [28].



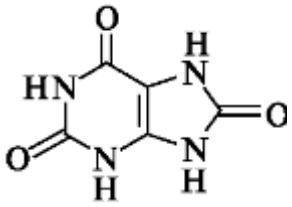
A **B** **C** **D**

Figure 8. Structural formulas of cyanuric acid A, ammelide B, ammelin C and melamine D

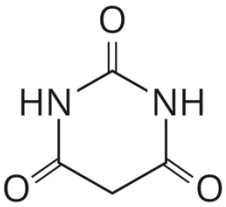
All of these heterocycles are products of cyclic trimerization of isocyanic acid and/or cyanamide.

Pyrimidine bases and hydroxypurines.

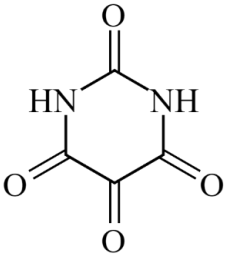
The methods of preparation of pyrimidinones and hydantoins and their chemical properties are quite well covered in the literature [29-37], the most important ones are given below.



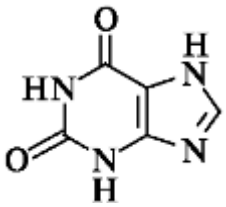
Uric acid. It was discovered by Carl Scheele (1776) as part of urinary stones and called by him acide lithique, then it was found by him in urine. Uric acid is oxidized to alloxane by nitric acid, under the action of potassium permanganate in neutral and alkaline medium or hydrogen peroxide from uric acid is formed first allantoin, then parabanic acid. I. J. was the first to synthesize uric acid. Gorbachevsky in 1882 by heating glycocol (aminoacetic acid) with urea to 200-230°C. Uric acid is the starting product for the industrial synthesis of caffeine.



Barbituric acid - Derivatives of barbituric acid containing alkyl or aryl substituents and their salts are called barbiturates[1]. Barbituric acid was first synthesized by Adolf Bayer in 1864 by condensation of urea with malonic acid [2]. A modern modification of Bayer's synthesis is the use of the diethyl ether of malonic acid in the presence of sodium ethylate. Barbituric acid is used to obtain riboflavin, pyrimidine, violuric acid and uric acid.

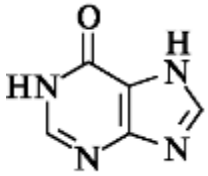


Alloxan (mesoxalylurea) is formed by the action of oxidizing agents on uric acid in the presence of free strong acids. Alloxan is formed by introducing uric acid in small portions into cooled concentrated nitric acid or by gradually adding bertolitic salt to the uric acid mixture. The salt solutions decompose on boiling to form mesoxalic acid and urea.

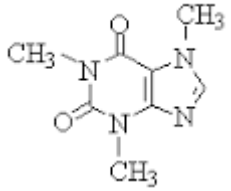


Xanthine was synthesized by Armand Gauthier in 1884. The imidazole cycle of xanthine is nucleophilic: xanthine is halogenated to form 8-halogenxanthines, azo-combination with diazonium salts also proceeds to form 8-azoxanthines, which can then be reduced to 8-aminoxanthine or hydrolyzed to uric acid. In neutral medium, xanthine is methylated by dimethyl sulfate on imidazole nitrogen atoms to form a dimethyl derivative of zwitter-ionic structure, depending on the pH of the reaction mixture, xanthine is methylated to 3,7-dimethyl- xanthine (theobromine), 1,3-dimethylxanthine (theophylline) or 1,3,7-trimethylxanthine (caffeine). Xanthine is reduced by sodium amalgam or zinc in hydrochloric acid to 6-deoxyxanthine; under the action of potassium permanganate in acidic medium xanthine is oxidized with degradation of the imidazole cycle to 2,4,5,6- tetraoxopyrimidine (alloxan). Xanthine is a product of purine catabolism and is formed

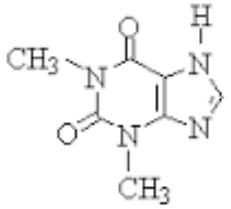
as a product of guanine degradation by guanine deaminase and by oxidation of hypoxanthine by xanthine oxidase. Under the action of the same xanthine oxidase, xanthine is further converted to uric acid. Xanthine derivatives include a number of stimulants such as caffeine and theobromine. Abiogenic xanthine (along with uracil) was discovered in the Murchison meteorite.



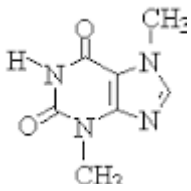
Hypoxanthine is a natural derivative of the nitrogenous base purine. It is sometimes found in nucleic acids, where it is present in the anticodon of tRNA in the form of the nucleoside inosine. Hypoxanthine is formed by the reduction of xanthine by the enzyme xanthine oxidoreductase. Hypoxanthine is also a product of spontaneous deamination of adenine.



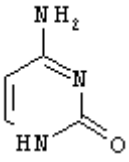
Caffeine (theine) is a purine alkaloid found in plants such as coffee, tea, cocoa, Paraguayan holly (yerba mate), guarana, cola and others. In medicine, caffeine is used as a headache remedy, in migraine, as a respiratory and cardiac stimulant in colds, to increase mental and physical performance, to eliminate drowsiness. In industry, caffeine is synthesized from uric acid and xanthine. Traditional synthesis from uric acid consists of 2 stages: the action of formamide on uric acid, resulting in the formation of xanthine. In the 2nd stage, xanthine undergoes methylation with dimethyl sulfate, and depending on the conditions, caffeine and theobromine may be obtained. Caffeine is obtained in a slightly alkaline medium at pH = 8.0-9.0. If methylation occurs in the presence of KOH and methanol at 60-70°C, theobromine is formed. An alternative semi-synthetic method is the heating of uric acid with acetic anhydride in the presence of a catalyst to form 8-methylxanthine. The obtained 8-methylxanthine is methylated, and depending on the reaction conditions, 1,3,7,8-tetramethylxanthine or 3,7,8-trimethylxanthine can be obtained. When 8-methylxanthine is methylated with excess dimethyl sulfate in slightly alkaline medium, 1,3,7,8-tetramethylxanthine is obtained, and when methylated with methyl ester of benzene(toluene)-sulfonic acid (220-230°C in the presence of CaO), 3,7,8- trimethylxanthine (8-methylteobromine) is obtained. There is also a synthesis from cyanacetic acid and dialkylurea, which is the most economical.



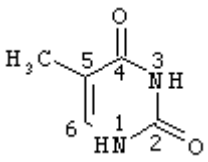
Theophylline (1,3-dimethylxanthine) is a methylxanthine, a drug used in the treatment of respiratory diseases such as chronic obstructive pulmonary disease and asthma, available under various trade names. It is a derivative of the xanthine family, structurally and pharmacologically similar to theobromine and caffeine. Theophylline is found in cocoa beans.



Theobromine is a purine alkaloid that can be converted into caffeine either by heating to 100°C with methyl iodide, caustic potassium and alcohol, or by precipitation of the silver salt of theobromine with methyl iodide. In medicine, theobromine is used to treat bronchopulmonary diseases. The double salt of theobromine with sodium salicylic acid, known as *diuretin*, is also used.

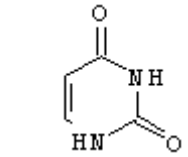


Cytosine is a nitrogenous base, a derivative of pyrimidine. Cytosine exhibits basic properties, reacts with alkalis and acids, reacting with nitric acid it is deaminated to become uracil. It enters into photohydration reaction with the formation of cytosine hydrate, attaching water under the action of ultraviolet rays.

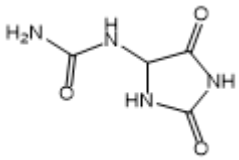


Thymine (5-methyluracil) is a pyrimidine derivative, one of the five nitrogenous bases. It is present in all living organisms, where together with deoxyribose it is part of thymidine nucleoside, thymine deoxyribonucleotides are part of DNA, in RNA it is replaced by uracil ribonucleotide. Thymine is complementary to adenine, forming hydrogen

bonds with it. According to research, thymine dissipates the energy of ultraviolet radiation, protecting DNA from its damaging effects

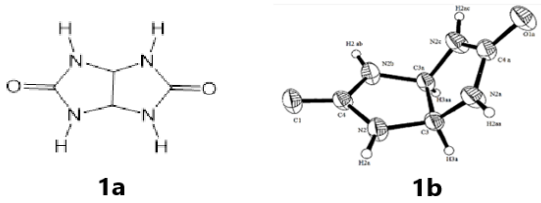


Uracil(2,4-dioxopyrimidine)-pyrimidine base, which is a component of RNA and is usually absent in DNA, is part of the nucleotide. In nucleic acids, it can bind complementarily to adenine, forming two hydrogen bonds. First detected in the products of yeast nucleic acid cleavage.



Allantoin is a heterocyclic compound, a five-membered cycle containing a carbamide substituent at the 4th position. Allantoin was discovered in the callus of the coffee plant Coffea Arabica. Several methods are currently known for the isolation of allantoin from natural raw materials from cell culture of Coffea arabica and from leaf explants and apical shoots of Mertensia maritima. Allantoin has found wide application as one of the active components in skin care products, promotes healing of scar tissues and scars, which makes it in demand in cosmetology and pharmaceutical practice. Today allantoin is included in more than 1300 different cosmetic products. The main consumers of allantoin are manufacturers of cosmetic products, as well as enterprises of the pharmaceutical industry, which use it as a raw material for the production of drugs for the treatment of various diseases. In addition, allantoin is used in agriculture, as a plant growth regulator, as part of fertilizers and veterinary disinfectants.

Glycoluriles. In the chemistry of heterocyclic compounds, bicyclic bisurea(BBM) occupy a special place, among which 2,4,6,8-tetraazabicyclo[3.3.0.]octane-3,7- dione 1 (glycoluryl) (Figure 9) and its derivatives are of the greatest interest.[38-48]. The history of glycoluryl chemistry dates back to the second half of the 19th century, when a number of researchers succeeded in synthesizing the progenitor of this class of compounds. The first report on the synthesis of glycoluriles was made by Schiff in 1877. Since then, the chemistry of glycoluriles, primarily due to the polyfunctionality of their structure, has undergone rapid development, which is reflected in the creation of valuable substances based on them in various spheres of human activity: disinfectants, drugs, stabilizers of polymers, independent explosives or their components and other important substances and materials.



1a **1b**

Figure 9. Structural formula of glycoluryl 1 (1a) and its spatial configuration in the crystal (1b)

As can be seen from Figure 9, the glycoluryl molecule is non-flat. It looks like a "half-open" book, which mainly determines its tendency to form macrocyclic compounds with different number of glycoluryl links. Glycoluryl is a polyfunctional compound in which the urea fragment (Figure 9) essentially determines the properties of the molecule, which are due to the presence of two reaction centers in the molecule (4 donor groups (-NH) and 2 acceptor groups (C=O)). Glycoluryl has the properties of a very active n- nucleophile and an essentially deactivated p-nucleophile. It enters into N-alkylation, N-acylation, N-halogenation, N- nitration, N-nitrosation, N-hydroxyalkylation, etc. reactions. However, the presence of the bond (NH-C=O) with the electron acceptor carbonyl group makes it less reactive base, therefore, it is difficult to protonate, and its products formed as a result of electrophilic attack on the nitrogen atom are prone to decomposition, and the weak electrophilic properties of the carbonyl group, due to the

influence of two unshared pairs of electrons from nitrogen atoms, which compensate for the electron acceptor effect of the carbonyl group.

Many synthesis methods have been developed during the study of bicyclic bisurea (BBM), where one of the most convenient is the method for the preparation of glycoluriles based on urea and α-dicarbonyl compounds (Figure 10). Molecules of glycoluryl derivatives with different number of substituents on N-, C- atoms can be synthesized both directly and by further modification of glycoluryl itself. Due to the valuable properties of HBMs, methods of their synthesis using urea are constantly being improved. Classification of PMBMs, provides consideration of structural units, which are characterized by the size of cycles and methods of their joining[49]:

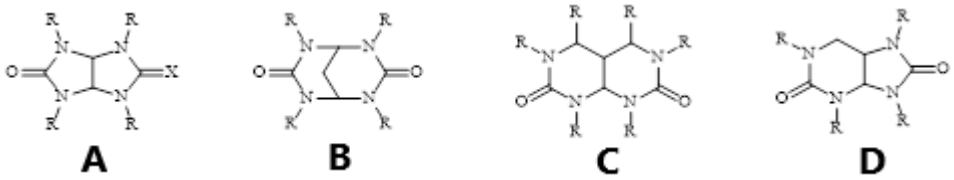
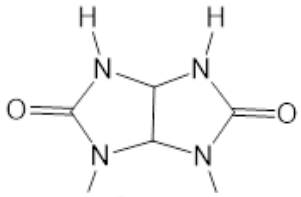


Figure 10. Bicyclic bisurea bisoureas of octane A, nonane B and decane series - C and D

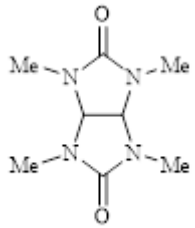
The above-mentioned PMs contain octane, nonane and decane skeletal bases in their structure. Bicyclooctane-type PBMs are synthesized by reaction of 1,2-diketones, a-hydroxyketones, a-ketomonooximes and a- isonitrosoketones with urea, mainly under acid catalysis conditions. The octane series PBMs can be prepared in a stepwise manner. Initially, 4,5-dihydroxyimidazolidin-2-ones are synthesized from the corresponding 1,2- bifunctional compounds (usually from 1,2-dicarbonyl compounds) and urea, which are then cyclized with urea. The advantage of the stepwise synthesis of BBMs is that this approach allows to obtain BBMs of asymmetric structure. BBMs of bicyclononan series are synthesized by reaction of 1,3-dicarbonyl compounds or their analogs with ureas. BDMs of bicyclodecane series are usually synthesized from preliminarily obtained ureidopyrimidines or by interaction of the latter with aldehydes.

Methods for the synthesis of glycoluriles are constantly evolving, since they are not only of independent interest as biologically active compounds, but also are precursors for obtaining a large number of compounds with practically significant properties.

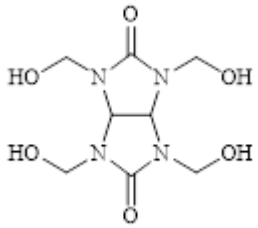
Practically valuable glycoluryl-based substances.



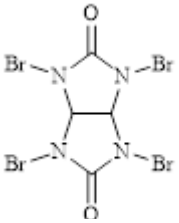
Glycoluryl has found industrial application as a slow-release agent, are also versatile precursors of polycyclic ring systems.

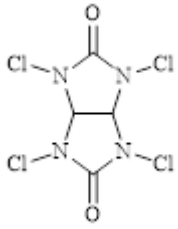


Mebicar is a daytime tranquilizer of wide application, It regulates disturbed night sleep without having a direct sleeping effect. Eases or relieves nicotine withdrawal.

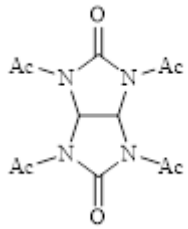


Tetrahydroxymethylglycoluryl - used as a cross-linking agent in the preparation of glycoluryl-formaldehyde resins and high-quality thermosetting coatings. It is used in the manufacture of negative-type photoresistors, is a stabilizer of water-based dyes, is used in the synthesis of supramolecular objects, and as a bactericidal agent of aqueous compositions.

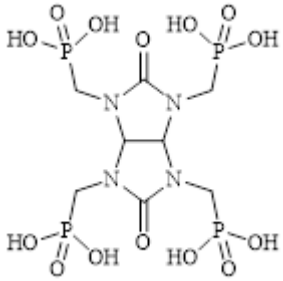




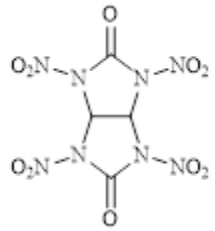
Halogen derivatives of glycoluryl - find wide application as oxidizing agents, halogenating agents, disinfectants, bleaching agents, detergents, have bactericidal activity, which depends on the type of halogen.



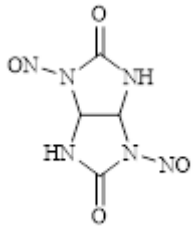
Tetraacetylglycoluril is a bleaching activator in synthetic detergents, a mild reagent for intermediate protection by acetyl group of biogenic substances (alcohols, sulfides, amines, enzymes) in order to preserve the configuration and optical orientation of the original molecules.



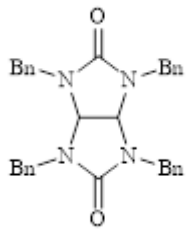
Tetrakis(methylene phosphoric acid)glycoluryl is an efficient catalyst for the synthesis of azagetherscycles



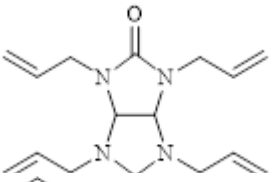
Tetranitroglycoluril - used in mixtures with high-energy explosives, as a component of propellants and gunpowder, booster charge and intermediates of other explosives.



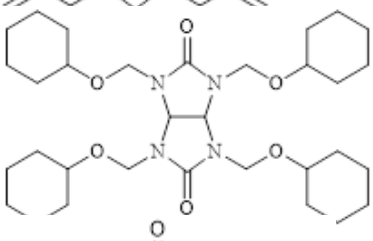
Dinitroglycoluryl - an efficient polymer pore former.



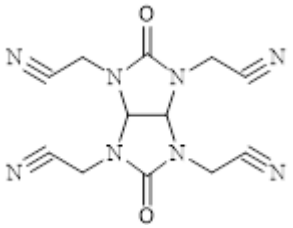
Tetrabenzylglycoluryl - an effective stabilizer for polymeric materials.



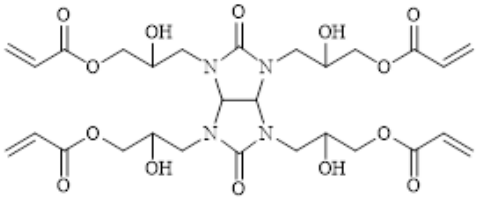
The new functional polymer was prepared by copolymerization of 4- vinylpyridine and **1, 3, 4, 6- tetraallylglycolsulfuryl**



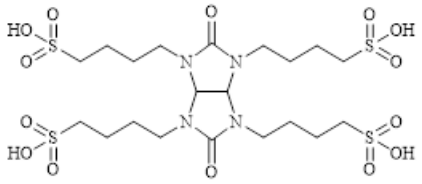
Included in an antireflective coating composition for use with a photoresistor coating.



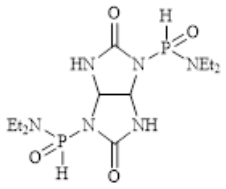
Tetra (2-cyanoethyl) glycoluryl is a convenient synthon for the preparation of novel macrocyclic compounds.

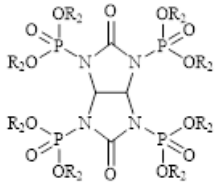


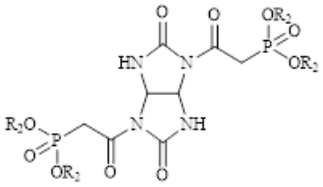
A convenient synthon for the preparation of new macrocyclic compounds.



Nanostructured catalyst for the synthesis of novel compounds.

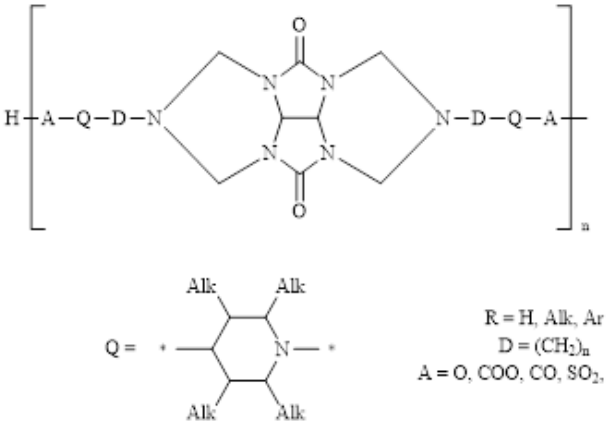




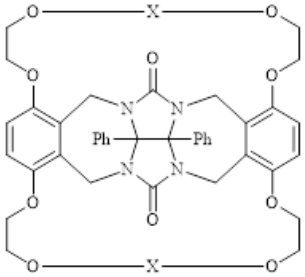


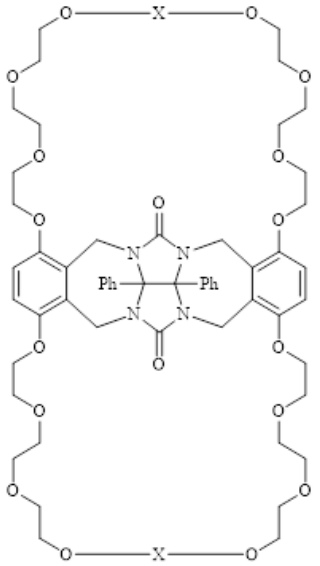
N-Phosphorylated glycoluryl derivatives are flame retardants and are excellent nitrogen-phosphorus synergistic flame retardants [50].

The reactions of glycoluriles with formaldehyde have provided the basis for rapid progress in the chemistry of condensed polycyclic derivatives of glycoluriles, the marocycles, which are of interest as objects of study in chemistry [51, 52].



Macrocyclic polymer with excellent light-stabilizing properties.





Crown ethers form complexes with cations and dicationes (alkali metals, NH_4^+, $AlkNH,H^+$+$3N(CH)_{2n}NH^+$ (n=39), xylene and phenylenediammonium) with 1:1 stoichiometry. According to the authors, the structure of these complexes represents the sandwich and "clamshell" type.

Cryptands (coronands) can form stable complexes with nitroaromatic compounds, e.g. nitrobenzenes.

In conclusion of this summary, we consider it necessary to draw the attention of researchers to the following points in the track of synthesis of new macrocyclic compounds based on glycoluriles.

Glycoluryl is not an ideal template for biomimetic cycling, primarily due to the low solubility of this compound in most organic solvents, which often leads to the use of very harsh conditions for the direct synthesis of targeted macrocyclics. One interesting possibility to overcome this barrier is to utilize other glycoluryl derivatives by adding a reagent to the parent glycoluryl template or, more efficiently, to its reactive adduct, generally leading to various interesting unexpected structures. The design of glycoluryl template in the synthesis of macrocyclic compounds is mostly based on condensation reactions and rarely some other reactions are presented. In addition, based on the generalization, it can be stated that the application of glycoluryl in the synthesis of high molecular weight compounds (polymers) is relatively understudied and has an underdeveloped potential for a wide range of new studies to obtain practically valuable substances. Synthesis and study of chemical properties of bicyclic

bismoureas allowed us to reach new classes of nitrogen-containing heterocyclic compounds with other practically useful properties, such polycyclic condensed systems as propellanes, cucurbit[n]urils and bambus[n]urils, the building blocks of which are glycoluryl.

Propellanes. Of independent interest in recent years is 3,7,10-trioxo-2,4,6,8,9,11-hexaaza [3.3.3] propellane (Figure 11), a cyclic urea derivative consisting of three condensed cycles linked by a common carbon-carbon bond that includes a glycolurilic fragment [53, 54].

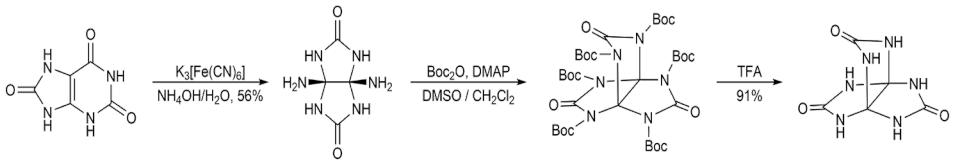


Figure 11. Synthesis of hexaazapropellanes

Interestingly, uric acid was used as the starting compound for the synthesis of this propellane, which led to 1,5-diaminoglycoluril under the oxidizing action of Na S O228. The subsequent tricyclization step was satisfactorily carried out using di-tert-butyl carbonate (Boc2 O), forming the intermediate 27 at room temperature. The final step of removing the protecting Boc group led to the formation of the target product 19, and the structures of 27 and 19 were confirmed by X-ray diffraction analysis. Judging from the experimental data, more successful results were achieved when carbonyldiimidazole was used as a carbonylating reagent instead of di-tert-butyl carbonate. The series of studies is aimed at finding ways to functionalize 3,7,10-trioxo-2,4,6,8,9,11-hexaaza [3.3.3] propellane. To search for new practically valuable substances, methods for preparation of hexaalkyl derivatives of 3,7,10-trioxo- 2,4,6,6,8,9,9,11-hexaase [3.3.3] propellane (methyl-, ethyl-, propyl derivatives), mono- and dinitro derivatives of 3,7,10-trioxo-2,4,6,8,9,11-hexaase [3.3.3] propellane were further developed. The complete acetylation of 3,7,10- trioxo-2,4,6,8,9,11-hexaase [3.3.3] propellane was found to occur in two stages through the formation and release of intermediate 2,6-di- and 2,6,9-triacetyl substituted derivatives of 3,7,10-trioxo-2,4,6,8,9,11- hexaase[3.3.3]propellane.

Macrocycles and supramolecular systems based on glycoluryls.

Cucurbituriles [55-78]. Cucurbituriles are macrocyclic molecules composed of glycoluryl monomers linked by methylene bridges (-CH2 -). The oxygen atoms are arranged along the plane and tilted inward, forming a partially closed cavity. Cucurbiturils are usually written as cucurbit[n]uril, where n is the number of glycoluril units. Two common abbreviations are adopted, CB[n] or simply CBn. and Q Cucurbituriles were first synthesized in 1905 by Behrend by condensation of glycoluryl with formaldehyde, but their structure was not determined until 1981. To date, all known cucurbituriles consisting of 5, 6, 7, 8, 10 and 14 repeating units have been isolated.

The initial process for the synthesis of CB [6] consisted of the interaction of glycoluryl and excess formaldehyde in the presence of HCl to yield a precipitate; this was dissolved in concentrated H2SO4 at 110°C and then diluted with water and crystallized, yielding CB [6]. Kim and coworkers modified the reaction parameters in the synthesis of cucurbituril and diversified the CB[n] family with new penta-, hepta-, and octameric homologues. Carrying out the reaction in 9 M H2 SO4 for 36h at 75-100 °C gives a mixture of isolated CB[n] homologs (n = 5-8, 10), the content of which is 60% CB [6], 20% CB [7], 10% CB [5] and 10% mixture of other homologs (Figure 12). The isolated homologs are further purified by recrystallization.

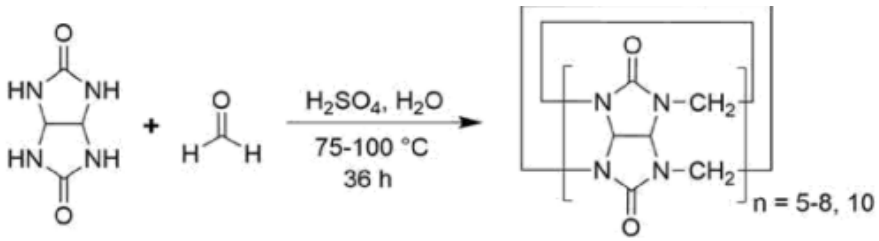
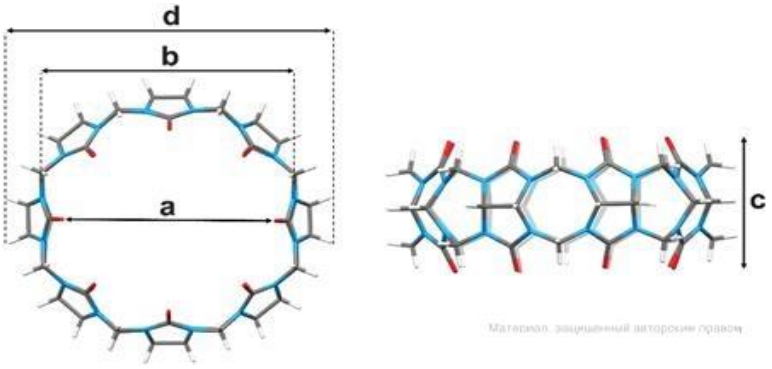


Figure 12. Scheme of synthesis by Kim CB[n] (n = 5-8, 10)

These separation and purification methods are convenient, but in most cases do not guarantee complete purification. Trace amounts of other CB[n] homologues, acids and solvents used in the precipitation and crystallization steps, or cationic particles such as NH4 +, often contaminate the desired CB[n].

Cucurbituriles are of particular interest in the field of chemistry because they are hosts for neutral and cationic compounds. Binding to neutral particles is thought to occur through hydrophobic interactions, and in the case of cationic compounds through cation-dipole interactions. The sizes of cucurbituriles are usually in the range of 10 Å. For example, the cavity of cucurbit [6] uril has a height of ~ 9.1 Å, an outer diameter of ~ 5.8 Å and an inner diameter of ~ 3.9 Å.

The major members of the CB[n] family (n = 5-8) have rather rigid skeletons, in contrast to other macrocycles. However, the largest homologs discovered so far, CB [10], CB [13], CB [14], and CB [15], have structural flexibility. For example, CB [10] has an elliptical crystal structure unlike the major members, while the other senior homologs of CB[n] have twisted crystal structures. The sizes of the most common CB[n] homologs and inverted iCB[n] homologs are shown in Figure 13. For example, for CB[n] (n = 5-8, 10), the cavity diameters are 2 Å larger than the portal diameters, and the difference between the outer and inner diameters is about 8.5-8.8 Å. All CB[n], including the inverted ones, have the same height of 9.1 Å. However, the cavity diameters for the inverted homologs are smaller than their non-inverted counterparts because of the presence of a single glycoluric linker with methyl protons pointing into the cavity.



	Mr	a[Å]	b[Å]	c[Å]	d[Å]	V[Å]
CB[5]	830	2.4	4.4	9.1	13.1	82
CB[6]	996	3.9	5.8	9.1	14.4	164
CB[7]	1163	5.4	7.3	9.1	16.0	279
CB[8]	1329	6.9	8.8	9.1	17.5	479
CB[10]	1661	9.5–10.6	11.3–12.4	9.1	20.0	870
iCB[6]	996	4.3–3.9	3.8–5.8	9.1	10.7–14.4	—
iCB[7]	1163	6.7–5.4	5.4–7.3	9.1	11.2–16.0	—

Figure 13. Structural parameters of the basic CB[n] homologs and inverted CB[n]

CB[n] binds to metal cations through two carbonylated portals; however, most metals interact with only a small fraction of the oxygen atoms at the CB[n] rim (i.e., the metal is usually not in the center of the portal, with the exception of cesium) .65-67 In the case of alkali and alkaline earth metals, multiple cations may occupy the same portal. Transition metal ions do not usually interact directly with the oxygen atoms of the CB[n] rim, and binding occurs between carbonyl groups. In the case of lanthanides, both direct metal-portal and metal-water-portal interactions have been observed. CB[n] can encapsulate numerous organic compounds and, in most cases, the thermodynamic parameters can be determined by UV spectroscopy, isothermal titration calorimetry and 1H NMR.

Applications of cucurbituriles. Cucurbituriles are used in supramolecular, synthetic, medical and material science industries, and find applications in drug delivery (Figure 14).

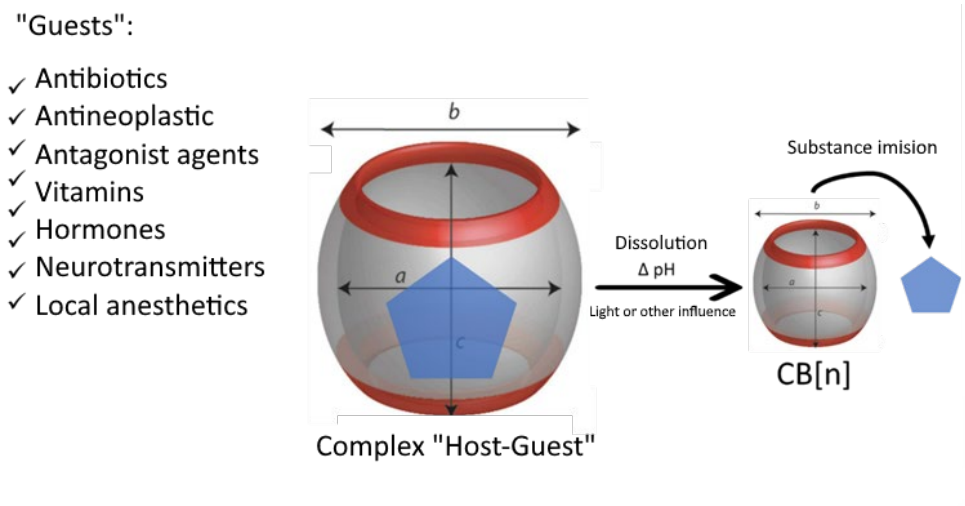


Figure 14. Cucurbituil-based supramolecular complexes and ligand release

In addition to the medicinal applications described above, CB[n] can be used as novel materials: CB[n]-containing polymers, dendrimers, metal nanoparticles, fullerenes, nanosheets, vesicles, films and surfaces, hydrogels. Such highly ordered hybrid materials are in demand for fine purification, separation and isolation of substances, target therapy against cancer, and in catalysis. Functional materials containing CB[n] have received increasing attention in recent years due to their versatile applications in fields including, but not limited to, theranostics, photonics, self-healing, sensing, and catalysis. Research work on the interaction of CB homologs and derivatives with biomolecules and drugs is presented because there have been many promising discoveries of supramolecular interactions between CB and biomolecules and small organic drug molecules that have potential implications in the field of medicine, which has become one of the most significant areas of potential applications for CB. Non- covalent interactions of peptides, proteins and drug molecules with CB homologs and derivatives are reviewed, and the ability of CB to modulate the function and bioactivity of these species through host-guest chemistry and the potential impact of CB on protein enrichment are discussed.

Bambusuriles [78-93]. Bambusuriles were first synthesized in 2010. Bambusuriles (BU[n]) are a family of macrocyclic compounds consisting of n-2,4-disubstituted glycoluryl units connected through a single row of n- methylene bridges at the equator of the macrocycle (Figure 15).

Bambusuriles are prepared by condensation reaction of 2,4- disubstituted glycoluryl with formaldehyde of Mannich reaction type in an acidic medium (Figure 15). The choice of solvent

depends on the glycoluryl linkage and can range from polar water to nonpolar chloroform. Most of the reactions studied lead to the formation of bambusuriles from four or six glycoluryl units. Using microwave synthesis, bambusuryls can be obtained because the reaction time is significantly reduced.

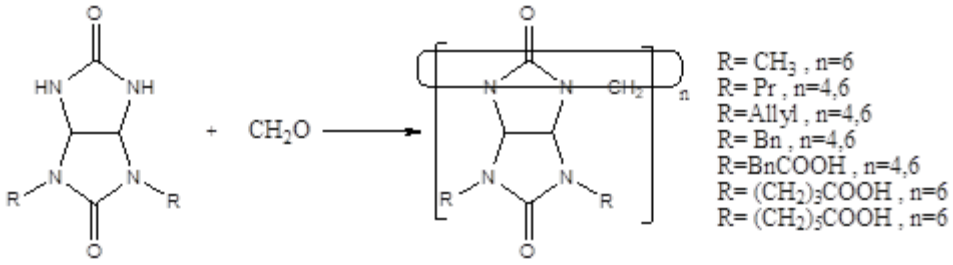


Figure 15. Scheme of bambusuryl synthesis

Currently, only two homologs of bambusuryl have been found, consisting of four (BU [4]) and six (BU [6]) glycoluryl units. These compounds have different supramolecular properties. BU [6] is an excellent receptor for various inorganic anions; however, BU [4] does not bind anions due to the small cavity size. In bambusurils, the methine protons are directed to the inside of the cavity. The shape of the bambusuryl macrocycle resembles part of a bamboo rod, hence the name. Two circles of methine fragment protons inside the macrocycle form the narrowest parts. The anion-binding site is usually located between these rows of methyl hydrogen atoms. Bambusuriles are excellent receptors for a variety of anions. The above-mentioned properties distinguish bambusurils from cucurbiturils. Bambusuryls have a number of advantages over hemicucurbituriles because of their alternative arrangement of building blocks and a single row of methylene bridges. A list of registered bambusuryl derivatives is shown in (Figure 16). The type of substituent has a great influence on the solubility of bambusuryl derivatives. BU [6] is practically insoluble in any solvent, substitution of methyl groups with benzylic groups causes it to be soluble in chloroform and dimethyl sulfoxide. Water-soluble bambusuriles were obtained by incorporating carboxyl functional groups into their structure. Another modification of the bambusuryl structure was achieved by replacing the oxygen atom with a carbon atom.

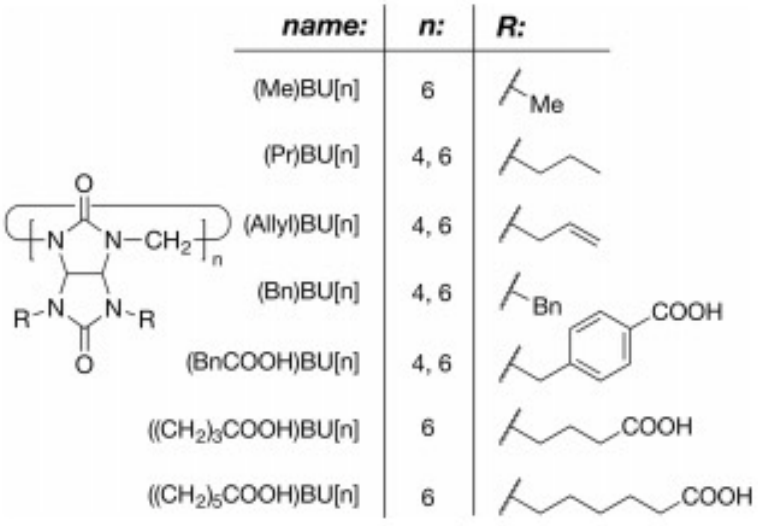


Figure 16. List of registered bambusuryl derivatives

Applications of bambusuriles. Bambusuryls have interesting supramolecular properties, and as a consequence, they can be applied in several fields. Bambusuriles can serve as a variety

of receptors for anions, which is used in organocatalysis, in developing new sensors and creating sensor matrices for anionic agents.

Applications of urea. Many years of research in urea chemistry have created valuable substances and materials that have found wide application in various aspects of human life [20-24, 28-34,37-40,44-49, 52]. Figure 17 schematically depicts the main directions of urea application in different fields of science and technology.

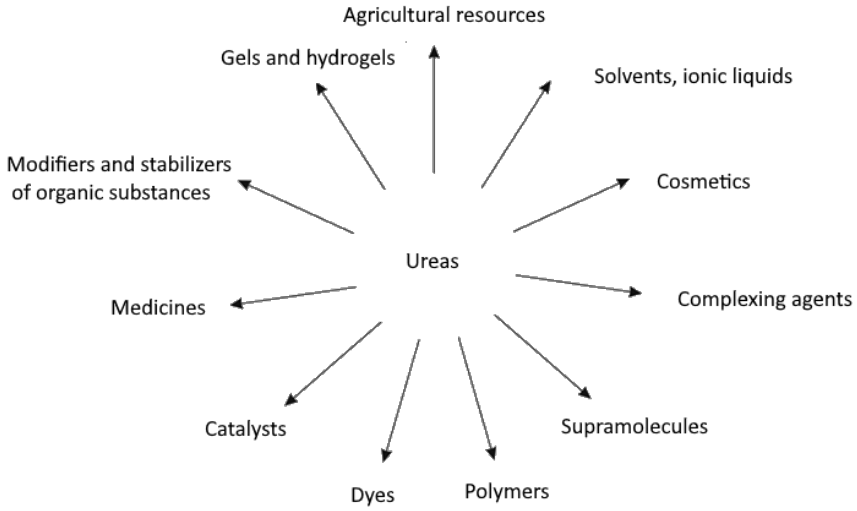


Figure 17. Main applications of urea

For example, urea-formaldehyde resins (UFRs) are the most widely used thermosetting binders in producing wood composite materials for structural purposes, a significant part of which is focused on producing particleboards. CFS is a product of polycondensation of urea and formaldehyde at different molar ratios, in aqueous solution in several stages with variable acidity. Along with other thermosetting, condensation binders, urea- formaldehyde resins are the cheapest and most available product with the ability to cure rapidly in the presence of catalysts, as well as a relatively high concentration at reduced viscosity, which provides low shrinkage in the process of pressing wood boards. The brand range of SFCs has reached an impressive size and continues to grow and improve by developing new grades to replace non-competitive grades. In addition to KPS, various polyureas have been obtained and studied [96-99].

Many complex compounds (CC) of metal salts with urea have been described in the literature. In these compounds, urea, as a rule, is coordinated through the oxygen atom, but there are known cases of its coordination through the nitrogen atom. With the salts of s-metals, urea forms adducts and complex compounds in coordination with the oxygen atom. With salts of p-metals urea forms adducts and complexes also with coordination through the oxygen atom. Coordination compounds of d-metal salts with urea have been studied well enough. Coordination of urea occurs through oxygen atoms, but there is information about coordination through nitrogen atoms. Information on complex compounds of d-metal salts with urea in the literature is presented in large quantities, which can be explained by the strong coordination ability of d-metals due to the presence of vacancies at the (n-1)d-sublevel and good solubility of these metal salts in nonpolar solvents. Coordination compounds of f-metal salts (lanthanides and actinides) with urea are studied quite well, the main interest is because these compounds with the necessary luminescence-spectral properties are promising for use in such areas as lighting engineering, optoelectronics, laser technology, etc.

Effective herbicides and pesticides have been developed based on urea [103-105]. Some ureas have proved to be convenient solvents (tetramethylurea [106] and silylurea [24], chiral ionic liquids) [107], valuable modifiers and stabilizers of organic materials [20], stabilisers of

photosensitizing materials in solar cells [108]. Among ureas, hydrogels have been found in the preparation of cyclodextrin/cellulose, biodegradable hydrogels with good mechanical properties, chiral urea derivatives are highly gel-forming towards organic solvents [109-110] and catalysts have been found for various processes [111-113].

Ureas are excellent reagents for synthesising many nitrogen-containing acyclic and heterocyclic compounds, the potential of which is illustrated in Figure 18.

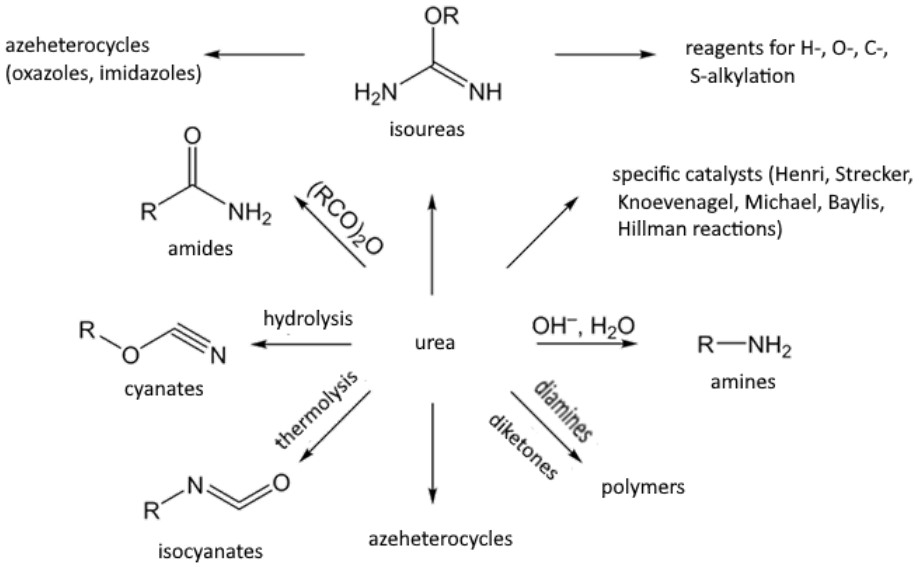


Figure 18. Ways of using urea in organic synthesis

Urea-based pharmaceuticals. Although urea itself as a medical drug has very modest capabilities, there are many examples of the use of its derivatives as sleeping pills, narcotic, antipyretic, analgesic and anticonvulsant agents, for the treatment of diabetes, glycemia and helminthic diseases [114-120]. High antimicrobial, proteolytic, inhibitor, antiepileptic activity, etc. were found among the first synthesized urea.

Due to the high biogenic activity of urea, the transport of which involves many processes in the body, introducing a urea fragment into substances with well-known biological activity allowed, in some cases, to obtain interesting results.

Drugbank (version 4.3), among approved and investigational drugs, contains 148 compounds derived from acyclic urea. The ChEMBL bioactivity database (version 20) includes 76,494 biologically active urea-containing molecules, corresponding to about 5% of the indexed molecules. Of these, 34232 preparations contain an N,N'-disubstituted urea moiety and 39426 contain a trisubstituted one (Figures 2, 19) [114-120].

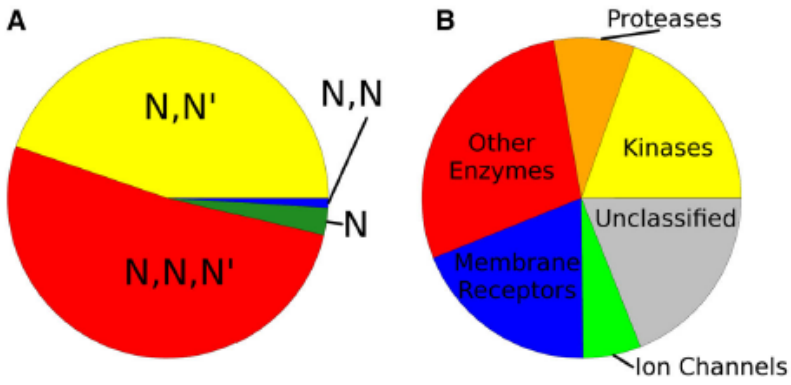
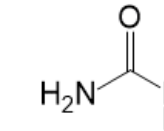


Figure 19. Biological activity of urea derivatives

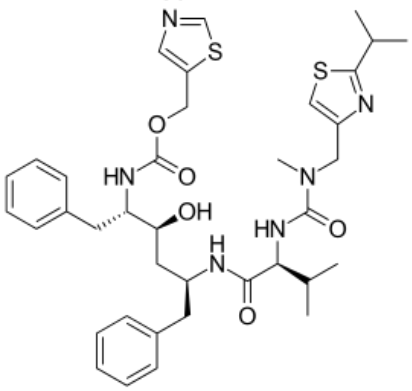
The vast majority of urea-containing compounds, in ChEMBL, are either N,N'-disubstituted (yellow) or trisubstituted (red). Monosubstituted ureas (green) as well as N,N-disubstituted ureas (blue) are less common. Urea derivatives are known to exhibit diverse biological activities toward kinases (yellow), proteases (orange), and other enzymes (red), as well as membrane receptors (blue) and ion channels (green).

Interestingly, preparations with terminal ureide groups are rare: 2092 molecules based on monosubstituted and 743 compounds as N,N-disubstituted urea. No tetrasubstituted urea was found in the ChEMBL database. The vast majority of urea-containing compounds in ChEMBL are either N,N'-disubstituted or trisubstituted. Monosubstituted ureas as well as N,N-disubstituted ureas are less common. Urea derivatives are known to exhibit diverse biological activities toward kinases, proteases and other enzymes, as well as membrane receptor ion channels.

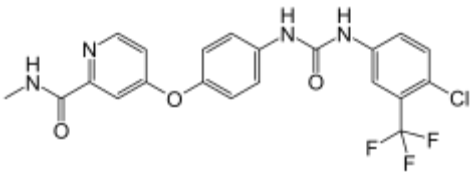
Urea is of great importance for cosmetology and dermatology, where it is used as a moisturizer to enhance transdermal drug penetration. In concentrations of 10-15% urea is used in surgery for wound treatment, as it dissolves coagulants and promotes epithelialization. In high concentrations (40%) urea breaks down proteins, which allows it to be used for the treatment of hyperkeratosis. Creams containing urea are prescribed for dermatitis, xerosis, ichthyosis, psoriasis, onychomycosis, eczema, dermatomycosis of the foot, etc. as a topical antifungal emollient and moisturizer. Urea clearance can be used as a relatively simple method to assess drug-induced changes in blood flow in human skin during microdialysis of vasoactive agents. The structures of known drugs in which the urea moiety is present are summarized below.



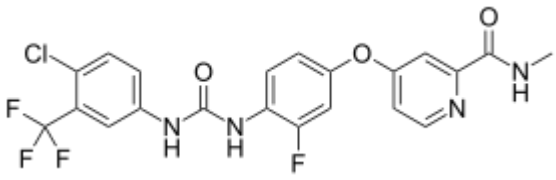
Gilroxycarbamide. Antitumor agent. The presumed mechanism of action is inhibition of DNA synthesis.



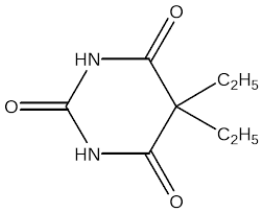
Ritonavir (Ritonavir)-an antiretroviral drug used in combination with other drugs to treat HIV/AIDS and HCV infection. Within two years of the approval of ritonavir (saquinavir), HIV-associated deaths in the United States dropped from more than 50,000 per year to about 18,000.



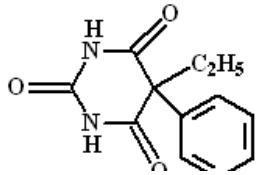
Sorafenib is a targeted antitumor agent, a small-molecule multikinase inhibitor. Clinical trials have shown that sorafenib inhibits tumor growth in human renal cell and hepatic cell cancers.



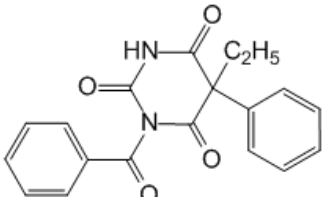
Regorafenib (commercial name Stivarga) is an oral multikinase inhibitor developed by Bayer that affects the processes of oncogenesis and angiogenesis in tumor tissue and disrupts the regulation of the tumor microenvironment by inhibiting various protein kinases.



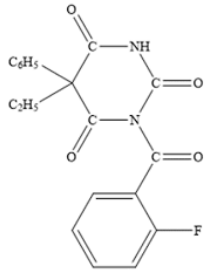
Veronal(Barbital) a medication sold under the brand name Veronal. The drug was used as a sleeping pill from 1903 until the mid-1950s. Currently, barbital has limited use.



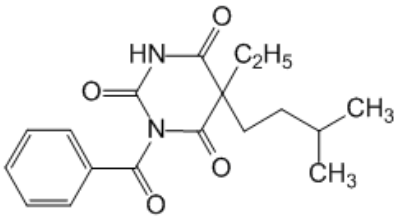
Luminal(Phenobarbital). An ancestor of barbiturate-type drugs, an antiepileptic psychotropic drug from the group of barbiturates. Phenobarbital does not belong to the first-line drugs because of its pronounced sedative (sedative) effect.



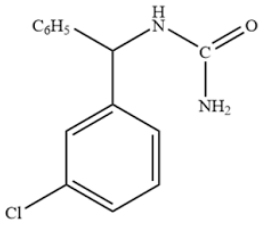
Benzonal. Antiepileptic drug. Practically has no sedative effect. The effect occurs in 20-60 min after oral administration.



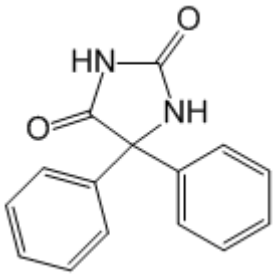
Halonal. Recommended for medical use and industrial release as an anticonvulsant drug.



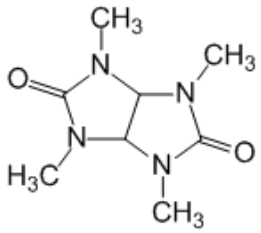
Benzobamyl. It has anticonvulsant, sedative effect. In large doses it may cause a sedative effect. It is used in epilepsy with localization of the focus of excitation mainly insubcortical formations. In subcortical localization of the epilepsy focus, the drug has a good therapeutic effect; it has not only anticonvulsant action, but also improves the general mental state (reduces or relieves headaches, lethargy, mood swings, etc.). The formulas of a number of barbiturate drugs (cyclobarbital, pentobarbital, ammobarbital), which are no longer used in clinical practice, are not listed here.



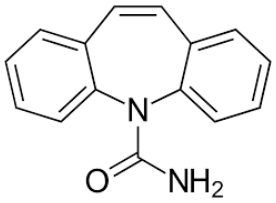
Galodif. It is an original anticonvulsant drug developed for the treatment and prevention of epilepsy, as well as for the treatment of alcohol dependence.



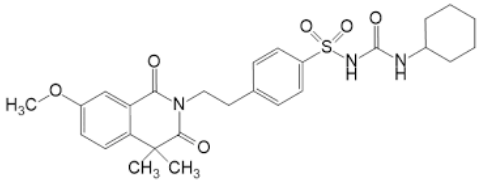
Phenytoin (diphenine). Anticonvulsant, has anticonvulsant, antiarrhythmic, analgesic, myorelaxant effect.



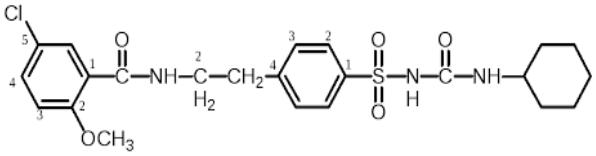
Mebicar (Adaptol). The drug belongs to anxiolytic, stress-protective, nootropic drugs. It regulates disturbed night sleep without having a direct sleeping effect. Eases or relieves nicotine withdrawal.



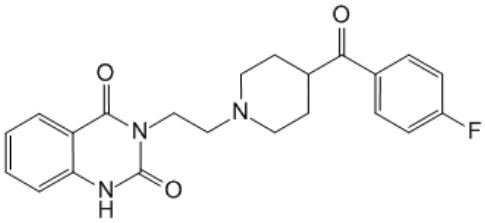
Carbamazepine (Tegretol). Antiepileptic drug (dibenzazepine derivative), which also has normotensive, antimanic, antidiuretic (in patients with non-sugar diabetes) and analgesic (in patients with neuralgia) effects.



Glyquidone. Oral hypoglycemic agent, sulfonylurea derivative of II generation. Stimulates insulin secretion by pancreatic β-cells, increases sensitivity of peripheral tissues to insulin, inhibits lipolysis in adipose tissue. It is characterized by a rapid and pronounced effect. Does not cause prolonged hyperinsulinemia.



Glibenclamide (Cyclamide). Oral hypoglycemic agent, sulfonylurea derivative of II generation. Stimulates insulin secretion by pancreatic β-cells, increases insulin release. Acts mainly during the second stage of insulin secretion.



Ketanserin (Serefrex, Surexal, Sufroxal). Causes dilation of blood vessels and has antihypertensive (blood pressure lowering) effect.

Conclusion

Since the discovery of urea synthesis from inorganic substances by F. Wöhler (1828), urea has always been the object of close research attention of both chemists and specialists of the widest profile. Almost two-century history of urea chemistry was marked by the creation of many dozens of valuable substances based on urea, which have been used as effective drugs, herbicides, polymers, monomers for polymeric materials, dyes, etc. The history of urea chemistry has been marked by the creation of many dozens of valuable substances. Despite the widespread popularity of urea as synthetic "simulator" objects in the hands of chemists, the chemistry of urea is constantly evolving, and the traditional ways of their use in chemistry are constantly being improved. In recent decades, the development of urea chemistry has led to the creation of specific self-organizing supramolecular systems on their basis, the growing interest in which is due to the unusual nature of their structure and the manifestation of their unique properties. Numerous studies in this area indicate that the attention of researchers will be attracted to further methods of synthesis and study of physicochemical properties of such supramolecular systems through the convergence of knowledge in the field of chemistry, physics, materials science, and, obviously, biomedical direction. The rapid progress in the utilization of urea for the preparation of such compounds has been accompanied by a rapid

development of theoretical insights in this field of knowledge, which is still ongoing. Although the chemistry and applications of urea have already been the subject of numerous topical review articles and separate sections in monographs, this article reflects almost all major aspects of the origin and evolution of urea chemistry. At the same time, considerable attention is paid to the various applications of acyclic and heterocyclic urea.

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Мочевинаның пребиотикалық молекуладан эволюциясы супрамолекулалық архитектура (шолу)

Аңдатпа: Мақалада мочевина бір жағынан архетиптік пребиотикалық қосылыс ретінде, ал екінші жағынан құрамында оттегі бар реактивті қосылыстар көрсетілген, олар әртүрлі ациклді және гетероциклді карбамид-құрамды заттар түріндегі химиялық қосылыстардың көптеген түрлерінің түзілуіне негіз болып табылатыны көрсетілген. Құрамында мочевина бар заттардың ішінде бұл жұмыста жаңа макроциклді және супрамолекулалық жүйелерді қоса алғанда, синтетикалық органикалық химияда бастапқы құрылыс материалы ретінде мочевинаның пребиотикалық мономерін пайдалануға ерекше назар аударылады. Мочевина химиясы бойынша жүргізілген тәжірибелердің көпшілігі пребиотик тәрізді жағдайлардан алыс жағдайда жүргізілгенімен, жүргізілген зерттеулердің кейбір аралық нәтижелері азотты құрамдас күрделі органикалық молекулалардың түзілу траекториясына жол ашады, олар мочевина мен реактивті компоненттерді итерациялық жинақтау. Ұсынылған жұмыста ациклді және гетероциклді мочевиналардың практикалық қолдануының әртүрлі салаларына айтарлықтай көңіл бөлінеді. Көптеген құнды ациклді және гетероциклді мочевиналардың ішінде адам өмірінде практикалық қолданысын тапқан ең маңызды заттар бөлек анықталған. Мочевинаның химиясы мен қолданылуы туралы жалпылама мәліметтер оның химия, физика, материалтану және медицина салаларындағы білімдердің жақындасуы арқылы тұрақты дамуын көрсетеді.

Түйін сөздер: мочевина, пребиотиктер, эволюция, ациклді және гетероциклді мочевина бар заттар, гликолурилдер, кукурбитурилдер, бамбусурилдер, супрамолекулалық жүйелер.

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Эволюция мочевины от пребиотической молекулы до супрамолекулярной архитектуры (обзор)

Аннотация: В статье показано, что мочевина - как архетипическое пребиотическое соединение, с одной стороны, и реакционноспособные кислородсодержащие соединения, с другой стороны, служат основой для формирования большого репертуара химических соединений, которые представлены различными ациклическими и гетероциклическими карбамидсодержащими веществами. В ряду карбамидсодержащих веществ в данной работе отдельное внимание уделено использованию пребиотического мономера мочевины в качестве стартового строительного блока в синтетической органической химии, в том числе и новых макроциклических и супрамолекулярных систем. Несмотря на то, что большинство выполненных экспериментов по химии мочевин проводились в условиях, которые далеки от пребиотикоподобных состояний, некоторые промежуточные результаты проведенных исследований открывают путь на траектории формирования сложных азотсодержащих органических молекул, которые могут появиться в результате итеративной сборки мочевины и реакционноспособных компонентов. В предлагаемой работе значительное внимание обращено различным областям практического применения ациклических и гетероциклических мочевин. Среди многочисленных ценных ациклических и гетероциклических мочевин отдельно выделены важнейшие вещества, нашедшие практическое приложение в человеческой жизнедеятельности. Обобщенные сведения о химии и применения мочевин указывают на постоянное ее развитие путем конвергенции знаний в области химии, физики, материаловедения и медицины.

Ключевые слова: мочевина, пребиотики, эволюция, ациклические и гетероциклические карбамидсодержащие вещества, гликольурилы, кукурбитурилы, бамбусурилы, супрамолекулярные системы.

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