NATIONAL ACADEMY OF SCIENCES OF UKRAINE
V.P. KUKHAR INSTITUTE OF BIOORGANIC CHEMISTRY AND PETROCHEMISTRY

APPROVED
by the decision of the Scientific Council
of the V. P. Kukhar Institute of Bioorganic Chemistry
and Petrochemistry of the NAS of Ukraine
Protocol No. 5
June 07, 2017.

SYLLABUS FOR "BIOORGANIC CHEMISTRY"

Third (PhD) educational level
Field: 102 "Chemistry"
Specialty "Bioorganic chemistry"

1. Introduction to Bioorganic Chemistry

Bioorganic chemistry as a science that studies the synthesis, structure and biological functions of low molecular weight bioregulators and biopolymers and the relationship between the structure and activity of natural and synthetic organic compounds. Chemical models and mechanisms of biological processes. History of development of chemistry of natural compounds and bioorganic chemistry. The place of bioorganic chemistry among the natural sciences and its role in solving scientific and applied problems. Current state of bioorganic chemistry, problems and prospects.

2. Physico-chemical methods of isolation and characterization of Biopolymers and Bioactive compounds

Basic methods of isolation of biomolecules. Methods of tissue and cell destruction, salting out, dialysis, ultrafiltration, lyophilization. Properties of biomolecules that determine the methods of their separation. Basic principles of centrifugation. Extraction and purification methods.

Electrophoresis and its application to biological systems. Gel electrophoresis. Two-dimensional gel electrophoresis. High-voltage electrophoresis. Theoretical aspects of Chromatography. Basic chromatographic methods and their applications. Ways to optimize the chromatographic process. Characteristics of High Performance Liquid Chromatography (HPLC). Adsorption chromatography.

Partition chromatography. Reversed phase chromatography. Ion exchange chromatography. Chromatofocusing. Size-exclusion (Gel filtration) chromatography. Affinity chromatography.

Investigation of the structure of natural and synthetic compounds by spectral methods. Application of NMR, electron and IR spectroscopy to determine the structure and properties of organic compounds. Mass spectroscopy. Spectral methods in studying the interaction of bioactive substances with potential protein targets. Fluorescence spectroscopy. EPR or ESR spectroscopy. X-ray crystallography.

3. Physico-chemical characteristics and reactivity of biomolecules

The most common functional groups in the structure of natural compounds and their main characteristics. Theory of Acids and Bases. pK values of the ionizable groups in biomolecules. Hydrogen bond and its characteristics. Intramolecular and intermolecular hydrogen bonds. Electrostatic interactions. Hydrophobic interactions. Van der Waals forces. Lipophilicity and hydrophilicity of biomolecules. Lipophilicity parameters and their definitions. Complexation properties by natural compounds. Supramolecular interactions between molecules.

Asymmetry of organic molecules and natural compounds. Influence of asymmetry of natural compounds and bioregulators on the course of biochemical reactions. Recognition of asymmetric molecules by biological targets. Chemical modeling of asymmetric transformations.

Mechanisms of reactivity of biomolecules. Intromolecular catalysis in bioorganic chemistry. Covalent catalysis. Nucleophilic catalysis. Nucleophilic groups in enzymes and proteins. Electrophilic catalysis. Catalysis by metal ions.

Reagent ionization and the effect of pH on the rate of model transformations. Total acid-base catalysis. Brønsted catalysis law. Differences between specific and general acid-base catalysis.

Influence of hydrophobic interactions on the rate of model transformations. Micellar complexes and micellar catalysis.

Classical charge transfer complexes and donor-acceptor interactions in bioorganic chemistry.

Thermodynamic activation parameters of chemical reactions. Enthalpy and entropy of activation. The relationship between the change in free energy and the equilibrium constant in the formation of complexes.

4. Basic principles for producing bioactive compounds

Discovery and synthesis of potentially bioactive compounds. Bioorganic synthesis. The concept of bioisostere groups. Creation of new bioactive substances by molecular modification of natural and synthetic compounds.

Modeling the activity of potential bioregulators in model systems. Molecular biotargets for determination of bioactivity and their classification. Restrictions on the nature of ligands. Lipinski rule of five. Stages of development of new drugs.

Computational methods in Drug Discovery. Molecular docking. QSAR methods. Virtual screening.

Combinatorial chemistry.

5. Low-molecular-weight bioregulators

Vitamins and coenzymes. Classification of vitamins and their role in biological processes. Vitamins of the aliphatic series. Ascorbic acid. Chemical and biochemical properties of ascorbic acid. Natural and synthetic antioxidants and their role in living organisms. Pantothenic acid (vitamin B3) and coenzyme A.

Vitamin A1 as a representative of alicyclic vitamins and provitamin A.

Naphthoquinone vitamins of group K. Vitamin K1 and synthetic provitamins - menadione, vikasol. Chemical properties of naphthoquinone vitamins. Plastoquinones and ubiquinones, their biochemical role.

Tocopherols - vitamins of group E. Isolation, structure of tocopherols, their biochemical functions.

Vitamins and coenzymes are derivatives of pyridinecarboxylic acids. Chemical properties of nicotinic acid (vitamin PP) and nicotinamide. Isoniazid. Biochemical functions of nicotinamide coenzymes in oxidoreductase transformations.

Hydroxymethylpyridine vitamins and coenzymes. Pyridoxine, pyridoxal (vitamin B6) and pyridoxamine. Pyridoxal-5-phosphate as a coenzyme of decarboxylases and aminotransferases.

Thiamine (vitamin B1). Chemical transformations of thiamine in model systems. Cocarboxylase. Mechanisms of thiamine diphosphate-dependent transformations.

Biotin (vitamin H) and its coenzyme form. Functions of N5-carboxybiotin in carboxylation reactions.

Flavin vitamins and coenzymes. Reduction of riboflavin (vitamin B2) to dihydroriboflavin. Flavin mononucleotide and flavinadenine dinucleotide. Biochemical functions of flavin coenzymes.

Folic acid (vitamin Bc) and *para*-aminobenzoic acid (PABA). Folic acid antagonists are aminopterin and methotrexate. Sulfanilamide drugs - sulfadimesine, sulfadimethoxine, norsulfazole, etazole, albucin, phthalazole and others.

Antibiotics. Penicillins, cephalosporins and related antibiotics. Representation of the mechanism of action of penicillins. Tetracyclines - the structure and mechanism of antimicrobial action. Antibiotics that affect the biosynthesis of proteins and nucleic acids. Antibiotics - tools for the study of ion transport across membranes (polyene macrolides, 3 gramicidins, cyclodepsipeptides). Antiviral drugs and mechanisms of their action. Synthetic structural analogues of nucleosides are antiviral drugs.

Alkaloids. Classification of alkaloids. Structure and biological action of alkaloids based on pyridine, quinoline and isoquinoline. Tropane alkaloids: cocaine and atropine groups. Bioactive benzodiazepine derivatives.

Steroids. Cholesterol biosynthesis. Structure and biological significance of the main representatives of steroid hormones. Estradiol and testosterone. Bile acids.

Neurotransmitters and hormones. Acetylcholine and acetylcholinesterase inhibitors. Natural and synthetic inhibitors of acetylcholine receptors. Neurotransmitters and hormones are derivatives of amino acids. Structure and functional role of adrenaline, dopamine, γ-aminobutyric acid. Cyclic AMP as a mediator in the action of hormones. Prostaglandins.

Phytohormones and pesticides. The main representatives of auxins, cytokinins, gibberellins. Abscisic acid. The main groups of herbicides by the nature of action (photosynthesis inhibitors, inhibitors of phytohormone transport, enzyme inhibitors and others). Structure of insecticides of pyrethroid nature. Organochlorine insecticides.

6. Proteins and Peptides. Structure, metabolism and cell functions

Amino acids. Nomenclature and structure of amino acids. Natural amino acids. Classification of amino acids. Stereochemistry of α-amino acids. Acid-base properties and pKa values of amino acids. Methods of synthesis and chemical properties of amino acids. β-Amino acids. γ-Amino acids.

Peptides. The nature of the peptide bond. Linear and cyclic peptides. Biological role of peptides. Peptide hormones and neuropeptides. Representation of peptides-neurotransmitters, neuromodulators, connectors. Immunoactive peptides. Peptide toxins and antibiotics. Peptides as antioxidants. Peptide antibiotics as drugs.

Chemical synthesis of peptides. Methods of protection of functional groups. Peptide bonding methods: azide, mixed and symmetric anhydrides, activated esters, carbodiimide and carboxyanhydride condensation methods. Representation of block and step synthesis of peptides. Solid phase synthesis of peptides.

Primary structure of proteins. General strategy for determining the structure of proteins. Analysis of amino acid composition. Determination of *N*- and *C*-terminal amino acid residues. Fragmentation of the polypeptide chain. Enzymatic hydrolysis. Limited proteolysis. Chemical methods of polypeptide chain cleavage.

Determination of amino acid sequence of proteins. Analysis of the location of sulfhydryl groups and disulfide bonds. Structure determination of peptides by Mass spectrometry and Nuclear Magnetic Resonance (NMR) spectroscopy.

Spatial protein structures. Electronic structure and configuration of the peptide bond. Types of interactions that determine the spatial structure of polypeptides. Relationship of the spatial structure of a protein with the sequence of amino acids.

Secondary structure of peptides and proteins: α-helix, β-structure, β-bend, other types of regular structures of the polypeptide chain. The concept of domains.

Tertiary structure of proteins. X-ray diffraction analysis as a method of studying the spatial structure of proteins. Nuclear magnetic resonance as a method for studying the conformation of peptides and proteins in solutions. Denaturation and renaturation.

Quaternary structure of proteins. Examples of subunit structures. Research methods of the quaternary structure of proteins.

Chemical modification of proteins. Problems solved by chemical modification of enzymes and proteins. Modification of individual amino acid residues of enzymes and proteins using selective reagents. The use of bifunctional reagents. Biospecific modification of enzymes and proteins. Introduction of fluorescent, spin and photoaffinity labels.

Enzymes. Classification of enzymes and their biological functions. The concept of active center. The effect of pH on the activity of enzymes. Cooperative effects and allosteric enzymes.

Principles of enzymatic kinetics. Factors affecting the rate of enzymatic reactions. Michaelis-Menten kinetics. Competitive and non-competitive enzyme inhibitors. Representation of molecular mechanisms of enzymatic catalysis.

Enzymes as targets for modeling the bioactivity of organic compounds. Enzyme inhibitors as drugs.

Enzymes as catalysts for organic reactions. Enzymatic reactions in organic solvents, immobilized enzymes. Artificial enzymes. Practical use of enzymatic processes.

Biological role of proteins. Hormone proteins. Insulin. Protective proteins. Immunoglobulins. Human leukocyte antigens (Major histocompatibility complex). Complement system. Proteins of the blood coagulation system and fibrinolysis. Contractile and structural proteins. Muscle and connective tissue proteins. Actomyosin complex. Troponins. Collagen.

7. Lipids and biological membranes

Fatty acids: structure and biological functions. Structure, classification and physicochemical properties of lipids. Methods of research and synthesis of lipids. Some classes of lipids. Glycolipids and phospholipids - structure, biosynthesis, biological role.

Structure of biological membranes. Membrane components and their interactions. Artificial membranes: monolayer, flat bilayer, liposomes (vesicles).

Membrane proteins are peripheral and integral. Membrane transport, passive and active. Characteristics of individual biological membrane systems. Cytochrome-oxidase complex. Transport ATPases.

8. Nucleic acids and chemical parameters of genetic engineering

Nomenclature of nucleic acids and their components. Biological function of nucleic acids.

Heterocyclic bases of nucleic acids: structure, physical and chemical properties. Acid-base properties of heterocyclic bases of nucleic acids, nucleosides, nucleotides. Stability of N-glycosidic bonds.

Primary structure of polynucleotide chains. 3'-5 '-Phosphodiester bond. Chemical inequality of 3 '- and 5' -terminal groups. Secondary structure of DNA.

Differences in the structures and properties of RNA and DNA. Structure and biological functions of RNA. Transport, matrix and ribosomal RNA.

Transfer of genetic information. DNA replication and its mechanism. Regulation of transcription. Broadcast - the main stages, mechanisms, regulation.

General idea of genetic engineering. Methods of creating recombinant DNA and their introduction into the cell. Enzymes used in genetic engineering.

9. Carbohydrates

Biological role and specific functions of carbohydrates. The main types of carbohydrates found in nature.

Monosaccharides. Structure and stereochemistry. Cyclic tautomeric forms of monosaccharides. Chemical properties of monosaccharides.

Oligo- and polysaccharides. Methods for determining the structure of carbohydrates. Spatial structure of monosaccharides, oligosaccharides and polysaccharides. Synthesis and chemical properties of glycosides, oligosaccharides and polysaccharides.

Glycoproteins: structure and basic functions. Mixed biopolymers containing carbohydrates.

Cellulose, starch. Use of cyclodextrins for biomimetic transformations.

SUGGESTED READING REFERENCES

The main literature

1. David L. Nelson; Michael M. Cox. *Leninger Principles of Biochemistry.* W.H. Freeman; 8th ed., 2021.
2. Jonathan Clayden; Nick Greeves; Stuart Warren. *Organic chemistry.* Oxford University Press; 2nd ed., 2012.
3. John A. Joule; Keith Mills. *Heterocyclic Chemistry*. Wiley-Blackwell; 5th ed., 2013.
4. Graham L. Patrik. *An Introduction to Medicinal Chemistry.* Oxford University Press; 5th ed., 2013.
5. H. Stephen Stoker. *General, Organic, and Biological chemistry.* Cengage Learning; 7th ed., 2015.
6. Bruce Alberts; Alexander Johnson; Julian Lewis; Martin Raff; Keith Roberts; Peter Walter. *Molecular Biology of the Cell.* W.W. Norton & Company; 6th ed., 2014.

The additionary literature

1. Richard B. Silverman; Mark W. Holladay. *The Organic Chemistry of Drug Design and Drug Action.* Academic Press; 3rd ed., 2014.
2. Francis A. Carey; Richard J. Sundberg. *Advanced Organic Chemistry (Part A, B).* Springer; 5th ed., 2007.
3. Reinhard Bruckner. *Organic Mechanisms: Reaction, Stereochemistry and Synthesis.* Springer; 2010.
4. Mihaly Nogradi; Laszlo Poppe; Jozsef Nagy; Gabor Hornyanszky; Zoltan Boros. *Stereochemistry and Stereoselective Synthesis: An Introduction.* Wiley-VCH; 1st ed., 2016.
5. Theodora W. Greene; Peter G. M. Wuts. *Protective Groups in Organic Synthesis.* Wiley-Interscience; 3rd ed., 1999.
6. William .A. Smith; Aleksey F. Bochkov; Ron Caple. *Organic Synthesis: The Science Behind the Art.* The Royal Society of Chemistry, London; 1998.