MINISTRY OF HEALTH OF UKRAINE
NATIONAL MEDICAL UNIVERSITY of O.O. BOGOMOLETS

WORK BOOK

FOR STUDENTS' INDEPENDENT WORK

(auditory and outside the auditorium)

Discipline of choice "Theoretical foundations of synthesis and the relationship between the structure and action of medicinal products"

Field of knowledge 22 Health care

Specialty 226 "Pharmacy, industrial pharmacy"

Specialization 226.01 "Pharmacy"

Form of study Day

Department of medicinal chemistry and toxicology

Approved at the meeting of the department on "30" August 2024, protocol No. 14

Head of the Department of medicinal chemistry and toxicology
Doctor of Medicine, Professor Nizhenkovska I.V.

Considered and approved:

on the meeting of cycle methodical commission of specialty 226 "Pharmacy, industrial pharmacy" dated August 30, 2024, protocol No. 1

INTRODUCTION

Workbook for students' independent classroom and outside the auditorium work of 3rd course of the specialty 226 "Pharmacy, industrial pharmacy" from the elective component "Theoretical bases of synthesis and the relationship between the structure and action of medicinal products" - a structured methodical development, containing the basic information for the successful assimilation of the educational material of each topic of the discipline and preparation for practical classes.

The main purpose of using the workbook is to optimize and increase the effectiveness of students' educational and cognitive activities by mastering the methods of independent acquisition, active assimilation and application of knowledge regarding modern approaches to the creation of medicinal products and biologically active compounds; strategies for the synthesis and modification of new organic molecules, taking into account the peculiarities of the chemical structure of the molecule and the presence of pharmacophore groups in its composition; the mechanism of influence of pharmacophore groups on the direction of biological action of a new chemical compound, a set of key factors and criteria for determining the mutual influence of the chemical structure of the molecule and its biological activity, approaches to the analysis of the relationship between structure and activity within a certain chemical group of organic substances, taking into account their physical, physico-chemical and biological properties and peculiarities of the chemical structure.

Features of the proposed tasks. The proposed tasks for classroom and extracurricular work are aimed at the development of abstract thinking, analysis and synthesis, the ability to work in a team and the formation of the ability to apply knowledge in practical situations.

The order of tasks for independent work

Tasks for independent out-of-class training must be completed before conducting a practical lesson on this topic.

Tasks for classroom independent work are completed during a practical lesson.

During independent work, the student must write down his answers to the assigned tasks in the workbook.

Evaluation criteria

When evaluating the performance of independent work, preference is given to standardized control methods: tests and structured written tasks.

Excellent grade "5" - student gives at least 90% correct answers to standardized test tasks, answers written tasks without errors.

Good grade "4" - the student gives at least 75% correct answers to standardized test tasks, has minor errors in the answers to written tasks.

Satisfactory grade "3" - student gives at least 60% correct answers to standardized test tasks, has significant errors in answers to written tasks.

Unsatisfactory grade "2" - student gives less than 60% correct answers to standardized test tasks, has gross errors in answers to written tasks or does not give answers to them.

Rules for keeping a workbook: consistent, written and neat.

Mandatory observance of academic integrity by students, namely:

 independent performance of all types of work, tasks, forms of control provided for by the work program of this educational discipline;

 references to sources of information in the case of using ideas, developments, statements, information;

 compliance with the legislation on copyright and related rights;

 provision of reliable information about the results of one's own educational (scientific, creative) activities, used research methods and sources of information.

Topic N 1. Implementation of the main stages of organic synthesis: delineation of the structure of the target molecule, consideration of possible synthesis schemes, selection of products, conducting chemical reactions, isolation of intermediate and target products, their analysis and purification. Single-reactor synthesis of multifunctional derivatives of biologically active substances (medicines).

Purpose: the ability to implement the main stages of organic synthesis (one-reactor synthesis): delineation of the structure of the target molecule, consideration of possible synthesis schemes, selection of products, conducting chemical reactions, isolation of intermediate and target products, their analysis and purification.

The student must:

 know the basic concepts, strategy and tactics of delineating the structure of the target molecule for synthesis;

 be able to propose possible synthesis schemes and choose reagents;

 evaluate the possibility of formation of by-products of the reaction;

 know methods of purification and analysis of synthesized products,

 interpret synthesis results.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
Organic synthesis	the section of organic chemistry and technology, which studies various aspects (methods, methods, identification, equipment, etc.), obtaining organic compounds, materials and products, as well as the process of obtaining substances
Subtle organic synthesis	the complexity of the objects of synthesis, the multi-stage process of obtaining target substances, the need for thorough purification, relatively small volumes of their production, a large assortment and high cost of synthesis products
One-pot synthesis	organic synthesis that takes place in one container, without the release of intermediate products
Computer synthesis	the field of chemoinformatics that encompasses the methods, algorithms, and computer programs that implement them and that assist the chemist in planning the synthesis of organic compounds, predicting outcomes, and designing new types of organic reactions based on the

	generalization of data on known synthetic transformations
Regioselectivity	the predominant course of the reaction along one of several possible reaction centers of the molecule
Enantioselectivity	the predominant formation during the reaction of one enantiomer
Click chemistry concept	describes a way to synthesize target molecules from smaller units, similar to what nature does

Recommended literature:

Basic

1.Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-2. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/.*
2. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. Describe organic synthesis. Its purpose and tasks.

2. Single-reactor synthesis. Its advantages.

3. Name the types of reactions by mechanism: radical, electrophilic, nucleophilic. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

4. Addition-detachment reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

5. Condensation reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

6. Cyclization reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

7. Rearrangement reactions. Give examples of such reactions in the synthesis of

biologically active compounds and drugs.

8. Aromatization reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

9. What is the essence of "click" synthesis. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

10. Name the sources of raw materials for organic synthesis. Cyclization reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs and indicate the sources of raw materials.

11. Reagents and solvents in synthesis. Give examples of such reactions in the synthesis of biologically active compounds and drugs and indicate which reagents and solvents are used in these reactions.

12. Electronic effects in a molecule. Give the chemical formulas of biologically active compounds and drugs. Indicate what electronic effects operate in this molecule. How does it affect its reactivity?

13. Functional groups. Give the chemical formulas of biologically active compounds and drugs. Indicate which functional groups are present in this molecule. How do they affect its reactivity?

14. Methods of purification of chemical substances (filtering, recrystallization, extraction, distillation). Describe the methods.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. Nucleophilic substitution reaction is used in the synthesis of organic substances. Specify a characteristic feature of a nucleophilic reagent:

A. the presence of an unshared pair of electrons

B. hyperconjugation effect

C. mesomeric effect

D. the presence of an unpaired electron

2. Radical reactions are accompanied by homolytic breaking of covalent bonds. What is the name of the active reagent in radical substitution reactions?

A. cation

B. neutral molecule

C. radical

D. anion

3. "Molecularity" of the reaction indicates the number of molecules in which changes in covalent bonds occur. What is the name of a reaction in which one molecule participates in the rate-limiting step?

A. monomolecular

B. bimolecular

C. polymolecular

D. trimolecular

4. When an alcoholate reacts with an alkyl halide (Williamson's reaction), a reaction product is formed. What is his name?

A. ester

B. alcohol

C. ether

D. carboxylic acid

5. Name the product of hydrolysis of isonitrile:

A. amine

B. nitro compound

C. amide of carboxylic acid

D. alkane

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. To carry out the distillation of a liquid organic substance for the purpose of its purification, a distillation device is used. Specify the chemical utensils that must be used to collect the device (Fig. 1):

Figure 1.

The answer and its justification

Auditory collective work:

Task 1. What chemical procedure is this device used for? Specify chemical utensils (Fig. 2):

Figure 2.

The answer and its justification

Task 2. Figures 3 and 4 show two devices for performing a chemical procedure. Name the purpose of these devices, indicate the difference in the use of devices.

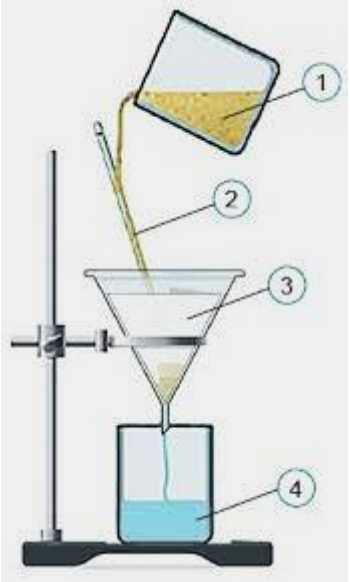


Figure 3.

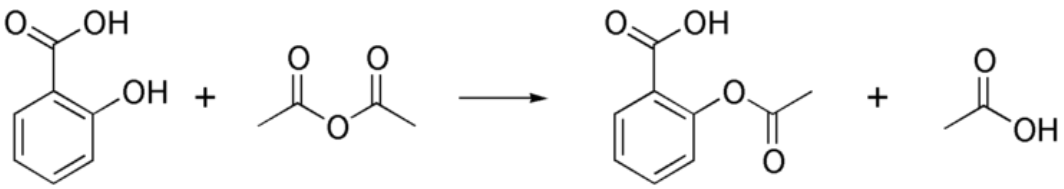
Figure 4.

The answer and its justification

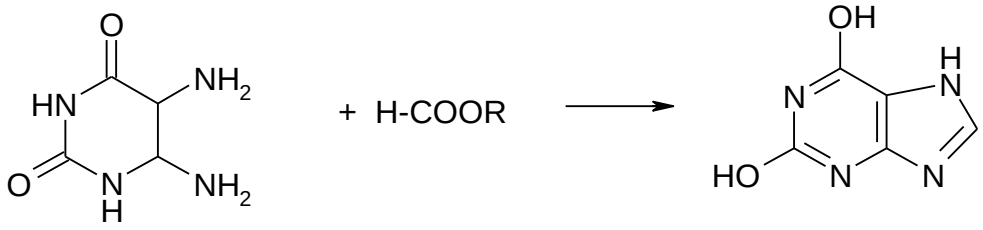
Auditory independent work (supervised by the teacher):

Task 1. Which of the indicated reactions are related to one-reactor synthesis? Name the reactants and products of the reactions.

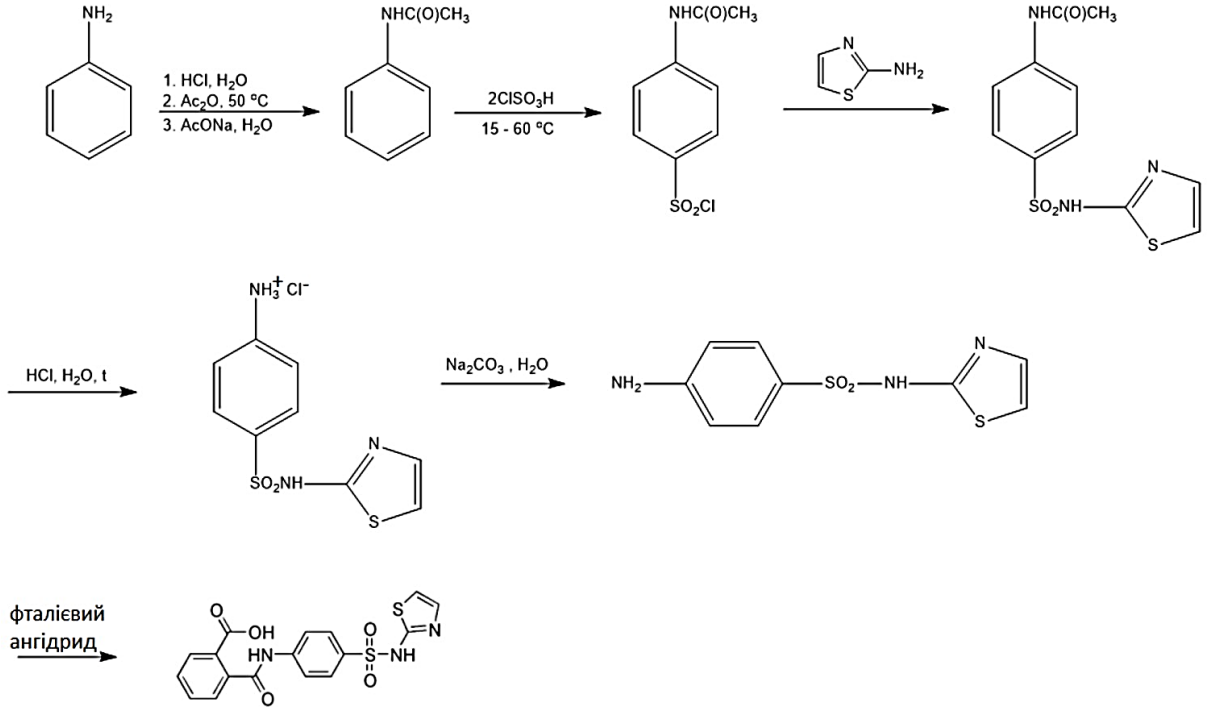
1.



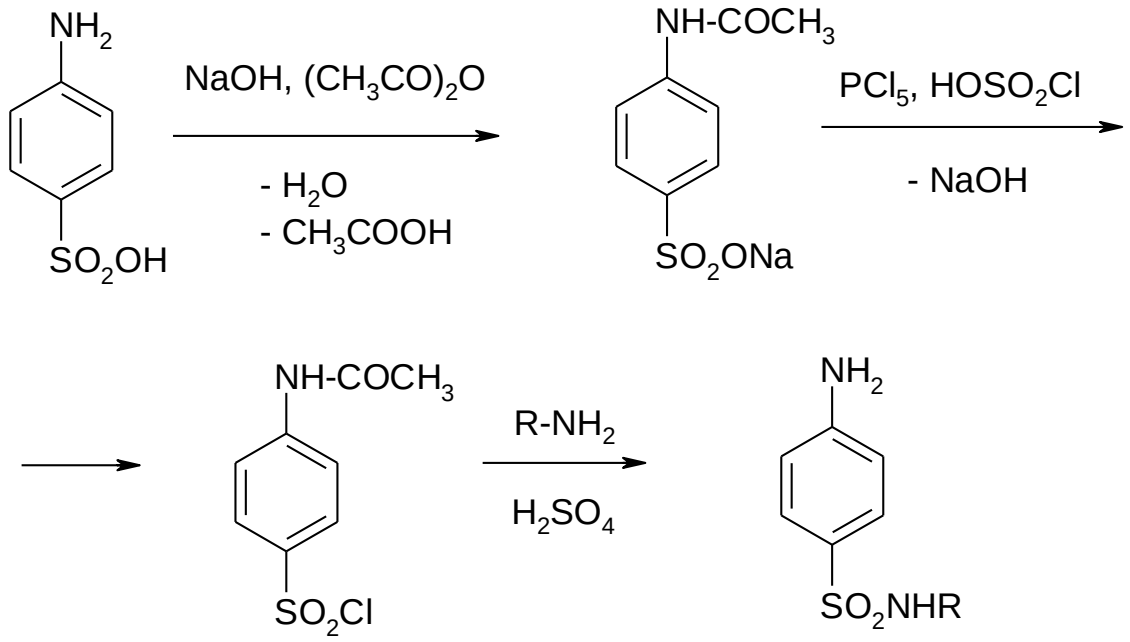
2.



3.



An example of a task with an answer standard:



Answer standard

The scheme shows the reactions of the multistage synthesis of sulfanilic acid amide derivatives. The starting compound is sulfanilic acid.

At the first stage of the reaction, acetylation of sulfanilic acid is carried out using acetic anhydride with parallel protection of the -OH group by reaction with sodium hydroxide.

At the II stage, the sodium atom is replaced by chlorine by reaction with phosphorus pentachloride.
At the III stage of the reaction, the chlorine atom is replaced by an alkylamino group and the amino group is released from the protective aceto group by hydrolysis.
The reactions are carried out with the separation of semi-products of the reactions, so the synthesis does not belong to the single-reactor synthesis.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 2. Pharmacophore groups. Variability of molecules based on bioisosteric substitution. Peptide and double bond; aldehyde and imine groups, SH, NH_2, CH_3, OH-groups, S, NH, CH_2O-linkers. QSAR, SAR analysis.

Purpose: the ability to operate with the main concepts of the topic - pharmacophore groupings, variability of molecules based on bioisosteric substitution (peptide and double bond; aldehyde and imine groups, SH, NH_2, CH_3, OH-groups, S, NH, CH_2O-linkers) and use of acquired knowledge in practice, ability to perform computer forecasting of chemical and biological properties of BARs and drugs using QSAR, SAR analysis.

The student must:

 know basic concepts - pharmacophore groupings, variability of molecules based on bioisosteric substitution (peptide and double bond; aldehyde and imine groups, SH, NH_2, CH_3, OH-groups, S, NH, CH_2O-linkers);

 be able to identify and propose schemes for creating pharmacophore groups;

 evaluate the possibility of variability of molecules based on bioisosteric substitution;

 know the rules of working with programs for computer prediction of chemical and biological properties of BARs and drugs (QSAR, SAR, SwissTargetPredictio).

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
Pharmacophore	it is an abstract description of the molecular features necessary for the molecular recognition of a ligand by a biological macromolecule. IUPAC defines a pharmacophore as "a set of steric and electronic properties necessary to ensure optimal supramolecular interaction with a specific biological target and to trigger (or block) its biological reaction"
Bioisoster	are chemical substituents or groups with similar physical or chemical properties that produce similar biological properties in the same chemical compound
Linker	these are groups of atoms (fragments of a molecule) that connect a functional (bio)molecule with a molecular label to form a conjugate
Docking	is a molecular modeling technique used to predict how a protein (enzyme) interacts with small molecules (ligands)
Molecular docking	is the study of the process of combining two or more molecular structures (a drug and an enzyme or protein)
QSAR (quantitative	quantitative structure-activity relationship

structure-activity relationship) *SAR* (structure-activity relationship)	structure-activity relationship
CADD (Computer-aided drug design)	automated drug design

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/*.
2. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. What is CADD? What are the positive features of automated drug design?
2. QSAR, SAR analysis and their role in predicting BAR activity.
3. What methods of "drug design" are relevant today?
4. Describe the concept of "molecular docking".
5. Pharmacophores. Give a description. Specify the pharmacophores in the structures of the molecules - the active substances of sulfonamides, benzodiazepines, barbiturates, phenanthrenisoquinolines, etc.
6. Scaffolds. Give examples of scaffolds in molecules of active substances - representatives of drug classes.
7. Task of bioisosteric substitution.
8. Linkers. Give examples of linkers: peptide and double bond; aldehyde and imine groups, SH, NH_2, CH_3, OH-groups, S, NH, CH_2O-linkers in the molecules of active substances - representatives of drug classes.
9. Design de novo. Main tasks.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. Abstract description of molecular features necessary for molecular recognition of a ligand by a biological macromolecule. This definition is applied to the concept of:

A. pharmacophore

B. chemical structure

C. tautomer

D. enantiomer

2. What is the role of the scaffold?

A. cation

B. the main structure is the framework of the molecule

C. radical

D. alkyl radical

3. What are linkers?

A. multiple connections

B. cyclic fragments

C. δ-bonds

D. groups of atoms (fragments of a molecule) that connect a functional (bio)molecule with a molecular label to form a conjugate

4. What are bioisosteres called?

A. are chemical substituents or groups with similar physical or chemical properties

B. are groups of atoms (fragments of a molecule) that connect a functional (bio)molecule with a molecular label to form a conjugate

C. bases of structures of compounds or series of compounds

D. biotarget

5. The process of finding new drugs based on knowledge of the biological target is called:

A. organic synthesis

B. rational drug design

C. SAR analysis

D. PMR analysis

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the scheme of the formation of scaffolds for the synthesis of biologically active compounds (BAS and MP). Based on the proposed examples of the formation of scaffolds from step 1 to step 4, write schemes for the formation of scaffolds during the synthesis of active active substances of medicinal products:

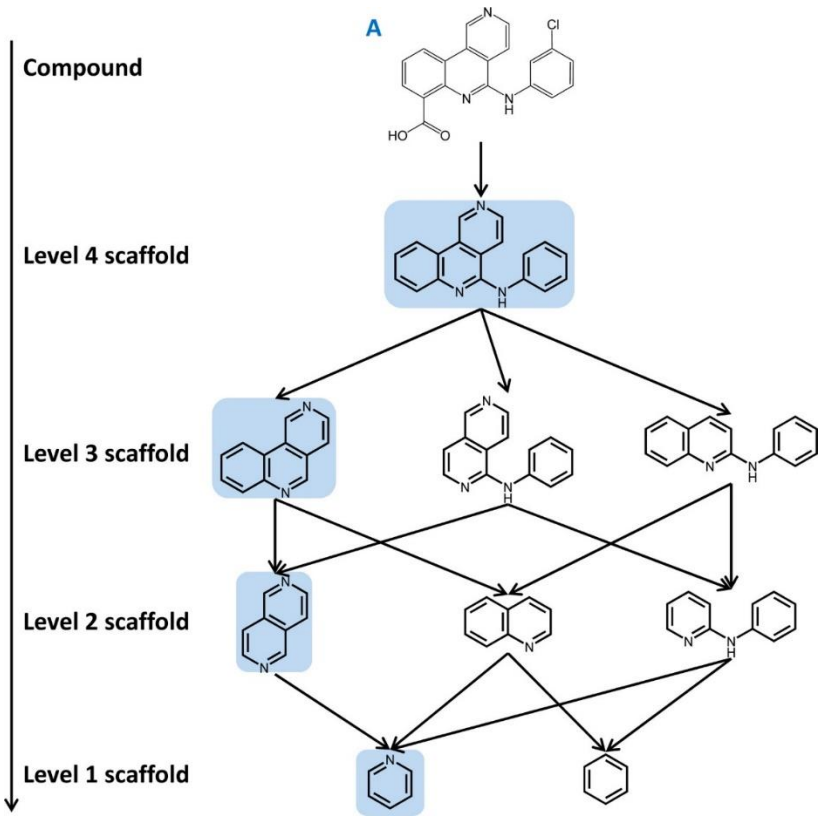


Figure 1.

- Novocainamide
- Diclofenac sodium
- Phthalazol
- Metamizole sodium
- Thiotriazolin
- Diethylamide of nicotinic acid

- Aceclidine
- Barbiturate
- Trimethoprim

Give your examples.

The answer and its justification

Auditory collective work:

Task 1. Figure 2 shows the chemical formulas of organic compounds with important components for structure design highlighted (in red):

a) Cyclic system
c) Linkers
c) Side chains
d) Main frame
e) Mureco frame
f) Graphic framework

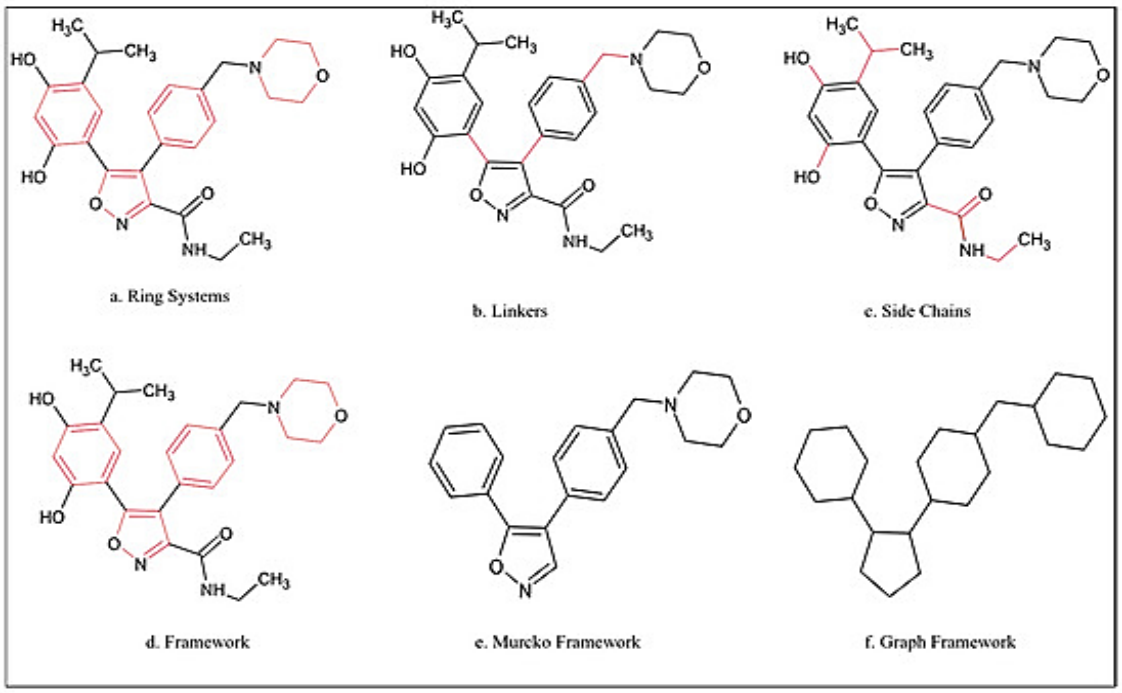
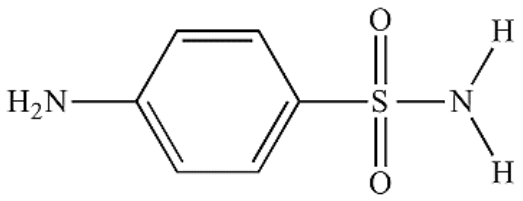
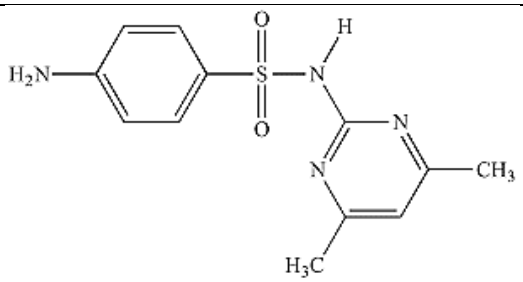
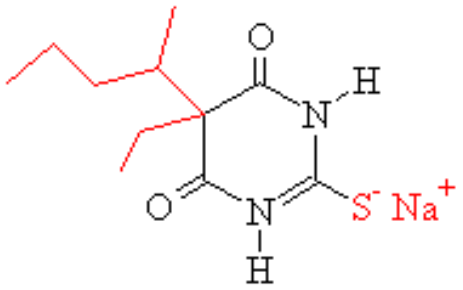


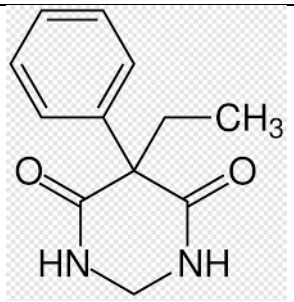
Figure 2.

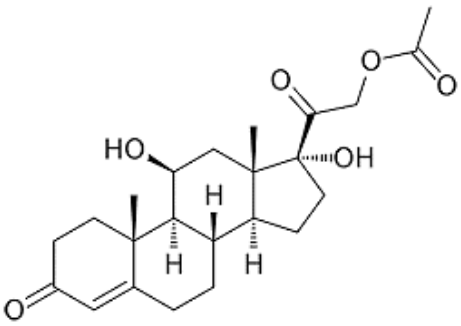
Using an example, identify these important components of a molecule that are used to design its structure in the following molecules:

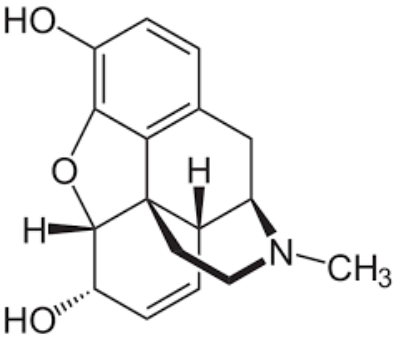


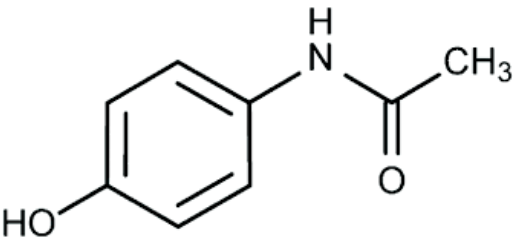


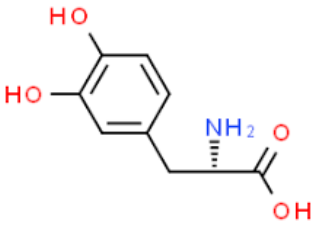


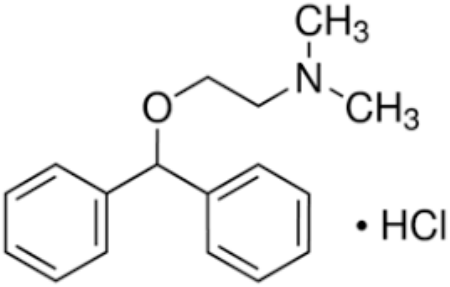


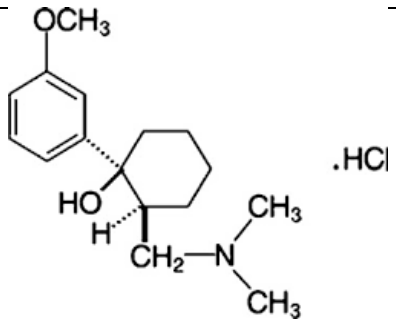


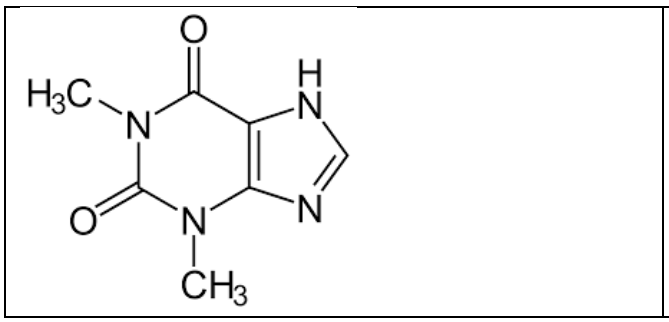


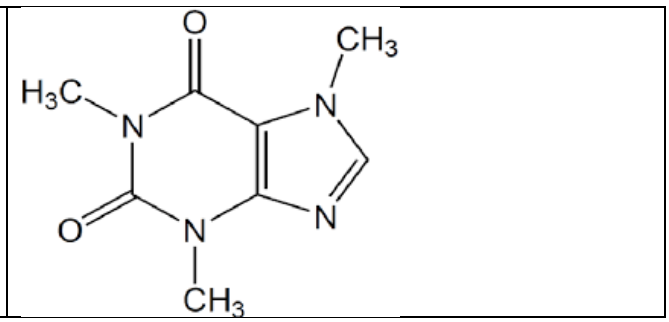












Name the given chemical compounds. What medicines are they the active ingredients of?

The answer and its justification

Task 2. Indicate the pharmacophore groups, electronic effects, and functional groups in the given chemical formulas:

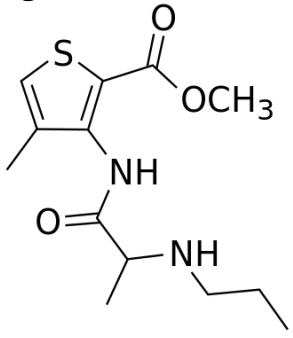


Figure 3. Articaine

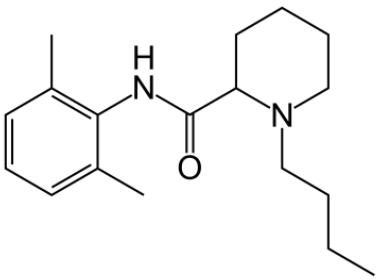
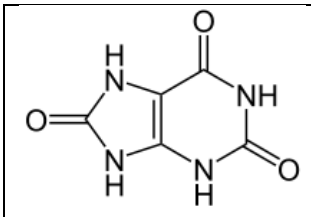
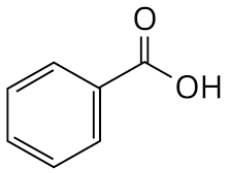
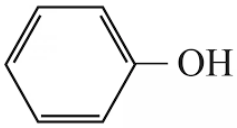
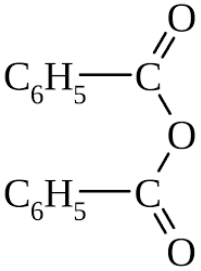
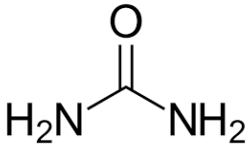
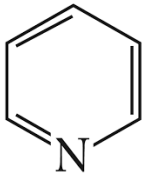


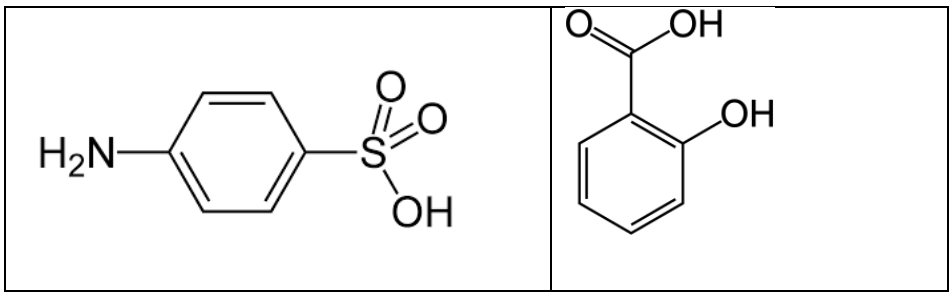
Figure 4. Bupivacaine

The answer and its justification

Auditory independent work (supervised by the teacher):

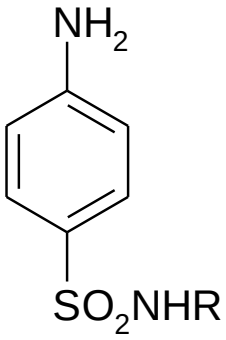
Task 1. Which of the indicated molecules (as starting compounds), the chemical structures of which are presented, are used for the creation (synthesis) of biologically active substances? Write the BAS and MP formulas that contain these structural components:



An example of a task with an answer standard:

Describe the features of the chemical structure of the substituted amide sulfanilic acid molecule.



Answer standard

- amphoteric molecule: the main properties are due to the presence of an aromatic NH2 group, acidic properties are due to the presence of a hydrogen atom in the sulfamide -SO2NHR group

- +M effect from the amino group

- -I, -M effects from the sulfo group

- aromatic ring, unsaturated aromatic system - three double bonds

- the presence of a coupled system

- carbon atoms of the aromatic ring in the state of sp2-hybridization

- the nitrogen atom in the amino group has an unshared pair of electrons, participates in conjugation

- high stability of "aromaticity" of the cycle

- considerable energy of cyclic delocalization.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 3. Ways to improve ADME/Tox parameters of biologically active compounds: modifications by hydroxy-, mercapto-, carboxy-, caralkyloxy-, carbonyl-, amino- groups.

Purpose: the ability to operate with the main concepts of the topic - ADME, ADME-Tox or ADMET, xenobiotics, modification of functional groups and the use of the acquired knowledge in practice, the ability to perform computer forecasting of the chemical and biological properties of BAS and drugs.

The student must:

 know basic concepts – ADME, ADME-Tox or ADMET, xenobiotics, modifications of functional groups;

 be able to detect and propose reactions of modifications of functional groups;

 evaluate the possibility of variability of molecules based on chemical modification.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
ADME	absorption, distribution, metabolism and excretion (pharmacokinetics and pharmacology)
ADME-Tox (ADMET)	potential or actual toxicity of the compound
Xenobiotics	foreign substances in the body
LD 50	*average lethal dose*
Absorotion	the process of selective absorption of a substance from a gaseous or liquid medium by the entire volume of a sorbent - solid or liquid
Metabolism	a set of chemical reactions in the body under the influence of the enzymatic system, as a result of which the products of these reactions are formed - metabolites
Toxicity	property of some chemical elements, compounds, biogenic substances, according to their maximum permissible concentration, to negatively affect a living organism

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/.*
2. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. ADME, role and tasks.

2. Describe the processes: absorption, distribution, metabolism, excretion.

3. Name the ways of excretion of substances.

4. SwissADME and protox-II programs and their purpose.

5. How does the chemical structure of substances affect ADME parameters?

6. What methods and reactions are used to modify the hydroxy group? Give examples. Write the reaction schemes.

7. What methods and reactions are used to modify the mercapto group? Give examples. Write the reaction schemes.

8. What methods and reactions are used to modify the carboxyl group? Give examples. Write the reaction schemes.

9. What methods and reactions are used to modify the carbolic group? Give examples. Write the reaction schemes.

10. What methods and reactions are used to modify the carbonyl (aldehyde and keto) group? Give examples. Write the reaction schemes.

11. What methods and reactions are used to modify the amino group? Give examples. Write the reaction schemes.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. What information does ADME (absorption, distribution, metabolism, excretion) provide?

A. about the location of the pharmaceutical compound in the body from the

moment of its entry to the moment of detection

B. about the level of xenobiotic toxicity

C. about the ways of xenobiotic metabolism

D. on pharmaceutical properties of xenobiotics

2. Which of the factors affects the distribution of xenobiotics in the body?

A. chemical structure of the xenobiotic molecule

B. chemical properties of xenobiotics

C. xenobiotic toxicity

D. regional blood flow rate

3. What substance is called a xenobiotic?

A. a lipophilic chemical

B. a toxic chemical

C. a chemical compound with multiple bonds in its structure

D. foreign chemical compound for the body, which is not synthesized in the body and is not used in the processes of building cells, energy production and other processes of ensuring the vital activity of the body

4. Where does the biotransformation of xenobiotics mainly take place in the body?

A. in the gastrointestinal tract
B. in the liver
C. in the thyroid gland
D. in the blood

5. What is the purpose of chemical modifications of the functional groups of the molecules of the active active substances of medicinal products?

A. to improve drug permeability and absorption
B. to expand the range of chemical properties of compounds
C. to complicate the chemical structure of molecules
D. to develop methods for their pharmaceutical analysis

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the scheme of the reaction of glucose (6 functional groups in the molecule) with acetic anhydride. Indicate which functional groups of the glucose

molecule are subject to this protection reaction? For what purpose? Write a scheme for the following reaction involving an unprotected functional group. How can functional groups be freed from protecting groups?

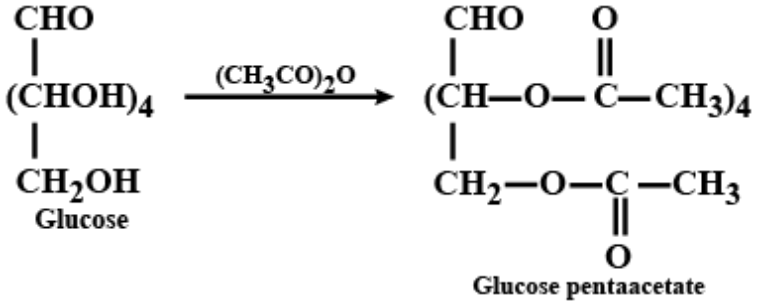


Figure 1.

The answer and its justification

Auditory collective work:

Delicate organic compounds often contain specific parts or groups that cannot withstand the influence of chemical reagents, or enter into undesirable reactions during the study. These parts or groups must be protected. For example, $LiAlH_4$ is highly active, able to reduce esters to alcohols. It will also react with intermediate products of the reaction on carbonyl groups. If it is necessary to carry out the reduction of the ester in the presence of $LiAlH_4$, its attack on the carbonyl group should be prevented. The carbonyl group is protected - it is converted into an acetal that does not react with hydrides. An acetal group is called a protecting group for a carbonyl group. After completion of the reaction step with LiAlH4, the acetal group is removed by reaction with an aqueous acid solution), returning the original carbonyl group. This procedure is called unprotecting.

Task 1. Figure 2 shows schemes of reactions during which protection of a functional group is carried out, and then - removal of protection. Specify the stages of reactions at which protection of a functional group is carried out, removal of

protection of a functional group. What reagents are used to perform these procedures? What functional group is subject to protection? At what stage of the reaction is the *protection of the functional group* not carried out?

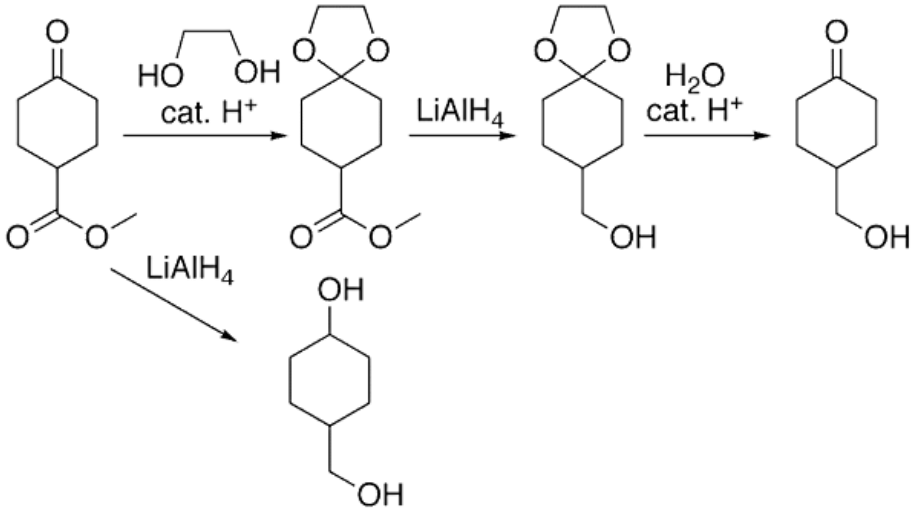


Figure 2.

The answer and its justification

Task 2. Figure 3 shows the scheme of the functional group protection reaction (in the scheme, the heterocycle is called tetrahydropyranyl). What reagent is used to perform this procedure? What functional group is subject to protection?

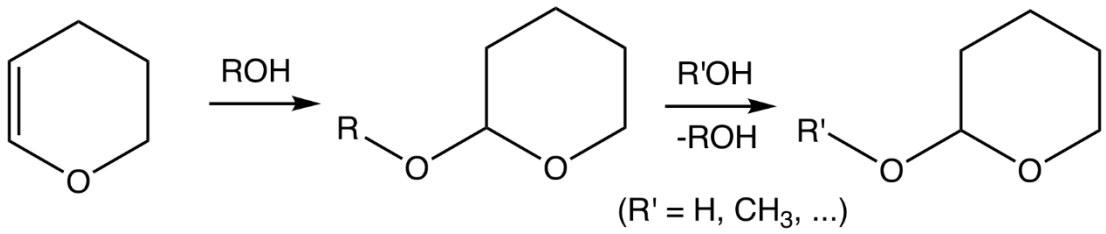


Figure 3.

The answer and its justification

Auditory independent work (supervised by the teacher):

Task 1. It is known that the protection of the amino group is performed with the help of:

- Carbobenzyloxy groups (Cbz) - removed by hydrogenolysis
- tert-butyloxycarbonyl group (BOC) - removed by a concentrated strong acid (for example, HCl or CF_3COOH)
- acetyl groups (Ac) - removed by treatment with a base, aqueous or gaseous ammonium or methylamine
- benzoyl groups (Bz) - removed by treatment with a base, aqueous or gaseous ammonium or methylamine
- benzyl group (Bn) - removed by hydrogenolysis
- p-methoxybenzyl group (PMB) – removed by hydrogenolysis
-3,4-dimethoxybenzyl groups (DMPM) – removed by hydrogenolysis, etc.

Which of the following protection reagents is shown in Figure 4?

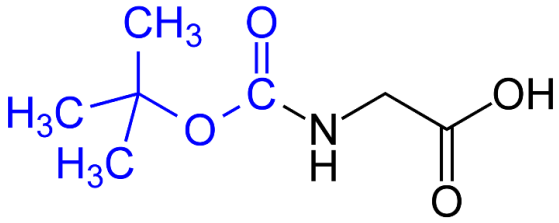


Figure 4.

An example of a task with an answer standard:
Name the functional groups in the tyrosine molecule that are protected by chemical reagents during the orthogonal protection of this molecule:

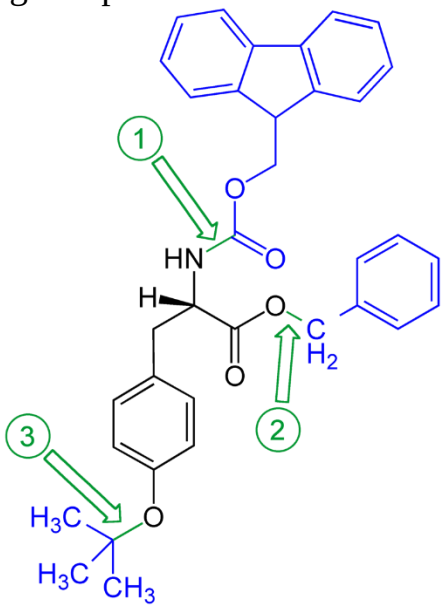


Figure 5. Protective groups are marked in blue colour.

Answer standard

Orthogonal protection is a strategy that allows deprotection of one protecting group in a multi-protected structure without affecting the others. In the tyrosine amino acid molecule, the amino group ((1) Fmoc-protected) can be protected with fluorenyl methyleneoxycarbamate (Fmoc), the carboxyl group with benzyl ester (2), and the phenolic hydroxyl (3) with tert-butyl ether. The benzyl ester can be removed by hydrogenolysis, the fluorenylmethyleneoxy group (Fmoc) by bases (piperidine), and the phenolic tert-butyl ether by acids (trifluoroacetic acid).

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 4. Synthetic methods of obtaining double-, hybrid-molecules as biologically active compounds, methods of synthesis of pro-drugs. Protective groups in organic synthesis. *Control work 1.*

Purpose: the ability to operate knowledge of synthetic methods of obtaining double, hybrid biologically active molecules, pro-drugs and the use of methods of protection of functional groups during the synthesis of biologically active molecules, the use of acquired knowledge in practice, the ability to perform computer prediction of chemical and biological properties BAS and MP.

The student must:

 know the basic and modern methods of synthesis of biologically active molecules and pro-drugs;

 be able to detect and propose reactions of modifications of functional groups;

 evaluate the possibility of variability of molecules based on chemical modification.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
Multistage synthesis	or the convergent synthesis of target oligomers or macromolecular compounds, which takes place in two or more stages of chemical transformations, with the formation of a "backbone" of the molecule and its dendrimer with a large number of branches (dendron - branching)
TM, target molecule	molecule of the compound that is planned to be synthesized
Synthetic transform	a chemical transformation during which the structure of the target molecule is maximally simplified
"Powerful" synthesis reactions	reactions into one stage, during which a significant complication of the molecule occurs
Building block	a compound containing one or more functional groups in its molecule, which allow the structural fragment of this molecule to be easily incorporated into the molecules of other compounds
Synthesis strategy	construction of the molecular skeleton of the target molecule with the required sequence of the required number of carbon atoms with the planned arrangement of functional groups in the molecule of the final product

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/.*
2. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. The concept of multistage syntheses. Give examples of multistage synthesis of a medicinal product.

2. Concept of target molecule (TM).

3. "Powerful reactions" of synthesis and their examples.

4. Building block. Give examples of a building block in the synthesis of a medicinal product.

5. Main types of strategic relationships.

6.Principles of Carbon-Carbon Bond Construction. Give examples of the construction of a C-C bond during the synthesis of a medicinal product.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. What is called convergent synthesis?
   A. polymerization
   B. multistage synthesis
   C. intramolecular condensation

D. cyclization reaction

2. During the synthesis of the target molecule, dendrimers are created. What are called dendrimers?

A. a double bond is formed

B. a triple bond is formed

C. C-C branching

D. rearrangement of atoms

3. What chemical transformation is called a synthetic transform?

A. during which maximum simplification of the structure of the target molecule occurs

B. during which oxidation of the hydroxy group occurs

C. during which the carbonyl group is reduced

D. during which polymerization occurs

4. What is a building block in organic synthesis?

A. a compound containing one or more functional groups in its molecule, which allow the structural fragment of this molecule to be easily incorporated into the molecules of other compounds

B. a chemical compound with multiple bonds in its structure

C. a foreign chemical compound for the body, which is not synthesized in the body and is not used in the processes of building cells, energy production and other processes of ensuring the vital activity of the body

D. a chemical compound with an aromatic fragment in its structure

5. What chemical transformation occurs in the Robinson reaction?

A. annealing

B. condensation

C. partial restoration

D. acylation

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the scheme of the reaction, which is called a "powerful" reaction in synthesis. Describe the reaction and its name.

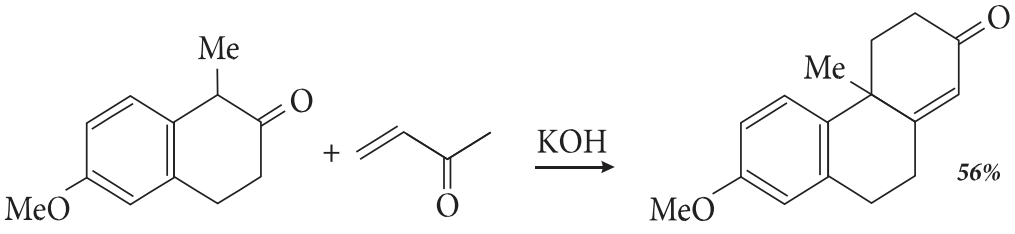


Figure 1.

The answer and its justification

Auditory collective work:

Task 1. "Powerful" synthesis reactions include condensation reactions: aldol condensation, acyloin condensation, Mannich condensation. Reactions occur according to the general scheme (Fig. 2):

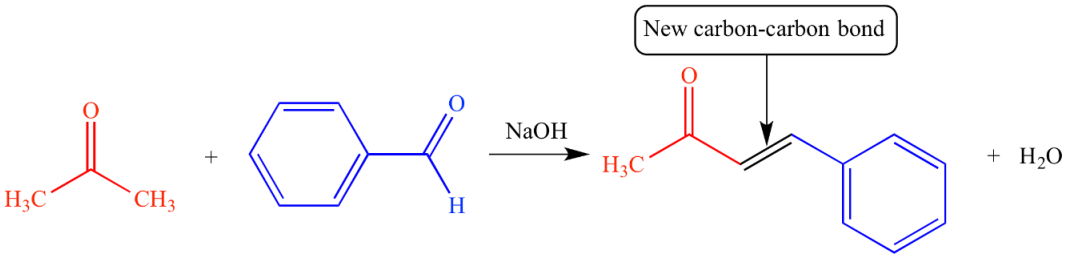


Figure 2.

Write the reaction schemes.

State how these condensation reactions differ and what products are formed?

The answer and its justification

Task 2. Figure 3 shows Diels-Alder reaction schemes. Describe these reactions. What reagents are used in the Diels-Alder reaction? To which class of organic compounds do the reaction products belong?

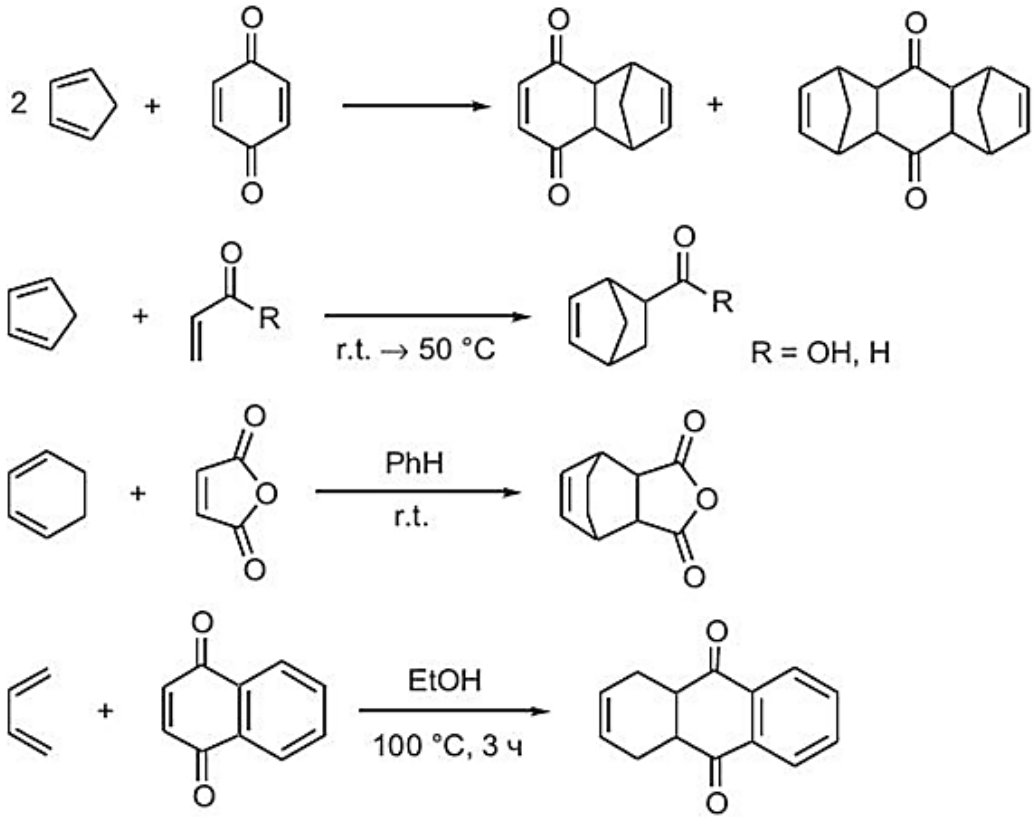


Figure 3.

The answer and its justification

Auditory independent work (supervised by the teacher):

Task 1. Figure 4 shows the scheme of the intramolecular radical π-cyclization reaction. Explain why this reaction is called a π-cyclization?

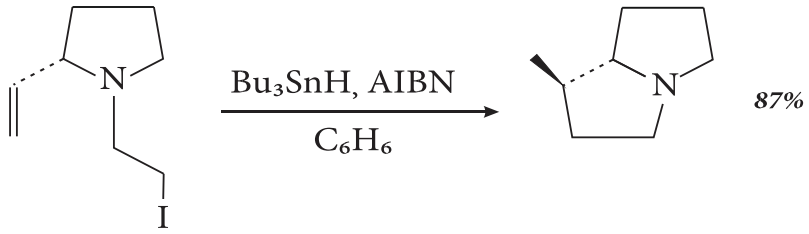


Figure 4.

An example of a task with an answer standard:

What is the Mannich reaction, which is used in the synthesis of new biologically active compounds?

Answer standard

The reaction of aminomethylation of compounds using formaldehyde and amine (or ammonium) is **a Mannich reaction**. The compound (more often, it is a ketone capable of enolization), which enters into the Mannich reaction, must contain an active (mobile) Hydrogen atom near the Carbon atom (Fig. 5).

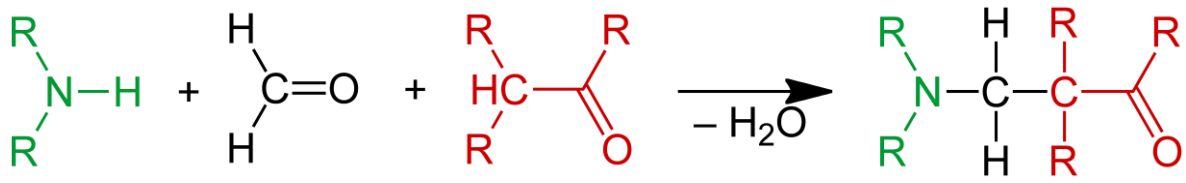


Figure 5. Scheme of Mannich reaction.

The Mannich reaction makes it possible to obtain organic compounds with an increased chain of carbon atoms by one methylene group -CH2- and two functional groups - keto- and amino- groups.

Control work No. 1 - on questions of topics 1-4.

List of questions for control work No. 1.

1. Describe organic synthesis. Its purpose and tasks.

2. Single-reactor synthesis. Its advantages.

3. Name the types of reactions by mechanism: radical, electrophilic, nucleophilic. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

4. Addition-detachment reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

5. Condensation reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

6. Cyclization reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

7. Rearrangement reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

8. Aromatization reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

9. What is the essence of "click" synthesis. Give examples of such reactions in the synthesis of biologically active compounds and drugs.

10. Name the sources of raw materials for organic synthesis. Cyclization reactions. Give examples of such reactions in the synthesis of biologically active compounds and drugs and indicate the sources of raw materials.

11. Reagents and solvents in synthesis. Give examples of such reactions in the synthesis of biologically active compounds and drugs and indicate which reagents and solvents are used in these reactions.

12. Electronic effects in the molecule. Give the chemical formulas of biologically active compounds and drugs. Indicate what electronic effects operate in this molecule. How does it affect her reactivity.

13. Functional groups. Give the chemical formulas of biologically active compounds and drugs. Indicate which functional groups are present in this molecule. How do they affect her reactivity.

14. Methods of purification of chemical substances (filtering, recrystallization, extraction, distillation). Describe the methods.

15. What is CADD? What are the positive features of automated drug design?

16. QSAR, SAR analysis and their role in predicting BAS activity.

17. What methods of "drug design" are relevant today?

18. Describe the concept of "molecular docking".

19. Pharmacophores. Give a description. Specify the pharmacophores in the structures of the molecules - the active substances of sulfonamides, benzodiazepines, barbiturates, phenanthrenisoquinolines, etc.

20. Scaffolds. Give examples of scaffolds in molecules of active substances - representatives of drug classes.

21. The task of bioisosteric substitution.

22. Linkers. Give examples of linkers: peptide and double bond; aldehyde and imine groups, SH, NH_2, CH_3, OH-groups, S, NH, CH_2O-linkers in the molecules of active substances - representatives of drug classes.

23. De novo design. Main tasks.

24. What does the abbreviation ADME stand for?

25. Describe the processes: absorption, distribution, metabolism, excretion.

26. Name the ways of excretion of substances.

27. SwissADME and protox-II programs and their purpose.

28. How does the chemical structure of substances affect ADME parameters?

29. What methods and reactions are used to modify the hydroxy group? Give examples. Write the reaction schemes.

30. What methods and reactions are used to modify the mercapto group? Give examples. Write the reaction schemes.

31. What methods and reactions are used to modify the carboxyl group? Give examples. Write the reaction schemes.

32. What methods and reactions are used to modify the carbonyl (aldehyde and keto) group? Give examples. Write the reaction schemes.

33. What methods and reactions are used to modify the amino group? Give examples. Write the reaction schemes.

34. The concept of multistage syntheses. Give examples of multistage synthesis of a medicinal product.

35. Concept of target molecule (TM).

36. "Powerful reactions" of synthesis and their examples.

37. Building block. Give examples of a building block in the synthesis of a medicinal product.

38. Main types of strategic relationships.

39. Principles of Carbon-Carbon Bond Construction. Give examples of the construction of a C-C bond during the synthesis of a medicinal product.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 5. Derivatives of phenyl(heteryl)ethylamines as biogenic amines and drugs, methods of synthesis/modification. Structure-activity relationship.

Purpose: ability to plan and implement methods of synthesis or modification of derivatives of phenyl(heteryl)ethylamines, analysis of the mutual influence of their features of chemical structure and biological activity, ability to perform computer forecasting of chemical and biological properties of BAS and drugs.

The student must:

 to know the basic and modern methods of synthesis of biologically active derivatives of phenyl(heteryl)ethylamines;

 be able to detect and propose reactions of modifications of functional groups of biologically active derivatives of phenyl(heteryl)ethylamines;

 evaluate the possibility of variability of molecules based on chemical modification.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
Phenyl(heteryl)ethylamines	ethylamines, which contain phenyl radicals and heterocyclic fragments in the chemical structure
Local anesthetics	drugs that reduce or completely suppress the excitability of nerve fibers, block the conduction of impulses to the central nervous system
The lipophilic group of the phenyl (heteryl)ethylamine molecule	aromatic ring
The "intermediate" chain of the phenyl (heteryl)ethylamine molecule	a fragment of a molecule with an ester or amide bond
Terminal functional group molecules of phenyl (heteryl)ethylamine	the amino group is tertiary or quaternary

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/.*
2. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. Methods of synthesis of phenyl(heteryl)ethylamine derivatives.

2. Peculiarities of the chemical structure of molecules of active substances of local anesthetic agents.

3. Classifications of local anesthetic agents.

4. Mechanism of action of local anesthetic agents.

5. Influence of the chemical structure of molecules on the solubility of local anesthetics.

6. Functional groups in the composition of molecules of active substances of local anesthetic agents.

7. Relationship between the structure and activity of the molecules of active substances of local anesthetic agents.

8. Structure-activity dependence of drugs affecting the serotonergic system.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. The molecule of the active substance of the local anesthetic contains a lipophilic group. What is her name?

A. aromatic ring

B. carbonyl group

C. hydroxy group

D. multiple bond

2. The intermediate chain of the molecule of the active substance of the local

anesthetic must have a specific connection. What is his name?

A. double bond

B. triple bond

C. ester bond

D. hydrogen bond

3. The chemical structure of the intermediate chain in the molecule of the active substance of the local anesthetic determines it:

A. method and rate of biotransformation

B. chemical properties

C. pH value

D. lipophilicity

4. The drug Procaine (2-diethylamino)ethyl-4-aminobenzoate) contains an intermediate chain with a specific bond. What is his name?

A. ester
B. hydrogen
C. amide
D. peptide

5. What is the name of the amino group contained in the Tetracaine molecule?

A. diethylamino
B. dimethylamino
C. amino
D. methylethylamino

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the structural formula of the active substance of the medicinal product Bupivacaine. Name the functional groups in the Bupivacaine molecule.

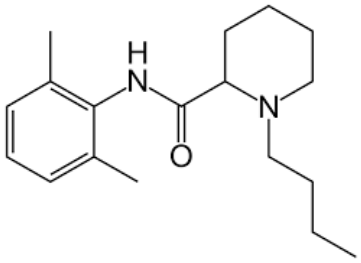


Figure 1.

The answer and its justification

Auditory collective work:

Task 1. Figure 2 shows the synthesis scheme of Bupivacaine.Аудиторна колективна робота:

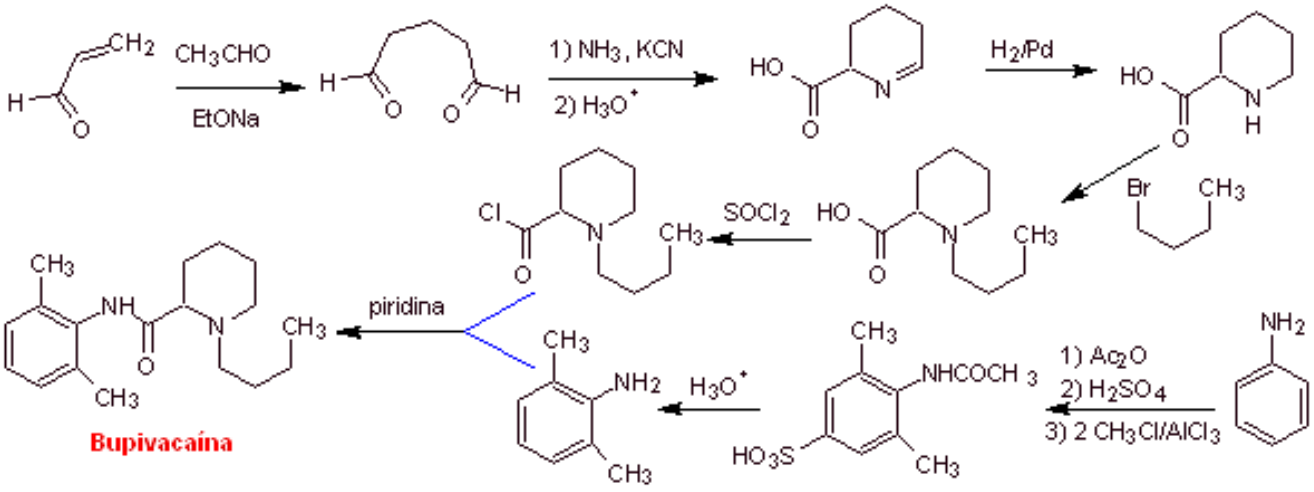


Figure 2.

Specify the stages of synthesis at which cyclization, reduction, halogenation, and sulfonation reactions take place. Write diagrams of these reactions. Specify the chemical reagents used for the synthesis of Bupivacaine.

The answer and its justification

Task 2. Figure 3 shows the synthesis scheme of Prilocaine.

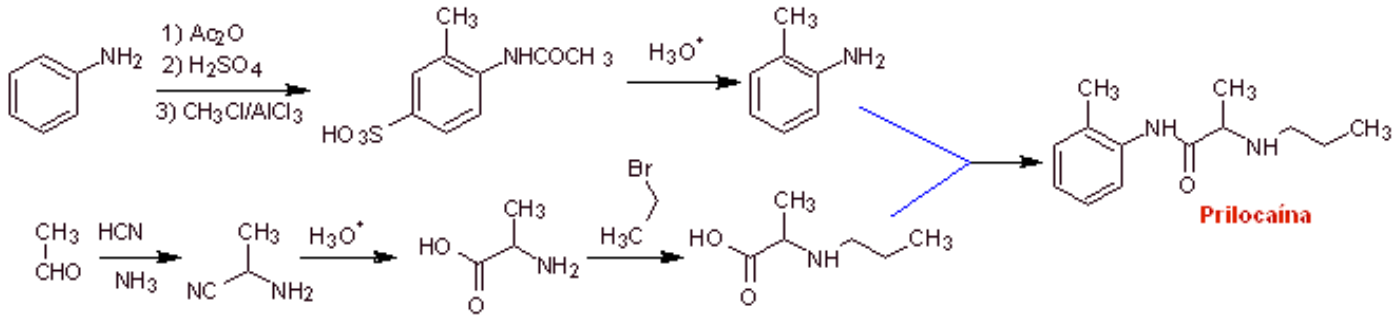


Figure 3.

Name the starting compound for the synthesis of Prilocaine. Specify the stages of synthesis at which sulfonation and acetylation reactions take place. Write diagrams of these reactions. Specify the chemical reagents used for the synthesis of Prilocaine. At which of the stages is protection of the functional group carried out? Name the functional group.

The answer and its justification

Auditory independent work (supervised by the teacher):

Task 1. Figure 4 and Figure 5 show the synthesis schemes of Articaine and Lidocaine. Name the starting compounds and chemical reagents for their synthesis. How many stages does the synthesis of Articaine and Lidocaine have? Make a comparative analysis of the reactions performed during both syntheses.

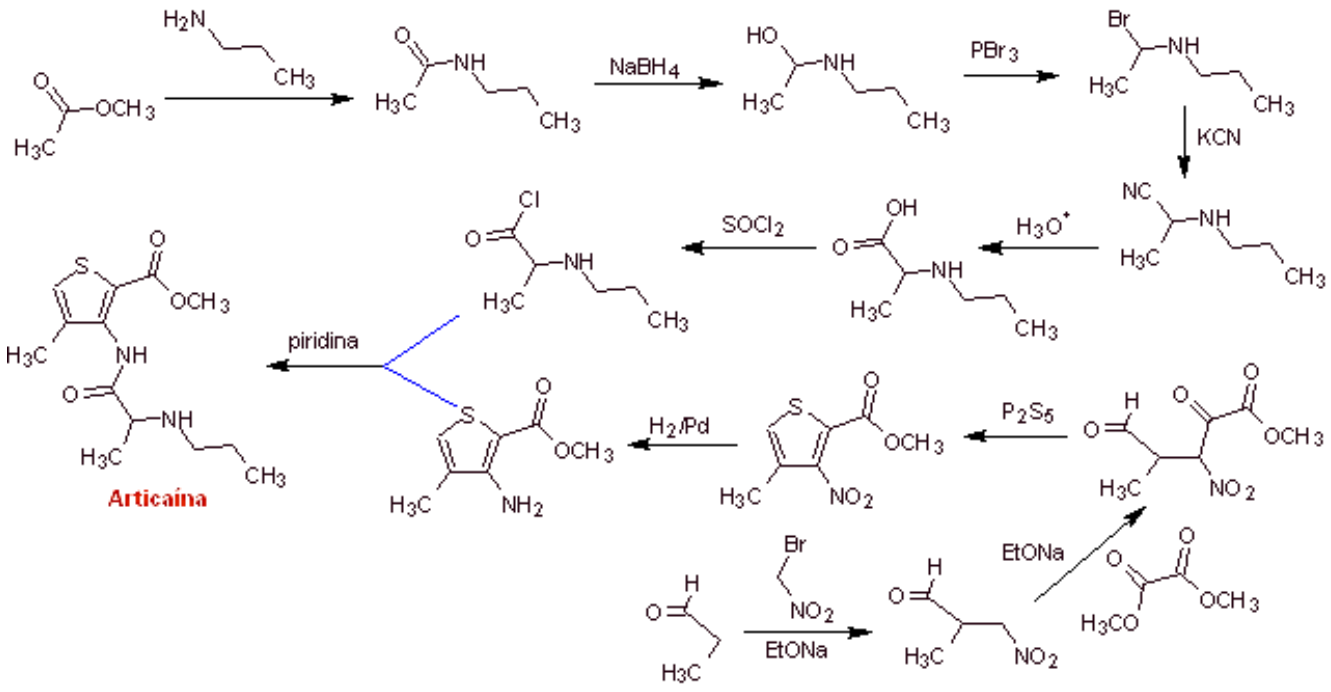


Figure 4. Synthesis of Articaine.

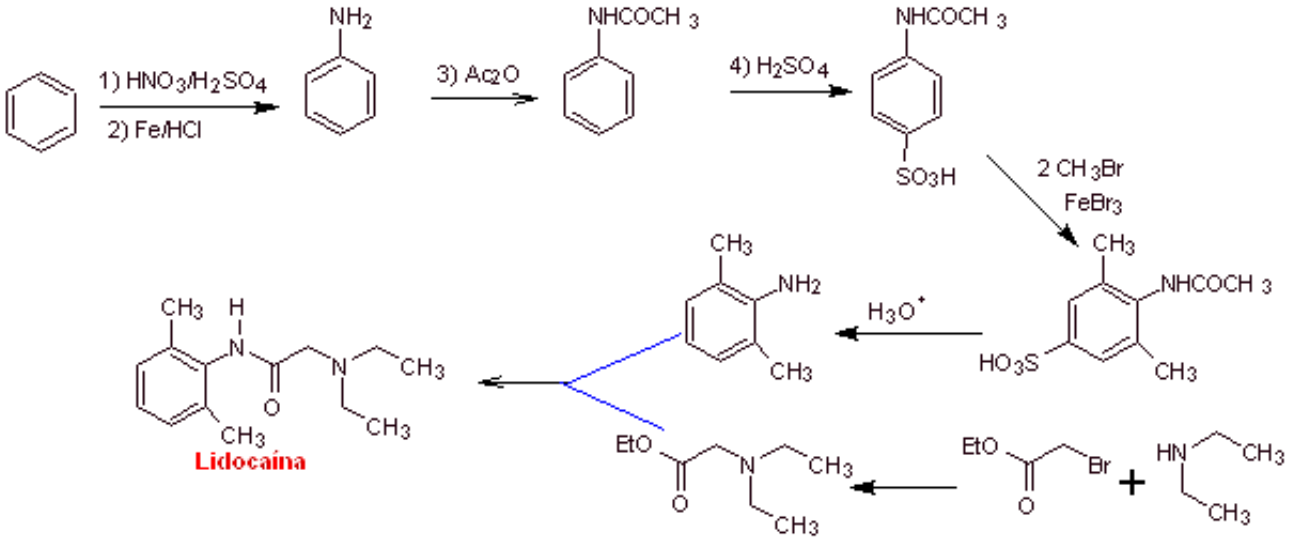


Figure 5. Synthesis of Lidocaine.

An example of a task with an answer standard:
Describe the synthesis of Tetracaine.

Answer standard

Tetracaine is produced using a two-stage synthesis. The starting compound is 4-butylaminobenzoic acid. At the first stage of the synthesis, the esterification reaction is performed in an acidic environment under the influence of ethanol. At the second stage of the synthesis, the transesterification of the ethyl ester of 4-butylaminobenzoic acid is carried out under the conditions of alkaline catalysis with sodium ethylate during boiling with an excess of 2-methylaminoethanol (Fig. 6).

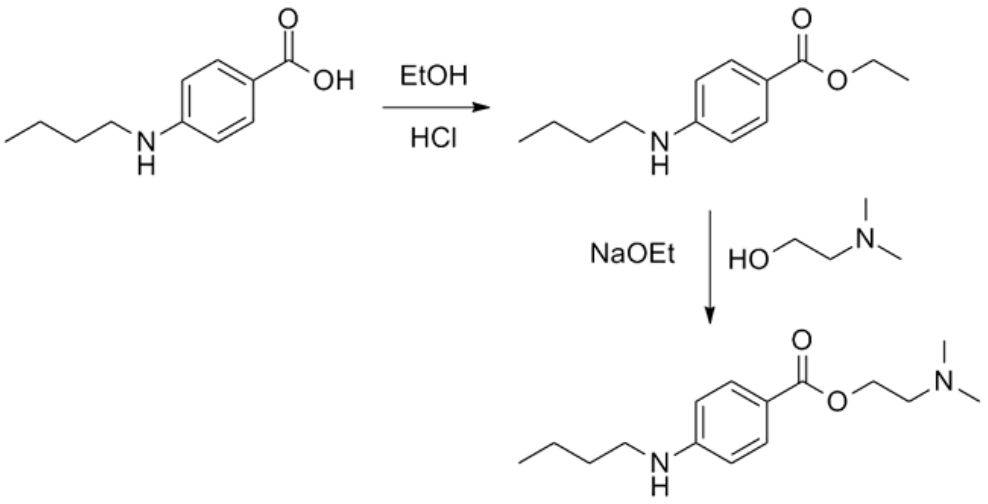


Figure 6. Synthesis of Tetracaine.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 6. Local anesthetic agents, methods of synthesis/modifications. Structure activity relationship. Establishment of pharmacophore grouping.

Purpose: ability to plan and implement methods of synthesis or modification of molecules of active active substances of local anesthetic agents, analysis of the mutual influence of their features of chemical structure and biological activity, ability to perform computer prediction of chemical and biological properties of BAS and drugs (SwissTargetPrediction, Swiss).

The student must:

 to know the basic and modern methods of synthesis of active substances of local anesthetic agents;

 be able to detect and propose reactions of modifications of functional groups in molecules of active substances of local anesthetic agents;

 evaluate the possibility of variability of molecules based on chemical modification.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
Local anesthetics	drugs that reduce or completely suppress the excitability of nerve fibers, block the conduction of impulses to the central nervous system
The lipophilic group of the molecule of the active substance of the local anesthetic	aromatic ring
The "intermediate" chain of the molecule of the active substance of the local anesthetic	a fragment of a molecule with an ester or amide bond
Hydrophilic group molecules of the active substance of a local anesthetic	the amino group is substituted or unsubstituted

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/.*
2. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*
3. Peng Wu, Joachim Demaerel, Deshen Kong, Ding Ma, Carsten Bolm. Copper-Catalyzed, Aerobic Synthesis of NH-Sulfonimidamides from Primary Sulfinamides and Secondary Amines. *Organic Letters* 2022, *24* (38), 6988-6992. https://doi.org/10.1021/acs.orglett.2c02804
4. Matthew A. Sguazzin, Jarrod W. Johnson, Jakob Magolan. Hexafluoroisopropyl Sulfamate: A Useful Reagent for the Synthesis of Sulfamates and Sulfamides. *Organic Letters* **2021**, *23* (9), 3373-3378. https://doi.org/10.1021/acs.orglett.1c00855
5. Thomas Q. Davies, Michael J. Tilby, David Skolc, Adrian Hall, Michael C. Willis. Primary Sulfonamide Synthesis Using the Sulfinylamine Reagent N-Sulfinyl-O-(tert-butyl)hydroxylamine, t-BuONSO. *Organic Letters* **2020**, *22* (24), 9495-9499. https://doi.org/10.1021/acs.orglett.0c03505

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. Describe the features of the chemical structure of molecules of active substances of local anesthetic agents: lipophilic and hydrophilic parts, intermediate chain.
2. Describe the "structure-activity" relationship in the Articaine molecule.
3. Articaine. Peculiarities of metabolism. What active metabolites are formed? What features of the chemical structure do active metabolites have?
4. Describe the "structure-activity" relationship in the Bupivacaine molecule.
5. Bupivacaine. Peculiarities of metabolism. What active metabolites are formed? What features of the chemical structure do active metabolites have?
6. Describe the "structure-activity" relationship in the Lidocaine molecule.
7. Lidocaine. Peculiarities of metabolism. What active metabolites are formed? What features of the chemical structure do active metabolites have?
8. Describe the main regularities of the influence of "structure-activity" of local anesthetic agents - Aminoesters.
9. Describe the main regularities of the "structure-activity" effect of local anesthetic agents - Aminoamides.
10. Describe the main regularities of the "structure-activity" effect of local

anesthetic agents - Aminoethers.

11. Describe the main regularities of the "structure-activity" influence of local anesthetic agents - Aminoketones.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. The molecule of the active substance of the local anesthetic contains a hydrophilic group. What is her name?

A. aromatic ring

B. carbonyl group

C. hydroxy group

D. amino group

2. How does the amino group affect the properties of the molecule?

A. improves solubility in water

B. increases lipophilicity

C. neutralizes the molecule

D. activates chemical properties

3. How does the lipophilic aromatic ring of a local anesthetic molecule affect its activity?

A. increases the pharmacological effect

B. inhibits the pharmacological effect

C. has a neutral effect

D. increases solubility

4. The drug Articaine contains a heterocyclic fragment in the molecule of the active substance. What is his name?

A. thiophene

B. furan

C. pyridine

D. piperidine

5. Does the drug Bupivacaine contain a heterocyclic fragment in the molecule of the

active substance? What is his name?

A. piperidine

B. purines

C. pyrimidine

D. pyrrole

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the structural formula of the active substance of the drug Lidocaine. Name the functional groups in the Lidocaine molecule.

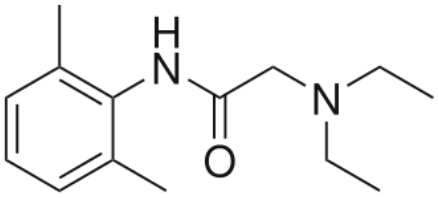


Figure 1.

The answer and its justification

Auditory collective work:

Task 1. Figure 2 shows the scheme of metabolism of Articaine.

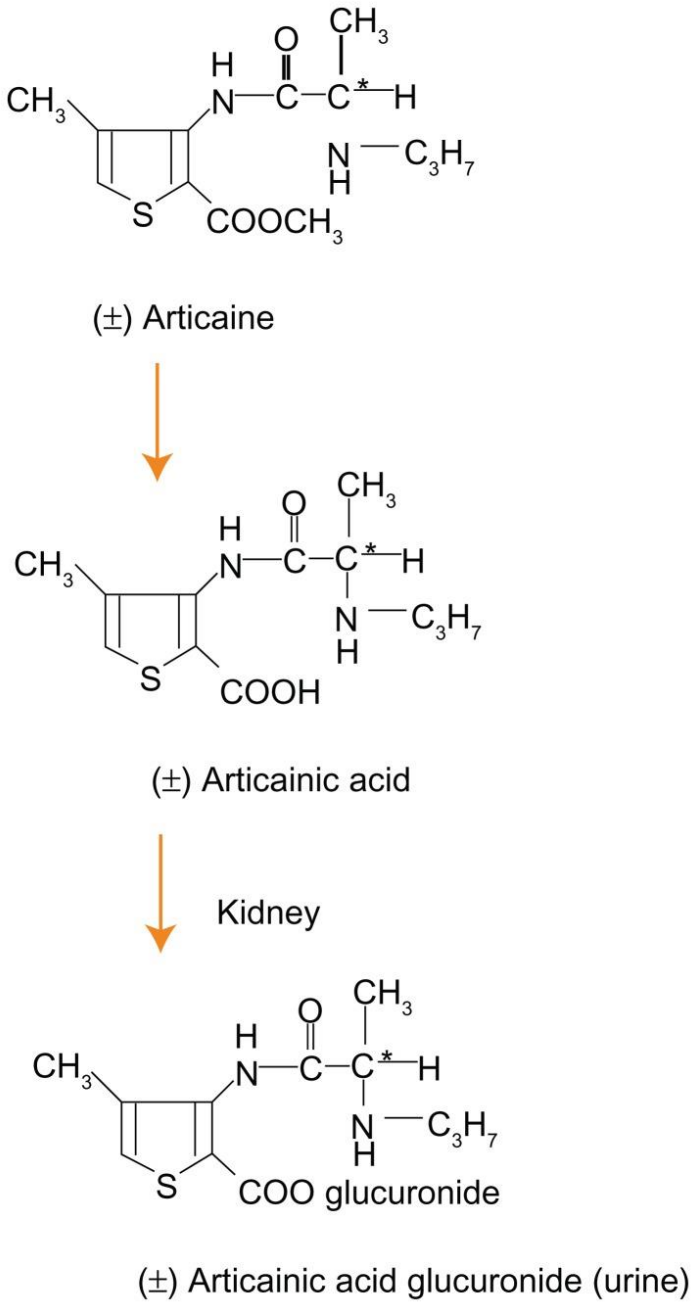


Figure 2.

Describe the chemical reactions of the metabolism of the Articaine molecule at each stage. What happens to the molecules? Under the influence of which enzymes do the transformations take place? At what stages of metabolism do transformations take place?

The answer and its justification

Task 2. Figure 3 shows the scheme of the construction of a local anesthetic molecule, which chemically belongs to aminoesters.

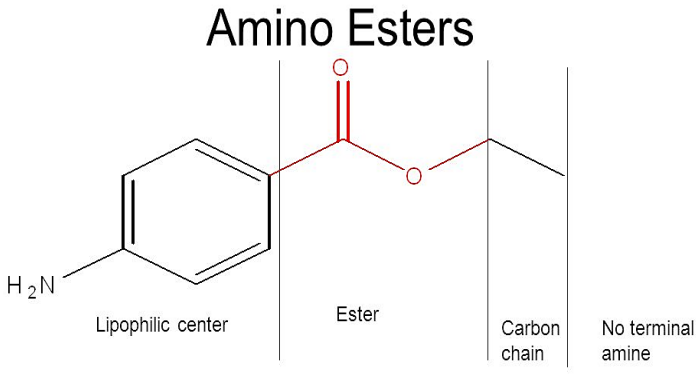


Figure 3.

Name the drug whose chemical structure corresponds to this scheme. Name the functional groups contained in the molecule.

The answer and its justification

Auditory independent work (supervised by the teacher):

Task 1. Figure 4 and Figure 5 show the construction schemes of Tetracaine and Procaine molecules. Name the differences in structures. Specify the substituents in the ortho and para positions. How do they affect pharmacological activity?

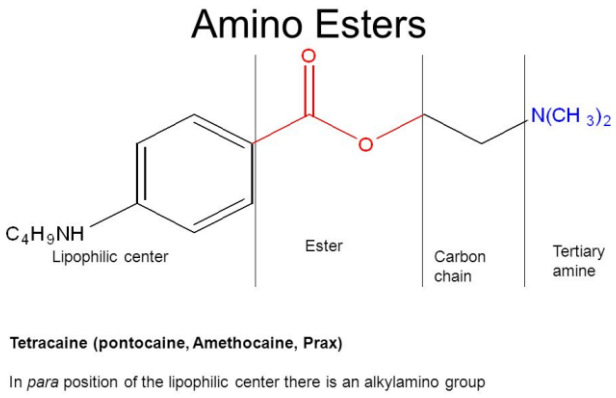


Figure 4. Tetracaine.

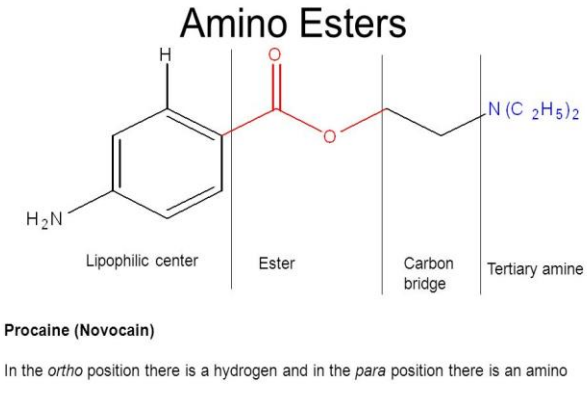


Figure 5. Procaine.

Using the computer program SwissPredictioTarget (Swiss), conduct an analysis of biotargets, pharmacological activity of structural analogues of Tetracaine, Procaine, Prilacaine, Mepivacaine (offer your examples).

An example of a task with an answer standard:
Lidocaine molecule contains two alkyl radicals $–CH_3$. What is the role of alkyl radicals (Fig. 6)?

Answer standard

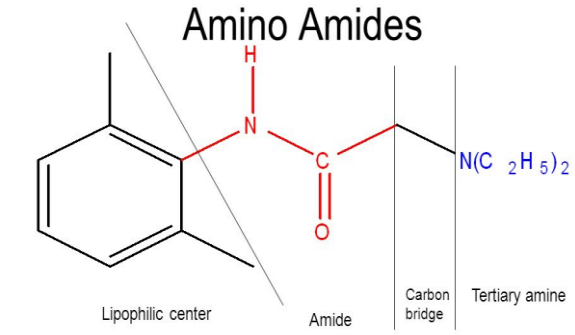


Figure 6. Lidocaine.

Lidocaine (Xylocaine) belongs to aminoamides according to its chemical structure. The molecule contains *o,o*-dimethyl groups, which are electron donors. It is known that electron-donating substituents in the *ortho*- or *para*-positions of the aromatic ring increase the local anesthetic effect. In addition, alkyl radicals in the ortho-positions of the aromatic ring are necessary to provide protection against amide hydrolysis to ensure the desired duration of action.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 7. Sulfanilamides, methods of synthesis/modifications. Structure-activity relationship.

Purpose: ability to plan and implement methods of synthesis or modification of molecules of active substances of sulfanilic acid derivatives, analysis of the interaction of their features of chemical structure and biological activity, ability to perform computer prediction of chemical and biological properties of BAS and drugs (SwissTargetPrediction, Swiss).

The student must:

 to know the basic and modern methods of synthesis of active substances of sulfonamides;

 to be able to detect and propose reactions of modifications of functional groups in molecules of sulfanilic acid derivatives;

 evaluate the possibility of variability of molecules based on chemical modification.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
Sulfanilic acid	*para*-sulfoaniline
The lipophilic group of the molecule of the active ingredient sulfonamide	aromatic ring
– SO_2NH_2; – SO_2NHR; *– SO_2NR_2*	primary, secondary and tertiary sulfamide groups
– SO_2NHAr; – SO_2NAr_2	replacing R with Ar increases toxicity

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/*.
2. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*
3. Peng Wu, Joachim Demaerel, Deshen Kong, Ding Ma, Carsten

Bolm. Copper-Catalyzed, Aerobic Synthesis of NH-Sulfonimidamides from Primary Sulfinamides and Secondary Amines. *Organic Letters* 2022, *24* (38), 6988-6992. https://doi.org/10.1021/acs.orglett.2c02804
4. Matthew A. Sguazzin, Jarrod W. Johnson, Jakob Magolan. Hexafluoroisopropyl Sulfamate: A Useful Reagent for the Synthesis of Sulfamates and Sulfamides. *Organic Letters* **2021**, *23* (9), 3373-3378. https://doi.org/10.1021/acs.orglett.1c00855
5. Thomas Q. Davies, Michael J. Tilby, David Skolc, Adrian Hall, Michael C. Willis. Primary Sulfonamide Synthesis Using the Sulfinylamine Reagent N-Sulfinyl-O-(tert-butyl)hydroxylamine, t-BuONSO. *Organic Letters* **2020**, *22* (24), 9495-9499. https://doi.org/10.1021/acs.orglett.0c03505
6. Ovung A, Bhattacharyya J. Sulfonamide drugs: structure, antibacterial property, toxicity, and biophysical interactions. Biophys Rev. 2021 Mar 29;13(2):259-272. doi: 10.1007/s12551-021-00795-9. PMID: 33936318; PMCID: PMC8046889.

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. Peculiarities of the chemical structure of sulfonamide molecules.
2. Classifications of sulfonamide drugs.
3. Mechanism of action, pharmacokinetics, indications, side effects.
4. Chemical formulas of sulfonamides and features of synthesis/modification of their molecules, bioisosteric substitutions, scaffold.
5. Sulfacetamide, Sulfacil sodium. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.
6. Sulfamethoxazole. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.
7. Phthalazole. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.
8. The main regularities of the interaction of the chemical structure and biological activity of sulfonamides.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. The molecule of the active ingredient sulfonamide contains a lipophilic group. What is her name?

A. aromatic ring

B. carbonyl group

C. hydroxy group

D. amino group

2. How does the methyl group in the para-position of the aromatic ring of the sulfonamide molecule affect its properties?

A. increases biological activity

B. increases lipophilicity

C. neutralizes the molecule

D. activates chemical properties

3. What is the nature of the methyl radical in the para-position of the aromatic ring of the sulfonamide molecule?

A. hydrophobic

B. lipophilic

C. hydrophilic

D. neutral

4. When replacing a hydrophobic group - methyl with a more voluminous radical - isopropyl, changes in the properties of the sulfonamide molecule occur. What is observed?

A. increased toxicity

B. increase in lipophilicity

C. pharmacological activity disappears

D. deactivation of all properties

5. Does Phthalazol contain a heterocyclic fragment in the molecule of the active substance? What is his name?

A. thiazole

B. purines

C. pyrimidine

D. pyrrole

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the structural formula of the active substance of the drug Phthalazol. Name the functional groups in the Phthalazole molecule.

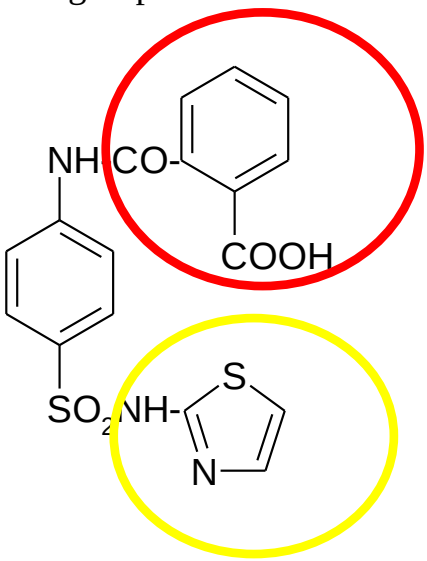


Figure 1.

The answer and its justification

Auditory collective work:

Task 1. Figure 2 shows the synthesis scheme of sulfonamide from sulfanilic acid.

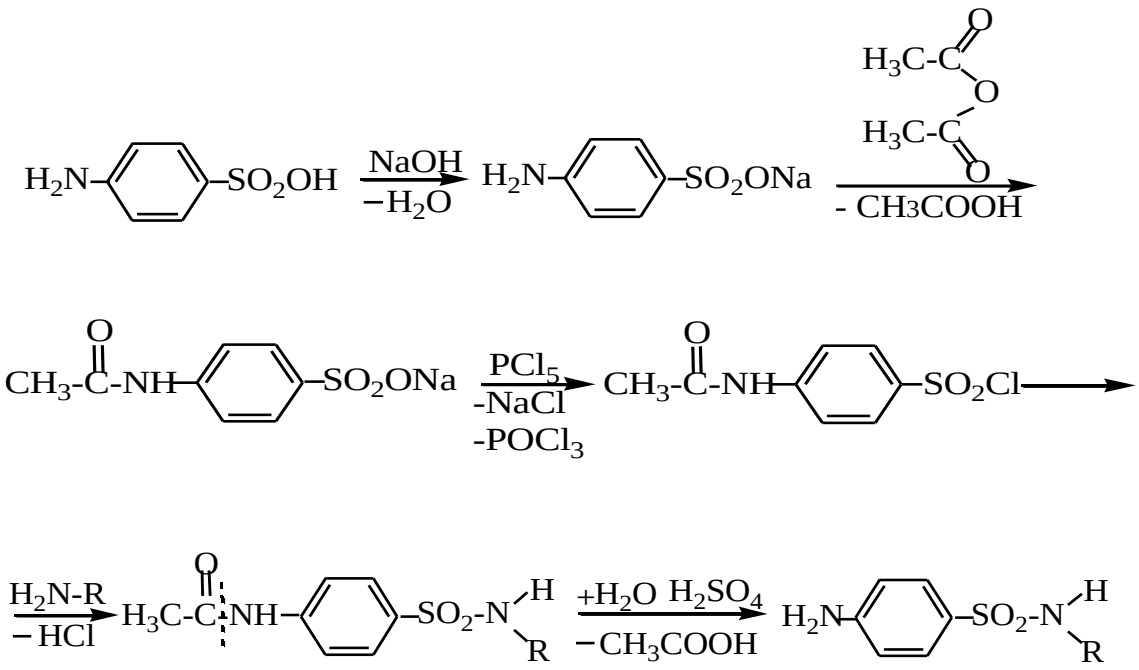


Figure 2.

Describe the chemical reactions of sulfonamide synthesis at each stage. What reagents are used? Do the reactions use the method of protection of the functional group? Does the synthesis of sulfonamide from sulfanilic acid belong to one-reactor syntheses?

The answer and its justification

Task 2. Figure 3 shows the construction scheme of a chemically modified sulfonamide molecule.

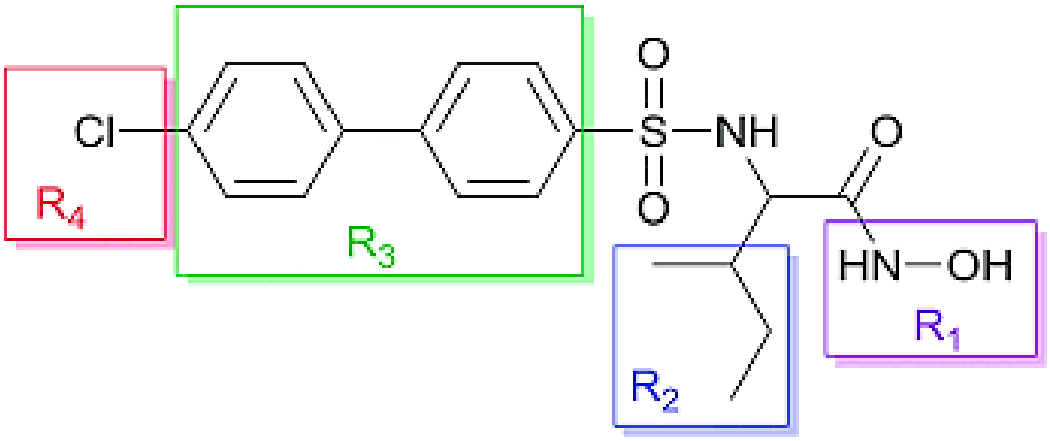


Figure 3.

Name the structural components of a molecule. Specify their chemical nature: hydrophilicity, hydrophobicity, lipophilicity.

The answer and its justification

Auditory independent work (supervised by the teacher):

Task 1. Figure 4 and Figure 5 show the chemical formulas of Sulfamethoxazole and Sodium Sulfacyl molecules. Name the differences in structures. Specify the substituents in the para-positions of the aromatic ring. How do they affect pharmacological activity?

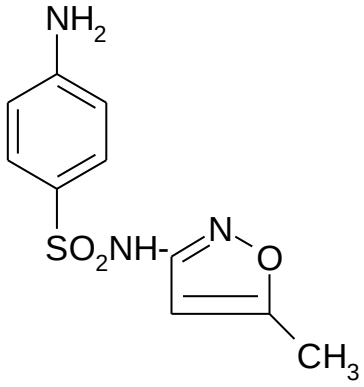


Figure 4. Sulfamethoxazole.

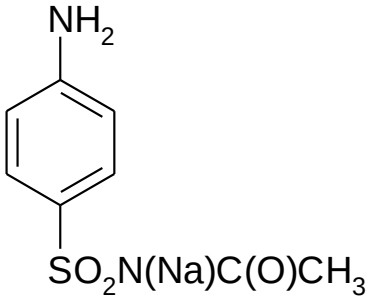


Figure 5. Sulfacil sodium.

Using the computer program SwissPredictioTarget (Swiss), conduct an analysis of biotargets, pharmacological activity of structural analogues of Sulfamethoxazole, Sulphametrol, Sulphathiazole, Sulfachlorpyridazine (offer your examples).

An example of a task with an answer standard:

The main regularities of the interaction of the chemical structure and biological activity of sulfonamides.

Answer standard

1. The compound is biologically active in the presence of a sulfonyl substituent. This part of the sulfonamide molecule is the basis for obtaining a pharmacological effect.
2. The compound is not biologically active if the amino group is in position 4 or the hydrogen atoms of the amino group are replaced by substituents that prevent the formation of a new free aromatic amino group in the body (hydrolysis of the substituted amino group does not occur).
3. The movement of the amino group from position 4 to position 2 or 3 of the benzene nucleus leads to a complete loss of pharmacological activity.
4. The introduction of additional substituents into the benzene nucleus leads to the destruction or significant reduction of pharmacological activity.

5. Substitution of a hydrogen atom in the composition of the sulfamide group with substituents of different chemical structure leads, depending on the structure of the substituent, to a decrease or increase in pharmacological activity (Fig. 6).

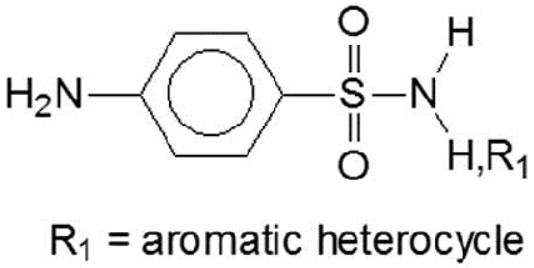


Figure 6. Common chemical formula of sulfonamide.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 8. The pyridine cycle as an example of «preferred structures», methods of synthesis/modifications of pyridine derivatives. Structure-activity relationship.

Purpose: ability to plan and implement methods of synthesis or modification of molecules of biologically active pyridine derivatives, analysis of the interaction of their features of chemical structure and biological activity, ability to perform computer prediction of chemical and biological properties of BARs and drugs (SwissTargetPrediction, Swiss).

The student must:

 to know the basic and modern methods of synthesis of biologically active pyridine derivatives;

 be able to detect and propose reactions of modifications of functional groups in molecules of biologically active pyridine derivatives;

 evaluate the possibility of variability of molecules based on chemical modification.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
Pyridine	a six-membered heterocycle with one Nitrogen heteroatom and an unsaturated system
Piperidine	hydrogenated form of pyridine
The lipophilic group of the molecule of the active substance of the pyridine derivative	unsaturated heterocyclic ring
Hantzsch method of synthesis	method of synthesis of pyridine and its derivatives by the interaction of β-keto acid (acetoacetate), aldehyde and ammonium
Ciamician-Dennstedt rearrangement	rearrangement reaction of the pyrrole ring to the pyridine ring (cycle enlargement)

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. Islam MB, Islam MI, Nath N, Emran TB, Rahman MR, Sharma R, Matin MM. Recent Advances in Pyridine Scaffold: Focus on Chemistry, Synthesis, and Antibacterial Activities. Biomed Res Int. 2023 May 18; 2023: 9967591. doi: 10.1155/2023/9967591. PMID: 37250749; PMCID: PMC10212683.
2. Eletmany, Mohamed & Albalawi, Marzough & Al-Harbi, Reem & Elamary, Rokaia & Harb, Abd & Selim, Moghraby & Abdelgeliel, Asmaa & Hassan, Entesar & Abdellah, Islam. (2023). Novel Arylazo Nicotinate Derivatives as Effective Antibacterial Agents: Green Synthesis, Molecular Modeling, and Structure-Activity Relationship Studies. Journal of Saudi Chemical Society. 10.1016/j.jscs.2023.101647.
3. *Organic Syntheses*: *http://www.orgsyn.org/*.
4. Esraa Ali Mohamed, Nasser S. M. Ismail, Mohamed Hagras and Hanan Refaat. Medicinal attributes of pyridine scaffold as anticancer targeting agents. Future Journal of Pharmaceutical Sciences (2021) 7:24 https://doi.org/10.1186/s43094-020-00165-4

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. Peculiarities of the chemical structure of the pyridine molecule and its derivatives.
2. Methods of synthesis of pyridine and its derivatives.
3. Substances of natural origin - pyridine derivatives. Alkaloids.
4. Toxicity of pyridine.
5. Metabolism of pyridine.
6. Chemical modifications of the pyridine molecule.
7. Medicinal products that contain a scaffold - a pyridine cycle.
8. Medicinal products are pyridine derivatives. Synthesis, features of the chemical structure and biological activity.
9. The main regularities of the interaction of the chemical structure and biological activity of pyridine derivatives.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. The molecule of the active substance of the medicinal product, a pyridine derivative, contains a lipophilic group. What is her name?

A. aromatic ring

B. carbonyl group

C. hydroxy group

D. heterocyclic ring

2. What is the name of the hydrogenated form of the pyridine molecule?

A. pyrrole

B. pyrimidine

C. pyrazole

D. piperidine

3. What reaction is the basis of the synthesis by the Bonnemann cyclization method?

A. oxidation

B. trimerization

C. restoration

D. regrouping

4. Which of these alkaloids belongs to pyridine derivatives?

A. theophylline

B. strychnine

C. ricin

D. nicotine

5. The presence of which pharmacophore group in the drug molecule - a pyridine derivative affects its high antituberculosis activity?

A. aromatic ring

B. hydroxy group

C. the carboxyl group is unsubstituted

D. hydrazino-phenyl group

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the structural formula of the active substance of the drug Pyriditol. Name the functional groups in the Pyriditol molecule.

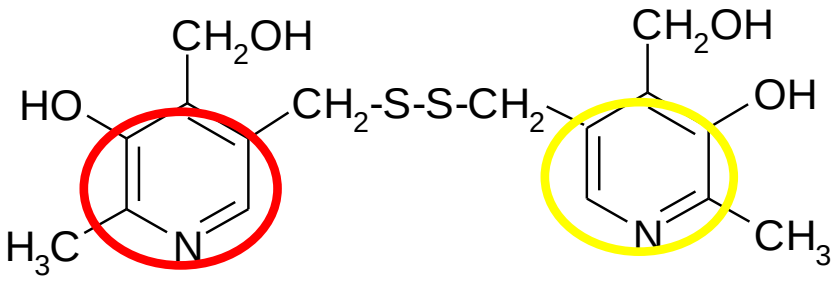


Figure 1.

The answer and its justification

Auditory collective work:

Task 1. Figure 2 shows the synthesis scheme of a pyridine derivative according to the Hantzsch method.

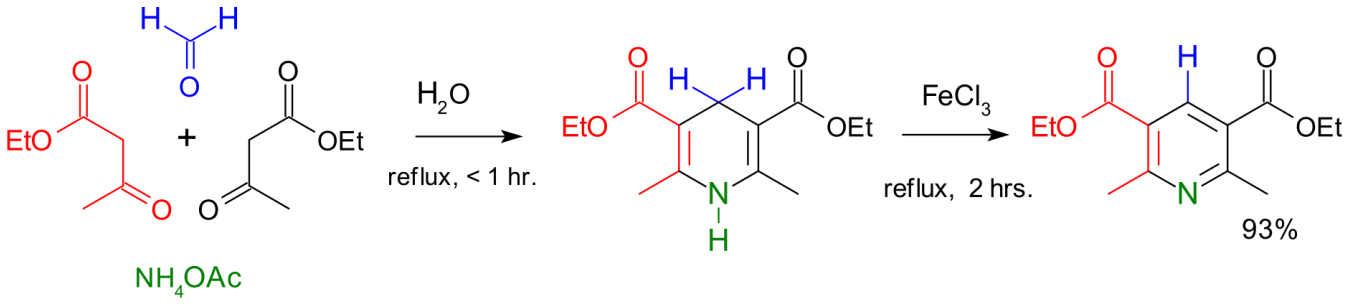


Figure 2.

Describe the chemical reactions of the synthesis of a pyridine derivative at each stage. What reagents are used? Do the reactions use the method of protection of the functional group?

The answer and its justification

Task 2. Figure 3 shows three chemical formulas of pyridine derivatives.

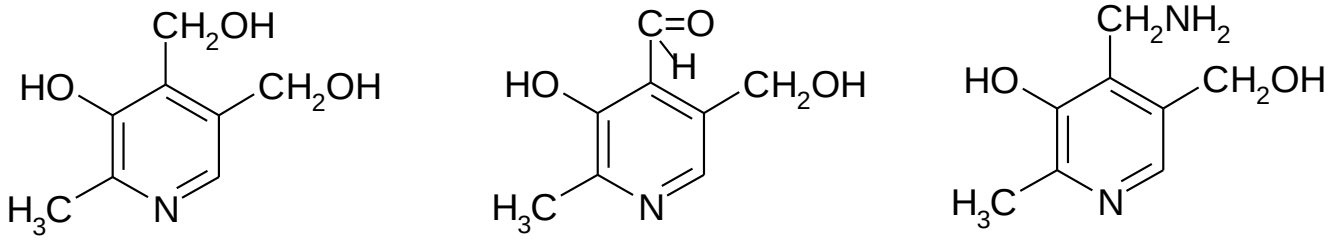


Figure 3.

Name these substances and name their field of application. State the functional groups by which the molecules differ.

The answer and its justification

Auditory independent work (supervised by the teacher):

Task 1. Figure 4 shows the chemical formula of the Mexidol molecule. Specify the substituents and functional groups of the aromatic ring. How do they affect pharmacological activity?

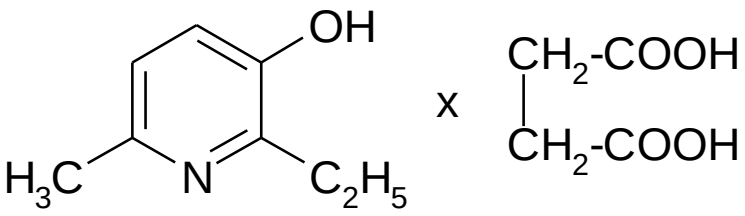


Figure 4. Mexidol.

Using the computer program SwissPredictioTarget (Swiss), conduct an analysis of biotargets, pharmacological or toxicological activity of structural analogues of Anabazin, Nicotine, Ozenoxacin, Isoniazid, Pyridoxine (offer your examples).

An example of a task with an answer standard:

Chemical modifications of the pyridine molecule using nucleophilic substitution reactions.

Answer standard

Pyridine actively participates in nucleophilic substitution reactions. The reason for this is the lower electron density of the carbon atoms of the heterocyclic ring. These reactions include substitution with elimination of the Carbon ion and elimination-addition with the formation of an intermediate aryne configuration and usually proceed in the 2- or 4-position (Fig. 6).

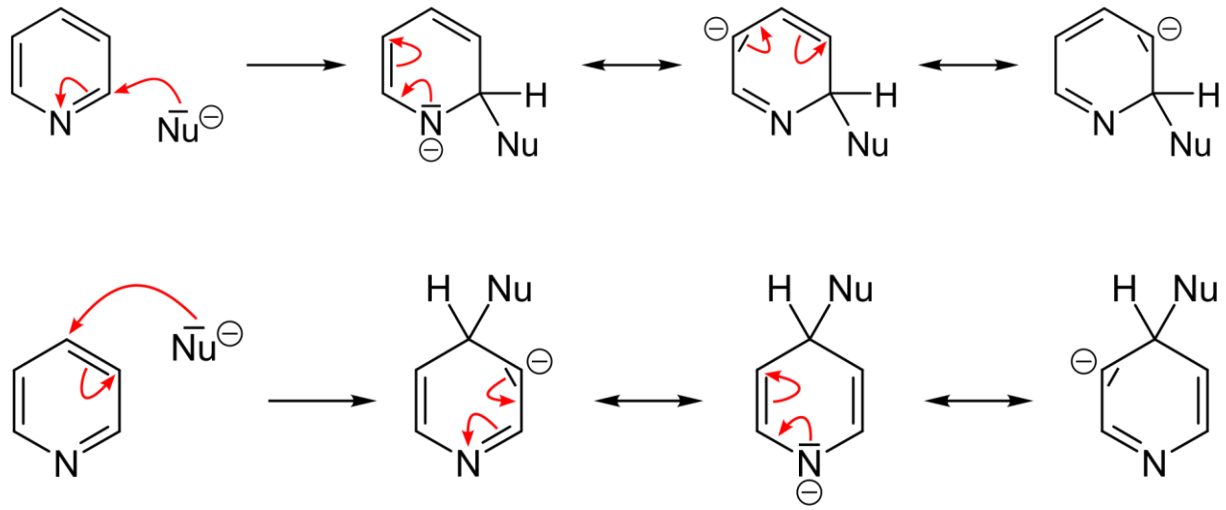


Figure 6. Nucleophylic substitution of pyridine.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 9. Derivatives of pyrimidine (barbiturates) as drugs and biological active compounds, methods of synthesis/modification. Structure-activity relationship. *Control work N2.*

Purpose: ability to plan and implement methods of synthesis or modification of molecules of biologically active pyrimidine derivatives, analysis of the interaction of their features of chemical structure and biological activity, ability to perform computer prediction of chemical and biological properties of BARs and drugs (SwissTargetPrediction, Swiss).

The student must:

 know the basic and modern methods of synthesis of biologically active pyrimidine derivatives;

 be able to detect and propose reactions of modifications of functional groups in molecules of biologically active pyrimidine derivatives;

 evaluate the possibility of variability of molecules based on chemical modification.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*
Pyrimidine	a six-membered heterocycle with two nitrogen heteroatoms and an unsaturated system
Barbituric acid	2,4,6-trihydroxypyrimidine
The lipophilic group of the molecule of the active substance of the pyrimidine derivative	unsaturated heterocyclic ring

Pyrimidine bases	uracil, cytosine, thymine
A scaffold for the synthesis of barbiturates	barbituric acid molecule

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/.*
2. Segovia C, Lebrêne A, Levacher V, Oudeyer S, Brière J-F. Enantioselective Catalytic Transformations of Barbituric Acid Derivatives. *Catalysts*. 2019; 9(2):131. https://doi.org/10.3390/catal9020131
3. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*
4. Oja, M.; Sild, S.; Piir, G.; Maran, U. Data for: Intrinsic aqueous solubility: mechanistically transparent data-driven modeling of drug substances. QsarDB repository, QDB.257. **2022**. http://dx.doi.org/10.15152/QDB.257

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. Features of the chemical structure of barbituric acid molecules and its derivatives.
2. Methods of synthesis of barbituric acid and its derivatives and their chemical modifications. Scaffold.
3. Toxicity of barbituric acid and its derivatives.
4. Metabolism of barbituric acid and its derivatives.
5. Medicinal products containing a pyrimidine cycle scaffold.
6. Medicinal products are derivatives of barbituric acid. Peculiarities of the chemical structure and biological activity.
7. The main regularities of the interaction of the chemical structure and biological activity of barbiturates.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. The molecule of the active substance of the medicinal product, a pyrimidine derivative, contains a lipophilic group. What is her name?

A. aromatic ring

B. carbonyl group

C. hydroxy group

D. heterocyclic ring

2. What heterocycle forms the basis of the barbituric acid molecule?

A. pyrrole

B. pyrimidine

C. pyrazole

D. piperidine

3. What is the chemical nomenclature of the Phenobarbital molecule?

A. 5,5'-diallyl barbituric acid

B. 5,5'-diethyl barbituric acid

C. 5,5'-dimethyl barbituric acid

D. 5-ethyl,5'-phenyl barbituric acid

4. Which of the indicated medicines contains a pyrimidine cycle in the molecule?

A. tegafur

B. paracetamol

C. phenacetin

D. aspirin

5. In which position of the heterocyclic ring is the thio group in the sodium thiopental molecule?

A. position 2

B. position 1

C. position 5

D. position 3

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the structural formula of the active substance of the medicinal product sodium thiopental. Name the functional groups in the sodium thiopental molecule.

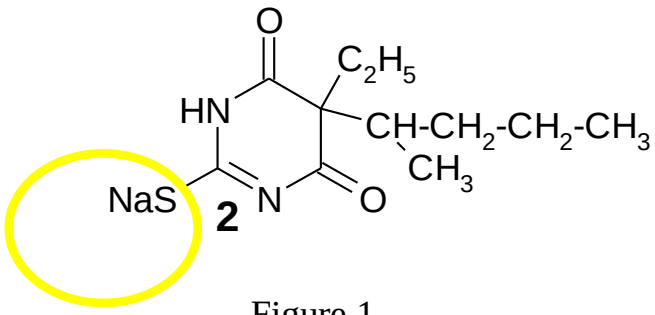


Figure 1.

The answer and its justification

Auditory collective work:

Task 1. Figure 2 shows the synthesis scheme of Phenobarbital.

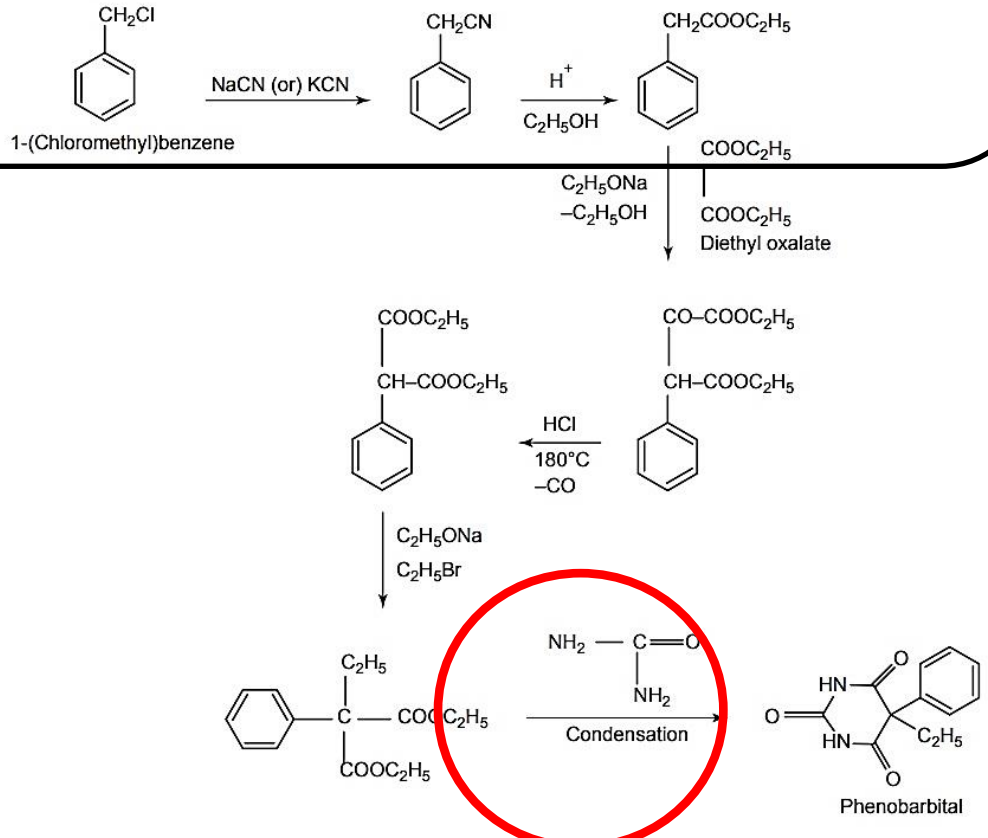


Figure 2.

Describe the chemical reactions of the synthesis of a pyridine derivative at each stage. What reagents are used? Do the reactions use the method of protection of the functional group?

The answer and its justification

Task 2. Figure 3 shows the chemical formula of barbiturate.

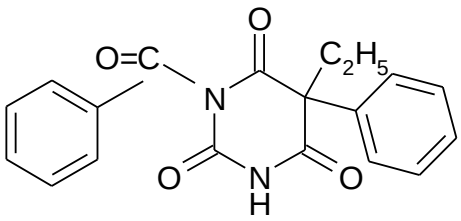


Figure 3.

Name this barbiturate. Specify the functional groups that are present in the molecule.

The answer and its justification

Auditory independent work (supervised by the teacher):

Task 1. Figure 4 shows the scheme of barbiturate synthesis. Indicate at which position (position in the heterocyclic ring) the reaction took place. Specify the substituents and functional groups of the aromatic ring. Give the chemical name of the synthesized barbiturate molecule.

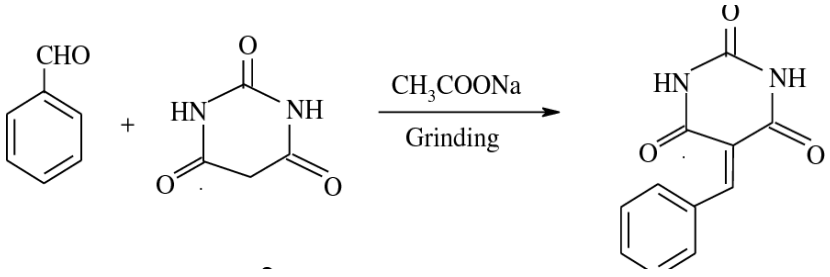


Figure 4. Scheme of barbiturate synthesis.

Using the computer program SwissPredictioTarget (Swiss), conduct an analysis of biotargets, pharmacological activity of structural analogs of Phenobarbital, Barbital, Tegafur, Amobarbital, Cyclobarbital (offer your examples).

An example of a task with an answer standard:
Features of the chemical structure of the barbituric acid molecule and its derivatives:

Answer standard

Features of the chemical structure:
- pyrimidine cycle
- three hydroxy groups (or keto groups in tautomeric forms) in positions **2, 4, 6** of the heterocycle
- heterocyclic nitrogen atoms in positions **1,3**
- the most frequent **chemical modifications** of the molecule - according to position **5** (Fig. 5).

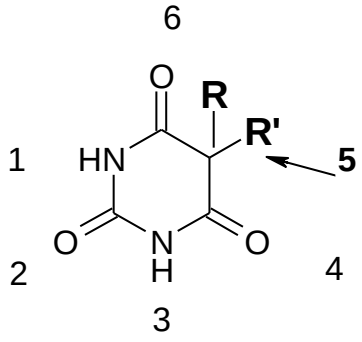


Figure 5. Barbiturate

Control work No. 2 - on questions of topics 5-9.

List of questions for control work No. 2.

1. Methods of synthesis of phenyl(heteryl)ethylamine derivatives.

2. Peculiarities of the chemical structure of molecules of active active substances of local anesthetics.

3. Classifications of local anesthetics.

4. Mechanism of action of local anesthetics.

5. Influence of the chemical structure of molecules on the solubility of local anesthetics.

6. Functional groups in the composition of molecules of active active substances of local anesthetics.

7. Relationship between the structure and activity of the molecules of active active substances of local anesthetics.

8. Features of the chemical structure of molecules of active substances of local anesthetic agents: lipophilic and hydrophilic parts, intermediate chain.

9. Articaine. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.

10. Bupivacaine. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.

11. Lidocaine. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.

12. Aminoesters. Characteristics of the "structure-activity" relationship.

13. Aminoamides. Characteristics of the "structure-activity" relationship.

14. Amino ethers. Characteristics of the "structure-activity" relationship.

15. Aminoketones. Characteristics of the "structure-activity" relationship.

16. Peculiarities of the chemical structure of sulfonamide molecules.

17. Classifications of sulfonamide drugs.

18. Mechanism of action, pharmacokinetics, indications, side effects.

19. Chemical formulas of sulfonamides and features of synthesis/modification of their molecules, bioisosteric substitutions, scaffold.

20. Sulfacetamide, Sulfacil sodium. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.

21. Sulfamethoxazole. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.

22. Phthalazole. Characteristics of the "structure-activity" relationship. Peculiarities of metabolism.

23. The main regularities of the interaction of the chemical structure and biological activity of sulfonamides.

24. Peculiarities of the chemical structure of the pyridine molecule and its derivatives.

25. Methods of synthesis of pyridine and its derivatives.

26. Substances of natural origin - pyridine derivatives. Alkaloids.

27. Toxicity of pyridine.

28. Metabolism of pyridine.

29. Chemical modifications of the pyridine molecule.

30. Medicinal products that contain a scaffold - a pyridine cycle.

31. Medicinal products are pyridine derivatives. Synthesis, features of the chemical structure and biological activity.

32. The main regularities of the interaction of the chemical structure and biological activity of pyridine derivatives.

33. Features of the chemical structure of barbituric acid molecules and its derivatives.

34. Methods of synthesis of barbituric acid and its derivatives and their chemical modifications. Scaffold.

35. Toxicity of barbituric acid and its derivatives.

36. Metabolism of barbituric acid and its derivatives.

37. Medicinal products containing a pyrimidine cycle scaffold.

38. Medicinal products are derivatives of barbituric acid. Peculiarities of the chemical structure and biological activity.

39. The main regularities of the interaction of the chemical structure and biological activity of barbiturates.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.

Topic N 10. Purine derivatives as drugs and biologically active compounds, methods of synthesis/modification. Structure-activity relationship. *Differentiated credit.*

Purpose: ability to plan and implement methods of synthesis or modification of molecules of biologically active purine (xanthine) derivatives, analysis of the interaction of their features of chemical structure and biological activity, ability to perform computer prediction of chemical and biological properties of BAS and drugs (SwissTargetPrediction, Swiss).

The student must:

 to know the basic and modern methods of synthesis of biologically active derivatives of purine (xanthine);

 be able to detect and propose reactions of modifications of functional groups in molecules of biologically active derivatives of purine (xanthine);

 evaluate the possibility of variability of molecules based on chemical modification.

Basic concepts of the topic:

Term, parameter, characteristic	*Definition*

Purine	imidazo[4,5-d]pyrimidine
Xanthine	methylated purine
The lipophilic group of the molecule of the active substance of the purine derivative	unsaturated heterocyclic rings of pyrimidine and imidazole
Purine bases	adenine, guanine
A scaffold for the synthesis of purine derivatives	a purine molecule

Recommended literature:

Basic

1. Jiashun Mao, Javed Akhtar, Xiao Zhang, Liang Sun, Shenghui Guan, Xinyu Li et al. Comprehensive strategies of machine-learning-based quantitative structure-activity relationship models. iScience 24, 103052, 2021, p.1-25. (Review Article). http://creativecommons.org/licenses/by-nc-nd/4.0/

Auxiliary

1. *Organic Syntheses*: *http://www.orgsyn.org/.*
2. Cicero, A.F.G.; Fogacci, F.; Di Micoli, V.; Angeloni, C.; Giovannini, M.; Borghi, C. Purine Metabolism Dysfunctions: Experimental Methods of Detection and Diagnostic Potential. Int. J. Mol. Sci. 2023, 24, 7027. https://doi.org/ 10.3390/ijms24087027
3. Hartmuth C. Kolb, M. G. Finn, K. Barry Sharpless: Click Chemistry: Diverse Chemical Function from a Few Good Reactions. In: Angew. Chem. Int. Ed. 2001, Band 40, S. 2004; *DOI:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.*
4. Oja, M.; Sild, S.; Piir, G.; Maran, U. Data for: Intrinsic aqueous solubility: mechanistically transparent data-driven modeling of drug substances. QsarDB repository, QDB.257. **2022**. http://dx.doi.org/10.15152/QDB.257

Information resources

1. http://nmu.ua/zagalni-vidomosti/kafedri/kafedra-farmatsevtycheskoj-byologycheskoj-y-toksykologycheskoj-hymyy/
2. Distance learning platform LIKAR_NMU https://likar.nmu.kiev.ua/
3. QSAR & Combinatorial Science (QSAR Comb. Sci.)

Questions for theoretical study:

1. Features of the chemical structure of purine (xanthine) molecules and its derivatives.
2. Natural sources of purine and its derivatives.
3. Methods of synthesis of purine (xanthine) and its derivatives. Scaffold.
4. Toxicity of purine (xanthine) and its derivatives.

5. Metabolism of purine (xanthine) and its derivatives.
6. Medicinal products that contain a scaffold - the purine cycle.
7. Medicinal products are derivatives of purine (xanthine). Peculiarities of the chemical structure and biological activity.
8. The main regularities of the interaction of the chemical structure and biological activity of purine (xanthine) derivatives.

Tasks for independent processing of the topic:

Test tasks

Choose and justify the correct answer.

1. The molecule of the active substance of the medicinal product – a purine derivative contains a lipophilic group. What is her name?

A. aromatic ring

B. carbonyl group

C. hydroxy group

D. heterocyclic ring

2. What heterocycle is part of the purine molecule?

A. pyrrole

B. pyrimidine

C. pyrazole

D. piperidine

3. Which xanthine derivative is the active substance of the drug Xanthynol nicotinate?

A. caffeine

B. theobromine

C. theophylline

D. paraxanthine

4. Which of the indicated medicines contains a xanthine cycle in the molecule?

A. diprofilin

B. paracetamol

C. phenacetin

D. aspirin

5. State the chemical name of caffeine?

A. 1,3,7-trimethylxanthine

B. 3,7-dimethylxanthine

C. 1,3-dimethylxanthine

D. 1,3,7,9-tetramethylxanthine

Enter in the cells ☐ the letters that indicate the correct answers to the test questions:

1-☐ 2-☐ 3-☐ 4-☐ 5-☐

Written assignments

Task 1. Figure 1 shows the structural formula of the active substance of the medicinal product Fopurin. Name the functional groups in the Fopurin molecule.

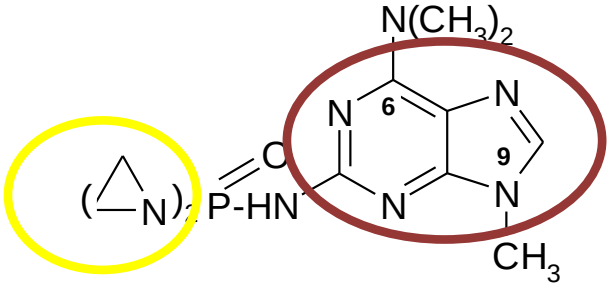


Figure 1.

The answer and its justification

Auditory collective work:

Task 1. Figure 2 shows the scheme of purine synthesis (according to Fisher).

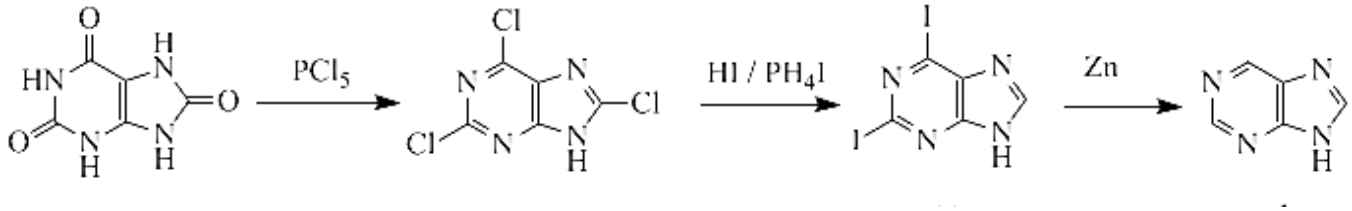


Figure 2.

Describe the chemical reactions of purine synthesis at each stage. What reagents are used? Do the reactions use the method of protection of the functional group?

The answer and its justification

Task 2. Figure 3 shows the scheme of metabolic transformations of caffeine.

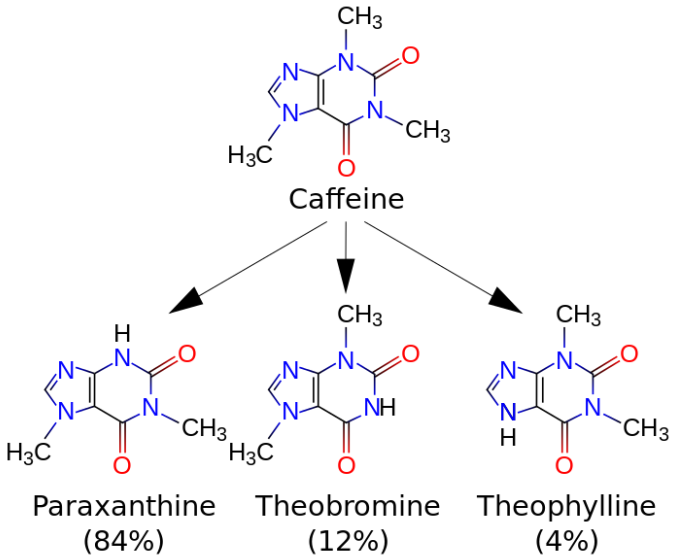


Figure 3.

Name the type of reactions that occur. At what position of the molecule do the changes occur?

The answer and its justification

Auditory independent work (supervised by the teacher):

Task 1. Analyzed the features of chemical structures, explain the dependence of toxicity on the features of the molecular structure of the following substances:

THEOPHYLLINE > DIPROPHYLLINE > CAFFEINE > THEOBROMINE

Toxicity

Using the computer program SwissPredictioTarget (Swiss), conduct an analysis of biotargets, pharmacological activity of structural analogues of Caffeine, Theophylline, Paraxanthine, Euphylline, Diprophylline (offer your examples).

An example of a task with an answer standard:
Features of the chemical structure of the purine molecule:

Answer standard

Features of the chemical structure:

- bigheterocycle
- electron-deficient condensed heterocyclic system (imidazole ring and pyrimidine ring)
- aromatic unsaturated conjugated system
- high stability of "aromaticity" of cycles
- considerable energy of cyclic delocalization
- amphoteric properties
- prototropic tautomerism – 7H and 9H tautomers (Fig. 4).

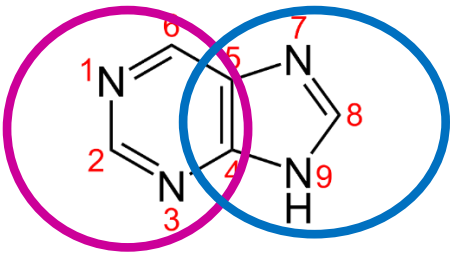


Figure 4. Purine.

The methodical development was made by: professor of the department, doctor of pharm. sc. Welchinska O.V.