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DESIGNING THE STRUCTURE OF NEW ANTIBACTERIAL DRUGS BASED ON CEPHALOTHIN

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Abstract. *The article presents a computer-generated modification of cephalothin sodium salt molecules with penicillin. This modification is a new structure with potential antibacterial activity. A correlation was found between pharmacological activity, pharmacokinetic parameters, and toxicological properties and the structure of the compound. The research uses the computer technologies allowing the pharmacological properties of new compounds to be modelled. The authors have proposed new structural modifications of the original molecules with improved beta-lactamase activity indicators.*

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Introduction

Antibiotics are natural or chemically synthesised substances with antimicrobial activity for the treatment of infectious diseases. Antimicrobial agents can exhibit bactericidal properties (microorganisms' termination) or bacteriostatic properties (stop bacteria reproduction) for the natural defence of the macroorganisms.

Penicillins are antimicrobial drugs of the class of β-lactam antibiotics produced by mould fungi of the genus *Penicillium*. The penicillin class is characterised by a significant bactericidal effect. Its mechanism based on inhibiting the synthesis of peptidoglycan – the main component of the bacterial cell wall. In addition, penicillins have good distribution in the body's biological fluids and exhibit relatively low toxicity to the organs and tissues of microorganisms. Nevertheless, penicillins demonstrate a high degree of bactericidal activity against microorganisms and are classified as broad-spectrum drugs. They can be given parenterally or taken orally.

Cephalosporins are a class of β-lactam antibiotics based on the chemical structure of 7-aminocephalosporanic acid. The mechanism of action of cephalosporins on microbial cells is

similar to that of penicillins: they block the synthesis of bacterial cell membrane proteins. They have a significant bactericidal effect, similar to penicillins, a broad spectrum of antibacterial activity, and relatively low toxic effect. Cephalosporins can be used in combination with other antibacterial drugs.

Purpose of the study. The purpose of the research includes the development of a model for a new active computer modification, representing a combination of cephalothin sodium salt with penicillin. The objectives of the research are as follows: computer screening of a number of similar compounds. assessment of their pharmacological activity, bioavailability parameters, and toxicological profile, identification of the molecule most likely to show *beta*-lactamase inhibition in the experiment.

Materials and methods

Information on penicillin and cephalosporin antimicrobial drugs was searched for and systematised. An analysis of scientific literature on the research topic was conducted. The scientific electronic libraries and databases eLibrary, CyberLeninka, and PubChem were used. The pharmacological parameters of new computer modifications were modelled on the PASS Online and ADMETlab 2.0 platforms. Theoretical spectral characteristics were calculated using the NMR Predict service: nuclear magnetic resonance spectra on hydrogen isotopes ^{1}H and carbon isotopes ^{13}C, spectrometer frequency 400 MHz. The structures of cephalothin and penicillin were used in the development of new compounds.

Results and discussions

To forecast the pharmacodynamic and pharmacokinetic parameters, we used the PASS online [1] and ADMETlab 2.0 [2] programmes, respectively.

The PASS online platform is a service to forecast the mechanisms of pharmacological effects of new chemical compounds based on their structural formula. The simulation results are the names of the probable activities of the compounds. They correlated with the estimates of the probabilities of presence (P_a) and absence (P_i) of each activity, with values ranging from 0 to 1. The higher the P_a value for a particular activity and the lower the P_i value, the greater the chance of detecting this activity in an experiment.

The approach used in PASS to forecast the biological activity of a chemical compound is based on the assumption that its activity is directly related to the organic structure of the compound. The structure is described by individual descriptors – pharmacophore groups of atoms [3].

The probability of pharmacological effects occurring has been assessed in relation to the following types of activity:

1. *Beta*-lactamase inhibition is a process associated with the mechanism of action and resistance of bacteria to beta-lactam antibiotics including penicillins, cephalosporins, and carbapenems. *Beta*-lactamases are enzymes produced by certain bacteria that are capable of destroying the *beta*-lactam ring of antibiotics, rendering them ineffective.

2. Inhibition of muramyl tetrapeptide carboxypeptidase – muramyl tetrapeptide is an important component of the cell wall of bacteria, particularly Gram-positive bacteria. It is a fragment participating in the formation of peptidoglycan, the main structural component of the cell wall. Inhibition of carboxypeptidases are responsible for the destruction or modification of this peptide. They can significantly affect the stability and integrity of the bacterial cell wall.

3. Antibacterial action – this effective antibacterial action destroys pathogenic bacteria and prevents the spread of infection.

ADMETlab 2.0 is a computer tool designed to evaluate the pharmacokinetic parameters/properties of medicinal substances based on their molecular structures. The paper presents the results for the following indicators:

1. The absorption of a drug compound through the human intestinal cell membrane (HIA) is an important property for potential drug candidates. It is one of the key processes determining the bioavailability of a drug when taken orally.

2. Blood-brain barrier permeability is an indicator that allows the ability of a chemical compound to pass through the BBB to be assessed. To determine this, the level of free diffusion is calculated, taking into account a number of characteristics of the substance: its lipophilicity, molar mass, number of hydrogen bonds, etc.

3. Plasma protein binding is a physiological process regulating the distribution and activity of various substances in the blood. It involves the interaction between plasma proteins, such as albumin and alpha-1 acid glycoprotein, and small molecules, such as drugs, hormones, and intermediate metabolic products.

4. CL (clearance) refers to the rate at which a drug is eliminated from the body. This is an important parameter that helps to understand how quickly a drug is eliminated from the blood and, accordingly, how long its effect can last.

5. LogS is an indicator of the solubility of a compound in water.

6. LogP is the common logarithm of the ratio of substance concentrations in two solvents (e.g., water and organic solvents). This parameter is used to assess the hydrophilicity and hydrophobicity of a substance.

7. LogD is an indicator that allows the lipophilicity of a compound to be assessed.

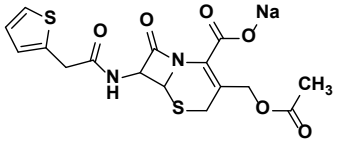
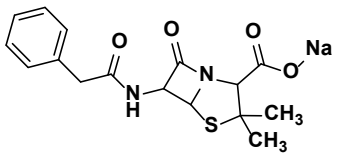
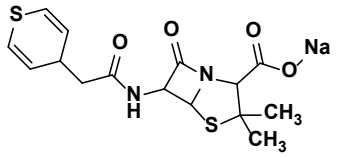
8. hERG blockers is a blockade of the hERG potassium channel is one of the most important targets determining the cardiotoxicity of potential drugs.

9. Human Hepatotoxicity (H-HT) is an indicator describing various types of liver damage that can lead to organ failure or even death.

10. Rat Oral Acute Toxicity is a standard method for assessing the toxicity of new drugs. This indicator allows you to determine the quantity of a substance to cause harm to an animal's body after a single oral dose. The main result of the test is the determination of the median lethal dose (LD_{50}) – the dose of a substance at which 50% of the test animals die. This value helps us to classify the substance according to its level of toxicity.

We will consider the structural formulas and some characteristics of the initial compounds and the new computer modification.

Table 1. Structures and their spectral characteristics

Item n/a	Structure	Name	Theoretical NMR spectra
1.		Cephalothin sodium salt ((6R,7S)-3-(acetyloxymethyl)-8-oxo-7-[(2-thiophen-2-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]octo-2-ene-2-carboxylate sodium)	^{1}H NMR (400 MHz): δ 2.06 (s, 3H), 3.75 (d, 1H, *J* = 13.1 Hz), 3.83-3.98 (3.88 (s, 1H), 3.88 (s, 1H), 3.91 (d, 1H, *J* = 13.1 Hz), 4.56-4.66 (4.61 (s, 1H), 4.64 (s, 1H)), 4.97 (d, 1H, *J* = 7.8 Hz), 5.34 (d, 1H, *J* = 7.8 Hz), 7.17 (dd, 1H, *J* = 7.5, 5.0 Hz), 7.31-7.45 (7.37 (dd, 1H, *J* = 5.0, 1.3 Hz), 7.39 (dd, 1H, *J* = 7.5, 1.3 Hz). ^{13}C NMR: δ 20.8, 24.7, 31.7, 57.3, 59.3, 64.7, 124.8, 126.0, 126.6, 127.1, 134.0, 136.2, 166.9, 167.8, 169.1, 178.5.
2.		Penicillin ((2S,5S,6R)-3,3-dimethyl-7-oxo-6-[(2-phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate sodium)	^{1}H NMR (400 MHz): δ 1.21-1.31 (1.26 (s, 1H), 1.26 (s, 1H)), 3.70-3.80 (3.75 (s, 1H), 3.75 (s, 1H)), 4.34 (s, 1H), 4.92-5.15 (4.98 (d, 1H, *J* = 8.1 Hz), 5.09 (d, 1H, *J* = 8.1 Hz)), 7.22-7.42 (5H, 7.30 (tt, *J* = 7.7, 1.5 Hz), 7.32 (DDTS, *J* = 7.8, 1.5, 1.2, 0.5 Hz), 7.35 (DDTS, *J* = 7.8, 7.7, 1.8, 0.5 Hz)). ^{13}C NMR: δ 26.6, 31.0, 42.5, 58.4, 65.4, 67.4, 69.8, 127.2, 128.7 (2C), 128.9 (2C), 134.8, 167.5, 171.5, 173.9.
3.		Modification ((2S,5R)-3-(2-thiophen-2-ylacetylcarbamoyl)-7,7-dimethyl-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate sodium	^{1}H NMR (400 MHz): δ 1.21-1.31 (1.26 (s, 3H), 1.26 (s, 3H)), 2.54-2.65 (2.60 (d, 1H, *J* = 7.0 Hz), 2.60 (d, 1H, *J* = 7.0 Hz)), 3.61 (DDTS, 1H, *J* = 7.0, 7.0, 1.8, 1.8 Hz), 4.34 (s, 1H), 4.92-5.15 (4.98 (d, 1H, *J* = 8.1 Hz), 5.09 (d, 1H, *J* = 8.1 Hz)), 5.75-5.88 (5.81 (dd, 1H, *J* = 9.7, 1.8 Hz), 5.81 (dd, 1H, *J* = 9.7, 1.8 Hz)), 6.26-6.38 (6.32 (d, 1H, *J* = 9.7 Hz), 6.32 (d, 1H, *J* = 9.7 Hz)). ^{13}C NMR: δ 26.6, 31.0, 40.4, 42.6, 58.4, 65.4, 67.4, 69.8, 129.6-129.7 (2C), 137.3-137.5 (2C), 167.5, 169.1, 171.5.

Based on the above criteria, probabilistic indicators of pharmacological activity were calculated for the initial compounds and their computer-generated modifications. A comparative analysis was performed.

Table 2. Comparative analysis of the molecules under study based on data from the PASS Online service according to pharmacological activity criteria

Compound name/activity	Cephalothin sodium salt	Penicillin	Modification
Beta-lactamase inhibitor	0.952	0.873	0.919
Muramoyl-tetrapeptide carboxypeptidase inhibitor	0.905	0.985	0.983
Antibacterial action	0.764	0.721	0.735

Based on the analysis of the probabilities of theoretical pharmacological effects, the new compound combines the properties of the two fragments: the probability of β-lactamase inhibition for the new modification in the experiment is close to that for cefalotin sodium salt and exceeds that for penicillin. The potential for suppressing the activity of muramyl tetrapeptide carboxypeptidase [4], according to the forecast for the new compound, has a level of values close to the initial fragments. The theoretical antibacterial activity of the identified modification also correlates with the initial structures and has a satisfactory value. At the next stage, the bioavailability was assessed.

Table 3. Comparative analysis of the molecules under study based on the ADMET service based on bioavailability criteria

Compound name/indicators	Cephalothin sodium salt	Penicillin	Modification
LogS	–2.396	–2.122	-3.038
LogP	0.453	0.857	2.408
LogD	0.921	0.432	1.997
HIA	0.919	0.147	0.05
PPB, %	55.30	54.89	38.60
BBB Penetration	0.002	0.113	0.058
CL	3.0	5.903	6.54

According to the ADMET platform, the new compound is more bioavailable: it is better distributed in the body, based on logarithmic solubility values, and has good absorption rates based on gastrointestinal absorption criteria. It has satisfactory plasma protein binding – an early indicator of high bioavailability. The rate of penetration through the blood-brain barrier exceeds that of cephalothin sodium salt. It provides grounds for hypothesising on the possibility of using the new modification as an antibacterial drug for the treatment of infectious lesions of nervous system tissue [5].

Table 4. Comparative analysis of the molecules under study based on the ADMET service according to toxicity criteria

Compound name/indicators	Cephalothin sodium salt	Penicillin	Modification
hERG Blockers	0.004	0.007	0.001
H-HT	0.181	0.311	0.017
Rat oral Acute Toxicity	0.124	0.092	0.056

According to the analysis of theoretical toxicological characteristics, the new compound has the lowest cardiotoxicity, hepatotoxicity, and toxicity in animal tests compared to the starting substances. These results increase the chances of the new modification being considered a safe potential drug substance.

Based on the screening results, one compound (cephalothin sodium salt + penicillin) was selected because it has the highest probability of pharmacological effect in the experiment. It is theoretically non-toxic, and its bioavailability indicators are within the optimal range.

Conclusions

According to the results of a study aimed at identifying an active combination of penicillin with cephalothin sodium salt, a computer modification was obtained. This modification is capable of exhibiting a pronounced antibacterial effect [6] and possesses *beta*-lactamase inhibitory properties. When compared with the original substances, it was found that the structure has better absorption and excretion from the body and lower toxicity compared to the compounds under consideration.

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Conflict of interest

The authors declare no conflict of interest in financial or other spheres.

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