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NEW METHOD FOR THE PREDICTION OF ANTIBACTERIAL PROPERTIES OF SEMISYNTHETIC PENICILLINS.

2.* EVALUATION OF ACTIVITY LEVELS

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In the case of various types of semisynthetic penicillins it is demonstrated that it is possible to use statistical indexes that characterize the probability of the development of structural elements in fixed positions of the side chain to predict the antibacterial properties of semisynthetic penicillins.

Predictive information regarding the optimal location of functional groups, heteroatoms, and cyclic systems in the side chain of the antibiotic was found as a result of an analysis of the structural-biological principles in a series of semisynthetic penicillins by means of the TOPLOG program system. This information can be used to obtain new compounds with improved antibacterial properties [1]. However, its practical application in synthetic planning is complicated by the lack of a method that makes it possible to pass from a fragmentary to an integral structural-statistical evaluation that quantitatively characterizes the activity levels of new compounds.

The fact is that the inclusion in the side chain of penicillin of groupings that intensify its antibacterial action is often inseparably associated with the development of accompanying structural elements with moderate or unfavorable predictive evaluations.

To solve these problems we proposed a computational predictive index (P_{am}) that takes into account the cumulative effect of all of the descriptor centers that form the side chain of the antibiotic. The P_{am} index is calculated as the arithmetic mean of the probabilities P_i of the structural characteristics that enter into the structural formulas of the side chains of compounds that one plans to synthesize:

$$P_{am} = \left(\sum_{i=1}^{N} P_i\right)/N,$$

where N is the number of characteristics. The following reasoning constitutes the basis for this calculation.

When the compounds are divided into activity classes in the TOPLOG system, either 1, which designates the presence of activity (exceeding of a predesignated threshold of minimal suppressing concentration (MSC) with respect to at least one of the activity tests) or 0, which designates the lact of activity (below the predesignated threshold of MSC with respect to all activity tests) is actually assigned to each compound as an activity characteristic;

*See [1] for Communication 1.

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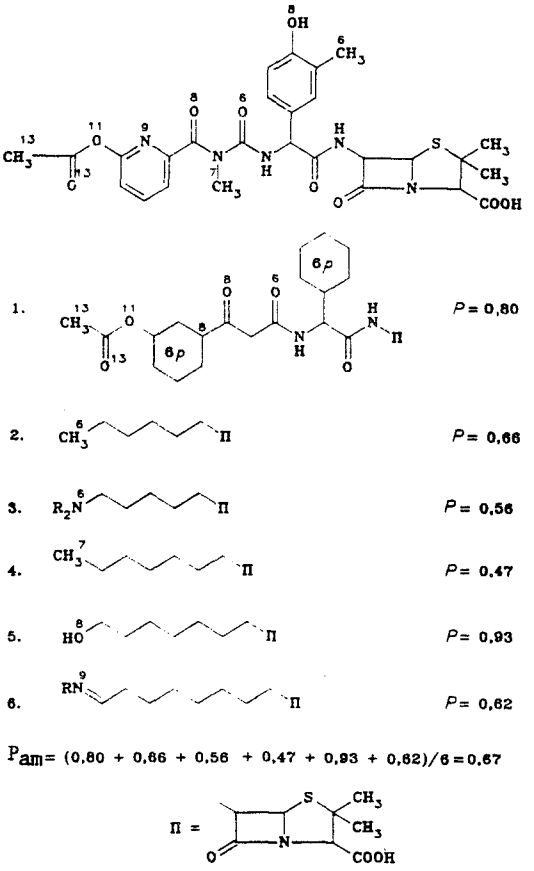
the probabilities of the characteristics P_i can be interpreted as the average contributions of the characteristics to the arbitrary antibacterial activity of the compound evaluated with respect to a two-point scale. The average contribution of a characteristic to the activity of the compound in this case is the arithmetic mean of the values (1 and 0) that characterize the activities of the compounds that contain the characteristic being evaluated. Then P_{am} is the quantitative evaluation of the activity level of the compound with respect to the arithmetic mean of the average contributions of the characteristics to the activity [2].

An example of the calculation of P_{am} for a hypothetical penicillin is presented below. The P_{am} values obtained in this way make it possible beforehand to quantitatively evaluate and compare with one with another the expected activities of antibiotics with any structure and to monitor the correctness of the prediction by means of experimentally determined MSC values with respect to test bacteria.



P_{am} = (0,80 + 0,66 + 0,56 + 0,47 + 0,93 + 0,62)/6 = 0,67

The numbers by the atoms designate the number of bonds before the penicillin ring (π).

Verification of this method in the case of semisynthetic penicillins synthesized for the first time (and not included in data base being analyzed) was carried out by comparison of the computational predictive evaluation P_{am} with the experimentally determined MSC values for compounds with different variants of the side chain (Table 1).

The data in Table 1 provide evidence for satisfactory agreement between the increase in the numerical values of P_{am} and the decrease in the MSC indexes: the coefficient of rank correlation between P_{am} and MSC determined by the method in [3] for the test microorganism *S. aur.* 209P $\tau = 0.92$, as compared with $\tau = 0.69$ for *E. coli*; both coefficients are substantial at a significance level of 0.05.

However, the calculation of P_{am} taking into account the statistical characteristics of all of the structural elements that enter into the side chain of the antibiotic is possible, as demonstrated by experiments, only for a small number of compounds. In the overwhelming majority of cases the lack of information on the promising character of the location of individual atoms or groupings in specific parts of the side change due to the introduction of original structures into the antibiotic molecule limits the use of this method to the comparison of compounds of the same type, for which the deficit of predictive information is

TABLE 1. Predictive Evaluation of the Antibacterial Properties of Some Semisynthetic Penicillins

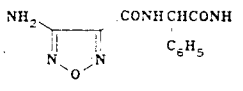
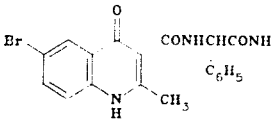
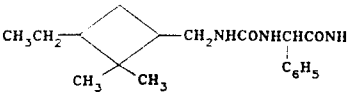
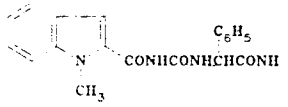
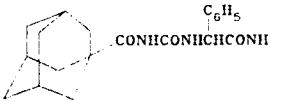
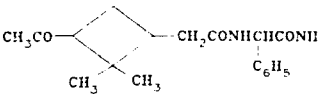
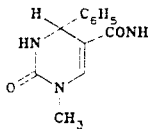
Structure of the side chain	Pam	MSC, μg/ml	
		Staphylococcus aureus 209P	*Escherichia coli* 675
	0,70	0,095	50
	0,69	0,19	100
	0,69	0,39	25
	0,68	0,39	100
	0,64	0,78	200
	0,63	0,78	100
	0,60	12,5	>200

TABLE 2. Predictive Evaluation of the Antibacterial Activities of Silicon-Containing Penicillins*

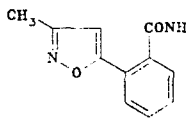
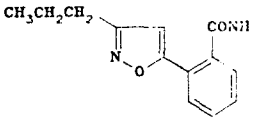
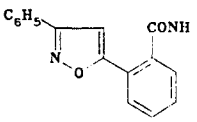
Structure of the side chain	MSC, μg/ml *S. aur.* 209P	Pam
$CH_3Si(C_6H_5)_2(CH_2)_3CONH$	0,39	0,43
$4\text{-}FC_6H_4Si(CH_3)_2(CH_2)_3CONH$	0,09	0,47
$C_6H_5Si(CH_3)_2(CH_2)_3CONH$	0,09	0,47
$(CH_3)_3Si(CH_2)_3CONH$	0,022	0,51
$4\text{-}CH_3C_6H_4Si(CH_3)_2(CH_2)_3CONH$	0,022	0,53

*Coefficient of rank correlation $\tau = 0.94$.

mutually compensated. Examples that demonstrate the good coincidence between the predicted and real levels of antibacterial activity for two types of semisynthetic penicillins are presented in Tables 2 and 3.

For one group of antibiotics the lack of statistical data on the location of the silicon atom is compensated by separation from the penicillin ring by six chemical bonds, while for the other the lack of statistical data on the location of the five-membered heteroring and the

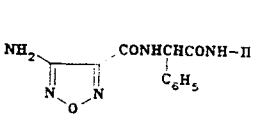
TABLE 3. Predictive Evaluation of the Antibacterial Activities of Penicillins that Contain an Isoazole System in the Side Chain*

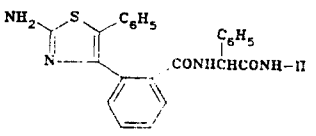
Structure of the side chain	MSC, μg/ml		P_{am}
	S. aur. 209P	*S. aur.* 186†	
	0,19	1,56	0,59
	0,19	0,19	0,69
	0,09	0,19	0,80

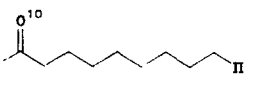
*Coefficient of rank correlation $\tau = 0.82$.
†Strain that produces β-lactamase.

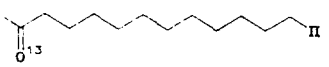
the oxygen atom is mutually compensated by this fact.

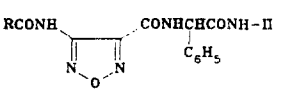
In individual cases even the partial use of the available statistical data makes it possible to substantiate the character of the change in the antibacterial properties of some types of semisynthetic penicillins. The the acylation of the aminofurazan system led to the

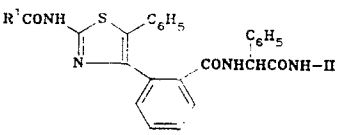

I (P_{am}=0,70)


III (P_{am} =0,63)


(P=0,38) (1)


(P=0,71) (2)


II (P_{am}<0,70)


IV (P_{am}>0,63)

R=NH_2CO, $BrCH_2CO$, 2-quinolylcarbonyl, 2-furylcarbonyl $R^1=C_6H_5C{\equiv}CCO$, 2-quinolylcarbonyl, 2-hydroxy-4-quinolylcarbonyl

development in the side chain of the corresponding antibiotics II of a carbonyl oxygen atom at a distance of 10 bonds from the penicillin ring, which, according to structural characteristic (1), is characterized by a low probability of development in active compounds. The corresponding decrease in the P_{am} for antibiotics II as compared with I explains the deterioration in their antimicrobial properties.

The opposite effect that is observed in the series of penicillins III and IV is due to the inclusion in the N-acyl fragment of the compounds of a carbonyl oxygen atom at a distance of 13 bonds from the penicillin ring [structural characteristic (2)]. This is confirmed by the increase in the P_{am} for compounds of the IV type as compared with antibiotic III.

Thus the computational method makes it possible to regard the modification process as the migration or introduction into the penicillin molecule of structural elements that is intended to achieve the maximum P_{am} values.

A comparison of the calculated predictive indexes and the experimentally obtained minimal suppressing concentrations (MSC) in the case of various types of semisynthetic penicillins also revealed deviations due to the deficit in the amount of predictive information and the

error in the statistical evaluation of the characteristics and the specific description of the molecular structures in matrix form [4].

However, on the whole, the results obtained provide evidence for the usefulness of the new method: first, for a comparative evaluation of the level of antimicrobial activity of diverse structural variants of semisynthetic penicillins; second, for a preliminary evaluation of the prospects of inclusion in the side chain of antibiotics of new structural systems that makes it possible in advance to exclude genuinely known unpromising modifications from the plan of the experimental research.

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POLYFUNCTIONAL MACROHETEROCYCLES.

3.* SYNTHESIS OF NITROGEN- AND SULFUR-CONTAINING CROWN-COMPOUNDS WITH EXOCYCLIC METHOXYCARBONYL- AND PHENETHYL GROUPS

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Reaction of 1-methoxycarbonylethyl- and 1-phenethylaziridines with hydrogen sulfide leads to the corresponding diaminosulfides which with formaldehyde form the derivatives 1,9-dithia-4,6,12,14-tetraazacyclohexadecanes. 7,9,18,20-Tetrakis(2-phenethyl)-1,4,12,15-tetrathia-7,9,18,20-tetraazacyclodocosane, which forms a stable crystalline complex with chloroform, is produced upon reaction of 1,8-bis(2-phenethylamino)-3,6-dithiaoctane with formaldehyde.

Nitrogen- and sulfur-containing macroheterocyclic compounds are used as complexing agents for transition metal ions [2, p. 158; 3, p. 86; 4]. They are effective extractants for silver(I), copper(II), mercury(II), platinum(II), palladium(II), and gold(III) [5]. The extractive properties of the crown-compounds are enhanced upon introduction of exocyclic functional groups into the macrocycle molecule.

The method developed earlier by us for synthesis of macroheterocycles with methoxycarbonyl-, cyan-, and phenethyl groups on the nitrogen atoms of the macrocycle is based on the reaction of functionally 1-substituted aziridine with α,ω-dithiols and subsequently cyclocondensation of the heterochains which form with diamines [6, 7]. In order to develop further the method and to prepare new types of macroheterocycles which contain exocyclic functional groups, and to study their complexation properties, we studied the reaction of N-substituted diaminosulfides with formaldehyde.

1,5-Bis(2-methoxycarbonylethylamino)-3-thiapentane (I) and 1,5-bis(phenethylamino)-3-thiapentane (II) were prepared by a known synthetic scheme for diaminosulfides [8] by reaction of 1-(2-methoxycarbonylethyl)- and 1-phenethylaziridines with hydrogen sulfide in methanol at 20°C with ∿80% yield.

*For Communication 2, see [1].

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