PREDICTION OF THE ACTIVITY OF β-LACTAM ANTIBIOTICS

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The pharmacological properties of penam, 3-cepheme, and semisynthetic penicillins were predicted by means of the ORAKUL automated system. A comparative evaluation of the similarity between the structures of these compounds and the structures of 8800 biologically active substances in the data base of the system made it possible to uncover the high probability of the manifestation of anti-inflammatory, analgesic, antitumorigenic, antiallergic, and anticoagulant activity by structural analogs of β-lactam antibiotics.

It is known that the antibacterial screening of synthetic analogs of β-lactam antibiotics leads to the elimination of more than 90% of the compounds as having little effectiveness or as not exhibiting this type of activity at all. However, until recently, the study of other types of specific activity that makes it possible to use with great efficiency the pharmacological potential inherent in these heterocyclic compounds (most of which are, by nature, acylated di- and tripeptides), which have low toxicities and bind well with the proteins of blood serum, was completely ignored for them.

It should be noted that in the process of a detailed study of the biological properties of medicinal antibiotics based on penicillin and cephalosporin the existence of other types of specific activity in addition to antibacterial activity was observed for some of them. However, serious importance was not attached to this, inasmuch as the chief goal of the researchers was to determine only such side properties as allergenic character, mutagenic character, carcinogenic character, etc.

The attitude toward this problem changed only in the 1980's, when the first research whose goal was to study the possibility of the creation of new β-lactamides or to use known β-lactamides for the treatment or prevention of pathological processes that are not related to infectious diseases was published. For example, an investigation of the ability of some semisynthetic cephalosporins to sensitize animals and humans to the action of alcohol in the same way as Captax was reported [1].

A preliminary evaluation of the activity peculiar to the β-lactam-containing rings of the antibiotic and of the substituents and their subsequent structural transformation in order to make necessary adjustments to the interrelationship between the structure and activity should promote the purposeful solution of this problem.

The experimental verification of this hypothesis for semisynthetic penicillins and cephalosporins containing various aliphatic, aromatic, and heterocyclic fragments in the N-acyl fragment was carried out by means of the ORAKUL automated system [2]. In the process of computer analysis each analyzed compound, in order to ascertain common structural elements, was compared with 8800 medicinal preparations or highly active compounds introduced into the data base of the system and representing 58 types of pharmacological agents. In the case of detection of these elements the substances should potentially exhibit the activity that preparations from the data base that contain similar molecular fragments have. The statistical evaluation of the degree of structural similarity and, consequently, the expected activity in the ORAKUL system is expressed in the form of confidence coefficient C_C.

The data in Table 1 demonstrate the very high probability of the manifestation of antibacterial properties by penam, cepheme, and β-lactam, since in the data base they are found virtually only in preparations from the group of β-lactam antibiotics. As regards thiazolidine and Δ3-dihydrothiazine, their presence as a component of anthelminthic, hypotensive, and tranquilizing preparations creates the prerequisites for predicting the corresponding activity for derivatives of the examined antibiotics.

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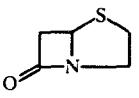
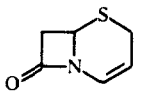
TABLE 2. Prediction of the Activity for Structural Analogs of Penicillin and Desacetoxycephalosporin III-X

Structure analyzed	C_c for the potential activities																
	alpha-adrenergic	analgesic (narcotic)	Anesthetizing (local)	antibacterial	antivirus	anti-inflammatory (non-steroidal)	anthelminthic	antitumorigenic	anticonvulsant	sedative	tranquilizing	cholinolytic	choleretic	coronary dilating	antiallergic	vasodilating	analgesic (non-narcotic)
III	0,07	0,14	0,08	0,94	—	0,13	0,07	—	—	—	0,06	0,07	—	—	—	—	—
IV	0,07	0,14	0,12	0,94	—	0,13	0,07	0,21	—	—	0,06	0,07	—	—	—	—	—
V	0,07	0,14	0,14	0,94	0,08	0,15	0,07	—	0,09	0,24	0,06	0,07	0,06	—	—	—	—
VI	0,07	0,14	0,14	0,94	0,08	0,15	0,07	0,21	0,09	0,24	0,06	0,07	0,06	—	—	—	—
VII	—	0,14	0,08	0,98	—	0,14	—	—	—	0,15	0,19	0,07	—	—	—	—	0,19
VIII	—	0,14	0,12	0,89	—	0,14	—	0,21	—	0,15	0,19	0,07	—	—	—	—	0,19
IX	—	0,14	0,12	0,89	—	0,33	—	—	0,08	0,24	0,19	0,07	0,08	0,09	0,11	0,12	0,26
X	—	0,14	0,12	0,89	—	0,33	—	0,21	0,08	0,24	0,19	0,07	0,08	0,09	0,11	0,12	0,26

TABLE 1. Prediction of the Biological Activity of Penam (I) and Cepheme (II)



I



II

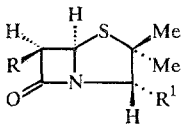
Structure analyzed	C_c for the potential activities			
	antibacterial	anthelminthic	hypotensive (sedative)	tranquilizing
Penam (I)	0,94	—	—	—
Δ3-Cepheme (II)	0,85	—	—	—
β-Lactam	0,89	—	—	—
Thiazolidine	0,53	0,07	—	—
Δ3-Dihydro-thiazine	0,63	—	0,15	0,19

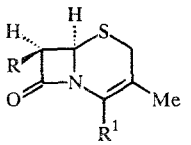
TABLE 3. Prediction of the Biological Activity for Ampicillin

Activity	Confidence coefficient C_c
Alpha-adrenoblocking	0,07
Alpha-adrenomimetic	0,10
Analgesic	0,14
Anesthetic (local action)	0,14
Antibacterial	0,94
Antivirus	0,08
Anti-inflammatory (nonsteroidal)	0,15
Anthelminthic	0,07
Antineoblastic	0,21
Anticonvulsant	0,20
Sedative	0,24
Vasoconstricting	0,07
Spasmolytic	0,20
Tranquilizing	0,06
Cholinolytic-M	0,22
Cholinolytic-N	0,10
Choleretic	0,06

The development of new types of activity as the analyzed fragments become simpler and their size decreases is in complete conformity with principle, since the probability of finding them in various types of medicinal substances increases in this case. In particular, linear fragments of the $R_2N—C—C—C=O$, $R_2N—C—C—SR$, $R_2N—CO$, and $R_2N—CR=CR_2$ type, which are components of penam (I) and Δ3-cepheme (II), in contrast to the latter, are found in substances that have anesthetizing, anti-inflammatory, tranquilizing, and alpha-adrenergic properties.

The inclusion of substituents (amino, carboxy, and methyl groups) in the corresponding positions of the heterocycles expands the set of potential types of activity for III-X, which are presented in Table 2, to an even greater extent.





III—VI VII—X

III R=R^1=H; IV R=NH_2, R^1=H; V R=H, R^1=COOH; VI R=NH_2, R^1=COOH; VII R=R^1=H; VIII R=NH_2, R^1=H; IX R=H, R^1=COOH; X R=NH_2, R^1=COOH

The structural diversity of the side chain of the antibiotics, which is located in the 6 and 7 positions, respectively, of the penam and cepheme rings of penicillin and desacetoxycephalosporin, substantially expands the set of predictable activities. This is confirmed by the results of analysis of the potential types of activity for the semisynthetic penicillin antibiotic ampicillin (XI) (Table 3).

TABLE 4. Structures of the N-Acyl Fragments of Penicillins Subjected to Prognostic Analysis

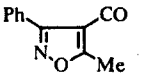
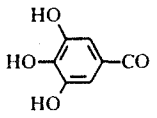
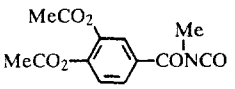
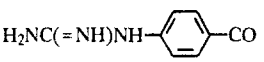
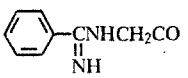
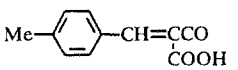
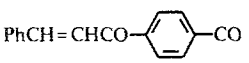
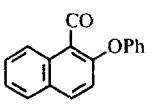
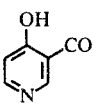
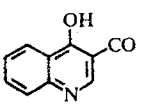
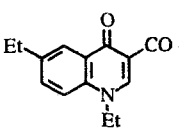
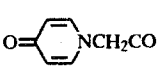
№	Side-chain fragment	Literature, preparation
1	2	3
1	$PhCH_2CO$	Benzylpenicillin
2		Oxacillin
3	$MeNHCONHCO$	[3]
4	$H_2NC(=NH)NHCH_2CO$	[4]
5	$H_2NC(=NH)SCH_2CO$	[5]
6		[6]
7		[6]
8		[4]
9		[7]
10		[8]
11		[10]
12		Nafcillin
13		[11]
14		[12]
15		[11]
16		[13]

TABLE 4. (Continued)

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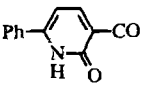
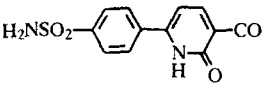
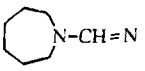
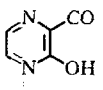
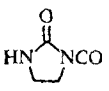
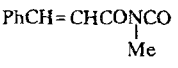
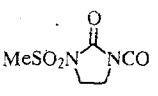
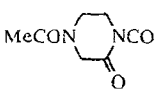
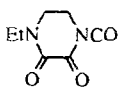
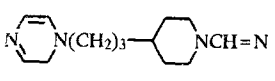
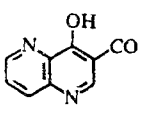
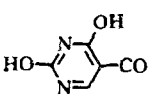
17		[14]
18		[15]
19		[16]
20		Mecillinam
21		[17]
22		Azlocillin
23		[9]
24		Mezlocillin
25		[18]
26		Piperacillin
27		[19]
28		Apalcillin
29		[20]

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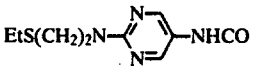
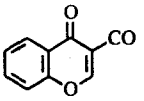
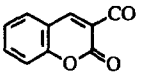
30		[21]
31		[22]
32		[23]
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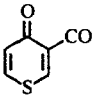
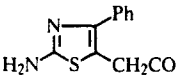
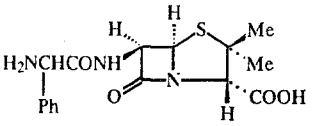
34		Thimoxycillin
35		[24]



XI

Unexpected results were obtained in an analysis of the predicted activity for 36 known semisynthetic penicillins that are characterized by pronounced antibacterial properties, some of which are antibacterial preparations (Tables 4 and 5). Taking into account the specific features of the ORAKUL system, to obtain nontrivial information from the molecules of the analyzed compounds the recurring fragments of 6-aminopenicillanic acid (VI) and 6-(2-amino-2-phenylacetamido)penicillanic acid (ampicillin) (XI), the prediction of the activity of which is presented in Tables 2 and 3, were removed, because when β-lactams VI and XI are present in the molecule, the ORAKUL system, which is orientated to recognizing highly informative features, "ignores" the less pronounced potential activities that characterize the side chain of the antibiotic.

The results of the prognostic analysis of the N-acyl fragments of penicillin enumerated in Table 4 are presented in Table 5; these results take into account only the types of activity with a confidence coefficient C_C of no less than 0.10 and were found for no less than 7 of the 35 analyzed structures (20%).

The diversity of the aliphatic, aromatic, and heterocyclic structures presented in Table 4 provide a basis for the assumption for them of a uniform distribution of the prediction over a wide set of activities. The data in Table 5, which presents 14 types of biological activity of the 58 contained in the data base of the ORAKUL system, correspond to a certain extent to this tendency. Another nine types were excluded from the table, since they were characterized by $C_C < 0.1$ or were found for less than 20% of the total number of analyzed antibiotics.

TABLE 5. Prediction of the Activities for the N-Acyl Fragments of Penicillin

Compound No. from Table 4 n	C_c for the expected activity													
	antiseptic	antibacterial	antitumorigenic	analgesic	anti-inflammatory	soporific, sedative	anticonvulsant	spasmolytic, bronchodilating	hypotensive	anticoagulant	monoamine oxidase inhibitor	antiallergic	vasodilating	hypoglycemic, nonhormonal
1	—	—	—	0,11	0,30	—	—	0,20	—	—	—	—	—	—
2	—	0,45	—	0,26	0,35	—	—	—	—	—	—	—	—	—
3	—	—	0,48	—	—	—	—	—	—	—	—	—	—	0,12
4	—	—	0,48	—	—	—	—	—	0,25	—	—	—	—	0,12
5	—	—	0,17	—	—	—	0,24	0,16	—	—	—	—	0,18	—
6	0,12	—	—	0,14	0,15	—	—	0,14	—	0,13	—	—	—	—
7	—	—	0,17	—	—	0,18	0,12	—	0,13	—	—	—	—	—
8	0,10	—	0,17	0,14	0,15	0,11	—	—	0,25	0,13	—	—	—	0,12
9	—	—	0,21	—	0,15	—	—	—	0,25	—	—	—	—	—
10	—	0,42	—	—	0,27	—	—	—	—	—	—	0,11	—	0,24
11	—	—	0,17	0,36	0,31	0,21	0,14	—	—	0,16	—	—	—	—
12	—	—	—	0,14	0,15	—	—	0,20	—	0,16	—	0,15	0,12	—
13	—	—	0,16	0,11	0,30	—	—	—	—	—	—	—	—	—
14	0,10	—	—	0,26	0,33	—	—	—	—	—	—	—	—	—
15	0,10	—	—	0,26	0,35	—	—	—	—	—	—	—	—	—
16	—	0,42	—	0,30	0,22	0,21	—	—	—	0,24	—	0,15	—	—
17	—	0,28	—	0,30	—	—	—	—	—	—	—	—	—	—
18	—	0,42	0,45	—	0,27	—	—	—	0,12	0,24	0,10	0,11	—	—
19	—	0,42	0,45	—	0,27	—	—	—	0,12	0,24	0,10	0,11	—	0,22
20	0,12	—	0,36	0,15	0,27	—	—	—	0,12	—	—	—	—	—
21	—	—	—	—	—	—	—	—	0,28	0,12	0,16	—	—	—
22	0,10	—	0,22	0,26	0,35	—	—	—	—	—	—	—	0,13	—
23	—	—	0,17	—	—	—	0,24	—	—	—	—	—	—	—
24	0,10	—	0,17	—	—	—	0,24	0,16	—	—	—	0,21	0,18	0,14
25	—	—	0,36	—	—	—	0,12	0,13	—	—	—	—	—	—
26	—	0,37	0,17	0,39	0,48	—	0,12	0,13	—	—	—	—	—	0,21
27	—	—	0,17	—	—	—	—	—	0,28	—	—	—	0,12	—
28	—	—	—	0,26	0,35	—	—	—	—	—	0,10	0,13	0,13	—
29	—	—	0,19	0,26	0,35	—	—	—	—	—	0,10	0,13	0,13	—
30	0,10	0,42	0,45	—	0,27	—	—	—	0,12	0,24	0,10	0,11	—	0,22
31	0,11	0,42	—	—	0,19	0,13	—	0,13	—	0,60	—	0,15	—	—
32	—	0,42	—	—	0,19	0,10	—	0,13	—	0,60	—	0,11	—	—
33	—	0,51	0,28	—	—	0,11	—	—	—	—	—	—	—	0,12
34	—	0,42	—	0,25	0,19	0,24	—	—	—	0,24	—	0,21	—	—
35	—	0,37	—	0,28	0,50	—	0,10	—	0,17	—	0,18	—	—	—
Frequency of manifestation of activity (n/35)·100%	26	37	57	51	68	24	24	28	31	31	24	40	28	28

Despite this, one observes an obvious tendency of the primary prediction of six types of activity, of which only the antibacterial and antiseptic activities have a direct relationship to the character of the biological activity of semisynthetic penicillins.

This result contradicts the stereotypy that has become a part of medicinal chemistry in the selection of structures designated for incorporation in an antibiotic molecule, according to which preference is given to molecular systems borrowed from other known classes of antimicrobial substances.

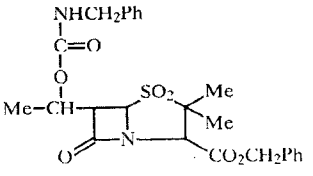
For example, the introduction into the side chain of an antibiotic of fragments that have, according to computer analysis, a similarity to antitumorigenic or anti-inflammatory compounds evidently cannot be regarded as a planned methodological way to purposefully improve the antibacterial properties of penicillin.

The basis for this is evidently the phenomenon of the interrelationship of activities for various types of pharmacological agents due either to the universal effect of certain structures on physiological systems or to the biochemical commonality of various physiological processes.

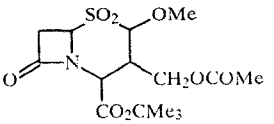
In examining this problem in a broader context it may be assumed that our analysis provides evidence for the potential possibilities of the manifestation by semisynthetic penicillins of a certain set of concomitant activities, of which the most likely are anti-inflammatory, antitumorigenic, analgesic, anticoagulant, and antiallergic activities.

The data obtained are in agreement with the published information regarding the nonspecific biological activity of analogs of β-lactam antibiotics. Thus the side activity of the preparations cephalothin, thicarcillin, and carbenicillin is manifested in a decrease in the amount of prothrombin and a deterioration in blood coagulability [25].

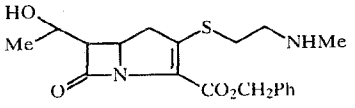
Since 1984, data on the inhibiting properties of derivatives of penicillin XII, cephalosporin XIII, and thienomycin XIV with respect to the enzyme elastase, which is formed in a stage of inflammatory edema, have been presented regularly [26-28].



XII



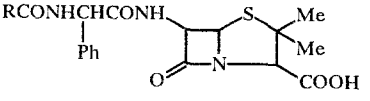
XIII



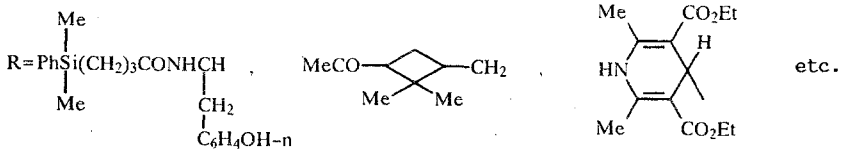
XIV

Similar results were obtained in the Bashkir State Medical Institute in a study of the anti-inflammatory properties of semisynthetic penicillins XV, which we synthesized, with respect to models of thermal and carrageenan edemas.

The specific activity found for these compounds coincides with the biological prediction based on their structural similarity to anti-inflammatory and analgesic preparations and glucocorticoids.



XV



Thus the data presented in this paper provide a serious basis for regarding derivatives of β-lactam antibiotics as a potential source of new medicinal agents with anti-inflammatory, analgesic, anticoagulant, and other types of activity. The methodology of their development should include: a) prediction of the activity for the structural analog of the antibiotic; b) where necessary, carrying out an additional modification that ensures suppression of the antibacterial properties of the desired compound (for example, esterification of the carboxy group in the penicillin or cephalosporin).

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