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PENICILLIN 70

E. Lukevics[1] and G. Veinberg[2]

It is 70 years since Nobel prize laureate Sir Alexander Fleming discovered penicillin. Consequently the antibiotic therapy concept based on the medical use of specific toxic metabolites produced by microorganisms in competition with one another in their natural environment has emerged. This event marked the beginning of the antibiotics era which had a revolutionary influence on the cure of infection and cancer. It is well known that penicillin appeared in pharmacy only 15 years after its discovery due to the investigations carried out by USA pharmaceutical companies within the frame of a united giant project. As a result a unique and efficient technology was created based on the employment of such novel approaches as depth fermentation, lyophilization, directed structural biotransformation of antibiotic side chain, etc. which has made this medicine available for wide use.

The deciphering of the penicillin structure by X-ray crystallographic analysis permitted explanation of the mechanism of its antibacterial action and the mechanism of its inactivation by resistant microorganisms as well. In the first case transpeptidase is irreversibly inhibited by the formation of a covalent ester bond between penicillin β-lactam carbonyl and the serine hydroxyl group in the active site of enzyme. In the second case the resistant species produce a special enzyme β-lactamase which catalyzes the hydrolytic splitting of the antibiotic β-lactam ring. Comprehension of these processes permitted realization in the 1950—1960s of an efficient strategy for the preparation of penicillin structural analogs with a modified side chain structure, the so-called semisynthetic penicillins lacking the substrate specificity towards β-lactamase and being capable, due to this property, to inhibit effectively the resistant pathogenic bacteria. The target changes in the side chain structure allowed the preparation of numerous penicillin analogs with improved pharmacological properties involving a broad spectrum of antibacterial action, stability towards gastric juice and therefore peroral stability, good permeability in the blood flow, etc.

This strategy appeared to be extremely fruitful in the case of a related antibiotic — cephalosporin C. During the 1960—1980s as a result of the modification of various fragments of its molecule there were developed about 40 highly effective derivatives promising for clinical use. Within the frame of these investigations there was discovered an original rearrangement of penicillin sulfoxide into deacetoxycephalosporin which made possible use of benzylpenicillin as a raw material for the preparation of cephalosporin drugs.

In the 1980s the β-lactam antibiotics family was supplemented with carbapenem, penem, clavulanic acid, monobactam, β-lactam, and their various structural analogs both of natural and synthetic origin.

The biological properties of β-lactam antibiotics are not limited only by their antibacterial activity. During the last decade among their analogs there were found specific inhibitors of elastase stipulating their antiinflammatory activity. There was also intensely developed the chemistry of substituted azetidinone-2 intermediates for the purpose of their insertion into the molecules of biologically active compounds in the form of chiral β-amino acid blocks.

The aforesaid is evidence of the inexhaustible pharmacological potency of the simple, if compared with the majority of other antibiotics, penicillin molecule and related β-lactams and also for the intensive search for novel methodological approaches of their transformation into new highly effective drugs.

And though the improvement of biological properties by means of structural transformation is universal for all types of antibiotics, only in the case of β-lactam containing substances does this approach appear to be the most fruitful. This phenomenon could be obviously explained by the incomparable large intellectual potential expended on the study of these compounds. The synthetic part of these investigations directly concerns the subjects of our Journal. In this connection we consider it to be expedient to dedicate a special issue of the Journal to this important event and to include in it the papers reflecting some aspects of the chemistry of heterocyclic antibiotics.

[1]Chemistry of Heterocyclic Compounds, Editor in Chief. [2]Head of the Group of Antibiotics, Latvian Institute of Organic Synthesis. Translated from Khimiya Geterosiklicheskikh Soedinenii, No. 11, pp. 1443-1444, November, 1998.

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