DESCRIPTION FOR THE GENERAL PUBLIC

The discovery of penicillin by Alexander Fleming and its introduction to the clinical use by Howard Florey and Ernst Chain has been one of the most spectacular and important achievements of 20th century science. It has been a milestone of the modern medicine which has improved the health and life expectancy of mankind since the middle of the 20th century. At the beginning of the fifties in British and US hospitals, a bacteria started resistance to the drug has observed.

Parallel to biological investigations, chemical degradation of the molecule and total synthesis of penicillin and later cephalosporin was being carried out. It was noticed that the exchange of the acyl substituent of penicillin's amino group with another one provided a new semisynthetic antibiotic, sometimes more active and more resistant to β-lactamase enzymes than the parent drug. During the seventies of the last century a number of new antibiotics, including β-lactams, were discovered, some of them having significant activity. It was noticed that the tendency of bacteria to develop antibiotic resistance has a permanent character. This caused a cycle: introduction of a new drug, effective therapy, development of drug resistance, new investigation and subsequently introduction of a new drug. Parallel to the investigations on chemical modifications of known drugs, new methodologies of β-lactam ring formation and new strategies of total synthesis of antibiotics have been elaborated. These works have been undertaken not only due to bacterial resistance, but since many new naturally occuring medicinally active compounds had been obtained by a fermentation process in minute amounts only. It should be stressed also that completely new structures of antibiotics have been designed, synthesized, and introduced to the clinical use, e.g. "penems".

During the nineties, a range of new activities of compounds containing a four-membered β-lactam ring have been discovered, among others "Ezetimibe", a potent inhibitor of cholesterol absorption.

Since thirty years, our group has focused attention on the methodology and strategy of the synthesis of β-lactam compounds. Oxygen analogs of penicillin and cephalosporin have been the targets of our syntheses. Parallel to β-lactams we have been interested in the synthesis of iminosugars, inhibitors of glycosidases. The crucial step in our syntheses of iminosugars involved the 1,3-dipolar cycloaddition of nitrones and α,β-unsaturated lactones. Directing our attention to Kinugasa reaction has been the natural consequence of both our research programs. The Kinugasa reaction between nitrones and terminal acetylenes in the presence of copper(I) salt leads to the β-lactam ring formation. It is a cascade process, in the first step of an isoxazoline ring is formed, which subsequently undergoes rearrangement to the β-lactam moiety.

Although the Kinugasa reaction has been discovered 30 years ago, it has received more attention in recent years. The great majority of Kinugasa reactions have used simple diaryl nitrones and aryl acetylenes. A significant contribution to this renewed interest has been made by our pioneering works which have begun seven years ago. We directed our attention to aliphatic, cyclic nitrones, both chiral and achiral.

The great attractiveness of the Kinugasa reaction has been engendered by the ready availability of both substrates, their stability, broad possibilities of stereocontrol of the process towards the desired absolute configuration, resistance of many functional groups to reaction conditions, and perfect atom economy of the process – all atoms of both substrates are found in the product. These advantages have been demonstrated by us in the formal synthesis of Ezetimibe, a new approach to thienamycin related antibiotics and in the synthesis of Kaneka β-lactam which is the starting material for industrial syntheses of carbapenems. Our recent works resulted in a review article recently published by us, and an invitation to contribute a chapter to "Organic Reactions", an important collective publication related to the synthesis and reactivity of organic compounds.

Despite obvious advantages, the Kinugasa reaction requires further methodological basic research to show its general applicability. The research directions proposed by us have not been investigated so far.

The main difficulty is the time required to complete the reaction, which enables side reactions such as deoxygenation of nitrones and oxidation of acetylenes to diacetylenes, which lowers the reaction yield. We intend to solve this problem by the use of additional ligands to activate the triple bond. We also plan on an intramolecular version of the Kinugasa reaction, which should allow high stereocontrol of the process not possible for the intermolecular reaction. The project involves introducing linkers between both reacting groups, which after formation of the β-lactam ring can be removed. A significant element of our project is directed to so far unknown possibilities for the Kinugasa reaction in the synthesis of complex carbapenem antibiotics related to 4-methyl derivatives and to monocyclic β-lactams, such as aztreonam, carumonam, and nocardicins. The basic research nature of our investigation will be expressed in demonstrating new attractive prospects for the reaction, particularly in target-oriented synthesis, since in the crucial synthetic step of the reaction is formed not only the β-lactam ring but also, depending on the nitrone structure, the basic scaffold of the antibiotic. We are certain that our work will demonstrate that the Kinugasa reaction deserves credit as one of the most important methods of β-lactam ring formation.