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ISSN:2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
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Vol. 4: (3), 2014, 441-452

MY SILVER JUBILEE WITH BETA LACTAMS

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Abstract:
In this perspective, our research on beta lactams for the past twenty five years is focused.

Introduction:
Research can be compared to our life. Nobody knows what will happen tomorrow. Like our life, research does not follow a definite or selective path. It is hard to believe for me that I have already spent 25 years of my research life and most of it on beta lactam research. I never knew this will happen to me, but this has happened. In 1989, I was working as a postdoctoral fellow in Professor R. G. Salomon's group at the Case Western Reserve University, Cleveland, Ohio, USA. I was told by one of my colleagues that postdoctoral fellows may not get renewal of the appointment due to the non-availability of grants. Consequently, knowing the uncertainty, Iwas in puzzle. I remembered I went to the library at the same day and started to open journals randomly. All of a sudden, I came across of a paper that describes the synthesis of 3-oxo-beta lactams by Professors A. K. Bose and M. S. Manhas of Stevens Institute of Technology, New Jersey and their group members. I became highly curious to know more about their work and found numerous publications in this field. Because of the Bayer Strain theory, I had the impression that 4-membered cyclic compounds are difficult to make, but become pleased to read many excellent papers on beta lactams. I was nervous, but called Professor Bose at Stevens for a postdoctoral fellowship. Professor Bose asked me a few questions on my scientific background. For example, he wanted to know the name of my Ph. D. thesis supervisor, type of research that I conducted, number of publications that I had and the reasons for my interest in beta lactam science. The answers of all of these questions were easy to me. I knew that beta lactams are antibiotics and I studied total synthesis of penicillin in my master class. Professor Bose called Professor Salomon and I was transferred in his group at the beginning of 1990. This was the way I became involved in beta lactam research which I am still continuing at an extremely rapid rate. This journey was very difficult to continue because of the poor funding situation in USA. However, I survived. Our research on beta lactams had received attention and popularity from scientific community as demonstrated by number of publications, presentations, citations and media exposures.

Background and Significance:
Due to their medicinal activity and potential use as synthetic starting materials, synthesis and biological studiesof beta-lactams has been intensely investigated for more than 70 years. Considerable work has been performed by chemists and biologistto continue updating their findings about beta-lactam synthesis, based on either new or established methods, or on the modifications of pre-existing groups linked to this ring system.

The first remarkably spectacular attempts to identify the active biochemicals found in antibacterial molds followed the discovery of penicillin antibiotics by Fleming. Then, identification of the chemical architecture by Hodgkin, and total synthesis by Chain, Heatley, and Florey, led to the successful preparation of penicillin antibiotics in 1940's[1]. Since the discovery and synthesis of penicillin, many other families of β-lactam antibiotics had been realized[2] and their extensive use worldwide continued to be a forefront line of action against infectious pathogens[3]. Notably, beta-lactams were found in other crucial applications to human, e. g. inhibitors of serine protease[4] and acyl coenzyme A cholesterol transferases (ACAT)[5].These types of molecules were used as starting materials for the preparation of various heterocycles of biological significance.[6] For example, substituted hydroxy beta-lactams were used in the semi-synthesis of Taxol and Taxotere.[7]Studies of human leukocyte elastase inhibitory mechanisms and the biological activity of this class of compounds were also available.[8]As a result of their significant practical use, the synthesis of new types of beta-lactams was the focus of active research. A number of important strategies are available for the synthesis of the 2-azetidinone core ring present in all β-lactams(Staudinger cycloaddition reaction[9], ester enolate-imine condensation[10], hydroxamate approach[11], alkene-isocyanate method[12] and the alkyne-nitrone reaction (Kinugasa reaction).[13] There are fascinating developments, such as catalytic asymmetric[14] and polymer-supported[15] synthesis of β-lactams. We and others are pursuing our work on the synthesis and biological evaluation of a number of novel anticancer and new beta-lactams.[16, 17, 18, 19]

Our Endeavor:
We demonstrated the preparation of vinyl beta lactams for the first time with diaryl imines. The stereochemical results were highly unpredictable. These vinyl beta lactams were then converted to many other heterocycles by chemical manipulations: oxidation, reduction and rearrangement. An extension of this method with optically active imines was not possible. A number of methods with unsaturated acid chloride with optically active imines were attempted, but no beta lactams were obtained. The cause of the failure is still a mystery.

Various optically active beta lactams were prepared with high level of asymmetric induction. In some instances, enantioselectivity and diasteroselectivity was not high and these reactions uncovered many theories of beta lactam formation reaction by Staudinger cycloaddition reaction. It was fascinating to observe formation of beta lactam with unpredictable and predictable absolute configuration. The number of chiral groups and their locations in the starting compounds was the key for the success of synthesizing enantiopure beta lactams. It was believed that addition of multiple chiral centers or groups may help to obtain beta lactams with high optical purity. However, this theory was turned out to be not true.

These optically active beta-lactams were used as the starting materials for the preparation of alkaloids, other beta lactams with additional complexity, amino acids and amino sugars with complete stereocontrol. Domestic microwave-induced reactions were found to have dramatic effects on stereochemistry and rate of the beta lactam formation reaction.[20, 21]The stereochemistry of many beta lactams was inverted using this techniqueand it was shown that this inversion was not due to epimerization to more stable products. Higher activation energy chemical pathways that were difficult and practically impossible to complete with conventional heating (oil bath, steam bath, and mantle) was performed spontaneously with microwave irradiation because of a much more facile energy transfer process. In thermal reactions, heat is applied externally and it passes through the walls of the reaction vessels and solvent/reactants. However, microwave-induced processeshavea number of advantages because of coupling, heating, irradiation and molecular heating. Microwave coupling is the direct transfer of energy to substrates that results in instantaneous heating. Microwave heating is the direct energy transfer method to the reaction mixtures. Microwave irradiation is a form of non-ionizing radiation that transfers energy by interacting with polar molecules, solvents and reaction mixtures. Several mechanisms were proposed to explain the diasteroselectivity and enantioselectivity of beta lactam formation reaction. However, it appeared none was adequately explain the mechanism conclusively. This was not surprising to us because of our direct involvement in this area. It was understandable that structures of the starting materials, conditions of the experiments, nature of the reagents, and methods adopted can alter the stereochemical distribution and yield of the products drastically. Despite complexity, research in this area did not stop rather it took us to a different, but to a totally new direction of beta-lactam research.

We conducted analyses of chrysene, phenanthrene and dihydrophenanthrenederivatives through an examination of their anticancer effects *in vitro* and *in vivo*. These antitumor agents were diamides in which a side chain is bound to the polycyclic system. During the course of this work, we anticipated that conformationally restricted compounds of these open chain molecules might increase the activity. Many examples of efficient conformationally restricted compounds were known. The hypothesis was that novel beta lactams can be synthesized that may demonstrate enhanced anticancer activity and low toxicity to healthy tissues. We synthesized numerous novel beta-lactams and showed that they possess promising antitumor activity *in vitro* and *in vivo*. An unprecedented observation on the stereochemistry of the resulting beta-lactams was observed. The mechanism of the process was explained and then this was further tuned by computer-assisted DFT calculation. The activity was superior to that of cisplatin *in vitro* in some examples. In addition, our studies of these compoundsdemonstrated a blockade of the G2/M checkpoint in cancer cell lines. Following this method, an extended series of carefully designed beta-lactam analogues, related to our lead compounds were synthesized in order to identify the structural and mechanistic correlates of antitumor properties. It appeared thatsome of these molecules have a potent and unique specific inhibition at the G2/M transition point in sensitive cancer cell lines. In addition, the compounds were monitored fortheir effect on a variety of enzymes related to DMA damage and repair. These were also investigated in the biochemical pharmacology studies to determine the mechanism ofaction. These included an overall assessment of the relative ability of lead beta-lactam to alter cellular apoptotic, cell cycle pathways and selected gene arrays designed to examine key elements of apoptosis. The same array was also be used to examine changes in genes known to be of importance in regulating the

cell cycle. It was highly interesting to realize that some beta-lactams exhibited anticancer activities against some tumor cell lines for which there are no treatment currently available.

Suitable synthetic methods are essential for the preparation of new molecules. Carbohydrates are easily accessible substrates with multiple stereocenters.[22] The configuration at the anomeric center, protective groups and nature of the ring systems in carbohydrates was manipulated by many researchers. Encouraging by these results, a number of carbohydrates were used as one of the key steps in the synthesis of optically active anticancer beta-lactams with diverse ratios. The protective group and the nature of the carbohydrates and amino acids were crucial in determining the enantioslectivity of the process.[23] New results were obtained during hydrogenolysis, hydrogenation and ring annulation processes. It was clear anomeric center has role in the beta lactam formation reaction.[24] Chiral beta lactams were also found to be highly selective anticancer agents that kill tumors cells at low micromolar concentration.

Beta-lactams derived from this study was converted to other heterocycles and multicyclic molecules of biological significance using rearrangement or conceptually new reaction pathways. Numerous polycyclic beta lactams were prepared through cyclization strategies that involve ionic and radical intermediates. The methods not only extended the scope of research on beta lactams, but also it opens up a complete new era of this subject as well as to explore this chemistry for the synthesis of other heterocycleswhich are very difficult to prepare using the currently available methods.

Conclusion:

Overall, our research on beta lactams for the past 25 years has become very exciting and useful. This has uncovered numerous methods, reaction mechanism, synthesis and biological activity. However, we believe this is just the beginning considering many exciting results as described herein.

Acknowledgment:

I am highly grateful to numerous of my mentors and colleagues, Professors U. R. Ghatak, Professor R. G. Salomon, Professor A. K. Bose, Professor M. S. Manhas, Professor F. F. Becker, Professor T. Slaga, Ms. Indrani Banik, Dr. Susanta Samajdar, Dr. Debasish Bandyopadhya and Dr. Ram Yadav. Many students and scientists have participated in our research. The name of their work can be seen in the reference section. I am also grateful to NIH, NCI, Kleberg Foundation, Stevens Institute of Technology, University of Texas M. d. Anderson cancer Center and university of Texas-Pan American for their support to our research.

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Received on May 18, 2014.