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REVIEW

A Personal Journey Toward β-Lactams: Synthesis and Medicinal Studies

Bimal K. Banik[1,2,3,4,✉]

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ABSTRACT

Synthesis and medicinal studies on β-lactams have attracted significant attention to a diverse group of scientists for the past many decades. But, the progress in this area remains uncontrolled. We have been engaged in β-lactam research for many years and contributed numerous papers. Our contributions on β-lactams have gained scientific values and merits as documented by excellent publications, books, patents, presentations, competitive grant funding, citations and media exposures and above all numerous invitations. In this perspective, a concise summary of our research on β-lactams is discussed.

KEYWORDS

β-Lactam, Synthesis, Stereochemistry, Optical activity, Medicinal activity.

Author affiliation:

[1]Department of Chemistry, The University of Texas-Pan American, 1201 West University Drive, Edinburg, Texas 78539, USA
[2]Department of Molecular Pathology, The University of Texas-M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, USA
[3]Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Castle Point on the Hudson, Hoboken, New Jersey 07030, USA
[4]Present Address: Vice President of Research and Education Development, Community Health Systems of South Texas, 3135 South Sugar Road, Edinburg, Texas 78539, USA

✉To whom correspondence to be addressed:

E-mail: bimalbanik10@gmail.com; bimal.banik@chsst.org

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INTRODUCTION

I had the opportunity to meet and talk to Prof. John C. Sheehan of MIT extensively in early 1990. Professor Sheehan's enthusiasm and comments on β-lactams had made me to come very close to him. According to him he had started β-lactam research "yesterday' only, although he was the most pioneering scientist in this field at that time. Prof. Sheehan had synthesized not only life-saving penicillin and cephalosporin, but also contributed much more in β-lactam research than anyone else in the world. His several discoveries have expanded the science of β-lactams significantly. I was involved in research with Prof. Ajay K. Bose at Stevens Institute of Technology, New Jersey, USA. After participating in discussions with Profs. Sheehan and Bose, I decided to start my endeavor on β-lactam as a collaborative and independent scientist.

In the meantime, some of my colleagues and experts told me that β-lactam field is very "saturated" and it would be difficult to obtain good unknown results. However, I was confident nothing is impossible and decided to perform research on β-lactam as one my principal research topics.

Background and significance: The antibacterial properties of β-lactams and synthesis of new and pharmacological studies of these types of compounds has been the subject of research activities of many research groups. In many instances chemists

discover new route or altered the known methods to create novel β-lactam ring systems.

A remarkable synthesis of penicillin antibiotics was made in 1940's [1]. Since then other classes of β-lactam antibiotics were obtained [2]. β-Lactam antibiotics had become the first line of treatment against infectious pathogens [3]. Some β-lactams were found to be effective in inhibiting serine protease [4] and acyl coenzyme A cholesterol transferases (ACAT) [5]. The ring strain of the β-lactam ring was exploited for novel synthesis of numerous heterocyclic compounds of promising medicinal values [6]. Notably, taxol and taxotere, the two crucial anticancer drugs were prepared from hydroxy β-lactams [7]. Some β-lactams had the power of inhibiting human leukocyte elastase [8].

The medicinal properties of certain specific β-lactams had prompted chemists to undertake synthesis of new types of β-lactams and this research had culminated in the development of various important strategies for the preparation of β-lactam rings of diverse structures. Of these, the most important methods were Staudinger cycloaddition reaction of imines and acid chloride (equivalent) [9], ester enolate-imine condensation [10], hydroxamate condensation [11], alkene-isocyanate addition [12] and the alkyne-nitrone addition [13].

Our endeavor: Our research on β-lactam is divided into several areas. For example, we demonstrated the followings: (a) cycloaddition reaction of alkyl, alkynyl, oxygen and nitrogen containing acid chloride with imines for the synthesis of β-lactams; (b) asymmetric synthesis of β-lactams through cycloaddition reaction; (c) cycloaddition reaction of imines derived from polyaromatic amines for the synthesis of β-lactams; (d) asymmetric synthesis of β-lactams obtained from multicyclic ring systems; (e) chemical manipulation of the functionalized β-lactams to amino acids, functionalized amides and alkaloids; (f) domestic and automated microwave-induced synthesis of β-lactams; (g) chemoenzymatic synthesis of β-lactams; (h) Mechanism of β-lactams formation reaction; (i) glycosylation of β-lactams; (j) Anticancer activities of β-lactams.

(a) Cycloaddition reaction of alkyl, alkenyl, oxygen and nitrogen containing acid chloride with imines for the synthesis of β-lactams: We explored the synthesis of alkyl, alkenyl, oxygen and nitrogen containing acid chlorides with imines in the presence of a tertiary base. The stereochemistry of the β-lactams depended on the conditions of the experiments and it varied from pure *cis* to pure *trans* or to a mixture of *cis*-*trans* isomer. The stereochemical ratios were unpredictable in numerous examples [1]. Synthesis of optically active alkenyl and alkynyl substituted β-lactams following cycloaddition failed completely. However, alkenyl and alkyl β-lactams were prepared efficiently using imines that have dicarboethoxy group. The presence of a dicarboethoxy group prevented the formation of isomeric β-lactams [13]. Importantly one of the esters in C-3/C-4-trisubstituted β-lactams was removed to form *cis*/*trans* C-3/C-4-disubstitued β-lactams. Application of solid phase synthesis of cycloaddition reaction using rink resin produced β-lactams in a similar diastereomeric ratio that was obtained in liquid phase [1,13b,13e].

(b) Asymmetric synthesis of β-lactam through cycloaddition reaction: Chiral β-lactams were synthesized in optically pure forms starting from chiral aldehydes and chiral acid chlorides (equivalent) [14]. Although asymmetric induction was introduced using chiral aldehydes, chiral amines and chiral acid chlorides, however, the degree of asymmetric induction varied considerably. Optical purity of the β-lactams was not high in some examples. A mixture of enantiomers and diastereomers were obtained in different ratios. It was also possible to obtain single enantiomerically pure β-lactam and its mirror image isomer by choosing chiral auxiliary of opposite configuration [14a-14c]. Based upon the results, suitable mechanism of β-lactam formation was proposed. However, it appears no mechanism can adequately explain the stereochemical results obtained from the experimental work (see below). The number and nature of the asymmetric centers and their locations in the starting imines or acid chloride was crucial to obtain optically active β-lactams in different enantiomeric excess [1]. It was not necessary to have multiple asymmetric centers at the C-component of the imine to obtain optically active β-lactams. In many examples, a single chiral center at the C-component of the imine was proved to be extremely useful for better asymmetric induction. In contrast, a single or multiple chiral centers at the N-part of the imine or acid chloride (equivalent) component resulted in optically active β-lactams with lower enantiomeric excess. Moreover, addition of chiral groups at the C- and N-part of the imine reduced enantioselectivity and diasteroselectivity. Surprisingly, chiral centers at the C- and N- of the imine as well as in acid chloride portion reduced asymmetric induction [1].

(c) Cycloaddition reaction of imines derived from polyaromatic amines: We synthesized numerous new and novel β-lactams derived from polyaromatic compounds [1b-d,15]. An unprecedented stereochemical distribution of the products was observed in this study [15]. Synthesis of β-lactams using polyaromatic imines was not investigated at all by any other groups. The formation of exclusive *trans* isomer when polyaromatic group was present at the –N of the imine deserved special attention [15a]. In contrast, *cis* isomer was the only isomer formed when the same polyaromatic group or a conjugated system was present at the –C of the imine [1b-d]. It was interesting to note that isomeric imines produced different ratios of isomeric products. The results appeared to be due to steric hindrance exerted by the polyaromatic groups. However, detailed analysis of numerous compounds confirmed that electronic contribution of the intermediate formed in this reaction was responsible for these unprecedented results. Computer-assisted charge density calculation of the intermediate indicated a better stabilization of the transition state that produces *trans*-isomer (see below).

(d) Asymmetric synthesis of β-lactams obtained from multicyclic ring systems: Carbohydrates (naturally occurring sugars) were used for the asymmetric synthesis of β-lactams [1,16]. Because of the presence of multiple stereocenter, sugars are versatile precursors for β-lactam synthesis. The stereochemistry at the anomeric center and other centers, nature of the protective groups and the ring systems in carbohydrates was altered to prepare diverse β-lactams depending upon the goals. A few sugars were used and chemically modified to make them like acid chloride equivalents. Cycloaddition

reaction was performed under various reaction conditions to obtain two isomeric *trans* β-lactams. The nature of the protective group and ring systems was important to obtain a specific isomer [16a-b]. It was believed that the stereochemistry at the anomeric center had a specific role in the cycloaddition reaction [16a-b]. Chiral β-lactams derived from polyaromatic compounds were highly selective anticancer agents at low micromolar concentration (see below).

(e) Chemical manipulation of the functionalized β-lactams to amino acids, functionalized amides and alkaloids: The non-racemic and racemic β-lactams were used as the starting materials for the preparation of alkaloids, tributyltin hydride and palladium-mediated annulations reaction and rearrangement reaction toward multicyclic β-lactams, polyhydroxy amino acids and amino sugars with retention of stereochemistry at each and every center [14a-b,17]. These procedures were fascinating since several heterocyclic compounds were made available. Highly selective hydrogenation of the reducible groups present in β-lactams were accomplished successfully [18d]. It was demonstrated that all bonds in the β-lactam ring can be broken for the synthesis of molecules of unusual significance by a judicial combination of reagents and functional groups present in the ring [14a-b,17c]. The mechanism of these processes was investigated. A new method was developed for the synthesis of 3-unsubstituted β-lactam by reacting with imine and ethyl bromoacetate in the presence of indium metal [17a-b]. In some instances, the intermediate β-amino ester was isolated. Polyaromatic imines failed to produce β-lactams under these conditions probably because of the less nucleophilic amino group present in the β-amino structures. Substituted bromoester was also used for the preparation of alkyl-substituted β-lactam. The reducing ability of indium was used successfully to prepare oxazines [17c]. Palladium and hydrogen combination was able to hydrogenate alkenyl, alkynyl, O-debenzylation and N-1/C-4 bond cleavage reactions and this method produced a variety of other molecules of interests [18d]. Tributyltin hydride-mediated aryl radical cyclization [17d] and palladium acetate-induced Heck cyclization [17*l*] were performed to prepare polycyclic β-lactams. During the course of investigation of bismuth nitrate-induced reactions [17f] facile nitration of the aromatic group present in the β-lactam ring was identified [17g]. Subsequently, we discovered bismuth nitrate-catalyzed reaction of 3-keto β-lactams with hydroxyl proline for the preparation of diverse optically active pyrrole-substituted β-lactams [17h-k].

(f) Domestic and automated microwave-induced synthesis of β-lactams: Automated and domestic microwave-induced reactions were proved to accelerate rate of reactions and have effects on stereochemistry in the synthesis of β-lactam [18]. The stereochemistry of certain β-lactams was controlled by this method. For example, a minor isomer formed under classical method was found to be the predominant isomer under microwave irradiation method. However, the alteration of stereochemistry is not because of thermal isomerization to thermodynamically more stable compounds. Clearly, β-lactam formation by cycloaddition method [15,16] followed two pathways and a single pathway becomes mostly exclusive under high power microwave irradiation. Polyaromatic β-lactams were prepared following this method within a few minutes and an identical distribution of products was also obtained in many instances [18e-h]. The advantages of microwave-induced β-lactam synthesis were identified through extensive investigations.

(g) Chemoenzymatic synthesis of β-lactams: Optically active β-lactams was made available by chemoenzymatic methods [19]. Hydrolysis of an 3-acetoxy group was successfully performed by different types of lipases and this method produced two optically active products. This reaction was believed to take place through partial hydrolysis of the acetoxy group to hydroxy group of one of the isomer present in the racemic mixtures. Therefore, it was crucial to stop the reaction at the middle of the process to obtain enantiomerically pure acetoxy and hydroxy compounds. As an extension, Bakar's yeast reduction of a 3-keto group in β-lactam was achieved and the resulting *trans* and *cis* alcohols was found to be optically pure. These reactions were performed in water-alcohol mixtures. The absolute stereochemistry of the products was determined from optical rotation and NMR experiments using chiral metal/organic complex.

(h) Mechanism of β-lactam formation reaction: The mechanism of the β-lactam formation reaction was investigated in detail following available literature knowledge and computer-assisted DFT calculation [1b-d,20]. The observed sterochemical behaviour and theoretical studied had close relationships. Two mechanistic routes needed to be considered to explain the stereochemistry of the products formation by the Staudinger cycloaddition of imines and acid chiral (equivalent). The acylation of imines by acid chloride mechanism seemed to explain the formation of the *cis* isomer adequately. However, the formation of both *cis* and *trans* isomer was explained following ketene mechanism. Isomerization of the initially formed iminium ion in this procedure appeared to have significant influence. In general, an isomerization of the iminium ion produced a *trans* isomer. Such isomerization of the iminium ion was highly possible when an electronegative group is present at the imine nitrogen. Extended conjugation present at the carbon of the imine was responsible for the formation of the *cis* isomer. Despite a number of seminal contributions on the mechanism of Staudinger β-lactam formation reaction by a number of authors, no mechanisms appeared to be conclusive.

(i) Glycosylation of β-lactams: As mentioned previously, several β-lactams that have sugars at different positions in the ring were synthesized. The presence of sugar in the β-lactam is important because they can be more soluble in water. The research in this area had culminated in the stereo-specific glycosylation of several hydroxy β-lactam derivatives through iodine-catalyzed reactions [21]. This reaction produced exclusively a single axially linked oxygen glycoside with an optically active hydroxy β-lactam. Reaction with a racemic hydroxy β-lactam producd two diastereomers in almost equal proportions. Acid induced cleavage was performed to remove the sugar group to obtain optically active β-lactams in good yield. Following an identical procedure, optically active ring system present in thienamycin antibiotic was synthesized. Studies directed toward the synthesis of glycosides uncovered numerous important observations. The nature of protective

groups in the sugar, stereochemistry at the C-4 position of the sugar unit and the nature of group present at the N-1 of the β-lactam ring was responsible for the success and failure of this reaction. An axial attack of hydroxy group of β-lactam to alkene bond of glycol with simultaneous isomerization was believed to occur in this mild acid-catalyzed process. An attack from the top-phase of the sugar moiety was ruled out because of the possible interaction of the two electron pairs that are present in the sugar ring system and 3-hydroxy group of the β-lactam ring structure [21c].

(j) Anticancer activities of β-lactams: The β-lactams derived from polyaromatic compounds demonstrated promising anticancer activity *in vitro* against a number of cancer cell lines (blood, breast, prostate, pancreas, colon, ovary and skin) [22]. It was found *trans* racemic isomer with N-polyaromatic system is much more active than the corresponding *cis* racemic compound with C-4-polyaromatic group. However, the activity of the *cis* isomer with N-polyaromatic system was found to be closer to the *trans* N-polyaromatic system. Very interestingly, the activity was dependent on the shape and number of the aromatic groups present at the –N of the β-lactam. Angular polyaromatic system (chrysene and phenanthrene) containing compounds exhibited anticancer activity whereas the linear polyaromatic derived compounds had no effects. However, symmetrical compounds with angular polyaromatic ring and ester containing β-lactam was not active. The presence of an ester group was obligatory for the anticancer activity. The activity was superior to that of cisplatin *in vitro* in some examples. In addition, our studies of these β-lactams demonstrated a blockade of the G_2/M checkpoint in a few cancer cell lines. A series of β-lactams were prepared in order to establish the structure-activity relationships toward their antitumor properties. A few of compounds inhibited cell cycle at the G_2/M phase in sensitive tumor cell lines. Moreover, the molecules were tested to identify their behaviour on a variety of enzymes widely used in cancer chemotherapy. Several other biochemical pathways studies were performed to identify their possible mechanism of action against cancer cell lines. Cell cycle, apoptosis, genomic studies and several enzyme-related studies were performed. The interaction of these agents against DNA, RNA and protein was assessed. An inhibition of protein was found to be much more significant than DNA and RNA in dose and time-dependent manner. From this study, a few lead molecules were developed for *in vivo* tests against colon, blood and ovarian cancer cell lines. The results were intriguing since reduction of tumor growth was observed after treatment with these lead molecules.

Conclusion

Overall, our research on β-lactams for the past many years has become very exciting and useful. This has uncovered numerous methods, reaction mechanism, synthesis and biological activity.

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