1. ***Beta-lactam antibiotics for clinical use. Clinical pharmacology series, volume 4.*** Edited by Sherry F. Queener, J. Alan Webber, and Stephen W. Queener. Marcel Dekker: New York. 1986.

   Book reference, which reviews the sources of beta-lactam antibiotics, their mechanisms of action, manufacture, clinical utility, and pharmacology. Includes microbiology, fermentation science, organic chemistry, clinical medicine, pharmacokinetics, pharmacodynamics ... and examines general manufacturing methods for preparing each antibiotic, including the fermentation of intermediates. Over 2,300 bibliographic citations.

2. ***β-Lactamases in the Biochemistry and Molecular Biology Laboratory***
   Amador, Paula; Prudencio, Cristina; Vieira, Monica; Ferraz, Ricardo; Fonte, Rosalia; Silva, Nuno; Coelho, Pedro; Fernandes, Ruben
   Biochemistry and Molecular Biology Education, v37 n5 p301-306 Sep-Oct 2009
   Abstract:
   β-lactamases are hydrolytic enzymes that inactivate the β-lactam ring of antibiotics such as penicillins and cephalosporins. The major diversity of studies carried out until now have mainly focused on the characterization of β-lactamases recovered among clinical isolates of Gram-positive staphylococci and Gram-negative enterobacteria, amongst others. However, only some studies refer to the detection and development of β-lactamases carriers in healthy humans, sick animals, or even in strains isolated from environmental stocks such as food, water, or soils. Biochemistry and Molecular Biology laboratory for majors in the health, environmental, and agronomical sciences will investigate basic techniques such as DNA extraction, bacterial transformation, polymerase chain reaction (PCR), gel electrophoresis, and the use of several bioinformatics tools. These laboratory exercises were conducted as a mini research project in which all the classes connected with the previous ones. This "curriculum" was compared with two groups of students from two different majors. Results showed that students who were enrolled in the new collaborative, project based "curriculum" obtained better results in the final exam than the students who were enrolled in the former individual based non-project "curriculum". Also, these students were found to be more enthusiastic during the laboratory classes than those from the former "curriculum".

3. ***Dual-action penems and carbapenems***
   Alfred J. Corraz, Scott L. Dax, Norma K. Dunlap, Nafsika H. Georgopapadakou, Dennis D. Keith, David L. Pruess, Pamela L. Rossman, Rudolf Then, Joel Unowsky, Chung Chen Wei
   J. Med. Chem., 1992, 35 (10), pp 1828–1839
   DOI: 10.1021/jm00088a019
   Abstract

Alfred J. Corraz, Scott L. Dax,* Norma K. Dunlap,* Nafsika H. Georgopapadakou, Dennis D. Keith, David L. Pruess, Pamela L. Rossman, Rudolph Then, Joel Unowsky, and Chung-Chen Wei

Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received November 5, 1991*

Two new series of dual-action antibacterial agents were synthesized in which penems and carbapenems were linked at the 2′-position to quinolones through either an ester or a carbamate moiety. Potent, broad-spectrum antibacterial activity was observed for both classes of compounds, indicative of a dual-mode of action.

Introduction

Dual-action agents are unique chemical entities comprised of two different types of antibacterial compounds covalently linked together in a single molecule in such a way that both components are able to exert their bactericidal properties. The antibacterial activity of quinolones occurs as a consequence of interaction with bacterial DNA gyrase,[1] while β-lactams act via inhibition of peptidoglycan transpeptidase(s).[2] By combining the two into a novel molecular hybrid, the result is inhibition of DNA replication and cell wall assembly. Furthermore, the antibacterial spectra of the two components are somewhat complementary; β-lactams possess potent Gram-positive activity, especially against *Streptococcus*, while quinolones display excellent activity against Gram-negative organisms, including *Pseudomonas aeruginosa* and β-lactam-resistant strains such as methicillin-resistant *Staphylococcus au-*

(1) Wolfson, J. S.; Hooper, D. C. The Fluoroquinolones: Structures, Mechanisms of Action and Resistance, and Spectra of Activity In Vitro. *Antimicrob. Agents Chemother.* **1985**, *28*, 581–586.

(2) Fiere, J. M.; Jovis, B. Penicillin-Sensitive Enzymes in Peptidoglycan Biosynthesis. *CRC Crit. Rev. Microbiol.* **1985**, *11*, 299–396.

4. ***Monobactams—monocyclic β-lactam antibiotics produced by bacteria***
R. B. Sykes, D. P. Bonner, K. Bush, N. H. Georgopapadakou and J. S. Wells
The Squibb Institute for Medical Research P.O. Box 4000, Princeton, NJ. 08540, U.S.A.
Journal of Antimicrobial Chemotherapy (1981) 8, 1-16
Abstract

Screening of bacteria for the production of β-lactam antibiotics has resulted in the discovery of a family of structurally similar monocyclic β-lactam-containing molecules. These compounds, referred to as monobactams, are produced by a range of bacterial species. Although relatively weak antibacterial agents, the naturally occurring monobactams are highly stable to the action of β-lactamases. Structure activity relationships among a range of chemically synthesized monobactams have led to the identification and progression of SQ 26,776. SQ 26,776 shows a high degree of activity against β-lactamase-producing aerobic Gramnegative rods and is stable to the majority of β-lactamases produced by these organisms.

5. ***Structure and absolute configuration of thienamycin***
Georg Albers-Schoenberg, Byron H. Arison, Otto D. Hensens, Jordan Hirshfield, Karst Hoogsteen, Edward A. Kaczka, Robert E. Rhodes, Jean S. Kahan, Frederick M. Kahan,
J. Am. Chem. Soc., 1978, 100 (20), pp 6491–6499
DOI: 10.1021/ja00488a038
Abstract

Abstract: The structure and stereochemistry of the potent new β-lactam antibiotic thienamycin were determined as shown in formula **22.**

Thienamycin (**1**) was discovered in fermentation broths of the soil microorganism *Streptomyces cattleya*.[1] It is a novel β-lactam antibiotic[2] of exceptional antibacterial potency and spectrum including activity against *Pseudomonas* and β-lactamase producing species.[3] Since its first publication in the patent literature[4] several closely related structures have been recognized.[5-7] Recently, the first total synthesis of the antibiotic has been reported.[8] In the first part of this paper we describe the chemical and spectroscopic observations which first led to the elucidation of the new structure. In the second part we discuss the relative and absolute stereochemistry at the three chiral centers of thienamycin.

Structure of Theinamycin

Thienamycin is a zwitterionic compound with an acidic dissociation constant of ca. 3.1. Broad infrared absorption at ca. 1580 cm^{-1} is characteristic of a carboxylate anion and a sharper band at 1765 cm^{-1} is reminiscent of the β-lactam carbonyl absorption of cephalosporins and cephamycins.[9,10] The characteristic ultraviolet absorption maximum at 296–297 nm (ε 7900) in the pH range from 4 to 8 shifts to 309 nm at pH 2 and can be abolished together with biological activity by treating the antibiotic with hydroxylamine at neutral pH. ^1H and ^{13}C NMR signals of thienamycin are listed in Table I. The elemental composition $C_{11}H_{16}N_2O_4S$, mol wt 272, was deduced from field-desorption mass spectra of the antibiotic (MH^+ 273) and from high-resolution mass spectra of the derivatives **2** and **3** (Scheme 1). These derivatives were first prepared when only small amounts of partially purified antibiotic were available. For each of them several spectra were averaged to obtain the most accurate *m/e* values. The resulting data sets ruled out alternative compositions which have similar fractional masses. Subsequently, the assignments were confirmed by measurements on and derivatization of the purified antibiotic. Molecular weight determination by ultracentrifugation, sulfur analysis by energy dispersive X-ray fluorescence,

6. ***A practical synthesis of (±)-thienamycin***
D. G. Melillo, I. Shinkai,, T. Liu, K. Ryan and M. Sletzinger
Tetrahedron Letters, Volume 21, Issue 29, 1980, Pages 2783-2786
Abstract

An efficient and operationally simple synthesis of (±)-thienamycin is described.

7. ***Total synthesis of thienamycin: a new approach from aspartic acid***
Paul J. Reider, * and Edward J. J. Grabowski
Tetrahedron Letters, Volume 23, Issue 22, 1982, Pages 2293-2296
Abstract

A practical stereospecific synthesis of thienamycin has been achieved. Key steps include a lead tetracetate oxidative decarboxylation and subsequent insertion of a four carbon diazo containing unit into a 3-acetoxy-2-azetidinene.

8. ***Total synthesis of (+/-)-thienamycin***

David B. R. Johnston, Susan M. Schmitt, F. Aileen Bouffard, B. G. Christensen
J. Am. Chem. Soc., 1978, 100 (1), pp 313–315
DOI: 10.1021/ja00469a069
Abstract

Total Synthesis of (±)-Thienamycin

Sir:

Thienamycin (**1**, R = R′ = R″ = H)[1] is a novel β-lactam antibiotic isolated from *Streptomyces cattleya*. Its unusually high potency against both gram-positive and gram-negative bacteria is quite surprising since the single 6-substituent is not only α but also lacks the traditional amide functionality. Of particular interest is its activity against *Pseudomonas* spp. and its resistance to bacterial β-lactamase.[2] Possibly the hydroxyl group can bind the same site normally bound by the 6β-amido group of the traditional β-lactam antibiotics when complexing with the bacterial cell wall enzymes, while the backbone of the 6α-substituent may mimic the 6α-methoxy group of the cephamycins to provide lactamase resistance. This unique and highly reactive compound offers a challenging synthetic problem, particularly the construction of the unusual ring

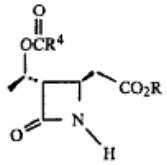
9. ***Synthesis of thienamycin via (3SR, 4RS)-3-((RS)-1-acyloxyethyl)-2-oxo-4-azetidineacetate***

Thomas M. H. Liu et. al.
U.S. Pat, 4,287,123 (1981)

[57] **ABSTRACT**

Disclosed is a process for the stereocontrolled total synthesis of thienamycin, which synthesis proceeds via intermediate II:

II



wherein R is a readily removable carboxyl protecting group; and

is a readily removable acyl group.