About OMICS Group

OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

OMICS International Conferences

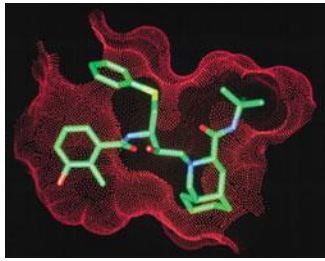
OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

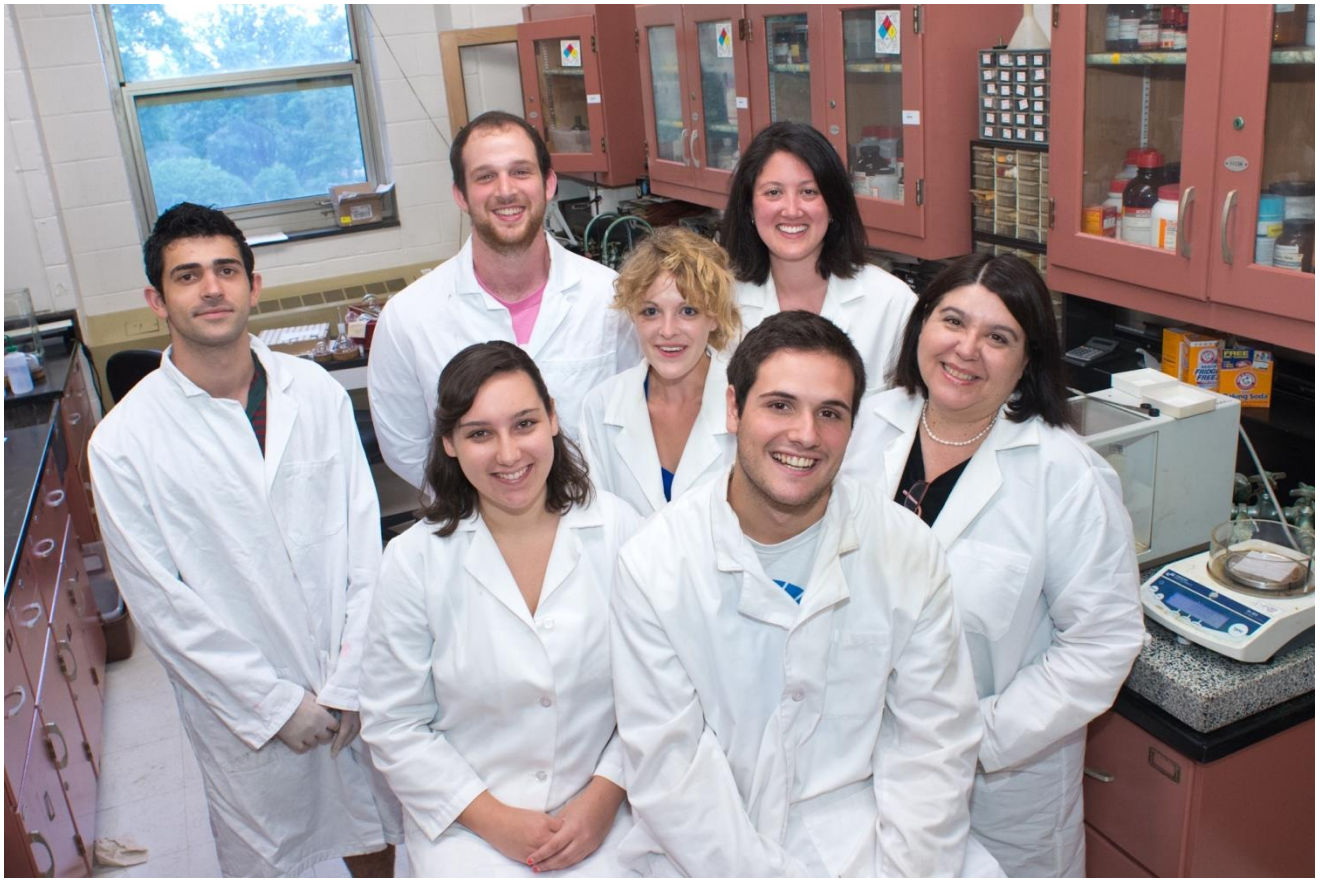
β-Lactams cidal against Mtb

Monika Konaklieva

American University



Synthesis and Characterization of Biologically Active Molecules



Overview

- Drug Resistance and Challenges for Drug Discovery
- Synthesis and Biological Evaluation of Novel Monocyclic β-Lactams against:
- *Mycobacterium tuberculosis*
- *Staphyloccocus aureus*

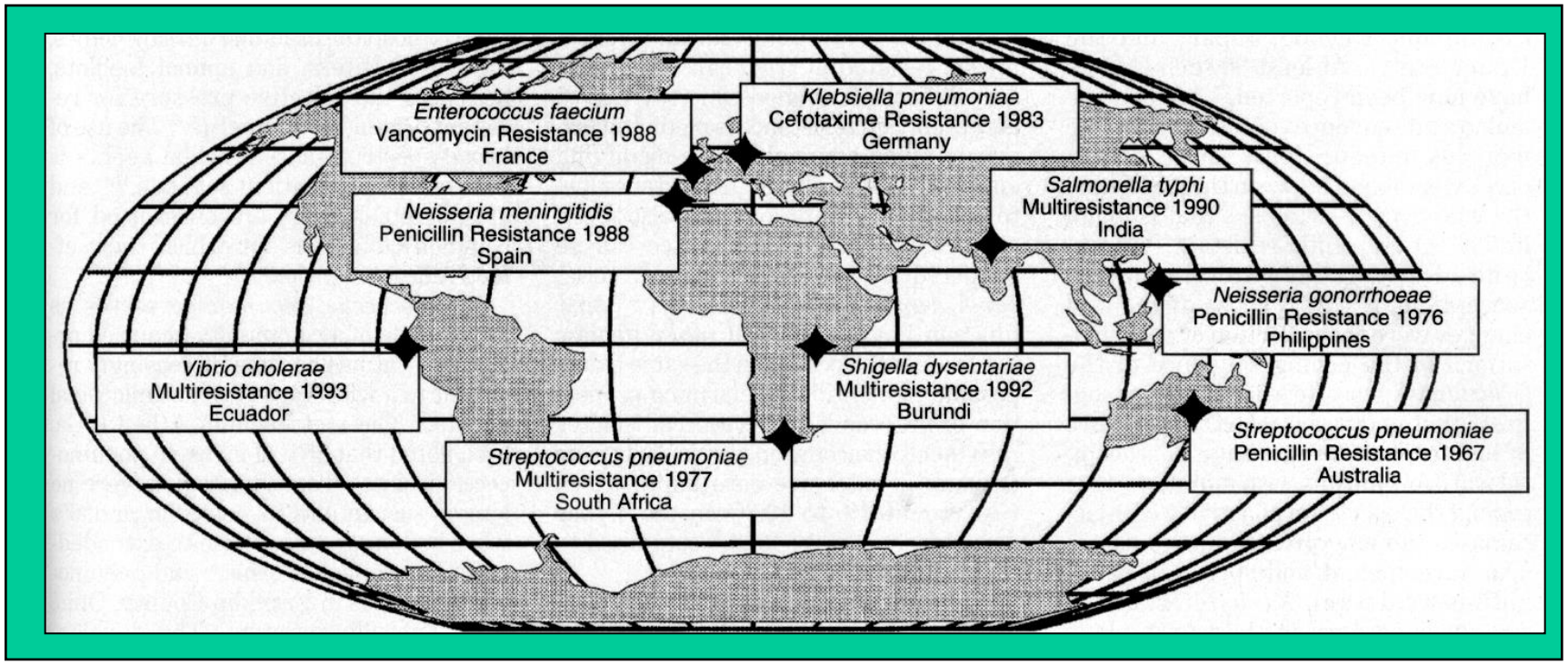
To Fight Resistant Microbes, FDA to Ban 2 Poutry Drugs

The removal would mark the first time the government has pulled any drug to combat infections that have grown resistant to antibiotics, a rising problem that public health officials have been warning for years could return the world to the days before penicillin and other infection-killers.
Washington Post, October 27, 2000

Poultry Antibiotics Pose Human Threat

…This is the first time FDA has approved banning any antibiotic because of bacterial resistance. It is also the first time FDA has proposed withdrawing approval for an antibiotic used in the livestock industry.
C & E News, November 6, 2000

Global Map showing Emergence of a Number of Antimicrobial- Resistance Organisms

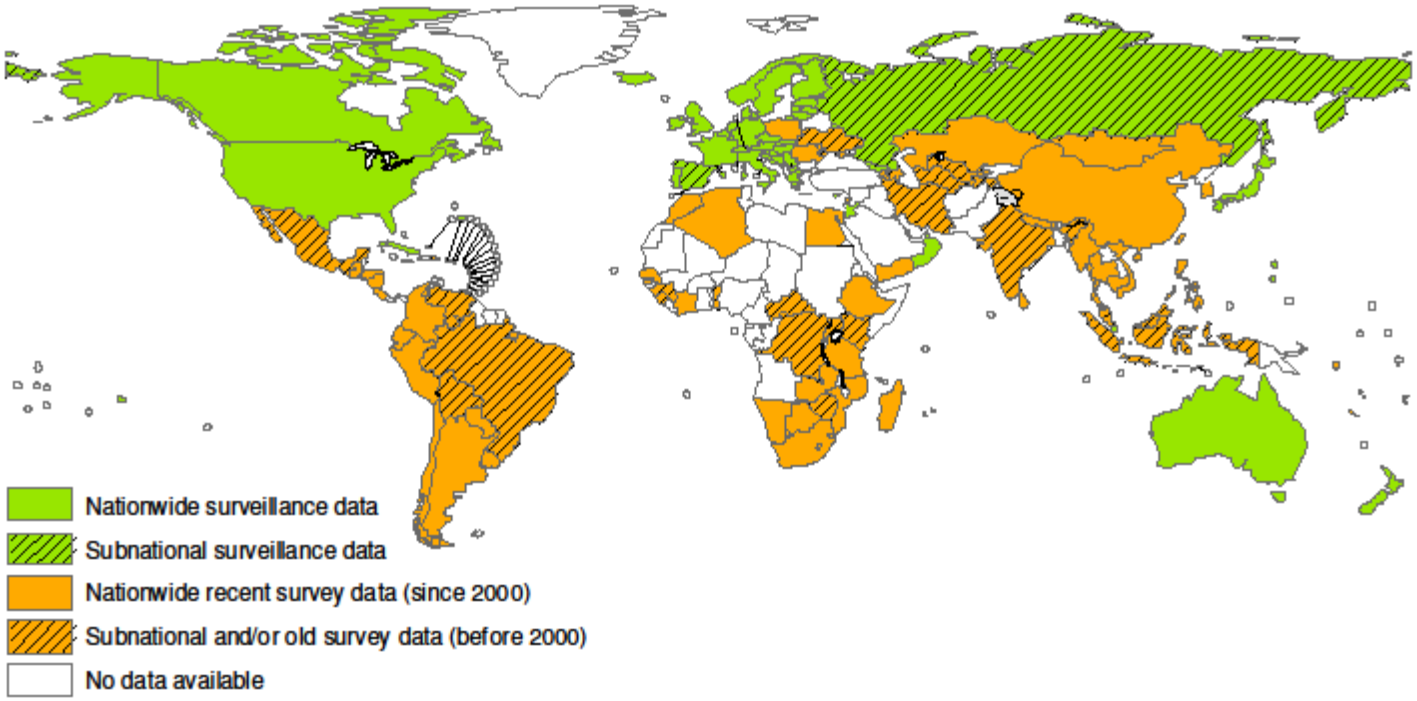


JAMA, 275, pp.300-304, 1996

Available data on anti-TB drug resistance, 2010

World Health Organization

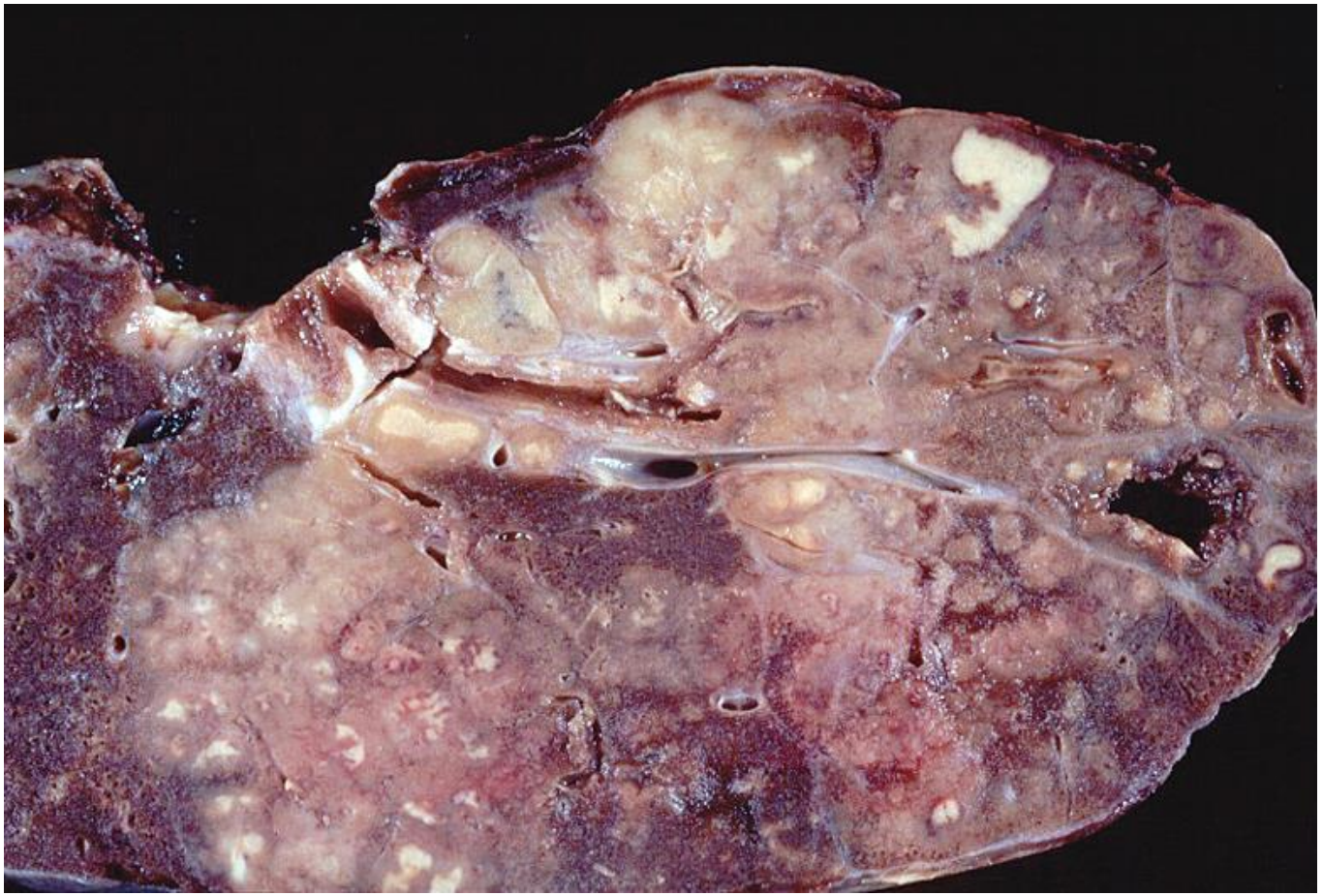
THE STOP TB DEPARTMENT



The Statistics for *Mycobacterium tuberculosis (Mtb)*

TB kills approximately one person every 20 seconds — nearly 4,700 people every day, or 1.7 million in 2009 alone, according to the latest estimates from the World Health Organization World Health Organization (WHO). TB is second only to HIV as the leading infectious killer of adults worldwide. It is among the three greatest causes of death of women aged 15-44 and is the leading infectious cause of death among people with HIV/AIDS.

The Effects of *Mycobacterium tuberculosis (Mtb)*



TB is Global

The WHO estimates that two billion people — one third of the world's population — are infected with *Mycobacterium tuberculosis* (*Mtb*), the bacillus that causes the disease. *Mtb's* unique cell wall, which has a waxy coating primarily composed of mycolic acids, allows the bacillus to lie dormant for many years. The body's immune system may restrain the disease, but it does not destroy it. While some people with this latent infection will never develop active TB, five to 10 percent of carriers will become sick in their lifetime.

Drug Resistant TB is a Growing, Deadly Threat

Extensively Drug Resistant TB (XDR-TB) is emerging as an ominous global health threat. The World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) have now identified XDR-TB cases in all regions of the world, and global health authorities have launched an intensive response to escalating global TB resistance. XDR-TB treatment is extremely complicated, with some strains virtually untreatable with current medicines.

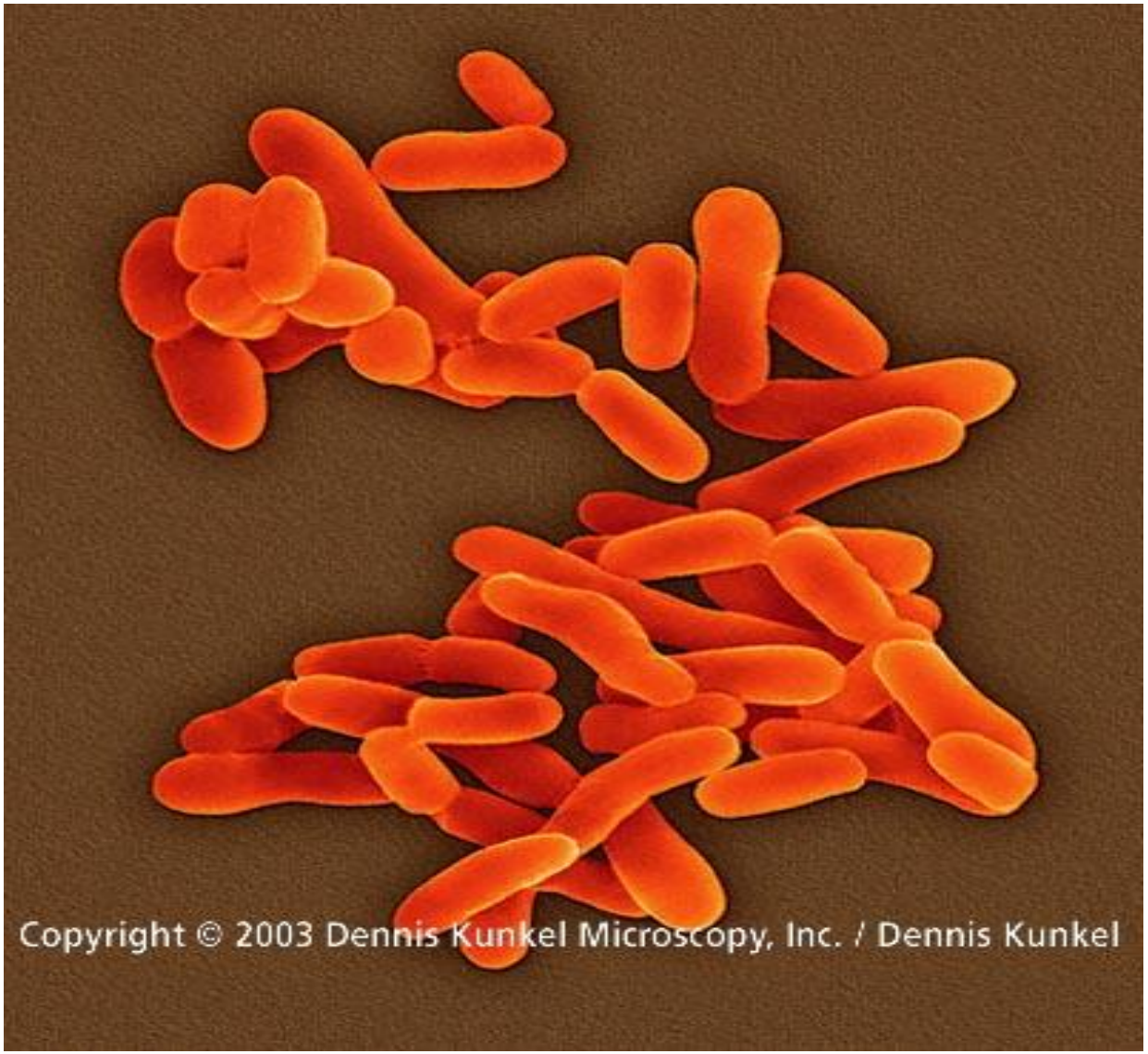
Superbugs Increasing Rapidly - Cost US $5 Billion a Year

WASHINGTON (Reuters) - Virtually all strains of the common staph bacterium are now resistant to penicillin, other bugs are rapidly developing drug-resistant forms, and the costs are skyrocketing, disease experts said Thursday.

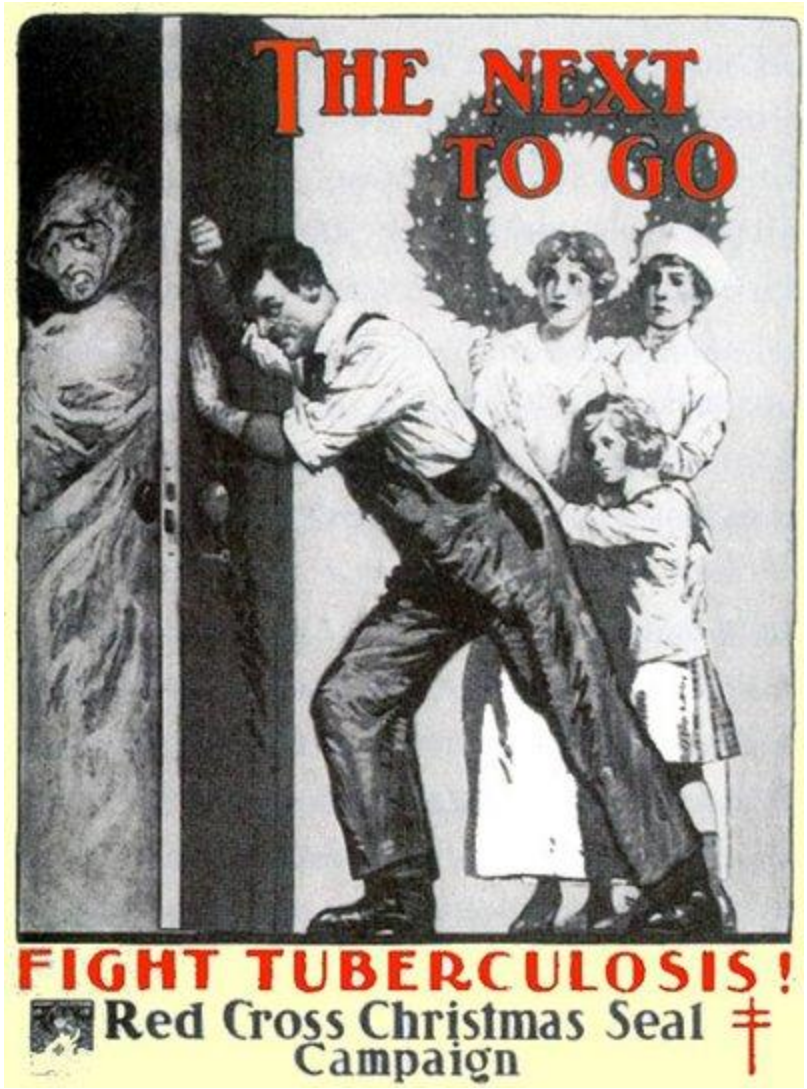
"This is a global public health problem."
Dr. James Hughes, Assistant Surgeon General and Director of the National Center for Infectious Diseases at the Centers for Disease Control and Prevention (CDC).

Early Ideas on Controlling Infectious Disease

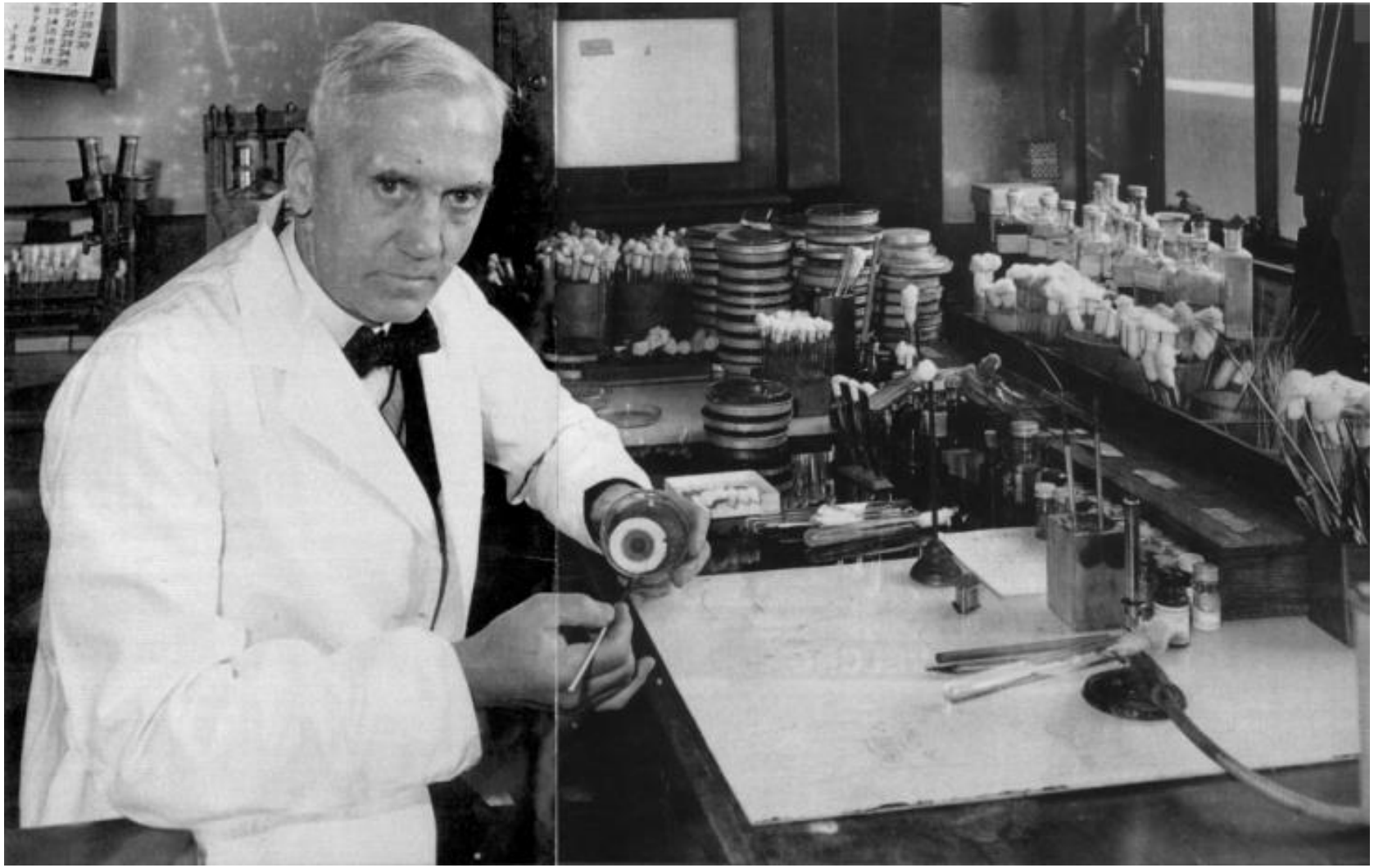
A Closeup Shot of *Mycobacterium tuberculosis*



Pre WW II Poster advertising Penicillin against TB



Alexander Fleming Introduces the World to Penicillin



Fleming's Culture of *Penicillium Notatum*

The Penicillins: The First Class of β-Lactam Antibiotics

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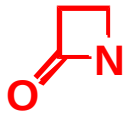

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a "beta-lactam"

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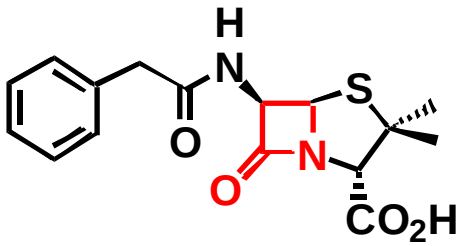

penicillin G (USA)

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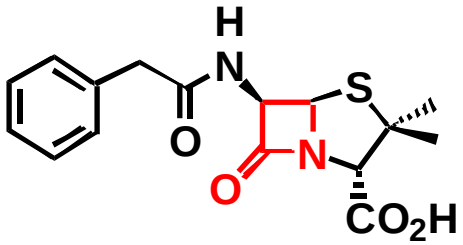

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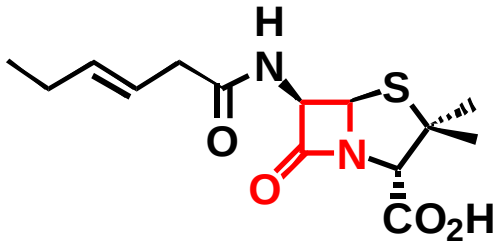
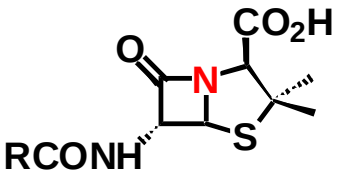
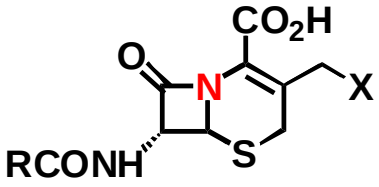


penicillin F (Great Britain)

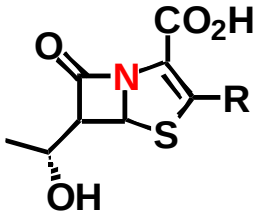
Common Classes of β-Lactam Antibiotics



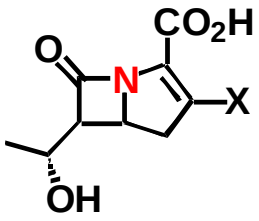
penicillins



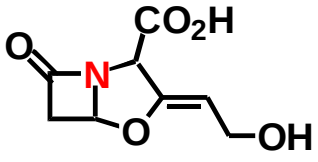
cephalosporins



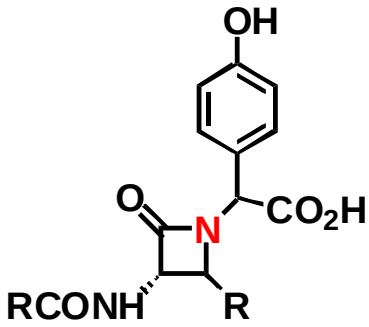
penems



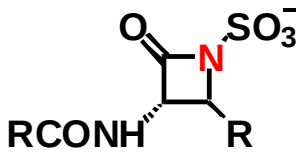
carbapenems



clavulanic acids

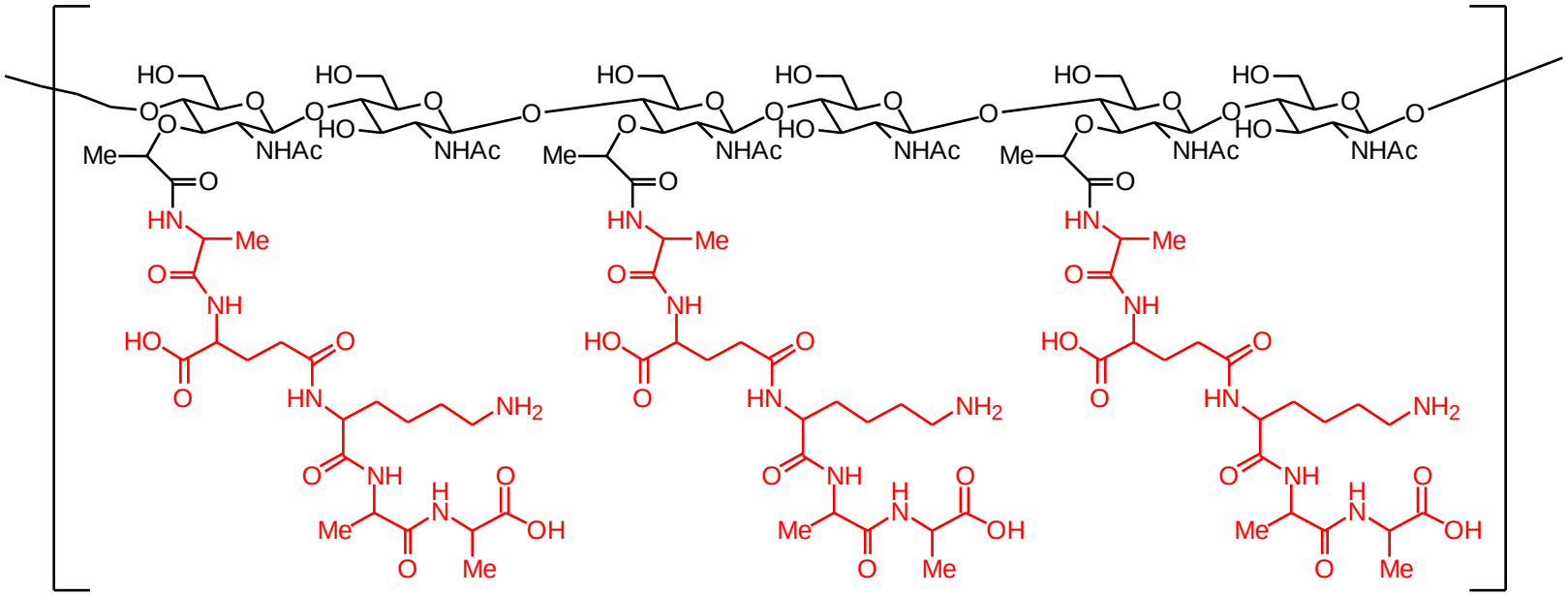


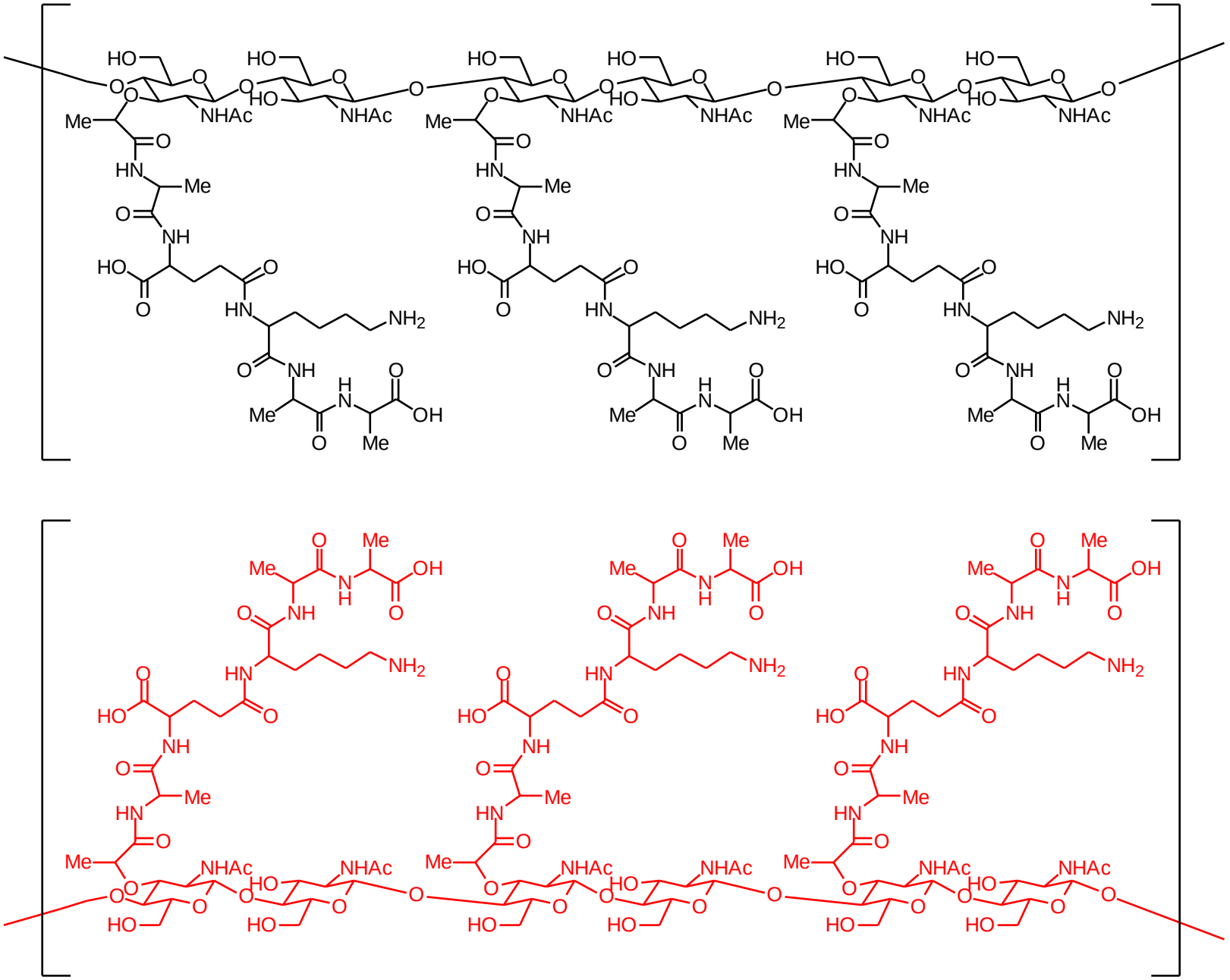
nocardicins

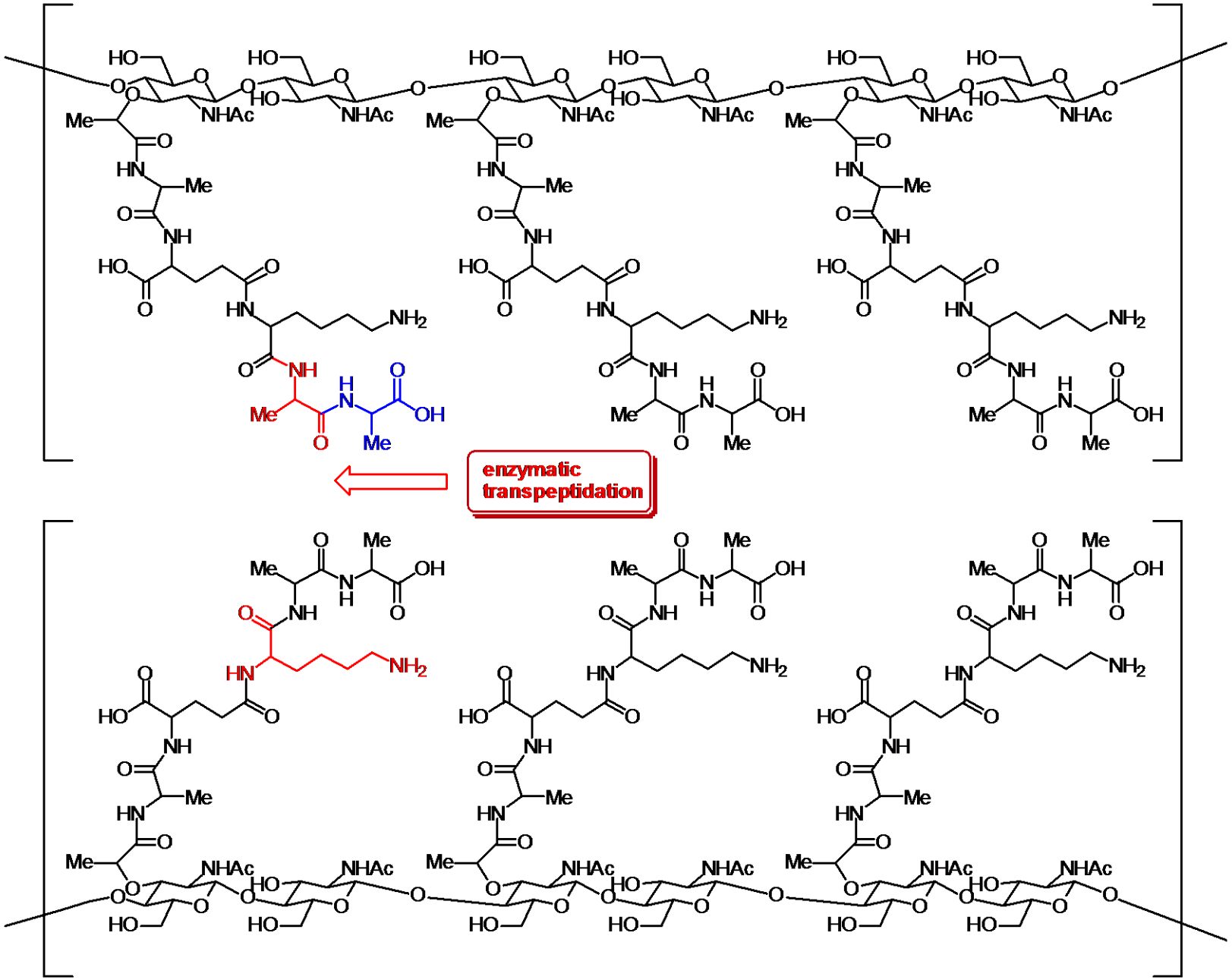


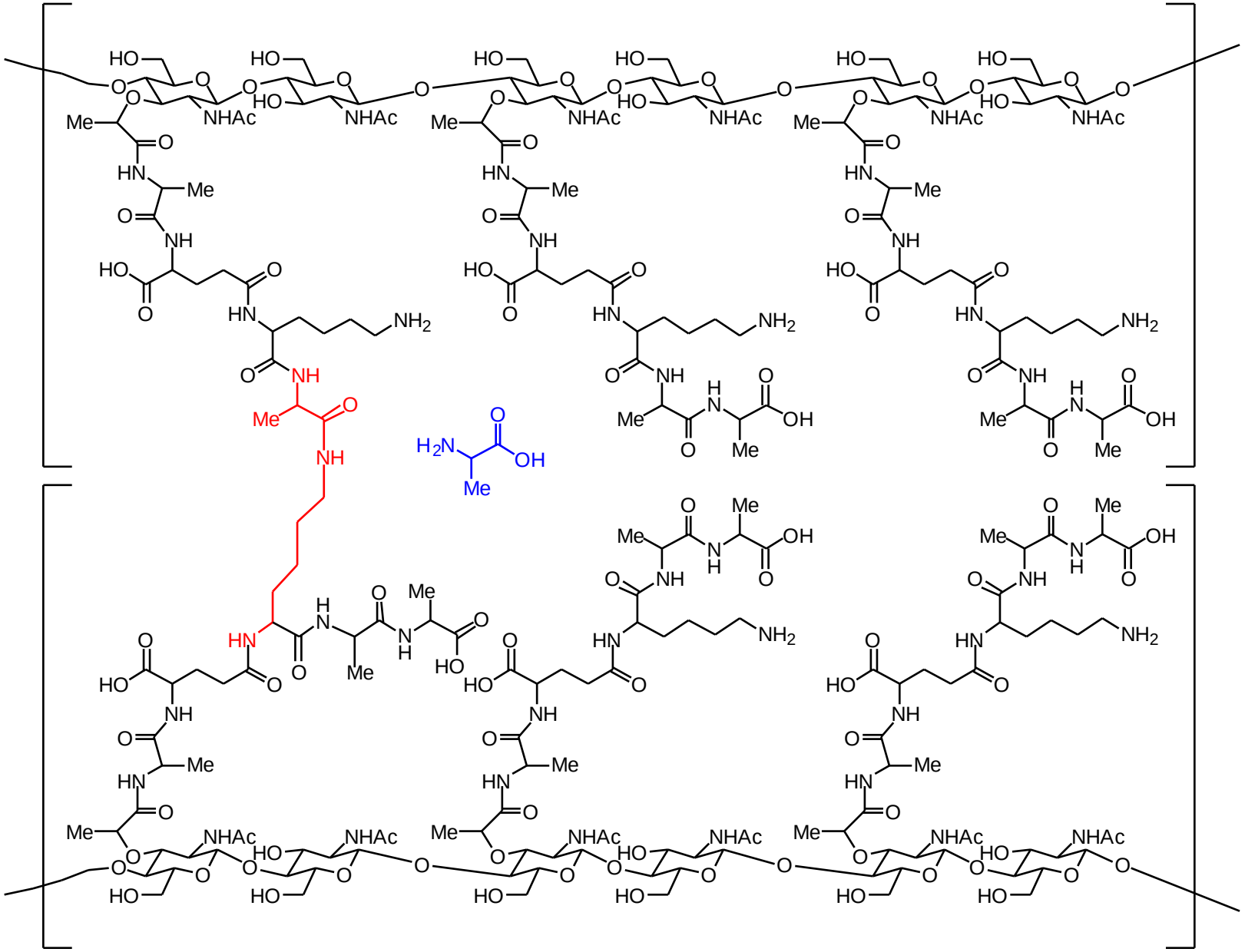
monobactams

Chemical Structure of the Bacterial Cell Wall

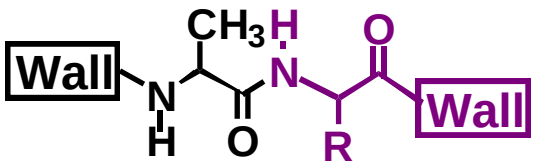




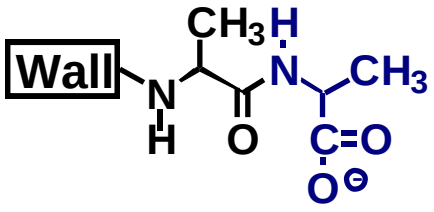

enzymatic
transpeptidation

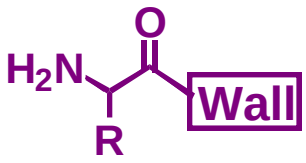


How is the Cell Wall Built?

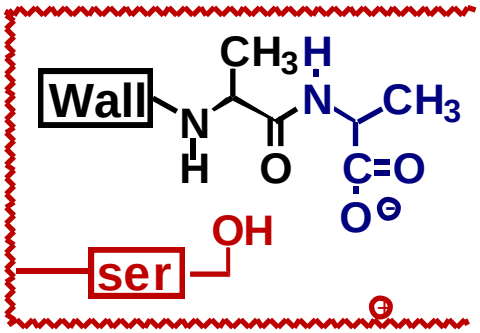


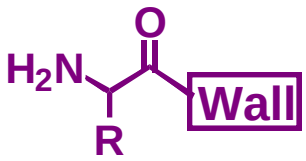
From the Coupling of Two Separate Pieces





Mechanism of Enzymatic Transpeptidation





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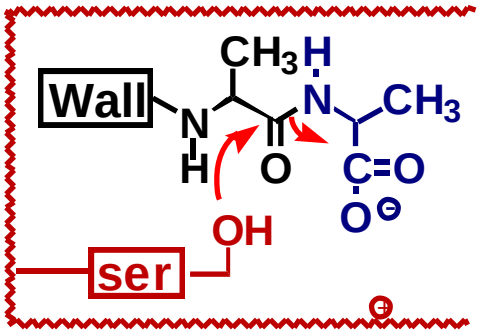

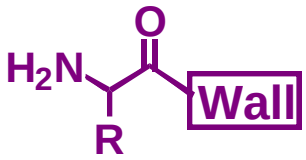

The enzyme usesa serine nucleophile to cleave the alanine-alanine amide bond

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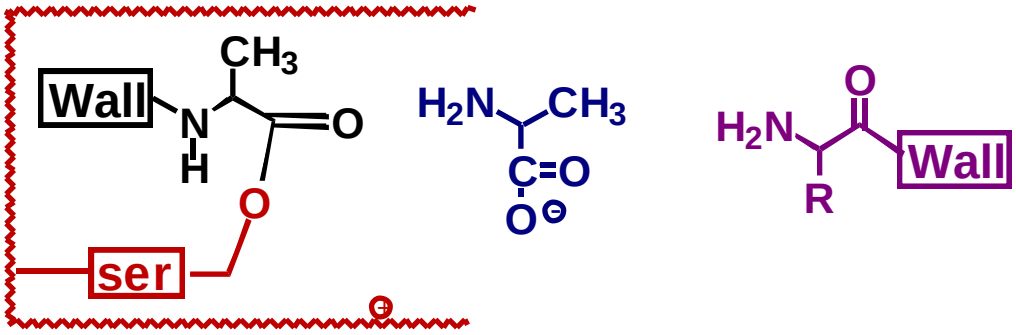

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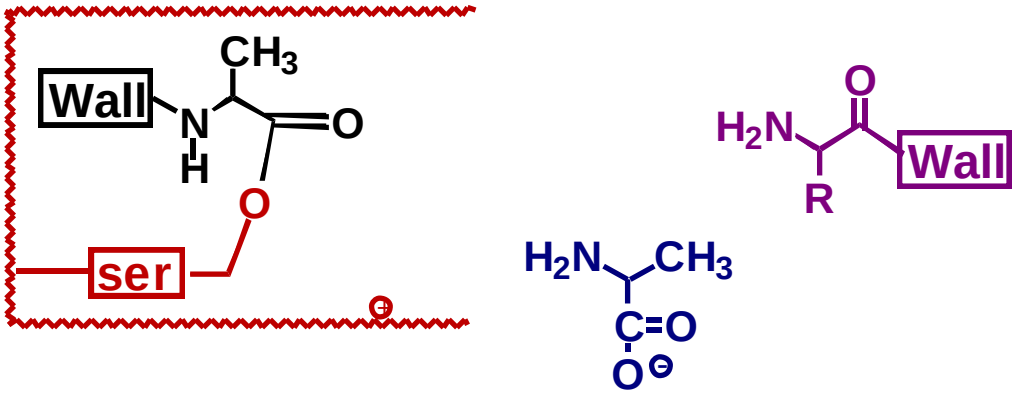

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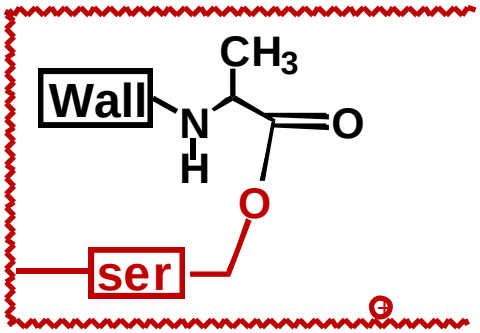

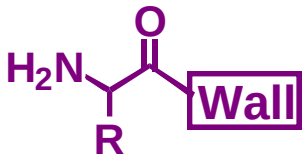

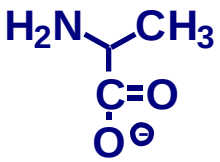

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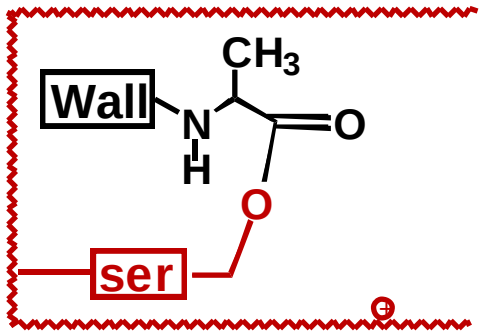
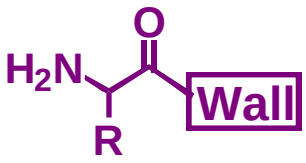
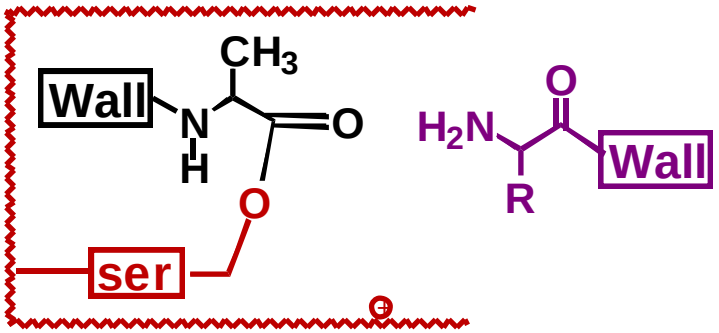




Second strand of wall now enters active site

Mechanism of Enzymatic Transpeptidation



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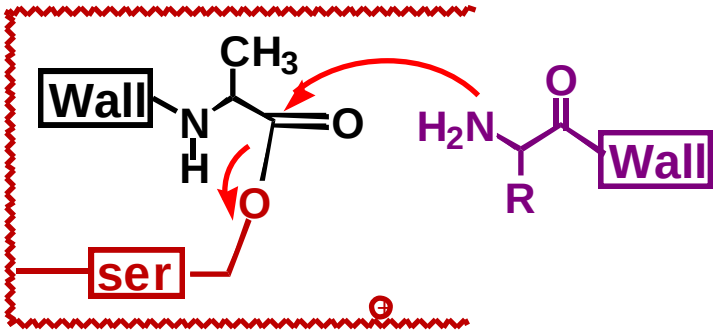

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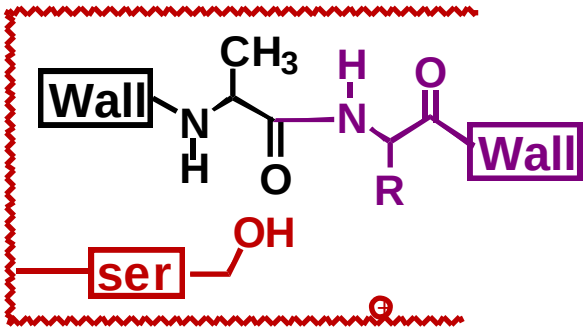

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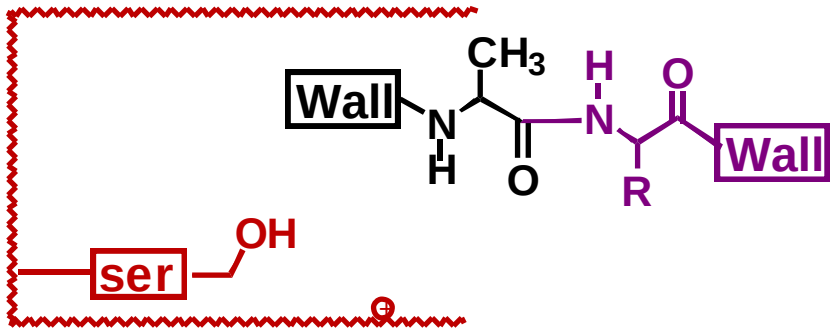

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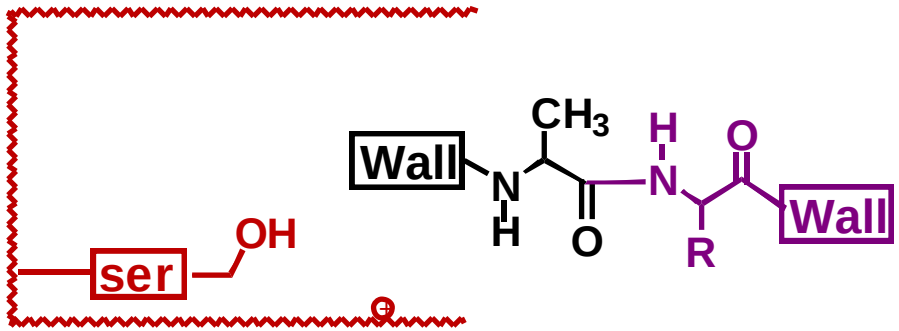

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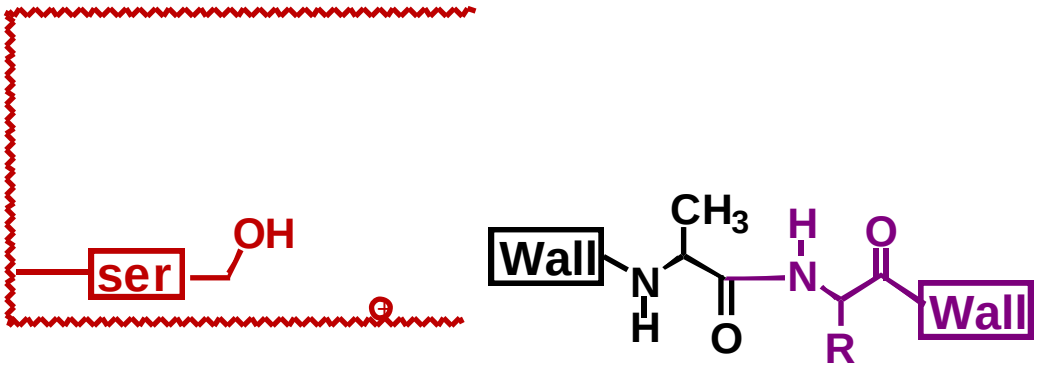
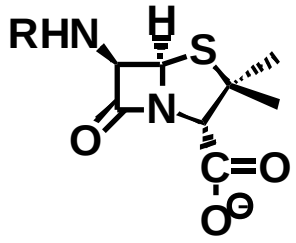
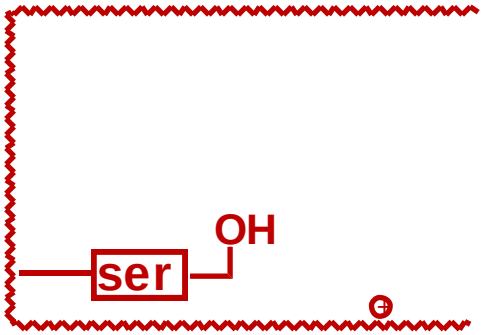
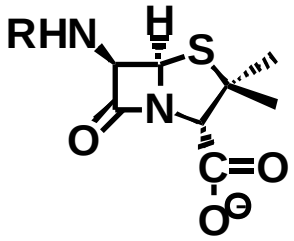


Penicillin's Mechanism of Action

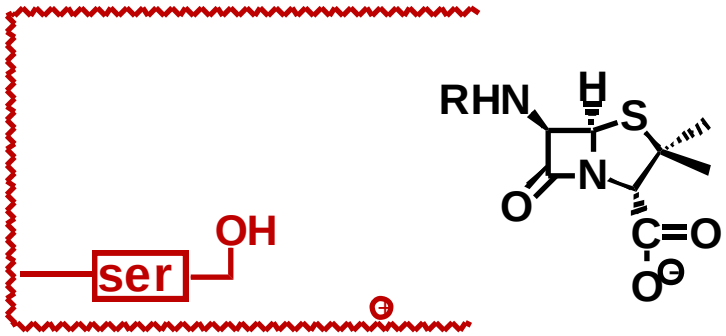


Penicillin's Mechanism of Action

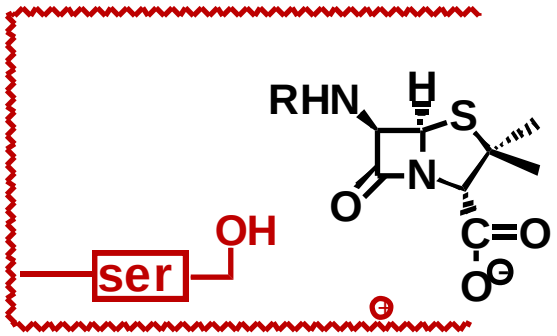




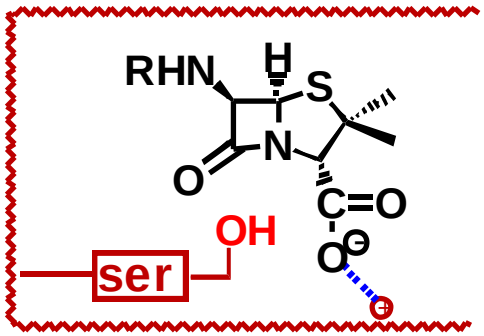
Penicillin's Mechanism of Action



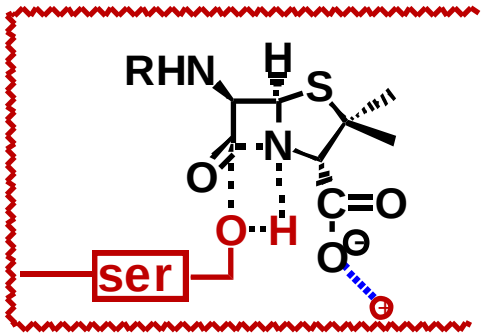
Penicillin's Mechanism of Action



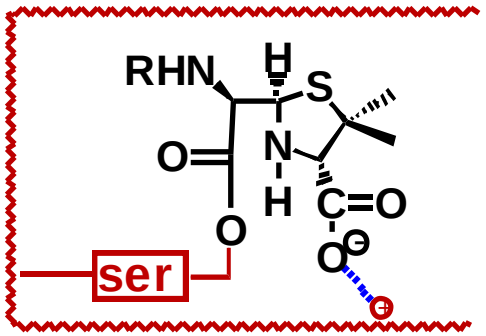
Penicillin's Mechanism of Action



Penicillin's Mechanism of Action



Penicillin's Mechanism of Action



death of bacterium

What is a drug-resistant infection?

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An infection that can not be easily treated with conventional antibiotics

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Reasons:

Natural resistance to new drugs

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Reasons:

- **Natural resistance to new drugs**
- **Man-made resistance to old drugs**

What Causes Drug Resistance?

Bacterial resistance to β-lactam drugs is due to the production of beta-lactamases

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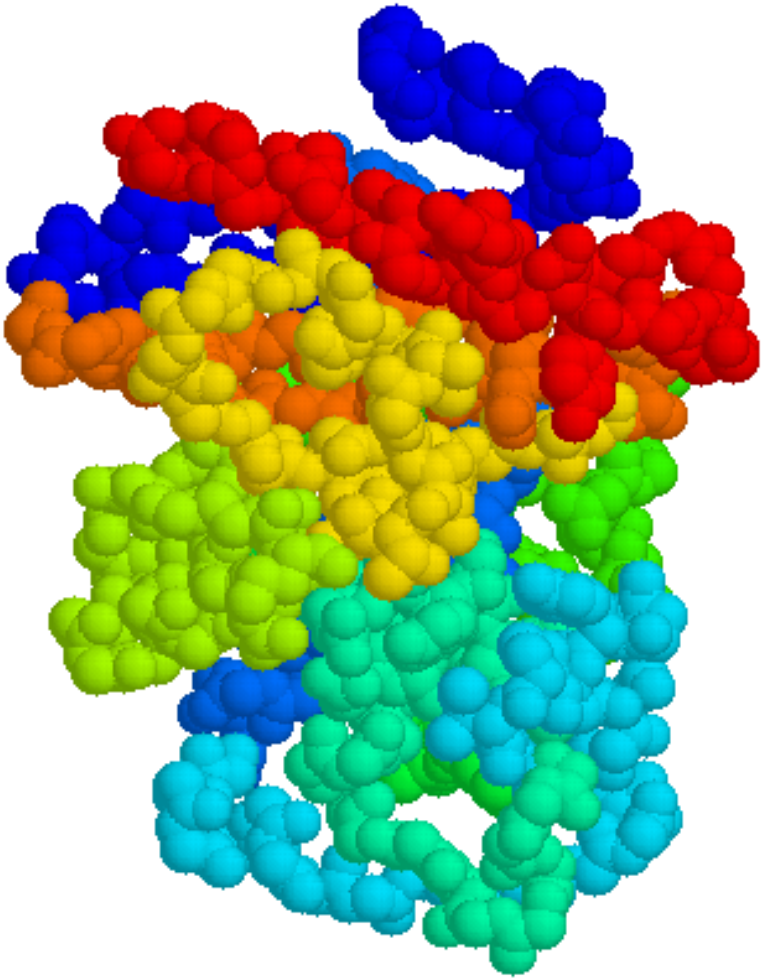
Bacterial resistance to β-lactam drugs is due to the production of beta-lactamases

To be effective, the drug must find a way to avoid being destroyed by these "warrior" proteins

β-Lactamase: A Protein That Destroys Penicillin



Drug Resistance in the '90's

Antibiotic resistance known since the 1940's

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Rate of resistant bacterial infections accelerated during the 1980's

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Effectiveness of most drugs has been significantly compromised

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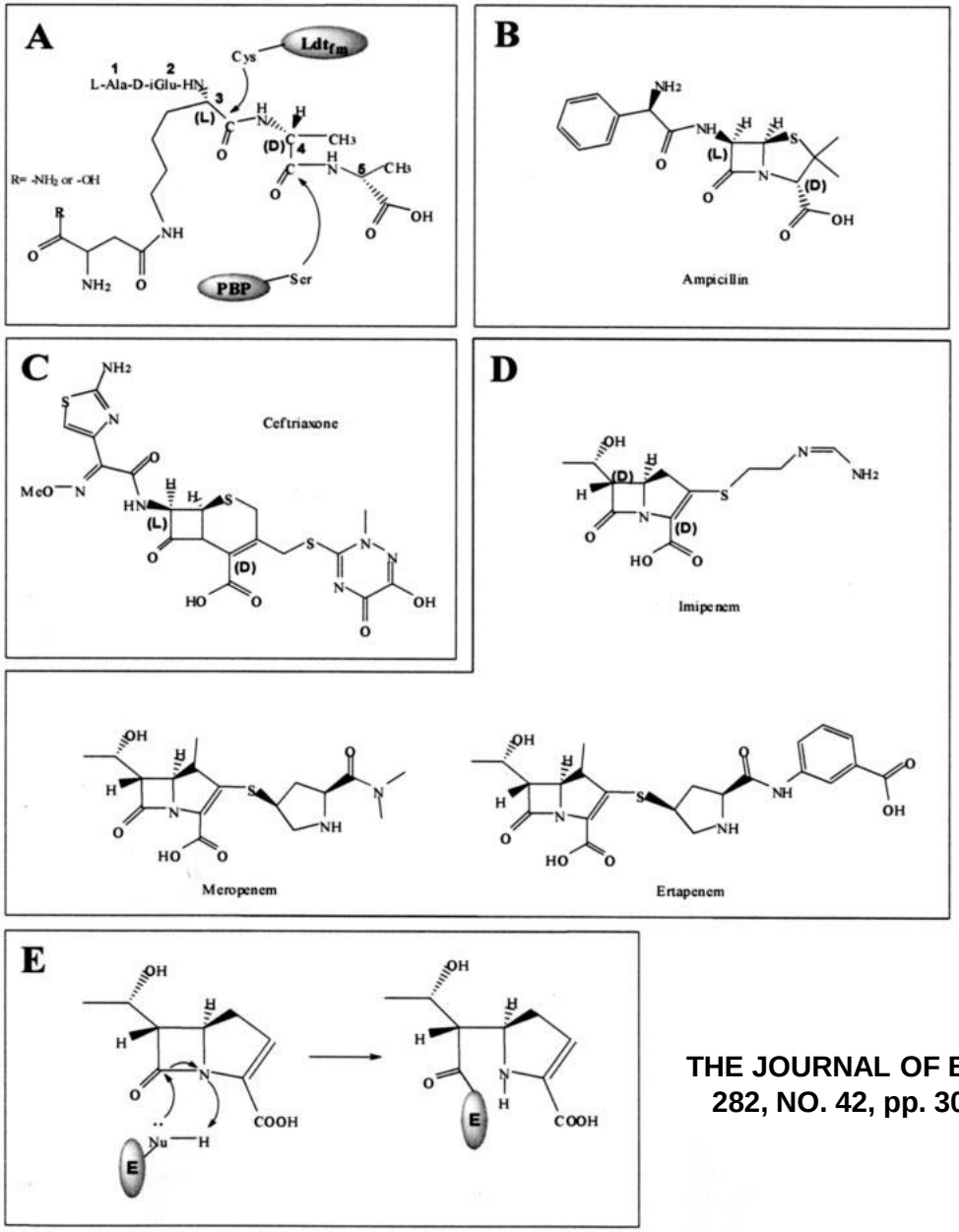
Rate of resistant bacterial infections accelerated during the 1980's

Effectiveness of most drugs has been significantly compromised

Need new antibiotics to combat drug resistance

Drug Resistance in 2000's
L, D-Transpeptidases as a "Plan B" Pathway of bacteria

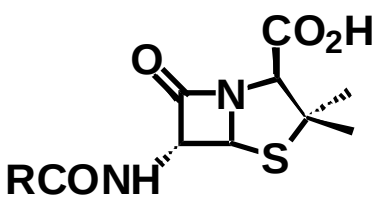


THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 282, NO. 42, pp. 30414–30422, October 19, 2007

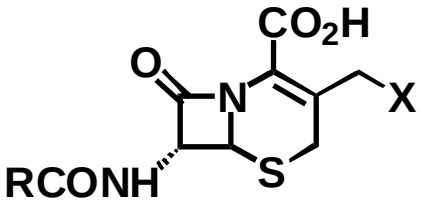
Outline

- Drug Resistance and Challenges for Drug Discovery
- Synthesis and Biological Evaluation of Novel Monocyclic β-Lactams

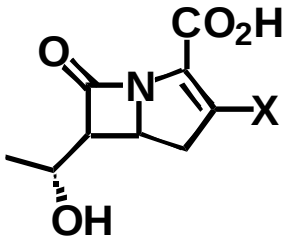
Common Classes of β-Lactam Antibiotics



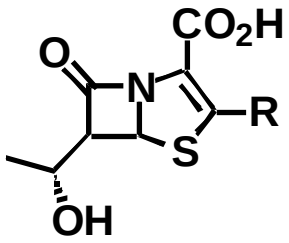
penicillins



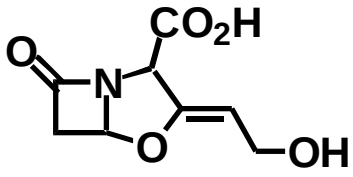
cephalosporins



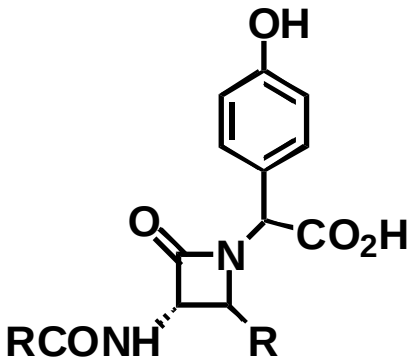
carbapenems



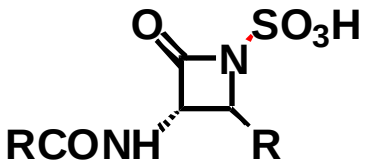
penems



clavulanic acids

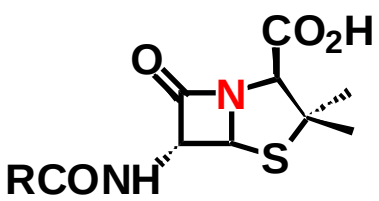


nocardicins

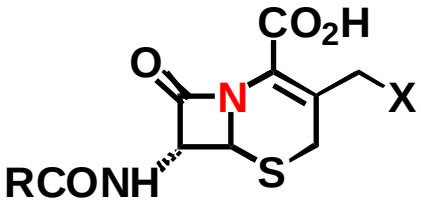


monobactams

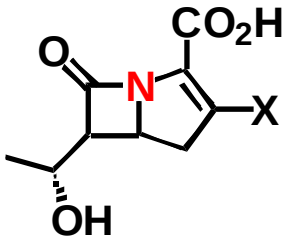
Common Classes of β-Lactam Antibiotics



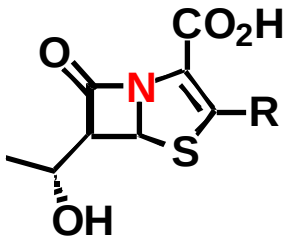
penicillins



cephalosporins



carbapenems



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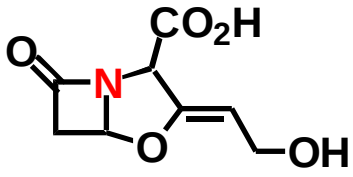
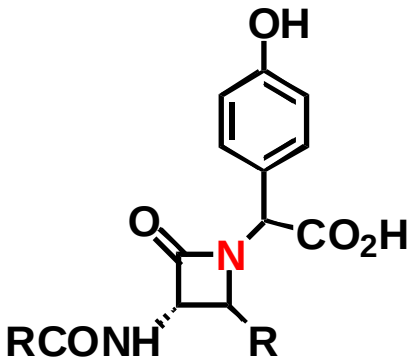


clavulanic acids



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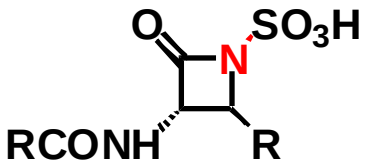
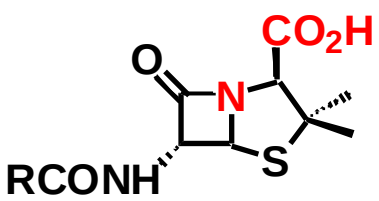
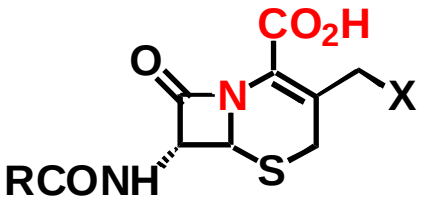


monobactams

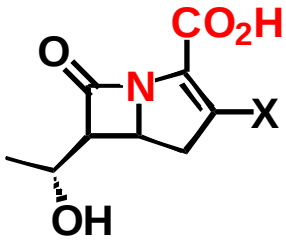
Common Classes of β-Lactam Antibiotics



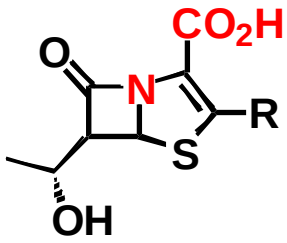
penicillins



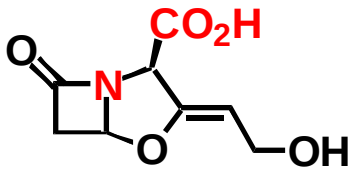
cephalosporins



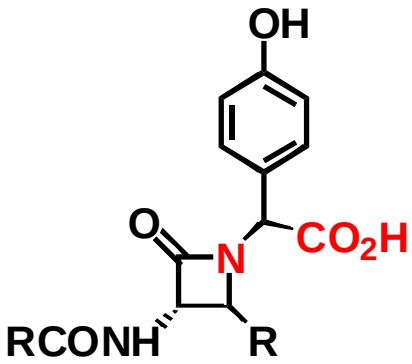
carbapenems



penems



clavulanic acids



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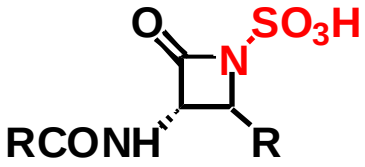
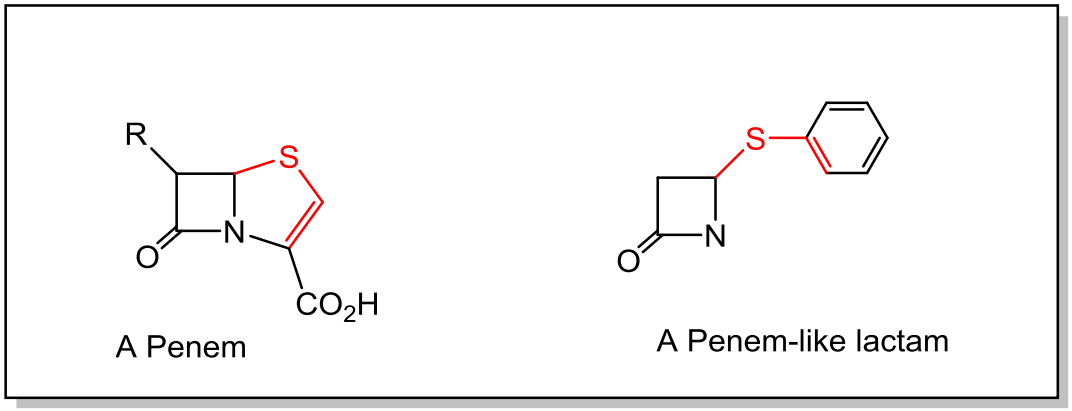
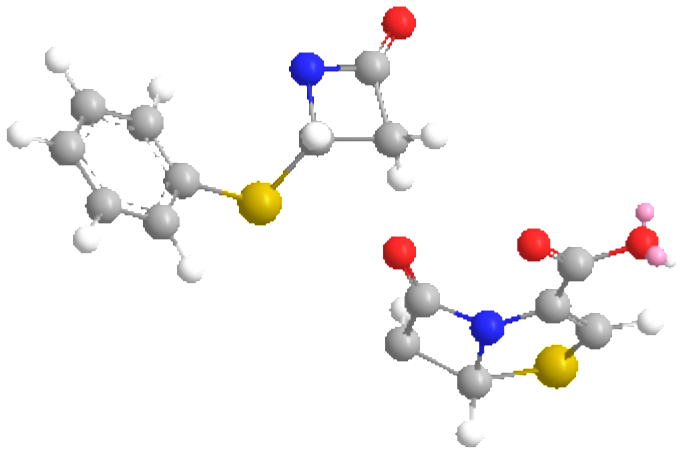
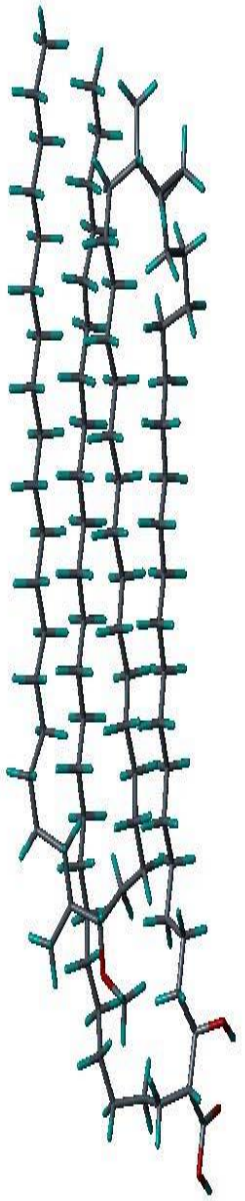


monobactams

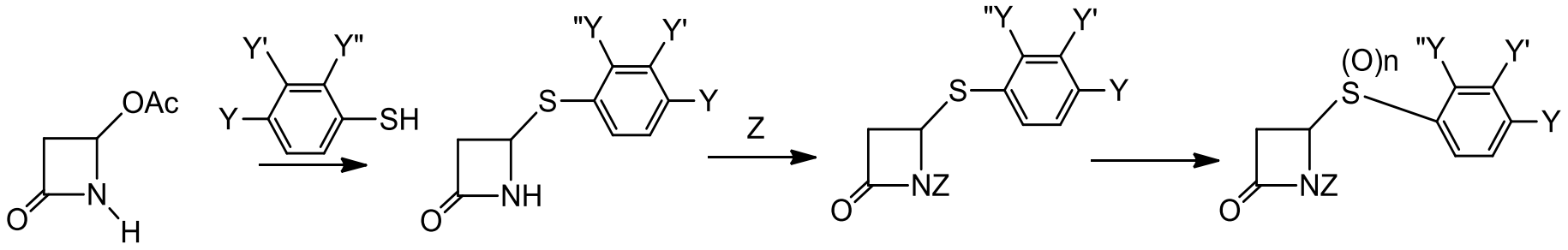
Design of penem-like β-Lactams







Synthesis of non-transpeptidase β-Lactams



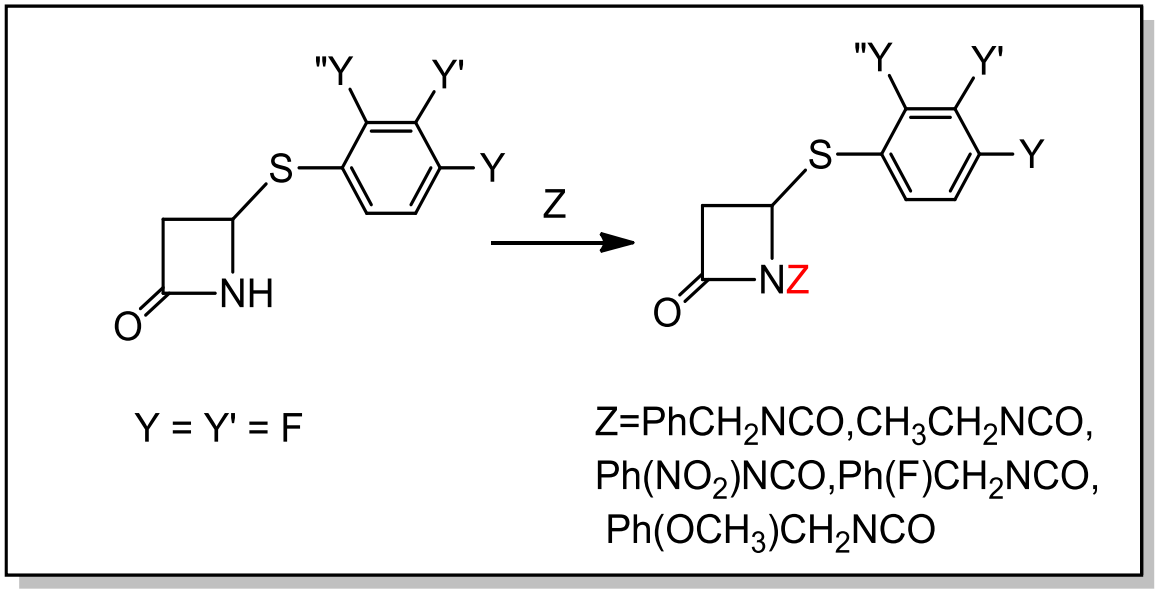
Y= Y' = H, Y" = F, CF_3, NO_2, CO_2H,
Y = Y" = H, Y' = F, CF_3, NO_2, CO_2H
Y = Y' = Y" = F

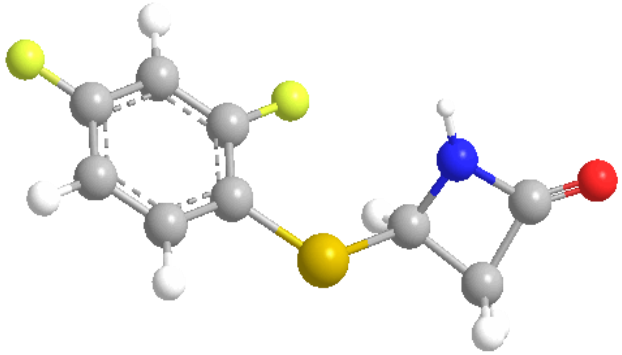
Z = $PhCH_2NCO$

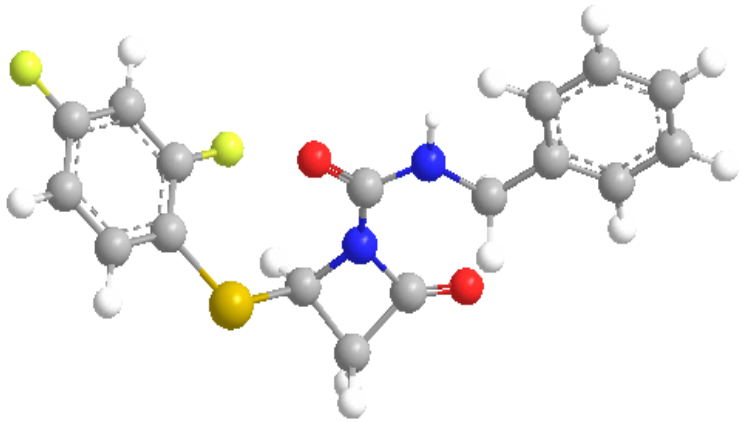
n = 0, 1 or 2

Synthesis of *N*-substituted C4 arylthio-β-lactams.

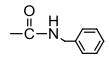
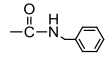
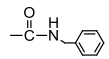
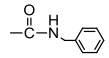
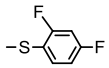
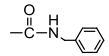
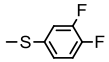
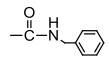
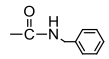
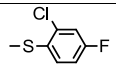
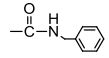
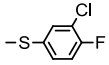
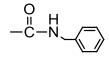
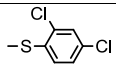
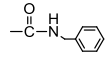
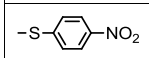
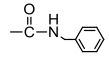
Synthesis of differently substituted at the lactam Nitrogen β-Lactams

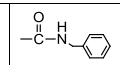
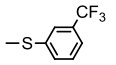
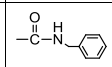
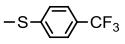
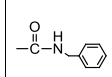
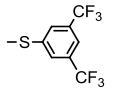
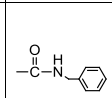
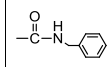
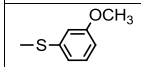
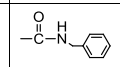
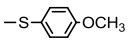
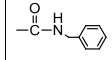
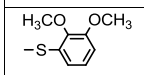
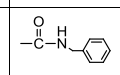
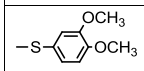
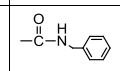






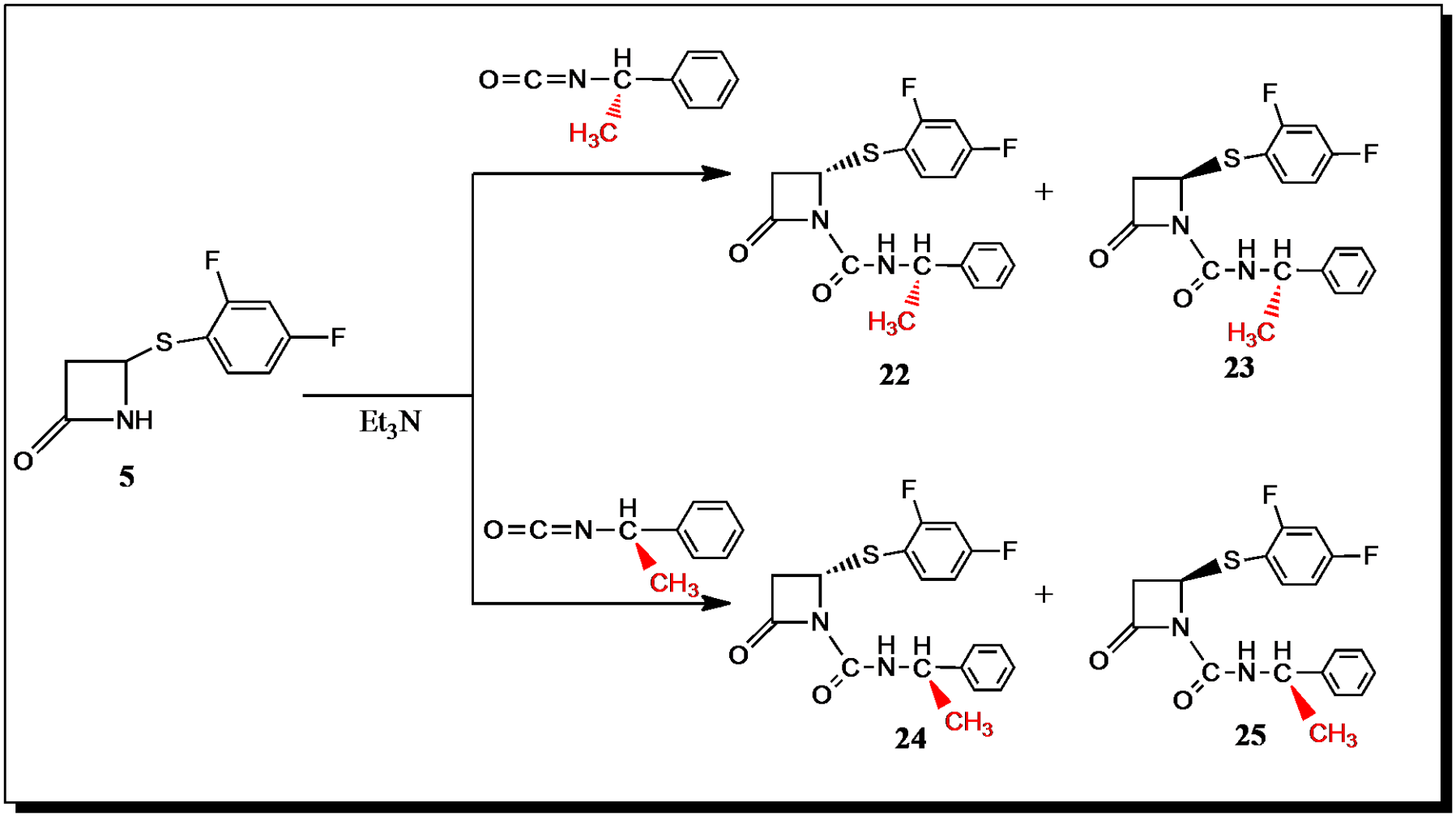
Synthesis of non-transpeptidase β-Lactams

R1[b]	#	R2	M.cat.[a] MIC/MBC µg/ml	Mtb w/out and with/clav. µg/ml	#	R2	M.cat. MIC/MBC µg/ml	Mtb w/out and with/clav. µg/ml
	**2**	H	>200	25/25	**30**		12.5/12.5	6.25/6.25
	**3**	H	200	25	**31**		25/50	3.125/3.125
	**4**	H	>200	100/25	**32**		25/100	NT
	**5**	H	>200	>100/25	**33**		25/25	6.25/6.25
	**6**	H	1.5/3.1	3.125/3.125	**34**		1.625/1.625	100/12.5
	**7**	H	50/50	50/25	**35**		12.5/25	6.25/6.25
	**8**	H	1.5/1.5	>100	**36**		3.1/6.25	>100
	**9**		12.5/50	NT yet	**37**		12.5/25	NT yet
	**10**		12.5/25	Nt yet	**38**		6.25/6.25	Nt yet
	**11**		6.25/6.25	Nt yet	**39**		3.13/6.25	Nt yet
	**12**	H	6.25/12.5	25/25	**40**		3.125/25	25/25

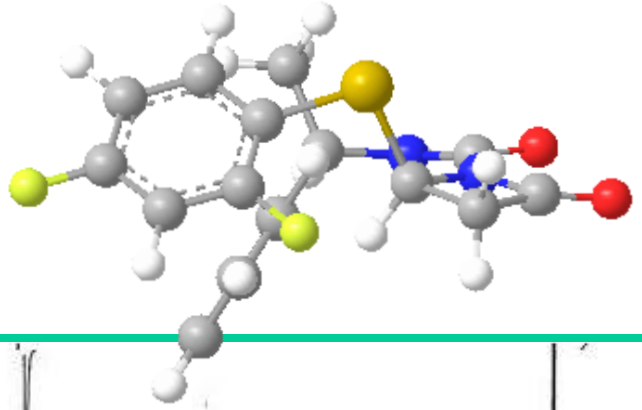
	**13**	H	1.5/1.5	≥100	**41**		25/25	125
	**14**	H	200	6.25/12.5	**42**		3.125/6.25	25/6.25
	**15**	H	100/100	12.5/6.25	**43**		1.625/12.5	12.5/6.25
	**16**	H	12.5/100	>100	**44**		6.25/6.25	6.25/25
	**17**	H	100/>200	250/>250	**45**		200/200	125-250
	**18**	H	100/>200	>100	**46**		200/200	100
	**19**	H	200/>200	100	**47**		200/200	125
	**20**	H	100/>200	250	**48**		100/200	50
	**21**	H	200/200	250	**49**		200/>200	250
	22	H	25/100	6.25/12.5	**50**		50/100	6.25/6.25
	23	H	100/100	>100	**51**		NE	>100
	24	H	100/>200	>250	**52**		200/>200	>100

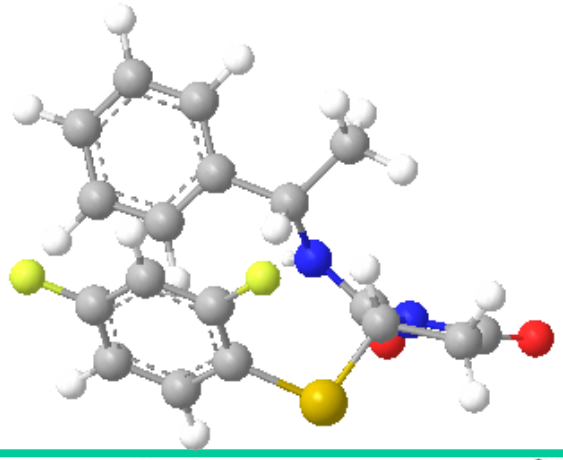
Non-transpeptidase binding arylthioether beta-lactams active against Mycobacterium tuberculosis and Moraxella catarrhalis. Konaklieva, M. et.al., ***Bioorg. And Med. Chem*. 2015, 23, 632-647**

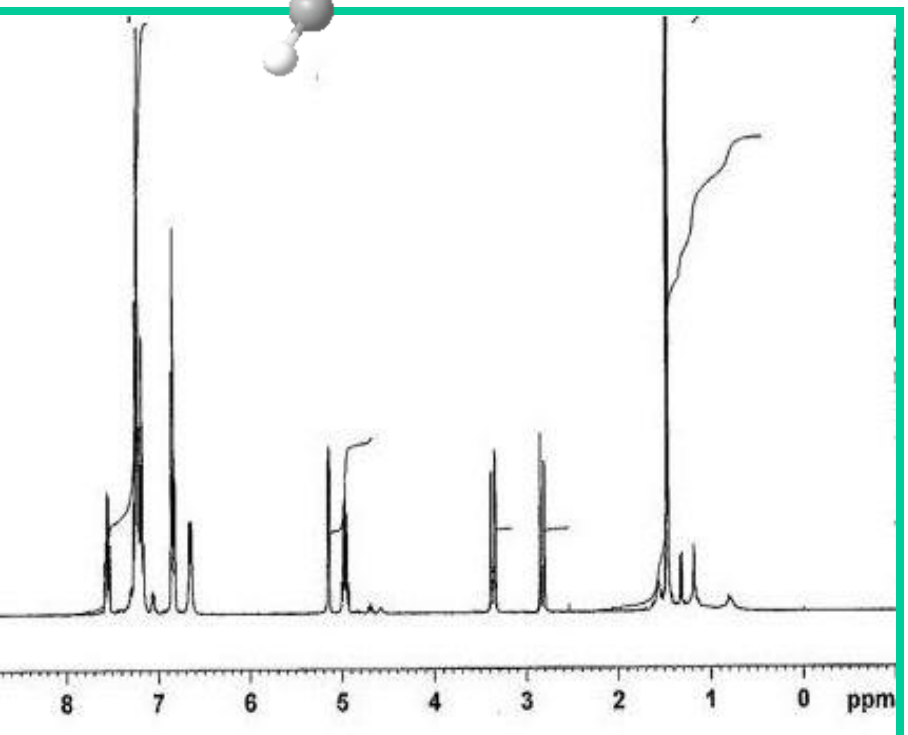
Synthesis of chiral β-Lactams

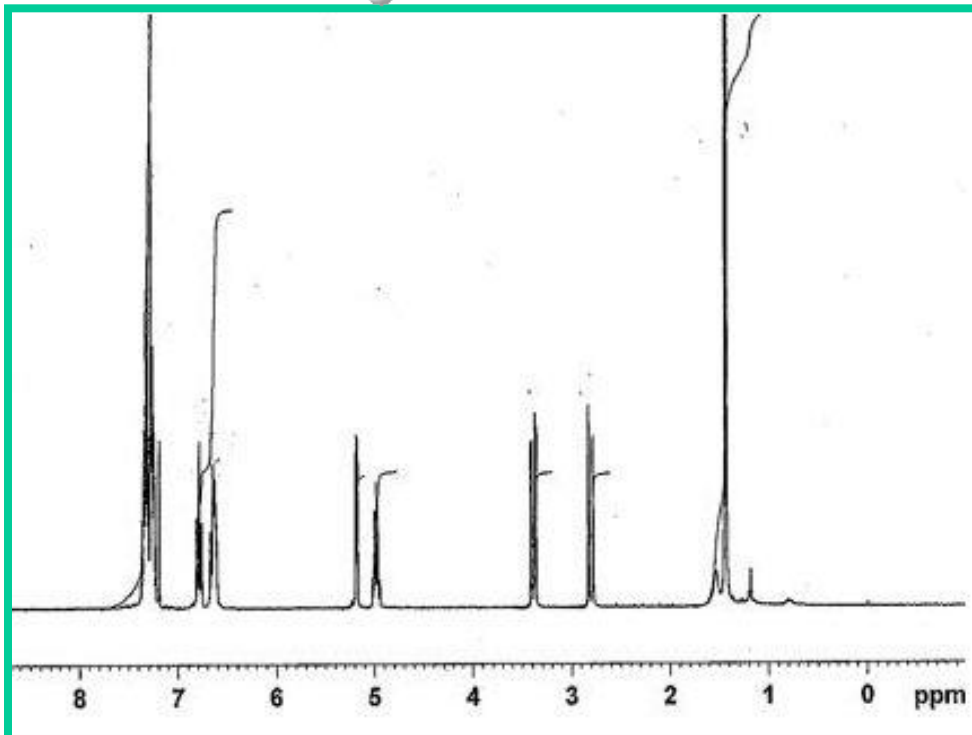


Purification of chiral β-Lactams

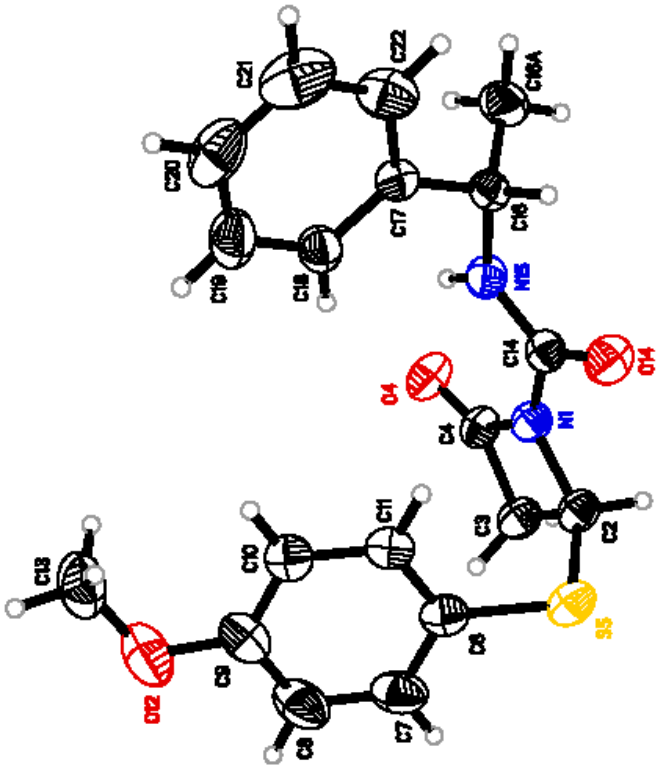








One of the pure diastereoisomers with determined, by X-ray analysis, absolute configuration: C2*S*, C16*S*



Minimal inhibitory concentrations in different media

S. No.	Compound name	7H9 (ug/ml)	GAST Fe (ug/ml)
		Day 14	Day 18
1	RK1	>100	0.19-0.39
2	RK2	100	<0.19
3	RK5	25	<0.19
4	RK6	12.5	<0.19
5	KL04	50-100	0.39
6	KL08	25	0.39-0.78
7	JF3	100	0.78
8	CM01	25	0.78
9	CM02	25	0.78
10	DL37	25-50	0.78
11	DL06	100	1.5
12	DL46	50	0.78
13	DL47	25	NG
14	RK-FITC	100	NG
15	B-lactam ring-SO-phenyl-mCF3*	25	NG
16	INH	0.07	NG

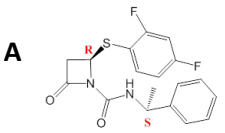
Notes:

1. Highest concentration tested was 100ug/ml for all test compounds except INH which was 10ug/ml.

2. At Day14 growth in GAST-Fe was still too low (due to higher dilution of cells than usual: 1:500 as opposed to 1:250) to effectively discern MIC hence day 18 values are reported.

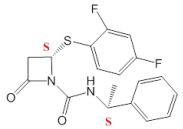
Intracellular killing of Mtb

A



(*R*)-2-((2,4-difluorophenyl)thio)-4-oxo-*N*-((*S*)-1-phenylethyl)azetidine-1-carboxamide

DL11



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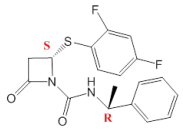
DL12



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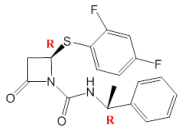
DL13



(*R*)-2-((2,4-difluorophenyl)thio)-4-oxo-*N*-((*R*)-1-phenylethyl)azetidine-1-carboxamide

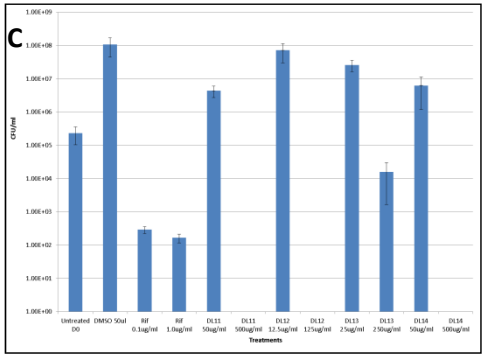
DL14

B

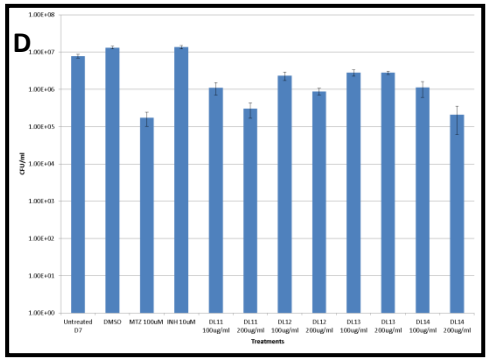
Compound	7H9 (µg/ml)		GAST/Fe (µg/ml)	
	Wk 1	Wk 2	Wk 1	Wk 2
DL11rs	25	50	NG	0.07
DL12ss	12.5	25	NG	0.03-0.07
DL13sr	25	25	ND	ND
DL14rr	50	50	NG	0.03
		Control		
INH	0.03	0.07	NG	0.015

NG: No growth ND: not determined

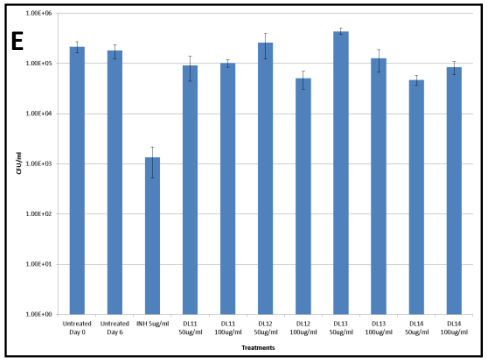
C

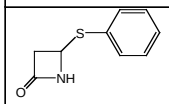
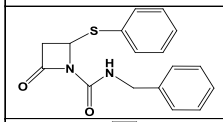
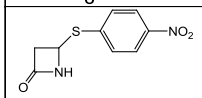
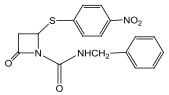
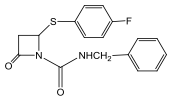
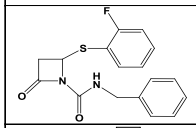
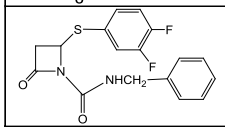


D



E



Structure	Moraxella Clinical strains MIC/MBC ug	Moraxella Clinical strains MIC/MBC µM	Mtb H37Rv Without/ With clavulanic acid µg/mL	Mtb H37Rv Without/ With clavulanic acid µM
	>200	>1000	139	>250
	12.5/12.5	40/40	6.25/6.25	20.03/20.03
	1.25-3.125/12.5	7.24-13.93/55.74	25/25	>100/>100
	3.125/100	8.74/69.95	25-50/25	70/70
	25/50	75.67/150	6.25/6.25	18.93/18.93
	25/50	75.6/150	3.125/3.125	9.47/9.47
	12.5/25	35.88/70	6.25/6.25	17.96/17.96

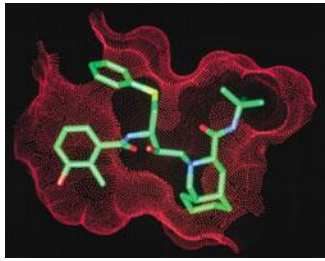
Acknowledgements

Department of Chemistry
American University

Synthesis
Tim Beck
Dina Lloyd
Rostislav Kuskovsky
Jeanette Minah
Juliana Fritz
Victor Schultz
Steven Moss
Susan Schultz
Klare Lazor
Carly Montanero
Moira Esson

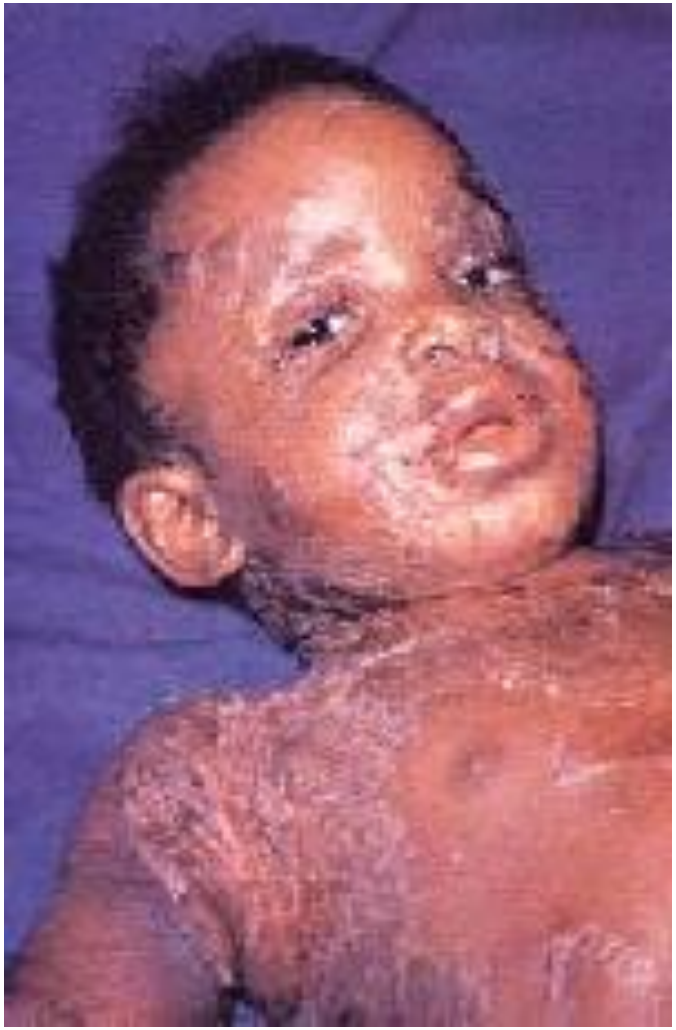
Collaborations
Clifton Barry, III (TRS, NIH)
Helena Boshoff (TRS, NIH)
Kriti Arora (TRS, NIH)
Balbina Plotkin, Ph.D. (MWU)

The Lawn in front of Beeghly building, Chemistry Department, AU Summer 2010

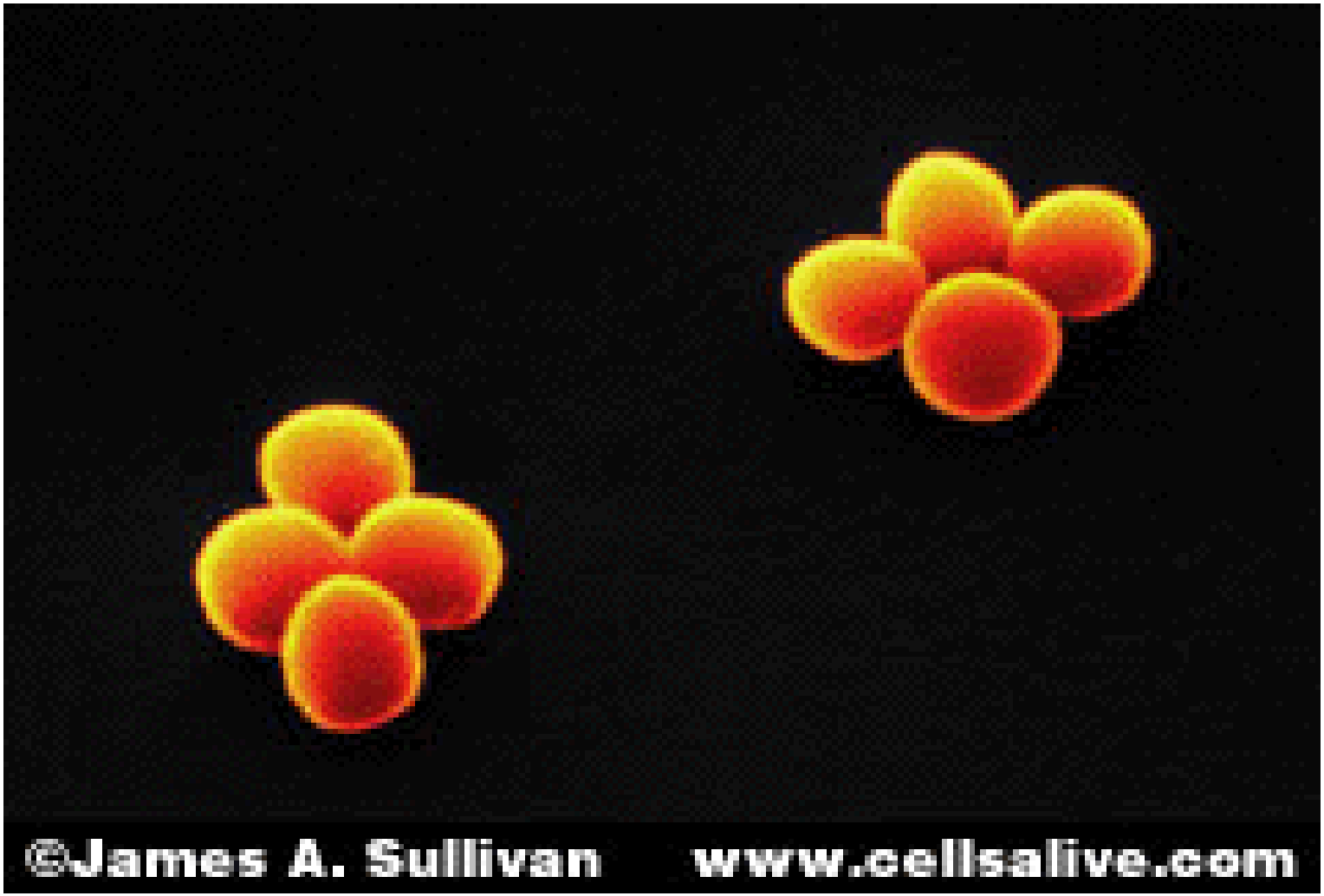


Synthesis and Characterization of Biologically Active Molecules

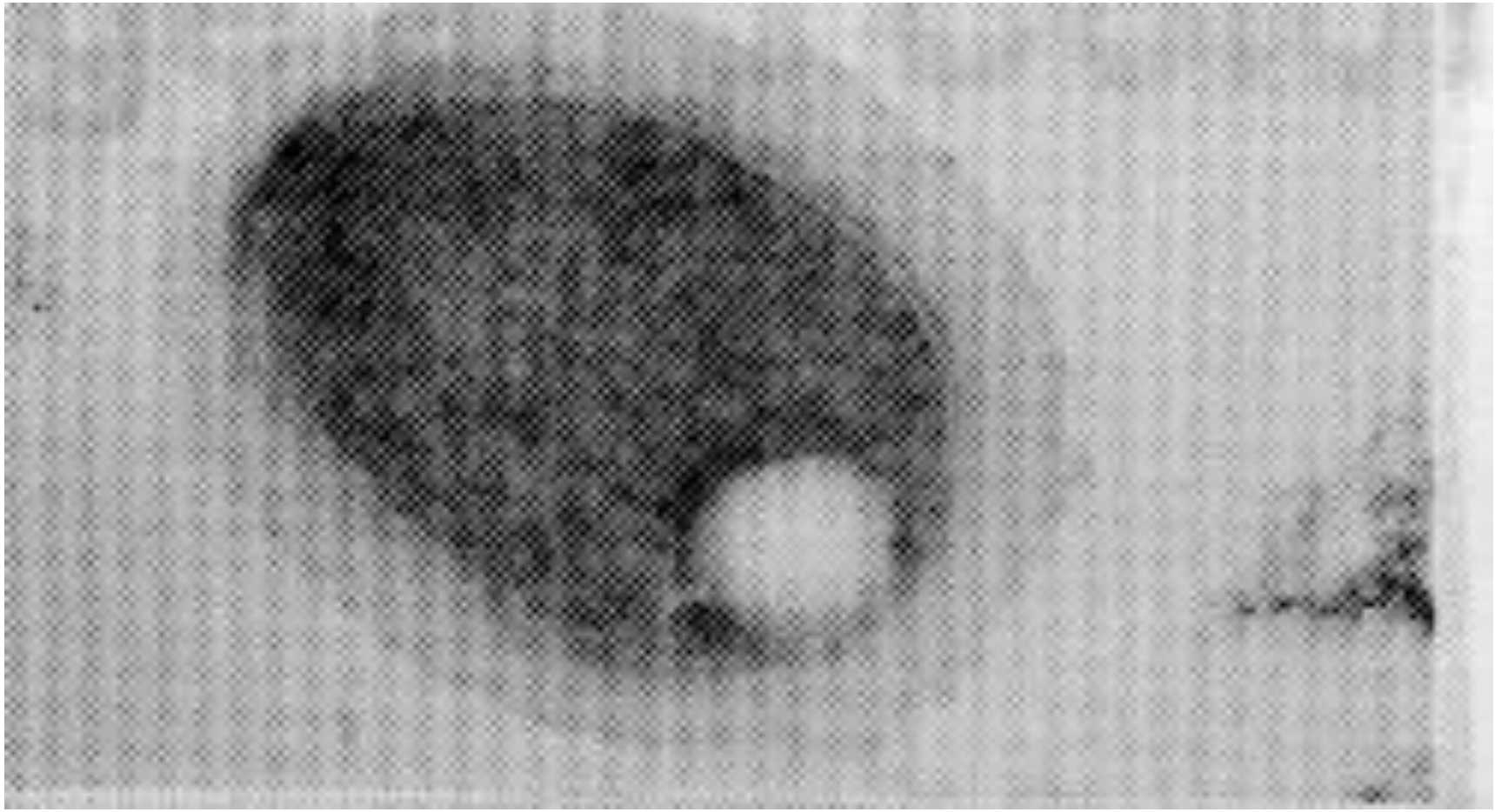
The Effects of *Staphylococcus Aureus*



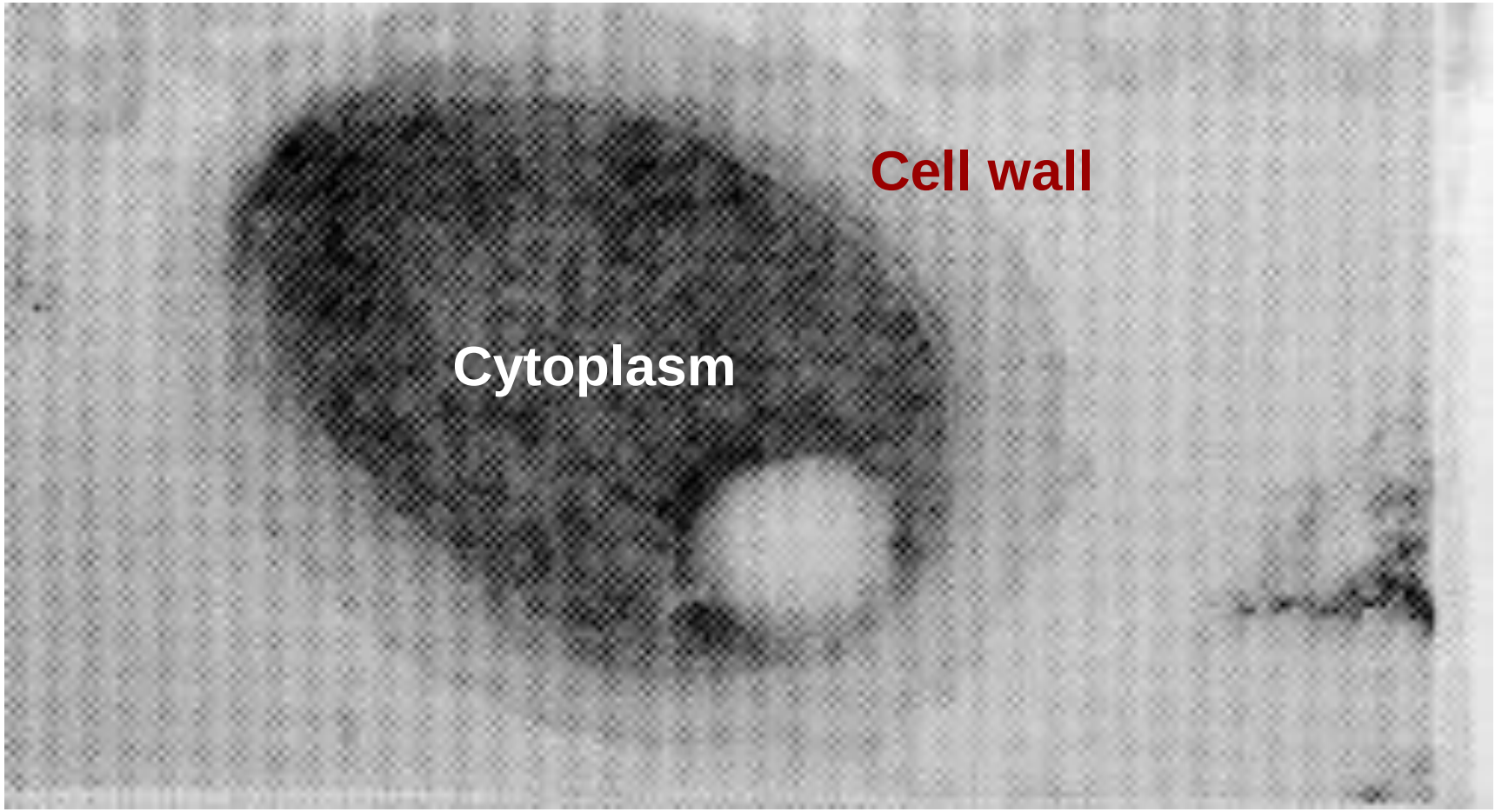
A Closeup Shot of *Staphylococcus Aureus*



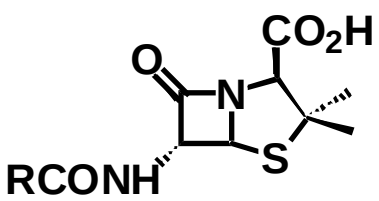
An Electron Micrograph of *Staphylococcus Aureus*



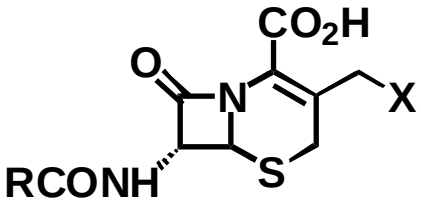
An Electron Micrograph of *Staphylococcus Aureus*



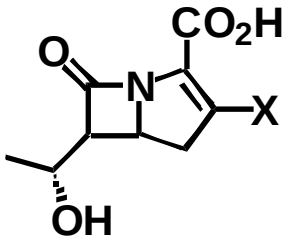
Common Classes of β-Lactam Antibiotics



penicillins



cephalosporins



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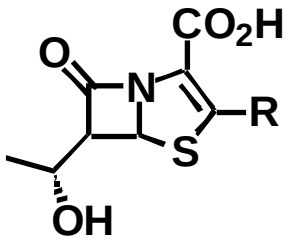
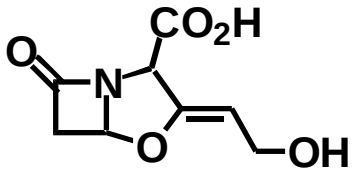


penems



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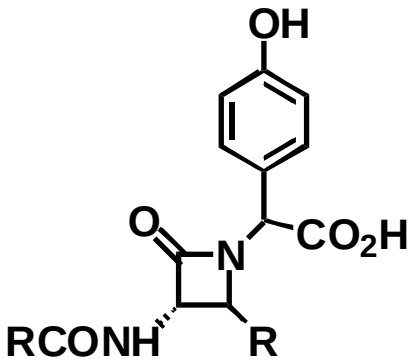
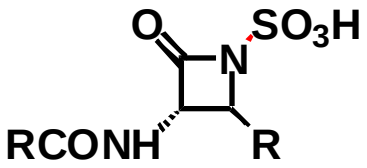
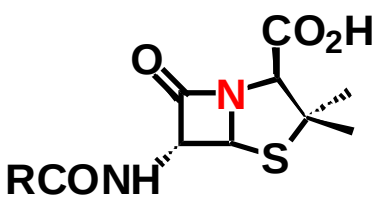


nocardicins

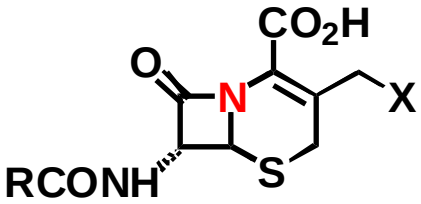


monobactams

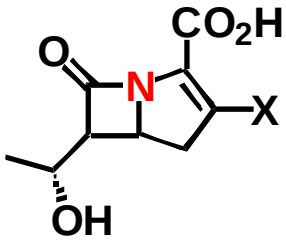
Common Classes of β-Lactam Antibiotics



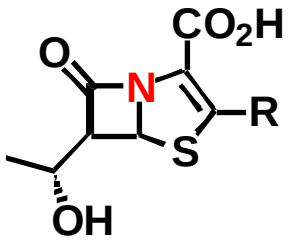
penicillins



cephalosporins



carbapenems



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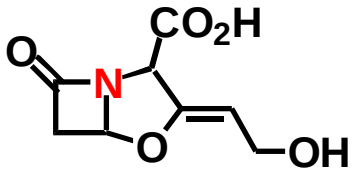
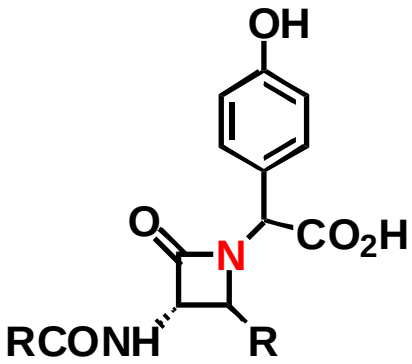
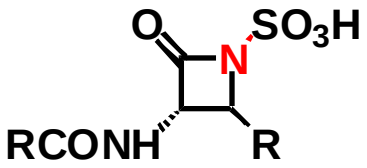


clavulanic acids

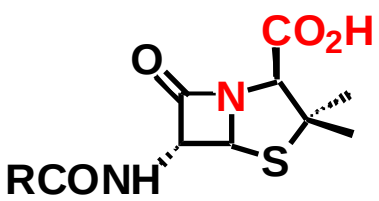


nocardicins

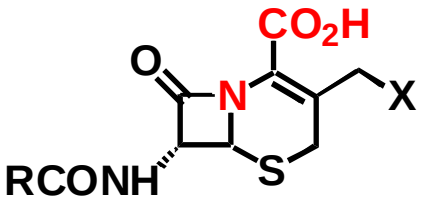


monobactams

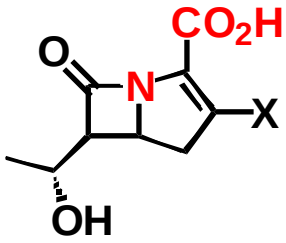
Common Classes of β-Lactam Antibiotics



penicillins



cephalosporins



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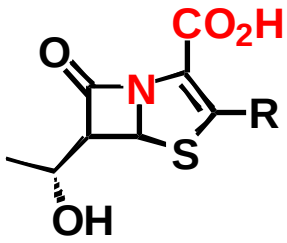
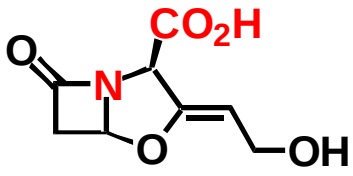
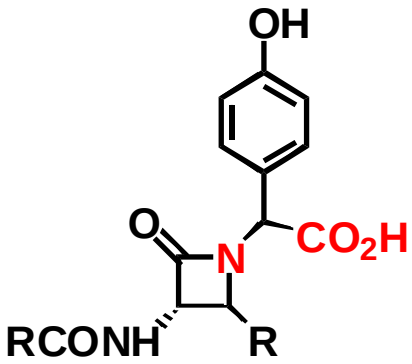


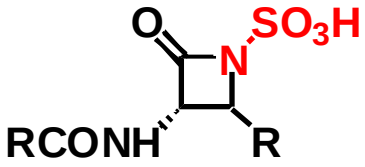
penems



clavulanic acids

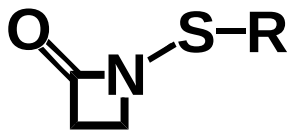


nocardicins

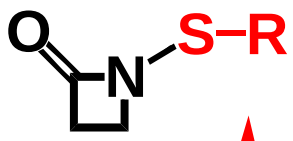


monobactams

N-Thiolated β-Lactams

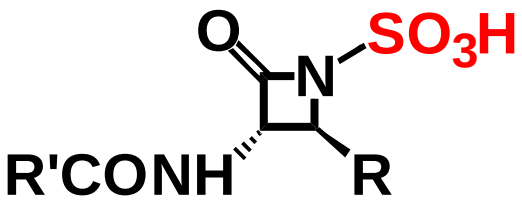


N-Thiolated β-Lactams

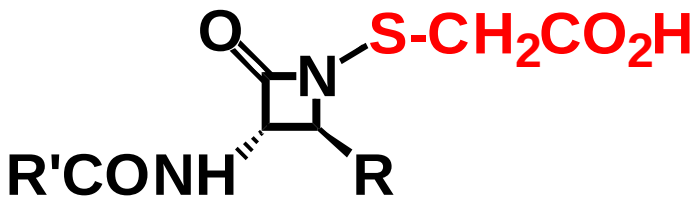


organothio group
on the nitrogen

N-Thiolated β-Lactams

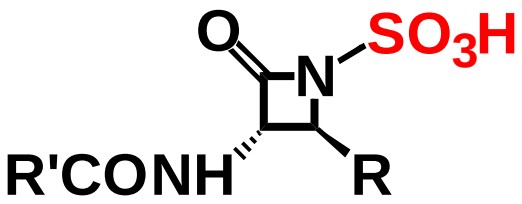


monobactams
(active)



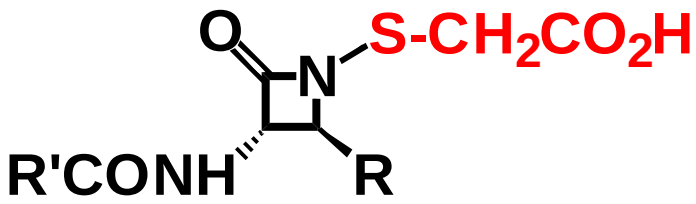
thiamazins
(inactive)

N-Thiolated β-Lactams



monobactams
(active)

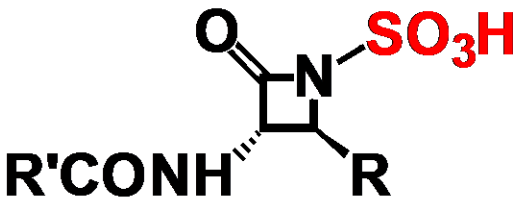
Nature **1981**, *289*, 590
Nature **1981**, *291*, 489



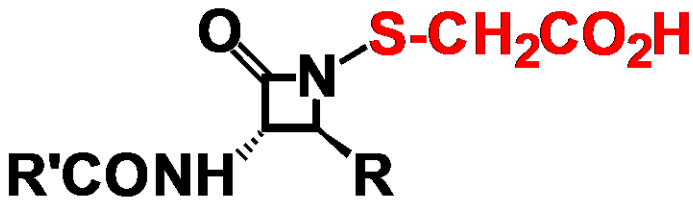
thiamazins
(inactive)

S.R. Woulfe and M.J. Miller
Tetrahedron Letters **1984**, *25*, 3293

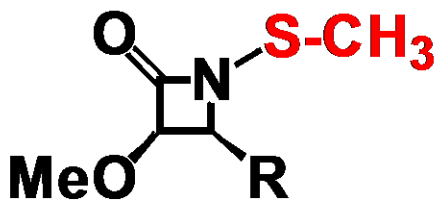
N-Thiolated β-Lactams



monobactams
(active)

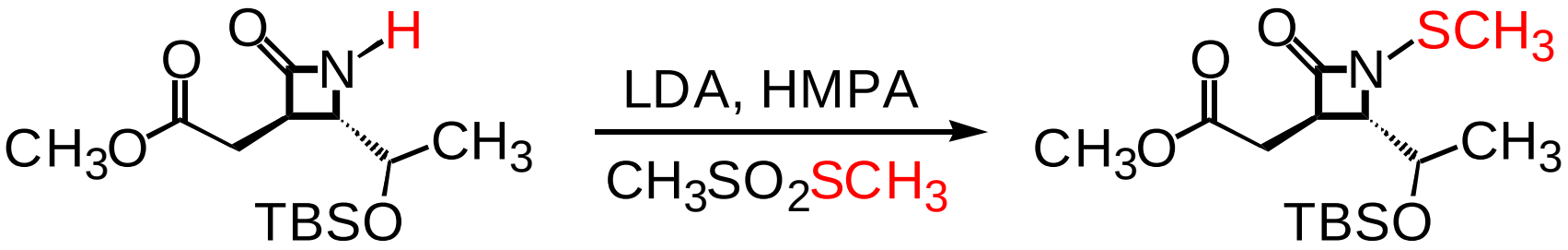


thiamazins
(inactive)

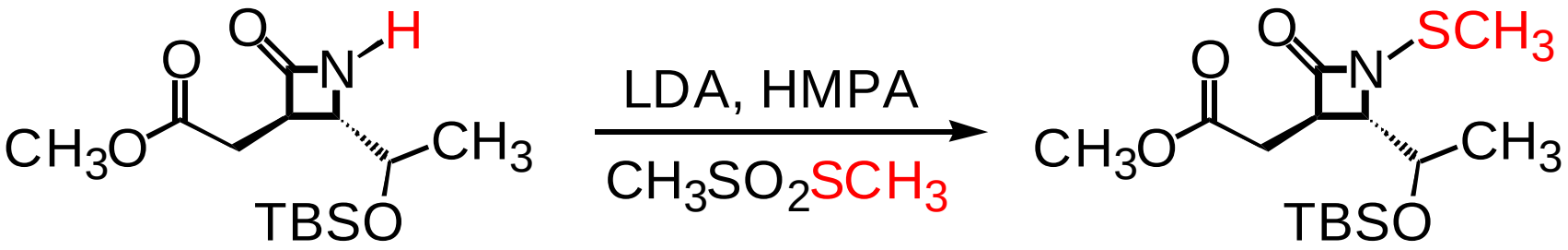


N-thiomethylated lactams
(active)

Literature on N-Thiomethyl β-Lactams



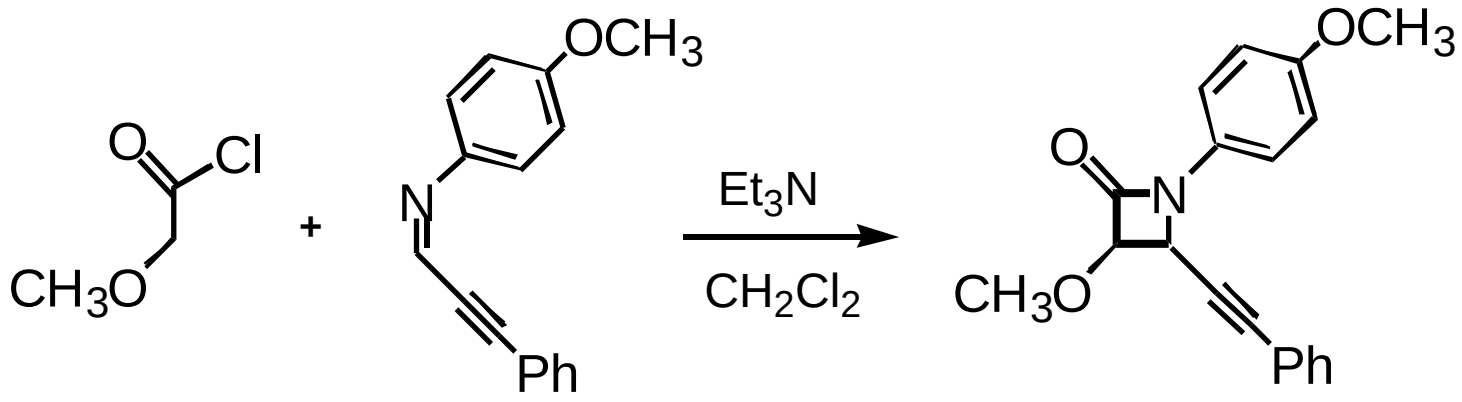
Literature on N-Thiomethyl β-Lactams



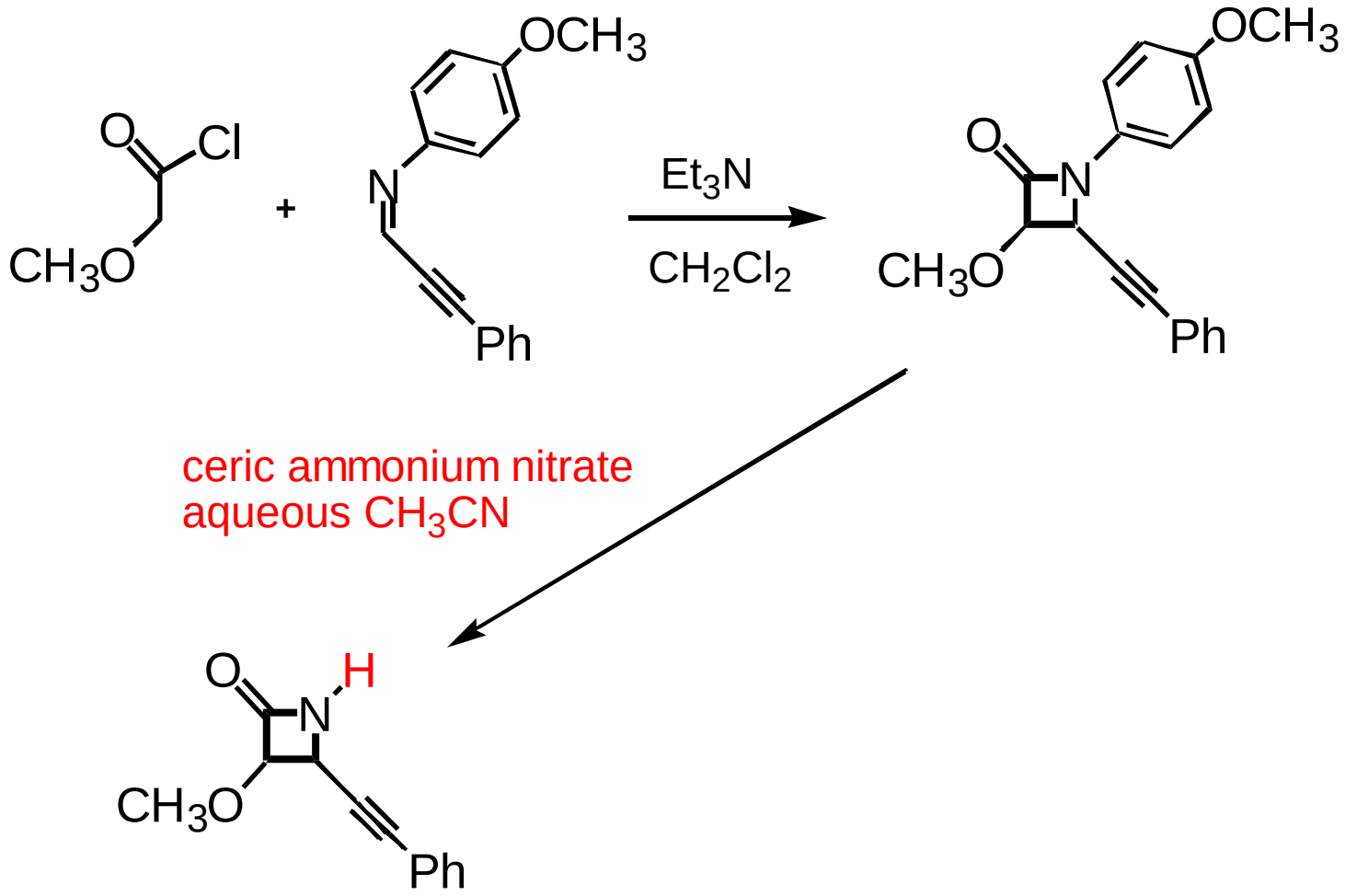
Developed as a nitrogen protecting group, stable to acid and base, but which can be easily removed with thiolate

Shah and Cama *Heterocycles* **1987**, *25*, 221

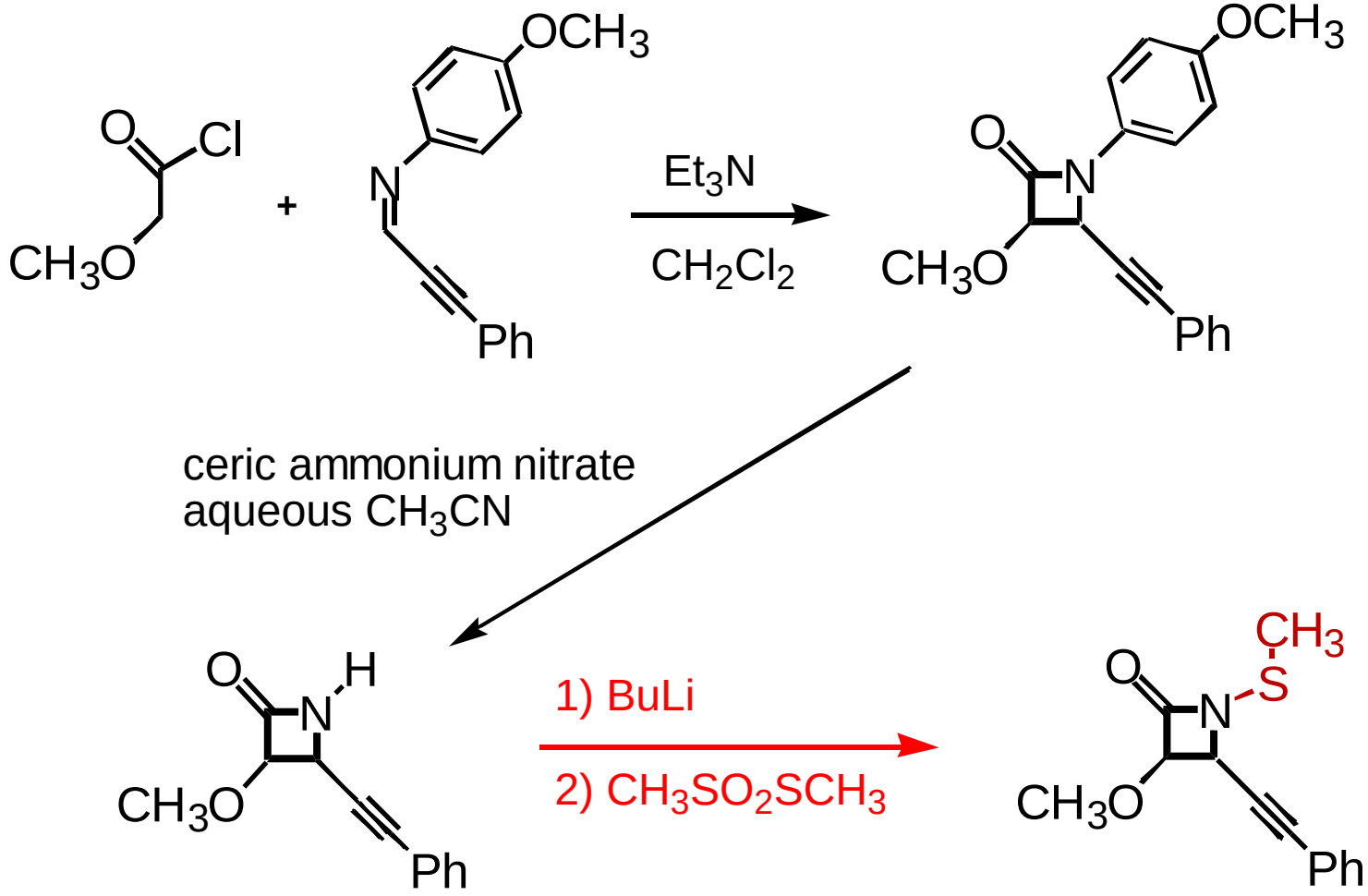
Synthesis of N-Thiomethylated β-Lactams



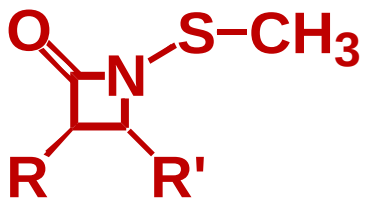
Synthesis of N-Thiomethylated β-Lactams



Synthesis of N-Thiomethylated β-Lactams

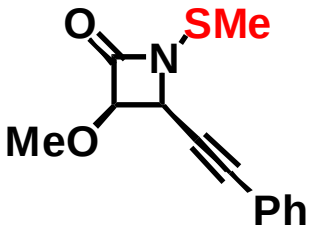


N-Thiolated β-Lactams



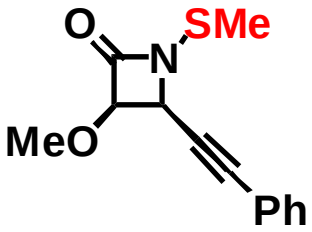
Why are they biologically-active?

Modifying the Lactam Nitrogen



(active)

Modifying the Lactam Nitrogen
Loss of Antimicrobial Activity!



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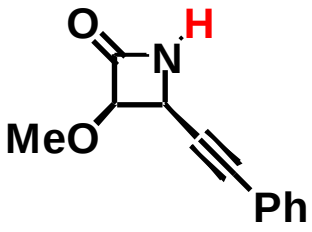

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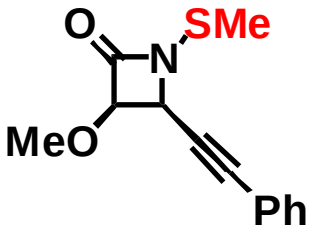
Modifying the Lactam Nitrogen
Loss of Antimicrobial Activity!



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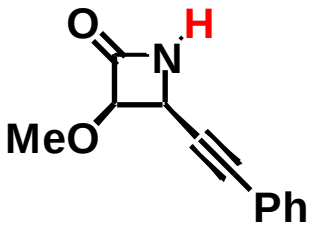

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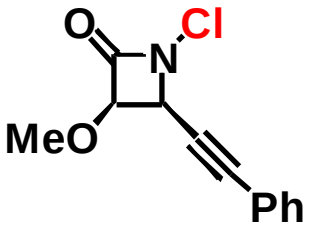

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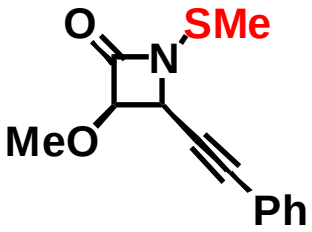
Modifying the Lactam Nitrogen
Loss of Antimicrobial Activity!



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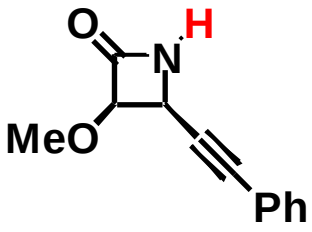

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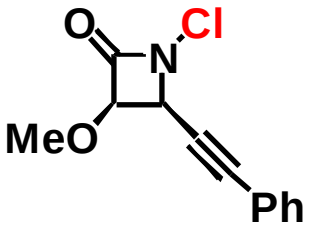

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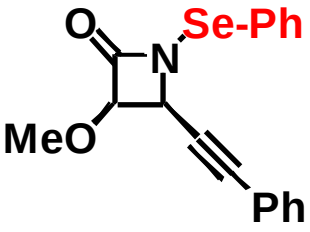

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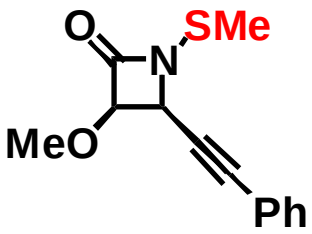
Modifying the Lactam Nitrogen
Loss of Antimicrobial Activity!



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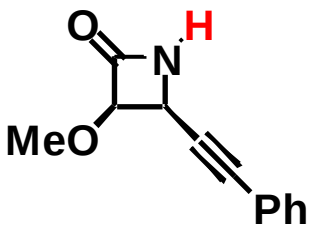

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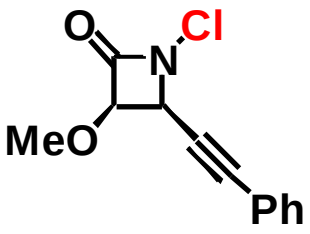

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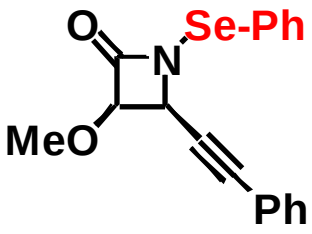

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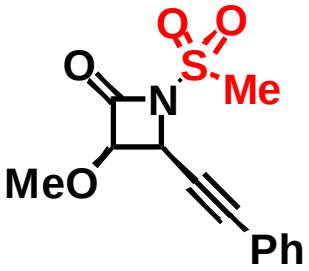

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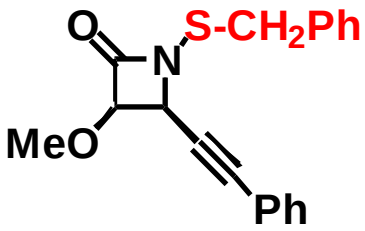
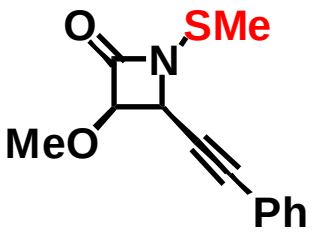


(weakly active)

Modifying the Lactam Nitrogen
Loss of Antimicrobial Activity!



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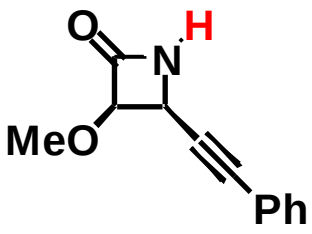

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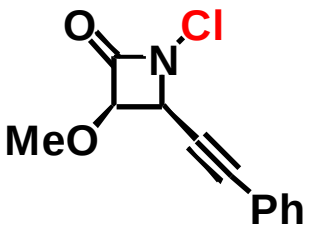

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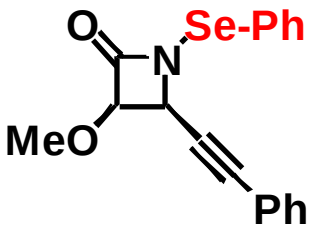

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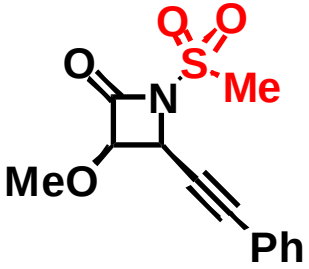

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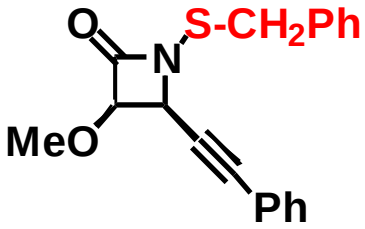
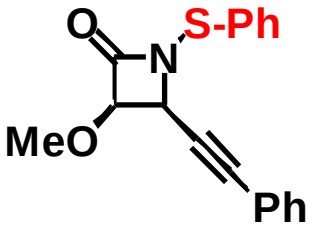


(weakly active)



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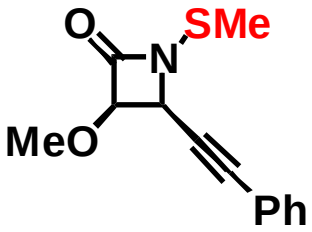
Modifying the Lactam Nitrogen
Loss of Antimicrobial Activity!



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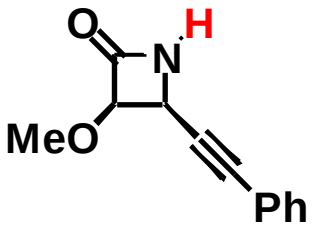

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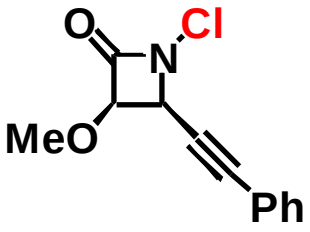

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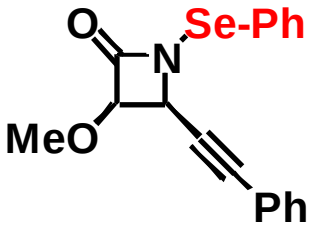

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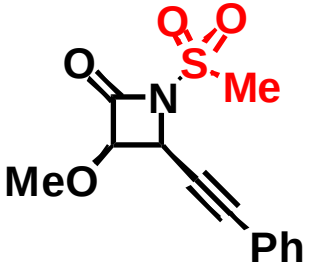

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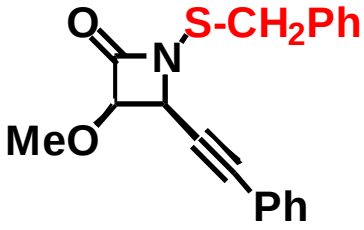
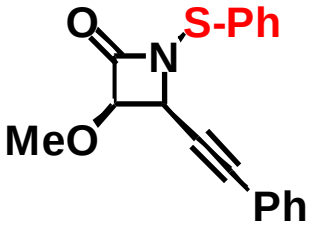


(weakly active)



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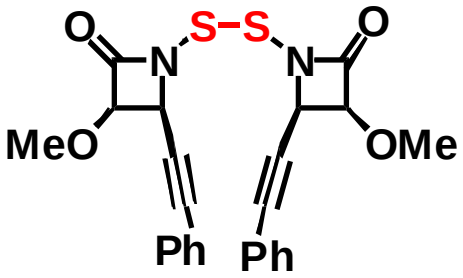
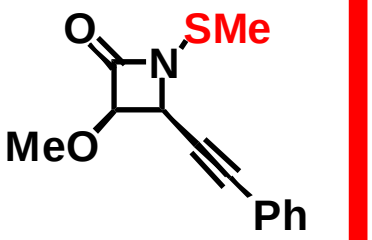


(inactive)

Modifying the Lactam Nitrogen
Loss of Antimicrobial Activity!



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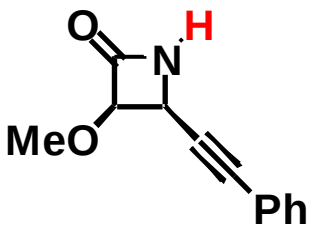

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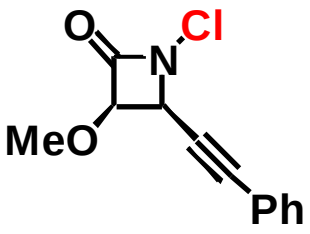

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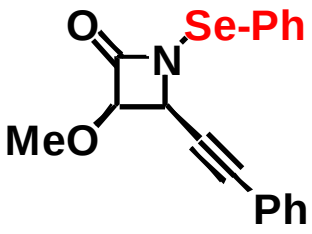

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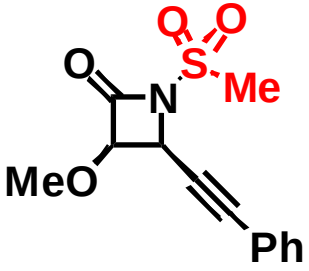

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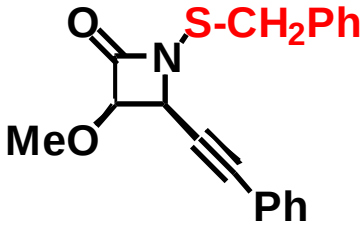
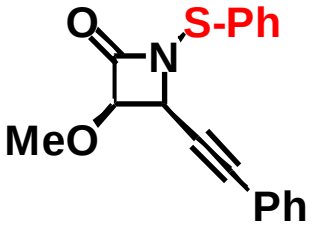


(weakly active)



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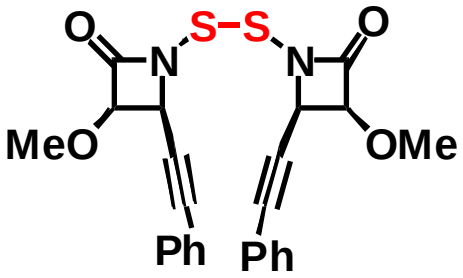

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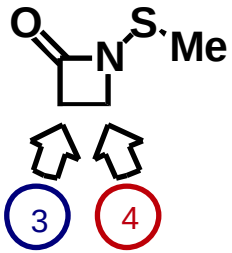
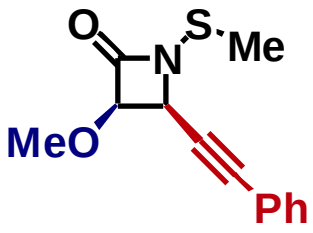
Effect of the C_3 and C_4 Ring Substituents





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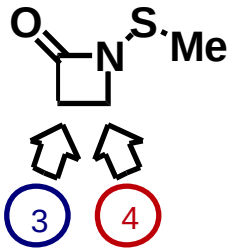
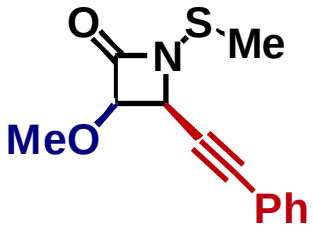
Effect of the C_3 and C_4 Ring Substituents





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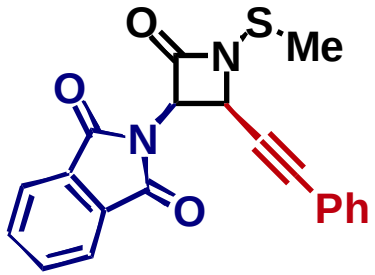

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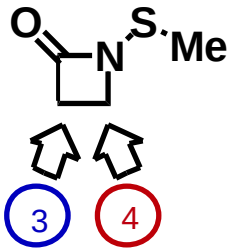
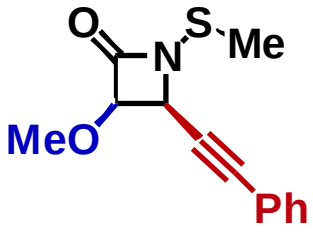
Effect of the C_3 and C_4 Ring Substituents





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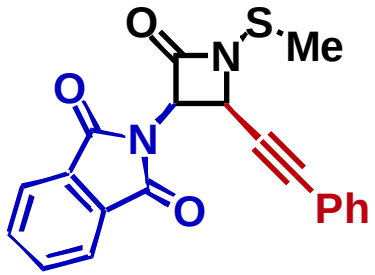

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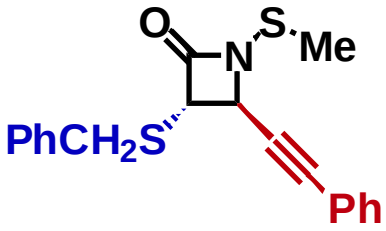

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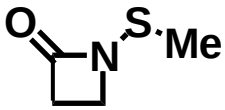

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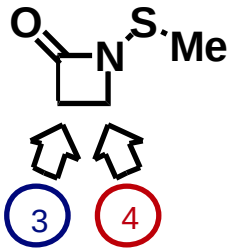
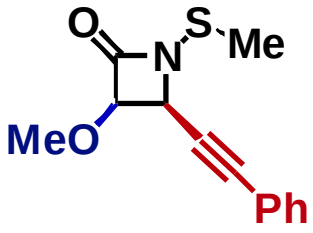
Effect of the C_3 and C_4 Ring Substituents





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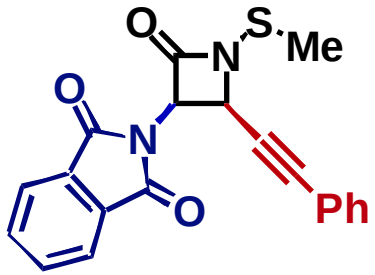

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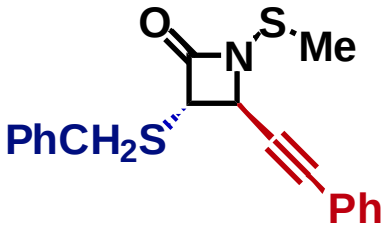

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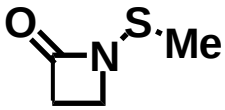

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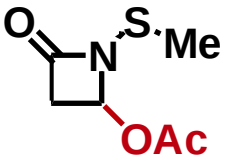
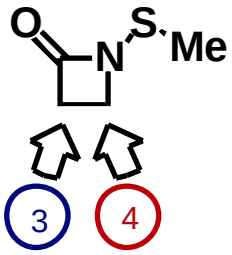
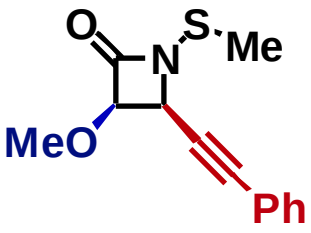


Effect of the C_3 and C_4 Ring Substituents





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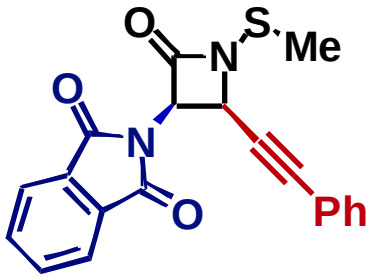

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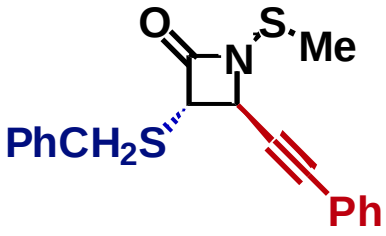

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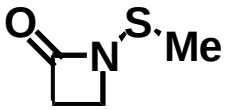

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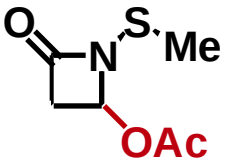
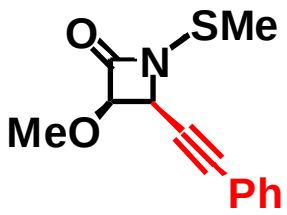


(broad-spectrum activity)

Effect of the C_4 Ring Substituent



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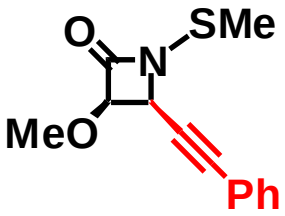
Effect of the C_4 Ring Substituent



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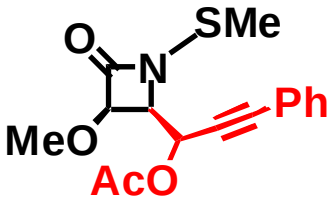

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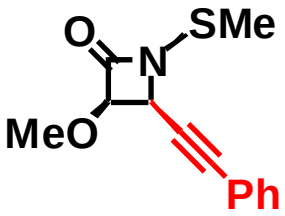
Effect of the C_4 Ring Substituent



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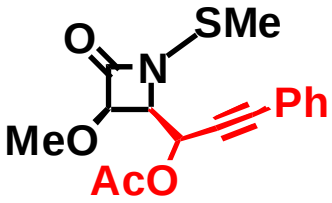

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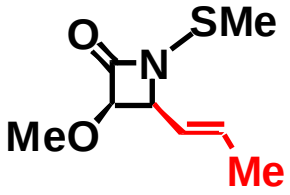

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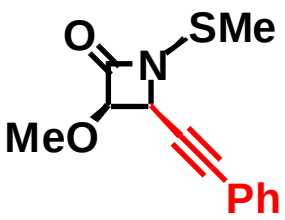
Effect of the C_4 Ring Substituent



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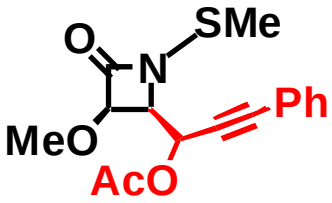

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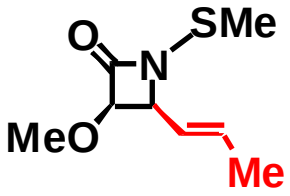

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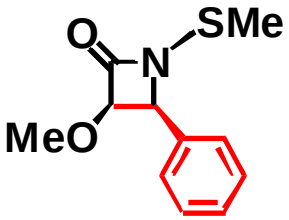

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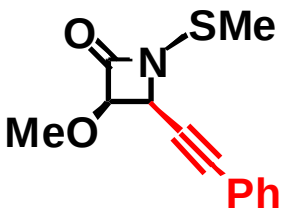
Effect of the C_4 Ring Substituent



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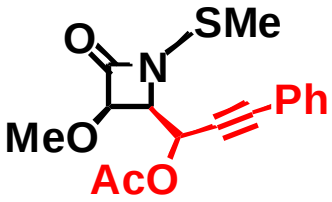

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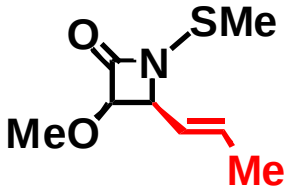

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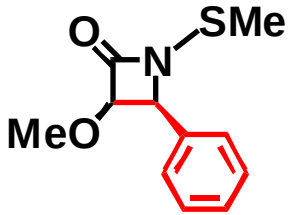

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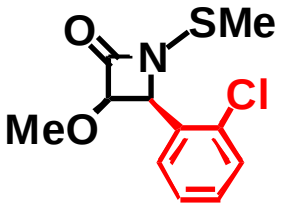
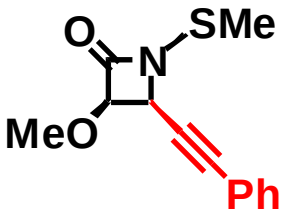


Effect of the C_4 Ring Substituent



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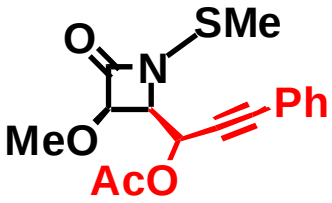

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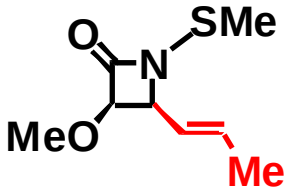

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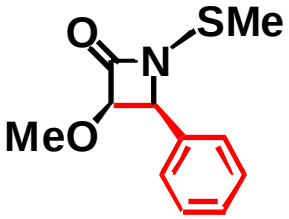

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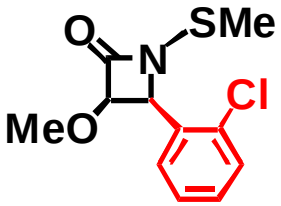

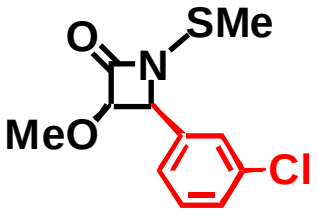

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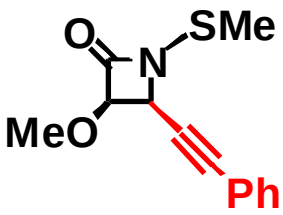

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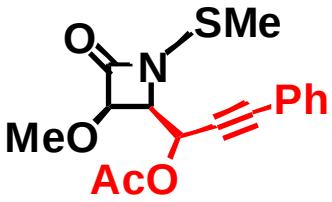

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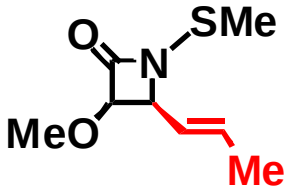

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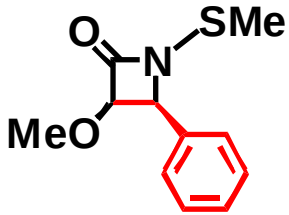

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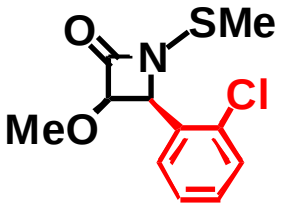
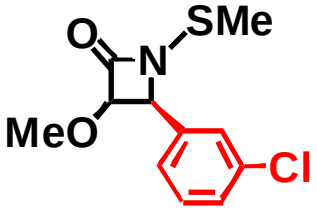
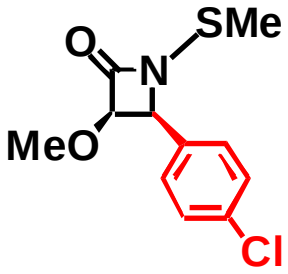
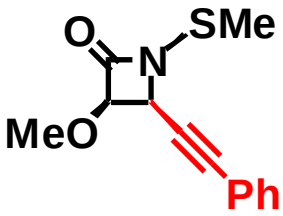






Effect of the C_4 Ring Substituent



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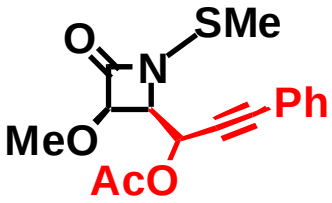

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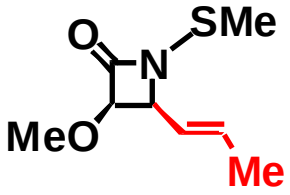

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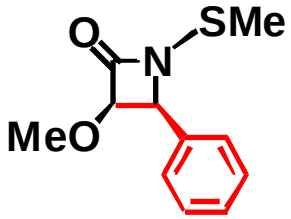

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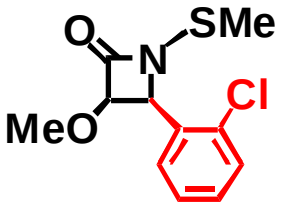

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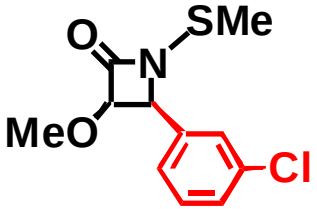

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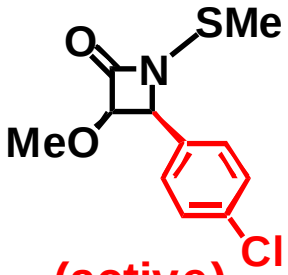

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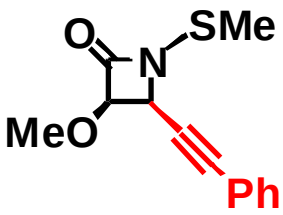

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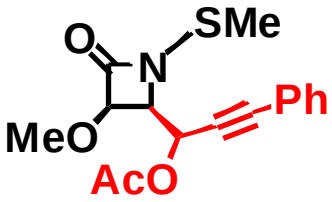

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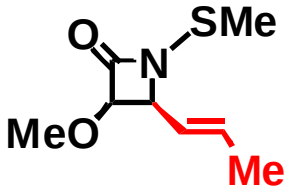

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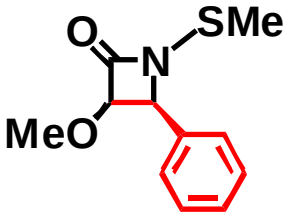

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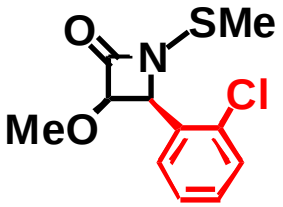

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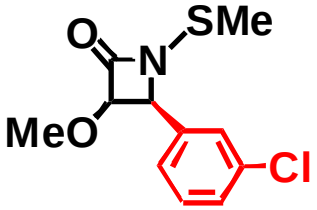

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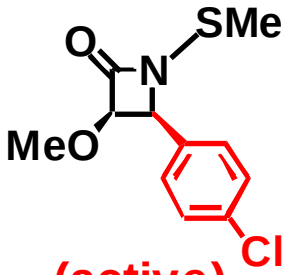

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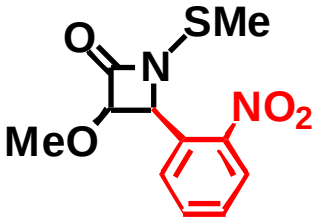

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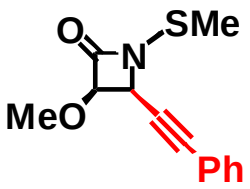

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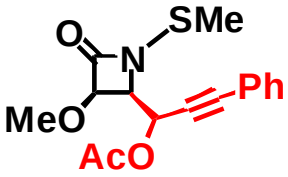

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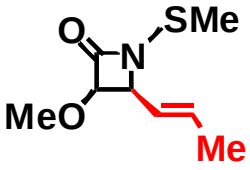

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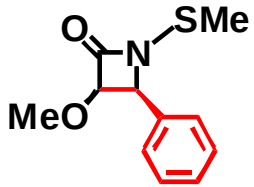

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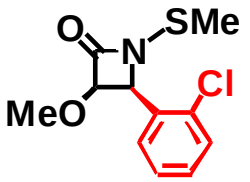

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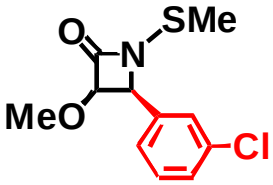

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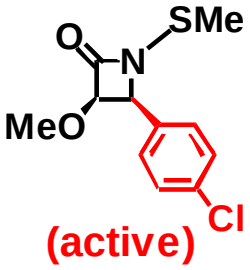

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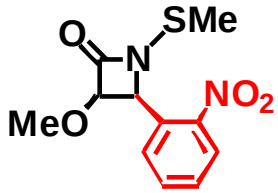

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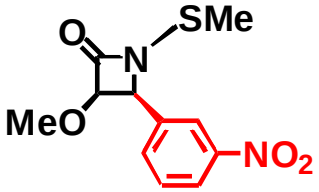

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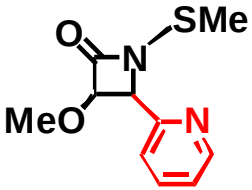

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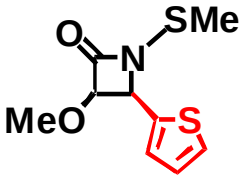

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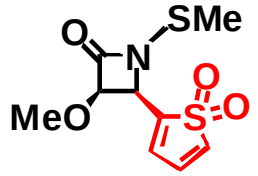

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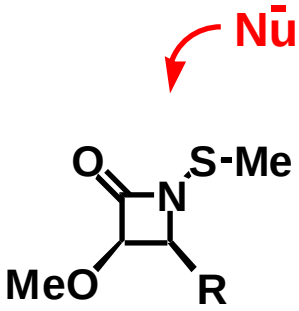
Turos, Edward; Long, Timothy E.; Konaklieva, Monika I.; Coates, Cristina; Shim, Jeung-Yeop; Dickey, Sonja; Lim, Daniel V.; Cannons, Andrew. N-Thiolated β-Lactams: novel antibacterial agents for methicillin-Resistant Staphylococcus aureus. *Bioorganic & Medicinal Chemistry Letters* (2002), *12(16)*, 2229-2231

Three Potential Modes of Nucleophilic Attack



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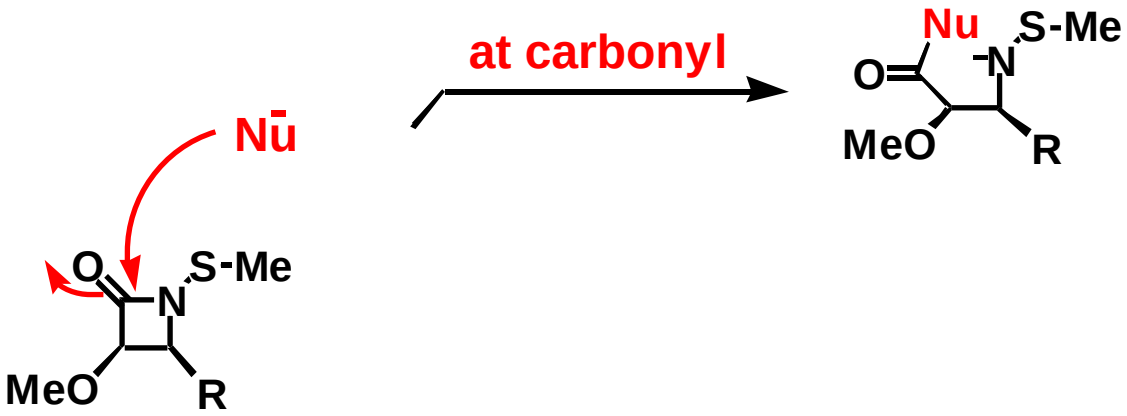

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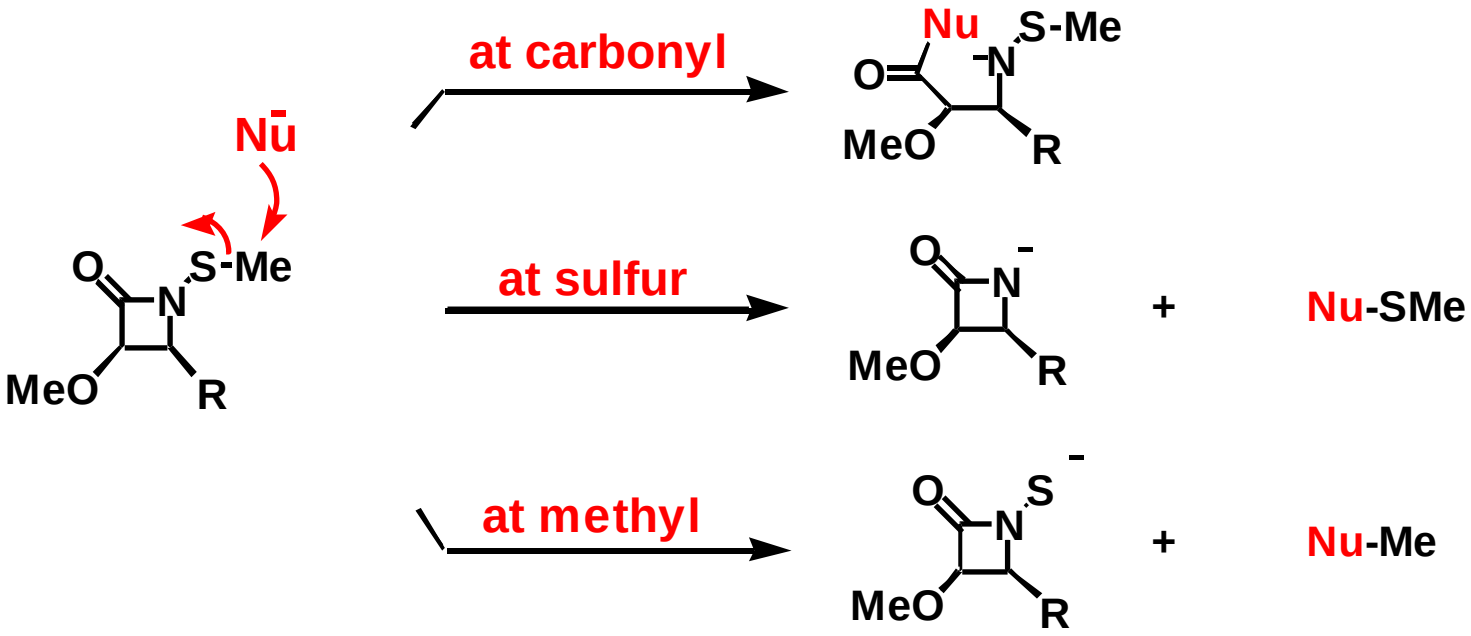

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The chemical and biological mechanisms of action appear to differ from that of all previously known classes of antibiotics

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