Chimica Farmaceutica e Tossicologica 2

- Antibiotici β-lattamici;
- Penicilline;
- Inibitori β-lattamasi;

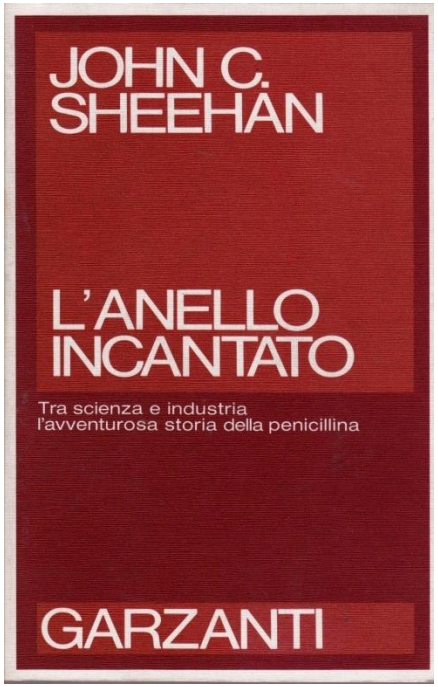
Scoperta della Penicillina: una storia che ha mutato la Storia

- 1896 - Ernest Augustin Duchesne (1874-1912)
  Penicillium glaucum proprietà antibatterica vs *E. coli* e bacillo tifoide. Primi test in vivo a dosi letali di bacillo tifoide con penicillum e sopravvivenza delle cavie. Duchesne aveva solo 23 anni! L'istituo Pasteur non diede credito alla sua dissertazione. Si arruolò!
- 1928 - Alexander Fleming
  Nota che la muffa di pane (*Penicillium notatum*), cresciuta in piastre di Petri, inibisce la crescita di stafilococchi.
- 1939 - Florey, Chain, e Collaboratori
  Isolano, caraterizzano e sintetizzano e la Penicillina (*G*).
- 1940 –1945 Produzione industriale ed uso durante la II guerra mondiale
- 1945 – Dorothy Hodgkins
  Risolve l'enigma della struttura della Penicillina *G* (Rx)
- 1945 – Florey, Chain, Fleming: Nobel per la Medicina
- 1958 – John C. Sheehan
  Sintesi totale della Penicillina *G*

- La potenza (purezza) di una penicillina viene misurata in Unita Internazionali (UI). L' UI è la q. (mg) di Penicillina che in condizioni sperimentali "standard" inibisce la crescita in vitro dello *Staph. Aureus* (1UI= 0.6 mg di Pen. *G* sodica ; 600 mg di Pen*G* sodica= 1.000.000 UI

The 1945 Nobel Prize in Physiology or Medicine went to Sir Alexander Fleming, Ernst Chain and Sir Howard Florey for their discovery of penicillin, a fungus, and its use as an antibiotic.

Dorothy Mary Hodgkin, was a British chemist. Nobel Prize 1964. The determinations by X-ray techniques of the structures of important biochemical substances (Vit. B12)



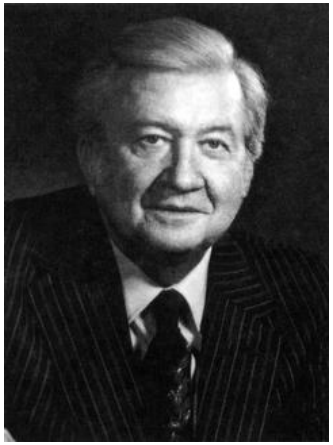
MENU TIME

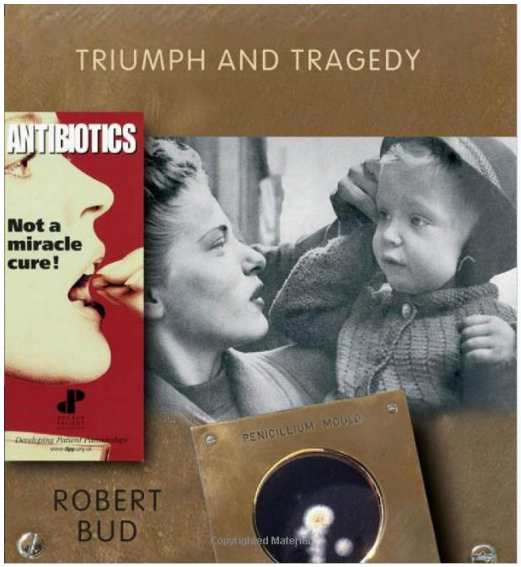
Science: Penicillin Synthesis

Monday, Mar. 18, 1957

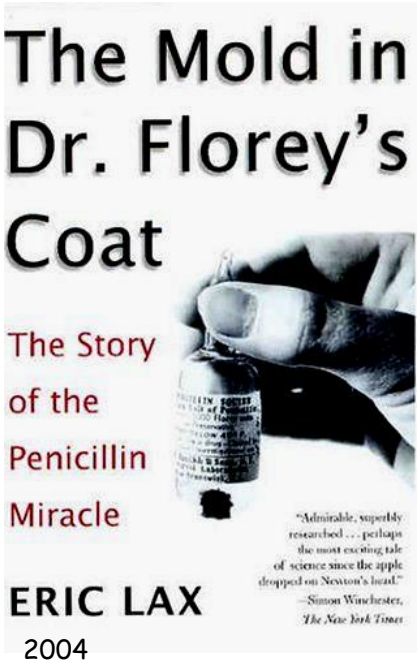
After nine years of dogged work, Chemist John C. Sheehan of M.I.T. announced last week that he had discovered a practical method of synthesizing penicillin V, one of the two most useful forms of the natural antibiotic made by the penicillin mold.

Dr. Sheehan had solved one of modern chemistry's most baffling problems. During World War II a thousand chemists working in 39 laboratories in the U.S. and Britain spent an estimated $20 million trying to accomplish it. One researcher succeeded, but he could not figure out how he had done it and could never do it again. Another group produced a...

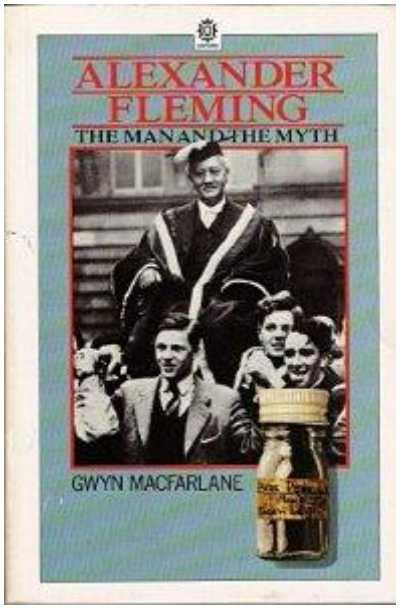




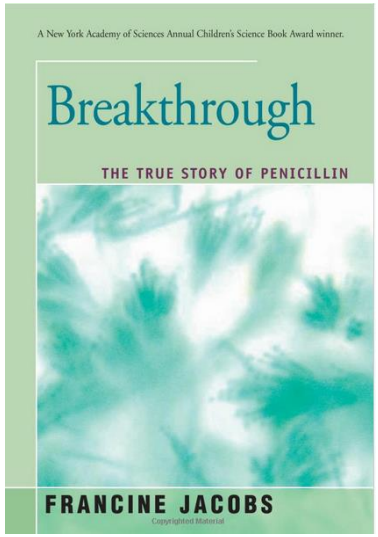
2007



2004

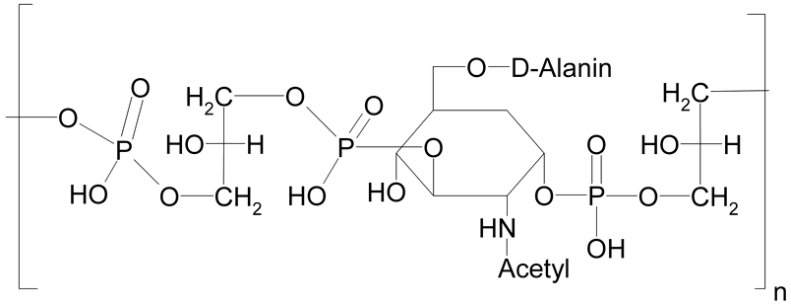


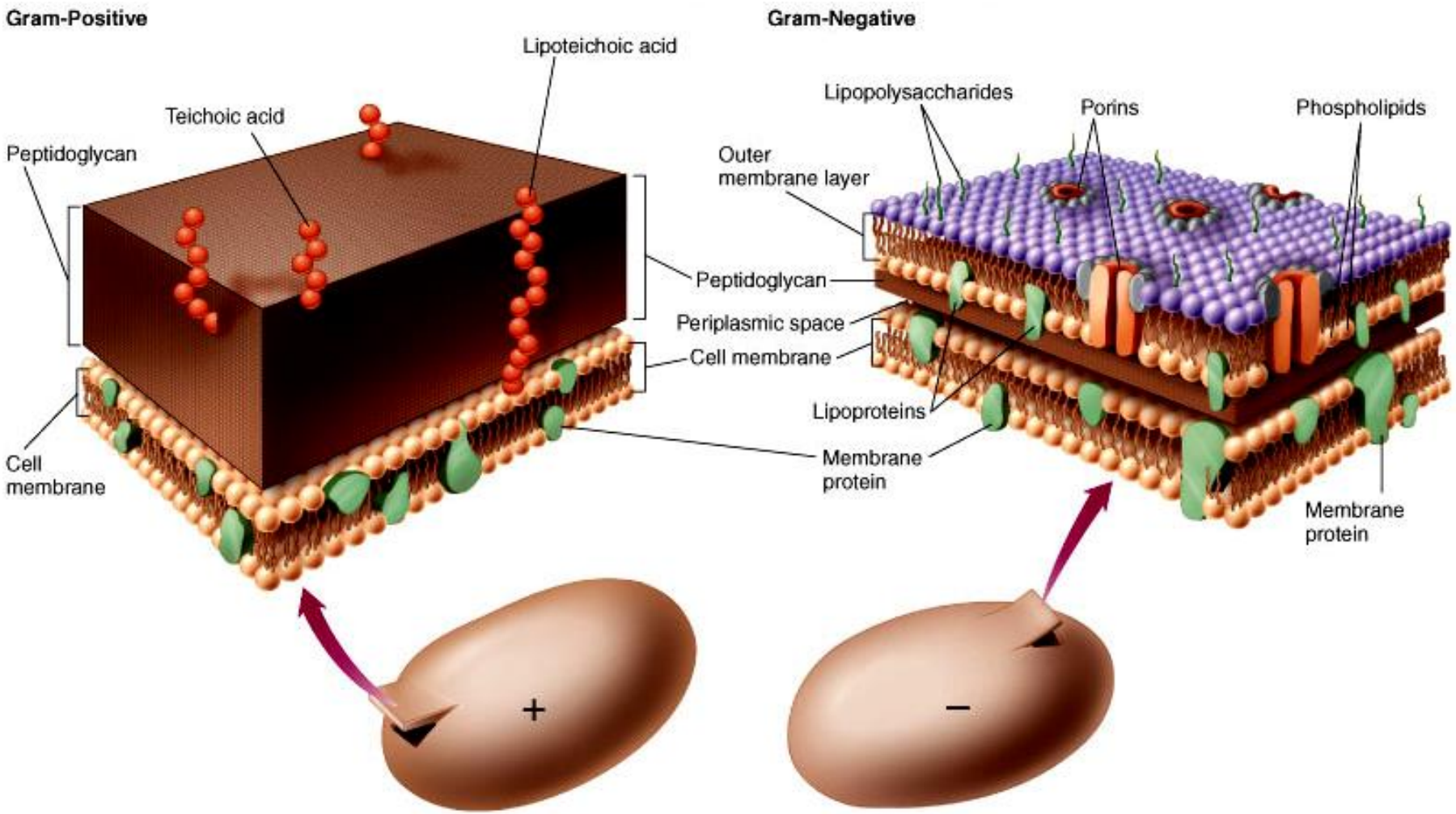
1985



2004

Parete batterica

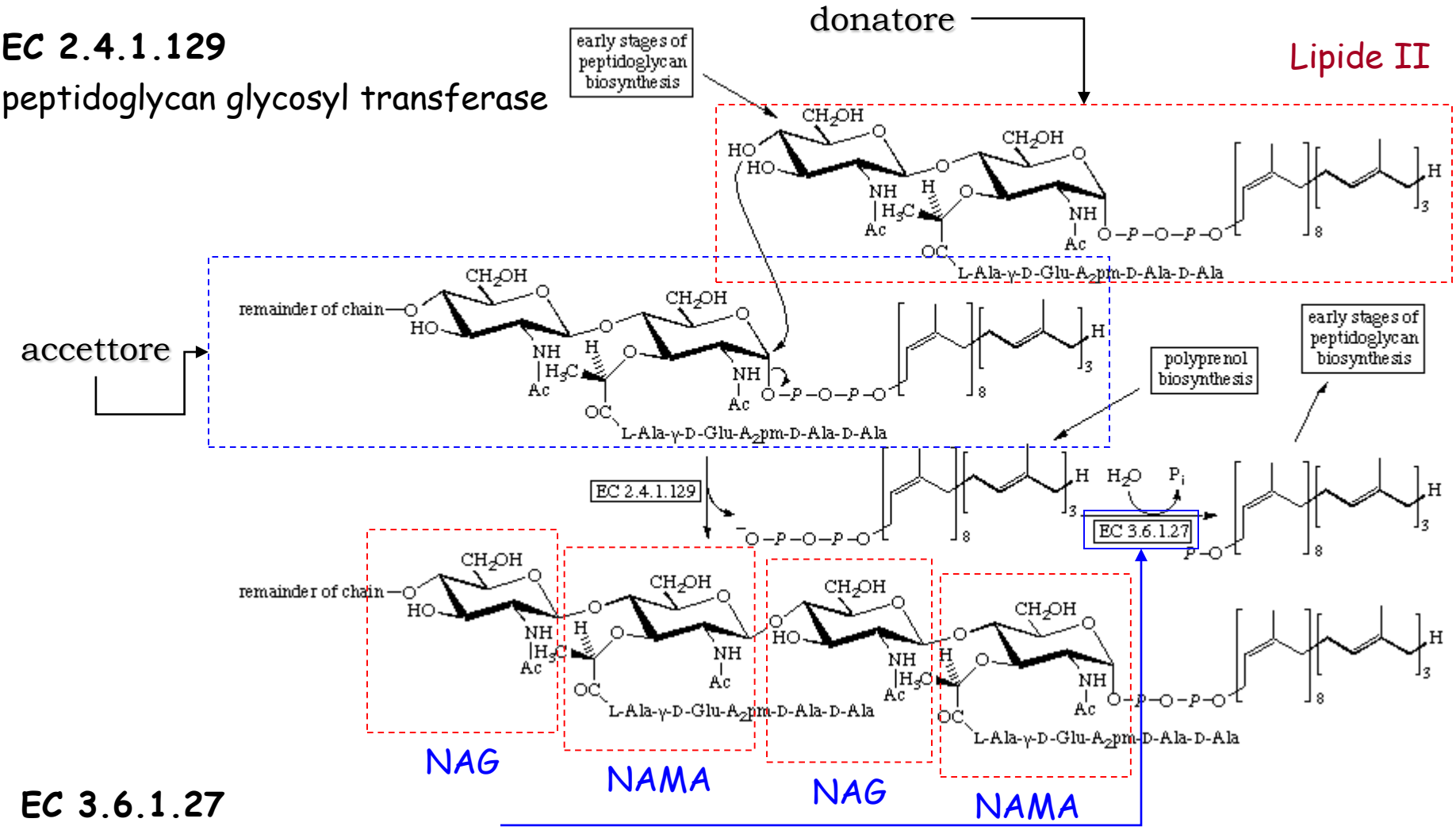




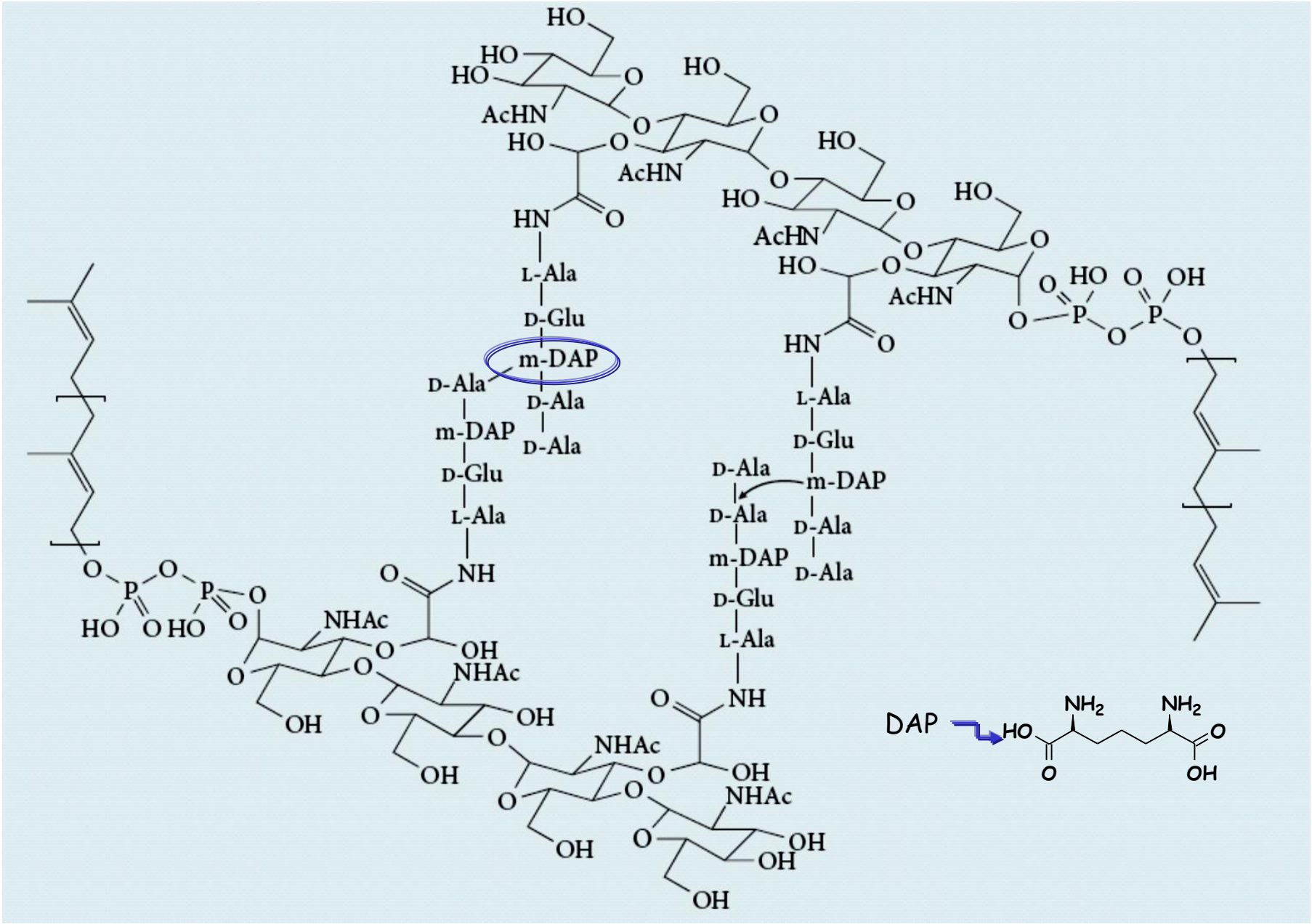
Biosintesi del Peptidoglicano (Parte 3)

Regione periplasmatica

EC 2.4.1.129
peptidoglycan glycosyl transferase

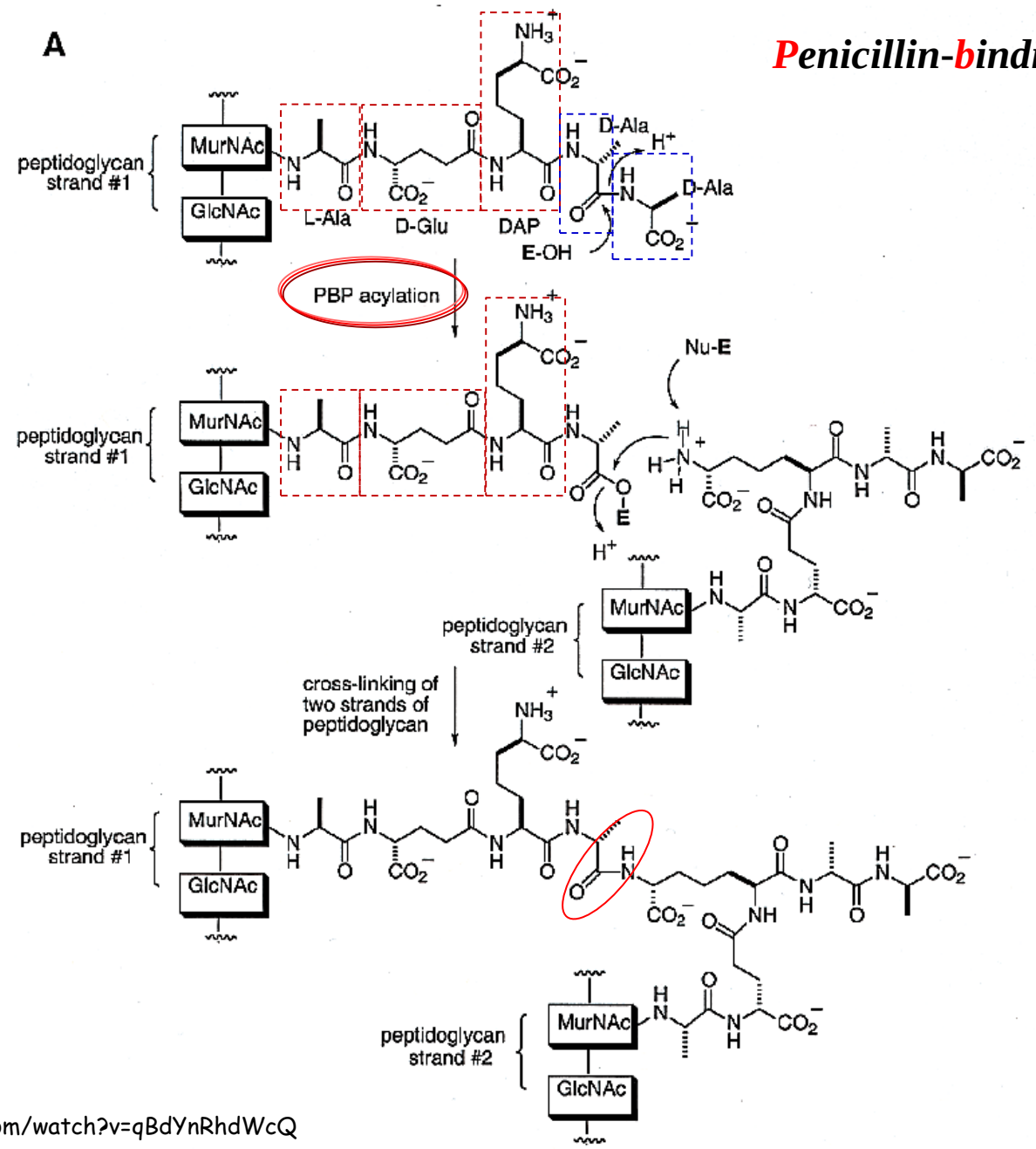


EC 3.6.1.27
undecaprenyl-diphosphatase

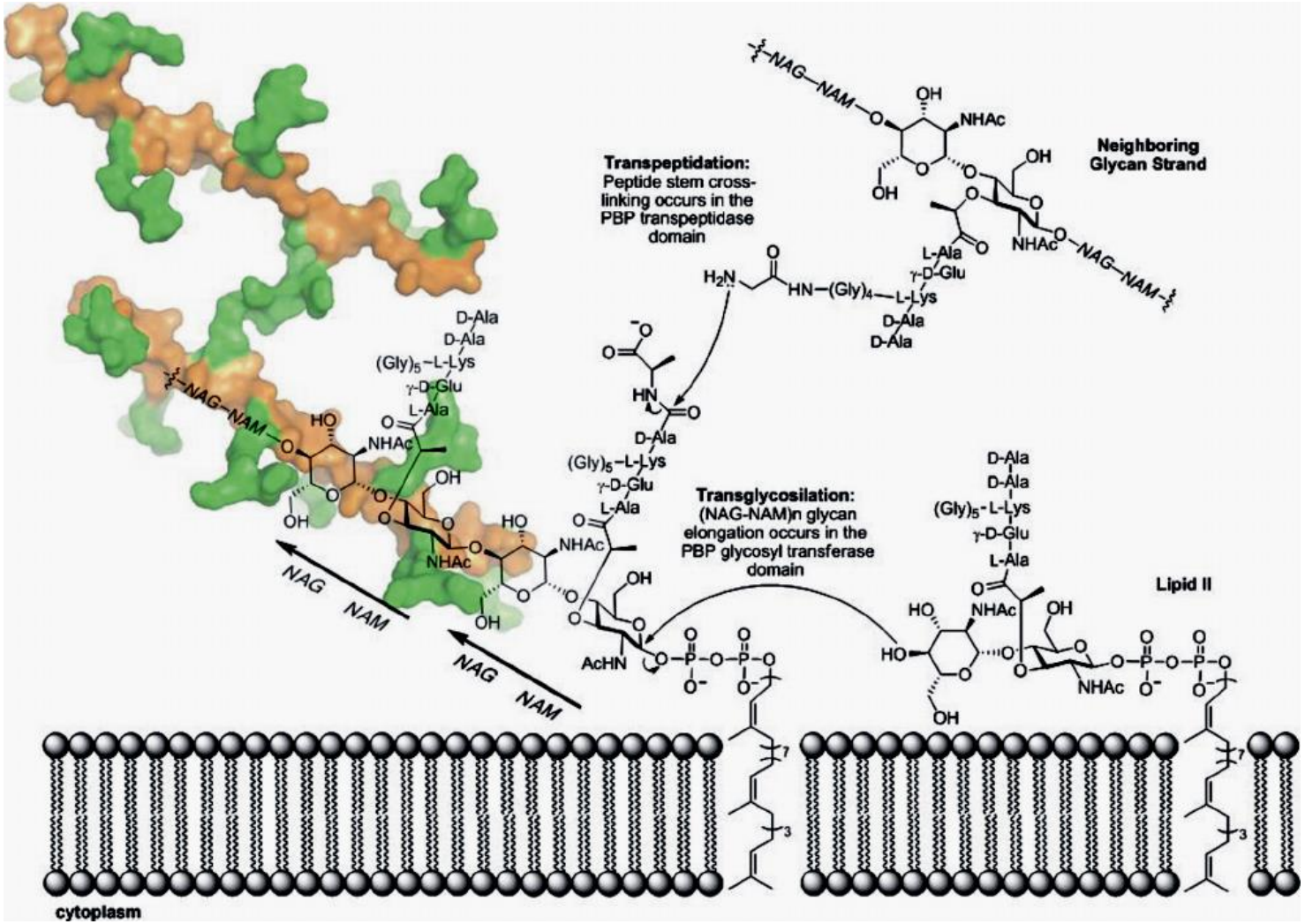


Linkers: Acido diaminopimelico (DAP); Lisina (Lys); Gly-$(Gly)_3$-Gly

Penicillin-binding proteins.



https://www.youtube.com/watch?v=qBdYnRhdWcQ



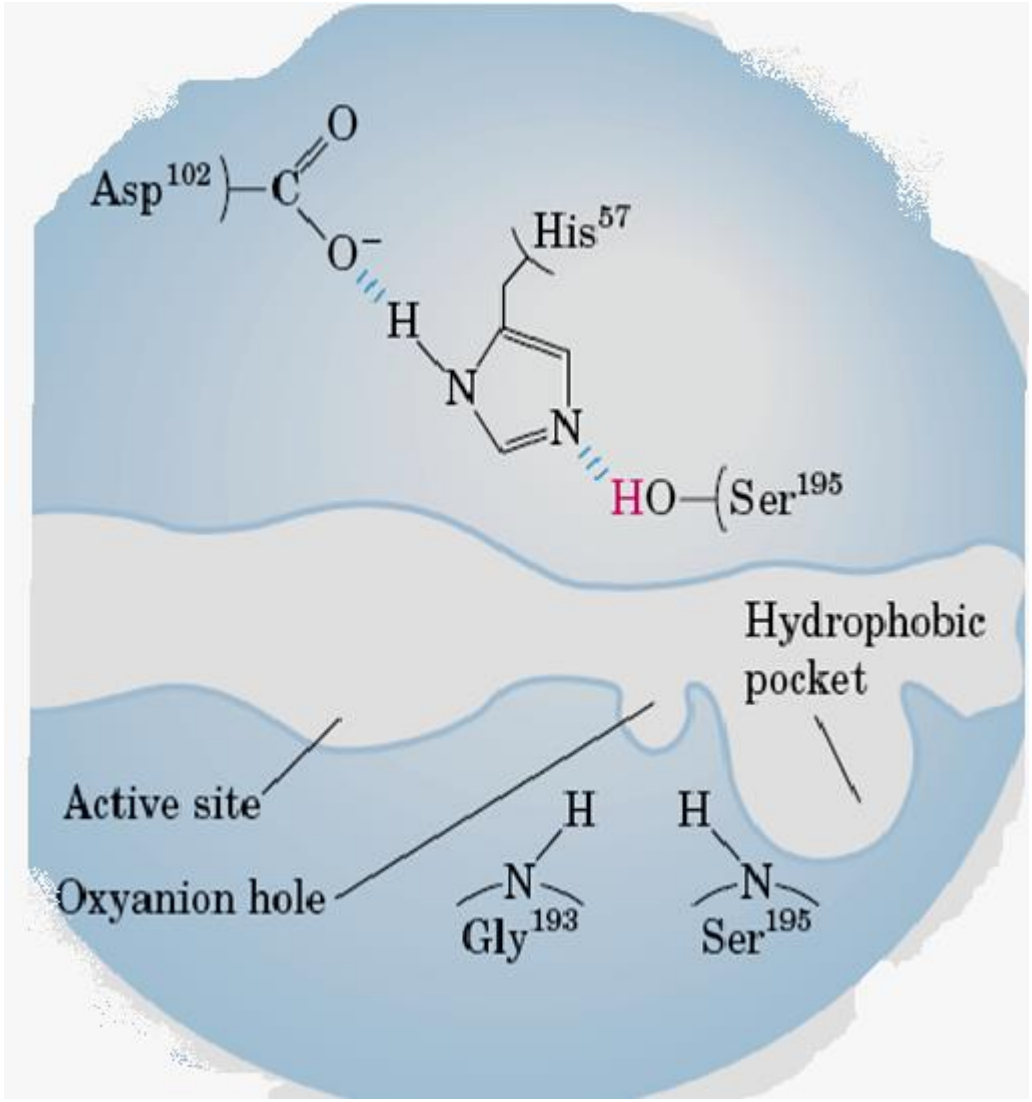
Molecular Basis and Phenotype of Methicillin Resistance inStaphylococcus aureusand Insights into New-LactamsThat Meet the Challenge
Molecular Basis and Phenotype of Methicillin Resistance in Staphylococcus aureus and Insights into New -Lactams That Meet the Challenge. Leticia I. Llarrull, Jed F. Fisher, and Shahriar Mobashery. ANTIMICROBIALAGENTS ANDCHEMOTHERAPY, Oct. 2009, p. 4051–4063

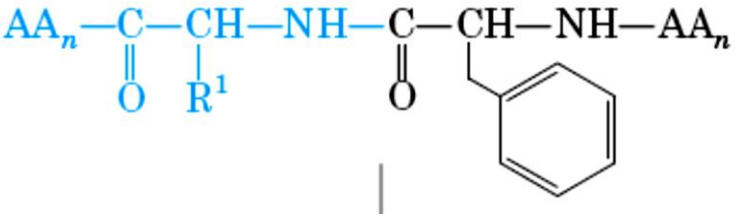
TABLE 2.1 Properties of penicillin-binding proteins of *Escherichia coli*

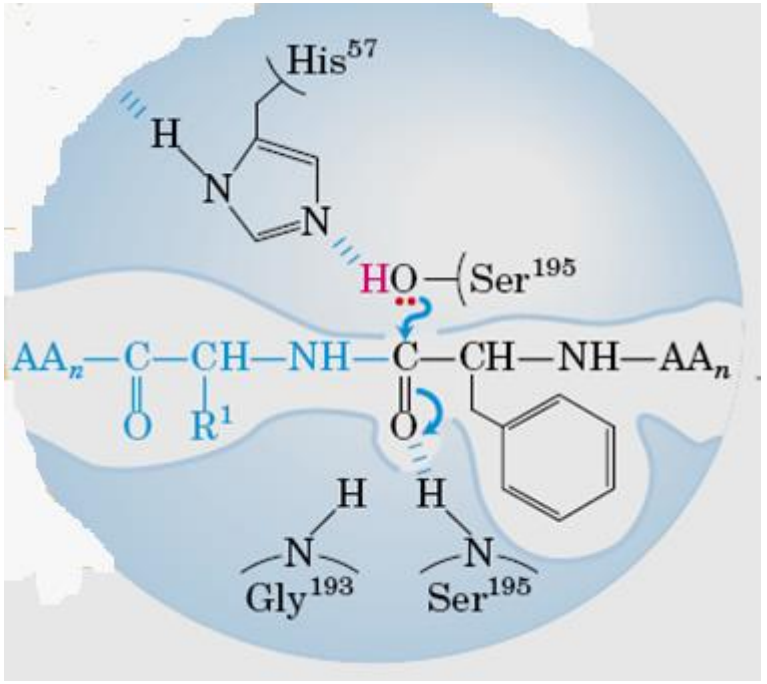
Protein no.		*Molecular mass (Kilodaltons)*	*Enzyme activities*	*Function*
1a	Due domini Classe A: transglicosilasi N-terminale; Classe B: monofunzionali solo trans-peptidasi	91	Transpeptidase Transglycosylase	Peptidoglycan cross-linking
1b		91	Transpeptidase Transglycosylase	Peptidoglycan cross-linking
2		66	Transpeptidase	Peptidoglycan cross-linking
3		60	Transpeptidase	Peptidoglycan cross-linking
4		49	DD-carboxypeptidase	Limitation of peptidoglycan cross-linking
5		41	DD-carboxypeptidase	Limitation of peptidoglycan cross-linking
6		40	DD-carboxypeptidase	Limitation of peptidoglycan cross-linking

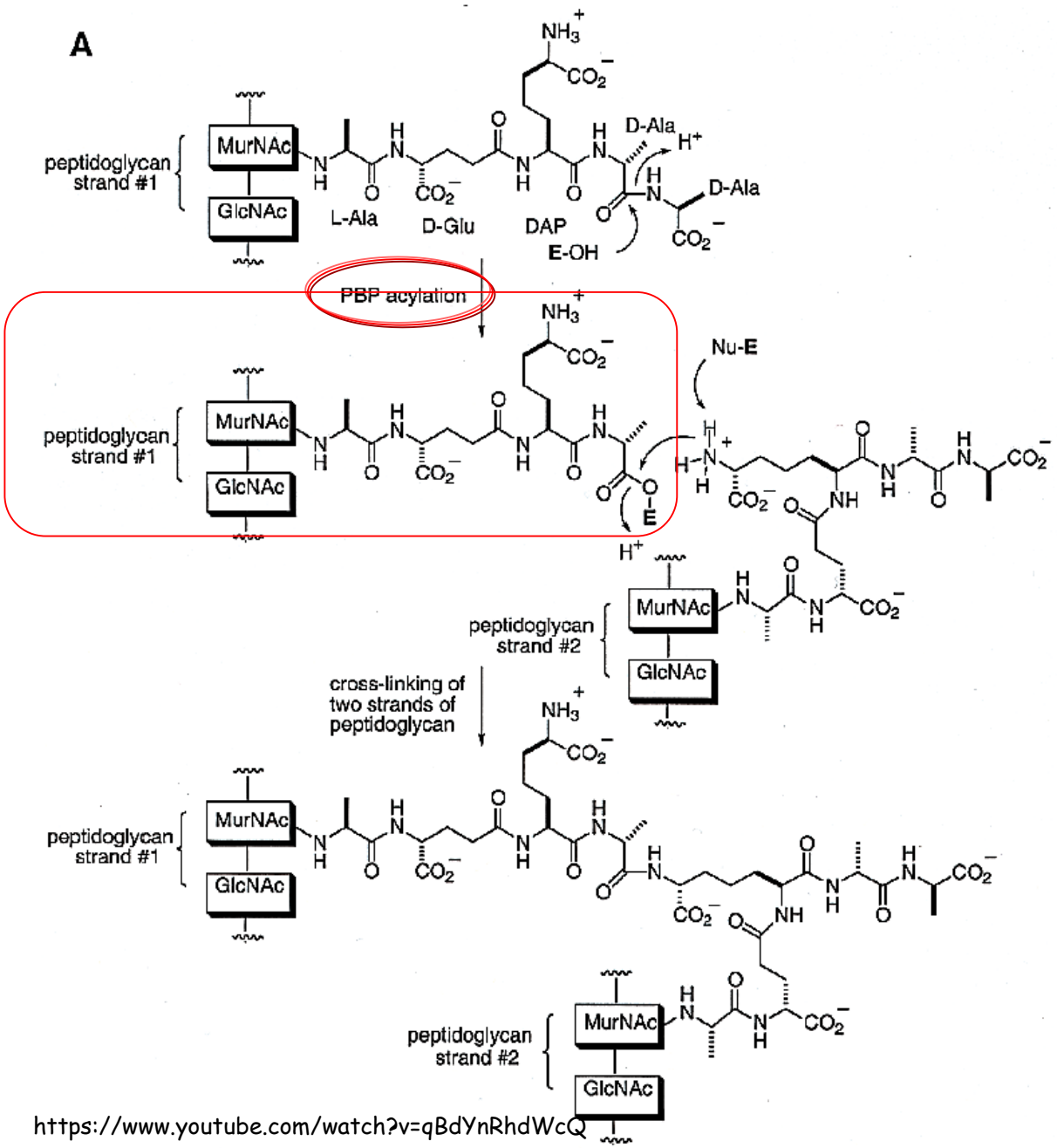
PBPIc, PBP7, DacD, AmpC and AmpH.

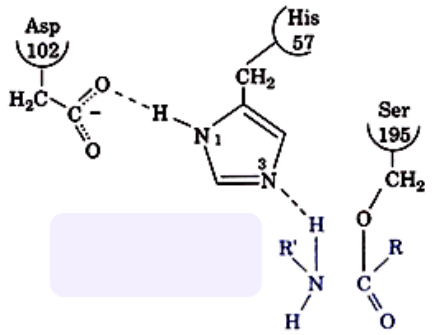
Chimotripsina







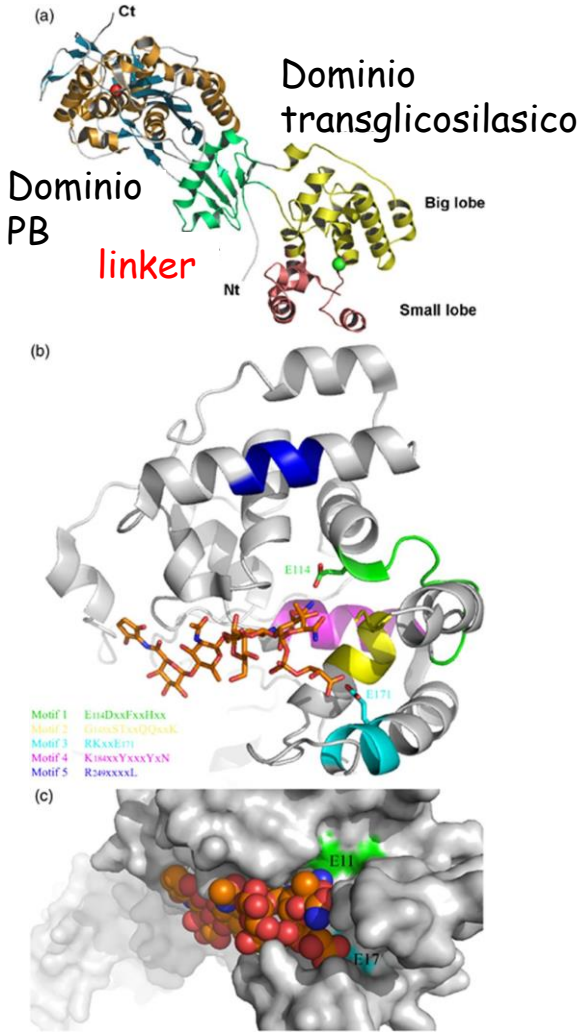




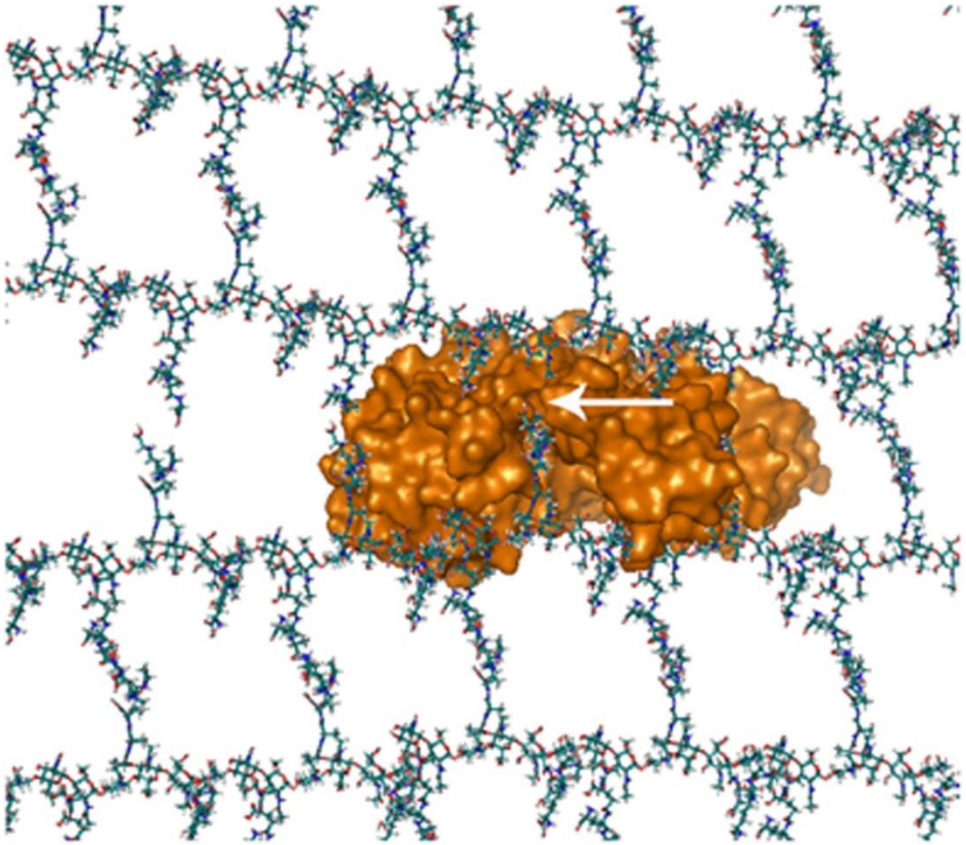
Acil-enzima intermedio

https://www.youtube.com/watch?v=qBdYnRhdWcQ

Structure of class A PBPs (Staphylococcus aureus PBP2).

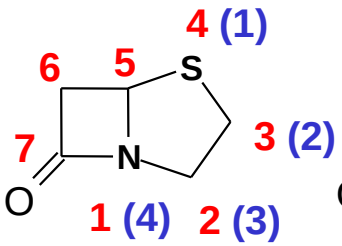


Endopeptidation by type-4 PBP. View of the peptidoglycan from the cytoplasmic membrane side.

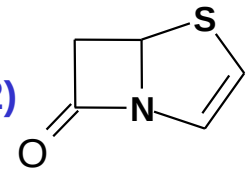


Eric Sauvage et al. FEMS Microbiol Rev 2008;32:234-258

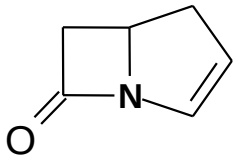
Strutture β-lattamiche



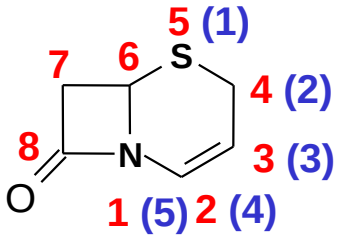
Pename



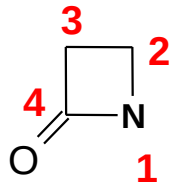
Peneme



Carbapeneme

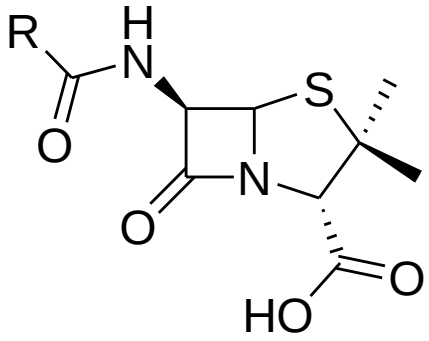


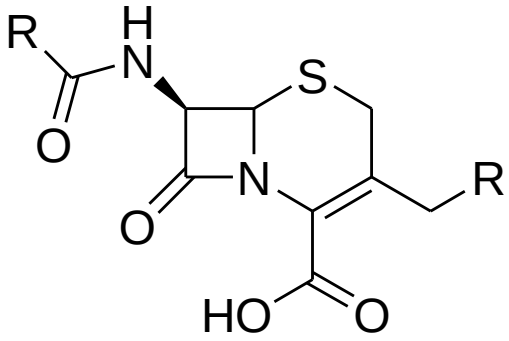
Cefeme



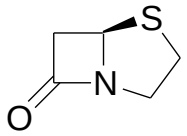
Monobactame

numerazione Chemical Abstract
numerazione USP



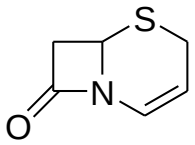


Nomi IUPAC di alcuni nuclei β-lattamici



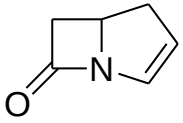
Pename

4-Tia-1-aza-biciclo[3.2.0]eptan-7-one



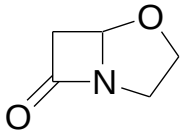
Cefeme

5-Tia-1-aza-biciclo[4.2.0]oct-2-en-8-one



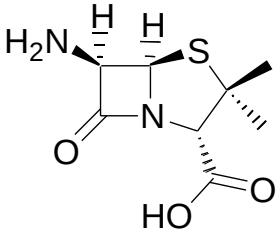
Carbapeneme

1-Aza-biciclo[3.2.0]ept-2-en-7-one



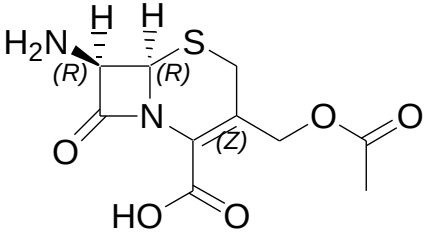
Clavame

4-Oxa-1-aza-biciclo[3.2.0]eptan-7-one



Acido 6-Amino-3,3-dimetil-7-oxo-4-tia-1-aza-biciclo [3.2.0]eptane-2-carbossilico

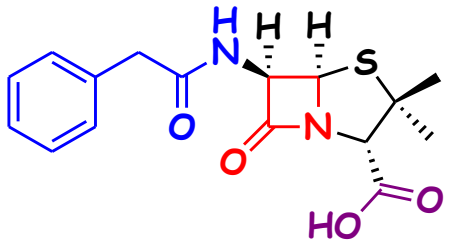
6-APA (Acido 6-aminopenicillanico)



Acido 3-Acetossimetil-7-amino-8-oxo-5-tia-1-aza -biciclo[4.2.0]oct-2-ene-2-carbossilico

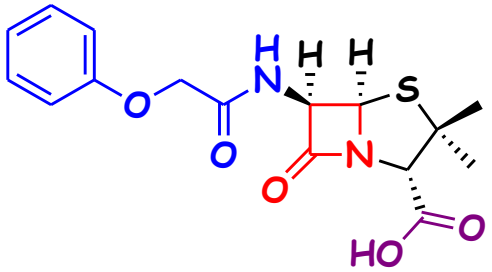
7-ACA (Acido 7-aminocefalosporanico)

NOMI IUPAC di alcuni composti β-lattamici



Benzilpenicillina (Pen.G)

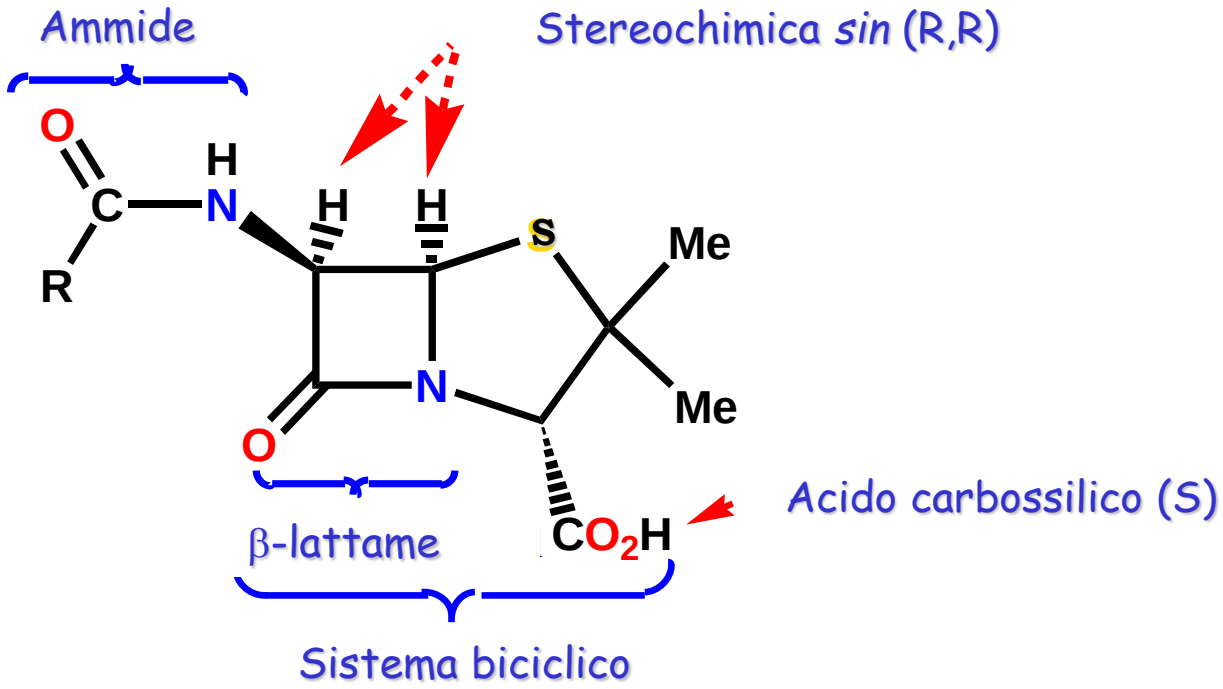
Acido
3,3-Dimetil-7-oxo-6-fenilacetilamino-4-tia-1-aza
-biciclo[3.2.0]eptan-2-carbosslico



Fenossimetilpenicillina (Pen.V)

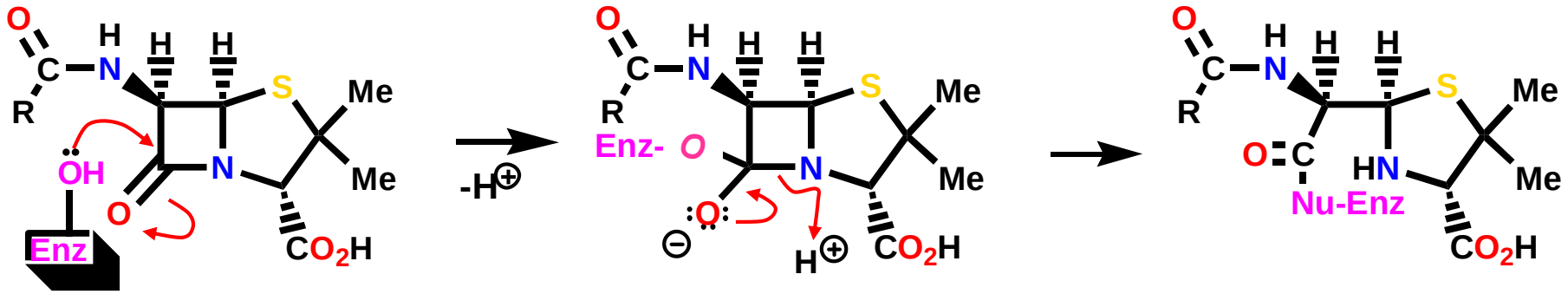
Acido
3,3-Dimetil-7-oxo-6-(2-fenossi-acetilamino)-4-tia-1-az
a-biciclo[3.2.0]eptan-2-carbossilico

SAR

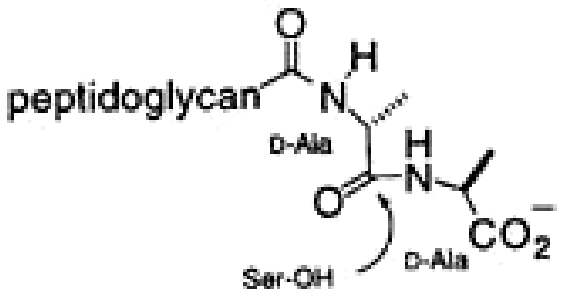


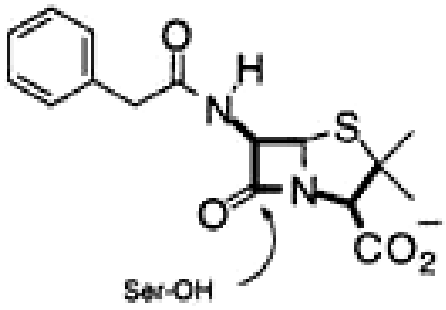
- Le funzioni ammidica e carbossilica (carbossilato) sono coinvolte nel *binding* all'enzima;
- Meccanismo d'azione *determinato* dal β-lattame;
- Attività determinata da parametri geometrici del β-lattame; (fattori di stabilità)
- La struttura biciclica incrementa la tensione sterica del β-lattame;
- Le modifiche strutturali possibili sono tipicamente limitate alla catena 6-β-acilammidica

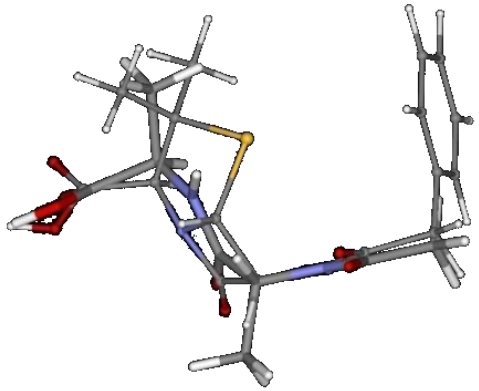
Meccanismo d'azione



Legame covalente al sito catalitico dell'enzima;
Inibizione *(quasi)* irreversibile (substrato suicida)

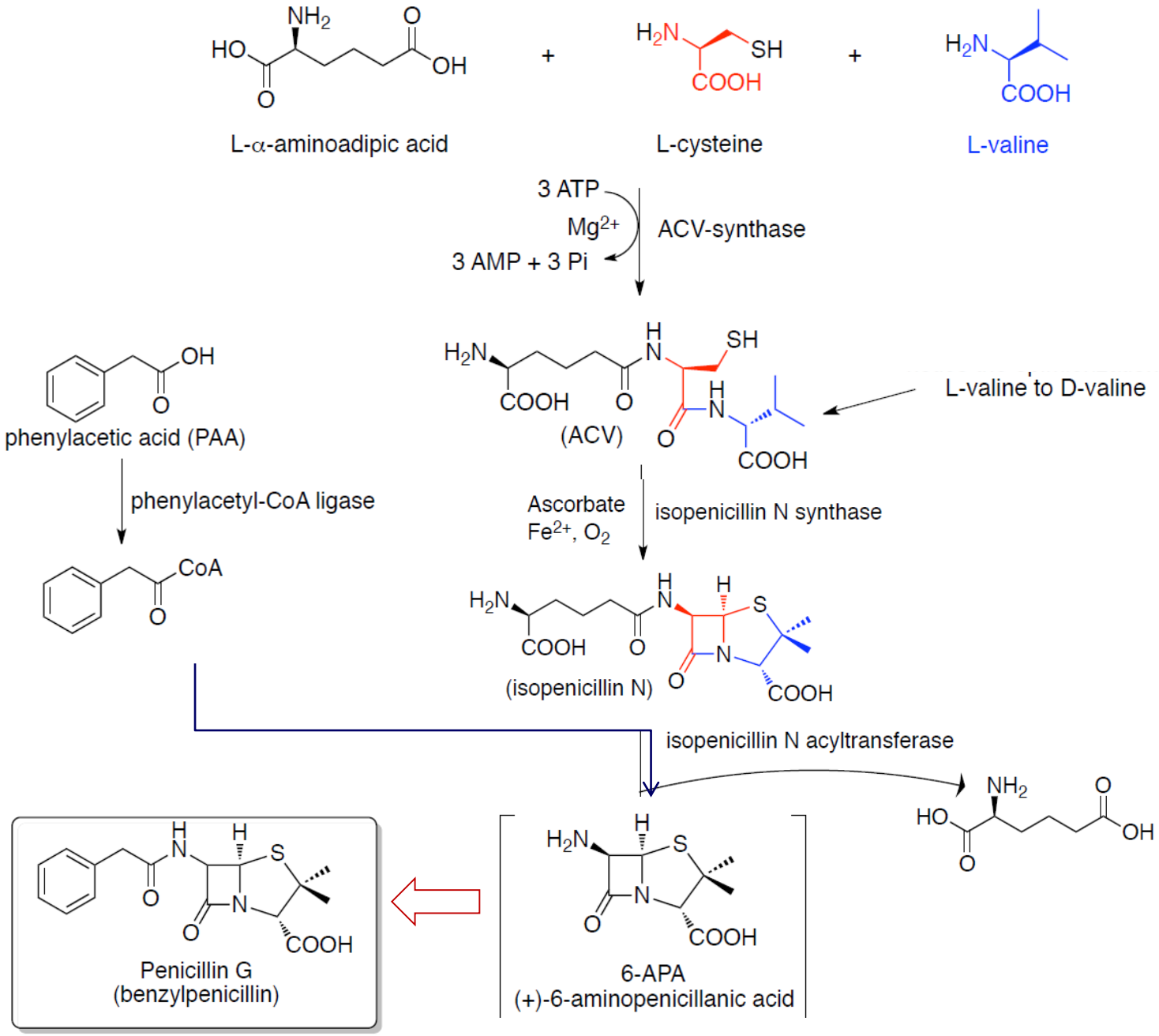






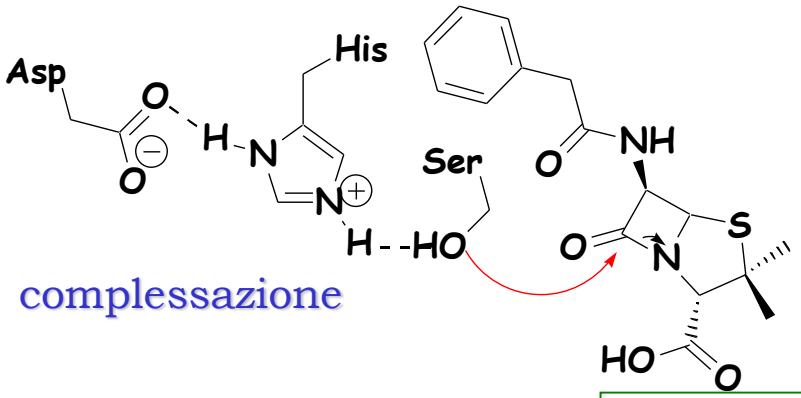
Tipper, D. J. & Strominger, J. L. (1965) Proc. Natl. Acad. Sci. USA 54, 1133-114

Biosynthetic pathway of penicillins

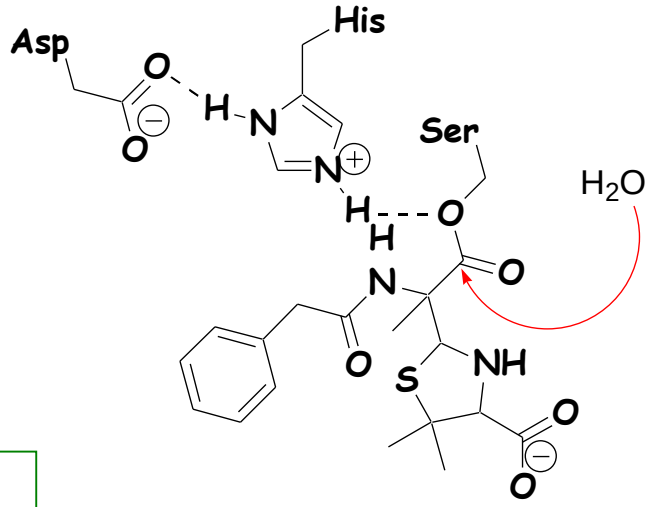


http://www.genome.jp/kegg-bin/show_pathway?map00311

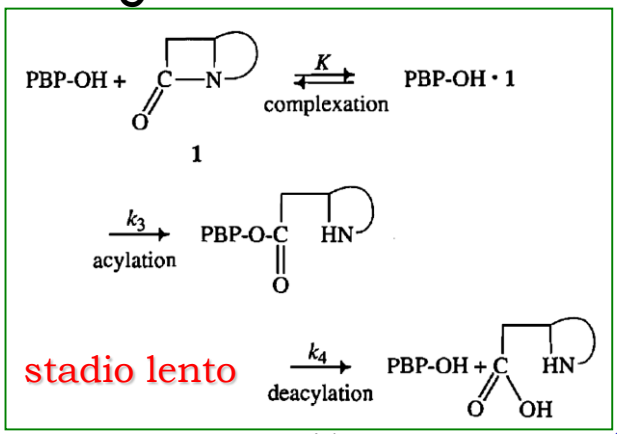
PbP-Proteasi seriniche



acilazione

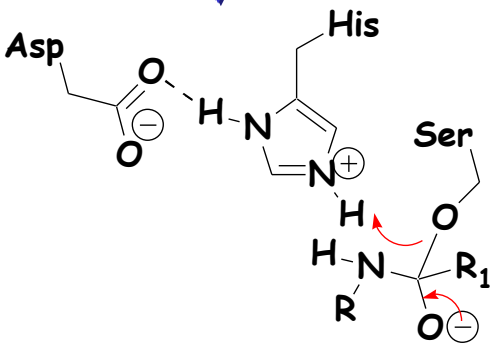


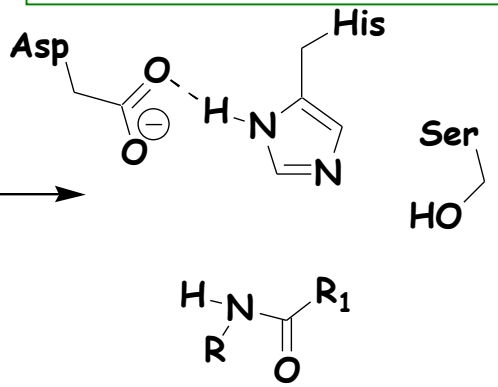
R_1= D-Ala-D-Ala-Lys(DAP;-Gly5-)-Glu-Ala-NAMA-NAG

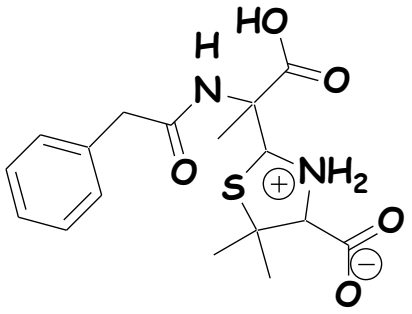


deacilazione

Acido benzil penicilloico





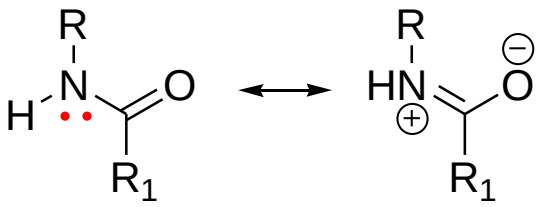


via cross-linking del peptidoglicano

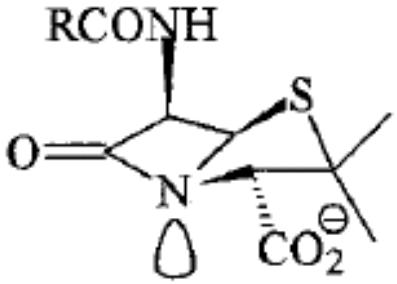
via inattivazione Pbp

Caratteristiche β-lattame

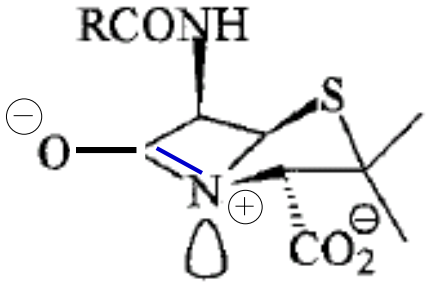
- Struttura instabile (*forte tensione angolare*)
- Elevata capacità elettrofila acilante
- *Acila le transpeptidasi e le β-lattamasi* -Labile (idrolisi) in ambiente acido e basico
- I prodotti di degradazione immunogenici



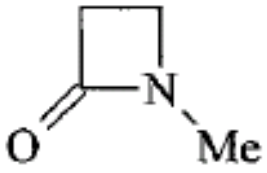
N↑ 0.4Å (pen)
N↑ 0.2-0-3Å (cef)
piramidalizzazione



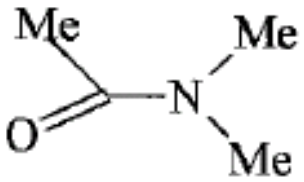
butterfly shape



struttura di risonanza stericamente "sfavorita"



6.1×10^{-6} dm^3 mol^{-1} s^{-1}

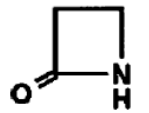
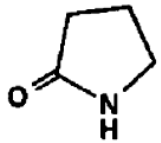
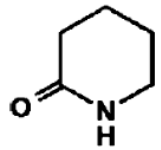
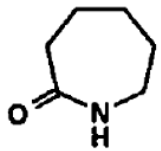
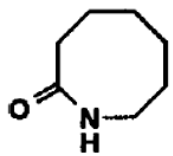
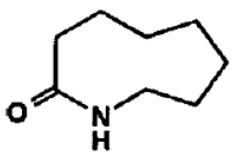
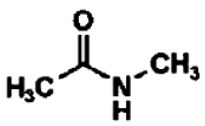


2.3×10^{-6} dm^3 mol^{-1} s^{-1}

- Reattività vs nucleofili: chetoni > ammidi (stab. risonanza 18 kcal/mol);
- Reazione che proceda con perdita della risonanza in TS è 10^{13} volte più rapida;
- E sterica β-lattame è 26-29 kcal/mol → reazione con apertura del ciclo è ~ 10^{20} volte di analogo aliciclico;

Michael I. Page and Andrew P. Laws *Tetrahedron* 56 **(2000)** 5631-5638

Table 1. Results of Hydrolysis Kinetics for Various Lactams

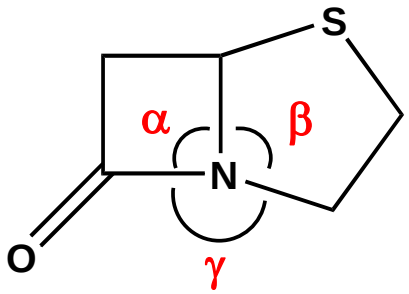
formula	no.	name	k_2 (M^{-1} s^{-1})	log k_2
	**8**	β-propiolactam	2.37×10^{-4}	−3.62
	**9**	γ-butyrolactam	5.59×10^{-6}	−5.34
	**10**	δ-valerolactam	1.21×10^{-4}	−3.92
	**11**	ϵ-caprolactam	3.21×10^{-6}	−5.49
	**12**	ω-oenantholactam	1.36×10^{-7}	−6.87
	**13**	ω-caprolactam	2.72×10^{-7}	−6.57
	**14**	*N*-methylacetamide	3.32×10^{-6}	−5.48

protonation of the lactam nitrogen by the neighboring carboxylic acid residue within the active site of the transpeptidases

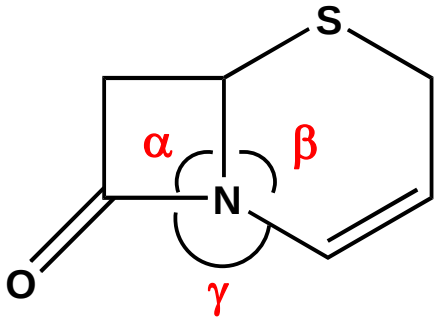
J. Med. Chem. **2000,** *43,* 4328-4331

NUCLEI β-LATTAMICI di PEN e CEF

(cfr. di angoli di legame all'azoto e conseguenze)



pename

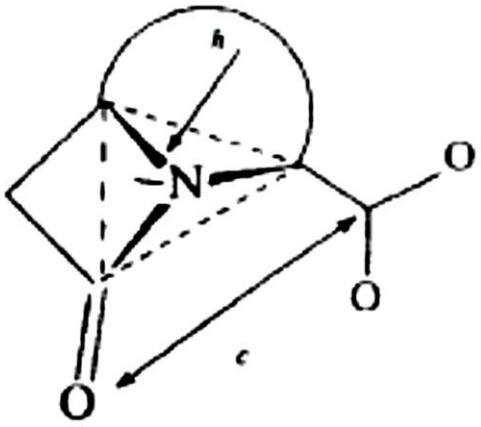


cefeme

	N piramidale (NH_3)	N tetraedrico sp^3 (NH_4^+)	Pename	Cefeme	N trigonale sp^2 (ammidi)
α	107°	109°	95°	95°	120°
β	107°	109°	117°	126°	120°
γ	107°	109°	128°	133°	120°
Σα, β, γ	321°	327°	340°	354°	360°
360°–Σ	39°	33°	20°	6°	0°

3.0 Å > **c** > 3.9 Å

Cohen



0.5 Å > **h** > 0.25 Å

Woodward

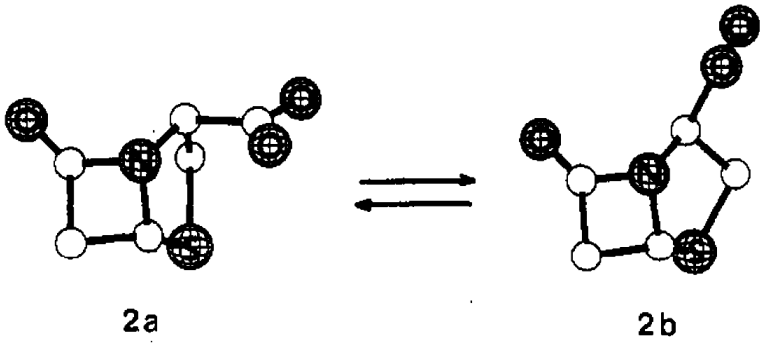
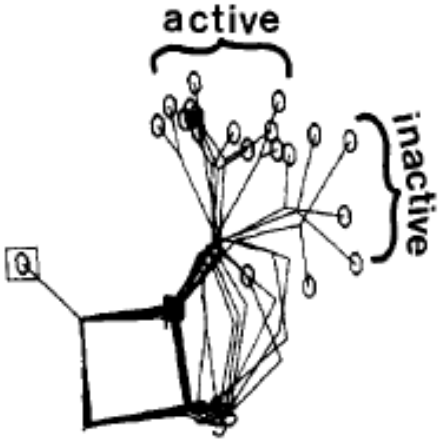
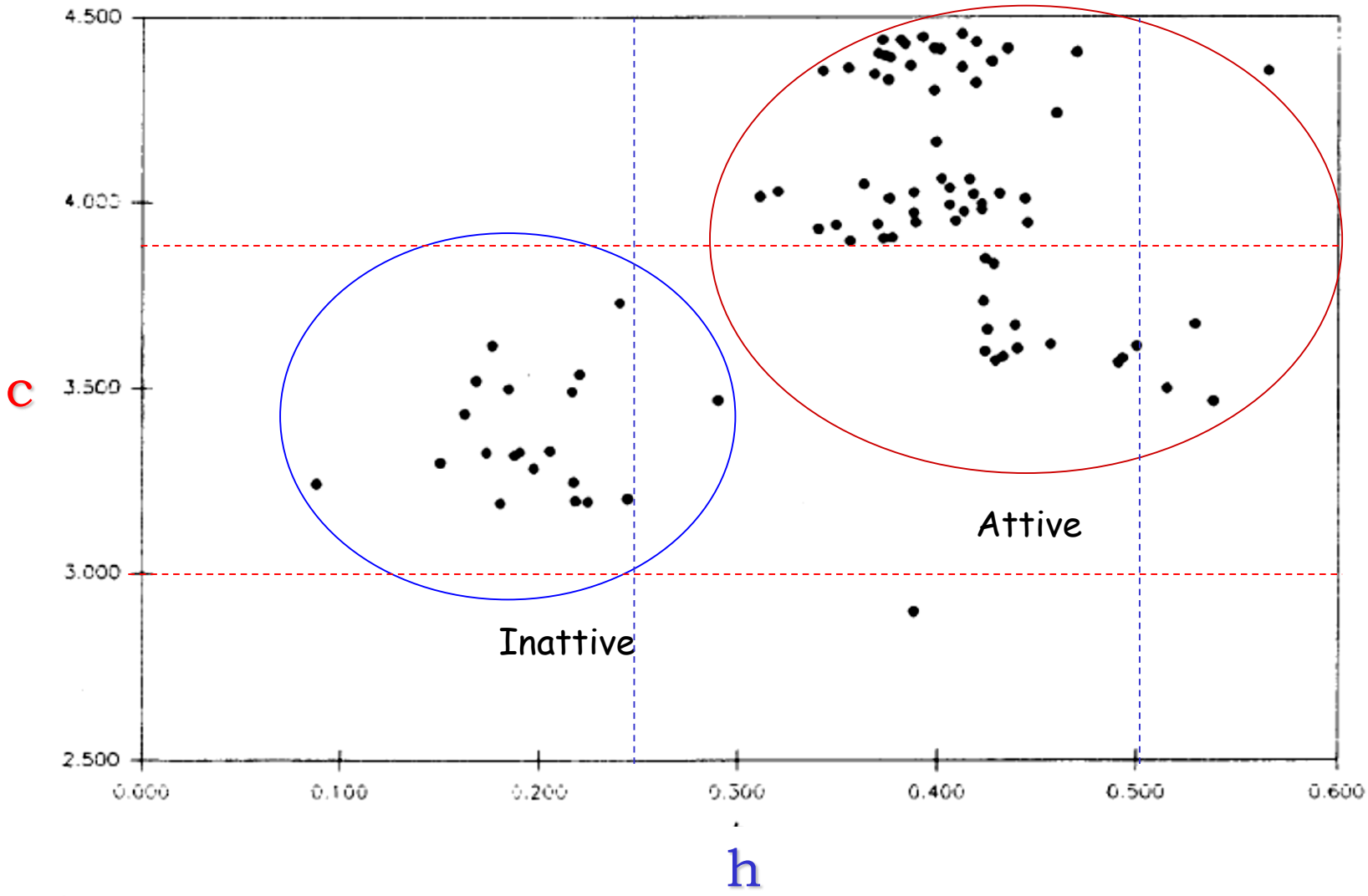


Figure 2. Pseudorotation of the penam nucleus.



(R.B. Woodward, Phil. Trans. R. Soc. Lond. 1980, B289).



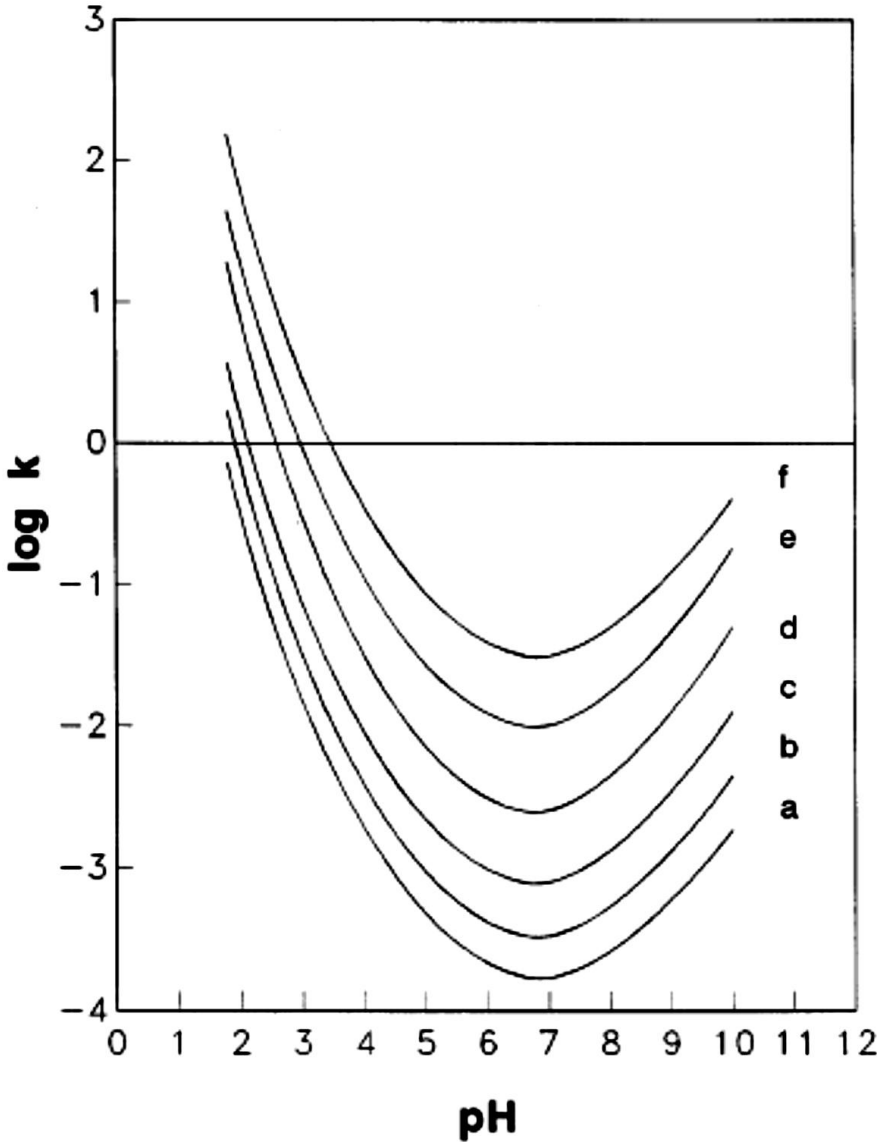
Cohen

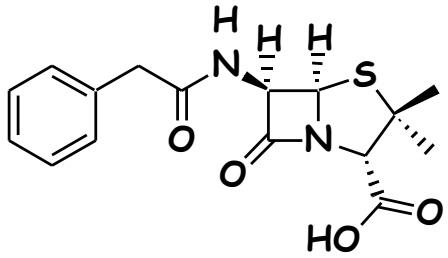
3.0 Å > ***c*** > 3.9 Å

Woodward

0.5 Å > ***h*** > 0.25 Å

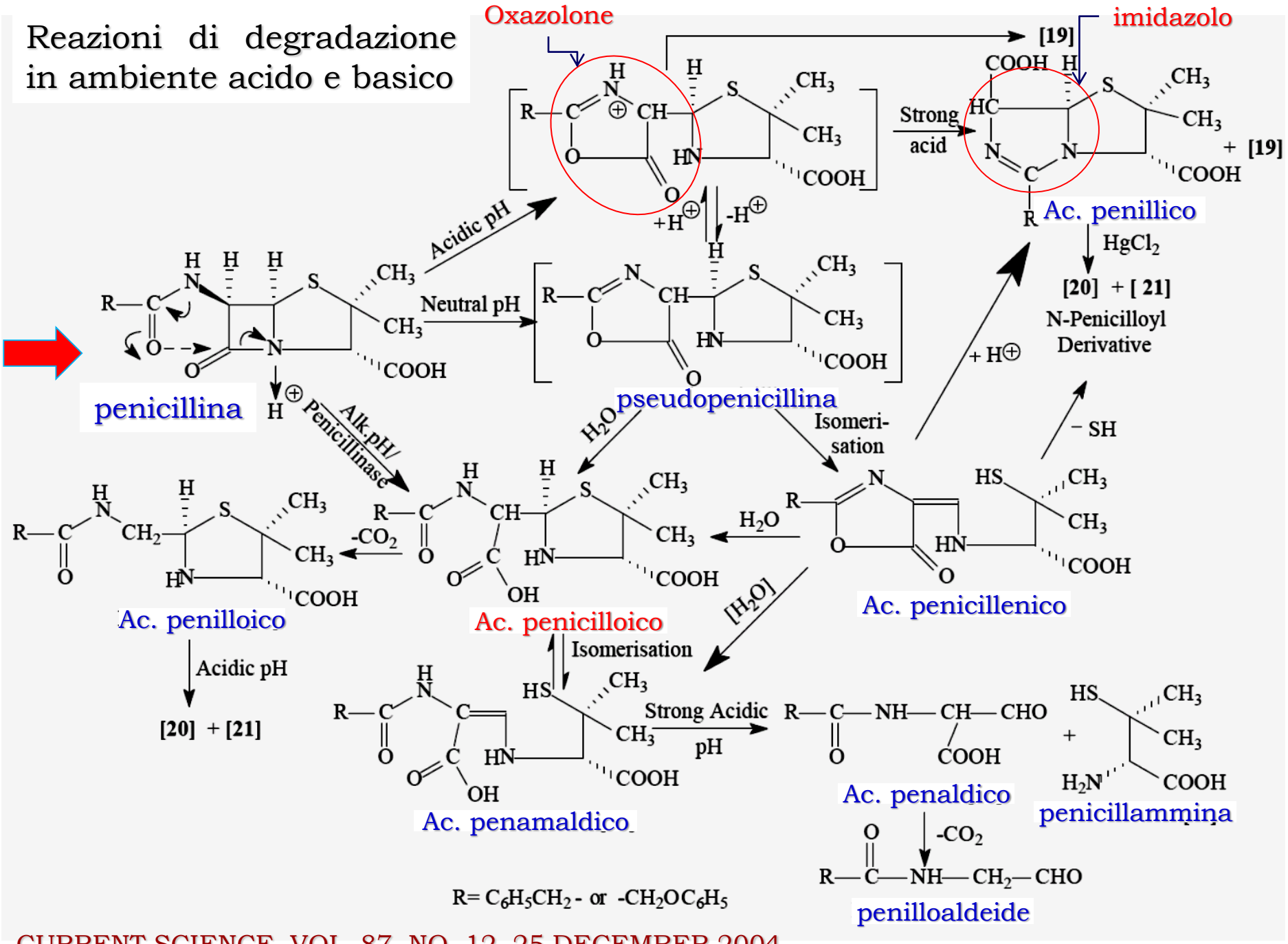
Stabilità in soluzione acquosa della Penicillina G



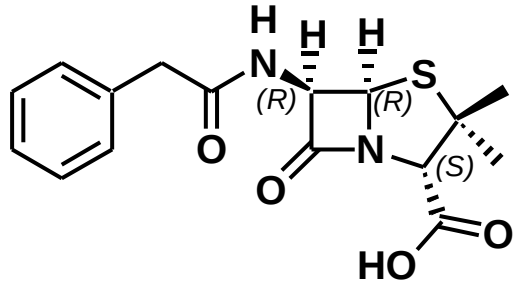


Valori di temperatura:
da 25°C (a) a 60°C (f)
V shape

Reazioni di degradazione in ambiente acido e basico

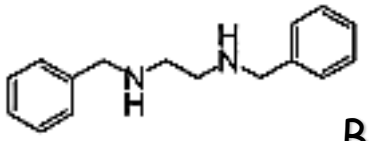


(I) Penicillina G (Benzilpenicillina)



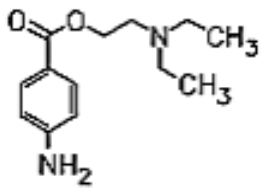
3,3-Dimethyl-7-oxo-6-phenylacetylamino-4-thia -1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

- Penicillina biosintetica (*Penicillium notatum Westling* o *Penicillium chrisogenum Thom* + ac.fenilacetico)
- Poco stabile in ambiente acido (no o.s.)
- Sensibile alla penicillinasi
- Attiva su Gram+ e solo su alcuni Gram- (spettro AM ristretto)
- Proprietà PK non ideali: rapidamente assorbita ed eliminata (alte dosi):
  - inattivata in parte dal succo gastrico (richiesta di dosi molto elevate);
  - sale di Na o di K per uso i.m. e e.v.;
  - rapida escrezione renale (si somministra ogni 4 h);
  - penicillina G sale di procaina, benzatina etc…. (sospensioni acq.):
    - lento assorbimento e lento rilascio del principio attivo;
    - durata di azione prolungata.



N,N'-dibenzyl-ethylenediamine (I)

Benzatina ▫ $(PenG)_2$

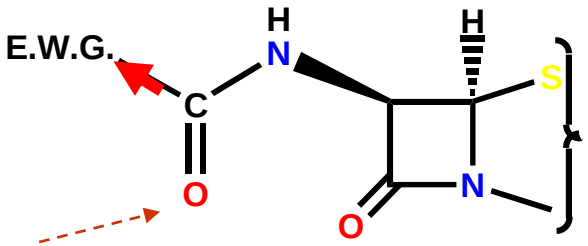


Procaina ▫ PenG

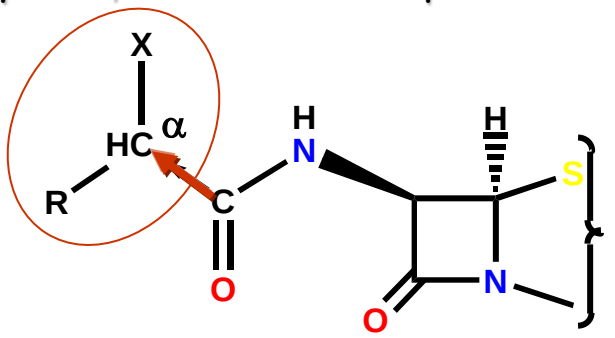
Penicilline stabili in ambiente acido (o.s.)

Strategia

Introdurre sostituenti elettronattrattori nel gruppo 6-β-acilammidico per ridurre la nucleofilia dell'ossigeno carbonilico



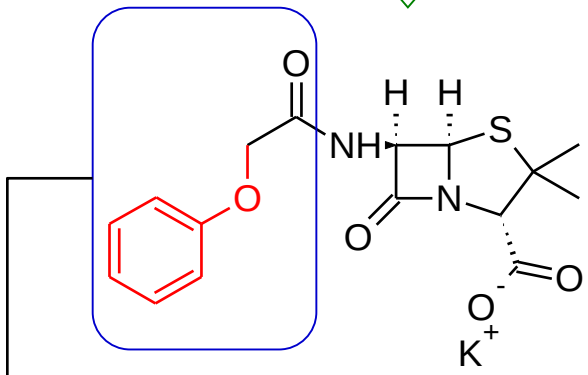
Riduzione della nucleofilia



Ampicillina

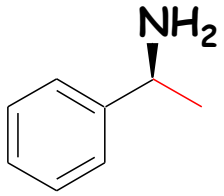
Amoxicillina

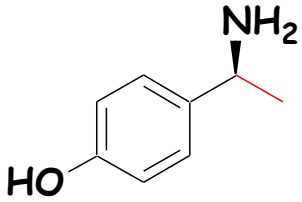
Carbenicillina

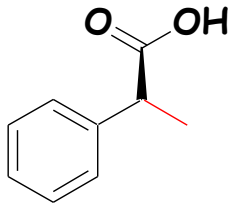


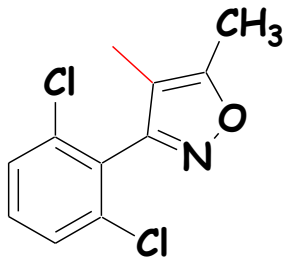
Penicillina V (attiva per o.s.)

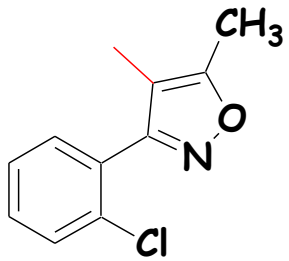
fenossiacetile







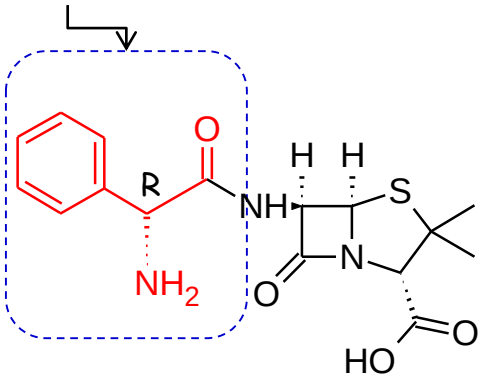




Dicloxacillina

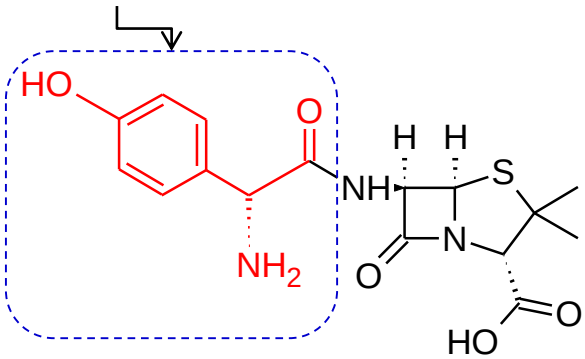
Cloxacillina

2-amino-
2-fenilacetile



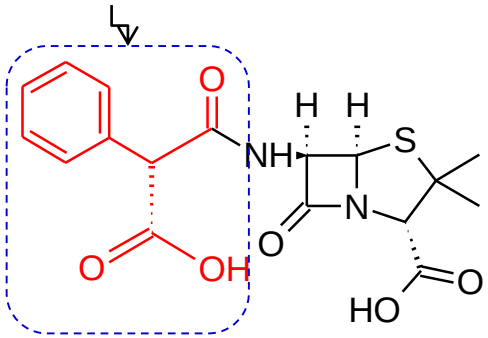
Ampicillina
(Amplital & eq)

2-amino-2-
(4-idrossifenil)acetile



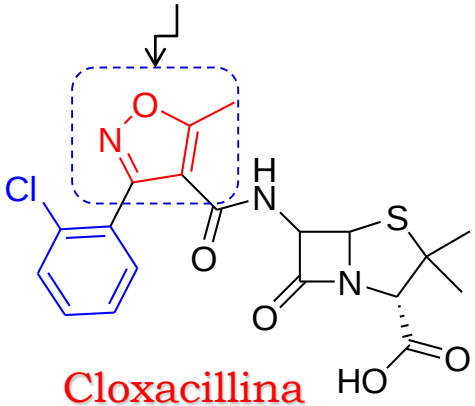
Amoxicillina
(Amosol, Amox, Amoxina, Amoxina, Mopen, Oralmox, Sievert, Sintopen, Velamox, Zimox)

2-carbossi-
2-fenilacetile

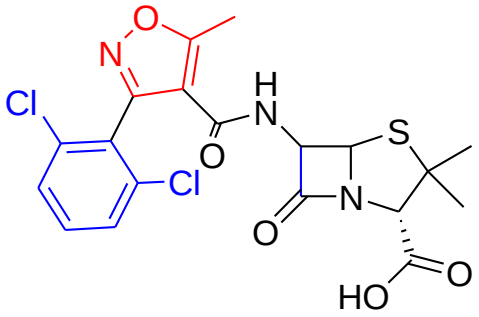


Carbenicillina

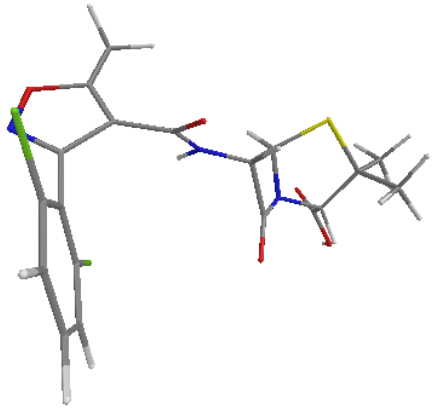
5-metilisossazolo



Cloxacillina



Dicloxacillina



PENICILLINE DI PRIMA GENERAZIONE

Il prototipo	*Penicillina G*
Acido resistenti	*Penicillina V*
Penicillinasi (β-lattamasi) resistenti	*Meticillina, Oxacillina*

PENICILLINE DI SECONDA GENERAZIONE

"Largo Spettro"	*Amoxicillina, Ampicillina*
+inibitori della β-lattamasi	***(Augmentin, Unasyn)***

PENICILLINE DI TERZA GENERAZIONE

"Antipseudomonas"	*Carbenecillina, Ticarcillina*
+inibitori della β-lattamasi	***(Timentin)***

PENICILLINE DI QUARTA GENERAZIONE

"Spettro esteso"	*Mezlocillina, Piperacillina, Mecillinam*

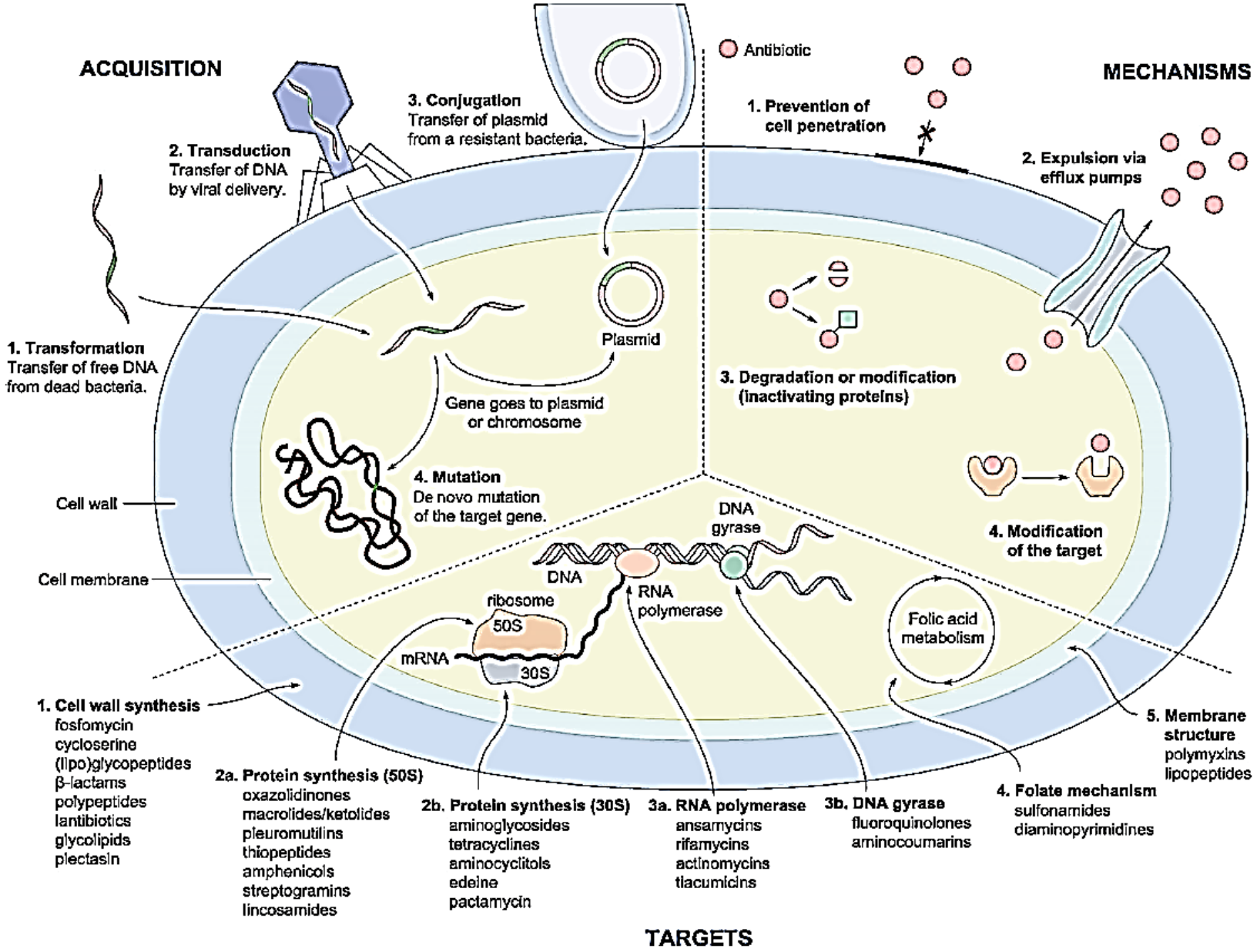


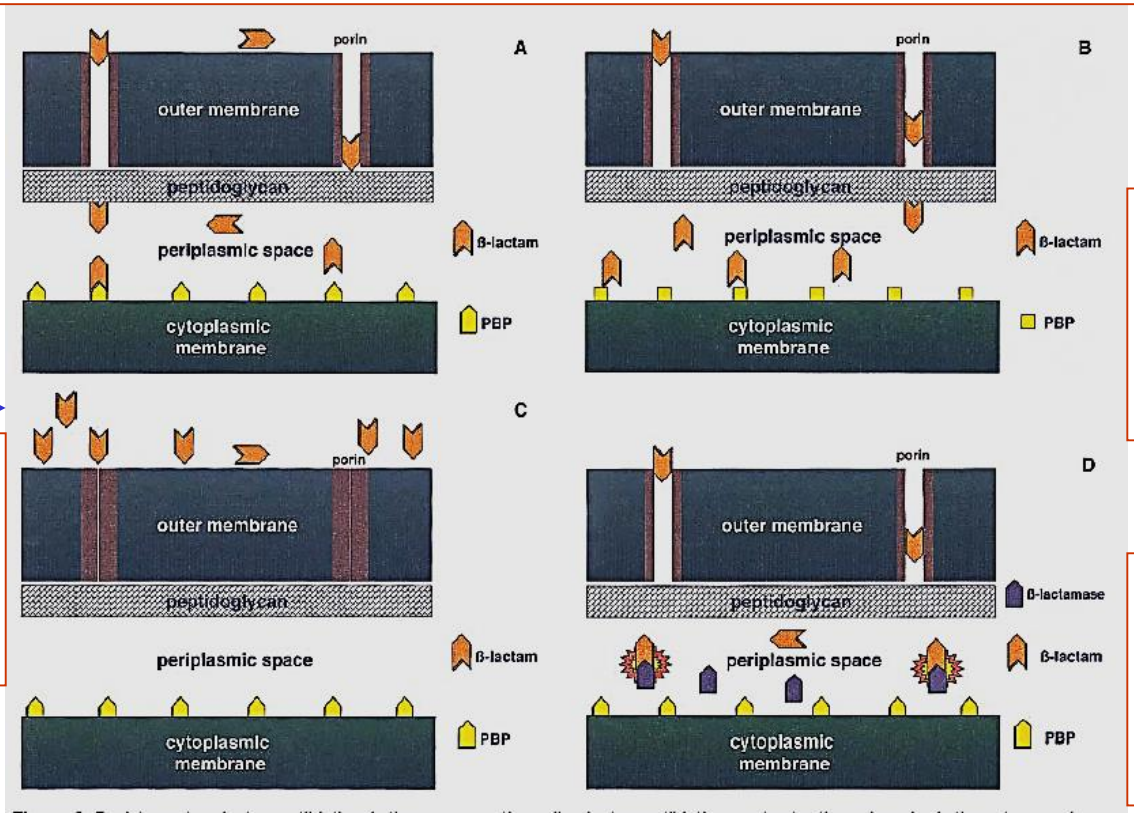
Figure 1. The four resistance acquisition pathways, the four main mechanisms of resistance, and the five main targets for antibiotics.

Targeting Antibiotic Resistance Angew. Chem. Int. Ed. **2016,** 55, 2–30

Penicilline β-lattamasi resistenti:
Meticillina, Nafcillina, Isossazolil-penicilline.

Resistenza agli Aβl:

•Nei Gram- gli Aβl devono permeare specifiche porine nella regione esterna della parete cellulare, attraversare lo spazio periplasmatico ed infine attaccare il target PbP, localizzate nella regione esterna della membrana citoplasmatica



Resistenza generata da modificazioni delle PbP

Resistenza generata da alterazioni delle porine

Resistenza generata da produzione di β-lattamasi

Resistenza generata pompe di efflusso

In 1965, the first plasmid mediated beta- lactamases was discovered. This occurred in a strain of *E.coli* isolated from the blood culture of a patient from Greece whose name was **Temoniera**. The beta -lactamases was named TEM-1 after the patient's name from whom it was isolated.

ANTIMICROBIAL AGENTS AND CHEMOTH ERAPY, Mar. 2010, p. 969–976

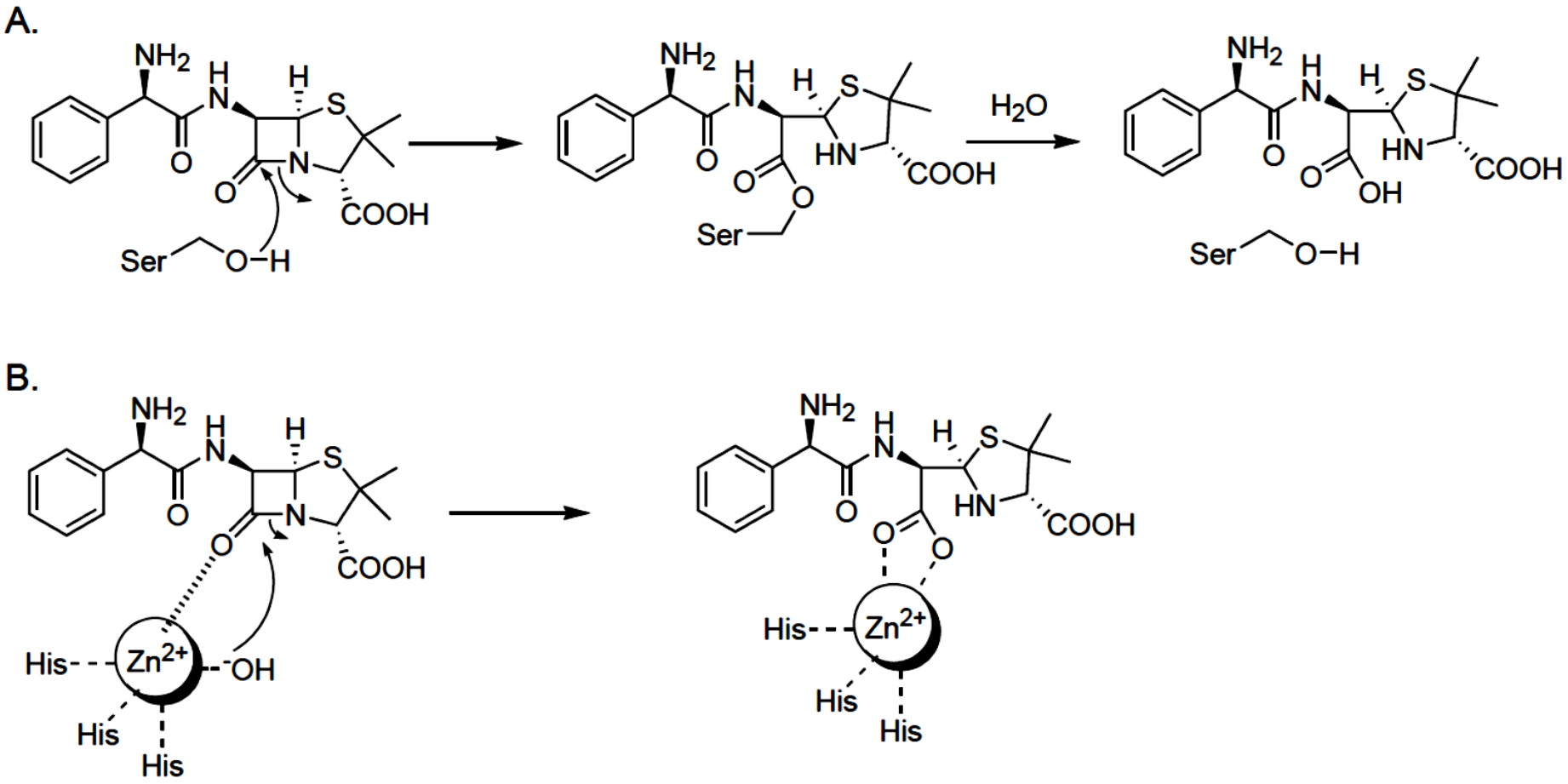
TABLE 1. Classification schemes for bacterial β-lactamases, expanded from Bush et al. (16)

Bush-Jacoby group (2009)	Bush-Jacoby-Medeiros group (1995)	Molecular class (subclass)	Distinctive substrate(s)	Inhibited by		Defining characteristic(s)	Representative enzyme(s)
				CA or TZB[a]	EDTA		
1	1	C	Cephalosporins	No	No	Greater hydrolysis of cephalosporins than benzylpenicillin; hydrolyzes cephamycins	*E. coli* AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
1e	NI[b]	C	Cephalosporins	No	No	Increased hydrolysis of ceftazidime and often other oxyimino-β-lactams	GC1, CMY-37
2a	2a	A	Penicillins	Yes	No	Greater hydrolysis of benzylpenicillin than cephalosporins	PC1
2b	2b	A	Penicillins, early cephalosporins	Yes	No	Similar hydrolysis of benzylpenicillin and cephalosporins	TEM-1, TEM-2, SHV-1
2be	2be	A	Extended-spectrum cephalosporins, monobactams	Yes	No	Increased hydrolysis of oxyimino-β-lactams (cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam)	TEM-3, SHV-2, CTX-M-15, PER-1, VEB-1
2br	2br	A	Penicillins	No	No	Resistance to clavulanic acid, sulbactam, and tazobactam	TEM-30, SHV-10
2ber	NI	A	Extended-spectrum cephalosporins, monobactams	No	No	Increased hydrolysis of oxyimino-β-lactams combined with resistance to clavulanic acid, sulbactam, and tazobactam	TEM-50
2c	2c	A	Carbenicillin	Yes	No	Increased hydrolysis of carbenicillin	PSE-1, CARB-3
2ce	NI	A	Carbenicillin, cefepime	Yes	No	Increased hydrolysis of carbenicillin, cefepime, and cefpirome	RTG-4
2d	2d	D	Cloxacillin	Variable	No	Increased hydrolysis of cloxacillin or oxacillin	OXA-1, OXA-10
2de	NI	D	Extended-spectrum cephalosporins	Variable	No	Hydrolyzes cloxacillin or oxacillin and oxyimino-β-lactams	OXA-11, OXA-15
2df	NI	D	Carbapenems	Variable	No	Hydrolyzes cloxacillin or oxacillin and carbapenems	OXA-23, OXA-48
2e	2e	A	Extended-spectrum cephalosporins	Yes	No	Hydrolyzes cephalosporins. Inhibited by clavulanic acid but not aztreonam	CepA
2f	2f	A	Carbapenems	Variable	No	Increased hydrolysis of carbapenems, oxyimino-β-lactams, cephamycins	KPC-2, IMI-1, SME-1
3a	3	B (B1)	Carbapenems	No	Yes	Broad-spectrum hydrolysis including carbapenems but not monobactams	IMP-1, VIM-1, CcrA, IND-1
		B (B3)					L1, CAU-1, GOB-1, FEZ-1
3b	3	B (B2)	Carbapenems	No	Yes	Preferential hydrolysis of carbapenems	CphA, Sfh-1
NI	4	Unknown					

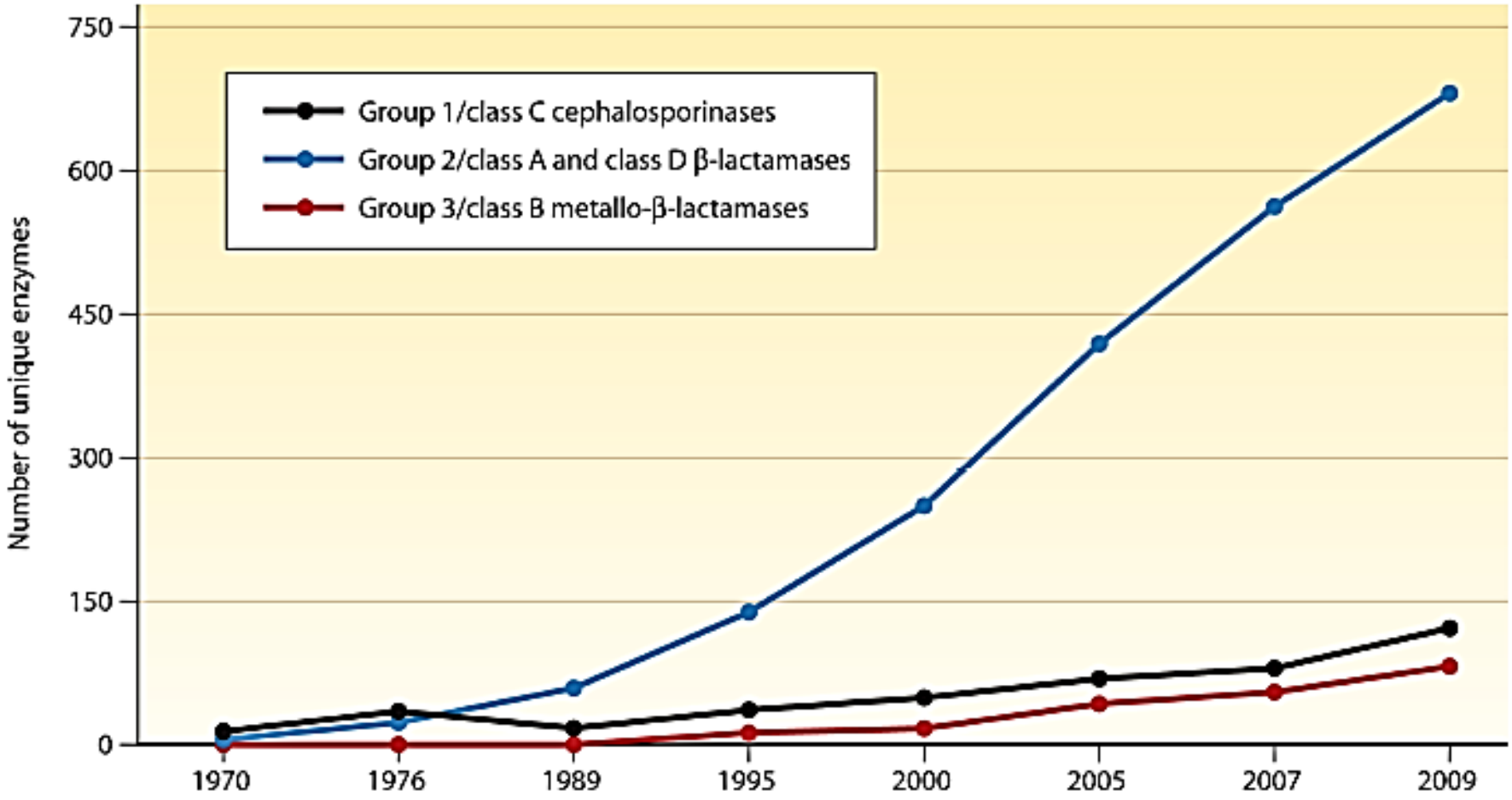
[a] CA, clavulanic acid; TZB, tazobactam.
[b] NI, not included.

A, C, D serin proteasi;

B Zn proteasi



Le Ser-β-lattamasi e le metallo-β-lattamasi possono essere ulteriormente classificate in base alla loro struttura terziaria, quaternaria, specificità di substrato e sensibilità a inibitori.

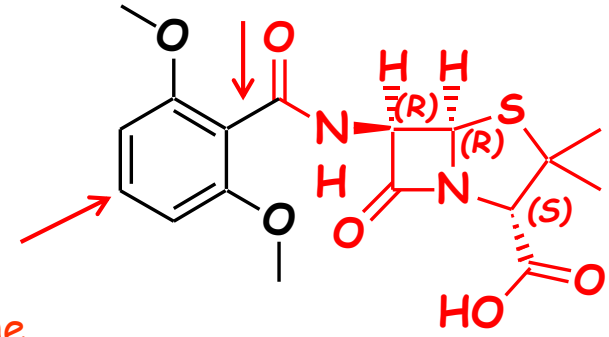


Gruppo 1: debole inibizione da acido clavulanico
Gruppo 2: sensibili acido clavulanico (lattamasi ampio spettro)

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. **2010**, p. 969–976

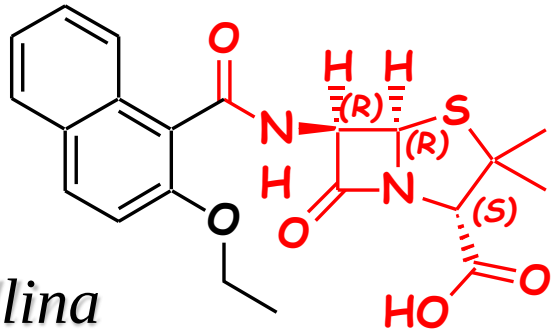
- Instabile in ambiente acido
- Resistente alle β-lattamasi
- Attiva verso Gram+,
- Attiva contro lo S. Aureus.
- La resistenza insorge per modificazione di PBPs (MRSA)

http://www.cdc.gov/mrsa/



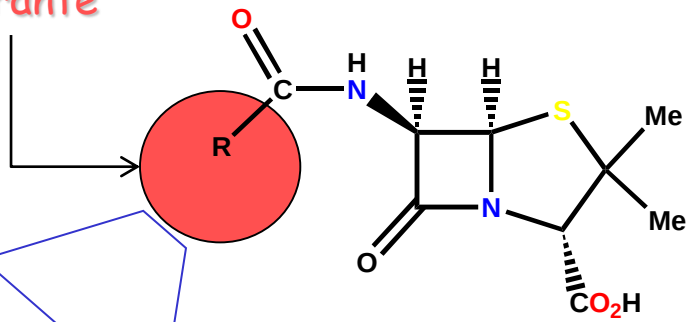
Meticillina

Impedimento sterico dei due OMe



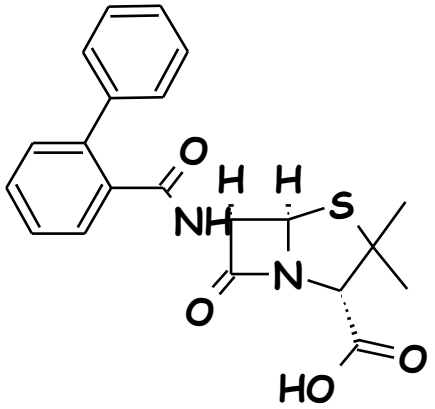
Nafcillina

Gruppo ingombrante



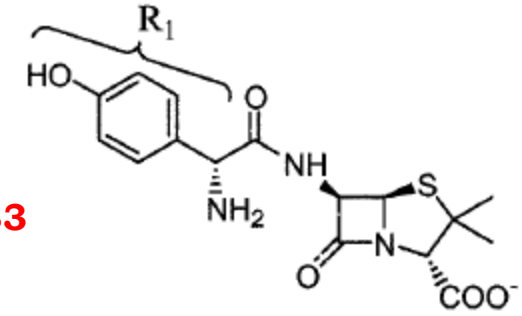
Sito catalitico dell'enzima

Ancillin



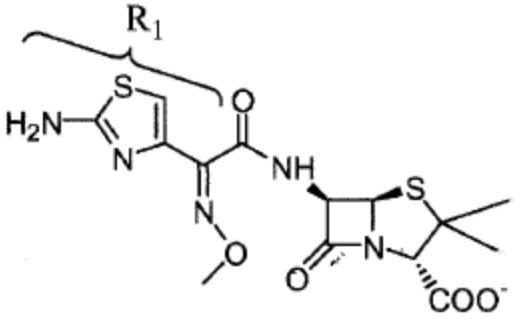
Kinetic Data for Hydrolysis of Analogous β-Lactams by AmpC -Lactamase

kcat (s^{-1}) 133



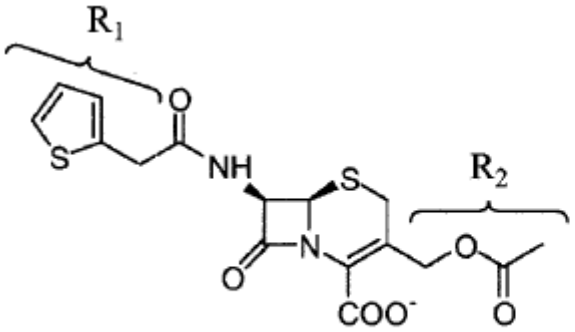
Amoxicillin (substrate)

kcat (s^{-1}) 5.0



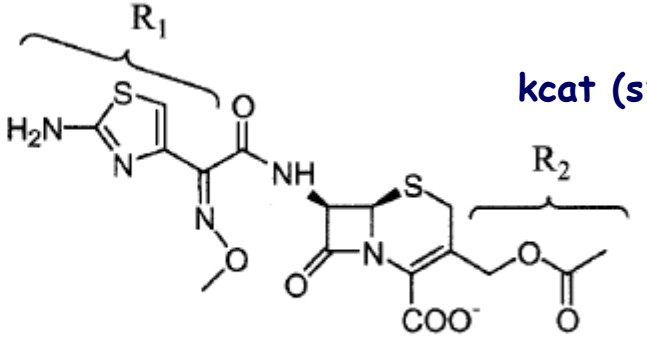
ATMO-penicillin (inhibitor)

kcat (s^{-1}) 263



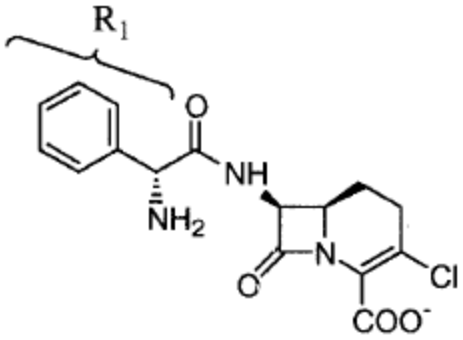
Cephalothin (substrate)

kcat (s^{-1}) 0.0048



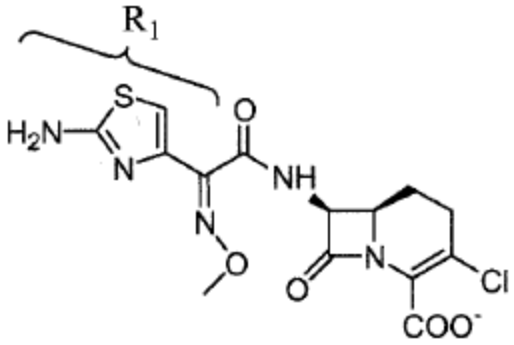
Cefotaxime (inhibitor)

kcat (s^{-1}) 118



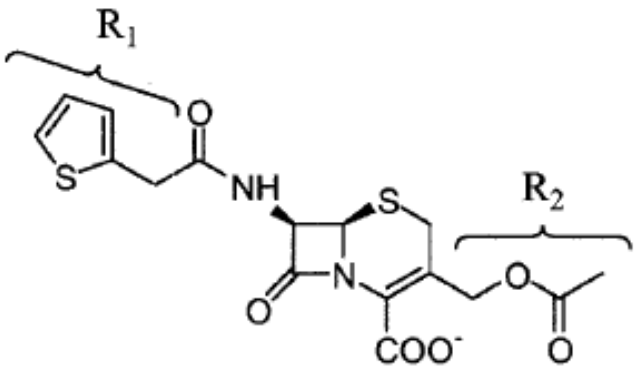
Loracarbef (substrate)

kcat (s^{-1}) 24

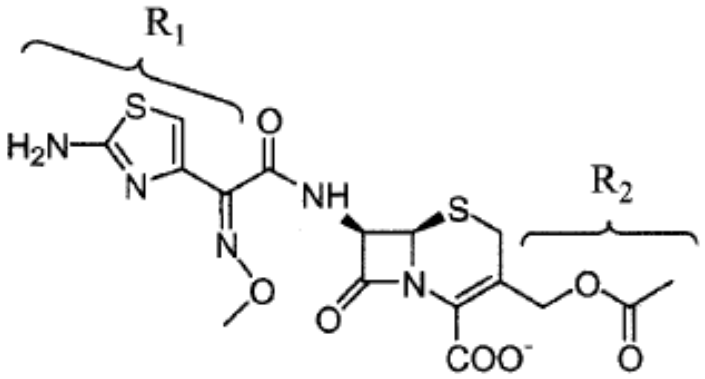


ATMO-carbacephem (inhibitor)

Minimum Inhibitory Concentrations (μg/ml) of Representative β-Lactams



Cephalothin (substrate)



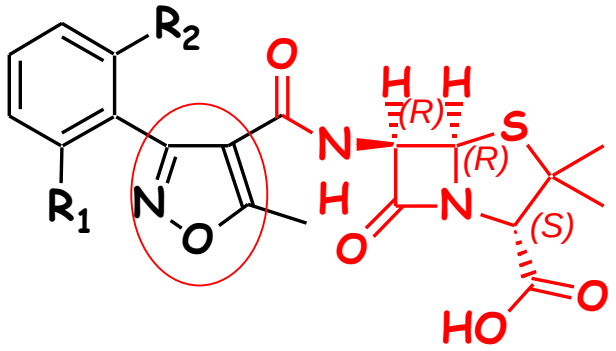
Cefotaxime (inhibitor)

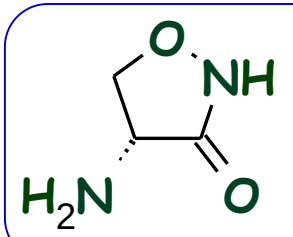
8	*E. coli* not expressing AmpC β-lactamase	0.00781
64	*E. coli* expressing AmpC β-lactamase	**0.0313**
>2048	*E. cloacae* expressing β-lactamase	64
0.25	*S. aureus* expressing β-lactamase	1

Trehan, I. et al. Using Steric Hindrance to Design New Inhibitors of Class C b-Lactamases. Chemistry & Biology, Vol. 9, 971–980, September, 2002

Isoxazolil-penicilline (penicillinasi resistenti, os)

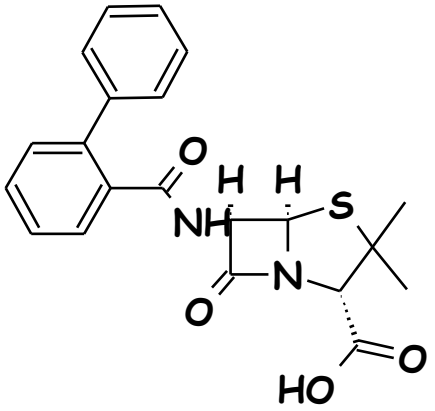
Oxacillina ($R_1 = R_2 = H$), *(Penstapho)*
Cloxacillina ($R_1 = Cl$; $R_2 = H$)
Dicloxacillina ($R_1 = R_2 = Cl$)
Flucloxacillina (*Floxacillin, Faifloc, Flucacid, Flucef, Liderclox,* ....)
($R_1 = Cl$; $R_2 = F$)





(cfr cicloserina)

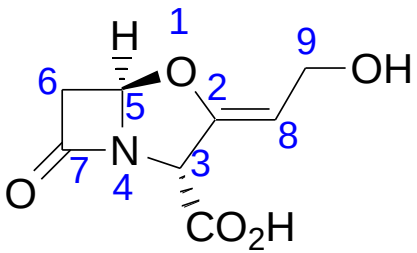
- Bioisosteria dell'anello isossazolico con il fenile
- Stabili alle β-lattamasi
- Stabili in ambiente acido
- Attive contro Gram+
- La Dicloxacillina è il composto più attivo
- Inattive verso MRSA



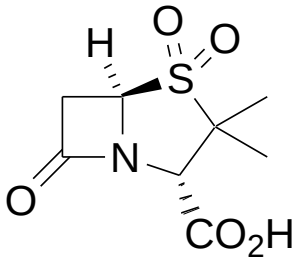
Ancillin

Inibitori β-lattamasi

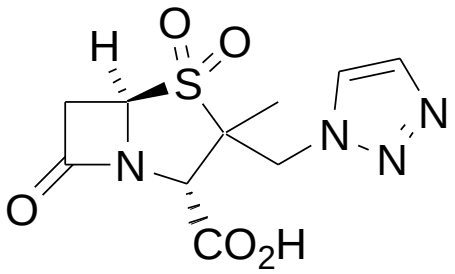
- Attività antibatterica trascurabile
- Associazioni con antibiotici β-lattamici (*sinergismo di farmaci*)
- *Augmentin® = amoxicillina + ac. clavulanico*
- *Unasyn® = ampicillina + sulbactam*
- *Zosyn ® = piperacillina + tazobactam*



Ac. clavulanico

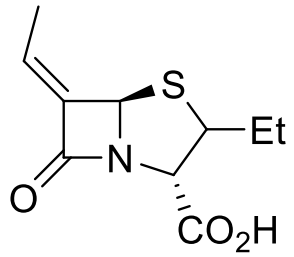


Sulbactam



Tazobactam

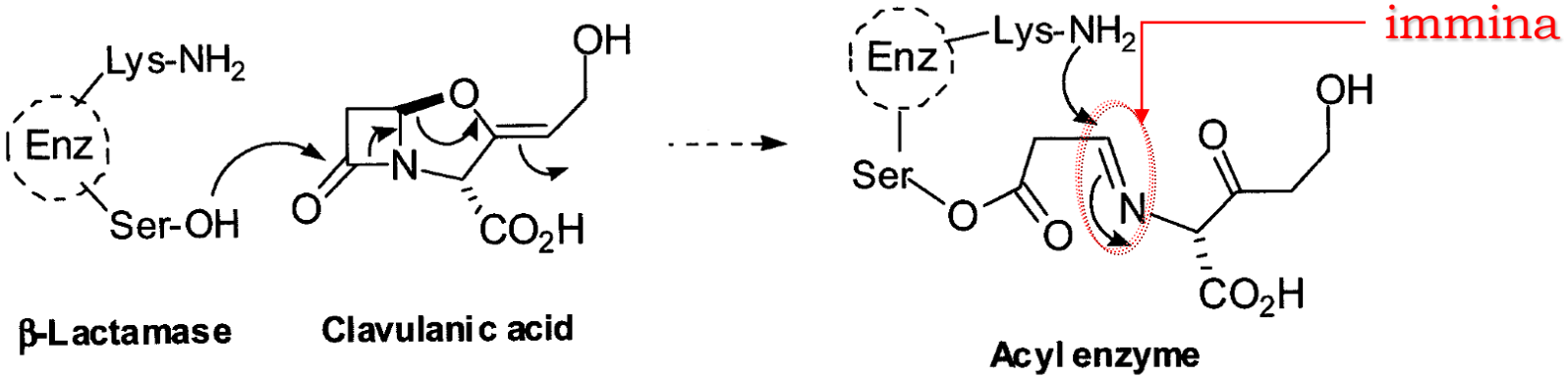
1976 (*Streptomyces clavuligerus*)



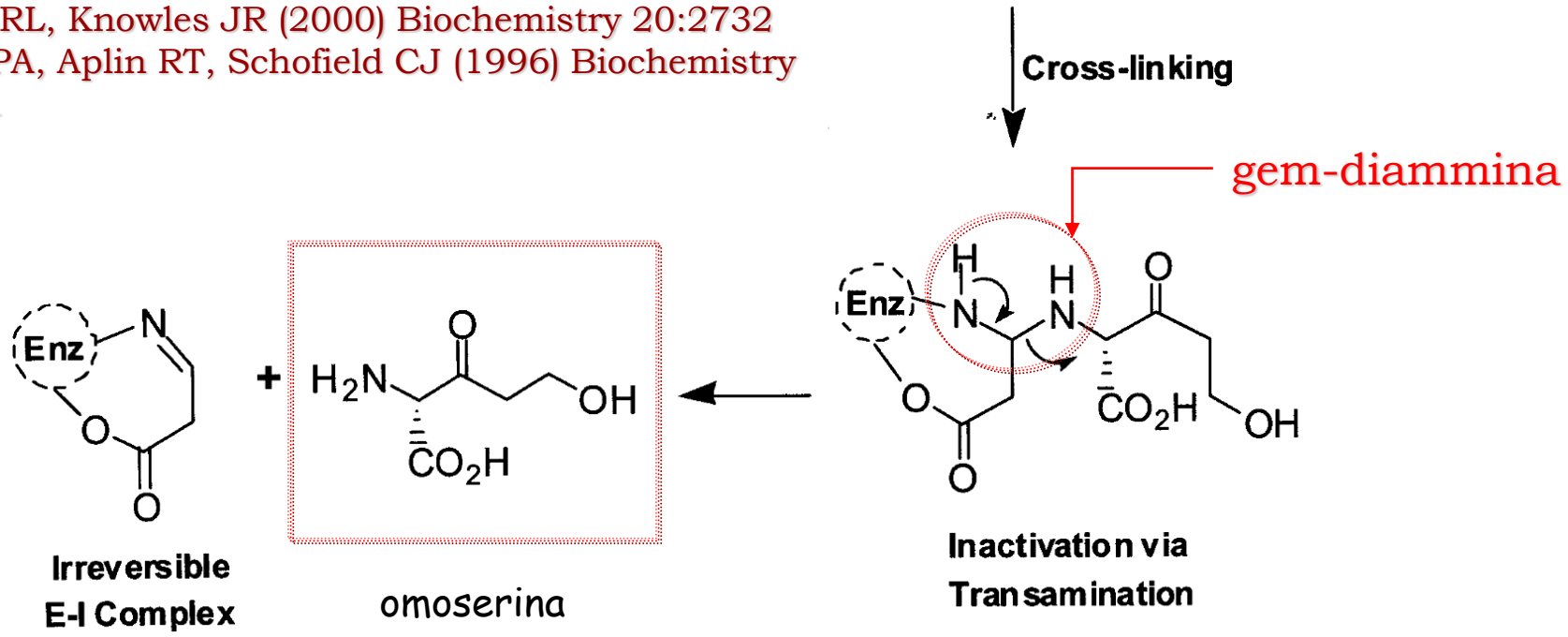
BRL-42715

Pivsulbactam, prodrug: 3-$COOCH_2O$-$COC(CH_3)_3$

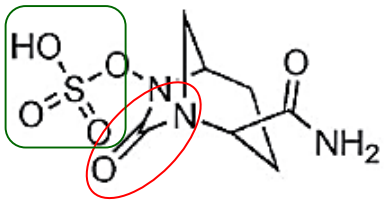
Acido Clavulanico: Meccanismo di inibizione delle β-Lattamasi



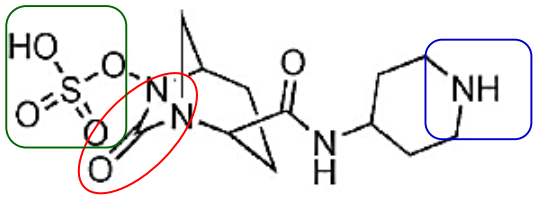
Charnas RL, Knowles JR (2000) Biochemistry 20:2732
Brown RPA, Aplin RT, Schofield CJ (1996) Biochemistry 35:12421



approved by the FDA in 2015 in combination with the β-lactam ceftazidime

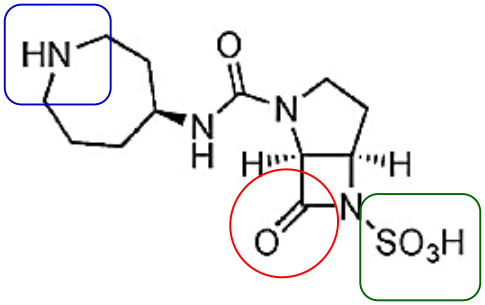


avibactam (**54**)

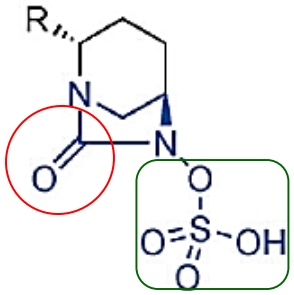


relebactam (**55**)

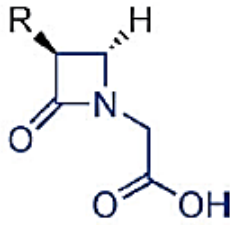
The diazabicyclooctane (DBO) non-β-lactam inhibitors and similarity with the β-lactam core.



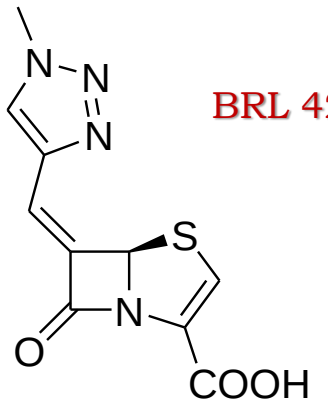
MK-8712 (**56**)



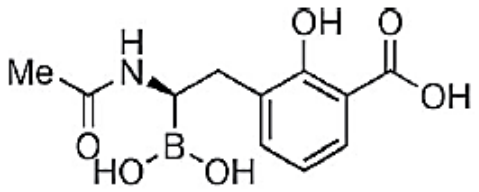
DBO core



β-lactam core



BRL 42715



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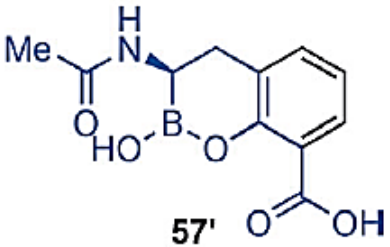

57'

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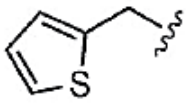
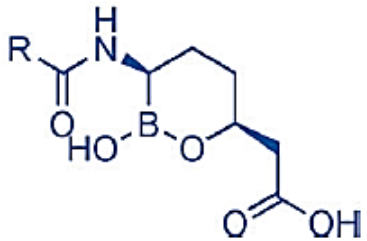


RPX7009 (**58**)



Inibizione β-lattamasi (IC_{50} μg/mL)

Patogeno	Classe enzima	Acido clavulanico	Sulbactam	Tazobactam	BRL 2715
S. aureus (+)	A	0.063	1.4	0.27	0.016
E. coli (TEM1) (-)	A	0.055	1.7	0.028	0.002
E. coli (SHV-1) (-)	A	0.035	13.0	0.14	0.001
Enter. cloacae (P99)(-)	C	>50	5.0	0.93	0.002
E. coli (OXA-1) (-)	D	0.71	2.2	1.1	0.001

Amoxicillina + Inibitore (μg/mL)

Patogeno	Classe enzima	Senza inibitore	Acido clavulanico	Sulbactam	Tazobactam	BRL 42715
P. Mirabilis (-)	A	>512	16	64	16	2
E. coli (TEM1) (-)	A	>512	8	128	8	2
K. pneumoniae (SHV-1) (-)	A	256	4	64	16	2
Enter. cloacae (-)	C	512	>510	256	256	2
E. coli (OXA-1) (-)	D	>512	>512	>512	>512	2

Estensione dello spettro di attività

Variabili batteriche

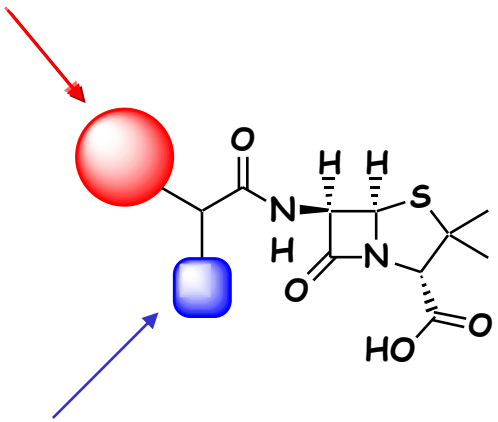
- pareti cellulari che presentano modificazioni tali da ridurre la permeazione degli Aβl;
- Iperespressione di PbB;
- Modificazioni delle PbB con conseguente resistenza agli Aβl;
- Presenza di β-lattamasi e loro trasferimento tra ceppi;
- Alterazione dei meccanismi di efflusso (ABC).

Strategie possibili

- Il numero delle variabili coinvolte rende, ad oggi, impossibile l'adozione di una singola strategia di disegno;
- Uso massivo del protocollo *trial-error* mediante modificazioni dei sostituenti 6-β-acilammidici;
- Identificazione di Aβl ad ampio spettro in conseguenza della sintesi e screening di migliaia di nuovi composti;
- Analisi di alcune relazioni generali tra struttura ed attività.

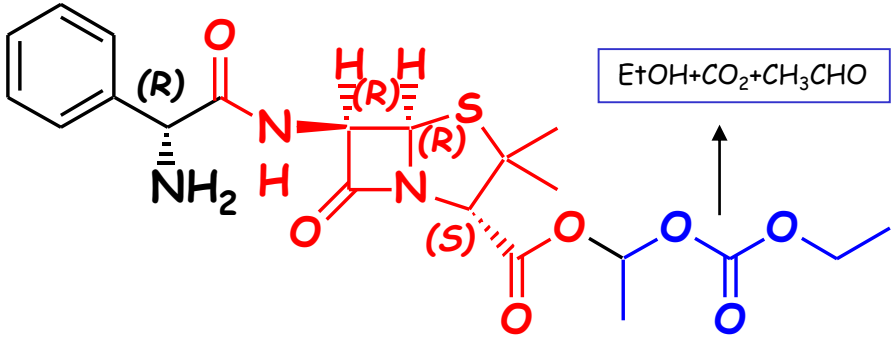
> logP: ≥ Gram+; « Gram-

< logP: ~ Gram+; > Gram-



NH_2; OH; COOH » Gram-

Profarmaci della ampicillina

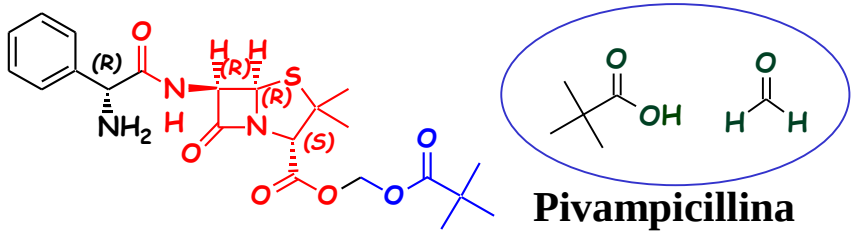


Bacampicillina

(Bacacin, Bacagen,..,Campixen)Penglobe,Rebacil,Winnipeg)

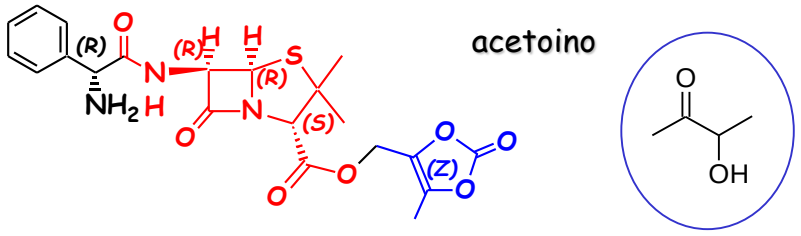
ANTIMCROBIAL AGzNTS AND CHEMOTHzRAPY, Nov. 1975, p. 518-526

- Composto basico (l'ampicillina è anfotera)
- L' idrolisi enzimatica nella parete intestinale libera: ampicillina, alcool etilico, CO_2 e acetaldeide
- Stesso spettro dell'ampicillina, meno effetti collaterali (diarrea)



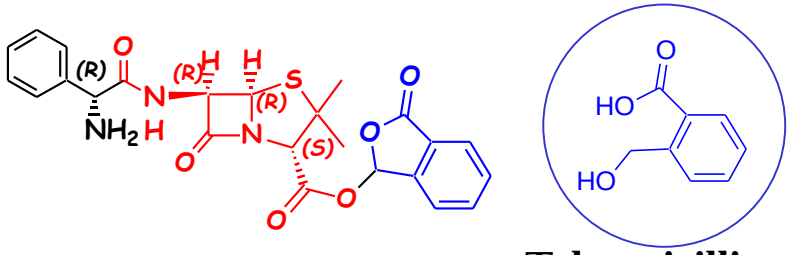
Pivampicillina

pivaloilossimetil estere dell'ampicillina



Lenampicillina (LAPC)

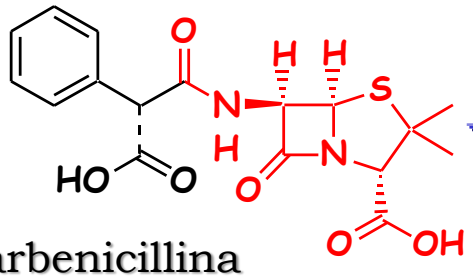
Antimicrob Agents Chemother. 1986 May; 29(5): 948-950.



Talampicillina

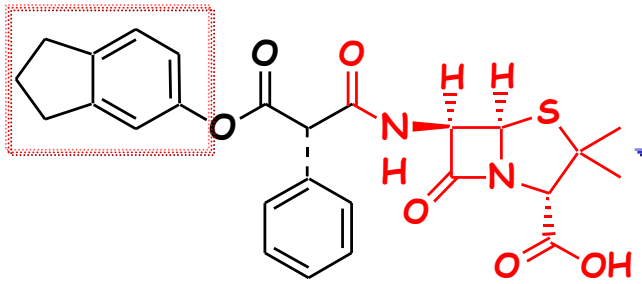
Br Med J. 1976 June 5; 1(6022): 1378-1380

Penicilline Antipseudomonas *(biacidi)*



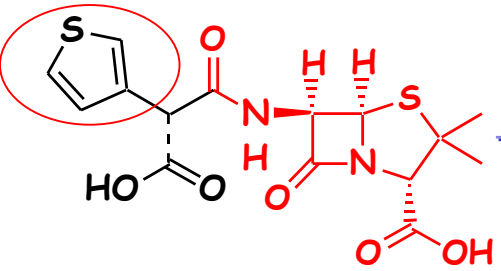
Carbenicillina

- Prima penicillina attiva contro *P. aeruginosa*
- Il gruppo carbossilico la rende + idrofila (Gram-)
- Miscela di epimeri (Stereocentro fenilmalonico)
- Instabile in ambente acido (decarbossila a Pen G)
- Sensibile alle β-lattamasi



Carindacillina

- Prodrug della carbenicillina *(estere aromatico).*
- *Il semplice estere fenolico, meno usato, si chiama* carfecillina)



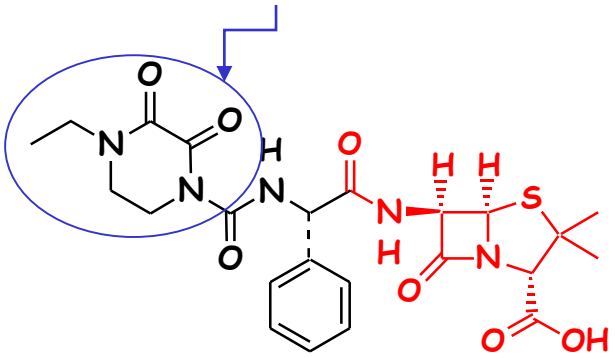
Ticarcillina

- Isostere della carbenicillina
- Associazione con ac. Clavulanico (*Timentin*) ESBL

La specie Pseudomonas aeruginosa è una delle più diffuse tanto da essere presente in molti campioni di feci umane e più raramente anche in zone di epidermide più umide come ascelle ed inguine. **È causa, in ospedali dove non sono seguite correttamente le norme di igiene, di vere e proprie piccole epidemie con conseguenze anche gravi. Generalmente provoca infezioni osteoarticolari, otite esterna, polmonite. È anche responsabile di follicoliti cutanee, infezioni oculari come congiuntivite ed endocardite.** Generalmente le varie specie di Pseudomonas sono resistenti alla maggior parte degli antibiotici, in quanto sono scarsamente permeabili, producono enzimi capaci di inattivare penicilline ed aminoglicosidi e sono dotate di meccanismi di espulsione di molti antibiotici.

Acilureido Penicilline

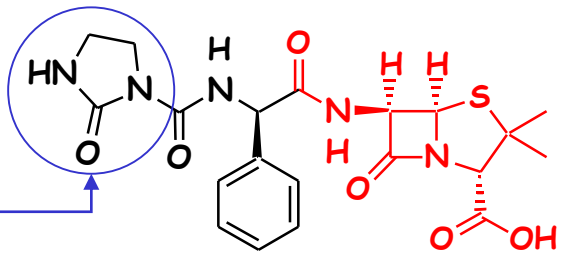
1-Etil-piperazina-2,3-dione



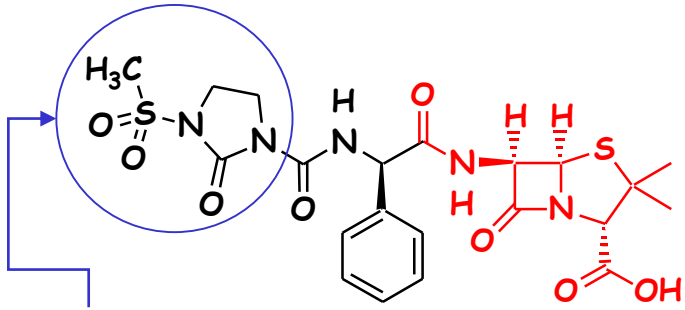
Piperacillina (*Ecosette, Farecillin, Ibitazina*, Limerik*, Limerik, Pipertex, Repita*, Taiper*, Tazocin*) (*+ tazobactam)*

- ampio spettro; Enterobacteriaceae produttrici di beta-lattamasi cosidette ad ampio spettro (ESBL)
- *H. influenzae, Klebsiella species,* ***Pseudomonas species*,*** *Proteus mirabilis, E. coli, Enterobacter species, Streptococcus faecelis, Peptococcus species, Peptostreptococcus species, Bacteriodes species (including B. fragilis), Morganella morganii, Serratia species, N. gonorrhoeae, P. vulgaris, and Providencia rettgeri.*
- Infezioni delle basse vie respiratorie, del tratto urinario, intraddominali e della cute; setticemie; appendicite complicata; infezioni in pazienti neutropenici.

Azlocillina



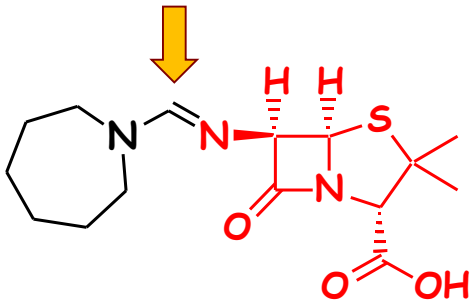
imidazolinone



Metansulfonil imidazolinone

Mezlocillina

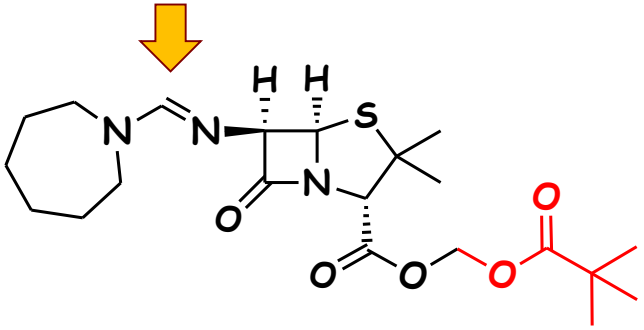
Ammidino Penicilline



Mecillinam

- *Gruppo ammidinico al C-6*
- *Solo Gram neg.; pseudomonas poco sens.; poco stabile β-lattamasi (Extended Spectrum Beta Lactamases)*
- *Pivmecillinam: prodrug attivo per os; per idrolisi vengono prodotti*
- *Ac. pivalico, aldeide formica e Mecillinam*

Pivmecillinam



Reazioni allergiche agli antibiotici β-lattamici

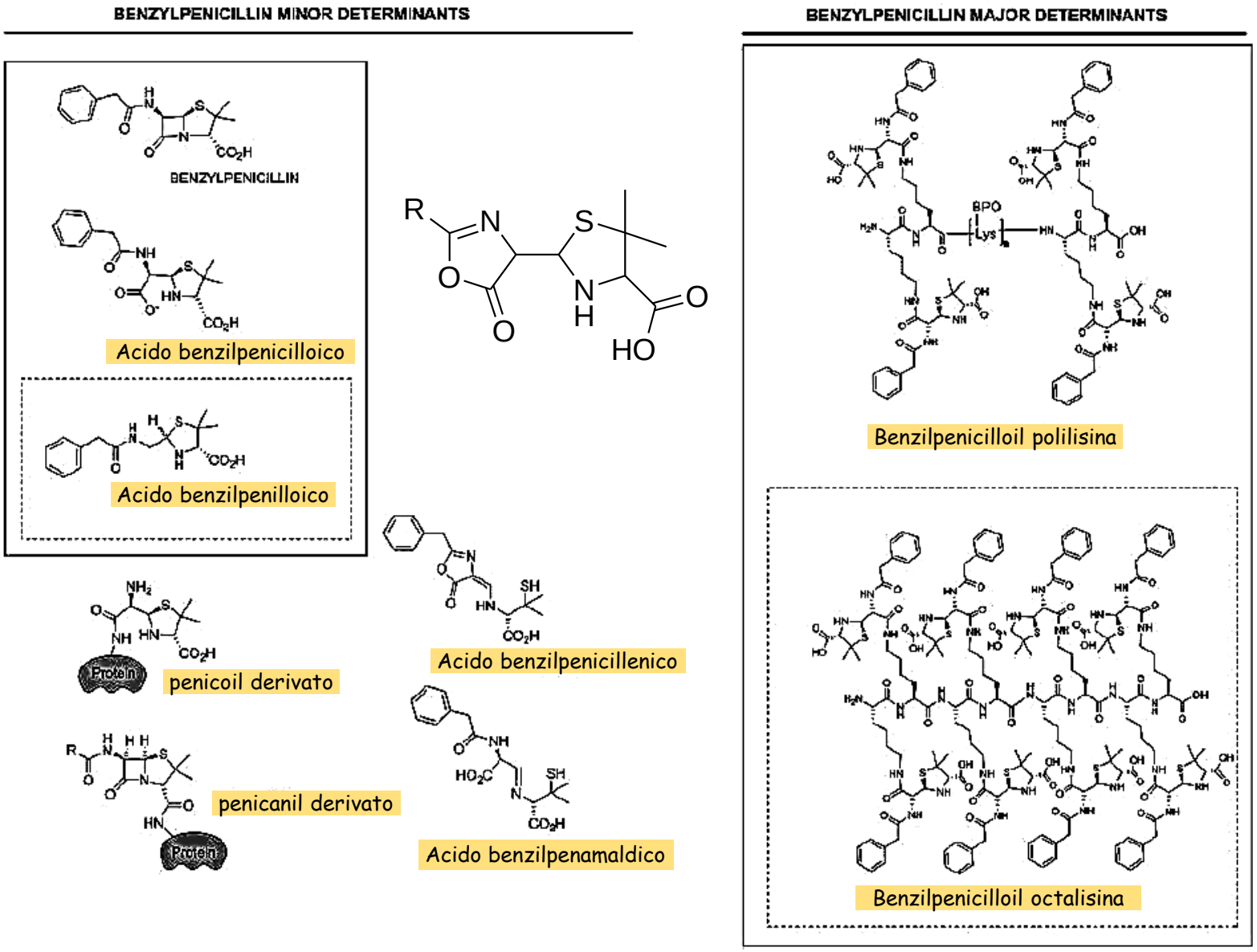


Figure 2. Minor and major determinants of benzylpenicillin. Previous commercially available structures are shown in the solid figure. Currently commercialized structures are shown in the dotted figure. BPO indicates benzylpenicilloyl.

Hypersensitivity Reactions to ß-Lactams. J Investig Allergol Clin Immunol 2015; Vol. 25(1): 12-25

Antibacterials: cell envelope antibiotics (J01C-J01D)				
Intracellular	Inhibit peptidoglycan subunit synthesis and transport: NAM synthesis inhibition (Fosfomycin) · DADAL/AR inhibitors (Cycloserine) · bactoprenol inhibitors (Bacitracin)			
Glycopeptide	Inhibit PG chain elongation: Vancomycin# (Oritavancin · Telavancin) · Teicoplanin (Dalbavancin) · Ramoplanin			
β-lactams/ (inhibit PBP cross-links)	**Penicillins (Penams)**	**Narrow spectrum**	**β-lactamase sensitive (1st generation)**	Benzylpenicillin (G)# · Benzathine benzylpenicillin# · Procaine benzylpenicillin# · Phenoxymethylpenicillin (V)# · Propicillin‡ · Pheneticillin‡ · Azidocillin‡ · Clometocillin‡ · Penamecillin‡
			β-lactamase resistant (2nd generation)	Cloxacillin# (Dicloxacillin · Flucloxacillin) · Oxacillin · Nafcillin · Methicillin‡
		Extended spectrum	**Aminopenicillins (3rd generation)**	Amoxicillin# · Ampicillin# (Pivampicillin · Hetacillin‡ · Bacampicillin‡ · Metampicillin‡ · Talampicillin‡) · Epicillin‡
			Carboxypenicillins (4th generation)	Ticarcillin · Carbenicillin‡ / Carindacillin‡ · Temocillin‡
			Ureidopenicillins (4th generation)	Piperacillin · Azlocillin‡ · Mezlocillin‡
			Other	Mecillinam‡ (Pivmecillinam‡) · Sulbenicillin‡
	Penems	Faropenem‡		
	Carbapenems	Ertapenem · Antipseudomonal (Doripenem · Imipenem · Meropenem) · Biapenem‡ · Panipenem‡		
	Cephalosporins/Cephamycins (Cephems)	**1st generation (PEcK)**	Cefazolin# · Cefalexin # · Cefadroxil · Cefapirin · Cefazedone‡ · Cefazaflur‡ · Cefradine‡ · Cefroxadine‡ · Ceftezole‡ · Cefaloglycin‡ · Cefacetrile‡ · Cefalonium‡ · Cefaloridine‡ · Cefalotin‡ · Cefatrizine‡	
		2nd generation (HEN)	Cefaclor · Cefotetan · Cephamycin (Cefoxitin · Cefprozil · Cefuroxime · Cefuroxime axetil · Cefamandole‡ · Cefminox‡ · Cefonicid‡ · Ceforanide‡ · Cefotiam‡ · Cefbuperazone‡ · Cefuzonam‡ · Cefmetazole)‡ · Carbacephem‡ (Loracarbef‡)	
		3rd generation	Cefixime# · Ceftriaxone# · Antipseudomonal (Ceftazidime# · Cefoperazone) · Cefdinir · Cefcapene · Cefdaloxime · Ceftizoxime · Cefmenoxime · Cefotaxime · Cefpiramide · Cefpodoxime · Ceftibuten · Cefditoren · Cefetamet‡ · Cefodizime‡ · Cefpimizole‡ · Cefsulodin‡ · Cefteram‡ · Ceftiolene‡ · Oxacephem (Flomoxef‡ · Latamoxef‡)	
		4th generation (Pseudomonas)	Cefepime · Cefozopran‡ · Cefpirome‡ · Cefquinome‡	
		5th generation	Ceftaroline fosamil · Ceftolozane · Ceftobiprole	
		Veterinary	Ceftiofur · Cefquinome · Cefovecin	
	Monobactams	Aztreonam · Tigemonam‡ · Carumonam‡ · Nocardicin A‡		
	β-lactamase inhibitors	Penam (Sulbactam · Tazobactam) · Clavam (Clavulanic acid) · Avibactam		
	Combinations	Amoxicillin/clavulanic acid# · Imipenem/cilastatin# · Ampicillin/flucloxacillin · Ampicillin/sulbactam (Sultamicillin) · Ceftazidime/avibactam · Piperacillin/tazobactam · Ceftolozane/tazobactam		
Other	polymyxins/detergent (Colistin · Polymyxin B) · depolarizing (Daptomycin) · Hydrolyze NAM-NAG (lysozyme) · Tyrothricin (Gramicidin · Tyrocidine) · Isoniazid · Teixobactin			

#WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III)