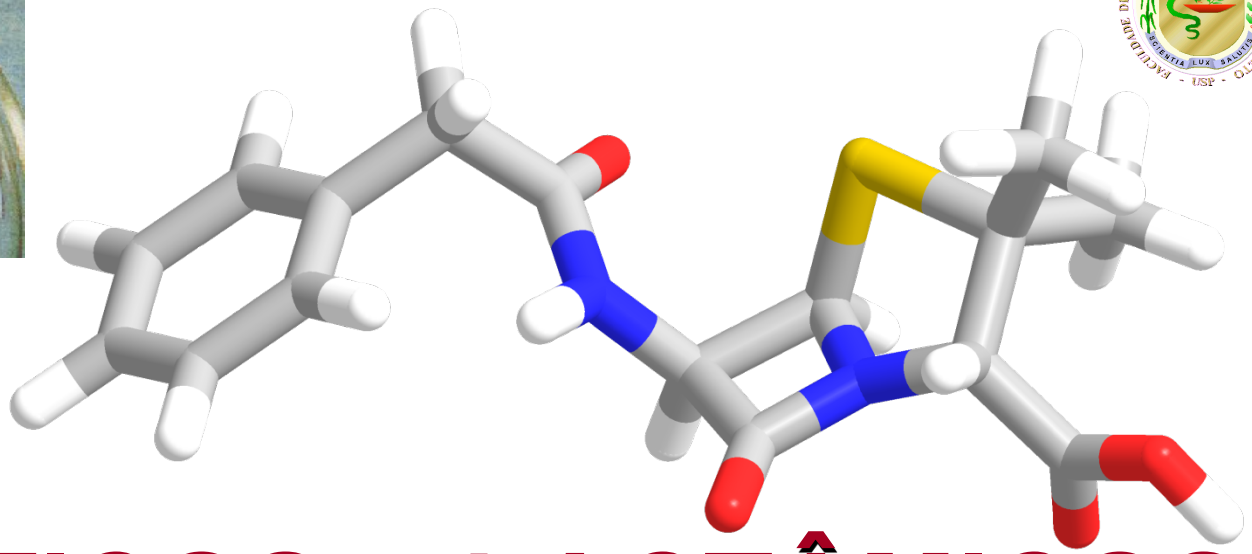

ANTIBIÓTICOS β-LACTÂMICOS

Profa. Mônica Tallarico Pupo

Química Farmacêutica II

Referências bibliográficas básicas

G. L. PATRICK. *An introduction to medicinal chemistry*, 2nd ed., Oxford University Press, **2001**, cap. 14
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5th ed, **2013**, cap. 19 (p. 413-467)

L. A. MITSCHER. *Antibiotics and antimicrobial agents.* In: "Foye's principles of medicinal chemistry", 5th ed., Lippincott Williams & Wilkins, **2002,** Cap. 34, p. 819-866. ou L. A. Mitscher, T. L. Lemke, E. J. Gentry. *Antibiotics and antimicrobial agents.* In: "Foye's principles of medicinal chemistry", 6th ed., Lippincott Williams & Wilkins, **2008,** Cap. 38, p. 1028-1083.

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Quim. Nova, Vol. 33, No. 3, 667-679, 2010

Revisão

ANTIBIÓTICOS: IMPORTÂNCIA TERAPÊUTICA E PERSPECTIVAS PARA A DESCOBERTA E DESENVOLVIMENTO DE NOVOS AGENTES

Denise Oliveira Guimarães, Luciano da Silva Momesso e Mônica Tallarico Pupo*
Departamento de Ciências Farmacêuticas, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Av. do Café, s/n, 14040-903 Ribeirão Preto – SP, Brasil

Recebido em 26/2/09; aceito em 21/8/09; publicado na web em 24/2/10

Química Nova, v.33, p.667-679, **2010**

Material adicional sugerido

Antibacterial Natural Products in Medicinal Chemistry—Exodus or Revival?

*Franz von Nussbaum, Michael Brands, Berthold Hinzen, Stefan Weigand, and Dieter Häbich**

Angew. Chem. Int. Ed. **2006**, 45, 5072–5129

A BACTERIAL BATTLE

The regulatory path to approving new antibiotics has been cleared, but work still remains to rebuild a HEALTHY DRUG PIPELINE

LISA M. JARVIS, C&EN CHICAGO

HOW CHEMISTRY CHANGED THE WORLD

ANTIBACTERIAL BOOM and BUST

After a flurry of discovery in the 20th century, the antibacterial drug pipeline is now drying up

MICHAEL TORRICE, C&EN WEST COAST NEWS BUREAU

Antibiotics: Actions, origins, resistance
by C. Walsh. 2003. Washington, DC: ASM Press. 345 pp.

São produtos derivados do metabolismo microbiano, análogos sintéticos baseados em protótipos naturais ou compostos sintéticos que antagonizam o crescimento ou sobrevivência de outras espécies de micro-organismos em baixas concentrações

naturais

ANTIBACTERIANOS
- β-Lactâmicos (penicilinas, cefalosporinas, carbapeninas, monobactamas)
- macrolídeos
- aminoglicosídeos
- tetraciclinas
- lincosaminas
- polipeptídeos
- outros

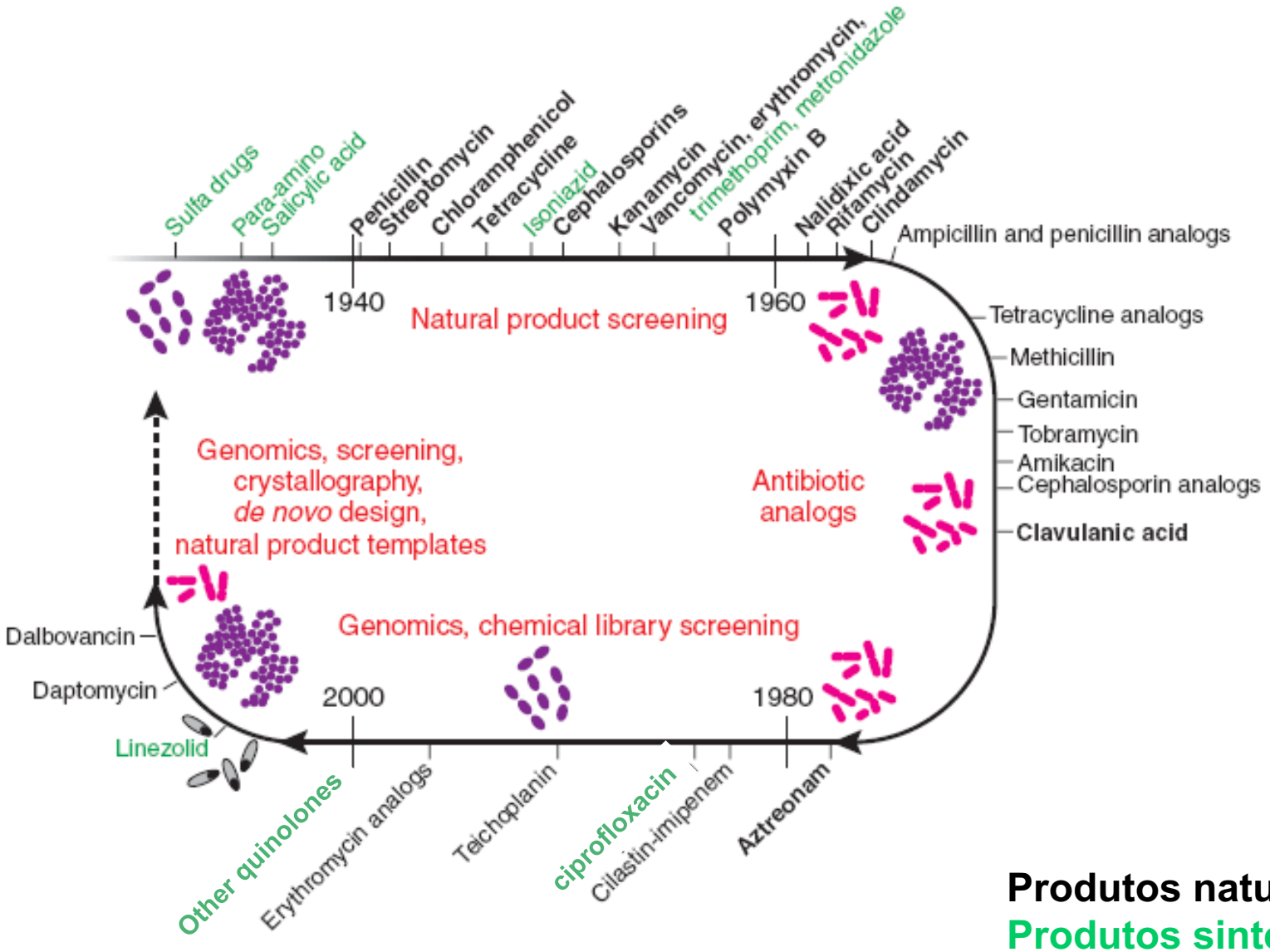
ANTINEOPLÁSICOS
- dactinomicinas
- antraciclinas
- bleomicinas
- derivados do ácido aureólico
- mitomicinas

ANTIFÚNGICOS
- anfotericina B
- nistatina
- griseofulvina

sintéticos

ANTIBACTERIANOS
- sulfas
- quinolonas
- oxazolidinonas

Pesquisa e desenvolvimento de antibióticos



Produtos naturais

Produtos sintéticos

Fernandes, P. *Nature Biotechnol.* 2006, **24**, 1497

Gerhard Domagk
(1895-1964)
Nobel laureate

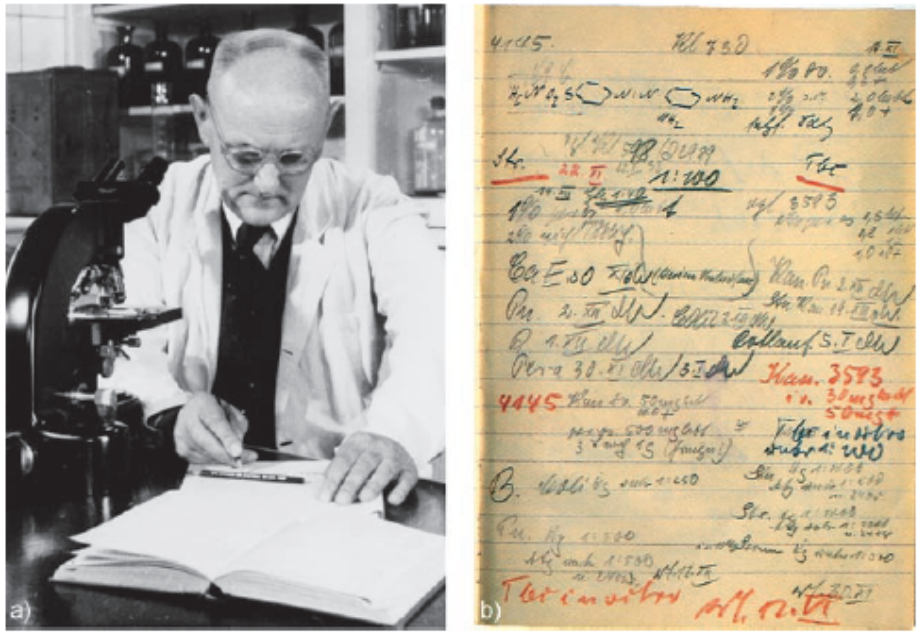
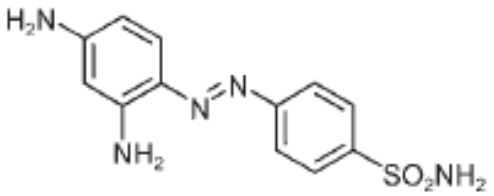


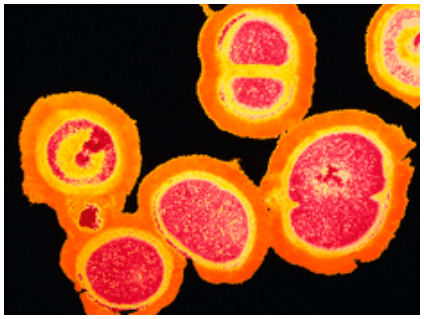
Figure 1. a) Nobel laureate, pioneer of antibacterial therapy, and inventor of the sulfonamides, Gerhard Domagk (1895–1964), with his most important working tool. Under the microscope he studied the effect of different chemicals on bacteria. b) Page from Domagk's laboratory notebook describing the exceptional activity of azo dye D 4145 on streptococci. D 4145, launched in 1935 as "prontosil", was a diazo prodrug of the active component 4-aminophenylsulfonamide that was marketed in 1936 under the name "prontalbin". At the outset, antibacterial chemotherapy stemmed from synthetic dyes rather than natural products. Essential principles of chemotherapy have been worked out with the sulfonamides.



Prontosil
1935

Von Nussbaum et al. *Angew. Chem. Int. Ed.* **2006**, *45*: 5072-5129

1877 - Pasteur e Joubert descobrem que certos fungos produzem substâncias tóxicas que matam bactérias

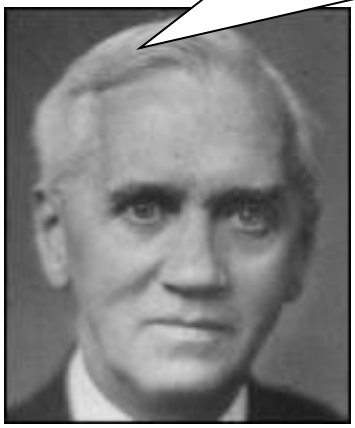


Staphylococcus aureus

Penicillium notatum

1928 - Alexander Fleming

"*When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer,*" Fleming would write later, "*But I guess that was exactly what I did.*"



St. Mary's Hospital de Londres

British Journal of Experimental Pathology (1929)

1936 - introdução das SULFONAMIDAS sintéticas

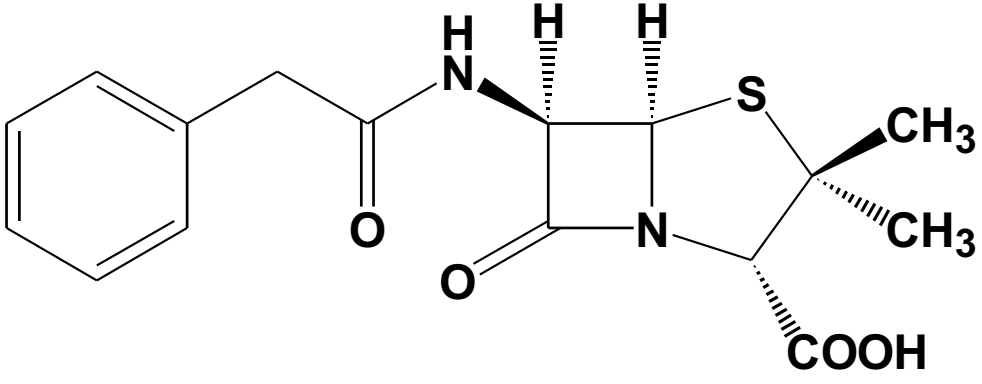
1938 - Florey e Chain (Oxford) - isolamento da PENICILINA G

1941 - primeiros testes clínicos com extratos brutos de penicilina

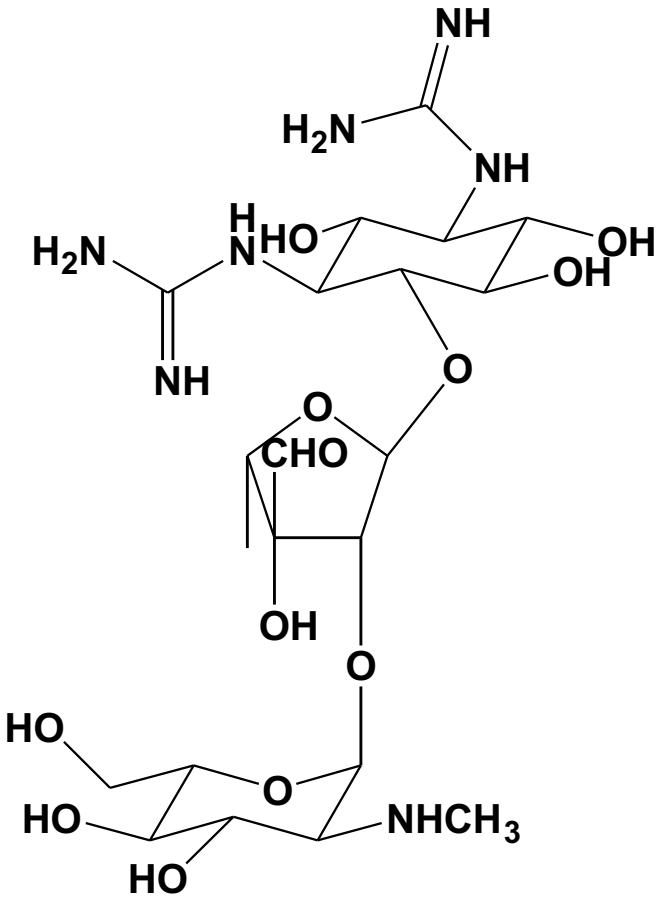
1940s - EUA - experimentos para produção em larga escala

1944 - penicilina disponível para uso dos Aliados

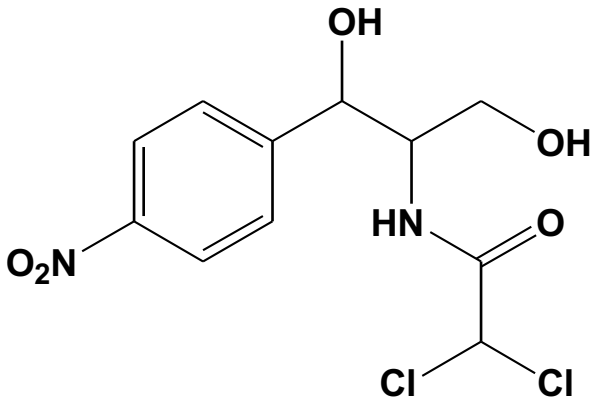
1945 - Hodgkins - estrutura da penicilina G (raio-X)



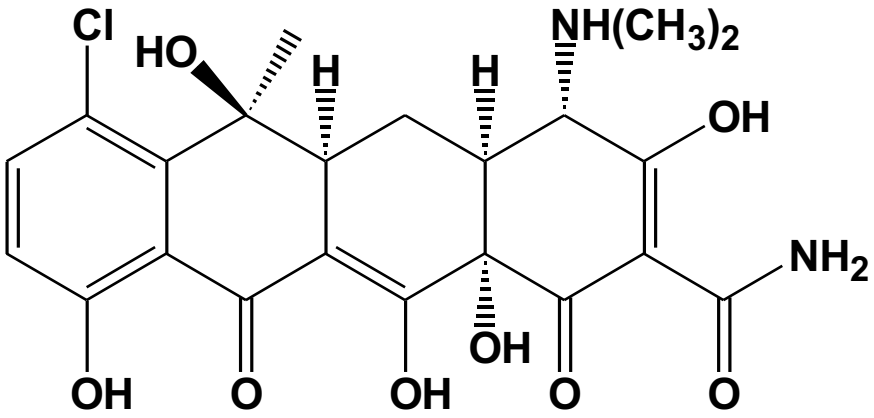
Antibióticos naturais



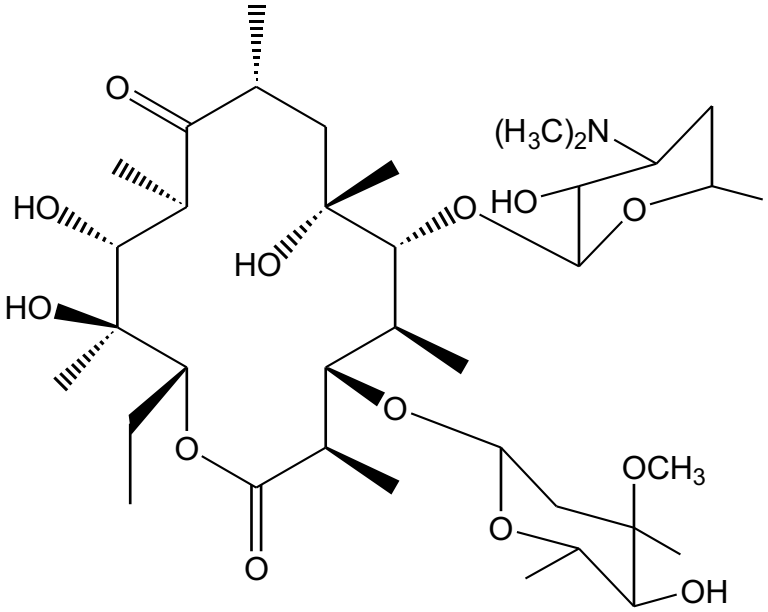
1944 - ESTREPTOMICINA
(Streptomyces griseus)



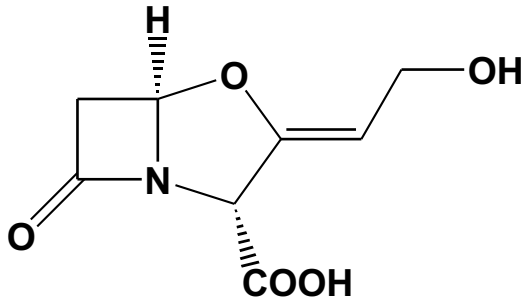
1947 - CLORANFENICOL
(Streptomyces venezuelae)



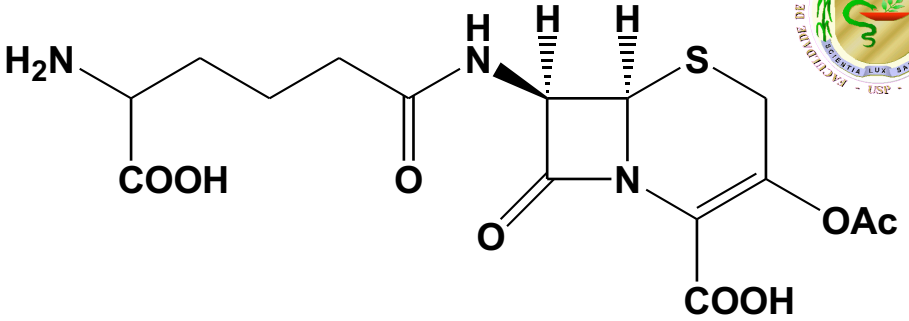
1948 - CLORTETRACICLINA
(Streptomyces)



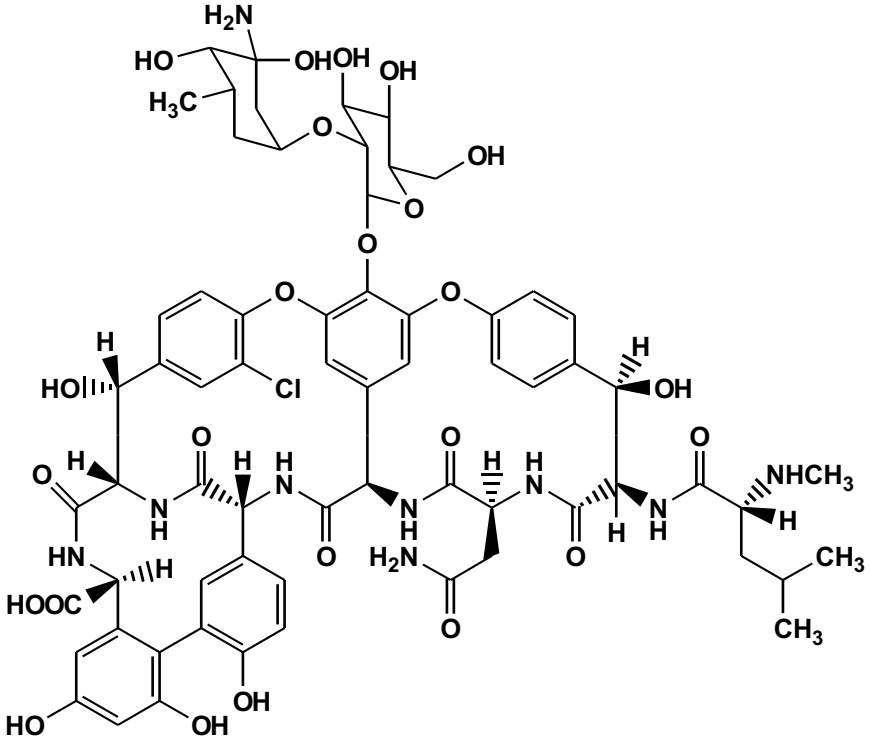
1952 - ERITROMICINA
(*Streptomyces erythreus*)



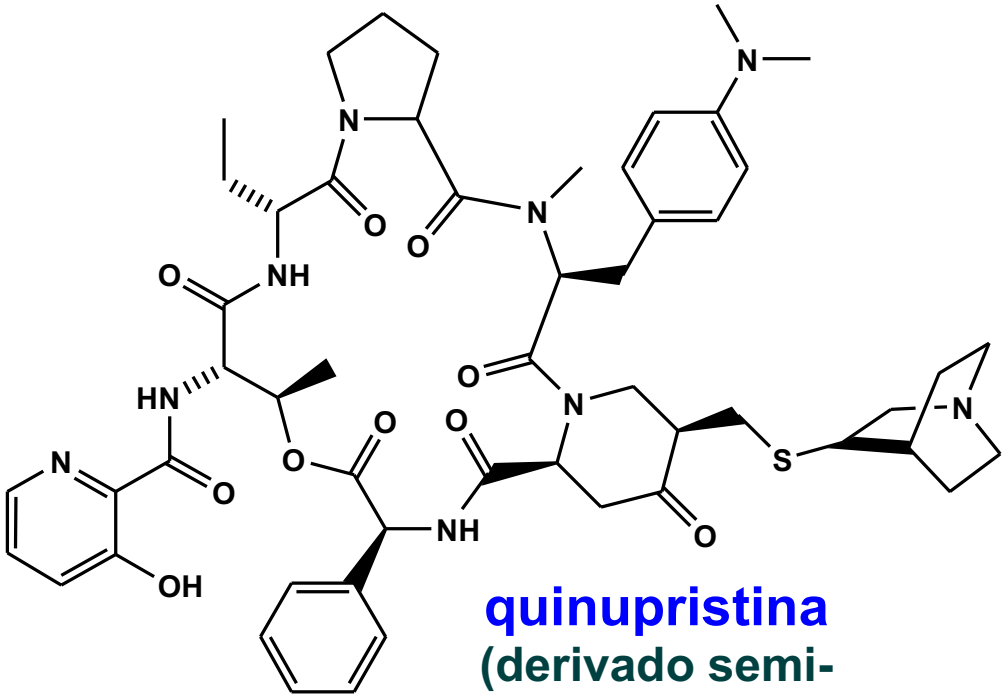
1976 - ÁCIDO CLAVULÂNICO
(*Streptomyces clavuligerus*)



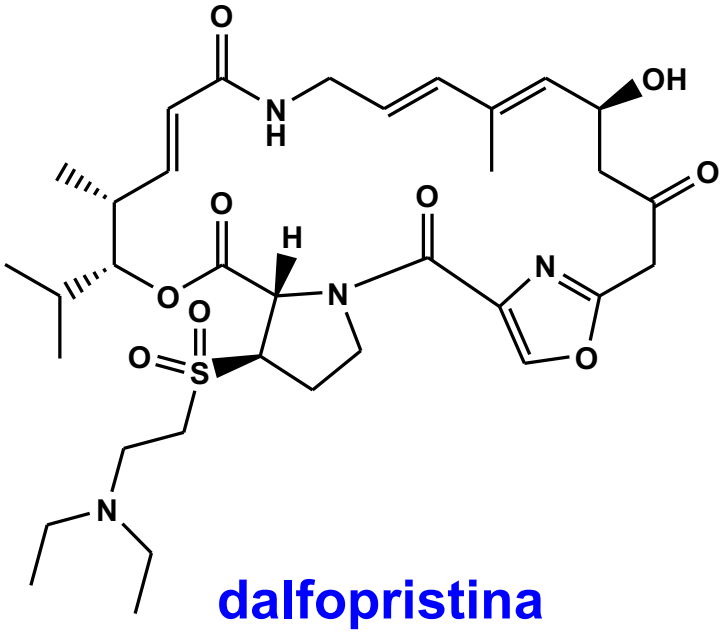
1956 - CEFALOSPORINA C
(*Cephalosporium acremonium*)



1956 - VANCOMICINA
(*Streptomyces orientalis*)

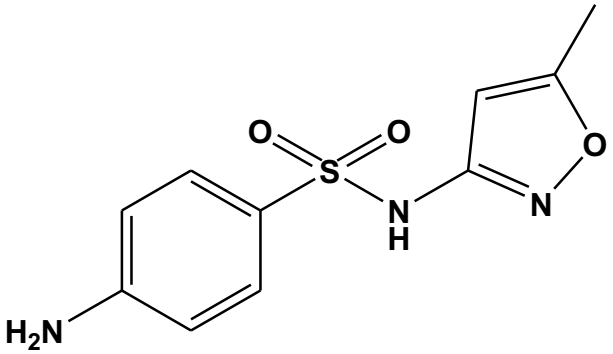


quinupristina
(derivado semi-sintético de PN produzido por *Streptomyces*)

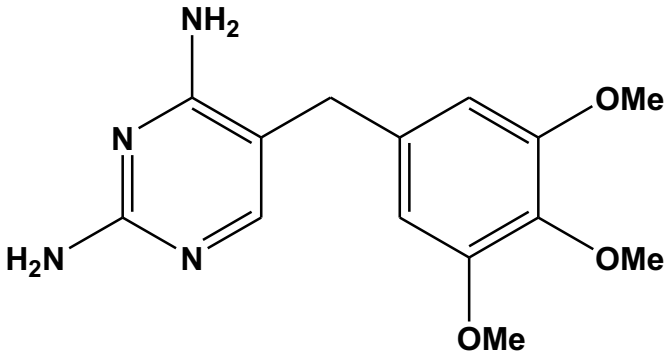


dalfopristina
(derivado semi-sintético de PN produzido por *Streptomyces*)

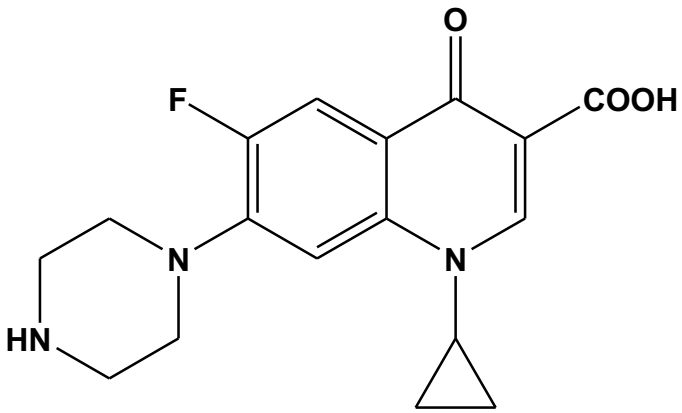
Antibióticos sintéticos



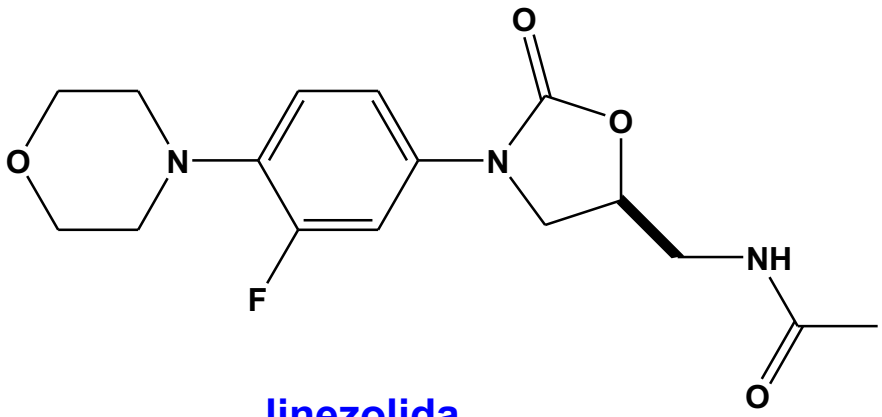
sulfametoxazol
(1930's)



trimetoprim
(1950's)

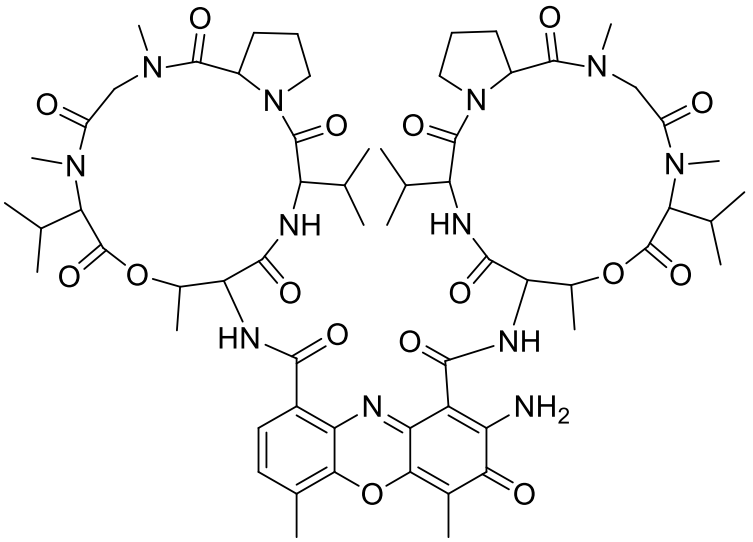


ciprofloxacina
(1960's, 1987)

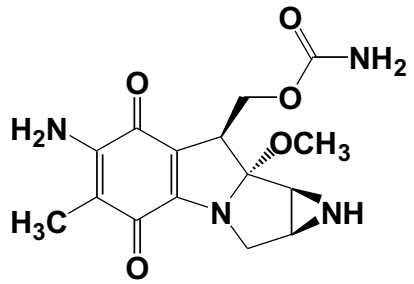


linezolida
(2000)

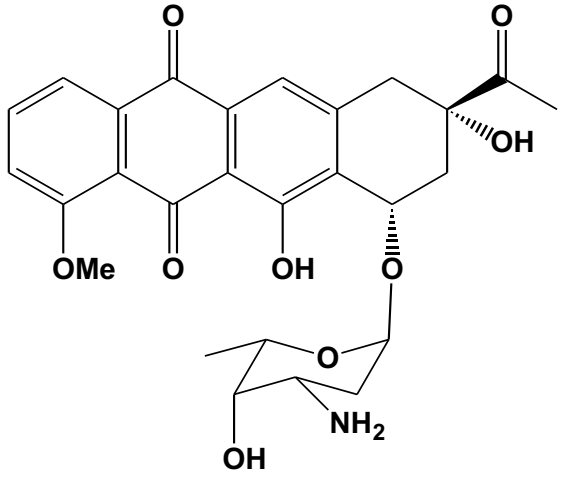
ANTIBIÓTICOS ANTINEOPLÁSICOS



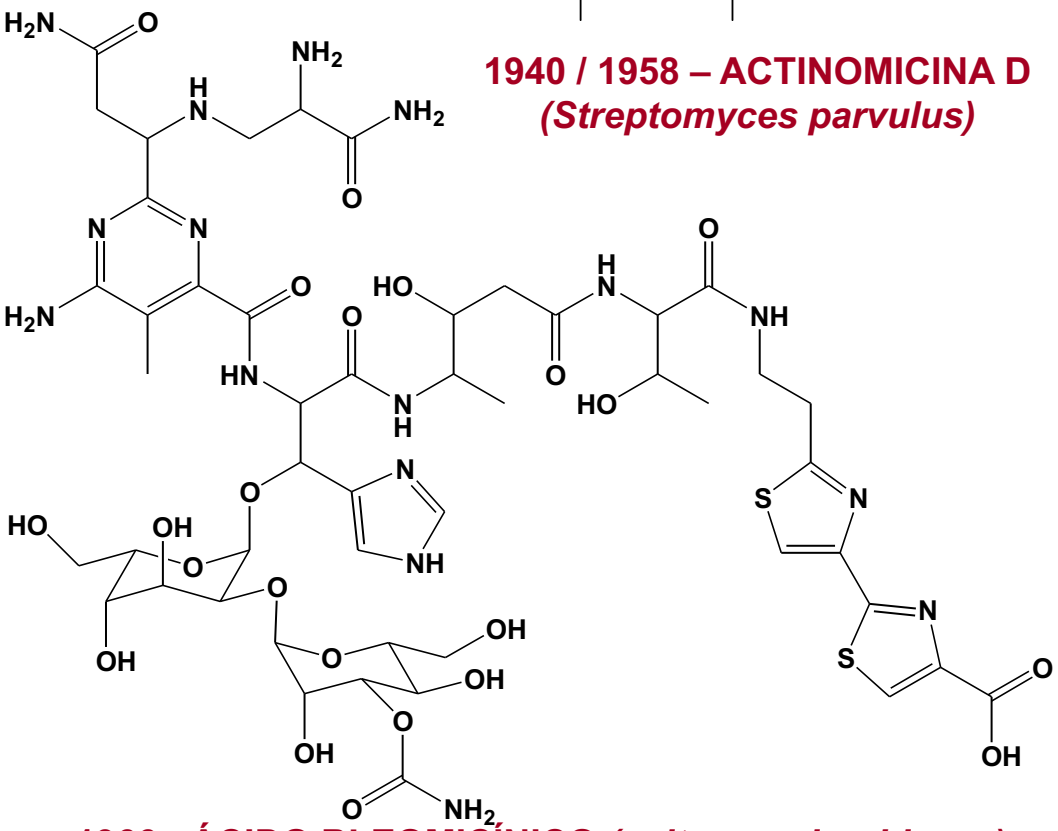
1940 / 1958 – ACTINOMICINA D
(Streptomyces parvulus)



1950s - MITOMICINA C
(Streptomyces caespitosus)

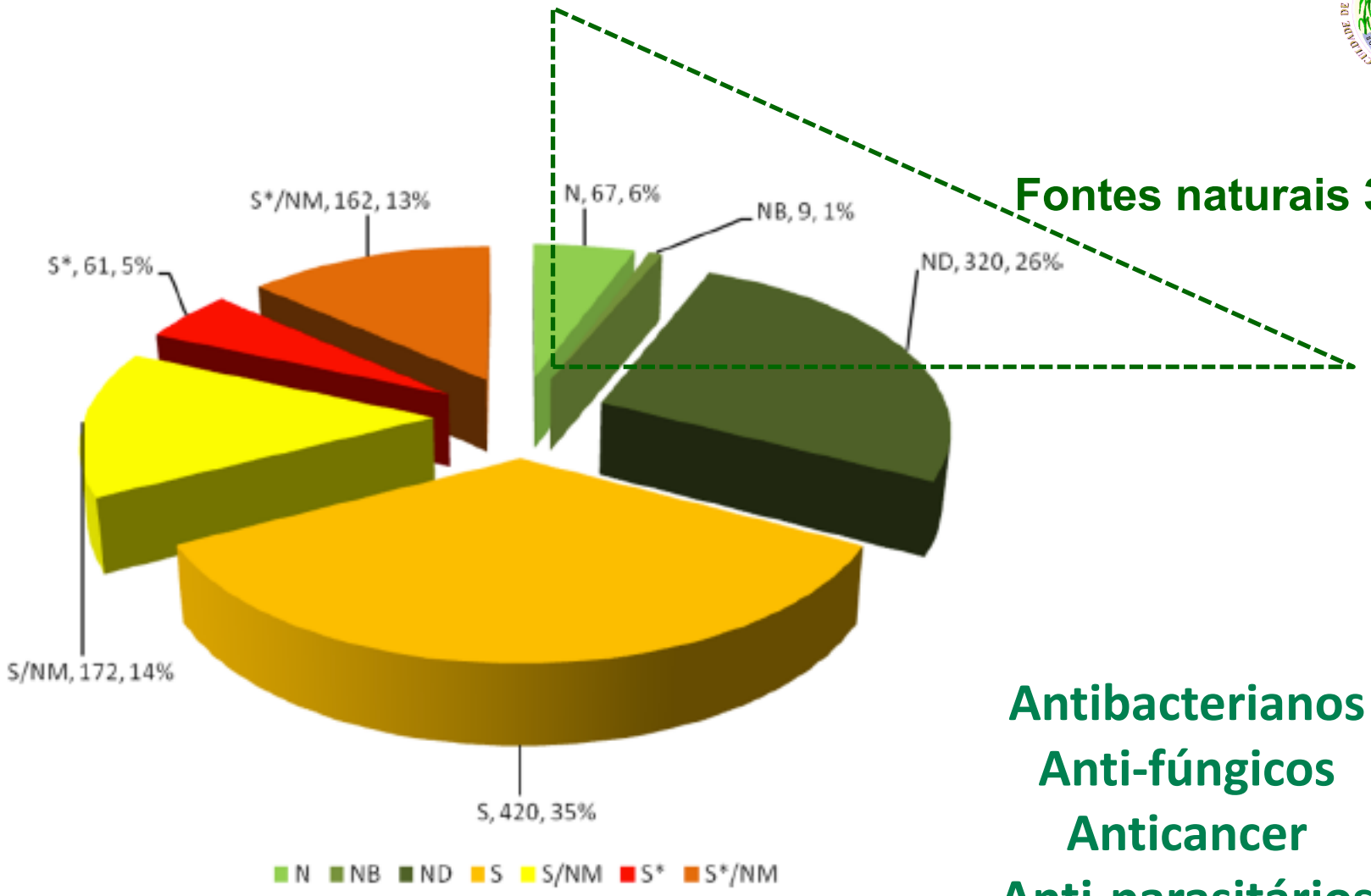


1963 - DAUNORRUBICINA
(Streptomyces caeruleorubidis)



1966 - ÁCIDO BLEOMICÍNICO *(culturas microbianas)*

Fármacos aprovados pelo FDA no período 1981-2014 (total = 1211)

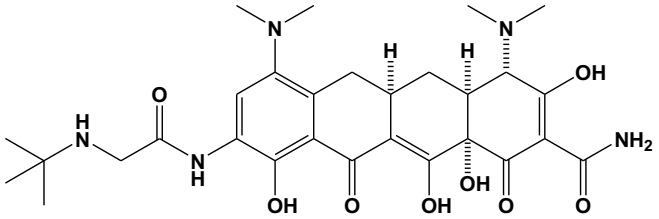


Fontes naturais 33%

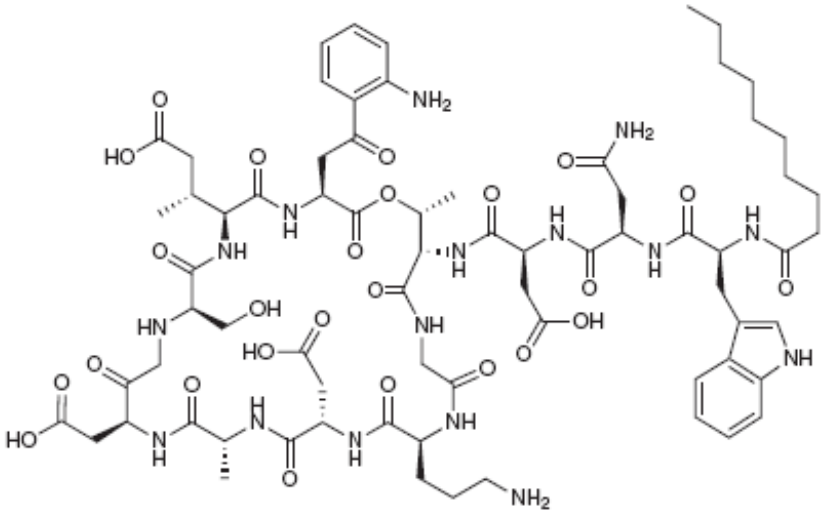
Antibacterianos
Anti-fúngicos
Anticancer
Anti-parasitários
Imunossuppresores

Newman; Cragg, *J. Nat. Prod*. **2016**, *79:* 629

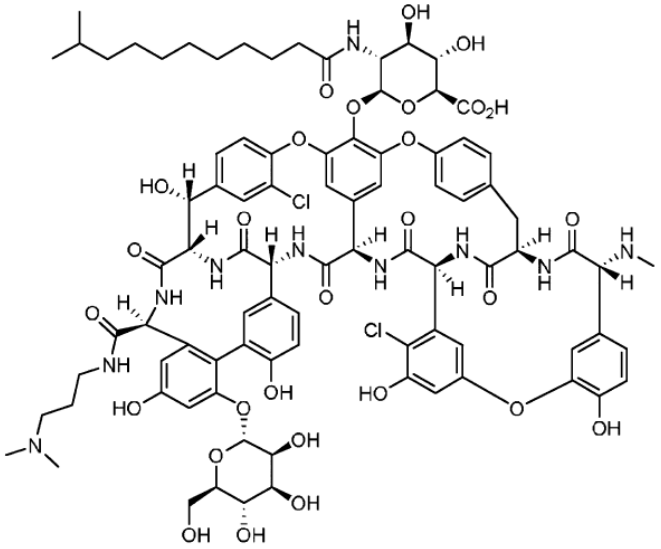
Fármacos aprovados pelo FDA no período 1981-2010 (total = 1355)



Tigeciclina – PND
Antibacteriano (2005)

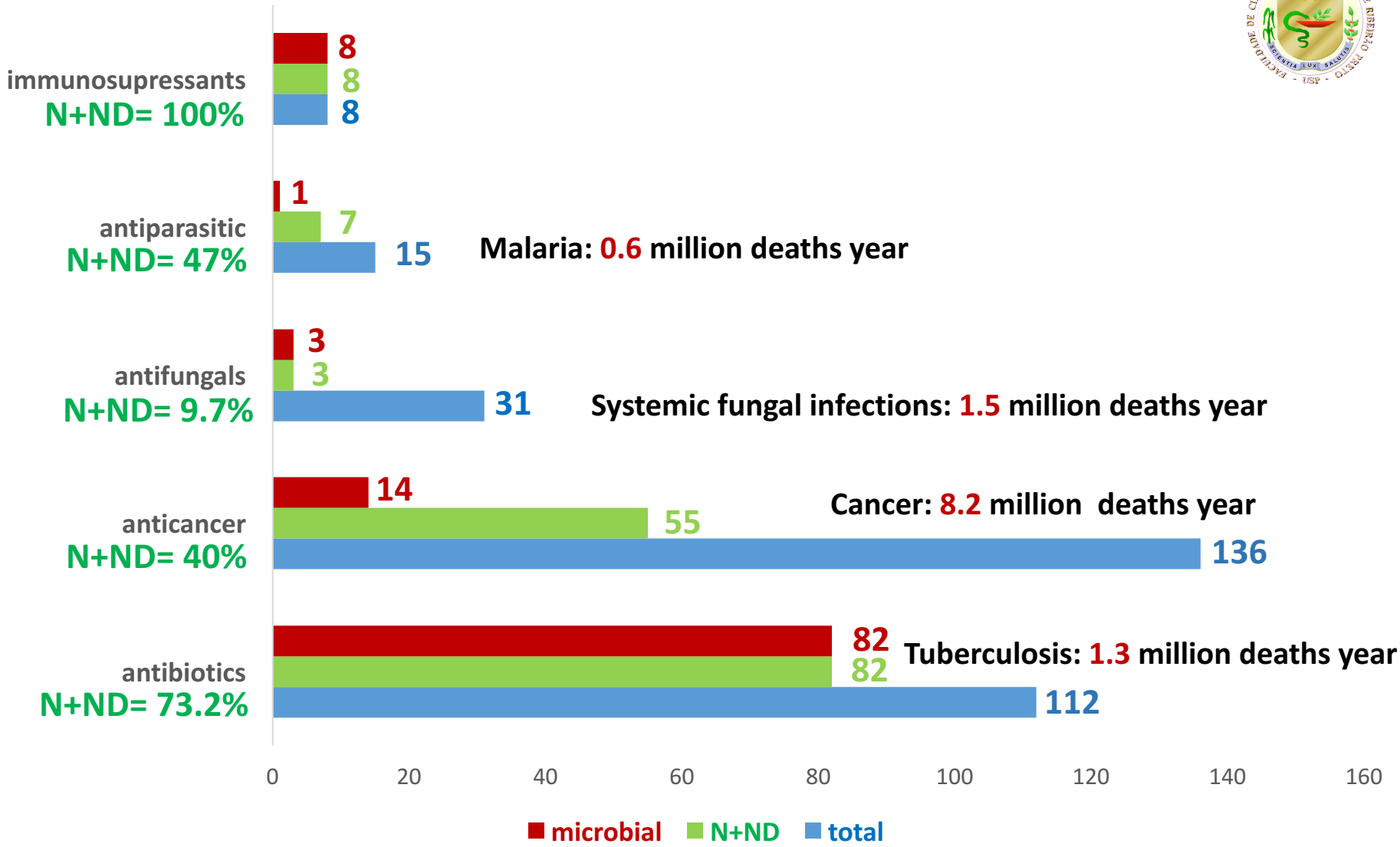


Daptomicina – *Spreptomyces roseosporum*
Antibacteriano (2003) - Cubicin®



Dalbavancina - PND
Antibacteriano (maio, 2014)

FDA Approved Drugs Over the Period 1981-2014 (total = 1211)



WHO data

J. Nat. Prod. **2016**, *79:* 629

Sci. Transl. Med. **2012** *4*, 165rv13

Five therapeutic areas: 302 drugs (25%)

N+ND: 155 drugs (51.3%)

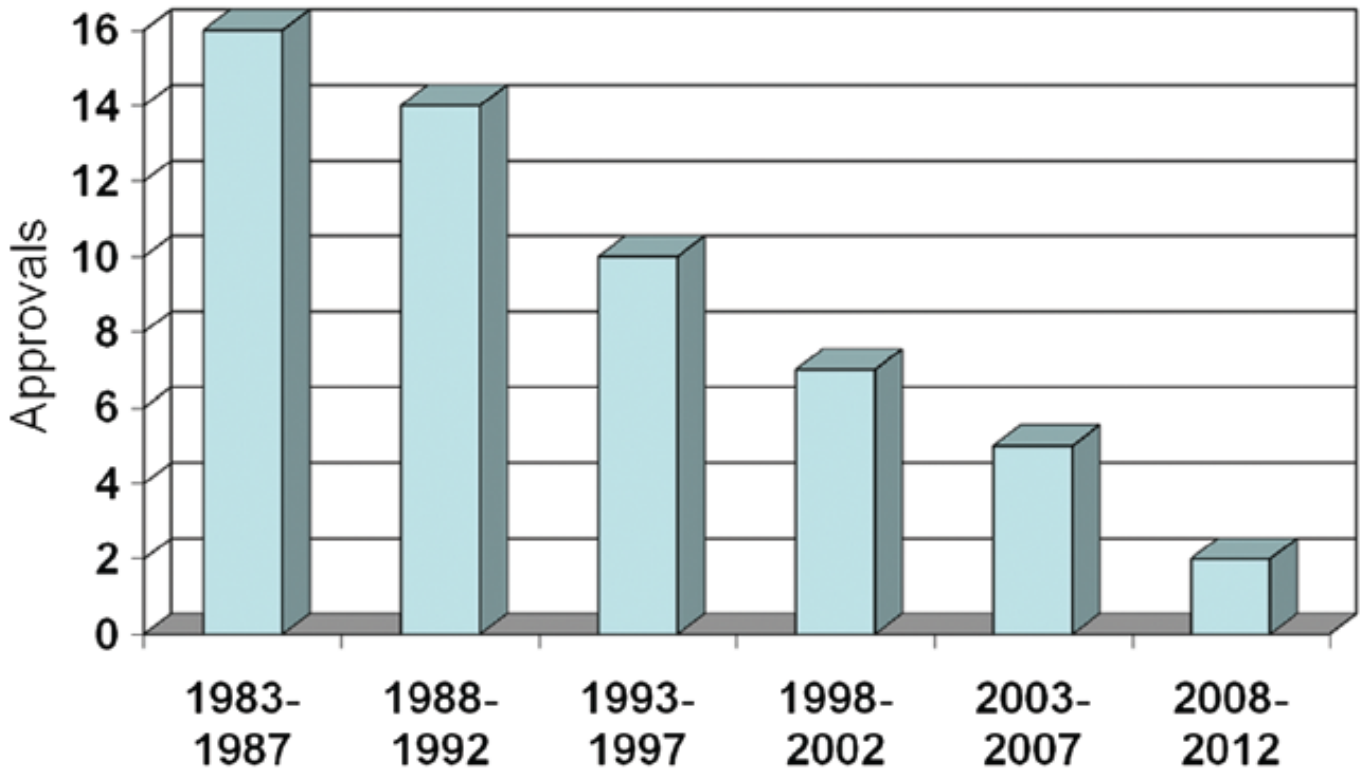


Figure 1. New systemic antibacterial agents approved by the US Food and Drug Administration per 5-year period, through 2012. Modified from Spellberg 2004 [23].

Boucher et. al. *Clin Infect Dis*. **2013**, 56 (12):1685-1694
doi: 10.1093/cid/cit152

β-Lactâmicos: ~ 50% das vendas globais em 2004

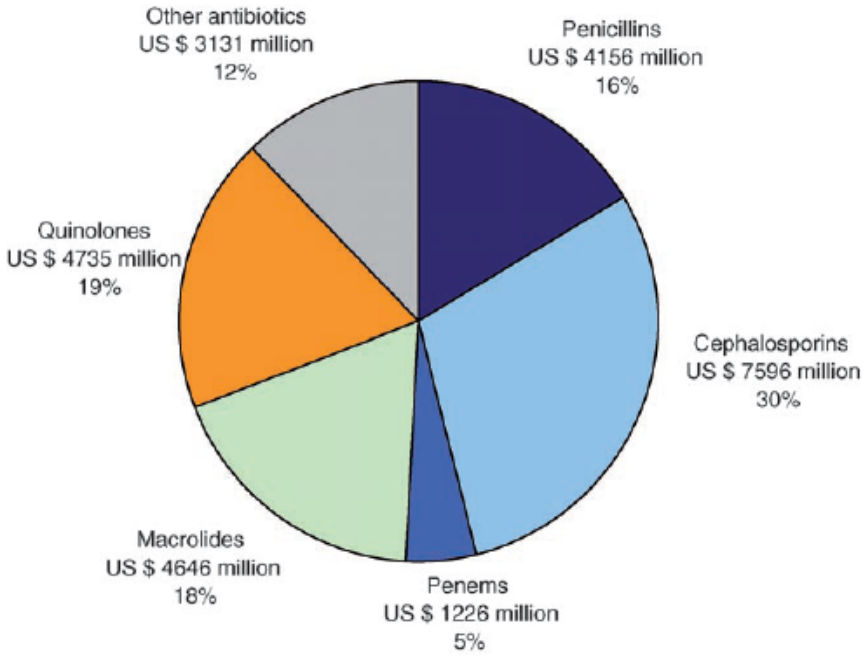


Figure 8. Global sales of the major antibacterial classes in 2004 (from Wood Mackenzie[69]).

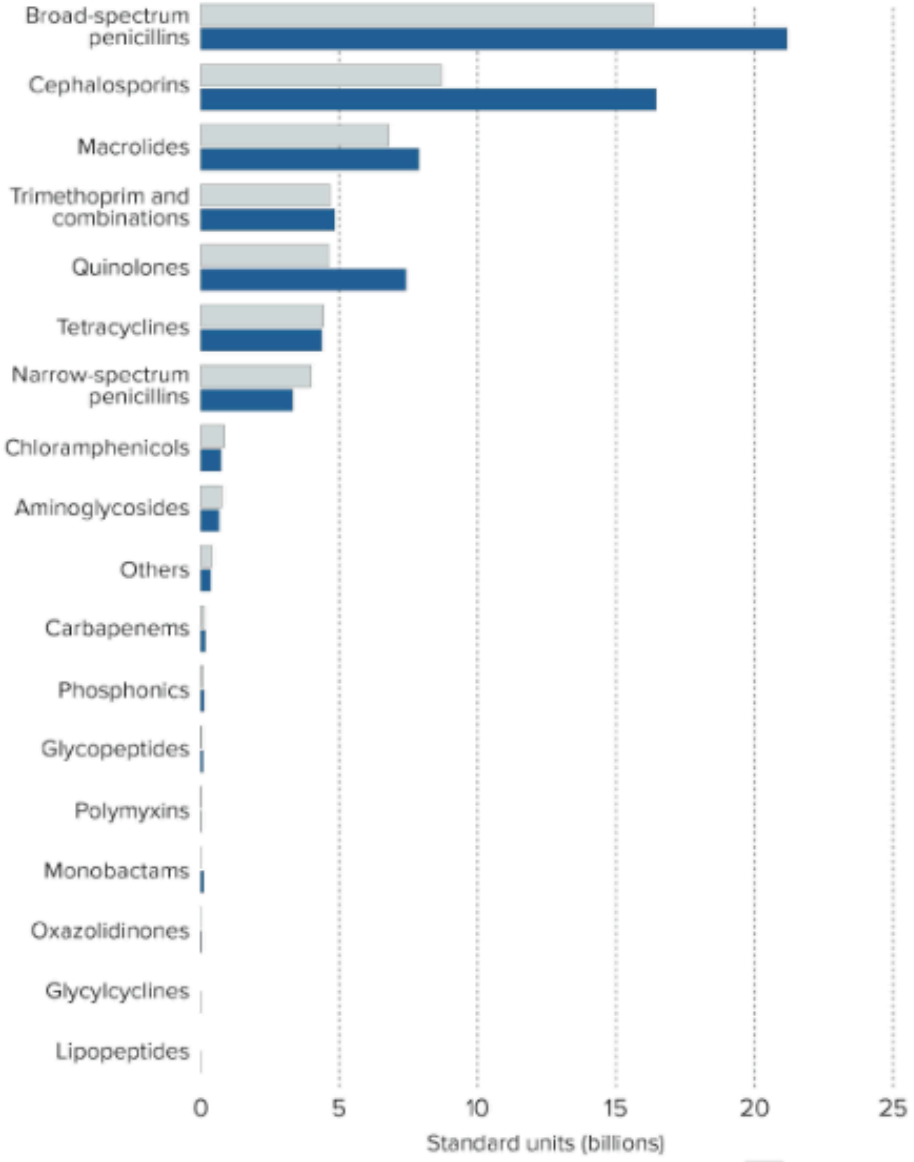
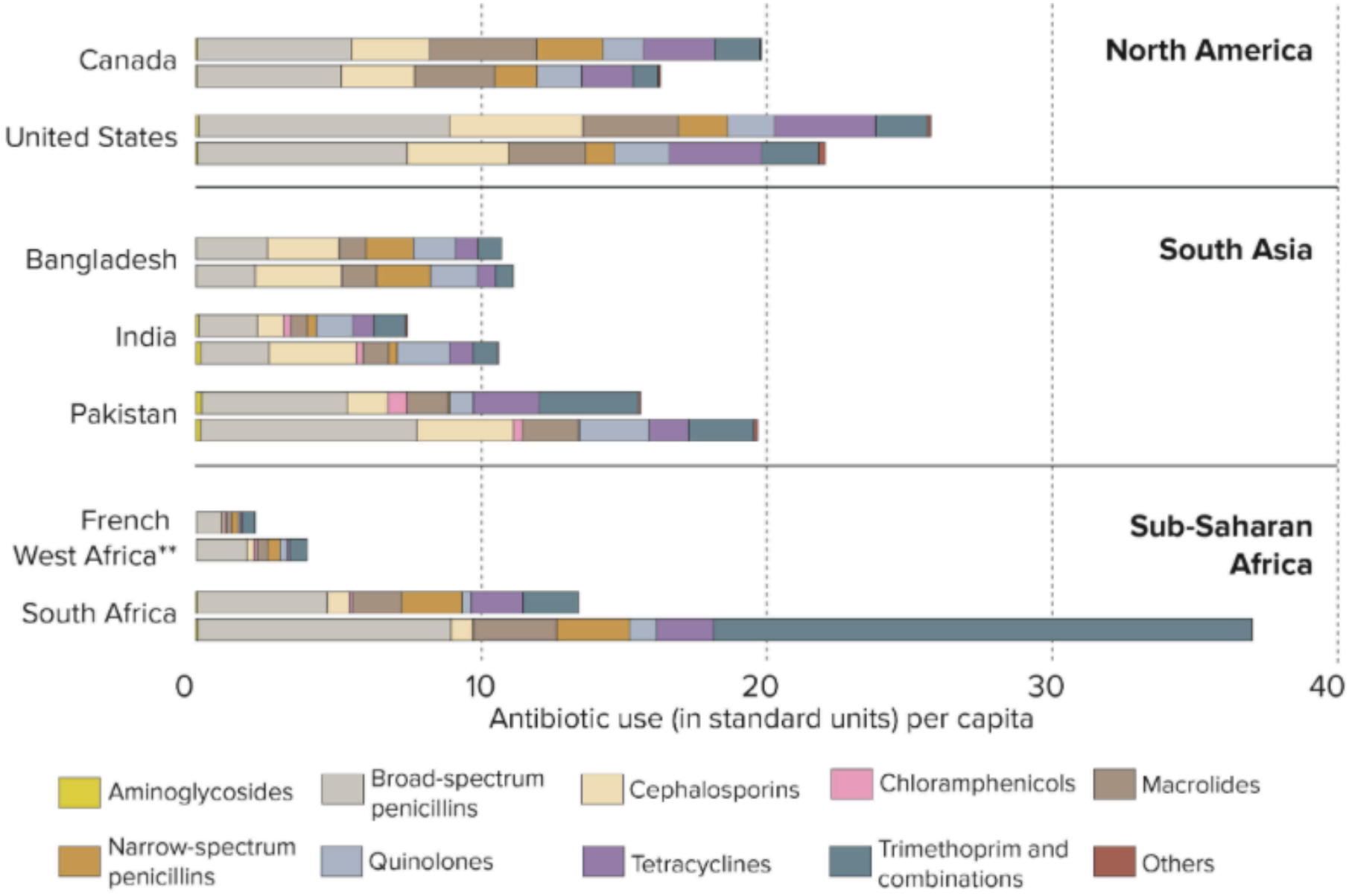


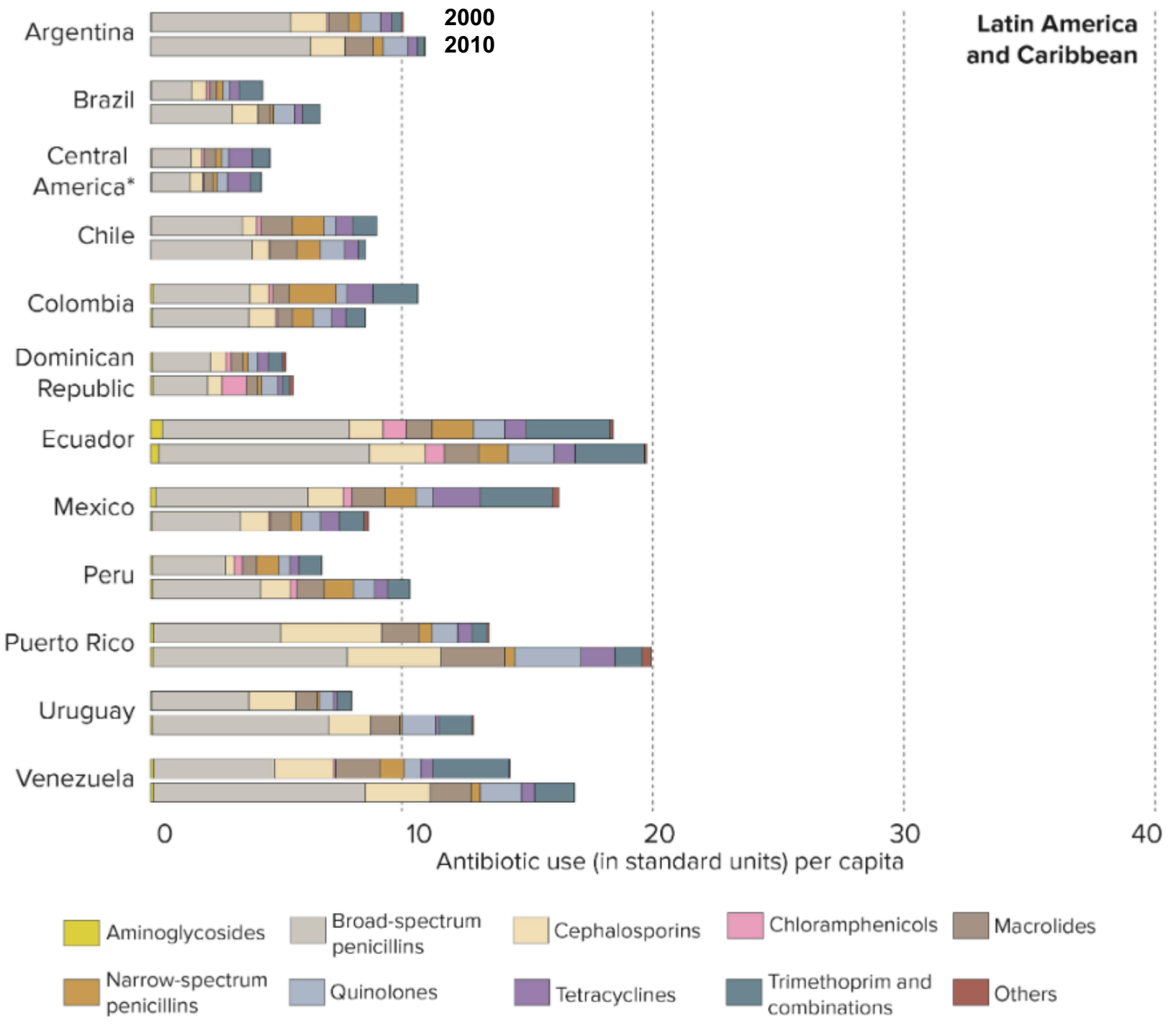
FIGURE 2-1: Global antibiotic use by class, 2000–2010

Van Boeckel et al. 2014 (adapted; based on IMS MIDAS)

Von Nussbaum et al.
Angew. Chem. Int. Ed. **2006**, *45*: 5072-5129

https://cddep.org/sites/default/files/swa_2015_final.pdf


Canada
United States
Bangladesh
India
Pakistan
French West Africa**
South Africa
North America
South Asia
Sub-Saharan Africa
0
10
20
30
40
Antibiotic use (in standard units) per capita
Aminoglycosides
Broad-spectrum penicillins
Cephalosporins
Chloramphenicols
Macrolides
Narrow-spectrum penicillins
Quinolones
Tetracyclines
Trimethoprim and combinations
Others


2000
2010
Latin America and Caribbean
Argentina
Brazil
Central America*
Chile
Colombia
Dominican Republic
Ecuador
Mexico
Peru
Puerto Rico
Uruguay
Venezuela
0
10
20
30
40
Antibiotic use (in standard units) per capita
Aminoglycosides
Broad-spectrum penicillins
Cephalosporins
Chloramphenicols
Macrolides
Narrow-spectrum penicillins
Quinolones
Tetracyclines
Trimethoprim and combinations
Others

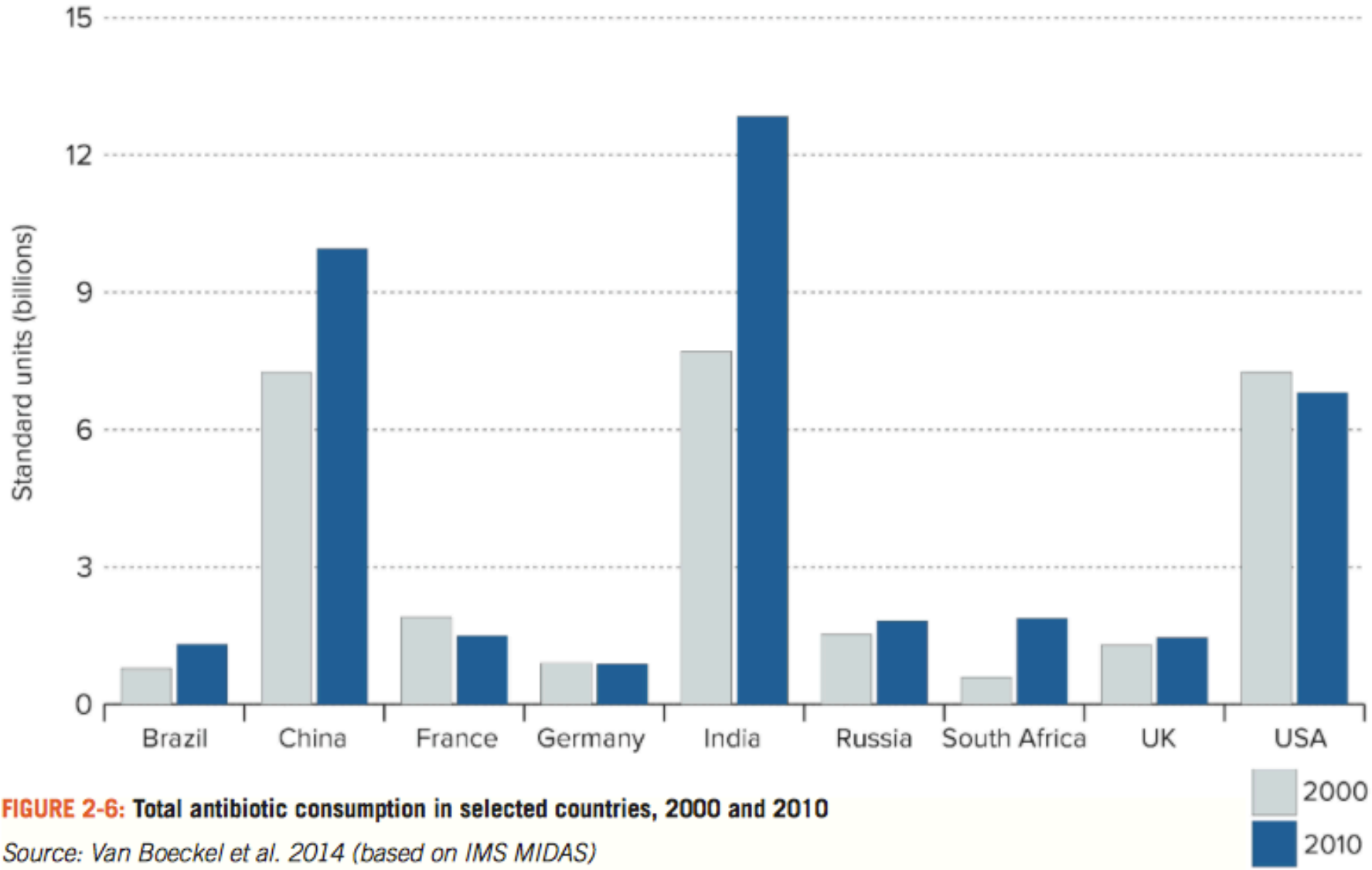


FIGURE 2-6: Total antibiotic consumption in selected countries, 2000 and 2010

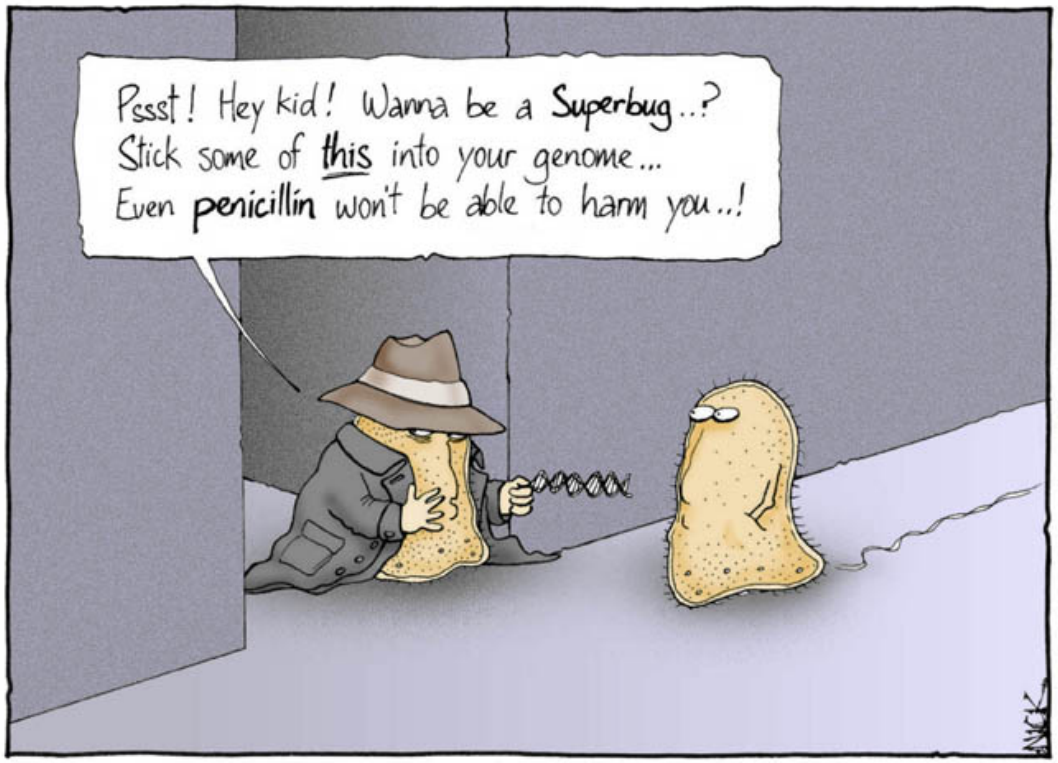
Source: Van Boeckel et al. 2014 (based on IMS MIDAS)

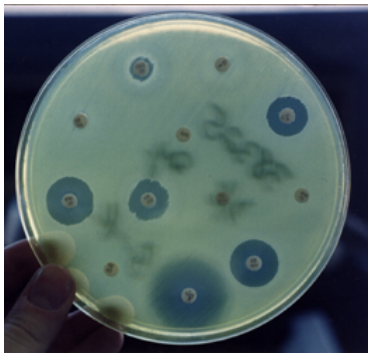
CONCLUSIONS

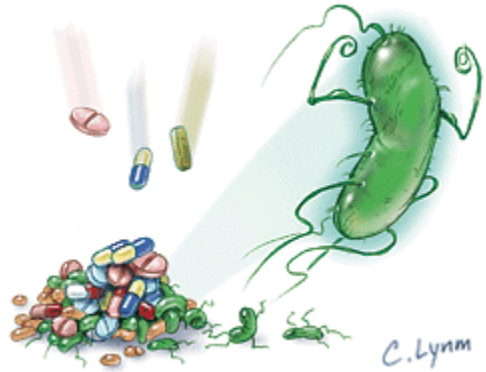
Antibiotic use in humans is increasing worldwide for first-line and some last-resort antibiotics. High-income countries tend to use more antibiotics per capita than LMICs, but consumption in most appears to be stabilizing or decreasing. The highest rates of increase are in middle-income countries, particularly the BRICS, a trend that is likely to continue as incomes continue to rise. Variation in use indicates that consumption is driven by factors other than disease and demography, such as seasonality, economic growth, and access.

Inappropriate antibiotic use is driven by both healthcare workers and consumers, particularly in the community, where 80 percent of antibiotic consumption takes place. In hospitals, the suboptimal use of broad-spectrum and postsurgical antibiotics remains prevalent. Interventions targeting these areas could significantly reduce global use. However, lack of or delayed access to antibiotics still kills more people than resistant infections. To achieve the maximum benefits to human health, measures to reduce inappropriate use of antibiotics must be combined with efforts to improve access when they are needed.

A necessidade contínua de novos antibióticos…







› **Resistência bacteriana**

› **Infecções hospitalares**

› **Pacientes imunocomprometidos**

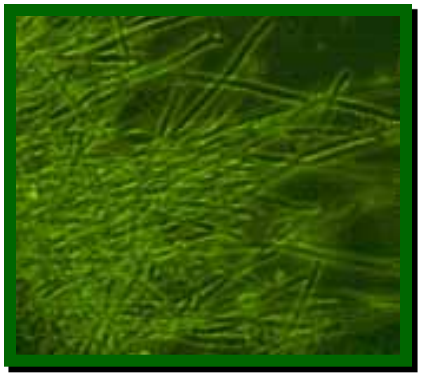
› **Bioterrorismo**

Clardy, J, Fischbach, MA, Walsh, CT *Nature Biotechnol.* 2006, **24**, 1541.
Baltz, RH *J. Ind. Microbiol. Biotechnol.* 2006, **33**, 507.

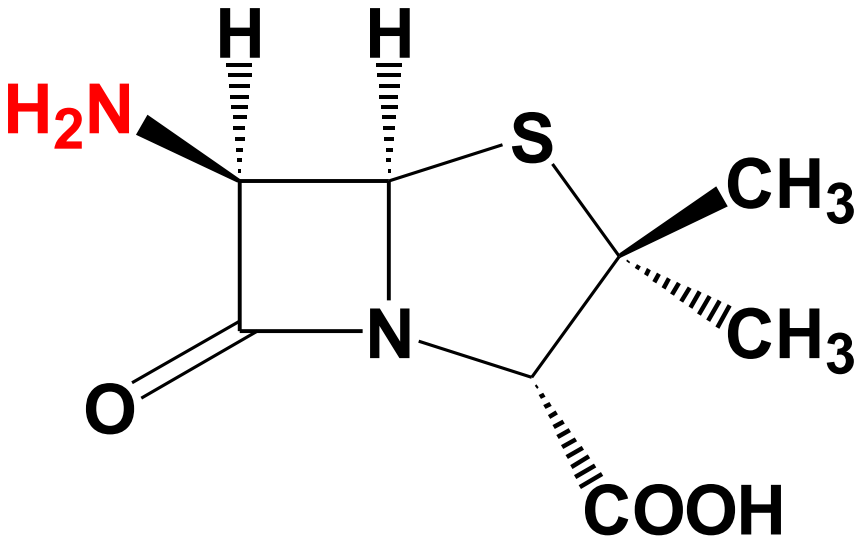
Antibióticos β-lactâmicos - PENICILINAS

1957 - Sheehan - síntese total da penicilina G

1958 - Beechams - isolamento do 6-APA

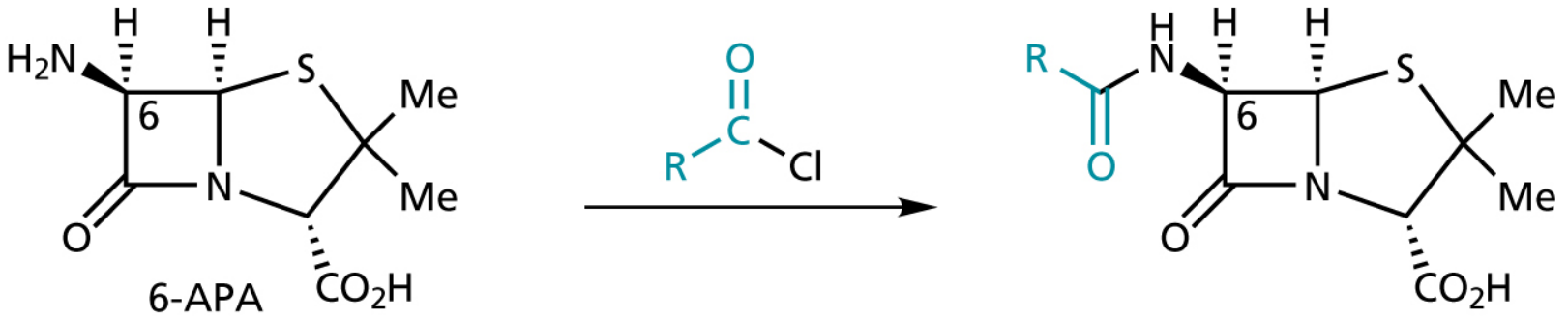


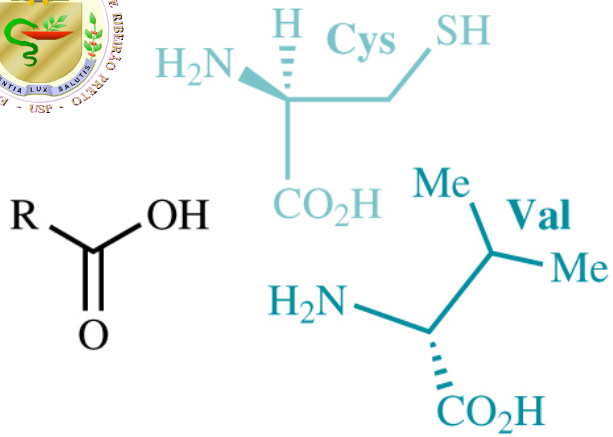
P. crysogenum

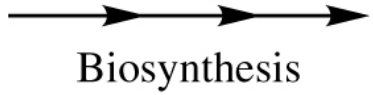


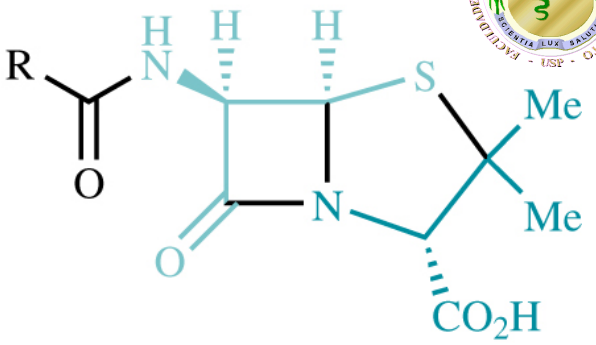
Ácido 6-aminopenicilânico

penicilinas semi-sintéticas





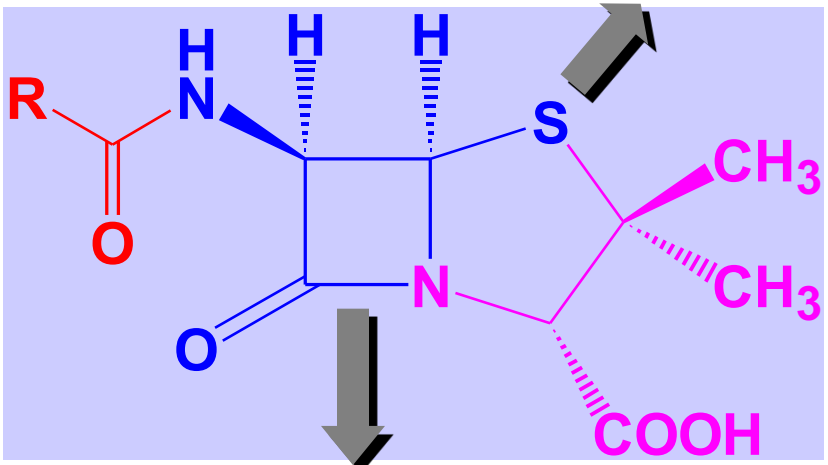


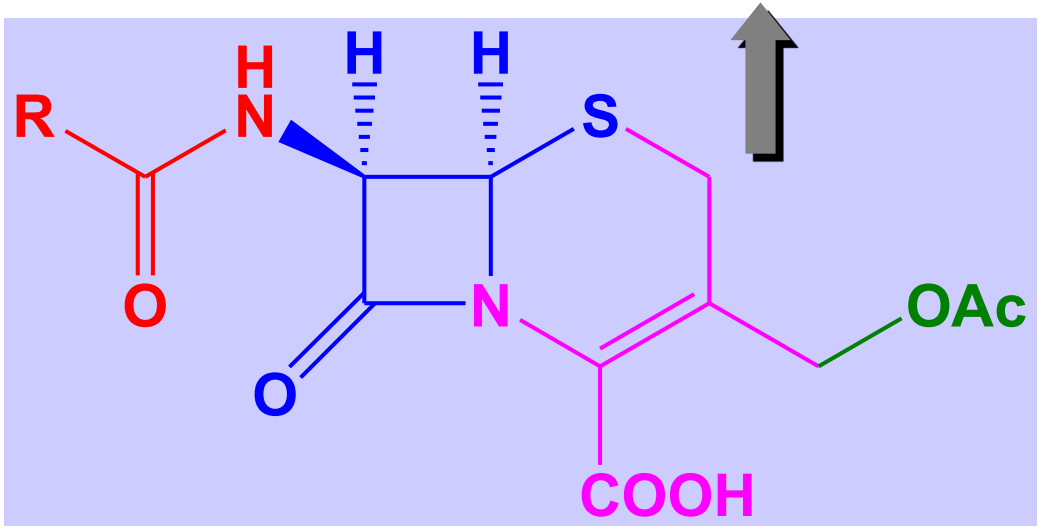


Cisteína

Anel tiazolidínico

Anel diidrotiazínico





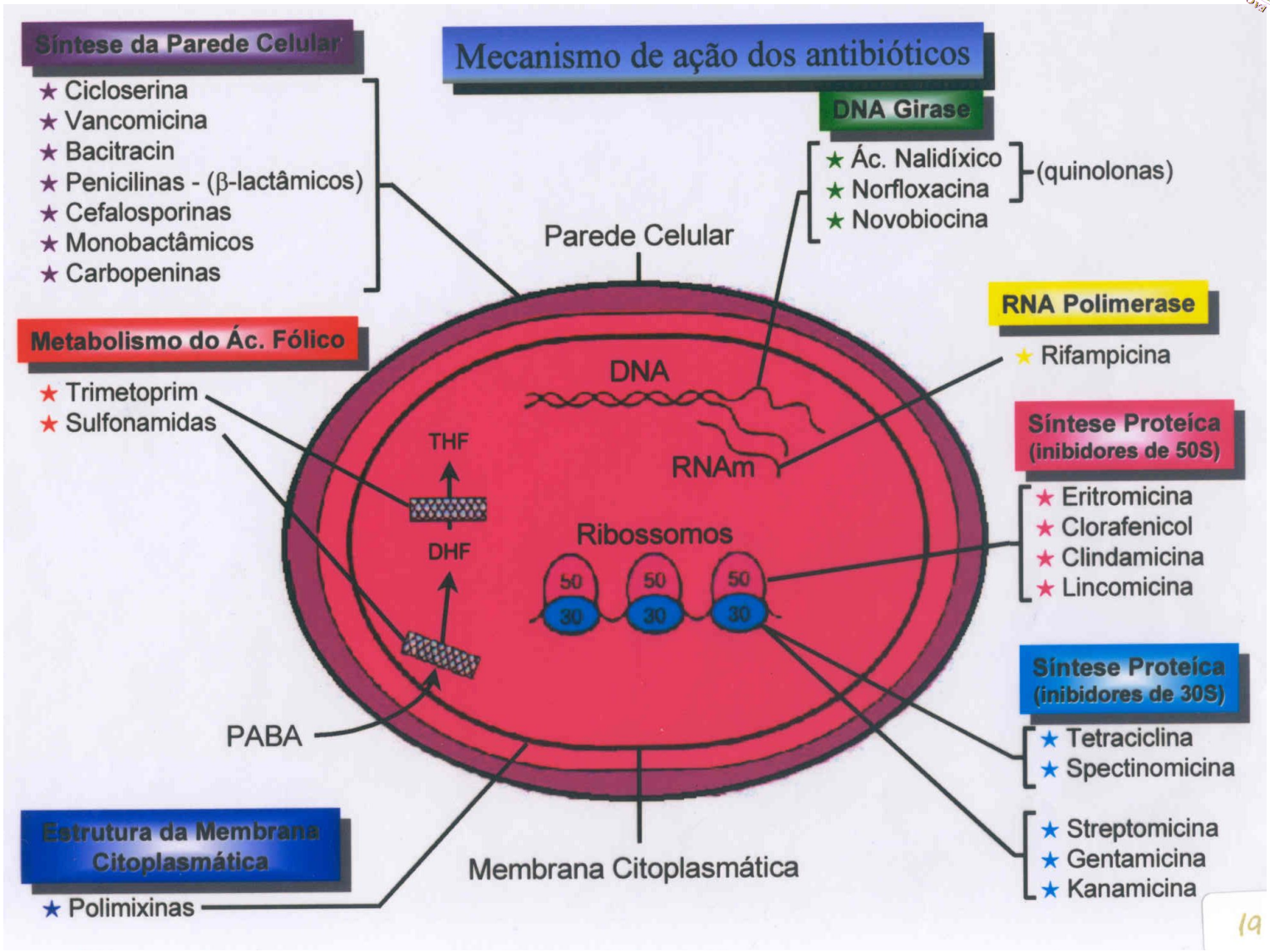
Anel β-lactâmico
ou Azetidinona

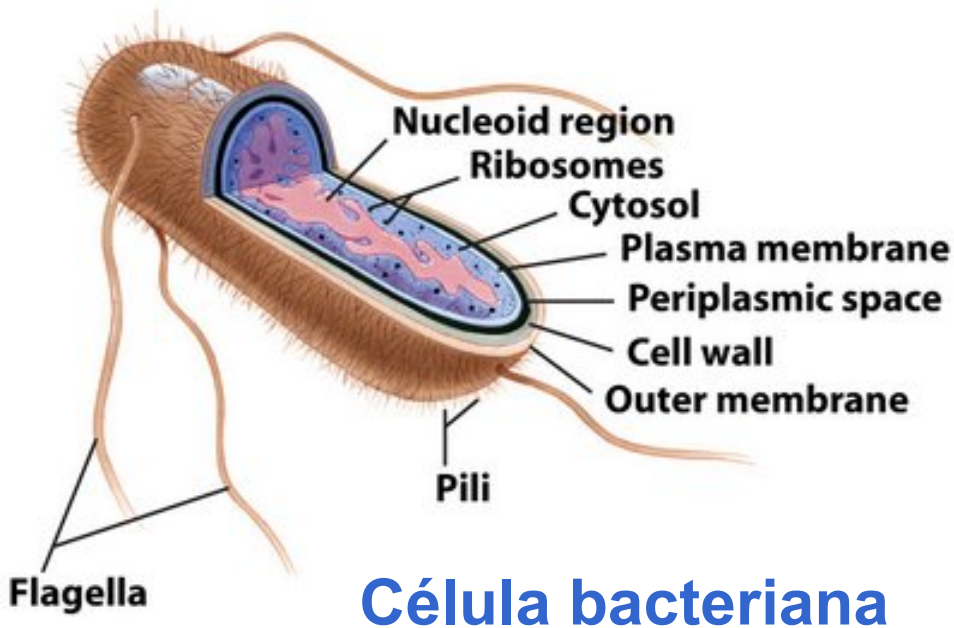
Valina

PENICILINAS

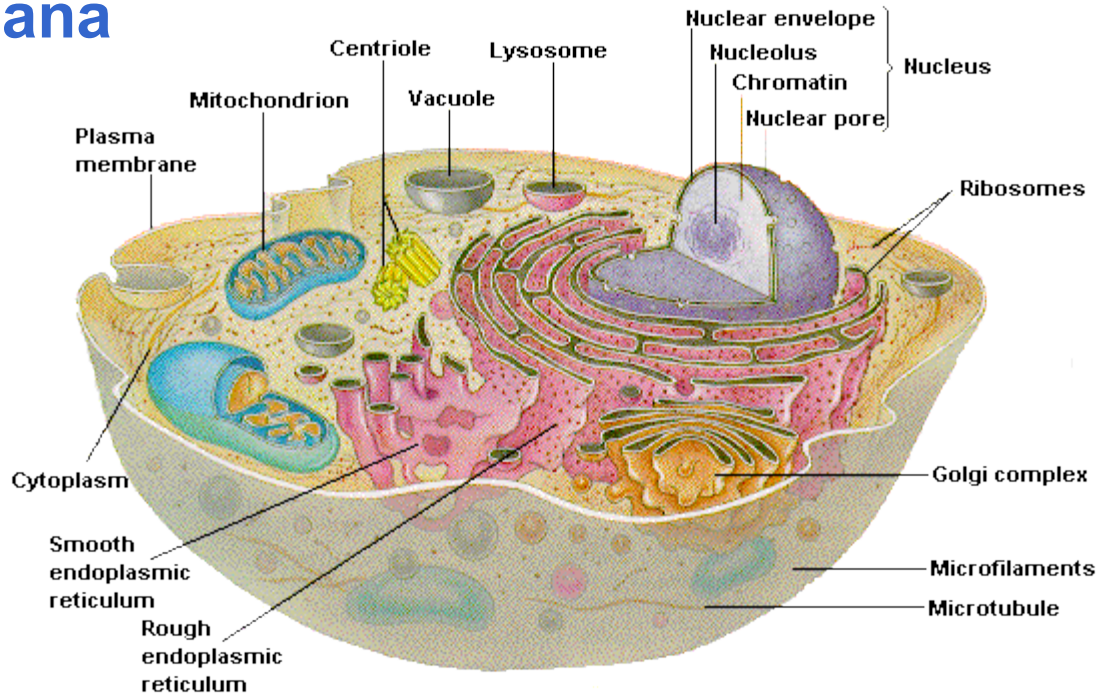
CEFALOSPORINAS

Sítios de ação dos antibióticos



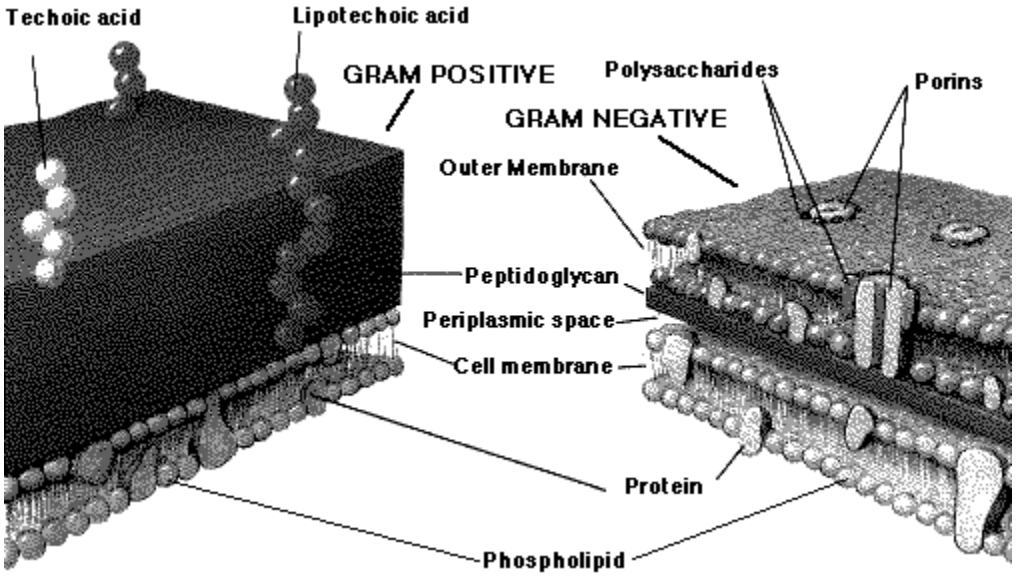


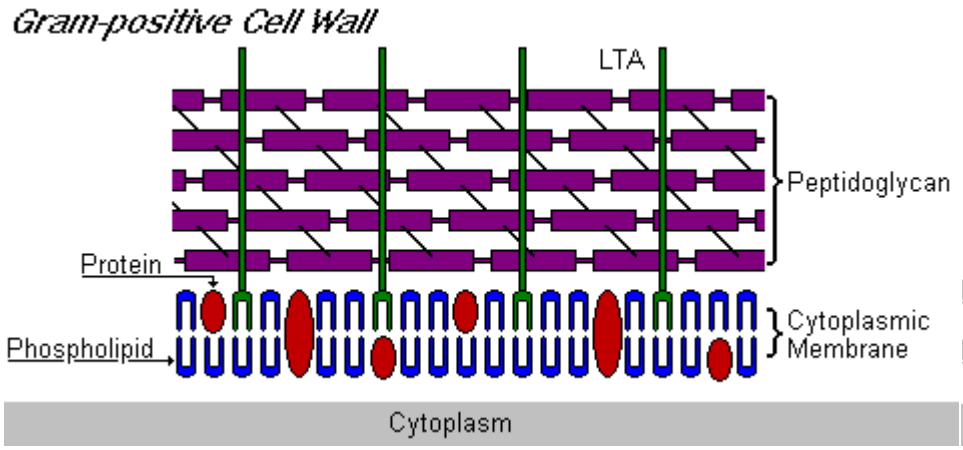
Célula bacteriana

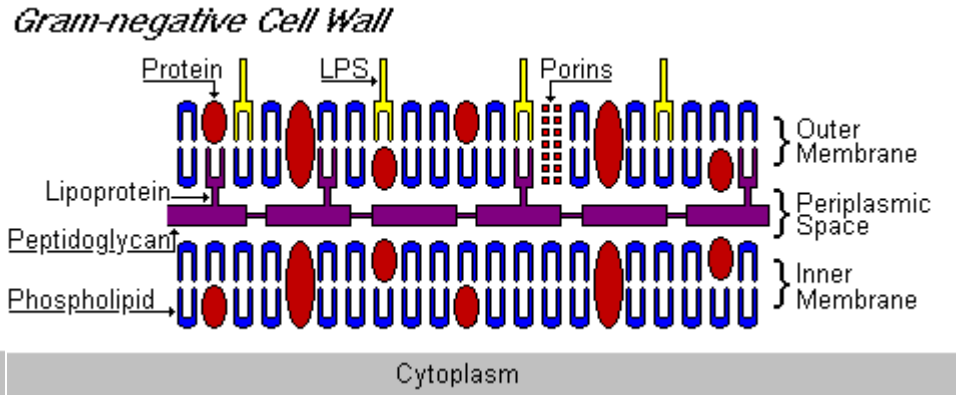


Célula animal

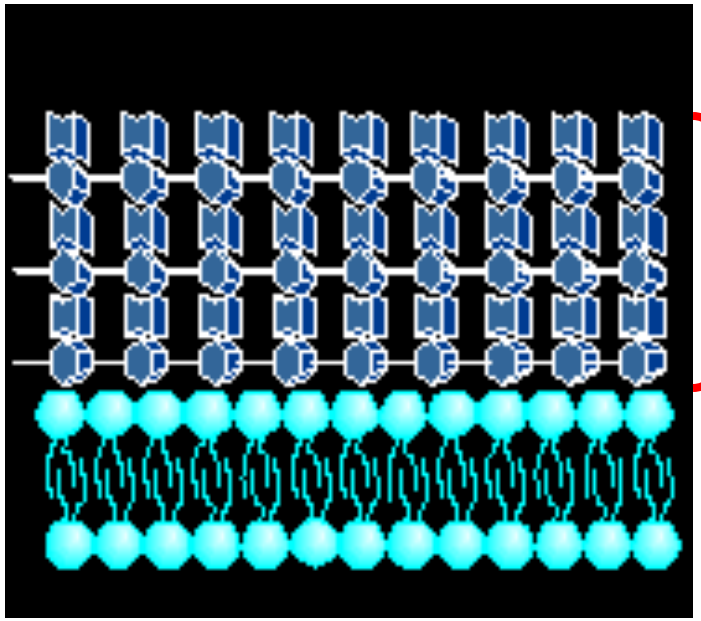
Parede celular bacteriana







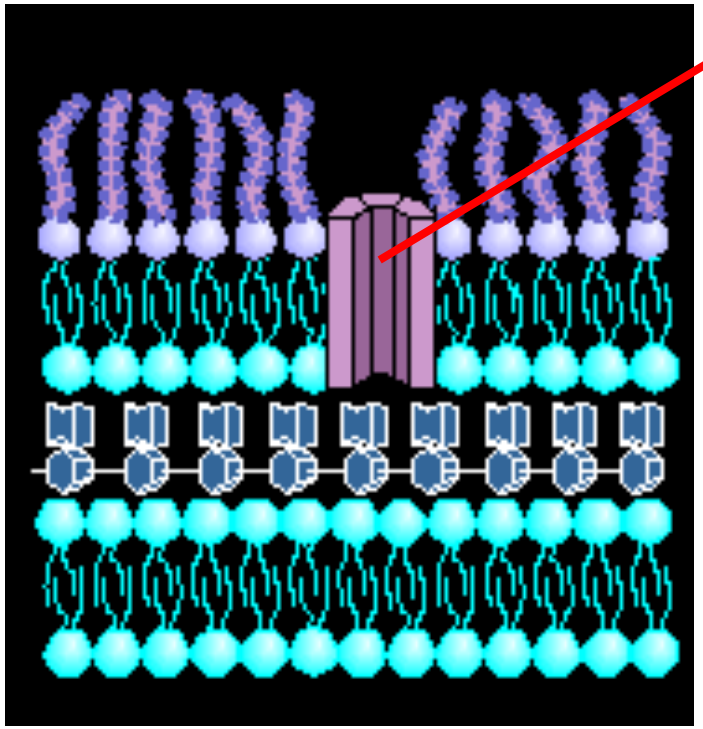
gram positivo



peptideoglicana

bicamada lipídica

gram negativo



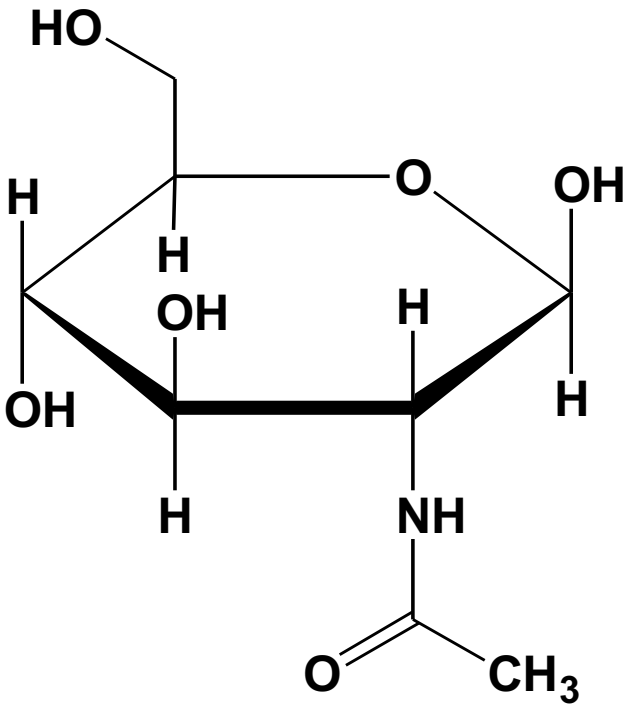
canais de porina

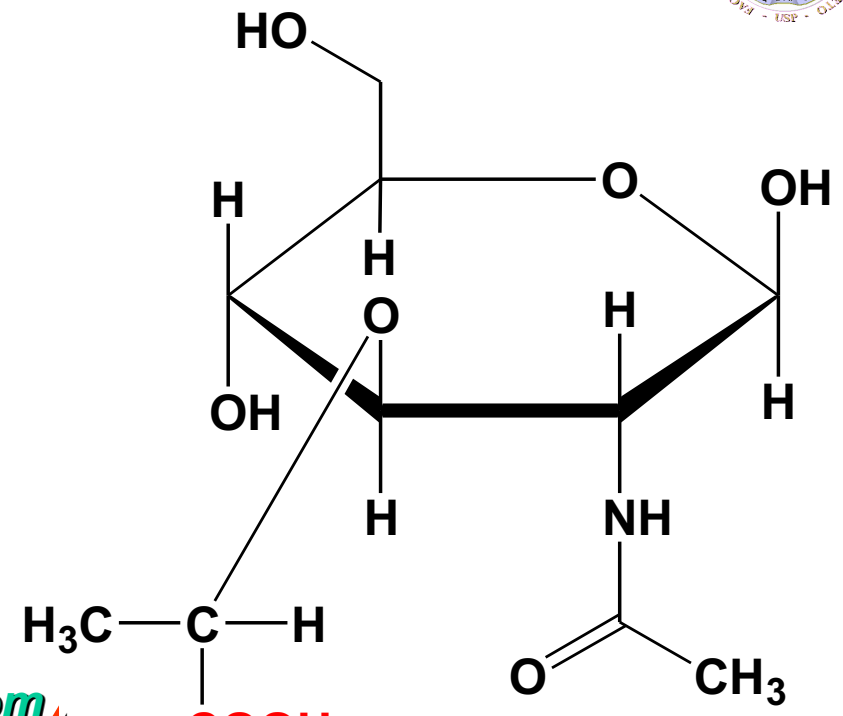
lipopolissacarídeos e lipídeos

peptideoglicana

bicamada lipídica

Estrutura glicopeptídica



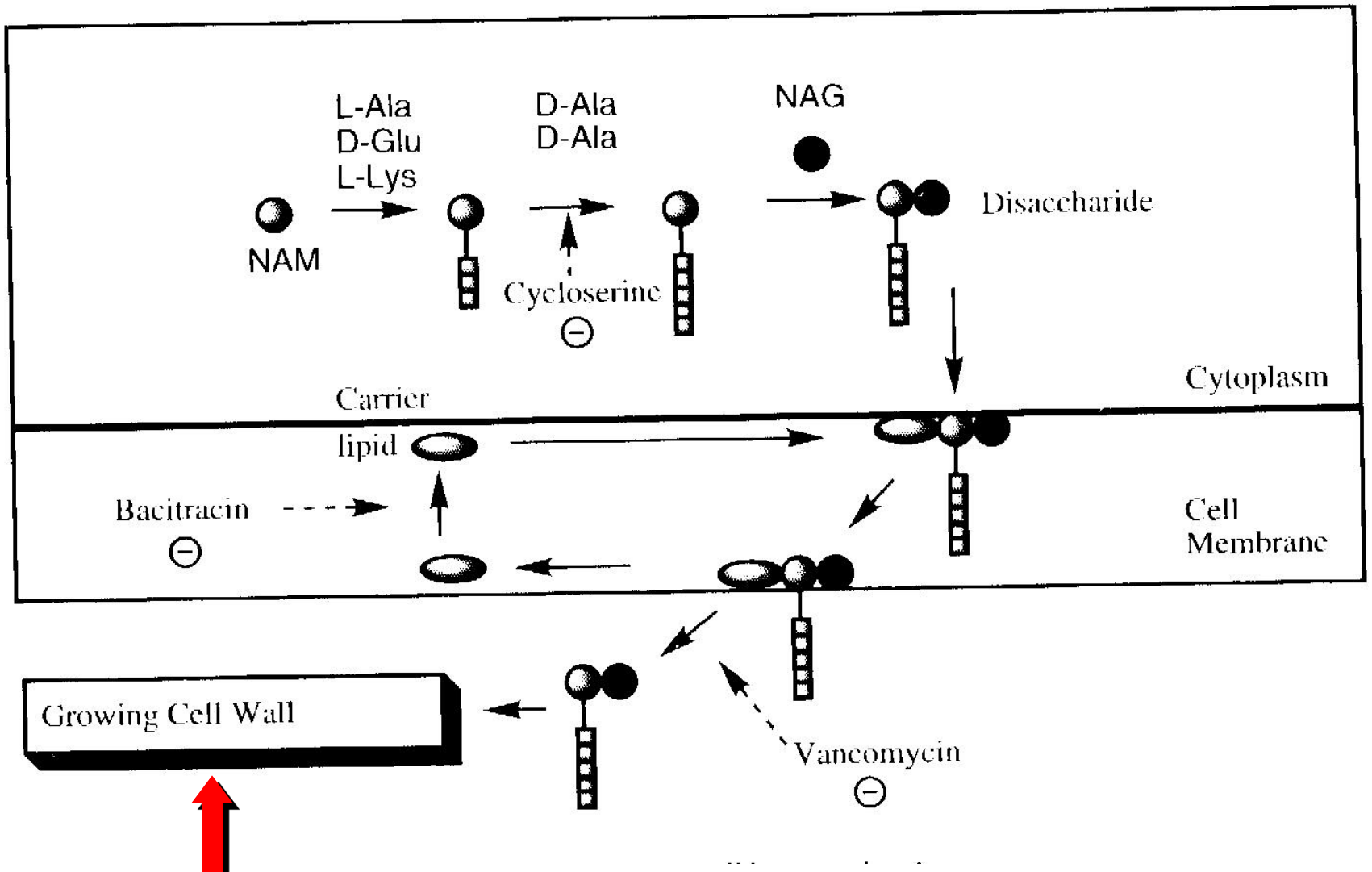


ligações com cadeias peptídicas

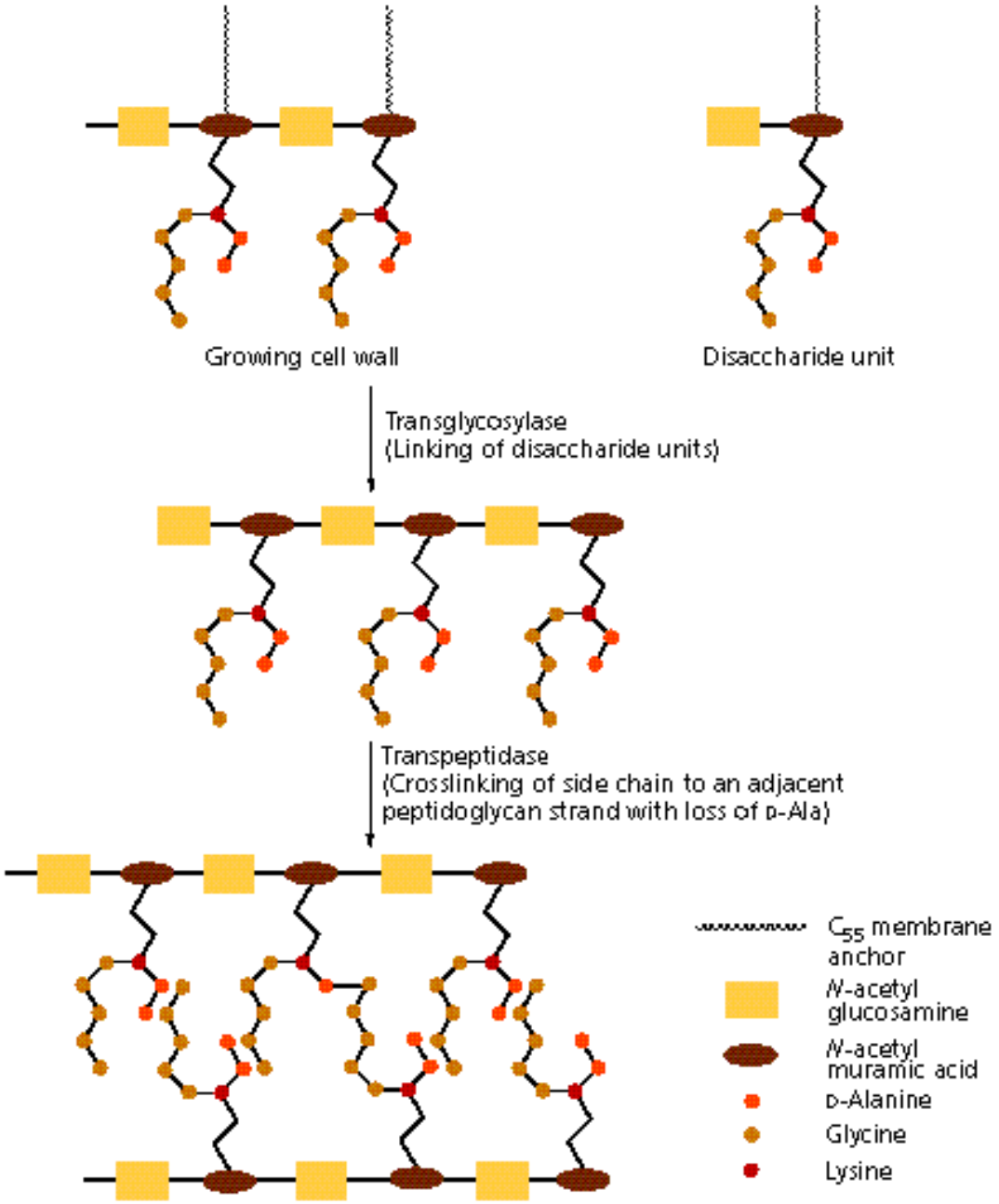
N-acetilglicosamina (NAG)

Ácido N-acetilmurâmico (NAM)

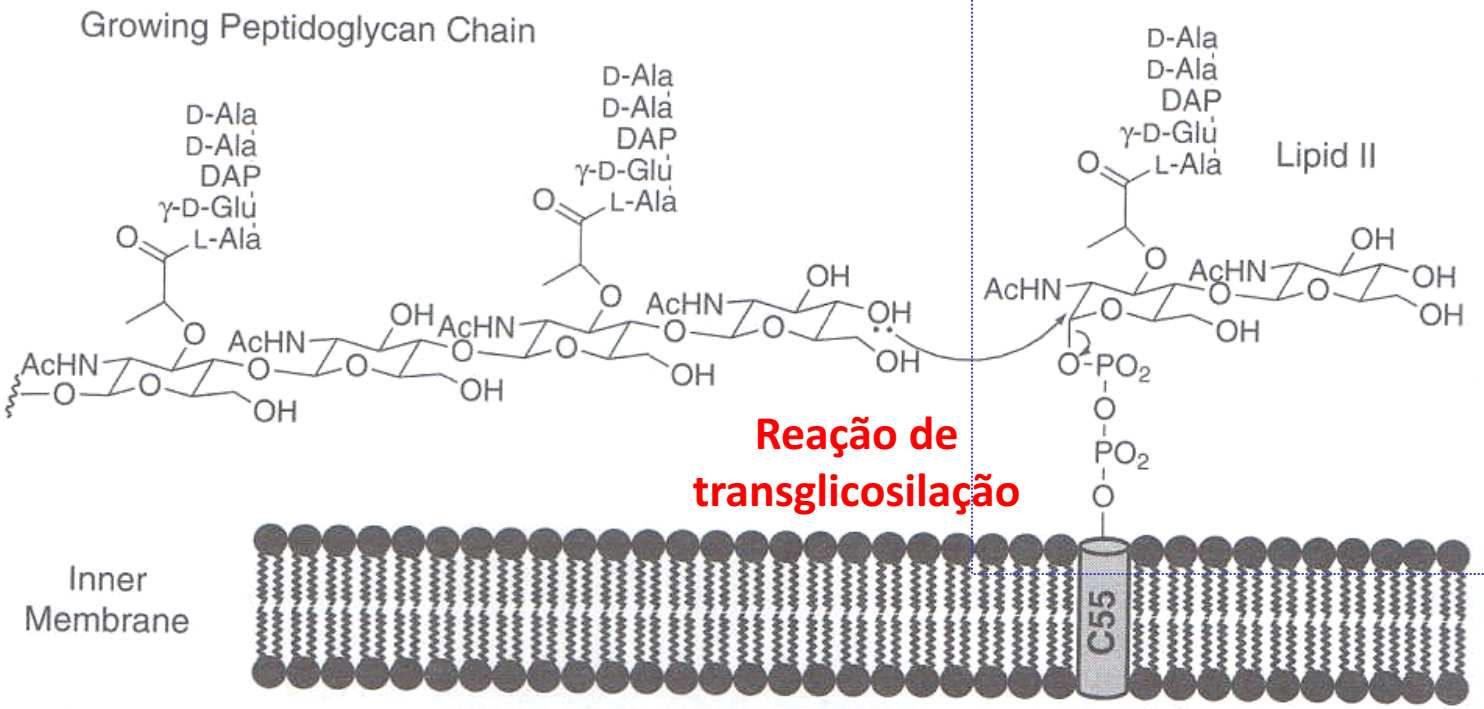
Biossíntese da parede celular bacteriana



β-lactâmicos


Growing cell wall
Disaccharide unit
Transglycosylase
(Linking of disaccharide units)
Transpeptidase
(Crosslinking of side chain to an adjacent
peptidoglycan strand with loss of D-Ala)
C_{55} membrane anchor
N-acetyl glucosamine
N-acetyl muramic acid
D-Alanine
Glycine
Lysine

Dissacarídeo+5 aminoácidos ancorado na membrana



Reação de transglicosilação

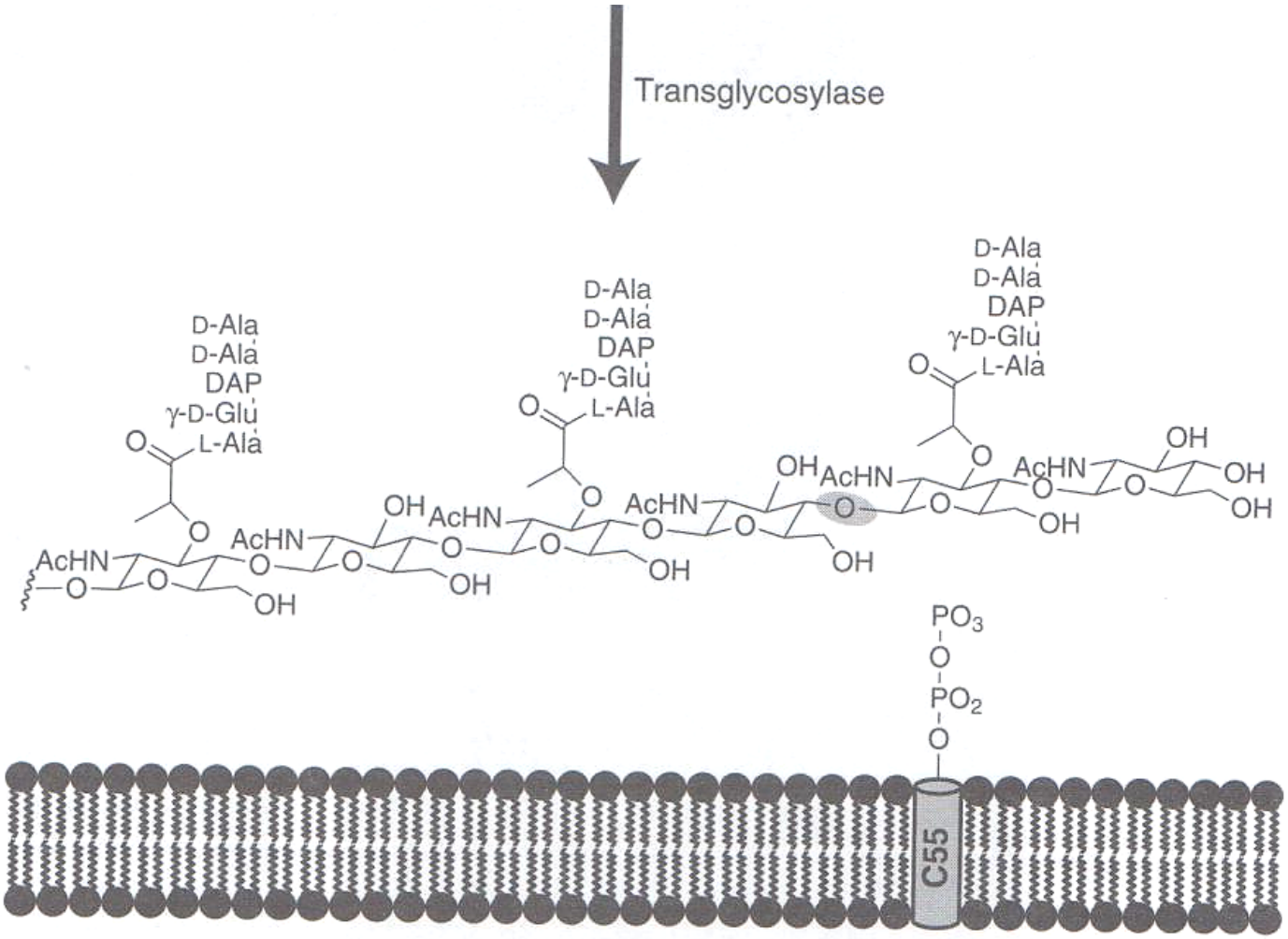
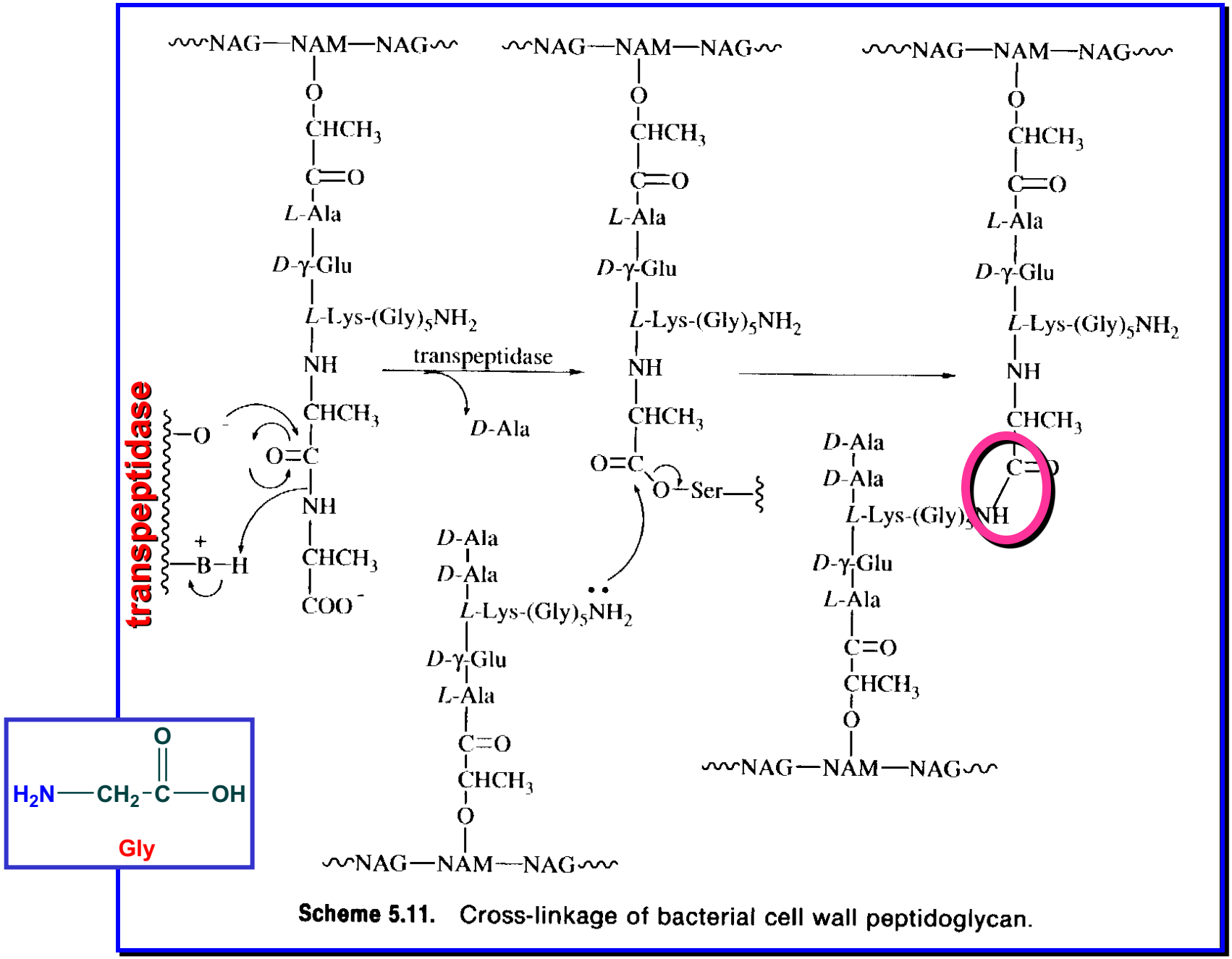
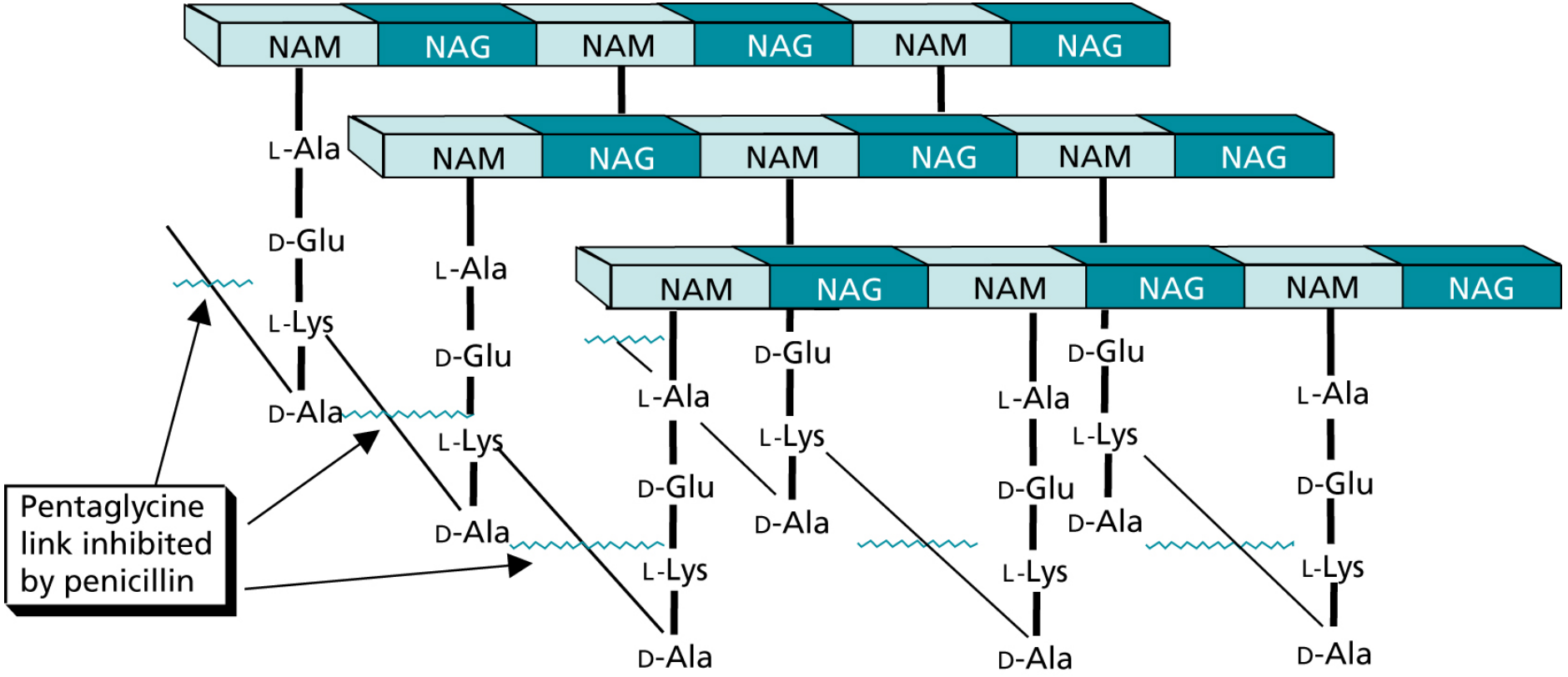


Figure 3.3 Action of cell wall transglycosylases on the C_{55}-lipid-linked *N*-acetyl-muramyl (MurNAc) pentapeptide substrate.

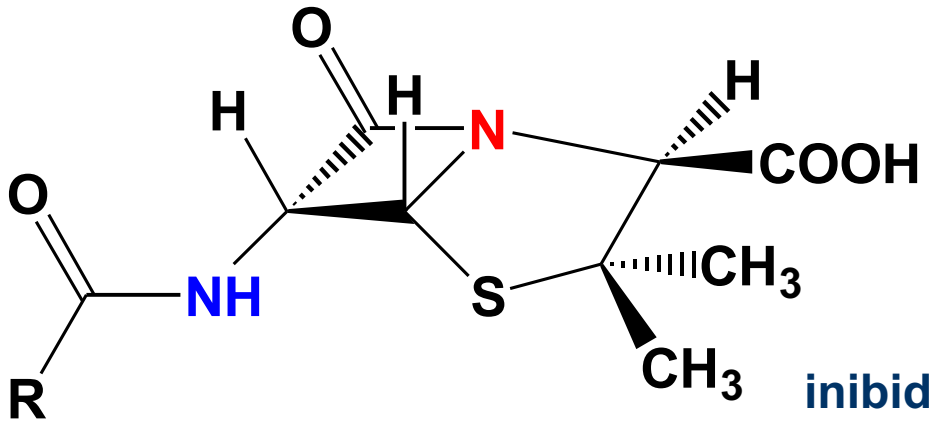


Scheme 5.11. Cross-linkage of bacterial cell wall peptidoglycan.

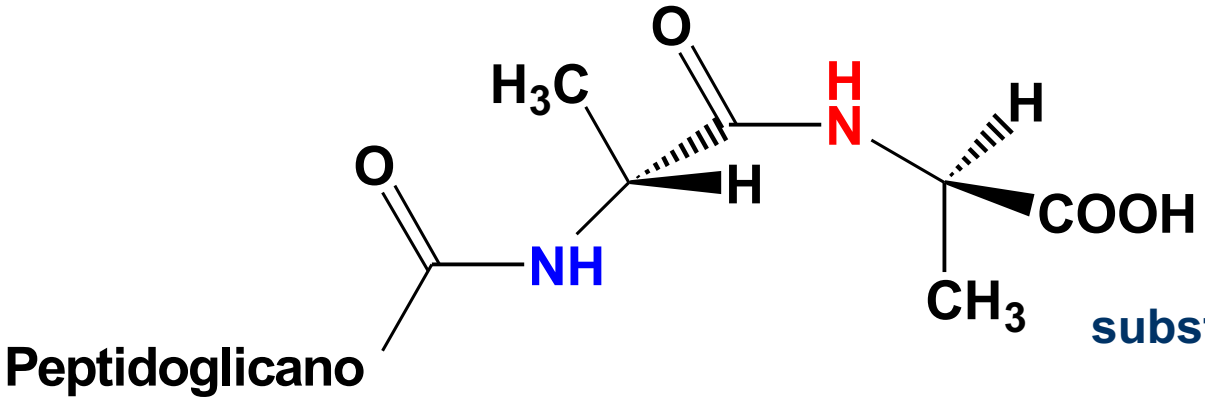
Múltiplas ligações cruzadas na parede celular bacteriana



Reconhecimento molecular

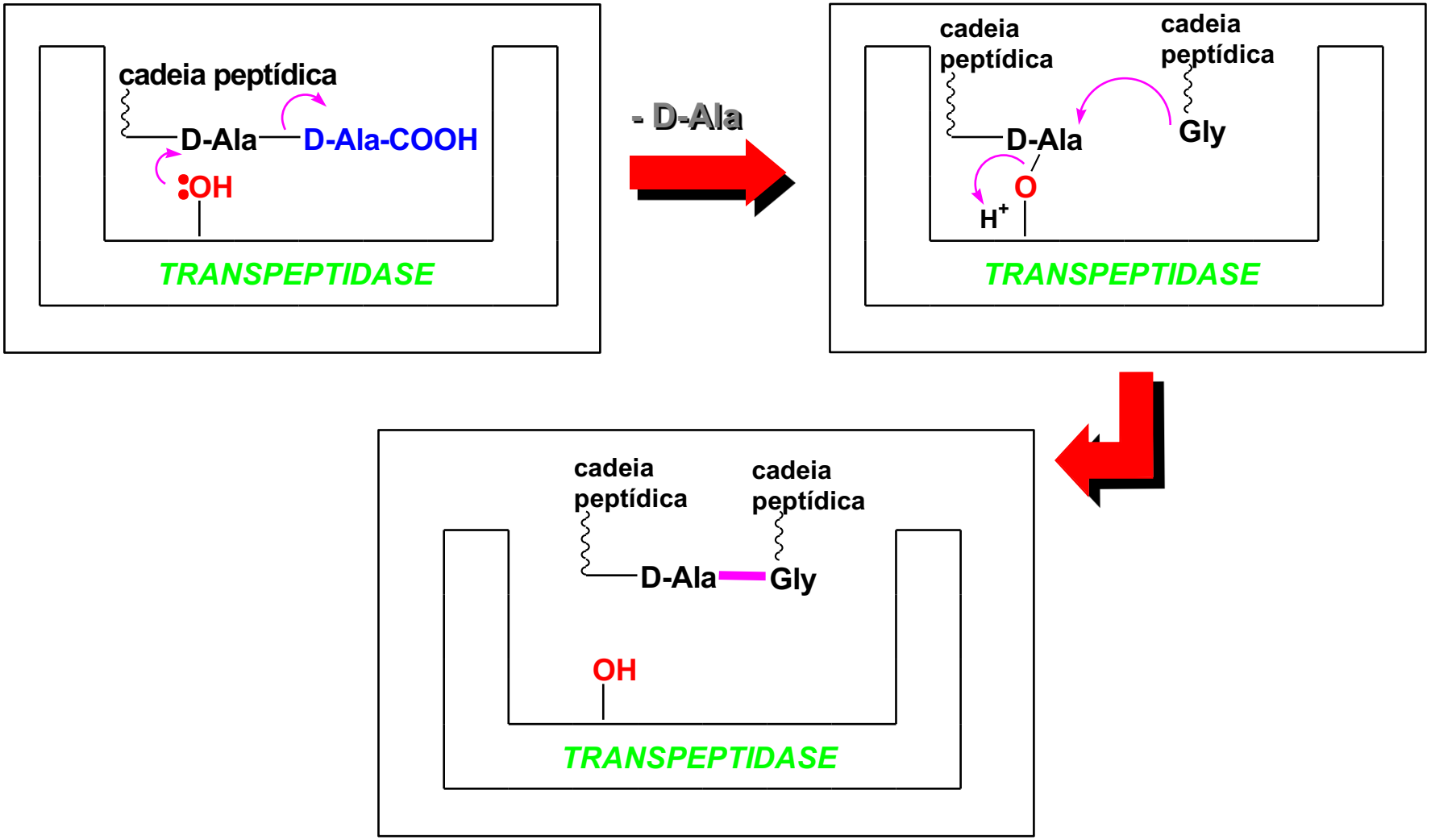


inibidor (penicilina)

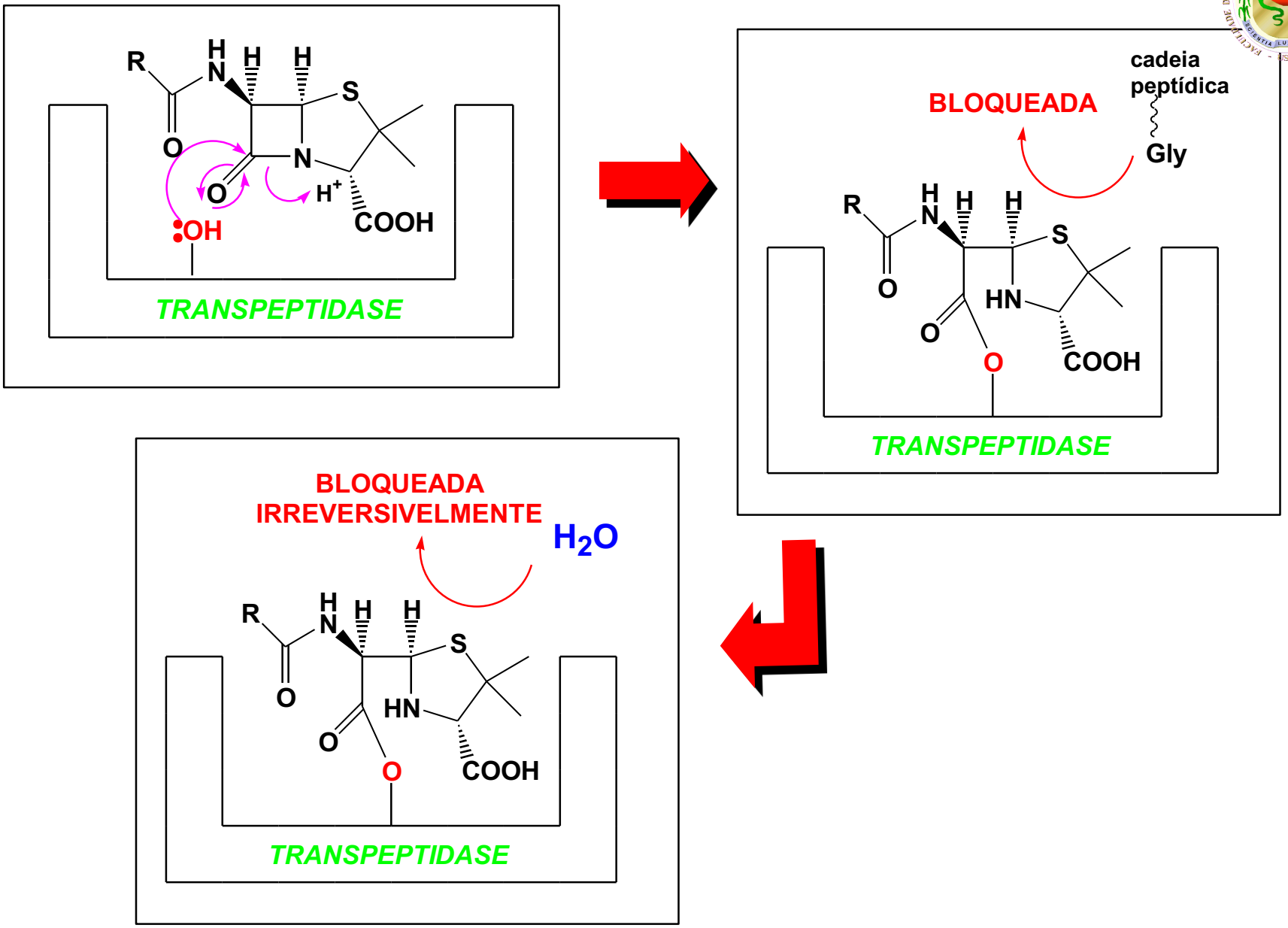


substrato D-alanil-D-alanina

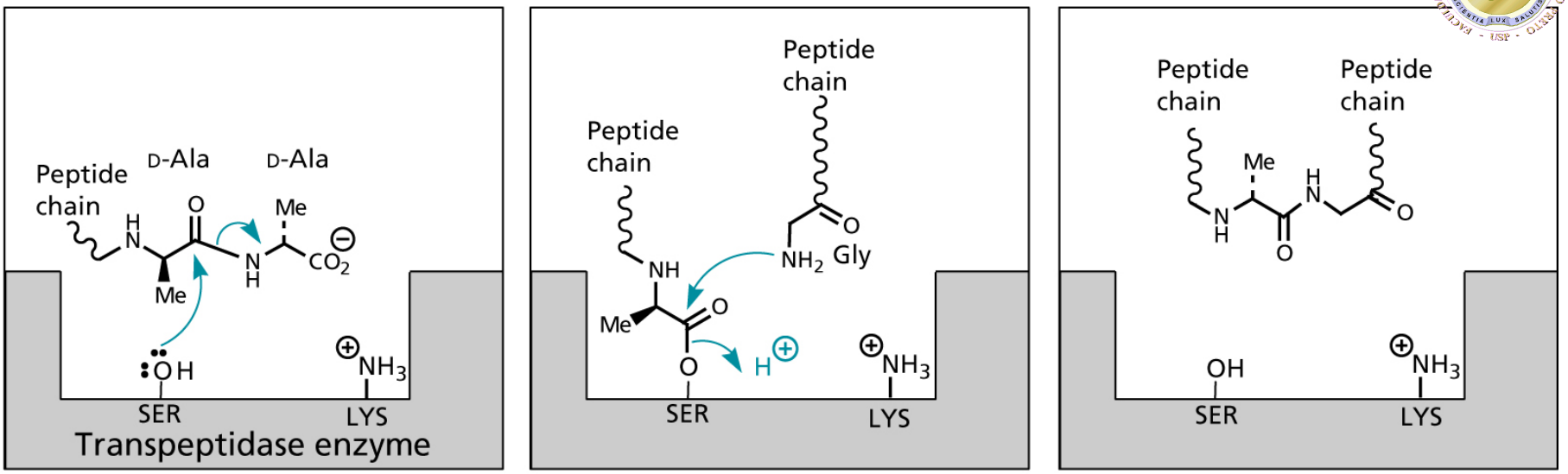
Formação da ligação cruzada na parede celular bacteriana catalisada pela transpeptidase (mecanismo normal)



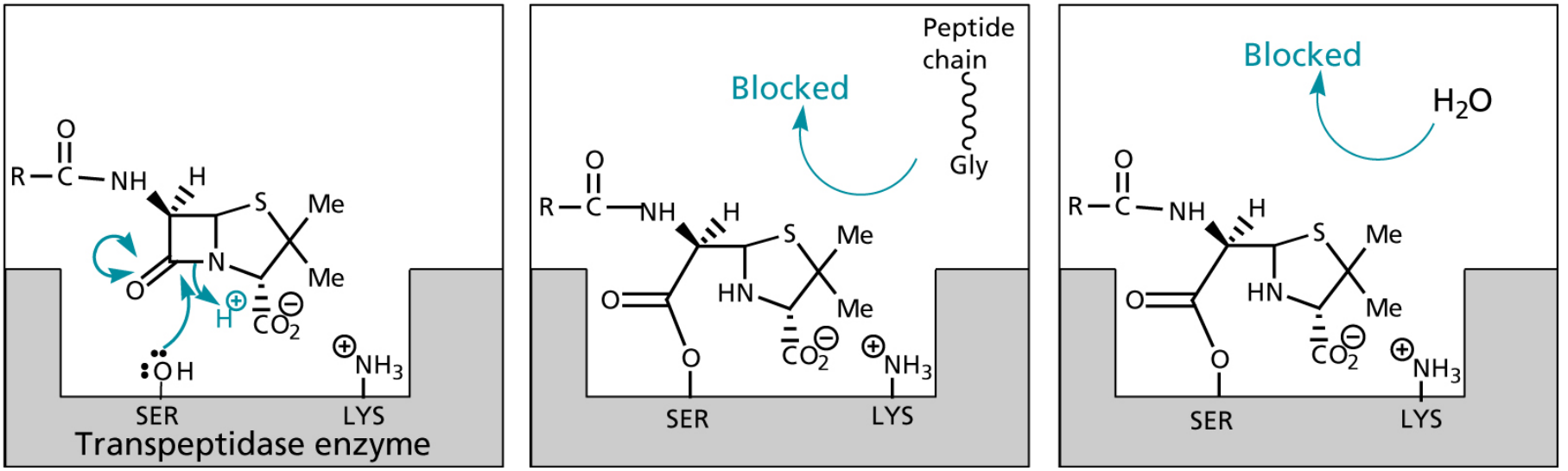
Mecanismo de inibição dos antibióticos β-lactâmicos



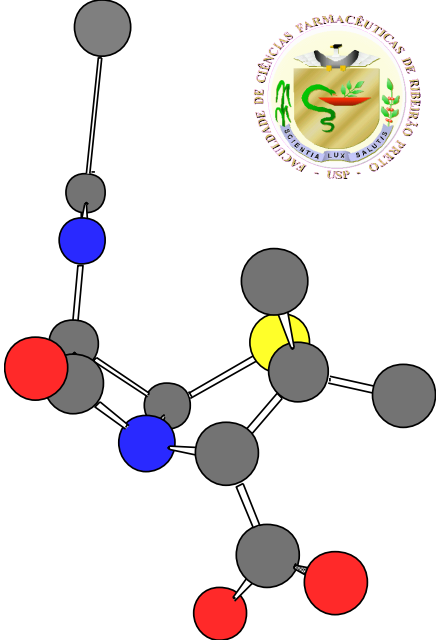
(a) Transpeptidase cross-linking



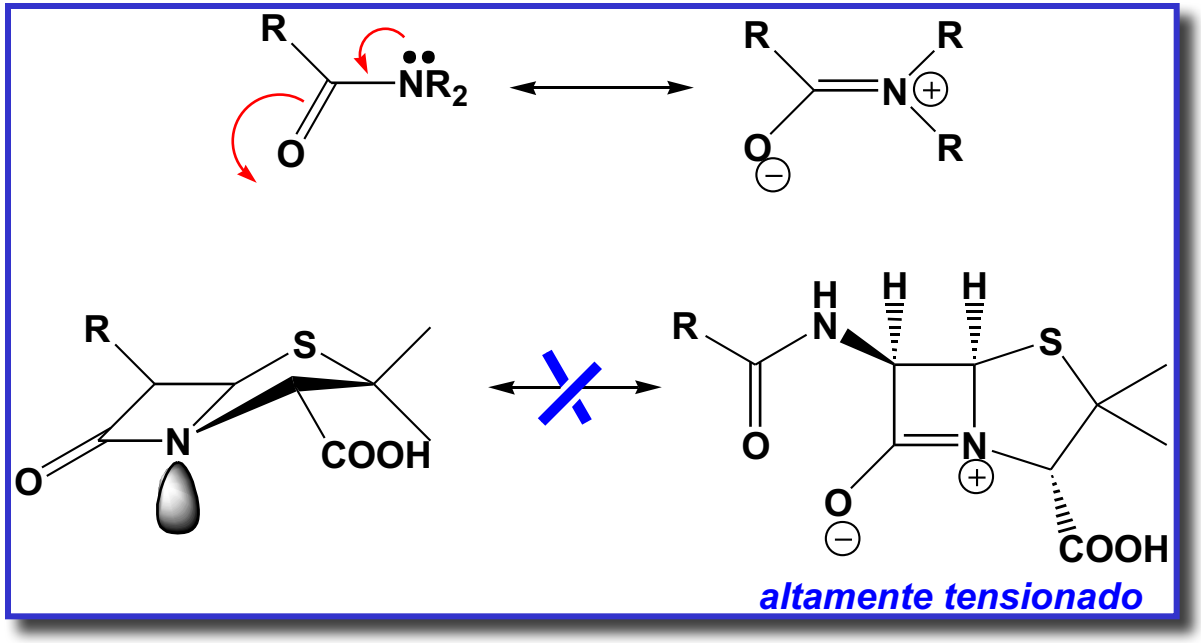
(b) Penicillin inhibition



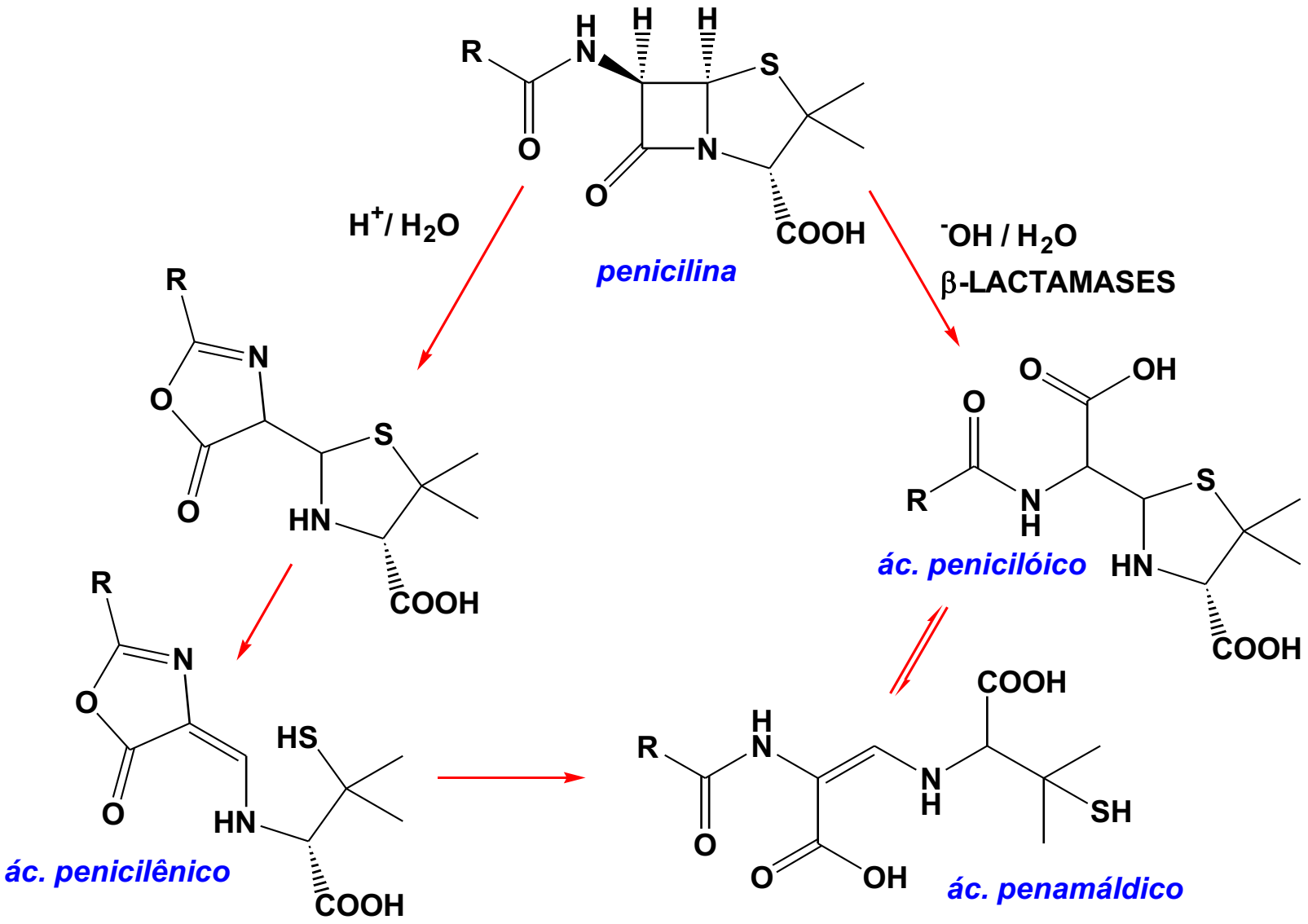
Instabilidade do anel β-lactâmico

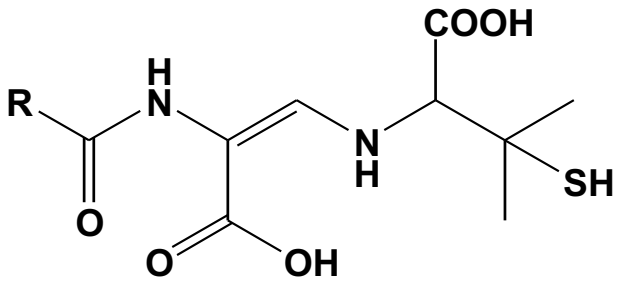


- tensão do anel
- C carbonílico da lactama é extremamente eletrofílico
  - hidrólise em meio ácido
  - hidrólise em meio básico
  - sensível ao ataque de β-lactamases
- participação do grupo vizinho

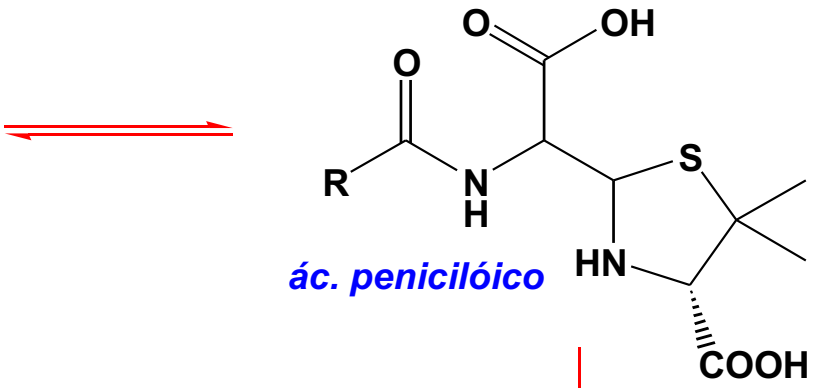


Reações de degradação das penicilinas

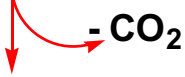


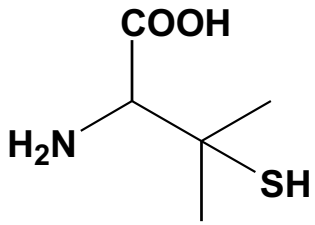


ác. penamáldico



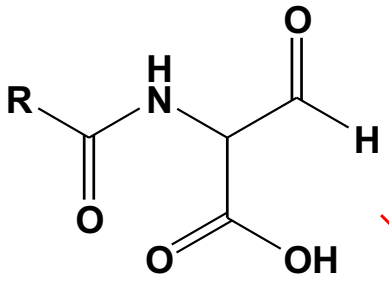
ác. penicilóico





penicilamina

+



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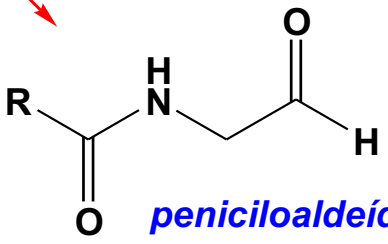
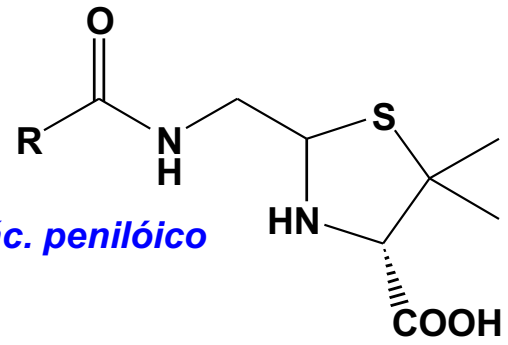
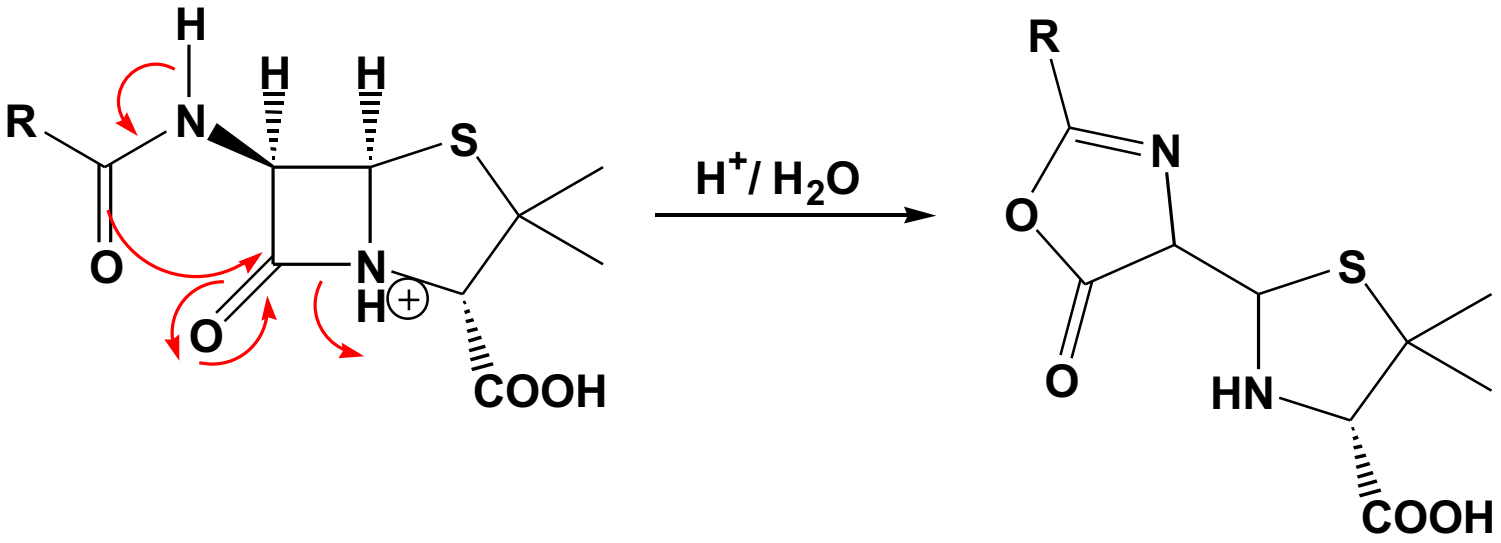


peniciloaldeído

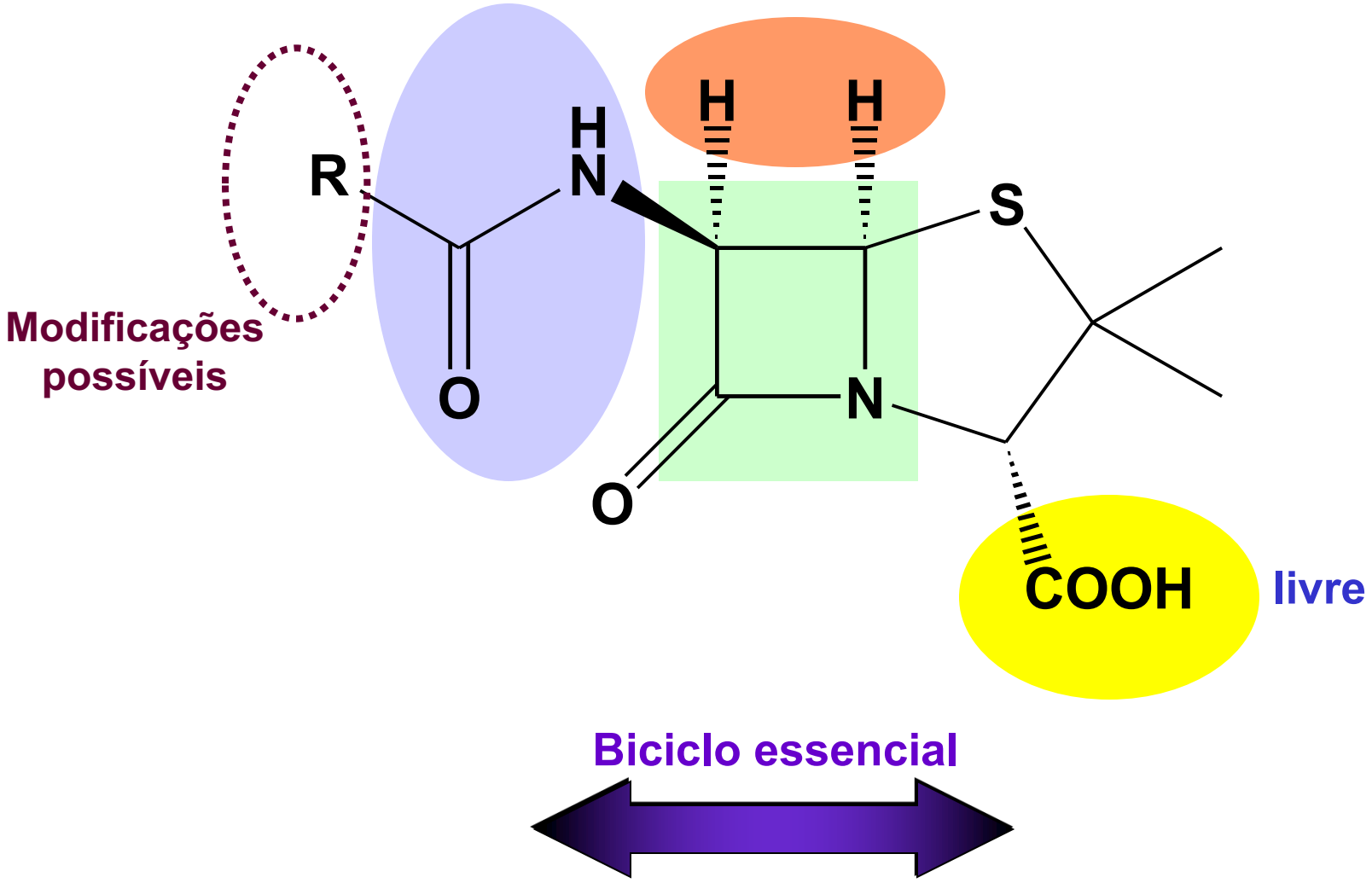


ác. penilóico

Participação do grupo vizinho na abertura do anel β-lactâmico

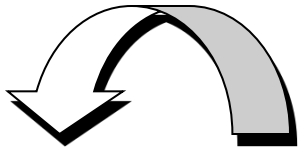


Relação estrutura-atividade

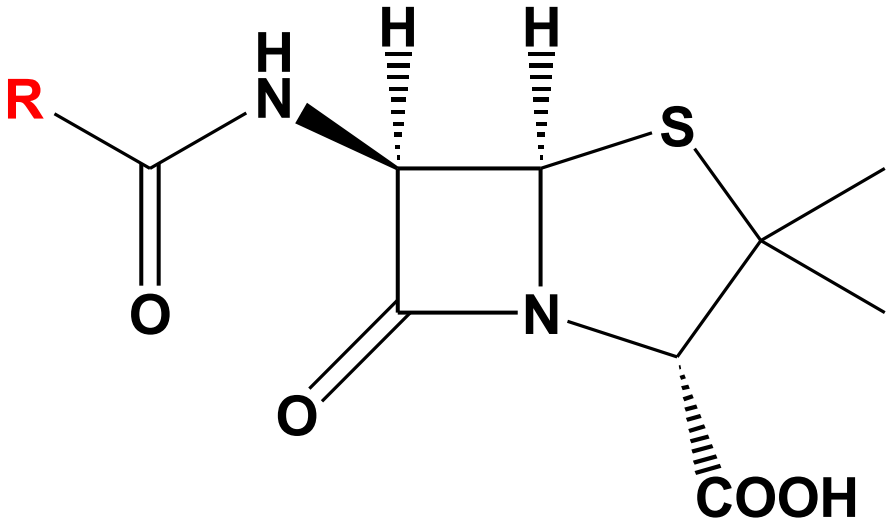


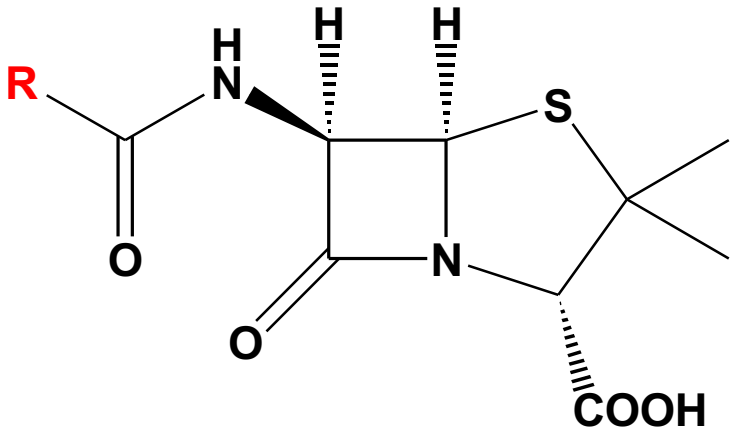
Instabilidade em meio ácido

Redução da participação do grupo vizinho



Grupo retirador de elétrons





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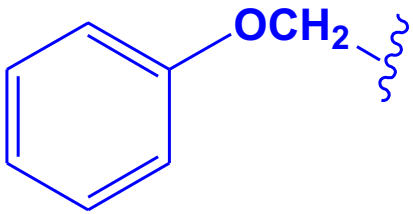
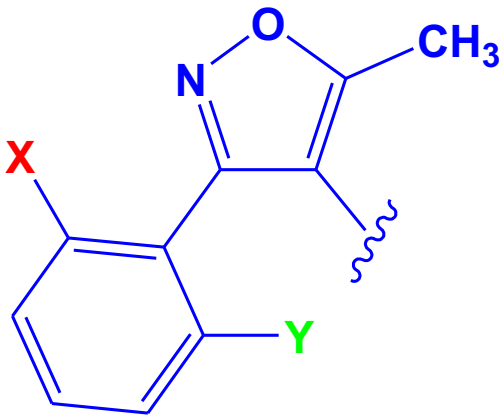
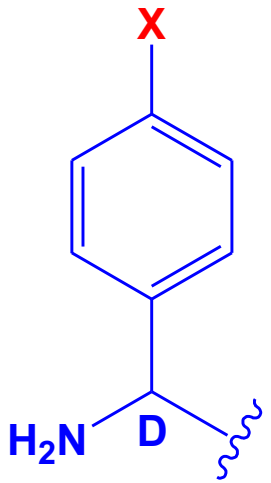


fenoximetilpenicilina
ou penicilina V

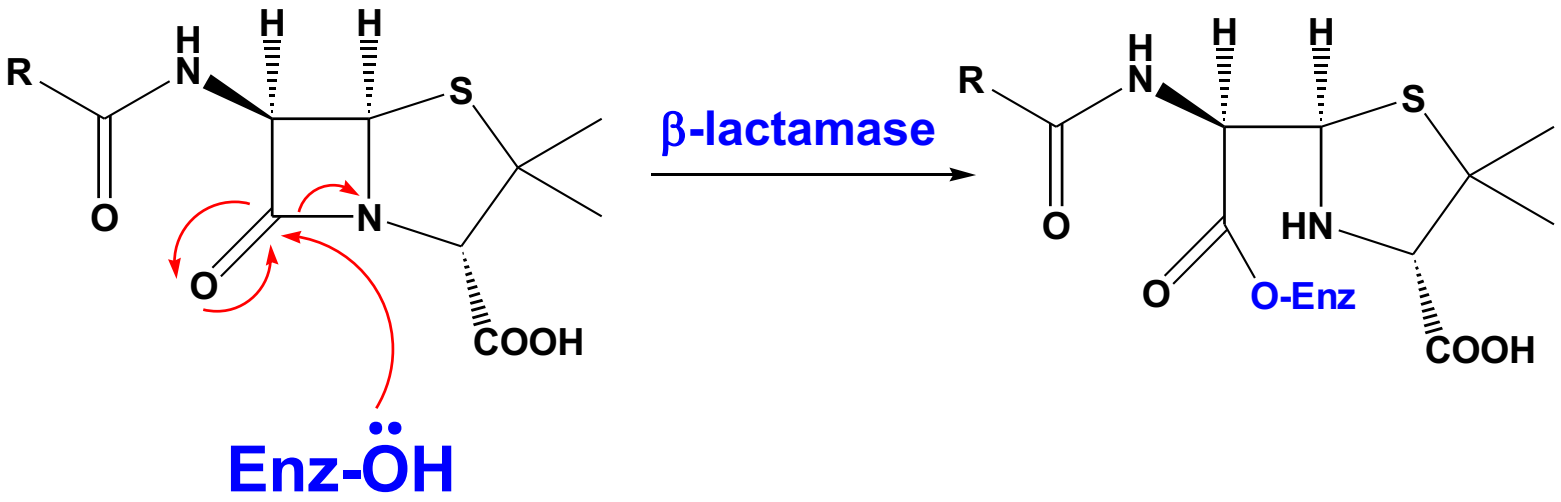


X = Y = H Oxacilina
X = H, Y = Cl Cloxacilina
X = Y = Cl Dicloxacilina

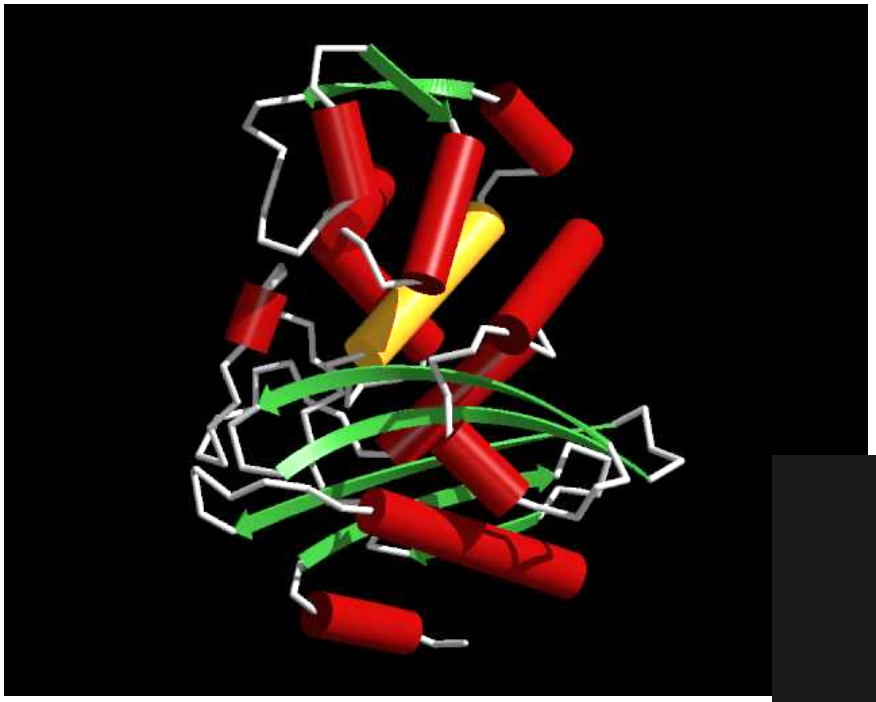


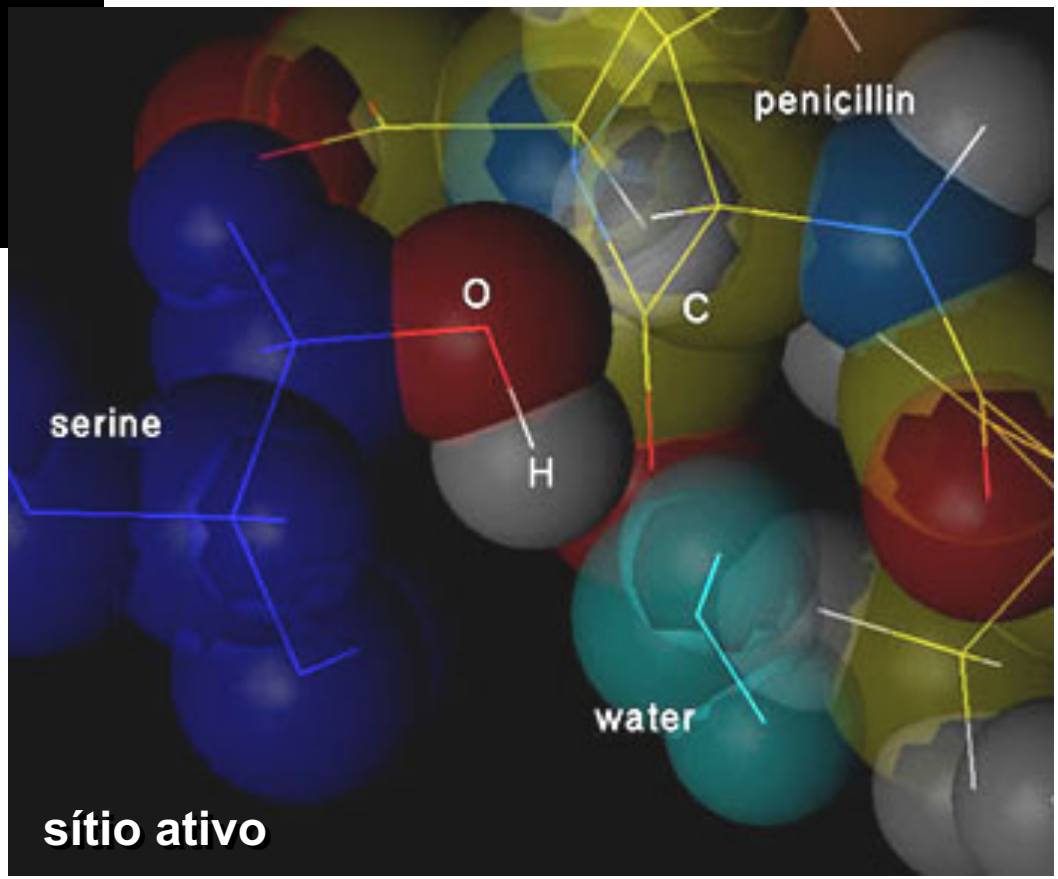
X = H Ampicilina
X = OH Amoxicilina

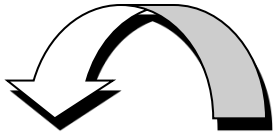
Instabilidade frente a β-lactamases



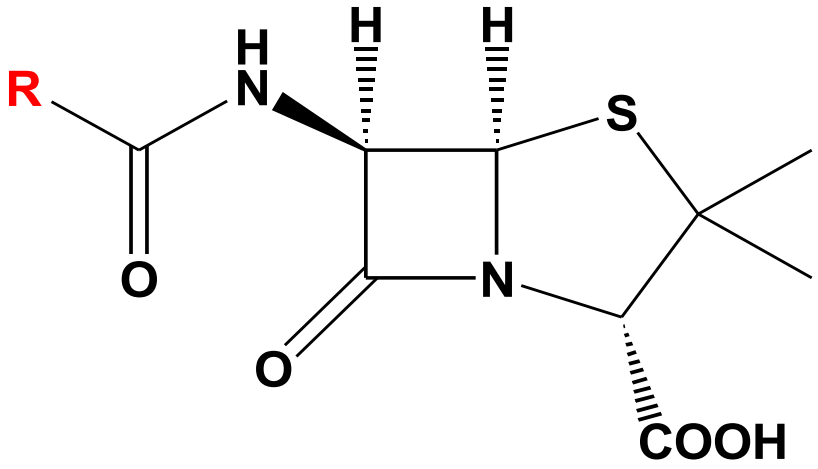
β-Lactamases

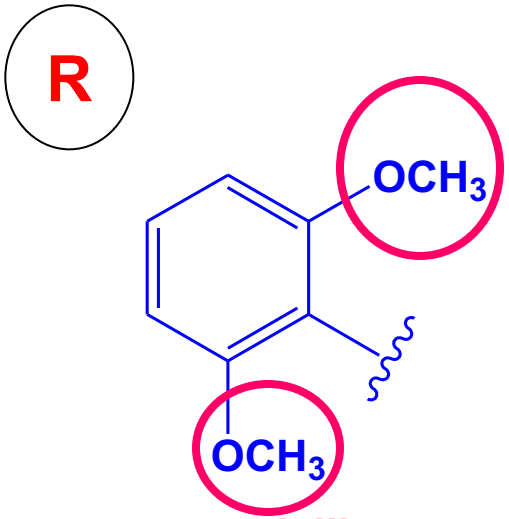




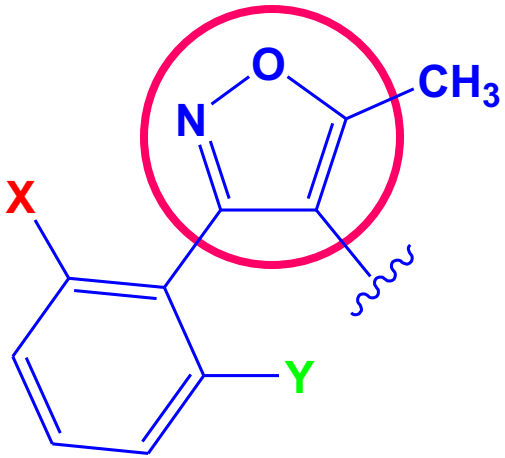


Grupo volumoso



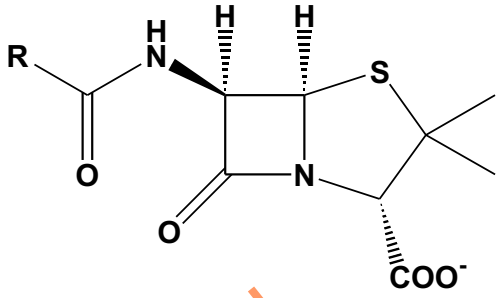


meticilina

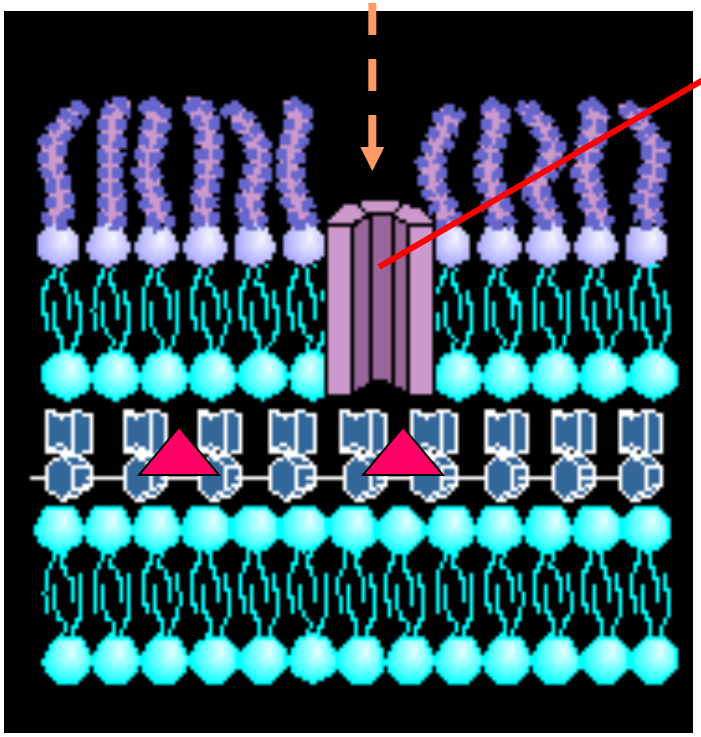


X = Y = H Oxacilina
X = H, Y = Cl Cloxacilina
X = Y = Cl Dicloxacilina

Espectro de ação reduzido



gram negativo

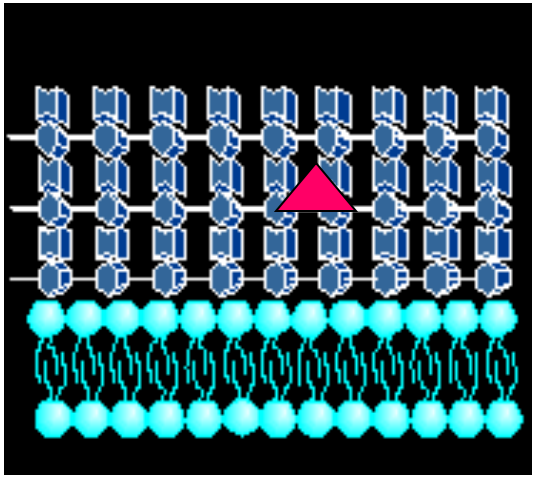


canais de porina

lipopolissacarídeos e lipídeos

peptideoglicana

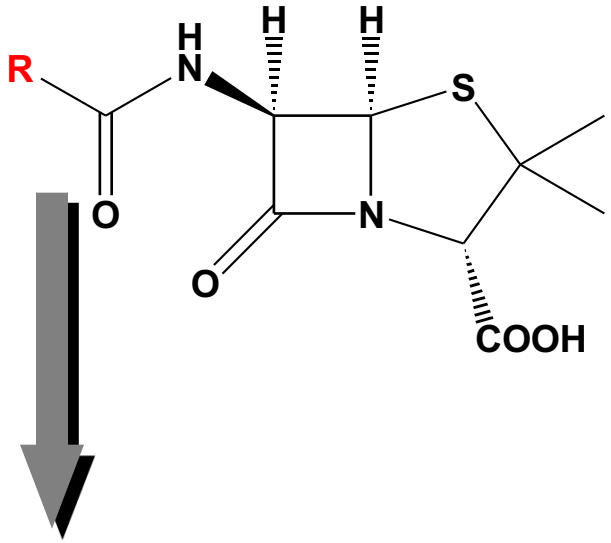
bicamada lipídica



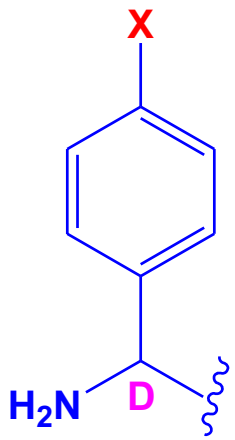
gram positivo

interior da célula

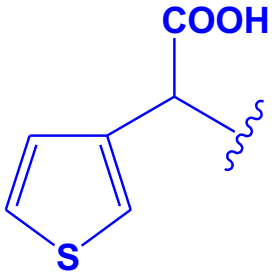
Enzima alvo



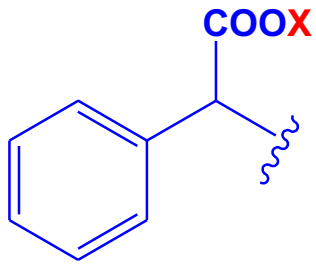
Grupos hidrofílicos

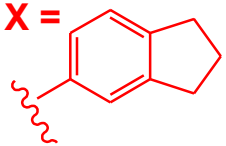


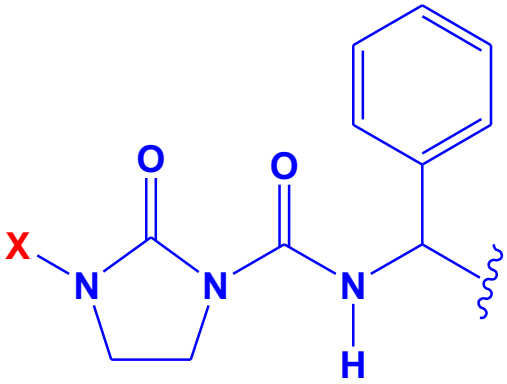
X = H Ampicilina
X = OH Amoxicilina



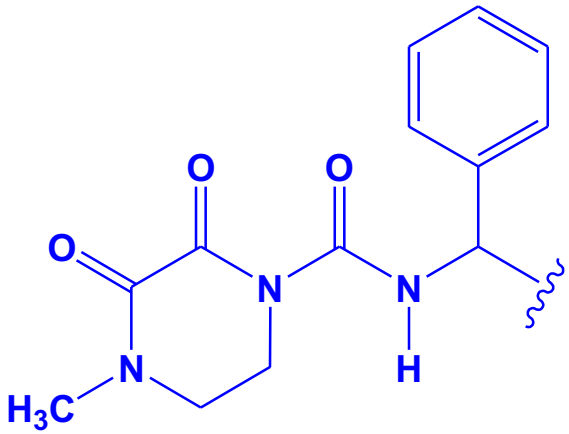
Ticarcilina



X = H Carbenicilina
X =  Carindacilina

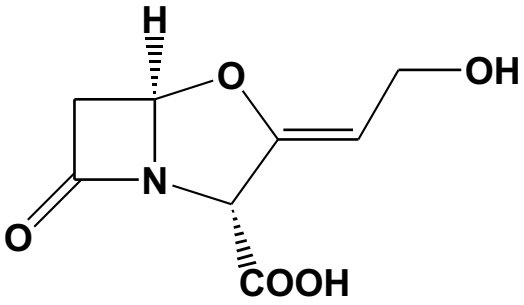


X = H Azlocilina
X = CH_3SO_3 Mezlocilina



Piperacilina

Inibidores de β-lactamases



ácido clavulânico

Streptomyces clavuligerus

Clavulin® - amoxicilina + ácido clavulânico

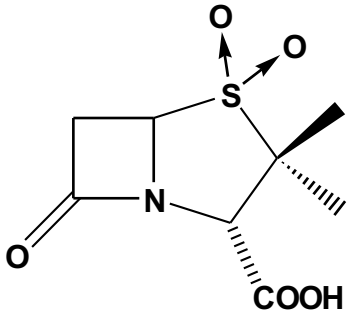
Fraca ação antibiótica

Alta afinidade por β-lactamases

Inibição irreversível

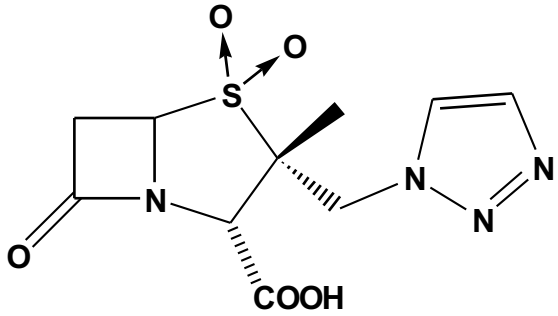
Combinações com penicilinas de amplo espectro

sintéticos



sulbactama

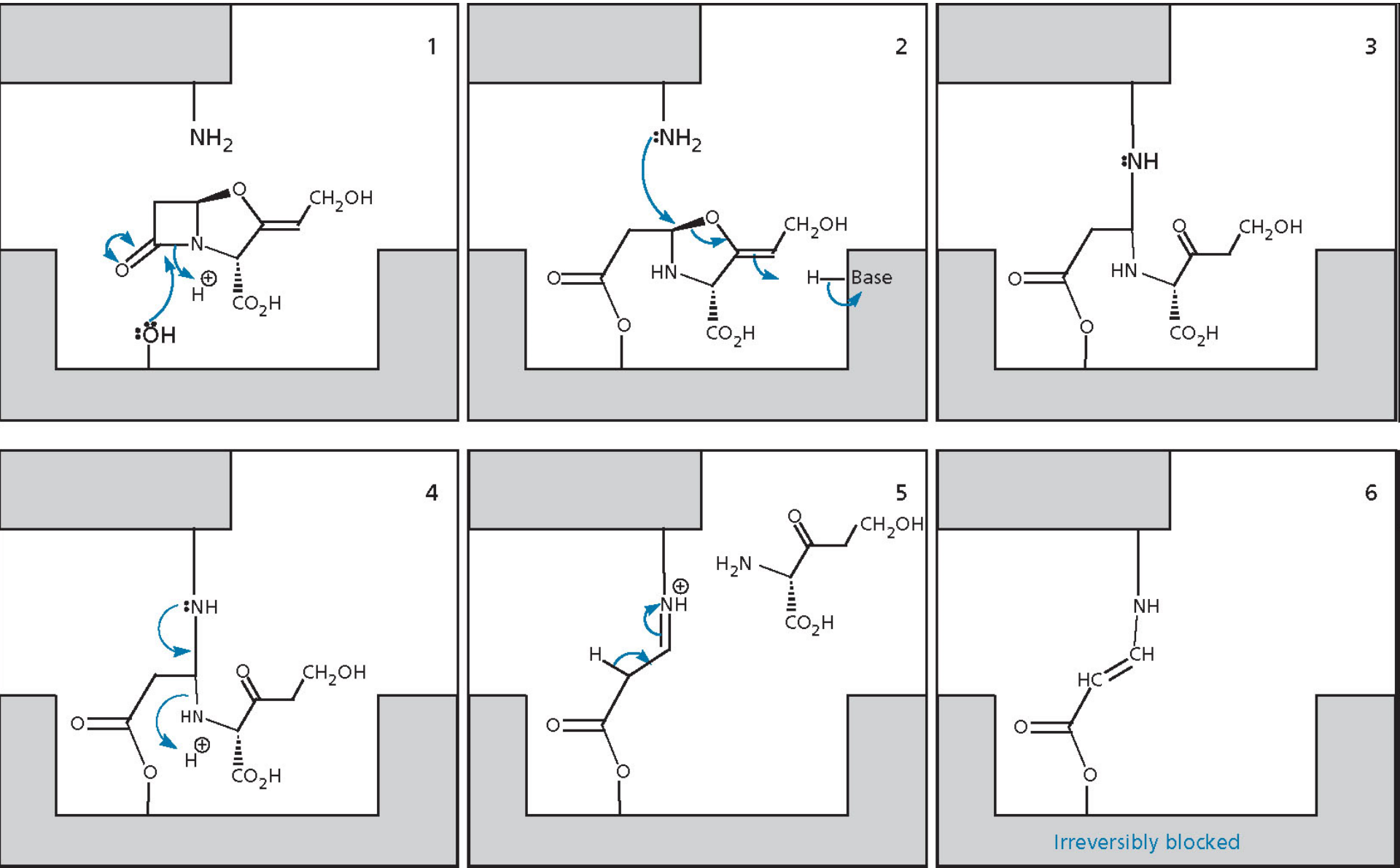
Unasyn® - ampicilina + sulbactama



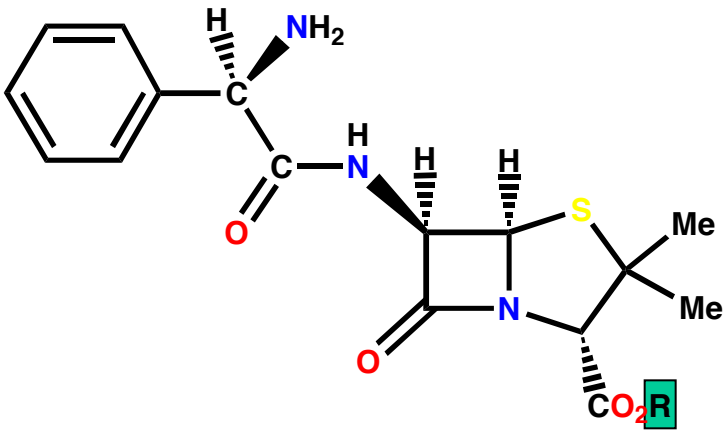
tazobactama

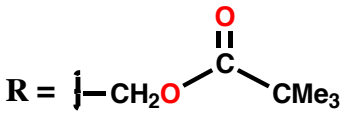
Zosyn® / tazocin ® - ampicilina + tazobactama

Mecanismo de inibição da β-lactamase por ácido clavulânico

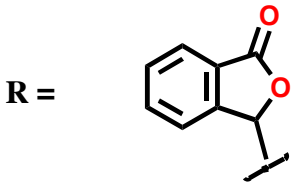


Pró-fármacos da ampicilina

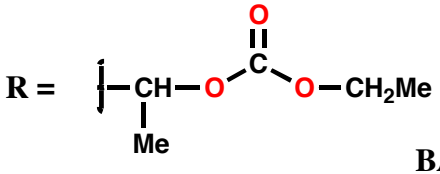




PIVAMPICILLIN



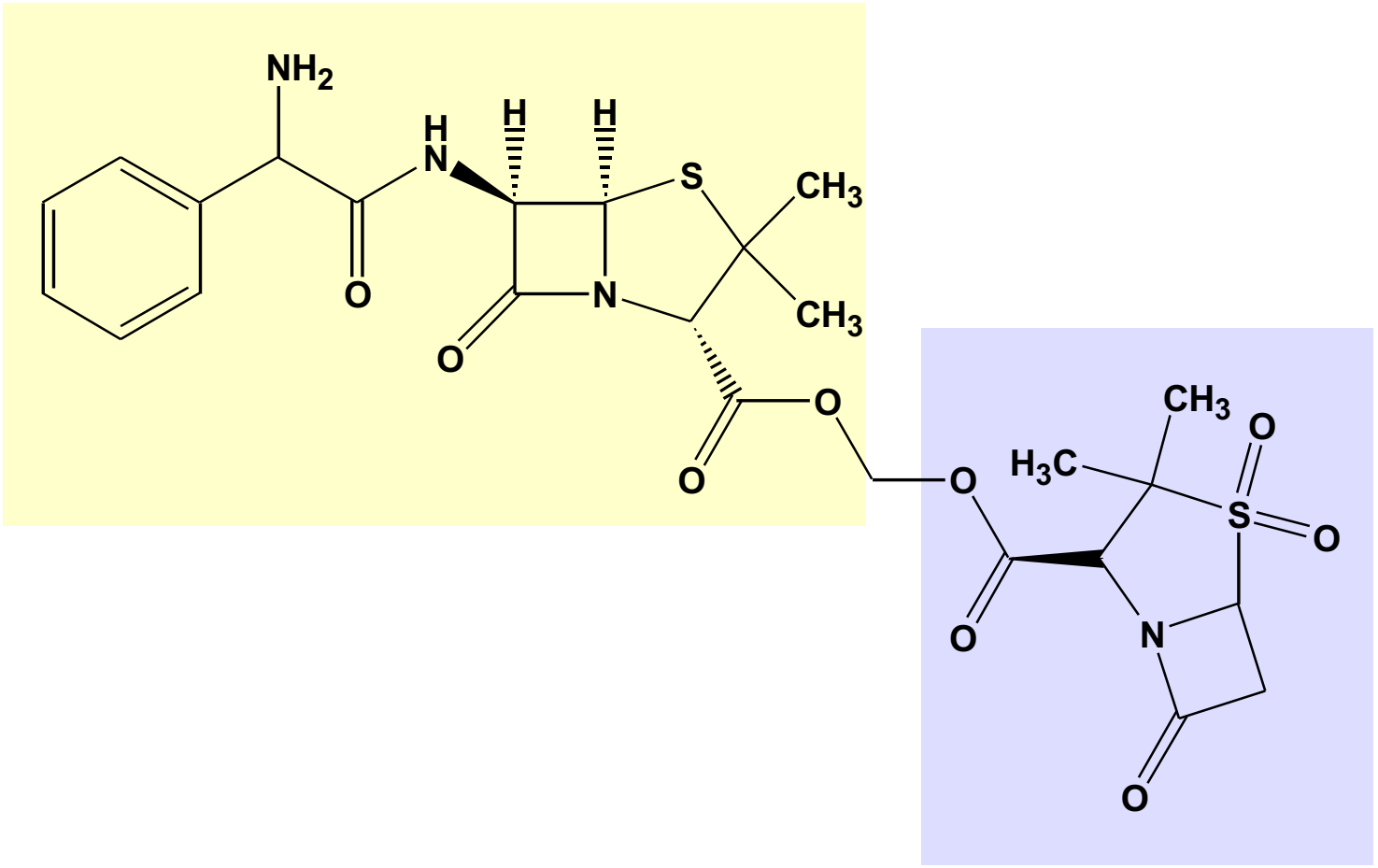
TALAMPICILLIN



BACAMPICILLIN

- Aumentam permeabilidade pelas membranas celulares
- Grupo ácido carboxílico polar é mascarado pelo éster
- Éster é metabolizado pelas esterases fornecendo o fármaco

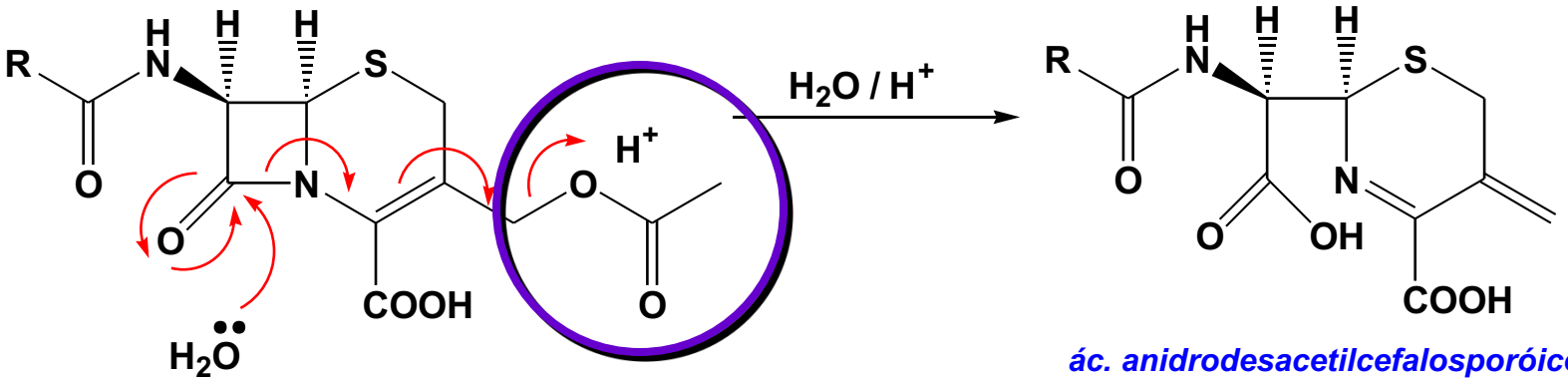
Pró-fármaco recíproco da ampicilina



Inibidor de β-lactamase

CEFALOSPORINAS

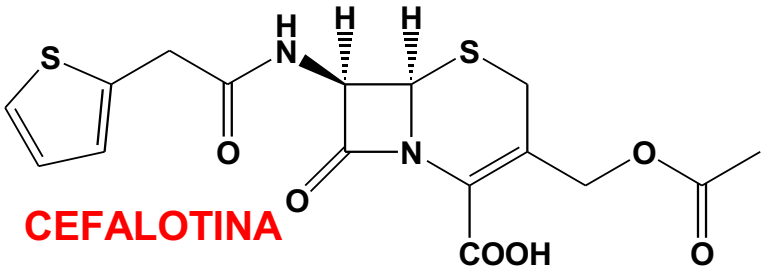
instabilidade em meio ácido X mecanismo de ação



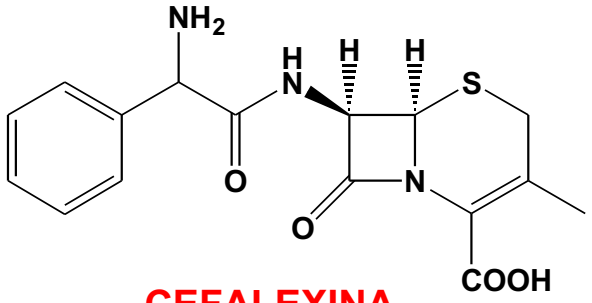
ác. anidrodesacetilcefalosporóico

Caráter abandonador do grupo em C-3

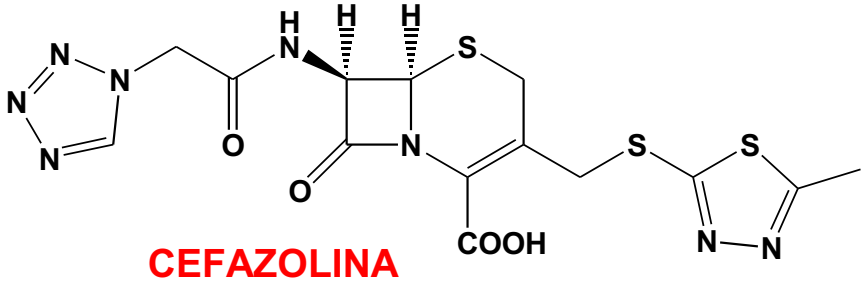
Cefalosporinas de 1ª geração



CEFALOTINA



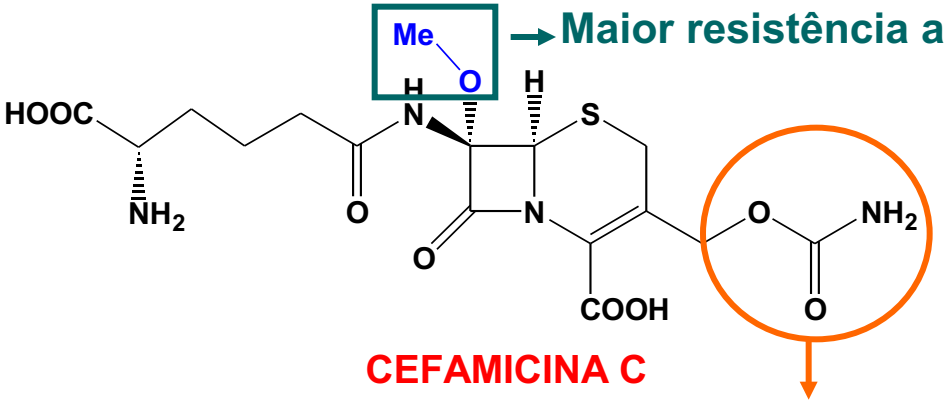
CEFALEXINA



CEFAZOLINA

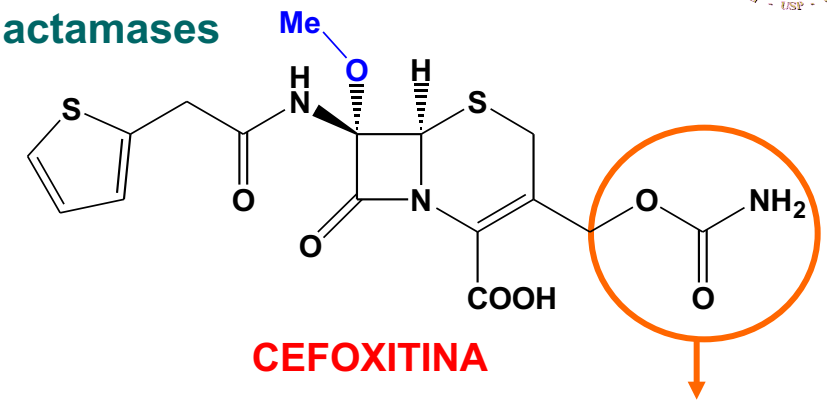
- em geral menos ativas que penicilinas
- mais ativas em Gram +
- resistência bacteriana (β-lactamases)

Cefalosporinas de 2ª geração



CEFAMICINA C

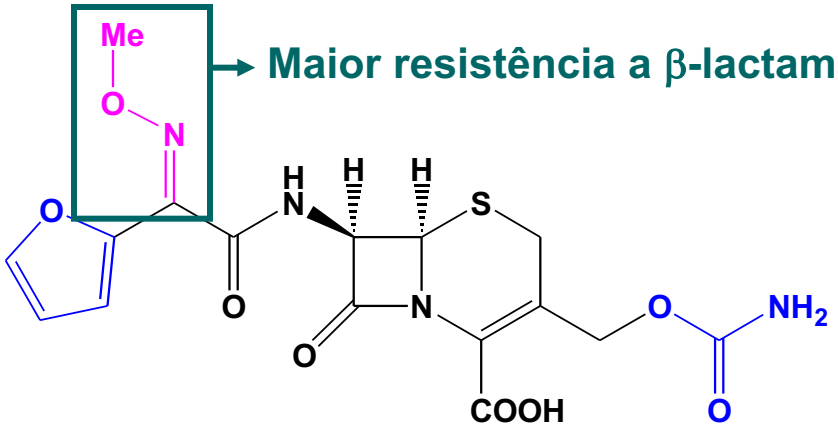
Maior estabilidade frente a esterases



CEFOXITINA

Maior estabilidade frente a esterases

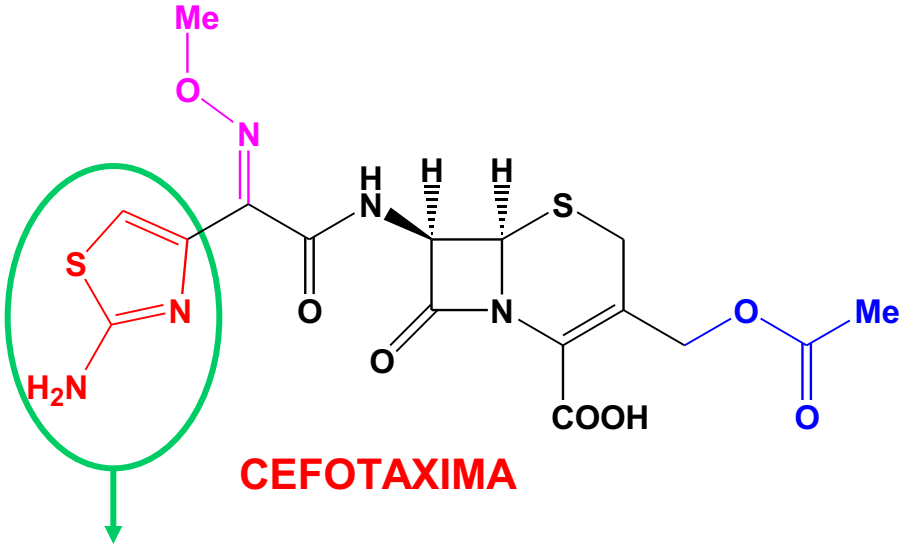
oximinocefalosporinas



CEFUROXIMA

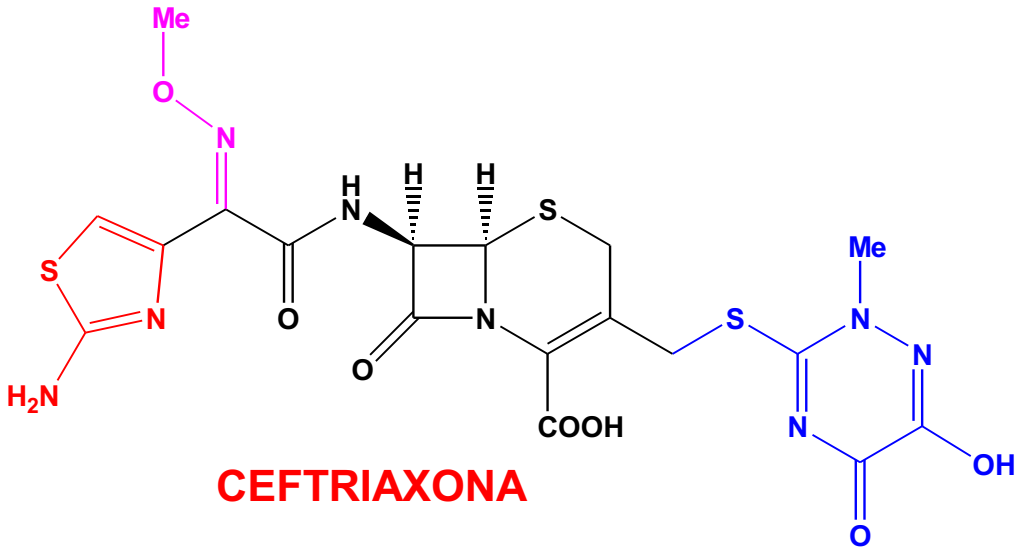
- em geral aumenta a atividade frente a Gram -
- maior resistência a β-lactamases (-OMe e oximino)

Cefalosporinas de 3ª geração

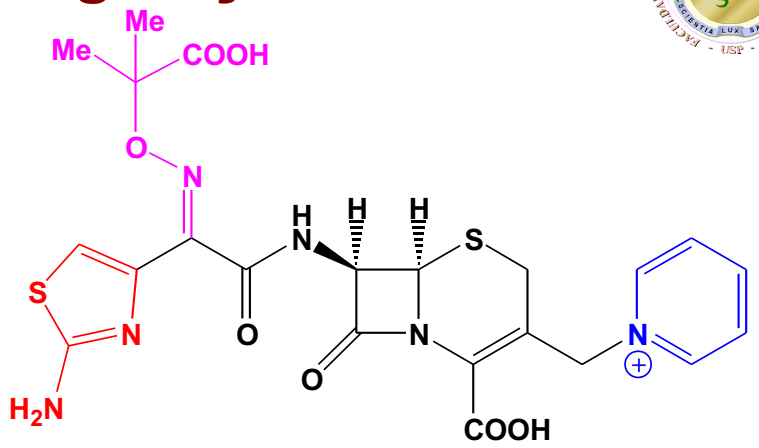


CEFOTAXIMA

Anel aminotiazol aumenta a penetração na membrana externa das bactérias Gram -

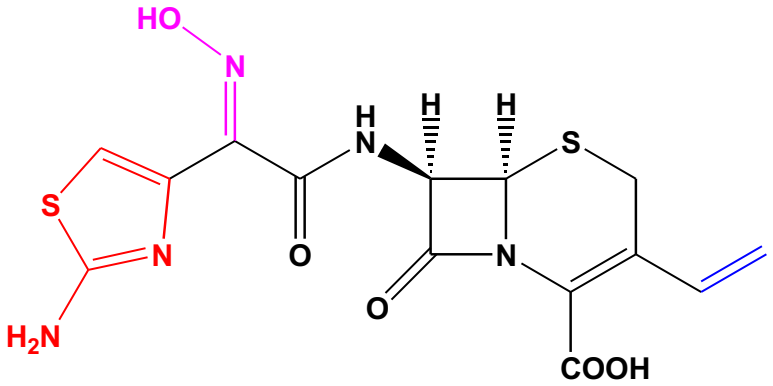


CEFTRIAXONA



CEFTAZIDIMA

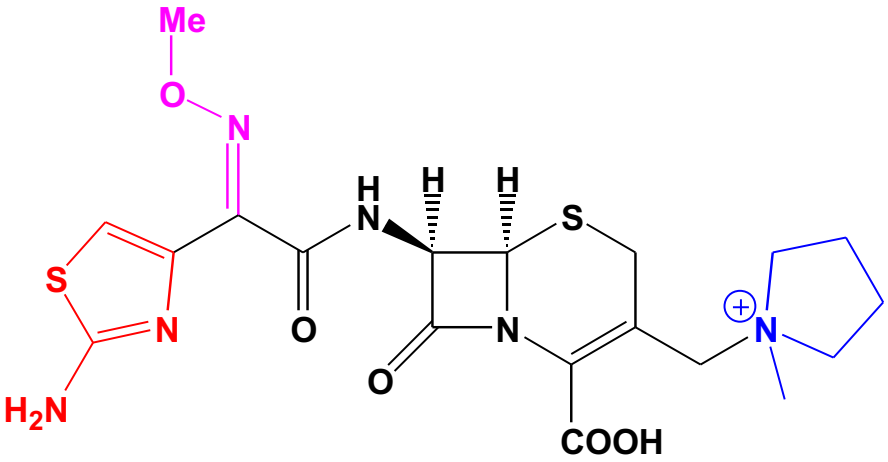
Não usual devido a excelente atividade em Gram – (4ª geração???)



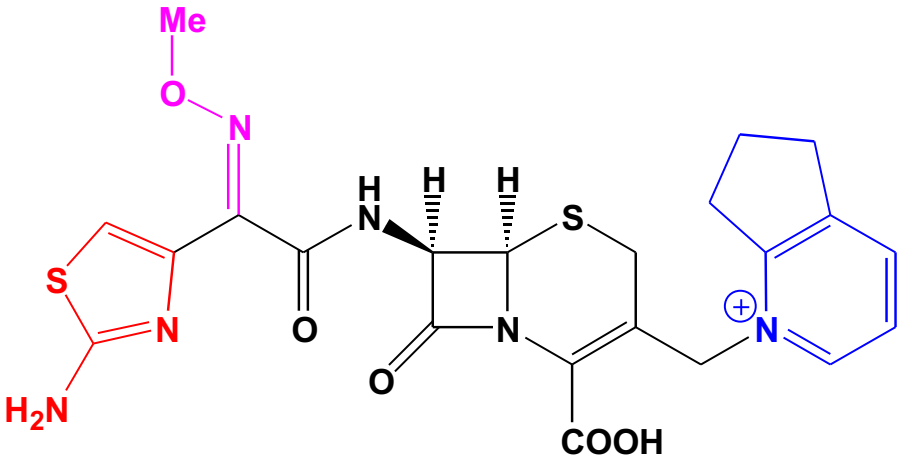
CEFDINIR

Cefalosporinas de 4ª geração

ZWITTERIONS



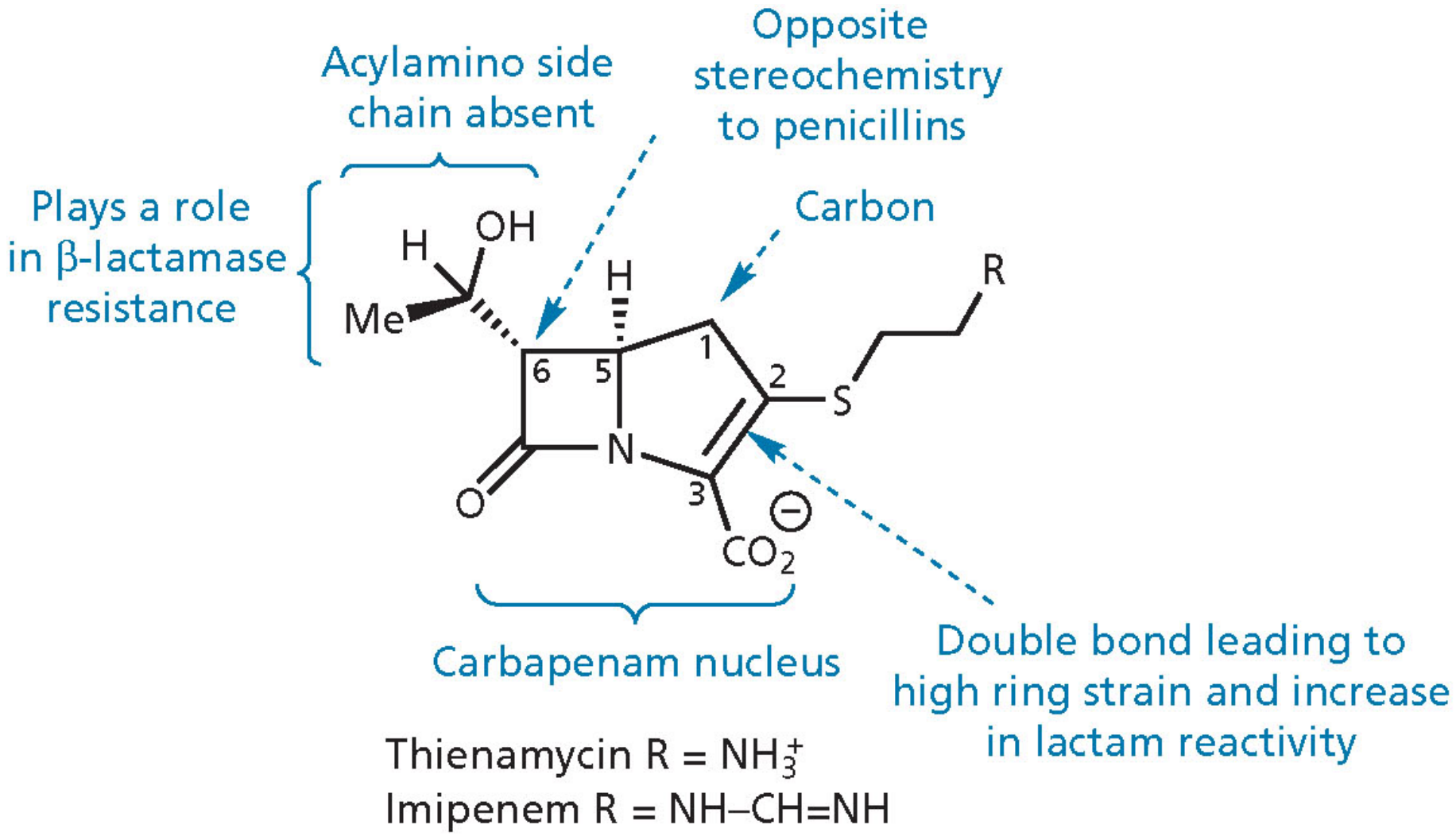
CEFEPIMA



CEFPIROMA

- maior atividade em Gram –
- alta afinidade por transpeptidases
- baixa afinidade por β-lactamases

CARBAPENEMS (carbapeninas)

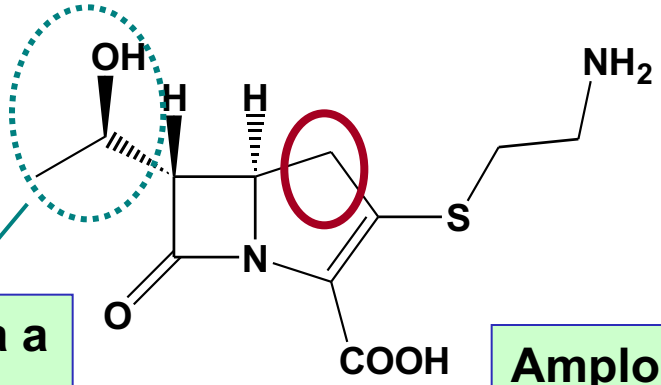


Thienamycin R = NH_3^+

Imipenem R = NH–CH=NH

CARBAPENEMS (carbapeninas)

Protótipo natural



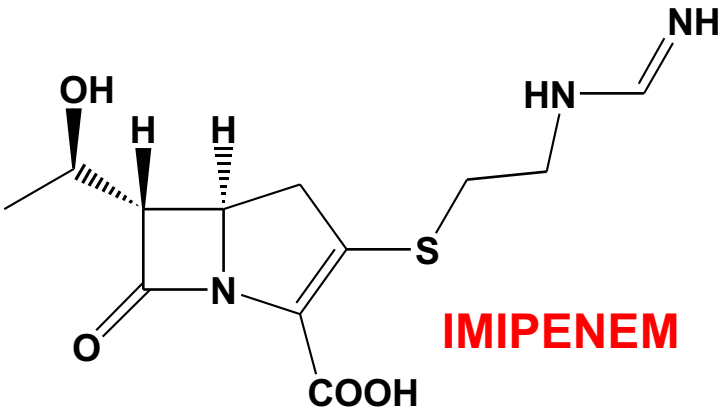
Alta resistência a β-lactamases

TIENAMICINA

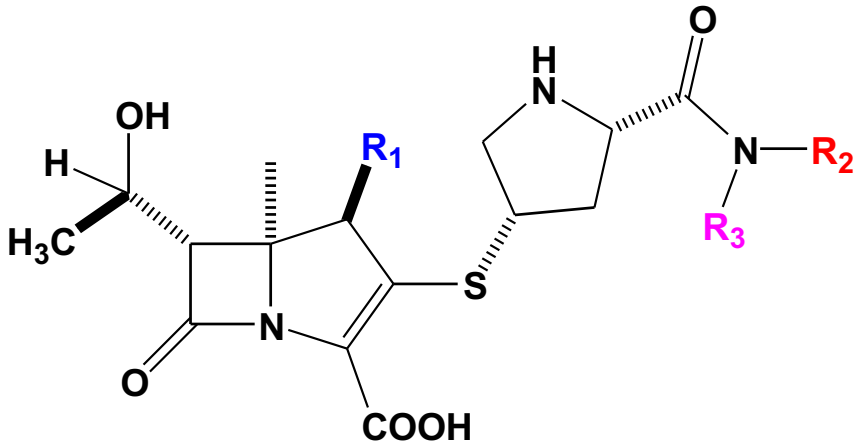
Amplo espectro contra gram + e -

✓ **Fraca estabilidade química e metabólica; baixa absorção no TGI**

Análogos sintéticos

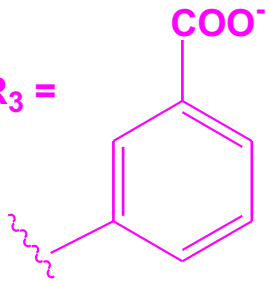


IMIPENEM

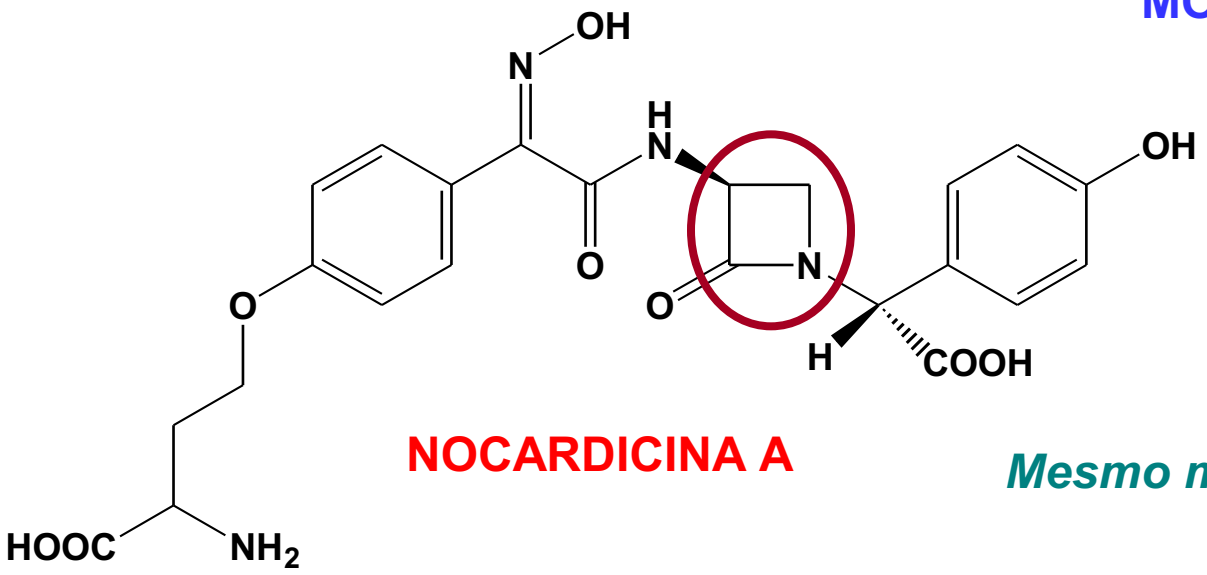


meropenem R_1 = H, R_2 = R_3 = CH_3

ertapenem R_1 = CH_3, R_2 = H, R_3 =



MONOBACTAMAS



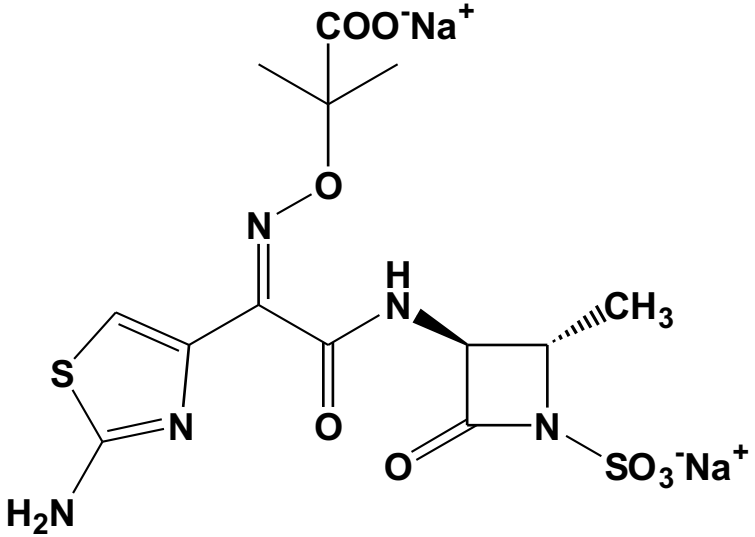
NOCARDICINA A

Mesmo mecanismo de ação?????

Protótipo natural

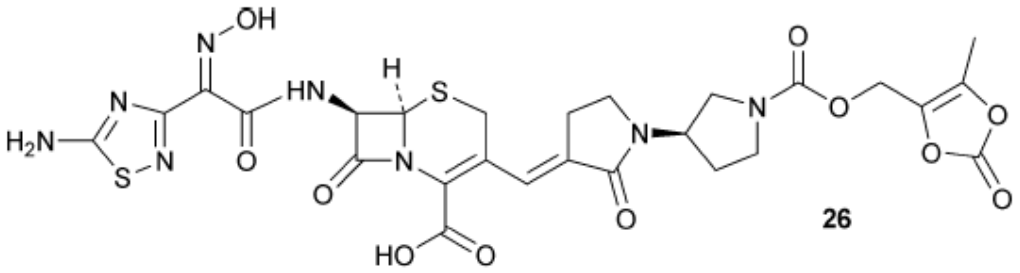
Análogo sintético

Atividade em gram negativos aeróbicos



AZTREONAM

Antibióticos β-lactâmicos derivados de PNs microbianos em triagens clínicas



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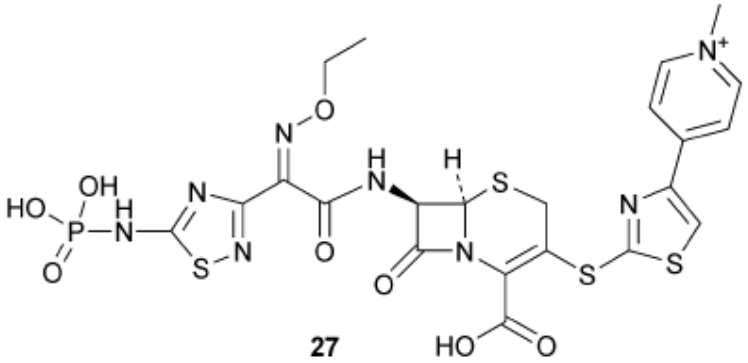

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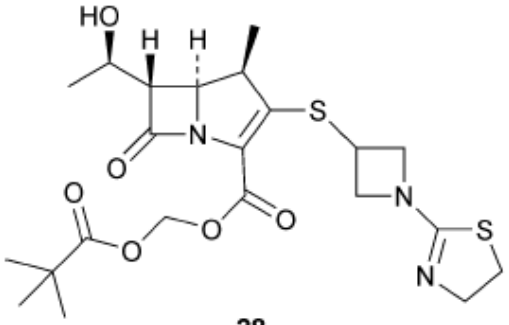

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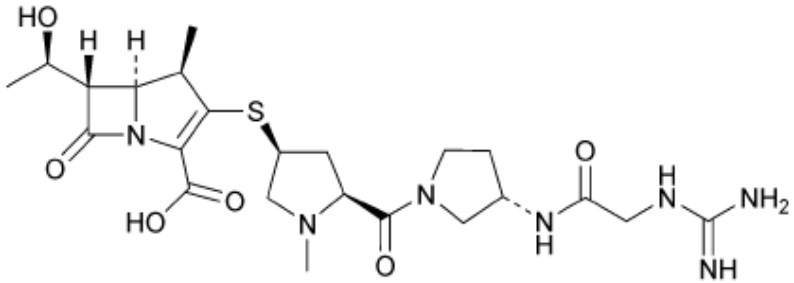

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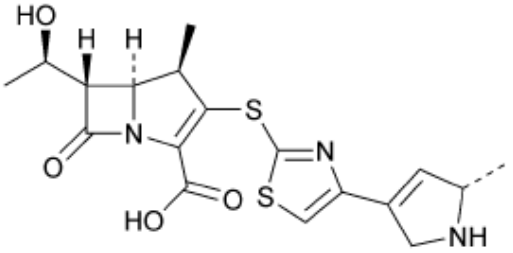

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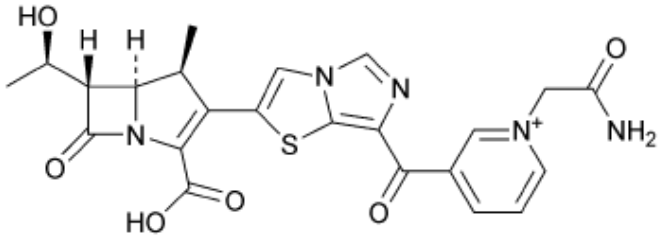

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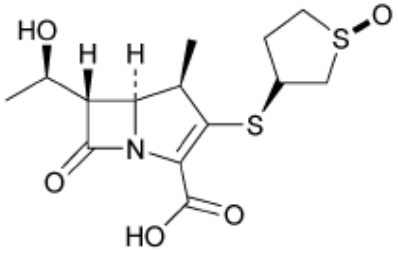

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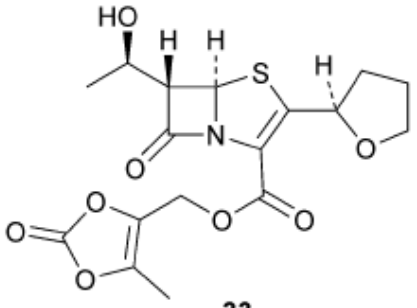

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