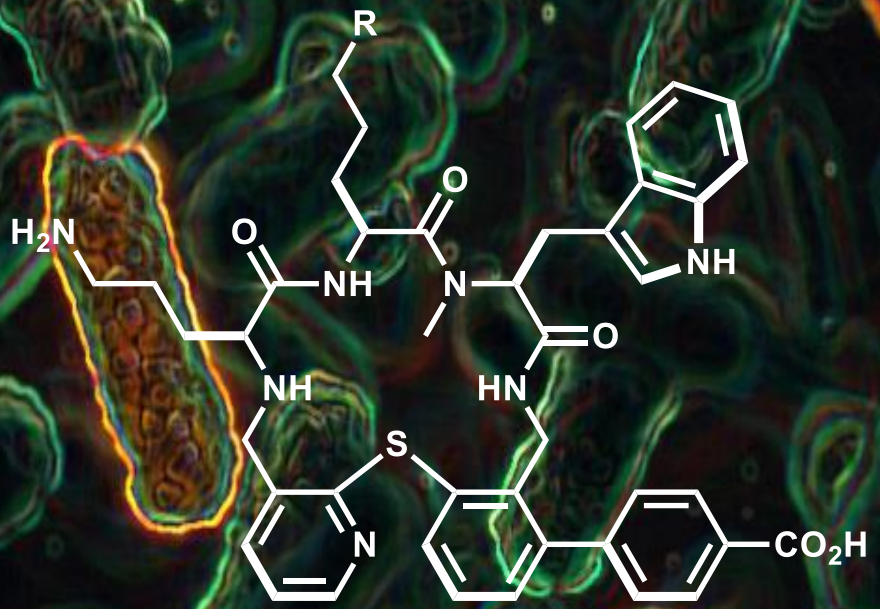
A Novel Antibiotic Class Targeting the Lipopolysaccharide Transporter

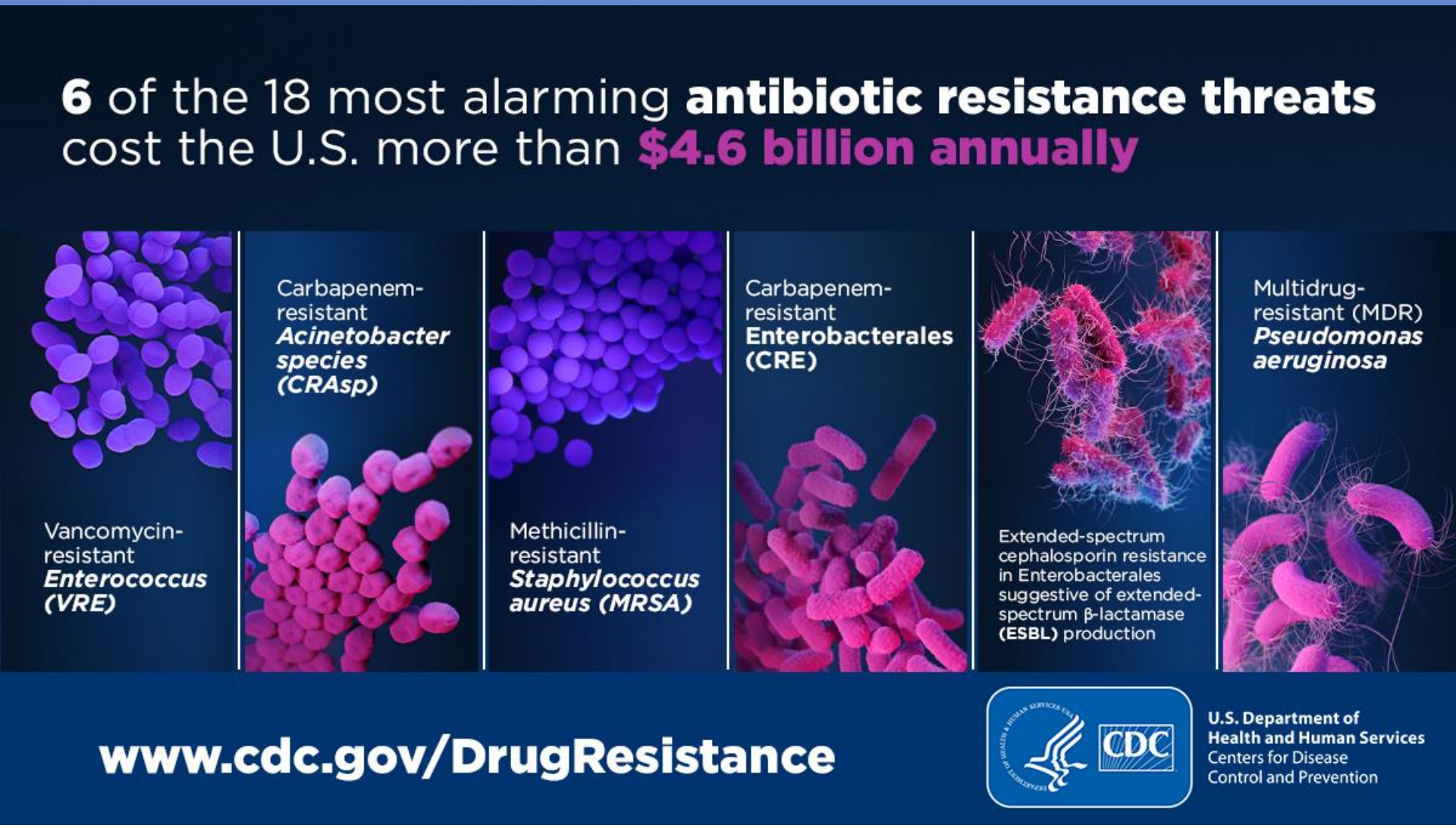


Zosurabalpin by Roche

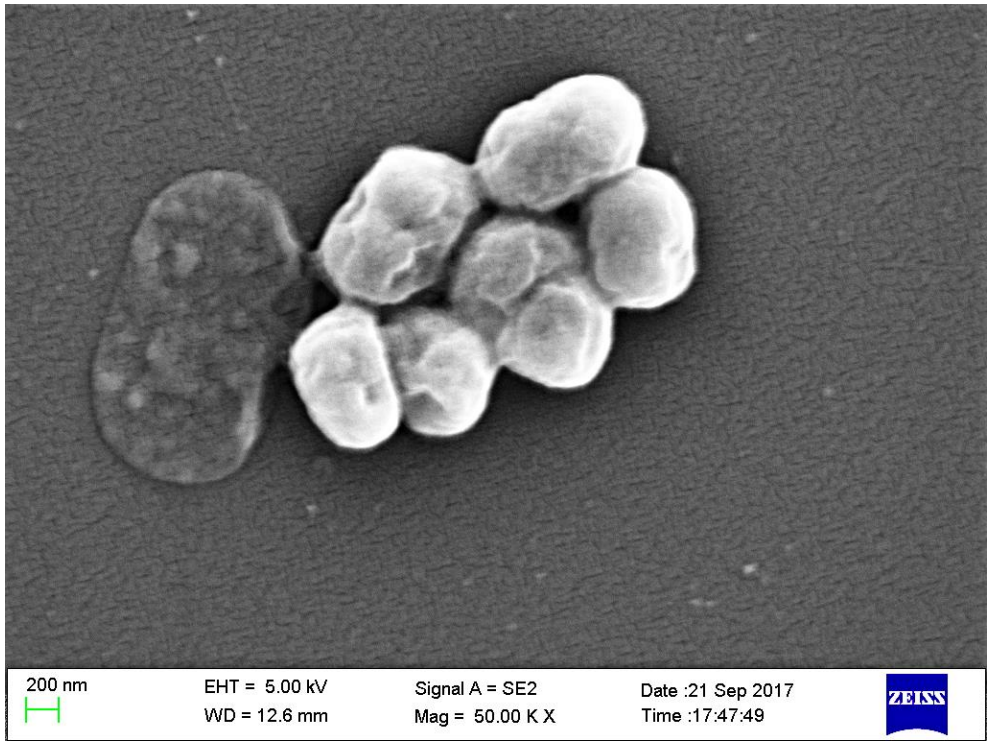
Zhang Ye

01/13/2024

doi.org/10.1038/s41586-023-06873-0



CDC Partners Estimate Healthcare Cost of Antibiotic-resistant Infections



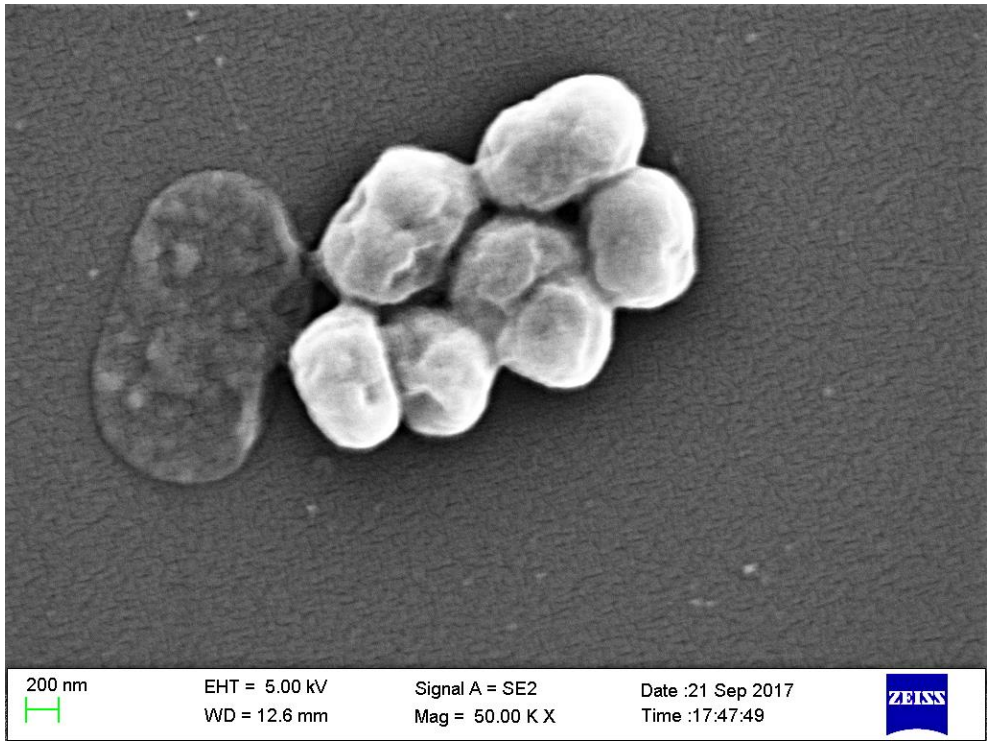
电子显微镜下的鲍氏不动杆菌
Acinetobacter baumannii

鲍氏不动杆菌
Acinetobacter baumannii
Domain: Becteria
Phylum: Pseudomonadota
Class: Gammaproteobecteria
Order: Pseudomonadales **假单胞菌目**
Family: Moraxellaceae **莫拉氏菌科**
Genus: Acinetobacter **不动杆菌属**
Species: ***A. baumannii***
Binomial name: *Acinetobacter baumannii.* Bouvet and Grimont 1986

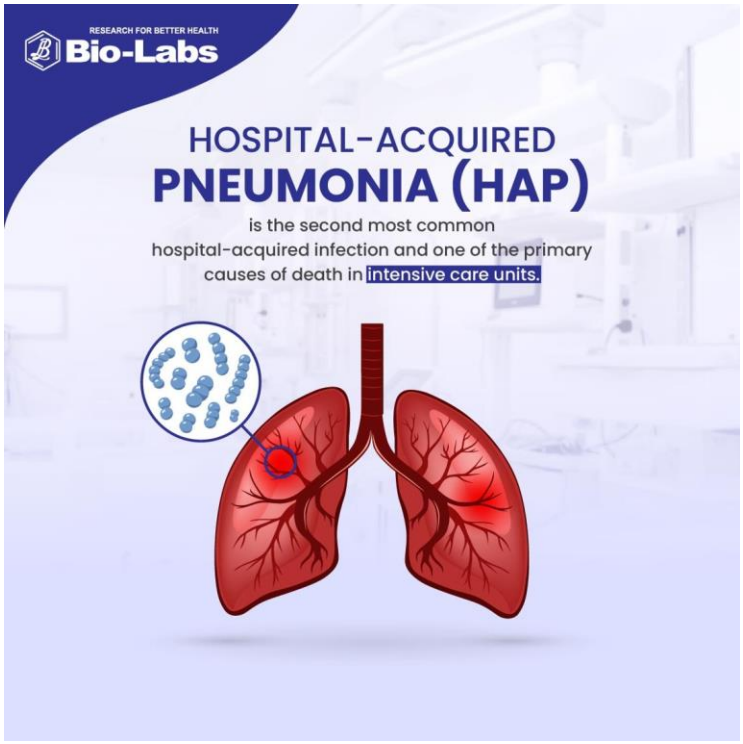
革兰氏阴性菌，需氧，**条件致病菌**，不具鞭毛，移动性不高，但生命力极强，广泛存在于大自然中。

机会性感染又名**伺机性感染**（opportunistic infection）是指由机会性病原体引发的感染。这些病原体寄生于免疫功能正常的健康宿主时不致病，但会在宿主出现免疫缺陷时入侵宿主。

https://en.wikipedia.org/wiki/Acinetobacter_baumannii

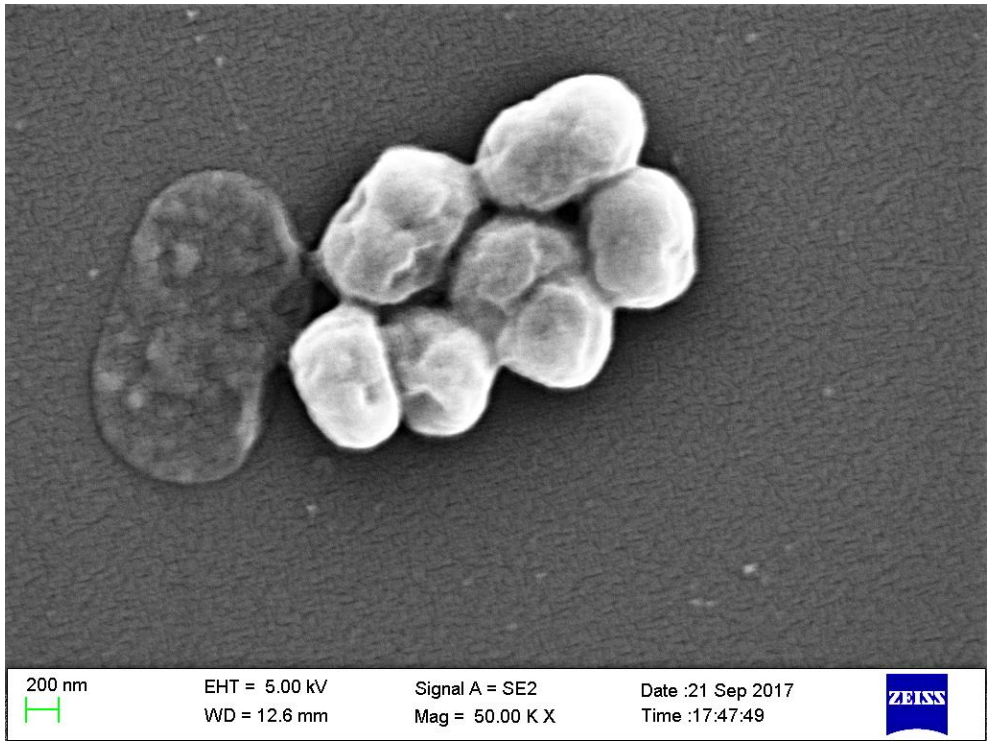


电子显微镜下的鲍氏不动杆菌
Acinetobacter baumannii



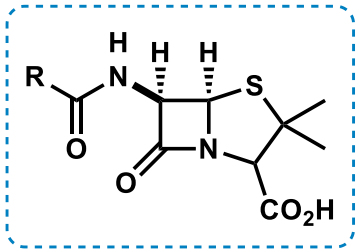
菌血症，肺炎，脑膜炎，腹膜炎，
心内膜炎，以及泌尿道和皮肤感染

鲍氏不动杆菌已经成为**医院感染**的主要来源，尤其是**重症监护室**。该病菌因为抗生素的滥用，导致鲍氏不动杆菌产生抗药性，变成“**多重抗药性**鲍氏不动杆菌”

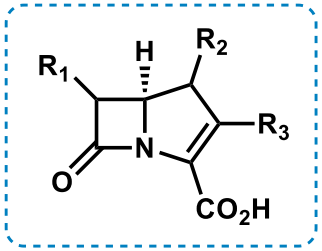


电子显微镜下的鲍氏不动杆菌

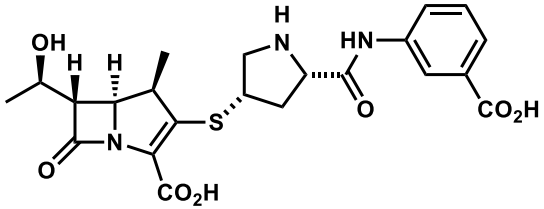
Carbapenem-resistant Enterobacteriaceae



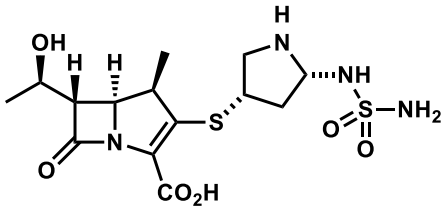
Penicillin



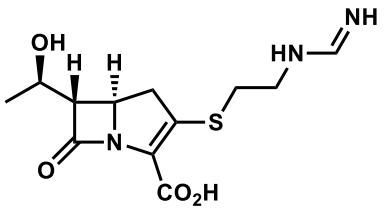
Carbapenem



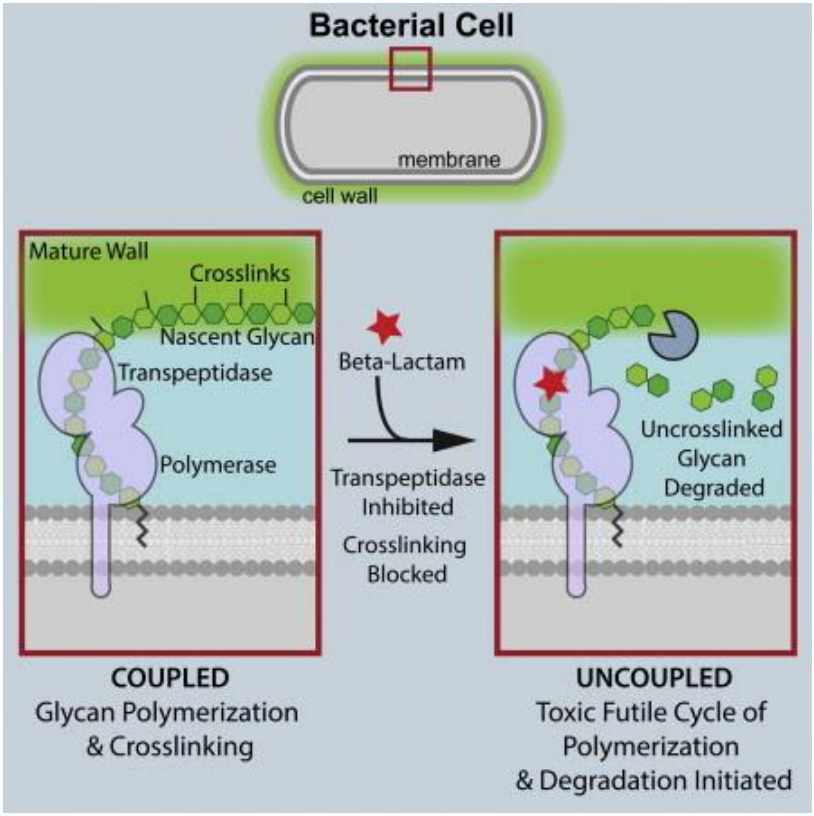
Ertapenem, Invanz, Merck



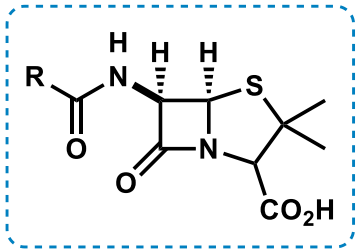
Doripenem, FInibax, Shionogi Co.



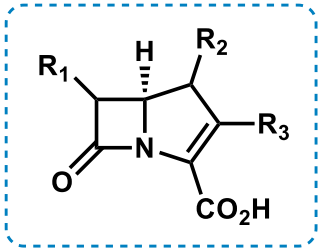
Imipenem, Primaxin, Merck



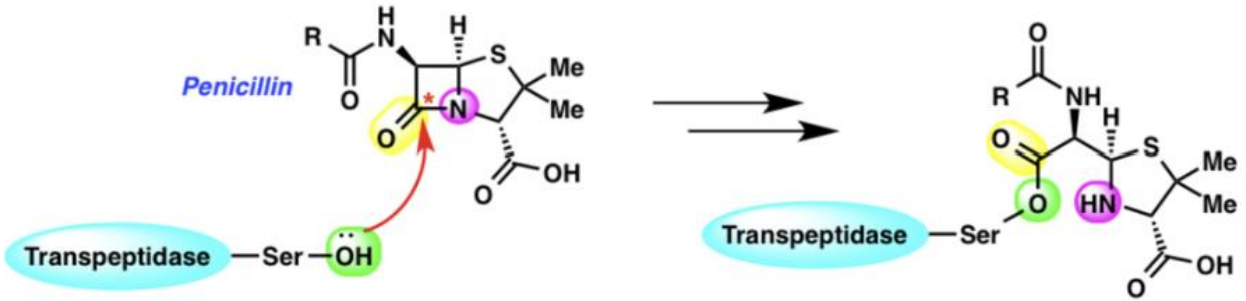
Carbapenem-resistant Enterobacteriaceae

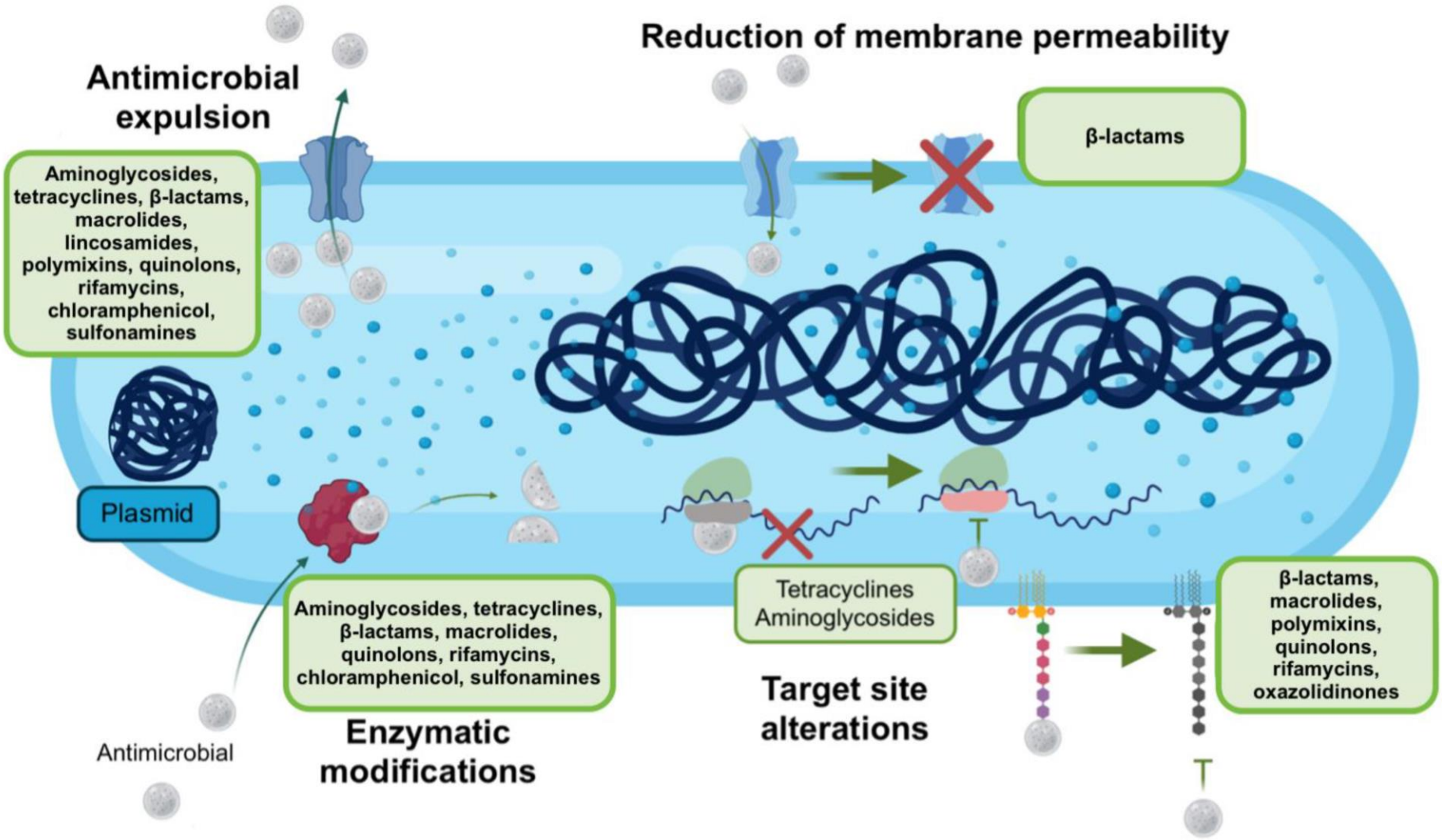


Penicillin

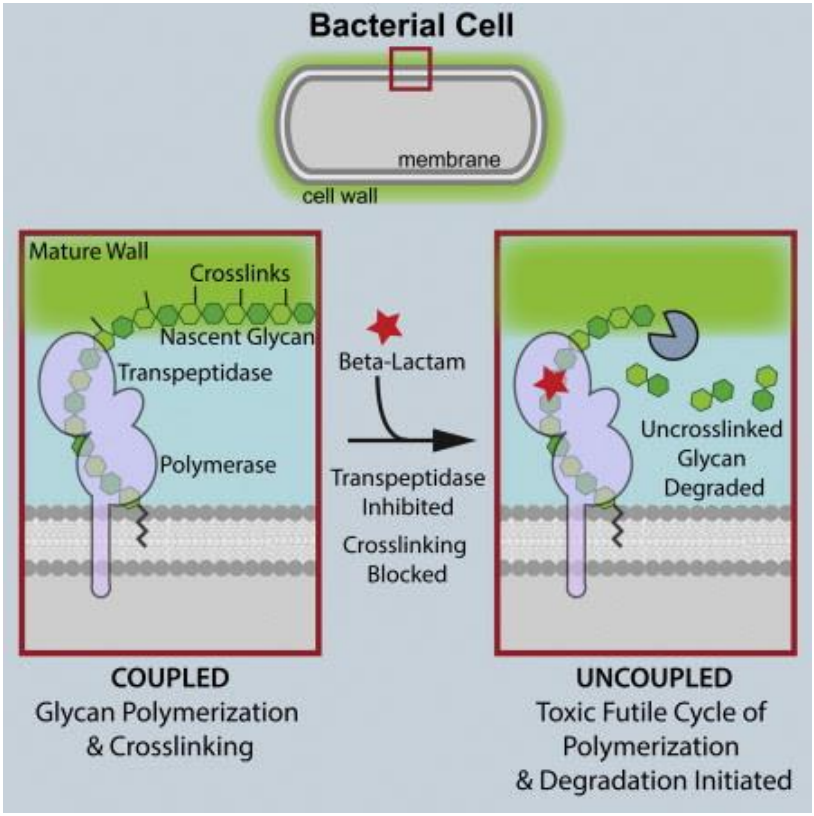


Carbapenem





Int. J. Mol. Sci. 2022, 23, 6582



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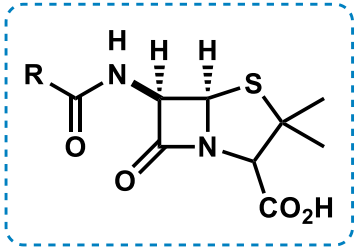
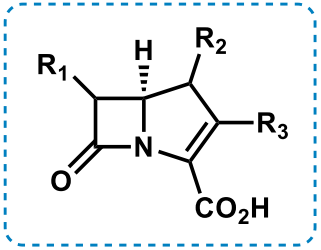
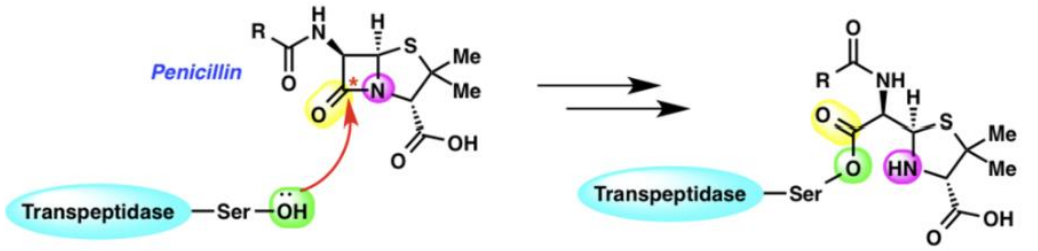
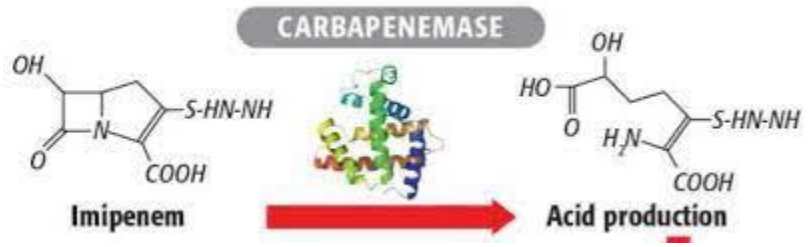


Penicillin



Carbapenem





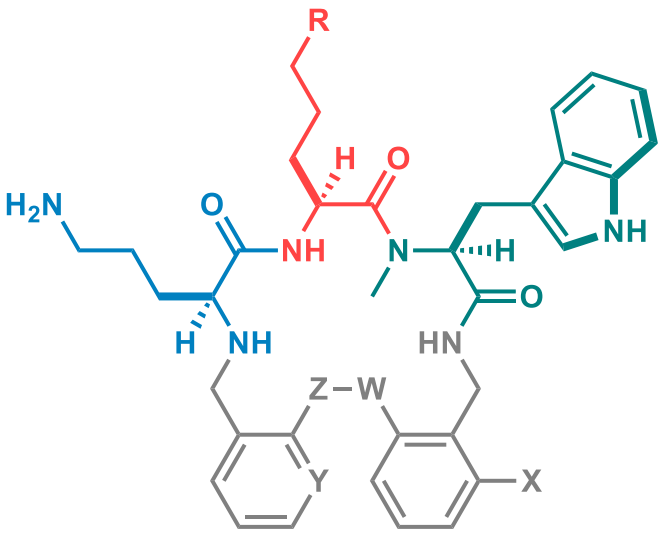
Carbapenem-resistant Acinetobacter can carry mobile genetic elements that are easily shared between bacteria. Some can make a **carbapenemase enzyme**, which makes carbapenem antibiotics ineffective and rapidly spreads resistance that destroys these important drugs.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

www.cdc.gov/drugresistance/pdf/threats-report/acinetobacter

Michael Lobritz is the Head of Infectious Diseases Early Development at F. Hoffmann-La **Roche**, Ltd, based in Basel, Switzerland. His group is responsible for the **translational development of Roche antibiotics and antivirals from Phase 0 through Phase 2**, including the demonstration of proof-of-mechanism and proof-of concept. Prior to joining Roche in 2017, Michael was attending physician in medicine and infectious diseases at Massachusetts General Hospital and Instructor in Medicine at Harvard Medical School, both in Boston, USA.

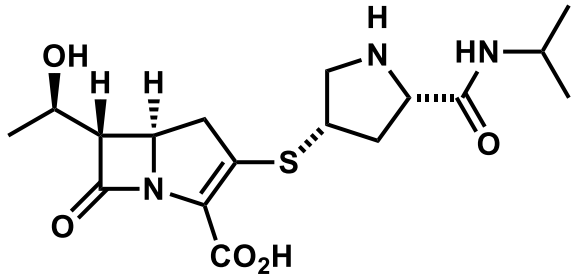
Michael previously completed postdoctoral research simultaneously at the **Broad Institute of MIT** and **Harvard** and at the **Wyss Institute** of Biologically Inspired Engineering at Harvard University, **infectious diseases clinical training at Massachusetts General Hospital**, **clinical medicine training at Stanford University Hospital**, **MD and PhD** (microbiology) degrees at **Case Western Reserve University**, and undergraduate degree (biochemistry) at the **University of Notre Dame**.



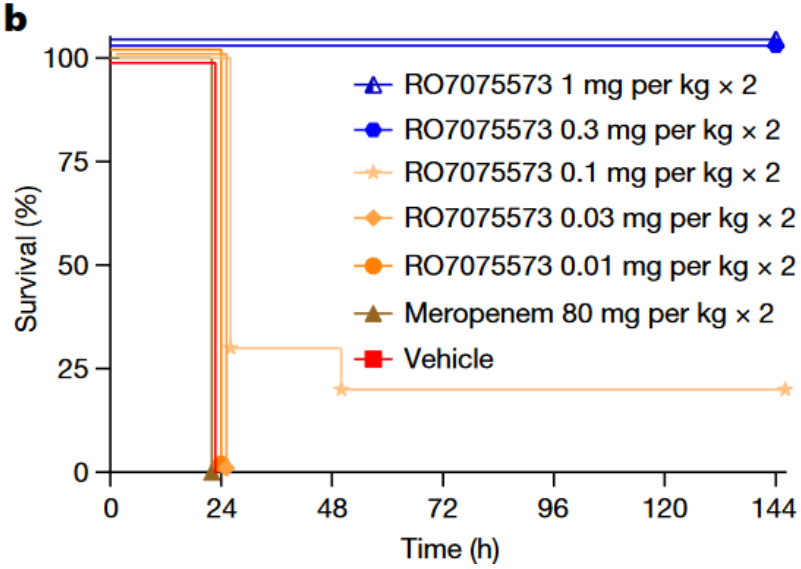
Tripeptide

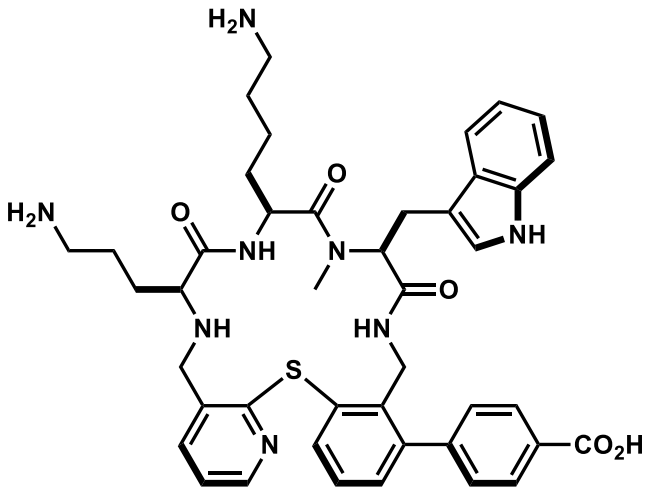
Tether

Compound ID	R	W	X	Y	Z
RO7036668	NH_2	–	H	CH	S
RO7075573	CH_2NH_2	–	Cl	N	S
RO7055137	NH_2	CH_2	H	CH	O

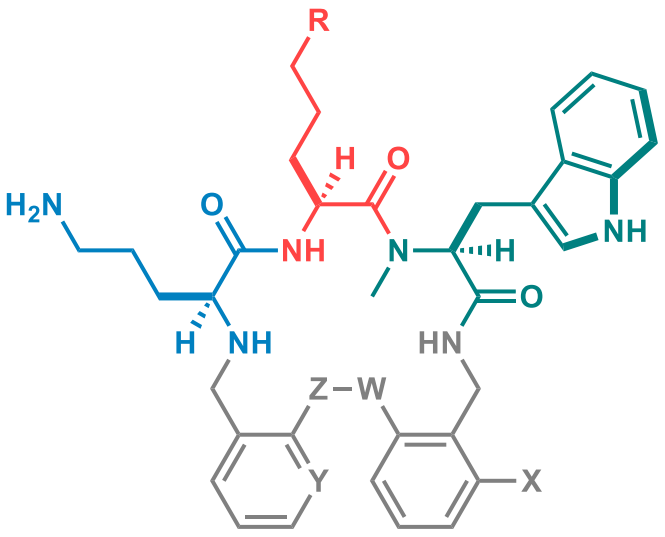


Meropenem





zosurabalpin (ZAB)



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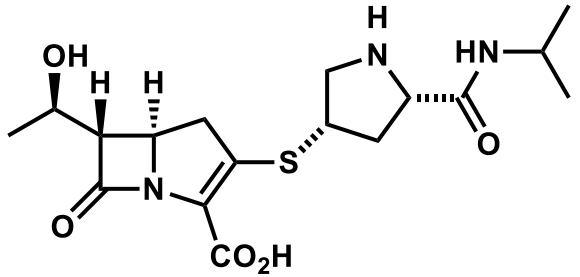
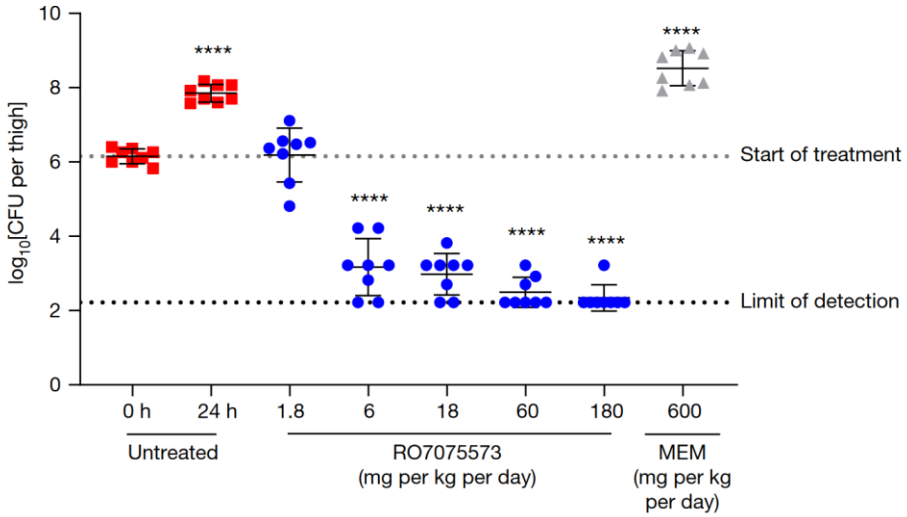
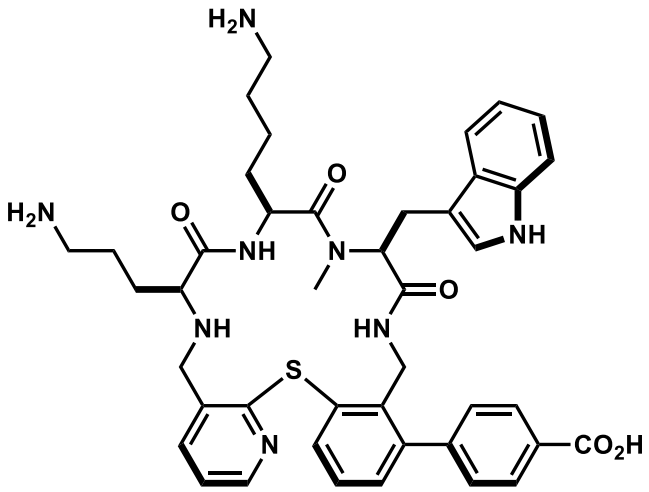
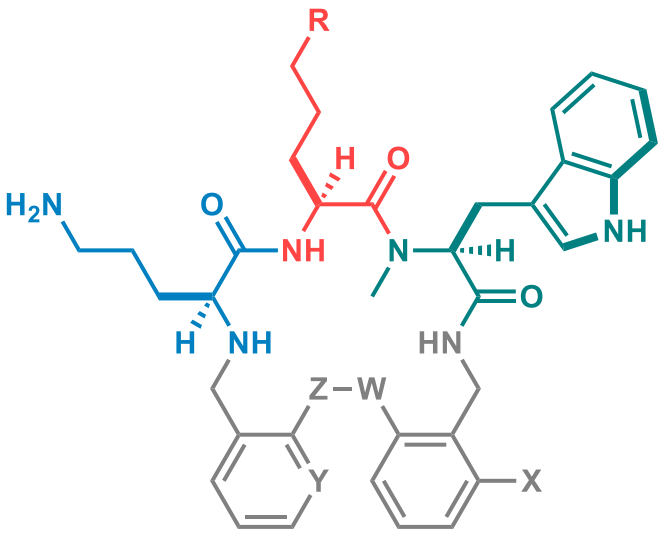


Meropenem





zosurabalpin (ZAB)



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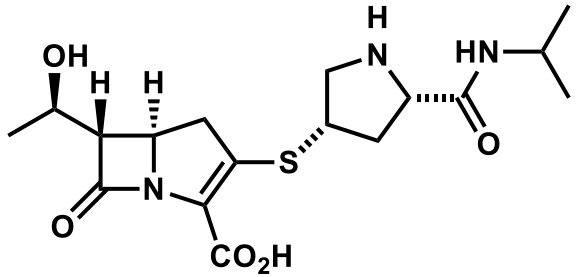
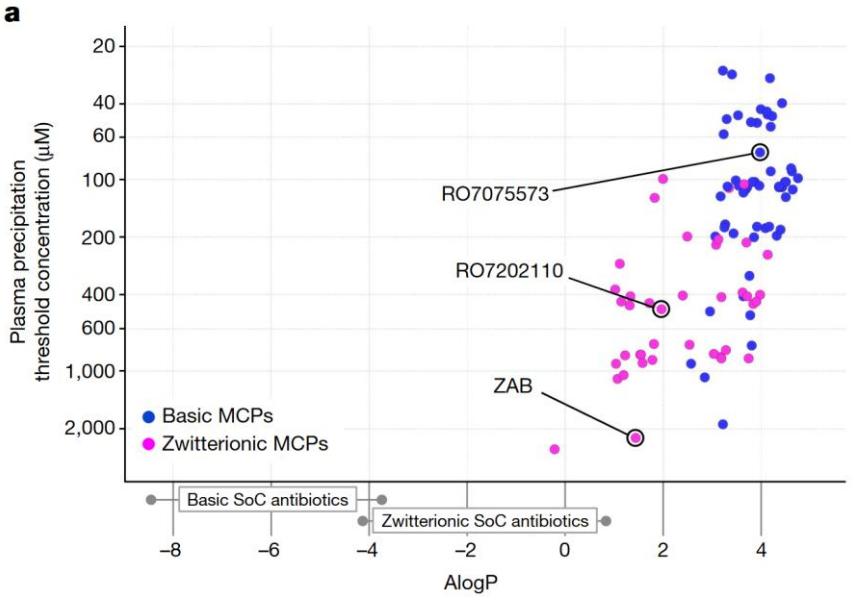
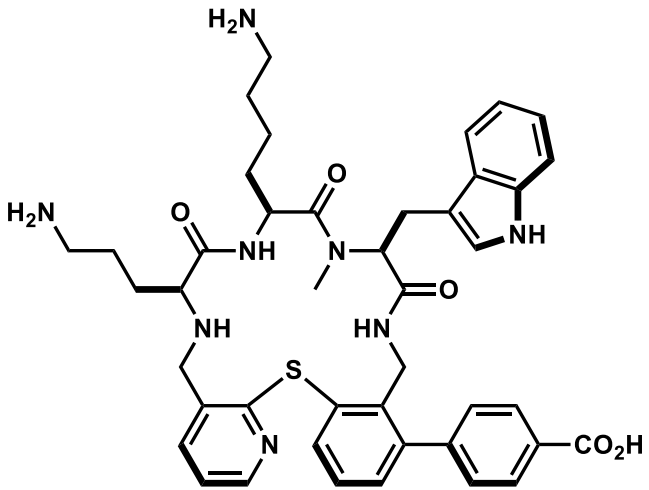
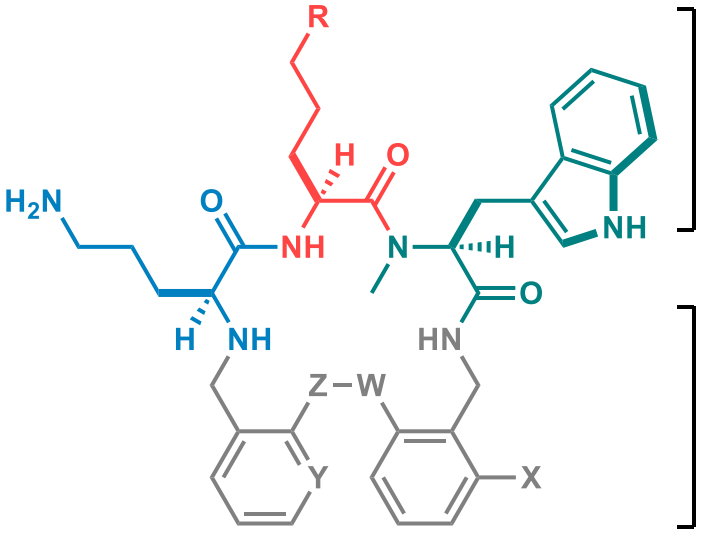


Meropenem



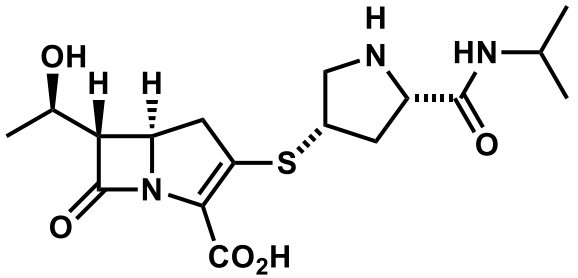


zosurabalpin (ZAB)

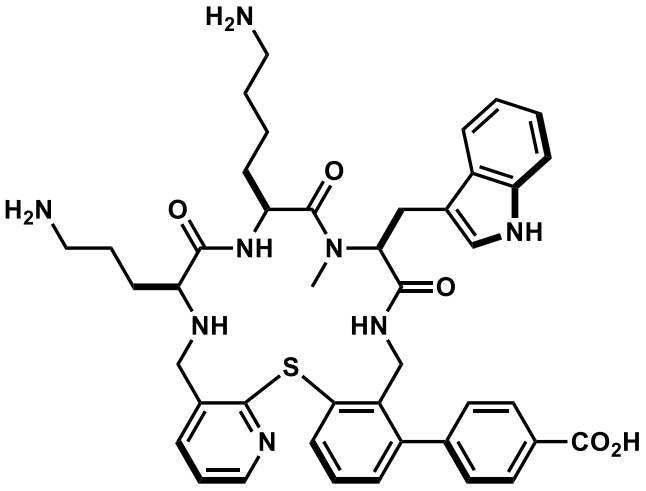


Tripeptide

Tether

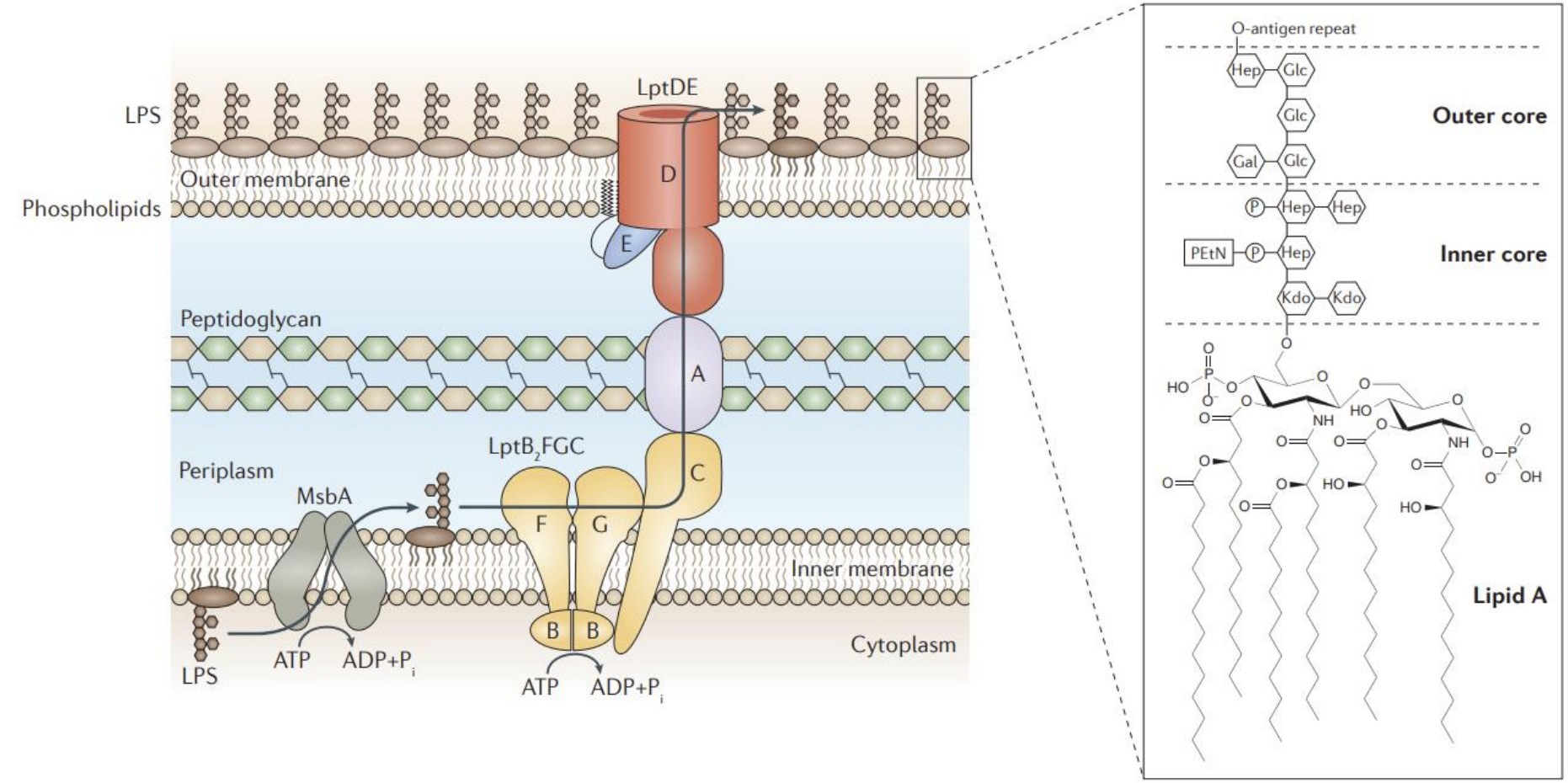


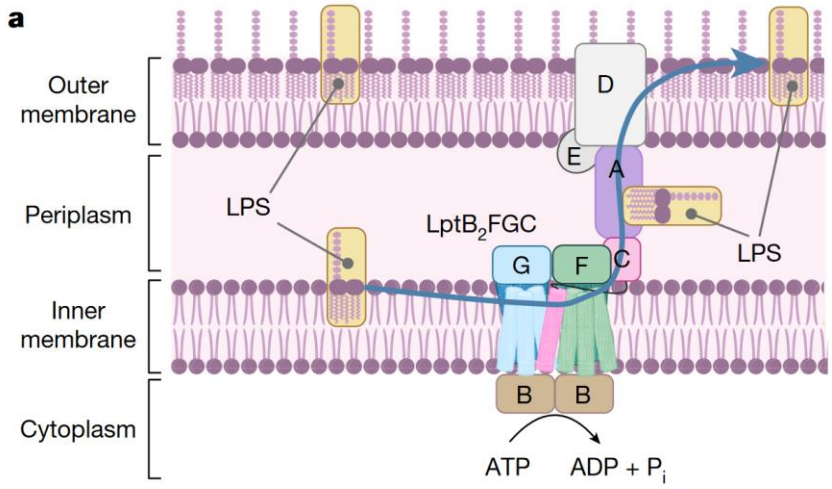
Meropenem, 美罗培南, 住友制药

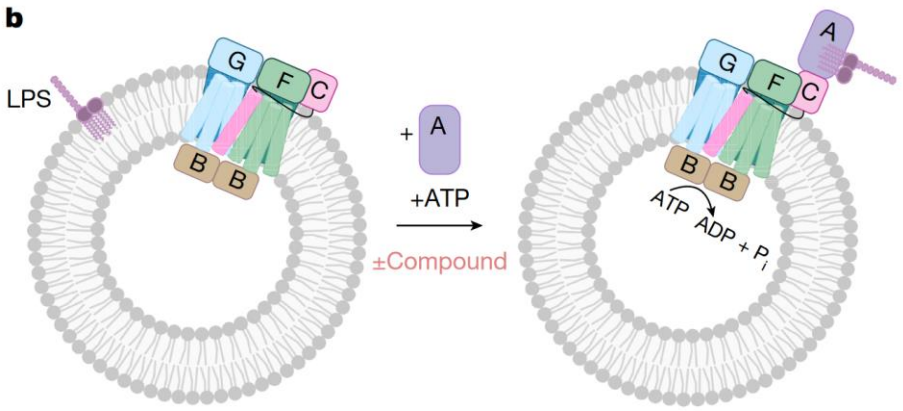


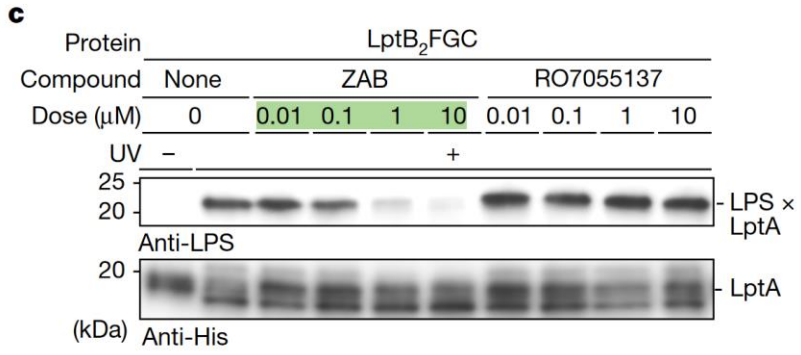
zosurabalpin (ZAB)

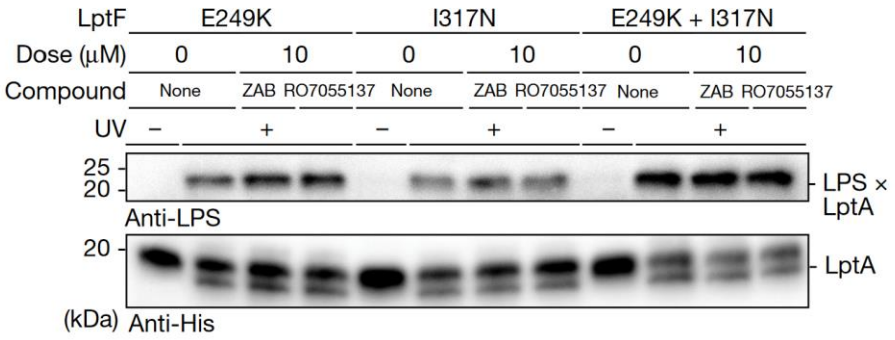
Microorganism	MIC (mg l^{-1})				
	RO7036668	RO7075573	RO7202110	ZAB	MEM
E. coli ATCC 25922	>64	>64	>64	>64	≤0.06
K. pneumoniae ATCC 700603	>64	>64	>64	>64	≤0.06
P. aeruginosa ATCC 27853	>64	>64	>64	>64	0.5
S. aureus ATCC 29213	32	>64	>64	>64	0.12
C. albicans ATCC 90028	64	>64	>64	>64	>64
A. baumannii ATCC 17978	NA	≤0.06	≤0.06	≤0.06	0.5
A. baumannii ATCC 19606	4	0.12	≤0.06	0.25	1
A. baumannii (10 MDR isolates)	16 (1–16)	0.5 (≤0.06–0.5)	0.12 (≤0.06 – 0.12)	0.25 (0.12–1)	64 (1–64)

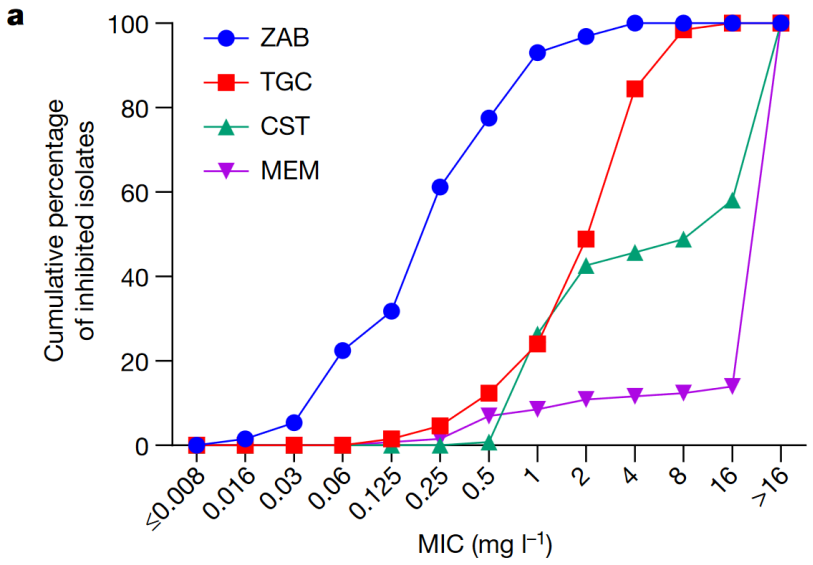

LPS
Outer membrane
Phospholipids
LptDE
D
E
Peptidoglycan
A
LptB2FGC
C
Periplasm
MsbA
F
G
Inner membrane
B
B
Cytoplasm
LPS
ATP
ADP+Pi
ATP
ADP+Pi
O-antigen repeat
Hep
Glc
Glc
Gal
Glc
Outer core
P
Hep
Hep
PEtN
P
Hep
Inner core
Kdo
Kdo
Lipid A

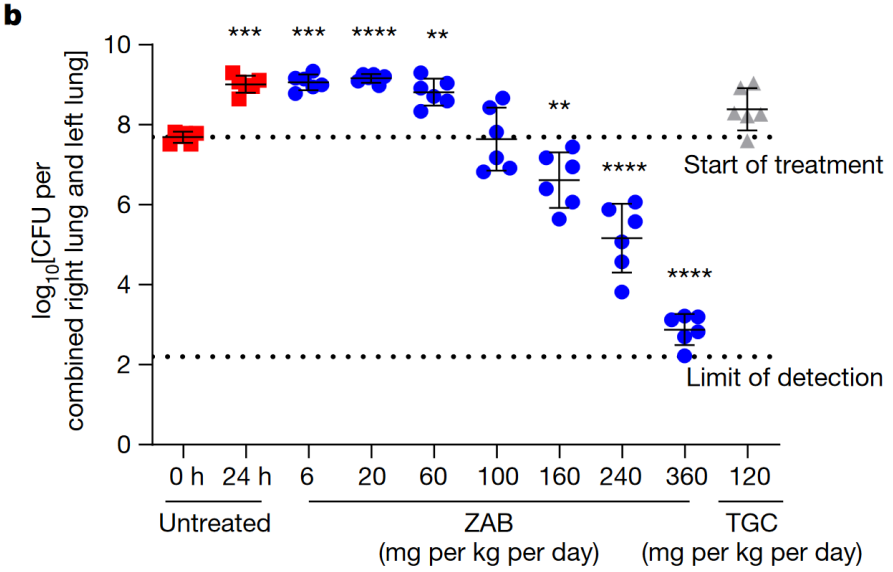

a
Outer membrane
Periplasm
Inner membrane
Cytoplasm
LPS
LptB2FGC
D
E
A
G
F
C
B
B
LPS
ATP
ADP + Pi


b
LPS
G
F
C
B
B
+
A
+ATP
±Compound
A
G
F
C
B
B
ATP
ADP + Pi

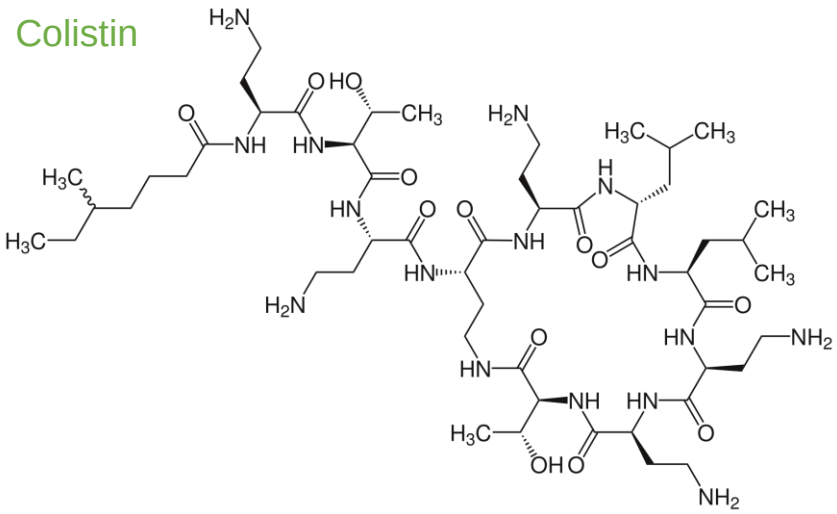

c
Protein
LptB2FGC
Compound
None
ZAB
RO7055137
Dose (μM)
0
0.01
0.1
1
10
0.01
0.1
1
10
UV
–
+
25
20
LPS × LptA
Anti-LPS
20
LptA
(kDa)
Anti-His


LptF
E249K
I317N
E249K + I317N
Dose (μM)
0
10
0
10
0
10
Compound
None
ZAB
RO7055137
None
ZAB
RO7055137
None
ZAB
RO7055137
UV
–
+
–
+
–
+
25
20
LPS × LptA
Anti-LPS
20
LptA
(kDa)
Anti-His

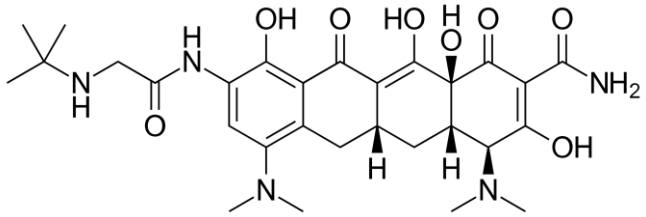




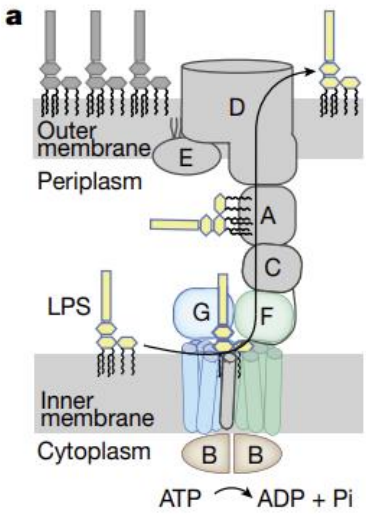
Colistin

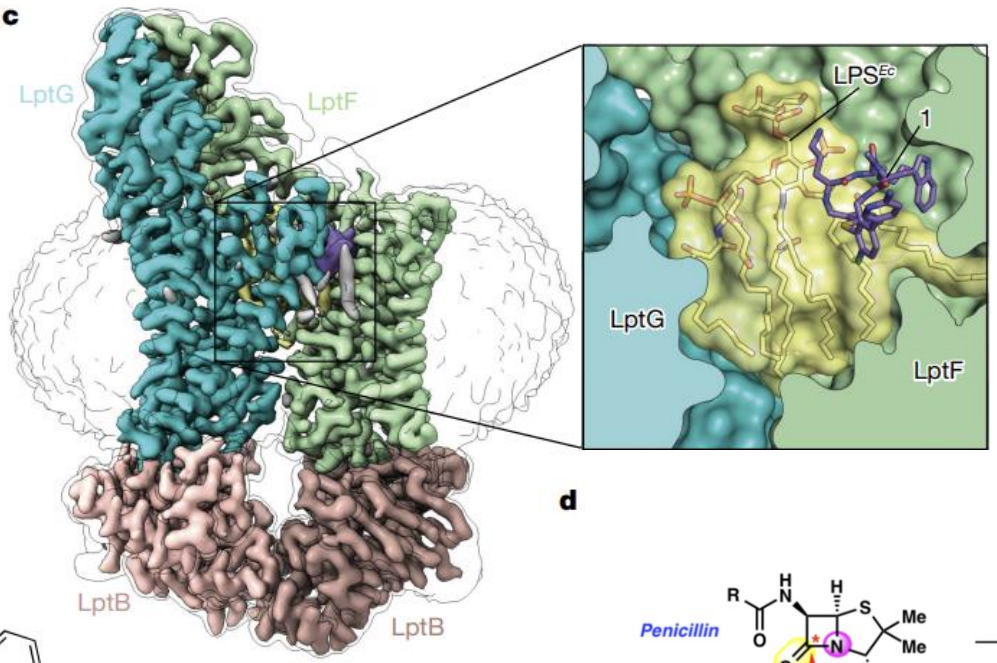


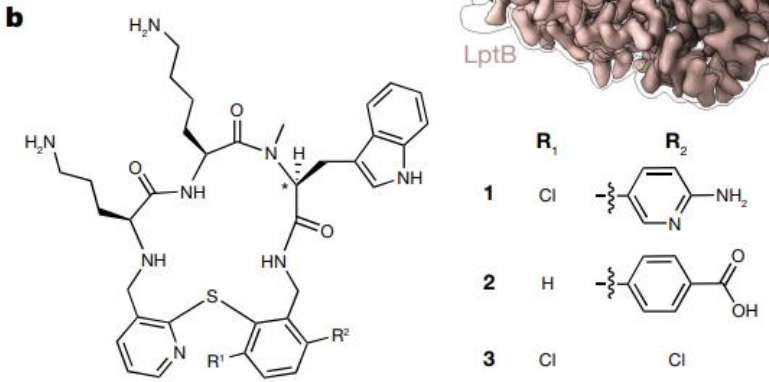
Tigecycline

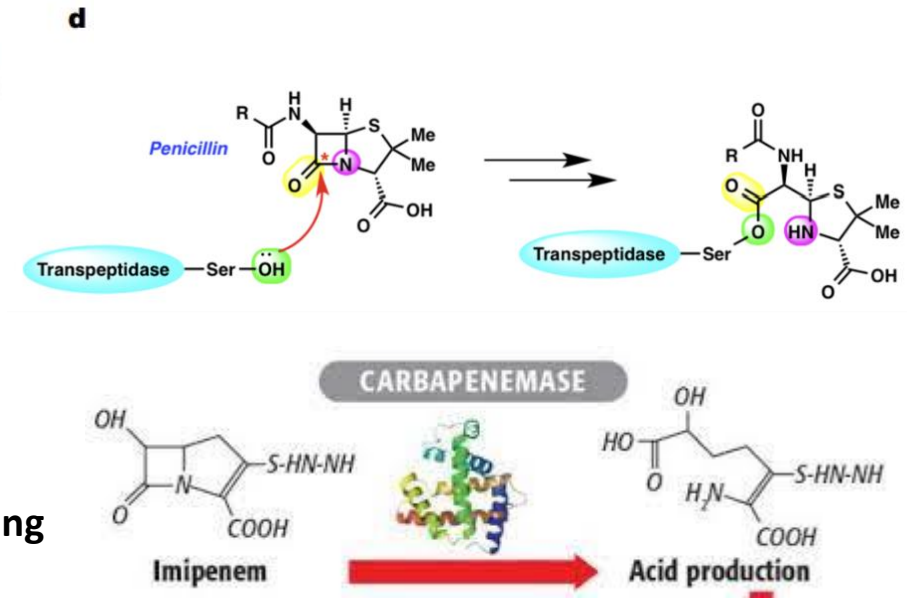


替加环素(Tigecycline)与粘菌素(Colistin)均为后线抗生素。粘菌素对多数革兰氏阴性菌有效，但具有较强的肾毒性与神经毒性。替加环素为第三代四环素。









Macrocyclic peptides block LPS transport by binding to the inner membrane complex

Thanks !