Antibiotics I

Chemistry of antibiotics and related drugs
(Mrinal K. Bhattacharjee, Springer)

Definition of antibiotics (ATB)

- ATB, chemicals that selectively inhibits a virulent (infectious) biological agent but causes minimal damage to the host
- **anti-infectives** alternative terms for antibiotics (also contain antiviral compounds)
- **antimicrobials**, which could be divided into three groups:
    - Antibiotics – kill or inhibit the microorganisms in the body
    - Antiseptics – are applied on living tissue to prevent infection
    - Disinfectants – kill or inhibit microorganisms non-living objects

Sterilization – killing microorganism in liquid media or on solid object by using chemicals such as oxidizing agents or alternatively using heat or irradiation

Sanitizing agents – means using disinfectants, antiseptics or sterilizing agent

History of antibiotics

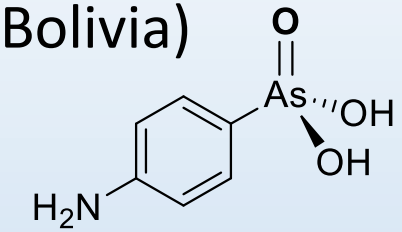
Ancient history: many examples……., extracts, dried plants, roots, inorganic compounds, natural compounds, etc.

Greeks – extract form male fern – to treat worm infestation

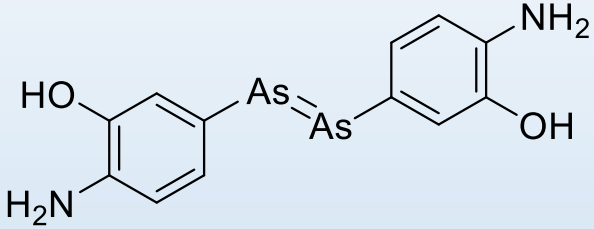
Cinchona barks – quinine to treat malaria (Peru, Bolivia)

Ipecacuanha root – diarrehea (Brasil)

And many others……



Atoxyl



Salvarsan

Modern history:

18th century: observation by Robert Koch and Louis Pasteur – diseases can be caused by germs (Pasteur used harmless bacteria to cure diseases caused by harmful bacteria)

1863: Antoine Bechamp – *Atoxyl (arsanilic acid)*

1888:

1904: Paul Ehrlich – use of chemical to kill bacteria – dyes as antibacterial agents *Trypan Red, Salvarsan*

1932: Gerhard Domagk – discovery of sulphonamides – *Prontosil*

1940s: Ian Fleming - Penicilin

Ideal antibiotic

- Selectivity
- Water solubility
- Minimal side effects
- Stability
- Low cost
- Slow resistance development

Source of antibiotics

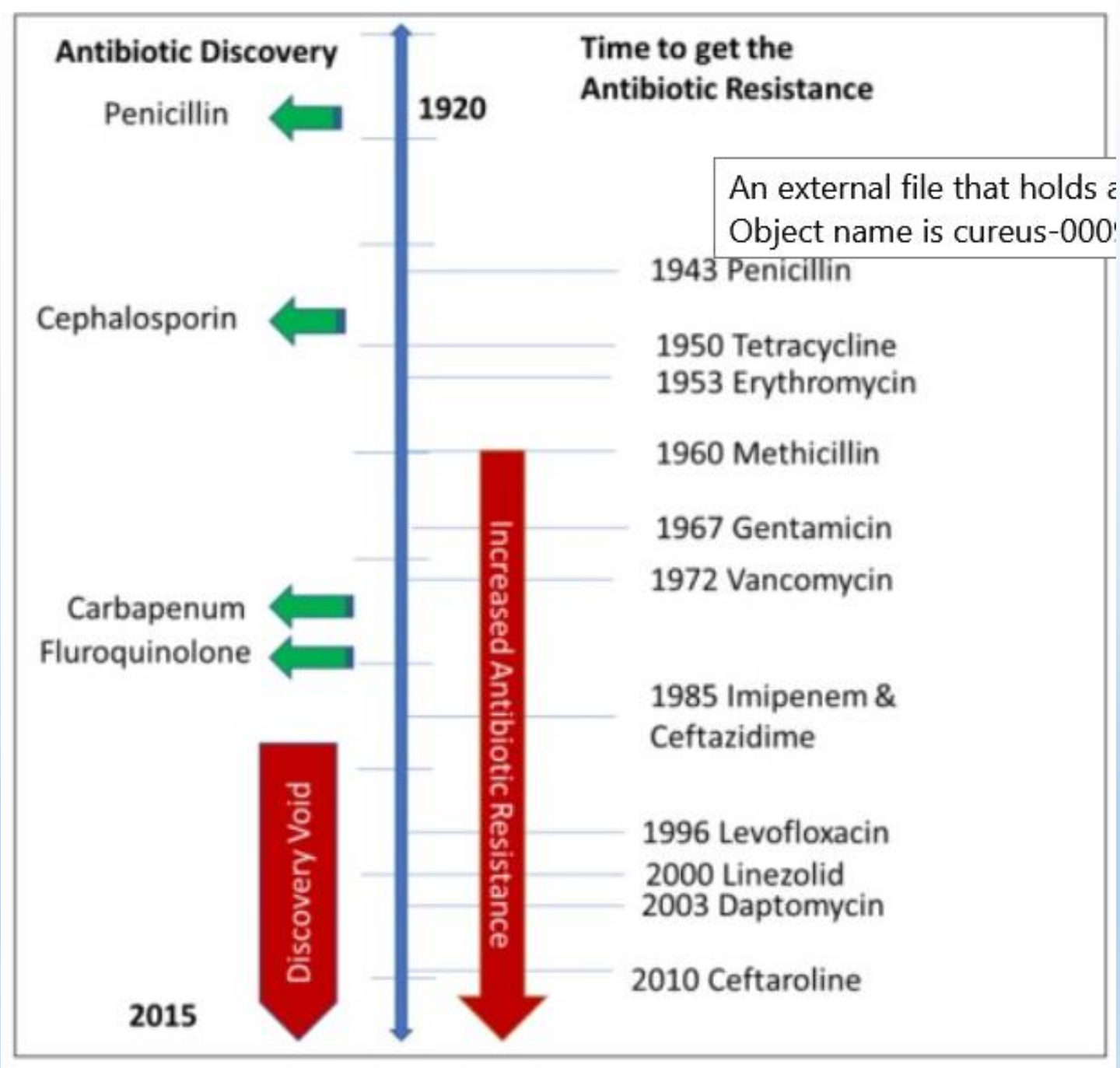
- Majority of antibiotics used today is produced by microorganims (bacteria, fungi)
- Chemically synthetized
- Natural sources (minimum)

Soil organisms – the best place to search for new antibiotics today
(soil is a very complex ecosystem in which inhabitants developed chemical defences against each other as a response to competition for nutrients – chemical war among bacteria, and fungi)

Discovery of modern antibiotics

- 1920 – discovery of lysozyme (Fleming), „A thick milky suspension of bacteria can be quickly cleared in few seconds by the addition of a drop of human tears of egg white“
- 1928 – discovery of penicillin (Fleming), 1945 Nobel price lecture held by Fleming „ My only merit is I did not neglet the observation and that I pursued the subject as bacteriologist“ , *Penicillinum mold*
- 1939 – discovery of gramicidin (Rene Dubos), *Bacilus brevis*
- 1940 – Howard Florey and Ernst Chain – method for purifiation of penilcilin (Oxford)
- 1943 – discovery of streptomycin (Selman Waksman, Albert Shatz), *Streptomyces griseus*
- 1944 – Merck company, penicillin for all….
- 1947 – chloramphenicol (Paul Burkholder, Yale), 1st broad spectrum antibiotic *Streptomyces venezuela*
- Chlorotetracyclin, 2nd broad spectrum antibiotic, *Streptomyces aurofaciens*

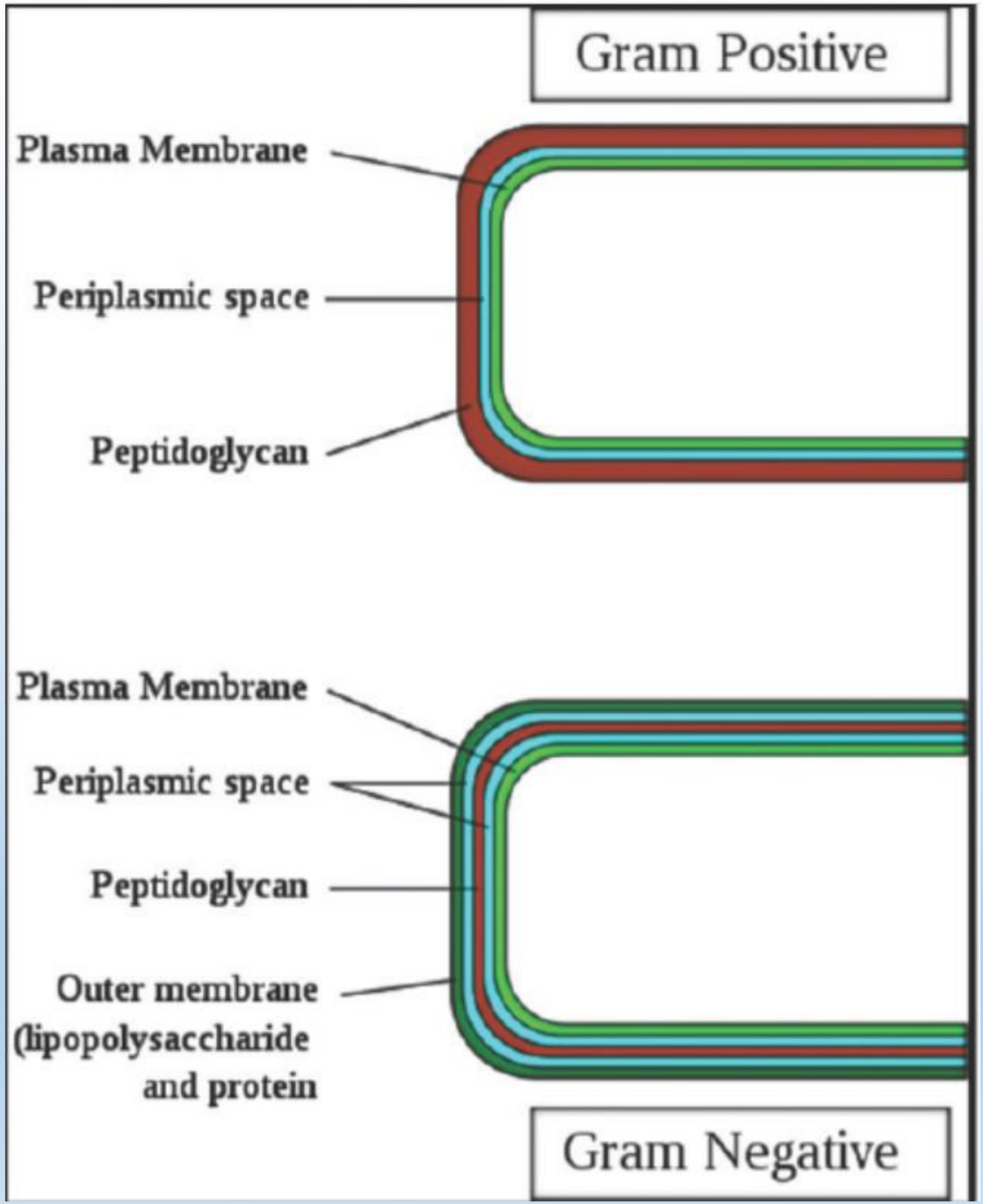
Discovery of antibiotics



A Review on Antibiotic Resistance: Alarm Bells are Ringing
doi: 10.7759/cureus.1403

Gram positive and negative bacteria

- Difference in cell wall composition

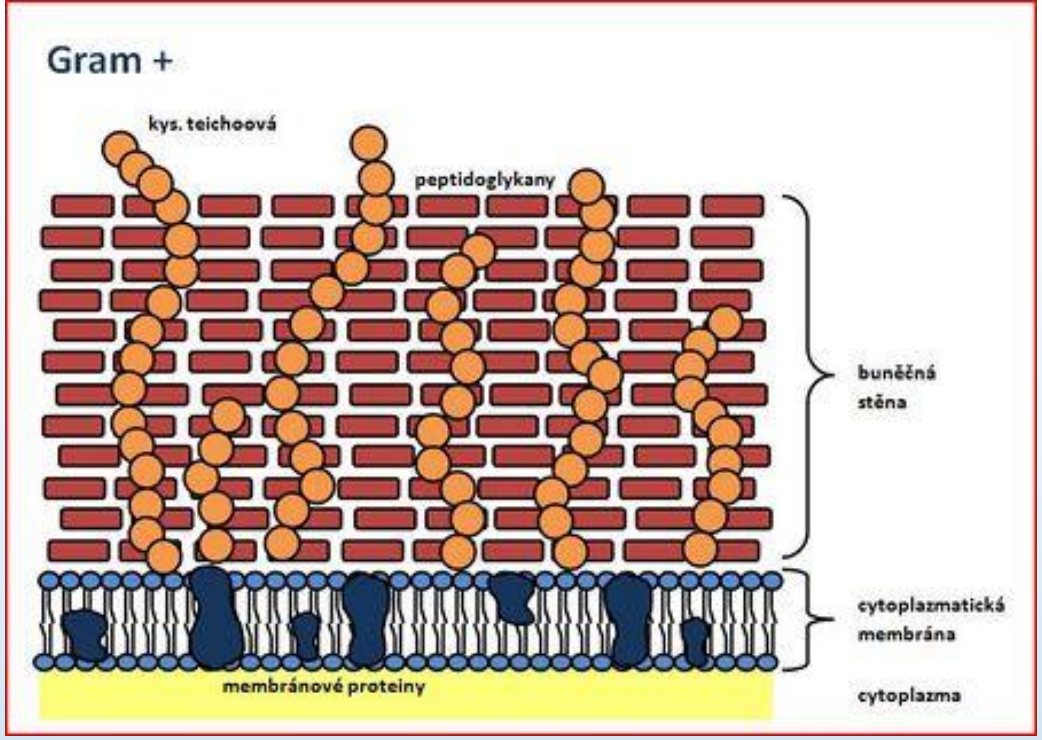


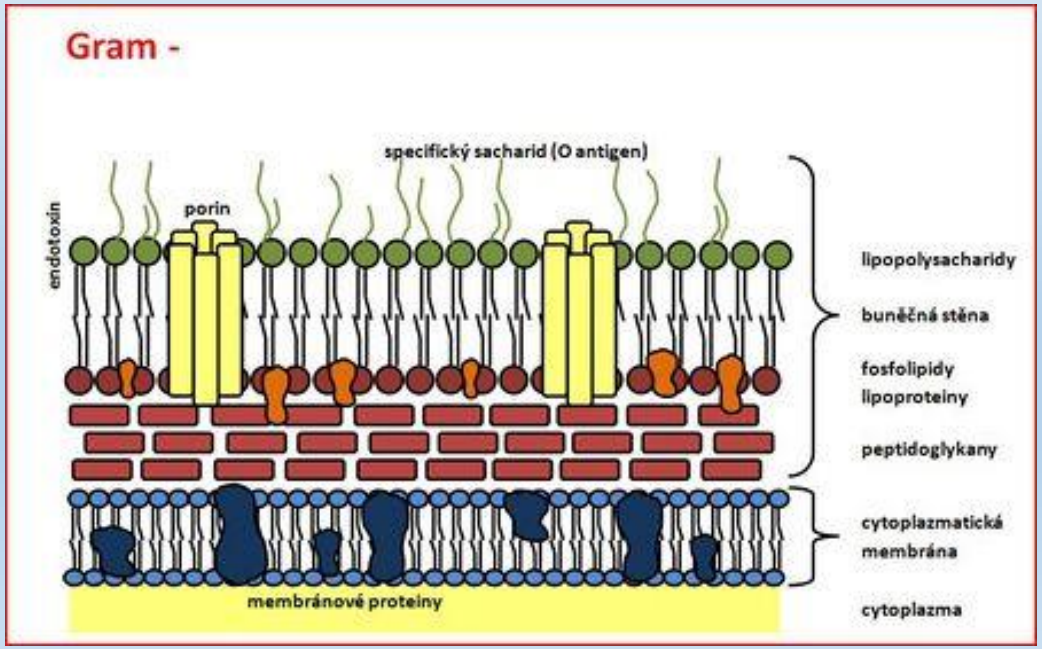
Action and resistance mechanisms of antibiotics: A guide for clinicians
DOI: 10.4103/joacp.JOACP_349_15

Gram test

Crystal violet, Lugol solution, safranin
G+ coccus: Staphylococcus, Streptococcus, Enterococcus;
G+ baccillus: Corynebacterium, Clostridium, Listeria, Bacillus.

G– coccus: Neisseria;
G– coccobacillus: Haemophilus influenzae, Bordetella pertussis, Legionella, Brucella, atd.
G– baccillus: Klebsiella, E. coli, Enterobacter, Citrobacter, Serratia, Vibrio, Pseudomonas, Proteus, Helicobacter pylori, Yersinia, Campylobacter, Salmonella





https://www.wikiskripta.eu/w/Gramovo_barven%C3%AD

Bacterial resistance

Development of resistance to antibiotics

- Detection of resistence – broth or agar dilution method, MIC (minimum inhibitory concentration)
- ATB resistence: intrinsic (natural, all bacteria is resitant, bacteria without prior exposure to ATB) and acquired (only a subpopulation is resistant, acquired resistence – by point mutation or by resistance gene aquisition

Point mutation

- Natural methods: *replication errors*, common bacteria replication time is 20 minutes which means that every 20 min. the number of bacteria will double.
- One bacteria, in 10 hours, will double 30x, …….2^{30} ca. one bilion of bacteria
- Induced methods: harsh environmental conditions, UV, oxidation agents, alkylating agents
- Effect of point mutation – change in protein sequence

Gene Acguisition

- E.g. Beta-lactamases
- Plasmids – are small (up to a 1000x smaller than the chromosome) piece of extrachromosomal DNA, usually circular
  - Can contain more than one resistence genes
  - Does not contain any usefull function fot the cells and may be lost in daughter cell during replication, the daughter cell who do not receive the copy is killed by ATBs – selection
  - Plasmid maintanence system – specific genes – each daughter cell always receive a copy of resistence gene

Gene Acguisition

- Transposons (or insertion sequence (IS) elements) – small pieces of DNA that can insert into the chromosome (randomly or specifically, jumping genes). Can also be excised and inserted somewhere else.
- Requirements: IS sequence contains direct or inverted repeat sequence at the two ends. And IS sequence is preceded or followed by the sequence for Transponase enzyme.
- Transposon sequence can have 1) gene for ATB resistance or 2) can be inserted into the gene which is responsible for proper functioning of an ATB

Gene Acguisition

- Integrons: similar to transposons – mobile genetic element with possibility of multiple ATB resistance. They do not have repeated sequence at the two ends and they contain an integrase enzyme sequence needed for insertion process
- Transfer of resistance gene between bacteria:
    1) bacterial conjugation – conjugative plasmids – capable of being transferred, and mobilizable plasmids – contain some, not all information for conjugation – can be transferred only with conjugative plasmid
    2) bacterial transformation – bacteria takes DNA from outside, usually released from dead bacteria
    3) bacterial transduction/transfection – DNA is transferred via bacteriophage

ATB resistance pool

ATB	Year introduced	Year resistence reported	Years taken for resistance development
penicillin	1943	1940	-3
tetracycline	1950	1959	9
methicillin	1960	1962	2
vancomycin	1972	1988	16
levofloxacin	1996	1996	0

- Taking insufficient dose
- Not completing the full ATB course
- Taking wrong ATBs, or using it against viral infections
- Other misuse: ATBs in animals – therapeutic and subtherapeutic used
- Mechanisms of antimicrobial resistance: 1) altering the target of the ATB (ATB no longer works), 2) decreasing the concentration of ATB to the level lower than MIC – a) preventing entry, b) pumping out the ATB after it enters the cell, c) degrading ATB

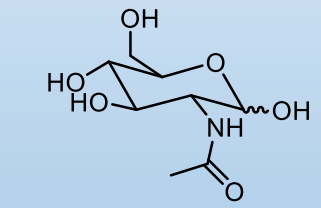
Multidrug resistant (MDR) microorganisms

- Microorganism which are resistant to at least 3 of the 4 antibiotic classes – ATBs which affect cell membrane, cell wall, nucleic acid synthesis, and protein synthesis.
- Great concern because most of the ATBs does not work against them.
- ESKAPE group of bacteria: *Eterococcus faecium* (vancomycin resistant), *Staphylococcus aureus* (methicilin or vancomycin resistant), *Klebsiella pneumonia, Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter spp.* (carbapenem resistant).

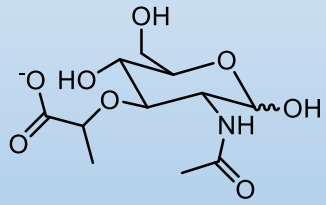
Antibiotics

ATBs that inhibit cell wall synthesis

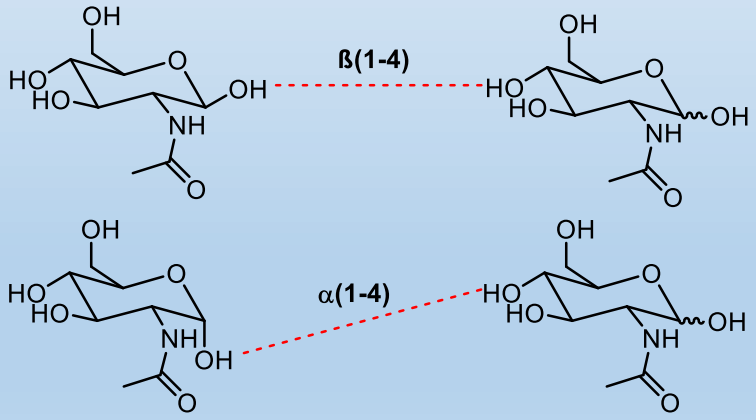
- Cell wall composition: mostly peptidoglycans („carbohydrate polymers (glycan) with some peptides linked to it“)
  glycan consist: *N*-acetylglucosamine (NAG), *N*-acetylmuramic acids (NAM) linked by *ß*(1→4) glycosidic bond



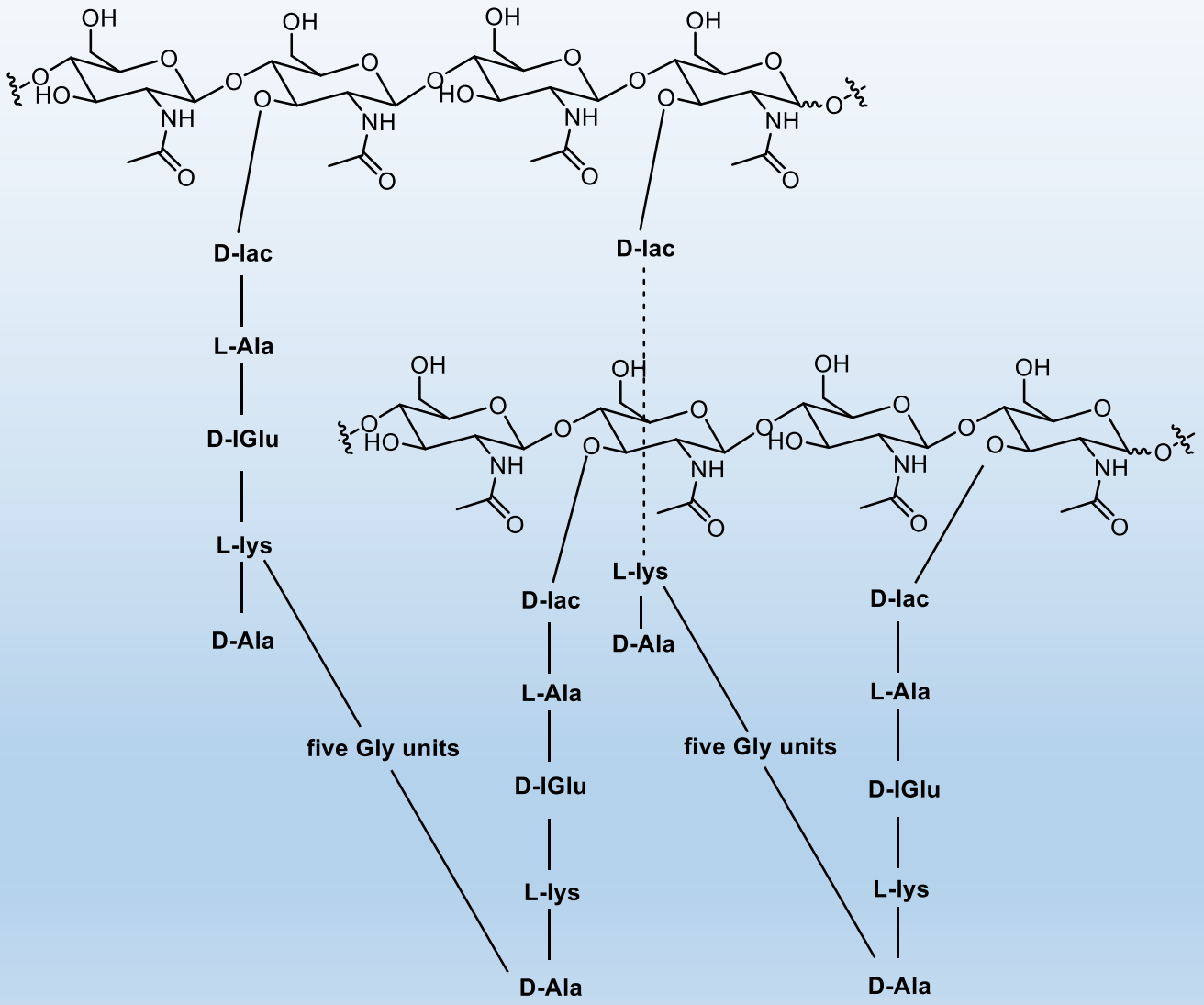
N-acetyl-2-D-glucosamine
NAG



N-acetyl-2-D-glucosamine-3-lactate
(N-acetyl muramic acid)
NAM

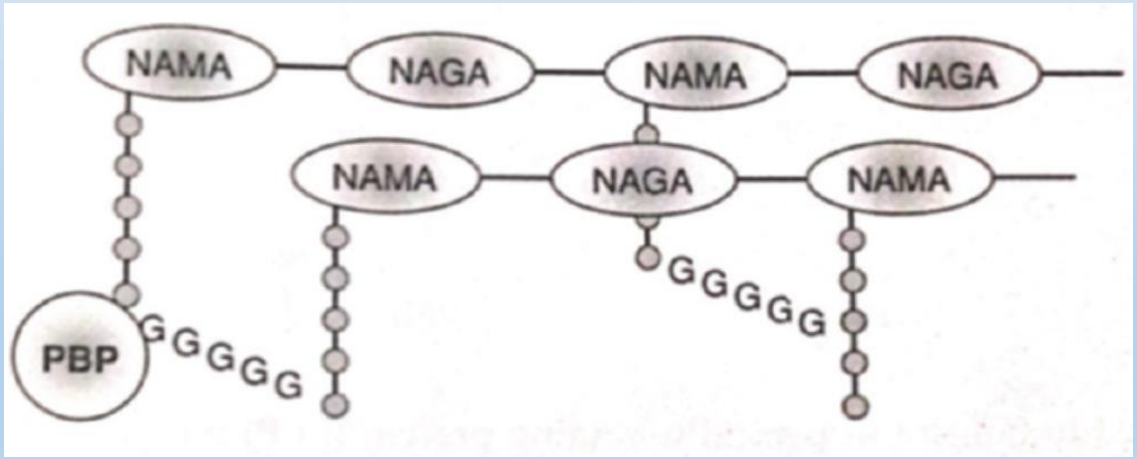


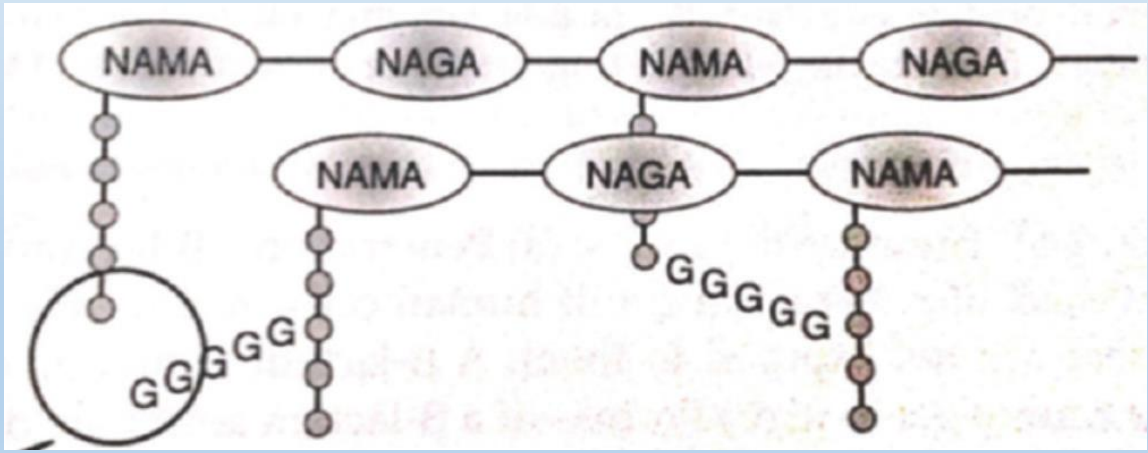
Bacterial cell wall – peptidoglycan cross-linking



Beta lactams

- Peptidoglycan biosynthesis – transglycosidases (cross linking the glycan strands with sugar bound peptide chain)
- Beta lactam mimics D-alanyl alanine, interaction with penicilin binding protein





Action and resistance mechanisms of antibiotics: A guide for clinicians
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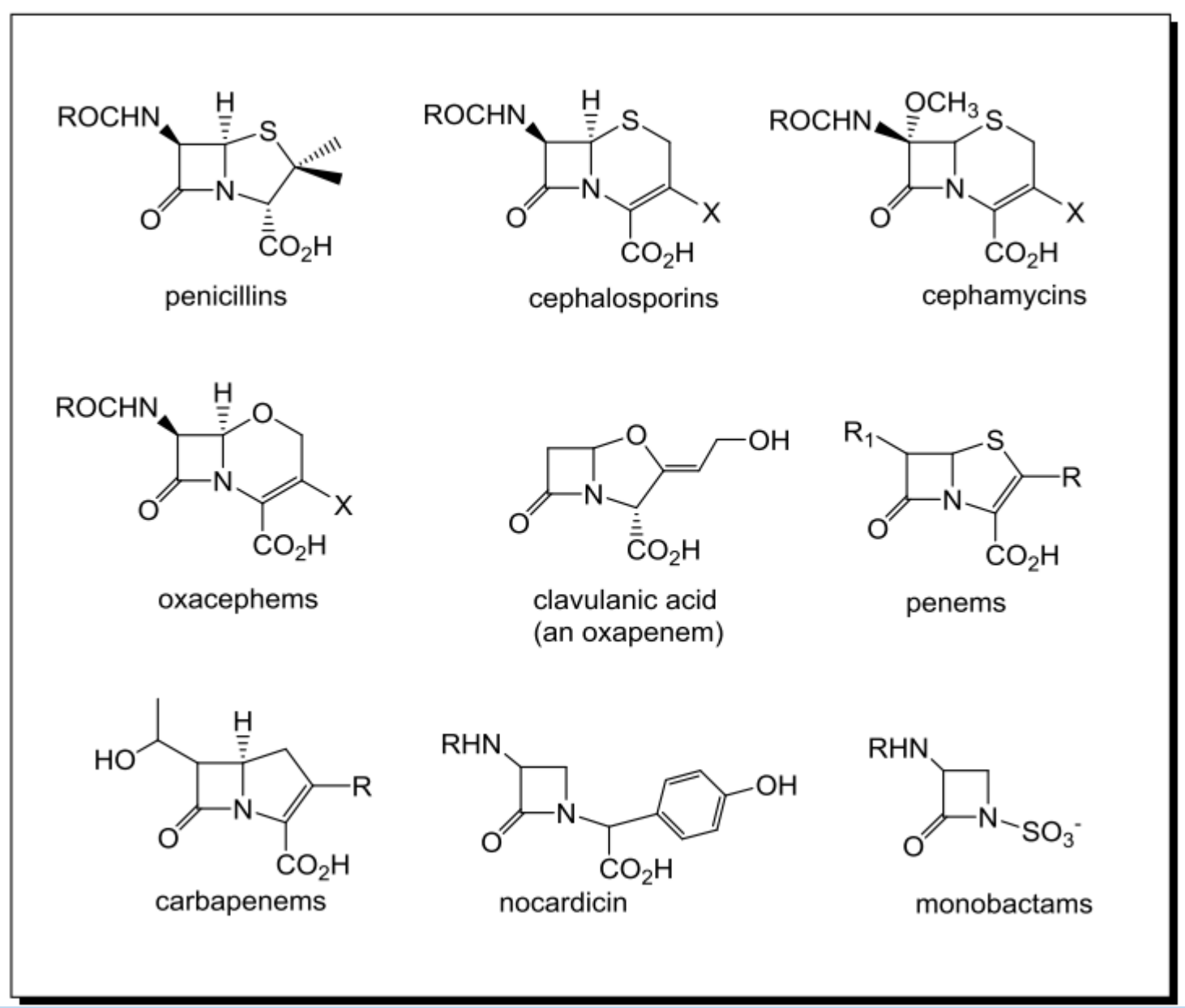
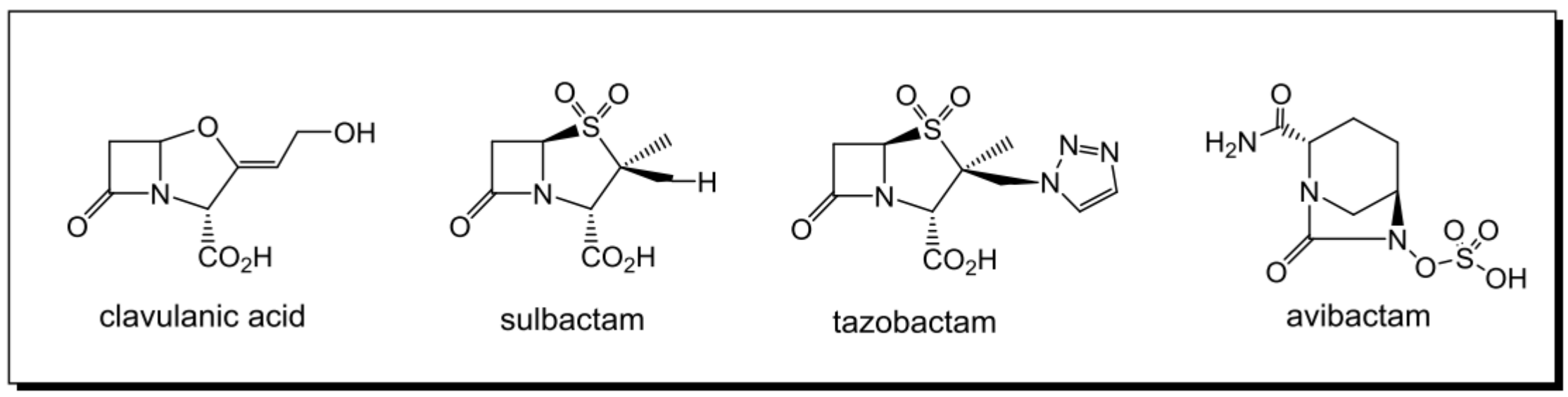
Beta-lactams



Antibiotics 2014, 3, 128-142; doi:10.3390/antibiotics3020128

Avoiding beta-lactamase resistance

- Beta-lactamase inhibitors



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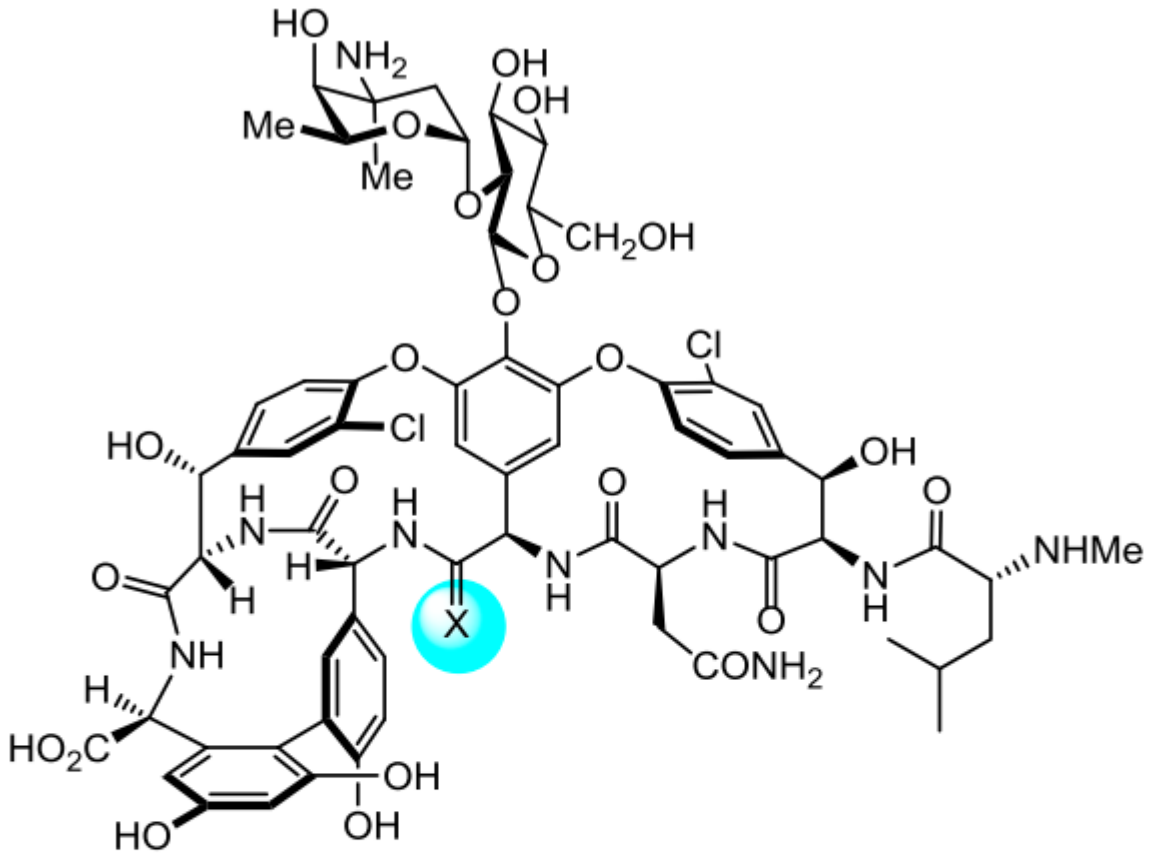
Glycopeptides

- Glycopeptides bind to D-alanyl alanine part of peptidoglycan subunit
- Vancomycin



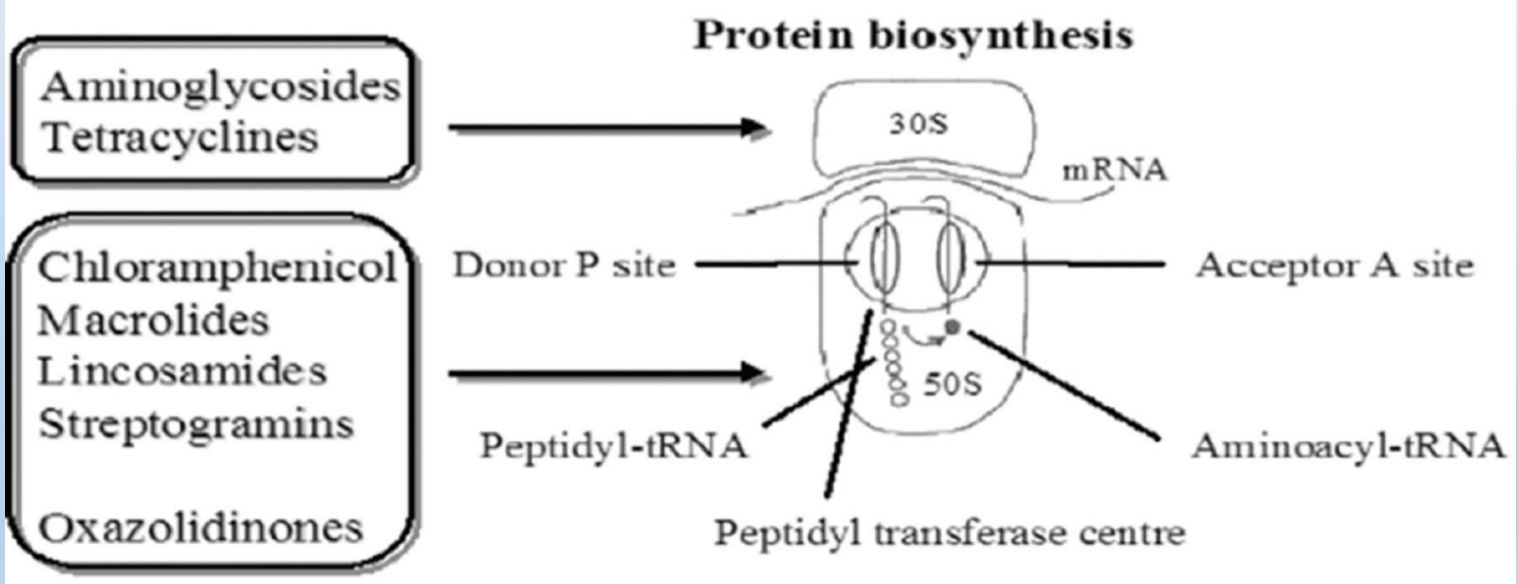
Antimicrobial Activity, MIC[a] (μg/mL)

	sensitive	MRSA	VanA		VanB
	S. aureus[b]	*S. aureus*[c]	*E. faecalis*[d]	*E. faecium*[e]	*E. faecalis*[f]
1, X = O	0.5	0.5	250	250	8
2, X = S	>32	>32	>32	>32	>32
3, X = NH	nd[g]	nd[g]	0.5	0.5	nd[g]
4, X = H_2	nd[g]	nd[g]	31	31	nd[g]

Peripheral modifications of
[Ψ[CH2NH]Tpg4]vancomycin
with added synergistic mechanisms of action
provide durable and potent antibiotics
www.pnas.org/cgi/doi/10.1073/pnas.1704125114

Inhibitors of protein biosynthesis

- DNA → RNA (mRNA) transcription
- Protein synthesis on ribosome
- Bacterial S70 ribosome: 2 subunits, S30 and S50



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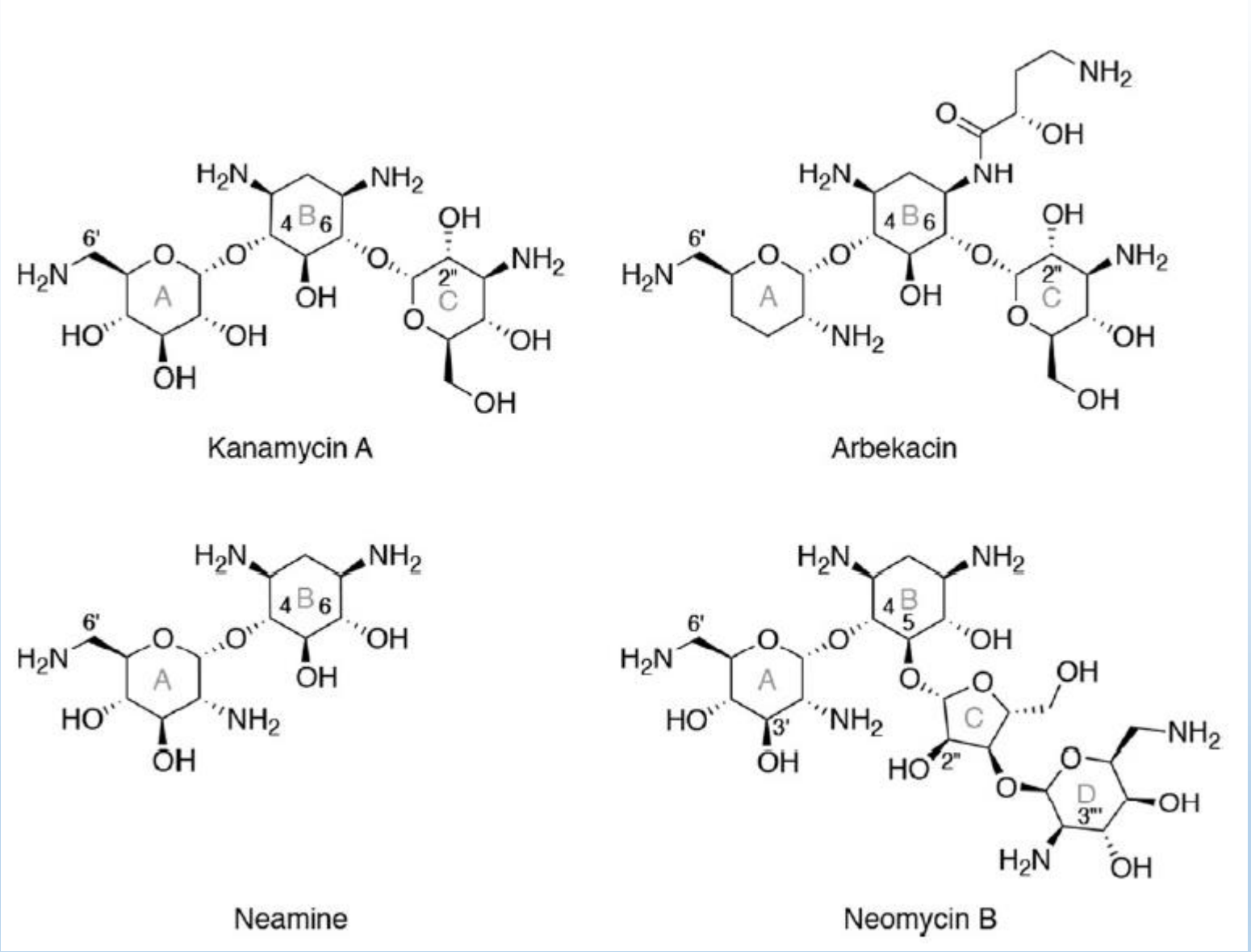
Inhibitors of S30 subunits

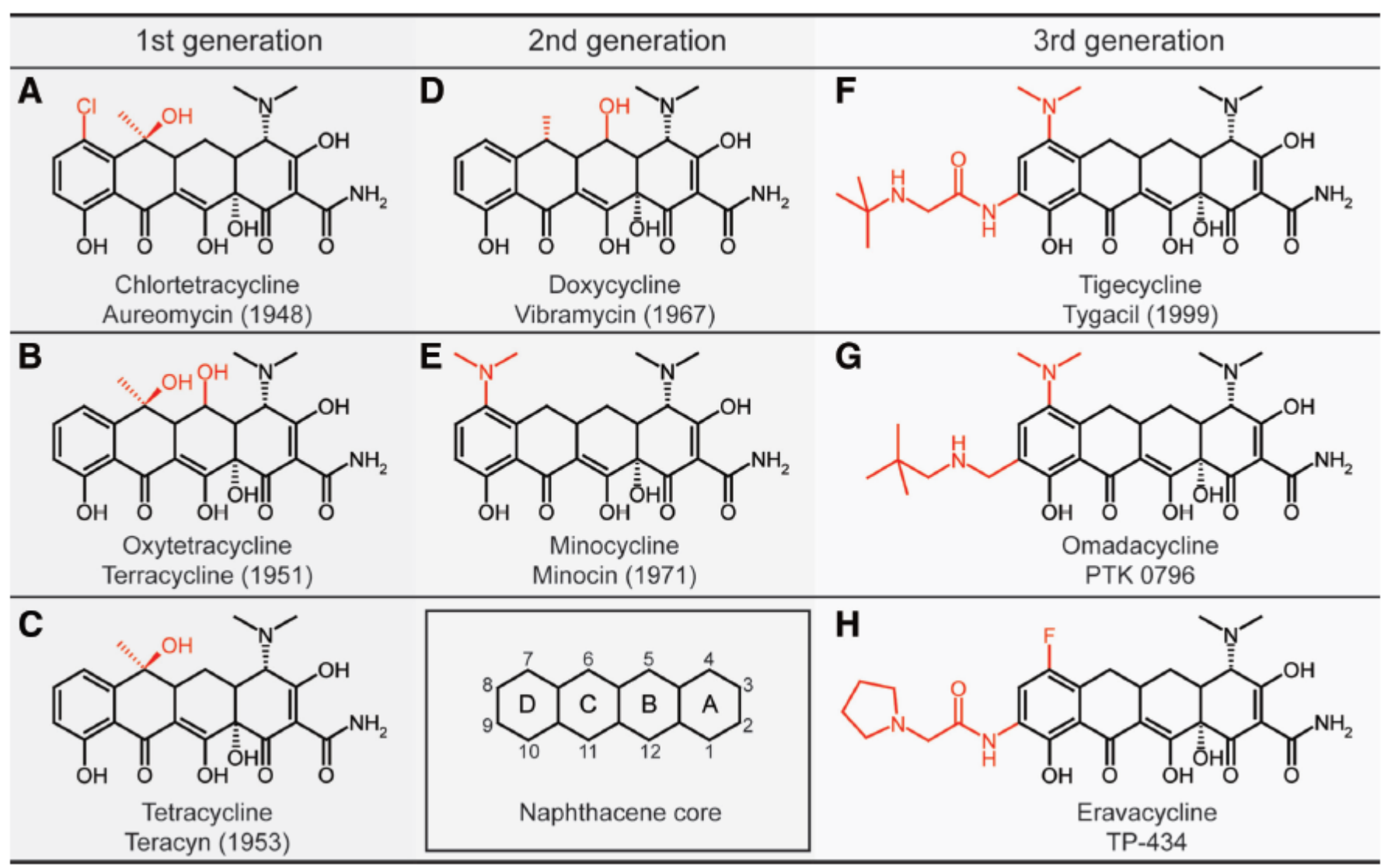
- **Aminoglycosides**
- Positively charged molecules (low cell penetration, active transport, oxygene and H^+ force)
- Synergism with beta-lactams and glycopeptides



THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 287, (52), pp. 43262–43269, 2012.

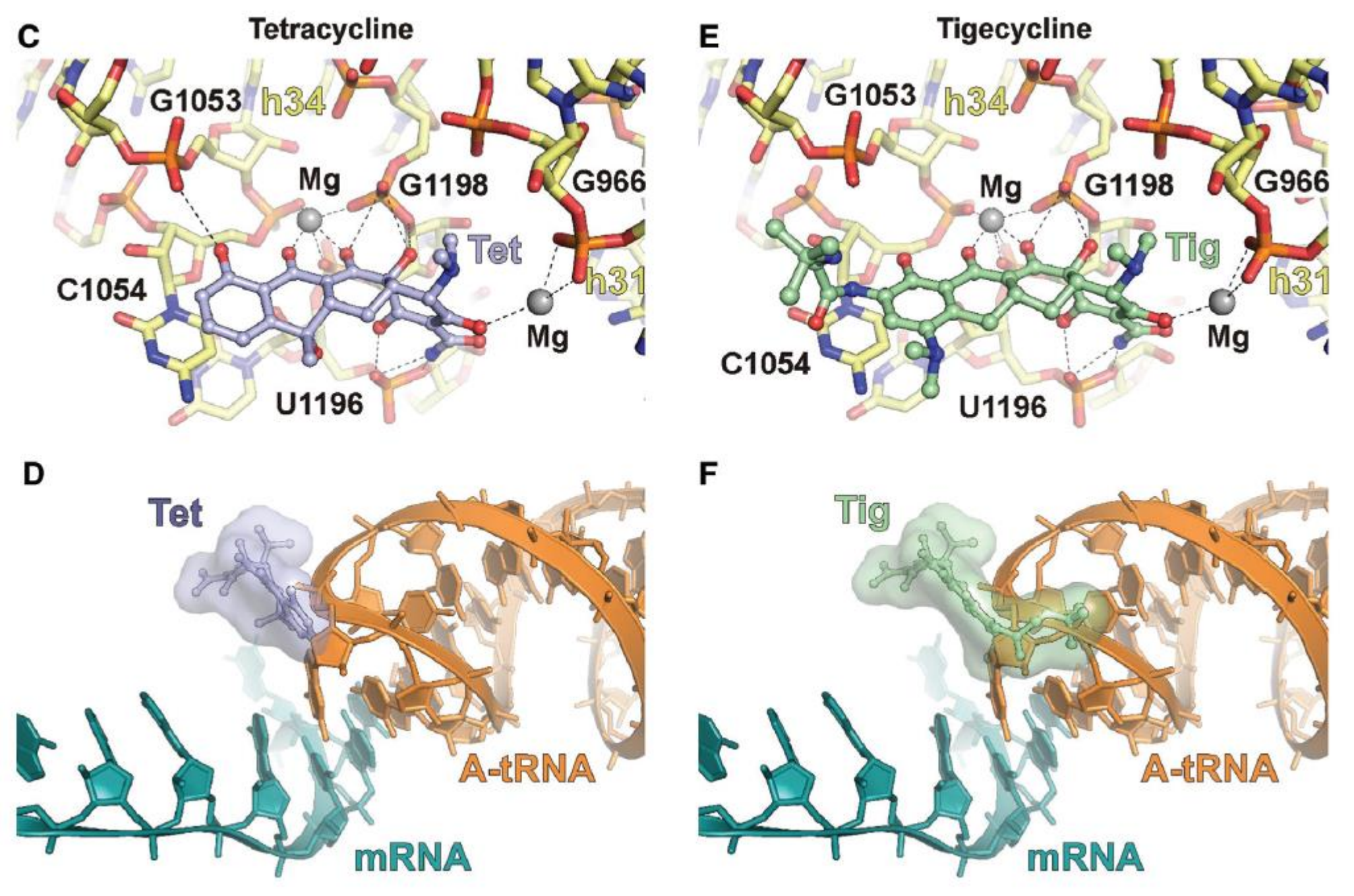
Inhibitors of S30 subunits

- **Tetracyclines** (tetracycline, chlortetracycline, doxycycline, minocycline)
- Inhibitions of t-RNA binding to A site of S30



DOI 10.1515/hsz-2013-0292 Biol. Chem. 2014; 395(5): 559–575

Tetracycline binding on ribosome

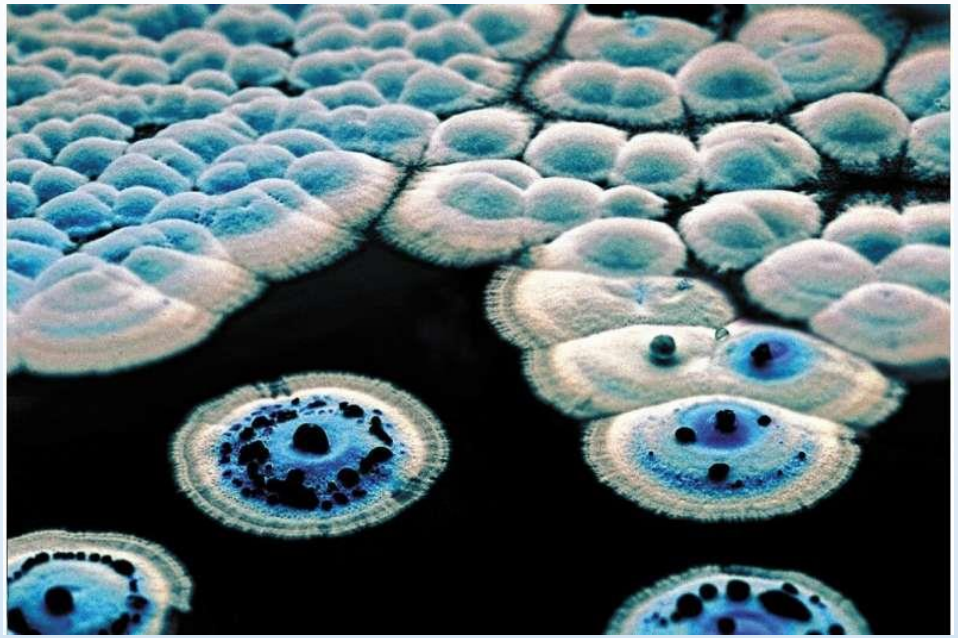


DOI 10.1515/hsz-2013-0292 Biol. Chem. 2014; 395(5): 559–575

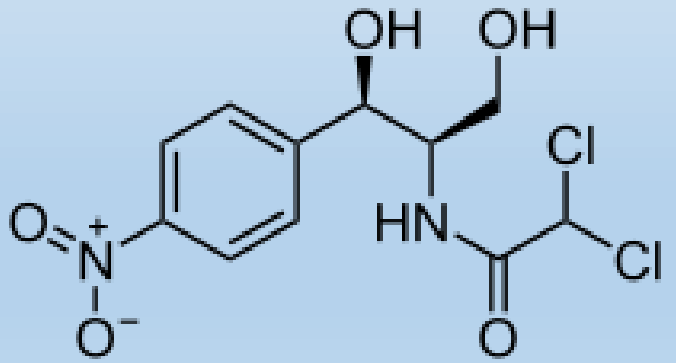
Inhibitors of S50 subunits

- **Chloramphenicol**
- Inhibitions of t-RNA binding to A site of S50 (peptidyl transferase cavity of the 23S r-RNA)
- used to treat meningitis, plague, and cholera
- Isolated from *Streptomyces venezuelae* in 1947

Streptomyces venezuelae



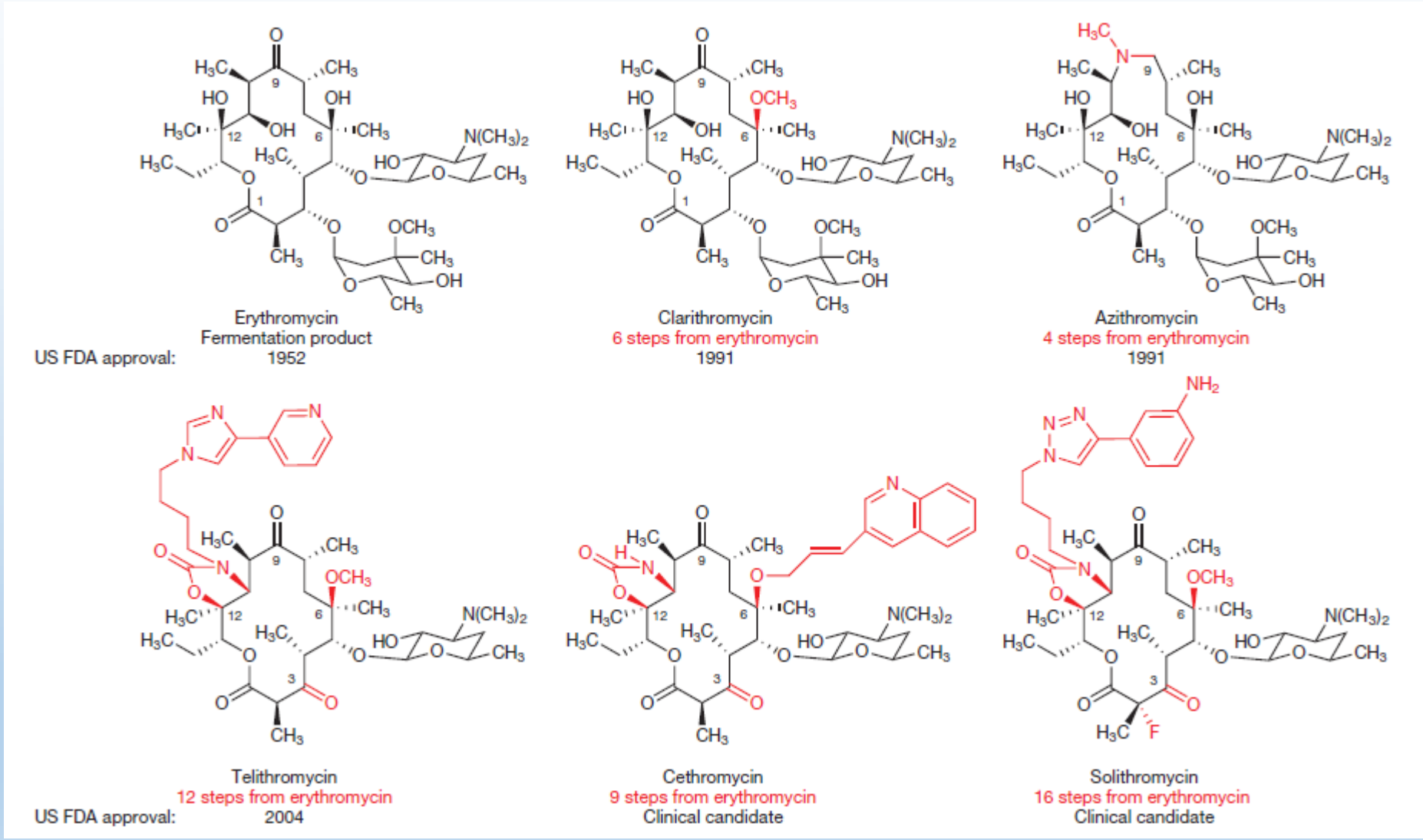
https://phys.org/news/2019-02-time-lapse-microscopy-reveal-mechanism-streptomyces.html



https://en.wikipedia.org/wiki/Chloramphenicol#:~:text=Chloramphenicol%20is%20an%20antibiotic%20useful,%2C%20cholera%2C%20and%20typhoid%20fever.

Inhibitors of S50 subunits

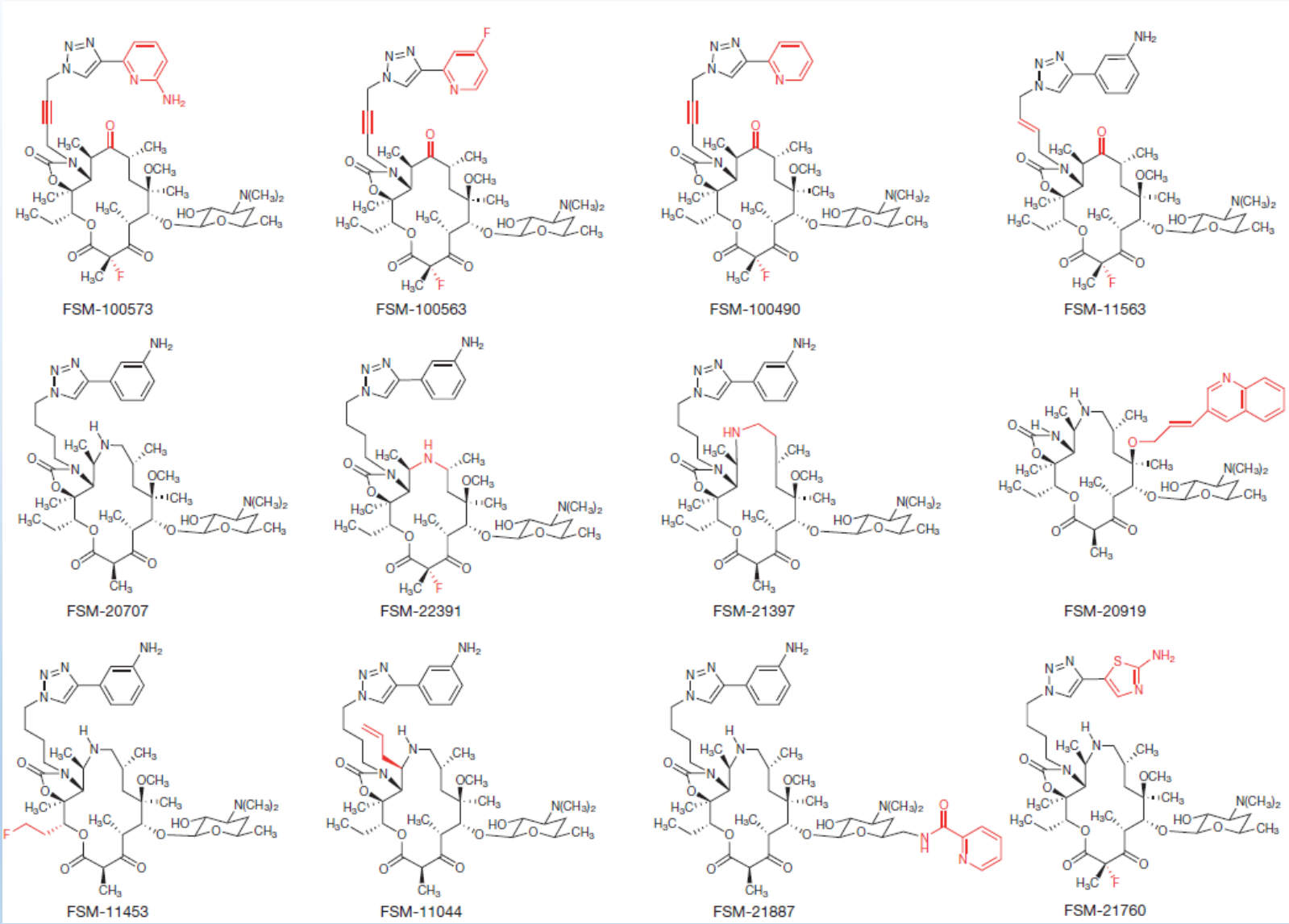
- **Macrolides**
- Inhibit protein translocation (peptidyl transferace center of the 23S r-RNA of the 50S ribosomal subunit)



A platform for the discovery of new macrolide antibiotics, nature.com, doi:10.1038/nature17967

Novel macrolides

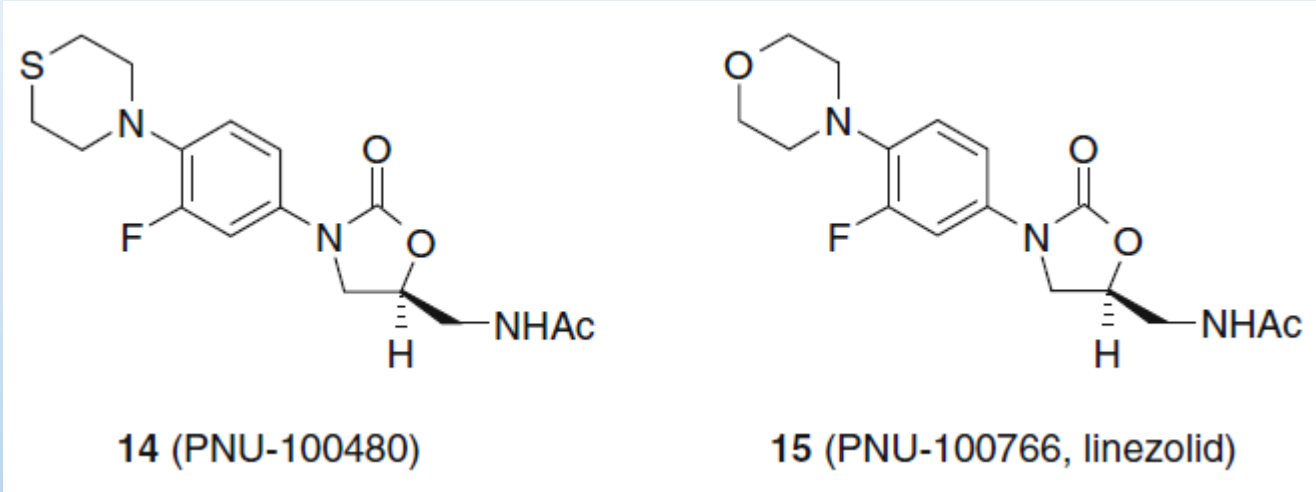
	Species	Strain description	Erythro	Azithro	Telithro	Solithro
Gram-positive	*S. aureus*	ATCC 29213	0.5	1	0.125	0.125
	S. aureus	BAA-977; iErmA	>256	>256	0.06	≤0.03
	S. aureus	MP513; MRSA; cErmA	>256	>256	256	>64
	S. aureus	NRS384; MRSA; MsrA	64	128	0.125	0.25
	S. pneumoniae	ATCC 49619	0.03	0.06	≤0.03	≤0.03
	S. pneumoniae	UNT-042; ErmB/MefA	>256	>256	0.125	0.25
	S. pyogenes	ATCC 19615	≤0.03	≤0.03	≤0.03	≤0.03
	E. faecalis	ATCC 29212	1	4	≤0.03	≤0.03
	E. faecalis	UNT-047; VRE; ErmB	>256	>256	16	32
Gram-negative	*H. influenzae*	ATCC 49247	4	2	2	4
	A. baumannii	ATCC 19606	16	32	4	16
	K. pneumoniae	ATCC 10031	4	2	4	4
	E. coli	ATCC 25922	64	4	16	32
	P. aeruginosa	ATCC 27853	64	64	64	64



A platform for the discovery of new macrolide antibiotics, nature.com, doi:10.1038/nature17967

Inhibitors of S50 subunits

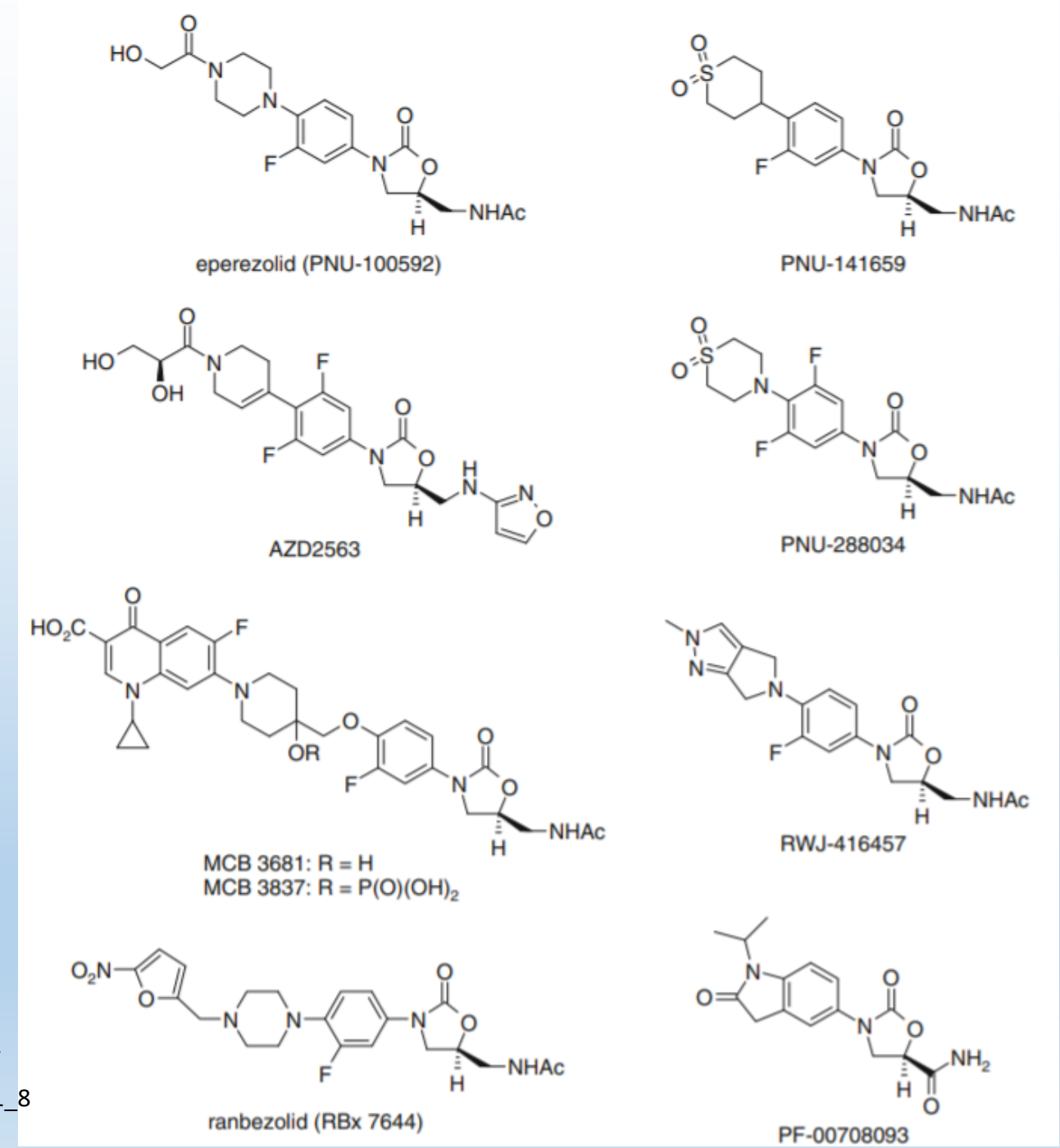
- **Oxazolidinones** (Linezolid)
- 1) Inhibition of 23Sr RNA of the 50S subunit and 2) suppresion of 70S inhibition and interact with peptidyl-t-RNA



14 (PNU-100480) **15** (PNU-100766, linezolid)

Barbachyn, M. R. (2011). *Oxazolidinone Antibacterial Agents. Antibiotic Discovery and Development, 271–299.* doi:10.1007/978-1-4614-1400-1_8

Post linezolid oxazolidines

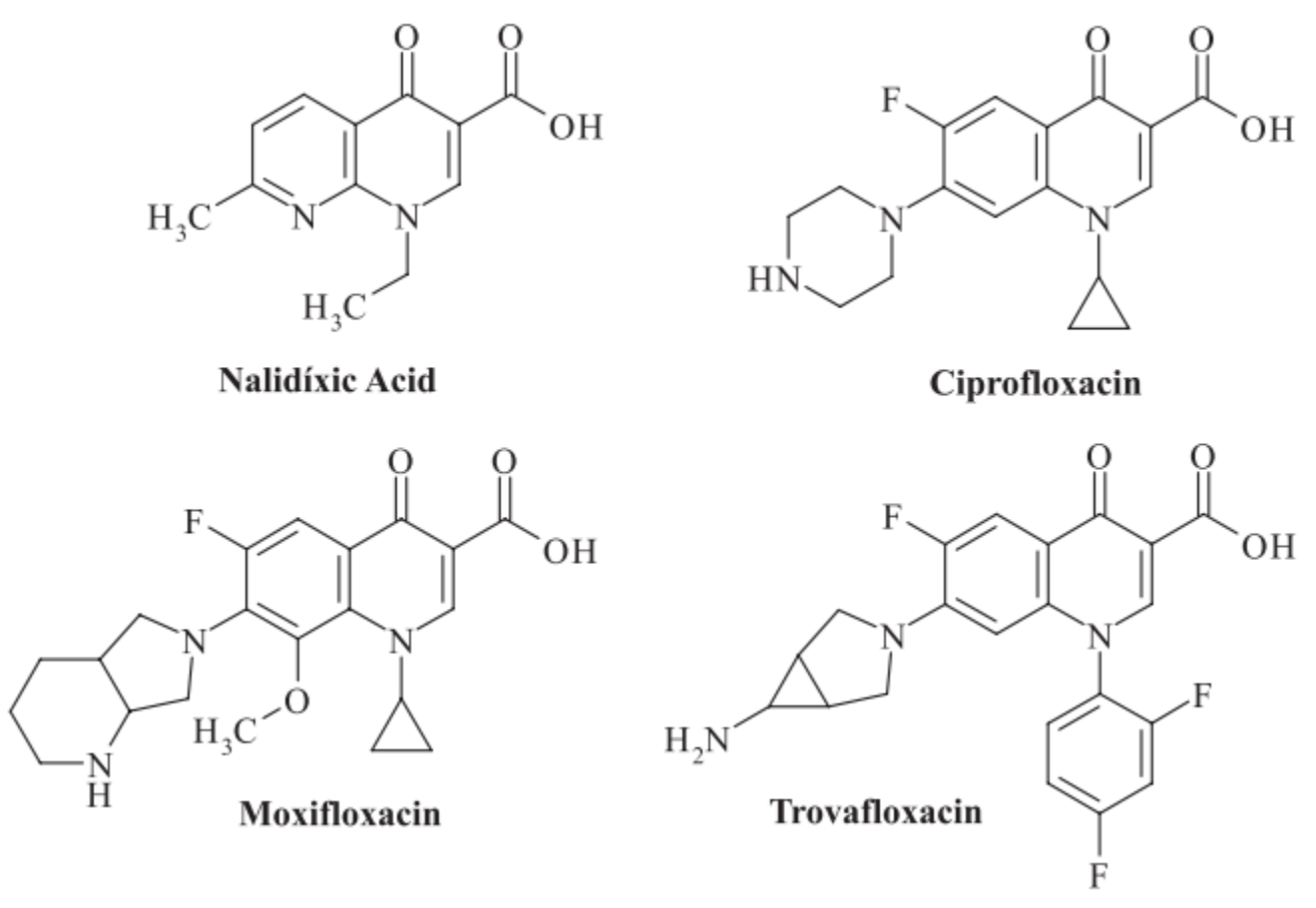


Barbachyn, M. R. (2011). *Oxazolidinone Antibacterial Agents. Antibiotic Discovery and Development, 271–299.* doi:10.1007/978-1-4614-1400-1_8

Inhibitors of DNA replication

- **Quinolones**
- Inhibition of bacterial gyrase (nicking of double stranded DNA – by formation of negative supercoils, and resealing the DNA ends) – separation of DNA strands to permit replication or transcription.
- Nadixilic acid isolated during the synthesis of chloroquine

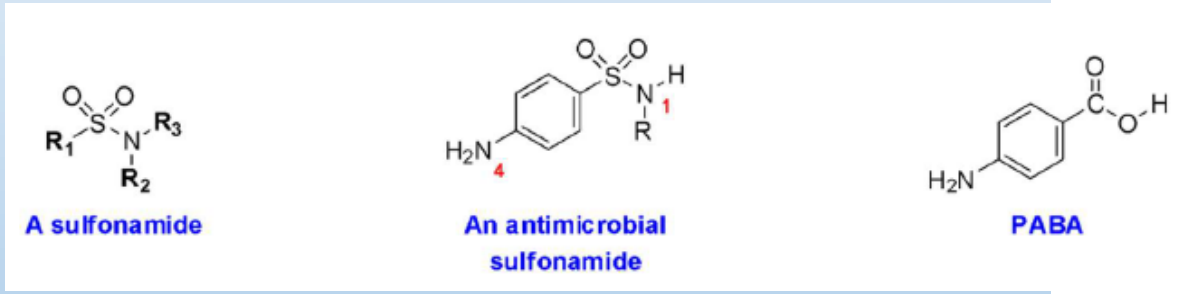
Chinolone antibiotics generation I-IV.



Brazilian Journal of Pharmaceutical Sciences vol. 47, n. 4, oct./dec., 2011

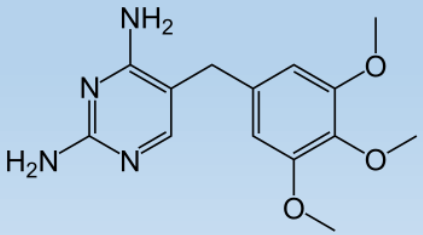
Folic acid metabolism inhibitors

- **Sulfonamides and trimetoprim**
- Inhibition of folate synthesis

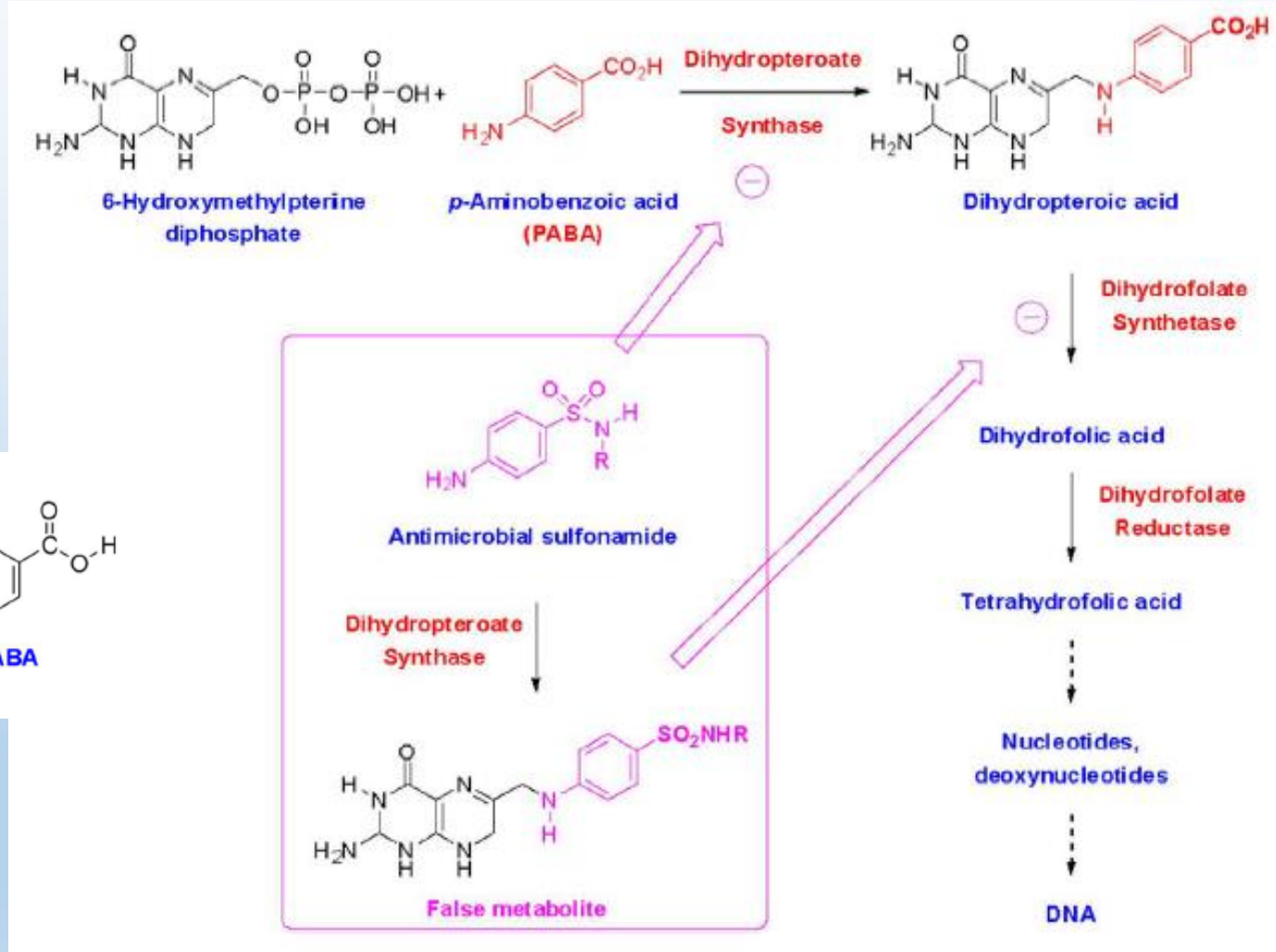


Pharmacy **2019**, 7, 132; doi:10.3390/pharmacy7030132

Trimethoprim



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



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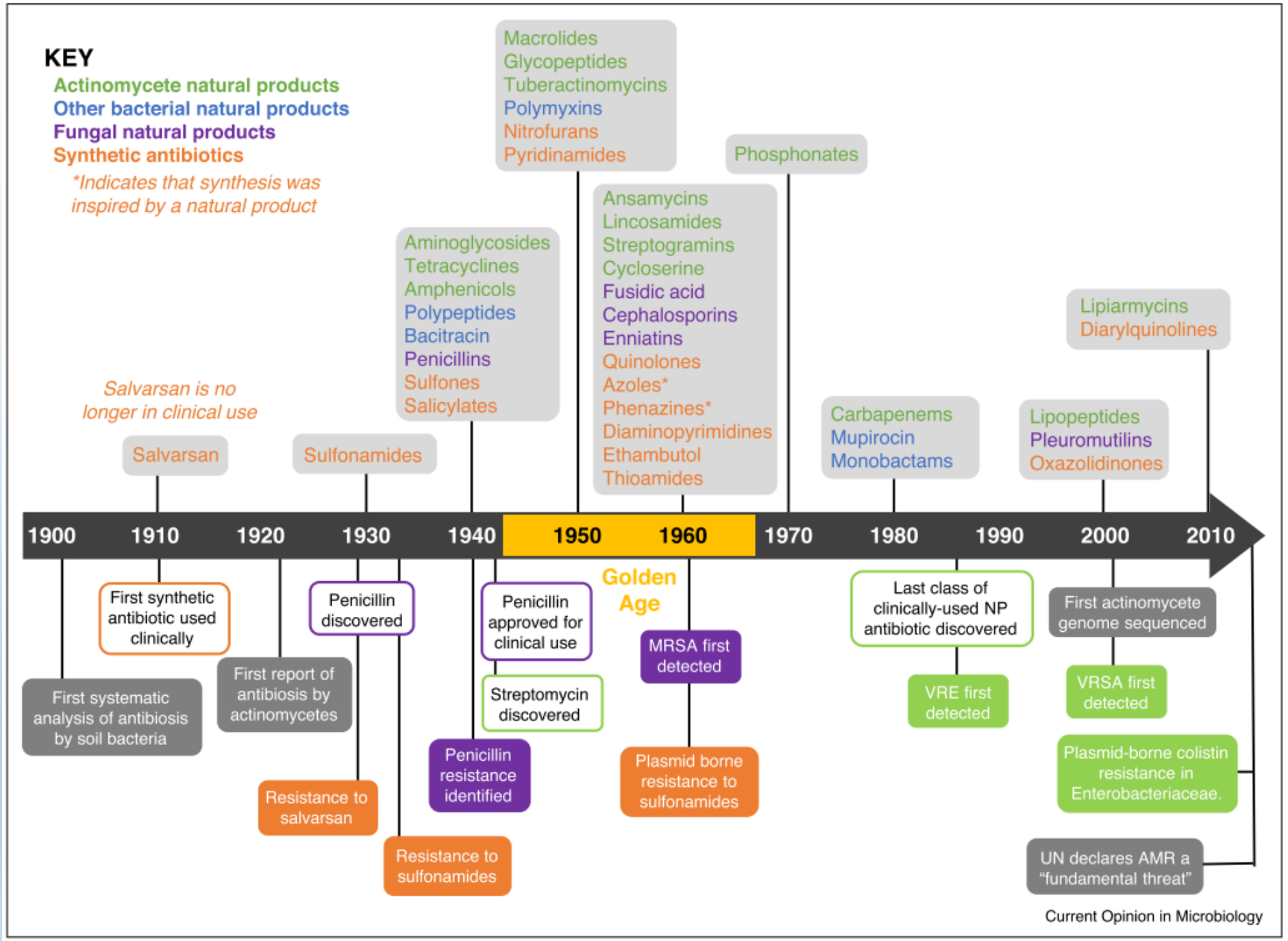
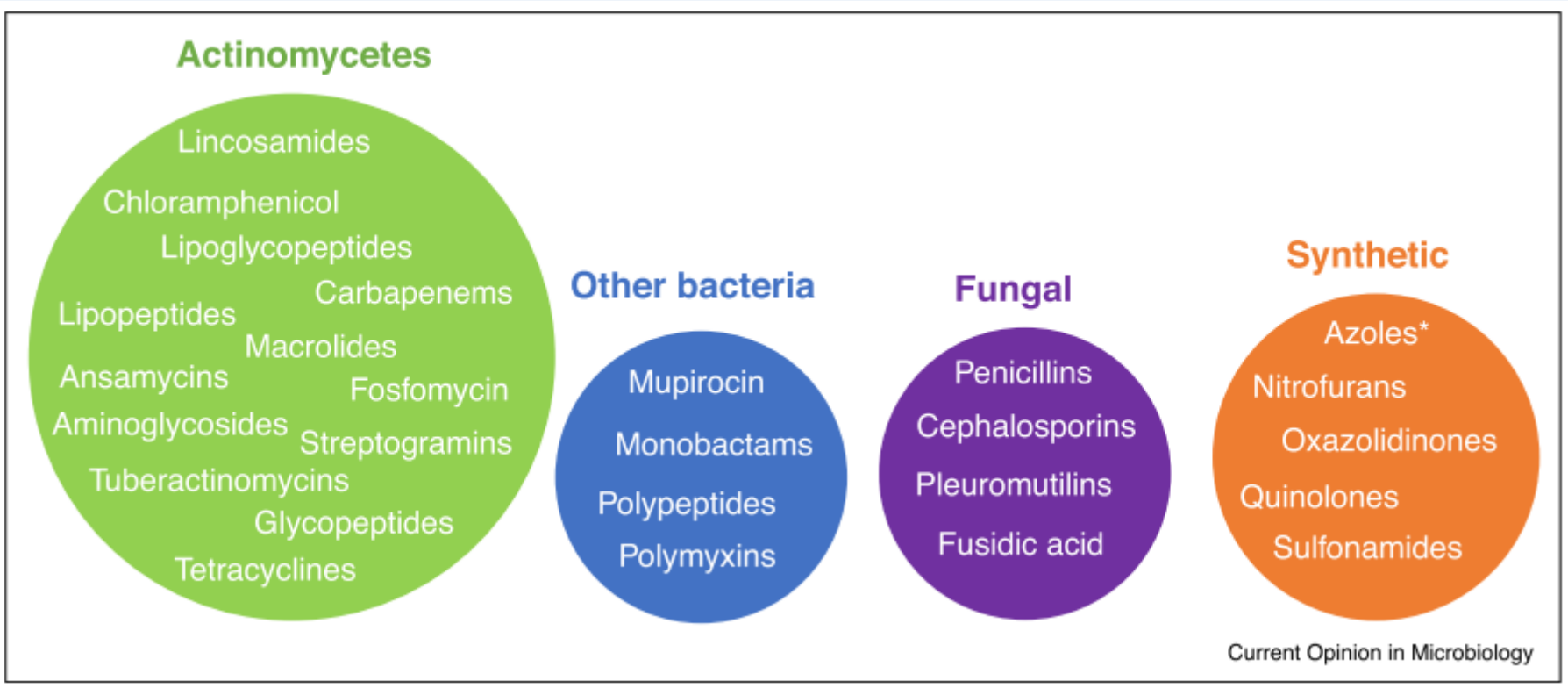
Nature derived antibiotics (produced by microorganisms)



Antibiotics: past, present and future. Matthew I Hutchings, Andrew W Truman and Barrie Wilkinson. The Current Opinion in Microbiology 2019, 51:72–80.

Most ATBs are derived from nature



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Clinically used ATBs (from actinomycetes)

- Aminoglycosides – Kanamycin A (*Streptomyces kanamyceticus*)
- Tetracyclines – Tetracycline (*Streptomyces aureofaciens*)
- Amphenicols – Chloramphenicol (*Streptomyces venezuelae*)
- Macrolides – Erythromycin (*Saccharopolyspora erythraea*)
- Glycopeptides – Vancomycin (*Amycolatopsis oirientalis*)
- Cycloserines – Seromycin (*Streptomyces orchidaceus*)
- Streptogramins – Pristinamycin (*Streptomyces pristinaespiralis*)
- Lipopetides – Daptomycin (*Streptomyces roseosporus*)

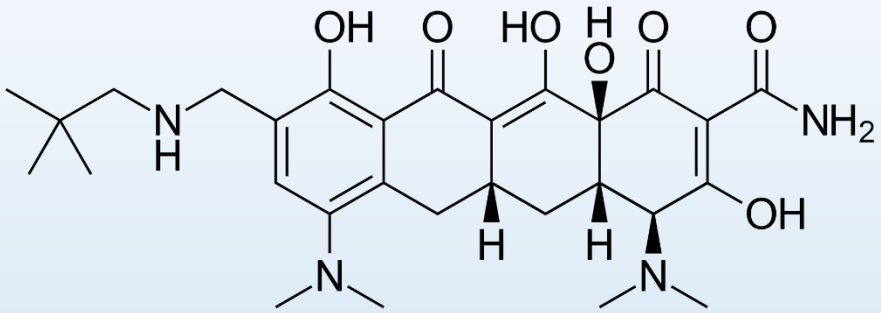
Clinically used ATBs (from other bacteria)

- Polypeptides – Gramicidin A (*Bacillus brevis*)
- Bacitracin – Bacitracin A (*Bacillus subtilis*)
- Polymyxins – Colistin (*Paenibacillus polymyxa*)
- Mupirocin – Mupirocin (*Pseudomonas fluorescens*)
- Monobactams – Aztreonam (semi synthetic, *Chromobacterium violaceum*)

Clinically used ATBs (from fungi)

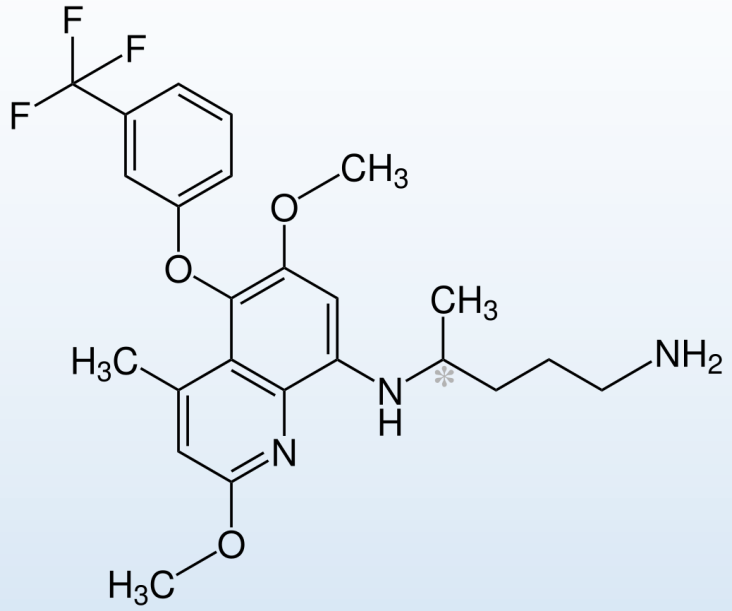
- Penicillins – Amoxicillin (semi synthetic, *Penicillinum chrysogenum*)
- Fusidic acid – (*Fusidium coccienum*)
- Enniatins – Fusafungine (*Fusarium lateritium*)
- Cefalosporins – Cefacetrile (*Acremonium chrysogenum*, semi syntetic)
- Pleuromutilins – Retapamulin (*Pleuritus mutilius*, semi syntetic)

2018 approvals



Omadacycline, brand name **Nuzyra**, is a broad spectrum antibiotic medication belonging to the aminomethylcycline subclass of tetracycline antibiotics. (bacterial pneumonia, acute skin infections)

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

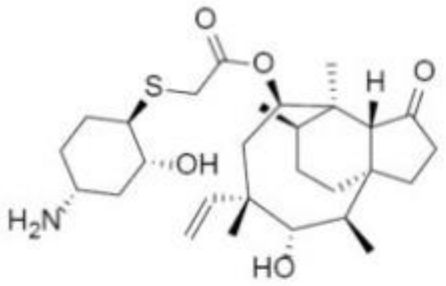


Tafenoquine, sold under the brand name **Krintafel**, is a medication used to prevent and to treat malaria. It may be used to prevent all types of malaria. Oral administration.

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

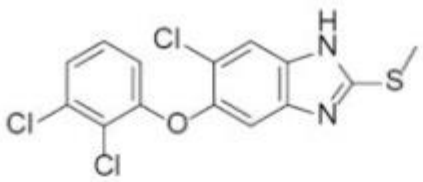
https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2018

2019 approvals



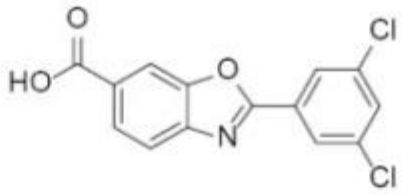
Lefamulin (Xenleta)

bact. ribosome 50S
bacterial pneumonia
oral: 600 mg BID



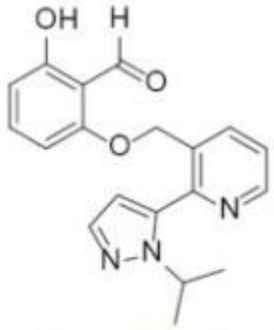
Triclabendazole (Egaten)

Fasciola anthelmintic
fascioliasis
oral: 10mg/kg BID



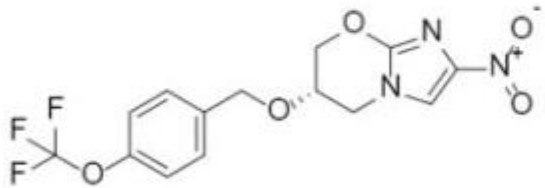
Tafamidis (Vyndaqel)

specific transthyretin stabilizer
cardiomyopathy
oral: 80 mg QD



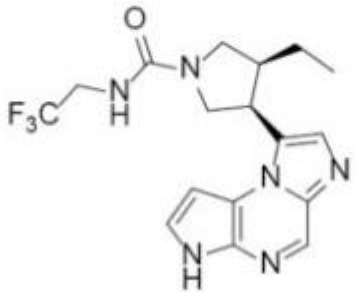
Voxelotor (Oxbryta)

HbS polymerization inhibitor
sickle cell disease
oral: 1500 mg QD



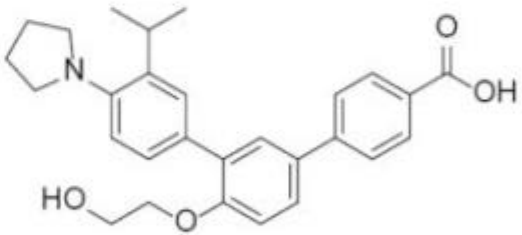
Pretomanid

mycolic acid biosynth. inh.
drug-resistant TB
oral: 200 mg QD



Upadacitinib (Rinvoq)

JAK1-sel. inhibitor
moderate/severe RA
oral: 15 mg QD

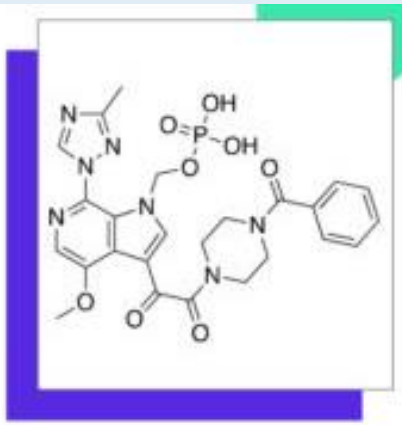


Trifarotene (Aklief)

RARγ-sel. agonist
acne vulgaris
topical only

https://drughunter.com/resource/2019newdrugs/

2020 approvals



fostemsavir (Rukobia)

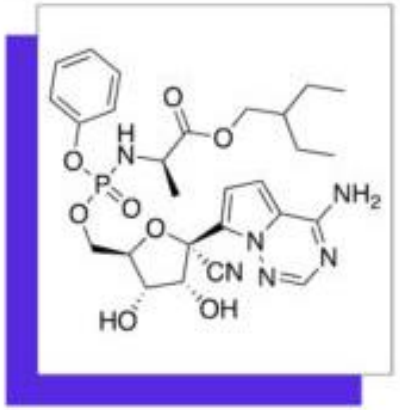
oral HIV-1 gp120 attachment inhibitor

600 mg BID

decline in HIV-1 RNA from d1-8 vs. placebo

NCT02362503/BRIGHTE (371 pts)

Infectious Disease - HIV



remdesivir (Veklury)

IV nucleotide RNA polymerase inhibitor

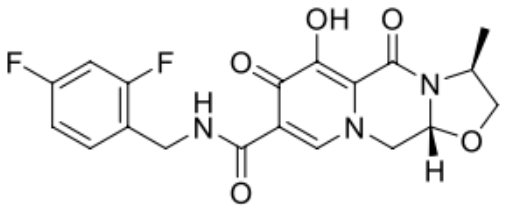
200 mg loading dose, 100 mg QD

time to recov., d11/14 clin. status category

04280705, 04292899/2730 (1062, 397, 584)

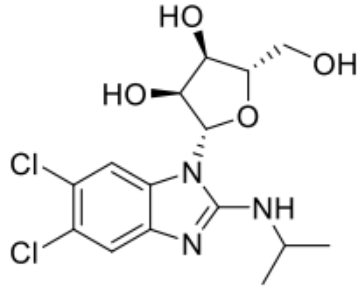
Infectious Disease - COVID-19

2021 approvals



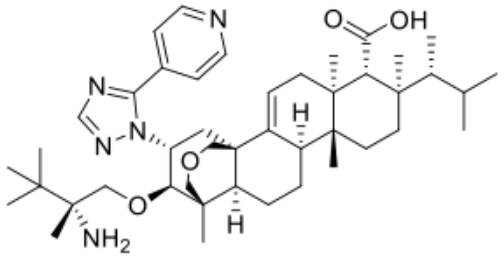
cabotegravir + rilpivirine (Cabenuva)

HIV1 integrase strand transfer inhibitor (INSTI)
HIV1 infection
IM: 400 + 600 mg Q1M*



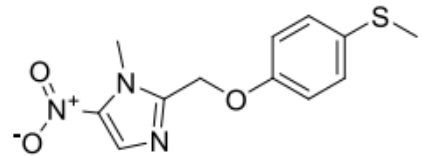
maribavir (Livtencity)

CMV pUL97 kinase inhibitor
post-transplant CMV infection
oral: 400 mg BID



ibrexafungerp (Brexafemme)

β-1,3-glucan synthesis inhibitor
vulvovaginal candidiasis
oral: 300 mg BID

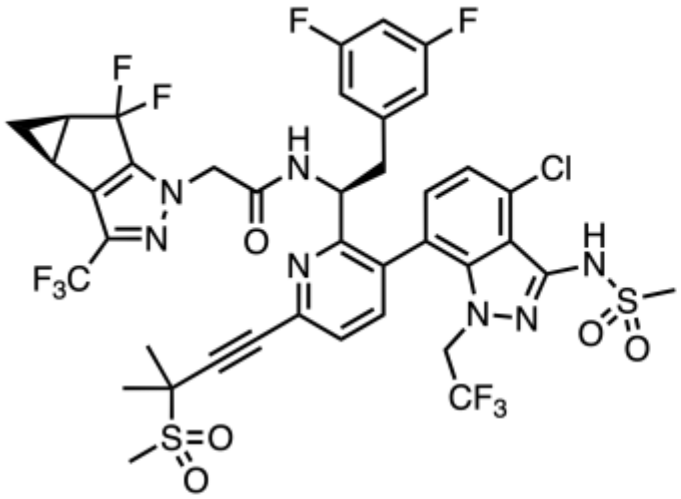


fexinidazole (Fexinidazole)

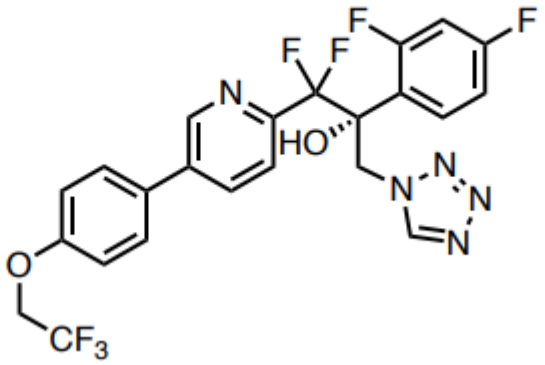
nitroimidazole antimicrobial
African trypanosomiasis
oral: up to 1200 mg QD

https://drughunter.com/wp-content/uploads/2022/01/2021-Small-Molecule-Drug-Approvals-Poster.pdf

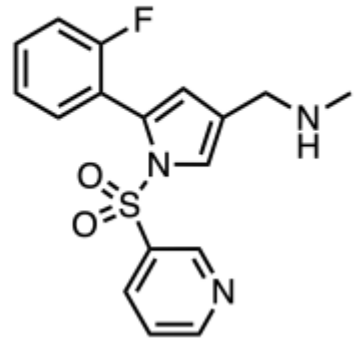
2022 approvals



Sunlenca,
HIV-1 capsid inhibitor
(lenacapavir)
for multidrug resistant HIV-1 infection
927 mg SC Q6M after loading period
GILEAD



Vivjoa, antifungal
(CYP51 inhibitor)
(oteseconazole)
for RVVC in non-reproductive females
600-150 mg oral 11 week regimen
MYCOVIA



Voquezna, K+/H+-ATPase
potassium channel blocker
(vonoprazan*, amoxicillin, and clarithromycin)
for H. pylori infection
20 mg BID for 14 days in combo
TAKEDA

Drug hunter 2022 approvals