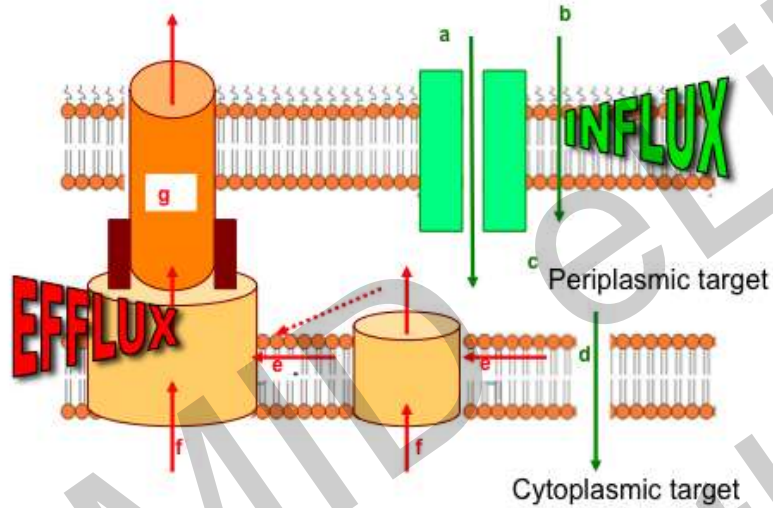




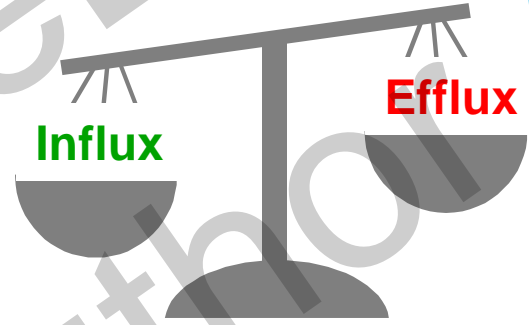
Targeting the membranes of the Gram-negatives

The intracellular concentration of drugs depends on:



- **Drugs** physicochemical properties,
- **Membrane** structure, e.g. proteins, LPS, lipids,
- **Diffusion pathway** : in Gram negatives porins are involved in the influx of a large majority of antibiotics (e.g. β -lactams, fluoroquinolones),
- Expression and activity of **efflux pumps**, e.g. AcrAB-TolC,
- **Synergy** between transporters.

Antibiotic Resistance : the membrane is the check point



Natural Resistance

- Impermeability
- Basal Efflux
-

Acquired Resistance

- Increased Impermeability
- Efflux Overproduction
-

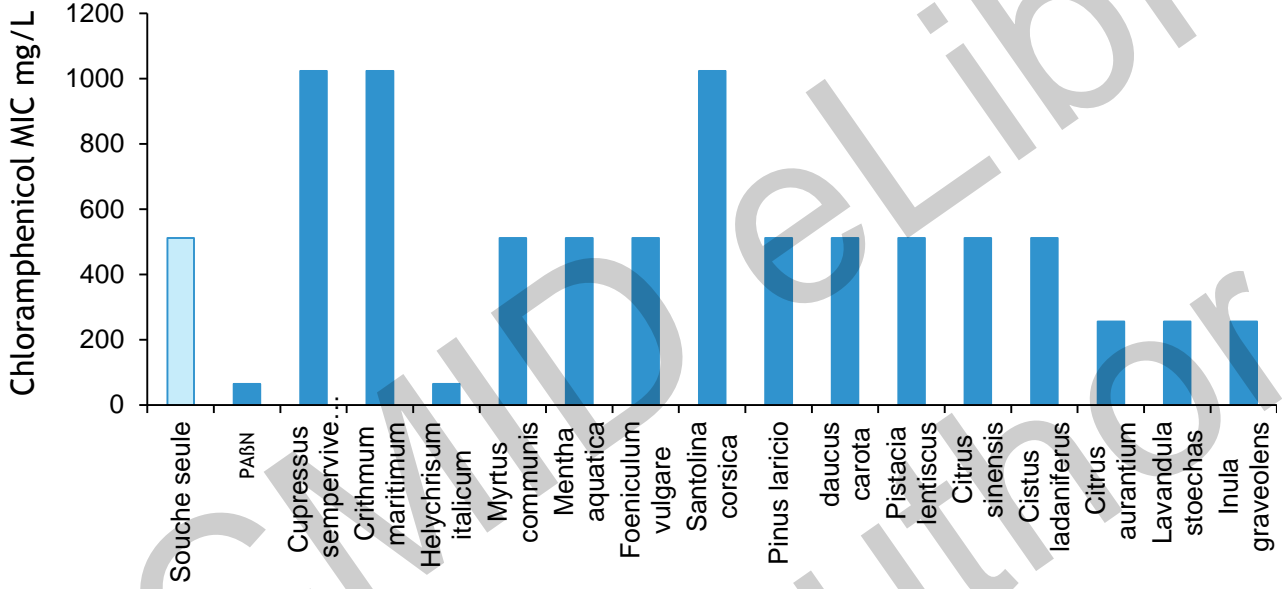
Four strategies being explored to overcome resistant bacteria

- Modify old molecules by a structure guided synthesis,
- Combining modern antibiotics in a one-two punch against infection,
- Find new compounds in Nature,
- Supplementing existing antibiotics with adjuvants that can render resistant pathogens susceptible once more.

Four strategies being explored to overcome resistant bacteria

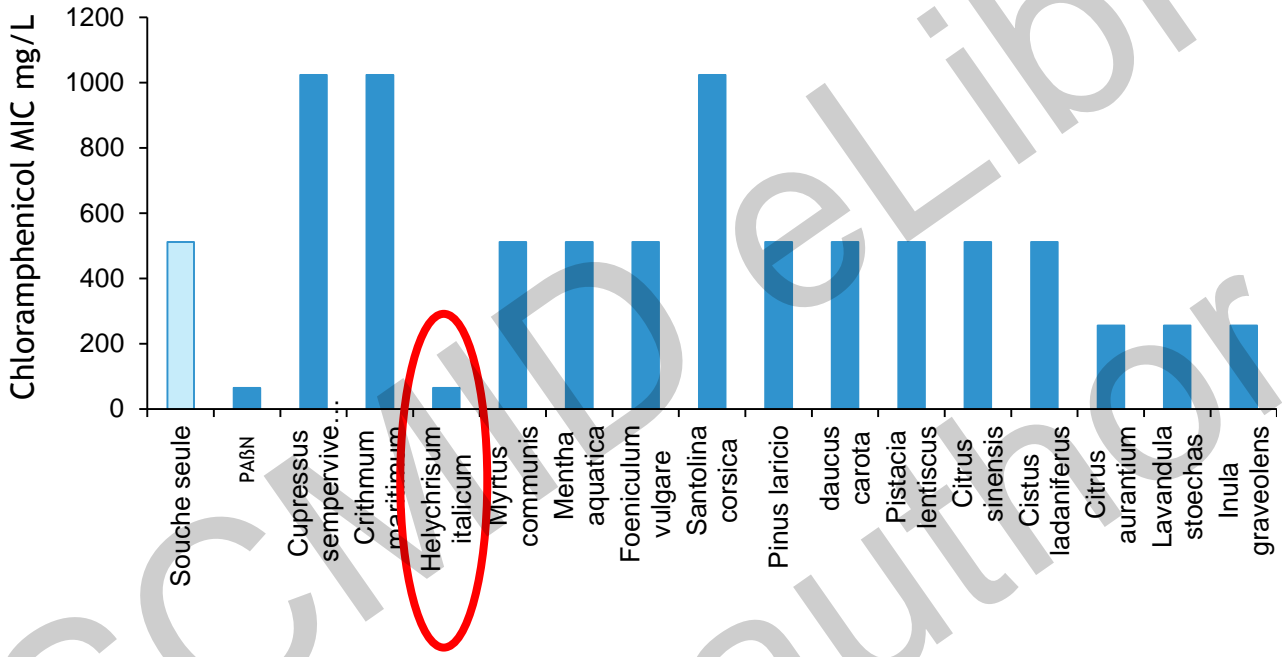
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Adjuvants from nature



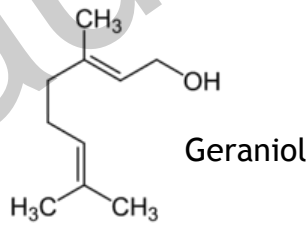
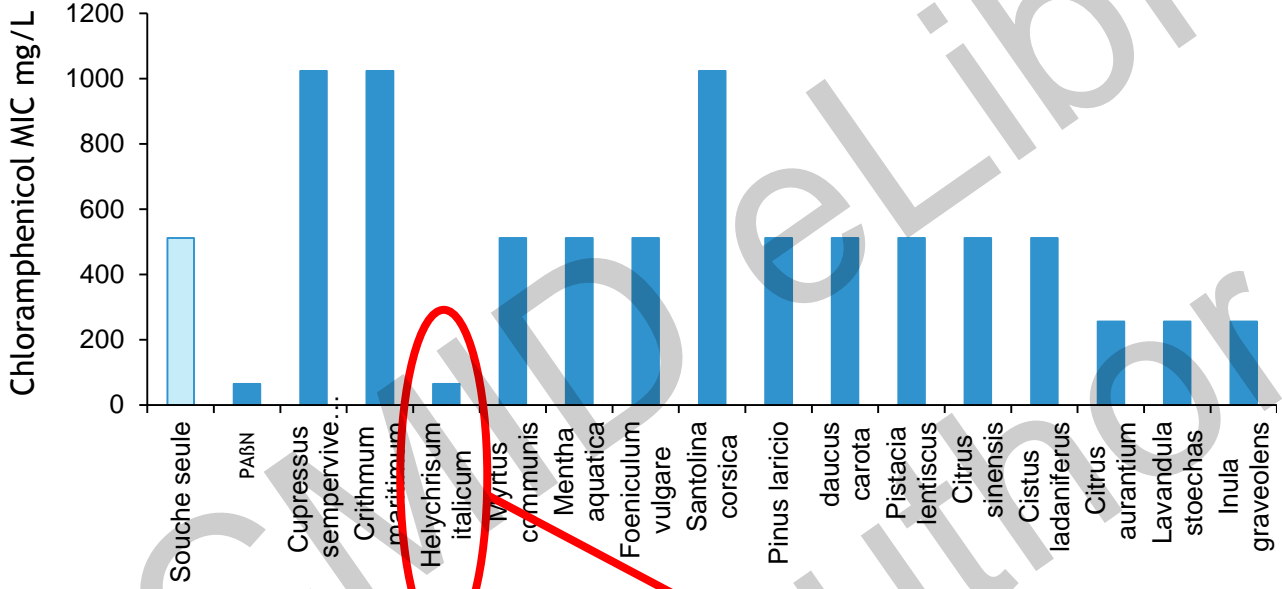
Essential oils from Corsica as adjuvants to Chloramphenicol

Adjuvants from nature

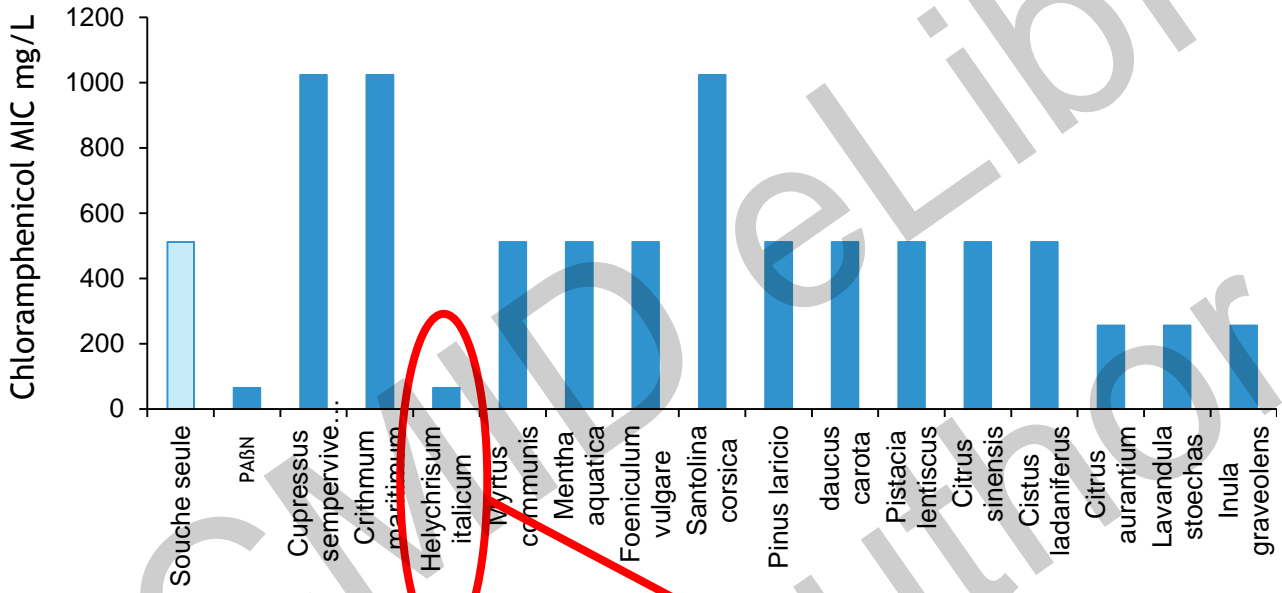


Essential oils from Corsica as adjuvants to Chloramphenicol

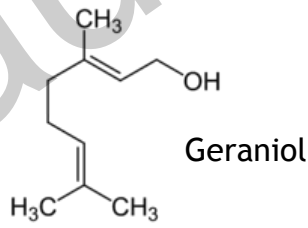
Adjuvants from nature



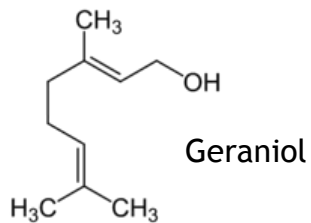
Adjuvants from nature



Added compound	Chloramphenicol MIC MDR strain
-	512
HI	128
geraniol	64



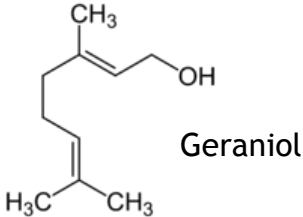
From nature to Chemistry



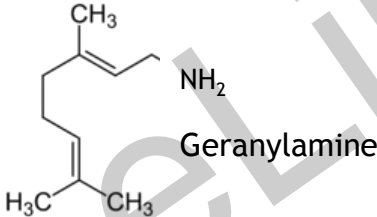
Water-Insoluble

ESCMID eLibrair
by author

From nature to Chemistry

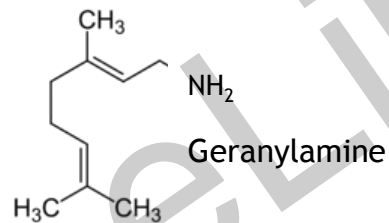
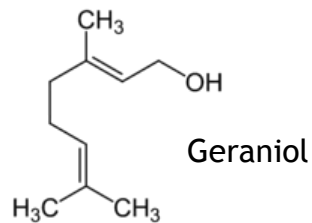


Water-Insoluble

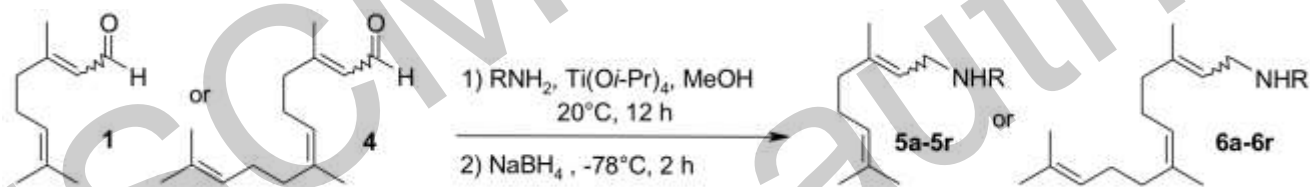


Soluble as hydrochloride

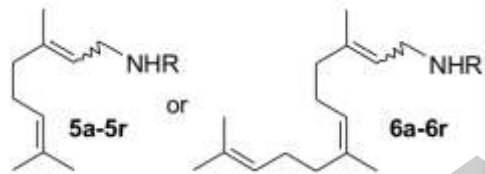
From nature to Chemistry



Synthesis of Polyamino-isoprenyl derivatives
obtained from citral (5a-5r) or farnesal (6a-6r)

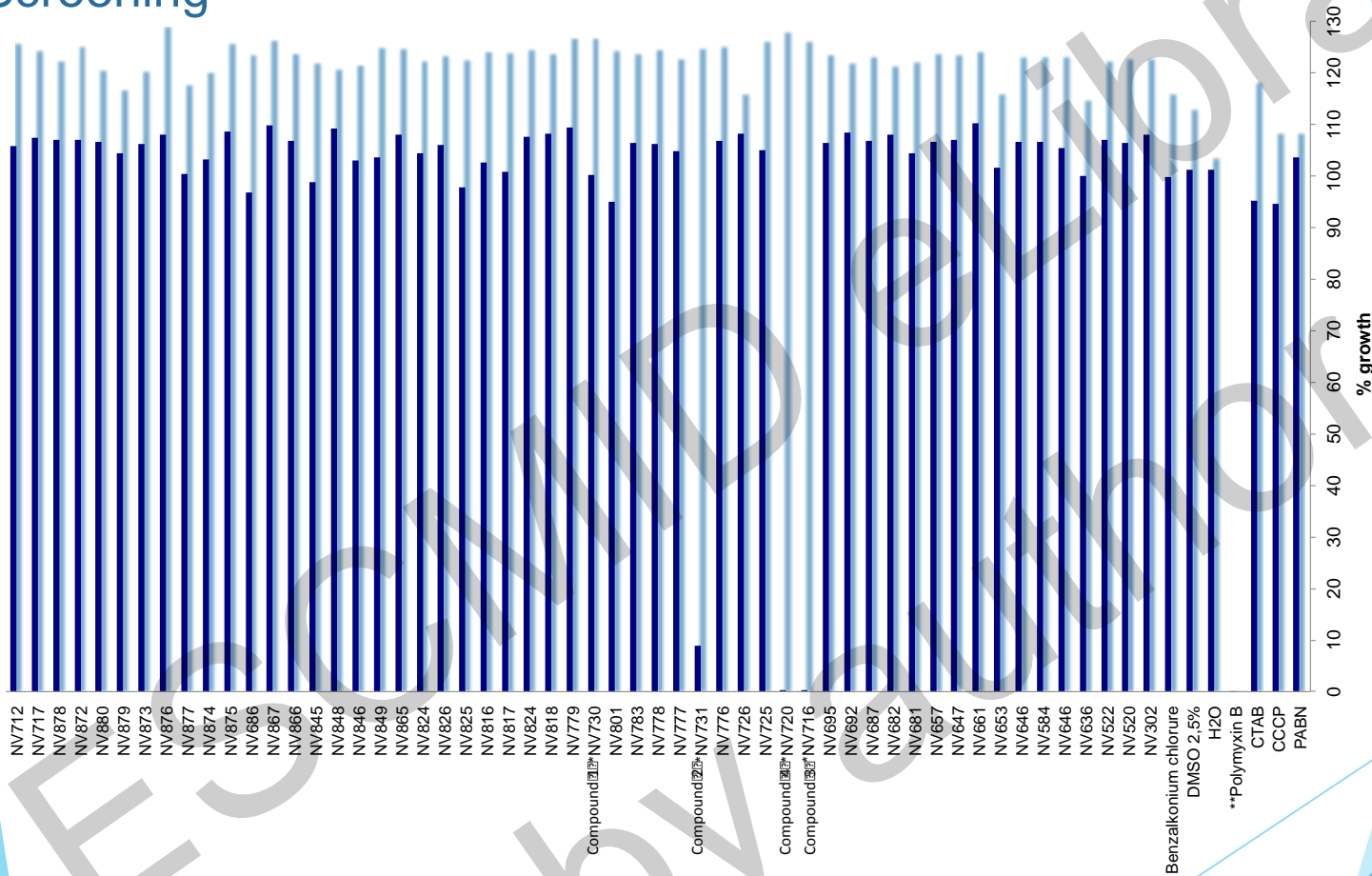


The Chemical Library



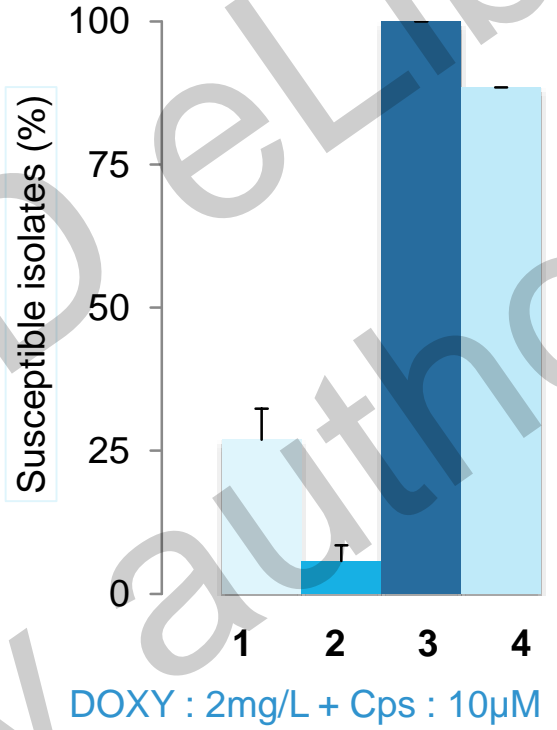
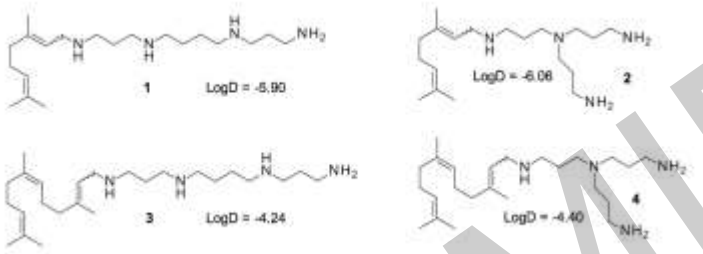
RNH ₂	Isolated Yield (%)		IC ₅₀ (μM) CHO	
	5a-5r	6a-6r	5a-5r	6a-6r
<chem>NCCCN</chem>	5a 49	6a 63	36.24	32.30
<chem>NCCCCN</chem>	5b 33	6b 49	>150	32.06
<chem>NCCCCCN</chem>	5c (NP)	6c 58	-	18.06
<chem>NCCCCCCN</chem>	5d (NP)	6d 38	-	38.38
<chem>NCCCN1CCCN1</chem>	5e 61	6e 71	>150	85.33
<chem>NCCCN1CC(=O)CC1</chem>	5f 51	6f (NP)	>150	-
<chem>NCCCN1CCOC1</chem>	5g 52	6g 56	>150	57.64
<chem>NCCCN1CCN(CCCN)CC1</chem>	5h (NP)	6h 62	-	33.75
<chem>NCCCN1CCN(CCCN)CC1</chem>	5i (NP)	6i 52	-	30.19
<chem>NCCCN1CCN(CCCN)CC1</chem>	5j 42	6j 58	>150	10.47
<chem>NCCCN1CCN(CCCN)CC1</chem>	5k 49	6k (NP)	30.92	-
<chem>NCCCN1CCN(CCCN)CC1</chem>	5l 64	6l (NP)	>150	-
<chem>NCCCN1CCN(CCCN)CC1</chem>	5m (NP)	6m 32	-	43.50
<chem>NCCCN1CCN(CCCN)CC1</chem>	5n 58	6n 47	>150	41.71
<chem>NCCCCCCCCCCCCCN</chem>	5o (NP)	6o 48	-	25.32
<chem>NCCCCCN1CCN(CCCN)CC1</chem>	5p 64	6p 72	>150	142.79
<chem>NCCCCCN1CCOCCN1</chem>	5q (NP)	6q 43	-	>150
<chem>NCCCCCN1CCN(CCCN)CC1</chem>	5r 49	6r (NP)	-	-

Screening

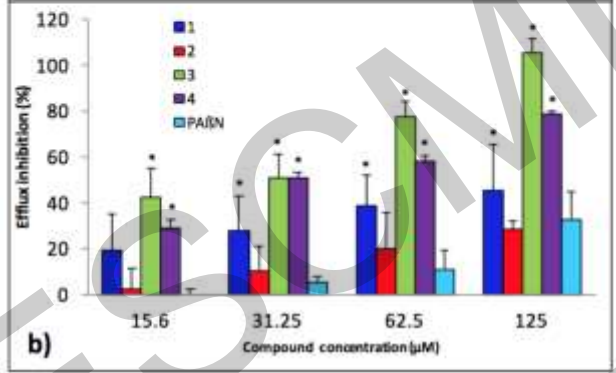
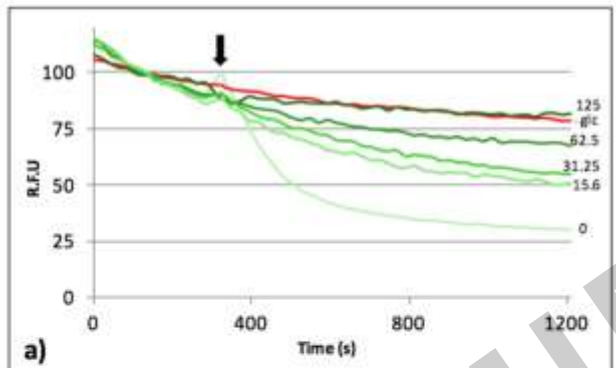


Strain PA01, Doxycycline 4 mg/L, Compounds 10 µM

Synergy with doxycycline on clinical isolates

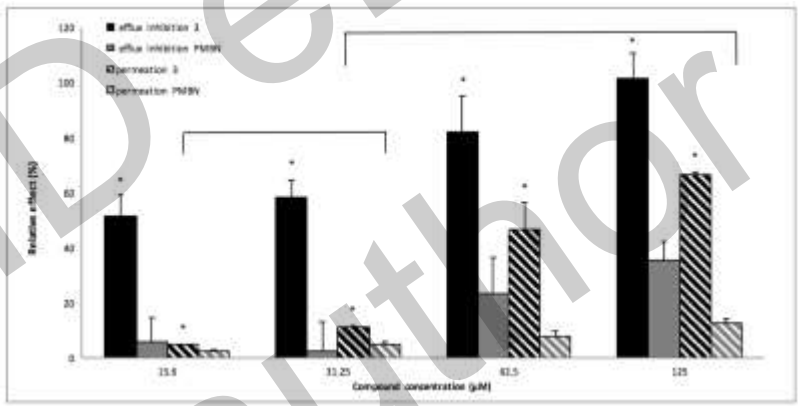
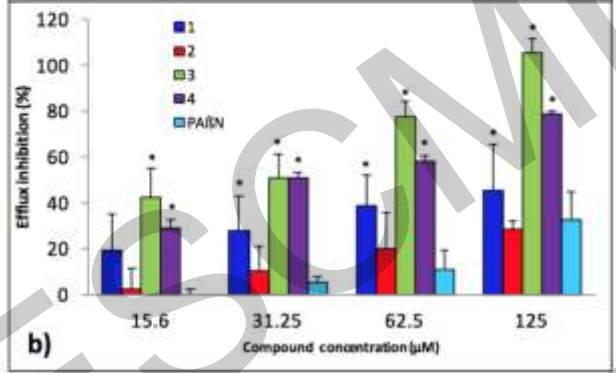
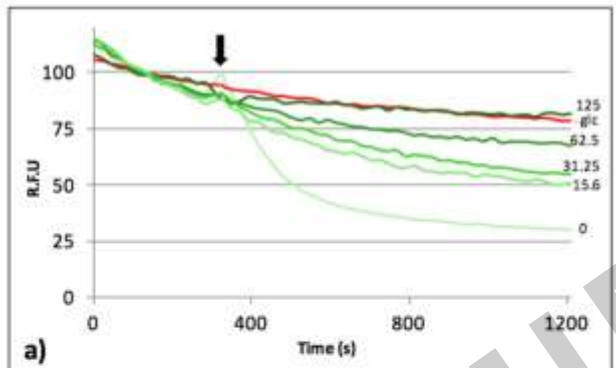


Mode of action on *Pseudomonas aeruginosa*



Real Time Efflux Inhibition

Mode of action on *Pseudomonas aeruginosa*

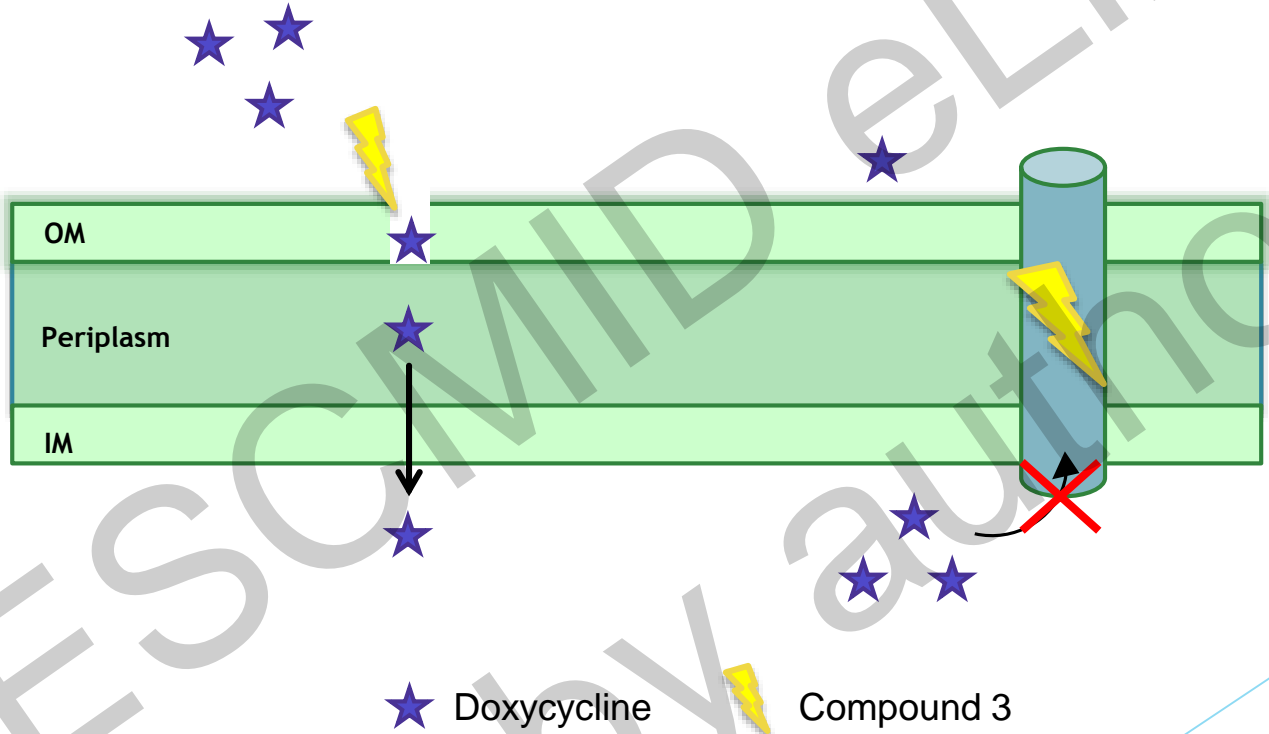


Outer Membrane Permeabilization

Real Time Efflux Inhibition

Conclusion

- Compound 3 improve doxycycline action
- by targeting natural resistance



They did the job...

- Diane Borselli, Ph-D



- Aurélie Lieutaud, RI



- Jean-Marie Pagès, Lab Director



- The chemist : Jean-Michel Brunel



Thank you...

