

Discovery of a Structural Class of Antibiotics with Explainable Deep Learning

Presenter: Farid Afshari Zadeh

Supervisor: Dr. Karbasi Zadeh

Introduction

- Antibiotic Resistance Crisis
- New approach to discover Antibiotics

GLOBAL

A failure to address the problem of antibiotic resistance could result in:

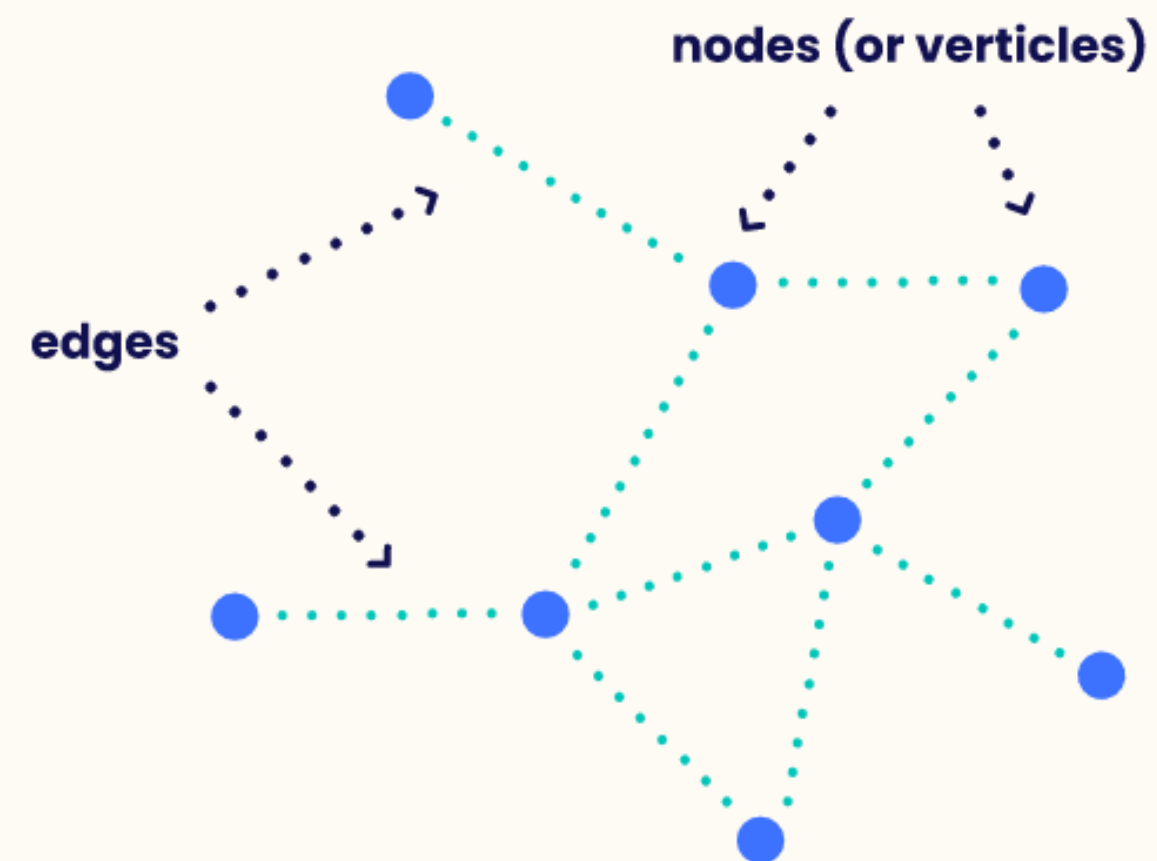
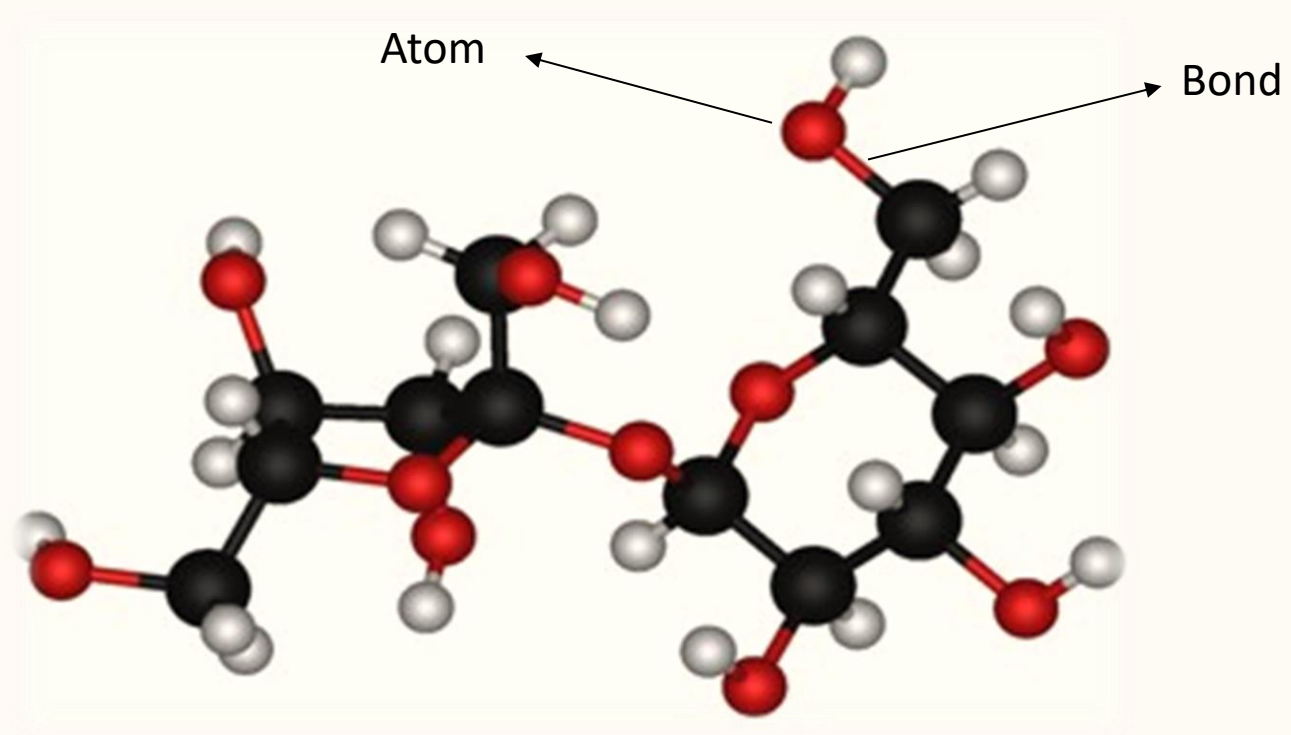


10m
deaths
per year
by 2050

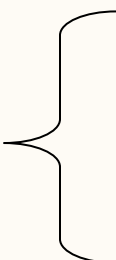
Costing
\$100
trillion
in economic output

Model Education

Graph Neural Network (GNN)

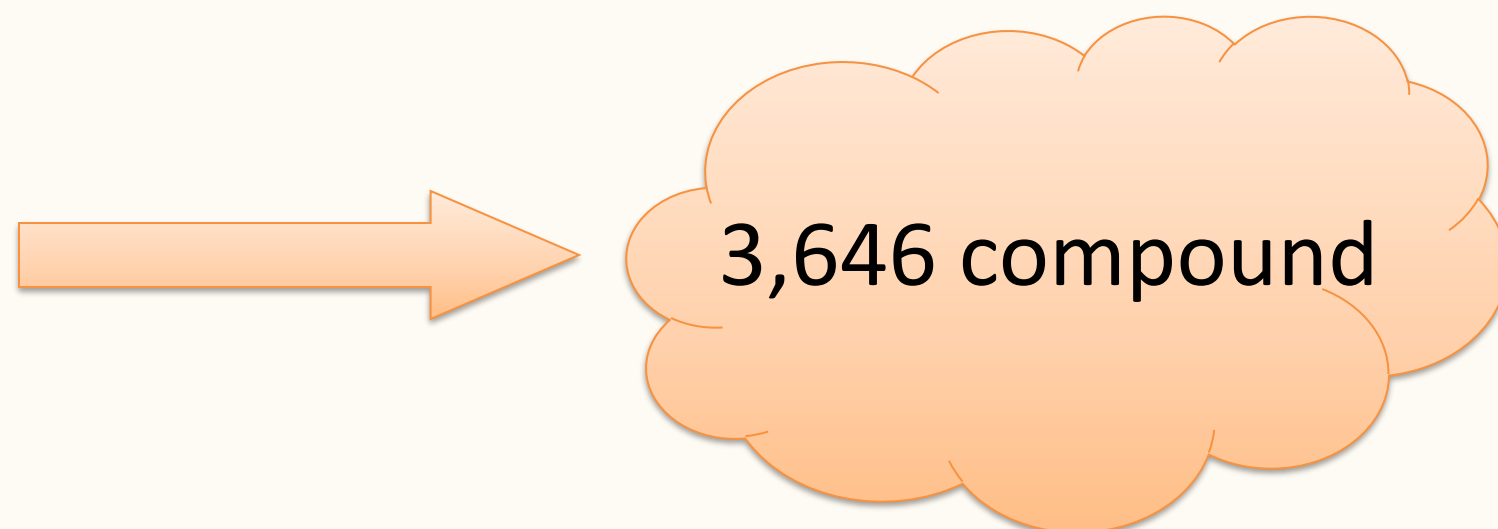


Developing Models for antibiotic activity

- ❖ Filtering **39,312** antibacterial compounds based on 
 - activity against *S.aureus*
 - cytotoxicity
- ❖ Of the 39,312 antibacterial compounds, **306** were active against *S.aureus* non-cytotoxic for cell types.

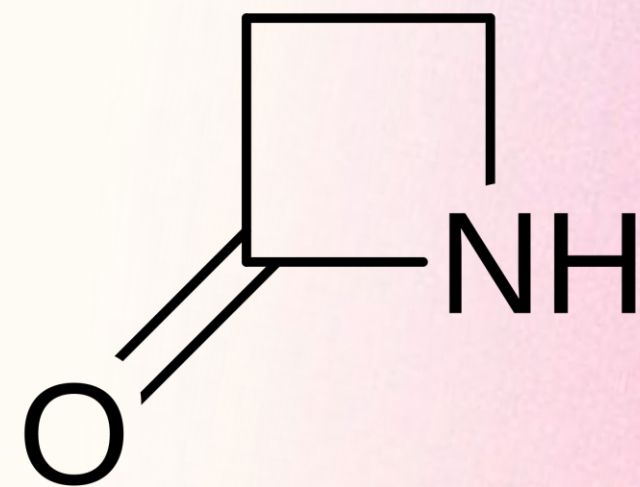
Filtering and visualizing chemical space

- 12 million compound
- Filtered based on
 - Antibiotic activity > 0.4
 - Cytotoxicity < 0.2



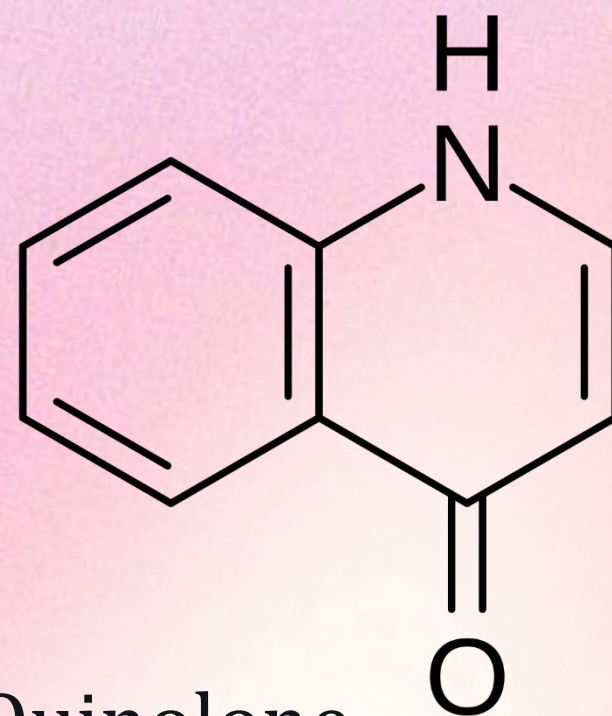
Leave-One-Out analyses

At least 4 similar atom

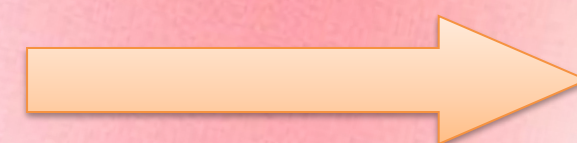


β -Lactam

At least 11 similar atom



Quinolone

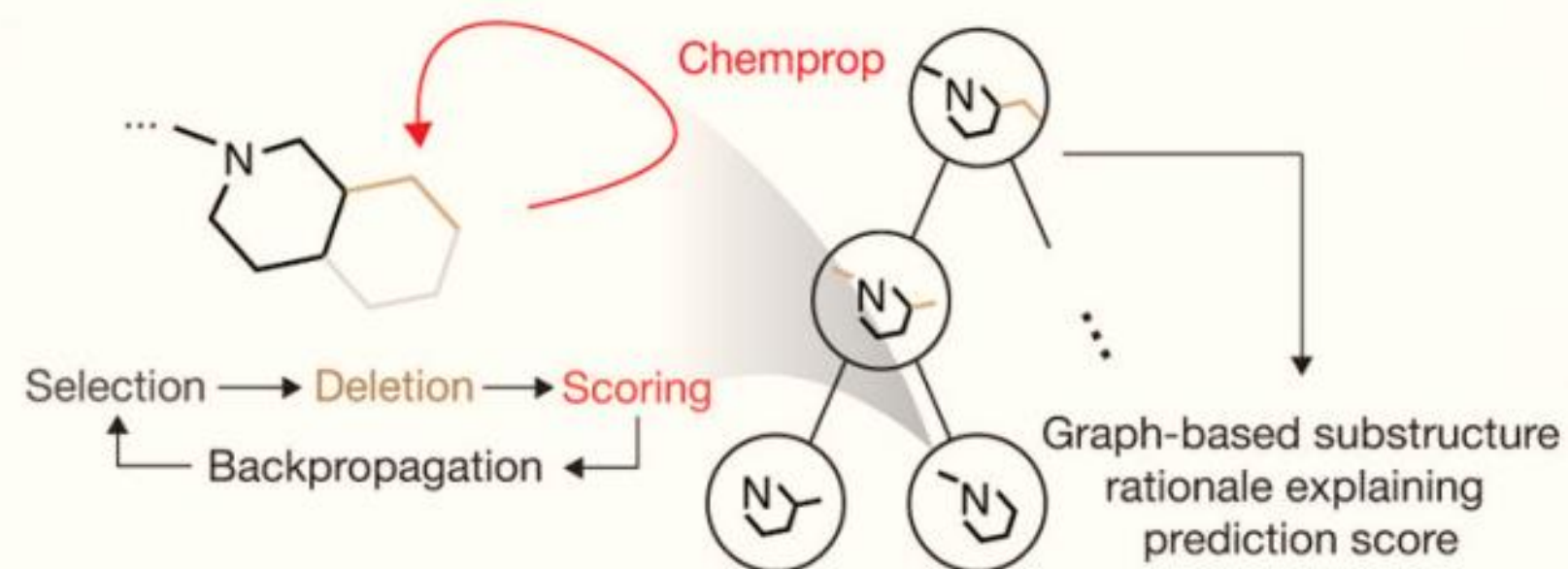


1,261 compound

Rationales predict antibiotic classes

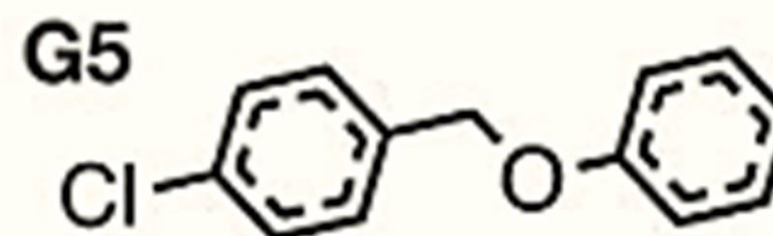
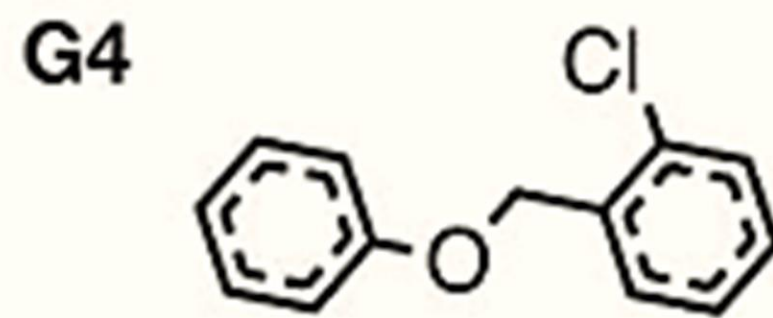
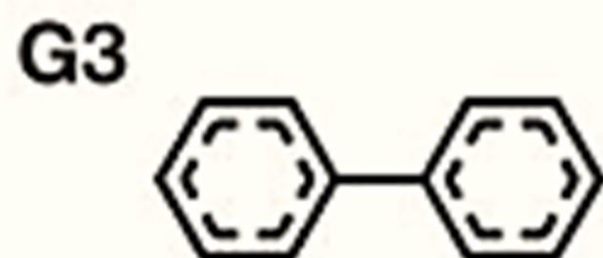
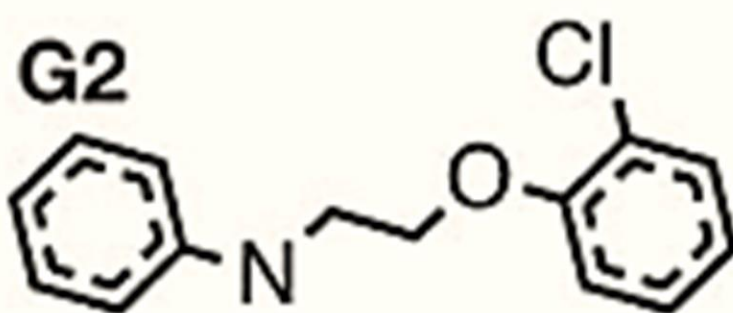
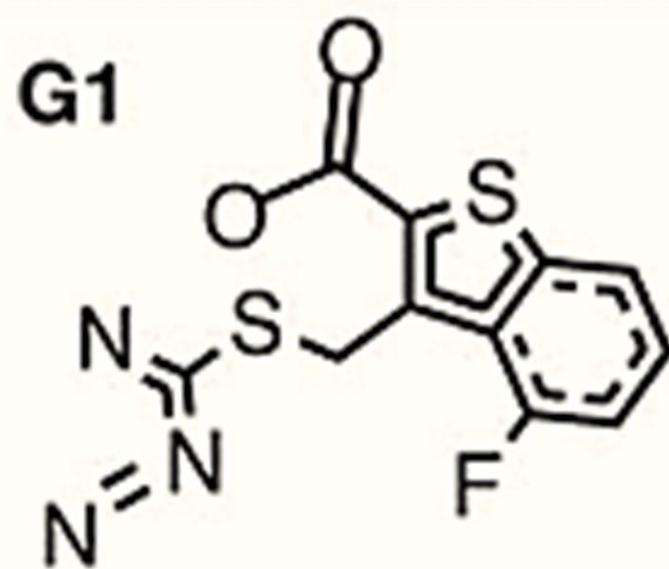
Finding Substructures:

- at least 8 atoms and
- antibiotic prediction scores >0.1



186 compound

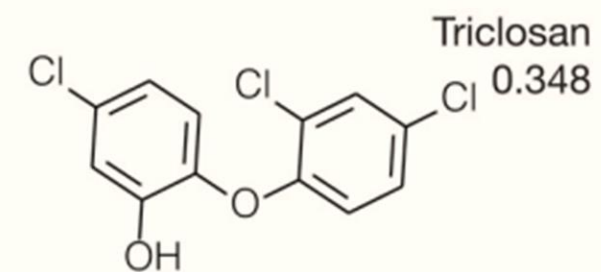
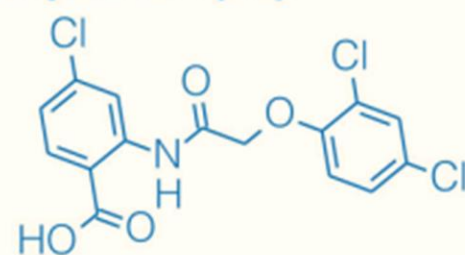
Novel, Filtered Substructures



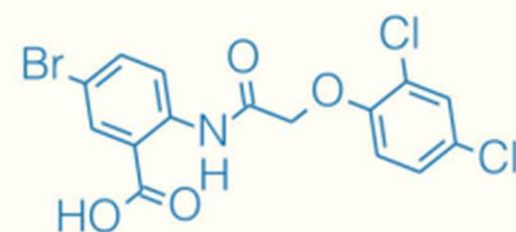
9 of 186 hits with
rationales
associated with 5
scaffolds

A structural class of antibiotics from rationales

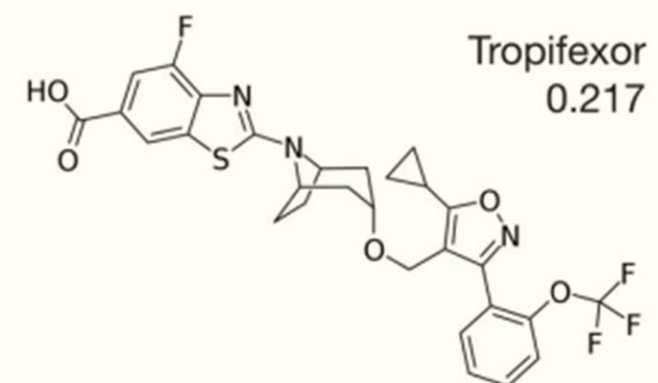
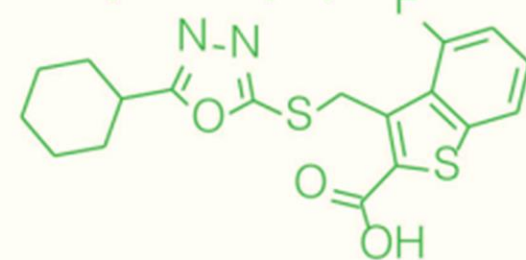
Compound 1 (G2)



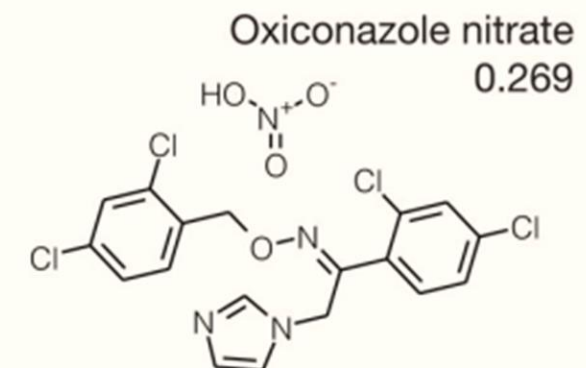
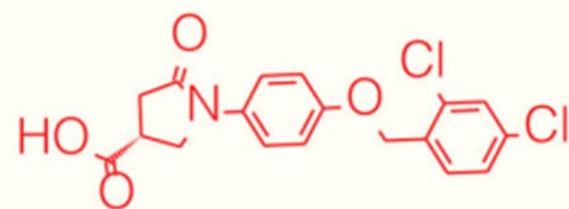
Compound 2 (G2)



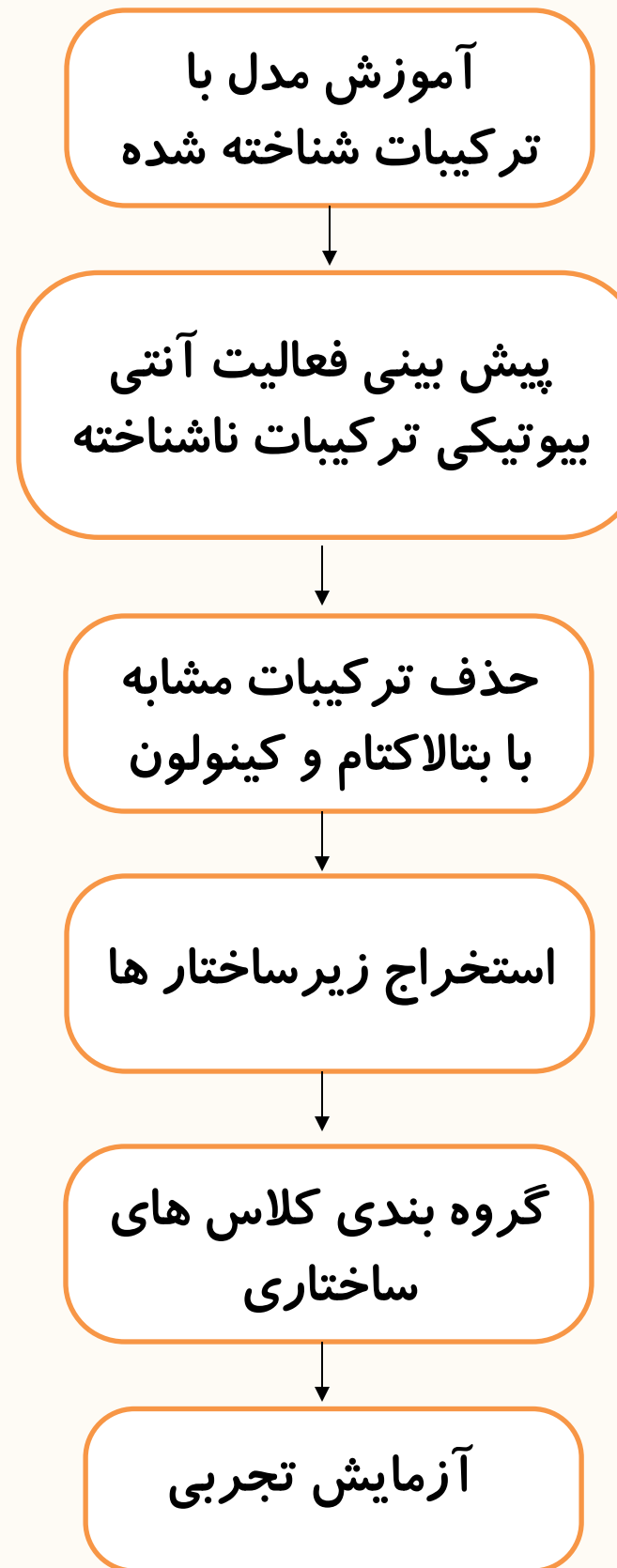
Compound I (G1)



Compound II (G5)



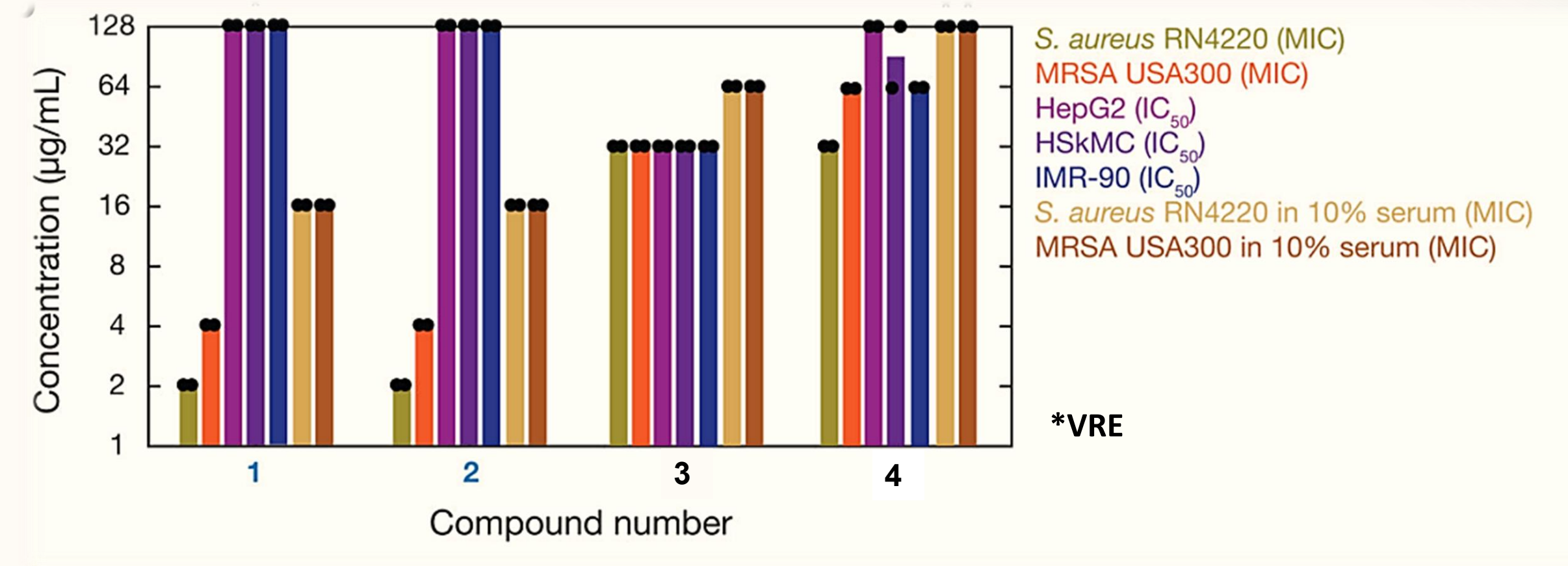
Overview



Final testing of active compounds

Cell Types Tested

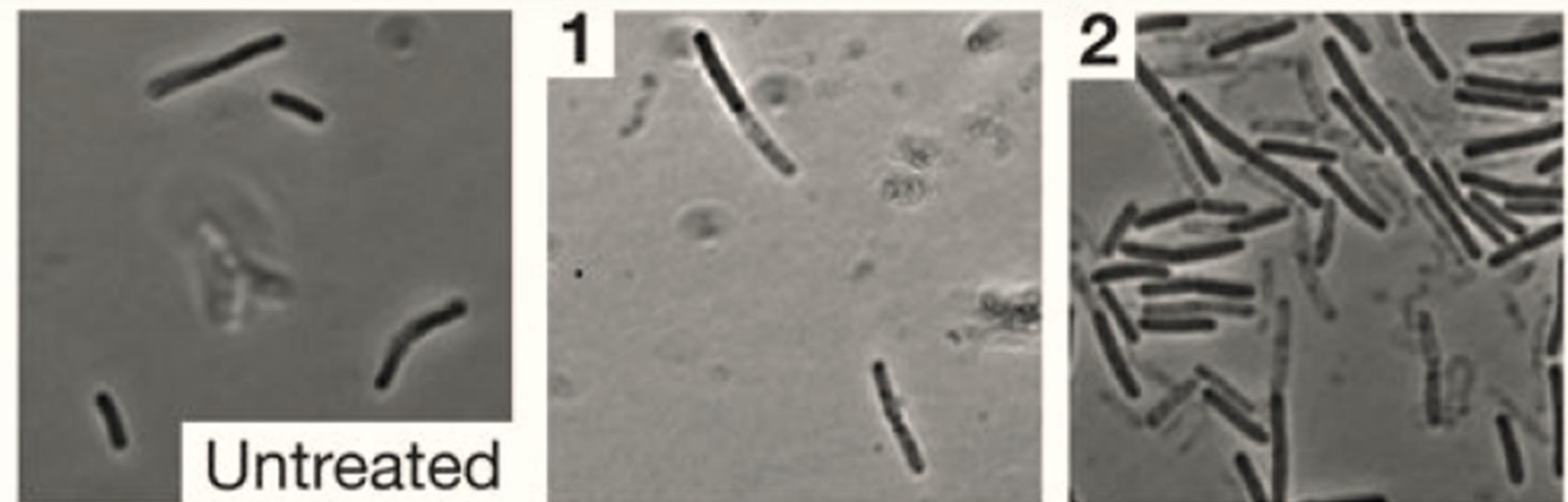
- HepG2 (human liver carcinoma cells)
- HSkMCs (human primary skeletal muscle cells)
- IMR-90 (human lung fibroblast cells)



Mechanism of action and resistance



Phenotypic Effects



B. subtilis 168

N-[2-(2-chlorophenoxy)ethyl]aniline

❖ cell membrane disruption

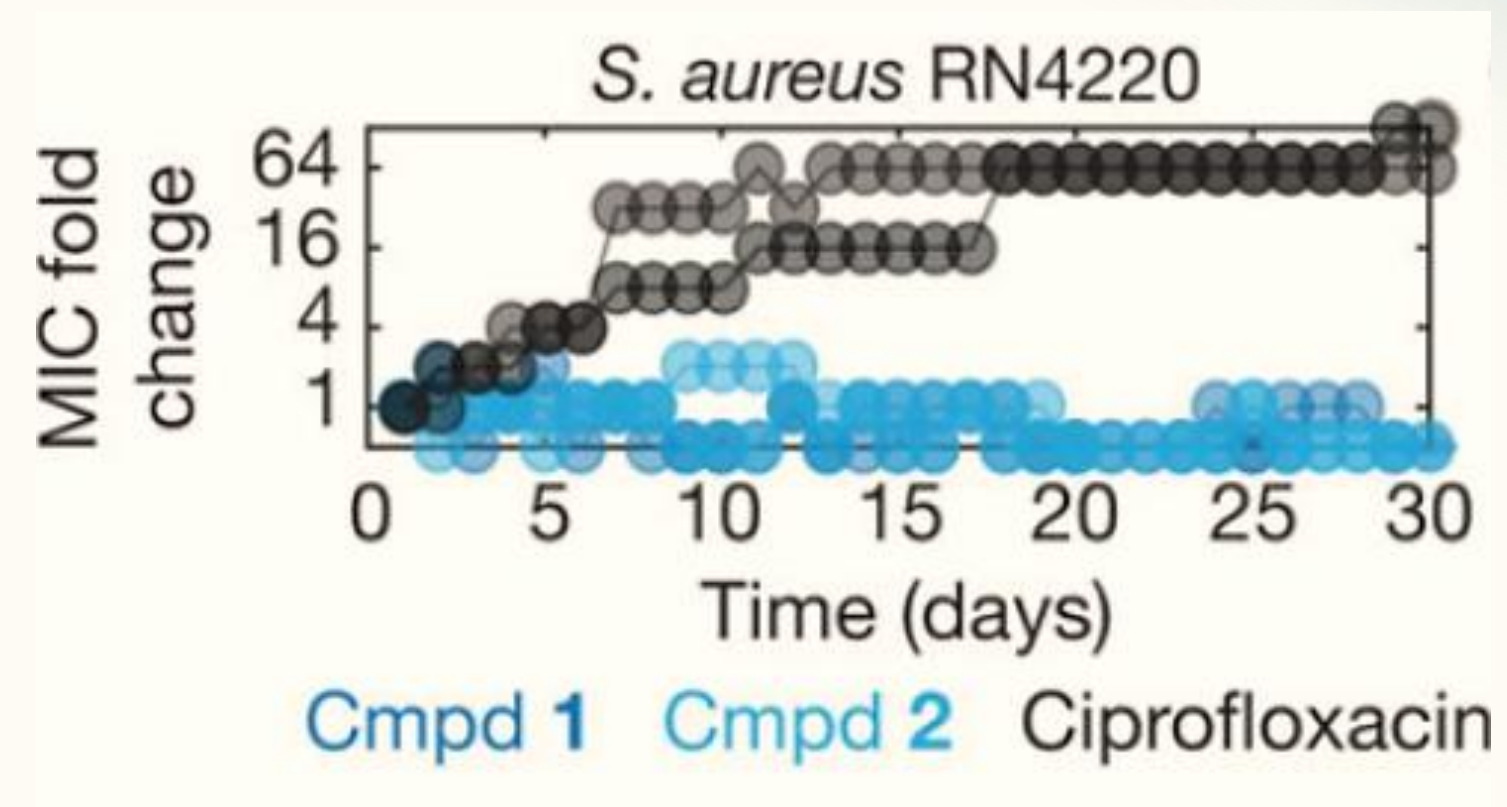
Mechanism of action and resistance

Using DiSC3 (PMF sensitive dye)

❖ $\Delta\Psi$

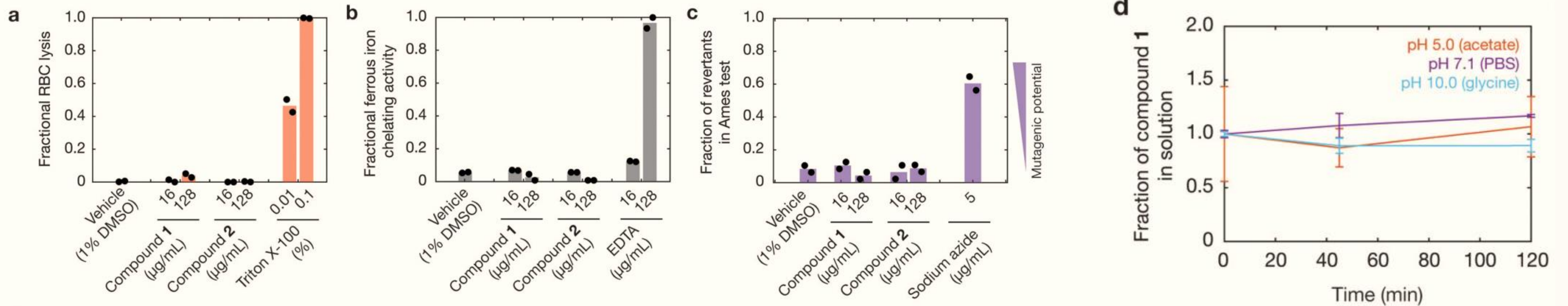
❖ ΔpH

Serial passage



Toxicology and chemical properties

- Hemolysis
- Iron binding
- Genotoxicity
- Chemical stability



Ex vivo human skin toxicity

❖ Non-toxic at 1%

Vehicle



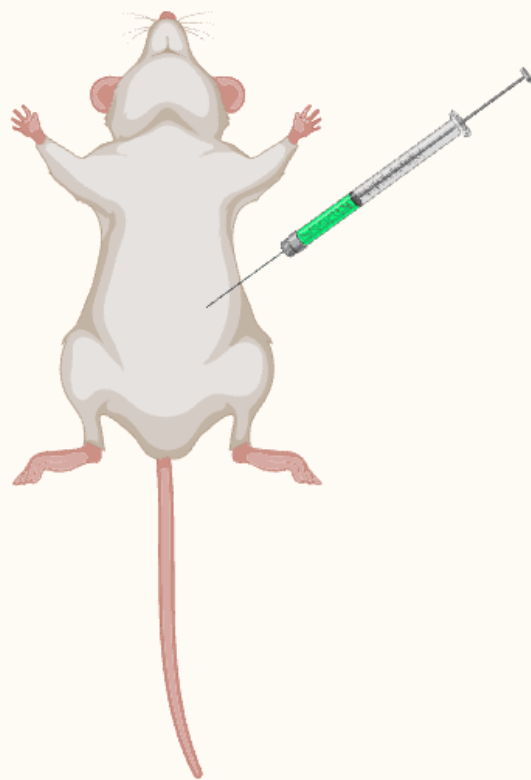
Compound **1** (1%)



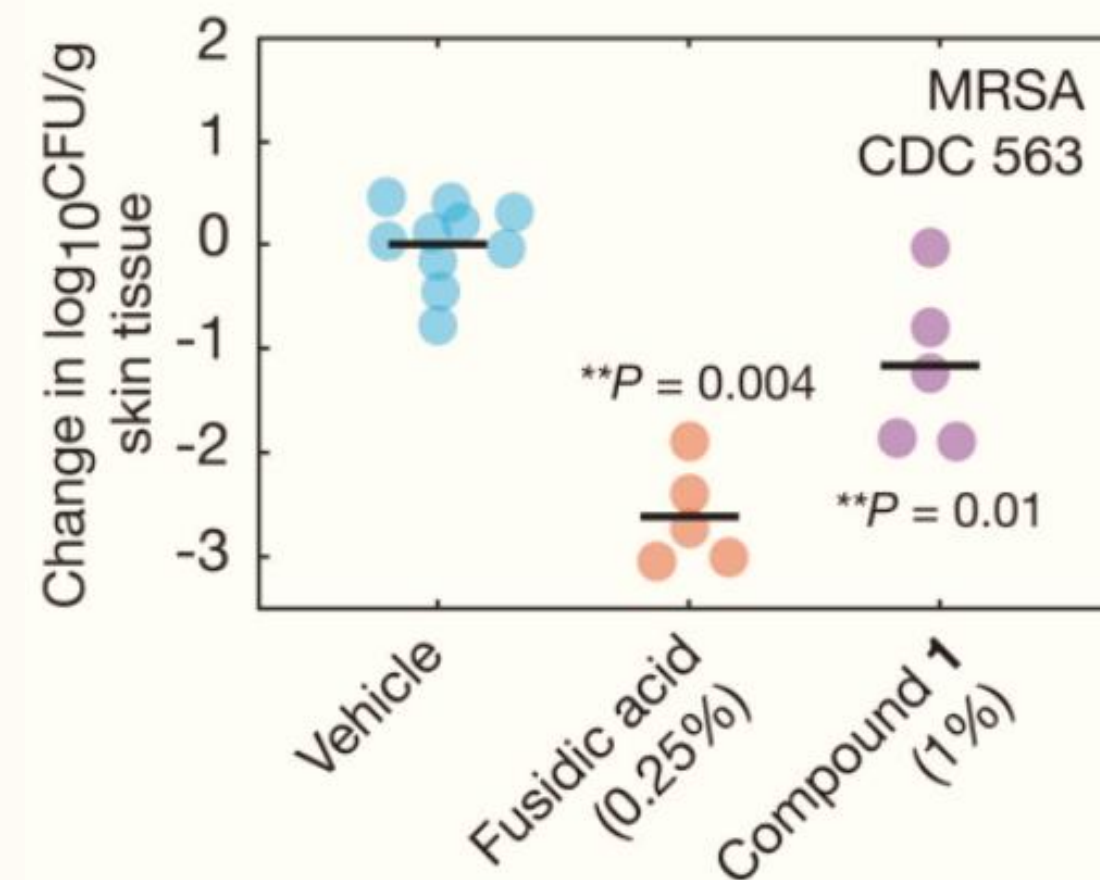
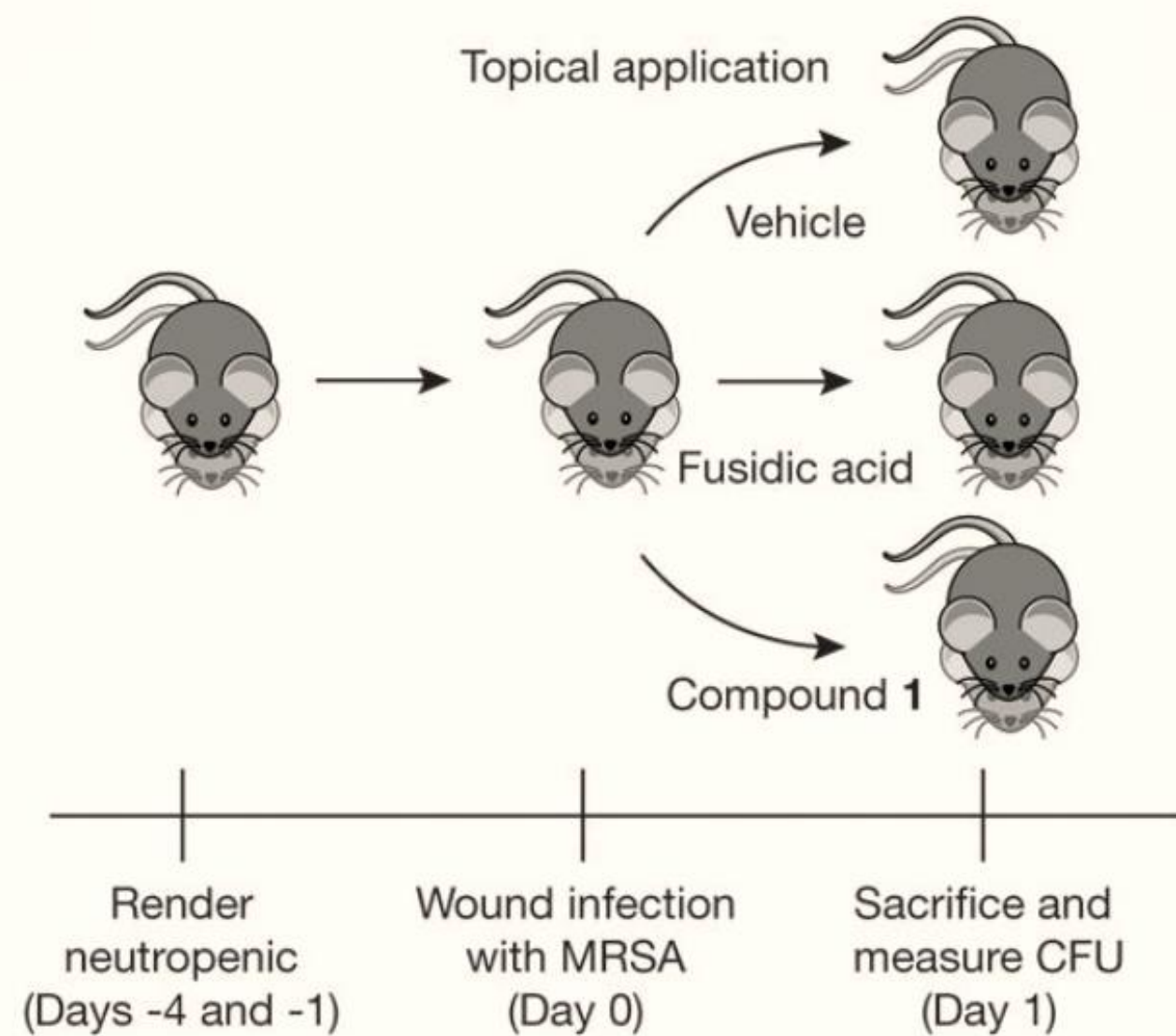
In vivo mouse toxicity

❖ Tolerated at 80 mg/kg

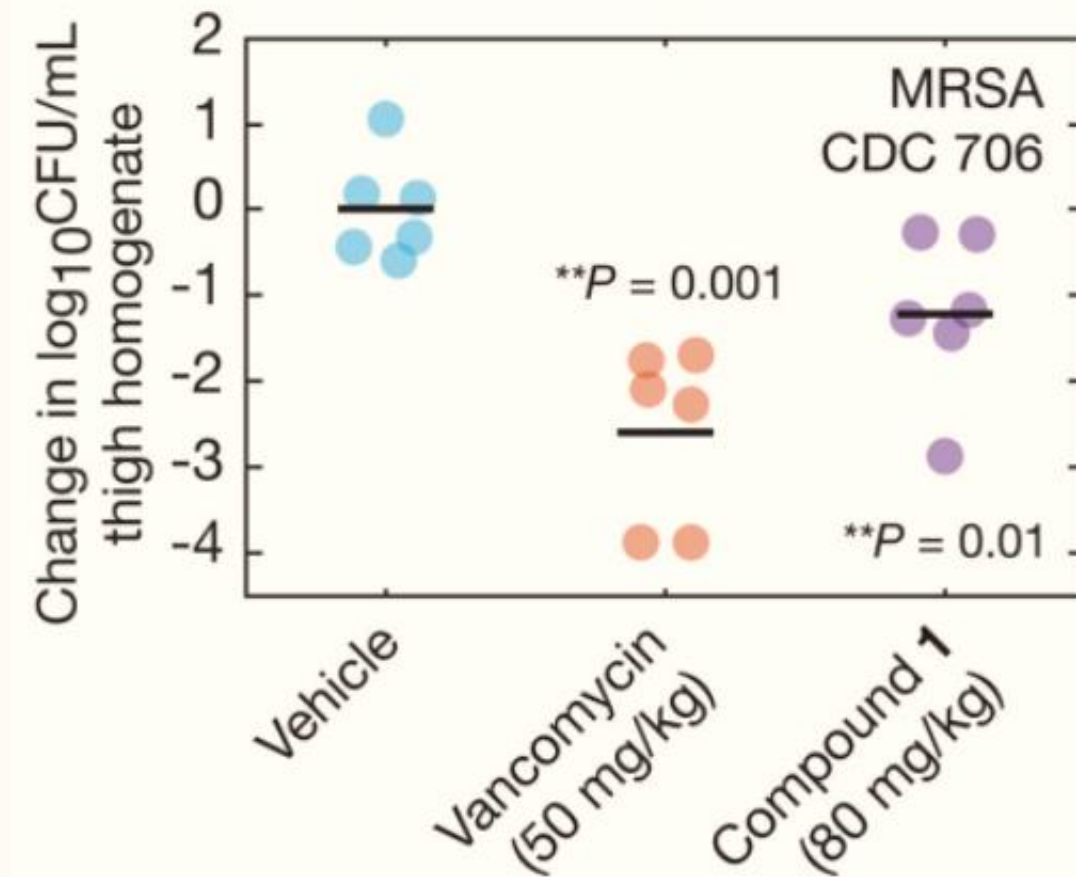
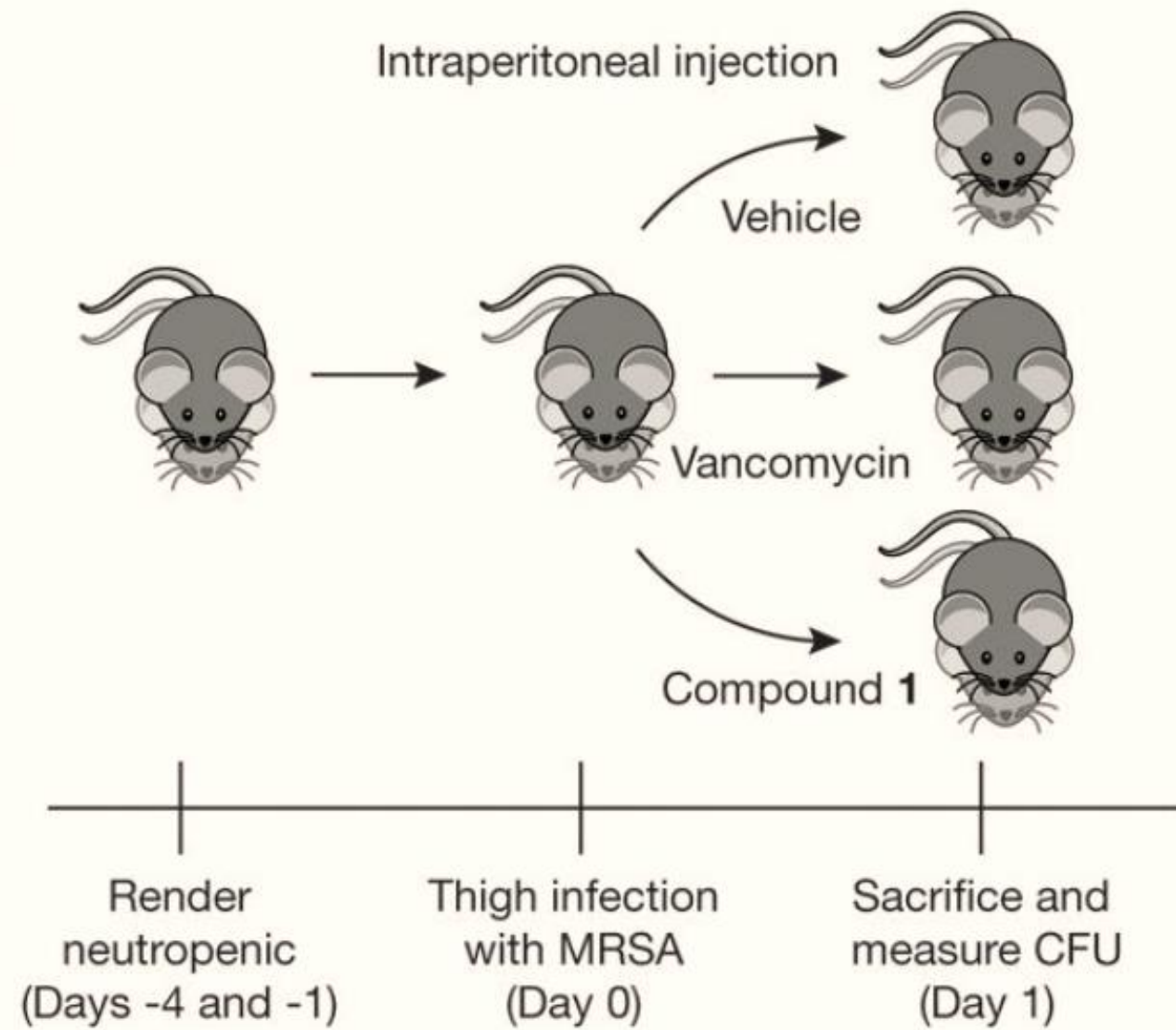
Intraperitoneal (IP)



Mouse Topical Wound Infection Model



Mouse Systemic Infection Model



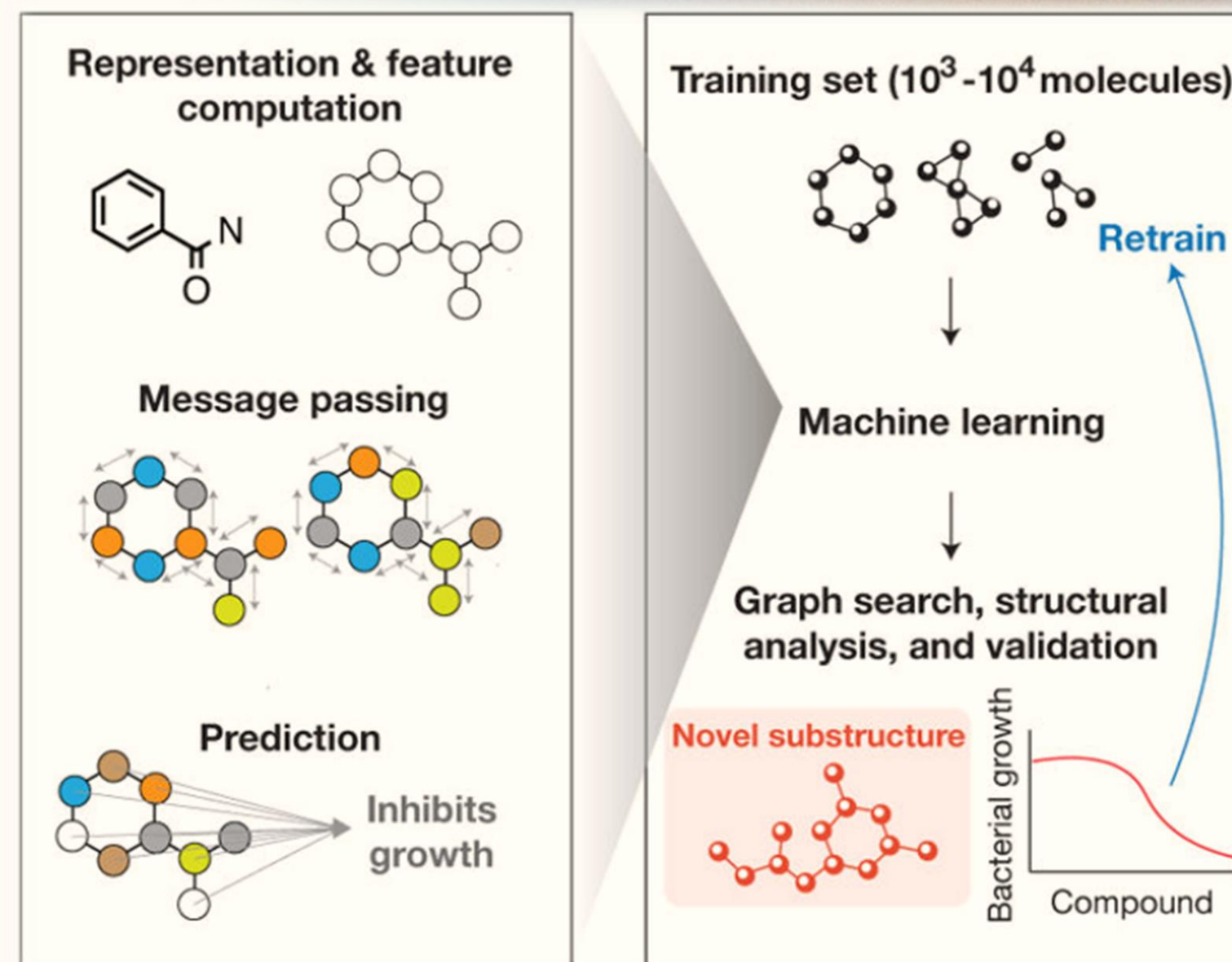
Discussion

1962 : Discovery of Quinolones

2000 : Discovery of Oxazolidinones

❖ Halicin

❖ Abaucin



Reference

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Q&A Session