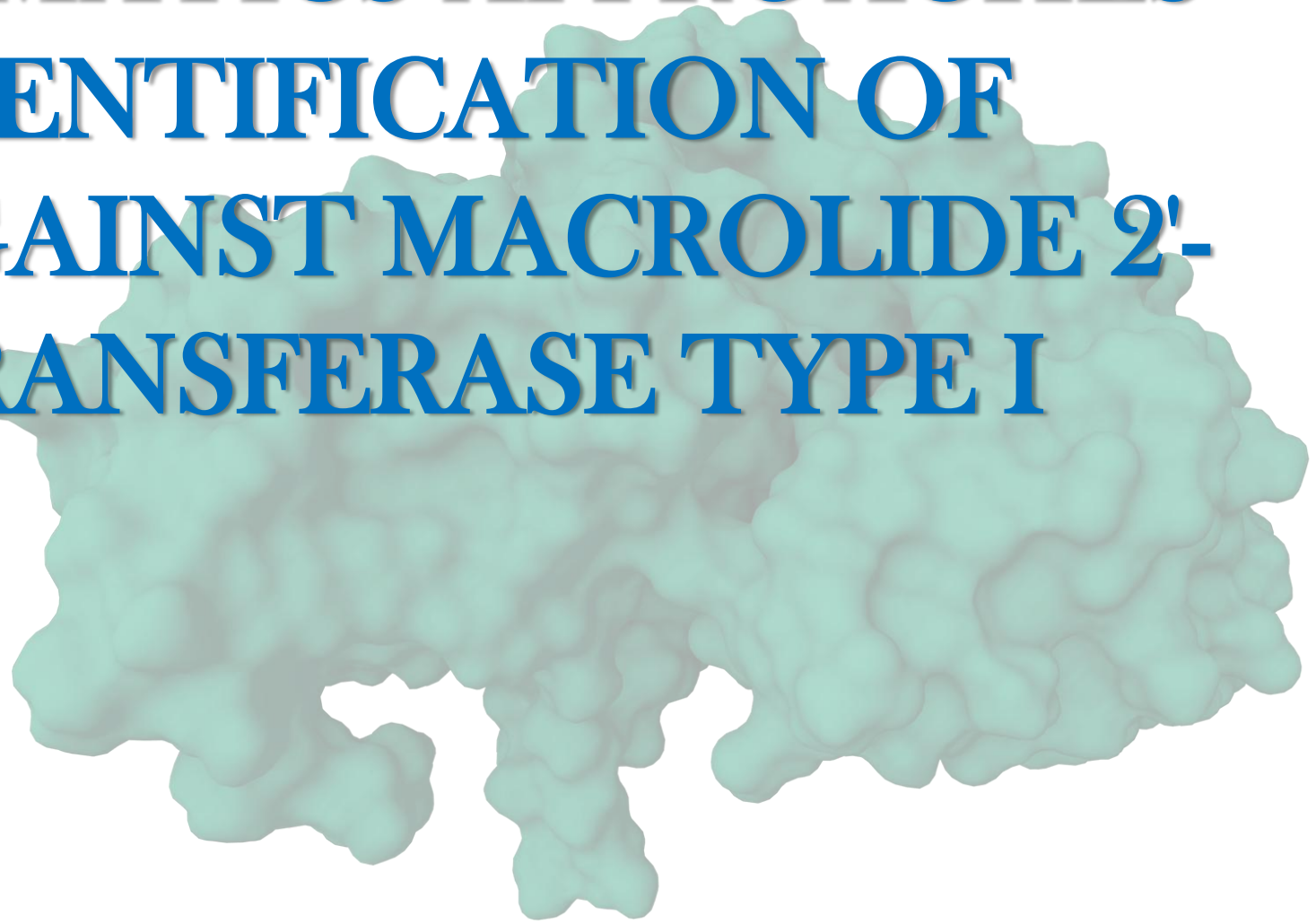
Universidad Politécnica Metropolitana DE PUEBLA

A CHEMINFORMATICS APPROACHES FOR THE IDENTIFICATION OF INHIBITORS AGAINST MACROLIDE 2'-PHOSPHOTRANSFERASE TYPE I



Dr. Carlos A. Lobato-Tapia

The problem

Antibiotic resistance is one of the greatest worldwide challenges to modern medicine, and society at large, and one of the least appreciated by practitioners and the lay community.

Between 2018 and 2023, antibiotic resistance rose in over 40% of the monitored antibiotics with an average annual increase of 5-15%.

Antibiotic resistant infections are estimated to claim up to 10 million lives per year by 2050, costing the global economy about $100 trillion.

Nicholas A. Church & John L. McKillip, 2021
WHO 2025

The problem

The new *Global Antibiotic Resistance Surveillance Report 2025* presents, **for the first time**, resistance prevalence estimates across **22 antibiotics** (infections of the urinary and gastrointestinal tracts, the bloodstream and those used to treat gonorrhoea).

The report covers **8 common bacterial pathogens:**

Acinetobacter spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, non-typhoidal *Salmonella spp.*, *Shigella spp.*, *Staphylococcus aureus* and *Streptococcus pneumoniae.*

Each linked to one or more of these infections.

WHO, 2025

The problem

The number of resistant bacteria and new ones that are becoming resistant to treatment with all known antibiotics is rising, and few new agents are in the pipeline, necessitating the urgent development of new classes of antibiotics to avoid major global health tragedies.

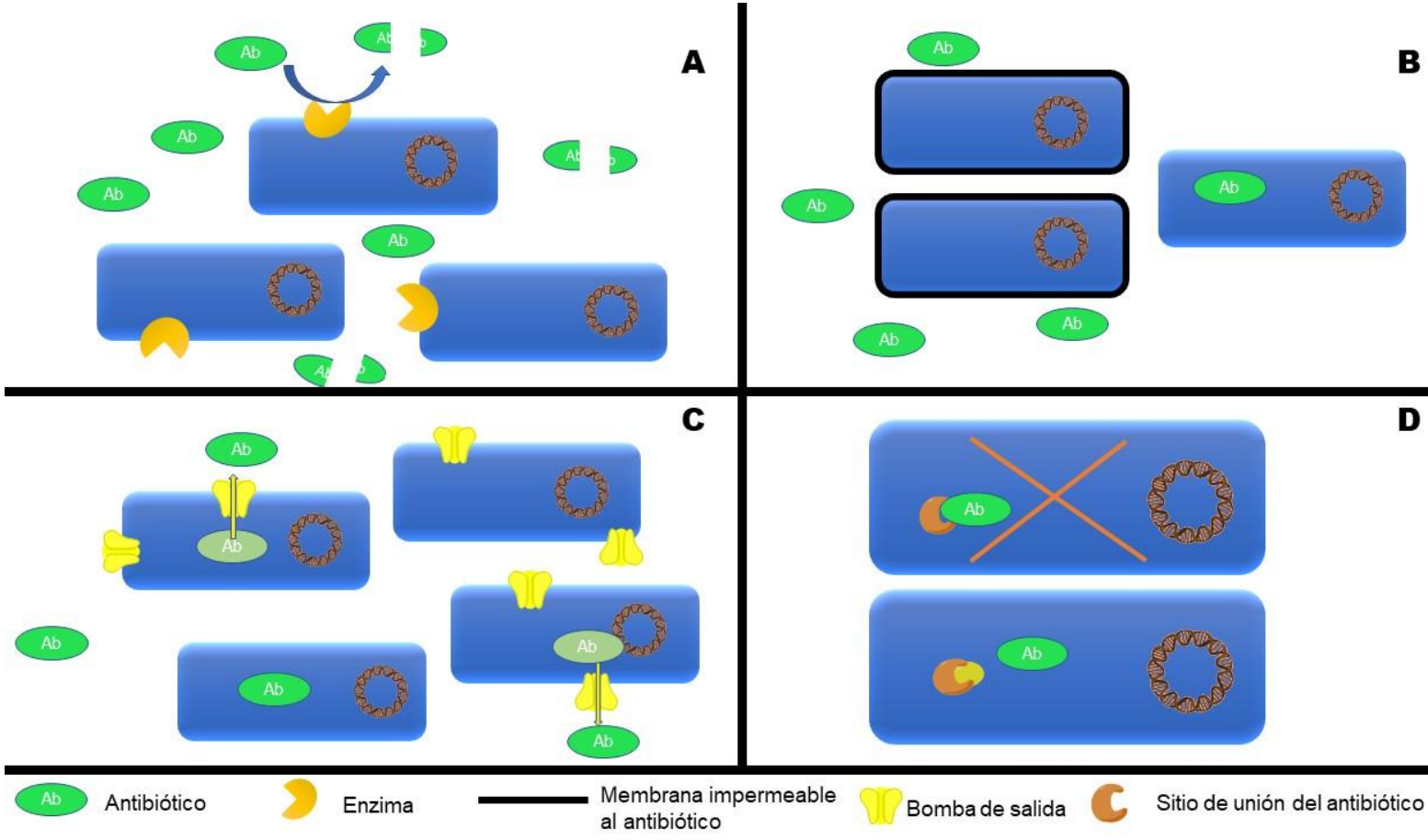
It is pertinent to state that the problem of antimicrobial resistance is aggravated by the lack of interest by pharmaceutical industries in new antimicrobial investment, as they view research for new antimicrobials as “low profit” and believe that resistance will develop for new antimicrobials sooner or later.

David Chinemerem Nwobodo, et al., 2022

Why?

Antibiotic-resistant bacteria develop mechanisms to resist the effects of drugs designed to eliminate them.
Antibiotic resistance mechanisms can be characterized into four main groups:

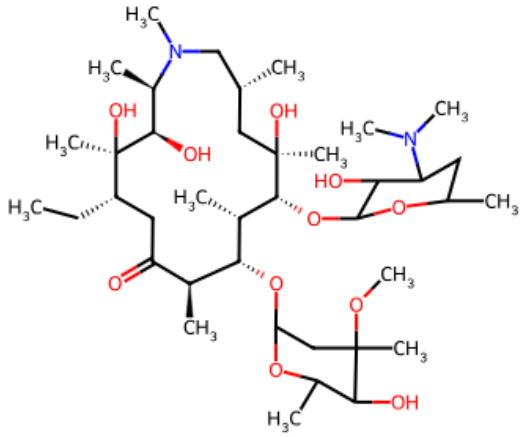
A. Drug inactivation
B. Limiting drug uptake
C. High levels of drug efflux
D. Altering drug target



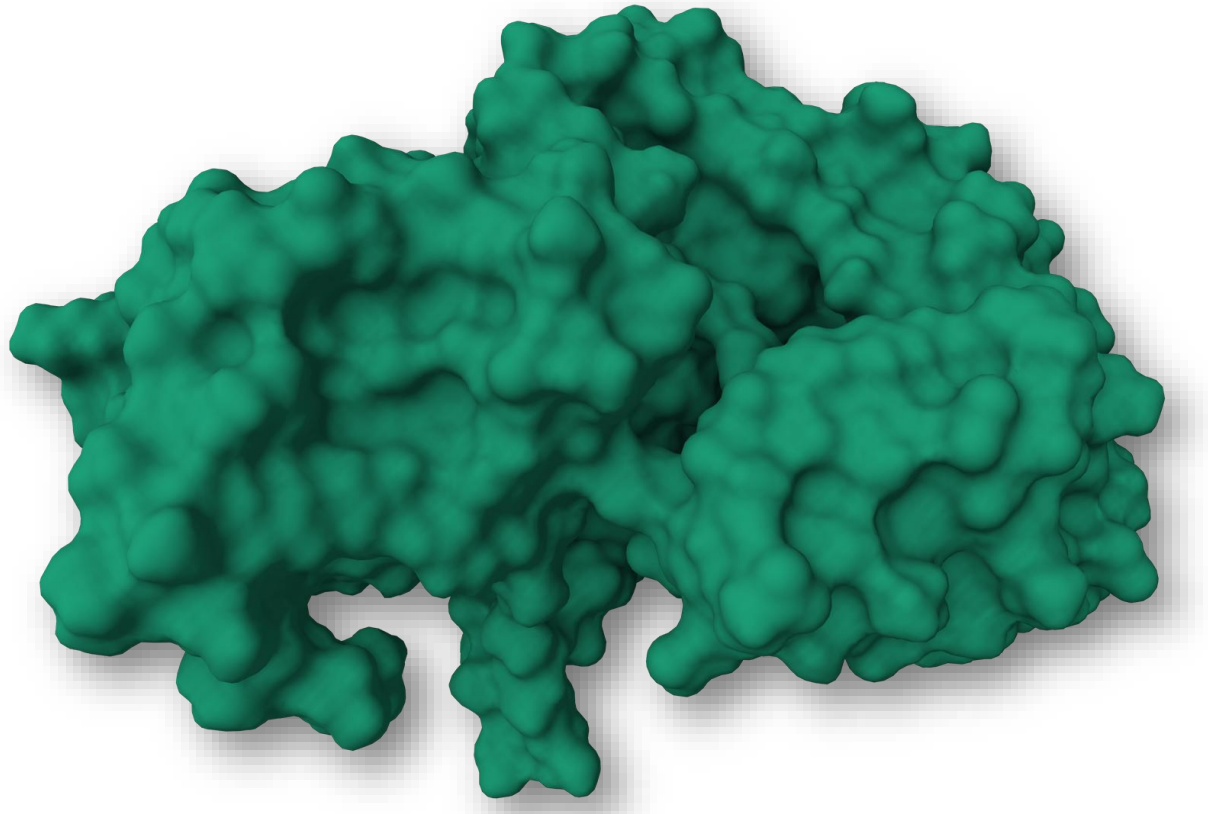
Anusha Gauba and Khondaker Miraz Rahman, 2023
Lobato-Tapia, 2019

Why?

One such mechanism involves the production of drug-neutralizing enzymes, such as macrolide 2'-phosphotransferase type I, which degrades macrolide antibiotics.



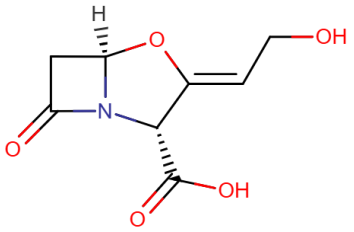
Azitromycin



Halawa, M. et al. (2023)

Possible solutions

Therefore, the search for novel enzyme-targeted inhibitors is an alternative strategy for defending against resistant bacterial strains.



Clavulanic acid is a beta-lactamase inhibitor that is frequently combined with Amoxicillin or Ticarcillin.

- Avibactam
- Brobactam
- Relebactam
- Durlobactam...

Barbier, F., Hraiech, S., Kernéis, S., et al. (2023)
Drugbank

Objective

Thus, the objective of this study was to search for compounds that could inhibit macrolide 2'-phosphotransferase type I in *Escherichia coli* using a cheminformatics approach.

Methodology

NPASS Database → 12,446 compounds → ADMET screening

NPASS
Natural Product Activity & Species Source Database

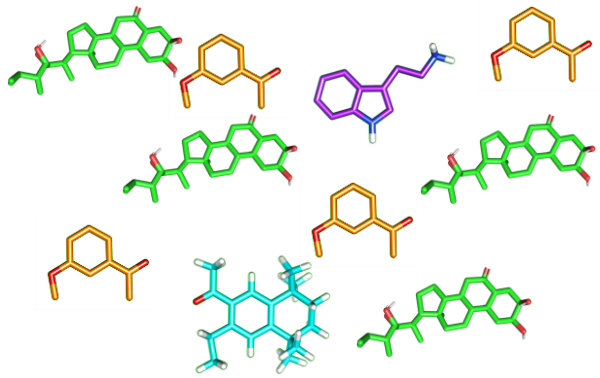
Deep-PK
prediction

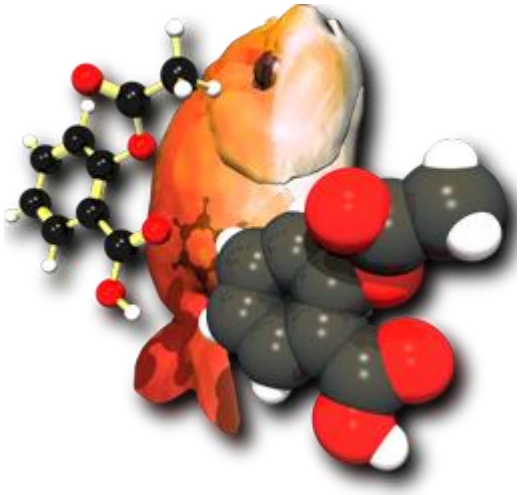
Methodology

1,462 compounds remained

Optimized with OpenBabel

Prepared for docking (Chimera)





Methodology

Macrolidase from PDB (5IGH)

MD 50 ns (Gromacs)

Molecular docking (AutodockVina)

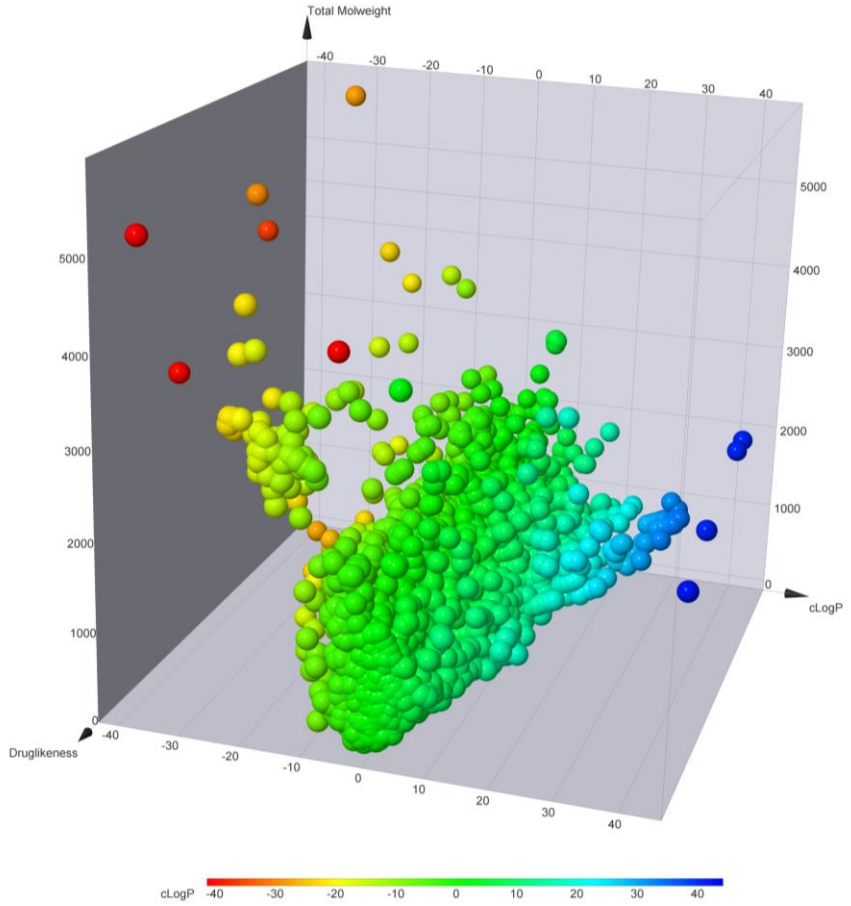
5IGH | pdb_00005igh

Macrolide 2'-phosphotransferase type I

FAST. FLEXIBLE. FREE.
GROMACS

Results

After ADMET screening 1462 compounds remained.



- QED
- Carcinogenicity
- hERG inhibitors
- Genotoxicity
- Hepatotoxicity...

Results

Of the 1,462 compounds, 19 had binding affinities between -10 and -11.3 kcal/mol.

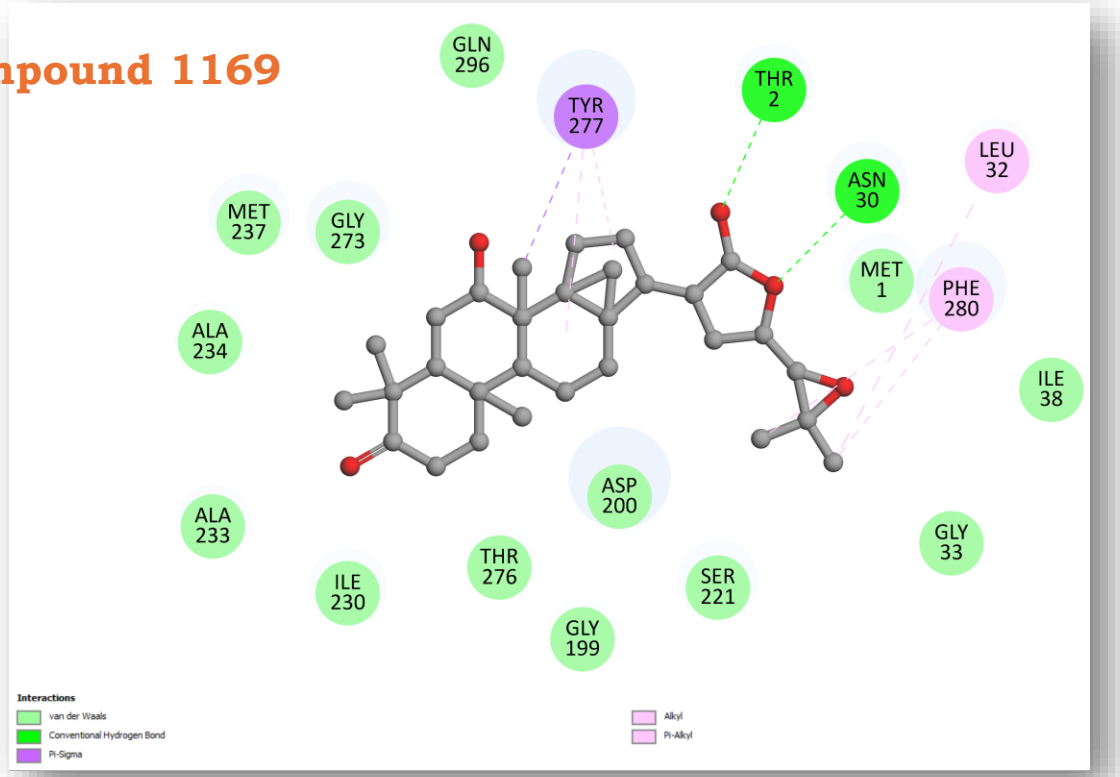
Ligando	Energía_kcal/mol
lig1169	-11.3
lig1248	-10.7
lig366	-10.7
lig255	-10.6
lig503	-10.6
lig733	-10.6
lig610	-10.5
lig1241	-10.4
lig1260	-10.4
lig450	-10.4

Ligando	Energía_kcal/mol
lig1001	-10.3
lig731	-10.2
lig1009	-10.1
lig294	-10.1
lig498	-10.1
lig514	-10.1
lig85	-10.1
lig759	-10
lig810	-10
lig878	-10

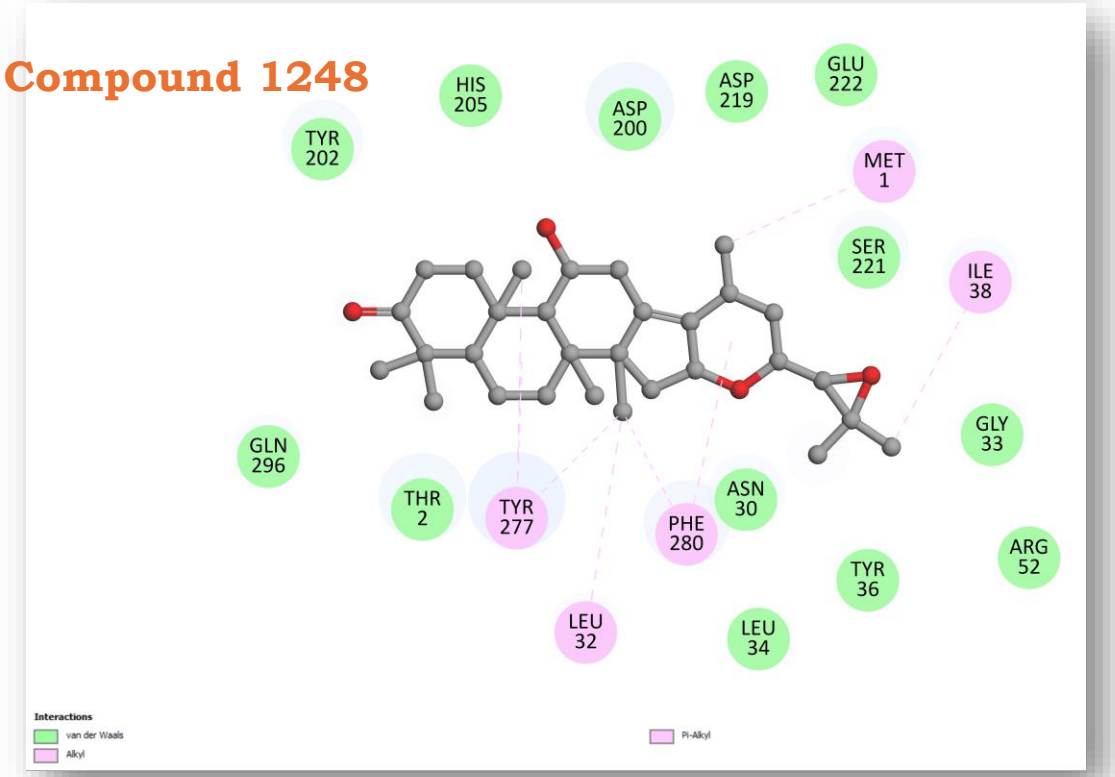
Results

Particularly the compound **1169** had the highest affinity **(-11.3 kcal/mol)**; the second highest affinity was compound **1248**, with an affinity energy of **-10.7** kCal/mol.
While **azithromycin** (control) had an affinity of **-7.2 kcal/mol**.

Compound 1169

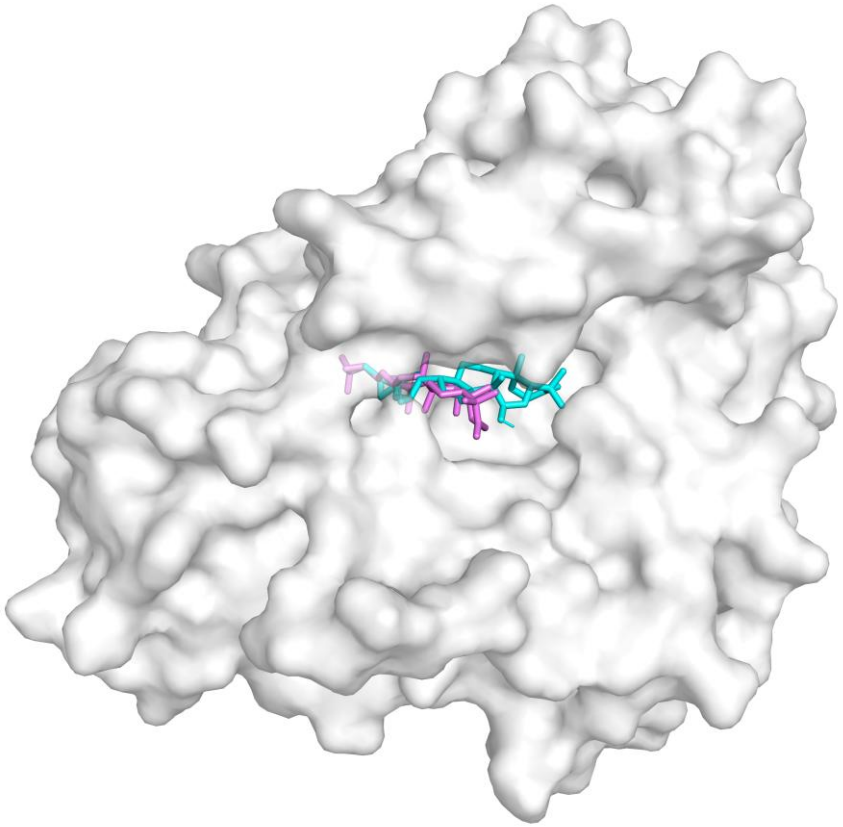


Compound 1248



Conclusion

These preliminary results indicate that there are natural compounds that could act as potential inhibitors of this enzyme and restore the activity of macrolide-type antibiotics, particularly compound 1169.



In the future

Evaluate the stability of the bond using molecular dynamics.

Experimental tests

Thank you for your attention

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