Repurposing sesquiterpene lactones for gonorrhea treatment: Docking and QSPR Studies of xerantholide and its analogues

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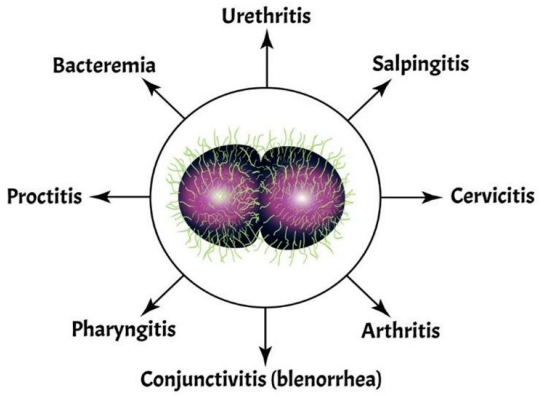
INTRODUCTION

- *Neisseria gonorrhoeae*, a causative agent of a sexually transmitted infection, gonorrhea is a global health threat.



- *N. gonorrhoeae* has an extraordinary capacity to develop resistance to antimicrobial agents [1].
- New anti-gonococcal agents with mechanism of action different from the current agents are needed.
- Important drug target: Carbonic anhydrases – drugs that inhibit or disrupt enzyme processes i.e. carbonic anhydrase inhibitors (CAIs) may bypass the challenge of antibiotic resistance[2].
- *N. gonorrhoeae* encodes α-CA called *Neisseria gonorrhoeae* carbonic anhydrase (NgCA)

1. Unemo M, del Rio C, Shafer WM. Antimicrobial Resistance Expressed by *Neisseria gonorrhoeae*: A Major Global Public Health Problem in the 21st Century. Microbiol Spectr. 2016;4(3):1–32.
2. Hewitt CS, Abutaleb NS, Elhassanny AEM, Nocentini A, Cao X, Amos DP, et al. Structure-activity relationship studies of acetazolamide-based carbonic anhydrase inhibitors with activity against *Neisseria gonorrhoeae*. ACS Infect Dis. 2021

Motivation

- The aim of this research therefore is to identify potential compounds with NgCA inhibition activity using computational drug repurposing approach.

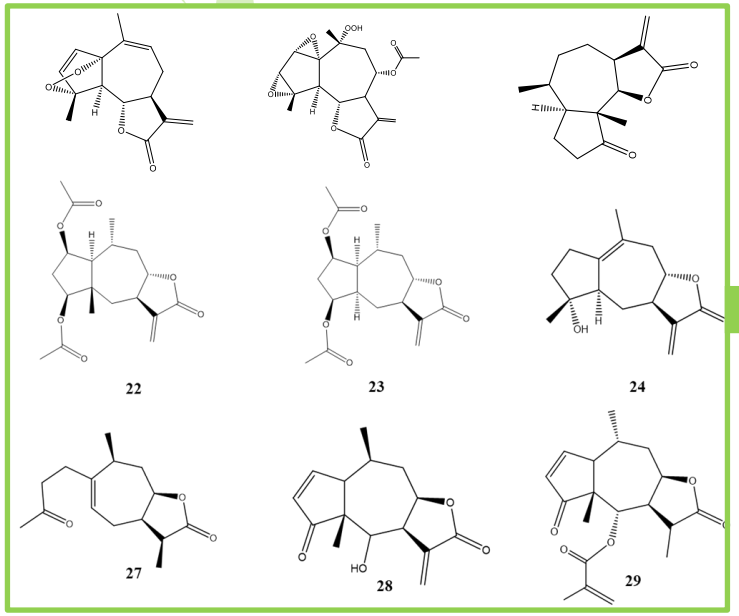
- Drug repurposing will significantly reduce the cost, time and effort to find new effective anti-gonococcal agents.

- Since xerantholide, a sesquiterpene lactone (SL) has been proven to inhibit the growth of *N. gonorrhoeae*, there is basis to explore other SLs for anti-gonococcal activity with enzyme inhibition mechanism of action.

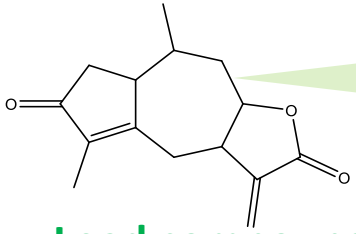
Methodology

Quantitative structure property relationship (QSPR)

83 Analogues



X-ray diffraction



Lead compound

Molecular docking

Structure optimization: DFT-B3LYP/6-311++G(d,p); ΔG°

QSPR:ALOGPS, E-DRAGON, DFT: Constitutional, Thermodynamic, electronic spatial and topological descriptors computed.

Molecular docking (ligand-NgCA), Autodock Vina: References = acetazolamide, ethoxzolamide-known NgCAI &tetracycline (antibiotic)

Figure 1. Illustration of the method used to optimize structures, before develop QSPR models and study SL-NgCA interaction

Results

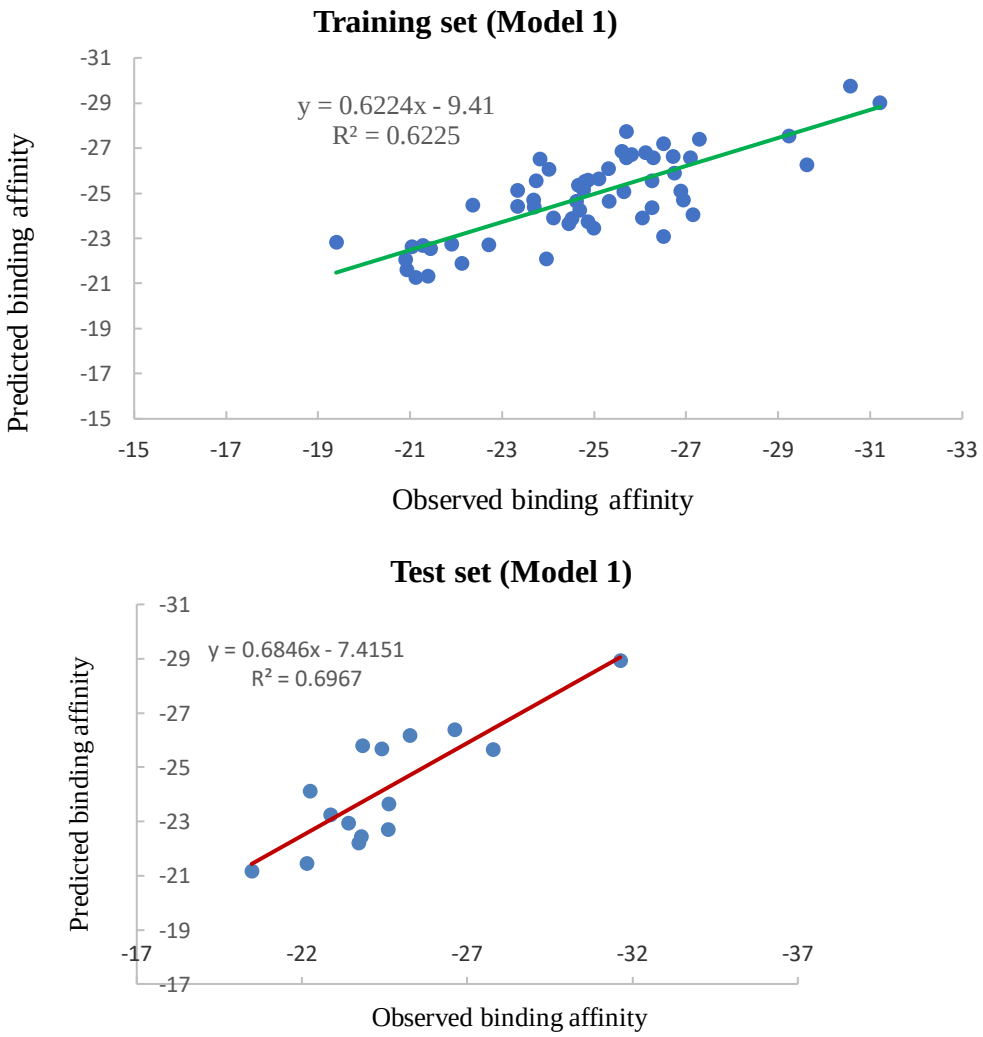


Figure 2. Plot of observed versus predicted logKd of the training and test sets using model 1.

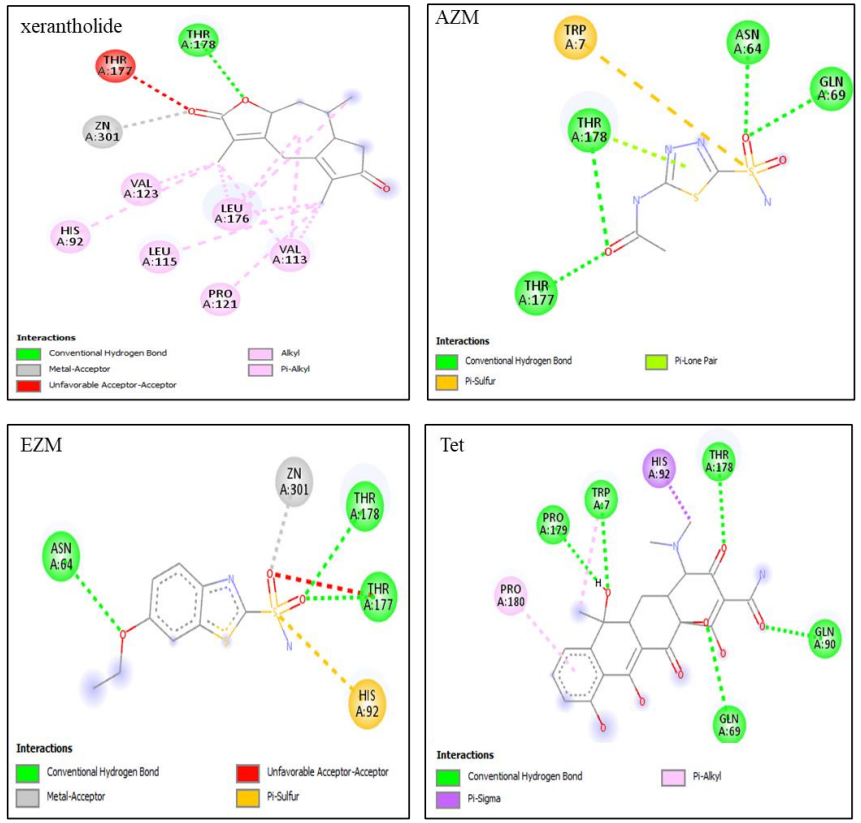
- **Developed model:**
  Binding affinity = 4.304+1.363×logS–68.198×HOMO+31.599×LUMO–3.033×HBD+ 0.180×MinElP–0.032×P-Area

  n_{train} = 58 R = 0.789 R^2 = 0.623 AdjR^2 = 0.578

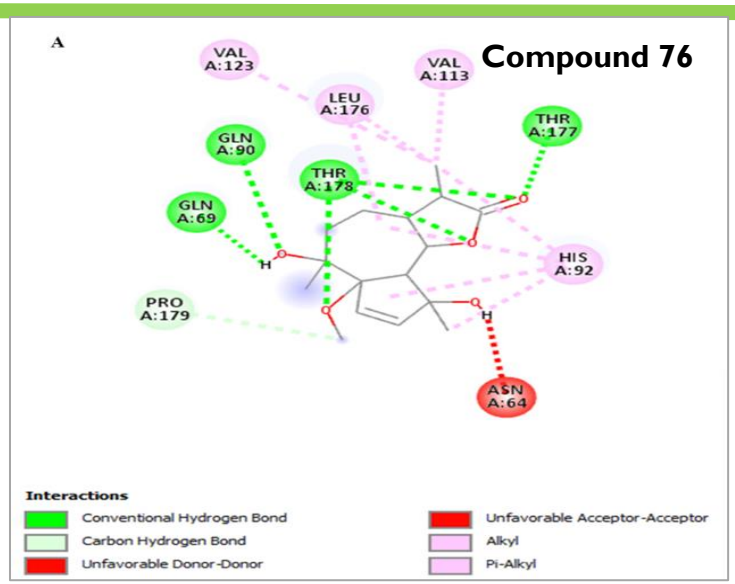
Table 1. Selected analogues to represent binding scores of studied structures (Molecular docking).

Conformer	DFT ΔG°kcal/mol	NgCA Docking score (kcal/mol)	NgCA# of polar interaction
xer_c1	-28.5	-6.8	4
xer_c2	-32.9	-5.9	1
a41_c1	-26.5	-6.4	3
a53_c21	-37.9	-6.6	7
a58_c2	-31.2	-6.7	4
a58_c4	-30.5	-6.4	4
a74_c1	-28.5	-7.0	4
a76_c4	-36.3	-7.4	8
a12_c2	-32.7	-6.9	3
azm	-	-5.7	4
ezm	-	-5.3	6
tet	-	-6.6	7

Results



Lead compound vs known carbonic anhydrase inhibitors (AZM&EZM) + antibiotic (Tet)



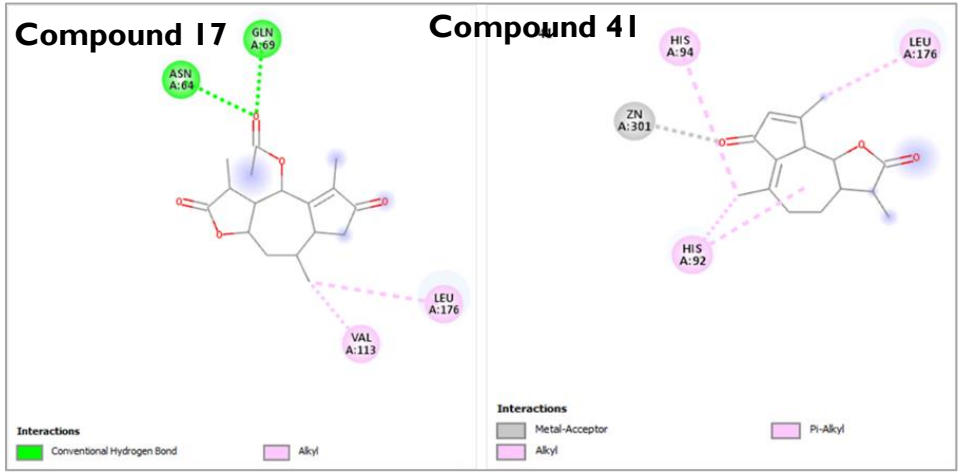


Figure 3. 2D view of binding mode and amino acid residues involved in the interaction of xerantholide with NgCA at the active site, in comparison to established inhibitor AZM and anti-gonococcal agents EZM and tetracycline. Compound 76 was predicted to have the highest binding affinity, while compounds17 and 41 has the lowest.

Conclusion

- The developed QSPR model can predict the binding affinity of xerantholide analogues to NgCA.
- Molecular docking study suggest the potential of xerantholide and several of its analogues as NgCA inhibitor.
- The results show many of the studied compounds have binding affinity to NgCA that is comparable to known carbonic anhydrase inhibitors as demonstrated by the calculated binding energy, binding score and binding mode observed *in-silico*.
- This study gives basis for future *in-vitro* studies aimed at identifying novel anti-gonorrheal agents with mechanism of action targeting the disruption of essential enzyme activity (NgCA).