Antibiotic discovery with artificial intelligence for the treatment of *Acinetobacter baumannii* infections

Yassir Boulaamane[1], Irene Molina Panadero[2], Abdelkrim Hmadcha[3,4], Celia Atalaya Reyes[2], Soukayna Baammi[5], Achraf El Allali[5], Amal Maurady[1,6], Younes Smani[2,3*]

[1]Laboratory of Innovative Technologies, National School of Applied Sciences of Tangier, Abdelmalek Essaadi University, Tetouan, Morocco, [2]Centro Andaluz de Biología del Desarrollo, Universidad Pablo de Olavide/CSIC/Junta de Andalucía, Seville, Spain, [3]Departamento de Biología Molecular e Ingeniería Bioquímica, Universidad Pablo de Olavide, Seville, Spain. [4]Biosanitary Research Institute (IIB-VIU), Valencian International University (VIU), Valencia, Spain. [5]African Genome Centre (AGC), Mohammed VI Polytechnic University, Benguerir, Morocco, 6Faculty of Sciences and Techniques of Tangier, Abdelmalek Essaadi University, Tetouan, Morocco

INTRODUCTION

Acinetobacter baumannii is a highly resistant pathogen, leading to severe infections worldwide [1]. Conventional antibiotics are becoming ineffective, highlighting the need for new therapeutic strategies. Outer membrane proteins (OMPs), especially OmpW, have been identified as promising drug targets [2]. This study explores artificial intelligence (AI) and natural compounds to discover novel antibiotics targeting OmpW [3].

MATERIALS AND METHODS

A library of 11,648 natural compounds was screened using QSAR models based on a ChEMBL dataset of ~7,000 compounds with known MICs. Top compounds underwent virtual screening against the OmpW protein via molecular docking. ADME analyses assessed pharmacokinetics, and molecular dynamics simulations evaluated compound-protein stability. Finally, *in vitro* experiments, including microdilution assays, bacterial growth curves, adhesion tests, and synergy with colistin, validated antibacterial activity.

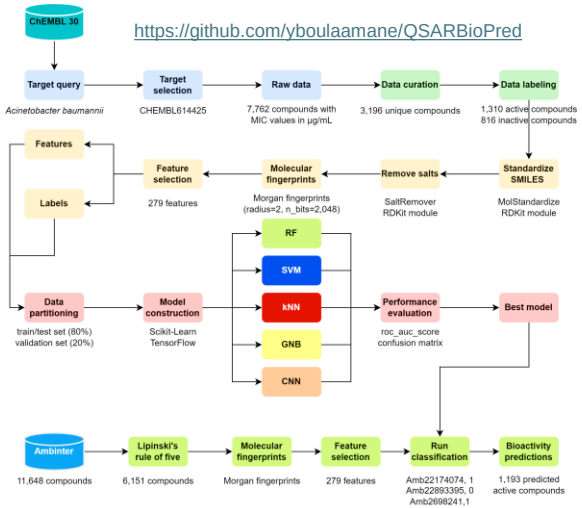

Fig 1. QSAR screening workflow

RESULTS

CNN-based QSAR model exhibited excellent performance achieving an AUC value of 0.96. Consequently, it was chosen to predict the activity of Ambinter drug-like natural compounds. The best compounds displayed docking scores between -7.8 and -7.0 kcal/mol. Demethoxycurcumin was identified as the most promising compound, showing stable binding in molecular dynamics simulations and favorable pharmacokinetic properties. *In vitro* testing demonstrated that demethoxycurcumin is active against all tested *A. baumannii* strains, especially when combined with colistin, suggesting potential synergy. Additionally, demethoxycurcumin reduced bacterial adhesion to host cells, indicating anti-virulence properties.

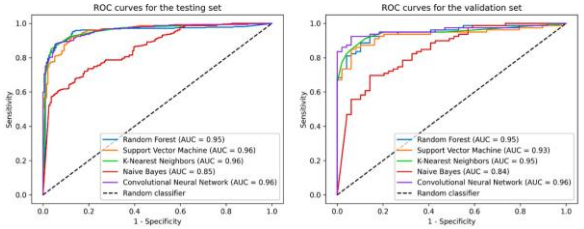

Fig 2. Performance of QSAR classification models on test and validation sets

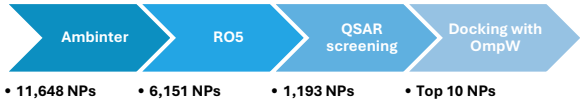

Fig 3. Number of compounds after each screening step

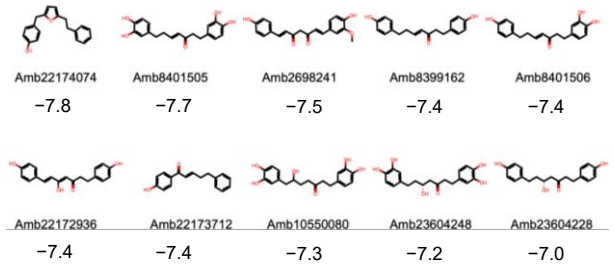

Fig 4. Chemical structures and binding scores (kcal/mol) of the top 10 compounds against OmpW

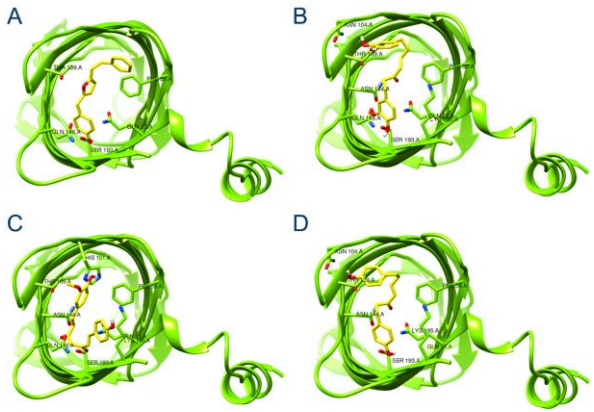

Fig 5. Binding conformations of the top 4 NPs with OmpW

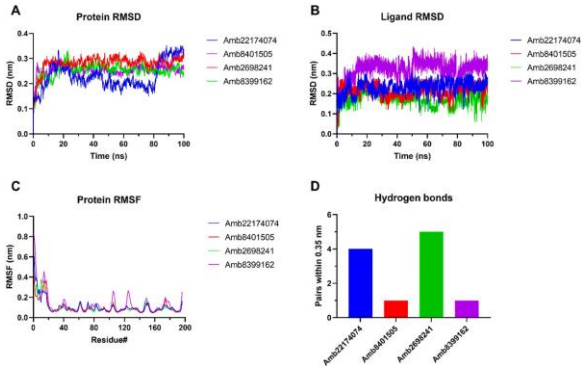

Fig 6. Molecular dynamics simulations analysis through protein RMSD (A), ligand RMSD (B), RMSF (C), and hydrogen bonds at 100 ns (D)

Table 1. MIC results for the studied compounds against different strains of *A. baumannii*

A. baumannii strain	MIC (mg/L)	
	Colistin	Demethoxycurcumin
ATCC 17978	0.25	64
ATCC17978 ΔOmpW	0.25	64
Ab11	256	64
Ab20	64	64
Ab21	128	64
Ab22	128	64
Ab99	64	64
Ab113	256	64
CR17	32	64

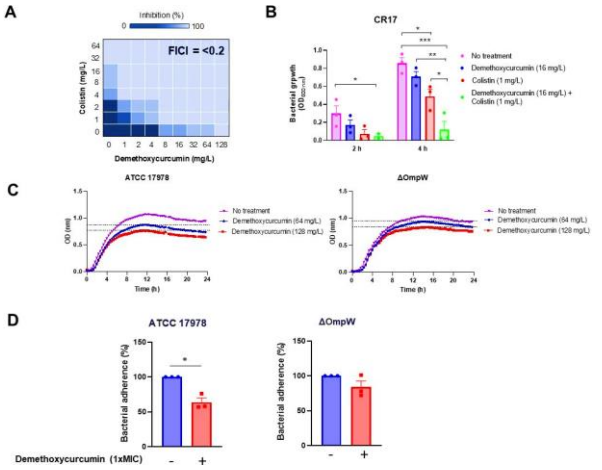

Fig 7. Antibacterial activity (C), synergetic activity (A, B) and adhesion assays (D) of desmethoxycurcumin against *A. baumannii*

CONCLUSION

This study highlights the potential of using AI-driven approaches and natural compounds to combat antibiotic-resistant *A. baumannii.* Demethoxy-curcumin shows promise as a novel therapeutic, particularly in combination with colistin, for treating multidrug-resistant infections. Further research is needed to validate these findings in clinical settings.

REFERENCES

[1] Antunes, L. C., Visca, P., & Towner, K. J. (2014). Acinetobacter baumannii: evolution of a global pathogen. Pathogens and disease, 71(3), 292-301. [2] Schmitt, B. L., Leal, B. F., Leyser, M., de Barros, M. P., Trentin, D. S., Ferreira, C. A. S., & de Oliveira, S. D. (2023). Increased ompW and ompA expression and higher virulence of Acinetobacter baumannii persister cells. *BMC microbiology*, *23*(1), 157. [3] Boulaamane, Y., Molina Panadero, I., Hmadcha, A., Atalaya Rey, C., Baammi, S., El Allali, A., ... & Smani, Y. (2024). Antibiotic discovery with artificial intelligence for the treatment of Acinetobacter baumannii infections. Msystems, e00325-24.

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