Harnessing Marine Alkaloid Chemistry to Overcome WHO Priority Multidrug-Resistant Infections: Study of Ascididemin Against ESKAPE, NMT and *Neisseria gonorrhoeae*

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Introduction

•Antibiotic resistance threats public health

•Urgent need for novel drug candidates

•Marine natural products – high chemodiversity & source of new scaffolds

•Pyridoacridine alkaloids: biological potential (cytotoxic, anticancer, antimicrobial, antiparasitic activities)

•Ascididemin: a marine pyridoacridine alkaloid

•Unexplored activity of ascididemin against multidrug-resistant bacteria

Objectives

To evaluate the antimicrobial potential of ascididemin, a fully synthetic marine alkaloid, against multidrug-resistant bacteria *Neisseria gonorrhoeae*, the WHO priority pathogens and non-tuberculous mycobacteria (NTM)

Methods

•**Compound preparation**: Total chemical synthesis of ascididemin

•**Bacterial panel**: Tested against *E. faecallis, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa, Enterobacter* spp., NTM species (*M. avium, M. intracellulare, M. abscessus*), and *N. gonorrhoeae*

•**Antimicrobial assays**:

•Minimum inhibitory concentrations (MICs) by CLSI-standard broth microdilution

•Minimal bactericidal concentrations (MBCs) and time–kill kinetics for *S. aureus* ATCC 25923

•**Safety assay**: Hemolytic activity in mouse erythrocytes

•***In silico* analysis**: Prediction of drug-like properties and pharmacokinetics using SwissADME

Results

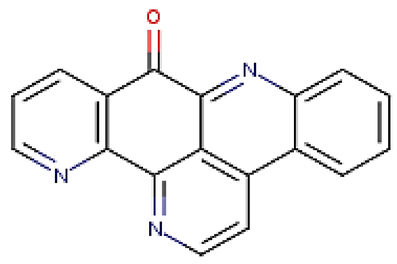

Figure 1. Structure of ascididemin.

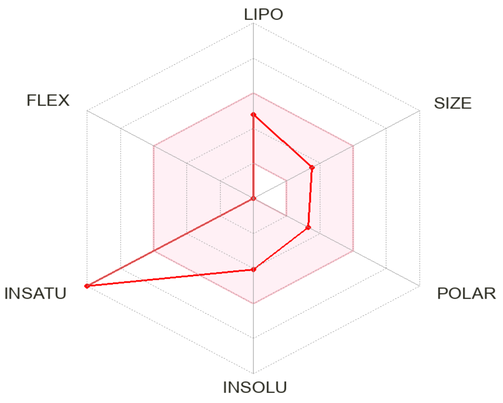

Figure 2. *In silico* radar plot of key physicochemical properties influencing drug bioavailability using Swiss ADME.

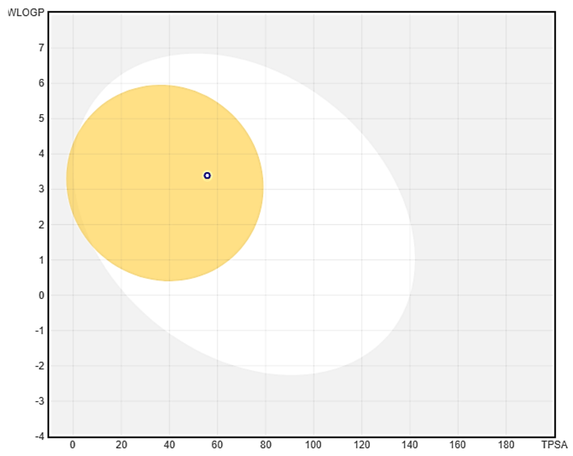

Figure 3. *In silico* permeability on blood-brain-barrier (BBB) and human intestinal absorption (HIA).

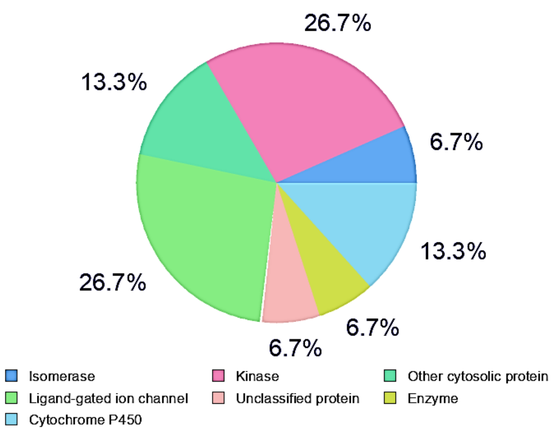

Figure 4. *In silico* target predictions on *Homo sapiens* using Swiss Target.

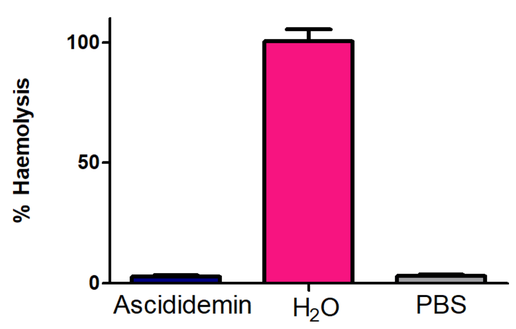

Figure 5. Hemolytic activity of ascididemin at 200 µM in murine erythrocytes.

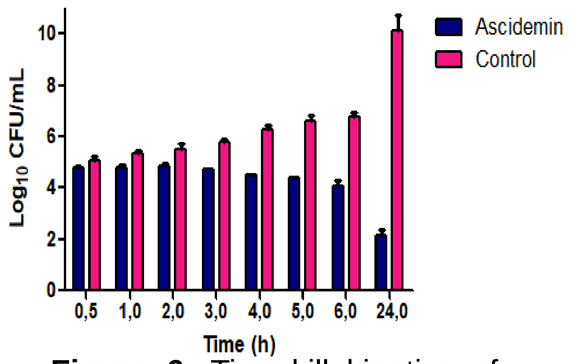

Figure 6. Time-kill kinetics of ascididemin at MBC concentration (0,78 µM**)** on *S. aureus* ATCC 25923 over 24h.

Table 1. MIC values of ascididemin against ESKAPE, *N. gonorrhoeae* and MNT strains.

Strain		MIC (µM)
E. faecallis	**ATCC 51299**	1.17
S. aureus	**ATCC 3591**	0.58
K. pneumoniae	***id*-146/19**	18.75
A. baumanii	***id*- 261/16**	18.75
P. aeruginosa	**S6065/06**	>100
E. cloacae	**534/17**	37.5
E. coli	**35218**	12.5
N. gonorhhoeae	**P9-17**	0.39
M. abscessus	***621/2010***	12.5
	4213/2011	3.12
	3209/2012	6.25
	381/10	12.5
	2720/2012	3.12
M. intracellulare	***8668/2023***	>100
	8724/2023	6.25
	13950	3.12
M. avium	***7384/2023***	50
	5962/2023	25
	700898	6.25

- Ascididemin showed a **broad spectrum** activity against Gram-positive and Gram-negative and MNT strains, including resistant strains.
- **Nanomolar** potency against the resistant strain *S. aureus* ATCC 33591
- No hemolytic activity against murine erythrocytes
- *In silico* studies demonstrated **adequate** physico-chemical profile

Conclusions

The marine alkaloid ascididemin represents a promising scaffold for the development of new antimicrobials to fight the global antimicrobial resistance.

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