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Lead optimization in the search for new antifouling compounds

Ana Rita Neves [1,2], Cátia Vilas-Boas [1,2], Joana Almeida [2], Vitor Vasconcelos [2,3]
Madalena Pinto[1,2], Emília Sousa and Marta Correia-da-Silva [1,2,*]

[1] Laboratory of Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, University of Porto, Portugal.
[2] Interdisciplinary Centre of Marine and Environmental Research (CIIMAR), University of Porto, Portugal.
[3] Biology Department, Faculty of Sciences, University of Porto, Portugal.
* Corresponding author: m_correiadasilva@ff.up.pt

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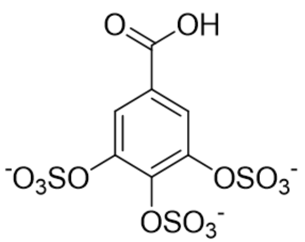
Lead optimization in the search for new antifouling compounds

Previous results



GAP

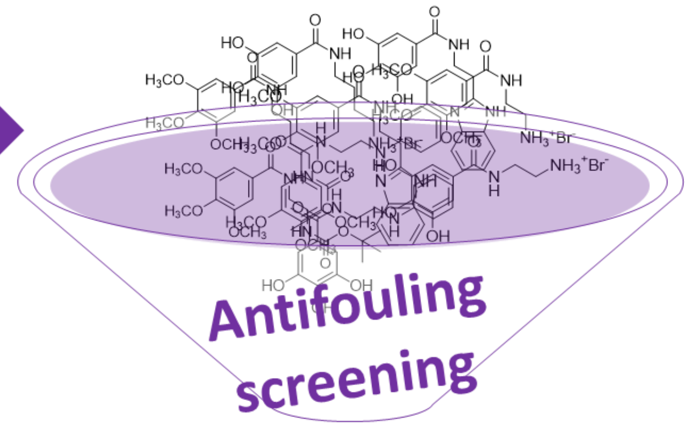
EC$_{50}$ (*M. galloprovincialis*)= 17.65 µM

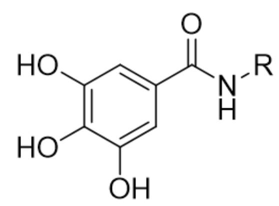
<10% mortality at 250 µM
(*Artemia salina*)

LogKOW (EPI Suite™)= -7.02

Lead Optimization

Small library of new compounds





EC$_{50}$ (*M. galloprovincialis*)= 2.74 µM

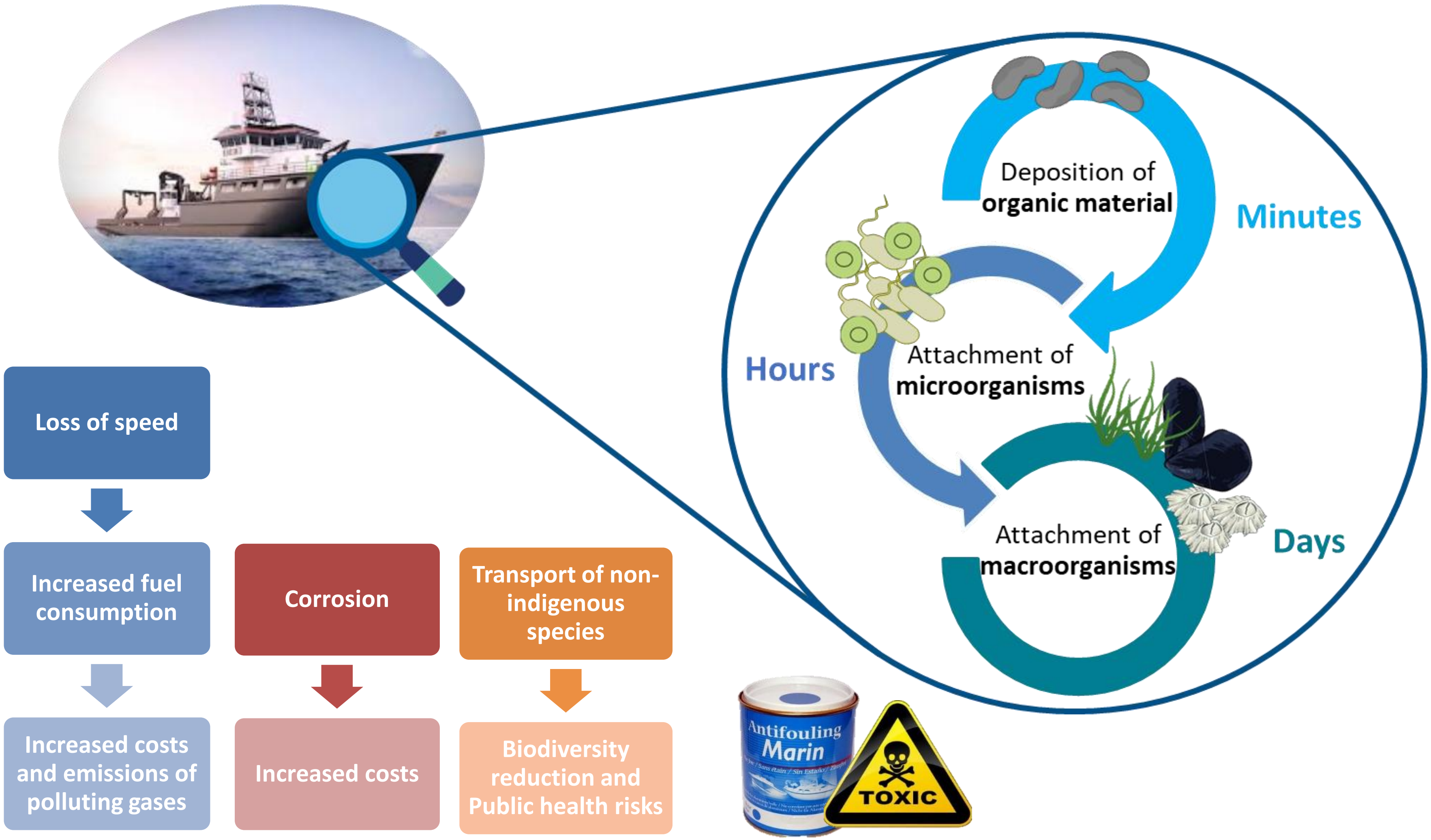
<3% mortality at 250 µM
(*Artemia salina*)

LogKOW (EPI Suite™)= -0.79

Abstract:
Innovative environmentally friendly technologies to combat marine biofouling is a **practical and urgent need**, since the associated economic, environmental, and human health consequences are enormous. Although the addition of biocides to marine paint coatings has been the most used solution to avoid marine biofouling, currently applied biocides are **persistent, bioaccumulative, and toxic to the oceans**. The most promising alternatives for fouling protection focus on the development of coatings whose active ingredients are **natural products or lab-synthesized products inspired in natural compounds**.
The recent **identification of a lead compound** by our lab group sparked the search for new compounds with optimized properties and therefore a **small library of new nine synthetic compounds** was obtained. An optimization was successfully accomplished for a structure-related polyphenolic compound, concerning potency (EC_{50} = 2.74 μM) against the settlement of the larvae of *Mytilus galloprovincialis* and **lipophilicity**, which will increase **compatibility with paint formulations** (LogKow = -0.79). Moreover, the new optimized compound showed **no toxicity against the non-target organism** *Artemia salina*, similar to GAP. This **optimized compound** will proceed for further studies, namely the mechanism of action exploration.

Keywords: lead optimization, polyphenols, antifouling.

Introduction



Callow ME, Callow JE. Biologist (London, England) **2002**; 49: 10-4. Schultz MP, Bendick JA, Holm ER, Hertel WM. Biofouling **2011**; 27: 87-98.

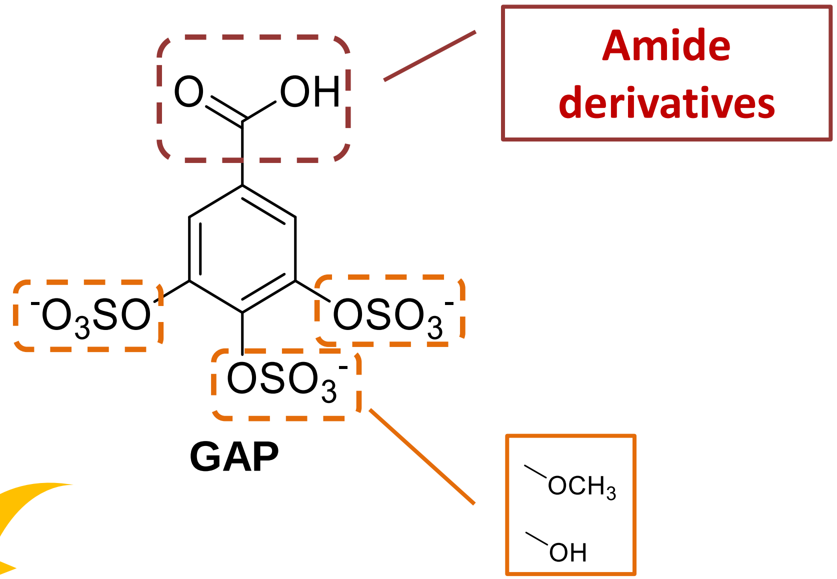
Introduction

Mytilus galloprovincialis

EC_{50}= 17.65 µM

Artemia salina sp.

<10% mortality at 250 µM



GAP

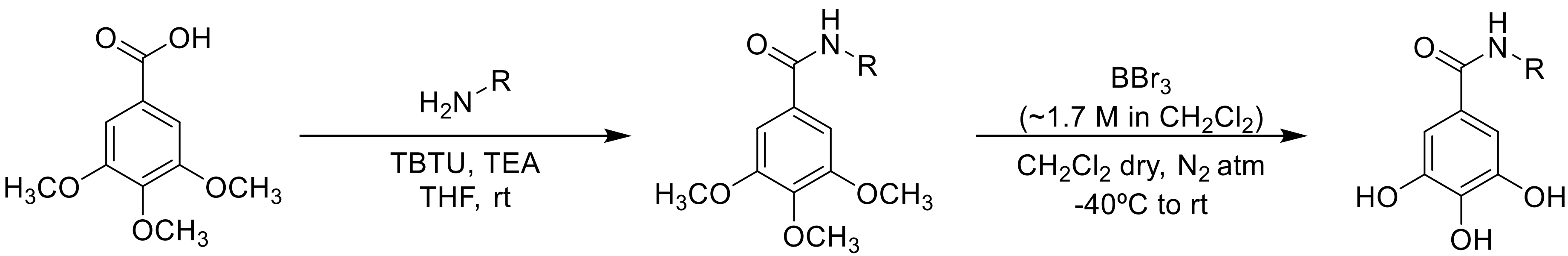
LogKOW (EPI Suite™)= -7.02

Lead optimization

Almeida, J.R., Correia-da-Silva, M., Sousa, E., Antunes, J., Pinto, M., Vasconcelos, V., et al. Sci. Rep. 2017, 742424; Vilas-Boas, C.; Carvalhal, F.; Pereira, B.; Carvalho, S.; Sousa, E.; Pinto, M.M.M.; Calhorda, M.J.; Vasconcelos, V.; Almeida, J.R.; Silva, E.R.; Correia-da-Silva, M. Mar. Drugs 2020, 18, 489.

Chemistry

Amide derivatives were obtained through a coupling reaction with TBTU, a coupling reagent, following removal of metoxyl groups.



1 **2, 5, 7, 9** **3, 4, 6, 8, 10**

Scheme 1. Synthesis of amide derivatives 2-10. TBTU - 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate; TEA – Triethylamine; THF – Tetrahydrofuran.

Fernandes C, Masawang K, Tiritan ME, Sousa E, de Lima V, Afonso C, Bousbaa H, Sudprasert W, Pedro M, Pinto MM, Bioorg Med Chem. 2014;22(3):1049-62; Wenxuan Zhang, Wenjie Xue, Yuqing Jia, Gang Wen, Xu Lian, Jing Shen, Ailin Liu and Song Wu, RSC Adv., 2018, 8, 14389–14392.

Antifouling screening


Mytilus galloprovincialis

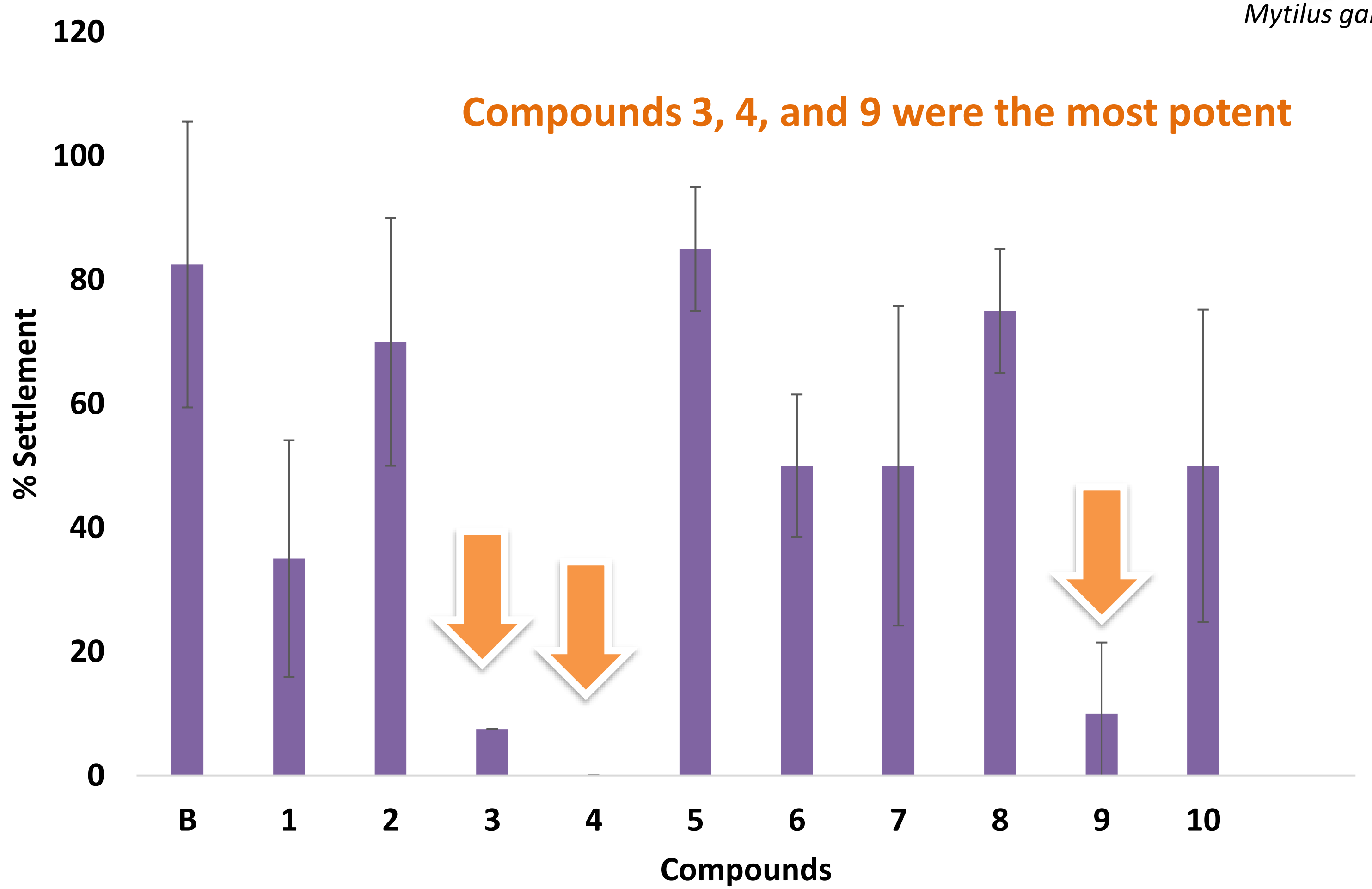


Figure 1. Anti-settlement activity of compounds 1-10 towards plantigrade larvae of the mussel *Mytilus galloprovincialis*. B: sterilized natural sea water.

Antifouling activity


Mytilus galloprovincialis

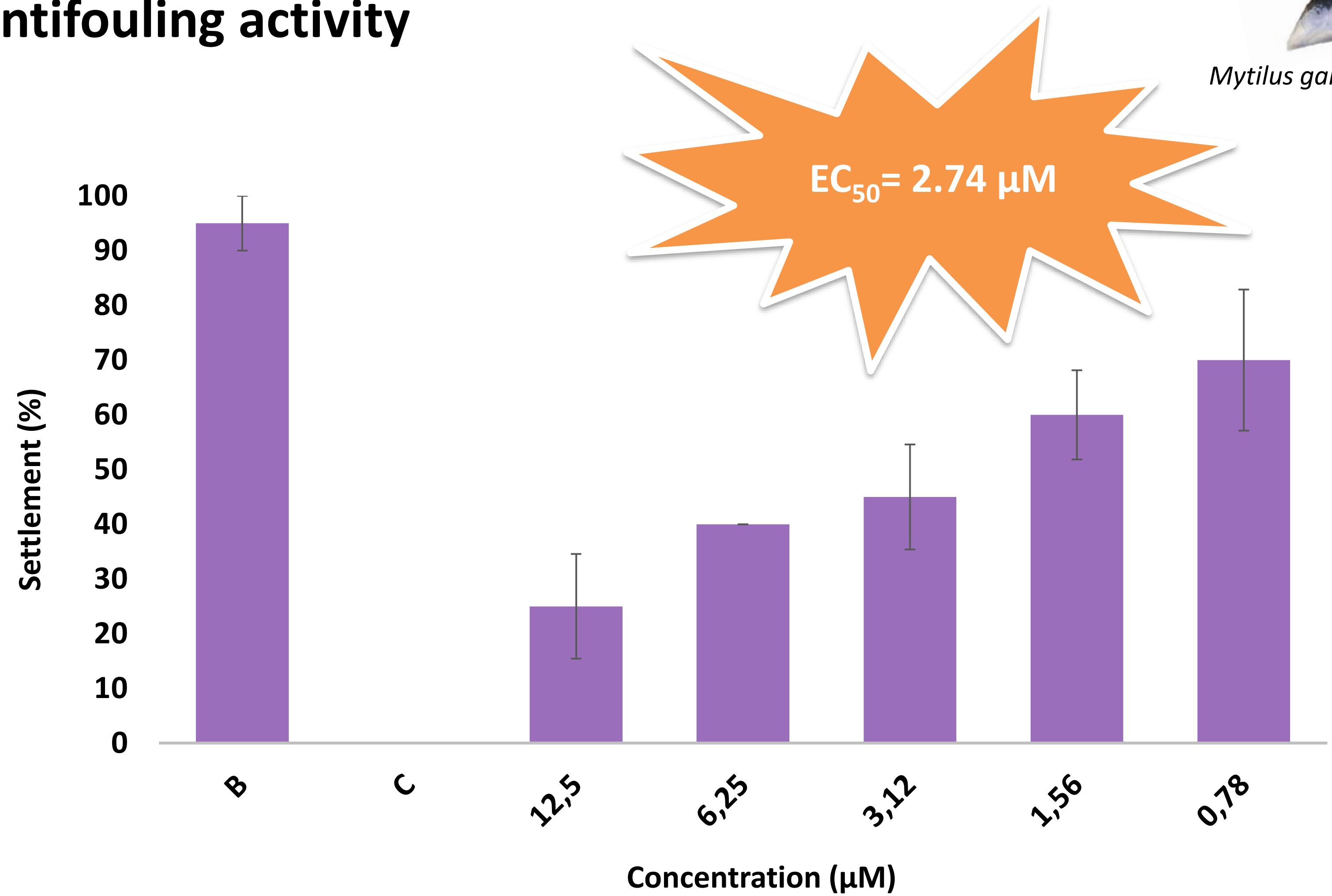


Figure 2. Concentration-response of anti-settlement activity of the promising AF compound 4 towards plantigrades of the mussel *Mytilus galloprovincialis*. B: ultra-pure water; $CuSO_4$ at 5 µM was used as positive control (C).

Toxicity against *Artemia salina*

Artemia salina sp.

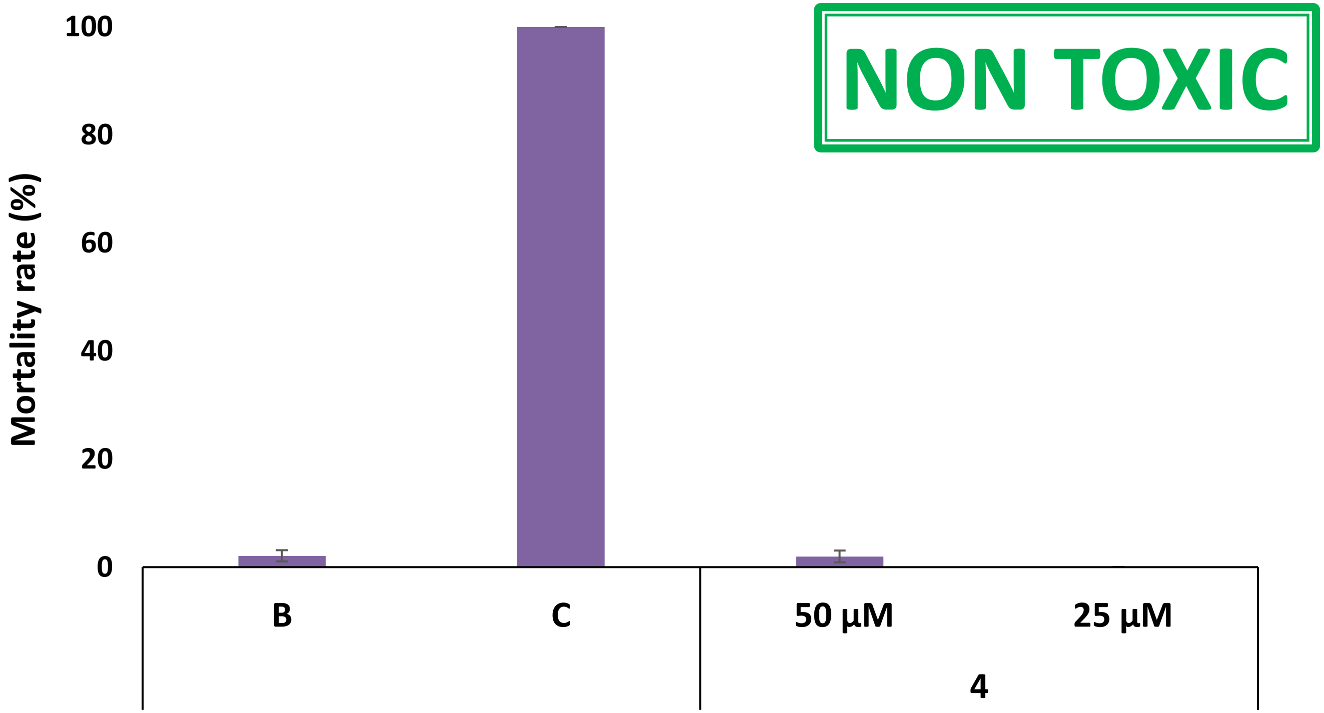


Figure 4. Mortality rate of *Artemia salina* nauplii after 48 h of exposure to compound 4 (50 and 25µM). B: filtered seawater. $K_2Cr_2O_7$ at 13.6 µM was used as positive control (C).

LogKOW calculation (EPISUITE™)

Table 1. Theoretical calculation of LogKow for the library of compounds (1-10) using EPISUITE™

Compounds	LogKOW
1	1.39
2	1.69
3	0.26
4	-0.79
5	2.67

Compounds	LogKOW
6	0.19
7	2.00
8	1.47
9	2.16
10	1.63

Conclusions

A small library of new nine amide compounds was successfuly obtained in yields between 18-88%.

After an antifouling screening with *Mytilus galloprovincialis*, compound **4** was identified as the most potent compound, with an EC_{50}=2.74µM, far lower than **GAP**.

Similarly to GAP, compound **4** was not toxic to the non-target species *Artemia salina* (<3% moratlity at 50 µM).

The LogKOW theoretical value may indicate that compound **4** will be more compatible with paint formulations.

Acknowledgments

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