FACULTY OF BIOSCIENCE ENGINEERING

N-ACYLATED HOMOSERINE LACTONE-DERIVED TETRAMIC ACIDS AS ALGICIDAL COMPOUNDS

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Introduction

As demand for novel herbicide and algicide chemistries grows, mining natural ecosystems for new lead compounds is becoming an increasingly common strategy. One underexplored ecosystem is the marine biofilm, a dense community of different species of algae and bacteria. In these highly complex systems, bacteria collaborate and compete with algae through the use of a broad palette of signalling molecules – some of which show promise as future herbicides and algicides.

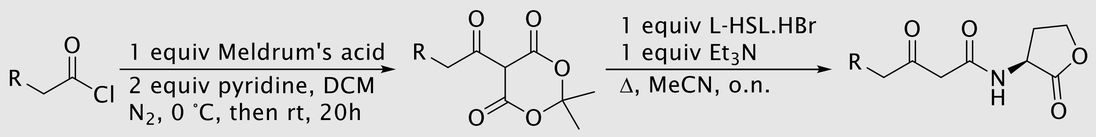
N-acylated homoserine lactones (AHLs) are an important class of bacterial signalling molecules. Although mostly known as quorum sensing molecules, they play a key role in interkingdom interactions with algae as well. Their effect on algal growth and development, as well as that of their derived tetramic acids, is the focus of this research.[1] The diatom *Phaeodactylum tricornutum* was used as a model system.

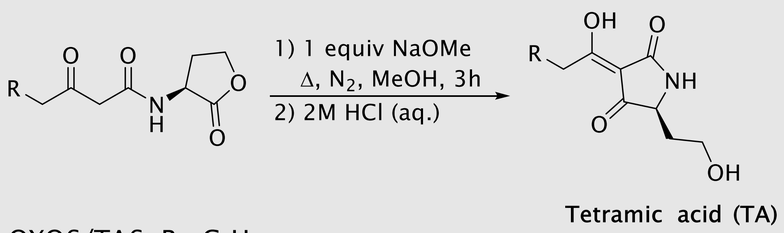
Objectives

- The identification and synthesis of novel, naturally occurring algicidal compounds
- Structure-activity relationship of the resulting compounds

Synthesis

- 3-oxo AHLs: via corresponding acylated Meldrum's acids
- Tetramic acids: via intramolecular Claisen condensation

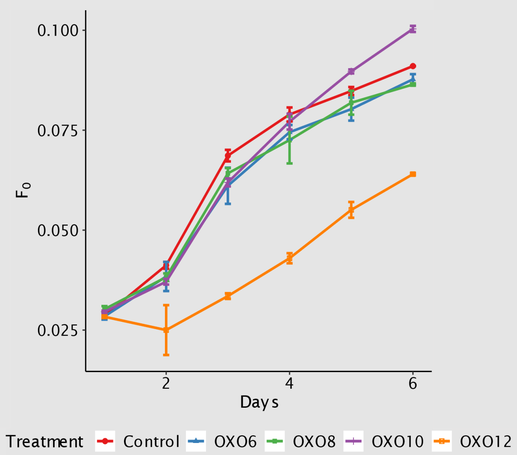




OXO6/TA6: R= C_2H_5
OXO8/TA8 : R= C_4H_9
OXO10/TA10: R= C_6H_{13}
OXO12/TA12: R= C_8H_{17}
OXO14/TA14: R= $C_{10}H_{21}$

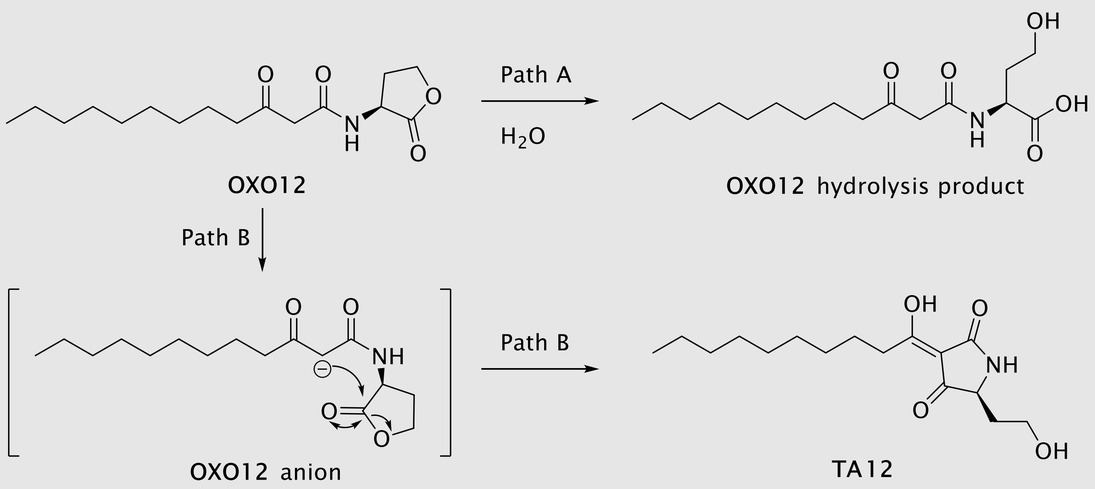
Initial screening

Daily administration of 10 µM of OXO-AHL to *P. tricornutum* showed that OXO12, but not AHLs with shorter side chains, significantly reduced chlorophyll fluorescence.



Unravelling the rearrangement of OXO12

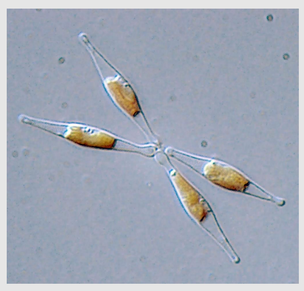
Re-arrangement of OXO12 to its corresponding tetramic acid[2], TA12, was suspected to be the causal mechanism behind the observed reduction in algal growth.

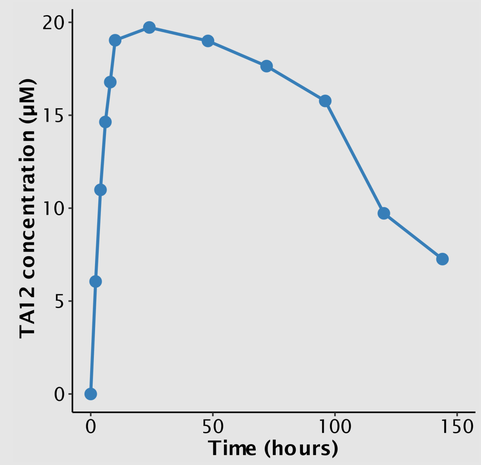


Future perspectives

- Determining the mode of action
- Structure-activity relationships of tetramic acids

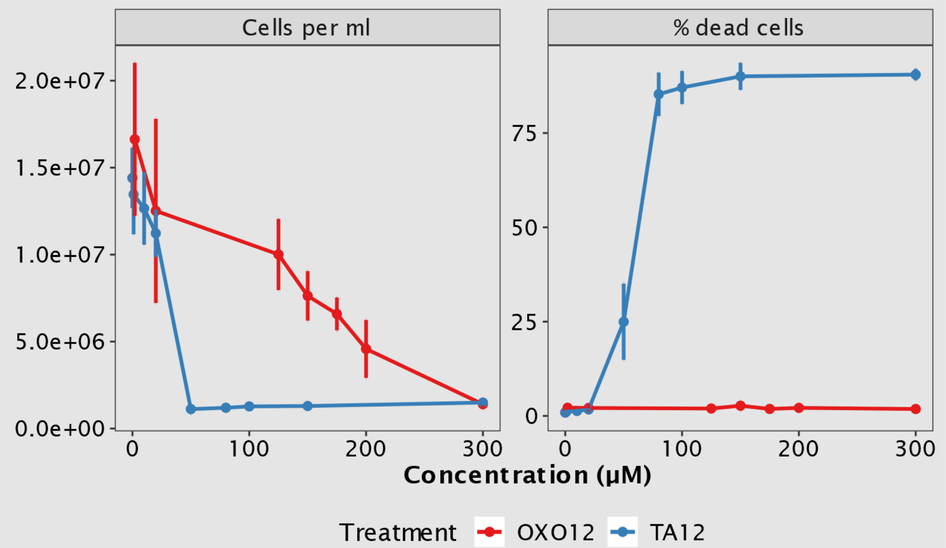
HPLC-MS follow-up of 100 µM OXO12 in the same conditions as present in the cell growth experiments shows that TA12 is indeed formed.





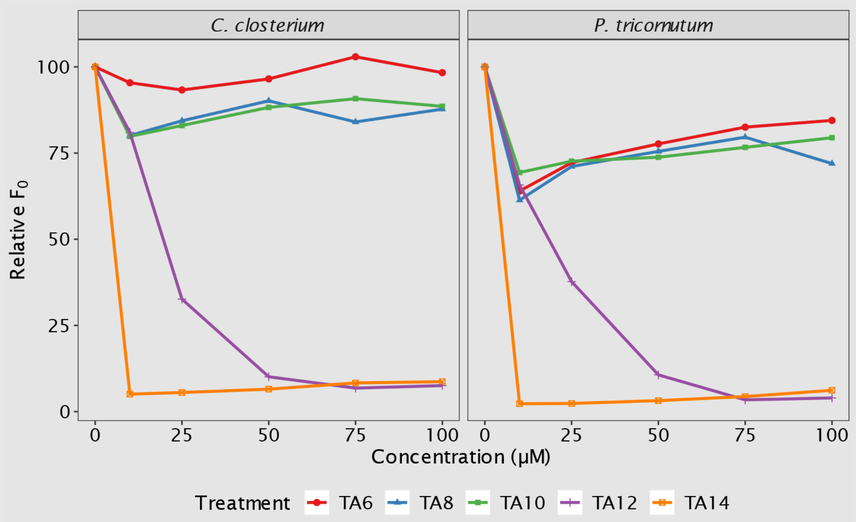
Measuring cell growth

The number of both living and dead cells in medium containing various concentrations of OXO12 and its rearrangement product, TA12, was measured. This experiment confirmed that it is indeed the rearrangement product TA12 that causes the algal mortality observed.



Tetramic acid screening

Administration of five different tetramic acids to two diatom species confirmed that increased mortality with increasing side chain length is not species-specific.



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[1] Stock, F.; Syrpas, M.; Graff van Creveld, S.; Backx, S.; Blommaert, L.; Dow, L.; Stock, W.; Ruysbergh, E.; Lepetit, B.; Bailleul, B.; Sabbe, K.; De Kimpe, N.; Willems, A.; Kroth, P. G.; Vardi, A.; Vyverman, W.; Mangelinckx, S. ACS Chem. Biol. 2019, 14 (2), 198–203.
[2] Kaufmann, G. F.; Sartorio, R.; Lee, S.-H.; Rogers, C. J.; Meijler, M. M.; Moss, J. A.; Clapham, B.; Brogan, A. P.; Dickerson, T. J.; Janda, K. D. Proc. Natl. Acad. Sci. U. S. A. 2005, 102 (2), 309–314.