The 7th International Electronic Conference on Medicinal Chemistry (ECMC 2021)

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Applying medicinal chemistry principles to solve environmental problems

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Applying medicinal chemistry principles to solve environmental problems

Graphical Abstract

SAR

HTS

HIT

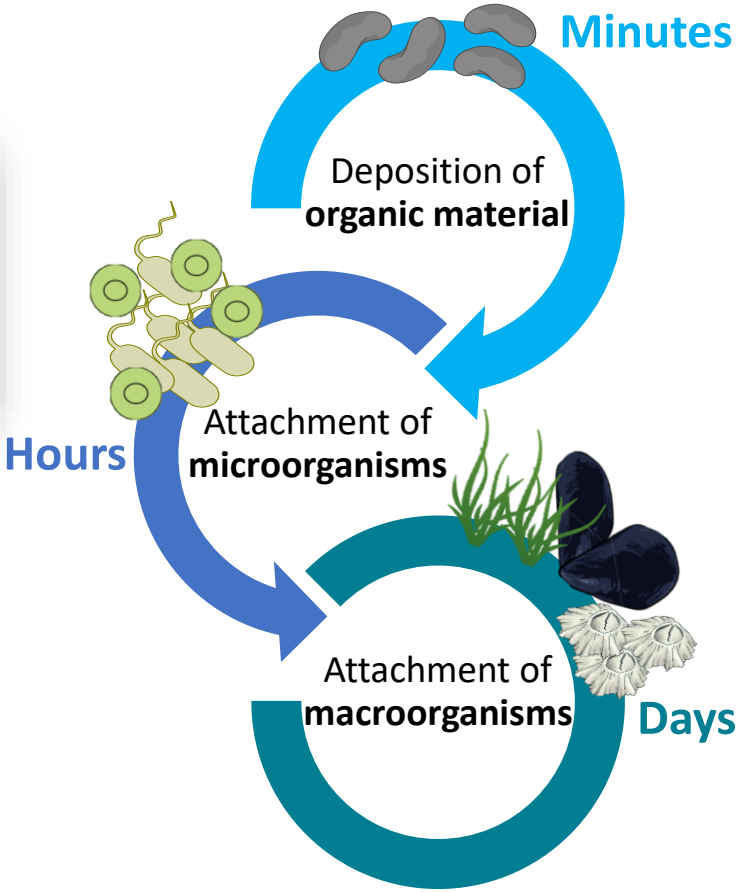
MOLECULAR TARGETS

LEAD

Abstract: Ocean-related activities are increasing every day and the successive build-up of organisms on the ship hulls (marine biofouling) leads to higher heavy oil consumption which incurs in increased costs and emissions of polluting gases, contributing to acceleration of greenhouse and acid rain effects. Other major ecological consequence of marine biofouling on the ship hulls is the marine biodiversity decline due to the trans-global contamination of ecosystems with non-indigenous species. On the other hand, antifouling paints in use are continuing leaching persistent, bioaccumulative and toxic substances to the oceans and the marine industry is facing the phase-out of most of the current biocide-based coatings, shortening the available alternatives. Climate changes and oceans temperature raising are changing the dynamic of species, also creating new challenges to combat marine biofouling. Therefore, the development of harmless and effective antifouling systems to prevent the marine biofouling is an urgent demand. The Natural Products and Medicinal Chemistry Group of CIIMAR has been synthesizing several antifouling (AF) compounds and applying the same principles of Drug Discovery process: high throughput screening to discover hits, lead generation after some optimization of hit compounds, and finally lead optimization. If this approach is followed, it is highly probable that the necessary balance between the feasible synthesis, antifouling potency, low toxicity and bioaccumulation will be found. From this work, it is possible to conclude that the application of Medicinal Chemistry principles to solve environmental problems becomes an extremely useful tool and fulfills the broad sense of the concept of this scientific area.

Keywords: antifouling, eco-friendly, proteomics, SAR, xanthones

Introduction: marine biofouling



Introduction: marine biofouling

OECD The Ocean Economy in 2030

Economic Impacts

Environmental Impacts

Human Health Impacts

Introduction: the problem

Loss of speed → Increase in propulsive energy → More fuel → Increased costs and emissions of polluting gases

Fuel consumption

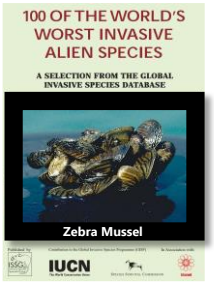
Greenhouse gases

Corrosion → Increased costs

Coating deterioration

Antifouling maintenance

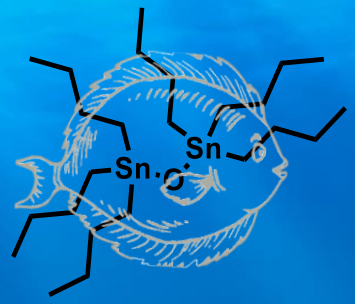
Transport of non-indigenous species → Biodiversity reduction and Public health risks

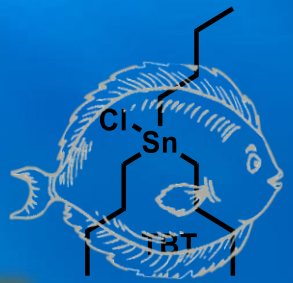


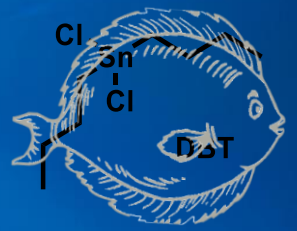
Legionnaire's Disease

Introduction: the problem

Tin-based antifouling coatings







Imposex
in female gastropods

Oysters
malformations

Nucella lapillus
extinction

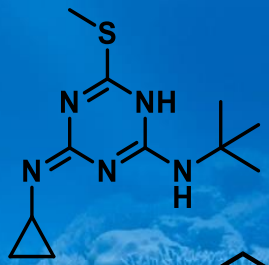
Introduction: the problem

Copper-based antifouling coatings

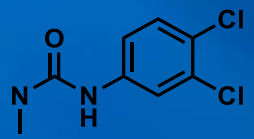
+booster biocides (herbicides/pesticides)

1 million tonnes of copper per year

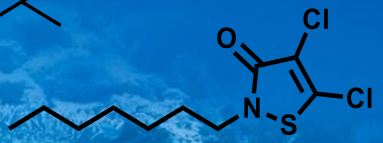
Irgarol 1051®



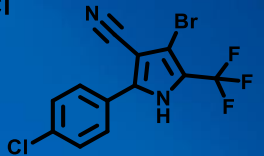
Diuron®



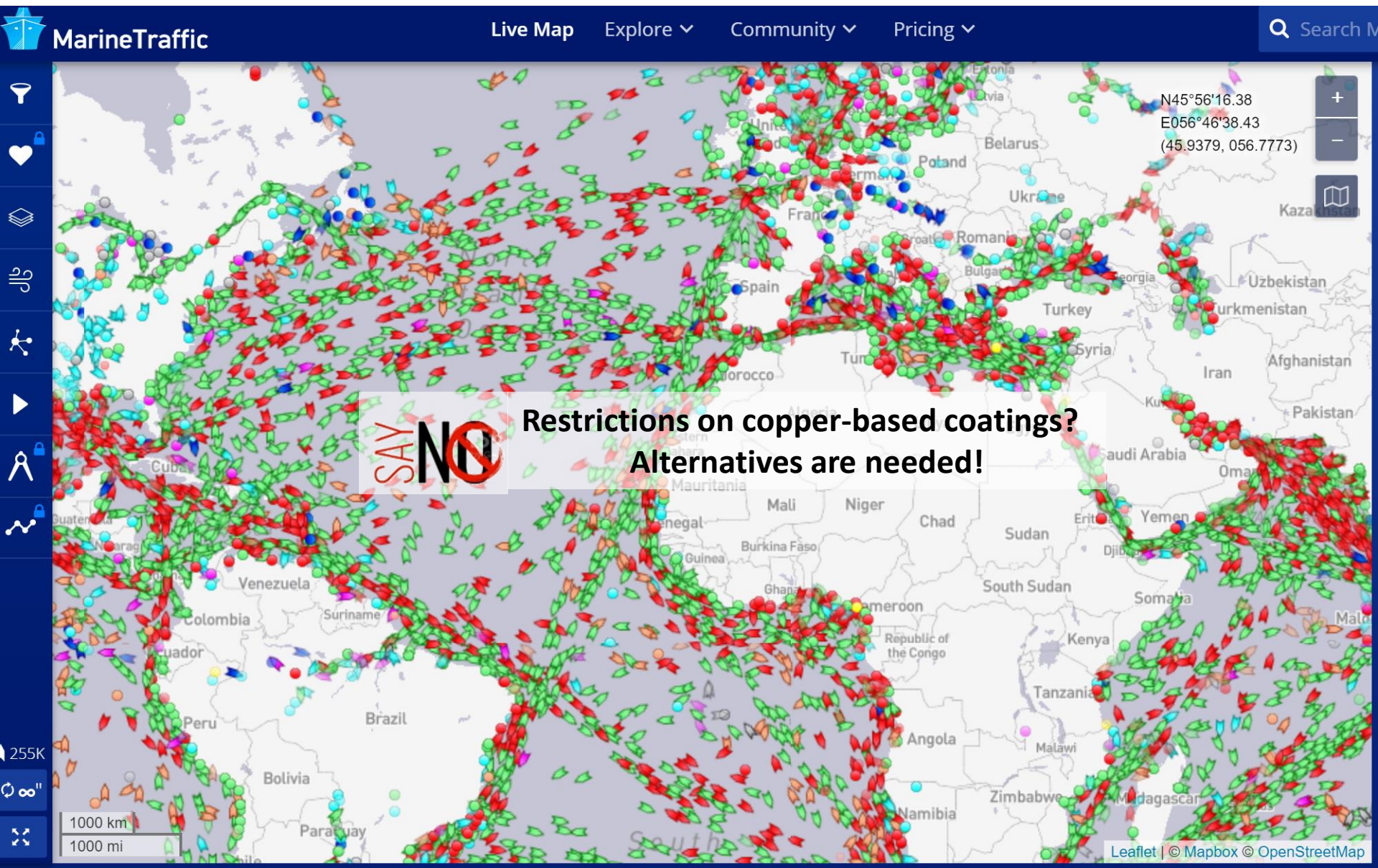
SeaNine 211®



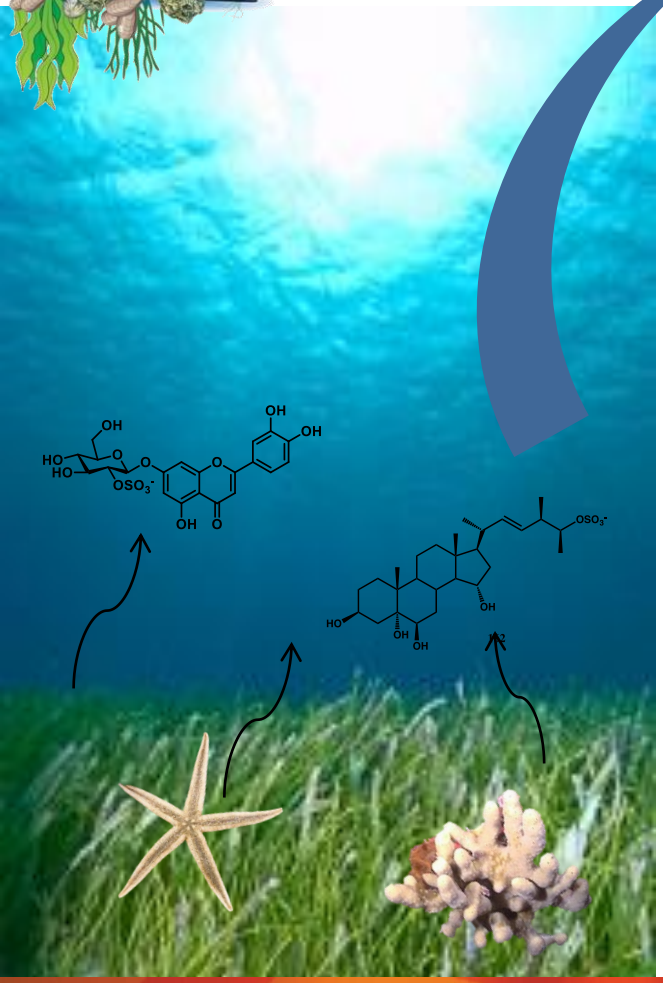
Econea®



Persistent and Toxic



Our strategy: synthesize Nature-inspired antifouling compounds



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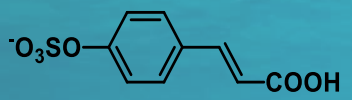
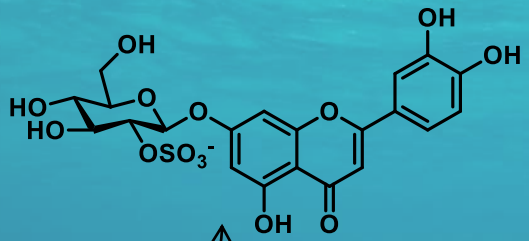
Four series of synthetic Nature-inspired antifouling compounds

Cinnamic and gallates



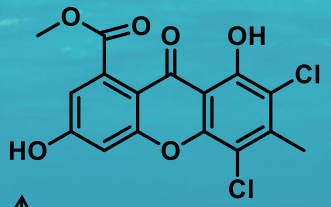
[1]

Flavonoids



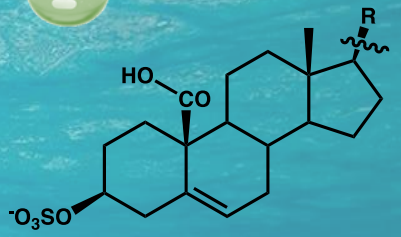
[2]

Xanthones



[3]

Steroids



[4]

Seagrass

Marine-derived fungus

Starfish

Sponge

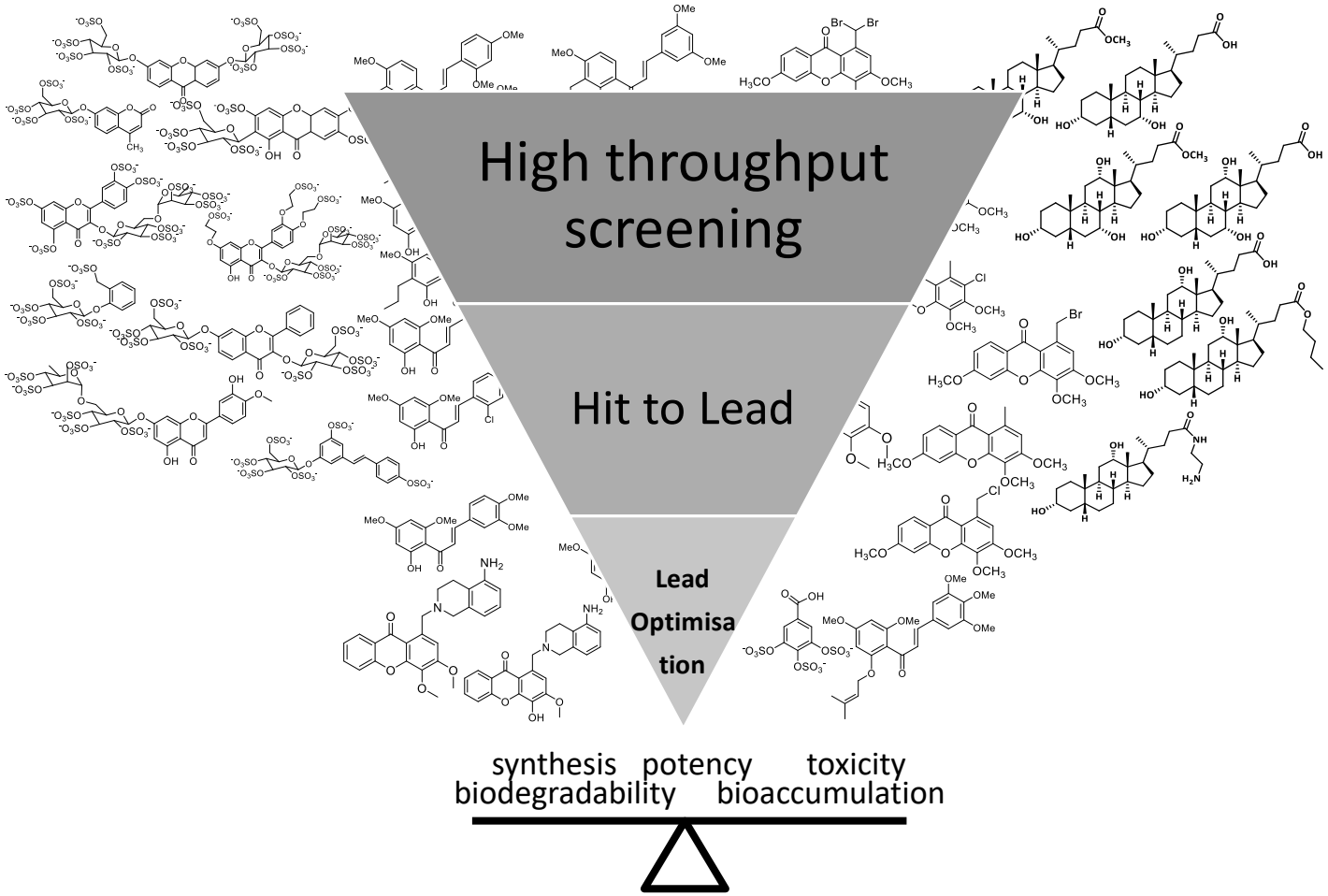
[1] *Biofouling*, **2017**, 33 (10), 927-942.

[2] *Natural Product Research*, **2018**, 3260-3272.

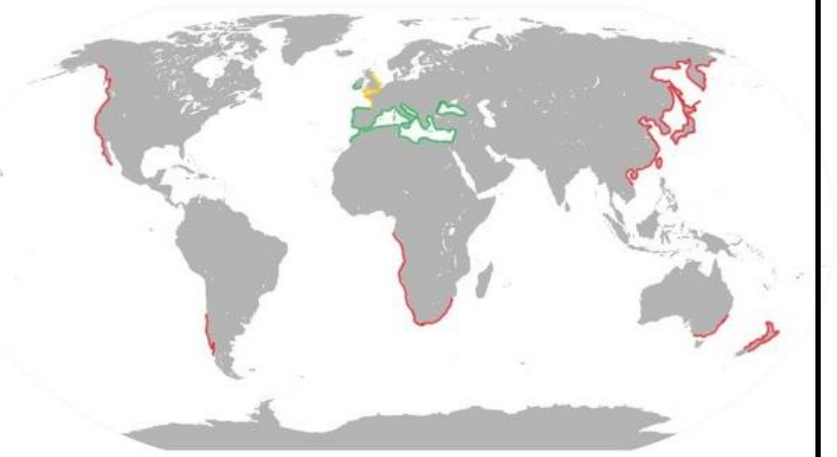
[3] *Marine Biotechnology*, **2013,** 15 (5), 552-558;
Nat Prod Commun, **2015**,10 (6), 1033-1034.

[4] *Journal of Molecular Endocrinology* 2018, 61(2), T211-T231.

Applying the same principles of the Drug Discovery process

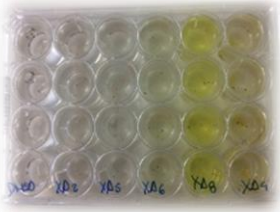


Evaluation of the settlement of *Mytilus galloprovincialis* larvae

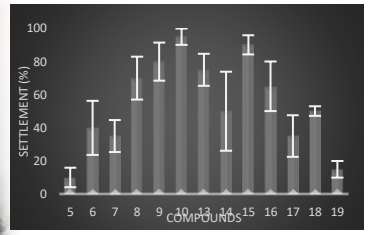


1.Collect *Mytilus galloprovincialis*

2.Select small and viable larvae



3.Incubate larvae with compounds solution



4.Count larvae adherence

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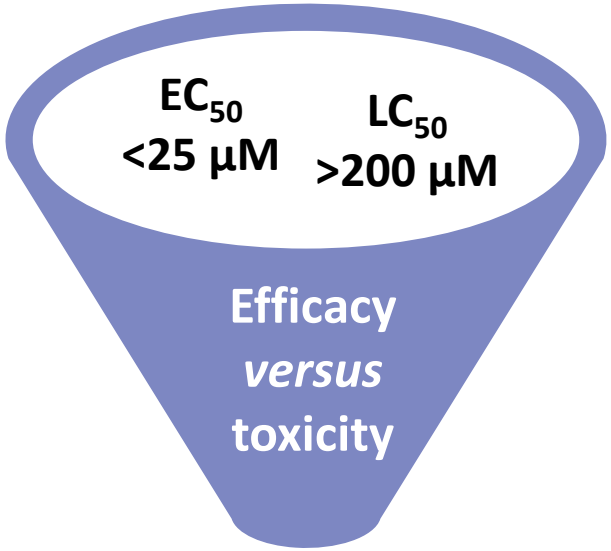
Non-toxic antifouling agents



LC_{50}, the median lethal dose

EC_{50}, concentration that inhibited 50% of larval settlement

LC_{50}/EC_{50}, therapeutic ratio

U.S. Navy recommendations:
$LC_{50}/EC_{50} > 15$

SERIES I

EC_{50} < 25 µM

LC_{50} > 500 µM

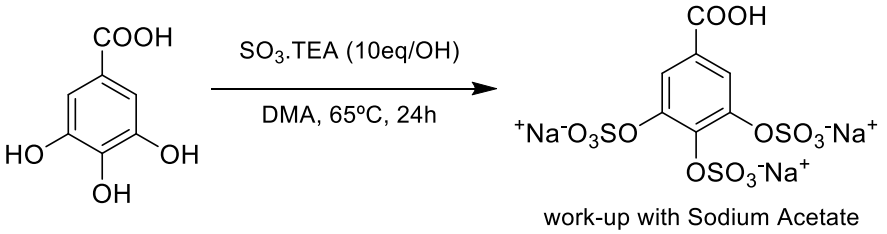
Efficacy *versus* toxicity

1 flavonoid

1 xanthone

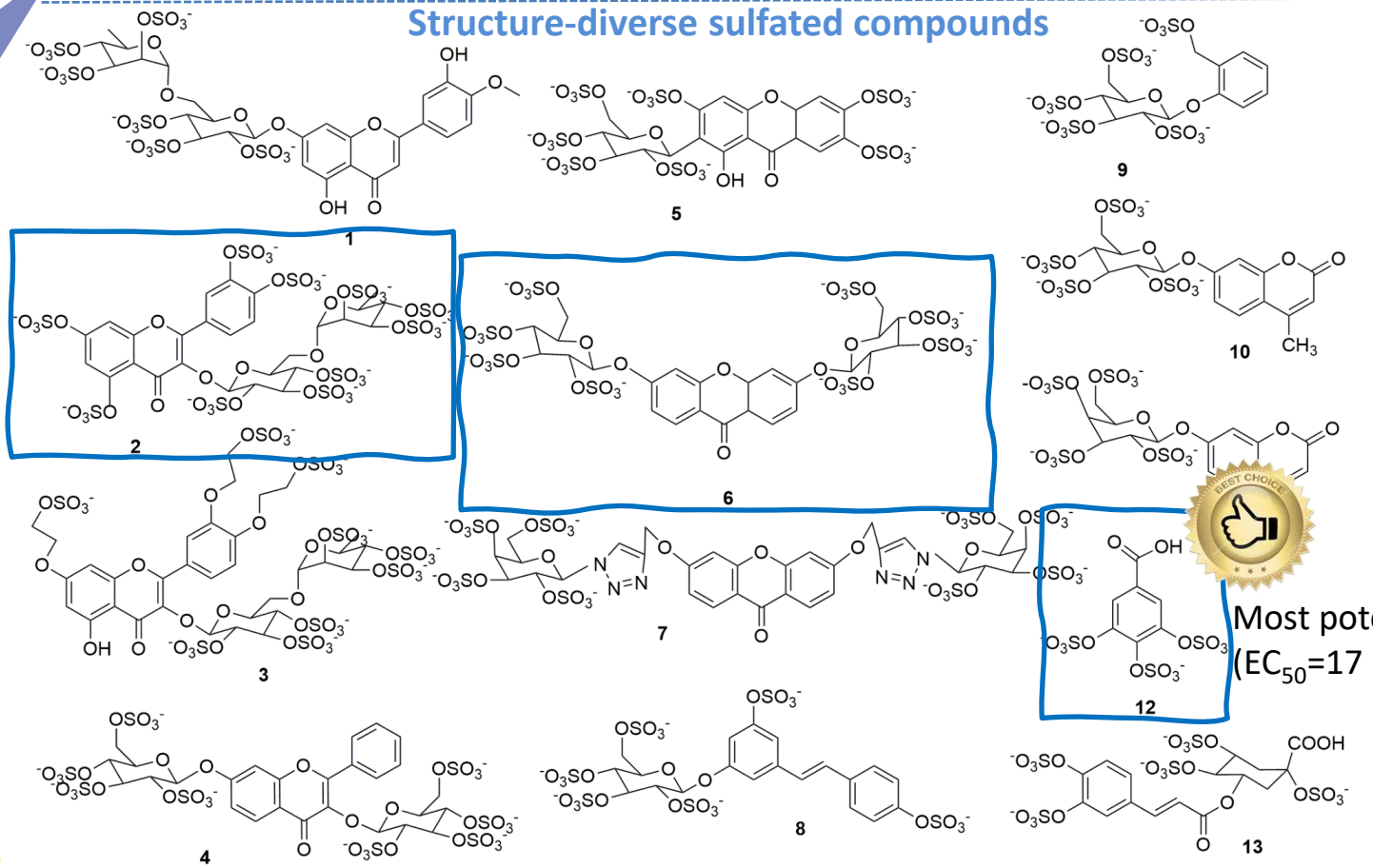
1 gallate

One step synthesis from natural raw materials



work-up with Sodium Acetate

Structure-diverse sulfated compounds



Less toxic than Econea (LC_{50} > 500 µM)

Econea®

EC_{50}=4 µM

LC_{50}=108 µM

Most potent (EC_{50}=17 µM)

Scientific reports, **2017**, 7, 42424.

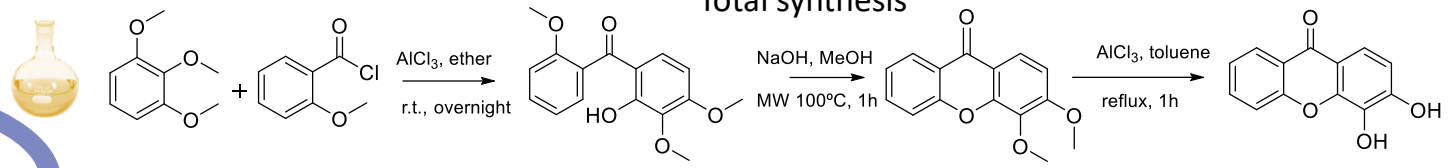
SERIES II

EC_{50} < 25 µM

LC_{50} > 500 µM

Efficacy *versus* toxicity

Total synthesis



Oxygenated xanthones and thioxanthones

4 oxygenated xanthones at 3 and/or 4 positions

1 thioxanthone

Less toxic than Econea (LC_{50} > 500 µM)

Econea®

EC_{50}=4 µM

LC_{50}=108 µM

EC_{50} similar to Econea (EC_{50} =3.53-4.60 µM)

International patent PCT/IB2019/059886; Biomolecules, **2020**, 10, 1126.

SERIES III

EC_{50} < 10 µM

LC_{50} > 200 µM

Efficacy *versus* toxicity

3 trimethoxyphenyl B ring flavonoids

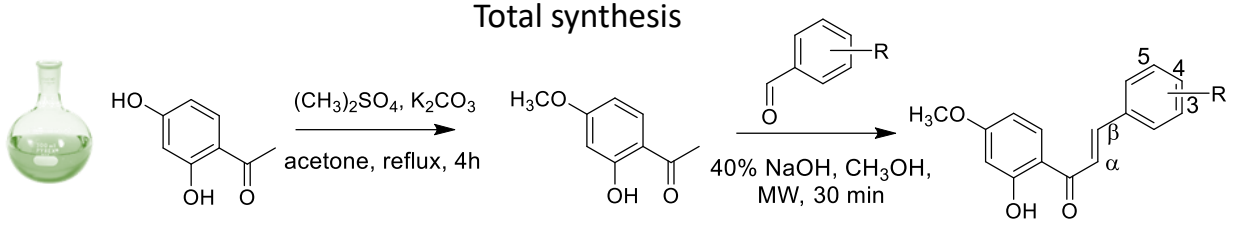
Less toxic than Econea (LC_{50} > 200 µM)

Econea®

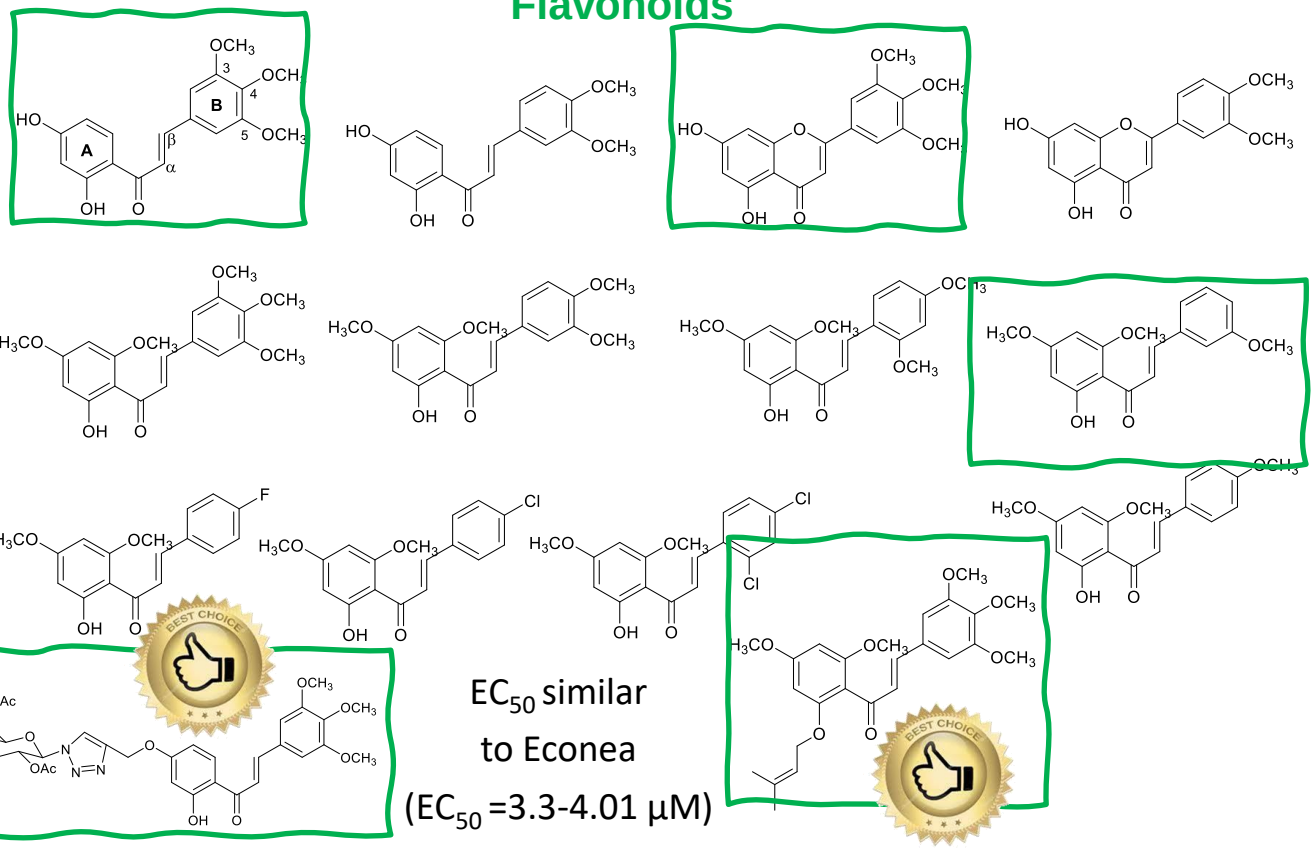
EC_{50}=4 µM

LC_{50}=108 µM

Total synthesis



Flavonoids



EC_{50} similar to Econea (EC_{50} =3.3-4.01 µM)

Science of the Total Environment, **2018**, 643, 98-106. Marine Drugs, **2021**, 19, 5.

SERIES IV

EC_{50}< 10 µM

LC_{50} > 200 µM

Efficacy *versus* toxicity

4 methyl ester derivatives

Less toxic than Econea (LC_{50} > 200 µM)

Econea®

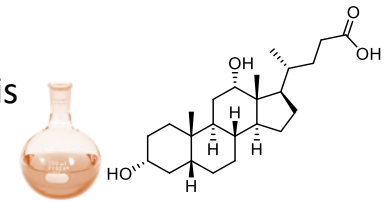
EC_{50}=4 µM

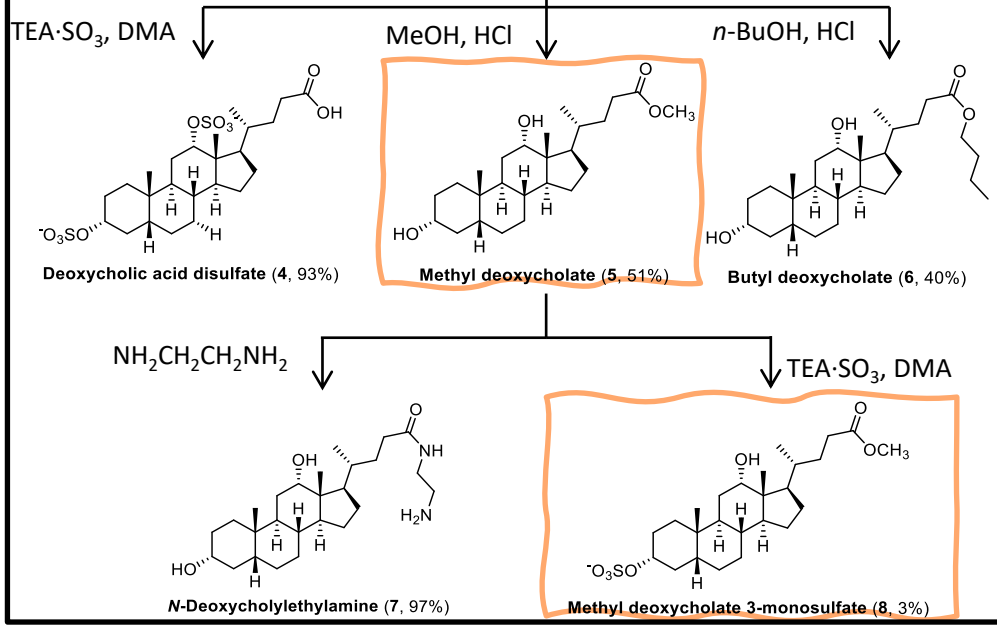
LC_{50}=108 µM

A

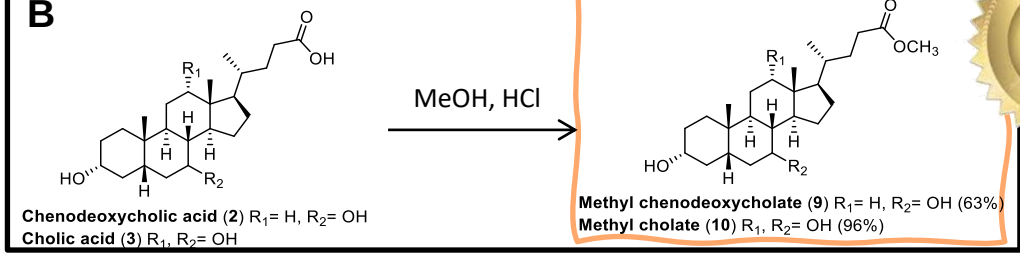
One step synthesis from natural raw materials

Bile acids





B



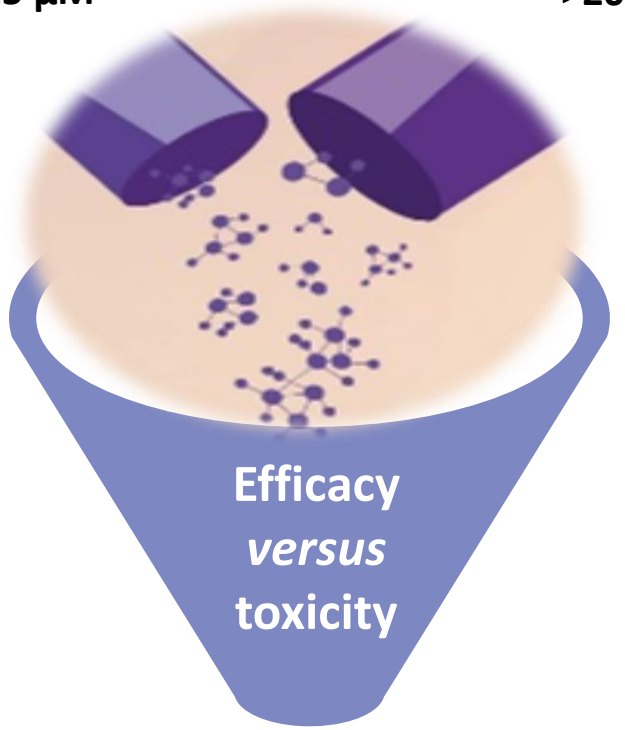
EC_{50} similar to Econea (EC_{50} =3.72-4.16 µM)

Ecotoxicology and Environmental Safety, **2020**, 187, 109812.

HIT selection

EC_{50}
<25 µM

LC_{50}/EC_{50}
>20



15 HIT compounds

3 sulfated derivatives

4 xanthones

4 flavonoids

4 bile acids

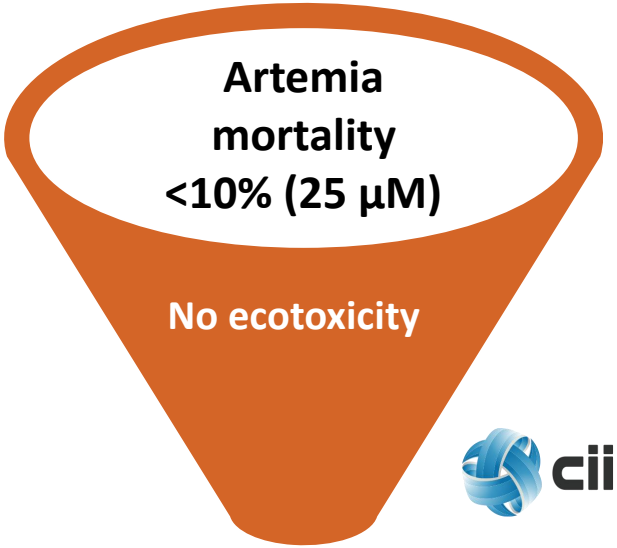
HIT TO LEAD

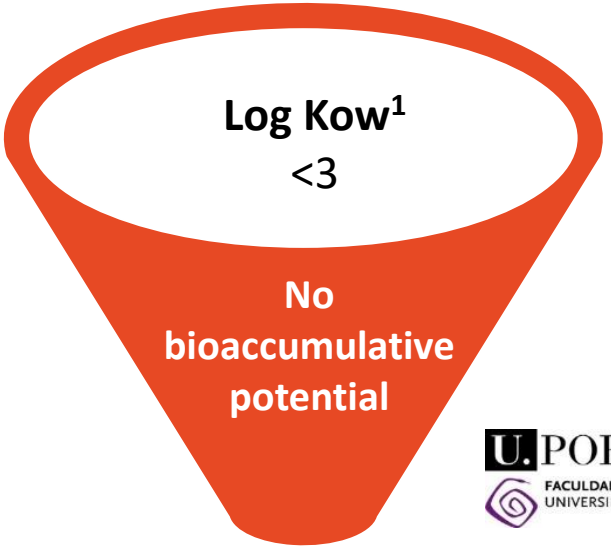
Ecotoxicity to marine nontarget organisms

***Artemia salina* mortality assay**

Bioaccumulation

[1] Partition coefficient n-octanol/water





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Ecotoxicity to marine nontarget organisms

Marine shrimp
Artemia salina

<10% mortality at 25 µM

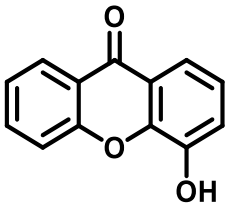
>10% mortality at 25 µM

Econea®

100% mortality at 25 µM

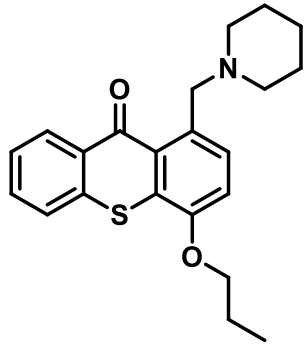
Structure-properties relationship for xanthones

Ecotoxicity — Potency



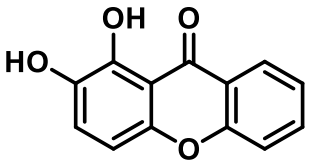
100% mortality at 50 µM

EC_{50} (Mytilus)= 21.48 µM



100% mortality at 50 µM

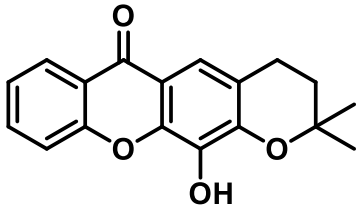
EC_{50} (Mytilus)= 3.53 µM



100% mortality at 50 µM

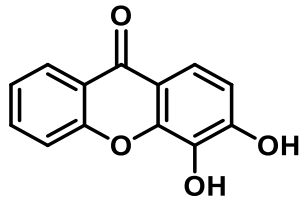
EC_{50} (Mytilus)= 15.46 µM

Potency — No ecotoxicity



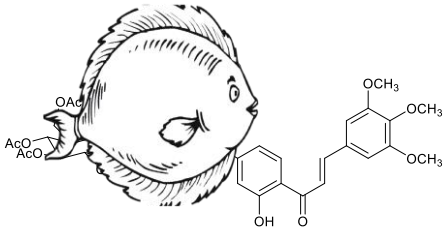
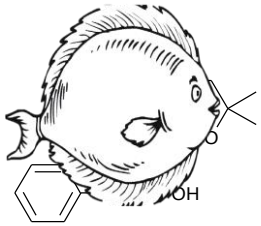
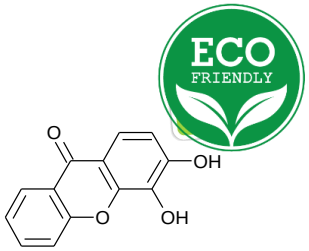
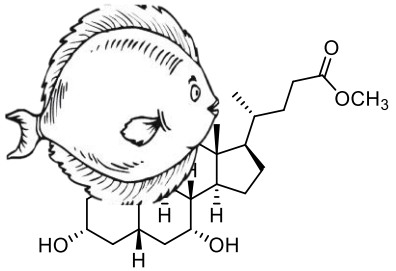
<10% mortality at 50 µM

EC_{50} (Mytilus)= 4.60 µM

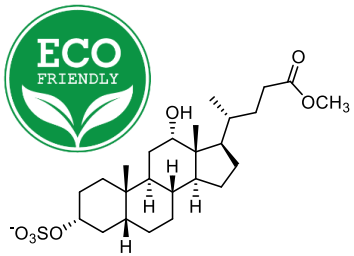
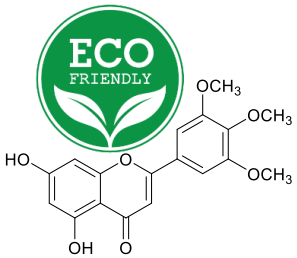
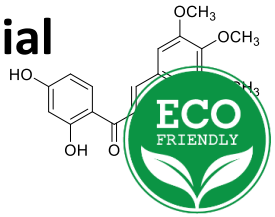
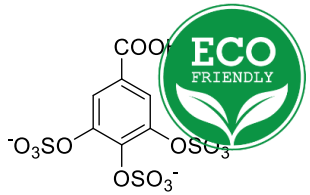


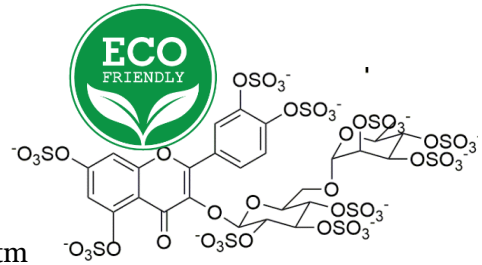
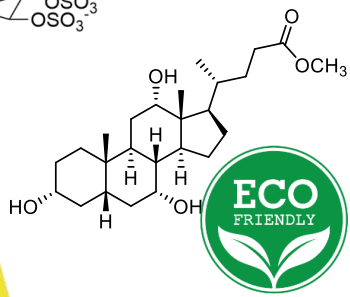
<10% mortality at 50 µM

EC_{50} (Mytilus)= 11.53 µM

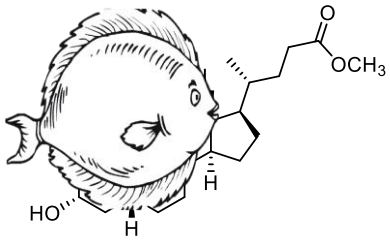





Bioaccumulative potential

www.epa.gov/opt/exposure/pubs/episuite.htm

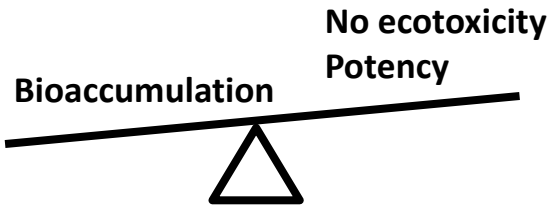


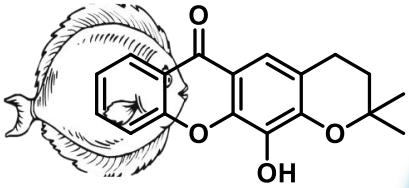
Log Kow < 3

Log Kow > 3

Log Kow, partition coefficient n-octanol/water

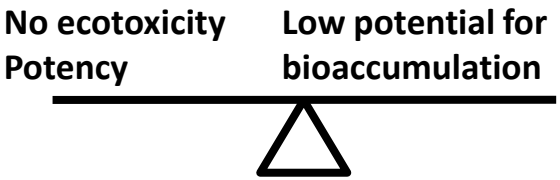
Structure-properties relationship for xanthones

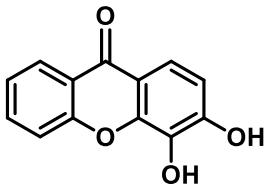




Log Kow= 5.24

EC_{50} (Mytilus)= 4.60 µM



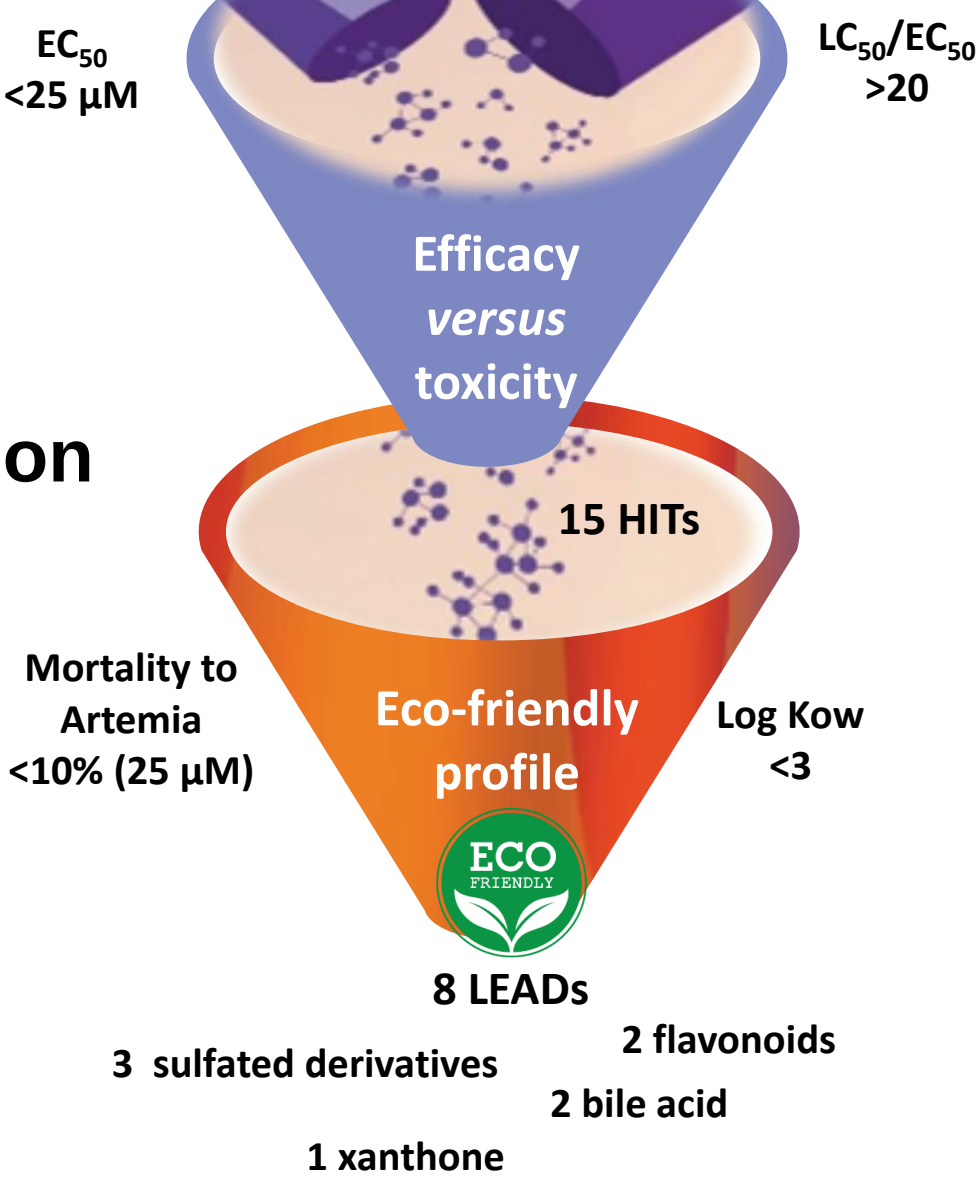


Log Kow= 2.88

EC_{50} (Mytilus)= 11.53 µM

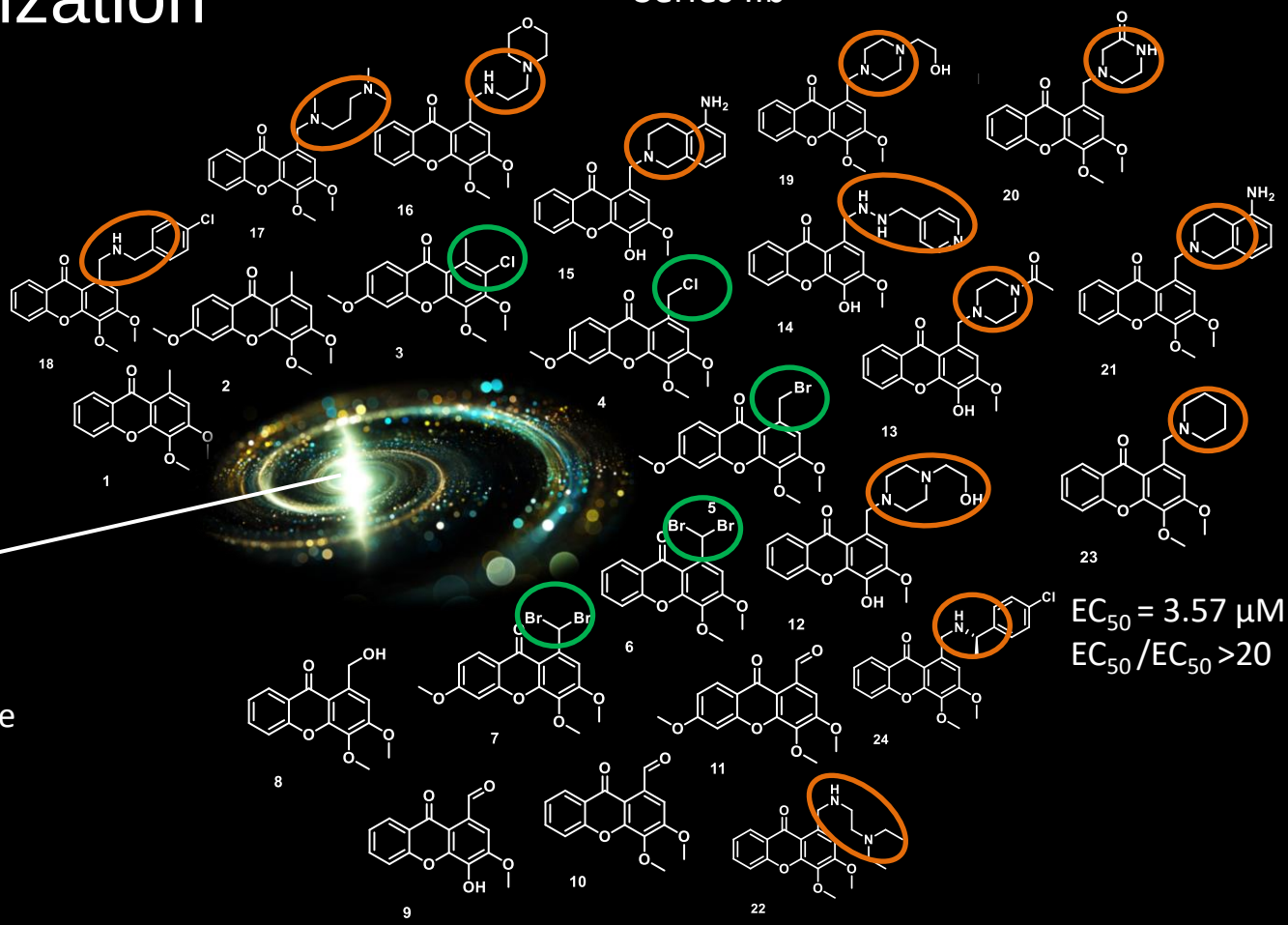
Log Kow, partition coefficient n-octanol/water

LEAD selection

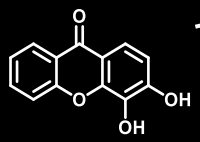


LEAD optimization

Series IIb



Series II



3,4-dihydroxyxanthone

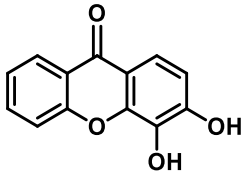
EC_{50} = 11.53 μM
EC_{50} /EC_{50} >20

EC_{50} = 3.57 μM
EC_{50} /EC_{50} >20

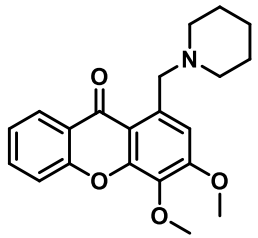
molecular extension strategy

Molecular targets on mussel settlement

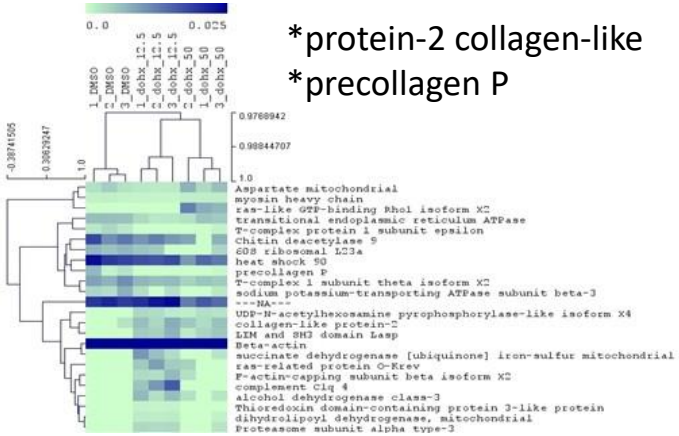
Proteome of mussel larvae in response to xanthones



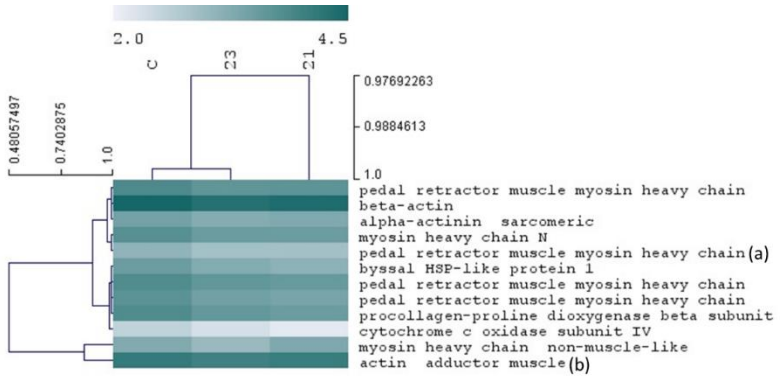
Mytilus collagen proteins (PreCols)*



Myosin isoforms from pedal retractor muscle



*protein-2 collagen-like
*precollagen P



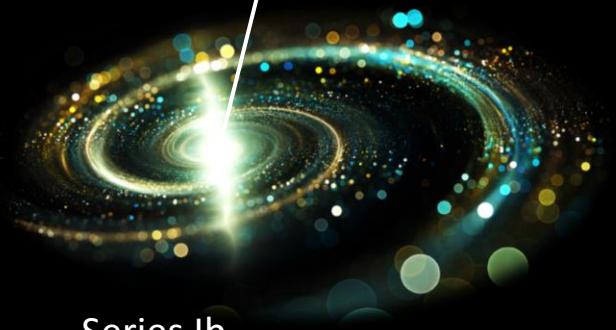
Division of Cell Biology, Linköping University, Sweden

LEAD optimization

Flavonoids

Series IIIb

Sulfated compounds



Series Ib

Bile acids

Series IVb

Conclusions

International patent PCT/IB2019/059886: Xanthonic compounds and their use as antifouling agents

Helping Mother Nature through Medicinal Chemistry

Acknowledgments

Synthesis and SAR studies

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Screening and ecotoxicity studies

Blue Biotechnology and Ecotoxicology Group - CIIMAR, University of Porto, Portugal

Joana R Almeida, Alexandre Campos, Vitor Vasconcelos

Proteomic studies

Division of Cell Biology, Linköping University, Sweden

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