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Development of triazolyl acetophenone hybrids as a new strategy for the prevention of marine biofouling

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pharmaceuticals MDPI

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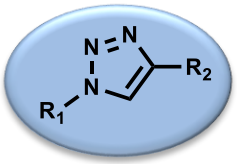
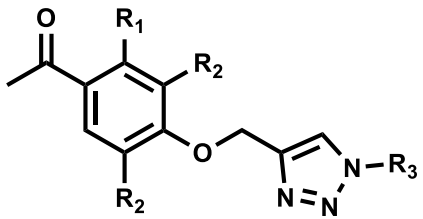
Development of triazolyl acetophenone hybrids as a new strategy for the prevention of marine biofouling



Antifouling potential

Synthesis of acetophenone-1,2,3-triazole hybrids



Antifouling activity and Ecotoxicity assay

- ✓ *Mytilus galloprovincialis*
- ✓ Marine bacteria
- ✓ *Navicula* sp.
- ✓ *Artemia salina*

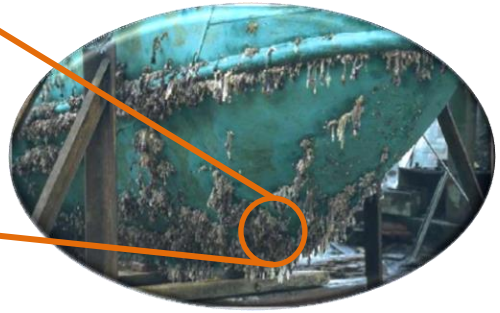
Abstract: The 1,2,3-triazole ring has been gaining increased attention in Medicinal Chemistry over the past years since it has been associated with metabolic stability and several biological activities, including antifouling. Therefore, the hybridization of this heterocycle with other pharmacophores which showed ability to prevent marine biofouling can be a strategy to obtain more effective and stable compounds. Marine biofouling remains a huge challenge for maritime industries and public health, causing economic, human, and ecological concerns, with few environmentally safe options to prevent this phenomenon. Considering that the incorporation of an acetophenone into coatings was found to decrease the attachment of marine micro and macroorganisms, and in an attempt to obtain new effective acetophenone derivatives, a series of triazolyl acetophenones were obtained, through hybridization with 1,2,3-triazole ring and other pharmacophores, using the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) methodology. Fourteen new acetophenone-1,2,3-triazole hybrids were obtained and the screening against the settlement of the macrofouling mussel *Mytilus galloprovincialis* and on five biofilm-forming marine bacteria allowed to identify promising compounds. Three compounds were able to inhibit the growth of marine bacteria *Roseobacter litoralis*, while other three compounds significantly inhibited the settlement of mussel larvae. For those, the ability to inhibit the growth of *Navicula* sp. microalgae was also evaluated. One acetophenone was found to display complementary antifouling activity against macrofouling mussel and microalgae *Navicula* sp. The most potent compounds also showed to be less toxic to the non-target species *Artemia salina* than the commercial biocide Econea®.

Keywords: 1,2,3-triazole ring; Acetophenone; Antifouling activity; Marine biofouling

INTRODUCTION

MARINE BIOFOULING

- ✓ Mussels
- ✓ Algae
- ✓ Bacteria
- ✓ Barnacles
- ✓ (…)



CONSEQUENCES

- ➢ Higher fuel costs
- ➢ Corrosion of equipments
- ➢ Spread of invasive species

PREVENTION BY USING MARINE COATINGS WITH BIOCIDES

TRIBUTYLTIN-BASED — BANNED

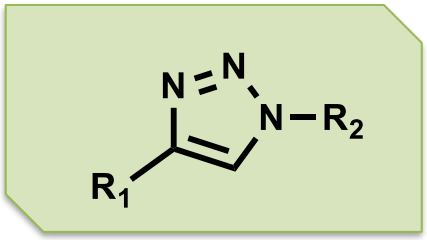
COPPER/ZINC AND BOOSTER BIOCIDES — Still harmful for environment

NEW SAFE ANTIFOULING COMPOUNDS ARE NEEDED

[1] Parisi, C. *et al*. Journal of Marine Science and Engineering, **2022**, *10*, 792.

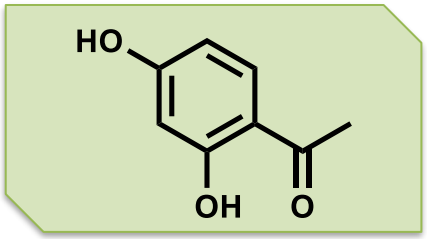
AIMS

1,2,3-Triazole Ring



- ✓ Easy and high-yield synthesis through copper (I) catalyzed azide-alkyne cycloaddition (CuAAC)
- ✓ High stability towards hydrolysis, enzymatic degradation and oxidative and reductive conditions
- ✓ Several biological activities associated to this heterocyclic moiety, including antifouling activity

Acetophenone



- ✓ Incorporated into a marine coating, 2',4'-dihydroxyacetophenone showed moderate antibacterial activity against marine bacterium *Bacillus macrolides*, and reduced the attachment of the diatom *Navicula incerta* and the macroalgal spore *Ulva pertusa*

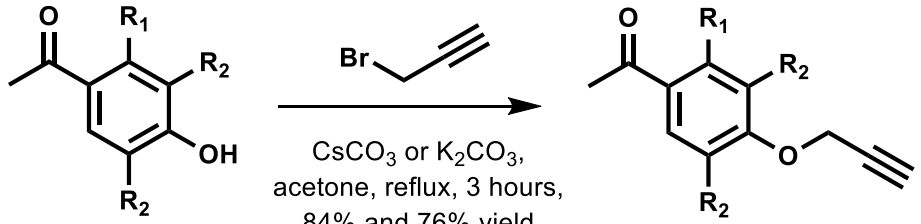
In order to obtain new effective antifoulants, these pharmacophores were combined through CuAAC and the resulted hybrids were evaluated for their antifouling activity

[2] Kantheti, S. *et al*. RSC Advances, **2015**, *5*, 3687-3708. [3] Pereira, D. *et al*. Molecules, **2022**, *27*, 230. [4] Jung, S. *et al*. Scientia Marina, **2017**, *81*, 449–456.

RESULTS AND DISCUSSION

✓ **Synthesis**

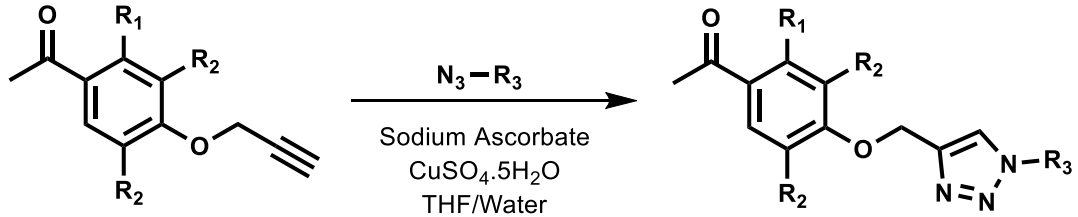
1st step: Synthesis of propargyloxyacetophenones **2a** and **2b**



1a: R_1=H, R_2=OCH_3
1b: R_1=OH, R_2=H

2a: R_1=H, R_2=OCH_3
2b: R_1=OH, R_2=H

2nd step: Synthesis of acetophenone-1,2,3-triazole hybrids **3a-9b** through CuAAC



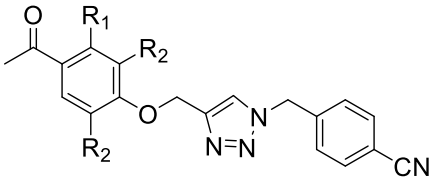
2a: R_1=H, R_2=OCH_3
2b: R_1=OH, R_2=H

3a–9b

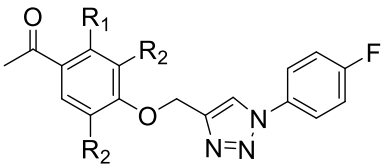
[5] Neves, A.R. *et al*. Marine Drugs, **2021**, *19*, 682.

RESULTS AND DISCUSSION

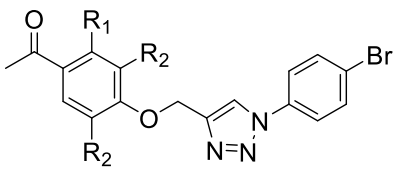
✓ **14 New acetophenone-1,2,3-triazole hybrids were obtained**



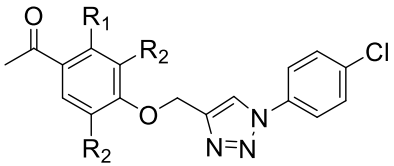
3a: R_1=H, R_2=OCH_3, η=65%
3b: R_1=OH, R_2=H, η=84%



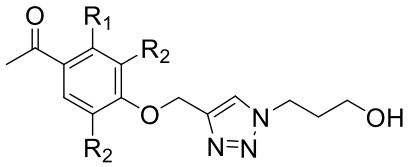
4a: R_1=H, R_2=OCH_3, η=53%
4b: R_1=OH, R_2=H, η=83%



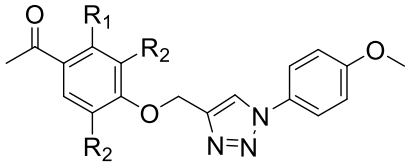
5a: R_1=H, R_2=OCH_3, η=65%
5b: R_1=OH, R_2=H, η=41%



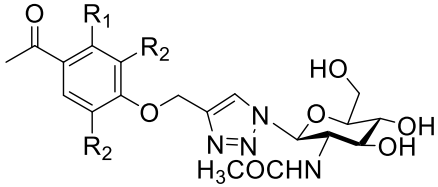
6a: R_1=H, R_2=OCH_3, η=47%
6b: R_1=OH, R_2=H, η=61%



7a: R_1=H, R_2=OCH_3, η=56%
7b: R_1=OH, R_2=H, η=40%



8a: R_1=H, R_2=OCH_3, η=30%
8b: R_1=OH, R_2=H, η=40%

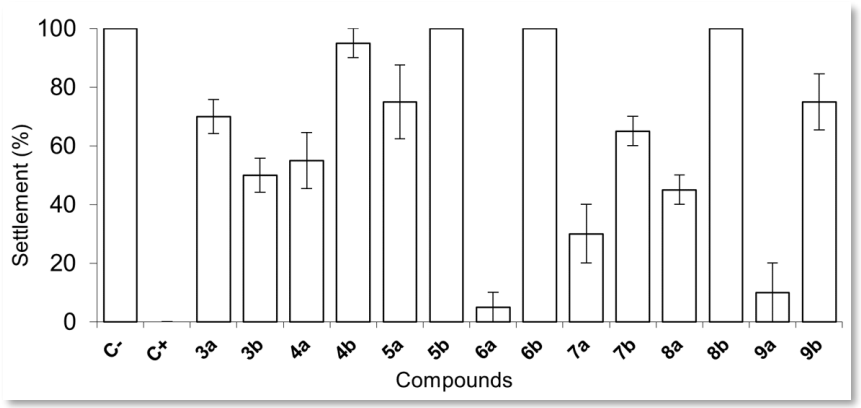


9a: R_1=H, R_2=OCH_3, η=65%
9b: R_1=OH, R_2=H, η=84%

[5] Neves, A.R. *et al*. Marine Drugs, **2021**, *19*, 682.

RESULTS AND DISCUSSION

✓ **Antimacrofouling activity against *Mytilus galloprovincialis* at 50 µM:**



For compounds with settlement lower than 40%, the EC_{50} value was determined:

6a	**EC_{50} 28.87 µM; 11.20 µg.mL^{-1}**
7a	**EC_{50} 40.14 µM; 13.46 µg.mL^{-1}**
9a	**EC_{50} 20.68 µM; 9.94 µg.mL^{-1}**

EC_{50} are recommend to be less than 25 µg.mL^{-1} for effective antifoulants

✓ **Bacterial growth inhibition assay against biofilm-forming marine bacteria *Vibrio harveyi*, *Cobetia marina*, *Halomonas aquamarina*, *Pseudoalteromonas atlantica* and *Roseobacter litoralis*:**

Compounds **3b** and **4b** showed moderate activity against *R. litoralis*

3b	**EC_{50} 49.81 µM; 17.35 µg.mL^{-1}**
4b	**EC_{50} 105.02 µM; 34.38 µg.mL^{-1}**

[5] Neves, A.R. *et al*. Marine Drugs, **2021**, *19*, 682.

RESULTS AND DISCUSSION

✓ **The most active compounds against *M. galloprovincialis* were subjected to additional assays:**

✓ **Antimicrofouling activity against marine diatom *Navicula* sp.**

Compound **7a** showed to have activity against this species with an EC_{50} of 26.73 µM; 8.96 µg.mL^{-1}

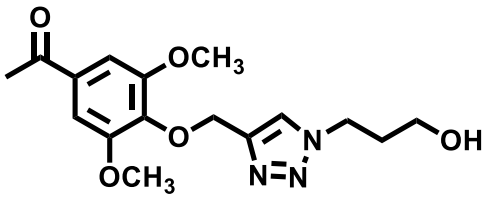
✓ **Ecotoxicity assay against non-target marine organism *Artemia salina***

Compounds **6a**, **7a** and **9a** are less toxic to *Artemia salina* than the commercial biocide ECONEA® at 25 and 50 µM concentrations. Mortality rates of acetophenones **7a** and **9a** were similar to the negative control

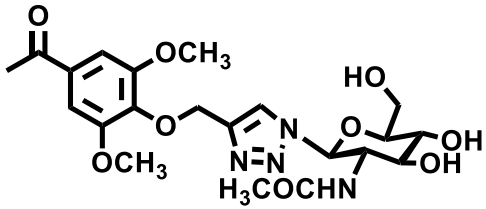
[5] Neves, A.R. *et al*. Marine Drugs, **2021**, *19*, 682.

CONCLUSIONS

- ✓ 14 New acetophenone-1,2,3-triazole hybrids were synthesized in two steps with moderate to good yields
- ✓ Three compounds (**6a**, **7a** and **9a**) had EC_{50} values lower than 25 $\mu g.mL^{-1}$ against *Mytilus galloprovincialis*
- ✓ Compound **7a** showed complementary antifouling activity against the microalgae *Navicula* sp.
- ✓ The most promising compounds **7a** and **9a** showed to be non-toxic in an ecotoxicity assay against the non-target species *Artemia salina*



7a



9a

ACKNOWLEDGMENTS

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