4th International Electronic Conference on Medicinal Chemistry

1-30 November 2018
chaired by Dr. Jean Jacques Vanden Eynde

sponsored by pharmaceuticals

Small molecules from the sea: models for innovative antimicrobial agents

Solida Long [1,2,†], Diana Resende [1,2,†], Patrícia Pereira-Terra [2,3,†], Ângela Inácio [2,3], Paulo Martins da Costa [2,3], Eugénia Pinto [2,4], Anake Kijjoa [2,3], Madalena Pinto[1,2], Emília Sousa [1,2*]

[1] Laboratory of Organic and Pharmaceutical Chemistry (LQOF), Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Portugal
[2] Interdisciplinary Centre of Marine and Environmental Research (CIIMAR), Matosinhos, Portugal
[3] ICBAS-Instituto de Ciências Biomédicas Abel Salazar, University of Porto, Portugal
[4] Laboratory of Microbiology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Portugal

* Corresponding author: : esousa@ff.up.pt

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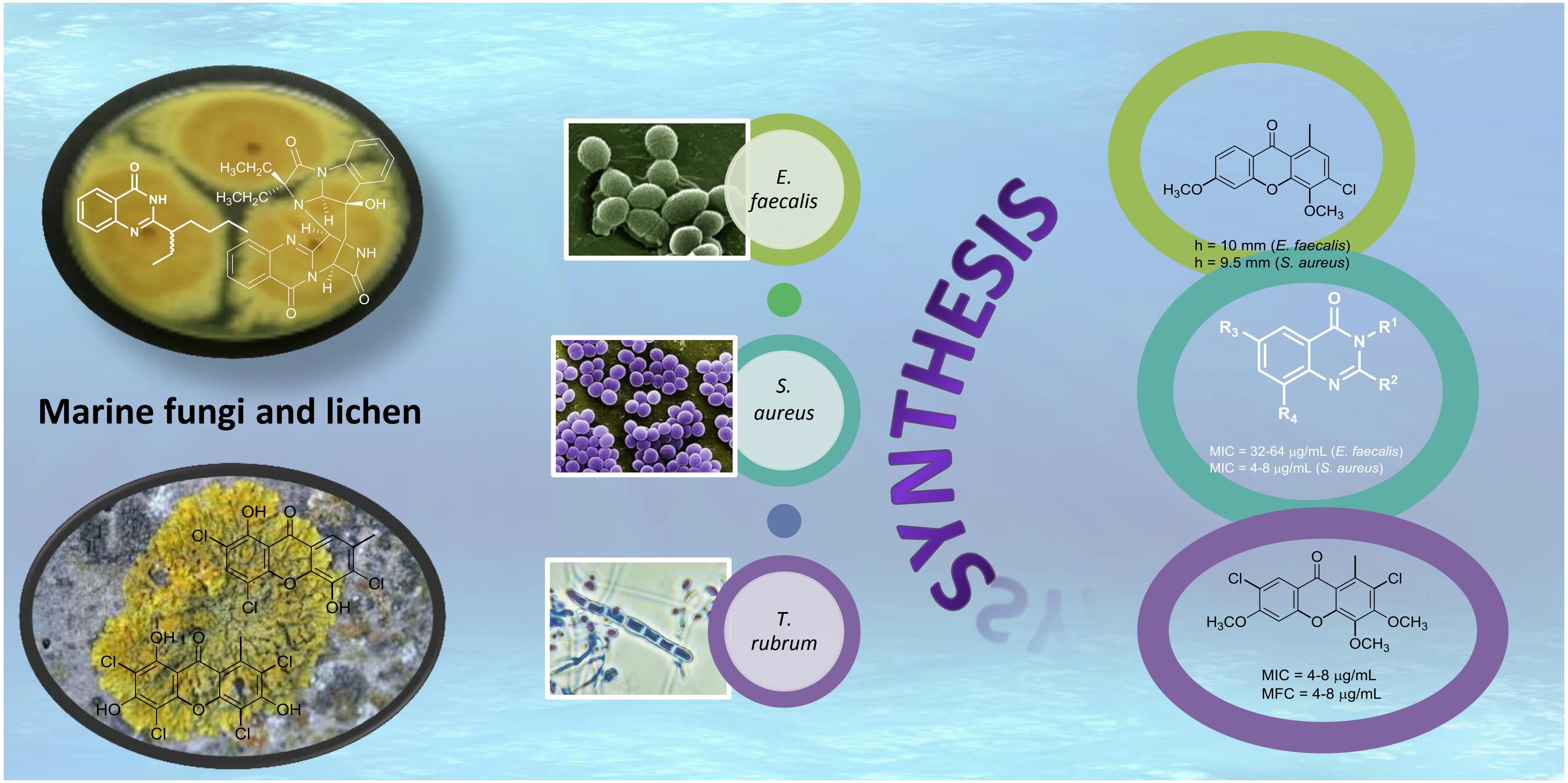
Small molecules from the sea: models for innovative antimicrobial agents

Graphical Abstract



Abstract:

Antimicrobial resistance is one of the most pressing health issues of our days. The marine environment has proven to be a very rich source of diverse natural products with broad-spectra of biologically activities being a very helpful resource in the search for novel antimicrobial compounds. These structurally distinct molecules are revealing promising biological activities against a very large number of drug-resistant pathogenic bacteria and fungi, catching marine natural products attention in the discovery of new antimicrobial agents. Inspired by antimicrobial lichen xanthones and fungi-derived alkaloids, two series of marine natural products mimics were prepared. The synthesized compounds were evaluated for their antimicrobial activity. Both series produced interesting compounds active against *E. faecalis* (ATCC 29212 and 29213) and *S. aureus* (ATCC 29213) with some synthetic alkaloids being active against a MRSA strain. Some revealed a potent fungistatic and fungicidal activity against dermatophytes clinical strains (*T. rubrum*, *M. canis*, and *E. floccosum*). These results highlight the potential of marine natural products as a source of new antimicrobial agents to revert resistance.

Keywords: marine natural products; xanthones, alkaloids; antifungal; antibacterial

Introduction

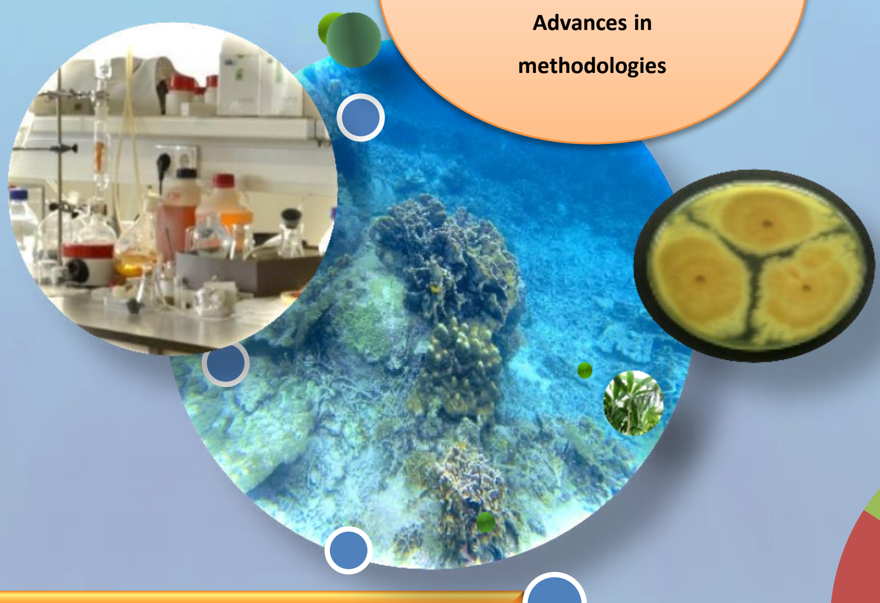
Centro Interdisciplinar de Investigação Marinha e Ambiental

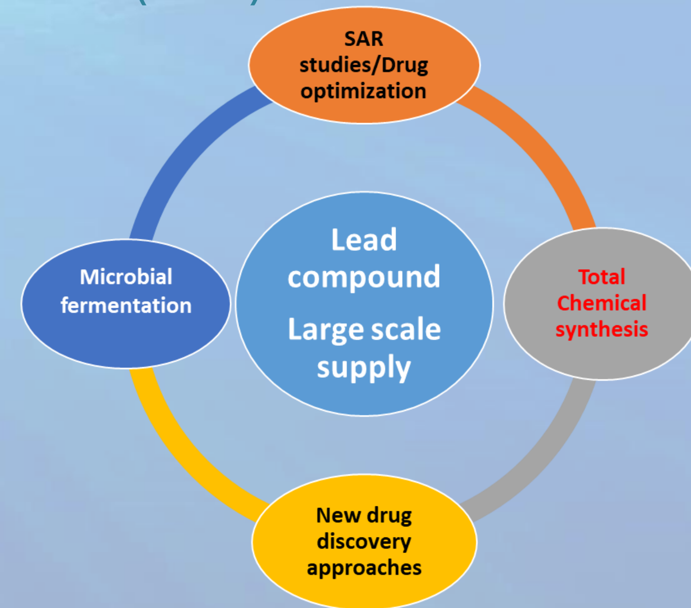
Interdisciplinary Centre of Marine and Environmental Research (CIIMAR)

Diverse habitats

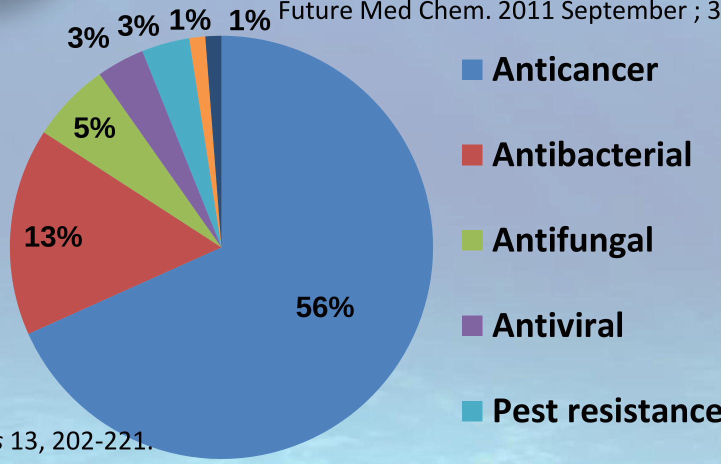
Diverse array of metabolites

Advances in methodologies





Future Med Chem. 2011 September ; 3(12): 1475–1489.



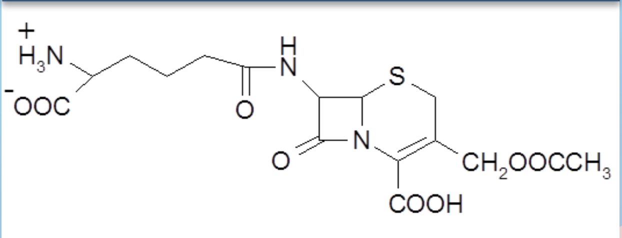
Bioactivities of new marine natural products discovered from 1985 – 2012

Hu, Y., Chen, J., Hu, G., Yu, J., Zhu, X., Lin, Y., Chen, S. & Yuan, J. (2015). *Marine drugs* 13, 202-221.

Introduction

Giuseppe Brotzu

CEPHALOSPORIN C



Marine-Fungi Antibacterial Agents

1850s

first marine fungi described

1948

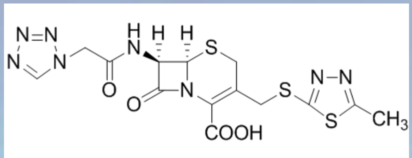
Discovery of cephalosporin β-lactam antibiotics

2010

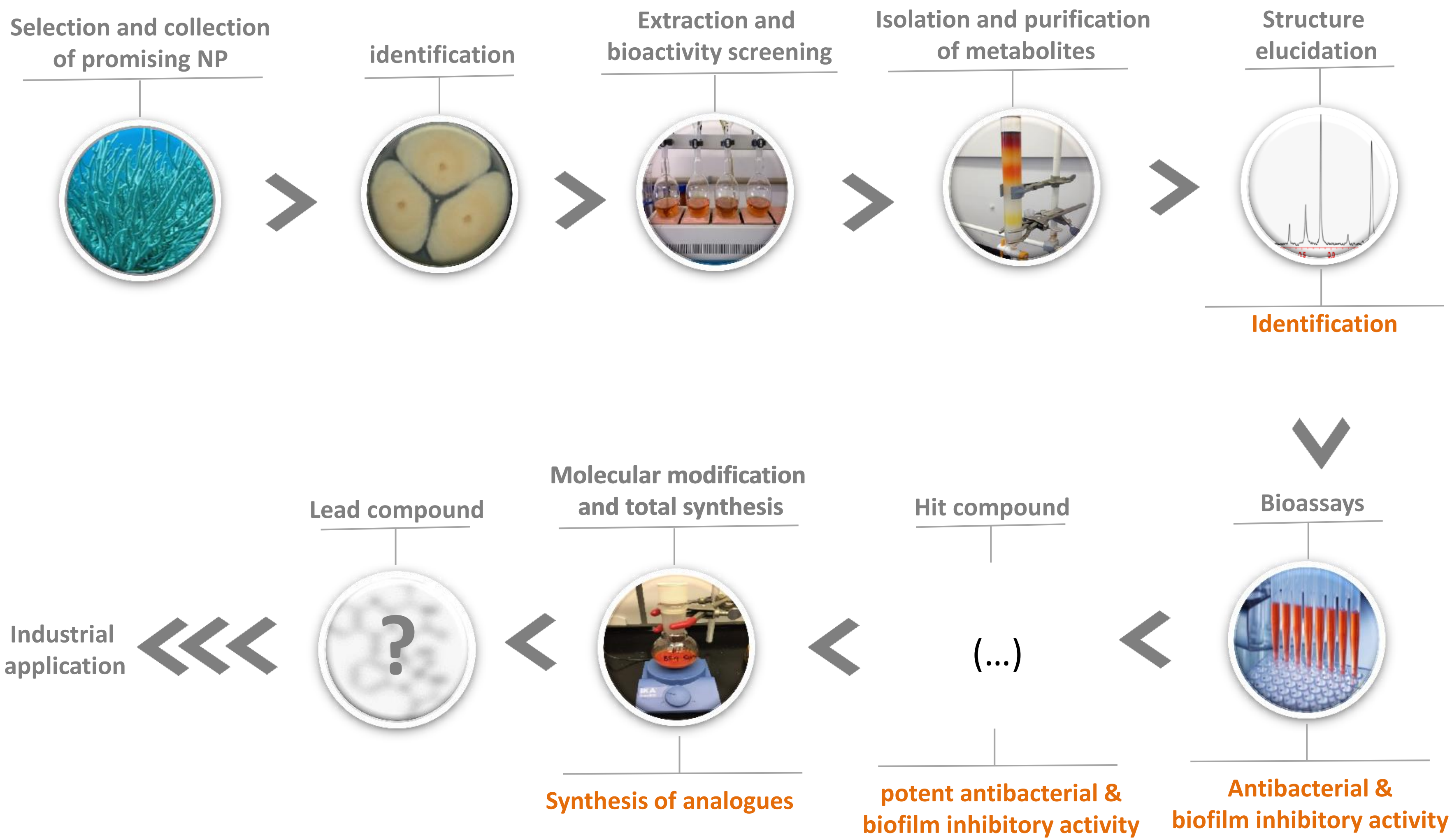
1000 new metabolites described

2017

1112 marine fungi have been documented

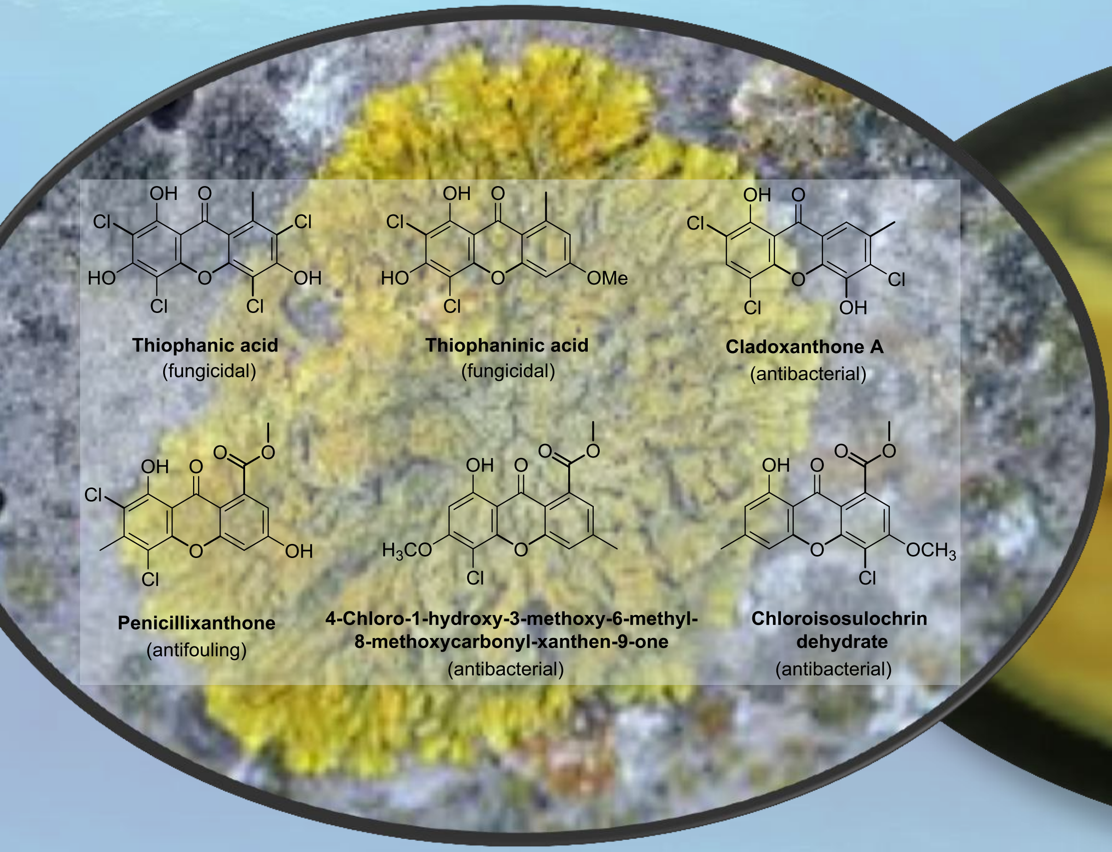


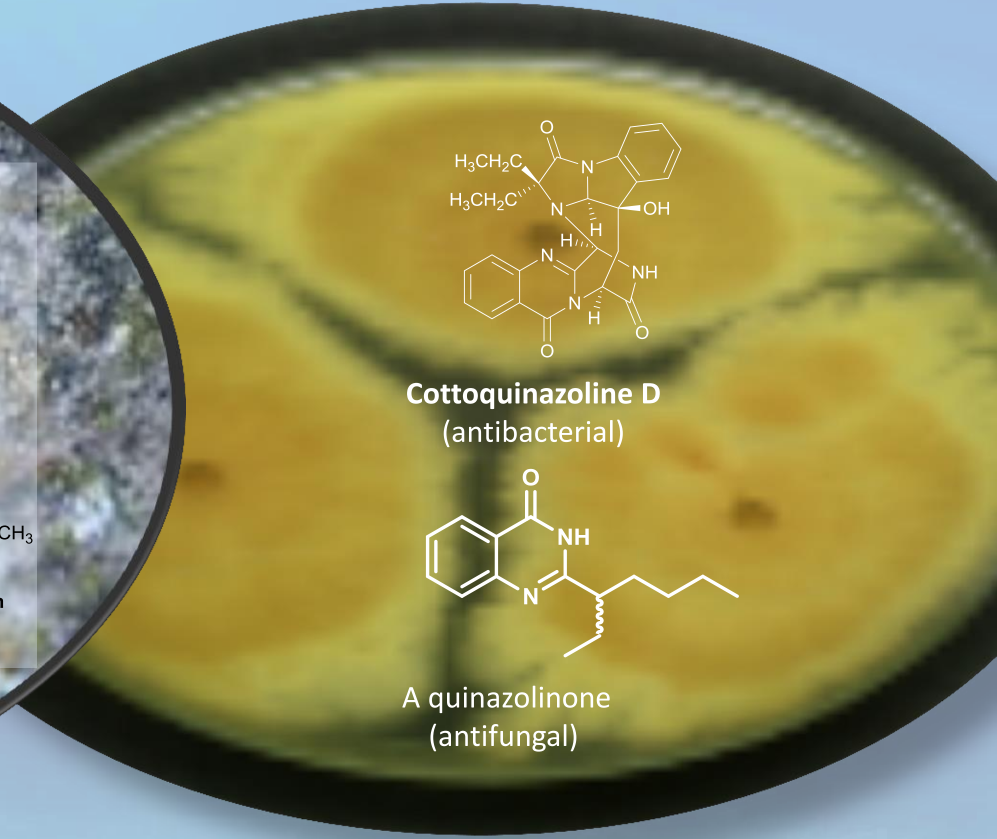
From Nature to the lab bench



Introduction

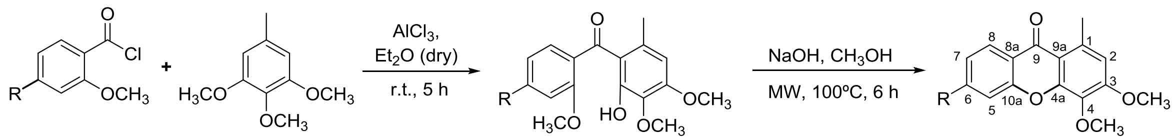
Xanthones and Quinazolinones as models for antimicrobial agents



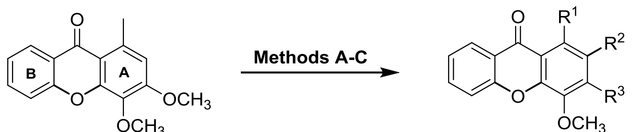


Results and discussion

Synthesis of chlorinated derivatives of 3,4-dimethoxy-1-methyl-9*H*-xanthen-9-one (6) and 3,4,6-trimethoxy-1-methyl-9*H*-xanthen-9-one (7).



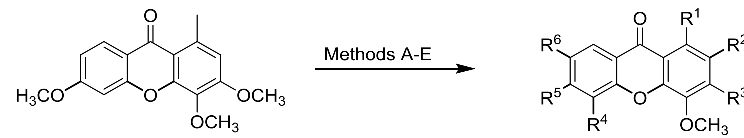
1, R = H
2, R = OCH_3
3
4, R = H
5, R = OCH_3
6, R = H, 63% (2 steps)
7, R = OCH_3, 15% (2 steps)



6 → **8-11**

Comp.	R¹	R²	R³	Method	Yield (%)
8	CH_2Cl	H	OCH_3	A	5
				B	6
9	CH_3	H	OH	A	2
				B	4
10	CH_3	H	Cl	A	12
				B	12
11	CH_3	Cl	OCH_3	C	26

Method A: $SOCl_2$, r.t., seven days; Method B: $SOCl_2$, 40 °C, seven days; Method C: NaCl, *p*-TsOH, NCS, H_2O, r.t., seven days.



7 → **12-20**

Comp.	R¹	R²	R³	R⁴	R⁵	R⁶	Method	Yield (%)
12	CH_3	Cl	OCH_3	H	OCH_3	H	A	7
							D	12
							E	14
13	CH_3	Cl	Cl	H	OCH_3	H	A	Traces
							B	12
							C	8
14	CH_2Cl	H	OCH_3	H	OCH_3	H	A	Traces
							B	8
							D	13
15	CH_3	H	Cl	H	OCH_3	H	B	5
							C	10
16	CH_3	H	Cl	H	Cl	H	C	6
17	CH_3	Cl	OCH_3	Cl	OCH_3	H	E	traces
18	CH_3	Cl	OCH_3	H	OCH_3	Cl	E	traces
19	CH_3	H	OCH_3	Cl	OCH_3	H	E	5
20	CH_3	H	OCH_3	H	OCH_3	Cl	E	1

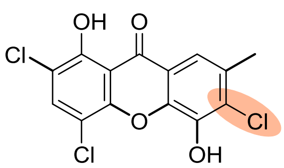
Method A: $SOCl_2$, r.t, seven days, Method B: $SOCl_2$, 40 °C,seven7 days, Method C: $SOCl_2$, Δ, seven days, Method D: NaCl, *p*-TsOH, NCS, H_2O, r.t., seven days.; Method E: H_2O_2, AcOH, NaCl, 40 °C, seven days.

Results and discussion

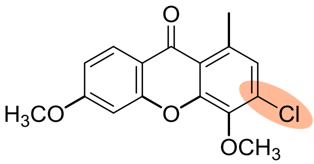
Antibacterial activity of the compounds 6–20

Comp.	*E. coli* ATCC 25922			*E. coli* SA/2			*P. aeruginosa* ATCC 27853			*E. faecalis* ATCC 29212			*E. faecalis* B3/101 (VRE)			*S. aureus* ATCC 29213			*S. aureus* 66/1 (MRSA)		
	Halo	MIC	MBC	Halo	MIC	MBC	Halo	MIC	MBC	Halo	MIC	MBC	Halo	MIC	MBC	Halo	MIC	MBC	Halo	MIC	MBC
6	0	>16	ND	0	ND	ND	0	>16	ND	0	>16	ND	0	ND	ND	0	>16	ND	0	ND	ND
7	0	>64	ND	0	ND	ND	0	>64	ND	0	>64	ND	0	ND	ND	0	>64	ND	0	ND	ND
8	0	>64	ND	0	ND	ND	0	>64	ND	0	>64	ND	0	ND	ND	0	>64	ND	0	ND	ND
9	0	>64	ND	0	ND	ND	0	>64	ND	0	>64	ND	0	ND	ND	0	>64	ND	0	ND	ND
10	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND
11	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND
12	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND
13	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND
14	0	>64	ND	0	ND	ND	0	>64	ND	0	>64	ND	0	ND	ND	0	>64	ND	0	ND	ND
15	0	>16	ND	0	ND	ND	0	>16	ND	10	>16	ND	0	ND	ND	9.5	>16	ND	0	ND	ND
16	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND
17	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND
18	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND
19	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND
20	0	>32	ND	0	ND	ND	0	>32	ND	0	>32	ND	0	ND	ND	0	>32	ND	0	ND	ND

MIC and MBC are expressed in µg/mL. Inhibition halos are expressed in mm. MIC—minimum inhibitory concentration; MBC—minimum bactericidal concentration; halo of partial inhibition; ND—Not determined.



Cladoxanthone A



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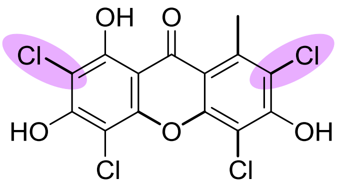
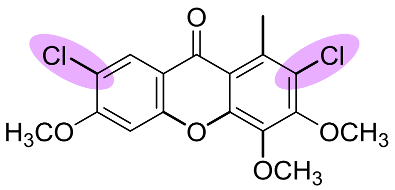
Results and discussion

Antifungal activity of compounds X6-X20

Comp.	*C. albicans* ATCC 10231		*A. fumigatus* ATCC 46645		*T. rubrum* FF5		*M. canis* FF1		*E. floccosum* FF9	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
6	>32	>32	>32	>32	>32	>32	ND	ND	ND	ND
7	>128	>128	>128	>128	>128	>128	ND	ND	ND	ND
8	>128	>128	>128	>128	≥128	>128	>128	>128	128	128
9	>128	>128	>128	>128	≥128	>128	≥128	>128	≥128	>128
10	>32	>32	>32	>32	>32	>32	ND	ND	ND	ND
11	>32	> 32	>32	>32	>32	>32	ND	ND	ND	ND
12	>32	>32	>32	>32	>32	>32	ND	ND	ND	ND
13	>128	>128	>128	>128	>128	>128	ND	ND	ND	ND
14	>128	>128	>128	>128	>128	>128	ND	ND	ND	ND
15	>32	>32	>32	>32	>32	>32	ND	ND	ND	ND
16	>32	>32	>32	>32	>32	>32	ND	ND	ND	ND
17	>32	>32	>32	>32	>32	>32	ND	ND	ND	ND
18*	>128	>128	>128	>128	8	8	8	8	4	4
19	>32	>32	>32	>32	>32	>32	ND	ND	ND	ND
20	>32	>32	>32	>32	>32	>32	ND	ND	ND	ND



Thiophanic acid



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MIC = 4-8 μg/mL
MFC = 4-8 μg/mL

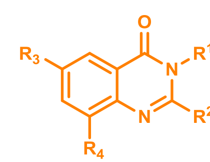
MIC - minimum inhibitory concentration; MFC - minimum fungicidal concentration, expressed in μg/mL; *Sinergy with fluconazole.

Results and discussion

Antibacterial activity of the compounds Q1–Q10

Compound	*E. coli* ATCC 25922		*P. aeruginosa* ATCC 27853		*E. faecalis* ATCC 29212		*E. faecalis* B3/101 (VRE)		*E. faecalis* A5/102 (VRE)		*S. aureus* ATCC 29213		*S. aureus* 40/61/24		*S. aureus* 66/1 (MRSA)	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
1-a	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
1-b	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
1-c	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
1-d	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
2-a	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
2-b	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
2-c	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
2-d	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
3-a	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
3-b	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
4-a	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND	> 64	ND
5-c	> 64	ND	> 64	ND	64	> 64	> 64	ND	64	ND	32	> 64	64	ND	> 64	ND
6-c	> 64	ND	> 64	ND	32	> 64	> 64	ND	64	ND	32	> 64	64	ND	> 64	ND
7-c	> 64	ND	> 64	ND	32	> 64	> 64	ND	64	ND	16	> 64	64	ND	> 64	ND
8-c	> 64	ND	> 64	ND	32	> 64	> 64	ND	64	ND	16	> 64	64	ND	> 64	ND
9-c	> 64	ND	> 64	ND	32	> 64	> 64	ND	64	ND	4	> 64	64	ND	8	> 64
10-c	> 64	ND	> 64	ND	32	> 64	> 64	ND	64	ND	4	> 64	64	ND	4	> 64

MIC and MBC are expressed in µg/mL. Inhibition halos are expressed in mm. MIC—minimum inhibitory concentration; MBC—minimum bactericidal concentration; halo of partial inhibition; ND—Not determined.



Conclusions

Weakness	Strengths
thionyl chloride gave a higher diversity of compounds but with low yields the low solubility displayed by some xanthones limited further screenings	NaCl, *p*-TsOH and NCS, were more selective and produced higher yields compounds X15 and X18 can be used in the future as models in order to improve drug-like properties
Antimicrobial resistance is one of the most pressing health issues of our days	Marine derived fungi and particularly xanthones and quinazolinones are fruitful models to develop innovative antimicrobial agents
Threats	**Opportunities**

D. I. S. P. Resende, P. Pereira-Terra, Â. S. Inácio, P. M. Costa, E. Pinto, E. Sousa, M. M. M. Pinto. Lichen Xanthones as Models for New Antifungal Agents. *Molecules* **2018**, 23, 2617; doi:10.3390/molecules23102617

Acknowledgments

This work was partially supported through national funds provided by FCT/MCTES—Foundation for Science and Technology from the Ministry of Science, Technology, and Higher Education (PIDDAC) and the European Regional Development Fund (ERDF) through the COMPETE—Programa Operacional Factores de Competitividade (POFC) programme, under the Strategic Funding UID/Multi/04423/2013, the projects POCI-01-0145-FEDER-028736 and POCI-01-0145-FEDER-016790 (PTDC/MAR-BIO/4694/2014; 3599-PPCDT) in the framework of the programme PT2020, as well as by the project INNOVMAR—Innovation and Sustainability in the Management and Exploitation of Marine Resources (reference NORTE-01-0145-FEDER-000035, within Research Line NOVELMAR), supported by North Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). Solida Long thanks Erasmus Mundus Action 2 (LOTUS+, LP15DF0205) for full PhD scholarship. Diana I. S. P. Resende also acknowledge for her grant (NOVELMAR/BPD_2/2016-019) and Patrícia Pereira-Terra for her grant (NOVELMAR/BPD/2017/012).