



# The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)

01-30 NOVEMBER 2022 | ONLINE

## Small molecule inhibitors of bacterial quorum sensing

Chaired by **DR. ALFREDO BERZAL-HERRANZ**;  
Co-Chaired by **PROF. DR. MARIA EMÍLIA SOUSA**



*pharmaceuticals*



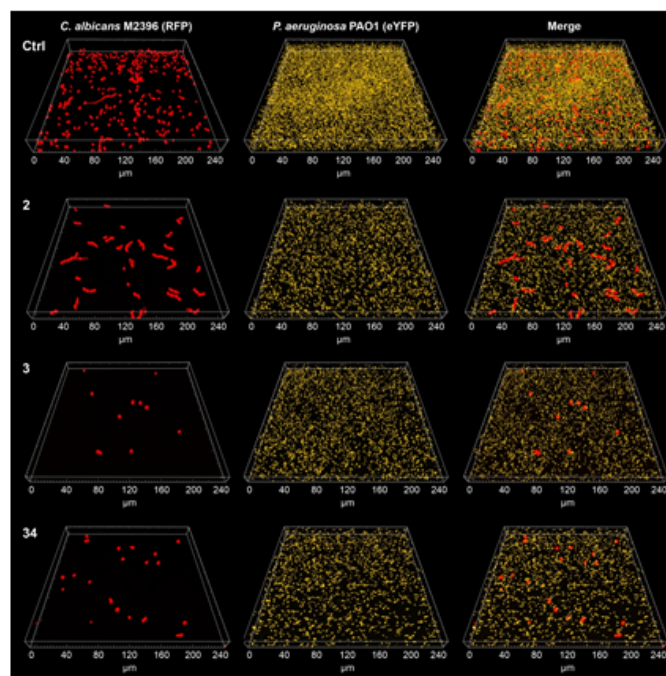
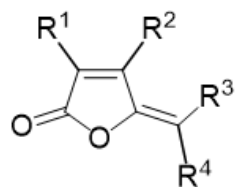
**Dr Tim O'Sullivan**

School of Chemistry and School of Pharmacy, Analytical and Biological Chemistry  
Research Facility, University College Cork, Cork, Ireland  
[tim.osullivan@ucc.ie](mailto:tim.osullivan@ucc.ie)



# Small molecule inhibitors of bacterial quorum sensing

## Graphical Abstract



ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

**Abstract:** Quorum sensing is a bacterial mechanism that is essential in the pathogenesis of many infections, such as *P. aeruginosa*. These infections are strongly influenced by specific quorum sensing molecules, such as Autoinducer-2 (AI-2). AI-2 binds to quorum sensing receptors within bacteria leading to the up-regulation of virulence genes that cause biofilm formation and toxin production. Naturally-occurring brominated furanones isolated from the marine algae *Delisea pulchra* were previously found to possess properties which inhibited bacterial quorum sensing in AI-2 sensitive species.

The aim of this work was to create a series of novel halogenated furanones which can act as quorum sensing inhibitors of AI-2. Based on the lead from *Delisea pulchra*, a library of compounds was synthesised *via* the functionalisation of *gem*-dibromoolefin and *gem*-dichloroolefin intermediates using palladium-catalysed couplings, namely Suzuki and Sonogashira reactions. These compounds were subsequently evaluated for their effects on biofilm formation in selected microbes. Several molecules were confirmed to be highly effective biofilm inhibitors in multiple pathogens, including *P. aeruginosa* and *C. albicans*.

**Keywords:** quorum sensing; resistance; biofilms; furanones.

ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE



# Introduction

20p Britain's first and only concise quality newspaper

## 'An end to modern medicine as we know it'

Margaret Chan  
World Health Organisation, speaking in Copenhagen

WHO chief's stark warning about danger of resistance to antibiotics  
'Growing crisis' may 'turn common infections into untreatable diseases'  
Calls for restrictions on use in animals to halt the spread of E.coli

Obama and PM in deal to fight fuel price rises

Police told to get in shape or face the sack

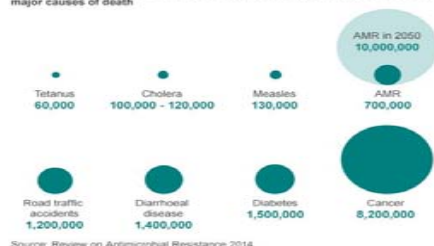
Barden on living the dream as a Bond villain

The essential daily briefing

INDEPENDENT

INSIDE TODAY  
Daily Codeword  
Daily Crosswords  
Daily

Deaths attributable to antimicrobial resistance every year compared to other major causes of death



Deaths attributable to antimicrobial resistance every year by 2050



become a supporter subscribe find a job

## theguardian

news opinion sport arts lifestyle

UK UK politics education media society law scotland wales northern ireland

Drug resistance The Observer

### 'Antibiotic apocalypse': doctors sound alarm over drug resistance

The terrifying prospect that even routine operations will be impossible to perform has been raised by experts alarmed by the rise of drug-resistant genes

Science Contents News Careers Journals

Profile immune responses to four SARS-CoV-2 proteins

SHARE

### Antibiotic treatment for COVID-19 complications could fuel resistant bacteria

By Sara Rearden | Apr. 16, 2020, 5:05 PM

## The antibiotic market has failed

Companies developing new antibiotics cannot recover the \$1bn+ required to develop new treatments

NUMBERS OF NEW ANTIBIOTICS BEING APPROVED

In 1990 there were 18 global pharmaceutical companies developing antibiotics

Today there are 5

Visit [wellcome.ac.uk/dri](http://wellcome.ac.uk/dri) to find out more

Source: [carb-x.org](http://carb-x.org), [amr-climicrob.biomedcentral.com](http://amr-climicrob.biomedcentral.com)

World Health Organization  
REGIONAL OFFICE FOR Europe

English Français Deutsch Русский

Home Health topics Countries Publications Data and evidence Media centre About us

Health topics > Disease prevention > Antimicrobial resistance > Preventing the COVID-19 pandemic from causing an antibiotic resistance catastrophe

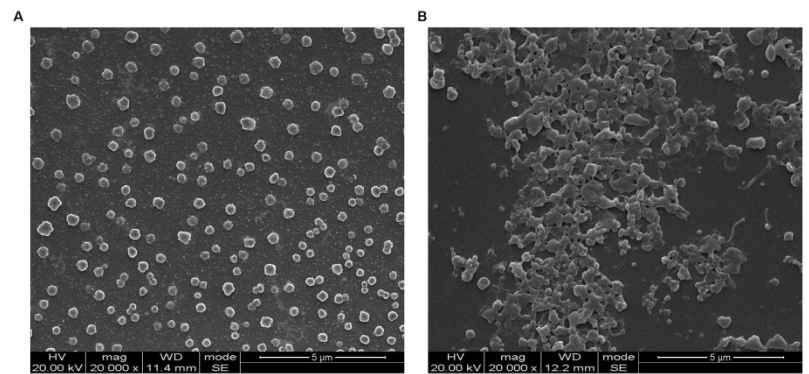
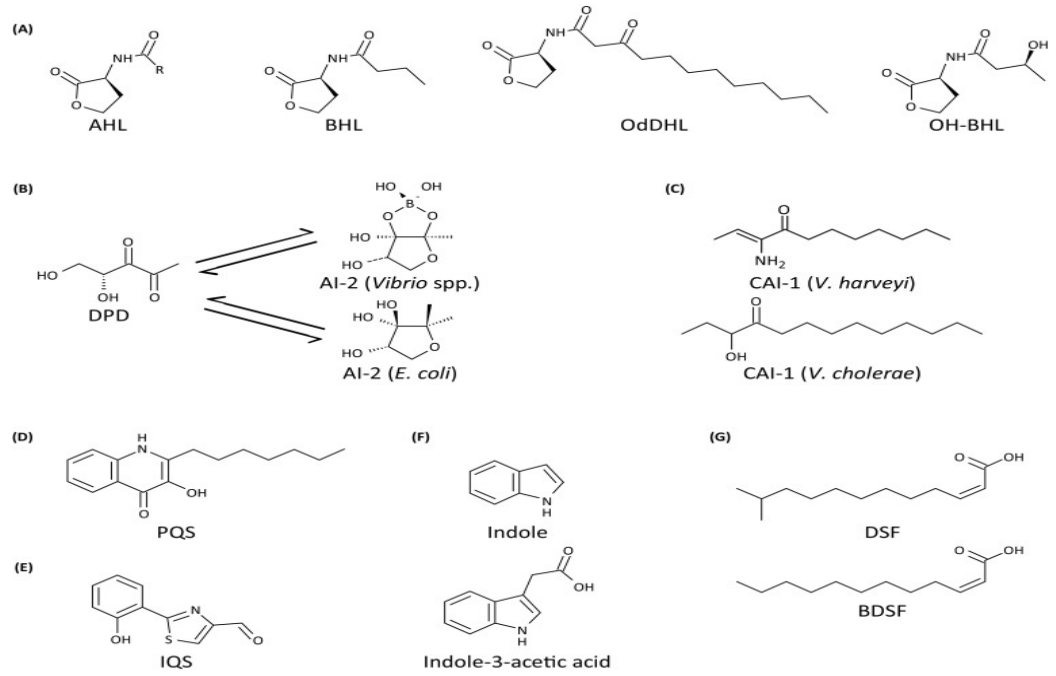
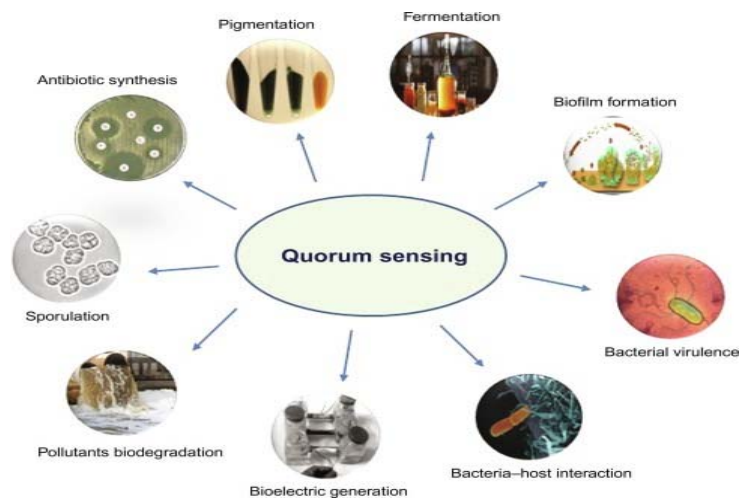
Antimicrobial resistance  
News  
Events

Preventing the COVID-19 pandemic from causing an antibiotic resistance catastrophe  
18-11-2020

ECMC  
2022

The 8th International Electronic Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

# Quorum Sensing



S. Chen et al., *Front. In Micro.* 2018, 9, 379

Trends in Microbiology

T. Defoidt, *Trends in Micro.* 2018, 26 (4), 313

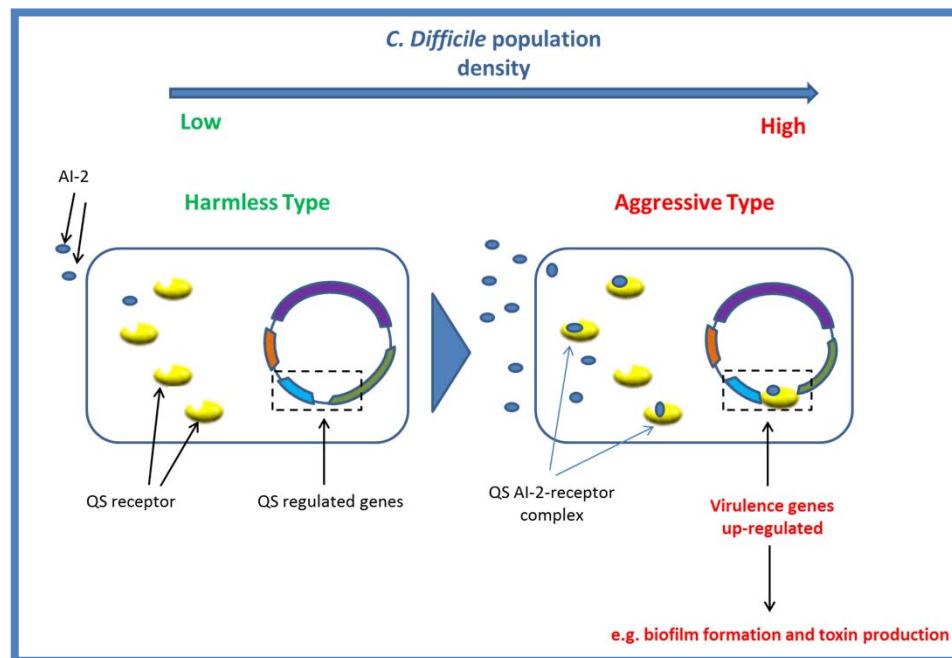
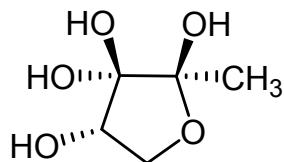
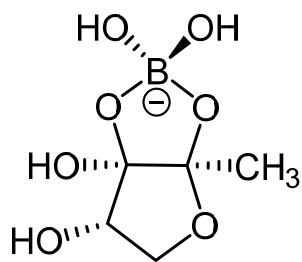
## ECMC 2022

# The 8th International Electronic Conference on Medicinal Chemistry

01-30 NOVEMBER 2022 | ONLINE

## Autoinducer-2 (AI-2)

- Bacterial communication mechanism
- Induced by QS signalling molecules
- AI-2 QS molecule

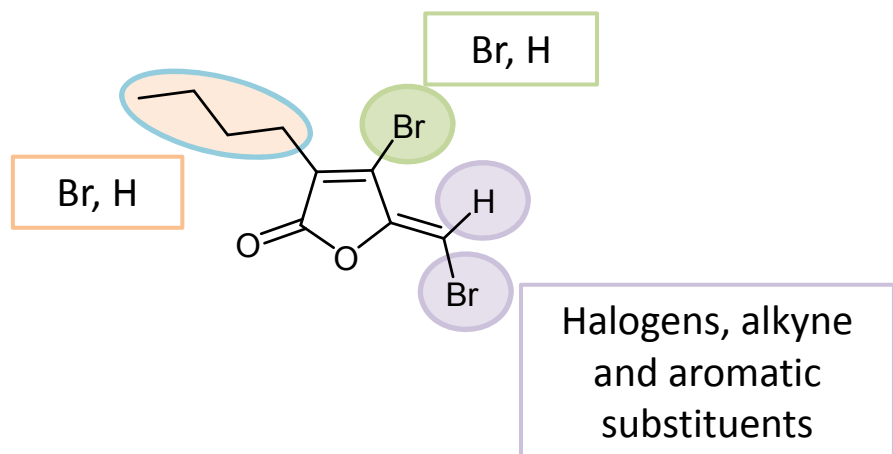


ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

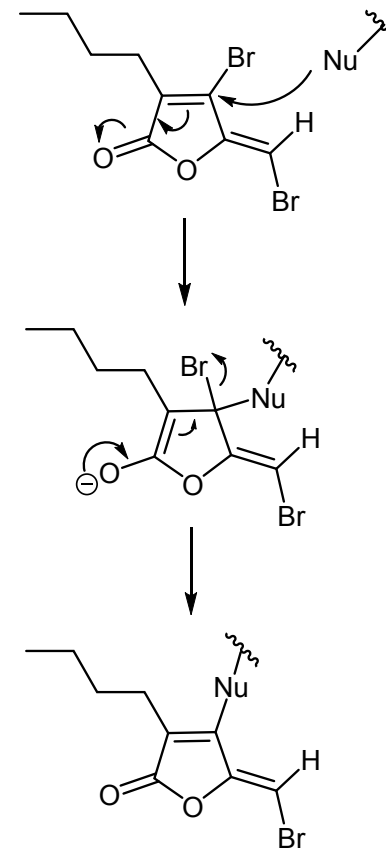
## Brominated Furanones

- Isolated from *Delisea pulchra*



- Mode of Action

- Covalently bind to LuxS
- Blocks the binding of AI-2 precursor
- QS inhibition



Lyons, T.; Gahan, C. G. M.; O'Sullivan, T. P., *Future Med. Chem.* **2020**, 12 (21), 1925-1943.

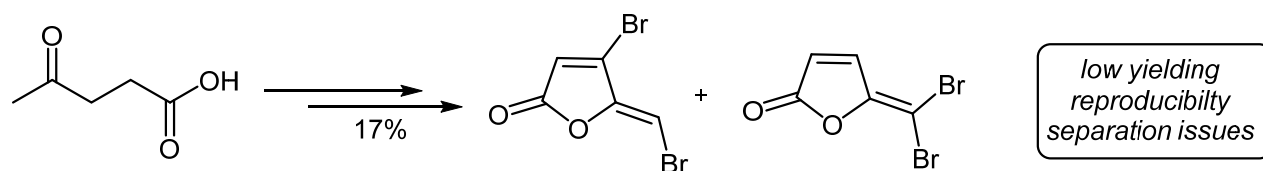
ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

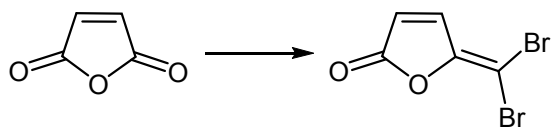


# Results and discussion

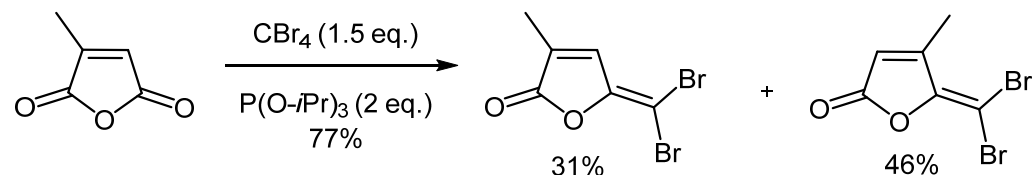
## Initial 2-step synthesis



## Novel route



## Further Applications



Entry	Reagents	Solvent	Temp	Yield
1	$\text{CBr}_4$ , $\text{PPh}_3$	$\text{CH}_2\text{Cl}_2$	r.t.	-
2	$\text{CBr}_4$ , $\text{PPh}_3$	THF	r.t.	-
3	$\text{CBr}_4$ , $\text{PPh}_3$ , $\text{Et}_3\text{N}$	THF	r.t.	-
4	$\text{CBr}_4$ , $\text{PPh}_3$ , Zn	$\text{CH}_2\text{Cl}_2$	r.t.	-
5	$\text{CBr}_4$ , $\text{P}(\text{O}-i\text{Pr})_3$	$\text{CH}_2\text{Cl}_2$	r.t.	21%
6	$\text{CBr}_4$ , $\text{P}(\text{O}-i\text{Pr})_3$	THF	r.t.	17%
7	$\text{CBr}_4$ , $\text{P}(\text{O}-i\text{Pr})_3$	$\text{CH}_2\text{Cl}_2$	0 °C	25%
8	$\text{CBr}_4$ , $\text{P}(\text{O}-i\text{Pr})_3$	$\text{CH}_2\text{Cl}_2$	0 °C-r.t.	29%

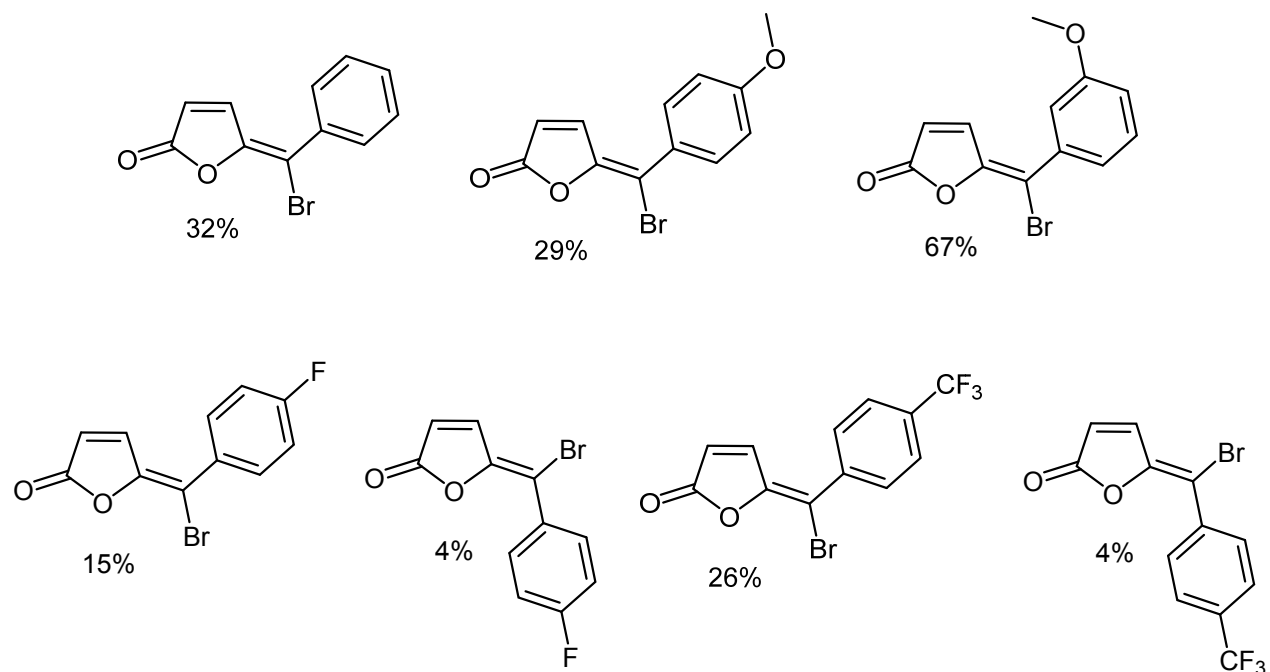
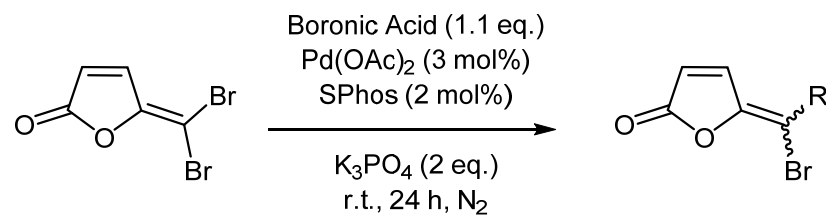
Lyons, T.; Gahan, C. G. M.; O'Sullivan, T. P., *Lett. Org. Chem.* **2022**, *19*, 921-929.  
Fang, YQ; Lifchits, O; Lautens, M *Synlett* **2008**, 413-417.

ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE



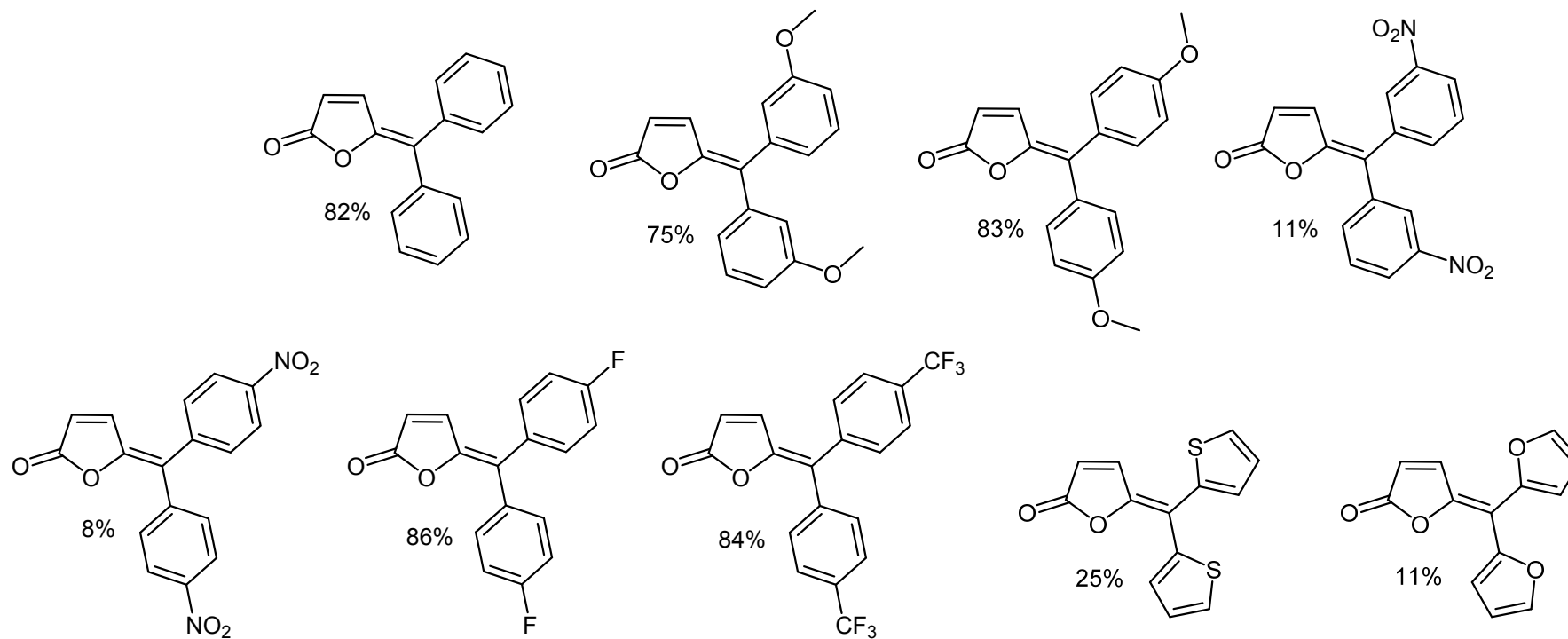
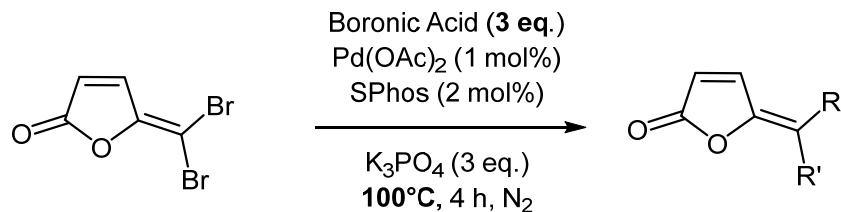
## Suzuki Coupling I



ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

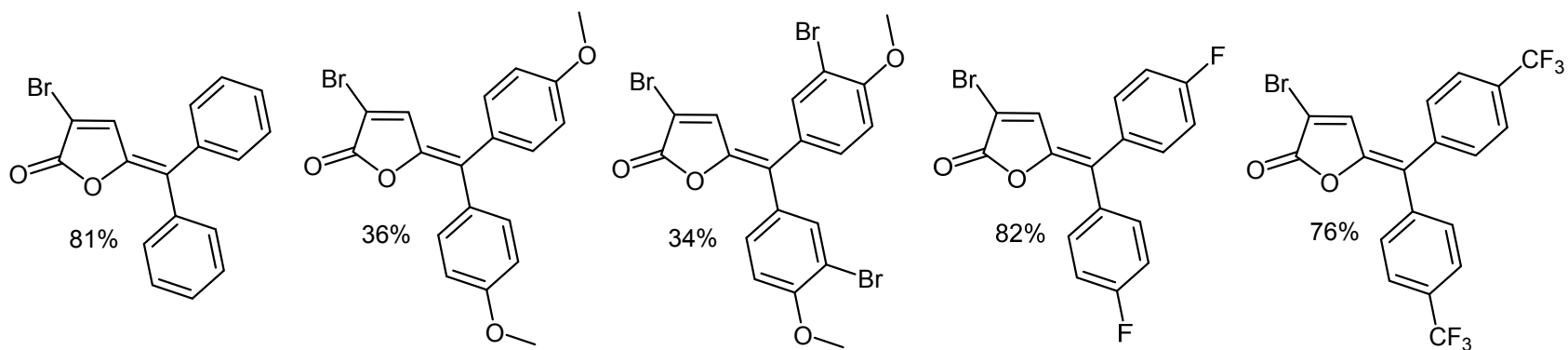
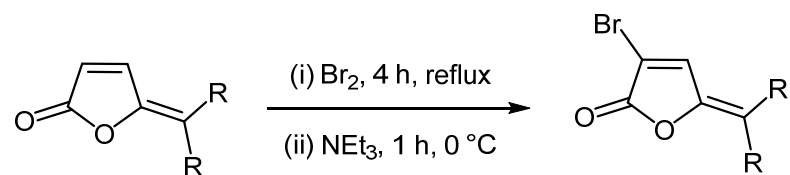
## Suzuki Coupling II



ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

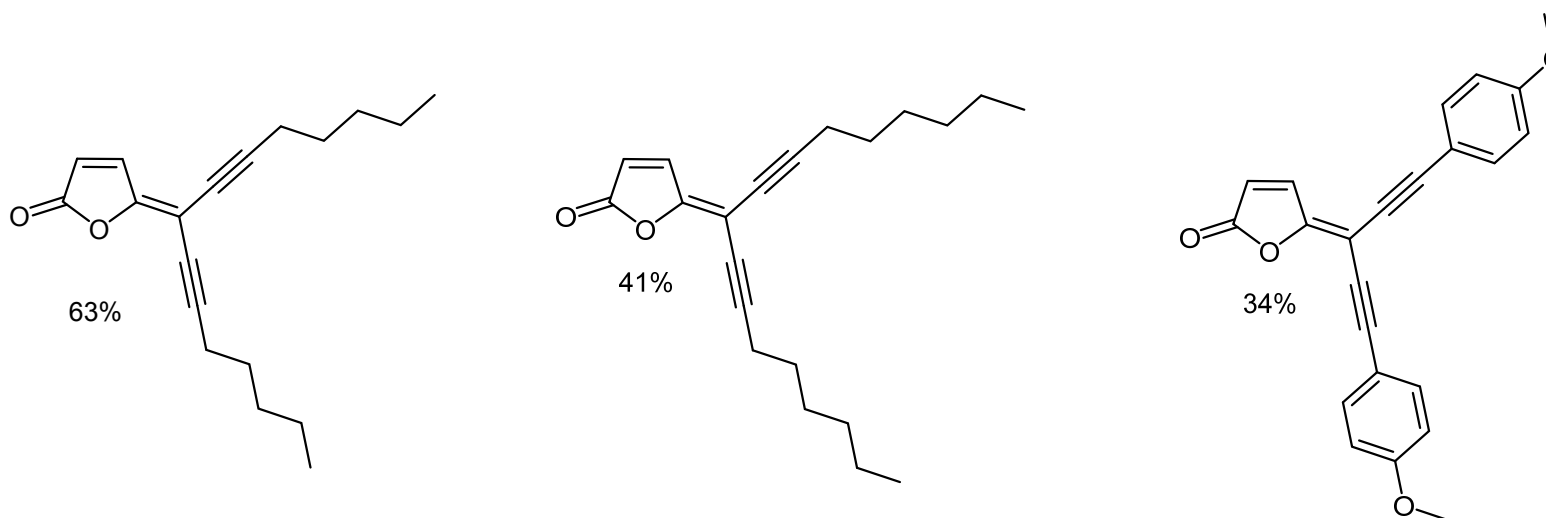
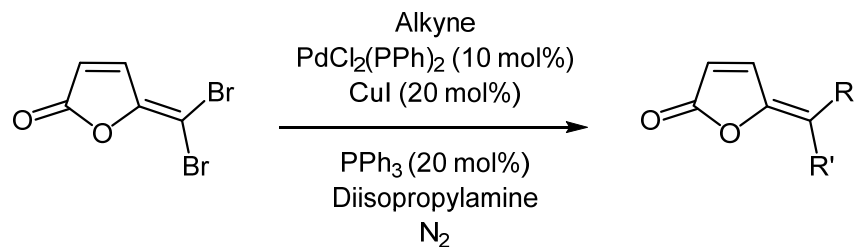
## Ring Bromination



ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

## Sonogashira Coupling

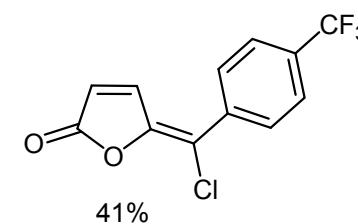
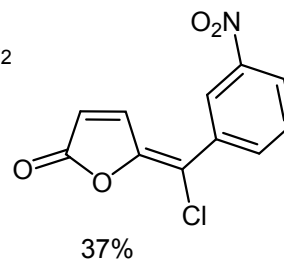
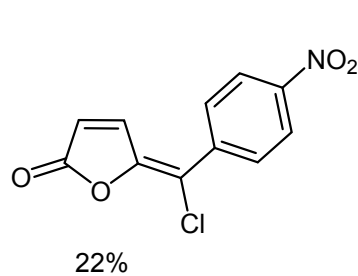
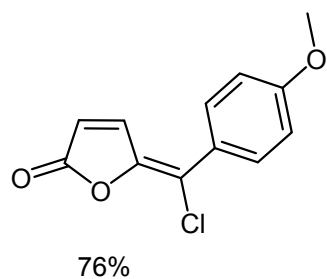
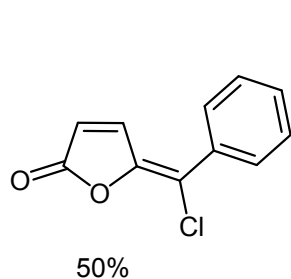
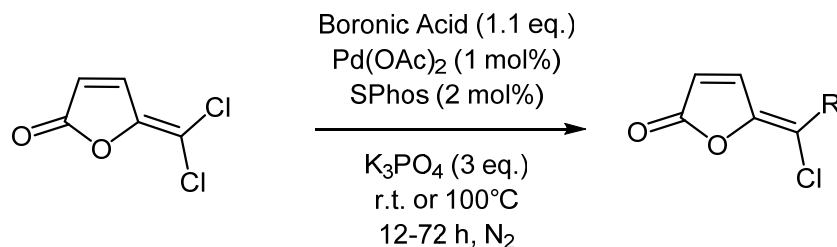
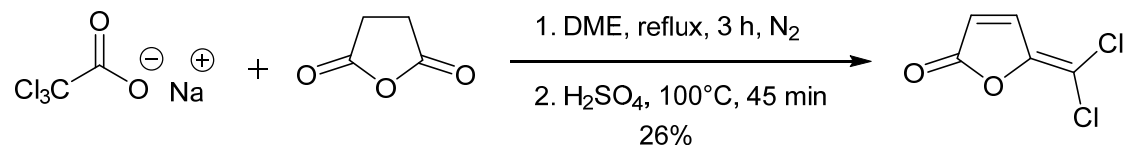


ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE



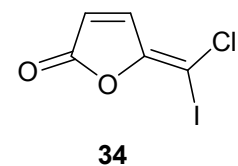
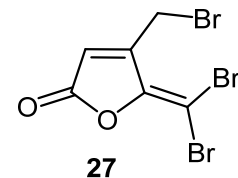
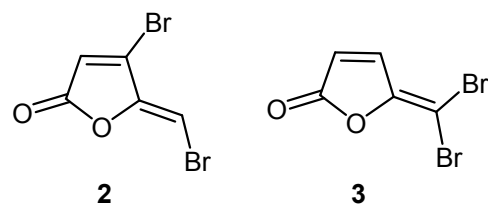
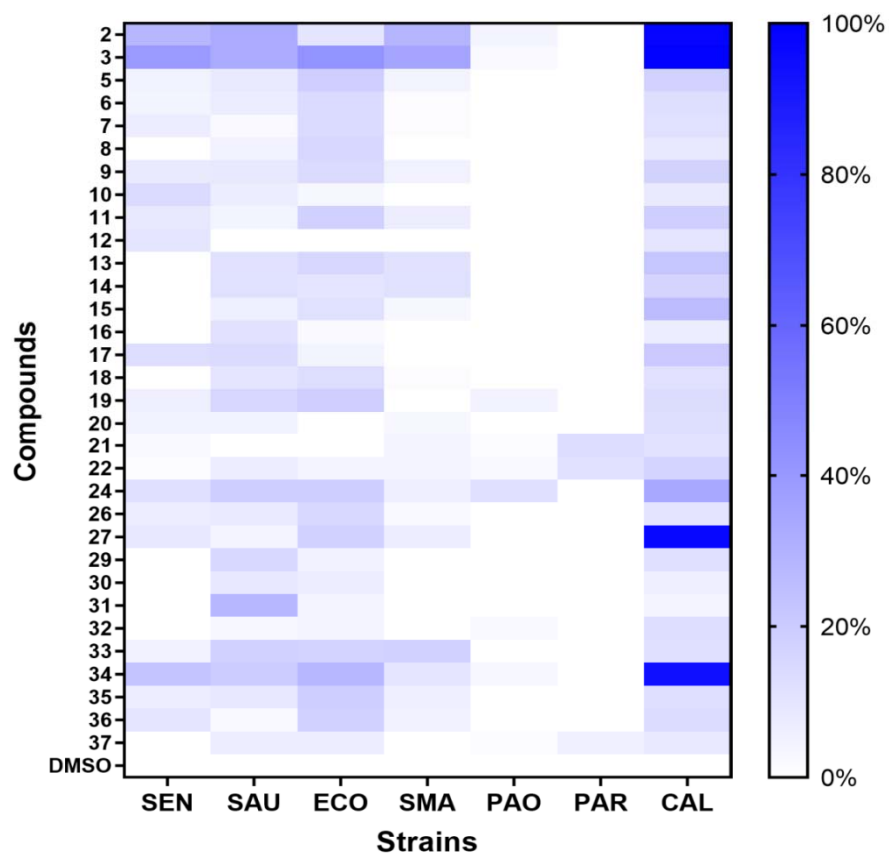
## Chlorine- and Iodine-containing Furanones



ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

## Evaluation – Impact on Bacterial Growth



*S. enterica* (SEN)

*E. coli* ATCC 9637 (ECO)

*P. aeruginosa* PAO1 (PAO)

*C. albicans* M2396 (CAL)

*S. aureus* Newman (SAU)

*S. maltophilia* K279a (SMA)

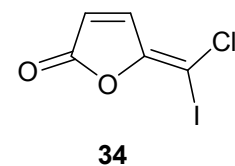
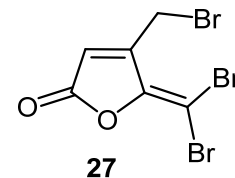
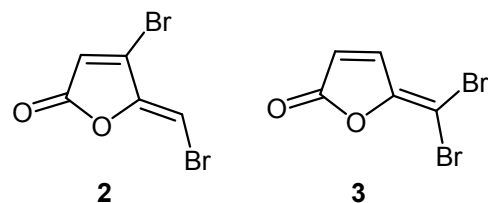
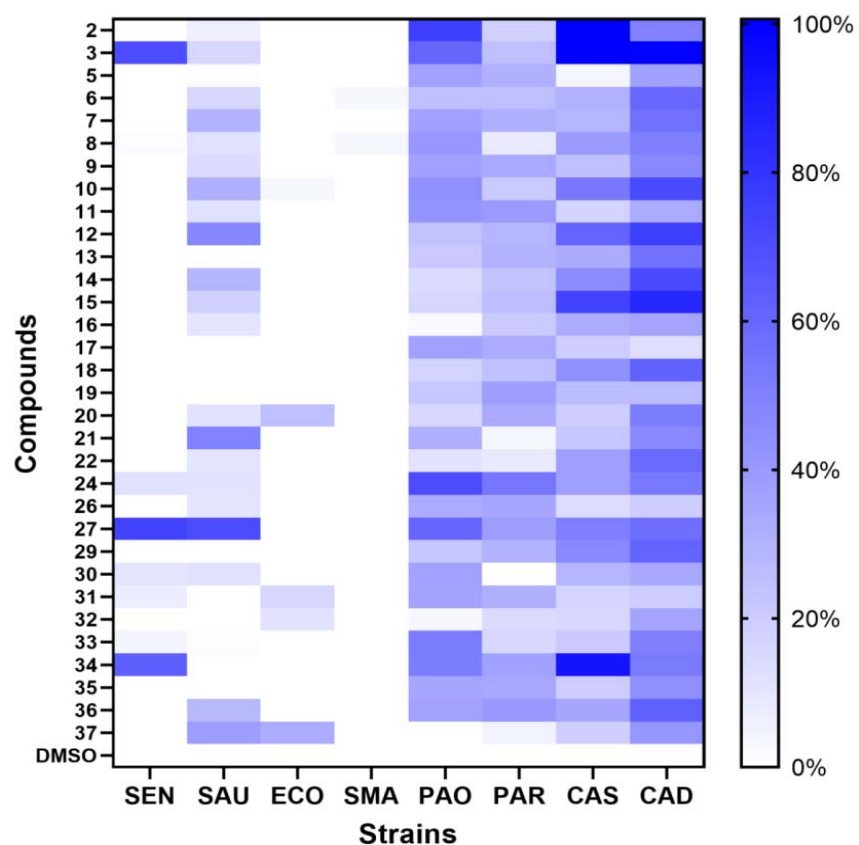
*P. aeruginosa* PAR7244 (PAR)

ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry

01-30 NOVEMBER 2022 | ONLINE

## Evaluation – Impact on Biofilm Formation



*S. enterica* (SEN)

*E. coli* ATCC 9637 (ECO)

*P. aeruginosa* PAO1 (PAO)

*C. albicans* M2396 (CAS/CAD)

*S. aureus* Newman (SAU)

*S. maltophilia* K279a (SMA)

*P. aeruginosa* PAR7244 (PAR)

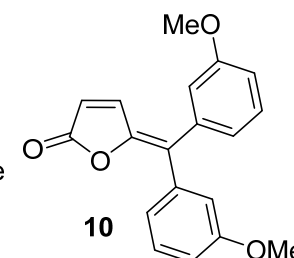
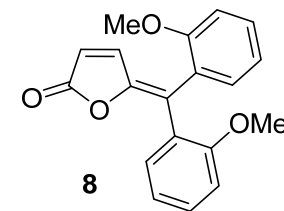
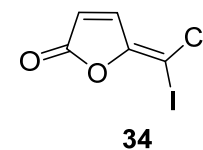
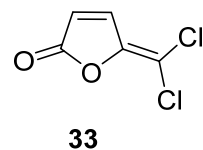
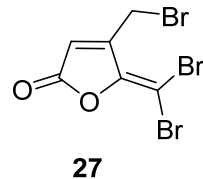
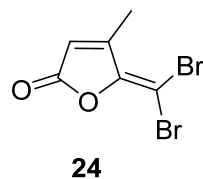
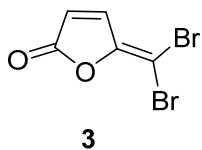
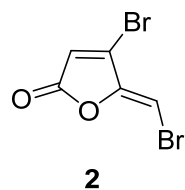
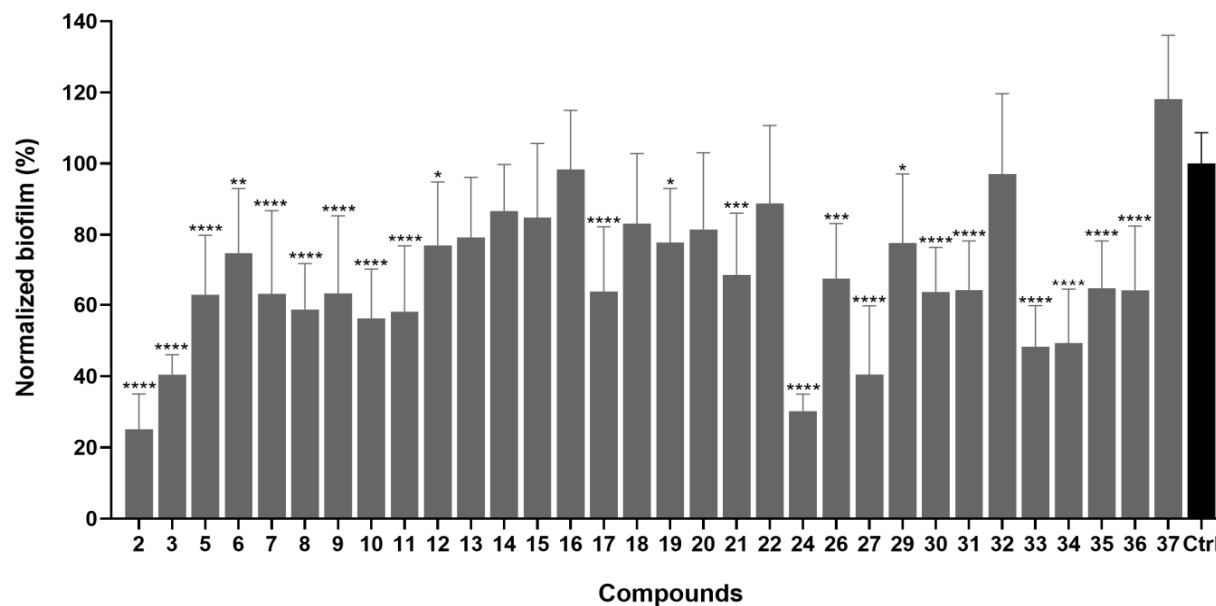
ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry

01-30 NOVEMBER 2022 | ONLINE

## Evaluation – Impact on *P. aeruginosa* Biofilm Formation

### *Pseudomonas aeruginosa* PAO1



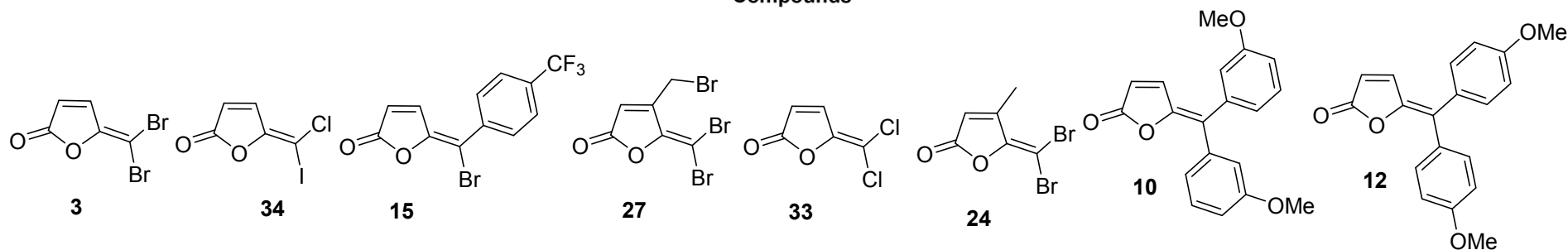
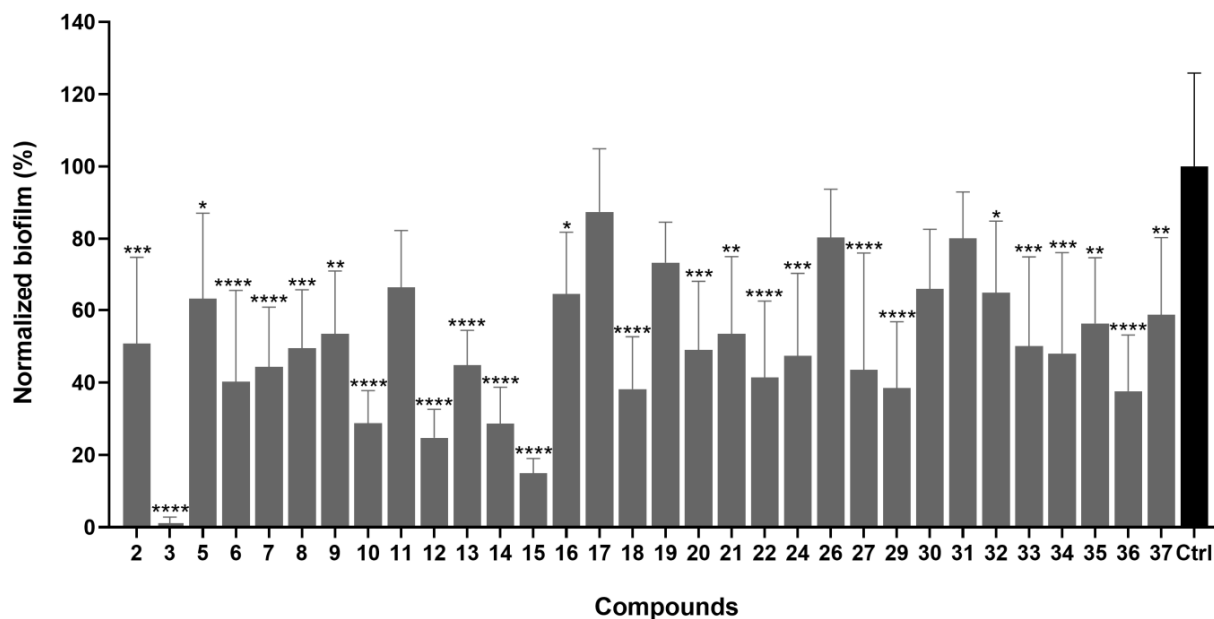
ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE



## Evaluation – Impact on *C. albicans* Biofilm Formation

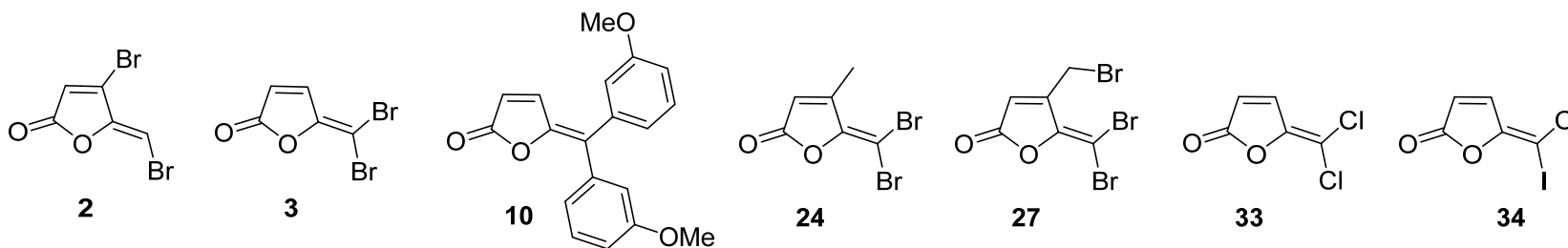
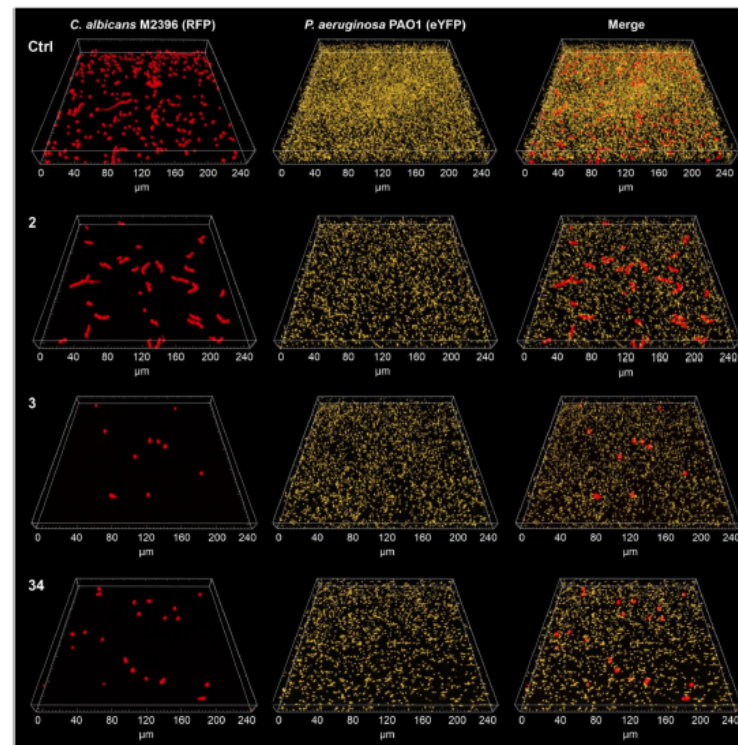
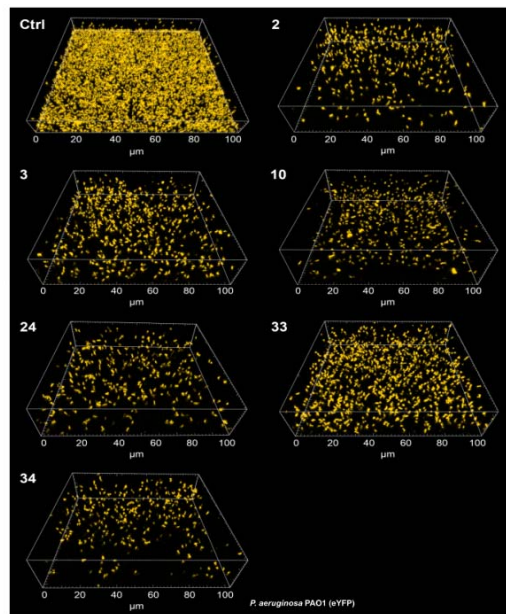
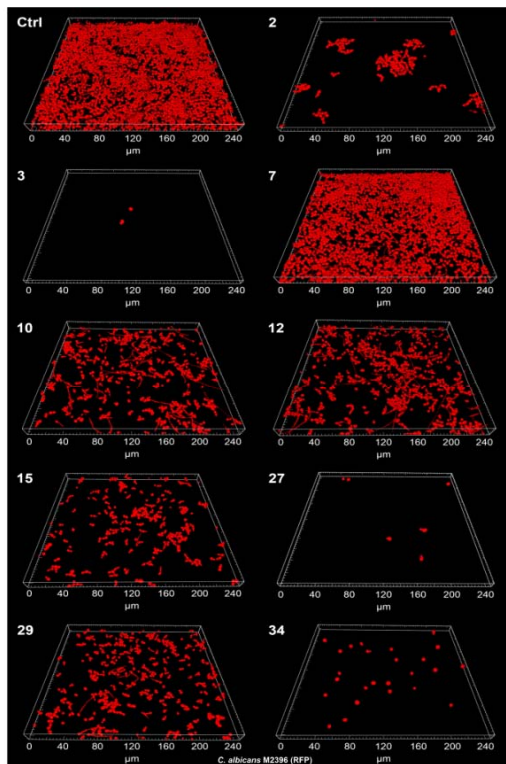
*Candida albicans* M2396



ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

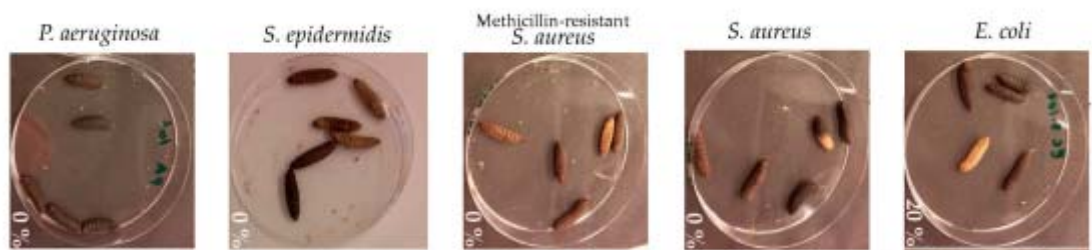
# Evaluation – Confocal Laser-scanning Microscopy



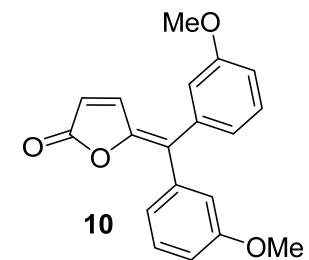
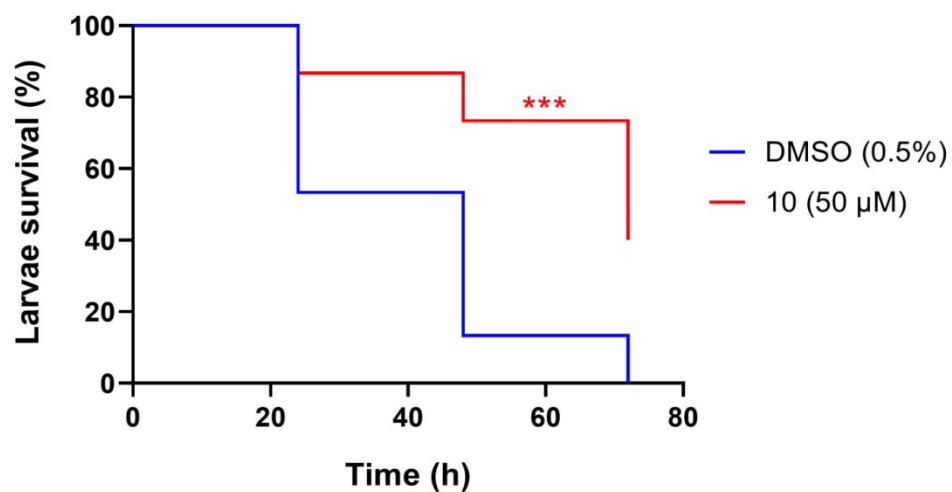
ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

## Evaluation *in vivo* – *Galleria* Model



A. Andrea *et al.*, *Microorganisms* 2019 7(3),85



ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry  
01-30 NOVEMBER 2022 | ONLINE

## Conclusions

- Established a concise route to *gem*-dibromofuranones
- Created a large library via Pd-mediated coupling
- Identified several novel compounds with potent anti-biofilm activity
- Effective against both bacterial and fungal pathogens
- Confirmed *in vivo* activity using Galleria model

ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry

01-30 NOVEMBER 2022 | ONLINE



## Acknowledgments

*University College Cork*

Dr Therese Lyons; Prof Cormac Gahan

*Autonomous University of Barcelona*

Dr Andromeda-Celeste Gómez; Dr Daniel Yero; Dr Marc Bravo; Dr Xavier Daura; Prof Isidre Gibert

*Leibniz Lung Center*

Dr Uwe Mamat

*Hans Knoell Institute*

Dr Osama Elshafee; Dr Sascha Brunke

ECMC  
2022

The 8th International Electronic  
Conference on Medicinal Chemistry

01–30 NOVEMBER 2022 | ONLINE