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Insights of chalcone-triazole hybrids in bacterial resistance modulation

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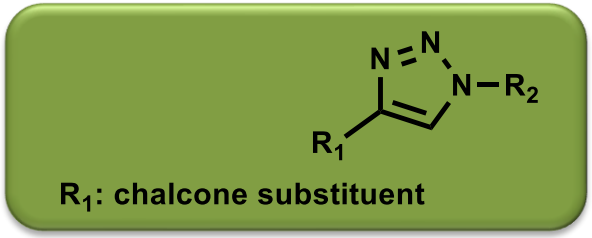
Insights of chalcone-triazole hybrids in bacterial resistance modulation



8 chalcone derivatives

Antimicrobial activity

Bacteria

Escherichia coli ATCC 25922
Staphylococcus aureus ATCC 25923
Pseudomonas aeruginosa ATCC 27853
Enterococcus faecalis 29212
S. aureus 272123
Salmonella Typhimurium SL1344

Fungi

Candida albicans ATCC 10231
Aspergillus fumigatus ATCC 204305
Trichophyton rubrum FF5

Studies on antimicrobial resistance

- Synergy with antimicrobials
- Inhibition of Efflux pumps
- Biofilm formation

Abstract:

Antimicrobial resistance is a huge public health threat, resulting in an increase of morbidity and mortality rates, high medical costs, among others. Several mechanisms are underlying bacterial resistance, such as the overexpression of drug efflux pumps, permeability changes in the bacterial cell wall or the biofilm formation. Therefore, the search for new antimicrobial agents is an urgent demand.
Chalcones are open-chain flavonoids well-known for their antimicrobial activities, as well as for their ability to revert antibiotic resistance through several mechanisms, including efflux pump inhibitory activity and the inhibition of biofilm formation. Moreover, hybridization of chalcones with 1,2,3-triazole has provided compounds with interesting antimicrobial activities. Considering this, a series of chalcone-1,2,3-triazole hybrids was synthesized and screened for its antibacterial, antifungal, and potential to establish synergy with antibiotics in resistant bacteria. Furthermore, these compounds were evaluated for their ability to act in different bacterial resistance mechanisms, namely the inhibition of bacterial efflux pumps, biofilm formation and quorum-sensing. Firstly, chalcone intermediates were synthesized by Claisen-Schmidt condensation. Then, the triazole ring was incorporated on the chalcone scaffold through the copper catalysed alkyne-azide cycloaddition, giving rise to eight hybrids. Some compounds showed synergic effect in association with antibiotics in resistant strains of *Escherichia coli* and *Enterococcus faecalis*, as well as ability to inhibit efflux pumps of *Salmonella enterica* serovar Typhimurium SL1344 and to inhibit the biofilm formation of *Staphylococcus aureus* 272123, a methicillin- and oxacillin-resistant clinical isolate. Overall results suggest the potential of these compounds as adjuvants in bacterial resistance modulation.

Keywords: Antimicrobial activity; Bacterial resistance; Chalcones; Click chemistry; Efflux pumps

Introduction

Antimicrobial resistance [1]

- **Overexpression of efflux pumps**
- Permeability changes in bacterial cell wall
- Biofilm formation
- Enzymatic modification or inactivation of antibiotics
- Target site modification

Leads to:

- Prolonged illness
- Increased mortality
- Higher medical costs [2]

Urgent to find new effective antimicrobial agents or antimicrobial adjuvants

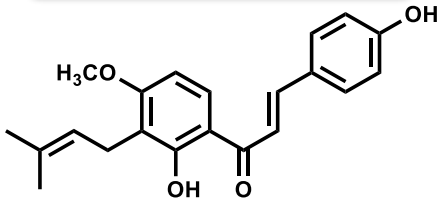
[1] Barbosa, F. *et al.*, International Journal of Antimicrobial Agents, 56 (2020) 106005.
[2] Tanwar, J. *et al.*, Interdisciplinary Perspectives on Infectious Diseases, 2014 (2014) 541340.

Introduction

Chalcones

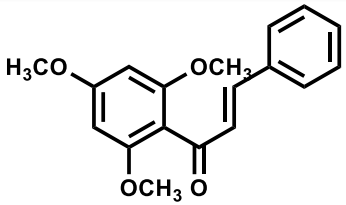
✓ **Open-chain flavonoids well-known for antimicrobial activities and for their ability to revert bacterial resistance:**

Antibacterial activity [3]



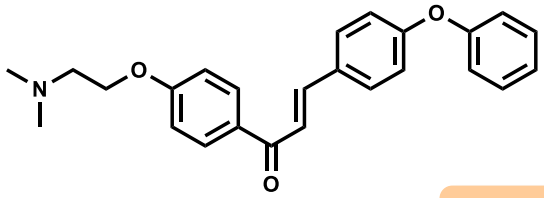
Activity against *B. subtilis*, *S. epidermidis* and *M. luteus* [3]

Antifungal activity [4]



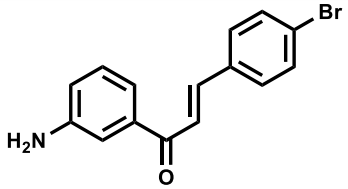
Activity against *C. albicans*, *C. glabrata* and *C. parapsilosis* [4]

Efflux pump inhibition [5]



Inhibitory activity of bacterial efflux pump NorA in *S. aureus* [5]

Inhibition of bacterial biofilm [6]

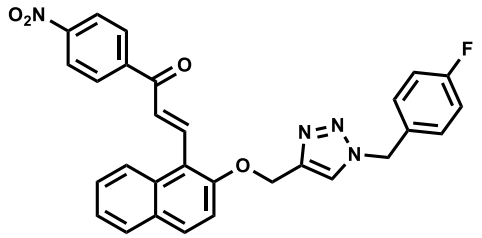


Reduction of MSSA and MRSA biofilm formation [6]

[3] W. Dan and J. Dai, European Journal of Medicinal Chemistry, 187 (2020), 111980. [4] Burmaoglu, S. *et al.*, Journal of Enzyme Inhibition and Medicinal Chemistry, 32 (2017), 490–495. [5] Durães, F. *et al.*, Current Medicinal Chemistry, 25 (2018) 6030-6069. [6] Garcia, M.A.R. *et al.*, Bioorganic Chemistry, 116 (2021) 105279.

Introduction

- ✓ **Hybridization of chalcones with other scaffolds, namely 1,2,3-triazole, has provided new compounds with interesting antimicrobial activities [7].**



Antibacterial activity against *E. coli*, *B. subtilis*, *S. epidermidis* and *P. aeruginosa*, and antifungal activity against *C. albicans* and *A. niger* [7].

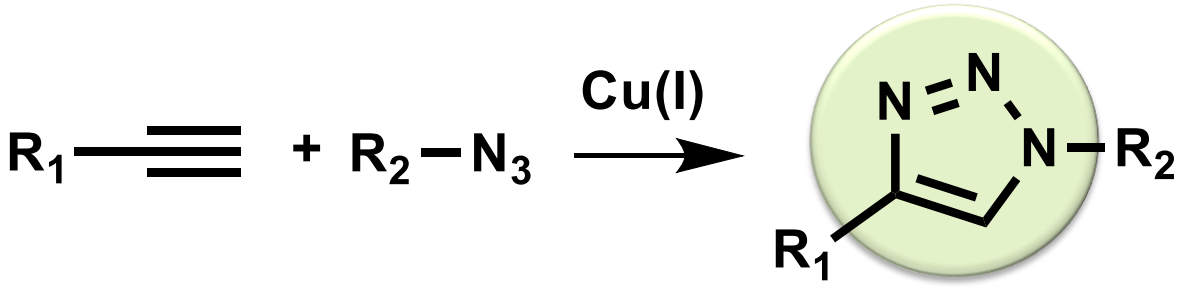
AIMS OF PRESENT RESEARCH WORK:
Synthesis of a library of chalcone-1,2,3-triazole derivatives and study of their potential as antimicrobials

[7] Yadav, P. *et al.*, European Journal of Medicinal Chemistry, 155 (2018) 263-274.

Results and discussion

Synthesis

✓ **Synthesis of 1,2,3-triazole ring through Copper-Catalysed Azide-Alkyne Cycloaddition (CuAAC), also known as "Click chemistry" [8]:**



R_1: chalcone substituent

Chalcone-triazole hybrids 1-8

[8] Rani, A. *et al.*, RSC Advances, 10 (2020) 5610-5635.

Results and discussion

Biological Activity

- ✓ **Antibacterial and Antifungal screening**
- ✓ **Evaluation of potential synergy with antibiotics in resistant bacterial strains**

Antibacterial activity

Escherichia coli ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 25923, *S. aureus* 272123, *Salmonella enterica* serovar Typhimurium SL1344 (SE03)

MIC 60 µM against *E. faecalis* ATCC 29212 for compound 5

Antifungal activity

Candida albicans ATCC 10231, *Aspergillus fumigatus* ATCC 204305, *Trichophyton rubrum* FF5

No compounds with promising activity

Synergy with antibiotics

Cefotaxime (CTX) with extended spectrum β–lactamase-producing *E. coli* SA/2 and vancomycin (VAN) for vancomycin-resistant *E. faecalis* B3/101

2-fold decrease in VAN MIC for compounds 3 and 5
4-fold decrease in VAN MIC for compound 7
2-fold decrease in CTX MIC for compounds 2 and 3

Results and discussion

Biological Activity

- ✓ **Influence on mechanisms of bacterial resistance**

Efflux pump inhibition

S. aureus 272123 and SE03

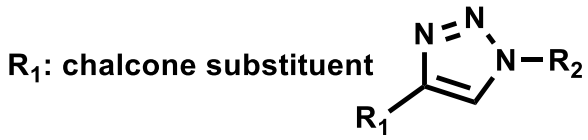
Inhibition of efflux pump in SE03 for compounds 2, 3, 4, 5 and 6

Inhibition of biofilm formation

S. aureus ATCC 25923 and methicillin and oxacillin-resistant *S. aureus* 272123 strains

Inhibition of biofilm formation in *S. aureus* 272123 for compounds 1, 4, 5, 6 and 8

Conclusions



8 chalcone derivatives

Antibacterial activity

Compound 5 displayed a MIC of 60 µM for *E. faecalis* ATCC 29212

Antifungal activity

No compounds were active for the tested strains

Synergy with antimicrobials

Compounds 3 and **5** reduced the MIC of VAN 2-fold
Compound 7 reduced the MIC of VAN 4-fold
Compounds 2 and **3** reduced the MIC of CTX 2-fold

Efflux pump inhibition

Compounds 2, **3**, **4**, **5**, and **6** inhibited efflux pumps in *Salmonella* Typhimurium SL1344

Biofilm formation inhibition

Compounds 1, **4, 5**, **6**, and **8** inhibited biofilm formation in *S. aureus* 272123

Chalcones are a promising scaffold towards the fight against antimicrobial resistance

Acknowledgements

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