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Development of new 2-heteroaryl-4-quinolones as potential antibiotics targeting multi-drug resistant ESKAPEE pathogens

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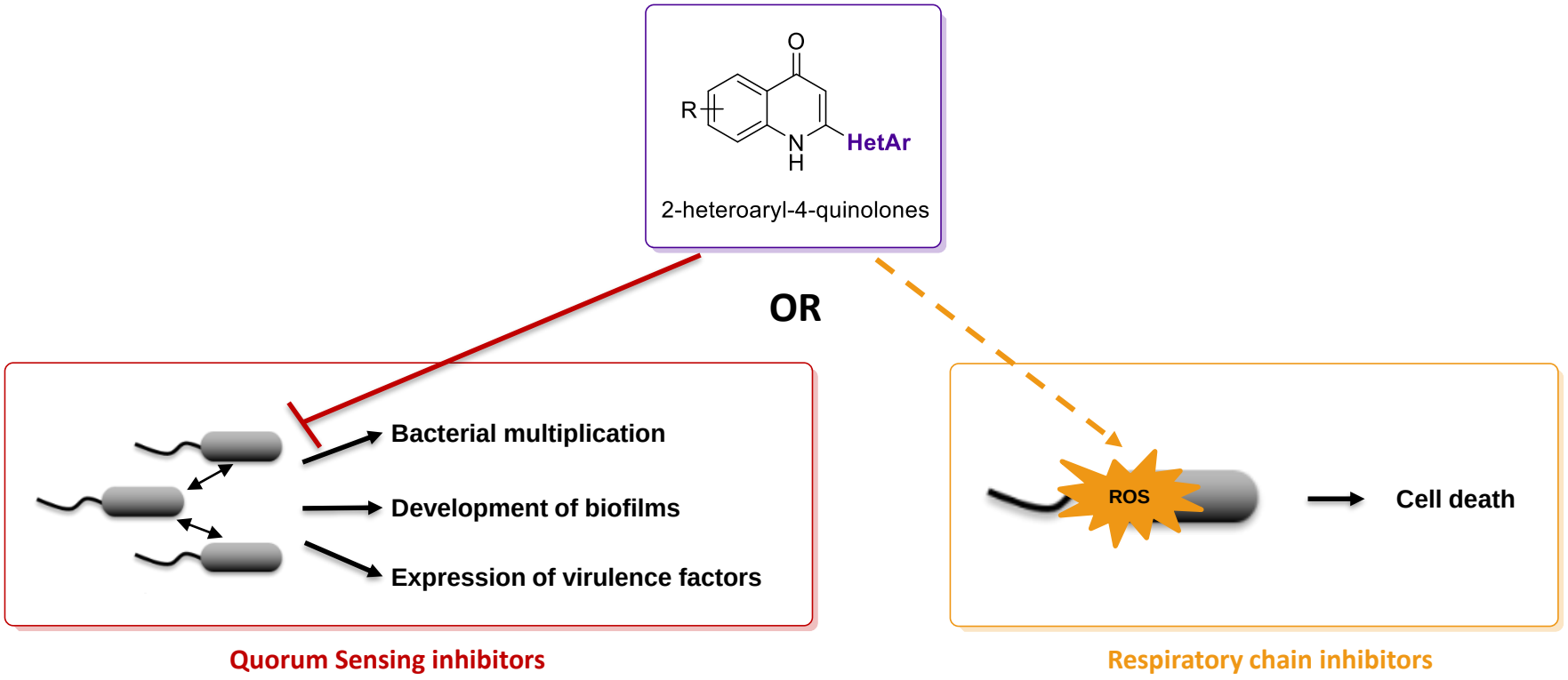
Development of new 2-heteroaryl-4-quinolones as potential antibiotics targeting multi-drug resistant ESKAPEE pathogens

Graphical Abstract



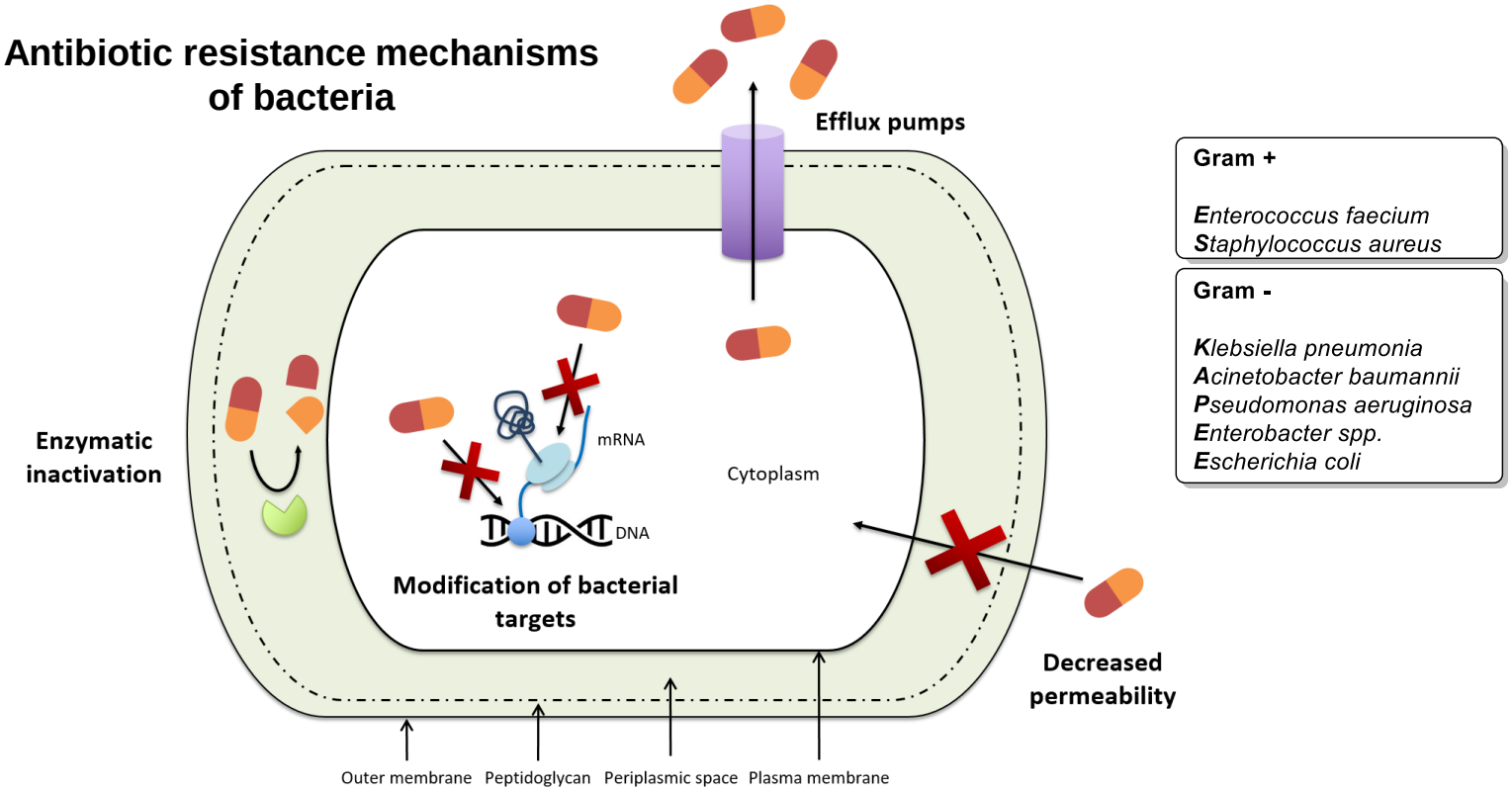
Abstract: Multi-drug resistant ESKAPEE pathogens are responsible for various nosocomial infections. Considering this serious threat to public health, new efficient treatments are urgently needed. The bacterial communication systems, called quorum sensing (QS), constitute a pool of new promising pharmacological targets for the development of antimicrobial molecules. The inhibition of QS could disrupt several intra/inter-species protective interactions (bacterial multiplication, biofilm formation) and virulence pathways. The intervention of three main small signaling molecules was described in the *pqs* intercellular communication system of *P. aeruginosa* : the *Pseudomonas* quinolone signal (PQS), its precursor 2-heptyl-4(1*H*)-quinolone (HHQ) and the 2-heptyl-4-hydroxyquinoline-*N*-oxide (HQNO) as a secondary metabolite from this pathway. Interestingly, HQNO appears to be a potent respiratory chain inhibitor for various competing microorganisms such as *S. aureus*. Furthermore, HHQ analogues and different 2-heteroaryl-4-quinolone series revealed efficient as QS inhibitors (PQS receptor antagonists) or as type II NADH/quinone oxidoreductase inhibitors. Taking these studies into account, the interest of the quinolone scaffold in the design of QS and respiratory chain inhibitors has emerged. In this context, we aim to develop new antibacterial 2-heteroaryl-4-quinolone series. The synthesis of the first series carrying out pallado-catalyzed C-C or C-N coupling reactions from 2-bromo-4-chloroquinoline precursors will be described in the presentation.

Keywords: ESKAPEE pathogens; bacterial communication systems; quorum sensing; quinolones; pallado-catalysed cross-coupling reactions.

Introduction

Infectious diseases are a serious threat to public health:

- Second cause of death in the world with 700 000 deaths/year
- Emergence of multi-resistant strains in ESKAPEE pathogens



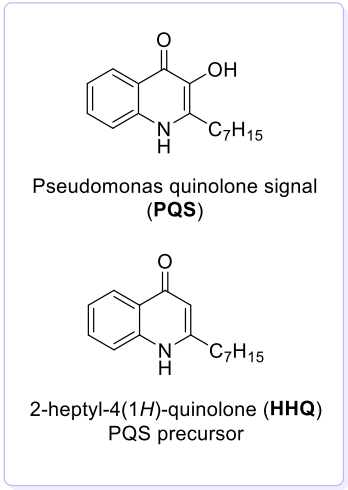
Antibiotic resistance = Urgent need to find new treatments

Introduction

Quorum Sensing (QS)

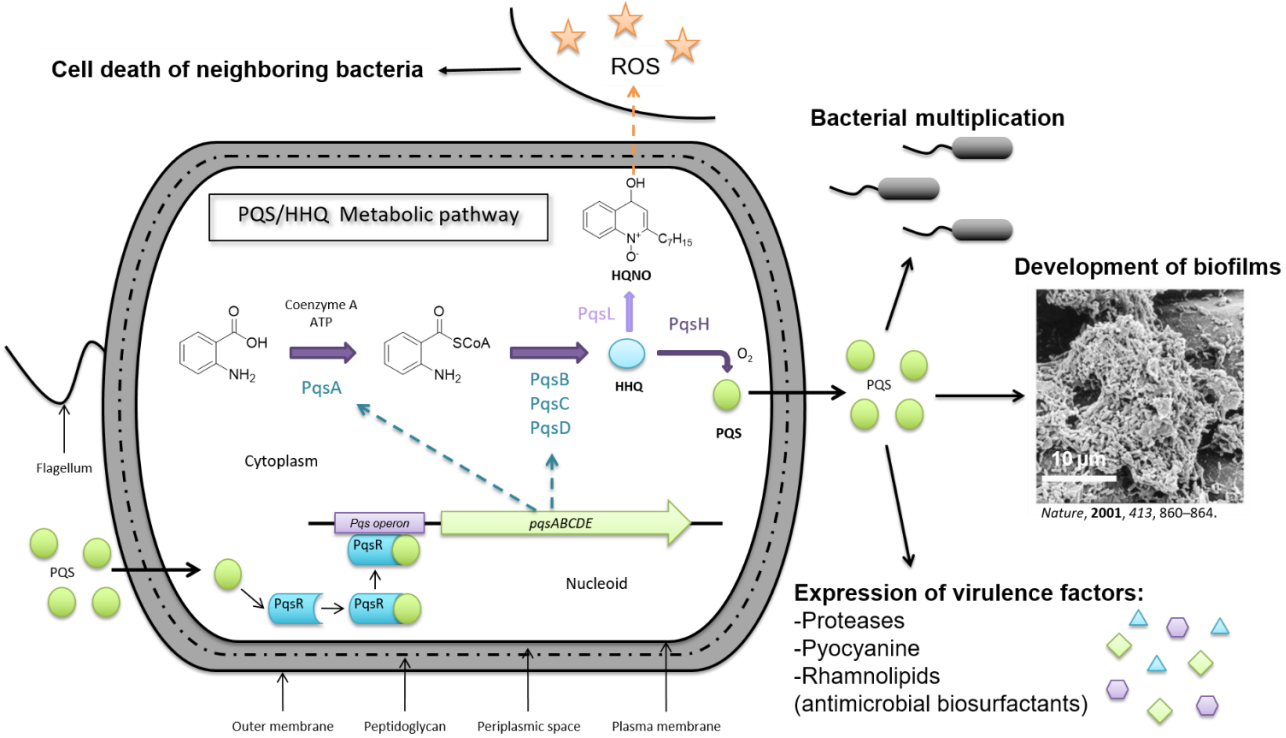
= Pool of bacterial communication systems regulating several intra/inter-species protective interactions and virulence pathways in response of environment factors

QS molecules produced by *P.aeruginosa*



Pseudomonas quinolone signal (**PQS**)

2-heptyl-4(1*H*)-quinolone (**HHQ**)
PQS precursor



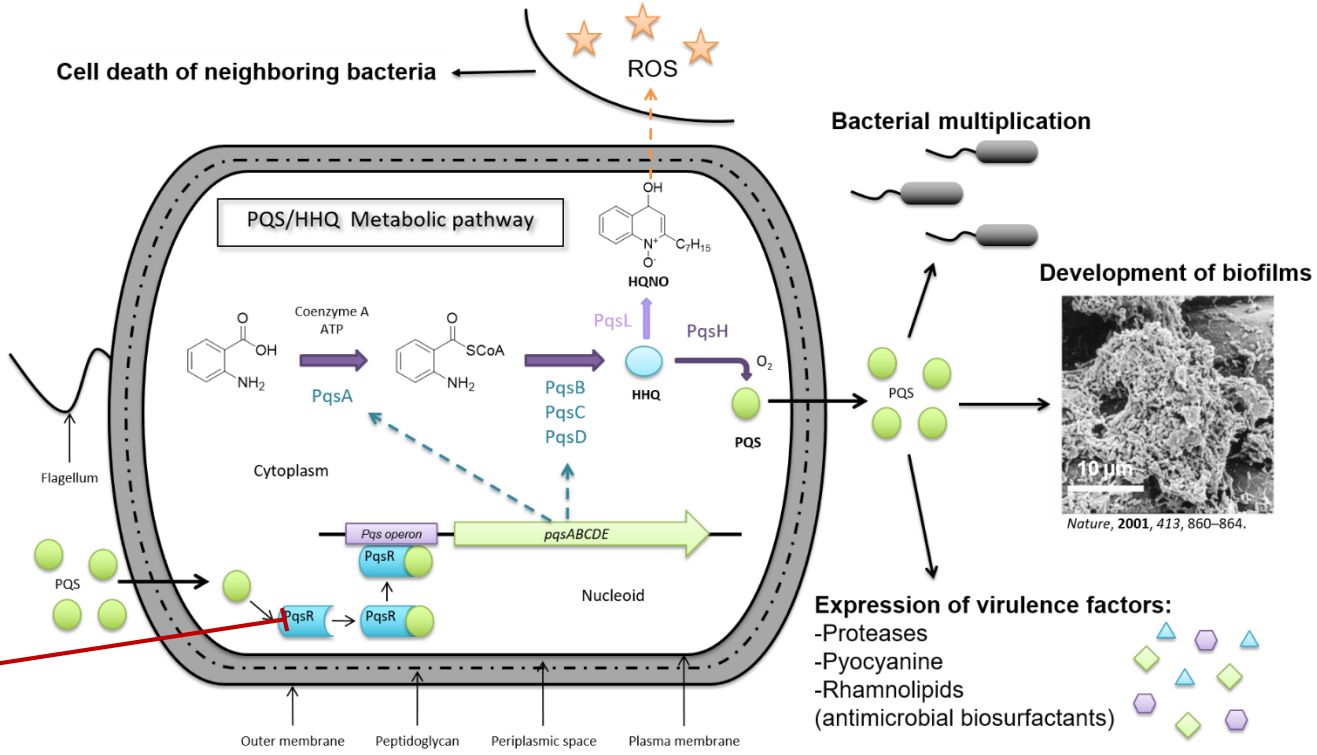
***P. aeruginosa* main communication system[1]**

➡ Promising **potential therapeutic targets** for the development of new antibiotics

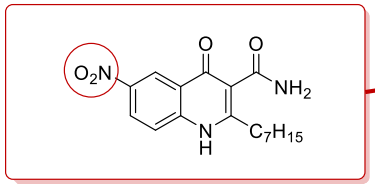
(1) *Chem. Sci.*, **2017**, *8*, 7403-7411.

Introduction

Development of QS inhibitors



Molecule described in literature



6-nitro-HHQ-3-carboxamide[2]

***P. aeruginosa* main communication system**

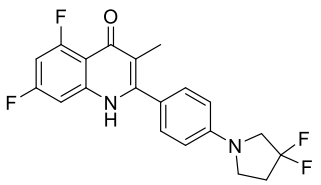
The introduction of a strong hydrogen bond acceptor group in position 6 of a HHQ analogue allowed the increase of the PqsR antagonist activity.

(2) *Org. Biomol. Chem.*, **2017**, *15,* 4620-4630.

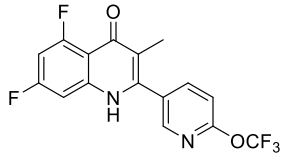
Introduction

Development of respiratory chain inhibitors

Molecules described in literature

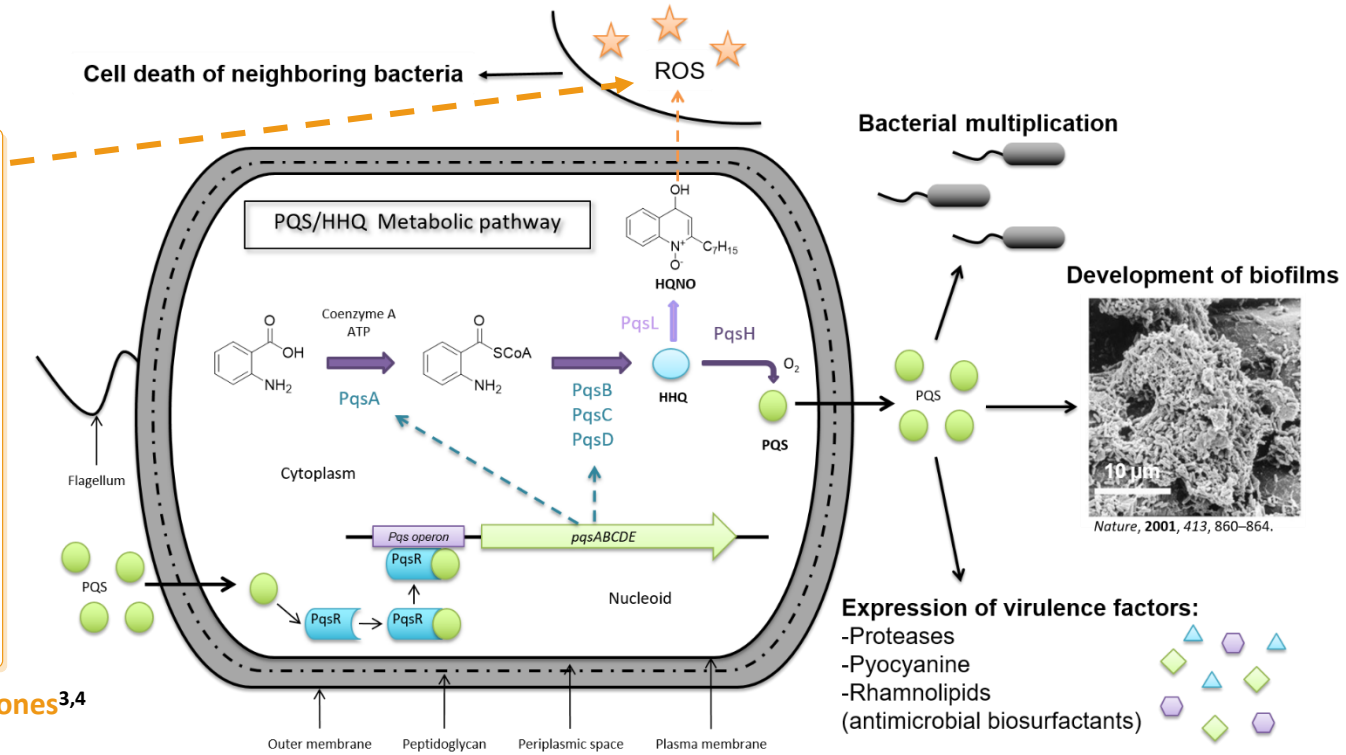


M. tuberculosis NDH-2 inhibitor
IC_{50} *(MDR Mtb)* = 140 nM



P. falciparum NDH-2 inhibitor
IC_{50} *(3D7 P. falciparum)* = 54 nM

2-phenyl and 2-pyridinyl-4-quinolones[3,4]

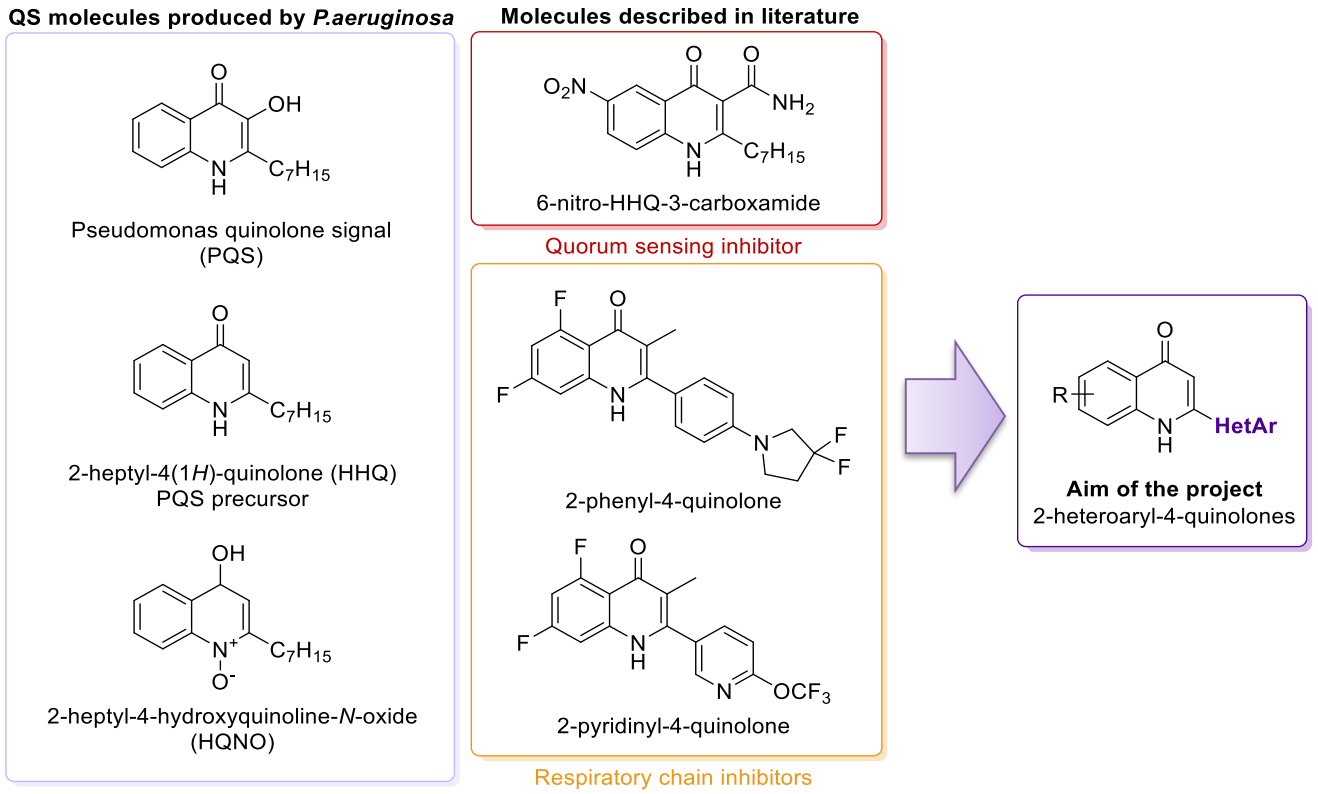


***P. aeruginosa* main communication system**

(3) *J. Med. Chem.*, **2017**, *60*, 3703-3726 ; (4) *J. Med. Chem.*, **2012**, *55*, 1844-1857.

Introduction

Taking these literature data into account, we decided to develop a 2-heteroaryl-4-quinolone family in order to find new potential antibiotics against ESKAPEE pathogens. These compounds could be active against two types of bacterial targets implicated in protective or virulence pathways.

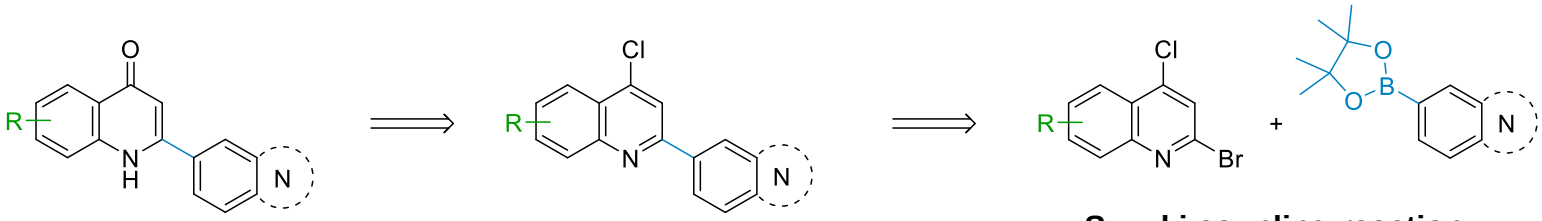


Introduction

Synthesis strategy

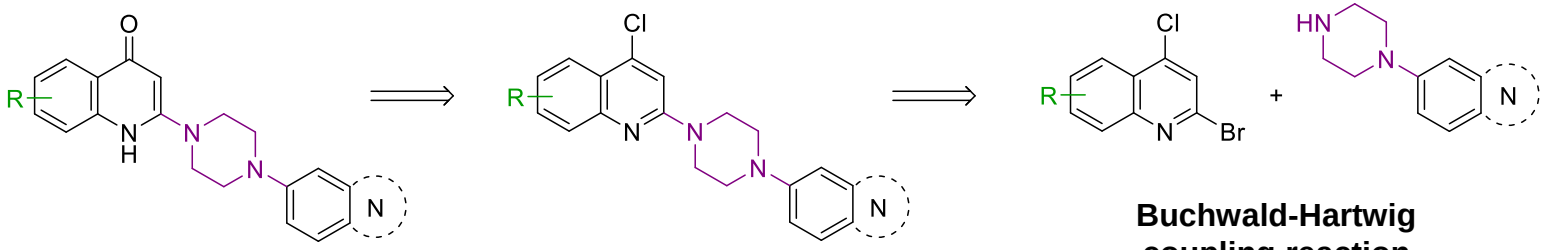
The synthesis of the expected 2-heteroaryl-4-quinolones relies on palladium-catalyzed cross-coupling reactions between the 2-bromo-4-chloroquinoline and a heteroarylboronic ester (series **I**) or a *N*-heteroarylpiperazine derivative (series **II**).

Series I : Synthesis of 2-heteroaryl-4-quinolones



Suzuki coupling reaction

Series II : Synthesis of 2-(4-heteroarylpiperazin-1-yl)-4-quinolones

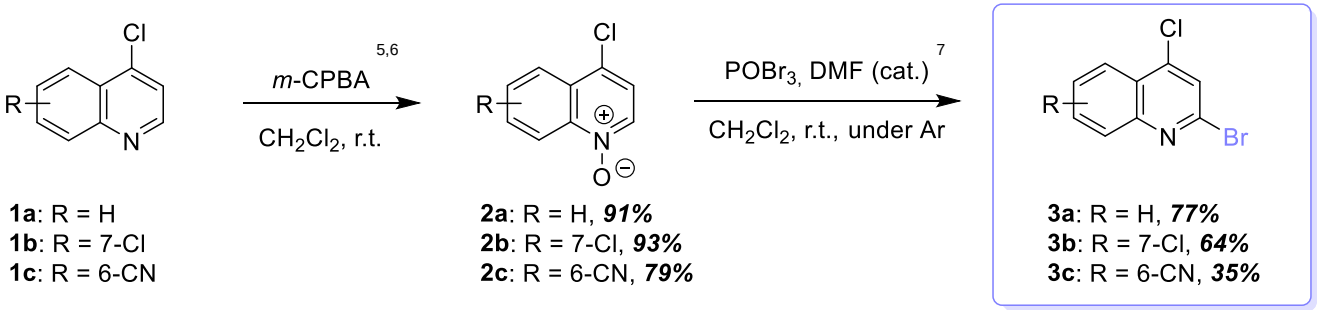


Buchwald-Hartwig coupling reaction

R = H, Cl, NO_2, CN, NH_2...

Results and discussion

Synthesis of diversely substituted 2-bromo-4-chloroquinoline precursors

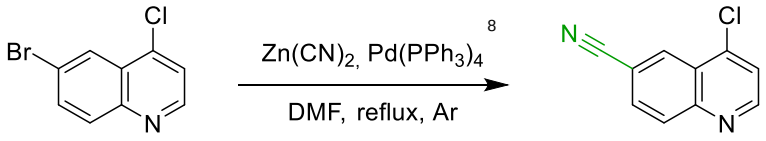


1a: R = H
1b: R = 7-Cl
1c: R = 6-CN

2a: R = H, ***91%***
2b: R = 7-Cl, ***93%***
2c: R = 6-CN, ***79%***

3a: R = H, ***77%***
3b: R = 7-Cl, ***64%***
3c: R = 6-CN, ***35%***

The 2-bromo-4-chloroquinoline precursors **3a-c** were synthetized carrying out a selective bromination in position 2 of the corresponding 4-chloroquinoline *N*-oxides **2a-c**.

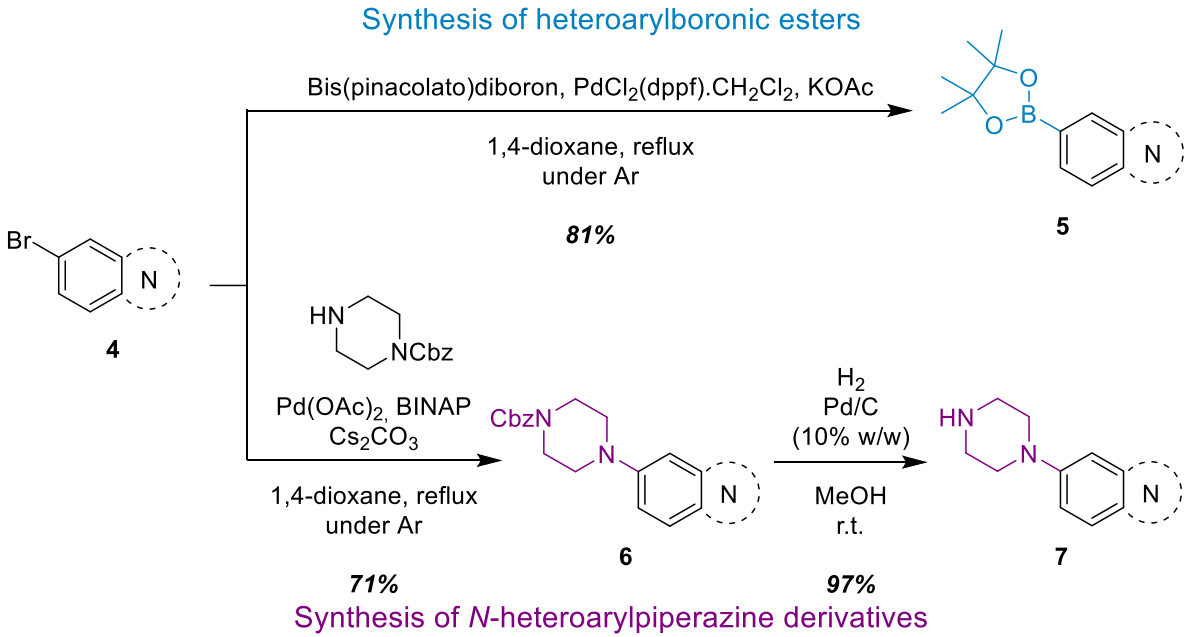


One of the first pharmacomodulation realized on the quinoline core corresponds to the introduction of a cyano group in position 6. In presence of an excess of $Zn(CN)_2$, the 4,6-dicyano derivative was mostly obtained. After an optimization of the reactant amounts, the desired product was finally prepared in good yield.

(5) WO 2012/069856A1; (6) *J. Med. Chem.*, **2012**, *55*, 1844-1857 ; (7) *Tetrahedron letters*, **2014**, *55*, 7130-7132 ; (8) EP2742039B1.

Results and discussion

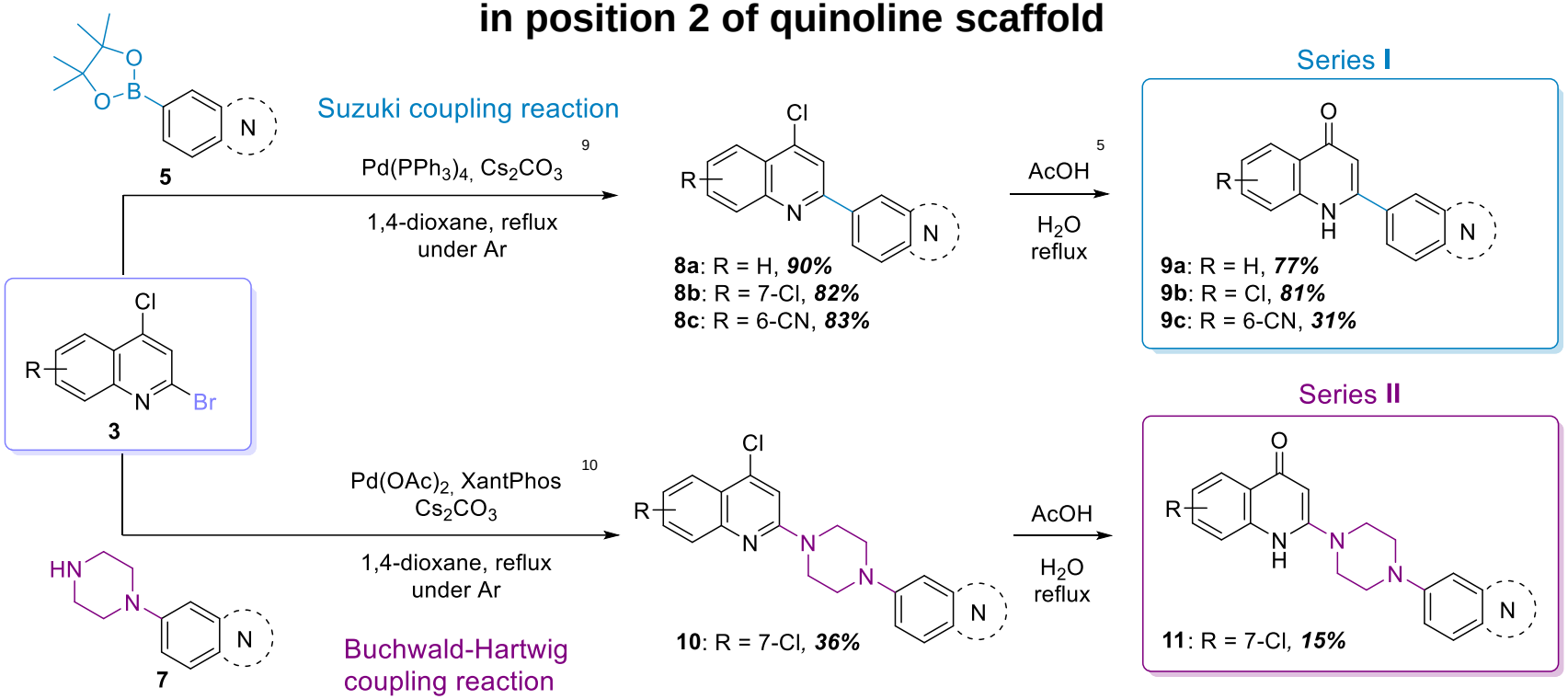
Synthesis of the second heteroaryl building blocks



- In the series **I**, a Miyaura borylation reaction provided the heteroarylboronic ester **5**.
- In the series **II**, the *N*-heteroarylpiperazine derivative **6** was prepared using a Buchwald-Hartwig coupling. This synthesis was optimized changing the BINAP ligand for XantPhos with an improved yield of 71% *vs* 24%. A subsequent catalytic hydrogenation successfully allowed the *N*-Cbz removal to prepare compound **7** thus available for a second C-N coupling.

Results and discussion

Palladium-catalyzed cross-coupling C-C or C-N reactions in position 2 of quinoline scaffold

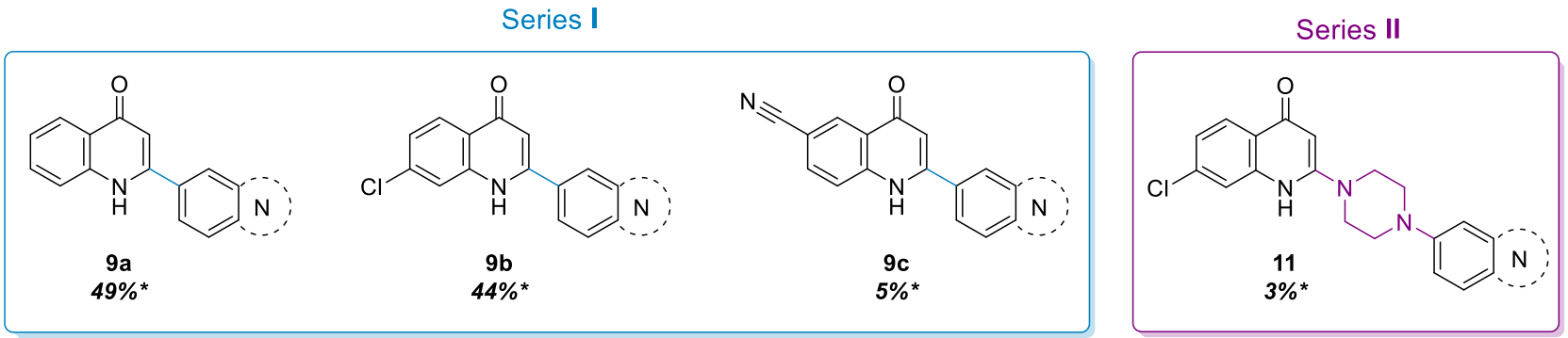


After conversion of the quinoline core of coupling products **8a-c** and **10** into a quinolone one under acidic conditions, expected products **9a-c** and **11** were respectively obtained.

(9) *Tetrahedron Letters*, **2006**, *47*, 7427-7430 ; (10) *Tetrahedron*, **2007**, *63*, 13000-13005.

Conclusion

- **Four final products** have been synthesized in **4-5 steps**.



Synthesis of four new promising 2-heteroaryl-4-quinolone derivatives

- Pharmacomodulations in positions 5 to 8 of 4-chloroquinoline precursors are currently in progress to develop a wide range of 2-heteroaryl-4-quinolones.
- The **antibiotic activity** of these potential QS or respiratory chain inhibitors against different bacteria species, especially *A. baumannii* and *P. aeruginosa,* will shortly be evaluated to **identify a first lead compound**.

Acknowledgments

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