

Valentin Duvauchelle,¹ Chaimae Majdi,¹ David Bénimélis,¹ Catherine Dunyach-Remy,² Patrick Meffre¹ and Zohra Benfodda.¹

¹UPR CHROME, Université de Nîmes, CEDEX 1, F-30021 Nîmes, France

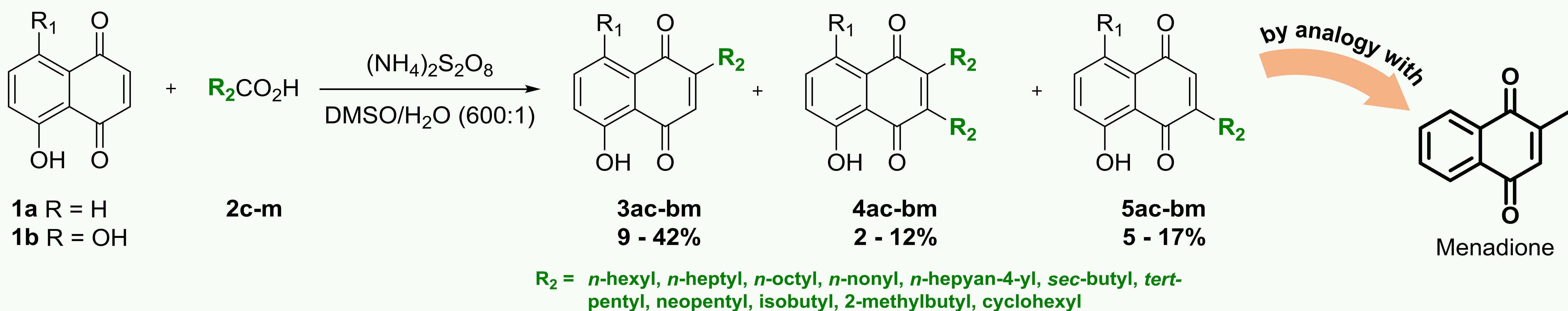
²VBIC, INSERM U1047, Service de Microbiologie et Hygiène Hospitalière, Université de Montpellier, CHU Nîmes, Nîmes, France

I. INTRODUCTION

The emergence of multidrug resistant (MDR) bacteria requires interest in the medical field and thereby an urgent need to develop efficient and specific methods in targeting unique bacterial cellular processes.^{1,2} Menadione (Vitamin K3) showed interesting properties as membrane integrity, two-component system and efflux pump disruptor.^{3,4} Novel series of 1,4-naphthoquinone based on menadione have been designed and synthesized starting from juglone and naphthazarin, following a Minisci-type reaction.⁵

II. CHEMISTRY

Scheme 1. Synthesis of juglone **1a** and naphthazarin **1b** derivatives



43 derivatives have been synthesized following this Minisci-type methodology in 6 – 42% yields after purification on flash chromatography.

III. ANTIBACTERIAL EVALUATIONS

Table 1. MIC values of compounds **3bm** on clinical resistant *S. aureus* strain with and without vancomycin and cloxacillin, fractional inhibitory concentration (FIC) and synergistic effect observed

MIC of drug alone (µg/mL)		MIC of drug when used in combination (µg/mL)		Fold MIC reduction		FICI	Effect
Vancomycin	3bm	Vancomycin	3bm	Vancomycin	3bm		
0.5	0.5	0.03	0.125	1/16	1/4	0.313	Synergy
Cloxacillin	3bm	Cloxacillin	3bm	Cloxacillin	3bm	0.313	Synergy
2	0.5	0.125	0.125	1/16	1/4		

Table 2. Interpretation of FIC index and FICI formula

Interpretation	FIC index value
Synergism	≤ 0.5
Additive	0.5 – 1
Indifferent	> 1 – 4
Antagonism	> 4

$$FICI = FIC_A + FIC_B = \frac{\text{MIC of A in combination with B}}{\text{MIC of A alone}} + \frac{\text{MIC of B in combination with A}}{\text{MIC of B alone}}$$

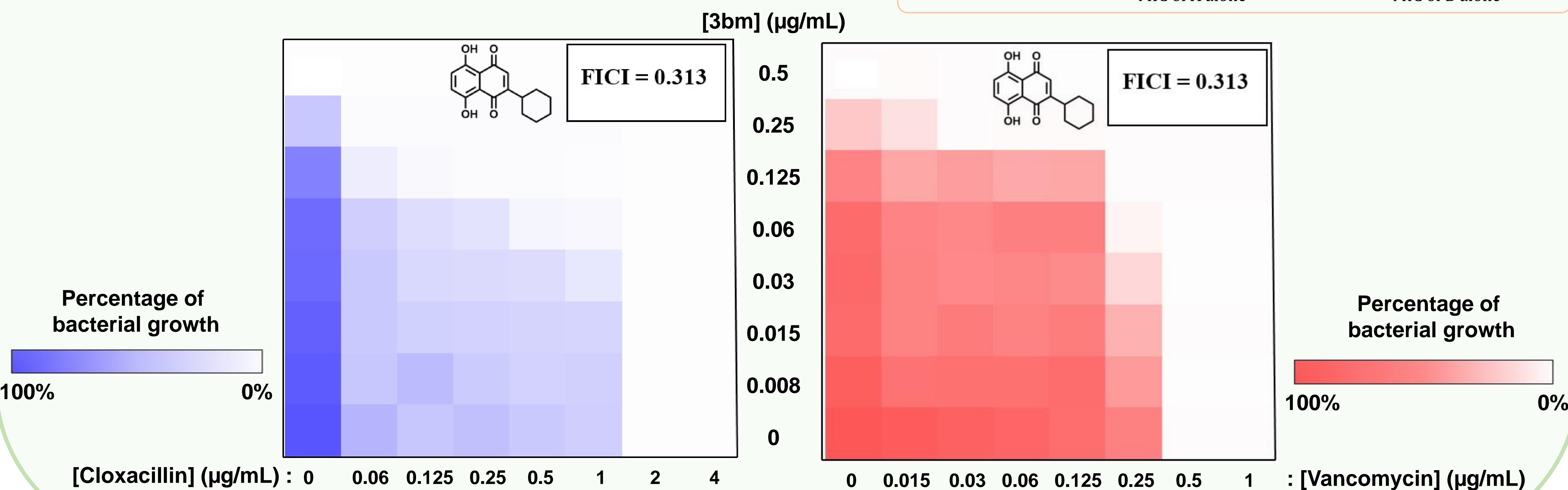


Figure 2. Heatmaps of checkerboard assays of compound **3bm** with vancomycin and cloxacillin.

IV. CONCLUSION

Among 43 synthesized derivatives, 5 compounds showed good antibacterial activities against clinical MRSA strain (MIC range 0.5 – 8 µg/mL). Antibacterial and synergistic properties have been measured on resistant and sensitive bacterial strains. One compound was shown to restore the sensitivity of a clinical strain resistant to cloxacillin and vancomycin (FICI < 0.5). The structural elucidation of regioisomers **3** and **5** has also been described for the first time with the help of HMBC NMR spectroscopy and confirmed with XRD.

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ACKNOWLEDGMENTS

The author would like thank the Occitanie Region, the MESRI, the University of Nîmes and the CHU of Nîmes