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# Synergistic Effects of Novel Naphthoquinone Derivatives Against Clinical Methicilin-Resistant *Staphylococcus aureus* Strain

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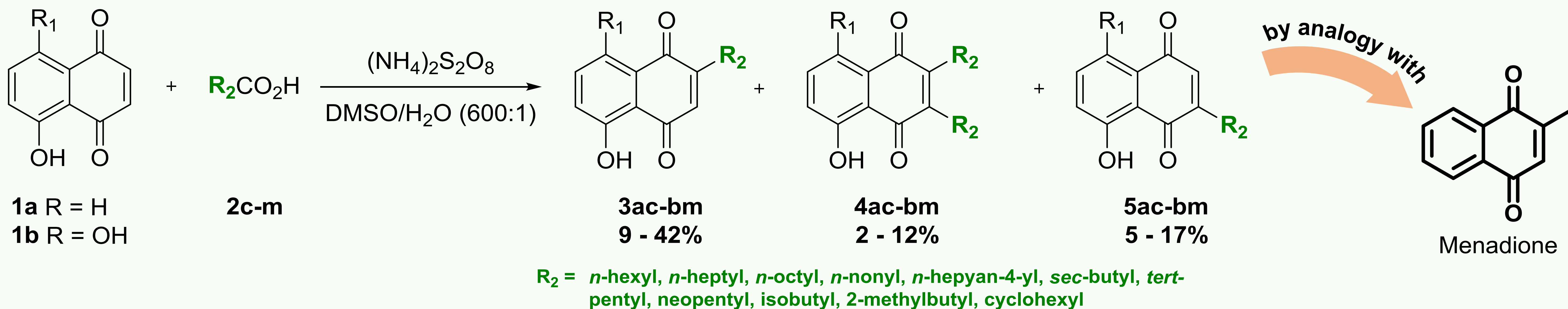
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## I. INTRODUCTION

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.<sup>1,2</sup> Menadione (Vitamin K3) showed interesting properties as membrane integrity, two-component system and efflux pump disruptor.<sup>3,4</sup> Novel series of 1,4-naphthoquinone based on menadione have been designed and synthesized starting from juglone and naphthazarin, following a Minisci-type reaction.<sup>5</sup>

## 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

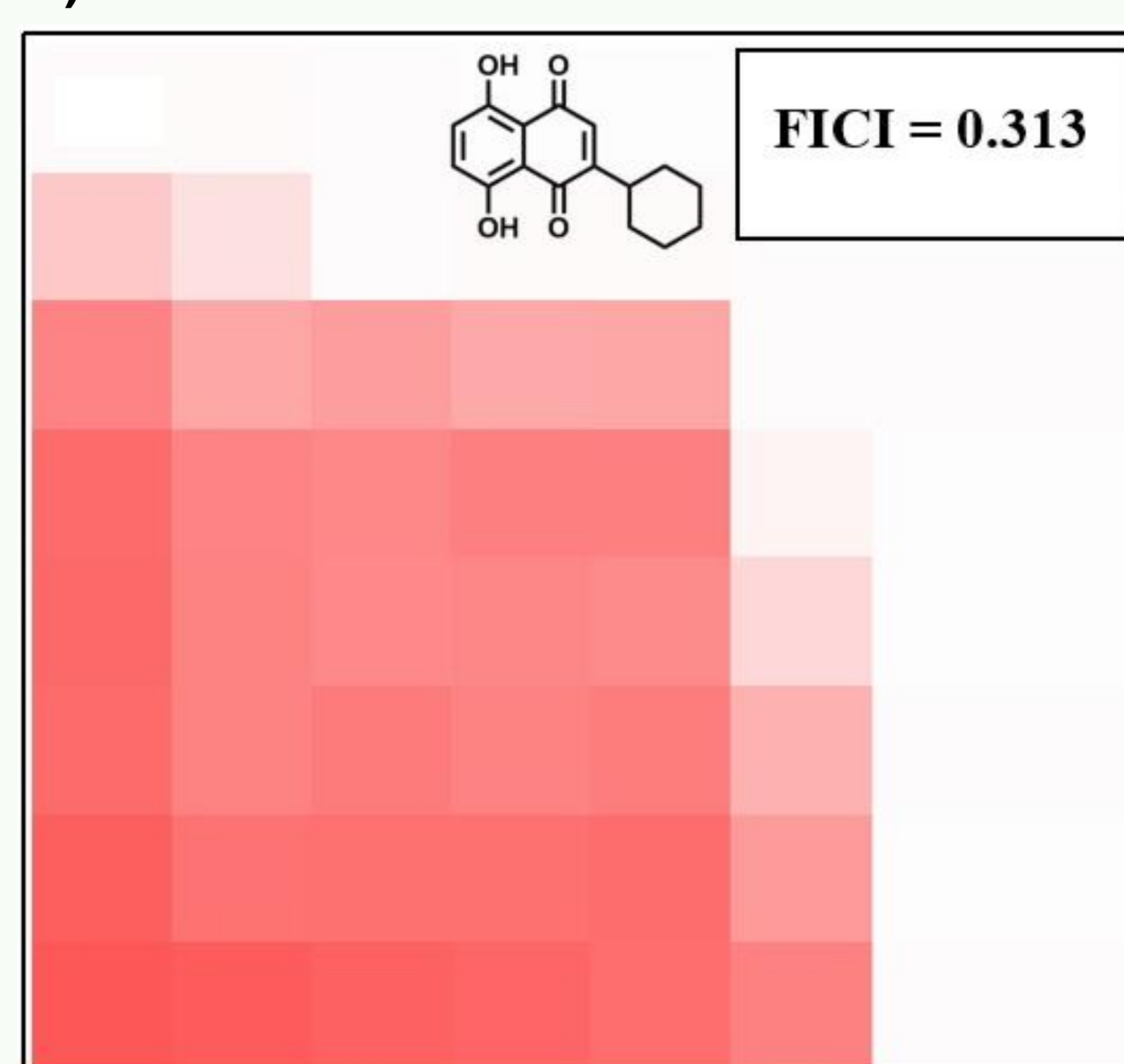
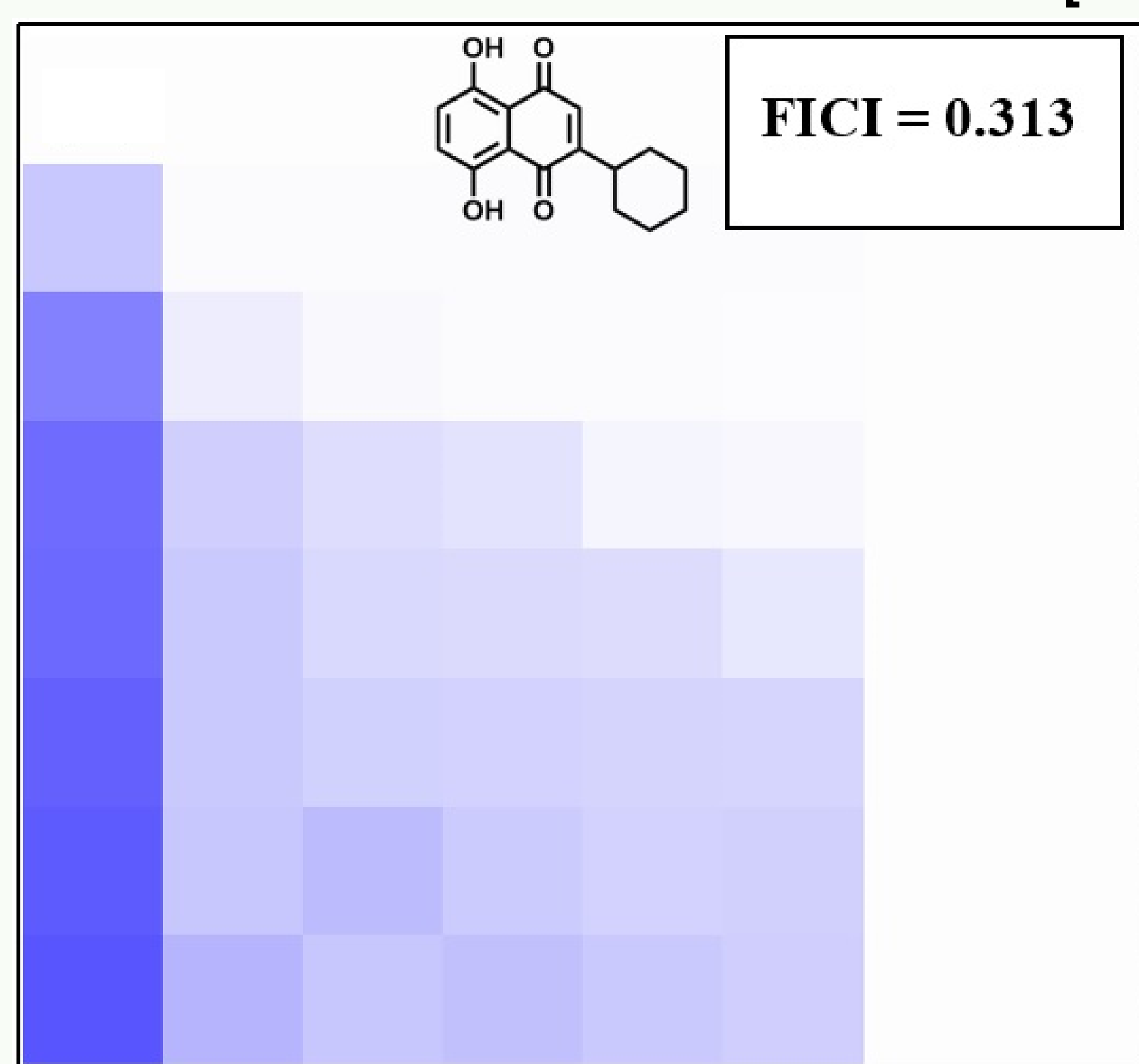
MIC of drug alone (µg/mL)		MIC of drug when used in combination (µg/mL)		Fold MIC reduction		FICI	Effect
Vancomycin	<b>3bm</b>	Vancomycin	<b>3bm</b>	Vancomycin	<b>3bm</b>		
0.5	0.5	0.03	0.125	1/16	1/4		
Cloxacillin	<b>3bm</b>	Cloxacillin	<b>3bm</b>	Cloxacillin	<b>3bm</b>	0.313	Synergy
2	0.5	0.125	0.125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

**Table 2.** Interpretation of FIC index and FICI formula

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

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

[**3bm**] (µg/mL)



**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.

## REFERENCES

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