

**TITLE:** SCREENING AND IDENTIFICATION OF COMPOUNDS PRESENT IN THE PATHOGEN BOX® WITH ANTIBACTERIAL ACTIVITY

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**ABSTRACT:** Antimicrobial resistance represents an alarming and ever-increasing threat that is nowadays alone responsible for 700.000 deaths every year, a number estimated to reach 10 million by the year 2050. In the last decades, the urgency for strategies that aim to constrain the spread of resistance while enable research, discovery, and development of new antimicrobials agents is of upmost priority amongst health organizations worldwide. In that context, alternatives such as the Pathogen Box® came to fruition (<https://www.mmv.org/mmv-open/pathogen-box/about-pathogen-box>). The Pathogen Box® contains approximately 400 drug-like compounds that are active against neglected diseases such as malaria, kinetoplastids, and cryptosporidiosis. The compounds are provided free of charge so that researches around the globe can investigate possible antimicrobial activities for different pathogens, provided that any obtained data be inserted in a public domain to disseminate knowledge access. In this study, we investigated the potential antibacterial activity of the Pathogen Box® compounds against the following strains: *Staphylococcus aureus* (ATCC® 29213), a methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli* (ATCC® 25922) and a *E. coli* resistant to ampicillin, sulbactam, and polymyxin (MCR-1). The assay was performed by obtaining minimal inhibitory concentration (MIC) via broth microdilution method followed by resazurin assay to confirm bacterial growth inhibition. For the *E. coli* ATCC® 25922 screening, 25 compounds showed an antibacterial activity with MIC ranging between 100uM – 1,56uM, and of these, for the *E. coli* MCR-1 screening, two compounds had a 1-fold increase in the MIC comparing sensitive x resistant (MMV675997: 12,5uM to 25uM; MMV004168: 25uM to 50uM). The *S. aureus* ATCC® 29213 screening resulted in 44 compounds with antibacterial activity at 100uM, and for MRSA 5 compounds had MIC between 12,5uM – 0,78uM, including one compound with a MIC of 1,56uM (MMV687700) and two compounds that inhibited MRSA growth at 0,78uM (MMV021057; MMV687699). Those 3 compounds also have a high selectivity index: MMV021057 (MRC5 – 35,9); MMV687699 (HepG2 - 49,09) and MMV687700 (HepG2 - 64,10). The selectivity index was calculated to assess the activity of the selected compound against the bacteria without damaging the cell viability. MRC5 (human lung fibroblast cells); HepG2 (human liver cells)

**Keywords:** Antibacterial activity *Escherichia coli*, *Staphylococcus aureus*, Pathogen box.

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