**PLB42**
**Paper Poster Session**
**Late breaker session: Other**

# WCK 5107 & WCK 5153: bicyclo-acyl hydrazides PBP2 inhibitors showing potent beta-lactam enhancer activity against Acinetobacter baumannii, including multidrug-resistant (MDR) carbapenemase-producing clinical strains

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**Background:** *Acinetobacter baumannii* has spread rapidly throughout the world during the last decades, and more than 60% of all *A. baumannii* clinical isolates are MDR, representing a major treatment challenge. WCK 5107 (Zidebactam) and WCK 5153 are Bicyclo-acyl Hydrazides (BCH) discovered at the Wockhardt Research Centre (India). The objectives of this work were to determine the penicillin-binding protein (PBP), OXA-23 inhibition profiles and antimicrobial activity of WCK 5107 and WCK 5153, alone and in combination with β-lactams, against an MDR *A. baumannii*.

**Material/methods:**

MICs and killing kinetics were performed against a MDR *A. baumannii* clinical strain producing the carbapenemase OXA-23 belonging to the widespread international clone ST2. OXA-23 inhibition potential was studied through nitrocefin based colorimetric method. Membranes containing the PBPs of *A. baumannii* ATCC 19606 were obtained by sonication and ultracentrifugation. PBPs were labelled with BOCILLIN FL, and 50% inhibitory concentrations ($IC_{50}$) of WCK 5107, WCK 5153, as well as first time ever - cefepime, mecillinam and sulbactam (range of concentrations tested 0.0156-2 mg/L) were determined.

**Results:**

WCK 5107 and WCK 5153 showed potent specific PBP2 affinity in *A. baumannii* (Table). Both the BCH NCEs had high IC50 for OXA-23 suggesting poor enzyme inhibition (2.076 - 2.162 µM). MICs of WCK 5107 and WCK 5153 were >1024 mg/L for wild type and MDR Acinetobacter strains. However, cefepime or sulbactam at their CLSI breakpoint concentrations in combination with 4-8 mg/L of 5107 and WCK 5153 led to potent synergistic killing, reaching for several of the combinations full bacterial eradication at 24h.

| | **$IC_{50}$ (mg/L)** | | | | |
|---|---|---|---|---|---|
| **PBP** | **CEFEPIME** | **MECILLINAM** | **SULBACTAM** | **WCK 5107** | **WCK 5153** |
| **1A** | 0.05±0.02 | >2 | >2 | >2 | >2 |

| | | | | | |
|---|---|---|---|---|---|
| **1B** | 1.32±0.27 | >2 | 0.9±0.5 | >2 | >2 |
| **1C** | 0.84±0.10 | >2 | >2 | >2 | >2 |
| **2** | 0.97±0.34 | 0.07±0.04 | >2 | 0.01±0.003 | 0.01±0.002 |
| **3** | 0.08±0.03 | >2 | 0.64±0.21 | >2 | >2 |

**Conclusions:** WCK 5107 and WCK 5153 are novel non-β-lactam PBP2 inhibitors, showing potent β-lactam enhancer effect against *A. baumannii,* including MDR OXA-23-producing ST2 international high-risk clone.