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Activity of novel pyrrolocytosine protein synthesis inhibitors against multi-resistant Gram-negative bacteria, including carbapenemase producers and those with MCR-1

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Background: Pyrrolocytosine antimicrobials bind the 50S ribosomal subunit, interfering with substrate positioning in the P-loop. Development at Melinta Therapeutics aimed to maximise target affinity and penetration while reducing efflux. These objectives were best achieved in basic molecules balancing shape and polarity. We investigated if these were compromised against (i) Enterobacteriaceae with MCR-1, which adds positive charge to surface lipopolysaccharides, (ii) multiresistant Enterobacteriaceae and *Acinetobacter* with carbapenemases and (ii) *P. aeruginosa* with altered efflux.

Material/methods: Four analogues were tested, RX04A, B, C and D. Panels comprised 96 referred clinical isolates, one recipient *E. coli* and its *mcr-1*- transformant, also, as controls, *E. coli* ATCC25922 and *P. aeruginosa* ATCC27583. Isolates' *mcr-1* and carbapenemase genes were detected by PCR; other mechanisms were inferred by interpretive reading. MICs were determined by CLSI microbroth dilution.

Results: MIC distributions for 66 Enterobacteriaceae isolates were unimodal, with peaks at 1, 1, 2 and 2 mg/L for analogues A, B, C and D respectively; geometric mean MICs were 1.0, 1.1, 1.7 and 2.3 mg/L respectively. For compound A, the most active analogue, 64/66 MICs for Enterobacteriaceae were from 0.5-2 mg/L and only one value – for a *Serratia* isolate – exceeded this range, at 8 mg/L. This isolate was also the most resistant to the other analogues, with MICs ≥ 16 mg/L. for compounds B, C and D. MICs were not raised, compared with the *E. coli* ATCC25922 control, for Enterobacteriaceae with carbapenemases (n=36) or *mcr-1* (n=12); likewise, acquisition of *mcr-1* did not raise MICs for *E. coli* DH10B. MIC distributions of analogues A-C straddled 1-8 mg/L for 10 A.

baumannii, D was less active; RX-04A had the lowest MICs, with 7/10 values from 1-2 mg/L. MICs for *A. baumannii* with OXA-23 carbapenemase were mostly two-fold higher than for carbapenem-susceptible isolates, but numbers were small. RX-04A remained the most active analogue against *P. aeruginosa* isolates, with 18/20 MICs from 1-4 mg/L; by comparison $\geq 50\%$ of MICs were ≥ 16 mg/L for analogues C and D. Geometric MICs of all analogues were *c.* 2-fold higher for *P. aeruginosa* with 'normal' vs. low efflux, but not further raised for those with elevated efflux.

Conclusions: The pyrrolocytosines showed promising activity: RX-04A was the most active, with MICs mostly 1-2 mg/L for Enterobacteriaceae and *A. baumannii* and 1-4 mg/L for *P. aeruginosa*. MICs were slightly raised against (i) multi-resistant *A. baumannii* and (ii) *P. aeruginosa* with normal vs. low efflux function but not for multiresistant Enterobacteriaceae and those with MCR-1.