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**Objective:** The US Centers for Disease Control has declared carbapenem-resistant Enterobacteriaceae (CRE) and multidrug-resistant *Acinetobacter* urgent and serious threats, respectively. TP-076, TP-138, and TP-600 are novel synthetic tetracycline antibiotics in development for use against multidrug-resistant Gram-negative pathogens, including those resistant to multiple classes of antibiotics including carbapenems. These compounds were tested against panels of molecularly characterized CRE (including *Escherichia coli*, *Enterobacter aerogenes*, *Enterobacter cloacae*, and *Klebsiella pneumoniae*), *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* to determine their activities against these difficult-to-treat pathogens.

**Methods:** Minimal inhibitory concentration (MIC) assays against panels of carbapenem-resistant isolates were performed according to Clinical Laboratory Standards Institute guidelines at IHMA. A total of 334 unique carbapenem-resistant isolates were screened. Among the 178 Enterobacteriaceae isolates, the following classes of extended spectrum beta-lactamase and carbapenemase enzymes were represented: ACT (n=6), CTX-M (n=54), DHA (n=4), KPC (n=128), MOX/CMY (n=4), NDM (n=11), OXA (n=24), SHV (148), TEM (n=108), VEB-1 (N=1), and VIM (n=14). All *P. aeruginosa* isolates were confirmed carbapenemase producers and the following classes of enzymes were represented in the panel: GES (n=18), IMP (n=5), KPC (n=8), PER-1 (n=7), SPM-1 (n=1), TEM (n=4), VIM (n=29), VEB (n=7). All 80 *A. baumannii* isolates contained an OXA gene.

**Results:** TP-076, TP-138, and TP-600 were highly active against panels of CRE and *A. baumannii* (see Table). TP-076, TP-138, and TP-600 had MIC<sub>50/90</sub> values of 0.06/0.125, 0.125/0.25, and 0.25/4 µg/mL, respectively, in comparison to MIC<sub>50/90</sub> values of 4/8, >16/>16 and >16/>16 µg/mL for tigecycline, ceftazidime, and imipenem, respectively. All three compounds showed greatly reduced MIC values versus comparators against Enterobacteriaceae, with MIC<sub>50/90</sub> values of 0.25/1, 0.25/1, and 4/4 µg/mL for TP-076, TP-138 and TP-600, respectively, versus MIC<sub>50/90</sub> values of 4/8, >16/>16 and >16/>16 µg/mL for tigecycline, ceftazidime and imipenem, respectively. The MIC<sub>50/90</sub> values of TP-076, TP-138, and TP-600 were 8/16, 4/16, and 16/16 µg/mL, respectively, against *P. aeruginosa*, showing greater potency than all 3 comparators (MIC<sub>50/90</sub> = >16/>16 µg/mL).

**Conclusions:** TP-076, TP-138, and TP-600 show promising potential as next generation tetracycline antibiotics for the treatment of serious multidrug-resistant Gram-negative infections.

Organism	n	MIC 50/90 (range)					
		TP-076	TP-138	TP-600	Tigecycline	Ceftazidime	Imipenem
Enterobacteriaceae	178	0.25/1 (0.03-8)	0.25/1 (0.06-8)	4/4 (0.06-16)	4/8 (0.5->16)	>16/>16 (1->16)	>16/>16 (4->16)
<i>Enterobacter</i> spp.	12	0.25/2 (0.125-4)	0.25/2 (0.125-8)	4/4 (0.25-8)	2/>16 (2->16)	>16/>16 (4->16)	16/>16 (4->16)
<i>Escherichia coli</i>	4	na (0.03-2)	na (0.06-2)	na (0.06-4)	na (0.5-16)	na (16->16)	na (4-8)
<i>Klebsiella pneumoniae</i>	162	0.25/0.5 (0.06-8)	0.25/1 (0.06-8)	4/4 (0.125-16)	4/8 (1->16)	>16/>16 (1->16)	>16/>16 (4->16)
<i>Acinetobacter baumannii</i>	80	0.06/0.125 (≤0.008-1)	0.125/0.25 (0.015-0.5)	0.25/4 (0.03-4)	4/8 (0.5-16)	>16/>16 (8->16)	>16/>16 (16->16)
<i>Pseudomonas aeruginosa</i>	76	8/16 (1->16)	4/16 (0.5->16)	16/16 (4->16)	>16/>16 (4->16)	>16/>16 (4->16)	>16/>16 (8->16)

na=not applicable