

Poster
F-1525

52nd Annual ICAAC
9 - 12 September, 2012
San Francisco, CA

TP-271 is a Potent, Broad-Spectrum Fluorocycline with Activity Against Community-Acquired Respiratory and Biothreat Pathogens

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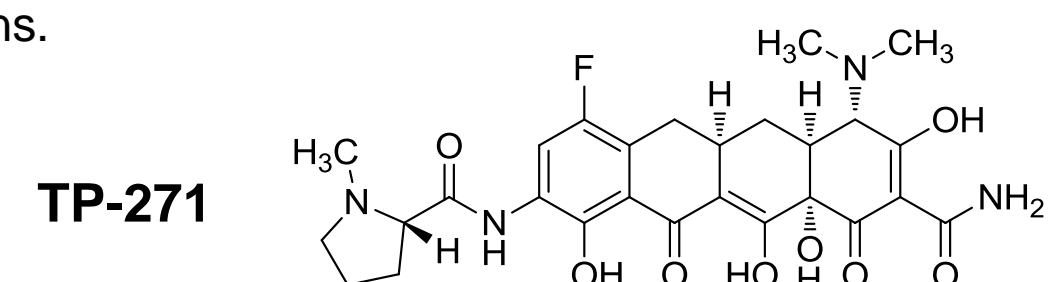
Revised Abstract

Background: TP-271 is a novel, fully synthetic fluorocycline antibiotic in preclinical development for IV/oral treatment of respiratory infections caused by susceptible and multidrug-resistant (MDR) public health and biothreat pathogens.

Method: *In vitro* susceptibility testing against recent isolates was done according to CLSI guidelines. Tetracycline-specific resistance and ES β L genes were detected by PCR.

Results: TP-271 was potent against *Streptococcus* spp., *Staphylococcus aureus*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates and Gram-positive pathogens vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (see Tables). The MIC_{50/90} values of TP-271 against ES β L+ *Escherichia coli* (n=34) and *Klebsiella pneumoniae* (n=48) were 1/ 2, and 1/ 4 μ g/ml, respectively. Against other Enterobacteriaceae, the MIC₅₀ and MIC₉₀ values of TP-271 were 0.25 – 4 and 1-8 μ g/ml, respectively. The MIC_{50/90} values against *Acinetobacter baumannii* (n=54), *Acinetobacter lwoffii* (n=29), and *Stenotrophomonas maltophilia* (n=35) were 0.13/1, 0.063/0.5, 0.25/2 μ g/ml, respectively. The MIC_{50/90} values against biothreat pathogens *Yersinia pestis* (n=30), *Bacillus anthracis* (n=30), *Francisella tularensis* (n=27), *Burkholderia mallei* (n=30) and *Burkholderia pseudomallei* (n=30) were 0.12/0.25, \leq 0.008/ \leq 0.008, 0.25/0.5, 0.06/0.12, and 1/4 μ g/ml, respectively.

Conclusions: TP-271 is active against community-acquired respiratory and biothreat pathogens, and problematic multidrug-resistant (MDR) pathogens.



Methods

Susceptibility testing. All minimal inhibitory concentration (MIC) assays were performed as per CLSI guidelines [1]. Testing of public health pathogens was performed at Tetraphase Pharmaceuticals, Inc. and International Health Management Associates (IHMA) using recent clinical isolates obtained from Eurofins Medinet and IHMA. Testing of biothreat agents was performed at United States Army Medical Research Institute for Infectious Diseases (USAMRIID). Genotypic characterization of ES β L-producing isolates was done by standard PCR methodology and sequence confirmation.

*Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Ninth Edition. CLSI document M07-A9. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2012.

Results

Table 1. Determination of MIC₅₀ and MIC₉₀ values for biothreat pathogens

Organism	N	MIC ₅₀ /MIC ₉₀ (μ g/ml)		
		(range)		
		TP-271	Doxycycline	Ciprofloxacin
<i>Yersinia pestis</i>	30	0.12/0.25 0.015-0.5	0.5/1 0.06-2	0.03/0.06 0.015-0.06
<i>Bacillus anthracis</i>	30	\leq 0.008/ \leq 0.008 \leq 0.008- \leq 0.008	\leq 0.008/ \leq 0.008 \leq 0.008-0.015	0.12/0.25 0.03-0.25
<i>Francisella tularensis</i>	27	0.25/0.5 0.03-2	0.12/0.25 0.015-1	0.06/0.5 0.015-8
TP-271		Doxycycline	Azithromycin	
<i>Burkholderia mallei</i>	30	0.06/0.12 \leq 0.008-1	0.03/0.12 \leq 0.008-1	1/2 0.25-2
TP-271		Doxycycline	Ceftazidime	
<i>Burkholderia pseudomallei</i>	30	1/4 0.25-8	1/8 0.06-16	2/2 0.25-32

Results

Table 2. Determination of MIC₅₀ and MIC₉₀ values for Gram-positive & respiratory pathogens

Organism	N	MIC ₅₀ /MIC ₉₀ (μ g/ml)						
		(range)						
		TP-271	Tetracycline	Tigecycline	Macrolide ^a	Fluoroquinolone ^b	Linezolid	Vancomycin
<i>Streptococcus pneumoniae</i>	137	\leq 0.016/ \leq 0.016 \leq 0.016- \leq 0.016	1/>32 ^c \leq 0.016->32	\leq 0.016/ \leq 0.016 \leq 0.016- \leq 0.016	4/>32 \leq 0.016->32	1/1 0.25-32	1/1 ^c 0.13-2	0.25/0.5 ^c \leq 0.016-0.5
<i>S. pneumoniae penicillin-R^d</i>	58	\leq 0.016/ \leq 0.016 \leq 0.016- \leq 0.016	32/>32 0.031->32	\leq 0.016/ \leq 0.016 \leq 0.016- \leq 0.016	>32/>32 \leq 0.016->32	1/1 0.5-1	1/1 0.5-2	0.25/0.5 0.25-0.5
<i>S. pneumoniae macrolide-R</i>	58	\leq 0.016/ \leq 0.016 \leq 0.016- \leq 0.016	32/>32 0.13->32	\leq 0.016/ \leq 0.016 \leq 0.016- \leq 0.016	>32/>32 1->32	1/1 0.25-32	1/1 0.25-2	0.25/0.5 0.13-0.5
<i>Streptococcus pyogenes</i>	64	\leq 0.016/ \leq 0.016 \leq 0.016- \leq 0.016	0.25/>32 0.13->32	\leq 0.016/ \leq 0.016 \leq 0.016-0.063	0.063/4 \leq 0.016->32	0.5/1 0.25-2	1/2 0.5-2	0.5/0.5 0.25-0.5
<i>Streptococcus agalactiae</i>	30	\leq 0.031/0.063 \leq 0.031-0.063	32/32 \leq 2->32	0.031/0.031 \leq 0.016-0.063	\leq 0.13/>4 \leq 0.13->4	1/1 0.5-2	1/2 1-2	\leq 0.5/ \leq 0.5 \leq 0.5- \leq 0.5
<i>Streptococcus anginosus</i>	73	\leq 0.031/ \leq 0.031 \leq 0.03-0.063	16/32 \leq 2->32	\leq 0.016/0.031 \leq 0.016-0.25	\leq 0.12/>4 ^m \leq 0.12->4	0.5/1 \leq 0.12-1	1/2 \leq 0.25-2	\leq 0.5/1 \leq 0.5-1
<i>Staphylococcus aureus</i>	155	0.06/0.25 \leq 0.03-1	\leq 2/32 0.063->32	0.12/0.25 \leq 0.016-0.5	>4/>4 0.25->4	>4/>4 \leq 0.13->4	2/4 0.5-64	1/1 \leq 0.5-8
<i>S. aureus (MRSA)</i>	124	0.063/0.13 \leq 0.016-1	\leq 2-32 0.063->32	0.13/0.25 \leq 0.016-0.5	>4/>4 0.25->4	>4/>4 \leq 0.13->4	2/4 1-64	1/1 \leq 0.5-8
<i>S. aureus (MRSA) PVL+</i>	25	0.063/0.12 0.063-0.12	\leq 2/ \leq 2 \leq 2-16	0.12/0.12 0.063-0.25	>4/>4 1->4	2/>4 \leq 0.13->4	2/2 1-4	1/1 \leq 0.5-1
<i>S. aureus (MSSA)</i>	31	0.12/0.25 \leq 0.031-0.25	\leq 2/ \leq 2 \leq 2-32	0.12/0.25 0.03-0.25	1/>4 0.5->4	0.25/0.5 \leq 0.13->4	2/4 0.5-4	1/1 \leq 0.5-1
<i>Staphylococcus epidermidis</i>	62	0.063/0.5 \leq 0.03-1	\leq 2/>32 \leq 2->32	0.25/0.5 0.06-1	>4/>4 \leq 0.13->4	0.25/>4 \leq 0.13->4	2/2 1-4	2/2 \leq 0.5-2
<i>S. epidermidis methicillin-S</i>	32	0.063/0.25 \leq 0.03-0.5	\leq 2/32 \leq 2->32	0.12/0.25 0.06-0.5	0.5/>4 \leq 0.13->4	0.25/0.5 \leq 0.13->4	2/2 1-4	2/2 \leq 0.5-2
<i>S. epidermidis methicillin-R</i>	30	0.25/0.5 0.06-1	\leq 2/>32 \leq 2->32	0.5/0.5 0.06-1	>4/>4 0.25->4	>4/>4 \leq 0.13->4	2/2 1-2	2/2 1-2
<i>Enterococcus faecalis</i>	113	\leq 0.031/0.063 \leq 0.031-0.5	>32/>32 0.13->32	0.12/0.25 \leq 0.016-1	>4/>4 ^e 0.5->4	2/>4 1->4	2/2 \leq 0.25-32	2/>16 \leq 0.5->16
<i>E. faecalis (VRE)</i>	37	\leq 0.031/0.063 \leq 0.03-0.25	32/>32 \leq 2->32	0.12/0.25 0.03-1	>4/>4 ^h 4->4	>4/>4 1->4	2/2 \leq 0.25-4	>16/>16 >16->16
<i>E. faecalis (VSE)</i>	68	\leq 0.031/0.063 \leq 0.03-0.5	>32/>32 0.13->32	0.12/0.25 \leq 0.016-1	>4/>4 ⁱ 0.5->4	2/>4 1->4	2/4 0.5-32	1/2 1-4
<i>Enterococcus faecium</i>	81	\leq 0.031/ \leq 0.031 \leq 0.031-0.063	\leq 2/>32 \leq 2->32	0.06/0.25 \leq 0.03-1	\leq 0.13/>4 ^j 4->4	>4/>4 0.25->4	2/4 0.5->4	>16/>16 \leq 0.5->16
<i>E. faecium (VRE)</i>	45	\leq 0.031/ \leq 0.031 \leq 0.031-0.031	16/>32 \leq 2->32	0.06/0.25 \leq 0.03-0.5	>4/>4 ^k 0.25->4	>4/>4 4->4	2/4 0.5->4	>16/>16 16->16
<i>E. faecium (VSE)</i>	36	\leq 0.031/ \leq 0.031 \leq 0.03-0.06	\leq 2/>32 \leq 2->32	0.06/0.25 \leq 0.03-1	>4/>4 ^l \leq 0.13->4	>4/>4 0.25->4	2/4 1-4	0.5/1 0.5-4
<i>Haemophilus influenzae</i>	65	0.031/0.13 \leq 0.016-0.25	0.5/4 0.13-16	0.063/0.25 \leq 0.016-0.5	8/8 0.063-16	\leq 0.016/0.031 \leq 0.016-0.13	8/16 4-32	>32/>32 ^e 16->32
<i>Moraxella catarrhalis</i>	57	\leq 0.016/ \leq 0.016 \leq 0.016-0.031	0.5/32 0.13->32	\leq 0.016/0.031 \leq 0.016-0.13	0.063/0.25 \leq 0.016-4	0.031/0.063 0.031-0.13	8/8 2-32	>32/>32 ^l 16->32

^aerythromycin, azithromycin or clarithromycin; ^bciprofloxacin or levofloxacin; ^c126 *S. pneumoniae* isolates; ^dpenicillin MIC \geq 2 μ g/ml; ^e51 *H. influenzae* isolates; ^f43 *M. catarrhalis* isolates; ^g74 *E. faecalis* isolates; ^h30 *E. faecalis* isolates; ⁱ36 *E. faecalis* isolates; ^j67 *E. faecalis* isolates; ^k32 *E. faecium* isolates; ^l35 *E. faecium* isolates; ^m51 *S. anginosus* isolates

These studies were funded in part by NIAID Partnership Grant # 1R01AI093484 – 01 and NIAID Contract #: HHSN272201100028C awarded to CUBRC and Tetraphase Pharmaceuticals

Table 3. Determination of MIC₅₀ and MIC₉₀ values for Gram-negative pathogens

Organism	N	MIC ₅₀ /MIC ₉₀ (μ g/ml)							
		(range)							
		TP-271	Tetracycline	Tigecycline	Carbapenem ^a	Fluoroquinolone ^b	3rd Gen Cep ^c	Piperacilin/Tazobactam	Aminoglycoside ^d
<i>Klebsiella pneumoniae</i> ESBL	48	1/4 0.25-32	8/>32 1->32	0.5/1 0.25-16	0.13/>32 0.031->32	32/>32 0.031->32	>32/>32 2->32	>128/>128 0.5->128	16/>32 0.5->32
<i>Klebsiella oxytoca</i>	41	0.25/2 0.031-8	\leq 4/>32 \leq 4->32	0.5/1 0.063-4	\leq 1/ \leq 1 \leq 1-1	\leq 0.25/>4 \leq 0.25->4	\leq 2/>32 \leq 2->32	2/64 \leq 1->64	\leq 2/>32 \leq 2->32
<i>Klebsiella oxytoca</i> ESBL	11	0.5/2 0.031-8	>32/>32 0.5->32	0.25/0.5 0.063-1	0.063/0.25 0.031-1	0.5/>32 0.031->32	>32/>32 4->32	8/>32 0.5->32	>32/>32 0.5->32
<i>Escherichia coli</i> ESBL	34	1/2 0.031-4	>32/>32 2->32	0.13/0.5 0.063-1	0.031/0.13 \leq 0.016-1	16/>32 0.031->32	>32/>32 0.5->32	8/>128 1->128	4/>32 1->32
<i>Enterobacter cloacae</i>	44	1/4 0.25-16	\leq 4/>32 \leq 4->32	1/2 0.25-8	\leq 1/>8 \leq 1->8	\leq 0.25/>4 \leq 0.25->4	\leq 2/>32 \leq 2->32	8/>64 \leq 1->64	\leq 2/>16 \leq 2->16
<i>Enterobacter</i> spp. AmpC ^e	15	1/8 0.25-16	8/>32 \leq 4 ->32	1/4 0.5-4	>8/>8 2->8	>4/>4 \leq 0.25 ->4	>32/>32 16->32	>64/>64 16->64	16/>16 \leq 2 ->16
<i>Enterobacter aerogenes</i>	30	0.5/1 0.25-4	\leq 4/16 \leq 4->32	0.5/2 0.25-2	\leq 1/ \leq 1 \leq 1->1	\leq 0.25/1 \leq 0.25->4	\leq 2/>32 \leq 2->32	4/>64 2->64	\leq 2/>16 \leq 2-8
<i>Citrobacter freundii</i>	30	0.12-2 0.12-2	\leq 4/>32 \leq 4->32	0.5/1 0.25-2	\leq 1/ \leq 1 \leq 1-8	\leq 0.25/2 \leq 0.25->4	2/>32 \leq 2->32	2/>64 \leq 1->64	\leq 2/>16 \leq 2->16
<i>Proteus mirabilis</i>	20	4/8 2-8	>32/>32 32->32	4/8 2-8	8/8 4-16	0.13/32 0.063-32	0.031/0.031 \leq 0.016-0.13	0.5/1 0.25-2	2/8 0.5->32
<i>Proteus vulgaris</i>	30	2/4 0.25-4	8/32 \leq 4->32	2/4 0.5-4	\leq 1/ \leq 1 \leq 1->1	\leq 0.25/ \leq 0.25 \leq 0.25->4	\leq 2/>32 \leq 2->32	\leq 1/ \leq 1 \leq 1->64	\leq 2/>16 \leq 2->16
<i>Serratia marcescens</i>	30	2/2 0.5-8	32/>32 \leq 4->32	1/2 0.5-4	\leq 1/ \leq 1 \leq 1->1	\leq 0.25/0.5 \leq 0.25-2	\leq 2/>32 \leq 2->32	2/16 \leq 1->64	\leq 2/>16 \leq 2->16
<i>Salmonella</i> spp.	35	0.5/2 0.12-16	\leq 4/>32 \leq 4->32	0.5/2 0.12-2	\leq 1/ \leq 1 \leq 1->1	\leq 0.25/0.5 \leq 0.25->4	\leq 2/2 \leq 2->32	2/16 \leq 1-64	\leq 2/>16 \leq 2->16
<i>Shigella</i> spp.	18	0.13/0.5 \leq 0.031-2	\leq 4/>32 \leq 4->32	0.5/1 0.12-2	\leq 1/ \leq 1 \leq 1->1	\leq 0.25/ \leq 0.25 \leq 0.25->4	\leq 2/>32 \leq 2->32	2/8 \leq 1->64	\leq 2/>16 \leq 2->16
<i>Morganella morganii</i>	30	4/8 1-16	32/>32 \leq 4->32	2/8 1-8	\leq 1/ \leq 1 \leq 1-2	\leq 0.25/>4 \leq 0.25->4	4/16 \leq 2->32	\leq 1/32 \leq 1->64	\leq 2/>16 \leq 2->16
<i>Providencia stuartii</i>	30	4/8 0.13->16	>32/>32 \leq 4->32	4/8 0.13-16	\leq 1/ \leq 1 \leq 1->1	4/>4 \leq 0.25->4	\leq 2/>16 \leq 2->16	4/64 $\$	