PTK 0796 (BAY 73-6944): *In Vitro* Potency and Spectrum of Activity Compared to Ten Other Antimicrobial Compounds

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ABSTRACT

Background PTK 0796 (7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline), is a novel antibacterial agent of the tetracycline family with potent and enhanced activity against resistant gram-positive and gram-negative pathogens.

Methods Using NCCLS microbroth dilution and agar dilution methodology, the present study was designed to: 1) assess the *in vitro* activity of PTK 0796 against 1084 clinical isolates representing a broad spectrum of pathogenic bacterial species in comparison with 10 other antimicrobials, and 2) compare the broth microdilution MICs of PTK 0796 with those achieved with agar dilution.

Results MIC_{90}s (µg/ml) for selected groups of isolates and antimicrobials are as follows:

Agent	*S. aureus*(160)	MRSA(104)	VRE(130)	PRSP(55)
PTK 0796	**0.25**	**0.25**	**0.12**	**0.12**
Doxycycline	8.0	8.0	16	8.0
Minocycline	4.0	4.0	16	8.0
Linezolid	2.0	2.0	2.0	2.0
Vancomycin	0.5	2.0	64	0.5
Ciprofloxacin	>16	>16	>16	2.0
Ceftriaxone	>64	>64	>64	8.0

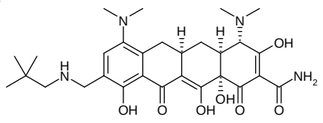
MIC_{90}s for gram-negative species range from 1-32 µg/ml. MICs by agar dilution were 1 dilution higher than microbroth dilution MICs.

Conclusions PTK 0796 had excellent activity against gram-positive pathogens. MIC's were generally ≤0.25 µg/ml (1 µg/ml for CNS) and were relatively consistent between and within species. Activity of PTK0796 was not affected by resistance to reference compounds and was notably active against MRSA, MRSE, VRE, and PRSP. The activity against gram-negative pathogens was more variable between species, having better activity against some species (eg *E. coli*, *Enterobacter, Shigella*) compared to others (eg *P. stuartii*, *P. rettgeri*, *M. morganii*). Agar dilution MICs were higher than broth microdilution MICs for all groups tested.

INTRODUCTION

PTK 0796 (BAY 73-6944) is a novel aminomethylcycline that exhibits excellent activity against susceptible and resistant gram positive and gram negative bacteria. Recent clinical isolates were obtained and the activity of PTK 0796 (BAY 73-6944) was determined compared to several currently available antibiotics.

Structure of PTK 0796 (BAY 73-6944)



METHODS

Microorganisms

- 1084 isolates representing 40 species; the majority were recent clinical strains collected in last two years.
- Species and numbers of each are listed in Table 1 and 1A.

Antibiotics

- PTK 0796 standardized powder was obtained from Paratek Pharmaceutical Inc.
- Comparative agents were obtained from their manufacturer or commercial sources.

Media

- Mueller-Hinton Broth (Difco lot 111300) was supplemented to a final concentrations of 25mg/L Ca++ and 10 mg/L Mg++
- Cation adjusted Mueller Hinton Broth was supplemented with 2-5% Lysed Horse Blood when testing streptococci
- Haemophilus Test Medium was used for MIC's on *Haemophilus influenzae*
- Mueller Hinton Agar was used for all agar dilution tests. When testing *S. pneumoniae*, 5% sheep blood was added

Susceptibility Tests

- The NCCLS M7-A6 standard method was followed for both broth and agar testing MIC panels were prepared in house and stored at -70 degrees C until use
- Agar Dilution plates were also prepared in house and used within 5 days of production

Quality Control (QC) Strains

- The following strains were tested throughout the study

Staph aureus **ATCC 29293** — *E. faecalis* **ATCC 29212**
E. coli **ATCC 25922** — *S. pneumoniae* **ATCC 49619**
P. aeruginosa **ATCC 27853** — *H. influenzae* **ATCC 49247**

RESULTS

Table 1

MIC Data Gram-Positive Species

Species	N	Drug	Min	Max	MIC_{50}	MIC_{90}
S. aureus, Methicillin S	**56**	**PTK 0796**	**0.06**	**0.25**	**0.25**	**0.25**
		Doxycycline	0.25	8	0.25	0.25
		Linezolid	1	2	2	2
		Quinupristin/Dalfopristin	0.25	1	0.25	0.5
		Vancomycin	0.25	2	1	1
		Ciprofloxacin	0.12	2	0.25	0.5
		Ceftriaxone	1	8	4	4
		Piperacillin/Tazobactam	0.50	4	2	2
S. aureus, Methicillin R	**104**	**PTK 0796**	**0.06**	**4**	**0.25**	**0.25**
		Doxycycline	0.25	16	0.25	8
		Linezolid	1	4	2	2
		Quinupristin/Dalfopristin	0.25	1	0.5	0.5
		Vancomycin	0.50	32	1	2
		Ciprofloxacin	0.12	>16	8	>16
		Ceftriaxone	4	>64	64	>64
		Piperacillin/Tazobactam	1	>32	32	>32
S. aureus, Vanco I	**4**	**PTK 0796**	**0.12**	**1**	**0.25**	**1**
		Doxycycline	0.25	0.25	0.25	0.25
		Linezolid	1	2	1	2
		Quinupristin/Dalfopristin	0.25	0.5	0.5	0.5
		Vancomycin	8	8	8	8
		Ciprofloxacin	>16	>16	>16	>16
		Ceftriaxone	16	>64	16	>64
		Piperacillin/Tazobactam	2	>32	4	>32
Staph, Coag Negative, Methicillin S	**53**	**PTK 0796**	**0.06**	**2**	**0.12**	**1**
		Doxycycline	0.25	16	0.25	8
		Minocycline	0.25	4	0.25	0.5
		Linezolid	1	2	1	2
		Quinupristin/Dalfopristin	0.25	1	0.25	0.5
		Vancomycin	1	2	2	2
		Ciprofloxacin	0.12	>16	0.25	4
		Ceftriaxone	0.50	16	2	8
		Piperacillin/Tazobactam	0.25	4	0.25	1
		Penicillin	0.03	>4	2	>4
		Oxacillin	0.25	8	0.25	0.5
Staph, Coag Negative, Methicillin R	**103**	**PTK 0796**	**0.06**	**2**	**0.25**	**1**
		Doxycycline	0.25	32	0.5	8
		Linezolid	0.50	2	1	2
		Quinupristin/Dalfopristin	0.25	4	0.25	1
		Vancomycin	0.50	4	2	2
		Ciprofloxacin	0.12	>16	4	>16
		Ceftriaxone	0.50	>64	16	>64
		Piperacillin/Tazobactam	0.25	>32	4	>32

Table 1 Continued

MIC Data Gram-Positive Species

E. faecalis, All Strains Combined	104	**PTK 0796**	**0.06**	**0.5**	**0.12**	**0.25**
		Doxycycline	0.25	32	4	8
INCLUDES:		Linezolid	0.50	16	2	2
		Quinupristin/Dalfopristin	1	>32	4	16
vancomycin S strains	72	Vancomycin	0.50	>32	1	>32
vancomycin R strains	32	Ciprofloxacin	0.50	>16	1	>16
		Ceftriaxone	1	>64	>64	>64
		Piperacillin/Tazobactam	1	8	4	8
E. faecium, All Strains Combined	155	**PTK 0796**	**0.03**	**0.25**	**0.12**	**0.12**
		Doxycycline	0.25	32.0	4	16
		Linezolid	0.25	32.0	2	2
INCLUDES:		Quinupristin/Dalfopristin	0.25	4.0	0.5	4
vancomycin S strains	52	Vancomycin	0.5	64.0	64	64
vancomycin R strains	103	Ciprofloxacin	0.12	32.0	>16	>16
		Ceftriaxone	0.5	128.0	>64	>64
		Piperacillin/Tazobactam	2	64.0	64	64
Streptococcus species, All Species Combined	**184**	**PTK 0796**	**0.016**	**0.5**	**0.06**	**0.12**
		Doxycycline	0.25	32	0.25	16
		Linezolid	0.50	4	2	2
INCLUDES:		Quinupristin/Dalfopristin	0.25	4	0.5	1
S. pneumoniae	107	Vancomycin	0.25	>32	0.5	0.5
S. pyogenes	26	Ciprofloxacin	0.25	4	1	2
S. agalactiae	26	Ceftriaxone	0.50	>64	0.5	4
S. viridans	25	Piperacillin/Tazobactam	0.25	>32	0.5	8
S. pneumoniae, Penicillin S	**26**	**PTK 0796**	**0.03**	**0.06**	**0.06**	**0.06**
		Doxycycline	0.25	8	0.25	0.25
		Linezolid	1	2	2	2
		Quinupristin/Dalfopristin	0.25	1	0.5	1
		Vancomycin	0.25	1	0.5	0.5
		Ciprofloxacin	0.50	2	1	2
		Ceftriaxone	0.50	0.5	0.5	0.5
		Piperacillin/Tazobactam	0.25	0.25	0.25	0.25
S. pneumoniae, Penicillin I	**26**	**PTK 0796**	**0.016**	**0.25**	**0.06**	**0.12**
		Doxycycline	0.25	16	0.25	8
		Linezolid	0.50	2	2	2
		Quinupristin/Dalfopristin	0.25	1	0.5	1
		Vancomycin	0.25	0.5	0.5	0.5
		Ciprofloxacin	0.50	4	1	2
		Ceftriaxone	0.50	1	0.5	0.5
		Piperacillin/Tazobactam	0.25	4	1	2
S. pneumoniae, Penicillin R	**55**	**PTK 0796**	**0.06**	**0.12**	**0.06**	**0.12**
		Doxycycline	0.25	16	0.25	8
		Linezolid	1	4	2	2
		Quinupristin/Dalfopristin	0.25	2	1	1
		Vancomycin	0.50	0.5	0.5	0.5
		Ciprofloxacin	0.50	4	1	2
		Ceftriaxone	0.50	16	4	8
		Piperacillin/Tazobactam	2	>32	8	16

TABLE 1. RESULTS

- PTK 0796 showed excellent activity against gram-positive pathogens
- 184 streptococci were inhibited by 0.5 µg/ml or less of PTK 0796 including Pen R *S. pneumoniae*
- MICs of all 632 gram-positive strains ranged from 0.03 – 4 µg/ml with an MIC_{90} of < 1.0 µg/ml
- PTK 0796 showed excellent activity against all enterococci
- All enterococci were inhibited by < 0.5 µg/ml of PTK 0796 regardless of vancomycin resistance
- The MIC_{90} for all *S. aureus* both methicillin susceptible and resistant was <0.25 µg/ml
- Vancomycin intermediate *S. aureus* (4 strains) had an MIC_{90} of < 1.0 µg/ml
- Coagulase negative staphylococci had MICs to PTK 0796 of 0.06 – 2.0 µg/ml with an MIC_{90} of < 1.0 µg/ml

Table 2

MIC Data Gram-Negative Species

Species	N	Drug	Min	Max	MIC_{50}	MIC_{90}
E. aerogenes	**10**	**PTK 0796**	**2**	**2**	**2**	**2**
		Doxycycline	1	4	1	2
		Ciprofloxacin	0.12	0.5	0.12	0.12
		Ceftriaxone	0.50	1	0.5	1
		Piperacillin/Tazobactam	1	4	2	4
E. cloacae	**10**	**PTK 0796**	**2**	**4**	**4**	**4**
		Doxycycline	2	4	4	4
		Ciprofloxacin	0.12	0.1	0.12	0.12
		Ceftriaxone	0.50	1	0.5	1
		Piperacillin/Tazobactam	2	4	2	4
E. coli	**21**	**PTK 0796**	**0.50**	**4**	**1**	**2**
		Doxycycline	1	32	2	16
		Ciprofloxacin	0.12	>16	0.12	0.12
		Ceftriaxone	0.50	64	0.5	0.5
		Piperacillin/Tazobactam	1	32	2	4
K. pneumoniae	**20**	**PTK 0796**	**2**	**8**	**2**	**8**
		Doxycycline	1	16	2	16
		Ciprofloxacin	0.12	>16	0.12	>16
		Ceftriaxone	0.50	4	0.5	1
		Piperacillin/Tazobactam	1	>32	2	>32
M. morganii	**10**	**PTK 0796**	**8**	**64**	**32**	**64**
		Doxycycline	2	32	32	32
		Ciprofloxacin	0.12	0.12	0.12	0.12
		Ceftriaxone	0.50	64	32	64
		Piperacillin/Tazobactam	0.25	4	0.5	1
P. mirabilis	**10**	**PTK 0796**	**8**	**32**	**16**	**16**
		Doxycycline	16	>32	32	>32
		Ciprofloxacin	0.12	0.12	0.12	0.12
		Ceftriaxone	0.50	0.5	0.5	0.5
		Piperacillin/Tazobactam	0.25	0.5	0.25	0.25
P. rettgeri	**5**	**PTK 0796**	**8**	**64**	**16**	**64**
		Doxycycline	4	>32	32	>32
		Ciprofloxacin	0.12	0.12	0.12	0.12
		Ceftriaxone	0.50	0.5	0.5	0.5
		Piperacillin/Tazobactam	0.25	8	1	8
P. stuartii	**5**	**PTK 0796**	**16**	**64**	**16**	**64**
		Doxycycline	>32	>32	>32	>32
		Ciprofloxacin	0.12	>16	16	>16
		Ceftriaxone	0.50	16	0.5	16
		Piperacillin/Tazobactam	1	8	4	8
P. vulgaris	**10**	**PTK 0796**	**4**	**16**	**8**	**16**
		Doxycycline	1	32	4	16
		Ciprofloxacin	0.12	0.12	0.12	0.12
		Ceftriaxone	0.50	>64	16	>64
		Piperacillin/Tazobactam	0.25	4	0.25	2
S. marcescens	**10**	**PTK 0796**	**4**	**4**	**4**	**4**
		Doxycycline	2	4	4	4
		Ciprofloxacin	0.12	0.25	0.12	0.12
		Ceftriaxone	0.50	2	0.5	1
		Piperacillin/Tazobactam	2	4	4	4
Salmonella spp.	**10**	**PTK 0796**	**2**	**4**	**2**	**4**
		Doxycycline	2	4	2	4
		Ciprofloxacin	0.12	0.12	0.12	0.12
		Ceftriaxone	0.50	0.5	0.5	0.5
		Piperacillin/Tazobactam	2	16	4	4
Shigella spp.	**10**	**PTK 0796**	**0.25**	**1**	**0.5**	**1**
		Doxycycline	16	32	16	32
		Ciprofloxacin	0.12	0.12	0.12	0.12
		Ceftriaxone	0.50	0.5	0.5	0.5
		Piperacillin/Tazobactam	0.25	8	0.25	8
A. baumannii	**21**	**PTK 0796**	**0.12**	**16**	**2**	**8**
		Doxycycline	0.25	>32	1	32
		Ciprofloxacin	0.12	>16	8	>16
		Ceftriaxone	8	>64	>64	>64
		Piperacillin/Tazobactam	0.25	>32	>32	>32
B. cepacia	**11**	**PTK 0796**	**0.12**	**>64**	**4**	**16**
		Doxycycline	0.25	>32	8	>32
		Ciprofloxacin	0.12	>16	1	4
		Ceftriaxone	0.50	>64	64	>64
		Piperacillin/Tazobactam	0.25	>32	8	>32

Table 2 Continued

MIC Data Gram-Negative Species

P. aeruginosa	**10**	**PTK 0796**	**16**	**64**	**32**	**32**
		Doxycycline	8	>32	16	16
		Ciprofloxacin	0.12	>16	0.12	0.25
		Ceftriaxone	4	>64	64	>64
		Piperacillin/Tazobactam	2	32	4	4
S. maltophilia	**11**	**PTK 0796**	**0.25**	**8**	**2**	**4**
		Doxycycline	0.25	4	1	2
		Ciprofloxacin	0.12	8	2	8
		Ceftriaxone	0.50	>64	>64	>64
		Piperacillin/Tazobactam	0.50	>32	>32	>32
H. influenzae	**74**	**PTK 0796**	**0.25**	**4**	**0.5**	**2**
		Doxycycline	0.25	2	0.5	1
INCLUDES:		Quin/Dalfo	0.50	16	4	8
B-lac positive	44	Vancomycin	16	>32	>32	>32
B-lac negative	22	Ciprofloxacin	0.12	0.12	0.12	0.12
B-lac negative amp R	8	Ceftriaxone	0.50	0.5	0.5	0.5
		Piperacillin/Tazobactam	0.25	0.5	0.25	0.25
M. catarrhalis	10	**PTK 0796**	**0.25**	**0.25**	**0.25**	**0.25**
		Doxycycline	0.25	0.25	0.25	0.25
		Linezolid	4	8	8	8
		Quin/Dalfo	0.25	0.5	0.5	0.5
		Vancomycin	>32	>32	>32	>32
		Ciprofloxacin	0.12	0.12	0.12	0.12
		Ceftriaxone	0.50	1	0.5	0.5
		Piperacillin/Tazobactam	0.25	0.25	0.25	0.25

TABLE 2. RESULTS

- *H. influenzae* were inhibited by < 4.0 µg/ml with an MIC_{90} of < 2.0 µg/ml
- *Moraxella catarrhalis* was uniformly susceptible to PTK 0796 and doxycycline.
- For other gram-negative species, the MICs were more variable
  - The first group included species with 100% of strains inhibited by < 4.0 µg/ml; these included *E. coli*, *E. aerogenes* and *E. cloacae*, *S.marcescens*, *Salmonella* species, *Shigella* species and *S. maltophilia*
  - The second group of species showed only 75% of the strains inhibited by < 4.0 µg/ml; these included *A. baumannii*, *B. cepacia* and *K. pneumoniae*
  - The third group either had no inhibition or MIC_{90}s of > 16 µg/ml; this included *P. aeruginosa*, *Providencia*, *Morganella* and *Proteus* spp.

CONCLUSIONS

PTK 0796 (BAY 73-6944) a potent new aminomethylcycline antimicrobial agent exhibited excellent activity against strains resistant to other antibiotics

- Enterococci regardless of vancomycin susceptibility
- Methicillin susceptible and resistant *S. aureus* and other staphylococci
- Streptococci including penicillin resistant *S. pneumoniae*
- *H. influenzae* and *M. catarrhalis*
- Also demonstrated activity with MICs at ≤ 4.0 µg/ml against many of the gram negative species including *E. coli*, *E aerogenes*, *E. cloacae*, *S. marcescens*, *Salmonella* spp., *Shigella* spp., and *S. maltophilia.*