

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

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PTK 0796: *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 MIC₉₀s (µg/ml) for selected groups of isolates and antimicrobials are as follows:

Agent	<i>S. aureus</i> (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

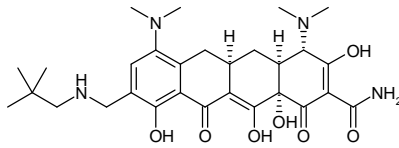
MIC₉₀s for gram-negative species range from 1-32 µg/ml. MICs by agar dilution were 1 dilution higher than microbroth dilution MICs.

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. morgani*). 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 concentration 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. coli ATCC 25922
P. aeruginosa ATCC 27853

S. faecalis ATCC 29212
S. pneumoniae ATCC 49619
H. influenzae ATCC 49247

RESULTS

Table 1 MIC Data Gram-Positive Species						
Species	N	Drug	Min	Max	MIC ₅₀	MIC ₉₀
<i>S. aureus</i> , Methicillin S	56	PTK 0796	0.06	4	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
<i>S. aureus</i> , 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
<i>S. aureus</i> , 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
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						
<i>E. faecalis</i> , All Strains Combined	104	PTK 0796	0.06	0.5	0.12	0.25
		Doxycycline	0.25	32	4	8
		Linezolid	0.50	16	2	2
		Quinupristin/Dalfopristin	1	>32	4	16
		Vancomycin	0.50	>32	1	>32
		Ciprofloxacin	0.50	>16	1	>16
		Ceftriaxone	1	>64	>64	>64
		Piperacillin/Tazobactam	1	8	4	8
<i>E. faecium</i> , 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
		Quinupristin/Dalfopristin	0.25	4.0	0.5	4
		Vancomycin	0.5	64.0	64	64
		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
		Quinupristin/Dalfopristin	0.25	4	0.5	1
		Vancomycin	0.25	>32	0.5	0.5
		Ciprofloxacin	0.25	4	1	2
		Ceftriaxone	0.50	>64	0.5	4
		Piperacillin/Tazobactam	0.25	>32	0.5	8
<i>S. pneumoniae</i> , 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
<i>S. pneumoniae</i> , 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
<i>S. pneumoniae</i> , 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 MIC₉₀ 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 MIC₉₀ for all *S. aureus* both methicillin susceptible and resistant was <0.25 µg/ml
- Vancomycin intermediate *S. aureus* (4 strains) had an MIC₉₀ of < 1.0 µg/ml
- Coagulase negative staphylococci had MICs to PTK 0796 of 0.06 – 2.0 µg/ml with an MIC₉₀ of < 1.0 µg/ml

Table 2 MIC Data Gram-Negative Species						
Species	N	Drug	Min	Max	MIC ₅₀	MIC ₉₀
<i>E. aerogenes</i>	10	PTK 0796	2	2	2	2
		Doxycycline	1	4	1	2
		Ciprofloxacin	0.12	0.5	0.12	0.12
		Ceftriaxone	0.50	0.5	0.5	1
		Piperacillin/Tazobactam	1	4	2	4
		PTK 0796	2	4	4	4
		Doxycycline	2	4	4	4
		Ciprofloxacin	0.12	0.1	0.12	0.12
<i>E. cloacae</i>	10	PTK 0796	2	4	2	4
		Doxycycline	0.12	0.1	0.12	0.12
		Ciprofloxacin	0.12	0.1	0.12	0.12
		Ceftriaxone	0.50	1	0.5	1
		Piperacillin/Tazobactam	2	4	2	4
		PTK 0796	0.50	4	1	2
		Doxycycline	1	32	2	16
		Ciprofloxacin	0.12	>16	0.12	0.12
<i>E. coli</i>	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
		PTK 0796	1	8	2	8
		Doxycycline	1	16	2	16
		Ciprofloxacin	0.12	>16	0.12	>16
<i>K. pneumoniae</i>	20	PTK 0796	1	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
		PTK 0796	8	64	32	64
		Doxycycline	7	32	32	32
		Ciprofloxacin	0.12	0.12	0.12	0.12
<i>M. morgani</i>	10	PTK 0796	8	64	32	64
		Doxycycline	7	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
		PTK 0796	8	32	16	16
		Doxycycline	8	>32	>32	>32
		Ciprofloxacin	0.12	0.12	0.12	0.12
<i>P. mirabilis</i>	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
		PTK 0796	8	64	16	64
		Doxycycline	4	>32	32	>32
		Ciprofloxacin	0.12	>16	0.12	>16
<i>P. rettgeri</i>	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	0.5	8
		PTK 0796	16	64	16	64
		Doxycycline	>32	>32	>32	>32
		Ciprofloxacin	0.12	0.12	0.12	0.12
<i>P. stuartii</i>	5	PTK 0796	16	64	16	64
		Doxycycline	>32	>32	>32	>32
		Ciprofloxacin	0.12	>16	0.12	>16
		Ceftriaxone	0.50	16	0.5	16
		Piperacillin/Tazobactam	1	8	4	8
		PTK 0796	4	16	8	16
		Doxycycline	1	32	4	16
		Ciprofloxacin	0.12	0.12	0.12	0.12
<i>P. vulgaris</i>	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	