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# Antimicrobial Activity of TD-1607 Tested against Contemporary (2010-2012) Methicillin-Resistant *Staphylococcus aureus* (MRSA) Strains

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## ABSTRACT

**Background**: TD-1607 is a novel heterodimer antibiotic composed of a glycopeptide covalently linked to a cephalosporin moiety (glycopeptide-cephalosporin heterodimer, GP-Ceph). TD-1607 possesses potent, bactericidal activity against Gram-positive organisms and exerts its antimicrobial activity through inhibition of cell wall biosynthesis. TD-1607 is currently in clinical development for the treatment of serious Gram-positive infections. We evaluated the *in vitro* activity of TD-1607 when tested against a large collection of recent clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA).

**Methods**: 1,026 MRSA isolates from surveillance networks in the USA (512 strains), Europe (EU; 312) and Latin America (LA; 202) were tested for susceptibility by the reference broth microdilution according to CLSI guidelines against TD-1607 and numerous comparison agents. The isolates were collected in 2010-2012 (mostly 2012) from skin/soft tissue infections (42%), bacteremias (31%), pneumonias (25%) and other sites.

**Results**: TD-1607 showed potent *in vitro* activity against MRSA strains ($MIC_{50/90}$, 0.03/0.03 µg/mL; highest MIC, 0.06 µg/mL) with no marked differences among geographic regions (**Table 1**). TD-1607 was 16- to 32-fold more active than daptomycin ($MIC_{50/90}$, 0.5/0.5 µg/mL), vancomycin ($MIC_{50/90}$, 1/1 µg/mL) and teicoplanin ($MIC_{50/90}$, 0.5/1 µg/mL), and 32- to 64-fold more active than linezolid and ceftaroline ($MIC_{50/90}$, 1/2 µg/mL for both). All isolates were susceptible to daptomycin, vancomycin, teicoplanin and linezolid, whereas susceptibility to ceftaroline was 93.6% in the USA sample. Resistance rates to comparator agents were generally higher for MRSA isolates from LA when compared to USA and EU.

**Conclusions**: TD-1607 demonstrated consistent potent activity when tested against a large collection of contemporary MRSA strains from USA, EU and LA.

## INTRODUCTION

*Staphylococcus aureus* continues to be a major cause of both community-acquired and healthcare-associated infections, including skin and skin structure infections (SSSI), bacteremia, endocarditis and pneumonia. The prevalence of nosocomial infections caused by methicillin-resistant *S. aureus* (MRSA) remains elevated in a large proportion of United States (USA) hospitals. Additionally, since its appearance in the 1990's, community-acquired MRSA (CA-MRSA) strains have increasingly caused community-onset infections as well as hospital- and healthcare-associated disease in various USA regions.

TD-1607 is a heterodimer antibiotic composed of a glycopeptide covalently linked to a cephalosporin moiety (glycopeptide-cephalosporin heterodimer, GP-Ceph; **Figure 1**). TD-1607 possesses potent, bactericidal activity *in vitro* against Gram-positive organisms and exerts its antimicrobial activity through inhibition of cell wall biosynthesis. TD-1607 is currently in clinical development for the treatment of serious Gram-positive infections. We evaluated the *in vitro* activity of TD-1607 when tested against a large collection of recent clinical isolates of methicillin-resistant *S. aureus* (MRSA).

## MATERIALS AND METHODS

Bacterial isolates: A total of 1,026 MRSA isolates collected through the SENTRY Antimicrobial Surveillance Program network, including 512 isolates from the USA, 312 from Europe and 202 from Latin America, were selected for this investigation. The isolates were collected in 2010-2012 (mostly 2012) from SSSI (42%), bacteremia (31%), pneumonia (25%) and other infection sites. Isolates were identified to species level by the participating laboratory and species identification was confirmed by the reference monitoring laboratory (JMI Laboratories) by standard algorithms and/or MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany), when necessary.

Susceptibility testing: Susceptibility testing was performed by reference broth microdilution methods (CLSI M07-A9; 2012) using frozen-form MIC panels prepared by JMI Laboratories with cation-adjusted Mueller-Hinton broth. For TD-1607 (lot # AS000261), a stock solution was prepared at 1600 µg/mL by adding powder to sterile phosphate buffer at pH 6.0 (0.01 mol/L). CLSI (M100-S24; 2014) and EUCAST (version 4.0; 2014) interpretive criteria were applied for comparator agents. Quality control was performed per CLSI M07-A9 (2012) and M100-S24 (2014) protocols using *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.

## RESULTS

- TD-1607 showed potent *in vitro* activity against MRSA strains. TD-1607 MIC values ranged from 0.008 to 0.06 µg/mL, with $MIC_{50}$ and $MIC_{90}$ of 0.03 µg/mL (**Table 1** and **Figure 2**).
- TD-1607 MIC values were slightly lower in the USA and Europe ($MIC_{50}$ and $MIC_{90}$ of 0.03 µg/mL for both regions) compared to Latin America ($MIC_{50}$, 0.03 µg/mL and $MIC_{90}$, 0.06 µg/mL; **Table 1**).
- Against the entire collection of MRSA (1,026 isolates), TD-1607 was 16- to 32-fold more active than daptomycin ($MIC_{50}$ and $MIC_{90}$, 0.5 µg/mL; **Figure 2**), vancomycin ($MIC_{50}$ and $MIC_{90}$, 1 µg/mL) and teicoplanin ($MIC_{50}$, 0.5 µg/mL and $MIC_{90}$, 1 µg/mL), and 32- to 64-fold more active than linezolid and ceftaroline ($MIC_{50}$, 1 µg/mL and $MIC_{90}$, 2 µg/mL for both compounds; **Table 2**).
- All isolates were susceptible to vancomycin ($MIC_{50}$ and $MIC_{90}$, 1 µg/mL), daptomycin ($MIC_{50}$ and $MIC_{90}$, 0.5 µg/mL) and linezolid ($MIC_{50}$, 1 µg/mL and $MIC_{90}$, 2 µg/mL) using CLSI and EUCAST breakpoint criteria (**Table 2**).
- When tested against teicoplanin ($MIC_{50}$, 0.5 µg/mL and $MIC_{90}$, 1 µg/mL; highest MIC, 4 µg/mL), 100.0 and 99.8% of MRSA strains were categorized as susceptible with CLSI and EUCAST criteria, respectively (**Table 2**). Teicoplanin non-susceptible strains were observed in the USA and Mexico (one strain each, both with teicoplanin MIC of 4 µg/mL; data not shown).
- Resistance rates to comparator agents were generally higher among MRSA isolates from Latin America compared to USA and Europe (data not shown).

**Figure 1**. Chemical structure of TD-1607.

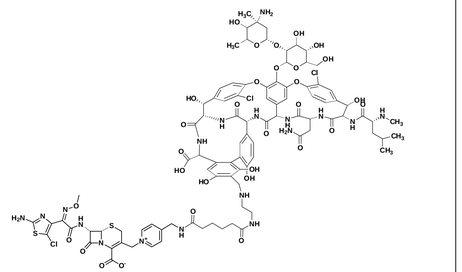


**Table 1**. MIC distributions for TD-1607 tested against contemporary strains of MRSA and stratified by geographic region.

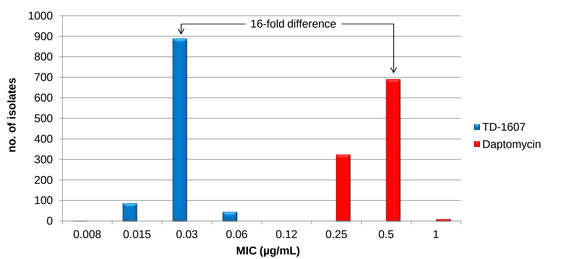
| Geographic region | No. of Isolates | MIC (µg/mL) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 0.004 | 0.008 | 0.015 | 0.03 | 0.06 | $MIC_{50}$ | $MIC_{90}$ |
| USA | 512 | 0 (0.0) | 1 (0.2) | 44 (8.8) | 458 (98.2) | 9 (100.0) | 0.03 | 0.03 |
| Europe | 312 | 0 (0.0) | 1 (0.3) | 33 (10.9) | 272 (98.1) | 6 (100.0) | 0.03 | 0.03 |
| Latin America | 202 | 0 (0.0) | 1 (0.5) | 11 (5.9) | 159 (84.7) | 31 (100.0) | 0.03 | 0.06 |
| All regions | 1,026 | 0 (0.0) | 3 (0.3) | 88 (8.9) | 889 (95.5) | 46 (100.0) | 0.03 | 0.03 |

**Table 2.** Activity of TD-1607 and comparator antimicrobial agents when tested against 1,026 isolates of MRSA (All regions).

| Antimicrobial agent | $MIC_{50}$ | $MIC_{90}$ | Range | CLSI[a] %S / %I / %R | EUCAST[a] %S / %I / %R |
|---|---|---|---|---|---|
| TD-1607 | 0.03 | 0.03 | 0.008 – 0.06 | - / - / - | - / - / - |
| Vancomycin | 1 | 1 | 0.25 – 2 | 100.0 / 0.0 / 0.0 | 100.0 / 0.0 / 0.0 |
| Daptomycin | 0.5 | 0.5 | 0.25 – 1 | 100.0 / - / - | 100.0 / 0.0 / 0.0 |
| Teicoplanin | 0.5 | 1 | 0.12 – 4 | 100.0 / 0.0 / 0.0 | 99.8 / 0.0 / 0.2 |
| Linezolid | 1 | 2 | 0.25 – 4 | 100.0 / 0.0 / 0.0 | 100.0 / 0.0 / 0.0 |
| Ceftaroline | 1 | 2 | 0.25 – 4 | 81.1 / 18.2 / 0.7 | 81.1 / 0.0 / 18.9 |
| Oxacillin | >4 | >4 | 4 – >4 | 0.0 / 0.0 / 100.0 | 0.0 / 0.0 / 100.0 |
| Levofloxacin | >4 | >4 | ≤0.12 – >4 | 23.2 / 0.7 / 76.1 | 23.2 / 0.7 / 76.1 |
| Trimethoprim/sulfamethoxazole | ≤0.12 | ≤0.12 | ≤0.12 – >4 | 97.3 / 0.0 / 2.7 | 97.3 / 0.1 / 2.6 |
| Clindamycin | ≤0.12 | >4 | ≤0.12 – >4 | 60.3 / 0.1 / 39.6 | 60.2 / 0.1 / 39.7 |
| Tetracycline | ≤0.5 | 2 | ≤0.5 – >16 | 92.1 / 0.4 / 7.5 | 90.0 / 2.0 / 8.0 |

a. Criteria as published by the CLSI (2014) and EUCAST (2014).

**Figure 2**. Comparison of TD-1607 and daptomycin MIC distributions when testing 1,026 clinical MRSA isolates collected worldwide.




## CONCLUSIONS

- TD-1607 demonstrated consistent potent *in vitro* activity when tested against a large collection (n = 1,026) of contemporary (2010-2012) MRSA strains from USA, Europe and Latin America.
- MRSA isolates from USA and European hospitals showed nearly identical TD-1607 MIC distributions ($MIC_{50}$ and $MIC_{90}$ of 0.03 µg/mL for both regions), whereas MRSA strains from Latin America exhibited TD-1607 MIC values slightly higher ($MIC_{50}$, 0.03 µg/mL and $MIC_{90}$, 0.06 µg/mL) compared to USA and Europe.
- These results warrant further investigations to determine the role of TD-1607 for the treatment of MRSA infections.

## ACKNOWLEDGEMENT

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