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CCC: 0377-8282/2004

Telavancin Hydrochloride

Glycopeptide Antibiotic

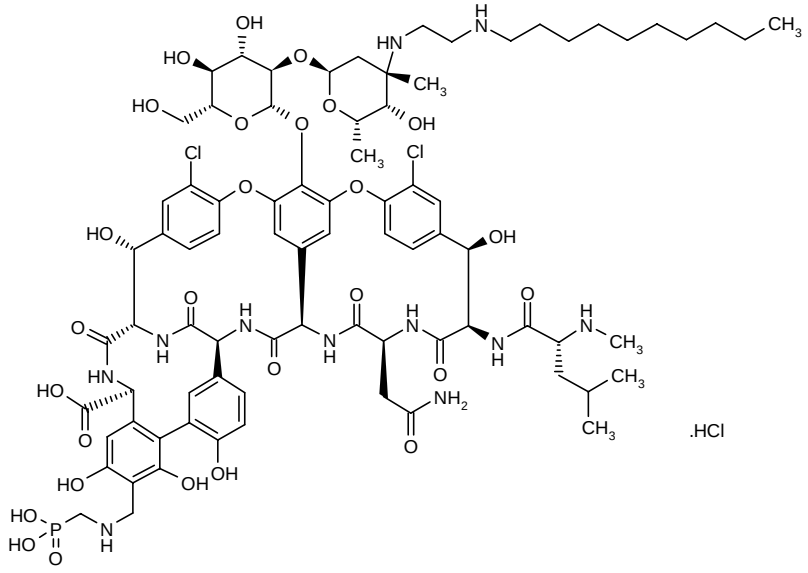
USAN; Prop INNM

TD-6424

Arbelic®

N$^{3''}$-[2-(Decylamino)ethyl]-29-(phosphonomethylaminomethyl)vancomycin monohydrochloride

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-3-(2-Amino-2-oxoethyl)-10,19-dichloro-44-[2-*O*-[3-[2-(decylamino)ethylamino]-3-*C*-methyl-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl]-β-D-glucopyranosyloxy]-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)pentanoylamino]-2,5,24,38,39-pentaoxo-29-[(phosphonomethyl)aminomethyl]-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-8,11:18,21-dietheno-23,36-(iminomethano)-22*H*-13,16:31,35-dimetheno-1*H*,13*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid monohydrochloride



$C_{80}H_{106}Cl_2N_{11}O_{27}P.HCl$

Mol wt: 1792.108

CAS: 560130-42-9

CAS: 372151-71-8 (as free base)

CAS: 380636-75-9 (as hydrochloride)

EN: 339576

Abstract

The emergence of multidrug-resistant Gram-positive pathogens has created a need for newer antibacterial agents with improved efficacy. Researchers have focused on modifying the antibiotic vancomycin and other glycopeptides by adding hydrophobic substituents in order to improve activity, absorption, distribution, metabolism and excretion. Telavancin (TD-6424) is one such novel antibiotic that was found to have multiple mechanisms of action, including inhibition of bacterial cell wall formation and disruption of cell membrane integrity. The agent showed potent activity against *Staphylococcus aureus* and vancomycin-resistant enterococci, among other bacterial species, *in vitro* and in *in vivo* infection models. Telavancin was also shown to have good pharmacokinetics and was effective in phase II clinical trials in patients with Gram-positive skin and soft tissue infections. Phase III clinical trials are in progress.

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Synthesis

Protection of 2-decylaminoethanol (I) with 9-fluorenylmethyl chloroformate by means of DIEA in CH_2Cl_2 affords the *N*-Fmoc-amino alcohol (II), which is subsequently oxidized to aldehyde (III) under Swern conditions. Then, reductive alkylation of vancomycin (IV) with aldehyde (III) by means of either sodium cyanoborohydride (1-4), borane-pyridine complex (5) or borane-*tert*-butylamine complex (5) and DIEA in DMF followed by treatment with methanol and trifluoroacetic acid gives the Fmoc-protected decylaminoethyl vancomycin derivative (V), which is submitted to *N*-Fmoc group removal by treatment with piperidine, *tert*-butylamine or methylamine in DMF, to provide the *N*-decylaminoethyl vancomycin derivative (VI). Finally, Mannich condensation of compound (VI) with (aminomethyl)phosphonic acid and formaldehyde by means of DIEA in acetonitrile/water produces telavancin (1-5). Scheme 1.

Introduction

With the emergence of multidrug-resistant Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), intermediate- and high-level resistant *S. aureus*, penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin-resistant enterococci (VRE), there is an ongoing need for novel effective antibacterial agents. Although several currently available agents such as linezolid and quinupristin/dalfopristin are effective against some resistant organisms, they can be associated with unwanted side effects and further resistance (6-12).

In the search for novel, more effective agents active against resistant bacteria, researchers have focused on modifying the activity of the antibiotic vancomycin and other glycopeptides. It was discovered that the addition of hydrophobic substituents on vancomycin maintains activity against MRSA and restores activity against VRE. However, the hydrophobic group can alter absorption, distribution, metabolism and excretion, resulting in increased elimination half-life values and high tissue accumulation (13-15).

In an effort to restore favorable distribution, reduce liver and kidney accumulation, and increase urinary excretion while maintaining antibacterial activity, a decylaminoethyl vancomycin analogue, THRX-689909, was further modified to yield telavancin (TD-6424). Telavancin exhibited excellent antibacterial activity against *S. aureus* and VRE *in vitro* and was selected for further development (4, 16)

Pharmacological Actions

Telavancin was shown in several studies to have potent antibacterial activity against numerous strains of Gram-positive pathogens *in vitro*. It displayed excellent *in vitro* activity against *S. aureus* (ATCC 13709), MRSA (ATCC 33591), vancomycin-resistant *Enterococcus faecalis* (ATCC 51575) and vancomycin-resistant *Enterococcus faecium* (KPB-01), with MIC values of 0.6, 0.8, 1.6 and 6.3 μg/ml, respectively (4).

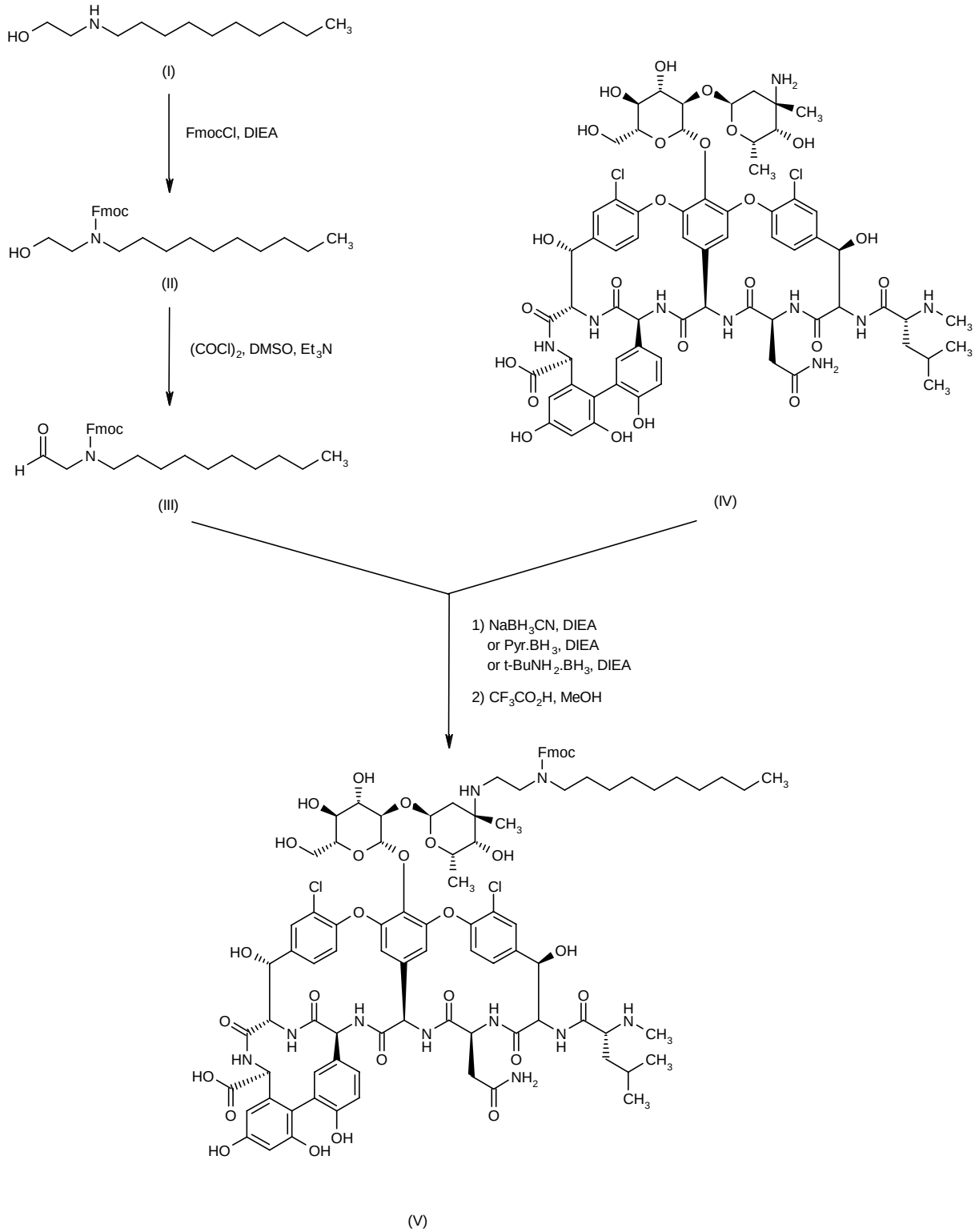
The antibacterial activity of telavancin *in vitro* was superior to vancomycin against MRSA (MIC_{90} = 1 μg/ml *vs.* 4 μg/ml), vancomycin-resistant *S. aureus* (MIC = 2 μg/ml *vs*. > 128 μg/ml), *S. pneumoniae* (MIC_{90} = 0.008 μg/ml *vs.* 0.5 μg/ml) and *Enterococcus* spp. VanA (MIC_{90} = 8 μg/ml *vs.* > 128 μg/ml) (16).

Another *in vitro* study demonstrated that telavancin was more potent than vancomycin, teicoplanin, linezolid and oxacillin against up to 128 clinical isolates of MRSA (MIC_{90} = 1 μg/ml *vs.* 2, 4, 4 and > 64 μg/ml, respectively) and more active than vancomycin, teicoplanin and linezolid against up to 47 clinical isolates of MSSA (MIC_{90} = 1 μg/ml *vs*. 2, 2 and 2 μg/ml, respectively). Telavancin was rapidly bactericidal against these strains and produced a postantibiotic effect (PAE) of 4-6 h as compared to 1 h for vancomycin (17).

The antibacterial activity of telavancin was compared with vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, moxifloxacin, ampicillin, penicillin and oxacillin against 401 Gram-positive isolates, including MSSA, MRSA, methicillin susceptible- and resistant *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Enterococcus* spp., *Streptococcus* spp., *Listeria monocytogenes* and *Lactobacillus* spp. Telavancin was active against all isolates, with MICs of 1 mg/l or less obtained for about 90% of the strains tested. It was comparable or superior to the other agents. The MIC ranges for telavancin against vancomycin-resistant enterococci and lactobacilli (vancomycin MICs > 64 mg/l) ranged from 0.5 to 16 mg/l. No cross-resistance was observed with any of the other agents examined (18).

The antibacterial activity of telavancin was also compared to vancomycin, daptomycin, linezolid, quinupristin/dalfopristin, imipenem, piperacillin/tazobactam and ampicillin against 268 clinical isolates of anaerobic Gram-positive organisms and 31 *Corynebacterium* strains. The MIC_{90} values for telavancin for all strains examined were 2 μg/ml or less. Telavancin was more potent than vancomycin against *Actinomyces* spp. (MIC_{90} = 0.25 μg/ml *vs.* 1 μg/ml), *Clostridium difficile* (MIC_{90} = 0.25 μg/ml *vs.* 1 μg/ml), *Clostridium ramosum* (MIC_{90} = 1 μg/ml *vs.* 4 μg/ml), *Clostridium innocuum* (MIC_{90} = 4 μg/ml *vs.* 16 μg/ml), *Eubacterium* group (MIC_{90} = 0.25 μg/ml *vs.* 2 μg/ml), *Lactobacillus* spp. (MIC_{90} = 0.5 μg/ml *vs.* 4 μg/ml), *Propionibacterium* spp. (MIC_{90} = 0.125 μg/ml *vs.* 0.5 μg/ml), *Peptostreptococcus* spp. (MIC_{90} = 0.125 μg/ml *vs.* 0.5 μg/ml) and *Corynebacterium* spp. (MIC_{90} = 0.03 μg/ml *vs.* 0.5 μg/ml); vancomycin was more active than telavancin against *Clostridium clostridioforme* (MIC_{90} = 1 μg/ml *vs.* 8 μg/ml). The activity of telavancin was similar to quinupristin/dalfopristin for most of the isolates, with the exception of *C. clostridioforme* and *Lactobacillus casei*, against which the latter was 3-5-fold more active. Daptomycin was less active (MICs > 4 μg/ml) than telavancin against strains of *Actinomyces*

Scheme 1: Synthesis of Telavancin



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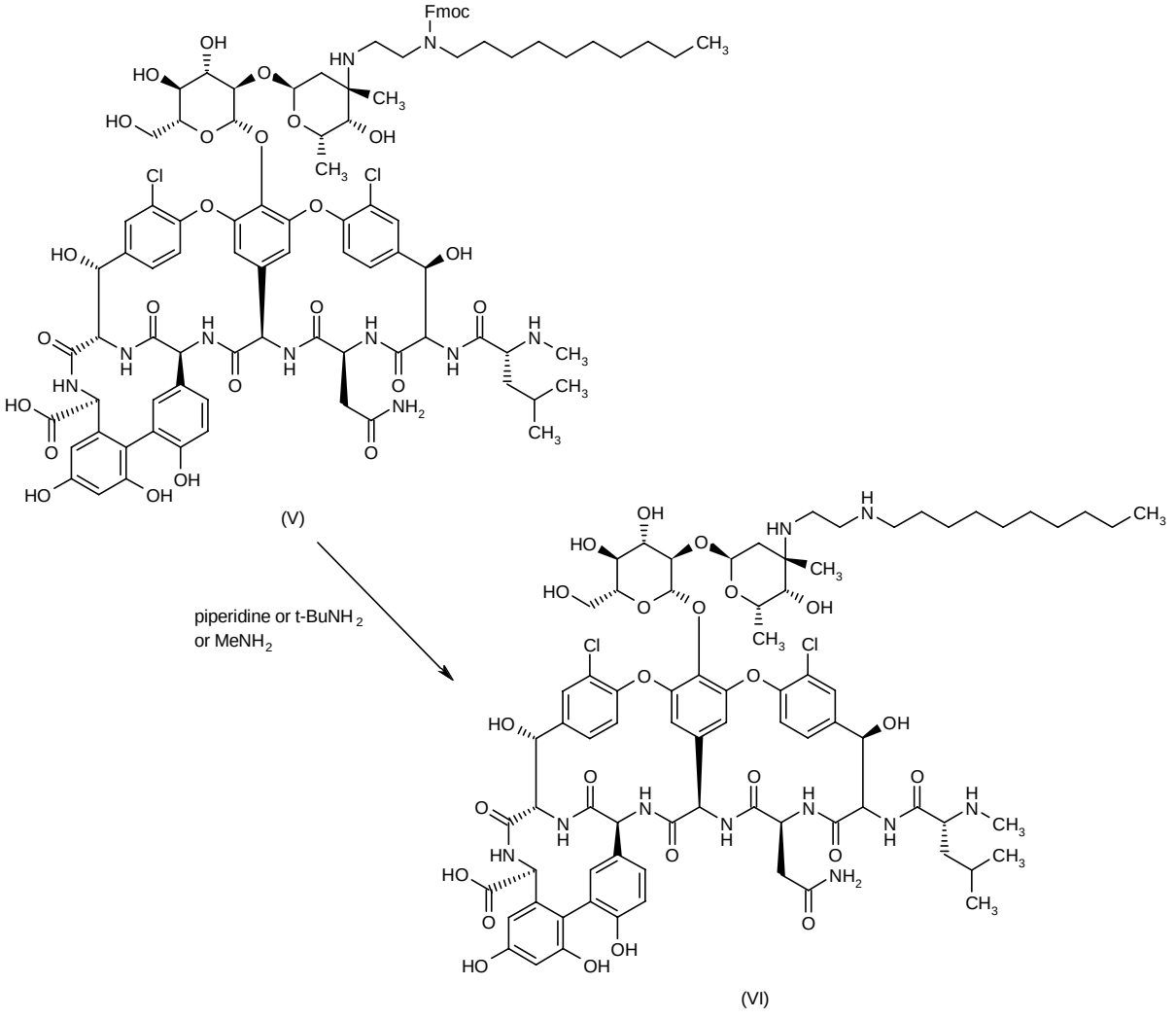
Scheme 1 (Cont.): Synthesis of Telavancin



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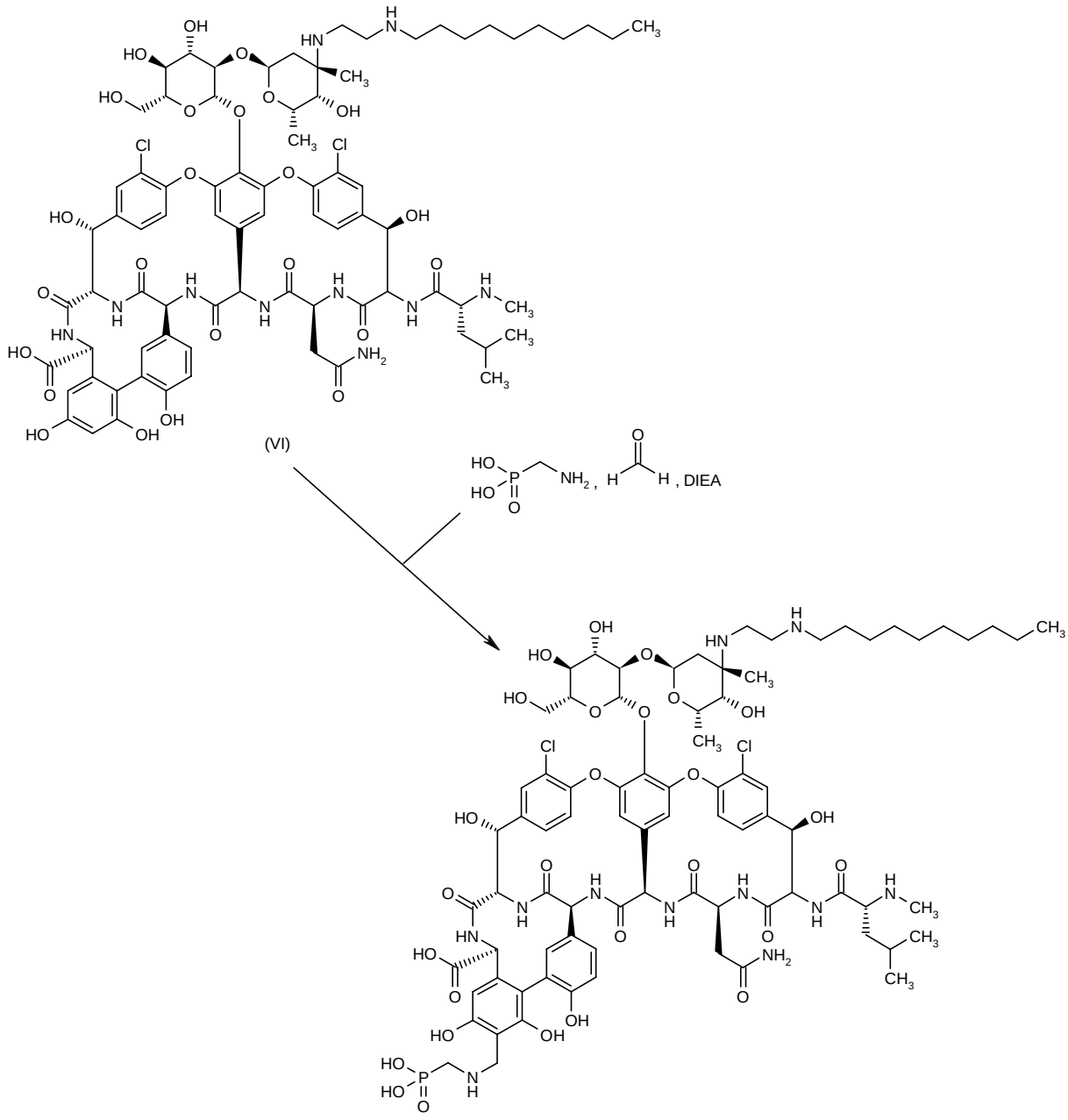
spp., *C. ramosum*, *Eubacterium lentum* and *Lactobacillus plantarum*. Linezolid was less active (MICs > 4 μg/ml) against *C. ramosum*, *C. difficile* and *Lactobacillus* spp. (19).

Telavancin was found to have potent activity against 15 strains of *Bacillus anthracis*, indicating potential use for the agent as a treatment for anthrax infections. The minimum bactericidal concentration (MBC) for telavancin against *B. anthracis* strain RA3R was 0.12 μg/ml, which was equivalent to the MIC. Its antibacterial activity against the majority of strains tested was superior to vancomycin, daptomycin and ceftriaxone, comparable to teicoplanin and less than penicillin, ciprofloxacin and doxycycline (20).

The mechanisms of antibacterial action of telavancin were examined. The agent was shown to be a specific and potent inhibitor of peptidoglycan biosynthesis in whole *S. aureus* cells (IC_{50} = 0.14 μM) and transglycosylase activity in *S. aureus* cell extracts (IC_{50} = 0.6 μM). When cells were treated with higher concentrations of the agent, a gradual dissipation in membrane potential was observed, in addition to an alteration in cell permeability. These events correlated with the loss of viability. It was concluded that the activity of telavancin is mediated via multiple mechanisms (21).

Another study using vancomycin-susceptible enterococci (VSE) and VRE showed that telavancin inhibited cell wall synthesis, produced significant dissipation of membrane potential (starting at 16 μM) and altered cell permeability (8 μM) in both VSE and VRE. These effects correlated with loss in cell viability. Although vancomycin also inhibited cell wall synthesis, it had no effect on mem-

Scheme 1 (Cont.): Synthesis of Telavancin



brane potential or permeability at concentrations up to 43 μM (22).

The effects of human serum on time-kill curves, MICs and MBCs of telavancin against staphylococci and enterococci were assessed. Results revealed that 50% serum had little effect on these properties against *S. aureus* and VSE. In contrast, telavancin was inactive against VanA VRE in the presence of 50% serum (MIC and MBC > 128 μg/ml). This was speculated to be due to free fatty acids or lipids in serum, in addition to serum protein binding (23).

A high *S. aureus* inoculum had little effect on the antibacterial activity of telavancin. At clinically relevant concentrations, the agent was shown to reduce an inoculum of 10^8 CFU/ml to levels that were undetectable within 24 and 48 h; this effect was not observed with vancomycin. Results indicate that telavancin may be effective in the treatment of infections involving large inocula (24).

Telavancin was active in a number of *in vivo* infection models. In the mouse neutropenic thigh model, tela-

vancin caused dose-dependent decreases (up to 3 $\log_{10}$ CFU/g) in thigh titers of organisms including MSSA, MRSA, penicillin-susceptible and -resistant strains of *S. pneumoniae* and vancomycin-resistant *E. faecalis* (ED_{50} = 0.5-6.6 mg/kg i.v.). Telavancin was 4- and 30-fold more potent than vancomycin and linezolid, respectively, against MRSA (ATCC 33591) infection and 16- and 40-fold more potent than vancomycin and nafcillin, respectively, against MSSA (ATCC 13709). Telavancin, vancomycin and linezolid were all effective in the mouse subcutaneous infection model and the antibacterial activity observed in this model against MRSA (ATCC 33591) was superior to that observed in the mouse neutropenic thigh model. The differences in activity of vancomycin and linezolid observed between the two models were greater than those noted for telavancin, suggesting that immune status has less of an effect on the activity of telavancin (25).

Telavancin (40 mg/kg i.v. b.i.d. starting 24 h postinoculation) was shown to be significantly superior to vancomycin (80 mg/kg i.v. b.i.d.) and linezolid (110 mg/kg b.i.d.) in reducing lung MRSA (ATCC 33591) titers in a mouse model of pneumonia. The lung titers for telavancin, vancomycin, linezolid and control groups at 24 h posttreatment were 4.4 ± 0.7, 7.0 ± 1.8, 7.6 ± 1.6 and 8.4 ± 0.2 $\log_{10}$ CFU/g, respectively. In addition, all animals treated with telavancin survived as compared to 88%, 88% and 38% in the vancomycin, linezolid and control groups, respectively (26).

Telavancin (30 mg/kg i.v. b.i.d. for 4 days) was effective and superior to vancomycin (30 mg/kg i.v. b.i.d. for 4 days) in an *in vivo* rabbit model of aortic valve endocarditis due to MRSA or vancomycin-intermediate *S. aureus* (VISA). Significant reductions in MRSA (2.66 ± 3.08 $\log_{10}$ CFU/g *vs.* 7.35 ± 0.20 $\log_{10}$ CFU/g in controls) and VISA (1.15 ± 2.57 $\log_{10}$ CFU/g *vs.* 6.73 ± 0.46 $\log_{10}$ CFU/g in controls) vegetation titers were only seen in animals treated with telavancin; treatment with vancomycin only tended to reduce titers (27).

Pharmacokinetics

The distribution and elimination properties of telavancin were examined in rats following a single i.v. dose (50 mg/kg), with results showing an improvement over the decylaminoethyl vancomycin analogue THRX-689909. At 24 h postdosing, liver and kidney distribution was 5% and 2%, respectively, as compared to 16% and 13%, respectively, for the analogue, and an increase in urinary clearance was also observed for telavancin (40% *vs.* 12% for the analogue) (4).

The pharmacokinetics of telavancin were evaluated in a randomized, double-blind, placebo-controlled, single- (0.25-15 mg/kg i.v. by 30-min infusion) and multiple-dose (7.5-15 mg/kg/day by 30-min i.v. infusion for 7 days) study in healthy male subjects. The pharmacokinetic parameters were approximately linear following single doses. Steady state was reached on day 3 following multiple dosing. No significant differences were noted in AUC, C_{max} and $t_{1/2}$ values on days 1 and 7, and little accumulation was seen; C_{min} increased slightly after multiple dosing. C_{max} and AUC_{ss} values on day 7 for doses of 7.5, 12.5 and 15 mg/kg were 97, 151 and 203 mg/l, respectively, and 700, 1033 and 1165 mg·h/l, respectively. Half-life and volume of distribution at steady state were about 9 h and 0.1 l/kg, respectively (28).

The pharmacokinetics and safety of telavancin (7.5 or 15 mg/kg once daily by 60-min i.v. infusion for 3 days) were examined in a study in healthy male and female subjects. Parameters obtained from 71 subjects revealed linear pharmacokinetics, with no significant differences between males and females. C_{max} values (males and females, respectively) were 89.0 ± 9.1 and 88.2 ± 10.0 μg/ml for the 7.5 mg/kg dose and 188 ± 27.1 and 183 ± 28.1 μg/ml for the 15 mg/kg dose. AUC_{ss} values (males and females, respectively) were 619 ± 58.2 and 588 ± 83.1 μg·h/ml for 7.5 mg/kg and 1331 ± 171 and 1194 ± 229 μg·h/ml for 15 mg/kg. Half-life values for both males and females ranged from 6.6 to 8.9 h. Mild taste disturbance, nausea and headache were the most common adverse events reported, with a greater incidence noted in the higher dose group. Other adverse events included vomiting, dizziness and infusion-associated reactions; gastrointestinal events and infusion-site reactions were more frequently observed in females. No significant alterations were recorded in laboratory parameters, including renal, hepatic and hematological function (29).

A single-dose study conducted in 16 healthy elderly (mean age = 71 years) male and female subjects with normal renal function compared the pharmacokinetics of telavancin (10 mg/kg by 60-min i.v. infusion) with those from a study conducted in young subjects (7.5 mg/kg telavancin by 60-min i.v. infusion). Although age did not alter the clearance of telavancin (12 ml/h/kg for both young and elderly subjects), distribution was more extensive (V_{dss} = 167 ml/kg *vs.* 100 ml/kg) and elimination $t_{1/2}$ values (11 h *vs.* 7 h) were longer in older subjects. Pharmacokinetics were similar for male and female subjects. Adverse events reported in this study were mild and transient and included taste disturbance in 2 subjects, flushing with postural hypotension in 1 subject, headache in 2 subjects, dizziness in 1 subject and throat paresthesia in 1 subject. It was concluded that no dose adjustments are required in elderly patients with normal renal function (30).

A study in subjects with mild, moderate and severe renal dysfunction (creatinine clearance = 51-80, 30-50 and < 30 ml/min, respectively) examined the single-dose pharmacokinetics of telavancin (7.5 mg/kg by 60-min i.v. infusion). Telavancin was well tolerated, with only 1 mild case of red man syndrome (pruritus, maculopapular rash) reported. Comparison of data collected from 9 subjects with results from another study in healthy subjects administered the same dose of telavancin indicated that subjects with moderate or severe renal impairment may require dose adjustments. Slightly higher AUC values (628 and 773 μg·h/ml, respectively, *vs.* 606 μg·h/ml),

reduced clearance (9 and 6 ml/h/kg, respectively, *vs.* 11 ml/h/kg) and longer $t_{1/2}$ (13.2 and 17.9 h, respectively, *vs.* 7.2 h) values were observed in subjects with moderate and severe renal impairment compared to healthy subjects. A significant correlation was found between telavancin clearance and creatinine clearance in subjects with renal impairment (31).

Clinical Studies

The effect of telavancin (7.5 or 15 mg/kg once daily by 60-min i.v. infusion for 3 days) on cardiac repolarization (Q-T_c interval duration) was examined in a randomized, double-blind, placebo-controlled, parallel-group phase I study conducted in 160 healthy subjects; moxifloxacin (400 mg once daily by 60-min iv. infusion for 3 days) was used as a positive control. Telavancin had a minimal effect on Q-T prolongation. The mean changes in Q-T_c values corrected for heart rate for the telavancin doses were 4.1 and 4.5 ms, respectively, as compared to 9.2 ms for moxifloxacin. There were no clinically significant changes in ECG parameters and no correlation between changes in Q-T_c and plasma telavancin concentrations (32).

A multicenter, randomized, double-blind, placebo-controlled phase II trial in 167 patients with complicated Gram-positive skin and soft tissue infections examined the safety and efficacy of telavancin as compared to standard treatment (ST; antistaphylococcal penicillin or vancomycin). All patients received at least 1 dose and approximately 5% of the patients in each group discontinued due to adverse events. Fewer cases of serious adverse events were reported in the telavancin group compared to the ST group, although the overall incidence of adverse events was similar for both groups. A mild increase in serum creatinine was observed in a few patients from both groups and transient thrombocytopenia was seen in a small proportion of patients in the telavancin group. Cure rates for telavancin-treated patients with *S. aureus* and MRSA at baseline were 80% and 82%, respectively, as compared to 77% and 69%, respectively, for the ST group. The microbiological eradication rate for telavancin-treated patients with baseline MRSA was 84% as compared to 74% for the patients in the ST group (33).

Similar positive results for telavancin were obtained in the FAST2 trial, a multicenter, randomized, double-blind phase II study in 201 patients with complicated Gram-positive skin and skin structure infections who received either telavancin (10 mg/kg) or ST. The overall incidence of adverse events was similar for both telavancin and ST groups. The cure rates for the evaluable population were 96.1% and 93.5% for the telavancin and ST groups, respectively. A significantly higher cure rate of 92.3% against MRSA was obtained for the telavancin group as compared to 68.4% in the ST group. Telavancin is currently undergoing phase III clinical evaluation for the treatment of complicated skin and skin structure infections (34).

Source

Theravance, Inc. (US).

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