Novel Glycopeptide Antibiotics: *N*-Alkylated Derivatives Active Against Vancomycin-Resistant Enterococci

MICHAEL J. RODRIGUEZ*, NANCY J. SNYDER, MARK J. ZWEIFEL, STEPHEN C. WILKIE, DOUGLAS R. STACK, ROBIN D. G. COOPER, THALIA I. NICAS, DEBORAH L. MULLEN, THOMAS F. BUTLER and RICHARD C. THOMPSON

Infectious Diseases Research, Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, IN 46285

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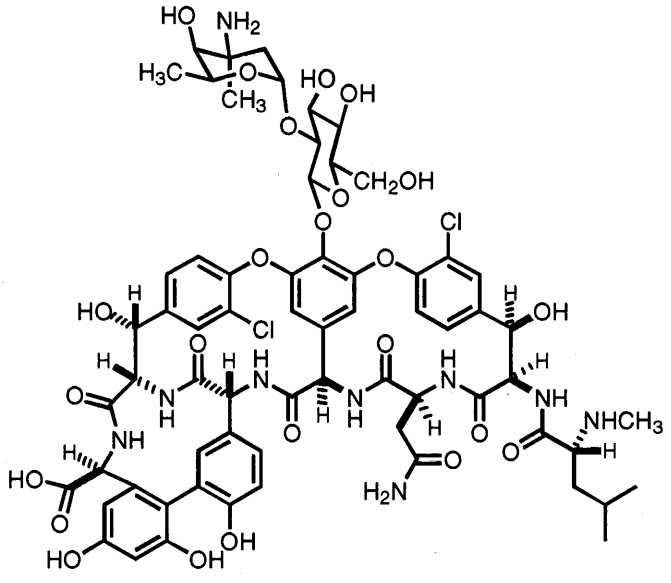
LY264826 (A82846B) is a naturally-occurring glycopeptide antibiotic, differing from vancomycin in the stereochemistry of the amino-sugar of the disaccharide function, and the presence of a third sugar attached at the benzylic position of amino acid residue 6. Despite these seemingly subtle differences, LY264826 is approximately 10 times more active than vancomycin against the enterococci. In the pursuit of new antibiotics active against multiresistant Gram-positive organisms, an extensive side chain SAR was developed focusing on the reductive alkylation of LY264826 at the amino function of the disaccharide moiety. A new series of derivatives having varying degrees of structural diversity in the side chain (*e.g.* varying lengths and degrees of rigidity) was found to have potent activity against vancomycin-resistant enterococci (MIC's $<1.0\,\mu g/ml$) as well as activity against staphylococci and streptococci as good or better than vancomycin.

The urgent medical need created by the recent emergence of drug resistant bacteria has intensified the search for more effective clinical agents. In particular, vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) are no longer treatable with traditional antibiotics. Currently, vancomycin (Fig. 1) is the drug of choice for serious enterococcal infections and is the only antibiotic that is effective in treating resistant strains of *S. aureus*[1,2].

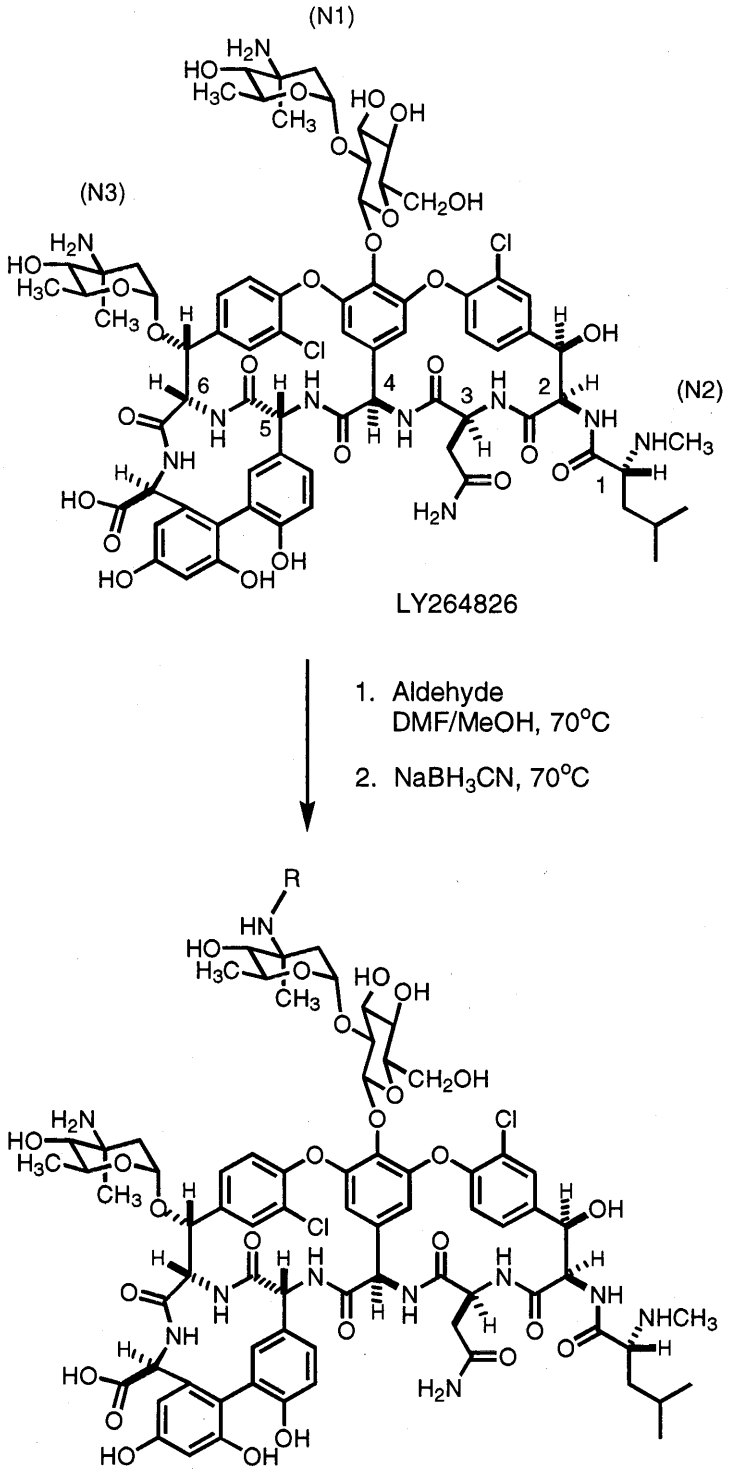
Recent advances with respect to the chemical derivatization of the vancomycin-related glycopeptide class of natural products have given researchers new opportunities to discover more effective clinical agents[3,4]. While most chemical modifications to vancomycin offer some advantages, alkylation of a related glycopeptide, LY264826 significantly improves activity against VRE. As reported in an earlier publication, the promising activity of the chlorobenzyl derivative of LY264826 prompted a structure-activity relationship (SAR) focused on substituted benzyl derivatives of LY264826[5]. Herein we report our findings for the extensive side chain SAR centered on the *N*-alkylation of the disaccharide amino group (N1) of LY264826 (Scheme 1). This research build on the discovery of the initial lead compound LY191145 and resulted in the discovery of the present clinical

Fig. 1. Structure of vancomycin.



Dedicated to Professor YOSHITO KISHI on the Occasion of his 60th Birthday.

Scheme 1. Preparation of *N*-alkyl LY264826 derivatives.



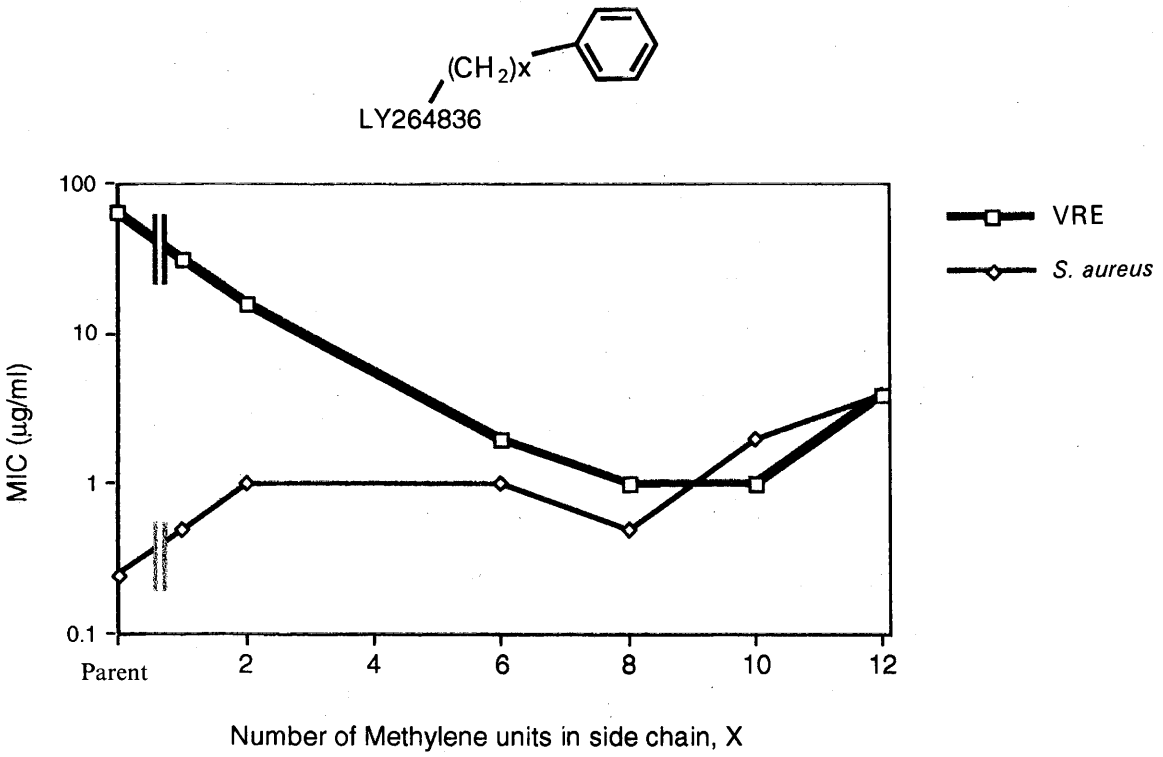
candidate LY333328.

Materials and Methods

Experimental Procedure

General Procedure: The aryl aldehydes not commercially available for side chain SAR were prepared using standard procedures[6,7]. A general procedure for the reductive alkylation chemistry with LY264826 was reported in a previous publication[9]. The experimental methods used for the reductive alkylation procedure are given. Method B is preferred over A for non benzylic aldehydes.

Fig. 2. Enterococci and staphylococci activity *vs.* chain length for *N*-alkyl LY264826 derivatives.



Method A

An excess of the aldehyde (~1.5 equivalents) was mixed with LY264826 triacetate (1.0 equivalent) under argon in 80 ml methanol and/or DMF and heated to 70°C for 2 hours. Sodium cyanoborohydride (1.5 equivalents) was added and the reaction mixture was stirred for an additional 2 hours. After cooling to room temperature, the reaction mixture was evaporated to dryness *in vacuo*. The crude product was purified by reverse-phase HPLC with a 0.1% TFA buffer. The organic solvent was removed from the desired fractions and the mixture was lyophilized to give a white solid of a tris-(trifluroacetate) salt A82846B derivative.

Method B

A mixture of LY264826·triacetate (1.0 equivalent), aldehyde (1.5 equivalents), and sodium cyanoborohydride (1.5 equivalents) in methanol (80 ml) under argon was heated to reflux for 2~3 hours. The reaction mixture was cooled to room temperature and evaporated to dryness *in vacuo*. The crude product was purified and isolated as described in Method A.

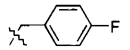
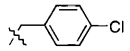
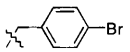
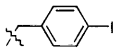
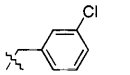
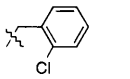
Antimicrobial Testing

In vitro evaluation of staphylococci and streptococci was carried out according to NCCLS recommendations for broth microdilution assay. *In vitro* evaluation of activity against enterococci was carried out in the same format using broth microdilution in Brain Heart Infusion broth (Difco Laboratories, Detroit MI). Data for a single screening reference strain is shown in the tables; in Figure 2, data is the geometric mean MIC of representative isolates. Strains shown in tables are: *Staphylococcus aureus* 489 (methicillin-resistant), *Staphylococcus epidermidis* 270, *Staphylococcus haemolyticus* ST105, *Enterococcus faecium* strain 180 (confirmed *vanA* genotype), and its vancomycin-susceptible derivative *Enterococcus faecium* 180-1.

Results and Discussion

LY264826 is similar in structure to vancomycin. The additional amino sugar present in the natural product, however, added more complexity to elaborate the side chain SAR. Instead of two amino groups susceptible to alkylation as with vancomycin, we now had three (N1, N2, N3). The alkylation of the N1 position of LY264826 was identified in previous work as a site that enhanced antimicrobial activity[8]. The potential to alkylate all three amines to produce complex mixtures of seven products presented a synthetic challenge initially. However, as the

Table 1. Derivatives of LY264826 with halogenated benzyl side chains [MIC (μg/ml)].

R	*Enterococcus faecium*		Staphylococci		
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270	*S. haemolyticus* 105
	32	1			
 LY191145	1	0.25	≤0.6	0.5	0.5
	2	0.25	≤0.6	0.125	0.25
	4	0.25	≤0.6	1	1
	32	0.25			
	128	1			

side chain SAR progressed, we successfully developed a general procedure to synthesize many analogs with high regioselectivity. The reductive alkylation conditions developed for this SAR allowed the coupling to occur selectively at the desired disaccharide amine (N1) (Scheme 1)[9].

We selected the *p*-chlorobenzyl derivative (LY191145), the first compound to demonstrate activity which might be efficacious against VRE (1 μg/ml), as a starting point to further investigate the effects of the side chain on antimicrobial activity. Further variation of the benzyl class of side chains with other halogen functional groups resulted in a series of novel derivatives. As shown (Table 1), the para bromo and iodo analogs, like the chloro analog improved biological activity (VRE 1~4 μg/ml). However, the derivative with the fluoro benzyl side chain only maintained the activity found with the natural product, LY264826 (VRE 32 μg/ml). In addition to the halogen type, we observed that the aryl substitution pattern was also tied to activity. For example, the chloro substituent residing in the para position retained better overall activity. As the side chain SAR was extended to include other classes of side chains, the aryl substitution pattern was seen again as an important structural feature.

As we explored the total benefits of attaching different functional groups to the benzylic side chain, we revisited the early side chain SAR performed on vancomycin which focused on the effects of linear aliphatic side chains (*e.g. n*-decyl), similar to those found naturally in teicoplanin (Table 2). The aliphatic side chain SAR on vancomycin demonstrated that these side chains had a positive effect on antimicrobial activity[3,10]. Likewise, the coupling of long aliphatic side chains to LY264826, resulted in an approximate 16-fold improvement in VRE activity over the natural products, including teicoplanin. Although, the effects of this modification towards activity against sensitive enterococci was minimal, the combination of a lipophilic side chain with an aryl ring proved to be a winning combination to improve overall antimicrobial activity. The alkyloxy benzyl class is one example where activity against resistant and sensitive enterococcus was clearly demonstrated (Table 3). The shortest side chain in this series, the methoxy benzyl (C1) shows an overall improvement in activity compared to the non substituted benzylic side chain. As the side chain length was extended from C1 to C12, we observed a minimum and maximum of biological activity. The pentyloxobenzyl derivative (C5) imparted the best overall activity against the pathogens tested, in particular resistant and sensitive enterococci and *S. heamolyticus*. A similar result occurred with the alkylbenzyl series. However, in this case, the SAR was optimized with a four carbon chain length. A similar trend is observed for a series of phenyl alkyl side chains, where the aromatic ring is removed from the point of attachment, repositioned, and linked at the tail end of the aliphatic tether. As shown graphically (Fig. 2), as the tether length was increased from C1 to C12, the mean MIC's against VRE improved from 23 to 2 μg/ml, while the MRSA activity

Table 2. Increased activity of *N*-alkyl LY264826 [MIC (μg/ml)].

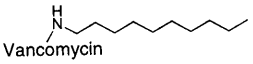
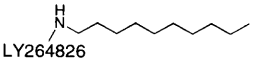
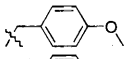
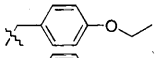
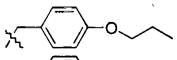
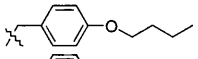
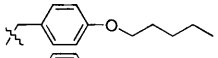
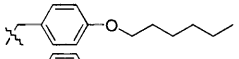
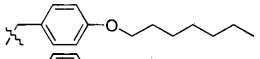
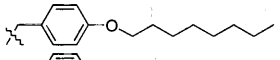
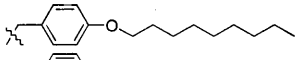
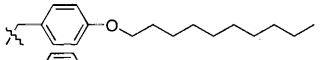
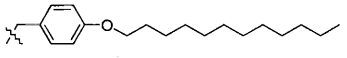
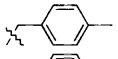
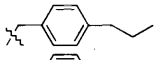
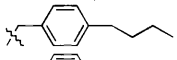
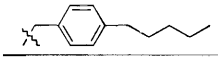
R	*Enterococcus faecium*		Staphylococci	
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270
Vancomycin	512	2	0.5	1
 Vancomycin	8	0.5	0.13	0.25
LY264826	32	0.25	0.06	0.25
 LY264826	2	1	0.5	1
Teicoplanin	32	0.25	0.06	0.06

Table 3. Alkyloxybenzyl derivatives of LY264826 [MIC (μg/ml)].

R	*Enterococcus faecium*		Staphylococci		
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270	*S. haemolyticus* 105
	16	0.5	0.125	1	8
	4	0.25	≤0.6	16	16
	4	0.125	≤0.6	32	16
	4	0.125	0.25	32	16
	0.5	0.125	1	0.5	0.5
	0.5	0.06	0.25	≤0.6	0.5
	0.25	0.06	0.25	4	1
	0.5	0.06	1	1	2
	0.25	0.06	4	2	4
	1	0.5	4	4	8
	2	1	8	0.125	16
	4	4	>64	>64	>64
	32	0.5	≤0.6	2	>64
	4	0.125	0.125	64	>64
	1	0.06	0.25	0.5	>64
	1	0.06	1	64	>64

decreased from 0.25 to 4 μg/ml. The chain length required to optimize both enterococci and staphylococci was found to be about 8 carbons.

Overall, it appeared that some degree of unsaturation was an important structural feature to have designed into the side chain. The importance of the aryl group in the

Table 4. Effect of polyaromatic side chains on activity of LY264826 derivatives [MIC (μg/ml)].

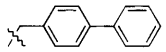
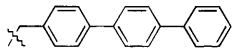
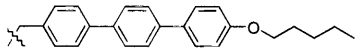
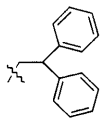
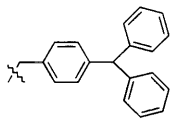
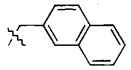
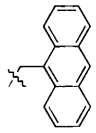
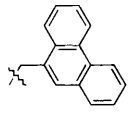
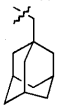
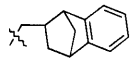
R	*Enterococcus faecium*		Staphylococci		
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270	*S. haemolyticus* 105
	16	0.5	0.125	1	8
	0.5	0.06	0.125	0.25	1
	0.5	0.25	2	2	4
	16	16	4	16	64

Table 5. Polyaromatic side chains [MIC (μg/ml)].

R	*Enterococcus faecium*		Staphylococci		
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270	*S. haemolyticus* 105
	4	0.5	0.25	1	4
	1	0.5	1	2	2
	1	0.125	≤0.06	8	4
	0.5	0.06	≤0.06	8	4
	32	0.5	1	8	8
	8	0.25	1	2	4

side chain was evident. To further investigate this group, a series of side chains with multiple aromatic rings was evaluated (Table 4). These polyaromatic derivatives revealed that a second aromatic ring produced one of most active compounds in this SAR. These biphenyls showed a substantial improvement in overall activity ($<1\,\mu$g/ml) against the enterococci as well as the staphylococci. This result prompted us to take a look at the effects of a third aromatic ring. We were encouraged to observe that this side chain showed promising activity against resistant and sensitive enterococci. However, the additional aromatic ring effected a slight decrease in staphylococci activity by 2~4 fold Unfortunately, in contrast to the mono benzyl series, there was no major advantage to impact biological activity by increasing the chain length with aliphatic "tails". Examination of other polyaromatic derivatives, where multiple aromatic rings are linked in the ortho, meta, para, or fused at the

Table 6. Multicyclic LY264826 derivatives [MIC (μg/ml)].

R	*Enterococcus faecium*		Staphylococci	
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270
	8	0.25	0.25	1
	8	0.25	0.25	1
	32	0.5	0.25	1
	32	0.5	≤0.6	1

ortho-meta or meta-para positions, showed improvements in activity against the resistant enterococci. As illustrated in (Table 5), the effect on VRE activity was correlated to the degree of steric bulk nearest the site of attachment. As a second or third aromatic ring was incorporated in the side chain that resulted in a non-para arrangement of the aromatic rings (*e.g.* 1-naphthalene and anthracene), the overall enterococci activity decreased. If suitable modifications were made such that the steric bulk is positioned away from the site of attachment; a para or meta-para orientation (*e.g.* biphenyl benzyl, 2-naphthalene), the activity against resistant and sensitive enterococci was restored and enhanced. Unfortunately, the activity against *S. aureus* did not improve with the more bulky polyaromatics. The effect of bulky side chains on antimicrobial activity was seen with a series of multicyclic analogs. The multicyclic derivatives (Table 6) afforded minimal improvement in activity against both VRE and MRSA as compared with the linear aliphatic/aryl alkyl side chains described earlier.

The incorporation of a second aromatic ring in the side chain was an important breakthrough in the SAR. We elaborated on side chains containing two aromatic rings to further pinpont the geometric requirements that would impact activity. A series of biphenyl derivatives coupled with $-CH_2-$, $-CHOH-$, $-S-$, $-N-$, $-O-$ linkers were investigated (Table 7). Examination of these derivatives illustrates that excellent activity against VRE did not require a linear geometry. With the exception of linker types with hydrogen bonding potential (*e.g.* $-NH-$, $-CHOH-$), these linkers were well tolerated. Of this series, the *p*-phenyloxybenzyl and *p*-phenylthiolbenzyl showed substantial improvement against VRE and staphylococci over the initial lead compound, LY191145. As observed with the mono benzyl substituted class, non para-substituted analogs affected antimicrobial activity. VRE activity was incrementally reduced as the oxygen or sulfur linker was moved from the *para* to the *ortho* position; possibly due to the increase of steric bulk near the point of attachment. In contrast, the reduction of VRE activity with this class is not as dramatic as shown with the mono substituted benzyl analogs.

As the phenyl benzyl side chain SAR was evaluated, we found that the degree and type of unsaturation was important to maintain activity. As shown (Table 8), complete saturation of one or two of the aromatic rings show increased activity toward both enterococci and staphylcocci over the natural products, LY264826, but the structural features provided by two aromatic rings was overall more active than the saturated analogs. Likewise replacement of one aromatic ring with heterocycles such as the thiophene group (bioisotere) provided no significant advantage over the phenyl benzyl analog, but as with most of the modifications described, we observed excellent activity against VRE and MRSA as compared to LY264826.

We continued to explore the features that enhance activity among the mono benzyl derivatives with the phenyl benzyl series. Differences in trends were found among the different classes of side chains. For example, unlike the alkyloxy mono benzyl series, the attachment of alkyloxy side chains did not yield a compound better

Table 7. Linker-containing analogs [MIC (μg/ml)].

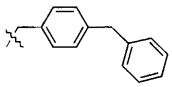
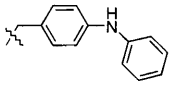
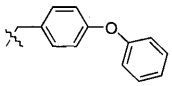
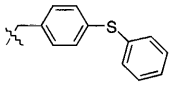
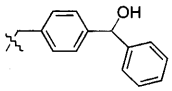
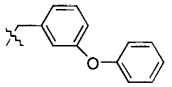
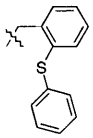
R	*Enterococcus faecium*		Staphylococci		
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270	*S. haemolyticus* 105
	1	0.06	≤0.06	0.5	0.5
	8	0.06	0.5	1	1
	1	0.06	≤0.06	0.5	0.5
	0.5	0.06	0.25	0.125	2
	16	0.125	≤0.06	0.25	1
	1	0.06	≤0.06	1	1
	8	0.25	0.125	0.5	1

Table 8. Phenylbenzyl saturation and heteroatom derivatization [MIC (μg/ml)].

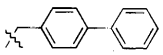
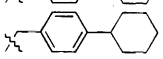
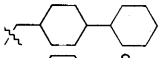
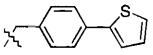
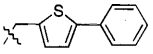
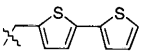
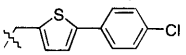
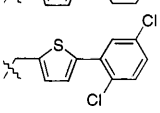
R	*Enterococcus faecium*		Staphylococci		
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270	*S. haemolyticus* 105
	0.5	0.03	0.125	0.25	1
	1	0.06	0.125	1	
	2	0.25	2	0.25	
	1	0.125	1	1	0.5
	2	0.06	≤0.06	0.5	64
	2	0.25	0.5	0.5	0.5
	4	0.06	0.125	≤0.06	0.125
	8	0.06	0.5	0.5	0.25

Table 9. (Alkyloxyphenyl)benzyl derivatives of LY264826 [MIC (μg/ml)].

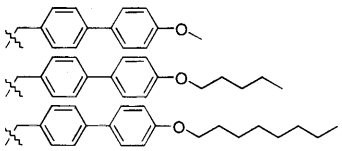
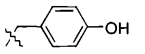
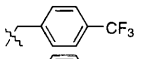
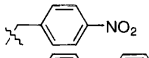
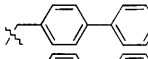
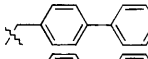
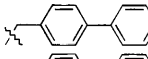
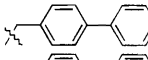
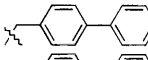
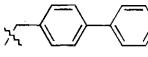
R	*Enterococcus faecium*		Staphylococci		
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270	*S. haemolyticus* 105
	2	0.5	≤0.06	0.25	2
	0.5	0.25	4	1	2
	8	8	16	32	>64

Table 10. Effect of electron-withdrawing and electron-donating groups on activity of phenylbenzyl analogs of LY264826 [MIC (μg/ml)].

R	*Enterococcus faecium*		Staphylococci		
	180 Van A resistant	180-1 Vancomycin-susceptible	*S. aureus* 489	*S. epidermidis* 270	*S. haemolyticus* 105
	32	0.5	≤0.06	1	2
	4	0.25	0.125	0.25	0.25
	16	1	≤0.06	0.5	0.5
	8	0.5	0.5	2	2
	0.5	0.03	1	0.25	0.25
	1	0.125	0.25	0.5	0.5
	0.5	0.03	0.25	0.5	0.5
	0.5	0.03	1	0.5	1
 LY333328	0.5	0.03	1	0.5	1

than the parent compound, phenyl benzyl (Table 9). The minimum chain length ($-OCH_3$) retained activity similar to that of the parent compound. As the length of the flexible lipophilic "tail" was increased to C5, the activity against VRE remained unchanged but the activity against staphylococci was impaired. Furthermore, the staphylococcal activity was dramatically diminished by alkyl chain lengths of six or more carbons.

The functional groups found to be the most effective substituents with the mono benzyl side chains produced the most active compounds in the phenyl benzyl series (Table 10). The electron withdrawing groups (*e.g.* F, Br, $-CF_3$, Cl, NO_2) substantially enhanced antimicrobial activity over the natural product, LY264826. Among these derivatives, LY333328, the *p*-chloro substituted analog, was selected as the pre-clinical candidate. As seen earlier, electron donating groups (alkyl, alkoxy, hydroxy) have minimal effect on activity especially those with protic elements.

Overall, this novel class of glycopeptide semi synthetics has illustrated the impact of the derivatization of the vancomycin-related natural products. The strategy of incorporating a wide range of structurally diverse side chains at the N1 position of LY264826 has produced novel analogs that are more effective in treating vancomycin-resistant and -sensitive enterococci and methi-

cillin-resistant *Staphylococcus aureus* isolates. Due to the structurally diverse nature of the side chains, it is unknown, but unlikely, that the observed activity is caused by steric, electronic or geometric effects alone. The large degree of structural diversity of side chains used in our SAR does not allow us to pinpoint one specific feature that is essential for activity. However, recent studies have shown that dimerization potential of the natural products and of the synthetic analogs may be important as well as the ability to interact with cell membranes[11~13]. The degree of dimerization potential of side chains on LY264826 must be in part responsible for the observed activity. The dimerization properties of LY264826 are enhanced as side chains of varying degrees of size and shape are coupled at the N1 position and as a result, increased antimicrobial activity is observed[14]. Studies are in progress to further elucidate the role of the side chains on the mechanism of action and to advance the evaluation of these new semisynthetic glycopeptides for clinical trials.

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