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Design and synthesis of new vancomycin derivatives

Wen Gu [a], Bei Chen [a], Min Ge [a,b,*]

[a] College of Biotechnology and Pharmaceutical Engineering, Nanjing University of Technology, Nanjing 210009, China
[b] Acesys PharmaTech, Inc., Science and Technology Building 24B, 5 Xing Mo Fang Road, Nanjing 210009, China

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ABSTRACT

A set of vancomycin derivatives with lipid chain attached via a glyceric acid linker was designed and synthesized. A concise synthesis towards these derivatives was developed and the IC_{50}s of these new lipoglycopeptides were tested. Some of them showed very potent activity against both vancomycin sensitive and resistant strains.

The glycopeptides antibiotics are the most important drugs in current use for the treatment of Gram-positive bacterial infections. They function through binding to the bacterial cell wall substrate D-Ala-D-Ala and thus inhibiting the transpeptidation step. In 1990s, vancomycin resistant *Enterococci* (VREs) and vancomycin-resistant *Staphylococcus aureus* (VRSA) emerged which posed a very serious public health problem. This led to new interests in the development of antibiotics of different class as well as new derivatives of the glycopeptides.

Many different types of vancomycin derivatives were prepared and studied. The most successful finding is the discovery by Nagarajan et al. that attaching lipid chain to the vancomycin carbohydrate portion led to significant potency boost towards both vancomycin sensitive and resistant strains.[1] These modifications eventually led to the development of a new glycopeptide antibiotic called oritavancin which is now close to FDA filing (Fig. 1). Studies suggest that these new vancomycin derivatives with lipid chain attached (lipoglycopeptides) have dual mechanisms by inhibiting both transpeptidation and the transglycosylation steps of the cell wall biosynthesis.[2] The alycone portion binds the cell wall substrate and the lipid carbohydrate portion inhibits the transglycosylases at the same time. Interestingly, we notice that another transglycosylase inhibitor—moenomycin (Fig. 1)—also has a similar structure feature where a long lipid chain is attached to its carbohydrate portion via a glyceric acid linker. Kahne group has extensively studied the functions of the C55 lipid chain as well as the carbohydrate portion.[3] However, the function of this glyceric acid phosphate linker remains unknown.

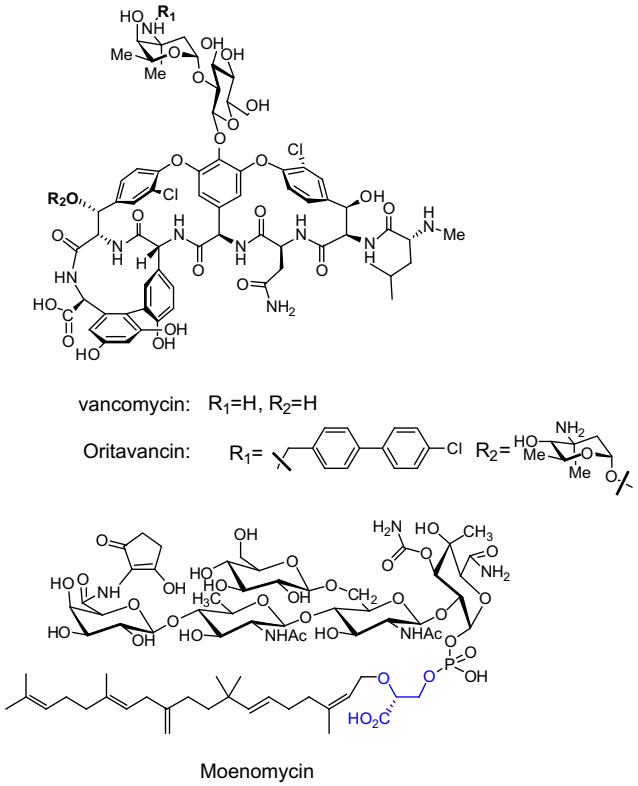

Figure 1. Chemical structures of vancomycin, oritavancin and moenomycin.

* Corresponding author. Tel.: +86 025 83421757; fax: +86 025 83172563.
E-mail address: minge88@gmail.com (M. Ge).

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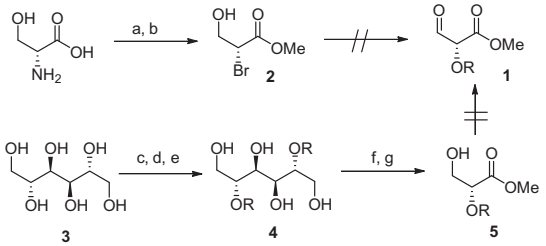
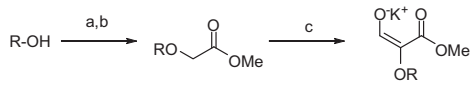


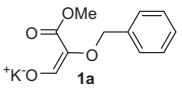
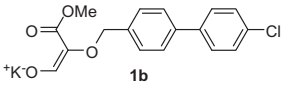
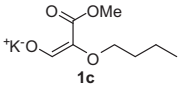
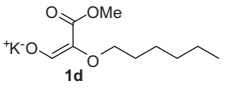
Scheme 1. Attempted syntheses of compound 1. Reagents and conditions: (a) $NaNO_2$, HBr; (b) MeOH, HCl; (c) PMB dimethoxy ketal, TsOH; (d) RBr, NaH; (e) AcOH, H_2O; (f) $NaIO_4$,THF, H_2O; (g) $NaClO_2$, NaH_2PO_4, H_2O, 2-methyl-2-butene; then MeOH, HCl.

During the development of the lipoglycopeptides, it was found that these derivatives have poorer solubility in water compared to vancomycin. In addition, the greasy chain caused unwanted ion-channel side effect. How to improve aqueous solubility while improving the potency is a challenging problem in this area.

We have noticed the similarity between the lipoglycopeptides and moenomycin. It was interesting to understand the role of the glyceric acid–phosphate portion of moenomycin is. Here we designed a set of vancomycin derivatives with lipid chains attached to the carbohydrate portion via a similar glyceric acid linker. Our assumption is that an important structural feature 'borrowed' from a transglycosylase inhibitor should also be helpful to the transglycosylase inhibiting effect of the vancomycin carbohydrate portion. In addition, the added polarity of this acid linker

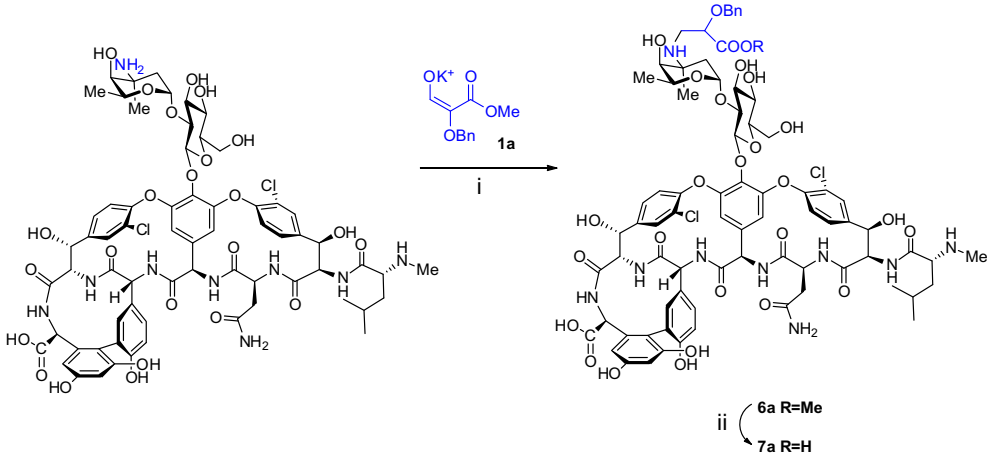
Table 1
Synthesis of various methyl 2-aloxy-3-oxo-propanoates[a]

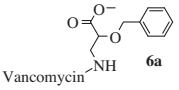
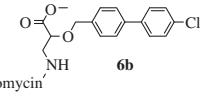
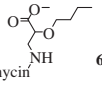
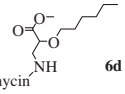


Entry	R=	Product	Yield (%)
1	Benzyl	 **1a**	63
2	Chlorobiphenyl methyl	 **1b**	79
3	*n*-Butyl	 **1c**	66
4	*n*-Hexyl	 **1d**	55

[a] Reagents and conditions: (a) chloroacetic acid, NaH, THF; (b) $SOCl_2$, MeOH; (c) KO^{t}Bu, methyl formate, ether.

Table 2
Synthesis of targeted vancomycin derivatives[a]



Entry	Substrates	Reaction conditions	Products	Yield (%)
1	**1a**	$NaBH(OAc)_3$/DMF	 **6a**	0
2	**1a**	$NaBH(OAc)_3$/DMF	**6a**	0
3	**1a**	$NaBH_3CN$/DMF	**6a**	0
4	**1a**	$NaBH_3CN$/DMF/AcOH	**6a**	62
5	**1b**	$NaBH_3CN$/DMF/AcOH	 **6b**	54
6	**1c**	$NaBH_3CN$/DMF/AcOH	 **6c**	80
7	**1d**	$NaBH_3CN$/DMF/AcOH	 **6d**	68

[a] Reagents and conditions: (i) $NaBH_3CN$, DMF/AcOH = 1:1, 80 °C; (b) LiOH·H_2O, THF/H_2O.