Synthesis and Antibacterial Activity of Derivatives of the Glycopeptide Antibiotic A-40926 *N*-alkylated at the Aminoglucuronyl Moiety

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In the last few years, chemical modification of glycopeptide antibiotics has been directed to the derivatives which would be active against highly glycopeptide-resistant (VanA) enterococci while retaining activity against susceptible Gram-positive bacteria including methicillin-resistant and coagulase-negative staphylococci[1]. To date the most promising results have been obtained by the reductive alkylation of antibiotic LY264826 with various lipophilic aldehydes[2]. *N*-(*p*-Phenylbenzyl), *N*-(*n*-decyl), *N*-(*p*-chlorobenzyl) and some other derivatives of LY264826 alkylated at the amino sugar disaccharide branch had demonstrated activity against both glycopeptide-resistant and susceptible Gram-positive bacteria.

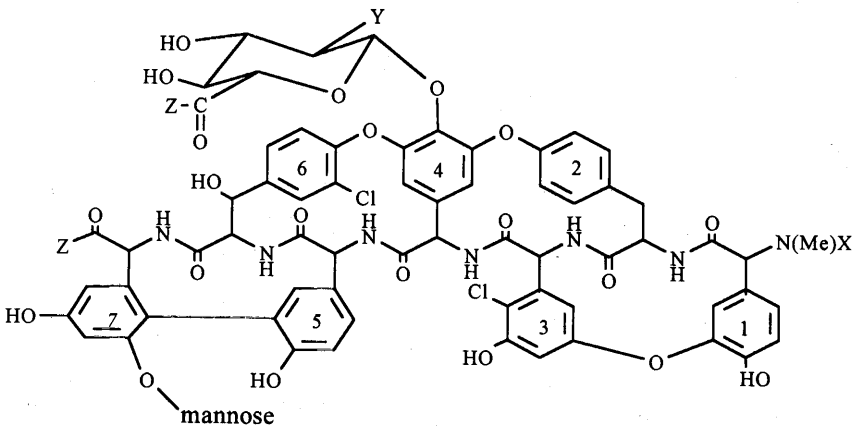
Here we report the application of the above approach to the derivatization of the glycopeptide antibiotic A-40926 (I)[3,4]. I is a complex of three main factors which differ in the fatty acid chains attached to a 2-aminoglucuronyl residue (Fig. 1, Table 1; shown is the main factor B, whose content in complex is about 70%). The nitrogen atom at the *N*-terminus of the peptide in A-40926 and its derivatives is designated as *N*, the nitrogen atom in the 2-aminoglucuronyl residue is designated as *N'*. Recently, *N'*-deacylation of A-40926 by microbial transformation with *Actinoplanes teichomyceticus* ATCC 31121 has been described[5]. *N*-Boc-*N'*-deacyl-A-40926 (III) was obtained by a similar procedure from *N*-Boc-A-40926 (II).

III is a suitable starting material for the preparation of derivatives containing different alkyl or aralkyl substituents at the amino group of the carbohydrate moiety. Besides, two carboxyl groups of III afford additional possibilities for chemical transformations, *e.g.* transfer to various carboxamides and esters.

The reductive alkylation of III with *p*-chlorobenzyl, *p*-phenylbenzyl or decyl aldehydes (1.5 eq.) in the presence of $NaBH_3CN$ (2 eq.) in MeOH and followed by deprotection with TFA produced corresponding *N'*-monoalkyl derivatives V, VI, and VII. For the synthesis of a *N'*,*N'*-didecyl derivative VIII, 5 eq. of decyl aldehyde and 6 eq. of $NaBH_3CN$ were used.

A series of di-(3-dimethylaminopropyl)amides (IX, X, XI and XII) were obtained by the amidation of *N*-Boc-*N'*-alkyl derivatives with 3-dimethylaminopro-

Fig. 1.



A-40926 (I) (factor B): X= H, Y= $NHCO(CH_2)_8CH(Me)_2$, Z=OH
N-Boc-A-40926 (II): X=Boc, Y=$NHCO(CH_2)_8CH(Me)_2$, Z=OH
N-Boc-*N'*-deacyl-A-40926 (III): X=Boc, Y=NH_2, Z=OH

Table 1. Derivatives of A-40926 (X=H). Structures and antibacterial activity *in vitro* (MIC, μg/ml)[a].

Compound	Y	Z	Molecular formula	ESI-MS data MW	Staphylococci clinical isolates			VanA enterococci	
					S. aureus L561	*S. epidermidis* L533	*S. haemolyticus* L602	*E. faecalis* L560	*E. faecium* L569
I[b]	$NHCO(CH_2)_8CH(Me)_2$	OH	$C_{83}H_{88}N_8O_{29}Cl_2$	—	8	16	32	>128	>128
IV	NH_2	OH	$C_{71}H_{66}N_8O_{28}Cl_2$	—	32	32	32	>128	>128
V	$NHCH_2C_6H_4Cl$-*p*	OH	$C_{78}H_{71}N_8O_{28}Cl_3$	1672.3	2	0.13	16	>128	>128
VI	$NHCH_2C_6H_4C_6H_5$-*p*	OH	$C_{84}H_{76}N_8O_{28}Cl_2$	1714.5	8	8	32	>128	>128
VII	$NHC_{10}H_{21}$	OH	$C_{81}H_{86}N_8O_{28}Cl_2$	1688.5	8	2	0.25	32	>128
VIII	$N(C_{10}H_{21})_2$	OH	$C_{91}H_{106}N_8O_{28}Cl_2$	1828.7	32	8	16	8	>128
IX	$NHCH_2C_6H_4Cl$-*p*	$NH(CH_2)_3N(Me)_2$	$C_{88}H_{95}N_{12}O_{26}Cl_3$	1840.5	1	0.25	0.25	128	64
X	$NHCH_2C_6H_4C_6H_5$-*p*	$NH(CH_2)_3N(Me)_2$	$C_{94}H_{100}N_{12}O_{26}Cl_2$	1882.5	2	0.13	0.13	128	128
XI	$NHC_{10}H_{21}$	$NH(CH_2)_3N(Me)_2$	$C_{91}H_{110}N_{12}O_{26}Cl_2$	1856.7	0.5	0.13	0.13	64	32
XII	$N(C_{10}H_{21})_2$	$NH(CH_2)_3N(Me)_2$	$C_{101}H_{130}N_{12}O_{26}Cl_2$	1996.5	8	2	0.25	64	>128

[a] Methods of determination of antibacterial activity *in vitro* and the bacterial strains used were described in a previous paper[7].
[b] Structure and molecular formula are presented for the main factor B.

pylamine (2.2 eq.) and PyBOP (2.5 eq.) as a condensing agent in DMSO followed by deprotection with TFA. Reductive alkylation, amidation and deprotection were performed in 90~95% yields. The resulting compounds were purified using column chromatography on Sephadex LH-20 as previously described[6]. The progress of the reactions, column eluates and the purity of the final compounds were checked by TLC in systems: EtOAc-*n*-PrOH-25% NH_4OH 1:1:1 or 2:1:1 and *n*-BuOH-AcOH-H_2O 5:1:1. The structures of the products were confirmed by ^1H NMR and ESI-MS spectrometry.

Antibacterial activity *in vitro* data are presented in Table 1. The substitution of fatty acid chains in I by alkyl (VII and VIII) or aralkyl (V and VI) residues differently affects the antibacterial activity. Among the *N'*-alkylated compounds V~VIII, the *p*-$ClC_6H_4CH_2$ group-containing derivative V was the most active against the *S. aureus* and *S. epidermidis* clinical isolates. However, similarly to I, compound V showed poor activity against *S. haemolyticus*. In contrast, *N'*-deacyl-*N'*-decyl-A-40926 (VII) was more active than I against *S. haemolyticus* and *S. epidermidis* but had a low activity against *S. aureus*. *N'*,*N'*-Didecyl (VIII) and *N'*-*p*-phenylbenzyl (VI) derivatives as well as I had poor activity against clinical isolates of staphylococci. As expected, diamides IX, X, XI, and XII were more active than the corresponding starting *N'*-alkyl derivatives V, VI, VII, and VIII, the $C_{10}H_{21}$ moiety-containing diamide XI being the most active among the above compounds. Compound XI had excellent activity against all susceptible Gram-positive bacteria tested, including clinical isolates of coagulase-negative staphylococci. Similar regularities were earlier demonstrated for the *N'*-decyl-containing eremomycin and teicoplanin aglycon derivatives, which were the most active among the modified derivatives investigated[6,7]. Unfortunately, among A-40926 derivatives, there were no compounds with significant activity against VanA enterococci. The compound VIII with MIC value equal to 8 μg/ml against VanA *E. faecalis* was an exception, but it was inactive against VanA *E. faecium*.

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