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Synthesis and Antibacterial Evaluation of Novel Vancomycin Derivatives Containing Quaternary Ammonium Moieties

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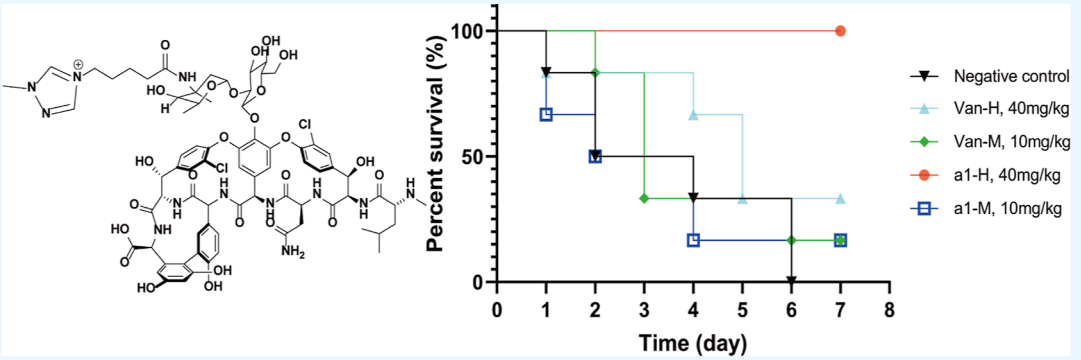

ABSTRACT: A series of novel vancomycin analogues with quaternary ammonium moieties have been designed and synthesized for fighting with clinically isolated drug-resistant bacteria. Partial target molecules exhibited potent activity against the tested strains. Among all of the compounds, a triazole quaternary ammonium vancomycin (QAV) derivative QAV-a1 exerted the best antibacterial activities. QAV-a1 was found to be 4- to 32-fold more efficacious than vancomycin against MRSA. Meanwhile, QAV-a1 showed a good pharmacokinetic profile with a half-life of 5.19 ± 0.10 h, which is longer than that of vancomycin (4.3 ± 1.9 h). These results provided guidance for the further exploitation of vancomycin derivatives against drug-resistant bacteria.

1. INTRODUCTION

Vancomycin has been a vital weapon in the arsenal of antibiotics to treat Gram-positive bacterial infection since its discovery in the 1950s. It was considered as the last resort for the treatment of serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[1−3] Vancomycin inhibits bacterial cell−wall biosynthesis by binding to a D-Ala-D-Ala terminus of peptidoglycan pentapeptide through five hydrogen bonds and eventually leading to cell death. However, with extensive use of vancomycin, bacteria gradually evolved drug resistance against its mode of action. The main mutation is that bacteria remodel their peptidoglycan pentapeptide terminus from D-Ala-D-Ala to D-Ala-D-Lac. This modification lessens the binding affinity of vancomycin to its target and results in >1000-fold loss of antibacterial activity.[4−6] The spread of those drug-resistant pathogens caused serious social concerns, and development of new antibiotics has become an urgent need.[7,8]

Semisynthetic approaches involving structural modifications proved to be promising strategies to tackle this resistance problem.[9−11] It could lead to an additional mechanism of action, which result in improved antibacterial efficacy against resistant bacteria. Recent studies have shown that moieties with positive charges conjugated to vancomycin can confer corresponding vancomycin derivatives with membrane-disruptive properties, which together with vancomycin's inherent hydrogen bond bindings can enhance antibacterial efficacy (Figure 1).[12−17] Herein, we designed and synthesized a series of novel vancomycin derivatives carrying different quaternary ammonium moieties (Scheme 1). The in vitro and in vivo antibacterial activities against clinically isolated drug-resistant bacteria were evaluated. Pharmacokinetics and acute toxicology studies were performed to validate its safety profile. We also investigated the binding mode by molecular docking to illustrate its possible mechanism.

2. RESULTS AND DISCUSSION

2.1. Chemistry. We synthesized five sets of QVAs, as illustrated in Scheme 1. Quaternary ammonium 1a−5d were prepared under the following procedure. Bromocarboxylic acid was refluxed with pyridine, *N*,*N*-dimethyl-1-phenylmethanamine, 1-methyl-1*H*-1,2,4-triazole, 4-methyl morpholine, and trimethylamine in THF for 4−12 h, respectively. QVAs (1−

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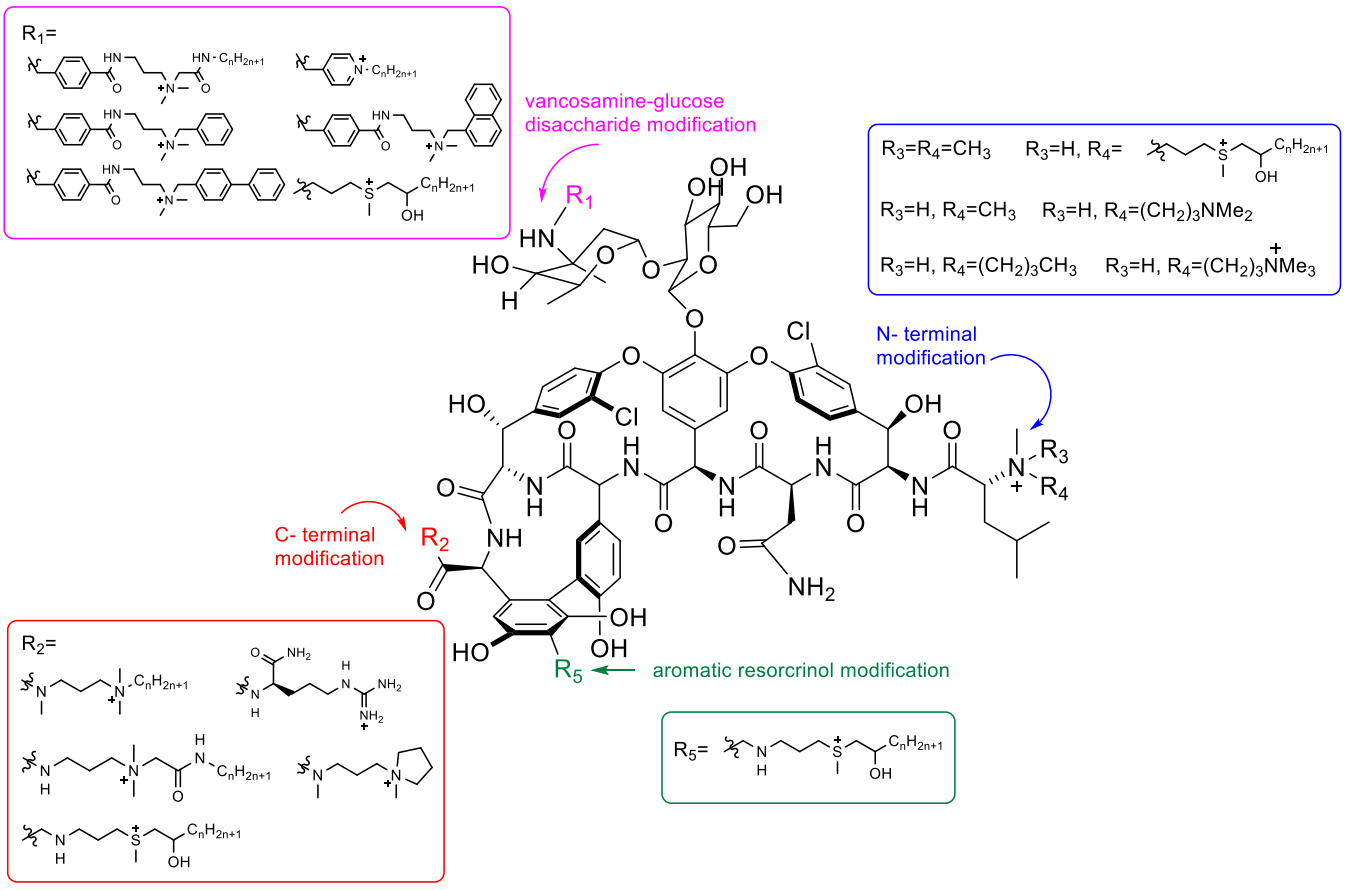

Figure 1. Reported vancomycin derivatives with cationic moieties.

20) were prepared by coupling the amino group of vancomycin with cationic moieties. Then, we applied two methods to couple the amino group of vancomycin with cationic moieties 1a−5d to prepare QVAs (1−20). At first, we used coupling agent *N*,*N*,*N*′, *N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)-uronium hexafluorophosphate (HBTU) to prepare QVAs as route 2 in Scheme 1. This method produced impurities, which in turn made the purification of the product difficult. Route 1 was using *N*-hydroxysuccinimide (NHS) and *N*,*N*′-diisopropylcarbodiimide (DIC) to prepare activated cationic moieties 6a−10d, which conjugated to vancomycin subsequently. A high-performance liquid chromatography (HPLC) monitor showed that the coupling reaction of route 1 was cleaner than route 2 (Figure S1). Although route 1 was one more reaction step than route 2, the cleaning of the conjugation step was beneficial for the further purification of final analogues. Thus, we used route 1 in Scheme 1 to prepare QVAs (1−20). All the derivatives of vancomycin were purified by reversed-phase high-performance liquid chromatography (RP-HPLC).

2.2. In Vitro Antibacterial Activity Assay. In vitro antibacterial activity data (Table 1) showed that among the pyridine quaternary ammonium vancomycin (QAV) derivatives, compound QAV-p1 with a five-carbon length side chain showed the best activity, which was 4- to 8-fold higher activity against MRSA than the control drug. Compound QAV-p2 had a MIC_{50} value of 32 μg/mL against MRSA2, which was higher than vancomycin (MIC > 512 μg/mL). QAV-p3 showed higher activity against MRSA4 and MRSA5, which was 4 and 8 times better than vancomycin, respectively. QAV-p4 showed 2- to 8-fold enhancement activity as compared to the control drug. Among *N*,*N*-dimethylbenzylamine QAV derivatives, QAV-b1 had a MIC value of 32 μg/mL against MRSA5, which was 8 times higher than vancomycin. QAV-b3 and QAV-b4 with longer side chains exhibited better activity than shorter side chain derivatives, especially compound QAV-b4 showed better activity against all five clinical strains, which was 4−16 times that of vancomycin. Among the 1-methyl-1,2,4-triazole QAV derivatives, QAV-a1 with a chain length of five-carbon atoms showed an up to 32-fold increase in activity against MRSA1 with a MIC value of 8 μg/mL as compared to vancomycin (256 μg/mL). Its MIC value against MRSA2 was 16 μg/mL, while the MIC value of vancomycin was >512 μg/mL. QAV-a2, QAV-a3, and QAV-a4 exhibited better activity than the control drug against MRSA. The antibacterial activity of QAV-a2 against MRSA5 was 8 times that of vancomycin. QAV-a3 showed 8-fold enhancement activity against MRSA1 as compared to vancomycin. Among the *N*-methylmorpholine-QAV derivatives, QAV-m4 showed 8-fold enhancement in antibacterial activity, with a MIC value of 64 μg/mL against MRSA3. QAV-m2 and QAV-m3 had better activity than the control drug against MRSA4, and the MIC value was eight times that of vancomycin. However, QAV-m1, QAV-m2, and QAV-m3 had the same MIC value of 512 μg/mL as vancomycin against MRSA3. Among the trimethylamine QAV derivatives, QAV-t1 had a MIC value of 32 μg/mL against MRSA1, which was 8 times that of vancomycin, and the MIC value of antibacterial activity against MRSA2 was 64 μg/mL, while the MIC of vancomycin was >512 μg/mL. The antibacterial activity of QAV-t2 against MRSA3 and MRSA5 was 8 times higher than that of vancomycin, and its

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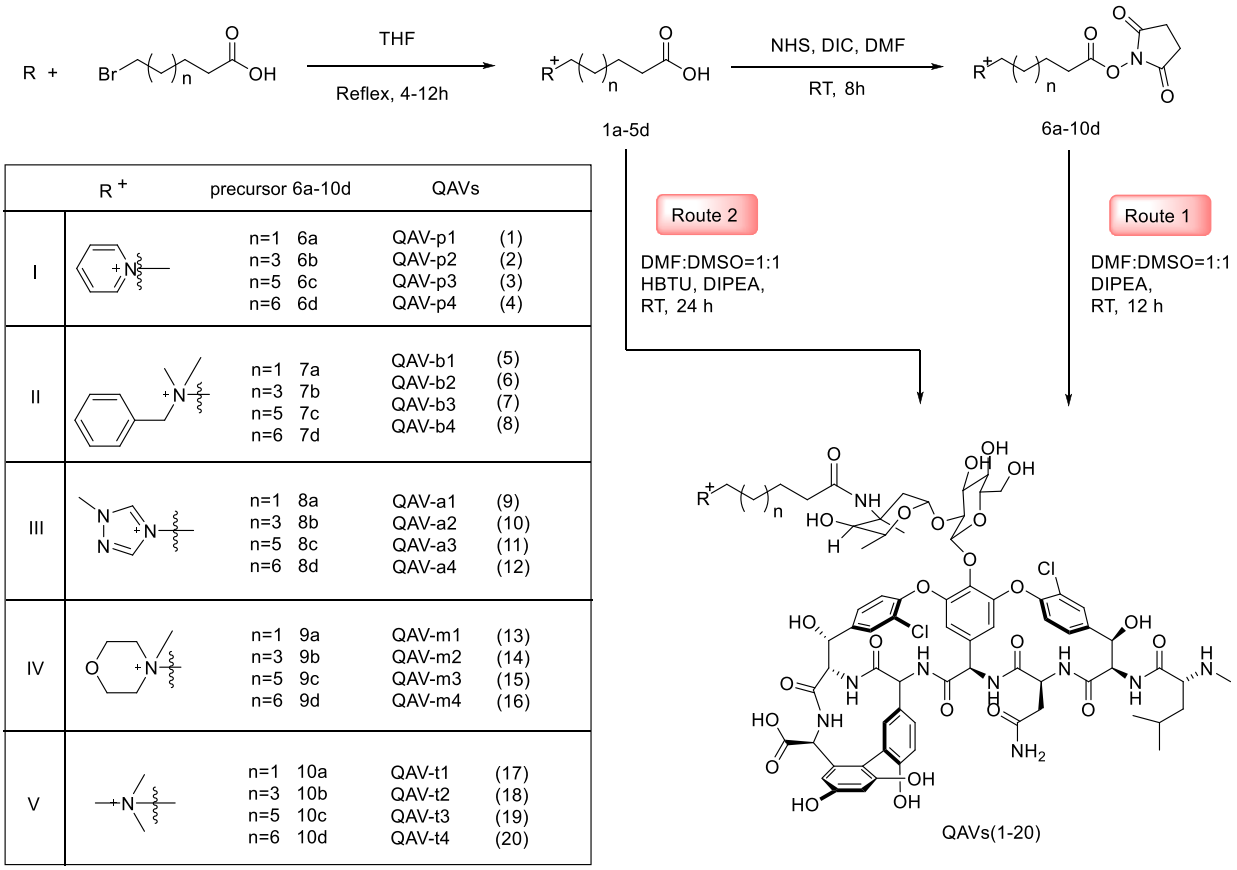
Scheme 1. Synthesis of QAV Analogues (1−20)



	R+	precursor 6a-10d	QAVs	
I		n=1 6a n=3 6b n=5 6c n=6 6d	QAV-p1 QAV-p2 QAV-p3 QAV-p4	(1) (2) (3) (4)
II		n=1 7a n=3 7b n=5 7c n=6 7d	QAV-b1 QAV-b2 QAV-b3 QAV-b4	(5) (6) (7) (8)
III		n=1 8a n=3 8b n=5 8c n=6 8d	QAV-a1 QAV-a2 QAV-a3 QAV-a4	(9) (10) (11) (12)
IV		n=1 9a n=3 9b n=5 9c n=6 9d	QAV-m1 QAV-m2 QAV-m3 QAV-m4	(13) (14) (15) (16)
V		n=1 10a n=3 10b n=5 10c n=6 10d	QAV-t1 QAV-t2 QAV-t3 QAV-t4	(17) (18) (19) (20)

Table 1. In Vitro Antibacterial Activity of QVAs (1−20) against Clinically Isolated Multidrug-Resistant Gram-Positive Bacteria

	MIC (μg/mL)									
compound	MRSA1	MRSA2	MRSA3	MRSA4	MRSA5	VRE1	VRE2	VRE3	VRE4	VRE5
QAV-p1	64	64	64	64	64	>512	512	>512	>512	512
QAV-p2	128	32	64	128	64	>512	512	512	>512	512
QAV-p3	256	512	512	64	32	>512	512	>512	128	>512
QAV-p4	64	128	64	128	32	>512	512	256	>512	>512
QAV-b1	64	512	512	64	32	>512	512	256	512	>512
QAV-b2	256	512	512	256	256	>512	512	512	512	>512
QAV-b3	64	64	64	128	64	>512	512	256	>512	>512
QAV-b4	64	64	32	32	16	>512	512	>512	>512	512
QAV-a1	8	16	32	64	64	>512	512	>512	>512	512
QAV-a2	256	512	512	64	32	>512	512	>512	512	512
QAV-a3	32	512	512	64	64	>512	512	256	512	>512
QAV-a4	64	512	512	256	64	>512	512	512	512	>512
QAV-m1	64	512	512	256	256	>512	512	256	512	>512
QAV-m2	128	64	512	32	64	>512	512	256	>512	>512
QAV-m3	64	64	512	32	32	>512	512	512	>512	>512
QAV-m4	128	64	64	128	64	>512	512	>512	>512	512
QAV-t1	32	64	512	128	32	>512	512	>512	128	512
QAV-t2	128	64	64	64	32	>512	512	512	>512	>512
QAV-t3	128	64	32	64	64	>512	512	256	>512	512
QAV-t4	128	64	512	32	64	>512	512	256	>512	>512
vancomycin	256	>512	512	256	256	>512	256	512	512	>512

antibacterial activity against MRSA4 was 4 times higher than that of vancomycin. The antibacterial activity of QAV-t3 was comparable to that of QAV-t2, and the best antibacterial activity was against MRSA3 with a MIC value of 32 μg/mL, which was 32 times that of vancomycin. QAV-t4 showed 8-fold increased activity against MRSA2 and MRSA4 as compared to vancomycin, and the antibacterial activity against MRSA3 was the same as that of the control.

In vitro, the antibacterial activity test showed that the introduction of quaternary ammonium cations into vancomy-

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cin is beneficial to improve the antibacterial activity against MRSA. Moreover, the cation containing nitrogen heteroatoms was more helpful for the improvement of antibacterial activity. Among these compounds, QAV-a1 resulted in the highest activity with up to 32-fold enhancement in activity against MRSA. Additionally, almost all compounds showed activity similar to that of vancomycin against VRE. Only part of the compounds showed potential antibacterial activity against part of the tested VRE strains. QAV-p3 and QAV-t1 showed the same MIC of 128 μg/mL against VRE4.

2.3. In Vivo Activity Assay. We further investigated in vivo activity of QAV-a1 (Figure 2 and Table 2). According to

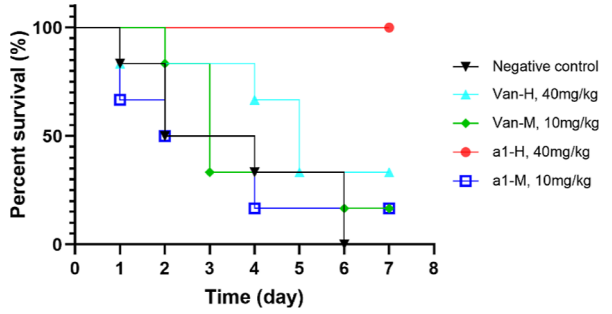

Figure 2. Survival chart of MRSA1 infected mice after treatment with QAV-a1.

Table 2. Number of Mice Surviving and Final Survival Rate after the Administration of QAV-a1

			vancomycin (mg/kg)			QAV-a1 (mg/kg)		
day	control	model	40	10	2.5	40	10	2.5
day0	6	6	6	6	6	6	6	6
day1	6	5	5	6	3	6	4	2
day2	6	3	5	5	2	6	3	1
day3	6	3	5	2	2	6	3	1
day4	6	2	4	2	2	6	1	1
day5	6	2	2	2	1	6	1	0
day6	6	2	2	1	1	6	1	0
day7	6	0	2	1	0	6	1	0
survival (%)	100	0	33.3	16.7	0	100	16.7	0

the test, all of the mice died gradually within 7 days in the model group. The survival rate of QAV-a1 in the low-dose (2.5 mg/kg) and medium-dose (10 mg/kg) groups was the same as the survival of vancomycin. In sharp contrast, the high-dose (40 mg/kg) QAV-a1 and vancomycin treatments afforded a high survival rate of infected mice, 100 and 33.3%, respectively. It showed that the in vivo antibacterial activity of QAV-a1 was higher than vancomycin in the high-dose group. The ED_{50} of QAV-a1 was 21.6 mg/kg, while the ED_{50} of vancomycin was 59.7 mg/kg. The result indicated that a single administration of high-dose QAV-a1 was more effective in vivo than vancomycin against the clinically isolated strain. In addition, we further performed histological analysis of pathological tissues using hematoxylin−eosin (H&E) staining. H&E staining revealed that mice in the QAV-a1 low-dose and medium-dose administration groups, vancomycin (low-, medium-, and high-dose) administration group, and model group had a severe kidney infection, while mice treated with a high-dose of QAV-a1 had mild kidney infection (Figure S2). It indicated that these kinds of vancomycin derivatives may be more efficient in treatment with kidney infections than vancomycin.

2.4. Pharmacokinetic Assay. Concentration−time profiles in plasma are presented in Table 3 and Figure 3. The

Table 3. Plasma Concentrations of QAV-a1 Administration Intravenous in SD Rat (μg/mL)

	QAV-a1			
time (h)	rat 1	rat 2	rat 3	mean ± SD
0.0833	5.53	7.98	8.89	7.47 ± 1.74
0.17	3.57	4.86	5.86	4.76 ± 1.15
0.25	3.49	4.68	5.07	4.41 ± 0.82
0.5	3.09	3.6	3.5	3.40 ± 0.27
0.75	2.64	3.4	3.41	3.15 ± 0.44
1	2.43	2.86	3.51	2.93 ± 0.54
2	1.72	2.69	2.24	2.22 ± 0.49
4	1.26	1.95	2.09	1.77 ± 0.44
6	0.995	1.94	1.78	1.57 ± 0.51
24	0.0919	0.147	0.143	0.13 ± 0.03

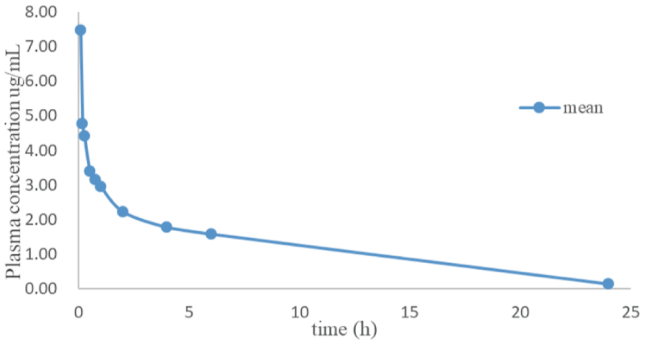

Figure 3. Concentration−time curve of QAV-a1 administrated intravenously.

pharmacokinetics of intravenously administered QAV-a1 showed (Table4) that compound QAV-a1 displayed a longer half-life ($T_{1/2}$) of 5.19 ± 0.10 h than vancomycin ($T_{1/2}$ = 4.3 ± 1.9 h), a slow clearance rate of 1.42 L/h/kg, and high AUC value of 28.95 μg/mL h.[18,19] Its maximal concentration (C_{max}) was 7.47 μg/mL. The above pharmacokinetic results indicate that these kinds of quaternary ammonium derivatives may be worth further study.

2.5. Acute Toxicity Study. An acute toxicity study of QAV-a1 was also carried out (Table 5). No mice died after receiving 45 mg/kg QAV-a1 by intravenous administration, when the dosage was raised to 75 mg/kg, all of the mice died. The result showed a regular dose-dependent increase in mortality. Its LD_{50} value was determined to be 60.5 mg/kg (95% confidence limit: 57.492−63.514 mg/kg).

2.6. Molecular Docking Analysis. Using our constructed structures of QAV-a1 and peptidoglycan, the molecular docking study was performed to investigate the binding mode and possible sites between active compound QAV-a1 and peptidoglycan. Molecular docking analysis was carried out on Sybyl 6.9 and AutoDock 4.2 software. The result was shown that active compound QAV-a1 formed seven H-bonds with peptidoglycan. Five of them are similar to the binding mode of vancomycin (Figure 4a), including three H-bonds between the amide protons (NH2−NH4) and the carboxyl oxygen on the C-terminus of the D-Ala-D-Ala segment (distance), one H-bond between the carbonyl oxygen on aglycon (CO4) and an amide

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Table 4. Pharmacokinetic Profile of QAV-a1 in SD Rat[a]

	$AUC_{(0-t)}$ (μg/mL h)	$AUC_{(0-\infty)}$ (μg/mL h)	$t_{1/2}$ (h)	CL (L/h/kg)	Vss (L/kg)	C_{max} (μg/mL)
1	20.17	20.87	5.27	1.92	11	5.53
2	34.05	35.18	5.22	1.14	6.8	7.98
3	32.63	33.68	5.08	1.19	6.95	8.89
mean	28.95	29.91	5.19	1.42	8.25	7.47
SD	7.64	7.86	0.10	0.44	2.38	1.74

[a]$AUC_{(0-t)}$, area under the concentration−time curve up to the last sample time; $AUC_{(0-\infty)}$, area under the concentration−time curve up to infinity time; $t_{1/2}$, half-time; CL, clearance; Vss, volume of distribution at steady state; and C_{max}, peak plasma concentration.

Table 5. In Vivo Acute Toxicity Study of QAV-a1

dosage (mg/kg)	number of animal	death	death percent (%)
75	10	10	100
70	10	9	90
65	10	7	70
60	10	4	40
55	10	2	20
50	10	1	10
45	10	0	0

proton of the terminal D-Ala, and a fifth H-bond between the amide proton of the seventh residue of aglycon (NH7) and the carbonyl oxygen of the L-Lys.[20] Meanwhile, QAV-a1 is able to enhance its binding ability by forming two new hydrogen bonds (3.7, 3.9 Å) with the glycine bridge $(Gly)_5$ backbone of the receptor through carboxyl groups (Figure 4b). In addition, the triazole hydrophobic substituent of the amino-saccharide part can enhance the binding interaction by forming hydrophobic interactions and van der Waals forces with the glycine bridge of the receptor. These binding modes might account for the higher binding capacity of compound QAV-a1 with peptidoglycan.

3. EXPERIMENTAL SECTION

3.1. General Information. Chemical reagents were purchased from Sigma-Aldrich, TCI Chemicals, and used without further purification. Vancomycin for synthesis was purchased from Huashan Hospital in Shanghai. All the reaction solvents were purchased from commercial suppliers, purified, and dried in accordance with standard procedures before being used. Reactions were monitored with analytical thin-layer chromatography (TLC) and RP-HPLC (Waters e2695) using a C18 column. Solvent systems were buffer A (0.1% TFA in CH_3CN) and buffer B (0.1% TFA in water). NMR spectra were recorded using a Bruker DRX-400 (400 MHz for ^1H) and Bruker DRX-600 (600 MHz for ^{12}C) in deuterated solvents. Tetramethylsilane (TMS) was used as the internal standard. Chemical shifts (δ) were recorded in parts per million (ppm) and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Low-resolution mass spectra (EST) were obtained using a Shimadzu LCMS-2012EV. High-resolution mass spectra were obtained from a IonSpec4.7 TFTMS (MALDI) or Bruker Daltonics APEX-III7.0 TESLA FMS (ESI).

3.2. General Procedure of Method for the Synthesis of 6a−10d. 5-Bromopentanoic acid (180 mg, 1.00 mmol) was dissolved in 5 mL pyridine and stirred at 80 °C for 7 h. When the reaction was completed, the reaction mixture was cooled to room temperature and evaporated under reduced pressure to obtain a crude product. Then, it was washed with dichloromethane three times to obtain 1-(4-carboxybutyl)pyridin-1-ium (1a, 173 mg) with 96.1% yield. To a mixture of 1-(4-carboxybutyl)pyridin-1-ium (100 mg, 0.56 mmol) and *N*-hydroxysuccinimide (NHS, 96.7 mg, 0.84 mmol) in 5 mL DMF, *N*,*N*′-diisopropylcarbodiimide (DIC, 143.3 mg, 1.12 mmol) was added, and the solution was stirred at room temperature for 4 h. When the reaction was completed, 15 mL ethyl ether was added. Then, the organic layer was abandoned, and the crude product was obtained. It was further purified by column chromatography to give 114.9 mg 1-(5-((2,5-dioxopyrrolidin-1-yl)oxy)-5-oxopentyl)pyridin-1-ium (6a)

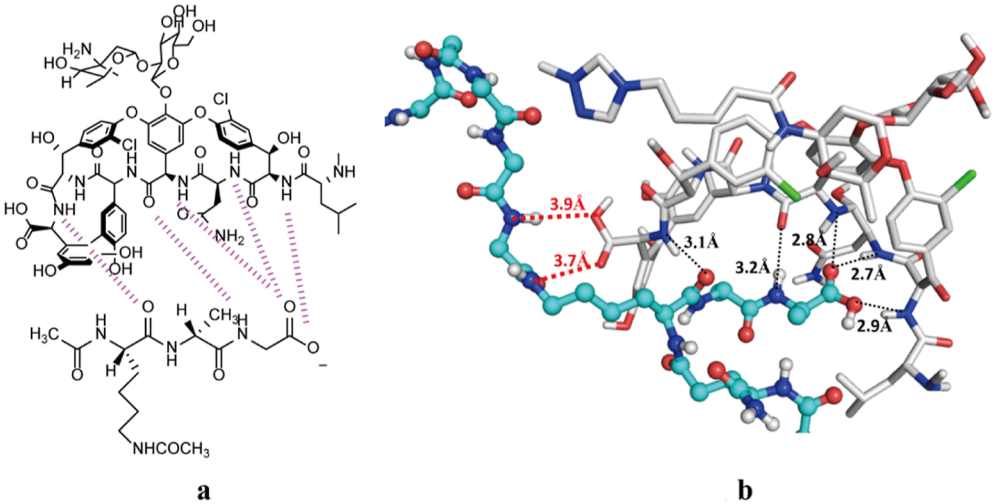

Figure 4. (a) Molecular interaction of vancomycin with D-Ala-D-Ala termini and (b) binding mode of QVAs-a1 with a D-Ala-D-Ala terminus of pentapeptide.

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ACS Omega 2023, 8, 28511−28518

with a 74% yield.[21−23] The quaternary ammonium modifications 6b−10d were synthesized by a similar procedure in 60−90% yield.[24−27]

3.3. General Procedure of Method for the Synthesis of QAVs, (1−20. To a solution of vancomycin (100 mg, 0.0673 mmol, 1.0 equiv) and DIEA (43.5 mg, 0.336 mmol, 5.0 equiv) in DMF (1 mL) and DMSO (1mL), the respective quaternary ammonium (6a−10d, 2.0 equiv) was added. The reaction mixture was stirred at room temperature for 8 h. When the reaction was completed, 3−5 times volume of anhydrous ethyl ether was added to afford the crude product as a precipitate. Pure products were isolated by purification using preparative RP-HPLC (gradient: 10−55% acetonitrile/water and 0.1% TFA, 30 min). The combined fractions were concentrated and lyophilized to afford a white solid powder.

3.4. In Vitro Antibacterial Activity. The antibacterial activities of the compounds are evaluated as their MIC, which is the minimum inhibitory concentration of the antibacterial agent at which no growth of bacteria is observed. All the synthesized compounds (1−20) were assayed using an agar dilution method as per the CLSI guideline.[28] Compound stock solutions (320 μg/mL) were prepared in DMSO/H_2O (V/V = 1:1). Clinical isolates of MRSA and VRE were obtained as a gift from the Shanghai Huashang Hospital for an antibacterial assay. Serial twofold dilutions prepared from the stock solutions with sterile H_2O were diluted tenfold with a Mueller−Hinton agar medium to obtain a concentration range of 0.024−50 μg/mL. The test organisms were incubated for 8 h at 35 °C in a Mueller−Hinton broth medium and were adjusted to a turbidity of 0.5 using the McFarland standard. The bacterial suspensions were seeded into the drug-supplemented Mueller−Hinton agar plates and incubated for 16 h at 35 °C.

3.5. In Vivo Antibacterial Activity. In vivo studies were carried out in the Shanghai Institute of Pharmaceutical Industry according to the relevant guidelines and regulations. The in vivo efficacies of QAV-a1 and vancomycin were investigated against MRSA1. Six-to-eight week female BALB/c mice (18−22 g) were used in vivo antibacterial experiments and divided into the negative control (model), positive control, and treated group. As per the standard protocol, the animals were placed in individual cages within a standard environment and housed under specific pathogen-free conditions. The infection model employed clinically isolated strain MRSA1, which was received from the Shanghai Huashan Hospital. A bacterial culture in a Columbia broth was diluted to OD_{600nm} = 1.5 to yield a bacterial suspension. 0.1 mL suspension was injected via a tail vein. One hour after injection of bacterial suspension, the test compound (QAV-a1) and positive-control compound (vancomycin) were injected at doses of 2.5, 10, and 40 mg/kg via the tail vein, respectively. Animals were monitored for 7 days. The number of dead mice caused by infection was recorded every day and used for the creation of the survival curve.

3.6. In Vivo Pharmacokinetic Assay. SD rats were used in pharmacokinetic research, and the animal room environment was controlled under standard conditions. Mice were administered a single intravenous dose of 40 mg/kg QAV-a1. Blood samples were collected at 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, and 24 h after intravenous administration. Serum samples were obtained through common procedures and the concentrations of compound in the supernatant were analyzed by an API-4000 mass spectrometer (Applied Biosystems, USA) with an Analyst 1.4.1 system (Applied Biosystems, USA). The Venusil XBP Phenyl C18 column (100 mm × 2.1 mm, 5 μm) was used for analysis. After analyzing the concentrations of the compound, the values of $T_{1/2}$, T_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, CL, Vss, and C_{max} were calculated from time−concentration curves.

3.7. In Vivo Acute Toxicity. The acute toxicity was performed with ICR mice (18−22 g). Mice were randomly assigned into 7 treatment groups (n = 10/group, 5 male and 5 female), acclimatized for 7 days, and fasted for 2 h prior to treatment administration. Then, compound QAV-a1 was given to mice intravenously at doses of 45, 50, 55, 60, 65, 70, and 75 mg/kg. The number of surviving mice in each group was monitored for 14 days after treatment. The values of LD_{50} were calculated using the Bliss method.

3.8. Molecular Docking Study. Molecular docking was performed with automated molecular docking program AutoDock 4.2 according to our previous study.[29,30] The three-dimensional structure of QAV-a1 was constructed with sketching tools Sybyl 6.9 encoded in Discovery Studio 3.5 software package using the crystal structure of vancomycin (PDB: 1FVM) as a template. A three-dimensional structure of peptidoglycan was constructed and optimized using the AMBER force field. The energy minimization was conducted for both ligands and receptors by using the Powell method with Tripos and MMFF94 charges for 1000 steps by means of Sybyl 6.9 software, respectively. During the docking process, the number of generations, energy evaluation, and docking runs were set to 380,000, 1,500,000, and 10, respectively. The atom type, generations, and number of runs for the LGA algorithm were edited and assigned according to the requirement of the AMBER force field. The optimal binding conformations were selected considering the low binding energy and geometrical complementarity.

4. CONCLUSIONS

In summary, a series of novel QAV analogues have been designed and synthesized. We evaluated them with clinically isolated drug-resistant bacteria both in vitro and in vivo. The antibacterial activity data suggested that the introduction of cationic moiety on the amino sugar of vancomycin is an effective approach to overcome resistance in bacteria. Pharmacokinetic and acute toxicity studies showed better pharmacokinetic properties and lower toxicity than vancomycin. This work provides us with clues and guidance for our further investigations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02879.

HPLC monitor of route 1 and route 2; histological analysis of kidney tissues through H&E staining; synthesis and structure characterization of the compound QAVs (1-20); and NMR and MS spectra data (PDF)

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All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

Notes

The authors declare no competing financial interest.

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