# Multivalent Antibiotics via Metal Complexes: Potent Divalent Vancomycins against Vancomycin-Resistant Enterococci

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Dimers of vancomycin (Van), linked by a rigid metal complex, $[Pt(en)(H_2O)_2]^{2+}$, exhibit potent activities (MIC ∼0.8 μg/mL, ∼720 times more potent than that of Van itself) against vancomycin-resistant enterococci (VRE). The result suggests that combining metal complexation and receptor/ligand interaction offers a useful method to construct multivalent inhibitors.



## Introduction

Drug resistance[1] of bacteria poses a serious public health threat and demands effective counter measures. Among promising approaches,[2−8] multi/polyvalency—multiple simultaneous binding of two or more ligands and receptors—is beginning to be explored systematically.[9−18] In the research of multivalency, the ligand−receptor pair of vancomycin (Van)-D-Ala-D-Ala has attracted a great deal of research attention because it relates to vancomycin[19−22]-resistant enterococci (VRE).[23,24] Walsh and colleagues[21,24−27] have deciphered the mechanism of vancomycin resistance: VRE mutates its terminal peptides from D-Ala-D-Ala to D-Ala-D-Lac (i.e., D-alanine-D-lactate), which has substantially lowered (∼$10^3$ times decrease) its affinity to Van.[25,26,28] Though Van self-associates to form homodimers upon binding to D-Ala-D-Ala, as elucidated by Williams et al.,[29−33] this noncovalent dimerization of Van alone is insufficient to act against VRE. Griffin et al.,[17,34] Nicolaou et al.,[15,16,19,20] and an Eli Lilly group[35] have used organic linkers to synthesize dimers of Van, and demonstrated that covalently linked dimeric Vans exhibit enhanced to potent activity against VRE. It was, however, suggested that the flexibility of the organic linker limited the avidity of the multivalent binding due to the loss of conformational entropy upon binding.[9,36,37] We believe that the combination of receptor/ligand interaction and a metal complex, which has special geometry, structural rigidity, and stability, can serve as an alternative approach to minimize the loss of conformational entropy.

To test this strategy, we used a derivative of cisplatin,[38] $[Pt(en)(H_2O)_2]^{2+}$(en: ethylenediamine)—a rigid, square planar metal complex—to form dimeric Vans, and evaluated their activities against VRE. These rigidly linked dimeric Vans exhibit enhanced activities against VRE and are up to ∼720 times more potent against VRE than Van itself in the best case (MIC: 0.8 μg/mL). Our results suggest that combining metal coordination and receptor/ligand interactions[39−42] offers a useful method to construct multivalent receptors.

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## Results and Discussions

We chose $[Pt(en)]^{2+}$ as the rigid linker to form dimeric Van via complexation due to its extensive developed chemistry, well understood properties, and well preserved planar rigidity. Moreover, the ionic nature of the $[Pt(en)]^{2+}$ retains—if not increases—the solubility of Van in aqueous media, which is necessary for in vitro study. As shown in Scheme 1, commercially available vancomycin (**1**) reacted with 3-picolylamine, 4-picolylamine, 3-(2-aminoethyl)pyridine, or 1-(3-aminopropyl)imidazole to give the vancomycin carboxamide derivatives (Van-CONH-L) **2a**−**d** in good yields (>65%), respectively. Compounds **2a**−**d** were purified using reversed-phase HPLC according to modified literature procedure[13] and characterized by high field $^1$H NMR spectroscopy and mass spectrometry (MS). The attachment of the ligands to the C-terminal of Van hardly changes conformation of Van, as indicated by $^1$H NMR—the chemical shifts of the protons belonging to Van on **2a**−**d** remain essentially the same as that in **1**, suggesting that the binding pockets of **2a**−**d** are undisrupted and should function similarly as that of **1**. $[Pt(en)(H_2O)_2]^{2+}$ (**3a**) coordinates with **2a**−**d** to give dimeric Vans **4a**−**d**, and $[Pt(en)(H_2O)(N\text{-pyridin-3-ylmethylacetamide})]^{2+}$ (**3b**) binds to **2a**,**b** to afford monomeric Vans **5a**,**b**.

As shown in Table 1, **2a**−**d** are inactive against VRE, and **3a** or **3b** alone is inactive against both the Van-sensitive strain and VREs (MIC > 128 μg/mL). A simple mixture of Van and $[Pt(en)(H_2O)_2](NO_3)_2$ (**1**+**3a**) or the monovalent complexes of Van and $Pt^{2+}$(**5a** or **5b**) behave similarly to the corresponding monomeric Vans. These results exclude the possibility that enhanced activities of dimeric Vans against VRE originate from some unrelated synergistic effects between monomeric Van and $[Pt(en)]^{2+}$. **4a**−**d** exhibits enhanced activity against VRE in comparison to Van. In fact, **4a** is ∼$10^3$ times more potent against VRE (genotype VanA) than Van itself. In an attempt to form the tetravalent compound, $[Zn(\mathbf{2d})_4]^{10+}$, the activity of the mixture of **2d** and $Zn(OAc)_2$ (4:1, at pH = 7) against VRE is the same as that

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**Scheme 1.** The Structures of Divalent and Monovalent Derivatives of Van

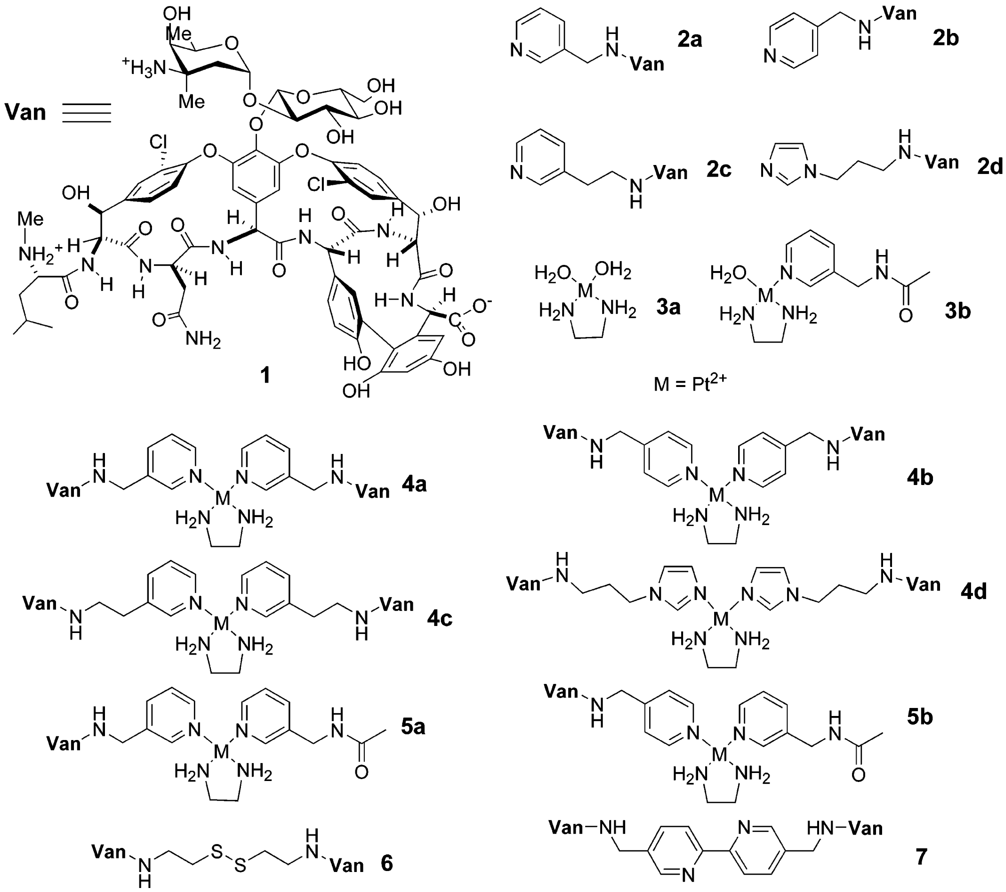



**Table 1.** Antibacterial Activity (MIC: $\mu$g/mL) of Vancomycin Derivatives and Dimeric Vans

| compound | ATCC29212 (sensitive) | *E. gall* (VanC) | *E. faecium* (VanB) | *E. faecalis* (VanA) |
|---|---|---|---|---|
| **1** | 2 | 8 | 102 | 576 |
| **2a** | 2 | 4 | 76.8 | >128 |
| **2b** | 2 | 4 | 70.4 | >128 |
| **2c** | 2 | 2 | 19 | 104 |
| **2d** | 2 | 2 | 22 | 64 |
| **3a** | >128 | >128 | >128 | >128 |
| **3b** | >128 | >128 | >128 | >128 |
| **1+3a** | 4 | 8 | 64 | 160 |
| **4a** | 1 | 0.03 | 0.28 | 0.8 |
| **4b** | 1 | 0.05 | 2 | 14 |
| **4c** | 1 | 1 | 1.2 | 3.3 |
| **4d** | 1 | 1 | 4.8 | 38 |
| **5a** | 1 | 2 | 14 | 84 |
| **5b** | 1 | 2 | 32 | 88 |
| **2d+Zn$^{2+}$** | 1 | 2 | 22 | 60 |
| **6** | 0.5 | 2 | 1 | 4 |
| **7** | 4 | 2 | 1.6 | 5.5 |

of **2d**, suggesting that there is no multivalent Van formed by metal complexation when **2d** and $Zn(OAc)_2$ react at the condition of the in vitro experiment. We also did not observe the formation of $[Zn(\mathbf{2d})_n]^{(2n+2)+}$ ($n$ = 1−4) by ESI-MS, which is consistent with the observed activity.

Figure 1 illustrates the plausible divalent interaction between **4a** and the terminal peptides of peptidoglycan precursors. According to this binding mode, both the configuration and rigidity of the dimeric Vans determine their activities.[34] To further understand the structural-activity relationship, we performed semiquantitative entropy analysis according to the reported methods.[36]

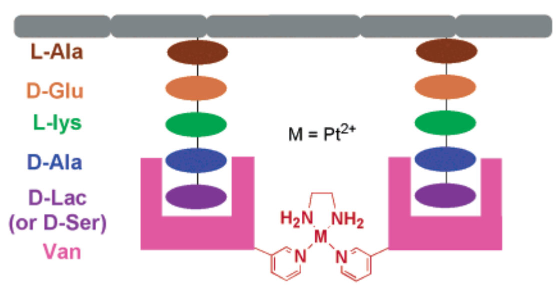
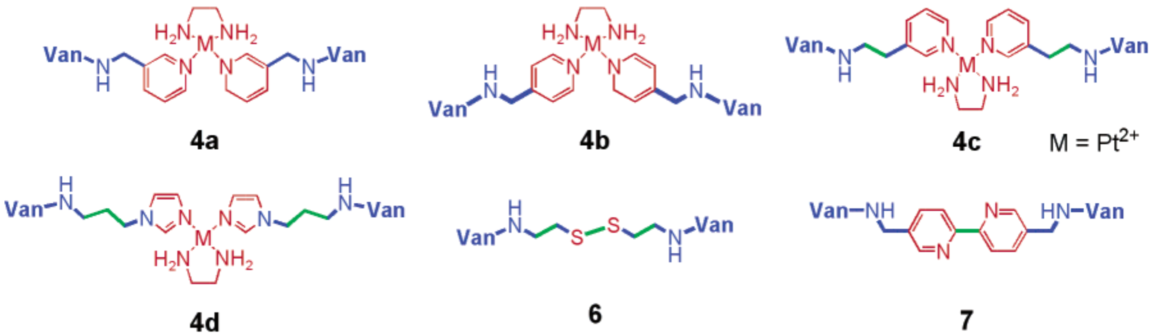



**Figure 1.** The illustration of possible divalent interaction of the dimeric Vans with the terminal peptides of VRE (D-Lac for VanA and VanB strains; D-Ser for the VanC strains).

Let the conformational entropies ($\Delta S_{conf}$) of Van plus the $CONHCH_2$ segment to be the same as in **4**−**7**, we compared the $\Delta S_{conf}$ of the different linkers (green portions) upon dimerization (assuming the $\Delta S_{conf}$ of the metal complex linker to be zero due to the rigidity of $[Pt(en)]^{2+}$). For example, the $\Delta S_{conf}$ of **6** would be the sum of torsional entropies of two C−C bonds and an S−S bond ($-\Sigma S_{tor} = 7.3 \times 2 + 3.5 = 18.1$ J/mol·K).[36] If we consider only the contribution of $\Delta S_{conf}$ to the $\Delta G$ and assume that the binding occurs at room temperature, the ratios of binding constants $K_{4a}/K_n$ of **4a-d**, **6**, and **7** can be calculated. In the case of VanA strains (Table 2), the ratios of binding constants $K_{4a}/K_n$ agree qualitatively with the MIC values (except **4b**). For example, **4a** is ~5 times more potent than **6**,[17] which agrees with their $\Delta S_{conf}$ values. **4c** resembles **4a** structurally except that it has an extra $CH_2$ increasing the flexibility its linker; therefore, **4c** exhibits lower activity against VRE. Similarly, additional flexibility in **4d** or

**Table 2.** Comparison between Conformational Entropies and Activity of Divalent Vans against VRE (VanA and VanB strains)




| n | $\Delta S_{conf}$(J/mol·K) ($-\Sigma S_{tor}$) | $K_{4a}/K_n$ | MIC ($\mu$g/mL) | |
|---|---|---|---|---|
| | | | VanA | VanB |
| **4a** | 0 | 1 | 0.8 | 0.28 |
| **4b** | 0 | 1 | 14 | 2 |
| **4c** | 14.6 | 5.9 | 3.3 | 1.2 |
| **4d** | 29.2 | 34 | 38 | 4.8 |
| **6** | 18.1 | 9 | 4 | 1 |
| **7** | 11.8 | 4 | 5.5 | 1.6 |

**7** results in the loss of $\Delta S_{conf}$ upon divalent binding and the decrease of its activity. Similar qualitative agreement also exhibits between $\Delta S_{conf}$ and the MIC values in the case of VanB strains. The discrepancy between $K_{4a}/K_{4b}$ and the MIC of **4b** apparently originates from the configuration of **4b**, which contributes to the changes of enthalpy. Though other mechanisms cannot be ruled out at this moment, the above analysis supports the hypothesis of the roles of rigidity in divalency for the case of VanA and VanB strains.

$\Delta S_{conf}$ correlates, however, to little enhancement of the activity of dimeric Vans against vancomycin-sensitive strains and the less resistant VRE (VanC), which has been observed in other systems of divalent Vans,[16,17,34] suggesting the enhancement of the activity of dimeric Vans may depend on the composition of peptidoglycan precursors produced by the strains.[43]

## Conclusion

In summary, we have demonstrated that a metal complex can be used as a new platform to construct multivalent inhibitors, which are as effective as other rigid linkers[44−46] used for multivalency. One of the concerns on platinum-based complexes is its cytotoxicity. Our preliminary study has shown that these *cis*-platin-based divalent Vans are not toxic toward mammalian cells (the detailed work will be published elsewhere). Our future work will examine other metal complex linkers, which may help further elucidate the structural basis of vancomycin resistance,[43,47] as well as the mechanism of multivalent Vans binding to vancomycin-sensitive strains,[48,49] which has yet to be established.

## Experimental Section

**General.** Chemical reagents and solvents were used as received from commercial sources. Dimethyl sulfoxide (DMSO) was dried over 4 Å molecular sieves and dimethylformamide (DMF) was dried over silica gel. $^1$H NMR spectra were obtained at 500 MHz Varian XL-500 in Me$_2$SO-$d_6$ and D$_2$O. Reversed-phase HPLC was carried out with Waters 600 Controller and 996 photodiode Array Detector, using XTerra RP18 C18 7 $\mu$m columns for both analytical and preparative purpose. HPLC elution employed linear gradients of [0.1% trifluoroacetic acid (TFA) in water (solution A)] and [0.1% TFA in acetonitrile (solution B)]. The linear gradient started from 90% solution A and 10% solution B, changed to 80% solution A and 20% solution B in 50 min, and to 0% solution A and 100% solution B in the following 5 min, and then to 90% solution A and 10% solution B in the next 5 min. The ESI-MS spectra were obtained on LCQ DECA XP/ESI&APCI (ThermoQuest/Finnigan), and the HR ToF-MS spectra of the key compounds, **4a** and **4b**, were obtained on Agilent HP1100/Sciex Q-Star Pulsar I (Applied Biosystem).

**Synthesis.** *Synthesis of dimeric Van **4c***: 2.5 mg of [Pt(en)-(H$_2$O)$_2$](NO$_3$)$_2$ (0.006 mmol, 1.0 equiv) was added to a solution of **2c** (20 mg, 0.0129 mmol, 2.15 equiv) in 1 mL of DMSO,. The mixture was stirred for 20 h at room temperature in dark. During the whole procedure, RP-HPLC was used to monitor the reaction. In the first 3 h, a vancomycin-3-ethylene pyridine-carboxamide peak exists at the elution time of 24 min. With increased time, a new peak at 18 min was found and the peak intensity of the starting material at 24 min was decreased. After 14 h, RP-HPLC indicated that almost all vancomycin-3-ethylene pyridine-carboxamide was consumed completely. Then by quenching the reaction with 10 mL of acetone, a white solid was precipitated. This crude product was filtered and washed three times with acetone and dried under vacuum before it was redissolved in H$_2$O and separated by RP-HPLC. After purification by HPLC, 15.6 mg of pure product was obtained (yield: 75.8%): $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.18-(v br s), 9.1(v br s), 8.77(v br s), 8.74(d, 5.5 Hz), 8.67(br s), 8.54(s), 8.30(s), 8.09(d, 7.8 Hz), 7.98 (s), 7.75(overlapped), 7.73-(d, 7.0 Hz), 7.59(d, 7.8 Hz), 7.57(s), 7.45(d, 8.6 Hz), 7.33(s), 7.31(d, 8.6 Hz), 7.15(v br s), 7.08(d, 10.1 Hz), 6.89(d, 8.5 Hz), 6.82(d, 8.5 Hz), 6.80(v br s), 6.64(v br s), 6.47(s), 6.34(s), 6.09-(br s), 5.87(d, 7.8 Hz), 5.69(s), 5.57(s), 5.38(s), 5.37(s), 5.35(s), 5.31(br s), 5.04(br m), 4.79(d, 6.2 Hz), 4.57(d, 3.1 Hz), 4.43(br q, 5.5 Hz), 4.34(d, 10.1 Hz), 4.04(d, 11.0 Hz), 3.37(s), 3.29(s), 2.96(m), 2.75(s), 2.65(d, 4.7 Hz), 2.52(s), 2.27(dd, 16.4 Hz, 6.5 Hz), 2.01(br d, 9.4 Hz), 1.85(br d, 10.6 Hz), 1.79(non 7.0 Hz), 1.69(q, 7.0 Hz), 1.66(q, 7.0 Hz), 1.42(s), 1.18(d, 6.2 Hz), 1.01-(d, 6.2 Hz), 0.96(d, 6.2 Hz). ESI-MS: The peaks at $m/z$ 1121.3, 1680.4, 1158.6, and 1737.5 correspond to $M^{3+}$, $M^{2+}$, $(M + TFA)^{3+}$, and $(M + TFA)^{2+}$, respectively.

*Synthesis of dimeric Van **4a***: Similar to the synthesis of **4c**, 2.5 mg of [Pt(en)(H$_2$O)$_2$](NO$_3$)$_2$ (0.0060 mmol, 1.0 equiv) was added to a solution of **2a** (20 mg, 0.0130 mmol, 2.16 equiv) in 1 mL of DMSO. After being purified by HPLC, 14.0 mg of pure product was obtained (yield: 69.6%): $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.18(v br s), 9.09(v br s), 8.81(d, 4.9 Hz), 8.76(s), 8.72(s), 8.69(br s), 8.54(v br s), 8.09(d, 8.6 Hz), 7.95 (s), 7.76-

(d, 8.5 Hz), 7.68(d, 8.6 Hz), 7.63(s), 7.59(s), 7.57(s), 7.56(s), 7.43-(d, 8.6 Hz), 7.39(br s), 7.30(d, 7.3 Hz), 7.11(br s), 6.89(d, 8.6 Hz), 6.82(d, 8.6 Hz), 6.80(v br s), 6.64(v br s), 6.51(s), 6.34(s), 6.00(v br s), 5.87(d, 7.3 Hz), 5.69(s), 5.58(v br s), 5.42(s), 5.37-(d, 7.3 Hz), 5.35(s), 5.31(br s), 5.21(br s), 5.05(br m), 4.78(q, 7.3 Hz), 4.66(d, 5.6 Hz), 4.59(s), 4.47(br q, 5.6 Hz), 4.40(d, 11.0 Hz), 3.79(d, 10.4 Hz), 3.67(t, 7.8 Hz), 3.57(br s), 3.37(s), 3.27-(br s), 2.97(s), 2.83(s), 2.26(dd, 15.5, 6.5 Hz), 2.01(br d, 10.4 Hz), 1.80(br d, 10.6 Hz), 1.77(non 7.1 Hz), 1.68(q, 7.1 Hz), 1.62-(q, 7.1 Hz), 1.41(s), 1.17(d, 6.5 Hz), 1.01(d, 6.5 Hz), 0.96(d, 6.5 Hz). ESI-MS: The peak at *m*/*z* 667.3, 833.7, 1111.5, 689.6, 862.2, and 1149.6 correspond to $M^{5+}$, $M^{4+}$, $M^{3+}$, $(M + TFA)^{5+}$, $(M + TFA)^{4+}$, and $(M + TFA)^{3+}$, respectively.

*Synthesis of dimeric Van **4b***: 2.5 mg of $[Pt(en)(H_2O)_2](NO_3)_2$ (0.0060 mmol, 1.0 equiv) was added to a solution of **2b** (20 mg, 0.0130 mmol, 2.16 equiv) in 1 mL of DMSO. After being purified by HPLC, 15.3 mg of pure product was obtained (yield: 76.1%): $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.43(v br s), 9.26(v br s), 9.13(v br s), 8.84(s), 8.8(d, 4.7 Hz), 8.75(triple), 8.67(d, 5.9 Hz), 8.64(s), 8.62(d, 4.2 Hz), 8.28(v br s), 8.07(d, 8.2 Hz), 7.93 (s), 7.91(d, 7.6 Hz), 7.80(s), 7.77(multiple), 7.75-(v br s), 7.67(d, 8.8 Hz), 7.66(v br s), 7.63 (v br s), 7.58(d, 5.3 Hz), 7.57(s), 7.56(s), 7.43(d, 8.2 Hz), 7.34(s), 7.29(d, 8.2 Hz), 7.12(br s), 6.86(d, 8.8 Hz), 6.82(d, 8.8 Hz), 6.79(v br s), 6.64-(overlapped), 6.50(d, 2.34 Hz), 6.35(d, 2.3 Hz), 6.00(v br s), 5.87-(d, 8.1 Hz), 5.68(v br s), 5.36(s), 5.35(s), 5.33(d, 3.7 Hz), 5.29(br s), 5.22(br s), 5.00(br m), 4.78(q, 6.6 Hz), 4.72(d, 5.9 Hz), 4.55-(d, 5.1 Hz), 4.47(br q, 5.6 Hz), 4.43(d, 5.9 Hz), 4.39(d, 11.0 Hz), 4.05(v br s), 3.79(d, 11.0 Hz), 3.66(t, 8.8 Hz), 3.55(br s), 3.39-(s), 3.29(br s), 2.75(s), 2.26(dd, 15.1 Hz, 6.5 Hz), 2.01-(overlapped), 1.82(br d, 10.6 Hz), 1.77(non 7.1 Hz), 1.68(q, 7.1 Hz), 1.62(q, 7.1 Hz), 1.41(s), 1.17(d, 6.4 Hz), 1.01(d, 6.5 Hz), 0.96(d, 6.5 Hz). ESI-MS: The peaks at *m*/*z* 834.16, 1111.15, and 1666.25 correspond to $M^{4+}$, $M^{3+}$, and $M^{2+}$, respectively.

*Synthesis of dimeric Van **4d***: Again, similar to the synthesis of **4c**, 2.5 mg of $[Pt(en)(H_2O)_2](NO_3)_2$ (0.0060 mmol, 1.0 equiv) was added to a solution of **2d** (20 mg, 0.0128 mmol, 2.15 equiv) in 1 mL of DMSO. After being purified by HPLC, 16.0 mg of pure product was obtained (yield: 78.8%): $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.47(v br s), 9.19(s), 9.12(v br s), 8.79(br s), 8.63-(s), 8.58(br s), 8.42(s), 8.25(d, 6.2 Hz), 7.94 (s), 7.78(s), 7.77-(overlapped), 7.70(s), 7.67(d, 8.6 Hz), 7.59(s), 7.57(d, 7.8 Hz), 7.45(d, 8.6 Hz), 7.40(s), 7.31(d, 8.6 Hz), 7.15(v br s), 6.88(s), 6.87(d, 8.2 Hz), 6.82(d, 8.2 Hz), 6.80(v br s), 6.64(v br s), 6.48-(s), 6.36(m), 6.31(s), 6.00(v br s), 5.87(d, 7.8 Hz), 5.68(s), 5.57-(s), 5.43(s), 5.37(s), 5.36(s), 5.34(d, 2.9 Hz), 5.30(br s), 5.02(br m), 4.79(d, 7.0 Hz), 4.58(d, 4.4 Hz), 4.42(br q, 5.4 Hz), 4.37(d, 10.2 Hz), 4.24(m), 4.16(m), 4.04(s), 3.37(s), 3.29(s), 3.15(m), 2.83(s), 2.76(s), 2.52(v br s), 2.27(dd, 16.3 Hz, 6.4 Hz), 2.07-(m), 2.02(br d, 9.4 Hz), 1.84(br d, 10.6 Hz), 1.81(non 7.1 Hz), 1.72(q, 7.1 Hz), 1.65(q, 7.1 Hz), 1.40(s), 1.17(d, 6.2 Hz), 1.01-(d, 6.2 Hz), 0.96(d, 6.2 Hz). ESI-MS:The peak at *m*/*z* 1161.3 corresponds to $M^{3+}$.

*Synthesis of monomeric Van **5a***: 6.0 mg of $[Pt(en)(H_2O)$-(N−Pyridin-3-ylmethyl-acetamide)]$(NO_3)_2$ (0.0124 mmol, 1.0 equiv) was added to a solution of **2a** (20 mg, 0.0130 mmol, 1.05 equiv) in 1 mL of DMSO. After being purified by HPLC, 14.7 mg of pure product was obtained (yield: 58.9%): $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.46(v br s), 9.26(v br s), 9.17(v br s), 9.09(v br s), 8.84(s), 8.8(d, 4.7 Hz), 8.69(d, 5.9 Hz), 8.67-(overlapped), 8.64(br d, 4.4 Hz), 8.61(d, 4.2 Hz), 8.28(v br s), 8.07(d, 8.2 Hz), 7.93 (s), 7.77(multiple), 7.67(d, 8.8 Hz), 7.66(v br s), 7.63 (v br s), 7.58(d, 5.3 Hz), 7.57(s), 7.55(multiple), 7.44-(d, 8.2 Hz), 7.32(s), 7.29(d, 8.2 Hz), 7.14(s), 6.87(br s), 6.85(d, 8.8 Hz), 6.81(d, 8.8 Hz), 6.78(v br s), 6.64(overlapped), 6.50(d, 2.34 Hz), 6.35(d, 2.3 Hz), 6.00(v br s), 5.87(d, 8.1 Hz), 5.68(v br s), 5.36(s), 5.35(s), 5.33(d, 3.7 Hz), 5.29(br s), 5.22(br s), 5.00-(br m), 4.78(q, 6.6 Hz), 4.55(d, 5.1 Hz), 4.47(br q, 5.6 Hz), 4.44-(d, 5.9 Hz), 4.39(d, 11.0 Hz), 4.05 (v br s), 3.79(d, 11.0 Hz), 3.66(t, 8.8 Hz), 3.55(br s), 3.39(s), 3.29(br s), 2.75(s), 2.26(dd, 15.1 Hz, 6.5 Hz), 2.01(overlapped), 1.82(br d, 10.6 Hz), 1.77-(non 7.1 Hz), 1.68(q, 7.1 Hz), 1.62(q, 7.1 Hz), 1.41(s), 1.17(d, 6.4 Hz), 1.01(d, 6.5 Hz), 0.96(d, 6.5 Hz). ESI-MS: The peaks at *m*/*z* 972.9 and 1028.5 correspond to $M^{2+}$ and $(M + TFA)^{2+}$, respectively.

*Synthesis of monomeric Van **5b***: 6.0 mg of $[Pt(en)(H_2O)$(*N*-pyridin-3-ylmethylacetamide)]$(NO_3)_2$ (0.0124 mmol, 1.0 equiv) was added to a solution of **2b** (20 mg, 0.0130 mmol, 1.05 equiv) in 1 mL of DMSO. After being purified by HPLC, 15.5 mg of pure product was obtained (yield: 62.0%): $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.43(v br s), 9.26(v br s), 9.13(v br s), 8.84(s), 8.8-(d, 4.7 Hz), 8.75(triple), 8.67(d, 5.9 Hz), 8.64(s), 8.62(d, 4.2 Hz), 8.28(v br s), 8.07(d, 8.2 Hz), 7.93 (s), 7.91(d, 7.6 Hz), 7.80(s), 7.77(multiple), 7.75(v br s), 7.67(d, 8.8 Hz), 7.66(v br s), 7.63 (v br s), 7.58(d, 5.3 Hz), 7.57(s), 7.56(s), 7.43(d, 8.2 Hz), 7.34-(s), 7.29(d, 8.2 Hz), 7.12(br s), 6.86(d, 8.8 Hz), 6.82(d, 8.8 Hz), 6.79(v br s), 6.64(overlapped), 6.50(d, 2.34 Hz), 6.35(d, 2.3 Hz), 6.00(v br s), 5.87(d, 8.1 Hz), 5.68(v br s), 5.36(s), 5.35(s), 5.33-(d, 3.7 Hz), 5.29(br s), 5.22(br s), 5.00(br m), 4.78(q, 6.6 Hz), 4.72(d, 5.9 Hz), 4.55(d, 5.1 Hz), 4.47(br q, 5.6 Hz), 4.43(d, 5.9 Hz), 4.39(d, 11.0 Hz), 4.05(v br s), 3.79(d, 11.0 Hz), 3.66(t, 8.8 Hz), 3.55(br s), 3.39(s), 3.29(br s), 2.75(s), 2.26(dd, 15.1 Hz, 6.5 Hz), 2.01(overlapped), 1.82(br d, 10.6 Hz), 1.77(non 7.1 Hz), 1.68(q, 7.1 Hz), 1.62(q, 7.1 Hz), 1.41(s), 1.17(d, 6.4 Hz), 1.01-(d, 6.5 Hz), 0.96(d, 6.5 Hz). ESI-MS: The peaks at *m*/*z* 648.9, 971.9, and 1028.5 correspond to $M^{3+}$, $M^{2+}$, and $(M + TFA)^{2+}$, respectively.

*Synthesis of dimeric Van **6***: Following to the same procedure as for **2a**, 6.8 mg of cystamide dihydrochloride (30 $\mu$mol, 1.0 equiv) was added to a solution of vancomycin hydrochloride (100 mg, 67 $\mu$mol, 2.2 equiv) in 1 mL of dry DMSO. The mixture was cooled to 0 °C and HBTU (90 $\mu$mol, 3 equiv) in 1 mL of DMF was added, followed by DIEA (0.057 mL, 328 $\mu$mol, 4.88 equiv). The reaction was allowed to rise to room temperature and stirred for overnight. At this time, analytical RP-HPLC showed that a vancomycin peak still existed. Further addition of HBTU (10 mg, 26 $\mu$mol, 0.39 equiv) and DIEA (0.024 mL, 164 $\mu$mol, 2.44 equiv) was made. After another 24 h, the reaction was monitored with HPLC again and almost all vancomycin was found to have been consumed. To quench the reaction, the reaction mixture was added dropwise into 15 mL of acetone by using syringe. A white solid was precipitated out and filtered, and 5 mL of acetone was used to wash the solid once. The white solid was purified by reversed-phase HPLC (RP-HPLC). The percentage yield is 52%. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.88(v br s), 9.44(v br s), 9.10(v br s), 8.71(br s), 8.51(br s), 8.27(d, 5.1 Hz), 7.98 (s), 7.83-(overlapped), 7.69(d, 7.8 Hz), 7.56(d, 8.6 Hz), 7.43(d, 8.6 Hz), 7.31(d, 8.6 Hz), 7.29 (s), 7.09(v br s), 6.86(d, 8.6 Hz), 6.82(d, 8.6 Hz), 6.80(v br s), 6.62(v br s), 6.49(s), 6.35(s), 6.07(v br s), 5.87(d, 7.8 Hz), 5.85(s), 5.69(s), 5.50(v br s), 5.41(s), 5.39(s), 5.37(s), 5.35(d, 2.8 Hz), 5.30(br s), 5.03(br m), 4.78(d, 6.2 Hz), 4.53(br q, 5.5 Hz), 4.32(d, 10.9 Hz), 4.03(s), 3.79(d, 10.9 Hz), 3.37(s), 3.27(s), 3.00(m), 2.72(s), 2.26(dd, 16.1 Hz, 6.3 Hz), 2.07-(m), 2.01(br d, 9.4 Hz), 1.82(br d, 10.4 Hz), 1.79(non 7.0 Hz), 1.74(q, 7.0 Hz), 1.67(q, 7.0 Hz), 1.44(s), 1.18(d, 6.7 Hz), 1.02-(d, 6.2 Hz), 0.97(d, 6.2 Hz). ESI-MS**:** The peak at *m*/*z* 1508.8 corresponds to $M^{2+}$.

**5,5′-Bis(bromomethyl)-2,2′-bipyridine (7a).** A solution of 5,5′-dimethyl-2,2′-bipyridine (1 g, 5.43 mmol, 1 equiv), NBS (5.1 g, 28.7 mmol, 5.3 equiv), and VAZO (265 mg, 1.09 mmol, 0.2 equiv) in $CCl_4$ (100 mL) was refluxed under nitrogen for 1 h, and the precipitated succinimide was removed immediately from the hot mixture by filtration. The precipitate was washed with $CCl_4$, and the combined $CCl_4$ phases were evaporated. The remaining solid was dissolved in $CH_2Cl_2$ (100 mL) and extracted with 1 M $Na_2S_2O_3$ solution (2 × 150 mL). The combined $Na_2S_2O_3$ fractions were extracted with $CH_2Cl_2$ (50 mL), and the combined $CH_2Cl_2$ layers were dried by $Na_2SO_4$. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane, 1:4) and yielded 412 mg (22%) to give white solid. $^1$H NMR ($CDCl_3$, $\delta$ 7.26 ppm) $\delta$ 8.68 (d, $J$ = 2.2 Hz, 1H, CH), 8.40 (d, $J$ = 8.2 Hz, 1H, CH), 7.86 (dd, $J$ = 8.2 Hz, 2.2 Hz, 1H, CH), 4.54 (s, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$, $\delta$ 77.7 ppm) $\delta$ 156.08, 150.05, 138.32, 134.59, 121.87, 30.22. ESI-MS: The peak at*m*/*z* 343 corresponds to $(M + 1)^+$.

**5,5′-Bis(azidomethyl)-2,2′-bipyridine (7b).** $NaN_3$ (42 mg, 0.64 mmol, 2.2 equiv) was added to a solution of 5,5′-bis-(bromomethyl)-2,2′-bipyridine (100 mg, 0.29 mmol, 1 equiv) in dry DMF (3 mL). The solution was heated for 17 h at 90 °C and then concentrated under vacuum to yield a mixture, which was treated with $CH_2Cl_2$. The solid (NaBr) was filtered off, and the extract was concentrated in a vacuum to yield the product (white solid), which was purified by flash column chromatography (silica gel, EtOAc/hexane, 40/60) and yielded 69 mg (90%) of pure white solid. $^1$H NMR ($CDCl_3$, $\delta$ 7.26 ppm) $\delta$ 8.64 (d, $J$ = 1.8 Hz, 1H, CH), 8.45 (d, $J$ = 8.2 Hz, 1H, CH), 7.81 (dd, $J$ = 8.2 Hz, 2.3 Hz, 1H, CH), 4.44 (s, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$, $\delta$ 77.7 ppm) $\delta$ 156.35, 149.44, 137.41, 131.99, 121.81, 52.68. ESI-MS: The peak at*m/z* 267 corresponds to $(M + 1)^+$.

**5,5′-Bis(aminomethyl)-2,2′-bipyridine (7c).** 10% Pd on activated carbon (15 mg) was dissolved in 1 mL of dry $CH_2Cl_2$ in a closed round-bottom flask with vigorous stirring. 6 M HCl was added to another round-bottom flask that contained zinc powder in order to generate hydrogen gas. These two round-bottom flasks were connected by a rubber pipe. Make sure that there is no leakage. An outlet was introduced in the round-bottom flask containing 10% Pd on activated carbon. 5,5′-bis-(azidomethyl)-2,2′-bipyridine (60 mg, 0.23 mmol, 1 equiv) in 2 mL of dry $CH_2Cl_2$ was added to the round-bottom flask contained 10% Pd on activated carbon 3 min after the outlet was introduced. The reaction was completed within 4 h. 10% Pd on activated carbon was filtered by Celite and $CH_2Cl_2$ was dried to obtain 39 mg of white solid (yield, 80%). $^1$H NMR ($CDCl_3$, $\delta$ 7.26 ppm) $\delta$ 8.62 (d, $J$ = 2.0 Hz, 1H, Ar−H), 8.35 (d, $J$ = 8.1 Hz, 1H, Ar−H), 7.80 (dd, $J$ = 8.1 Hz, 2.0 Hz, 1H, Ar−H), 3.97 (s, 2H, $CH_2$). 1.54(s, 2H, NH2). $^{13}$C NMR ($CDCl_3$, $\delta$ 77.7 ppm) $\delta$ 156.15, 150.12, 137.11, 131.08, 121.61, 43.8. ESI-MS: The peak at*m/z* 215 corresponds to $(M + 1)^+$.

**5,5′-Bis(aminomethyl)-2,2′-bipyridine Vancomycin (7).** The experiment procedure was same as for **2a**. The crude white solid was purified by reversed-phase HPLC (RP-HPLC). The percentage yield is 43%. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.11-(v br s), 8.76(v br s), 8.71(v br s), 8.68(br s), 8.62(br s), 8.40(d, 7.0 Hz), 8.04 (s), 7.95(s), 7.67(d, 8.5 Hz), 7.57(d, 8.6 Hz), 7.44-(d, 8.6 Hz), 7.34(d, 8.6 Hz), 7.29 (s), 7.12(v br s), 6.88(d, 9.0 Hz), 6.82(d, 8.6 Hz), 6.80(v br s), 6.63(v br s), 6.48(s), 6.36(s), 6.10(br s), 5.86(d, 7.3 Hz), 5.68(s), 5.39(s), 5.36(s), 5.34(s), 5.33-(d, 2.8 Hz), 5.29(br s), 5.04(br m), 4.78(d, 6.2 Hz), 4.65(d, 10.9 Hz), 4.54(br q, 4.9 Hz), 4.37(d, 10.9 Hz), 4.04(s), 3.79(d, 10.1 Hz), 3.37(s), 3.28(s), 3.02(m), 2.74(s), 2.26(dd, 16.6 Hz, 6.6 Hz), 2.00(br d, 9.4 Hz), 1.84(br d, 10.4 Hz), 1.78(non 7.1 Hz), 1.74-(q, 7.1 Hz), 1.67(q, 7.1 Hz), 1.62(q, 7.1 Hz), 1.39(s), 1.16(d, 6.2 Hz), 1.00(d, 6.2 Hz), 0.95(d, 6.2 Hz). ESI-MS: The peaks at*m/z* 770.3, 1026.8 and 1539.4 correspond to $M^{4+}$, $M^{3+}$ and $M^{2+}$, respectively.

**B. In Vitro Study.** Minimum concentrations of the Van, $[Pt(en)(H_2O)_2](NO_3)_2$+Van, and dimers of Van required to inhibit the growth of bacterial cells were measured using cation-adjusted Muller-Hinton broth as the growth media. One vancomycin-susceptible strain, one strain exhibiting low-level resistance to vancomycin, five strains exhibiting midlevel resistance to vancomycin, and four strains exhibiting high-level resistance to vancomycin were used to determine the MIC values. The average MIC values for the last two cases were shown in Table 1. The genotype of the strains was confirmed by PCR.

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**Supporting Information Available:** The synthetic scheme of **7** and the high-resolution mass spectra (in tabular form) of **4a** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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