Supporting Information

Silver(I)-Promoted Conversion of Thioamides to Amidines: Divergent Synthesis of a Key Series of Vancomycin Aglycon Residue 4 Amidines that Clarify Binding Behavior to Model Ligands

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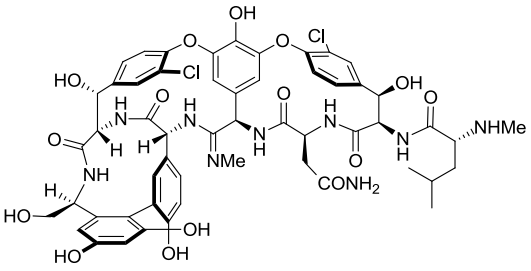
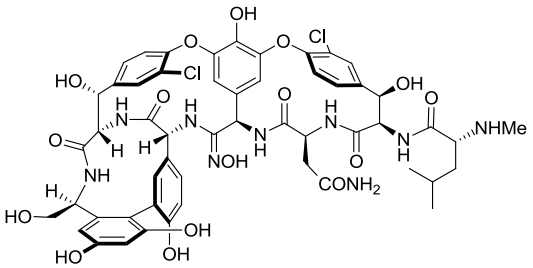
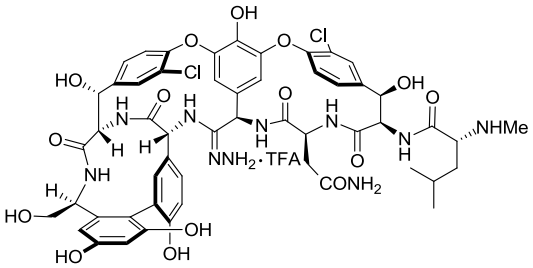


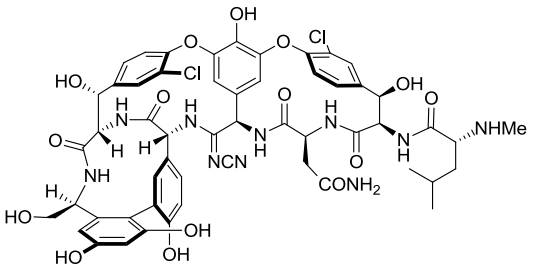
Compound 11: white film; ^{1}H NMR (DMSO-d_6, 600 MHz) inseparable geometrical isomers (*ca* A:B = 1:1) δ 10.1–10.0 (br m, 1H), 9.26–9.22 (m, 1H), 9.19–9.16 (br m, 1H), 8.82–8.81 (m, 1H), 8.25–8.17 (m, 3H), 8.15–8.12 (m, 2H), 7.56–7.45 (m, 5H), 7.37–7.35 (br m, 1H), 7.28–7.23 (m, 3H), 7.18–7.15 (m, 1H), 7.12–7.06 (m, 3H), 7.01–6.97 (m, 1H), 6.81–6.80 (br m, 1H), 6.77 (d, 1H, J = 4.2 Hz), 6.66–6.63 (br m, 1H), 6.29 (d, 1H, J = 1.8 Hz), 6.09–6.04 (br m, 1H), 6.03–6.01 (m, 1H), 5.93 (d, 1H, J = 7.2 Hz), 5.84–5.82 (m, 1H), 5.76 (d, 1H, J = 3.0 Hz), 5.65 (d, 1H, J = 7.2 Hz), 5.61–5.57 (m, 1H), 5.44 (d, 1H, J = 6.0 Hz), 5.21–5.17 (m, 2H), 4.95–4.93 (br m, 1H), 4.50–4.45 (m, 1H), 4.17–4.16 (m, 2H), 3.66–3.55 (m, 8H), 2.75 (d, 2H, J = 11.6 Hz), 2.69–2.66 (m, 3H), 2.09–2.06 (br m, 1H), 2.00–1.96 (m, 6H), 1.77–1.73 (m, 2H), 0.94–0.91 (m, 6H), 0.90–0.84 (m, 6H); ESI-TOF HRMS *m/z* 1142.3417 (M + H$^+$, $C_{54}H_{58}Cl_2N_9O_{15}$ requires 1142.3424).



Compound 12: white film; ^{1}H NMR (CD_3OD, 600 MHz) δ 8.19–8.13 (m, 1H), 7.73–7.68 (m, 1H), 7.65–7.57 (m, 1H), 7.42–7.26 (m, 2H), 7.08 (d, 1H, J = 8.4 Hz), 7.01 (d, 1H, J = 3.6 Hz), 6.98–6.95 (br m, 1H), 6.82 (d, 1H, J = 8.4 Hz), 6.66–6.61 (m, 1H), 6.42–6.38 (m, 1H), 5.60–5.47 (m, 3H), 5.44–5.39 (m, 1H), 5.36–5.32 (m, 1H), 5.27–5.22 (m, 1H), 5.01–4.96 (m, 1H), 4.38–4.20 (m, 3H), 4.05–3.99 (m, 1H), 3.98–3.91 (m, 1H), 3.88–3.85 (m, 1H), 3.46–3.40 (m, 1H), 2.84 (s, 3H), 2.43 (br d, 1H, J = 18.4 Hz), 2.22–2.16 (m, 1H), 2.06–1.99 (m, 1H), 1.81–1.74 (m, 1H), 1.63–1.50 (m, 4H), 0.88–0.81 (m, 6H); ESI-TOF HRMS *m/z* 1144.3213 (M + H^+, $C_{53}H_{56}Cl_2N_9O_{16}$ requires 1144.3217).



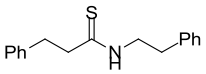
Compound 13: white film; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.24 (br s, 1H) 8.54–8.12 (m, 1H), 7.64–7.61 (m, 2H), 7.22–7.17 (m, 4H), 7.11–7.07 (m, 2H), 7.02–6.99 (br m, 1H), 6.68–6.63 (m, 2H), 6.54–6.52 (m, 2H), 6.35–6.32 (m, 1H), 5.85–5.82 (m, 1H), 5.77–5.74 (br m, 2H), 5.16–5.13 (m, 2H), 5.07–5.03 (m, 4H), 4.87 (d, 1H, J = 5.4 Hz), 4.72–4.69 (m, 1H), 4.64–4.62 (m, 1H), 3.58–3.55 (m, 2H), 3.49–3.47 (m, 4H), 2.85 (d, 1H, J = 12.0 Hz), 2.27–2.22 (m, 4H), 2.18–2.14 (m, 3H), 2.07–2.05 (m, 2H), 1.72 (br s, 1H), 1.54–1.51 (m, 1H), 0.89–0.79 (m, 6H); LCMS *m/z* 1257.3 (M + H^+, $C_{55}H_{58}Cl_2F_3N_{10}O_{17}$ requires 1257.1 for TFA salt); ESI-TOF HRMS *m/z* 1371.3159 (M + H^+, $C_{57}H_{59}Cl_2F_6N_{10}O_{19}$ requires 1371.3239 for bis TFA salt).



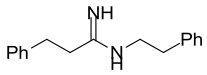
Compound 14: white film; ^{1}H NMR (CD_3OD, 600 MHz) δ 8.85 (d, 1H, J = 6.0 Hz), 8.20–8.18 (m, 1H), 7.89–7.86 (m, 1H), 7.63–7.62 (m, 1H), 7.57–7.49 (m, 6H), 7.18 (d, 1H, J = 8.4 Hz), 6.94–6.91 (br m, 1H), 6.66 (d, 1H, J = 6.6 Hz), 6.56 (d, 1H, J = 1.8 Hz), 6.53–6.52 (m, 1H), 6.30 (d, 1H, J = 2.4 Hz), 5.72–5.62 (m, 2H), 5.15–5.11 (m, 1H), 4.54 (br s, 1H), 4.28–4.21 (m, 1H), 4.18–4.17 (m, 1H), 4.13–4.11 (m, 1H), 4.00–3.94 (m, 1H), 3.91–3.88 (m, 3H), 3.87–3.84 (m, 1H), 2.88 (s, 3H), 2.81–2.79 (m, 3H), 1.78–1.74 (m, 1H), 1.60–1.54 (m, 2H), 0.82–0.79 (m, 6H); ESI-TOF HRMS *m/z* 1153.3220 (M + H^+, $C_{54}H_{55}Cl_2N_{10}O_{15}$ requires 1153.3225).

General Procedure for Amidine Formation: (16) (Figure 4).

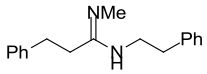
A mixture of **15** (10.0 mg, 37.2 μmol) and silver tetrafluoroborate (21.7 mg, 0.112 mmol, 3.0 equiv) was treated with saturated NH_3–CH_3OH (0.37 mL) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 2 h and concentrated under N_2 stream. The residue was purified by PTLC (SiO_2, 10% CH_3OH–CH_2Cl_2) to afford **16** (7.5 mg, 83%).



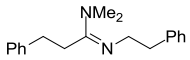
Compound 15: white solid; m.p. 68–69 ^{o}C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.31–7.18 (m, 10H), 3.78 (t, 2H, J = 7.5 Hz), 3.05 (t, 2H, J = 7.5 Hz), 2.88–2.85 (m, 4H), 2.17 (br s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 205.3, 141.9, 140.2, 129.7, 129.6, 129.5, 129.4, 127.4, 127.2, 48.1, 36.8, 34.5, 30.7; IR (film) ν_{max} 1647, 1199, 1121 cm^{-1}; ESI-TOF HRMS *m/z* 270.1306 (M + H^+, $C_{17}H_{20}NS$ requires 270.1311).



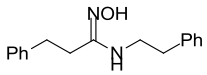
Compound 16: light pink film; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.36–7.32 (m, 4H), 7.28–7.20 (m, 6H), 3.50 (t, 2H, J = 7.0 Hz), 2.95 (t, 2H, J = 7.5 Hz), 2.88 (t, 2H, J = 7.0 Hz), 2.73 (t, 2H, J = 7.5 Hz); ^{13}C NMR (CD_3OD, 150 MHz) δ 168.5, 140.0, 139.0, 129.81, 129.79, 129.76, 129.4, 127.9, 44.6, 36.0, 34.6, 34.2; IR (film) ν_{max} 1743, 1121, 1117 cm^{-1}; ESI-TOF HRMS *m/z* 253.1700 (M + H$^+$, $C_{17}H_{20}N_2$ requires 253.1699).



Compound 17: white film; ^{1}H NMR (CD_3OD, 400 MHz) inseparable geometrical isomers (isomer A:B = 1.1:1) δ 7.38–7.15 (m, 20H), 3.59 (t, 2H, J = 6.8 Hz), 3.47 (t, 2H, J = 7.2 Hz), 2.93 (t, 2H, J = 7.6 Hz), 2.96–2.80 (m, 8H), 2.93 (s, 3H), 2.88 (s, 3H), 2.79 (t, 2H, J = 7.6 Hz), 2.56 (t, 2H, J = 7.2 Hz); ^{13}C NMR (CD_3OD, 150 MHz) inseparable geometrical isomers (isomer A:B = 1.1:1) δ 167.4, 167.3, 139.3, 139.2, 138.49, 138.48, 129.6, 129.34, 129.30, 129.29, 129.24, 129.23, 129.0, 128.9, 127.53, 127.50, 127.4, 46.1, 43.7, 36.3, 34.0, 32.74, 32,72, 32.3, 32.1, 30.1, 29.9, 28.3; IR (film) ν_{max} 1647, 1116, 1021 cm^{-1}; ESI-TOF HRMS *m/z* 267.1858 (M + H$^+$, $C_{18}H_{23}N_2$ requires 267.1856).

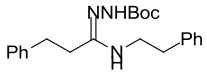


Compound 18: light pink solid; m.p. 146–148 ^{o}C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.37–7.20 (m, 10H), 3.53 (t, 2H, J = 7.2 Hz), 3.35–3.33 (m, 2H), 3.15 (s, 3H), 3.13 (s, 3H), 2.90 (t, 2H, J = 7.2 Hz), 2.83–2.81 (m, 2H); ^{13}C NMR (CD_3OD, 150 MHz) δ 175.5, 147.7, 147.0, 138.0, 137.9, 137.8, 137.5, 136.2, 136.0, 55.3, 49.3, 47.5, 44.9, 40.2, 37.7; IR (film) ν_{max} 1627, 1121, 1093 cm^{-1}; ESI-TOF HRMS *m/z* 281.2013 (M + H$^+$, $C_{19}H_{25}N_2$ requires 281.2012).

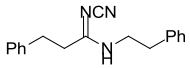


Compound 19: white film; ^{1}H NMR (CD_3OD, 500 MHz) inseparable geometrical isomers (isomer A:B = 18:1) δ (for isomer A) 7.32–7.17 (m, 10H), 3.40 (t, 2H, J = 7.0 Hz),

2.81 (t, 2H, J = 7.0 Hz), 2.77–2.73 (m, 2H), 2.34–2.31 (m, 2H); ^{13}C NMR (CD_3OD, 150 MHz) inseparable geometrical isomers δ (for isomer A) 156.2, 141.2, 139.4, 129.0, 128.6, 128.5, 128.4, 126.5, 126.2, 43.9, 37.7, 33.6, 30.4; IR (film) ν_{max} 3317, 1623, 1121, 1092 cm^{-1}; ESI-TOF HRMS *m/z* 269.1650 (M + H$^+$, $C_{17}H_{21}N_2O$ requires 269.1648).



Compound 20: white film; ^{1}H NMR (CD_3OD, 500 MHz) inseparable geometrical isomers (isomer A:B = *ca* 1:1) δ 7.30–7.21 (m, 20H), 3.45–3.42 (m, 4H), 3.40–3.38 (br m, 2H), 2.86–2.78 (m, 8H), 2.56–2.52 (m, 2H), 2.47–2.43 (m, 2H), 1.51 (s, 18H); ^{13}C NMR (CD_3OD, 150 MHz) inseparable geometrical isomers (isomer A:B = *ca* 1:1) δ 168.8, 163.4, 157.1, 156.5, 141.5, 141.0, 140.3, 139.2, 129.5, 129.3, 129.2, 129.03, 128.96, 128.9, 128.84, 128.80, 127.1, 126.9, 126.8, 126.7, 80.9, 80.1, 45.2, 43.4, 37.3, 35.0, 33.8, 33.5, 32.8, 32.2, 30.2, 28.3, 28.1; IR (film) ν_{max} 1828, 1697, 1121, 1094 cm^{-1}; ESI-TOF HRMS *m/z* 368.2331 (M + H$^+$, $C_{22}H_{29}N_3O_2$ requires 368.2332).



Compound 21: white solid; m.p. 131–132 ^{o}C; ^{1}H NMR (CD_3OD, 500 MHz) inseparable geometrical isomers (isomer A:B = 26:1) δ (for isomer A) 7.33–7.18 (m, 10H), 3.47 (t, 2H, J = 7.0 Hz), 3.00–2.96 (m, 2H), 2.81–2.77 (m, 4H); ^{13}C NMR (CD_3OD, 150 MHz) inseparable geometrical isomers (isomer A:B = 26:1) δ (for isomer A) 205.2, 142.0, 140.2, 129.7, 129.6, 129.57, 129.52, 129.4, 127.4, 127.2, 48.1, 36.8, 34.5; IR (film) ν_{max} 2215, 1623, 1121 cm^{-1}; ESI-TOF HRMS *m/z* 278.1653 (M + H$^+$, $C_{18}H_{20}N_3$ requires 278.1652).

Titration Binding Assays with Model D-Ala-D-Ala and D-Ala-D-Lac Ligands 6 and 7. The binding constants for all compounds for association with the model ligands *N,N'*-Ac_2-Lys-D-Ala-D-Ala (**6**) and *N,N'*-Ac_2-Lys-D-Ala-D-Lac (**7**) were determined according to literature protocol.[23] UV difference experiments were carried out on a CARY 3E UV-Vis spectrometer. UV scans were run with a baseline correction that consisted of

0.02 M sodium citrate buffer (pH = 5.1) and covered a range from 200 to 345 nm. A solution of the vancomycin aglycon derivative (7.7×10^{-5} M in 0.02 M sodium citrate buffer) was placed into a quartz UV cuvette (0.1 cm path length) and the UV spectrum recorded versus a reference cell containing 0.02 M sodium citrate buffer. UV spectra were recorded after each addition of a solution of *N,N'*-Ac_2-Lys-D-Ala-D-Ala (**6**) or *N,N'*-Ac_2-Lys-D-Ala-D-Lac (**7**) in 0.02 M sodium citrate buffer to each cell from 0.1 to 60.0 equivalents. The absorbance value at the λ_{max} was recorded and the running change in absorbance, $\Delta A_{x\ equiv}$ ($A_{initial} - A_{x\ equiv}$), measured. The number of ligand equivalents was plotted versus ΔA to afford the ligand binding titration curve. The break point of this curve is the saturation point of the system and its xy coordinates were determined by establishing the intersection of the linear fits of the pre and postsaturation curves. $\Delta A_{saturation}$ was calculated and employed to determine the concentration of free ligand in solution at each titration point. ΔA was plotted versus ΔA/free ligand concentration to give a Scatchard plot from which the binding constants were determined.

Antimicrobial Assays. *S. Aureus* (ATCC 25923) and *E. Faecalis* (BM4166) were propagated and MICs were determined in duplicate by the broth microdilution method according to standard microbiological practice.[S1]

S1. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically;* Approved Standard, 7th ed.; CLSI document M07-A8; Clinical and Laboratory Standards Institute: Wayne, PA, 2009.