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Chemistry & Drug Discovery

# Supporting Information

# Supporting information

**4-Hydroxy-*N*-(4´-hydroxyphenyl)benzamide (2).** NaOEt (2.07 g, 30.5 mmol) was added at room temperature to a solution of **6** (7.5 g, 27.7 mmol) in ethanol (100 mL) and the mixture was stirred until TLC (75%:12.5%:12.5% toluene/acetone/methanol) indicated complete removal of the acetyl group (~1h). The solution was neutralized by addition of 2N HCl (15.5 mL, 31 mmol) and the mixture was concentrated in vacuo. The resulting suspension was dissolved in EtOAc (400 mL) and water (100 mL) and transferred to a separation funnel. The organic layer was separated and washed once with 2N HCl (50 mL), twice with 1N $NaHCO_3$ (50 mL) and once with brine (50 mL). After drying ($MgSO_4$) the mixture was concentrated in vacuo and the remainig residue was purified by flash-chromatography (75%:12.5%:12.5% toluene/acetone/methanol) to afford **2** as a white solid (6.0 g, 26.3 mmol, 95%). $^1$H NMR (200 MHz, $d_6$-DMSO): δ 6.71 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 7.48 (d, 2H, *J* = 8.8 Hz), 7.81 (d, 2H, *J* = 8.4 Hz), 9.18 (bs, 1H), 9.74 (s, 1H), 10.0 (bs, 1H) ppm. $^{13}$C NMR (50.2 MHz, $d_6$-DMSO): δ 114.8, 114.9, 122.2, 125.7, 129.4, 130.9, 153.4, 160.2, 164.5 ppm. HRMS: calcd for $C_{13}H_{12}NO_3$ $[M+H]^+$ 230.0812, found 230.0805. MS (ESI): *m/z* 230.0 $[M+H]^+$, 252.1 $[M+Na]^+$. FTIR (thin film): 1647, 1609, 1514, 1435, 1367, 1323, 922, 824 $cm^{-1}$. TLC: $R_f$ = 0.39 (66%:17%:17% toluene/acetone/methanol).

**(*S*)-Propyloxy-3-(*N*-[4-(tert-butyldimethylsilyloxy)phenyl]benzamidyl)-2-piperidine carboxylate (14b).** Starting from **13b** (0.36 g, 0.59 mmol), **14b** was synthesized according to General Procedure D. Flash-chromatography (47/38/5% ? 45/45/10% toluene/acetone/methanol) provided **14b** as a slightly yellow oil (0.22 g, 0.43 mmol, 73%). $^1$H NMR (200 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.97 (s, 9H), 1.49-1.81 (m, 5H), 1.91-2.15 (m, 3H), 2.62-2.78 (m, 1H), 3.19-3.30 (m, 1H), 3.48-3.58 (m, 1H), 4.04 (t, 2H, *J* = 5.9 Hz), 4.32 (t, 2H, *J* = 5.9 Hz), 5.34 (bs, 1H), 6.80 (d, 2H, *J* = 8.8 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 7.48 (d, 2H, *J* = 8.8 Hz), 7.78 (d, 2H, *J* = 8.8 Hz), 8.07 (s, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$): δ –4.6, 18.0, 22.9, 23.7, 25.5, 27.5, 28.1, 44.6, 57.5, 62.2, 64.1, 114.0, 120.0, 122.1, 127.1, 128.0, 129.0, 131.8, 152.1, 161.1, 165.5, 171.7 ppm. HRMS: calcd for $C_{28}H_{43}N_2O_6Si$ $[M+H_2O+H]^+$ 531.2885, $C_{29}H_{45}N_2O_6Si$ $[M+MeOH+H]^+$ 545.3041, found 531.2899, 545.3039. MS (ESI): *m/z* 545.5 $[M+MeOH+H]^+$. FTIR (thin film): 2932, 1745, 1643, 1605, 1504, 1250, 1173, 1126, 1049, 910, 833, 756 $cm^{-1}$. $[\alpha]_D^{20}$: –4.4° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.30 (50% toluene/acetone).

**(*S*)-Butyloxy-4-(*N*-[4-(tert-butyldimethylsilyloxy)phenyl]benzamidyl)-2-piperidine carboxylate (14c).** Starting from **13c** (0.36 g, 0.57 mmol), **14c** was synthesized according to General Procedure D. Flash-chromatography (47/38/5% ? 45/45/10% toluene/acetone/methanol) provided **14c** as a slightly yellow oil (0.26 g, 0.49 mmol, 87%). $^1$H NMR (200 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.98 (s, 9H), 1.39-1.71 (m, 4H),

1.72-1.90 (m, 5H), 1.99-2.10 (m, 1H), 2.69-2.80 (m, 1H), 3.25-3.40 (m, 1H), 3.49-3.56 (m, 1H), 4.00 (bs, 2H), 4.22 (bs, 2H), 5.20 (bs, 1H), 6.81 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 7.48 (d, 2H, *J* = 8.8 Hz), 7.79 (d, 2H, *J* = 8.4 Hz), 7.97 (s, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$): δ –4.5, 18.1, 22.9, 23.6, 25.1, 25.6, 27.3, 44.7, 57.6, 65.4, 67.2, 114.2, 120.2, 121.9, 127.1, 129.0, 131.8, 152.3, 161.5, 165.3, 171.5 ppm. HRMS: calcd for $C_{29}H_{45}N_2O_6Si$ $[M+H_2O+H]^+$ 545.3041, $C_{30}H_{47}N_2O_6Si$ $[M+MeOH+H]^+$ 559.3198, found 545.3021, 559.3172. MS (ESI): *m/z* 559.3 $[M+MeOH+H]^+$. FTIR (thin film): 2947, 1745, 1643, 1605, 1504, 1466, 1250, 1173, 1134, 1049, 910, 833, 756 $cm^{-1}$. $[\alpha]_D^{20}$: –3.8° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.32 (50% toluene/acetone).

**(*S*)-Pentyloxy-5-(*N*-[4-(tert-butyldimethylsilyloxy)phenyl]benzamidyl)-2-piperidine carboxylate** (**14d).** Starting from **13d** (0.24 g, 0.37 mmol), **14d** was synthesized according to General Procedure D. Flash-chromatography (47/38/5% ? 45/45/10% toluene/acetone/methanol) provided **14d** as a slightly yellow oil (0.19 g, 0.35 mmol, 94%). $^1$H NMR (200 MHz, $CDCl_3$): δ 0.17 (s, 6H), 0.97 (s, 9H), 1.40-1.80 (m, 11H), 1.99-2.11 (m, 1H), 2.70-2.80 (m, 1H), 3.20-3.40 (m, 1H), 3.50-3.60 (m, 1H), 3.96 (t, 2H, *J* = 6.0 Hz), 4.16 (t, 2H, *J* = 6.0 Hz), 5.89 (bs, 1H), 6.79 (d, 2H, *J* = 8.8 Hz), 6.86 (d, 2H, *J* = 8.8 Hz), 7.47 (d, 2H, *J* = 8.8 Hz), 7.78 (d, 2H, *J* = 8.8 Hz), 8.10 (s, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$): δ –4.6, 18.0, 22.1, 25.6, 27.0, 27.9, 28.4, 44.5, 57.4, 65.7, 67.5, 114.0, 120.0, 122.1, 126.8, 128.9, 131.8, 152.2, 161.5, 165.6, 171.6 ppm. HRMS: calcd for $C_{30}H_{47}N_2O_6Si$ $[M+H_2O+H]^+$ 559.3198, $C_{31}H_{49}N_2O_6Si$ $[M+MeOH+H]^+$ 573.3354, found 559.3217, 573.3352. MS (ESI): *m/z* 573.4 $[M+MeOH+H]^+$. FTIR (thin film): 2947, 1745, 1674, 1605, 1504, 1250, 1180, 1134, 910, 833, 756 $cm^{-1}$. $[\alpha]_D^{20}$: –4.2° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.34 (50% toluene/acetone).

**(*S*)-Propyloxy-3-(*N´*-[4-(tert-butyldimethylsilyloxy)phenyl]benzamidyl) *N*-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl)]-2-piperidine carboxylate** (**16b)**. Starting from **14b** (190 mg, 0.37 mmol) and **15** (133 mg, 0.56 mmol), **16b** was synthesized according to General Procedure E. Flash-chromatography (91% ? 80% toluene/acetone) provided **16b** as a colorless oil (249 mg, 0.34 mmol, 92%). $^1$H NMR (200 MHz, $CDCl_3$, 4:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 0.18 (s, 6H), 0.98 (s, 9H), 1.40-1.90 (m, 5H), 2.10-2.40 (m, 3H), 3.15-3.30 (m, 1H), 3.40-3.55 (m, 1H), 3.90 (s, 6H), 3.93 (s, 3H), 4.12 (t, 2H, *J* = 6.0 Hz), 4.39 (t, 2H, *J* = 6.0 Hz), 5.30-5.40 (m, 1H), 6.80 (d, 2H, *J* = 8.8 Hz), 6.91 (d, 2H, *J* = 8.8 Hz), 7.32 (s, 2H), 7.47 (d, 2H, *J* = 8.8 Hz), 7.81 (d, 2H, *J* = 8.8 Hz), 8.05 (s, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 4:1 mixture of trans-cis amide rotamers, data for major rotamer): δ –4.7, 17.9, 20.8, 24.4, 25.4, 26.0, 28.2, 44.0, 51.5, 56.1, 60.7, 62.1, 63.9, 106.6, 113.8, 119.9, 121.7, 127.2, 127.7, 128.8, 131.9, 143.7, 151.8, 153.2, 160.9, 165.0, 167.7, 170.0, 190.5 ppm. HRMS: calcd for $C_{39}H_{51}N_2O_{10}Si$ $[M+H]^+$ 735.3308, $C_{39}H_{50}N_2O_{10}SiNa$ $[M+Na]^+$ 757.3127, found 735.3290, 757.3095. MS (ESI): *m/z* 735.5 $[M+H]^+$, 757.5 $[M+Na]^+$, 1469.8 $[2M+H]^+$. FTIR (thin film): 2947, 1736, 1643, 1605, 1504, 1458, 1412, 1327,

1250, 1126, 1003, 910, 833, 779 $cm^{-1}$. $[\alpha]_D^{20}$: –6.0° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.56 (80% toluene/acetone).

**(*S*)-Butyloxy-4-(*N´*-[4-(tert-butyldimethylsilyloxy)phenyl]benzamidyl) *N*-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl)]-2-piperidine carboxylate** (**16c)**. Starting from **14c** (247 mg, 0.47 mmol) and **15** (169 mg, 0.71 mmol), **16c** was synthesized according to General Procedure E. Flash-chromatography (91% ? 80% toluene/acetone) provided **16c** as a white foam (265 mg, 0.35 mmol, 75%). $^1$H NMR (200 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 0.19 (s, 6H), 0.98 (s, 9H), 1.50-2.00 (m, 9H), 2.30- 2.40 (m, 1H), 3.10-3.32 (m, 1H), 3.40-3.55 (m, 1H), 3.92 (s, 6H), 3.94 (s, 3H), 4.07 (t, 2H, *J* = 5.9 Hz), 4.28 (t, 2H, *J* = 5.9 Hz), 5.30-5.40 (m, 1H), 6.81 (d, 2H, *J* = 8.8 Hz), 6.92 (d, 2H, *J* = 8.8 Hz), 7.35 (s, 2H), 7.48 (d, 2H, *J* = 8.8 Hz), 7.82 (d, 2H, *J* = 8.8 Hz), 7.91 (s, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ –4.7, 17.9, 20.9, 24.4, 25.3, 25.4, 25.9, 44.0, 51.5, 56.1, 56.5, 60.7, 65.0, 67.0, 106.6, 113.8, 119.8, 121.7, 127.0, 127.7, 128.8, 132.0, 143.7, 151.8, 153.2, 161.0, 165.0, 167.7, 170.0, 190.6 ppm. HRMS: calcd for $C_{40}H_{53}N_2O_{10}Si$ $[M+H]^+$ 749.3464, $C_{40}H_{52}N_2O_{10}SiNa$ $[M+Na]^+$ 771.3283, found 749.3447, 771.3267. MS (ESI): *m/z* 749.4 $[M+H]^+$, 771.3 $[M+Na]^+$, 1497.6 $[2M+H]^+$. FTIR (thin film): 2947, 1736, 1643, 1504, 1458, 1412, 1327, 1250, 1119, 1003, 910, 833, 779 $cm^{-1}$. $[\alpha]_D^{20}$: –5.6° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.62 (80% toluene/acetone).

**(*S*)-Pentyloxy-5-(*N´*-[4-(tert-butyldimethylsilyloxy)phenyl]benzamidyl) *N*-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl)]-2-piperidine carboxylate** (**16d)**. Starting from **14d** (166 mg, 0.31 mmol) and **15** (112 mg, 0.47 mmol), **16d** was prepared according to General Procedure E. Flash-chromatography (91% ? 80% toluene/acetone) provided **16d** as a colorless oil (166 mg, 0.22 mmol, 71%). $^1$H NMR (200 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 0.17 (s, 6H), 0.97 (s, 9H), 1.49-1.90 (m, 11H), 2.30-2.40 (m, 1H), 3.10-3.30 (m, 1H), 3.40-3.51 (m, 1H), 3.90 (s, 6H), 3.92 (s, 3H), 4.01 (t, 2H, *J* = 6.2 Hz), 4.22 (t, 2H, *J* = 6.2 Hz), 5.30-5.40 (m, 1H), 6.79 (d, 2H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 7.33 (s, 2H), 7.46 (d, 2H, *J* = 8.8 Hz), 7.79 (d, 2H, *J* = 8.8 Hz), 7.94 (s, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ –4.7, 17.9, 20.9, 22.3, 24.5, 25.5, 26.0, 28.1, 28.4, 44.1, 51.6, 56.1, 60.7, 65.2, 67.5, 106.7, 113.9, 119.9, 121.7, 126.9, 127.8, 128.8, 132.0, 143.7, 151.9, 153.3, 161.3, 165.1, 167.7, 170.1, 190.6 ppm. HRMS: calcd for $C_{41}H_{55}N_2O_{10}Si$ $[M+H]^+$ 763.3621, $C_{41}H_{54}N_2O_{10}SiNa$ $[M+Na]^+$ 785.3440, found 763.3598, 785.3436. MS (ESI): *m/z* 763.5 $[M+H]^+$, 785.3 $[M+Na]^+$. FTIR (thin film): 2939, 1736, 1643, 1504, 1458, 1412, 1327, 1250, 1119, 1003, 910, 833, 779 $cm^{-1}$. $[\alpha]_D^{20}$: –5.6° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.68 (80% toluene/acetone).

**(*S*)-Propyloxy-3-(*N´*-[4-(hydroxy)phenyl]benzamidyl) *N*-[2-oxo-2-(3,4,5-trimethoxy-phenyl)acetyl)]-**

**2-piperidine carboxylate** (**3b).** Starting from **16b** (235 mg, 0.32 mmol), **3b** was synthesized according to General Procedure F. Flash-chromatography (75% toluene/acetone) provided **3b** as a colorless oil (161 mg, 0.26 mmol, 81%). $^{1}$H NMR (500 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 1.21-1.32 (m, 1H), 1.42-1.53 (m, 1H), 1.58-1.62 (m, 1H), 1.70-1.79 (m, 2H), 2.09-2.20 (m, 2H), 2.29-2.34 (m, 1H), 3.23 (dt, 1H, *J* = 13.1, 3.1 Hz), 3.40-3.47 (m, 1H), 3.83 (s, 6H), 3.89 (s, 3H), 4.05 (t, 2H, *J* = 6.0 Hz), 4.32-4.40 (m, 2H), 5.29-5.32 (m, 1H), 6.72 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 7.29 (s, 2H), 7.31 (d, 2H, *J* = 8.8 Hz), 7.41 (bs, 1H), 7.76 (d, 2H, *J* = 8.8 Hz), 8.28 (bs, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 20.9, 24.4, 26.1, 28.3, 44.3, 51.8, 56.2, 60.8, 62.4, 64.1, 106.8, 114.0, 115.5, 122.9, 126.8, 127.7, 129.0, 130.1, 143.9, 153.4, 153.6, 161.2, 165.9, 168.0, 170.1, 190.6 ppm. HRMS: calcd for $C_{33}H_{37}N_2O_{10}$ $[M+H]^+$ 621.2443, $C_{33}H_{36}N_2O_{10}Na$ $[M+Na]^+$ 643.2262, found 621.2416, 643.2258. MS (ESI): *m/z* 621.4 $[M+H]^+$, 643.3 $[M+Na]^+$, 1241.6 $[2M+H]^+$. FTIR (thin film): 1736, 1636, 1504, 1450, 1327, 1242, 1119, 1049, 995, 918, 833, 756 $cm^{-1}$. $[\alpha]_D^{20}$: –5.4° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.32 (75% toluene/acetone).

**(*S*)-Butoxy-4-(*N´*-[4-(hydroxy)phenyl]benzamidyl) *N*-[2-oxo-2-(3,4,5-trimethoxy-phenyl)acetyl)]-2-piperidine carboxylate** (**3c).** Starting from **16c** (260 mg, 0.35 mmol), **3c** was synthesized according to General Procedure F. Flash-chromatography (75% toluene/acetone) provided **3c** as a white foam (178 mg, 0.28 mmol, 80%). $^{1}$H NMR (500 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 1.22-1.38 (m, 1H), 1.42-1.56 (m, 1H), 1.59-1.64 (m, 1H), 1.69-1.78 (m, 3H), 1.80-1.84 (m, 3H), 2.20-2.34 (m, 1H), 3.24 (dt, 1H, *J* = 13.1, 3.0 Hz), 3.40- 3.48 (m, 1H), 3.87 (s, 6H), 3.91 (s, 3H), 3.93-3.98 (m, 2H), 4.20-4.30 (m, 2H), 5.26-5.29 (m, 1H), 6.71 (d, 2H, *J* = 8.8 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 7.29-7.33 (m, 4H), 7.63 (bs, 1H), 7.76 (d, 2H, *J* = 8.8 Hz), 8.34 (s, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 20.9, 24.5, 25.2, 26.0, 44.3, 51.7, 56.2, 60.8, 65.2, 67.1, 106.8, 114.0, 115.4, 122.8, 126.6, 127.7, 128.9, 130.1, 143.8, 153.3, 153.5, 161.3, 165.9, 167.9, 170.1, 190.7 ppm. HRMS: calcd for $C_{34}H_{39}N_2O_{10}$ $[M+H]^+$ 635.2599, $C_{34}H_{38}N_2O_{10}Na$ $[M+Na]^+$ 657.2419, found 635.2583, 657.2388. MS (ESI): *m/z* 635.4 $[M+H]^+$, 657.8 $[M+Na]^+$, 1269.9 $[2M+H]^+$. FTIR (thin film): 1736, 1636, 1504, 1450, 1327, 1242, 1119, 1049, 1003, 833, 756 $cm^{-1}$. $[\alpha]_D^{20}$: –6.0° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.36 (75% toluene/acetone).

**(*S*)-Pentyloxy-5-(*N´*-[4-(hydroxy)phenyl]benzamidyl) *N*-[2-oxo-2-(3,4,5-trimethoxy-phenyl)acetyl)]-2-piperidine carboxylate** (**3d).** Starting from **16d** (160 mg, 0.21 mmol), **3d** was synthesized according to General Procedure F. Flash-chromatography (80% ? 75% toluene/acetone) provided **3d** as a colorless oil (121 mg, 0.19 mmol, 89%). $^{1}$H NMR (500 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 1.30-1.57 (m, 4H), 1.59-1.64 (m, 1H), 1.70-1.83 (m, 6H), 2.30-2.35 (m, 1H), 3.25 (dt, 1H, *J* = 13.0, 3.0 Hz), 3.40-3.48 (m, 1H), 3.89 (s, 6H), 3.91 (s, 3H), 3.96 (t, 2H, *J* = 6.3 Hz), 4.20 (t, 2H,

*J* = 6.4 Hz), 5.30-5.3 (m, 1H), 6.73 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 7.30-7.34 (m, 4H), 7.77 (d, 2H, *J* = 8.8 Hz), 8.18 (s, 1H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 21.0, 22.4, 24.6, 26.1, 27.3, 28.2, 28.5, 44.3, 51.8, 56.3, 60.9, 65.4, 67.6, 106.9, 114.1, 115.6, 122.9, 126.6, 127.8, 128.9, 130.1, 143.9, 153.4, 153.6, 161.6, 165.9, 167.9, 170.2, 190.7 ppm. HRMS: calcd for $C_{35}H_{41}N_2O_{10}$ $[M+H]^+$ 649.2756, $C_{35}H_{40}N_2O_{10}Na$ $[M+Na]^+$ 671.2575, found 649.2734, 671.2557. MS (ESI): *m/z* 649.4 $[M+H]^+$, 671.3 $[M+Na]^+$, 1297.8 $[2M+H]^+$. FTIR (thin film): 1736, 1636, 1504, 1450, 1327, 1242, 1119, 1049, 1003, 833, 748 $cm^{-1}$. $[\alpha]_D^{20}$: –5.6° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.43 (75% toluene/acetone).

**(*S*)-Methyl 1-(2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl)pyrrolidine-2-carboxylate (26).** Starting from **19** (500 mg, 1.5 mmol) and methanol (used as solvent), **26** was synthesized according to General Procedure C. Flash-chromatography (96% ? 92% toluene/acetone) provided **26** as a slightly yellow foam (0.47 g, 1.35 mmol, 90%). $^1$H NMR (200 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 1.93-2.15 (m, 3H), 2.20-2.40 (m, 1H), 3.49-3.65 (m, 2H), 3.80 (s, H), 3.95 (s, 9H), 4.60-4.71 (m, 1H), 7.41 (s, 2H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 24.0, 28.4, 46.6, 51.7, 55.7, 57.6, 60.2, 106.6, 127.2, 143.4, 152.9, 165.0, 171.3, 189.7 ppm. HRMS: calcd for $C_{17}H_{22}NO_7$ $[M+H]^+$ 352.1391, found 352.1389. MS (ESI): *m/z* 351.9 $[M+H]^+$, 374.0 $[M+Na]^+$, 703.3 $[2M+H]^+$, 725.3 $[2M+Na]^+$. FTIR (thin film): 1744, 1643, 1582, 1450, 1412, 1327, 1096, 1049, 995, 872 $cm^{-1}$. $[\alpha]_D^{20}$: +23.0° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.56 (75% toluene/acetone).

**(*S*)-*S*-Methyl 1-(2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl)pyrrolidine-2-carbothioate (27).** A suspension of $LiAlH_4$ (76 mg, 2 mmol) and 1,2-dimethyldisulfide (188 mg, 178 µL, 2 mmol) in dry diethylether (5 mL) was stirred at room temperature for 1 h under argon. The suspension was filtered through Hyflo and added dropwise at a temperature of 0°C to a solution of **19** (1.35 g, 4 mmol) and EDC*HCl (0.77 g, 4 mmol) in dry diethylether (30 mL). After 30 min the mixture was allowed to warm up to room temperature and stirring was continued for 16 h. Subsequently, the mixture was concentrated in vacuo and the remainig residue was purified by flash-chromatography (80% petroleum ether/acetone) providing **27** as a colorless foam (1.03 g, 2.8 mmol, 70%). $^1$H NMR (200 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 1.90-2.33 (m, 4H), 2.37 (s, 3H), 3.53-3.64 (m, 2H), 3.94 (s, 3H), 3.96 (s, 6H), 4.84-4.90 (m, 1H), 7.39 (s, 2H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ - 11.3, 24.3, 29.9, 47.3, 56.2, 60.9, 65.3, 107.2, 127.7, 144.0, 153.3, 165.5, 190.0, 198.9 ppm. HRMS: calcd for $C_{17}H_{22}NO_6S$ $[M+H]^+$ 368.1162, found 368.1155. MS (ESI): *m/z* 367.9 $[M+H]^+$, 390.0 $[M+Na]^+$, 735.2 $[2M+H]^+$. FTIR (thin film): 1639, 1582, 1504, 1458, 1416, 1327, 1234, 1157, 1088, 1045, 999, 748 $cm^{-1}$. $[\alpha]_D^{20}$: –7.0° (c = 10mg/mL, $CHCl_3$). TLC: $R_f$ = 0.77 (67%

toluene/acetone).

**(*S*)-*N*-Methyl-1-(2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl)pyrrolidine-2-carboxamide (28).** Methylamine hydrochloride (0.27 g, 4 mmol) was added at a temperature of 0°C to a solution of **19** (1.35 g, 4 mmol), EDC*HCl (0.77 g, 4 mmol), HOBt (1.11 g, 8 mmol), DIPEA (1.03 g, 1.32 mL, 8 mmol) and a catalytic amount of DMAP in absolute dichloromethane (50 mL). After 30 min the cooling bath was removed and stirring was continued for 16h. The mixture was concentrated in vacuo and the remaining residue was purified by flash-chromatography (80% toluene/acetone) providing **28** as a mix of the rotamers (0.56 g, 1.6 mmol, 40%). $^{1}$H NMR (200 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 1.94-2.22 (m, 4H), 2.83 (d, 2H, *J* = 4.8 Hz), 3.48-3.56 (m, 2H), 3.85 (s, 3H), 3.95 (s, 6H), 4.56-4.63 (m, 1H), 6.85 (bq, 1H), 7.35 (s, 2H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, 5:1 mixture of trans-cis amide rotamers, data for major rotamer): δ 24.4, 25.9, 29.0, 47.3, 56.1, 59.3, 60.5, 106.9, 127.3, 133.2, 143.6, 153.1, 165.7, 171.2, 190.1 ppm. HRMS: calcd for $C_{17}H_{23}N_2O_6$ $[M+H]^+$ 351.1551, found 351.1543. MS (ESI): *m/z* 351.0 $[M+H]^+$, 373.0 $[M+Na]^+$, 701.3 $[2M+H]^+$, 723.3 $[2M+Na]^+$. FTIR (thin film): 2970, 2160, 1636, 1582, 1450, 1412, 1327, 1234, 1119, 1049, 995, 748 $cm^{-1}$. $[\alpha]_D^{20}$: –40.7° (c = 10 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.26 (75% toluene/acetone).

**(*S*)-1-(2-(1-(Methoxyimino)ethyl)pyrrolidin-1-yl)-2-(3,4,5-trimethoxyphenyl)ethane-1,2-dione (30).** Acetic acid (2 mL) was added at room temperature to a solution of **25** (335 mg, 1 mmol) and methoxylamine hydrochloride (84 mg, 1 mmol) in a mix of ethyl acetate, methanol and water (15 mL, 12:2:1). After stirring for 4 h at room temperature, the mixture was transferred with EtOAc (100 mL) to a separation funnel. The organic layer was washed twice with 1N $NaHCO_3$ (20 mL) and with brine (20 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo and the remaining residue was purified by flash-chromatography (33% petroleum ether/ethyl acetate) providing **30** as an unseparable mixture of rotamers and E/Z isomers (145 mg, 0.4 mmol, 40%). $^{1}$H NMR (200 MHz, $CDCl_3$, data for major isomer): δ 1.88 (s, 3H), 1.90-2.42 (m, 4H), 3.45-3.75 (m, 2H), 3.87 (s, 3H), 3.90 (s, 6H), 3.94 (s, 3H), 4.69-4.76 (m, 1H), 7.29 (s, 2H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$, data for major isomer): δ 16.2, 25.1, 29.1, 47.8, 56.3, 60.1, 60.6, 61.6, 107.7, 127.8, 144.3, 153.3, 157.5, 164.8, 189.6 ppm. HRMS: calcd for $C_{18}H_{24}N_2O_6$ $[M+H]^+$ 365.1707, found 365.1701. MS (ESI): *m/z* 365.20 $[M+H]^+$, 387.20 $[M+Na]^+$, 751.27 $[2M+Na]^+$. FTIR (thin film): 1680, 1647, 1582, 1501, 1412, 1327, 1157, 1123, 999, 860, 745 $cm^{-1}$. $[\alpha]_D^{20}$: –74.5° (c = 5 mg/mL, $CHCl_3$). TLC: $R_f$ = 0.67 (33% toluene/ethyl acetate).

***N*-(Hydroxybutoxy)phthalimide (34).** 4-Bromo-1-propanol (5 g, 32.7 mmol) was dissolved in DMF (15 mL) and added dropwise over a period of three hours to a solution of *N*-Hydroxyphthalimide (6.4 g, 39.2 mmol) and $NEt_3$ (5.4 mL, 3.95 g, 39.2 mmol) in DMF (40 mL) at 85°C. The mixture was stirred at 85°C for 16 h after which it was concentrated in vacuo and the residue was transferred to a separation funnel with

EtOAc (300 mL). The organic layer was washed with 100 mL portions of 1N $NaHCO_3$ until disappearance of the red colour of the *N*-Hydroxyphthalimide anion (~six times). The organic layer was washed once with 1N HCl (100 mL) and once with brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Flash-chromatography (83% toluene/acetone 5:1) provided **34** as waxy solid (1.93 g, 8.20 mmol, 25%). The analytical data is in agreement with the reported data.[1]

**2-(Tritylthio)acetic acid (37).** A mixture of α-bromoacetic acid (4.03 g, 29 mmol), triphenylmethyl mercaptan (8.82 g, 31.9 mmol) and DIPEA (4.65 g, 5.95 mL, 36 mmol) in DMF (30 mL) was stirred at room temperature for 4 h. The mixture was tranferred with 1N $NaHCO_3$ (150 mL) and ethyl acetate (50 mL) to a separation funnel. The basic layer was separated and washed another time with ethyl acetate (50 mL), then it was acidified with 2N HCl (200 mL) and the aqueous layer was ectracted twice with ethyl acetate (2x 300 mL). The combined organic layers were washed with brine (50 mL) and concentrated in vacuo. **37** was obtained as colorless foam (8.1 g, 24.2 mmol, 84%). The analytical data is in agreement with reported data.[2]

***N*-(2-Hydroxyethyl)-2-(tritylthio)acetamide (38).** Ethanolamine (1.22 g, 1.2 mL, 20 mmol) was added at -78°C to a solution of **37** (1.67 g, 5 mmol), EDC*HCl (1.44 g, 7.5 mmol) and HOBt (1.36 g, 10 mmol) in a mixture of absolute dichloromethane and THF (1:1, 100 mL). After 30 min the mixture was allowed to warm up to room temperature and was stirred for another 16 h. The mixture was concentrated in vacuo and the remaining residue was purified by flash-chromatography (75% toluene/acetone) to afford **38** as a white solid (1.32 g, 3.5 mmol, 70%). $^1$H NMR (200 MHz, $CDCl_3$): δ 2.74 (bs, 1H), 3.08 (dt, $J$ = 5.1, 5.5 Hz, 2H), 3.12 (s, 2H), 3.48 (t, $J$ = 5.1 Hz), 6.43 (bt, 1H), 7.20-7.33 (m, 15H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$): δ 35.6, 42.1, 60.7, 67.4, 126.7, 127.9, 129.1, 143.6, 168.9 ppm. HRMS: calcd for $C_{23}H_{23}NO_2SNa$ $[M+Na]^+$ 400.1342, found 400.1338. MS (ESI): *m/z* 400.0 $[M+Na]^+$, 755.5 $[2M+H]^+$,777.5 $[2M+Na]^+$. FTIR (thin film): 1628, 1551, 1396, 1288, 1211, 1173, 1034 $cm^{-1}$. TLC: $R_f$ = 0.37 (75% toluene/acetone).

**1-(Aziridin-1-yl)-2-(tritylthio)ethanone.** Was the major product formed from **38** during the attempted synthesis of **43** via Mitsunobu coupling. $^1$H NMR (200 MHz, $CDCl_3$): δ 2.93 (s, 2H), 3.73 (t, $J$ = 9.5 Hz, 2H), 4.16 (t, $J$ = 9.5 Hz, 2H), 7.10-7.45 (m, 15H) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$): δ 28.4, 54.3, 66.6, 67.5, 126.6, 127.7, 129.2, 143.8, 164.2 ppm. HRMS: calcd for $C_{23}H_{22}NOS$ $[M+H]^+$ 360.1417, found 360.1406. MS (ESI): *m/z* 360.0 $[M+H]^+$, 382.0 $[M+Na]^+$. FTIR (thin film): 1740, 1651, 1443, 1412, 1327, 1042, 995, 918, 833, 748, 694 $cm^{-1}$. TLC: $R_f$ = 0.71 (80% toluene/acetone).

**4-(2-Azidoethyl)benzoic acid (46).** Trifluoromethanesulfonyl azide was prepared fresh prior to the reaction as follows. Six molar equivalents per substrate amine of $NaN_3$ (1.94 g, 29.75 mmol) were dissolved in a minimum volume of water (5 mL) and cooled to 0°C. An equal volume of $CH_2Cl_2$ (5 mL) was added,

followed by slow addition of trifluoromethanesulfonic anhydride (2.5 mL, 14.88 mmol, 3 equiv. per substrate amine) to the vigorously stirred solution. The reaction was stoppered and stirring was continued at 0ºC for 2 h. Saturated $NaHCO_3$ was added carefully while stirring continued and subsequently the mixture was transferred to a separatory funnel after $CO_2$ evolution had ceased. The aqueous phase was washed twice with $CH_2Cl_2$ (3.6 mL) and the combined organic layers were washed once with saturated $NaHCO_3$. The solution, approximately 0.6 M of $TfN_3$ based on 50% conversion, was used without further purification. Amine **45** (1.0 g, 4.96 mmol), $K_2CO_3$ (1.03 g, 7.44 mmol, 1.5 equiv.) and $CuSO_4 \cdot 5H_2O$ (12.5 mg, 0.05 mmol) were dissolved in water (12 mL). The freshly prepared $TfN_3$-containing $CH_2Cl_2$ solution (1.5 equiv.) was added at once under vigorous stirring. Methanol (40 mL) was added slowly, to obtain the desired 3:10:3 ratio of $H_2O/CH_3OH/CH_2Cl_2$. The reaction was stirred until TLC (10% EtOAc/MeOH) indicated complete consumption of starting material (~16 h). For safety reasons, the flask was left open for several hours to allow residual $TfN_3$ to evaporate. Subsequently, the mixture was concentrated in vacuo. The aqueous solution was acidified with 1N HCl to pH2 and was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash-chromatography (95% ? 90% toluene/methanol) to afford **46** as a yellowish powder (0.94 g, 4.91 mmol, 99%). $^1$H NMR (200 MHz, $CDCl_3$): δ 2.97 (t, 2H, *J* = 7.1 Hz), 3.57 (t, 2H, *J* = 7.1 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 8.08 (d, 2H, *J* = 8.4 Hz) ppm. $^{13}$C NMR (50.2 MHz, $CDCl_3$): δ 35.4, 51.9, 127.9, 128.9, 130.6, 144.5, 171.7 ppm. MS (ESI): *m/z* calcd 192.0 $[M+H]^+$, found 192.1. FTIR (thin film): 2100, 1674, 1605, 1420, 1288, 1234, 1042, 941, 895, 849, 764 $cm^{-1}$. TLC: $R_f$ = 0.49 (66% toluene/acetone).


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[2] Z. Kupihar, Z. Schmel, Z. Kele, B. Penke, L. Kovacs, *Bioorg. Med. Chem.* **2001**, *9*, 1241 – 1248.