Supporting Information

Discovery of the Novel Antithrombotic Agent 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)-phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (BAY 59-7939) – an Oral, Direct Factor Xa Inhibitor

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Experimental Section

Chemistry

General. Unless otherwise noted, all non-aqueous reactions were carried out under an argon atmosphere with commercial-grade reagents and solvents. Melting points (uncorrected) were determined in open capillaries using a Büchi 530 apparatus. NMR spectra were recorded on Bruker Avance spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. Mass spectra were obtained on PE SIEX API 150 (ESIpos) or on AMD M40-DF (DCI). High-resolution mass spectra (HR MS) were acquired on a Waters LTC. Analytical HPLC was performed using Hewlett-Packard 1100 instruments under the following conditions: UV detection at 210 nm; column: Reprosil ODS-A 5 µm, 250 mm × 4 mm, temperature: 25°C, flow: 1.0 $mLmin^{-1}$, eluents: A: water, B: acetonitrile, [method 1a]: isocratic 50%/50%, [method 1b]: isocratic 60%/40%; column: Inertsil Phenyl 5 µm, 250 mm × 3 mm, temperature: 25°C, flow: 0.6 $mLmin^{-1}$, eluents: A: water, B: acetonitrile, [method 2]: isocratic 60%/40%; column: Kromasil C18 60 mm × 2 mm, temperature: 30°C, flow: 0.75 $mLmin^{-1}$, eluents: A: 0.01 M H_3PO_4, B: acetonitrile, [method 3]: gradient: 0–0.5 min 90%A, 0.5–4.5 min 90%→10%A, 4.5–6.5 min 10%A, 6.5–7.5 min 90%A; column: Kromasil C18 60 mm × 2 mm, temperature: 30°C, flow: 0.75 $mLmin^{-1}$, eluents: A: 5 mL 70% $HClO_4$ in 1 L water, B: acetonitrile, [method 4a]: gradient: 0–0.5 min 98%A, 0.5–4.5 min 98%→10%A, 4.5–6.5 min 10%A, 6.5–6.7 min 10%→98%A, 6.7–7.5 min 98%A; [method 4b]: gradient: 0–0.5 min 98%A, 0.5–4.5 min 98%→10%A, 4.5–9.0 min 10%A, 9.0–9.2 min 10%→98%A, 9.2–10.0 min 98%A. Flash chromatography was performed using silica gel 60 (230–400 mesh). HPLC purifications were performed using RP phase (250 mm × 30 mm GROM-SIL 120, ODS-4HE 10 µm).

General Procedure A: Formation of amide VII. *N*‘-(3-Dimethylaminopropyl)-*N*-ethylcarbodiimide (EDCI) (1.3 eq.) and diisopropylethylamine (DIEA) (2.0 eq.) were added to a solution of amine **V**, carboxylic acid **VI** (1.0 eq.) and 1-hydroxy-1*H*-benzotriazol-hydrate (HOBt) (1.3 eq.) in dimethylformamide (5 $mLmmol^{-1}$) at room temperature. The reaction mixture was stirred at room temperature overnight and evaporated *in vacuo*. Purification by chromatography afforded amide **VII**.

5-Chloro-*N*-{[(5*S*)-3-(3-fluoro-4-thiomorpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}thiophene-2-carboxamide (4). Compound **4** was synthesized according to the general procedure A from 5-chlorothiophene-2-carboxylic acid and (5*S*)-5-(aminomethyl)-3-(3-fluoro-4-thiomorpholin-4-ylphenyl)-1,3-oxazolidin-2-one[1]. The residue was purified by Flash-LC (toluene/ethyl acetate gradient) to afford the title compound **4** (82% yield) as a colorless solid. mp: 193°C; ^{1}H-NMR (DMSO-d_6, 200 MHz): 8.98 (t, *J* = 5.7 Hz, 1H), 7.69 (d, *J* = 3.8 Hz, 1H), 7.53–7.40 (m, 1H), 7.25–7.03

(m, 2H), 7.22 (d, *J* = 3.8 Hz, 1H), 4.90–4.74 (m, 1H), 4.15 (t, *J* = 9.1 Hz, 1H), 3.87–3.72 (m, 1H), 3.59 (t, *J* = 5.7 Hz, 2H), 3.28–3.14 (m, 4H), 2.81–2.69 (m, 4H); MS (ESIpos): m/z: 456 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{19}H_{19}ClFN_3O_3S_2$): calcd 456.0614, found 456.0612; degree of purity: HPLC: rt (method 1a): 19.46 min (98%), rt (method 4b): 4.35 min (100%).

5-Chloro-*N*-{[(5*S*)-3-(3-fluoro-4-morpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}thiophene-2-carboxamide (6). Compound **6** was synthesized according to the general procedure A from 5-chlorothiophene-2-carboxylic acid and (5*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)-1,3-oxazolidin-2-one[2]. The residue was purified by Flash-LC (toluene/ethyl acetate gradient) to afford the title compound **6** (62% yield) as a colorless solid. mp: 197°C; ^{1}H-NMR (DMSO-d_6, 300 MHz): 8.92 (t, *J* = 5.7 Hz, 1H), 7.67 (d, *J* = 3.8 Hz, 1H), 7.46 (dd, *J* = 15.1 Hz, 2.7 Hz, 1H), 7.22–7.14 (m, 2H), 7.05 (t, *J* = 9.1 Hz, 1H), 4.88–4.76 (m, 1H), 4.13 (t, *J* = 9.1 Hz, 1H), 3.79 (dd, *J* = 9.1 Hz, 6.0 Hz, 1H), 3.76–3.68 (m, 4H), 3.59 (t, *J* = 5.7 Hz, 2H), 3.00–2.90 (m, 4H); MS (DCI, NH_3): m/z: 440 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{19}H_{19}ClFN_3O_4S$): calcd 440.0842, found 440.0849; degree of purity: HPLC: rt (method 1a): 7.97 min (95%), rt (method 2): 10.80 min (98%).

5-Chloro-*N*-{[(5*S*)-3-(3-fluoro-4-pyrrolidin-1-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}thiophene-2-carboxamide (8). Compound **8** was synthesized according to the general procedure A from 5-chlorothiophene-2-carboxylic acid and (5*S*)-5-(aminomethyl)-3-(3-fluoro-4-pyrrolidin-1-ylphenyl)-1,3-oxazolidin-2-one[3]. The residue was purified by Flash-LC (toluene/ethyl acetate gradient) to afford the title compound **8** (63% yield) as a colorless solid. mp: 216°C; ^{1}H-NMR (DMSO-d_6, 300 MHz): 8.97 (t, *J* = 5.7 Hz, 1H), 7.69 (d, *J* = 4.2 Hz, 1H), 7.37 (dd, *J* = 15.9 Hz, 2.5 Hz, 1H), 7.20 (d, *J* = 4.0 Hz, 1H), 7.08 (dd, *J* = 8.9 Hz, 2.5 Hz, 1H), 6.74 (t, *J* = 9.3 Hz, 1H), 4.86–4.73 (m, 1H), 4.11 (t, *J* = 9.1 Hz, 1H), 3.77 (dd, *J* = 9.1 Hz, 6.0 Hz, 1H), 3.58 (t, *J* = 5.7 Hz, 2H), 3.30–3.21 (m, 4H), 1.92–1.84 (m, 4H); MS (ESIpos): m/z: 424 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{19}H_{19}ClFN_3O_3S$): calcd 424.0893, found 424.0888; degree of purity: HPLC: rt (method 1a): 23.70 min (95%), rt (method 4b): 3.84 min (97%).

5-Chloro-*N*-({(5*S*)-3-[4-(dimethylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (9). Compound **9** was synthesized according to the general procedure A from 5-chlorothiophene-2-carboxylic acid and (5*S*)-5-(aminomethyl)-3-[4-(dimethylamino)phenyl]-1,3-oxazolidin-2-one[4]. The residue was purified by Flash-LC (toluene/ethyl acetate gradient) to afford the title compound **9** (51% yield) as a colorless solid. mp: 234°C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 8.96 (t, *J* = 5.6 Hz, 1H), 7.69 (d, *J* = 4.2 Hz, 1H), 7.31 (d, *J* = 9.1 Hz, 2H), 7.20 (d, *J* = 4.2 Hz, 1H), 6.73 (d, *J* =

9.3 Hz, 2H), 4.82–4.72 (m, 1H), 4.09 (t, *J* = 9.0 Hz, 1H), 3.76 (dd, *J* = 9.1 Hz, 6.1 Hz, 1H), 3.58 (t, *J* = 5.6 Hz, 2H), 2.86 (s, 6H); MS (ESIpos): m/z: 380 ($[M+H]^+$, 47%), 135 (100%); HR MS ($[M+H]^+$ for $C_{17}H_{18}ClN_3O_3S$): calcd 380.0831, found 380.0851; degree of purity: HPLC: rt (method 1a): 9.21 min (96%), rt (method 4b): 3.63 min (100%).

5-Chloro-*N*-{[(5*S*)-3-(4-morpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}thiophene-2-carboxamide (7). Compound **7** was synthesized from 4-morpholin-4-ylaniline according to the procedure described for **11**. mp: 198°C; ^{1}H-NMR (DMSO-d_6, 300 MHz): 8.93 (t, *J* = 5.9 Hz, 1H), 7.68 (d, *J* = 4.1 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 2H), 7.19 (d, *J* = 4.0 Hz, 1H), 6.95 (d, *J* = 9.1 Hz, 2H), 4.85–4.72 (m, 1H), 4.11 (t, *J* = 9.1 Hz, 1H), 3.78 (dd, *J* = 9.1 Hz, 6.2 Hz, 1H), 3.77–3.70 (m, 4H), 3.58 (t, *J* = 5.7 Hz, 2H), 3.10–3.01 (m, 4H); MS (ESIpos): m/z: 422 ($[M+H]^+$, 36%), 145 (100%); HR MS ($[M+H]^+$ for $C_{19}H_{20}ClN_3O_4S$): calcd 422.0936, found 422.0933; degree of purity: HPLC: rt (method 1a): 5.92 min (92%), rt (method 4b): 3.68 min (96%).

5-Chloro-*N*-{[(5*S*)-3-(3-fluoro-4-piperazin-1-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}thiophene-2-carboxamide (10). Compound **10** was synthesized by deprotection (trifluoroacidic acid in dichloromethane) of *tert*-butyl 4-{4-[(5*S*)-5-({[(5-chloro-2-thienyl)carbonyl]-amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]-2-fluorophenyl}piperazine-1-carboxylate, synthesized from *tert*-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate[5] according to the procedure described for **11**. ^{1}H-NMR (DMSO-d_6, 200 MHz): 9.00 (t, *J* = 5.6 Hz, 1H), 8.63–8.16 (broad s, 1H), 7.69 (d, *J* = 4.0 Hz, 1H), 7.50 (dd, *J* = 15.0 Hz, 2.3 Hz, 1H), 7.25–7.04 (m, 2H), 7.20 (d, *J* = 4.0 Hz, 1H), 4.91–4.73 (m, 1H), 4.14 (t, *J* = 9.2 Hz, 1H), 3.80 (dd, *J* = 9.1 Hz, 6.2 Hz, 1H), 3.59 (t, *J* = 5.4 Hz, 2H), 3.26–3.14 (m, 4H), 3.14–3.02 (m, 4H); MS (ESIpos): m/z: 439 ($[M+H]^+$, 52%), 145 (100%); HR MS ($[M+H]^+$ for $C_{19}H_{20}ClFN_4O_3S$): calcd 439.1002, found 439.0999; degree of purity: HPLC: rt (method 4b): 3.90 min (100%).

5-Chloro-*N*-{[(5*S*)-3-(2-methyl-4-morpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}thiophene-2-carboxamide (15). Compound **15** was synthesized from 2-methyl-4-morpholin-4-ylaniline[6] according to the procedure described for **11**. ^{1}H NMR (DMSO-d_6, 300 MHz): 9.02 (t, *J* = 5.9 Hz, 1H), 7.73 (d, *J* = 4.0 Hz, 1H), 7.22 (d, *J* = 4.0 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.86–6.75 (m, 2H), 4.88–4.75 (m, 1H), 3.97 (t, *J* = 8.9 Hz, 1H), 3.77–3.68 (m, 4H), 3.65–3.55 (m, 3H), 3.12–3.03 (m, 4H), 2.10 (s, 3H); MS (ESIpos): m/z: 436 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{20}H_{22}ClN_3O_4S$): calcd 436.1093, found 436.1078; degree of purity: HPLC: rt (method 1b): 12.75 min (97%), rt (method 4a): 3.77 min (98%).

5-Chloro-*N*-({(5*R*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (16). Compound **16** was synthesized from 2-[(2*R*)-oxiran-2-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione[7] and 4-(4-aminophenyl)morpholin-3-one[8] (**31**) according to the procedure described for **5**. ^{1}H NMR (DMSO-d_6, 300 MHz): 8.97 (t, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 4.0 Hz, 1H), 7.55 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 7.20 (d, *J* = 4.0 Hz, 1H), 4.89–4.78 (m, 1H), 4.25–4.12 (m, 1H), 4.19 (s, 2H), 4.01–3.92 (m, 2H), 3.85 (dd, *J* = 9.0 Hz, 6.0 Hz, 1H), 3.75–3.68 (m, 2H), 3.60 (t, *J* = 5.5 Hz, 2H); MS (ESIpos): m/z: 436 ([M+H]$^+$, 100%); HR MS ([M+H]$^+$ for $C_{19}H_{18}ClN_3O_5S$): calcd 436.0729, found 436.0726; degree of purity: HPLC: rt (method 1b): 5.77 min (100%), rt (method 4a): 3.82 min (100%).

4-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzamide (20). 4-Chlorobenzoyl chloride (72.1 mg, 0.4 mmol) was added to a solution of **34** (80.0 mg, 0.3 mmol) in pyridine (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h and diluted with pyridine (4 mL). Aminomethylpolystyrol resin (2.5 eq.) was added, and the reaction mixture was shaken for 1.5 h at room temperature. The resin was filtered and washed several times with a mixture of dichlormethane/methanol (5:1). The combined filtrates were evaporated *in vacuo*, and the resulting residue was purified by Flash-LC (mixtures of dichlormethane/methanol). The title compound **20** (105.1 mg, 89% yield) was obtained as a colorless solid. ^{1}H NMR (DMSO-d_6, 300 MHz): 8.90 (t, *J* = 5.9 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.60–7.50 (m, 4H), 7.40 (d, *J* = 8.9 Hz, 2H), 4.92–4.82 (m, 1H), 4.24–4.15 (m, 1H), 4.19 (s, 2H), 4.00–3.93 (m, 2H), 3.89 (dd, *J* = 9.3 Hz, 6.0 Hz, 1H), 3.76–3.68 (m, 2H), 3.68–3.59 (m, 2H); MS (DCI, NH_3): m/z: 447 ([M+NH_4]$^+$, 100%); HR MS ([M+H]$^+$ for $C_{21}H_{20}ClN_3O_5$): calcd 430.1165, found 430.1162; degree of purity: HPLC: rt (method 2): 5.53 min (95%), rt (method 4a): 3.76 min (98%).

The following compounds were synthesized according to the general procedure A from 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (**34**) and the respective carboxylic acid:

5-Bromo-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (17). ^{1}H NMR (DMSO-d_6, 300 MHz): 8.92 (t, *J* = 5.7 Hz, 1H), 7.62 (d, *J* = 4.1 Hz, 1H), 7.55 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 7.29 (d, *J* = 4.0 Hz, 1H), 4.90–4.78 (m, 1H), 4.24–4.13 (m, 1H), 4.19 (s, 2H), 4.00–3.92 (m, 2H), 3.85 (dd, *J* = 9.3 Hz, 6.2 Hz, 1H), 3.76–3.68 (m, 2H), 3.60 (t, *J* = 5.7 Hz, 2H); MS (ESIpos): m/z: 480 ([M+H]$^+$, 100%, Br-pattern); HR MS ([M+H]$^+$ for $C_{19}H_{18}BrN_3O_5S$): calcd 480.0224, found 480.0228; degree of purity: HPLC: rt (method 4a): 3.87 min (100%).

5-Methyl-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (18). ^{1}H NMR (DMSO-d_6, 200 MHz): 8.74 (t, *J* = 5.7 Hz, 1H), 7.62–7.50 (m, 3H), 7.40 (d, *J* = 9.0 Hz, 2H), 6.89–6.80 (m, 1H), 4.92–4.75 (m, 1H), 4.26–4.11 (m, 1H), 4.19 (s, 2H), 4.02–3.92 (m, 2H), 3.85 (dd, *J* = 9.1 Hz, 6.2 Hz, 1H), 3.78–3.68 (m, 2H), 3.58 (t, *J* = 5.6 Hz, 2H), 2.45 (s, 3H); MS (ESIpos): m/z: 831 ($[2M+H]^+$, 100%), 416 ($[M+H]^+$, 66%); HR MS ($[M+H]^+$ for $C_{20}H_{21}N_3O_5S$): calcd 416.1275, found 416.1271; degree of purity: HPLC: rt (method 1b): 4.13 min (100%), rt (method 4a): 3.65 min (100%).

5-Bromo-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-furamide (19). ^{1}H NMR (DMSO-d_6, 300 MHz): 8.79 (t, *J* = 5.7 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 2H), 7.41 (d, *J* = 9.1 Hz, 2H), 7.19 (d, *J* = 3.5 Hz, 1H), 6.77 (d, *J* = 3.6 Hz, 1H), 4.88–4.77 (m, 1H), 4.19 (s, 2H), 4.18 (t, *J* = 9.1 Hz, 1H), 4.00–3.93 (m, 2H), 3.86 (dd, *J* = 9.3 Hz, 6.0 Hz, 1H), 3.75–3.67 (m, 2H), 3.57 (t, *J* = 5.9 Hz, 2H); MS (ESIpos): m/z: 464 ($[M+H]^+$, 100%, Br-pattern); HR MS ($[M+H]^+$ for $C_{19}H_{18}BrN_3O_6$): calcd 464.0452, found 464.0441; degree of purity: HPLC: rt (method 2): 4.52 min (97%), rt (method 3): 3.31 min (100%).

3-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzamide (21). ^{1}H NMR (DMSO-d_6, 300 MHz): 8.98 (t, *J* = 5.7 Hz, 1H), 7.90–7.84 (m, 1H), 7.80 (m, 1H), 7.66–7.46 (m, 2H), 7.56 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 4.92–4.80 (m, 1H), 4.20 (t, *J* = 9.1 Hz, 1H), 4.19 (s, 2H), 4.01–3.92 (m, 2H), 3.89 (dd, *J* = 9.3 Hz, 6.1 Hz, 1H), 3.76–3.69 (m, 2H), 3.64 (m, *J* = 5.7 Hz, 2H); MS (DCI, NH_3): m/z: 447 ($[M+NH_4]^+$,100%); HR MS ($[M+H]^+$ for $C_{21}H_{20}ClN_3O_5$): calcd 430.1165, found 430.1164; degree of purity: HPLC: rt (method 1b): 5.48 min (100%), rt (method 4a): 3.79 min (100%).

2-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzamide (22). ^{1}H NMR (DMSO-d_6, 200 MHz): 8.86 (t, *J* = 5.8 Hz, 1H), 7.63–7.50 (m, 3H), 7.48–7.32 (m, 5H), 4.97–4.81 (m, 1H), 4.29–4.14 (m, 1H), 4.19 (s, 2H), 4.03–3.86 (m, 3H), 3.78–3.56 (m, 4H); MS (DCI, NH_3): m/z: 447 ($[M+NH_4]^+$, 100%); HR MS ($[M+H]^+$ for $C_{21}H_{20}ClN_3O_5$): calcd 430.1165, found 430.1176; degree of purity: HPLC: rt (method 1b): 3.70 min (100%), rt (method 3): 3.25 min (100%).

4-Amino-5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (23). The compound **23** was synthesized from **34** and 4-amino-5-chlorothiophene-2-carboxylic acid[9] according to the general procedure A. ^{1}H NMR (DMSO-d_6,

300 MHz): 8.80 (t, *J* = 5.8 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 7.25 (s, 1H), 5.17 (broad s, 2H), 4.88–4.77 (m, 1H), 4.19 (s, 2H), 4.17 (t, *J* = 9.1 Hz, 1H), 4.01–3.92 (m, 2H), 3.84 (dd, *J* = 9.3 Hz, 6.2 Hz, 1H), 3.76–3.68 (m, 2H), 3.56 (t, *J* = 5.7 Hz, 2H); MS (ESIpos): m/z: 451 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{19}H_{19}ClN_4O_5S$): calcd 451.0838, found 451.0827; degree of purity: HPLC: rt (method 1b): 3.52 min (99%), rt (method 4b): 3.36 min (100%).

2-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1,3-thiazole-5-carboxamide (24). ^{1}H NMR (DMSO-d_6, 300 MHz): 9.16 (t, *J* = 5.8 Hz, 1H), 8.27 (s, 1H), 7.56 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 4.90–4.80 (m, 1H), 4.24–4.15 (m, 1H), 4.19 (s, 2H), 4.01–3.91 (m, 2H), 3.85 (dd, *J* = 9.3 Hz, 6.2 Hz, 1H), 3.75–3.67 (m, 2H), 3.62 (t, *J* = 5.7 Hz, 2H); MS (ESIpos): m/z: 437 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{18}H_{17}ClN_4O_5S$): calcd 437.0681, found 437.0685; degree of purity: HPLC: rt (method 1b): 3.75 min (100%), rt (method 4a): 3.57 min (100%).

5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)pyridine-2-carboxamide (25). The compound **25** was synthesized from **34** and 5-chloropyridine-2-carboxylic acid[10] according to the general procedure A. ^{1}H NMR (DMSO-d_6, 300 MHz): 9.12 (t, *J* = 5.9 Hz, 1H), 8.72 (d, *J* = 2.4 Hz, 1H), 8.13 (dd, *J* = 8.3 Hz, 2.4 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 4.93–4.83 (m, 1H), 4.20 (s, 2H), 4.19 (t, *J* = 9.1 Hz, 1H), 4.00–3.93 (m, 2H), 3.92 (dd, *J* = 9.1 Hz, 6.3 Hz, 1H), 3.74–3.59 (m, 4H); MS (ESIpos): m/z: 431 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{20}H_{19}ClN_4O_5$): calcd 431.1122, found 431.1123; degree of purity: HPLC: rt (method 1b): 3.66 min (100%), rt (method 4b): 3.63 min (100%).

6-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)nicotinamide (26). ^{1}H NMR (DMSO-d_6, 300 MHz): 9.08 (t, *J* = 5.8 Hz, 1H), 8.82 (d, *J* = 2.5 Hz, 1H), 8.22 (dd, *J* = 8.3 Hz, 2.5 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 4.95–4.82 (m, 1H), 4.20 (t, *J* = 9.1 Hz, 1H), 4.19 (s, 2H), 4.02–3.93 (m, 2H), 3.89 (dd, *J* = 9.2 Hz, 6.0 Hz, 1H), 3.75–3.62 (m, 4H); MS (ESIpos): m/z: 431 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{20}H_{19}ClN_4O_5$): calcd 431.1122, found 431.1121; degree of purity: HPLC: rt (method 1b): 3.21 min (100%), rt (method 4b): 3.50 min (100%).

5-Chloro-*N*-methyl-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (27). Sodium hydride (60% dispersion in mineral oil, 10.1 mg, 0.25 mmol) was added to a solution of **5** (100 mg, 0.3 mmol) in dimethylformamide (2 mL) at room temperature. The reaction mixture was stirred for 15 min, iodomethane (16 µL, 0.25 mmol) was added

and the reaction mixture stirred at room temperature overnight. Water was added, and the formed precipitate was filtered, washed with water and dried. The title compound **27** (77.6 mg, 75% yield) was obtained as a colorless solid. ^{1}H NMR (DMSO-d_6, 300 MHz): 7.55 (d, *J* = 8.9 Hz, 2H), 7.49–7.41 (m, 1H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.16 (d, *J* = 4.2 Hz, 1H), 5.04–4.91 (m, 1H), 4.25–4.14 (m, 1H), 4.19 (s, 2H), 4.02–3.92 (m, 2H), 3.90–3.78 (m, 3H), 3.78–3.69 (m, 2H); MS (ESIpos): m/z: 450 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{20}H_{20}ClN_3O_5S$): calcd 450.0885, found 450.0887; degree of purity: HPLC: rt (method 1b): 7.32 min (98%), rt (method 4a): 3.97 min (100%).

5-Chloro-*N*-({(5*R*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-sulfonamide (28). A solution of 5-chlorothiophene-2-sulfonyl chloride (57 µL, 0.36 mmol) in tetrahydrofuran (0.5 mL) was added to a solution of **34** (87.4 mg, 0.3 mmol) in tetrahydrofuran (2 mL) and pyridine (0.75 mL) at 0°C. The reaction mixture was stirred at room temperature for 4 h and quenched with water. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried (sodium sulfate), filtered and evaporated *in vacuo*. The residue was purified by HPLC (mixtures of acetonitrile/water) to give the title compound **28** (60.6 mg, 43% yield) as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz): 8.59–8.43 (broad s, 1H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 4.0 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 4.0 Hz, 1H), 4.80–4.71 (m, 1H), 4.19 (s, 2H), 4.15 (t, *J* = 9.2 Hz, 1H), 4.01–3.92 (m, 2H), 3.79 (dd, *J* = 9.2 Hz, 6.1 Hz, 1H), 3.76–3.68 (m, 2H), 3.31–3.17 (m, 2H); MS (ESIpos): m/z: 472 ($[M+H]^+$, 100%); HR MS ($[M+H]^+$ for $C_{18}H_{18}ClN_3O_6S_2$): calcd 472.0399, found 472.0403; degree of purity: HPLC: rt (method 1b): 7.86 min (100%), rt (method 4b): 3.98 min (100%).

References

[1] Barbachyn, M.R.; Hutchinson, D.K.; Brickner, S.J.; Cynamon, M.H.; Kilburn, J.O.; Klemens, S.P.; Glickman, S.E.; Grega, K.C.; Hendges, S.K.; Toops, D.S.; Ford, C.W.; Zurenko, G.E. Identification of a Novel Oxazolidinone (U-100480) with Potent Antimycobacterial Activity. *J. Med. Chem.* **1996**, *39*, 680-685.

[2] Brickner, S.J.; Hutchinson, D.K.; Barbachyn, M.R.; Manninen, P.R.; Ulanowicz, D.A.; Garmon, S.A.; Grega, K.C.; Hendges, S.K.; Toops, D.S.; Ford, C.W.; Zurenko, G.E. Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections. *J. Med. Chem.* **1996**, *39*, 673-679.

[3] Tokuyama, R.; Takahashi, Y.; Tomita, Y.; Tsubouchi, M.; Yoshida, T.; Iwasaki, N.; Kado, N.; Okezaki, E.; Nagata, O. Structure-Activity Relationship (SAR) Studies on Oxazolidinone Antibacterial Agents. *Chem. Pharm. Bull.* **2001**, *49*, 353-360.

[4] Gregory, W.A.; Brittelli, D.R.; Wang, C.-L.J.; Kezar, H.S.; Carlson, R.K.; Park, C.-H.; Corless, P.F.; Miller, S.J.; Rajagopalan, P.; Wuonola, M.A.; McRipley, R.J.; Eberly, V.S.; Slee, A.M.; Forbes, M. Antibacterials. Synthesis and structure-activity studies of 3-aryl-2-oxooxazolidines. 2. The "A" group. *J. Med. Chem.* **1990**, *33*, 2569-2578.

[5] Hutchinson, D.K.; Brickner, S.J.; Barbachyn, M.R.; Gammill, R.B.; Patel, M.V. Oxazolidinones containing a substituted diazine moiety and their use as antimicrobials. PCT Int. Appl. WO 93/23384, Chem. Abstr. **1994**, *120*, 323599.

[6] LuValle, J.E.; Glass, D.B.; Weissberger, A. Oxidation Processes. XXI.1 The Autoxidation of the p-Phenylenediamines. *J. Am. Chem. Soc.* **1948**, *70*, 2223-2233.

[7] Gutcait, A.; Wang, K.-C.; Liu, H.-W.; Chern, J.-W. Studies on quinazolines. 6. Asymmetric synthesis of (*S*)-(+)- and (*R*)-(-)-3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-5-methylthio-2,3-dihydroimidazo-[1,2c]quinazolines. *Tetrahedron Asym.* **1996**, *7*, 1641-1648.

[8] Straub, A.; Lampe, T.; Pohlmann, J.; Roehrig, S.; Perzborn, E.; Schlemmer, K.-H.; Pernerstorfer, J. Substituierte Oxazolidinone und ihre Verwendung. PCT Int. Appl. WO 01/47919, Chem. Abstr. **2001**, *135*, 92625.

[9] Gol'dfarb, Y.L.; Bulgakova, V.N.; Fabrichnyi, B.P. Reductive acetylation of nitrocarboxylic acids of the thiophene and furan series or their esters. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1983**, *19*, 1283-1286.

[10] Graf, R. Über das 2-Methyl-5-aminpyridin und seine Derivate. *J. Prakt. Chem.* **1932**, *133*, 19-35.

Table 1. Purity data for compounds **4-28** in two diverse HPLC systems

compd	HPLC system 1			HPLC system 2		
	HPLC method	Retention time [min]	Degree of purity [%]	HPLC method	Retention time [min]	Degree of purity [%]
4	1a	19.46	98	4b	4.35	100
5	1b	5.76	100	4a	3.84	100
6	1a	7.97	95	2	10.80	98
7	1a	5.92	92	4b	3.68	96
8	1a	23.70	95	4b	3.84	97
9	1a	9.21	96	4b	3.63	100
10	n.a.	n.a.	n.a.	4b	3.90	100
11	1a	4.54	98	4b	3.92	100
12	1b	7.58	95	2	6.74	95
13	1b	12.08	100	4b	4.08	100
14	1b	4.45	98	4a	3.68	100
15	1b	12.75	97	4a	3.77	98
16	1b	5.77	100	4a	3.82	100
17	n.a.	n.a.	n.a.	4a	3.87	100
18	1b	4.13	100	4a	3.65	100
19	2	4.52	97	3	3.31	100
20	2	5.53	95	4a	3.76	98
21	1b	5.48	100	4a	3.79	100
22	1b	3.70	100	3	3.25	100
23	1b	3.52	99	4b	3.36	100
24	1b	3.75	100	4a	3.57	100
25	1b	3.66	100	4b	3.63	100
26	1b	3.21	100	4b	3.50	100
27	1b	7.32	98	4a	3.97	100
28	1b	7.86	100	4b	3.98	100