SUPPORTING INFORMATION

Discovery of Novel 5-Benzylidenerhodanine and 5-Benzylidenethiazolidine-2,4-dione Inhibitors of MurD Ligase

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1. Crystal Structure Solution and Model Refinement

Statistics on data collection and refinement are summarized in Table 1S. Data were indexed and scaled with XDS¹ solved by employing the structure of MurD (3UAG)² as a search model in a molecular replacement approach using the PHASER³ program. The COOT⁴ program was used for manual corrections of the model and cycles of refinement were performed by REFMAC 5.5⁵ as implemented in the CCP4-6.1.1⁶ suite of programs. In addition, water molecules were added to the residual electron density map using ARP/ wARP.⁷ After several cycles of refinement R_{work} and R_{free} converged. The stereo chemical quality of the refined models was verified with PROCHECK.⁸ The secondary structure assignment was performed by DSSP⁹ and STRIDE.¹⁰ All the crystals tested were of $P4_1$ space group and had one molecule per asymmetric unit. Detailed representation of binding mode of (R)-**32** in MurD active site was made by Ligplot¹¹ and is presented in Figure 1S.

Table 1S. Data Collection, Molecular Replacement and Structure Refinement Statistics

Data Collection	
X-ray source	BM30A
detector	ADSC Q210
wavelength (Å)	0.9797
scan-range (deg)	120
oscillation (deg)	1.0
space group	P4 ₁
cell dimensions <i>a</i> , <i>b</i> , <i>c</i> (Å)	66.091, 66.091, 135.781
mosaicity (°)	0.156
resolution (Å) (last shell)	1.46 (1.46–1.55)
no. observed/unique reflections	499140/93804
completeness (%) (last shell)	86.2 (52.0)
<i>R</i> _{sym} (last shell)	5.4 (59.3)
<i>I</i> /(<i>I</i>) (last shell)	19.95 (2.8)
mean B factor (Å ²)	18.28
Molecular replacement	
Mol/ASU	1
Phaser RFZ/LLG, TFZ/LLG	33.3/3201, 25.4/4845
Refinement	
resolution (Å)	1.46
<i>R</i> _{work} / <i>R</i> _{free} (%)	18.68/21.67
no. of atoms (protein/water)	3401/535
mean B factor (Å ²)	13.81
compound (<i>R</i>)- 32 mean B factor (Å ²)	24.30
rmsd bonds (Å)	0.014
rmsd angles (deg)	1.454
residues in most favored/allowed region of Ramachandran plot (%)	100

Figure 1S. Ligplot representation of interactions of (*R*)-**32** with MurD from *E. coli*.

2. General Information - Chemistry

Chemicals were obtained from Acros, Aldrich Chemical Co., and Fluka and used without further purification. THF was kept over sodium and distilled immediately prior to use. Analytical TLC was performed on silica gel Merck 60 F₂₅₄ plates (0.25 mm), using visualization with UV light and ninhydrin. Column chromatography was carried out on silica gel 60 (particle size 240–400 mesh). HPLC analyses were performed on an Agilent Technologies 1100 instrument with a G1365B UV-VIS detector, a G1316A thermostat and a G1313A autosampler, using a Phenomenex Luna 5 μ m C18 column (4.6 $\times$ 150 mm). The eluent consisted of trifluoroacetic acid (0.1% in water) and methanol or acetonitrile. Microwave-assisted reactions were performed using a CEM Discover microwave reactor (CEM Corp.). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded at 300 and 75 MHz on a Bruker AVANCE DPX300 spectrometer in CDCl₃ or DMSO-*d*₆ solution, with TMS as the internal standard. Spectra were assigned using gradient COSY, HSQC and ¹H-coupled ¹³C NMR experiments. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Mass spectra were obtained using a VGAnalytical Autospec Q mass spectrometer. Optical rotations were measured on a Perkin-Elmer 1241 MC polarimeter. The reported values for specific rotation are average values of 10 successive measurements using an integration time of 5 s. Since chiral 5-benzylidenethiazolidine-2,4-diones showed ellipticity and circular dichroism, their specific rotation values are not reported. Microanalyses were performed on a Perkin-Elmer C, H, N analyzer 240 C. Analyses indicated by the symbols of the elements were within 0.4% of the theoretical values. The purity of the tested compounds was established to be $\geq 95\%$.

3. Experimental Procedures

General procedure A. Benzaldehydes (*R*)-4, (*R*)-5 and (*S*)-5.

A solution of H-Glu(OMe)-OMe-HCl (0.500 g, 2.36 mmol), carboxybenzaldehyde (0.426 g, 2.83 mmol) and HOBt (0.488 g, 3.07 mmol) in DMF (25 mL) was prepared and the pH adjusted to 8 with *N*-methylmorpholine. EDC (0.634 g, 3.31 mmol) was added and the reaction mixture stirred overnight at room temperature. The solvent was evaporated *in vacuo* and the oily residue dissolved in ethyl acetate (60 mL) and washed successively with 10% citric acid (3 $\times$ 20 mL), saturated aqueous NaHCO₃ solution (3 $\times$ 20 mL) and brine (20 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure. The crude product was purified with flash column chromatography using ethyl acetate/petroleum ether (2:1) as eluent.

(*R*)-Dimethyl 2-(3-formylbenzamido)pentanedioate [(*R*)-4]. Yield: 25%; white solid; m.p. 66–69 °C; $[\alpha]_{\text{D}}^{23} +1.3$ (*c* 0.235, DMF); IR (KBr): $\nu = 3412, 3312, 2954, 2849, 1734, 1702, 1636, 1524, 1337, 1415, 1374, 1304, 1265, 1200, 1166, 1104, 1080, 980, 945, 902, 882, 829, 814, 780, 767, 749, 678, 668, 650$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.97–2.21 (m, 2H, CHCH₂CH₂), 2.48 (t, 2H, *J* = 7.5 Hz, CHCH₂CH₂), 3.59 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 4.48–4.55 (m, 1H, CH), 7.73 (t, 1H, *J* = 7.7 Hz, H-5), 8.10 (dt, 1H, ³*J* = 7.7 Hz, ⁴*J* = 1.4 Hz, Ar-H-4/6), 8.19 (dt, 1H, ³*J* = 7.7 Hz, ⁴*J* = 1.4 Hz, Ar-H-4/6), 8.42 (t, 1H, *J* = 1.4 Hz, Ar-H-2), 9.01 (d, 1H, *J* = 7.5 Hz, NH), 10.09 (s, 1H, CHO). MS (ESI): *m/z* (%) = 308 (MH⁺). Anal. (C₁₅H₁₇NO₆) C, H, N.

(R)-Dimethyl 2-(4-formylbenzamido)pentanedioate [(R)-5]. Yield: 53%; white crystals; m.p. 74-76 °C; $[\alpha]_{\text{D}}^{23} +7.1$ (c 0.274, DMF); IR (KBr): $\nu = 3320, 2956, 2829, 1728, 1700, 1641, 1610, 1574, 1532, 1501, 1437, 1412, 1355, 1295, 1210, 1153, 1105, 1016, 979, 947, 887, 858 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.97-2.20 (m, 2H, CHCH₂CH₂), 2.43-2.50 (2H, CHCH₂CH₂, signal overlapped with DMSO- d_5), 4.47-4.54 (m, 1H, CH), 3.59 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 8.02 (d, 2H, $J = 8.4$ Hz, Ar-H-2,6/3,5), 8.07 (d, 2H, $J = 8.4$ Hz, Ar-H-2,6/3,5), 8.98 (d, 1H, $J = 7.5$ Hz, NH), 10.10 (s, 1H, CHO). MS (EI): m/z (%) = 308 (MH⁺, 19), 133 (100). Anal. (C₁₅H₁₇NO₆) C, H, N.

(S)-Dimethyl 2-(4-formylbenzamido)pentanedioate [(S)-5]. Yield: 40%; white crystals; m.p. 74-76 °C; $[\alpha]_{\text{D}}^{23} -7.1$ (c 0.274, DMF); IR (KBr): $\nu = 3320, 3006, 2956, 2829, 1729, 1700, 1641, 1610, 1574, 1500, 1437, 1412, 1356, 1295, 1210, 1153, 1105, 1016, 979, 947, 858, 844 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.97-2.20 (m, 2H, CHCH₂CH₂), 2.43-2.50 (2H, CHCH₂CH₂, signal overlapped with DMSO- d_5), 4.47-4.54 (m, 1H, CH), 3.59 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 8.02 (d, 2H, $J = 8.4$ Hz, Ar-H-2,6/3,5), 8.07 (d, 2H, $J = 8.4$ Hz, Ar-H-2,6/3,5), 8.98 (d, 1H, $J = 7.5$ Hz, NH), 10.10 (s, 1H, CHO). MS (ESI): m/z (%) = 308 (MH⁺, 16), 133 (100). Anal. (C₁₅H₁₇NO₆) C, H, N.

General procedure B. Nitrobenzylidene-rhodanines and -thiazolidine-2,4-diones 10-13.

To a suspension of rhodanine (**9**) or thiazolidine-2,4-dione (**8**) (5.26 mmol) and nitrobenzaldehyde **6** or **7** (0.870 g, 5.78 mmol) in absolute ethanol (5 mL) in a 10 mL process vial, glacial acetic acid (25 μL , 0.26 mmol) and piperidine (26 μL , 0.26 mmol) were added. The vial was sealed, placed in a microwave reactor and heated at 150 °C for 20 minutes (max. power 30 W). The reaction mixture was cooled and the precipitate filtered off and dried.

(Z)-5-(3-Nitrobenzylidene)thiazolidine-2,4-dione (10). Yield: 80%; yellow crystals; m.p. 239-243 °C (lit.¹² 245 °C). ^1H NMR (DMSO- d_6): δ 7.82 (t, 1H, $J \approx 8$ Hz, H-5), 7.95 (s, 1H, CH), 8.02 (d, 1H, $J = 7.8$ Hz, Ar-H-4/6), 8.29 (dd, 1H, $^3J = 8.1$ Hz, $^4J = 1.4$ Hz, Ar-H-4/6), 8.44 (t, 1H, $J \approx 1.5$ Hz, Ar-H-2), 12.77 (br s, 1H, NH).

(Z)-5-(3-Nitrobenzylidene)-2-thioxothiazolidin-4-one (11). Yield: 74%; yellow crystals; m.p. 265-267 °C (lit.¹³ 269-270 °C). ^1H NMR (DMSO- d_6): δ 7.79 (s, 1H, CH), 7.82 (t, 1H, $J \approx 8.0$ Hz, Ar-H-5), 8.00 (d, 1H, $J = 7.8$ Hz, Ar-H-4/6), 8.30 (dd, 1H, $^3J = 8.1$ Hz, $^4J = 2.1$ Hz, Ar-H-4/6), 8.43 (s, 1H, H-2).

(Z)-5-(4-Nitrobenzylidene)thiazolidine-2,4-dione (12). Yield: 85%; yellow crystals; m.p. 274-278 °C (lit.¹² 280 °C); IR (ATR): $\nu = 3187, 3113, 3047, 2731, 1747, 1704, 1669, 1606, 1591, 1525, 1342, 1311, 1143, 1007, 902, 844 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 7.86 (d, 2H, $J = 8.7$ Hz, Ar-H-2,6), 7.90 (s, 1H, CH), 8.34 (d, 2H, $J = 8.7$ Hz, Ar-H-3,5), 12.8 (s, 1H, NH). MS (EI): $m/z = 250$ (M⁺).

(Z)-5-(4-Nitrobenzylidene)-2-thioxothiazolidin-4-one (13). Yield: 77%; brown crystals; m.p. 259-262 °C (lit.¹³ 255-256 °C). ^1H NMR (DMSO- d_6): δ 7.73 (s, 1H, CH), 7.86 (d, 2H, $J = 8.8$ Hz, Ar-H-2,6), 8.34 (d, 2H, $J = 8.8$ Hz, Ar-H-3,5), 13.96 (s, 1H, NH).

General procedure C. (Z)-5-(Aminobenzylidene)thiazolidine-2,4-diones 14 and 16.

(Z)-5-(Nitrobenzylidene-thiazolidine-2,4-dione **10** or **12**) (0.500 g, 2.00 mmol) was dissolved in a mixture of tetrahydrofuran (15 mL) and methanol (15 mL), 10% Pd/C (150 mg) was added and the reaction mixture stirred under hydrogen atmosphere for 5 hours. The catalyst was filtered off and the solvent removed under reduced pressure.

(Z)-5-(3-Aminobenzylidene)thiazolidine-2,4-dione (14). Yield: 95%; yellow crystals; m.p. 208-212 °C (lit.¹² 215 °C). ¹H NMR (DMSO-*d*₆): δ 5.12 (br s, 2H, NH₂), 6.50 (dd, 1H, ³*J* = 7.9 Hz, ⁴*J* = 1.9 Hz, Ar-H-4), 6.66 (d, 1H, *J* = 7.7 Hz, Ar-H-6), 6.71 (s, 1H, Ar-H-2) 7.04 (t, 1H, *J* ≈ 7.7 Hz, Ar-H-5), 7.11 (s, 1H, CH), broad signal for NH not seen.

(Z)-5-(4-Aminobenzylidene)thiazolidine-2,4-dione (16). Yield: 95%; yellow crystals; m.p. 225-228 °C (lit.¹² 231 °C). ¹H NMR (DMSO-*d*₆): δ 6.08 (br s, 2H, NH₂), 6.66 (d, 2H, *J* = 8.7 Hz, Ar-H-3,5), 7.28 (d, 2H, *J* = 8.7 Hz, Ar-H-2,6), 7.60 (s, 1H, CH), 12.20 (br s, 1H, NH).

General procedure D. (Z)-5-(Aminobenzylidene)rhodanines 15 and 17.

To a stirred solution of (Z)-5-(nitrobenzylidene)rhodanine **11** or **13** (1.70 g, 6.38 mmol) in ethanol (100 mL), tin(II) chloride (6.05 g, 31.9 mmol) was added and the reaction mixture was heated under reflux for 2 h. The solvent was evaporated under reduced pressure. The residue was dissolved in saturated aqueous NaHCO₃ solution (100 mL) and the product extracted with ethyl acetate (5 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over Na₂SO₄ and the solvent removed under reduced pressure.

(Z)-5-(3-Aminobenzylidene)-2-thioxothiazolidin-4-one (15). Yield: 60%; red crystals; m.p. 205-208 °C; IR (KBr): ν = 3345, 1687, 1593, 1440, 1300, 1218, 1177, 1069, 765 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 6.68-6.76 (m, 3H, Ar-H-2,4,6), 7.17 (t, 1H, *J* = 7.8 Hz, Ar-H-5), 7.44 (s, 1H, CH), broad signals for NH and NH₂ not seen. MS (EI): *m/z* (%) = 237 (MH⁺, 100), 158 (62), 141 (20). Anal. (C₁₀H₈N₂OS₂) C, H, N.

(Z)-5-(4-Aminobenzylidene)-2-thioxothiazolidin-4-one (17). Yield: 61%; red crystals; m.p. 247-250 °C (lit.¹⁴ 242-244 °C). ¹H NMR (DMSO-*d*₆): δ 6.23 (s, 2H, NH₂), 6.67 (d, 2H, *J* = 8.6 Hz, Ar-H-3,5), 7.30 (d, 2H, *J* = 8.6 Hz, Ar-H-2,6), 7.44 (s, 1H, CH), 13.54 (br s, 1H, NH).

General procedure E. Compounds (R)-18, (S)-18, (R)-19, (S)-19, (R)-22, (S)-22, (R)-23, (S)-23, (R)-26, (R)-27, (R)-30 and (R)-31.

To a stirred solution of amine **14-17** (3.41 mmol) in anhydrous DMF (40 mL), benzaldehyde (*R*)-**4**, (*R*)-**5** or (*S*)-**5** (1.048 g, 3.41 mmol) and NaCNBH₃ (0.258 g, 4.09 mmol) were added and the reaction mixture was stirred overnight at room temperature under an argon atmosphere. The solvent was evaporated under reduced pressure and the crude product recrystallized from methanol or ethyl acetate.

(R,Z)-Dimethyl 2-(4-((3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioate [(R)-18]. Yield: 38%; yellow crystals; m.p. 150-153 °C; IR (KBr): ν = 3851, 1738, 1699, 1645, 1601, 1533, 1437, 1329, 1299, 1018, 846, 780 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 2.00-2.13 (m, 2H, CHCH₂CH₂), 2.44 (t, 2H, *J* = 7.5 Hz, CHCH₂CH₂), 3.58 (s, 3H, CH₃), 3.64 (s, 3H, CH₃), 4.30-4.49 (m, 3H, CH₂NH, CHCH₂CH₂), 6.69-6.77 (m, 4H, Ar-H-2,4,6, CH₂NH), 7.19 (t, 1H, *J* = 8.3 Hz, Ar-H-5), 7.47 (d, 2H, *J* = 8.1 Hz, Ar-H-3',5'), 7.59 (s, 1H, CH=C), 7.83 (d, 2H, *J* = 8.1 Hz, Ar-H-2',6'), 8.67 (d, 1H, *J* = 7.5 Hz, CONH), 12.50 (br s, 1H, CONHCO). ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 26.62 (CH₂), 30.82 (CH₂), 46.88 (CH₂), 52.23 (CH₃), 52.80 (CHNH), 52.80 (CH₃), 113.37 (Ar-C/CH=C), 115.90 (Ar-C/CH=C), 119.19 (Ar-C/CH=C), 123.54 (Ar-C/CH=C), 127.78 (Ar-C/CH=C), 128.48 (Ar-C/CH=C), 130.60 (Ar-C/CH=C), 133.06 (Ar-C/CH=C), 133.55 (Ar-C/CH=C), 134.41 (Ar-C/CH=C), 144.53 (Ar-C/CH=C), 149.83 (Ar-C/CH=C), 167.35 (C=O), 168.29 (C=O), 168.99 (C=O), 173.10 (C=O), 173.54 (C=O). MS (ESI): *m/z* (%) = 512 (MH⁺, 100), 484 (6). Anal. (C₂₅H₂₅N₃O₇S) C, H, N.

(S,Z)-Dimethyl 2-(4-((3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioate [(S)-18]. Yield: 46%; yellow crystals; m.p. 145-152 °C; IR (KBr): $\nu = 3300, 2950, 1738, 1699, 1629, 1561, 1543, 1476, 1461, 1339, 1149, 1015, 766 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 2.00-2.13 (m, 2H, CHCH_2CH_2), 2.44 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.30-4.49 (m, 3H, CH_2NH , CHCH_2CH_2), 6.69-6.77 (m, 4H, Ar-H-2,4,6, CH_2NH), 7.19 (t, 1H, $J = 8.3 \text{ Hz}$, Ar-H-5), 7.47 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-3',5'), 7.59 (s, 1H, $\text{CH}=\text{C}$), 7.83 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-2',6'), 8.67 (d, 1H, $J = 7.5 \text{ Hz}$, CONH), 12.50 (br s, 1H, CONHCO). MS (ESI): m/z (%) = 512 (MH^+ , 100). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_7\text{S}$) C, H, N.

(R,Z)-Dimethyl 2-(4-((3-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)-methyl)benzamido)pentanedioate [(R)-19]. Yield: 11%; orange crystals; m.p. 159-163 °C; IR (KBr): $\nu = 3376, 1729, 1646, 1599, 1438, 1342, 1234, 1019, 838, 751 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.96-2.17 (m, 2H, CHCH_2CH_2), 2.45 (t, 2H, $J = 7.3 \text{ Hz}$, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 4.30-4.50 (m, 3H, CH_2NH , CHCH_2CH_2), 6.70-6.79 (m, 4H, Ar-H-2,4,6, CH_2NH), 7.20 (t, 1H, $J = 7.7 \text{ Hz}$, Ar-H-5), 7.43 (s, 1H, $\text{CH}=\text{C}$), 7.47 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-3',5'), 7.84 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-2',6'), 8.67 (d, 1H, $J = 7.5 \text{ Hz}$, CONH), 13.71 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 528 (MH^+ , 100), 512 (45). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_6\text{S}_2$) C, H, N.

(S,Z)-Dimethyl 2-(4-((3-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)-methyl)benzamido)pentanedioate [(S)-19]. Yield: 30%; orange crystals; m.p. 158-162 °C; IR (KBr): $\nu = 3414, 2948, 2846, 2041, 1723, 1639, 1527, 1431, 1332, 1214, 1171, 1059, 1013, 829, 770 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.94-2.18 (m, 2H, CHCH_2CH_2), 2.45 (t, 2H, $J = 7.3 \text{ Hz}$, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.32-4.49 (m, 3H, CH_2NH , CHCH_2CH_2), 6.70-6.79 (m, 4H, Ar-H-2,4,6, CH_2NH), 7.20 (t, 1H, $J = 7.7 \text{ Hz}$, Ar-H-5), 7.43 (s, 1H, $\text{CH}=\text{C}$), 7.47 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-3',5'), 7.84 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-2',6'), 8.67 (d, 1H, $J = 7.5 \text{ Hz}$, CONH), 13.71 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 528 (MH^+ , 70), 512 (45), 484 (18), 336 (48), 312 (68), 267 (100). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_6\text{S}_2$) C, H, N.

(R,Z)-Dimethyl 2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioate [(R)-22]. Yield: 24%; yellow crystals; m.p. 153-156 °C; IR (KBr): $\nu = 3365, 1732, 1694, 1634, 1586, 1521, 1337, 1263, 1185, 1149, 815, 690 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.93-2.17 (m, 2H, CHCH_2CH_2), 2.45 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.32-4.49 (m, 3H, CH_2NH , CHCH_2CH_2), 6.69 (d, 2H, $J = 8.7 \text{ Hz}$, Ar-H-2,6), 7.28-7.33 (m, 3H, Ar-H-3,5, CH_2NH), 7.44 (d, 2H, $J = 8.4 \text{ Hz}$, Ar-H-3',5'), 7.60 (s, 1H, $\text{CH}=\text{C}$), 7.84 (d, 2H, $J = 8.4 \text{ Hz}$, Ar-H-2',6'), 8.68 (d, 1H, $J = 7.5 \text{ Hz}$, CONH), 12.28 (br s, 1H, CONHCO). MS (ESI): m/z (%) = 512 (MH^+ , 100), 337 (40), 292 (25), 141 (22). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_7\text{S} \times 0.3 \text{ H}_2\text{O}$) C, H, N.

(S,Z)-Dimethyl 2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioate [(S)-22]. Yield: 30%; yellow crystals; m.p. 153-156 °C; IR (KBr): $\nu = 3366, 1734, 1686, 1586, 1522, 1338, 1290, 1185, 1149, 816 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.93-2.17 (m, 2H, CHCH_2CH_2), 2.44 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.32-4.49 (m, 3H, CH_2NH , CHCH_2CH_2), 6.69 (d, 2H, $J = 8.7 \text{ Hz}$, Ar-H-2,6), 7.28-7.33 (m, 3H, Ar-H-3,5, CH_2NH), 7.44 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-3',5'), 7.60 (s, 1H, $\text{CH}=\text{C}$), 7.83 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-2',6'), 8.68 (d, 1H, $J = 7.5 \text{ Hz}$, CONH), 12.28 (br s, 1H, CONHCO). MS (ESI): m/z (%) = 512 (97, MH^+), 376 (22), 214 (47), 158 (60), 141 (100). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_7\text{S}$) C, H, N.

(R,Z)-Dimethyl 2-(4-(((4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)-methyl)benzamido)pentanedioate [(R)-23]. Yield: 10%; orange crystals; m.p. 164-169 °C; IR (KBr): ν = 3366, 1734, 1636, 1560, 1518, 1438, 1333, 1279, 1205, 1174, 685 cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 1.96-2.18 (m, 2H, CHCH_2CH_2), 2.47 (t, 2H, J = 7.6 Hz, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.42-4.49 (m, 3H, CH_2NH , CHCH_2CH_2), 6.72 (d, 2H, J = 8.8 Hz, Ar-H-2,6), 7.33 (d, 2H, J = 8.8 Hz, Ar-H-3,5), 7.43-7.49 (m, 4H, Ar-H-3',5', CH_2NH , $\text{CH}=\text{C}$), 7.83 (d, 2H, J = 8.2 Hz, Ar-H-2',6'), 8.67 (d, 1H, J = 7.4 Hz, CONH), 13.53 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 528 (MH^+ , 100), 413 (24), 353 (25), 292 (22). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_6\text{S}_2$) C, H, N.

(S,Z)-Dimethyl 2-(4-(((4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)-methyl)benzamido)pentanedioate [(S)-23]. Yield: 35%; orange crystals; m.p. 160-165 °C; IR (KBr): ν = 3410, 2847, 2037, 1639, 1620, 1563, 1515, 1450, 1333, 1270, 1172, 1015, 818 cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 1.94-2.18 (m, 2H, CHCH_2CH_2), 2.45 (t, 2H, J = 7.6 Hz, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.42-4.49 (m, 3H, CH_2NH , CHCH_2CH_2), 6.71 (d, 2H, J = 8.9 Hz, Ar-H-2,6), 7.33 (d, 2H, J = 8.9 Hz, Ar-H-3,5), 7.43-7.45 (m, 4H, Ar-H-3',5', CH_2NH , $\text{CH}=\text{C}$), 7.84 (d, 2H, J = 8.1 Hz, Ar-H-2',6'), 8.68 (d, 1H, J = 7.5 Hz, CONH), 13.53 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 528 (MH^+ , 100), 512 (15), 312 (50), 267 (57). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_6\text{S}_2$) C, H, N.

(R,Z)-Dimethyl 2-(3-(((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)pentanedioate [(R)-26]. Yield: 32%; yellow crystals; m.p. 81-87 °C; IR (KBr): ν = 3386, 1741, 1702, 1606, 1528, 1438, 1291, 1207, 746, 683 cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 1.96-2.18 (m, 2H, CHCH_2CH_2), 2.47 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.31-4.50 (m, 3H, CH_2NH , CHCH_2CH_2), 6.65-6.78 (m, 4H, 3 $\times$ Ar-H, CH_2NH), 7.21 (m, 1H, Ar-H), 7.44 (m, 1H, Ar-H), 7.54 (m, 1H, Ar-H), 7.60 (s, 1H, $\text{CH}=\text{C}$), 7.77 (m, 1H, Ar-H), 7.90 (m, 1H, Ar-H), 8.67 (d, 1H, J = 7.5 Hz, CONH), 12.50 (br s, 1H, CONHCO). MS (ESI): m/z (%) = 534 (MNa^+ , 50), 512 (MH^+ , 35), 413 (70), 337 (100). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_7\text{S}$) C, H, N.

(R,Z)-Dimethyl 2-(3-(((4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)-methyl)benzamido)pentanedioate [(R)-27]. Yield: 32%; orange crystals; m.p. 122-128 °C; IR (KBr): ν = 3338, 3048, 2843, 1734, 1687, 1654, 1602, 1522, 1438, 1302, 1221, 1175, 1065, 1011, 764, 742, 676 cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 1.96-2.18 (m, 2H, CHCH_2CH_2), 2.45 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.34-4.49 (m, 3H, CH_2NH , CHCH_2CH_2), 6.70-6.76 (m, 4H, 3 $\times$ Ar-H, CH_2NH), 7.22 (t, 1H, J = 8.3 Hz, Ar-H), 7.44-7.46 (m, 2H, Ar-H, $\text{CH}=\text{C}$), 7.56 (d, 1H, J = 7.2 Hz, Ar-H), 7.77 (d, 1H, J = 7.2 Hz, Ar-H), 7.91 (s, 1H, Ar-H), 8.72 (d, 1H, J = 7.2 Hz, CONH), 13.72 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 528 (MH^+ , 100), 501 (39), 353 (80), 280 (28). Anal. ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_6\text{S}_2$) C, H, N.

(R,Z)-Dimethyl 2-(3-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)-methyl)benzamido)pentanedioate [(R)-30]. Yield: 32%; yellow crystals; m.p. 148-153 °C; IR (KBr): ν = 3583, 3488, 3434, 2850, 2040, 1718, 1639, 1561, 1541, 1510, 1456, 1341, 1292, 1185, 1147, 812, 626 cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 1.95-2.19 (m, 2H, CHCH_2CH_2), 2.45 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.41-4.50 (m, 3H, CH_2NH , CHCH_2CH_2), 6.72 (d, 2H, J = 8.7 Hz, Ar-H-2,6), 7.28 (t, 1H, J = 6.0 Hz CH_2NH), 7.33 (d, 2H, J = 8.7 Hz, Ar-H-3,5), 7.44 (t, 1H, J = 7.5 Hz, Ar-H-5'), 7.52 (d, 1H, J = 7.5 Hz, Ar-H-4'), 7.60 (s, 1H, $\text{CH}=\text{C}$), 7.77 (d, 1H, J = 7.5 Hz, Ar-H-6'), 7.88 (s, 1H, Ar-H-2'), 8.74

(d, 1H, $J = 7.5$ Hz, CONH), 12.28 (br s, 1H, CONHCO). MS (ESI⁻): m/z (%) = 510 ([M-H]⁻, 100), 478 (5), 439 (20), 407 (20), 281 (30), 255 (30). Anal. (C₂₅H₂₅N₃O₇S) C, H, N.

(*R,Z*)-Dimethyl 2-(3-((4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)pentanedioate [(*R*)-31]. Yield: 35%, m.p. 155-157 °C; IR (KBr): $\nu = 3378, 1734, 1559, 1522, 1437, 1331, 1168, 812, 680$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.95-2.19 (m, 2H, CHCH₂CH₂), 2.45 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 3.58 (s, 3H, CH₃), 3.64 (s, 3H, CH₃), 4.43-4.50 (m, 3H, CH₂NH, CHCH₂CH₂), 6.74 (d, 2H, $J = 8.7$ Hz, Ar-H-2,6), 7.35 (d, 2H, $^3J = 8.7$ Hz, Ar-H-3,5), 7.42-7.54 (m, 4H, CH₂NH, CH=C, Ar-H-4',5'), 7.78 (d, 1H, $J = 7.5$ Hz, Ar-H-6'), 7.88 (s, 1H, Ar-H-2'), 8.74 (d, 1H, $J = 7.5$ Hz, CONH), 13.53 (s, 1H, CONHCS). MS (ESI): m/z (%) = 528 (MH⁺, 100), 550 (MNa⁺, 72). Anal. (C₂₅H₂₅N₃O₆S₂) C, H, N.

General procedure F. Compounds (*R*)-20, (*S*)-20, (*R*)-21, (*S*)-21, (*R*)-24, (*S*)-24, (*R*)-25, (*S*)-25, (*R*)-28, (*R*)-29, (*R*)-32, (*R*)-33, (*R*)-62, (*R*)-66 and (*R*)-68.

To a stirred solution of the corresponding methyl ester (0.226 mmol) in MeOH/water (1:1) (10 mL), 2.2 M LiOH (0.41 mL, 0.902 mmol) was added and the reaction mixture stirred overnight at room temperature. The solution was neutralized with 1 M HCl and concentrated under reduced pressure. The residual aqueous solution was acidified with 1 M HCl to pH 2 and the product extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with brine (2 × 15 mL), dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure.

(*R,Z*)-2-(4-((3-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(*R*)-20]. Yield: 79%; yellow crystals; m.p. 125-128 °C; IR (KBr): $\nu = 3401, 3200, 2038, 1736, 1698, 1638, 1618, 1560, 1541, 1455, 1420, 1153, 835, 780, 835, 780, 619$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.88-2.15 (m, 2H, CHCH₂CH₂), 2.35 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 4.31-4.43 (m, 3H, CH₂NH, CHCH₂CH₂), 6.69-6.77 (m, 4H, Ar-H-2,4,6, CH₂NH), 7.19 (t, 1H, $J = 7.8$ Hz, Ar-H-5), 7.46 (d, 2H, $J = 8.1$ Hz, Ar-H-3',5'), 7.59 (s, 1H, CH=C), 7.84 (d, 2H, $J = 8.1$ Hz, Ar-H-2',6'), 8.52 (d, 1H, $J = 7.8$ Hz, CONH), 12.40 (br s, 1H, CONHCO). MS (ESI): m/z (%) = 484 (MH⁺, 100), 466 (8), 337 (12). Anal. (C₂₃H₂₁N₃O₇S × 0.4 EtOAc) C, H, N. HPLC: Phenomenex Luna Sum C18 column; mobile phase: 40-80% of methanol in trifluoroacetic acid (0.1%) in 15 minutes; flow rate 1.0 mL/min; injection volume: 20 μ L; retention time: 17.452 min (95.00% at 220 nm, 95.19% at 254 nm).

(*S,Z*)-2-(4-((3-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(*S*)-20]. Yield: 67%; yellow crystals; m.p. 128-132 °C; IR (KBr): $\nu = 3412, 3238, 2759, 2037, 1736, 1694, 1618, 1531, 1415, 1288, 1213, 1157, 836, 780, 683, 617$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.88-2.15 (m, 2H, CHCH₂CH₂), 2.35 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 4.31-4.43 (m, 3H, CH₂NH, CHCH₂CH₂), 6.68-6.77 (m, 4H, Ar-H-2,4,6, CH₂NH), 7.19 (t, 1H, $J = 7.8$ Hz, Ar-H-5), 7.46 (d, 2H, $J = 8.4$ Hz, Ar-H-3',5'), 7.59 (s, 1H, CH=C), 7.84 (d, 2H, $J = 8.4$ Hz, Ar-H-2',6'), 8.52 (d, 1H, $J = 7.8$ Hz, CONH), 12.40 (br s, 1H, CONHCO). ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 26.82 (CH₂), 31.28 (CH₂), 46.89 (CH₂), 52.79 (CHNH), 113.44 (Ar-C/CH=C), 115.82 (Ar-C/CH=C), 119.13 (Ar-C/CH=C), 121.73 (Ar-C/CH=C), 127.74 (Ar-C/CH=C), 128.44 (Ar-C/CH=C), 130.60 (Ar-C/CH=C), 133.37 (Ar-C/CH=C), 133.47 (Ar-C/CH=C), 134.44 (Ar-C/CH=C), 144.36 (Ar-C/CH=C), 149.85 (Ar-C/CH=C), 167.27 (C=O), 168.99 (C=O), 169.08 (C=O), 174.25 (C=O), 174.71 (C=O). MS (ESI): m/z (%) = 484 (MH⁺, 100), 466 (8), 337 (12). Anal. (C₂₃H₂₁N₃O₇S) C, H, N.

(*R,Z*)-2-(4-((3-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioic acid [(*R*)-21]. Yield: 55%; orange crystals; m.p. 128-130 °C; IR (KBr): $\nu = 3398, 3032, 2854, 1700, 1636, 1601, 1578, 1527, 1500, 1438, 1284, 1229, 1181, 1099, 1068, 1016, 901, 835, 775, 679 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.88-2.15 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 4.36-4.43 (m, 3H, CH_2NH , CHCH_2CH_2), 6.71-6.79 (m, 4H, Ar-H-2,4,6, CH_2NH), 7.21 (t, 1H, $J = 7.8 \text{ Hz}$, Ar-H-5), 7.45 (s, 1H, $\text{CH}=\text{C}$), 7.47 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-3',5'), 7.84 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-2',6'), 8.51 (d, 1H, $J = 7.8 \text{ Hz}$, CONH), 12.35 (br s, 2H, $2 \times \text{COOH}$), 13.74 (br s, 1H, CSNHCO). MS (ESI-): m/z (%) = 498 ($[\text{M}-\text{H}]^-$, 100), 477 (55), 471 (90), 439 (20), 411 (60), 377 (20). Anal. ($\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_6\text{S}_2 \times 0.5 \text{ H}_2\text{O}$) C, H, N. HPLC: Phenomenex Luna 5um C18 column; mobile phase: 40-80% of methanol in trifluoroacetic acid (0.1%) in 15 minutes; flow rate 1.0 mL/min; injection volume: 20 μL ; retention time: 19.997 min (97.22% at 220 nm, 96.98% at 254 nm).

(*S,Z*)-2-(4-((3-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioic acid [(*S*)-21]. Yield: 72%; orange crystals; m.p. 128-133 °C; IR (KBr): $\nu = 3414, 2853, 2038, 1700, 1638, 1618, 1541, 1504, 1435, 1281, 1218, 1177, 1067, 1017, 841, 776, 6797, 621 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.88-2.14 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 4.36-4.43 (m, 3H, CH_2NH , CHCH_2CH_2), 6.71-6.78 (m, 4H, Ar-H-2,4,6, CH_2NH), 7.21 (t, 1H, $J = 7.8 \text{ Hz}$, Ar-H-5), 7.44 (s, 1H, $\text{CH}=\text{C}$), 7.47 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-3',5'), 7.84 (d, 2H, $J = 8.1 \text{ Hz}$, Ar-H-2',6'), 8.52 (d, 1H, $J = 7.8 \text{ Hz}$, CONH), 12.35 (br s, 2H, $2 \times \text{COOH}$), 13.71 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 500 (MH^+ , 85), 353 (25), 312 (100). Anal. ($\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_6\text{S}_2$) C, H, N.

(*R,Z*)-2-(4-((4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(*R*)-24]. Yield: 64%; yellow crystals; m.p. 137-146 °C; IR (KBr): $\nu = 3413, 2925, 2038, 1638, 1619, 1561, 1541, 1522, 1402, 1183, 1150, 1018, 819, 758, 620 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.88-2.15 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 4.36-4.45 (m, 3H, CH_2NH , CHCH_2CH_2), 6.69 (d, 2H, $J = 8.7 \text{ Hz}$, Ar-H-2,6), 7.28-7.33 (m, 3H, Ar-H-3,5, CH_2NH), 7.44 (d, 2H, $J = 8.3 \text{ Hz}$, Ar-H-3',5'), 7.59 (s, 1H, $\text{CH}=\text{C}$), 7.84 (d, 2H, $J = 8.3 \text{ Hz}$, Ar-H-2',6'), 8.53 (d, 1H, $J = 7.8 \text{ Hz}$, CONH), 12.32 (br s, 3H, CONHCO, $2 \times \text{COOH}$). MS (ESI): m/z (%) = 484 (MH^+ , 65), 466 (12), 337 (92), 312 (25), 221 (48), 141 (100). Anal. ($\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_7\text{S} \times 0.5 \text{ H}_2\text{O}$) C, H, N.

(*S,Z*)-2-(4-((4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(*S*)-24]. Yield: 65%; yellow crystals; m.p. 136-144 °C; IR (KBr): $\nu = 3414, 3236, 2924, 2039, 1686, 1619, 1580, 1562, 1522, 1415, 1335, 1286, 1183, 1150, 1016, 904, 822, 688, 608 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.88-2.15 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 4.36-4.45 (m, 3H, CH_2NH , CHCH_2CH_2), 6.69 (d, 2H, $J = 8.7 \text{ Hz}$, Ar-H-2,6), 7.28-7.33 (m, 3H, Ar-H-3,5, CH_2NH), 7.44 (d, 2H, $J = 8.3 \text{ Hz}$, Ar-H-3',5'), 7.60 (s, 1H, $\text{CH}=\text{C}$), 7.84 (d, 2H, $J = 8.3 \text{ Hz}$, Ar-H-2',6'), 8.53 (d, 1H, $J = 7.8 \text{ Hz}$, CONH), 12.31 (br s, 3H, CONHCO, $2 \times \text{COOH}$). ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 26.78 (CH_2), 31.24 (CH_2), 46.42 (CH_2), 52.75 (CHNH), 113.47 (Ar-C/ $\text{CH}=\text{C}$), 116.29 (Ar-C/ $\text{CH}=\text{C}$), 121.15 (Ar-C/ $\text{CH}=\text{C}$), 127.71 (Ar-C/ $\text{CH}=\text{C}$), 128.47 (Ar-C/ $\text{CH}=\text{C}$), 133.19 (Ar-C/ $\text{CH}=\text{C}$), 133.46 (Ar-C/ $\text{CH}=\text{C}$), 133.91 (Ar-C/ $\text{CH}=\text{C}$), 143.85 (Ar-C/ $\text{CH}=\text{C}$), 151.60 (Ar-C/ $\text{CH}=\text{C}$), 167.23 (C=O), 168.41 (C=O), 169.03 (C=O), 174.21 (C=O), 174.68 (C=O). MS (ESI): m/z (%) = 484 (MH^+ , 63), 466 (12), 337 (45), 312 (70), 221 (78), 141 (100). Anal. ($\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_7\text{S} \times \text{H}_2\text{O}$) C, H, N.

(*R,Z*)-2-(4-((4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioic acid [(*R*)-25]. Yield: 91%; orange crystals; m.p. 135-139 °C; IR (KBr): ν = 3402, 2974, 2853, 1706, 1636, 1616, 1576, 1560, 1522, 1437, 1338, 1288, 1244, 1200, 1172, 1090, 1018, 820, 756, 683 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.88-2.15 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 4.36-4.47 (m, 3H, CH_2NH , CHCH_2CH_2), 6.72 (d, 2H, J = 8.6 Hz, Ar-H-2,6), 7.34 (d, 2H, J = 8.6 Hz, Ar-H-3,5), 7.42-7.46 (m, 4H, Ar-H-3',5', $\text{CH}=\text{C}$, CH_2NH), 7.85 (d, 2H, J = 8.1 Hz, Ar-H-2',6'), 8.53 (d, 1H, J = 7.8 Hz, CONH), 12.37 (br s, 2H, 2 $\times$ COOH), 13.53 (br s, 1H, CSNHCO). MS (ESI $^-$): m/z (%) = 498 ($[\text{M}-\text{H}]^-$, 100), 482 (5), 471 (5), 439 (15), 411 (85), 377 (5). HRMS (ESI $^-$) for $\text{C}_{23}\text{H}_{20}\text{N}_3\text{O}_6\text{S}_2$: calculated 498.0794; found 498.0787. Anal. ($\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_6\text{S}_2 \times 0.5 \text{ H}_2\text{O}$) C, H, N. HPLC: Phenomenex Luna 5 μm C18 column; mobile phase: 40-80% of methanol in trifluoroacetic acid (0.1%) in 15 minutes; flow rate 1.0 mL/min; injection volume: 20 μL ; retention time: 19.602 min (95.72% at 220 nm, 95.02% at 254 nm).

(*S,Z*)-2-(4-((4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioic acid [(*S*)-25]. Yield: 60%; orange crystals; m.p. 133-138 °C; IR (KBr): ν = 3414, 2849, 2039, 1680, 1639, 1617, 1557, 1522, 1453, 1336, 1286, 1252, 1210, 1177, 1017, 852, 815, 754, 684, 622 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.88-2.15 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 4.36-4.47 (m, 3H, CH_2NH , CHCH_2CH_2), 6.72 (d, 2H, J = 8.7 Hz, Ar-H-2,6), 7.34 (d, 2H, J = 8.7 Hz, Ar-H-3,5), 7.42-7.46 (m, 4H, Ar-H-3',5', $\text{CH}=\text{C}$, CH_2NH), 7.85 (d, 2H, J = 8.4 Hz, Ar-H-2',6'), 8.54 (d, 1H, J = 7.8 Hz, CONH), 12.35 (br s, 2H, 2 $\times$ COOH), 13.52 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 500 (MH^+ , 38), 419 (20), 353 (18), 312 (25), 214 (48), 196 (70), 141 (100). Anal. ($\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_6\text{S}_2 \times 0.5 \text{ H}_2\text{O}$) C, H, N.

(*R,Z*)-2-(3-((3-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(*R*)-28]. Yield: 64%; yellow crystals; m.p. 95-100 °C; IR (KBr): ν = 3400, 3041, 1741, 1696, 1605, 1529, 1407, 1288, 1207, 745, 681 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.89-2.16 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 4.30-4.44 (m, 3H, CH_2NH , CHCH_2CH_2), 6.65 (t, 1H, J = 5.7 Hz, CH_2NH), 6.71-6.77 (m, 3H, 3 $\times$ Ar-H), 7.20 (t, 1H, J = 8.0 Hz, Ar-H), 7.43 (t, 1H, J = 7.5 Hz, Ar-H), 7.55 (d, 1H, J = 7.5 Hz, Ar-H), 7.60 (s, 1H, $\text{CH}=\text{C}$), 7.77 (d, 1H, J = 7.5 Hz, Ar-H), 7.91 (s, 1H, Ar-H), 8.57 (d, 1H, J = 7.5 Hz, CONH), 12.40 (br s, 3H, CONHCO, 2 $\times$ COOH). MS (ESI $^-$): m/z (%) = 482 ($[\text{M}-\text{H}]^-$, 48), 465 (35), 381 (38), 367 (50), 339 (65), 325 (80), 281 (100). Anal. ($\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_7\text{S} \times 0.5 \text{ EtOAc}$) C, H, N.

(*R,Z*)-2-(3-((3-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioic acid [(*R*)-29]. Yield: 74%; orange crystals; m.p. 115-124 °C; IR (KBr): ν = 3384, 3048, 2843, 1718, 1602, 1550, 1438, 1302, 1214, 1175, 677 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.89-2.16 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 4.30-4.44 (m, 3H, CH_2NH , CHCH_2CH_2), 6.73-6.79 (m, 4H, 3 $\times$ Ar-H, CH_2NH), 7.22 (t, 1H, J = 8.1 Hz, Ar-H), 7.41-7.47 (m, 2H, Ar-H, $\text{CH}=\text{C}$), 7.55 (d, 1H, J = 7.8 Hz, Ar-H), 7.78 (d, 1H, J = 7.8 Hz, Ar-H), 7.91 (s, 1H, Ar-H), 8.57 (d, 1H, J = 7.5 Hz, CONH), 12.50 (br s, 2H, 2 $\times$ COOH), 13.75 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 522 (MNa^+ , 50), 500 (MH^+ , 100), 482 (15), 353 (62). Anal. ($\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_6\text{S}_2 \times 0.25 \text{ EtOAc} \times 0.125 \text{ H}_2\text{O}$) C, H, N.

(*R,Z*)-2-(3-((4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(*R*)-32]. Yield: 73%; yellow crystals; m.p. 125-128 °C; IR (KBr): ν = 3412, 3237, 2776, 2044, 1719, 1685, 1639, 1618, 1574, 1561, 1538, 1524, 1421, 1329, 1291, 1185, 1148, 1027, 815, 690, 610 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.89-2.16 (m, 2H,

CHCH₂CH₂), 2.36 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 4.37-4.43 (m, 3H, CH₂NH, CHCH₂CH₂), 6.72 (d, 2H, $J = 8.7$ Hz, Ar-H-2,6), 7.27 (t, 1H, $J = 5.7$ Hz, CH₂NH), 7.33 (d, 2H, $J = 8.7$ Hz, Ar-H-3,5), 7.44 (t, 1H, $J = 7.7$ Hz, Ar-H-5'), 7.51 (d, 1H, $J = 7.7$ Hz, Ar-H-4'), 7.60 (s, 1H, CH=C), 7.78 (d, 1H, $J = 7.7$ Hz, Ar-H-6'), 7.89 (s, 1H, Ar-H-2'), 8.58 (d, 1H, $J = 7.5$ Hz, CONH), 12.32 (br s, 3H, CONHCO, 2 × COOH). MS (ESI[−]): m/z (%) = 482 ([M-H][−], 100), 464 (3), 353 (22). Anal. (C₂₃H₂₁N₃O₇S) C, H, N.

(*R,Z*)-2-(3-((4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentanedioic acid [(*R*)-33]. Yield: 83%, m.p. 207-209 °C; IR (KBr): $\nu = 3392$, 1699, 1521, 1422, 1336, 1162, 816 cm^{−1}. ¹H NMR (DMSO-*d*₆): δ 1.90-2.17 (m, 2H, CHCH₂CH₂), 2.36 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 4.38-4.44 (m, 3H, CHCH₂CH₂, CH₂NH), 6.74 (d, 2H, $J = 8.7$ Hz, Ar-H-2,6), 7.35 (d, 2H, $J = 8.7$ Hz, Ar-H-3,5), 7.42-7.53 (m, 4H, CH₂NH, CH=C, Ar-H-4',5'), 7.79 (d, 1H, $J = 7.5$ Hz, Ar-H-6'), 7.89 (s, 1H, Ar-H-2'), 8.59 (d, 1H, $J = 7.5$ Hz, CONH), 12.38 (br s, 2H, COOH), 13.52 (s, 1H, CONHCS). ¹³C NMR (DMSO-*d*₆): δ 25.83, 30.29, 45.63, 51.83, 112.67, 117.00, 120.19, 125.88, 126.47, 128.24, 130.01, 133.10, 133.34, 134.04, 139.30, 151.20, 166.38, 169.32, 173.23, 173.71, 194.95. MS (ESI): m/z (%) = 500 (MH⁺, 30), 501 (100). Anal. (C₂₃H₂₁N₃O₆S₂) C, H, N.

General procedure G. Compounds [(*R*)-36] and [(*R*)-37].

To a solution of D-glutamic acid dimethyl ester hydrochloride [(*R*)-1] (1.00 g, 4.72 mmol) and triethylamine (1.97 mL, 14.18 mmol) in dichloromethane (30 mL), cooled to 0 °C on an ice bath, a solution of chloroacetyl chloride or 5-bromovaleryl chloride (5.20 mmol) in dichloromethane (5 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 3 hours, after which it was washed with water (2 × 15 mL), 10% citric acid (2 × 15 mL) and brine (2 × 10 mL), dried over Na₂SO₄ and concentrated under reduced pressure.

(*R*)-Dimethyl 2-(2-chloroacetamido)pentanedioate [(*R*)-36]. Yield: 90%; colourless oil; [α]₅₄₆²³ +37.0 (*c* 0.319, DMF); IR (neat): $\nu = 3319$, 3008, 2957, 2851, 2090, 1738, 1732, 1682, 1539, 1436, 1372, 1338, 1219, 1176, 1123, 1087, 1015, 985, 825, 778 cm^{−1} (lit.^{15,16} 3317, 2956, 1733, 1667, 1528, 1206, 1170 cm^{−1}). ¹H NMR (DMSO-*d*₆): δ 1.81-2.09 (m, 2H, CHCH₂CH₂), 2.39 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 3.59 (s, 3H, CH₃), 3.64 (s, 3H, CH₃), 4.11 (s, 2H, CH₂Cl), 4.28-4.36 (m, 1H, CHCH₂CH₂) 8.63 (d, 1H, $J = 7.5$ Hz, NH).

(*R*)-Dimethyl 2-(5-bromopentanamido)pentanedioate [(*R*)-37]. Yield: 92%; colourless oil; [α]₅₄₆²³ +2.3 (*c* 0.341, DMF); IR (neat): $\nu = 3400$, 2996, 1998, 1742, 1708, 1646, 1549, 1513, 1450, 1183, 1088, 816 cm^{−1}. ¹H NMR (DMSO-*d*₆): δ 1.56-1.66 (m, 2H, CH₂), 1.75-2.05 (m, 4H, 2 × CH₂), 2.16 (t, 2H, $J = 7.2$ Hz, NHCOCH₂), 2.39 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 3.53 (t, 2H, $J = 6.6$ Hz, CH₂Br), 3.59 (s, 3H, CH₃), 3.62 (s, 3H, CH₃), 4.22-4.29 (m, 1H, CHCH₂CH₂), 8.23 (d, 1H, $J = 7.5$ Hz, NH). MS (ESI): m/z (%) = 338 (MH⁺, 25), 258 (50), 176 (70), 144 (100). Anal. (C₁₂H₂₀BrNO₅ × H₂O) C, H, N.

General procedure H. Compounds (*R*)-40, (*R*)-41 and (*R*)-42.

Compound (*R*)-36 or (*R*)-37 (1.00 mmol), hydroxybenzaldehyde (122 mg, 1.00 mmol), potassium carbonate (276 mg, 2.00 mmol) and potassium iodide (199 mg, 1.20 mmol) were suspended in acetonitrile (10 mL) and heated at 85 °C for 3 hours. The solvent was evaporated, the residue dissolved in ethyl acetate (20 mL), washed with water (2 × 10 mL) and brine (2 × 10 mL), dried over Na₂SO₄ and concentrated under reduced pressure.

(R)-Dimethyl 2-(2-(3-formylphenoxy)acetamido)pentanedioate [(R)-40]. Yield: 89%; colourless oil; $[\alpha]_{546}^{23} +22.1$ (c 0.348, DMF); IR (neat): $\nu = 3355, 3067, 3002, 2955, 2850, 2736, 2091, 1717, 1616, 1594, 1539, 1488, 1456, 1436, 1386, 1374, 1260, 1173, 1082, 1062, 1016, 996, 870, 792, 744, 683 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.84-2.12 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 4.34-4.42 (m, 1H, CHCH_2CH_2), 4.63 (d, 1H, AB system, $^2J = 15.0 \text{ Hz}$, H_A from CH_2O), 4.69 (d, 1H, AB system, $^2J = 15.0 \text{ Hz}$, H_B from CH_2O), 7.29-7.33 (m, 1H, Ar-H), 7.44 (d, 1H, $J = 2.7 \text{ Hz}$, Ar-H), 7.52-7.59 (m, 2H, $2 \times$ Ar-H), 8.55 (d, 1H, $J = 7.5 \text{ Hz}$, NH), 9.98 (s, 1H, CHO). MS (ESI): m/z (%) = 360 (MNa^+ , 100), 338 (MH^+ , 63), 278 (50), 246 (48), 218 (45). HRMS for $\text{C}_{16}\text{H}_{19}\text{NO}_7\text{Na}$: calculated 360.1059; found 360.1068. Anal. ($\text{C}_{16}\text{H}_{19}\text{NO}_7$) C, H, N.

(R)-Dimethyl 2-(2-(4-formylphenoxy)acetamido)pentanedioate [(R)-41]. Yield: 93%; colourless oil; $[\alpha]_{546}^{23} +21.5$ (c 0.409, DMF); IR (neat): $\nu = 3348, 3073, 3002, 2955, 2848, 2746, 2616, 2101, 1732, 1716, 1652, 1636, 1601, 1582, 1539, 1506, 1456, 1436, 1373, 1311, 1258, 1165, 1056, 1016, 986, 861, 836, 769, 645 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.84-2.13 (m, 2H, CHCH_2CH_2), 2.37 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 3.59 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.34-4.41 (m, 1H, CHCH_2CH_2), 4.68 (d, 1H, AB system, $^2J = 15.0 \text{ Hz}$, H_A from CH_2O), 4.73 (d, 1H, AB system, $^2J = 15.0 \text{ Hz}$, H_B from CH_2O), 7.14 (d, 2H, $J = 8.7 \text{ Hz}$, Ar-H-2,6), 7.88 (d, 2H, $J = 8.7 \text{ Hz}$, Ar-H-3,5), 8.57 (d, 1H, $J = 7.8 \text{ Hz}$, NH), 9.89 (s, 1H, CHO). MS (ESI): m/z (%) = 360 (MNa^+ , 100), 338 (MH^+ , 10), 184 (40). HRMS for $\text{C}_{16}\text{H}_{19}\text{NO}_7\text{Na}$: calculated 360.1059; found 360.1068. Anal. ($\text{C}_{16}\text{H}_{19}\text{NO}_7$) C, H, N.

(R)-Dimethyl 2-(5-(4-formylphenoxy)pentanamido)pentanedioate [(R)-42]. The crude product was purified with flash column chromatography using ethyl acetate/petroleum ether (2:1) as eluent. Yield: 43%; white crystals; m.p. 92-97 °C; $[\alpha]_{546}^{23} +17.7$ (c 0.305, DMF); IR (KBr): $\nu = 3326, 2954, 2820, 2736, 1728, 1650, 1598, 1531, 1254, 1205, 1153, 965, 835, 814 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.61-2.05 (m, 6H, $3 \times \text{CH}_2$), 2.20 (t, 2H, $J = 6.9 \text{ Hz}$, NHCOCH_2), 2.38 (t, 2H, $J = 7.8 \text{ Hz}$, CHCH_2CH_2), 3.59 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 4.10 (t, 2H, $J = 6.3 \text{ Hz}$, CH_2O), 4.23-4.30 (m, 1H, CHCH_2CH_2), 7.12 (d, 2H, $J = 8.7 \text{ Hz}$, Ar-H-2,6), 7.86 (d, 2H, $J = 8.7 \text{ Hz}$, Ar-H-3,5), 8.23 (d, 1H, $J = 7.8 \text{ Hz}$, NH), 9.87 (s, 1H, CHO). ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 22.56 (CH_2), 26.91 (CH_2), 28.77 (CH_2), 30.55 (CH_2), 35.33 (CH_2), 51.94 (CH), 52.25 (CH_3), 52.72 (CH_3), 68.60 ($\text{CH}_2\text{-O}$), 115.79 (Ar-C), 130.41 (Ar-C), 132.67 (Ar-C), 164.52 (Ar-C), 173.13 (C=O), 173.16 (C=O), 173.40 (C=O), 192.12 (CHO). MS (ESI): m/z (%) = 402 (MNa^+ , 100), 380 (MH^+ , 63), 258 (25). Anal. ($\text{C}_{19}\text{H}_{25}\text{NO}_7$) C, H, N.

(R,Z)-Dimethyl 2-(2-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetamido)pentanedioate [(R)-43]. Prepared from (R)-40 and thiazolidine-2,4-dione (8) according to general procedure B. Yield: 55%; white crystals; m.p. 122-125 °C; IR (KBr): $\nu = 3374, 3100, 2957, 2777, 1732, 1698, 1537, 1432, 1300, 1245, 1213, 1193, 1146, 1062, 1018, 783 \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6): δ 1.84-2.12 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, $J = 7.5 \text{ Hz}$, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 4.34-4.42 (m, 1H, CHCH_2CH_2), 4.60 (d, 1H, AB system, $^2J = 15.6 \text{ Hz}$, H_A from CH_2O), 4.65 (d, 1H, AB system, $^2J = 15.6 \text{ Hz}$, H_B from CH_2O), 7.08 (dd, 1H, $^3J = 8.1 \text{ Hz}$, $^4J = 2.1 \text{ Hz}$, Ar-H-6), 7.15 (s, 1H, Ar-H-2), 7.21 (d, 1H, $J = 7.8 \text{ Hz}$, Ar-H-4), 7.47 (dd, 1H, $J_1 = 8.1 \text{ Hz}$, $J_2 = 7.8 \text{ Hz}$, Ar-H-5), 7.76 (s, 1H, $\text{CH}=\text{C}$), 8.54 (d, 1H, $J = 7.8 \text{ Hz}$, CONH), 12.62 (br s, 1H, CONHCO). MS (ESI): m/z (%) = 459 (MNa^+ , 100), 437 (MH^+ , 33), 413 (28), 400 (15), 141 (31), 77 (50). HRMS for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_8\text{SNa}$: calculated 459.0838; found 459.0826. Anal. ($\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_8\text{S}$) C, H, N.

(*R,Z*)-Dimethyl 2-(2-(3-((2-oxo-4-thioxothiazolidin-5-ylidene)methyl)phenoxy)acetamido)pentanedioate [(*R*)-44]. Prepared from (*R*)-40 and rhodanine (9) according to general procedure B. Yield: 57%; yellow crystals; m.p. 121-124 °C; IR (KBr): ν = 3417, 2920, 2849, 1721, 1641, 1436, 1296, 1254, 1213, 1176, 1059, 776 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.85-2.13 (m, 2H, CHCH_2CH_2), 2.35 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 3.58 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 4.34-4.42 (m, 1H, CHCH_2CH_2), 4.61 (d, 1H, AB system, 2J = 15.6 Hz, H_A from CH_2O), 4.66 (d, 1H, AB system, 2J = 15.6 Hz, H_B from CH_2O), 7.10 (dd, 1H, 3J = 8.0 Hz, 4J = 2.3 Hz, Ar-H-6), 7.15 (s, 1H, Ar-H-2), 7.22 (d, 1H, J = 7.8 Hz, Ar-H-4), 7.48 (dd, 1H, J_1 = 8.0 Hz, J_2 = 7.8 Hz, Ar-H-5), 7.61 (s, 1H, $\text{CH}=\text{C}$), 8.55 (d, 1H, J = 7.8 Hz, CONH), 13.84 (br s, 1H, CSNHCO). MS (ESI): m/z (%) = 475 (MNa^+ , 100), 453 (MH^+ , 90), 421 (43), 393 (50), 184 (50), 77 (70). Anal. ($\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_7\text{S}_2$) C, H, N.

(*R,Z*)-2-(2-(3-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)acetamido)pentanedioic acid [(*R*)-45]. Prepared by hydrolysis of (*R*)-43 according to general procedure F. Yield: 85%; white crystals; m.p. 185-189 °C; IR (KBr): ν = 3386, 3200, 3069, 2900, 1743, 1730, 1709, 1685, 1628, 1544, 1429, 1321, 1275, 1226, 1190, 1130, 802, 777 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.79-2.10 (m, 2H, CHCH_2CH_2), 2.27 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 4.27-4.34 (m, 1H, CHCH_2CH_2), 4.59 (d, 1H, AB system, 2J = 15.3 Hz, H_A from CH_2O), 4.64 (d, 1H, AB system, 2J = 15.3 Hz, H_B from CH_2O), 7.09 (dd, 1H, 3J = 8.1 Hz, 4J = 2.1 Hz, Ar-H-6), 7.17-7.21 (m, 2H, Ar-H-2,4), 7.46 (t, 1H, J = 8.1 Hz, Ar-H-5), 7.75 (s, 1H, $\text{CH}=\text{C}$), 8.38 (d, 1H, J = 8.1 Hz, CONH), 12.50 (br s, 3H, CONHCO, 2 $\times$ COOH). ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 26.95 (CH_2), 30.94 (CH_2), 51.89 (CHNH), 67.59 (CH_2O), 116.88 (Ar-C/ $\text{CH}=\text{C}$), 117.86 (Ar-C/ $\text{CH}=\text{C}$), 123.50 (Ar-C/ $\text{CH}=\text{C}$), 125.01 (Ar-C/ $\text{CH}=\text{C}$), 131.24 (Ar-C/ $\text{CH}=\text{C}$), 132.37 (Ar-C/ $\text{CH}=\text{C}$), 135.26 (Ar-C/ $\text{CH}=\text{C}$), 159.05 (Ar-C/ $\text{CH}=\text{C}$), 168.14 (C=O), 168.48 (C=O), 168.72 (C=O), 173.78 (C=O), 174.61 (C=O). MS (ESI-): m/z (%) = 407 ($[\text{M}-\text{H}]^-$, 100), 212 (35). HRMS for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_8\text{S}$: calculated 407.0549; found 407.0547. Anal. ($\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_8\text{S}$) C, H, N.

(*R,Z*)-2-(2-(3-((2-Oxo-4-thioxothiazolidin-5-ylidene)methyl)phenoxy)acetamido)pentanedioic acid [(*R*)-46]. Prepared by hydrolysis of (*R*)-44 according to general procedure F. Yield: 75%; yellow crystals; m.p. 195-198 °C; IR (KBr): ν = 3371, 3200, 2925, 2850, 1716, 1606, 1574, 1549, 1491, 1422, 1275, 1207, 1063, 678 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.80-2.10 (m, 2H, CHCH_2CH_2), 2.27 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 4.27-4.34 (m, 1H, CHCH_2CH_2), 4.63 (s, 2H, CH_2O), 7.11 (dd, 1H, 3J = 8.1 Hz, 4J = 2.3 Hz, Ar-H-6), 7.17-7.22 (m, 2H, Ar-H-2,4), 7.47 (t, 1H, J = 8.1 Hz, Ar-H-5), 7.61 (s, 1H, $\text{CH}=\text{C}$), 8.38 (d, 1H, J = 8.1 Hz, CONH), 12.44 (br s, 2H, 2 $\times$ COOH), 13.84 (br s, 1H, CSNHCO). ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 26.95 (CH_2), 30.95 (CH_2), 51.90 (CHNH), 67.60 (CH_2O), 117.20 (Ar-C/ $\text{CH}=\text{C}$), 118.26 (Ar-C/ $\text{CH}=\text{C}$), 123.97 (Ar-C/ $\text{CH}=\text{C}$), 127.01 (Ar-C/ $\text{CH}=\text{C}$), 131.38 (Ar-C/ $\text{CH}=\text{C}$), 132.20 (Ar-C/ $\text{CH}=\text{C}$), 135.19 (Ar-C/ $\text{CH}=\text{C}$), 159.11 (Ar-C/ $\text{CH}=\text{C}$), 168.46 (C=O), 170.26 (C=O), 173.78 (C=O), 174.61 (C=O), 196.59 (C=S). MS (ESI-): m/z (%) = 423 ($[\text{M}-\text{H}]^-$, 100), 369 (25), 336 (80), 302 (35). HRMS for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_7\text{S}_2$: calculated 423.0321; found 423.0332. Anal. ($\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_7\text{S}_2$) C, H, N.

(*R,Z*)-Dimethyl 2-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetamido)pentanedioate [(*R*)-47]. Prepared from (*R*)-41 and thiazolidine-2,4-dione (8) according to general procedure B. Yield: 55%; white crystals; m.p. 145-150 °C; IR (KBr): ν = 3389, 3220, 3038, 2953, 2746, 1741, 1696, 1660, 1597, 1538, 1508, 1440, 1292, 1258, 1208, 1180, 1048, 823 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.84-2.12 (m, 2H, CHCH_2CH_2), 2.37 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 3.59 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.34-4.41 (m, 1H, CHCH_2CH_2), 4.63 (d, 1H, AB system, 2J = 15.6 Hz, H_A from CH_2O), 4.68 (d, 1H, AB system, 2J = 15.6 Hz, H_B

from CH₂O), 7.10 (d, 2H, *J* = 8.9 Hz, Ar-H-2,6), 7.57 (d, 2H, *J* = 8.9 Hz, Ar-H-3,5), 7.76 (s, 1H, CH=C), 8.54 (d, 1H, *J* = 7.8 Hz, CONH), 12.51 (br s, 1H, CONHCO). MS (ESI): *m/z* (%) = 459 (MNa⁺, 65), 437 (MH⁺, 33), 413 (15), 236 (22), 214 (100), 158 (35). Anal. (C₁₉H₂₀N₂O₈S) C, H, N.

(*R,Z*)-Dimethyl 2-(2-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenoxy)-acetamido)pentanedioate [(*R*)-48]. Prepared from (*R*)-41 and rhodanine (9) according to general procedure B. Yield: 74%; yellow crystals; m.p. 132-136 °C; IR (KBr): ν = 3404, 2951, 2848, 1731, 1691, 1592, 1508, 1435, 1257, 1237, 1195, 1172, 1056, 1007, 824 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.85-2.12 (m, 2H, CHCH₂CH₂), 2.37 (t, 2H, *J* = 7.5 Hz, CHCH₂CH₂), 3.59 (s, 3H, CH₃), 3.64 (s, 3H, CH₃), 4.34-4.41 (m, 1H, CHCH₂CH₂), 4.64 (d, 1H, AB system, ²*J* = 15.6 Hz, H_A from CH₂O), 4.69 (d, 1H, AB system, ²*J* = 15.6 Hz, H_B from CH₂O), 7.12 (d, 2H, *J* = 8.7 Hz, Ar-H-2,6), 7.58 (d, 2H, *J* = 8.7 Hz, Ar-H-3,5), 7.63 (s, 1H, CH=C), 8.55 (d, 1H, *J* = 7.8 Hz, CONH), 13.75 (br s, 1H, CSNHCO). MS (ESI): *m/z* (%) = 475 (MNa⁺, 100), 453 (MH⁺, 77), 413 (43), 400 (58), 214 (30), 241 (48), 77 (43). Anal. (C₁₉H₂₀N₂O₇S₂) C, H, N.

(*R,Z*)-Dimethyl 2-(5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)pentanamido)-pentanedioate [(*R*)-49]. Prepared from (*R*)-42 and thiazolidine-2,4-dione (8) according to general procedure B. Yield: 36%; pale yellow crystals; m.p. 128-132 °C; IR (KBr): ν = 3523, 3445, 3304, 3144, 2953, 1739, 1687, 1647, 1587, 1540, 1511, 1262, 1205, 1178, 1020, 825 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.60-2.05 (m, 6H, 3 × CH₂), 2.20 (t, 2H, *J* = 6.9 Hz, NHCOCH₂), 2.38 (t, 2H, *J* = 7.5 Hz, CHCH₂CH₂), 3.59 (s, 3H, CH₃), 3.62 (s, 3H, CH₃), 4.05 (t, 2H, *J* = 6.2 Hz, CH₂O), 4.23-4.30 (m, 1H, CHCH₂CH₂), 7.09 (d, 2H, *J* = 9.0 Hz, Ar-H-2,6), 7.55 (d, 2H, *J* = 9.0 Hz, Ar-H-3,5), 7.75 (s, 1H, CH=C), 8.23 (d, 1H, *J* = 7.5 Hz, CONH), 12.49 (br s, 1H, CONHCO). MS (ESI-): *m/z* (%) = 477 ([M-H]⁻, 100), 449 (3), 406 (5). Anal. (C₂₂H₂₆N₂O₈S) C, H, N.

(*R,Z*)-Dimethyl 2-(5-(4-((2-oxo-4-thioxothiazolidin-5-ylidene)methyl)phenoxy)-pentanamido)pentanedioate [(*R*)-50]. Prepared from (*R*)-42 and rhodanine (9) according to general procedure B. Yield: 81%; yellow crystals; m.p. 160-163 °C; IR (KBr): ν = 3547, 3412, 3258, 3071, 2941, 2860, 1734, 1690, 1644, 1587, 1561, 1517, 1431, 1268, 1244, 1202, 1183, 998, 836 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.61-2.05 (m, 6H, 3 × CH₂), 2.20 (t, 2H, *J* = 7.1 Hz, NHCOCH₂), 2.38 (t, 2H, *J* = 7.5 Hz, CHCH₂CH₂), 3.59 (s, 3H, CH₃), 3.62 (s, 3H, CH₃), 4.07 (t, 2H, *J* = 6.0 Hz, CH₂O), 4.23-4.30 (m, 1H, CHCH₂CH₂), 7.11 (d, 2H, *J* = 8.7 Hz, Ar-H-2,6), 7.56 (d, 2H, *J* = 8.7 Hz, Ar-H-3,5), 7.62 (s, 1H, CH=C), 8.23 (d, 1H, *J* = 7.5 Hz, CONH), 13.74 (br s, 1H, CSNHCO). MS (ESI): *m/z* (%) = 517 (MNa⁺, 60), 495 (MH⁺, 90), 413 (40), 214 (50), 158 (70), 141 (100). HRMS for C₂₂H₂₇N₂O₇S₂: calculated 495.1260; found 495.1238. Anal. (C₂₂H₂₆N₂O₇S₂) C, H, N.

(*R,Z*)-Dimethyl 2-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetamido)-pentanedioate [(*R*)-51]. Prepared by hydrolysis of (*R*)-47 according to general procedure F. Yield: 55%; white crystals; m.p. 170-175 °C; IR (KBr): ν = 3388, 2932, 2764, 1738, 1691, 1598, 1542, 1508, 1418, 1261, 1176, 1155, 1047, 825 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.80-2.09 (m, 2H, CHCH₂CH₂), 2.27 (t, 2H, *J* = 7.5 Hz, CHCH₂CH₂), 4.25-4.32 (m, 1H, CHCH₂CH₂), 4.62 (s, 2H, CH₂O), 7.09 (d, 2H, *J* = 8.9 Hz, Ar-H-2,6), 7.53 (d, 2H, *J* = 8.9 Hz, Ar-H-3,5), 7.60 (s, 1H, CH=C), 8.33 (d, 1H, *J* = 7.8 Hz, CONH), 12.26 (br s, 3H, CONHCO, 2 × COOH). ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 27.18 (CH₂), 31.11 (CH₂), 52.07 (CHNH), 67.57 (CH₂O), 116.34 (Ar-C/CH=C), 125.21 (Ar-C/CH=C), 127.76 (Ar-C/CH=C), 129.88 (Ar-C/CH=C), 132.38 (Ar-C/CH=C), 159.72 (Ar-C/CH=C), 168.22 (C=O), 170.90 (C=O), 172.47

(C=O), 173.81 (C=O), 174.71 (C=O). MS (ESI): m/z (%) = 431 (MNa^+ , 100), 409 (MH^+ , 28), 389 (9), 365 (10). HRMS for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_8\text{SNa}$: calculated 431.0525; found 431.0533. Anal. ($\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_8\text{S} \times 0.8 \text{ H}_2\text{O}$) C, H, N.

(*R,Z*)-Dimethyl 2-(2-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenoxy)-acetamido)pentanedioate [(*R*)-52]. Prepared by hydrolysis of (*R*)-48 according to general procedure F. Yield: 74%; yellow crystals; m.p. 184-187 °C; IR (KBr): ν = 3410, 2918, 2849, 1723, 1694, 1636, 1590, 1508, 1421, 1236, 1198, 1172, 1059, 1012, 823 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 1.79-2.10 (m, 2H, CHCH_2CH_2), 2.28 (t, 2H, J = 7.5 Hz, CHCH_2CH_2), 4.27-4.34 (m, 1H, CHCH_2CH_2), 4.63 (d, 1H, AB system, 2J = 15.0 Hz, H_A from CH_2O), 4.69 (d, 1H, AB system, 2J = 15.0 Hz, H_B from CH_2O), 7.12 (d, 2H, J = 8.9 Hz, Ar-H-2,6), 7.57 (d, 2H, J = 8.9 Hz, Ar-H-3,5), 7.61 (s, 1H, $\text{CH}=\text{C}$), 8.40 (d, 1H, J = 7.8 Hz, CONH), 12.41 (br s, 2H, 2 $\times$ COOH), 13.73 (br s, 1H, CSNHCO). ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz): δ 26.95 (CH_2), 30.93 (CH_2), 51.90 (CHNH), 67.53 (CH_2O), 116.67 (Ar-C/ $\text{CH}=\text{C}$), 123.88 (Ar-C/ $\text{CH}=\text{C}$), 127.00 (Ar-C/ $\text{CH}=\text{C}$), 132.31 (Ar-C/ $\text{CH}=\text{C}$), 133.35 (Ar-C/ $\text{CH}=\text{C}$), 160.60 (Ar-C/ $\text{CH}=\text{C}$), 168.25 (C=O), 170.75 (C=O), 173.77 (C=O), 174.62 (C=O), 196.63 (C=O). MS (ESI): m/z (%) = 447 (MNa^+ , 20), 425 (MH^+ , 70), 391 (15), 301 (13), 158 (40), 149 (100). HRMS for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_7\text{S}_2\text{Na}$: calculated 447.0297; found 447.0315. Anal. ($\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_7\text{S}_2$) C, H, N.

(*R,Z*)-2-(5-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)pentanamido)-pentanedioic acid [(*R*)-53]. Prepared by hydrolysis of (*R*)-49 according to general procedure F. Yield: 71%; pale yellow crystals; m.p. 160-165 °C; IR (KBr): ν = 3418, 2935, 2800, 1740, 1690, 1650, 1598, 1512, 1419, 1297, 1262, 1180, 1152, 1018, 827 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 1.60-2.02 (m, 6H, 3 $\times$ CH_2), 2.20 (t, 2H, J = 6.8 Hz, NHCOCH_2), 2.28 (t, 2H, J = 7.2 Hz, CHCH_2CH_2), 4.05 (t, 2H, J = 5.6 Hz, CH_2O), 4.17-4.24 (m, 1H, CHCH_2CH_2), 7.09 (d, 2H, J = 8.7 Hz, Ar-H-2,6), 7.55 (d, 2H, J = 8.7 Hz, Ar-H-3,5), 7.75 (s, 1H, $\text{CH}=\text{C}$), 8.08 (d, 1H, J = 7.8 Hz, CONH), 12.41 (br s, 3H, CONHCO, 2 $\times$ COOH). MS (ESI $^-$): m/z (%) = 449 ($[\text{M}-\text{H}]^-$, 100), 431 (12), 405 (10), 378 (25), 320 (20). HRMS for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_8\text{S}$: calculated 449.1019; found 449.1010. Anal. ($\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_8\text{S}$) C, H, N.

(*R,Z*)-2-(5-(4-((2-Oxo-4-thioxothiazolidin-5-ylidene)methyl)phenoxy)pentanamido)-pentanedioic acid [(*R*)-54]. Prepared by hydrolysis of (*R*)-50 according to general procedure F. Yield: 72%; yellow crystals; m.p. 152-157 °C; IR (KBr): ν = 3500, 3412, 3072, 2926, 2851, 1710, 1637, 1618, 1585, 1510, 1424, 1261, 1198, 1171, 996, 828, 807 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 1.60-2.02 (m, 6H, 3 $\times$ CH_2), 2.20 (t, 2H, J = 6.5 Hz, NHCOCH_2), 2.28 (t, 2H, J = 7.2 Hz, CHCH_2CH_2), 4.03-4.06 (m, 2H, CH_2O), 4.23-4.30 (m, 1H, CHCH_2CH_2), 7.09 (d, 2H, J = 8.6 Hz, Ar-H-2,6), 7.54 (d, 2H, J = 8.6 Hz, Ar-H-3,5), 7.58 (s, 1H, $\text{CH}=\text{C}$), 8.09 (d, 1H, J = 7.5 Hz, CONH), 12.41 (br s, 2H, 2 $\times$ COOH), 13.20 (br s, 1H, CSNHCO). MS (ESI $^-$): m/z (%) = 465 ($[\text{M}-\text{H}]^-$, 88), 438 (40), 406 (38), 378 (100), 212 (68). HRMS for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_7\text{S}_2$: calculated 465.0790; found 465.0790. Anal. ($\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_7\text{S}_2$) C, H, N.

General procedure I. Compounds 55-57.

To a stirred suspension of compound **11**, **12** or **13** (7.45 mmol) in toluene (100 mL) was added diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate (2.45 g, 9.69 mmol) and silica gel 60 (7.45 g, 1 g/mmol), previously activated by heating at 120 °C for 5 h. The mixture was heated to 100 °C for 24h under an argon atmosphere in the dark. The reaction mixture was then cooled and filtered. The filter cake was rinsed with ethyl acetate. The combined filtrate and rinse were evaporated to dryness. The residue was redissolved in ethyl acetate (100 mL), washed with 1 M HCl (3 $\times$ 50 mL) and brine (50 mL), dried over Na_2SO_4 ,

filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography using dichloromethane/methanol (40:1) as an eluent.

5-(3-Nitrobenzyl)-2-thioxothiazolidin-4-one (55). Yield: 84%; yellow crystals; m.p. 165-168 °C; IR (KBr): ν = 3068, 2874, 1718, 1581, 1529, 1454, 1349, 1307, 1269, 1234, 1208, 1103, 1083, 939, 908, 833, 814, 736, 722, 680, 662, 585, 509 cm^{-1} . ^1H NMR (DMSO- d_6): δ 3.40 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 7.9 Hz, H_A from Ar- CH_2CH), 3.52 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 5.4 Hz, H_B from Ar- CH_2CH), 5.12 (dd, 1H, J_1 = 7.9 Hz, J_2 = 5.4 Hz, SCHCO), 7.63 (dt, 1H, 3J = 7.7 Hz, 4J = 0.8 Hz, Ar-H-5), 7.73 (d, 1H, J = 7.7 Hz, Ar-H-6), 8.12-8.16 (m, 2H, Ar-H-2,4), 13.17 (s, 1H, CSNHCO). MS (ESI $^-$): m/z (%) = 267 ([M-H] $^-$, 100). HRMS (ESI $^-$) for $\text{C}_{10}\text{H}_7\text{N}_2\text{O}_3\text{S}_2$: calculated 266.9898; found 266.9888.

5-(4-Nitrobenzyl)thiazolidine-2,4-dione (56). Yield: 80%; brown crystals; m.p. 178-181 °C; IR (KBr): ν = 3255, 1759, 1743, 1700, 1597, 1512, 1448, 1347, 1314, 1264, 1224, 1175, 1138, 1108, 1040, 956, 924, 865, 852, 745, 719, 698, 661, 601, 541, 481 cm^{-1} . ^1H NMR (DMSO- d_6): δ 3.36 (dd, 1H, AB system, 3J = 8.6 Hz, H_A from Ar- CH_2CH , signal partially overlapped with H_2O), 3.52 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 4.9 Hz, H_B from Ar- CH_2CH), 5.01 (dd, 1H, J_1 = 8.6 Hz, J_2 = 4.9 Hz, SCHCO), 7.55 (d, 1H, J = 8.6 Hz, Ar-H-2,6), 8.20 (d, 1H, J = 8.6 Hz, Ar-H-3,5), 12.09 (s, 1H, CONHCO). MS (ESI $^-$): m/z (%) = 251 ([M-H] $^-$, 13), 77 (100). HRMS (ESI $^+$) for $\text{C}_{10}\text{H}_9\text{N}_2\text{O}_4\text{S}$: calculated 253.0283; found 253.0282.

5-(4-Nitrobenzyl)-2-thioxothiazolidin-4-one (57). Yield: 64%; yellow crystals; m.p. 125-128 °C; IR (KBr): ν = 2978, 2932, 1724, 1592, 1559, 1520, 1444, 1369, 1352, 1298, 1223, 1108, 1044, 865, 771, 696, 566 cm^{-1} . ^1H NMR (DMSO- d_6): δ 3.38 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 8.3 Hz, H_A from Ar- CH_2CH), 3.52 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 5.3 Hz, H_B from Ar- CH_2CH), 5.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 5.3 Hz, SCHCO), 7.54 (d, 1H, J = 8.7 Hz, Ar-H-2,6), 8.19 (d, 1H, J = 8.7 Hz, Ar-H-3,5), 13.21 (s, 1H, CSNHCO). MS (ESI $^-$): m/z (%) = 267 ([M-H] $^-$, 100). HRMS (ESI $^-$) for $\text{C}_{10}\text{H}_7\text{N}_2\text{O}_3\text{S}_2$: calculated 266.9898; found 266.9890.

5-(3-Aminobenzyl)-2-thioxothiazolidin-4-one (58). Prepared from compound **55** according to general procedure D. Yield: 96%; yellow crystals; m.p. 71-74 °C; IR (KBr): ν = 3414, 2368, 2345, 1618, 1431, 1296, 1254, 1220, 1182, 1066, 863, 778, 723, 618, 475 cm^{-1} . ^1H NMR (DMSO- d_6): δ 2.96 (dd, 1H, AB system, 2J = 14.0 Hz, 3J = 9.7 Hz, H_A from Ar- CH_2CH), 3.23 (dd, 1H, AB system, 2J = 14.0 Hz, 3J = 4.3 Hz, H_B from Ar- CH_2CH), 4.93 (dd, 1H, J_1 = 9.7 Hz, J_2 = 4.3 Hz, SCHCO), 6.36-6.46 (m, 3H, Ar-H-2,4,6), 6.95 (t, 1H, J = 7.6 Hz, Ar-H-5), signals for Ar- NH_2 and CSNHCO not seen. MS (ESI $^+$): m/z (%) = 239 ([M+H] $^+$, 33), 108 (85), 77 (100). HRMS (ESI $^+$) for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{OS}_2$: calculated 239.0313; found 239.0311.

5-(4-Aminobenzyl)thiazolidine-2,4-dione (59). Prepared from compound **56** according to general procedure C. Yield: 95%; yellow crystals; m.p. 154-157 °C; IR (KBr): ν = 3381, 3316, 2928, 2686, 1740, 1694, 1614, 1694, 1614, 1516, 1442, 1314, 1251, 1224, 1156, 1038, 1020, 938, 883, 841, 806, 737, 711, 666, 648, 601, 563, 505, 486 cm^{-1} . ^1H NMR (DMSO- d_6): δ 2.89 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 9.3 Hz, H_A from Ar- CH_2CH), 3.20 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 4.1 Hz, H_B from Ar- CH_2CH), 4.74 (dd, 1H, J_1 = 9.3 Hz, J_2 = 4.1 Hz, SCHCO), 6.49 (d, 1H, J = 8.3 Hz, Ar-H-3,5), 6.87 (d, 1H, J = 8.3 Hz, Ar-H-2,6), signals for Ar- NH_2 and CONHCO not seen. MS (EI): m/z (%) = 222 (M^+ , 31), 106 (100). Anal. ($\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$) C, H, N.

5-(4-Aminobenzyl)-2-thioxothiazolidin-4-one (60). Prepared from compound **57** according to general procedure D. Yield: 32%; orange crystals; m.p. 174-177 °C; IR (KBr): ν = 3355, 3290, 2614, 1718, 1611, 1516, 1481, 1297, 1238, 1194, 1180, 1069, 964, 913, 866, 837, 800, 771, 729, 689, 650, 565, 502 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 2.96 (dd, 1H, AB system, 2J = 14.2 Hz, 3J = 9.0 Hz, H_A from $\text{Ar}-\text{CH}_2\text{CH}$), 3.18 (dd, 1H, AB system, 2J = 14.2 Hz, 3J = 4.5 Hz, H_B from $\text{Ar}-\text{CH}_2\text{CH}$), 4.90 (dd, 1H, J_1 = 9.0 Hz, J_2 = 4.5 Hz, SCHCO), 6.48 (d, 1H, J = 8.4 Hz, Ar-H-3,5), 6.87 (d, 1H, J = 8.4 Hz, Ar-H-2,6), signals for Ar-NH₂ and CSNHCO not seen. MS (ESI+): m/z (%) = 239 ($[\text{M}+\text{H}]^+$, 88), 107 (100). Anal. ($\text{C}_{10}\text{H}_{10}\text{N}_2\text{OS}_2$) C, H, N.

General procedure J. Synthesis of Compounds (R)-61, 63 and 64.

A suspension of amine **58**, **59** or **60** (3.15 mmol) and benzaldehyde **3** or (R)-**4** (3.62 mmol) in methanol (60 mL), was heated at 65 °C for 2 hours and then cooled to room temperature. NaCNBH₃ (257 mg, 4.10 mmol) was added and the reaction mixture stirred overnight under an argon atmosphere. The solvent was evaporated under reduced pressure, the residue dissolved in ethyl acetate (40 mL) and washed with water (2 × 20 mL) and brine (20 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. The crude product was purified with flash column chromatography using dichloromethane/methanol (20:1) as an eluent.

(2R)-Dimethyl 2-(3-((4-((4-oxo-2-thioxothiazolidin-5-yl)methyl)phenylamino)methyl)benzamido)pentanedioate [(R)-61]. Yield: 49%; yellow crystals; m.p. 54-56 °C; IR (KBr): ν = 3401, 2950, 2849, 2346, 1735, 1640, 1616, 1586, 1522, 1482, 1436, 1324, 1294, 1263, 1219, 1181, 1101, 1069, 927, 816, 745, 688, 562, 475 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 1.97-2.16 (m, 2H, CHCH_2CH_2), 2.46 (t, 2H, J = 7.6 Hz, CHCH_2CH_2), 2.96 (dd, 1H, AB system, 2J = 14.2 Hz, 3J = 9.1 Hz, H_A from $\text{Ar}-\text{CH}_2\text{CH}$), 3.19 (dd, 1H, AB system, 2J = 14.2 Hz, 3J = 4.3 Hz, H_B from $\text{Ar}-\text{CH}_2\text{CH}$), 3.59 (s, 3H, CH₃), 3.65 (s, 3H, CH₃), 4.29 (d, 2H, J = 5.4 Hz, CH_2NH), 4.44-4.48 (m, 1H, CHCH_2CH_2), 4.90 (dd, 1H, J_1 = 9.1 Hz, J_2 = 4.3 Hz, SCHCO), 6.24 (t, 1H, J = 6.0 Hz, CH_2NH), 6.52 (d, 2H, J = 8.5 Hz, Ar-H-2,6), 6.92 (d, 2H, J = 8.5 Hz, Ar-H-3,5), 7.42 (t, 1H, J = 7.6 Hz, Ar-H-5'), 7.52 (d, 1H, J = 7.6 Hz, Ar-H-4'), 7.74 (d, 1H, J = 7.6 Hz, Ar-H-6'), 7.98 (s, 1H, Ar-H-2'), 8.72 (d, 1H, J = 7.5 Hz, CONH), 13.09 (br s, 1H, CSNHCO). MS (ESI+): m/z (%) = 530 ($[\text{M}+\text{H}]^+$, 68), 141 (100). Anal. ($\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_6\text{S}_2$) C, H, N.

4-((3-((4-Oxo-2-thioxothiazolidin-5-yl)methyl)phenylamino)methyl)benzoic acid (63). Yield: 45%; yellow crystals; m.p. 79-81 °C; IR (KBr): ν = 2852, 1686, 1605, 1426, 1222, 1176, 1069, 844, 763, 694, 670, 498 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 2.97 (dd, 1H, AB system, 2J = 14.0 Hz, 3J = 9.8 Hz, H_A from $\text{Ar}-\text{CH}_2\text{CH}$), 3.23 (dd, 1H, AB system, 2J = 14.0 Hz, 3J = 4.2 Hz, H_B from $\text{Ar}-\text{CH}_2\text{CH}$), 4.32 (s, 2H, CH_2NH), 4.93 (dd, 1H, J_1 = 9.8 Hz, J_2 = 4.2 Hz, SCHCO), 6.36-6.46 (m, 4H, Ar-H-2,4,6, CH_2NH), 6.97 (t, 1H, 3J = 7.7 Hz, Ar-H-5), 7.45 (d, 2H, J = 8.2 Hz, Ar-H-3',5'), 7.89 (d, 2H, J = 8.2 Hz, Ar-H-2',6'), 12.79 (br s, 1H, COOH), 13.13 (br s, 1H, CSNHCO). MS (ESI+): m/z (%) = 373 ($[\text{M}+\text{H}]^+$, 94), 355 (100). Anal. ($\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3\text{S}_2$) C, H, N.

4-((4-((2,4-Dioxothiazolidin-5-yl)methyl)phenylamino)methyl)benzoic acid (64). Yield: 71%; white crystals; m.p. 255-258 °C; IR (KBr): ν = 3377, 3048, 1752, 1685, 1608, 1578, 1512, 1471, 1427, 1320, 1298, 1165, 1018, 942, 886, 806, 767, 724, 701, 669, 605, 550, 504 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 2.90 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 9.4 Hz, H_A from $\text{Ar}-\text{CH}_2\text{CH}$), 3.20 (dd, 1H, AB system, 2J = 14.1 Hz, 3J = 4.1 Hz, H_B from $\text{Ar}-\text{CH}_2\text{CH}$), 4.31 (s, 2H, CH_2NH), 4.77 (dd, 1H, J_1 = 9.4 Hz, J_2 = 4.1 Hz, SCHCO), 6.28 (t, 1H, J = 4.9 Hz, CH_2NH), 6.50 (d, 2H, J = 8.5 Hz, Ar-H-2,6), 6.92 (d, 2H, J = 8.5 Hz, Ar-H-3,5), 7.46 (d, 2H,

$J = 8.3$ Hz, Ar-H-3',5'), 7.89 (d, 2H, $J = 8.3$ Hz, Ar-H-2',6'), 12.02 (br s, 1H, CONHCO/COOH), 12.75 (br s, 1H, CONHCO/COOH). MS (ESI+): m/z (%) = 357 ([M+H]⁺, 30), 141 (100). Anal. (C₁₈H₁₆N₂O₄S × 0.2 H₂O) C, H, N.

General procedure K. Compounds (R)-65 and (R)-67.

A solution of D-glutamic acid dimethyl ester hydrochloride [(R)-1] (212 mg, 1.00 mmol), acid **63** or **64** (1.00 mmol) and HOBt (191 mg, 1.20 mmol) in DMF (25 mL) was prepared and pH adjusted to 8 with *N*-methylmorpholine. EDC (249 mg, 1.47 mmol) was added and the reaction mixture stirred overnight at room temperature. The solvent was evaporated under reduced pressure, the residue dissolved in ethyl acetate (50 mL) and washed successively with 10% citric acid (3 × 15 mL) and brine (2 × 10 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography using dichloromethane/methanol (20:1) as an eluent.

(2R)-Dimethyl 2-(4-((3-((4-oxo-2-thioxothiazolidin-5-yl)methyl)phenylamino)methyl)benzamido)pentanedioate [(R)-65]. Yield: 22%; yellow crystals; m.p. 114-116 °C; IR (KBr): $\nu = 3419, 3340, 3251, 2948, 1742, 1637, 1607, 1526, 1499, 1437, 1337, 1281, 1217, 1181, 1108, 1070, 1018, 986, 837, 768, 699, 500$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.94-2.18 (m, 2H, CHCH₂CH₂), 2.45 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 2.97 (dd, 1H, AB system, ² $J = 14.1$ Hz, ³ $J = 9.8$ Hz, H_A from Ar-CH₂CH), 3.24 (dd, 1H, AB system, ² $J = 14.1$ Hz, ³ $J = 4.3$ Hz, H_B from Ar-CH₂CH), 3.58 (s, 3H, CH₃), 3.64 (s, 3H, CH₃), 4.32 (d, 2H, $J = 5.0$ Hz, CH₂NH), 4.42-4.49 (m, 1H, CHCH₂CH₂), 4.93 (dd, 1H, $J_1 = 9.8$ Hz, $J_2 = 4.3$ Hz, SCHCO), 6.33 (t, 1H, $J = 6.2$ Hz, CH₂NH), 6.38-6.44 (m, 2H, Ar-H-4,6), 6.48 (s, 1H, Ar-H-2), 6.97 (t, 1H, $J = 7.8$ Hz, Ar-H-5), 7.44 (d, 2H, $J = 8.3$ Hz, Ar-H-3',5'), 7.82 (d, 2H, $J = 8.3$ Hz, Ar-H-2',6'), 8.66 (d, 2H, $J = 7.5$ Hz, CONH), 13.14 (br s, 1H, CSNHCO). MS (ESI+): m/z (%) = 530 ([M+H]⁺, 100). Anal. (C₂₅H₂₇N₃O₆S₂) C, H, N.

(2R)-Dimethyl 2-(4-((4-((2,4-dioxothiazolidin-5-yl)methyl)phenylamino)methyl)benzamido)pentanedioate [(R)-67]. Yield: 65%; yellow crystals; m.p. 66-69 °C; IR (KBr): $\nu = 3552, 3409, 3234, 3026, 2952, 2851, 2775, 1741, 1700, 1654, 1639, 1615, 1571, 1560, 1523, 1500, 1438, 1413, 1327, 1265, 1214, 1155, 1017, 820, 753, 714, 603, 563, 492$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.94-2.18 (m, 2H, CHCH₂CH₂), 2.45 (t, 2H, $J = 7.5$ Hz, CHCH₂CH₂), 2.90 (dd, 1H, AB system, ² $J = 14.2$ Hz, ³ $J = 9.4$ Hz, H_A from Ar-CH₂CH), 3.20 (dd, 1H, AB system, ² $J = 14.2$ Hz, ³ $J = 4.1$ Hz, H_B from Ar-CH₂CH), 3.58 (s, 3H, CH₃), 3.64 (s, 3H, CH₃), 4.31 (d, 2H, $J = 5.8$ Hz, CH₂NH), 4.42-4.49 (m, 1H, CHCH₂CH₂), 4.77 (dd, 1H, $J_1 = 9.4$ Hz, $J_2 = 4.1$ Hz, SCHCO), 6.28 (t, 1H, $J = 6.0$ Hz, CH₂NH), 6.49 (d, 2H, $J = 8.5$ Hz, Ar-H-2,6), 6.91 (d, 2H, $J = 8.5$ Hz, Ar-H-3,5), 7.44 (d, 2H, $J = 8.3$ Hz, Ar-H-3',5'), 7.82 (d, 2H, $J = 8.3$ Hz, Ar-H-2',6'), 8.67 (d, 2H, $J = 7.5$ Hz, CONH), 11.94 (br s, 1H, CONHCO). MS (ESI-): m/z (%) = 512 ([M-H]⁻, 100). Anal. (C₂₅H₂₇N₃O₇S) C, H, N.

(2R)-2-(3-((4-((4-Oxo-2-thioxothiazolidin-5-yl)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(R)-62]. Prepared from compound (R)-61 according to general procedure F. Yield: 58%; yellow crystals; m.p. 108-110 °C; IR (KBr): $\nu = 3412, 2924, 2059, 1719, 1638, 1618, 1585, 1522, 1483, 1438, 1409, 1184, 1101, 1072, 1020, 816, 748, 693, 610, 558, 477$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.91-2.14 (m, 2H, CHCH₂CH₂), 2.36 (t, 2H, $J = 7.4$ Hz, CHCH₂CH₂), 2.71 (dd, 1H, AB system, ² $J = 13.8$ Hz, ³ $J = 9.2$ Hz, H_A from Ar-CH₂CH), 3.19 (dd, 1H, AB system, ² $J = 13.8$ Hz, ³ $J = 4.2$ Hz, H_B from Ar-CH₂CH), 4.03-4.10 (m, 1H, CHCH₂CH₂), 4.28 (s, 2H, CH₂NH), 4.37-4.44 (dd, 1H, $J_1 = 9.2$ Hz, $J_2 = 4.2$ Hz, SCHCO), 6.16-6.27 (m, 1H, CH₂NH), 6.51 (t, 2H, $J = 8.5$ Hz, Ar-H-2,6), 6.89-6.93 (m, 2H, Ar-H-3,5),

7.41 (t, 1H, $J = 7.7$ Hz, Ar-H-5'), 7.51 (d, 1H, $J = 7.7$ Hz, Ar-H-4'), 7.75 (d, 1H, $J = 6.9$ Hz, Ar-H-6'), 7.88 (s, 1H, Ar-H-2'), 8.56 (d, 1H, $J = 7.7$ Hz, CONH), 12.41 (br s, 3H, CSNHCO, COOH). MS (ESI+): m/z (%) = 502 ($[M+H]^+$, 47), 461 (100). Anal. ($C_{23}H_{23}N_3O_6S_2$) C, H, N.

(2R)-2-(4-((3-((4-Oxo-2-thioxothiazolidin-5-yl)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(R)-66]. Prepared from compound (R)-65 according to general procedure F. Yield: 96%; yellow crystals; m.p. 89-91 °C; IR (KBr): $\nu = 2926, 2060, 1735, 1607, 1542, 1438, 1184, 1071, 696$ cm^{-1} . 1H NMR (DMSO- d_6): δ 1.90-2.13 (m, 2H, $CHCH_2CH_2$), 2.35 (t, 2H, $J = 7.4$ Hz, $CHCH_2CH_2$), 2.97 (dd, 1H, AB system, $^2J = 14.2$ Hz, $^3J = 9.7$ Hz, H_A from Ar- CH_2CH), 3.24 (dd, 1H, AB system, $^2J = 14.2$ Hz, $^3J = 4.2$ Hz, H_B from Ar- CH_2CH), 4.31 (s, 2H, CH_2NH), 4.36-4.43 (m, 1H, $CHCH_2CH_2$), 4.94 (dd, 1H, $J_1 = 9.7$ Hz, $J_2 = 4.2$ Hz, SCHCO), 6.37-6.44 (m, 2H, Ar-H-4,6), 6.49 (s, 1H, Ar-H-2), 6.97 (t, 1H, $J = 7.8$ Hz, Ar-H-5), 7.44 (d, 2H, $J = 8.2$ Hz, Ar-H-3',5'), 7.83 (d, 2H, $J = 8.2$ Hz, Ar-H-2',6'), 8.52 (d, 2H, $J = 7.7$ Hz, CONH), 12.46 (br s, 2H, COOH), 13.15 (s, 1H, CSNHCO), signal for CH_2NH not seen. MS (ESI-): m/z (%) = 500 ($[M-H]^-$, 100). Anal. ($C_{23}H_{23}N_3O_6S_2 \times 0.25$ EtOAc) C, H, N.

(2R)-2-(4-((4-((2,4-Dioxothiazolidin-5-yl)methyl)phenylamino)methyl)benzamido)pentanedioic acid [(R)-68]. Prepared from compound (R)-67 according to general procedure F. Yield: 74%; yellow crystals; m.p. 112-114 °C; IR (KBr): $\nu = 3410, 3031, 2925, 1694, 1639, 1616, 1522, 1438, 1410, 1326, 1263, 1215, 1153, 1017, 813, 753, 662, 603, 562, 474$ cm^{-1} . 1H NMR (DMSO- d_6): δ 1.90-2.13 (m, 2H, $CHCH_2CH_2$), 2.35 (t, 2H, $J = 7.4$ Hz, $CHCH_2CH_2$), 2.90 (dd, 1H, AB system, $^2J = 14.1$ Hz, $^3J = 9.4$ Hz, H_A from Ar- CH_2CH), 3.20 (dd, 1H, AB system, $^2J = 14.1$ Hz, $^3J = 4.1$ Hz, H_B from Ar- CH_2CH), 4.31 (s, 2H, CH_2NH), 4.36-4.43 (m, 1H, $CHCH_2CH_2$), 4.77 (dd, 1H, $J_1 = 9.4$ Hz, $J_2 = 4.1$ Hz, SCHCO), 6.28 (s, 1H, CH_2NH), 6.50 (d, 2H, $J = 8.5$ Hz, Ar-H-2,6), 6.91 (d, 2H, $J = 8.5$ Hz, Ar-H-3,5), 7.44 (d, 2H, $J = 8.2$ Hz, Ar-H-3',5'), 7.82 (d, 2H, $J = 8.2$ Hz, Ar-H-2',6'), 8.51 (d, 2H, $J = 7.7$ Hz, CONH), 12.25 (br s, 3H, CONHCO, COOH). MS (ESI-): m/z (%) = 484 ($[M-H]^-$, 100). Anal. ($C_{23}H_{23}N_3O_7S \times H_2O$) C, H, N.

General procedure L. Synthesis of Compounds 69, 70 and 72.

The suspension of amine 14 or 16 (220 mg, 2.11 mmol) and carboxybenzaldehyde 2 or 3 (365 mg, 2.43 mmol) in methanol (60 mL) was heated at 65 °C for 2 hours, then cooled to room temperature. NaCNBH₃ (172 mg, 2.74 mmol) was added and the reaction mixture stirred overnight under an argon atmosphere. The solid was filtered off, washed with methanol and dried in air.

(Z)-3-((4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzoic acid (69). Yield: 70%; yellow crystals; m.p. 270-275 °C; IR (KBr): $\nu = 3551, 3415, 3333, 3237, 3133, 3037, 2788, 2040, 1721, 1688, 1639, 1616, 1573, 1521, 1493, 1454, 1421, 1336, 1292, 1218, 1182, 1160, 1080, 1020, 975, 911, 820, 796, 755, 694$ cm^{-1} . 1H NMR (DMSO- d_6): δ 4.44 (d, 2H, $J = 6.0$ Hz, CH_2NH), 6.71 (d, 2H, $J = 8.7$ Hz, Ar-H-2',6'), 7.27-7.34 (m, 3H, CH_2NH , Ar-H-3',5'), 7.47 (t, 1H, $J = 7.7$ Hz, Ar-H-5), 7.59-7.61 (m, 2H, $CH=C$, Ar-H-4), 7.82 (d, 1H, $J = 7.7$ Hz, Ar-H-6), 7.94 (s, 1H, Ar-H-2), 12.29 (br s, 1H, CONHCO/COOH), 12.92 (br s, 1H, CONHCO/COOH). MS (ESI-): m/z (%) = 353 ($[M-H]^-$, 72), 325 (10), 311 (10), 282 (100), 255 (15), 218 (30). HRMS for $C_{18}H_{13}N_2O_4S$: calculated 353.0596; found 353.0603. Anal. ($C_{18}H_{14}N_2O_4S \times 0.2$ H₂O) C, H, N.

(Z)-4-((4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzoic acid (70). Yield: 79%; yellow crystals; m.p. 315-320 °C; IR (KBr): $\nu = 3414, 3329, 3043, 2850, 2040, 1725, 1685, 1654, 1636, 1616, 1578, 1560, 1520, 1490, 1429, 1318, 1300, 1268, 1223, 1185,$

1162, 1020, 950, 821, 610 cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 4.45 (d, 2H, $J = 5.7$ Hz, CH_2NH), 6.70 (d, 2H, $J = 8.7$ Hz, Ar-H-2',6'), 7.29-7.34 (m, 3H, CH_2NH , Ar-H-3',5'), 7.46 (d, 2H, $J = 8.4$ Hz, Ar-H-3,5), 7.60 (s, 1H, $\text{CH}=\text{C}$), 7.89 (d, 2H, $J = 8.4$ Hz, Ar-H-2,6), 12.30 (br s, 1H, CONHCO/COOH), 12.86 (br s, 1H, CONHCO/COOH). MS (EI): m/z (%) = 354 (54), 299 (15), 283 (76), 201 (78), 148 (75), 69 (100). Anal. ($\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_4\text{S} \times \text{H}_2\text{O}$) C, H, N.

(Z)-4-((3-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzoic acid (72). Yield: 58%; yellow crystals; m.p. > 350 $^\circ\text{C}$; IR (KBr): $\nu = 3550, 3414, 3236, 3036, 2785, 2042, 1745, 1700, 1636, 1616, 1415, 1396, 1328, 1287, 1193, 1163, 1021, 988, 912, 860, 763, 677, 618$ cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 4.38 (d, 2H, $J = 5.7$ Hz, CH_2NH), 6.57-6.63 (m, 2H, CH_2NH , Ar-H-4'), 6.69-6.74 (m, 2H, Ar-H-2',6'), 7.14 (t, 1H, $J = 7.8$ Hz, Ar-H-5'), 7.34 (s, 1H, $\text{CH}=\text{C}$), 7.48 (d, 2H, $J = 8.3$ Hz, Ar-H-3,5), 7.90 (d, 2H, $J = 8.3$ Hz, Ar-H-2,6), 12.65 (br s, 2H, CONHCO , COOH). MS (EI): m/z (%) = 354 (100), 283 (43), 226 (8), 195 (7), 162 (13), 135 (70). Anal. ($\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_4\text{S} \times 1.2 \text{H}_2\text{O}$) C, H, N.

(Z)-4-((4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzoic acid (71). To a stirred solution of amine **17** (200 mg, 0.846 mmol) in anhydrous DMF (30 mL), 4-carboxybenzaldehyde (**3**) (152 mg, 1.02 mmol) and NaCNBH_3 (74 mg, 1.18 mmol) were added and the reaction mixture was stirred overnight at room temperature under an argon atmosphere. The solvent was evaporated under reduced pressure, methanol (30 mL) was added to the crude product and the suspension heated to 65 $^\circ\text{C}$. After cooling to room temperature, the solid was filtered off, washed with methanol and dried in air. Yield: 61%; orange crystals; m.p. $313\text{--}318$ $^\circ\text{C}$; IR (KBr): $\nu = 3551, 3414, 3345, 3237, 3079, 2851, 2066, 1696, 1683, 1653, 1637, 1616, 1576, 1560, 1521, 1443, 1427, 1336, 1320, 1294, 1265, 1200, 1176, 1014, 951, 820, 762, 690, 618$ cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 4.47 (d, 2H, $J = 5.7$ Hz, CH_2NH), 6.72 (d, 2H, $J = 8.7$ Hz, Ar-H-2',6'), 7.33 (d, 2H, $J = 8.7$ Hz, Ar-H-3',5'), 7.43-7.47 (m, 4H, CH_2NH , $\text{CH}=\text{C}$, Ar-H-3,5), 7.90 (d, 2H, $J = 8.1$ Hz, Ar-H-2,6), 12.84 (br s, 1H, COOH), 13.51 (br s, 1H, CSNHCO). MS (ESI $^-$): m/z (%) = 369 ($[\text{M-H}]^-$, 31), 353 (32), 339 (60), 311 (75), 297 (65), 265 (82), 169 (100). Anal. ($\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_3\text{S}_2$) C, H, N.

General procedure M. Synthesis of Compounds (S)-73, (S)-76, (S)-77 and (S)-82.

A solution of H-Lys(Boc)-OMe-HCl (352 mg, 1.19 mmol), the corresponding carboxylic acid **69-72** (1.13 mmol) and HOBt (215 mg, 1.35 mmol) in DMF (25 mL) was prepared and the pH adjusted to 8 with *N*-methylmorpholine. EDC (281 mg, 1.47 mmol) was added and the reaction mixture stirred overnight at room temperature. The solvent was evaporated under reduced pressure, the residue dissolved in ethyl acetate (50 mL) and washed successively with 10% citric acid (3×15 mL) and brine (2×10 mL). The organic phase was dried over Na_2SO_4 , filtered and the solvent evaporated under reduced pressure. The crude product was crystallized from ethyl acetate.

(S,Z)-Methyl 6-(tert-butoxycarbonylamino)-2-(3-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)hexanoate [(S)-73]. Yield: 40%; yellow crystals; m.p. $125\text{--}130$ $^\circ\text{C}$; IR (KBr): $\nu = 3551, 3475, 3413, 2940, 2771, 2066, 1734, 1718, 1684, 1636, 1617, 1560, 1577, 1540, 1522, 1337, 1288, 1225, 1184, 1149, 1018, 820, 756, 632, 608$ cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ 1.29-1.35 (m, 13H, *t*-Bu, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.78-1.82 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 2.89-2.91 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 3.64 (s, 3H, CH_3), 4.36-4.43 (m, 3H, CH_2NHAr , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 6.70-6.75 (m, 3H, $\text{BocNH/CH}_2\text{NHAr}$, Ar-H-2',6'), 7.26-7.34 (m, 3H, $\text{BocNH/CH}_2\text{NHAr}$, Ar-H-3',5'), 7.44 (t, 1H, $J = 7.5$ Hz, Ar-H-5), 7.52 (d, 1H, $J = 7.5$ Hz, Ar-H-4), 7.61 (s, 1H, $\text{CH}=\text{C}$), 7.78 (d, 1H, $J = 7.5$ Hz, Ar-H-6), 7.88 (s, 1H, Ar-H-2), 8.67 (d, 1H, $J = 7.2$ Hz, CONH), 12.28 (br s, 1H, CONHCO). MS (ESI $^-$): m/z (%) =

595 ([M-H]⁻, 100), 524 (2), 495 (3), 397 (3), 265 (20). HRMS for C₃₀H₃₅N₄O₇S: calculated 595.2226; found 595.2211. Anal. (C₃₀H₃₆N₄O₇S × 0.5 H₂O) C, H, N.

(S,Z)-Methyl 6-(tert-butoxycarbonylamino)-2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)-methyl)phenylamino)methyl)benzamido)hexanoate [(S)-76]. Yield: 47%; yellow crystals; m.p. 145-150 °C; IR (KBr): ν = 3548, 3476, 3413, 3237, 2927, 2043, 1735, 1718, 1686, 1636, 1618, 1589, 1527, 1340, 1290, 1228, 1186, 1148, 1019, 816, 760, 690, 608 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.28-1.38 (m, 13H, *t*-Bu, CH₂CH₂CH₂CH₂CH), 1.76-1.81 (m, 2H, CH₂CH₂CH₂CH₂CH), 2.87-2.90 (m, 2H, CH₂CH₂CH₂CH₂CH), 3.63 (s, 3H, CH₃), 4.35-4.45 (m, 3H, CH₂NHAr, CH₂CH₂CH₂CH₂CH), 6.68-6.76 (m, 3H, BocNH/CH₂NHAr, Ar-H-2',6'), 7.30-7.33 (m, 3H, BocNH/CH₂NHAr, Ar-H-3',5'), 7.43 (d, 2H, *J* = 8.1 Hz, Ar-H-3,5), 7.60 (s, 1H, CH=C), 7.84 (d, 2H, *J* = 8.1 Hz, Ar-H-2,6), 8.61 (d, 1H, *J* = 7.5 Hz, CONH), 12.28 (br s, 1H, CONHCO). MS (ESI⁻): *m/z* (%) = 595 ([M-H]⁻, 100), 521 (10), 495 (2), 450 (2). HRMS for C₃₀H₃₅N₄O₇S: calculated 595.2226; found 595.2220. Anal. (C₃₀H₃₆N₄O₇S) C, H, N.

(S,Z)-Methyl 6-(tert-butoxycarbonylamino)-2-(4-((4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)hexanoate [(S)-77]. Yield: 63%; orange crystals; m.p. 125-130 °C; IR (KBr): ν = 3552, 3477, 3413, 3237, 2930, 2858, 2042, 1734, 1684, 1636, 1617, 1576, 1560, 1540, 1522, 1458, 1336, 1283, 1245, 1200, 1169, 1018, 817, 755, 620 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.28-1.40 (m, 13H, *t*-Bu, CH₂CH₂CH₂CH₂CH), 1.76-1.81 (m, 2H, CH₂CH₂CH₂CH₂CH), 2.88-2.90 (m, 2H, CH₂CH₂CH₂CH₂CH), 3.63 (s, 3H, CH₃), 4.35-4.46 (m, 3H, CH₂NHAr, CH₂CH₂CH₂CH₂CH), 6.70-6.76 (m, 3H, BocNH/CH₂NHAr, Ar-H-2',6'), 7.33 (d, 2H, *J* = 8.1 Hz, Ar-H-3',5'), 7.42-7.45 (m, 4H, BocNH/CH₂NHAr, CH=C, Ar-H-3,5), 7.84 (d, 2H, *J* = 8.1 Hz, Ar-H-2,6), 8.61 (d, 1H, *J* = 7.2 Hz, CONH), 13.50 (br s, 1H, CSNHCO). MS (ESI⁻): *m/z* (%) = 611 ([M-H]⁻, 100), 595 (15), 581 (2), 281 (22), 255 (23), 212 (20). HRMS for C₃₀H₃₅N₄O₆S₂: calculated 611.1998; found 611.1993. Anal. (C₃₀H₃₆N₄O₆S₂ × 0.5 H₂O) C, H, N.

(S,Z)-Methyl 6-(tert-butoxycarbonylamino)-2-(4-((3-((2,4-dioxothiazolidin-5-ylidene)-methyl)phenylamino)methyl)benzamido)hexanoate [(S)-82]. Yield: 48%; yellow crystals; m.p. 182-187 °C; IR (KBr): ν = 3552, 3474, 3434, 3236, 3040, 2977, 2941, 2771, 2042, 1744, 1696, 1636, 1617, 1522, 1364, 1331, 1292, 1223, 1160, 1019, 840, 773, 610 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.29-1.35 (m, 13H, *t*-Bu, CH₂CH₂CH₂CH₂CH), 1.76-1.80 (m, 2H, CH₂CH₂CH₂CH₂CH), 2.88-2.90 (m, 2H, CH₂CH₂CH₂CH₂CH), 3.63 (s, 3H, CH₃), 4.36-4.39 (m, 3H, CH₂NHAr, CH₂CH₂CH₂CH₂CH), 6.69-6.77 (m, 5H, BocNH, CH₂NHAr, Ar-H-2',4',6'), 7.19 (t, 1H, *J* = 8.3 Hz, Ar-H-5'), 7.46 (d, 2H, *J* = 8.1 Hz, Ar-H-3,5), 7.59 (s, 1H, CH=C), 7.84 (d, 2H, *J* = 8.1 Hz, Ar-H-2,6), 8.60 (d, 1H, *J* = 7.2 Hz, CONH), 12.51 (br s, 1H, CONHCO). MS (ESI⁻): *m/z* (%) = 595 ([M-H]⁻, 100), 565 (72), 459 (50), 454 (76), 438 (62). Anal. (C₃₀H₃₆N₄O₇S) C, H, N.

(S,Z)-6-(Tert-butoxycarbonylamino)-2-(3-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-phenylamino)methyl)benzamido)hexanoic acid [(S)-74]. Prepared by hydrolysis of (S)-73 according to general procedure F (instead of 4.0 equivalents of LiOH, only 2.5 equivalents were used). Yield: 96%; yellow crystals; m.p. 110-115 °C; IR (KBr): ν = 3545, 3414, 3236, 2976, 2931, 2757, 2042, 1637, 1617, 1590, 1540, 1364, 1330, 1283, 1184, 1147, 1020, 820, 745, 607 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.30-1.39 (m, 13H, *t*-Bu, CH₂CH₂CH₂CH₂CH), 1.74-1.80 (m, 2H, CH₂CH₂CH₂CH₂CH), 2.87-2.92 (m, 2H, CH₂CH₂CH₂CH₂CH), 4.30-4.43 (m, 3H, CH₂NHAr, CH₂CH₂CH₂CH₂CH), 6.70-6.77 (m, 3H, BocNH/CH₂NHAr, Ar-H-2',6'), 7.26-7.34 (m, 3H, BocNH/CH₂NHAr, Ar-H-3',5'), 7.43 (t, 1H, *J* = 7.5 Hz, Ar-H-5), 7.51 (d, 1H, *J* = 7.5 Hz, Ar-H-4), 7.60 (s, 1H, CH=C), 7.78 (d, 1H, *J* = 7.5 Hz, Ar-H-6), 7.88 (s, 1H,

Ar-H-2), 8.52 (d, 1H, $J = 7.5$ Hz, CONH), 12.28 (br s, 1H, CONHCO/COOH), 12.56 (br s, 1H, CONHCO/COOH). MS (ESI⁻): m/z (%) = 581 ([M-H]⁻, 100), 555 (1), 538 (1), 507 (10), 265 (20). HRMS for C₂₉H₃₃N₄O₇S: calculated 581.2070; found 581.2075. Anal. (C₂₉H₃₄N₄O₇S) C, H, N.

(*S,Z*)-6-(Tert-butoxycarbonylamino)-2-(4-(((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)hexanoic acid [(*S*)-78]. Prepared by hydrolysis of (*S*)-76 according to general procedure F (instead of 4.0 equivalents of LiOH, only 2.5 equivalents were used). Yield: 97%; yellow crystals; m.p. 135-140 °C; IR (KBr): $\nu = 3551, 3478, 3414, 3236, 2931, 1718, 1684, 1636, 1617, 1584, 1560, 1523, 1338, 1280, 1185, 1153, 1018, 821, 755, 691, 632, 608$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.27-1.40 (m, 13H, *t*-Bu, CH₂CH₂CH₂CH₂CH), 1.71-1.84 (m, 2H, CH₂CH₂CH₂CH₂CH), 2.87-2.91 (m, 2H, CH₂CH₂CH₂CH₂CH), 4.29-4.36 (m, 1H, CH₂CH₂CH₂CH₂CH), 4.44 (d, 2H, $J = 5.1$ Hz, CH₂NHAr), 6.68-6.76 (m, 3H, BocNH/CH₂NHAr, Ar-H-2',6'), 7.30-7.33 (m, 3H, BocNH/CH₂NHAr, Ar-H-3',5'), 7.43 (d, 2H, $J = 8.1$ Hz, Ar-H-3,5), 7.60 (s, 1H, CH=C), 7.84 (d, 2H, $J = 8.1$ Hz, Ar-H-2,6), 8.47 (d, 1H, $J = 7.8$ Hz, CONH), 12.29 (br s, 1H, CONHCO/COOH), 12.49 (br s, 1H, CONHCO/COOH). MS (ESI⁻): m/z (%) = 581 ([M-H]⁻, 100), 555 (17), 538 (1), 507 (10), 481 (8). HRMS for C₂₉H₃₃N₄O₇S: calculated 581.2070; found 581.2079. Anal. (C₂₉H₃₄N₄O₇S × 0.4 H₂O) C, H, N.

(*S,Z*)-6-(Tert-butoxycarbonylamino)-2-(4-(((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)hexanoic acid [(*S*)-79]. Prepared by hydrolysis of (*S*)-77 according to general procedure F (instead of 4.0 equivalents of LiOH, only 2.5 equivalents of LiOH were used). Yield: 91%; orange crystals; m.p. 123-127 °C; IR (KBr): $\nu = 3552, 3476, 3413, 3236, 2976, 2933, 2858, 2042, 1684, 1636, 1617, 1560, 1540, 1523, 1438, 1365, 1337, 1284, 1246, 1201, 1171, 1018, 819, 754, 680, 622$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.25-1.41 (m, 13H, *t*-Bu, CH₂CH₂CH₂CH₂CH), 1.72-1.88 (m, 2H, CH₂CH₂CH₂CH₂CH), 2.88-2.90 (m, 2H, CH₂CH₂CH₂CH₂CH), 4.29-4.36 (m, 1H, CH₂CH₂CH₂CH₂CH), 4.46 (d, 2H, $J = 4.8$ Hz, CH₂NHAr), 6.70-6.73 (m, 3H, BocNH/CH₂NHAr, Ar-H-2',6'), 7.33 (d, 2H, $J = 9.0$ Hz, Ar-H-3',5'), 7.41-7.49 (m, 4H, BocNH/CH₂NHAr, CH=C, Ar-H-3,5), 7.84 (d, 2H, $J = 8.4$ Hz, Ar-H-2,6), 8.47 (d, 1H, $J = 7.8$ Hz, CONH), 12.50 (br s, 1H, COOH), 13.53 (br s, 1H, CSNHCO). MS (ESI⁻): m/z (%) = 597 ([M-H]⁻, 100), 581 (25), 555 (12), 510 (15), 377 (14), 212 (25). HRMS for C₂₉H₃₃N₄O₆S₂: calculated 597.1842; found 597.1865. Anal. (C₂₉H₃₄N₄O₆S₂ × 0.5 H₂O) C, H, N.

(*S,Z*)-6-(Tert-butoxycarbonylamino)-2-(4-(((3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)benzamido)hexanoic acid [(*S*)-83]. Prepared by hydrolysis of (*S*)-82 according to general procedure F (instead of 4.0 equivalents of LiOH, only 2.5 equivalents were used). Yield: 90%; yellow crystals; m.p. 175-178 °C; IR (KBr): $\nu = 3552, 3477, 3413, 3236, 2042, 1747, 1718, 1684, 1636, 1618, 1540, 1328, 1297, 1270, 1214, 1162, 1021, 849, 779, 614$ cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.32-1.38 (m, 13H, *t*-Bu, CH₂CH₂CH₂CH₂CH), 1.72-1.78 (m, 2H, CH₂CH₂CH₂CH₂CH), 2.88-2.90 (m, 2H, CH₂CH₂CH₂CH₂CH), 4.28-4.39 (m, 3H, CH₂NHAr, CH₂CH₂CH₂CH₂CH), 6.69-6.77 (m, 5H, BocNH, CH₂NHAr, Ar-H-2',4',6'), 7.19 (t, 1H, $J = 8.1$ Hz, Ar-H-5'), 7.46 (d, 2H, $J = 8.4$ Hz, Ar-H-3,5), 7.59 (s, 1H, CH=C), 7.84 (d, 2H, $J = 8.4$ Hz, Ar-H-2,6), 8.45 (d, 1H, $J = 7.5$ Hz, CONH), 12.50 (br s, 2H, CONHCO, COOH). MS (ESI⁻): m/z (%) = 581 ([M-H]⁻, 100), 570 (3), 538 (1), 481 (3). HRMS for C₂₉H₃₃N₄O₇S: calculated 581.2070; found 581.2084. Anal. (C₂₉H₃₄N₄O₇S × 0.4 H₂O) C, H, N.

General Procedure N. Synthesis of Compounds (S)-75, (S)-80, (S)-81 and (S)-84.

A solution of compound (S)-74, (S)-78, (S)-79 or (S)-83 (0.250 mmol) in glacial acetic acid (10 mL) was saturated with gaseous HCl and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, the solid was filtered off and washed with diethyl ether.

(S,Z)-5-Carboxy-5-(3-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentan-1-aminium chloride [(S)-75]. Yield: 67%; yellow crystals; m.p. 165-170 °C; IR (KBr): ν = 3552, 3475, 3414, 3235, 2934, 2737, 1734, 1700, 1636, 1617, 1323, 1289, 1186, 1151, 1014, 822, 750, 687, 610 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.34-1.64 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.78-1.86 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 2.74-2.80 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 4.34-4.43 (m, 3H, CH_2NHAr , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 6.73 (d, 2H, J = 8.7 Hz, Ar-H-2',6'), 7.33 (d, 2H, J = 8.7 Hz, Ar-H-3',5'), 7.43 (t, 1H, J = 7.5 Hz, Ar-H-5), 7.52 (d, 1H, J = 7.5 Hz, Ar-H-4), 7.60 (s, 1H, CH=C), 7.79-7.92 (m, 5H, NH_3^+ , Ar-H-2,6), 8.52 (d, 1H, J = 7.5 Hz, CONH), 12.29 (br s, 1H, CONHC), broad signals for COOH and CH_2NHAr not seen. MS (ESI $^-$): m/z (%) = 481 ([M-HCl-H] $^-$, 100), 470 (1), 438 (3), 410 (3), 286 (12), 255 (15), 212 (22). HRMS for $\text{C}_{24}\text{H}_{25}\text{N}_4\text{O}_5\text{S}$: calculated 481.1546; found 481.1542. Anal. ($\text{C}_{24}\text{H}_{27}\text{ClN}_4\text{O}_5\text{S} \times 2.2 \text{ H}_2\text{O}$) C, H, N.

(S,Z)-5-Carboxy-5-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentan-1-aminium chloride [(S)-80]. Yield: 86%; yellow crystals; m.p. 175-180 °C; IR (KBr): ν = 3552, 3476, 3414, 3236, 2935, 2743, 2539, 2030, 1743, 1717, 1690, 1636, 1617, 1559, 1327, 1292, 1184, 1155, 1016, 691, 634, 612 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.33-1.63 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.74-1.85 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 2.73-2.81 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 4.32-4.40 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 4.44 (s, 2H, CH_2NHAr), 6.69 (d, 2H, J = 8.7 Hz, Ar-H-2',6'), 7.32 (d, 2H, J = 8.7 Hz, Ar-H-3',5'), 7.43 (d, 2H, J = 8.4 Hz, Ar-H-3,5), 7.60 (s, 1H, CH=C), 7.85-7.90 (m, 5H, NH_3^+ , Ar-H-2,6), 8.54 (d, 1H, J = 7.8 Hz, CONH), 12.29 (br s, 1H, CONHCO), broad signals for COOH and CH_2NHAr not seen. MS (ESI $^-$): m/z (%) = 481 ([M-HCl-H] $^-$, 100), 438 (2), 410 (5), 269 (10), 233 (5). HRMS (ESI $^-$) for $\text{C}_{24}\text{H}_{25}\text{N}_4\text{O}_5\text{S}$: calculated 481.1546; found 481.1545. HPLC: Phenomenex Luna 5 μm C18 column; mobile phase: 20-60% of acetonitrile in trifluoroacetic acid (0.1%) in 30 minutes; flow rate 1.0 mL/min; injection volume: 20 μL ; retention time: 11.246 min (97.88% at 220 nm, 98.41% at 254 nm).

(S,Z)-5-Carboxy-5-(4-((4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenylamino)-methyl)benzamido)pentan-1-aminium chloride [(S)-81]. Yield: 92%; orange crystals; m.p. 175-178. °C; IR (KBr): ν = 3552, 3479, 3414, 3237, 2032, 1700, 1684, 1636, 1618, 1437, 1287, 1233, 1194, 1167, 1066, 1015, 825, 620 cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.33-1.63 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.77-1.85 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 2.73-2.80 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 4.33-4.40 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 4.46 (s, 2H, CH_2NHAr), 6.72 (d, 2H, J = 8.9 Hz, Ar-H-2',6'), 7.33 (d, 2H, J = 8.9 Hz, Ar-H-3',5'), 7.43 (d, 2H, J = 8.4 Hz, Ar-H-3,5), 7.46 (s, 1H, CH=C), 7.84-7.88 (m, 5H, NH_3^+ , Ar-H-2,6), 8.54 (d, 1H, J = 7.8 Hz, CONH), 13.54 (br s, 1H, CSNHCO), broad signals for COOH and CH_2NHAr not seen. MS (ESI $^-$): m/z (%) = 497 ([M-H] $^-$, 100), 481 (20), 465 (5), 438 (10), 269 (38). HRMS for $\text{C}_{24}\text{H}_{25}\text{ClN}_4\text{O}_4\text{S}_2$: calculated 497.1317; found 497.1307. Anal. ($\text{C}_{24}\text{H}_{27}\text{ClN}_4\text{O}_4\text{S}_2 \times 1.1 \text{ H}_2\text{O}$) C, H, N.

(S,Z)-5-Carboxy-5-(4-((3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylamino)methyl)-benzamido)pentan-1-aminium chloride [(S)-84]. Yield: 98%; yellow crystals; m.p. 167-169 °C; IR (KBr): ν = 3552, 3479, 3414, 3235, 3045, 2033, 1750, 1700, 1636, 1617, 1326, 1289,

1157, 1016, 791, 682, 616 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 1.33-1.64 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.77-1.84 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 2.72-2.78 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 4.32-4.39 (m, 3H, CH_2NHAr , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 6.71-6.79 (m, 3H, Ar-H-2',4',6'), 7.20 (dd, 1H, $J_1 = 8.7$ Hz, $J_2 = 7.5$ Hz, Ar-H-5'), 7.47 (d, 2H, $J = 8.1$ Hz, Ar-H-3,5), 7.59 (s, 1H, CH=C), 7.84-7.89 (m, 5H, NH_3^+ , Ar-H-2,6), 8.53 (d, 1H, $J = 7.8$ Hz, CONH), 12.54 (br s, 1H, CONHCO), broad signals for COOH and CH_2NHAr not seen. ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz): δ 23.68 (CH_2), 27.38 (CH_2), 30.83 (CH_2), 39.27 (CH_2), 47.55 (CH_2), 53.35 (CHNH), 114.69 (Ar-C/CH=C), 117.01 (Ar-C/CH=C), 120.44 (Ar-C/CH=C), 123.79 (Ar-C/CH=C), 128.08 (Ar-C/CH=C), 128.50 (Ar-C/CH=C), 130.69 (Ar-C/CH=C), 133.30 (Ar-C/CH=C), 133.56 (Ar-C/CH=C), 134.46 (Ar-C/CH=C), 143.39 (Ar-C/CH=C), 148.52 (Ar-C/CH=C), 167.23 (C=O), 168.18 (C=O), 168.91 (C=O), 174.51 (C=O). MS (ESI): m/z (%) = 483 [$(\text{M}-\text{Cl})^+$, 100], 389 (7), 343 (12), 301 (11), 196 (22), 149 (58), 118 (48), 77 (95). HRMS for $\text{C}_{24}\text{H}_{27}\text{N}_4\text{O}_5\text{S}$: calculated 483.1702; found 483.1700. Anal. ($\text{C}_{24}\text{H}_{27}\text{ClN}_4\text{O}_5\text{S} \times 1.7 \text{ H}_2\text{O}$) C, H, N.

4. Inhibitory Potencies of Compounds with Alkanediyl Linker, Reduced Compounds and Compounds with a Lysine Residue

Table 2. MurD Inhibitory Potencies of Compounds with Alkanediyl Linker (Scheme 2), Reduced Compounds (Scheme 3) and Compounds with a Lysine Residue (Scheme 4).

Compound	X	n	Substitution	X	Substitution		X	Substitution		MurD
			Ring B		Ring A	Ring B		Ring A	Ring B	
(R)-45	O	1	1,3							92
(R)-46	S	1	1,3							63
(R)-51	O	1	1,4							105
(R)-52	S	1	1,4							99
(R)-53	O	4	1,4							103
(R)-54	S	4	1,4							91
(R)-62				S	1,3	1,4				67
(R)-66				S	1,4	1,3				75
(R)-68				O	1,4	1,4				86
(S)-75							O	1,3	1,4	90
(S)-80							O	1,4	1,4	89
(S)-81							S	1,4	1,4	89
(S)-84							O	1,4	1,3	107

^a Residual activity of the enzyme. ^b Concentration of the tested compound was 500 μM , except for (R)-54 which was tested in 250 μM concentration. ^c Results represent means of two independent experiments. Standard deviations were within $\pm 10\%$ of the means.

5. Microanalysis or HRMS Data for New Compounds

Comp	Formula	Calcd (%)			Found (%)		
		C	H	N	C	H	N
(R)-4	C ₁₅ H ₁₇ NO ₆	58.63	5.58	4.56	58.42	5.84	4.54
(R)-5	C ₁₅ H ₁₇ NO ₆	58.63	5.58	4.56	58.90	5.33	4.61
(S)-5	C ₁₅ H ₁₇ NO ₆	58.63	5.58	4.56	59.03	5.82	4.61
15	C ₁₀ H ₈ N ₂ OS ₂	50.83	3.41	11.85	50.57	3.59	12.01
(R)-18	C ₂₅ H ₂₅ N ₃ O ₇ S	58.70	4.93	8.21	58.45	4.73	8.12
(S)-18	C ₂₅ H ₂₅ N ₃ O ₇ S	58.70	4.93	8.21	58.39	5.01	8.10
(R)-19	C ₂₅ H ₂₅ N ₃ O ₆ S ₂	56.91	4.78	7.96	56.67	4.63	7.88
(S)-19	C ₂₅ H ₂₅ N ₃ O ₆ S ₂	56.91	4.78	7.96	57.19	4.55	8.00
(R)-20	C ₂₃ H ₂₁ N ₃ O ₇ S × 0.4 EtOAc	56.96	4.70	8.10	56.98	4.68	8.13
(S)-20	C ₂₃ H ₂₁ N ₃ O ₇ S	57.14	4.38	8.69	56.93	4.58	8.45
(R)-21	C ₂₃ H ₂₁ N ₃ O ₆ S ₂ × 0.5 H ₂ O	54.32	4.36	8.26	54.43	4.39	7.90
(S)-21	C ₂₃ H ₂₁ N ₃ O ₆ S ₂	55.30	4.24	8.41	55.08	4.43	8.20
(R)-22	C ₂₅ H ₂₅ N ₃ O ₇ S × 0.33 H ₂ O	58.02	5.00	8.12	58.06	4.93	7.95
(S)-22	C ₂₅ H ₂₅ N ₃ O ₇ S	58.70	4.93	8.21	58.33	5.01	8.12
(R)-23	C ₂₅ H ₂₅ N ₃ O ₆ S ₂	56.91	4.78	7.96	56.55	4.78	7.81
(S)-23	C ₂₅ H ₂₅ N ₃ O ₆ S ₂	56.91	4.78	7.96	56.82	4.71	7.75
(R)-24	C ₂₃ H ₂₁ N ₃ O ₇ S × 0.5 H ₂ O	56.09	4.50	8.53	55.99	4.51	8.21
(S)-24	C ₂₃ H ₂₁ N ₃ O ₇ S × H ₂ O	55.08	4.62	8.38	55.38	4.41	8.00
(R)-25	C ₂₃ H ₂₁ N ₃ O ₆ S ₂ × 0.5 H ₂ O	54.32	4.36	8.26	54.43	4.39	7.90
(S)-25	C ₂₃ H ₂₁ N ₃ O ₆ S ₂ × 0.5 H ₂ O	54.32	4.36	8.26	53.97	4.41	8.07
(R)-26	C ₂₅ H ₂₅ N ₃ O ₇ S	58.70	4.93	8.21	58.47	5.21	7.96
(R)-27	C ₂₅ H ₂₅ N ₃ O ₆ S ₂	56.91	4.78	7.96	56.74	4.59	8.01
(R)-28	C ₂₃ H ₂₁ N ₃ O ₇ S × 0.5 EtOAc	56.92	4.78	7.97	56.62	4.92	8.11
(R)-29	C ₂₃ H ₂₁ N ₃ O ₆ S ₂ × 0.25 EtOAc × 0.125 H ₂ O	55.03	4.47	8.02	54.75	4.89	8.42
(R)-30	C ₂₅ H ₂₅ N ₃ O ₇ S	58.70	4.93	8.21	58.75	4.88	8.26
(R)-31	C ₂₅ H ₂₅ N ₃ O ₆ S ₂	56.91	4.78	7.96	56.98	4.76	7.93
(R)-32	C ₂₃ H ₂₁ N ₃ O ₇ S	57.14	4.38	8.69	56.88	4.51	8.45
(R)-33	C ₂₃ H ₂₁ N ₃ O ₆ S ₂	55.30	4.24	8.41	55.11	4.11	8.31
(R)-37	C ₁₂ H ₂₀ BrNO ₅ × H ₂ O	40.46	6.23	3.93	40.61	6.64	4.09
(R)-40	C ₁₆ H ₁₉ NO ₇	56.97	5.68	4.15	57.07	6.07	4.15
(R)-41	C ₁₆ H ₁₉ NO ₇	56.97	5.68	4.15	57.24	6.01	4.14
(R)-42	C ₁₉ H ₂₅ NO ₇	60.15	6.64	3.69	60.38	6.77	3.79
(R)-43	C ₁₉ H ₂₀ N ₂ O ₈ S	52.29	4.62	6.42	52.38	4.62	6.50
(R)-44	C ₁₉ H ₂₀ N ₂ O ₇ S ₂	50.43	4.45	6.19	50.60	4.40	6.31
(R)-45	C ₁₇ H ₁₆ N ₂ O ₈ S	50.00	3.95	6.86	49.87	3.76	6.92
(R)-46	C ₁₇ H ₁₆ N ₂ O ₇ S ₂	48.11	3.80	6.60	48.02	3.72	6.48
(R)-47	C ₁₉ H ₂₀ N ₂ O ₈ S	52.29	4.62	6.42	52.21	4.58	6.44
(R)-48	C ₁₉ H ₂₀ N ₂ O ₇ S ₂	50.43	4.45	6.19	50.36	4.33	6.26
(R)-49	C ₂₂ H ₂₆ N ₂ O ₈ S	55.22	5.48	5.85	55.30	5.40	5.99
(R)-50	C ₂₂ H ₂₆ N ₂ O ₇ S ₂	53.43	5.30	5.66	53.47	5.16	5.84
(R)-51	C ₁₇ H ₁₆ N ₂ O ₈ S × 0.8 H ₂ O	48.29	4.20	6.63	48.67	3.98	6.68
(R)-52	C ₁₇ H ₁₆ N ₂ O ₇ S ₂	48.11	3.80	6.60	47.85	3.92	6.51
(R)-53	C ₂₀ H ₂₂ N ₂ O ₈ S	53.33	4.92	6.22	52.98	5.20	6.05
(R)-54	C ₂₀ H ₂₂ N ₂ O ₇ S ₂	51.49	4.75	6.00	51.74	4.76	5.97
55	C ₁₀ H ₇ N ₂ O ₃ S ₂	266.9898			266.9888		
56	C ₁₀ H ₉ N ₂ O ₄ S	253.0283			253.0282		
57	C ₁₀ H ₇ N ₂ O ₃ S ₂	266.9898			266.9890		
58	C ₁₀ H ₁₁ N ₂ OS ₂	239.0313			239.0311		
59	C ₁₀ H ₁₀ N ₂ O ₂ S	54.04	4.53	12.60	54.11	4.41	12.30

60	$C_{10}H_{10}N_2OS_2$	50.40	4.23	11.75	50.54	4.21	11.54
(R)- 61	$C_{25}H_{27}N_3O_6S_2$	56.69	5.14	7.93	56.66	5.15	7.69
(R)- 62	$C_{23}H_{23}N_3O_6S_2$	55.08	4.62	8.38	54.97	4.78	8.36
63	$C_{18}H_{16}N_2O_3S_2$	58.04	4.33	7.52	57.72	4.47	7.68
64	$C_{18}H_{16}N_2O_4S \times 0.2 H_2O$	60.05	4.59	7.78	60.04	4.25	7.67
(R)- 65	$C_{25}H_{27}N_3O_6S_2$	56.69	5.14	7.93	56.99	4.83	7.91
(R)- 66	$C_{23}H_{23}N_3O_6S_2 \times 0.25 EtOAc$	55.05	4.81	8.03	55.36	4.85	7.67
(R)- 67	$C_{25}H_{27}N_3O_7S$	58.47	5.30	8.18	58.14	5.35	8.14
(R)- 68	$C_{23}H_{23}N_3O_7S \times H_2O$	54.86	5.00	8.35	54.46	4.79	8.20
69	$C_{18}H_{14}N_2O_4S \times 0.2 H_2O$	60.39	4.05	7.83	60.28	3.92	8.07
70	$C_{18}H_{14}N_2O_4S \times H_2O$	58.05	4.33	7.52	58.12	4.17	7.68
71	$C_{18}H_{14}N_2O_3S_2$	58.36	3.81	7.56	58.08	4.04	7.42
72	$C_{18}H_{14}N_2O_4S \times 1.2 H_2O$	57.50	4.40	7.45	57.28	4.02	7.52
(S)- 73	$C_{30}H_{36}N_4O_7S \times 0.5 H_2O$	59.49	6.16	9.25	59.43	6.02	9.65
(S)- 74	$C_{29}H_{34}N_4O_7S$	59.78	5.88	9.62	59.49	6.08	9.26
(S)- 75	$C_{24}H_{27}ClN_4O_5S \times 2.2 H_2O$	51.60	5.67	10.03	51.99	5.46	9.63
(S)- 76	$C_{30}H_{36}N_4O_7S$	60.39	6.08	9.39	60.09	6.08	9.30
(S)- 77	$C_{30}H_{36}N_4O_6S_2 \times 0.5 H_2O$	57.95	6.00	9.01	58.03	6.02	9.03
(S)- 78	$C_{29}H_{34}N_4O_7S \times 0.4 H_2O$	59.05	5.95	9.50	59.19	5.98	9.30
(S)- 79	$C_{29}H_{34}N_4O_6S_2 \times 0.5 H_2O$	57.31	5.80	9.22	57.31	5.91	8.93
(S)- 80	$C_{24}H_{25}N_4O_5S$	481.1546			481.1545		
(S)- 81	$C_{24}H_{27}ClN_4O_4S_2 \times 1.1 H_2O$	51.95	5.30	10.10	51.66	4.92	9.93
(S)- 82	$C_{30}H_{36}N_4O_7S$	60.39	6.08	9.39	60.18	6.04	9.49
(S)- 83	$C_{29}H_{34}N_4O_7S \times 0.4 H_2O$	59.05	5.95	9.50	59.19	5.86	9.39
(S)- 84	$C_{24}H_{27}ClN_4O_5S \times 1.7 H_2O$	52.44	5.57	10.19	52.06	5.18	10.01

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