Supporting Information

Two-Carbon-Elongated HIV-1 Protease Inhibitors with a Tertiary-Alcohol-Containing Transition- State Mimic

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1. General information

Chemistry. Column chromatography was performed on Merck silica gel 60 (40-63 μm) or Al_2O_3 90 (standardized). Analytical thin layer chromatography was done using aluminium sheets precoated with silica gel 60 F_{254} . Analytical RPLC-MS was performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a C18 (Onyx Monolithic C18 (50 $\times$ 4.6 mm)) column, using CH_3CN in 0.05% aqueous HCOOH as mobile phase at a flow rate of 4 mL/min with UV (254 nm) and MS (ESI) detection. Preparative RPLC-MS was performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a C8 (Zorbax SB-C8 (5 μm , 21.2 $\times$ 150 mm) column, using CH_3CN in 0.05% aqueous HCOOH as mobile phase at a flow rate of 15 mL/min with UV (254 nm) and MS (ESI) detection. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury Plus instruments; ^1H at 399.9 MHz and ^{13}C at 100.6 MHz. The microwave reactions were performed in a SmithSynthesizer producing controlled irradiation at 2450 MHz with a power of 0-300 W. The reaction temp was determined using the built-in on-line IR-sensor. Analytische Laboratorien, Lindlar, Germany performed elemental analyses. Compounds **9a** and **9d** was synthesized and characterized as previously reported.¹ The synthesis of compound **2** is described in the literature but with a lower isolated yield.²

2. Experimental details and spectroscopic data for compounds 2–6

(S)-5-Benzyl-2,2-dimethyl-[1,3]dioxolan-4-one (2). A solution of (S)-2-hydroxy-3-phenylpropionic acid (1.662 g, 10.0 mmol), 2,2-dimethoxypropane (8.328 g, 80.0 mmol) and pyridinium *p*-toluenesulphonate (1.257 g, 5.00 mmol) in CHCl_3 was stirred at 70 $^\circ\text{C}$ for one hour. Concentration of the mixture and purification (silica, EtOAc/petroleum ether, 10:90) gave **2** (2.010 g, 97%) as a white solid. ^1H NMR (CDCl_3 , 400 MHz) δ 1.37 (s, 3H), 1.50 (s, 3H), 3.05 (dd, J = 14.4, 6.4 Hz, 1H), 3.20 (dd, J = 14.4, 4.4 Hz, 1H), 4.66 (dd, J = 6.4, 4.4 Hz, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 26.4, 27.2, 37.9, 75.3, 111.1, 127.3, 128.6, 130.1, 136.0, 172.7; Anal. ($\text{C}_{27}\text{H}_{35}\text{NO}_4\text{Si} \times 1/3\text{H}_2\text{O}$) C, H, N:

3-(4-Benzyl-2,2-dimethyl-5-oxo-[1,3]dioxolan-4-yl)-propionic acid methyl ester (3). To a solution of **2** (3.180 g, 15.42 mmol) in THF was added LDA (1.8 M in THF, 9.42 mL, 16.96 mmol) at -78°C . Methyl acrylate (1.460 g, 16.96 mmol) was added to the solution at -78°C after 15 min of stirring. After 1 h the reaction was quenched with saturated NH_4Cl (aq.). Extraction with EtOAc (3 $\times$ 30 mL), drying (MgSO_4) and purification (silica, EtOAc/petroleum ether, 8:92-17:83) gave **3** (2.418 g, 54%) as a colorless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 0.95 (s, 3H), 1.51 (s, 3H), 2.15 (t, J = 8.0 Hz, 2H), 2.36-2.62 (m, 2H), 2.92 (d, J = 13.6 Hz, 1H), 3.10 (d, J = 13.6 Hz, 1H), 3.67 (s, 3H), 7.15-7.30 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 27.7, 28.8, 28.9, 33.1, 42.5, 52.1, 83.3, 110.4, 127.5, 128.6, 131.1, 135.1, 173.1, 174.1; Anal. ($\text{C}_{16}\text{H}_{20}\text{O}_5$) C, H.

(2R or S)-2-Benzyl-5-oxo-tetrahydro-furan-2-carboxylic acid ((1S,2R)-2-hydroxy-indan-1-yl)-amide ((R)-4 and (S)-4). A solution of **3** (2.418 g, 8.272 mmol) in TFA/ H_2O (6:1, 6 mL) was stirred at 80 $^\circ\text{C}$ overnight and then concentrated. The residue was dissolved in EtOAc followed by concentration of the solution, a procedure repeated two times to evaporate excess of TFA. (1S,2R)-1-amino-2-indanol (1.234 g, 8.272 mmol), EDC (1.744 g, 9.099 mmol), HOBT (1.229 g, 9.099 mmol) and dry CH_2Cl_2 (60 mL) were added. The mixture was stirred for one hour at room temp and then quenched with water (30 mL), filtered and extracted with CH_2Cl_2 (2 $\times$ 30 mL). The combined organic layers were concentrated and purified (silica, MeOH/ CH_2Cl_2 , 1:99-6:94) to give (R)-**4** (1.206 g, 41%) and (S)-**4** (1.192 g, 41%) as white solids. X-ray crystallography confirmed the absolute configuration of (S)-**4**. (R)-**4**: ^1H NMR (CDCl_3 , 400 MHz) δ 0.93 (d, J = 4.4 Hz, 1H, OH), 2.32-2.48 (m, 2H), 2.50-

2.64 (m, 1H), 2.76-2.86 (m, 2H), 3.04 (dd, $J = 16.4, 5.2$ Hz, 1H), 3.13 (d, $J = 14.0$ Hz, 1H), 3.36 (d, $J = 14.0$ Hz, 1H), 4.18-4.26 (m, 1H), 5.23 (dd, $J = 8.8, 4.8$ Hz, 1H), 6.68 (d, $J = 8.8$ Hz, 1H), 7.02-7.08 (m, 1H), 7.14-7.24 (m, 3H), 7.28-7.38 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 28.1, 31.0, 39.2, 44.2, 57.4, 73.0, 88.3, 123.7, 125.2, 127.1, 127.6, 128.3, 128.5, 130.5, 134.8, 139.4, 140.1, 171.4, 175.0; MS (m/z 352, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{21}\text{H}_{21}\text{NO}_4 \times 1/5 \text{H}_2\text{O}$) C, H, N. (*S*)-**4**: ^1H NMR (CDCl_3 , 400 MHz) δ 2.20-2.35 (m, 2H), 2.40-2.55 (m, 1H), 2.58-2.70 (m, 1H), 2.81 (dd, $J = 16.4, 2.4$ Hz, 1H), 2.85-3.15 (m, 3H), 3.28 (d, $J = 14.0$ Hz, 1H), 4.50 (m, 1H), 5.18 (dd, $J = 8.4, 5.6$ Hz, 1H), 6.46 (d, $J = 16.0$ Hz, 1H), 6.89 (d, $J = 8.8$ Hz, 1H), 7.04-7.10 (m, 1H), 7.14-7.21 (m, 2H), 7.22-7.34 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 28.0, 30.6, 39.6, 43.8, 57.1, 73.0, 88.2, 124.3, 125.0, 126.9, 127.2, 128.2, 128.5, 130.4, 134.3, 139.5, 139.9, 171.7, 175.8; MS (m/z 352, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{21}\text{H}_{21}\text{NO}_4$) C, H, N.

(2*R*)-2-Benzyl-5-oxo-tetrahydro-furan-2-carboxylic acid [(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-yl]-amide ((*R*)-5). TBSOTf (1.3606 g, 5.148 mmol) was added to a solution of (*R*)-**4** (1.206 g, 3.432 mmol) and Et_3N (1.042 g, 10.30 mmol) in CH_2Cl_2 at 0 °C and the resulting solution was stirred for 1 h at room temp. Concentration, extraction ($\text{Et}_2\text{O}/\text{H}_2\text{O}$), drying of the ether layer (MgSO_4) and purification (silica, EtOAc /petroleum ether, 20:80-50:50) gave (*R*)-**5** (1.470 g, 92%), ^1H NMR (CDCl_3 , 400 MHz) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.80-1.95 (m, 1H), 2.25-2.45 (m, 2H), 2.45-2.60 (m, 1H), 2.92 (dd, $J = 12.4, 2.4$ Hz, 1H), 3.12 (dd, $J = 16.0, 5.2$ Hz, 1H), 3.19 (d, $J = 14.0$ Hz, 1H), 3.34 (d, $J = 14.0$ Hz, 1H), 4.56 (m, 1H), 5.30 (dd, $J = 8.0, 5.6$ Hz, 1H), 7.15-7.40 (m, 10H); ^{13}C NMR (CDCl_3 , 100 MHz) δ -4.7, -4.6, 18.2, 25.9, 28.3, 30.1, 40.6, 43.2, 56.8, 73.8, 87.7, 124.7, 125.1, 127.6, 128.2, 128.8, 130.8, 134.3, 140.0, 141.2, 172.1, 175.2; MS (m/z 466, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{27}\text{H}_{35}\text{NO}_4\text{Si}$) C, H, N.

(2*R*)-2-Benzyl-2-(*tert*-butyl-dimethyl-silanyloxy)-5-hydroxy-pentanoic acid [(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-yl]-amide ((*R*)-6). LiBH_4 (115.9 mg, 4.872 mmol) was added to a solution of (*R*)-**5** (0.5672 g, 1.218 mmol) in Et_2O (15 mL) at 0 °C. The reaction mixture was stirred until full conversion and then quenched with saturated NH_4Cl (aq.) and extracted with EtOAc (3 x 30 mL). Drying of the combined organic layers (MgSO_4) and concentration gave 0.5214 g of the crude diol. The residue was dissolved in dry pyridine (4 mL) and then trimethylacetyl chloride (0.6693 g, 5.550 mmol) was added and stirred at room temp for 1.5 h (sometimes overnight). Water (15 mL) was added to the mixture, which was then extracted with Et_2O (3 x 15 mL), dried (MgSO_4) and concentrated to give a raw intermediate. Dry CH_2Cl_2 (15 mL) and Et_3N (0.6734 g, 6.66 mmol) were added and after 5 min TBSOTf (0.8801 g, 3.33 mmol) was added at 0 °C and the stirring was continued at room temp for 3 hour. The solution was concentrated, extracted with $\text{Et}_2\text{O}/\text{H}_2\text{O}$ and the ether layer was dried (MgSO_4) and concentrated to give the protected alcohol as colourless oil. LiBH_4 (0.140 g, 5.887 mmol) was added to an ether solution (15 mL) of the intermediate at room temp. Portions of LiBH_4 were added every two hours until full conversion was achieved. Saturated NH_4Cl (aq.) was added to quench the reaction and then extraction with Et_2O (3 x 15 mL), drying (MgSO_4), concentration and purification (silica, EtOAc /petroleum ether, 25:75-45:55) gave (*R*)-**6** (518.6 mg, 73%) as colourless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.75 (s, 9H), 0.81 (s, 9H), 1.04-1.28 (m, 1H), 1.48-1.64 (m, 2H), 1.75 (br s, 1H), 1.92- 2.06 (m, 1H), 2.83 (dd, $J = 15.6, 6.0$ Hz, 1H), 2.91 (d, $J = 14.0$ Hz, 1H), 2.99 (dd, $J = 15.6, 6.0$ Hz, 1H), 3.12 (d, $J = 14.0$ Hz, 1H), 3.26-3.42 (m, 2H), 4.54-4.62 (m, 1H), 5.13 (dd, $J = 8.0, 6.0$ Hz, 1H), 7.05-7.20 (m, 8H), 7.30-7.40 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ -4.7, -4.3, -2.0, -1.5, 18.5, 18.7, 26.2, 26.4, 27.1, 35.0, 39.9, 47.5, 56.6, 62.3, 74.1, 82.6, 124.9, 125.7, 126.7, 126.9, 128.0, 128.2, 130.4, 136.5, 139.6, 141.8, 174.4; MS (m/z 584, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{33}\text{H}_{53}\text{NO}_4\text{Si}_2$) C, H, N.

(*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-4-[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-ylcarbamoyl]-5-phenyl-pentanoic acid ((*R*)-6-acid). Dry CH_2Cl_2 (10 mL) was

added to alcohol (*R*)-**6** (85.0 mg, 0.146 mmol) and Dess-Martin reagent (123.4 mg, 0.291 mmol). The solution was stirred at room temp for 1 h, concentrated and the residue was dissolved in Et₂O (15 mL). Washing with saturated NaHCO₃ (aq., 15 mL) and saturated Na₂S₂O₃ (aq., 4 mL) was performed and then the combined aqueous layers were extracted with Et₂O (2 x 15 mL). The ether layers were combined, dried (MgSO₄) and concentrated to yield the crude aldehyde. 2-Methyl-2-butene (61.2 mg, 0.873 mmol), *t*-BuOH (3.0 mL) and water (1.0 mL) were added to the crude aldehyde followed by a mixture of NaClO₂ (80%, 32.9 mg, 0.291 mmol) and NaH₂PO₄ (69.8 mg, 0.582 mmol). After stirring at room temp for 6 h, water (10 mL) was added. Extraction with Et₂O (3 x 15 mL), drying (MgSO₄), concentration and purification (silica, MeOH/CH₂Cl₂, 4:96-5:95) gave (*R*)-**6**-acid (86.1 mg, 99%). ¹H NMR (CDCl₃, 400 MHz) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.13 (s, 3H), 0.15 (s, 3H), 0.83 (s, 9H), 0.89 (s, 9H), 1.90- 2.00 (m, 1H), 2.10-2.24 (m, 1H), 2.24-2.36 (m, 1H), 2.38-2.48 (m, 1H), 2.90 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.02 (d, *J* = 13.6 Hz, 1H), 3.09 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.22 (d, *J* = 13.6 Hz, 1H), 4.66 (m, 1H), 5.22 (m, 1H), 7.15-7.30 (m, 8H), 7.35-7.45 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ -4.6, -4.2, -1.9, -1.5, 18.6, 18.7, 26.3, 26.4, 29.1, 34.0, 40.1, 46.9, 56.7, 74.2, 81.9, 125.0, 125.7, 127.0, 127.2, 128.3, 128.4, 130.6, 136.2, 139.6, 141.7, 173.8, 178.6; MS (*m/z* 598, M+H⁺); Anal. (C₃₃H₅₁NO₅Si₂) C, H, N.

3. Experimental details and spectroscopic data for hydrazides **9b**, **9c**, and **9e**–**s**

General procedure A. Synthesis of hydrazides **9b, **9c**, and **9e**–**r**.** A solution of aldehyde **7** (1.0 equiv), hydrazine **8** (1.0–1.1 equiv, synthesized according to a literature procedure³) and TsOH (1.0 equiv) in THF was stirred at room temp 1 h. NaBH₃CN (1.5–7.5 equiv) was added to the solution and the mixture was stirred overnight. EtOAc was added to dilute the reaction mixture and then saturated NaHCO₃ (aq.) was added at room temp. Extraction (2 x EtOAc), combination of the organic layers and concentration afforded a crude intermediate, which was dissolved in CH₂Cl₂. NaOH (1.5 N, 4.0 mL) was added and the mixture was stirred at room temp for 1 h to overnight, the reactions were monitored by RPLC-MS until the borane complex (M + 39)⁺ was hydrolyzed. Extraction with CH₂Cl₂, drying (MgSO₄) and purification by flash chromatography gave the corresponding products **9a**–**r** in yields varying from 6% to 85%.

{(S)-1-[N'-(4-Fluoro-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (9b**).** According to general method A, compound **9b** was prepared using **7b** (150 mg, 1.209 mmol), **8** (257.9 mg, 1.269 mmol), TsOH (230.0 mg, 1.209 mmol) and NaBH₃CN (303.9 mg, 4.836 mmol). Purification (silica, EtOAc/petroleum ether, 40:60-70:30) gave **9b** (244.7 mg, 65%). ¹H NMR (CDCl₃, 400 MHz) δ 0.94 (s, 9H), 3.56 (s, 3H), 3.85-4.05 (m, 3H), 4.92 (br s, 1H), 5.87 (d, *J* = 9.6 Hz, 1H), 6.90-7.00 (m, 2H), 7.20-7.30 (m, 2H), 8.63 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.5, 34.6, 52.4, 55.1, 61.1, 115.3 (d, *J* = 21.3 Hz), 130.6 (d, *J* = 8.0 Hz), 133.3 (d, *J* = 3.6 Hz), 157.3, 162.3 (d, *J* = 245 Hz); MS (*m/z* 312, M+H⁺); Anal. (C₁₅H₂₂FN₃O₃) C, H, N.

{(S)-1-[N'-(4-Chloro-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (9c**).** According to general method A, compound **9c** was prepared using **7c** (151.4 mg, 1.077 mmol), **8** (218.8 mg, 1.077 mmol), TsOH (204.8 mg, 1.077 mmol) and NaBH₃CN (270.7 mg, 4.308 mmol). Purification (silica, EtOAc/petroleum ether, 30:70-60:40) gave **9c** (199.8 mg, 57%). ¹H NMR (CD₃OD, 400 MHz) δ 0.90 (s, 9H), 3.63 (s, 3H), 3.82 (s, 1H), 3.84-4.00 (m, 2H), 7.20-7.40 (m, 4H); ¹³C NMR (CD₃OD, 100 MHz) δ 27.0, 35.1, 52.7, 55.4, 62.8, 129.4, 131.6, 134.2, 137.8, 159.0, 171.7; MS (*m/z* 328, M+H⁺, 330, M+H⁺); Anal. (C₁₅H₂₂ClN₃O₃) C, H, N.

{(S)-1-[N'-(4-Cyano-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (9e**).** According to general method A, compound **9e** was prepared using **7e** (165.2 mg, 1.259 mmol), **8** (281.5 mg, 1.385 mmol), TsOH (239.5 mg, 1.259 mmol) and

NaBH₃CN (237.3 mg, 3.777 mmol). Purification (silica, EtOAc/petroleum ether, 45:55-75:25) gave **9e** (205.2 mg, 51%). ¹H NMR (CDCl₃, 400 MHz) δ 0.89 (s, 9H), 2.72 (s, 3H), 3.55 (s, 3H), 3.90-4.05 (m, 3H), 5.01 (br s, 1H), 5.79 (d, *J* = 10.0 Hz, 1H), 7.35-7.45 (m, 2H), 7.50-7.60 (m, 2H), 8.63 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.4, 34.4, 52.3, 55.2, 61.0, 111.3, 118.7, 129.4, 132.1, 143.3, 157.2, 170.7; MS (*m/z* 319, M+H⁺); Anal. (C₁₆H₂₂N₄O₃) C, H, N.

{(S)-1-[N'-(4-Dimethylamino-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (9f). According to general method A, compound **9f** was prepared using **7f** (200.0 mg, 1.341 mmol), **8** (286.1 mg, 1.408 mmol), TsOH (255.1 mg, 1.341 mmol) and NaBH₃CN (337.1 mg, 5.364 mmol). Purification (silica, EtOAc) gave **9f** (347.9 mg, 73%). ¹H NMR (CDCl₃, 400 MHz) δ 0.97 (s, 9H), 2.91 (s, 6H), 3.58 (s, 3H), 3.84-3.88 (m, 2H), 3.99 (d, *J* = 9.6 Hz, 1H), 4.83 (br s, 1H), 5.83 (d, *J* = 9.6 Hz, 1H), 6.60-6.75 (m, 2H), 7.15-7.25 (m, 2H), 8.51 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 34.7, 40.7, 52.4, 55.6, 61.2, 112.6, 125.2, 130.0, 150.2, 157.2, 170.1; MS (*m/z* 337, M+H⁺); Anal. (C₁₇H₂₈N₄O₃) C, H, N.

{(S)-1-(N'-Isobutyl-hydrazinocarbonyl)-2,2-dimethyl-propyl}-carbamic acid methyl ester (9g). According to general method A, compound **9g** was prepared using **7g** (144.2 mg, 2.0 mmol), **8** (406.4 mg, 2.0 mmol), TsOH (380.4 mg, 2.0 mmol) and NaBH₃CN (502.7 mg, 8.0 mmol). Purification (silica, EtOAc/petroleum ether, 50:50-100:0 and then Al₂O₃, MeOH/CH₂Cl₂, 5:95) gave **9g** (216.3 mg, 42%). ¹H NMR (CDCl₃, 400 MHz) δ 0.9-0.95 (m, 6H), 0.99 (s, 9H), 1.72 (m, 1H), 2.58-2.70 (m, 2H), 3.67 (s, 3H), 3.89 (d, *J* = 10 Hz, 1H), 5.57 (br d, *J* = 9.2 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 20.6, 20.7, 26.6, 27.2, 34.8, 52.6, 60.0, 61.3, 157.3, 170.1; MS (*m/z* 260, M+H⁺); Anal. (C₁₂H₂₅N₃O₃) C, H, N.

{(S)-2,2-Dimethyl-1-[N'-(4-pyridin-2-yl-benzyl)-hydrazinocarbonyl]-propyl}-carbamic acid methyl ester (9h). According to general method A, compound **9h** was prepared using **7h** (183.2 mg, 1.0 mmol), **8** (223.5 mg, 1.1 mmol), TsOH (190.2 mg, 1.0 mmol) and NaBH₃CN (251.2 mg, 4.0 mmol). Purification (silica, EtOAc) gave **9h** (250 mg, 64%). ¹H NMR (CDCl₃, 400 MHz) δ 0.95 (s, 9H), 3.57 (s, 3H), 3.90-4.06 (m, 3H), 4.99 (br s, 1H), 5.73 (d, *J* = 9.6 Hz, 1H), 7.18-7.22 (m, 1H), 7.38-7.44 (m, 2H), 7.64-7.74 (m, 2H), 7.88-7.94 (m, 2H), 8.48 (br s, 1H), 8.62-8.68 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 34.6, 52.4, 55.6, 61.2, 120.5, 122.2, 127.0, 129.3, 136.8, 138.4, 138.7, 149.7, 157.1, 157.2, 170.5; MS (*m/z* 371, M+H⁺).

{(S)-2,2-Dimethyl-1-[N'-(4-pyrimidin-5-yl-benzyl)-hydrazinocarbonyl]-propyl}-carbamic acid methyl ester (9i). According to general method A, compound **9i** was prepared using **7i** (232.0 mg, 1.259 mmol), **8** (255.9 mg, 1.259 mmol), TsOH (239.5 mg, 1.259 mmol) and NaBH₃CN (316.5 mg, 5.036 mmol). Purification (silica, MeOH/CH₂Cl₂, 5:95 and then Al₂O₃, MeOH/CH₂Cl₂, 5:95) gave **9i** (26 mg, 6%). ¹H NMR (CDCl₃, 400 MHz) δ 0.97 (s, 9H), 3.63 (s, 3H), 3.89 (d, *J* = 9.2 Hz, 1H), 3.95-4.15 (m, 2H), 5.02 (br s, 1H), 5.55 (d, *J* = 9.2 Hz, 1H), 7.45-7.55 (m, 4H), 8.12 (br s, 1H), 8.89 (s, 1H), 9.18 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 34.6, 52.5, 55.5, 61.3, 127.1, 130.1, 133.6, 134.0, 138.8, 154.9, 157.2, 157.6, 170.6; MS (*m/z* 372, M+H⁺); Anal. (C₁₉H₂₅N₅O₃·x 1/3 H₂O) C, H, N.

{(S)-2,2-Dimethyl-1-[N'-(4-morpholin-4-yl-benzyl)-hydrazinocarbonyl]-propyl}-carbamic acid methyl ester (9j). According to general method A, compound **9j** was prepared using **7j** (245.8 mg, 1.285 mmol), **8** (287.3 mg, 1.414 mmol), TsOH (244.4 mg, 1.285 mmol) and NaBH₃CN (323.0 mg, 5.14 mmol). Purification (silica, EtOAc/petroleum ether, 50:50-100:0) gave **9j** (117 mg, 24%). ¹H NMR (CDCl₃, 400 MHz) δ 0.97 (s, 9H), 3.10-3.20 (m, 4H), 3.63 (s, 3H), 3.75-3.95 (m, 7H), 4.84 (s, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 6.80-6.90 (m, 2H), 7.15-7.30 (m, 2H), 7.72 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 34.7, 49.5, 52.5, 55.5, 61.4, 67.0, 115.8, 128.7, 130.0, 151.0, 157.2, 170.2; MS (*m/z* 379, M+H⁺); Anal. (C₁₉H₃₀N₄O₄) C, H, N.

{{(S)-2,2-Dimethyl-1-[N'-(4-morpholin-4-ylmethyl-benzyl)-hydrazinocarbonyl]-propyl}-carbamic acid methyl ester (9k)}. According to general method A, compound **9k** was prepared using **7k** (224 mg, 1.091 mmol), **8** (243.9 mg, 1.2 mmol), TsOH (207.5 mg, 1.091 mmol) and NaBH₃CN (274.2 mg, 4.364 mmol). Purification (silica, EtOAc/petroleum ether, 50:50-100:0 and then Al₂O₃, MeOH/CH₂Cl₂, 5:95) gave **9k** (160 mg, 37%). ¹H NMR (CDCl₃, 400 MHz) δ 0.94 (s, 9H), 2.36-2.46 (m, 4H), 3.45 (s, 2H), 3.60 (s, 3H), 3.64-3.70 (m, 4H), 3.84-3.98 (m, 3H), 4.90 (br s, 1H), 5.6-5.71 (m, 1H), 7.20-7.35 (m, 4H), 8.21 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.5, 34.6, 52.5, 53.7, 55.7, 61.2, 63.2, 67.1, 128.9, 129.4, 136.4, 137.3, 157.2, 170.3; MS (*m/z* 393, M+H⁺); Anal. (C₂₀H₃₂N₄O₄) C, H, N.

{{(S)-1-[N'-(4-Imidazol-1-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (9l)}. According to general method A, compound **9l** was prepared using **7l** (222.4 mg, 1.230 mmol), **8** (250 mg, 1.292 mmol), TsOH (380.4 mg, 1.230 mmol) and NaBH₃CN (115.9 mg, 1.845 mmol). Purification (silica, MeOH/EtOAc, 5:95-7:93) gave **9l** (110.5 mg, 25%). The crude product was not hydrolyzed with aqueous NaOH. ¹H NMR (CDCl₃, 400 MHz) δ 0.97 (s, 9H), 3.65 (s, 3H), 3.88-4.06 (m, 3H), 5.03 (br s, 1H), 5.54 (d, *J* = 9.6 Hz, 1H), 7.19 (s, 1H), 7.24 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.64 (s, 1H), 8.56 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 34.6, 52.5, 55.3, 61.3, 118.3, 121.4, 130.4, 130.6, 135.6, 136.7, 137.5, 157.2, 170.6; MS (*m/z* 360, M+H⁺); Anal. (C₁₈H₂₅N₅O₃ x ¾ H₂O) C, H, N.

{{(S)-2,2-Dimethyl-1-{N'-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-hydrazinocarbonyl}-propyl}-carbamic acid methyl ester (9m)}. According to general method A, compound **9m** was prepared using **7m** (256.3 mg, 1.362 mmol), **8** (304.4 mg, 1.498 mmol), TsOH (259.1 mg, 1.362 mmol) and NaBH₃CN (342.4 mg, 5.448 mmol). Purification (silica, EtOAc and then Al₂O₃, MeOH/CH₂Cl₂, 5:95) gave **9m** (313 mg, 61%). ¹H NMR (CDCl₃, 400 MHz) δ 0.93 (s, 9H), 2.64 (s, 3H), 3.59 (s, 3H), 3.90 (d, *J* = 10 Hz, 1H), 3.94-4.10 (m, 2H), 5.60 (d, *J* = 9.2 Hz, 1H), 7.40-7.50 (m, 2H), 7.90-8.10 (m, 2H), 8.18 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 12.5, 26.5, 34.6, 52.4, 55.5, 61.1, 126.1, 127.5, 129.4, 140.9, 157.3, 168.2, 170.6, 176.6; MS (*m/z* 376, M+H⁺); Anal. (C₁₈H₂₅N₅O₄) C, H, N.

{{(S)-2,2-Dimethyl-1-[N'-(4-thiazol-2-yl-benzyl)-hydrazinocarbonyl]-propyl}-carbamic acid methyl ester (9n)}. According to general method A, compound **9n** was prepared using **7n** (250 mg, 1.321 mmol), **8** (295.3 mg, 1.453 mmol), TsOH (251.3 mg, 1.321 mmol) and NaBH₃CN (332.0 mg, 5.284 mmol). Purification (Al₂O₃, MeOH/CH₂Cl₂, 2:98-5:95 and then silica, MeOH/CH₂Cl₂, 2:98-5:95) gave **9n** (297.2 mg, 60%). ¹H NMR (CDCl₃, 400 MHz) δ 0.94 (s, 9H), 3.56 (s, 3H), 3.90-4.10 (m, 3H), 4.99 (m, 1H), 5.73 (d, *J* = 9.6 Hz, 1H), 7.29 (d, *J* = 3.2 Hz, 1H), 7.34-7.42 (m, 2H), 7.83 (d, *J* = 3.2 Hz, 1H), 7.84-7.90 (m, 2H), 8.52 (d, *J* = 5.6 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.5, 34.6, 52.4, 55.5, 61.2, 118.9, 126.7, 129.5, 132.9, 139.7, 143.8, 157.2, 168.1, 170.6; MS (*m/z* 377, M+H⁺); Anal. (C₁₈H₂₄N₄O₃S) C, H, N.

{{(S)-2,2-Dimethyl-1-{N'-[4-(2-methyl-thiazol-4-yl)-benzyl]-hydrazinocarbonyl}-propyl}-carbamic acid methyl ester (9o)}. According to general method A, compound **9o** was prepared using **7o** (250.0 mg, 1.230 mmol), **8** (274.9 mg, 1.353 mmol), TsOH (233.9 mg, 1.230 mmol) and NaBH₃CN (463.8 mg, 7.380 mmol). Purification (silica, EtOAc/petroleum ether, 50:50-100:0) gave **9o** (409.0 mg, 85%). ¹H NMR (CDCl₃, 400 MHz) δ 0.94 (s, 9H), 2.72 (s, 3H), 3.53 (s, 3H), 3.90-4.05 (m, 3H), 4.97 (br s, 1H), 5.83 (d, *J* = 10.0 Hz, 1H), 7.30-7.40 (m, 2H), 7.70-7.80 (m, 2H), 8.65 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 19.3, 26.5, 34.6, 52.4, 55.6, 61.1, 112.3, 126.4, 129.3, 133.9, 137.3, 154.8, 157.3, 165.9, 170.4; MS (*m/z* 391, M+H⁺); Anal. (C₁₉H₂₆N₄O₃S x 7/6 H₂O) C, H, N.

{{(S)-1-{N'-[4-(4-tert-Butyl-thiazol-2-yl)-benzyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl}-carbamic acid methyl ester (9p)}. According to general method A, compound **9p** was prepared using **7p** (185.7 mg, 0.757 mmol), **8** (153.8 mg, 0.757 mmol), TsOH (144.0 mg, 0.757 mmol) and NaBH₃CN (190.3 mg, 4.0 mmol). Purification (silica, EtOAc/petroleum

ether, 50:50-70:30) gave **9p** (298.1 mg, 69%). ¹H NMR (CDCl₃, 400 MHz) δ 0.96 (s, 9H), 1.38 (s, 9H), 3.60 (s, 3H), 3.80-4.10 (m, 3H), 5.70 (d, *J* = 9.6 Hz, 1H), 6.86 (s, 1H), 7.37 (m, 2H), 7.88 (m, 2H), 8.38 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 30.2, 34.6, 35.1, 52.5, 55.6, 61.2, 110.3, 126.7, 129.4, 133.7, 139.1, 157.3, 166.6, 167.8, 170.5; MS (*m/z* 433, M+H⁺); Anal. (C₂₂H₃₂N₄O₃S) C, H, N.

{(S)-1-[N'-(4-Imidazo[2,1-*b*]thiazol-6-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (9q). According to general method A, compound **9q** was prepared using **7q** (266.2 mg, 1.166 mmol), **8** (248.8 mg, 1.224 mmol), TsOH (221.8 mg, 1.166 mmol) and NaBH₃CN (550 mg, 8.752 mmol). Purification (silica, MeOH/CH₂Cl₂, 2:98-5:95 and then Al₂O₃, MeOH/CH₂Cl₂, 5:95) gave **9q** (160 mg, 33%). ¹H NMR (CDCl₃, 400 MHz) δ 0.95 (s, 9H), 3.58 (s, 3H), 3.85-4.05 (m, 3H), 5.61 (d, *J* = 9.6 Hz, 1H), 6.79 (d, *J* = 4.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 4.4 Hz, 1H), 7.71 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 8.16 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 34.6, 52.5, 55.8, 61.3, 108.1, 112.6, 118.6, 125.4, 129.4, 133.6, 136.6, 147.7, 150.3, 157.2, 170.4; MS (*m/z* 416, M+H⁺); Anal. (C₂₀H₂₅N₅O₃S x 1/3H₂O) C, H, N.

((S)-1-[N'-(4-(2-Chloro-thiazol-5-ylmethoxy)-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl)-carbamic acid methyl ester (9r). According to general method A, compound **9r** was prepared using **7r** (249.2 mg, 1.226 mmol), 4-(2-chloro-thiazol-5-yl)-methoxybenzaldehyde (311.4 mg, 1.227 mmol), p-toluene sulfonic acid (237.1 mg, 1.247 mmol) and NaBH₃CN (314.0 mg, 4.997 mmol). Purification (silica, ethyl acetate/petroleum ether, 50:50-70:30 and then preparative RPLC-MS, MeCN/0.05% aqueous formic acid, 30:70-85:15) to give **9r** (283.6 mg, 31 %). ¹H NMR (CD₃OD, 400 MHz) δ 0.90 (s, 9H), 3.64 (s, 3H), 3.83 (s, 1H), 3.88 (s, 2H), 5.27 (d, *J* = 1.0 Hz, 2H), 6.93-6.97 (m, 2H), 7.28-7.33 (m, 2H), 7.62 (m, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 27.0, 35.2, 52.7, 55.6, 62.9, 63.4, 116.1, 131.4, 132.1, 139.1, 141.2, 153.7, 158.6, 159.0, 171.5; MS (*m/z* 440, M+H⁺); Anal. (C₁₉H₂₅ClN₄O₄S) C, H, N.

{(S)-1-[N'-(4-Iodo-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (9s). This compound was prepared in 15% yield according to literature procedures from 4-iodo-benzylbromide and hydrazine hydrate to obtain the corresponding 4-iodo-benzyl hydrazine.⁴ The hydrazine was then coupled to compound **11**³ as described previously.¹ ¹H NMR (CDCl₃, 400 MHz) δ 0.95 (s, 9H), 3.62 (s, 3H), 3.75-3.95 (m, 3H), 5.47 (d, *J* = 9.6 Hz, 1H), 7.00-7.10 (m, 2H), 7.60-7.70 (m, 2H), 7.79 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 34.6, 52.6, 55.4, 61.3, 93.3, 131.0, 137.2, 137.7, 157.2, 170.6; MS (*m/z* 420, M+H⁺); Anal. (C₁₅H₂₂IN₃O₃) C, H, N.

4. Experimental details and spectroscopic data for inhibitors 12a–c and 12e–s

General procedure B. Synthesis of inhibitors 12a–c and 12e–s. Dry CH₂Cl₂ (15 mL) was added to alcohol (**R**)-**6** (1.0-2.0 equiv) and Dess-Martin reagent (1.05-2.2 equiv). The solution was stirred at room temp for 1 h and then concentrated and the residue was dissolved in Et₂O (15 mL), washed with saturated NaHCO₃ (aq., 15 mL) and saturated Na₂S₂O₃ (aq., 4 mL). The aqueous layers were extracted with Et₂O (2 x 15 mL). The ether layers were combined, dried (MgSO₄) and concentrated to yield the crude aldehyde. Hydrazide **9** (1.0 equiv) and AcOH (1.7-2.6 equiv) in THF (10 mL) were added to the aldehyde and stirred for 15 min at room temp. Na(OAc)₃BH (3.3-4.0 equiv) was added and the mixture was stirred at room temp overnight. The reaction was quenched with saturated NH₄Cl (aq.), extracted with CH₂Cl₂ (3 x 20 mL), dried (MgSO₄) and concentrated. Purification by flash chromatography was performed and the fractions with desired mass value were combined and concentrated to give the raw product with TBS protected alcohol groups. TBAF (3.5-10.0 equiv based on the amount of starting material **9**.) in THF was added to the intermediate and stirred overnight.

Purification by flash chromatography gave the corresponding products **12a–c** and **12e–s** as white solids in yields varying from 19% to 91%.

((S)-1-{[N'-Benzyl-N'-[(R)-4-hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (12a). Compound **12a** was prepared according to general procedure B, using (*R*)-**6** (74.7 mg, 0.1279 mmol), Dess-Martin reagent (59.7 mg, 0.1407 mmol), **9a** (30.0 mg, 0.1023 mmol), AcOH (12.3 mg, 0.2046 mmol), Na(OAc)₃BH (86.7 mg, 0.4092 mmol) and TBAF (1.0 M in THF, 1.023 mL, 1.023 mmol). Purification (silica, MeOH/CH₂Cl₂, 4:96-5:95) gave **12a** (27.5 mg, 43%). ¹H NMR (CD₃OD, 400 MHz) δ 0.76 (s, 9H), 1.58-1.84 (m, 3H), 2.02-2.13 (m, 1H), 2.70-2.95 (m, 4H), 3.01-3.15 (m, 2H), 3.55 (s, 3H), 3.70 (s, 1H), 3.80-3.95 (m, 2H), 4.15-4.23 (m, 1H), 5.10 (d, *J* = 4.8 Hz, 1H), 7.14-7.40 (m, 14H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.5, 26.9, 34.9, 37.8, 40.9, 47.0, 52.7, 58.3, 58.6, 62.7, 63.0, 74.0, 79.6, 125.4, 126.2, 127.5, 127.9, 128.4, 128.8, 128.9, 129.2, 130.5, 131.7, 138.2, 138.4, 141.6, 142.5, 158.9, 171.8, 177.3; MS (*m/z* 631, M+H⁺); Anal. (C₃₆H₄₆N₄O₆ x 1/2H₂O) C, H, N.

((S)-1-{[N'-(4-Fluoro-benzyl)-N'-[(R)-4-hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (12b). Compound **12b** was prepared according to general procedure B using (*R*)-**6** (100.0 mg, 0.1712 mmol), Dess-Martin reagent (79.9 mg, 0.1883 mmol), **9b** (50 mg, 0.1606 mmol), AcOH (19.3 mg, 0.3212 mmol), Na(OAc)₃BH (136.1 mg, 0.6424 mmol) and TBAF (1.0 M in THF, 1.606 mL, 1.606 mmol). Purification (silica, MeOH/CH₂Cl₂, 5:95) gave **12b** (63 mg, 60%). ¹H NMR (CD₃OD, 400 MHz) δ 0.77 (s, 9H), 1.55-1.70 (m, 1H), 1.70-1.84 (m, 2H), 2.03-2.15 (m, 1H), 2.70-2.95 (m, 4H), 3.01-3.15 (m, 2H), 3.55 (s, 3H), 3.69 (s, 1H), 3.80-3.90 (m, 2H), 4.17-4.23 (m, 1H), 5.11 (d, *J* = 4.4 Hz, 1H), 6.92-7.02 (m, 2H), 7.14-7.30 (m, 9H), 7.32-7.40 (m, 2H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.5, 26.9, 34.8, 37.7, 40.9, 47.0, 52.7, 58.2, 58.7, 61.9, 63.0, 73.9, 79.5, 115.7 (d, *J* = 21.2 Hz) 125.3, 126.2, 127.5, 127.8, 128.8, 128.84, 131.6, 132.3 (d, *J* = 8.1 Hz), 134.4, 138.2, 141.6, 142.4, 158.9, 163.6 (d, *J* = 242.6 Hz), 171.9, 177.3; MS (*m/z* 649, M+H⁺); Anal. (C₃₆H₄₅FN₄O₆ x 1/3H₂O) C, H, N.

((S)-1-{[N'-(4-Chloro-benzyl)-N'-[(R)-4-hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (12c). Compound **12c** was prepared according to general procedure B using (*R*)-**6** (100 mg, 0.1712 mmol), Dess-Martin reagent (79.9 mg, 0.1883 mmol), **9c** (41.0 mg, 0.125 mmol), AcOH (12.5 mg, 0.208 mmol), Na(OAc)₃BH (88.3 mg, 0.4167 mmol) and TBAF (1.0 M in THF, 1.25 mL, 1.25 mmol). Purification (silica, MeOH/CH₂Cl₂, 2:98-5:95) gave **12c** (59.4 mg, 71%). ¹H NMR (CD₃OD, 400 MHz) δ 0.77 (s, 9H), 1.56-1.80 (m, 3H), 2.00-2.10 (m, 1H), 2.65-2.96 (m, 4H), 3.00-3.10 (m, 2H), 3.55 (s, 3H), 3.68 (s, 1H), 3.83 (s, 2H), 4.10 (m, 1H), 5.11 (d, *J* = 4.8 Hz, 1H), 7.10-7.40 (m, 13H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.6, 26.9, 33.5, 36.1, 40.2, 46.0, 51.5, 58.3, 58.7, 61.0, 62.9, 74.0, 79.5, 124.6, 125.3, 126.6, 127.3, 128.0, 128.5, 131.0, 131.5, 133.7, 136.6, 137.6, 141.0, 142.0, 158.4, 171.4, 176.7; MS (*m/z* 665, M+H⁺, 667, M+H⁺); Anal. (C₃₆H₄₅ClN₄O₆ x 1/2H₂O) C, H, N.

((S)-1-{[N'-(4-Cyano-benzyl)-N'-[(R)-4-hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (12e). Compound **12e** was prepared according to general procedure B using (*R*)-**6** (99.6 mg, 0.1705 mmol), Dess-Martin reagent (75.9 mg, 0.1790 mmol), **9e** (40.7 mg, 0.1042 mmol), AcOH (12.5 mg, 0.2084 mmol), Na(OAc)₃BH (88.3 mg, 0.4168 mmol) and TBAF (1.0 M in THF, 0.925 mL, 0.925 mmol). Purification (silica, MeOH/CH₂Cl₂, 2:98-5:95) gave **12e** (59.2 mg, 64%). ¹H NMR (CD₃OD, 400 MHz) δ 0.75 (s, 9H), 1.56-1.84 (m, 3H), 2.04-2.16 (m, 1H), 2.76-2.94 (m, 4H), 3.00-3.14 (m, 2H), 3.55 (s, 3H), 3.64 (s, 1H), 3.90-4.00 (m, 2H), 4.19 (m, 1H), 5.09 (d, *J* = 5.2 Hz, 1H), 7.12-7.30 (m, 9H), 7.52-7.64 (m, 4H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.6, 26.8, 34.8, 40.9, 47.0, 52.7, 54.2, 58.3, 59.0, 62.1,

62.9, 73.9, 79.5, 112.1, 119.8, 125.3, 126.2, 127.5, 127.8, 128.8, 128.9, 131.3, 131.7, 133.0, 138.1, 141.6, 142.5, 144.6, 158.9, 172.0, 177.3; MS (m/z 656, $M+H^+$); Anal. ($C_{37}H_{45}N_5O_6 \times 1/2H_2O$) C, H, N.

((S)-1-[N'-((R)-4-Dimethylamino-benzyl)-N'-((R)-4-hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl)-carbamic acid methyl ester (12f). Compound **12f** was prepared according to general procedure B using (*R*)-**6** (100 mg, 0.1712 mmol), Dess-Martin reagent (79.9 mg, 0.1883 mmol), **9f** (39.8 mg, 0.125 mmol), AcOH (15.0 mg, 0.250 mmol), $Na(OAc)_3BH$ (106.0 mg, 0.50 mmol) and TBAF (1.0 M in THF, 0.836 mL, 0.836 mmol). Purification (silica, MeOH/ CH_2Cl_2 , 3:97-5:95) gave **12f** (52.4 mg, 73%). 1H NMR (CD_3OD , 400 MHz) δ 0.80 (s, 9H), 1.55-1.80 (m, 3H), 2.00-2.10 (m, 1H), 2.65-2.93 (m, 10H), 3.00-3.15 (m, 2H), 3.56 (s, 3H), 3.70-3.82 (m, 3H), 4.18 (m, 1H), 5.10 (d, $J = 5.2$ Hz, 1H), 6.66-6.72 (m, 2H), 7.14-7.28 (m, 11H); ^{13}C NMR (CD_3OD , 100 MHz) δ 22.5, 27.0, 35.0, 37.8, 40.9, 41.2, 47.0, 52.7, 58.0, 58.3, 62.4, 63.0, 74.0, 79.5, 114.0, 125.4, 126.1, 126.3, 127.5, 127.9, 128.78, 128.83, 131.5, 131.6, 138.2, 141.5, 142.4, 151.8, 158.9, 171.7, 177.3; MS (m/z 674, $M+H^+$); Anal. ($C_{38}H_{51}N_5O_6$) C, H, N.

((S)-1-[N'-((R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl)-N'-isobutyl-hydrazinocarbonyl]-2,2-dimethyl-propyl)-carbamic acid methyl ester (12g). Compound **12g** was prepared according to general procedure B using (*R*)-**6** (95.0 mg, 0.1627 mmol), Dess-Martin reagent (75.9 mg, 0.1790 mmol), **9g** (26.7 mg, 0.1031 mmol), AcOH (12.4 mg, 0.2062 mmol), $Na(OAc)_3BH$ (87.4 mg, 0.4124 mmol) and TBAF (1.0 M in THF, 1.031 mL, 1.031 mmol). Purification (silica, MeOH/ CH_2Cl_2 , 4:96-5:95) gave **12g** (56.0 mg, 91%). 1H NMR (CD_3OD , 400 MHz) δ 0.90 (d, $J = 6.8$ Hz, 3H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.95 (s, 9H), 1.50-1.83 (m, 4H), 2.00-2.13 (m, 1H), 2.40-2.55 (m, 2H), 2.60-2.93 (m, 4H), 3.00-3.15 (m, 2H), 3.58 (s, 3H), 3.83 (s, 1H), 4.19 (m, 1H), 5.11 (d, $J = 4.8$ Hz, 1H), 7.10-7.30 (m, 9H); ^{13}C NMR (CD_3OD , 100 MHz) δ 21.1, 21.3, 22.5, 27.1, 27.5, 35.1, 37.7, 40.9, 47.0, 52.7, 58.2, 59.8, 63.1, 66.7, 73.9, 79.5, 125.3, 126.2, 127.5, 127.8, 128.77, 128.80, 131.6, 138.1, 141.6, 142.5, 159.0, 171.9, 177.3; MS (m/z 597, $M+H^+$); Anal. ($C_{33}H_{48}N_4O_6 \times 1/2H_2O$) C, H, N.

{(S)-1-[N'-((R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl)-N'-(4-pyridin-2-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12h). Compound **12h** was prepared according to general procedure B using (*R*)-**6** (100.0 mg, 0.1712 mmol), Dess-Martin reagent (79.9 mg, 0.1883 mmol), **9h** (36.4 mg, 0.0982 mmol), AcOH (11.8 mg, 0.1964 mmol), $Na(OAc)_3BH$ (83.2 mg, 0.3928 mmol) and TBAF (1.0 M in THF, 0.982 mL, 0.982 mmol). Purification (silica, MeOH/ CH_2Cl_2 , 2:98-5:95) gave **12h** (49.7 mg, 72%). 1H NMR (CD_3OD , 400 MHz) δ 0.77 (s, 9H), 1.60-1.72 (m, 1H), 1.72-1.86 (m, 2H), 2.05-2.15 (m, 1H), 2.75-2.95 (m, 4H), 3.00-3.15 (m, 2H), 3.46 (s, 3H), 3.72 (s, 1H), 3.90-4.00 (m, 2H), 4.16-4.22 (m, 1H), 5.11 (d, $J = 5.2$ Hz, 1H), 7.10-7.40 (m, 10H), 7.50 (m, 2H), 7.75-7.90 (m, 4H), 8.55-8.62 (m, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 22.6, 26.9, 34.9, 37.8, 40.9, 47.0, 52.6, 58.3, 58.6, 62.4, 63.0, 74.0, 79.5, 106.2, 122.5, 123.6, 125.3, 126.1, 127.5, 127.9, 128.8, 128.85, 131.0, 131.6, 138.2, 138.9, 139.5, 139.6, 141.6, 142.4, 150.2, 158.7, 158.9, 171.9, 177.3; MS (m/z 708, $M+H^+$); Anal. ($C_{36}H_{45}N_4O_6 \times 4/3H_2O$) C, H, N.

{(S)-1-[N'-((R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl)-N'-(4-pyrimidin-5-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12i). Compound **12i** was prepared according to general procedure B using (*R*)-**6** (56.1 mg, 0.09613 mmol), Dess-Martin reagent (42.8 mg, 0.1009 mmol), **9i** (25.0 mg, 0.0673 mmol), AcOH (10.4 mg, 0.1730 mmol), $Na(OAc)_3BH$ (57.0 mg, 0.2692 mmol) and TBAF (1.0 M in THF, 0.501 mL, 0.501 mmol). Purification (silica, MeOH/ CH_2Cl_2 , 1:99-5:95) gave **12i** (25.7 mg, 54%). 1H NMR (CD_3OD , 400 MHz) δ 0.76 (s, 9H), 1.60-1.84 (m, 3H), 2.04-2.16 (m, 1H), 2.76-2.94 (m, 4H), 3.00-3.14 (m, 2H), 3.47 (s,

3H), 3.70 (s, 1H), 3.94 (s, 2H), 4.18 (m, 1H), 5.09 (d, $J = 4.8$ Hz, 1H), 7.10-7.30 (m, 9H), 7.50-7.65 (m, 4H), 9.01 (s, 2H), 9.11 (s, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 22.6, 26.9, 34.9, 37.8, 40.9, 47.0, 52.7, 58.3, 58.7, 62.4, 63.0, 74.0, 79.6, 125.3, 126.2, 127.5, 127.9, 128.8, 128.9, 131.65, 131.70, 134.2, 135.9, 138.2, 139.8, 141.6, 142.5, 156.0, 157.8, 158.9, 171.9, 177.3; MS (m/z 709, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{40}\text{H}_{48}\text{N}_6\text{O}_6 \times \text{H}_2\text{O}$) C, H, N.

{(S)-1-[N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-(4-morpholin-4-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12j). Compound **12j** was prepared according to general procedure B using (*R*)-**6** (83.3 mg, 0.1426 mmol), Dess-Martin reagent (63.6 mg, 0.1499 mmol), **9j** (45 mg, 0.1189 mmol), AcOH (14.3 mg, 0.2378 mmol), $\text{Na}(\text{OAc})_3\text{BH}$ (100.8 mg, 0.4756 mmol) and TBAF (1.0 M in THF, 0.85 mL, 0.85 mmol). Purification (silica, MeOH/ CH_2Cl_2 , 3:97-5:95) gave **12j** (50.5 mg, 59%). ^1H NMR (CD_3OD , 400 MHz) δ 0.78 (s, 9H), 1.56-1.82 (m, 3H), 2.00-2.12 (m, 1H), 2.66-2.92 (m, 4H), 3.00-3.14 (m, 6H), 3.55 (s, 3H), 3.70-3.85 (m, 7H), 4.18 (m, 1H), 5.09 (d, $J = 5.2$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 2H), 7.12-7.30 (m, 11H); ^{13}C NMR (CD_3OD , 100 MHz) δ 21.4, 25.8, 33.8, 36.6, 39.7, 45.8, 49.7, 51.6, 57.1, 61.1, 61.9, 66.8, 72.8, 78.4, 115.6, 124.2, 125.0, 126.3, 126.7, 127.6, 127.7, 128.5, 130.3, 130.5, 137.0, 140.4, 141.3, 151.1, 157.8, 170.6, 176.1; MS (m/z 716, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{40}\text{H}_{53}\text{N}_5\text{O}_7 \times \text{H}_2\text{O}$) C, H, N.

{(S)-1-[N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-(4-morpholin-4-ylmethyl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12k). Compound **12k** was prepared according to general procedure B using (*R*)-**6** (101.2 mg, 0.1733 mmol), Dess-Martin reagent (77.2 mg, 0.1820 mmol), **9k** (40 mg, 0.1019 mmol), AcOH (12.2 mg, 0.2038 mmol), $\text{Na}(\text{OAc})_3\text{BH}$ (86.4 mg, 0.4076 mmol) and TBAF (1.0 M in THF, 1.019 mL, 1.019 mmol). Purification (silica, MeOH/ CH_2Cl_2 , 5:95-7:93) gave **12k** (55mg, 74%); ^1H NMR (CD_3OD , 400 MHz) δ 0.73 (s, 9H), 1.55-1.85 (m, 3H), 2.02-2.15 (m, 1H), 2.35-2.48 (m, 4H), 2.70-2.95 (m, 4H), 3.00-3.15 (m, 2H), 3.47 (s, 2H), 3.54 (s, 3H), 3.60-3.75 (m, 5H), 3.75-3.95 (m, 2H), 41.8 (m, 1H), 5.09 (d, $J = 4.4$ Hz, 1H), 7.10-7.40 (m, 13H); ^{13}C NMR (CD_3OD , 100 MHz) δ 22.6, 27.0, 34.9, 37.8, 40.9, 46.9, 52.8, 54.5, 58.3, 58.7, 62.4, 63.0, 64.1, 67.7, 74.0, 79.6, 125.4, 126.2, 127.5, 127.9, 128.8, 130.46, 130.49, 131.6, 137.3, 137.7, 138.2, 141.6, 142.5, 158.9, 171.8, 177.3; MS (m/z 730, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{41}\text{H}_{55}\text{N}_5\text{O}_7 \times 1/2\text{H}_2\text{O}$) C, H, N.

{(S)-1-[N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-(4-imidazol-1-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12l). Compound **12l** was prepared according to general procedure B using (*R*)-**6** (125.0 mg, 0.2140 mmol), Dess-Martin reagent (95.3 mg, 0.2247 mmol), **9l** (50.0 mg, 0.1393 mmol), AcOH (16.7 mg, 0.2786 mmol), $\text{Na}(\text{OAc})_3\text{BH}$ (118.1 mg, 0.5572 mmol) and TBAF (1.0 M in THF, 0.486 mL, 0.486 mmol). Purification (silica, MeOH/ CH_2Cl_2 , 5:95-7:93) gave **12l** (62.8 mg, 65%). ^1H NMR (CD_3OD , 400 MHz) δ 0.80 (s, 9H), 1.60-1.85 (m, 3H), 2.05-2.15 (m, 1H), 2.75-2.95 (m, 4H), 3.00-3.15 (m, 2H), 3.48 (s, 3H), 3.69 (s, 1H), 3.85-4.00 (m, 2H), 4.23 (m, 1H), 5.11 (d, $J = 4.8$ Hz, 1H), 7.10-7.30 (m, 10H), 7.36-7.54 (m, 5H), 8.01 (s, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 22.6, 26.9, 34.9, 37.8, 40.9, 47.0, 52.6, 58.3, 58.7, 62.1, 63.0, 73.9, 79.6, 119.7, 121.9, 125.3, 126.2, 127.5, 127.8, 128.8, 128.9, 130.2, 131.6, 132.1, 136.9, 137.6, 138.2, 141.6, 142.5, 158.9, 171.9, 177.3; MS (m/z 697, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{39}\text{H}_{48}\text{N}_6\text{O}_6 \times \text{H}_2\text{O}$) C, H, N.

{(S)-1-[N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12m). Compound **12m** was prepared according to general procedure B using (*R*)-**6** (101.2 mg, 0.1733 mmol), Dess-Martin reagent (77.2 mg, 0.1820 mmol), **9m** (40.0 mg, 0.1065 mmol), AcOH (12.3 mg, 0.2054 mmol), $\text{Na}(\text{OAc})_3\text{BH}$ (87.0 mg, 0.4108 mmol) and TBAF (1.0 M in THF, 1.027 mL, 1.027 mmol). Purification

(silica, MeOH/CH₂Cl₂, 6:94) gave **12m** (66.3 mg, 88%). ¹H NMR (CD₃OD, 400 MHz) δ 0.74 (s, 9H), 1.56-1.84 (m, 3H), 2.04- 2.16 (m, 1H), 2.62 (s, 3H), 2.76-2.94 (m, 4H), 3.00-3.14 (m, 2H), 3.50 (s, 3H), 3.69 (s, 1H), 3.93 (s, 2H), 4.19 (m, 1H), 5.10 (d, *J* = 5.2 Hz, 1H), 7.10-7.30 (m, 9H), 7.45-7.55 (m, 2H), 7.75-7.90 (m, 2H); ¹³C NMR (CD₃OD, 100 MHz) δ 12.1, 22.6, 26.9, 34.8, 37.7, 40.9, 47.0, 52.7, 58.3, 58.8, 62.3, 62.9, 74.0, 79.5, 125.3, 126.1, 127.1, 127.5, 127.9, 128.0, 128.81, 128.86, 131.1, 131.7, 138.2, 141.6, 142.1, 142.4, 158.9, 169.3, 171.9, 177.3, 178.7; MS (*m/z* 713, M+H⁺); Anal. (C₃₉H₄₈N₆O₇ x H₂O) C, H, N.

{(S)-1-[N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-(4-thiazol-2-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12n). Compound **12n** was prepared according to general procedure B using (*R*)-**6** (110 mg, 0.1883 mmol), Dess-Martin reagent (87.9 mg, 0.2072 mmol), **9n** (49.0 mg, 0.1302 mmol), AcOH (14.9 mg, 0.2486 mmol), Na(OAc)₃BH (105.4 mg, 0.4972 mmol) and TBAF (1.0 M in THF, 0.849 mL, 0.849 mmol). Purification (silica, MeOH/CH₂Cl₂, 3:97-5:95) gave **12n** (50.5 mg, 54%). ¹H NMR (CD₃OD, 400 MHz) δ 0.75 (s, 9H), 1.58-1.86 (m, 3H), 2.04-2.18 (m, 1H), 2.74-2.96 (m, 4H), 3.00-3.14 (m, 2H), 3.47 (s, 3H), 3.69 (s, 1H), 3.92 (s, 2H), 4.19 (m, 1H), 5.10 (d, *J* = 5.2 Hz, 1H), 7.10-7.30 (m, 9H), 7.45-7.50 (m, 2H), 7.56 (d, *J* = 3.2 Hz, 1H), 7.80-7.90 (m, 3H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.6, 26.9, 34.9, 37.7, 40.9, 47.0, 52.7, 58.3, 58.8, 62.3, 63.0, 74.0, 79.5, 120.6, 125.3, 126.1, 127.3, 127.5, 127.9, 128.8, 128.9, 131.3, 131.6, 133.6, 138.2, 141.0, 141.6, 142.4, 144.3, 158.9, 170.1, 171.9, 177.3; MS (*m/z* 714, M+H⁺); Anal. (C₃₉H₄₇N₅O₆S x H₂O) C, H, N.

((S)-1-{N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-[4-(2-methyl-thiazol-4-yl)-benzyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (12o). Compound **12o** was prepared according to general procedure B using (*R*)-**6** (99.6 mg, 0.1705 mmol), Dess-Martin reagent (75.9 mg, 0.1790 mmol), **9o** (40.7 mg, 0.1042 mmol), AcOH (12.5 mg, 0.2084 mmol), Na(OAc)₃BH (88.3mg, 0.4168 mmol) and TBAF (1.0 M in THF, 0.925 mL, 0.925 mmol). Purification (silica, MeOH/CH₂Cl₂, 2:98-5:95) gave **12o** (59.2 mg, 78%). ¹H NMR (CD₃OD, 400 MHz) δ 0.76 (s, 9H), 1.55-1.70 (m, 1H), 1.70-1.85 (m, 2H), 2.00-2.20 (m, 1H), 2.72 (s, 3H), 2.76-2.94 (m, 4H), 3.04 (dd, *J* = 16.4, 5.2 Hz, 1H), 3.10 (d, *J* = 13.2 Hz, 1H), 3.48 (s, 3H), 3.71 (s, 1H), 3.84-3.96 (m, 2H), 4.18 (m, 1H), 5.10 (d, *J* = 5.2 Hz, 1H), 7.12-7.29 (m, 9H), 7.39-7.44 (m, 2H), 7.54 (s, 1H), 7.74-7.79 (m, 2H); ¹³C NMR (CD₃OD, 100 MHz) δ 18.8, 22.6, 26.9, 34.9, 37.8, 40.9, 47.0, 52.7, 58.3, 58.6, 62.5, 63.0, 74.0, 79.5, 114.0, 125.3, 126.1, 127.1, 127.5, 127.9, 128.8, 130.9, 131.6, 134.8, 138.2, 138.3, 141.5, 142.4, 156.1, 158.9, 168.1, 171.8, 177.3; MS (*m/z* 728, M+H⁺); Anal. (C₄₀H₄₉N₅O₆S x 1/2H₂O) C, H, N.

((S)-1-{N'-[4-(4-*tert*-Butyl-thiazol-2-yl)-benzyl]-N'-[(R)-4-hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (12p). Compound **12p** was prepared according to general procedure B using (*R*)-**6** (100 mg, 0.1712 mmol), Dess-Martin reagent (76.3 mg, 0.1798 mmol), **9p** (74.0 mg, 0.1712 mmol), AcOH (20.6 mg, 0.3424 mmol), Na(OAc)₃BH (145.1 mg, 0.6848 mmol) and TBAF (1.0 M in THF, 0.428 mL, 0.428 mmol). Purification (silica, MeOH/CH₂Cl₂, 3:97-5:95) gave **12p** (25 mg, 19%). ¹H NMR (CD₃OD, 400 MHz) δ 0.77 (s, 9H), 1.38 (s, 9H), 1.56-1.70 (m, 1H), 1.70 (m, 2H), 2.05-2.18 (m, 1H), 2.75-2.95 (m, 4H), 3.04 (dd, *J* = 16.4, 4.8 Hz, 1H), 3.10 (d, *J* = 13.2 Hz, 1H), 3.47 (s, 3H), 3.70 (s, 1H), 3.83-3.95 (m, 2H), 4.19 (m, 1H), 5.11 (d, *J* = 4.8 Hz, 1H), 7.10-7.30 (m, 9H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.6, 26.9, 30.5, 34.9, 35.9, 37.7, 40.9, 47.0, 52.7, 58.3, 58.7, 62.4, 62.9, 74.0, 79.5, 111.8, 125.3, 126.2, 127.2, 127.5, 127.9, 128.81, 128.86, 131.1, 131.7, 134.4, 138.2, 140.3, 141.6, 142.4, 158.9, 168.4, 168.7, 171.9, 177.3; MS (*m/z* 770, M+H⁺); Anal. (C₄₃H₅₅N₅O₆S x 1/2H₂O) C, H, N.

{(S)-1-[N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-(4-imidazo[2,1-*b*]thiazol-6-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-

propyl}-carbamic acid methyl ester (12q). Compound **12q** was prepared according to general procedure B using (*R*)-**6** (140.6 mg, 0.2408 mmol), Dess-Martin reagent (224.7 mg, 0.5298 mmol), **9q** (50 mg, 0.1204 mmol), AcOH (14.5 mg, 0.2408 mmol), Na(OAc)₃BH (102.1 mg, 0.4816 mmol) and TBAF (1.0 M in THF, 1.204 mL, 1.204 mmol). Purification (silica, MeOH/CH₂Cl₂, 6:94) gave **12q** (61mg, 67%). ¹H NMR (CD₃OD, 400 MHz) δ 0.76 (s, 9H), 1.55-1.70 (m, 1H), 1.70-1.85 (m, 2H), 2.05-2.15 (m, 1H), 2.70-2.95 (m, 4H), 3.00-3.15 (m, 2H), 3.48 (s, 3H), 3.71 (s, 1H), 3.80-3.95 (m, 2H), 4.18 (m, 1H), 5.09 (d, *J* = 5.2 Hz, 1H), 7.05-7.30 (m, 10H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.65-7.75 (m, 3H), 7.97 (d, *J* = 1.6 Hz, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.6, 26.9, 34.9, 37.8, 40.9, 47.0, 52.7, 58.3, 58.6, 62.5, 63.0, 74.0, 79.5, 110.1, 114.0, 120.9, 125.3, 126.0, 126.1, 127.5, 127.9, 128.80, 128.84, 130.9, 131.6, 134.3, 137.6, 138.2, 141.5, 142.4, 148.4, 151.7, 158.9, 171.8, 177.3; MS (*m/z* 753, M+H⁺); Anal. (C₄₁H₄₈N₆O₆S x H₂O) C, H, N.

((S)-1-[N'-(4-(2-Chloro-thiazol-5-ylmethoxy)-benzyl)-N'-[(R)-4-hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl]-2,2-dimethyl-propyl)-carbamic acid methyl ester (12r) Compound **12r** was prepared according to general procedure B using (*R*)-**6** (101.2 mg, 0.1733 mmol), Dess-Martin reagent (132.5 mg, 0.3124 mmol), **9r** (105.3 mg, 0.2389 mmol), AcOH (20.8 mg, 0.3461 mmol), Na(OAc)₃BH (147.0 mg, 0.6936 mmol) and TBAF (1.0 M in THF, 5.0 mL, 5.0 mmol). Purification (Preparative RPLC-MS, MeCN/0.05% aqueous formic acid, 35:65-75:25) gave **12r** (40 mg, 30%). ¹H NMR (CD₃OD, 400 MHz) δ 0.74 (s, 9H), 1.56-1.82 (m, 3H), 2.04-2.10 (m, 1H), 2.70-2.85 (m, 3H), 2.89 (d, *J* = 13.3 Hz, 1H), 3.06 (dd, *J* = 16.4 Hz, 4.8 Hz, 1H), 3.09 (d, *J* = 13.3 Hz, 1H), 3.55 (s, 3H), 3.70 (s, 1H), 3.75-3.88 (m, 2H), 4.19 (m, 1H), 5.10 (d, *J* = 4.9 Hz, 1H), 5.25 (m, 2H), 6.86-6.92 (m, 2H), 7.14-7.32 (m, 11H), 7.61-7.62 (m, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.5, 26.9, 34.9, 40.9, 47.0, 52.7, 58.3, 58.6, 62.1, 63.0, 63.4, 74.0, 80.0, 115.8, 125.4, 126.2, 127.5, 127.9, 128.8, 128.9, 131.61, 131.65, 131.9, 138.2, 139.3, 141.2, 141.6, 142.5, 153.6, 158.5, 159.0, 171.8, 177.3; MS (*m/z* 777, M+H⁺); Anal. (C₄₀H₄₈ClN₅O₇S) C, H, N.

{(S)-1-[N'-(4-(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl)-N'-(4-iodo-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12s). Compound **12s** was prepared according to general procedure B using (*R*)-**6** (99.6 mg, 0.1705 mmol), Dess-Martin reagent (75.9 mg, 0.1790 mmol), **9s** (43.7 mg, 0.1042 mmol), AcOH (12.5 mg, 0.2084 mmol), Na(OAc)₃BH (88.3 mg, 0.4168 mmol) and TBAF (1.0 M in THF, 0.925 mL, 0.925 mmol). Purification (silica, EtOAc/petroleum ether, 50:50-100:0 and then silica, MeOH/CH₂Cl₂, 2:98-5:95) gave **12s** (38 mg, 48%). ¹H NMR (CD₃OD, 400 MHz) δ 0.78 (s, 9H), 1.57-1.82 (m, 3H), 2.00-2.10 (m, 1H), 2.70-3.00 (m, 4H), 3.00-3.15 (m, 2H), 3.54 (s, 3H), 3.66 (s, 1H), 3.82 (s, 2H), 4.09 (m, 1H), 5.10 (d, *J* = 4.8 Hz, 1H), 7.10-7.30 (m, 11H), 7.50-7.65 (m, 2H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.6, 26.9, 33.5, 36.1, 40.2, 46.0, 51.5, 58.3, 58.7, 61.0, 62.9, 74.0, 79.5, 92.7, 124.7, 125.8, 126.7, 127.1, 128.2, 131.0, 132.3, 137.8, 137.9, 141.0, 142.2, 158.3, 171.4, 176.7; MS (*m/z* 757, M+H⁺); Anal. (C₃₆H₄₅IN₄O₆) C, H, N.

5. Experimental details and spectroscopic data for inhibitors 13, 12d, 14 and 15

[(S)-1-(N'-(4-Bromo-benzyl)-N'-{(R)-4-(tert-butyl-dimethyl-silanyloxy)-4-[(1S,2R)-2-(tert-butyl-dimethyl-silanyloxy)-indan-1-ylcarbamoyl]-5-phenyl-pentyl}-hydrazinocarbonyl)-2,2-dimethyl-propyl]-carbamic acid methyl ester (13). To a mixture of (*R*)-**6** (412.9 mg, 0.7070 mmol) and Dess-Martin reagent (314.9 mg, 0.7424 mmol) was added dry CH₂Cl₂ (15 mL). The mixture was stirred at room temp for about 1 h and then the residue was concentrated, dissolved in Et₂O (15 mL) and washed with water (15 mL). The water phase was extracted with Et₂O (2 x 15 mL) and the combined ether layers were dried (MgSO₄) and

concentrated. Hydrazide **12d** (263.2 mg, 0.7070 mmol), THF (20 mL) and AcOH (85.0 mg, 1.414 mmol) were added to the residue and stirred for 15 min at room temp. Then Na(OAc)₃BH (599.3 mg, 2.828 mmol) was added and the mixture was stirred at room temp for 2 h. The reaction was quenched with saturated NH₄Cl (aq.), extracted with CH₂Cl₂ (3 x 20 mL), dried (MgSO₄), concentrated and purified (silica, EtOAc/petroleum ether, 20:80-40:60) to give **13** (320.0 mg, 48%). About 165 mg of (*R*)-**6** was recovered. ¹H NMR (CDCl₃, 400 MHz) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.806 (s, 9H), 0.812 (s, 9H), 0.90 (s, 9H), 1.25-1.40 (m, 1H), 1.45-1.65 (m, 2H), 1.95- 2.12 (m, 1H), 2.55-2.70 (m, 1H), 2.80-3.00 (m, 3H), 3.07 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.12 (d, *J* = 13.6 Hz, 1H), 3.50-3.65 (m, 4H), 3.75-3.90(m, 2H), 4.60-4.70 (m, 1H), 5.15-5.25 (m, 1H), 5.33 (d, *J* = 9.2 Hz, 1H), 6.77 (s, 1H), 7.06-7.28 (m, 10H), 7.34-7.46 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ -4.7, -4.3, -1.9, -1.6, 18.5, 18.6, 21.8, 26.1, 26.3, 26.4, 34.4, 36.9, 39.9, 46.7, 52.4, 55.7, 56.5, 59.4, 61.2, 74.2, 82.7, 121.2, 124.9, 125.9, 126.6, 126.8, 128.0, 128.2, 130.4, 130.9, 131.3, 136.5, 136.6, 139.7, 141.9, 156.8, 169.7, 174.2; MS (*m/z* 937, M+H⁺, 939, M+H⁺); Anal. (C₄₈H₇₃BrN₄O₆ Si₂) C, H, N.

((*R*)-1-{*N'*-(4-Bromo-benzyl)-*N'*-[(*S*)-4-hydroxy-4-((1*S*,2*R*)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (12d**).** To a solution of **13** (82.4 mg, 0.0878 mmol) in THF (0.5 mL) TBAF (1.0 M in THF, 10.0 equiv, 0.878 mmol) was added and the solution was stirred at room temp overnight. The mixture was concentrated and the residue was extracted with Et₂O (3 x 15 mL) and H₂O (10 mL). The organic layers were dried (MgSO₄), concentrated and purified (silica, EtOAc/petroleum ether, 30:70-100:0) to give **12d** (52.8 mg, 85%). ¹H NMR (CDCl₃, 400 MHz) δ 0.86 (s, 9H), 1.58-1.72 (m, 2H), 2.10-2.20 (m, 1H), 2.22-2.32 (m, 1H), 2.74-2.96 (m, 4H), 3.02 (dd, *J* = 16.4, 5.2 Hz, 1H), 3.14 (d, *J* = 13.2 Hz, 1H), 3.54-3.64 (m, 4H), 3.84-3.98 (m, 4H), 4.23 (m, 1H), 5.14-5.24 (m, 2H), 6.74 (br s, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 7.10-7.24 (m, 5H), 7.26-7.37 (m, 5H), 7.40-7.45 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 21.1, 26.4, 33.9, 36.5, 39.2, 46.6, 52.7, 57.2, 57.4, 61.7, 61.8, 73.2, 78.6, 121.7, 123.9, 125.3, 126.9, 128.05, 128.10, 130.8, 130.9, 131.6, 135.3, 137.3, 140.5, 140.6, 157.2, 170.9, 174.8; MS (*m/z* 709, M+H⁺, 711, M+H⁺); Anal. (C₃₆H₄₅BrN₄O₆ x 1/2H₂O) C, H, N.

((*S*)-1-{*N'*-(4-Bromo-benzyl)-*N'*-[(*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-4-((1*S*,2*R*)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (14**).** To a solution of **13** (25 mg, 0.0266 mmol) in THF (0.5 mL) TBAF (1.0 M in THF, 1.0 equiv, 0.0266 mmol) was added and the solution was stirred for 1 h at room temp. The residue was concentrated and extracted with Et₂O (3 x 5 mL) and H₂O (5 mL). The organic layers were dried (MgSO₄), concentrated and purified (preparative RPLC-MS, MeCN/0.05% aqueous formic acid, 40:60-100:0) to give **14** (16.5 mg, 75%). ¹H NMR (CD₃OD, 400 MHz) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.79 (s, 18H), 1.65-1.90 (m, 3H), 2.15-2.25 (m, 1H), 2.70-2.92 (m, 3H), 2.98 (d, *J* = 14.8 Hz, 1H), 3.09 (dd, *J* = 16.4, 4.8 Hz, 1H), 3.34 (s, 1H), 3.54 (s, 3H), 3.68-3.75 (m, 1H), 3.80-3.95 (m, 2H), 4.33 (m, 1H), 5.14 (dd, *J* = 8.8, 5.2 Hz, 1H), 6.46 (d, *J* = 9.6 Hz, 1H), 7.10-7.45 (m, 13H), 7.82 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ -1.6, -1.5, 19.4, 23.3, 26.7, 26.9, 35.2, 39.1, 41.1, 47.2, 52.7, 58.5, 61.9, 62.8, 73.8, 84.1, 122.2, 125.4, 126.3, 127.5, 127.9, 128.88, 128.92, 131.3, 132.3, 132.4, 137.9, 138.0, 141.6, 142.6, 158.8, 171.5, 176.4; MS (*m/z* 823, M+H⁺, 825, M+H⁺); Anal. (C₄₂H₅₉BrN₄O₆ Si) C, H, N.

((*S*)-1-{*N'*-(4-Bromo-benzyl)-*N'*-[(*R*)-4-hydroxy-4-((1*S*,2*R*)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentanoyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (15**).** A solution of (*R*)-**6**-acid (150 mg, 0.2509 mmol), **9d** (93.2 mg, 0.2509mmol), EDC (52.9 mg, 0.276 mmol), HOBT (37.3 mg, 0.276 mmol) and NMM (27.9 mg, 0.276) in EtOAc was stirred at room temp overnight. The mixture was diluted with Et₂O (15 mL) and washed with water (20 mL). The water phase was extracted with Et₂O (2 x 15

mL) and the combined organic layers were dried (MgSO₄), concentrated and purified (silica, EtOAc/petroleum ether, 20:80-40:60) to give the silyl protected **15**, 106 mg. Deprotection with TBAF (1.0 M in THF, 10.0 equiv, 1.11 mmol) and purification (silica, MeOH/CH₂Cl₂, 3:97-7:93 and then preparative RPLC-MS, MeCN/0.05% aqueous formic acid, 20:80-100:0) to give **15** (70 mg 39%). ¹H NMR (CDCl₃, 400 MHz) δ 0.89 (s, 9H), 2.00-2.15 (m, 1H), 2.20-2.40 (m, 1H), 2.40-2.65 (m, 2H), 2.70-3.10 (m, 4H), 3.54 (s, 3H), 3.75 (m, 1H), 3.90-4.20 (m, 2H), 4.99 (m, 1H), 5.20-5.40 (m, 1H), 6.80-7.40 (m, 15H), 8.51 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 28.2, 33.5, 34.1, 39.3, 46.4, 50.8, 52.9, 57.8, 61.2, 73.5, 78.7, 122.3, 124.2, 125.3, 127.02, 127.06, 128.1, 128.2, 130.8, 132.0, 134.6, 136.9, 140.0, 140.1, 140.4, 157.3, 170.1, 175.1, 176.9; MS (*m/z* 723, M+H⁺); Anal. (C₃₆H₄₃BrN₄O₇ x ½H₂O) C, H, N.

6. Experimental details and spectroscopic data for compounds (S)-6 and (S)-12d

(S)-2-Benzyl-2-(tert-butyl-dimethyl-silanyloxy)-5-hydroxy-pentanoic acid [(1S,2R)-2-(tert-butyl-dimethyl-silanyloxy)-indan-1-yl]-amide ((S)-6). Et₃N (122.4 mg, 1.209 mmol) was added to a solution of (S)-4 (70.8 mg, 0.2015 mmol) in CH₂Cl₂ at room temp. After 10 min TBSOTf (106.5 mg, 0.403 mmol) was added to the solution and the stirring was continued for 1 h. The solution was concentrated, the residue was extracted with CH₂Cl₂ (3 x 10 mL) and the organic phases were dried (MgSO₄) and concentrated. Et₂O (10 mL) and LiBH₄ (13.2 mg, 0.6045 mmol) were added and the resulting mixture was stirred at room temp for about 2 h. Concentration, extraction with CH₂Cl₂, drying of the organic layers (MgSO₄) and concentration again gave a crude intermediate. Dry CH₂Cl₂ and Et₃N (122.4 mg, 1.209 mmol) were added to the residue and after about 10 min TBSOTf (159.8 mg, 0.6045 mmol) was added at room temp and the stirring was continued overnight. Saturated NH₄Cl (aq. 10 mL) was added to the solution and extraction with CH₂Cl₂ (3 x 15 mL), drying (MgSO₄) and purification (silica, MeOH/CH₂Cl₂, 2:98-4:96) gave the trisilylated compound (90 mg, 64%). ¹H NMR (CDCl₃, 400 MHz) δ 0.056 (s, 3H), 0.062 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.18 (s, 3H), 0.67 (s, 9H), 0.87 (s, 9H), 0.91 (s, 9H), 1.48-1.69 (m, 1H), 1.70-1.84 (m, 2H), 1.92-2.04 (m, 1H), 2.77 (d, *J* = 14.4 Hz, 1H), 2.85 (dd, *J* = 15.6, 5.6 Hz, 1H), 3.04 (dd, *J* = 15.6, 6.4 Hz, 1H), 3.52 (d, *J* = 14.4 Hz, 1H), 3.56-3.70 (m, 2H), 4.53-4.62 (m, 1H), 5.06-5.15 (m, 1H), 6.85-7.22 (m, 9H), 7.31 (d, *J* = 7.2 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ -5.23, -5.21, -4.7, -4.3, -1.7, -1.2, 18.45, 18.49, 26.1, 26.2, 26.3, 27.6, 38.1, 39.9, 45.7, 56.8, 63.2, 74.2, 82.8, 124.8, 125.8, 126.2, 126.9, 127.8, 128.1, 130.3, 136.8, 139.7, 141.4, 174.3; MS (*m/z* 698, M+H⁺). A mixture of the trisilylated intermediate (119.9 mg, 0.1718 mmol) and Pd/C (5%, 47.7 mg) in MeOH was stirred under H₂ (1 atm) overnight. Since full conversion not was reached, another 24 mg 5% Pd/C was added and stirring was continued under H₂ overnight. The mixture was filtered, concentrated and purified (silica, EtOAc/petroleum ether, 40:60) to give (S)-6 (60.2 mg, 60%). (S)-6 was also synthesized according to the method for (S)-5 in 64% yield. ¹H NMR (CDCl₃, 400 MHz) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.16 (s, 3H), 0.18 (s, 3H), 0.69 (s, 9H), 0.88 (s, 9H), 1.60-1.74 (m, 1H), 1.76-2.00 (m, 3H), 2.10-2.22 (m, 1H), 2.74-2.90 (m, 2H), 3.04 (dd, *J* = 15.6, 6.4 Hz, 1H), 3.49 (d, *J* = 14.4 Hz, 1H), 3.60-3.72 (m, 2H), 4.64 (m, 1H), 5.16 (dd, *J* = 7.6, 5.6 Hz, 1H), 6.90-7.05 (m, 4H), 7.05-7.30 (m, 5H), 7.42 (d, *J* = 7.6 Hz, 1H); ¹³C NMR -4.7, -4.4, -1.7, -1.3, 18-4. 18-5, 26.1, 26.3, 27.6, 37.4, 39.8, 46.0, 56.8, 62.7, 74.1, 82.8, 124.8, 125.8, 126.2, 126.9, 127.8, 128.2, 130.2, 136.5, 139.6, 141.3, 174.5; MS (*m/z* 584, M+H⁺); Anal. (C₃₃H₅₃NO₄Si₂) C, H, N.

((S)-1-{N'-(4-Bromo-benzyl)-N'-[(S)-4-hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester ((S)-12d). To a mixture of (S)-6 (60.2 mg, 0.103 mmol) and PDC (58.1 mg, 0.155 mmol) was added dry CH₂Cl₂ (5 mL). The solution was stirred for 2 h and then

concentrated; the residue was dissolved in Et₂O (5 mL), filtered and washed with Et₂O twice. The ether layers were concentrated and then **9d** (28.8 mg, 0.0773 mmol), THF (5 mL) and AcOH (8.7 mg, 0.145 mmol) were added. The solution was stirred for 10 min followed by addition of Na(OAc)₃BH (65.5 mg, 0.309 mmol) and stirring was continued overnight. The reaction mixture was concentrated, extracted with saturated NH₄Cl (aq.)/CH₂Cl₂ (3 x 10 mL) dried (MgSO₄) and concentrated again. TBAF (1.0 M in THF, 0.773 mL, 0.773 mmol) was added and the mixture was stirred overnight. Concentration, extraction with H₂O/CH₂Cl₂ (3 x 10 mL), drying (MgSO₄), concentration and purification (silica, MeOH/CH₂Cl₂, 3:97-5:95) gave (*S*)-**12d** (20.2 mg, 37%). ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (s, 9H), 1.55-1.75 (m, 4H), 2.50-2.70 (m, 2H), 2.82 (d, *J* = 16.8 Hz, 1H), 2.95 (d, *J* = 13.2 Hz, 1H), 3.05-3.20 (m, 2H), 3.40-3.55 (m, 2H), 3.59 (s, 3H), 3.91 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.4 Hz, 1H), 4.49 (m, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.34 (m, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 7.00-7.21 (m, 5H), 7.27-7.40 (m, 8H), 7.99 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 22.3, 26.3, 34.2, 39.2, 40.2, 46.7, 53.1, 56.3, 56.5, 59.8, 60.6, 73.0, 79.2, 121.8, 124.7, 125.1, 126.6, 127.0, 128.1, 128.2, 131.0, 131.3, 131.6, 134.8, 137.1, 139.8, 140.8, 157.5, 171.1, 175.4; MS (*m/z* 709, M+H⁺, 711, M+H⁺); Anal. (C₃₆H₄₅BrN₄O₆ x 1/2H₂O) C, H, N.

7. Experimental details and spectroscopic data for inhibitors 12t–w

General procedure C. Palladium-catalyzed reactions. Aryl bromide **13** (1.0 equiv), boronic acid (3.0 equiv), Herrmans palladacycle (0.05 equiv), HP(*t*-Bu)₃BF₄ (0.10 equiv), K₂CO₃ (3.0 equiv), DME and H₂O were added to a 2-5 mL process vial. The mixture was radiated under microwaves at 120 °C or 130 °C for 20 min. The mixture was then extracted with EtOAc and the organic layer was dried (MgSO₄) and concentrated. TBAF (1.0 M in THF, 10.0 equiv) was added to the residue and stirred at room temp overnight. Water (10 mL) was added to the mixture, followed by extraction with CH₂Cl₂, drying (MgSO₄), concentration and purification on silica to afford the products as white solids in 61–80% yield.

((*S*)-1-{*N'*-Biphenyl-4-ylmethyl-*N'*-[(*R*)-4-hydroxy-4-((1*S*,2*R*)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (12t**).** The title compound was made according to general procedure C, using **13** (70 mg, 0.0746 mmol), phenylboronic acid (27.3 mg, 0.224 mmol), palladacycle (3.5 mg, 0.00373 mmol), HP(*t*-Bu)₃BF₄ (2.2 mg, 0.00746 mmol), K₂CO₃ (30.9 mg, 0.224 mmol), DME (0.9 mL) and H₂O (0.2 mL), which were radiated at 130 °C for 20 min. TBAF (1.0 M, in THF, 0.746 mL, 0.746 mmol) was used for deprotection. Purification (silica, MeOH/CH₂Cl₂, 1:99-5:95) gave **12t** (39.5 mg, 75%). ¹H NMR (CD₃OD, 400 MHz) δ 0.76 (s, 9H), 1.58-1.84 (m, 3H), 2.04-2.16 (m, 1H), 2.74-2.94 (m, 4H), 3.00-3.14 (m, 2H), 3.46 (s, 3H), 3.84-3.98 (m, 2H), 4.18 (m, 1H), 5.10 (d, *J* = 5.2 Hz, 1H), 7.14-7.34 (m, 10H), 7.36-7.60 (m, 8H); ¹³C NMR (CD₃OD, 100 MHz) δ 22.6, 26.9, 34.9, 37.8, 40.9, 47.0, 52.7, 58.3, 58.7, 62.5, 63.0, 74.0, 79.6, 125.4, 126.2, 127.5, 127.7, 127.89, 127.91, 128.3, 128.81, 128.86, 129.8, 131.1, 131.7, 137.4, 138.2, 141.56, 141.62, 142.3, 142.4, 158.9, 171.9, 177.3; MS (*m/z* 707, M+H⁺); Anal. (C₄₂H₅₀N₄O₆ x H₂O) C, H, N.

{(*S*)-1-[*N'*-[(*R*)-4-Hydroxy-4-((1*S*,2*R*)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-*N'*-(4-pyridin-3-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12u**).** The title compound was made according to general procedure C, using **13** (100.0 mg, 0.1066 mmol), 3-pyridinylboronic acid (39.2 mg, 0.3198 mmol), palladacycle (5.0 mg, 0.00533 mmol), HP(*t*-Bu)₃BF₄ (3.1 mg, 0.01066 mmol), K₂CO₃ (44.2 mg, 0.3198 mmol), DME (1.0 mL) and H₂O (0.3 mL), which were radiated at 120 °C for 20 min. TBAF (1.0 M in THF, 1.06 mL, 1.066 mmol) was used for deprotection. Purification (silica, MeOH/CH₂Cl₂, 1:99-5:95) gave **12u** (60.5 mg, 80%). ¹H NMR (CD₃OD, 400 MHz) δ

0.76 (s, 9H), 1.56-1.71 (m, 1H), 1.71-1.86 (m, 2H), 2.04-2.16 (m, 1H), 2.74-2.95 (m, 4H), 3.00-3.14 (m, 2H), 3.46 (s, 3H), 3.71 (s, 1H), 3.88-3.98 (m, 2H), 4.16-4.22 (m, 1H), 5.10 (d, $J = 4.8$ Hz, 1H), 7.10-7.30 (m, 9H), 7.46-7.56 (m, 5H), 7.98-8.06 (m, 1H), 8.49 (dd, $J = 4.8, 0.8$ Hz, 1H), 8.74 (d, $J = 1.2$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 22.6, 26.9, 34.9, 37.8, 40.9, 47.0, 52.6, 58.3, 58.7, 62.4, 63.0, 73.9, 79.5, 125.3, 125.5, 126.2, 127.5, 127.9, 128.8, 128.85, 131.5, 131.6, 136.4, 137.6, 138.2, 138.4, 138.8, 141.6, 142.5, 148.3, 148.6, 158.9, 171.8, 177.3; MS (m/z 708, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{41}\text{H}_{49}\text{N}_5\text{O}_6 \times \text{H}_2\text{O}$) C, H, N.

{(S)-1-[N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-(4-pyridin-4-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12v).

The title compound was made according to general procedure C, using **13** (100.0 mg, 0.1066 mmol), 4-pyridinylboronic acid (39.2 mg, 0.3198 mmol), palladacycle (5.0 mg, 0.00533 mmol), $\text{HP}(t\text{-Bu})_3\text{BF}_4$ (3.1 mg, 0.01066 mmol), K_2CO_3 (44.2 mg, 0.3198 mmol), DME (1.0 mL) and H_2O (0.3 mL), which were radiated at 120 °C for 20 min. TBAF (1.0 M in THF, 1.06 mL, 1.066 mmol) was used for deprotection. Purification (silica, $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 1:99-5:95) gave **12v** (52.9 mg, 70%). ^1H NMR (CD_3OD , 400 MHz) δ 0.75 (s, 9H), 1.56-1.70 (m, 1H), 1.70-1.86 (m, 2H), 2.03-2.16 (m, 1H), 2.74-2.94 (m, 4H), 3.01-3.14 (m, 2H), 3.46 (s, 3H), 3.70 (s, 1H), 3.88-4.00 (m, 2H), 4.16-4.22 (m, 1H), 5.09 (d, $J = 4.8$ Hz, 1H), 7.10-7.30 (m, 9H), 7.50-7.70 (m, 6H), 8.50-8.60 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.4, 25.7, 33.7, 36.6, 39.7, 45.8, 51.5, 57.1, 57.6, 61.2, 61.8, 72.8, 78.4, 105.0, 121.8, 124.2, 125.0, 126.3, 126.65, 126.68, 127.62, 127.67, 130.3, 130.5, 136.6, 137.0, 139.0, 140.4, 141.3, 149.4, 157.7, 170.7, 176.1; MS (m/z 708, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{41}\text{H}_{49}\text{N}_5\text{O}_6 \times \text{H}_2\text{O}$) C, H, N.

{(S)-1-[N'-[(R)-4-Hydroxy-4-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-5-phenyl-pentyl]-N'-(4-thiophen-3-yl-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (12w). The title compound was made according to general procedure C, using **13** (65 mg, 0.0693 mmol), 3-thiopheneboronic acid (26.6 mg, 0.208 mmol), palladacycle (3.2 mg, 0.00347 mmol), $\text{HP}(t\text{-Bu})_3\text{BF}_4$ (2.0 mg, 0.00693 mmol), K_2CO_3 (28.7 mg, 0.208 mmol), DME (1.0 mL) and H_2O (0.3 mL), which were radiated at 130 °C for 20 min. TBAF (1.0 M in THF, 0.693 mL, 0.693 mmol) was used for deprotection. Purification (silica, $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 1:99-5:95) gave **12w** (30 mg, 61%). ^1H NMR (CD_3OD , 400 MHz) δ 0.76 (s, 9H), 1.55-1.85 (m, 3H), 2.00-2.18 (m, 1H), 2.72-2.94 (m, 4H), 3.00-3.14 (m, 2H), 3.47 (s, 3H), 3.70 (s, 1H), 3.84-3.94 (m, 2H), 4.18 (m, 1H), 5.09 (d, $J = 4.8$ Hz, 1H), 7.14-7.30 (m, 9H), 7.36-7.48 (m, 4H), 7.52-7.58 (m, 2H); ^{13}C NMR (CD_3OD , 100 MHz) δ 22.6, 26.9, 34.9, 37.8, 40.9, 47.0, 52.7, 58.3, 58.6, 62.5, 63.0, 74.0, 79.6, 121.1, 125.4, 126.2, 127.07, 127.12, 127.2, 127.5, 127.9, 128.8, 128.9, 131.1, 131.7, 136.4, 137.1, 138.2, 141.6, 142.4, 143.4, 158.9, 171.9, 177.3; MS (m/z 713, $\text{M}+\text{H}^+$); Anal. ($\text{C}_{40}\text{H}_{48}\text{N}_4\text{O}_6\text{S} \times \text{H}_2\text{O}$) C, H, N.

8. Table of elemental analysis data

Cmpd	Formula	Theoretical			Analyzed		
		C	H	N	C	H	N
3		65.74	6.90		65.70	6.86	
(R)-4	$\text{C}_{21}\text{H}_{21}\text{NO}_4 \cdot 1/5\text{H}_2\text{O}$	71.05	6.08	3.95	71.11	5.82	3.74
(S)-4	$\text{C}_{21}\text{H}_{21}\text{NO}_4$	71.78	6.02	3.99	71.61	5.95	3.81
(R)-5	$\text{C}_{27}\text{H}_{35}\text{NO}_4\text{Si}$	69.64	7.58	3.01	69.85	7.69	2.88
(S)-5	$\text{C}_{27}\text{H}_{35}\text{NO}_4\text{Si} \cdot 1/3\text{H}_2\text{O}$	68.75	7.62	2.97	68.46	7.21	2.97
(R)-6	$\text{C}_{33}\text{H}_{53}\text{NO}_4\text{Si}_2$	67.87	9.15	2.40	68.08	9.30	2.29
(S)-6	$\text{C}_{33}\text{H}_{53}\text{NO}_4\text{Si}_2$	67.87	9.15	2.40	67.64	9.12	2.58
(R)-6-acid	$\text{C}_{33}\text{H}_{51}\text{NO}_5\text{Si}_2$	66.29	8.60	2.34	66.68	8.84	2.34
9b	$\text{C}_{15}\text{H}_{22}\text{FN}_3\text{O}_3$	57.86	7.12	13.50	57.71	7.26	13.24

9c	C ₁₅ H ₂₂ ClN ₃ O ₃	54.96	6.76	12.82	54.81	6.64	12.76
9e	C ₁₆ H ₂₂ N ₄ O ₃	60.36	6.97	17.60	60.48	7.13	17.65
9f	C ₁₇ H ₂₈ N ₄ O ₃	60.69	8.39	16.65	60.45	8.53	16.60
9g	C ₁₂ H ₂₅ N ₃ O ₃	55.57	9.72	16.20	55.47	9.82	16.28
9i	C ₁₉ H ₂₅ N ₅ O ₃ ·1/3H ₂ O	60.46	6.85	18.55	60.65	6.98	18.55
9j	C ₁₉ H ₃₀ N ₄ O ₄	60.30	7.99	14.80	60.08	7.82	14.68
9k	C ₂₀ H ₃₂ N ₄ O ₄	61.20	8.22	14.27	61.20	8.32	14.09
9l	C ₁₈ H ₂₅ N ₅ O ₃ ·3/4H ₂ O	57.97	7.16	18.78	57.81	7.15	18.46
9m	C ₁₈ H ₂₅ N ₅ O ₄	57.59	6.71	18.65	57.41	6.81	18.47
9n	C ₁₈ H ₂₄ N ₄ O ₃ S	57.43	6.43	14.88	57.57	6.52	14.71
9o	C ₁₉ H ₂₆ N ₄ O ₃ S·7/6H ₂ O	55.45	6.94	13.61	55.20	6.53	13.20
9p	C ₂₂ H ₃₂ N ₄ O ₃ S	61.08	7.46	12.95	61.14	7.55	12.76
9q	C ₂₀ H ₂₅ N ₅ O ₃ S·1/3H ₂ O	56.99	6.14	16.61	57.07	6.23	16.57
9r	C ₁₉ H ₂₅ ClN ₄ O ₄ S	51.75	5.71	12.71	51.88	5.84	12.54
9s	C ₁₅ H ₂₂ IN ₃ O ₃	42.97	5.29	10.02	43.09	5.44	9.76
12a	C ₃₆ H ₄₆ N ₄ O ₆ ·1/2H ₂ O	67.58	7.40	8.76	67.55	7.28	8.59
12b	C ₃₆ H ₄₅ FN ₄ O ₆ ·1/3H ₂ O	66.04	7.03	8.58	66.13	7.05	8.45
12c	C ₃₆ H ₄₅ ClN ₄ O ₆ ·1/2H ₂ O	64.13	6.88	8.31	64.41	6.70	8.19
12d	C ₃₆ H ₄₅ BrN ₄ O ₆ ·1/2H ₂ O	60.16	6.45	7.80	60.31	6.22	7.65
12e	C ₃₇ H ₄₅ N ₅ O ₆ ·1/2H ₂ O	66.85	6.97	10.53	66.88	6.78	10.38
12f	C ₃₈ H ₅₁ N ₅ O ₆	67.13	7.66	10.30	67.14	7.67	10.26
12g	C ₃₃ H ₄₈ N ₄ O ₆ ·1/2H ₂ O	65.43	8.15	9.25	65.47	8.07	9.22
12h	C ₃₆ H ₄₅ N ₄ O ₆ ·4/3H ₂ O	67.28	7.12	9.57	67.40	6.93	9.43
12i	C ₄₀ H ₄₈ N ₆ O ₆ ·H ₂ O	66.10	6.93	11.56	66.20	6.64	11.38
12j	C ₄₀ H ₅₃ N ₅ O ₇ ·H ₂ O	65.46	7.55	9.54	65.72	7.31	9.42
12k	C ₄₁ H ₅₅ N ₅ O ₇ ·1/2H ₂ O	66.64	7.64	9.48	66.46	7.63	9.36
12l	C ₃₉ H ₄₈ N ₆ O ₆ ·H ₂ O	65.53	7.05	11.76	65.84	6.89	11.78
12m	C ₃₉ H ₄₈ N ₆ O ₇ ·H ₂ O	64.09	6.90	11.50	64.47	6.77	11.50
12n	C ₃₉ H ₄₇ N ₅ O ₆ S·H ₂ O	64.00	6.75	9.57	64.32	6.42	9.50
12o	C ₄₀ H ₄₉ N ₅ O ₆ S·1/2H ₂ O	65.19	6.84	9.50	65.19	6.75	9.50
12p	C ₄₃ H ₅₅ N ₅ O ₆ S·1/2H ₂ O	66.30	7.25	8.99	66.39	7.05	8.89
12q	C ₄₁ H ₄₈ N ₆ O ₆ S·H ₂ O	63.88	6.54	10.90	63.56	6.63	10.78
12r	C ₄₀ H ₄₈ ClN ₅ O ₇ S	61.72	6.22	9.00	61.56	6.38	8.86
12s	C ₃₆ H ₄₅ IN ₄ O ₆	57.14	5.99	7.40	56.92	5.86	7.24
12t	C ₄₂ H ₅₀ N ₄ O ₆ ·H ₂ O	69.59	7.23	7.73	69.89	6.86	7.55
12u	C ₄₁ H ₄₉ N ₅ O ₆ ·H ₂ O	67.84	7.08	9.65	67.98	6.79	9.54
12v	C ₄₁ H ₄₉ N ₅ O ₆ ·H ₂ O	67.84	7.08	9.65	68.10	6.85	9.51
12w	C ₄₀ H ₄₈ N ₄ O ₆ S·H ₂ O	65.73	6.90	7.67	65.84	6.57	7.49
13	C ₄₈ H ₇₃ BrN ₄ O ₆ Si ₂	61.45	7.84	5.97	61.22	7.85	5.84
14	C ₄₂ H ₅₉ BrN ₄ O ₆ Si	61.22	7.22	6.80	60.88	7.15	6.59
15	C ₃₆ H ₄₃ BrN ₄ O ₇ ·1/2H ₂ O	59.02	6.05	7.65	59.10	5.79	7.44

9. HIV protease inhibition

The HIV-1 protease was cloned and heterologously expressed in *Escherichia coli* and purified as described elsewhere.⁵ The K_i values for the synthesized compounds were determined from two individual measurements by a fluorometric assay.⁶ Assay variability was checked by inclusion of a known inhibitor and the standard deviation for the enzyme assays was $\pm 50\%$ of the mean.

10. In vitro anti-HIV activity

The in vitro anti-HIV activity was assayed in MT4 cells according to a previously published procedure⁶ using the colorimetric XTT assay to monitor the cytopathogenic effects.

11. Determination of cytotoxicity

MT4 cells were maintained in RPMI supplemented with 10% heat inactivated fetal calf serum, penicillin (100 U/mL) and streptomycin (100 µg/mL). Briefly, compounds in serial dilutions were added to MT4 cells (2×10^4 cells/well) in microplates. After five days of incubation at 37 °C, the number of viable cells in each well was assessed by using a soluble formazan (XTT) assay⁷ and the concentration causing 50% decrease in cell proliferation (CC_{50}) was determined.

12. Caco-2 cell penetration assay

The transport was measured in one direction (apical to basolateral compartment). 0.1 mL of the apical 1X HBSS buffer (pH 7.4) with a final concentration of 10µM test compound (0.5% DMSO) was added to the apical compartment and after 60 minutes samples were withdrawn from the basolateral compartment. The basolateral buffer (0.6 mL) contained 1% BSA and 1X HBSS. The permeability classification system used: $P_{app} < 2-3 \times 10^{-6}$ cm/s: low permeability, $P_{app} 3 \times 10^{-6}$ cm/s $< 20 \times 10^{-6}$ cm/s: medium permeability, $P_{app} > 20 \times 10^{-6}$ cm/s: high permeability.⁸

13. Metabolic stability

In the stability assay the final volume for each sample was 100µL containing Tris-HCl (pH 7.4), NADPH regenerating system, human liver microsomes and test compound, 1µL of a 100µM solution (final DMSO concentration 0.5%). The test compounds were incubated for 30 minutes at 37°C. The parent compound remaining was analysed by LC-MS/MS.⁸

14. X-ray structure determination details

Production of the protease material and co-crystallization of the inhibitor with the protease was performed at +4 °C by hanging drop procedure according to the procedures described earlier.⁹ The crystals belonged to the space group P21212.

X-ray data were recorded on MarResearch CCD-detectors on the synchrotron beam lines at I911 at MAX-lab Lund, Sweden. Data processing and scaling was performed with MOSFLM¹⁰ and SCALA¹¹ from the CCP4 program suite.¹² The structure was built in O and refined with the CNS programs.^{13, 14} The structure refinements were monitored with the parameters R_{crystal} and R_{free}.¹⁵ PDB-ID for structures **12d** and **15** are 2uxz and 2uy0 respectively. A summary of data collection statistics is given in the table below. Figures were made in O and rendered in Molray¹⁶

15. Table of crystallographic structure determination statistics

Compound in complex	12d	15
Data collection details		
Cell axial lengths (Å)	58.16 86.66 46.54	57.88 85.71 46.61
Resolution range (Å)	15.76-1.75	15.77-1.76
No. of reflections measured	293533	76511
No. of unique reflections	20040	20195
Average multiplicity	4.2(3.9)	4.2(4.0)
Completeness (%)	86.9(85.8)	86.9(85.8)
R _{merge} (%)	0.059(0.14)	0.04(0.074)
$\langle I \rangle / \sigma \langle I \rangle$	8.00 (5.2)	27.95 (10.3)
Refinement statistics		
Resolution range (Å)	15- 1.75	15- 1.75
No. of reflections used in working set	19016	19160
No. of reflections used for R _{free} calculation	1014	1028
R value, R _{free}	0.26 (0.29)	0.23 (0.25)
No. of atoms	1717	1714
No. of solvent waters	154	150
Mean B factor, protein (Å ²)	14.1	14.1
Mean B factor, ligand (Å ²)	17.3	20.2
Mean B factor, solvent (Å ²)	25.0	24.4
Ramachandran plot outliers (%)	0	0
r.m.s. deviation from ideal bond length (Å)	0.007	0.006
r.m.s. deviation from ideal bond angle	1.286	1.31

16. X-ray pictures of 12d, 15 and B

Figure S1: X-ray structure of **12d**. PDB-ID 2uxz, resolution 1,75 Å, R/R_{free} 0.26/0.29. The depicted arrow highlights the lack of hydrogen bonding to Asp 125.

Figure S2: X-ray structure of **15**. PDB-ID 2uy0, resolution 1,76 Å, R/R_{free} 0.23/0.25. The depicted arrow highlights the absences of hydrogen bonding to the carbonyl oxygen.

Figure S3: X-ray structure of **B**. PDB-ID 2bqv, resolution 1.8 Å, R/R_{free} 0.20/0.24.¹⁷ The depicted arrows highlight the two hydrogen bonds to Asp 25 and Asp 125.

17. References

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