# Supporting Information

## Sulfamide as Zinc Binding Motif in Small Molecule Inhibitors of Activated Thrombin Activatable Fibrinolysis Inhibitor (TAFIa)

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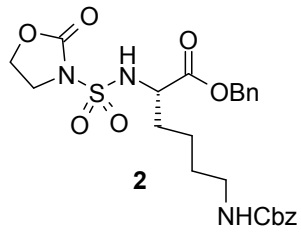
## S1 Chemistry

All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of argon. Starting materials used were available from commercial sources. $^{1}$H-NMR spectra were recorded in the indicated deuterated solvent at 400 or 500 MHz. Purity of all compounds tested in biological assays were determined to be of >95% purity by LCMS.

All sulfamides were prepared according to Scheme 1 as exemplified by the synthesis of **7a**.

*(S)-6-Benzyloxycarbonylamino-2(2-oxo-oxazolidine-sulfonylamino)-hexanoic acid benzyl ester* **2**

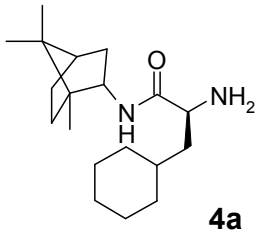



**2**

To a solution of 5.21 g chlorosulfonylisocyanate (36.9 mmol, 1.0 equiv.) in dichloromethane (300 mL) under argon at 0 °C was slowly added a solution of 2.61 mL 2-bromoethanol (36.9 mmol, 1.0 equiv.) in dichloromethane (20 mL) at a rate so that the internal temperature was kept below 10 °C. After addition the reaction mixture was allowed to stir for an additional 30 min at 0 °C. To this solution was dropwise added a mixture of 15.00 g H-Lys(Z)-OBzL•HCl (36.9 mmol, 1.0 equiv.) and 16.5 mL triethylamine (118.0 mmol, 3.2 equiv.) in 120 mL $CH_2Cl_2$, keeping the temperature of the reaction mixture below 10 °C. After addition the ice bath was removed and the mixture stirred at ambient temperature for 4 hours. Then the reaction mixture was washed three times with 100 mL 0.2M HCl (aq.), dried over $Na_2SO_4$ and evaporated to afford 18.4 g of the crude title compound **2** as a

colorless oil that was used directly in the next step. $^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.24-1.44 (m, 4H), 1.54-1.63 (m, 1H), 1.68-1.77 (m, 1H), 2.95 (q, 2H, *J* = 6.5 Hz), 3.85 (q, 1H, *J* = 7.8 Hz), 3.94 (q, 1H, *J* = 8.6 Hz), 4.08-4.14 (m, 1H), 4.27 (t, 2H, *J* = 8.2 Hz), 5.00 (s, 2H), 5.12 (s, 2H), 7.18-7.25 (m, 1H), 7.27-7.42 (m, 10H), 9.05 (d, 1H, *J* = 8.4 Hz); MS (ES+) Calcd.: [M+H] 520.17, Found. 520.30.

*[(S)-2-Cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester* **4a**

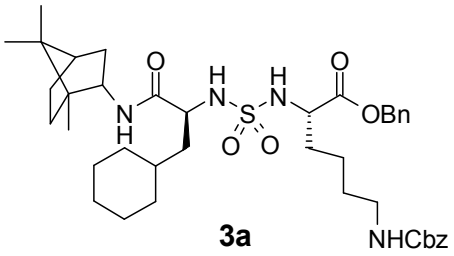



**4a**

To a solution of 5.0 g (S)-2-tert-butoxycarbonylamino-3-cyclohexyl-propionic acid (Boc-Cha-OH, 18.4 mmol, 1.0 equiv.) in DMF (60 mL) under argon at 0 °C was added 3.53 g 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (18.4 mmol, 1.0 equiv.), 1.25 g 1-hydroxybenzotriazole (9.2 mmol, 0.5 equiv.) and 7.3 mL Hünigs base and the mixture was stirred for 30 min. Then 2.83 g (R)-(+)-bornylamine (18.4 mmol, 1.0 equiv.) and 3.7 mL Hünigs base were added and the reaction stirred for 16 h at ambient temperature. The reaction mixture was quenched with $NaHCO_3$ (sat, aq) and extracted with EtOAc three times. The combined organic phases were washed with water two times and dried over $Na_2SO_4$ before evaporation. Purification by flash chromatography using silica gel as the stationary phase and heptane/EtOAc as the eluent afforded 6.58 g (88% yield) of the title compound as a colorless solid. $^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.65 (s, 3H), 0.80-0.91 (m, 3H), 0.82 (s, 3H) 0.89, (s, 3H), 1.06-1.41 (m, 7H), 1.37 (s, 9H), 1.56-1.74 (m, 8H), 2.06-2.16 (m, 1H), 4.02 (q, 2H,

*J* = 7.6 Hz), 4.09 (m, 1H), 6.67 (d, 1H, *J* = 8.1 Hz), 7.56 (d, 1H, *J* = 8.6 Hz); MS (ES+) Calcd.: [M+H] 407.33, Found. 407.32.

(*S)-6-Benzyloxycarbonylamino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexanoic acid benzyl ester* **3a**

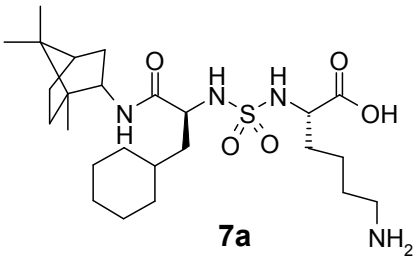



**3a**

To a solution of 6.5 g [(S)-2-Cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester **4a** (16.0 mmol) in 50 mL $CH_2Cl_2$ under argon at 0 °C was slowly added 50 mL TFA and the reaction was allowed to warm to ambient temperature. After 3h the reaction mixture was evaporated to remove excess TFA and $CH_2Cl_2$ to afford 4.9 g of crude (S)-2-Amino-3-cyclohexyl-N-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-propionamide trifluoroacetic acid salt (16.0 mmol, 1.0 equiv.) as a slightly yellow oil that was dissolved in MeCN (80 mL) and 8.9 mL $Et_3N$ was added together with 11.63 g (S)-6-Benzyloxycarbonylamino-2(2-oxo-oxazolidine-sulfonylamino)-hexanoic acid benzyl ester **2** (22.4 mmol, 1.4 equiv.). The reaction mixture was heated to reflux for 20h. After cooling the volatiles were evaporated and the crude reaction mixture purified directly by flash chromatography using silica gel as the stationary phase and heptane/EtOAc as the eluent. This afforded 9.0 g (76% yield) of (*S*)-6-Benzyloxycarbonylamino-2-{[(*S*)-2-cyclohexyl-1-((1*R*,2*S*,4*R*)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexanoic acid benzyl ester **3a** as a colorless foam after evaporation. $^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.79-0.92 (m, 3H), 0.81 (s, 3H) 0.86, (s, 3H), 1.05-1.43 (m, 12H), 1.37,

1.53-1.79 (m, 10H), 2.06-2.15 (m, 1H), 2.93 (q, 2H, *J* = 6.4 Hz), 3.73-3.83 (m, 2H), 4.08 (m, 1H), 4.99 (s, 2H), 5.12 (d, 2H, *J* = 5.2 Hz), 6.96 (d, 1H, *J* = 8.9 Hz), 7.18-7.22 (m, 2H), 7.28-7.41 (m, 10H), 7.64 (d, 1H, *J* = 8.8 Hz); MS (ES+) Calcd.: [M+H] 739.41, Found. 739.43.

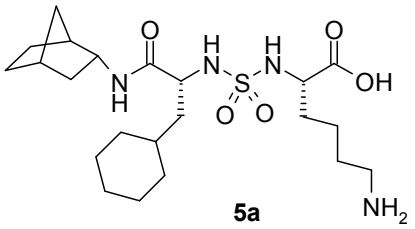
*(S)-6-Amino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexanoic acid* **7a**




**7a**

9.0 g (*S*)-6-Benzyloxycarbonylamino-2-{[(*S*)-2-cyclohexyl-1-((1*R*,2*S*,4*R*)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexanoic acid benzyl ester **3a** (12.2 mmol) was dissolved in 90 mL methanol and 600 mg 10% Pd/C was added and the reaction flask was kept under a hydrogen atmosphere at ambient temperature and pressure and stirred for 3.5h. The reaction mixture was then filtered using celite filter aid and evaporated under vacuum to afford 6.1g (97%) of the title compound as a colorless oil. The product was dissolved in MeCN and water was added to afford a suspension in a 1:10 MeCN/water mixture. The solvents were removed by freeze drying to afford the title compound as a colorless solid. $^{1}$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.82 (s, 3H), 0.83-0.91 (m, 2H), 0.89 (s, 3H), 0.97 (dd, 1H, *J* = 4.8, 13.0 Hz), 1.08-1.34 (m, 7H), 1.35-1.55 (m, 5H), 1.56-1.72 (m, 9H), 1.78 (d, 1H, *J* = 13.0 Hz), 2.04-2.13 (m. 1H), 2.75 (t, 2H, *J* = 7.1 Hz), 3.51 (t, 1H, *J* = 5.5 Hz), 3.83 (t, 1H, *J* = 7.0 Hz), 4.03-4.10 (m, 1H), 6.91-7.05 (br, 1H), 7.77 (d, 1H, *J* = 8.8 Hz), 7.5-8.2 (br, 2H); MS (ES+) Calcd.: [M+H] 515.33, Found. 515.35.

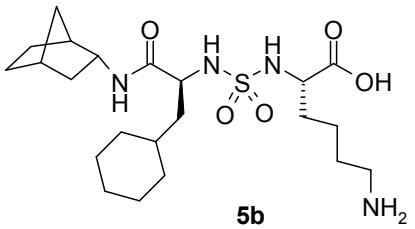
(2S)-6-amino-2-[[(1R)-1-(cyclohexylmethyl)-2-(norbornan-2-ylamino)-2-oxo-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid (mixture of diastereomers) **5a**



**5a**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.78-0.92 (m, 3H), 1.06-1.19 (m, 3H), 1.21-1.40 (m, 9H), 1.43-1.67 (m, 10H), 1.72 (d, 2H, *J* = 12.4 Hz), 2.14 (s, 1H), 2.22 (s, 1H), 1.06-1.19 (m, 2H), 3.62 (quintet, 1H, *J* = 7.2 Hz), 3.74 (q, 1H, *J* = 7.5 Hz), 3.80-3.93 (m, 1H), 6.97 (d, 1H, *J* = 8.5 Hz), 6.99 (d, 1H, *J* = 8.5 Hz), 7.60-7.70 (br, 3H), 7.83 (d, 1H, *J* = 7.0 Hz), 12.67 (br s, 1H); MS (ES+) Calcd.: [M+H] 473.28, Found. 473.36.

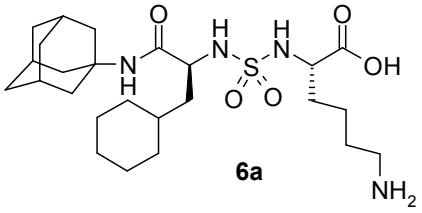
(*2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-(norbornan-2-ylamino)-2-oxo-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* (mixture of diastereomers) **5b**



**5b**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.78-0.91 (m, 3H), 1.08-1.19 (m, 3H), 1.20-1.41 (m, 9H), 1.44-1.75 (m, 11H), 1.80-1.89 (m, 1H), 2.14 (s, 1H), 2.22 (s, 0.5H), 2.28 (s, 0.5H), 2.71-2.80 (m, 2H), 3.68 (quintet, 1H, *J* = 7.1 Hz), 3.75 (quintet, 1H, *J* = 8.1 Hz), 3.79-3.91 (m, 1H), 6.79 (d, 0.5H, *J* = 7.6 Hz), 6.90-6.95 (m, 1.5H), 7.63 (br, 3H), 7.67 (d, 0.5H, *J* = 7.0 Hz), 7.67 (d, 0.5H, *J* = 7.0 Hz), 12.75 (br, 1H); MS (ES+) Calcd.: [M+H] 473.28, Found. 473.30.

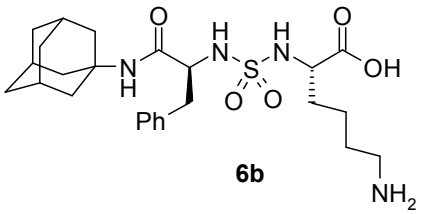
(*2S)-2-[[(1S)-2-(1-adamantylamino)-1-(cyclohexylmethyl)-2-oxo-ethyl]sulfamoylamino]-6-amino-hexanoic acid; 2,2,2-trifluoroacetic acid* **6a**



**6a**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.77-0.91 (m, 2H), 1.06-1.21 (m, 3H), 1.28-1.41 (m, 5H), 1.51 (quintet, 2H, *J* = 7.5 Hz), 1.55-1.75 (m, 6H); 1.61 (s, 6H), 1.90 (s, 6H), 2.00 (s, 3H), 2.71-2.79 (m, 2H), 3.60-3.69 (m, 3H), 6.82 (d, 1H, *J* = 8.6 Hz), 6.97 (d, 1H, *J* = 8.2 Hz), 7.17 (s, 1H), 7.62 (br, 3H), 12.76 (br, 1H); MS (ES+) Calcd.: [M+H] 513.31, Found. 513.33.

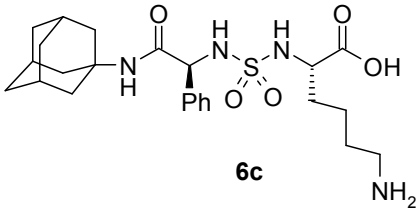
*(2S)-2-[[(1S)-2-(1-adamantylamino)-1-benzyl-2-oxo-ethyl]sulfamoylamino]-6-amino-hexanoic acid; 2,2,2-trifluoroacetic acid* **6b**



**6b**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.07-1.23 (m, 2H), 1.23-1.33 (m, 1H), 1.36-1.49 (m, 3H), 1.60 (s, 6H), 1.86 (s, 6H), 1.99 (s, 3H), 2.68-2.78 (m, 3H), 2.83 (dd, 1H, *J* = 5.7, 13.3 Hz), 3.30-3.35 (m, 1H), 3.80 (dt, 1H, *J* = 6.0, 8.4 Hz), 6.91 (d, 1H, *J* = 9.2 Hz), 6.93 (d, 1H, *J* = 8.5 Hz), 7.19-7.29 (m, 6H), 7.65 (br, 3H), 12.64 (br, 1H); MS (ES+) Calcd.: [M+H] 507.26, Found. 507.24.

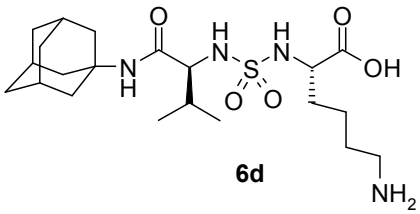
(*2S)-2-[[(1S)-2-(1-adamantylamino)-2-oxo-1-phenyl-ethyl]sulfamoylamino]-6-amino-hexanoic acid; 2,2,2-trifluoroacetic acid* **6c**



**6c**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.11-1.19 (m, 1H), 1.25-1.41 (m, 2H), 1.43-1.63 (m, 2H), 1.59 (s, 6H), 1.86 (d, 6H, *J* = 5.6 Hz), 1.99 (s, 3H), 2.61-2.69 (m, 1H), 2.71-2.78 (m, 1H), 3.32-3.34 (m, 1H), 3.55 (q, 0.5H, *J* = 6.8 Hz), 3.65 (q, 0.5H, *J* = 6.9 Hz), 4.83 (t, 1H, *J* = 8.6 Hz), 7.15-7.44 (m, 8H), 7.53-7.66 (m, 3H), 12.69 (br, 1H); MS (ES+) Calcd.: [M+H] 493.25, Found. 493.28.

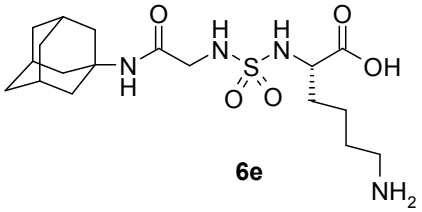
*(2S)-2-[[(1S)-1-(1-adamantylcarbamoyl)-2-methyl-propyl]sulfamoylamino]-6-amino-hexanoic acid; 2,2,2-trifluoroacetic acid* **6d**



**6d**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.80 (d, 3H, *J* = 6.8 Hz), 0.87 (d, 3H, *J* = 6.8 Hz), 1.26-1.44 (m, 2H), 1.51 (quintet, 2H, *J* = 6.8 Hz), 1.56-1.72 (m, 2H), 1.61 (s, 6H), 1.84 (sextet, 1H, *J* = 6.7 Hz), 1.92 (s, 6H), 2.00 (s, 3H), 2.76 (br, 2H), 3.42-3.46 (m, 1H), 3.66-3.72 (m, 1H), 6.45 (d, 1H, *J* = 8.8 Hz), 7.01 (d, 1H, *J* = 8.3 Hz), 7.31 (s, 1H), 7.61 (br, 3H), 12.76 (br, 1H); MS (ES+) Calcd.: [M+H] 459.26, Found. 459.26.

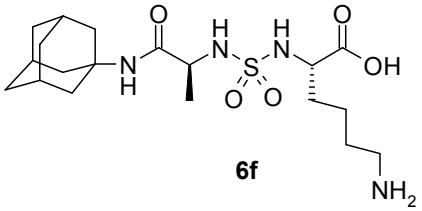
*(2S)-2-[[2-(1-adamantylamino)-2-oxo-ethyl]sulfamoylamino]-6-amino-hexanoic acid; 2,2,2-trifluoroacetic acid* **6e**



**6e**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.31-1.41 (m, 2H), 1.46-1.69 (m, 4H), 1.62 (s, 6H), 1.91 (s, 6H), 2.01 (s, 3H), 2.76 (br, 2H), 3.36-3.41 (m, 2H), 3.66-3.74 (m, 1H), 6.90 (t, 1H, *J* = 5.8 Hz), 7.12 (s, 1H), 7.33 (d, 1H, *J* = 8.8 Hz), 7.63 (br, 3H), 12.67 (br, 1H); MS (ES+) Calcd.: [M+H] 417.22, Found. 417.13.

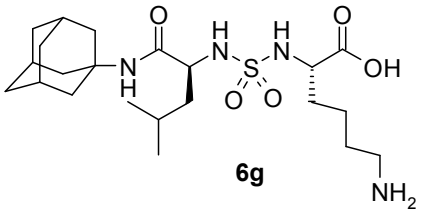
(2S)-2-[[(1S)-2-(1-adamantylamino)-1-methyl-2-oxo-ethyl]sulfamoylamino]-6-amino-hexanoic acid; 2,2,2-trifluoroacetic acid **6f**



**6f**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.18 (d, 3H, *J* = 7.0 Hz), 1.36 (quintet, 2H, *J* = 6.9 Hz), 1.47-1.70 (m, 4H), 1.62 (s, 6H), 1.91 (s, 6H), 2.00 (s, 3H), 2.76 (br, 2H), 3.59-3.71 (m, 2H), 6.94 (d, 1H, *J* = 8.0 Hz), 7.05 (s, 1H), 7.15 (d, 1H, *J* = 8.5 Hz), 7.62 (br, 3H), 12.60 (br, 1H); MS (ES+) Calcd.: [M+H] 431.23, Found. 431.13.

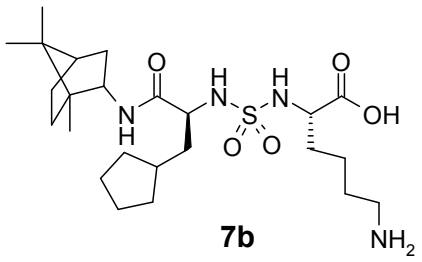
(2S)-2-[[(1S)-1-(1-adamantylcarbamoyl)-3-methyl-butyl]sulfamoylamino]-6-amino-hexanoic acid; 2,2,2-trifluoroacetic acid **6g**



**6g**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.86 (d, 3H, *J* = 6.6 Hz), $\delta$ 0.87 (d, 3H, *J* = 6.6 Hz), 1.29-1.42 (m, 4H), 1.51 (quintet, 2H, *J* = 7.6 Hz), 1.55-1.71 (m, 3H), 1.61 (s, 6H), 1.91 (s, 6H), 2.00 (s, 3H), 2.75 (br, 2H), 3.61 (q, 1H, J = 8.0 Hz), 3.68 (q, 1H, *J* = 7.4 Hz), 6.85 (d, 1H, *J* = 8.6 Hz), 6.98 (d, 1H, *J* = 8.1 Hz), 7.19 (s, 1H), 7.63 (br, 3H), 12.76 (br, 1H); MS (ES+) Calcd.: [M+H] 473.28, Found. 473.29.

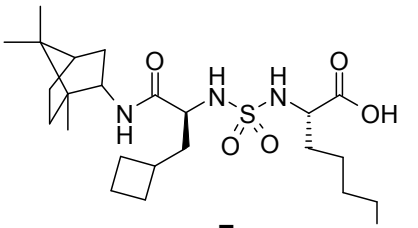
(2S)-6-amino-2-[[(1S)-1-(cyclopentylmethyl)-2-oxo-2-[[(1*R*,2*S*,4*R*)-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]hexanoic acid hydrochloride **7b**



**7b**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.67 (s, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 0.89-0.93 (m, 1H), 1.00-1.14 (m, 2H), 1.15-1.29 (m, 2H), 1.29-1.87 (m, 17H), 2.08-2.17 (m, 1H), 2.69-2.78 (m, 2H), 3.69 (q, 1H, *J* = 6.2 Hz), 3.75 (q, 1H, *J* = 7.5 Hz), 4.07 (br, 1H), 6.87-6.92 (m, 2H), 7.70 (d, 2H, *J* = 8.5 Hz), 7.81 (br, 3H), 12.76 (br, 1H); MS (ES+) Calcd.: [M+H] 501.31, Found. 501.44.

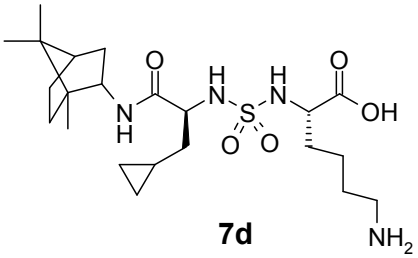
*(2S)-6-amino-2-[[(1S)-1-(cyclobutylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]hexanoic acid* **7c**



**7c**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.83 (s, 3H), 0.88 (s, 3H), 0.99 (dd, 1H, *J* = 4.6, 13.0 Hz), 1.15-1.25 (m, 2H), 1.30-1.37 (m, 1H), 1.38-1.82 (m, 14H), 1.93-2.11 (m, 3H), 2.29 (quintet, 1H, *J* = 7.9 Hz), 2.71-2.81 (m, 2H), 3.61 (t, 1H, *J* = 6.9 Hz), 4.04 (br, 1H), 7.05 (br, 1H), 7.73 (d, 1H, J = 8.7 Hz); MS (ES+) Calcd.: [M-H] 485.28, Found. 485.39.

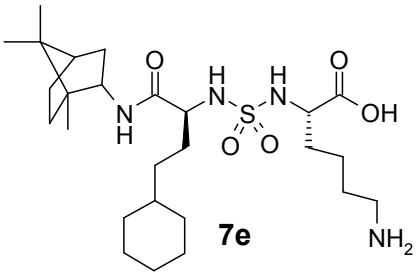
*(2S)-6-amino-2-[[(1S)-1-(cyclopropylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]hexanoic acid hydrochloride* (mixture of diastereomers) **7d**



**7d**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.01-0.10 (m, 2H), 0.32-0.43 (m, 2H), 0.66-0.74 (m, 1H), 0.68 (s, 1.5H), 0.73 (s, 1.5H), 0.82 (s, 1.5H), 0.83 (s, 1.5H), 0.84-0.91 (m, 1H), 0.89 (s, 3H), 1.15-1.27 (m, 2H), 1.28-1.78 (m, 11H), 2.13 (br, 1H), 2.70-2.80 (m, 2H), 3.63-2.72 (m, 1H), 3.73-3.85 (m, 1H), 3.99-4.10 (m, 1H), 6.91 (d, 0.5H, *J* = 8.8 Hz), 6.93-6.99 (m, 1H), 7.12 (d, 0.5H, *J* = 8.8 Hz), 7.63 (br, 4H), 12.72 (br, 1H); MS (ES+) Calcd.: [M+H] 473.28, Found. 473.39.

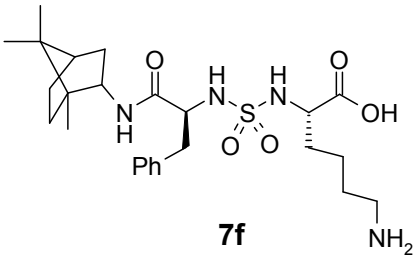
*(2S)-6-amino-2-[[(1S)-3-cyclohexyl-1-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]carbamoyl]propyl]sulfamoylamino]hexanoic acid* **7e**



**7e**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.67 (s, 3H), 0.82 (s, 3H), 0.75-0.86 (m, 2H), 0.88 (s, 3H), 0.98 (dd, 1H, *J* = 4.6, 13.0 Hz), 1.06-1.23 (m, 8H), 1.27-1.34 (m, 1H), 1.36-1.54 (m, 3H), 1.55-1.70 (m, 12H), 2.03-2.12 (m, 1H), 2.69-2.79 (m, 2H), 3.37 (t, 1H, *J* = 4.9 Hz), 3.72 (t, 1H, *J* = 6.3 Hz), 4.06 (br, 1H), 6.97 (br, 1H), 7.77 (d, 1H, *J* = 8.7 Hz), 8.04 (br, 2H); MS (ES+) Calcd.: [M+H] 529.34, Found. 529.34.

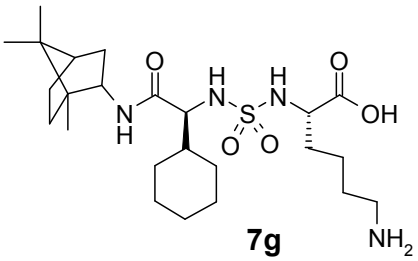
(*2S)-6-amino-2-[[(1S)-1-benzyl-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* **7f**



**7f**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.57 (s, 3H), 0.77-0.87 (m, 2H), 0.80 (s, 3H), 0.87 (s, 3H), 1.03-1.23 (m, 4H), 1.24-1.69 (m, 7H), 2.06-2.17 (m, 1H), 2.67-2.89 (m, 4H), 3.35 (q, 1H, *J* = 6.6 Hz), 3.86-4.07 (m, 2H), 6.84 (d, 1H, *J* = 8.2 Hz), 7.08 (d. 1H, *J* = 9.4 Hz), 7.16-7.31 (m, 5H), 7.65 (br, 3H), 12.63 (br, 1H); MS (ES+) Calcd.: [M+H] 509.28, Found. 509.40.

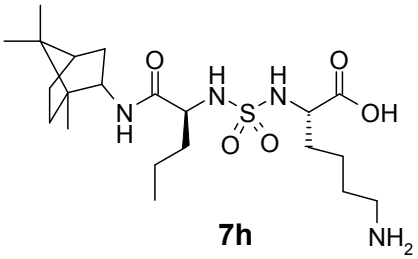
*(2S)-6-amino-2-[[(1S)-1-cyclohexyl-2-oxo-2-[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl)amino]ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* **7g**



**7g**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.69 (s, 3H), 0.83 (s, 3H), 0.85-0.90 (m, 1H), 0.89 (s, 3H), 0.93-1.73 (m, 22H), 2.09-2.20 (m, 1H), 2.70-2.81 (m, 2H), 3.64 (dd, 1H, J = 5.5, 8.9 Hz), 3.69 (q, 1H, J = 7.0 Hz), 4.08 (br, 1H), 6.46 (d, 1H, J = 9.2 Hz), 6.93 (d, 1H, J = 8.1 Hz), 7.64 (br, 3H), 7.73 (d, 1H, J = 8.6 Hz), 12.74 (br, 1H); MS (ES+) Calcd.: [M+H] 501.31, Found. 501.29.

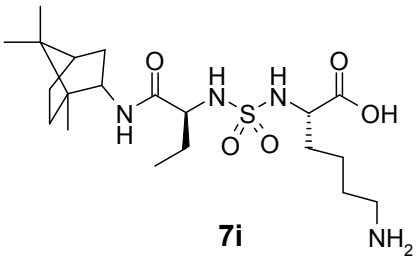
*(2S)-6-amino-2-[[(1S)-1-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]carbamoyl]butyl]sulfamoylamino]hexanoic acid* **7h**



**7h**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.67 (s, 3H), 0.82 (s, 3H), 0.86 (t, 3H, *J* = 8.6 Hz), 0.89 (s, 3H), 096(dd, 1H, *J* = 4.7, 12.9 Hz), 1.14-1.34 (m, 5H), 1.36-1.71 (m, 10H), 2.04-2.13 (m, 1H), 2.68-2.77 (m, 2H), 3.39 (t, 1H, *J* = 5.0 Hz), 3.75 (t, 1H, *J* = 6.8 Hz), 4.03-4.10 (m, 1H), 7.06 (br, 1H), 7.75 (d, 1H, *J* = 8.8 Hz); MS (ES+) Calcd.: [M+H] 461.28, Found. 461.23.

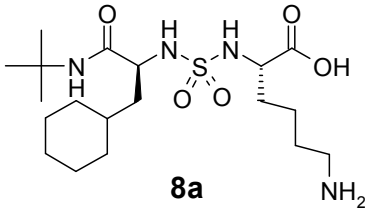
*(2S)-6-amino-2-[[(1S)-1-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]carbamoyl]propyl]sulfamoylamino]hexanoic acid* **7i**



**7i**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.80-0.86 (m, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 0.94 (dd, 1H, *J* = 4.6, 12.9 Hz), 1.31-1.34 (m, 3H), 1.34-1.71 (m, 10H), 2.05-2.15 (m, 1H), 2.73-2.80 (t, 2H, *J* = 6.9 Hz), 3.45-3.49 (m, 2H), 3.67-3.73 (m, 2H), 4.03-4.12 (m, 1H), 6.96 (br, 1H), 7.74 (d, 1H, *J* = 8.8 Hz); MS (ES+) Calcd.: [M+H] 447.26, Found. 447.28.

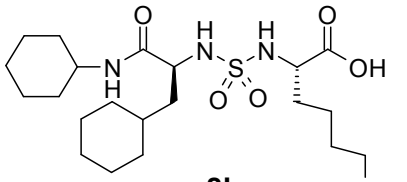
*(2S)-6-amino-2-[[(1S)-2-(tert-butylamino)-1-(cyclohexylmethyl)-2-oxo-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* **8a**



**8a**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.83 (quintet, 2H, *J* = 10.6 Hz), 1.06-1.21 (m, 3H), 1.24 (s, 9H), 1.28-1.42 (m, 5H), 1.48-1.75 (m, 9H), 2.71-2.80 (m, 2H), 3.62-3.70 (m, 2H), 6.82 (d, 1H, *J* = 8.8 Hz), 6.96 (d, 1H, *J* = 8.2 Hz), 7.33 (s, 1H), 7.67 (br, 3H), 12.74 (br, 1H); MS (ES+) Calcd.: [M+H] 435.26, Found. 435.28.

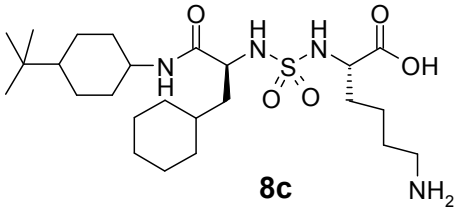
*(2S)-6-amino-2-[[(1S)-2-(cyclohexylamino)-1-(cyclohexylmethyl)-2-oxo-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* **8b**



**8b**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.84 (quintet, 2H, *J* = 11.3 Hz), 1.07-1.41 (m, 13H), 1.47-1.75 (m, 14H), 2.71-2.79 (m, 2H), 3.45-3.53 (m, 1H), 3.65-3.71 (m, 2H), 6.87 (d, 1H, *J* = 7.9 Hz), 6.92 (d, 1H, *J* = 8.7 Hz), 7.64 (br, 3H), 7.66 (d, 1H, *J* = 7.8 Hz), 12.75 (br, 1H); MS (ES+) Calcd.: [M+H] 461.28, Found. 461.27.

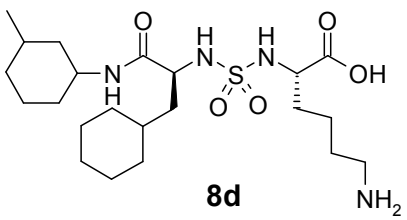
(*2S)-6-amino-2-[[(1S)-2-[(4-tert-butylcyclohexyl)amino]-1-(cyclohexylmethyl)-2-oxo-ethyl]sulfamoylamino]hexanoic acid (mixture of diastereomers)* **8c**



**8c**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.82 (s, 9H), 0.82-0.84 (m, 2H), 0.89-1.04 (m, 3H), 1.07-1.22 (m, 6H), 1.26-1.53 (m, 7H), 1.56-1.86 (m, 11H), 2.68-2.78 (m, 2H), 3.36-3.41 (m, 2H), 3.66 (t, 0.6H, *J* = 7.9 Hz), 3.77-3.83 (m, 0.4H), 7.07 (br, 1H), 7.77 (d, 1H, *J* = 7.8 Hz), 8.0 (br, 2H); MS (ES+) Calcd.: [M+H] 517.34, Found. 517.49.

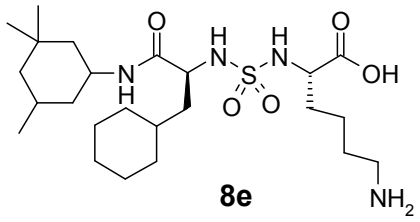
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-[(3-methylcyclohexyl)amino]-2-oxo-ethyl]sulfamoylamino]hexanoic acid* (mixture of diastereomers) **8d**



**8d**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.70-0.88 (m, 6H), 0.91-1.79 (m, 25H), 2.68-2.79 (m, 2H), 3.36-3.41 (m, 1H), 3.43-3.53 (m, 1H), 3.62-3.89 (m, 1H), 7.10 (br, 1H), 7.63-7.81 (m, 1H), 7.95 (br, 2H); MS (ES+) Calcd.: [M+H] 475.30, Found. 475.45.

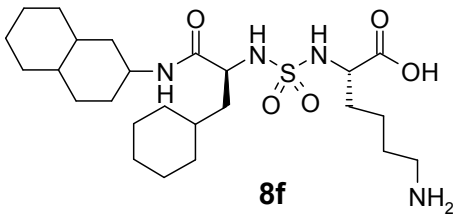
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[(3,3,5-trimethylcyclohexyl)amino]ethyl]sulfamoylamino]hexanoic acid* (mixture of diastereomers) **8e**




**8e**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.61-0.74 (m, 2H), 0.77-0.99 (m, 12H), 1.06-1.23 (m, 4H), 1.26-1.78 (m, 18), 2.68-2.78 (m, 2H), 3.40 (t, 1H, *J* = 5.0 Hz), 3.62-3.74 (m, 2H), 7.09 (br, 1H), 7.71 (d, 1H, *J* = 8.0 Hz), 8.02 (br, 2H); MS (ES+) Calcd.: [M+H] 503.33, Found. 503.49.

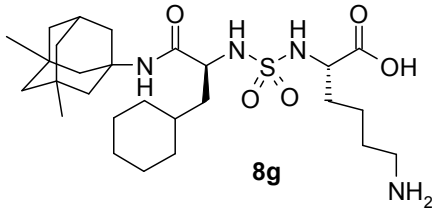
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-(decalin-2-ylamino)-2-oxo-ethyl]sulfamoylamino]hexanoic acid* (mixture of diastereomers) **8f**




**8f**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.76-0.97 (m, 3H), 1.06-1.79 (m, 33H), 2.67-2.76 (m, 2H), 3.38-3.53 (m, 2H), 3.61-3.70 (m, 1H), 7.07 (br, 1H), 7.63-7.83 (m, 1H), 8.07 (br, 2H); MS (ES+) Calcd.: [M+H] 515.33, Found. 515.34.

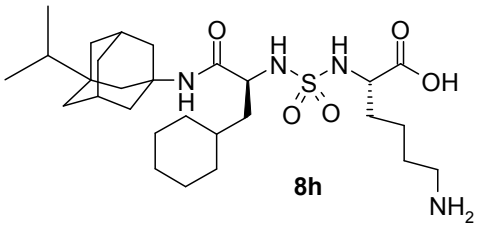
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-[(3,5-dimethyl-1-adamantyl)amino]-2-oxo-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* **8g**




**8g**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.77-0.88 (m, 2H), 0.81 (s, 6H), 1.08-1.40 (m, 14H), 1.48-1.75 (m, 15H), 2.04-2.09 (m, 1H), 2.72-2.79 (m, 2H), 3.59-3.68 (m, 2H), 6.77 (d, 1H, *J* = 8.6 Hz), 6.99 (d, 1H, *J* = 8.2 Hz), 7.18 (s, 1H), 7.62 (br, 3H), 12.74 (br,1H); MS (ES+) Calcd.: [M+H] 541.34, Found. 541.39.

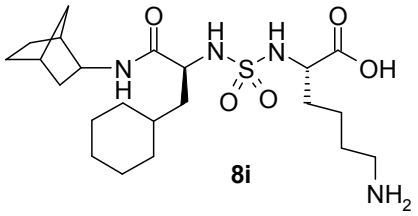
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-[(3-isopropyl-1-adamantyl)amino]-2-oxo-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* **8h**




**8h**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.78 (s, 3H), 0.79 (s, 3H), 0.80-0.88 (m, 2H), 1.05-1.19 (m, 3H), 1.23 (quintet, 1H, *J* = 6.8 Hz), 1.29-1.41 (m, 9H), 1.46-1.81 (m, 15H), 1.85-1.93 (m, 2H), 2.06 (s, 2H), 2.75 (sextet, 2H, *J* = 6.6 Hz), 3.59-3.68 (m, 2H), 6.79 (d, 1H, *J* = 8.6 Hz), 6.98 (d, 1H, *J* = 8.2 Hz), 7.18 (s, 1H), 7.65 (br, 3H), 12.74 (br, 1H); MS (ES+) Calcd.: [M+H] 555.36, Found. 555.36.

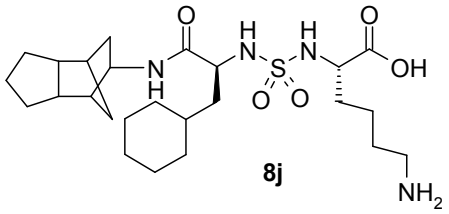
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-[[(1R,2R,4S)-norbornan-2-yl]amino]-2-oxo-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* (mixture of diastereomers) **8i**



**8i**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.77-0.89 (m, 2H), 1.03-1.25 (m, 7H), 1.26-1.74 (m, 19), 1.99-2.21 (m, 2H), 2.71-2.79 (m, 2H), 3.63-3.71 (m, 2H), 6.81-6.95 (m, 2H), 7.53-7.65 (m, 1H), 7.63 (br, 1H), 12.75 (br, 1H); MS (ES+) Calcd.: [M+H] 473.28, Found. 473.30.

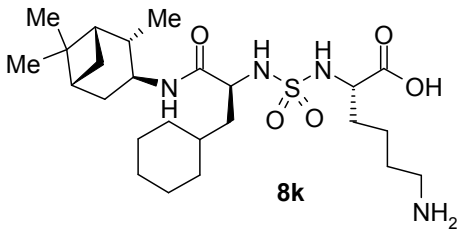
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-[octahydro-4,7-methano-inden-5-ylamino]-2-oxo-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* (mixture of diastereomers) **8j**



**8j**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.77-0.88 (m, 2H), 1.04-1.20 (m, 4H), 1.26-1.74 (m 22H), 1.83-1.98 (m, 2H), 2.06-2.15 (m, 1H), 2.24-2.41 (m, 2H), 2.71-2.79 (m, 2H), 3.62-3.70 (m, 2H), 3.72-3.77 (m, 1H), 6.83-6.86 (m, 1H), 6.91 (d, 0.5H, *J* = 8.1 Hz), 6.98 (d, 0.5H, *J* = 8.4 Hz), 7.60 (d, 0.5H, *J* = 7.1 Hz), 7.64 (d, 0.5H, *J* = 7.1 Hz), 7.66 (br, 3H), 12.73 (br, 1H); MS (ES+) Calcd.: [M+H] 513.31, Found. 513.34.

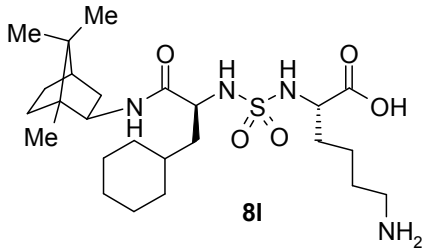
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]amino]ethyl]sulfamoylamino]hexanoic acid* **8k**




**8k**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.77-0.89 (m, 2H), 0.97 (d, 3H, *J* = 7.2 Hz), 0.99 (s, 3H), 1.05-1.22 (m, 5H), 1.20 (s, 3H), 1.24-1.32 (m, 1H), 1.34-1.44 (m, 2H), 1.46-1.53 (m, 3H), 1.54-1.69 (m, 7H), 1.71-1.77 (m, 2H), 1.83-1.89 (m, 2H), 2.26-2.34 (m, 2H), 2.68-2.78 (m, 2H), 3.40 (t, 1H, *J* = 5.1 Hz), 3.71 (t, 1H, *J* = 7.4 Hz), 4.03 (quintet, 1H, *J* = 7.3 Hz), 7.04 (br, 1H), 7.97 (d, 1H, *J* = 8.4 Hz), 8.06 (br, 2H); MS (ES+) Calcd.: [M+H] 515.33, Found. 513.56.

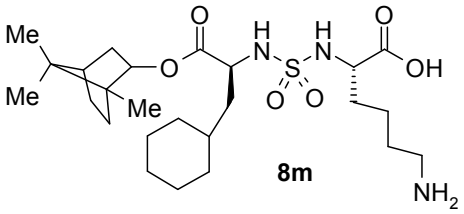
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[(1R,2R,4R)-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* **8l**




**8l**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.73-0.89 (m, 2H), 0.77 (s, 3H), 0.78 (s, 3H), 0.91 (s, 3H), 1.05-1.20 (m, 5H), 1.29-1.42 (m, 5H), 1.46-1.73 (m, 14H), 2.71-2.79 (m, 2H), 3.59-3.74 (m, 3H), 6.94 (d, 1H, *J* = 8.2 Hz), 7.11 (d, 1H, *J* = 8.3 Hz), 7.14 (d, 1H, *J* = 8.2 Hz), 7.64 (br, 3H), 12.70 (br, 1H); MS (ES+) Calcd.: [M+H] 515.33, Found. 515.51.

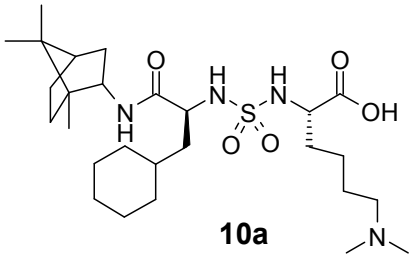
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-(1,7,7-trimethylnorbornan-2-yl)oxy-ethyl]sulfamoylamino]hexanoic acid; 2,2,2-trifluoroacetic acid* **8m**




**8m**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.78-0.96 (m, 3H), 0.80 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 1.08-1.88 (m, 21H), 1.90-2.00 (m, 1H), 2.20-2.30 (m, 1H), 2.71-2.81 (m, 2H), 3.62 (q, 1H, *J* = 7.6 Hz), 3.80 (q, 1H, *J* = 7.6 Hz), 4.77 (d, 1H, *J* = 9.6 Hz), 7.20 (d, 1H, *J* = 8.5 Hz), 7.43 (d, 1H, *J* = 8.8 Hz), 7.66 (br, 3H), 12.61 (br, 1H); MS (ES+) Calcd.: [M+H] 516.31, Found. 516.47.

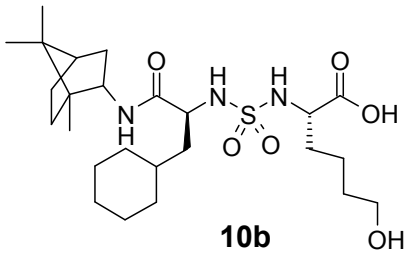
*(2S)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-6-dimethylamino-hexanoic acid; 2,2,2-trifluoroacetic acid* **10a**




**10a**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.80-0.93 (m, 3H), 0.83 (s, 3H), 0.89 (s, 3H), 1.06-1.42 (m, 9H), 1.49-1.80 (m, 11H), 2.06-2.11 (m, 2H), 2.75 (s, 3H), 2.76 (s, 3H), 2.97-3.04 (m, 2H), 3.71 (q, 1H, *J* = 6.9 Hz), 3.81 (quintet, 1H, *J* = 7.8 Hz), 4.04-4.13 (m, 2H), 6.83-7.00 (m, 2H), 7.65-7.71 (m, 1H), 9.24 (br, 1H), 12.75 (br, 1H); MS (ES+) Calcd.: [M+H] 543.36, Found. 543.54.

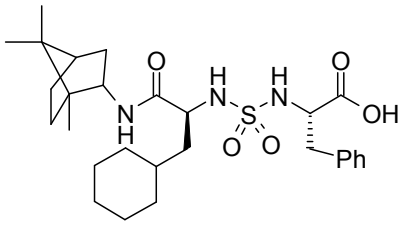
(*2S)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-6-hydroxy-hexanoic acid* **10b**



**10b**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.80-0.91 (m, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 1.07-1.43 (m, 13H), 1.54-1.79 (m, 11H), 2.08-2.16 (m, 1H), 3.65 (q, 1H, *J* = 6.5 Hz), 3.78 (q, 1H, *J* = 7.2 Hz), 4.04-4.11 (m, 1H), 4.33-4.38 (m, 1H), 6.82-6.88 (m, 1H), 7.63 (d, 1H, *J* = 8.8 Hz), 12.60 (br, 1H); MS (ES+) Calcd.: [M+H] 516.31, Found. 516.39.

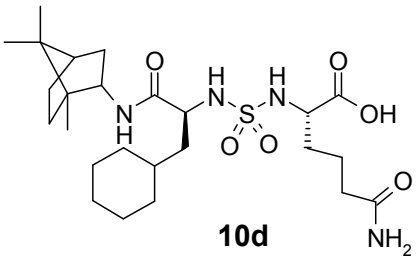
*(2R)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-3-phenyl-propanoic acid* **10c**



**10c**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.74-0.90 (m, 4H), 0.82 (s, 3H), 0.89 (s, 3H), 1.07-1.39 (m, 8H), 1.55-1.78 (m, 8H), 2.06-2.14 (m, 1H), 2.90-2.99 (m, 2H), 3.74-3.80 (m, 1H), 3.94-3.99 (m, 1H), 4.04-4.10 (m, 1H), 6.66 (d, 1H, *J* = 7.6 Hz), 7.01 (d, 1H, *J* = 9.0 Hz), 7.19-7.23 (m, 3H), 7.25-7.30 (m, 2H), 7.68 (d, 1H, *J* = 8.8 Hz), 12.71 (br, 1H); MS (ES+) Calcd.: [M+H] 534.30, Found. 534.31.

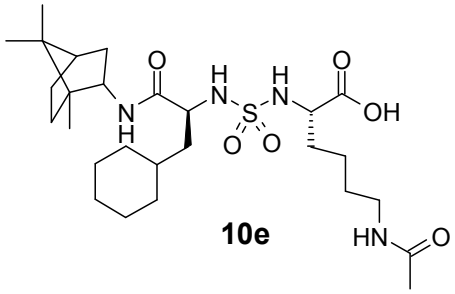
*(2S)-6-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-6-oxo-hexanoic acid; 2,2,2-trifluoroacetic acid* **10d**



**10d**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.81-0.91 (m, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 1.08-1.43 (m, 8H), 1.46-1.79 (m, 12H), 1.99-2.05 (m, 2H), 2.09-2.17 (m, 1H), 3.67 (q, 1H, *J* = 5.5 Hz), 3.79 (q, 1H, *J* = 7.0 Hz), 4.05-4.12 (m, 1H), 6.70 (s, 1H), 6.81-6.90 (m, 2H), 7.22 (s, 1H), 7.65 (d, 1H, *J* = 8.9 Hz), 12.63 (br, 1H); MS (ES+) Calcd.: [M+H] 529.31, Found. 529.31.

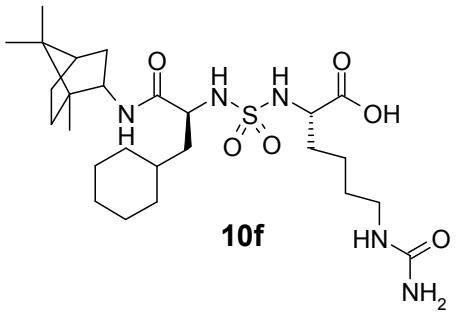
*(2S)-6-acetamido-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]hexanoic acid* **10e**



**10e**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.79-0.91 (m, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 1.07-1.43 (m, 12H), 1.50-1.76 (m, 10H), 1.77 (s, 3H), 2.07-2.16 (m, 1H), 2.98 (q, 2H, *J* = 6.6 Hz), 3.65 (q, 1H, *J* = 6.8 Hz), 3.78 (q, 1H, *J* = 8.2 Hz), 4.04-4.12 (m, 1H), 6.85 (d, 1H, *J* = 8.1 Hz), 6.86 (d, 1H, *J* = 9.0 Hz), 7.45 (br, 1H), 7.64 (d, 1H, *J* = 8.8 Hz), 7.77 (t, 1H, *J* = 5.2 Hz), 12.63 (br, 1H); MS (ES+) Calcd.: [M+H] 557.34, Found. 557.36.

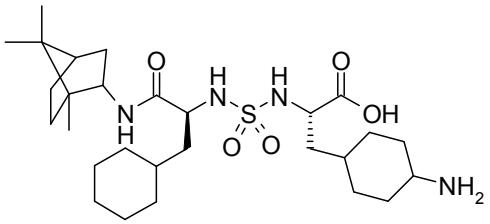
*(2S)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-6-ureido-hexanoic acid; 2,2,2-trifluoroacetic acid* **10f**



**10f**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.75-0.92 (m, 4H), 0.82 (s, 3H), 0.89 (s, 3H), 1.07-1.44 (m, 11H), 1.54-1.85 (m, 10H), 2.06-2.17 (m, 1H), 2.92 (q, 2H, *J* = 5.9 Hz), 3.59-3.69 (m, 1H,), 3.79 (q, 1H, *J* = 8.0 Hz), 4.00-4.13 (m, 1H), 5.33 (s, 2H), 5.88 (t, 1H, *J* = 5.2 Hz), 6.81-6.88 (m, 2H), 7.64 (d, 1H, *J* = 8.7 Hz), 8.92 (br, 1H), 12.63 (br, 1H); MS (ES+) Calcd.: [M+H] 558.33, Found. 558.34.

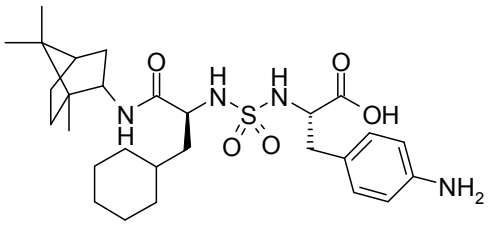
*(2S)-3-(4-aminocyclohexyl)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]propanoic acid hydrochloride* **10g**



**10g**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.69 (s, 3H), 0.79-0.99 (m, 4H), 0.83 (s, 3H), 0.90 (s, 3H), 1.08-1.95 (m, 26H), 2.07-2.17 (m, 1H), 2.87-2.96 (m, 1H), 3.67-3.75 (m, 1H), 3.77-3.85 (m, 1H), 4.04-4.12 (m, 1H), 6.70-6.76 (m, 1H), 6.97-7.07 (m, 1H), 7.65 (d, 1H, *J* = 8.8 Hz), 7.79 (br, 3H); MS (ES+) Calcd.: [M+H] 555.36, Found. 555.49.

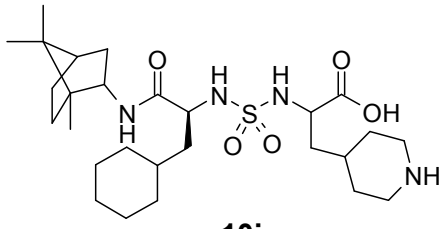
*(2S)-3-(4-aminophenyl)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]propanoic acid; 2,2,2-trifluoroacetic acid* **10h**



**10h**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.79-0.92 (m, 4H), 0.82 (s, 3H), 0.89 (s, 3H), 1.07-1.78 (m, 18H), 2.06-2.15 (m, 1H), 2.84-2.94 (m, 2H), 3.80 (q, 1H, *J* = 7.1 Hz), 3.94 (q, 1H, *J* = 6.5 Hz), 4.03-4.11 (m, 1H), 6.60 (d, 1H, *J* = 7.5 Hz), 6.89-6.96 (m, 2H), 7.01 (d, 1H, *J* = 8.8 Hz), 7.12 (d, 2H, *J* = 7.8 Hz), 7.69 (d, 1H, *J* = 8.6 Hz), 12.70 (br, 1H); MS (ES+) Calcd.: [M+H] 549.31, Found. 549.35.

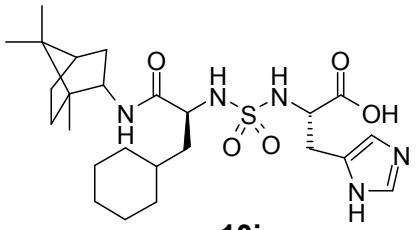
*2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-3-(4-piperidyl)propanoic acid* (mixture of diastereomers) **10i**



**10i**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 1.5H), 0.69 (s, 1.5H) 0.75-0.94 (m, 3H), 0.82 (s, 3H), 0.88 (s, 1.5H), 0.89 (s, 1.5H), 1.04-1.88 (m, 25H), 2.00-2.12 (m, 1H), 2.71-2.81 (m, 2H), 3.15-3.22 (m, 2H), 3.70-3.86 (m, 1H), 4.02-4.11 (m, 1H), 6.41 (br, 1H), 7.07-7.21 (m, 1H), 7.77 (d, 0.5H, *J* = 8.8 Hz), 7.85 (d, 0.5H, *J* = 8.7 Hz), 8.60 (br, 1H); MS (ES+) Calcd.: [M+H] 541.34, Found. 541.39.

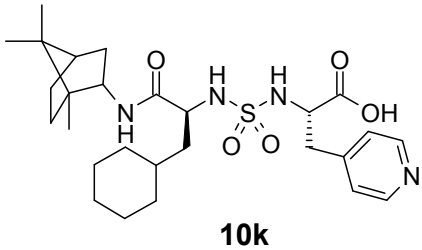
*2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-3-(1H-imidazol-4-yl)propanoic acid* (mixture of diastereomers) **10j**



**10j**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 1.5H), 0.69 (s, 1.5H) 0.80-0.92 (m, 4H), 0.82 (s, 3H), 0.88 (s, 1.5H), 0.89 (s, 1.5H), 1.06-1.43 (m, 9H), 1.55-1.81 (m, 9H), 1.98-2.14 (m, 1H), 2.86-3.03 (m, 2H), 3.82 (q, 1H, *J* = 6.5 Hz), 3.94-4.12 (m, 2H), 6.95-7.06 (m, 1H), 7.11 (s, 1H), 7.74 (d, 0.5H, *J* = 8.8 Hz), 7.79 (d, 0.5H, *J* = 8.7 Hz), 8.24 (br, 1H); MS (ES+) Calcd.: [M+H] 524.29, Found. 524.25.

*2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-3-(4-pyridyl)propanoic acid* (mixture of diastereomers) **10k**

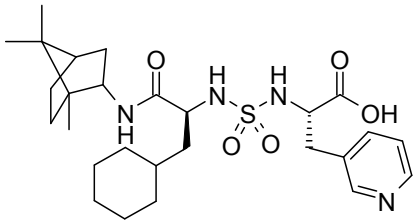


**10k**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.67 (s, 1.5H), 0.68 (s, 1.5H) 0.79-0.92 (m, 3H), 0.81 (s, 1.5H), 0.82 (s, 1.5H), 0.88 (s, 1.5H), 0.89 (s, 1.5H), 1.06-1.87 (m, 16H), 1.92-2.15 (m, 1H), 2.75-3.03 (m, 2H), 3.69-3.86 (m, 2H), 3.95-4.16 (m, 2H), 6.74-6.81 (m, 1H), 6.95-7.18 (m, 1H),

7.35-7.41 (m, 1H), 7.64-7.85 (m, 1H), 8.17 (br, 0.5H), 8.46 (br, 0.5H), 8.52-8.57 (m, 1H), 8.96 (br, 1H), 12.89 (br, 1H); MS (ES-) Calcd.: [M-H] 533.28, Found. 533.23.

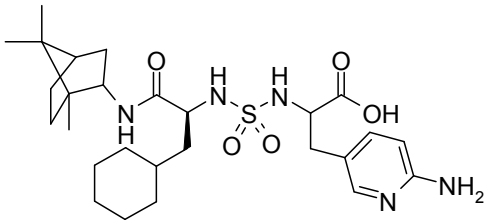
*2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-3-(3-pyridyl)propanoic acid* (mixture of diastereomers) **10l**



**10l**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.67 (s, 1.5H), 0.69 (s, 1.5H) 0.76-0.91 (m, 3H), 0.81 (s, 3H), 0.88 (s, 3H), 1.06-1.87 (m, 16H), 1.07-1.78 (m, 17H), 1.92-2.15 (m, 1H), 2.82-3.05 (m, 2H), 3.73-4.19 (m, 3H), 6.61-6.68 (m, 1H), 7.00-7.15 (m, 1H), 7.29-7.32 (m, 1H), 7.59-7.66 (m, 1H), 7.70-7.86 (m, 1H), 8.39-8.43 (m, 2H), 12.84 (br, 1H); MS (ES-) Calcd.: [M-H] 533.28, Found. 533.17.

*3-(6-amino-3-pyridyl)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]propanoic acid; 2,2,2-trifluoroacetic acid* (mixture of diastereomers) **10m**

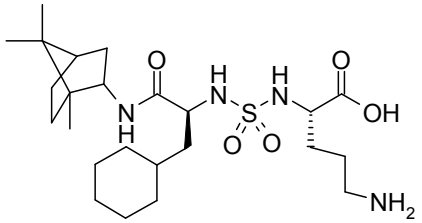


**10m**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.67 (s, 1.5H), 0.69 (s, 1.5H), 0.73-0.92 (m, 3H), 0.82 (s, 3H), 0.84 (s, 1.5H), 0.88 (s, 1.5H), 1.07-1.39 (m, 8H), 1.54-1.78 (m, 8H), 1.96-2.14 (m, 1H),

2.66-2.98 (m, 2H), 3.74-4.13 (m, 3H), 6.76-7.04 (m, 2H), 7.11 (d, 0.5H, *J* = 8.8 Hz), 7.18 (d, 0.5H, *J* = 9.2 Hz), 7.68-7.74 (m, 2H), 7.77-7.86 (m, 2H), 7.93 (br, 2H), 13.21 (br, 1H); MS (ES+) Calcd.: [M+H] 550.31, Found. 550.39.

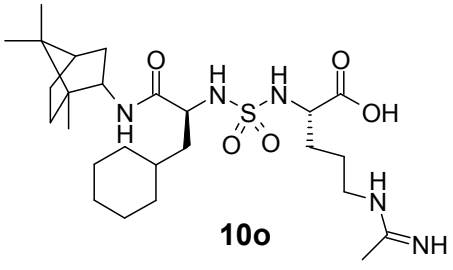
*(2S)-5-amino-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]pentanoic acid* **10n**



**10n**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.67 (s, 3H), 0.76-0.91 (m, 2H), 0.82 (s, 3H), 0.89 (s, 3H), 0.97 (dd, 1H, *J* = 4.8, 13.0 Hz), 1.07-1.22 (m, 4H), 1.26-1.81 (m, 14H), 2.02-2.14 (m, 1H), 2.65-2.76 (m, 2H), 3.42 (t, 1H, *J* = 4.8 Hz), 3.83 (t, 1H, *J* = 7.0 Hz), 4.02-4.10 (m, 1H), 6.98 (br, 1H), 7.77 (d, 1H, *J* = 8.8 Hz), 7.98 (br, 1H); MS (ES+) Calcd.: [M+H] 501.31, Found. 501.36.

(*2S)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-5-(ethanimidoylamino)pentanoic acid; 2,2,2-trifluoroacetic acid* **10o**

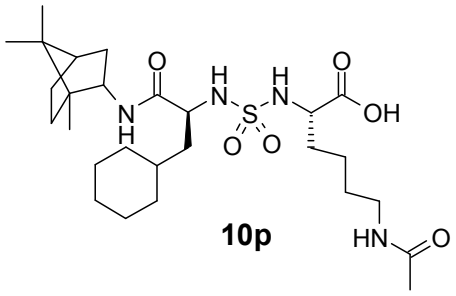


**10o**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.79-0.92 (m, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 1.08-1.27 (m, 5H), 1.30-1.43 (m, 3H), 1.51-1,78 (m, 12H), 2.08-2.16 (m, 1H), 2.12 (s, 3H),

3.11-3.19 (m, 2H), 3.72 (q, 1H, *J* = 6.4 Hz), 3.83 (q, 1H, *J* = 7.4 Hz), 4.04-4.11 (m, 1H), 6.84-6.91 (m, 2H), 7.69 (d, 1H, *J* = 8.8 Hz), 8.50 (s, 1H), 9.02 (s, 1H), 9.34 (s, 1H), 12.80 (br, 1H); MS (ES+) Calcd.: [M+H] 542.34, Found. 542.30.

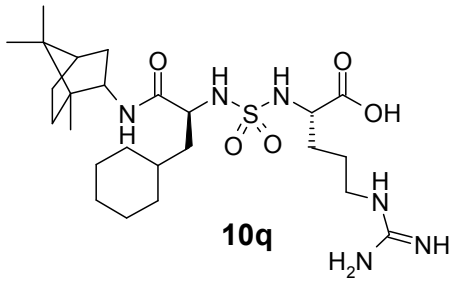
*(2S)-2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-6-(ethanimidoylamino)hexanoic acid; 2,2,2-trifluoroacetic acid* **10p**




**10p**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.68 (s, 3H), 0.76-0.92 (m, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 1.08-1.79 (m, 21H), 2.10-2.16 (m, 1H), 2.12 (s, 3H), 3.14 (q, 2H, *J* = 6.3 Hz), 3.69 (q, 1H, *J* = 6.6 Hz), 3.80 (q, 1H, *J* = 7.8 Hz), 4.04-4.11 (m, 1H), 6.85 (d, 2H, *J* = 8.6 Hz), 7.66 (d, 1H, *J* = 8.7 Hz), 8.49 (s, 1H), 9.00 (s, 1H), 9.31 (s, 1H), 12.73 (br, 1H); MS (ES+) Calcd.: [M+H] 556.35, Found. 556.36.

*2-[[(1S)-1-(cyclohexylmethyl)-2-oxo-2-[[*(1*R*,2*S*,4*R*)*-1,7,7-trimethylnorbornan-2-yl]amino]ethyl]sulfamoylamino]-5-guanidino-pentanoic acid* (mixture of diastereomers) **10q**




**10q**

$^1$H-NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.67 (s, 1.5H), 0.68 (s, 1.5H), 0.76-0.98 (m, 3H), 0.81 (s, 1.5H), 0.82 (s, 1.5H), 0.88 (s, 1.5H), 0.89 (s, 1.5H), 1.06-1.82 (m, 21H), 1.78 (d, 1H, *J* = 12.8 Hz), 2.09 (t, 1H, *J* = 10.1 Hz), 3.04 (s, 2H), 3.44 (m, 1H), 3.73 (q, 0.5H, *J* = 8.0 Hz), 3.73 (q, 0.5H, *J* = 7.6 Hz), 4.03-4.11 (m, 1H), 6.03-6.14 (m, 1H), 6.90-6.98 (m,1H), 7.34 (br, 2H), 7.71 (d, 0.5H, *J* = 8.5 Hz), 7.75 (d, 0.5H, *J* = 8.9 Hz), 9.13 (br, 1H); MS (ES+) Calcd.: [M+H] 543.33, Found. 543.38.

## S2 Crystallographic studies on TAFI inhibitor – tafinized CPB complexes

A mutated "tafinized" porcine carboxypeptidase B (T111-L416; SwissProt sequence) was used where 8 residues, closest to the active site that were different between CPB and TAFI, were mutated to their TAFI equivalents. These mutations were F175I, T302S, M309H, L311V, I355L, P357L, A359P and S362G. The recombinant protein was expressed in P. pastoris GS115.

The purified protein was dissolved in 50 mM Tris-HCl, pH 7.5 and concentrated to 11 mg/mL. 1 µl of protein solution was equilibrated against 1 µL of reservoir solutions containing 16-20% PEG3350, 100 mM MES pH 5.5 and 50 mM ZnAcetate. Crystals were soaked with inhibitors by adding 1 µL of a 10 mM solution of inhibitor in DMSO to a CPB crystal in 9 µL reservoir solution. After overnight incubation, the crystal was transferred to a drop of 8 µL soakbuffer with 2 µL glycerol and the crystal was picked with a nylon loop and flash frozen in liquid nitrogen.

Data were collected at the European Synchrotron Radiation Facility (ESRF). Data processing and scaling were carried out using the XDS package.[1] Model building and inhibitor fitting was done with Quanta and Coot[2] and refinement was done with Buster[3] (compound **1**) and Refmac[4] (urea lead and compounds **7a** and **8a**).

The crystals diffracted to between 1.64 and 2.02 Å resolution with an overall $R_{meas}$ between 7.1 and 11.0% (see table S1). The resulting maps were of excellent quality and clearly and unambiguously revealed the binding modes of the inhbitors (see figure S1).

[1] Kabsch, W. (1988) Evaluation of single-crystal X-ray diffraction data from a position-sensitive detector. *Journal of Applied Crystallography* **21**, 916-924

[2] Emsley, P., Lohkamp, B., Scott, W. G., and Cowtan, K. (2010) Features and development of Coot. *Acta Crystallographica Section D* **66**, 486-501

[3] Bricogne G., Blanc E., Brandl M., Flensburg C., Keller P., Paciorek W., Roversi P, Sharff A., Smart O.S., Vonrhein C., Womack T.O. (2016). BUSTER version 2.11.6. Cambridge, United Kingdom: Global Phasing Ltd.

[4] Murshudov, G. N., Skubak, P., Lebedev, A. A., Pannu, N. S., Steiner, R. A., Nicholls, R. A., Winn, M. D., Long, F., and Vagin, A. A. (2011) REFMAC5 for the refinement of macromolecular crystal structures. *Acta Crystallographica Section D* **67**, 355-367

**Table S1:** Crystallographic Data Collection and Refinement Statistics

| inhibitor | **1** | **Urea lead** | **7a** | **6a** |
|---|---|---|---|---|
| Data collection | | | | |
| space group | P41212 | P41212 | P41212 | P41212 |
| cell dimensions | | | | |
| a,b,c (Å) | 82.32 82.32 95.04 | 81.49 81.49 95.73 | 82.04 82.04 95.81 | 82.51 82.51 95.13 |
| α,β,γ (°) | 90.00 90.00 90.00 | 90.00 90.00 90.00 | 90.00 90.00 90.00 | 90.00 90.00 90.00 |
| resolution (Å) | 62.26 -2.02 (2.08-2.02)* | 81.42 -2.01 (2.10-2.01)* | 95.79 -1.64 (1.71-1.64)* | 82.53 -1.83 (1.89-1.83)* |
| <I>/sig<I> | 14.19 (4.42) | 15.74 (7.99) | 23.68 (5.82) | 20.89 (5.81) |
| observed reflections | 155309 (12795) | 226132 (23014) | 411038 (30128) | 319238 (29095) |
| Rmeas (%) | 7.9 (50.3) | 11.9 (30.0) | 6.9 (39.2) | 10.7 (48.9) |
| completeness (%) | 99.9 (100.0) | 98.7 (90.7) | 98.9 (92.5) | 98.1 (97.5) |
| redundancy | 7.1 (7.1) | 10.4 (9.4) | 10.2 (6.9) | 11.0 (11.2) |
| Refinement | | | | |
| protein atoms: | 2446 | 2446 | 2452 | 2446 |
| inhibitor atoms: | 14 | 31 | 35 | 35 |
| water atoms: | 329 | 582 | 625 | 646 |
| other atoms: | 5** | 3** | 3** | 3** |
| Resolution (Å) | 21.93 -2.02 (2.12-2.02) | 49.39-2.01 (2.07-2.01)* | 58.03-1.64 (1.68-1.64)* | 62.38-1.83 (1.88-1.83)* |
| Rwork (%) | 17.7 (19.7) | 18.4 (23.8) | 15.4 (22.1) | 14.1 (16.5) |
| Rfree (%) | 19.5 (20.9) | 30.5 (38.6) | 19.1 (28.8) | 19.9 (23.8) |
| average Bfactors (Å²) | | | | |
| protein: | 39.88 | 17.63 | 14.79 | 11.01 |
| inhibitor: | 36.68 | 22.54 | 12.79 | 8.93 |
| water: | 56.46 | 35.4 | 38.75 | 37.7 |
| other: | 53.46 | 31.52 | 20.07 | 12.75 |
| rmsd bond lengths (Å) | 0,004 | 0.022 | 0.009 | 0.011 |
| rmsd bond angles (°) | 0,9 | 1.96 | 1.22 | 1.26 |

* the highest resolution bin is given in brackets

** one catalytic zinc ion and 2-4 zinc ions present in crystal contacts due to the presence of 50 mM ZnAcetate in the crystallization cocktail.

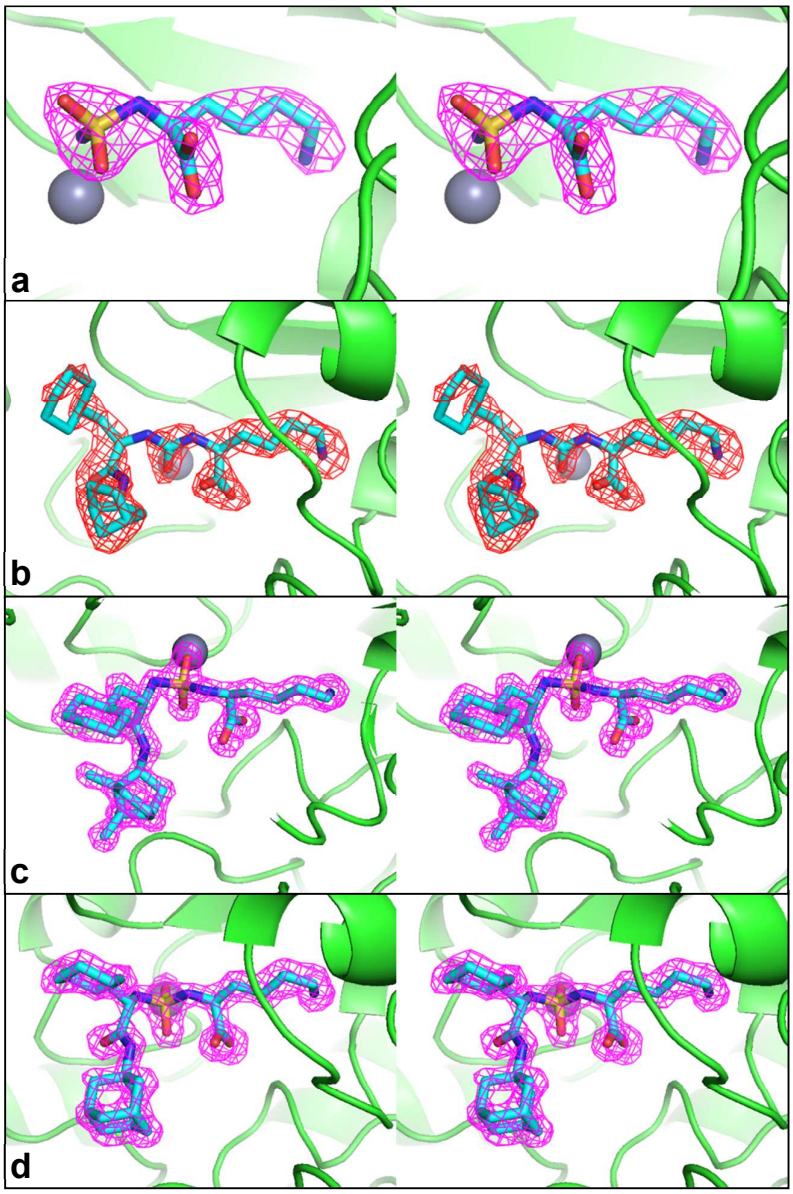
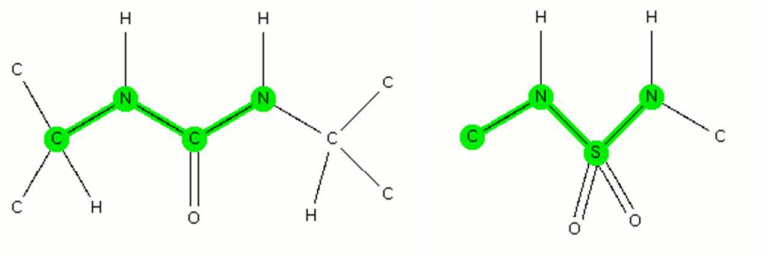



**Figure S1:** Stereo pictures of omit maps of tafinized porcine carboxypeptidase B complexed with different inhibitors. a) Compound **1**, resolution 2.02 Å, contour level 4σ. b) Urea lead, resolution 2.01 Å, contour level 3σ. c) Compound **7a**, resolution 1.64 Å, contour level 4σ. d) Compound **6a**, resolution 1.83 Å, contour level 4σ. The electron density of the urea lead is somewhat weaker as the density for the other compounds, which may be due to a lower occupancy. However, no attempt was made to refine occupancies.

## S3 Analysis of the distribution of torsion angles across urea and sulfamide groups in the Cambridge Structural Database (CSD)

Intrigued by a different geometry across the central C-N/S-N bond between urea and sulfamide TAFI inhibitors (see appendix) requiring an opposite stereochemistry, we decided to look in the Cambridge Structural Database (CSD) for the geometry of similar bonds. The CSD contains all published small-molecule crystal structures.

Using the CSD conquest program we searched for urea and sulfonamide compounds using the following queries:




Urea Sulfamide

The green torsion angles were calculated and plotted by bins of 5° (Figure S2). Cyclic structures and structures involving coordination of the oxygen(s) by metal ions were excluded. 34 ureas (68 torsion angles) and 22 sulfonamides (44 torsion angles) were found.

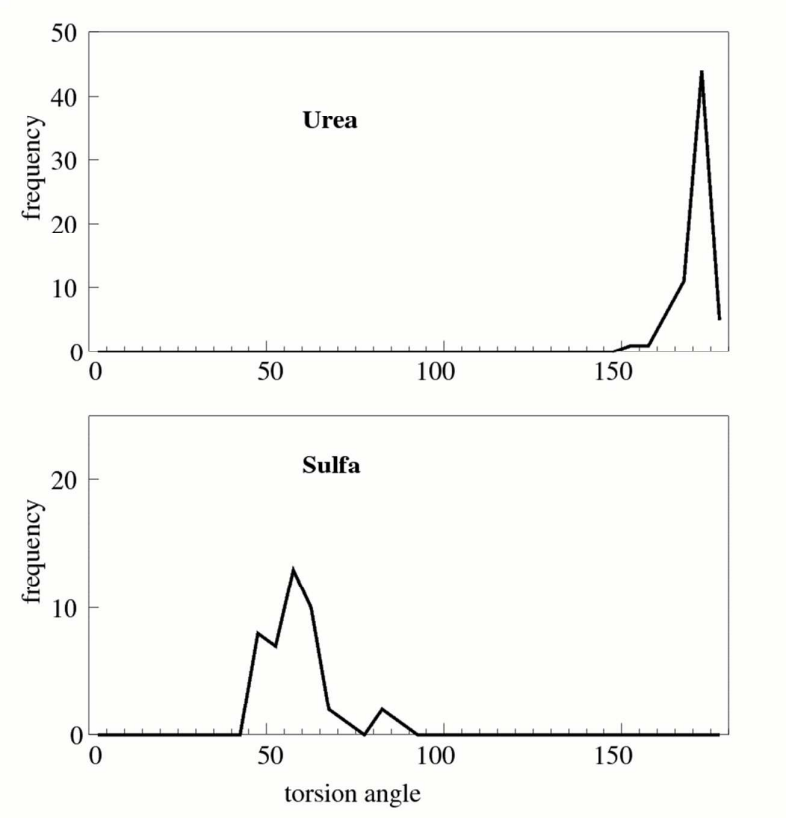



Figure S2: Distribution of torsion angles across the central C-N/S-N bond in urea and sulfamide compounds. The absolute value of the torsion angle is used, so positive and negative values are grouped together.

For the urea compounds a sharp antiperiplanar distribution was observed with an average torsion angle of 173°. For the sulfamide compounds, a somewhat broader synclinal distribution was observed with an average torsion angle of 61°. The torsion angles of 176° and 175° found in our **9** complex fit excellently within the distribution found in the CSD. Also the synclinal torsion angle of 52°, found in the **7a** complex fits very well in the distribution found in the CSD. In fact, it is the antiperiplanar second torsion angle of 177° of the **7a**complex which does not fit in the distribution observed in the CSD.

Reasons for the latter "outlier" are the very precise spatial constraints, posed by the enzyme active site. A sulfamide compound with two synclinal torsion angles would not fit at all. Given that the S1' pocket of CPB and TAFIa is very specific for arginines and lysines and that peptides have normally trans (antiperiplanar) peptide bonds, it comes as no surprise that the bond involving the lysine is forced by the enzyme in the trans (antiperiplanar) conformation, while the other bond retained its synclinal conformation.

## S4 In Vitro Methods for the Determination of IC50s of TAFIa

The prepared substances were tested for TAFla inhibition using the Actichrome plasma TAFI activity kit from American Diagnostica (Pr. No. 874). This entailed adding 29 µL of assay buffer (20 mM Hepes, 150 mM NaCl, pH 7.4) and 10 µL of TAFla (American Diagnostica Pr. No. 874TAFIA; 2.5 µg/mL) to 1 µL of 5 mM DMSO solution of the substance and incubating in a 96 half-well microtiter plate at room temperature for 15 minutes. The enzymic reaction was started by adding 10 µL of TAFla developer (prediluted 1:2 with water). The time course of the reaction was followed at 420 nm in a microtiter plate reader (SpectraMax plus 384; Molecular Devices) for 15 minutes. The IC50 was calculated from the averaged values (duplicate determination) of serial dilutions of the substance with the aid of the Grafit 4 software (Erithacus Software, UK).

## S5 Metabolic stability on liver microsomes

Incubation conditions with hepatic microsomal fractions and further experimental conditions used throughout were as follows: microsomal proteins concentration = 1 mg/mL, bovine serum albumin (BSA) concentration = 1 mg/mL; substrate concentration = 5 µM; incubation duration = 20 min; cytochrome P-450 monooxygenases (CYPs) and flavin-containing monooxygenases (FMOs) cofactor = 1 mM NADPH. Enzyme activity was stopped with 1 volume of acetonitrile (ACN). Hepatic microsomal fractions: from Swiss CD1 male mouse (m7), Sprague−Dawley male rat (m21), humans (pool of H-19, six donors). Inhibitor: quinidine at a final concentration of 8 µM (20-fold its Ki for CYP2D6) was used for the specific and potent inhibition of enzyme reactions catalyzed by CYP2D6. Ketoconazole at a final concentration of 1.5 µM (100-fold its Ki for CYP3A4) was used for the specific and potentinhibition of enzyme reactions catalyzed by CYP3A4. For each test compound and for each microsomal preparation, three incubations were prepared: absolute reference in buffer (without enzyme material, i.e., microsomes); incubation without NADPH cofactor (with microsomal fractions); incubation with NADPH (with microsomal fractions). For most compounds, biotransformation, as observed in hepatic microsomal fractions in the presence of the NADPH cofactor, consists of oxidative reactions catalyzed by either CYP or FMO. In these conditions, the percentage of total metabolism, which corresponds to oxidative metabolism, was determined as follows: [% total metabolism] ≈ [% oxidative metabolism] = [1(UCpeak area − NADPH UC peak area + NADPH)] × 100, where NADPH corresponds to the enzyme cofactor for oxidation reactions catalyzed by either CYP or FMO, and UC represents the unchanged compound.

## S6 IC50 determination for CYP P450 enzyme inhibition

The in vitro procedure for IC50 determination of a test compound as direct, reversible inhibitor against CYP3A4, CYP2D6 and CYP2C9 in human liver microsomes (HLM) was as follows: inhibition of the turn-over of probe substrates of CYP3A4 (Midazolam 3µM, 10 minutes and Testosterone 50µM, 30 minutes), CYP2D6 (Dextromethorphan 5µM, 30 minutes) and CYP2C9 (Diclofenac 5 µM, 10 minutes) to their specific metabolites i.e. 1´-Hydroxymidazolam, 6ß-Hydroxytestosterone, Dextrorphan and 4´-Hydroxydiclofenac by NCEs was evaluated. For scientific reasons, CYP3A4 inhibition was studied with two different probe substrates.

The specific metabolites were quantified by LC-MS/MS analysis.

CYP Inhibition conditions: 50 mM Phosphate buffer (no BSA in incubation medium), 0.5 mM EDTA, 6 mM $MgCl_2$, 1mM NADPH, 0.1 or 0.2 mg microsomal protein/mL, maximum 0.5% DMSO with test compound(s) concentration range including 30, 10, 3, 1, 0.3 µM). Incubations were carried out at 37°C. Incubations were terminated at the appropriate time with acetonitrile containing an appropriate internal standard.

## S7 Permeability testing using CACO-2 TC7 cells

Cellular permeability was tested using CACO-2 TC7 cells at passages 20 to 70, 21 to 28 days post seeding on filters (HTS plate membrane PET 1 µm, 3 wells). Transport medium forapical compartment : Hank's balanced salt solution; HEPES 10 mM; 0.5 % BSA; adjusted pH 6.5; for basal compartment : Hank's balanced salt solution; HEPES 10 mM; 5 % BSA; adjusted pH 7.4. Test compound concentration was 20 µM; incubation duration = 120 minutes under agitation at 37°C without $CO_2$.

Sampling was done at Time 0 (Apical compartment) and Time 120 (Apical and Basal compartments), Calibration curve used 3 concentration levels (at least) and transport in the "Apical-to-Basal" direction was evaluated. Following protein precipitation with acetonitrile and their removal by centrifugation, supernatant fluids were analysed by UPLC/ESI-MS-MS or equivalent assays.

Permeability values were calculated as follows:

$$\text{Permeability coefficient (in nm/sec)} = \frac{\text{Amount Basal at time 120}}{\text{Time} * \text{Filter Area} * \text{Apical concentration at time 0}}$$

## S8 Molecular Modelling Methods

Virtual library enumeration processes were carried out using Pipeline Pilot (Pipeline Pilot, Scitegic Inc., San Diego, CA.). Docking was carried out with GOLD. Docking poses were scored and ranked using DrugScore.

## S9 Pharmacokinetic Studies

All experimental procedures have been conducted in accordance to German Animal Protection Law, as well as according to international animal welfare legislation and rules.

Male Sprague Dawley rats from Harlan Winkelmann, Germany were used in the described PK study (weight range 200-250 g).

Plasma and urine concentrations of **7a** were determined in a serial sampling study after an intravenous bolus administartion of 1.0 mg/kg in a 0.9% NaCl solution containing 2% Tween 80 to male Sprague Dawley rats (sampling time 0.083; 0.25; 0.5; 1; 2; 4; 8; 24h).