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Supporting Information

Sugar-Based Arylsulfonamide Carboxylates as Selective and Water-Soluble Matrix Metalloproteinase-12 Inhibitors

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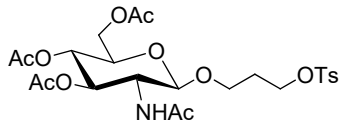
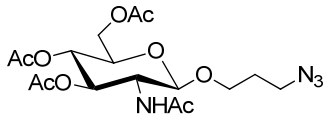
Experimental procedures

3-*O*-tosyl-1-propyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyde (13):



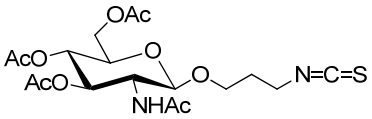
A solution of known oxazoline **12**[1] (4.61 g, 14.1 mmol) in anhydrous DCE (56 mL) containing 4Å powdered molecular sieves (3.60 g) was stirred under argon for 30 min at 80°C. Camphorsulphonic acid (CSA, 1.64 g, 7.05 mmol) and 3-*O*-tosyl-1,3-propandiol[2] (4.9 g, 21.1 mmol, 1.5 equiv) were added and the resulting suspension was stirred at 80°C. After 12 h, TLC analysis (EtOAc) revealed the complete disappearance of the starting material and the formation of a major product (R_f = 0.40). The reaction mixture was filtered through paths of Celite, washed with CH_2Cl_2, washed by saturated aq $NaHCO_3$ (30 mL) and brine (30 mL) and dried ($MgSO_4 \cdot H_2O$), filtered and concentrated under diminished pressure. Flash chromatographic purification over silica gel (*n*-hexane/EtOAc 1:4 + 0.1% Et_3N) of the crude product gave pure **13** (5.50 g, 69% yield) as a white foam; R_f = 0.40 (EtOAc); $[\alpha]_D^{23}$ = -47.6 (c=1.05 in $CHCl_3$); ^{1}H NMR (250.12 MHz, CD_3CN): δ =7.88-7.55 (AA'XX' system, 2H, Ar-*H*), 6.52 (d, $J_{2,NH}$ = 9.1 Hz, 1H; NH), 5.21 (dd, $J_{2,3}$ =10.6 Hz, $J_{3,4}$ = 9.4 Hz, 1H; H-3), 5.02 (dd, $J_{4,5}$ = 10.0 Hz, 1H; H-4), 4.66 (d, $J_{1,2}$ = 8.5 Hz, 1H; H-1), 4.29 (dd, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 12.2 Hz, 1H; H-6b), 4.20-4.05 (m, 3H; H-6b, C*H*$_2$OTs), 3.91-3.75 (m, 2H; H-2, H-5), 3.84 (m, 1H; C*H*$_2$O), 3.63 (dt, J_{vic} = 6.3 Hz, J_{gem} = 10.4 Hz, 1H; C*H*$_2$O), 2.54 (s, 3H; Ar-*Me*), 2.10, 2.06, 2.03 (3s, each 3H; 3×*Me*COO), 1.94 (m, 2H; C*H*$_2$), 1.88 (s, 3H; *Me*CON); ^{13}C NMR (62.9 MHz, CD_3CN): δ = 171.3, 171.1, 170.8, 170.5 (4×*C*=O), 146.3, 133.7 (2×Ar-*C*), 131.0, 128.6 (2×Ar-*C*H), 101.5 (C-1), 73.4 (C-3), 72.3 (C-5), 69.6 (C-4), 68.7 (*C*H$_2$OTs), 66.1 (*C*H$_2$O), 62.9 (C-6), 54.6 (C-2), 29.7 (*C*H$_2$), 23.0 (*Me*CON), 21.6 (Ar-*Me*), 20.8 (3×*Me*COO); elemental analysis calcd (%) for $C_{24}H_{33}NO_{12}S$: C 51.51, H 5.94, N 2.50; found: C 51.53, H 5.96, N 2.52.

3-azido-1-propyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyde (14):



A solution of **13** (5.46 g, 9.7 mmol) in dry DMF (130 mL) was treated with NaN_3 (1.91 g, 29.3 mmol, 3 equiv) and Bu_4NI (7.22 g, 19.5 mmol, 2 equiv), warmed at 50°C and stirred under argon atmosphere until the starting material was consumed (1 h, TLC, EtOAc). The mixture was cooled to RT concentrated and partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (5×30 mL). The combined extracts were collected, dried ($MgSO_4 \cdot H_2O$), filtered and concentrated under diminished pressure. Purification of the residue by flash chromatography on silica gel (*n*-hexane/EtOAc 1:4) afforded the known **14** (4.14 g, 98% yield) as a white solid, $[\alpha]_D^{23}$ = -8.6 (*c*=1.04 in $CHCl_3$), Lit.[3] $[\alpha]_D$ = -8.3 (*c*=0.6 in $CHCl_3$), m.p. 109-111°C, Lit[3b] m.p. 108-110°C. NMR data were in full accordance with that reported.[3]

3-isothiocyanate-1-propyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (16):

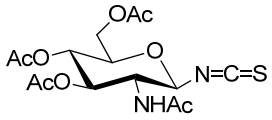


To a solution of azide **14** (250 mg, 0.581 mmol) in 20:1 THF/H_2O mixture (2.0 mL), PPh_3 (329 mg, 0.987 mmol, 1.7 equiv) supported on resin (3 mmol/g) was added and the mixture was stirred at RT until the starting compound was completely reacted (TLC, EtOAc, 24 h). After filtration over a small layer of Celite the solution was concentrated under diminished pressure and the crude residue was constituted mainly by amine **15** (230 mg, 98% yield). ^{13}C NMR (62.9 MHz, CD_3OD): δ = 172.4, 172.2, 171.9, 171.4 (4×*C*=O), 101.5 (C-1), 74.5 (C-3), 73.1 (C-5), 70.4 (C-4), 69.1 (*C*H_2O), 63.6 (C-6), 55.4 (C-2), 37.4 (*C*H_2NH_2), 30.8 (*C*H_2), 23.7 (*Me*CON), 21.6 (3×*Me*COO).

Without further purification, a solution of amine **15** (230 mg) in dry CH_2Cl_2 (8.2 mL) was treated with 2-pyridyl-thiocarbonate (DPT, 126 mg, 0.544 mmol, 1 equiv) and stirring at RT. After 3

h the TLC analysis (*n*-hexane/EtOAc 1:9) revealed the complete disappearance of the starting material and the formation of a major product (R_f = 0.31). The mixture was diluted with CH_2Cl_2 (20 mL) and treated with water (20 mL) and then extracted with CH_2Cl_2 (4×20 mL). The combined organic extracts were dried ($MgSO_4 \cdot H_2O$), filtered and concentrated under diminished pressure. Purification of the residue by flash chromatography on silica gel (*n*-hexane/EtOAc 1:9) to give **16** (167 mg, 64% yield calculated from azide **14**) as a solid foam, R_f = 0.31 (*n*-hexane/EtOAc 1:9); $[\alpha]_D^{23}$ = -10.8 (*c*=1.04 in $CHCl_3$); ^{1}H NMR (250.12 MHz, CD_3CN): δ = 6.58 (d, $J_{2,NH}$ = 9.3 Hz, 1H; NH), 5.15 (dd, $J_{2,3}$ =10.6 Hz, $J_{3,4}$ = 9.4 Hz, 1H; H-3), 4.93 (dd, $J_{4,5}$ = 10.0 Hz, 1H; H-4), 4.63 (d, $J_{1,2}$ = 8.5 Hz, 1H; H-1), 4.21 (dd, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 12.2 Hz, 1H; H-6b), 4.05 (dd, $J_{5,6a}$ = 2.5 Hz, 1H; H-6a), 3.88 (dt, J_{vic}= 5.5 Hz, J_{gem}= 10.5 Hz, 1H; C*H*$_2$O), 3.82-3.76 (m, 2H; H-2, H-5), 3.61 (dt, J_{vic}= 6.2 Hz, J_{gem}= 10.5 Hz, 1H; C*H*$_2$O), 3.60 (t, 2H; C*H*$_2$NCS), 2.01, 1.96, 1.93 (3s, each 3H; 3×*Me*COO), 1.88 (m, 2H; C*H*$_2$), 1.83 (s, 3H; *Me*CON); ^{13}C NMR (62.9 MHz, CD_3CN): δ = 171.3, 171.0, 170.9, 170.5 (4×*C*=O), 141.3 (C=S), 101.6 (C-1), 73.3 (C-3), 72.3 (C-5), 69.7 (C-3), 66.8 (*C*H_2O), 62.9 (C-6), 54.7 (C-2), 42.6 (*C*H_2NCS), 30.3 (*C*H_2), 23.1 (*Me*CON), 20.9 (3×*Me*COO); elemental analysis calcd (%) for $C_{18}H_{26}N_2O_9S$: C 48.42, H 5.87, N 6.27; found: C 48.40, H 5.85, N 6.24.

2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl isothiocyanate (19):



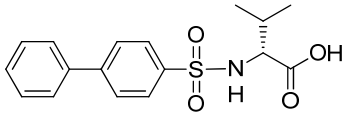
To a solution of the known azide **17**[4] (200 mg, 0.537 mmol) in 20:1 THF-H_2O mixture (1.7 mL), PPh_3 (304 mg, 0.913 mmol, 1.7 equiv) supported on resin (3 mmol/g) commercial was added and the mixture was stirred at RT until the starting compound was completely reacted (TLC, EtOAc, 24 h). After filtration over a small layer of Celite the solution was concentrated under diminished pressure and the crude residue was constituted exclusively by amine **18** (167.3 mg, 90% yield). NMR parameters was accordance with those reported.[4] Without further purification, a solution of

amine **18** (167.3 mg) in dry CH_2Cl_2 (8.7 mL) was treated with 2-pyridyl-thiocarbonate (DPT, 124.7 mg, 0.535 mmol, 1 equiv) and stirring at RT. After 1.5 h the TLC analysis (EtOAc) revealed the complete disappearance of the starting material and the formation of a major product (R_f = 0.51). The mixture was diluted with CH_2Cl_2 (20 mL) and treated with water (20 mL) and then extracted with CH_2Cl_2 (4×20 mL). The combined organic extracts were dried ($MgSO_4 \cdot H_2O$), filtered and concentrated under diminished pressure. Purification of the residue by flash chromatography on silica gel (*n*-hexane/EtOAc 3:7) to give the known **19**[5] (93 mg, 46% yield calculated from azide **17**) as a syrup, R_f = 0.51 (EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz) data were in full accordance with that reported.[5] ^{13}C NMR (CD_3CN, 62.9 MHz): δ = 171.3, 171.2, 170.9, 170.4 (4×C=O), 142.4 (C=S), 84.8 (C-1), 74.5 (C-5), 72.5 (C-3), 69.1 (C-4), 62.6 (C-6), 55.9 (C-2), 23.1 (MeCON), 20.8 (3×*Me*CON).

General procedure for the synthesis of sulfonamide derivatives 20a,b.

Biphenyl-4-sulfonyl chloride or *p*-bromobenzenesulfonyl chloride (17 mmol) was added to a solution of D-valine (2.0 g, 17 mmol) in H_2O (13 mL) and dioxane (13 mL) containing Et_3N (3.5 mL, 25.5 mmol). The mixture was stirred at RT overnight, then dioxane was evaporated. The residue was treated with EtOAc (200 mL), extracted with 1 N HCl (80 mL) and washed with brine (40 mL) and a saturated solution of $NaHCO_3$ (150 mL). The aqueous phase was acidified to pH 1-2 with 1 N HCl and extracted with EtOAc (200 mL). The organic phase was dried over Na_2SO_4, and evaporated *in vacuo*.

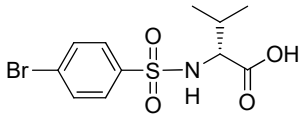
(*R*)-2-(Biphenyl-4-ylsulfonamido)-3-methylbutanoic acid (20a):



The title compound was prepared from biphenyl-4-sulfonyl chloride following the general procedure. The crude product was triturated with *n*-hexane to yield the known sulfonamide **20a**[6] as a white solid (2.57 g, 45% yield). R_f=0.29 (*n*-hexane/EtOAc 2:1); m.p. 157-158°C; ^{1}H NMR [400

MHz, $(CD_3)_2CO$]: δ = 7.96-7.93 (m, 2H; Ar-H), 7.87-7.84 (m, 2H; Ar-*H*), 7.76-7.74 (m, 2H; Ar-H), 7.55-7.51 (m, 2H; Ar-H), 7.48-7.43 (m, 1H; Ar-*H*), 6.66 (d, $J_{H,N}$ = 9.8 Hz, 1H; N*H*), 3.83 (dd, J_{vic} = 4.4 Hz, 1H; C*H*NH), 2.17-2.10 (m, 1H; Me_2CH), 0.99 (d, J_{vic} = 6.7 Hz, 3H; Me_2CH), 0.93 (d, J_{vic} = 6.7 Hz, 3H; Me_2CH). ^{13}C NMR [100.57 MHz, $(CD_3)_2CO$)]: δ = 172.6 (C=O), 145.7, 141.0, 140.2 (3×Ar-C), 130.1 (2×Ar-CH), 129.4 (Ar-CH), 128.7 (2×Ar-CH), 128.2 (2×Ar-CH), 128.1 (2×Ar-CH), 62.2 (*CH*NH), 32.1 (Me_2CH), 19.6, 18.2 (Me_2CH).

(*R*)-2-(4-bromophenylsulfonamido)-3-methylbutanoic acid (20b):[7]

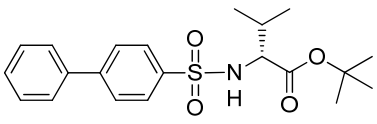


The title compound was prepared from *p*-bromobenzenesulfonyl chloride following the general procedure. White solid, 44% yield. R_f= 0.15 (*n*-hexane/EtOAc 4:1); m.p. 122-124°C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71-7.69 (m, 2H; Ar-*H*), 7.64-7.61 (m, 2H, Ar-*H*), 5.15 (d, $J_{H,N}$ = 10.0 Hz, 1H; N*H*), 3.82 (dd, J_{vic} = 4.6 Hz, 1H; C*H*$NHSO_2$), 2.15-2.10 (m, 1H; Me_2CH), 0.98 (d, J_{vic} = 6.8 Hz, 3H; Me_2CH), 0.87 (d, J_{vic} = 6.9 Hz, 3H; Me_2CH); ^{13}C NMR (100.57 MHz, $CDCl_3$): δ = 175.9 (C=O), 138.9 (Ar-C), 132.4 (2×Ar-CH), 128.9 (2×Ar-CH), 128.1 (Ar-C), 60.8 (*CH*NH), 31.5 (Me_2CH), 19.2, 17.2 (Me_2CH); elemental analysis calcd (%) for $C_{11}H_{14}BrNO_4S$: C 39.30, H 4.20, N 4.17; found: C 39.20, H 4.11, N 4.22.

General procedure for the synthesis of tert-butyl ester derivatives 21a,b.

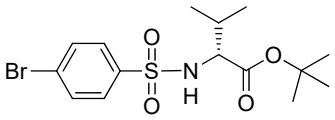
A solution of carboxylic acid **20a** or **20b** (7.5 mmol) in anhydrous toluene (14 mL) containing *N*,*N*-dimethylformamide di-*tert*-butyl acetal (7.2 mL, 30 mmol) was heated to 95ºC for 3 h. The solvent was then evaporated and the crude product was purified by flash chromatography on silica gel.

(*R*)-*tert*-Butyl 2-(biphenyl-4-ylsulfonamido)-3-methylbutanoate (21a):



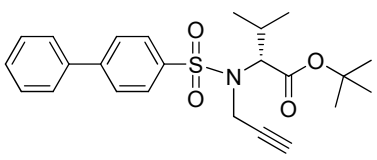
The title compound was prepared from **20a** following the general procedure. The crude product was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 4:1) to give the known **21a**[6] (1.8 g, 60% yield) as a white solid. R_f=0.20 (*n*-hexane/EtOAc 6:1); m.p. 119-121°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92-7.88 (m, 2H; Ar-*H*), 7.69-7.67 (m, 2H; Ar-*H*), 7.57-7.54 (m, 2H; Ar-H), 7.49-7.41 (m, 3H, Ar-*H*), 5.14 (d, $J_{H,N}$ = 9.8 Hz, 1H; N*H*), 3.66 (dd, J_{vic} = 4.6 Hz, 1H; C*H*N), 2.09-2.04 (m, 1H; Me_2C*H*), 1.19 (s, 9H; *Me*$_3$C), 1.02 (d, J_{vic} = 6.7 Hz, 3H; *Me*$_2$CH), 0.86 (d, J_{vic} = 6.7 Hz, 3H; *Me*$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 170.9 (*C*=O), 149.0, 146.3, 138.9 (3×Ar-*C*), 129.7 (2×Ar-*C*H), 129.1 (Ar-*C*H), 128.6 (2×Ar-*C*H), 128.3 (2×Ar-*C*H), 127.9 (2×Ar-*C*H), 83.0 (Me_3C), 61.9 (*CH*NH), 32.3 (Me_2CH), 28.3 (*Me*$_3$C), 19.7, 17.7 (*Me*$_2$CH).

(*R*)-*tert*-Butyl 2-(4-bromophenylsulfonamido)-3-methylbutanoate (21b):



The title compound was prepared from **20b** following the general procedure. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 20:1) using a Isolute Flash Si II cartridge to give the known **21b**[7] (46.5% yield) as a white solid. R_f= 0.32 (*n*-hexane/EtOAc 8:1); m.p. 111-114°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.73-7.71 (m, 2H; Ar-*H*), 7.65-7.63 (m, 2H; Ar-*H*), 5.13 (d, J_{vic} = 9.9 Hz, 1H; N*H*), 3.62 (dd, J_{vic} = 4.4 Hz, 1H; C*H*NHSO$_2$), 2.09-2.04 (m, 1H; Me_2C*H*), 1.26 (s, 9H; *Me*$_3$C), 1.02 (d, J_{vic} = 6.8 Hz, 3H; *Me*$_2$CH), 0.86 (d, J_{vic} = 6.8 Hz, 3H; *Me*$_2$CH); ^{13}C NMR (100.57 MHz, $CDCl_3$): δ = 170.3 (C=O), 138.9 (Ar-*C*), 132.4 (2×Ar-*C*H), 129.1 (2×Ar-*C*H), 127.8 (Ar-C), 82.8 (Me_3CO), 61.4 (*CH*NH), 31.7 (Me_2CH), 27.8 (*Me*$_3$C), 19.2, 17.1 (*Me*$_2$CH); elemental analysis calcd (%) for $C_{15}H_{22}BrNO_4S$: C 45.92, H 5.65, N 3.57; found: C 45.86, H 5.60, N 3.60.

(*R*)-*tert*-Butyl 3-methyl-2-(*N*-(prop-2-ynyl)biphenyl-4-ylsulfonamido)butanoate (22):

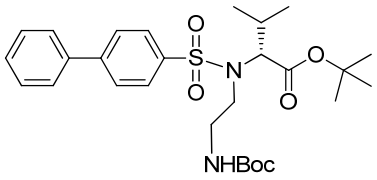


To a solution of **21a** (100 mg, 0.25 mmol) in DMF (3.9 mL) propargyl bromide (80% in toluene, 28 µL, 0.308 mmol) and potassium carbonate (355 mg, 2.57 mmol) were added. The resulting suspension was stirred at RT for 2 days under argon atmosphere. The mixture was diluted with water (30 mL) and extracted with EtOAc (3×30 mL). The combined organic phases were washed with brine (30 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to give **22** as a brown solid after crystallization (EtOAc/*n*-hexane) (98 mg, 82.6% yield). R_f=0.47 (*n*-hexane/EtOAc 6:1); m.p. 113-115°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01-7.98 (m, 2H; Ar-*H*), 7.72-7.69 (m, 2H; Ar-*H*), 7.62-7.58 (m, 2H, Ar-*H*), 7.52-7.42 (m, 3H, Ar-*H*), 4.45 (dd, J_{gem} = 18.4 Hz, *J* = 2.4 Hz, 1H; C*H*$_2$N), 4.23 (dd, J_{gem} = 18.4 Hz, *J* = 2.4 Hz, 1H; C*H*$_2$N), 4.03 (d, *J* = 10.3 Hz, 1H; *CH*N), 2.26-2.20 (m, 2H; Me$_2$C*H,* ≡*CH*), 1.31 (s, 9H, *Me*$_3$C), 1.10 (d, J_{vic} = 6.6 Hz, 3H; *Me*$_2$CH), 0.99 (d, J_{vic} = 6.6 Hz, 3H; *Me*$_2$CH); ^{13}C NMR (100.57 MHz, $CDCl_3$): δ = 169.6 (C=O), 145.6, 139.4, 138.8 (3×Ar-*C*), 129.1 (2×Ar-*C*H), 128.5 (Ar-*C*H), 128.3 (2×Ar-*C*H), 127.4 (2×Ar-*C*H), 127.3 (2×Ar-*C*H), 82.1 (Me$_3$*C*), 79.7 (≡C), 72.1 (≡CH), 65.9 (*CH*N), 33.7 (*C*H$_2$N), 28.9 (Me$_2$*CH*), 27.8 (*Me*$_3$C), 19.8, 19.2 (*Me*$_2$CH); elemental analysis calcd (%) for $C_{24}H_{29}NO_4S$: C 67.42, H 6.84, N 3.28; found: C 67.30, H 6.70, N 3.30.

General procedure for the synthesis of tert-butyl ester derivatives 24a,b.

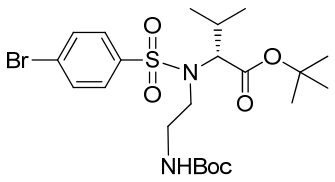
Diisopropyl azodicarboxylate (DIAD) (0.4 mL, 2.47 mmol) was added dropwise to a solution containing the alcohol **23** (160 mg, 0.99 mmol), the sulfonamide **21a** or **21b** (1.28 mmol) and triphenylphosphine (863 mg, 2.97 mmol) in anhydrous THF (14 mL) under argon atmosphere at 0ºC. The resulting solution was stirred overnight at RT and evaporated under reduced pressure to afford a crude product, which was purified by flash chromatography.

(*R*)-*tert*-Butyl 2-(*N*-(2-(*tert*-butoxycarbonylamino)ethyl)biphenyl-4-ylsulfonamido)-3-methylbutanoate (24a):



The title compound was prepared from **21a** following the general procedure. The crude product was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 8:1) to yield **24a** as a yellow oil (62% yield). R_f=0.25 (*n*-hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92-7.89 (m, 2H; Ar-*H*), 7.69-7.67 (m, 2H; Ar-*H*), 7.58-7.55 (m, 2H; Ar-H), 7.49-7.41 (m, 3H; Ar-*H*), 3.99 (d, J_{vic} = 9.6 Hz, 1H; C*H*N), 3.81-3.76 (m, 1H; CH_2N), 3.43-3.41 (m, 2H; CH_2NH), 3.34-3.28 (m, 1H, CH_2N), 2.11-2.08 (m, 1H; Me$_2$C*H*), 1.44 (s, 9H; *Me*$_3$CNH), 1.24 (s, 9H; *Me*$_3$CO), 1.06 (d, J_{vic} = 6.4 Hz, 3H; *Me*$_2$CH), 0.96 (d, J_{vic} = 6.4 Hz, 3H; *Me*$_2$CH); ^{13}C NMR (100.57 MHz, $CDCl_3$): δ = 169.6 (C=O), 155.8 (NHC=O), 145.6, 139.3, 138.3 (3×Ar-*C*), 129.1 (2×Ar-*C*H), 128.5 (Ar-*C*H), 128.1 (2×Ar-*C*H), 127.6 (2×Ar-CH), 127.3 (2×Ar-CH), 82.1 (Me$_3$*C*O), 79.2 (Me$_3$*C*NH), 66.7 (*CH*N), 44.7, 41.3 (2×*C*H$_2$N), 29.3 (Me$_2$*CH*), 28.5, 27.8 (2×*Me*$_3$C), 20.1, 19.3 (*Me*$_2$CH); elemental analysis calcd (%) for $C_{28}H_{40}N_2O_6S$: C 63.13, H 7.57, N 5.26; found: C 63.20, H 7.30, N 5.43.

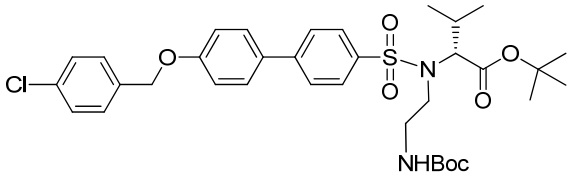
(*R*)-*tert*-Butyl 2-(4-bromo-*N*-(2-(*tert*-butoxycarbonylamino)ethyl)phenylsulfonamido)-3-methylbutanoate (24b):



The title compound was prepared from **21b** following the general procedure. The crude product was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 8:1) to give **24b** (85% yield) as a yellow oil. R_f=0.34 (*n*-hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.74-7.72 (m, 2H; Ar-*H*), 7.65-7.63 (m, 2H; Ar-*H*); 5.01 (bs, 1H; N*H*), 3.95 (d, J_{vic} = 10.4 Hz, 1H; C*H*N), 3.81-3.72 (m, 1H; CH_2N), 3.43-3.38 (m, 2H; CH_2NH), 3.29-3.22 (m, 1H; CH_2N), 2.14-2.07 (m, 1H; Me$_2$C*H*), 1.45 (s, 9H; *Me*$_3$CNH), 1.30 (s, 9H; *Me*$_3$CO), 1.06 (d, J_{vic} = 6.6 Hz, 3H; *Me*$_2$CH), 0.97 (d, J_{vic} = 6.6 Hz, 3H; *Me*$_2$CH); ^{13}C NMR (100.57 MHz, $CDCl_3$): δ = 169.7 (C=O), 155.9 (NHC=O), 138.9 (Ar-

C), 132.3 (2×Ar-*C*H), 129.2 (2×Ar-*C*H), 127.7 (Ar-C), 82.4 (Me_3CO), 79.4 (Me_3CNH), 66.8 (*CH*N), 44.8, 41.1 (2×CH_2N), 29.8 (Me_2CH), 28.5, 27.9 (2×Me_3C), 20.0, 19.4 (Me_2CH); elemental analysis calcd (%) for $C_{22}H_{35}BrN_2O_6S$: C 49.34, H 6.59, N 5.23; found: C 49.30, H 6.40, N 5.28.

(*R*)-*tert*-Butyl 2-(*N*-(2-(*tert*-butoxycarbonylamino)ethyl)-4'-(4-chlorobenzyloxy)biphenyl-4-ylsulfonamido)-3-methylbutanoate (26):



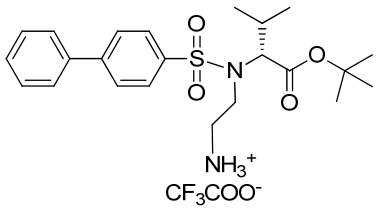
To a mixture of arylbromide **24b** (1.37 mmol, 0.73 g), 4-(4'-chlorobenzyloxy)-phenylboronic acid (2.33 mmol, 0.61 g) and K_3PO_4 (3.15 mmol, 0.67 g) in H_2O/dioxane 1:4.4 (16.85 mL) was added $Pd(PPh_3)_4$ (0.06 mmol, 0.07 g). The solution was stirred under nitrogen at 70°C for 2 h. After this time a black solution was observed, which was diluted with a saturated solution of $NaHCO_3$ (80 mL) and then extracted with EtOAc (200 mL). The organic layer was filtered to remove the palladium precipitate and evaporated in vacuum to give a black crude product that was purified by flash chromatography (*n*-hexane/EtOAc 12:1) using a Isolute Flash Si II cartridge to give **26** (0.74 g, 80.6%) as an orange foam. R_f=0.20 (*n*-hexane/EtOAc 5:1), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89-7.87 (m, 2H; Ar-*H*), 7.65-7.62 (m, 2H; Ar-*H*), 7.53-7.50 (m, 2H; Ar-*H*), 7.42-7.37 (m, 4H; Ar-*H*), 7.06-7.04 (m, 2H; Ar-*H*), 5.10 (s, 2H; CH_2O), 3.99 (d, J_{vic} = 10.4 Hz, 1H; C*H*N), 3.82-3.78 (m, 1H; CH_2N), 3.45-3.40 (m, 2H; CH_2NH), 3.33-3.28 (m, 1H; CH_2N), 2.15-2.07 (m, 1H Me_2CH), 1.44 (s, 9H; Me_3CNH), 1.26 (s, 9H; Me_3CO), 1.07 (d, J_{vic} = 6.6 Hz, 3H; Me_2CH), 0.96 (d, J_{vic} = 6.6 Hz, 3H; Me_2CH); ^{13}C NMR (100.57 MHz, $CDCl_3$): δ = 169.6 (C=O), 159.26 (Ar-*C*O), 155.8 (NHC=O), 145.8 (Ar-*C*S), 136.4, 135.3, 134.1, 132.0 (4×Ar-*C*), 129.0 (2 × Ar-*C*H), 128.9 (2 × Ar-*C*H), 128.6 (2×Ar-*C*H), 128.2 (2×Ar-*C*H), 127.4 (2×Ar-*C*H), 115.6 (2×Ar-*C*H), 83.5 (Me_3C), 79.3 (Me_3CNH), 69.8 (CH_2O), 65.9 (*C*HN), 42.4, 41.5 (2×CH_2N), 28.9 (Me_2CH), 28.5, 27.9 (2×Me_3C), 20.2, 19.3

(*Me*$_2$CH); elemental analysis calcd (%) for $C_{35}H_{45}ClN_2O_7S$: C 62.44, H 6.74, N 4.16; found: C 62.30, H 6.71, N 4.28.

General procedure for the synthesis of trifluoroacetate salts 25 and 27.

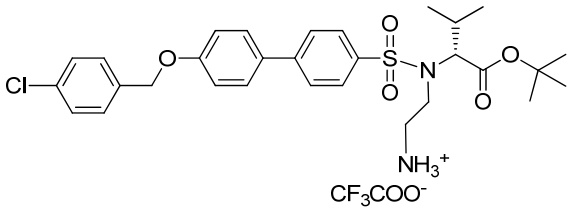
Trifluoroacetic acid (5.8 mL, 76.19 mmol) was added dropwise to a stirred solution of *tert*-butyl ester **24a** or **26** (2.54 mmol) in dry CH_2Cl_2 (30 mL) under argon atmosphere, cooled to 0 °C. The solution was stirred for 1 h at 0 °C and the solvent was removed *in vacuo*.

(*R*)-2-[(Biphenyl-4-sulfonyl)-(1-*tert*-butoxycarbonyl-2-methyl-propyl)-amino]-ethyl-ammonium trifluoroacetate (25):



The title compound was prepared from **24a** following the general procedure. The crude product was purified by flash chromatography ($CHCl_3$/MeOH 20:1 to 10:1) using a Isolute Flash Si II cartridge to yield **25** as a clear syrup (78% yield). R_f=0.33 ($CHCl_3$/MeOH 8:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (bs, 3H; NH_3^+), 7.93-7.89 (m, 2H; Ar-*H*), 7.74-7.71 (m, 2H; Ar-H), 7.59-7.56 (m, 2H; Ar-*H*), 7.49-7.42 (m, 3H; Ar-*H*), 4.02-3.97 (m, 1H; C*H*$_2$N), 3.91 (d, J_{vic} = 9.6 Hz , 1H; C*H*N), 3.59-3.37 [m, 3H; C*H*$_2$N, C*H*$_2$NH$_3$ (2H)], 2.05-1.97 (m, 1H; Me$_2$C*H*), 1.38 (s, 9H; *Me*$_3$C), 0.97 (d, J_{vic} = 6.4 Hz, 3H; *Me*$_2$CH), 0.77 (d, J_{vic} = 6.4 Hz, 3H; *Me*$_2$CH); ^{13}C NMR (100.57 MHz, $CDCl_3$): δ = 170.2 (C=O), 145.8, 139.2, 138.0 (3×Ar-*C*), 129.1 (2×Ar-*C*H), 128.5 (Ar-*C*H), 128.1 (2×Ar-*C*H), 127.7 (2×Ar-*C*H), 127.3 (2×Ar-*C*H), 82.5 (Me$_3$*C*), 66.7 (*C*HN), 45.2, 41.7 (2×*C*H$_2$N), 29.1 (Me$_2$*CH*), 27.8 (*Me*$_3$C), 20.0, 19.4 (*Me*$_2$CH); elemental analysis calcd (%) for $C_{25}H_{33}F_3N_2O_6S$: C 54.93, H 6.09, N 5.13; found: C 54.99, H 6.03, N 5.10.

(*R*)-2-(*N*-(1-(*tert*-butoxy)-3-methyl-1-oxobutan-2-yl)-4'-((4-chlorobenzyl)oxy)-[1,1'-biphenyl]-4-ylsulfonamido)ethanaminium trifluoroacetate (27):



The title compound was prepared from **26** following the general procedure. The crude product was purified by flash chromatography ($CHCl_3$/MeOH 35:1) using a Isolute Flash Si II cartridge to give **27** as a transparent oil (74% yield). R_f=0.32 ($CHCl_3$/MeOH 15:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (bs, 3H; NH_3^+), 7.92-7.88 (m, 2H; Ar-*H*), 7.71-7.67 (m, 2H; Ar-*H*), 7.56-7.52 (m, 2H; Ar-*H*), 7.42-7.38 (m, 4H; Ar-*H*), 7.09-7.04 (m, 2H; Ar-*H*), 5.10 (s, 2H; C*H*$_2$O), 4.02-3.96 (m, 1H; C*H*$_2$N), 3.92 (d, J_{vic} = 10.4 Hz, 1H; C*H*N), 3.64-3.57 (m, 1H; C*H*$_2$N), 3.43-3.38 (m, 2H; C*H*$_2$NH$_3$), 2.09-1.97 (m, 1H; Me$_2$C*H*), 1.37 (s, 9H; *Me*$_3$C), 0.98 (d, J_{vic} = 6.6 Hz, 3H; *Me*$_2$CH), 0.81 (d, J_{vic} = 6.5 Hz, 3H; *Me*$_2$CH). ^{13}C NMR (100.57 MHz, $CDCl_3$): δ = 171.6 (C=O), 159.26 (Ar-*C*O), 145.8 (Ar-*C*S), 136.4, 135.3, 134.1, 132.0 (4×Ar-*C*), 129.0 (2×Ar-*C*H), 128.9 (2×Ar-*C*H), 128.6 (2×Ar-*C*H), 128.2 (2×Ar-*C*H), 127.4 (2×Ar-*C*H), 115.6 (2×Ar-*C*H), 83.5 (Me$_3$*C*), 69.5 (*C*H$_2$O), 66.9 (*C*HN), 42.3, 41.3 (2×*C*H$_2$N), 28.8 (Me$_2$*CH*), 27.9 (*Me*$_3$C), 20.2, 19.3 (*Me*$_2$CH); elemental analysis calcd (%) for $C_{32}H_{38}ClF_3N_2O_7S$: C 55.93, H 5.57, N 4.08; found: C 55.87, H 5.50, N 4.13.

Table 1S: Data Collection and Refinement Statistics for glycoconjugate co-crystals

PDB code	5I12	5IOL	5I3M	5I2Z	5I4O	5I43
Protein●Ligand	hMMP9wt●**2**	hMMP12wt●**2**	hMMP-12(E219Q)●**3**	hMMP-12(E219Q)●**6**	hMMP-12(E219Q)●**7**	hMMP-12(E219Q)●**8**
Crystallization	40% MPEG-5K, 0.1 M Bicine, pH 7.25	34% PEG-4K, 25% dioxane, 0.15 M imidazole piperidine, pH 8.5	29% PEG-4K, 10% dioxane, 0.13 M imidazole piperidine, pH 8.5	35% PEG-4K, 15% dioxane, 0.15 M imidazole piperidine, pH 8.5	40% PEG-4K, 2% ethylene glycol, 0.18 M imidazole piperidine, pH 8.5	36.5 PEG-4K, 9% dioxane, 0.15 M imidazole piperidine, pH 8.5
Cryoprotectant	40% cryomix CM2*, 10% PEG 10K, 200 mM NaCl, 100 mM PCTP¶ (50% acid / 50% basic) pH 7.0 with 1 mM compound **2**.	40% cryomix SM6*, 25% MPEG 6K, 100 mM AAB¶ (10% acid / 90% basis), pH 8.5.	40% cryomix SM1*, 11% MPEG 4K, 2.5% dioxane, 100 mM imidazole piperidine, pH 8.5.	40% cryomix CM12*, 25% PEG 6K, 100 mM Tris-HCl, pH 8.0.	40% cryomix CM12*, 25% PEG 6K, 100 mM Tris-HCl, pH 8.0 with 1 mM compound **7**.	40% cryomix SM2*, 11% MPEG 4K, 2.5% dioxane, 100 mM imidazole piperidine, pH 8.5
Data Collection						
Source	ESRF ID23-2	ESRF ID30A-1	SOLEIL Proxima 1	SOLEIL Proxima 1	SOLEIL Proxima 2A	SOLEIL Proxima 1
Wavelength (Å)	0.8729	0.9650	0.97857	0.97857	0.9801	0.97857
Space group	$P3_221$	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Unit-cell (Å/°)	139.56 39.56 163.55	39.09 62.86 63.75 β=102.54°	63.72 63.140 78.92 β=103.09°	63.99 63.12 78.75 β=102.37°	63.98 63.51 78.64 β=102.31°	64.03 63.66 79.03 β= 103.03°
Molec./asym.	1	2	4	4	4	4
Resolution (Å)	34.3-1.59 (1.63-1.59)	45.0-2.45 (2.51-2.45)	48.8-2.17 (2.23-2.17)	48.8-2.29 (2.35-2.29)	44.6-1.95 (2.00-1.95)	44.6-1.95 (2.00-1.95)
$CC_{1/2}$ [#](%)	100 (84.3)	98.3 (96.1)	99.7 (93.5)	98.9 (92.7)	98.4 (73.5)	99.3 (85.0)
$\langle I/\sigma(I)\rangle$[&]	15.04 (1.65)	9.6 (5.23)	9.44 (3.06)	6.53 (2.96)	4.79 (1.68)	7.24 (2.02)
R_{fact}(%)	11.1 (157.2)	9.2 (19.0)	8.9 (45.1)	16.2 (47.8)	20.4 (86.8)	15.7 (62.4)
R_{meas}(%)	11.5 (163.5)	11.1 (23.0)	10.0 (52.3)	18.3 (53.9)	23.0 (98.5)	17.2 (71.6)
Completeness (%)	99.7 (96.8)	99.2 (99.3)	99.3 (98.9)	99.7 (100.0)	98.4 (97.7)	99.8 (99.8)
Multiplicity	13.2 (13.7)	3.1 (3.2)	4.3 (3.7)	4.6 (4.7)	4.5 (4.3)	6.0 (4.0)
Refinement						
Resolution (Å)	34.26-1.59 (1.67-1.59)	44.2-2.45 (2.7- 2.45)	48.8-2.17 (2.23-2.17)	44.4-2.29 (2.38-2.29)	32.9-2.05 (2.10-2.05)	44.6-1.95 (2.00- 1.95)
No. of reflections	20929 (2717)	11075 (2575)	30719 (2245)	27354 (2585)	36421 (2675)	43013 (3157)
R_{work} (%)	18.8 (34.9)	17.5 (24.9)	20.6 (25.3)	21.4 (26.3)	21.0 (24.9)	20.0 (32.0)
R_{free} (%)	22.8 (37.5)	25.3 (34.2)	28.4 (30.3)	21.9 (32.2)	26.5 (30.8)	23.3 (31.0)
R.m.s. deviations						
Bond lengths (Å)	0.006	0.015	0.017	0.010	0.020	0.021
Bond angles (°)	1.033	1.754	1.904	1.422	1.938	1.989
Ramachandran[‖]						
favoured (%)	97	96	96	96	95	96
outliers (#)	0	0	0	0	0	0

Cryomixes:*[8] **CM2: 25% di-ethylene glycol + 25% glycerol + 25% 1,2-propanediol; **SM1:** 12.5% diethylene glycol + 12.5% glycerol + 12.5% 1,2-propanediol + 25% DMSO + 25% 1,4-dioxane; **SM2:** 12.5% ethylene glycol + 12.5% glycerol + 12.5% 1,2-propanediol + 25% DMSO + 37.5% 1,4-dioxane; **SM6:** 12.5% diethylene glycol + 12.5% glycerol + 12.5% 1,2-propanediol + 12.5% 2,3-butanediol + 25% DMSO + 30% 1,4-dioxane.

¶ *Mixed linear buffers:*[9] **PCTP:** sodium propionate, sodium cacodylate, Bis-Tris-propane; **AAB:** sodium acetate, ADA, Bicine.

[#] Correlation coefficient between intensities from random half-datasets.[10]

[‖] Ramachandran statistics from PDB validation report.[11]

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