Supporting Information

A new class of highly potent matrix metalloproteinase inhibitors based on triazole-substituted hydroxamates:

(Radio)synthesis, in vitro and first in vivo evaluation

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**General.** All chemicals, reagents and solvents for the synthesis of the compounds were analytical grade, purchased from commercial sources and used without further purification unless otherwise specified. All air and moisture-sensitive reactions were performed under argon atmosphere. Solvents were purified and dried by literature methods where necessary. The melting points (mp) are uncorrected and were determined in capillary tubes on a Stuart Scientific SMP3 capillary melting point apparatus. Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). Thin layer chromatography (TLC) was carried out on silica gel-coated polyester backed TLC plates (Polygram, SIL G/UV254, Macherey-Nagel) using solvent mixtures of cyclohexane (CH), ethyl acetate (EA) and methanol (MeOH). Compounds were visualized by UV light (254 nm). NMR spectra were recorded in CDCl$_3$, CD$_3$OD or DMSO-$d_6$ on a Bruker ARX300, a Bruker DPX300 (1$^\text{H}$ NMR, 300 MHz, 1$^\text{3}$C NMR, 75MHz, 1$^\text{9}$F NMR, 282 MHz), a Bruker AMX 400 (1$^\text{H}$ NMR, 400 MHz, 1$^\text{3}$C NMR, 100 MHz) and a Varian Unity plus 600 (1$^\text{H}$ NMR, 600 MHz, 1$^\text{3}$C NMR, 151 MHz) spectrometer. TMS (1$^\text{H}$), CDCl$_3$, DMSO-$d_6$, CD$_3$OD (1$^\text{3}$C) and CFCl$_3$ (1$^\text{9}$F) were used as internal standards and all chemical shift values were recorded in ppm (δ). Values of the coupling constant $J$ are given in Hertz (Hz); the following abbreviations are used for the description of 1$^\text{H}$ NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), doublet of triplets (dt), broad singlet (br s). The chemical shifts of complex multiplets are given as the range of their occurrence. For some long chain compounds 1$^\text{3}$C NMR signals at δ ~ 70 ppm do have multiple intensities. Exact mass analyses were conducted on a Bruker MicroTof apparatus. The chemical purities of each new non-radioactive compound were ≥ 95% assessed by analytical gradient reversed phase HPLC system A or B ($\lambda$=254 nm). HPLC System A: Two Smartline 1000 pumps and a Smartline UV detector 2500 (Herbert Knauer GmbH), a GabiStar γ-detector (Raytest Isotopenmessgeräte GmbH) and a Nucleosil 100-5 C-18 column (250 mm × 4.6 mm). The recorded data were processed by the GINA Star software (Raytest Isotopenmessgeräte...
GmbH). The HPLC method A1 started with a linear gradient from 10% to 90% CH₃CN in water (0.1% TFA) over 9 min, followed by a linear gradient from 90% to 10% CH₃CN in water (0.1% TFA) over 6 min, with a flow rate of 1 mL·min⁻¹ (unless otherwise specified). HPLC method A2 started with 30% CH₃CN in water (0.1% TFA) for 15 min, followed by a linear gradient from 30% to 90% CH₃CN in water (0.1% TFA) over 3 min, followed by a linear gradient from 90% to 30% CH₃CN in water (0.1% TFA) over 2 min with a flow rate of 1 mL·min⁻¹. HPLC system B: Two K-1800 pumps and an S-2500 UV detector (Herbert Knauer GmbH), a GabiStar γ-detector (Raytest Isotopenmessgeräte GmbH). The recorded data were processed by the ChromGate HPLC software (Herbert Knauer GmbH). HPLC method B1 using a Nucleosil 100-5 C18 column (250 mm × 4.6 mm) started with a linear gradient from 10% to 80% CH₃CN in water (0.1% TFA) over 18 min, holding for 20 min and followed by a linear gradient from 80% to 10% CH₃CN in water (0.1% TFA) over 2 min, with a flow rate of 1.5 mL·min⁻¹. HPLC method B2 using a ACE 5 AQ column (250 mm × 10 mm) started with a linear gradient from 10% to 80% CH₃CN in water (0.1% TFA) over 18 min, holding for 20 min and followed by a linear gradient from 80% to 10% CH₃CN in water (0.1% TFA) over 2 min, with a flow rate of 5.5 mL·min⁻¹.

Synthesis of the PEGylated building blocks 7 and 8

**3,6,9,12-Tetraoxapentadec-14-yn-1-ol (2).** Tetraethylenglycol (20.00 g, 103 mmol) was dissolved in THF (200 mL) and cooled to 0°C. NaH (2.72 g, 113 mmol) was added slowly and the suspension was stirred at 0°C for 10 min. Subsequently propargylbromide (113 mmol) was added dropwise. After stirring at room temperature for 16 h the solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel, EA) yielding a yellow liquid (9.84 g, 42 mmol, 41%). ¹H NMR (300 MHz, CDCl₃) δ 4.21 (d, OCH₂C≡CH ⁴Jₜ,H = 2.4 Hz, 2H), 3.76 – 3.64 (m, CH₂OH, CH₂CH₂O 14H), 3.64 – 3.58 (m, CH₂CH₂OH, 2H), 2.80 (t, OH, ⁴Jₜ,H = 5.9 Hz, 1H), 2.46 (t, C≡CH, ⁴Jₜ,H = 2.4 Hz, 1H). ¹³C
NMR (75 MHz, CDCl$_3$) $\delta$ 79.49 (C≡CH), 74.47 (C≡CH), 72.37 (CH$_2$CH$_2$OH), 70.47, 70.42, 70.38, 70.25, 70.19, 68.95 (CH$_2$CH$_2$O), 61.55 (CH$_2$OH), 58.24 (CH$_2$CCH). MS-ES(+)-EM: $m/z$ = 255.1195 [(M+Na)$^+$] calcd for C$_{11}$H$_{20}$O$_3$Na$: 255.1203.

3,6,9,12-Tetraoxapentadec-14-yn-1-yl methanesulfonate (3). A solution of 3,6,9,12-tetraoxapentadec-14-yn-1-ol (2, 8.0 g, 34.5 mmol) and triethylamine (5.7 mL, 41.4 mmol, 1.2 eq.) in CH$_2$Cl$_2$ (60 mL) was cooled to 0°C and methanesulfonyl chloride (3.1 mL, 39.7 mmol) was added dropwise. After the reaction mixture was stirred for 1 h at 0°C and for additional 16 h at ambient temperature the resulting precipitate was filtered off and washed with small amounts of CH$_2$Cl$_2$. The combined organic layer were washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The product was obtained as a yellow oil (9.9 g, 32.09 mmol, 93%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.44 – 4.34 (m, CH$_3$SO$_2$CH$_2$, 2H), 4.21 (d, CH$_2$C≡CH, $^4$J$_{H,H}$ = 2.4 Hz, 2H), 3.81 – 3.75 (m, CH$_3$SO$_2$CH$_2$CH$_2$O, 2H), 3.74 – 3.60 (m, CH$_2$CH$_2$O, 12H), 3.09 (s, CH$_3$, 3H), 2.46 (t, C≡CH, $^4$J$_{H,H}$ = 2.4 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 79.50 (C≡CH), 74.53 (C≡CH), 70.47, 70.45, 70.40, 70.38, 70.26 (CH$_2$CH$_2$O), 69.27 (CH$_3$SO$_2$CH$_2$CH$_2$O), 68.95 (CH$_3$SO$_2$CH$_2$CH$_2$O), 68.87 (CH$_2$CH$_2$O), 58.26 (CH$_2$C≡CH), 37.60 (CH$_3$). MS-ES(+)-EM: $m/z$ = 333.0980 [(M+Na)$^+$] calcd for C$_{12}$H$_{22}$O$_7$Na$: 333.0978.

4-(3,6,9,12-Tetraoxapentadec-14-yn-1-yloxy)benzaldehyde (4). To a solution of 3,6,9,12-tetraoxapentadec-14-yn-1-yl methanesulfonate (3, 9.00 g, 29.0 mmol) and 4-hydroxybenzaldehyde (5.55 g, 45.5 mmol, 1.57 eq.) in DMF (120 mL) caesium carbonate (30.00 g, 91.1 mmol, 3.14 eq.) was added and the resulting suspension was stirred at 100°C for 2 h. After cooling to room temperature ethyl acetate (240 mL) and water (240 mL) were added and the organic layer was washed with 1N NaOH-solution (3 × 100 mL). After washing with water (3 × 100 mL) and brine (1 × 100 mL), drying over magnesium sulfate and removing the solvent under reduced pressure, the crude product was purified by column
chromatography (CH/EA, 1:1). The product was obtained as a yellow oil (5.74 g, 17.1 mmol, 59%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.88 (d, CHO, $^4$J$_{H,H}$ = 0.8 Hz, 1H), 7.83 (d, ArH, $^3$J$_{H,H}$ = 8.0 Hz, 2H), 7.03 (d, ArH, $^3$J$_{H,H}$ = 7.8 Hz, 2H), 4.25 – 4.18 (m, CH$_2$CH$_2$O, 4H), 3.92 – 3.87 (m, CH$_2$CH$_2$O, 2H), 3.76 – 3.72 (m, CH$_2$CH$_2$O, 2H), 3.72 – 3.63 (m, CH$_2$CH$_2$O, 10H), 2.44 (t, C≡CH, $^4$J$_{H,H}$ = 2.4 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 190.70 (C=O), 163.76 (qArC=O), 131.84 (ArCH), 129.93 (qArCCHO), 114.78 (ArCH), 79.56 (C=CH), 74.47 (C=CH), 70.80, 70.54, 70.51, 70.31, 69.36, 69.01 (CH$_2$CH$_2$O), 67.68 (CH$_3$SO$_2$CH$_2$CH$_2$), 58.30 (CH$_2$C=CH). MS-ES(+) -EM: m/z = 359.1471 [(M+Na)$^+$] calcd for C$_{18}$H$_{24}$O$_6$Na$: 359.1465; m/z = 337.1654 [(M+H)$^+$] calcd for C$_{18}$H$_{24}$O$_6$: 337.1646.

(4-(3,6,9,12-Tetraoxapentadec-14-yn-1-yl oxy)phenyl)methanol (5). To a solution of 4-(3,6,9,12-tetraoxapentadec-14-yn-1-yl oxy)benzaldehyde (4, 4.00 g, 11.89 mmol) in methanol (45 mL) sodium borohydride (0.67 g, 17.84 mmol, 1.5 eq.) was added at 0°C. After stirring for 2 h at 0°C the excess of sodium borohydride was destroyed by adding 1N aqueous HCl. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, CH/EA, 1:1). The product was obtained as a yellow oil (3.74 g, 11.06 mmol, 93%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.27 (d, ArH, $^3$J$_{H,H}$ = 8.7 Hz, 2H), 6.89 (d, ArH, $^3$J$_{H,H}$ = 8.7 Hz, 2H), 4.60 (s, CH$_2$OH, 1H), 4.19 (d, CH$_2$C=CH, $^4$J$_{H,H}$ = 2.4 Hz, 2H), 4.16 – 4.08 (m, CH$_2$CH$_2$O, 2H), 3.90 – 3.81 (m, CH$_2$CH$_2$O, 2H), 3.78 – 3.70 (m, CH$_2$CH$_2$O, 2H), 3.70 – 3.62 (m, CH$_2$CH$_2$O, 10H), 2.43 (t, C≡CH, $^4$J$_{H,H}$ = 2.4 Hz, 1H), 1.92 (s, OH, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.27 (qArCO), 133.29 (qArCCHO), 128.50 (ArCH), 114.55 (ArCH), 79.57 (C=CH), 74.51 (C=CH), 70.73, 70.55, 70.51, 70.30 (CH$_2$CH$_2$O), 69.64 (CH$_2$CH$_2$O), 69.01 (CH$_2$CH$_2$O), 67.35 (ArCOCH$_2$CH$_2$O), 64.85 (CH$_2$OH), 58.31 (CH$_2$C=CH). MS-ES(+) -EM: m/z = 361.1617 [(M+Na)$^+$] calcd for C$_{18}$H$_{26}$O$_6$Na$: 361.1622.
Trifluoroacetic acid anhydride (1.28 mL, 9.21 mmol, 1.24 eq.) was added dropwise to a stirred solution of (4-(3,6,9,12-tetraoxapentadec-14-yn-1-yloxy)phenyl)methanol (5, 2.51 g, 7.43 mmol). The mixture was heated to reflux for 30 minutes. After cooling to room temperature the reaction mixture was diluted with diethyl ether (100 mL) and washed with saturated aqueous NaHCO₃. The organic layer was dried over magnesium sulfate and concentrated to give a yellow oil (3.22 g, 7.43 mmol, 100%).

**1H NMR** (300 MHz, CDCl₃) δ 7.33 (d, ArH, 3JH,H = 8.7 Hz, 2H), 6.93 (d, ArH, 3JH,H = 8.7 Hz, 2H), 5.29 (s, CF₃COOC₂H₂, 2H), 4.20 (d, CH₂CH≡CH, 4JH,H = 2.4 Hz, 2H), 4.18 – 4.09 (m, CH₂CH₂O, 2H), 3.91 – 3.82 (m, CH₂CH₂O, 2H), 3.78 – 3.71 (m, CH₂CH₂O, 2H), 3.71 – 3.57 (m, CH₂CH₂O, 10H), 2.43 (t, C≡CH, 4JH,H = 2.4 Hz, 1H).

**13C NMR** (75 MHz, CDCl₃) δ 159.54 (qArC=O), 157.34 (CF₃C=O, 2JCF = 42.3 Hz), 130.65 (ArCH), 125.40 (qArCH₂OCOCF₃), 114.78 (ArCH), 114.39 (CF₃, 1JC,F = 285.7 Hz), 79.57 (C=CH), 74.47 (C=CH), 70.76, 70.56, 70.53, 70.33 (CH₂CH₂O), 69.54 (CH₂CH₂O), 69.02 (CH₂CH₂O), 67.89 (ArCOCH₂CH₂O), 67.40 (CH₂OCOCF₃), 58.32 (CH₂C=CH). MS-ES(+)-EM: m/z = 457.1440 [(M+Na)+] calcd for C₂₀H₂₅F₃O₇Na+: 457.1445.

1-(4-(Bromomethyl)phenoxy)-3,6,9,12-tetraoxapentadec-14-yne (7).

4-(3,6,9,12-tetraoxapentadec-14-yn-1-yloxy)benzyl 2,2,2-trifluoroacetate (6, 3.10 g, 7.13 mmol) was dissolved in dry tetrahydrofurane (15 mL) and dry lithium bromide (0.79 g, 9.13 mmol, 1.28 eq.) was added to the stirred solution. The reaction mixture was heated to reflux for 20 h. After removing the solvent under reduced pressure the crude product was purified by column chromatography (silca gel, CH/EA, 2:1) to give a yellow oil (2.86 g, 7.13 mmol, 100%).

**1H NMR** (300 MHz, CDCl₃) δ 7.31 (d, ArH, 3JH,H = 8.8 Hz, 2H), 6.88 (d, ArH, 3JH,H = 8.7 Hz, 2H), 4.49 (s, CH₂Br, 2H), 4.20 (d, CH₂C=CH, 4JH,H = 2.4 Hz, 2H), 4.17 – 4.07 (m, CH₂CH₂O, 2H), 3.91 – 3.81 (m, CH₂CH₂O, 2H), 3.78 – 3.61 (m, CH₂CH₂O, 12H), 3.52 – 3.37 (m, CH₂CH₂O, 2H), 2.43 (t, C≡CH, 4JH,H = 2.4 Hz, 1H). **13C NMR** (75 MHz, CDCl₃) δ 158.82 (qArCO), 130.36 (ArCH), 130.02 (qArCH₂Br), 114.79 (ArCH), 79.58 (C=CH), 74.58.
(C≡CH), 70.74, 70.54, 70.51, 70.31 (CH₂CH₂O), 69.55 (CH₂CH₂O), 69.01 (CH₂CH₂O), 67.40 (ArCOCH₂CH₂O), 58.31 (CH₂C≡CH), 33.88 (C₂H₂Br).

1-Fluoro-3,6,9,12,15-pentaoxaoctadec-17-yne (8). 3,6,9,12-Tetraoxapentadec-14-yn-1-ol (2, 1.387 g, 5.97 mmol) was dissolved in THF (14 mL) and cooled to 0°C. Sodium hydride (190 mg, 7.83 mmol, 1.31 eq.) was added. After stirring at 0°C for 10 min 2-fluoroethyl 4-methylbenzenesulfonate (7.83 mmol, 1.707 g, 1.31 eq.) was added and the reaction mixture was stirred at ambient temperature for 16 h. The solvent was removed under reduced pressure and column chromatographic purification (silica gel, CH/EE, 1:1) yielded the product as a colorless oil (1.495 g, 5.37 mmol, 90%).

1H NMR (300 MHz, CDCl₃) δ 4.57 (dm, 2J_H,F = 47.9 Hz, C₂H₂F, 2H), 4.20 (d, CH₂C≡CH, 4J_H,H = 2.4 Hz, 2H), 3.76 (dm, 3J_H,F = 29.7 Hz, C₂H₂C≡CH₂F, 2H), 3.74 – 3.60 (m, C₂H₂CH₂O, 16H), 2.46 (t, C≡CH, 3J_H,H = 2.4 Hz, 2H). 13C NMR (75 MHz, CDCl₃) δ 82.96 (d, 1J_C,F = 168.8 Hz, CH₂F), 79.48 (C≡CH), 74.44 (C≡CH), 70.40, 70.38, 70.36, 70.34, (CH₂CH₂O), 70.20 (d, 2J_C,F = 19.7 Hz, CH₂CH₂F), 68.91 (CH₂CH₂O), 58.2 (CH₂C≡CH). 19F NMR (282 MHz, CDCl₃) δ – 222.93 (tt, 2J_H,F = 47.7 Hz, 3J_H,F = 29.7 Hz).

Synthesis of MMPI precursor 14

(R)-tert-Butyl 2-(4-methoxyphenylsulfonamido)-3-methylbutanoate (10). A white solid, yield: 75%, mp 120.3 °C, analytical data see ref. [2].

(R)-tert-Butyl 2-(N-(4-(3,6,9,12-tetraoxapentadec-14-yn-1-yloxy)benzyl)-4-methoxyphenylsulfonamido)-3-methylbutanoate (11). To a solution of (R)-tert-butyl 2-(4-methoxyphenylsulfonamido)-3-methylbutanoate (10) (2.13 g, 6.19 mmol) in DMF (ca. 65 µmol/mL, 230 mL) 1-(4-(bromomethyl)phenoxy)-3,6,9,12-tetraoxapentadec-14-yn (7, 6.19 mmol, 2.48 g) and potassium carbonate (61.9 mmol, 8.56 g) was added. The resulting suspension was stirred at room temperature for 2 days. The mixture was diluted with water (100 mL) and extracted with EA (3 × 50 mL). The combined organic phases were washed
with brine, dried over magnesium sulfate and the solvent was removed under reduced
pressure. The crude product was purified by column chromatography (silica gel, CH/EA 2:1).
The product was obtained as colorless oil (3.25 g, 4.89 mmol, 79%). \(^1\)H NMR (400 MHz,
CDCl\(_3\)) \(\delta\) 7.67 (d, ArH, \(^3\)J\(_{H,H}\) = 9.0 Hz, 2H), 7.33 (d, ArH, \(^3\)J\(_{H,H}\) = 8.6 Hz, 2H), 6.88 (d, ArH,
\(^3\)J\(_{H,H}\) = 9.0 Hz, 2H), 6.78 (d, ArH, \(^3\)J\(_{H,H}\) = 8.7 Hz, 2H), 4.67 (AB, d, NCH\(_2\), \(^2\)J\(_{H,H}\) = 15.4 Hz,
1H), 4.41 (AB, d, NCH\(_2\), \(^2\)J\(_{H,H}\) = 15.5 Hz, 1H), 4.20 (d, OCH\(_2\)C=CH, \(^4\)J\(_{H,H}\) = 2.4 Hz, 2H), 4.17
– 4.03 (m, OCH\(_2\)CH\(_2\), 2H), 3.88 – 3.82 (m, OCH\(_2\)CH\(_2\), 2H), 3.84 (s, CH\(_3\), 3H), 3.77 – 3.64 (m, NCH,
OCH\(_2\)CH\(_2\), 13H), 2.43 (t, C≡CH, \(^4\)J\(_{H,H}\) = 2.4 Hz, 1H), 1.89 (m, CH(CH\(_3\))\(_2\), 1H), 1.32 (s, CH\(_3\), 9H), 0.83 (d, CH(CH\(_3\))\(_2\), \(^3\)J\(_{H,H}\) = 6.6 Hz, 3H), 0.79 (d, CH(CH\(_3\))\(_2\), \(^3\)J\(_{H,H}\) = 6.6 Hz, 3H).
\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.82 (C=OCH(CH\(_3\))\(_3\)), 162.49 (qAr COCH\(_3\)), 158.08
(qAr COCH\(_2\)CH\(_2\)), 132.85 (qAr C=O), 130.37 (ArCH), 129.63 (qAr CCH\(_2\)N), 129.49 (ArCH),
114.07 (ArCH), 113.80 (ArCH), 81.71 (CH(CH\(_3\))\(_3\)), 79.62 (C=CH), 74.48 (C=CH), 70.78,
70.60, 70.58, 70.37, 69.71 (CH\(_2\)CH\(_2\)O), 69.1 (CH\(_2\)CH\(_2\)O), 67.34 (ArCOCH\(_2\)CH\(_2\)), 66.94
(NCH), 58.36 (CH\(_2\)C=CH), 55.55 (OCH\(_3\)), 47.82 (NCH\(_2\)), 28.88 (CH(CH\(_3\))\(_2\)) 27.83
(C(CH\(_3\))\(_3\)), 19.49 (CH(CH\(_3\))\(_2\)), 19.34 (CH(CH\(_3\))\(_2\)). MS-ES(+)-EM: \(m/z = 686.2969\) [(M+Na)\(^+\) ]
calcld for C\(_{34}\)H\(_{49}\)NO\(_{10}\)SNa\(^+\): 686.2969.

(R)-2-(N-(4-(3,6,9,12-Tetraoxapentadec-14-yn-1-yloxy)benzyl)-4-methoxyphenyl-
sulfonamido)-3-methylbutanoic acid (12). A stirred solution of the carboxylic acid ester 11
(3.12 g, 4.70 mmol) in dichloromethane (50 mL) was cooled to 0°C. Hydrochloric acid gas
was bubbled through the solution. TLC was used to monitor the reaction progress (EA). After
complete conversion the solvent was removed under reduced pressure. Column
chromatographic purification (silica gel, CH/EA, 1:1) gave 12 as a colorless wax (2.71 g, 4.47
mmol, 95%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.70 (d, ArH, \(^3\)J\(_{H,H}\) = 9.0 Hz, 2H), 7.26 (d, ArH,
\(^3\)J\(_{H,H}\) = 8.0 Hz, 2H), 6.88 (d, ArH, \(^3\)J\(_{H,H}\) = 9.0 Hz, 2H), 6.79 (d, ArH, \(^3\)J\(_{H,H}\) = 8.7 Hz, 2H), 4.56
(AB, d, NCH\(_2\), \(^3\)J\(_{H,H}\) = 15.6 Hz, 1H), 4.37 (AB, d, NCH\(_2\), \(^3\)J\(_{H,H}\) = 15.6 Hz, 1H), 4.20 (d, CH\(_2\)C=CH, \(^4\)J\(_{H,H}\) = 2.4 Hz, 2H), 4.17 – 4.03 (m, CH\(_2\)CH\(_2\)O, 2H), 3.90 – 3.79 (m, CH\(_2\)CH\(_2\)O,
(2R)-2-(N-(4-(3,6,9,12-Tetraoxapentadec-14-yn-1-yloxy)benzyl)-4-methoxyphenylsulfonamido)-3-methyl-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide (13). To a solution of the carboxylic acid 12 (1.82 g, 3.00 mmol) in DMF (15 mL) 1-hydroxybenzotriazole hydrate (HOBT, 0.49 g, 3.60 mmol, 1.2 eq.), 4-methylmorpholine (NMM, 0.99 mL, 9.00 mmol, 3.0 eq.), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (THPONH₂, 1.09 g, 9.30 mmol, 3.1 eq.) and N-((dimethylamino)-propyl)-N'-ethylcarbodiimide hydrochloride (EDC, 0.80 g, 4.20 mmol, 1.4 eq.) were added. After stirring for 16 h at room temperature the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed successively with water, 5% aqueous KH₂SO₄, saturated aqueous NaHCO₃ and brine (25 mL) and dried over magnesium sulfate. After removing the solvent under reduced pressure column chromatographic purification (silica gel, cyclohexane/ethyl acetate 1:1) yielded the THP-protected hydroxamic acid 13 as diastereomeric mixture (1.78 g, 2.52 mmol, 84%). ¹H NMR (300 MHz, CDCl₃) δ 9.11 (s, NH, 1H), 8.90 (s, NH, 1H), 7.60 (d, ArH, ³J_H,H = 8.9 Hz, 2H), 7.58 (d, ArH, ³J_H,H = 8.9 Hz, 2H), 7.30 (d, ArH, ³J_H,H = 8.6 Hz, 2H), 7.29 (d, ArH, ³J_H,H = 8.6 Hz, 2H), 6.87 (d, ArH, ³J_H,H = 8.6 Hz, 2H), 6.84 (d, ArH, ³J_H,H = 8.7 Hz, 2H), 6.79 (d, ArH,
\(^3J_{H,H} = 8.7 \text{ Hz, 2H}\), 6.76 (d, Ar\(^H\), \(^2J_{H,H} = 8.7 \text{ Hz, 2H}\) ), 4.92 (m, THP-CH\(_1\) , 1H), 4.78 (m, THP-CH\(_1\) , 1H), 4.64 (AB, d, NCH\(_2\), \(^2J_{H,H} = 15.3 \text{ Hz, 1H}\) ), 4.45 (AB, d, NCH\(_2\), \(^2J_{H,H} = 15.3 \text{ Hz, 1H}\) ), 4.20 (d, CH\(_2\)C=CH, \(^4J_{H,H} = 2.4 \text{ Hz, 2H}\) ), 4.14 – 4.02 (m, CH\(_2\)CH\(_2\)O, 2H), 3.98 – 3.79 (m, NCH, CH\(_2\)CH\(_2\)O, THP-CH\(_2\), 1H), 2.43 (t, C≡CH, \(^4J_{H,H} = 2.4 \text{ Hz, 1H}\) ), 2.17 (m, C(CH\(_3\))\(_2\)), 1.93 – 1.50 (m, THP-CH\(_2\), 6H), 0.87 (d, CH(CH\(_3\))\(_2\), \(^3J_{H,H} = 6.4 \text{ Hz, 3H}\) ), 0.82 (d, CH(CH\(_3\))\(_2\), \(^3J_{H,H} = 6.4 \text{ Hz, 3H}\) ), 0.56 (d, CH(CH\(_3\))\(_2\), \(^3J_{H,H} = 6.5 \text{ Hz, 3H}\) ), 0.48 (d, CH(CH\(_3\))\(_2\), \(^3J_{H,H} = 6.6 \text{ Hz, 3H}\) ).\(^{13}\)C NMR (101 MHz, CDCl\(_3\) ) \(\delta\) 167.04 (C\(ONH\)), 166.85 (C\(ONH\)), 162.83 (qArC\(OCH\(_3\)\)), 162.73 (qArC\(OCH\(_3\)\)), 158.18 (qArC\(SO\(_2\)\)), 132.12 (qArC\(SO\(_2\)\)), 131.97 (qArC\(SO\(_2\)\)), 130.88 (Ar\(CH\)), 130.83 (Ar\(CH\)), 129.40 (Ar\(CH\)), 129.09, (qArC\(CH\(_2\)\)N), 114.13 (Ar\(CH\)), 114.06 (Ar\(CH\)), 114.05 (Ar\(CH\)), 113.97 (Ar\(CH\)), 102.17 (THP-CH), 101.70 THP-CH), 79.61 (C≡CH), 74.49 (C≡CH), 70.79, 70.57, 70.37 (CH\(_2\)CH\(_2\)O), 69.69 (CH\(_2\)CH\(_2\)O), 69.06 (CH\(_2\)CH\(_2\)O), 67.32 (CH\(_2\)CH\(_2\)O), 64.13 (NCH), 64.08 (NCH), 61.98 (THP-OCH\(_2\)), 58.35 (CH\(_2\)C=CH), 55.56 (OCH\(_3\) ), 55.54 (OCH\(_3\)), 47.74 (NCH\(_2\) ), 47.65 (NCH\(_2\)), 27.78 (THP-CH\(_2\)), 27.49 (CH(CH\(_3\))\(_2\)), 27.47 (CH(CH\(_3\))\(_2\)), 24.96 (THP-CH\(_2\)), 19.67 (CH(CH\(_3\))\(_2\)), 19.63 (CH(CH\(_3\))\(_2\)), 19.18 (CH(CH\(_3\))\(_2\)), 18.17 (THP-CH\(_2\)).

MS-ES(+)-EM: \(m/z = 729.3027 [(\text{M+Na})^+] \) calcd for C\(_{35}\)H\(_{50}\)N\(_3\)O\(_{11}\)Na\(^+\): 729.3028.

\((R\)-2-(N-(4-(3,6,9,12-Tetraoxapentadec-14-yn-1-yloxy)benzyl)-4-methoxyphenyl-sulfonamido)-N-hydroxy-3-methylbutanamide \((14)\). \((2R\)-2-(N-(4-(3,6,9,12-Tetraoxapentadec-14-yn-1-yloxy)benzyl)-4-methoxyphenyl-sulfonamido)-3-methyl-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide \((13, 917 \text{ mg, } 1.30 \text{ mmol})\) was dissolved in dry dioxane \((2.6 \text{ mL})\). 4 N hydrochloric acid in dioxane \((1.3 \text{ mL}, 5.2 \text{ mmol, } 4.0 \text{ eq.})\) and dry methanol \((2.6 \text{ mL})\) were added. After stirring for 1.5 h at room temperature the reaction mixture was diluted with ethyl acetate \((10 \text{ mL})\). The organic layer was washed with water, dried over magnesium sulfate and the solvent was removed under reduced pressure yielding the hydroxamic acid \(14\) \((722 \text{ mg, } 1.16 \text{ mmol, } 89\%)\).\(^1\)H NMR (300 MHz, CDCl\(_3\) ) \(\delta\) 9.15 (s, S11
Synthesis of MMPI precursor 23\(^3\)

\((R)\)-\textit{tert}-Butyl 2-((4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)benzyl)amino)-3-methylbutanoate (18). D-Valin-\textit{tert}-butylester hydrochloride (8.16 g, 38.93 mmol, 1.05 eq.) and 4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)benzaldehyde (17, 11.99 g, 37.08 mmol), prepared following literature procedure,\(^3\) were dissolved in dichloroethane (13 mL) under argon atmosphere. Triethylamine (7.7 mL, 55.62 mmol, 1.50 eq.), molecular sieve and sodium triacetoxy borohydride (NaBH(OAc))\(_3\), 95\%, 11.71 g, 51.91 mmol, 1.4 eq.) were added and the reaction mixture was stirred under argon atmosphere at room temperature. After 24 h again NaBH(OAc))\(_3\) (5.00 g, 22.16 mmol) was added and the mixture was stirred for another 18 hours. Quenching with saturated aqueous NaHCO\(_3\) (200 mL), extraction with ethyl acetate (3 \(\times\) 100 mL), drying over magnesium sulfate and concentration under reduced pressure yielded the crude product, which was purified by column chromatography (silica gel,
The product was isolated as a colorless oil (16.00 g, 33.37 mmol, 90%). ¹H NMR (300 MHz, CDCl₃) δ 7.24 (d, ArH, ³J_H,H = 8.7 Hz, 2H), 6.86 (d, ArH, ³J_H,H = 8.7 Hz, 2H), 4.15 – 4.09 (m, CH₂CH₂O, 2H), 3.89 – 3.82 (m, CH₂CH₂O, 2H), 3.76 (AB, d, NHCH₂, ³J_H,H = 11.4 Hz, 1H), 3.76 – 3.63 (m, CH₂CH₂O, 10H), 3.51 (AB, d, NHCH₂, ³J_H,H = 12.7 Hz, 1H), 3.38 (t, C(H₃)₂N, ³J_H,H = 5.0 Hz, 2H), 2.85 (d, NHCH, ³J_H,H = 5.0 Hz, 1H), 1.87 (m, CH(CH₃)₂, 1H), 1.72 (s, NH, 1H), 1.48 (s, C(CH₃)₃, 9H), 0.94 (d, CH(CH₃)₂, ³J_H,H = 6.8 Hz, 1H), 0.93 (d, CH(CH₃)₂, ³J_H,H = 6.8 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 174.62 (C(=O)), 157.78 (qArC(OCH₂CH₂O), 132.67 (qArC(CH₃)₂), 129.35 (ArC), 114.36 (ArC), 80.76 (C(CH₃)₂), 70.8, 70.68, 70.67, 70.01 (CH₂CH₂O), 69.75 (CH₂CH₂O), 67.4 (CH₂CH₂O), 66.91 (NCH), 51.83 (CH₂N), 50.65 (NCH₂), 31.65 (CH(CH₃)₂), 28.19 (C(CH₃)₃), 19.23 (CH(CH₃)₂), 18.66 (CH(CH₃)₂). MS-ES(+)·EM: m/z = 481.3012 [(M+H)⁺] calcd for C₂₄H₴₀N₄O₆H⁺: 481.3021. MS-ES(+)·EM: m/z = 503.2831 [(M+Na)⁺] calcd for C₂₄H₴₀N₄O₆Na⁺: 503.2840.

(R)-tert-Butyl 2-(N-(4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)ethoxy)benzyl)-4-methoxyphenylsulfonamido)-3-methylbutanoate (20). Compound 18 (7.86 g, 16.36 mmol) was dissolved in pyridine (40 mL) and p-methoxybenzenesulfonylchloride (20.28 g, 98.16 mmol, 6 eq.) was added. After heating to 60°C for 18 h the reaction mixture was cooled to room temperature and diluted with dichloromethane. The organic layer was washed with 1N aqueous hydrochloric acid, water and brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. Column chromatographic purification (silica gel, CH/EA, 2:1) gave a yellow oil (9.80 g, 15.05 mmol, 92%). ¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, ArH, ³J_H,H = 9.0 Hz, 2H), 7.33 (d, ArH, ³J_H,H = 8.6 Hz, 2H), 6.88 (d, ArH, ³J_H,H = 9.0 Hz, 2H), 6.79 (d, ArH, ³J_H,H = 8.7 Hz, 2H), 4.68 (AB, d, NCH₂, ³J_H,H = 15.5 Hz, 1H), 4.41 (AB, d, NCH₂, ³J_H,H = 15.5 Hz, 1H), 4.17 – 4.10 (m, CH₂CH₂O, 2H), 3.91 – 3.85 (m, CH₂CH₂O, 4H), 3.84 (s, OCH₃, 3H), 3.78 – 3.63 (m, CH₂CH₂O, NCH, CH₂CH₂N, 9H), 3.38 (t, ³J_H,H = 5.0 Hz, CH₂N, 2H), 1.89 (m, CH(CH₃)₂, 1H), 1.34 (s, C(CH₃)₃, 9H), 0.83 (d,
CH(CH₃)₂; ³J_H,H = 6.6 Hz, 3H), 0.78 (d, CH(CH₃)₂; ³J_H,H = 6.6 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 169.74 (COO), 162.43 (qArCOC, 158.01 (qArCOCH₂CH₂O), 132.71 (qArCSO₂), 130.29 (ArCH), 129.57 (qArCC₂N), 129.41 (ArCH), 113.98 (ArCH), 113.74 (ArCH), 81.66 (C(CH₃)₃), 70.72, 70.59, 70.58, 70.56 (CH₂CH₂O), 69.93 (CH₂CH₂O), 69.64 (CH₂CH₂N₃), 67.25 (CH₂CH₂O), 66.86 (NCH), 55.50 (OCH₃), 50.55 (NCH₂), 47.74 (CH₂N₃), 28.81 (CH(CH₃)₂), 27.75 (C(CH₃)₃), 19.42 (CH(CH₃)₂), 19.28 (CH(CH₃)₂). MS-ES(+)-EM: m/z = 673.2881 [(M+Na)⁺] calcd for C₃₁H₄₆N₄O₉SNa⁺: 673.2878.

(R)-2-(N-(4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)benzyl)-4-methoxyphenylsulfonamido)-3-methylbutanoic acid (21). A solution of the carboxylic acid ester 20 (9.80 g, 15.05 mmol) in dichloromethane (100 mL) was cooled to 0°C and hydrochloric acid gas was bubbled slowly through the solution. TLC was used to monitor the reaction progress (EA). After removing the solvent under reduced pressure the product was purified by column chromatography (silica gel, CH/EA, 1:1) and was obtained as a colorless wax (7.15 g, 10.99 mmol, 73%). For spectroscopic data see ref. [3].

(2R)-2-(N-(4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)benzyl)-4-methoxyphenylsulfonamido)-3-methyl-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide (22). To a solution of the carboxylic acid 21 (1.37 g, 2.30 mmol) in DMF (11 mL) HOBT (365 mg, 2.76 mmol, 373 mg, 1.2 eq.), NMM (0.76 mL, 6.90 mmol, 3.0 eq.), THPONH₂ (834 mg, 7.13 mmol, 3.1 eq.) and EDC (618 mg, 3.22 mmol, 1.4 eq.) were added. After stirring at room temperature for 16 h the reaction mixture was diluted with water (150 mL) and extracted with EA (3 × 50 mL). The combined organic phases were washed with water, 5% aqueous KHSO₄, saturated aqueous NaHCO₃ and brine. After drying over magnesium sulfate the solvent was removed under reduced pressure. The product was purified by column chromatography (silica gel, CH/EA 1:1) yielding a diastereomeric mixture of THP-protected hydroxamic ester 22 as a colorless wax (1.46 g, 2.12 mmol, 92%). ¹H NMR (300 MHz,
CDCl₃) δ 9.08 (s, NH, 1H), 8.89 (s, NH, 1H), 7.60 (d, ArH, 3J_H,H = 8.9 Hz, 2H), 7.58 (d, ArH, 3J_H,H = 8.9 Hz, 2H), 7.30 (d, ArH, 3J_H,H = 8.6 Hz, 2H), 7.28 (d, ArH, 3J_H,H = 8.7 Hz, 2H), 6.87 (d, ArH, 3J_H,H = 9.0 Hz, 2H), 6.85 (d, ArH, 3J_H,H = 8.9 Hz, 2H), 6.79 (d, ArH, 3J_H,H = 8.6 Hz, 2H), 6.76 (d, ArH, 3J_H,H = 8.5 Hz, 2H), 4.92 (m, THP-C,H, 1H), 4.78 (m, THP-C,H, 1H), 4.63 (AB, d, NCH₂, 2J_H,H = 15.3 Hz, 1H), 4.45 (AB, d, NCH₂, 2J_H,H = 15.3 Hz, 1H), 4.14 – 4.02 (m, C,H₂CH₂O, 2H), 3.90 – 3.79 (m, CH₂CH₂O, 2H), 3.84 (s, OCH₃, 3H), 3.83 (s, OCH₃, 3H), 3.77 – 3.50 (m, NCH, CH₂CH₂O, THP-CH₂, 1H), 3.45 – 3.31 (m, CH₂N₃, 2H), 2.17 (m, CH(CH₃)₂, 1H), 1.93 – 1.43 (m, THP-CH₂, 6H), 0.87 (d, CH(CH₃)₂, 3J_H,H = 6.4 Hz, 3H), 0.55 (d, CH(CH₃)₂, 3J_H,H = 6.5 Hz, 3H), 0.47 (d, CH(CH₃)₂, 3J_H,H = 6.6 Hz, 3H). 13C NMR (101 MHz, CDCl₃) δ 167.04 (C-ONH), 166.85 (C-ONH), 162.85 (qArC=OCH₃), 162.76 (qArC=OCH₃), 158.19 (qArC=OCH₂CH₂O), 158.17 (qArC=OCH₂CH₂O), 132.10 (qArCSO₂), 131.96 (qArCSO₂), 130.89 (ArCH), 130.84 (ArCH), 129.42 (ArCH), 129.11, (qArCCH₂N), 128.94 (qArCCH₂N), 114.15 (ArCH), 114.08 (ArCH), 114.07 (ArCH), 113.99 (ArCH), 102.21 (C(CH₃)₃), 101.74 (C(CH₃)₃), 70.80, 70.68, 70.64 (CH₂CH₂O), 70.01 (CH₂CH₂O), 69.71 (CH₂CH₂N₃), 67.33 (CH₂CH₂O), 64.14 (NCH), 64.10 (NCH), 62.07 (THP-OCH₂), 62.01 (THP-OCH₂), 55.58 (OCH₃), 55.56 (OCH₃), 50.65 (CH₂N₃), 47.75 (NCH₂), 47.68 (NCH₂), 27.81 (THP-CH₂), 27.49 (CH(CH₃)₂), 27.45 (CH(CH₃)₂), 24.98 (THP-CH₂), 24.96 (THP-CH₂), 19.70 (CH(CH₃)₂), 19.65 (CH(CH₃)₂), 19.19 (CH(CH₃)₂), 19.11 (CH(CH₃)₂), 18.23 (THP-CH₂), 18.19 (THP-CH₂). MS-ES (+)-EM: m/z = 716.2930 [M+Na⁺] calcd for C₃₂H₄₇N₅O₁₀SNa⁺:716.2936.

(R)-2-(N-(4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)benzyl)-4-methoxyphenyl-sulfonamido)-N-hydroxy-3-methylbutanamide (23). Compound 22 (1.09 g, 1.57 mmol) was dissolved in dry dioxane (3.0 mL). 4 N hydrochloric acid in dioxane (1.57 mL, 6.28 mmol, 4.0 eq.) and dry methanol (3.0 mL) were added. After stirring for 1.5 h at room temperature the reaction mixture was diluted with ethyl acetate (10 mL). The organic layer was washed with water, dried over magnesium sulfate and the solvent was removed under
reduced pressure yielding the hydroxamic acid 23 (823 mg, 1.35 mmol, 86%). For spectroscopic data see reference [3].

**NMR data of compounds 25–28.**

<table>
<thead>
<tr>
<th>compound</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>25</strong></td>
<td>$^1$H NMR (300 MHz, CDCl$<em>3$) δ 7.84 (d, ArCH, $^3$J$</em>{HH}$ = 9.1 Hz, 2H), 6.94 (d, ArCH, $^3$J$<em>{HH}$ = 9.0 Hz, 2H), 4.38 (AB, dd, NCH$<em>2$, $^2$J$</em>{HH}$ = 18.7 Hz, $^4$J$</em>{HH}$ = 2.5 Hz, 1H), 4.16 (AB, dd, NCH$<em>2$, $^2$J$</em>{HH}$ = 18.7 Hz, $^4$J$<em>{HH}$ = 2.4 Hz, 1H), 3.94 (d, NCH, $^3$J$</em>{HH}$ = 10.3 Hz, 1H), 3.85 (s, OCH$<em>3$, 3H), 2.17 (t, C=C=H, $^4$J$</em>{HH}$ = 2.5 Hz, 1H), 2.15 (m, CH(CH$_3$)$_2$, 1H), 1.32 (s, C(CH$_3$)$_3$, 9H), 1.04 (d, CH(CH$_3$)$<em>2$, $^3$J$</em>{HH}$ = 6.6 Hz, 3H), 0.96 (d, CH(CH$_3$)$<em>2$, $^3$J$</em>{HH}$ = 6.6 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.67 (COOC(CH$_3$)$_3$), 162.84 (qArCOCH$_3$), 131.85 (qArCSO$_2$), 129.81 (ArCH), 113.80 (ArCH), 81.93 (C(CH$_3$)$_3$), 79.84 (C=CH), 71.84 (C=CH), 65.74 (NCH), 55.54 (OCH$_3$), 33.40 (NCH$_2$), 28.89 (CH(CH$_3$)$_2$), 27.72 (C(CH$_3$)$_3$), 19.77 (CH(CH$_3$)$_2$), 19.08 (CH(CH$_3$)$_2$).</td>
</tr>
<tr>
<td><strong>26</strong></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) δ 9.02 (s, OH, 1H), 7.83 (d, ArH, $^3$J$</em>{HH}$ = 9.0 Hz, 2H), 6.94 (d, ArH, $^3$J$<em>{HH}$ = 9.0 Hz, 2H), 4.27 (AB, dd, NCH$<em>2$, $^2$J$</em>{HH}$ = 18.9 Hz, $^4$J$</em>{HH}$ = 2.5 Hz, 1H), 4.21 (AB, dd, NCH$<em>2$, $^2$J$</em>{HH}$ = 18.9 Hz, $^4$J$<em>{HH}$ = 2.5 Hz, 1H), 4.03 (d, NCH, $^3$J$</em>{HH}$ = 10.2 Hz, 1H), 3.86 (s, OCH$<em>3$, 3H), 2.17 (t, C=C=CH, $^4$J$</em>{HH}$ = 2.4 Hz, 1H), 2.15 (m, CH(CH$_3$)$_2$, 1H), 0.98 (d, CH(CH$_3$)$<em>2$, $^3$J$</em>{HH}$ = 6.6 Hz, 3H), 0.96 (d, CH(CH$_3$)$<em>2$, $^3$J$</em>{HH}$ = 6.6 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.98 (COOH), 163.09 (qArCOCH$_3$), 130.96 (qArCSO$_2$), 129.89 (ArCH), 79.03 (C=CH), 72.39 (C=CH), 64.90 (NCH), 55.57 (OCH$_3$), 33.53 (NCH$_2$), 28.42 (CH(CH$_3$)$_2$), 19.80 (CH(CH$_3$)$_2$), 19.22 (CH(CH$_3$)$_2$).</td>
</tr>
<tr>
<td><strong>27</strong></td>
<td>$^1$H NMR (300 MHz, CDCl$<em>3$) δ 8.38 (s, NH, 1H), 7.87 (d, ArH, $^3$J$</em>{HH}$ = 8.9 Hz, 2H), 6.96 (d, ArH, $^3$J$_{HH}$ = 8.9 Hz, 2H), 4.36 (d, NCH$<em>2$, $^4$J$</em>{HH}$ = 2.5 Hz, 2H), 3.87 (s, OCH$<em>3$, 3H), 3.57 (d, NCH, $^3$J$</em>{HH}$ = 10.9 Hz, 1H), 2.31 (m, CH(CH$_3$)$<em>2$, 1H), 2.18 (t, C=C=CH, $^4$J$</em>{HH}$ = 2.4 Hz, 1H), 1.27 (s, C(CH$_3$)$_3$, 9H), 0.89 (d, CH(CH$_3$)$<em>2$, $^3$J$</em>{HH}$ = 6.5 Hz, 3H), 0.65 (d, CH(CH$_3$)$<em>2$, $^3$J$</em>{HH}$ = 6.6 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.38 (CONH), 163.15 (qArCOCH$_3$), 131.65 (qArCSO$_2$), 129.71 (ArCH), 113.97 (ArCH), 82.35 (C(CH$_3$)$_3$), 79.06 (C=CH), 72.42 (C=CH), 63.73 (NCH), 55.59 (OCH$_3$), 32.81 (NCH$_2$), 27.12 (CH(CH$_3$)$_2$), 26.21 (C(CH$_3$)$_3$), 19.66 (CH(CH$_3$)$_2$), 19.42 (CH(CH$_3$)$_2$).</td>
</tr>
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</table>
Experimental data of compounds 16a-c, 24, 30a and 30c-h.

According to the general procedure for the preparation of triazoles described in the experimental section in the manuscript the following compounds were synthesised.

(R)-2-((N-(4-((1-(1-(2-fluoroethyl)-1H-1,2,3-triazol-4-yl)-2,5,8,11-tetraoxatridecan-13-yl)oxy)benzyl)-4-methoxyphenylsulfonamido)-N-hydroxy-3-methylbutanamide (16a).

Obtained from 14 (20 mg, 0.032 mmol) and 1-azido-2-fluoroethane (15a, 0.040 mmol), prepared from 2-fluoroethyl 4-methylbenzenesulfonate and sodium azide following the literature procedure, after 5 h stirring at room temperature. Column chromatographic purification with EA gave a colorless oil (5 mg, 0.007 mmol, 21%).

$^1$H NMR (300 MHz, DMSO) δ 10.75 (d, OH, $^3$J$_{H,H}$ = 1.3 Hz, 1H), 8.97 (d, NH, $^3$J$_{H,H}$ = 1.5 Hz, 1H), 7.78 (d, ArH, $^3$J$_{H,H}$ = 9.0 Hz, 2H), 7.07 (d, ArH, $^3$J$_{H,H}$ = 9.0 Hz, 2H), 4.67 (AB, dd, NCH$_2$, $^2$J$_{H,H}$ = 18.8 Hz, $^4$J$_{H,H}$ = 2.4 Hz, 1H), 4.06 (AB, dd, NCH$_2$, $^2$J$_{H,H}$ = 18.8 Hz, $^4$J$_{H,H}$ = 2.4 Hz, 1H), 3.84 (s, OCH$_3$, 3H), 3.66 (d, NCH, $^3$J$_{H,H}$ = 10.7 Hz, 1H), 3.13 (t, C≡CH, $^4$J$_{H,H}$ = 2.4 Hz, 1H), 2.12 (m, CH(CH$_3$)$_2$, 1H), 0.87 (d, CH(CH$_3$)$_2$, $^3$J$_{H,H}$ = 6.5 Hz, 3H), 0.81 (d, CH(CH$_3$)$_2$, $^3$J$_{H,H}$ = 6.6 Hz, 3H). $^{13}$C NMR (75 MHz, DMSO) δ 165.90 (C=ONH), 162.51 (qAr C=OCH$_3$), 131.35 (qAr C=SCH$_3$), 129.28 (ArCH), 114.21 (ArCH), 80.53 (C=CH), 73.97 (C=CH), 61.92 (NCH$_2$), 61.40 (NCH$_2$), 32.88 (NCH$_2$), 28.11 (CH(CH$_3$)$_2$), 19.94 (CH(CH$_3$)$_2$), 18.90 (CH(CH$_3$)$_2$).
(CCHN), 131.78 (qArCSO₂), 130.37 (ArCH), 129.40 (ArCH), 128.89 (qArCCH₂N), 123.73 (CCHN), 114.26 (ArCH), 114.16 (ArCH), 81.54 (d, CH₂F, \(^1J_{CF} = 172.5\) Hz), 70.79, 70.59, 70.49 (CH₂CH₂O), 69.70 (CH₂CH₂O), 67.38 (CH₂CH₂O), 64.57 (NCH), 63.31 (OCH₂CCHN), 55.66 (OCH₃), 50.49 (d, CH₂CH₂F, \(^2J_{CF} = 20.6\) Hz), 47.94 (NCH), 45.29 (CH(CH₃)₂), 19.89 (CH(CH₃)₂), 18.96 (CH(CH₃)₂). \(^19F\) NMR (282 MHz, CDCl₃) \(\delta/\text{ppm} -221.56\) (tt, \(^2J_{HF} = 46.1\) Hz, \(^3J_{HF} = 26.8\) Hz, 1F). HRMS-ES(+)–EM: \(m/z = 734.2834\) [(M+Na)⁺] calcd for C₃₂H₄₆FN₁₀O₁₀SNa⁺: 734.2842. HPLC system A, method A1: \(t_R = 8.42\) min (96%).

(R)-2-(N-((4-((1-(1-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)-1H-1,2,3-tetraoxatridecan-13-yl)oxy)benzyl)-4-methoxyphenylsulfonamido)-N-hydroxy-3-methylbutanamide (16b). Obtained from 14 (219 mg, 0.35 mmol) and 1-azido-2-(2-(2-fluoroethoxy)ethoxy)ethane (15b, 77 mg, 0.35 mmol), prepared following the literature procedure,⁵ after 5 h stirring at room temperature. Column chromatographic purification (silica gel, EA/MeOH, 6:1) gave a colourless oil (80 mg, 0.10 mmol, 27%). \(^1H\) NMR (400 MHz, CDCl₃) \(\delta/\text{ppm} 9.25\) (br s, OₗH, 1H), 7.77 (s, CCHN, 1H), 7.60 (d, ArH, \(^3J_{HH} = 8.7\) Hz, 2H), 7.27 (d, ArH, \(^3J_{HH} = 8.4\) Hz, 2H), 6.89 (d, ArH, \(^3J_{HH} = 8.6\) Hz, 2H), 6.78 (d, ArH, \(^3J_{HH} = 8.5\) Hz, 2H), 4.68 (s, OCH₂CCHN, 2H), 4.57 (AB, d, NCH₂, \(^2J_{HH} = 15.4\) Hz, 1H), 4.56 (dm, CH₂F, \(^2J_{HF} = 47.7\) Hz, 2H), 4.56 – 4.51 (m, NCH₂CH₂O, 2H), 4.43 (AB, d, NCH₂, \(^2J_{HH} = 15.4\) Hz, 1H), 4.13 – 4.06 (m, CH₂CH₂O, 2H), 3.89 – 3.81 (m, CH₂CH₂O, CH₂CH₂F, 3H), 3.84 (s, OCH₃, 3H), 3.78 (m, CH₂CH₂F, 1H), 3.74 – 3.54 (m, NCH, CH₂CH₂O, 23H), 2.19 (m, CH(CH₃)₂, 1H), 0.81 (d, CH(CH₃)₂, \(^3J_{HH} = 6.3\) Hz, 3H), 0.49 (d, CH(CH₃)₂, \(^3J_{HH} = 6.6\) Hz, 3H). \(^13C\) NMR (101 MHz, CDCl₃) \(\delta/\text{ppm} 167.06\) (CONH), 162.93 (qArCOCH₃), 158.20 (qArCOCH₂CH₂), 144.87 (CCHN), 131.84 (qArCSO₂), 130.45 (ArCH), 129.36 (ArCH), 128.92 (qArCCH₂N), 123.90 (CCHN), 114.25 (ArCH), 114.10 (ArCH), 83.12 (d, CH₂F, \(^1J_{CF} = 168.9\) Hz), 70.78, 70.76, 70.58, 70.57, 70.53, 70.51, 70.49, (CH₂CH₂O), 70.37 (d, CH₂CH₂F, \(^2J_{CF} = 19.6\) Hz), 69.70 (CH₂CH₂O), 69.61 (CH₂CH₂O),
(R)-2-(N-(4-((1-(1-(2R,3R,4S,5S,6R)-3-fluoro-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-1H-1,2,3-triazol-4-yl)-2,5,8,11-tetraoxatridecan-13-yl)oxy)benzyl)-4-methoxyphenylsulfonamido)-N-hydroxy-3-methylbutanamide (16c). Obtained from 14 (156 mg, 0.25 mmol) and 2-deoxy-2-fluoro-β-glucopyranos-1-yl azide (15c, 52 mg, 0.25 mmol), prepared following the literature procedure, after 4 h stirring at room temperature. Column chromatographic purification (silica gel, EA/MeOH, 6:1) gave a colorless oil (13 mg, 0.015 mmol, 6%).

**^{1}H NMR** (300 MHz, CD$_3$OD) $\delta$/ppm 8.27 (s, CCHN, 1H), 7.53 (d, ArH, $^3J_{HH}$ = 8.9 Hz, 2H), 7.26 (d, ArH, $^3J_{HH}$ = 8.6 Hz, 2H), 6.89 (d, ArH, $^3J_{HH}$ = 8.9 Hz, 2H), 6.74 (d, ArH, $^3J_{HH}$ = 8.6 Hz, 2H), 5.94 (dd, N$_3$CHCHF, $^3J_{HH}$ = 9.0 Hz, $^3J_{HF}$ = 2.4 Hz, 1H), 4.78 – 4.74 (dm, CHF, $^2J_{HF}$ = 50.8 Hz, 1H), 4.71 (d, AB, NCH$_2$, $^2J_{HH}$ = 15.6 Hz, 1H), 4.66 (s, CH$_2$CCHN, 2H), 4.62 (d, AB, NCH$_2$, $^2J_{HH}$ = 15.7 Hz, 1H), 4.12 – 3.99 (m, CH$_2$CH$_2$O, 2H), 3.98 – 3.44 (m, NCH, CH$_2$CH$_2$O, glycosyl-H, 5H), 3.83 (s, OCH$_3$, 3H), 3.75 – 3.47 (m, CH$_2$CH$_2$O, glycosyl-H, glycosyl-CH$_2$, 15H), 2.99 (s, glycosyl-OH, 1H), 2.86 (s, glycosyl-OH, 1H), 2.19 – 1.98 (m, CH(CH$_3$)$_2$, 1H), 1.29 (s, glycosyl-OH, 1H), 0.86 (d, CH(CH$_3$)$_2$, $^3J_{HH}$ = 6.5 Hz, 3H), 0.80 (d, CH(CH$_3$)$_2$, $^3J_{HH}$ = 6.5 Hz, 3H).

**^{13}C NMR** (75 MHz, CD$_3$OD) $\delta$/ppm 169.16 (CONH), 164.16 (qArCOCH$_3$), 159.57 (qArCOCH$_2$CH$_2$O), 146.46 (CCHN), 134.05 (qArCOSO$_2$), 131.76 (ArCH), 130.96 (qArCCH$_2$N), 130.30 (ArCH), 124.55 (CCHN), 115.08 (ArCH), 114.96 (ArCH), 92.17 (d, CHF, $^1J_{CF}$ = 188.1 Hz), 86.48 (d, CHCHF, $^2J_{CF}$ = 24.4 Hz), 81.24 (glycosyl-CHCH$_2$OH), 76.41 (d, CHFCHOH, $^2J_{CF}$ = 16.7 Hz), 71.74, 71.56, 71.50,
70.84 (CH$_2$CH$_2$O), 70.64 (d, CHFCHCOH, $^3$J$_{C,F}$ = 7.8 Hz), 68.60 (CH$_2$CH$_2$O), 65.33 (glycosyl-CH$_2$CH$_2$OH), 64.90 (NCH), 62.12 (OCH$_2$CCHN), 56.18 (OCH$_3$), 48.84 (NCH$_2$), 29.49 (CH(CH$_3$)$_2$), 20.09 (CH(CH$_3$)$_2$), 19.64 (CH(CH$_3$)$_2$). $^{19}$F NMR (282 MHz, CD$_2$OD) δ/ppm -200.51 (ddd, $^2$J$_{H,F}$ = 50.9, $^3$J$_{H,F}$ = 15.1 Hz, $^3$J$_{H,F}$ = 2.3 Hz, 1F). HRMS-ES(+) - EM: m/z = 852.3121 [(M+Na)$^+$] calcd for C$_{36}$H$_{52}$FN$_5$O$_{14}$SNa$: 852.3108$. HLPC system A, method A1: $t_R$ = 7.32 min (100%).

(R)-2-(N-(4-(2-2-2-(2-4-(16-fluoro-2,5,8,11,14-pentaoxahexadecyl)-1H-1,2,3-triazol-1-
yl)ethoxy)ethoxy)ethoxy)ethoxy)benzyl)-4-methoxyphenylsulfonamido)-N-hydroxy-3-
methylbutanamide (24). Obtained from 23 (251 mg, 0.41 mmol) and 1-fluoro-3,6,9,12,15-
pentaoxaoctadec-17-yne (8, 114 mg, 0.41 mmol) after 5 h stirring at room temperature.

Column chromatographic purification (silica gel, EA/MeOH, 6:1) gave a colorless oil (23 mg, 0.02 mmol, 6%). $^1$H NMR (400 MHz, CDCl$_3$) δ/ppm 9.25 (br s, O$_H$, 1H), 7.77 (s, CC$_H$N, 1H), 7.61 (d, ArH, $^3$J$_{H,H}$ = 8.3 Hz, 2H), 7.27 (d, ArH, $^3$J$_{H,H}$ = 8.4 Hz, 2H), 6.89 (d, ArH, $^3$J$_{H,H}$ = 8.3 Hz, 2H), 6.78 (d, ArH, $^3$J$_{H,H}$ = 8.4 Hz, 2H), 4.67 (s, CHCC$_H$2O, 2H), 4.64 – 4.47 (dm, CH$_2$F, $^2$J$_{H,F}$ = 47.6 Hz, 2H), 4.58 (AB, d, NCH$_2$, $^3$J$_{H,H}$ = 15.5 Hz, 1H), 4.56 – 4.51 (t, OCH$_2$CH$_2$N, $^3$J$_{H,H}$ = 5.03 Hz, 2H), 4.41 (AB, d, NCH$_2$, $^3$J$_{H,H}$ = 15.5 Hz, 1H), 4.13 – 4.06 (m, CH$_2$CH$_2$O, 2H), 3.89 – 3.81 (m, CH$_2$CH$_2$O, CH$_2$CH$_2$F, 3H), 3.84 (s, OCH$_3$, 3H), 3.78 (m, CH$_2$CH$_2$F, 1H), 3.77 – 3.54 (m, NCH, CH$_2$CH$_2$O, 27H), 2.22 (m, CH(CH$_3$)$_2$, 1H), 0.81 (d, CH(CH$_3$)$_2$, $^3$J$_{H,H}$ = 6.1 Hz, 3H), 0.49 (d, CH(CH$_3$)$_2$, $^3$J$_{H,H}$ = 6.5 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ/ppm 167.03 (CONH), 162.92 (qArCOCH$_3$), 158.14 (qArCOCH$_2$CH$_2$), 144.80 (CCHN), 131.85 (qArCO$_2$), 130.40 (ArCH), 129.36 (ArCH), 129.00 (qArCCH$_2$N), 123.93 (CCHN), 114.19 (ArCH), 114.10 (ArCH), 83.14 (d, $^1$J$_{C,F}$ = 168.8 Hz, CH$_2$F), 70.78, 70.75, 70.57, 70.54, 70.53, 70.51, 70.49, (CH$_2$CH$_2$O), 70.35 (d, $^2$J$_{C,F}$ = 20.0 Hz, CH$_2$CH$_2$F), 69.72 (CH$_2$CH$_2$O), 69.59 (CH$_2$CH$_2$O), 69.43 (CH$_2$CH$_2$N), 67.34 (CH$_2$CH$_2$O), 64.47 (NCH), 63.48 (CHCCH$_2$O), 55.62 (OCH$_3$), 50.20 (CH$_2$CH$_2$N), 47.91 (NCH$_2$), 26.98 (CH(CH$_3$)$_2$), 19.81 (CH(CH$_3$)$_2$), 19.04 (CH(CH$_3$)$_2$). $^{19}$F NMR (282 MHz, CDCl$_3$) δ/ppm -222.85 (tt, $^2$J$_{H,F}$ = 47.7
Hz, $^3J_{HF} = 29.7$ Hz, 1F). HRMS-ES(+)−EM: $m/z = 910.3898$ [(M+Na)$^+$] calcd for C$_{40}$H$_{62}$FN$_5$O$_{14}$SNa$^+$: 910.3890. HPLC system B, method B1: $t_R = 18.13$ min (95%).

(R)-2-(4-((N-(1-(Hydroxyamino)-3-methyl-1-oxobutan-2-yl)-4-methoxyphenylsulfonamido)-methyl)-1H-1,2,3-triazol-1-yl)ethyl 4-methylbenzenesulfonate (30a). Obtained from 28 (340 mg, 1.0 mmol) and 2-azidoethyl 4-methylbenzenesulfonate (29a, 261 mg, 1.2 mmol), prepared following the literature procedure,$^6$ after 4 h stirring at room temperature. Column chromatographic purification (silica gel, EA) gave a colorless wax (539 mg, 0.88 mmol, 88%). $^1$H NMR (300 MHz, CDCl$_3$) δ/ppm 9.32 (br s, OH, 1H), 7.74 (d, ArH, $^3J_{HH} = 8.3$ Hz, 2H), 7.68 (s, CCN, 1H), 7.66 (d, ArH, $^3J_{HH} = 9.0$ Hz, 2H), 7.34 (d, ArH, $^3J_{HH} = 8.0$ Hz, 2H), 6.94 (d, ArH, $^3J_{HH} = 8.8$ Hz, 2H), 4.79 (AB, d, NCH$_2$, $^2J_{HH} = 16.4$ Hz, 1H), 4.59 (t, NCH$_2$CH$_2$O, $^3J_{HH} = 4.7$ Hz, 2H), 4.49 (AB, d, NCH$_2$, $^2J_{HH} = 16.4$ Hz, 1H), 4.40 (t, NCH$_2$CH$_2$O, $^3J_{HH} = 4.7$ Hz, 2H), 3.85 (s, OC$_3$H$_3$, 3H), 3.68 (d, NCH, $^3J_{HH} = 10.6$ Hz, 1H), 2.44 (s, ArCH$_3$, 3H), 2.44 (m, CH(CH$_3$)$_2$, 1H), 0.87 (d, CH(CH$_3$)$_2$, $^3J_{HH} = 6.3$ Hz, 3H), 0.81 (d, CH(CH$_3$)$_2$, $^3J_{HH} = 6.6$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ/ppm 167.72 (C ONH), 163.24 (qArC OCH$_3$), 145.58 (CCHN), 144.72 (qArCCH$_3$), 131.89 (qArCSO$_2$O), 131.04 (qArCSO$_2$N), 130.14 (ArCH), 129.50 (ArCH), 127.98 (ArCH), 124.68 (CCHN), 114.26 (ArCH), 67.42 (NCH$_2$CH$_2$O), 63.62 (NCH), 55.67 (OCH$_3$), 49.02 (NCH$_2$CH$_2$O), 39.46 (NCH$_2$), 27.07 (CH(CH$_3$)$_2$), 21.68 (ArCH$_3$), 19.58 (CH(CH$_3$)$_2$), 19.03 (CH(CH$_3$)$_2$). HRMS-ES(+)−EM: $m/z = 604.1506$ [(M+Na)$^+$] calcd for C$_{24}$H$_{31}$N$_5$O$_8$S$_2$Na$^+$: 604.1506. HPLC system A, method A1: 8.47 min (96%).

(R)-2-(2-(2-(2-(4-((N-(1-(Hydroxyamino)-3-methyl-1-oxobutan-2-yl)-4-methoxyphenylsulfonamido)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonylate (30c). Obtained from 28 (289 mg, 0.84 mmol) and 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (29b, 313 mg, 0.84 mmol), prepared following the literature procedure,$^5$ after 4 h stirring at room temperature. Column chromatographic purification (silica gel, EA/MeOH, 6:1) gave a colourless, waxy oil
(440 mg, 0.62 mmol, 73%). \(^1\)H NMR (300 MHz, DMSO) \(\delta/\text{ppm} 9.80\) (s, \(\text{OH}, 1\)H), 7.81 (s, CCHN, 1H), 7.79 (d, ArH, \(^3\)J\(_{\text{H,H}}\) = 8.4 Hz, 2H), 7.68 (d, ArH, \(^3\)J\(_{\text{H,H}}\) = 9.0 Hz, 2H), 7.34 (d, ArH, \(^3\)J\(_{\text{H,H}}\) = 7.9 Hz, 2H), 6.91 (d, ArH, \(^3\)J\(_{\text{H,H}}\) = 8.9 Hz, 2H), 4.90 (AB, d, NCH\(_3\), \(^2\)J\(_{\text{H,H}}\) = 16.5 Hz, 1H), 4.55 – 4.46 (m, NCH\(_2\)CH\(_2\)O, 2H), 4.50 (AB, d, NCH\(_2\), \(^2\)J\(_{\text{H,H}}\) = 16.5 Hz, 1H), 4.18 – 4.13 (m, CH\(_2\)CH\(_2\)OSO\(_2\), 2H), 3.91 – 3.80 (m, NCH\(_2\)CH\(_2\)O, 2H), 3.84 (s, OC\(_3\)H\(_3\), 3H), 3.80 – 3.57 (m, NCH, CH\(_2\)CH\(_2\)O, 11H), 2.44 (s, ArCH\(_3\), 3H), 2.36 (m, CH(CH\(_3\))\(_2\), 1H), 0.86 (d, CH(CH\(_3\))\(_2\), \(^3\)J\(_{\text{H,H}}\) = 6.5 Hz, 3H), 0.57 (d, CH(CH\(_3\))\(_2\), \(^3\)J\(_{\text{H,H}}\) = 6.6 Hz, 3H). \(^13\)C NMR (75 MHz, DMSO) \(\delta/\text{ppm} 167.05\) (CONH), 162.98 (qArCOCH\(_3\)), 144.84 (CCHN), 144.51 (qArCH\(_3\)), 132.85 (qArCSO\(_2\)O), 131.39 (qArCSO\(_2\)N), 129.82 (ArCH), 129.41 (ArCH), 127.91 (ArCH), 124.76 (CCHN), 114.11 (d, ArCH), 70.65, 70.46, 70.40 (CH\(_2\)CH\(_2\)O), 69.43 (CH\(_2\)CH\(_2\)O), 69.28 (NCH\(_2\)CH\(_2\)O), 68.59 (CH\(_2\)CH\(_2\)OS), 63.63 (NCH), 55.58 (OCH\(_3\)), 50.07 (NCH\(_2\)CH\(_2\)O), 39.78 (NCH), 27.21 (CH(CH\(_3\))\(_2\)), 21.58 (ArCH\(_3\)), 19.47 (CH(CH\(_3\))\(_2\)), 19.11 (CH(CH\(_3\))\(_2\)).

HRMS-ES(+)-EM: \(m/z = 736.2295\) [(M+Na\(^+\)] calcd for C\(_{30}\)H\(_{43}\)N\(_5\)O\(_{11}\)S\(_2\)Na\(^+\): 736.2293. HPLC system B, method B1: \(t_R = 18.98\) min (91%).

(R)-2-(N-((1-(2-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxyphenylsulfonamido)-N-hydroxy-3-methylbutanamide (30d).

Obtained from 28 (340 mg, 1.0 mmol) and 1-azido-2-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethane (15b, 221 mg, 1.0 mmol), prepared following the literature procedure\(^5\), after 2 h stirring at room temperature. Column chromatographic purification (silica gel, EA) gave a colourless, waxy oil (300 mg, 0.53 mmol, 53%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta/\text{ppm} 9.86\) (br s, \(\text{OH}, 1\)H), 7.82 (s, CCHN, 1H), 7.67 (d, ArH, \(^3\)J\(_{\text{H,H}}\) = 8.9 Hz, 2H), 6.91 (d, ArH, \(^3\)J\(_{\text{H,H}}\) = 8.6 Hz, 2H), 4.90 (d, AB, NCH\(_2\), \(^2\)J\(_{\text{H,H}}\) = 16.5 Hz, 1H), 4.68 – 4.43 (dm, CH\(_2\)F, \(^2\)J\(_{\text{H,F}}\) = 47.8 Hz, 2H), 4.51 (d, AB, NCH\(_2\), \(^2\)J\(_{\text{H,H}}\) = 16.5 Hz, 1H), 4.55 – 4.46 (m, NCH\(_2\)CH\(_2\)O, 2H), 3.90 – 3.82 (m, NCH\(_2\)CH\(_2\)O, 2H), 3.84 (s, OCH\(_3\)), 3H), 3.82 – 3.58 (m, NCH, CH\(_2\)CH\(_2\)O, 11H), 2.33 (m, CH(CH\(_3\))\(_2\)), 0.85 (d, CH(CH\(_3\))\(_2\), \(^3\)J\(_{\text{H,H}}\) = 6.5 Hz, 3H), 0.58 (d, CH(CH\(_3\))\(_2\), \(^3\)J\(_{\text{H,H}}\) = 6.6 Hz, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta/\text{ppm} 167.04\) (CONH),
162.95 (qArCOCH₃), 144.49 (CCHN), 131.29 (qArSO₂N), 129.38 (ArCH), 124.85 (CCHN), 114.09 (ArCH), 83.08 (d, CH₂F, JCF = 168.6 Hz), 70.67, 70.47, 70.44, (CH₂CH₂O), 70.34 (d, CH₂CH₂F, JCF = 19.6 Hz), 69.41 (NCH₂CH₂O), 63.64 (NCH), 55.56 (OCH₃), 50.07 (NCH₂CH₂O), 39.67 (NCH₂), 27.20 (CH(CH₃)₂), 19.39 (CH(CH₃)₂), 19.08 (CH(CH₃)₂).

19F NMR (282 MHz, CDCl₃) δ/ppm -222.72 (tt, JHF = 47.7 Hz, JHF = 30.0 Hz, 1F). HRMS-ES-EM m/z = 584.2165 [(M+Na)+] calcd for C₂₃H₃₆FN₅O₈Na⁺ 584.2161. HPLC system A, method A₁: tR = 7.05 min (92%).

(R)-2-(N-((1-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxyphenylsulfonamido)-N-hydroxy-3-methylbutanamide (30e).

Obtained from 28 (681 mg, 2.00 mmol) and 1-azido-2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethane (29c, 489 mg, 2.00 mmol), prepared following the literature procedure, after 4 h stirring at room temperature. Column chromatographic purification (silica gel, EA/MeOH, 6:1) gave a colourless waxy oil (428 mg, 0.73 mmol, 37%). 1H NMR (300 MHz, CDCl₃) δ 9.46 (s, OH, 1H), 7.81 (s, CHN, 1H), 7.67 (d, ArH, JHH = 8.4 Hz, 2H), 6.93 (d, ArH, JHH = 8.4 Hz, 2H), 4.81 (AB, d, NCH₂, JHH = 16.3 Hz, 1H), 4.56 – 4.49 (m, NCH₂CH₂O, 2H), 4.48 (AB, d, NCH₂, JHH = 16.7 Hz, 1H), 3.90 – 3.82 (m, NCH₂CH₂O, 2H), 3.85 (s, OCH₃, 3H), 3.79 – 3.56 (m, NCH, CH₂CH₂O, 11H), 3.47 – 3.24 (m, CH₂N₂, 2H), 2.41 (m, CH(CH₃)₂, 1H), 0.88 (d, CH(CH₃)₂, JHH = 6.1 Hz, 3H), 0.54 (d, CH(CH₃)₂, JHH = 6.4 Hz, 3H). 13C NMR (75 MHz, DMSO) δ 167.14 (CONH), 163.11 (qArCOCH₃), 144.29 (CCHN), 131.35 (qArSO₂), 129.43 (ArCH), 124.61 (CCHN), 114.18 (ArCH), 71.27, 70.63, 70.59, 70.55, 70.52, 70.47 (CH₂CH₂O), 69.94 (CH₂CH₂N₂), 69.48 (NCH₂CH₂O), 63.61 (NCH), 55.64 (OCH₃), 50.06 (NCH₂CH₂O), 42.80 (CH₂CH₂N₂), 39.77 (NCH₂), 26.88 (CH(CH₃)₂), 19.80 (CH(CH₃)₂), 19.08 (CH(CH₃)₂). HRMS-ES(+)-EM: m/z = 607.2273 [(M+Na)+] calcd for C₂₃H₃₆N₅O₈SNa⁺: 607.2269. HPLC system A, method A₁: tR = 7.92 min (95%).
(2R,2'R)-2,2'-((((Oxy-bis(ethane-1,2-diyl))bis(oxy))-bis(ethane-1,2-diyl))-bis(1H-1,2,3-triazole-1,4-diyl))-bis(methylene))-bis(((4-methoxyphenyl)sulfonyl)azanediyl))-bis(N-hydroxy-3-methyl-butanamide) (30h).

Obtained as a byproduct from the synthesis of 30e. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta/\text{ppm} 9.91\) (s, OH, 2H), 7.83 (s, CCHN, 2H), 7.68 (d, ArH, \(^3\)J\(_{H,H}\) = 8.7 Hz, 4H), 6.89 (d, ArH, \(^3\)J\(_{H,H}\) = 8.8 Hz, 4H), 4.90 (AB, d, NCH\(_2\), \(^2\)J\(_{H,H}\) = 16.5 Hz, 2H), 4.56 – 4.34 (m, NCH\(_2\)CH\(_2\)O, 4H), 4.54 (AB, d, NCH\(_2\), \(^2\)J\(_{H,H}\) = 16.7 Hz, 2H), 3.90 – 3.74 (m, NCH\(_2\)C\(_2\)H\(_2\)O, 4H), 3.82 (s, OCH\(_3\), 6H), 3.68 – 3.54 (m, NCH, CH\(_2\)CH\(_2\)O, 10H), 2.43 – 2.19 (m, CH(CH\(_3\))\(_2\), 2H), 0.82 (d, CH(CH\(_3\))\(_2\), \(^3\)J\(_{H,H}\) = 6.2 Hz, 6H), 0.53 (d, CH(CH\(_3\))\(_2\), \(^3\)J\(_{H,H}\) = 6.5 Hz, 6H). \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta/\text{ppm} 167.58\) (C\(_{ONH}\), 162.99 (qArC\(_{OCH_3}\)), 144.66 (CCHN), 131.36 (qArCSO\(_2\)N), 129.48 (ArCH), 125.01 (CCHN), 114.13 (ArCH), 70.59, 70.38 (CH\(_2\)CH\(_2\)O), 69.43 (NCH\(_2\)CH\(_2\)O), 63.51 (NCH), 55.60 (OCH\(_3\)), 50.17 (NCH\(_2\)CH\(_2\)O), 39.67 (NCH\(_2\)), 27.11 (CH(CH\(_3\))\(_2\)), 19.04 (CH(CH\(_3\))\(_2\)). HRMS-ES(+)-EM: \(m/z = 947.3359\) [(M+Na\(^+\)] calcd for C\(_{38}\)H\(_{56}\)N\(_{10}\)O\(_{13}\)S\(_2\)Na\(^+\): 947.3362. HPLC system A, method A1: \(t\_R = 7.67\) min (100%).

(R)-2-(N-((1-(2-((2-((2-Fluoropyridin-3-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxyphenylsulfonamido)-N-hydroxy-3-methylbutanamide (30f). Obtained from 28 (85 mg, 0.25 mmol) and 3-(2-((2-((2-azidoethoxy)ethoxy)ethoxy)ethoxy)-2-fluoropyridine (29d, 85 mg, 0.27 mmol), prepared following the literature procedure,\(^7\) after 4 h stirring at room temperature. Column chromatographic purification (silica gel, EA/MeOH, 6:1) gave a colourless, waxy oil (30 mg,
0.05 mmol, 18%). $^1$H NMR (300 MHz, CDCl$_3$) δ/ppm 9.46 (br s, OH, 1H), 7.81 (s, CCHN, 1H), 7.74 (dd, $^3$J$_{H,H} = 4.9$ Hz, $^4$J$_{H,F} = 1.6$ Hz, pyridinyl-$_H$, 1H), 7.67 (d, Ar$H$, $^3$J$_{H,H} = 8.9$ Hz, 2H), 7.33 (ddd, $^4$J$_{H,F} = 9.9$ Hz, $^3$J$_{H,H} = 7.9$ Hz, $^4$J$_{H,H} = 1.5$ Hz, pyridinyl-$_H$, 1H), 7.10 (dd, $^3$J$_{H,H} = 7.9$ Hz, $^3$J$_{H,H} = 4.9$ Hz, pyridinyl-$_H$, 1H), 6.92 (d, Ar$H$, $^3$J$_{H,H} = 8.9$ Hz, 2H), 4.81 (AB, d, NCH$_2$, $^2$J$_{H,H} = 16.2$ Hz, 1H), 4.55 – 4.39 (m, CH$_2$O-pyridinyl, 2H), 4.47 (AB, d, NCH$_2$, $^2$J$_{H,H} = 15.7$ Hz, 1H), 4.32 – 4.14 (m, NCH$_2$CH$_2$O, 2H), 3.97 – 3.76 (m, NCH, $^3$J$_{H,H} = 8.9$ Hz, NCH$_2$CH$_2$O, 3H), 3.85 (s, OCH$_3$, 3H), 3.78 – 3.57 (m, CH$_2$CH$_2$O, 10H), 2.37 (m, CH(CH$_3$)$_2$, 1H), 0.86 (d, CH(CH$_3$)$_2$, $^3$J$_{H,H} = 6.1$ Hz, 3H), 0.53 (d, CH(CH$_3$)$_2$, $^3$J$_{H,H} = 6.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ/ppm 167.17 (C ONH), 163.10 (qAr$C$OCH$_3$), 153.86 (d, pyridinyl-$C$, $^1$J$_{C,F} = 239.2$ Hz), 144.33 (CCHN), 142.18 (d, pyridinyl-$qC$, $^2$J$_{C,F} = 25.4$ Hz), 137.59 (d, pyridinyl-$C$, $^3$J$_{C,F} = 13.1$ Hz), 131.36 (qArCSO$_2$N), 129.43 (Ar$CH$), 124.66 (CCHN), 123.47 (d, pyridinyl-$C$, $^3$J$_{C,F} = 4.5$ Hz), 121.78 (d, pyridinyl-$C$, $^4$J$_{C,F} = 4.5$ Hz), 114.17 (Ar$CH$), 70.91 (CH$_2$CH$_2$O-pyridinyl), 70.76 (d, CH$_2$CH$_2$O-pyridinyl, $^4$J$_{C,F} = 2.5$ Hz), 70.54, 70.48, 69.46, 69.36 (CH$_2$), 69.03 (NCH$_2$CH$_2$O), 63.66 (NCH), 55.62 (OCH$_3$), 50.09 (NCH$_2$CH$_2$O), 43.76 (NCH$_2$), 26.95 (CH(CH$_3$)$_2$), 19.62 (CH(CH$_3$)$_2$), 19.05 (CH(CH$_3$)$_2$). $^{19}$F NMR (282 MHz, CDCl$_3$) δ/ppm -83.70 (dm, $^4$J$_{H,F} = 10.2$ Hz). HRMS-ES(+)-EM: m/z = 677.2365 [(M+Na)$^+$] calcd for C$_{28}$H$_{39}$FN$_6$O$_9$SNa$: 677.2375$. HPLC system A, method A1: $t_R = 8.07$ min (95%).

(R)-2-(N-(((2R,3R,4S,5S,6R)-3-Fluoro-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxyphenylsulfonamido)-N-hydroxy-3-methyl-butylanamide (30g). Obtained from 28 (85 mg, 0.25 mmol) and 2-deoxy-2-fluoro-β-glucopyranosyl azide (15c, 52 mg, 0.25 mmol), prepared following literature procedure, after 3.5 h stirring at room temperature. Column chromatographic purification (silica gel, EA/MeOH, 10:1) gave a colourless wax (30 mg, 0.06 mmol, 22%). $^1$H NMR (300 MHz, CD$_3$OD) δ/ppm 8.13 (br s, OH, 1H), 7.98 (s, CCHN, 1H), 7.66 (d, Ar$H$, $^3$J$_{H,H} = 8.6$ Hz, 2H), 6.98 (d, Ar$H$, $^3$J$_{H,H} = 8.5$ Hz, 2H), 5.88 (dd, N$_3$CHCHF, $^3$J$_{H,F} = 8.6$ Hz, $^3$J$_{H,H} = 1.2$ Hz, 1H),
5.15 (AB, dd, NCH$_2$J$_{HH}$ = 16.4 Hz, 1H), 4.97 – 4.69 (dm, CHF, J$_{HF}$ = 50.9 Hz, 1H), 4.66 (AB, dd, NCH$_2$J$_{HH}$ = 16.4 Hz, 1H), 3.85 (s, OCH$_3$, 3H), 4.00 – 3.47 (m, NCH, glycosyl-H, glycosyl-OH, 7H), 2.29 (m, CH(CH$_3$)$_2$, 1H), 1.99 (s, glycosyl-OH, 1H), 1.50 (s, glycosyl-OH, 1H), 0.91 (d, CH(CH$_3$)$_2$, J$_{HH}$ = 6.2 Hz, 3H), 0.71 (d, CH(CH$_3$)$_2$, J$_{HH}$ = 6.2 Hz, 3H).

$^{13}$C NMR (75 MHz, CD$_3$OD) δ/ppm 169.07 (C ONH), 164.86 (qAr COCH$_3$), 146.57 (CCHN), 132.90 (qArSO$_2$N), 130.46 (ArCH), 125.78 (CCHN), 115.25 (ArCH), 92.14 (d, CHF, J$_{CF}$ = 188.0 Hz), 86.43 (d, N$_3$CHCHF, J$_{CF}$ = 24.2 Hz), 81.25 (glycosyl-CHCH$_2$OH), 76.44 (d, CHFCHOH, J$_{CF}$ = 16.8 Hz), 70.63 (d, CHFCHCOH J$_{CF}$ = 7.8 Hz), 64.76 (NCH), 62.13 (OCHCH$_2$OH), 56.17 (OCH$_3$), 40.27 (NCH$_2$), 29.47 (CH(CH$_3$)$_2$), 20.02 (CH(CH$_3$)$_2$), 19.44 (CH(CH$_3$)$_2$). $^{19}$F NMR (282 MHz CD$_3$OD) δ/ppm -200.21 (dd, J$_{HF}$ = 50.8 Hz, J$_{HH}$ = 14.8 Hz). HR MS-ES(+)-EM: m/z = 570.1609 [(M+Na)$^+$] calcd for C$_{21}$H$_{30}$FN$_5$O$_9$SNa$: 570.1604.

HPLC system B, method B2: t$_R$ = 9.72 min (91%).

**In vitro stability of [$^{18}$F]30b in mouse blood serum.** The radioligand [$^{18}$F]30b was formulated in phosphate-buffered saline (PBS). The serum stability of [$^{18}$F]30b was evaluated by incubation in mouse serum at 37 °C for up to 120 min. An aliquot of the PBS-formulated $^{18}$F-labeled compound (20 µL, 5 MBq) was added to a sample of mouse blood serum (200 µL), and the mixture was incubated at 37 °C. Samples of 20 µL each were taken after periods of 10, 20, 30, 60, 90 and 120 min and quenched in methanol/CH$_2$Cl$_2$ (1:1 (v/v), 100 µL) followed by centrifugation for 2 min. The organic layer was analysed by analytical radio-HPLC (t$_R$ = 8.20 min; analytical HPLC system A, starting with 30% CH$_3$CN in water (0.1% TFA) for 11 min, followed by a linear gradient from 30% to 90% CH$_3$CN in water (0.1% TFA) over 3 min, followed by a linear gradient from 90% to 30% CH$_3$CN in water (0.1% TFA) over 3 min with a flow rate of 1 mL·min$^{-1}$).
Figure 1. Stability of $[^{18}\text{F}]30\text{b}$ in mouse blood serum ($t_R = 8.20$ min; analytical HPLC system A, starting with 30% CH$_3$CN in water (0.1% TFA) for 13 min, followed by a linear gradient from 30% to 90% CH$_3$CN in water (0.1% TFA) over 3 min, followed by a linear gradient from 90% to 30% CH$_3$CN in water (0.1% TFA) over 2 min with a flow rate of 1
mL·min⁻¹ after incubation in human serum in vitro at 37°C for 30 min (top), 90 min (middle), and 120 min (bottom).


6 Macleod, F.; Lang, S.; Murphy, J. A. The 2-(2-Azidoethyl)cycloalkanone strategy for bridged amides and medium-sized amine derivatives in the Aubé-Schmidt reaction. Synlett 2010, 529-534.