Supporting Information

for

Synthesis and Evaluation of a Library of Trifunctional Scaffold-Derived Compounds as Modulators of the Insulin Receptor

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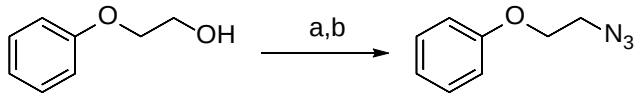
Synthesis of azides

General. Unless otherwise stated, reagents and solvents used in this study were obtained from commercial suppliers (Sigma-Aldrich, Fluka, Merck) and used without purification. The solvents were evaporated at 50°C and 2 kPa, and the products were dried over phosphorus pentoxide at r. t. and 13 Pa. **TLC analysis** were performed on silica gel coated aluminum plates ($60F_{254}$, Merck, Darmstadt, Germany). The compounds were visualized by exposure to UV light at 254 nm, by ninhydrin spraying (dark blue color of amines or BocNH species), by 1 % $KMnO_4$ spraying (yellow color of oxidizable compounds) and by spraying with a 10% PPh_3 dichloromethane solution followed by treating with ninhydrin solution (azido functional group)[1] **Flash chromatography** purifications were carried out on silica gel (40-63 μm, Merck). **Melting points** were determined on a Boetius block and are uncorrected. **^{1}H and ^{13} NMR** spectra were measured on a Bruker AVANCE-600 spectrometer (^{1}H at 600.13 MHz, ^{13}C at 150.9 MHz) in $CDCl_3$, DMSO-d_6, CD_3OD or D_2O solution at 300 K. The 2D-H,H-COSY, 2D-H,C-HSQC and 2D-H,C-HMBC spectra were recorded and used for the structural assignment of proton and carbon signals. **IR** spectra were recorded on Bruker IFS 55 Equinox apparatus. **HRMS** spectra were obtained on a FTMS mass spectrometer LTQ-orbitrap XL (Thermo Fisher, Bremen, Germany) in electrospray ionisation mode or in case HRMS (EI) on GCT Premier (Waters).

Azide moieties were introduced by standard methods.[2]

1-Azido-2-phenoxyethane (1, Azide A1), Scheme 1



1

Scheme 1. Reagents, conditions and yield: (a) MsCl, TEA, DCM, 0.5 h at 0°C; (b) NaN_3, DMSO, 80°C overnight (yield over two steps: 83%).

TEA (7.3 g; 72.4 mmol) was added to a solution of 2-phenoxyethanol (5 g; 36.2 mmol) in DCM (50 mL). The reaction mixture was cooled with an ice bath, MsCl (4.6 g; 39.8 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C. After 30 minutes, TLC showed disappearance of the starting alcohol. The excess of base was neutralized with a 1 M solution of citric acid. The organic layer was separated, washed with water (2 x 50 mL), brine (2 x 50 mL),

dried over anhydrous Na_2SO_4, filtered and evaporated to give the corresponding mesyl derivative. This crude intermediate was suspended together with NaN_3 (4.7 g; 72.4 mmol) in DMSO (50 mL). The resulting mixture was heated overnight at 80°C. After cooling to room temperature, water (100mL) was added, and the product was extracted with diethyl ether (4 x 50 mL). The organic extracts were combined, washed with water (2 x 50 mL), brine (2 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was evaporated to afford a yellow residue, which was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in petroleum ether. Azide **1** was obtained as a colorless liquid (4.9 g, 83% yield over two steps). R_f = 0.72 (toluene). ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 3.43 (2H, m, -CH_2-N_3), 3.99 (2H, m, -CH_2-O), 6.82 (2H, m, 2x CH_{arom}), 6.88 (1H, m, CH_{arom}), 7.19 (2H, m, CH_{arom}). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ_C 49.97 (1C, –CH_2–N_3), 66.67 (1C, -CH_2-O), 114.43 (2C, 2x CH_{arom}), 121.17 (3C, 3x CH_{arom}), 158.08 (1C, C_{arom}). IR (CCl_4) ν_{max} cm^{-1} 2112 vs (N_3); 1243 vs, 1063 m (Ar-O-CH_2); 2930 m, 2871 m, 1477 w (CH_2); 3096 w, 3066 w, 3044 w, 1602 s, 1590 s, 1497 vs, 1461 m, 1302 s, 1081 m, 690 s (ring). HRMS (CI) calc for $C_8H_9N_3O$ $[M]^+$ 163.0746, found: 163.0748.

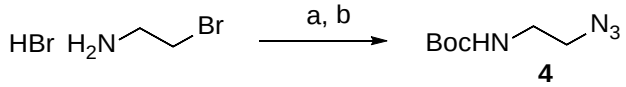
3,4-(Methylendioxy)benzylazide (2, Azide A2)

The synthesis and the physico-chemical characteristics of azide **2** were described previously.[3]

***N*-(2-Azidoethyl)benzamide (3, Azide A3)**

The synthesis and the physico-chemical characteristics of azide **3** were described previously.[3]

1-(*tert*-Butoxycarbonylamino)-2-azidoethane (4, Azide A4), Scheme 2



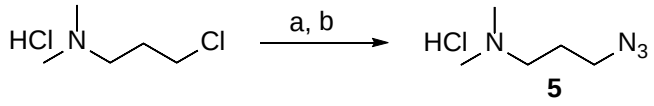
4

Scheme 2. Reagents, conditions and yield: (a) NaN_3, water, 80 °C, overnight; (b) TEA, Boc_2O, DCM, 1 h at 0°C then overnight at rt (yield over two steps: 80%).

2-Bromoethylamine hydrobromide (10 g; 48. 8 mmol) and NaN_3 (6.3 g; 97.6 mmol) in water (100 mL) were heated overnight at 80°C. After cooling, the free amine was obtained by addition of NaOH (2 g; 48.8 mmol) and extracted with DCM (4 x 50 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4. After filtration, TEA (4.9 g; 48.8 mmol) was added to the filtrate

and the resulting solution was cooled to 0 °C. A solution of Boc_2O (11.7 g; 53.7 mmol) in DCM (50 mL) was then added dropwise. The reaction mixture was stirred at 0 °C for one hour and overnight at room temperature. The solvent was evaporated under reduced pressure and the resulting yellow residue was purified by flash chromatography on silica gel, using a linear gradient of ethyl acetate in petroleum ether, to yield azide **4** as a colorless oil (7.3 g, 80% yield over two steps. R_f = 0.75 (50% ethyl acetate/toluene). ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 1.45 (9H, s, -$C(CH_3)_3$), 3.30 (2H, br q, $^3J_{HH}$ = 5.6 Hz, -CH_2-N), 3.42 (2H, br t, $^3J_{HH}$ = 5.6 Hz, -CH_2-N_3), 4.88 (1H, br, -NH-CO-O). ^{13}C NMR (125.8 MHz; $CDCl_3$): δ_C 28.30 (3C, –C(<u>C</u>$H_3)_3$), 40.01 (1C, –CH_2–N), 51.20 (1C, –CH_2–N_3), 79.72 (1C, –<u>C</u>$(CH_3)_3$), 155.69 (1C, -NH-CO-O). IR (CCl_4) ν_{max} cm^{-1} 2103 vs (N_3); 3465 m, 3373 w (NH); 1721 vs (C=O); 1502 vs (amide II); 2980 s, 1392 m, 1367 s (CH_3); 2932 m, 1452 m (CH_2), 1171 vs ($C(CH_3)$). HRMS (CI) calc for $C_7H_{15}N_4O_2$ $[M]^+$ 187.1195, found: 187.1193.

***N*,*N*-Dimethyl-*N*-(3-azidopropyl)amine hydrochloride (5, Azide A5)**, Scheme 3

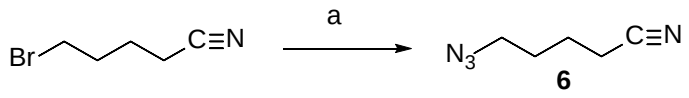


Scheme 3. Reagents, conditions and yield: (a) NaN_3, NaI, water, 80 °C, overnight; (b) 3 M HCl/dioxane (yield over two steps: 63%).

A solution of *N*,*N*-dimethyl-3-chloropropylamine hydrochloride (10 g; 63 mmol), NaI (9.4 g; 63 mmol) and NaN_3 (8.2 g; 126 mmol) in water (100 mL) was stirred overnight at 80 °C. After cooling down to room temperature, the reaction mixture was basified with NaOH (2.5 g; 63 mmol) and the product was extracted with diethyl ether (4 x 50 mL). The organic solutions were combined, washed with a minimal amount of saturated aqueous solution of sodium metabisulfite and dried over anhydrous Na_2SO_4. After filtration, the filtrate was treated with 3 M HCl/dioxane solution until the product precipitated. The solid was filtered off, washed with diethyl ether, dried and recrystallized from methanol/ether to yield azide **5** as a white powder (6.6 g, 63% yield over two steps, m.p. 110-111 °C). R_f = 0.25 (ethyl acetate-methanol-acetone-water 4-1-1-1). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 1.93 (2H, m, -CH_2-), 2.70 (6H, br s, -N$(CH_3)_2$), 3.05 (2H, m, –CH_2–N), 3.47 (2H, t, $^3J_{HH}$ = 7.2 Hz, –CH_2–N_3), 11.16 (1H, br s, >NH). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C

23.55 (1C, –CH_2–), 42.04 (2C, –$N(CH_3)_2$), 48.17 (1C, –CH_2–N_3), 54.02 (1C, –CH_2–N). IR (KBr) ν_{max} cm^{-1} 2691 s, 1631 m ($RN^+(CH_3)_2$); 2098 vs (N_3); 2942 m (CH_2). HRMS (ESI) calc for $C_5H_{13}N_4$ $[M]^+$ 129.11347, found: 129.11355.

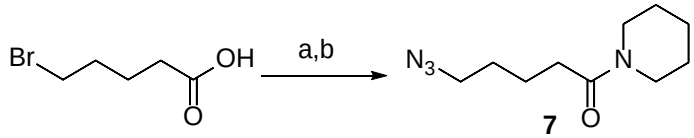
5-Azidopentanenitrile (6, Azide A6), Scheme 4



Scheme 4. Reagents, conditions and yield: (a) NaN_3, DMSO, 80 °C overnight (87%).

5-Bromovaleronitrile (6 g; 37 mmol) was heated with NaN_3 (4.8 g; 74 mmol) at 80°C overnight in 50 mL DMSO. After cooling, water (100 mL) was added and the product was extracted with diethyl ether (4 x 50 mL). The organic solutions were combined, washed with water (2 x 50 mL), brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and filtrated. The filtrate was carefully evaporated and the residue was subjected to flash chromatography on silica gel using a linear gradient of ether in petroleum ether. Azide **6** (4 g, 87% yield) was obtained as a colorless liquid. R_f = 0.65 (10% ethyl acetate/toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.76 (4H, m, -CH_2-CH_2-), 2.40 (2H, m, –CH_2–C≡N), 3.37 (2H, m, –CH_2–N_3). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 16.72 (1C, -CH_2-), 22.59 (1C, -CH_2-), 27.75 (1C, -CH_2-), 50.38 (1C, –CH_2–N_3), 119.07 (1C, –C≡N). IR (film) ν_{max} cm^{-1} 2246 w (C≡N); 2100 vs (N_3); 2954 m, 2875 w, 1457 w (CH_2). HRMS (CI) calc for $C_5H_9N_4$ $[M+1]^+$ 125.0827, found: 125.0825.

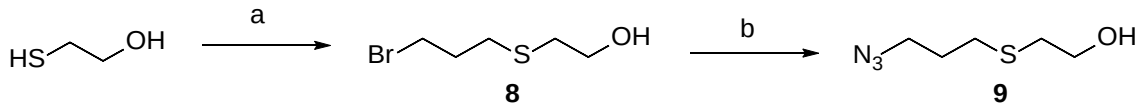
1-(5-Azidopentanoyl)piperidine (7, Azide A7), Scheme 5



Scheme 5. Reagents, conditions and yield: (a) NaN_3, DMSO, 80 °C overnight; (b) $SOCl_2$, DCM, 40°C 1 h then piperidine, TEA, DCM at 0 °C then rt overnight (yield over two steps: 62%).

A mixture of 5-bromovaleric acid (10 g; 55 mmol) and NaN_3 (7.2 g; 110 mmol) in DMSO (50 mL) was stirred overnight at 80°C. After cooling, water (100 mL) was added and the product was extracted with ethyl acetate (4 x 50 mL). The organic solutions were combined, washed with water (50 mL) and brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and evaporated. The resulting crude 5-azidovaleric acid was dissolved in DCM (25 mL) and reacted with $SOCl_2$ at 40 °C for two hours. The excess of thionyl chloride and DCM was evaporated under reduced pressure. The resulting 5-azidovaleroyl chloride was dissolved in DCM (50 mL) and cooled to 0 °C. A solution of TEA (4.6 g; 55 mmol) and piperidine (10.9 g; 108 mmol) in DCM (100 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for one hour and overnight at room temperature. Volatile materials were evaporated, and the resulting crude product was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in petroleum ether to yield azide **7** (7.2 g, 62% yield, yellow oil). R_f = 0.56 (50% ethyl acetate/toluene). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 1.54 (2H, m, –CH_2–), 1.56 (2H, m, –CH_2–), 1.64 (2H, m, –CH_2–), 1.66 (2H, m, –CH_2–), 2.35 (2H, t, $^3J_{HH}$ = 7.3 Hz, -CH_2-CO), 3.31 (2H, t, $^3J_{HH}$ = 6.8 Hz, -CH_2-N_3), 3.40 (2H, m, –CH_2–), 3.55 (2H, m, –CH_2–N). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 22.33 (1C, –CH_2–), 24.39 (1C, –CH_2–), 25.42 (1C, –CH_2–), 26.39 (1C, –CH_2–), 28.45 (1C, –CH_2–), 32.45 (1C, –CH_2–), 42.52 (1C, –CH_2–N), 46.47 (1C, –CH_2–N), 51.11 (1C, –CH_2–N_3), 170.40 (1C, >N-C=O). IR (film) ν_{max} cm^{-1} 2937 s, 2856 m 1465 s (CH_2); 2095 vs (N_3); 1643 vs (C=O). HRMS (CI) calc for $C_{10}H_{19}N_4O$ $[M+1]^+$ 211.1559, found: 211.1557.

2-((3-Azidopropyl)thio)ethan-1-ol (9, Azide A8), Scheme 6



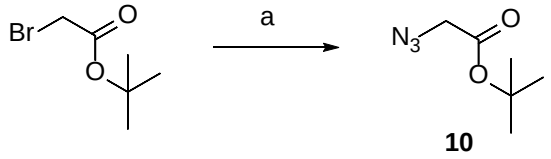
Scheme 6. Reagents, conditions and yields: (a) NaH, THF 0.5 h at 0°C then $Br(CH_2)_3Br$, rt overnight (yield: 49%) (b) NaN_3, DMSO, 80 °C, overnight (yield: 92%).

2-((3-Bromopropyl)thio)ethan-1-ol (**8**): 60% sodium hydride (1.5 g; 64 mmol) was added to an ice-cold solution of 2-mercaptoethanol (5 g; 64 mmol) in THF (250 mL). After 30 minutes, the ice bath was removed, and 1,3-dibromopropane (38.7 g; 192 mmol) was added in one portion. The reaction mixture was stirred overnight at room temperature. The volatile materials were evaporated

under reduced pressure. The resulting brown residue was purified on silica gel using a linear gradient of ethyl acetate in petroleum ether to afford **8** (6.2 g, 49% yield, colorless oil). R_f = 0.51 (5% methanol/chloroform). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 2.03 (2H, m, –CH_2–), 2.56 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2-S), 2.62 (2H, t, $^3J_{HH}$ = 7.1 Hz, -CH_2-S), 3.52 (2H, t, $^3J_{HH}$ = 7.0 Hz, -CH_2-O), 3.58 (2H, t, $^3J_{HH}$ = 6.5 Hz, -CH_2-Br).^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 29.81 (1C, –CH_2–S), 32.47 (1C, –CH_2–), 33.76 (1C, –CH_2–Br), 34.02 (1C, –CH_2–S), 61.06 (1C, –CH_2–O). IR (film) ν_{max} cm^{-1} 3359 vs (OH); 2920 s, 2874 s, 1432 s, 1425 s, 1290 m, 1242 s (CH_2); 1062 vs, 1046 vs (C-O); 561 w (C-Br). HRMS (CI) calc for $C_5H_{11}OSBr$ $[M]^+$ 197.9714, found: 197.9716.

2-((3-Azidopropyl)thio)ethan-1-ol (**9**): Compound **9** was prepared by reaction of **8** and NaN_3 (4 g; 62 mmol) following the protocol described for compound **6**. After flash chromatography, azide **9** (4.5g, 92% yield) was obtained as a colorless liquid. R_f = 0.58 (50% ethyl acetate/toluene). ^{1}H NMR (500 MHz; d_6DMSO): δ_H 1.76 (2H, m, –CH_2–), 2.56 (4H, m, 2x –CH_2–S), 3.40 (2H, t, $^3J_{HH}$ = 6.8 Hz, -CH_2-N_3), 3.52 (2H, td, $^3J_{HH}$ = 6.8 and 5.5 Hz, -CH_2-O), 4.80 (1H, br t, J_{HH} = 5.5 Hz, –OH). ^{13}C NMR (125.7 MHz; d_6DMSO): δ_C 28.65 (1C, –CH_2–S), 28.80 (1C, –CH_2–), 34.09 (1C, –CH_2–S), 49.75 (1C, –CH_2–N_3), 61.10 (1C, –CH_2–O). IR (film) ν_{max} cm^{-1} 3401 s (OH); 2100 vs (N_3); 2925 s, 2874 m (CH_2); 1059 m, 1045 m (C-O). HRMS (CI) calc for $C_5H_{12}N_3SO$ $[M+1]^+$ 162.0701, found: 162.0705.

***tert*-Butyl-2-azidoacetate (10, Azide A9)**, Scheme 7



10

Scheme 7. Reagents, conditions and yield: (a) NaN_3, DMSO, 80 °C, overnight (70%).

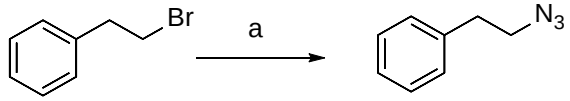
Compound **10** was prepared by reaction of *tert*-butyl-2-bromoacetate (10 g; 51.2 mmol) and NaN_3 (6.7 g; 100 mmol) following the protocol described for compound **6**. After flash chromatography, compound **10** (5.7 g, 70% yield) was obtained as a colorless liquid. R_f = 0.78 (10% ethyl acetate/toluene). ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 1.51 (9H, s, -C(CH_3)$_3$), 3.75 (2H, s, -CH_2-N_3). ^{13}C NMR (125.7 MHz; $CDCl_3$): δ_C 27.94 (3C, –C(CH_3)$_3$), 50.85 (1C, –CH_2–N_3), 82.94 (1C, –C(CH_3)$_3$), 167.31 (1C, -O–C=O). IR (CCl_4) ν_{max} cm^{-1} 2983 s, 1478 m, 1394 s, 1370 vs (CH_3); 2110

vs, 1299 vs (N_3); 1747 vs (C=O); 1223 vs (C-O); 2933 m (CH_2); 1155 vs ($(CCH_3)_3$). HRMS (CI) calc for $C_6H_{12}N_3O_2$ $[M+1]^+$ 158.0930, found: 158.0924.

1-Azidoheptane (11, Azide A10)

The synthesis and the physico-chemical characteristics of azide **11** were described earlier.[4]

2-Phenylethyl azide (12, Azide B1), Scheme 8



12

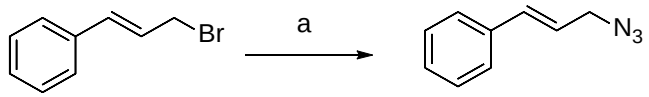
Scheme 8. Reagents, conditions and yield: (a) NaN_3, DMSO, 80 °C, overnight (88%).

Azide **12** was prepared by reaction of 2-phenylethyl bromide (5 g; 27 mmol) and NaN_3 (3.5 g; 54 mmol) following the protocol described for compound **6**. After flash chromatography, azide **12** (3.5g, 88% yield) was obtained as a colorless liquid. R_f = 0.90 (toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 2.89 (2H, t, $^3J_{HH}$ = 7.3 Hz, -CH_2-), 3.50 (2H, t, $^3J_{HH}$ = 7.3 Hz, -CH_2-N_3), 7.21 (2H, m, 2x CH_{arom}), 7.24 (1H, m, CH_{arom}), 7.31 (2H, m, 2x CH_{arom}). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 35.33 (1C, –CH_2–), 52.44 (1C, –CH_2–N_3), 126.75 (1C, CH_{arom}), 128.62 (2C, 2x CH_{arom}), 128.72 (2C, 2x CH_{arom}), 138.00 (1C, C_{arom}). IR (CCl_4) ν_{max} cm^{-1} 2096 vvs (N_3); 2929 m, 2873 m (CH_2); 3089 w, 3067 w, 3031 w, 3006 w, 1498 m, 1455 m, 1082 w, 1031 w, 698 s (ring). HRMS (CI) calc for $C_8H_{10}N_3$ $[M+1]^+$ 148.0875, found: 148.0881.

***N*-(2-Azidoethyl)-4-methylbenzensulfoamide (13, Azide B2)**

The synthesis and the physico-chemical characteristics of azide **13** were described earlier.[3]

(*E*)-3-Azido-1-phenyl-1-propene (14, Azide B3), Scheme 9

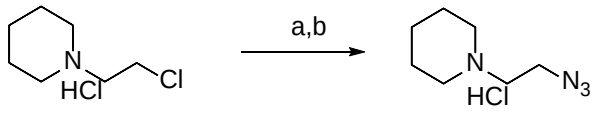


14

Scheme 9. Reagents, conditions and yield: (a) NaN_3, DMSO, 80 °C, overnight (60%).

Azide **14** was prepared by reaction of (*E*)-3-bromo-1-phenyl-1-propene (5 g; 25.4 mmol) and NaN_3 (3.3 g; 50.4 mmol) following the protocol described for compound **6**. After flash chromatography, azide **14** (2.4 g, 60% yield) was obtained as a colorless liquid. R_f = 0.89 (toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 3.93 (2H, dd, $^3J_{HH}$ = 6.6 and $^4J_{HH}$ = 1.5 Hz, -CH_2-N_3), 6.23 (1H, dt, $^3J_{HH}$ = 15.8 and 6.6 Hz, -CH=), 6.64 (1H, dt, $^3J_{HH}$ = 15.8 and $^4J_{HH}$ = 1.5 Hz, -CH=), 7.27 (1H, m, CH_{arom}), 7.33 (2H, m, 2x CH_{arom}), 7.39 (2H, m, 2x CH_{arom}). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 52.98 (1C, –CH_2–N_3), 122.36 (1C, –CH=), 126.60 (2C, 2x CH_{arom}), 128.14 (1C, CH_{arom}), 128.62 (2C, 2x CH_{arom}), 134.51 (1C, –CH=), 135.97 (1C, C_{arom}). IR (CCl_4) ν_{max} cm^{-1} 2102 vvs (N_3); 3085 w, 3064 w, 3030 w, 1497 m, 692 s (ring); 966 vs (C=C-H); 1654 w (C=C); 2925 w, 2870 w (CH_2). HRMS (CI) calc for $C_9H_9N_3$ $[M]^+$ 159.0796, found: 159.0798.

1-(2-Azidoethyl)piperidine hydrochloride (15, Azide B4), Scheme 10

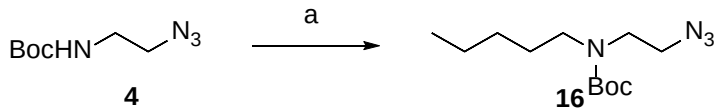


15

Scheme 10. Reagents, conditions and yield: (a) NaN_3, NaI, water, 80 °C, overnight (b) 3 M HCl/dioxane (yield over two steps: 77%).

Azide **15** was prepared by reaction of 1-(2-chloroethyl)piperidine hydrochloride (10 g; 54.3 mmol), NaN_3 (7.1 g; 108.6 mmol) and NaI (8.1 g; 54.3 mmol) following the protocol described for compound **5**. Azide 1**5** (8 g, 77% yield, white powder, m.p. 159-161 °C) was obtained by recrystallization from isopropyl alcohol/diethyl ether. R_f = 0.38 (ethyl acetate-acetone-methanol-water = 4-1-1-1). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 1.36 and 1.67 (2H, 2x m,-CH_2-), 1.76 and 1.81 (4H, m, 2 x -CH_2-), 2.90 and 3.38 (4H, m, 2 x -CH_2-N), 3.20 (2H, t, $^3J_{HH}$ = 6.2 Hz, -CH_2-N), 3.88 (2H, t, $^3J_{HH}$ = 6.2 Hz, -CH_2-N_3). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 21.41 (1C, -CH_2-), 22.39 (2C, 2 x -CH_2-), 45.21 (1C, –CH_2–N_3), 52.46 (2C, 2x -CH_2-N), 54.23 (1C, -CH_2-N). IR (KBr) ν_{max} cm^{-1} 2103 vs (N_3); 2944 m, 1458 m (CH_2); 2694 m, 2670 m, 2647 s, 2620 m, 2584 m, 2543 s, 2508 m (R_3NH^+). HRMS (ESI) calc for $C_7H_{15}N_4$ $[M]^+$ 155.12912, found: 155.12882.

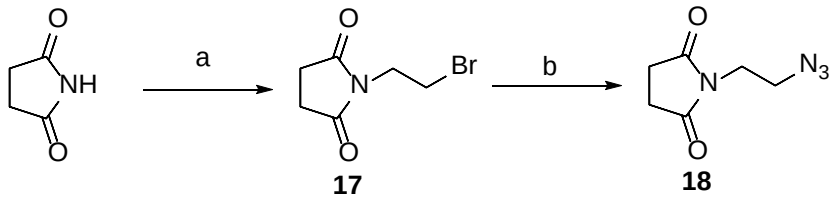
***N*-(2-Azidoethyl)-*N*-pentyl-*N*-(*tert*. butyloxycarbonyl)amine (16, Azide B5)**, Scheme 11



Scheme 11. Reagents, conditions and yield: (a) NaH, THF 0.5 h at 0 °C then $CH_3(CH_2)_4I$, rt, overnight (yield: 38%).

Azide **16** was prepared by reaction of 1-(*tert*-butoxycarbonylamino)-2-azidoethane **4** (5 g; 26.9 mmol), 60% NaH (1.1 g; 28.2 mmol) and pentyl iodide (5.3 g; 26.9 mmol) following the protocol described for compound **8**. After flash chromatography, azide **16** (2.6 g, 38% yield) was obtained as a pale yellow oil. R_f = 0.79 (20% ethyl acetate/toluene). ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 0.90 (3H, t, $^3J_{HH}$ = 7.3 Hz, -CH_3) 1.25 (2H, m, -CH_2-), 1.33 (2H, m, -CH_2-), 1.46 (9H, s, -$C(CH_3)_3$), 1.52 (2H, m,-CH_2-), 3.22 (2H, br t, $^3J_{HH}$ = 7.2 Hz,-CH_2-N), 3.35 (2H, um,-CH_2-N_3), 3.42 (2H, um,-CH_2-N).^{13}C NMR (125.7 MHz; $CDCl_3$, some signals are doubled due to the presence of *trans*- and *cis*-isomer on >N-CO- bond): δ_C 13.89 (1C, –CH_3), 22.28 (1C, -CH_2-), 27.82 and 28.19 (1C, -CH_2-), 28.26 (3C, –C(<u>C</u>H_3)$_3$), 28.80 (1C, -CH_2-), 46.34 and 46.60 (1C, –CH_2–N_3), 47.73 and 48.38 (1C, -CH_2-N), 49.54 and 49.89 (1C, -CH_2-N), 79.62 (1C, –<u>C</u>$(CH_3)_3$). IR (film) ν_{max} cm^{-1} 2101 vs (N_3); 1696 vs (C=O); 2961 s, 2873 s, 1469 m, 1392 m, 1366 m (CH_3); 2932 s, 2862 m, 1456 m (CH_2); 1151 vs ((C(CH_3)). HRMS (CI) calc for $C_{12}H_{25}N_4O_2$ $[M+1]^+$ 257.1978, found: 257.1974

1-(2-Bromoethyl)pyrrolidine-2,5-dione (17, Azide B6), Scheme 12



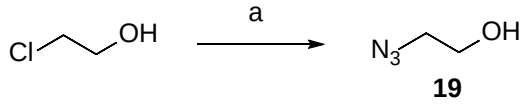
Scheme 12. Reagents, conditions and yields: (a) K_2CO_3, 1,2-dibromoethane, TBAB, ACN, 70 °C, overnight (yield: 98%) (b) NaN_3, DMSO, 80 °C, overnight (yield: 51%).

<u>1-(2-Bromoethyl)pyrrolidine-2,5-dione (**17**)</u>: A suspension of succinimide (7.5 g; 75.5 mmol), 1,2-dibromoethane (56.8 g; 302 mmol), K_2CO_3 (10.5 g; 75.5 mmol) and tetrabutylammonium bromide (TBAB, 5 g) in acetonitrile (250 mL) was heated overnight at 70°C. After cooling, the solid

material was filtered off. The filtrate was evaporated purified on silica gel using a linear gradient of ethyl acetate in toluene to give **17** (15.2 g, 97% yield, m.p. 55-56°C) as a colorless oil, which solidified upon standing. R_f = 0.45 (50% ethyl acetate/toluene). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 2.65 (4H, s, 2 x -CH_2-CO), 3.57 (2H, t, $^3J_{HH}$ = 6.8 Hz,-CH_2-Br), 3.76 (2H, t, $^3J_{HH}$ = 6.8 Hz,-CH_2-N).^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 28.88 (2C, 2x -CH_2-), 29.05 (1C, -CH_2-Br), 39.75 (1C, –CH_2–N), 177.69 (2C, -CO-N-CO-). IR (KBr) ν_{max} cm^{-1} 1775 m, 1703 vs (C=O); 569 w (C-Br). HRMS (CI) calc for $C_6H_9NO_2Br$ $[M+1]^+$ 205.9817, found: 205.9819.

1-(2-Azidoethyl)pyrrolidine-2,5-dione (**18**): Azide **18** was prepared by reacting **17** (14.6 g; 71 mmol) and NaN_3 (9.2 g ; 142 mmol) following the protocol described for compound **6**. After flash chromatography, azide **18** (6.1 g, 51% yield) was obtained as a white solid (m.p. 46-48°C). R_f = 0.57 (50% ethyl acetate/toluene). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 2.65 (4H, s, 2x -CH_2-CO), 3.44 (2H, t, $^3J_{HH}$ = 5.9 Hz, -CH_2-N_3), 3.56 (2H, t, $^3J_{HH}$ = 5.9 Hz, -CH_2-N). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 28.25 (2C, 2x -CH_2-), 37.40 (1C, -CH_2-N), 48.00 (1C, –CH_2–N_3), 177.93 (2C, -CO-N-CO-). IR (KBr) ν_{max} cm^{-1} 2109 vs (N_3); 1784 m, 1714 vs (C=O); 2944 m, 2876 w (CH_2). HRMS (CI) calc for $C_6H_9N_4O_2$ $[M+1]^+$ 169.0726, found: 169.0725

2-Azidoethanol (19, Azide B7), Scheme 13



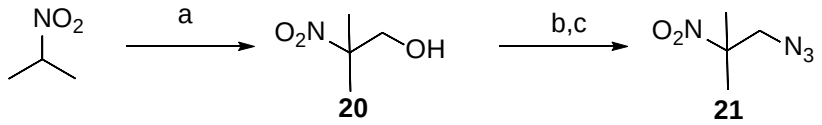
19

Scheme 13. Reagents, conditions and yield: (a) NaN_3, NaI, water, 80 °C, overnight (yield: 65%).

A solution of 2-chloroethanol (10 g; 0.124 mol), NaN_3 (16.1 g; 0.248 mol) and NaI (18.6 g; 0.124 mol) in water (100 mL) was heated overnight at 80 °C. After cooling, the reaction mixture was saturated with NaCl, and the product was extracted with diethyl ether (4 x 100 mL). The organic extracts were combined, dried over Na_2SO_4, filtrated and carefully evaporated (explosive!) under reduced pressure. The resulting liquid was purified on silica gel using a linear gradient of petroleum ether in ether to afford azide **19** (7 g, 65% yield) as a colorless liquid. R_f = 0.59 (50% ethyl acetate/toluene). ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 2.50 (1H, br s,-OH), 3.45 (2H, m, -CH_2-N_3), 3.78 (2H, m,-CH_2-O). ^{13}C NMR (125.7 MHz; $CDCl_3$): δ_C 53.42 (1C, -CH_2-N_3), 61.35 (1C, -CH_2-OH).

IR (film) ν_{max} cm^{-1} 2100 vs, 1296 s (N_3); 3374 m (OH); 1065 m (C-O); 2936 m, 2881 m, 1142 m (CH_2). HRMS (CI) calc for $C_2H_6N_3O$ $[M]^+$ 88.0511, found: 88.0512.

1-Azido-2-methyl-2-nitropropane (21, Azide B8), Scheme 14



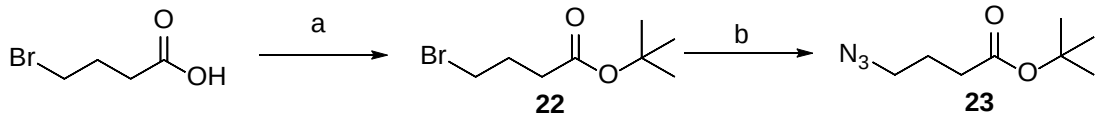
Scheme 14. Reagents, conditions and yields: (a) paraformaldehyde, KOH, 1 hour at rt (yield: 60%) (b) MsCl, TEA, DCM, 0.5 hour at 0 °C (c) NaN_3, DMSO, 80 °C, overnight (yield over steps b and c: 77%).

2-methyl-2-nitropropan-1-ol (**20**): A modified procedure of Noland[5] was used here: A saturated solution of KOH in methanol was added dropwise to a stirred suspension of paraformaldehyde (3.2 g; 0.11 mol) in 2-nitropropane (10.4 g; 0.12 mol) until pH ~ 8 was reached (the slurry became clear). The reaction mixture was then stirred at room temperature for one hour. Volatile materials were evaporated and the residue was taken up in DCM (50 mL). The organic solution was washed with acidified brine (20 mL, pH ~ 1), with standard brine (20 mL), dried over anhydrous Na_2SO_4 filtered and evaporated to afford an oil, which quickly solidified. This solid was recrystallized from ethyl acetate/petroleum ether to afford compound **20** (8.3 g, 60% yield) as a white solid (m.p. 84-86 °C). R_f = 0.81 (ethyl acetate). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 1.47 (6H, s, -C(CH_3)$_2$), 3.67 (2H, s,-CH_2-O), 5.37 (1H, br s, -OH). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 22.27 (2C, 2x -CH_3), 67.87 (1C, -CH_2-O), 89.28 (1C, -C(CH_3)$_2$). IR (KBr) ν_{max} cm^{-1} 3426 s (OH); 1066 m (C-O); 1540 vs, 1350 m (NO_2); 2992 w, 2880 w, 1473 m, 1374 m (CH_3); 2943 w (CH_2). HRMS (CI) calc for $C_4H_{10}NO_3$ $[M]^+$ 120.0661, found: 120.0663.

1-Azido-2-methyl-2-nitropropane (**21**): Azide **21** was prepared following the protocol described for compound **2**: alcohol **20** (7.9 g; 66.5 mmol) was transformed to a mesyl derivative by the reaction with TEA (8.1 g; 79.5 mmol) and MsCl (8.4 g; 73 mmol) in DCM (100 mL). The mesyl derivative was then allowed to react with NaN_3 (8.6 g; 133 mmol) in DMSO (100 mL) to yield azide **21** (7.4 g, 77% yield over two steps) as a colorless liquid. R_f = 0.69 (10% ethyl acetate/toluene). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 1.59 (6H, s, -C(CH_3)$_2$), 3.72 (2H, s, -CH_2-N_3). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 23.78 (2C, -C(CH_3)$_2$), 58.20 (1C, -CH_2-N_3), 86.64 (1C, -C(CH_3)$_2$). IR (CCl_4) ν_{max} cm^{-1} 2105 vs (N_3); 1545 vs, 1344 s (NO_2); 2922 m, 2880 m, 1470 s, 1399

s, 1373 s (CH_3); 2942 m, 2858 m (CH_2). HRMS (CI) calc for $C_4H_9N_4O_2$ $[M+1]^+$ 145.0726, found: 145.0728.

***tert*-Butyl 4-azidobutanoate (23, Azide B9)**, Scheme 15

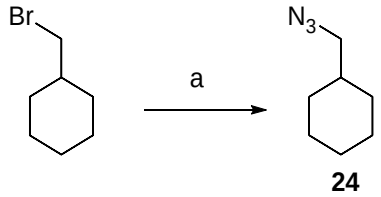


Scheme 15. Reagents, conditions and yields: (a) $(CH_3)_3COH$, $MgSO_4$, H_2SO_4, DCM, 72 hours at rt (yield: 79%); (b) NaN_3, DMSO, 80 °C, overnight (yield: 92%).

tert-Butyl 4-bromobutanoate (**22**): Ester **22** was prepared from 4-bromobutanoic acid (5 g; 29.9 mmol) *tert*-butyl alcohol (11 g; 0.149 mol), $MgSO_4$ (20 g) and conc. H_2SO_4 (1.6 mL) in DCM (200 mL) as described in Ref.[6] Azide **22** (5.3 g, 79% yield) was obtained as a colorless liquid. R_f = 0.79 (10% ethyl acetate/toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.45 (9H, s, -C(CH_3)$_3$), 2.13 (2H, m, -CH_2-), 2.40 (2H, t, $^3J_{HH}$ = 7.2 Hz, -CH_2-CO), 3.46 (2H, t, $^3J_{HH}$ = 6.6 Hz, -CH_2-Br).^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 27.89 (1C, -CH_2-), 28.03 (3C, -C(<u>C</u>H_3)$_3$), 32.78 (1C, -CH_2-Br), 33.67 (1C, -CH_2-), 80.52 (1C, <u>C</u>(CH_3)$_3$), 171.76 (1C, -O-C=O). IR (film) ν_{max} cm^{-1} 1729 vs (C=O); 1158 s, 1129 m (C-O); 2979 m, 1393 m, 1367 s (CH_3); 2933 m, 1457 w (CH_2); 561 w (C-Br). HRMS (ESI) calc for $C_8H_{15}O_2NaBr$ $[M+Na]^+$ 245.01476, found: 245.01479.

tert-Butyl 4-azidobutanoate (**23**): Azide **23** was prepared by reaction of **22** (8.7 g; 39 mmol) and NaN_3 (5.1 g; 78 mmol) following the protocol described for compound **6**. After flash chromatography, azide **23** (6.6 g, 92% yield) was obtained as a bright yellow liquid. R_f = 0.81 (10% ethyl acetate/toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.45 (9H, s, -C(CH_3)$_3$), 1.87 (2H, m, -CH_2-), 2.32 (2H, t, $^3J_{HH}$ = 7.3 Hz, -CH_2-CO), 3.33 (2H, t, $^3J_{HH}$ = 6.8 Hz, -CH_2-N_3). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 24.38 (1C, -CH_2-), 28.04 (3C, -C(<u>C</u>H_3)$_3$), 32.38 (1C, -CH_2-), 50.70 (1C, –CH_2–N_3), 80.57 (1C, -<u>C</u>(CH_3)$_3$), 171.96 (1C, -O-C=O). IR (film) ν_{max} cm^{-1} 2099 vs N_3; 1730 vs (C=O); 1153 vs (C-O); 2979 m, 2873 w, 1393 w, 1368 m (CH_3); 2932 m, 1479 w, 1457 w (CH_2). HRMS (CI) calc for $C_8H_{16}O_2N_3O_2$ $[M+1]^+$ 186.1243, found: 186.1245.

(Azidomethyl)cyclohexane (24, Azide B10), Scheme 16

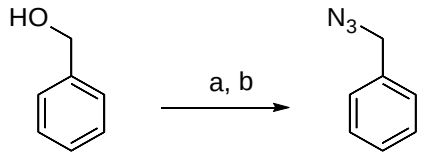


24

Scheme 16. Reagents, conditions and yield: (a) NaN_3, DMSO, 80 °C, overnight (Yield: 75%).

Azide **24** was prepared by reaction of (bromomethyl)cyclohexane (10 g; 35.4 mmol) and NaN_3 (7.3 g; 112.8 mmol) following the protocol described for compound **6**. After flash chromatography, azide **24** (5.9 g, 75% yield) was obtained as a bright yellow liquid. R_f = 0.63 (petroleum ether). ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 0.96 and 1.75 (4H, m, 2x -CH_2-), 1.17 and 1.68 (2H, 2x m, -CH_2-), 1.25 and 1.74 (4H, m, 2x -CH_2-), 1.55 (1H, m, >CH-), 3.11 (2H, d, $^3J_{HH}$ = 6.8 Hz, -CH_2-N_3). ^{13}C NMR (125.7 MHz; $CDCl_3$): δ_C 25.69 (2C, 2x -CH_2-), 26.20 (1C, -CH_2-), 30.59 (2C, 2x –CH_2–), 38.01 (1C, >CH-), 58.00 (1C, -CH_2-N_3). IR (film) ν_{max} cm^{-1} 2099 vs (N_3); 2926 s, 2854 s, 1451 m (CH_2). HRMS (CI) calc for $C_7H_{14}O_2N_3$ $[M+1]^+$ 140.1188, found: 140.1187.

Benzylazide (25, Azide C1), Scheme 17



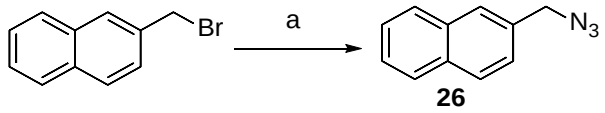
25

Scheme 17. Reagents, conditions and yield: (a) MsCl, TEA, DCM, 0.5 hour at 0 °C (b) NaN_3, DMSO, 80 °C, overnight (yield over two steps 65%).

Azide **25** was prepared as described for the compound **1**: the intermediate mesyl derivative was obtained by reaction of benzyl alcohol (5 g; 46.2 mmol), TEA (9.3 g; 92.4 mmol) and MsCl (5.8 g; 50.9 mmol) in DCM (100 mL) and was then converted to **23** by heating with NaN_3 (5 g; 78.4 mmol) in DMSO (100 mL). The azide **25** (4 g, 65% yield over two steps) was obtained as a colorless liquid. R_f = 0.81 (toluene). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 4.44 (2H, s, -CH_2-N_3), 7.36 (1H, m, CH_{arom}), 7.37 (2H, m, 2x CH_{arom}), 7.39 (2H, m, 2x CH_{arom}). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 53.80 (1C, –CH_2–N_3), 128.38 (1C, CH_{arom}), 128.69 (2C, 2x CH_{arom}), 128.94 (2C, 2x

CH_{arom}), 135.80 (1C, C_{arom}). IR (film) ν_{max} cm^{-1} 2097 vs (N_3); 2930 w, 2876 w (CH_2); 3089 w, 3066 w, 3033 w, 1455 m, 698 m (ring). HRMS (CI) calc for $C_7H_7N_3$ $[M]^+$ 133.0640, found: 133.0635.

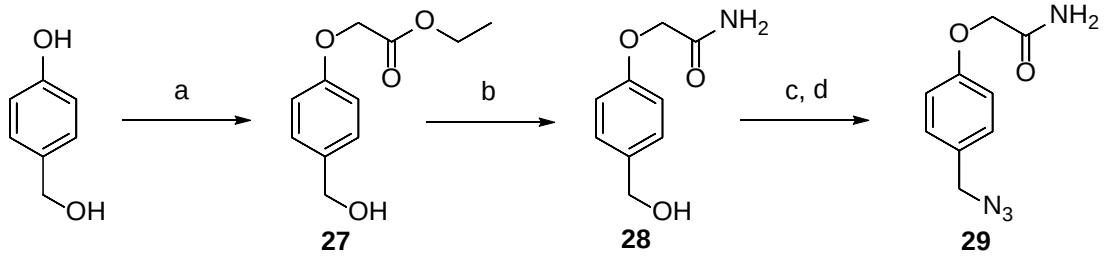
2-(Azidomethyl)naphthalene (26, Azide C2), Scheme 18



Scheme 18. Reagents, conditions and yield: (a) NaN_3, DMSO, 80 °C, overnight (yield: 75%).

Azide **26** was prepared by reaction of 2-(bromomethyl)naphtalene (5 g; 22.6 mmol) and NaN_3 (2.9 g; 45.2 mmol) following the protocol described for compound **6**. After flash chromatography, azide **26** (3.7 g, 75% yield) was obtained as a white solid (m.p. 36-37 °C). R_f = 0.88 (toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 4.48 (2H, s, -CH_2-N_3), 7.41 (1H, dd, $^3J_{HH}$ = 8.4 and $^4J_{HH}$ = 1.8 Hz, CH_{arom}), 7.49 (2H, m, 2x CH_{arom}), 7.76 (1H, m, CH_{arom}), 7.84 (2H, m, 2x CH_{arom}), 7.85 (1H, br d, $^3J_{HH}$ = 8.4 Hz, CH_{arom}). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 54.99 (1C, –CH_2–N_3), 125.82 (1C, CH_{arom}), 126.31 (1C, CH_{arom}), 126.44 (1C, CH_{arom}), 127.15 (1C, CH_{arom}), 127.72 (1C, CH_{arom}), 127.91 (1C, CH_{arom}), 128.74 (1C, CH_{arom}), 132.78 (1C, C_{arom}), 133.06 (1C, C_{arom}), 133.23 (1C, C_{arom}). IR (KBr) ν_{max} cm^{-1} 2127 vs, 2102 s (N_3); 2852 w (CH_2); 3055 w, 3022 w, 1508 m, 1365 m, 826 s, 736 m (ring). HRMS (CI) calc for $C_{11}H_9N_3$ $[M]^+$ 183.0796, found: 183.0802.

[4-(Azidomethyl)phenoxy]acetatamide (29, Azide C3), Scheme 19



Scheme 19. Reagents, conditions and yields: (a) ethyl bromoacetate, K_2CO_3, ACN 60 °C, overnight (74%) (b) NH_3, methanol, 72 hours at rt (70%) (c) MsCl, TEA, DCM, 0.5 hour at 0 °C (d) NaN_3, DMSO, 80°C, overnight (yield over the steps c and d: 43%).

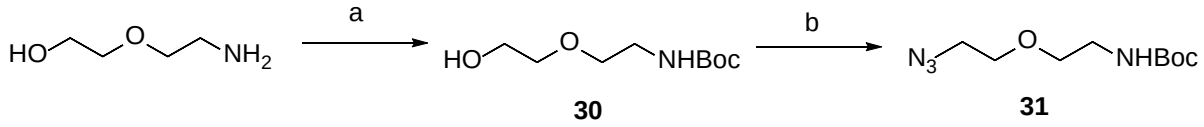
Ethyl [4-(hydroxymethyl)phenoxy]acetate (**27**): A modified procedure of Lusin et al[7] was used here. Briefly, 4-hydroxybenzyl alcohol (6.4 g; 51.6 mmol), ethyl bromoacetate (9.5 g; 56.8 mmol) and potassium carbonate (28.5 g; 206.4 mmol) were heated overnight at 60°C. After cooling, the solid was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified on silica gel using a linear gradient of toluene in ethyl acetate to yield ester **27** (8 g, 74%) as a colorless liquid. R_f = 0.55 (50% ethyl acetate/toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.29 (3H, t, $^3J_{HH}$ = 6.7 Hz, -CH_3), 4.26 (2H, q, $^3J_{HH}$ = 6.7 Hz, -CH_2-O), 4.60 (2H, s, -CH_2-O), 4.61 (2H, s, -CH_2-O), 6.89 (2H, m, 2x CH_{arom}), 7.28 (2H, m, 2x CH_{arom}). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 14.09 (1C, -CH_3), 61.34 (1C, -CH_2-O), 64.76 (1C, –CH_2–O), 65.44 (1C, –CH_2–O), 114.70 (2C, 2x CH_{arom}), 128.55 (2C, 2x CH_{arom}), 134.22 (1C, C_{arom}), 157.34 (1C, C_{arom}), 168.88 (1C, –O–CO–). IR (CCl_4) ν_{max} cm^{-1} 3616 w (OH); 1765 vs, 1740 vs (C=O); 1191 vs, 1033 m (Ar-O-C); 3069 w, 3037 w, 1613 m, 1512 s (ring); 1088 m (C-OH). HRMS (ESI) calc for $C_{11}H_{14}O_4Na$ $[M+Na]^+$ 233.07843, found: 233.07849.

[4-(Hydroxymethyl)phenoxy]acetatamide (**28**): Ester **27** (8 g ; 38 mmol) was dissolved in a saturated solution of ammonia in methanol (100 mL) and stirred at room temperature for 72 h. After evaporation, the resulting solid was recrystallized from methanol/ethyl acetate to afford the primary amide **28** (4.8 g, 70% yield) as a white solid (m.p. 124-126 °C). R_f = 0.73 (ethyl acetate-methanol-acetone-water = 6-1-1-0.5). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 4.40 (2H, s, -CH_2-O), 4.42 (2H, d, $^3J_{HH}$ = 5.7 Hz, -CH_2-O), 6.90 (2H, m, 2x CH_{arom}), 7.23 (2H, m, 2x CH_{arom}), 7.37 and 7.49 (2H, 2x br s, -CO-NH_2). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 62.72 (1C, –CH_2–O), 67.04 (1C, –CH_2–O), 114.51 (2C, 2x CH_{arom}), 128.06 (2C, 2x CH_{arom}), 135.40 (1C, C_{arom}), 156.85 (1C, C_{arom}), 170.27 (1C, -CO-NH_2).IR (KBr) ν_{max} cm^{-1} 3461 vs, 3356 s, 1645 vs (NH_2); 1683 vs (C=O); 1421 s (C-N); 1250 s, 1065 s (Ar-O-R); 3041 m, 1610 s, 1588 m, 1518 vs, 1442 m, 1179 m, 1118 m, 639 m, 519 m (ring); 2913 m, 2856 w (CH_2). HRMS (ESI) calc for $C_9H_{11}O_3Na$ $[M+Na]^+$ 204.06311, found: 204.06301.

[4-(Azidomethyl)phenoxy]acetatamide (**29**): Azide **29** was prepared as described for compound **1**: the intermediate mesyl derivative was obtained from the alcohol **28** (4.7 g; 25.9 mmol), TEA (3.9 g; 38.9 mmol) and MsCl (3.6 g; 31.1 mmol) in DCM (100 mL) and transformed to **29** by heating with NaN_3 (3.4 g; 51.8 mmol) in DMSO (100 mL). Recrystallization from ethyl acetate/petroleum ether yielded the azide **29** (2.3 g, 43% yield over two steps) as a white solid (m. p. 92-93 °C). R_f = 0.54 (ethyl acetate). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 4.36 (2H, s, -CH_2-N_3), 4.44 (2H, s, -CH_2-

O), 6.97 (2H, m, 2x CH_{arom}), 7.31 (2H, m, 2x CH_{arom}), 7.39 and 7.53 (2H, 2x br s, -CO-NH_2). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 53.33 (1C, $–CH_2–N_3$), 66.91 (1C, $–CH_2–O$), 115.03 (2C, 2x CH_{arom}), 128.35 (1C, C_{arom}), 130.15 (2C, 2x CH_{arom}), 157.86 (1C, C_{arom}), 170.00 (1C, -CO-NH_2). IR (KBr) ν_{max} cm^{-1} 3466 s, 3281 m, 1588 m (NH_2); 2104 vs (N_3); 1705 vs, 1672 vs (C=O); 1250 vs, 1067 m (Ar-O-R); 1515 s, 1425 m, 1184 m (ring). HRMS (ESI) calc for $C_9H_{10}O_2N_4Na$ $[M+Na]^+$ 229.06960, found: 229.06941.

1-(2-(*tert*-Butoxycarbonylamino)ethoxy)-2-azidoethan (31, Azide C4), Scheme 20



30 **31**

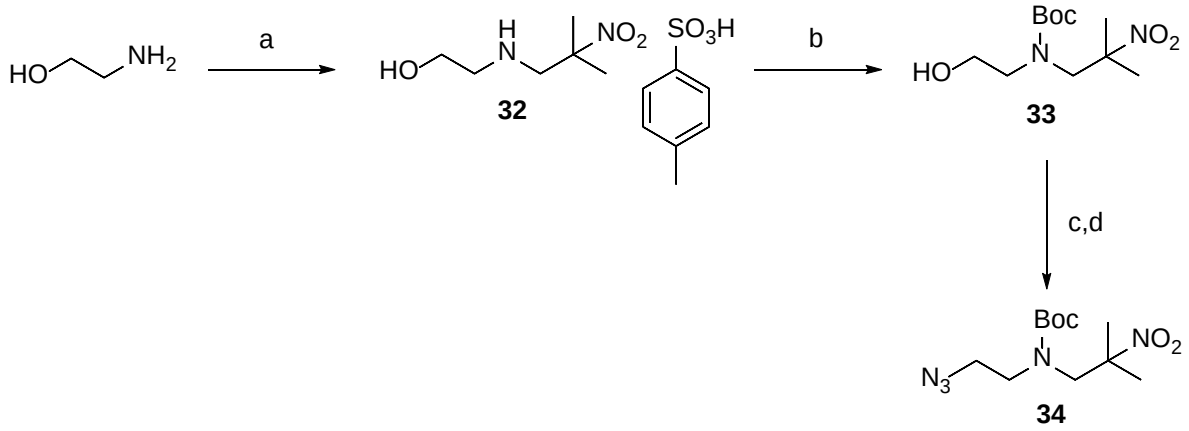
Scheme 20. Reagents, conditions and yields: (a) TEA, Boc_2O, DCM, 0 °C for 1 hour then overnight at rt (yield: 92%); (b) MsCl, TEA, DCM, 0.5 hour at 0 °C then NaN_3, DMSO, 80 °C, overnight (yield over two steps 85%).

2-(2-(*tert*-Butoxycarbonylamino)ethoxy)ethanol (**30**): A solution of Boc_2O (10.9 g; 49.9 mmol) in DCM (50 mL) was added dropwise to an ice-cooled mixture of 2-(2-aminoethoxy)ethanol (5 g; 47.5 mmol) and TEA (4.8 g; 47.5 mmol) in DCM (50 mL). The resulting mixture was stirred at 0 °C for 1 hour and overnight at room temperature. The volatile materials were evaporated and the yellow residue was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene to give **30** (8.9 g, 92% yield) as a colorless oil. R_f = 0.42 (ethyl acetate). ^1H NMR (600 MHz; d_6DMSO): δ_H 1.37 (9H, s, $C(CH_3)_3$), 3.07 (2H, q, $^3J_{HH}$ = 6.0 Hz, $–CH_2–N$), 3.37 (2H, t, $^3J_{HH}$ = 6.0 Hz, $–CH_2–O$), 3.39 (2H, t, $^3J_{HH}$ = 5.6 Hz, $–CH_2–O$), 3.47 (2H, q, $^3J_{HH}$ = 5.6 Hz, $–C\underline{H_2}–OH$), 4.55 (1H, t, $^3J_{HH}$ = 5.6 Hz, –OH). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 28.42 (3C, $–C(\underline{C}H_3)_3$), 39.97 (1C, $–CH_2–N$), 60.41 (1C, $–CH_2–OH$), 69.38 (1C, $–CH_2–O$), 72.26 (1C, $–CH_2–O$), 77.78 (1C, $–\underline{C}(CH_3)_3$), 155.80 (1C, NH–C=O). IR (CCl_4) ν_{max} cm^{-1} 3609 w (OH); 3460 m, 3374 m (NH); 1067 s (C-OH); 1126 vs (C-O-C); 1717 vs (C=O); 1504 vs (amide II); 2931 s, 2868 m, 1455 m (CH_2); 2979 s, 2890 m, 1477 m, 1392 s, 1367 s (CH_3); 1174 vs ($C(CH_3)_3$). HRMS (ESI) calc for $C_9H_{19}NO_4Na$ $[M+Na]^+$ 228.12063, found: 228.12061.

1-(2-(*tert*-Butoxycarbonylamino)ethoxy)-2-azidoethan (**31**): Azide **31** was prepared as described for compound **1**: the intermediate mesyl derivative was obtained from alcohol **30** (9.1 g; 44.4 mmol), TEA (6.8 g; 66.5 mmol) and MsCl (5.6 g; 48.8 mmol) in DCM (100 mL), and transformed

to **31** by heating with NaN_3 (5.7 g; 88.8 mmol) in DMSO (100 mL). Azide **31** (8.7 g, 85% yield over two steps) was obtained as a colorless oil. R_f = 0.47 (toluene/ethyl acetate 80/20). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 1.37 (9H, s, $C(CH_3)_3$), 3.08 (2H, q, $^3J_{HH}$ = 6.3 Hz, $–CH_2–N$), 3.38 (2H, m, $–CH_2–N_3$), 3.42 (2H, t, $^3J_{HH}$ = 6.3 Hz, $–CH_2–O$), 3.57 (2H, m, $–CH_2–O$), 6.74 (1H, t, J_{HH} = 6.3 Hz, >NH). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 28.39 (3C, $–C(\underline{C}H_3)_3$), 39.76 (1C, $–CH_2–N$), 50.18 (1C, $–CH_2–N_3$), 69.09 (1C, $–CH_2–O$), 69.19 (1C, $–CH_2–O$), 77.79 (1C, $–\underline{C}(CH_3)_3$), 155.78 (1C, NH–C=O). IR (CCl_4) ν_{max} cm^{-1} 2110 vvs (N_3); 3462 m, 3380 w (NH); 1126 vs (C-O-C); 1718 vs (C=O); 1503 vs (amide II); 2931 s, 2867 m, 1456 m (CH_2); 2980 s, 2893 m, 1478 m, 1392 s, 1367 s (CH_3); 1174 vs ($C(CH_3)_3$). HRMS (ESI) calc for $C_9H_{18}N_4O_3Na$ $[M+Na]^+$ 253.12711, found: 253.12714.

***N*-(*tert*-Butyloxycarbonyl)-*N*-(2-azidoethyl)-*N*-(2-methyl-2-nitropropyl)amine (34, Azide C5)**, Scheme 21



Scheme 21. Reagents, conditions and yields: (a) formaldehyde, 2-nitropropane, NaOH, water and isopropyl alcohol (50%); (b) TEA, Boc_2O, DCM, 1 h at 0 °C then overnight at rt (88%); (c) MsCl, TEA, DCM, 0.5 hour at 0 °C; (d) NaN_3, DMSO, 80 °C, overnight (yield over the steps c and d: 38 %).

N-(2-Methyl-2-nitropropyl)-*N*-(2-hydroxyethyl)amine toluenesulfonic salt (**32**): Nitro intermediate was prepared by Mannich reaction from 2-aminoethanol (7.6 g; 124 mmol), 2-nitropropane (11.1 g; 124 mmol) and 37% aq. formaldehyde (9.2 mL) as described in the literature.[8] Compound **32** (20.9 g, 50% yield, white solid, m. p. 134-137 °C) was isolated as a toluenesulfonic acid salt. R_f = 0.89 (ethyl acetate-methanol-acetone-water = 6-1-1-1). ^{1}H NMR (600 MHz;

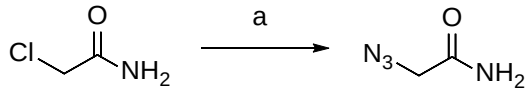
d_6DMSO): δ_H 1.62 (6H, s, -C(CH_3)$_2$, 2.29 (3H, br s, -CH_3), 3.08 (2H, m, -CH_2-N), 3.63 (2H, s, -CH_2-N), 3.70 (2H, m, -CH_2-O), 7.13 (2H, m, 2x CH_{arom}), 7.50 (2H, m, 2x CH_{arom}), 8.69 (2H, br, >NH_2^+). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 21.06 (1C, -CH_3), 24.26 (2C, -C(<u>C</u>H_3)$_2$), 50.75 (1C, -CH_2-N), 52.61 (1C, –CH_2–N), 56.14 (1C, –CH_2–O), 85.82 (1C, -<u>C</u>(CH_3)$_2$), 125.77 (2C, 2x CH_{arom}), 128.46 (2C, 2x CH_{arom}), 138.29 (1C, C_{arom}), 145.41 (1C, C_{arom}). IR (KBr) ν_{max} cm^{-1} 3339 br, s (OH); 1543 vs, 1349 s (NO_2); 1055 m (C-OH); 1579 m (>N^+); 2977 m, 2879 m, 1391 m, 1376 m (CH_3); 2948 m, 1476 m (CH_2); 1189 vs, 1125 vs (SO_3^-); 3015 w, 1600 m, 1496 m, 1010 s, 951 m, 856 m, 812 s, 689 s (ring). HRMS (ESI) calc for $C_6H_{15}O_3N_2$ $[M]^+$ 163.10772, found: 163.10746.

<u>*N*-(*tert*-Butyloxycarbonyl)-*N*-(2-hydroxyethyl)-*N*-(2-methyl-2-nitropropyl)amine (**33**)</u>: TEA (6.2 g; 61 mmol) was added to a suspension of **32** (20.4 g; 61 mmol) in DCM (250 mL). When the solution turned clear it was ice-cooled and a solution of Boc_2O (14.6 g; 67.1 mmol) in DCM (50 mL) was added dropwise. The resulting mixture was stirred at 0°C for 1 hour and overnight at room temperature. The volatile materials were evaporated and the yellow residue was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene. **33** (14.1 g, 88% yield) was obtained as a colorless oil. R_f = 0.51 (50% ethyl acetate/toluene). ^{1}H NMR (600 MHz; d_6DMSO, some signals are broadened or doubled due to the presence of *trans*- and *cis*-isomer on >N-CO- bond): δ_H 1.34 and 1.37 (6H, br s, -C(CH_3)$_2$), 1.50 (9H, s, -C(CH_3)$_3$), 3.08 and 3.16 (2H, 2x br,-CH_2-N), 3.43 (2H, m, -CH_2-O), 3.74 (2H, br s, -CH_2-N), 4.70 (1H, br, -OH). ^{13}C NMR (150.9 MHz; d_6DMSO, some signals are broadened or doubled due to the presence of *trans*- and *cis*-isomer on >N-CO- bond): δ_C 23.66 (3C, -C(<u>C</u>H_3)$_3$), 27.85 and 28.10 (2C, -C(<u>C</u>H_3)$_2$, 50.80 (1C, -CH_2-N), 55.87 and 56.19 (1C, -CH_2-N), 58.82 and 59.44 (1C, -CH_2-O), 79.52 and 79.94 (1C, -<u>C</u>(CH_3)$_2$), 88.14 and 88.50 (1C, -<u>C</u>(CH_3)$_3$), 154.63 and 155.63 (1C, –N–CO-O). IR (CCl_4) ν_{max} cm^{-1} 3639 w, 3477 w (OH); 1053 w (C-OH); 1701 vs, 1685 m (C=O); 1453 vs, 1343 m (NO_2); 2980 m, 2880 w , 1478 m, 1395 m, 1368 s (CH_3); 1158 s (C(CH_3)); 2949 w, 1474 m, 1458 m (CH_2). HRMS (ESI) calc for $C_{11}H_{22}O_5N_2Na$ $[M+Na]^+$ 285.14209, found: 285.14216.

<u>*N*-(*tert*-Butyloxycarbonyl)-*N*-(2-azidoethyl)-*N*-(2-methyl-2-nitropropyl)amine (**34**)</u>: Azide **34** was prepared as described for compound **1**: The intermediate mesyl derivative was obtained from alcohol **33** (14.7 g; 56 mmol), TEA (11.3 g; 112 mmol) and MsCl (7.7 g; 67.2 mmol) in DCM (200 mL), and transformed to **34** by heating with NaN_3 (6.8 g; 105 mmol) in DMSO (200 mL). Azide **34** (6.1 g, 38% yield over two steps) was obtained as a colorless oil. R_f = 0.58 (10% ethyl acetate/toluene). ^{1}H NMR (600 MHz; $CDCl_3$, some signals are doubled due to the presence of

trans- and *cis*-isomer on >N-CO- bond): δ_H 1.39 (9H, br s, -C(CH_3)$_3$), 1.51 (6H, s, -C(CH_3)$_2$), 3.19 and 3.23 (2H, 2x br, -CH_2-N_3), 3.28 and 3.38 (2H, 2x br, -CH_2-N), 3.77 and 3.79 (2H, 2x br, -CH_2-N). ^{13}C NMR (150.9 MHz; $CDCl_3$, some signals are doubled due to the presence of *trans*- and *cis*-isomer on >N-CO- bond): δ_C 23.80 and 24.00 (2C, -C(<u>C</u>H_3)$_2$, 28.04 (3C, -C(<u>C</u>H_3)$_3$), 47.04 and 47.74 (1C, -CH_2-N_3), 49.16 and 49.72 (1C, -CH_2-N), 55.20 and 56.30 (1C, -CH_2-N), 80.97 and 81.36 (1C, -<u>C</u>(CH_3)$_3$), 87.78 and 88.54 (1C, -<u>C</u>(CH_3)$_2$), 154.79 and 155.59 (1C, –N–CO-O). IR (CCl_4) ν_{max} cm^{-1} 2103 vs (N_3); 1705 vs, (C=O); 1543 vs, 1343 m (NO_2); 2981 m, 2873 w , 1478 m, 1394 m, 1368 s (CH_3); 1155 s (C(CH_3)); 2941 w, 1456 m (CH_2). HRMS (ESI) calc for $C_{11}H_{21}O_4N_5Na$ $[M+Na]^+$ 310.14858, found: 310.14862.

2-Azidoacetamide (35, Azide C6), Scheme 22

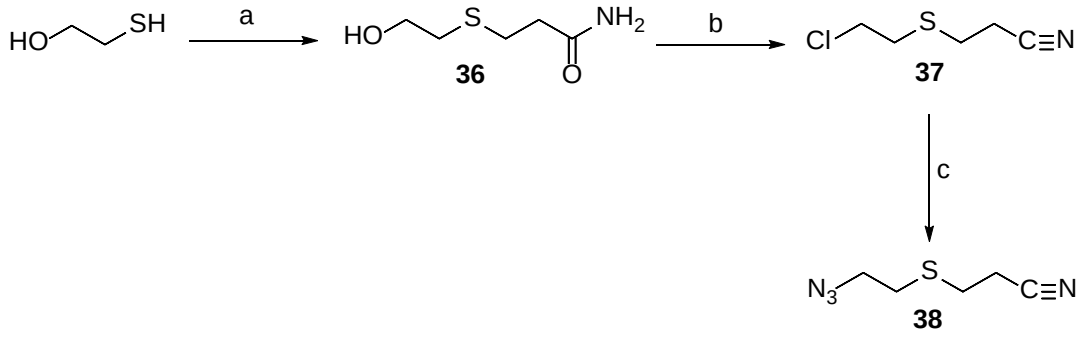


35

Scheme 22. Reagents, conditions and yield: (a) NaN_3, NaI, water 80 °C, overnight (yield 49%)

A solution of 2-chloro acetetamide (10 g; 110 mmol), NaI (16.5 g; 110 mmol) and NaN_3 (16.5 g; 220 mmol) in water (100 mL) was heated at 80 °C overnight. After cooling, the product was extracted with ethyl acetate (3 x 100 mL). The organic extracts were combined, washed with a small amount of a saturated solution of sodium metasulfite, dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting solid was recrystallized from ethyl acetate/petroleum ether to yield azide **35** (5.2 g, 49% yield) as a white powder (m.p. 52-53 °C). R_f = 0.60 (ethyl acetate). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 3.77 (2H, s, -CH_2-N), 7.24 and 7.51 2 H, 2x br s, -CO-NH_2). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 50.85 (1C, -CH_2-N_3), 169.92 (1C, -CO-NH_2). IR (KBr) ν_{max} cm^{-1} 2117 vs (N_3); 1669 vs (C=O); 1617 m (NH_2), 2923 w (CH_2). HRMS (CI) calc for $C_2H_5N_4O$ $[M+1]^+$ 101.0463, found: 101.0461.

3-((2-Azidoethyl)thio)propionitrile (38, Azide C7), Scheme 23



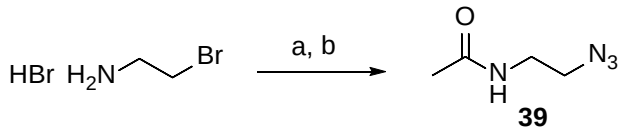
Scheme 23. Reagents, conditions and yields (a) acrylamide, borax, water, 2 h at rt (96%); (b) $SOCl_2$, $CHCl_3$ reflux overnight (85%); (c) NaN_3, NaI, water, 80 °C, overnight (89%).

3-((2-Hydroxyethyl)thio)propionamide (**36**): Amide **36** was prepared from acrylamide (7.1 g; 0.1 mol), 2-mercaptoethanol (7.8 g; 0.1 mol) and $Na_2B_4O_7.10H_2O$ (3.8 g; 0.01 mol) as described in the literature.[9] Primary amide **36** (14.3 g, 96% yield) was obtained as a white powder (m.p. 49-51 °C). R_f = 0.57 (ethyl acetate-acetone-methanol-water 6-1-1-0.5). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 2.31 (2H, t, $^3J_{HH}$ = 7.4 Hz, -CH_2-S), 2.56 (2H, t, $^3J_{HH}$ = 6.8 Hz, -CH_2-S), 2.67 (2H, t, $^3J_{HH}$ = 7.4 Hz, -CH_2-CO), 3.52 (2H, td, $^3J_{HH}$ = 6.8 and 5.6 Hz, -CH_2-O), 4.76 (1H, t, $^3J_{HH}$ = 5.6 Hz, -OH), 6.81 and 7.32 (2H, 2x br s, -CO-NH_2). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 27.44 (1C, -CH_2-), 34.07 (1C, -CH_2-S), 35.93 (1C, -CH_2-S), 61.06 (1C, -CH_2-O), 172.79 (1C, -CO-NH_2). IR (KBr) ν_{max} cm^{-1} 3395 vs, 3199 vs (NH); 1652 vs (C=O); 1619 vs (NH_2); 1050 s (C-OH); 2954 m, 1429 s (CH_2). HRMS (ESI) calc for $C_5H_{12}O_2NS$ $[M+1]^+$ 150.05833, found: 150.05825.

3-((2-chloroethyl)thio)propionitrile (**37**): Thionyl chloride (18.9 g ; 159 mmol) was added to a suspension of primary amide **36** (7.9 g; 53 mmol) in chloroform (100 mL). The resulting mixture was refluxed overnight. The volatile materials were evaporated and the brown residue was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene. **37** (6.7 g, 85% yield) was obtained as a pale yellow liquid. R_f =0.64 (20% ethyl acetate/toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 2.68 (2H, m, -CH_2-), 2.87 (2H, m, -CH_2-S), 2.96 (2H, m, -CH_2-S), 3.67 (2H, m, -CH_2-Cl). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 19.01 (1C, -CH_2-), 27.92 (1C, -CH_2-S), 34.36 (1C, –CH_2–S), 42.98 (1C, –CH_2–Cl), 117.95 (1C, -C≡N). IR (CCl_4) ν_{max} cm^{-1} 2253 m (C≡N); 2965 m, 2932 m, 1145 s, 1431 s, 1422 s (CH_2); 705 vs (C-Cl). HRMS (CI) calc for C_5H_9NSCl $[M+1]^+$ 150.0144, found: 150.0145.

3-((2-Azidoethyl)thio)propionitrile (**38**): A mixture of **37** (6.5 g; 43.5 mmol), NaN_3 (8.5 g; 130.2 mmol) and NaI (6.5 g; 43.4 mmol) in DMSO (125 mL) was heated overnight at 80 °C. After cooling, water (100 mL) was added and the product was extracted with diethyl ether (4 x 100 mL). The organic extracts were combined, washed with water (2 x 50 mL) and brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was carefully evaporated and the residue was purified by flash chromatography on silica gel using a linear gradient of ether in petroleum ether to yield azide **38** (6.1 g, 89% yield) as a colorless liquid. R_f = 0.51 (10% ethyl acetate/toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 2.68 (2H, t, $^3J_{HH}$ = 7.2 Hz, -CH_2-), 2.81 (2H, t, $^3J_{HH}$ = 6.6 Hz, -CH_2-S), 2.87 (2H, t, $^3J_{HH}$ = 7.2 Hz, -CH_2-S), 3.53 (2H, t, $^3J_{HH}$ = 6.6 Hz, -CH_2-N). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 18.97 (1C, -CH_2-), 27.94 (1C, -CH_2-S), 31.59 (1C, –CH_2–S), 51.21 (1C, –CH_2–N), 118.06 (1C, -C≡N). IR (CCl_4) ν_{max} cm^{-1} 2103 vs (N_3); 2253 w (C≡N); 2929 m, 2859 w, 1445 m (CH_2). HRMS (CI) calc for $C_5H_9N_4S$ $[M+1]^+$ 157.0548, found: 157.0547.

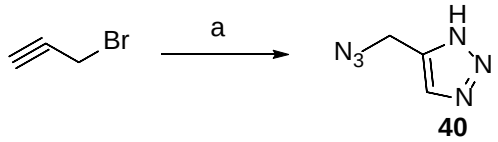
***N*-(2-Azidoethyl)acetamide (39, Azide C8)**, Scheme 24



Scheme 24. Reagents, conditions and yield: (a) NaN_3, water, 80 °C, overnight; (b) TEA, acetanhydride, DCM, 1 h at 0 °C then overnight at rt (yield over two steps 65%).

Azide **39** was prepared from 2-bromoethylamine hydrobromide (10 g; 48.8 mmol), NaN_3 (6.3 g; 97.6 mmol), TEA (4.9 g; 48.8 mmol) and acetic anhydride (5 g; 48.8 mmol) following the procedure described for compound **4**. Azide **39** (4 g, 65% yield) was obtained as a colorless liquid. R_f = 0.43 (ethyl acetate). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 2.02 (3H, s, -CH_3), 3.43 (4H, m, N-CH_2-CH_2-N_3), 6.51 (1H, br, -CO-NH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 22.88 (1C, -CH_3), 38.85 (1C, -CH_2-N), 50.59 (1C, –CH_2–N_3), 170.81 (1C, -CO-NH). IR (film) ν_{max} cm^{-1} 3290 s (NH); 2105 vs, 1289 s (N_3); 1657 vs (C=O); 1552 s (amide II); 2935 m, 1447 m (CH2); 1369 m (CH_3). HRMS (CI) calc for $C_4H_9N_4O$ $[M+1]^+$ 129.0776, found: 129.0772.

5-(Azidomethyl)-1*H*-1,2,3-triazole (40, Azide C9), Scheme 25

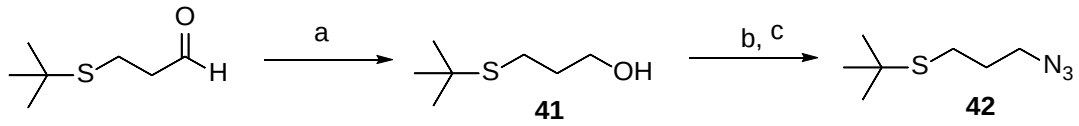


40

Scheme 25. Reagents, conditions and yield: (a) NH_4Cl, NaN_3 aqueous dioxane, 16 hours at 75°C (yield: 57%).

Azide **40** was prepared following protocol reported by Loren et al[10] with small modifications. Azide **40** (6 g, 57% yield) was obtained from propargyl bromide (80% solution in toluene, 10 g; 84 mmol), NH_4Cl (9 g; 168 mmol) and NaN_3 (21.8 g; 336 mmol) in dioxane/water (2:1, 240 mL) and isolated as a pale yellow liquid. R_f = 0.52 (50% ethyl acetate/toluene). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 3.46 (1H, br, >NH), 4.53 (2H, s, -CH_2-N_3), 7.92 (1H, s, -CH=). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 44.61 (1C, -CH_2-N_3), 129.41 (1C, -CH=), 141.16 (1C, >C=). IR (CCl_4) ν_{max} cm^{-1} 2101 vs (N_3); 3455 m (NH); 1447 w, 1124 w, 1075 w, 975 w, 702 w (triazole). 2926 w, 2857 w, 1465 w (CH_2). HRMS (ESI) calc for $C_3H_4N_6Na[M+Na]^+$ 147.03897, found: 147.03896.

(3-Azidopropyl)(*tert*-butyl)sulfane (42, Azide C10), Scheme 26



41 **42**

Scheme 26. Reagents, conditions and yields: (a) $NaBH_4$, methanol 1 hour at 0 °C then overnight at room temperature (95%); (b) MsCl, TEA, DCM, 0.5 hour at 0 °C; (c) NaN_3, DMSO, 80 °C, overnight (yield over the steps b and c: 77 %).

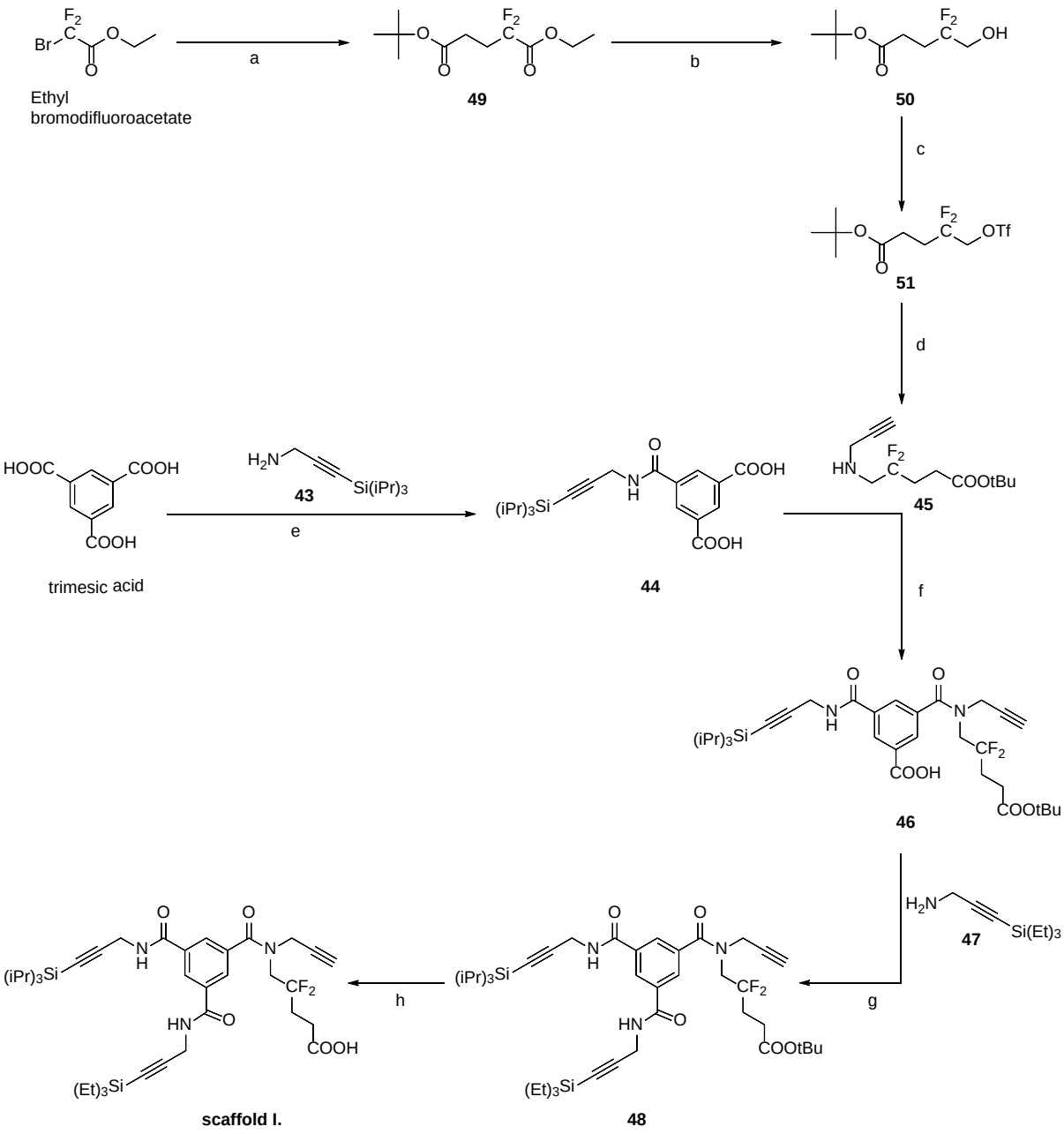
3-(*tert*-Butylthio)propan-1-ol (**41**): Compound **41** was prepared according to Pícha et al:[11] $NaBH_4$ (7.2 g; 189.4 mmol) was added to an ice-cooled solution of 3-(*tetr*-butylsulfanyl)propanal (13.9 g; 94.7 mmol) in methanol (150 mL). The cooling bath was removed and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was acidified with 2 M HCl at 0 °C until the solution became clear. The product was extracted with ethyl acetate (3 x 100 mL). The organic solutions were combined, washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was subjected to flash chromatography on silica gel using a linear gradient of ethyl acetate in petroleum ether to give **41** (13.3 g, 95% yield)

as a colorless liquid. R_f = 0.59 (50% ethyl acetate/toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.33 (9H, s, -C(CH_3)$_3$), 1.84 (2H, m, -CH_2-), 2.64 (2H, t, $^3J_{HH}$ = 7.3 Hz, -CH_2-S), 3.74 (2H, t, $^3J_{HH}$ = 6.3 Hz, -CH_2-O). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 24.89 (1C, -CH_2-S), 30.81 (1C, -C(CH_3)$_3$), 32.22 (1C, -CH_2-), 42.02 (1C, -C(CH_3)$_3$), 61.84 (1C, -CH_2-O). IR (film) ν_{max} cm^{-1} 3362 s (OH); 2960 s, 1390 m, 1364 s (CH_3); 2865 s (CH_2); 1164 s (C(CH_3)); 1054 s (C-O). HRMS (CI) calc for $C_7H_{16}OS[M+1]^+$ 148.0922, found: 148.0921.

(3-Azidopropyl)(*tert*-butyl)sulfane (**42**): Azide **42** was prepared as described for compound **1**: the intermediate mesyl derivative was obtained from alcohol **41** (10 g; 67.4 mmol), TEA (8.2 g; 80.9 mmol) and MsCl (8.5 g; 74.1 mmol) in DCM (150 mL), and was transformed to **42** by heating with NaN_3 (8.7 g; 134 mmol) in DMSO (150 mL). Azide **42** (9 g, 77% yield over two steps) was obtained as a colorless liquid. R_f = 0.85 (toluene). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.31 (9H, s, -C(CH_3)$_3$), 1.84 (2H, m, -CH_2-), 2.59 (2H, t, $^3J_{HH}$ = 7.4 Hz, -CH_2-S), 3.40 (2H, t, $^3J_{HH}$ = 6.7 Hz, -CH_2-N_3). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 25.15 (1C, -CH_2-S), 29.07 (1C, -CH_2-), 30.82 (1C, -C(CH_3)$_3$), 42.06 (1C, -C(CH_3)$_3$), 50.31 (1C, -CH_2-N_3). IR (KBr) ν_{max} cm^{-1} 2098 vs (N_3); 2961 s, 1391 w, 1364 m (CH3); 2864 m, 1460 m (CH_2); 1164 m (C(CH_3)). HRMS (CI) calc for $C_7H_{16}N_3S$ $[M+1]^+$ 174.1065, found: 174.1061.

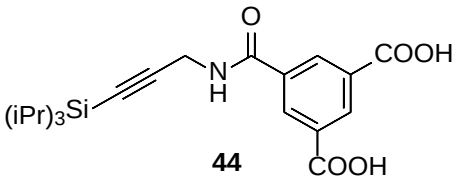
Synthesis of scaffold I

Compounds **43**, **47**, **49**, **50** and scaffold **I** were prepared following the procedures described in our previous work.[3] Separation of monoamide **44** from reaction mixture was slightly modified to remove the unreacted trimesic acid more easily. Diamide **46** (as well as triamide **48**) were prepared in higher yield applying different reagent proportions and modified work-up procedure. Isolation of highly unstable triflate **51** was omitted and amine **45** was prepared using crude triflate, which enhanced the yield substantially (Scheme **27**).



Scheme 27. Reagents, conditions and yields: (a) *tert*-butyl acrylate, Cu, TMEDA, AcOH, THF, 50 °C, 30 min, quantitative; (b) $NaBH_4$, EtOH, 0-15 °C, 1.5 h, 94 %; (c) Tf_2O, Py, CH_2Cl_2, -78 °C, 15 min; (d) propargylamine, K_2CO_3, ACN, rt, 2 d, 78 % over two steps from **50**; (e) TEA, PyBroP, DMF, rt, 12 h, 48 %; (f) TEA, PyBroP, DMF, rt, 2 d, 72 %; (g) TEA, PyBroP, DMF, rt, 72 h, 78 %; (h) TFA-CH_2Cl_2, rt, 1.5 h, 67 %.

5-((3-(Triisopropylsilyl)prop-2-yn-1-yl)carbamoyl)isophthalic acid (44)

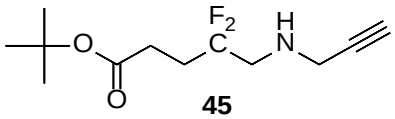


44

Triethylamine (29.52 g, 40.4 mL, 291.7 mmol, 7 equiv) was added to a solution of amine **43** (8.81 g, 10.13 mL, 41.67 mmol), trimesic acid (52.54 g, 250 mmol, 6 equiv), and PyBroP (27.20 g, 58.34 mmol, 1.4 equiv) in DMF (300 mL), and the solution was stirred for 12 h at rt. TLC was performed in (ethyl acetate-acetone-methanol-water = 4-1-1-1) on silica coated aluminium foil pretreated with NH_3, and the spots were detected by UV and/or ninhydrin spraying, R_f = 0.20. The solvent was then evaporated at 70 °C *in vacuo* and the solid residue was suspended in the AcOH-acetone mixture (50+200 mL). The resulting slurry was filtered through an S3-frit, the solid was washed with acetone (200 mL), suspended again in acetone (200 mL) and filtered once more. The solid (mostly unreacted trimesic acid) was then discarded, and the filtrate was evaporated *in vacuo* to give a pale yellow residue. The residue was partitioned between Et_2O (400 mL) and DMF-H_2O (1:1 v/v, 600 mL in total), and the aqueous layer was further extracted with Et_2O (2x150 mL). The combined organic layers were then washed successively with 50% aqueous DMF (3x200 mL to remove the rest of the unreacted trimesic acid) and brine (2x250 mL), dried over anhydrous sodium sulphate, evaporated *in vacuo*, co-evaporated with 100 mL of MeOH, and evaporated to dryness. The crude product was obtained as a pale yellow solid (12.1 g) containing desired monoamide (66.1 % by NMR), diamide (7.8 % by NMR) and tri(pyrrolidin-1-yl)phosphine oxide (24.5 % by NMR) as by-products. The solid was then crushed, transferred to a flask containing toluene (240 mL, i.e. 20 mL/1 g), and heated to reflux for 1 h under intensive stirring. After cooling, the slurry was filtered through an S4-frit, and the solid was washed with a small amount of hexane and dried *in vacuo* (white solid, 9.08 g). Analysis by NMR and HPLC revealed complete disappearance of phosphinoxide and a significantly lowered (<3.0 %) diamide content. The solid was then dissolved in isopropyl alcohol (150 mL), the dark yellow turbid solution was filtered through Celite and the clear filtrate was evaporated. The residue was dissolved again in iPrOH (32.0 mL, i.e. 3.5 mL/1 g) at 60 °C, the source of heat was removed, and hexane (254 mL, i.e. 28 mL/1 g) was added under stirring. The product was allowed to precipitate overnight at 4 °C, the solid was then filtered off,

washed with a small amount of hexane, and dried *in vacuo* to give pure monoamide **44** as a white powder (8.05 g, 47.9 %, diamide content below the HPLC detection limit).

***tert*-Butyl 4,4-difluoro-5-(prop-2-yn-1-ylamino)pentanoate (45)**

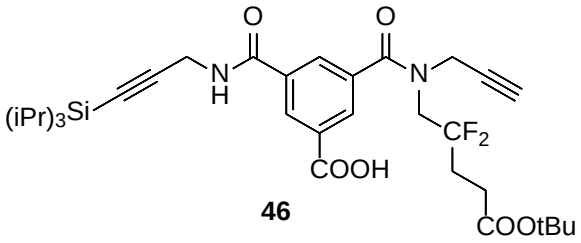


45

A solution of alcohol **50** (20.99 g, 99.8 mmol) and pyridine (24.17 mL, 299.4 mmol, 3 equiv) in dichloromethane (290 mL) was placed into a flask equipped with a magnetic stirrer and vented addition funnel. The flask was cooled to -78 °C by a dry ice bath, and a solution of triflic anhydride (25.19 mL, 149.7 mmol, 1.5 equiv) in dichloromethane (60 mL) was added dropwise from the addition funnel under vigorous stirring (*ca.* 15 min). After the addition had finished, the flask was transferred to an ice cooling bath (0 °C), and the reaction was quenched by a dropwise addition of water (25 mL) upon cooling. The reaction mixture was further diluted with water (500 mL) in a separatory funnel, the organic layer was separated, and the aqueous phase was extracted with dichloromethane (2x100 mL). The combined organic phase was washed with brine (500 mL), dried over anhydrous sodium sulphate, filtered, and carefully evaporated *in vacuo* at 40 °C. The crude triflate **51** was directly used in the next step without purification.

Dry powdered potassium carbonate (48.25 g, 349 mmol, 3.5 equiv) was added to a solution of crude triflate **51** (considered 99.8 mmol) and propargylamine (19.55 mL, 299.4 mmol, 3 equiv) in ACN (600 mL), and the solution was stirred for 3 days at rt. The reaction mixture was concentrated to *ca.* 1/3 volume *in vacuo*, the residue was diluted with water (500 mL), and the crude product was extracted with diethyl ether (500 mL, 2x100 mL). The combined organic phase was washed with brine (300 mL), dried over anhydrous sodium sulphate, filtered, and evaporated. The crude product was purified by flash chromatography on silica (elution with a linear gradient of EtOAc in toluene) to give secondary amine **45** as a light yellow oil (19.33 g, 78.3 % over two steps from alcohol **50**; R_f 0.46 in 20% ethyl acetate/toluen).

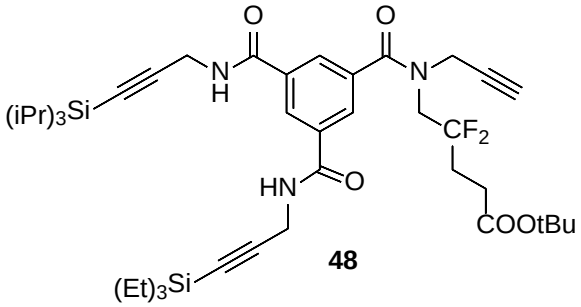
3-((5-(*tert*-Butoxy)-2,2-difluoro-5-oxopentyl)(prop-2-yn-1-yl)carbamoyl)-5-((3-(triisopropylsilyl)prop-2-yn-1-yl)carbamoyl)benzoic acid (46)



46

Triethylamine (11.73 mL, 84.6 mmol, 7 equiv) was added to a solution of monoamide **44** (4.88 g, 12.09 mmol), secondary amine **45** (3.89 g, 15.72 mmol, 1.3 equiv), and PyBroP (9.02 g, 19.35 mmol, 1.6 equiv) in DMF (70 mL), and the solution was stirred for 2 days at rt. The solvent was then evaporated *in vacuo*, and the residue was partitioned between water (200 mL) and diethyl ether (3x100 mL). The combined organic phase was washed with brine (200 mL), dried over anhydrous sodium sulphate, filtered, and evaporated. The crude product was purified by flash chromatography on triethylamine-pretreated silica column (elution with a linear gradient of ethyl acetate-acetone-methanol-water = 4-1-1-1 in EtOAc) to give diamide **46** as a pale yellow solid (triethylamine salt, 6.411 g, 72%; R_f 0.45 in (ethyl acetate-acetone-methanol-water = 6-1-1-0.5) on NH_3-pretreated TLC plate).

***tert*-Butyl 4,4-difluoro-5-(*N*-(prop-2-yn-1-yl)-3-((3-(triethylsilyl)prop-2-yn-1-yl)carbamoyl)-5-((3-(triisopropylsilyl)prop-2-yn-1-yl)carbamoyl)benzamido)pentanoate (48)**



48

Triethylamine (5.53 mL, 39.9 mmol, 2.5 equiv) was added to a solution of diamide salt **46** (11.72 g, 15.97 mmol), amine **47** (6.27 g, 7.29 mL, 31.9 mmol, 2 equiv), and PyBroP (14.89 g, 31.9 mmol, 2 equiv) in DMF (70 mL), and the solution was stirred for 72 h at rt. The reaction mixture was then diluted with water (600 mL), and the product was extracted with diethyl ether (250 mL, 2x100

mL). The combined organic phase was washed with brine (250 mL), dried over anhydrous sodium sulphate, filtered, and evaporated. The crude product was purified by flash chromatography on silica (elution with a linear gradient of EtOAc in toluene) to give triamide **48** as a white foam (9.83 g, 78.5 %; R_f 0.92 in ethyl acetate-acetone-methanol-water = 6-1-1-0.5).

Methods to remove copper

We investigated other methods to remove copper from the **C1**-**C10** sub-libraries; using C4 cartridges, Amberlite resin or preparative RP-HPLC (see below). However, none of these alternative approaches provided better result than treatment with hydrogen sulfide.

C-4 cartridges: A sample of **C4** sub-library (12 mg) was dissolved in 25% AcOH/H_2O. The solution was loaded on an activated Chromabond® C-4 cartridge (3 mL/500 mg). HPLC analysis of the filtrate showed that the most polar part of the library was not retained in the cartridge. This filtrate was then loaded on an activated Chromabond® C-8 cartridge (6 mL/1000 mg) with similar results. Furthermore, it appeared difficult to elute all the compounds retained in the C-8 cartridge.

Amberlite resin: A sample of the **C10** sub-library (18 mg) was dissolved in MeOH/H_2O and eluted through a column containing a pre-activated, thiol-based cation exchange resin (Ambersep® GT74). The elution was followed by HPLC analyses. It was found that most of the sub-library could not be washed out of the resin and was lost.

Preparative HPLC: A sample of the **C9** sub-library (6 mg) was dissolved in 25% AcOH/H_2O and loaded on a preparative C-4 column (Vydac 214TP101522, 250×22 mm, 10-15 μm). The column was washed with 0.1%TFA/H_2O for 10 minutes and eluted with 0.1% TFA/ACN (at aflow rate 9 mL/min for 20 minutes). The eluted fraction that absorbed at both 218 and 254 nm was collected, concentrated, lyophilized and analyzed by HPLC: the whole sub-library **C9** was qualitatively recovered. This method seems to be convenient for quantitative removal of copper from **C9**, however, it is time-consuming because only relatively few amounts (about 6 mg) of material can be purified in one HPLC run.

RP-HPLC analyses of the sub-library C4B7 and compounds C4B7A1-C4B7A10

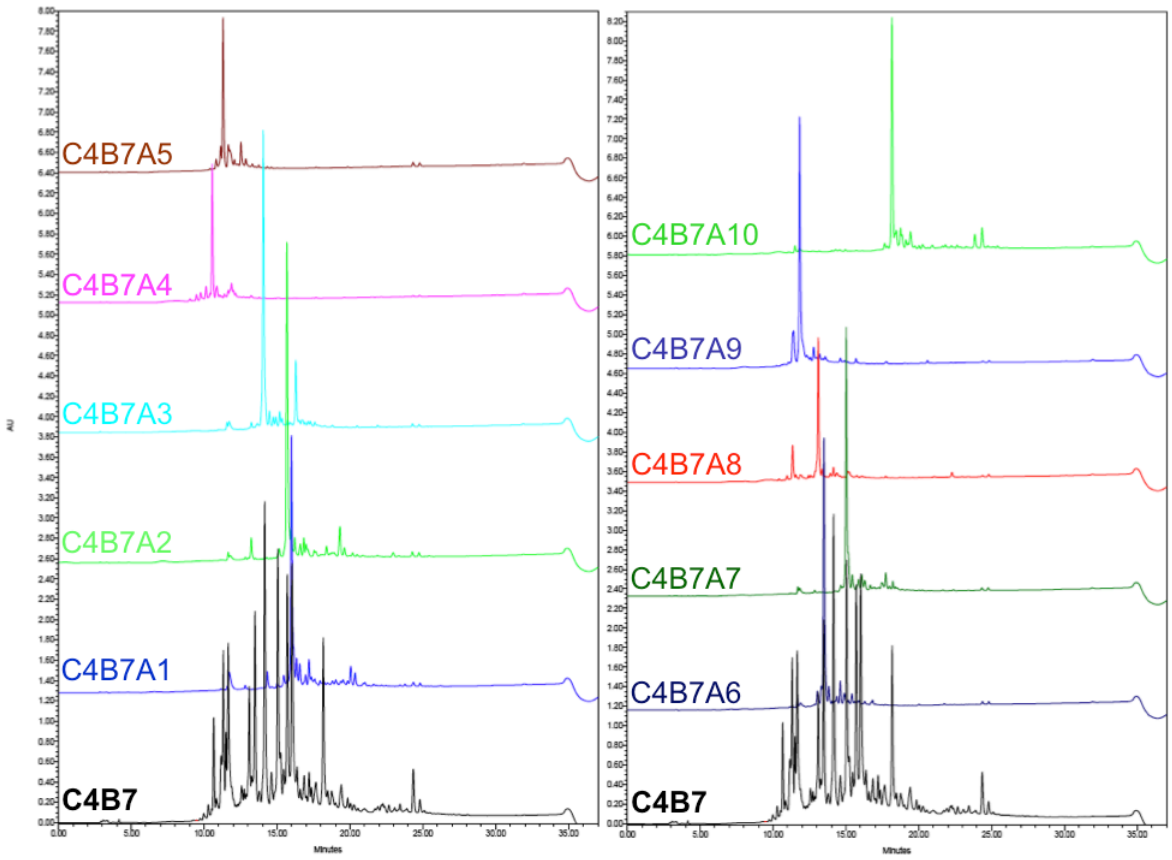


Figure S1. Superimposed RP-HPLC profiles of the sub-library **C4B7** (down, black) and of the compounds **C4B7A1-C4B7A10**. The 10 main peaks observed in the sub-library **C4B7** correspond to the compounds **C4B7A1-C4B7A10**. *Conditions*: analytical RP-HPLC chromatography was carried out on a Waters HPLC system (Waters 1525 Binary HPLC Pump and Waters 2787 Dual λ Absorbance Detector) using EC Nucleosil 120-5 C8 column (250 x 4.6 mm, 5 µm) at a flow rate of 1 mL/min. Solvent A: 0.1% TFA (v/v) in H_2O. Solvent B: 0.1% TFA (v/v) in ACN. The following gradient was used: t = 0 min /5 % B, t = 30 min/80% B, t = 31 min/5% B. The compounds were detected at 218 nm.

LC-MS analysis of the sub-library C4B7

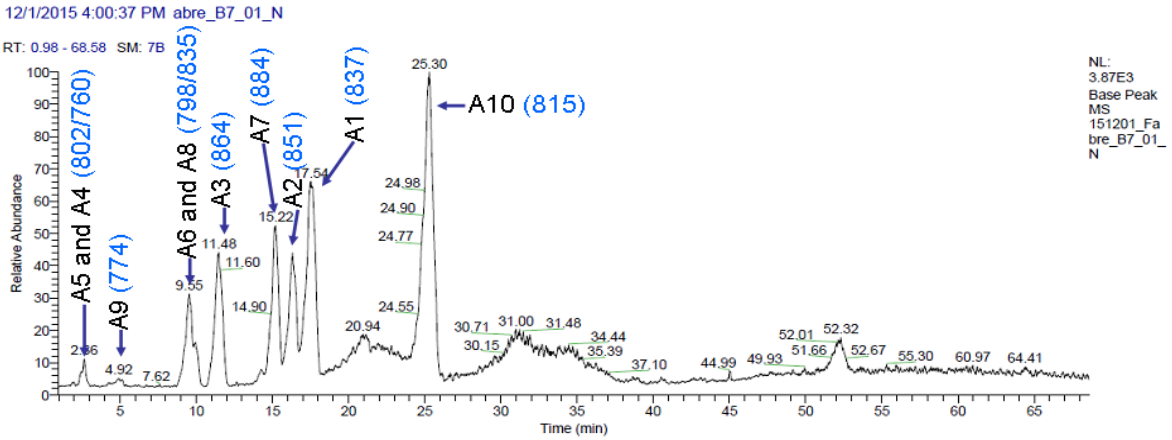


Figure S2. LC-MS analysis (base peak chromatogram) of the sub-library **C4B7**. The main ions (*m/z* ratio, in blue) of the expected compounds **C4B7A1-C4B7A10** (named here **A1-A10** for clarity) are given. *Condition for LC*: solvent A = 0.1% formic acid (v/v) in H_2O, solvent B = 0.1% formic acid (v/v) in ACN. The following gradient was used: t = 0min/5% B, 5min/20% B, 45min/40% B, 50min/80% B, 55min/5% B, 65min/5% B. Flow = 300 µl/min. *Conditions for MS*: Positive ionization mode, detected range = 300-2000 m/z, ion-trap mass spectrometer LCQ Fleet detector (Thermo Scientific).

Table S1. RP-HPLC, MS/LC-MS/HRMS and ICP analyses of the selected sub-libraries/compounds synthesized in this study.

Sub-library / compound	Yields[a] (%)	HPLC Purity[b] (%)	Mass theo. (MH^+)	Mass found (MH^+)	Cu content[c] (%, w/w)
C9	-	-	-	-	0.06
C10	-	-	-	-	0.01
C4B3	-	-	-	-	0.17
C4B7	-	-	-	*See LC-MS*[d]	0.34
C4B7A1	-	53	837,3715	837	-
C4B7A2	-	61	851,3507	851	-
C4B7A3	-	65	864,3824	864	-
C4B7A4	-	46	760,3562	760	-
C4B7A5	-	54	802,4031	802	-
C4B7A6	-	68	798,3718	798	-
C4B7A7	-	70	884,4450	884	-
C4B7A8	-	48	835,3592	835	3.18
C4B7A9	-	71	775,3194	775	7.02
C4B7A10	-	58	815,4235	815	-
C4B2A10	59	71	968.4483	968.4485	0.15
C4B3A6	28	54	850.4395	850.4397	-
C4A10A10	51	61	869.5068	869.5070	-
C4A6A10	33	66	852.4551	852.4555	-
C4B3A10	30	51	887.4599	887.4602	-
C4A6A6	45	74	835.4034	835.4037	-
C4B2A6	23	64	951.3966	951.3968	-
C4B2B2	64	69	870.4082	870.4084	-
C4B3B2	22	51	1067.3898	1067.3902	0.09
C4B3B3	52	65	986.4014	986.4018	-

[a] Yields over the whole process (based on the quantity of scaffold **1** introduced) and calculated after purification of the final compounds by preparative RP-HPLC. [b] Determined by integration of the whole HPLC chromatogram of the crude products at 218 nm. [c] In each library, the two samples that kept darkest coloration after the treatment with hydrogen sulfide were analyzed by ICP to determine their copper content. For the compounds from the focused library, all the crude mixtures appeared visually free of copper and we randomly selected the crude compounds **C4B2A10** and **C4B3B2**. [d] Details of the analysis are shown in Figure S2 (page S31).

Biological data:

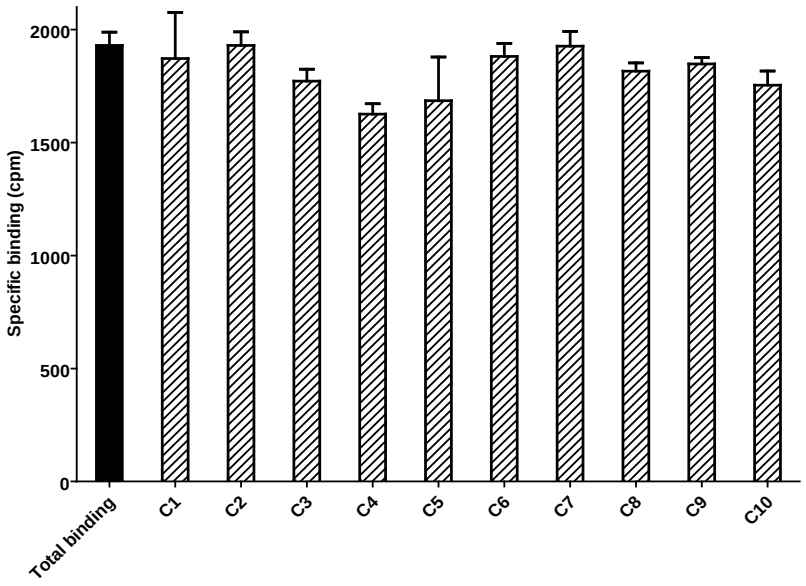


Figure S3. Inhibition of binding of ^{125}I-insulin to IR-A by sub-libraries **C1-C10** at 0.1 mM concentration. Total binding is maximum binding (in cpm) of ^{125}I-insulin to IR-A without any competitor. Non-specific binding was subtracted from all data. The data are shown as mean ± S.E. (n = 3-4).

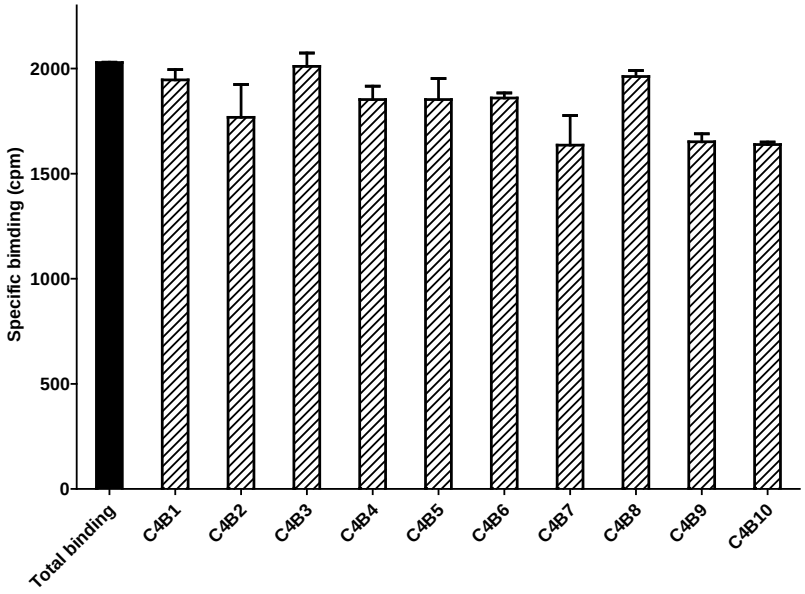


Figure S4. Inhibition of binding of ^{125}I-insulin to IR-A by sub-libraries **C4B1-C4B10** at 0.1 mM concentration. Total binding is maximum binding (in cpm) of ^{125}I-insulin to IR-A without any competitor. Non-specific binding was subtracted from all data. The data are shown as mean ± S.E. (n = 3-4).

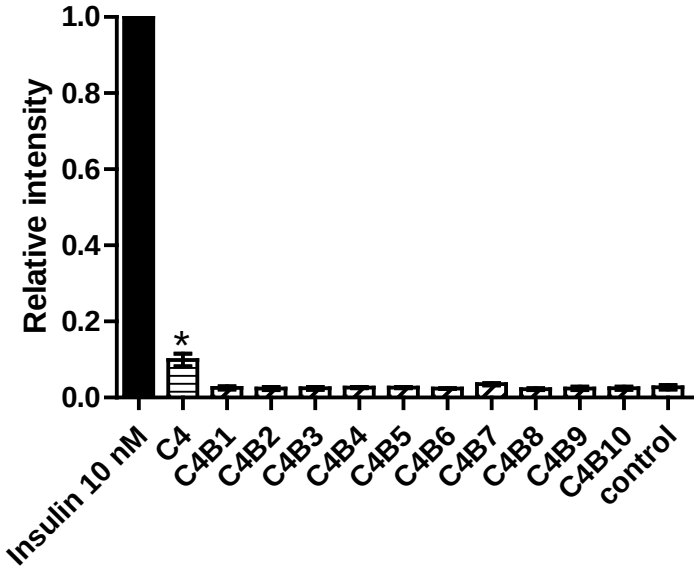


Figure S5. Stimulation of phosphorylation of IR-A receptor by sub-libraries **C4B1-C4B10** (deconvoluted from the library **C4**) at 0.1 mM concentration. The experimental values were related to activity of human insulin at 10 nM concentration. Asterisks indicate that autophosphorylation of the receptor induced by the library differs significantly from background (* $p < 0.05$).

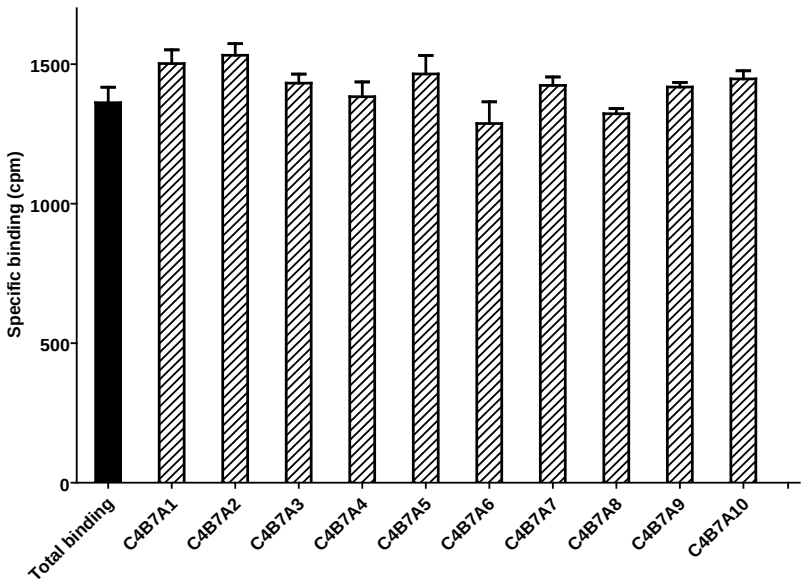


Figure S6. Inhibition of binding of ^{125}I-insulin to IR-A by compounds **C4B7A1-C4B7A10** at 0.1 mM concentration. Total binding is maximum binding (in cpm) of ^{125}I-insulin to IR-A without any competitor. Non-specific binding was subtracted from all data. The data are shown as mean ± S.E. (n = 3-4).

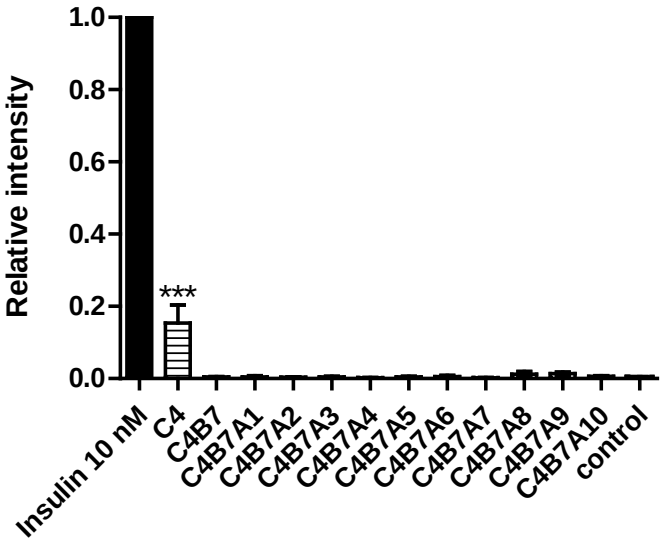


Figure S7. Stimulation of phosphorylation of IR-A receptor by compounds **C4B7A1-C4B7A10** deconvoluted from library **C4B7** and the original **C4** library**.** The experimental values were related to activity of human insulin at 10 nM concentration. The concentration of each compound was 0.1 mM. Asterics indicate that autophosphorylation of the receptor induced by the library differs significantly from the control (background) (***, $p < 0.001$).

HPLC chromatograms of the compounds from the focused library

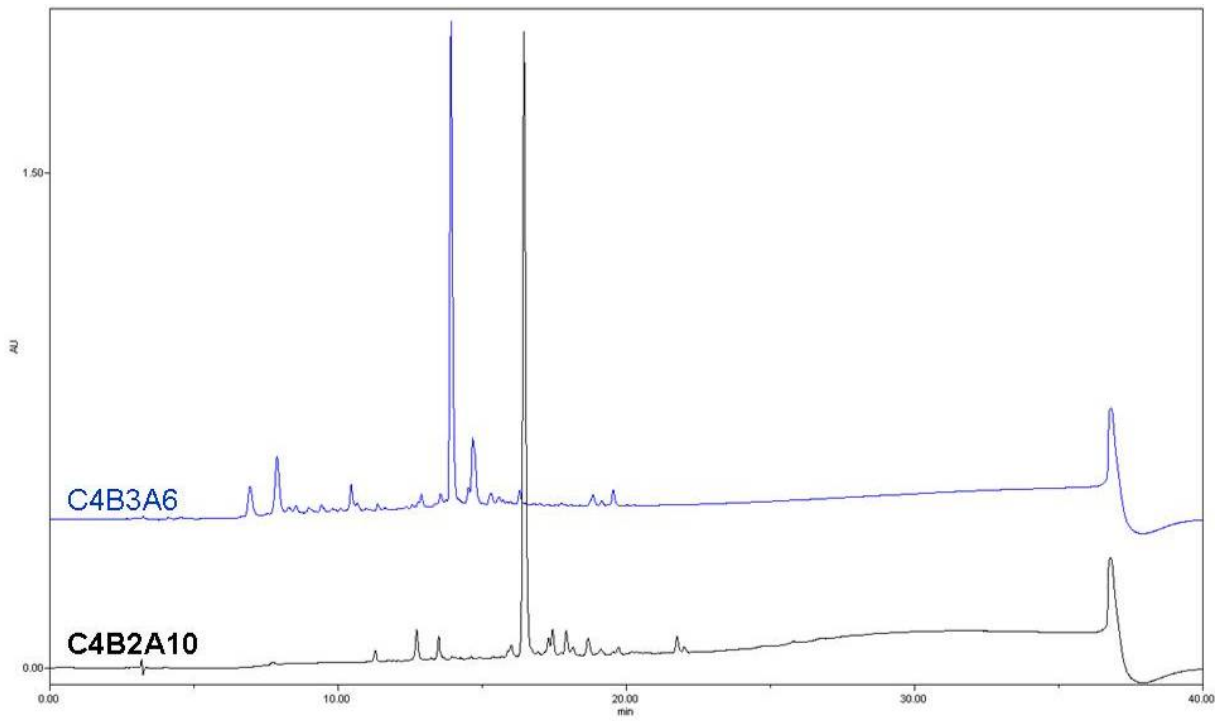


Figure S8. RP-HPLC chromatograms of the crude compounds **C4B2A10** and **C4B3A6**. *Conditions*: analytical RP-HPLC chromatography were carried out on a Waters HPLC system (Waters 1525 Binary HPLC Pump and Waters 2787 Dual λ Absorbance Detector) using EC Nucleosil 120-5 C8 column (250 x 4.6 mm, 5 μm) at a flow rate of 1 mL/min. Solvent A: 0.1% TFA (v/v) in H_2O. Solvent B: 0.1% TFA (v/v) in ACN. The following gradient was used: t = 0 min /20 % B, t = 30 min/100% B, t = 31 min/20% B. The compounds were detected at 218 nm.

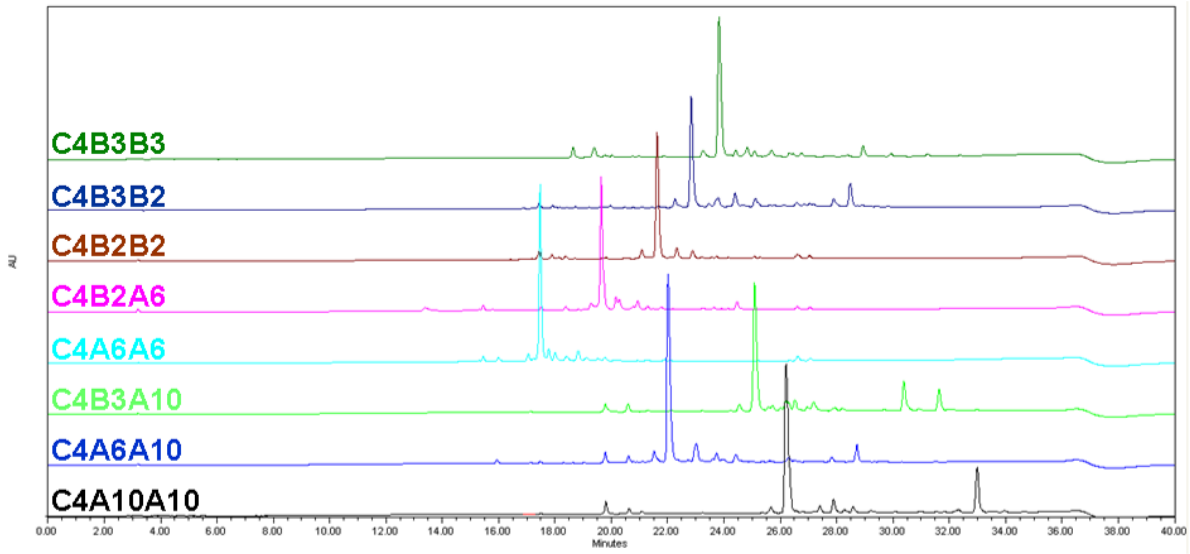


Figure S9. RP-HPLC chromatograms of crude compounds from **C4A10A10**, **C4A6A10**, **C4B3A10**, **C4A6A6**, **C4B2A6**, **C4B2B2**, **C4B3B2** and **C4B3B3**. *Conditions*: analytical RP-HPLC chromatography were carried out on a Waters HPLC system (Waters 1525 Binary HPLC Pump and Waters 2787 Dual λ Absorbance Detector) using EC Nucleosil 120-5 C8 column (250 x 4.6 mm, 5 µm) at a flow rate of 1 mL/min. Solvent A: 0.1% TFA (v/v) in H_2O. Solvent B: 0.1% TFA (v/v) in ACN. The following gradient was used: t = 0 min /5 % B, t = 30 min/100% B, t = 31 min/5% B. The compounds were detected at 218 nm.

Crude yields of the sub-libraries C1-C10, the sub-libraries C4B1-C4B10 and the compounds C4B7A1-C4B7A10

Table S2. Crude yields (in mg) for the sub-libraries and compounds after the cleavage from the resin.

Sub-library	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**
(mg)	109	101	99	87	94	81	102	95	96	92
Sub-library	**C4B1**	**C4B2**	**C4B3**	**C4B4**	**C4B5**	**C4B6**	**C4B7**	**C4B8**	**C4B9**	**C4B10**
(mg)	80	71	62	100	107	72	55	57	92	82
Compound	**C4B7A1**	**C4B7A2**	**C4B7A3**	**C4B7A4**	**C4B7A5**	**C4B7A6**	**C4B7A7**	**C4B7A8**	**C4B7A9**	**C4B7A10**
(mg)	61	84	77	55	58	65	79	51	66	82

Table S3. Final crude yields (in mg) for the sub-libraries and compounds after the diethyl ether extraction and treatment with gaseous hydrogen sulfide.

Sub-library	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**
(mg)	50	53	48	44	53	46	55	53	45	31[a]
Sub-library	**C4B1**	**C4B2**	**C4B3**	**C4B4**	**C4B5**	**C4B6**	**C4B7**	**C4B8**	**C4B9**	**C4B10**
(mg)	60	53	46	63	58	51	41	43	52	51
Compound	**C4B7A1**	**C4B7A2**	**C4B7A3**	**C4B7A4**	**C4B7A5**	**C4B7A6**	**C4B7A7**	**C4B7A8**	**C4B7A9**	**C4B7A10**
(mg)	37	45	50	43	31	34	45	31	40	42

[a] Part of the **C10** sub-library (18 mg) was lost during the treatment with Amberlite resin when trying to remove copper (see discussion on page S29).

Extraction of sub-library C2 with diethyl ether

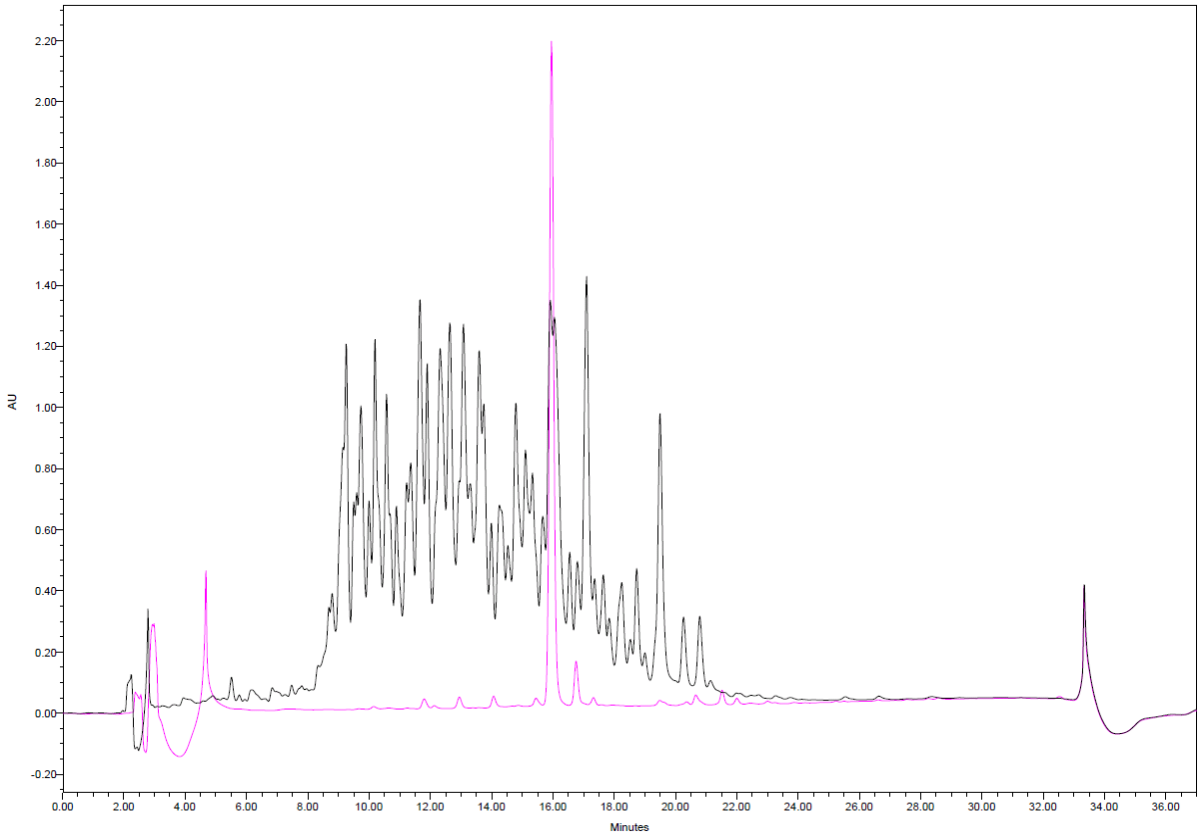


Figure S10. Superposition of the RP-HPLC chromatograms of the **C-2** sub-library before Et_2O extraction (black) and of the Et_2O extract (magenta). *Conditions*: analytical RP-HPLC chromatography were carried out on a Waters HPLC system (Waters 1525 Binary HPLC Pump and Waters 2787 Dual λ Absorbance Detector) using EC Nucleosil 120-5 C8 column (250 x 4.6 mm, 5 µm) at a flow rate of 1 mL/min. Solvent A: 0.1% TFA (v/v) in H_2O. Solvent B: 0.1% TFA (v/v) in ACN. The following gradient was used: t = 0 min /20 % B, t = 30 min/100% B, t = 31 min/20% B. The compounds were detected at 218 nm.

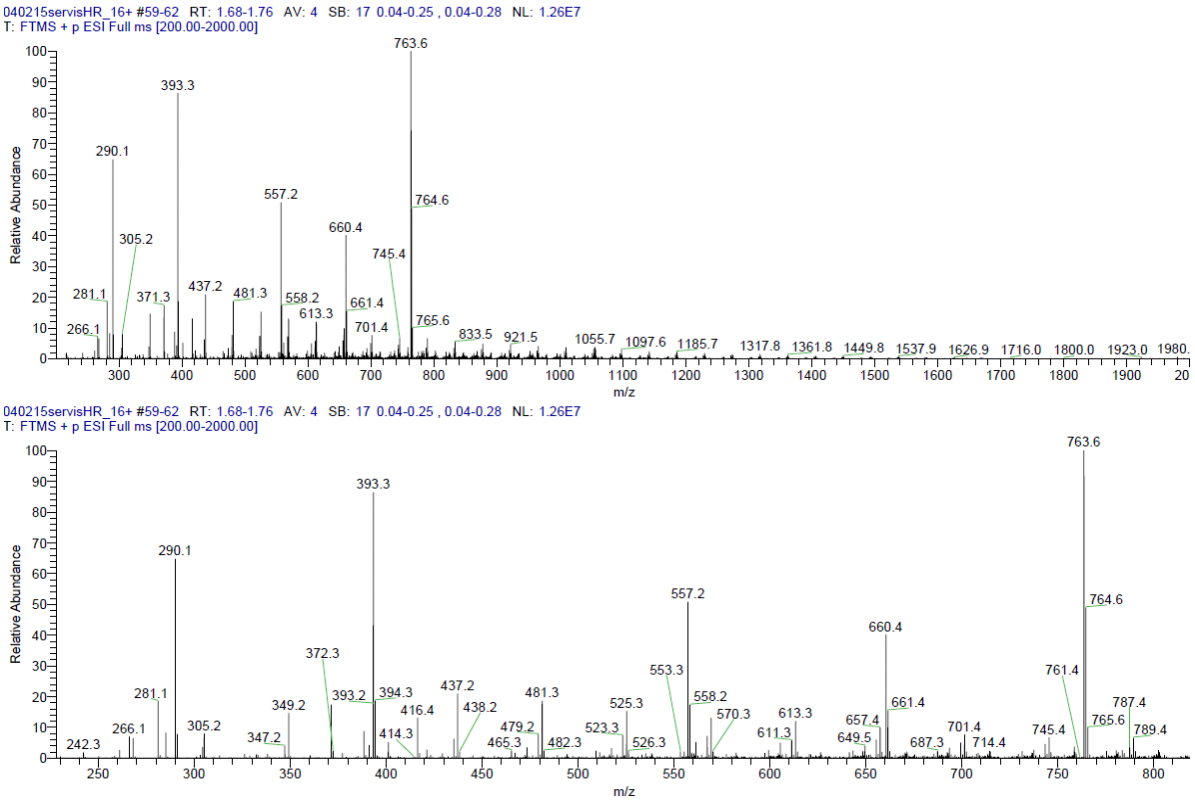


Figure S11. MS spectrum (top: full spectrum; bottom: zoom) of the Et_2O extract of the **C-2** sub-library. The ions seen did not correspond to any expected compound of this sub-library. *Conditions*: MS spectrum was obtained on an LTQ-orbitrap XL FTMS mass spectrometer (Thermo Fisher, Bremen, Germany) in electrospray ionization mode (Waters).

Removal of copper ions in the sub-library C1 with hydrogen sulfide

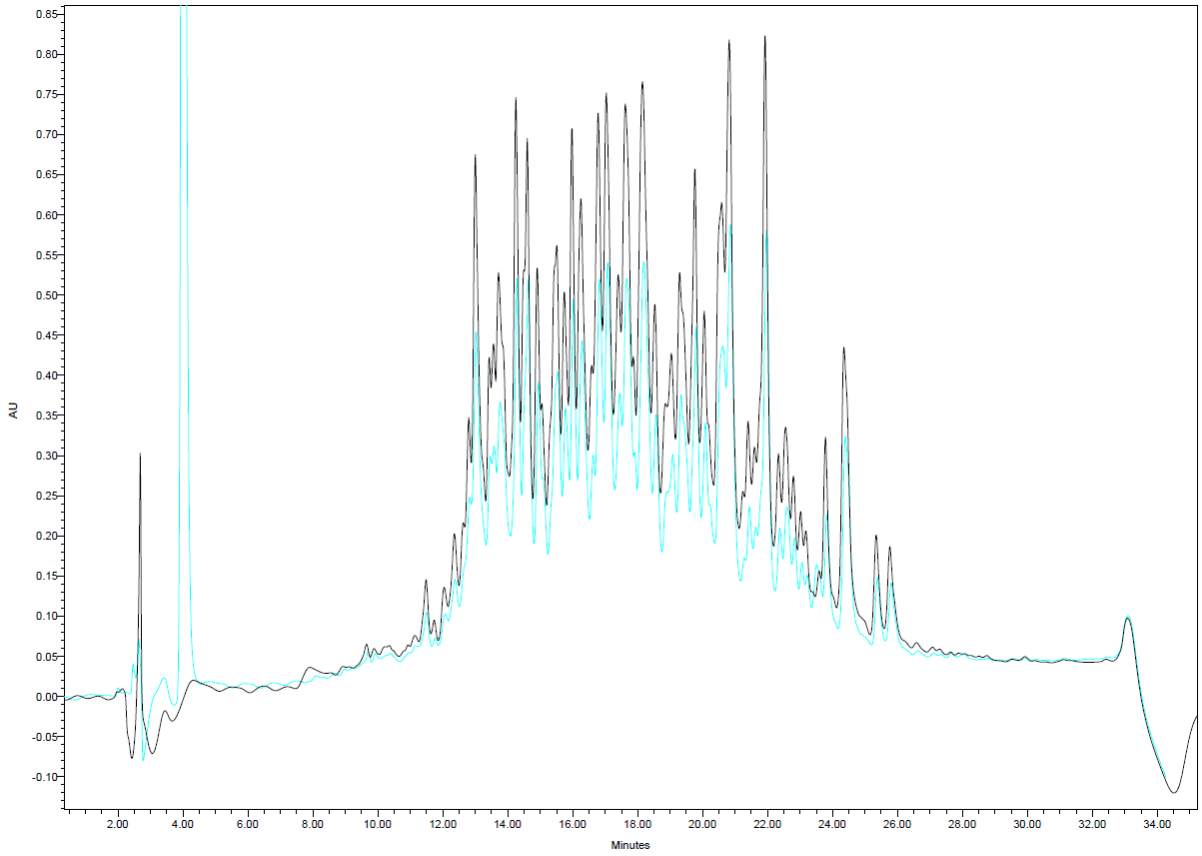


Figure S12. Superposition of the RP-HPLC chromatograms of the sub-library **C1** before (black) and after (blue) treatment with hydrogen sulfide. The library was dissolved in 50% ACN/H_2O and the resulting solution was injected in HPLC (black chromatogram). The solution was treated with hydrogen sulfide, filtered and injected again to HPLC (blue chromatogram). *Conditions*: analytical RP-HPLC chromatography were carried out on a Waters HPLC system (Waters 1525 Binary HPLC Pump and Waters 2787 Dual λ Absorbance Detector) using EC Nucleosil 120-5 C8 column (250 x 4.6 mm, 5 μm) at a flow rate of 1 mL/min. Solvent A: 0.1% TFA (v/v) in H_2O. Solvent B: 0.1% TFA (v/v) in ACN. The following gradient was used: t = 0 min /5 % B, t = 30 min/80% B, t = 31 min/5% B. The compounds were detected at 218.

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