

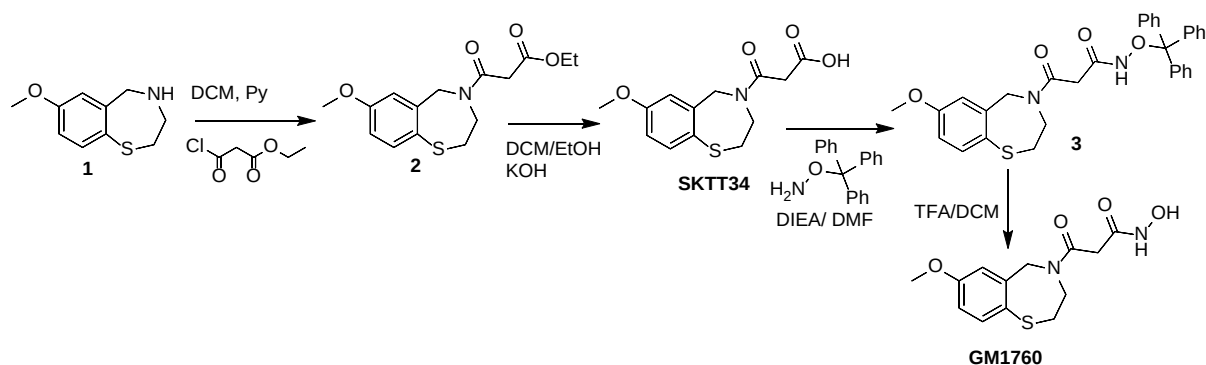
Supplemental Information

Synthesis

General materials and methods. All reagents and solvents were purchased from commercial sources and used without further purification. Flash chromatography was performed using Biotage Isolera ONE flash purification system with a cartridge and solvent gradient indicated. NMR spectra were recorded at ambient temperature on Agilent 400-MR spectrometer (MPI NAT Göttingen) at 400.06 MHz (^1H) and 100.60 MHz (^{13}C), and the chemical shifts are reported in ppm. All ^1H spectra are referenced to tetramethylsilane ($\delta = 0$ ppm) using the signals of the residual protons of CHCl_3 (7.26 ppm) in CDCl_3 , CHD_2CN (1.94 ppm) in CD_3CN , CHD_2OD (3.31 ppm) in CD_3OD or $\text{DMSO}-d_5$ (2.50 ppm) in $\text{DMSO}-d_6$. ^{13}C spectra are referenced to tetramethylsilane ($\delta = 0$ ppm) using the signals of the solvent: CDCl_3 (77.16 ppm), CD_3CN (1.32 ppm), CD_3OD (49.00 ppm) or $\text{DMSO}-d_6$ (39.52 ppm). Multiplicities of signals are described as follows: s = singlet, br. s = broad singlet, d = doublet, q = quartet, dq = doublet of quartets, m = multiplet or overlap of signals. Low resolution mass spectra (50 – 3500 m/z) with electro-spray ionization (ESI) were recorded on a Varian 500-MS spectrometer (Agilent) at MPI NAT Göttingen. High resolution mass spectra (ESI-HRMS) were recorded on a MICROTOF spectrometer (Bruker) equipped with ESI ion source (Apollo) and direct injector with LC autosampler Agilent RR 1200 in the Institute of Organic and Biomolecular Chemistry (Georg-August-Universität Göttingen).

Liquid chromatography: analytical HPLC was performed with Knauer AZURA liquid chromatography system. Analytical column: Knauer Eurosphere II 100-5, C18-H, 5 μm , 150 $\times$ 4.6 mm (unless otherwise stated); solvent A: H_2O + 0.1% v/v TFA, solvent B: MeCN + 0.1% v/v TFA; temperature 25 $^\circ\text{C}$. Analytical TLC was performed on MERCK ready-to-use plates with silica gel 60 (F_{254}).

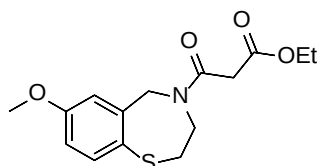
General procedure 1 for the synthesis of *N*-hydroxypropanediamides



Scheme 1. Synthesis of compounds with hydroxylamine residues.

Compound 2

Ethyl 3-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)-3-oxopropanoate



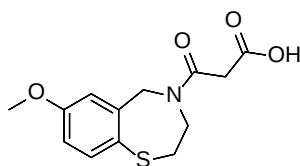
To 50 mg of 7-methoxy-2,3,4,5-tetrahydrobenzo[1,4-*f*]thiazepine **1** (BLD Pharm, 0.26 mmol) in DCM (5 ml), 50 μ l pyridine was added; then the reaction mixture was cooled to 0°C. After that, 1.5 eq. ethyl (chloroformyl)acetate (BLD Pharm, 69 mg, 0.39 mmol) was added dropwise. The reaction mixture was stirred for 2 h at 0 °C. After warming up to room temperature, the reaction mixture was washed with sat. aq. NaHCO₃, 1 M HCl and water. The organic layer was separated and dried over Na₂SO₄. The solvent was evaporated under reduced pressure on a rotary evaporator. The title compound was isolated by means of flash chromatography (Biotage® HP-Sfär Silica HC Duo 20 μ m 10 g, gradient 5% to 50% MeOH in DCM) to afford the **2** as a yellowish solid (27 mg, 33% yield). (Marks et al., US7879840B2, 2011).

¹H NMR (400 MHz, CDCl₃): mixture of rotamers δ 7.50 (d, *J* = 8.5 Hz, 0.4H), 7.41 (d, *J* = 8.4 Hz, 0.6H), 7.12 (d, *J* = 2.9 Hz, 0.6H), 6.83 (d, *J* = 2.7 Hz, 0.4H), 6.74 (dd, *J* = 8.5, 2.8 Hz, 0.4H), 6.70 (dd, *J* = 8.5, 2.8 Hz, 0.6H), 4.73 (br.s, 1H), 4.63 (s, 1H), 4.14 (qd, *J* = 7.1, 1.7 Hz, 2H), 4.09 (br.s, 1H), 3.94 (br. s, 1H), 3.80 (s, 1.2H), 3.78 (s, 1.8H), 3.52 (s, 0.8H), 3.38 (s, 1.2H), 2.81–2.73 (m, 2H), 1.29 – 1.15 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): mixture of rotamers δ 219.1, 167.5, 167.4, 166.2, 165.1, 159.6, 159.4, 143.2, 142.6, 135.0, 134.0, 126.9, 126.2, 117.1, 116.5, 113.6, 112.5, 62.6, 62.0, 61.7, 61.5, 55.6, 55.5, 55.0, 53.7, 52.5, 51.0, 41.7, 41.7, 41.0, 35.0, 33.6, 14.1, 14.1, 14.0.

SKTT34

3-(7-Methoxy-2,3-dihydrobenzo[1,4-f]thiazepin-4(5H)-yl)-3-oxopropanoic acid¹



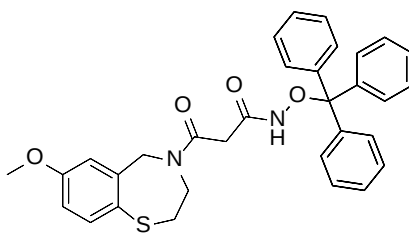
To the solution of **2** (27 mg, 0.09 mmol) in EtOH (0.4 ml), 10 mg (0.25 mmol) NaOH in 0.4 ml H₂O was added. The reaction mixture was stirred at rt for 1 h. After pH was adjusted to 2 with 6 N HCl, the product was extracted with DCM. The organic layer was dried over Na₂SO₄ and the solvent evaporated giving 15 mg (60%) of the title compound.

¹H NMR (400 MHz, CDCl₃): mixture of rotamers δ 7.53 (d, J = 8.4 Hz, 0.5H), 7.47 (d, J = 8.5 Hz, 0.5H), 7.10 (d, J = 2.8 Hz, 1H), 6.90 (d, J = 2.7 Hz, 1H), 6.80–6.73 (m, 1H), 4.77 (s, 1H), 4.15 (s, 1H), 3.98 (d, J = 16.8 Hz, 1H), 3.82 (s, 1.5H), 3.81 (s, 1.5H), 3.52 (s, 1H), 3.32 (s, 1H), 2.86 – 2.73 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): mixture of rotamers δ 170.3, 169.1, 168.3, 168.2, 159.8, 159.7, 141.9, 141.0, 135.4, 134.5, 126.5, 126.0, 117.6, 116.8, 113.7, 113.3, 55.7, 55.6, 54.3, 52.9, 52.7, 51.3, 35.5, 35.0, 34.6, 33.3.

Compound 3

3-(7-Methoxy-2,3-dihydrobenzo[1,4-f]thiazepin-4(5H)-yl)-3-oxo-*N*-(trityloxy)propanamide



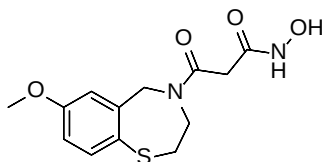
To the solution of **SKTT34** (50 mg, 0.18 mmol) in DMF (0.5 ml), *O*-tritylhydroxylamine (BLD Pharm, 85 mg, 0.31 mmol) and 77 mg (0.6 mmol) *N,N*-diisopropylethylamine (DIEA) were added followed by 102 mg *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 0.27 mmol). The reaction mixture was stirred at room temperature for 1 h. After the solvent was evaporated, the title compound was isolated by means of flash chromatography (eluent Hex/EtOAc) as a yellowish solid. Yield – 58 mg (58%). The compound was used in the next step without further purification.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.41 – 7.12 (m, 16H), 6.96 (dd, $J = 9.2, 2.9$ Hz, 1H), 6.81 – 6.74 (m, 1H), 4.42 (d, $J = 22.7$ Hz, 2H), 3.77 – 3.67 (m, 3H), 3.59 (d, $J = 17.8$ Hz, 2H), 3.02 (d, $J = 29.5$ Hz, 2H), 2.70 – 2.59 (m, 2H).

ESI-MS, positive mode: m/z (rel. int., %) = 561 (100) $[M+\text{Na}]^+$.

GM1760

N-Hydroxy-3-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)-3-oxopropanamide



Compound **3** (58 mg, 0.11 mmol) was dissolved in 2 ml 2% TFA in DCM giving the yellow solution. Then 100 μl (77 mg, 0.48 mmol) triisopropylsilane was added, and the reaction mixture was stirred at rt for 5 min. After the solvent was evaporated, the title compound was isolated by means of flash

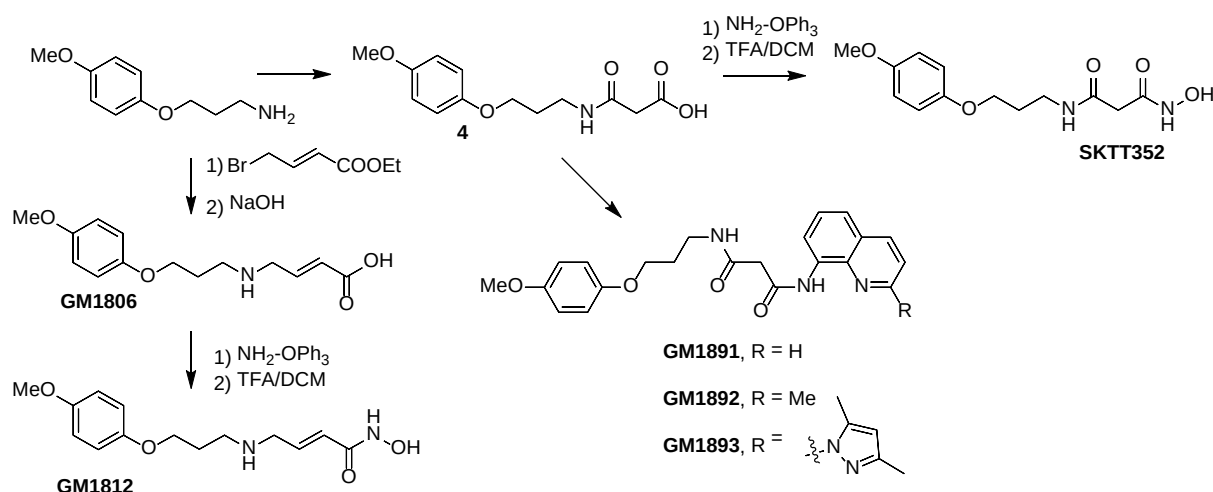
chromatography (Biotage® HP-Sfär Silica HC Duo 20 µm 10 g, gradient 5% to 50% MeOH in DCM) to afford **GM1760** as an yellowish solid. Yield –13 mg, 36%.

¹H NMR (400 MHz, DMSO-*d*₆): 2:1 mixture of rotamers δ 10.49 (s, 1H), 7.42 (dd, *J* = 9.9, 8.5 Hz, 0.7H), 7.16 (d, *J* = 2.8 Hz, 0.3H), 6.98 (d, *J* = 2.9 Hz, 0.3H), 6.82 (dd, *J* = 8.5, 2.8 Hz, 0.7H), 6.77 (dd, *J* = 8.4, 2.9 Hz, 1H), 4.71 (s, 0.7H), 4.54 (s, 1.3H), 4.00 – 3.90 (m, 2H), 3.77 (s, 1H), 3.74 (s, 2H), 3.20 (s, 0.7H), 3.11 (s, 1.3H), 2.87 – 2.81 (m, 1.3H), 2.74 (t, *J* = 5.0 Hz, 0.7H).

¹³C NMR (101 MHz, DMSO-*d*₆): 2:1 mixture of rotamers δ 167.0, 165.9, 163.3, 163.2, 158.9, 158.5, 143.6, 143.2, 142.7, 133.9, 133.4, 126.2, 126.1, 117.5, 116.4, 112.8, 112.4, 55.4, 55.2, 53.0, 51.8, 49.8, 34.6, 33.0.

ESI-MS, positive mode: *m/z* (rel. int., %) = 297 (100) [*M*+H]⁺, 319 [*M*+Na]⁺.

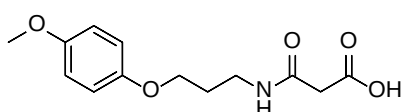
HRMS (*m/z*): [*M*+H]⁺ calcd. for *M* = C₁₃H₁₆N₂O₄S, 297.0904; found, 297.0904.



Scheme 2. Synthesis of 3-(4-methoxyphenoxy)propan-1-amine derivatives.

Compound 4

3-((3-(4-Methoxyphenoxy)propyl)amino)-3-oxopropanoic acid



was obtained from 3-(4-methoxyphenoxy)propan-1-amine (BLD Pharm, 226 mg, 1.25 mmol), ethyl (chloroformyl)acetate (324 mg, 2.15 mmol) using two-step procedure as described for **SKTT34**.

Overall yield – 227 mg (82 %).

^1H NMR (400 MHz, CD_3OD) δ 6.90 – 6.76 (m, 4H), 3.97 (t, J = 6.2 Hz, 2H), 3.73 (s, 3H), 3.40 (t, J = 6.8 Hz, 2H), 3.26 (s, 2H), 2.00 – 1.90 (m, 2H).

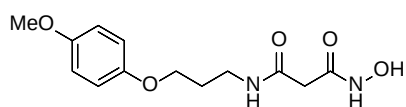
^{13}C NMR (101 MHz, CD_3OD) δ 171.4, 169.1, 155.4, 154.5, 116.5, 115.6, 67.1, 56.1, 42.7, 42.5, 37.8, 30.1.

ESI-MS, positive mode: m/z (rel. int., %) = 290 (100) $[\text{M}+\text{Na}]^+$.

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{M} = \text{C}_{13}\text{H}_{17}\text{NO}_5$, 270.1336; found, 270.1327.

SKTT352

*N*¹-Hydroxy-*N*³-(3-(4-methoxyphenoxy)propyl)malonamide



was obtained from **4** (227 mg, 0.85 mmol) and *O*-tritylhydroxylamine (350 mg, 1.28 mmol) using two-step procedure as described for **GM1760** (Scheme 1). The product was isolated by preparative HPLC with gradient elution (B/A, 20/80 → 100/0). Overall yield – 67 mg (28%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.49 (d, J = 1.6 Hz, 1H, OH), 8.89 (d, J = 1.6 Hz, 1H, NH), 8.12 – 8.00 (m, 1H, NH), 6.92 – 6.77 (m, 4H), 3.92 (t, J = 6.3 Hz, 2H), 3.69 (s, 3H), 2.88 (s, 2H), 1.82 (p, J = 6.6 Hz, 2H).

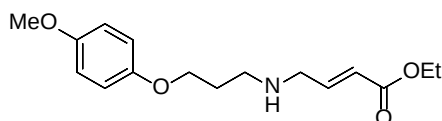
^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 166.3, 163.8, 153.3, 152.5, 115.4, 114.6, 65.6, 55.3, 40.9, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 35.8, 28.8, 17.5, 7.3.

ESI-MS, negative mode: m/z (rel. int., %) = 281 (100) $[\text{M}-\text{H}]^-$.

HRMS (*m/z*): [*M*+*H*]⁺ calcd. for *M* = C₁₃H₁₈N₂O₅, 283.1288; found, 283.1291.

Compound 5

Ethyl (*E*)-4-((3-(4-methoxyphenoxy)propyl)amino)but-2-enoate



To 383 mg of 3-(4-methoxyphenoxy)propan-1-amine (BLD Pharm, 2.11 mmol) in DCM (5 ml), 60 μ l DIEA was added; then the reaction mixture was cooled to 0°C. After that, ethyl (*E*)-4-bromo-2-butenate (191 mg, 1.06 mmol) was added dropwise. The reaction mixture was stirred at rt for 15 min. The reaction mixture was washed with sat. aq. NaHCO₃ and water. The organic layer was separated and dried over Na₂SO₄. The solvent was evaporated under reduced pressure. The title compound was isolated by means of flash chromatography (Biotage® HP-Sfär Silica HC Duo 20 μ m 10 g, gradient 2% to 20% MeOH in DCM) to afford **5** as a yellowish solid (150 mg, 48% yield).

¹H NMR (400 MHz, CDCl₃) δ 6.98 (dt, *J* = 15.7, 5.5 Hz, 1H, CH), 6.82 (d, *J* = 0.6 Hz, 4H), 5.98 (dt, *J* = 15.7, 1.8 Hz, 1H, CH), 4.18 (q, *J* = 7.1 Hz, 2H, NCH₂), 3.99 (t, *J* = 6.1 Hz, 2H, CH₂), 3.75 (s, 3H, OCH₃), 3.42 (dd, *J* = 5.5, 1.9 Hz, 2H, CH₂), 2.81 (t, *J* = 6.8 Hz, 2H, CH₂), 1.98 – 1.89 (m, 2H, CH₂), 1.28 (t, *J* = 7.1 Hz, 3H, CH₃).

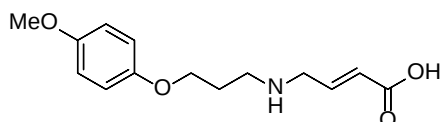
¹³C NMR (101 MHz, CDCl₃) δ 166.5, 153.9, 153.1, 146.8, 121.7, 115.6, 115.5, 114.7, 66.9, 60.4, 55.8, 50.5, 46.6, 29.9, 14.4.

ESI-MS, positive mode: *m/z* (rel. int., %) = 294 (100) [*M*+*H*]⁺.

HRMS (*m/z*): [*M*+*H*]⁺ calcd. for *M* = C₁₆H₂₃NO₄, 294.1700; found, 294.1699.

GM1806

(*E*)-4-((3-(4-Methoxyphenoxy)propyl)amino)but-2-enoic acid



was obtained by saponification of **5** (150 mg, 0.5 mmol) as described for **SKTT34**. After pH was adjusted to **2** with 6 N HCl, the title product precipitated and was filtered out. Yield – 96 mg (72%) of white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 6.92 – 6.78 (m, 5H), 6.17 (dt, J = 15.8, 1.4 Hz, 1H, CH), 3.99 (t, J = 6.1 Hz, 1H, CH₂), 3.78 (dd, J = 6.4, 1.6 Hz, 1H, CH₂), 3.68 (s, 3H, CH₃), 3.07 – 2.98 (m, 2H, CH₂), 2.14 – 2.05 (m, 2H, CH₂).

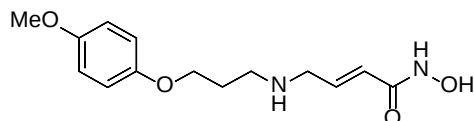
^{13}C NMR (101 MHz, DMSO- d_6) δ 166.0, 153.5, 152.3, 137.7, 127.1, 115.4, 115.2, 114.6, 65.2, 55.4, 46.5, 43.7, 25.5.

ESI-MS, positive mode: m/z (rel. int., %) = 266 (100) [$M+H$]⁺.

HRMS (m/z): [$M+H$]⁺ calcd. for M = C₁₄H₁₉NO₄, 266.1387; found, 266.1388.

GM1812

(*E*)-*N*-hydroxy-4-((3-(4-methoxyphenoxy)propyl)amino)but-2-enamide



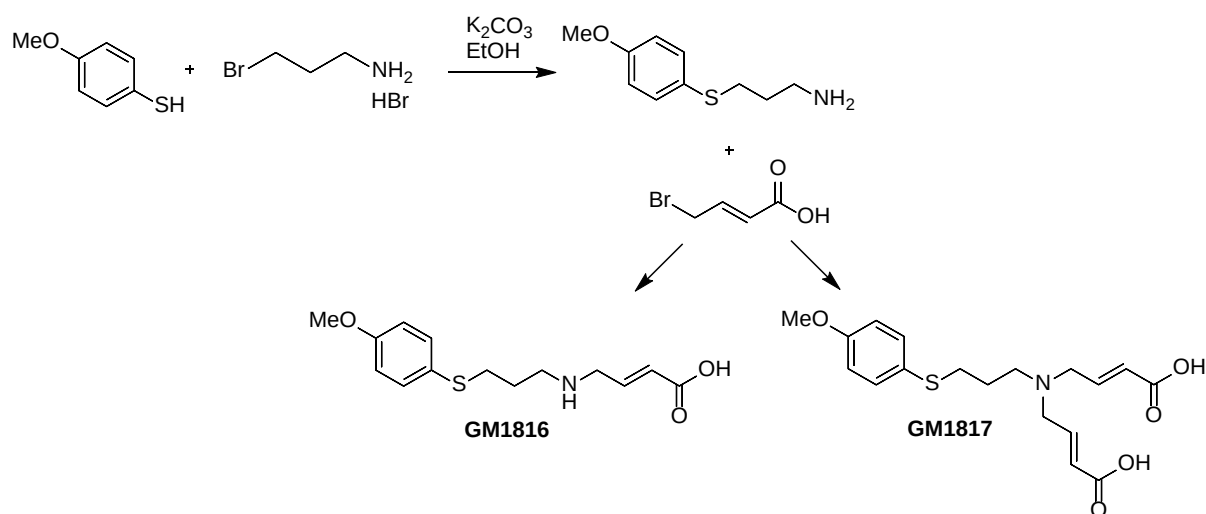
was obtained from compound **GM1806** (Scheme 2, 49 mg, 0.13 mmol) and *O*-tritylhydroxylamine (36 mg, 0.13 mmol) using the two-step-procedure similar to that for **SKTT352** (Scheme 2). The product was isolated by preparative HPLC with gradient elution (B/A, 30/70 → 100/0). Overall yield – 20 mg (55%) of beige solid.

^1H NMR (400 MHz, CD₃OD) δ 6.90 – 6.82 (m, 4H), 6.81 – 6.72 (m, 1H, CH), 6.21 (d, J = 15.3 Hz, 1H, CH), 4.05 (t, J = 5.7 Hz, 2H, CH₂), 3.89 – 3.83 (m, 2H, CH₂), 3.74 (s, 3H, OCH₃), 3.28 – 3.20 (m, 2H, CH₂), 2.21 – 2.09 (m, 2H, CH₂).

^{13}C NMR (101 MHz, CD₃OD) δ 163.9, 162.8, 162.4, 155.7, 153.9, 132.8, 128.4, 116.5, 115.7, 66.6, 56.1, 46.5, 27.3, 18.7, 17.3.

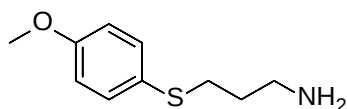
ESI-MS, positive mode: m/z (rel. int., %) = 281 (100) [$M+H$]⁺.

HRMS (m/z): $[M+H]^+$ calcd. for $M = C_{14}H_{20}N_2O_4$, 281.1496; found, 281.1495.



Scheme 3. Synthesis of 3-[(4-Methoxyphenyl)thio]-1-propanamine derivatives.

3-[(4-Methoxyphenyl)thio]-1-propanamine



was prepared from 4-methoxybenzenethiol (BLD Pharm, 1.4 g, 10 mmol), 3-bromopropan-1-amine hydrobromide (BLD Pharm, 2.37 g, 11 mmol) and potassium carbonate (2.8 g, 20.3 mmol) in 60 ml ethanol. After the reaction mixture was refluxed over-night, it was poured into cold water (30 ml) and extracted with $CHCl_3$ (4×25 ml). The extracts were combined and washed with water (3×30 ml) and dried over anhydrous Na_2SO_4 . The solvent was evaporated *in vacuo* affording the title compound as a yellowish oil. Yield – 1.18 g (60%).

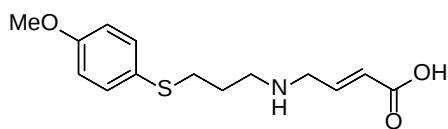
1H NMR (400 MHz, CD_3OD) δ 7.37 – 7.30 (m, 2H), 6.90 – 6.83 (m, 2H), 4.84 (s, 2H, NH), 3.77 (s, 3H, OCH_3), 2.86 (t, $J = 7.2$ Hz, 2H, CH_2), 2.73 (t, $J = 7.1$ Hz, 2H, CH_2), 1.71 (p, $J = 7.1$ Hz, 2H, CH_2).

^{13}C NMR (101 MHz, CD_3OD) δ 160.5, 134.3, 127.7, 115.6, 55.8, 41.3, 33.9, 33.1.

ESI-MS, positive mode: m/z (rel. int., %) = 198 (100) $[M+H]^+$.

GM1816

(E)-4-((3-((4-methoxyphenyl)thio)propyl)amino)but-2-enoic acid



was obtained from 3-[(4-methoxyphenyl)thio]-1-propanamine (140 mg, 0.71 mmol) and (*E*)-4-bromo-2-butenolate (43 mg, 0.35 mmol) using the two-step-procedure described for **GM1806**. The product isolated by preparative HPLC with gradient elution (B/A, 30/70 → 100/0). Overall yield – 34 mg (35%) of white solid.

^1H NMR (400 MHz, CD_3OD) δ 7.44 – 7.34 (m, 2H, H-Ar), 6.95 – 6.86 (m, 2H, H-Ar), 6.83 (dt, J = 15.7, 6.6 Hz, 1H, $\text{CH}_2\text{CH=}$), 6.18 (dt, J = 15.7, 1.5 Hz, 1H, CH=), 3.82 (dd, J = 6.6, 1.5 Hz, 2H, $\text{CH}_2\text{CH=}$), 3.78 (s, 3H, OCH_3), 3.19 – 3.10 (m, 2H, CH_2), 2.92 (t, J = 7.0 Hz, 2H, CH_2), 1.98 – 1.86 (m, 2H, CH_2).

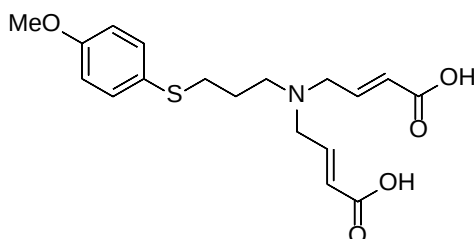
^{13}C NMR (101 MHz, CD_3OD) δ 168.0 (CO), 160.9 (C-Ar), 137.3(CH=), 134.9 (CH-Ar), 129.3 (C-Ar), 126.3 (CH=), 115.8 (CH-Ar), 55.8 (CH_3), 48.6 ($\text{CH}_2\text{CH=}$), 47.4 (CH_2), 33.2 (CH_2), 26.8 (CH_2).

ESI-MS, positive mode: m/z (rel. int., %) = 282 (100) $[\text{M}+\text{H}]^+$.

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{M} = \text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$, 282.1158; found, 282.1164.

GM1817

(2*E*,2'*E*)-4,4'-((3-((4-methoxyphenyl)thio)propyl)azanediyl)bis(but-2-enoic acid)

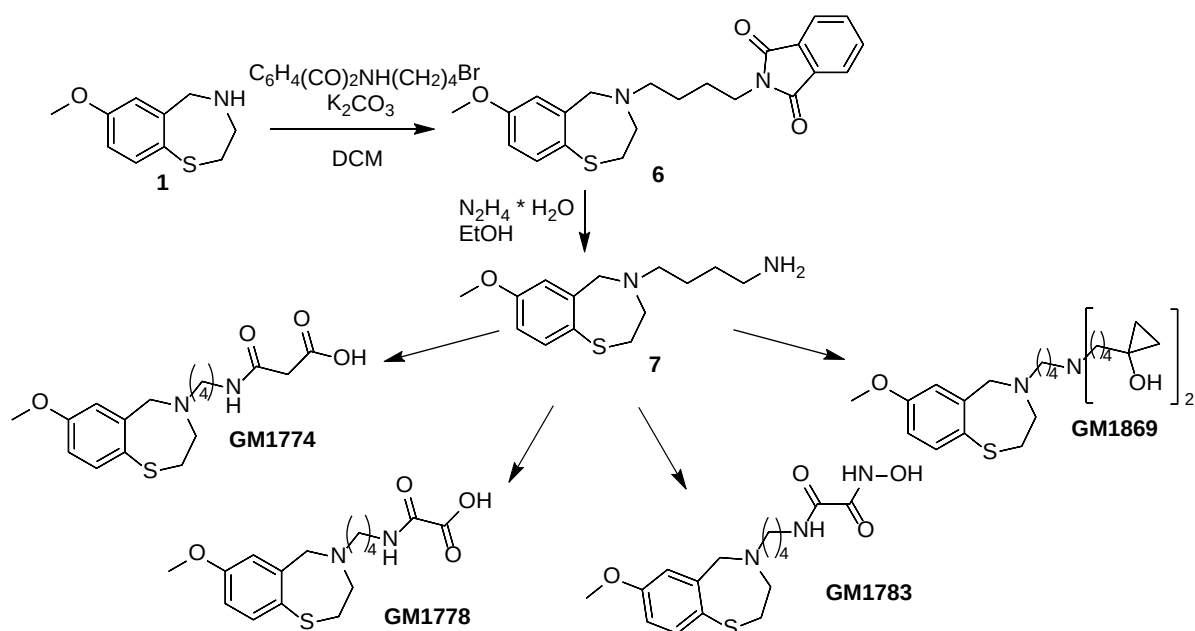


was obtained from 3-[(4-methoxyphenyl)thio]-1-propanamine (125 mg, 0.63 mmol) and (*E*)-4-bromo-2-butenolate (122 mg, 0.63 mmol) using the two-step-procedure described for **GM1806**. The product was isolated by preparative HPLC with gradient elution (B/A, 10/70 → 100/0). Overall yield – 64 mg (28%) of white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.41 – 7.25 (m, 2H), 6.96 – 6.86 (m, 2H), 6.86 – 6.70 (m, 2H, CH), 6.13 (dd, J = 17.8, 15.7 Hz, 2H, CH), 3.90 (d, J = 34.9 Hz, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.00 (d, J = 45.5 Hz, 2H), 2.89 (q, J = 7.4, 6.9 Hz, 2H), 2.49 (p, J = 1.9 Hz, 2H), 1.84 (d, J = 16.4 Hz, 2H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 166.4, 159.0, 137.9, 133.0, 132.9, 127.6, 125.5, 115.3, 55.7, 55.6, 51.6, 49.0, 32.0, 25.7.

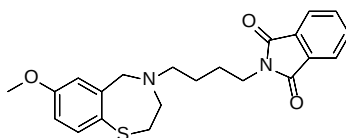
ESI-MS, positive mode: m/z (rel. int., %) = 366 (100) $[\text{M}+\text{H}]^+$.



Scheme 4. Synthesis of 1,4-benzodiazepine derivatives with 4-aminobutyl linker.

Compound 6

2-(4-(7-methoxy-2,3-dihydrobenzo[1,4-f]thiazepin-4(5H)-yl)butyl)isoindoline-1,3-dione



To a solution of **1** (0.9 g, 4.6 mmol) in anhydrous 1,4-dioxane (32 ml), 2-(4-bromobutyl)isoindoline-1,3-dione (BLD Pharm, 1.3 g, 4.6 mmol) and K_2CO_3 (635 mg, 4.6 mmol) were added, and the reaction mixture was refluxed overnight in the argon atmosphere. After the reaction mixture was filtered from the precipitate, 20 ml DCM and 20 ml water were added to the filtrate. The organic

phase was separated, the aqueous layer extracted with DCM (2×5 ml). The combined organic solutions were dried over Na₂SO₄. The filtrate was evaporated, and the product isolated by flash column chromatography using Biotage® SNAP Ultra 50 g cartridge with SiO₂ (gradient: ethyl acetate in hexane 20% – 80%). Yield – 1.1 g (61%) of yellowish oil

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.78 (m, 2H), 7.73 – 7.66 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.09 (s, 2H, NCH₂), 3.77 (s, 3H, OCH₃), 3.68 (t, *J* = 7.1 Hz, 2H, CH₂), 3.33 – 3.26 (m, 2H, CH₂), 2.67 (dd, *J* = 6.6, 3.3 Hz, 2H, CH₂), 2.45 – 2.35 (m, 2H, CH₂), 1.73 – 1.63 (m, 2H, CH₂), 1.57 – 1.48 (m, 2H, CH₂).

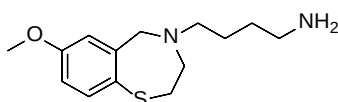
¹³C NMR (101 MHz, CDCl₃) δ 168.5, 159.2, 134.1, 134.0, 133.7, 132.2, 127.8, 123.4, 123.3, 116.9, 112.4, 59.6, 58.3, 55.4, 51.4, 37.9, 30.2, 26.4, 24.7.

ESI-MS, positive mode: *m/z* (rel. int., %) = 397 (100) [M+H]⁺.

HRMS (*m/z*): [M+H]⁺ calcd. for *M* = C₂₂H₂₄N₂O₃S, 397.1580; found, 397.1583.

Compound 7

4-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)butan-1-amine



To the compound **6** (330 mg, 0.84 mmol) in 2 ml ethanol, hydrazine hydrate (ABCR, 96 mg, 1.9 mmol) was added. The reaction mixture was stirred at 50 °C for 30 min. Then 5 ml of water was added, and the aqueous solution was extracted with DCM (2×5 ml). The combined organic solutions were dried over Na₂SO₄. The filtrate was evaporated, and the product isolated by preparative HPLC with gradient elution (B/A, 20/80 → 100/0). Yield – 210 mg (94%) of yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 2.8 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 4.27 (s, 2H, NCH₂), 3.79 (s, 3H, OCH₃), 3.48 – 3.40 (m, 2H, CH₂), 3.08 (t, *J* = 6.1 Hz, 2H, CH₂), 2.78 (dd, *J* = 6.6, 3.2 Hz, 2H, CH₂), 2.58 (t, *J* = 6.1 Hz, 2H, CH₂), 1.94 (p, *J* = 6.2 Hz, 2H, CH₂), 1.77 (q, *J* = 6.3 Hz, 2H, CH₂).

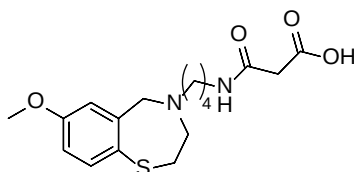
^{13}C NMR (101 MHz, CDCl_3) δ 159.2, 144.8, 133.7, 127.9, 117.1, 112.1, 77.5, 77.4, 77.2, 76.8, 59.6, 58.4, 55.5, 51.9, 42.1, 31.2, 30.2, 28.1, 25.0, 24.8.

ESI-MS, positive mode: m/z (rel. int., %) = 267 (100) $[\text{M}+\text{H}]^+$.

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{M} = \text{C}_{14}\text{H}_{22}\text{N}_2\text{OS}$, 267.1526; found, 267.1527.

GM1774

3-((4-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)butyl)amino)-3-oxopropanoic acid



was obtained from compound **7** (300 mg, 1.13 mmol), ethyl (chloroformyl)acetate (170 mg, 1.12 mmol) using the two-step-procedure similar to that for **SKTT34** (Scheme 1). The product isolated by preparative HPLC with gradient elution (B/A, 30/70 $\rightarrow$ 100/0). Overall yield – 50 mg (12.5%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.22 – 8.12 (m, 1H, NH), 7.50 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 6.97 (dd, J = 8.5, 2.8 Hz, 1H), 4.54 (s, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 3.78 – 3.53 (m, 2H, CH_2), 3.25 – 2.93 (m, 2H, CH_2), 1.76 (m, 2H, CH_2), 1.43 (q, J = 7.2 Hz, 2H, CH_2).

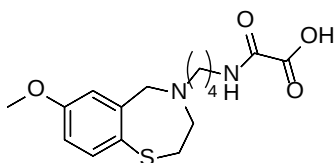
^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 169.9, 166.2, 159.7, 135.9, 134.2, 128.2, 119.6, 115.4, 56.0, 43.0, 42.1, 40.9, 38.3, 38.2, 26.5, 21.1.

ESI-MS, positive mode: m/z (rel. int., %) = 353 (100) $[\text{M}+\text{H}]^+$.

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{M} = \text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$, 353.1530; found, 353.1536.

GM1778

2-((4-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)butyl)amino)-2-oxoacetic acid



was obtained from compound **7** (300 mg, 1.13 mmol) and methyl 2-chloro-2-oxoacetate (136 mg, 1.12 mmol) (170 mg, 1.12 mmol) using the two-step-procedure similar to that for **SKTT34**. The product isolated by preparative HPLC with gradient elution (B/A, 20/80 → 100/0). Yield – 210 mg (94%) of yellowish oil. Yield – 210 mg (94%) of yellowish oil. Overall yield – 145 mg (38%).

^1H NMR (400 MHz, CD_3OD) δ 7.56 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 2.8 Hz, 1H), 6.98 (dd, J = 8.5, 2.7 Hz, 1H), 4.68 (s, 2H), 3.84 (s, 3H), 3.80 – 3.62 (m, 3H), 3.38 – 3.31 (m, 2H), 3.09 (d, J = 73.5 Hz, 0H), 1.85 (s, 2H), 1.71 – 1.58 (m, 2H).

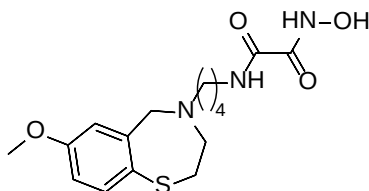
^{13}C NMR (101 MHz, CD_3OD) δ 162.6, 161.7, 160.5, 136.6, 135.5, 129.5, 119.8, 116.6, 60.1, 56.2, 53.8, 49.4, 39.6, 27.2, 22.5.

ESI-MS, positive mode: m/z (rel. int., %) = 339 (100) $[M+H]^+$.

HRMS (m/z): $[M+H]^+$ calcd. for $M = \text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$, 339.1373; found, 339.1378.

GM1783

*N*¹-hydroxy-*N*²-(4-(7-methoxy-2,3-dihydrobenzo[1,4-*b*]thiazepin-4(5*H*)-yl)butyl)oxalamide



was obtained from compound **GM1778** (70 mg, 0.2 mmol) and *O*-tritylhydroxylamine (68 mg, 0.25 mmol) using the similar two-step-procedure, as for **GM1760** (Scheme 1). The product isolated by preparative HPLC with gradient elution (B/A, 5/95 → 80/20). Overall yield – 12 mg (17%) of beige solid.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.48 (s, 1H), 8.80 (t, J = 6.1 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 2.8 Hz, 1H), 6.98 (dd, J = 8.5, 2.8 Hz, 1H), 4.56 (s, 2H), 3.79 (s, 16H), 3.14 (q, J = 6.7 Hz, 2H), 2.99 – 2.87 (m, 2H), 1.69 (s, 2H), 1.48 (q, J = 7.2 Hz, 2H).

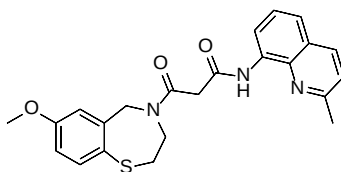
^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 159.8, 159.2, 156.8, 133.8, 127.8, 119.0, 115.0, 55.6, 37.9, 25.8, 20.9.

ESI-MS, positive mode: m/z (rel. int., %) = 354 (100) $[M+H]^+$.

HRMS (m/z): $[M+H]^+$ calcd. for $M = \text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_4\text{S}$, 354.1482; found, 354.1485.

GM1840

3-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)-*N*-(2-methylquinolin-8-yl)-3-oxopropanamide



To the solution of **SKTT34** (35 mg, 0.12 mmol) in DMF (0.5 ml), 2-methylquinolin-8-amine (24 mg, 0.15 mmol) and 46 mg (0.36 mmol) *N,N*-Diisopropylethylamine (DIEA) were added followed by 47 mg HATU (0.12 mmol). The reaction mixture was stirred at room temperature for 30 min. After the solvent was evaporated, the title compound was isolated by means of flash chromatography (Biotage® HP-Sfär Silica HC Duo 20 μm 10 g, gradient 12% to 100% EtOAc in hexane) to afford the title compound as a yellowish oil (30 mg, 59% yield).

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.56 (td, J = 7.7, 1.3 Hz, 1H), 8.24 (dd, J = 8.4, 2.5 Hz, 1H), 7.58 (ddd, J = 8.3, 2.5, 1.3 Hz, 1H), 7.48 (ddd, J = 8.0, 4.0, 2.7 Hz, 2H), 7.39 (dd, J = 23.1, 8.4 Hz, 1H), 7.14 (dd, J = 62.0, 2.8 Hz, 1H), 6.74 (ddd, J = 15.9, 8.4, 2.9 Hz, 1H), 4.80 (s, 1H), 4.63 (s, 1H), 4.08 – 3.97 (m, 3H), 3.81 (d, J = 32.9 Hz, 2H), 3.74 (d, J = 1.6 Hz, 3H), 3.35 (s, 2H), 2.87 (dt, J = 21.1, 4.9 Hz, 2H), 2.71 (d, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 167.7, 166.8, 166.7, 165.6, 165.5, 165.2, 165.1, 158.8, 158.6, 157.4, 157.4, 143.5, 142.9, 137.4, 137.4, 136.5, 133.9, 133.8, 133.8, 133.7, 133.5, 126.2, 126.0, 125.9, 125.9, 125.8, 122.8, 122.7, 121.7, 121.7, 117.6, 116.3, 116.2, 112.9, 112.4, 55.3, 55.2, 53.3, 52.8, 51.9, 49.9, 42.6, 42.3, 34.5, 32.9, 24.9, 24.9.

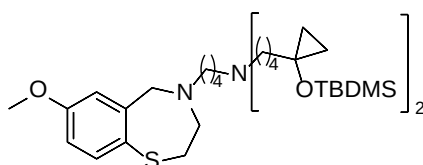
ESI-MS, positive mode: m/z (rel. int., %) = 422 (100) $[M+H]^+$; 444 (70) $[M+Na]^+$.

HRMS (m/z): $[M+H]^+$ calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$, 422.1533; found, 422.1517.

(1-(4-Bromobutyl)cyclopropoxy)(tert-butyl)dimethylsilane was obtained from in three steps from 5-(benzyloxy)pentan-1-ol (BLD Pharm, 2 g, 10.4 mmol) as described by Elek et al., *Org. Lett.* **2019**, 21 (20), 8473-8478.

Compound 8

4-(1-((tert-butyl)dimethylsilyl)oxy)cyclopropyl)-N-(4-(1-((tert-butyl)dimethylsilyl)oxy)cyclopropyl)butyl)-N-(4-(7-methoxy-2,3-dihydrobenzo[1,4-f]thiazepin-4(5H)-yl)butyl)butan-1-amine



To the suspension of NaH (60 % in mineral oil, 119 mg, 0.39 mmol) in 1.5 ml anhydrous DMF compound 7 (244 mg, 0.92 mmol) was added, and the reaction mixture was stirred at rt for 5 min. Then (1-(4-bromobutyl)cyclopropoxy)(tert-butyl)dimethylsilane was added and the reaction mixture was stirred overnight at rt. After the solvent was removed *in vacuo*, 5 ml water and 5 ml DCM were added. The organic solution was separated, the aqueous solution extracted with DCM (2×5 ml). The combined organic solutions were dried over Na_2SO_4 . The filtrate was evaporated, and the product isolated by flash column chromatography using Biotage® SNAP Ultra 10g cartridge (gradient: methanol in DCM 4 % → 40 %). Yield – 63 mg (14 %) of yellowish oil.

^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, J = 8.4 Hz, 1H, $\text{H}_{\text{Ar-5}}$), 6.79 (d, J = 2.8 Hz, 1H, $\text{H}_{\text{Ar-8}}$), 6.68 (dd, J = 8.4, 2.8 Hz, 1H, $\text{H}_{\text{Ar-6}}$), 4.09 (s, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 3.35 – 3.29 (m, 2H, CH_2), 2.72 – 2.64 (m, 2H, CH_2), 2.37 (t, J = 7.2 Hz, 8H, CH_2), 1.51 – 1.33 (m, 16H, CH_2), 0.84 (s, 18H, CH_3), 0.71 – 0.62 (m, 4H, CH_2), 0.42 – 0.35 (m, 4H, CH_2), 0.08 (s, 12H, CH_3).

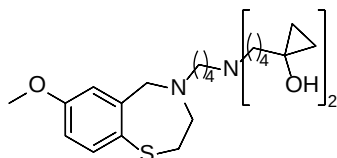
^{13}C NMR (101 MHz, CDCl_3) δ 159.2, 145.2, 133.7, 127.9, 117.0, 112.0, 59.8 (CH_2), 58.5 (CH_2), 57.0 (CH_2), 55.5 (OCH_3), 39.2 (CH_2), 30.4 (CH_2), 25.9 (CH_3), 24.1, 17.9, 13.2 (CH_2), -3.3 (CH_3).

ESI-MS, positive mode: m/z (rel. int., %) = 719 (100) $[\text{M}+\text{H}]^+$.

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{M} = \text{C}_{40}\text{H}_{74}\text{N}_2\text{O}_3\text{SSi}_2$, 719.5031; found, 719.5033.

GM1869

1,1'-(((4-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)butyl)azanediyl)bis(butane-4,1-diyl))bis(cyclopropan-1-ol)



t-Butyldimethylsilyl deprotection of compound **8** (28 mg, 0.04 mmol) was performed in 200 μl 1 M tetrabutylammonium fluoride in THF. The reaction mixture was stirred overnight at rt. The title compound was isolated by preparative HPLC with gradient elution (B/A: 20/80 $\rightarrow$ 100/0). Yield 8 mg (41 %) of clear oil.

^1H NMR (400 MHz, CD_3OD) δ 7.55 (d, J = 8.5 Hz, 1H, $\text{H}_{\text{Ar-5}}$), 7.21 (d, J = 2.8 Hz, 1H, $\text{H}_{\text{Ar-8}}$), 6.98 (dd, J = 8.5, 2.8 Hz, 1H, $\text{H}_{\text{Ar-6}}$), 4.68 (br. s, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 3.76 – 3.68 (d, J = 19.5 Hz, 2H, NCH_2), 3.24 – 3.06 (s, 10H, CH_2), 1.97 – 1.74 (m, 8H, CH_2), 1.67 – 1.55 (d, J = 3.6 Hz, 8H, CH_2), 0.59 – 0.48 (m, 4H, CH_2), 0.40 – 0.19 (m, 4H, CH_2).

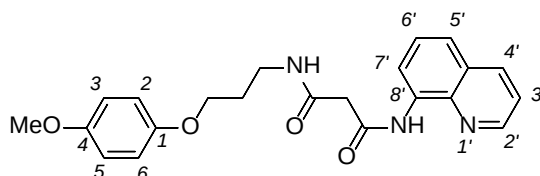
^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 159.2, 158.5, 158.2, 133.8, 127.8, 119.2, 114.9, 55.5, 53.5, 52.1, 51.1, 40.6, 37.4, 35.0, 23.0, 22.9, 20.7, 20.2, 12.8, 7.6.

ESI-MS, positive mode: m/z (rel. int., %) = 491 (100) $[\text{M}+\text{H}]^+$.

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{M} = \text{C}_{28}\text{H}_{46}\text{N}_2\text{O}_3\text{S}$, 491.3302; found, 491.3289.

GM1891

N^1 -(3-(4-methoxyphenoxy)propyl)- N^3 -(quinolin-8-yl)malonamide



To 18 mg (67 μmol) of **4** in DMSO (1 ml), 50 μl Et_3N was added, then ethyl 8-aminoquinoline (BLD Pharm, 12 mg, 84 μmol) and HATU (28 mg, 74 μmol) were added. The reaction mixture was stirred at rt for 20 min. Then the solvent was evaporated *in vacuo*, 20 ml DCM added, and the reaction mixture washed with water several times. The organic layer was separated and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure, and the title compound was isolated by flash chromatography (Biotage® HP-Sfär Silica HC Duo 20 μm 10 g, gradient 2% to 20% EtOAc in hexane) to afford the title compound as a yellowish solid (14 mg, 36% yield).

^1H NMR (400 MHz, CDCl_3) δ 10.61 (s, 1H, NH), 8.86 (dd, $J = 4.2, 1.7$ Hz, 1H, H-2'), 8.72 (dd, $J = 6.0, 3.0$ Hz, 1H, H-4'), 8.16 (dd, $J = 8.3, 1.7$ Hz, 1H, H-7'), 7.57 – 7.51 (m, 2H, H-5', 6'), 7.46 (dd, $J = 8.3, 8.3$ Hz, 1H, H-3'), 7.36 (d, $J = 5.1$ Hz, 1H, NH), 6.89 – 6.74 (m, 4H, H_{Ar} , H-2,3,5,6), 4.00 (t, $J = 5.9$ Hz, 2H, OCH_2), 3.75 (d, $J = 0.6$ Hz, 3H, OCH_3), 3.60 – 3.49 (m, 4H, CH_2), 2.09 – 1.96 (m, 2H, CH_2).

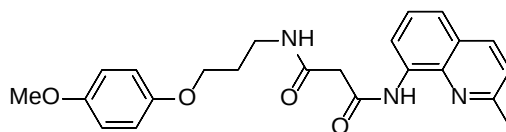
^{13}C NMR (101 MHz, CDCl_3) δ 166.6 (CO), 166.2 (CO), 154.0, 152.9, 148.7, 138.7, 136.4, 134.2, 128.1, 127.3, 122.4, 121.9, 117.0, 115.6, 114.8, 66.9 (OCH_3), 55.8 (CH_2), 45.0 (CH_2), 37.7 (CH_2), 29.1 (CH_2).

ESI-MS, positive mode: m/z (rel. int., %) = 416 (100) $[\text{M}+\text{Na}]^+$.

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{M} = \text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_4$, 394.1761; found, 394.1758.

GM1892

*N*¹-(3-(4-methoxyphenoxy)propyl)- *N*³-(2-methylquinolin-8-yl)malonamide



was obtained similarly to **GM1891** (Scheme 2) from 3-((3-(4-methoxyphenoxy)propyl)amino)-3-oxopropanoic acid (**4**, 24 mg, 90 μ mol) and 2-methylquinolin-8-amine (BLD Pharm, 18 mg, 114 μ mol). The title compound was isolated by means of flash chromatography (Biotage® HP-Sfär Silica HC Duo 20 μ m 10 g, gradient 22% to 100% EtOAc in hexane) to afford the title compound as a yellowish solid (24 mg, 66% yield).

¹H NMR (400 MHz, CDCl₃) δ 10.44 (s, 1H, NH), 8.67 (dd, *J* = 7.3, 1.7 Hz, 1H, H-7'), 8.04 (d, *J* = 8.4 Hz, 1H, H-4'), 7.61 – 7.41 (m, 3H, NH, H-5',6'), 7.33 (d, *J* = 8.4 Hz, 1H, H-3'), 6.91 – 6.73 (m, 4H, H_{Ar}, H-2,3,5,6), 4.00 (t, *J* = 5.9 Hz, 2H, OCH₂), 3.75 (s, 3H, OCH₃), 3.60 – 3.44 (m, 4H, CH₂), 2.76 (s, 3H, CH₃), 2.10 – 1.94 (m, 2H, CH₂).

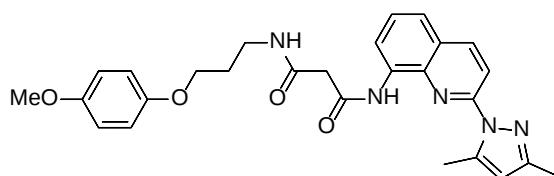
¹³C NMR (101 MHz, CDCl₃) δ 166.4 (CO), 166.4 (CO), 157.8, 154.0, 153.0, 138.0, 136.5, 133.5, 126.2, 126.2, 122.8, 122.2, 116.9, 115.6, 114.7, 66.9 (OCH₃), 55.9 (CH₂), 45.1 (CH₂), 37.6 (CH₂), 29.2 (CH₂), 25.4 (CH₃).

ESI-MS, positive mode: *m/z* (rel. int., %) = 430 (100) [*M*+Na]⁺.

HRMS (*m/z*): [*M*+H]⁺ calcd. for M = C₂₃H₂₅N₃O₄, 408.1918; found, 408.1922.

GM1893

*N*¹-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)quinolin-8-yl)-*N*³-(3-(4-methoxyphenoxy)propyl)malonamide



was obtained similarly to **GM1891** (Scheme 2) from 3-((3-(4-methoxyphenoxy)propyl)amino)-3-oxopropanoic acid (**4**, 17 mg, 60 μ mol) and 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)quinolin-8-amine (Fluorochem, 19 mg, 80 μ mol). The title compound was isolated by means of flash chromatography (Biotage® HP-Sfär Silica HC Duo 20 μ m 10 g, gradient 22% to 100% EtOAc in hexane) to afford the title compound as a yellowish solid (24 mg, 66% yield).

^1H NMR (400 MHz, CDCl_3) δ 9.87 (s, 1H, NH), 8.69 (dd, $J = 7.6, 1.4$ Hz, 1H, H-7'), 8.25 – 8.15 (m, 2H, H-3',4'), 7.55 – 7.41 (m, $J = 7.9$ Hz, 2H, NH, H-5',6'), 6.88 – 6.73 (m, 4H, H_{Ar} , H-2,3,5,6), 6.10 (d, $J = 1.0$ Hz, 1H, H-10'), 3.99 (t, $J = 5.9$ Hz, 2H, CH_2), 3.75 (d, $J = 7.6$ Hz, 3H, OCH_3), 3.59 – 3.49 (m, 2H, CH_2), 3.46 (s, 2H, CH_2), 2.87 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.02 (p, $J = 6.3$ Hz, 2H, CH_2).

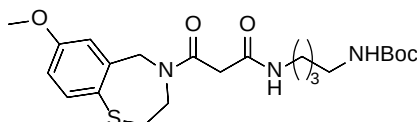
^{13}C NMR (101 MHz, CDCl_3) δ 166.1 (CO), 154.0 (CO), 153.0, 152.9, 151.2, 150.7, 141.7, 139.1, 136.5, 133.5, 126.3, 126.0, 122.4, 118.1, 115.8, 115.6, 114.8, 114.7, 110.4, 66.9 (OCH_3), 55.8 (CH_3), 45.2 (CH_3), 37.7 (CH_2), 37.6 (CH_2), 29.1 (CH_2), 15.6 (CH_2).

ESI-MS, positive mode: m/z (rel. int., %) = 510 (100) [$M+\text{Na}$] $^+$.

HRMS (m/z): [$M+\text{H}$] $^+$ calcd. for $\text{M} = \text{C}_{27}\text{H}_{29}\text{N}_3\text{O}_4$, 488.2292; found, 488.2295.

Compound 9

***tert*-butyl (2-(3-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)-3-oxopropanamido)ethyl)carbamate**



To the solution of **SKTT34** (50 mg, 0.18 mmol) in DMSO (5 ml), *O*-(*N*-succinimidyl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TSTU, 75 mg, 0.25 mmol) and 10 μ l Et_3N were added. After 10

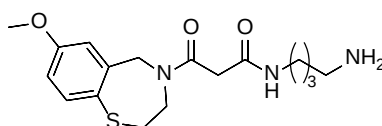
min, *N*-(*tert*-butoxycarbonyl)-1,4-diaminobutane (51 mg, 0.27 mmol) was added, and the reaction mixture was stirred for 3 h at rt. Then the volatiles were evaporated *in vacuo*, and the title compound was isolated by means of flash chromatography (Biotage® HP-Sfär Silica HC Duo 20 µm 10 g, gradient 22% to 100% MeOH in DCM) as a yellowish oil (74 mg, 94% yield).

¹H NMR (400 MHz, CDCl₃) 1:1 mixture of rotamers: δ 7.47 (d, *J* = 8.5 Hz, 0.5H), 7.47 (d, *J* = 8.5 Hz, 0.5H), 7.08 (d, *J* = 2.8 Hz, 0.5H), 7.01 (d, *J* = 2.8 Hz, 0.5H), 6.77 – 6.69 (m, 1H), 4.75 (s, 1H, NCH₂), 4.70 – 4.57 (m, 1H, NCH₂), 4.05 (br. s, 2H, CH₂), 3.82 (s, 1.5H, OCH₃) 3.80 (s, 1.5H, OCH₃), 3.33 – 3.02 (m, 6H, CH₂), 2.86 – 2.76 (m, 2H, CH₂), 1.75 – 1.57 (m, 2H, CH₂), 1.49 – 1.32 (m, 12H, CH₂, CH₃).

ESI-MS, positive mode: *m/z* (rel. int., %) = 452 (100) [*M*+H]⁺.

GM1938

N-(4-aminobutyl)-3-(7-methoxy-2,3-dihydrobenzo[1,4-*f*]thiazepin-4(5*H*)-yl)-3-oxopropanamide



74 mg (0.17 mmol) of **9** was dissolved in 10 % TFA/DCM mixture (1.5 ml), and the reaction mixture stirred at room temperature overnight. Then the solvent was evaporated *in vacuo*, and the title compound was isolated by preparative HPLC with gradient elution (B/A: 10/90 → 70/30). Yield 30 mg (50 %) of white solid.

¹H NMR (400 MHz, CD₃OD) 1:2 mixture of rotamers: δ 7.47 (d, *J* = 8.4 Hz, 0.33H), 7.42 (d, *J* = 8.4 Hz, 0.67H), 7.07 (d, *J* = 2.9 Hz, 0.67H), 7.04 (d, *J* = 2.9 Hz, 0.33H), 6.81 (dd, *J* = 8.4, 2.9 Hz, 0.33H), 6.74 (dd, *J* = 8.4, 2.9 Hz, 0.67H), 4.76 (s, 0.66H, NCH₂), 4.69 (s, 1.34H, NCH₂), 4.07 (br. s, 0.66H, CH₂), 4.01 (br. s, 1.34H, CH₂), 3.81 (s, 1H, OCH₃), 3.78 (s, 2H, OCH₃), 3.35 – 3.27 (m, 1.33H), 3.26 – 3.17 (m, 2.67H), 2.97 – 2.88 (m, 2H, CH₂), 2.83 (q, *J* = 4.7 Hz, 1.34H, CH₂), 2.78 (t, *J* = 5.0 Hz, 0.66H, CH₂), 1.77 – 1.49 (m, 4H, CH₂).

^{13}C NMR (101 MHz, CD_3OD) 1:2 mixture of rotamers: δ 213.2, 169.8, 169.5, 169.5, 168.8, 162.4, 161.0, 160.7, 144.5, 143.9, 135.5, 134.9, 128.1, 128.0, 118.5, 117.5, 113.9, 113.8, 56.0, 55.8, 55.2, 54.8, 53.5, 51.8, 41.8, 40.2, 39.5, 39.5, 36.5, 35.8, 34.3, 27.2, 25.6, 24.8, 22.9, 21.3, 13.9, 8.0.

ESI-MS, positive mode: m/z (rel. int., %) = 352 (100) $[M+\text{H}]^+$.

HRMS (m/z): $[M+\text{H}]^+$ calcd. for $\text{M} = \text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$, 352.1689; found, 352.1694.