Supporting Information

Tacrine-mefenamic acid hybrids for inhibition and of acetylcholinesterase

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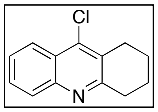
Content

1. Materials and instrumentation.

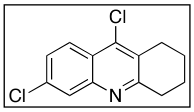
All reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. Reactions were monitored by TLC (Merck, Silica gel 60 F_{254}). Visualization was achieved using one or more of the following methods: UV absorption by fluorescence quenching, a cerium-molybdate stain ($(NH_4)_2Ce(NO_3)_6$ (5 g), $(NH_4)_6Mo_7O_{24}$•$4H_4O$ (120 g), H_2SO_4 (80 mL), H_2O (720 mL)), a ninhydrin stain (ninhydrin (1.5 g, *n*-butanol (100 mL), AcOH (3 mL)), a $KMnO_4$ stain ($KMnO_4$ (1.5 g), K_2CO_3 (10 g), NaOH (1.25 mL 10%), H_2O (200 mL)), a bromocresol green stain (bromocresol green (0.04 g), EtOH (100 mL, absolute), slowly drip NaOH (0.1 M) until the solution just turns pale blue), or Dragendorff's reagent (solution A: $BiNO_3$ (0.17 g) in AcOH (2 mL), H_2O (8 mL); solution B: KI (4 g) in AcOH (10 mL) and H_2O (20 mL). Solutions A and B were mixed and diluted to 100 mL with H_2O). Compounds were purified by SiO_2 flash chromatography (Dynamic Adsorbents Inc., Flash Silica Gel 32-63u). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance^{TM} DPX 300 or 500 spectrometers. Liquid chromatography mass spectrometry (LCMS) was performed on a Shimadzu LCMS-2019EV equipped with a SPD-20AV UV-Vis detector and a LC-20AD liquid chromatograph. IR measurements were taken by using a Perkin-Elmer SpectrumBX FT-IR system. Analyses by UV-Vis assays were done on a multimode SpectraMax M5 plate reader using 96-well plates (Fisher Scientific). Molecular modeling was performed using AutoDock 4.2 and Cygwin 1.7.

2. Methods (chemistry).

2.1. General procedure for the synthesis of 9-chlorotacrine derivatives.

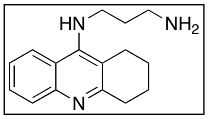


9-Chloro-1,2,3,4-tetrahydroacridine (3). The known compound **3**[1] was prepared using the following procedure. To a mixture of anthranilic acid (5.00 g, 36.5 mmol, 1 eq) and cyclohexanone (4.0 mL, 38.6 mmol, 1.1 eq) at 0 °C was carefully added $POCl_3$ (20 mL, 214.5 mmol, 5.9 eq). After being refluxed for 2 h, the reaction was cooled down to rt and concentrated under reduced pressure. The crude product was diluted with EtOAc (100 mL) and neutralized with a 10% aq. K_2CO_3 solution. The organic layer was washed with brine (2x100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Further purification by flash column chromatography (SiO_2; 5:1/hexane:EtOAc, R_f 0.59 (2:1/hexane:EtOAc)) gave **3** (7.30 g, 92%) as a light yellow powder: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 7.94 (d, 1H, J = 8.8 Hz), 7.62 (ddd, 1H, J_1 = 8.8 Hz, J_2 = 7.2 Hz, J_3 = 1.6 Hz), 7.48 (ddd, 1H, J_1 = 8.0 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz), 3.08 (t, 2H, J = 6.8 Hz), 2.95 (t, 2H, J = 6.8 Hz), 1.91 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 146.5, 141.5, 129.2, 128.8, 128.5, 126.5, 125.3, 123.6, 34.1, 27.4, 22.61, 22.57; *m/z* calcd for $C_{13}H_{12}ClN$: 217.07; found 218.15 $[M+H]^+$.

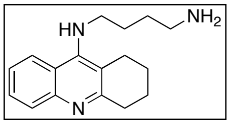


6,9-Dichloro-1,2,3,4-tetrahydroacridine (4). The known compound **4**[1] was prepared as described for the synthesis of **3**. Reaction of 2-amino-4-chlorobenzoic acid (5.00 g, 29.2 mmol, 1 eq), cyclohexanone (3.02 mL, 29.2 mmol, 1 eq), and $POCl_3$ (20 mL, 215 mmol, 5.9 eq) yielded, after purification by flash column chromatography (SiO_2; 5:1/hexane:EtOAc, R_f 0.76 (2:1/hexane:EtOAc)) **4** (6.62 g, 90%) as a light yellow powder: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, 1H, J = 9.0 Hz), 7.97 (d, 1H, J = 2.0 Hz), 7.47 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 3.11 (t, 2H, J = 6.4 Hz), 3.00 (t, 2H, J = 6.4 Hz), 1.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 147.0, 141.4, 135.2, 129.2, 127.6, 127.4, 125.2, 123.9, 34.2, 27.5, 22.5; *m/z* calcd for $C_{13}H_{11}Cl_2N$: 252.14; found 253.95 $[M+H]^+$.

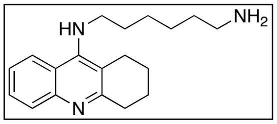
2.2. General procedure for attachment of amine linkers to tacrine and 6-chlorotacrine.



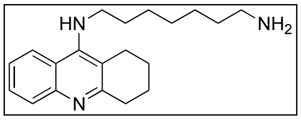
N^1-(1,2,3,4-Tetrahydroacridin-9-yl)propane-1,3-diamine (5a). 9-Chloro-1,2,3,4-tetrahydroacridine (**3**) (0.4 g, 1.84 mmol, 1 eq), 1,3-diaminopropane (0.7 mL, 8.38 mmol, 3.65 eq) and 1-pentanol (3 mL) were combined and heated to reflux for 48 h. The reaction was cooled to rt, diluted with CH_2Cl_2 (50 mL), and washed with 10% aq. KOH (2x50 mL), H_2O (2x50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.05) to afford **5a** (310 mg, 66%) as a yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (dd, 1H, J_1 = 8.6 Hz, J_2 = 0.8 Hz), 7.98 (d, 1H, J = 8.4 Hz), 7.56 (m, 1H), 7.33 (m, 1H), 3.68 (t, 2H, J = 6.5 Hz), 3.07 (m, 2H), 2.93 (t, 2H, J = 6.3 Hz), 2.70 (m, 2H), 2.34 (br s, 2H), 1.90 (m, 4H), 1.82 (p, 2H, J = 6.4 Hz), 1.45 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4, 151.0, 147.4, 128.6, 128.3, 123.5, 122.9, 120.2, 115.9, 48.1, 40.5, 34.4, 34.0, 25.1, 23.1, 22.8; *m/z* calcd for $C_{16}H_{21}N_3$: 255.17; found 256.00 $[M+H]^+$.



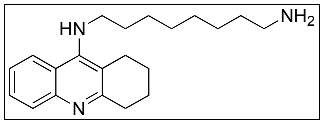
N^1-(1,2,3,4-Tetrahydroacridin-9-yl)butane-1,4-diamine (5b). Compound **5b** was prepared as described for the synthesis of **5a**. The reaction of 9-chloro-1,2,3,4-tetrahydroacridine (**3**) (0.5 g, 2.30 mmol, 1 eq), 1,4-diaminobutane (0.803 mL, 8.00 mmol, 3.48 eq), and 1-pentanol (3.5 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.05) **5b** (345 mg, 56%) as a yellow solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (t, 2H, *J* = 8.4 Hz), 7.35 (t, 1H, *J* = 7.6 Hz), 7.13 (t, 1H, *J* = 7.6 Hz), 3.89 (br s, 1H), 3.25 (t, 2H, *J* = 7.1 Hz), 2.87 (t, 2H, *J* = 6.0 Hz), 2.49 (m, 4H), 1.70 (m, 4H), 1.45 (p, 2H, *J* = 7.4 Hz), 1.28 (p, 2H, *J* = 7.4 Hz), 1.08 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.3, 150.5, 147.4, 128.7, 128.0, 123.3, 122.8, 120.1, 115.8, 49.1, 41.7, 34.0, 30.8, 29.0, 24.7, 22.9, 22.7; *m/z* calcd for $C_{17}H_{23}N_3$: 269.19; found 282.25 $[M+2Li]^+$.



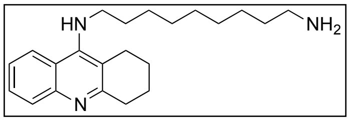
N^1-(1,2,3,4-Tetrahydroacridin-9-yl)hexane-1,6-diamine (5c). Compound **5c** was prepared as described for the synthesis of **5a**. The reaction of 9-chloro-1,2,3,4-tetrahydroacridine (**3**) (0.84 g, 2.30 mmol, 1 eq), 1,6-diaminohexane (2.31 mL, 15.9 mmol, 4.2 eq), and 1-pentanol (5 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.10) **5c** (452 mg, 56%) as a yellow solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.90 (d, 1H, *J* = 8.5 Hz), 7.85 (d, 1H, *J* = 8.6 Hz), 7.49 (t, 1H, *J* = 7.6 Hz), 7.28 (t, 1H, *J* = 7.6 Hz), 3.89 (br s, 1H), 3.41 (t, 2H, *J* = 7.1 Hz), 3.01 (m, 2H), 2.61 (m, 4H), 1.85 (m, 4H), 1.59 (m, 4H), 1.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.4, 150.7, 147.5, 128.8, 128.2, 123.5, 122.8, 120.2, 115.9, 49.4, 42.0, 34.1, 33.5, 31.7, 26.8, 26.6, 24.8, 23.0, 22.8; *m/z* calcd for $C_{19}H_{27}N_3$: 297.22; found 298.05 $[M+H]^+$.



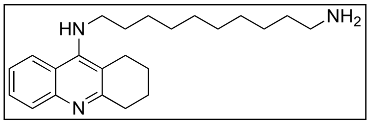
N^1-(1,2,3,4-Tetrahydroacridin-9-yl)heptane-1,7-diamine (5d). Compound **5d** was prepared as described for the synthesis of **5a**. The reaction of 9-chloro-1,2,3,4-tetrahydroacridine (**3**) (250 mg, 1.15 mmol, 1 eq), 1,7-diaminoheptane (449 mg, 3.45 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.13) **5d** (144 mg, 40%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, 1H, *J* = 8.5 Hz), 7.86 (d, 1H, *J* = 8.5 Hz), 7.50 (t, 1H, *J* = 7.4 Hz), 7.29 (t, 1H, *J* = 7.7 Hz), 3.93 (br s, 1H), 3.41 (t, 2H, *J* = 7.2 Hz), 3.01 (m, 2H), 2.65 (br s, 4H), 2.48 (br s, 2H), 1.86 (m, 4H), 1.59 (p, 2H, *J* = 7.0 Hz), 1.40 (br p, 2H), 1.32 (br p, 2H), 1.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4, 150.7, 147.5, 128.7, 128.2, 123.5, 122.9, 120.2, 115.8, 49.4, 41.9, 34.0, 33.1, 31.7, 29.2, 26.9, 26.7, 24.8, 23.0, 22.8; *m/z* calcd for $C_{20}H_{29}N_3$: 311.24; found 312.10 $[M+H]^+$.



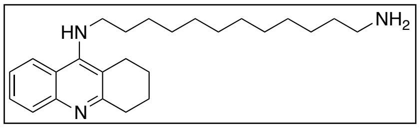
N^1-(1,2,3,4-Tetrahydroacridin-9-yl)octane-1,8-diamine (5e). Compound **5e** was prepared as described for the synthesis of **5a**. The reaction of 9-chloro-1,2,3,4-tetrahydroacridine (**3**) (250 mg, 1.15 mmol, 1 eq), 1,8-diaminooctane (498 mg, 3.45 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.10) **5e** (208 mg, 56%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.92 (d, 1H, *J* = 8.5 Hz), 7.87 (d, 1H, *J* = 8.4 Hz), 7.51 (t, 1H, *J* = 7.1 Hz), 7.30 (t, 1H, *J* = 7.3 Hz), 3.91 (br s, 1H), 3.41 (t, 2H, *J* = 6.9 Hz), 3.02 (m, 2H), 2.67 (m, 4H), 1.87 (m, 4H), 1.58 (p, 2H, *J* = 7.1 Hz), 1.44 (br p, 2H), 1.31 (br p, 2H), 1.25 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4, 150.7, 147.5, 128.8, 128.2, 123.5, 122.8, 120.2, 115.8, 49.4, 41.6, 34.1, 31.7, 29.3, 26.9, 26.8, 24.8, 23.1, 22.8; *m/z* calcd for $C_{21}H_{31}N_3$: 325.25; found 326.00 $[M+H]^+$.



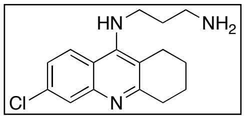
N^1-(1,2,3,4-Tetrahydroacridin-9-yl)nonane-1,9-diamine (5f). Compound **5f** was prepared as described for the synthesis of **5a**. The reaction of 9-chloro-1,2,3,4-tetrahydroacridine (**3**) (250 mg, 1.15 mmol, 1 eq), 1,9-diaminononane (546 mg, 3.45 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.08) **5f** (276 mg, 71%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, 1H, *J* = 8.5 Hz), 7.80 (d, 1H, *J* = 8.4 Hz), 7.42 (t, 1H, *J* = 7.3 Hz), 7.21 (t, 1H, *J* = 7.4 Hz), 3.91 (br s, 1H), 3.76 (br s, 1H) 3.34 (m, 2H) 2.94 (m, 2H), 2.61 (t, 2H, *J* = 7.0 Hz), 2.56 (m, 2H), 1.77 (br s, 4H), 1.50 (p, 2H, *J* = 7.1 Hz), 1.38 (br p, 2H), 1.23 (br p, 2H), 1.15 (br s, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.2, 150.8, 147.3, 128.4, 128.2, 123.4, 122.9, 120.1, 115.6, 49.3, 41.5, 33.9, 32.2, 31.6, 29.4, 29.22, 29.19, 26.79, 26.75, 24.7, 23.0, 22.7; *m/z* calcd for $C_{22}H_{33}N_3$: 339.27; found 340.10 $[M+H]^+$.



N^1-(1,2,3,4-Tetrahydroacridin-9-yl)decane-1,10-diamine (5g). Compound **5g** was prepared as described for the synthesis of **5a**. The reaction of 9-chloro-1,2,3,4-tetrahydroacridine (**3**) (250 mg, 1.15 mmol, 1 eq), 1,10-diaminodecane (595 mg, 3.45 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.09) **5g** (143 mg, 35%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (d, 1H, *J* = 8.5 Hz), 7.87 (d, 1H, *J* = 8.5 Hz), 7.51 (t, 1H, *J* = 7.4 Hz), 7.30 (t, 1H, *J* = 7.6 Hz), 3.92 (br s, 1H), 3.43 (t, 2H, *J* = 7.1 Hz) 3.02 (m, 2H), 2.64 (m, 4H), 1.87 (m, 4H), 1.80 (very br s, 2H), 1.60 (p, 2H, *J* = 7.4 Hz), 1.39 (br p, 2H), 1.33 (m, 2H), 1.24 (br s, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4, 150.7, 147.5, 128.8, 128.2, 123.5, 122.9, 120.2, 115.8, 49.5 , 42.1, 34.1, 33.5, 31.8, 29.49, 29.46, 29.43, 29.3, 26.91, 26.85, 24.8, 23.1, 22.8; *m/z* calcd for $C_{23}H_{35}N_3$: 353.28; found 354.15 $[M+H]^+$.

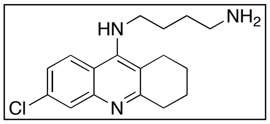


N^1-(1,2,3,4-Tetrahydroacridin-9-yl)dodecane-1,12-diamine (5h). Compound **5h** was prepared as described for the synthesis of **5a**. The reaction of 9-chloro-1,2,3,4-tetrahydroacridine (**3**) (250 mg, 1.15 mmol, 1 eq), 1,12-diaminododecane (691 mg, 3.45 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.11) **5h** (313 mg, 71%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (d, 1H, *J* = 8.5 Hz), 7.90 (d, 1H, *J* = 8.5 Hz), 7.54 (t, 1H, *J* = 7.6 Hz), 7.34 (t, 1H, *J* = 7.6 Hz), 3.96 (br s, 1H), 3.47 (t, 2H, *J* = 6.8 Hz) 3.06 (m, 2H), 2.71 (m, 2H), 2.67 (t, 2H, *J* = 7.1 Hz), 1.92 (m, 4H), 1.65 (p, 2H, *J* = 7.0 Hz), 1.39 (m, 4H), 1.26 (m, 16H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4, 150.8, 147.5, 128.8, 128.2, 123.5, 122.9, 120.2, 115.8, 49.6, 42.3, 34.1, 33.8, 31.8, 29.6, 29.56 , 29.53, 29.50, 29.41, 29.37, 26.94, 26.90, 24.8, 23.1, 22.8; *m/z* calcd for $C_{25}H_{39}N_3$: 381.31; found 382.10 $[M+H]^+$.

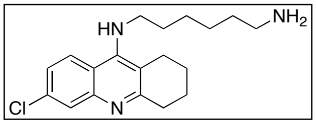


N^1-(6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)propane-1,3-diamine (6a). Compound **6a** was prepared as described for the synthesis of **5a**. The reaction of 6,9-dichloro-1,2,3,4-tetrahydroacridine (**4**) (756 mg, 3 mmol, 1 eq), 1,3-diaminopropane (1.00 mL, 12 mmol, 4 eq), and 1-pentanol (6 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.13), **6a** (703 mg, 81%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500

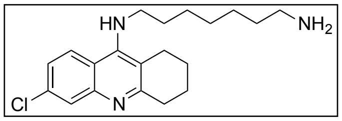
MHz) δ 7.96 (d, 1H, J = 9.1 Hz), 7.90 (d, 1H, J = 1.9 Hz), 7.27 (dd, 1H, J_1 = 9.1 Hz, J_2 = 1.9 Hz), 5.03 (br s, 1H), 3.65 (t, 2H, J = 6.4 Hz), 3.04 (br s, 2H), 2.94 (t, 2H, J = 6.4 Hz), 2.70 (br s, 2H), 1.92 (br s, 4H), 1.82 (p, 2H, J = 6.4 Hz), 1.58 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5, 151.1, 148.2, 133.9, 127.5, 124.7, 124.1, 118.3, 115.7, 48.5, 40.6, 34.0, 25.0, 23.0, 22.7; *m/z* calcd for $C_{16}H_{20}ClN_3$: 289.13; found 289.95 $[M+H]^+$.



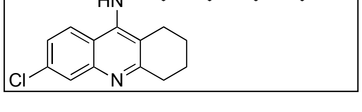
N^1-(6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)butane-1,4-diamine (6b). Compound **6b** was prepared as described for the synthesis of **5a**. The reaction of 6,9-dichloro-1,2,3,4-tetrahydroacridine (**4**) (756 mg, 3 mmol, 1 eq), 1,4-diaminobutane (1.21 mL, 12 mmol, 4 eq), and 1-pentanol (6 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.13) **6b** (758 mg, 83%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (d, 1H, J = 9.1 Hz), 7.87 (d, 1H, J = 1.5 Hz), 7.26 (dd, 1H, J_1 = 9.1 Hz, J_2 = 1.5 Hz), 4.07 (br s, 1H), 3.49 (t, 2H, J = 7.1 Hz), 3.02 (br s, 2H), 2.75 (t, 2H, J = 6.9 Hz), 2.67 (br s, 2H), 1.91 (bt t, 4H), 1.71 (p, 2H, J = 7.5 Hz), 1.55 (p, 2H, J = 7.3 Hz), 1.49 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.6, 150.7, 148.2, 133.9, 127.6, 124.6, 124.2, 118.5, 115.9, 49.5, 41.8, 34.1, 30.9, 29.2, 24.7, 22.9, 22.7; *m/z* calcd for $C_{17}H_{22}ClN_3$: 303.15; found 304.05 $[M+H]^+$.



N^1-(6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)hexane-1,6-diamine (6c). Compound **6c** was prepared as described for the synthesis of **5a**. The reaction of 6,9-dichloro-1,2,3,4-tetrahydroacridine (**4**) (756 mg, 3 mmol, 1 eq), 1,6-diaminohexane (1.74 mL, 12 mmol, 4 eq), and 1-pentanol (6 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.13), **6c** (830 mg, 83%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (d, 1H, J = 9.1 Hz), 7.87 (d, 1H, J = 1.5 Hz), 7.26 (dd, 1H, J_1 = 9.1 Hz, J_2 = 1.5 Hz), 3.98 (br s, 1H), 3.47 (t, 2H, J = 7.0 Hz), 3.02 (br s, 2H), 2.69 (t, 2H, J = 7.0 Hz), 2.65 (br s, 2H), 2.23 (br s, 2H), 1.91 (br t, 4H), 1.65 (p, 2H, J = 7.0 Hz), 1.46 (p, 2H, J = 7.3 Hz), 1.37 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5, 150.8, 148.1, 133.9, 127.5, 124.6, 124.2, 118.4, 115.7, 49.5, 41.9, 34.0, 33.2, 31.8, 26.8, 26.6, 24.6, 22.9, 22.6; *m/z* calcd for $C_{19}H_{26}ClN_3$: 331.18; found 331.95 $[M+H]^+$.

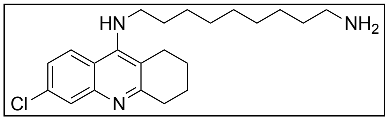


N^1-(6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)heptane-1,7-diamine (6d). Compound **6d** was prepared as described for the synthesis of **5a**. The reaction of 6,9-dichloro-1,2,3,4-tetrahydroacridine (**4**) (250 mg, 0.99 mmol, 1 eq), 1,7-diaminoheptane (388 mg, 2.98 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.11) **6d** (61 mg, 18%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, 1H, J = 9.3 Hz), 7.85 (s, 1H), 7.22 (dd, 1H, J_1 = 9.0 Hz, J_2 = 1.4 Hz), 3.93 (br s, 1H), 3.43 (m, 2H), 2.99 (br s, 2H), 2.64 (m, 4H), 1.88 (m, 4H), 1.62 (p, 2H, J = 7.0 Hz), 1.50 (br s, 2H), 1.38 (m, 4H), 1.29 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5, 150.7, 148.2, 133.8, 127.6, 124.6, 124.1, 118.4, 115.7, 49.6, 42.1, 34.1, 33.6, 31.7, 29.2, 26.87, 26.77, 24.6, 22.9, 22.7; *m/z* calcd for $C_{20}H_{28}ClN_3$: 345.20; found 345.95 $[M+H]^+$.

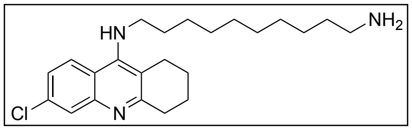


N^1-(6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)octane-1,8-diamine (6e). Compound **6e** was prepared as described for the synthesis of **5a**. The reaction of 6,9-dichloro-1,2,3,4-tetrahydroacridine (**4**)

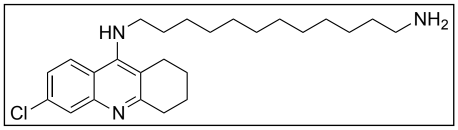
(250 mg, 0.99 mmol, 1 eq), 1,8-diaminooctane (429 mg, 2.98 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R$_f$ 0.13) **6e** (232 mg, 65%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, 1H, J = 9.4 Hz), 7.85 (s, 1H), 7.23 (dd, 1H, J_1 = 9.0 Hz, J_2 = 1.9 Hz), 3.93 (br s, 1H), 3.44 (m, 2H), 2.99 (br t, 2H), 2.64 (m, 4H), 1.88 (m, 4H), 1.71 (br s, 2H), 1.61 (p, 2H, J = 7.1 Hz), 1.40 (br p, 2H), 1.33 (br p, 2H), 1.27 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5, 150.8, 148.2, 133.8, 127.6, 124.6, 124.1, 118.4, 115.7, 49.6, 42.1, 34.1, 33.5, 31.8, 29.33, 29.28, 26.82, 26.75, 24.5, 22.9, 22.7; *m/z* calcd for $C_{21}H_{30}ClN_3$: 359.21; found 359.95 $[M+H]^+$.



N^1-(6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)nonane-1,9-diamine (6f). Compound **6f** was prepared as described for the synthesis of **5a**. The reaction of 6,9-dichloro-1,2,3,4-tetrahydroacridine (**4**) (250 mg, 0.99 mmol, 1 eq), 1,9-diaminononane (471 mg, 2.98 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R$_f$ 0.15) **6f** (237 mg, 64%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (d, 1H, J = 9.1 Hz), 7.83 (s, 1H), 7.20 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.0 Hz), 3.91 (br s, 1H), 3.41 (br t, 2H), 2.97 (br s, 2H), 2.64 (t, 2H, J = 7.1 Hz), 2.60 (br s, 2H), 1.86 (m, 4H), 1.78 (very br s, 2H), 1.59 (p, 2H, J = 7.0 Hz), 1.39 (br p, 2H), 1.31 (br p, 2H), 1.24 (br s, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5, 150.7, 148.2, 133.8, 127.6, 124.6, 124.0, 118.4, 115.6, 49.6, 42.1, 34.1, 33.4, 31.7, 29.4, 29.3, 29.2, 26.85, 26.81, 24.5, 22.9, 22.7; *m/z* calcd for $C_{22}H_{32}ClN_3$: 373.23; found 374.00 $[M+H]^+$.

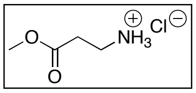


N^1-(6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)decane-1,10-diamine (6g). Compound **6g** was prepared as described for the synthesis of **5a**. The reaction of 6,9-dichloro-1,2,3,4-tetrahydroacridine (**4**) (250 mg, 0.99 mmol, 1 eq), 1,10-diaminodecane (513 mg, 2.98 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R$_f$ 0.15) **6g** (190 mg, 49%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, 1H, J = 7.0 Hz), 7.80 (s, 1H), 7.17 (dd, 1H, J = 9.0 Hz, J_2 = 2.1 Hz), 3.89 (br t, 1H), 3.39 (q, 2H, J = 6.7 Hz), 2.95 (br s, 2H), 2.60 (m, 4H), 1.83 (m, 4H), 1.56 (p, 2H, J = 7.1 Hz), 1.36 (br p, 4H), 1.30 (br p, 2H), 1.21 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5, 150.7, 148.2, 133.7, 127.6, 124.6, 124.0, 118.3, 115.6, 49.5, 42.2, 34.1, 33.7, 31.7, 29.45, 29.41, 29.3, 26.8, 24.5, 22.9, 22.6; *m/z* calcd for $C_{23}H_{34}ClN_3$: 387.24; found 388.05 $[M+H]^+$.

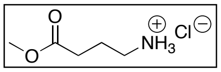


N^1-(6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)dodecane-1,12-diamine (6h). Compound **6h** was prepared as described for the synthesis of **5a**. The reaction of 6,9-dichloro-1,2,3,4-tetrahydroacridine (**4**) (250 mg, 0.99 mmol, 1 eq), 1,12-diaminododecane (596 mg, 2.98 mmol, 3 eq), and 1-pentanol (3 mL) yielded, after purification by flash column chromatography (SiO_2; 7:3/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R$_f$ 0.15) **6h** (207 mg, 50%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, 1H, J = 6.9 Hz), 7.79 (d, 1H, J = 1.8 Hz), 7.16 (dd, 1H, J_1 = 9.1 Hz, J_2 = 1.8 Hz), 3.88 (br t, 1H), 3.37 (br q, 2H), 2.94 (br s, 2H), 2.62 (t, 2H, J = 7.1 Hz), 2.56 (br s, 2H), 1.82 (m, 4H), 1.55 (p, 2H, J = 7.1 Hz), 1.36 (br p, 2H), 1.28 (br p, 2H), 1.18 (m, 16H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.4, 150.7, 148.2, 133.7, 127.6, 124.6, 123.9, 118.3, 115.6, 49.5, 42.0, 34.1, 33.4, 31.7, 29.57, 29.52, 29.48, 29.46, 29.45, 29.3, 26.8, 24.5, 22.9, 22.6; *m/z* calcd for $C_{25}H_{38}ClN_3$: 415.28; found 416.10 $[M+H]^+$.

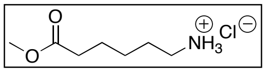
2.3. General procedure for esterification for the preparation of mefenamic acid linkers.



3-Methoxy-3-oxopropan-1-aminium chloride (7b). β-Alanine (3.00 g, 33.7 mmol, 1 eq) was dissolved in MeOH (60 mL). HCl (3.05 mL of 12.1 M, 37.1 mmol, 1.1 eq) was added dropwise. The reaction mixture was stirred for 18 h at rt before being concentrated under reduced pressure. The residue was redissolved in MeOH (50 mL) and concentrated under reduced pressure to yield **7b** (4.66 g, 99%) as a white powder: ^{1}H NMR (DMSO-d6, 300 MHz) δ 8.29 (s, 3H), 3.62 (s, 3H), 2.98 (t, 2H, *J* = 4.3 Hz), 2.73 (t, 2H, *J* = 4.3 Hz); ^{13}C NMR (DMSO-d6, 75 MHz) δ 171.2, 52.2, 35.0, 31.7; IR (CD_3OD cast): ν 3033 (NH_3^+), 1740 (C=O), 1597, 1570, 1526, 1424, 1349, 1228 (C-O), 1007, 797 cm^{-1}.

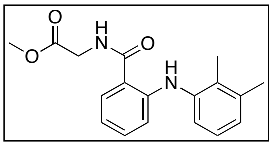


4-Methoxy-4-oxobutan-1-aminium chloride (7c). Compound **7c** was prepared as described for the synthesis of **7b**. Reaction of γ-aminobutyric acid (3.48 g, 33.7 mmol, 1 eq) and HCl (3.05 mL of 12 M, 37.1 mmol, 1.1 eq) yielded **7c** (5.12 g, 99%) as a white powder: ^{1}H NMR (DMSO-d6, 500 MHz) δ 8.26 (s, 3H), 3.59 (s, 3H), 2.77 (m, 2H), 2.43 (t, 2H, *J* = 7.5 Hz), 1.82 (p, 2H, *J* = 7.5 Hz); ^{13}C NMR (DMSO-d6, 75 MHz) δ 173.1, 51.9, 38.4, 30.6, 22.8; IR (CD_3OD cast): ν 2956 (NH_3^+), 1733 (C=O), 1600, 1518, 1430, 1386, 1295, 1215 (C-O), 1155, 970 cm^{-1}.

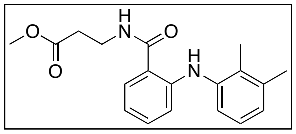


6-Methoxy-6-oxohexan-1-aminium chloride (7d). Compound **7d** was prepared as described for the synthesis of **7b**. Reaction of 6-aminocaproic acid (3.50 g, 26.7 mmol, 1 eq) and HCl (2.3 mL of 12.1 M, 27.8 mmol, 1.04 eq) yielded **7d** (4.80 g, 99%) as a white powder: ^{1}H NMR (DMSO-d6, 300 MHz) δ 8.07 (s, 3H), 3.59 (s, 3H), 2.72 (m, 2H), 2.30 (t, 2H, *J* = 7.3 Hz), 1.54 (m, 4H), 1.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9, 51.6, 39.7, 33.6, 27.2, 25.9, 24.2; IR (CD_3OD cast): ν 2950 (NH_3^+), 1732 (C=O), 1623, 1582, 1516, 1426, 1315, 1253, 1196 (C-O), 1155, 978 cm^{-1}.

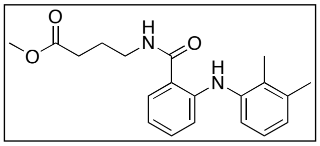
2.4. General procedure for attachment of linkers to mefenamic acid.



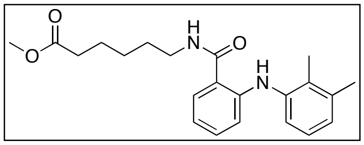
Methyl 2-(2-((2,3-dimethylphenyl)amino)benzamido)acetate (8a). Under anhydrous conditions, mefenamic acid (1.09 g, 4.5 mmol, 1 eq) and DCC (2.79 g, 13.5 mmol, 3 eq) were dissolved in DMF (45 mL). HOBt hydrate (1.82 g, 13.5 mmol, 3 eq) and DIPEA (5.49 mL, 31.5 mmol, 7 eq) were added, followed by glycine methyl ester hydrochloride (**7a**) (1.70 g, 13.5 mmol, 3 eq). The reaction progress was monitored by TLC for product formation (1:1/hexane:EtOAc, R_f 0.57). After stirring for 72 h at rt, the reaction mixture was diluted in EtOAc (150 mL). The organic mixture was successively washed with H_2O (90 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Further purification by flash column chromatography (SiO_2; 3:1/hexane:EtOAc, R_f 0.24) gave **8a** (793 mg, 56%) as an orange oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.18 (s, 1H), 7.53 (d, 1H, *J* = 7.9 Hz), 7.25 (t, 1H, *J* = 7.8 Hz), 7.18 (d, 1H, *J* = 7.9 Hz), 7.10 (t, 1H, *J* = 7.7 Hz), 6.99 (d, 1H, *J* = 7.4 Hz), 6.91 (d, 1H, *J* = 8.5 Hz), 6.73 (t, 1H, *J* = 7.5 Hz), 6.71 (br s, 1H), 4.26 (d, 2H, *J* = 5.0 Hz), 3.84 (s, 3H), 2.35 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 169.6, 147.5, 139.3, 138.1, 132.7, 131.2, 127.7, 125.9, 125.8, 121.4, 116.7, 115.6, 114.8, 52.5, 41.6, 20.7, 13.9; *m/z* calcd for $C_{18}H_{20}N_2O_3$: 312.15; found 312.90 $[M+H]^+$.



Methyl 3-(2-((2,3-dimethylphenyl)amino)benzamido)propanoate (8b). Compound **8b** was prepared as described for the synthesis of **8a**. The reaction of mefenamic acid (967 mg, 4.0 mmol, 1 eq), DCC (2.48 g, 12.0 mmol, 3 eq), DMF (40 mL), HOBt hydrate (1.62 g, 12.0 mmol, 3 eq), DIPEA (4.88 mL, 28.0 mmol, 7 eq) and **7b** (1.67 g, 12.0 mmol, 3 eq) was monitored by TLC for product formation (1:1/hexane:EtOAc, R_f 0.73). Purification by flash column chromatography (SiO_2; 3:1/hexane:EtOAc, R_f 0.35) gave **8b** (338 mg, 26%) as a yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.32 (s, 1H), 7.46 (d, 1H, J = 7.9 Hz), 7.24 (m, 2H), 7.11 (t, 1H, J = 7.7 Hz), 7.01 (s, 1H), 6.99 (d, 1H, J = 7.6 Hz), 6.96 (d, 1H, J = 8.5 Hz), 6.70 (t, 1H, J = 7.5 Hz), 3.75 (m, 5H), 2.69 (t, 2H, J = 6.0 Hz), 2.38 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 169.6, 147.2, 139.5, 138.1, 132.4, 130.9, 127.5, 125.8, 125.6, 120.9, 116.8, 116.5, 114.8, 51.9, 35.1, 33.8, 20.7, 13.9; *m/z* calcd for $C_{19}H_{22}N_2O_3$: 326.16; found 327.00 $[M+H]^+$.

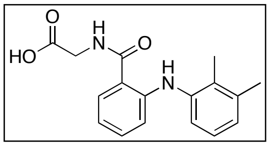


Methyl 4-(2-((2,3-dimethylphenyl)amino)benzamido)butanoate (8c). Compound **8c** was prepared as described for the synthesis of **8a**. The reaction of mefenamic acid (725 mg, 3 mmol, 1 eq), DCC (1.86 g, 9 mmol, 3 eq), DMF (30 mL), HOBt hydrate (1.22 g, 9 mmol, 3 eq), DIPEA (3.66 mL, 21 mmol, 7 eq) and **7c** (1.37 g, 9 mmol, 3 eq) was monitored by TLC for product formation (1:1/hexane:EtOAc, R_f 0.69). Purification by flash column chromatography (SiO_2; 3:1/hexane:EtOAc, R_f 0.30) gave **8c** (362 mg, 36%) as a yellow oil: ^1H NMR (DMSO-d6, 300 MHz) δ 9.62 (s, 1H), 8.58 (t, 1H, J = 4.9 Hz), 7.66 (d, 1H, J = 7.9 Hz), 7.22 (t, 1H, J = 7.9 Hz), 7.09 (d, 1H, J = 7.9 Hz), 7.04 (m, 1H), 6.89 (d, 1H, J = 7.4 Hz), 6.86 (d, 1H, J = 8.7 Hz), 6.72 (t, 1H, J = 7.4 Hz), 3.58 (s, 3H), 3.30 (q, 2H, J = 5.9 Hz), 2.38 (t, 2H, J = 7.3 Hz), 2.25 (s, 3H), 2.10 (s, 3H), 1.81 (p, 2H, J = 7.0 Hz); ^{13}C NMR (DMSO-d6, 75 MHz) δ 173.6, 169.6, 146.6, 139.7, 138.1, 132.3, 129.7, 129.1, 126.2, 125.4, 120.0, 117.5, 117.2, 114.3, 51.7, 38.8, 31.2, 24.8, 20.7, 13.9; *m/z* calcd for $C_{20}H_{24}N_2O_3$: 340.18; found 341.00 $[M+H]^+$.



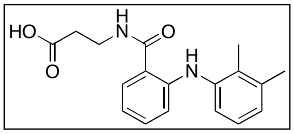
Methyl 6-(2-((2,3-dimethylphenyl)amino)benzamido)hexanoate (8d). Compound **8d** was prepared as described for the synthesis of **8a**. The reaction of mefenamic acid (725 mg, 3 mmol, 1 eq), DCC (1.86 g, 9 mmol, 3 eq), DMF (30 mL), HOBt hydrate (1.22 g, 9 mmol, 3 eq), DIPEA (3.66 mL, 21 mmol, 7 eq), and **7d** (1.63 g, 9 mmol, 3 eq) was monitored by TLC for product formation (1:1/hexane:EtOAc, R_f 0.73). Purification by flash column chromatography (SiO_2; 3:1/hexane:EtOAc, R_f 0.35) gave **8d** (389 mg, 35%) as an orange oil: ^1H NMR (DMSO-d6, 300 MHz) δ 9.61 (s, 1H), 8.54 (t, 1H, J = 5.4 Hz), 7.64 (d, 1H, J = 7.9 Hz), 7.22 (t, 1H, J = 7.8 Hz), 7.09 (d, 1H, J = 7.9 Hz), 7.04 (t, 1H, J = 7.7 Hz), 6.89 (d, 1H, J = 7.2 Hz), 6.86 (d, 1H, J = 8.4 Hz), 6.72 (t, 1H, J = 7.5 Hz), 3.57 (s, 3H), 3.25 (q, 2H, J = 6.5 Hz), 2.29 (t, 2H, J = 7.5 Hz), 2.26 (s, 3H), 2.10 (s, 3H), 1.54 (m, 4H), 1.31 (m, 2H); ^{13}C NMR (DMSO-d6, 75 MHz) δ 173.8, 169.4, 146.5, 139.8, 138.1, 132.2, 129.6, 129.0, 126.2, 125.4, 119.9, 117.8, 117.2, 114.4, 51.6, 39.2, 33.7, 29.2, 26.4, 24.7, 20.7, 13.9; *m/z* calcd for $C_{22}H_{28}N_2O_3$: 368.21; found 369.05 $[M+H]^+$.

2.5. General procedure for ester hydrolysis of mefenamic acid linkers.

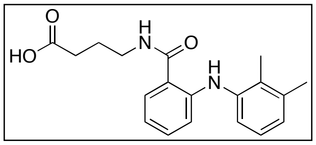


2-(2-((2,3-Dimethylphenyl)amino)benzamido)acetic acid (9a). 1 M NaOH (70 mL) was added to **8a** (793 mg, 2.4 mmol) dissolved in THF

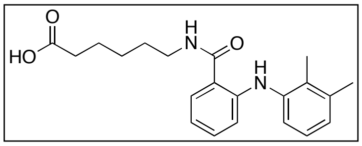
(30 mL). After stirring for 48 h at 40 °C, the reaction mixture was cooled to 0 °C and acidified to pH 1-2 using 1 M HCl. The product was extracted from the reaction mixture using EtOAc (2x200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield **9a** (759 mg, 99%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.12 (br s, 1H), 7.51 (d, 1H, *J* = 7.8 Hz), 7.25 (t, 1H, *J* = 7.8 Hz), 7.17 (d, 1H, *J* = 7.8 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), 6.99 (d, 1H, *J* = 7.4 Hz), 6.90 (d, 1H, *J* = 8.5 Hz), 6.73 (m, 2H), 4.29 (d, 2H, *J* = 3.0 Hz), 2.34 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0, 170.0, 147.6, 139.2, 138.1, 132.9, 131.3, 127.7, 126.0, 125.8, 121.5, 116.8, 115.3, 114.9, 41.6, 20.7, 13.9; *m/z* calcd for $C_{17}H_{18}N_2O_3$: 298.13; found 299.05 $[M+H]^+$.



3-(2-((2,3-Dimethylphenyl)amino)benzamido)propanoic acid (9b). Compound **9b** was prepared as described for the synthesis of **9a**. The reaction of **8b** (338 mg, 1.04 mmol, 1 eq) in THF (30 mL) with 1 M NaOH (70 mL) yielded **9b** (323 mg, 99%) as a pink powder: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.16 (s, 1H), 7.42 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.23 (m, 2H), 7.10 (t, 1H, *J* = 7.6 Hz), 6.98 (d, 1H, *J* = 7.4 Hz), 6.94 (d, 1H, *J* = 8.4 Hz), 6.90 (m, 1H), 6.70 (t, 1H, *J* = 7.3 Hz), 3.73 (q, 2H, *J* = 5.9 Hz), 2.74 (t, 2H, *J* = 5.8 Hz), 2.35 (s, 3H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.0, 169.8, 147.3, 139.4, 138.1, 132.5, 130.9, 127.4, 125.8, 125.7, 121.0, 116.8, 116.3, 114.9, 34.9, 33.7, 20.7, 13.9; *m/z* calcd for $C_{18}H_{20}N_2O_3$: 312.15; found 313.10 $[M+H]^+$.

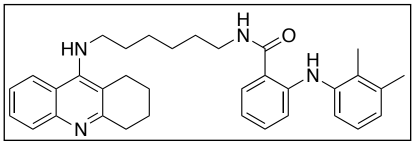


4-(2-((2,3-Dimethylphenyl)amino)benzamido)butanoic acid (9c). Compound **9c** was prepared as described for the synthesis of **9a**. The reaction of **8c** (360 mg, 1.06 mmol, 1 eq) in THF (30 mL) with 1 M NaOH (70 mL) yielded **9c** (346 mg, 99%) as a pink powder: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.19 (s, 1H), 7.41 (d, 1H, *J* = 6.8 Hz), 7.23 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.17 (d, 1H, *J* = 7.7 Hz), 7.08 (t, 1H, *J* = 7.7 Hz), 6.97 (d, 1H, *J* = 7.5 Hz), 6.93 (d, 1H, *J* = 8.5 Hz), 6.70 (t, 1H, *J* = 7.5 Hz), 6.49 (br t, 1H), 3.54 (q, 2H, *J* = 6.5 Hz), 2.52 (t, 2H, *J* = 6.9 Hz), 2.34 (s, 3H), 2.20 (s, 3H), 2.00 (p, 2H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.5, 170.1, 147.2, 139.4, 138.1, 132.4, 130.9, 127.3, 125.8, 125.7, 121.0, 116.8, 116.4, 114.9, 39.2, 31.5, 24.6, 20.7, 13.9; *m/z* calcd for $C_{19}H_{22}N_2O_3$: 326.16; found 327.00 $[M+H]^+$.



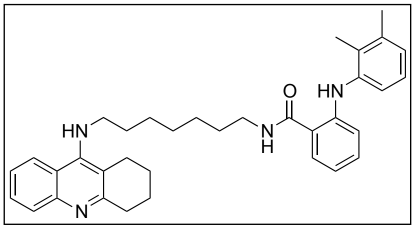
6-(2-((2,3-Dimethylphenyl)amino)benzamido)hexanoic acid (9d). Compound **9d** was prepared as described for the synthesis of **9a**. The reaction of **8d** (382 mg, 1.04 mmol, 1 eq) in THF (30 mL) with 1 M NaOH (70 mL) yielded **9d** (368 mg, 99%) as a pink powder: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.16 (s, 1H), 7.41 (d, 1H, *J* = 7.8 Hz), 7.23 (d, 1H, *J* = 7.3 Hz), 7.19 (t, 1H, *J* = 8.4 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.95 (d, 1H, *J* = 7.1 Hz), 6.94 (d, 1H, *J* = 8.5 Hz), 6.70 (t, 1H, *J* = 7.5 Hz), 6.28 (br t, 1H), 3.45 (q, 2H, *J* = 6.6 Hz), 2.38 (t, 2H, *J* = 7.4 Hz), 2.34 (s, 3H), 2.21 (s, 3H), 1.68 (m, 4H), 1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.3, 169.8, 147.0, 139.5, 138.1, 132.2, 130.8, 127.3, 125.7, 125.5, 120.7, 117.1, 116.8, 114.9, 39.6, 33.9, 29.3, 26.4, 24.3, 20.7, 13.9; *m/z* calcd for $C_{21}H_{26}N_2O_3$: 354.19; found 354.95 $[M+H]^+$.

2.6. General procedure for coupling of tacrine and 6-chlorotacrine to mefenamic acid.

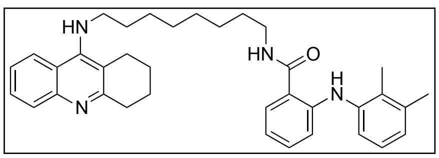


2-((2,3-Dimethylphenyl)amino)-N-(6-((1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)benzamide (10a).

Under anhydrous conditions, EDAC hydrochloride (40 mg, 0.209 mmol, 1.1 eq) and HOBt hydrate (32 mg, 0.209 mmol, 1.1 eq) were added to mefenamic acid (**2**) (46 mg, 0.190 mmol, 1 eq) in DMF (3 mL). After 3 min, **5c** (57 mg, 0.190 mmol, 1 eq) dissolved in DMF (1 mL) was added to the reaction mixture. After 5 min, Et_3N (47 μL, 0.342 mmol, 1.8 eq) was added and the reaction mixture was stirred for 72 h at rt before dilution with CH_2Cl_2 (100 mL). The organic mixture was successively washed with 1 M HCl (80 mL), 1 M NaOH (90 mL), H_2O (100 mL), and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Further purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.29) gave **10a** (97 mg, 74%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.20 (s, 1H), 7.97 (d, 1H, *J* = 8.5 Hz), 7.93 (d, 1H, *J* = 8.5 Hz), 7.57 (t, 1H, *J* = 7.4 Hz), 7.40 (d, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 7.6 Hz), 7.22 (t, 1H, *J* = 7.8 Hz), 7.18 (d, 1H, *J* = 7.9 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.96 (m, 2H), 6.70 (t, 1H, *J* = 7.4 Hz), 6.22 (br t, 1H), 3.99 (very br s, 1H), 3.51 (t, 2H, *J* = 7.2 Hz), 3.44 (q, 2H, *J* = 6.7 Hz), 3.08 (br t, 2H), 2.73 (br t, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 1.94 (m, 4H), 1.70 (p, 2H, *J* = 7.0 Hz), 1.65 (p, 2H, *J* = 6.9 Hz), 1.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 158.5, 150.7, 147.5, 147.0, 139.6, 138.1, 132.2, 130.8, 128.8, 128.3, 127.2, 125.7, 125.6, 123.7, 122.8, 120.8, 120.3, 117.1, 116.8, 116.0, 114.9, 49.4, 39.6, 34.1, 31.7, 29.6, 26.7, 26.6, 24.8, 23.1, 22.8, 20.7, 13.9; *m/z* calcd for $C_{34}H_{40}N_4O$: 520.32; found 521.25 $[M+H]^+$.

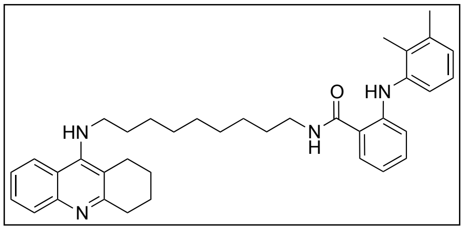


2-((2,3-Dimethylphenyl)amino)-*N*-(7-((1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)benzamide (10b). Compound **10b** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (57 mg, 0.235 mmol, 1 eq), EDAC hydrochloride (50 mg, 0.259 mmol, 1.1 eq), HOBt hydrate (40 mg, 0.259 mmol, 1.1 eq), **5d** (88 mg, 0.282 mmol, 1.2 eq), and Et_3N (59 μL, 0.423 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.32), **10b** (44 mg, 40%) as a pale yellow solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.22 (s, 1H), 7.97 (d, 1H, *J* = 8.5 Hz), 7.92 (d, 1H, *J* = 8.4 Hz), 7.56 (t, 1H, *J* = 7.0 Hz), 7.42 (d, 1H, *J* = 7.9 Hz), 7.35 (t, 1H, *J* = 7.2 Hz), 7.21 (t, 1H, *J* = 7.2 Hz), 7.18 (d, 1H, *J* = 7.9 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.95 (d, 2H, *J* = 7.8 Hz), 6.69 (t, 1H, *J* = 7.2 Hz), 6.35 (br t, 1H), 3.98 (very br s, 1H), 3.49 (t, 2H, *J* = 7.2 Hz), 3.42 (q, 2H, *J* = 7.0 Hz), 3.07 (br t, 2H), 2.72 (br t, 2H), 2.33 (s, 3H), 2.22 (s, 3H), 1.93 (m, 4H), 1.67 (p, 2H, *J* = 6.3 Hz), 1.60 (p, 2H, *J* = 6.3 Hz), 1.39 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 158.5, 150.8, 147.5, 147.0, 139.6, 138.0, 132.1, 130.7, 128.7, 128.3, 127.3, 125.7, 125.5, 123.6, 122.9, 120.7, 120.3, 117.2, 116.7, 115.9, 114.9, 49.4, 39.7, 34.1, 31.7, 29.6, 29.0, 26.9, 26.8, 24.8, 23.1, 22.8, 20.7, 13.9; *m/z* calcd for $C_{35}H_{42}N_4O$: 534.34; found 535.25 $[M+H]^+$.

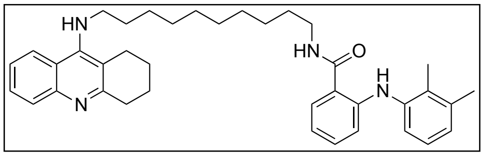


2-((2,3-Dimethylphenyl)amino-N-(8-((1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)benzamide (10c). Compound **10c** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (43 mg, 0.177 mmol, 1 eq), EDAC hydrochloride (37 mg, 0.194 mmol, 1.1 eq), HOBt hydrate (30 mg, 0.194 mmol, 1.1 eq), **5e** (69 mg, 0.212 mmol, 1.2 eq), and Et_3N (44 μL, 0.318 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.42), **10c** (17 mg, 17%) as a pale yellow oil: ^1H NMR

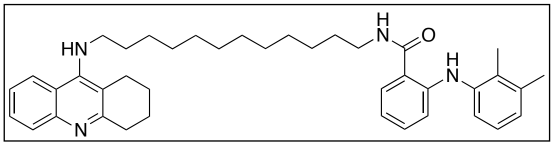
($CDCl_3$, 500 MHz) δ 9.21 (s, 1H), 8.00 (d, 2H, *J* = 8.6 Hz), 7.59 (t, 1H, *J* = 7.7 Hz), 7.43 (d, 1H, *J* = 7.3 Hz), 7.38 (t, 1H, *J* = 7.7 Hz), 7.22 (t, 1H, *J* = 7.8 Hz), 7.18 (d, 1H, *J* = 7.9 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.96 (d, 2H, *J* = 8.1 Hz), 6.70 (t, 1H, *J* = 7.4 Hz), 6.26 (br t, 1H), 4.21 (very br s, 1H), 3.56 (t, 2H, *J* = 7.1 Hz), 3.43 (q, 2H, *J* = 6.8 Hz), 3.12 (br t, 2H), 2.71 (br t, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 1.94 (m, 4H, *J* = 3.1 Hz), 1.70 (p, 2H, *J* = 7.1 Hz), 1.62 (p, 2H, *J* = 6.7 Hz), 1.37 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 157.5, 151.5, 147.0, 146.3, 139.6, 138.1, 132.1, 130.7, 128.9, 127.6, 127.3, 125.7, 125.5, 123.8, 123.1, 120.7, 119.6, 117.2, 116.8, 115.1, 114.9, 49.4, 39.8, 33.2, 31.7, 29.6, 29.2, 29.1, 26.9, 26.8, 24.6, 22.9, 22.5, 20.7, 13.9; *m/z* calcd for $C_{36}H_{44}N_4O$: 548.35; found 549.30 $[M+H]^+$.



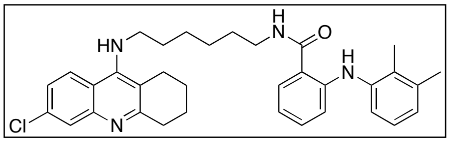
2-((2,3-Dimethylphenyl)amino)-*N*-(9-((1,2,3,4-tetrahydroacridin-9-yl)amino)nonyl)benzamide (10d). Compound **10d** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (45 mg, 0.185 mmol, 1 eq), EDAC hydrochloride (39 mg, 0.204 mmol, 1.1 eq), HOBt hydrate (31 mg, 0.204 mmol, 1.1 eq), **5f** (76 mg, 0.222 mmol, 1.2 eq), and Et_3N (46 μL, 0.333 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.37), **10d** (39 mg, 37%) as an orange solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.22 (s, 1H), 7.98 (d, 1H, *J* = 8.5 Hz), 7.93 (d, 1H, *J* = 8.4 Hz), 7.57 (t, 1H, *J* = 7.1 Hz), 7.43 (d, 1H, *J* = 7.8 Hz), 7.36 (t, 1H, *J* = 7.3 Hz), 7.22 (t, 1H, *J* = 7.3 Hz), 7.18 (d, 1H, *J* = 7.9 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.95 (d, 2H, *J* = 8.0 Hz), 6.70 (t, 1H, *J* = 7.4 Hz), 6.30 (br t, 1H), 4.00 (very br s, 1H), 3.51 (t, 2H, *J* = 7.2 Hz), 3.43 (q, 2H, *J* = 7.0 Hz), 3.09 (br s, 2H), 2.73 (br s, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 1.94 (br s, 4H), 1.67 (p, 2H, *J* = 7.2 Hz), 1.62 (p, 2H, *J* = 7.4 Hz), 1.39 (m, 4H), 1.32 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 158.3, 150.9, 147.4, 147.0, 139.6, 138.0, 132.1, 130.7, 128.6, 128.4, 127.3, 125.7, 125.5, 123.6, 122.9, 120.7, 120.2, 117.3, 116.7, 115.7, 114.9, 49.5, 39.8, 34.0, 31.8, 29.6, 29.4, 29.24, 29.16, 26.94, 26.86, 24.8, 23.1, 22.8, 20.7, 13.9; *m/z* calcd for $C_{37}H_{46}N_4O$: 562.37; found 563.45 $[M+H]^+$.



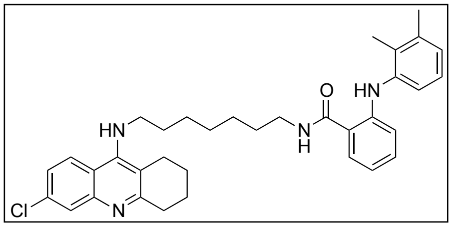
2-((2,3-Dimethylphenyl)amino-N-(10-((1,2,3,4-tetrahydroacridin-9-yl)amino)decyl)benzamide (10e). Compound **10e** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (35 mg, 0.146 mmol, 1 eq), EDAC hydrochloride (31 mg, 0.160 mmol, 1.1 eq), HOBt hydrate (24 mg, 0.160 mmol, 1.1 eq), **5g** (62 mg, 0.175 mmol, 1.2 eq), and Et_3N (37 μL, 0..263 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.42), **10e** (10 mg, 12%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.21 (s, 1H), 8.00 (d, 1H, *J* = 8.7 Hz), 7.98 (d, 1H, *J* = 11.5 Hz), 7.59 (t, 1H, *J* = 7.3 Hz), 7.42 (d, 1H, *J* = 7.8 Hz), 7.38 (t, 1H, *J* = 7.5 Hz), 7.22 (t, 1H, *J* = 7.6 Hz), 7.19 (d, 1H, *J* = 8.0 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.96 (d, 2H, *J* = 8.2 Hz), 6.70 (t, 1H, *J* = 7.4 Hz), 6.23 (br t, 1H), 4.11 (br s, 1H), 3.55 (t, 2H, *J* = 7.0 Hz), 3.44 (q, 2H, *J* = 6.8 Hz), 3.11 (br s, 2H), 2.72 (br s, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 1.95 (m, 4H), 1.69 (p, 2H, *J* = 7.1 Hz), 1.63 (p, 2H, *J* = 7.3 Hz), 1.40 (m, 4H), 1.31 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 157.9, 151.3, 147.0, 146.7, 139.6, 138.1, 132.1, 130.7, 128.7, 128.1, 127.3, 125.7, 125.5, 123.7, 123.0, 120.7, 119.8, 117.3, 116.7, 115.3, 114.9, 49.5, 39.8, 33.5, 31.8, 29.6, 29.41, 29.38, 29.28, 29.24, 27.0, 26.9, 24.7, 23.0, 22.6, 20.7, 13.9; *m/z* calcd for $C_{38}H_{48}N_4O$: 576.38; found 577.30 $[M+H]^+$.



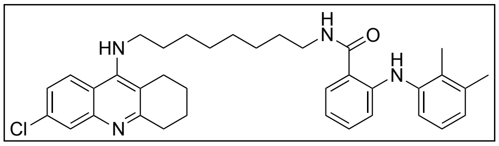
2-((2,3-Dimethylphenyl)amino)-*N*-(12-((1,2,3,4-tetrahydroacridin-9-yl)amino)dodecyl)benzamide (10f). Compound **10f** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (57 mg, 0.236 mmol, 1 eq), EDAC hydrochloride (50 mg, 0.259 mmol, 1.1 eq), HOBt hydrate (40 mg, 0.259 mmol, 1.1 eq), **5h** (108 mg, 0.283 mmol, 1.2 eq), and Et_3N (59 μL, 0.425 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.38), **10f** (27 mg, 19%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.21 (s, 1H), 7.99 (d, 1H, *J* = 8.5 Hz), 7.93 (d, 1H, *J* = 8.5 Hz), 7.57 (t, 1H, *J* = 7.3 Hz), 7.41 (d, 1H, *J* = 7.8 Hz), 7.36 (t, 1H, *J* = 7.5 Hz), 7.22 (t, 1H, *J* = 7.7 Hz), 7.19 (d, 1H, *J* = 8.0 Hz), 7.08 (t, 1H, *J* = 7.7 Hz), 6.95 (d, 2H, *J* = 8.8 Hz), 6.70 (t, 1H, *J* = 7.6 Hz), 6.27 (br t, 1H), 4.00 (very br s, 1H), 3.51 (t, 2H, *J* = 7.2 Hz), 3.44 (q, 2H, *J* = 6.8 Hz), 3.09 (br s, 2H), 2.73 (br s, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 1.94 (m, 4H), 1.68 (p, 2H, *J* = 7.4 Hz), 1.63 (p, 2H, *J* = 7.3 Hz), 1.40 (m, 4H), 1.29 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 158.4, 150.9, 147.4, 147.0, 139.6, 138.0, 132.1, 130.8, 128.6, 128.3, 127.3, 125.7, 125.5, 123.6, 122.9, 120.7, 120.2, 117.3, 116.7, 115.7, 114.9, 49.6, 39.9, 34.0, 31.8, 29.72, 29.67, 29.52, 29.51, 29.49, 29.4, 29.3, 27.0, 26.9, 24.8, 23.1, 22.8, 20.7, 13.9; *m/z* calcd for $C_{40}H_{52}N_4O$: 604.41; found 605.40 $[M+H]^+$.



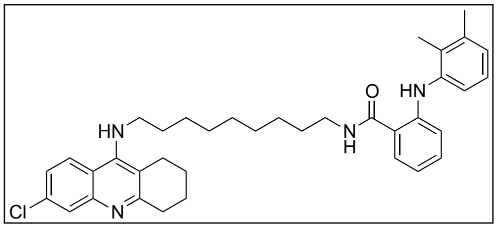
N-(6-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)-2-((2,3-dimethylphenyl)amino)benzamide (11a). Compound **11a** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (57 mg, 0.238 mmol, 1 eq), EDAC hydrochloride (41 mg, 0.262 mmol, 1.1 eq), HOBt hydrate (35 mg, 0.262 mmol, 1.1 eq), **6c** (95 mg, 0.285 mmol, 1.2 eq), and Et_3N (60 μL, 0.428 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.48), **11a** (97 mg, 74%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.21 (br s, 1H), 7.90 (d, 1H, *J* = 8.6 Hz), 7.89 (s, 1H), 7.40 (d, 1H, *J* = 7.9 Hz), 7.26 (d, 1H, *J* = 9.6 Hz), 7.21 (t, 1H, *J* = 7.4 Hz), 7.17 (d, 1H, *J* = 8.0 Hz), 7.07 (t, 1H, *J* = 7.7 Hz), 6.95 (d, 2H, *J* = 8.2 Hz), 6.67 (t, 1H, *J* = 7.5 Hz), 6.40 (br t, 1H), 3.99 (br s, 1H), 3.48 (br t, 2H), 3.43 (q, 2H, *J* = 6.7 Hz), 3.03 (br s, 2H), 2.66 (br s, 2H), 2.33 (s, 3H), 2.21 (s, 3H), 1.91 (br s, 4H), 1.65 (m, 4H), 1.44 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.8, 159.6, 150.8, 148.2, 147.0, 139.6, 138.1, 133.9, 132.2, 130.7, 127.6, 127.3, 125.7, 125.5, 124.6, 124.2, 120.6, 118.4, 117.2, 116.8, 115.8, 114.9, 49.5, 39.6, 34.1, 31.7, 29.6, 26.7, 26.6, 24.6, 22.9, 22.7, 20.7, 13.9; *m/z* calcd for $C_{34}H_{39}ClN_4O$: 554.28; found 555.20 $[M+H]^+$.



N-(7-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)-2-((2,3-dimethylphenyl)amino)benzamide (**11b**). Compound **11b** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (30 mg, 0.123 mmol, 1 eq), EDAC hydrochloride (26 mg, 0.136 mmol, 1.1 eq), HOBt hydrate (21 mg, 0.136 mmol, 1.1 eq), **6d** (57 mg, 0.148 mmol, 1.2 eq), and Et_3N (31 μL, 0.222 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.50), **11b** (29 mg, 41%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.20 (s, 1H), 7.91 (d, 1H, *J* = 7.1 Hz), 7.90 (d, 1H, *J* = 1.9 Hz), 7.41 (d, 1H, *J* = 7.8 Hz), 7.28 (dd, 1H, J_1 = 8.9 Hz, J_2 = 1.9 Hz), 7.22 (t, 1H, *J* = 7.6 Hz), 7.18 (d, 1H, *J* = 7.6 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.95 (d, 2H, *J* = 8.2 Hz), 6.70 (t, 1H, *J* = 7.5 Hz), 6.27 (br t, 1H), 3.98 (br s, 1H), 3.49 (t, 2H, *J* = 7.4 Hz), 3.43 (q, 2H, *J* = 6.8 Hz), 3.04 (br s, 2H), 2.68 (br s, 2H), 2.33 (s, 3H), 2.22 (s, 3H), 1.92 (m, 4H), 1.67 (p, 2H, *J* = 7.1 Hz), 1.62 (p, 2H, *J* = 6.9 Hz), 1.40 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 159.5, 150.9, 148.1, 147.0, 139.6, 138.1, 134.0, 132.2, 130.7, 127.5, 127.2, 125.7, 125.5, 124.6, 124.2, 120.7, 118.4, 117.2, 116.8, 115.8, 114.9, 49.6, 39.7, 34.0, 31.7, 29.6, 29.0, 26.9, 26.8, 24.6, 22.9, 22.7, 20.7, 13.9; *m/z* calcd for $C_{35}H_{41}ClN_4O$: 568.30; found 569.20 $[M+H]^+$.

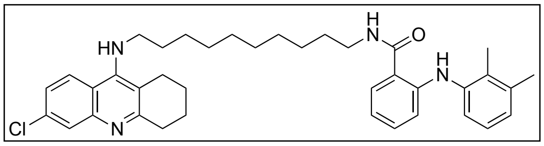


N-(8-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)-2-((2,3-dimethylphenyl)amino)benzamide (**11c**). Compound **11c** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (38 mg, 0.158 mmol, 1 eq), EDAC hydrochloride (33 mg, 0.173 mmol, 1.1 eq), HOBt hydrate (26 mg, 0.173 mmol, 1.1 eq), **6e** (68 mg, 0.189 mmol, 1.2 eq), and Et_3N (40 μL, 0.284 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.79), **11c** (24 mg, 26%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.20 (s, 1H), 7.92 (d, 1H, *J* = 9.6 Hz), 7.90 (s, 1H), 7.42 (d, 1H, *J* = 7.8 Hz), 7.28 (dd, 1H, J_1 = 9.0 Hz, J_2 = 1.9 Hz), 7.22 (t, 1H, *J* = 8.2 Hz), 7.18 (d, 1H, *J* = 7.9 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.96 (d, 2H, *J* = 8.2 Hz), 6.70 (t, 1H, *J* = 7.5 Hz), 6.26 (br t, 1H), 3.98 (br s, 1H), 3.49 (t, 2H, *J* = 7.1 Hz), 3.43 (q, 2H, *J* = 6.6 Hz), 3.04 (br s, 2H), 2.68 (br s, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 1.93 (m, 4H), 1.67 (p, 2H, *J* = 7.3 Hz), 1.62 (p, 2H, *J* = 7.1 Hz), 1.38 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 159.5, 150.9, 148.2, 147.0, 139.6, 138.1, 134.0, 132.1, 130.7, 127.6, 127.2, 125.7, 125.5, 124.7, 124.2, 120.7, 118.4, 117.2, 116.7, 115.7, 114.9, 49.6, 39.8, 34.0, 31.8, 29.6, 29.20, 29.16, 26.9, 26.8, 24.6, 22.9, 22.7, 20.7, 13.9; *m/z* calcd for $C_{36}H_{43}ClN_4O$: 582.31; found 583.20 $[M+H]^+$.

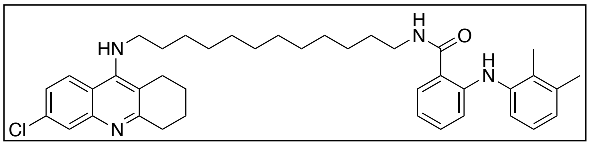


N-(9-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)nonyl)-2-(2,3-dimethylphenyl)amino)benzamide (11d). Compound **11d** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (38 mg, 0.159 mmol, 1 eq), EDAC hydrochloride (34 mg, 0.175 mmol, 1.1 eq), HOBt hydrate (27 mg, 0.175 mmol, 1.1 eq), **6f** (71 mg, 0.191 mmol, 1.2 eq), and Et_3N (40 μL, 0.287 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.53), **11d** (42 mg, 44%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.23 (s, 1H), 7.91 (d, 1H, *J* = 10.6 Hz), 7.90 (s, 1H), 7.42 (d, 1H *J* = 7.8 Hz), 7.27 (d, 1H, *J* = 10.7 Hz), 7.21 (t, 1H, *J* = 7.5 Hz), 7.18 (d, 1H, *J* = 8.5 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 6.95 (d, 2H, *J* = 8.1 Hz), 6.68 (t, 1H, *J* = 7.5 Hz), 6.36 (br t, 1H), 4.01 (br s, 1H), 3.49 (t, 2H, *J* = 6.9 Hz), 3.43 (q, 2H, *J* = 6.8 Hz), 3.03 (br s, 2H), 2.67 (br s, 2H), 2.33 (s, 3H), 2.22 (s, 3H), 1.92 (m, 4H), 1.68-1.58 (m, 4H), 1.35 (m, 12H);

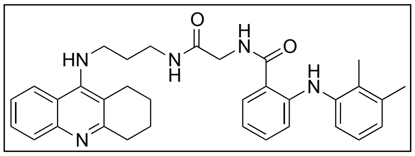
^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 159.4, 150.9, 148.1, 147.0, 139.6, 138.0, 134.0, 132.1, 130.7, 127.5, 127.3, 125.7, 125.5, 124.7, 124.2, 120.7, 118.4, 117.3, 116.7, 115.6, 114.9, 49.6, 39.8, 34.0, 31.8, 29.6, 29.4, 29.22, 29.16, 26.9, 26.8, 24.6, 22.9, 22.7, 20.7, 13.9; *m/z* calcd for $C_{37}H_{45}ClN_4O$: 596.32; found 597.20 $[M+H]^+$.



N-(10-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)decyl)-2-((2,3-dimethylphenyl)amino)benzamide (11e). Compound **11e** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) 35 mg, 0.146 mmol, 1 eq), EDAC hydrochloride (31 mg, 0.160 mmol, 1.1 eq), HOBt hydrate (24 mg, 0.160 mmol, 1.1 eq), **6g** (68 mg, 0.175 mmol, 1.2 eq), and Et_3N (37 µL, 0.263 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.69), **11e** (35 mg, 39%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.21 (s, 1H), 7.93 (d, 1H, *J* = 9.5 Hz), 7.92 (d, 1H, *J* = 2.1 Hz), 7.42 (d, 1H, *J* = 7.8 Hz), 7.28 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.1 Hz), 7.22 (t, 1H, *J* = 7.6 Hz), 7.18 (d, 1H, *J* = 8.0 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.95 (d, 2H, *J* = 8.2 Hz), 6.69 (t, 1H, *J* = 7.4 Hz), 6.30 (br t, 1H), 4.09 (very br s, 1H), 3.52 (t, 2H, *J* = 7.2 Hz), 3.44 (q, 2H, *J* = 6.8 Hz), 3.04 (br s, 2H), 2.67 (br s, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 1.93 (m, 4H), 1.67 (p, 2H, *J* = 7.4 Hz), 1.62 (p, 2H, *J* = 7.3 Hz), 1.38 (m, 4H), 1.30 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 159.1, 151.1, 147.7, 147.0, 139.6, 138.0, 134.2, 132.1, 130.7, 127.3, 127.1, 125.7, 125.5, 124.7, 124.3, 120.7, 118.2, 117.3, 116.7, 115.4, 114.9, 49.6, 39.8, 33.7, 31.8, 29.6, 29.40, 29.38, 29.26, 29.24, 27.0, 26.8, 24.5, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{38}H_{47}ClN_4O$: 610.34; found 611.30 $[M+H]^+$.

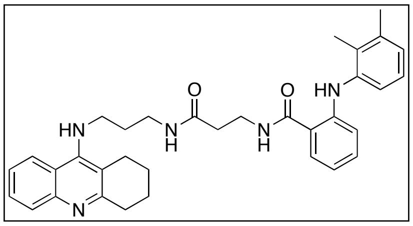


N-(12-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)dodecyl)-2-((2,3-dimethylphenyl)amino)benzamide (11f). Compound **11f** was prepared as described for the synthesis of **10a**. The reaction of mefenamic acid (**2**) (32 mg, 0.131 mmol, 1 eq), EDAC hydrochloride (28 mg, 0.144 mmol, 1.1 eq), HOBt hydrate (22 mg, 0.144 mmol, 1.1 eq), **6h** (66 mg, 0.157 mmol, 1.2 eq), and Et_3N (33 µL, 0..234 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.51), **11f** (43 mg, 55%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.22 (s, 1H), 7.91 (d, 1H, *J* = 9.3 Hz), 7.90 (s, 1H), 7.41 (d, 1H, *J* = 7.8 Hz), 7.28 (d, 1H, *J* = 9.0 Hz), 7.21 (t, 1H, *J* = 7.5 Hz), 7.18 (d, 1H, *J* = 8.6 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.95 (d, 2H, *J* = 8.2 Hz), 6.69 (t, 1H, *J* = 7.4 Hz), 6.31 (br t, 1H), 3.99 (br s, 1H), 3.50 (t, 2H, *J* = 6.9 Hz), 3.44 (q, 2H, *J* = 6.6 Hz), 3.04 (br s, 2H), 2.68 (br s, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 1.93 (m, 4H), 1.69-1.60 (m, 4H), 1.33 (m, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 159.5, 150.9, 148.2, 147.0, 139.6, 138.0, 134.0, 132.1, 130.7, 127.6, 127.3, 125.7, 125.5, 124.7, 124.2, 120.7, 118.4, 117.3, 116.7, 115.6, 114.9, 49.6, 39.9, 34.1, 31.8, 29.7, 29.53, 29.49, 29.3, 27.0, 26.9, 24.6, 23.0, 22.7, 20.7, 13.9; *m/z* calcd for $C_{40}H_{51}ClN_4O$: 638.37; found 639.35 $[M+H]^+$.

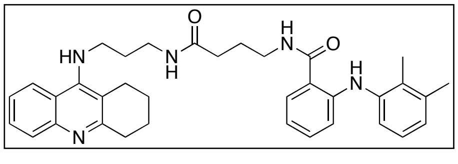


2-((2,3-Dimethylphenyl)amino)-*N*-(2-oxo-2-((3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)ethyl)benzamide (12a). Compound

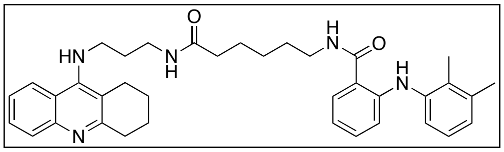
12a was prepared as described for the synthesis of **10a**. The reaction of **9a** (78 mg, 0.261 mmol, 1 eq), EDAC hydrochloride (55 mg, 0.287 mmol, 1.1 eq), HOBt hydrate (44 mg, 0.287 mmol, 1.1 eq), **5a** (80 mg, 0.313 mmol, 1.2 eq), and Et_3N (65 μL, 0.470 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.28), **12a** (38 mg, 41%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 8.00 (d, 1H, *J* = 8.4 Hz), 7.93 (d, 1H, *J* = 8.4 Hz), 7.55 (t, 1H, *J* = 7.5 Hz), 7.51 (d, 1H, *J* = 7.5 Hz), 7.35 (t, 1H, *J* = 7.5 Hz), 7.22 (t, 2H, *J* = 7.2 Hz), 7.12 (d, 1H, *J* = 7.8 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 6.97 (d, 1H, *J* = 7.3 Hz), 6.88 (d, 1H, *J* = 8.5 Hz), 6.84 (br t, 1H), 6.65 (t, 1H, *J* = 7.4 Hz), 4.91 (br s, 1H), 4.14 (d, 2H, *J* = 5.3 Hz), 3.52 (m, 2H), 3.48 (q, 2H, *J* = 6.2 Hz), 3.05 (m, 2H), 2.71 (m, 2H), 2.32 (s, 3H), 2.19 (s, 3H), 1.88 (m, 4H), 1.83 (p, 2H, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 170.0, 151.1, 147.6, 146.3, 139.2, 138.1, 136.4, 132.9, 131.1, 129.9, 128.7, 127.8, 126.0, 125.9, 124.1, 122.6, 121.3, 120.0, 116.9, 116.3, 115.3, 115.0, 45.4, 43.7, 37.0, 33.4, 31.2, 25.0, 22.9, 22.5, 20.7, 13.9; *m/z* calcd for $C_{33}H_{37}N_5O_2$: 535.29; found 536.25 $[M+H]^+$.



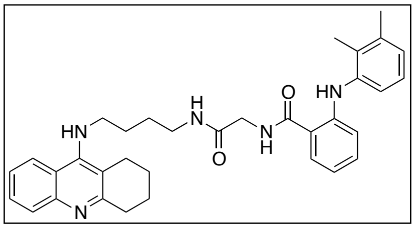
2-((2,3-Dimethylphenyl)amino)-*N*-(3-oxo-3-((3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)propyl)benzamide (12b). Compound **12b** was prepared as described for the synthesis of **10a**. The reaction of **9b** (83 mg, 0.264 mmol, 1 eq), EDAC hydrochloride (56 mg, 0.291 mmol, 1.1 eq), HOBt hydrate (44 mg, 0.291 mmol, 1.1 eq), **5a** (80 mg, 0.317 mmol, 1.2 eq), and Et_3N (66 μL, 0.474 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.19), **12b** (46 mg, 32%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.30 (s, 1H), 7.99 (d, 1H, *J* = 8.5 Hz), 7.90 (d, 1H, *J* = 8.5 Hz), 7.54 (t, 1H, *J* = 7.6 Hz), 7.45 (d, 1H, *J* = 7.9 Hz), 7.33 (m, 2H), 7.20 (t, 1H, *J* = 7.8 Hz), 7.16 (d, 1H, *J* = 7.9 Hz), 7.07 (t, 1H, *J* = 7.7 Hz), 6.96 (d, 1H, *J* = 7.4 Hz), 6.93 (d, 1H, *J* = 8.5 Hz), 6.64 (m, 2H), 4.78 (br t, 1H,), 3.74 (q, 2H, *J* = 5.9 Hz), 3.48 (q, 2H, *J* = 6.2 Hz), 3.42 (q, 2H, *J* = 6.3 Hz), 3.05 (t, 2H, *J* = 5.9 Hz), 2.73 (t, 2H, *J* = 5.7 Hz), 2.56 (t, 2H, *J* = 5.9 Hz), 2.32 (s, 3H), 2.20 (s, 3H), 1.89 (m, 4H), 1.79 (p, 2H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 169.9, 158.3, 150.7, 147.2, 147.0, 139.5, 138.1, 132.4, 130.8, 128.5, 128.3, 127.6, 125.8, 125.6, 123.9, 122.6, 120.8, 120.3, 116.9, 116.44, 116.42, 114.9, 45.4, 36.7, 35.8, 35.5, 33.8, 31.4, 25.1, 23.0, 22.7, 20.7, 13.9; *m/z* calcd for $C_{34}H_{39}N_5O_2$: 549.31; found 550.20 $[M+H]^+$.



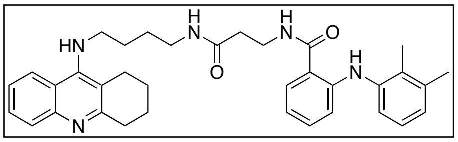
2-((2,3-Dimethylphenyl)amino)-N-(4-oxo-4-((3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)butyl)benzamide (12c). Compound **12c** was prepared as described for the synthesis of **10a**. The reaction of **9c** (85 mg, 0.261 mmol, 1 eq), EDAC hydrochloride (55 mg, 0.287 mmol, 1.1 eq), HOBt hydrate (44 mg, 0.287 mmol, 1.1 eq), **5a** (80 mg, 0.313 mmol, 1.2 eq), and Et_3N (65 μL, 0.470 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.19), **12c** (52 mg, 35%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.30 (s, 1H), 8.02 (d, 1H, *J* = 8.2 Hz), 7.90 (d, 1H, *J* = 8.2 Hz), 7.54 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz), 7.50 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.3 Hz), 7.33 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 7.1 Hz, J_3 = 1.0 Hz), 7.18 (m, 3H), 7.07 (t, 1H, *J* = 7.7 Hz), 6.95 (m, 2H), 6.85 (t, 1H, *J* = 5.9 Hz), 6.67 (m, 1H), 4.83 (br t, 1H), 3.50 (m, 4H), 3.41 (q, 2H, *J* = 6.3 Hz), 3.04 (t, 2H, *J* = 6.1 Hz), 2.74 (t, 2H, *J* = 5.9 Hz), 2.35 (t, 2H, *J* = 6.5 Hz), 2.32 (s, 3H), 2.20 (s, 3H), 1.97 (p, 2H, *J* = 6.3 Hz), 1.89 (m, 4H), 1.79 (p, 2H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 170.3, 158.3, 150.7, 147.1, 147.0, 139.5, 138.1, 132.3, 130.7, 128.5, 128.3, 127.6, 125.8, 125.6, 123.9, 122.7, 120.7, 120.3, 116.9, 116.6, 116.4, 114.9, 45.4, 39.4, 36.7, 34.0, 33.8, 31.4, 25.4, 25.1, 23.0, 22.7, 20.7, 13.9; *m/z* calcd for $C_{35}H_{41}N_5O_2$: 563.33; found 564.30 $[M+H]^+$.



2-((2,3-Dimethylphenyl)amino)-N-(6-oxo-6-((3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)hexyl)benzamide (12d). Compound **12d** was prepared as described for the synthesis of **10a**. The reaction of **9d** (104 mg, 0.294 mmol, 1 eq), EDAC hydrochloride (62 mg, 0.323 mmol, 1.1 eq), HOBt hydrate (50 mg, 0.323 mmol, 1.1 eq), **5a** (90 mg, 0.352 mmol, 1.2 eq), and Et_3N (73 μL, 0.529 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.19), **12d** (58 mg, 33%) as a pale yellow: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.24 (s, 1H), 8.04 (d, 1H, *J* = 8.5 Hz), 7.89 (d, 1H, *J* = 8.4 Hz), 7.53 (d, 1H, *J* = 7.2 Hz), 7.49 (t, 1H, *J* = 9.0 Hz), 7.32 (t, 1H, *J* = 7.6 Hz), 7.15 (m, 2H), 7.04 (t, 1H, *J* = 7.6 Hz), 6.91 (m, 2H), 6.82 (t, 1H, *J* = 5.5 Hz), 6.76 (t, 1H, *J* = 5.8 Hz), 6.62 (t, 1H, *J* = 7.5 Hz), 5.30 (br s, 1H), 3.50 (m, 2H), 3.38 (m, 4H), 3.02 (m, 2H), 2.71 (m, 2H), 2.30 (s, 3H), 2.23 (m, 2H), 2.21 (s, 3H), 1.86 (m, 4H), 1.76-1.58 (m, 6H), 1.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.2, 169.9, 157.4, 151.4, 146.9, 146.0, 139.6, 138.1, 132.1, 130.6, 128.9, 127.6, 127.1, 125.7, 125.5, 124.0, 123.0, 120.5, 119.7, 117.1, 116.8, 115.6, 114.8, 45.0, 39.4, 36.34, 36.28, 33.1, 31.4, 29.1, 26.4, 25.2, 25.0, 22.9, 22.5, 20.7, 13.9; *m/z* calcd for $C_{37}H_{45}N_5O_2$: 591.36; found 592.35 $[M+H]^+$.

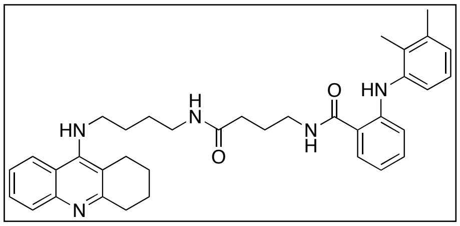


2-((2,3-Dimethylphenyl)amino)-*N*-(2-oxo-2-((4-((1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)amino)ethyl)benzamide (12e). Compound **12e** was prepared as described for the synthesis of **10a**. The reaction of **9a** (83 mg, 0.278 mmol, 1 eq), EDAC hydrochloride (59 mg, 0.306 mmol, 1.1 eq), HOBt hydrate (47 mg, 0.306 mmol, 1.1 eq), **5b** (90 mg, 0.334 mmol, 1.2 eq), and Et_3N (70 μL, 0.500 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.29), **12e** (54 mg, 36%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.23 (s, 1H), 7.91 (t, 2H, *J* = 9.1 Hz), 7.57 (d, 2H, *J* = 6.6 Hz), 7.53 (t, 1H, *J* = 7.2 Hz), 7.31 (t, 1H, *J* = 7.3 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 7.12 (d, 1H, *J* = 7.9 Hz), 7.05 (t, 2H, *J* = 7.3 Hz), 6.95 (d, 1H, *J* = 7.4 Hz), 6.86 (d, 1H, *J* = 8.4 Hz), 6.65 (t, 1H, *J* = 7.3 Hz), 4.10 (d, 3H, *J* = 5.2 Hz), 3.46 (br s, 2H), 3.31 (q, 2H, *J* = 6.6 Hz), 3.03 (t, 2H, *J* = 5.4 Hz), 2.64 (t, 2H, *J* = 5.9 Hz), 2.29 (s, 3H), 2.15 (s, 3H), 1.87 (m, 4H), 1.66 (m, 2H), 1.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 169.4, 158.1, 150.9, 147.6, 146.9, 139.3, 138.1, 132.8, 131.2, 128.6, 128.00, 127.98, 126.0, 125.9, 123.8, 122.9, 121.4, 120.1, 116.8, 116.0, 115.4, 114.8, 48.8, 43.7, 39.2, 33.6, 28.8, 27.0, 24.8, 22.9, 22.6, 20.6, 13.9; *m/z* calcd for $C_{34}H_{39}N_5O_2$: 549.31; found 550.25 $[M+H]^+$.

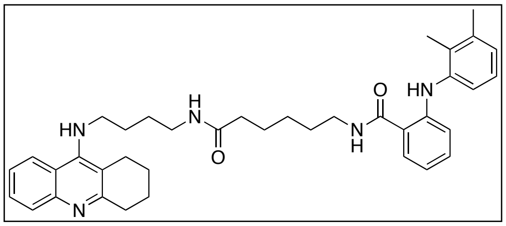


2-((2,3-Dimethylphenyl)amino)-N-(3-oxo-3-((4-((1,2,3,4-tetrahydroacridin-9-

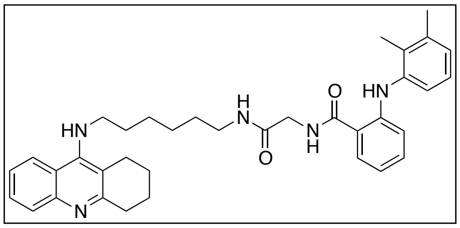
yl)amino)butyl)amino)propyl)benzamide (12f). Compound **12f** was prepared as described for the synthesis of **10a**. The reaction of **9b** (75 mg, 0.2404 mmol, 1 eq), EDAC hydrochloride (50.7 mg, 0.2644 mmol, 1.1 eq), HOBt hydrate (40.5 mg, 0.2644 mmol, 1.1 eq), **5b** (127.2 mg, .4722 mmol, 1.96 eq), and Et$_3$N (60 μL, 0.4327 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.19), **12f** (65 mg, 48%) as a pink powder: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 9.32 (s, 1H), 7.92 (d, 1H, J = 6.0 Hz), 7.90 (d, 1H, J = 7.1 Hz), 7.53 (t, 1H, J = 7.6 Hz), 7.46 (d, 1H, J = 7.9 Hz), 7.40 (t, 1H, J = 5.6 Hz), 7.32 (t, 1H, J = 7.7 Hz), 7.18 (t, 1H, J = 7.0 Hz), 7.14 (d, 1H, J = 5.0 Hz), 7.05 (t, 1H, J = 7.7 Hz), 6.93 (d, 1H, J = 4.9 Hz), 6.91 (d, 1H, J = 8.4 Hz), 6.65 (t, 1H, J = 7.5 Hz), 6.60 (t, 1H, J = 5.9 Hz), 4.17 (br s, 1H), 3.69 (q, 2H, J = 5.8 Hz), 3.46 (m, 2H), 2.28 (q, 2H, J = 6.3 Hz), 3.03 (br t, 2H), 2.64 (br t, 2H), 2.51 (t, 2H, J = 5.8 Hz), 2.30 (s, 3H), 2.18 (s, 3H), 1.87 (m, 4H), 1.64 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.9, 169.8, 157.8, 151.0, 147.2, 146.6, 139.5, 138.1, 132.3, 130.7, 128.7, 127.8, 127.7, 125.8, 125.6, 123.9, 122.9, 120.7, 119.9, 116.8, 116.5, 115.8, 114.8, 48.7, 39.1, 35.8, 35.4, 33.5, 28.9, 27.0, 24.7, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{35}H_{41}N_5O_2$: 563.33; found 564.30 [M+H]$^+$.



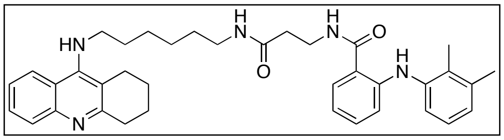
2-((2,3-Dimethylphenyl)amino)-N-(4-oxo-4-((4-((1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)amino)butyl)benzamide (12g). Compound **12g** was prepared as described for the synthesis of **10a**. The reaction of **9c** (114 mg, 0.348 mmol, 1 eq), EDAC hydrochloride (73 mg, 0.383 mmol, 1.1 eq), HOBt hydrate (59 mg, 0.383 mmol, 1.1 eq), **5b** (122 mg, 0.453 mmol, 1.3 eq), and Et$_3$N (87 μL, 0.627 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.14), **12g** (32 mg, 16%) as a pink solid: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 9.33 (s, 1H), 7.94 (d, 1H, J = 8.5 Hz), 7.91 (d, 1H, J = 8.4 Hz), 7.53 (t, 2H, J = 8.0 Hz), 7.32 (t, 1H, J = 7.5 Hz), 7.26 (br t, 1H), 7.18 (t, 1H, J = 7.4 Hz), 7.14 (d, 1H, J = 7.9 Hz), 7.04 (t, 1H, J = 7.7 Hz), 6.92 (m, 2H), 6.74 (br t, 1H), 6.69 (t, 1H, J = 7.3 Hz), 4.28 (br s, 1H), 3.48 (m, 4H), 3.31 (m, 2H), 3.04 (m, 2H), 2.65 (m, 2H), 2.32 (m, 5H), 2.17 (s, 3H), 1.93 (m, 2H), 1.87 (m, 4H), 1.70 (m, 2H), 1.61 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.2, 170.3, 157.6, 151.2, 147.1, 146.3, 139.6, 138.1, 132.3, 130.6, 128.8, 127.8, 127.5, 125.8, 125.6, 123.9, 123.0, 120.7, 119.8, 116.9, 116.6, 115.7, 114.8, 48.8, 39.4, 39.2, 34.1, 33.3, 28.9, 27.0, 25.2, 24.7, 22.9, 22.5, 20.7, 13.9; *m/z* calcd for $C_{36}H_{43}N_5O_2$: 577.34; found 578.30 [M+H]$^+$.



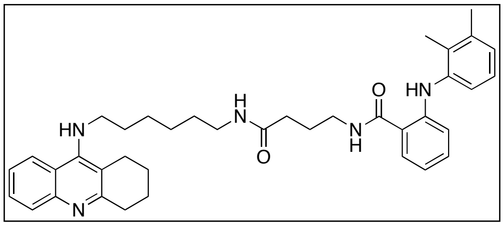
2-((2,3-Dimethylphenyl)amino)-N-(6-oxo-6-((4-((1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)amino)hexyl)benzamide (12h). Compound **12h** was prepared as described for the synthesis of **10a**. The reaction of **9d** (80 mg, 0.226 mmol, 1 eq), EDAC hydrochloride (47.6 mg, 0.248 mmol, 1.1 eq), HOBt hydrate (38 mg, 0.248 mmol, 1.1 eq), **5b** (102 mg, 0.377 mmol, 1.7 eq), and Et$_3$N (57 μL, 0.406 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.17), **12h** (43 mg, 31%) as a pink powder: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 9.23 (s, 1H), 7.91 (t, 2H, J = 8.7 Hz), 7.53 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 7.45 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.3 Hz), 7.32 (td, 1H, J_1 = 7.4 Hz, J_2 = 1.1 Hz), 7.17 (td, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.14 (d, 1H, J = 7.6 Hz), 7.04 (t, 1H, *J* = 7.7 Hz), 6.93 (br s, 1H), 6.90 (br s, 1H), 6.65 (m, 2H), 5.99 (t, 1H, *J* = 5.7 Hz), 4.10 (br s, 1H), 3.46 (m, 2H), 3.39 (q, 2H, *J* = 6.8 Hz), 3.24 (q, 2H, *J* = 6.5 Hz), 3.03 (br t, 2H), 2.66 (br t, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 2.14 (t, 2H, *J* = 7.3 Hz), 1.88 (m, 4H), 1.62 (m, 8H), 1.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 169.9, 158.0, 150.9, 146.9, 146.7, 139.6, 138.1, 132.1, 130.6, 128.6, 127.9, 127.6, 125.7, 125.5, 123.8, 122.9, 120.6, 120.0, 117.1, 116.8, 115.9, 114.8, 48.8, 39.3, 39.0, 36.3, 33.5, 29.1, 28.9, 27.1, 26.3, 25.0, 24.8, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{38}H_{47}N_5O_2$: 605.37; found 606.30 $[M+H]^+$.



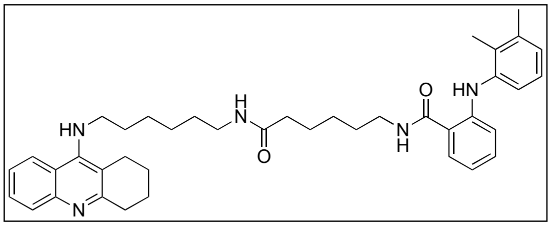
2-((2,3-Dimethylphenyl)amino)-N-(2-oxo-2-((6-((1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)amino)ethyl)benzamide (12i). Compound **12i** was prepared as described for the synthesis of **10a**. The reaction of **9a** (73 mg, 0.246 mmol, 1 eq), EDAC hydrochloride (52 mg, 0.270 mmol, 1.1 eq), HOBt hydrate (41 mg, 0.270 mmol, 1.1 eq), **5c** (88 mg, 0.295 mmol, 1.2 eq), and Et_3N (62 μL, 0.442 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.30), **12i** (123 mg, 87%) as a pale yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.21 (s, 1H), 7.95 (d, 1H, *J* = 8.5 Hz), 7.93 (d, 1H, *J* = 8.4 Hz), 7.55 (m, 2H), 7.35 (t, 1H, *J* = 7.6 Hz), 7.21 (m, 2H), 7.15 (d, 1H, *J* = 7.9 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.97 (d, 1H, *J* = 7.3 Hz), 6.88 (d, 1H, *J* = 8.4 Hz), 6.69 (t, 1H, *J* = 7.5 Hz), 6.37 (br t, 1H), 4.09 (d, 2H, *J* = 4.9 Hz), 4.08 (br s, 1H), 3.46 (m, 2H), 3.30 (q, 2H, *J* = 6.3 Hz), 3.08 (br t, 2H), 2.70 (br t, 2H), 2.32 (s, 3H), 2.19 (s, 3H), 1.93 (m, 4H), 1.63 (p, 2H, *J* = 7.0 Hz), 1.53 (p, 2H, *J* = 7.0 Hz), 1.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 169.0, 158.2, 150.9, 147.6, 147.2, 139.3, 138.1, 132.8, 131.2, 128.5, 128.4, 127.8, 126.0, 125.9, 123.7, 122.9, 121.4, 120.1, 116.8, 115.8, 115.4, 114.9, 49.3, 43.7, 39.4, 33.8, 31.6, 29.4, 26.53, 26.50, 24.8, 23.0, 22.7, 20.7, 13.9; *m/z* calcd for $C_{36}H_{43}N_5O_2$: 577.34; found 578.25 $[M+H]^+$.



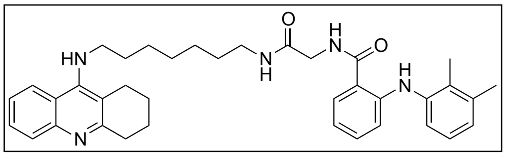
2-((2,3-Dimethylphenyl)amino)-N-(3-oxo-3-((6-((1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)amino)propyl)benzamide (12j). Compound **12j** was prepared as described for the synthesis of **10a**. The reaction of **9b** (85 mg, 0.272 mmol, 1 eq), EDAC hydrochloride (57 mg, 0.299 mmol, 1.1 eq), HOBt hydrate (46 mg, 0.299 mmol, 1.1 eq), **5c** (110 mg, 0.369 mmol, 1.36 eq), and Et_3N (68 μL, 0.490 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.50), **12j** (113 mg, 70%) as a pale yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.34 (s, 1H), 7.95 (d, 1H, *J* = 8.5 Hz), 7.91 (d, 1H, *J* = 8.5 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.40 (br t, 1H), 7.34 (t, 1H, *J* = 7.6 Hz), 7.18 (m, 2H), 7.06 (t, 1H, *J* = 7.7 Hz), 6.93 (t, 2H, *J* = 8.6 Hz), 6.66 (t, 1H, *J* = 7.5 Hz), 6.33 (br t, 1H), 4.04 (br s, 1H), 3.70 (q, 2H, *J* = 5.7 Hz), 3.46 (br t, 2H), 3.24 (q, 2H, *J* = 6.6 Hz), 3.06 (br t, 2H), 2.69 (br t, 2H), 2.51 (t, 2H, *J* = 5.8 Hz), 2.32 (s, 3H), 2.20 (s, 3H), 1.91 (br s, 4H), 1.61 (p, 2H, *J* = 7.1 Hz), 1.49 (p, 2H, *J* = 7.1 Hz), 1.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.7, 169.8, 158.2, 150.9, 147.2, 139.5, 138.1, 132.3, 130.8, 128.5, 128.4, 127.7, 125.8, 125.6, 123.7, 122.9, 120.8, 120.1, 116.8, 116.5, 115.8, 114.8, 49.3, 39.4, 35.8, 35.5, 33.8, 31.6, 29.5, 26.6, 26.5, 24.8, 23.0, 22.7, 20.7, 13.9; *m/z* calcd for $C_{37}H_{45}N_5O_2$: 591.36; found 592.35 $[M+H]^+$.



2-((2,3-Dimethylphenyl)amino)-N-(4-oxo-4-((6-((1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)amino)butyl)benzamide (12k). Compound **12k** was prepared as described for the synthesis of **10a**. The reaction of **9c** (70 mg, 0.214 mmol, 1 eq), EDAC hydrochloride (45 mg, 0.236 mmol, 1.1 eq), HOBt hydrate (36 mg, 0.236 mmol, 1.1 eq), **5c** (77 mg, 0.257 mmol, 1.2 eq), and Et_3N (54 μL, 0.386 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.19), **12k** (46 mg, 35%) as a pink powder: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.38 (s, 1H), 7.96 (d, 1H, J = 8.5 Hz), 7.92 (d, 1H, J = 8.5 Hz), 7.55 (t, 1H, J = 7.6 Hz), 7.51 (d, 1H, J = 7.9 Hz), 7.34 (t, 1H, J = 7.6 Hz), 7.30 (t, 1H, J = 5.1 Hz), 7.18 (m, 2H), 7.06 (t, 1H, J = 7.7 Hz), 6.93 (d, 2H, J = 8.1 Hz), 6.68 (t, 1H, J = 7.5 Hz), 6.53 (br t, 1H), 4.11 (br s, 1H), 3.47 (m, 4H), 3.23 (q, 2H, J = 6.5 Hz), 3.06 (br t, 2H), 2.68 (br t, 2H), 2.30 (m, 5H), 2.20 (s, 3H), 1.94 (m, 2H, J = 6.4 Hz), 1.90 (m, 4H), 1.63 (p, 2H, J = 7.0 Hz), 1.49 (p, 2H, J = 6.9 Hz), 1.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 170.2, 158.0, 151.1, 147.1, 146.9, 139.6, 138.1, 132.2, 130.6, 128.6, 128.0, 127.8, 125.8, 125.5, 123.7, 123.0, 120.7, 119.9, 116.9, 116.6, 115.5, 114.8, 49.2, 39.5, 39.4, 34.1, 33.6, 31.6, 29.5, 26.6, 26.5, 25.2, 24.7, 23.0, 22.6, 20.7, 13.9; *m/z* calcd for $C_{38}H_{47}N_5O_2$: 605.37; found 606.30 $[M+H]^+$.

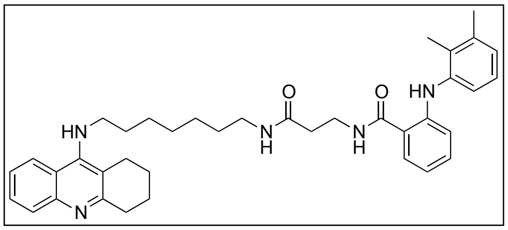


2-((2,3-Dimethylphenyl)amino)-N-(6-oxo-6-((6-((1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)amino)hexyl)benzamide (12l). Compound **12l** was prepared as described for the synthesis of **10a**. The reaction of **9d** (88 mg, 0.247 mmol, 1 eq), EDAC hydrochloride (42 mg, 0.272 mmol, 1.1 eq), HOBt hydrate (37 mg, 0.272 mmol, 1.1 eq), **5c** (90 mg, 0.302 mmol, 1.2 eq), and Et_3N (62 μL, 0.445 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.56), **12l** (97 mg, 62%) as a pale yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.27 (s, 1H), 7.95 (d, 1H, J = 9.1 Hz), 7.89 (d, 1H, J = 8.5 Hz), 7.52 (t, 1H, J = 7.2 Hz), 7.47 (d, 1H, J = 7.8 Hz), 7.31 (t, 1H, J = 7.4 Hz), 7.14 (m, 2H), 7.02 (t, 1H, J = 7.6 Hz), 6.95 (t, 1H, J = 5.5 Hz), 6.90 (m, 2H), 6.62 (t, 1H, J = 7.4 Hz), 6.27 (t, 1H, J = 5.5 Hz), 4.18 (br s, 1H), 3.45 (t, 2H, J = 7.0 Hz), 3.38 (q, 2H, J = 6.7 Hz), 3.17 (q, 2H, J = 6.6 Hz), 3.02 (br t, 2H), 2.65 (br t, 2H), 2.28 (s, 3H), 2.17 (s, 3H), 2.13 (t, 2H, J = 7.4 Hz), 1.87 (br s, 4H), 1.61 (m, 6H), 1.44 (m, 2H), 1.35 (m, 4H), 1.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 169.9, 157.9, 151.1, 146.9, 146.8, 139.6, 138.0, 132.0, 130.5, 128.6, 128.0, 127.7, 125.7, 125.4, 123.7, 123.1, 120.5, 119.9, 117.2, 116.8, 115.5, 114.7, 49.2, 39.4, 39.2, 36.3, 33.6, 31.6, 29.5, 29.1, 26.6, 26.5, 26.4, 25.1, 24.7, 23.0, 22.6, 20.7, 13.9; *m/z* calcd for $C_{40}H_{51}N_5O_2$: 633.40; found 634.35 $[M+H]^+$.

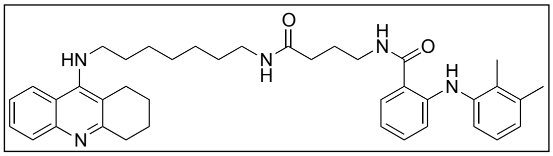


2-((2,3-Dimethylphenyl)amino)-*N*-(2-oxo-2-((7-((1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)amino)ethyl)benzamide (12m). Compound **12m** was prepared as described for the synthesis of **10a**. The reaction of **9a** (56 mg, 0.186 mmol, 1 eq), EDAC hydrochloride (39 mg, 0.205 mmol, 1.1 eq), HOBt hydrate (31 mg, 0.205

mmol, 1.1 eq), **5d** (70 mg, 0.223 mmol, 1.2 eq), and Et_3N (47 μL, 0.335 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.29), **12m** (35 mg, 32%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.24 (s, 1H), 7.97 (d, 1H, J = 8.3 Hz), 7.93 (d, 1H, J = 8.4 Hz), 7.56 (m, 2H), 7.36 (m, 2H), 7.21 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.15 (d, 1H, J = 7.8 Hz), 7.07 (t, 1H, J = 7.6 Hz), 6.96 (d, 1H, J = 7.4 Hz), 6.88 (d, 1H, J = 8.4 Hz), 6.67 (t, 1H, J = 7.2 Hz), 6.55 (t, 1H, J = 5.5 Hz), 4.11 (d, 2H, J = 5.2 Hz), 3.48 (t, 2H, J = 7.2 Hz), 3.27 (q, 2H, J = 6.8 Hz), 3.07 (br s, 2H), 2.70 (br s, 2H), 2.32 (s, 3H), 2.18 (s, 3H), 1.92 (m, 4H), 1.63 (p, 2H, J = 7.2 Hz), 1.48 (br p, 2H, J = 6.4 Hz), 1.33 (m, 7H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 169.0, 157.9, 151.2, 147.6, 146.8, 139.3, 138.1, 132.7, 131.2, 128.6, 128.0, 127.9, 125.9, 125.8, 123.7, 123.0, 121.4, 119.9, 116.8, 115.53, 115.48, 114.8, 49.3, 43.6, 39.6, 33.6, 31.6, 29.3, 28.9, 26.70, 26.65, 24.7, 23.0, 22.6, 20.7, 13.9; *m/z* calcd for $C_{37}H_{45}N_5O_2$: 591.36; found 592.30 $[M+H]^+$.

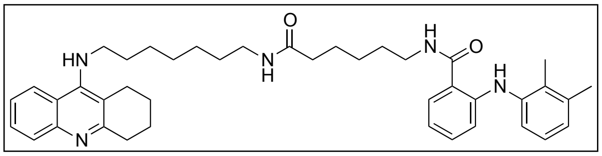


2-((2,3-dimethylphenyl)amino)-*N*-(3-oxo-3-((7-((1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)amino)propyl)benzamide (12n). Compound **12n** was prepared as described for the synthesis of **10a**. The reaction of **9b** (56 mg, 0.178 mmol, 1 eq), EDAC hydrochloride (38 mg, 0.196 mmol, 1.1 eq), HOBt hydrate (30 mg, 0.196 mmol, 1.1 eq), **5d** (67 mg, 0.214 mmol, 1.2 eq), and Et_3N (45 μL, 0.320 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.24), **12n** (50 mg, 47%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.34 (s, 1H), 7.96 (d, 1H, J = 8.5 Hz), 7.91 (d, 1H, J = 8.5 Hz), 7.56 (t, 1H, J = 7.2 Hz), 7.45 (d, 1H, J = 7.9 Hz), 7.34 (m, 2H), 7.19 (t, 1H, J = 7.6 Hz), 7.17 (d, 1H, J = 7.4 Hz), 7.07 (t, 1H, J = 7.6 Hz), 6.95 (d, 1H, J = 7.6 Hz), 6.92 (d, 1H, J = 8.4 Hz), 6.67 (t, 1H, J = 7.4 Hz), 6.10 (t, 1H, J = 5.3 Hz), 4.02 (br s, 1H), 3.72 (q, 2H, J = 5.8 Hz), 3.48 (t, 2H, J = 7.2 Hz), 3.23 (q, 2H, J = 6.7 Hz), 3.07 (br s, 2H), 2.71 (br s, 2H), 2.52 (t, 2H, J = 5.8 Hz), 2.33 (s, 3H), 2.21 (s, 3H), 1.92 (m, 4H), 1.63 (p, 2H, J = 7.0 Hz), 1.46 (br p, 2H, J = 6.8 Hz), 1.32 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 169.8, 158.3, 150.9, 147.3, 147.2, 139.6, 138.0, 132.3, 130.8, 128.4, 127.7, 125.8, 125.6, 123.7, 122.9, 120.8, 120.1, 116.8, 116.5, 115.8, 114.7, 49.4, 39.5, 35.8, 35.5, 33.9, 31.7, 29.4, 28.9, 26.7, 24.8, 23.0, 22.8, 20.7, 13.9; *m/z* calcd for $C_{38}H_{47}N_5O_2$: 605.37; found 606.35 $[M+H]^+$.

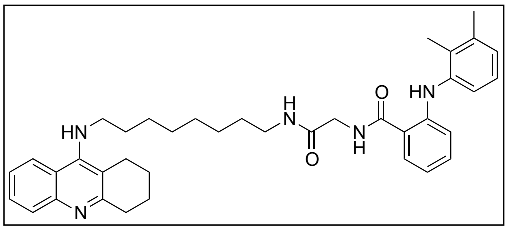


2-((2,3-Dimethylphenyl)amino)-*N*-(4-oxo-4-((7-((1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)amino)butyl)benzamide (12o). Compound **12o** was prepared as described for the synthesis of **10a**. The reaction of **9c** (61 mg, 0.188 mmol, 1 eq), EDAC hydrochloride (40 mg, 0.207 mmol, 1.1 eq), HOBt hydrate (32 mg, 0.207 mmol, 1.1 eq), **5d** (70 mg, 0.226 mmol, 1.2 eq), and Et_3N (47 μL, 0.338 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.40), **12o** (27 mg, 23%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.36 (s, 1H), 7.96 (d, 1H, J = 8.3 Hz), 7.92 (d, 1H, J = 8.4 Hz), 7.56 (t, 1H, J = 7.2 Hz), 7.49 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.2 Hz), 7.35 (t, 1H, J = 8.0 Hz), 7.20 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.17 (d, 1H, J = 8.0 Hz), 7.15 (br t, 1H, J = 5.4 Hz), 7.07 (t, 1H, J = 7.7 Hz), 6.94 (m, 2H), 6.70 (t, 1H, J = 7.3 Hz), 6.25 (br t, 1H), 4.00 (very br s, 1H), 3.49 (p, 4H, J =

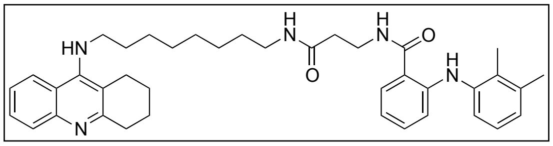
6.6 Hz), 3.23 (q, 2H, *J* = 6.7 Hz), 3.07 (br t, 2H), 2.71 (br t, 2H), 2.32 (m, 5H), 2.21 (s, 3H), 1.97 (p, 2H, *J* = 6.3 Hz) 1.93 (m, 4H), 1.63 (p, 2H, *J* = 7.4 Hz), 1.46 (br p, 2H, *J* = 6.7 Hz), 1.31 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 170.2, 158.3, 150.9, 147.3, 147.2, 139.6, 138.1, 132.2, 130.7, 128.5, 128.4, 127.6, 125.7, 125.5, 123.6, 122.9, 120.7, 120.1, 116.9, 116.6, 115.8, 114.8, 49.4, 39.6, 39.5, 34.2, 33.9, 31.7, 29.4, 28.9, 26.8, 26.7, 25.1, 24.8, 23.0, 22.8, 20.7, 13.9; *m/z* calcd for $C_{39}H_{49}N_5O_2$: 619.39; found 620.30 $[M+H]^+$.



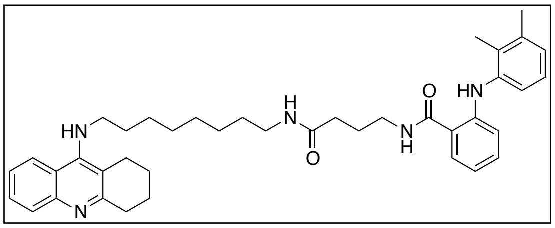
2-((2,3-Dimethylphenyl)amino)-*N*-(6-oxo-6-((7-((1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)amino)hexyl)benzamide (12p). Compound **12p** was prepared as described for the synthesis of **10a**. The reaction of **9d** (53 mg, 0.148 mmol, 1 eq), EDAC hydrochloride (31 mg, 0.163 mmol, 1.1 eq), HOBt hydrate (25 mg, 0.163 mmol, 1.1 eq), **5d** (55 mg, 0.178 mmol, 1.2 eq), and Et_3N (37 μL, 0.266 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.23), **12p** (35 mg, 37%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.24 (s, 1H), 7.97 (d, 1H, *J* = 8.5 Hz), 7.92 (d, 1H, *J* = 8.4 Hz), 7.57 (t, 1H, *J* = 7.5 Hz), 7.45 (d, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 7.6 Hz), 7.21 (t, 1H, *J* = 7.6 Hz), 7.17 (d, 1H, *J* = 7.9 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 6.94 (d, 2H, *J* = 8.4 Hz), 6.68 (t, 1H, *J* = 7.5 Hz), 6.48 (br t, 1H), 5.66 (br t, 1H), 4.02 (very br s, 1H), 3.49 (t, 2H, *J* = 7.2 Hz), 3.44 (q, 2H, *J* = 6.7 Hz), 3.21 (q, 2H, *J* = 6.7 Hz), 3.07 (br s, 2H), 2.71 (br s, 2H), 2.33 (s, 3H), 2.21 (s, 3H), 2.18 (t, 2H, *J* = 7.3 Hz), 1.93 (m, 4H), 1.68 (m, 6H), 1.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 169.8, 158.3, 150.9, 147.3, 147.0, 139.6 , 138.1, 132.1, 130.7, 128.5, 128.4, 127.4, 125.7, 125.5, 123.6, 122.9, 120.6, 120.1, 117.2, 116.8, 115.8, 114.9, 49.4, 39.4, 36.4, 33.9, 31.7, 29.6, 29.2, 28.9, 26.8, 26.7, 26.4, 25.0, 24.8, 23.0, 22.8, 20.7, 13.9; *m/z* calcd for $C_{41}H_{53}N_5O_2$: 647.42; found 648.30 $[M+H]^+$.



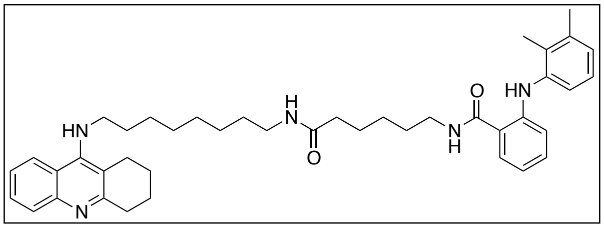
2-((2,3-Dimethylphenyl)amino)-*N*-(2-oxo-2-((8-((1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)amino)ethyl)benzamide (12q). Compound **12q** was prepared as described for the synthesis of **10a**. The reaction of **9a** (44 mg, 0.146 mmol, 1 eq), EDAC hydrochloride (31 mg, 0.161 mmol, 1.1 eq), HOBt hydrate (25 mg, 0.161 mmol, 1.1 eq), **5e** (57 mg, 0.175 mmol, 1.2 eq), and Et_3N (37 μL, 0.263 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.30), **12q** (36 mg, 41%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.24 (s, 1H), 7.97 (d, 1H, *J* = 8.2 Hz), 7.91 (d, 1H, *J* = 8.3 Hz), 7.56 (m, 2H), 7.35 (m, 2H), 7.21 (t, 1H, *J* = 7.3 Hz), 7.16 (d, 1H, *J* = 7.8 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.97 (d, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.4 Hz), 6.68 (t, 1H, *J* = 7.2 Hz), 6.51 (br t, 1H, *J* = 5.4 Hz), 4.11 (d, 2H, *J* = 5.2 Hz), 3.99 (very br s, 1H), 3.48 (t, 2H, *J* = 7.2 Hz), 3.27 (q, 2H, *J* = 6.8 Hz), 3.07 (br s, 2H), 2.71 (br s, 2H), 2.33 (s, 3H), 2.19 (s, 3H), 1.93 (m, 4H), 1.64 (p, 2H, *J* = 7.1 Hz), 1.48 (br p, 2H), 1.35 (br p, 2H), 1.28 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 168.9, 158.3, 150.9, 147.6, 147.3, 139.3, 138.1, 132.7, 131.2, 128.5, 128.4, 127.9, 125.9, 125.8, 123.6, 123.0, 121.5, 120.1, 116.8, 115.7, 115.5, 114.8, 49.4, 43.6, 39.6, 33.9, 31.8, 29.4, 29.14, 29.08, 26.8, 26.7, 24.8, 23.1, 22.8, 20.7, 14.0; *m/z* calcd for $C_{38}H_{47}N_5O_2$: 605.37; found 606.30 $[M+H]^+$.



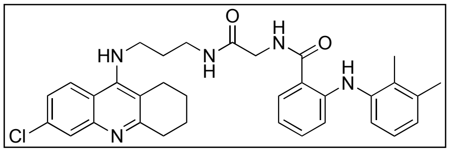
2-((2,3-Dimethylphenyl)amino)-N-(3-oxo-3-((8-((1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)amino)propyl)benzamide (12r). Compound **12r** was prepared as described for the synthesis of **10a**. The reaction of **9b** (54 mg, 0.172 mmol, 1 eq), EDAC hydrochloride (36 mg, 0.189 mmol, 1.1 eq), HOBt hydrate (29 mg, 0.189 mmol, 1.1 eq), **5e** (67 mg, 0.206 mmol, 1.2 eq), and Et$_3$N (43 μL, 0.310 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.39), **12r** (30 mg, 28%) as a pale yellow powder: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.34 (s, 1H), 7.97 (d, 1H, *J* = 8.5 Hz), 7.91 (d, 1H, *J* = 8.5 Hz), 7.56 (t, 1H, *J* = 7.1 Hz), 7.45 (d, 1H, *J* = 6.8 Hz), 7.34 (m, 2H), 7.19 (m, 2H), 7.07 (t, 1H, *J* = 7.6 Hz), 6.94 (t, 2H, *J* = 9.2 Hz), 6.68 (t, 1H, *J* = 7.2 Hz), 6.10 (t, 1H, *J* = 5.3 Hz), 4.00 (very br s, 1H), 3.72 (q, 2H, *J* = 5.8 Hz), 3.49 (t, 2H, *J* = 7.2 Hz), 3.24 (q, 2H, *J* = 6.8 Hz), 3.07 (br t, 2H), 2.71 (br t, 2H), 2.52 (t, 2H, *J* = 5.9 Hz), 2.33 (s, 3H), 2.21 (s, 3H), 1.93 (m, 4H), 1.64 (p, 2H, *J* = 7.1 Hz), 1.46 (br p, 2H, *J* = 6.7 Hz), 1.35 (br p, 2H), 1.27 (br s, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 171.7, 169.8, 158.3, 150.9, 147.3, 147.2, 139.6, 138.0, 132.3, 130.8, 128.5, 128.4, 127.7, 125.7, 125.5, 123.6, 122.9, 120.8, 120.1, 116.8, 116.5, 115.7, 114.7, 49.4, 39.6, 35.8, 35.5, 33.9, 31.8, 29.5, 29.14, 29.10, 26.78, 26.75, 24.8, 23.1, 22.8, 20.7, 13.9; *m/z* calcd for C$_{39}$H$_{49}$N$_5$O$_2$: 619.39; found 620.35 [M+H]$^+$.



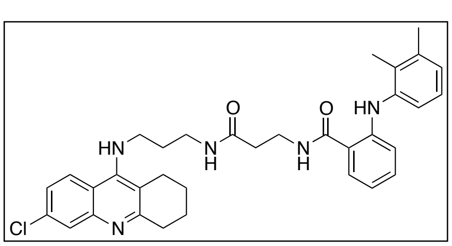
2-((2,3-Dimethylphenyl)amino)-N-(4-oxo-4-((8-((1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)amino)butyl)benzamide (**12s**). Compound **12s** was prepared as described for the synthesis of **10a**. The reaction of **9c** (61 mg, 0.187 mmol, 0.87 eq), EDAC hydrochloride (45 mg, 0.237 mmol, 1.1 eq), HOBt hydrate (36 mg, 0.237 mmol, 1.1 eq), **5e** (84 mg, 0.258 mmol, 1.2 eq), and Et$_3$N (54 μL, 0.387 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.44), **12s** (60 mg, 51%) as a yellow oil: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.38 (s, 1H), 7.99 (d, 1H, *J* = 8.5 Hz), 7.95 (d, 1H, *J* = 8.4 Hz), 7.56 (t, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 7.9 Hz), 7.34 (m, 2H), 7.18 (t, 1H, *J* = 8.4 Hz), 7.16 (d, 1H, *J* = 7.2 Hz), 7.06 (t, 1H, *J* = 7.6 Hz), 6.93 (m, 2H), 6.67 (t, 1H, *J* = 7.8 Hz), 6.53 (t, 1H, *J* = 5.2 Hz), 4.23 (br s, 1H), 3.52 (t, 2H, *J* = 7.1 Hz), 3.48 (q, 2H, *J* = 8.4 Hz), 3.22 (q, 2H, *J* = 6.7 Hz), 3.07 (br s, 2H), 2.69 (br s, 2H), 2.32 (m, 5H), 2.20 (s, 3H), 1.96 (p, 2H, *J* = 6.5 Hz), 1.91 (m, 4H), 1.65 (p, 2H, *J* = 7.1 Hz), 1.46 (br p, 2H), 1.36 (br p, 2H), 1.27 (br s, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 173.1, 170.2, 157.6, 151.5, 147.1, 146.5, 139.7, 138.0, 132.2, 130.6, 128.8, 127.8, 127.6, 125.7, 125.5, 123.8, 123.1, 120.7, 119.7, 116.9, 116.7, 115.2, 114.8, 49.3, 39.6, 39.5, 34.2, 33.3, 31.6, 29.5, 29.11, 29.07, 26.8, 26.7, 25.2, 24.6, 22.9, 22.5, 20.7, 13.9; *m/z* calcd for C$_{40}$H$_{51}$N$_5$O$_2$: 633.40; found 634.65 [M+H]$^+$.



2-((2,3-Dimethylphenyl)amino)-N-(6-oxo-6-((8-((1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)amino)hexyl)benzamide (**12t**). Compound **12t** was prepared as described for the synthesis of **10a**. The reaction of **9d** (63 mg, 0.177 mmol, 0.80 eq), EDAC hydrochloride (47 mg, 0.244 mmol, 1.1 eq), HOBt hydrate (37 mg, 0.244 mmol, 1.1 eq), **5e** (87 mg, 0.266 mmol, 1.2 eq), and Et_3N (57 μL, 0.399 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.31), **12t** (70 mg, 60%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.25 (s, 1H), 7.99 (d, 1H, *J* = 8.5 Hz), 7.91 (d, 1H, *J* = 8.4 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.46 (d, 1H, *J* = 7.5 Hz), 7.34 (t, 1H, *J* = 7.7 Hz), 7.18 (t, 1H, *J* = 8.0 Hz), 7.16 (d, 1H, *J* = 7.9 Hz), 7.06 (d, 1H, *J* = 7.7 Hz), 6.93 (d, 2H, *J* = 8.1 Hz), 6.70 (t, 1H, *J* = 5.4 Hz), 6.66 (t, 1H, *J* = 7.4 Hz), 5.95 (t, 1H, *J* = 5.5 Hz), 4.08 (br s, 1H), 3.49 (t, 2H, *J* = 6.9 Hz), 3.42 (q, 2H, *J* = 6.7 Hz), 3.19 (q, 2H, *J* = 6.6 Hz), 3.05 (m, 2H), 2.69 (m, 2H), 2.31 (s, 3H), 2.20 (s, 3H), 2.16 (t, 2H, *J* = 7.4 Hz), 1.91 (m, 4H), 1.64 (m, 6H), 1.40 (m, 6H), 1.27 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 169.9, 158.1, 151.1, 147.1, 146.9, 139.6, 138.0, 132.1, 130.6, 128.5, 128.3, 127.6, 125.7, 125.4, 123.6, 123.0, 120.6, 120.0, 117.2, 116.8, 115.6, 114.8, 49.4, 39.5, 39.4, 36.4, 33.8, 31.7, 29.6, 29.2, 29.15, 29.10, 26.79, 26.76, 26.4, 25.1, 24.7, 23.0, 22.7, 20.7, 13.9; *m/z* calcd for $C_{42}H_{55}N_5O_2$: 661.44; found 662.40 $[M+H]^+$.

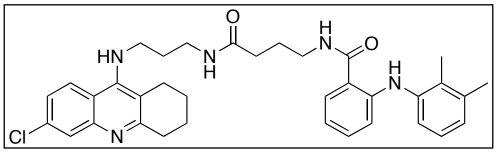


N-(2-((3-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)-2-oxoethyl)-2-((2,3-dimethylphenyl)amino)benzamide (13a). Compound **13a** was prepared as described for the synthesis of **10a**. The reaction of **9a** (64 mg, 0.213 mmol, 1 eq), EDAC hydrochloride (45 mg, 0.234 mmol, 1.1 eq), HOBt hydrate (36 mg, 0.234 mmol, 1.1 eq), **6a** (74 mg, 0.255 mmol, 1.2 eq), and Et_3N (53 μL, 0.383 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.48), **13a** (65 mg, 53%) as a pale yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.18 (s, 1H), 7.90 (d, 1H, *J* = 9.1 Hz), 7.84 (s, 1H), 7.52 (d, 1H, *J* = 7.9 Hz), 7.45 (t, 1H, *J* = 5.2 Hz), 7.21 (m, 2H), 7.13 (t, 1H, *J* = 6.0 Hz), 7.09 (br s, 1H), 7.06 (t, 1H, *J* = 7.8 Hz), 6.97 (d, 1H, *J* = 7.2 Hz), 6.87 (d, 1H, *J* = 8.5 Hz), 6.63 (t, 1H, *J* = 7.5 Hz), 4.76 (br t, 1H), 4.13 (d, 2H, *J* = 5.2 Hz), 3.45 (p, 4H, *J* = 6.6 Hz), 2.99 (t, 2H, *J* = 6.0 Hz), 2.67 (t, 2H, *J* = 5.8 Hz), 2.30 (s, 3H), 2.14 (s, 3H), 1.86 (m, 4H), 1.79 (p, 2H, *J* = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 170.1, 159.7, 150.6, 147.8, 147.6, 139.2, 138.2, 134.0, 132.9, 131.1, 127.8, 127.3, 126.1, 125.9, 124.5, 124.2, 121.4, 118.6, 116.9, 116.6, 115.2, 115.0, 45.4, 43.8, 36.8, 33.9, 31.2, 24.9, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{33}H_{36}ClN_5O_2$: 569.26; found 570.20 $[M+H]^+$.

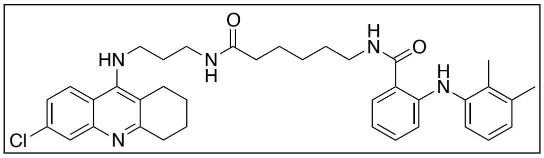


N-(3-((3-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)-3-oxopropyl)-2-((2,3-dimethylphenyl)amino)benzamide (13b). Compound **13b** was prepared as described for the synthesis of **10a**. The reaction of **9b** (73 mg, 0.234 mmol, 1 eq), EDAC hydrochloride (49 mg, 0.257 mmol, 1.1 eq), HOBt hydrate (39 mg, 0.257 mmol, 1.1 eq), **6a** (81 mg, 0.280 mmol, 1.2 eq), and Et_3N (59 μL, 0.420 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.33), **13b** (70 mg, 51%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.28 (s, 1H), 7.90 (d, 1H, *J* = 9.0 Hz), 7.81 (s, 1H), 7.55 (br t, 1H), 7.46 (d, 1H, *J* = 7.7 Hz), 7.26 (br t, 1H), 7.19 (d, 1H, *J* = 9.1 Hz), 7.17 (d, 1H, *J* = 8.0 Hz), 7.12 (d, 1H, *J* = 7.9 Hz), 7.04 (t, 1H, *J* = 7.7 Hz), 6.92 (d, 1H, *J* = 7.4 Hz), 6.89 (d, 1H, *J* = 8.4 Hz), 6.61 (t, 1H, *J* = 7.4 Hz), 4.89 (br s, 1H), 3.71 (q, 2H, *J* = 5.3

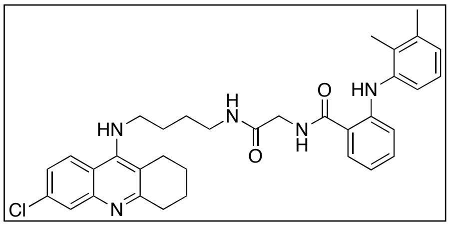
Hz), 3.43 (q, 2H, *J* = 5.8 Hz), 3.37 (q, 2H, *J* = 5.8 Hz), 2.97 (br s, 2H), 2.66 (br t, 2H), 2.56 (br t, 2H), 2.29 (s, 3H), 2.16 (s, 3H), 1.84 (br s, 4H), 1.74 (br p, 2H, *J* = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 169.9, 159.5, 150.7, 147.7, 147.2, 139.5, 138.1, 134.0, 132.3, 130.7, 127.7, 127.0, 125.8, 125.6, 124.4, 124.3, 120.8, 118.5, 116.9, 116.5, 116.2, 114.8, 45.2, 36.5, 36.0, 35.5, 33.9, 33.8, 31.3, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{34}H_{38}ClN_5O_2$: 583.27; found 584.20 $[M+H]^+$.



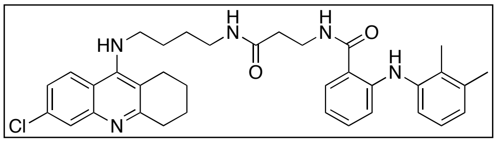
N-(4-((3-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)-4-oxobutyl)-2-((2,3-dimethylphenyl)amino)benzamide (13c). Compound **13c** was prepared as described for the synthesis of **10a**. The reaction of **9c** (84 mg, 0.257 mmol, 1 eq), EDAC hydrochloride (54 mg, 0.283 mmol, 1.1 eq), HOBt hydrate (43 mg, 0.283 mmol, 1.1 eq), **6a** (95 mg, 0.327 mmol, 1.2 eq), and Et_3N (64 μL, 0.555 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.54), **13c** (77 mg, 50%) as a white powder: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.26 (s, 1H), 7.94 (d, 1H, *J* = 9.1 Hz), 7.85 (d, 1H, *J* = 2.0 Hz), 7.48 (d, 1H, *J* = 7.1 Hz), 7.24 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 7.17 (m, 2H), 7.08 (br s, 1H), 7.06 (t, 1H, *J* = 7.6 Hz), 6.81 (t, 1H, *J* = 5.8 Hz), 6.67 (t, 1H, *J* = 7.5 Hz), 4.87 (t, 1H, *J* = 6.5 Hz), 3.48 (m, 4H), 3.39 (q, 2H), 3.00 (m, 2H), 2.71 (br t, 2H), 2.36 (m, 2H), 2.31 (s, 3H), 2.18 (s, 3H), 1.96 (m, 2H), 1.88 (m, 4H), 1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9, 170.4, 159.7, 150.6, 148.0, 147.1, 139.5, 138.1, 133.9, 132.4, 130.6, 127.5, 127.4, 125.8, 125.6, 124.4, 124.3, 120.7, 118.6, 116.9, 116.54, 116.49, 114.9, 45.3, 39.4, 36.6, 34.0, 25.6, 25.5, 25.03, 24.95, 22.9, 22.7, 20.7, 13.9; *m/z* calcd for $C_{35}H_{40}ClN_5O_2$: 597.29; found 598.25 $[M+H]^+$.



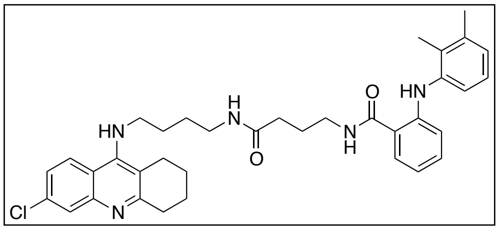
N-(6-((3-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)-6-oxohexyl)-2-((2,3-dimethylphenyl)amino)benzamide (13d). Compound **13d** was prepared as described for the synthesis of **10a**. The reaction of **9d** (83 mg, 0.235 mmol, 1 eq), EDAC hydrochloride (50 mg, 0.259 mmol, 1.1 eq), HOBt hydrate (40 mg, 0.259 mmol, 1.1 eq), **6a** (82 mg, 0.282 mmol, 1.2 eq), and Et_3N (60 μL, 0.423 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.28), **13d** (111 mg, 75%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 7.95 (d, 1H, *J* = 9.1 Hz), 7.86 (d, 1H, *J* = 1.5 Hz), 7.42 (d, 1H, *J* = 7.8 Hz), 7.26 (dd, 1H, J_1 = 9.0 Hz, J_2 = 1.5 Hz), 7.19 (t, 1H, *J* = 7.8 Hz), 7.15 (d, 1H, *J* = 7.9 Hz), 7.06 (t, 1H, *J* = 7.6 Hz), 6.94 (t, 2H, *J* = 7.9 Hz), 6.66 (t, 1H, *J* = 7.5 Hz), 6.49 (br t, 1H), 6.13 (t, 1H, *J* = 5.8 Hz), 4.96 (br s, 1H), 3.43 (m, 4H), 3.37 (q, 2H, *J* = 6.2 Hz), 3.01 (m, 2H), 2.71 (br t, 2H), 2.32 (s, 3H), 2.22 (t, 2H, *J* = 7.3 Hz), 2.20 (s, 3H), 1.89 (br s, 4H), 1.71 (m, 4H), 1.64 (p, 2H, *J* = 7.3 Hz), 1.42 (p, 2H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.0, 169.9, 159.6, 150.7, 147.8, 147.0, 139.6, 138.1, 133.9, 132.2, 130.6, 127.4, 127.2, 125.8, 125.5, 124.4, 124.3, 120.6, 118.5, 117.1, 116.8, 116.4, 114.9, 45.1, 39.4, 36.4, 36.3, 33.9, 31.5, 29.3, 26.4, 25.2, 25.0, 23.0, 22.6, 20.7, 13.9; *m/z* calcd for $C_{37}H_{44}ClN_5O_2$: 625.32; found 626.25 $[M+H]^+$.



N-(2-((4-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)amino)-2-oxoethyl)-2-((2,3-dimethylphenyl)amino)benzamide (13e). Compound **13e** was prepared as described for the synthesis of **10a**. The reaction of **9a** (59 mg, 0.198 mmol, 1 eq), EDAC hydrochloride (42 mg, 0.218 mmol, 1.1 eq), HOBt hydrate (33 mg, 0.218 mmol, 1.1 eq), **6b** (72 mg, 0.238 mmol, 1.2 eq), and Et_3N (50 μL, 0.357 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.24), **13e** (86 mg, 74%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 7.86 (d, 1H, J = 2.0 Hz), 7.83 (d, 1H, J = 9.1 Hz), 7.53 (d, 1H, J = 7.8 Hz), 7.29 (m, 1H), 7.24 (m, 1H), 7.22 (t, 1H, J = 8.5 Hz), 7.12 (d, 1H, J = 7.5 Hz), 7.05 (t, 1H, J = 7.6 Hz), 6.95 (d, 1H, J = 7.1 Hz), 6.87 (d, 1H, J = 8.4 Hz), 6.70 (m, 1H), 6.66 (t, 1H, J = 7.4 Hz), 4.09 (d, 2H, J = 5.2 Hz), 3.96 (br s, 1H), 3.44 (br t, 2H), 3.32 (q, 2H, J = 6.2 Hz), 3.01 (br t, 2H), 2.62 (br t, 2H), 2.29 (s, 3H), 2.15 (s, 3H), 1.89 (m, 4H), 1.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 169.2, 159.6, 150.6, 148.0, 147.6, 139.2, 138.2, 134.0, 132.9, 131.2, 127.8, 127.4, 126.0, 125.9, 124.5, 124.4, 121.4, 118.5, 116.9, 116.2, 115.3, 114.9, 48.9, 43.7, 39.2, 34.0, 28.9, 27.0, 24.6, 22.9, 22.6, 20.6, 13.9; *m/z* calcd for $C_{34}H_{38}ClN_5O_2$: 583.27; found 584.25 $[M+H]^+$.

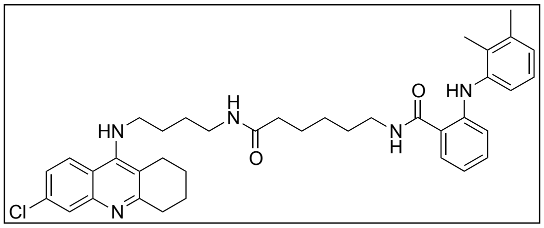


N-(3-((4-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)amino)-3-oxopropyl)-2-((2,3-dimethylphenyl)amino)benzamide (13f). Compound **13f** was prepared as described for the synthesis of **10a**. The reaction of **9b** (75 mg, 0.240 mmol, 1 eq), EDAC hydrochloride (51 mg, 0.264 mmol, 1.1 eq), HOBt hydrate (40 mg, 0.264 mmol, 1.1 eq), **6b** (151 mg, 0.496 mmol, 1.2 eq), and Et_3N (60 μL, 0.433 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.44), **13f** (67 mg, 47%) as a white powder: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.30 (s, 1H), 7.85 (d, 1H, J = 2.0 Hz), 7.83 (d, 1H, J = 9.1 Hz), 7.44 (d, 1H, J = 7.8 Hz), 7.33 (br s, 1H), 7.23 (dd, 1H, J_1 = 9.1 Hz, J_2 = 2.0 Hz), 7.16 (t, 2H, J = 7.8 Hz), 7.04 (t, 1H, J = 7.7 Hz), 6.93 (d, 1H, J = 5.9 Hz), 6.91 (d, 1H, J = 7.9 Hz), 6.64 (t, 1H, J = 7.5 Hz), 6.45 (br t, 1H), 4.00 (br s, 1H), 3.70 (q, 2H, J = 5.8 Hz), 3.42 (br t, 2H), 3.28 (q, 2H, J = 6.1 Hz), 2.99 (br t, 2H), 2.61 (br t, 2H), 2.50 (t, 2H, J = 5.8 Hz), 2.30 (s, 3H), 2.18 (s, 3H), 1.87 (br s, 4H), 1.63 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 169.9, 159.4, 150.7, 147.8, 147.2, 139.4, 138.1, 134.1, 132.4, 130.7, 127.6, 127.2, 125.8, 125.7, 124.5, 124.4, 120.8, 118.4, 116.9, 116.4, 116.0, 114.8, 48.9, 39.1, 35.8, 35.5, 33.8, 28.9, 27.0, 24.6, 22.8, 22.5, 20.7, 13.9; *m/z* calcd for $C_{35}H_{40}ClN_5O_2$: 597.29; found 598.20 $[M+H]^+$.

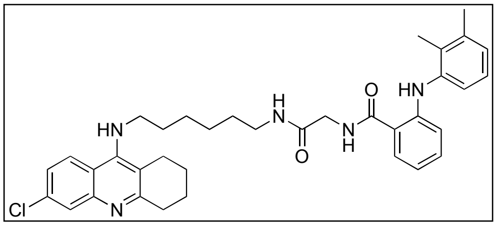


N-(4-((4-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)amino)-4-oxobutyl)-2-((2,3-dimethylphenyl)amino)benzamide (13g). Compound **13g** was prepared as described for the synthesis of **10a**. The reaction of **9c** (58 mg, 0.177 mmol, 1 eq), EDAC hydrochloride (42 mg, 0.218 mmol, 1.1 eq), HOBt hydrate (33 mg, 0.218 mmol, 1.1 eq), **6b** (72 mg, 0.238 mmol, 1.2 eq), and Et_3N (50 μL, 0.357 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2;

9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.30), **13g** (102 mg, 94%) as a white powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.29 (s, 1H), 7.89 (d, 1H, J = 2.1 Hz), 7.86 (d, 1H, J = 9.1 Hz), 7.49 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.4 Hz), 7.25 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.1 Hz), 7.21 (m, 1H), 7.14 (d, 1H, J = 7.9 Hz), 7.06 (t, 1H, J = 7.7 Hz), 6.98 (br t, 1H, J = 5.5 Hz), 6.95 (d, 1H, J = 7.5 Hz), 6.92 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.7 Hz), 6.71 (m, 1H), 6.39 (br t, 1H), 4.04 (br s, 1H), 3.48 (m, 4H), 3.31 (q, 2H, J = 6.5 Hz), 3.02 (br t, 2H), 2.65 (br t, 2H), 2.31 (m, 5H), 2.18 (s, 3H), 1.96 (p, 2H, J = 6.3 Hz), 1.89 (m, 4H), 1.70 (m, 2H), 1.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 170.3, 159.5, 150.7, 147.9, 147.2, 139.5, 138.1, 134.1, 132.4, 130.7, 127.6, 127.4, 125.8, 125.7, 124.5, 124.4, 120.8, 118.4, 116.9, 116.5, 116.2, 114.89, 49.0, 39.4, 39.2, 34.1, 33.9, 29.0, 27.1, 25.3, 24.6, 22.9, 22.6, 20.7, 13.9; m/z calcd for $C_{36}H_{42}ClN_5O_2$: 611.30; found 612.30 $[M+H]^+$.

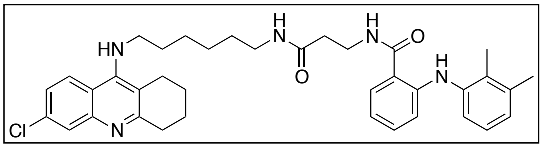


N-(6-((4-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)amino)-6-oxohexyl)-2-((2,3-dimethylphenyl)amino)benzamide (13h). Compound **13h** was prepared as described for the synthesis of **10a**. The reaction of **9d** (66 mg, 0.185 mmol, 1 eq), EDAC hydrochloride (39 mg, 0.204 mmol, 1.1 eq), HOBt hydrate (31 mg, 0.204 mmol, 1.1 eq), **6b** (68 mg, 0.223 mmol, 1.2 eq), and Et_3N (51 μL, 0.367 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.44), **13h** (23 mg, 20%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.21 (s, 1H), 7.89 (d, 1H, J = 2.3 Hz), 7.87 (d, 1H, J = 9.0 Hz), 7.45 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.0 Hz), 7.27 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.1 Hz), 7.20 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.0 Hz), 7.16 (d, 1H, J = 7.9 Hz), 7.06 (t, 1H, J = 7.7 Hz), 6.94 (t, 2H, J = 7.1 Hz), 6.69 (t, 1H, J = 7.3 Hz), 6.49 (t, 1H, J = 5.5 Hz), 5.79 (t, 1H, J = 5.4 Hz), 4.06 (br s, 1H), 3.47 (t, 2H), 3.44 (q, 2H, J = 6.8 Hz), 3.27 (q, 2H, J = 6.7 Hz), 3.03 (br t, 2H), 2.66 (br t, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 2.18 (t, 2H, J = 7.4 Hz), 1.91 (m, 4H), 1.65 (m, 6H), 1.58 (p, 2H, J = 8.2 Hz), 1.41 (p, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 169.8, 159.5, 150.7, 147.9, 147.0, 139.6, 138.1, 134.1, 132.2, 130.7, 127.4, 125.7, 125.5, 124.5, 124.4, 120.7, 118.4, 117.1, 116.8, 116.1, 114.9, 49.0, 39.3, 39.0, 36.4, 33.9, 29.2, 28.9, 27.2, 26.3, 25.0, 24.7, 22.9, 22.6, 20.7, 13.9; m/z calcd for $C_{38}H_{46}ClN_5O_2$: 639.33; found 640.30 $[M+H]^+$.

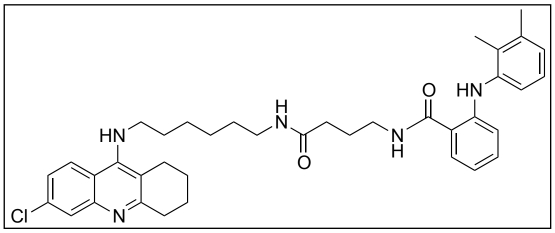


N-(2-((6-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)amino)-2-oxoethyl)-2-((2,3-dimethylphenyl)amino)benzamide (13i). Compound **13i** was prepared as described for the synthesis of **10a**. The reaction of **9a** (55 mg, 0.185 mmol, 1 eq), EDAC hydrochloride (39 mg, 0.204 mmol, 1.1 eq), HOBt hydrate (31 mg, 0.204 mmol, 1.1 eq), **6c** (74 mg, 0.223 mmol, 1.2 eq), and Et_3N (51 μL, 0.367 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.49), **13i** (44 mg, 38%) as a pale yellow powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.21 (s, 1H), 7.90 (d, 1H, J = 1.6 Hz), 7.89 (d, 1H, J = 5.0 Hz), 7.52 (d, 1H, J = 7.9 Hz), 7.29 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 7.24 (t, 1H, J = 7.3 Hz), 7.16 (d, 1H, J = 7.8 Hz), 7.09 (t, 1H, J = 7.6 Hz), 6.99 (m, 2H), 6.90 (d, 1H, J = 8.5 Hz), 6.72 (t, 1H, J = 7.3 Hz), 6.14 (br t, 1H), 4.10 (d, 2H, J = 5.2

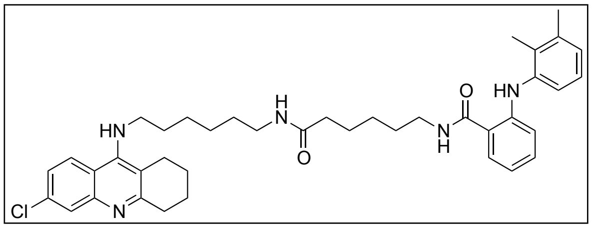
Hz), 3.96 (br s, 1H), 3.46 (t, 2H, *J* = 7.0 Hz), 3.31 (q, 2H, *J* = 6.6 Hz), 3.05 (br s, 2H), 2.67 (br s, 2H), 2.33 (s, 3H), 2.20 (s, 3H), 1.93 (m, 4H), 1.64 (p, 2H, *J* = 7.1 Hz), 1.54 (p, 2H, *J* = 7.4 Hz), 1.39 (m, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 170.1, 169.0, 159.5, 150.8, 148.1, 147.6, 139.3, 138.1, 134.0, 132.8, 131.2, 127.8, 127.4, 126.0, 125.9, 124.6, 124.2, 121.4, 118.4, 116.8, 115.8, 115.4, 114.9, 49.4, 43.7, 39.4, 34.0, 31.6, 29.4, 26.52, 26.49, 24.6, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{36}H_{42}ClN_5O_2$: 611.30; found 612.25 [M+H]$^+$.



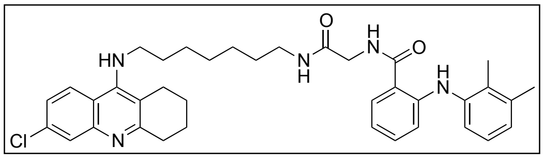
N-(3-((6-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)amino)-3-oxopropyl)-2-((2,3-dimethylphenyl)amino)benzamide (13j). Compound **13j** was prepared as described for the synthesis of **10a**. The reaction of **9b** (94 mg, 0.301 mmol, 1 eq), EDAC hydrochloride (64 mg, 0.331 mmol, 1.1 eq), HOBt hydrate (51 mg, 0.331 mmol, 1.1 eq), **6c** (130 mg, 0.391 mmol, 1.2 eq), and Et$_3$N (76 μL, 0.542 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.29), **13j** (28 mg, 15%) as a white powder: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.32 (s, 1H), 7.90 (d, 1H, *J* = 2.7 Hz), 7.89 (d, 1H, *J* = 8.2 Hz), 7.44 (d, 1H, *J* = 7.8 Hz), 7.28 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.3 Hz), 7.20 (t, 1H, *J* = 7.5 Hz), 7.19 (m, 1H), 7.17 (d, 1H, *J* = 8.2 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.96 (d, 1H, *J* = 7.5 Hz), 6.93 (d, 1H, *J* = 8.5 Hz), 6.68 (t, 1H, *J* = 7.4 Hz), 5.86 (m, 1H), 4.01 (br s, 1H), 3.73 (q, 2H, *J* = 5.8 Hz), 3.47 (t, 2H, *J* = 7.2 Hz), 3.27 (q, 2H, *J* = 6.7 Hz), 3.04 (m, 2H), 2.67 (m, 2H), 2.52 (t, 2H, *J* = 5.8 Hz), 2.33 (s, 3H), 2.21 (s, 3H), 1.93 (m, 4H), 1.63 (p, 2H, *J* = 6.9 Hz), 1.52 (p, 2H, *J* = 7.4 Hz), 1.37 (m, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 171.6, 169.8, 159.5, 150.9, 147.2, 139.5, 138.1, 134.1, 132.3, 130.8, 127.6, 127.4, 125.8, 125.6, 124.6, 124.3, 120.8, 118.3, 116.8, 116.5, 115.7, 114.8, 49.4, 39.4, 35.8, 35.6, 33.9, 31.6, 29.5, 26.6, 26.5, 24.6, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{37}H_{44}ClN_5O_2$: 625.32; found 626.35 [M+H]$^+$.



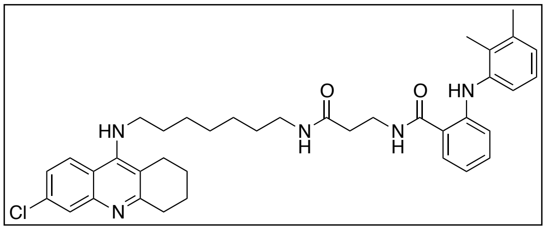
N-(4-((6-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)amino)-4-oxobutyl)-2-((2,3-dimethylphenyl)amino)benzamide (13k). Compound **13k** was prepared as described for the synthesis of **10a**. The reaction of **9c** (78 mg, 0.238 mmol, 1 eq), EDAC hydrochloride (50 mg, 0.262 mmol, 1.1 eq), HOBt hydrate (40 mg, 0.262 mmol, 1.1 eq), **6c** (95 mg, 0.285 mmol, 1.2 eq), and Et$_3$N (60 μL, 0.428 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.38), **13k** (21 mg, 13%) as a pale yellow powder: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.33 (s, 1H), 7.90 (s, 1H), 7.89 (d, 1H, *J* = 9.3 Hz), 7.49 (d, 1H, *J* = 7.1 Hz), 7.27 (dd, 1H, J_1 = 9.1 Hz, J_2 = 2.1 Hz), 7.21 (t, 1H, *J* = 7.4 Hz), 7.17 (d, 1H, *J* = 7.9 Hz), 7.07 (t, 1H, *J* = 7.7 Hz), 7.02 (br t, 1H), 6.94 (t, 2H), 6.71 (t, 1H, *J* = 7.3 Hz), 6.19 (br t, 1H), 4.00 (br s, 1H), 3.50 (q, 2H, *J* = 6.2 Hz), 3.46 (t, 2H, *J* = 7.2 Hz), 3.26 (q, 2H, *J* = 6.8 Hz), 3.04 (br t, 2H), 2.66 (br t, 2H), 2.31 (m, 5H), 2.21 (s, 3H), 1.97 (p, 2H, *J* = 6.2 Hz), 1.92 (m, 4H), 1.64 (p, 2H, *J* = 7.2 Hz), 1.51 (p, 2H, *J* = 7.0 Hz), 1.36 (m, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 173.0, 170.2, 159.5, 150.8, 148.0, 147.1, 139.6, 138.1, 134.0, 132.3, 130.7, 127.7, 127.4, 125.8, 125.6, 124.7, 124.2, 120.7, 118.3, 116.9, 116.6, 115.7, 114.8, 49.4, 43.7, 39.5, 39.4, 34.1, 34.0, 31.6, 29.5, 26.6, 26.5, 25.2, 24.6, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{38}H_{46}ClN_5O_2$: 639.33; found 640.30 [M+H]$^+$.



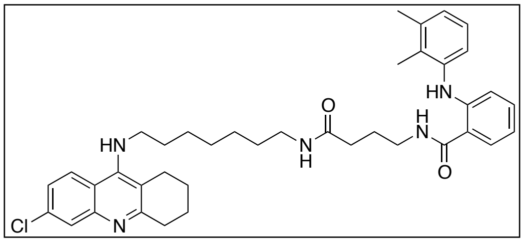
N-(6-((6-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)hexyl)amino)-6-oxohexyl)-2-((2,3-dimethylphenyl)amino)benzamide (13l). Compound **13l** was prepared as described for the synthesis of **10a**. The reaction of **9d** (96 mg, 0.271 mmol, 1 eq), EDAC hydrochloride (57 mg, 0.298 mmol, 1.1 eq), HOBt hydrate (46 mg, 0.298 mmol, 1.1 eq), **6c** (108 mg, 0.325 mmol, 1.2 eq), and Et_3N (68 μL, 0.488 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.50), **13l** (96 mg, 53%) as a pale yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.24 (s, 1H), 7.88 (d, 1H, J = 9.1 Hz), 7.85 (d, 1H, J = 1.8 Hz), 7.45 (d, 1H, J = 7.8 Hz), 7.23 (dd, 1H, J_1 = 9.0 Hz, J_2 = 1.8 Hz), 7.17 (t, 1H, J = 7.4 Hz), 7.14 (d, 1H, J = 8.6 Hz), 7.04 (t, 1H, J = 7.7 Hz), 6.91 (d, 2H, J = 8.0 Hz), 6.75 (t, 1H, J = 5.3 Hz), 6.64 (t, 1H, J = 7.4 Hz), 6.02 (t, 1H, J = 5.4 Hz), 4.03 (br s, 1H), 3.41 (m, 4H), 3.19 (q, 2H, J = 6.8 Hz), 2.99 (br s, 2H), 2.63 (br s, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 2.15 (t, 2H, J = 7.3 Hz), 1.88 (br s, 4H), 1.65 (p, 2H, J = 7.5 Hz), 1.60 (p, 4H, J = 7.3 Hz), 1.45 (p, 2H, J = 7.4 Hz), 1.37 (m, 4H), 1.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 169.9, 159.5, 150.8, 148.1, 146.9, 139.6, 138.0, 133.9, 132.1, 130.6, 127.6, 127.4, 125.7, 125.5, 124.7, 124.1, 120.6, 118.4, 117.2, 116.8, 115.7, 114.8, 49.4, 39.4, 39.2, 36.4, 34.0, 31.6, 29.6, 29.2, 26.6, 26.5, 26.4, 25.1, 24.6, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{40}H_{50}ClN_5O_2$: 667.37; found 668.30 $[M+H]^+$.



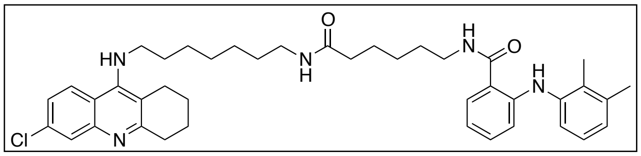
N-(2-((7-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)amino)-2-oxoethyl)-2-((2,3-dimethylphenyl)amino)benzamide (13m). Compound **13m** was prepared as described for the synthesis of **10a**. The reaction of **9a** (53.4 mg, 0.179 mmol, 1 eq), EDAC hydrochloride (38 mg, 0.197 mmol, 1.1 eq), HOBt hydrate (30 mg, 0.197 mmol, 1.1 eq), **6d** (74.2 mg, 0.2155 mmol, 1.2 eq), and Et_3N (45 μL, 0.323 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.50), **13m** (11 mg, 10%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.22 (s, 1H), 7.91 (d, 1H, J = 5.7 Hz), 7.89 (d, 1H, J = 2.8 Hz), 7.53 (d, 1H, J = 7.9 Hz), 7.28 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.8 Hz), 7.23 (t, 1H, J = 7.5 Hz), 7.15 (d, 1H, J = 7.9 Hz), 7.14 (m, 1H), 7.08 (t, 1H, J = 7.6 Hz), 6.97 (d, 1H, J = 7.4 Hz), 6.89 (d, 1H, J = 8.5 Hz), 6.70 (t, 1H, J = 7.4 Hz), 6.27 (t, 1H, J = 5.5 Hz), 4.10 (d, 2H, J = 5.2 Hz), 3.90 (very br s, 1H), 3.47 (t, 2H, J = 7.3 Hz), 3.29 (q, 2H, J = 6.8 Hz), 3.05 (br s, 2H), 2.67 (br s, 2H), 2.33 (s, 3H), 2.19 (s, 3H), 1.93 (m, 4H), 1.64 (p, 2H, J = 7.1 Hz), 1.50 (p, 2H, J = 6.7 Hz), 1.33 (m, 6H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 168.9, 160.0, 151.0, 149.8, 147.6, 139.3, 138.1, 132.8, 132.6, 131.2, 127.8, 127.3, 126.0, 125.8, 124.6, 124.3, 121.4, 118.3, 116.8, 115.6, 115.4, 114.9, 49.5, 43.6, 39.6, 33.9, 31.7, 29.4, 28.9, 26.7, 26.6, 24.6, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{37}H_{44}ClN_5O_2$: 625.32; found 626.25 $[M+H]^+$.



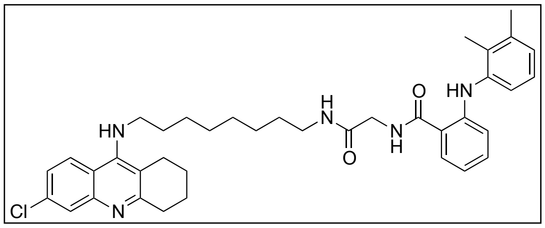
N-(3-((7-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)amino)-3-oxopropyl)-2-((2,3-dimethylphenyl)amino)benzamide (13n). Compound **13n** was prepared as described for the synthesis of **10a**. The reaction of **9b** (51 mg, 0.164 mmol, 0.86 eq), EDAC hydrochloride (40 mg, 0.209 mmol, 1.1 eq), HOBt hydrate (32 mg, 0.209 mmol, 1.1 eq), **6d** (79 mg, 0.228 mmol, 1.2 eq), and Et_3N (48 μL, 0.342 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.46), **13n** (61 mg, 58%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.33 (s, 1H), 7.87 (d, 1H, J = 9.0 Hz), 7.86 (d, 1H, J = 2.0 Hz), 7.45 (d, 1H, J = 7.7 Hz), 7.41 (t, 1H, J = 5.6 Hz), 7.25 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 7.17 (t, 1H, J = 7.7 Hz), 7.15 (d, 1H, J = 7.6 Hz), 7.05 (t, 1H, J = 7.6 Hz), 6.93 (d, 1H, J = 7.5 Hz), 6.90 (d, 1H, J = 8.5 Hz), 6.65 (t, 1H, J = 7.3 Hz), 6.36 (t, 1H, J = 5.5 Hz), 3.98 (br s, 1H), 3.70 (q, 2H, J = 5.8 Hz), 3.44 (t, 2H, J = 6.7 Hz), 3.22 (q, 2H, J = 6.7 Hz), 3.01 (br t, 2H), 2.64 (br t, 2H), 2.50 (t, 2H, J = 5.9 Hz), 2.30 (s, 3H), 2.19 (s, 3H), 1.89 (m, 4H), 1.60 (p, 2H, J = 7.2 Hz), 1.46 (p, 2H, J = 6.7 Hz), 1.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 169.8, 159.5, 150.8, 148.1, 147.2, 139.5, 138.0, 133.9, 132.2, 130.7, 127.7, 127.4, 125.7, 125.5, 124.7, 124.2, 120.8, 118.4, 116.8, 116.5, 115.7, 114.7, 49.5, 39.5, 35.8, 35.4, 34.0, 31.7, 29.4, 28.9, 26.8, 26.7, 24.6, 22.9, 22.6, 20.7, 13.9; m/z calcd for $C_{38}H_{46}ClN_5O_2$: 639.33; found 640.30 $[M+H]^+$.



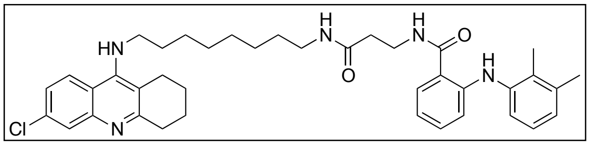
N-(4-((7-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)amino)-4-oxobutyl)-2-((2,3-dimethylphenyl)amino)benzamide (**13o**). Compound **13o** was prepared as described for the synthesis of **10a**. The reaction of **9c** (52 mg, 0.158 mmol, 0.87 eq), EDAC hydrochloride (38 mg, 0.200 mmol, 1.1 eq), HOBt hydrate (31 mg, 0.200 mmol, 1.1 eq), **6d** (84 mg, 0.258 mmol, 1.2 eq), and Et_3N (46 μL, 0.387 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.50), **13o** (59 mg, 57%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.35 (s, 1H), 7.87 (d, 1H, J = 9.2 Hz), 7.86 (d, 1H, J = 2.1 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.39 (t, 1H, J = 7.0 Hz), 7.23 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.1 Hz), 7.17 (t, 1H, J = 7.5 Hz), 7.14 (d, 1H, J = 8.4 Hz), 7.04 (t, 1H, J = 7.6 Hz), 6.91 (d, 2H, J = 8.1 Hz), 6.66 (t, 1H, J = 7.4 Hz), 6.62 (t, 1H, J = 5.5 Hz), 4.01 (br s, 1H), 3.47 (t, 2H, J = 5.9 Hz), 3.44 (q, 2H, J = 5.4 Hz), 3.21 (q, 2H, J = 6.7 Hz), 3.00 (br t, 2H), 2.63 (br t, 2H), 2.29 (t, 2H, J = 7.2 Hz), 2.29 (s, 3H), 2.18 (s, 3H), 1.94 (p, 2H, J = 6.5 Hz), 1.88 (m, 4H), 1.60 (p, 2H, J = 7.0 Hz), 1.45 (p, 2H, J = 6.5 Hz), 1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 170.2, 159.4, 150.9, 148.0, 147.1, 139.6, 138.0, 134.0, 132.1, 130.6, 127.8, 127.3, 125.7, 125.5, 124.7, 124.1, 120.7, 118.3, 116.8, 116.7, 115.6, 114.7, 49.5, 39.6, 39.5, 34.1, 33.9, 31.7, 29.4, 28.9, 26.8, 26.7, 25.2, 24.6, 22.9, 22.6, 20.7, 13.9; m/z calcd for $C_{39}H_{48}ClN_5O_2$: 653.35; found 654.25 $[M+H]^+$.



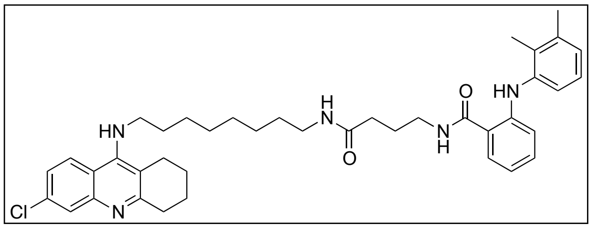
N-(6-((7-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)heptyl)amino)-6-oxohexyl)-2-((2,3-dimethylphenyl)amino)benzamide (**13p**). Compound **13p** was prepared as described for the synthesis of **10a**. The reaction of **9d** (55 mg, 0.155 mmol, 0.80 eq), EDAC hydrochloride (41 mg, 0.214 mmol, 1.1 eq), HOBt hydrate (33 mg, 0.214 mmol, 1.1 eq), **6d** (81 mg, 0.233 mmol, 1.2 eq), and Et_3N (49 μL, 0.350 mmol, 1.8 eq) in DMF (3 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.42), **13p** (51 mg, 48%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.23 (s, 1H), 7.89 (d, 1H, *J* = 9.0 Hz), 7.87 (d, 1H, *J* = 2.1 Hz), 7.44 (d, 1H, *J* = 7.1 Hz), 7.25 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.1 Hz), 7.18 (t, 1H, *J* = 7.5 Hz), 7.15 (d, 1H, *J* = 7.7 Hz), 7.05 (t, 1H, *J* = 7.7 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 6.66 (t, 1H, *J* = 7.4 Hz), 6.61 (t, 1H, *J* = 5.5 Hz), 5.85 (t, 1H, *J* = 5.5 Hz), 4.01 (br s, 1H), 3.46 (t, 2H, *J* = 7.0 Hz), 3.42 (q, 2H, *J* = 6.8 Hz), 3.19 (q, 2H, *J* = 6.7 Hz), 3.01 (m, 2H), 2.65 (m, 2H), 2.31 (s, 3H), 2.19 (s, 3H), 2.17 (t, 2H, *J* = 7.4 Hz), 1.90 (m, 4H), 1.68 (p, 2H, *J* = 7.4 Hz), 1.63 (p, 4H, *J* = 7.1 Hz), 1.42 (m, 4H), 1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 169.8, 159.5, 150.9, 148.1, 147.0, 139.6, 138.0, 133.9, 132.1, 130.6, 127.5, 127.4, 125.7, 125.5, 124.7, 124.2, 120.6, 118.4, 117.2, 116.8, 115.7, 114.8, 49.5, 39.40, 39.38, 36.4, 34.0, 31.7, 29.6, 29.2, 28.9, 26.8, 26.7, 26.4, 25.1, 24.6, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{41}H_{52}ClN_5O_2$: 681.38; found 682.40 $[M+H]^+$.



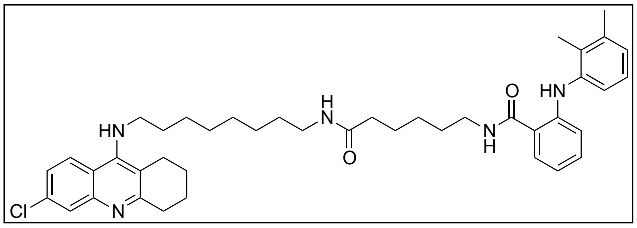
N-(2-((8-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)amino)-2-oxoethyl)-2-((2,3-dimethylphenyl)amino)benzamide (13q). Compound **13q** was prepared as described for the synthesis of **10a**. The reaction of **9a** (47 mg, 0.158 mmol, 1 eq), EDAC hydrochloride (33 mg, 0.173 mmol, 1.1 eq), HOBt hydrate (27 mg, 0.173 mmol, 1.1 eq), **6e** (68 mg, 0.205 mmol, 1.2 eq), and Et_3N (40 μL, 0.284 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.37), **13q** (46 mg, 54%) as a pale yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.23 (s, 1H), 7.90 (d, 1H, *J* = 10.5 Hz), 7.88 (s, 1H), 7.56 (d, 1H, *J* = 7.9 Hz), 7.41 (t, 1H, *J* = 4.8 Hz), 7.27 (d, 1H, *J* = 9.0 Hz), 7.20 (t, 1H, *J* = 7.6 Hz), 7.15 (d, 1H, *J* = 7.8 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.97 (d, 1H, *J* = 7.3 Hz), 6.87 (d, 1H, *J* = 8.5 Hz), 6.66 (t, 1H, *J* = 7.6 Hz), 6.64 (t, 1H, *J* = 5.4 Hz), 4.10 (d, 2H, *J* = 5.1 Hz), 3.99 (br s, 1H), 3.46 (t, 2H, *J* = 6.7 Hz), 3.27 (q, 2H, *J* = 6.7 Hz), 3.03 (br s, 2H), 2.66 (br s, 2H), 2.32 (s, 3H), 2.18 (s, 3H), 1.92 (m, 4H), 1.62 (p, 2H, *J* = 7.0 Hz), 1.48 (br p, 2H), 1.34 (m, 2H), 1.27 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 169.0, 159.5, 150.9, 148.1, 147.6, 139.3, 138.1, 134.0, 132.7, 131.2, 127.9, 127.4, 126.0, 125.8, 124.7, 124.2, 121.5, 118.4, 116.8, 115.7, 115.5, 114.8, 49.5, 43.7, 39.6, 34.0, 31.7, 29.4, 29.14, 29.07, 26.8, 26.7, 24.6, 22.9, 22.7, 20.7, 13.9; *m/z* calcd for $C_{38}H_{46}ClN_5O_2$: 639.33; found 640.35 $[M+H]^+$.



N-(3-((8-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)amino)-3-oxopropyl)-2-((2,3-dimethylphenyl)amino)benzamide (13r). Compound **13r** was prepared as described for the synthesis of **10a**. The reaction of **9b** (50 mg, 0.159 mmol, 1 eq), EDAC hydrochloride (34 mg, 0.175 mmol, 1.1 eq), HOBt hydrate (27 mg, 0.175 mmol, 1.1 eq), **6e** (69 mg, 0.207 mmol, 1.2 eq), and Et_3N (40 μL, 0.286 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO_2; 9:1/CH_2Cl_2:MeOH with NH_4OH (7 mL/L of solvent), R_f 0.45), **13r** (20 mg, 20%) as a pale yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.32 (s, 1H), 7.90 (d, 1H, *J* = 9.0 Hz), 7.89 (d, 1H, *J* = 2.0 Hz), 7.45 (d, 1H, *J* = 7.8 Hz), 7.29 (m, 1H), 7.27 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 7.20 (t, 1H, *J* = 8.0 Hz), 7.17 (d, 1H, *J* = 8.7 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 6.95 (d, 1H, *J* = 7.4 Hz), 6.92 (d, 1H, *J* = 8.5 Hz), 6.68 (t, 1H, *J* = 7.4 Hz), 6.00 (t, 1H, *J* = 5.3 Hz), 3.99 (br s, 1H), 3.72 (q, 2H, *J* = 5.8 Hz), 3.48 (t, 2H, *J* = 7.0 Hz), 3.25 (q, 2H, *J* = 6.6 Hz), 3.03 (m, 2H), 2.67 (m, 2H), 2.52 (t, 2H, *J* = 5.8 Hz), 2.33 (s, 3H), 2.21 (s, 3H), 1.92 (m, 4H), 1.64 (p, 2H, *J* = 7.4 Hz), 1.47 (br p, 2H), 1.36 (m, 4H), 1.28 (s, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 171.7, 169.8, 159.5, 150.9, 148.1, 147.2, 139.6, 138.0, 134.0, 132.3, 130.8, 127.6, 127.5, 125.7, 125.6, 124.7, 124.2, 120.8, 118.4, 116.8, 116.5, 115.7, 114.8, 49.5, 39.6, 35.8, 35.5, 34.00, 33.96, 31.7, 29.5, 29.13, 29.09, 26.8, 24.6, 22.9, 22.7, 20.7, 13.9; *m/z* calcd for $C_{39}H_{48}ClN_5O_2$: 653.35; found 654.35 [M+H]$^+$.



N-(4-((8-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)amino)-4-oxobutyl)-2-((2,3-dimethylphenyl)amino)benzamide (13s). Compound **13s** was prepared as described for the synthesis of **10a**. The reaction of **9c** (45 mg, 0.137 mmol, 1 eq), EDAC hydrochloride (29 mg, 0.150 mmol, 1.1 eq), HOBt hydrate (23 mg, 0.150 mmol, 1.1 eq), **6e** (64 mg, 0.177 mmol, 1.2 eq), and Et$_3$N (34 μL, 0.247 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.35), **13s** (28 mg, 31%) as a pale yellow powder: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.35 (s, 1H), 7.91 (d, 1H, *J* = 8.8 Hz), 7.92 (s, 1H), 7.49 (d, 1H, *J* = 7.2 Hz), 7.29 (m, 1H), 7.22 (t, 1H, *J* = 7.3 Hz), 7.18 (d, 1H, *J* = 7.8 Hz), 7.08 (t, 1H, *J* = 7.7 Hz), 6.99 (br t, 1H), 6.95 (m, 2H) 6.72 (t, 1H, *J* = 7.4 Hz), 6.07 (br t, 1H), 4.02 (very br s, 1H), 3.51 (p, 4H, *J* = 6.4 Hz), 3.25 (q, 2H, *J* = 6.7 Hz), 3.05 (br t, 2H), 2.68 (br t, 2H), 2.33 (m, 5H), 2.22 (s, 3H), 1.99 (m, 2H), 1.94 (m, 4H), 1.66 (p, 2H, *J* = 7.3 Hz), 1.48 (m, 2H), 1.35 (m, 2H), 1.29 (m, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 172.9, 170.1, 147.2, 139.6, 138.0, 135.3, 134.7, 134.2, 132.2, 130.7, 127.6, 126.8, 125.7, 125.5, 124.7, 124.3, 120.8, 116.9, 116.6, 114.8, 49.5, 39.6, 39.5, 34.2, 34.0, 31.7, 29.5, 29.11, 29.08, 26.8, 25.1, 25.0, 24.5, 22.9, 22.6, 20.7, 13.9; *m/z* calcd for $C_{40}H_{50}ClN_5O_2$: 667.37; found 668.40 [M+H]$^+$.



N-(6-((8-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)octyl)amino)-6-oxohexyl)-2-((2,3-dimethylphenyl)amino)benzamide (13t). Compound **13t** was prepared as described for the synthesis of **10a**. The reaction of **9d** (48 mg, 0.137 mmol, 1 eq), EDAC hydrochloride (29 mg, 0.152 mmol, 1.1 eq), HOBt hydrate (23 mg, 0.152 mmol, 1.1 eq), **6e** (65 mg, 0.180 mmol, 1.2 eq), and Et$_3$N (34 μL, 0.244 mmol, 1.8 eq) in DMF (4 mL) yielded, after purification by flash column chromatography (SiO$_2$; 9:1/CH$_2$Cl$_2$:MeOH with NH$_4$OH (7 mL/L of solvent), R$_f$ 0.29), **13t** (80 mg, 84%) as a pale yellow powder: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.23 (s, 1H), 7.92 (d, 1H, *J* = 7.7 Hz), 7.91 (d, 1H, *J* = 1.9 Hz), 7.45 (d, 1H, *J* = 7.3 Hz), 7.28 (dd, 1H, J_1 = 9.0 Hz, J_2 = 1.9 Hz), 7.21 (t, 1H, *J* = 7.3 Hz), 7.17 (d, 1H, *J* = 7.9 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 6.94 (m, 2H), 6.69 (t, 1H, *J* = 7.2 Hz), 6.44 (br t, 1H), 5.62 (br t, 1H), 4.10 (very br s, 1H), 3.51 (t, 2H, *J* = 7.1 Hz), 3.45 (q, 2H, *J* = 6.3 Hz), 3.22 (q, 2H, *J* = 6.7 Hz), 3.05 (br t, 2H), 2.67 (br t, 2H), 2.33 (s, 3H), 2.21 (s, 3H), 2.20 (t, 2H, *J* = 7.4 Hz), 1.93 (m, 4H), 1.69 (m, 6H), 1.45 (p, 4H, *J* = 7.1 Hz), 1.38 (br p, 2H), 1.30 (m, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 172.8, 169.8, 162.5, 151.2, 147.0, 144.0, 139.6, 138.0, 132.1, 130.7, 127.4, 125.7, 125.5, 124.7, 124.3, 120.7, 118.9, 118.1, 117.2, 116.8, 116.6, 115.5, 114.9, 49.5, 39.44, 39.38, 36.5, 31.7, 30.9, 29.6, 29.2, 29.12, 29.06, 26.74, 26.71, 26.4, 25.0, 24.5, 22.9, 22.5, 20.7, 13.9; *m/z* calcd for $C_{42}H_{54}ClN_5O_2$: 695.40; found 696.45 [M+H]$^+$.

3. Biochemical methods.

3.1. *In vitro* acetylcholinesterase (AChE) assay. Compounds were dissolved in sodium phosphate (dibasic) buffer ((125 μL), 0.1 M, pH 8.0 (adjusted at rt)) and a five-fold dilution was performed. To the solution of inhibitors was added AChE cocktail (50 μL, containing 0.08 U/mL (~0.29 nM) AChE (final concentration) (Sigma-Aldrich cat #C2888 from eel) in sodium phosphate (dibasic) buffer (0.1 M, pH 8.0 (adjusted at rt)). The mixture of inhibitor and enzyme were incubated for 10 min before initiation with DTNB (50 μL, 0.25 mM final concentration) and acetylthiocholine (ATC) (0.5 mM final concentration) in phosphate buffer. The reaction was monitored at 412 nm taking measurements every 30 sec for 30 min on a SpectraMax M5 plate reader. Data was corrected with the negative control (no ATC) and normalized to the positive control (no inhibitor) using the initial rates (first 2-5 min). All assays were performed at least in triplicate. The resulting curve rate vs concentration of inhibitor was fitted to a sigmoidal curve and IC_{50} values calculated using KaleidaGraph 4.1.1. Three representative examples of IC_{50} curves are provided in Fig. 2. All IC_{50} values are provided in Table 1.

3.2. Studies of the mode of inhibition. Non-competitive inhibition was determined by incubating 4 concentrations of inhibitor (0, 0.2, 1, and 5 μM) with AChE (as described above). The enzymatic reaction was then initiated by the addition of various concentrations of ATC (62.5, 250, 500, and 1000 μM). The rates of the reactions were calculated using the first 2 min of the reaction and plotted on a Lineweaver-Burk plot. Separate lines were drawn for each concentration of enzyme and observation of intersection on the negative side of the x axis indicated non-competitive inhibition. A representative plot is provided in Fig. 3.

3.3. *In vitro* AChE ROS inactivation assay. In the wells of a 96-well plate, horseradish peroxidase (0.25 μM), H_2O_2 (100 μM), AChE (0.08 U/mL, ~0.29 nM), mefenamic acid compound (25 μM – 13 pM), and DETAPAC (100 μM) were dissolved in acetate buffer (pH 6.0) (50 mM) and incubated at 37 °C for 30 min. Note: all concentrations are reported as final concentrations. Reactions are added to a mixture of ATC (0.5 mM), and DTNB (0.25 mM) in sodium phosphate (dibasic) buffer (pH 7.4) (50 mM). Reaction rates were monitored at 25 °C for 20 min taking measurements every 30 sec, rates were calculated using the initial rate of the first 2-5 min. Total reaction volume was 200 μL. Rates were normalized to the reaction without compounds and plotted in KaleidaGraph 4.1.1 to calculate the IC_{50}. Three representative examples of IC_{50} curves are provided in Fig. 2. All IC_{50} values are provided in Table 1.

4. Molecular modeling.

Molecular docking studies were run on an Intell Premium 4 CPU (3.19 GHz, 0.99 GB of RAM, Windows XP Professional (Version 2002)), using the modeling program AutoDock 4.2 (2009. The Scripps Research Institute. 10550 North Torrey Pines Road, La Jolla, CA 92037. http://autodock.scripps.edu). Additionally, the program Cygwin (version 1.7. http://www.cygwin.com) was used to properly run the Autogrid and AutoDock applications. The crystal structure of acetylcholinesterase from *Torpedo californica* in complex with tacrine (PDB ID: 1ACJ, 2.8 Å resolution) was first edited in PyMOL (http://www.pymol.org, (PyMOL Molecular Graphics System, version 1.1r1, Schrödinger, LLC)) by manually removing all H_2O molecules. The tacrine molecule was also removed from the active site. The enzyme was then loaded into AutoDock where all polar hydrogens were added and Kollman charges were assigned. The various ligands were prepared in ChemBio3D Ultra 12.0 (http://www.cambridgesoft.com), and then loaded into AutoDock. The scoring grid for Autodock was centered approximately in between the CAS and PAS (x-center: 4.795, y-center: 66.845, z-center: 72.226). The grid size was selected be 60×60×60 points with a spacing between grid points of 0.375 Å. A Lamarckian genetic search algorithm was run 100 times using 150 population size and a maximum number of energy evaluations of 2,500,000 while the rest of the docking study parameters were kept at their default quantity. After the docking was finished, conformations that were shown to be the in the largest cluster or most thermodynamically stable were examined in PyMOL. All docking figures were made in PyMOL.

5. Abbreviations.

AChE, acetylcholinesterase; ATC, acetylthiocholine; DCC, N,N'-dicyclohexylcarbodiimide; DETAPAC, diethylenetriaminepentaacetic acid; DIPEA, diisopropylethylamine; DTNB, 5,5′-dithiobis(2-nitrobenzoic acid); HOBt, hydroxybenzotriazole.

6. Supporting information references.

1. M. K. Hu, L. J. Wu, G. Hsiao and M. H. Yen, *J Med Chem*, 2002, **45**, 2277-2282.