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Chemistry & Drug Discovery

# Supporting Information

SUPPORTING INFORMATION for:

# Dimerizable redox-sensitive triazine-based cationic lipids for *in vitro* gene delivery

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## Materials and methods

*Plasmids and chemicals*

Plasmid DNA (3 kb) encoding green fluorescent protein under the control of the spleen necrosis virus promoter (pEGFP) was purchased from Clontech Laboratories. Lipofectamine™ 2000 and Opti-MEM® were obtained from Invitrogen Life Technologies. DOTAP was purchased from Avanti Polar Lipids. All chemicals were of reagent grade or higher quality and were purchased from Sigma if not differently specified.

*DNA Binding Assay*

The DNA binding ability of the cationic lipids was assessed by gel retardation assay on a 0.75%-agarose gel. 0.8 µg of pEGFP plasmid was complexed with the compound 4 (at a cationic lipid/DNA charge ratio (CR) 0.2:1, 1:1, 2:1, 5:1, 10:1, 15:1 and 20:1) in a total volume of 20 µl of distilled water and incubated at room temperature for 30 min. 8 µl of gel loading solution (0.05% w/v bromphenol blue, 40% w/v sucrose, 0.1 M EDTA pH 8 and 0.5% w/v SDS) was added, and the total solution was loaded into wells. The samples were electrophoresed at 100 V for 1 h and half in

TAE buffer, and the DNA bands were detected under UV light after incubating overnight with 10 µl of SYBR® GREEN I in TAE buffer.

*SEM analysis*

For visualization of the surface morphology of lipoplexes by a scanning electron microscope (SEM), a drop of DNA-compound 4 at CR 10 suspension was added to a Ti SEM stage, freeze dried, sputter coated with gold and examined with a Leica–Cambridge Stereoscan 440 microscope at a 3–7 keV acceleration voltage.

*Critical micellar concentration (cmc) by fluorimetry*

Fluorimetric cmc determination was conducted utilizing the characteristic of the hydrophobic fluorescent probe N-phenyl-1-naphthylamine (NPN) to partition into the hydrophobic core of molecular aggregates resulting in an increase of its fluorescence intensity. Decreasing concentrations of Compound 4 stock solution in dH2O (130 mM) were diluted to a final volume of 100 µL, then 10 µM NPN was added. The fluorescence of NPN (excitation and emission wavelengths at 350 and 410 nm, respectively) was measured at 30°C and plotted versus the logarithm of Compound 4 concentration. The sharp break was taken as the cmc.

*Cell culture and in vitro transfection studies*

PC3, COS-7, HeLa, NRK, P19, U87, L929 and MG63 cells were purchased from Sigma and were mycoplasma-free. PC3, COS-7, HeLa, NRK and L929 cell lines were cultured with Dulbecco's Modified Eagle Medium (D-MEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. P19 cells were grown in a-Minimum Essential Medium (a-MEM) supplemented with 2.5% FBS, 7.5% fetal calf serum (FCS) and 1% non-essential amino acids (NEAA). MG63 were cultured in Eagle’s Minimum Essential Medium (E-MEM) supplemented with 10% FBS, 1% NEAA and 1% penicillin-streptomycin. The cells were plated in 25 $cm^2$ culture flasks and allowed to adhere overnight before experiments at 37°C in a humidified atmosphere of 5% $CO_2$ in air. The day of transfection, the 50-60% confluency cells were washed once in PBS and the culture medium was replaced with 5 ml of Opti-MEM® containing either 100 µl of naked DNA or cationic lipid-DNA nanoparticles. Briefly, cationic lipids were solubilised in 100 µl of distilled water and 2 µg of pEGFP plasmid was added and gently mixed by pipetting. The final solution was left at room temperature for 30 min to form complexes. Lipofectamine™ 2000 and DOTAP were used as positive control, according to the manufacturer’s procedures. Following 4 h incubation, the cells were washed once with PBS and incubated 48 h posttransfection in D-MEM complete medium. Adherent cells were observed and photographed with Zeiss Axioplan microscope for GFP expression and with Leica DMIRD inverted microscope for cell morphology. The cells were trypsinized, counted, fixed in 300 µl of fixation buffer (4% w/v PFA in PBS) and stored at 4°C for FACS analysis (Calibur, Becton Dickinson).

*Statistical analysis*

The statistical analysis of experimental data was done using Student's t-test and results are presented as mean ± S.E.M. Statistical significance was accepted when $p<0.05$.

**Synthesis of (4,6-dichloro-[1,3,5]triazin-2-yl)-tetradecyl-amine (1).**

1-Tetradecylamine (213 mg, 1.0 mmol) in acetone (5 mL) was added to a stirred ice-cooled (0°C) solution of 2,4,6-trichloro-[1,3,5]triazine (1 mmol, 184 mg) in $H_2O$ (1 mL) / acetone (4 ml) solution followed by the addition of $NaHCO_3$ (1 mmol, 84 mg) in $H_2O$ (2 ml). The reaction mixture was stirred for 2 h at rt and then the acetone was evaporated under vacuum, water (1 ml) was added and the organics were extracted with AcOEt ( 3 x 1 mL) and with $CHCl_3$ (2 x 5 mL). The combined extracts were dried over anhydrous $Na_2SO_4$, filtered, the solvents were evaporated under vacuum and the residue was purified by flash chromatography on silica gel (*n*-hexane/AcOEt 9:1) to yield **1** (67% – 85% conversion): white powder; $R_F$ = 0.35; m.p. 70 – 75°C; $^1$H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta$=6.9 (br t, 1H; NH), 3.5 (dt, $^3J$(H,H)=6.9 and 6.6 Hz, 2H; $NCH_2$), 1.6 (m, 2H; C$H_2$Me), 1.4 – 1.15 (br m, 22H; 11 x $CH_2$), 0.8 (t, $^3J$(H,H)=6.6 Hz, 3H; $CH_3$); $^{13}$C NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta$=170.9 (q), 169.4 (q), 165.6 (q), 41.5 (s), 31.8 (s), 29.6 (4 x C, s), 29.5 (s), 29.4 (s), 29.3 (s), 29.1 (s), 28.9 (s), 26.6 (s), 22.6 (s), 14.0 (p); IR (microscope): $\tilde{\nu}$=3266 (s), 2931 (s), 1645 (ss), 1417 (s), 1331 (s) , 1239 (s), 1203 (w), 1186 (m), 1148 (m), 1106 (m), 1049 (w), 1011 (w), 987 (w), 936 (w), 914 (w), 851 (s), 796 (m), 766 (m), 721 (w), 647 (w), 582 cm$^{-1}$ (m); MS (70 eV): *m/z* (%): 361 (70) [$M^+$], 360 (30) [$M^+$–H], 325 (100) [$C_{17}H_{30}N_4Cl^+$], 289 (23) [$C_{17}H_{29}N_4^+$], 219 (30) [$C_{12}H_{19}N_4^+$], 206 (38) [$C_{11}H_{18}N_4^+$], 177 (45) [$C_9H_{15}N_4^+$], 129 (8) [$C_5H_9N_4^+$].

**Synthesis of [3-(4-chloro-6-tetradecylamino-[1,3,5]triazin-2-ylamino)-propyl]-carbamic acid *tert*-butyl ester (2).**

(3-Amino-propyl)-carbamic acid *tert*-butyl ester (0.4 mmol, 70 mg) in acetone (4 mL) was added to a stirred ice-cooled (0°C) solution of **1** (0.4 mmol, 144 mg) in acetone (1.5 mL) followed by an aqueous (2.5 mL) solution of $NaHCO_3$ (0.4 mmol, 34 mg). The reaction was stirred for 2 hs at 50°C. The acetone was evaporated under vacuum, $H_2O$ (1 mL) was added and the organics were extracted in AcOEt (3 x 5 mL) and $CHCl_3$ (2 x 2.5 mL). The combined organics were dried over anhydrous $Na_2SO_4$, filtered, the solvents were evaporated under vacuum and the residue was purified by flash chromatography on silica gel in *n*-hexane/AcOEt 7:3 and pure AcOEt to yield **2** (97%): white powder; $R_F$=0.35; m.p. 118 – 120°C; $^1$H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta$=6.9 (br t, 1H; NH), 6.5 (br t, 1H; NH), 6.25 (broad signal, 1H; NH), 3.5 – 3.4 (m, 2H; $CH_2$), 3.45 – 3.3 (m, 2H; $CH_2$), 3.2 – 3.1 (m, 2H; $CH_2$), 1.8 – 1.6 (m, 2H; $CH_2$), 1.6 – 1.5 (m, 2H; $CH_2$), 1.4 (br s, 9H; 3 x Me), 1.35 – 1.15 (br m, 22H; 11 x $CH_2$), 0.85 (t, $^3J$(H,H)=7.0 Hz, 3H; Me); $^{13}$C NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta$=167.8 (q), 165.9 (q), 165.6 (q), 156.1 (q, CO), 79.2 (q), 41.0 (s), 40.9 (s), 37.9 (s), 37.5 (s), 31.9 (s), 30.4 (s), 30.0 (s), 29.7 (s), 29.6 (s, 4 x C), 29.3 (s, 2 x C), 29.0 (p, 3 x C), 28.4 (s), 22.7 (s), 14.1 (p); IR (microscope): $\tilde{\nu}$=3266 (m), 2919 (s), 2851 (m), 1629 (ss), 1560 (ss), 1519 (ss), 1466 (m), 1409 (s), 1375 (m) , 1348 (m), 1327 (m), 1237 (s), 1186 (m), 1147 (m), 1104 (m), 987 (w), 936 (w), 914 (w), 849 (s), 795 (m), 766 (w), 720 (w), 646 (w), 582 $cm^{-1}$ (w); MS (70eV): *m/z* (%): 500 (100) [$M^+$ + H], 444 (30) [$C_{21}H_{41}ClN_6O_2^+$], 400 (5) [$C_{18}H_{33}ClN_6O_2^+$], 368 (78) [$C_{19}H_{35}ClN_5^+$], 342 (10) [$C_{17}H_{32}ClN_5$], 242 (14) [$C_{10}H_{19}ClN_5^+$], 186 (12) [$C_6H_9ClN_5^+$], 158 (3) [$C_4H_5ClN_5^+$], 57 (18) [$C_4H_9^+$], 43 (14) [$C_3H_7^+$].

**Synthesis of {3-[4-tetradecylamino-6-(2-tritylsulfanyl-ethylamino)-1-[1,3,5]triazin-2-ylamino]-propyl}-carbamic acid *tert*-butylester (3).**

A solution of **2** (0.40 mmol, 200 mg) in benzene (3 mL) was kept in a vial flask. 3-Tritylsulfanyl-propylamine hydrochloride (0.80 mmol, 280 mg) and DIPEA (2.0 mmol, 258 μL) were added at rt. The sealed vial was shaken for 24 hs at 120°C. The solvent was evaporated under vacuum to give a residue that, upon flash chromatography on silica gel (*n*-hexane/AcOEt 4:6), yielded **3** (65%): dense yellowish syrup; $R_F$=0.35; $^1$H NMR (400 MHz, $CDCl_3$, 47°C, TMS): δ=7.5 – 7.15 (m, 15H; ArH), 4.95 (broad signal, 2H; 2 x NH), 4.75 (broad signal, 1H; NH), 3.4 (m, 2H; $CH_2$), 3.3 (m, 2H; $CH_2$), 3.2 (m, 2H; $CH_2$), 3.1 (m, 2H; $CH_2$), 2.45 (br t, $^3J$(H,H)=6.7 and 6.4 Hz, 2H; $SCH_2$), 1.6 (dt, $^3J$(H,H)=5.9 and 5.7 Hz, 2H; $CH_2$), 1.5 (m, 2H; $CH_2$), 1.4 (br s, 9H; 3 x Me), 1.35 – 1.2 (br m, 22H; 11 x $CH_2$), 0.9 (t, $^3J$(H,H)=6.7 Hz, 3H; Me); $^{13}$C NMR (400 MHz, $CDCl_3$, 47°C, TMS): δ=166.0 (q), 165.6 (q), 165.5 (q), 156.1 (q, CO), 144.8 (q, 3 x C), 129.6 (t, 6 x C, Ar), 127.8 (t, 6 x C, Ar), 126.6 (t, 3 x C, Ar), 78.8 (q), 66.7 (q), 40.7 (s), 40.6 (s), 39.5 (s), 37.2 (s), 37.1 (s), 32.1 (s), 31.8 (s), 30.4 (s), 29.8 (s), 29.6 (s), 29.5 (s, 4 x C), 29.3 (s), 29.2 (s), 28.4 (p, 3 x C), 26.9 (s), 22.6 (s), 14.0 (p); IR (microscope): $\tilde{\nu}$=3281 (s), 3060 (w), 2923 (ss), 2854 (m), 1701 (ss), 1569 (s), 1443 (m), 1364 (m) , 1348 (m), 1272 (w), 1254 (w), 1172 (s), 1081 (m), 1035 (w), 812 (m), 743 (m), 700 (m), 622 $cm^{-1}$ (w); MS (70 eV): *m/z* (%): 782 (30) [$M^+$+ H], 682 (10) [$C_{41}H_{60}N_7S^+$], 538 (5) [$C_{27}H_{52}N_7O_2S^+$], 438 (15) [$C_{22}H_{44}N_7S^+$], 349 (8) [$C_{19}H_{37}N_6^+$], 243 (100) [$C_{19}H_{15}^+$], 165 (55) [$C_6H_9N_6^+$], 152 (11) [$C_5H_8N_6^+$], 139 (5) [$C_4H_6N_6^+$], 77 (17) [$C_2H_7NS^+$], 56 (6) [$C_4H_8^+$].

**Synthesis of 2-[4-(2-amino-propylamino)-6-tetradecylamino-[1,3,5]triazin-2-ylamino]-ethanethiol bis trifluoroacetic acid salt (4).**

Trifluoroacetic acid (20%) in $CH_2Cl_2$ (10 mL) was added to a solution of **3** (0.16 mmol, 70 mg) in $CH_2Cl_2$ (10 mL) and the reaction was stirred for 1 h at rt. As soon as **3** disappeared (TLC monitoring), neat triethyl-silane (0.12 mmol, 17 μL) was added. A white precipitate formed and the slurry was filtered on a celite pad. The filtrate was evaporated to dryness under vacuum to give a residue that, upon flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 9:1) yielded pure **4** (98%): white amorphous solid; $R_F$=0.35; m.p. > 300°C (290°C dec.); $^1$H NMR (400 MHz, $D_2O$, 47°C, TMS): δ=3.65 and 3.5 and 3.4 (m, 2H; NHC$H_2$), 3.4 (m, 2H; NHC$H_2$), 3.3 (m, 2H; NHC$H_2$), 3.05 (br t, 2H; $H_2$NC$H_2$), 2.9 and 2.8 and 2.65 (br s, 2H; $SCH_2$), 1.95 (br t, 2H; $CH_2$), 1.55 (m, 2H; $CH_2$), 1.75 – 1.2 (br m, 22H; 11 x $CH_2$), 0.85 (br t, 3H; Me); $^1$H NMR (400 MHz, $CD_3OD$, 47°C, TMS): δ=3.7 and 3.5 (br t, $^3J$(H,H)=6.9 Hz, 2H; HNC$H_2$), 3.4 (br t, $^3J$(H,H)=5.7 Hz, 2H; HNC$H_2$), 3.3 (m, 2H; HNC$H_2$), 2.9 (br t, $^3J$(H,H)=7.4 Hz, 2H; $H_2$NC$H_2$), 2.9 and 2.7 (br t, $^3J$(H,H)=6.9 Hz, 2H; $SCH_2$), 1.85 (br t, $^3J$(H,H)=7.4 and 6.7 Hz, 2H; $CH_2$), 1.59 (m, 2H; $CH_2$), 1.4 – 1.2 (m, 22H; 11 x $CH_2$), 0.9 (br t, $^3J$(H,H)=6.7 Hz, 3H; Me); $^1$H NMR (400 MHz, [$D_6$]DMSO, 57°C, TMS): δ=8.4 – 8.0 (br m, 3H; $NH_3$), 7.9 – 7.5 (br m, 3H; 3 x NH), 3.6 and 3.45 (br t, $^3J$(H,H)=6.7 Hz, 2H; HNC$H_2$), 3.3 (br m, 4H; 2 x HNC$H_2$), 2.8 (br m, 4H; $H_2$NC$H_2$ and $SCH_2$), 1.8 (br m, 2H; $CH_2$), 1.45 (br m, 2H; $CH_2$), 1.35 – 1.15 (br m, 22H; 11 x $CH_2$), 0.8 (br t, 3H; Me); $^{19}$F NMR (400 MHz, $CD_3OD$, 47°C, TMS): δ= – 74.55 (s; 3F); $^{19}$F NMR (400 MHz, [$D_6$]DMSO, 57°C, TMS): δ= – 74.05 (s; 3F); $^{19}$F NMR (400 MHz, $D_2O$, 47°C, TMS): δ= – 72.0 (s; 3F); $^{13}$C NMR (400 MHz, [$D_6$]acetone, 25°C, TMS): δ=165.5 (q), 165.4 (q), 163.9 (q), 161.6 (q, Q, $^2J$(C,F)=33.6 Hz; CO), 117.3 (q, Q, $J$(C,F)=294.6 Hz; $CF_3$), 45.9 (s), 44.3 (s), 40.7 (s), 36.3 (s), 32.1 (s), 31.0 (s), 29.9 (s, 3 x C), 29.8 (s), 29.7 (s, 2 x C), 29.5 (s), 29.3 (s), 28.2 (s), 27.2 (s), 23.9 (s), 22.8 (s), 13.9 (p); IR (microscope): $\tilde{\nu}$=3289 (s), 2926 (ss), 2855 (m), 1681 (ss), 1633 (ss), 1435 (m), 1338 (m) , 1203 (m), 1139 (m), 1029 (m), 840 (w), 800 (w), 787 (w), 724 $cm^{-1}$ (m); Mass (70 eV): *m/z* (%): 438 (100) [$M^+$ – H], 409 (94) [$C_{21}H_{43}N_6S^+$], 349 (90) [$C_{19}H_{37}N_6^+$], 335 (25) [$C_{18}H_{35}N_6^+$], 323 (20) [$C_{17}H_{35}N_6^+$], 183 (23) [$C_7H_{15}N_6^+$], 169 (33) [$C_6H_{13}N_6^+$],153 (26) [$C_5H_9N_6^+$], 141 (30) [$C_4H_9N_6^+$], 127 (22) [$C_3H_7N_6^+$], 111 (23) [$C_3H_5N_5$], 55 (98) [$C_4H_7^+$].

**Synthesis of the 2-(4,6-Dichloro-[1,3,5]triazin-2-yl-amino)-ethanethiol disulfide dimer (5).**
2,4,6-Trichloro-[1,3,5]triazine (440 mg, 2.4 mmol) in acetone (8 mL) and $H_2O$ (12 mL) was added to a stirred ice-cooled (0°C) solution of 2-(2-amino-ethyldisulfanyl)-ethylamine hydroiodide (500 mg, 1.2 mmol) and $NaHCO_3$ (310 mg, 3.6 mmol) in $H_2O$ (2 mL). The reaction mixture was stirred for 1 h at rt, then the acetone was evaporated under vacuum, $H_2O$ (10 mL) was added and the organics were extracted with $CHCl_3$ (3 x 100 mL). The combined organics were dried over anhydrous $Na_2SO_4$, filtered, the solvent was evaporated under vacuum and the residue was purified by crystallization (AcOEt) to yield **5** (74%): white amorphous solid; $R_F$=0.35 (*n*-hexane/AcOEt=8:2), $R_F$=0.35 ($CHCl_3$/MeOH=95:5); m.p. 280 – 282°C; $^1$H NMR (400 MHz, [$D_6$]DMSO, 57°C, TMS): δ=9.2 (t, $^3J$(H,H)=5.5 Hz, 2H; 2 x NH), 3.6 (q, $^3J$(H,H)=6.6 Hz, 4H; 2 x HNC$H_2$), 2.9 (t, $^3J$(H,H)=6.6 Hz, 4H; $SCH_2$); $^{13}$C NMR (400 MHz, [$D_6$]DMSO, 57°C, TMS): δ=169.4 (q, 2 x C), 168.5 (q, 2 x C), 165.3 (q, 2 x C), 40.3 (s, 2 x C), 36.2 (s, 2 x C); IR (microscope): $\tilde{\nu}$=3194 (s), 2844 (ss), 1443 (m), 1329 (m) , 1291 (m), 1244 (m), 1226 (m), 1187 (w), 1157 (w), 1112 (w), 1067 (w), 1057 (w), 1041 (w), 958 (m), 795 (s), 750 (s) $cm^{-1}$ (m); LC/MS (ESI Ion Trap): *m/z* (%): 447 [$M^+$+ H].

**Synthesis of 2-(4-Chloro-6-tetradecylamino-[1,3,5]triazin-2-ylamino)-ethanethiol disulfide dimer (6).**

1-Tetradecylamine (263 mg, 1.2 mmol) in acetone (4 mL) and $NaHCO_3$ (104 mg, 1.2 mmol) in $H_2O$ (2 mL) were added to a stirred solution of **5** (280 mg, 0.6 mmol) in acetone (4 mL) and $H_2O$ (6 mL). The reaction mixture was stirred overnight at 60°C, then the acetone was evaporated under vacuum, $H_2O$ (10 mL) was added and the organics were extracted with AcOEt (3 x 100 mL). The combined extracts were dried over anhydrous $Na_2SO_4$, filtered, the solvent was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (*n*-hexane/AcOEt = 8:2) to yield **6** (58%): dense yellowish syrup; $R_F$=0.35 (*n*-hexane/AcOEt=8:2), $R_F$=0.37 ($CHCl_3$/MeOH=95:5); $^1$H NMR (400 MHz, [D$_6$]DMSO, 62°C, TMS): δ=7.5 (m, 4H; 4 x NH), 3.5 (m, 4H; 2 x HNC$H_2$), 3.2 (m, 4H; 2 x HNC$H_2$), 2.9 (t, $^3J$(H,H) = 5.5 Hz, 4H; 2 x $SCH_2$); $^{13}$C NMR (400 MHz, [D$_6$]DMSO, 62°C, TMS): δ=165.3 (q, 2 x C), 165.2 (q, 2 x C), 163.0 (q, 2 x C), 40.0 (s, 2 x C), 39.8 (s, 2 x C), 36.9 (s, 2 x C), 31.1 (s, 2 x C), 28.8 (s, 6 x C), 28.7 (s, 4 x C), 28.5 (s, 4 x C), 28.1 (s, 2 x C), 26.2 (s, 2 x C), 21.9 (s, 2 x C), 13.7 (p, 2 x C); IR (microscope): $\tilde{\nu}$=3194 (s), 2844 (ss), 1443 (m), 1329 (m) , 1291 (m), 1244 (m), 1226 (m), 1187 (w), 1157 (w), 1112 (w), 1067 (w), 1057 (w), 1041 (w), 958 (m), 795 (s), 750 (s) cm$^{-1}$ (m); LC/MS (ESI Ion Trap): *m/z* (%): 823 [$M^+$+ Na].

**Synthesis of {3-[4-(3-Mercapto-propyl)-6-tetradecylamino-[1,3,5]triazin-2-ylamino]-propyl}-carbamic acid tert-butyl ester disulfide dimer (7)**

A solution of **6** (0.3 mmol, 270 mg) in benzene (5 mL) was kept in a vial flask. (3-Amino-propyl)-carbamic acid *tert*-butyl ester (0.6 mmol, 124 mg) and DIPEA (0.6 mmol, 116 µL) were added. The sealed vial was shaken for 24 hs at 125°C. The solvent was evaporated under vacuum to give a residue that, upon flash chromatography on silica gel ($CHCl_3$/MeOH=95:5), yielded **7** (75%): dense yellowish syrup; $R_F$=0.35; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): δ=6.4 (m, 2H; 2 x NH), 6.3 (m, 2H; 2 x NH), 6.1 (m, 4H; 4 x NH), 3.5 (dt, $^3J$(H,H)=7.4 and 6.3 Hz, 4H; 2 x HNC$H_2$), 3.25 (t, $^3J$(H,H)=6.6 Hz, 4H; 2 x HNC$H_2$), 3.2 (t, $^3J$(H,H)=7.0 Hz, 4H; 2 x HNC$H_2$), 3.0 (dt, $^3J$(H,H)=6.6 and 6.2 Hz, 4H; 2 x HNC$H_2$), 2.9 (t, $^3J$(H,H)=7.0 Hz, 4H; 2 x $SCH_2$), 1.6 (m, 4H; 2 x $CH_2$), 1.5 (m, 4H; 2 x $CH_2$), 1.4 (br s, 18H; 6 x Me), 1.3 – 1.2 (br m, 44H; $CHCl_3$/MeOH=95:5), yielded **7** (75%): $R_F$=0.35; $^{13}$C NMR (400 MHz, DMSO-d$_6$, 320K, TMS): δ=170.0 (q, 2 x C), 167.3 (q, 2 x C), 165.6 (q, 2 x C), 155.5 (q, 2 x C; CO), 77.5 (q, 2 x C), 43.6 (s, 2 x C), 42.2 (s, 2 x C), 39.8 (s, 2 x C), 37.7 (s, 2 C), 37.6 (s, 2 x C), 37.2 (s, 2 x C), 31.2 (s, 2 x C), 30.6 (s, 2 x C), 29.8 (s, 2 x C), 29.3 (s, 2 x C), 29.0 (s, 2 x C), 28.9 (s, 6 x C), 28.8 (s, 2 x C), 28.6 (s, 2 x C), 28.2 (p, 6 x C), 26.4 (s, 2 x C), 22.0 (s, 2 x C), 13.8 (p, 2 x C); IR (microscope): $\tilde{\nu}$=3289 (s), 2926 (ss), 2855 (m), 1681 (ss), 1633 (ss), 1435 (m), 1338 (m) , 1203 (m), 1139 (m), 1029 (m), 840 (w), 800 (w), 787 (w), 724 cm$^{-1}$ (m); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 1077 [$M^+$+ H].

**Synthesis of 2-[4-(2-amino-propylamino)-6-tetradecylamino-[1,3,5]triazin-2-ylamino]-ethanethiol disulfide dimer tetra trifluoroacetic acid salt (8).**

Trifluoroacetic acid (20%) in $CH_2Cl_2$ (2.5 mL) was added to a solution of **7** (0.44 mmol, 470 mg) in $CH_2Cl_2$ (1 mL) and the reaction was stirred for 1 h at rt. As soon as **7** disappeared (TLC monitoring), $CH_2Cl_2$ was evaporated to dryness under vacuum and TFAA was removed by addition of cyclohexane (3 x 5 mL) to give a residue that, upon flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 7:3) yielded pure **8** (70%): yellowish foam; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): $\delta$=8.0 – 7.5 (m, 10H; 6 x NH + 2 x $NH_2$), 3.6 (m, 4H; 2 x NHC$H_2$), 3.4 (t, $^3J$(H,H)=6.25 Hz, 4H; 2 x NHC$H_2$), 3.3 (m, 4H; 2 x NHC$H_2$), 2.95 (t, $^3J$(H,H)=7.35 Hz, 4H; 2 x $H_2$NC$H_2$), 2.85 (t, $^3J$(H,H)=7.35 Hz, 4H; 2 x $SCH_2$), 1.85 (m, 4H; 2 x $CH_2$), 1.5 (m, 4H; 2 x $CH_2$), 1.3 (br m, 44H; 22 x $CH_2$), 0.9 (t, $^3J$(H,H)=7.0 Hz, 6H; 2 x Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 57°C): $\delta$= – 98.0 (s; 3F); $^{13}$C NMR (400 MHz, [D$_6$]acetone, 25°C, TMS): $\delta$=165.5 (q, 2 x C), 164.8 (q, 2 x C), 162.4 (q, Q, $^2J$(C,F)=35.1 Hz, 2 x C; CO), 157.8 (s, 2 x C), 118.2 (q, Q, $J$(C,F)=283.3 Hz; $CF_3$), 45.9 (s, 2 x C), 41.4 (s, 2 x C), 41.3 (s, 2 x C), 38.5 (s, 2 x C), 39.4 (s, 2 x C), 38.3 (s, 2 x C), 32.7 (s, 2 x C), 30.5 (s, 6 x C), 30.4 (s, 4 x C), 30.3 (s, 2 x C), 30.2 (2 x C), 29.9 (s, 2 x C), 29.8 (s, 2 x C), 27.6 (s, 2 x C), 23.4 (s, 2 x C), 14.4 (p, 2 x C); IR (microscope): $\tilde{\nu}$=3289 (s), 2926 (ss), 2855 (m), 1681 (ss), 1633 (ss), 1435 (m), 1338 (m) , 1203 (m), 1139 (m), 1029 (m), 840 (w), 800 (w), 787 (w), 724 cm$^{-1}$ (m); LC/MS (ESI Ion Trap + HCOOH 0.1%): $m/z$ (%): 877 [$M^+$+ H].

Following the same experimental conditions described for the synthesis of **4**, five thio derivatives (**9-13**) were prepared as bis trifluoroacetic acid salts.

(1) 2-[4-(3-Amino-propylamino)-6-octylamino-[1,3,5]triazine-2-ylamino]-ethanethiol (**9**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 95:5) yielded pure **9** (99%): yellowish foam; $^1$H NMR (400 MHz, $CD_3OD$, 50°C, TMS): $\delta$=3.55 (m, 4H; 2 x HNC$H_2$), 3.4 (m, 2H; HNC$H_2$), 3.0 (m, 2H; $H_2$NC$H_2$), 2.7 (m, 2H; SC$H_2$), 1.95 (m, 2H; $CH_2$), 1.6 (m, 2H; $CH_2$), 1.4 – 1.2 (m, 10H; 5 x $CH_2$), 0.9 (br t, $^3J$(H,H)=6.5 Hz, 3H; Me); $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): $\delta$=8.0 – 7.5 (br m, 6H; 3 x NH + $NH_3^+$), 3.45 (m, 2H; HNC$H_2$), 3.35 (br m, 2H; HNC$H_2$), 3.25 (m, 2H; HNC$H_2$), 2.8 (m, 2H; $H_2$NC$H_2$), 2.7 (m, 2H; $SCH_2$), 2.3 (broad signal, 1H; SH), 1.8 (br m, 2H; $CH_2$), 1.5 (br m, 2H; $CH_2$), 1.3 – 1.2 (br m, 10H; 5 x $CH_2$), 0.85 (m, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 57°C): $\delta$= – 95.9 (s; 3F); $^{13}$C NMR (400 MHz, [D$_6$]acetone, 25°C, TMS): $\delta$=164.5 (q; CO), 162.5 (q, $^3J$(H,F)=34.6 Hz; CO), 157.1 (q), 156.4 (q), 117.9 (q, $^3J$(H,F)=292.7 Hz; $CF_3$), 45.9 (s), 44.9 (s), 41.5 (s), 38.5 (s), 37.6 (s), 32.5 (s), 29.9 (s, 2 x C), 27.9 (s), 27.4 (s), 23.8 (s), 23.3 (s), 14.3 (p); IR (microscope): $\tilde{\nu}$=3296 (s), 3080 (s), 2930 (ss), 2856 (m), 2106 (w), 1706 (ss), 1693 (ss), 1558 (m), 1528 (m), 1442 (m), 1345 (s), 1213 (s), 1144 (s), 1041 (w), 967 (w), 840 (m), 800 (m), 788 (m), 724 cm$^{-1}$ (m); LC/MS (ESI Ion Trap + HCOOH 0.1%): $m/z$ (%): 356 [$M^+$+ H].

(2) 2-[4-(3-Amino-propylamino)-6-decylamino-[1,3,5]triazine-2-ylamino]-ethanethiol (**10**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 9:1) yielded pure **10** (94%): yellowish foam; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): $\delta$=8.1 – 7.7 (br m, 6H; 3 x NH + $NH_3^+$), 3.45 (m,

2H; $HNCH_2$), 3.35 (br m, 2H; $HNCH_2$), 3.3 (m, 2H; $HNCH_2$), 2.85 (m, 2H; $H_2NCH_2$), 2.7 (m, 2H; $SCH_2$), 2.3 (broad signal, 1H; SH), 1.8 (br m, 2H; $CH_2$), 1.5 (br m, 2H; $CH_2$), 1.3 – 1.2 (br m, 14H; 7 x $CH_2$), 0.85 (br t, $^3J$(H,H)=7.1 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 47°C): δ= – 95.9 (s; 3F); $^{13}$C NMR (400 MHz, [D$_6$]acetone, 25°C, TMS): δ=164.5 (q), 163.2 (q, Q, $^2J$(C,F)=29.8 Hz; CO), 157.7 (q), 156.4 (q), 118.8 (q, Q, $J$(C,F)=291.8 Hz; $CF_3$), 45.9 (s), 44.7 (s), 41.6 (s), 38.5 (s), 37.6 (s), 32.6 (s), 30.3 (s, 3 x C), 30.0 (s, 2 x C), 27.5 (s), 23.8 (s), 23.4 (s), 14.4 (p); IR (microscope): $\tilde{\nu}$=3308 (s), 3100 (s), 2937 (ss), 2856 (m), 2106 (w), 1710 (ss), 1697 (ss), 1650 (m), 1441 (m), 1341 (s), 1219 (s), 1156 (s), 1044 (w), 966 (w), 842 (m), 801 (m), 785 (m), 725 cm$^{-1}$ (m); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 384 [$M^+$+ H].

(3) 2-[4-(3-Amino-propylamino)-6-dodecylamino-[1,3,5]triazine-2-ylamino]-ethanethiol (**11**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 95:5) yielded pure **11** (99%): yellowish foam; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): δ=8.1 – 7.7 (br m, 6H; 3 x NH + $NH_3^+$), 3.45 (m, 2H; $HNCH_2$), 3.35 (br m, 2H; $HNCH_2$), 3.3 (m, 2H; $HNCH_2$), 2.85 (m, 2H; $H_2NCH_2$), 2.65 (m, 2H $SCH_2$), 2.3 (broad signal, 1H; SH), 1.8 (br m, 2H; $CH_2$), 1.5 (br m, 2H; $CH_2$), 1.3 – 1.2 (br m, 18H; 9 x $CH_2$), 0.85 (br t, $^3J$(H,H)=6.6 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 57°C): δ= – 98.2 (s; 3F); $^{13}$C NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): δ=162.9 (q), 160.1 (q, Q, $^2J$(C,F)=33.6 Hz; CO), 155.6 (q), 155.3 (q), 117.2 (q, Q, $J$(C,F)=296.8 Hz; $CF_3$), 43.9 (s), 40.7 (s), 38.0 (s), 37.3 (s), 37.0 (s), 31.6 (s), 29.35 (s), 29.3 (s), 29.25 (s), 29.0 (s, 3 x C), 27.2 (s), 26.6 (s), 23.4 (s), 22.4 (s), 14.0 (p); IR (microscope): $\tilde{\nu}$=3292 (s), 3076 (s), 2935 (ss), 2856 (m), 2119 (w), 1701 (ss), 1699 (ss), 1648 (m), 1541 (m), 1438 (m), 1341 (s), 1212 (s), 1179 (s), 1139 (w), 967 (w), 841 (m), 800 (m), 788 (m), 723 cm$^{-1}$ (m); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 412 [$M^+$+ H].

(4) 2-[4-(3-Amino-propylamino)-6-hexadecylamino-[1,3,5]triazine-2-ylamino]-ethanethiol (**12**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 95:5) yielded pure **12** (99%): yellowish foam; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): δ=8.0 – 7.6 (br m, 6H; 3 x NH + $NH_3^+$), 3.45 (m, 2H; $HNCH_2$), 3.35 (br m, 2H; $HNCH_2$), 3.25 (m, 2H; $HNCH_2$), 2.85 (m, 2H; $H_2NCH_2$), 2.65 (m, 2H; $SCH_2$), 2.3 (broad signal, 1H; SH), 1.8 (br m, 2H; $CH_2$), 1.5 (br m, 2H; $CH_2$), 1.3 – 1.2 (br m, 26H; 13 x $CH_2$), 0.85 (br t, $^3J$(H,H)=6.1 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 57°C): δ= – 95.8 (s; 3F); $^{13}$C NMR (500 MHz, [D$_6$]acetone, 25°C, TMS): δ=165.3 (t), 163.4 (t, Q, $^3J$(C,F)=35.0 Hz; CO), 158.5 (s), 157.6 (t), 119.0 (t, Q, $^2J$H(C,F)=293.0 Hz; $CF_3$), 46.7 (s), 42.5 (s), 42.3 (s), 42.1 (s), 39.2 (s), 38.6 (s), 33.4 (s), 31.2 (s), 31.1 (s), 30.95 (s), 30.9 (s), 30.85 (s), 30.8 (s), 30.7 (s), 30.6 (s), 30.5 (s), 30.3 (s), 28.8 (s), 28.3 (s), 24.0 (s), 15.1 (p); IR (microscope): $\tilde{\nu}$=3292 (s), 3076 (s), 2927 (ss), 2855 (m), 2122 (w), 1700 (ss), 1691 (ss), 1642 (m), 1575 (m), 1559 (m), 1522 (m), 1457 (m), 1438 (m), 1340 (m), 1248 (w), 1209 (s), 1142 (s), 966 (w), 841 (m), 800 (m), 785 (m), 724 cm$^{-1}$ (m); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 468[$M^+$+ H].

(5) 2-[4-(3-Amino-propylamino)-6-octadecylamino-[1,3,5]triazine-2-ylamino]-ethanethiol (**13**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 75:25) yielded pure **13** (99%): m.p. 210 – 212°C; white amorphous solid; $^1$H NMR (400 MHz, [D$_6$]DMSO, 32°C, TMS): δ=7.8 (br m, 3H; 3 x NH), 6.5 (br m, 3H; $NH_3^+$), 3.4 (dt, $^3J$(H,H)=6.9 and 6.3 Hz, 2H; HNC$H_2$), 3.25 (br m, 2H; HNC$H_2$), 3.15 (m, 2H; HNC$H_2$), 2.8 (t, $^3J$(H,H)=7.3 Hz, 2H; $H_2$NC$H_2$), 2.65 (t, $^3J$(H,H)=6.6 Hz, 2H; $SCH_2$), 2.15 (broad signal, 1H; SH), 1.75 (br m, 2H; $CH_2$), 1.5 (br m, 2H; $CH_2$), 1.3 – 1.2 (br m, 30H; 15 x $CH_2$), 0.9 (br t, $^3J$(H,H)=6.9 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 32°C): δ= – 95.6 (s; 3F); $^{13}$C NMR (400 MHz, [D$_6$]acetone, 25°C, TMS): δ=165.8 (q), 165.0 (q), 162.5 (q, Q, $^2J$(C,F)=35.9 Hz; CO), 160.8 (q), 118.0 (q, Q, $J$(C,F)=294.4 Hz; $CF_3$), 46.7 (s), 45.2 (s), 41.7 (s), 38.8 (s), 37.5 (s), 33.0 (s), 30.5 (s, 8 x C), 30.4 (s), 30.3 (s), 30.2 (s), 30.1 (s), 28.1 (s), 28.0 (s), 24.8 (s), 23.7 (s), 14.7 (p); IR (microscope): $\tilde{\nu}$=3339 (ss), 2921 (s), 2852 (m), 2120 (w), 1719 (s), 1684 (s), 1560 (m), 1539 (m), 1507 (m), 1448 (m), 1421 (m), 1348 (m), 1214 (m), 1198 (m), 1145 (m), 954 (w), 858 (m), 841 (m), 802 (m), 724 cm$^{-1}$ (m); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 496 [$M^+$ + H].

Following the same experimental conditions described for the synthesis of **8**, five thio derivatives (**14-18**) were prepared as tetra trifluoroacetic acid salts.

(6) 2-[4-(3-Amino-propylamino)-6-octylamino-[1,3,5]triazine-2-ylamino]-ethanethiol disulfide dimer (**14**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 95:5) yielded pure **14** (95%): brownish foam; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): δ=8.1 (br m, 3H; 3 x NH), 7.75 (br m, 3H, $NH_3^+$), 3.6 (m, 2H; HNC$H_2$), 3.4 (m, 2H; HNC$H_2$), 3.3 (m, 2H; HNC$H_2$), 2.95 (t, $^3J$(H,H)=7.0 Hz, 2H; $H_2$NC$H_2$), 2.85 (m, 2H; $SCH_2$), 2.15 (broad signal, 1H; SH), 1.85 (m, 2H; $CH_2$), 1.55 (m, 2H; $CH_2$), 1.35 – 1.2 (br m, 10H; 5 x $CH_2$), 0.85 (br t, $^3J$(H,H)=6.6 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 57°C): δ= – 99.4 (s; 3F); $^{13}$C NMR (500 MHz, [D$_6$]acetone, 25°C, TMS): δ=165.4 (t, 2 x C), 162.2 (t, Q, $^3J$(C,F)=35.9 Hz, CO), 158.3 (s, 2 x C), 157.2 (s, 2 x C), 118.1 (t, Q, $^2J$H(C,F)=291.5 Hz, $CF_3$), 46.9 (s, 2 x C), 42.15 (s, 2 x C), 41.9 (s, 2 x C), 41.3 (s, 2 x C), 39.2 (s, 2 x C), 38.9 (s, 2 x C), 33.4 (s, 2 x C), 31.3 (s, 2 x C), 31.0 (s, 2 x C), 30.7 (s, 2 x C), 30.5 (s, 2 x C), 30.2 (s, 2 x C), 28.4 (s, 2 x C), 24.1 (s, 2 x C), 15.2 (p, 2 x C); IR (microscope): $\tilde{\nu}$=3268 (ss), 3080 (ss), 2930 (s), 2860 (m), 2090 (w), 1695 (s), 1689 (s), 1634 (m), 1559 (m), 1522 (w), 1437 (w), 1340 (m), 1208 (s), 1143 (m), 840 (m), 797 (m), 787 (m), 723 (m), 668 cm$^{-1}$ (w); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 709 [$M^+$ + H].

(7) 2-[4-(3-Amino-propylamino)-6-decylamino-[1,3,5]triazine-2-ylamino]-ethanethiol disulfide dimer (**15**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 95:5) yielded pure **15** (95%): brownish foam; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): δ=8.0 – 7.5 (br m, 12H; 6 x NH + 2 x $NH_3^+$), 3.6 (m, 2H; HNC$H_2$), 3.35 (m, 2H; HNC$H_2$), 3.3 (m, 2H; HNC$H_2$), 2.95 (t, $^3J$(H,H)=7.0 Hz,

2H; $H_2NCH_2$), 2.85 (t, $^3J$(H,H)=7.4 Hz, 2H; $SCH_2$), 1.85 (m, 2H; $CH_2$), 1.5 (m, 2H; $CH_2$), 1.35 – 1.2 (br m, 28H; 14 x $CH_2$), 0.85 (br t, $^3J$(H,H)=6.6 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 57°C): δ= – 69.7 (s; 3F); $^{13}$C NMR (400 MHz, [D$_6$]acetone, 25°C, TMS): δ=165.5 (t, 2 x C), 163.3 (t, Q, $^3J$(C,F)=30.5 Hz, CO), 158.2 (t, 2 x C), 157.3 (t, 2 x C), 118.7 (t, Q, $^2J$H(C,F)=286.0 Hz; $CF_3$), 46.7 (s, 2 x C), 42.7 (s, 2 x C), 42.1 (s, 2 x C), 41.4 (s, 2 x C), 39.5 (s, 2 x C), 38.7 (s, 2 x C), 33.5 (s, 2 x C), 31.1 (s, 2 x C), 31.0 (s, 2 x C), 30.7 (s, 2 x C), 30.5 (s, 2 x C), 30.3 (s, 2 x C), 30.1 (s, 2 x C), 28.8 (s, 2 x C), 28.3 (s, 2 x C), 24.2 (s, 2 x C), 15.2 (p, 2 x C); IR (microscope): $\tilde{\nu}$=3268 (ss), 3080 (ss), 2930 (s), 2860 (m), 2090 (w), 1695 (s), 1689 (s), 1634 (m), 1559 (m), 1522 (w), 1437 (w), 1340 (m), 1208 (s), 1143 (m), 840 (m), 797 (m), 787 (m), 723 (m), 668 cm$^{-1}$ (w); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 765 [$M^+$ + H].

(8) 2-[4-(3-Amino-propylamino)-6-dodecylamino-[1,3,5]triazine-2-ylamino]-ethanethiol disulfide dimer (**16**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 95:5) yielded pure **16** (97%): brownish foam; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): δ=8.3 – 8.0 (br m, 6H; 6 x NH), 7.75 (br s, 6H; 2 x $NH_3^+$), 3.6 (m, 2H; $HNCH_2$), 3.4 (br m, 4H; 2 x $HNCH_2$), 3.3 (m, 4H; 2 x $HNCH_2$), 2.95 (t, $^3J$(H,H)=7,0 Hz, 4H; 2 x $H_2NCH_2$), 2.85 (m, 4H; 2 x $SCH_2$), 1.85 (br m, 4H; 2 x $CH_2$), 1.55 (br m, 4H; 2 x $CH_2$), 1.35 – 1.2 (br m, 36H; 18 x $CH_2$), 0.85 (br t, $^3J$(H,H)=6.6 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 57°C): δ= – 74.8 (s; 3F); $^{13}$C NMR (400 MHz, [D$_6$]acetone, 25°C, TMS): δ=165.5 (s, 2 x C), 161.8 (q, Q, $^3J$(C,F)=36.6 Hz; CO), 158.5 (s, 2 x C), 157.3 (s, 2 x C), 117.9.0 (q, Q, $^3J$(H,F)=290.0 Hz; $CF_3$), 47.0 (s, 2 x C), 43.0 (s, 2 x C), 42.0 (s, 2 x C), 41.4 (s, 2 x C), 39.3 (s, 2 x C), 38.7 (s, 2 x C), 33.5 (s, 2 x C), 31.4 (s, 2 x C), 31.2 (s, 2 x C), 30.9 (s, 2 x C), 30.7 (s, 2 x C), 30.5 (s, 2 x C), 28.4 (s, 2 x C), 28.3 (s, 2 x C), 28.2 (s, 2 x C), 24.2 (s, 2 x C), 15.2 (p, 2 x C); IR (microscope): $\tilde{\nu}$=3292 (s), 3292 (s), 3080 (s), 2928 (ss), 2856 (m), 2119 (w), 1695 (ss), 1644 (ss), 1559 (m), 1522 (m), 1508 (m), 1457 (w), 1437 (m), 1340 (s), 1207 (s), 1142 (s), 840 (m), 799 (m), 787 (m), 724 (m), 667 cm$^{-1}$ (w); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 821 [$M^+$+ H].

(9) 2-[4-(3-Amino-propylamino)-6-hexadecylamino-[1,3,5]triazine-2-ylamino]-ethanethiol disulfide dimer (**17**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 85:15) yielded pure **17** (95%): brownish foam; $^1$H NMR (400 MHz, [D$_6$]DMSO, 57°C, TMS): δ=8.2 – 8.0 (br m, 6H; NH), 7.75(br s, 6H; 2 x $NH_3^+$), 3.6 (m, 4H; 2 x $HNCH_2$), 3.4 (br m, 4H; 2 x $HNCH_2$), 3.3 (m, 4H; 2 x $HNCH_2$), 2.95 (t, $^3J$(H,H)=7.0 Hz, 4H; 2 x $H_2NCH_2$), 2.85 (m, 4H; 2 x $SCH_2$), 1.85 (br m, 2H; $CH_2$), 1.55 (br m, 2H; $CH_2$), 1.35 – 1.2 (br m, 52H; 26 x $CH_2$), 0.85 (br t, $^3J$(H,H)=6.6 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [D$_6$]DMSO, 57°C): δ= – 70.2 (s; 3F); $^{13}$C NMR (400 MHz, [D$_6$]acetone, 25°C, TMS): δ=164.5 (q, 2 x C), 161.7 (q, Q, $^2J$(C,F)=35.1 Hz; CO), 157.5 (q, 2 x C), 156.5 (q, 2 x C), 117.6 (q, Q, $J$(C,F)=292.2 Hz; $CF_3$), 46.0 (s, 2 x C), 41.8 (s, 2 x C), 41.4 (s, 2 x C), 40.7 (s, 2 x C), 38.4 (s, 2 x C), 37.8 (s, 2 x C), 32.7 (s, 2 x C), 30.5 (s, 12 x C), 30.4 (s, 2 x C), 30.3 (s, 2 x C), 30.2 (s, 2 x C), 30.1 (s, 2 x C), 28.0 (s, 2 x C), 27.5 (s, 2 x C), 23.4 (s, 2 x C), 14.4 (p, 2 x C); IR

(microscope): $\tilde{\nu}$=3292 (s), 3072 (s), 2934 (ss), 2852 (m), 1703 (ss), 1690 (s), 1438 (m), 1341 (s), 1212 (s), 1144 (s), 1059 (w), 968 (w), 840 (m), 800 (m), 787 (m), 724 (m), 668 $cm^{-1}$ (w); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 933 [$M^+$+ H].

(10) 2-[4-(3-Amino-propylamino)-6-octadecylamino-[1,3,5]triazine-2-ylamino]-ethanethiol disulfide dimer (**18**): flash chromatographic purification on silica gel ($CHCl_3$/MeOH = 75:25) yielded pure **18** (96%): brownish foam; $^1$H NMR (400 MHz, [$D_6$]DMSO, 57°C, TMS): δ=8.4 – 8.1 (br m, 6H; 6 x NH), 7.8 (br s, 6H; 2 x $NH_3^+$), 3.6 (m, 4H; 2 x HNC$H_2$), 3.4 (br m, 4H; 2 x HNC$H_2$), 3.3 (m, 4H; 2 x HNC$H_2$), 2.95 (br t, 4H; 2 x $H_2$NC$H_2$), 2.85 (m, 4H; 2 x $SCH_2$), 1.85 (m, 4H; 2 x $CH_2$), 1.5 (m, 4H; 2 x $CH_2$), 1.3 – 1.2 (br m, 60H; 30 x $CH_2$), 0.85 (br t, $^3J$(H,H)=6.6 Hz, 3H; Me); $^{19}$F NMR (400 MHz, [$D_6$]DMSO, 57°C): δ= – 96.5 (s; 3F); $^{13}$C NMR (400 MHz, [$D_6$]acetone, 25°C, TMS): δ=164.8 (q, 2 x C), 161.1 (q, Q, $^2J$(C,F)=37.4 Hz; CO), 157.5 (q, 2 x C), 156.5 (q, 2 x C), 117.5 (q, Q, *J*(C,F)=299.2 Hz; $CF_3$), 46.2 (s, 2 x C), 41.4 (s, 2 x C), 40.6 (s, 2 x C), 39.0 (s, 2 x C), 38.5 (s, 2 x C), 37.9 (s, 2 x C), 32.7 (s, 2 x C), 30.5 (s, 16 x C), 30.45 (s, 2 x C), 30.4 (s, 2 x C), 30.15 (s, 4 x C), 27.8 (s, 2 x C), 27.5 (s, 2 x C), 23.4 (s, 2 x C), 14.4 (p, 2 x C); IR (microscope): $\tilde{\nu}$=3339 (ss), 2921 (s), 2852 (m), 2120 (w), 1719 (s), 1684 (s), 1560 (m), 1539 (m), 1507 (m), 1448 (m), 1421 (m), 1348 (m), 1214 (m), 1198 (m), 1145 (m), 954 (w), 858 (m), 841 (m), 802 (m), 724 $cm^{-1}$ (m); LC/MS (ESI Ion Trap + HCOOH 0.1%): *m/z* (%): 989 [$M^+$ + H].

[1]H NMR of **4** ([D$_6$]DMSO at 330 K)