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1. Chemistry

1.1. General methods

Solvents and liquid reagents were purified and dried according to recommended procedures. Chemical reagents were purchased from Sigma-Aldrich, Alfa Aesar or TCI Europe and were used as received. Analytical thin-layer chromatography was performed with silica gel 60 F254, 0.25 mm pre-coated TLC plates (Merck). Compounds were visualized using UV light (254 nm) and a solution of cerium sulfate tetrahydrate and phosphomolybdic acid in 10% aqueous sulfuric acid as developing agent. Column chromatographies were performed using a Grace Reveleris[®] apparatus using 40-50 μ M silica gel. NMR spectra were recorded at 303K on a Bruker DPX250 (250 MHz for ¹H and 62.9 MHz for ¹³C) spectrometer. When specified, they were recorded on a Bruker DRX400 (400 MHz for ¹H and 100.6 MHz for ¹³C) spectrometer. The chemical shifts are reported in ppm (δ) relative to residual solvent peak.^[1] Mass spectra (MS) were recorded on a micrOTOFq (Bruker) ESI/QqTOF spectrometer. Melting points (M.p.) were determined with a Kofler bench and are uncorrected. FTIR spectra were recorded on a Perkin-Elmer spectrum 1000 spectrophotometer using a thin film deposition on NaCl window or KBr pellets. Elemental analyses were performed using a Thermofinnigan Flash EA 1112 apparatus.

1.2. Calculation of the clogP

The clogP values (octanol/water partition coefficients) were calculated in order to estimate the lipophilicity character of compounds **32** to **45**. These calculations were achieved using MarvinSketch software (Marvin 16.8.22.0, 2016, ChemAxon (<http://www.chemaxon.com>)).

1.3. Synthesis of bis-thiazoliums **4-17**

General procedure: to a solution of α,ω -diiodoalkane (2.00 mmol) in CH₃CN (15 mL) was added 4-methyl-5-(2-hydroxyethyl)thiazole (0.96 mL, 8.00 mmol) or 4-methyl-5-(2-methoxyethyl)thiazole^[2] (1.257 g, 8.00 mmol). The solution was heated to reflux under argon for 72 h, and the solvent was evaporated. The following is not related to compounds **13** to **17**. The residue was dissolved in water (40 mL), the solution was washed with ether (3 x 40 mL) and concentrated to dryness.

1,4-Butamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**4**). The residue was dissolved in hot EtOH (200 mL). Crystallization occurred at -18°C to afford 0.958 g (1.61 mmol, 80% yield) of yellow crystals. M.p. 175 °C. IR (KBr) ν (cm⁻¹): 3323, 3047, 1455, 1589, 1179, 1057. ¹H NMR (DMSO-*d*₆): δ 1.88 (m, 2H, linker CH₂), 2.48 (s, 3H, CH₃), 3.03 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OH), 3.65 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OH), 4.51 (m, 2H, linker CH₂), 10.00 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆): δ 11.5, 25.5, 29.5, 51.9, 59.6, 135.5, 141.5, 156.2. ESI-MS: *m/z* = 170.90 [M]²⁺. Anal. Calcd for C₁₆H₂₆I₂N₂O₂S₂ (596.33): C, 32.22; H, 4.39; N, 4.70. Found: C, 32.46; H, 4.43; N, 4.80.

1,5-Pentamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**5**). The residue was kept at 4°C until crystals appeared. They were suspended in a 1:1 mixture of CH₂Cl₂ and *i*PrOH and sonicated.

Filtration and washing with the same solvent mixture gave 0.639 g (1.04 mmol, 52% yield) of pale-yellow crystals. M.p. 103 °C. IR (KBr) ν (cm⁻¹): 3369, 2940, 1594, 1451, 1047. ¹H NMR (DMSO-*d*₆): δ 1.38 (m, 1H, linker CH₂), 1.88 (m, 2H, linker CH₂), 2.49 (s, 3H, CH₃), 3.04 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OH), 3.65 (t, *J* = 5.2 Hz, 2H, CH₂CH₂OH), 4.48 (t, *J* = 7.4 Hz, 2H, linker CH₂), 5.17 (br s, 1H, OH), 10.03 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆): δ 11.4, 22.2, 28.2, 29.5, 52.4, 59.6, 135.5, 141.5, 156.1. ESI-MS: *m/z* = 177.99 [M]²⁺. Anal. Calcd for C₁₇H₂₈I₂N₂O₂S₂ (610.35): C, 33.45; H, 4.62; N, 4.59. Found: C, 33.49; H, 4.55; N, 4.45.

1,6-Hexamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**6**). The residue was dissolved in hot EtOH (100 mL). Crystallization occurred at -18 °C. Crystals were washed with a mixture of Et₂O/hexane to give 0.707 g (1.13 mmol, 57% yield) of pale-yellow crystals. M.p. 123 °C. IR (KBr) ν (cm⁻¹): 3286, 3013, 2939, 1596, 1488, 1067. ¹H NMR (DMSO-*d*₆): δ 1.38 (m, 2H, linker CH₂), 1.82 (m, 2H, linker CH₂), 2.48 (s, 3H, CH₃), 3.03 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OH), 3.64 (m, 2H, CH₂CH₂OH), 4.46 (br t, *J* = 7.3 Hz, 2H, linker CH₂), 5.16 (t, *J* = 4.8 Hz, 1H, OH), 10.00 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆): δ 11.3, 24.9, 28.6, 29.5, 52.6, 59.6, 135.4, 141.5, 156.0. ESI-MS: *m/z* = 184.84 [M]²⁺. Anal. Calcd for C₁₈H₃₀I₂N₂O₂S₂ (624.38): C, 34.62; H, 4.84; N, 4.48. Found: C, 34.86; H, 4.74; N, 4.55.

1,7-Heptamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**7**). Careful drying of the residue afforded 1.203 g (1.88 mmol, 94% yield) of yellow liquid. IR (KBr) ν (cm⁻¹): 3347, 2920, 1585, 1455, 1047. ¹H NMR (DMSO-*d*₆): δ 1.37 (m, 3H, linker CH₂), 1.83 (m, 2H, CH₂ linker), 2.51 (s, 3H, CH₃), 3.05 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OH), 3.67 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OH), 4.48 (br t, *J* = 7.5 Hz, 2H, linker CH₂), 5.17 (br s, 1H, OH), 10.06 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆): δ 11.3, 25.3, 27.7, 28.7, 29.5, 52.7, 59.6, 135.5, 141.5, 156.0. ESI-MS: *m/z* = 192.16 [M]²⁺. Anal. Calcd for C₁₉H₃₂I₂N₂O₂S₂ (638.40): C, 35.74; H, 5.05; N, 4.39. Found: C, 35.48; H, 5.27; N, 4.13.

1,8-Octamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**8**). Careful drying of the residue afforded 0.834 g (1.28 mmol, 64% yield) of orange liquid. IR (KBr) ν (cm⁻¹): 3368, 2930, 1585, 1453, 1048. ¹H NMR (DMSO-*d*₆): δ 1.32 (m, 4H, linker CH₂), 1.83 (m, 2H, linker CH₂), 2.49 (s, 3H, CH₃), 3.03 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OH), 3.64 (m, 2H, CH₂CH₂OH), 4.45 (br t, *J* = 7.5 Hz, 2H, linker CH₂), 5.16 (t, *J* = 5.0 Hz, 1H, OH), 10.02 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆): δ 11.3, 25.5, 28.2, 28.8, 29.5, 52.7, 59.6, 135.5, 141.5, 156.0. ESI-MS: *m/z* = 199.11 [M]²⁺. Anal. Calcd for C₂₀H₃₄I₂N₂O₂S₂ (652.42): C, 36.82; H, 5.25; N, 4.29. Found: C, 36.68; H, 5.45; N, 4.29.

1,9-Nonamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**9**). Careful drying of the residue afforded 1.292 g (1.94 mmol, 97% yield) of yellow liquid. IR (KBr) ν (cm⁻¹): 3366, 2929, 1586, 1452, 1064. ¹H NMR (DMSO-*d*₆): δ 1.32 (m, 5H, linker CH₂), 1.82 (m, 2H, linker CH₂), 2.52 (s, 3H, CH₃), 3.05 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OH), 3.66 (m, 2H, CH₂CH₂OH), 4.47 (br t, *J* = 7.5 Hz, 2H, linker CH₂), 5.18 (t, *J* = 5.0 Hz, 1H, OH), 10.04 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆): δ 11.3, 25.5, 28.3, 28.6, 28.9, 29.5, 52.7, 59.6, 135.5, 141.5, 156.0. ESI-MS: *m/z* = 206.05 [M]²⁺. Anal. Calcd for C₂₁H₃₆I₂N₂O₂S₂ (666.46): C, 37.84; H, 5.44; N, 4.20. Found: C, 37.89; H, 5.62; N, 4.10.

1,10-Decamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**10**). The residue was dissolved in hot *i*PrOH (150 mL). Crystallization occurred at -18 °C to give 1.093 g (1.61 mmol, 80% yield) of light-yellow crystals. M.p. 129-130 °C. IR (KBr) ν (cm⁻¹): 3328, 2916, 1581, 1441, 1079. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 1.30 (m, 6H, linker CH₂), 1.79 (m, 2H, linker CH₂), 2.47 (s, 3H, CH₃), 3.03 (t, *J* = 5.5 Hz, 2H, CH₂CH₂OH), 3.64 (m, 2H, CH₂CH₂OH), 4.44 (br t, *J* = 7.5 Hz, 2H, linker CH₂), 5.17 (t, *J* = 4.8 Hz, 1H, OH), 10.01 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆, 100.6 MHz): δ 11.3, 25.5, 28.3, 28.7, 28.8,

29.5, 52.7, 59.6, 135.4, 141.5, 155.9. ESI-MS: $m/z = 212.98 [M]^{2+}$. Anal. Calcd for $C_{22}H_{38}I_2N_2O_2S_2$ (680.48): C, 38.83; H, 5.63; N, 4.12. Found: C, 38.96; H, 5.63; N, 4.13.

1,11-Undecamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**11**). Careful drying of the residue afforded 1.358 g (1.96 mmol, 98% yield) of yellow liquid. IR (KBr) ν (cm^{-1}): 3363, 2925, 1585, 1452, 1048. 1H NMR (DMSO- d_6): δ 1.32 (m, 7H, linker CH_2), 1.81 (m, 2H, linker CH_2), 2.52 (s, 3H, CH_3), 3.05 (t, $J = 5.6$ Hz, 2H, CH_2CH_2OH), 3.66 (m, 2H, CH_2CH_2OH), 4.47 (br t, $J = 7.5$ Hz, 2H, linker CH_2), 5.18 (t, $J = 5.0$ Hz 1H, OH), 10.05 (s, 1H, thiazolium H). ^{13}C NMR (DMSO- d_6): δ 11.3, 25.5, 25.6, 28.4, 28.8, 28.8, 29.5, 52.7, 59.6, 135.4, 141.5, 156.0. ESI-MS: $m/z = 220.12 [M]^{2+}$. Anal. Calcd for $C_{23}H_{40}I_2N_2O_2S_2$ (694.51): C, 39.78; H, 5.81; N, 4.03. Found: C, 39.74; H, 6.01; N, 3.91.

1,12-Dodecamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**12**). The residue was dissolved in hot *i*PrOH (400 mL). Crystallization occurred at $-18^\circ C$ to give 0.745 g (1.051 mmol, 53% yield) of light orange crystals. M.p. $94^\circ C$. IR (KBr) ν (cm^{-1}): 3344, 2917, 1585, 1450, 1078. 1H NMR (DMSO- d_6): δ 1.27 (m, 8H, linker CH_2), 1.79 (m, 2H, linker CH_2), 2.47 (s, 3H, CH_3), 3.03 (t, $J = 5.6$ Hz, 2H, CH_2CH_2OH), 3.64 (m, 2H, CH_2CH_2OH), 4.45 (br t, $J = 7.5$ Hz, 2H, linker CH_2), 5.15 (m, 1H, OH), 10.04 (s, 1H, thiazolium H). ^{13}C NMR (DMSO- d_6): δ 11.3, 25.4, 25.5, 28.4, 28.8, 28.9, 29.5, 52.7, 59.6, 135.4, 141.5, 156.0. ESI-MS: $m/z = 227.14 [M]^{2+}$. Anal. Calcd for $C_{24}H_{42}I_2N_2O_2S_2$ (708.54): C, 40.68; H, 5.97; N, 3.95. Found: C, 40.62; H, 6.04; N, 3.76.

1,14-Tetradecamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**13**). After evaporation of the acetonitrile, the residue was dissolved in hot *i*PrOH (300 mL). Crystallization occurred at $-18^\circ C$ to give 1.096 g (1.49 mmol, 74% yield) of yellow crystals. M.p. $79-80^\circ C$. IR (KBr) ν (cm^{-1}): 3297, 2920, 1588, 1468, 1075. 1H NMR (DMSO- d_6): δ 1.27 (m, 10H, linker CH_2), 1.79 (m, 2H, linker CH_2), 2.46 (s, 3H, CH_3), 3.02 (t, $J = 5.5$ Hz, 2H, CH_2CH_2OH), 3.64 (m, 2H, CH_2CH_2OH), 4.43 (br t, 7.5 Hz, 2H, linker CH_2), 5.17 (t, 4.9 Hz 1H, OH), 10.00 (s, 1H, thiazolium H). ^{13}C NMR (DMSO- d_6): δ 11.2, 25.6, 28.4, 28.9 (2 peaks), 29.0, 29.1, 29.5, 52.7, 59.7, 135.5, 141.5, 156.0. ESI-MS: $m/z = 241.15 [M]^{2+}$. Anal. Calcd for $C_{26}H_{46}I_2N_2O_2S_2$ (736.59): C, 42.39; H, 6.29; N, 3.80. Found: C, 42.68; H, 6.51; N, 3.94.

1,16-Hexadecamethylene bis[4-methyl-5-(2-hydroxyethyl)thiazol-3-ium] diiodide (**14**). After evaporation of the acetonitrile, the residue was dissolved in hot *i*PrOH (230 mL). Crystallization occurred at $-18^\circ C$ to give 1.342 g (1.76 mmol, 88% yield) of yellow crystals. M.p. $89^\circ C$. IR (KBr) ν (cm^{-1}): 3294, 2920, 1588, 1468, 1447, 1070. 1H NMR (DMSO- d_6 , 400 MHz): δ 1.27 (m, 12H, linker CH_2), 1.79 (m, 2H, linker CH_2), 2.46 (s, 3H, CH_3), 3.02 (t, $J = 5.6$ Hz, 2H, CH_2CH_2OH), 3.64 (m, 2H, CH_2CH_2OH), 4.43 (br t, $J = 7.7$ Hz, 2H, linker CH_2), 5.19 (t, $J = 4.7$ Hz, 1H, OH), 10.00 (s, 1H, thiazolium H). ^{13}C NMR (DMSO- d_6 , 100.6 MHz): δ 11.2, 25.6, 28.4, 28.8, 28.9, 29.0, 29.1, 29.2, 29.5, 52.8, 59.7, 135.5, 141.5, 156.0. ESI-MS: $m/z = 255.17 [M]^{2+}$. Anal. Calcd for $C_{28}H_{50}I_2N_2O_2S_2$ (764.65): C, 43.98; H, 6.59; N, 3.66. Found: C, 44.26; H, 6.78; N, 3.85.

1,10-Decamethylene bis[4-methyl-5-(2-methoxyethyl)thiazol-3-ium] diiodide (**15**). After evaporation of the acetonitrile, the residue was dissolved in hot *i*PrOH (150 mL). Crystallization occurred at $-18^\circ C$. Very hygroscopic material was obtained, thus it was filtered under argon flow and washed with Et_2O to give 0.694 g (0.98 mmol, 49% yield) of pale-yellow crystals. M.p. $91^\circ C$. IR (KBr) ν (cm^{-1}): 3435, 2982, 2922, 1449, 1111, 858. 1H NMR (DMSO- d_6): δ 1.29 (m, 6H, linker CH_2), 1.80 (m, 2H, linker CH_2), 2.47 (s, 3H, CH_3), 3.14 (t, $J = 5.6$ Hz, 2H, $CH_2CH_2OCH_3$), 3.30 (s, 3H, OCH_3), 3.57 (t, $J = 5.6$ Hz, 2H, $CH_2CH_2OCH_3$), 4.44 (br t, $J = 7.4$ Hz, 2H, linker CH_2), 10.04 (s, 1H, thiazolium H). ^{13}C NMR (DMSO- d_6): δ 11.3, 25.5, 26.5, 28.3, 28.7, 28.8, 52.8, 58.0, 70.2, 135.0, 141.7, 156.2. ESI-MS: $m/z = 227.14 [M]^{2+}$. Anal. Calcd for $C_{24}H_{42}I_2N_2O_2S_2$ (708,54): C, 40.68; H, 5.97; N, 3.95. Found: C, 40.81; H, 5.89; N, 3.69.

1,11-Undecamethylene bis[4-methyl-5-(2-methoxyethyl)thiazol-3-ium] diiodide (**16**). After evaporation of the acetonitrile, the residue was dissolved in hot *i*PrOH (150 mL). Crystallization occurred at -18°C. Very hygroscopic material was obtained, thus it was filtered under argon flow and washed with Et₂O to give 0.724 g (1.00 mmol, 49% yield) of pale-yellow crystals. M.p. 81 °C. IR (KBr) ν (cm⁻¹): 3436, 2922, 1578, 1440, 1111, 739. ¹H NMR (DMSO-*d*₆): δ 1.26 (m, 7H, linker CH₂), 1.78 (m, 2H, linker CH₂), 2.46 (s, 3H, CH₃), 3.13 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OCH₃), 3.32 (s, 3H, OCH₃), 3.56 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OCH₃), 4.43 (br t, *J* = 7.4 Hz, 2H, linker CH₂), 10.02 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆): δ 11.2, 25.6, 26.5, 28.4, 28.8 (3 peaks), 52.8, 58.0, 70.2, 135.1, 141.7, 156.2. ESI-MS: *m/z* = 234.12 [M]²⁺. Anal. Calcd for C₂₅H₄₄I₂N₂O₂S₂ (722,57): C, 41.56; H, 6.14; N, 3.88. Found: C, 41.57; H, 6.05; N, 3.57.

1,12-Dodecamethylene bis[4-methyl-5-(2-methoxyethyl)thiazol-3-ium] diiodide (**17**). After evaporation of the acetonitrile, the residue was dissolved in hot *i*PrOH (200 mL). Crystallization occurred at -18°C. Very hygroscopic material was obtained, thus it was filtered under argon flow and washed with Et₂O to give 1.209 g (1.67 mmol, 84% yield) of pale-yellow crystals. M.p. 110 °C. IR (KBr) ν (cm⁻¹): 3434, 2924, 1578, 1457, 1108. ¹H NMR (DMSO-*d*₆): δ 1.25 (m, 8H, linker CH₂), 1.79 (m, 2H, linker CH₂), 2.47 (s, 3H, CH₃), 3.14 (t, *J* = 5.6 Hz, 2H, CH₂CH₂OCH₃), 3.30 (s, 3H, OCH₃), 3.57 (t, *J* = 5.7 Hz, 2H, CH₂CH₂OCH₃), 4.43 (br t, *J* = 7.4 Hz, 2H, linker CH₂), 10.03 (s, 1H, thiazolium H). ¹³C NMR (DMSO-*d*₆): δ 11.2, 25.6, 26.5, 28.4, 28.8 (2 peaks), 28.9, 52.8, 58.0, 70.2, 135.1, 141.7, 156.3. ESI-MS: *m/z* = 241.15 [M]²⁺. Anal. Calcd for C₂₆H₄₆I₂N₂O₂S₂ (736,59): C, 42.39; H, 6.29; N, 3.80. Found: C, 42.17; H, 6.21; N, 3.62.

1.4. Synthesis of bis-imidazoliums **32-38**

1-(4-*tert*-Butylbenzyl)imidazole (**23**)^[3]

To a solution of imidazole (2.042 g, 30 mmol) in anhydrous DMF (20 mL) was added K₂CO₃ (2.764 g, 20 mmol) and 4-*tert*-butylbenzyl bromide (1.83 mL, 10 mmol). The suspension was stirred at 80 °C under argon for 7 h. EtOAc (50 mL) was added and the mixture was washed with water (5 x 30 mL). The organic phase was dried (MgSO₄) and concentrated to dryness to give 1.53 g of yellow liquid which was purified by column chromatography (eluent: CH₂Cl₂ → CH₂Cl₂/MeOH, 95/5) to give 1.451 g (6.77 mmol, 68% yield) of yellow liquid. ¹H NMR (CDCl₃): δ 1.31 (s, 9H, *t*-Bu), 5.08 (s, 2H, CH₂), 6.90 (s, 1H, CH_{imid}), 7.08 (s, 1H, CH_{imid}), 7.09 (d, *J* = 8.3 Hz, 2H, H_{arom}), 7.37 (d, *J* = 8.3 Hz, 2H, H_{arom}), 7.53 (s, 1H, NCHN).

1-(Naphthalen-2-ylmethyl)imidazole (**24**)^[4]

To a solution of imidazole (2.042 g, 30 mmol) in anhydrous DMF (20 mL) was added K₂CO₃ (2.764 g, 20 mmol) and naphthalen-2-ylmethyl bromide (2.21 g, 10 mmol). The suspension was stirred at 80 °C under argon for 12 h. EtOAc (50 mL) was added and the mixture was washed with water (5 x 30 mL). The organic phase was dried (MgSO₄) and concentrated to dryness to give 1.53 g of yellow liquid which was purified by column chromatography (eluent: CH₂Cl₂ → CH₂Cl₂/MeOH, 95/5) to give 1.221 g (5.86 mmol, 53% yield) of yellow liquid. ¹H NMR (CDCl₃): δ 5.25 (s, 2H, CH₂), 6.93 (s, 1H, CH_{imid}), 7.11 (s, 1H, CH_{imid}), 7.24 (d, *J* = 7.5 Hz, 1H, H_{arom}), 7.49 (m, 2H, H_{arom}), 7.59 (br s, 2H, CH_{imid} + H_{arom}), 7.81 (m, 3H, H_{arom}).

1-Decylimidazole (**25**)^[5]

To a solution of imidazole (2.042 g, 30 mmol) in anhydrous DMF (20 mL) was added K_2CO_3 (2.764 g, 20 mmol) and 1-bromodecane (2.07 mL, 10 mmol). The suspension was stirred at 80 °C under argon for 12 h. EtOAc (50 mL) was added and the mixture was washed with water (5 x 30 mL). The organic phase was dried ($MgSO_4$) and concentrated to dryness to give 1.77 g of yellow liquid which was purified by column chromatography (eluent: $CH_2Cl_2 \rightarrow CH_2Cl_2/MeOH$, 95/5) to give 1.477 g (7.09 mmol, 71% yield) of light-yellow liquid. 1H NMR ($CDCl_3$): δ 0.87 (m, 3H, CH_3), 1.25 (br s, 14H, 7 x CH_2), 1.76 (m, 2H, CH_2), 3.91 (t, $J = 7.5$ Hz, 2H, NCH_2), 6.89 (s, 1H, H_{imid}), 7.04 (s, 1H, H_{imid}), 7.44 (s, 1H, H_{imid}).

General procedure for the preparation of bis-imidazolium dibromides **32-38**.

To a solution of 1-alkylimidazole (2.5 equ.) in CH_3CN (4 mL) was added α,ω -dibromoalkane (1.0 equ.) and the mixture was stirred at reflux under argon for 48h. The solvent was evaporated, and the compound was usually purified by crystallization, except compound **32** which was chromatographed.

1,10-Decamethylene bis[3-(4-*tert*-butylbenzyl)imidazol-1-ium] dibromide (**32**)

Compound **23** (429 mg, 2 mmol) was reacted with 1,10-dibromodecane (240 mg, 0.8 mmol). After reflux, the mixture was purified by column chromatography (eluent: $CH_2Cl_2 \rightarrow CH_2Cl_2/MeOH$, 75/25), afforded a residue which was dissolved in water and lyophilized to give 0.530 g (7.27 mmol, 91% yield) of a white powder. M.p. 112 °C. IR (KBr) ν (cm^{-1}): 3435, 2929, 1560, 1157. 1H NMR ($DMSO-d_6$): δ 1.25 (m, 15H, *tbu* + linker CH_2), 1.78 (m, 2H, linker CH_2), 4.17 (t, $J = 7.1$ Hz, 2H, linker CH_2), 5.39 (s, 2H, *tbuPhCH_2*), 7.34, 7.43 (AB system, $J = 3.5$ Hz, 4H, *tbuPhCH_2*), 7.82 (m, 2H, CH_{imid}), 9.36 (s, 1H, NCHN H). ^{13}C NMR ($DMSO-d_6$): δ 25.5, 28.3, 28.7, 29.3, 31.0, 34.3, 48.9, 51.6, 122.6, 122.7, 125.7, 128.0, 132.0, 136.0, 151.3. ESI-MS: $m/z = 284.23$ [M] $^{2+}$. Anal. Calcd for $C_{38}H_{56}Br_2N_4$ (728.69): C, 62.63; H, 7.75; N, 7.69. Found: C, 62.25; H, 7.53; N, 7.52.

1,11-Undecamethylene bis[3-(4-*tert*-butylbenzyl)imidazol-1-ium] dibromide (**33**)

Compound **23** (348 mg, 1.63 mmol) was reacted with 1,11-dibromoundecane (204 mg, 0.65 mmol). After reflux, the solvent was evaporated, and the residue was dissolved in *i*PrOH (15 mL), then Et_2O (15 mL) was added portionwise. The mixture was kept at -18°C for 24h. The resulting crystals were filtered and washed with Et_2O to give upon drying 399 mg (0.54 mmol, 83% yield) of white crystals. M.p. 135 °C. IR (KBr) ν (cm^{-1}): 3423, 2927, 1560, 1160. 1H NMR ($DMSO-d_6$): δ 1.25 (m, 16H, *tbu* + linker CH_2), 1.78 (m, 2H, linker CH_2), 4.16 (t, $J = 7.1$ Hz, 2H, linker CH_2), 5.38 (s, 2H, *tbuPhCH_2*), 7.33, 7.44 (AB system, $J = 3.5$ Hz, 4H, *tbuPhCH_2*), 7.81 (m, 2H, CH_{imid}), 9.33 (s, 1H, NCHN). ^{13}C NMR ($DMSO-d_6$): δ 25.5, 28.3, 28.8, 29.2, 31.0, 34.3, 48.9, 51.6, 122.6, 122.7, 125.7, 128.0, 131.9, 136.0, 151.3. ESI-MS: $m/z = 291.24$ [M] $^{2+}$. Anal. Calcd for $C_{39}H_{58}Br_2N_4$ (742.71): C, 63.07; H, 7.87; N, 7.54. Found: C, 63.19; H, 7.80; N, 7.65.

1,12-Dodecamethylene bis[3-(4-*tert*-butylbenzyl)imidazol-1-ium] dibromide (**34**)

The previous protocol was used with the same quantity of **23** and 1,12-dibromododecane (213 mg, 0.65 mmol) to give after crystallization 475 mg (0.63 mmol, 96% yield) of white crystals. M.p. 155 °C. IR (KBr) ν (cm^{-1}): 3445, 2920, 1563, 1164. 1H NMR ($DMSO-d_6$): δ 1.25 (m, 17H, *tbu* + linker CH_2), 1.78 (m, 2H, linker CH_2), 4.16 (t, $J = 7.1$ Hz, 2H, linker CH_2), 5.39 (s, 2H, *tbuPhCH_2*), 7.34, 7.44 (AB system, $J = 3.6$ Hz, 4H, *tbuPhCH_2*), 7.82 (m, 2H, CH_{imid}), 9.36 (s, 1H, NCHN). ^{13}C NMR ($DMSO-d_6$): δ 25.5, 28.3, 28.8, 28.9, 29.2, 31.0, 34.3, 48.9, 51.6, 122.5, 122.7, 125.7, 128.0, 132.0, 136.0, 151.2. ESI-MS: $m/z =$

298.24 [M]²⁺. Anal. Calcd for C₄₀H₆₀Br₂N₄ (756.74): C, 63.49; H, 7.99; N, 7.40. Found: C, 63.88; H, 8.11; N, 7.54.

1,10-Decamethylene bis[3-(naphthalen-2-ylmethyl)imidazol-1-ium] dibromide (**35**)

Compound **24** (287 mg, 1.38 mmol) was reacted with 1,10-dibromodecane (165 mg, 0.55 mmol). After reflux, the solvent was evaporated, and the residue was dissolved in hot *i*PrOH (30 mL), and then let for 12h at room temperature. The solid matter was then filtered and washed with a mixture of *i*PrOH and Et₂O to afford 383 mg (0.53 mmol, 96% yield) of white crystals. M.p. 80 °C. IR (KBr) ν (cm⁻¹): 3435, 2927, 1560, 1152, 761. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 1.20 (m, 6H, linker CH₂), 1.78 (m, 2H, linker CH₂), 4.17 (t, *J* = 7.2 Hz, 2H, linker CH₂), 5.60 (s, 2H, naphthylCH₂), 7.55 (m, 3H, naphthyl H), 7.92 (m, 6H, naphthyl H + CH_{imid}), 9.37 (s, 1H, NCHN). ¹³C NMR (DMSO-*d*₆, 100.6 MHz): δ 25.5, 28.3, 28.8, 29.3, 49.0, 52.2, 122.7, 122.8, 125.7, 126.8 (2 peaks), 127.5, 127.7, 127.9, 128.8, 132.3, 132.7 (2 peaks), 136.2. ESI-MS: *m/z* = 278.18 [M]²⁺. Anal. Calcd for C₃₈H₄₄Br₂N₄, H₂O (734.63): C, 62.13; H, 6.31; N, 7.63. Found: C, 62.49; H, 6.36; N, 7.32.

1,11-Undecamethylene bis[3-(naphthalen-2-ylmethyl)imidazol-1-ium] dibromide (**36**)

The previous protocol was used with the same quantity of **24** and 1,11-dibromoundecane (173 mg, 0.55 mmol). After dissolution in hot *i*PrOH (30 mL), a solid matter appeared at -18 °C. Precipitation was completed by the addition of Et₂O (10 mL). Filtration and washing with Et₂O afforded 396 mg (0.542 mmol, 98% yield) of white crystals. M.p. 78 °C. IR (KBr) ν (cm⁻¹): 3435, 2927, 1560, 1152, 760. ¹H NMR (DMSO-*d*₆): δ 1.05 (m, 7H, linker CH₂), 1.78 (m, 2H, linker CH₂), 4.17 (t, *J* = 7.1 Hz, 2H, linker CH₂), 5.60 (s, 2H, naphthylCH₂), 7.56 (m, 3H, naphthyl H), 7.91 (m, 6H, naphthyl H + CH_{imid}), 9.38 (s, 1H, NCHN). ¹³C NMR (DMSO-*d*₆): δ 25.5, 28.3, 28.8 (2 peaks), 29.2, 49.0, 52.1, 122.7, 122.8, 125.6, 126.8 (2 peaks), 127.5, 127.7, 127.9, 128.8, 132.3, 132.7 (2 peaks), 136.2. ESI-MS: *m/z* = 285.19 [M]²⁺. Anal. Calcd for C₃₉H₄₆Br₂N₄, 0.5 H₂O (739.63): C, 63.33; H, 6.41; N, 7.58. Found: C, 63.11; H, 6.49; N, 7.33.

1,12-Dodecamethylene bis[3-(naphthalen-2-ylmethyl)imidazol-1-ium] dibromide (**37**)

The previous protocol was used with the same quantity of **24** and 1,12-dibromododecane (180 mg, 0.55 mmol). After dissolution of the residue in hot *i*PrOH (40 mL), the solution was let at room temperature for 12h. The precipitate was filtered and washed with Et₂O to give 390 mg (0.52 mmol, 95% yield) of white crystals. M.p. 105 °C. IR (KBr) ν (cm⁻¹): 3421, 2925, 1559, 1152, 760. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 1.03 (m, 8H, linker CH₂), 1.78 (m, 2H, linker CH₂), 4.17 (t, *J* = 7.2 Hz, 2H, linker CH₂), 5.60 (s, 2H, naphthylCH₂), 7.55 (m, 3H, naphthyl H), 7.91 (m, 6H, naphthyl H + CH_{imid}), 9.38 (s, 1H, NCHN). ¹³C NMR (DMSO-*d*₆, 100.6 MHz): δ 25.6, 28.4, 28.9 (2 pics), 29.3, 49.0, 52.2, 122.7, 122.8, 125.7, 126.8 (2 pics), 127.5, 127.7, 127.9, 128.8, 132.3, 132.7 (2 pics), 136.3. ESI-MS: *m/z* = 292.20 [M]²⁺. Anal. Calcd for C₄₀H₄₈Br₂N₄, 0.5 H₂O (753.66): C, 63.75; H, 6.55; N, 7.43. Found: C, 63.63; H, 6.47; N, 7.30.

1,10-Decamethylene bis[3-decylimidazol-1-ium] dibromide (**38**)

Compound **25** (417 mg, 2.00 mmol) was reacted with 1,10-dibromodecane (240 mg, 0.80 mmol) in 5 mL of CH₃CN. After 48 h of reflux, the solvent was evaporated, and the residue was kept at 4 °C for two hours. Et₂O (15 mL) was then added and the mixture was carefully sonicated, which generated some crystals. Filtration and washing with Et₂O afforded 518 mg (0.72 mmol, 90% yield) of white crystals. M.p. 58-61 °C. IR (KBr) ν (cm⁻¹): 3449, 2920, 2852, 1560, 1466, 1156. ¹H NMR (DMSO-*d*₆): δ 0.85 (m, 3H, CH₃), 1.23 (s, 20H, linker CH₂+ decyl CH₂), 1.78 (m, 4H, linker CH₂+ decyl CH₂), 4.16 (t, *J* = 6.9 Hz, 4H, linker CH₂+ decyl CH₂), 7.80 (s, 2H, CH_{imid}), 9.22 (s, 1H, NCHN). ¹³C NMR (DMSO-*d*₆): δ 13.9, 22.0, 25.4,

25.5, 28.2, 28.3, 28.6, 28.8 (3 peaks), 29.2, 29.3, 31.2, 48.8 (2 peaks), 122.4 (2 peaks), 135.9. ESI-MS: $m/z = 278.27$ $[M]^{2+}$. Anal. Calcd for $C_{36}H_{68}Br_2N_4 \cdot 0.5 H_2O$ (725.76): C, 59.58; H, 9.58; N, 7.72. Found: C, 59.25; H, 9.78; N, 7.81.

1.5. Synthesis of bis-triazoliums **39-45**

1-(4-*tert*-Butylbenzyl)-1,2,4-triazole (**26**)^[6]

To a solution of 1,2,4-triazole (2.07 g, 30.00 mmol) in DMF (30 mL) was added K_2CO_3 (2.764 g, 20.00 mmol) and 4-*tert*-butylbenzyl bromide (1.83 mL, 10 mmol). The suspension was stirred at 80 °C under argon for 12 h. EtOAc (50 mL) was added and the mixture was extracted with water (3 x 50 mL). The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (eluent: Cyclohexane/EtOAc, 7/3 \rightarrow Cyclohexane/EtOAc, 3/7) to give 1.576 g (7.32 mmol, 73% yield) of pale-yellow liquid. 1H NMR ($CDCl_3$): δ 1.31 (s, 9H, *t*Bu), 5.31 (s, 2H, CH_2), 7.20 (d, $J = 8.2$ Hz, 2H, H_{arom}), 7.39 (d, $J = 8.2$ Hz, 2H, H_{arom}), 7.96 (s, 1H, CH_{triaz}), 8.03 (s, 1H, CH_{triaz}).

1-(Naphthalen-2-ylmethyl)-1,2,4-triazole (**27**)

To a solution of 1,2,4-triazole (2.07 g, 30.00 mmol) in DMF (15 mL) was added K_2CO_3 (2.764 g, 20.00 mmol) and a solution of 2-(bromomethyl)naphthalene (2.21 g, 10 mmol) in DMF (5 mL). The suspension was stirred at 80 °C under argon for 12 h. EtOAc (50 mL) was added and the mixture was extracted with water (5 x 30 mL). The organic phase was dried ($MgSO_4$) and evaporated to give a residue which was purified by column chromatography (eluent: $CH_2Cl_2 \rightarrow CH_2Cl_2/MeOH$, 97/3) to give 869 mg (4.15 mmol, 42% yield) of white crystals. M.p. 108 °C. IR (KBr) ν (cm^{-1}): 3104, 2919, 1507, 1275, 1139, 779. 1H NMR ($CDCl_3$): δ 5.51 (s, 2H, CH_2), 7.36 (m, 1H, naphthyl H), 7.52 (m, 2H, naphthyl H), 7.73 (br s, 1H, naphthyl H), 7.84 (m, 3H, naphthyl H), 8.00 (s, 1H, CH_{triaz}), 8.09 (s, 1H, CH_{triaz}). ^{13}C NMR ($CDCl_3$): δ 54.0, 125.4, 126.8, 126.9, 127.5, 127.9, 128.1, 129.2, 132.0, 133.3, 133.4, 143.3, 152.4. ESI-MS: $m/z = 210.10$ $[MH]^+$. Anal. Calcd for $C_{13}H_{11}N_3$ (209.25): C, 74.62; H, 5.30; N, 20.08. Found: C, 74.60; H, 5.31; N, 20.09.

1-Decyl-1,2,4-triazole (**28**)^[7]

To a solution of 1,2,4-triazole (2.07 g, 30.00 mmol) in DMF (15 mL) was added K_2CO_3 (2.764 g, 20.00 mmol) and dropwise a solution of 1-bromodecane (2.07 mL, 10 mmol) in DMF (5 mL). The suspension was stirred at 80 °C under argon for 12 h. EtOAc (50 mL) was added and the mixture was extracted with water (5 x 30 mL). The organic phase was dried ($MgSO_4$) and concentrated to dryness to give 1.99 g of yellow liquid which was purified by column chromatography (eluent: $CH_2Cl_2 \rightarrow CH_2Cl_2/MeOH$, 95/5) to give 1.556 g (7.43 mmol, 74% yield) of light-yellow liquid. 1H NMR ($CDCl_3$): δ 0.85 (m, 3H, CH_3), 1.26 (m, 14 H, 7 x CH_2), 1.66 (m, 2H, CH_2), 4.13 (t, $J = 7.5$ Hz, 2H, NCH_2), 7.90 (s, 1H, H_{triaz}), 8.01 (s, 1H, H_{triaz}). More polar fractions afforded 177 mg (0.84 mmol, 8% yield) of yellow liquid which revealed to be the 4-isomer which exhibited more symmetrical patterns. 1H NMR ($CDCl_3$): δ 0.88 (m, 3H, CH_3), 1.26 (m, 14 H, 7 x CH_2), 1.81 (m, 2H, CH_2), 4.00 (t, $J = 7.5$ Hz, 2H, NCH_2), 8.14 (s, 2H, H_{triaz}).

General procedure for the preparation of bis-1,2,4-triazolium dibromides **39-45**.

To a solution of 1-alkyl-1,2,4-triazole (2.5 equ.) in CH_3CN (4 mL) was added α,ω -dibromoalkane (1.0 equ.) and the mixture was stirred at reflux under argon for 48h. A white precipitate appeared upon

cooling at room temperature. The mixture was kept at 4 °C for two hours, filtered and washed with a 1:1 mixture of CH₃CN and Et₂O.

1,10-Decamethylene bis[1-(4-*tert*-butylbenzyl)-1,2,4-triazol-4-ium] dibromide (**39**)

Compound **26** (484 mg, 2.25 mmol) was reacted with 1,10-dibromodecane (270 mg, 0.9 mmol). Filtration afforded 498 mg (0.68 mmol, 75% yield) of white crystals. M.p. 180 °C. IR (KBr) ν (cm⁻¹): 3435, 2959, 1577, 1155, 668. ¹H NMR (DMSO-*d*₆): δ 1.27 (s, 15H, *t*bu + linker CH₂), 1.83 (m, 2H, linker CH₂), 4.23 (t, *J* = 7.3 Hz, 2H, linker CH₂), 5.58 (s, 2H, *t*buPhCH₂), 7.41 (m, 4H, *t*buPhCH₂), 9.25 (s, 1H, H_{triaz}), 10.29 (s, 1H, H_{triaz}). ¹³C NMR (DMSO-*d*₆): δ 25.5, 28.4, 28.7, 31.0, 34.4, 47.6, 54.5, 125.6, 128.7, 130.3, 142.5, 144.9, 151.5. ESI-MS: *m/z* = 285.22 [M]²⁺. Anal. Calcd for C₃₆H₅₄Br₂N₆ (730.66): C, 59.18; H, 7.45; N, 11.50. Found: C, 59.47; H, 7.32; N, 11.55.

1,11-Undecamethylene bis[1-(4-*tert*-butylbenzyl)-1,2,4-triazol-4-ium] dibromide (**40**)

Compound **26** (430 mg, 2.00 mmol) was reacted with 1,11-dibromoundecane (251 mg, 0.8 mmol). Filtration afforded 587 mg (0.79 mmol, 98% yield) of white crystals. M.p. 194 °C. IR (KBr) ν (cm⁻¹): 3435, 2931, 1572, 1154, 625. ¹H NMR (DMSO-*d*₆): δ 1.27 (s, 16H, *t*bu + linker CH₂), 1.83 (m, 2H, linker CH₂), 4.23 (t, *J* = 7.3 Hz, 2H, linker CH₂), 5.58 (s, 2H, *t*buPhCH₂), 7.41 (m, 4H, *t*buPhCH₂), 9.25 (s, 1H, H_{triaz}), 10.30 (s, 1H, H_{triaz}). ¹³C NMR (DMSO-*d*₆): δ 25.5, 28.4, 28.7, 28.8, 28.9, 31.0, 34.4, 47.6, 54.5, 125.6, 128.7, 130.3, 142.5, 144.9, 151.5. ESI-MS: *m/z* = 292.44 [M]²⁺. Anal. Calcd for C₃₇H₅₆Br₂N₆ (744.69): C, 59.68; H, 7.58; N, 11.29. Found: C, 59.92; H, 7.69; N, 11.48.

1,12-Dodecamethylene bis[1-(4-*tert*-butylbenzyl)-1,2,4-triazol-4-ium] dibromide (**41**)

Compound **26** (430 mg, 2.00 mmol) was reacted with 1,12-dibromododecane (262 mg, 0.80 mmol). Filtration afforded 604 mg (0.78 mmol, 99% yield) of white crystals. M.p. 228 °C. IR (KBr) ν (cm⁻¹): 3435, 2926, 1571, 1157, 625. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 1.26 (s, 17H, *t*bu + linker CH₂), 1.82 (m, 2H, linker CH₂), 4.23 (t, *J* = 7.3 Hz, 2H, linker CH₂), 5.58 (s, 2H, *t*buPhCH₂), 7.38, 7.44 (AB system, *J* = 4.0 Hz, 4H, *t*buPhCH₂), 9.25 (s, 1H, H_{triaz}), 10.28 (s, 1H, H_{triaz}). ¹³C NMR (DMSO-*d*₆, 100.6 MHz): δ 25.5, 28.4, 28.7, 28.9, 29.0, 31.0, 34.4, 47.6, 54.5, 125.6, 128.7, 130.3, 142.5, 145.0, 151.5. ESI-MS: *m/z* = 299.24 [M]²⁺. Anal. Calcd for C₃₈H₅₈Br₂N₆ (758.72): C, 60.16; H, 7.71; N, 11.08. Found: C, 60.27; H, 7.80; N, 11.13.

1,10-Decamethylene bis[1-(naphthalen-2-ylmethyl)-1,2,4-triazol-4-ium] dibromide (**42**)

Compound **27** (288 mg, 1.38 mmol) was reacted with 1,10-dibromodecane (165 mg, 0.55 mmol). Filtration afforded 390 mg (0.54 mmol, 98% yield) of white crystals. M.p. 255 °C. IR (KBr) ν (cm⁻¹): 3435, 2930, 1585, 1155, 831. ¹H NMR (DMSO-*d*₆): δ 1.26 (s, 6H, linker CH₂), 1.83 (m, 2H, linker CH₂), 4.24 (t, *J* = 7.3 Hz, 2H, linker CH₂), 5.79 (s, 2H, naphthylCH₂), 7.57 (m, 3H, naphthyl H), 7.97 (m, 4H, naphthyl H), 9.27 (s, 1H, H_{triaz}), 10.29 (s, 1H, H_{triaz}). ¹³C NMR (DMSO-*d*₆): δ 25.5, 28.4, 28.7 (2 peaks), 47.6, 55.0, 126.1, 126.8, 126.9, 127.7, 127.9, 128.3, 128.6, 130.6, 132.6, 132.8, 142.7, 145.0. ESI-MS: *m/z* = 279.18 [M]²⁺. Anal. Calcd for C₃₆H₄₂Br₂N₆ (718.57): C, 60.17; H, 5.89; N, 11.70. Found: C, 60.38; H, 5.84; N, 11.60.

1,11-Undecamethylene bis[1-(naphthalen-2-ylmethyl)-1,2,4-triazol-4-ium] dibromide (**43**)

Compound **27** (232 mg, 1.11 mmol) was reacted with 1,11-dibromoundecane (139 mg, 0.44 mmol). Filtration afforded 317 mg (0.43 mmol, 79% yield) of white crystals. M.p. 228-229 °C. IR (KBr) ν (cm⁻¹): 3435, 2926, 1578, 1154, 830. ¹H NMR (DMSO-*d*₆): δ 1.25 (s, 7H, linker CH₂), 1.84 (m, 2H, linker CH₂), 4.25 (t, *J* = 7.3 Hz, 2H, linker CH₂), 5.80 (s, 2H, naphthylCH₂), 7.57 (m, 3H, naphthyl H), 7.97 (m, 4H, naphthyl H), 9.28 (s, 1H, H_{triaz}), 10.33 (s, 1H, H_{triaz}). ¹³C NMR (DMSO-*d*₆): δ 25.5, 28.4, 28.7, 28.8 (2 peaks), 47.6,

55.0, 126.1, 126.7, 126.8, 127.6, 127.8, 128.3, 128.6, 130.6, 132.6, 132.8, 142.7, 145.0. ESI-MS: $m/z = 286.18 [M]^{2+}$. Anal. Calcd for $C_{37}H_{44}Br_2N_6$ (732.61): C, 60.66; H, 6.05; N, 11.47. Found: C, 60.67; H, 6.04; N, 11.55.

1,12-Dodecamethylene bis[1-(naphthalen-2-ylmethyl)-1,2,4-triazol-4-ium] dibromide (**44**)

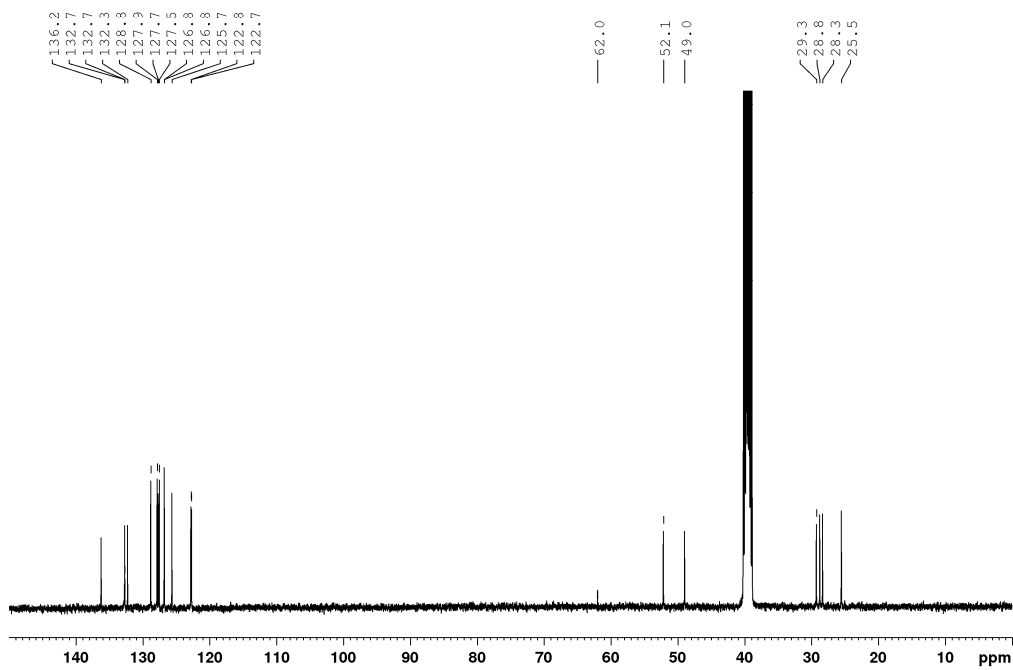
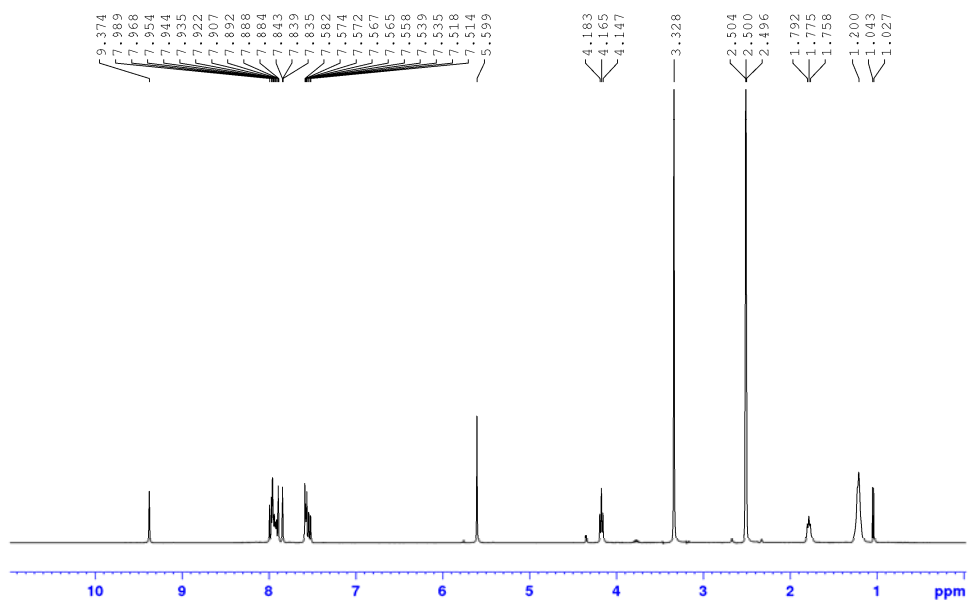
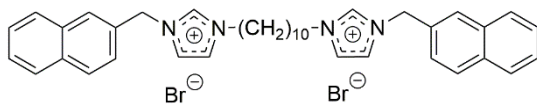
Compound **27** (288 mg, 1.38 mmol) was reacted with 1,12-dibromododecane (180 mg, 0.55 mmol). Filtration afforded 402 mg (0.54 mmol, 98% yield) of white crystals. M.p. 233 °C. IR (KBr) $\nu(\text{cm}^{-1})$: 3435, 2924, 1578, 1161, 780. ^1H NMR ($\text{DMSO-}d_6$): δ 1.24 (s, 8H, linker CH_2), 1.84 (m, 2H, linker CH_2), 4.25 (t, $J = 7.3$ Hz, 2H, linker CH_2), 5.80 (s, 2H, naphthyl CH_2), 7.57 (m, 3H, naphthyl H), 7.96 (m, 4H, naphthyl H), 9.28 (s, 1H, H_{triaz}), 10.32 (s, 1H, H_{triaz}). ^{13}C NMR ($\text{DMSO-}d_6$): δ 25.5, 28.4, 28.7, 28.8, 28.9, 47.6, 55.0, 126.1, 126.7, 126.8, 127.7, 127.9, 128.3, 128.6, 130.6, 132.6, 132.8, 142.7, 145.0. ESI-MS: $m/z = 293.19 [M]^{2+}$. Anal. Calcd for $C_{38}H_{46}Br_2N_6$ (746.62): C, 61.13; H, 6.21; N, 11.26. Found: C, 61.36; H, 6.11; N, 11.27.

1,10-Decamethylene bis[1-decyl-1,2,4-triazol-4-ium] dibromide (**45**)

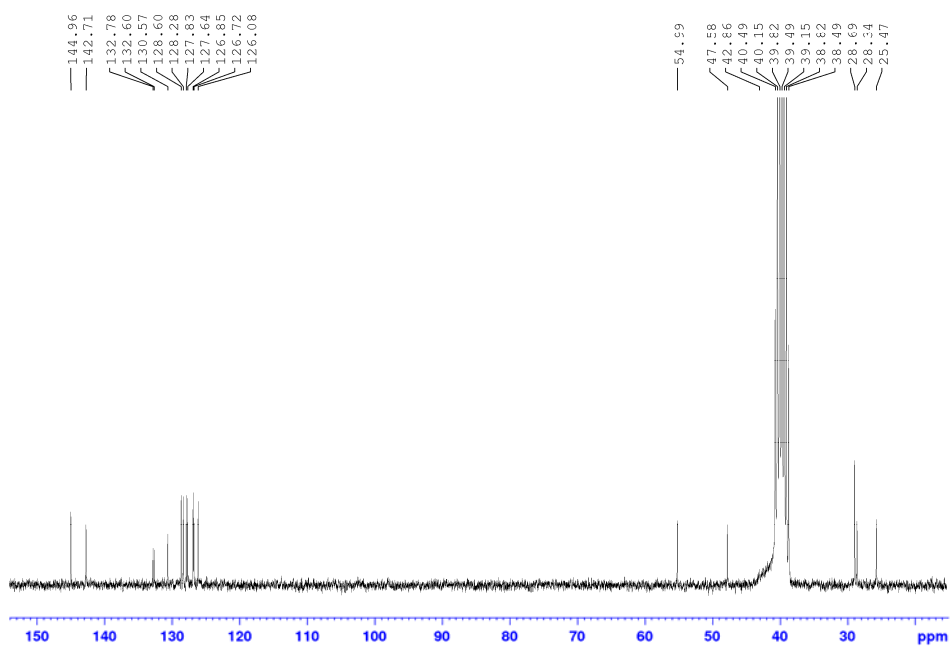
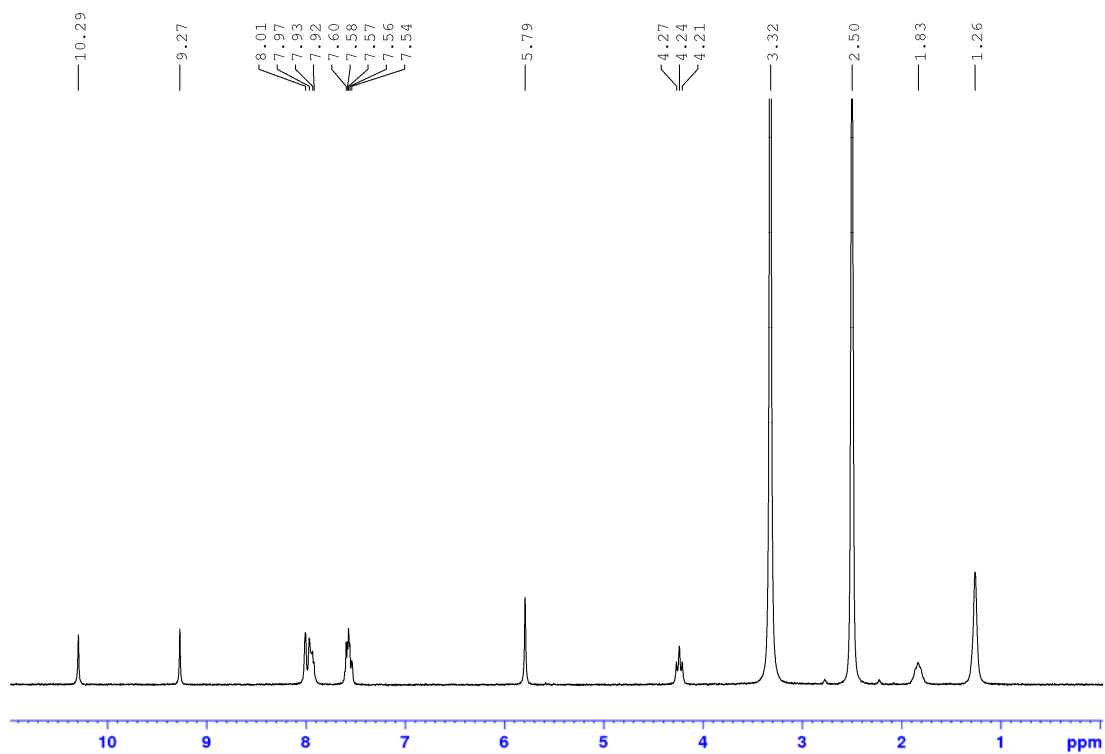
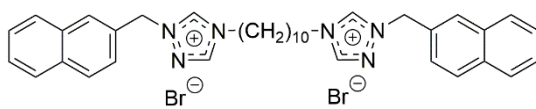
Compound **28** (419 mg, 2.00 mmol) was reacted with 1,10-dibromodecane (240 mg, 0.80 mmol). Filtration afforded 249 mg (0.35 mmol, 44% yield) of white crystals. M.p. 210 °C. IR (KBr) $\nu(\text{cm}^{-1})$: 3435, 2922, 1583, 1466, 1162, 626. ^1H NMR ($\text{DMSO-}d_6$): δ 0.84 (m, 3H, CH_3), 1.25 (m, 20H, linker CH_2 + decyl CH_2), 1.85 (m, 4H, linker CH_2 + decyl CH_2), 4.24 (t, $J = 7.2$ Hz, 2H, linker CH_2), 4.36 (t, $J = 6.9$ Hz, 2H, decyl CH_2), 9.25 (s, 1H, H_{triaz}), 10.18 (s, 1H, H_{triaz}). ^{13}C NMR ($\text{DMSO-}d_6$): δ 14.0, 22.1, 25.4, 25.5, 27.5, 28.0, 28.1, 28.3 (2 peaks), 28.4, 28.7, 28.8 (2 peaks), 28.9, 31.3, 32.2, 35.2, 47.5, 51.6, 142.4, 144.7. ESI-MS: $m/z = 279.27 [M]^{2+}$. Anal. Calcd for $C_{34}H_{66}Br_2N_6$ (718.74): C, 56.82; H, 9.26; N, 11.69. Found: C, 56.95; H, 8.89; N, 11.71.

1.6. NMR spectra of representative compounds

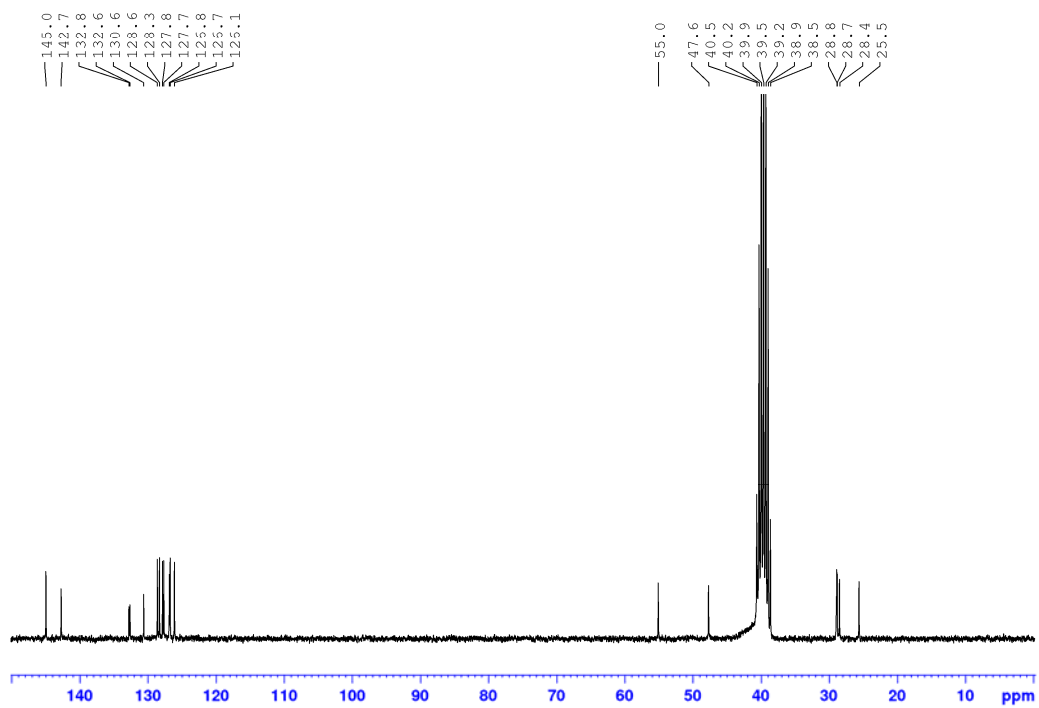
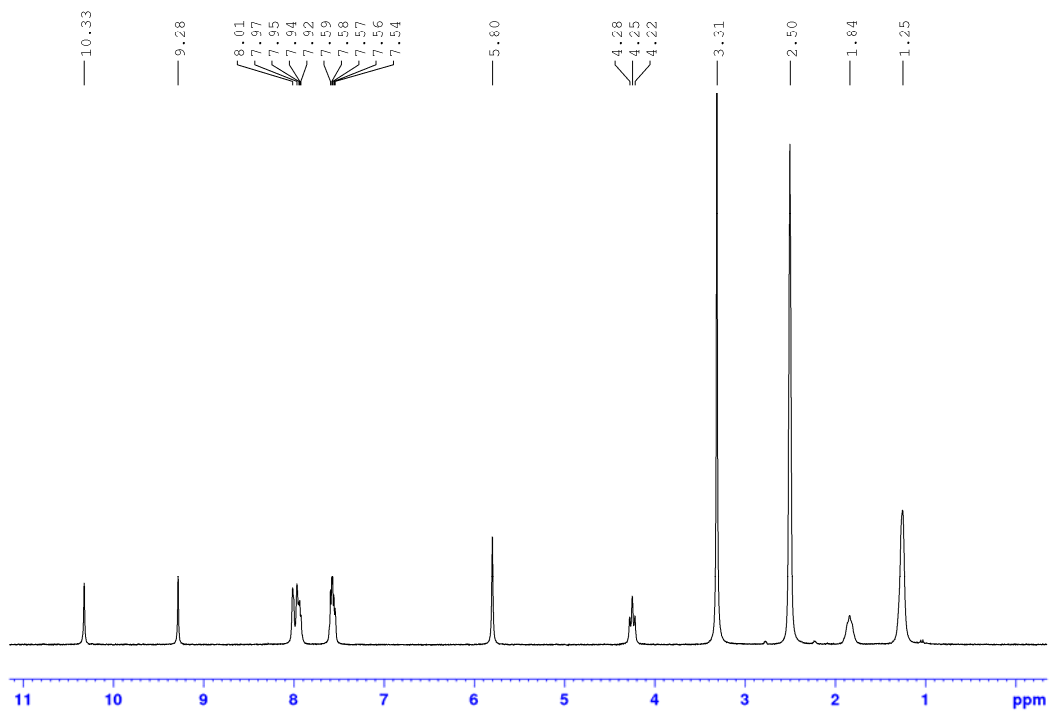
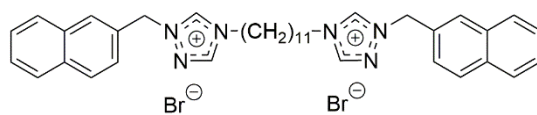
Compound 35



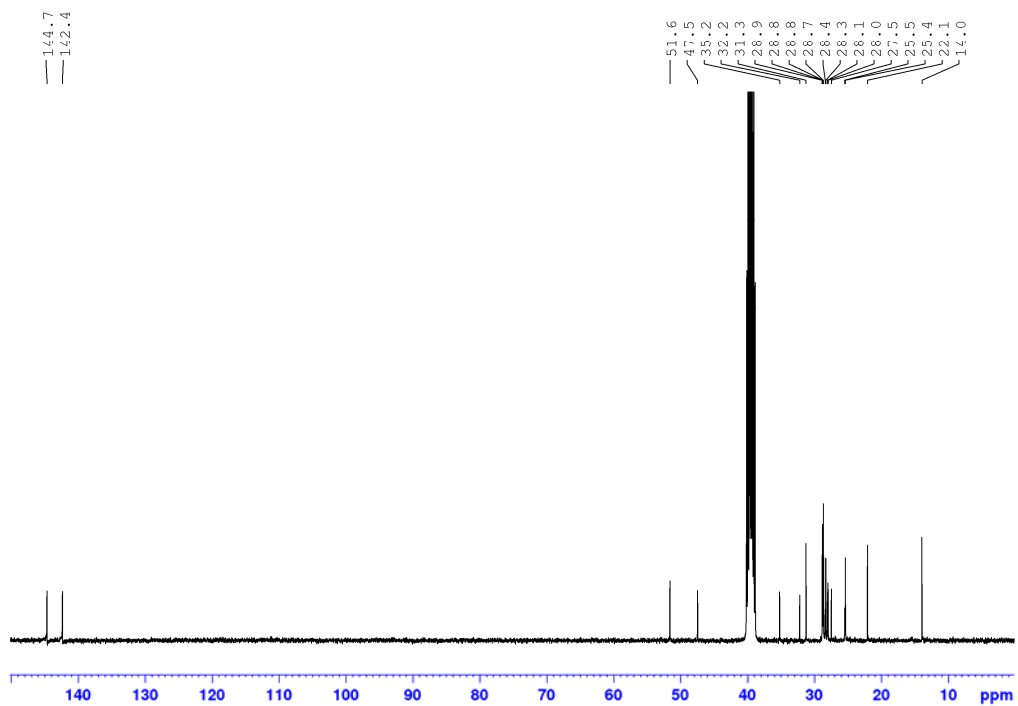
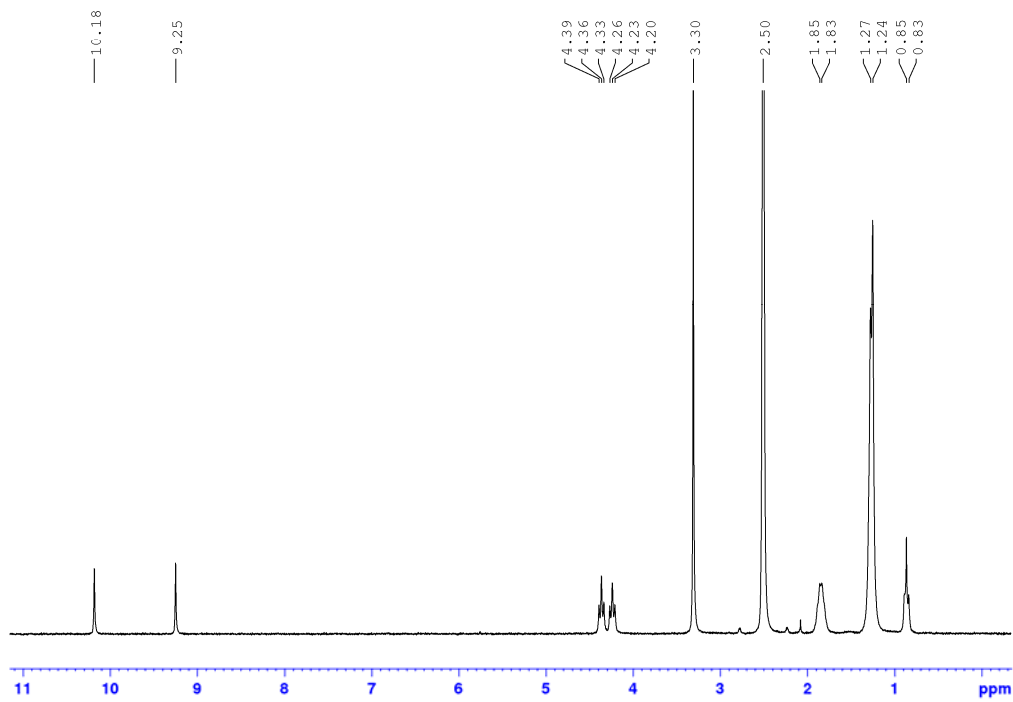
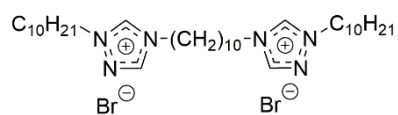
Compound 42



Compound 43



Compound 45



2. Microbiology

2.1. Cell culture and reagents

Bacterial strains

For all experiments, the following bacteria have been used: *Enterococcus faecalis* (ATCC 29212, ABC 3), *Staphylococcus aureus* (ATCC 29213, ABC 1), *Escherichia coli* (ATCC 25922, ABC 5), *Pseudomonas aeruginosa* (ATCC 27853, ABC 4) and resistant clinical isolates: Vancomycin-Resistant *E. faecalis* (VRE, *vanA*, ABC 100), Methicillin-Resistant *S. aureus* (MRSA, *mecA*, ABC 61), Extended-Spectrum β -lactamase producing *E. coli* (ESBLE, ABC 28) and *P. aeruginosa* resistant to ticarcillin + clavulanic acid (PAR, efflux pumps, ABC 132).

All strains were kindly provided by the ABC Platform® Bugs Bank.

All bacterial strains were grown on Mueller Hinton Agar (MHA, Difco 225250) or Mueller Hinton Broth (MHB, Difco, 275730).

For bactericidal evaluation, strains were grown on Mueller-Hinton Agar, Cation Adjusted (MHA-CA, Difco 211438) or Mueller-Hinton Broth, Cation-Adjusted (MHB-CA, Difco 212322).

Eukaryotic cells

For the cytotoxicity assays, MRC-5 cells (ATCC CCL-171, human lung fibroblasts) were used. Cells were grown in Minimum Essential Medium (MEM, 31095-029, Life Technologies-Gibco®) supplemented with 10% heat-inactivated fetal calf serum (CVFSV00-0U, Eurobio, Courtaboeuf, France) and 2 mM L-glutamine (G7513-100 mL, Sigma Aldrich), at 37°C in a 5% CO₂ humidified atmosphere.

2.2. Antibacterial assay

To evaluate the antibacterial activities of the compounds, the Minimal Inhibitory Concentration (MIC) were determined by broth dilution method. Briefly, bacterial suspensions were prepared by suspending one isolated colony from MHA plates in 5 mL of MHB. After 24 h of growth, the suspensions were diluted in distilled water to obtain a final inoculum of 5×10^5 to 5×10^6 CFU (Colony Forming Units). The purity of the isolates was checked throughout the study by examination of colony morphology and Gram stain procedure. Twofold serial dilutions of the compounds were prepared in MHB in round-bottomed, untreated 96-well plates starting from a stock solution at 1024 $\mu\text{g/mL}$. An equal volume of bacterial inoculum was added to each well on the microtiter plate containing 0.05 mL of the serial compound dilutions. Each condition was repeated in 8 wells. After incubation for 18–24 h at 35°C, the MICs were determined with an ELISA reader (read at 540 nm Multiskan EX, Thermo Electron Corporation, France) as the lowest concentration of compound whose absorbance was comparable with the negative control wells (broth with compound, without bacteria). Results were expressed by means of at least two independent experiments.^[8]

To evaluate the bactericidal activity, bacterial suspensions were prepared by suspending 3 to 5 isolated colonies from MHA-CA in 5 mL of MHB-CA. After 24 h of growth at 35°C, the medium was removed by centrifugation (5 min at 3000 g) and cells were resuspended in 0.85% NaCl to obtain a 0.5 McFarland suspension. This suspension was then adjusted in MHB-CA at 1×10^6 [0.4×10^6 – 1.6×10^6] CFU/mL. Twofold serial dilutions of the compounds were prepared in 0.05 mL MHB-CA in round-bottom, untreated 96-well plates. An equal volume (0.05 mL) of bacterial inoculum was added to each well. Each condition was repeated in the 8 lines of the microplate. Final bacterial concentration in the wells was 5×10^5 [2×10^5 – 8×10^5] CFU/mL, and the compounds concentrations ranged from 256 to 1 $\mu\text{g/mL}$ except for

compound **42** (64 to 0.25 $\mu\text{g} / \text{mL}$) for a final volume of 0.1 mL. In each line, a positive growth control (compound diluent, without compound) and two negative controls (0.05 mL MHB-CA with or without compound at the highest assayed concentration, and without bacteria) were included.

After incubation for 24 h at 35°C the content (0.1 mL) of wells at 1 x MIC and 4 x MIC were spread on MHA-CA plates and incubated overnight at 35°C for numeration. In order to evaluate the initial inoculum, 10 μL of a growth control well were diluted at 1/1000 in NaCl 0.85% prior to initial incubation. 100 μL were then spread on MHA-CA and incubated 16-20h at 35°C for numeration. In all cases the plate counts, performed in triplicate, were in the defined range between 20 and 80 CFU/plate (2×10^5 to 8×10^5 CFU/mL in the growth control well).

The bactericidal activity was defined as a ≥ 3 -log reduction of the initial inoculum with treatment compared with the untreated control, for a compound concentration not greater than 4 x MIC, after 24 h of incubation at 35°C.^[9] To control the sensitivity of the two reference strains, the MICs were also evaluated in the same conditions against two antibiotics (gentamicin and vancomycin). Results were in agreement with the expected values ($\leq 1 \mu\text{g}/\text{mL}$ for both antibiotics on *S. aureus* ATCC 29213 and for gentamicin on *E. coli* ATCC 25922, and $> 256 \mu\text{g}/\text{mL}$ for vancomycin on *E. coli* ATCC 25922).^[10,11]

2.3. Cytotoxicity assay

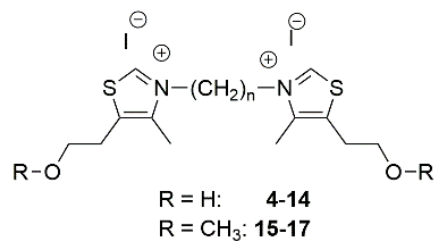
The MTT assay is based on the capacity of the metabolism of living cells to reduce MTT (yellow colour) to its insoluble formazan form (purple colour). This colour can be measured spectrophotometrically and the absorbance is proportional to the number of living cells.^[12]

Cells were plated at 10^4 cells per well in 96-well tissue culture plates (83.1835, Sarstedt) and grown for 48 h at 37°C in a 5% CO_2 humidified atmosphere. The medium was then discarded and replaced by fresh medium containing increasing amounts of the compounds (range 1–256 $\mu\text{g}/\text{mL}$) previously dissolved in dimethylsulfoxide (DMSO). The final concentration of DMSO never exceeded 2% of the final volume. Three different (negative) controls were added: medium alone, cells in medium and 256 $\mu\text{g}/\text{mL}$ extract in medium (without cells). Each condition was repeated in eight wells. After 48 h incubation the medium was discarded, and cells were washed with PBS 100 μL of medium containing 0.5 mg/mL MTT prepared previously in PBS were added to each well and the plates were incubated for 4 h at 37°C. Then formazan crystals were dissolved by the addition of 100 μL of SDS (100 $\mu\text{g}/\text{mL}$), followed by incubation for 3 h at 37°C. Finally, the absorbance was measured at 540 nm *versus* 690 nm using a 96-well plate reader (Multiskan EX, Thermo Electron Corporation, France). Percentages of survival and the half maximal inhibitory concentration (IC_{50}) were then calculated. Experiments were repeated three times.^[8]

2.4. Minimum Inhibitory Concentration and IC₅₀ in μMol/L

2.4.1. Bis-thiazoliums 4-17

Table 1. Minimum inhibitory concentration (MIC, μMol/L) values of prepared bis-thiazoliums



Entry ^[a]	n	<i>S.a.</i>	<i>E.f.</i>	<i>E.c.</i>	<i>P.a.</i>	M ^[c]
Chx ^[b]		1.98	3.96	0.99	15.83	505.45
4	4	>429.29	>429.29	>429.29	>429.29	596.33
5	5	>419.43	>419.43	>419.43	>419.43	610.35
6	6	205.00	205.00	205.00	>410.01	624.38
7	7	>401.00	>401.00	>401.00	>401.00	638.40
8	8	>392.39	>392.39	>392.39	>392.39	652.42
9	9	>384.12	>384.12	>384.12	>384.12	666.46
10	10	94.05	188.10	94.05	188.10	680.48
11	11	368.60	>368.60	>368.60	>368.60	694.51
12	12	22.58	>361.31	22.58	>361.31	708.54
13	14	43.44	347.55	347.55	347.55	736.59
14	16	20.92	83.70	167.40	334.79	764.65
15	10	>361.31	>361.31	>361.31	>361.31	708.54
16	11	354.29	>354.29	354.29	>354.29	722.57
17	12	86.89	>347.55	173.78	>347.55	736.59

[a] Organisms used in this study: *S.a.* (*Staphylococcus aureus* ATCC 29213), *E.f.* (*Enterococcus faecalis* ATCC 29212), *E.c.* (*Escherichia coli* ATCC 25922), *P.a.* (*Pseudomonas aeruginosa* ATCC 27853). [b] Reference compound used: Chx (Chlorhexidine). [c] molecular weight (g/mol)

2.4.2. Bis-imidazoliums **32-38** and bis-triazoliums **39-45**

Table 2. Minimum inhibitory concentration (MIC, $\mu\text{Mol/L}$) and IC₅₀ ($\mu\text{Mol/L}$) values of prepared bis-imidazoliums and bis-triazoliums



Entry ^[a]	n	clogP	R ^[c]	S.a.	MRSA	<i>E.f.</i>	VRE	<i>E.c.</i>	ESBLE	<i>P.a.</i>	PAR	IC ₅₀ ^[e]	M ^[f]
Chx ^[b]				1.98	1.98	3.96	3.96	0.99	1.98	15.83	31.66	44.12	505.45
32	10	2.68	4- <i>tbb</i>	1.37	1.37	1.37	2.74	1.37	2.74	21.96	87.83	20.86	728.69
33	11	3.08	4- <i>tbb</i>	0.67	0.67	1.35	1.35	1.35	1.35	21.54	21.54	12.92	742.71
34	12	3.48	4- <i>tbb</i>	0.33	0.66	0.66	0.66	0.66	1.32	5.29	10.57	8.72	756.74
35	10	1.43	2- <i>mn</i>	1.36	0.68	0.69	5.44	1.36	5.44	87.12	174.24	34.30	734.63
36	11	1.83	2- <i>mn</i>	1.35	1.35	1.35	1.35	1.35	1.35	43.26	86.52	17.98	739.63
37	12	2.23	2- <i>mn</i>	0.66	0.66	0.66	0.66	1.33	1.33	21.23	21.23	5.17	753.66
38	10	3.05	decyl	0.69	0.69	1.38	0.69	1.38	1.38	2.76	2.76	2.34	725.76
39	10	3.35	4- <i>tbb</i>	1.37	1.37	2.74	5.47	1.37	5.47	21.90	43.80	13.41	730.66
40	11	3.74	4- <i>tbb</i>	0.67	0.67	0.67	2.68	1.34	2.68	21.48	21.48	11.28	744.69
41	12	4.14	4- <i>tbb</i>	nd ^[d]	nd	nd	nd	nd	nd	nd	nd	nd	758.72
42	10	2.1	2- <i>mn</i>	1.39	1.39	2.78	2.78	1.39	2.78	89.06	89.06	52.33	718.57
43	11	2.49	2- <i>mn</i>	0.68	0.68	2.73	2.73	2.73	5.46	21.84	43.68	28.25	732.61
44	12	2.89	2- <i>mn</i>	1.34	1.34	1.34	1.34	1.34	1.34	10.71	21.43	11.38	746.62
45	10	3.71	decyl	0.70	0.70	0.70	0.70	0.70	1.39	2.78	2.78	2.50	718.74

[a] Organisms used in this study: *S.a.* (*Staphylococcus aureus* ATCC 29213), MRSA (Methicillin-Resistant *Staphylococcus aureus*, *mecA*), *E.f.* (*Enterococcus faecalis* ATCC 29212), VRE (Vancomycin-Resistant *Enterococcus faecalis*, *van A*), *E.c.* (*Escherichia coli* ATCC 25922), ESBLE (Extended-Spectrum β -Lactamase producing *Escherichia coli*), *P.a.* (*Pseudomonas aeruginosa* ATCC 27853), PAR (*Pseudomonas aeruginosa* Resistant, efflux pump). [b] Reference compound used: Chx (Chlorhexidine). [c] 4-*tbb* = 4-*tert*-Butylbenzyl; 2-*mn* = 2-Methylnaphthalenyl. [d] Not determined (insoluble compound). [e] IC₅₀ ($\mu\text{g/mL}$) was determined on MRC-5 cells according to the literature. [f] molecular weight (g/mol)

2.5. Hemolysis assay

We examined the cytotoxic effects of compound **42** on human red blood cells (RBCs) from different blood group types (ABO, and Rh) and the results of the assay for 1 h are presented in the following Figure. The overall results show that the tested molecule has not a harmful effect on RBCs at IC₅₀ relevant concentration. The molecule exhibited no hemolytic activity on RBCs after 1 h of incubation at 37°C, regardless of the blood group tested.

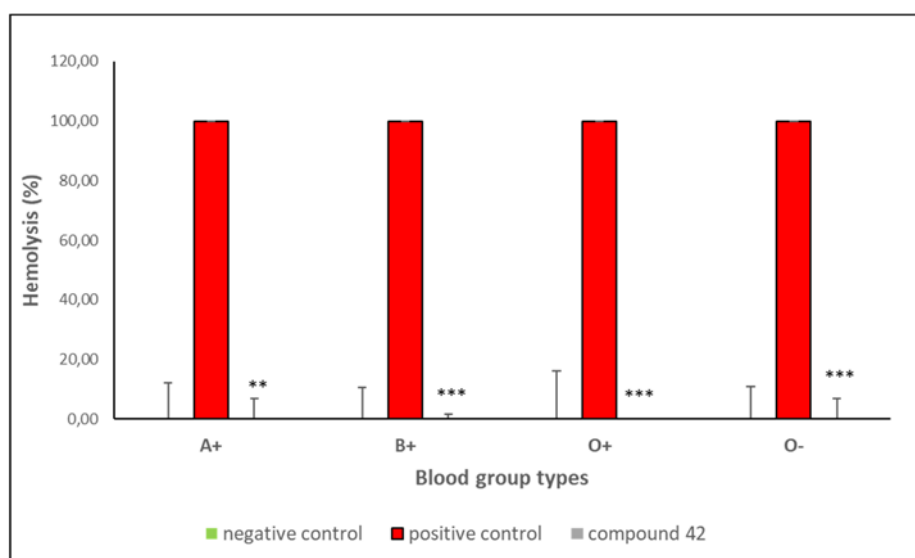


Figure. Hemolysis assay of compound **42** using human red blood cells (RBCs) at 1 h post exposure. Compound **42** and RBCs samples were prepared in PBS. IC₅₀ relevant concentration of compound **42** at 40 µg/ mL was tested in the hemolysis assay in order to estimate their potential effects on the integrity of red blood cells from A, B, O blood types, including Rh-positive and Rh-negative samples. Sixteen independent RBCs samples were prepared and consequently analyzed. Shown is mean (n = 4) ± standard deviation (SD, bars). Triton X-100 was used as a positive control. PBS was used as the negative control. *P* values are indicated above each bar (significance of *P* levels vs control: *P* < 0,05 *, *P* < 0,01 **, *P* < 0,001 ***).

Materials and methods

The hemolytic activity of compound **42** was determined in peripheral human blood, from consenting adult healthy donors from three different blood types: A, B and O, including Rh-positive and Rh-negative individuals within the O blood type. Briefly, EDTA-anticoagulated blood was washed three times with PBS. Following dilution in PBS, 10⁷ RBCs were treated with compound **42** (40 µg/ mL) molecule, and incubated at 37°C for 1 h. Following centrifugation at 800 g for 5 min, the supernatants were transferred to 96-well plates, and absorbance measured at 405 nm for released hemoglobin. Controls for 0 and 100% hemolysis consisted of cells suspended in PBS only and in 0,1% Triton X-100, respectively. The percentage of hemolysis was calculated as $[(A_{405nm, \text{molecule}} - A_{405nm, \text{PBS}}) / (A_{405nm, \text{0,1\% Triton X-100}} - A_{405nm, \text{PBS}})] / 100$.

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