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Electronic Supporting Information

Lipid Nanoparticle Formulations including Stereochemically Defined Glycomacromolecules for Delivery of saRNA

Jonas Becker, †, a Beatriz Dias-Barbieri, †, b Robin J. Shattock, b* and C. Remzi Becer a*

[a] Department of Chemistry, University of Warwick, Coventry, CV4 7AL, United Kingdom

[b] Department of Infectious Diseases, Imperial College London, London W21PG, United Kingdom

Corresponding authors: Remzi.Becer@warwick.ac.uk and r.shattock@imperial.ac.uk

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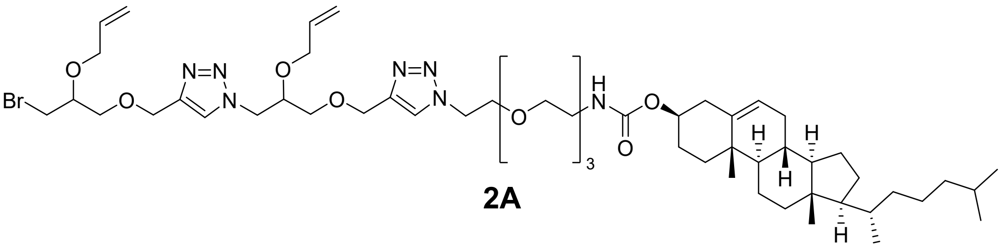
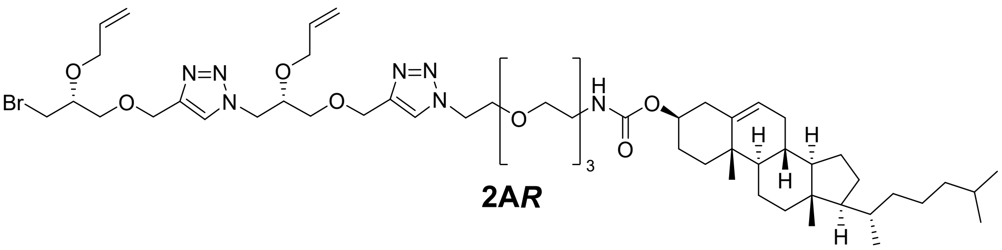
CuAAC of triazole backbone with chol-TEG-azide



2A

Under inert atmosphere, allyl-IEG-dimer **1** (0.021 g, 0.05 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min. Tetrabutylammonium fluoride solution (1 M in THF, 0.053 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.038 g, 0.06 mmol, 1.2 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.15 eq) and PMDETA (1.6 µL, 0.008 mmol, 0.15 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **2A** (0.044 g) was obtained as a viscous oil and used in the next step without further purification.

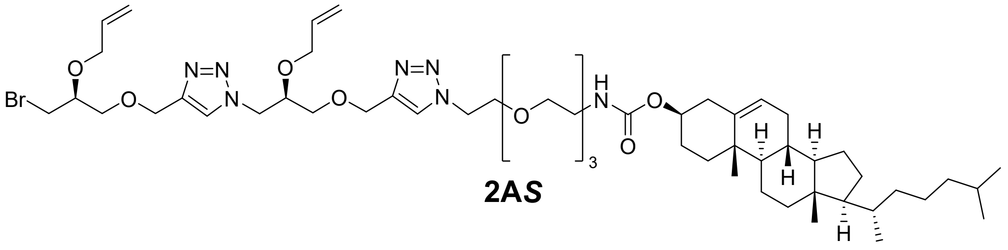
^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.76 (s, 1H, Ar-*H*), 7.65 (s, 1H, Ar-*H*), 6.03-5.83 (m, 1H, C*H*=CH_2), 5.80-5.62 (m, 1H, C*H*=CH_2), 5.34 (bs, 2H, Chol-C=C*H*), 5.26-5.07 (m, 4H, CH=CH_2), 4.71-4.61 (m, 4H, OCH_2-Ar), 4.60-4.52 (m, 4H), 4.51-4.35 (m, 4H), 4.30-4.20 (m, 3H), 4.10 (s, 2H), 4.05-3.96 (m, 3H), 3.93-3.81 (m, 4H), 3.66 (s, 4H), 3.65-3.57 (m, 13H), 3.57-3.47 (m, 7H), 3.41-3.26 (m, 5H), 2.40-2.19 (m, 4H), 2.08-1.90 (m, 5H), 1.90-1.75 (m, 7H), 1.61-1.39 (m, 16H), 1.38-1.28 (m, 8H), 1.24 (s, 6H), 1.17-1.08 (m, 11H), 1.02-0.95 (m, 16H), 0.90 (d, J = 6.4 Hz, 8H), 0.85 (d, J = 6.5 Hz, 14H), 0.66 (6H).



2A*R*

Under inert atmosphere, allyl-IEG-dimer **1*R*** (0.021 g, 0.05 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min. Tetrabutylammonium fluoride solution (1 M in THF, 0.053 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.038 g, 0.06 mmol, 1.2 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.15 eq) and PMDETA (1.6 μL, 0.008 mmol, 0.15 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **2A*R*** (0.042 g) was obtained as a viscous oil and used in the next step without further purification.

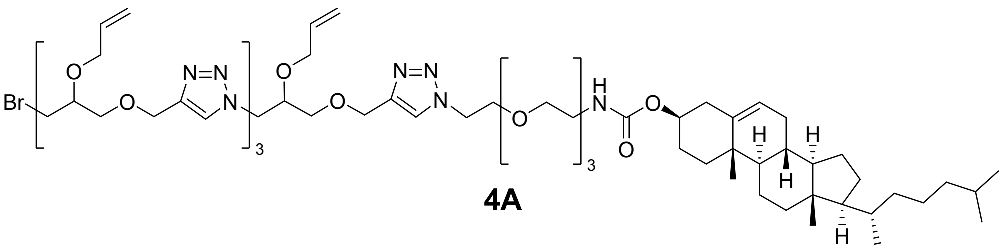
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.76 (s, 1H, Ar-*H*), 7.65 (s, 1H, Ar-*H*), 6.03-5.83 (m, 1H, C*H*=CH_2), 5.80-5.62 (m, 1H, C*H*=CH_2), 5.34 (bs, 2H, Chol-C=C*H*), 5.26-5.07 (m, 4H, CH=C*H*$_2$), 4.71-4.61 (m, 4H, OC*H*$_2$-Ar), 4.60-4.52 (m, 4H), 4.51-4.35 (m, 4H), 4.30-4.20 (m, 3H), 4.10 (s, 2H), 4.05-3.96 (m, 3H), 3.93-3.81 (m, 4H), 3.66 (s, 4H), 3.65-3.57 (m, 13H), 3.57-3.47 (m, 7H), 3.41-3.26 (m, 5H), 2.40-2.19 (m, 4H), 2.08-1.90 (m, 5H), 1.90-1.75 (m, 7H), 1.61-1.39 (m, 16H), 1.38-1.28 (m, 8H), 1.24 (s, 6H), 1.17-1.08 (m, 11H), 1.02-0.95 (m, 16H), 0.90 (d, J = 6.4 Hz, 8H), 0.85 (d, J = 6.5 Hz, 14H), 0.66 (6H).



2A*S*

Under inert atmosphere, allyl-IEG-dimer **1*S*** (0.021 g, 0.05 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min. Tetrabutylammonium fluoride solution (1 M in THF, 0.053 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.038 g, 0.06 mmol, 1.2 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.15 eq) and PMDETA (1.6 μL, 0.008 mmol, 0.15 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **2A*S*** (0.044 g) was obtained as a viscous oil and used in the next step without further purification.

^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.76 (s, 1H, Ar-*H*), 7.65 (s, 1H, Ar-*H*), 6.03-5.83 (m, 1H, C*H*=CH_2), 5.80-5.62 (m, 1H, C*H*=CH_2), 5.34 (bs, 2H, Chol-C=C*H*), 5.26-5.07 (m, 4H, CH=C*H*$_2$), 4.71-4.61 (m, 4H, OC*H*$_2$-Ar), 4.60-4.52 (m, 4H), 4.51-4.35 (m, 4H), 4.30-4.20 (m, 3H), 4.10 (s, 2H), 4.05-3.96 (m, 3H), 3.93-3.81 (m, 4H), 3.66 (s, 4H), 3.65-3.57 (m, 13H), 3.57-3.47 (m, 7H), 3.41-3.26 (m, 5H), 2.40-2.19 (m, 4H), 2.08-1.90 (m, 5H), 1.90-1.75 (m, 7H), 1.61-1.39 (m, 16H), 1.38-1.28 (m, 8H), 1.24 (s, 6H), 1.17-1.08 (m, 11H), 1.02-0.95 (m, 16H), 0.90 (d, J = 6.4 Hz, 8H), 0.85 (d, J = 6.5 Hz, 14H), 0.66 (6H).

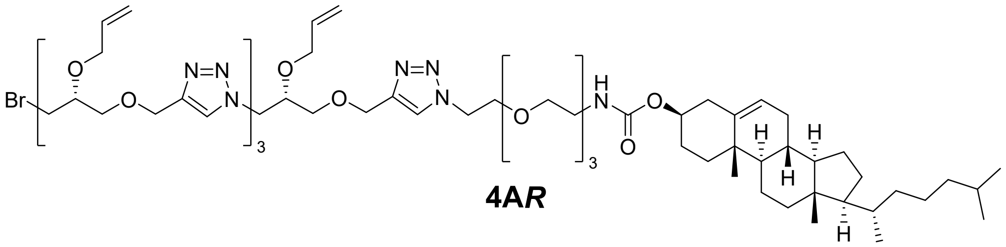


4A

Under inert atmosphere, allyl-IEG-tetramer **1** (0.049 g, 0.05 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min. Tetrabutylammonium fluoride solution (1 M in THF, 0.053 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.038 g, 0.05 mmol, 1.2 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.15 eq) and PMDETA (1.6 µL, 0.008 mmol, 0.15 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **4A** (0.069 g) was obtained as a viscous oil and used in the next step without further purification.

^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.77 (s, 1H, Ar-*H*), 7.70-7.62 (m, 3H, Ar-*H*), 6.03-5.83 (m, 1H, C*H*=CH_2), 5.79-5.66 (m, 3H, C*H*=CH_2), 5.38-5.32 (m, 2H, Chol-C=C*H*), 5.23-5.08 (m, 8H, CH=C*H*$_2$), 4.71-4.63 (m, 8H, OC*H*$_2$-Ar), 4.62-4.58 (m, 2H), 4.58-4.53 (m, 4H), 4.51-4.35 (m, 4H), 4.29-4.17 (m, 1H), 4.13-4.08 (m, 2H), 4.07-3.97 (m, 4H), 3.94-3.83 (m, 9H), 3.73-3.67 (m, 1H), 3.67-3.57 (m, 14H), 3.57-3.47 (m, 9H), 3.39-3.27 (m, 3H), 2.38-

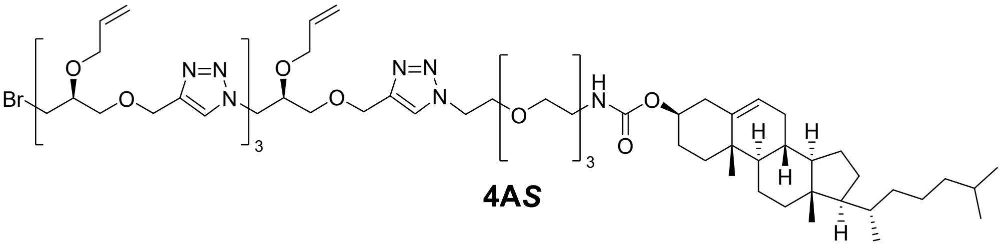
2.19 (m, 4H), 2.06-1.90 (m, 5H), 1.90-1.70 (m, 11H), 1.61-1.40 (m, 11H), 1.39-1.30 (m, 5H), 1.25 (s, 4H), 1.17-1.06 (m, 10H), 1.03-0.96 (m, 12H), 0.90 (d, J = 6.5 Hz, 5H), 0.86 (dd, J = 6.6 Hz, 1.7 Hz, 10H), 0.67 (4H).



4A*R*

Under inert atmosphere, allyl-IEG-tetramer **1** (0.049 g, 0.05 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min. Tetrabutylammonium fluoride solution (1 M in THF, 0.053 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.038 g, 0.05 mmol, 1.2 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.15 eq) and PMDETA (1.6 µL, 0.008 mmol, 0.15 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **4A*R*** (0.074 g) was obtained as a viscous oil and used in the next step without further purification.

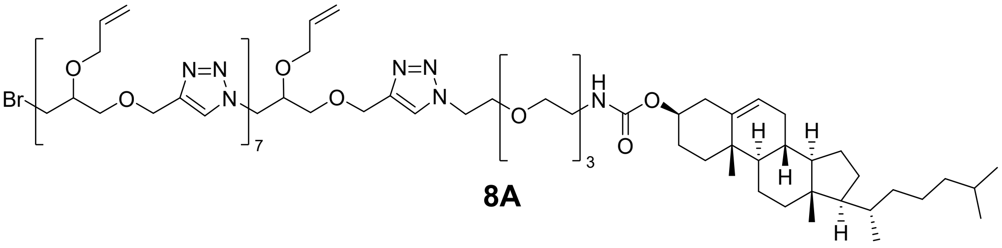
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.77 (s, 1H, Ar-*H*), 7.70-7.62 (m, 3H, Ar-*H*), 6.03-5.83 (m, 1H, C*H*=CH$_2$), 5.79-5.66 (m, 3H, C*H*=CH$_2$), 5.38-5.32 (m, 2H, Chol-C=C*H*), 5.23-5.08 (m, 8H, CH=C*H*$_2$), 4.71-4.63 (m, 8H, OC*H*$_2$-Ar), 4.62-4.58 (m, 2H), 4.58-4.53 (m, 4H), 4.51-4.35 (m, 4H), 4.29-4.17 (m, 1H), 4.13-4.08 (m, 2H), 4.07-3.97 (m, 4H), 3.94-3.83 (m, 9H), 3.73-3.67 (m, 1H), 3.67-3.57 (m, 14H), 3.57-3.47 (m, 9H), 3.39-3.27 (m, 3H), 2.38-2.19 (m, 4H), 2.06-1.90 (m, 5H), 1.90-1.70 (m, 11H), 1.61-1.40 (m, 11H), 1.39-1.30 (m, 5H), 1.25 (s, 4H), 1.17-1.06 (m, 10H), 1.03-0.96 (m, 12H), 0.90 (d, J = 6.5 Hz, 5H), 0.86 (dd, J = 6.6 Hz, 1.7 Hz, 10H), 0.67 (4H).



4A*S*

Under inert atmosphere, allyl-IEG-tetramer **1** (0.039 g, 0.04 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min. Tetrabutylammonium fluoride solution (1 M in THF, 0.042 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.028 g, 0.044 mmol, 1.1 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.2 eq) and PMDETA (1.6 µL, 0.008 mmol, 0.2 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **4A*S*** (0.058 g) was obtained as a viscous oil and used in the next step without further purification.

^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.77 (s, 1H, Ar-*H*), 7.70-7.62 (m, 3H, Ar-*H*), 6.03-5.83 (m, 1H, C*H*=CH_2), 5.79-5.66 (m, 3H, C*H*=CH_2), 5.38-5.32 (m, 2H, Chol-C=C*H*), 5.23-5.08 (m, 8H, CH=CH_2), 4.71-4.63 (m, 8H, OCH_2-Ar), 4.62-4.58 (m, 2H), 4.58-4.53 (m, 4H), 4.51-4.35 (m, 4H), 4.29-4.17 (m, 1H), 4.13-4.08 (m, 2H), 4.07-3.97 (m, 4H), 3.94-3.83 (m, 9H), 3.73-3.67 (m, 1H), 3.67-3.57 (m, 14H), 3.57-3.47 (m, 9H), 3.39-3.27 (m, 3H), 2.38-2.19 (m, 4H), 2.06-1.90 (m, 5H), 1.90-1.70 (m, 11H), 1.61-1.40 (m, 11H), 1.39-1.30 (m, 5H), 1.25 (s, 4H), 1.17-1.06 (m, 10H), 1.03-0.96 (m, 12H), 0.90 (d, J = 6.5 Hz, 5H), 0.86 (dd, J = 6.6 Hz, 1.7 Hz, 10H), 0.67 (4H).

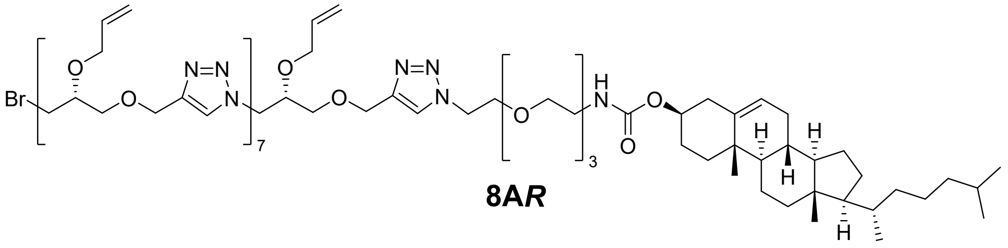


8A

Under inert atmosphere, allyl-IEG-octamer **1** (0.058 g, 0.033 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min.

Tetrabutylammonium fluoride solution (1 M in THF, 0.035 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.023 g, 0.036 mmol, 1.1 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.25 eq) and PMDETA (1.6 µL, 0.008 mmol, 0.25 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **8A** (0.074 g) was obtained as a viscous oil and used in the next step without further purification.

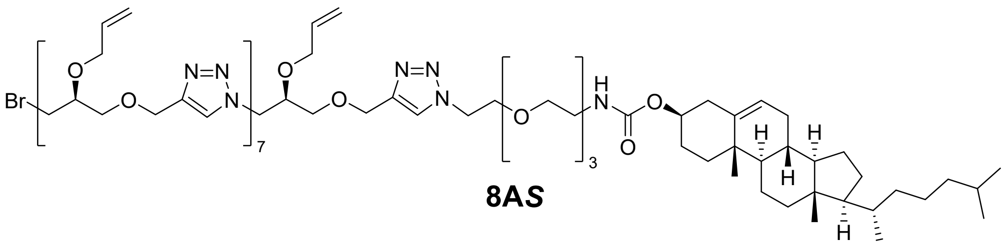
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.75 (s, 1H, Ar-*H*), 7.66 (s, 6H, Ar-*H*), 7.63 (s, 1H, Ar-*H*), 5.93-5.81 (m, 1H, C*H*=CH_2), 5.76-5.61 (m, 7H, C*H*=CH_2), 5.37-5.29 (m, 2H, Chol-C=C*H*), 5.25-5.03 (m, 16H, CH=CH_2), 4.69-4.60 (m, 15H, OCH_2-Ar), 4.60-4.56 (m, 4H), 4.56-4.51 (m, 6H), 4.48-4.33 (m, 8H), 4.10-4.05 (m, 2H), 4.05-3.95 (m, 8H), 3.91-3.80 (m, 16H), 3.70-3.67 (m, 1H), 3.70-3.55 (m, 15H), 3.55-3.45 (m, 17H), 3.36-3.26 (m, 3H), 2.38-2.16 (m, 4H), 2.01-1.88 (m, 4H), 1.87-1.73 (m, 4H), 1.59-1.38 (m, 11H), 1.34-1.27 (m, 4H), 1.22 (s, 7H), 1.15-1.00 (m, 15H), 1.00-0.93 (m, 10H), 0.88 (d, J = 6.5 Hz, 5H), 0.83 (dd, J = 6.6 Hz, 1.7 Hz, 10H), 0.64 (4H).



8A*R*

Under inert atmosphere, allyl-IEG-octamer **1** (0.049 g, 0.028 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min. Tetrabutylammonium fluoride solution (1 M in THF, 0.029 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.019 g, 0.031 mmol, 1.1 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.29 eq) and PMDETA (1.6 µL, 0.008 mmol, 0.29 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **8A*R*** (0.052 g) was obtained as a viscous oil and used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.75 (s, 1H, Ar-*H*), 7.66 (s, 6H, Ar-*H*), 7.63 (s, 1H, Ar-*H*), 5.93-5.81 (m, 1H, C*H*=CH_2), 5.76-5.61 (m, 7H, C*H*=CH_2), 5.37-5.29 (m, 2H, Chol-C=C*H*), 5.25-5.03 (m, 16H, CH=C*H*$_2$), 4.69-4.60 (m, 15H, OC*H*$_2$-Ar), 4.60-4.56 (m, 4H), 4.56-4.51 (m, 6H), 4.48-4.33 (m, 8H), 4.10-4.05 (m, 2H), 4.05-3.95 (m, 8H), 3.91-3.80 (m, 16H), 3.70-3.67 (m, 1H), 3.70-3.55 (m, 15H), 3.55-3.45 (m, 17H), 3.36-3.26 (m, 3H), 2.38-2.16 (m, 4H), 2.01-1.88 (m, 4H), 1.87-1.73 (m, 4H), 1.59-1.38 (m, 11H), 1.34-1.27 (m, 4H), 1.22 (s, 7H), 1.15-1.00 (m, 15H), 1.00-0.93 (m, 10H), 0.88 (d, J = 6.5 Hz, 5H), 0.83 (dd, J = 6.6 Hz, 1.7 Hz, 10H), 0.64 (4H).



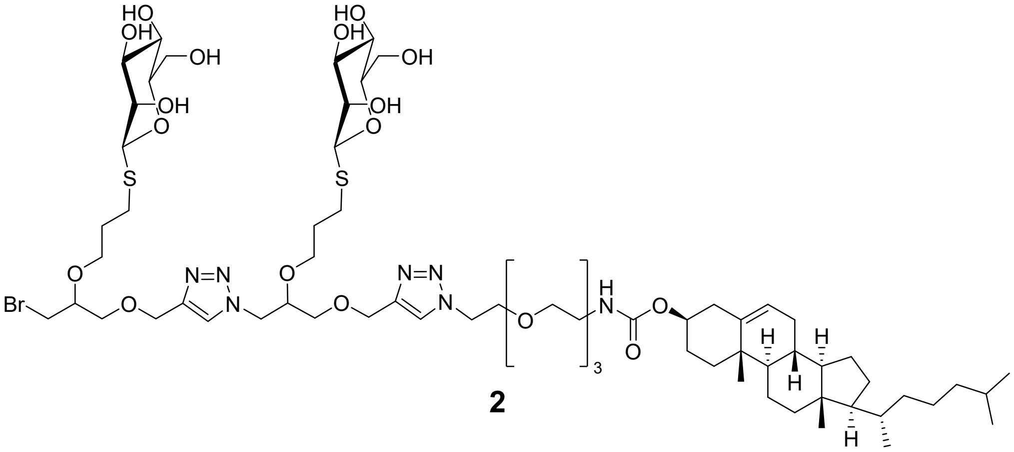
8A*S*

Under inert atmosphere, allyl-IEG-octamer **1** (0.053 g, 0.03 mmol, 1 eq) was dissolved in dry THF (0.25 mL) and the solution was degassed with an N_2 stream for 2 min. Tetrabutylammonium fluoride solution (1 M in THF, 0.032 mL, 1.1 eq) was added and the mixture was stirred for 2 h at r.t. In a separate vial, cholesteryl-TEG-azide (0.021 g, 0.033 mmol, 1.1 eq) was dissolved in dry THF (0.25 mL), degassed, and added to the reaction mixture. Copper(I) bromide (0.001 g, 0.008 mmol 0.27 eq) and PMDETA (1.6 µL, 0.008 mmol, 0.27 eq) were added and the mixture was heated to 45 °C for 18 h. After completion, the solvent was removed under reduced pressure and dissolved in DCM (10 mL). The organic layer was washed with H_2O (3x10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **8A*S*** (0.048 g) was obtained as a viscous oil and used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.75 (s, 1H, Ar-*H*), 7.66 (s, 6H, Ar-*H*), 7.63 (s, 1H, Ar-*H*), 5.93-5.81 (m, 1H, C*H*=CH_2), 5.76-5.61 (m, 7H, C*H*=CH_2), 5.37-5.29 (m, 2H, Chol-C=C*H*), 5.25-5.03 (m, 16H, CH=C*H*$_2$), 4.69-4.60 (m, 15H, OC*H*$_2$-Ar), 4.60-4.56 (m, 4H), 4.56-4.51 (m, 6H), 4.48-4.33 (m, 8H), 4.10-4.05 (m, 2H), 4.05-3.95 (m, 8H), 3.91-3.80 (m, 16H), 3.70-3.67 (m, 1H), 3.70-3.55 (m, 15H), 3.55-3.45 (m, 17H), 3.36-3.26 (m, 3H), 2.38-

2.16 (m, 4H), 2.01-1.88 (m, 4H), 1.87-1.73 (m, 4H), 1.59-1.38 (m, 11H), 1.34-1.27 (m, 4H), 1.22 (s, 7H), 1.15-1.00 (m, 15H), 1.00-0.93 (m, 10H), 0.88 (d, J = 6.5 Hz, 5H), 0.83 (dd, J = 6.6 Hz, 1.7 Hz, 10H), 0.64 (4H).

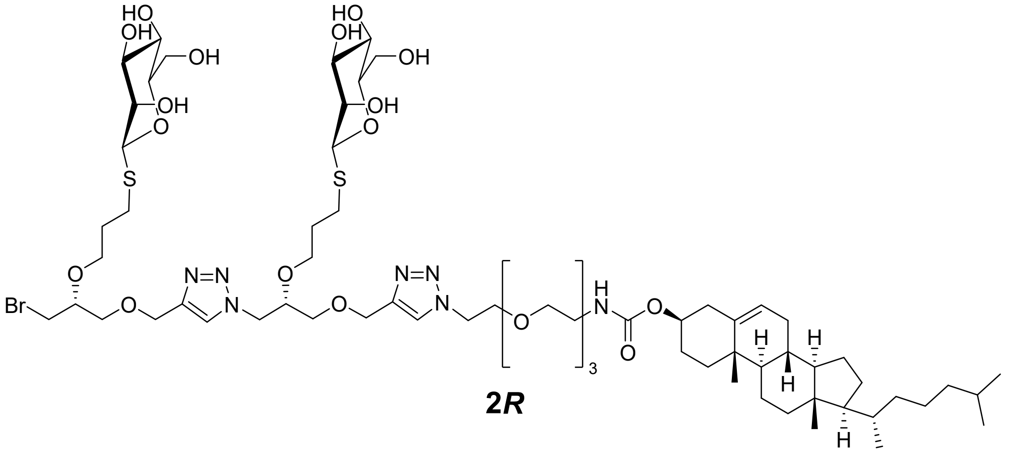
Thiol-ene reaction with Ac_4ManSH



2

Under inert atmosphere, **2A** (0.016 g, 0.015 mmol, 1 eq) was dissolved in dry acetonitrile (0.4 mL) and Ac_4ManSH (0.066 g, 0.180 mmol, 12 eq) and AIBN (0.001 g, 0.008 mmol, 0.5 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 20 µL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H_2O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 100-500 Da) and dialysed against H_2O for 48 h. Lyophilisation afforded the product **2** (0.010 g, 46%) as a white solid.

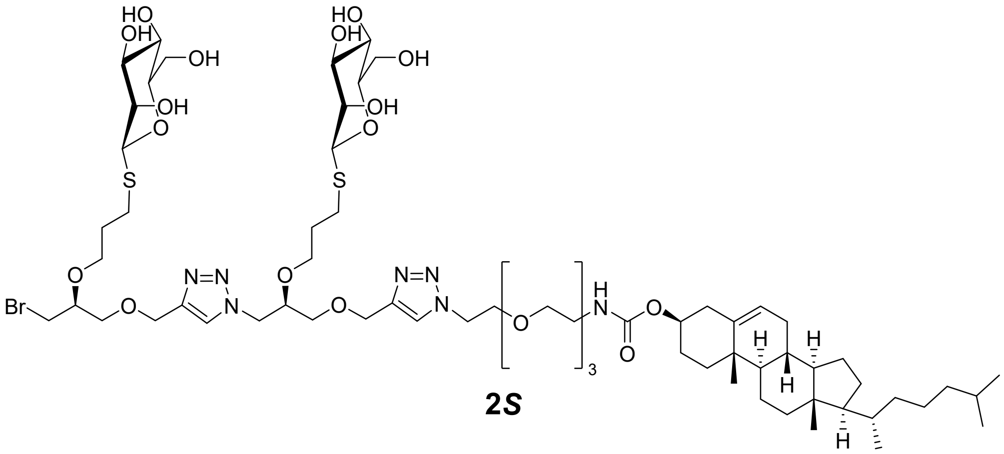
^1H NMR (400 MHz, DMSO-*d*6): δ(ppm) 8.09 (s, 1H, Ar-*H*), 8.05 (s, 1H, Ar-*H*), 7.06 (t, J = 5.7 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 4.80-4.70 (m, 4H, Man-C*H*), 4.69-4.63 (m, 2H, Man-C*H*), 4.60 (s, 1H,), 4.56 (s, 3H, OCH_2-Ar), 4.54-4.47 (m, 6H, OCH_2), 4.46-4.41 (m, 2H), 4.41-4.33 (m, 2H), 4.33-4.24 (m, 2H), 3.85-3.78 (m, 3H), 3.70-3.60 (m, 5H), 3.54-3.44 (m, 14H, TEG-CH_2), 3.29 (bs, 4H), 3.13-3.00 (m, 5H), 2.69-2.61 (m, 2H), 2.54 (s, 5H), 2.35-2.13 (m, 4H), 1.99-1.86 (m, 3H), 1.86-1.70 (m, 5H), 1.68-1.58 (m, 3H), 1.57-1.42 (m, 8H), 1.42-1.28 (m, 7H), 1.23 (s, 5H), 1.15-0.98 (m, 10H), 0.95 (s, 5H), 0.89 (d, J = 6.4 Hz, 4H), 0.84 (d, J = 6.6 Hz, 8H), 0.64 (s, 3H).



2*R*

Under inert atmosphere, **2A*R*** (0.042 g, 0.041 mmol, 1 eq) was dissolved in dry acetonitrile (0.4 mL) and Ac_4ManSH (0.179 g, 0.492 mmol, 12 eq) and AIBN (0.003 g, 0.021 mmol, 0.5 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 30 μL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H_2O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 100-500 Da) and dialysed against H_2O for 48 h. Lyophilisation afforded the product **2*R*** (0.018 g, 30%) as a white solid.

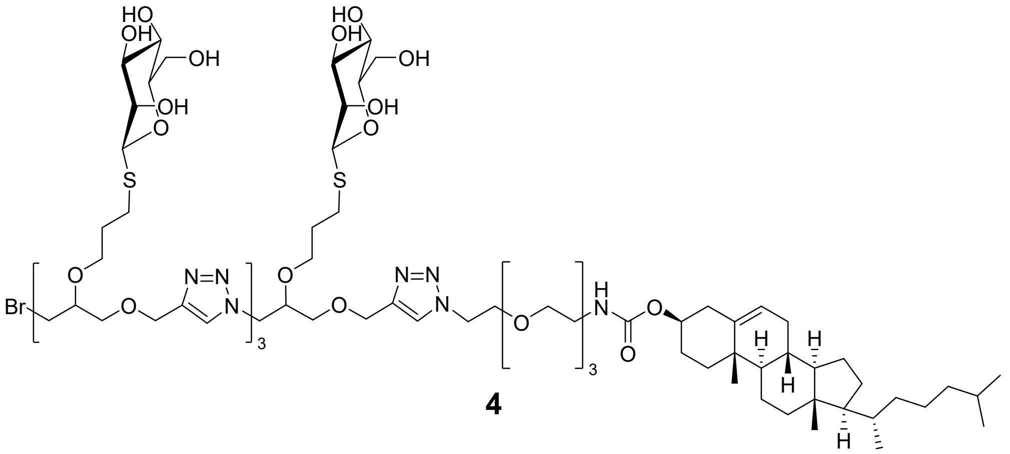
^{1}H NMR (400 MHz, DMSO-*d*6): δ(ppm) 8.09 (s, 1H, Ar-*H*), 8.05 (s, 1H, Ar-*H*), 7.06 (t, J = 5.7 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 4.80-4.70 (m, 4H, Man-C*H*), 4.69-4.63 (m, 2H, Man-C*H*), 4.60 (s, 1H,), 4.56 (s, 3H, OC*H*$_2$-Ar), 4.54-4.47 (m, 6H, OC*H*$_2$), 4.46-4.41 (m, 2H), 4.41-4.33 (m, 2H), 4.33-4.24 (m, 2H), 3.85-3.78 (m, 3H), 3.70-3.60 (m, 5H), 3.54-3.44 (m, 14H, TEG-C*H*$_2$), 3.29 (bs, 4H), 3.13-3.00 (m, 5H), 2.69-2.61 (m, 2H), 2.54 (s, 5H), 2.35-2.13 (m, 4H), 1.99-1.86 (m, 3H), 1.86-1.70 (m, 5H), 1.68-1.58 (m, 3H), 1.57-1.42 (m, 8H), 1.42-1.28 (m, 7H), 1.23 (s, 5H), 1.15-0.98 (m, 10H), 0.95 (s, 5H), 0.89 (d, J = 6.4 Hz, 4H), 0.84 (d, J = 6.6 Hz, 8H), 0.64 (s, 3H).



2*S*

Under inert atmosphere, **2A*S*** (0.044 g, 0.042 mmol, 1 eq) was dissolved in dry acetonitrile (0.4 mL) and Ac_4ManSH (0.184 g, 0.504 mmol, 12 eq) and AIBN (0.003 g, 0.021 mmol, 0.5 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 30 μL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H_2O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 100-500 Da) and dialysed against H_2O for 48 h. Lyophilisation afforded the product **2*S*** (0.021 g, 34%) as a white solid.

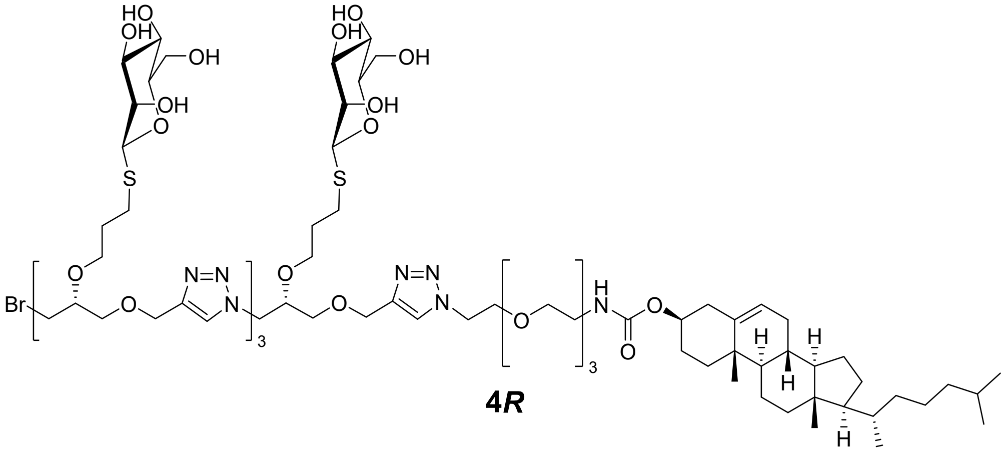
^{1}H NMR (400 MHz, DMSO-*d*6): δ(ppm) 8.09 (s, 1H, Ar-*H*), 8.05 (s, 1H, Ar-*H*), 7.06 (t, J = 5.7 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 4.80-4.70 (m, 4H, Man-C*H*), 4.69-4.63 (m, 2H, Man-C*H*), 4.60 (s, 1H,), 4.56 (s, 3H, OC*H*$_2$-Ar), 4.54-4.47 (m, 6H, OC*H*$_2$), 4.46-4.41 (m, 2H), 4.41-4.33 (m, 2H), 4.33-4.24 (m, 2H), 3.85-3.78 (m, 3H), 3.70-3.60 (m, 5H), 3.54-3.44 (m, 14H, TEG-C*H*$_2$), 3.29 (bs, 4H), 3.13-3.00 (m, 5H), 2.69-2.61 (m, 2H), 2.54 (s, 5H), 2.35-2.13 (m, 4H), 1.99-1.86 (m, 3H), 1.86-1.70 (m, 5H), 1.68-1.58 (m, 3H), 1.57-1.42 (m, 8H), 1.42-1.28 (m, 7H), 1.23 (s, 5H), 1.15-0.98 (m, 10H), 0.95 (s, 5H), 0.89 (d, J = 6.4 Hz, 4H), 0.84 (d, J = 6.6 Hz, 8H), 0.64 (s, 3H).



4

Under inert atmosphere, **4A** (0.029 g, 0.020 mmol, 1 eq) was dissolved in dry acetonitrile (0.4 mL) and Ac_4ManSH (0.262 g, 0.720 mmol, 36 eq) and AIBN (0.003 g, 0.02 mmol, 1 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 30 µL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H_2O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 1 kDa) and dialysed against H_2O for 48 h. Lyophilisation afforded the product **4** (0.039 g, 87%) as a white solid.

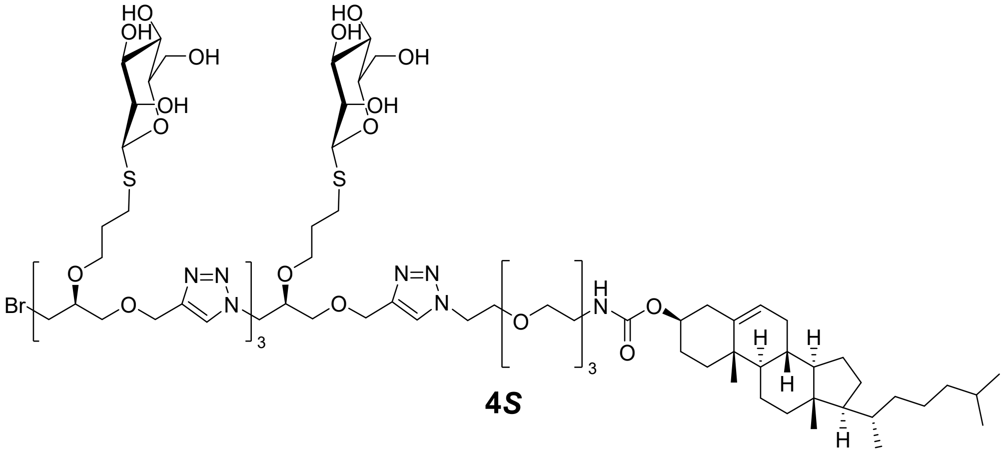
^{1}H NMR (400 MHz, DMSO-*d6*): δ(ppm) 8.09 (s, 1H, Ar-*H*), 8.05 (s, 3H, Ar-*H*), 7.06 (t, J = 5.7 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 4.99-4.82 (m, 3H, Man-C*H*), 4.56 (bs, 9H, OCH_2-Ar), 4.52 (bs, 10H, OCH_2 + Man-C*H*), 4.44-4.34 (m, 4H, OCH_2), 4.33-4.24 (m, 2H), 3.88-3.78 (m, 7H), 3.72-3.60 (m, 13H), 3.30 (bs, 14H), 3.13-3.00 (m, 8H), 2.71-2.58 (m, 2H), 2.54 (s, 5H), 2.34-2.13 (m, 3H), 1.99-1.86 (m, 3H), 1.86-1.70 (m, 5H), 1.68-1.58 (m, 3H), 1.56-1.42 (m, 7H), 1.42-1.28 (m, 6H), 1.25-1.18 (m, 3H), 1.15-0.97 (m, 11H), 0.95 (s, 4H), 0.89 (d, J = 6.3 Hz, 4H), 0.86-0.81 (m, 7H), 0.64 (s, 3H).



4*R*

Under inert atmosphere, **4A*R*** (0.029 g, 0.020 mmol, 1 eq) was dissolved in dry acetonitrile (0.4 mL) and Ac_4ManSH (0.262 g, 0.720 mmol, 36 eq) and AIBN (0.003 g, 0.02 mmol, 1 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 30 µL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H_2O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 1 kDa) and dialysed against H_2O for 48 h. Lyophilisation afforded the product **4*R*** (0.032 g, 72%) as a white solid.

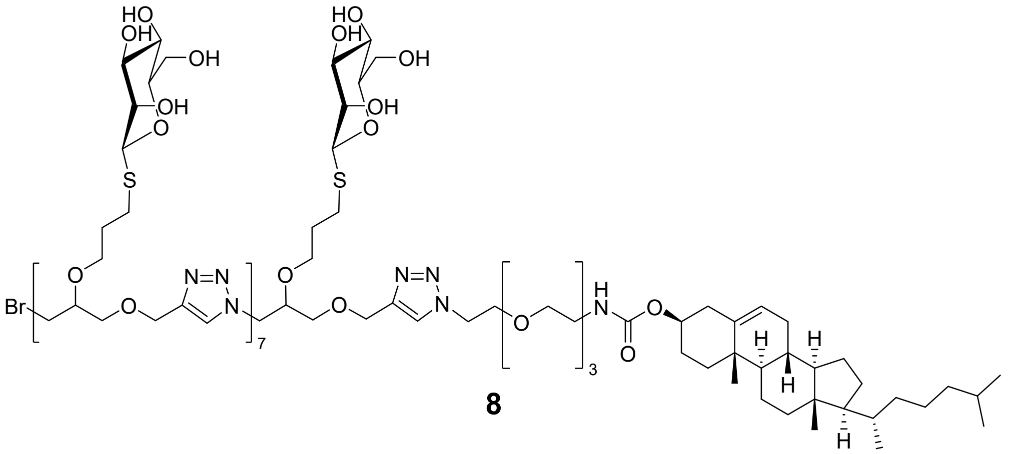
^{1}H NMR (400 MHz, DMSO-*d6*): δ(ppm) 8.09 (s, 1H, Ar-*H*), 8.05 (s, 3H, Ar-*H*), 7.06 (t, J = 5.7 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 4.99-4.82 (m, 3H, Man-C*H*), 4.56 (bs, 9H, OC*H*$_2$-Ar), 4.52 (bs, 10H, OC*H*$_2$ + Man-C*H*), 4.44-4.34 (m, 4H, OC*H*$_2$), 4.33-4.24 (m, 2H), 3.88-3.78 (m, 7H), 3.72-3.60 (m, 13H), 3.30 (bs, 14H), 3.13-3.00 (m, 8H), 2.71-2.58 (m, 2H), 2.54 (s, 5H), 2.34-2.13 (m, 3H), 1.99-1.86 (m, 3H), 1.86-1.70 (m, 5H), 1.68-1.58 (m, 3H), 1.56-1.42 (m, 7H), 1.42-1.28 (m, 6H), 1.25-1.18 (m, 3H), 1.15-0.97 (m, 11H), 0.95 (s, 4H), 0.89 (d, J = 6.3 Hz, 4H), 0.86-0.81 (m, 7H), 0.64 (s, 3H).



4*S*

Under inert atmosphere, **4A*S*** (0.029 g, 0.020 mmol, 1 eq) was dissolved in dry acetonitrile (0.4 mL) and Ac_4ManSH (0.262 g, 0.720 mmol, 36 eq) and AIBN (0.003 g, 0.02 mmol, 1 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 30 µL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H_2O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 1 kDa) and dialysed against H_2O for 48 h. Lyophilisation afforded the product **4*S*** (0.027 g, 60%) as a white solid.

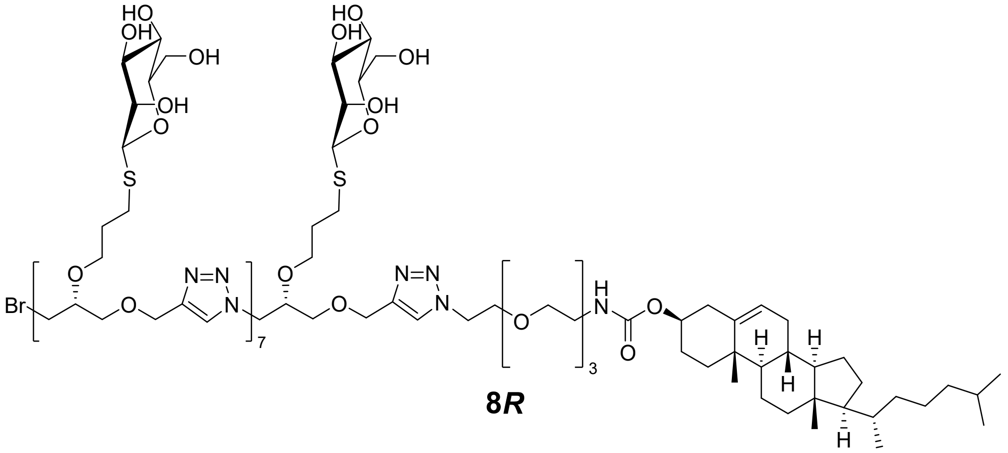
^{1}H NMR (400 MHz, DMSO-*d*6): δ(ppm) 8.09 (s, 1H, Ar-*H*), 8.05 (s, 3H, Ar-*H*), 7.06 (t, J = 5.7 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 4.99-4.82 (m, 3H, Man-C*H*), 4.56 (bs, 9H, OC*H*$_2$-Ar), 4.52 (bs, 10H, OC*H*$_2$ + Man-C*H*), 4.44-4.34 (m, 4H, OC*H*$_2$), 4.33-4.24 (m, 2H), 3.88-3.78 (m, 7H), 3.72-3.60 (m, 13H), 3.30 (bs, 14H), 3.13-3.00 (m, 8H), 2.71-2.58 (m, 2H), 2.54 (s, 5H), 2.34-2.13 (m, 3H), 1.99-1.86 (m, 3H), 1.86-1.70 (m, 5H), 1.68-1.58 (m, 3H), 1.56-1.42 (m, 7H), 1.42-1.28 (m, 6H), 1.25-1.18 (m, 3H), 1.15-0.97 (m, 11H), 0.95 (s, 4H), 0.89 (d, J = 6.3 Hz, 4H), 0.84 (dd, J = 6.5, 1.4 Hz, 7H), 0.64 (s, 3H).



8

Under inert atmosphere, **8A** (0.033 g, 0.015 mmol, 1 eq) was dissolved in dry acetonitrile (1 mL) and Ac_4ManSH (0.525 g, 1.440 mmol, 96 eq) and AIBN (0.005 g, 0.03 mmol, 2 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 40 µL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H_2O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 1 kDa) and dialysed against H_2O for 48 h. Lyophilisation afforded the product **8** (0.032 g, 56%) as a white solid.

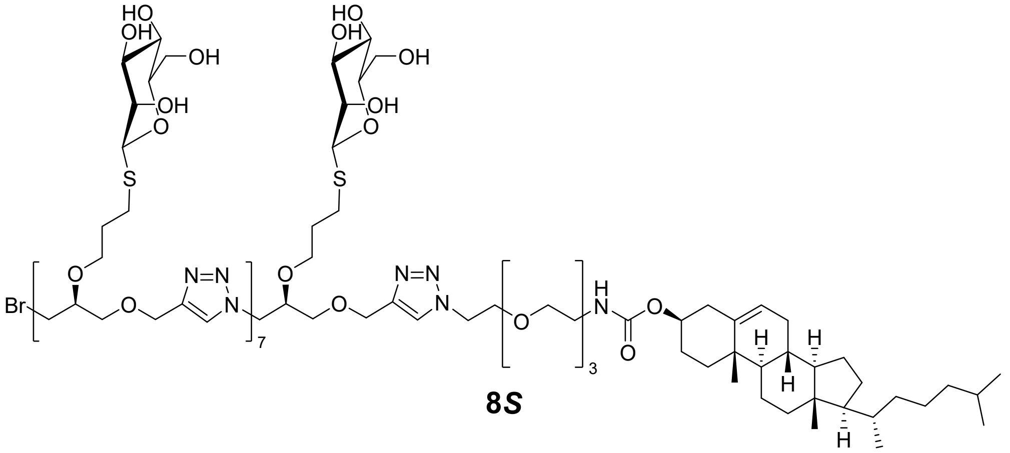
^{1}H NMR (400 MHz, DMSO-*d6*): δ(ppm) 8.08 (s, 1H, Ar-*H*), 8.05 (s, 7H, Ar-*H*), 7.01 (t, J = 5.3 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 5.20-4.76 (m, 19H), 4.68 (bs, 9H), 4.57 (bs, 18H), 4.53 (bs, 13H), 4.51-4.43 (m, 11H), 4.42-4.33 (m, 9H), 4.31-4.21 (m, 3H), 3.88-3.78 (m, 12H), 3.72-3.58 (m, 25H), 3.56-3.47 (m, 36H), 3.31 (bs, 22H), 3.13-3.00 (m, 9H), 2.72-2.58 (m, 2H), 2.48-2.38 (m, 7H), 1.99-1.86 (m, 3H), 1.85-1.71 (m, 5H), 1.62 (bs, 17H), 1.55-1.44 (m, 5H), 1.42-1.14 (m, 18H), 1.14-0.97 (m, 13H), 0.95 (s, 4H), 0.89 (d, J = 6.3 Hz, 4H), 0.83 (dd, J = 6.6, 1.6 Hz, 7H), 0.64 (s, 3H).



8*R*

Under inert atmosphere, **8A*R*** (0.033 g, 0.015 mmol, 1 eq) was dissolved in dry acetonitrile (1 mL) and Ac_4ManSH (0.525 g, 1.440 mmol, 96 eq) and AIBN (0.005 g, 0.03 mmol, 2 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 40 µL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H_2O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 1 kDa) and dialysed against H_2O for 48 h. Lyophilisation afforded the product **8*R*** (0.020 g, 35%) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*6): δ(ppm) 8.08 (s, 1H, Ar-*H*), 8.05 (s, 7H, Ar-*H*), 7.01 (t, J = 5.3 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 5.20-4.76 (m, 19H), 4.68 (bs, 9H), 4.57 (bs, 18H), 4.53 (bs, 13H), 4.51-4.43 (m, 11H), 4.42-4.33 (m, 9H), 4.31-4.21 (m, 3H), 3.88-3.78 (m, 12H), 3.72-3.58 (m, 25H), 3.56-3.47 (m, 36H), 3.31 (bs, 22H), 3.13-3.00 (m, 9H), 2.72-2.58 (m, 2H), 2.48-2.38 (m, 7H), 1.99-1.86 (m, 3H), 1.85-1.71 (m, 5H), 1.62 (bs, 17H), 1.55-1.44 (m, 5H), 1.42-1.14 (m, 18H), 1.14-0.97 (m, 13H), 0.95 (s, 4H), 0.89 (d, J = 6.3 Hz, 4H), 0.83 (dd, J = 6.6, 1.6 Hz, 7H), 0.64 (s, 3H).



8*S*

Under inert atmosphere, **8A*S*** (0.033 g, 0.015 mmol, 1 eq) was dissolved in dry acetonitrile (1 mL) and Ac$_4$ManSH (0.525 g, 1.440 mmol, 96 eq) and AIBN (0.005 g, 0.03 mmol, 2 eq) were added. The suspension was degassed with a stream of nitrogen for 5 min and was heated to 70 °C for 18 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in methanol (0.5 mL). Sodium methoxide solution (25w% in MeOH, 40 µL) was added and the mixture was stirred at r.t. for 2 h. A mixture of H$_2$O/DMSO 1:1 (5 mL) was added, and the solution was transferred into a dialysis bag (MWCO: 1 kDa) and dialysed against H$_2$O for 48 h. Lyophilisation afforded the product **8*S*** (0.025 g, 44%) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*6): δ(ppm) 8.08 (s, 1H, Ar-*H*), 8.05 (s, 7H, Ar-*H*), 7.01 (t, J = 5.3 Hz, 1H, N*H*), 5.32 (bs, 1H, Chol-C=C*H*), 5.20-4.76 (m, 19H), 4.68 (bs, 9H), 4.57 (bs, 18H), 4.53 (bs, 13H), 4.51-4.43 (m, 11H), 4.42-4.33 (m, 9H), 4.31-4.21 (m, 3H), 3.88-3.78 (m, 12H), 3.72-3.58 (m, 25H), 3.56-3.47 (m, 36H), 3.31 (bs, 22H), 3.13-3.00 (m, 9H), 2.72-2.58 (m, 2H), 2.48-2.38 (m, 7H), 1.99-1.86 (m, 3H), 1.85-1.71 (m, 5H), 1.62 (bs, 17H), 1.55-1.44 (m, 5H), 1.42-1.14 (m, 18H), 1.14-0.97 (m, 13H), 0.95 (s, 4H), 0.89 (d, J = 6.3 Hz, 4H), 0.83 (dd, J = 6.6, 1.6 Hz, 7H), 0.64 (s, 3H).

NMR Spectra

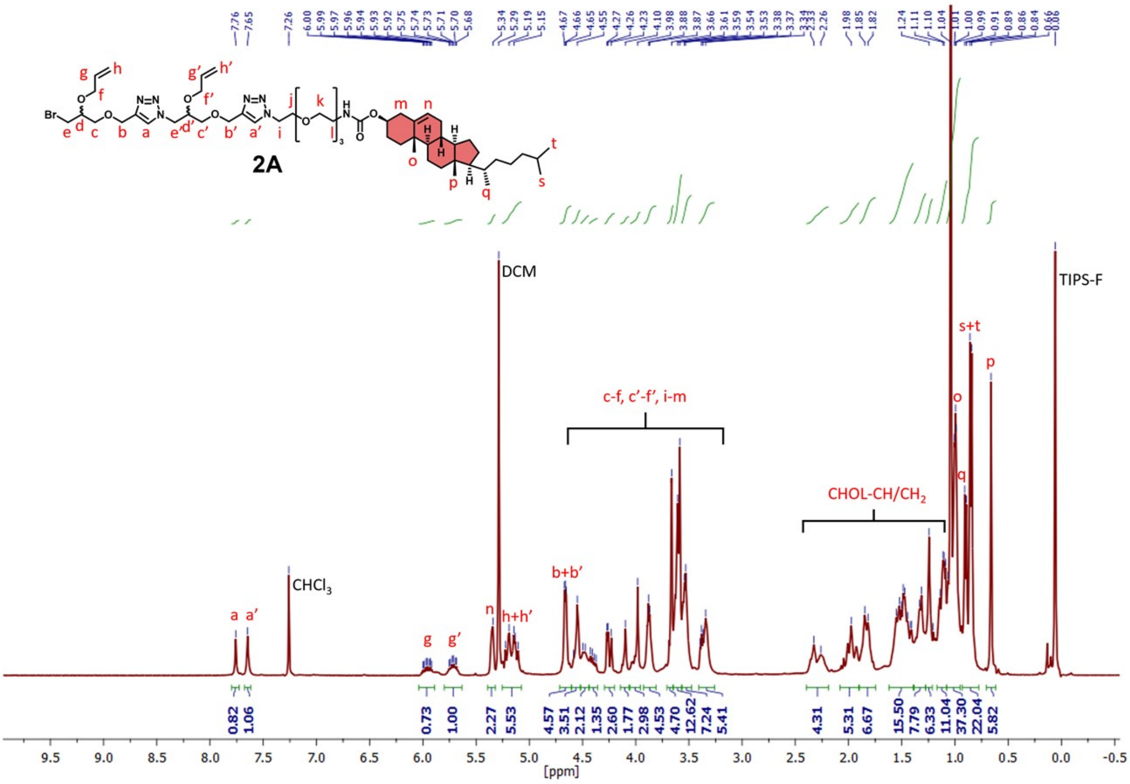


Figure S1. Assigned ^{1}H NMR spectrum (400 MHz, CDCl$_3$) of **2A**.

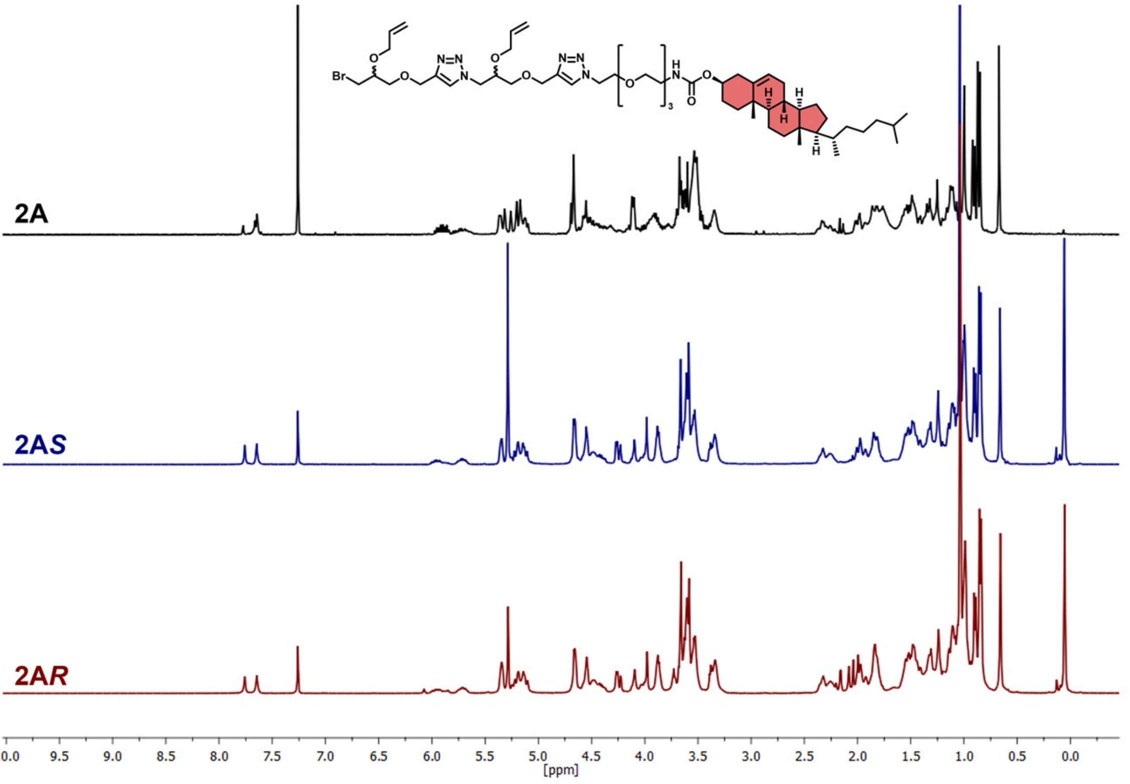


Figure S2. Stacked ^{1}H NMR spectra (400 MHz, CDCl$_3$) of **2A**, **2A*S*** and **2A*R***.

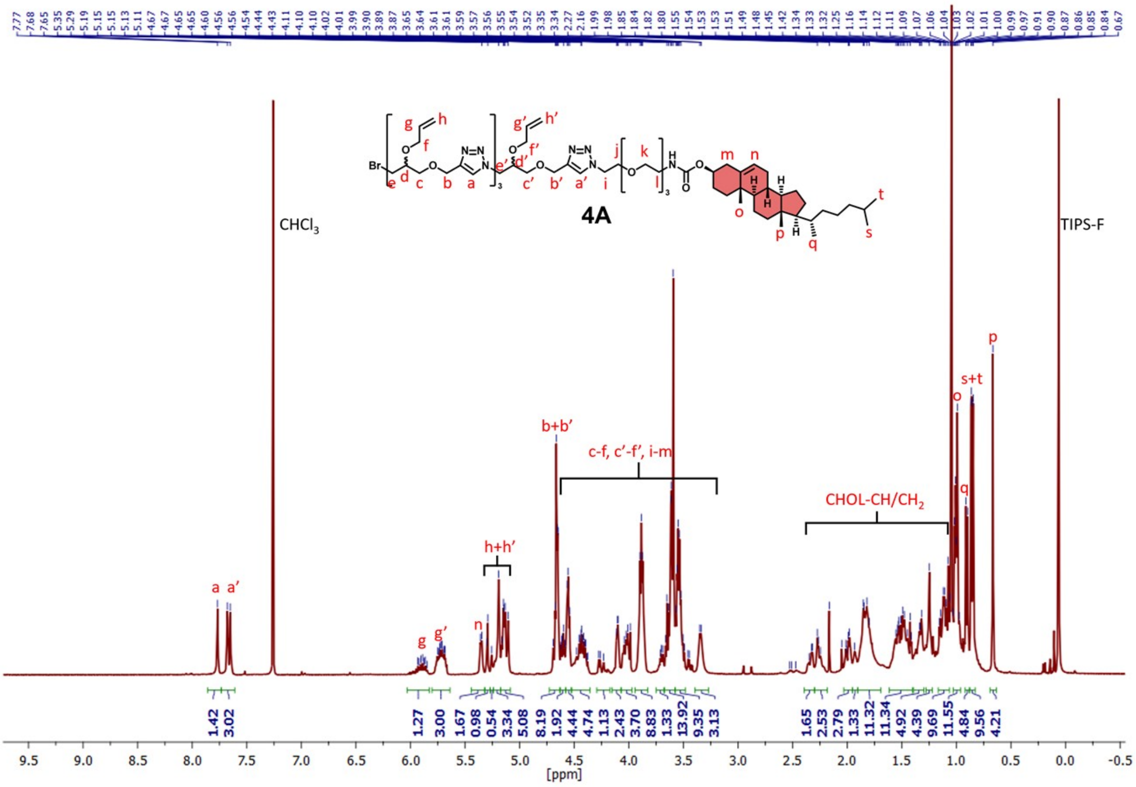


Figure S3. Assigned ^{1}H NMR spectrum (400 MHz, CDCl$_3$) of **4A**.

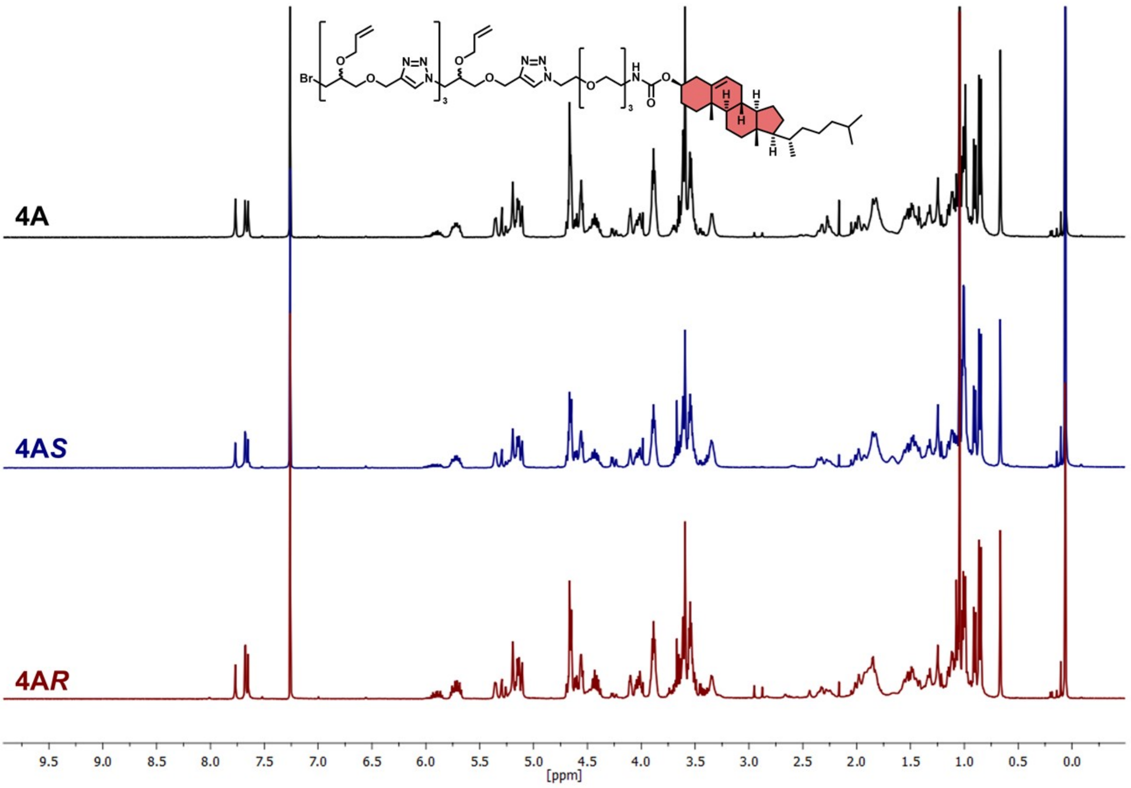


Figure S4. Stacked ^{1}H NMR spectra (400 MHz, CDCl$_3$) of **4A**, **4A*S*** and **4A*R***.

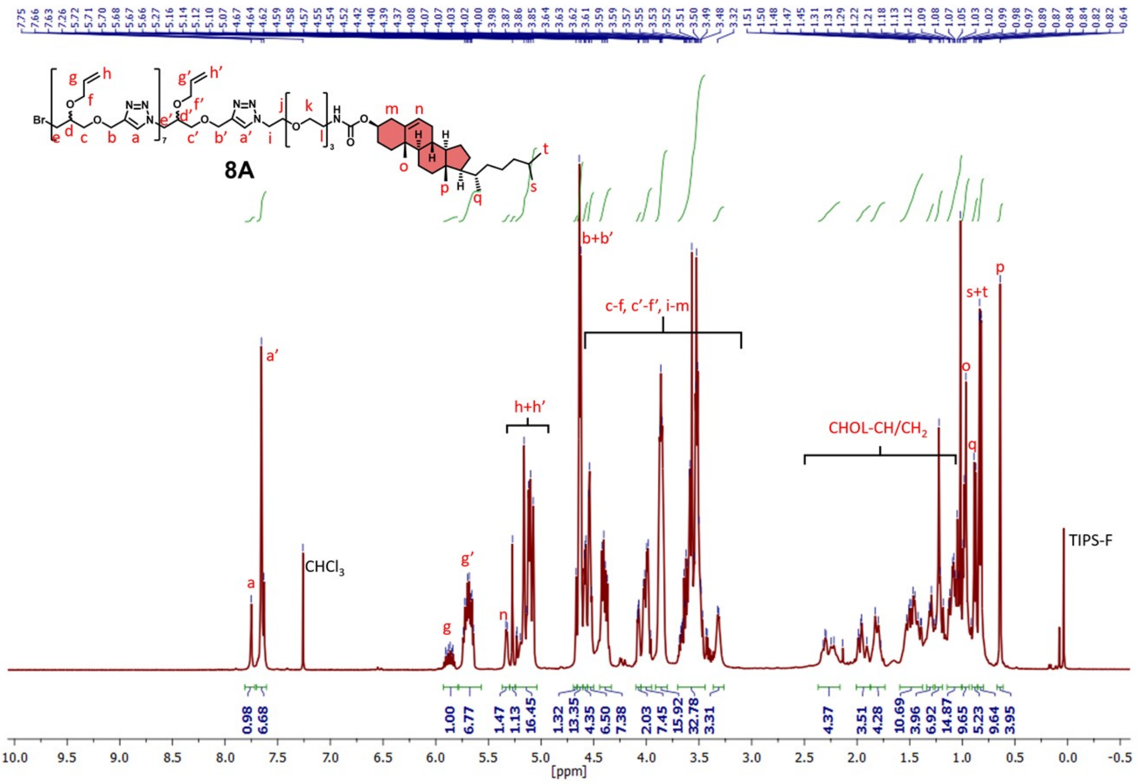


Figure S5. Assigned ^1H NMR spectrum (400 MHz, $CDCl_3$) of **8A**.

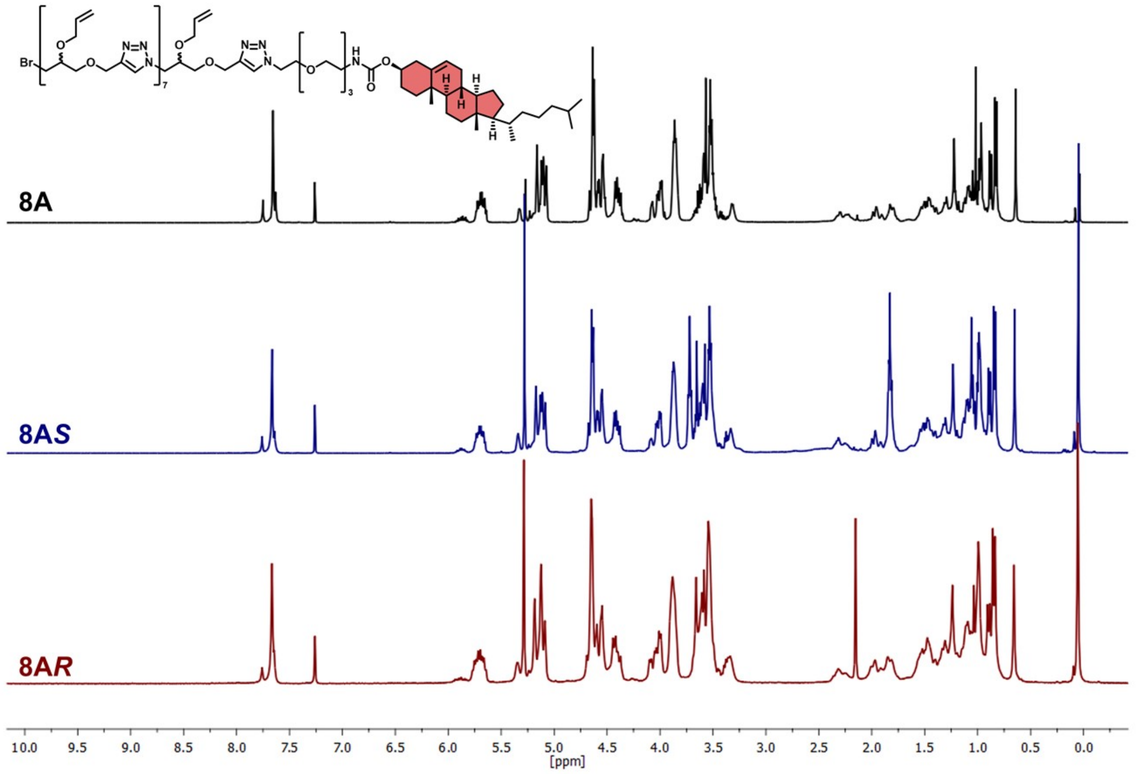


Figure S6. Stacked ^1H NMR spectra (400 MHz, $CDCl_3$) of **8A**, **8A*S*** and **8A*R***.

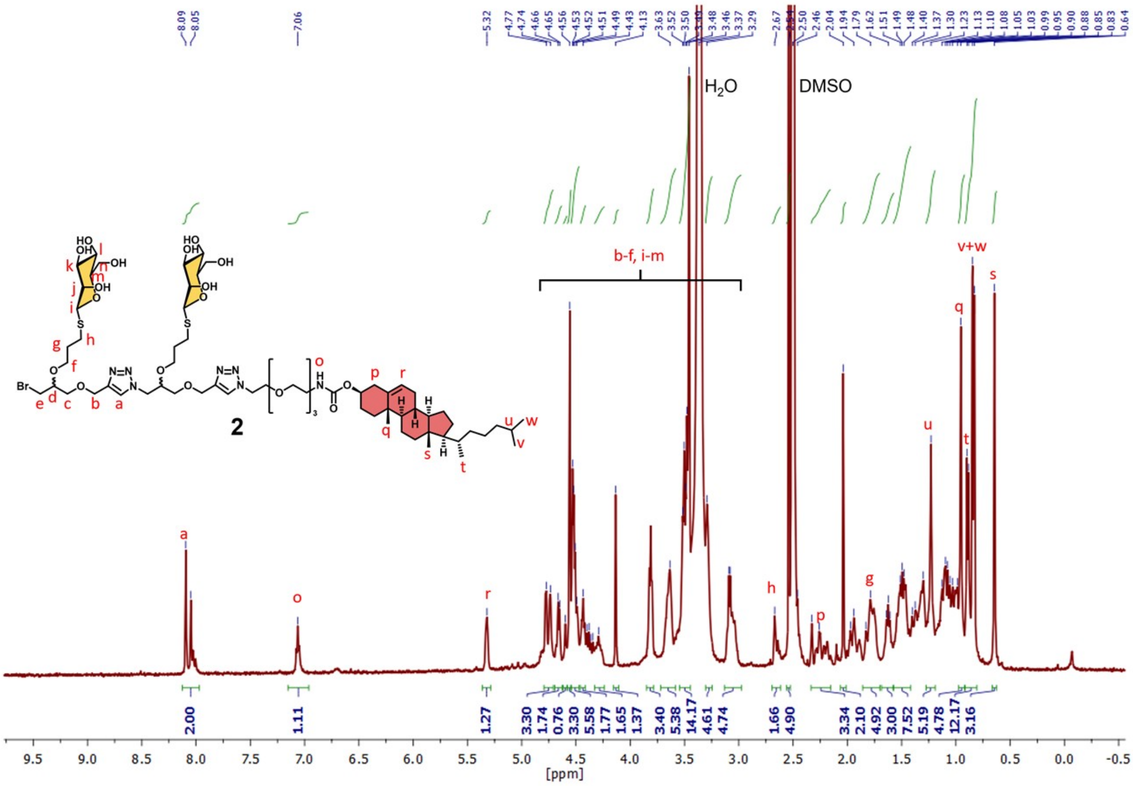


Figure S7. Assigned ^{1}H NMR spectrum (400 MHz, DMSO-*d*6) of **2**.

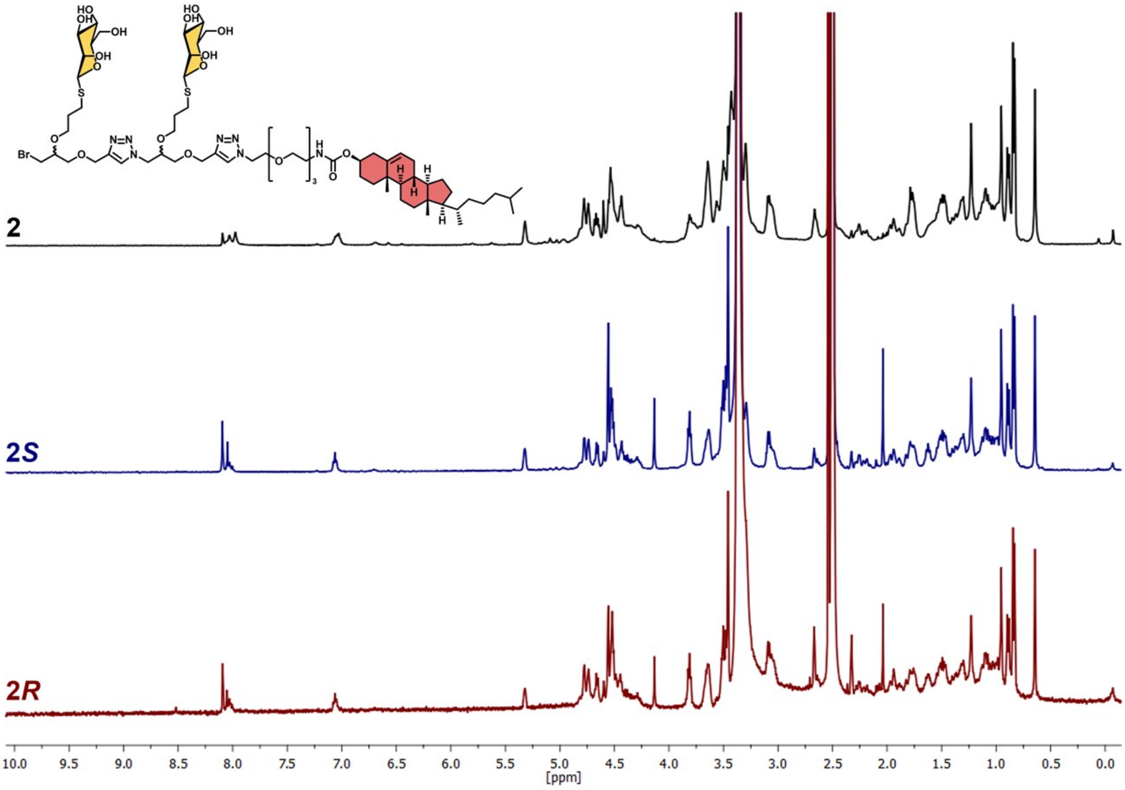


Figure S8. Stacked ^{1}H NMR spectra (400 MHz, DMSO-*d*6) of **2**, **2S** and **2*R***.

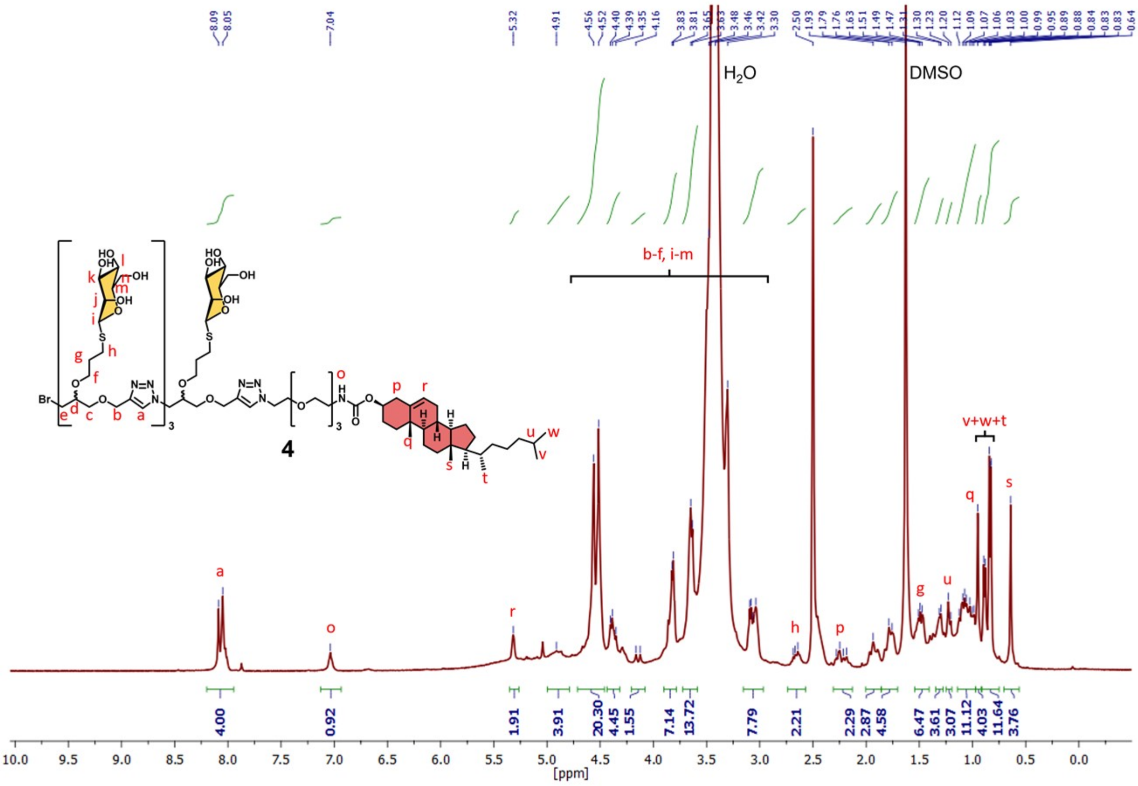


Figure S9. Assigned ^{1}H NMR spectrum (400 MHz, DMSO-*d6*) of **4**.

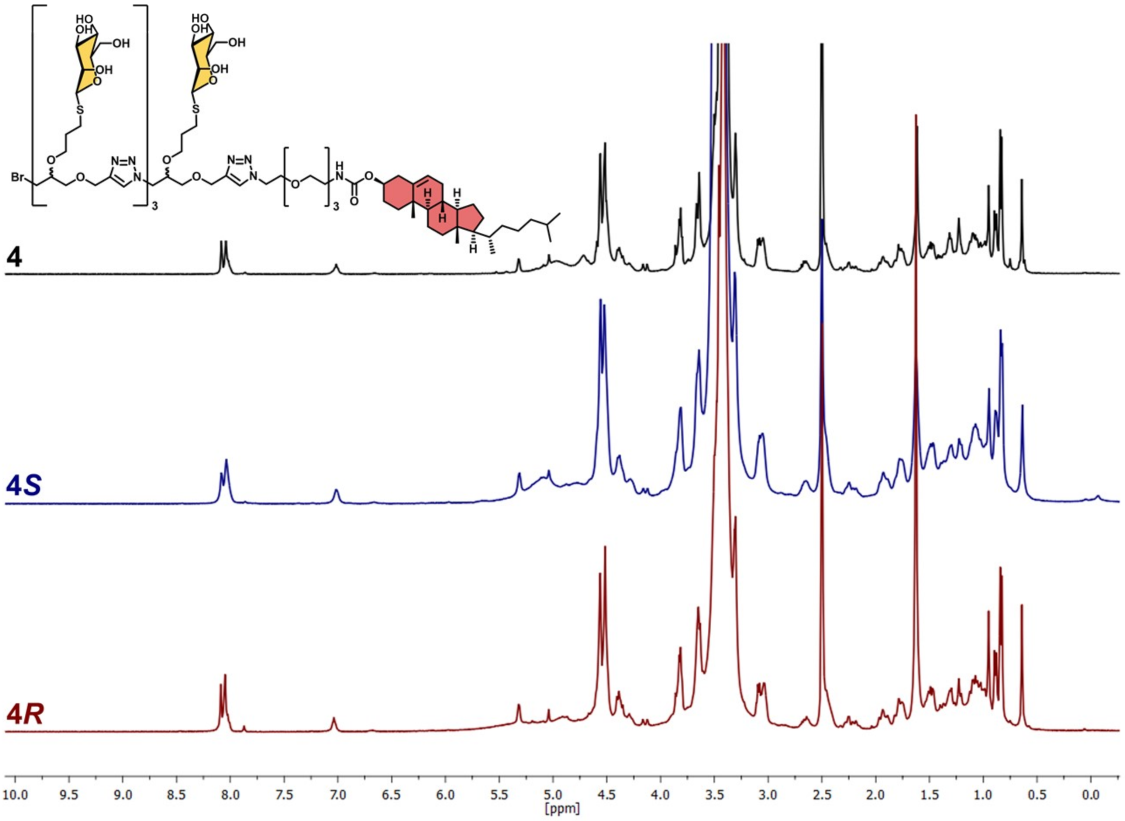


Figure S10. Stacked ^{1}H NMR spectra (400 MHz, DMSO-*d6*) of **4**, **4S** and **4*R***.

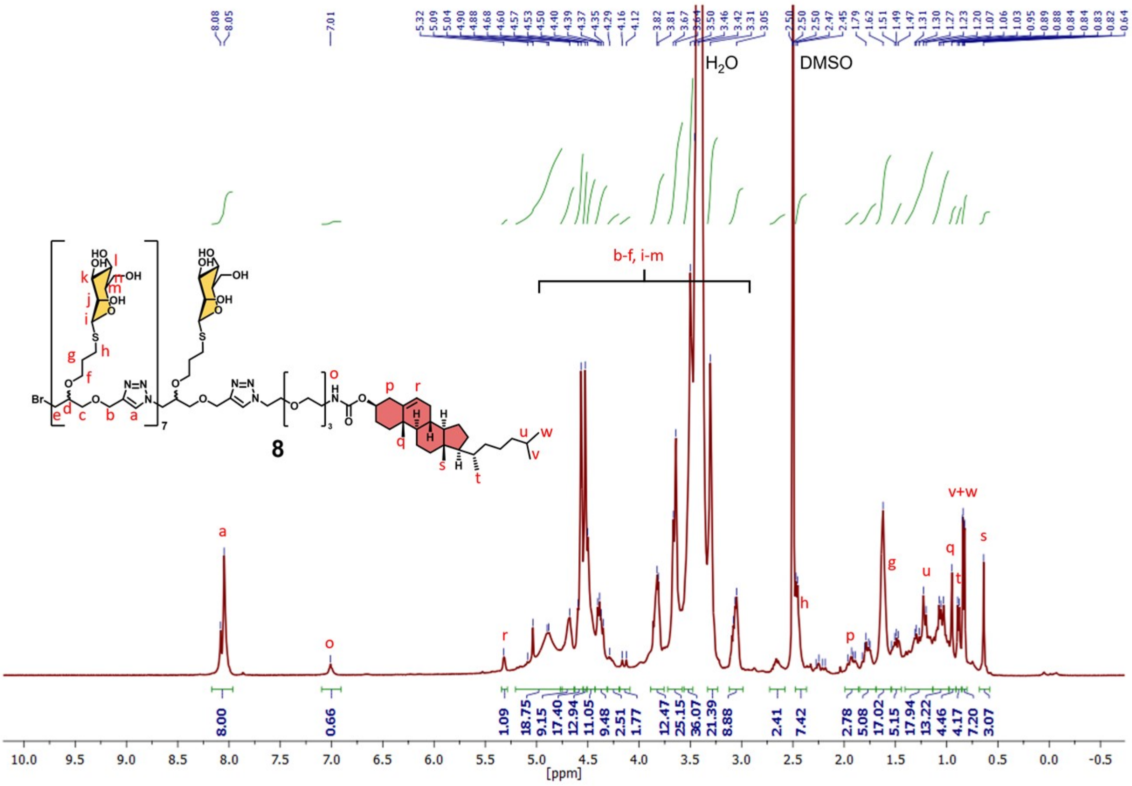


Figure S11. Assigned ^{1}H NMR spectrum (400 MHz, DMSO-*d*6) of **8**.

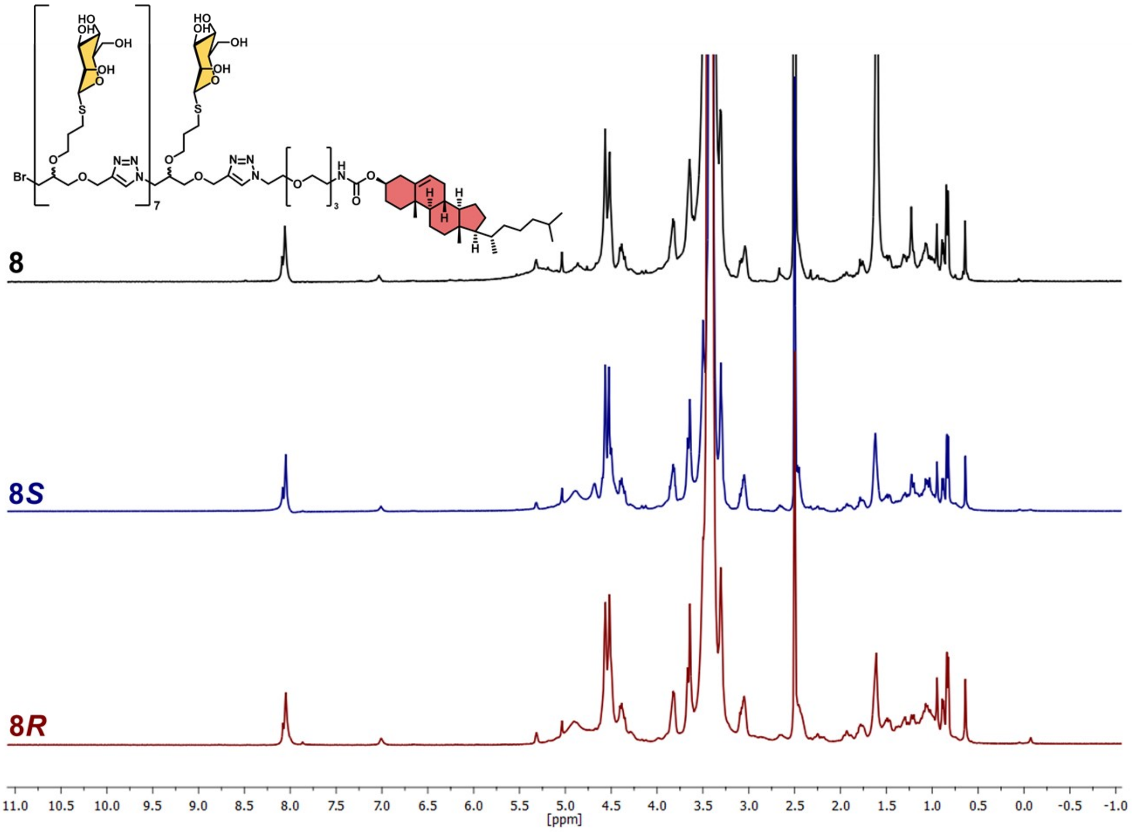


Figure S12. Stacked ^{1}H NMR spectra (400 MHz, DMSO-*d*6) of **8**, **8S** and **8*R***.

ESI-MS of Chol-Glyco-IEGmers

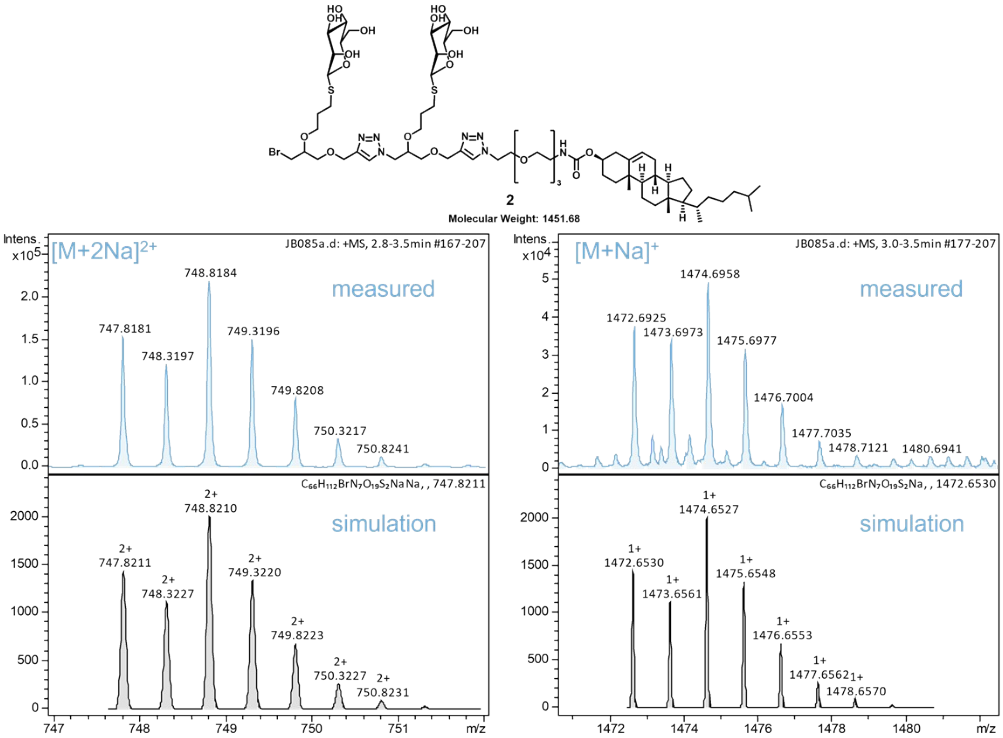


Figure S13. Overlay of HR ESI-MS spectra of **2** (top) with the peak prediction (bottom) of molecular ion peaks $[M+Na]^+$ and $[M+2Na]^{2+}$.

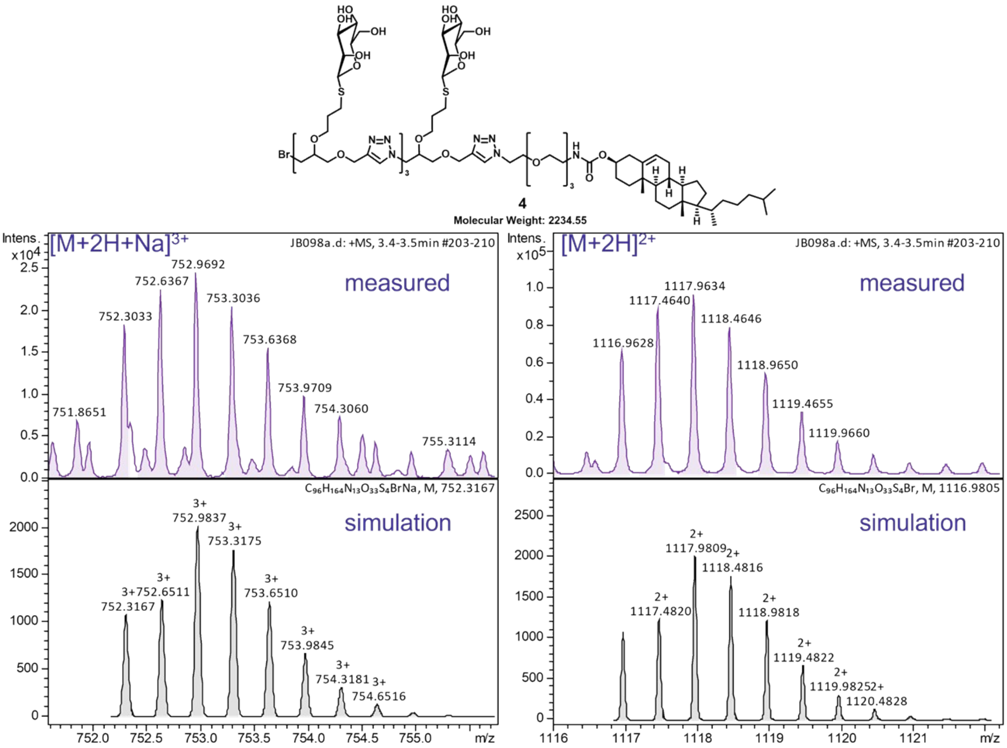


Figure S14. Overlay of HR ESI-MS spectra of **4** (top) with the peak prediction (bottom) of molecular ion peaks $[M+2H]^{2+}$ and $[M+2H+Na]^{3+}$.

SPR Binding Curves of Glyco-Chol-IEGmers

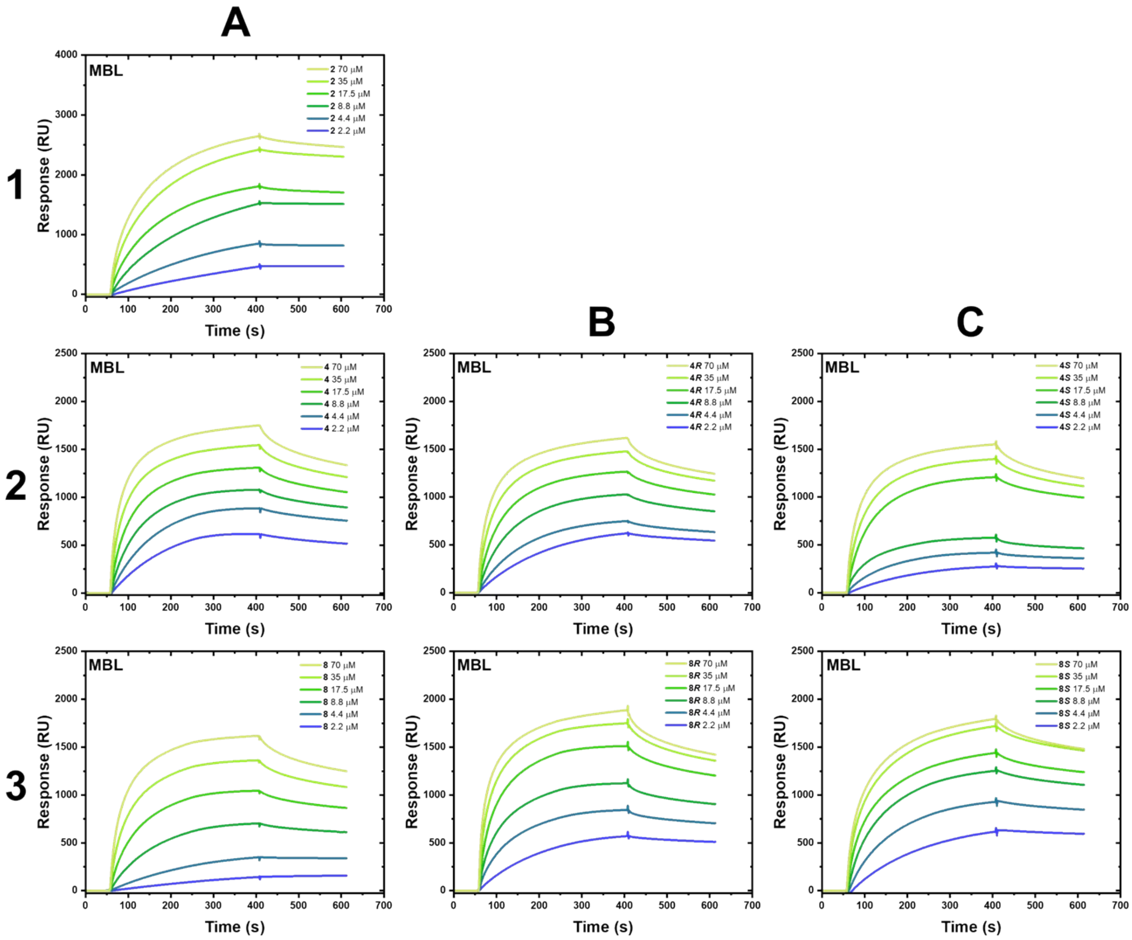


Figure S15. SPR binding curves of immobilised MBL with glycomacromolecules in varying concentrations from 2.2 µM to 70 µM in HBS. **1A: 2**, **2A: 4**, **2B: 4*R***, **2C: 4*S***, **3A: 8**, **3B: 8*R***, **3C: 8*S***.

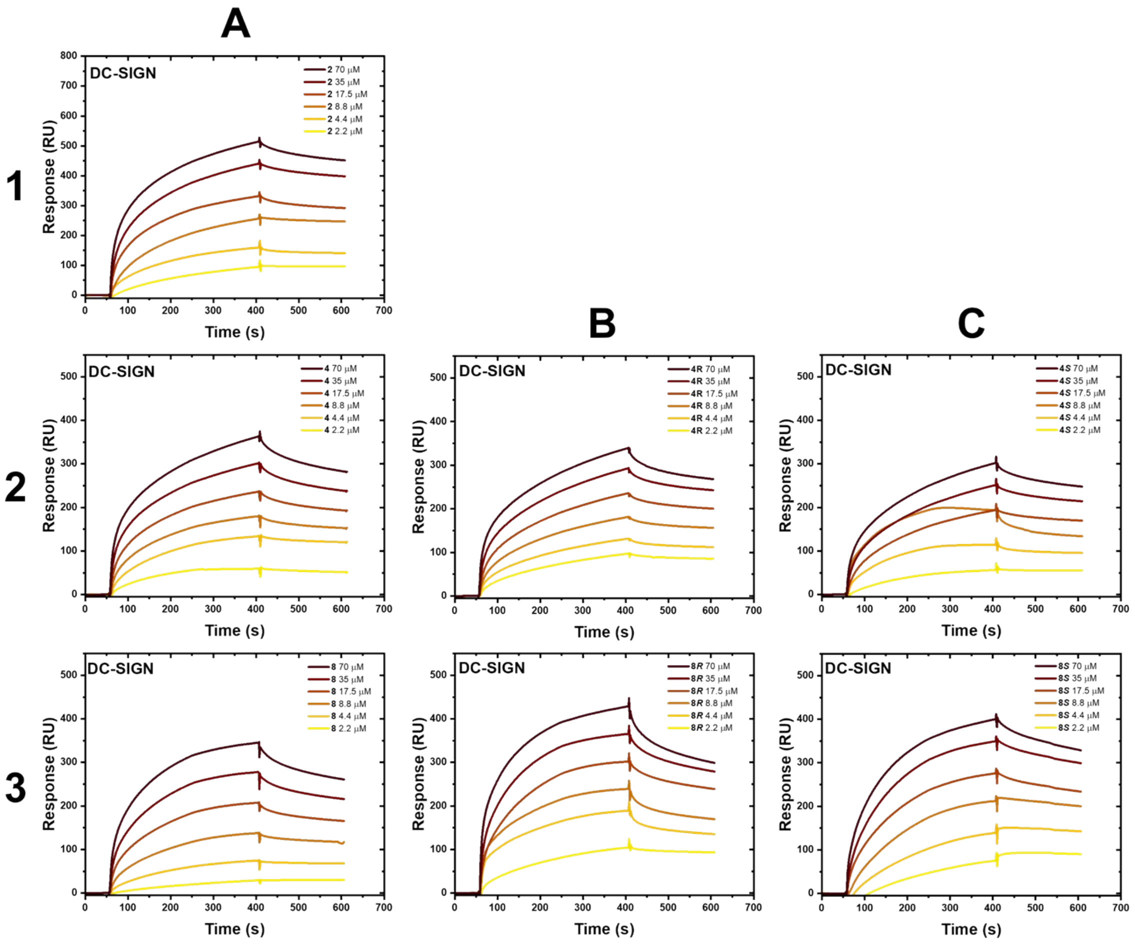


Figure S16. SPR binding curves of immobilised DC-SIGN with glycomacromolecules in varying concentrations from 2.2 µM to 70 µM in HBS. **1A: 2**, **2A: 4**, **2B: 4*R***, **2C: 4*S***, **3A: 8**, **3B: 8*R***, **3C: 8*S***.

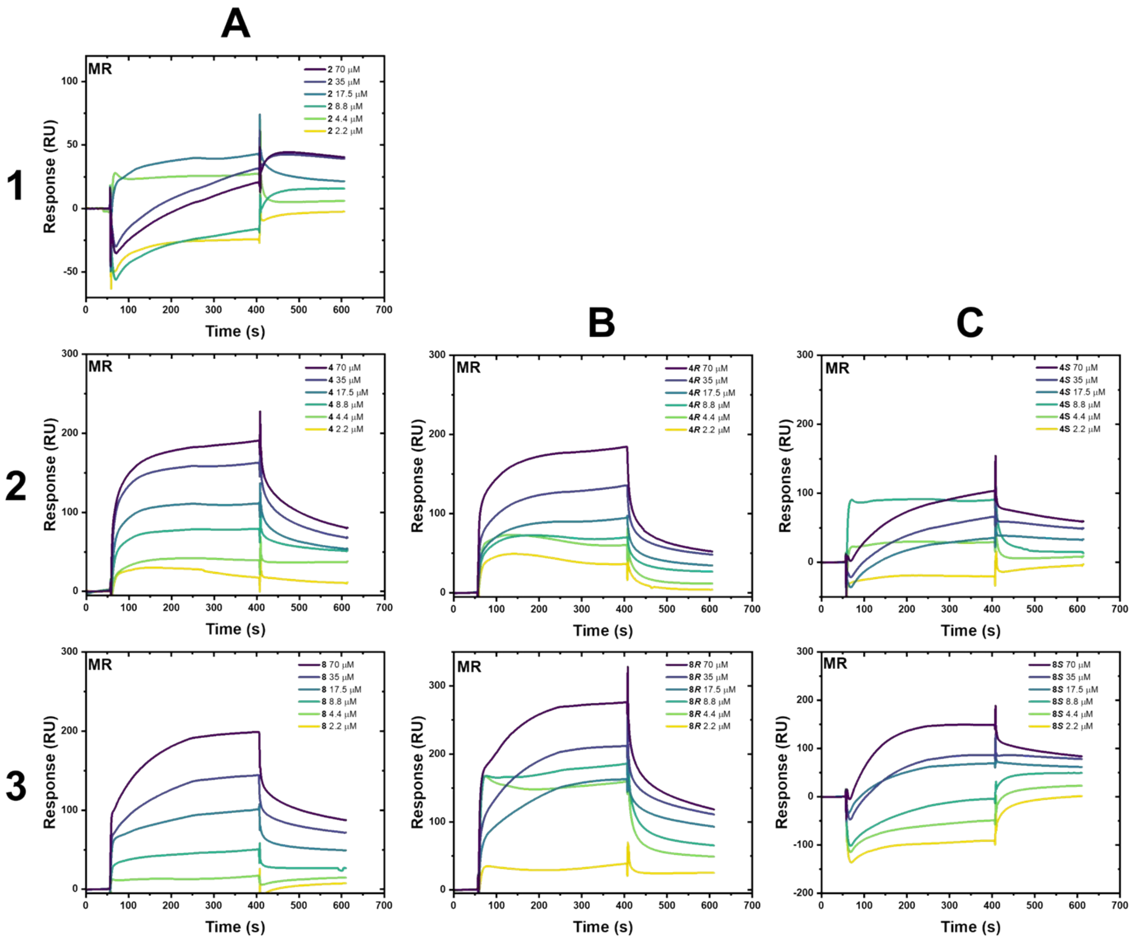


Figure S17. SPR binding curves of immobilised MR with glycomacromolecules in varying concentrations from 2.2 μM to 70 μM in HBS. **1A: 2**, **2A: 4**, **2B: 4*R***, **2C: 4*S***, **3A: 8**, **3B: 8*R***, **3C: 8*S***.

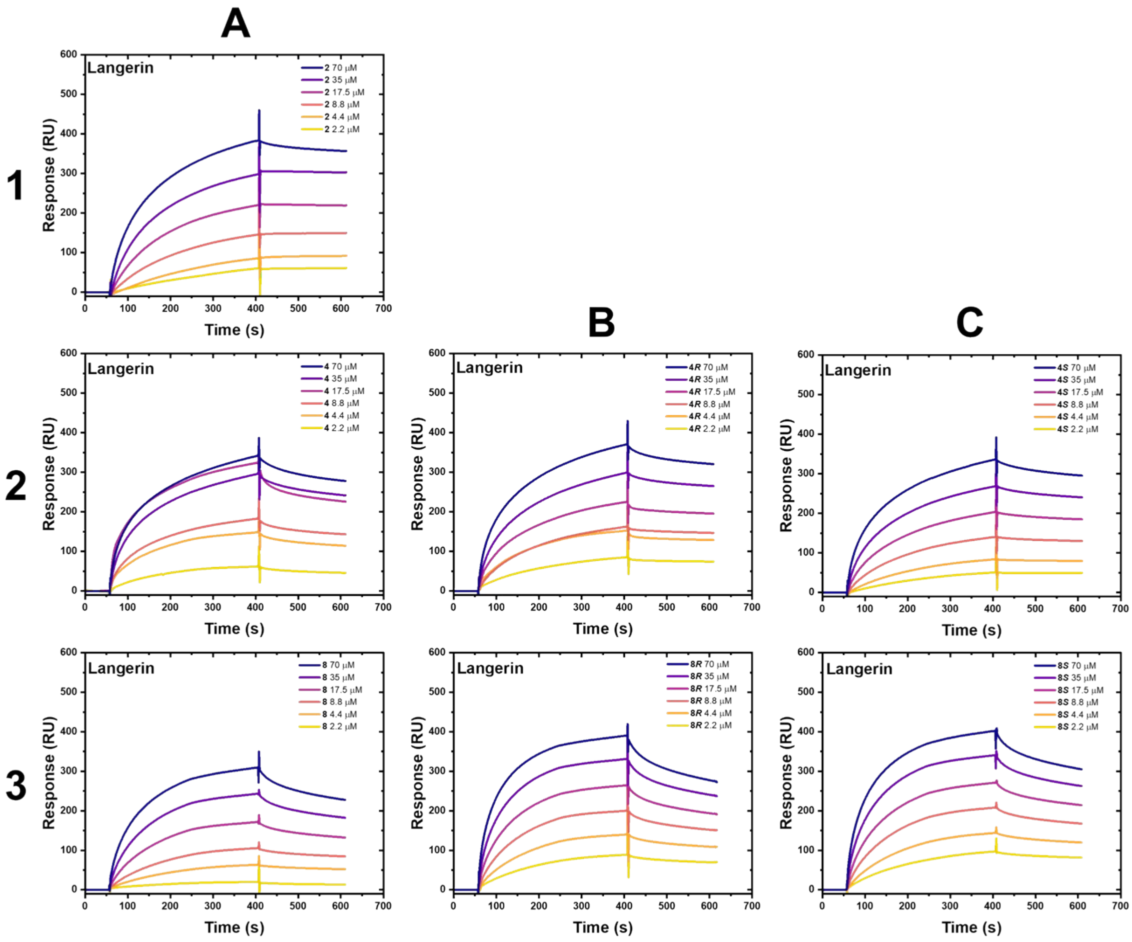


Figure S18. SPR binding curves of immobilised Langerin with glycomacromolecules in varying concentrations from 2.2 µM to 70 µM in HBS. **1A: 2**, **2A: 4**, **2B: 4*R***, **2C: 4*S***, **3A: 8**, **3B: 8*R***, **3C: 8*S***.

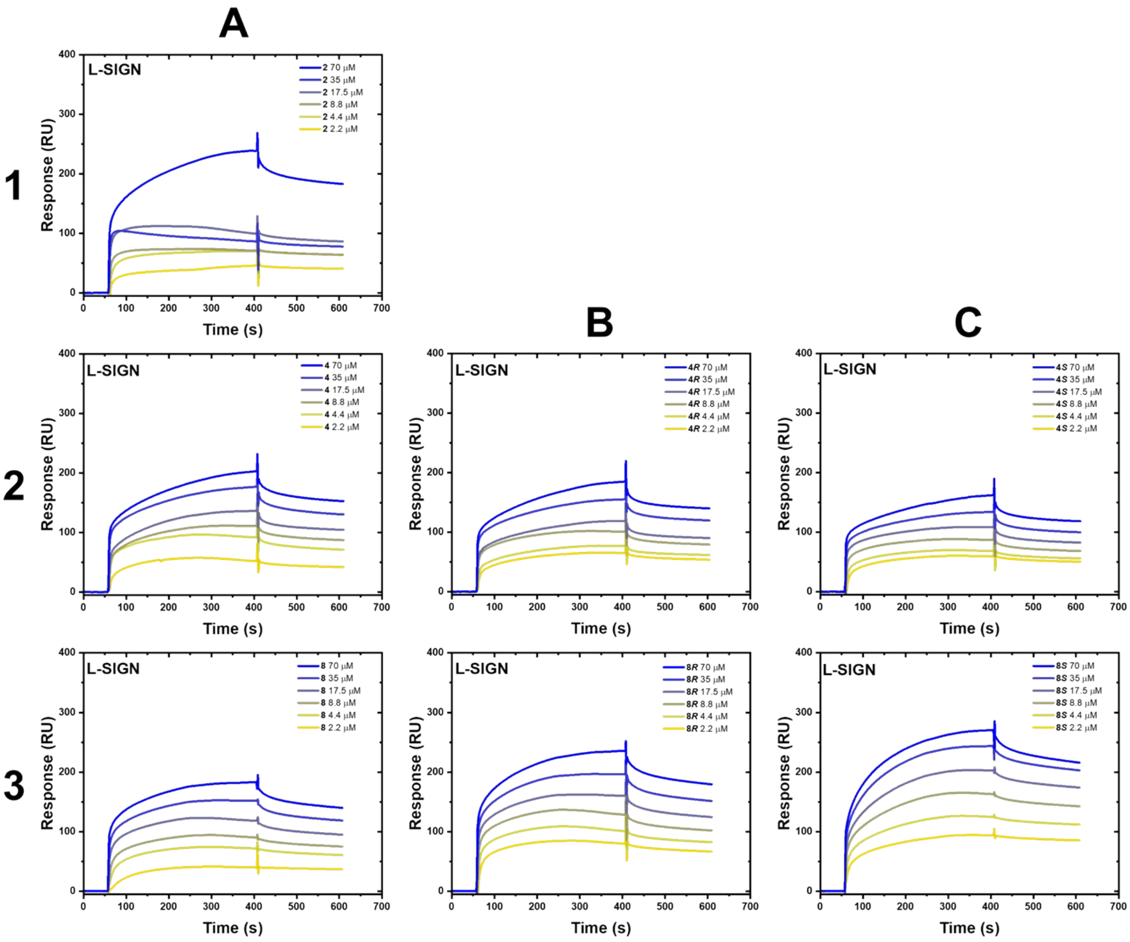


Figure S19. SPR binding curves of immobilised L-SIGN with glycomacromolecules in varying concentrations from 2.2 µM to 70 µM in HBS. **1A: 2**, **2A: 4**, **2B: 4*R***, **2C: 4*S***, **3A: 8**, **3B: 8*R***, **3C: 8*S***.

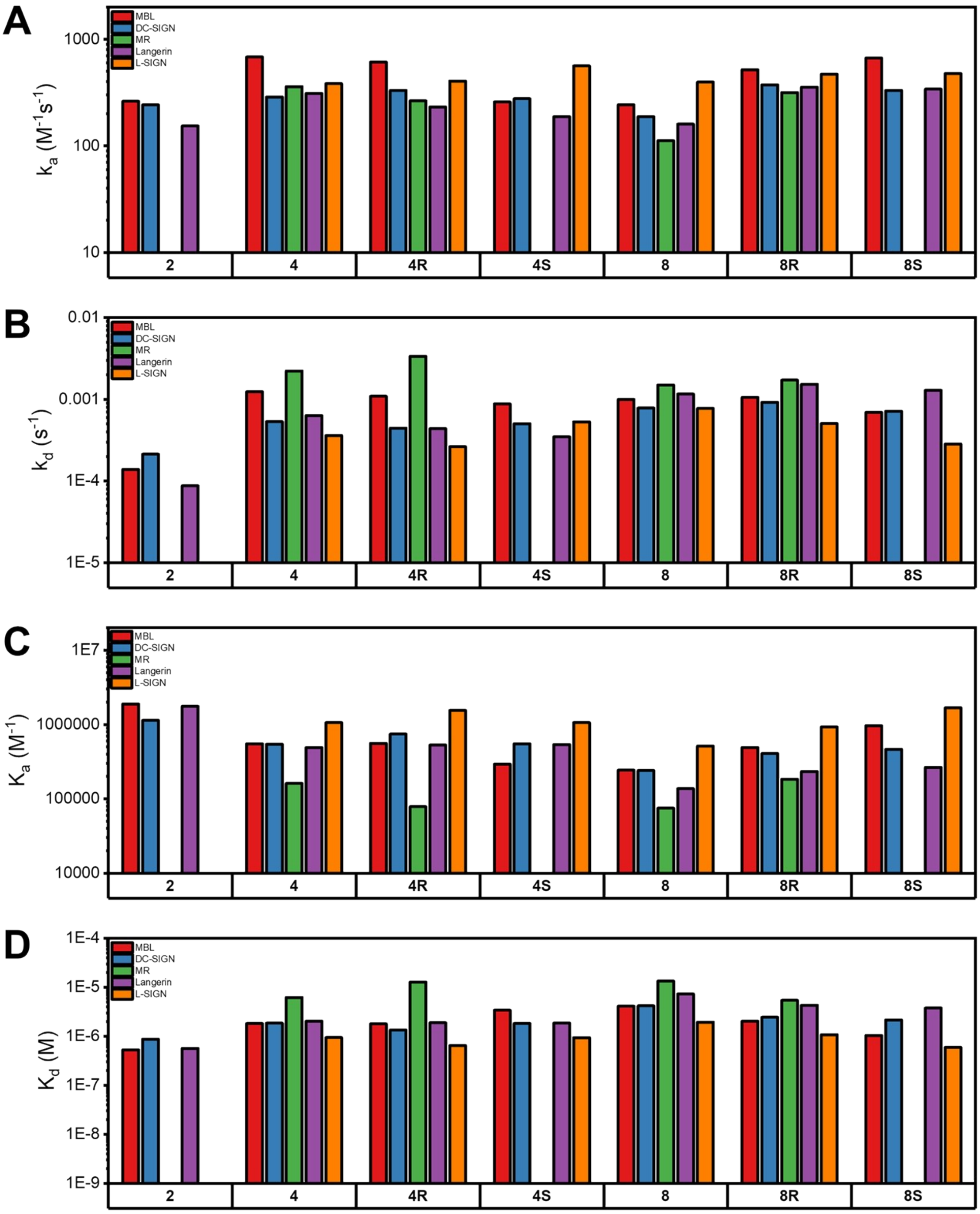


Figure S20. Bar plot of the kinetic data evaluated from SPR binding curves for cholesterol-containing glycomacromolecules and lectins using a Langmuir 1:1 binding model. **A:** k_a, **B:** k_d, **C:** K_a, **D:** K_d.

Table S1. Kinetic data of cholesterol-containing glycomacromolecules evaluated from SPR binding curves using a Langmuir 1:1 binding model.

Sample	Lectin	k_a [M^{-1}s^{-1}]	k_d [s^{-1}]	R_{max} [RU]	K_a [M^{-1}]	K_d [M]
2	MBL	262	1.39 x10^{-4}	2500	1.89 x10^{6}	5.29 x10^{-7}
	DC-SIGN	243	2.13 x10^{-4}	456	1.14 x10^{6}	8.76 x10^{-7}
	MR	-	-	-	-	-
	Langerin	154	8.74 x10^{-5}	372	1.76 x10^{6}	5.68 x10^{-7}
	L-SIGN	-	-	-	-	-
4	MBL	683	1.24 x10^{-3}	1560	5.50 x10^{5}	1.82 x10^{-6}
	DC-SIGN	288	5.32 x10^{-4}	303	5.42 x10^{5}	1.85 x10^{-6}
	MR	360	2.23 x10^{-3}	127	1.61 x10^{5}	6.20 x10^{-6}
	Langerin	311	6.33 x10^{-4}	313	4.90 x10^{5}	2.04 x10^{-6}
	L-SIGN	384	3.61 x10^{-4}	148	1.06 x10^{6}	9.41 x10^{-7}
4*R*	MBL	611	1.09 x10^{-3}	1470	5.58 x10^{5}	1.79 x10^{-6}
	DC-SIGN	332	4.45 x10^{-4}	285	7.46 x10^{5}	1.34 x10^{-6}
	MR	265	3.38 x10^{-3}	109	7.83 x10^{4}	1.28 x10^{-5}
	Langerin	232	4.38 x10^{-4}	332	5.29 x10^{5}	1.89 x10^{-6}
	L-SIGN	406	2.63 x10^{-4}	128	1.55 x10^{6}	6.47 x10^{-7}
4*S*	MBL	258	8.81 x10^{-4}	1460	2.93 x10^{5}	3.41 x10^{-6}
	DC-SIGN	277	5.04 x10^{-4}	267	5.50 x10^{5}	1.82 x10^{-6}
	MR	-	-	-	-	-
	Langerin	188	3.48 x10^{-4}	313	5.38 x10^{5}	1.86 x10^{-6}
	L-SIGN	563	5.30 x10^{-4}	110	1.06 x10^{6}	9.40 x10^{-7}
8	MBL	243	9.97 x10^{-4}	1500	2.43 x10^{5}	4.11 x10^{-6}
	DC-SIGN	188	7.83 x10^{-4}	314	2.40 x10^{5}	4.17 x10^{-6}
	MR	112	1.50 x10^{-3}	146	7.48 x10^{4}	1.34 x10^{-5}
	Langerin	160	1.16 x10^{-3}	307	1.37 x10^{5}	7.28 x10^{-6}
	L-SIGN	397	7.74 x10^{-4}	140	5.13 x10^{5}	1.95 x10^{-6}
8*R*	MBL	519	1.06 x10^{-3}	1690	4.91 x10^{5}	2.04 x10^{-6}
	DC-SIGN	375	9.20 x10^{-4}	359	4.08 x10^{5}	2.45 x10^{-6}
	MR	317	1.72 x10^{-3}	181	1.84 x10^{5}	5.42 x10^{-6}
	Langerin	356	1.53 x10^{-3}	355	2.33 x10^{5}	4.30 x10^{-6}
	L-SIGN	470	5.06 x10^{-4}	172	9.28 x10^{5}	1.08 x10^{-6}
8*S*	MBL	667	6.92 x10^{-4}	1650	9.64 x10^{5}	1.04 x10^{-6}
	DC-SIGN	332	7.16 x10^{-4}	375	4.64 x10^{5}	2.16 x10^{-6}
	MR	-	-	-	-	-
	Langerin	341	1.29 x10^{-3}	371	2.65 x10^{5}	3.78 x10^{-6}
	L-SIGN	477	2.84 x10^{-4}	217	1.68 x10^{6}	5.95 x10^{-7}

Physicochemical Characterisation of LNP formulations

Table S2. Overview over formulation composition and physicochemical characterisation results of LNPs used for transfection assay with HEK and THP-1 cell lines.

Sample	Ionisable Lipid	Helper Lipid	Hydrodynamic Diameter [nm]*	s.d.	PDI	s.d.	Zeta potential [mV]	s.d.	saRNA Loading Efficiency [%] **
C12 DSPC Control	C12-200	DSPC	75.01	1.40	0.22	0.00	-9.15	1.37	97.9
C12+**2**	C12-200	DSPC	112.40	1.50	0.38	0.01	-7.29	0.68	96.6
C12+**2*S***	C12-200	DSPC	93.17	1.95	0.20	0.01	-8.08	0.98	97.7
C12+**2*R***	C12-200	DSPC	76.84	2.40	0.21	0.02	-8.41	1.31	98.1
C12+**4**	C12-200	DSPC	93.82	1.68	0.23	0.02	-9.54	0.66	94.8
C12+**4*S***	C12-200	DSPC	82.71	2.24	0.22	0.03	-8.40	1.58	97.8
C12+**4*R***	C12-200	DSPC	83.83	2.15	0.25	0.01	-9.55	0.33	96.5
C12+**8**	C12-200	DSPC	81.50	1.23	0.21	0.01	-9.02	0.53	97.5
C12+**8*S***	C12-200	DSPC	99.57	0.65	0.18	0.01	-9.20	1.09	96.6
C12+**8*R***	C12-200	DSPC	85.01	1.48	0.23	0.00	-14.40	1.39	97.1

*from DLS, intensity weighted ** from RiboGreen assay

Table S3. Overview over formulation composition and physicochemical characterisation results of LNPs used for transfection assay with HEK 293T/17 cell line and BMDCs.

Sample	Ionisable Lipid	Helper Lipid	Hydrodynamic Diameter [nm]*	s.d.	PDI	s.d.	Zeta potential [mV]	s.d.	saRNA Loading Efficiency [%] **
C12 DSPC Control	C12-200	DSPC	78.50	8.60	0.30	0.04	-5.09	0.84	97.0
C12+**4**	C12-200	DSPC	86.97	3.08	0.40	0.02	-4.13	0.41	97.2
C12+**8**	C12-200	DSPC	94.41	40.41	0.30	0.06	-8.60	1.72	98.2
C12+**8*S***	C12-200	DSPC	97.00	3.77	0.41	0.02	-5.17	1.07	97.7
C12+**8*R***	C12-200	DSPC	141.58	2.81	0.40	0.08	-7.39	1.04	97.6

*from DLS, intensity weighted ** from RiboGreen assay