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LIPOSOME-LIKE FUCOPEPTIDES AS SIALYL LEWIS X MIMETICS

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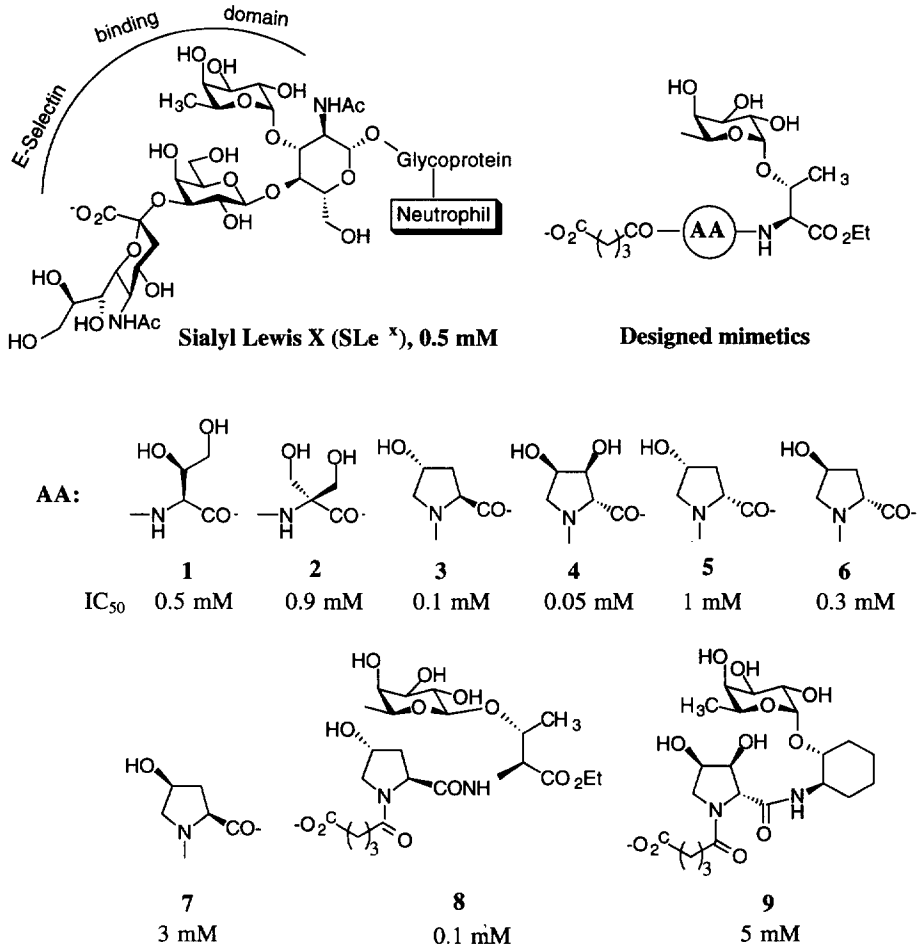
Abstract: Several fucodipeptides and their liposome-like derivatives were prepared and tested as inhibitors of sialyl Lewis X binding to E-selectin. It has been found that *trans*-hydroxyproline (D or L) can be used to mimic the galactose residue of sialyl Lewis X, and the mimetic containing 3,4-dihydroxy-D-proline is the most active with IC_{50} value (50 μM) 10-fold greater than sialyl Lewis X. Derivatization of a hydroxythreonine-containing fucodipeptides into a covalent liposome-like derivative, however, provides a mimetic with only IC_{50} ~ 30 μM.

The early stage of neutrophil migration from the blood stream to the site of inflammation or tissue injury occurs with the rolling adhesion of neutrophils to vascular endothelium.[1] The adhesion process involves the interaction of sialyl Lewis X (SLe^X, Figure 1), a terminal tetrasaccharide of cell-surface glycoproteins and glycolipids, and the endothelial leukocyte adhesion molecule-1 (E-selectin).[2] Inhibition of the SLe^X/E-selectin interaction has been shown to be effective in animal models of certain inflammatory diseases such as reperfusion injury.[3] Although the synthesis of SLe^X on a large scale has been developed for clinical evaluation,[4] this natural saccharide is relatively weak regarding its activity (IC_{50} ~ 0.5 mM) against E-selectin and can only be used in its injectable form for acute symptoms as it is orally inactive and unstable in the blood stream.[5] Development of SLe^X mimetics with higher affinity for the receptor and better activity and stability against glycosidase[5] has been of current interest.[6]

The bound conformation of SLe^X to E-selectin[7] and the functional groups essential for recognition by E-selectin have been determined to include the carboxylate group of the NeuAc moiety, the 2-, 3-, and 4-OH groups of the fucose moiety and the 4- and 6-OH groups of the galactose moiety.[8] This recognition model provides useful information for the design of mimetics,[6] and our effort in this regard has shown that α-*O*-L-fucosyl-L-threonine ethyl ester coupled with γ-hydroxy-L-Thr (**1**), α-hydroxymethyl-L-Ser (**2**) or hydroxyproline (**3** and **4**) gives mimetics with activity[6c] equivalent or greater than SLe^X (Figure 1). We report here further investigation of other hydroxyproline and liposome-like derivatives as inhibitors of E-selectin.

We chose α-*O*-fucosyl-L-threonine ethyl ester as a core structure[6c] linked to D-hydroxythreonine or hydroxyproline to mimic the active conformation of the Le^X portion of SLe^X. Since the *trans*-hydroxyamine moiety of Thr is equivalent to the *trans*-diol orientation of the GlcNAc moiety in SLe^X, the *O*-fucosyl-Thr derivative is expected to mimic the Fuc-α-1,3-GlcNAc portion of SLe^X. Incorporation of a designed amino acid to the amine group via a peptide linkage will not only provide the functionality's equivalent to the Gal moiety of SLe^X but also rigidify the conformation. A glutaryl group was used to provide the negative charge equivalent to the NeuAc moiety. In addition, (1*R*, 2*R*)-2-aminocyclohexanol was used to replace the Thr moiety as this cyclic aminoalcohol was also shown to be an effective template.[6d]

Figure 1. Sialyl Lewis X and designed mimetics with IC_{50} against E-selectin

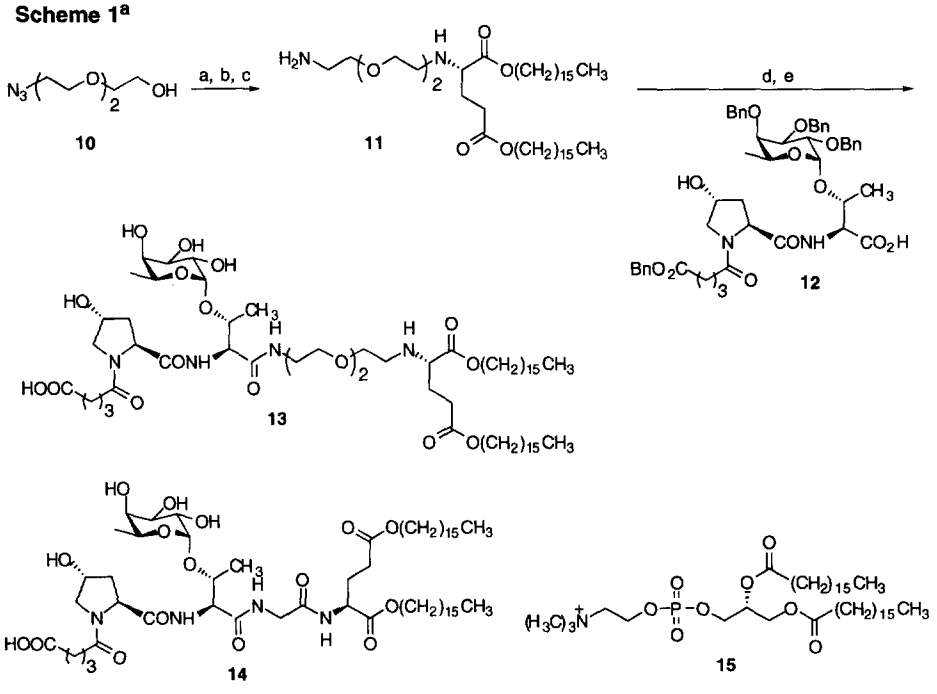


The IC_{50} values of **1-9** are shown in Figure 1 (SLe^X = 0.5 mM). Interestingly, compound **4** is 10-fold better while compound **9** is 10-fold weaker than SLe^X in binding to E-selectin.[9] Compounds **3** and **6** are slightly better, and as expected, **5** and **7** are weaker than SLe^X (due to the inappropriate orientation of the *cis*-OH group from the hydroxyproline residue). Surprisingly, the β-isomer **8** is essentially as active as the α-isomer. L-Threonine is apparently better than the 2-amino-cyclohexanol as a template for the design of SLe^X mimetics in this study, though the aminocyclohexanol template works very well when γ-hydroxy-L-threonine is used to mimic the Gal residue.[6c] The liposome-like mimetics **13** and **14** (IC_{50} = 0.5 mM), Scheme 1, do not show good activities as expected,[10] probably because the dihexadecyl L-glutamate tail can not form a stable liposome with phosphatidylcholine. The covalent liposome-like[11] mimetics **22** and **24** were then prepared (Scheme 2), and interestingly **22** is relatively active (IC_{50} = 30 μM) but **24** is inactive. Whether the positive charge of **24**

contributes to the negative result remains to be investigated. It is noted that **22** and **24** were tested directly as inhibitors of E-selectin and work is in progress to formulate compounds **2-8** as liposomes for inhibition analysis.

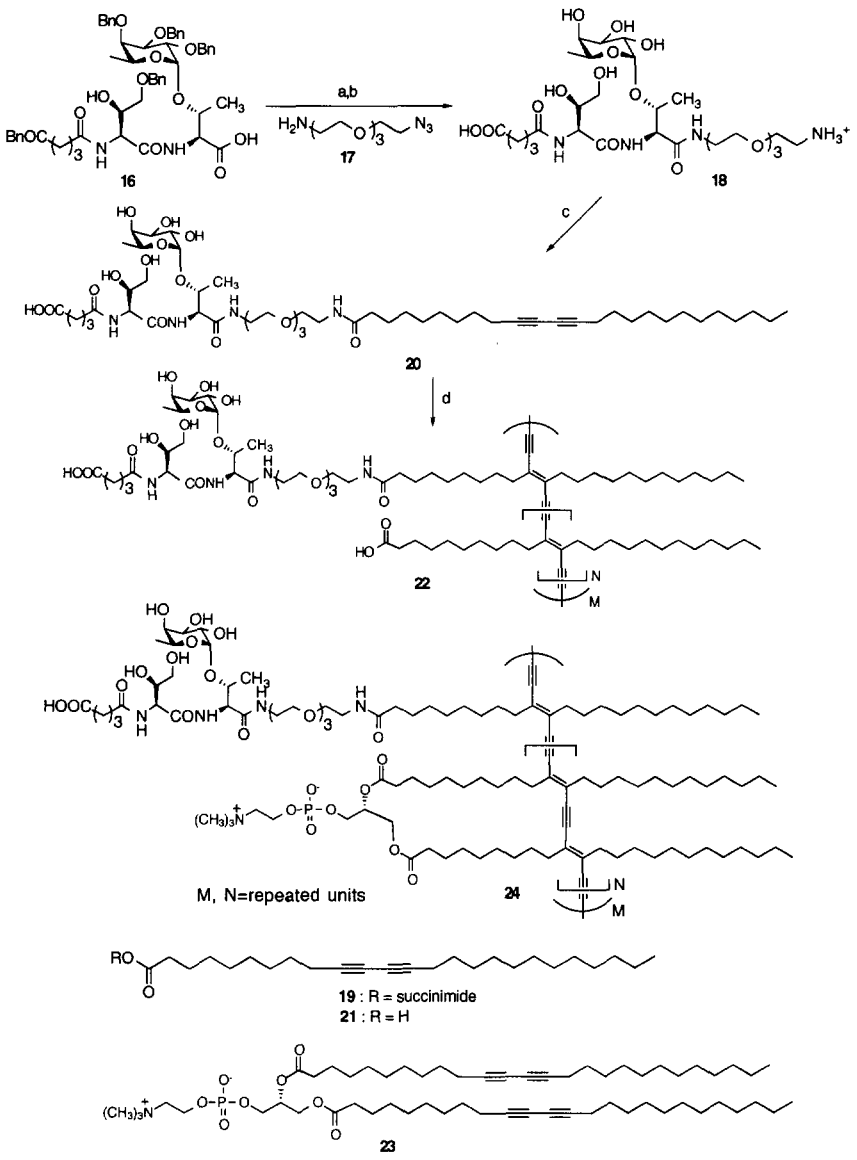
With regard to the synthesis, compounds **5-9** were prepared according to the procedures described previously.[6c,12] Schemes 1 and 2 illustrate the synthesis of lipids **13**, **14**, **22**, and **24**. Azide aldehyde, which was derived from Swern oxidation of azido alcohol **14**,[13] was linked to dihexadecyl L-glutamate[14] via reductive amination (65%) followed by catalytic hydrogenation (100%), to give the anchor moiety **11**. Compound **11** was coupled with mimetic moiety **12**[15] (52%) and hydrogenated to give the desired lipid **13** (60%). Compound **14** was synthesized similarly.[16] Liposomes of **13** and **14** were prepared[17] with phosphtidylcholine **15** containing 5% of **13** or **14** in 20 mM HEPES buffer (pH 7.2), using the probe sonication method. To synthesize polymerized liposome, compound **16**[15] was coupled with **17**[15] followed by hydrogenation to yield **18.** The lipid conjugate **20** was synthesized by treating active ester **19** with **18** in DMF and Et_3N.[18] The liposome of **20** (5 mol%) with **21** or **23** were formed as described in the scheme. The liposomes were then polymerized by irradiating 254 nm UV lamp at 0 °C to generate lipid polymers **22** and **24**.[19]

Scheme 1[a]



[a]Conditions: (a) Swern oxidation; (b) 1',3'-dihexadecyl L-glutamate·TsOH salt, $NaCNBH_3$/THF-MeOH; (c) H_2, Pd/C, 1 N HCl/MeOH; (d) **12**, EDC, HOBT, CH_2Cl_2, 6 h; (e) H_2 (1 atm), Degussa type Pd(OH EtOH/H_2O (2:1), 5 h.

Scheme 2[a]



[a]Conditions: (a) **17**, EDC, HOBT, CH_2Cl_2, 6 h, 79%; (b) H_2, $Pd(OH)_2$/C, EtOH/H_2O/dioxane/AcOH (2:1:2:1), 94%; (c) **19**, DMF, Et_3N, 1 day, 84%; (d) (i) **21**, sonication/HEPES buffer, heat; (ii) *hν*, 0 °C.

References and Notes

†On sabbatical leave from Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan.

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12. Compound **5**: ^1H NMR (500 MHz, D_2O) δ 4.86 (d, J = 3.8 Hz, $1H_a$), 4.84 (d, J = 3.9 Hz, $1H_b$), 4.50 (d, J = 2.2 Hz, $1H_b$), 4.48 (d, J = 2.1 Hz, $1H_a$), 4.43-4.29 (m, 3H), 4.14-3.99 (m, 2H), 3.71 (dd, J = 11.4, 3.9 Hz, $1H_b$), 3.64-3.56 (m, $4H_b$, $6H_a$), 3.49 (dd, J = 11.4, 2.7 Hz, $1H_b$), 2.53-2.49 (m, $1H_a$), 2.43-2.37 (m, $1H_b$), 2.28 (t, J = 7.3 Hz, $2H_b$), 2.30-2.20 (m, 3 H_a), 2.10 (t, J = 7.5 Hz, $2H_b$), 2.06 (t, J = 7.9 Hz, $2H_a$), 1.94-1.90 (m, $1H_b$), 1.71-1.64 (m, $2H_a$, $2H_b$), 1.14 (t, J = 7.2 Hz, $3H_b$), 1.14 (t, J = 7.2 Hz, $3H_a$), 1.11 (d, J = 6.3 Hz, $3H_a$), 1.05 (d, J = 6.2 Hz, $3H_b$), 1.05 (d, J = 6.6 Hz, $3H_b$), 1.05-1.04 (3 H_a); ^{13}C NMR (125 MHz, D_2O) δ 182.6, 182.2, 175.9, 175.6, 175.5, 175.3, 172.2, 172.2, 94.9, 94.7, 71.9, 71.3, 70.7, 70.0, 69.7, 69.7, 68.7, 68.0, 67.4, 67.3, 63.4, 63.0, 60.0, 59.6, 58.2, 57.6, 55.5, 55.1, 39.8, 37.4, 36.7, 36.5, 33.9, 33.6, 21.5, 15.6, 14.6, 13.8, 13.7, 13.6 (rotamers present in NMR); HRMS calcd for negative electrospray $C_{22}H_{35}N_2O_{12}$ (M-H): 519, found 519. Compound **6:** ^1H NMR (500 MHz, D_2O) δ 4.86 (d, J = 3.9 Hz, $1H_a$), 4.84 (d, J = 3.8 Hz, $1H_b$), 4.54 (d, J = 2.3 Hz, $1H_b$), 4.49 (d, J = 2.2 Hz, $1H_a$), 4.47 (br, $1H_b$), 4.45 (br, $1H_a$), 4.54-4.41 (m, $1H_b$), 4.40-4.36 (m, $1H_a$), 4.35 (qd, J = 6.3, 2.2 Hz, $1H_a$), 4.30 (qd, J = 6.2, 2.4

Hz, $1H_b$), 4.17-4.08 (m, 1H), 4.05-3.97 (m, 1H), 3.67-3.51 (m, $5H_a$, $6H_b$), 3.44-3.41 (m, $1H_a$), 2.39-2.34 (m, $1H_a$), 2.32-2.12 (m, $2H_a$, $1H_b$), 2.27 (t, J = 7.4 Hz, $2H_b$), 2.17 (t, J = 7.4 Hz, $2H_b$), 2.15 (t, J = 7.4 Hz, $2H_a$), 2.12-2.06 (m, $1H_a$), 1.95 (ddd, J = 13.2, 9.1, 4.5 Hz, $1H_b$), 1.69 (quintet, J = 7.4 Hz, 2H), 1.14 (t, J = 7.2 Hz, $3H_b$), 1.13 (t, J = 7.1 Hz, $3H_a$), 1.08 (d, J = 6.3 Hz, $3H_a$), 1.05 (d, J = 6.8 Hz, $3H_b$), 1.03 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, D_2O) δ 175.7, 175.3, 175.2, 175.1, 172.2, 171.9, 94.7, 94.6, 71.9, 70.9, 70.6, 70.0, 69.7, 68.5, 67.9, 67.4, 67.3, 63.4, 63.3, 59.3, 59.1, 58.0, 57.6, 55.9, 55.0, 39.1, 37.9, 33.7, 33.1, 20.9, 15.6, 14.4, 14.2, 13.7, 13.6 (rotamers present in NMR); HRMS calcd for $C_{22}H_{36}N_2O_{12}Na$ (M+Na): 543.2166, found 543.2148. Compound **7:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (d, J = 3.5 Hz, 1H), 4.42 (dd, J = 9.0, 5.0 Hz, 1H), 4.39-4.32 (m, 2H), 4.14-4.08 (m, 2H), 4.04-4.00 (m, 1H), 3.74 (dd, J = 11.4, 5.4 Hz, 1H), 3.65-3.54 (m, 4H), 3.44 (dd, J = 10.9, 3.5 Hz, 1H), 2.42 (ddd, J = 13.6, 9.1, 5.4 Hz, 1H), 2.27 (t, J = 7.5 Hz, 2H), 2.08 (t, J = 7.5 Hz, 2H), 1.89-1.85 (m, 1H), 1.67 (quintet, J = 7.5 Hz, 2H), 1.13 (dt, J = 7.2, 1.0 Hz, 3H), 1.10 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 175.5, 175.2, 172.2, 94.8, 71.9, 71.3, 69.9, 69.8, 68.0, 67.3, 63.3, 59.2, 57.6, 55.3, 37.0, 36.9, 33.9, 21.5, 15.6, 14.5, 13.7; HRMS calcd for $C_{22}H_{35}N_2O_{12}Cs_2$ (M-H+2Cs): 785.0299, found 785.0328. Compound **8:** ^{1}H NMR (500 MHz, D_2O) δ 4.48-4.41 (m, 4H), 4.18 (d, J=7.9 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.64 (dd, J = 11.8, 3.9 Hz, 1H), 3.59 (q, J = 6.5 Hz, 1H), 3.57-3.45 (m, 2H), 3.43 (dd, J = 9.8, 3.4 Hz, 1H), 3.24 (dd, J = 9.8, 7.9 Hz, 1H), 2.35-2.15 (m, 5H), 1.96-1.90 (m, 1H), 1.72-1.66 (m, 2H), 1.16 (d, J = 6.4 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, D_2O) δ 180.1, 175.0, 174.9, 171.8, 103.7, 76.7, 72.9, 70.1, 68.4, 63.3, 63.2, 59.0, 57.4, 55.9, 46.9, 37.6, 34.6, 33.5, 20.6, 18.5, 15.7, 13.6; HRMS calcd for $C_{22}H_{36}N_2O_{12}Na$ (M+Na): 543.2166, found 543.2175. Compound **9:** ^{1}H NMR (500 MHz, D_2O) δ 4.95 (d, J = 3.8 Hz, 1H), 4.16 (dd, J = 6.2, 3.8 Hz, 1H), 4.02 (dd, J = 7.1, 3.8 Hz, 1H), 3.95 (q, J = 6.5 Hz, 1H), 3.88 (d, J = 7.1 Hz, 1H), 3.67 (dd, J = 11.8, 4.1 Hz, 1H), 3.64-3.53 (m, 3H), 3.60 (br., 1H), 3.51 (dd, J = 11.8, 2.2 Hz, 1H), 3.36-3.31 (m, 1H), 2.29-2.05 (m, 4H), 2.09 (t, J = 7.3 Hz, 2H), 1.76-1.55 (m, 6H), 1.25-1.05 (m, 2H), 1.03 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, D_2O) δ 182.1, 175.5, 172.4, 92.9, 75.1, 74.6, 72.2, 70.7, 69.9, 68.2, 66.9, 64.9, 53.5, 52.9, 36.2, 33.0, 31.6, 30.5, 28.6, 24.4, 23.5, 21.1, 15.6; HRMS calcd for $C_{22}H_{36}N_2O_{11}Cs$ (M+Cs): 637.1373, found 637.1353.

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15. Compounds **12** and **16** were obtained as reported in ref 6c. Compound **17** was purchased from Toronto Research Chemicals Inc., Canada.
16. Compound **13:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (brs, 1H), 4.56-4.44 (m, 3H), 4.26-4.04 (m, 4H), 3.98-3.88 (m, 1H), 3.87-3.79 (m, 1H), 3.71-3.50 (m, 14H), 3.40-3.31 (m, 3H), 3.09-2.97 (m, 2H), 2.27-2.66 (m, 2H), 2.60-2.31 (m, 6H), 2.17-2.04 (m, 2H), 1.71-1.60 (m, 4H), 1.41-1.23 (m, 52H), 1.16 (d, J = 5.5 Hz, 6H), 0.80 (t, J = 6.5 Hz, 6H); HRMS calcd for $C_{60}H_{22114}N_4O_{17}Cs$ (M+Cs): 1319.7233, found 1319.7264. Compound **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (d, J = 2.6 Hz, 1H), 4.46 (t, J = 8.5 Hz, 1H), 4.42-4.40 (m, 4H), 4.05-3.95 (m, 6H), 3.76-3.43 (m, 6H), 2.23 (t, J = 7.7 Hz, 2H), 2.30-2.20 (m, 3H), 2.12-2.01 (m, 2H), 1.98-1.91 (m, 4H), 1.85-1.77 (m, 1H), 1.57-1.50 (m, 4H), 1.25-1.13 (br., >50H), 1.11 (d, J = 6.3 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.78 (t, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, D_2O) δ 178.8, 178.4, 173.6, 172.0, 171.6, 170.0, 163.7, 94.4, 72.5, 71.5, 70.5, 69.7, 69.2, 66.9, 66.1, 65.3, 60.2, 59.2, 55.9, 52.1, 49.5, 49.3, 49.3, 49.2, 49.2, 49.1, 49.1, 49.8, 48.8, 48.8, 48.7, 48.7, 48.6, 48.6, 48.5, 42.6, 38.2, 37.0, 34.0, 32.3, 31.7, 31.0, 30.0, 29.9,29.7, 29.6, 28.9, 28.8, 26.2, 26.6, 23.0, 16.1, 14.6, 14.3; HRMS calcd for $C_{59}H_{106}N_4O_{16}Cs$ (M+Cs): 1259.6658, found 1259.6620
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18. Compound **20:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br, 1H), 7.94 (br, 1H), 7.51 (br, 1H), 6.63 (br, 1H), 4.94 (br, 1H), 4.65-4.53 (m, 3H), 3.89-3.43 (m, 23H), 2.36 (br, 4H), 2.24 (t, J = 7.0 Hz, 4H), 2.18 (t, J = 7.5 Hz, 2H), 1.92 (br, 2H), 1.59 (br, 2H), 1.54-1.47 (m, 4H), 1.36-1.11 (m, 26H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 1.74.1, 174.0, 172.5, 169.8, 77.6, 77.4, 70.2, 69.8, 65.3, 65.2, 39.1, 36.5, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.8, 28.8, 28.3, 25.7, 22.7, 19.2, 16.2, 14.7, 14.1; HRMS calcd for $C_{52}H_{90}N_4O_{16}Cs$ (M+Cs^+): 1159.5406, found 1159.5438.
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