Supporting Information.

Cytomimetic Modeling in which One Phospholipid Liposome Chemically Attacks Another

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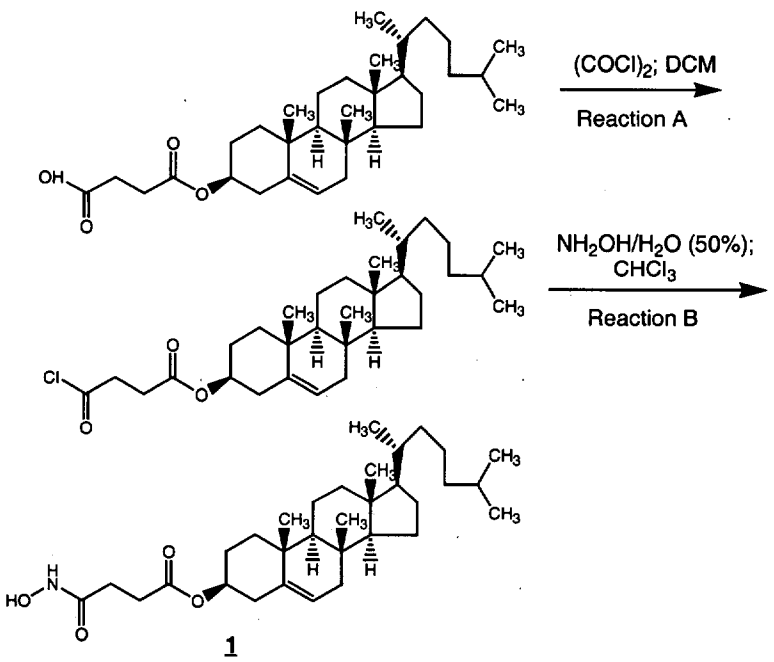
General.

^1H and ^{13}C NMR spectra were recorded with a Varian INOVA 400 or Mercury 300 spectrometer working at 400 or 300 MHz and 100 or 75 MHz respectively in deutero chloroform ($CDCl_3$) with chloroform (7.26 ppm ^1H, 77.23 ppm ^{13}C) as an internal reference. For cholesteryl derivatives ^1H signals corresponding to the cholesterol moiety will be noted with a prime (H') and ^{13}C signals will be omitted. MS (low and high resolution) was performed by the Mass Spectrometry Center of Emory University. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and uncorrected.



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Scheme 1. Synthesis of the compound 1.

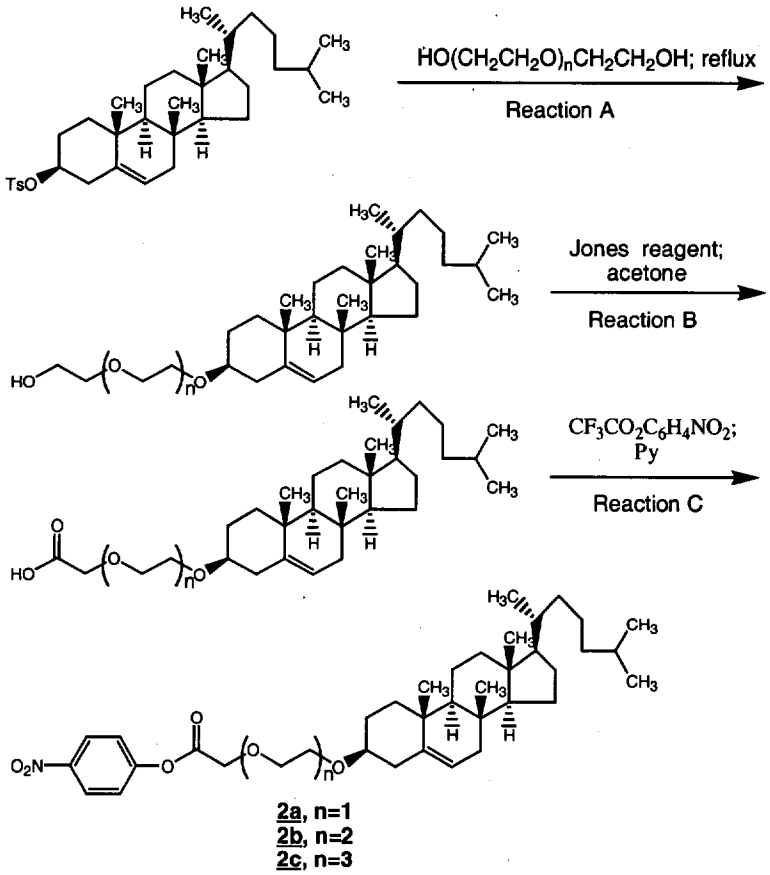
Experimental procedures for Scheme 1.

Reaction A. To a cold (0°C) stirred solution of cholesteryl hemisuccinate (1.17 g, 2.40 mmol, supplied by Sigma Chemical Co.) in dry DCM (20 ml) oxalyl chloride (0.84 ml, 9.6 mmol) was added dropwise, the mixture was allowed to warm to RT and stirred for 3 hours under Ar atmosphere. Then it was concentrated and dried in vacuum to give acid chloride as a white solid that was used without further purification. Yield – 1.19 g (2.36 mmol), 98%.

Reaction B. To a stirred solution of acid chloride (0.800 g, 1.54 mmol) in chloroform (15 ml) at 0°C 50% water solution of hydroxylamine (1.5 ml, 23 mmol) was added dropwise, the mixture was allowed to warm to RT and stirred for 2 hours. Strong emulsion formed. Then 50 ml of 1M hydrochloric acid, 50 ml of saturated sodium chloride solution and 50 ml of chloroform were added. After separation organic layer was dried over sodium sulfate and evaporated to dryness. Product was purified by column chromatography on

silica gel ($CHCl_3/Et_2O$, gradient 0-10%; then $CHCl_3/Et_2O$ 9:1 + MeOH, gradient 0-10%). Yield – 390 mg (0.777 mmol), 50%. White crystals.

Compound 1. M. p. 140-143°C; TLC: R_f 0.35 ($CHCl_3/Et_2O$/MeOH, 85:10:5, silica gel); ^{1}H NMR ($CDCl_3$): δ 0.67-2.37 (m, 43H, H cholesterol), 2.45 (bt, 5.0Hz, 2H, CH_2CO_2Chol), 2.67 (bt, 5.0Hz, 2H, CH_2CONHOH), 4.63 (m, 1H, H'-3), 5.38 (bd, 1H, H'-6), 8.63 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 28.63, 29.88 ($2CH_2$), 170.66 (*C*ONHOH), 172.60 (CO_2Chol). FAB HRMS: calc. for $C_{31}H_{51}O_4NLi^+$ 508.3996, observed 508.3978. Anal. calc. for $C_{31}H_{51}O_4N$ (501.76): C, 74.21; H, 10.25; N, 2.79. Found: C, 73.69; H, 10.27; N, 2.75.



Scheme 2. Synthesis of the compounds **2a-2c.**

Experimental procedures for Scheme 2.

Reaction A. To a solution of cholesteryl tosylate (3.5 g, 6.47 mmol) in dry 1,4-dioxane (40 ml) di-, tri- or tetraethylene glycol (20 ml) was added and refluxed for about 4 hours under an Ar atmosphere until complete disappearance of the starting material (monitored by TLC). After concentration of the reaction mixture it was dissolved in 75-100 ml of chloroform. Solution was washed 2 times with 100 ml of saturated sodium bicarbonate solution and distilled water (2-3 times, until two layers started to separate quickly) and saturated sodium chloride solution. After separation water layers were extracted with chloroform every time. Combined organic extract was dried with sodium sulfate, evaporated and purified by column chromatography on silica gel ($CHCl_3/Et_2O$, gradient 0-15%; then $CHCl_3/Et_2O$ 5:1 + MeOH, gradient 0-5%). Yields 69-75%.

Reaction B. To a solution of cholesteryl oligoethyleneglycol (1 mmol) in 20 ml of acetone about 1.6 eq. of 2M Jones reagent were added while stirring. The mixture was kept at RT for 40 minutes, then green precipitate was filtered off and solvent evaporated to dryness. Residue was dissolved in chloroform, washed with saturated sodium chloride solution and dried with sodium sulfate, resulting in opaque solution. Then it was filtered through Celite and evaporated to dryness. Final purification of the product was done by the column chromatography on silica gel ($CHCl_3/Et_2O$ 1:1 + MeOH, gradient 0-35%). Yields 61-69%.

Reaction C. To a solution of 0.5 mmol of cholesterol derivative in 5 ml of dry pyridine 0.8 mmol (188 mg) of *p*-nitrophenyltrifluoroacetate were added. The mixture was stirred for 2 days under Ar atmosphere. After that 0.25 ml of water added and the solvent was evaporated to dryness and co-evaporated with heptane several times to get rid of pyridine

traces. Residue was dissolved in 25 ml of chloroform and washed 5 times with deionized water and with saturated sodium chloride solution. Organic layer was dried with sodium carbonate and evaporated; further purification by column chromatography yielded the expected compounds.

Compound 2a. Purified by column chromatography on silica gel ($CHCl_3/Et_2O$, gradient 0-3%), white crystals. Yield – 389 mg (0.638 mmol), 64%. M. p. 87-90°C; TLC: R_f 0.5 ($CHCl_3/Et_2O$, 95:5, silica gel); ^{1}H NMR ($CDCl_3$): δ 0.67-2.41 (m, 43H, H cholesterol), 3.20 (m, 1H, H'-3), 3.72 (m, 2H, CH_2O), 3.82 (m, 2H, CH_2O), 4.48 (s, 2H, OCH_2CO_2), 5.33 (bd, 1H, H'-6), 7.33 (d, 9.3Hz, 2H, C$_6H_4$NO_2), 8.28 (d, 9.3Hz, 2H, C$_6H_4$NO_2); ^{13}C NMR ($CDCl_3$): δ 67.74, 68.88, 71.84 (3CH_2O), 121.86, 125.40 (C$_6$H$_4$NO_2), 168.27 (CO_2Ar). FAB HRMS: calc. for $C_{37}H_{55}O_6NLi^+$ 616.4189, observed 616.4163. Anal. calc. for $C_{37}H_{55}O_6N$ (609.854): C, 72.87; H, 9.09; N, 2.30. Found: C, 72.69; H, 8.99; N, 2.30.

Compound 2b. Purified by column chromatography on silica gel ($CHCl_3/Et_2O$, gradient 0-10%), colorless partially crystallizing syrup. Yield – 371 mg (0.567 mmol), 57%. TLC: R_f 0.3 ($CHCl_3/Et_2O$, 90:10, silica gel); ^{1}H NMR ($CDCl_3$): δ 0.67-2.41 (m, 43H, H cholesterol), 3.18 (m, 1H, H'-3), 3.65 (bs, 4H, 2CH_2O), 3.75 (m, 2H, CH_2O), 3.83 (m, 2H, CH_2O), 4.48 (s, 2H, OCH_2CO_2), 5.32 (bd, 1H, H'-6), 7.32 (d, 9.3Hz, 2H, C$_6H_4$NO_2), 8.28 (d, 9.3Hz, 2H, C$_6H_4$NO_2); ^{13}C NMR ($CDCl_3$): δ 67.48, 68.84, 71.09, 71.19, 71.39 (5CH_2O), 121.72, 125.38, 145.51, 154.92 (C$_6$H$_4$NO_2), 168.23 (CO_2Ar). FAB HRMS: calc. for $C_{39}H_{59}O_7NLi^+$ 660.4452, observed 660.4464. Anal. calc. for $C_{39}H_{59}O_7N$ (653.908): C, 71.64; H, 9.09; N, 2.14. Found: C, 71.90; H, 9.02; N, 2.11.

Compound 2c. Purified by column chromatography on silica gel ($CHCl_3/Et_2O$, gradient 0-15%), colorless syrup. Yield – 386 mg (0.553 mmol), 55%. TLC: R_f 0.15 ($CHCl_3/Et_2O$,

90:10, silica gel); ^{1}H NMR ($CDCl_3$): δ 0.67-2.41 (m, 43H, H cholesterol), 3.16 (m, 1H, H'-3), 3.63 (bs, 4H, 2CH_2O), 3.67 (bs, 4H, 2CH_2O), 3.74 (m, 2H, CH_2O), 3.83 (m, 2H, CH_2O), 4.47 (s, 2H, OCH_2CO$_2$), 5.32 (bd, 1H, H'-6), 7.33 (d, 9.3Hz, 2H, C$_6H_4$NO$_2$), 8.28 (d, 9.3Hz, 2H, C$_6H_4$NO$_2$); ^{13}C NMR ($CDCl_3$): δ 67.51, 68.81, 70.81, 70.87, 71.02, 71.12, 71.42 (7CH$_2$O), 121.68, 125.39, 145.51, 154.90 (C_6H$_4$NO$_2$), 168.20 (CO$_2$Ar). FAB HRMS: calc. for $C_{41}H_{63}O_8NLi^+$ 704.4714, observed 704.4685. Anal. calc. for $C_{41}H_{63}O_8N$ (697.961): C, 70.56; H, 9.10; N, 2.01. Found: C, 70.28; H, 9.26; N, 1.92.

Table 1. Summary of Unpublished Rates for Compounds 2b and 2c.

	10^3[hydroxamate], mol/l[b]	10^4[ester], mol/l[c]	pH	k_{obs}, min^{-1} [d]
2b$_{ves}$, buffer	-	1.0	9.0	$3.1x10^{-3}$
2c$_{ves}$, buffer	-	1.0	9.0	$2.8x10^{-3}$
AH + **2b**$_{ves}$	1.0	1.0	9.0	$6.6x10^{-2}$
AH + **2c**$_{ves}$	1.0	1.0	9.0	$7.4x10^{-2}$
AH + **2b**$_{ves}$	0.10	1.0	9.0	$1.1x10^{-2}$
AH + **2c**$_{ves}$	0.10	1.0	9.0	$1.2x10^{-2}$
1$_{ves}$ + **2b**$_{ves}$	0.10	0.50	9.0	$4.4x10^{-3}$
1$_{ves}$ + **2c**$_{ves}$	0.10	0.50	9.0	$4.9x10^{-3}$
(**1** + **2b**)$_{ves}$	0.10	0.50	8.0[e]	1.9 (stage1) $8.4x10^{-2}$ (stage2)
(**1** + **2c**)$_{ves}$	0.10	0.50	8.0[e]	2.0 (stage1) $5.9x10^{-2}$ (stage2)