Encapsulation of 5-Fluorouracil in Cholesteryl-Modified Cyclodextrin: Thermal, Spectral, and Computational Assessment of Drug Inclusion Efficiency

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Electronic Supplementary Information

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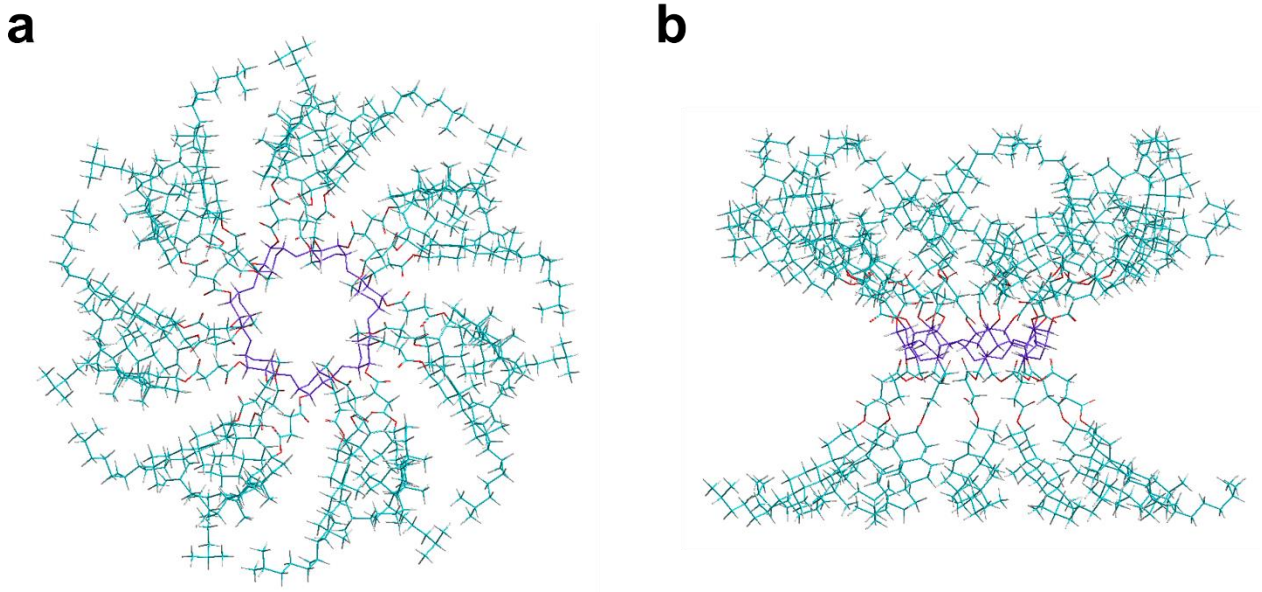

Fig. S1 The initial structure of the CD21chol molecule used to create other conformers: a) top view, b) side view. The CD ring is marked in violet, while atom colors in cholesteryl-containing moieties are carbon - cyan, oxygen - red, and hydrogen – grey.

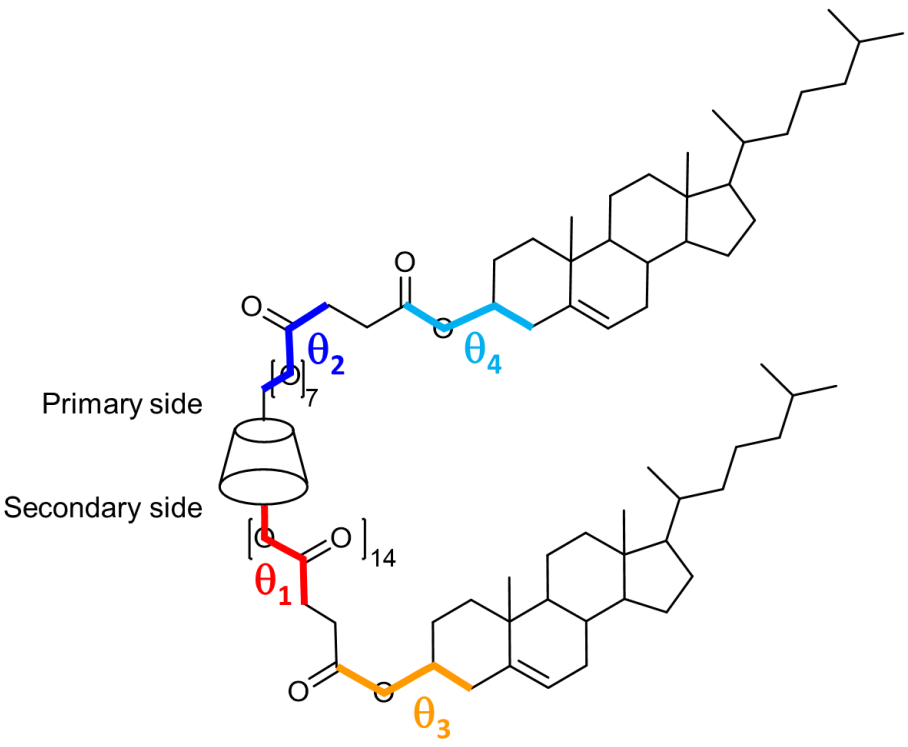

Fig. S2 The torsion angles in the CD21chol molecule varied in the molecular mechanics' conformational search.

Procedure S1

Initial search for low-energy conformers of CD21chol

In the initial structure shown in Fig. S1, two sets of substituents were distinguished: the first consisting of seven cholesteryl moieties on the CD's primary (narrower) side and the second consisting of fourteen groups on the secondary (wider) side. In each substituent within a given set, two torsion angles were selected, which were responsible for the rotation of the entire group or only its fragment (Fig. S2). Next, in the Hyperchem program [RS1], each selected torsion angle was varied by 45° in the 0-360° range, independently on the other three angles, with rotation within each set co-occurring. This way, 4096 structures were created, which were then fully optimized with the force field BIO+ available in the Hyperchem program. The BIO+ was used with the newest parameter set charmm27 available in Hyperchem. This is the biomolecular force field developed to study macromolecules, such as lipids, proteins and nucleic acids [RS2]. All these structures were re-optimized with the semiempirical PM7 method in vacuo and the MOZYME procedure using the program MOPAC [RS3]. After optimization, incorrect geometries (for example, with non-physical positions of some fragments relative to others) were eliminated. From the remaining 1793 structures, the conformer having the lowest heat of formation was selected and used as the initial structure in the first energy scan for the complex 1:1 described in Procedure S2a.

Procedure S2

a) Energy scans were performed for the complex of the 5-FU monomer with CD21chol

To study the 1:1 complex, seven different orientations of 5-FU with respect to CD21chol were considered (Fig. 1a in the main article): one with the 5-FU plane parallel to the β-CD ring and six with the drug plane perpendicular to it. For each orientation, the drug was placed on the Z-axis and moved along this axis upward or downward between −10 and 30 Å (in steps of 0.2 Å), as shown in Fig. 1a in the main article. At each step, the CD21chol structure in the complex was fully optimized, except for three oxygen atoms in the CD ring, which were frozen in order to preserve the relative positions of CD21chol and 2-FU, using the semiempirical method PM7 in vacuo and the MOZYME procedure. Additionally, after each scan, the CD21chol structures corresponding to the local minima and end points in the scans were extracted from the complex and re-optimized to examine whether some lower energy conformer could be found. In such a case, all scans were conducted again with the new structure of CD21chol. This procedure was repeated five times until the energy profiles were consistent and no lower energy conformer of CD21chol was obtained.

b) Energy scans were performed for the complex of the $(5\text{-FU})_2$ dimer with CD21chol

The scans for the complex with the $(5\text{-FU})_2$ dimer were conducted similarly to the 1:1 complexes, using as the host the most stable structure of CD21chol found from the calculations for the 5-FU monomer. For the dimer, its initial structure was the geometry reported earlier in the literature [RS4,RS5] as the lowest energy configuration (denoted in ref. RS5 as $A_{1\text{-}2}$-$A_{1\text{-}2}$) obtained with the TPSSTPSS functional and the 6-311+G(d,p) basis set. To maintain the consistency of the method used in the present work, the dimer structure was optimized using the PM7 method in vacuo. The structure of the dimer is planar. Therefore, its plane was set perpendicular to the CD ring, with the first 5-FU molecule closer and the second further away from CD21chol, as shown in Fig. 1b in the main article. The closer 5-FU was placed at -10 and 30 Å, and the upward and downward energy scans were performed using two different approaches. Only the first 5-FU molecule, closer to CD21chol, was moved in the first approach. Its coordinates were frozen, while the remaining part of the system, including the second 5-FU, was optimized (DIM1 case). In the second approach, the entire dimer $(5\text{-FU})_2$ was moved downward or upward along the Z-axis with its structure frozen. Thus, only the structure of CD21chol was optimized at each step (DIM2 case). In both cases, the z-positions of three oxygen atoms belonging to the CD ring were frozen during optimization to preserve the relative positions of the host and drug along the Z-axis. Since in these scans, the dimer position was defined by

the z-coordinate of the center of mass of the first 5-FU molecule, in order to allow the second 5-FU to leave the host, the final position in each direction was set more distant from CD21chol than in the scans for monomer.

a) Energy scans performed for the 5-FU monomer approaching the complex CD21chol:(5-FU)$_2$

The scans for the 1:3 complex were carried out according to principles similar to those used in the previous calculations, except that the most stable 1:2 complex found in the previous research stage was used as the host (Fig. 1c in the main article). Since the terminal F and O atoms in the dimer have a partial negative charge, the orientation of the monomer was chosen in which the adjacent hydrogens with a partial positive charge (H-C and H-N) were directed towards the dimer, and its plane was parallel to the plane of the closer 5-FU from the dimer. For each such initial configuration, two monomer orientations were tested: the one shown in Fig. 1c and marked in the article as x, in which electrostatically attractive monomer-dimer N-H...F-C and C-H...O=C interactions are possible, and the second one, marked as y, with the monomer rotated around the Z axis by 180°, thus enabling the monomer-dimer N-H...O=C and C-H...F-C interactions.

b) Formulas used in the calculations of the complexation enthalpies

The final complexation enthalpies H_{compl} for the complex with 5-FU monomer were calculated according to the formula:

$$H_{\mathrm{compl}} = H^{\mathrm{OPT}}_{\mathrm{host:drug}} - \left(H^{\mathrm{OPT}}_{\mathrm{host}} + H^{\mathrm{OPT}}_{\mathrm{drug}}\right) \quad (1)$$

where $H^{\mathrm{OPT}}_{\mathrm{host:drug}}$, $H^{\mathrm{OPT}}_{\mathrm{host}}$ and $H^{\mathrm{OPT}}_{\mathrm{drug}}$ are, respectively, the heats of formation of the fully optimized complex and its isolated components.

For the complex 1:2 with two monomers, the complexation enthalpy was calculated as:

$$H_{\mathrm{compl}}(\mathrm{I/NI}) = H^{\mathrm{OPT}}_{\mathrm{host:2drugs}} - \left(H^{\mathrm{OPT}}_{\mathrm{host}} + 2H^{\mathrm{OPT}}_{\mathrm{drug}}\right) \quad (2)$$

while for the complexes with the dimer (5-FU)$_2$:

$$H_{\mathrm{compl}}(\mathrm{DIMER}) = H^{\mathrm{OPT}}_{\mathrm{host:dimer}} - \left(H^{\mathrm{OPT}}_{\mathrm{host}} + H^{\mathrm{OPT}}_{\mathrm{dimer}}\right) \quad (3)$$

The total enthalpy of complexation of both dimer and monomer by CD21chol was obtained using to the formula:

$$H_{\mathrm{compl}}(\mathrm{TRIMER}) = H^{\mathrm{OPT}}_{\mathrm{host:(5-FU)_3}} - \left(H^{\mathrm{OPT}}_{\mathrm{host}} + H^{\mathrm{OPT}}_{\mathrm{dimer}} + H^{\mathrm{OPT}}_{\mathrm{5-FU}}\right) \quad (4)$$

while the enthalpy of complexation of the monomer by the complex CD21chol:dimer was calculated as:

$$H_{\mathrm{compl}}(\mathrm{MONtoDIM1}) = H^{\mathrm{OPT}}_{\mathrm{host:(5-FU)_3}} - \left(H^{\mathrm{OPT}}_{\mathrm{host:dimer}} + H^{\mathrm{OPT}}_{\mathrm{5-FU}}\right) \quad (5)$$

For the 1:4 complex I/NI with two dimers the following formula was used:

$$H_{\mathrm{compl}}(\mathrm{2DIM}) = H^{\mathrm{OPT}}_{\mathrm{host:(5-FU)_4}} - \left(H^{\mathrm{OPT}}_{\mathrm{host}} + 2H^{\mathrm{OPT}}_{\mathrm{dimer}}\right) \quad (6)$$

while the enthalpy of complexation of the dimer by the complex CD21chol:dimer was calculated as:

$$H_{\mathrm{compl}}(\mathrm{dimer\_toDIM1}) = H^{\mathrm{OPT}}_{\mathrm{host:(5-FU)_4}} - \left(H^{\mathrm{OPT}}_{\mathrm{host:dimer}} + H^{\mathrm{OPT}}_{\mathrm{dimer}}\right) \quad (7)$$

The DFT complexation energies E_{compl} were obtained from the SP DFT energies using similar formulas.

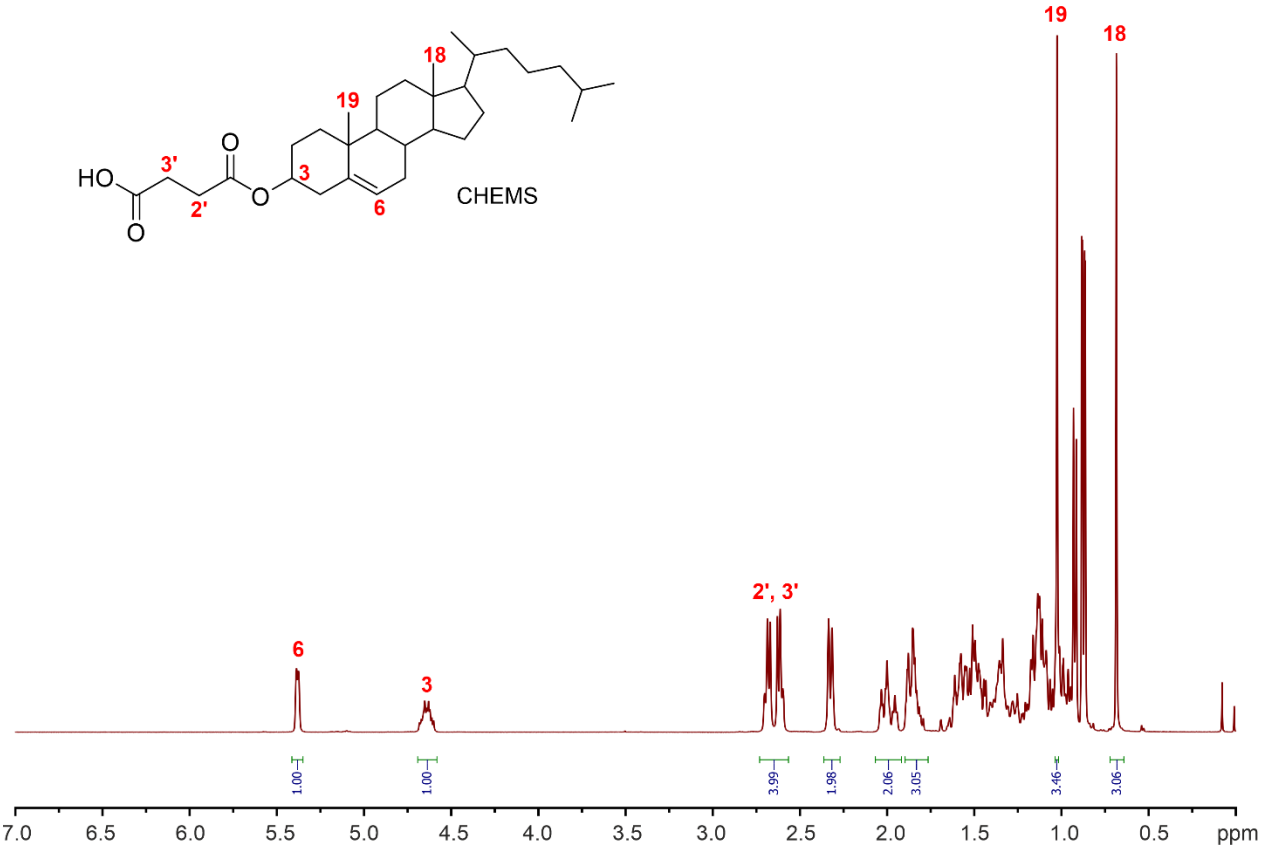

Fig. S3 ^{1}H NMR (400 MHz, $CDCl_3$) of CHEMS.

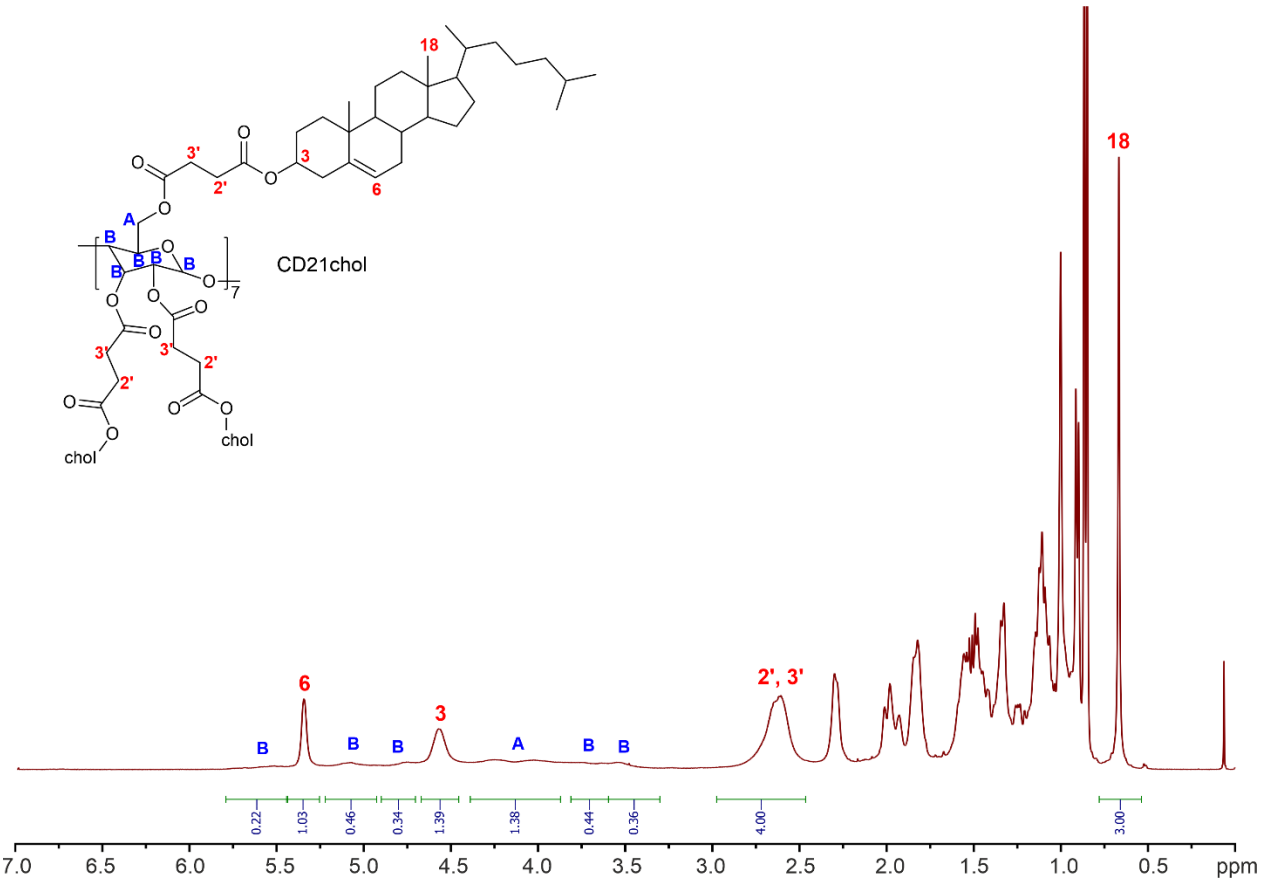

Fig. S4 ^{1}H NMR (400 MHz, $CDCl_3$) of CD21chol. The signal from protons in position 3 was chosen for comparison because it occurs on the same hill as signals from protons from the CD core. Its integration is subject to a similar error, which can be seen in contrast to the CHEMS' 1H NMR spectrum; this signal has an overestimated integral compared to the others. There are 21 of these protons, and their integration calculated for 49 protons (because there are so many A and B protons in the entire molecule) gives a value of 3.24. This value correlates with the sum of the integration of signals A and B, which is 3.20. This proves that a derivative with modified 21 arms has been obtained.

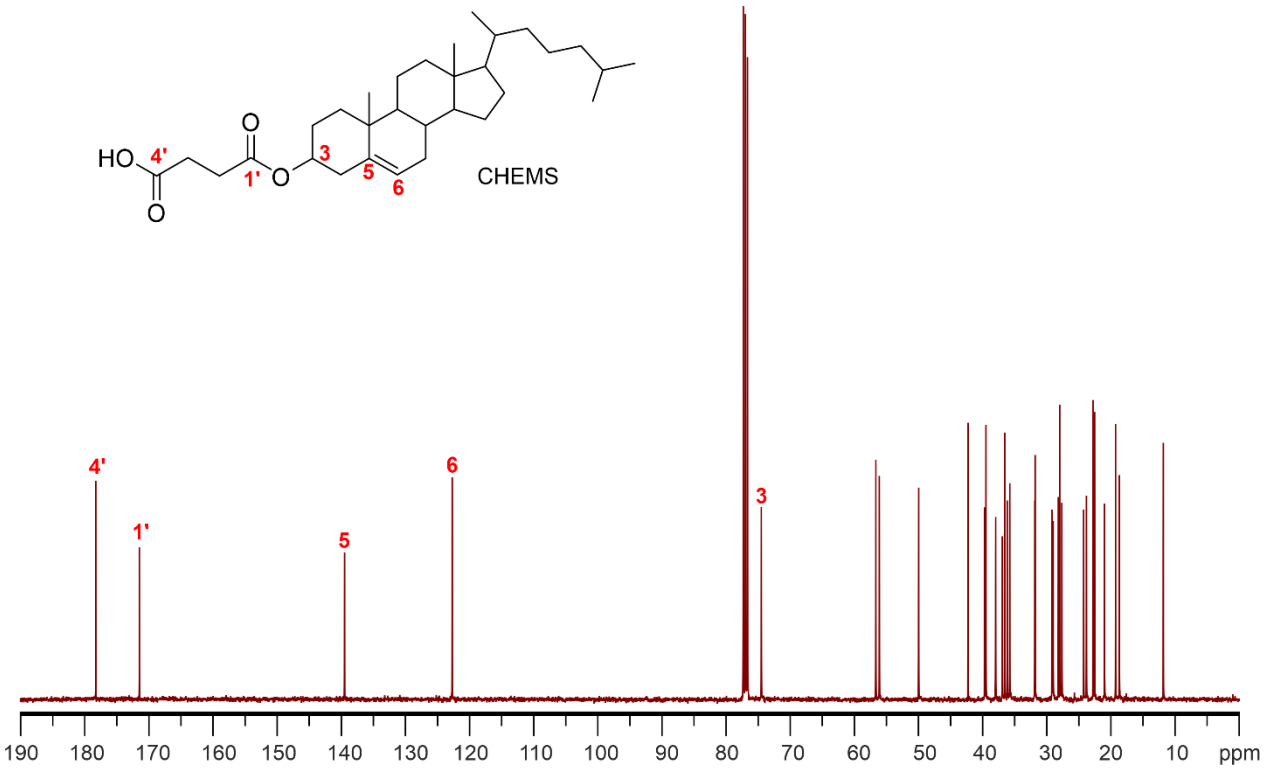

Fig. S5 ^{13}C NMR (100 MHz, $CDCl_3$) of CHEMS.

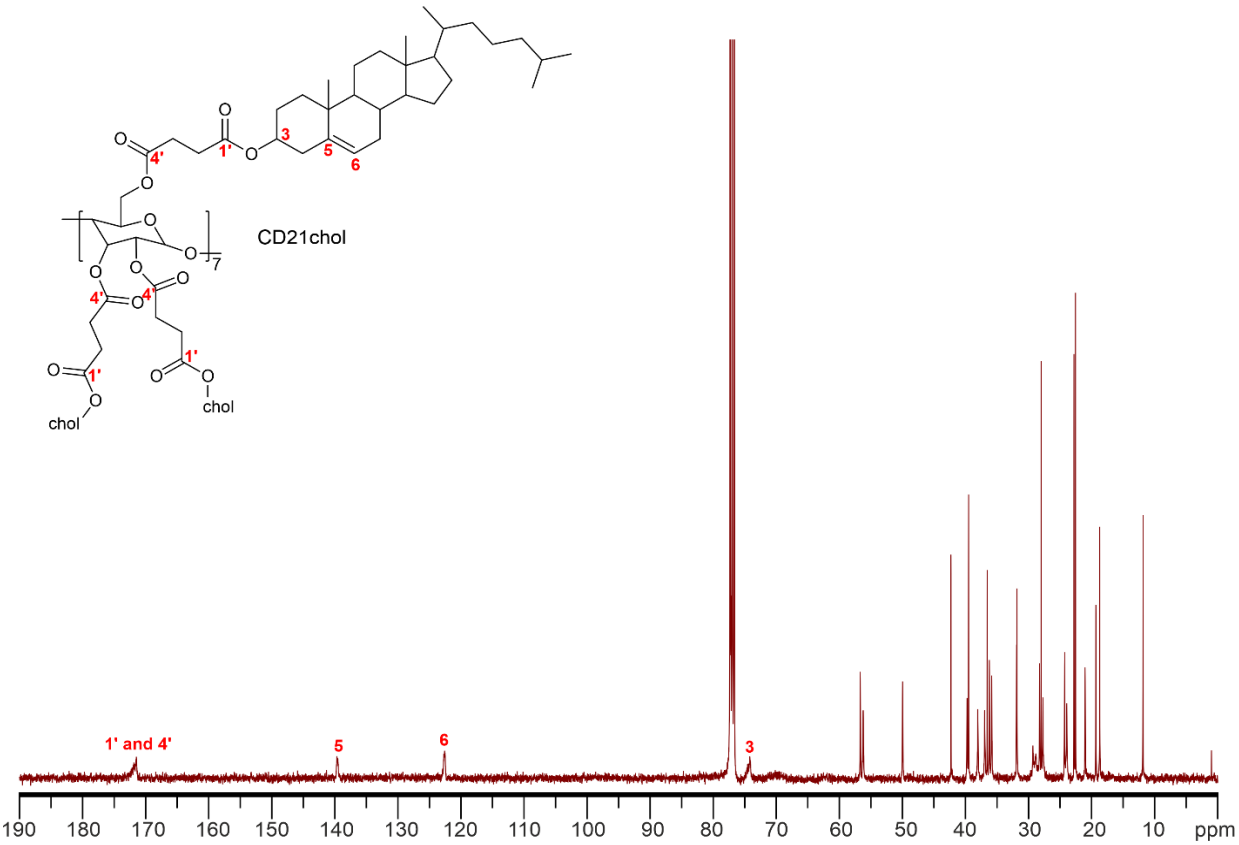

Fig. S6 ^{13}C NMR (100 MHz, $CDCl_3$) of CD21chol.

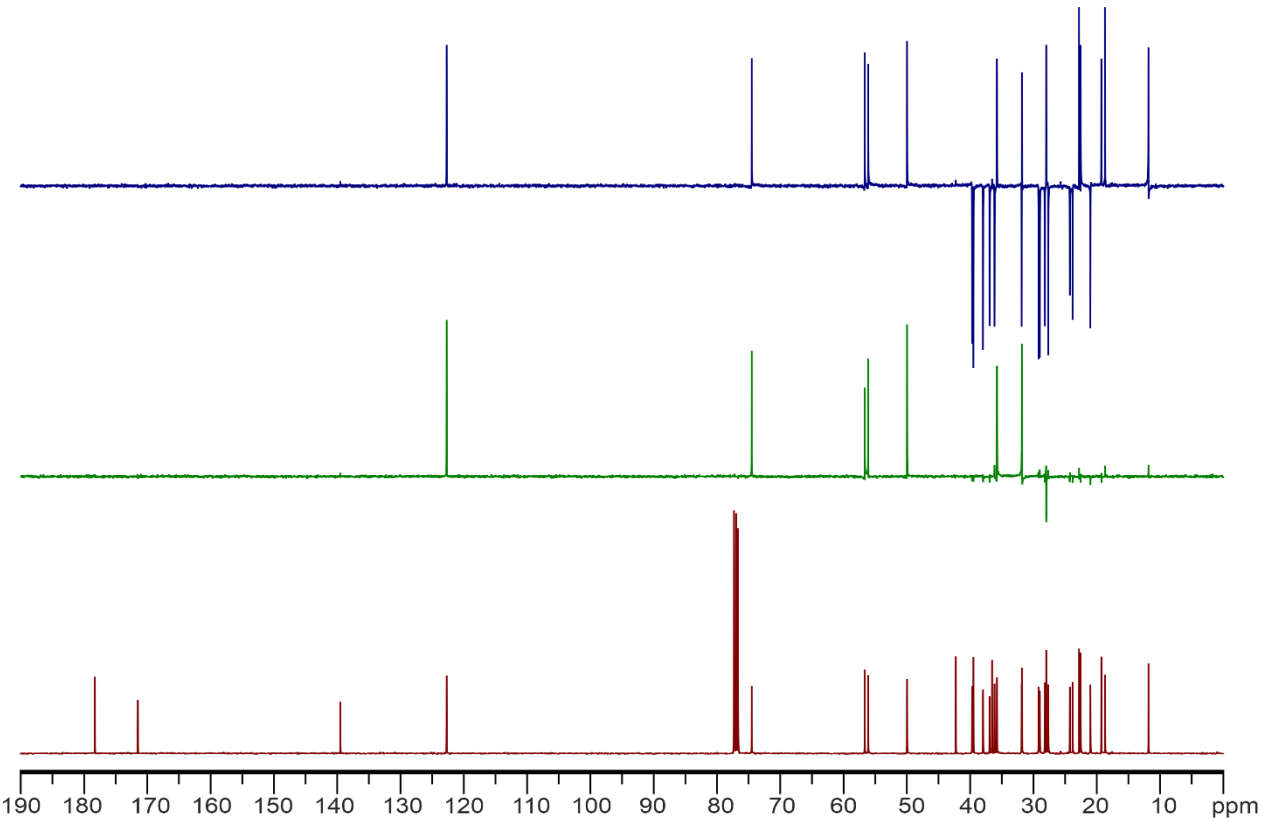

Fig. S7 ^{13}C NMR spectrum (bottom) with pulse angles of 135 (top) and 90 (middle) degrees of CHEMS.

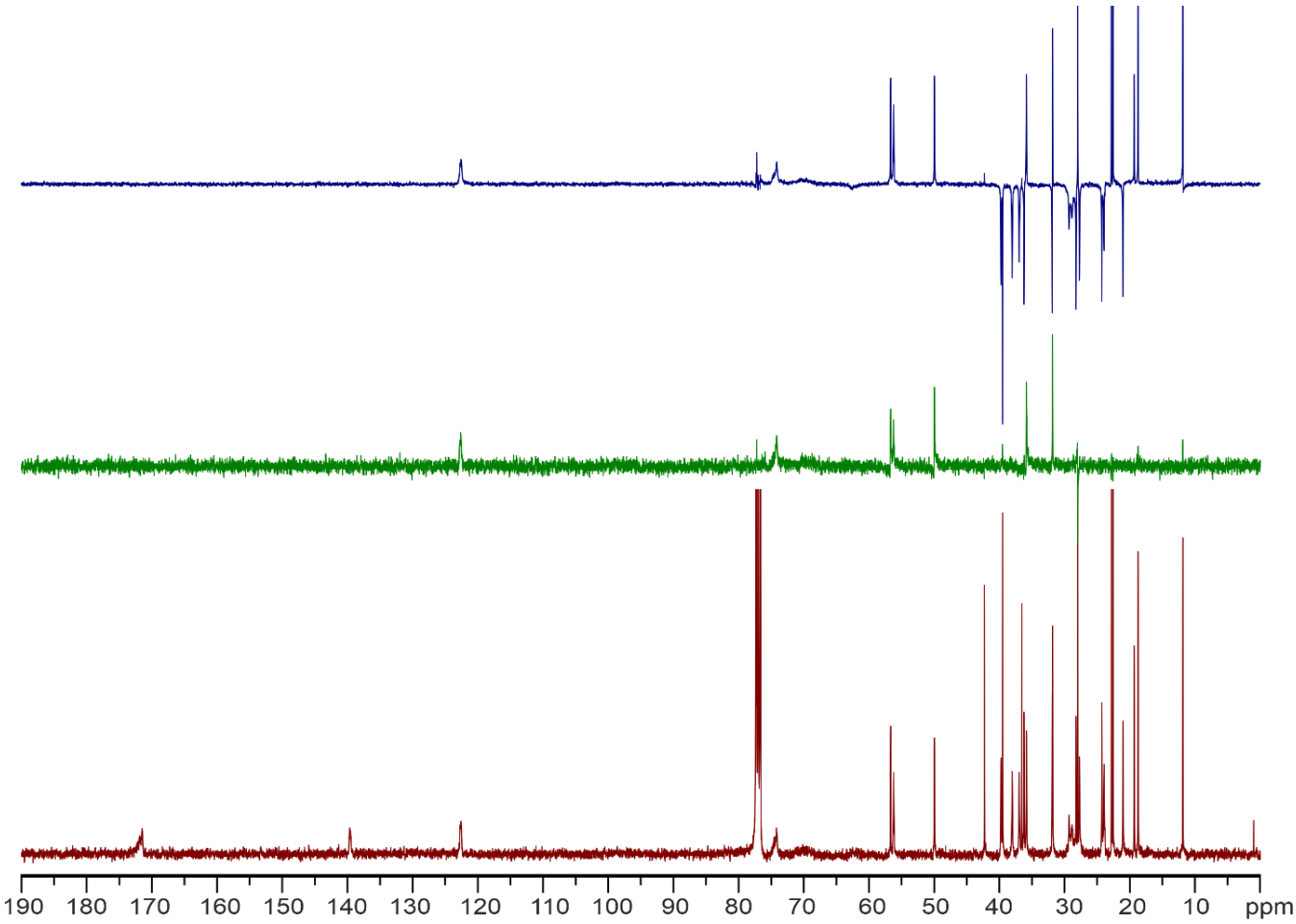

Fig. S8 ^{13}C NMR spectrum (bottom) with pulse angles of 135 (top) and 90 (middle) degrees of CD21chol.

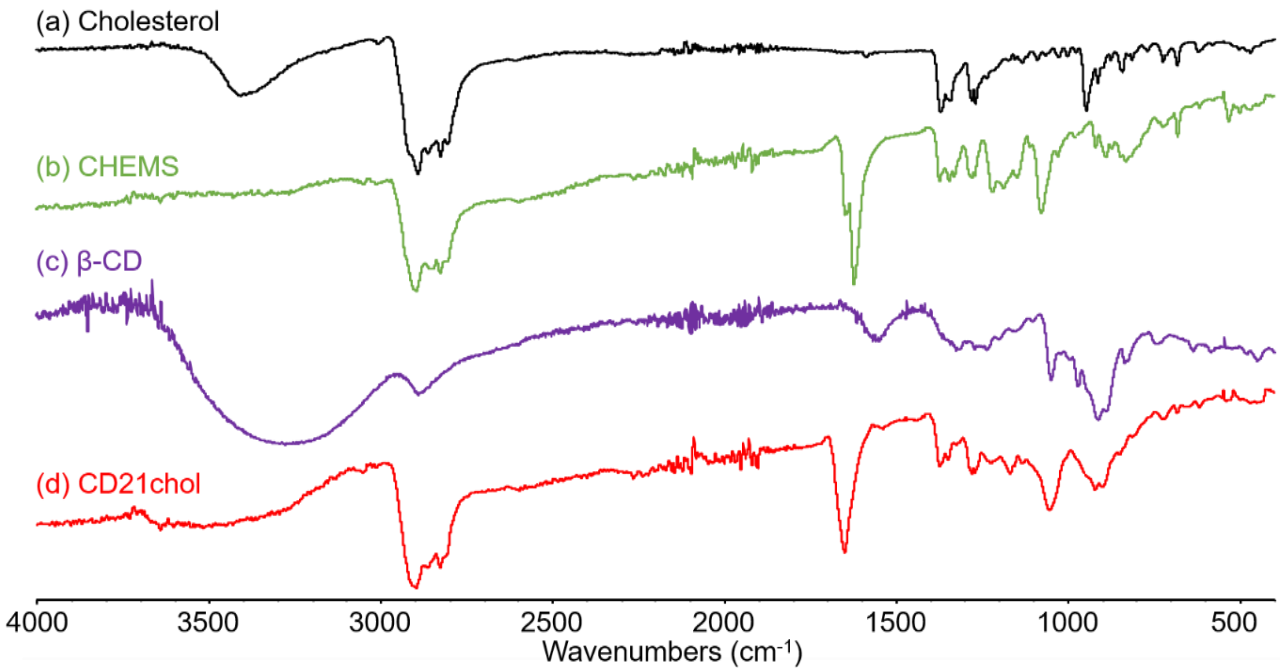

Fig. S9 Stacked ATR-FTIR spectra of (a) cholesterol, (b) CHEMS, (c) β-CD, and (d) CD21chol.

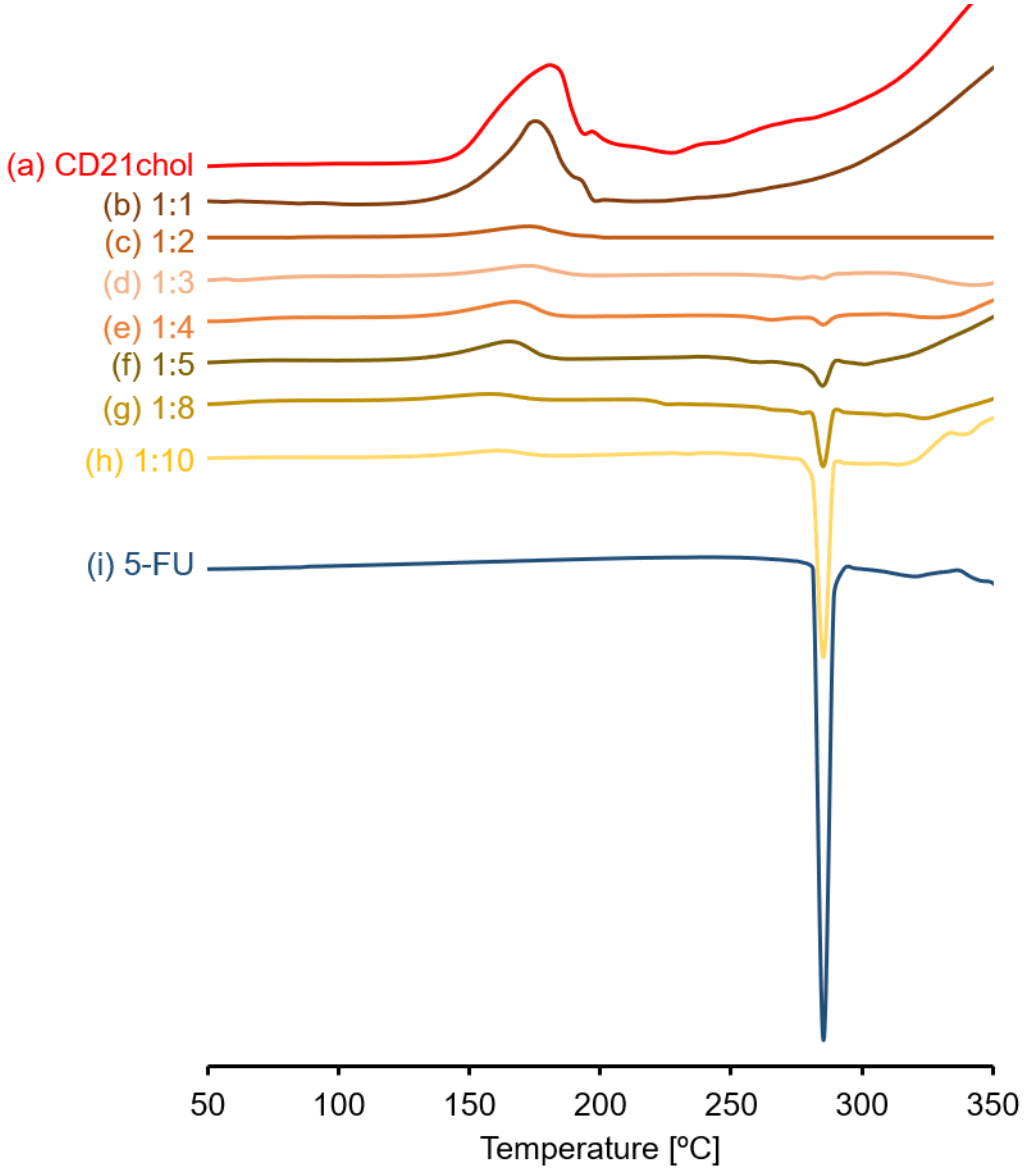

Fig. S10 DSC curves of (a) CD21chol, (b-h) physical mixtures of CD21chol and 5-FU in different molar ratios, and (i) 5-FU.

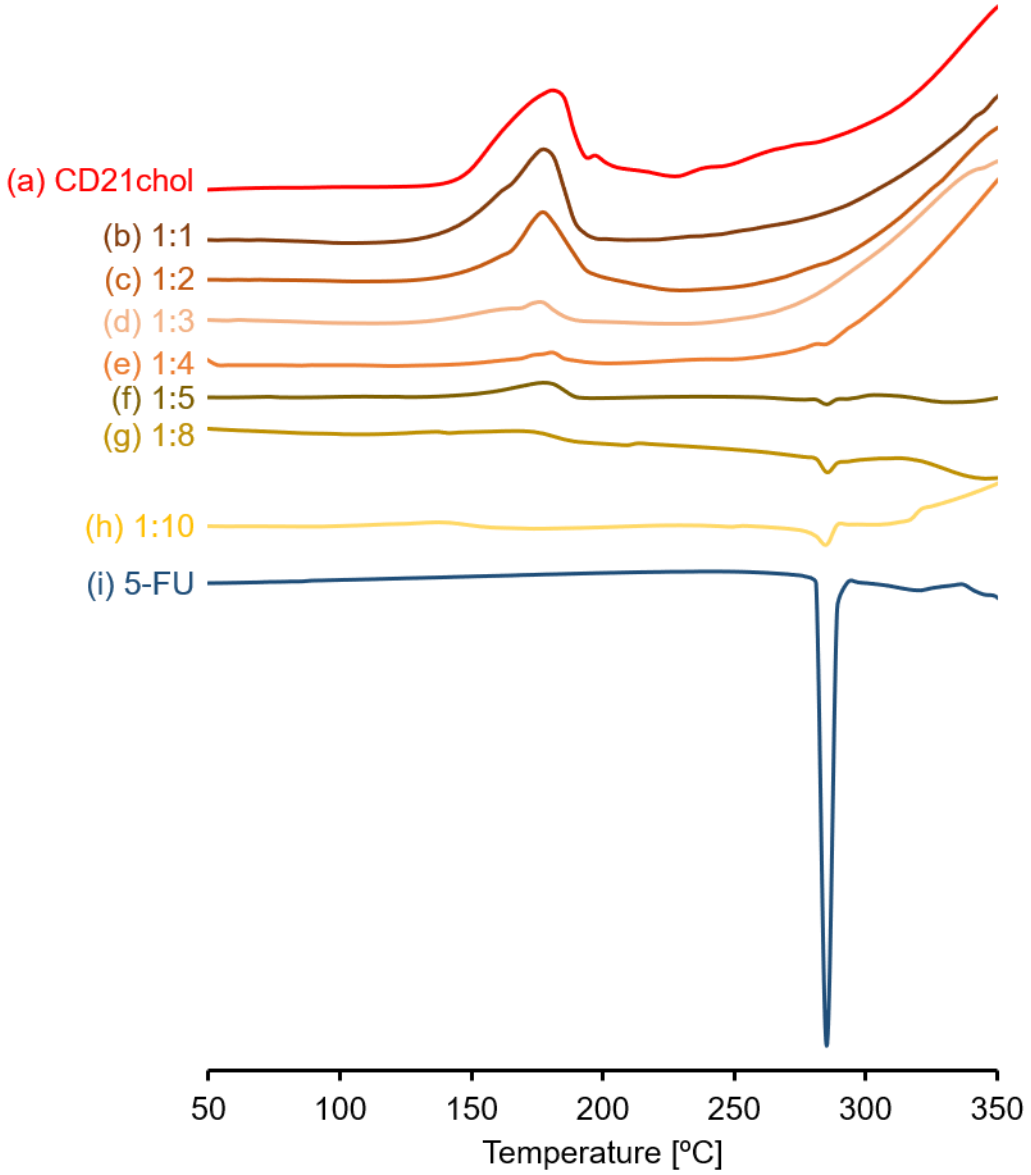

Fig. S11 DSC curves of (a) CD21chol, (b-h) dried solutions after complexation of CD21chol and 5-FU in different molar ratios, and (i) 5-FU.

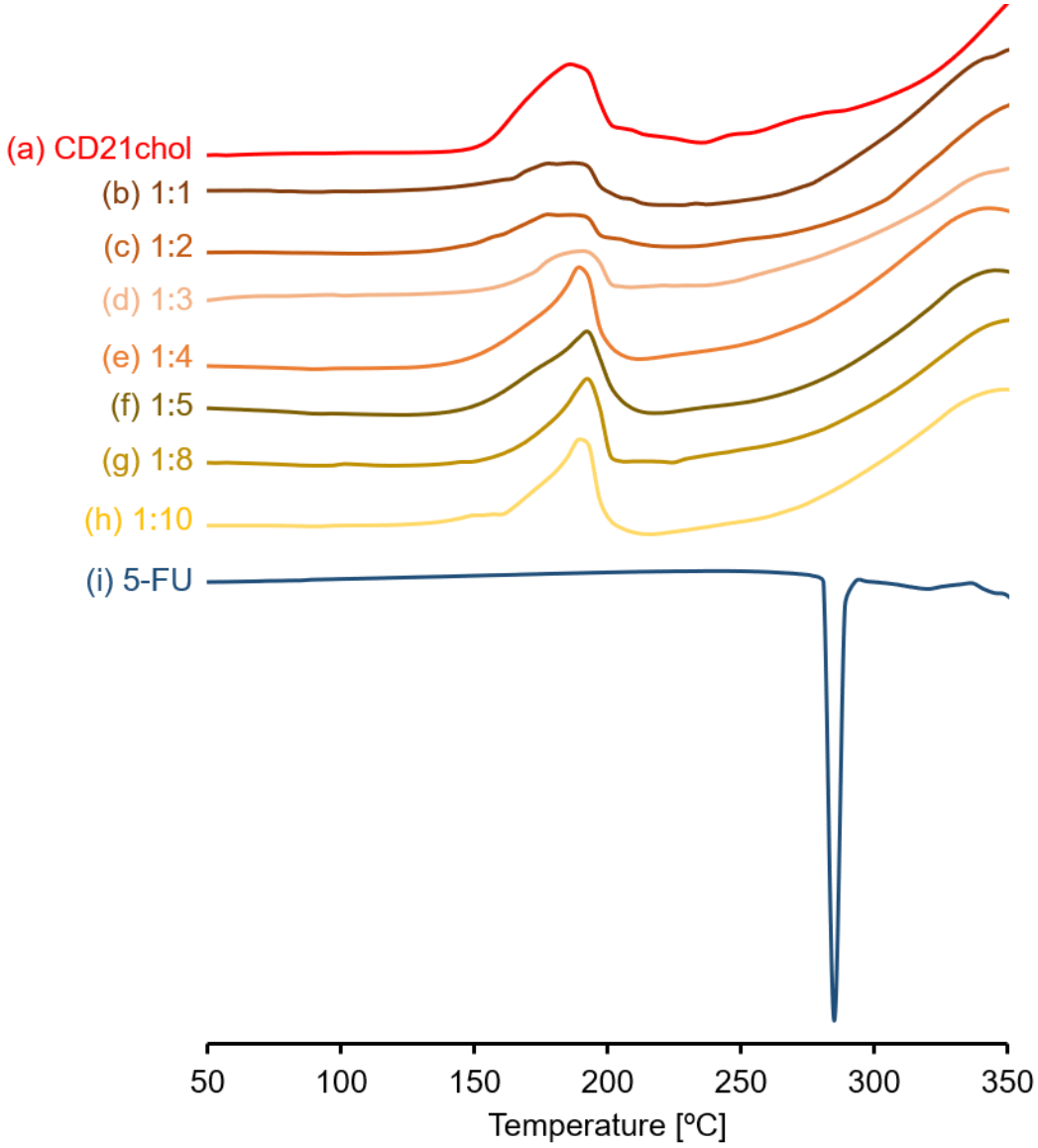

Fig. S12 DSC curves of (a) CD21chol, (b-h) CD21chol, and 5-FU complexes obtained from solutions of different molar ratios, and (i) 5-FU.

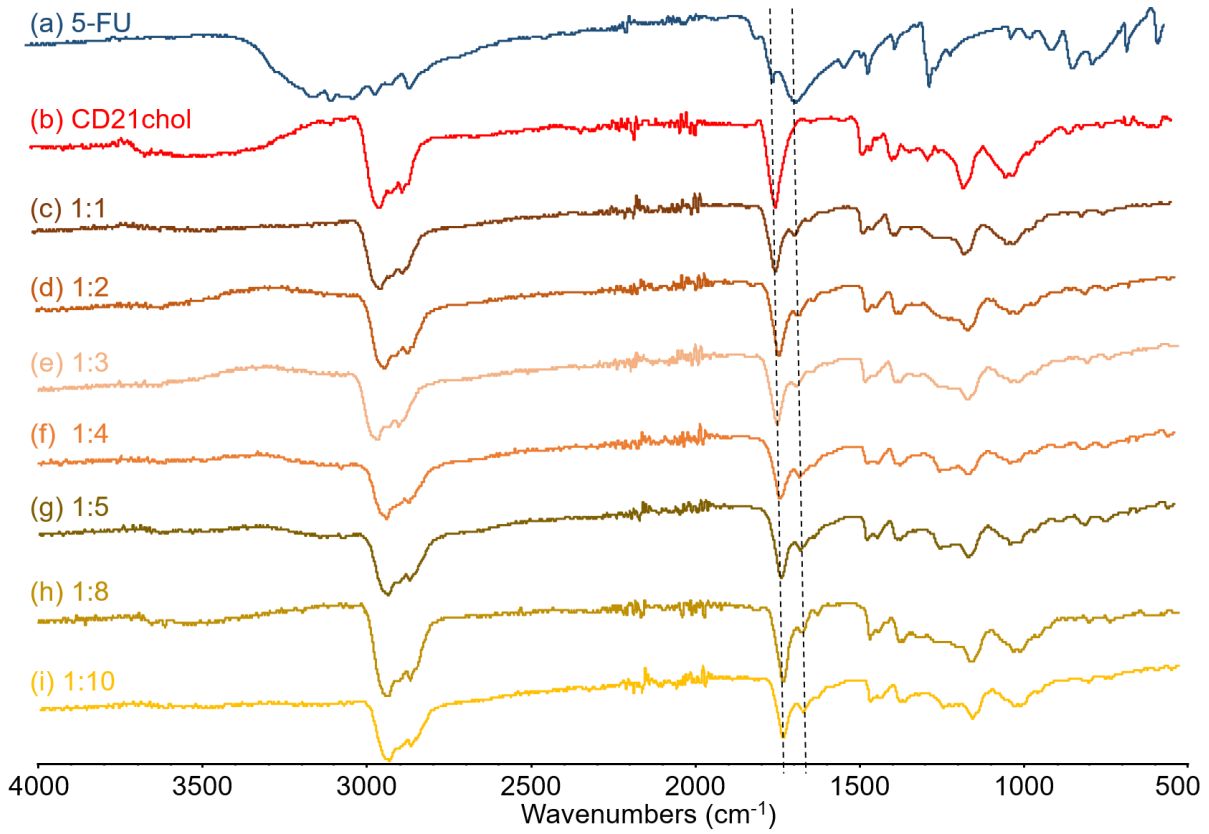

Fig. S13 Stacked ATR-FTIR spectra of (a) 5-FU, (b) CD21chol, and (c-i) physical mixtures of CD21chol and 5-FU in different molar ratios.

Table S1 Reflectance intensity ratios of $C=O_{ester}$ to $C=O_{amide}$ for different molar ratios of CD21chol and 5-FU in physical mixtures and solutions after complexation.

Molar ratios		1:1	1:2	1:3	1:4	1:5	1:8	1:10
Reflectance ratios of $C=O_{ester}/C=O_{amide}$	Physical mixtures	1.45	1.42	1.40	1.36	1.35	1.23	1.19
	solution	n.d.	n.d.	n.d.	2.41	2.02	1.73	1.15

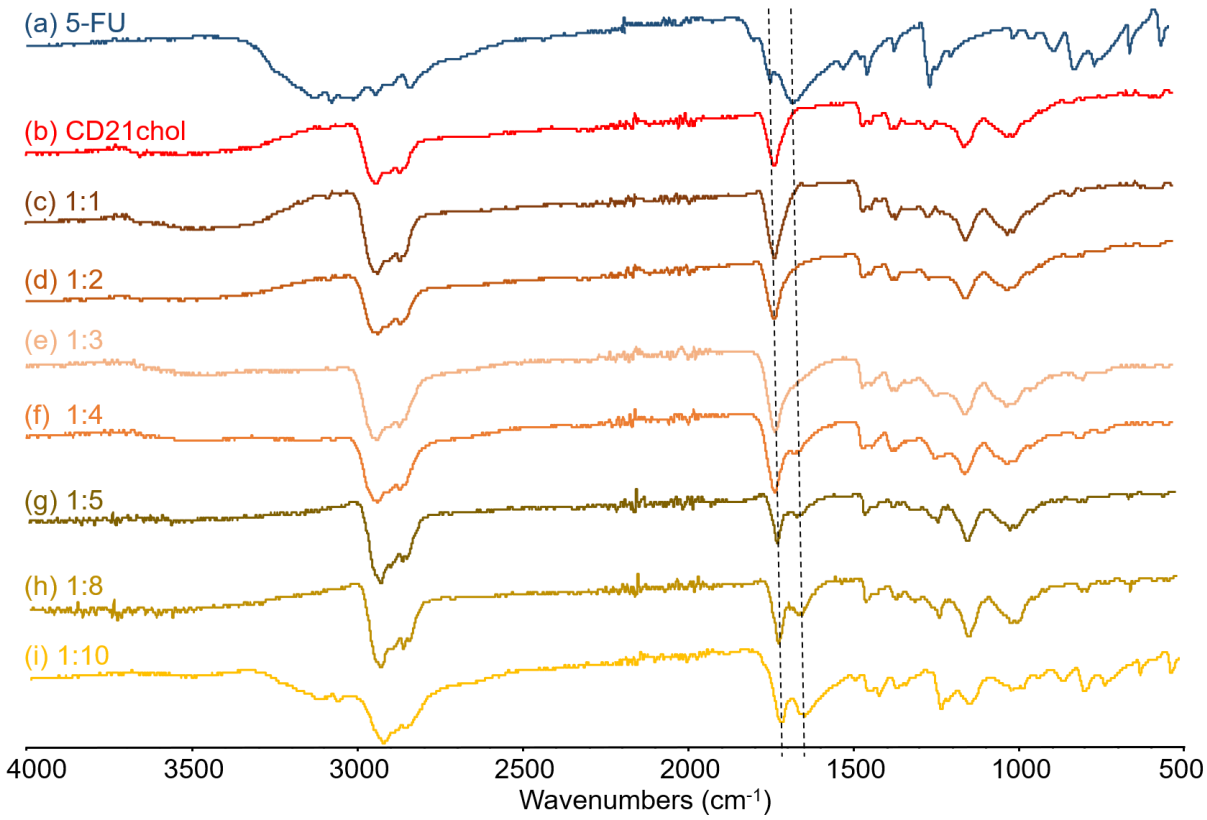

Fig. S14 Stacked ATR-FTIR spectra of (a) 5-FU, (b) CD21chol, and (c-i) dried solutions after complexation of CD21chol and 5-FU in different molar ratios.

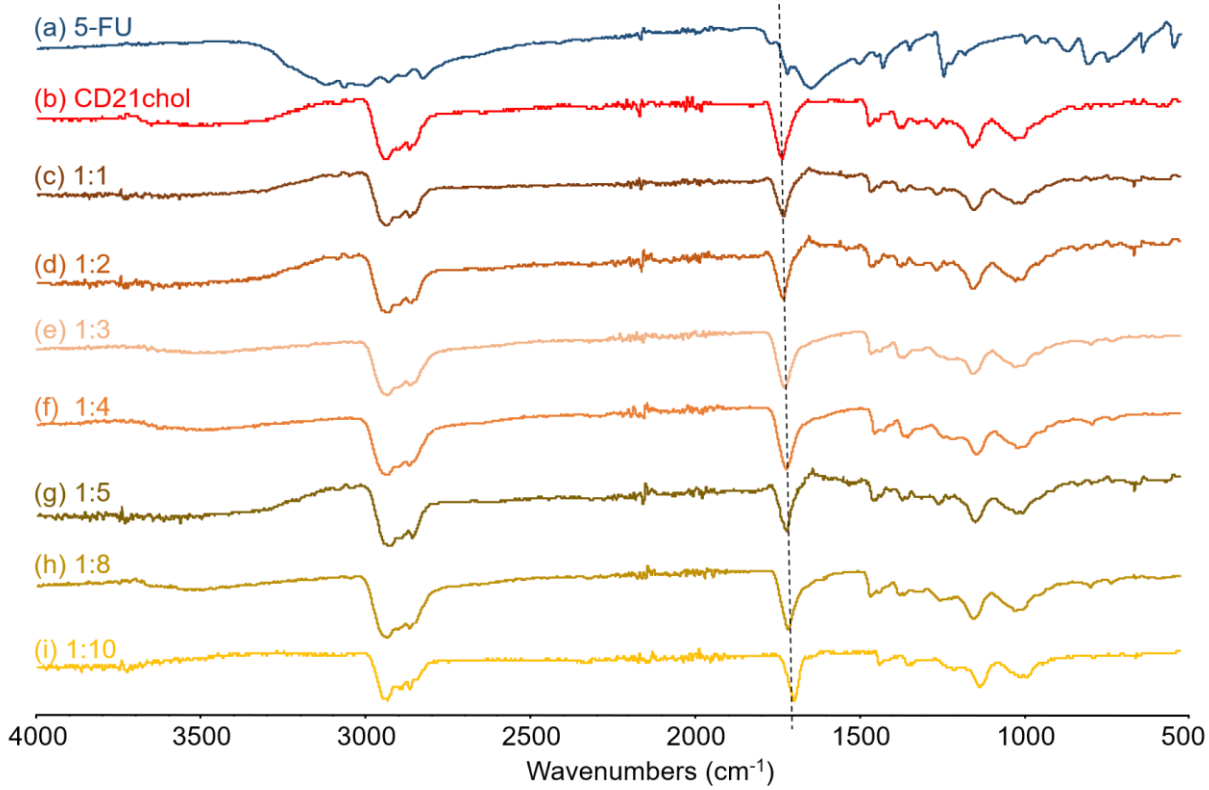

Fig. S15 Stacked ATR-FTIR spectra of (a) 5-FU, (b) CD21chol, and (c-i) CD21chol and 5-FU complexes obtained from solutions of different molar ratios.

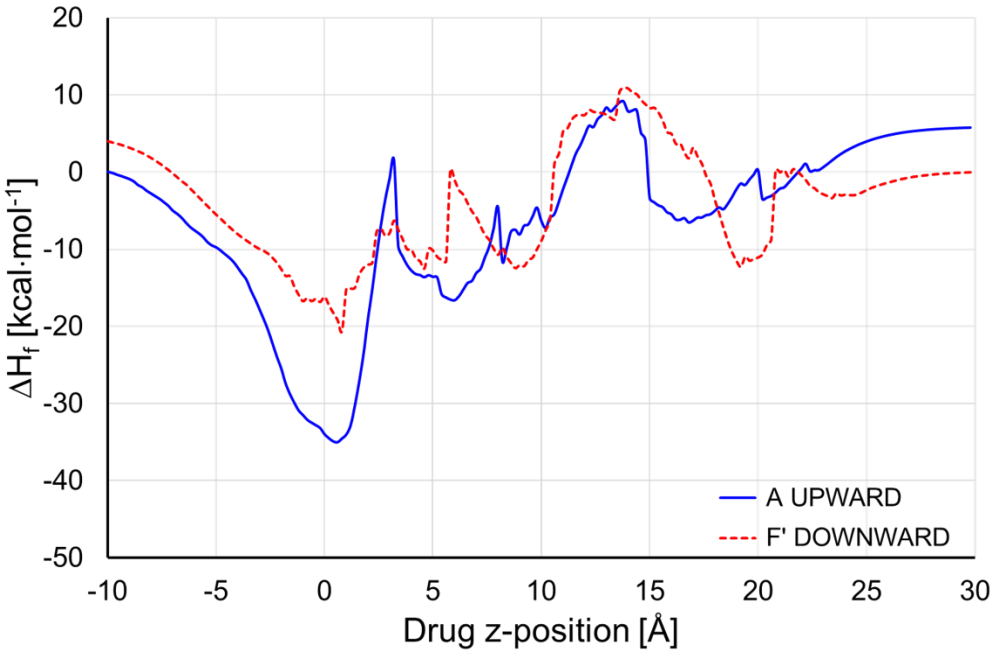

Fig. S16 Plots of relative changes in the heat of formation ΔH_f as a function of the z-position of 5-FU (its center of mass), obtained from the PM7 scans for the complex CD21chol:5-FU in stoichiometry 1:1. The results are shown for two orientations of the drug: A in the upward scan and F' in the downward scan. The CD ring of CD21chol is set at z=0 Å.

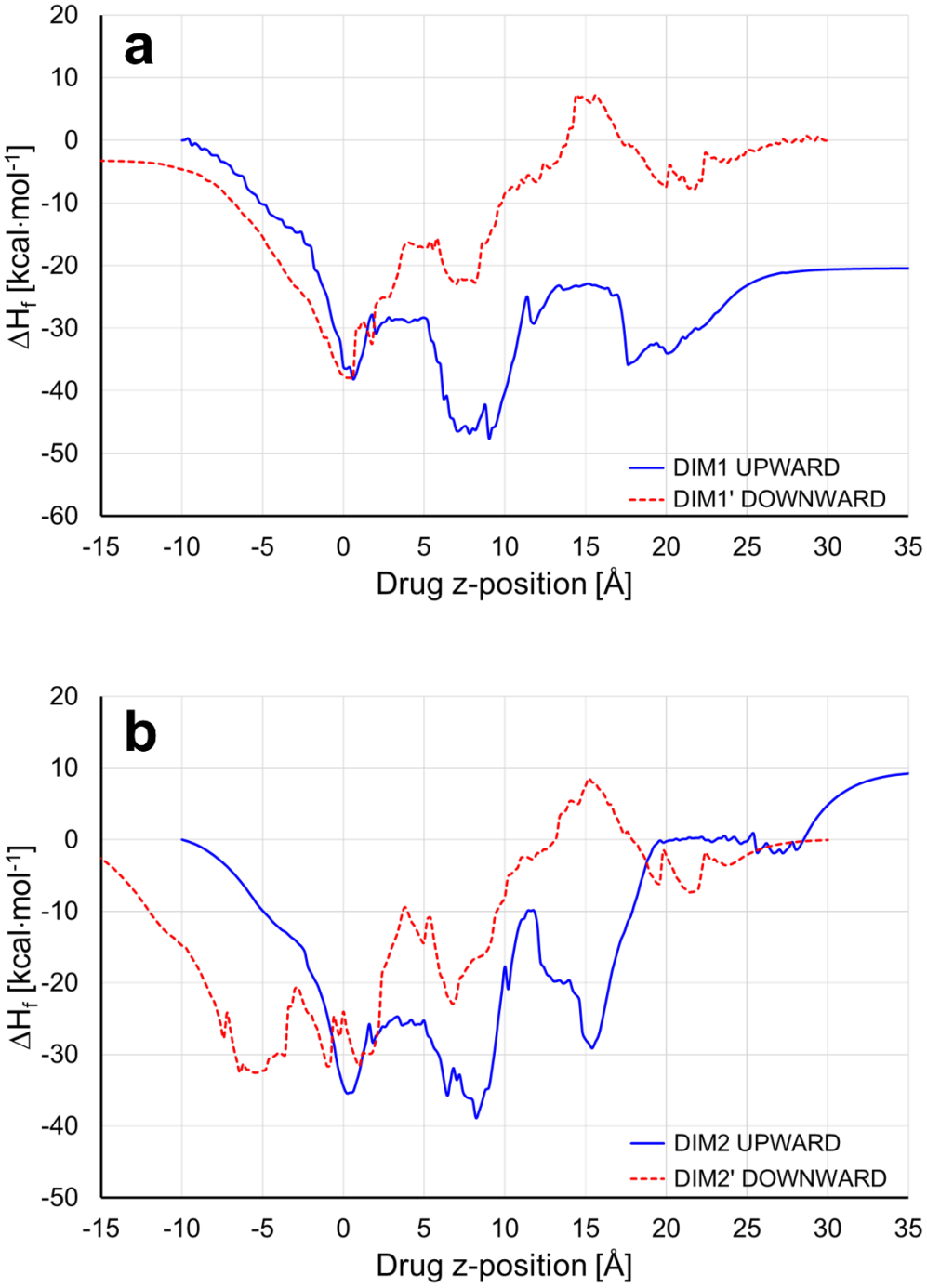

Fig. S17 Plots of relative changes in the heat of formation ΔH_f as a function of the z-position of 5-FU, obtained from the PM7 scans for the complex of CD21chol with the $(5\text{-FU})_2$ dimer, when: a) only one 5-FU (closer to CD21chol) from the dimer was moved and the second one could adjust its position and orientation, b) the entire dimer was moved. The CD ring of CD21chol is set at z=0 Å, and the drug position is defined by the z-coordinate of the center of mass of the 5-FU molecule closer to CD21chol.

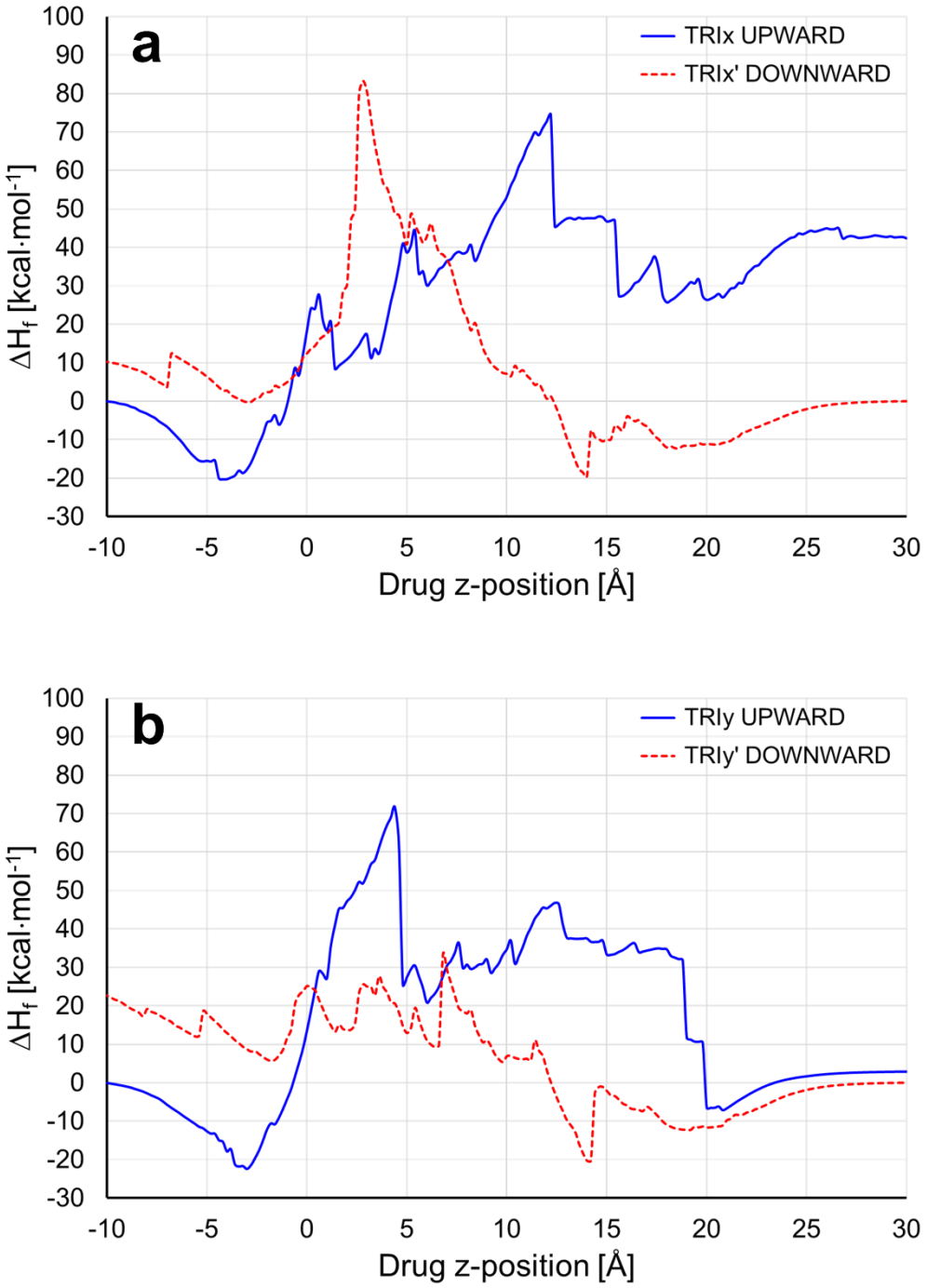

Fig. S18 Plots of relative changes in the heat of formation ΔH_f as a function of the z-position of the 5-FU monomer obtained from the PM7 upward and downward scans performed for the 5-FU monomer approaching the most stable configuration (DIM1-I2) of the complex of CD21chol:$(5\text{-FU})_2$. The scans were performed for two different orientations of the monomer with respect to the dimer: x (a) and y (b), as described in Procedure S2c.

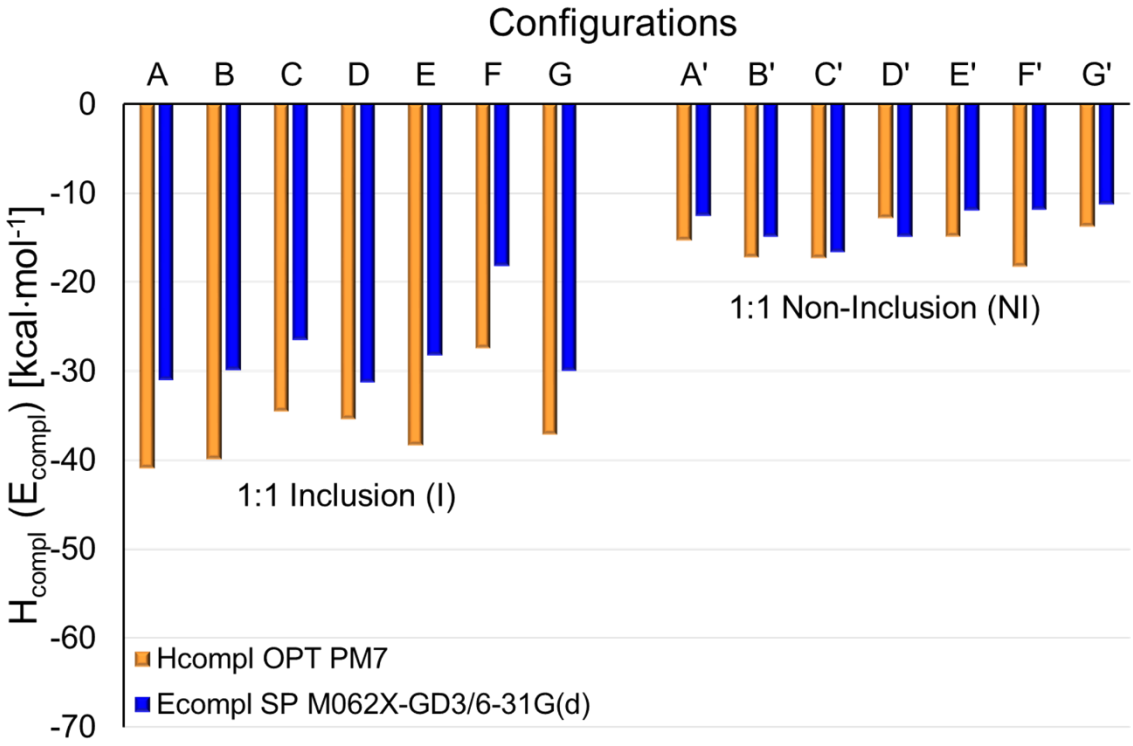

Fig. S19 The complexation enthalpies (H_{compl}) and energies (E_{compl}) obtained for the CD21chol:5-FU complex in the stoichiometry 1:1 for different 5-FU orientation from the PM7 optimization (OPT) and the DFT single point (SP) calculations (without the BSSE corrections).

Table S2 The PM7 heats of formation (H_f) and the DFT SP energies (E) as well as the corresponding complexation enthalpies H_{compl} and energies E_{compl} (without and, for the most stable structures, with the BSSE corrections) obtained in vacuo for the inclusion (I) and non-inclusion (NI) complexes 1:1 and 1:2 with two 5-FU monomers (I/NI). The values for the optimized structures of the 5-FU monomer and CD21chol molecule are also included.

Configuration	H_f (OPT) [kcal/mol]	E (SP) [au]	H_{compl} [kcal/mol]	E_{compl} [kcal/mol]	E_{compl}^{BSSE} [kcal/mol]
Inclusion complex 1:1 (I)					
A	-6937.58452	-34930.01370920	-41.0	-31.0	-19.4
B	-6936.57699	-34930.01193160	-40.0	-29.9	
C	-6931.15845	-34930.00652230	-34.5	-26.5	
D	-6932.04540	-34930.01407350	-35.4	-31.3	-17.6
E	-6935.00247	-34930.00934280	-38.4	-28.3	
F	-6924.11082	-34929.99326860	-27.5	-18.2	
G	-6933.76714	-34930.01209120	-37.2	-30.0	
Non-inclusion complex 1:1 (NI)					
A'	-6912.00609	-34929.98443490	-15.4	-12.7	
B'	-6913.89938	-34929.98805160	-17.3	-14.9	
C'	-6913.97194	-34929.99082210	-17.4	-16.7	
D'	-6909.52643	-34929.98806340	-12.9	-14.9	
E'	-6911.56266	-34929.98335150	-14.9	-12.0	
F'	-6914.92996	-34929.98323220	-18.3	-11.9	
G'	-6910.46788	-34929.98237550	-13.9	-11.4	
Inclusion complex 1:1 M1 (I) (z = ~8 Å)					
A	-6922.48078	-34929.99771340	-25.9	-21.0	
D	-6920.63813	-34930.01015540	-24.0	-28.8	
Inclusion complex 1:1 M2 (I) (z = ~17 Å)					
C	-6911.89073	-34930.00824150	-15.3	-27.6	
Inclusion/Non-inclusion complex 1:2 (I/NI)			H_{compl} (I/NI) [kcal/mol]	E_{compl} (I/NI) [kcal/mol]	E_{compl}^{BSSE} (I/NI) [kcal/mol]
AF'	-7071.94695	-35443.86820590	-62.0	-40.6	-22.3
DC'	-7062.47351	-35443.87674530	-52.5	-46.0	-26.5
Isolated molecules					
5-FU	-113.33498	-513.83917609			
CD21chol	-6783.28059	-34416.12508010			

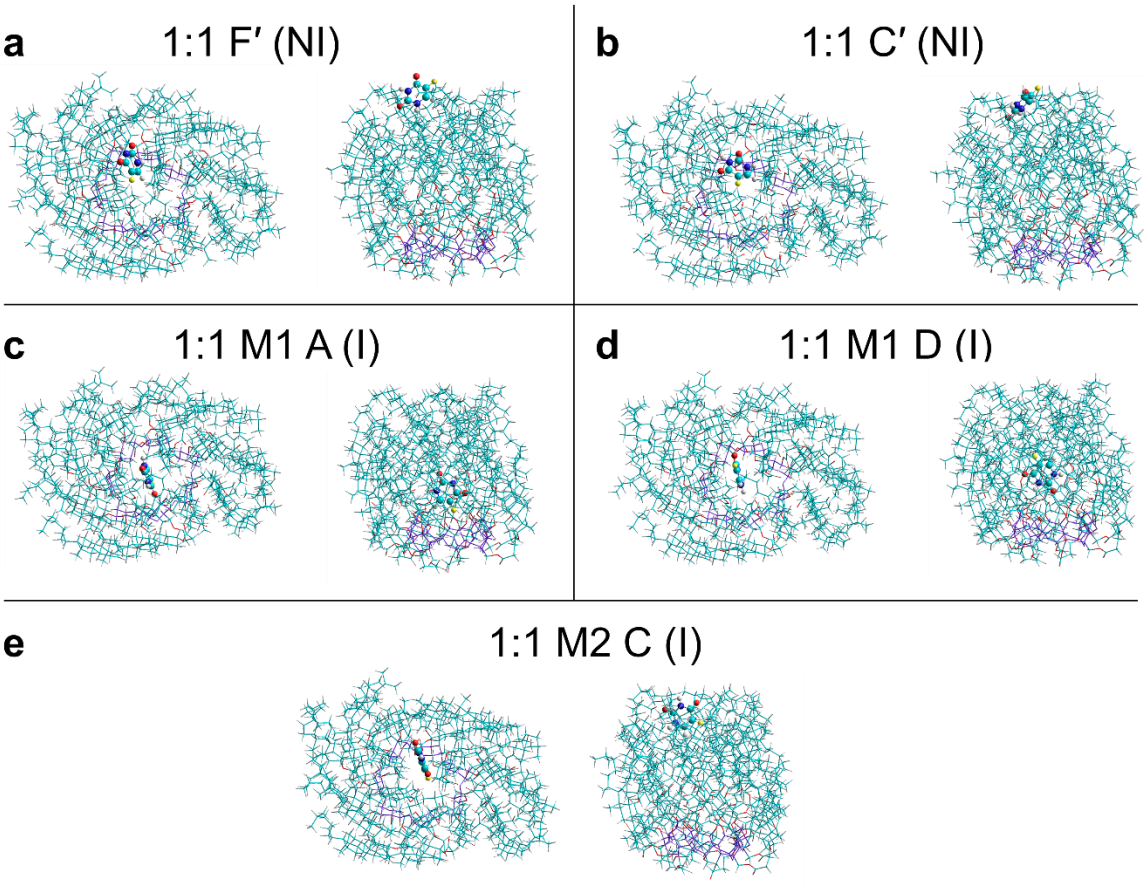

Fig. S20 The most stable non-inclusion structures of complexes of CD21chol with the monomer 5-FU indicated by the results obtained from the PM7 optimizations (a) and from the DFT SP calculations (b), as well as some additional stable inclusion complexes (denoted in the main article as M1 and M2) found for the complex 1:1 from the upward scans at z around 8 Å (c, d) and 17 Å (e). For each complex, the top and side views are shown. 5-FU is rendered with spheres and cylinders. The CD ring is marked in violet, while the remaining atoms' colors are carbon - cyan, nitrogen - dark blue, fluorine - yellow, oxygen - red, and hydrogen – grey.

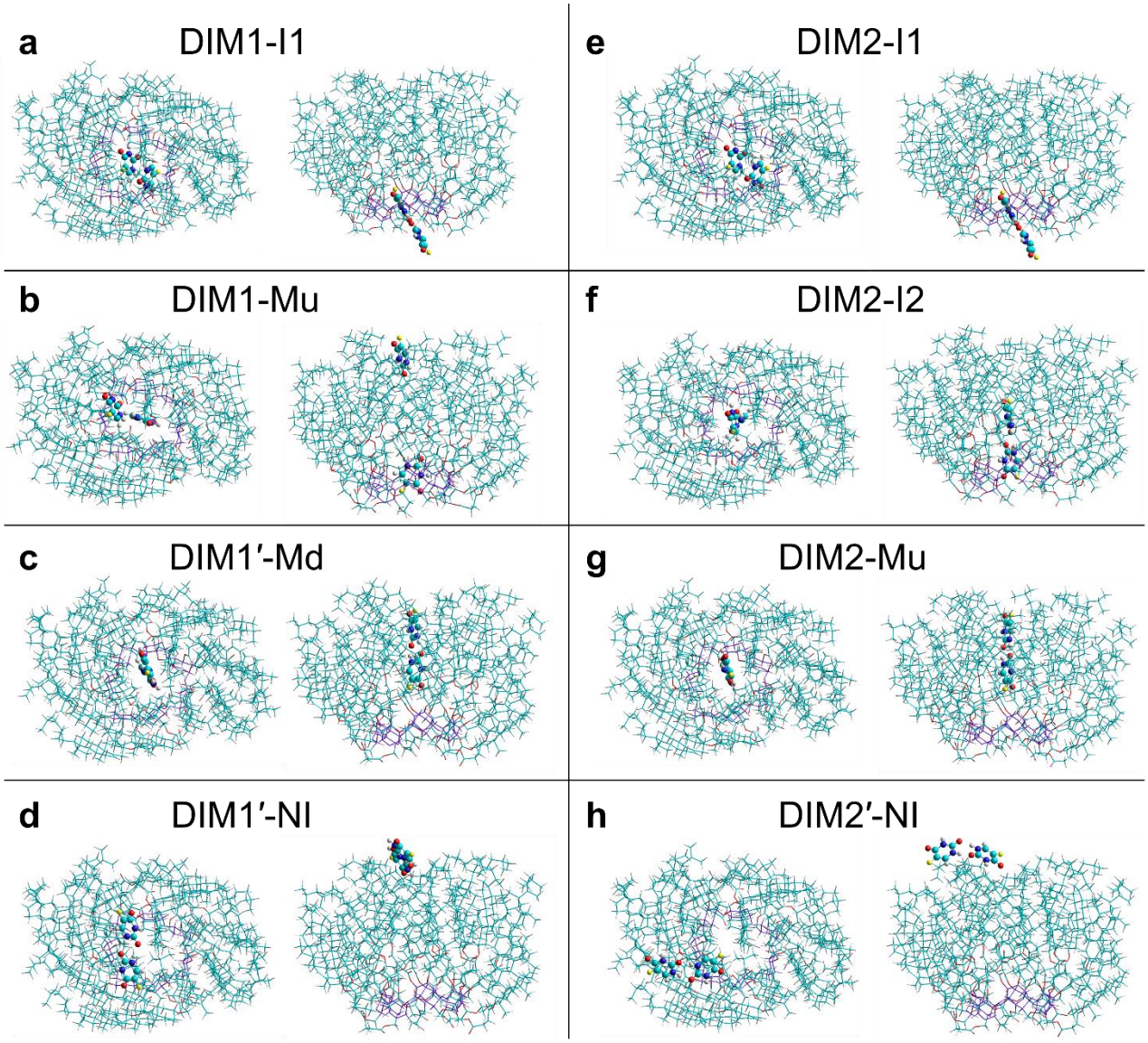

Fig. S21 Additional stable structures of complexes of CD21chol with the dimer 5-FU found from the scans when only one 5-FU from the dimer was moved, while the second could adjust its position (DIM1) and when the entire dimer was moved (DIM2). The atom colors are the same as in Fig. S20.

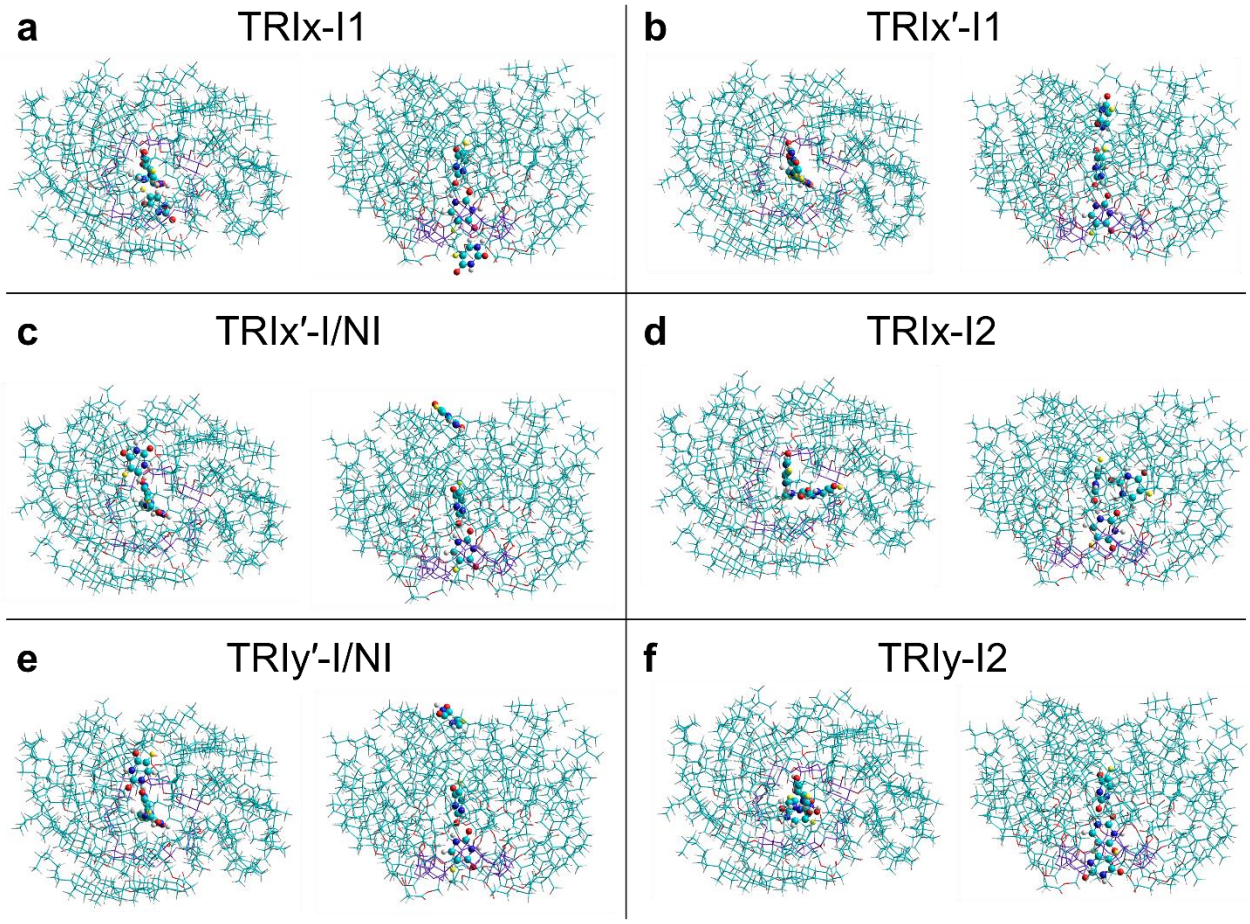

Fig. S22 Additional stable structures of complexes of CD21chol with three 5-FU molecules. The atom colors are the same as in Fig. S20.

Table S3 The PM7 heats of formation (H_f) and the DFT SP energies (E) as well as the corresponding complexation enthalpies and energies (without and, for the most stable structures, with the BSSE corrections) obtained in vacuo for selected complexes with $(5\text{-FU})_2$ dimer, with three 5-FU molecules (dimer plus monomer) and with two $(5\text{-FU})^2$ dimers. In the case of the complex 1:3, MONtoDIM1 denotes the enthalpies or energies of complexation of the monomer by the complex DIM1-I2, while TRIMER – the total energy gain from the complexation of the dimer and monomer by the CD21chol molecule. For the complex 1:4, dimer_toDIM1 denotes the enthalpies or energies of complexation of the (5-FU)2 dimer by the complex DIM1-I2, while 2DIM - the total energy gain from the complexation of two $(5\text{-FU})_2$ dimers by the CD21chol molecule. The values for the $(5\text{-FU})_2$ dimer alone are also included.

Complex 1:2 of CD21chol with dimer								
Config.	H_f (OPT) [kcal/mol]	E (SP) [au]	H_{compl} (DIMER) [kcal/mol]	E_{compl} (DIMER) [kcal/mol]	E_{compl}^{BSSE} (DIMER) [kcal/mol]			
DIM1-I1	-7073.04339	-35443.88666540	-45.7	-31.9				
DIM1-I2	-7086.03748	-35443.92233670	-58.7	-54.2	-28.7			
DIM1-Mu[a]	-7068.65988	-35443.87621650	-58.7[a]	-45.7[a]				
DIM1'-Md	-7061.05509	-35443.89712240	-33.7	-38.4				
DIM1'-NI	-7054.48102	-35443.87358820	-27.2	-23.6				
DIM2-I1	-7073.02662	-35443.88626080	-45.7	-31.6				
DIM2-I2	-7085.23976	-35443.91071350	-57.9	-46.9				
DIM2-Mu	-7061.98114	-35443.89786150	-34.7	-38.9				
DIM2'-NI	-7049.05563	-35443.86790970	-21.7	-20.1				
Complex 1:3 of CD21chol with dimer and monomer			H_{compl} (MONtoDIM1) [kcal/mol]	E_{compl} (MONtoDIM1) [kcal/mol]	E_{compl}^{BSSE} (MONtoDIM1) [kcal/mol]	H_{compl} (TRIMER) [kcal/mol]	E_{compl} (TRIMER) [kcal/mol]	E_{compl}^{BSSE} (TRIMER) [kcal/mol]
TRIx-I1	-7228.94788	-35957.79536380	-29.6	-21.2		-88.3	-75.5	
TRIx'-I1	-7225.73380	-35957.81334880	-26.4	-32.5		-85.1	-86.8	
TRIx'-I/NI	-7217.35997	-35957.78546680	-18.0	-15.0		-76.7	-69.3	
TRIx-I2	-7226.99724	-35957.80310170	-27.6	-26.1		-86.3	-80.3	
TRIy-I1	-7232.91170	-35957.79509700	-33.5	-21.1	-12.8	-92.3	-75.3	-41.6
TRIy'-I1	-7230.01853	-35957.83153020	-30.6	-43.9	-32.6	-89.4	-98.2	-62.5
TRIy'-I/NI	-7217.98221	-35957.78841330	-18.6	-16.9		-77.3	-71.1	
TRIy-I2	-7215.96219	-35957.76698000	-16.6	-3.4		-75.3	-57.7	
Complex 1:4 of CD21chol with two dimers			H_{compl} (dimer_toDIM1) [kcal/mol]	E_{compl} (dimer_toDIM1) [kcal/mol]	E_{compl}^{BSSE} (dimer_toDIM1) [kcal/mol]	H_{compl} (2DIM) [kcal/mol]	E_{compl} (2DIM) [kcal/mol]	E_{compl}^{BSSE} (2DIM) [kcal/mol]
2DIM I/NI	-7356.00901	-36471.66997630	-25.9	-23.1	-13.8	-84.7	-77.3	-42.2
Isolated molecules								
$(5\text{-FU})_2$ dimer	-244.03215	-1027.71082274						

[a] The configuration DIM1-Mu was the inclusion/non-inclusion complex with two monomers. Therefore, the complexation enthalpy and energy were calculated for the (I/NI) complex (formula (2) in Procedure S2d).

Table S4 The PM7/COSMO heats of formation (H_f) and the DFT/PCM SP energies (E) as well as the corresponding complexation enthalpies and energies (without the BSSE corrections) obtained for the most stable complexes in selected solvents.

Solvent	THF (COSMO)	METHANOL (COSMO)	WATER (COSMO)	THF (PCM)	METHANOL (PCM)	WATER (PCM)
	H_f (OPT) [kcal/mol]	H_f (OPT) [kcal/mol]	H_f (OPT) [kcal/mol]	E (SP) [au]	E (SP) [au]	E (SP) [au]
Substrates						
CD21chol	-6842.14416	-6854.36385	-6856.67848	-34416.19013250	-34416.20815510	-34416.21280870
5-FU	-125.86002	-128.90188	-129.49614	-513.85115385	-513.85332320	-513.85374419
$(5\text{-FU})_2$ dimer	-259.97097	-263.69195	-264.41377	-1027.72565952	-1027.72864735	-1027.72937995
Complexes						
1:1 (I) A	-6993.23551	-7004.78661	-7006.91879	-34930.07594500	-34930.09427000	-34930.09875330
1:1 (I) D	-6988.52422	-7000.75011	-7002.97191	-34930.07895300	-34930.09820890	-34930.10266240
1:2 (I/NI) AF'	-7130.75290	-7143.38146	-7145.58492	-35443.93628780	-35443.95516940	-35443.95935450
1:2 (I/NI) DC'	-7124.32742	-7137.09894	-7139.54759	-35443.94818130	-35443.96691100	-35443.97225120
1:2 (I) DIM1-I2	-7140.15996	-7151.23402	-7153.31774	-35443.98204920	-35443.99893310	-35444.00277920
1:3 (I) TRIy-I1	-7288.70909	-7300.79831	-7303.07713	-35957.86111620	-35957.88008010	-35957.88404980
1:3 (I) TRIy'-I1	-7285.91314	-7297.53054	-7299.75552	-35957.89381890	-35957.91095840	-35957.91559820
1:4 (I/NI) 2DIM	-7418.32640	-7431.30561	-7433.59759	-36471.74103360	-36471.75991420	-36471.76360320
Complexation energies	THF (COSMO)	METHANOL (COSMO)	WATER (COSMO)	THF (PCM)	METHANOL (PCM)	WATER (PCM)
Structure	H_{compl} [kcal/mol]	H_{compl} [kcal/mol]	H_{compl} [kcal/mol]	E_{compl} [kcal/mol]	E_{compl} [kcal/mol]	E_{compl} [kcal/mol]
1:1 (I) A	-25.2	-21.5	-20.7	-21.7	-20.6	-20.2
1:1 (I) D	-20.5	-17.5	-16.8	-23.6	-23.0	-22.7
1:2 (I/NI) AF'	-36.9	-31.2	-29.9	-27.5	-25.3	-24.5
1:2 (I/NI) DC'	-30.5	-24.9	-23.9	-35.0	-32.7	-32.6
1:2 (I) DIM1-I2	-38.0	-33.2	-32.2	-41.6	-39.0	-38.0
1:3 (I) TRIy-I1	-60.7	-53.8	-52.5	-59.1	-56.4	-55.3
1:3 (I) TRIy'-I1	-57.9	-50.6	-49.2	-79.6	-75.8	-75.1
1:4 (I/NI) 2DIM	-56.2	-49.6	-48.1	-62.5	-59.3	-57.8

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