Synthesis of the first POSS cage-anthracycline conjugates via amide bond

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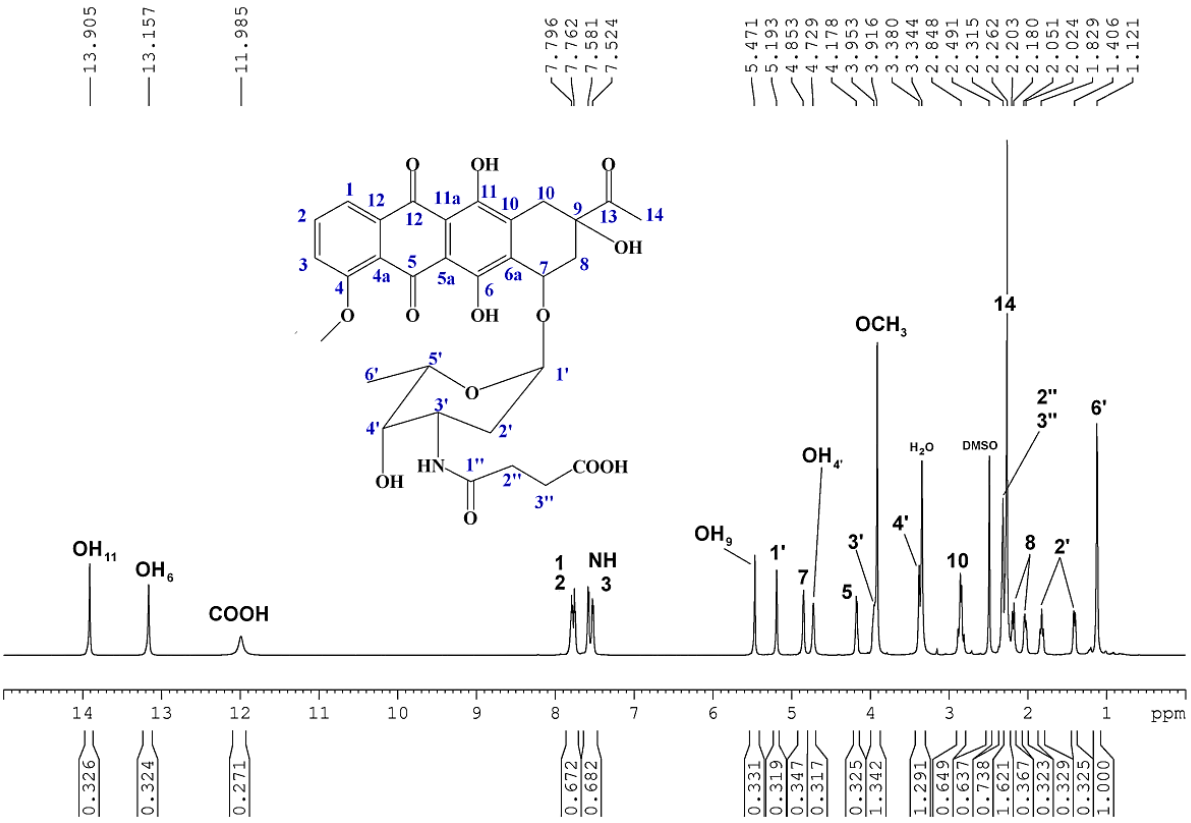
Experimental Section

Materials. Octavinylsilsesquioxane (Hybrid Plastics), succinic anhydride (Sigma-Aldrich), 11-mercaptoundecanoic acid (Sigma-Aldrich), 2,2-dimethoxy-2-phenylacetophenone (DMPA) (POCh), N-hydroxysuccinimide (NHS) (Sigma-Aldrich), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (Sigma-Aldrich), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) (Sigma-Aldrich), doxorubicin (Dox) and daunorubicin (Dau) (Beijing Packbuy M&C) were used as supplied. Triethylamine (Et_3N, CHEMPUR), methylene chloride (POCh), THF (POCh), MeOH (POCh) and DMF (POCh) were purified as described in the literature[1].

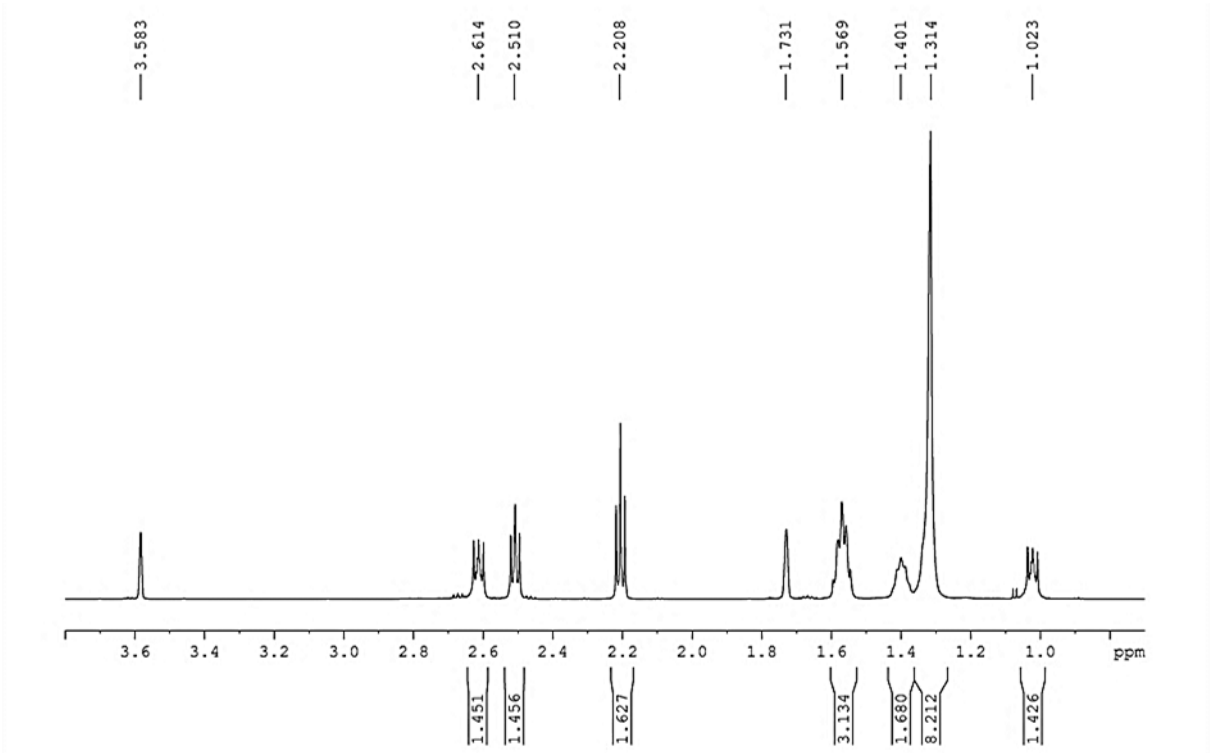
Synthesis of succinic anhydride-modified daunorubicin (SAMDAU). A solution of daunorubicin hydrochloride (DAU) (0.5 g, $8.88 \cdot 10^{-4}$ mol) and succinic anhydride (0.11 g, $1.1 \cdot 10^{-3}$ mol) in DMF (50 ml) was stirred under nitrogen in the dark, while triethylamine (0.28 g, $2.73 \cdot 10^{-3}$ mol) was added dropwise. The reaction mixture was stirred for 72 hours at room temperature, then volatiles were removed under vacuum, chloroform (10 ml) and deionized water (200 ml) were added. After 1 hour the red-brownish solid product was filtered, washed 3 times with deionized water (50 ml) and dried on a vacuum line to give 0.45 g of SAMDAU with 80.8% yield. MALDI-TOF: m/z calcd for $C_{31}H_{33}NO_{13}$ $[M+K^+]$ = 666.5; found 665.6.

Synthesis of $T^8[(CH_2)_2S(CH_2)_{10}COOH]_8$ – octa[10-(carboxydecylthio)ethyl]silsesquioxane (2). Octa(vinyl)silsesquioxane (T_8-Vi) (0.63 g, $9.95 \cdot 10^{-4}$ mol) and 11-mercaptoundecanoic acid (2.42 g, 0.01 mol), 2,2-dimethoxy-2-phenylacetophenone (DMPA) (0,048 g) were introduced into a quartz reactor and dissolved in THF (30 ml). The reaction mixture was irradiated with a UV lamp at 350 nm for 1.5 hr. Volatiles were removed under vacuum. The residue was dissolved in THF (5 ml), precipitated in hexane (30 ml), separated, washed with hexane (50 ml) and dried under vacuum to give 2,3 g (97.1% yield) of the product.
^{1}H NMR (600 MHz, THF-D6, TMS, ppm): δ = 1.02 (t, 2H, $SiCH_2$), 1.31 (m, 10H, $SCH_2CH_2CH_2\underline{CH_2CH_2CH_2CH_2CH_2}CH_2CH_2CH_2COOH$), 1.40 (m, 2H, $SCH_2CH_2\underline{CH_2}CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2COOH$), 1.57 (m, 4H, $SCH_2\underline{CH_2}CH_2CH_2CH_2CH_2CH_2CH_2CH_2\underline{CH_2}CH_2COOH$), 2.21 (t, 2H, CH_2COOH), 2.51 (t, 2H, SCH_2), 2.61 (t, 2H, CH_2S). ^{13}C NMR (500MHz, THF-D6, TMS, ppm): δ = 13.83 (Si-O-Si-CH_2), 25.92 ($SCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2\underline{CH_2}CH_2COOH$),26.55 ($CH_2S$), 30.02-30.67 ($SCH_2\underline{CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2}CH_2CH_2COOH$32.47 ($SCH_2$), 34.34 ($\underline{CH_2}COOH$), 174.63 (COOH). ^{29}Si NMR (600MHz, THF-D6, TMS, ppm): δ = -68.48 (Si-O-Si). MALDI-TOFF: m/z calcd for $C_{104}H_{200}O_{28}S_8Si_8$ $[M+Ag^+]$, 2487.7; found 2487.6.

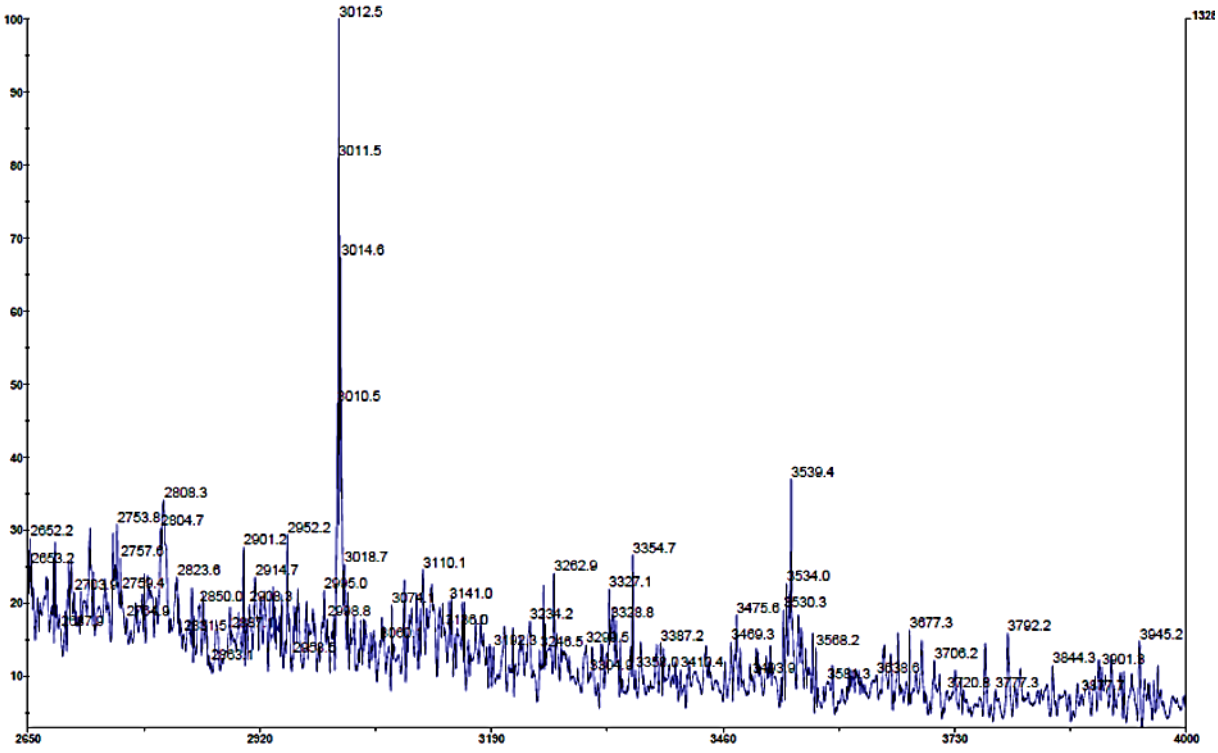
Exemplary analytical data (spectra)



^{1}H NMR (DMSO-D6, 600MHz) of SAMDAU



^{1}H NMR (THF-D6, 600MHz) of $T^{8}[(CH_2)_2S(CH_2)_{10}COOH]_8$



MALDI TOF of $(DOX)_n$-$T_8[(CH_2)_2S(CH_2)_{10}COOH]_{8-n}$: m/z 3012.5 (n=1); 3539.4 (n=2)