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Complexes and Conjugate of Daunorubicin with β-Cyclodextrin and Its Dimeric Diaminocationic Derivatives. Synthesis and Study of Antiproliferative Activity

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Individual complexes and a conjugate of the antitumor compound Daunorubicin with β-cyclodextrin and its dimeric derivatives of various compositions were obtained and their antiproliferative activity against a number of cancer cells was studied.

Keywords: Daunorubicin, cyclodextrins, dimeric derivatives, inclusion compounds, NMR spectroscopy, MALDI-TOF mass spectra.

Комплексы и конъюгат Даунорубицина с β-циклодекстрином и его димерными диаминокатионными производными. Синтез и изучение антипролиферативной активности

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Получены индивидуальные комплексы и конъюгат противоопухолевого соединения Даунорубицин с β-циклодекстрином и его димерными производными различных составов и исследована их антипролиферативная активность в отношении ряда раковых клеток.

Ключевые слова: Даунорубицин, циклодекстрины, димерные производные, соединения включения, спектроскопия ЯМР, масс-спектры MALDI-TOF.

Introduction

Daunorubicin is an anthracycline antibiotic, which has found wide application in the therapy of tumor diseases of various etiologies.[1] Unfortunately, the use of anthracyclines leads to a number of side effects, such as cardiotoxicity, mutagenicity, immunodepression, and also leads to the emergence of drug resistance.[2] Therefore, the development of new methods of using Daunorubicin, as well as the use of its chemically modified derivatives, remains a relevant direction in the development of modern medicinal chemistry (see, for example, reviews[3,4]). In this

regard, it is known that Daunorubicin can form complexes with cyclodextrins in solution[5] and undergo easy and diverse chemical modification by the accessible NH_2-group.[6] In recent decades, the special physicochemical properties and cavity structure of cyclodextrins have determined their high value as *excipients* in the creation of drugs. Binding of drug compounds usually occurs through the formation of inclusion complexes with cyclodextrin,[*e.g.* 7] less often through conjugation (covalent binding), which ultimately leads to an improvement in certain properties of drugs, such as water solubility, stability and bioavailability. It should be noted that among β-cyclodextrin derivatives their dimeric derivatives attract special attention due to several sites for binding various compounds (multivalence), which often leads to the so-called *cooperative* (non *additive*) enhanced effect on the inclusion of various guests. This is especially evident, for example, in the case of "charged" dimeric diaminocationic derivatives of cyclodextrins in relation to the strong incorporation of such antitumor compounds as *Methotrexate*[8] and *Doxorubicin.* [9]

In this paper we aimed to obtain some complexes and conjugate of β-cyclodextrin and its dimeric diaminocationic derivatives with anticancer compound Daunorubicin and to study their antiproliferative activity in relation to inhibit tumor cells.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX–400 instrument at the frequencies of 399.78 and 100.52 MHz, respectively. The ^{1}H and ^{13}C chemical shifts are given relative to the $SiMe_4$ signal in a solution of [D6]DMSO. Elemental analysis was performed on a FlashEA 1112 HT instrument. The assignment of signals in the ^{1}H and ^{13}C NMR spectra of the synthesized compounds was additionally confirmed by the analysis of the spectra of two-dimensional HOMOCOR {^{1}H–^{1}H} and HETCOR {^{1}H–^{13}C} NMR spectroscopy and by recording the spectrum of the sample solution in the DEPT mode. The positions of the hydroxyl proton signals were refined by a significant signal shift (by 0.3–0.7 ppm) when recording the spectrum of a solution of the same sample at an elevated temperature (80 °C). For thin-layer chromatography, aluminum plates with a fixed layer of silica gel (Silufol UV-254) were used, eluent: n-butanol–ethanol–25% ammonia–pyridine (4:1:3:2). β-Cyclodextrin from Chemical Line was used in the work. All experiments were performed in dry purified solvents.

MALDI-TOF mass spectra were obtained in the positive ion registration mode on a Shimadzu AXIMA Confidence MALDI-TOF time-of-flight mass spectrometer (Japan) equipped with a nitrogen UV laser (λ = 337 nm) and a reflectron as a detector. The mass scanning range is *m/z* 200–3000. Solutions (1:1) of CHCA (α-cyano-4-hydroxycinnamic acid, 50 mg/mL solution in MeOH) with the addition of LiCl (100 mg/mL solution in water) or DHB (2,5-dihydroxybenzoic acid, 50 mg/ mL solution in MeOH) with the addition of LiCl (100 mg/mL solution in water) were used as a matrix. To prepare an analyte solution with a concentration of 1 mg/mL, the required compounds were dissolved in water. 20 mL of matrix solution were combined with 20 mL of analyte solution, 1 mL of that solution was taken from the resulting mixture, applied to a separate well of a steel plate and dried in air. A layer-by-layer method of applying the sample to the plate in the order: matrix – analyte – matrix (0.5 mL of each) was also used.

*Inclusion compound of β-cyclodextrin with daunorubicin (**3**).* 0.248 g (0.44 mmol) of daunorubicin hydrochloride **1** were added under stirring to a solution of 0.50 g (0.44 mmol) of β-cyclodextrin **2** in 8 mL of water at 70 °C and stirred at 70 °C for 1 hr. The reaction mixture was cooled to room temperature, the formed precipitate was filtered off, washed with acetone (2×5 mL) and dried in a vacuum (1 mm Hg) over P_2O_5 for 8 hrs at 70 °C. Yield 0.60 g (80%), m.p. 195–199 °C (decomp.); R_f=0.57. Found, %: C 47.80; H 5.87; N 0.81. $C_{69}H_{100}ClNO_{45}$ requires, %: C 48.78; H 5.93; N 0.82. ^{1}H NMR δ_H ppm, daunorubicin **1**: 1.13 d (3H, $C^{5'}HCH_3$, ^3J=6.4 Hz), 1.66 d (1H, C^8H, ^3J=6.2 Hz), 1.84 d (1H, C^8H, ^3J=5.4 Hz), 2.04 d (1H, $C^{2'}H$, ^3J=7.1 Hz), 2.11 d (1H, $C^{2'}H$, ^3J=11.9 Hz), 2.25 s (3H, $COC^{14}H_3$), 2.86 d (2H, $C^{10}H$, ^3J=6.0 Hz), 2.91 d (1H, $C^{3'}H$, ^3J=14.2 Hz), 3.73 t (1H, $C^{4'}H$, ^3J=10.0 Hz), 3.94 br.s (3H, $C^4{}_{arom}OC^{15}H_3$), 4.18 d (1H, $C^{5'}H$, ^3J=6.6 Hz), 4.88 s (1H, $C^{1'}H$), 5.26 s (1H, C^7H), 5.44 d (1H, $C^{4'}OH$, ^3J=6.4 Hz), 5.51 s (1H, C^9OH), 7.60 d (1H, C^3H, ^3J=7.4 Hz), 7.80 d (1H, C^1H, ^3J=6.4 Hz), 7.83 d (1H, C^2H, ^3J=15.1 Hz), 7.86 m (2H, NH_2), 13.20 s (1H, $C^{11}OH$), 13.95 s (1H, C^6OH); cyclodextrin **2**: 3.30–3.39 m (14H, C^6H_2), 3.56–3.64 m (28H, C^2H-C^5H) , 4.46 br.s (7H, C^6OH), 4.85 br.s (7H, C^1H), 5.77-5.79 br.s (14H, C^2OH, C^3OH). MALDI-TOF: found *m/z* 1660.48; calculated for $C_{69}H_{98}NO_{45}$ $[MH]^+$ 1660.54.

Inclusion compound of β-cyclodextrin with daunorubicin (**4**). 0.248 g (0.44 mmol) of daunorubicin hydrochloride **1** were added under stirring to a solution of 1.00 g (0.88 mmol) of β-cyclodextrin **2** in 8 mL of water at 70 °C and stirred at 70 °C for 1 hr. The reaction mixture was cooled to room temperature, 20 mL of benzene was added and water was distilled off with a Dean-Stark trap, the formed precipitate was dried in a vacuum (1 mm Hg) over P_2O_5 for 8 hrs at 70 °C. Yield 0.98 g (79%), m.p. 198–202 °C (decomp.); R_f =0.57. Found, %: C 46.55; H 5.99; N 0.48. $C_{111}H_{170}ClNO_{80}$ requiers C 47.02; H 6.05; N 0.49. ^{1}H NMR δ_H ppm, daunorubicin **1**: 1.12 d (3H, $C^{5'}CH_3$, ^3J=6.9 Hz), 1.64 d (1H, C^8H, ^3J=8.2 Hz), 1.86 d (1H, C^8H, ^3J=7.8 Hz), 2.04 d (1H, $C^{2'}H$, ^3J=7.4 Hz), 2.15 d (1H, $C^{2'}H$, ^3J= 9.6 Hz), 2.24 s (3H, $COC^{14}H_3$), 2.69 d (2H, $C^{10}H$, ^3J=6.4 Hz), 2.87 d (1H, $C^{3'}H$, ^3J=14.2 Hz), 3.81 t (1H, $C^{4'}H$, ^3J=10.1 Hz), 3.95 br.s (3H, $C^4{}_{arom}OC^{15}H_3$), 4.17 d (1H, $C^{5'}H$, ^3J=6.4 Hz), 4.90 s (1H, $C^{1'}H$), 5.26 s (1H, C^7H), 5.44 d (1H, $C^{4'}OH$, ^3J=6.0 Hz), 5.49 s (1H, C^9OH), 7.62 d (1H, C^3H, ^3J=4.6 Hz), 7.82 d (1H, C^1H, ^3J=6.4 Hz), 7.86 d (1H, C^2H, ^3J=7.4 Hz), 7.91 m (2H, NH_2), 12.98 s (1H, $C^{11}OH$), 13.75 s (1H, C^6OH); cyclodextrin **2**: 3.26–3.46 m (28H, C^6H_2) , 3.52–3.67 m (56H, C^2H-C^5H), 4.45 br. s (14H, C^6OH), 4.81 br.s (14H, C^1H), 5.69–5.74 br.s (28H, C^2OH, C^3OH); MALDI-TOF: found *m/z* 2796.84; calculated for $C_{111}H_{169}NO_{80}$ $[M+H]^+$ 2796.93.

Conjugate (**5**). 0.1245 g (0.236 mmol) of daunorubicin as a base[11] was added under stirring to a solution of 0.294 g (0.236 mmol) of mono-6-iodo-6-deoxy-β-cyclodextrin[10] in 10 mL of DMF. The solution was stirred for 40 hrs at 120–130 ºC and cooled to room temperature. The solution was evaporated to dryness in a vacuum, the residue was triturated in 15 mL of acetone, filtered, washed with acetone (2×5 mL) and dried in a vacuum (1 mm Hg). Yield 0.20 g (48%), m.p. 250–253 °C (decomp.); R_f =0.65. Found, %: C 46.29; H 5.51; N 0.78. $C_{69}H_{98}INO_{44}$ required C 46.76; H 5.57; N 0.79. ^{1}H NMR δ_H ppm, residue of mono-6-iodo-6-deoxy-β-cyclodextrin: 3.29–3.42 m (14H, C^6H_2) , 3.56–3.68 m (28H, C^2H-C^5H) , 4.47 br.s (7H, C^6OH), 4.84 br.s (7H, C^1H), 5.69–5.80 br.s (14H, C^2OH, C^3OH); residue of daunorubicin: 1.06 d (3H, $C^{6'}H_3$, ^3J=4.0 Hz), 2.09 d (1H, C^8H, ^3J=6.4 Hz), 2.24 d (1H, C^8H, ^3J=5.2 Hz), 2.29 d (1H, $C^{2'}H$, ^3J=6.8 Hz), 2.31 d (1H, $C^{2'}H$, ^3J=11.4 Hz), 3.87 s (3H, $C^{14}H_3$), 3.89 d (2H, $C^{10}H$, ^3J=5.8 Hz), 3.92 d (1H, $C^{3'}H$, ^3J=13.8 Hz), 3.93 t (1H, $C^{4'}H$, ^3J=9.8 Hz), 4.01 s (3H, $C^{15}H_3$), 4.89 d (1H, $C^{5'}H$, ^3J=6.4 Hz), 4.90 s (1H, $C^{1'}H$), 5.66 s (1H, C^7H), 7.11 d (1H, $C^{4'}OH$, ^3J=6.0 Hz), 7.12 s (1H, C^9OH), 7.37 m (2H, NH_2), 7.47 d (1H, C^3H, ^3J=7.1 Hz), 7.49 d (1H, C^1H, ^3J=6.2 Hz), 7.96 d (1H, C^2H, ^3J=14.5 Hz), 14.77 s (2H, $C^{11}OH$, C^6OH); ^{13}C NMR δ_c ppm, residue of mono-6-iodo-6-deoxy-β-cyclodextrin: 45.2 ($C6^{'}$), 60.4 (C^6), 71.9 (C^3), 72.4 (C^2), 73.0 (C^5), 81.5–81.8 (C^4), 101.9 (C^1); residue of daunorubicin: 19.8 ($C^{6'}$), 30.7 (CH_3), 35.7 (C^8), 39.9 (C^{10}), 40.1 ($C^{2'}$), 56.5 ($C^{3'}$), 59.9 ($C^{15}H_3$), 65.7 ($C^{4'}$), 72.6 ($C^{5'}$), 82.8 (C^7), 83.1 (C^9), 125.4 ($C^{1'}$), 127.9 (C^{18} and C^{21}), 130.7 (C^3), 135.1 (C^1), 139.4

(C^{17}), 147.1 (C^{2}), 156.1–156.9 (C^{16}, C^{19}, C^{20}), 162.2 (C^{6} and C^{11}), 176.8 (C^{12}), 189.3 (C^{5}), 218.8 (C^{13}).

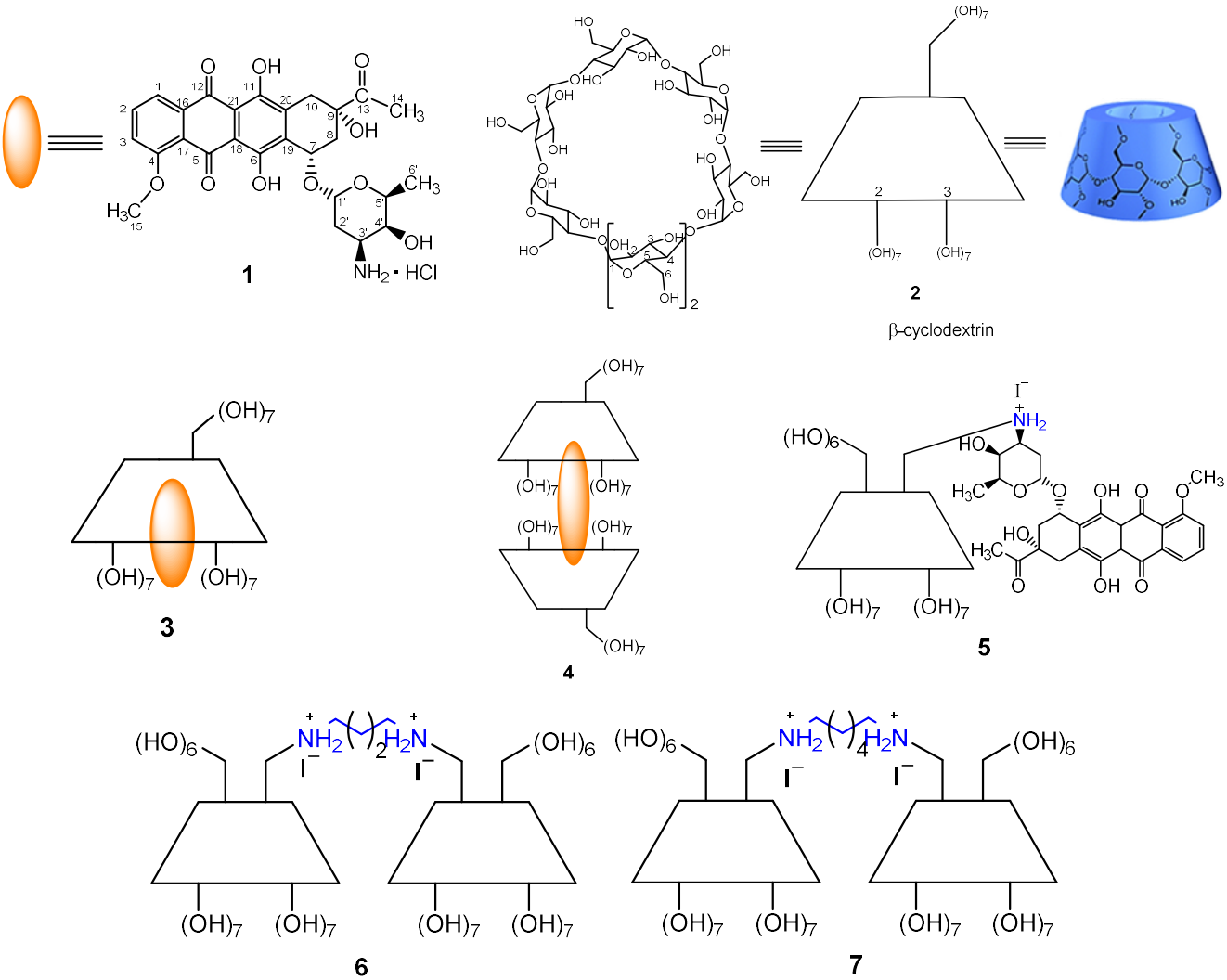
Inclusion compound **8** was prepared similarly to complex **3** from 0.0720 g (0.0279 mmol) of the dimeric derivative of β-cyclodextrin **6**[12] and 0.0315 g (0.0558 mmol) of daunorubicin hydrochloride **1**. Yield 0.0536 g (61%), m.p. 203–205 ºC (decomp.); R_f=0.65. Found, %: C 43.52; H 5.72; N 1.32. $C_{115}H_{180}ClI_2N_3O_{78}$ required C 43.96; H 5.77; N 1.34. ^{1}H NMR δ_H ppm, daunorubicin **1**: 1.11 d (3H, $C^{5'}HCH_3$, ^3J=6.4 Hz), 1.65 m (2H, $C^{8}H$), 2.01 s (1H, $C^{2'}H$), 2.18 s (1H, $C^{2'}H$), 2.73 s (3H, $COC^{14}H_3$), 2.90 d (2H, $C^{10}H$, ^3J=7.6 Hz), 2.89 s (1H, $C^{3'}H$), 3.82 s (1H, $C^{4'}H$), 3.95 br.s (3H, $C^{4}_{arom}OC^{15}H_3$), 4.15 d (1H, $C^{5'}H$, ^3J=7.4 Hz), 4.90 s (1H, $C^{1'}H$), 5.25 s (1H, $C^{7}H$), 5.48 d (1H, $C^{4'}OH$, ^3J=6.4 Hz), 5.52 s (1H, $C^{9}OH$), 5.69 t (1H, $C^{3}H$, ^3J=7.6 Hz), 7.78 s (1H, $C^{1}H$), 7.94 d (1H, $C^{2}H$, ^3J=4.6 Hz), 8.04 m (2H, NH_2), 13.15 s (1H, $C^{11}OH$), 13.98 s (1H, $C^{6}OH$); dimeric derivative of β-cyclodextrin **6**: 1.46 m (4H, NCH_2CH_2), 2.63 m (4H, NCH_2), 3.19–3.24 m (28H, $C^{6}H_2$), 3.56–3.74 m (56H, $C^{2}H$-$C^{5}H$), 4.48 br. s (12H, $C^{6}OH$), 4.78 m (14H, $C^{1}H$), 5.71 br.s (32H, $N^{+}H_2$, $C^{2}OH$, $C^{3}OH$); MALDI-TOF: found *m/z* 862.49; calculated for $C_{115}H_{178}N_3O_{78}$ [(M +2 H)/ 4]$^{2+}$ 862.79.

Inclusion compound **9** was prepared similarly to complex **3** from a solution of 0.30 g (0.115 mmol) of the dimeric derivative of β-cyclodextrin **7**[12] and 0.0130 g (0.230 mmol) of daunorubicin hydrochloride **1**. Yield 0.082 g (19%), m.p. 205–207 ºC (decomp.); R_f=0.83. Found, %: C 45.86; H 5.72; N 1.40. $C_{144}H_{214}Cl_2I_2N_4O_{88}$ required C 46.32; H 5.78; N 1.50. ^{1}H NMR δ_H ppm, daunorubicin **1**: 1.13 d (6H, $C^{5'}CH_3$, ^3J=6.4 Hz), 1.49 m (4H, $C^{8}H$), 1.65 s (2H, $C^{2'}H$), 1.86 s (2H, $C^{2'}H$), 2.70 s (6H, $COC^{14}H_3$), 2.86 s (4H, $C^{10}H$), 2.92 s (2H, $C^{3'}H$), 3.17 s (2H, $C^{4'}H$), 3.97 br. s (6H, $C^{4}_{arom}OC^{15}H_3$), 4.17 d (2H, $C^{5'}H$, ^3J=6.9 Hz), 4.93 s (2H, $C^{1'}H$), 5.27 s (1H, $C^{7}H$), 5.42 d (2H, $C^{4'}OH$, ^3J=6.4 Hz), 5.50 s (2H, $C^{9}OH$), 7.65 t (2H, $C^{3}H$, ^3J=7.6 Hz), 7.80 s (2H, $C^{1}H$), 7.91 d (2H, $C^{2}H$, ^3J=4.6 Hz), 8.02 m (4H, NH_2), 13.15 s (2H, $C^{11}OH$), 13.98 s (2H, $C^{6}OH$); dimeric derivative of β-cyclodextrin **7**: 1.24 m (4H, $NCH_2CH_2CH_2$), 2.23 m (4H, NCH_2CH_2), 2.26 m (4H, NCH_2), 3.26–3.34 m (28H, $C^{6}H_2$), 3.51–3.60 m (56H, $C^{2}H$-$C^{5}H$), 4.44 br.s (12H, $C^{6}OH$), 4.80 m (14H, $C^{1}H$), 5.66 br.s (28H, $C^{2}OH$, $C^{3}OH$). MALDI-TOF: found *m/z* 1741.86; calculated for $C_{144}H_{214}Cl_2N_4O_{88}$ $[M/2+2H]^{2+}$ 1741.10.

Results and Discussion

In this work we obtained individual inclusion complexes of Daunorubicin **1** with β-cyclodextrin **2** compositions 1:1 **3** , 2:1 **4** and conjugate **5**.

In addition, inclusion complexes of Daunorubicin **1** with dimeric diaminocationic derivatives of β-cyclodextrin **6** and **7**, connected by linkers of different lengths, of various compositions **8** and **9** were obtained.



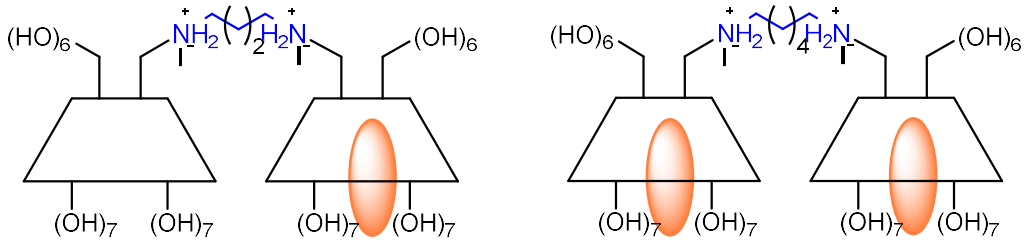


Table 1. Cytotoxicity of inclusion compounds **3**, **4**, **8**, **9** and conjugate **5.**

Compound	IC 50 (μM /l)			
	A549 (lung carcinoma)	HCT116 (colorectal carcinoma)	HEK293 (embryonic kidney)	HeLa (cervix adenocarcinoma)
1	0.56 ± 0.05	0.29 ± 0.01	0.03 ± 0.00	0.85 ± 0.04
3	0.46 ± 0.01	0.28 ± 0.01	0.07 ± 0.00	0.32 ± 0.04
4	1.73 ± 0.05	0.51 ± 0.04	0.40 ± 0.01	0.98 ± 0.09
8	**0.20 ± 0.03**	0.22 ± 0.02	0.16 ± 0.02	**0.15 ± 0.02**
9	**0.01 ± 0.00**	**0.011 ± 0.001**	**0.006 ± 0.001**	**0.008 ± 0.001**
5	no effect	no effect	no effect	no effect

Inclusion compounds **3**, **4**, **8** and **9** were prepared according to the general method described by us in the work[13] by joint heating of β-cyclodextrin **2** or its dimeric derivatives **6** and **7** with the corresponding molar equivalent of Daunorubicin **1** in an aqueous solution, cooling, washing the resulting precipitate with acetone and subsequent drying in a vacuum. Conjugate **5**, which is a cationic derivative, was obtained by the interaction of mono-6-iodo-6-deoxy-β-cyclodextrin with Daunorubicin *as a base* in a DMF solution. The structure and composition of the obtained complexes and conjugate were confirmed by ^{1}H, ^{13}C NMR spectroscopy, MALDI-TOF mass spectrometry, TLC and elemental analysis (see the Experimental section).

In conclusion of the work, a primary screening (MTT-test) of inclusion compounds **3**, **4**, **8**, **9** and the cationic conjugate **5** with Daunorubicin on a number of cancer cell lines: A549 (lung carcinoma), HCT116 (colorectal carcinoma), HEK293 (embryonic kidney) and HeLa (cervix adenocarcinoma) was carried out (Table 1).

Analysis of cytotoxicity showed that mainly complexation with cyclodextrin (compounds **3**, **4**) demonstrates a cytotoxic effect comparable to Daunorubicin **1** itself, whereas complexes with dimeric cyclodextrins **8** and **9** are more effective in inhibiting tumor cell (A549 and HeLa), making them potential antiproliferative agents. It is important that complex **9** significantly exceeds Daunorubicin **1** in cytotoxicity in relation to all cell lines taken for the experiment. Unfortunately, the conjugate **5** did not exhibit cytotoxic activity. The presented data confirm the perspectivity of further pharmacological studies of complexes of dimeric cyclodextrin derivatives with antitumor compounds.

Thus, we obtained new complexes of β-cyclodextrin, its dimeric dicationic derivatives and conjugate with anticancer compound Daunorubicin. It was revealed that inclusion complexis of Daunorubicin with dimeric dicationic derivatives of β-cyclodextrin have a high antiproliferative activity against a number of cancer cells.

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