SYNTHESIS AND BIOLOGICAL ACTIVITY OF THE DAUNORUBICIN DERIVATIVES BEARING A BENZO[*d*][1,3]DIOXOL-5-YL MOIETY

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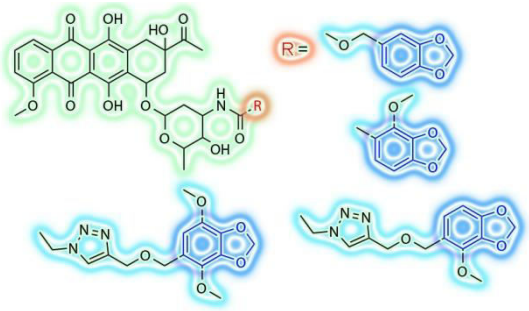
Abstract

The *N*-Functionalization of the daunorubicin amino group allows for introducing different functional and pharmacophore groups into the anthracycline core. Herein, the possibility of introduction of a benzo[*d*][1,3]dioxol-5-yl moiety and its derivatives into the structure of the initial moiety is demonstrated by the examples of four new anthracyclines. The biological activity of the resulting compounds is explored.



Key words: daunorubicin, anthracycline derivatives, synthesis, cytotoxicity.

Introduction

The modification of natural compounds with different functional and pharmacophore groups is a well-known and widely used approach to new biologically active compounds that can be used in medical practice [1]. The introduction of these groups can be accompanied by a considerable increase in the biological activity [2] or a change of a biological target which one or another drug binds with, when being ingested by the organism [3]. Anthracycline antibiotics are attractive starting compounds for such modifications. First of all, the anthracycline structure contains many functional groups, such as keto, phenol, hydroxy, and amino groups, which offer ample opportunities for structural modifications. Secondly, any change in the anthracycline structure leads to major alterations in the cytotoxicity of the resulting derivatives and also significantly affects other characteristics, including the emergence of multidrug resistance [4], reduction in the cardiotoxicity [5], and other negative properties of these compounds [6].

In this work, daunorubicin was chosen as a convenient precursor. The main direction of its structural modification was the *N*-functionalization of the daunosamine amino group. Despite a variety of opportunities offered by the anthracycline modification involving other functional groups (keto, phenol, and hydroxy), the *N*-functionalization appears to be the most fruitful approach to new derivatives that can exhibit high cytotoxicity [7].

Among anthracycline antibiotics, daunorubicin and doxorubicin (Fig. 1) amount to the first-generation antitumor agents. In clinical practice, they are used most frequently as the chemotherapeutic agents against leukemia and non-Hodgkin lymphoma [8, 9].

There are numerous examples of the first-generation anthracycline derivatives that contain the following functional groups: mono- and dialkyl [10, 11], small and medium-size rings [12, 13], sugar [14] and amino acid [15] residues, as well as different organoelement groups (sulfur-, fluorine-, phosphorus-, iodine-, tin-, and selenium-containing groups) [16–21].

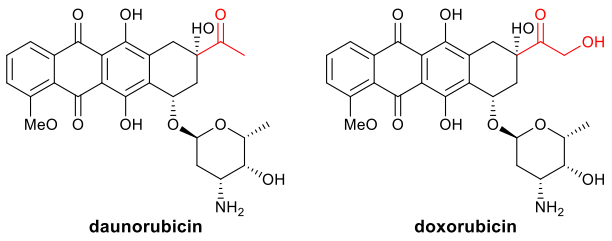


Figure 1. Main anthracycline representatives.

Earlier we have already reported the synthesis and biological activity of the daunorubicin derivatives which structures included the Br- and NO_2-substituted piperonal residues [22]. The extremely high cytotoxicity rates against different tumor cells were detected in the case of the anthracyclines bearing a piperonal unit or its dimethoxy-substituted derivative [23].

A benzo[*d*][1,3]dioxol-5-yl moiety is involved in many clinically used drugs, including cytotoxic agents (Fig. 2): kobusin **1**, atrasentan **2**, and (–)-bursehernin **3**.

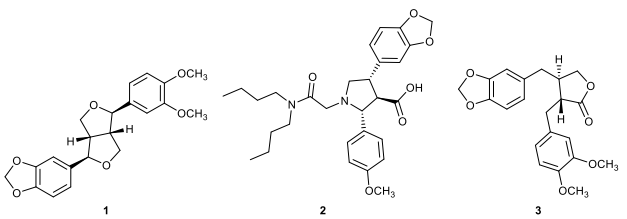


Figure 2. Drugs containing a benzo[*d*][1,3]dioxol-5-yl moiety.

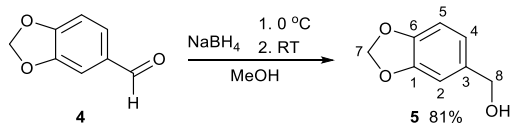
Hence, the introduction of piperonal and its substituted derivatives into the structure of biologically active molecules opens the way to potential drugs with prominent anticancer activity. These pharmacophore groups were used in the present work to obtain the daunorubicin derivatives by three different methods: the synthesis of a carbamic acid derivative, direct amidation, and click chemistry approach.

Results and discussion

Synthesis of a daunorubicin carbamate

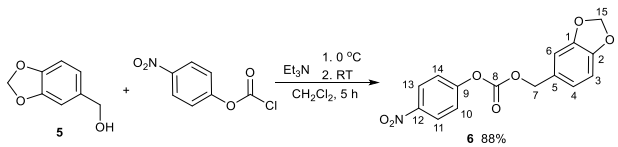
The synthesis of daunorubicin carbamates is a highly convenient method for introducing alcohol residues into the anthracycline structure, which can contain both various functional groups [24] and different pharmacophore moieties [25]. This approach can be accomplished using the derivatives with good leaving groups, such as a 4-nitrophenol moiety, which can be obtained from the alcohols and 4-nitrophenyl chlorocarbonate. Then, the resulting compounds are reacted with the initial daunorubicin.

Commercially available piperonal **4** was readily reduced to corresponding alcohol **5** under the action of sodium borohydride [26]. The use of a mild reducing agent such as $NaBH_4$ allowed for performing the reaction at room temperature and reducing selectively the aldehyde to the corresponding alcohol, leaving the benzo[*d*][1,3]dioxolyl moiety intact (Scheme 1).



Scheme 1. Synthesis of piperonyl alcohol **5**.

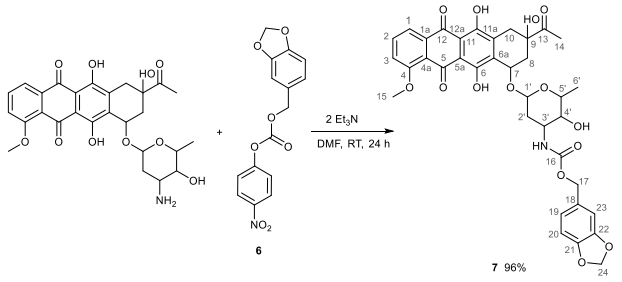
The physicochemical characteristics of alcohol **5** after purification by the recrystallization coincided with the previously published ones [27]; therefore, it was introduced into the reaction with 4-nitrophenyl chlorocarbonate (Scheme 2). After purification, product **6** was isolated as a white crystalline solid with the melting point of 124.6–125.0 °C. Its composition and structure were confirmed by the elemental analysis and ^1H and ^{13}C NMR spectroscopy.



Scheme 2. Synthesis of 4-nitrophenyl carbonate **6**.

Finally, target daunorubicin carbamate **7** was obtained by the reaction of daunorubicin with compound **6** in the presence of Et_3N in DMF (Scheme 3). These reactions typically proceed under very mild conditions that ensure the integrity of the anthracycline core.

This reaction does not require the preliminary synthesis of a free daunorubicin base from its hydrochloride salt since it is generated *in situ* in the reaction mixture upon addition of the second equivalent of a base. The application of a polar aprotic solvent, namely, dimethylformamide allowed for accomplishing



Scheme 3. Synthesis of daunorubicin carbamate **7**.

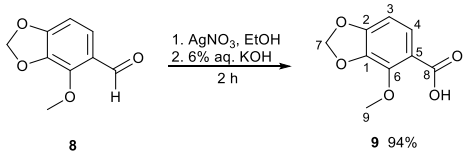
the reaction under mild conditions (at room temperature) and afforded target product **7** as a red powder in 24 h, which was isolated by column chromatography in the yield close to the quantitative one (96%). The structure of compound **7** was elucidated using a complex of spectral techniques (IR, ^1H and ^{13}C NMR spectroscopy). Its composition was confirmed by the elemental analysis. The NMR signals of the hydrogen and carbon nuclei were readily assigned based on the earlier reported data for starting daunorubicin [28] since the signals corresponding to the piperonal moiety did not overlap with those of the anthracycline core.

Hence, a new daunorubicin derivative was obtained that contains a carbamate group and a piperonal residue, which testifies the convenience of the chosen method for introducing pharmacophore groups into the anthracycline derivatives.

Direct amidation of daunorubicin

The amide derivatives of daunorubicin are widely represented in the literature [15, 21, 29]. Owing to the existence of a large number of coupling agents, this method appears to be the most facile one for introducing different pharmacophore and functional groups even into complex labile structures such as daunorubicin.

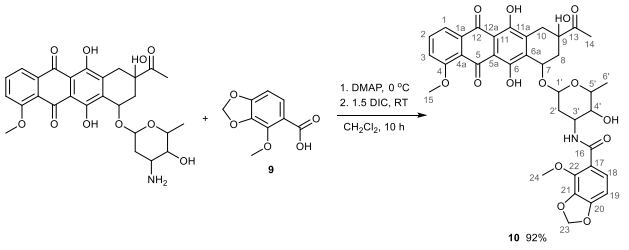
The starting compound was carboxylic acid **9** that contains a methoxy-substituted piperonyl moiety. The most convenient method for the oxidation of corresponding aldehyde **8** appeared to be one that utilizes freshly precipitated silver oxide (Scheme 4). Substituted piperonal **8** was suspended in a mixture of an aqueous solution of $AgNO_3$ and EtOH. Then, 6% aq. KOH was added dropwise under stirring [30]. The reaction was controlled visually: as soon as it became homogeneous and transparent, the process was terminated. Metallic silver that precipitated from the mixture can be recycled: after the separation and dissolution in HNO_3, resulting silver nitrate can be reused in similar reactions.



Scheme 4. Synthesis of acid **9** bearing a benzo[*d*][1,3]dioxol-5-yl moiety.

The purity of acid **9** [31] was confirmed by the ^1H and ^{13}C NMR spectroscopic data. Then, it was introduced into the target reaction that led to daunorubicin amide **10** (Scheme 5) in the presence of a base, namely, 4-dimethylaminopyridine and a

coupling agent, diisopropylcarbodiimide (DIC), according to the published procedure [32].



Scheme 5. Synthesis of daunorubicin amide **10**.

New amide **10** was isolated after the chromatographic purification as a red microcrystalline powder. Its structure was unambiguously confirmed by the IR and NMR spectroscopic data, while its composition was supported by high-resolution mass spectrometry.

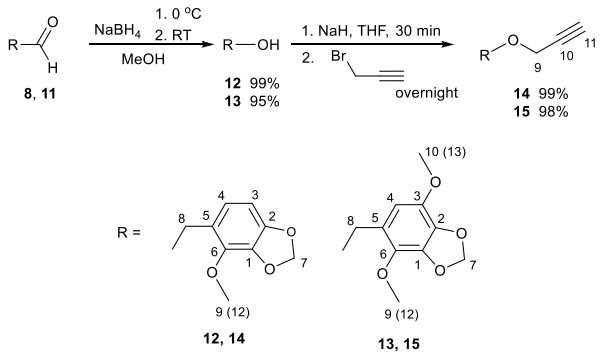
Hence, we extended the range of the daunorubicin amides with the new derivative bearing both a benzo[*d*][1,3]dioxol-5-yl moiety and a methoxy group.

Application of 1,3-dipolar cycloaddition of azides to terminal acetylenes

Click chemistry is a well-known and convenient method for introducing pharmacophore groups that offers simplicity and economic feasibility [33]. The 1,3-dipolar cycloaddition of terminal alkynes to azides can be used to readily modify the molecules with different functional groups or to conjugate natural compounds *via* a triazole linker [32].

In order to construct a 1,2,3-triazole core, it is necessary to modify first the structure of starting anthracycline by the introduction of an azide group or a terminal triple bond. As is known, an azide derivative of daunorubicin can readily be obtained from azidoacetic acid by the above-mentioned direct amidation [32].

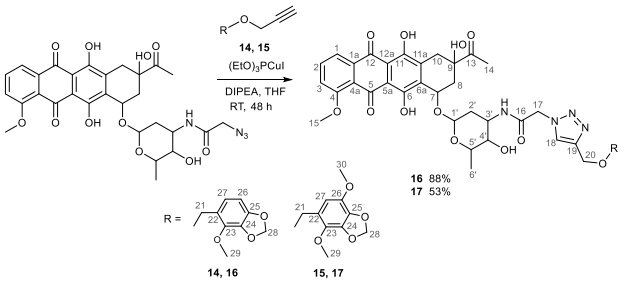
The acetylene components were propargyl ethers of mono- and dimethoxy-substituted piperonals **8** and **11**. The chosen aldehydes were reduced to the corresponding alcohols under the action of sodium borohydride (Scheme 6) [26]. The resulting alcohols, isolated in almost quantitative yields (99% and 95%), represented slightly colored crystalline solids which were characterized using ^{1}H and ^{13}C NMR spectroscopy and then, without additional purification, were introduced into the reaction for the synthesis of propargyl derivatives (Scheme 6).



Scheme 6. Synthesis of propargyl ethers **14**, **15**.

Compounds **14** and **15** were obtained by the one pot Williamson reaction. The interaction of alcohols **12**, **13** with sodium hydride in THF afforded the corresponding sodium derivatives. Their further reaction with propargyl bromide was readily accomplished upon heating in THF for 24 h (TLC and ^{1}H NMR control). The products were yellow oils which were isolated by the chromatographic purification and characterized by the NMR spectroscopic techniques. Their compositions were confirmed by the elemental analysis. Target propargyl ethers **14** and **15** were obtained in quantitative yields (98–99%).

To accomplish the 1,3-dipolar addition of azides to acetylenes, diisopropylethylamine (DIPEA) was used as a base and $CuI{\cdot}P(OEt)_3$ was used as a catalyst (Scheme 7) [32]. Other commonly used catalysts for this type of transformations—*in situ* generated Cu^I salts, CuI or CuBr—appeared to be inefficient for such a complex and labile structure as daunorubicin. The reaction proceeded for 48 h at room temperature. The following spectroscopic analysis (IR, ^{1}H and ^{13}C NMR spectroscopy) allowed for unambiguous assignment that the reaction proceeds without complications, regioselectively affording target 1,2,3-triazole derivatives **16** and **17** that contain a benzo[*d*][1,3]dioxol-5-yl moiety as well as one or two methoxy groups.



Scheme 7. Application of the click chemistry methodology.

Compounds **16** and **17** were isolated after the chromatographic purification as red crystalline powders. The yields were 88% and 53%, respectively. Their compositions were confirmed by high-resolution mass spectrometry.

Hence, using the click chemistry methodology, two new daunorubicin derivatives were obtained that contain a benzo[*d*][1,3]dioxol-5-yl pharmacophore group with one or two methoxy groups.

Cytotoxicity of the compounds obtained

All the new compounds obtained in the current study were screened for preliminary cytotoxic activity at the Institute of Physiologically Active Substances, Russian Academy of Sciences (Chernogolovka, Moscow Oblast). The cancer cell lines were lung carcinoma A549, rabdomyosarcoma RD, colon carcinoma HCT116, and breast adenocarcinoma MCF7 (Table 1). Furthermore, all the compounds were tested also against immortalized human embryonic epithelial kidney cells HEK293. The resulting cytotoxicities were compared to that of the reference—starting daunorubicin (**DR**).

The results presented in Table 1 show that all the derivatives have moderate cytotoxic effects on all four cancer lineages explored. When comparing the IC_{50} values for the cancer cells

with those obtained for non-cancerous HEK293 cells, one can note quite a high selectivity of their action on the cancer cells.

Table 1. Cytotoxicity of the compounds obtained

Comp.	IC_{50}, μM				
	A549	RD	HCT116	MCF7	HEK293
7	16.0 ± 0.2	12.6 ± 0.5	61.2± 4.2	96.7 ± 3.9	654.4 ± 15.2
10	20.5 ± 2.4	34.0 ± 1.7	21.3 ± 1.6	53.5 ± 6.6	530.5 ± 28.0
16	47.4 ± 2.2	71.4 ± 5.5	17.1 ± 0.6	109.9 ± 4.5	776.0 ± 32.9
17	43.4 ± 4.1	157.8 ± 5.3	27.6 ± 4.0	37.8 ±2.3	447.7 ± 13.9
DR	< 0.5	2.5 ± 0.1	< 0.2	< 0.6	11.2 ± 0.2

The comparison of the compounds bearing the carbamate and amide linkers with the 1,2,3-triazole derivatives revealed that they display similar cytotoxic effects. There are no essential advantages of the more complex (1,2,3-triazole) linkers compared to its simple analogs. Analyzing the effect of the introduced functional groups, more precisely, the effect of different substituted piperonal residues, it should be noted that the highest cytotoxicity among the compounds obtained was characteristic of those bearing a piperonal residue, *i.e.*, carbamate **7** (on A549 and RD cell lines) and its monosubstituted analog, namely, amide **10** (on A549 and HCT116 lines). The results obtained show the potential of this type of daunorubicin derivatives for further investigations.

Experimental

General remarks

The multinuclear ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (at 400.13 and 100.61 MHz operating frequencies, respectively) in D_2O and $CDCl_3$ solutions using residual or deuterated solvent signals (^{1}H, ^{13}C) as internal references. The ^{13}C NMR spectra were recorded in the $^{13}C\{^{1}H\}$ *J*MODECHO mode; the signals of carbon nuclei with even and odd numbers of protons had opposite polarity. The signals of the daunorubicin derivatives were assigned according to Ref. [28]. The IR spectra were obtained on a FT-IR spectrometer (InfraRed Bruker Tensor 37) for sample pellets in KBr in the range of 400–4000 cm^{-1} with the resolution of 2 cm^{-1} using 32 scans. The high-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The measurements were performed in a positive ion mode (interface capillary voltage 4500 V) in the mass range from *m*/*z* 50 to *m*/*z* 3000; the external or internal calibration was accomplished with an ESI Tuning Mix, Agilent. A syringe injection was used for acetonitrile solutions (flow rate 4 μL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 or 200 °C. The reactions were monitored by TLC on alumina TLC plates w/UV254. The chromatographic purification of the compounds was carried out on Macherey-Nagel silica gel (MN Kieselgel 60, 70–230 mesh) using gradient solvent systems: petroleum ether–CH_2Cl_2 (100:1 → 1:1) and $CHCl_3$–MeOH (100:1 → 10:1). Daunorubicin hydrochloride was purchased from Aldrich. The commercially available starting materials were used without further purification. The structures of all the obtained compounds were studied using the equipment of the Center for Molecular Composition Studies of INEOS RAS. The elemental analyses were carried out in the Laboratory for Microanalysis of INEOS RAS. The HRMSs were recorded at the Department of Structural Studies of Zelinsky Institute of Organic Chemistry (Moscow). The anticancer studies were performed at the Institute of Physiologically Active Substances, Russian Academy of Sciences (Chernogolovka, Moscow Oblast). All the resulting daunorubicin derivatives decompose when heated above 200 °C. All the products form strong complexes with $CHCl_3$, which do not decompose even after prolonged exposure to P_2O_5 under vacuum.

Syntheses

General procedure for the synthesis of the alcohols. $NaBH_4$ (0.95 g, 25.1 mmol) was added portionwise to a stirred solution of the corresponding aldehyde (16.7 mmol) in MeOH (25 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. Then, the solvent was evaporated and water (5 mL) was added to the residue obtained. The target product was extracted with ethyl acetate (3×7 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Products **12**, **13** were purified by the recrystallization from Et_2O–petroleum ether [26].

(4-Methoxybenzo[*d*][1,3]dioxol-5-yl)methanol (12). White fine-crystalline compound [34], yield 0.94 g (99%). ^{1}H NMR ($CDCl_3$, 400 MHz, *δ*, ppm, *J*, Hz): 6.76 (d, 1H, $^{3}J_{HH}$ = 7.9, $C^{3}H$), 6.50 (d, 1H, $^{3}J_{HH}$ = 7.9, $C^{4}H$), 5.94 (s, 2H, $C^{7}H_2$), 4.59 (s, 2H, $C^{8}H_2$), 4.07 (s, 3H, $C^{9}H_3$), 2.27 (br. s, 1H, OH). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, *δ*, ppm): 149.19 (C^{6}), 141.52 (C^{1}), 135.82 (C^{2}), 125.92 (C^{5}), 121.86 (C^{3}), 102.10 (C^{4}), 100.83 (C^{7}), 61.71 (C^{8}), 59.56 (C^{9}).

(4,7-Dimethoxybenzo[*d*][1,3]dioxol-5-yl)methanol (13). White fine-crystalline compound, m. p. 84–85 °C, yield 0.71 g (95%). ^{1}H NMR ($CDCl_3$, 400 MHz, *δ*, ppm, *J*, Hz): 6.50 (s, 1H, $C^{4}H$), 5.99 (s, 2H, $C^{7}H_2$), 4.60 (s, 2H, $C^{8}H_2$), 3.98 and 3.88 (both s, 3H + 3H, $C^{9}H_3$ and $C^{10}H_3$), 2.06 (br. s, 1H, OH). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, *δ*, ppm): 138.67, 137.88 (C^{3}, C^{6}), 136.38, 136.09 (C^{1}, C^{2}), 125.95 (C^{5}), 107.56 (C^{4}), 101.58 (C^{7}), 61.53 (C^{8}), 59.98, 56.73 (C^{9}, C^{10}). Anal. Calcd for $C_{10}H_{12}O_4$: C, 56.60; H, 5.70. Found: C, 56.66; H, 5.79%.

Benzo[*d*][1,3]dioxol-5-ylmethyl(4-nitrophenyl)carbonate (6). A solution of 4-nitrophenyl chlorocarbonate (1.09 g, 5.4 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of alcohol **5** (0.82 g, 5.4 mmol) and triethylamine (0.55 g, 5.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon atmosphere. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. Then ice water (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2×10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under vacuum. The residue obtained was purified by column chromatography on SiO_2 (eluent: petroleum ether–CH_2Cl_2) to give the target compound as white crystals [25]. M. p.: 124.6–125.0 °C. Yield: 3.30 g (88%). ^{1}H NMR ($CDCl_3$, 400 MHz, *δ*, ppm, *J*, Hz): 8.30 and 8.28 (both br. s, 1H + 1H, $C^{11}H$, $C^{13}H$), 7.41 and 7.39 (both br. s, 1H + 1H, $C^{10}H$, $C^{14}H$), 6.96–6.94 (m, 2H, $C^{4}H$, $C^{6}H$), 6.86 (br. s, 1H, $C^{3}H$), 6.02 (s, 2H, $C^{15}H_2$), 5.22 (s, 2H, $C^{7}H_2$). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, *δ*, ppm): 155.42 (C^{9}), 152.31 (C^{8}), 148.25, 147.90 (C^{1}, C^{2}), 145.29 (C^{12}), 127.74 (C^{5}), 125.17 (C^{11}, C^{13}), 122.97 (C^{4}), 121.65 (C^{10}, C^{14}), 109.27 (C^{3}), 108.31 (C^{6}), 101.26 (C^{15}), 70.94 (C^{7}). Anal.

Calcd for $C_{15}H_{11}NO_7$: C, 56.79; H, 3.49; N, 4.41. Found: C, 56.64; H, 3.54; N, 4.71%.

4-Methoxybenzo[*d*][1,3]dioxole-5-carboxylic acid (9). A solution of $AgNO_3$ (1.05 g, 6.2 mmol) in water (1 mL) was added to stirred ethanol (15 mL), then aldehyde **8** (0.38 g, 2.5 mmol) was suspended. 6% aq. KOH (11 mL) was added dropwise to the resulting mixture, after which it was stirred for 2 h. All the solids were filtered off and washed with 1% aq. KOH (10 mL). The alkaline filtrate was extracted with diethyl ether (20 mL); then the aqueous layer was separated, acidified with HCl (pH = 3), and extracted with $CHCl_3$ (4×20 mL). The organic extracts were combined, washed with water, dried over anhydrous Na_2SO_4, and evaporated under vacuum. Product **9** was isolated as a pink fine-crystalline solid [31] and used in the following syntheses without additional purification. Yield: 0.61 g (94%). ^{1}H NMR (D_2O, 400 MHz, δ, ppm, J, Hz): 6.86 (d, 1H, $^3J_{HH}$ = 8.0, C^4H), 6.52 (d, 1H, $^3J_{HH}$ = 8.0, C^3H), 5.88 (s, 2H, C^7H_2), 3.82 (s, 3H, C^9H_3). $^{13}C\{^1H\}$ NMR (D_2O, 100 MHz, δ, ppm): 175.40 (C^8), 149.35 (C^2), 143.27 (C^6), 137.18 (C^1), 126.21 (C^4), 103.69 (C^3), 101.45 (C^7), 63.35 (C^9).

General procedure for the syntheses of the propargyl ethers. Sodium hydride (0.10 g, 2.5 mmol) was added portionwise to a stirred solution of the corresponding alcohol (1.5 mmol) in THF (10 mL). The resulting mixture was stirred for 30 min under argon atmosphere until the release of hydrogen completed and the solution became transparent. A solution of bromoprop-1-yne (0.27 g, 2.3 mmol) in THF (5 mL) was added under vigorous stirring to the resulting mixture of the sodium alkoxide. The reaction mixture was stirred at 50 °C for 24 h. After cooling to room temperature, water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Products **14**, **15** were purified by column chromatography on SiO_2 (eluent: petroleum ether–CH_2Cl_2).

4-Methoxy-5-((prop-2-yn-1-yloxy)methyl)benzo[*d*][1,3]-dioxole (14). Yellow oil, yield 0.33 g (99%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm, J, Hz): 6.85 and 6.54 (both d, 1H + 1H, $^3J_{HH}$ = 8.0, C^3H, C^4H), 5.95 (s, 2H, C^7H_2), 4.57 (s, 2H, C^8H_2), 4.19 (d, 2H, $^4J_{HH}$ = 2.1, C^9H_2), 4.03 (s, 3H, $C^{12}H_3$), 2.48 (t, 1H, $^4J_{HH}$ = 1.9, $C^{11}H$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, δ, ppm): 149.33, 142.00, 136.33 (C^1, C^2, C^6), 123.25 (C^4), 122.50 (C^5), 102.32 (C^3), 100.86 (C^7), 79.82 (C^{10}), 74.17 (C^{11}), 66.51 (C^8), 59.79 (C^{12}), 56.76 (C^9). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found, %: C, 65.25; H, 5.44%.

4,7-Dimethoxy-5-((prop-2-yn-1-yloxy)methyl)benzo-[*d*][1,3]dioxole (15). Yellow oil, yield 0.45 g (98%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm, J, Hz): 6.56 (s, 1H, C^4H), 5.99 (s, 2H, C^7H_2), 4.56 (s, 2H, C^8H_2), 4.20 (d, 2H, $^4J_{HH}$ = 2.4, C^9H_2), 3.93 and 3.88 (both s, 3H + 3H, $C^{12}H_3$, $C^{13}H_3$), 2.49 (t, 1H, $^4J_{HH}$ = 2.4, $C^{11}H$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, δ, ppm): 138.96, 138.34, 136.60, 136.58 (C^1, C^2, C^3, C^6), 122.68 (C^5), 108.39 (C^4), 101.61 (C^7), 79.69 (C^{10}), 74.31 (C^{11}), 66.36 (C^8), 60.29, 56.67 (C^{12}, C^{13}), 56.98 (C^9). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.65. Found, %: C, 62.45; H, 5.69%.

Benzo[*d*][1,3]dioxol-5-ylmethyl(6-([(*1S*,*3S*)-3-acetyl-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexa-hydrotetracen-1-yl]oxy)-(*2S*,*3S*,*4S*,*6R*)-3-hydroxy-2-methyl-tetrahydro-*2H*-pyran-4-yl)carbamate (7). A solution of 4-nitrophenyl carbonate **6** (0.13 g, 0.4 mmol), daunorubicin (0.23 g, 0.4 mmol), and Et_3N (0.08 g, 0.8 mmol) in DMF (5 mL) was stirred at room temperature for 24 h. The reaction course was monitored by TLC ($CHCl_3$–MeOH = 50 : 5). After addition of cold water (10 mL), the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue obtained was purified by column chromatography on SiO_2 (eluent: $CHCl_3$–MeOH) to give the target compound as a dark red powder [24]. Yield: 0.24 g (96%). M. p.: > 200 °C (dec.). IR (KBr, ν, cm^{-1}): 3483(br, m) and 3432(br, m) (both ν_{OH}), 2972(sh, w), 2935(m) and 2904(sh, w) (three ν_{CH}), 1716(br, s) ($\nu_{C=O}$), 1618(s) and 1578(s) (both $\nu_{C=C}$), 1504(m), 1492(s), 1446(s) and 1414(s) (both δ_{OH}), 1352(m), 1286(vs), 1235(s) and 1209(s) (both $\nu_{C–O}$), 1118(m), 1085(sh, m), 1069(m), 1035(s), 1010(sh, s) and 985 (vs) ($\delta_{C=C}$), 930(m), 873(w), 820(sh, m), 809 (m), 793(m), 766(w), 729(vw), 696(vw), 613(vw), 463(vw). ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm, J, Hz): 13.85 (s, 1H, C^6OH), 13.07 (s, 1H, $C^{11}OH$), 7.90 (d, 1H, $^3J_{HH}$ = 7.5, C^1H), 7.69 (t, 1H, $^3J_{HH}$ = 7.9, C^2H), 7.31 (d, 1H, $^3J_{HH}$ = 8.7, C^3H), 6.71 (s, 1H, $C^{19}H$), 6.69–6.64 (m, 2H, $C^{20}H$, $C^{23}H$), 5.87 (s, 2H, $C^{24}H_2$), 5.46 (br. s, 2H, $C^{17}H_2$), 5.14 (s, 1H, $C^{1''}H$), 4.86 (br. s, 2H, C^7H, OH), 4.50 (br. s, 1H, OH), 4.19 (q, 1H, $^3J_{HH}$ = 6.0, $C^{5'}H$), 4.01 (s, 3H, $C^{15}H_3$), 3.88 (br. s, 1H, $C^{4'}H$), 3.66 (s, 1H, $C^{3'}H$), 3.08 (d, 1H, $^2J_{HH}$ = 18.6, $C^{10}H_{eq}$), 2.65 (d, 1H, $^2J_{HH}$ = 18.6, $C^{10}H_{ax}$), 2.40 (s, 3H, $C^{14}H_3$), 2.27 (d, 1H, $^2J_{HH}$ = 14.2, C^8H_{eq}), 2.05 (d, 1H, $^2J_{HH}$ = 14.2, C^8H_{ax}), 1.88–1.80 (m, 2H, $C^{2'}H_2$), 1.27 (d, 3H, $^3J_{HH}$ = 6.0, $C^{6'}H_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, δ, ppm): 212.23 (C^{13}), 186.41, 186.03 (C^5, C^{12}), 160.62 (C^4), 156.09, 155.39, 155.33 (C^6, C^{11}, C^{16}), 147.40, 147.18 (C^{21}, C^{22}), 135.42 (C^2), 134.99 (C^{1a}), 134.11, 133.74 (C^{6a}, C^{11a}), 129.90 (C^{18}), 121.84 (C^{19}), 120.29 (C^{4a}), 119.44, 118.16 (C^1, C^3), 110.98, 110.83 (C^{5a}, C^{12a}), 108.67, 107.90 (C^{20}, C^{23}), 100.86 ($C^{1'}$), 76.45 (C^9), 69.83, 69.37, 67.05 (C^7, $C^{4'}$, $C^{5'}$), 66.39 (C^{17}), 56.31 (C^{15}), 46.94 ($C^{3'}$), 34.74, 33.02, 29.92 (C^8, C^{10}, $C^{2'}$), 24.76 (C^{14}), 16.55 ($C^{6'}$). Anal. Calcd for $C_{36}H_{35}NO_{14}\cdot 0.5CHCl_3$: C, 57.28; H, 4.68; N, 1.83. Found: C, 57.03; H, 5.00; N, 2.05%.

***N*-(6-([(*1S*,*3S*)-3-Acetyl-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl]oxy)-(*2S*,*3S*,*4S*,*6R*)-3-hydroxy-2-methyltetrahydro-*2H*-pyran-4-yl)-4-methoxybenzo[*d*][1,3]dioxole-5-carboxamide (10)**. A solution of daunorubicin hydrochloride (0.23 g, 0.4 mmol), acid **9** (0.08 g, 0.4 mmol), and DMAP (0.05 g, 0.4 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and stirred for 1 h. Then, DIC (0.08 g, 0.6 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 10 h. The resulting precipitate was separated by filtration; the filtrate was washed with saturated aqueous solution of NH_4Cl, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue obtained was purified by column chromatography on SiO_2 (eluent: $CHCl_3$–MeOH) [22] to give the target product as a red powder. Yield: 0.23 g (92%). M. p.: > 200 °C (dec.). IR (KBr, ν, cm^{-1}): 3465(br, m) and 3385 (br, m) (both ν_{OH}), 2973(sh, w), 2935(m) and 2843 (sh, w) (three ν_{CH}), 1716(m) ($\nu_{C=O}$), 1647(s), 1616(s) and 1578(s) (both $\nu_{C=C}$), 1529(m), 1470(s), 1445(s) and 1414(s) (both δ_{OH}), 1345(m), 1285(sh, vs), 1272(s), 1231(s) and 1209(s) (both $\nu_{C–O}$), 1119(m), 1068(s), 1036(m), 1012(sh, s) and 985(vs) ($\delta_{C=C}$), 919(m), 820(m), 793(m), 764(m), 735(w), 696(vw), 614(vw), 469(w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm, J,

Hz): 13.99 (br. s, 2H, C^6OH, $C^{11}OH$), 8.06 (d, 1H, $^3J_{HH}$ = 7.6, C^1H), 7.81 (t, 1H, $^3J_{HH}$ = 8.0, C^2H), 7.42 (d, 1H, $^3J_{HH}$ = 8.5, C^3H), 6.67 (d, 1H, $^3J_{HH}$ = 8.1, $C^{18}H$), 6.44 (d, 1H, $^3J_{HH}$ = 7.9, $C^{19}H$), 5.90 (s, 2H, $C^{23}H_2$), 5.55–5.54 (m, 1H, OH), 5.32 (br. s, 1H, $C^{1'}H$), 4.73 (br. s, 1H, OH), 4.11 (br. s, 5H, $C^{15}H_3$, C^7H, $C^{5'}H$), 4.00 (s, 3H, $C^{24}H_3$), 3.79–3.75 (m, 1H, $C^{4'}H$), 3.63–3.59 (m, 1H, $C^{3'}H$), 3.25 (d, 1H, $^2J_{HH}$ = 19.0, $C^{10}H_{eq}$), 2.99 (d, 1H, $^2J_{HH}$ = 18.9, $C^{10}H_{ax}$), 2.45 (s, 3H, $C^{14}H_3$), 2.39 (d, 1H, $^2J_{HH}$ = 15.7, C^8H_{eq}), 2.14–2.10 (m, 1H, C^8H_{ax}), 1.87–1.80 and 1.66–1.62 (both m, 1H + 1H, $C^{2'}H_2$), 1.42 (d, 3H, $^3J_{HH}$ = 6.5, $C^{6'}H_3$). $^{13}C\{^1H\}$ ($CDCl_3$, 100 MHz, δ, ppm): 212.24 (C^{13}), 186.77, 186.37 (C^5, C^{12}), 166.89 (C^{16}), 160.72 (C^4), 156.30, 155.68 (C^6, C^{11}), 151.63 (C^{22}), 141.83 (C^{20}), 136.67 (C^{1a}), 135.47 (C^2), 135.24 (C^{21}), 134.33, 133.00 (C^{6a}, C^{11a}), 125.97 (C^{18}), 120.57 (C^{17}), 118.45 (C^{4a}), 119.51, 118.15 (C^1, C^3), 111.25, 111.01 (C^{5a}, C^{12a}), 103.33 (C^{19}), 101.68 (C^{23}), 100.83 ($C^{1'}$), 76.58 (C^9), 70.06, 69.18, 67.01 (C^7, $C^{4'}$, $C^{5'}$), 60.21 (C^{24}), 56.42 (C^{15}), 45.78 ($C^{3'}$), 34.98, 33.21, 29.84 (C^8, C^{10}, $C^{2'}$), 24.78 (C^{14}), 16.73 ($C^{6'}$). HRMS (ESI): m/z found 706.2146, 723.2406, 744.1688; calcd for $C_{36}H_{35}NO_{14}$ 706.2130 ($M + H^+$), 723.2396 ($M + NH_4^+$), 744.1689 ($M + K^+$).

General procedure for the syntheses of the daunorubicin 1,2,3-triazole derivatives. DIPEA (0.3 mol %) and catalyst $(EtO)_3P{\cdot}CuI$ (0.2 mol %) were added to a stirred solution of the corresponding acetylene (**14** or **15**) (0.5 mmol) and the azide derivative of daunorubicin (0.5 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature for 48 h (TLC monitoring). The volatile products were removed under reduced pressure. The target products (**16**, **17**) were purified by column chromatography on SiO_2 (eluent: $CHCl_3$–MeOH) [22].

***N*-(6-([(*1S*,*3S*)-3-Acetyl-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl]oxy)-(*2S*,*3S*,*4S*,*6R*)-3-hydroxy-2-methyltetrahydro-*2H*-pyran-4-yl)-2-(4-((4-methoxybenzo[*d*][1,3]dioxol-5-ylmethoxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (16).** Bright red powder, yield 0.12 g (88%), m. p. > 200 °C (dec.). IR (KBr, ν, cm^{-1}): 3414(br, m) (ν_{OH}), 2973(sh, w) and 2936(m) (both ν_{CH}), 1715(s) and 1675(s) (both $\nu_{C=O}$), 1618(s) and 1579(s) (both $\nu_{C=C}$), 1534(m), 1470(s), 1436(sh, s) and 1414(s) (both δ_{OH}), 1377(m), 1352(m), 1285(vs), 1262(s), 1232(s) and 1209(s) (both $\nu_{C–O}$), 1122(m), 1069(vs), 1046(s), 1016(s) and 987(vs) ($\delta_{C=C}$), 939(w), 918(w), 812(sh, m), 794(m), 765(w), 740(vw), 696(vw), 463(vw). ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm, J, Hz): 13.97 (s, 1H, C^6OH), 13.27 (s, 1H, $C^{11}OH$), 8.02 (d, 1H, $^3J_{HH}$ = 7.6, C^1H), 7.78 (t, 1H, $^3J_{HH}$ = 8.2, C^2H), 7.38 (d, 1H, $^3J_{HH}$ = 8.5, C^3H), 7.29 (s, 1H, $C^{18}H$), 6.80 (d, 1H, $^3J_{HH}$ = 7.2, $C^{27}H$), 6.49 (d, 1H, $^3J_{HH}$ = 7.7, $C^{26}H$), 5.92 (s, 2H, $C^{28}H_2$), 5.48 (br. s, 1H, OH), 5.23 (br. s, 1H, $C^{1'}H$), 5.11 and 5.04 (both br. s, 1H + 1H, $C^{17}H_2$), 4.68 and 4.52 (both br. s, 2H + 2H, $C^{20}H_2$, $C^{21}H_2$), 4.19–4.11 (m, 2H, C^7H, $C^{5'}H$), 4.06 (s, 3H, $C^{15}H_3$), 3.97 (br. s, 4H, $C^{29}H_3$, $C^{4'}H$), 3.61 (br. s, 1H, $C^{3'}H$), 3.23 and 2.93 (both d, 1H + 1H, $^2J_{HH}$ = 18.8, $C^{10}H_2$), 2.42 (s, 3H, $C^{14}H_3$), 2.32 and 2.10 (both dd, 1H + 1H, $^2J_{HH}$ = 14.7, $^3J_{HH}$ = 3.7, C^8H_2), 1.83 (br. s, 2H, $C^{2'}H_2$), 1.27 (d, 3H, $^3J_{HH}$ = 6.0, $C^{6'}H_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, δ, ppm): 211.98 (C^{13}), 186.17, 185.87 (C^5, C^{12}), 164.61 (C^{16}), 160.51 (C^4), 156.02, 155.22 (C^6, C^{11}), 155.26 (C^{19}), 149.19 (C^{23}), 141.69 (C^{25}), 136.10 (C^{24}), 135.36 (C^2), 135.28 (C^{18}), 134.87 (C^{1a}), 134.04, 133.89 (C^{6a}, C^{11a}), 123.06 (C^{27}), 122.53 (C^{4a}), 120.19 (C^{22}), 119.35, 118.15 (C^1, C^3), 110.88, 110.69 (C^{5a}, C^{12a}), 102.24 (C^{26}), 100.83 (C^{28}), 100.25 ($C^{1'}$), 76.36 (C^9), 69.25, 68.28, 67.11 (C^7, $C^{4'}$, $C^{5'}$), 67.36 (C^{20}), 62.85 (C^{21}), 59.62 (C^{29}), 56.25 (C^{15}), 52.31 (C^{17}), 46.07 ($C^{3'}$), 34.62, 33.01, 29.01 (C^8, C^{10}, $C^{2'}$), 24.69 (C^{14}), 16.54 ($C^{6'}$). HRMS (ESI): m/z found 831.2738, 848.2992, 853.2543, 869.2282; calcd for $C_{41}H_{42}N_4O_{15}$ 831.2719 ($M + H^+$), 848.2985 ($M + NH_4^+$), 853.2539 ($M + Na^+$), 869.2278 ($M + K^+$).

***N*-(6-([(*1S*,*3S*)-3-Acetyl-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl]oxy)-(*2S*,*3S*,*4S*,*6R*)-3-hydroxy-2-methyltetrahydro-*2H*-pyran-4-yl)-2-(4-((4,7-dimethoxybenzo[*d*][1,3]dioxol-5-ylmethoxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide** (**17**). Burgundy powder, yield 0.06 g (53%), m. p. > 200 °C (dec.). IR (KBr, ν, cm^{-1}): 3422(br, m) (ν_{OH}), 2973(sh, w), 2936(m) and 2845(sh, w) (three ν_{CH}), 1715(m) ($\nu_{C=O}$), 1672(m), 1617(s) and 1578(s) (both $\nu_{C=C}$), 1507(m), 1447(s), 1432(s) and 1414(s) (both δ_{OH}), 1377(m), 1352(m), 1286(vs), 1231(s) and 1209(s) (both $\nu_{C–O}$), 1128(m), 1067(s), 1048(s), 1017(s), 987(vs) ($\delta_{C=C}$), 873(w), 851(sh, w), 824(m), 765(m), 695(vw), 463(w) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm, J, Hz): 13.83 (s, 1H, C^6OH), 13.04 (s, 1H, $C^{11}OH$), 7.88 (d, 1H, $^3J_{HH}$ = 8.1, C^1H), 7.77 (s, 1H, $C^{18}H$), 7.69 (t, 1H, $^3J_{HH}$ = 8.0, C^2H), 7.26 (d, 1H, $^3J_{HH}$ = 8.6, C^3H), 6.47 (s, 1H, $C^{27}H$), 5.92 (s, 2H, $C^{28}H_2$), 5.38 (br. s, 1H, OH), 5.17–5.00 (m, 4H, $C^{1'}H$, C^7H, $C^{17}H_2$), 4.62 and 4.45 (both br. s, 2H + 2H, $C^{20}H_2$, $C^{21}H_2$), 4.15–4.05 (m, 2H, $C^{5'}H$, $C^{4'}H$), 3.92 (s, 3H, $C^{15}H_3$), 3.82 and 3.78 (both s, 3H + 3H, $C^{29}H_3$, $C^{30}H_3$), 3.59 (br. s, 1H, $C^{3'}H$), 3.06 and 2.69 (both d, 1H + 1H, $^2J_{HH}$ = 18.6, $C^{10}H_2$), 2.37 (s, 3H, $C^{14}H_3$), 2.21 and 1.95 (both d, 1H + 1H, $^2J_{HH}$ = 14.6, C^8H_2), 1.82 and 1.78 (both br. s, 1H + 1H, $C^{2'}H_2$), 1.24 (d, 3H, $^3J_{HH}$ = 6.1, $C^{6'}H_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, δ, ppm): 211.88 (C^{13}), 186.32, 186.00 (C^5, C^{12}), 164.48 (C^{16}), 160.59 (C^4), 156.06, 155.31 (C^6, C^{11}), 155.45 (C^{19}), 138.82, 138.16 (C^{24}, C^{25}), 136.47, 136.36 (C^{23}, C^{26}), 135.39 (C^2), 134.98 (C^{1a}), 134.08, 133.86 (C^{6a}, C^{11a}), 122.77 (C^{4a}), 120.32 (C^{22}), 119.42, 118.16 (C^1, C^3), 117.68 (C^{18}), 110.98, 110.78 (C^{5a}, C^{12a}), 108.52 (C^{27}), 101.56 (C^{28}), 100.25 ($C^{1'}$), 76.37 (C^9), 69.38, 68.40, 67.06 (C^7, $C^{4'}$, $C^{5'}$), 67.17 (C^{20}), 62.98 (C^{21}), 60.17 (C^{15}), 56.71, 56.28 (C^{29}, C^{30}), 52.47 (C^{17}), 46.03 ($C^{3'}$), 34.68, 33.05, 29.12 (C^8, C^{10}, $C^{2'}$), 24.66 (C^{14}), 16.53 ($C^{6'}$). HRMS (ESI): m/z found 861.2831, 878.3103, 883.2656; calculated for $C_{42}H_{44}N_4O_{16}$ 861.2825 ($M + H^+$), 878.3091 ($M + NH_4^+$), 883.2645 ($M + Na^+$).

Biological studies

The antiproliferative activities of the compounds obtained were determined by the conventional MTT assay. Human cell cultures A549 (ATCC® CCL-185™), RD (ATCC® CC-136™), and HCT116 (ATCC® CCL-247™) were incubated in DMEM (NLP PanEko) supplemented with 10% FBS (HyClone®, Thermo Scientific), 2 mmol of L-glutamine (NLP PanEco), and 1% gentamicin (JSC Biochemist) at 37°C in an atmosphere with 5% CO_2. The cells were seeded in a 96-well plate (Costar®) in the amount of 1×104 cells/200 μL and cultured at 37 °C in the humid environment containing 5% CO_2. After 24 h of incubation, the tested compounds were added to the cell cultures as the solutions with different concentrations (from 100 to 0.0012 μM) and then the cells were cultured under the same conditions for 72 h. For each concentration, the experiments were performed in triplicate. All the compounds were dissolved initially in DMSO (PANREAC QUIMICA S.L.U). The final concentration of DMSO in the well did not exceed 0.1% and

was not toxic to cells. The control wells were added to the solvent in the amount of 0.1%. After incubation, 20 μL of a solution of 5 mg/mL of MTT [bromide 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium] (Sigma Aldrich) in PBS was added and the cells were incubated for further 2 h. Then, the medium was removed and 100 μL of DMSO was added to each well to dissolve the resulting formazan crystals. The optical density at 536 nm was determined with a BioTek Instruments Cytation 3 Imager plate analyzer. The concentration values that cause 50% inhibition of cell population growth (IC_{50}) were estimated from the dose-dependent curves using the OriginPro 9.0 program.

Conclusions

Hence, three different methods for introducing the pharmacophore groups with a benzo[*d*][1,3]dioxol-5-yl unit or its derivatives into the structure of daunorubicin antibiotic were demonstrated. They included the syntheses of carbamates, amides, and 1,2,3-triazoles, which allowed for extending the anthracycline family with four new representatives featuring both interesting structures and prominent biological activity.

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