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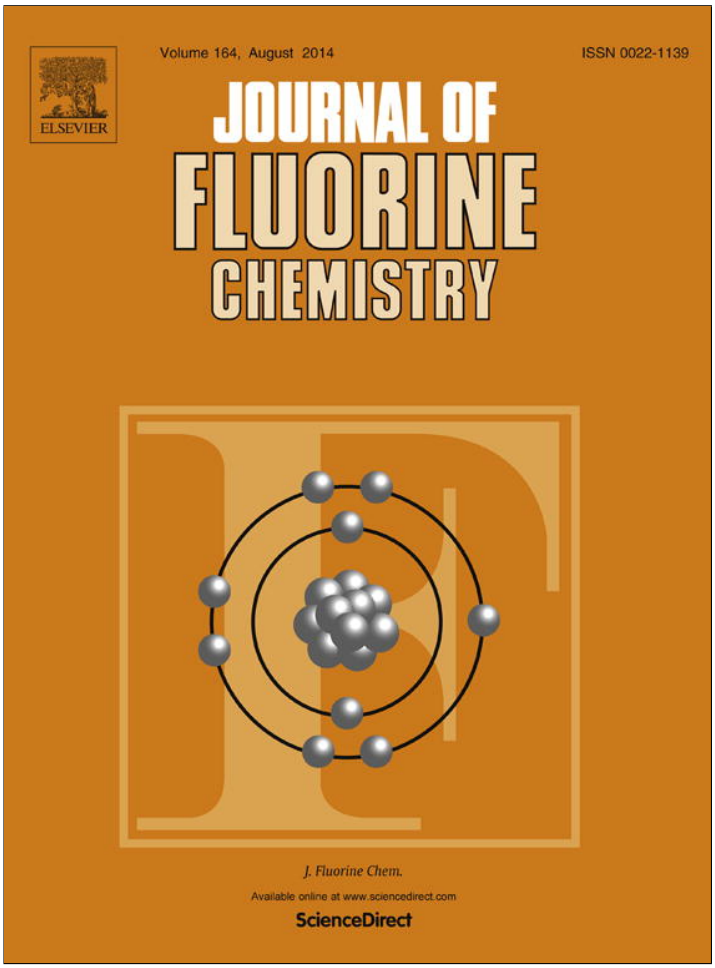

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Synthesis and cytotoxicity evaluation of polyfluorinated 1,4-naphthoquinones containing amino acid substituents

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ABSTRACT

New conjugates of polyfluorinated 1,4-naphthoquinone core with amino acid fragments were synthesized by the reactions of hexafluoro-1,4-naphthoquinone (**1**) with ethyl aminoacetate, glycine, 3-aminopropanoic, 4-aminobutanoic, and 6-aminohexanoic acids. In all the cases, the quinone **1** aminodefluorination on the 2-position occurred to give ethyl (3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)aminoacetate (**2**), (3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]acetic (**3**), 3-[(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]propanoic (**4**), 4-[(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]butanoic (**5**), and 6-[(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]hexanoic acid (**6**), respectively. A possibility to further modify a carboxylic function of ω-[5,6,7,8-tetrafluoro-1,4-naphthoquinon-2-yl]aminocarboxylic acids was demonstrated by transformation of acids **3** and **5** into the corresponding acyl chlorides **10** and **12** followed by their *in situ* conversion into N,N-diethylamides **13** and **14** or ethyl esters **15** and **16**. Upon the analogous treatment of acid **4** the primary generated acyl chloride **11** underwent an intramolecular N-acylation to yield 2,5,6,7,8-pentafluoro-3-(2-oxopyrrolidin-1-yl)naphthalene-1,4-dione (**17**) which was smoothly diethylaminodefluorinated at the 3-position to afford 2-(2-oxopyrrolidin-1-yl)-3-diethylamino-5,6,7,8-tetrafluoronaphthalene-1,4-dione (**18**). The cytotoxicity evaluation of twelve new quinones in human myeloma, human mammary adenocarcinoma, human hepatocellular carcinoma HepG2 epithelial tumor cells, normal mouse fibroblasts and Chinese hamster Ag 17 cells as well as their mutagenic and antioxidant properties in a *Salmonella* tester strain was performed. All the compounds effectively suppressed the growth of three lines of tumor cells. These data together with the better cytotoxic effect against cancer cells compared to normal mammalian cells, the bacterial cells protection against spontaneous and H_2O_2-dependent mutagenesis, and lower general toxicity toward different cells, reveal quinones **2**, **13**, **15**, **16**, and **18** as best inhibitors of tumor cells growth among the tested substances.

1. Introduction

Cyclin-dependent kinases (Cdk) are central regulators of the eukaryotic cell cycle, their phosphorylate proteins being responsible for the activation of structural and regulatory genes in transitions between G1, S, G2, and M cell cycle phases. Cdc25A, B and C are members of the family of dual specificity protein phosphatases regulating cyclin-dependent kinases by removing phosphate groups from the cyclin-dependent kinases and thus activating the cyclin-Cdk complexes, which control the cell cycle progression [1,2]. Cdc25A and Cdc25B are overexpressed in a number of tumors of various origins, frequently showing correlations with higher-grade or more aggressive tumors and poor prognosis [3]. Abnormalities in these kinases and phosphatases are closely related to many human diseases including cancer. The putative involvement of the Cdc25 phosphatases in tumorigenesis

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makes them potential targets for cancer therapy [4,5]. Among numerous substances investigated, several were found to inhibit Cdc25 family enzymes [6,7], NSC 95397 [2,3-bis-(2-hydroxyethylthio)-1,4-naphthoquinone] from the National Cancer Institute Library being the most potent Cdc25 inhibitor [8]. The *para*-quinone core is of fundamental significance for the biological activity of at least 14 clinically used therapeutics [9]. Naphthoquinone, quinoline- and isoquinoline-5,8-quinone are core scaffolds of the effective inhibitors of Cdc25 phosphatases [8–18]. Quinoline-5,8-quinones can also generate toxic oxygen species [15], which may cause toxicity toward normal tissues, their therapeutic utility thus being reduced.

One strategy for overcoming the intrinsic toxicity of quinones might be to use derivatives that are more stable in their reduced state and thus are less likely to initiate formation of radicals and indiscriminately damage cells. Interestingly, the fluorinated quinone compound – 5,6,7,8-tetrafluoro-2-(2-mercaptoethanol)-3-methyl-[1,4]-naphthoquinone (F-Cpd5), in contrast to its non-fluorinated analog (Cpd5), was predicted not to generate reactive oxygen species [16]. Overall, the calculated reduction potential of F-Cpd5 was suggestive of its higher possible therapeutic index. Indeed, F-Cpd5 is three times more potent than Cpd5 in suppressing Hep3B cell growth [16–18], inhibiting, at that, the mitogen-induced DNA synthesis in normal rat hepatocytes 12-fold less than in Hep3B cells [17]. Besides, in addition to inhibiting and redox potential functionality, fluorinated naphthoquinones (depending on the structure) might behave as polyfunctional substances, thus interacting with other cellular targets and displaying toxic, mutagenic or carcinogenic properties. Since all of them are inhibitors of Cdc25 phosphatases, only the data on toxic, mutagenic or carcinogenic properties could help to estimate their perspective as antitumor drugs. In this sense, a determination of their affinity for Cdc25 phosphatases and redox potentials seems to be of secondary importance.

For rational searching of new effective inhibitors of Cdc25 phosphatases with better inhibition of tumor cells growth and diminished unfavorable side effects, we have recently proposed to compare their cytotoxicity in human and mouse tumor cells and in primary mouse fibroblast cells in parallel with evaluation of their antioxidant and mutagenic properties using special bacterial test system. The diversely functionalized polyfluoro-1,4-naphtoquinones were shown to suppress the growth of cancer cells at significantly lower concentrations compared with normal cells. In so doing, their antioxidant and mutagenic properties in the bacterial system significantly depend upon the nature of functional groups, some of the compounds under investigation appearing highly promising [19]. This concerns, in particular, pentafluoro-1,4-naphthoquinones with functionalized alkylamino substituent in the 2-position, prepared by reactions of hexafluoro-1,4-naphthoquinone (**1**) with relevant N-nucleophiles [20]. In developing this structural motif to search new inhibitors of Cdc25 phosphatases and tumor cell growth, exerting minor or no side effects, we considered reasonable to synthesize new quinones of this type with 2-N-ω-carboxyalkyl substituents and initially assess their bioactivity mentioned above. Besides, these structural entities potentially provide numerous options for molecular design of new bioactive polyfluoro-1,4-naphthoquinone functional derivatives. For these reasons, in this article the reactions of quinone **1** with some aminoalkanoic acids, as anticipated N-centered nucleophiles, and with glycine ethyl ester were investigated as a method to synthesize the respective N-(pentafluoro-1,4-naphthoquinon-2-yl)amino acids. To ascertain a possibilities for the further refunctionalization of these acids, two of them were transformed to ethyl esters and N,N-diethylamides. Finally, for the quinones thus synthesized the cytotoxicity against cancer cells and the ability to protect bacterial cells from spontaneous and H_2O_2-induced mutagenesis were evaluated.

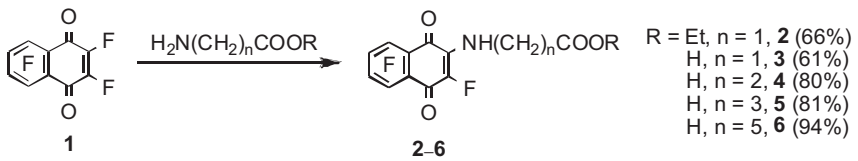
2. Results and discussion

2.1. Synthesis

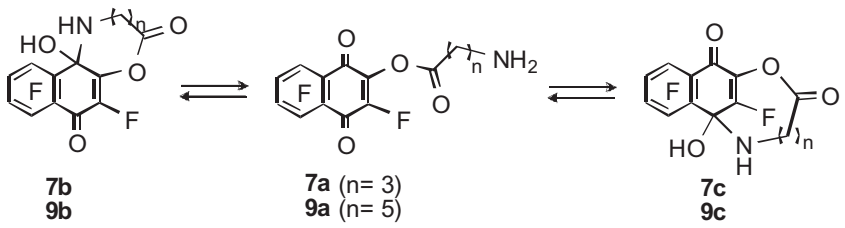
Quinone **1** reacted easily with ethyl glycinate hydrochloride in the presence of KOH in DMSO at 20 °C to afford ethyl N-(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)aminoacetate (**2**) in 66% isolated yield that reveals the ethyl glycinate amino group to be sufficiently nucleophilic for aminodefluorination on the quinone moiety of **1** despite a geminal location of the electron accepting ethylcarboxylate group. However, nothing happened with glycine in anhydrous dioxane, obviously due to the glycine insignificant solubility. In compliance with this suggestion, in aqueous dioxane quinone **1** with glycine afforded (3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)aminoacetic acid (**3**) as practically the sole product. Unlike glycine, in anhydrous dioxane 3-aminopropanoic, 4-aminobutanoic, or 6-aminohexanoic acid with quinone **1** gave acid **3** (61% isolated yield), 3-[(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]propanoic (**4**, 80%), 4-[(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]butanoic (**5**, 81%), and 6-[(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]hexanoic acid (**6**, 94%), respectively (Scheme 1).

The regioselectivity of fluorine replacement thus observed is characteristic for **1** in its reactions with various heteroatom-centered nucleophiles [19,20]. Typically for the 2-fluorine substitution by an alkylamine [20a] the reaction is practically limited to monosubstitution that testifies to retarding further replacement by the first introduced 2-(carboxyalkyl)- or 2-(ethylcarboxymethyl)amino group.

Unlike the reaction with glycine, in aqueous dioxane (20–25 vol % of water) quinone **1** with 3-aminopropanoic, 4-aminobutanoic and 6-aminohexanoic acids gave the products of both amino- and carboxydefluorination in a ~1:1 ratio (the NMR data). The latter type products are easily hydrolyzed and difficult to isolate from mixtures with the aminodefluorination products, minor educt and unidentified admixtures, so we managed to isolate only the 4-aminobutanoyloxydefluorination product (**7**) in 25% yield. The NMR (a $CDCl_3$ solution) and IR (KBr) characteristics of **7** are not in compliance with the expected primarily formed 3,5,6,7,8-pentafluoro-1,4-naphthoquinon-2-yl 4-aminobutanoate (**7a**). In particular, a somewhat broadened N–H resonance in the ^{1}H NMR spectrum (δ = 5.75 ppm) displays a unit proton intensity. In the IR spectrum only one N–H absorption (ν = 3233 cm^{-1}) is observed. These data suggest the product **7** to be one of the ring tautomers (cyclohexadienones **7b** and **7c**) of quinone **7a** (Scheme 2). In the ^{1}H NMR spectrum of **7** the O–H signal is not seen obviously because of its broadening by proton exchange. The ^{19}F NMR spectrum of **7**



Scheme 1. Synthesis of quinones **2**–**6**.



Scheme 2. Chain-ring tautomerism of the carboxydefluorination products **7** and **9**.

(Table 1, the discussion see below) is also better consistent with the ring tautomers, **7c** being more likely. The product **7** is easily hydrolyzed upon keeping unprotected toward atmospheric moisture to the known 2-hydroxypentafluoro-1,4-naphthoquinone (**8**) [21]. This seems quite understandable taking into account that tautomers **7a**,**b** are akin to carboxylic acid anhydrides. In the product mixture of the quinone **1** interaction with 6-aminohexanoic acid also recorded was a putative carboxydefluorination product (**9**) which was isolated but failed to be purified for elemental analysis because of its rapid hydrolysis. Thus, it was characterized only by ^{19}F NMR (Table 1), ^{1}H NMR (the broad O–H signal centered at $\delta \approx 7.5$ ppm is observed in this case) and IR (only one N–H absorption at $\nu = 3329$ cm^{-1} is observed) spectra which, analogously to the stated above for **7**, testify in favor of the ring-tautomer **9c** rather than tautomers **9a** and **9b**.

It seems obvious that the N- vs O-competition in the interaction of amino acids with quinone **1** depends on a correlation of concentrations and nucleophilicities of non-ionized ($H_2N(CH_2)_nCOOH$) and zwitter-ionic ($^{+}H_3N(CH_2)_nCO^{-}$) forms, taking into account the change of a reacting system polarity in going from an initial (IS) to a transition state (TS) and the solvent influence on this change. In dioxane a superposition of these factors in all cases is in favor of N-substitution, in part likely because the amino acids are substantially non-ionized. Obviously, in going from dioxane to aqueous dioxane the enhanced solvent polarity increases the content of the zwitter-ionic forms thus promoting O-substitution. The similar effect was not observed for glycine in aqueous dioxane, probably, owing to essential weakening the zwitter-ion $^{-}OOCCH_2NH_3^{+}$O-nucleophilicity by the closely located electron-withdrawing ammonium group. As to the reacting system polarity, it increases in going from ISs to both N-TSs and O-TSs (the respective modeling structures are depicted in Fig. 1) due to increasing the opposite charges separation. The latter seems practically the same in the N-TSs for all the amino acids. Unlike this, in the O-TSs the opposite charge separation obviously increases with the number (n) of methylene groups in the amino acid.

This means that the more is n (other things being equal), the more favored should be the O-substitution in its competition with the N-substitution with increased solvent polarity. Thus, the changes of product distribution both in the reactions of quinone **1** with acids $H_2N(CH_2)_nCOOH$ (n = 2, 3, and 5) in going from dioxane to aqueous dioxane, and in the latter solvent in going from n = 1 to n = 2, 3, 5 are qualitatively in line with the above expectations.

A possibility to further modify the carboxylic function of ω-[5,6,7,8-tetrafluoro-1,4-naphthoquinon-2-yl]aminocarboxylic acids was demonstrated by transformation of acids **3** and **5** into the corresponding acyl chlorides followed by their *in situ* conversion into N,N-diethylamides **13** and **14** or ethyl esters **15** and **16**. Upon the analogous treatment of acid **4** the primary generated acyl chloride **11** undergone an intramolecular acylation to yield lactamized quinone **17** which was subjected to diethylaminodefluorination at the 3-position to afford quinone **18** in 86% isolated yield (Scheme 3). Thus, as soon as formed, acylchloride **11** rapidly undergoes intramolecular N-acylation by analogy with what was reported for the attempted acylation of 4-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)butanoic acid with acetic anhydride [22] 2-Alkylamino groups were reported to retard the aminodefluorination on the 3-position of 2-alkylaminopentafluoro-1,4-naphthoquinone and direct it on the tetrafluorobenzene ring [20a]. At the same time, N-acylation of 2-amino-3-chloro-1,4-naphthoquinone sharply increases a nucleofugicity of Cl-3 [23]. The facile transformation of **17**–**18** we observed is in compliance with this finding (Scheme 3).

The first synthesized compounds have been characterized by ^{19}F (Table 1), ^{1}H, and (in most cases) ^{13}C NMR spectra, elemental analysis and/or high resolution mass-spectrometry. In the ^{19}F NMR spectra indicative is the position and structure of the F^3 signals as compared with the starting **1**: δ_F F^{5,8} −137.5; F^{2,3} −140.9; F^{6,7} −144.4 ppm ($CDCl_3$). For quinones **2**–**6** and **13**–**16** this resonance is markedly up-field shifted ($\Delta\delta_F$ 15.8–16.4 ppm) compared with **1** by an electron-releasing effect of a ω-(carboxy)alkylamino group, what is similar to the effect of alkylamino groups in 2-alkylamino-3,5,6,7,8-pentafluoro-1,4-naphthoquinones [20a]. Thereupon indicative is the enormously down-field shifted F^3 resonance in a ^{19}F spectrum of quinone **17** (−113.2 ppm), possibly testifying a significantly larger out-of-plane rotation of the pyrrolidin-2-one moiety from a quinone plane compared with the other 2-N-substituents under consideration. In all these cases, the F^3 signal is widened by the unresolved weak spin couplings with F^5–F^8.

Of special attention are the ^{19}F NMR spectra of carboxydefluorination products **7** and **9** in the light of their ring–chain tautomerism (see above). Significantly, the ^{19}F chemical shift differences ($\Delta\delta$) in pairs of fluorine atoms occupying the structurally similar positions in a benzene moiety of the naphthoquinone scaffold (F^5 vs F^8 or F^6 vs F^7) are larger than 1 ppm (Table 1). This is not expected for the chain-tautomers **7a** and **9a**, taking into account a weak electron-donating effect of 2-acyloxy group, so that a difference between the electron-withdrawing effects exerted by two C=O groups toward the benzene ring should be quite small. Basically, for 2-X-pentafluoro-1,4-naphthoquinones with weakly electron-donating 2-X-substituents (X = α-$OC_{10}F_7$, $OCOC_6F_5$ [24] and even OMe [20a,c]) these $\Delta\delta_F$ values do not exceed 0.6 ppm for F^5 vs F^8 and 0.8 ppm for F^6 vs F^7.

Similarly, in quinone **17** the $\Delta\delta_F$ values of 0.2 and 0.9 ppm are observed (Table 1). Unlike this, in 2-X-pentafluoro-1,4-naphthoquinones in which an electron-withdrawing ability of the 4-C=O group is substantially suppressed by its conjugation with a strong electron-donating 2-X-substituent (for example, quinones **2**–**6** and other 2-alkylaminopentafluoronaphthoquinones [20a,c]) these $\Delta\delta_F$ values are distinctly larger than 1 ppm (1.5–2.0 ppm for F^5 vs F^8 and 3.7–4.7 ppm for F^6 vs F^7). Nearly the same pattern is expected for the ring-tautomers **7b**,**c** and 9**b**,**c** where the 4-C=O group is absent. This expectation is in compliance with the observed $\Delta\delta_F$ values of 1.1–1.2 ppm for F^5 vs F^8 and 2.6–2.8 ppm for F^6 vs F^7 (Table 1). As regards discrimination between two ring tautomers **7b**,**c** or **9b**,**c**, revealing are the δ_F values of −143.4 and −144.2 ppm, respectively, for the fluorine atoms located in their putative 2,5-cyclohexadien-1-one moieties. Such a down-field

Table 1
^{19}F NMR spectra of 2-substituted pentafluoro-1,4-naphthoquinones **2–9** and **13–18**.

Compd	δ, ppm (J, Hz)				
	F^3	F^5	F^6	F^7	F^8
2[b]	−156.3 (bs)	−138.5 (ddd, $J_{5,6}$ ~19, $J_{5,7}$, $J_{5,8}$ 10–12)	−143.2 (dddd, $J_{5,6}$, $J_{6,7}$ 19–20, $J_{6,8}$ 12.2, $J_{3,6}$ 4.5)	−147.2 (ddd, $J_{5,7}$ 10.5, $J_{6,7}$, $J_{7,8}$ 19–20)	−136.9 (ddd, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ ~20)
3[a]	−156.7 (bs)	−140.0 (m, $J_{5,6}$ ~19, $J_{5,7}$, $J_{5,8}$ ~10)	−145.2 (dddd, $J_{5,6}$, $J_{6,7}$ ~19, $J_{6,8}$ 11–12, $J_{3,6}$ 3.9)	−148.9 (ddd, $J_{5,7}$ ~10, $J_{6,7}$, $J_{7,8}$ ~19)	−138.0 (m, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ ~19)
4[a]	−157.1 (bs)	−140.2 (ddd, $J_{5,6}$ ~19, $J_{5,7}$ 9.4, $J_{5,8}$ 12.1)	−145.3 (dddd, $J_{5,6}$, $J_{6,7}$ ~19, $J_{6,8}$ 11.3, $J_{3,6}$ 4.3)	−149.2 (ddd, $J_{5,7}$ 9.4, $J_{6,7}$, $J_{7,8}$ ~19)	−138.2 (m, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ ~19)
5[a]	−157.3 (bs)	−140.3 (ddd, $J_{5,6}$ ~19, $J_{5,7}$ 9.2, $J_{5,8}$ 12.2)	−145.5 (dddd, $J_{5,6}$, $J_{6,7}$ ~19, $J_{6,8}$ 11.1, $J_{3,6}$ 4.3)	−149.5 (ddd, $J_{5,7}$ 9.2, $J_{6,7}$, $J_{7,8}$ ~19)	−138.4 (ddd, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ ~19)
6[b]	−157.1 (bs)	−138.7 (ddd, $J_{5,6}$ 19.6, $J_{5,7}$ 10.1, $J_{5,8}$ 12.0)	−143.2 (dddd, $J_{5,6}$, $J_{6,7}$ 19–20, $J_{6,8}$ 12.2, $J_{3,6}$ 4.6)	−147.9 (ddd, $J_{5,7}$ 10.1, $J_{6,7}$, $J_{7,8}$ 19–20)	−137.1 (ddd, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ ~20)
7[b,c]	−143.4 (dd, $J_{3,6}$ 4.7, $J_{3,5}$ 0.9)	−136.6 (dddd, $J_{5,6}$ 19–20, $J_{5,7}$ 11.7, $J_{5,8}$ 12–13, $J_{3,5}$ 0.9)	−142.0 (dddd, $J_{6,5}$, $J_{6,7}$ 19–20, $J_{6,8}$ 12.7, $J_{6,3}$ 4.7)	−144.8 (ddd, $J_{7,5}$ 11.7, $J_{7,6}$, $J_{7,8}$ 19–20)	−135.4 (ddd, $J_{8,5}$, $J_{8,6}$ 12–13, $J_{8,7}$ 20.0)
8[a]	−147.0 (bs)	−139.2 (dddd, $J_{5,6}$ ~19, $J_{5,7}$, $J_{5,8}$ ~11)	−145.2 (dddd, $J_{5,6}$, $J_{6,7}$ ~19, $J_{6,8}$ ~11, $J_{3,6}$ 4.3)	−147.0 (ddd, $J_{5,7}$ ~11, $J_{6,7}$, $J_{7,8}$ ~19)	−138.1 (ddd, $J_{5,8}$, $J_{6,8}$ ~11, $J_{7,8}$ ~19)
9[b,d]	−144.2 (bs)	−137.1 (ddd, $J_{5,6}$ ~20, $J_{5,7}$, $J_{5,8}$ ~12)	−142.6 (dddd, $J_{6,5}$, $J_{6,7}$ ~19–20, $J_{6,8}$ 12–13, $J_{6,3}$ 4.2)	−145.2 (ddd, $J_{7,6}$, $J_{7,8}$ ~19–20, $J_{7,5}$ ~12)	−136.0 (ddd, $J_{8,5}$, $J_{8,7}$ ~20, $J_{8,6}$ ~12)
13[a]	−157.2 bs	−140.3 (ddd, $J_{5,6}$ ~19, $J_{5,7}$ ~9, $J_{5,8}$ 12.0)	−145.3 (dddd, $J_{5,6}$, $J_{6,7}$ ~19, $J_{6,8}$ ~11, $J_{3,6}$ 4.2)	−149.4 (ddd, $J_{5,7}$ ~9, $J_{6,7}$, $J_{7,8}$ ~19)	−138.1 (ddd, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ ~19)
14[b]	−157.3 bs	−138.9 (ddd, $J_{5,6}$ ~20, $J_{5,7}$ ~10, $J_{5,8}$ 12.0)	−143.3 (dddd, $J_{5,6}$, $J_{6,7}$ 19–20, $J_{6,8}$ 12.2, $J_{3,6}$ 4.6)	−148.0 (ddd, $J_{5,7}$ 10.1, $J_{6,7}$, $J_{7,8}$ 19–20)	−137.3 (ddd, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ ~20)
15[b]	−156.7 bs	−138.7 (ddd, $J_{5,6}$ 19.6, $J_{5,7}$, $J_{5,8}$ ~11)	−143.2 (dddd, $J_{5,6}$, $J_{6,7}$ 19–20, $J_{6,8}$ 12.2, $J_{3,6}$ 4.5)	−147.6 (ddd, $J_{5,7}$ 10.5, $J_{6,7}$, $J_{7,8}$ 19–20)	−137.0 (ddd, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ 19.8)
16[b]	−157.3 bs	−138.9 (ddd, $J_{5,6}$ ~20, $J_{5,7}$ 10–11, $J_{5,8}$ ~12)	−143.3 dddd, $J_{5,6}$, $J_{6,7}$ 19–20, $J_{6,8}$ ~12, $J_{3,6}$ 4.5)	−148.0 (ddd, $J_{5,7}$ 10–11, $J_{6,7}$, $J_{7,8}$ ~20)	−137.3 (ddd, $J_{5,8}$, $J_{6,8}$ ~12, $J_{7,8}$ ~20)
17[b]	−113.1 bs	−136.8 or −137.0 (m)	−143.0 or −143.9 (m)	−143.0 or −143.9 (m)	−136.8 or −137.0 (m)
18[b]		−140.2 or −141.3 (ddd, $J_{5,6}$ ~20, $J_{5,7}$ ~10, $J_{5,8}$ 13.8)	−145.9 or −148.7 (dddd, $J_{5,6}$, $J_{6,7}$ ~20, $J_{6,8}$ ~10)	−145.9 or −148.7 (ddd, $J_{5,7}$ ~10, $J_{6,7}$, $J_{7,8}$ ~20)	−140.2 or −141.3 (ddd, $J_{5,8}$ 13.8, $J_{6,8}$ ~10, $J_{7,8}$ ~20)

[a] In acetone-d_6.
[b] In $CDCl_3$.
[c] Tautomer **7c** is presumed.
[d] Tautomer **9c** is presumed.

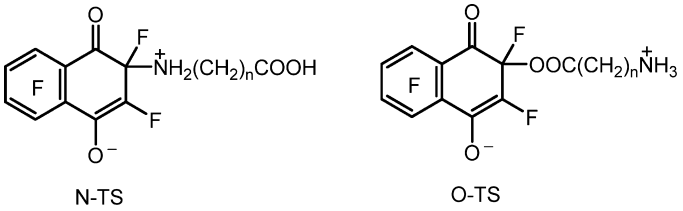


Fig. 1. Canonical structures modeling the TSs of N- (N-TS) and O-substitution (O-TS) of F-2 in quinone **1** by amino acids.

location of these resonances is typical for the F-3 atoms conjugated with the 1-C=O group whereas the F-2 resonances are as a rule observed in the range of −153.0 to −163.0 ppm [25]. Based on this, tautomers **7c** and **9c** are believed to be more likely than **7b** and **9b**. The ^{1}H NMR characteristics of quinones **2–6** and **13–18** (Section 4) are consistent with the proposed structures. Notably, quinones **13** and **14** display a non-equivalency of the ethyl groups caused by a restricted rotation of the NEt_2 groups.

2.2. Biological studies

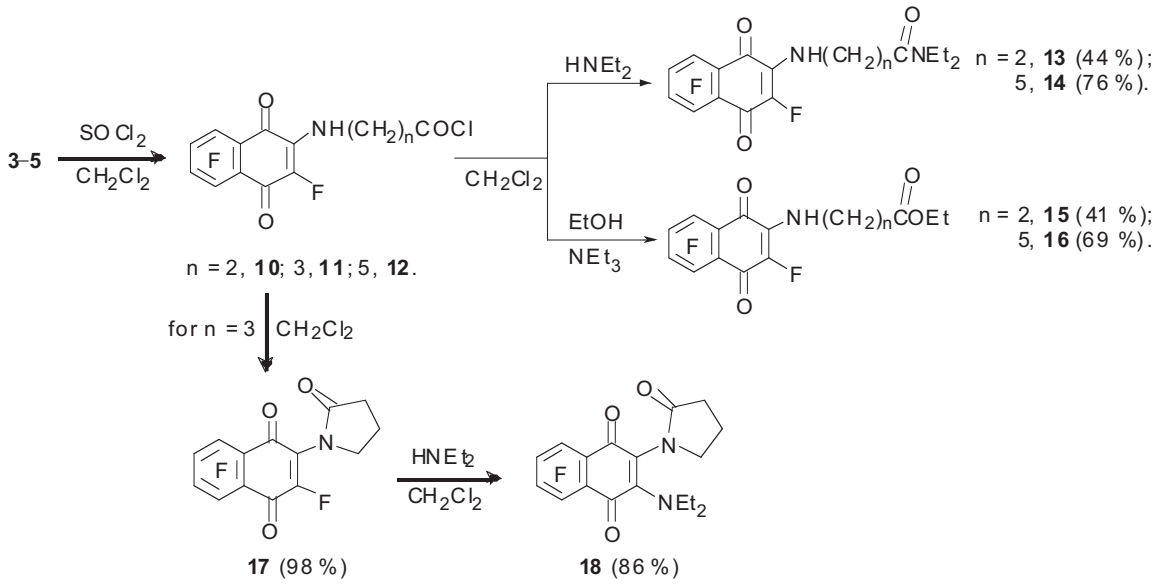
At the first step of evaluation of biological properties of quinones **2–8**, **13–16** and **18**, we have analyzed their ability to inhibit the growth of three mammalian cell lines: tumor cell lines from human myeloma (RPMI 8226), human mammary adenocarcinoma (MCF-7), human hepatocellular carcinoma HepG2 epithelial tumor cells (HEP) as well as normal mouse fibroblasts (LMTK), and normal Chinese hamster Ag 17 cells (AG).

Fig. 2 shows representative data for quinones **2**, **4** and **6** in the case of MCF-7 cells. The results obtained for quinones **2–8**, **13–16**, and **18** with all types of cells are summarized in Table 2. It can be seen that quinones **13**, **15**, and **16** demonstrated the best inhibition of RPMI, MCF-7, and HEP cancer cells (IC_{50} = 1.5–3.2 μM; Table 2).

The averaged suppressing efficiencies toward three lines of tumor cells decreased in the order (average IC_{50}, μM): **16** (2.1) ≥ **13** (2.2) ≥ **15** (2.3) > **18** (5.5) = **2** (5.5) > **14** (8.5) > **3** (22) ≥ **6** (24) > **4** (43.6) > **5** (68.7) > **8** (94.5). The average IC_{50} values for the best inhibitors containing amino acid fragments (quinones **13**, **15**, and **16**) are approximately 43-fold lower than those for 2-hydroxyquinone **8**.

Recently we have compared the growth-inhibiting properties of the control F-Cpd5 with those for nineteen 2-X-3-Y-5,6,7,8-tetrafluoro-1,4-naphthoquinones, among which the quinones with X, Y = EtHN, F; n-Bu, F; t-BuHN, F; Et_2N, F; Ph, F; $(HOCH_2CH_2)HN$, F; $O(CH_2CH_2)_2N$, F; $(HOCH_2CH_2)MeN$, F; $(MeSCH_2CH_2)HN$, F; $(HOCH_2CH_2)HN$, $(HOCH_2CH_2)HN$; MeO, F; MeO, MeO; $HOCH_2CH_2S$, $HOCH_2CH_2S$; $C_5H_5N^+$, O^- exhibited IC_{50} in 2–72-fold lower concentration compared with that for F-Cpd5 (IC_{50} = 14.8 ± 0.9 μM for RPMI and 173.0 ± 21.0 μM for MCF cells) [19]. Now we found out that toward the RPMI cancer cells, quinones **2**, **6**, **13**, **15**, **16**, **18** demonstrate the 2.2–6.7-fold lower IC_{50} values, while compounds **3–5** and **14** are 1.2–4.3-fold less active compared with F-Cpd5. Toward the MCF cells all compounds **2–6**, **13–16** and **18** were 3.5–115-fold better inhibitors than F-Cpd5 (Table 2). The data suggest a common mechanism of cancer cell growth inhibition by F-Cpd5 [12,15–18] and quinones **2–6**, **8**, **13–16** and **18**.

Antitumor drugs may be considered potentially more useful when they are better suppressors of tumor than normal mammalian cells. Therefore, we have compared the effects of these compounds on three cancer cell lines and normal mouse fibroblasts LMTK and AG cells. Overall, the compounds demonstrated various ratios in suppression of tumor vs normal cells, the best difference in inhibition of tumor and normal cells being observed for quinones **2**, **3**, **5**, **13**, **15–16**, and **18** (Table 2).



Scheme 3. Refunctionalizations of acids **3**–**5** via generation and in situ transformations of the respective acylchlorides.

To judge about a possible role of the nature of various substituents of the quinones under investigation in their interaction with Cdc phosphatases of tumor cells, we have used the averaged suppressing efficiencies of the cells grooving (averaged IC_{50} values) found in the case of LMTK, MCF, and HEP cells (see above). A replacement of OH groups in quinone **8** (IC_{50} = 94.5 μM) by the $NHCH_2COOH$ group (compound **3;** 22 μM) led to a 4.3-fold decrease in average IC_{50} values characterizing inhibition of RPMI, MCF, and HEP tumor cells growth (Table 2). The following increase in the methylene groups number of the $NH(CH_2)_nCOOH$ moiety resulted in an approximately 2-fold increase of IC_{50} in the case of compound **4** (n = 2; 43.6 μM), and a 3.1-fold increase in the case of **5** (n = 3; 68.7 μM) in comparison with quinone **3** (n = 1) (Table 2). Interestingly, IC_{50} values for quinones **3** (n = 1) and **6** (n = 5; 24 μM) were comparable. Keeping in mind that the carboxylic group of the compounds under investigation can be involved in the dissociative equilibrium as a proton donor toward closely located enzyme amino acid residues, it may be considered as the negatively charged carboxylate group capable to form electrostatic contacts or hydrogen bondings, thus, probably, diminishing the inhibition efficiency of the quinones under study. One cannot exclude, that protein fragment of Cdc phosphatases interacting with quinones **4** and **5** (n = 2 and 3, respectively) has no amino acid groups capable to interact with the carboxylic group, while in the case of compound **6** (n = 5) a contacting protein surface can form any of contacts mentioned above. Therefore, it is noteworthy in this respect that quinone **18**, having no carboxyl group due to its lactamization, demonstrated IC_{50} (5.5 μM) 12.5-fold lower than the carboxylic quinone **5** (68.7 μM). Also it is notably that removal of the carboxylate negative charge of quinone **3** (IC_{50} = 22 μM) by its ethylation leading to compound **2** (5.5 μM) resulted in a 4-fold decrease in the average IC_{50} values characterizing the inhibition efficiency of three type of tumor cells (Table 2).

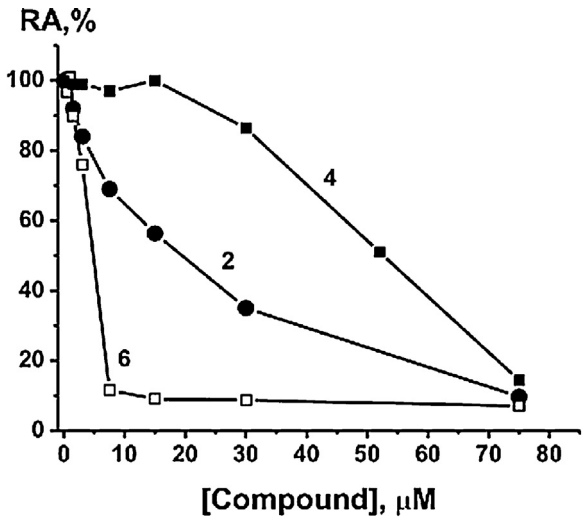


Fig. 2. Effects of quinones **2**, **4** and **6** (relative activity, RA) on the growth of MCF-7 cells. The average error in three experiments for any compound concentration did not exceed 5–15%.

Compound **4** (43.6 μM) suppressed the growth of RPMI, MCF, and HEP tumor cells on average 19–20-fold worse than its ethyl ester **15** (2.3 μM) and diethylamide **13** (2.2 μM) (Table 2). In going from acid **6** (IC_{50} = 24 μM) to its diethylamide **14** (8.5 μM) and ester **16** (2.1 μM) the IC_{50} value decreased by factors of 2.8 and 11.5, respectively. Thus, the loss of the carboxyl group possibility to form the electrostatic contacts or hydrogen bonds in the compounds with n = 2, 3, and 5, caused by its esterification or by replacing OH by $N(Et)_2$, leads to a decrease in the IC_{50} values (Table 2). These data testify that recognition sites of Cdc phosphatases may form electrostatic contacts or hydrogen bonds with the ω-carboxylate groups of the residues located at the 2-position of the quinones under study. In addition, one cannot exclude the putative increased Cdc phosphatases complexation with the ethyl ester functionalities to result from a strengthening of weak hydrophobic and/or van der Waals interactions of enzymes with the quinones.

It is known that some compounds interacting with many cell targets at the same time may behave as polyfunctional and possess cytoprotective properties, or, on the contrary, may be cytotoxic, mutagenic or carcinogenic. Obviously, drugs are more perspective when they are not mutagenic at least at the therapeutic concentrations. The *Salmonella typhimurium* TA102 strain is often used both for evaluation of mutagenicity of different compounds and for detection of antioxidant properties, as judged from suppression of spontaneous mutagenesis in this strain and from a decrease in mutagenicity of oxidants, usually H_2O_2 [19a]. We evaluated the mutagenic activity of compounds **2**–**6**, **8**, **13**–**16**, and

Table 2
Cytotoxicity (IC_{50}) of the fluorinated derivatives of 1,4-naphthoquinone.

Compd	IC_{50} (μM) for different cell lines[a]				
	Tumor cells[c]			Control cells	
	RPMI	MCF-7	HEP	LMTK	AG
2	6.8 ± 1.8	3.2 ± 0.6	6.6 ± 1.8	13.0 ± 3.0	40.0 ± 6.0
3	25.4 ± 5.0	20.0 ± 4.0	21.0 ± 4.0	60 ± 12.0	Inhib. 30%[b]
4	63.5 ± 12	53 ± 12	14.2 ± 4.0	No inhib.[b]	50 ± 12
5	24.2 ± 8.0	50 ± 10	132 ± 13.0	Inhib. 10.0%[b]	Inhib. 15.0%
6	6.7 ± 1.7	11.0 ± 3.0	50.5 ± 5.0	43.0 ± 8.0	52 ± 8.0
7	56.2 ± 11	43.9 ± 7.0	47.5 ± 6.0	No inhib.[b]	Inhib. 40.0%
8	72.0 ± 12	66.5 ± 9.0	145 ± 14	No inhib.[b]	64 ± 6.0
13	2.2 ± 0.7	1.5 ± 0.2	2.9 ± 0.3	8.0 ± 0.8	13.8 ± 0.8
14	18.2 ± 1.9	4.0 ± 0.5	3.2 ± 0.3	4.3 ± 0.4	15.4 ± 2.0
15	3.0 ± 0.4	2.0 ± 0.2	2.0 ± 0.2	7.0 ± 0.7	10 ± 1.2
16	2.8 ± 0.3	1.4 ± 0.2	2.1 ± 0.2	10.8 ± 1.5	11.9 ± 1.3
18	5.0 ± 2.0	3.7 ± 0.4	7.8 ± 0.8	15.8 ± 2.0	24.7 ± 3.0

[a] Mean ± S.E. from three independent experiments.
[b] When the cytotoxicity was low, the percent of inhibition of cell growth at the highest used concentration (75 μM) of the compound was determined; in some cases there was no detectable inhibition of cell growth even at 75 μM of the compound.
[c] RPMI, human myeloma; MCF-7, human mammary adenocarcinoma; HEP, human hepatocellular carcinoma HepG2 epithelial tumor cells; LMTK, normal mouse fibroblasts; AG, Chinese hamster Ag 17 cells.

18 in the Ames test [26] using *S. typhimurium* TA102 as reported by Kemeleva et al. [27]. The mutation induction in the Ames assay was estimated by calculating the frequency of reversion from histidine auxotrophy to prototrophy in response to the substance under testing [26,27]. Fig. 3 shows the representative data for quinones **8** and **15**.

Interestingly, quinones **13** and **14** displayed the higher potency (IC_{50} values of 0.5–0.6 μM) (Table 3) in suppression of the spontaneous appearance of mutants compared with the control F-Cpd5 (0.81 μM). All other compounds demonstrated IC_{50} values of 0.6–0.9 μM comparable with that for F-Cpd5. Previously analyzed polyfluorinated naphthoquinones demonstrated the widely variable IC_{50} of 0.4–275 μM [19a–c], four alkylamino- and phenylamino-containing derivatives possessing IC_{50} = 0.6–18.5 μM [19b].

Some previously studied polyfluorinated naphthoquinones were found to efficiently decrease the mutagenic effect of H_2O_2 [19]. In the present Ames assays, H_2O_2 was added to TA102 cells at the optimal concentration of 3 mM [19], and the test compound concentrations were varied (Fig. 3). At low concentrations (0.031–0.055 μM) only derivatives **8**, **13**–**16**, and **18** efficiently suppressed the H_2O_2-dependent formation of mutants from 130 to 100% of revertants (the number of revertants observed in the controls without H_2O_2 was taken for 100%), quinones **5** and **6** did it at concentrations 0.08–0.09 μM, while compounds **2**–**4** at higher (0.2–0.4 μM) concentrations. The concentrations causing the 100–50% suppression of the H_2O_2-induced mutagenesis were also different for the various quinones. The data indicate that quinones **2**–**6**, **8**, **13**–**16**, and **18** are not mutagenic themselves and decrease efficiently the level of spontaneous mutagenesis and the mutagenic effect of H_2O_2.

Interestingly, a potency of the majority of previously studied polyfluorinated naphthoquinones in suppressing spontaneous mutagenesis (IC_{50}) in the absence of H_2O_2 was 1.8–7.0-fold lower than in decreasing H_2O_2-dependent mutagenesis, while some other compounds showed in some extent comparable IC_{50} values in the presence and in the absence of H_2O_2 [19]. For all quinones **2**–**6**, **8**, **13**–**16**, and **18** the 50% suppression of spontaneous and H_2O_2-dependent mutagenesis was observed at approximately comparable concentrations, like the control compound F-Cpd5 (Table 3). Since quinones **2**–**6**, **8**, **13**–**16** and **18** did not enhance the spontaneous mutagenesis and effectively suppressed the mutagenic effect of H_2O_2, they can be considered as efficient

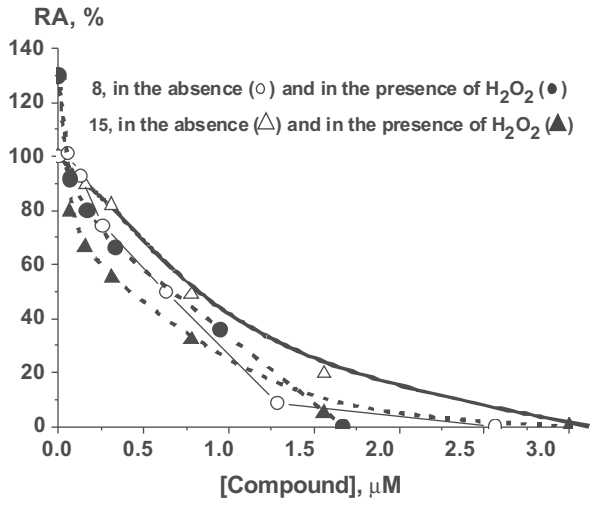


Fig. 3. Analysis of the mutagenic and antioxidant activity of quinones **8** and **15** by a standard Ames test using the *S. typhimurium* strain TA102 in the absence and in the presence of 3 mM H_2O_2. The number of revertants in the absence of H_2O_2 was taken for 100%. The average error in three experiments for any compound concentration did not exceed 5–10%.

Table 3
IC_{50} values characterizing suppression of spontaneous and H_2O_2-induced mutagenesis by polyfluorinated derivatives of 1,4-naphthoquinone.

Compd	IC_{50}, μM[a]		
	Suppression of spontaneous mutagenesis (from 100 to 50%), without H_2O_2	Suppression of H_2O_2-induced and spontaneous mutagenesis (+H_2O_2)	
		From 130 to 100%	From 100 to 50%
2	0.77 ± 0.08	0.26 ± 0.03	0.83 ± 0.07
3	0.9 ± 0.1	0.4 ± 0.06	1.0 ± 0.08
4	0.83 ± 0.07	0.27 ± 0.03	0.9 ± 0.07
5	0.77 ± 0.07	0.086 ± 0.009	0.57 ± 0.05
6	0.63 ± 0.05	0.08 ± 0.009	0.66 ± 0.07
8	0.9 ± 0.1	0.055 ± 0.006	0.71 ± 0.08
13	0.56 ± 0.06	0.043 ± 0.04	0.61 ± 0.06
14	0.5 ± 0.05	0.039 ± 0.004	0.55 ± 0.06
15	0.8 ± 0.09	0.042 ± 0.005	0.42 ± 0.04
16	0.87 ± 0.09	0.033 ± 0.003	0.42 ± 0.05
18	0.66 ± 0.07	0.031 ± 0.003	0.39 ± 0.04

[a] Mean ± S.E. from three independent experiments.

antioxidants. At the same time, it was not possible to exclude that the complete suppression of mutant cell appearance by these quinones at high concentration may result not only from their ability to suppress spontaneous and H_2O_2-induced mutagenesis but also from their higher general toxicity toward bacterial cells. However, the 50% decrease in spontaneous and H_2O_2-dependent mutagenesis of bacterial cells including their possible general toxicity for all the compounds was observed at significantly lower concentrations (IC_{50} = 0.5–0.9 μM, Table 3) than those providing a detectable effect on tumor cells (IC_{50} = 1.5–145 μM, Table 2). It means that quinones **2**–**6**, **8**, **13**–**16**, and **18** do not possess appreciable general toxicity toward cells at low concentrations. In addition, compounds **3**–**5** and **8** suppress the growth of normal LMTK and AG cells only at very high concentrations (Table 2).

It is possible that all these compounds including F-Cpd5 play a double role, acting both as inhibitors of cell phosphatases and as antioxidants. Overall, fluorinated 1,4-naphthoquinone derivatives are less active in generating reactive oxygen species and may be more promising inhibitors of Cdc phosphatases as compared to 1,4-naphthoquinone [16–18]. The best difference in inhibition of tumor and normal cells was observed for quinones **2**, **13**, **15**, **16**, and **18** demonstrating the lowest IC_{50} values and for compounds **3** and **5** with the higher IC_{50} values (Table 2). Since all of these compounds show the comparable IC_{50} values in suppressing the spontaneous and H_2O_2-induced mutagenesis, they may be considered as potentially perspective for inhibition of tumor cells growth. At the same time, quinones **4** and **8** also cannot be excluded as perspective suppressors of tumor cells growth since they are active against the normal cells at higher concentrations compared with some of the tumor cells.

3. Conclusions

In this paper we have studied the reactions of quinone **1** with several ω-aminoalkanoic acids in dioxane and aqueous dioxane to reveal a mode and regioselectivity of interaction, an effect of water as a polar co-solvent on the competition of N- and O-nucleophilicities of the amino acids as bifunctional nucleophiles, and to use the reaction as a general way to N-(pentafluoro-1,4-naphthoquinon-2-yl)-ω-aminoalkanoic acids as potential bioactive compounds and versatile building blocks for their functional derivatives. The possibilities of their modifications on a carboxylic group have been exhibited by conversion of the acids thus prepared to their chloroanhydrides which were used (*in situ*) to obtain the respective N,N-diethylamides and ethyl esters. The ^{19}F, ^{1}H, and (in most cases) ^{13}C spectra of the quinones thus synthesized have been registered, the NMR spectral peculiarities having been discussed in terms of their connection with a nature of the 2-located substituent. The best difference in inhibition of tumor and normal cells was observed for **2**, **13**, **15**, **16** and **18** demonstrating the lowest IC_{50} values.

4. Experimental

Chemistry. General Methods. Commercially supplied glycine ethyl ester hydrochloride, 6-aminohexanoic acid, aminoacetic acid, 3-aminopropanoic, 4-aminobutanoic, and 6-aminohexanoic acids were used without purification. Quinone **1** was prepared accordingly to the reported method [28]. Diethylamine, triethylamine, dioxane, ethanol and DMSO were distilled vacuum *in vacuo* (0.04 mm Hg) onto molecular sieves (4 Å). ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker AV-300 (^{1}H at 300, ^{19}F at 282, ^{13}C at 75 MHz), AV-400 (^{1}H at 400, ^{13}C at 100 MHz) and DRX-500 NMR spectrometers (^{13}C at 126 MHz) for solutions in $CDCl_3$ or $(CD_3)_2CO$ and calibrated relatively C_6F_6 (δ_F = −163.0 ppm) or residual nondeuterated solvent admixtures as internal references. High-resolution mass spectra (HRMS) were measured with a DFS thermo scientific instrument (EI, 70 eV). Melting points of quinones **3**–**7** and **17** were determined using a "Mettler Toledo" device with FP 900 Thermosystem cell. TLC was performed using silica gel 60 PF_{254} containing gypsum ("Merck"). The isolated reaction products were found to be >95% purity by NMR analysis.

4.1. Synthetic procedures

4.1.1. Ethyl [(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]acetate (**2**)

A mixture of quinone **1** (0.200 g, 0.75 mmol), glycine ethyl ester hydrochloride (0.157 g, 1.127 mmol), KOH (0.063 г, 1.127 mmol) and DMSO (2 ml) was stirred at ~20 °C for 24 h. Water (5 ml) was added, the precipitate was centrifuged off, washed with water (2 × 2 ml) and air-dried. The crude product was crystallized from ethanol to yield **2** as red crystals (0.173 g, 66%), m.p. 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.89 (bs, 1H, NH), 4.31–4.21 (m, 4H, $2CH_2$), 1.29 (t, 3H, J = 7.2 Hz, CH_3). ^{13}C NMR (75 MHz, acetone-d_6) δ_C: 177.8 (d, CO, J = 14.1 Hz), 170.5 (d, CO, J = 21.4 Hz), 169.1 (CO), 147.1 (dm, J_{CF} ~ 272 Hz), 146.6 (dm, J_{CF} ~ 259 Hz), 145.0 (dm, J_{CF} ~ 261 Hz), 143.3 (dm, J_{CF} ~ 259 Hz), 141.4 (d, J_{CF} ~ 249 Hz), 133.6, 114.8, 114.4, 60.9, 45.0 (d, J ~ 7 Hz), 13.4. Anal. calcd for $C_{14}H_8F_5NO_4$: C, 48.15; H, 2.31; N, 4.01; F, 27.20; found: C, 48.37; H, 2.28; N, 4.02; F, 26.81. HRMS (EI) for $C_{14}H_8F_5NO_4$ (M^+): calcd, 349.0368; found, 349.0362.

4.1.2. [(3,5,6,7,8-Pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]acetic acid (**3**)

A solution of glycine (0.147 g, 1.955 mmol) in water (0.5 ml) was added dropwise to a suspension of quinone **1** (0.200 g, 0.752 mmol) in dioxane (2.5 ml). The mixture was stirred for 23 days at ~20°C. The solvents were distilled off *in vacuo*, the residue was purified by TLC (silicagel, ethyl acetate) to yield quinone **3** as red-orange crystals (0.147 g, 61%). After crystallization from acetone: mp > 120°C (decomp.). ^{1}H NMR (400 MHz, acetone-d_6) δ: 6.64 (bs, 1H, NH), 4.35–4.30 (m, 2H, CH_2). Anal. calcd for $C_{12}H_4F_5NO_4$: C, 44.88; H, 1.26; N, 4.36; found: C, 45.00; H, 1.27; N, 4.57.

4.1.3. 3-[(3,5,6,7,8-Pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]propanoic acid (**4**)

A mixture of quinone **1** (0. 301 g, 1.127 mmol), 3-aminopropanoic acid (0.143 g, 1.578 mmol) and dioxane (5 ml) was stirred for 15 days at ~20 °C. The solvent was removed *in vacuo* (0.05 mm Hg) and crystallized from methanol to yield quinone **4** as maroon crystals (0.302 g, 80%). M.p.: >160 °C (decomp.). ^{1}H NMR (300 MHz, acetone-d_6) δ: 6.46 (bs, 1H, NH), 3.81 (tm, 2H, J = 6.7 Hz, CH_2,), 2.72 (t, J = 6.7 Hz, 2H, CH_2). Anal. calcd for $C_{13}H_6F_5NO_4$: C, 46.58; H, 1.80; N, 4.18; found: C, 46.32; H, 1.80; N, 4.29.

4.1.4. 4-[(3,5,6,7,8-Pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]butanoic acid (**5**)

A mixture of quinone **1** (0.100 g, 0.380 mmol), 4-aminobutanoic acid (0.051 g, 0.495 mmol) and dioxane (7 ml) was stirred for 11 days at ~20 °C. The precipitate was centrifuged off and dried *in vacuo* (0.05 mm Hg) to give acid **5** as red crystals (0.108 g, 81%). After crystallization from methanol m.p. >192 °C (decomp.). ^{1}H NMR (300 MHz, acetone-d_6) δ: 6.56 (bs, 1H, NH), 3.66–3.54 (m, 2H, CH_2), 2.40 (t, 2H, J = 7.3 Hz, CH_2), 1.99–1.88 (m, 2H, CH_2). ^{13}C NMR (75 MHz, acetone-d_6) δ: 179.0 (d, J = 10.8 Hz), 174.2, 171.1 (d, J = 18.8 Hz), 147.9 (dm, J_{CF} ~ 270 Hz), 147.4 (dm, J_{CF} ~ 269 Hz), 145.8 (dm, J_{CF} ~ 261 Hz), 144.4 (dm, J_{CF} ~ 258 Hz), 141.7 (d, J_{CF} ~ 247 Hz), 135.0, 116.0, 115.5, 44.2 (dd, J = 7.7, 9.5 Hz), 31.2, 26.4 (d, J = 3.5 Hz). Anal. calcd for $C_{14}H_8F_5NO_4$: C, 48.15; H, 2.31; N, 4.01; F, 27.20; found: C, 47.86; H, 2.33; N, 4.43; F, 26.93.

*4.1.5. 6-[(3,5,6,7,8-Pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino]hexanoic acid (**6**)*

A mixture of quinone **1** (0.300 g, 1.127 mmol), 6-aminohexanoic acid (0.192 g, 1.470 mmol) and dioxane (5 ml) was stirred for 5 days at ~20 °C. Water (8 ml) was added; the precipitate was centrifuged off, washed with water (2 × 2 ml), air-dried and crystallized from methanol to give acid **6** as maroon crystals (0.401 g, 94%), m.p. 168–170 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.47 (bs, 1H, NH), 3.59–3.47 (m, 2H, CH_2), 2.37 (t, 2H, J = 7.2 Hz, CH_2), 1.75–1.60 (m, 4H, $2CH_2$), 1.50–1.30 (m, 2H, CH_2); ^{13}C NMR (126 MHz, acetone-d_6) δ: 178.0 (d, J = 11.7 Hz), 173.4, 170.0 (d, J = 20.3 Hz), 146.7 (dm, $J_{CF} \sim 267$ Hz), 146.4 (dm, $J_{CF} \sim 267$ Hz), 144.8 (dm, $J_{CF} \sim 258$ Hz), 143.1 (dm, $J_{CF} \sim 258$ Hz), 140.2 (d, $J_{CF} \sim 247$ Hz), 133.8, 115.0, 114.4, 43.7 (d, J = 7.6 Hz), 32.9, 29.8 (d, J = 3.2 Hz), 25.7, 24.1. Anal. calcd for $C_{16}H_{12}F_5NO_4$: C 50.94; H 3.21; N 3.71; found: C 50.64; H 3.20; N 3.74.

*4.1.6. The products of the quinone **1** 4-aminobutanoyl- and 6-hexanoiloxydefluorination (**7** and **9**) and its hydrolysis*

A solution of 4-aminobutanoic acid (0.101 g, 0.977 mmol) in water (0.5 ml) was added dropwise to a suspension of quinone **1** (0.200 g, 0.752 mmol) in dioxane (2 ml). The mixture was stirred for 48 h at ~20 °C. The solvents were removed *in vacuo*, the residue was extracted by chloroform (4 × 5 ml) to isolate compound **7** (presumably **7c**) (0.066 g, 25%). The analytically pure sample was obtained by additional crystallization from the same solvent as yellow crystals, m.p. >120 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.75 (bs, 1H, NH), 3.42 (t, 2H, J = 6.9 Hz, CH_2), 2.37–2.28 (m, 4H, CH_2). Anal. calcd for $C_{14}H_8F_5NO_4$: C, 48.15; H, 2.31; N, 4.01; found: C, 47.83; H, 2.34; N, 4.05.

After a 2 week storage without protection against atmospheric moisture quinone **7** completely turned into quinone **8**, a ^{19}F NMR spectrum of which (Table 1) coincides with a spectrum of the authentic specimen [21]. HRMS (EI) for $C_{10}HF_5O_3$ (M^+): calcd, 263.9840; found, 263.9844.

Quinone **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (bs, OH), 6.30 (bs, 1H, NH), 3.31–3.15 (m, 2H, CH_2), 2.59–2.41 (m, 2H, CH_2), 1.85–1.57 (m, 6H, CH_2).

*4.1.7. 3-(3,5,6,7,8-Pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)propanoyl chloride (**10**) or 6-(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)hexanoyl chloride (**12**)*

3-(3,5,6,7,8-Pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)propanoyl chloride (**10**) or 6-(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)hexanoyl chloride (**12**) were generated according to the literature protocol, reported for preparation of 3-aminopropionyl chloride [29] (see below for preparing quinone **17**), from quinones **4** or **6** (0.285 mmol) and thionyl chloride (0.068 g, 0.580 mmol) in practically quantitative yields and were in situ used to obtain amides **13** or **14** and esters **15** or **16**.

*4.1.8. General procedure for synthesis of **13** or **14***

Diethylamine (0.040 g, 0.580 mmol) dissolved in CH_2Cl_2 (1 ml) was added to a stirred solution of acyl chloride **10** or **12** (0.290 mmol) in CH_2Cl_2 (3 ml) at 0 °C under argon and stirred at room temperature for 1.5 h. Water (3 ml) was added, the organic layer was evaporated and the residue was separated by TLC to isolate quinone **13** or **14**.

*4.1.8.1. N,N-Diethyl-3-(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)propanamide (**13**).* The reaction of **10** with diethylamine, conducted according to the above general procedure (TLC: $CHCl_3$, R_f = 0.13), afforded the title quinone **13** (0.05 r, 44%) as red crystals, m.p. 132–133 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ: 6.68 (bs, 1H, NH), 3.83–3.76 (m, 2H, CH_2), 3.41–3.31 (m, 4H, $2CH_2$), 2.75 (t, 2H, J = 6.3 Hz, CH_2), 1.15 (t, 3H, J = 7.1 Hz, CH_3), 1.05 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ: 178.1 (d, J = 13.6 Hz), 170.2 (d, J = 19.8 Hz), 169.5, 147.0 (dm, $J_{CF} \sim 259$ Hz), 146.6 (dm, $J_{CF} \sim 257$ Hz), 145.1 (dm, $J_{CF} \sim 261$ Hz), 143.2 (dm, $J_{CF} \sim 258$ Hz), 140.5 (d, $J_{CF} \sim 247$ Hz), 133.8, 115.2, 114.6, 41.4, 40.4, 39.6, 32.9, 13.5, 12.5. Anal. calcd for $C_{17}H_{15}F_5N_2O_3$: C, 52.31; H, 3.87; N, 7.18; found: C, 52.38; H, 3.77; N, 7.14.

*4.1.8.2. N,N-Diethyl-6-(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)hexanamide (**14**).* The reaction of **12** with diethylamine, conducted according to the above general procedure (TLC: $CHCl_3$, R_f = 0.2), afforded the title quinone **14** (0.095 r, 76%) as red crystals, m.p. 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.53 (bs, 1H, NH), 3.58–3.47 (m, 2H, CH_2), 3.35 (q, 2H, J = 7.1 Hz, CH_2), 3.27 (q, 2H, J = 7.1 Hz, CH_2), 2.28 (t, 2H, J = 7.3 Hz, CH_2), 1.76–1.58 (m, 4H, $2CH_2$), 1.47–1.33 (m, 2H, CH_2), 1.15 (t, 3H, J = 7.1 Hz, CH_3), 1.08 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2 (d, CO, J = 13.1 Hz), 171.6 (CO), 170.7 (d, CO, J = 18.9 Hz), 147.2 (dm, $J_{CF} \sim 273$ Hz), 147.0 (dm, $J_{CF} \sim 270$ Hz), 145.4 (dm, $J_{CF} \sim 266$ Hz), 143.4 (dm, $J_{CF} \sim 263$ Hz), 140.4 (d, $J_{CF} \sim 251$ Hz), 133.5, 114.9, 113.8, 44.3 (d, J = 7.5 Hz), 41.9, 40.1, 32.7, 30.4 (d, J = 2.8 Hz), 26.4, 24.7, 14.4, 13.1. Anal. calcd for $C_{20}H_{21}F_5N_2O_3$: C, 55.56; H, 4.90; N, 6.48; F, 21.97; found: C, 55.97; H, 5.31; N, 6.74; F, 21.83. HRMS (EI) for $C_{20}H_{21}F_5N_2O_3$ (M) calcd, 432.1467; found, 432.1466.

*4.1.9. General procedure for synthesis of **15** or **16***

Ethanol (0.050 g, 1.160 mmol) and triethylamine (0.060 g, 0.580 mmol) dissolved in CH_2Cl_2 (1 ml) was added to a stirred solution of acyl chloride **10** or **12** (0.290 mmol) in CH_2Cl_2 (3 ml) at 0 °C under argon and stirred at room temperature for 2 h. Water (3 ml) was added, the organic layer was evaporated, the residue was separated by TLC to isolate quinone **15** or **16**.

*4.1.9.1. Ethyl 3-(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)propanoate (**15**).* The reaction of **10** with ethanol and triethylamine, conducted according to the above general procedure (TLC: $CHCl_3$–hexane, 3:1, R_f = 0.26), afforded the title quinone **15** (0.043 g, 41%) as orange crystals. The analytically pure sample was obtained by additional crystallization from ethanol, m.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.94 (bs, 1H, NH), 4.22 (q, 4H, J = 7.2 Hz, $2CH_2$), 3.90–3.82 (m, 2H, CH_2), 2.70 (t, 2H, J = 6.0 Hz, CH_2), 1.32 (t, 6H, J = 7.2 Hz, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8 (d, J = 12.7 Hz), 171.3, 170.8 (d, J = 19.6 Hz), 147.3 (dm, $J_{CF} \sim 274$ Hz), 147.0 (dm, $J_{CF} \sim 272$ Hz), 145.5 (dm, $J_{CF} \sim 265$ Hz), 143.5 (dm, $J_{CF} \sim 263$ Hz), 140.8 (d, $J_{CF} \sim 252$ Hz), 133.0, 114.7, 113.8, 61.1, 39.9 (d, J = 8.2 Hz), 34.8 (d, J = 3.4 Hz), 14.2. Anal. calcd for $C_{15}H_{10}F_5NO_4$: C, 49.60; H, 2.77, N 3.86; found: C, 49.94; H, 2.78, N 4.08. HRMS (EI) for $C_{15}H_{10}F_5NO_4$ (M^+) calcd, 363.0525; found, 363.0529.

*4.1.9.2. Ethyl 6-(3,5,6,7,8-pentafluoro-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)hexanoate (**16**).* The reaction of **12** with ethanol and triethylamine was carried out according to the above general procedure (TLC: $CHCl_3$, R_f = 0.52), afforded the title quinone **16** (0.081 r, 69%) as red crystals, m.p. 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.47 (bs, 1H, NH), 4.11 (q, 2H, J = 7.1 Hz, CH_2), 3.55–3.48 (m, 2H, CH_2), 2.29 (t, 2H, J = 7.3 Hz, CH_2), 1.75–1.53 (m, 4H, $2CH_2$), 1.48–1.31 (m, 2H, CH_2), 1.23 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0 (d, J = 13.0 Hz), 173.3, 170.6 (d, J = 20.6 Hz), 147.1 (dm, $J_{CF} \sim 273$ Hz), 146.9 (dm, $J_{CF} \sim 272$ Hz), 145.2 (dm, $J_{CF} \sim 266$ Hz), 143.1 (dm, $J_{CF} \sim 263$ Hz), Hz), 140.2 (d, $J_{CF} \sim 252$ Hz), 133.2, 114.7, 113.6, 60.2, 44.1 (d, J = 7.5 Hz), 33.9, 30.1 (d, J = 2.7 Hz). 26.0, 24.3, 14.1. Anal. calcd for $C_{18}H_{16}F_5NO_4$: C, 53.34; H, 3.98, N 3.46; found: C, 53.71; H, 4.05, N 3.42. HRMS (EI) for $C_{18}H_{16}F_5NO_4$ (M^+): calcd, 405.0994; found, 405.0996.

*4.1.10. 2,5,6,7,8-Pentafluoro-3-(2-oxopyrrolidin-1-yl)naphthalene-1,4-dione (**17**)*

A solution of quinone **5** (0.030 g, 0.090 mmol) and thionyl chloride in CH_2Cl_2 (2 ml) was boiled under reflux for 2.5 h. The mixture was washed with water till pH = 7. The organic layer was evaporated to afford the title quinone **17** (0.028 g, 98%) as yellow crystals, m.p. >166 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82 (t, 2H, J = 6.9 Hz, CH_2), 2.54 (t, 2H, J = 7.9 Hz, CH_2), 2.20–2.36 (m, 2H, CH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ: 176.7 (d, J = 9.7 Hz), 174.0, 173.2(d, J = 24.3 Hz), 154.3 (d, J_{CF} = 286 Hz), 147.1 (dm, $J_{CF} \sim$ 273 Hz), 147.0 (dm, $J_{CF} \sim$ 260 Hz), 144.8 (dm, $J_{CF} \sim$ 261 Hz), 144.5 (dm, $J_{CF} \sim$ 265 Hz), 127.4, 116.0, 115.0, 48.5, 29.9, 19.8. HRMS (EI) for $C_{14}H_6F_5NO_3$ (M^+): calcd, 331.0262; found, 331.0265.

*4.1.10.1. 2-(Diethylamino)-5,6,7,8-tetrafluoro-3-(2-oxopyrrolidin-1-yl)naphthalene-1,4-dione (**18**).* Diethylamine (0.060 g, 0.830 mmol) dissolved in CH_2Cl_2 (1 ml) was added to a stirred solution of quinone **17** (0.150 g, 0.450 mmol) in CH_2Cl_2 (3 ml) at 0 °C. The stir was continued at the same temperature for 10 min and then at room temperature for 30 min and the mixture was separated by TLC ($CHCl_3$, R_f = 0.33) to yield the title quinone **18** (0.140 g, 86%) as oily red crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.72 (q, 1H, J = 8.6 Hz, CH_2), 3.43 (q, 4H, J = 7.1 Hz, $2CH_2$), 3.40–3.34 (m, 1H, CH_2), 2.68–2.56 (m, 1H, CH_2), 2.49–2.38 (m, 1H, CH_2), 2.30–2.18 (m, 1H, CH_2), 2.14–2.01 (m, 1H, CH_2), 1.22 (t, 6H, J = 7.1 Hz, $2CH_3$). ^{13}C NMR (100 MHz, acetone-d_6) δ: 180.0, 177.0, 173.7, 152.1, 146.1 (dm, $J_{CF} \sim$ 269 Hz, 2C), 144.6 (dm, $J_{CF} \sim$ 264 Hz), 143.2 (dm, $J_{CF} \sim$ 262 Hz), 119.6, 116.9, 116.1, 49.6, 46.8 (2C), 30.4, 19.3, 13.8 (2C). HRMS (EI) for $C_{18}H_{16}F_4N_2O_3$ (M^+): calc. 384.1092; found 384.1091.

4.2. Biological experiments

4.2.1. Determination of mutagenisity

In the Ames test, the histidine-dependent strain of *S. typhimurium* TA102 was used, which carries a mutation at the histidine operon. The mutagenic activity of the samples was analyzed by the standard method without metabolic activation [26]. The Ames test was carried out using the described double-layer method [26,27]. The overnight culture of bacteria (100 μl) containing one of the tested compounds in different concentrations and, if required, 3 mM H_2O_2, were mixed at 42 °C with 2 ml of liquid 0.6% top agar. The mixture was poured onto plates with a minimal medium containing 0.2% glucose and 3% agar, taking care to distribute the mixture uniformly on the surface of the solid agar. The plates were incubated for 48 h at 37 °C, and the revertants were counted. The cells incubated with H_2O_2 in the absence of compounds analyzed were used as positive controls, and the cells grown in the absence of H_2O_2 and antioxidants served as negative controls for the mutation induction. The results are expressed as mean ± standard deviation of at least 3 independent experiments.

4.2.2. Cytotoxicity assays

Tumor cell lines from human myeloma RPMI 8226, human mammary adenocarcinoma MCF-7, mouse fibroblasts LMTK and primary mouse fibroblast cell line (PMF) (~2000 cells per well) were incubated for 24 h at 37 °C in IMDM or RPMI 1640 medium (5% CO_2) and then were treated with quinones **2–8** and **13–17.** After 72 h of cell incubation, the relative amount of live cells was determined using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (a standard colorimetric MTT-test [30] and the drug concentration that caused 50% cell growth inhibition (IC_{50}) was determined. The results are expressed as mean ± standard deviation of at least 3 independent experiments.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.04.014.

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