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Synthesis and Cytotoxic Evaluation of 1*H*-1,2,3-Triazol-1-ylmethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-diones

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ABSTRACT

The 1,2-naphthoquinone compound was previously considered active against solid tumors. Moreover, glycosidase inhibitors such as 1,2,3-1*H* triazoles has been pointed out as efficient compounds in anticancer activity studies. Thus, a series of eleven 1,2-naphthoquinones tethered in C2 to 1,2,3-1*H*-triazoles **9a-k** were designed, synthesized and their cytotoxic activity evaluated using HCT-116 (colon adenocarcinoma), MCF-7 (breast adenocarcinoma) and RPE (human nontumor cell line from retinal epithelium). The chemical synthesis was performed from C-3 allylation of lawsone followed by iodocyclization with subsequent nucleophilic displacement with sodium azide and, finally, the 1,3-dipolar cycloaddition catalyzed by Cu(I) with terminal alkynes led to the formation of 1*H*-1,2,3-Triazol-1-ylmethyl-2,3-dihydronaphtho[1,2-*b*] furan-4,5-diones in good yields. Compounds containing aromatic group linked to 1,2,3-triazole ring (**9c**, **9d**, **9e**, **9i**) presented superior cytotoxic activity against cancer cell lines with IC_{50} in the range of 0.74 to 4.4 μM indicating that the presence of aromatic rings substituents in the 1,2,3-1*H*-triazole moiety is probably responsible for the improved cytotoxic activity.

Keywords: Naphthoquinones, lawsone, 1,2,3-triazoles, cancer, colon adenocarcinoma, breast adenocarcinoma.

INTRODUCTION

There are several synthetic and natural low molecular weight naphthoquinones with many applications in various scientific and technological fields. These naphthoquinones also have potential clinical utility in the treatment of various diseases (da Silva and Ferreira 2016, Ferreira et al. 2016).

The quinones can be cytotoxic through several mechanisms of action (Klotz et al. 2014, de Paiva et al. 2015), including redox cycle (dos Santos et al. 2004, Ferreira et al. 2010), arylation of thiol groups of proteins, intercalation, induction of breaks in the DNA chain, generation of free radicals and reactive oxygen species (ROS) (de Castro et al. 2013,

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Kumagai et al. 2012) and bioreductive alkylation via formation of quinone-methoxy (Cao and Peng 2014, Paz et al. 2012).

Although 1,2,3-triazoles are not natural, this class of substances has already been investigated against several important disease targets (Dheer 2017) and the conjugation of these two moieties has shown that it is a molecular combination with potential antitumor synergism. Figure 1 shows some examples of 1,2,3-triazoles and naphthoquinones conjugates such as 1,2-naphthoquinone **1**, with activities against MDA-MB-435 melanoma cells (Ferreira et al. 2009), and **2** for MOLT leukemia cells (Cardoso et al. 2014), and also the 1,4-naphthoquinones **3-5** which are active against HL-60 leukemia cells (da Cruz et al. 2014).

Considering that structural combinations between the naphthoquinone and 1,2,3-triazole units may considerably alter their bioavailability and, in particular, their cytotoxicity, we synthesized several naphthoquinone-1,2,3-triazole hybrids and evaluated their cytotoxic activity using HCT-116 (colon adenocarcinoma), MCF-7 (breast adenocarcinoma) and RPE (human nontumor cell line from retinal epithelium).

MATERIALS AND METHODS

The reagents were purchased from Sigma-Aldrich Brazil and were used without further purification. Column chromatography was performed with silica gel 60 (Merck 70-230 mesh). Analytical thin layer chromatography was performed with silica gel plates (Merck, TLC silica gel 60 F254), and the plates were visualized using UV light or aqueous solutions of ammonium sulfate. The indicated yields refer to chromatographically and spectroscopically homogeneous materials. Melting points were obtained on a Fischer-Johns apparatus and were uncorrected. Infrared spectra were collected using KBr pellets on a Perkin-Elmer model 1420 FT-IR spectrophotometer, and the spectra were calibrated relative to the 1601.8 cm^{-1} absorbance of polystyrene. NMR spectra were recorded on a Varian Unity Plus VXR (500 MHz) instrument in DMSO-d_6 or $CDCl_3$ solution. The chemical shift data were reported in units of d (ppm) downfield from solvent, and solvent was

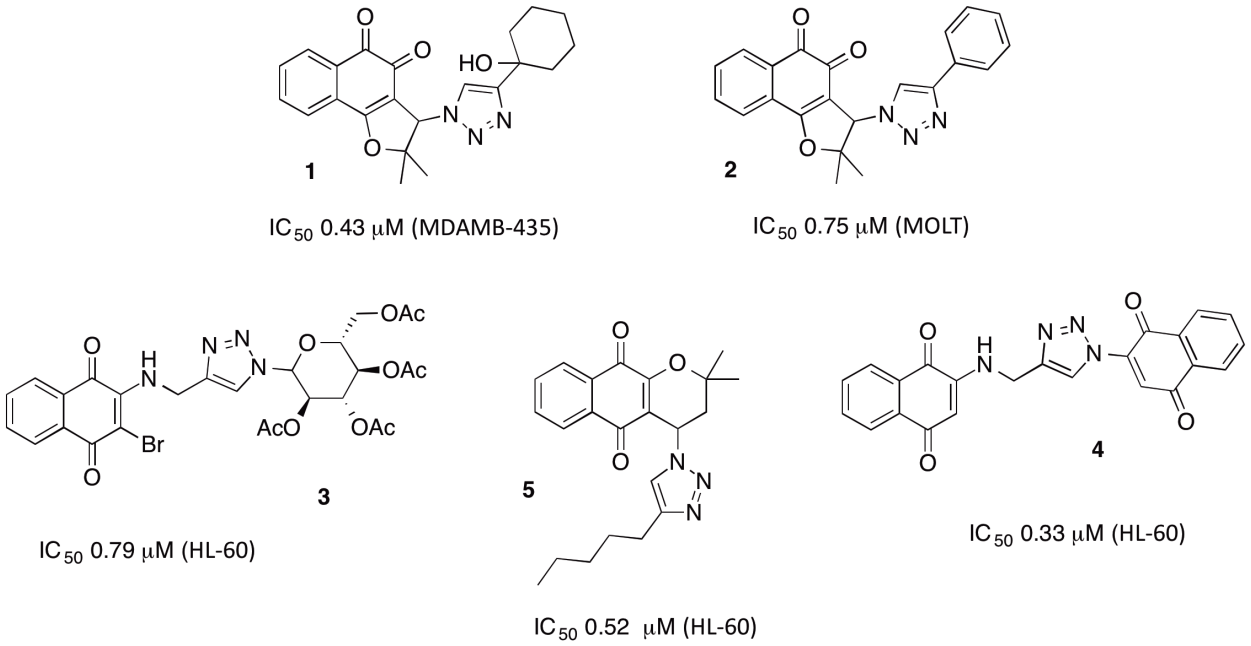

Figure 1 - Examples of cytotoxic hybrids naphthoquinones 1,2,3-triazoles.

used as an internal standard; coupling constants (*J*) are reported in hertz and refer to apparent peak multiplicities. High-resolution mass spectra (HRMS) were recorded on a MICROMASS Q-TOF mass spectrometer (Waters).

The physical and spectroscopic data for **9a-f** were previously reported in our studies (Chipoline et al. 2015).

*General procedure for **9a-k***: A solution of 1 mmol of 3-allyl-1,4-naphthoquinone (**6**) and iodine (1.5 mmol) in DMSO was stirred for 2 hours and monitored by TLC. Then, sodium azide (1.5 mmol) was added, and the mixture was heated to 70 °C for 15 minutes. After, water, copper(II) sulfate (5 mol%), alkyne (1.5 mmol) and sodium ascorbate (0.15 mmol) were added. Finally, the mixture was extracted with ethyl acetate and the organic phase was washed with water and dried with anhydrous sodium sulfate. The crude mixture was purified by column chromatography.

- **2-((4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (9g)**. Orange solid, 50 % yield; m.p. 164-166 ºC; IR (KBr, cm^{-1}): 3478, 1686, 1651, 1617, 1589, 1571, 1491, 1412, 1244, 1221, 1152, 1026; ^{1}H NMR (DMSO-d_6, 500.00 MHz): **δ 2.85 (1H, dd,** *J* 6.6 and 15.5 Hz), 3.19 (1H, dd, *J* 10.1 and 15.5 Hz), 4.51 (1H, dd, *J* 1.6 and 15.5 Hz), 4.78 (1H, dd, *J* 7.4 and 14.7 Hz), 4.83 (1H, dd, *J* 3.9 and 14.7 Hz), 5.14 (HO, *J* t, 5.5 Hz), 5.57-5.60 (1H, m), 7.57 (1H, dd, *J* 1.0 and 7.6 Hz), 7.69 (1H, td, *J* 1.0 and 7.6 Hz), 7.78 (1H, td, *J* 1.0 and 7.6 Hz), 7.94 (1H, dd, *J* 1.0 and 7.6 Hz), 8.03 (1H, s); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT): 29.0, 52.4, 54.9, 62.7, 84.7, 114.8, 123.5, 124.1, 126.8, 128.6, 130.4, 132.0, 134.8, 167.9, 174.8, 180.5; HRESIMS *m/z* 334.0806 $[M+Na]^+$ (Calcd. for $C_{16}H_{13}N_3O_4$ Na^+: 334.0804). D = 0.6 ppm.
- **2-((4-butyl-1*H*-1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (9h)**. Red solid, 60 % yield; m.p. 132-134 ºC; IR (KBr, cm^{-1}): 3137, 2927, 1651, 1616, 1588, 1572, 1494, 1412, 1361, 1251, 1218, 1153, 1084, 1049, 840; NMR-^{1}H (DMSO-d_6, 500 MHz): **δ 0.76 (1H, t,** *J* 7.4 Hz), 1.12-1.17 (1H, m), 1.36-1.43 (1H, m), 2.53 (1H, t, *J* 7.4 Hz), 2.84 (1H, dd, *J* 6.1 and 15.5 Hz), 3.15 (1H, dd, *J* 10.2 and 15.5 Hz), 4.71 (1H, dd, *J* 6.3 and 14.8 Hz), 4.79 (1H, dd, *J* 3.6 and 14.8 Hz), 5.53-5.59 (1H, m), 7.57 (1H, d, *J* 7.6 Hz), 7.66 (1H, td, *J* 1.0 and 7.6 Hz), 7.77 (1H, td, *J* 1.0 and 7.6 Hz), 7.84 (1H, s), 7.89-7.91 (1H, m); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT): 13.1, 21.1, 24.2, 28.6, 30.7, 52.2, 84.3, 114.6, 122.4, 123.8, 126.6, 128.3, 131.7, 134.5, 146.7, 167.6, 174.4, 180.1; HRESIMS *m/z* 360.1333 $[M+Na]^+$ (Calcd. for $C_{19}H_{19}N_3NaO_3^+$: 360.1324). D = 2.5 ppm.
- **2-((4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (9i).** Orange soilid, 55 % yield; m. p.158-158 ºC; IR (KBr, cm^{-1}): 1658, 1626, 1598, 1588, 1574, 1489, 1406, 1308, 1278, 1241, 1230, 1213, 1084, 1029, 758; NMR-^{1}H (DMSO-d_6, 500 MHz): **δ 2.85 (1H, dd,** *J* 6.5 and 15.6 Hz), 3.20 (1H, dd, *J* 10.2 and 15.6 Hz), 4.81 (1H, dd, *J* 7.2 and 14.7 Hz), 4.89 (1H, dd, *J* 3.8 and 14.7 Hz), 5.14 (1H, s), 6.91-7.02 (3H, m), 7.28 (2H, dd, *J* 4.6 and 11.4 Hz), 7.52 (1H, d, *J* 7.5 Hz), 7.68 (1H, td, 1.1 and 7.5 Hz), 7.77 (1H, td, *J* 1.1 and 7.5 Hz), 7.92-7.95 (1H, m). NMR-^{13}C (DMSO-d_6, 125 MHz APT): 28.9, 52.5, 60.9, 84.5, 114.6, 114.7, 120.7, 124.0, 125.2, 126.7, 128.6, 129.3, 130.3, 131.9, 134.7, 142.9, 157.8, 167.7, 174.7, 180.2; HRESIMS *m/z* 410.1120 $[M+Na]^+$ (Calcd. for $C_{22}H_{17}N_3NaO_4^+$: 410.1117). D = 0.7 ppm.
- **2-((4-hexyl-1*H*-1,2,3-triazol-1-yl)**

methyl)-2,3-dihydronaphtho[1,2-*b*] furan-4,5-dione (9j). Red solid, 47 % yield; m.p. 75-76 ºC; IR (KBr, cm^{-1}): 3541, 2952, 2923, 2856, 1703, 1652, 1659, 1622, 1573, 1492, 1453, 1409, 1311, 1276, 1255, 1217, 1151, 1083; NMR-^{1}H (DMSO-d_6, 500 MHz): **δ 0.83 (1H, t,** *J* 6.8 Hz), 1.18-1.24 (3H, m), 1.43-1.48 (1H, m), 2.55 (1H, t, *J* 7.5 Hz), 2.86 (1H, dd, *J* 6.2 and 15.5 Hz), 3.17 (1H, dd, *J* 10.2 and 15.5 Hz), 4.73 (1H, dd, *J* 6.4 and 14.7 Hz), 4.81 (1H,dd, *J* 3.6 and 14.7 Hz), 5.54-5.61 (1H, m), 7.59 (1H, d, *J* 7.5 Hz), 7.69 (1H, t, *J* 7.5 Hz), 7.78 (1H, t, *J* 7.5 Hz), 7.85 (1H, s), 7.98 (1H, d, *J* 7.5 Hz). NMR-^{13}C (DMSO-d_6, 125 MHz APT): 13.7, 21.8, 24.8, 28.1, 28.7, 28.8, 30.8, 52.3, 84.5, 114.8, 122.6, 124.1, 126.7, 128.5, 130.3, 131.9, 134.7, 146.9, 167.8, 174.6, 180.2; HRESIMS *m/z* 388.1637 $[M+Na]^+$ (Calcd. for $C_{21}H_{23}N_3NaO_3^+$: 388.1637). D = 0 ppm.

- **2-((4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (9k**). Orange solid, 48 % yield; m.p.179-180 ºC; IR (KBr, cm^{-1}): 3499, 1647, 1608, 1588, 1570, 1490, 1412, 1359, 1246, 1218, 1146, 1136, 1012; NMR-^{1}H (DMSO-d_6, 500 MHz): **δ 1.34 (1H, s), 1.41 (1H, s), 2.87 (1H, dd,** *J* 6.1 and 15.5 Hz), 3.18 (1H, dd, *J* 10.1 and 15.5 Hz), 4.45 (1H, dd, *J* 6.7 and 14.7 Hz), 4.81 (1H, dd, *J* 3.9 and 14.7 Hz), 5.55-5.62 (1H, m). 7.58 (1H, d, *J* 7.5 Hz), 7.68 (1H, td, *J* 1.0 and 7.5 Hz), 7.79 (1H, td, *J* 1.0 and 7.5 Hz), 7.89 (1H, s), 7.98 (1H, d, *J* 7.5 Hz); NMR-^{13}C (DMSO-d_6, 125 MHz APT): 28.8, 30.3, 30.3, 52.2, 66.7, 84.3, 114.6, 121.0, 123.8, 126.6, 128.3, 130.2, 131.7, 134.5, 155.6, 167.6, 174.5, 180.1; HRESIMS *m/z* 362.1112 $[M+Na]^+$ (Calcd. $C_{18}H_{17}N_3NaO_4^+$: 362.1117). D = 1.4 ppm.

BIOLOGICAL ASSAYS

Naphtoquinones citotoxicity was evaluated against HCT-116 (colon adenocarcinoma), MCF-7 (breast adenocarcinoma) and RPE (non tumour human retinal epithelium) cell lines. Cells were maintained in RPMI 1640 (HCT-116) and DMEM Glutamax (RPE and MCF-7) medium supplemented with 10% fetal bovine serum (v/v), 2 mM glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin at 37 ºC under a 5 % CO_2 atmosphere.

Cells were plated into 96-well plates (5×10^4 cells/mL) and cultured for 24 h prior to screening. After this period, samples were incubated in duplicate at 5 mM and incubated during 72 h. Negative and positive controls were given by DMSO (C-) and doxorubicin (C+) respectively. Three hours before the end of the incubation period, 150 μL of MTT (5 mg/mL) was added to each well and the absorbance was read at 595 nm using a Multiskan FC multiplate reader (Fisher Scientific) (Mosmann 1983). The samples which presented growth inhibition superior to 75% were selected for IC_{50} (the half maximal inhibitory concentration) determination.

IC_{50} values were calculated along with the respective 95% confidence intervals by non-linear regression using GraphPad Prism 5.0 (Intuitive Software for Science).

RESULTS AND DISCUSSION

Initially, we prepared 3-allyl-lausone (**6**) through C-3 alkylation of lausone by treatment with allyl bromide in basic medium (K_2CO_3/DMF) at 120 ºC for 24 h. Next, we promoted the iodociclization of **6** with iodine (DMSO/pyridine) leading to the intermediate 2-(iodomethyl)-2,3-dihydronaphtho-[1,2-*b*]-furan-4,5-dione (**7**). After, nucleophilic displacement with sodium azide in DMSO at 70 ºC produced the key template 2-(azidomethyl)-2,3-dihydronaphtho-[1,2-*b*]-furan-4,5-dione (**8**) in 78% overall yield. Finally, for the synthesis of the

compounds 2-((4-alkyl or aryl-1*H*-1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho-[1,2-*b*]-furan-5-dione (**9a-k**) we used a variant of the Huisgen 1,3-dipolar cycloaddition experimental protocol in which the azido-quinone **8** was reacted with up to eleven different alkynes under Cu(I) catalysis, obtaining only the regioisomer 1,4-disubstituted as an orange solid (35-70%, Figure 2).

The structures of the compounds were elucidated by spectroscopic techniques (see Supplementary Material – Figures S1-S34). Taking as an example the compound **9g**, the IR spectrum presents stretches at 3478, related to O-H bond, 1686 and 1651 cm^{-1} to C=O bonds of carbonyls. In the ^{1}H-NMR spectrum, the signals at 7.57 (1H, dd, *J* 1.0 and 7.6 Hz), 7.69 (1H, td, *J* 1.0 and 7.6 Hz), 7.78 (1H, td, *J* 1.0 and 7.6 Hz), 7.94 (1H, dd, *J* 1.0 and 7.6 Hz), reflect the signal pattern for aromatic hydrogens of 1,2-naphthoquinones, a singlet at 8.03 ppm is related to hydrogen of the ring 1,2,3-triazole, and the mutiplet at 5.57-5.60 is associated with methinic hydrogen from furan ring.

The anticancer activity of naphthoquinones **9a-k** was assessed against two human cancer and a non-tumor cell lines in comparison to doxorubicin (positive control) using the MTT assay (Mosmann 1983). At 5 μM concentration, seven out of ten tested substances presented growth inhibition superior to 75% to MCF-7 cells, while only three of them were active against HCT-116 cells, as reported in Table I. Most of the substances were also active against the nontumor cells at 5 μM.

The IC_{50} values demonstrated that compounds **9c**, **9d**, **9e**, **9i**, **9j** showed highest activity against all cancer cell lines with IC_{50} ranged from 0.74 to 4.4 μM (Table II). The aryl triazolic derivatives **9c** and **9d** presented selective activity in MCF-7 while **9i** seems to be selective to HCT-116 cell line being almost four times more potent than to the other tested cells, appearing as good prototypes for an anti-breast and colon cancer lead molecules, respectively.

In terms of selectivity, the presence of methyl group on aromatic ring in **9d** increased toxicity in non-cancer cells compared to **9c**, with similar results for **9j** which contains the hexyl group. One addition of halogen to propyl group in **9b** enhanced anticancer activity, however, decreased the selectivity.

The results indicate that the presence of aryl substituents (**9c**, **9d**, **9e** and **9i**) in the triazole moiety is relevant for cytotoxic activity and selectivity against cancer cells.

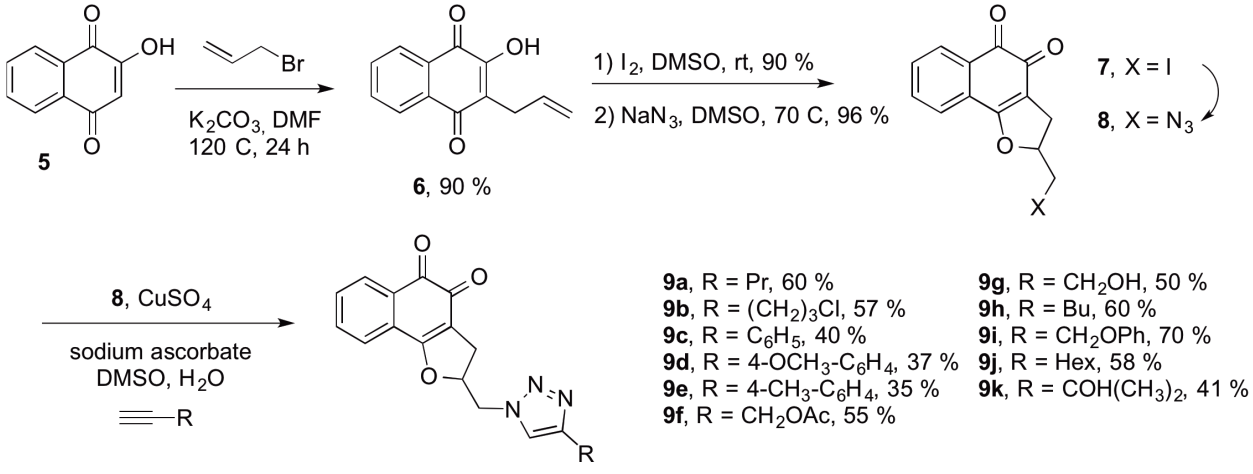

Figure 2 - Synthesis of 1*H*-1,2,3-triazoles-linked to 2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione.

TABLE I
Growth inhibition (%) of 3 cell lines: HCT-116 (colon adenocarcinoma); MCF-7 (breast adenocarcinoma) and RPE (human non-tumor cell line from retinal epithelium) of naphtoquinones after 72 hours of incubation.

	HCT-116	MCF-7	RPE
	Growth inhibition (%) at 5 mM		
9a	60.78 ± 8.00	90.60 ± 4.34	98.9 2 ± 1.79
9b	99.77 ± 0.64	88.61 ± 6.00	100.42 ± 0.10
9c	69.93 ± 2.11	89.66 ± 1.82	82.05 ± 1.26
9d	70.04 ± 5.30	90.99 ± 1.45	50.61 ± 2.02
9e	63.77 ± 7.32	89.29 ± 3.86	100.16 ± 0.71
9f	23.88 ± 2.62	-10.81 ± 3.35	58.31 ± 5.04
9g	19.75 ± 4.45	14.30 ± 1.02	41.46 ± 1.00
9h	66.53 ± 9.69	92.88 ± 1.35	96.62 ± 1.04
9i	61.99 ± 27.02	93.41 ± 3.00	98.98 ± 0.24
9j	74.77 ± 11.08	91.86 ± 4.19	98.09 ± 1.95
9k	23.35 ± 1.63	26.18 ± 17.99	44.28 ± 3.19

TABLE II
IC_{50} values presented in µM against 3 cell lines: HCT-116 (colon adenocarcinoma); MCF-7 (breast adenocarcinoma) and RPE (human non-tumor cell line from retinal epithelium) after 72 hours of incubation.

	IC_{50} (µM)		
	HCT-116	MCF-7	RPE
9a	> 5	> 5	> 5
9b	> 5	4.10 2.62 - 6.42	2.12 0.99 - 4.53
9c	> 5	1.10 0.70 - 1.73	> 5
9d	> 5	2.92 1.69 - 5.05	> 5
9e	1.36 0.66 - 2.83	0.74 0.37 - 1.49	1.77 1.00 - 3.13
9f	> 5	> 5	> 5
9g	> 5	> 5	> 5
9h	> 5	> 5	> 5
9i	1.30 0.58 - 2.92	> 5	> 5
9j	0.98 0.47 - 2.04	4.38 1.68 - 11.37	0.31 0.06 - 1.61
9k	> 5	> 5	> 5
Doxorubicin (C+)	0.02 0.02 - 0.03	0.16 0.09 - 0.29	2.31 0.85 - 6.29

CONCLUSIONS

In summary, this study allowed to identify some promising antitumor prototypes of 1,2,3-triazole-1,2-naphthoquinone hybrids in C-2. We have found that the presence of aromatic substituents at C-5 position of the triazole ring is relevant for improving the cytotoxicity against cancer cell lines.

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SUPPLEMENTARY MATERIAL

Figures S1-S34.