


Article

Synthesis of Selenium-Quinone Hybrid Compounds with Potential Antitumor Activity via Rh-Catalyzed C-H Bond Activation and Click Reactions

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Abstract: In continuation of our quest for new redox-modulating catalytic antitumor molecules, selenium-containing quinone-based 1,2,3-triazoles were synthesized using rhodium-catalyzed C-H bond activation and click reactions. All compounds were evaluated against five types of cancer cell lines: HL-60 (human promyelocytic leukemia cells), HCT-116 (human colon carcinoma cells), SF295 (human glioblastoma cells), NCIH-460 (human lung cells) and PC3 (human prostate cancer cells). Some compounds showed good activity with IC₅₀ values below 1 μM. The cytotoxic potential of the naphthoquinoidal derivatives was also evaluated in non-tumor cells, exemplified by L929 cells. Overall, these compounds represent promising new lead derivatives and stand for a new class of chalcogenium-containing derivatives with potential antitumor activity.

Keywords: lapachol; naphthoquinone; cancer; selenium; click chemistry; C-H activation

1. Introduction

Cancer is considered one of the major leading causes of death worldwide, accounting for 8.8 million deaths in 2015, and responsible for one in six deaths globally [1]. It is a generic term for a large group of diseases characterized by abnormal cell growth which can invade adjoining parts of the body and general organs [2]. Each year, more than 14 million people are diagnosed with cancer, the majority of whom live in low- and middle-income countries [3]. Chemotherapy is one of the conventional treatments for patients diagnosed with cancer, together with radiation and surgery [4]. This systemic treatment consists in the circulation of anticancer drugs through the body by the blood circulatory system to reach cancer cells wherever they are, with the goal of annihilate both cancerous colonies and metastasized cancer cells within a patient's body [5]. The side effects of chemotherapy are anemia, diarrhea, nausea, vomiting, hair loss and weakening of the immune system, as the actual anticancer drugs usually present low discrimination between normal and cancer cells [6].

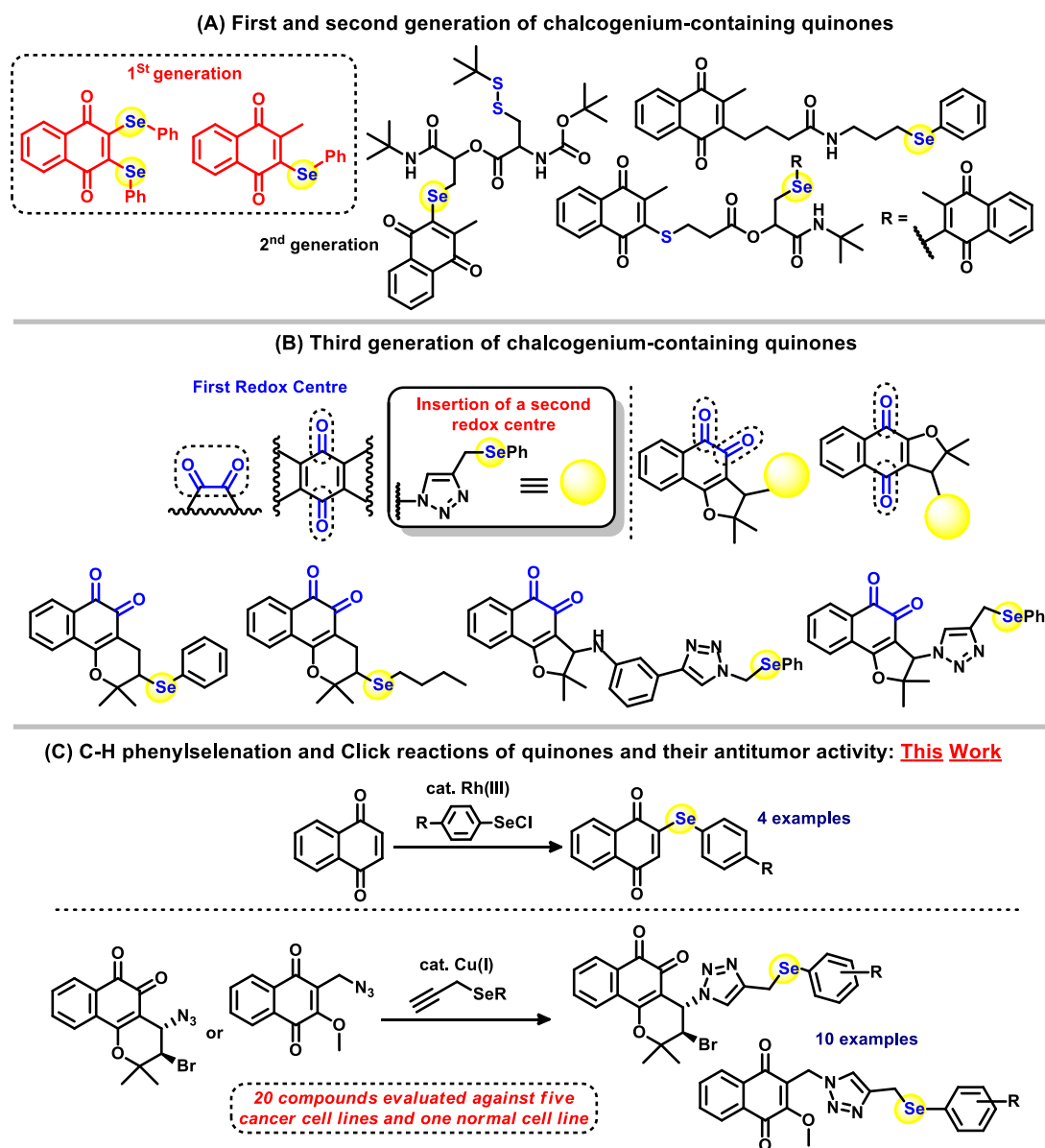
Naphthoquinones are known to be widely distributed in Nature, occurring in animals [7], plants [8], and microorganisms [9]. This group of molecules is considered privileged structures in Medicinal Chemistry due to the variety of biological activities they display, such as antiallergic [10], antifungal [11], antiviral [12], antibacterial [13], and anti-inflammatory properties [14], among others [15–17]. Most of these activities are associated with the—often catalytic—generation of Reactive Oxygen Species (ROS) [18]. Among the various quinones, 1,4-naphthoquinones are well represented in cancer therapy by solid tumour anticancer drugs such as doxorubicin, mitomycin and mitoxantrone [19]. Considering natural quinones, we also find important cytotoxic 1,4-naphthoquinones, including lapachol [20], plumbagin [21] and shikonin [22].

Over the years our research group has concentrated its efforts on the investigation of the naturally occurring quinones from the tree species of the *Bignoniaceae* family, especially the ones extracted from the Ipe tree, like lapachol and β -lapachone [23]. The last one has a history of anticancer activity against various cancer molecular targets [24,25], being in Phase II clinical trials in the US for the treatment of solid tumors [26]. Derivatization of β -lapachone by insertion of the 1,2,3-triazole moiety proved to be an interesting strategy for enhancement of cytotoxic activity, and β -lapachone-based 1,2,3-triazoles were obtained in moderate to high yields, showing significant activities against HCT-8 cell-lines [27].

The underlying mode of cytotoxic biological action of such quinones is rather interesting and in many aspects sets these redox active agents apart from conventional anticancer agents. Various studies have demonstrated that cancer cells exhibit an abnormal redox status associated with increased basal levels of ROS and alterations of the antioxidant systems [28]. The use of redox-modulating and often catalytic compounds therefore appears as an efficient therapeutic approach by taking advantage of this biochemical singularity to selectively target cancer cells, as long as normal cells maintain their own redox homeostasis by controlling the balance between ROS generation and elimination [29]. Indeed, normal cells often can tolerate a certain level of exogenous ROS whereas cancer cells cannot [30]. Eventually, this pre-existing difference between cancer cells on the one side, and normal cells on the other, may provide a certain degree of selectivity which would be most welcome in any targeted anticancer therapy.

Following this notion of redox regulation in cancer cells by redox active small molecules, the strategy of combining—catalytic—ROS generators such as 1,4-naphthoquinones with ROS modulators such as selenium atoms in the same molecule for enhanced activity and selectivity has already been successfully explored by Jacob and co-workers a couple of years ago (Scheme 1A) [31–33]. These initial studies have confirmed that the selectivity of quinone compounds can be improved by these kinds of “molecular hybridization” without compromising the cytotoxicity of the compounds. Chalcogens, such as selenium and tellurium, are known to play a major role in the chemoprevention and possibly even in the treatment of cancer, a notion highlighted once more by the recent publications of Kieliszek, Lipinski, Błażejczak and colleagues [34–36]. The choice of one or more chalcogen atoms as additional redox site(s) is therefore evident. Indeed, in fine agreement with these pioneering studies, our research group has recently described chalcogen-containing β -lapachones with remarkable activity against some cancer cell lines, including HL-60 with IC₅₀ values of 0.94 μ M and 0.53 μ M and MOLT-4 (leukaemia) with IC₅₀ values between 0.73 and 1.89 μ M [37]. In previous work, selenium-containing β -lapachone-based 1,2,3-triazoles derivatives were also synthesized and exhibited high activity with IC₅₀ values below 2 μ M against cancer cells such as HL-60 and PC3 (human prostate) cells [38] (Scheme 1B).

Encouraged by these results, we now report the synthesis and biological evaluation of new selenium containing 1,4-naphthoquinone derivatives, obtained by two main synthetic strategies: C-H bond activation [39–41], and copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) [42–45] (Scheme 1C). Chalcogen-containing β -lapachones derivatives were also synthesized and their biological activity has been evaluated against cancer and normal cell lines.

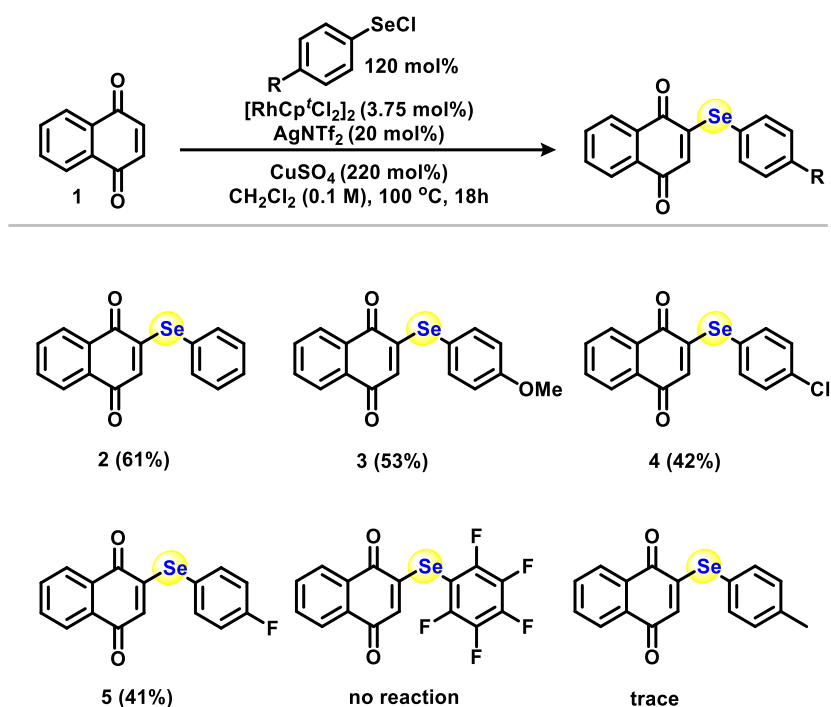


Scheme 1. Overview of the different generations of hybrid redox molecules for the first and second generation (Panel (A)) to the third generation with lapachones (Panel (B)) and the products of Rh-activated C-H bond activation and click reactions (Panel (C)).

2. Results and Discussion

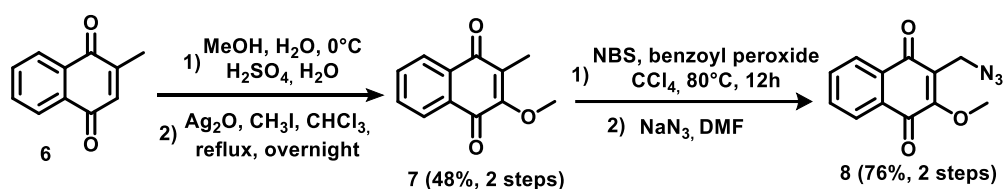
2.1. Chemistry

Recently, our research group developed methodologies which enable the functionalization of quinones via rhodium catalyzed C-H activation [46,47], paving the way to new molecules containing iodine, bromine and selenium atoms with remarkable biological activity [48]. Encouraged by that fact, the same catalyst system was explored with other electrophilic selenium sources, focusing on obtaining new molecules with a substituent in the phenyl selenium moiety. 1,4-naphthoquinone (**1**) was reacted with substituted phenyl hypochloroselenoites and derivatives **2–5** were obtained with moderate yields. The reaction failed when electron deficient perfluorophenyl hypochloroselenoite was employed and only traces of product were observed for *p*-tolyl hypochloroselenoite (Scheme 2).



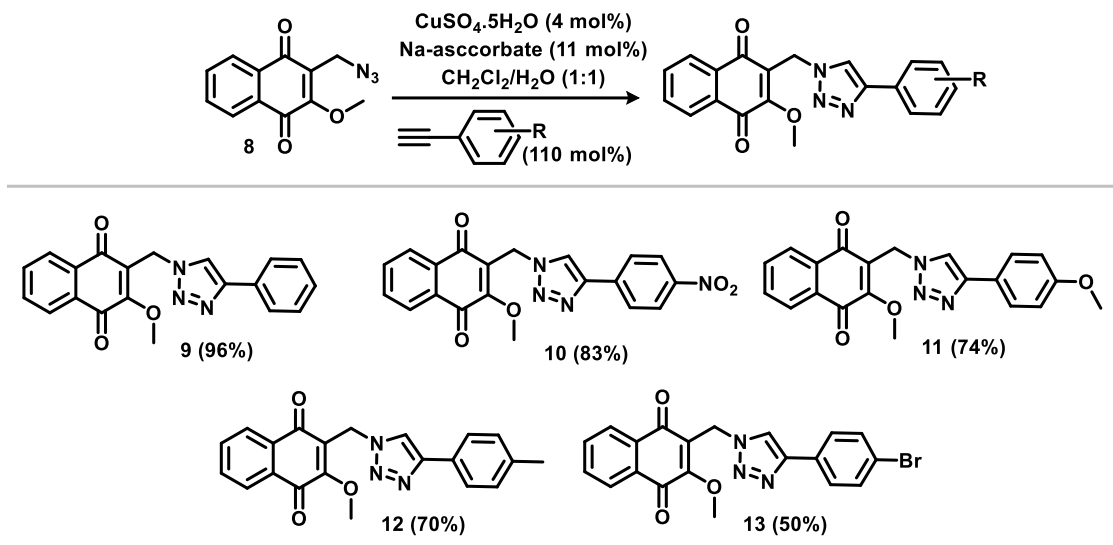
Scheme 2. Functionalization of 1 via rhodium-catalyzed C-H activation.

Menadione (6) was reacted with hydrogen peroxide in methanol resulting in menadione oxide, that was promptly acidified with H_2SO_4 to obtain 2-hydroxy-3-methyl-1,4-naphthoquinone [49]. Methylation of the hydroxyl group was achieved by reaction with iodomethane and Ag_2O in CHCl_3 under reflux overnight, affording 7 in 48% over two steps. Next, 7 was reacted with NBS and benzoyl peroxide in CCl_4 and bromination occurred in 76% yield [50]. Reaction with NaN_3 in DMF gave 8 in quantitative yield (Scheme 3).



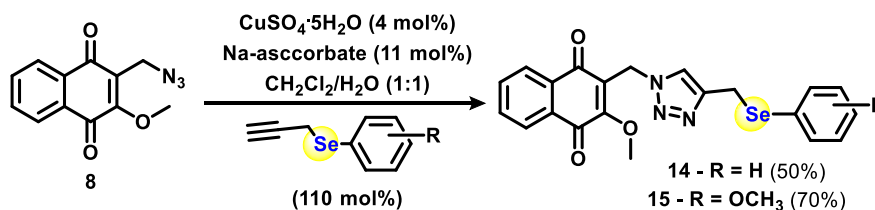
Scheme 3. Synthetic pathway for obtaining azide derivative 8.

Since 2002, copper-catalyzed “click” cycloadditions offer access to an almost unlimited array of triazole-containing structures [51]. For this reaction, copper(II) sulfate in aqueous media in the presence of sodium ascorbate, both in catalytic amounts, constitute the preferred catalytic system for this sort of transformation due to practicality, cost and robustness [52–54]. Besides more complicated multicomponent reactions, such as the Passerini or Ugi reaction, click reactions are ideally suited to assemble hybrid molecules, such as catalysts featuring two or more redox centers. Hence the second class of compounds was designed by adding a triazole portion in the 1,4-naphthoquinone backbone. In order to obtain 1,2,3-triazole derivatives, a classical copper(I) catalyzed “click” reaction [51,55] was employed to generate derivatives with substitution pattern in the 4-position of the benzene ring. Reaction with phenyl acetylene afforded 9 in 96% yield. Treatment of a more electron-deficient alkyne gave derivative 10 in excellent yield. Alkynes with electron donating groups, such as methoxy and methyl afforded derivatives 11 and 12 in good yields. Reaction with alkyne with presence of bromine in the benzene ring afforded 13 in moderate yield (Scheme 4).



Scheme 4. 1,2,3-triazole derivatives obtained via classical copper(I) catalyzed “click” reaction.

Next, in order to investigate the effect of a selenium atom in the bioactivity of the previous molecules, azide 8 was reacted with two different phenyl(prop-2-yn-1-yl)selenanes substituted at the position 4 of the benzene ring (Scheme 5).

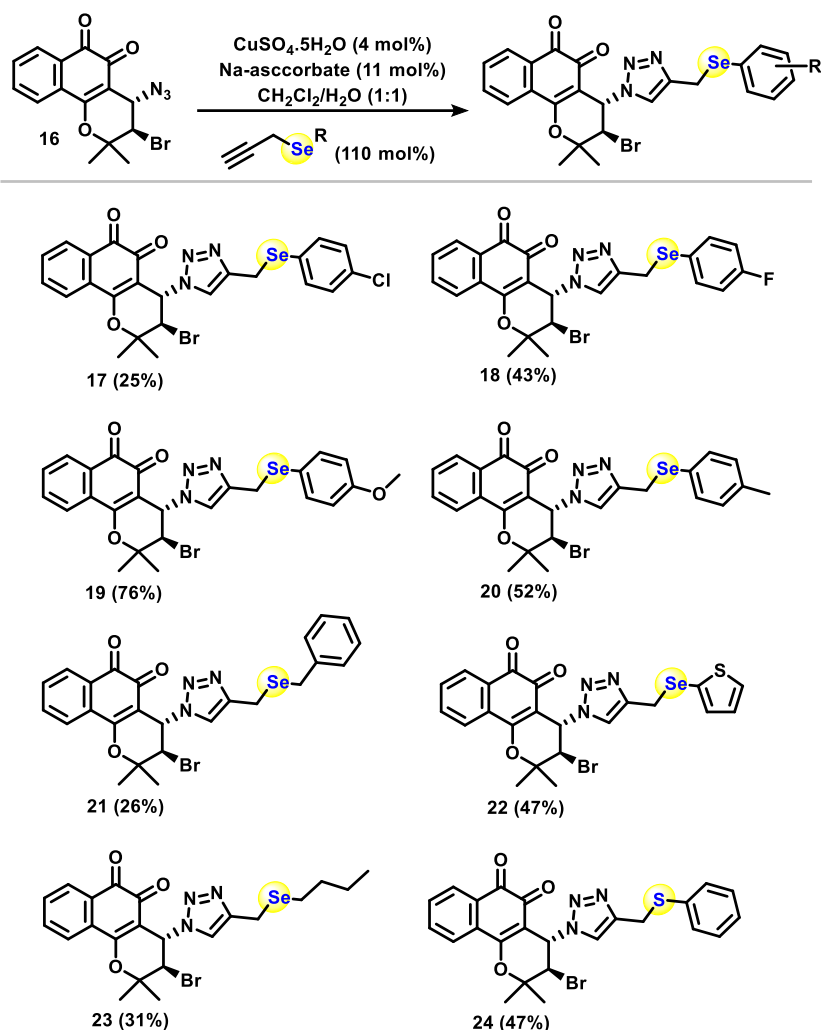


Scheme 5. Selenium containing-1,2,3-triazole derivatives obtained via classical copper(I) catalyzed “click” reaction.

In contrast to menadione and its *para*-quinone derivatives, lapachones represent a class of highly reactive *ortho*-quinones and are renowned for their high activity against trypomastigote forms of *Trypanosoma cruzi* [56], the causative agent of Chagas disease. In this context, β -lapachone, in particular, is considered an effective substance against *Trypanosoma cruzi* [57]. This pathogenic microorganism seems to be rather sensitive to redox changes and therefore also to agents able to modulate its intracellular redox homeostasis. Recently, our research group has reported a novel selenium-containing β -lapachone derivative that showed remarkable activity against a series of cancer cell lines, proving that insertion of a second redox center contributes to an enhanced biological activity [38].

Motivated by those findings, β -lapachone-1,2,3-triazole-selenium derivatives were synthesized using CuAAC and were obtained in poor to good yields. Substituents at the aromatic ring of the selenium alkynes have shown to affect the yield of the reaction, and derivatives 17 and 18 containing chlorine and fluorine atoms in the position 4 of the aromatic ring were obtained in 25% and 43% yield, respectively. Electron-rich selenium alkyne bearing a methoxy group in the same position afforded derivative 19 in 76% yield. Interestingly, insertion of a methylene group in the alkyl chain and a less electron donating group such as methyl had a drastic effect on the reaction and derivatives 20 and 21 were obtained in moderate to poor yields. Modification of the benzene terminal group by a heterocyclic ring such as thiophene and an alkyl chain also influenced reactivity and derivatives 22 and 23 were

obtained in 47% and 31% yield, respectively. Finally, exchanging the selenium atom by a sulfur one afforded derivative **24** in 47% yield (Scheme 6).



Scheme 6. β -Lapachone selenium containing-1,2,3-triazoles. Note: Compounds were obtained in racemic form, but the stereochemistry *trans* was defined by X-ray crystallography as part of previous studies [27].

2.2. Biology

The various compounds synthesized as part of this study were subsequently evaluated for possible activity against different cancer cell lines, including HL-60, HCT-116, SF295, NCIH-460 and PC3 and one normal cell line, L929 (murine fibroblasts normal cells) (Table 1). Overall the IC_{50} and $\text{CI}_{95\%}$ values obtained reflect a considerable cytotoxicity associated with the quinones under investigation. Nonetheless, there are also some striking differences. Glancing over the data available so far, it is immediately apparent that the lapachone derivatives exhibit a considerably higher activity when compared to the menadiones. Whilst the IC_{50} values for the 1,4-quinones are usually between 10 and 100 μM , the lapachone derivatives are active well below this, generally between 1 and 10 μM , with some of the most active lapachones, such as compound **18**, even active in sub-micromolar concentrations. Indeed, this compound exhibits IC_{50} values of 0.59 μM , 0.37 μM and 0.36 μM against HL-60, HCT-116 and L929 cell lines, which are in the range of the ones measured for the benchmark anticancer drug doxorubicin (0.21 μM and 1.72 μM against HCT-116 and L929 cell lines, respectively).

Interestingly, the exceptional activity of compound **18** seems to result from a combination of (a) the lapachone; (b) selenium and (c) an electron-withdrawing substituent in *para*-position to Se which may render this chalcogen more (re-)active. Although the data available to date is very limited, and hence any structure-reactivity relationship is still highly speculative, there is some support for this notion. First of all, the menadione-derivatives, as mentioned already, are considerably less active, often with a factor of ten or even more between their activities and the ones of the lapachones. Secondly, compound **24**, which contains a sulfur instead of selenium, is the least active of the lapachone derivatives tested—although its activity still compares favourably with the ones of the menadione derivatives. And finally, the electron-donating analogues of compound **18** are also less active, although the differences are minor.

Apart from the considerable activity of some of the compounds presented, which compares well with the one of the common drug doxorubicin, there is also some selectivity against certain cancer cell lines. These differences in IC₅₀ values are minor yet notable. Still, there is no significant “selective cytotoxicity” against one particular cell line, which is somewhat disappointing yet not entirely unexpected, as none of the cell lines employed in this study represents truly “normal human cells”.

Table 1. Cytotoxic activity expressed by IC₅₀ μM (95% CI) of compounds in cancer and normal cell lines after 72 h exposure, obtained by nonlinear regression for all cell lines from three independent experiments.

Compounds	HL-60	HCT-116	SF295	NCIH-460	PC3	L929
2	1.96 (1.66–2.33)	>10	>10	>10	>10	>10
3	4.68 (3.93–5.58)	>10	>10	>10	>10	>10
4	2.25 (1.88–2.71)	>10	>10	>10	>10	>10
5	2.16 (1.81–2.59)	>10	>10	>10	>10	>10
8	>10	>10	>10	>10	>10	>10
9	5.39 (3.78–7.73)	>10	>10	>10	>10	>10
10	>10	>10	>10	>10	>10	>10
11	2.32 (1.72–3.25)	>10	>10	>10	>10	>10
12	>10	>10	>10	>10	>10	>10
13	>10	>10	>10	>10	>10	>10
14	>10	>10	>10	>10	>10	>10
15	>10	>10	>10	>10	>10	>10
17	0.81 (0.73–0.86)	>8.0	2.60 (2.47–2.72)	2.06 (1.95–2.22)	2.03 (1.90–2.25)	0.52 (0.44–0.81)
18	0.59 (0.45–0.70)	0.37 (0.24–0.56)	1.48 (1.34–1.63)	1.32 (1.23–1.53)	1.06 (0.90–1.27)	0.36 (0.30–0.49)
19	1.28 (1.16–1.31)	>8.0	1.75 (1.57–1.82)	2.33 (2.23–2.45)	1.55 (1.40–1.94)	0.68 (0.53–0.82)
20	1.00 (0.93–1.07)	2.03 (1.79–2.28)	3.12 (2.91–3.24)	3.26 (3.15–3.42)	2.70 (3.15–3.42)	0.61 (0.58–0.68)
21	1.00 (0.91–1.03)	>8.0	1.63 (1.42–1.84)	1.49 (1.38–1.59)	1.77 (1.66–1.98)	1.28 (1.19–1.38)
22	0.53 (0.48–0.59)	>8.0	2.13 (2.01–2.43)	2.75 (2.54–3.00)	2.47 (2.26–2.68)	3.16 (3.04–3.27)
23	0.71 (0.61–0.76)	0.97 (0.88–1.10)	3.43 (3.20–3.69)	2.64 (2.44–2.90)	1.64 (1.55–1.69)	2.12 (1.92–2.27)
24	1.94 (1.85–2.08)	4.38 (4.24–4.54)	2.34 (2.16–2.44)	4.91 (4.70–5.26)	2.10 (1.85–2.28)	0.84 (0.71–1.06)
DOXO	0.02 (0.01–0.02)	0.21 (0.16–0.29)	0.41 (0.21–0.47)	0.15 (0.13–0.18)	0.76 (0.59–0.93)	1.72 (1.58–1.87)

3. Materials and Methods

3.1. General Information

Starting materials available from commercial suppliers were used as received, unless stated otherwise. All reagents requiring purification were purified using standard laboratory techniques, according to methods published by Perrin, Armarego, and Perrin (Pergamon Press, 1966). Catalytic reactions were performed under an atmosphere of dry nitrogen or argon; glassware, syringes and needles were either flame dried immediately prior to use or placed in an oven (200 °C), for at least 2 h, and allowed to cool either in a desiccator or under an atmosphere of nitrogen or argon; liquid reagents, solutions or solvents were added via syringe through rubber septa; solid reagents were added inside a glovebox. Column chromatography was performed on silica gel (SiliaFlash G60 UltraPure 60–200 μm, 60 Å, Quebec City, QC, Canada). ¹H- and ¹³C-NMR were recorded at room temperature using an AVANCE DRX200 or an DRX400 MHz instrument (Bruker, Billerica, MA, USA) in the solvents indicated. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in Hertz (Hz). All assignments of NMR spectra were based on 2D NMR data (DEPT-135, COSY, HSQC and

HMBC). Mass spectra were recorded using a FT-ICRMS Apex 4e 7.0T FT-MS (ESI⁺ mode) (Bruker Daltonics) or a GCMS QP2010+ (EI⁺ mode) instrument (Shimadzu). Infrared spectra were recorded on a Spectrum One FTIR spectrometer (Perkin Elmer, 710 Bridgeport Avenue, Shelton, CT, USA) as thin films or solids compressed on a diamond plate and are uncorrected. Data were processed employing Bruker Data Analysis software version 4.0. Compounds were named following IUPAC rules as applied by ChemBioDraw Ultra (version 12.0).

1,4-Naphthoquinone (**1**) and menadione (**6**) were purchased from Sigma Aldrich (St. Louis, MI, USA), purified via reduced pressure sublimation using a cold finger sublimation apparatus (50 °C, 0.9 mbar) and stored in a glovebox to prevent contact with moisture. Lapachol was extracted from the heartwood of *Tabebuia* sp. (Tecoma). A saturated aqueous sodium carbonate solution was added to the sawdust of ipe tree. Upon observing rapid formation of lapachol sodium salt, hydrochloric acid was added, allowing the precipitation of lapachol. Subsequently, the solution was filtered and a yellow solid was obtained. This solid was purified by recrystallizations with hexane. β -Lapachone was synthesised from lapachol by cyclization with concentrated sulfuric acid.

3.1.1. General Procedure for Phenylselenation at the 2-Position

An oven dried re-sealable tube was charged with 1,4-naphthoquinone (**1**) (15.8 mg, 0.10 mmol), [RhCp[†]Cl₂]₂ (3.75 mol %, 2.6 mg), silver bis(trifluoromethanesulfonyl)imide (20 mol %, 7.8 mg), anhydrous copper sulfate (220 mol %, 0.22 mmol, 34.9 mg) and the corresponding substituted phenylselenenyl chloride (120 mol %, 0.12 mmol). The tube was connected to a Schlenk line and an inert atmosphere was achieved. Anhydrous CH₂Cl₂ (1 mL) was added via a syringe and the tube was sealed. The mixture was heated at 100 °C for 18 h. After cooling, the mixture was filtered through a pad of Celite and purified via column chromatography (toluene) under the conditions noted.

2-(Phenylselenanyl)naphthalene-1,4-dione (**2**): Phenylselenenyl chloride (23.0 mg, 0.12 mmol) was used as substrate. The product was obtained in 61% yield as red crystals; m.p. (°C) = 152.8–153.7; IR (solid, cm⁻¹) ν : 2930 (w), 1664 (s), 1296 (m), 690 (s); HRMS (EI⁺): 313.9848 [M]⁺. Calcd. for [C₁₆H₁₀SeO₂]: 313.9846; ¹H-NMR (400 MHz, CDCl₃) δ : 8.14 (dd, *J* = 7.2, 1.9 Hz, 1H), 8.03 (dd, *J* = 6.1, 1.9 Hz, 1H), 7.82–7.67 (m, 2H), 7.68–7.61 (m, 2H), 7.57–7.42 (m, 3H), 6.40 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ : 183.0, 181.7, 157.0, 137.1, 134.3, 133.3, 132.8, 132.3, 131.6, 130.4, 130.2, 126.9, 126.7, 124.4.

2-((4-Methoxyphenyl)selenanyl)naphthalene-1,4-dione (**3**): 4-Methoxyphenylselenenyl chloride (26.6 mg, 0.12 mmol) was used. The product was obtained in 53% yield as an orange solid; m.p. (°C) = 140.7–148.3; IR (solid, cm⁻¹) ν : 2921 (w), 1641 (s), 1246 (m), 694 (w); HRMS (ESI⁺): 345.0015 [M + H]⁺. Calcd. for [C₁₇H₁₃SeO₃]⁺: 345.0024; ¹H-NMR (400 MHz, CDCl₃) δ : 8.14 (d, *J* = 6.9 Hz, 1H), 8.05 (d, *J* = 7.1 Hz, 1H), 7.77–7.69 (m, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.40 (s, 1H), 3.89 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 183.1, 181.7, 161.3, 157.7, 138.6, 134.3, 133.3, 132.8, 132.4, 131.8, 126.9, 126.7, 116.2, 114.5, 55.4.

2-((4-Chlorophenyl)selenanyl)naphthalene-1,4-dione (**4**): 4-Chlorophenylselenenyl chloride (27.1 mg, 0.12 mmol) was used. The product was obtained in 42% yield as an orange solid; m.p. (°C) = 154.8–155.7; IR (solid, cm⁻¹) ν : 2917 (m), 1648 (s), 1085 (m), 694 (m); HRMS (ESI⁺): 348.9515 [M + H]⁺. Calcd. for [C₁₆H₁₀ClSeO₂]⁺: 348.9529; ¹H-NMR (400 MHz, CDCl₃) δ : 8.12 (dd, *J* = 6.7, 2.1 Hz, 1H), 8.04 (dd, *J* = 6.7, 2.1 Hz, 1H), 7.78–7.68 (m, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.37 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ : 182.9, 181.6, 156.4, 138.4, 137.0, 134.4, 133.4, 132.8, 132.30, 131.6, 130.7, 127.0, 126.8, 122.6.

2-((4-Fluorophenyl)selenanyl)naphthalene-1,4-dione (**5**): 4-Fluorophenylselenenyl chloride (25.1 mg, 0.12 mmol) was used. The product was obtained in 41% yield as an orange solid; m.p. (°C) = 139.2–139.9; IR (solid, cm⁻¹) ν : 2924 (w), 1651 (s), 1243 (m), 690 (w); HRMS (EI⁺): 332.9810 [M + H]⁺. Calcd. for [C₁₆H₁₀FSeO₂]⁺: 332.9825; ¹H-NMR (400 MHz, CDCl₃) δ : 8.13 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.04 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.78–7.68 (m, 2H), 7.61 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.17 (t, *J* = 8.6 Hz, 2H), 6.35 (s, 1H).

^{13}C -NMR (100 MHz, CDCl_3) δ : 182.9, 181.6, 165.3, 162.8, 156.8, 139.26 (d, $J = 8.3$ Hz), 134.4, 133.4, 132.8, 132.3, 131.6, 126.86 (d, $J = 13.7$ Hz), 119.24 (d, $J = 3.6$ Hz), 117.84 (d, $J = 21.8$ Hz).

2-Hydroxy-3-methylnaphthalene-1,4-dione [49] (*menadione*, **6**): (1.0 g; 5.8 mmol) was dissolved in 10 mL methanol and chilled on an ice bath. A solution of 0.2 g of anhydrous Na_2CO_3 and 1 mL of 30% H_2O_2 in 5 mL of water were added slowly with the reaction mixture maintained at 0 °C. Then 100 mL of water were added and 2-methyl-1,4-naphthoquinone oxide precipitated as colourless crystals, which were collected by filtration and dried. The solid was treated with 5 mL concentrated H_2SO_4 and the mixture was allowed to stand for 10 min. Subsequent addition of 20 mL water resulted in a yellow precipitate which was filtered, dried in vacuum and purified by column chromatography (EtOAc/hexane 1:4). The product was obtained in 78% yield as yellow needles; m.p. (°C) = 178.2–179.1; IR (solid, cm^{-1}) ν : 3332 (s), 1657 (s), 1276 (m), 726 (s); HRMS (EI⁺): 188.0467 [M]⁺. Cald. for [$\text{C}_{11}\text{H}_8\text{O}_3$]: 188.0473; ^1H -NMR (400 MHz, CDCl_3) δ : 8.13 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.08 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.75 (td, $J = 7.5, 1.3$ Hz, 1H), 7.68 (td, $J = 7.5, 1.3$ Hz, 1H), 7.33 (s, 1H), 2.11 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 185.0, 181.2, 153.1, 134.8, 132.9, 132.9, 129.4, 126.7, 126.1, 120.5, 8.7.

2-Methoxy-3-methylnaphthalene-1,4-dione (**7**): To a solution of 2-hydroxy-3-methylnaphthalene-1,4-dione (188.2 mg, 1 mmol) in CHCl_3 (30 mL) were added Ag_2O (463.5 mg, 2.0 mmol) and iodomethane (125.0 μL , 2 mmol). The reaction was refluxed for 48 h, filtered through a pad of Celite and the solvent was removed under reduced pressure. The residue was purified via column chromatography (EtOAc/hexane 1:5). The product was obtained in 62% yield as a yellow solid; m.p. (°C) = 99.3–100.7; IR (solid, cm^{-1}) ν : 2953 (w), 1674 (s), 1269 (m), 720 (s); HRMS (EI⁺): 202.0627 [M]⁺. Cald. for [$\text{C}_{12}\text{H}_{10}\text{O}_3$]: 202.0630; ^1H -NMR (400 MHz, CDCl_3) δ : 8.20–7.89 (m, 2H), 7.84–7.58 (m, 2H), 4.12 (s, 3H), 2.09 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 185.7, 181.2, 157.8, 133.7, 133.2, 132.0, 131.69, 131.5, 126.1, 126.1, 61.0, 9.2.

2-(Bromomethyl)-3-methoxynaphthalene-1,4-dione: 2-(Bromomethyl)-3-methoxynaphthalene-1,4-dione was prepared as described in reference [50]. To a stirred solution of 2-methoxy-3-methyl-1,4-naphthoquinone (**7**) (1.0 g, 5 mmol) in CCl_4 (30 mL) were added NBS (900 mg, 5.0 mmol) and benzoyl peroxide (0.5 g, 2.1 mmol). The mixture was stirred under white light irradiation (60 W) at 80 °C for 12 h. The solvent was then removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (60 mL) and washed with H_2O (4 \times 30 mL). The organic layer was dried with Na_2SO_4 , filtered, evaporated and purified by column chromatography (EtOAc/hexane 1:4). The product was obtained in 76% yield as a yellow solid; m.p. (°C) = 117.4–118.7; IR (solid, cm^{-1}) ν : 2953 (w), 1677 (s), 1217 (s), 723 (s); ^1H -NMR (400 MHz, CDCl_3) δ : 8.12 (dd, $J = 6.8, 2.2$ Hz, 1H), 8.06 (dd, $J = 6.8, 2.2$ Hz, 1H), 7.78–7.70 (m, 2H), 4.48 (s, 2H), 4.35 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 182.7, 181.3, 158.1, 134.3, 133.6, 131.6, 131.5, 129.1, 126.5, 126.4, 61.7, 20.0.

2-(Azidomethyl)-3-methoxynaphthalene-1,4-dione (**8**): To a stirred solution of 2-(bromomethyl)-3-methoxynaphthalene-1,4-dione (281.1 mg, 1 mmol) in DMF (5 mL) was added NaN_3 (195.0 mg, 3 mmol). The reaction was allowed to stir for 20 min and quenched with H_2O (15 mL). Then, the mixture was extracted with ethyl acetate (30 mL), and the organic phase was separated and dried with Na_2SO_4 . The solvent was removed under vacuum and the residue was purified via column chromatography (EtOAc/Hexane 1:5). The product was obtained in 100% yield as a dark yellow solid; m.p. (°C) = 69.1–70.0; IR (solid, cm^{-1}) ν : 2957 (w), 2100 (s), 1677 (s), 1273 (s), 730 (s); MS (ESI⁺): 244.1 [M + H]⁺. Cald. for [$\text{C}_{12}\text{H}_{10}\text{N}_3\text{O}_3$]⁺: 244.1; ^1H -NMR (400 MHz, CDCl_3) δ : 8.05 (dd, $J = 6.4, 2.5$ Hz, 1H), 8.01 (dd, $J = 6.4, 2.5$ Hz, 1H), 7.75–7.66 (m, 2H), 4.30 (s, 2H), 4.25 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 184.0, 181.4, 158.9, 134.3, 133.6, 131.5, 131.4, 126.4, 126.0, 61.9, 42.7.

3.1.2. General Procedure for the Synthesis of Triazoles

The corresponding alkynes (1.1 mmol) were reacted with 2-(azidomethyl)-3-methoxy-naphthalene-1,4-dione (**8**) (243.2 mg, 1 mmol) or (3*R*,4*S*)-4-azido-3-bromo-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]

chromene-5,6-dione (**18**) (362.2 mg, 1 mmol) in 12 mL of CH₂Cl₂/H₂O (1:1) using CuSO₄·5H₂O (9.3 mg, 0.04 mmol) and sodium ascorbate (22 mg, 0.11 mmol) as the catalytic system. The mixture was stirred at room temperature and monitored by TLC until total consumption of starting material. The mixture was extracted with CH₂Cl₂, dried with Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a gradient mixture of hexane/ethyl acetate with increasing polarity up to 100% ethyl acetate as eluent.

2-Methoxy-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (9): Ethynylbenzene (112.3 mg, 1.1 mmol) was used. The product was obtained in 96% yield as a dark yellow solid; m.p. (°C) = 103.8–104.7; IR (solid, cm⁻¹) ν : 2921 (m), 1671 (s), 1263 (m), 763 (s); HRMS (ESI⁺): 346.1160 [M + H]⁺. Cald. for [C₂₀H₁₆N₃O₃]⁺: 346.1186; ¹H-NMR (400 MHz, CDCl₃) δ : 8.09–7.99 (m, 2H), 7.95 (s, 1H), 7.79 (d, *J* = 7.4 Hz, 2H), 7.75–7.64 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 5.55 (s, 2H), 4.30 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 184.0, 181.3, 159.4, 147.5, 134.4, 133.8, 131.5, 131.3, 130.7, 128.7, 128.0, 126.5, 126.4, 125.7, 125.1, 120.8, 62.1, 42.3, 29.7.

2-Methoxy-3-((4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (10): 1-Ethynyl-4-nitrobenzene (161.8 mg, 1.1 mmol) was used. The product was obtained in 83% yield as a bright yellow solid; m.p. (°C) = 205.8–206.7; IR (solid, cm⁻¹) ν : 3134 (w), 2924 (w), 1667 (s), 1338 (m), 756 (w); HRMS (ESI⁺): 391.1010 [M + H]⁺. Cald. for [C₂₀H₁₅N₄O₅]⁺: 391.1037; ¹H-NMR (400 MHz, CDCl₃) δ : 8.26 (d, *J* = 8.5 Hz, 2H), 8.14 (s, 1H), 8.09 (t, *J* = 6.5 Hz, 2H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.81–7.70 (m, 2H), 5.62 (s, 2H), 4.37 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 184.1, 181.3, 159.5, 147.3, 136.9, 134.6, 133.9, 131.5, 131.2, 126.7, 126.4, 126.1, 124.4, 124.2, 122.4, 62.3, 42.6, 29.7.

2-Methoxy-3-((4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (11): 1-Ethynyl-4-methoxybenzene (145.4 mg, 1.1 mmol) was used. The product was obtained in 74% yield as a yellow solid; m.p. (°C) = 149.3–150.7; IR (solid, cm⁻¹) ν : 3088 (w), 1671 (s), 1266 (m), 720 (w); HRMS (ESI⁺): 376.1370 [M + H]⁺. Cald. for [C₂₁H₁₈N₃O₄]⁺: 376.1292; ¹H-NMR (400 MHz, CDCl₃) δ : 8.12–7.98 (m, 2H), 7.91 (s, 1H), 7.76–7.66 (m, 4H), 7.19 (d, *J* = 7.9 Hz, 2H), 5.55 (s, 2H), 4.31 (s, 3H), 2.35 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 184.1, 181.3, 159.4, 147.6, 137.8, 134.4, 133.7, 131.5, 131.3, 129.4, 127.9, 126.5, 126.4, 125.6, 125.2, 120.4, 62.1, 42.2, 21.2.

2-Methoxy-3-((4-(p-tolyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (12): 1-Ethynyl-4-methylbenzene (127.8 mg, 1.1 mmol) was used. The product was obtained in 70% yield as a yellow solid; m.p. (°C) = 123.1–124.5; IR (solid, cm⁻¹) ν : 3112 (w), 1644 (s), 1217 (m), 819 (s); HRMS (ESI⁺): 360.134 [M + H]⁺. Cald. for [C₂₁H₁₈N₃O₃]⁺: 360.1343; ¹H-NMR (400 MHz, CDCl₃) δ : 8.09–8.00 (m, 2H), 7.86 (s, 1H), 7.78–7.65 (m, 4H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.54 (s, 2H), 4.30 (s, 3H), 3.81 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 184.1, 181.3, 159.5, 159.4, 147.4, 134.4, 133.7, 131.5, 131.3, 127.0, 126.5, 126.4, 125.2, 123.4, 120.0, 114.2, 62.1, 55.3, 42.2.

2-((4-(4-Bromophenyl)-1H-1,2,3-triazol-1-yl)methyl)-3-methoxynaphthalene-1,4-dione (13): 1-Bromo-4-ethynylbenzene (199.1 mg, 1.1 mmol) was used. The product was obtained in 50% yield as an orange solid; m.p. (°C) = 174.1–175.0; IR (solid, cm⁻¹) ν : 2914 (w), 1674 (s), 1213 (m), 822 (s); HRMS (ESI⁺): 425.9820 [M+2]⁺. Cald. for [C₂₀H₁₆BrN₃O₃]⁺: 425.0364; ¹H-NMR (400 MHz, CDCl₃) δ : 8.15–8.01 (m, 2H), 7.96 (s, 1H), 7.79–7.71 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 5.58 (s, 2H), 4.34 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 184.1, 181.3, 159.4, 146.6, 134.5, 133.8, 131.9, 131.5, 131.3, 129.6, 127.2, 126.6, 126.4, 124.9, 121.9, 120.9, 62.2, 42.4.

2-Methoxy-3-((4-((phenylselanyl)methyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (14): Phenyl (prop-2-yn-1-yl)selane (214.6 mg, 1.1 mmol) was used. The product was obtained in 50% yield as a bright yellow solid; m.p. (°C) = 69–71; IR (solid, cm⁻¹) ν : 2921 (w), 1679, 1645 (s), 964, 734 (m); HRMS (ESI⁺): 440.0520 [M + H]⁺. Cald. for [C₂₁H₁₈N₃O₃Se]⁺: 440.0508; ¹H-NMR (400 MHz, CDCl₃) δ : 8.09–8.03 (m, 2H), 7.77–7.71 (m, 2H), 7.43 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.37 (s, 1H), 7.18–7.10 (m, 3H), 5.43 (s, 2H), 4.24 (s, 3H), 4.14 (s, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ : 183.8, 181.3, 159.2, 145.2, 134.5, 133.8, 133.3, 131.5, 131.3, 129.9, 129.0, 127.3, 126.5, 126.4, 125.0, 122.8, 62.0, 42.1, 20.6.

2-Methoxy-3-((4-(((4-methoxyphenyl)selenanyl)methyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (15): (4-Methoxyphenyl)(prop-2-yn-1-yl)selane (247.7 mg, 1.1 mmol) was used. The product was obtained in 70% yield as a dark yellow oil; IR (oil, cm^{-1}): 2957 (w), 1677 (s), 1243 (m), 726 (s); MS (ESI⁺): 440.0 [M + H]⁺. Calcd. for [C₂₁H₁₈ N₃O₃Se]⁺: 440.0; ¹H-NMR (400 MHz, CDCl₃) δ : 8.08–8.03 (m, 2H), 7.77–7.70 (m, 2H), 7.37 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 5.43 (s, 2H), 4.26 (s, 3H), 4.04 (s, 2H), 3.73 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 183.9, 181.4, 159.6, 159.3, 145.5, 136.3, 134.5, 133.8, 131.5, 131.3, 126.6, 126.4, 125.0, 122.8, 119.7, 114.8, 62.1, 55.27, 42.2, 21.6.

3-Bromo-4-(4-(((4-chlorophenyl)selenanyl)methyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (17): (4-Chlorophenyl)(prop-2-yn-1-yl)selane (252.5 mg, 1.1 mmol) was used. The product was obtained in 25% yield as a yellow powder. m.p. (°C) = 185.3–187.1, IR (solid, cm^{-1}): 1656 (s), 782 (w), HRMS (EI⁺): 591.9556 [M]⁺. Calcd. for [C₁₆H₁₀SeO₂]: 591.9536; ¹H-NMR (400 MHz, CDCl₃) δ : 8.10 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.54 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.56 (d, *J* = 9.2 Hz, 1H), 4.90 (d, *J* = 9.1 Hz, 1H), 4.12 (s, 2H), 1.75 (s, 3H), 1.64 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 177.8, 176.4, 162.6, 135.7, 135.2, 134.0, 132.3, 130.6, 130.5, 129.2, 129.2, 127.3, 125.2, 125.0, 110.4, 83.4, 58.9, 54.5, 27.5, 21.0, 20.5.

3-Bromo-4-(4-(((4-fluorophenyl)selenanyl)methyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (18): (4-Fluorophenyl)(prop-2-yn-1-yl)selane (234.4 mg, 1.1 mmol) was used. The product was obtained in 43% yield as an orange powder. m.p. (°C) = 187.1–190.0, IR (solid, cm^{-1}): 1660 (s), 1214 (w), HRMS (EI⁺): 575.9885 [M]⁺. Calcd. for [C₁₆H₁₀SeO₂]: 575.9837; ¹H-NMR (400 MHz, CDCl₃) δ : 8.08 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.52 (s, 1H), 7.36 (s, 1H), 7.46 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.95 (t, *J* = 8.7 Hz, 2H), 5.57 (d, *J* = 9.1 Hz, 1H), 4.90 (d, *J* = 9.1 Hz, 1H), 4.09 (s, 2H), 1.75 (s, 3H), 1.64 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 178.0, 176.6, 164.2, 162.8, 161.7, 144.6, 137.2 (d, *J* = 8.0 Hz), 135.4, 132.5, 130.8, 130.7, 129.4, 125.3 (d, *J* = 32.7 Hz), 123.8 (d, *J* = 3.4 Hz), 116.5 (d, *J* = 21.4 Hz), 110.6, 83.7, 59.1, 54.8, 27.7, 21.6, 20.7.

3-Bromo-4-(4-(((4-methoxyphenyl)selenanyl)methyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (19): (4-Methoxyphenyl)(prop-2-yn-1-yl)selane (247.6 mg, 1.1 mmol) was used. The product was obtained in 76% yield as an orange powder. m.p. (°C) = 113.5–114.6, IR (solid, cm^{-1}): 1654 (s), 1246 (w), HRMS (EI⁺): 588.0093 [M]⁺. Calcd. for [C₁₆H₁₀SeO₂]: 588.0032, ¹H-NMR (400 MHz, CDCl₃) δ : 8.11 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 9.4 Hz, 3H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.58 (d, *J* = 9.0 Hz, 1H), 4.93 (d, *J* = 9.0 Hz, 1H), 4.06 (s, 2H), 3.79 (s, 3H), 1.75 (s, 3H), 1.66 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 178.1, 176.6, 162.8, 159.9, 144.9, 137.2, 135.4, 132.5, 130.8, 130.7, 129.2, 125.5, 124.9, 119.3, 115.0, 110.5, 83.6, 58.9, 55.4, 54.8, 21.8, 21.0, 14.4.

4-(4-((Benzylselenanyl)methyl)-1H-1,2,3-triazol-1-yl)-3-bromo-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (20): Benzyl(prop-2-yn-1-yl)selane (230.1 mg, 1.1 mmol) was used. The product was obtained in 52% yield as a yellow powder. m.p. (°C) = 112.2–115.6, IR (solid, cm^{-1}): 1656 (s), HRMS (EI⁺): 572.0089 [M]⁺. Calcd. for [C₁₆H₁₀SeO₂]: 572.0083; ¹H-NMR (400 MHz, CDCl₃) δ : 8.10 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.47 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 7.7 Hz, 2H), 5.56 (d, *J* = 8.9 Hz, 1H), 4.92 (d, *J* = 8.9 Hz, 1H), 4.10 (d, *J* = 4.1 Hz, 2H), 2.30 (s, 3H), 1.72 (s, 3H), 1.65 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 178.1, 176.7, 162.9, 145.7, 139.2, 135.5, 132.6, 130.9, 130.8, 129.4, 129.4, 128.8, 126.9, 125.5, 125.2, 110.6, 83.7, 59.1, 54.8, 27.7, 21.0, 16.0.

3-Bromo-2,2-dimethyl-4-(4-((p-tolyl)selenanyl)methyl)-1H-1,2,3-triazol-1-yl)-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (21): Prop-2-yn-1-yl(p-tolyl)selane (230.1 mg, 1.1 mmol) was used. The product was obtained in 26% yield as a yellow powder. m.p. (°C) = 114.1–116.6, IR (solid, cm^{-1}): 1656 (s), HRMS (EI⁺): 572.0062 [M]⁺. Calcd. for [C₁₆H₁₀SeO₂]: 572.0083; ¹H-NMR (400 MHz, CDCl₃) δ : 8.08 (d, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.69 (s, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.35–7.24 (m, 4H), 7.18 (t, *J* = 7.0 Hz, 1H), 5.64 (d, *J* = 8.9 Hz, 1H), 4.96 (d, *J* = 8.9 Hz, 1H), 3.81 (s, 2H), 3.75 (s, 2H),

1.75 (s, 3H), 1.67 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 178.0, 176.7, 162.8, 144.9, 137.9, 135.4, 134.8, 132.5, 130.9, 130.8, 130.1, 129.4, 125.8, 125.5, 125.1, 110.5, 83.6, 59.1, 54.6, 27.6, 21.3, 21.2, 21.0.

3-Bromo-2,2-dimethyl-4-(4-((thiophen-2-ylselanyl)methyl)-1H-1,2,3-triazol-1-yl)-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (22): 2-(Prop-2-yn-1-ylselanyl)thiophene (221.3 mg, 1.1 mmol) was used. The product was obtained in 47% yield as a yellow powder. m.p. ($^{\circ}\text{C}$) = 104.3–108.6, IR (solid, cm^{-1}) ν : 1656 (s), 710 (w), HRMS (EI^+): 563.9529 $[\text{M}]^+$. Calcd. for $[\text{C}_{16}\text{H}_{10}\text{SeO}_2]$: 563.9490; ^1H -NMR (400 MHz, CDCl_3) δ : 8.10 (d, $J = 7.6$ Hz, 1H), 7.90 (d, $J = 7.6$ Hz, 1H), 7.74 (t, $J = 7.7$ Hz, 1H), 7.63 (t, $J = 7.2$ Hz, 1H), 7.43 (s, 1H), 7.37 (d, $J = 5.3$ Hz, 1H), 7.11 (d, $J = 4.2$ Hz, 1H), 6.95 (dd, $J = 5.2, 3.5$ Hz, 1H), 5.58 (d, $J = 9.0$ Hz, 1H), 4.94 (d, $J = 9.0$ Hz, 1H), 4.05 (s, 2H), 1.75 (s, 3H), 1.65 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 178.0, 176.6, 162.9, 144.2, 137.2, 135.4, 132.5, 131.7, 130.8, 130.7, 129.4, 128.4, 125.5, 125.2, 123.0, 110.6, 83.6, 59.2, 54.6, 27.7, 24.0, 20.9.

3-Bromo-4-(4-((butylselanyl)methyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (23): Butyl(prop-2-yn-1-yl)selane (192.6 mg, 1.1 mmol) was used. The product was obtained in 31% yield as a yellow powder. m.p. ($^{\circ}\text{C}$) = 123.1–124.4, IR (solid, cm^{-1}) ν : 2914 (s), 1670 (s), 782 (w), HRMS (EI^+): 538.0343 $[\text{M}]^+$. Calcd. for $[\text{C}_{16}\text{H}_{10}\text{SeO}_2]$: 538.0239; ^1H -NMR (400 MHz, CDCl_3) δ : 8.07 (d, $J = 7.6$ Hz, 1H), 7.91 (d, $J = 7.7$ Hz, 1H), 7.79 (s, 1H), 7.73 (t, $J = 7.6$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 5.65 (d, $J = 9.0$ Hz, 1H), 4.96 (d, $J = 9.0$ Hz, 1H), 3.83 (d, $J = 3.1$ Hz, 2H), 2.57 (d, $J = 7.3$ Hz, 2H), 1.76 (s, 3H), 1.67 (s, 3H), 1.61 (dd, $J = 15.0, 7.5$ Hz, 2H), 1.37 (dd, $J = 14.4, 7.3$ Hz, 2H), 0.89 (t, $J = 7.3$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 178.0, 162.8, 145.7, 135.4, 130.9, 130.7, 129.3, 125.5, 125.1, 110.6, 83.6, 59.1, 54.8, 32.4, 27.6, 24.2, 23.1, 20.9, 15.4, 13.8.

3-Bromo-2,2-dimethyl-4-(4-((phenylthio)methyl)-1H-1,2,3-triazol-1-yl)-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (24): Phenyl(prop-2-yn-1-yl)sulfane (163.0 mg, 1.1 mmol) was used. The product was obtained in 47% yield as a yellow powder. m.p. ($^{\circ}\text{C}$) = 119.5–121.4, IR (solid, cm^{-1}) ν : 1656 (s), 754 (w), HRMS (EI^+): 510.0859 $[\text{M}]^+$. Calcd. for $[\text{C}_{16}\text{H}_{10}\text{SeO}_2]$: 510.0482; ^1H -NMR (400 MHz, CDCl_3) δ : 8.09 (d, $J = 8.2$ Hz, 1H), 7.89 (d, $J = 7.6$ Hz, 1H), 7.73 (t, $J = 8.2$ Hz, 1H), 7.65–7.59 (m, 2H), 7.34 (d, $J = 7.4$ Hz, 2H), 7.29–7.24 (m, 2H), 7.18 (t, $J = 7.3$ Hz, 1H), 5.58 (d, $J = 9.0$ Hz, 1H), 4.89 (d, $J = 9.0$ Hz, 1H), 4.21 (d, $J = 7.2$ Hz, 2H), 1.71 (s, 3H), 1.63 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 178.0, 176.6, 162.9, 144.1, 135.4, 135.3, 132.5, 130.9, 130.8, 130.7, 129.4, 129.2, 128.4, 127.0, 125.5, 125.5, 110.5, 83.6, 59.2, 54.6, 29.5, 27.6, 20.9.

3.1.3. Activity Against Cancer Cell Lines

Compounds were evaluated for antitumor activity in cell culture in vitro using several human cancer cell lines obtained from the National Cancer Institute, NCI (Bethesda, MD, USA). The L929 cells (mouse fibroblast L cells NCTC clone 929) employed in this study as a control cell line, were obtained from the American Type Culture Collection (Manassas, VA, USA). All cancer cell lines were maintained in RPMI 1640 medium. The L929 cells were cultivated under standard conditions in DMEM with Earle's salts. All culture media were supplemented with 10% (cancer and L929 cells) fetal bovine serum, 2 mM L-glutamine, 100 IU/mL penicillin, 100 $\mu\text{g}/\text{mL}$ streptomycin at 37 $^{\circ}\text{C}$ with 5% CO_2 . In cytotoxicity experiments, cells were plated in 96-well plates (0.1×10^6 (SF295); 0.7×10^5 (HCT-116); 0.5×10^5 (NCIH-460), 0.1×10^6 (PC3 and L929)). All compounds tested were dissolved in DMSO. The final concentration of DMSO in the culture medium was kept constant (0.1%, v/v). Doxorubicin (0.001–1.10 μM) was used as the positive control, and negative control groups received the same amount of vehicle (DMSO). The cell viability was determined by reduction of the yellow dye 3-(4,5-dimethyl-2-thiazol)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to a purple formazan product as described by Mosmann [58]. At the end of the incubation time (72 h), the plates were centrifuged and the medium was replaced by fresh medium (200 μL) containing 0.5 mg/mL MTT. After 3 h, the MTT formazan product was dissolved in DMSO (150 μL) and the absorbance was measured using a multiplate reader (Spectra Count, Packard, ON, Canada). The impact of compounds

on cell proliferation was quantified as the percentage of control absorbance of the reduced dye at 550 nm. All cell culture based studies were performed in triplicate. All cells were mycoplasma-free.

4. Conclusions

We have demonstrated in previous reports that the strategy of conjoining two redox centers, namely a quinoidal moiety and the atom of selenium or sulfur, represents a promising avenue to prepare new compounds with antitumor activity. Here, we have prepared and assayed 24 such compounds against five cancer cell lines and have identified several such quinone-selenium hybrid molecules with moderate to high activity. Notably, in the past quinone-based triazole chalcogenium-containing agents were considered as potent antitumor derivatives, with IC_{50} values below 1 μ M, and we have now added a new class of naphthoquinonoid compounds with improved cytotoxicity against cancer cells. These compounds provide a lead for the further development of redox active and often catalytic molecules based on natural products which eventually may be able to distinguish between cancer and normal cells by modulating the specific pre-existing differences in redox state which for a number of reasons is often found between those cells.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ROS	Reactive Oxygen Species
IC_{50}	Half Maximal Inhibitory Concentration
CuAAC	Copper(I) Catalyzed Azide-Alkyne Cycloaddition
NBS	<i>N</i> -bromosuccinimide
DMF	Dimethylformamide
CI	Confidence Interval
μ M	Micromole
NMR	Nuclear Magnetic Resonance
EtOAc	Ethyl Acetate
DMSO	Dimethyl sulfoxide

References

1. Stewart, B.W.; Wild, C.P. *World Cancer Report*; IARC Publications: Lyon, France, 2014.
2. World Health Organization (WHO). *Guide to Cancer Early Diagnosis*; WHO: Geneva, Switzerland, 2017.
3. World Health Organization. *Global Health Observatory: The Data Repository*; World Health Organization: Geneva, Switzerland, 2017.
4. Barbounaki-Konstantakou, E. *Chemotherapy*; Beta Medical Arts: Athens, Greece, 1989.
5. Epstein, R.J. Maintenance therapy to suppress micrometastasis: The new challenge for adjuvant cancer treatment. *Clin. Cancer Res.* **2005**, *11*, 5337–5341. [[CrossRef](#)] [[PubMed](#)]
6. Rampling, R.; James, A.; Papanastassiou, V. The present and future management of malignant brain tumours: Surgery, radiotherapy, chemotherapy. *J. Neurol. Neurosurg. Psychiatry* **2004**, *75*, 24–30. [[CrossRef](#)]

7. Scudamore, K.A.; Atkin, P.M.; Buckle, A.E. Natural occurrence of the naphthoquinone mycotoxins, xanthomegnin, viomellein and vioxanthin in cereals and animal feedstuffs. *J. Stored Prod. Res.* **1986**, *22*, 81–84. [[CrossRef](#)]
8. Machado, T.B.; Pinto, A.V.; Pinto, M.C.F.R.; Leal, I.C.R.; Silva, M.G.; Amaral, A.C.F.; Kuster, R.M.; Netto-dos Santos, K.R. In vitro activity of Brazilian medicinal plants, naturally occurring naphthoquinones and their analogues, against methicillin-resistant *Staphylococcus aureus*. *Int. J. Antimicrob. Agents* **2003**, *21*, 279–284. [[CrossRef](#)]
9. Lester, R.L.; White, D.C.; Smith, S.L. The 2-Desmethyl vitamin K₂'s. A new group of naphthoquinones isolated from *Hemophilus parainfluenzae*. *Biochemistry* **1964**, *3*, 949–954. [[CrossRef](#)] [[PubMed](#)]
10. Huang, L.J.; Chang, F.C.; Lee, K.H.; Wang, J.P.; Teng, C.M.; Kuo, S.C. Synthesis and antiplatelet, antiinflammatory, and antiallergic activities of substituted 3-chloro-5,8-dimethoxy-1,4-naphthoquinone and related compounds. *Bioorg. Med. Chem.* **1998**, *6*, 2261–2269. [[CrossRef](#)]
11. Tandon, V.K.; Chhor, R.B.; Singh, R.V.; Rai, S.; Yadav, D.B. Design, synthesis and evaluation of novel 1,4-naphthoquinone derivatives as antifungal and anticancer agents. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1079–1083. [[CrossRef](#)] [[PubMed](#)]
12. Iliina, T.V.; Semenova, E.A.; Pronyaeva, T.R.; Pokrovskii, A.G.; Nechepurenko, I.V.; Shults, E.E.; Andreeva, O.I.; Kochetkov, S.N.; Tolstikov, G.A. Inhibition of HIV-1 reverse transcriptase by aryl-substituted naphtho- and anthraquinones. *Dokl. Biochem. Biophys.* **2002**, *382*, 56–59. [[CrossRef](#)] [[PubMed](#)]
13. Huang, S.T.; Kuo, H.S.; Hsiao, C.L.; Lin, Y.L. Efficient synthesis of 'redox-switched' naphthoquinone thiol-crown ethers and their biological activity evaluation. *Bioorg. Med. Chem.* **2002**, *10*, 1947–1952. [[CrossRef](#)]
14. Lien, J.C.; Huang, L.J.; Wang, J.P.; Teng, C.M.; Lee, K.H.; Kuo, S.C. Synthesis and antiplatelet, antiinflammatory and antiallergic activities of 2,3-disubstituted 1,4-naphthoquinones. *Chem. Pharm. Bull.* **1996**, *44*, 1181–1187. [[CrossRef](#)] [[PubMed](#)]
15. Ting, C.Y.; Hsu, C.T.; Hsu, H.T.; Su, J.S.; Chen, T.Y.; Tarn, W.Y.; Kuo, Y.H.; Whang-Peng, J.; Liu, L.F.; Hwang, J. Isodiospyrin as a novel human DNA topoisomerase I inhibitor. *Biochem. Pharmacol.* **2003**, *66*, 1981–1991. [[CrossRef](#)] [[PubMed](#)]
16. Wurm, G.; Schwandt, S. Methylated 2-aryl-1,4-naphthoquinone derivatives with diminished antioxidative activity. *Pharmazie* **2003**, *58*, 531–538. [[PubMed](#)]
17. Song, G.Y.; Kim, Y.; You, Y.J.; Cho, H.; Kim, S.H.; Sok, D.E.; Ahn, B.Z. Naphthazarin derivatives (VI): Synthesis, inhibitory effect on DNA topoisomerase-I and antiproliferative activity of 2- or 6-(1-oxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones. *Arch. Pharm.* **2000**, *333*, 87–92. [[CrossRef](#)]
18. De Castro, S.L.; Emery, F.S.; da Silva Júnior, E.N. Synthesis of quinoidal molecules: Strategies towards bioactive compounds with an emphasis on lapachones. *Eur. J. Med. Chem.* **2013**, *69*, 678–700. [[CrossRef](#)] [[PubMed](#)]
19. Kovacic, P.; Somanathan, R. Recent developments in the mechanism of anticancer agents based on electron transfer, reactive oxygen species and oxidative stress. *Anticancer Agents Med. Chem.* **2011**, *11*, 658–668. [[CrossRef](#)] [[PubMed](#)]
20. Sunassee, S.N.; Veale, C.G.L.; Shunmoogam-Gounden, N.; Osoniyi, O.; Hendricks, D.T.; Caira, M.R.; la Mare, J.A.; Edkins, A.L.; Pinto, A.V.; da Silva Júnior, E.N.; et al. Cytotoxicity of lapachol, β -lapachone and related synthetic 1,4-naphthoquinones against oesophageal cancer cells. *Eur. J. Med. Chem.* **2013**, *62*, 98–110. [[CrossRef](#)] [[PubMed](#)]
21. Srinivas, P.; Gopinath, G.; Banerji, A.; Dinakar, A.; Srinivas, G. Plumbagin induces reactive oxygen species, which mediate apoptosis in human cervical cancer cells. *Mol. Carcinog.* **2004**, *40*, 201–211. [[CrossRef](#)] [[PubMed](#)]
22. Papageorgiou, V.S.; Assimopoulou, A.N.; Couladouros, E.A.; Hepworth, D.; Nicolau, K.C. The Chemistry and biology of alkannin, shikonin, and related naphthazarin natural products. *Angew. Chem. Int. Ed.* **1999**, *38*, 270–300. [[CrossRef](#)]
23. Li, C.J.; Li, Y.Z.; Pinto, A.V.; Pardee, A.B. Potent inhibition of tumor survival in vivo by β -lapachone plus taxol: Combining drugs imposes different artificial checkpoints. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 13369–13374. [[CrossRef](#)] [[PubMed](#)]
24. Lee, J.I.; Choi, D.Y.; Chung, H.S.; Seo, H.G.; Woo, H.J.; Choi, B.T.; Choi, Y.H. β -lapachone induces growth inhibition and apoptosis in bladder cancer cells by modulation of Bcl-2 family and activation of caspases. *Exp. Oncol.* **2006**, *28*, 30–35. [[PubMed](#)]

25. Li, Y.Z.; Sun, X.G.; Lamont, J.T.; Pardee, A.B.; Li, C.J. Selective killing of cancer cells by β -lapachone: Direct checkpoint activation as a strategy against cancer. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 2674–2678. [[CrossRef](#)] [[PubMed](#)]
26. Cragg, G.M.; Grothaus, P.G.; Newman, D.J. Impact of natural products on developing new anti-cancer agents. *Chem. Rev.* **2009**, *109*, 3012–3043. [[CrossRef](#)] [[PubMed](#)]
27. da Silva Júnior, E.N.; Guimarães, T.T.; Menna-Barreto, R.F.S.; Pinto, M.C.F.R.; de Simone, C.A.; Pessoa, C.; Cavalcanti, B.C.; Sabino, J.R.; Andrade, C.K.Z.; Goulart, M.O.F.; et al. The evaluation of quinonoid compounds against *Trypanosoma cruzi*: Synthesis of imidazolic anthraquinones, nor- β -lapachone derivatives and β -lapachone-based 1,2,3-triazoles. *Bioorg. Med. Chem.* **2010**, *18*, 3224–3230. [[CrossRef](#)] [[PubMed](#)]
28. Sztatowski, T.P.; Nathan, C.F. Production of large amounts of hydrogen peroxide by human tumor cells. *Cancer Res.* **1991**, *51*, 794–798. [[PubMed](#)]
29. Verrax, J.; Beck, R.; Dejeans, N.; Glorieux, C.; Sid, B.; Pedrosa, R.C.; Benites, J.; Vásquez, D.; Valderrama, J.A.; Calderon, P.B. Redox-active quinones and ascorbate: An innovative cancer therapy that exploits the vulnerability of cancer cells to oxidative stress. *Anticancer Agents Med. Chem.* **2011**, *11*, 213–221. [[CrossRef](#)] [[PubMed](#)]
30. Trachootham, D.; Alexandre, J.; Huang, P. Targeting cancer cells by ROS-mediated mechanisms: A radical therapeutic approach? *Nat. Rev. Drug Discov.* **2009**, *8*, 579–591. [[CrossRef](#)] [[PubMed](#)]
31. Jamier, V.; Ba, L.A.; Jacob, C. Selenium- and tellurium-containing multifunctional redox agents as biochemical redox modulators with selective cytotoxicity. *Chem. Eur. J.* **2010**, *16*, 10920–10928. [[CrossRef](#)] [[PubMed](#)]
32. Doering, M.; Ba, L.A.; Lilienthal, N.; Nicco, C.; Scherer, C.; Abbas, M.; Zada, A.A.P.; Coriat, R.; Burkholz, T.; Wessjohann, L.; et al. Synthesis and selective anticancer activity of organochalcogen based redox catalysts. *J. Med. Chem.* **2010**, *53*, 6954–6963. [[CrossRef](#)] [[PubMed](#)]
33. Mecklenburg, S.; Shaaban, S.; Ba, L.A.; Burkholz, T.; Schneider, T.; Diesel, B.; Kiemer, A.K.; Roseler, A.; Becker, K.; Reichrath, J.; et al. Exploring synthetic avenues for the effective synthesis of selenium- and tellurium-containing multifunctional redox agents. *Org. Biomol. Chem.* **2009**, *7*, 4753–4762. [[CrossRef](#)] [[PubMed](#)]
34. Kieliszek, M.; Lipinski, B.; Błażej, S. Application of sodium selenite in prevention and treatment of cancers. *Cells* **2017**, *6*, 39. [[CrossRef](#)] [[PubMed](#)]
35. Kieliszek, M.; Błażej, S. Current knowledge on the importance of selenium in food for living organisms: A review. *Molecules* **2016**, *21*, 609. [[CrossRef](#)] [[PubMed](#)]
36. Kieliszek, M.; Błażej, S. Selenium: Significance, and outlook for supplementation. *Nutrition* **2013**, *29*, 713–718. [[CrossRef](#)] [[PubMed](#)]
37. Vieira, A.A.; Brandão, I.R.; Valença, W.O.; de Simone, C.A.; Cavalcanti, B.C.; Pessoa, C.; Carneiro, T.R.; Braga, A.L.; da Silva Júnior, E.N. Hybrid compounds with two redox centres: Modular synthesis of chalcogen-containing lapachones and studies on their antitumor activity. *Eur. J. Med. Chem.* **2015**, *101*, 254–265. [[CrossRef](#)] [[PubMed](#)]
38. Da Cruz, E.H.G.; Silvers, M.A.; Jardim, G.A.M.; Resende, J.M.; Cavalcanti, B.C.; Bomfim, I.S.; Pessoa, C.; de Simone, C.A.; Botteselle, G.V.; Braga, A.L.; et al. Synthesis and antitumor activity of selenium-containing quinone-based triazoles possessing two redox centres, and their mechanistic insights. *Eur. J. Med. Chem.* **2016**, *122*, 1–16. [[CrossRef](#)] [[PubMed](#)]
39. Roudesly, F.; oble, J.; Poli, G. Metal-catalyzed C-H activation/functionalization: The fundamentals. *J. Mol. Catal. A Chem.* **2017**, *426*, 275–296. [[CrossRef](#)]
40. Gensch, T.; Hopkinson, M.N.; Glorius, F.; Wencel-Delord, J. Mild metal-catalyzed C–H activation: Examples and concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900–2936. [[CrossRef](#)] [[PubMed](#)]
41. Hartwig, J.F. Evolution of C–H bond functionalization from methane to methodology. *J. Am. Chem. Soc.* **2016**, *138*, 2–24. [[CrossRef](#)] [[PubMed](#)]
42. Bahia, S.B.B.B.; Reis, W.J.; Jardim, G.A.M.; Souto, F.T.; De Simone, C.A.; Gatto, C.C.; Menna-Barreto, R.F.S.; De Castro, S.L.; Cavalcanti, B.C.; Pessoa, C.; et al. Molecular hybridization as a powerful tool towards multitarget quinoidal systems: Synthesis, trypanocidal and antitumor activities of naphthoquinone-based 5-iodo-1,4-disubstituted-, 1,4- and 1,5-disubstituted-1,2,3-triazoles. *Med. Chem. Commun.* **2016**, *7*, 1555–1563. [[CrossRef](#)]

43. Jardim, G.A.M.; Calado, H.D.R.; Cury, L.A.; da Silva Júnior, E.N. Synthesis of a phenazine-based 1,2,3-triazole from naturally occurring naphthoquinone designed as a probe for Cd ions. *Eur. J. Org. Chem.* **2015**, *38*, 703–709. [[CrossRef](#)]
44. Jardim, G.A.M.; Reis, W.J.; Ribeiro, M.F.; Ottoni, F.M.; Alves, R.J.; Silva, T.L.; Goulart, M.O.F.; Braga, A.L.; Menna-Barreto, R.F.S.; Salomão, K.; et al. On the investigation of hybrid quinones: Synthesis, electrochemical studies and evaluation of trypanocidal Activity. *RSC Adv.* **2015**, *5*, 78047–78060. [[CrossRef](#)]
45. Cruz, E.H.G.; Carvalho, P.H.P.R.; Correa, J.R.; Silva, D.A.C.; Diogo, E.B.T.; Souza Filho, J.D.; Coelho, B.; Pessoa, C.; Oliveira, H.C.B.; Guido, B.C.; et al. Design, synthesis and application of fluorescent 2,1,3-benzothiadiazole-triazole-linked biologically active lapachone derivatives. *New J. Chem.* **2014**, *38*, 2569–2580. [[CrossRef](#)]
46. Jardim, G.A.M.; da Silva Júnior, E.N.; Bower, J.F. Overcoming naphthoquinone deactivation: Rhodium-catalyzed C-5 selective C–H iodination as a gateway to functionalized derivatives. *Chem. Sci.* **2016**, *7*, 3780–3784. [[CrossRef](#)]
47. Jardim, G.A.M.; Bower, J.F.; da Silva Júnior, E.N. Rh-Catalyzed Reactions of 1,4-Benzoquinones with Electrophiles: C–H Iodination, Bromination, and Phenylselenation. *Org. Lett.* **2016**, *18*, 4454–4457. [[CrossRef](#)] [[PubMed](#)]
48. Jardim, G.A.M.; Silva, T.L.; Goulart, M.O.F.; de Simone, C.A.; Barbosa, J.M.C.; Salomão, K.; de Castro, S.L.; Bower, J.F.; da Silva Júnior, E.N. Rhodium-catalyzed C–H bond activation for the synthesis of quinonoid compounds: Significant Anti-*Trypanosoma cruzi* activities and electrochemical studies of functionalized quinones. *Eur. J. Med. Chem.* **2017**, *136*, 406–419. [[CrossRef](#)] [[PubMed](#)]
49. Kathawate, L.; Gejji, S.P.; Yeole, S.D.; Verma, P.L.; Puranik, V.G.; Salunke-Gawali, S. The first naphthosemiquinone complex of K⁺ with vitamin K3 analog: Experiment and density functional theory. *J. Mol. Struct.* **2015**, *1088*, 56–63. [[CrossRef](#)]
50. Biyogo, A.M.; Khoumeri, O.; Terme, T.; Curti, C.; Vanelle, P. Synthesis of new 2,4-disubstituted 2,3-dihydrobenzo[*g*]indol-5-ones by an SRN1 strategy. *Synthesis* **2015**, *47*, 2647–2653. [[CrossRef](#)]
51. Sharpless, K.B.; Fokin, V.V.; Green, L.G.; Rostovtsev, V.V. A stepwise Huisgen cycloaddition process: Copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.
52. Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. Click chemistry for drug development and diverse chemical-biology applications. *Chem. Rev.* **2013**, *113*, 4905–4979. [[CrossRef](#)] [[PubMed](#)]
53. Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. Alkaloids and isoprenoids modification by copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (Click Chemistry): Toward new functions and molecular architectures. *Chem. Rev.* **2016**, *116*, 5689–5743. [[CrossRef](#)] [[PubMed](#)]
54. Iha, R.K.; Wooley, K.L.; Nystro, A.M.; Burke, D.J.; Kade, M.J.; Hawker, C.J. Applications of orthogonal "click" chemistries in the synthesis of functional soft materials. *Chem. Rev.* **2009**, *109*, 5620–5686. [[CrossRef](#)] [[PubMed](#)]
55. Maarseveen, J.H.; Hiemstra, H.; Bock, V.D. CuI-catalyzed alkyne-azide "click" cycloadditions from a mechanistic and synthetic perspective. *Eur. J. Org. Chem.* **2006**, *1*, 51–68.
56. Pinto, C.N.; Dantas, A.P.; De Moura, K.C.G.; Emery, F.S.; Polequevitch, P.F.; Pinto, M.C.F.R.; De Castro, S.L.; Pinto, A.V. Chemical Reactivity Studies with Naphthoquinones from *Tabebuia* with Anti-trypanosomal Efficacy. *Arzneimittelforschung* **2000**, *50*, 1120–1128. [[CrossRef](#)] [[PubMed](#)]
57. Pinto, A.V.; Pinto, C.N.; Pinto, M.C.; Rita, R.S.; Pezzella, C.A.C.; de Castro, S.L. Trypanocidal activity of synthetic heterocyclic derivatives of active quinones from *Tabebuia* sp. *Arzneimittelforschung* **1997**, *47*, 74–79. [[PubMed](#)]
58. Mosmann, T. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. *J. Immunol. Methods* **1983**, *65*, 55–63. [[CrossRef](#)]

Sample Availability: Samples of all compounds are available from the C. Jacob (c.jacob@mx.uni-saarland.de) and E. N. da Silva Júnior (eufranio@ufmg.br) laboratories.



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