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RESEARCH ARTICLE

Preparation of Dearomatized *p*-Coumaric Acid Derivatives as DNA Damage Response Inhibitors with Potent *In Vitro* Antitumor Effect

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Abstract: Our research group previously identified graviquinone (**1**) as a promising antitumor metabolite that is formed *in situ* when the antioxidant methyl caffeate scavenges free radicals. Furthermore, it exerted a DNA damaging effect on cancer cells and a DNA protective effect on normal keratinocytes. To expand and explore chemical space around qraviquinone, in the current work we synthesized 9 new alkyl-substituted derivatives and tested their *in vitro* antitumor potential. All new compounds bypassed ABCB1-mediated multidrug resistance and showed highly different cell line specificity compared with **1**. All compounds were more potent in MDA-MB-231 than on MCF-7 cells. The *n*-butyl-substituted derivatives **2** and **8** modulated the cell cycle and inhibited the ATR-mediated phosphorylation of

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checkpoint kinase-1 in MCF-7 cells. As a significant expansion of our previous findings, our results highlight the potential antitumor value of alkyl-substituted graviquinone derivatives.

Introduction

Hydroxycinnamic acids are among the most commonly occurring antioxidants in dietary plants, and can be found in many foodstuffs including cereals, vegetables, fruits and nuts. [1] These phenolic compounds have been previously described for their noticeable bioactivities; not only for their antioxidant, [2] but also anti-inflammatory [3], antimicrobial [4], anti-melanogenic [5] and chemo-preventive effects. [6] Lately the potential benefit of hydroxycinnamic acid derivatives on obesity and lipid management was described. [7] Moreover, they are also widely applied for cosmetical purposes, as they are claimed to interact with several biochemical processes in the skin. [8]

Hydroxycinnamic acids and several of their derivatives are also widely known for their anticancer activities. [9] Some oxidized cinnamic acid derivatives are particularly potent in this regard, for example, a dihydrobenzofuran dimer of methyl caffeate that showed strong antimetastatic activity both *in vitro* and *in vivo*, [10] and our group identified it as a metabolite that forms when methyl-*p*-caffeate scavenges peroxyl radicals or peroxynitrite. [11]

Another potent antitumor hydroxycinnamic acid derivative is the natural product graviquinone which was previously isolated from *Gravillea robusta* A. CUNN (Proteaceae). [12] We have previously reported that this oxidized derivative of methyl-p-coumarate induces DNA damage in both sensitive and multidrug-resistant (MDR) non-small cell lung carcinoma cell lines (NCI-H460 and NCI-H460/R, respectively), but has a DNA protective effect on normal human keratinocytes. [13] Graviquinone modulates the response to DNA damage through inhibition of ATR-dependent phosphorylation of Chk1-S345. [13] A similar effect has been previously reported for protoapigenone (PA), a natural oxidized derivative of apigenin, which has a *p*-quinol B-ring moiety, [14] i.e., the same pharmacophore as graviquinone. To assess structure-activity relationships, we have prepared many 1'-O-alkyl substituted protoflavones and found that butyl and propargyl-ether analogs exert selective cytotoxicity against several MDR cancer cell lines. [15]

Inspired by the potent and selective antitumor activity of protoflavones and graviquinone, in this work, we aimed to prepare substituted *O*-alkyl and non-substituted *p*-quinol analogs starting from *p*-coumaric acid esters and to evaluate their in vitro antitumor potential and mechanism of action.

Experimental procedures

General experimental procedures

The starting material *p*-coumaric acid and all reagents were purchased from Sigma-Aldrich (Munich, Germany) and used without further purification. 96% Ethanol was obtained from Molar Chemicals Ltd. The reaction was monitored by normal phase TLC on silica plates (Silica gel 60F254, Merck, Darmstadt, Germany). Purification was carried out by flash chromatography using a Combiflash Rf+ Lumen Instrument (Teledyne Isco, USA) with integrated UV-VIS, PDA, and ELS detection on commercially available prefilled columns (Teledyne Isco, USA) for normal phase separation. The purity of the compounds was checked by analytical high-performance liquid chromatography (HPLC, Jasco Analytical Instruments, Tokyo, Japan) on a Luna C18 (5 µm, 100 Å, 250 x 4.6 mm) column, included a binary pump (LC-20AD) and a diode array detector (SPD-M10A VP, Shimadzu, Kyoto, Japan), and on a Kinetex XB-C18 (5 µm, 100 Å, 250 x 4.6 mm) column on a system of two PU-2080 pumps connected to MD-2010 Plus photodiode array detector (Jasco Analytical Instruments, Tokyo, Japan). For preparative purposes, an Armen Spot Prep II integrated HPLC purification system (Gilson, Middleton, USA) was applied. Structure determination was carried out by nuclear magnetic resonance (NMR) spectroscopy, on a Bruker Avance NEO 500 MHz spectrometer (Bruker Corporation, Billerica, USA) equipped with a Prodigy BBO 5 mm CryoProbe, and on a JEOL JNM ECS 400 SS (400 MHz) spectrometer in methanol-*d*4 and acetone-*d*6. High-resolution mass spectrometry (HRMS) and MS/MS analyses were conducted using a Thermo Velos Pro Orbitrap Elite system (Thermo Fisher Scientific). The ionization method employed was electrospray ionization (ESI) in positive ion mode. Protonated molecular ion peaks were fragmented by collision-induced dissociation (CID) at a normalized collision energy of 35%, with helium serving as the collision gas. The samples were dissolved in methanol. Data acquisition and analysis were performed using Xcalibur software version 2.0 (Thermo Fisher Scientific).

Cytotoxicity studies

MTT assay

The growth inhibitory effects of the compounds were determined by a standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay on mouse lymphoma and human gynecological malignant cell lines. L5178 mouse T-cell lymphoma cells were purchased and an MDR (L5178B1) cell line was produced by transfection with pHa MDR1/A retrovirus [16]. Cells were cultured in McCoy 5A medium supplemented with nystatin, L-glutamine, penicillin, streptomycin, and inactivated horse serum, at 37 °C and 5% CO_2. The L5178B1 cell line was selected by culturing the transfected cells with 60 µg/L of colchicine (Sigma-Aldrich, Munich, Germany). Human gynecological malignant cell lines included HeLa, SiHa (cervical cancers), MDA-MB-231, and MCF-7 (breast cancers). Human cells were kept in minimal essential medium supplemented with 10% fetal bovine serum, 1% non-essential amino acids, and 1% penicillin-streptomycin at 37 °C in a humidified atmosphere containing 5% CO_2. Cell lines were purchased from ECACC (European Collection of Cell Cultures, Salisbury, UK) except for SiHa obtained from ATCC (American Tissue Culture Collection, Manassas, USA). All media and supplements were obtained from Lonza Group Ltd. (Basel, Switzerland). Adherent cell lines were seeded in 96-well plates (5,000 cells/well), after an overnight incubation, the tested compounds were added at 10 µM and 30 µM and incubated for 72 hours. 20 µL MTT solution (5 mg/mL) was added to each sample. Medium were removed after 4 hours of incubation and the precipitated formazan crystals were dissolved in DMSO with 60 minutes of shaking at 37 °C. Finally, the absorbance was measured at 545 nm by a microplate reader

using untreated cells as controls. To determine IC_{50} values, assays were conducted twice, using the most potent compounds in the concentration range of 0.1 - 30 μM. Each experiment was carried out independently with five wells per condition. Cisplatin (Ebewe GmbH, Unterach, Austria) served as the positive control. Statistical analysis was carried out using GraphPad Prism 5.01 software (GraphPad Software Inc., San Diego, USA). [17]

Rhodamine accumulation assay

The function of P-glycoprotein was assessed through the rhodamine accumulation assay. To evaluate the inhibition of efflux function, cells (1206 cells/mL) were treated with different concentrations (2 μM and 20 μM) of the selected compounds. After 10 minutes incubation, rhodamine 123, a fluorescent dye (obtained from Sigma-Aldrich, Munich, Germany) was introduced at a final concentration of 5.2 μM and the samples were incubated at 37 °C in a water bath for 20 minutes. The samples were then centrifuged (Heraeus Labofuge 400, Thermo Fisher Scientific, Waltham, USA) at 2000 rpm for 2 minutes and washed twice with phosphate buffer saline (PBS; Sigma-Aldrich, Munich, Germany). The final samples were resuspended in 0.5 mL PBS, and their fluorescence was measured using a Partec CyFlow flow cytometer (Partec GmBH, Munster, Germany). For comparison, tariquidar, provided by Dr. Milica Pesic from the Institute for Biological Research 'Sinisa Stankovic', Belgrade, Serbia, was used as a positive control at a concentration of 50 nM. [18]

Flow cytometry

The cellular DNA content of the treated cells was determined by flow cytometric analysis. Using DNA-specific dyes for fluorescent staining, changes in the distribution of cells in the different cell-cycle phases (G0/G1, S, and G2/M) including hypodiploid populations (subG1) were detected.
MDA-MB-231 cells were seeded in 6-well plates at density of 300,000-400,000 cells/well. After an overnight incubation, cells were treated with compounds **2** (1 μM and 3 μM) and **8** (3 μM and 5 μM) for 24 h. After incubation, cells were harvested by trypsinization, washed with PBS, and fixed in ice-cold 70% ethanol. The samples were stained with 0.1 mg/mL of PI dye solution containing 0.02 mg/mL RNAse A for 60 min in the dark at room temperature. The samples were analyzed by flow cytometry (Partec CyFlow, Partec, Munster GmBH, Germany) and using ModFit LT 3.3.11 software (Verity Software House, Topsham, USA) for data evaluation. Approximately 20,000 events were recorded in each analysis and three parallel measurements were carried out in each condition. [19]

DNA damage response assay (DDR)

The MCF-7 cells were cultured in 60 mm adherent culture plates, using 700,000 cells per plate, and incubated overnight. Subsequently, they were pretreated with 10 μM of compound **2** and **8** for 30 minutes, while a positive control group was treated with 10 μM of PA. Afterward, cells were exposed to UV irradiation at a dose of 10 J/m^2 for 1 hour or treated with 1 μM of doxorubicin to induce DDR. Protein collection and Western blot assays were conducted following the methodology described in our previous study. [14] Proteins were extracted using lysis buffer containing 1 mM EDTA, 10 mM tris (hydroxymethyl) aminoomethane (pH 7.5), 0.5% NP-40, 10% glycerol, and 420 mM NaCl, supplemented with a cocktail of protease and phosphatase inhibitors (Roche Applied Science) and 1 mM DL-dithiothreitol. After sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the separated proteins in the gel were transferred to nitrocellulose membranes by electrophoretic transfer. The membranes with the transferred proteins were probed with specific primary antibodies, followed by secondary antibodies coupled with horseradish peroxidase (Jackson ImmunoResearch, Baltimore, USA). Proteins were detected using an enhanced chemiluminescence reagent (Millipore, Burlington, USA), and images were captured using a LAS-4000 luminescent image analyzer system (Fujifilm, Tokyo, Japan). Primary antibodies against Chk1-S345 and Chk2-T68 were obtained from Cell Signaling Technology (Danvers, USA), while Chk1, Chk2, and β-actin were purchased from Santa Cruz (Dallas, USA). β-Actin expression served as an internal control. The ratio of Chk1-S345 to Chk1 expression and Chk2-T68 to Chk2 expression was calculated and the means between the groups were compared using one-way ANOVA followed by Dunnett's test. The data presented are the mean ± standard deviation of three independent experiments, with significance levels indicated as *, **, and *** corresponding to $p < 0.05$, 0.01, and 0.001, respectively.

Preparation and structure elucidation of dearomatized *p*-coumarate derivatives

Synthesis of *p*-coumarate esters

Four ester derivatives of *p*-coumaric acid were prepared by Fischer esterification. Briefly, of *p*-coumaric acid (1.66 mmol) was dissolved in the corresponding anhydrous alcohol (R^1-OH: methanol, ethanol, butanol, isopropyl alcohol) previously dried with molecular sieve (0.3 nm, Molar Chemicals, Halásztelek, Hungary). The solution was continuously stirred under reflux, when concentrated H_2SO_4 (2 mL) was added. After the disappearance of the starting material, the reaction was cooled down to room temperature and neutralized (pH = 7) with saturated $NaHCO_3$ solution. The alcohol was removed under vacuum and the remaining aqueous phase was extracted with dichloromethane (5 × 50 mL). The organic phase was combined, dried (anhydrous Na_2SO_4) and concentrated to afford the esters.

Synthesis of *p*-quinols from *p*-coumarate esters

The corresponding *p*-coumaric acid ester was dissolved in a 9:1 mixture of acetonitrile and R^2OH (water, *n*-butanol, or propargyl alcohol) at a concentration of 1 mg/mL. During continuous stirring at room temperature 2 equivalents of hypervalent iodine reagent was added at room temperature [PIDA, (Diacetoxyiodo) benzene,) in the case of *p*-quinols and PIFA [Bis(trifluoroacetoxy)iodo] benzene) in the case of *O*-alkyl ethers]. When the reaction was complete, the reaction mixture was

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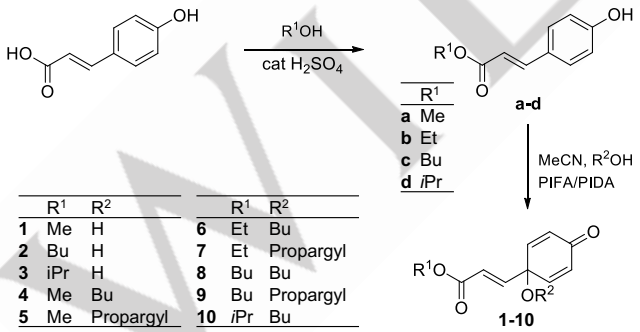
concentrated under vacuo, redissolved in methanol and dry loaded on silica and purified by flash chromatography applying gradient elution of ethyl-acetate from 0-100 % in n-hexane at a flow rate of 30 mL/min. The fractions were combined based on TLC fingerprints.

Compounds **2**, **4**, **6**, **8**, and **10** were isolated in pure form after flash chromatography. Compound **1**, as previously reported, was purified by preparative HPLC, using isocratic elution with 42% aqueous acetonitrile [13]. Compound **3** was obtained by semipreparative HPLC, using Luna C18 (5 µm, 100 Å, 250 × 10 mm) column, with an isocratic elution of 32% aqueous acetonitrile at a flow rate of 2.5 mL/min. Compound **5** was isolated with semipreparative HPLC on a Kinetex XB-C18 (5 µm, 100 Å, AX, 250 × 21.2 mm), with isocratic elution of 50% acetonitrile in water. Compounds **7** and **9** were purified by semipreparative HPLC on a Luna C18 column (5 µm, 100 Å, 250 × 10 mm), with isocratic elution [60% aqueous acetonitrile (**7**), 62% aqueous acetonitrile (**9**), flow rate: 2.5 mL/min].

Results and Discussion

As a first step, the methyl, ethyl, isopropyl, and butyl esters of *p*-coumaric acid (**a**–**d**) were prepared via Fischer esterification. Nonaromatic metabolites were formed by oxidation with hypervalent iodine(III) reagents, PIDA or PIFA. In total, 10 derivatives were synthesized, 3 bearing the non-aromatic *p*-quinol moiety (**1**–**3**), and 7 butyl- or propargyl substituted ether derivatives (**4**–**10**). The reaction steps and the structures of the synthesized compounds are presented in Figure 1. Structure elucidation, ^{1}H and ^{13}C NMR, and HR-MS data of the newly prepared compounds are summarized in the Supporting material, and in Figures S1–S27.



	R^1	R^2
1	Me	H
2	Bu	H
3	iPr	H
4	Me	Bu
5	Me	Propargyl
6	Et	Bu
7	Et	Propargyl
8	Bu	Bu
9	Bu	Propargyl
10	*i*Pr	Bu

Figure 1. Synthesis of *p*-coumaric acid esters (**a**–**d**), dearomatized *p*-quinols (**1**–**3**), and their *O*-alkyl ether derivatives (**4**–**10**).

The antiproliferative activity of hydroxycinnamate esters (**a**–**d**) and their dearomatized derivatives (**1**–**10**) was investigated on a drug-sensitive mouse lymphoma cell line (L5178) and its multidrug-resistant counterpart ($L5178_{B1}$) transfected to overexpress the human ABCB1 transporter (Table 1). The antiproliferative activity of selected compounds was further tested in HeLa, SiHa, MCF-7, and MDA-MB-231 human cancer cell lines; the results are summarized in Table 2.

Although there were some differences in the antiproliferative activities against the drug-sensitive and MDR mouse lymphoma cell line pairs for some compounds, it did not reach a twofold increase in either direction. Similarly, PA did not exert weaker activity on the MDR than on the drug-sensitive cell line, albeit it showed a much stronger potency against both (IC_{50} values of 0.79 µM and 0.76 µM, respectively for MDR and drug-sensitive cells). [20] These data suggest that, unlike doxorubicin (8.6 vs. 0.61, respectively for MDR and drug-sensitive cells), [20] compounds **1**–**10** are not subject to a relevant level of cross-resistance, that is, they can efficiently bypass ABCB1 efflux-mediated MDR. The alkyl-substituted derivatives showed a remarkable change in their cell line specificity compared to that of compound **1**: whenever the *p*-quinol ring was substituted by an alkyl group, antilymphoma activity dramatically decreased while in the efficacy against the adherent cell lines relatively mild changes were observed.

Table 1. Antiproliferative activity of the compounds in a sensitive (L5178) and a multidrug-resistant mouse lymphoma cell line ($L5178_{B1}$), n.d.: not determined; n=3–5.

	IC_{50} [95% CI] (µM)	
	L5178	$L5178_{B1}$
a	n.d.	n.d.
b	58.2 [49.7–68.2]	56.7 [51.1–62.8]
c	71.6 [66.6–77.0]	72.3 [60.6–86.1]
d	44.1 [35.0–59.9]	47.8 [42.7–53.4]
1	0.40 [0.38–0.42]	0.61 [0.57–0.64]
2	21.1 [17.4–25.6]	34.4 [30.7–38.6]
3	0.60 [0.54–0.68]	1.06 [0.96–1.16]
4	57.2 [52.3–62.6]	54.3 [48.4–60.9]
5	35.6 [33.1–38.3]	49.3 [45.4–53.5]
6	57.4 [50.2–65.7]	47.3 [39.7–56.2]
7	44.2 [37.1–52.6]	40.0 [29.8–53.9]
8	64.5 [57.6–72.2]	42.0 [36.9–47.6]
9	60.2 [50.0–72.3]	58.3 [48.4–70.2]
10	63.2 [55.5–72.0]	48.6 [42.5–55.5]

Table 2. Antiproliferative activity of selected compounds in human cancer cell lines (HeLa, SiHa, MCF-7, MDA-MB-231), n=3–5.

	IC_{50} [95% CI] (µM)			
	HeLa	SiHa	MCF-7	MDA-MB-231
a	>100	>100	>100	>100
1	6.04 [5.24–6.96]	5.54 [5.00–6.14]	5.04 [4.58–5.58]	3.25 [2.84–3.73]
2	6.03 [5.18–7.01]	2.10 [1.81–2.44]	3.17 [2.95–3.41]	1.79 [1.62–1.97]
3	12.2 [10.9–13.7]	4.98 [4.46–5.58]	3.60 [3.36–3.86]	2.51 [2.29–2.76]
6	15.3 [14.1–16.5]	10.9 [9.81–12.0]	11.2 [10.0–12.4]	7.19 [5.59–9.25]
8	13.5 [12.3–14.9]	8.20 [0.31–22.0]	11.2 [10.3–12.2]	6.65 [4.30–10.3]
9	8.75 [7.61–10.1]	8.11 [6.89–9.56]	9.41 [8.34–10.6]	4.66 [2.61–8.33]
10	16.9 [14.1–20.3]	8.95 [7.76–10.3]	10.5 [9.61–14.4]	5.46 [3.94–7.57]

A longer alkyl group in the ester moiety also decreased the antiproliferative activity against the lymphoma cell line pair, while it had the potential to improve efficacy against gynecological cell lines. In particular, butyl ester **2** had a stronger activity against

SiHa, MCF-7, and MDA-MB-231 cell lines than the previously reported promising antitumor agent, compound **1**, and it showed comparable activity against MCF-7 and MDA-MB-231 as it was reported for PA (IC_{50} values of 1.70 μM and 1.35 μM, respectively). [21] Furthermore, all compounds showed a mild but significant selectivity towards the aggressive and highly metastatic triple-negative breast cancer cell line (TNBC) MDA-MB-231 as compared to the estrogen and progesterone receptor positive, poorly aggressive, and non-invasive MCF-7 cell line. [22] This is an important finding in view of the many unresolved challenges in TNBC treatment (see Table 2). [23]

The inhibitory potential of the synthesized compounds was also evaluated using a rhodamine accumulation assay on $L5178_{B1}$ mouse T-lymphoma cells transfected to express human P-glycoprotein. Low inhibitory activity was observed in all cases: the percentage of inhibition did not exceed 7%, even at a concentration of 20 μM.

Compounds **2** and **8** were selected for further studies based on their potent antiproliferative activity. The cell cycle phase distribution of the treated cells was determined by flow cytometry with 24 hours of incubation with two different concentrations. Treatment with **2** resulted in a concentration-dependent increase of cell number in the subG1 phase. Incubation with **8** caused a significant increase in cell number in G2/M. Both changes were observed at the expense of the G1 population (Figure 2). The effect of compound **8** on MDA-MB-231 cells is consistent with our previous observations on structurally similar synthetic protoflavone analogs that induced cell cycle disruption and G2/M arrest in various carcinoma cell lines. [24] Similarly to compound **2**, the natural protoflavone, PA was also reported to promote a dose-dependent accumulation of the sub-G1 population in H1299 human lung carcinoma cells. [25]

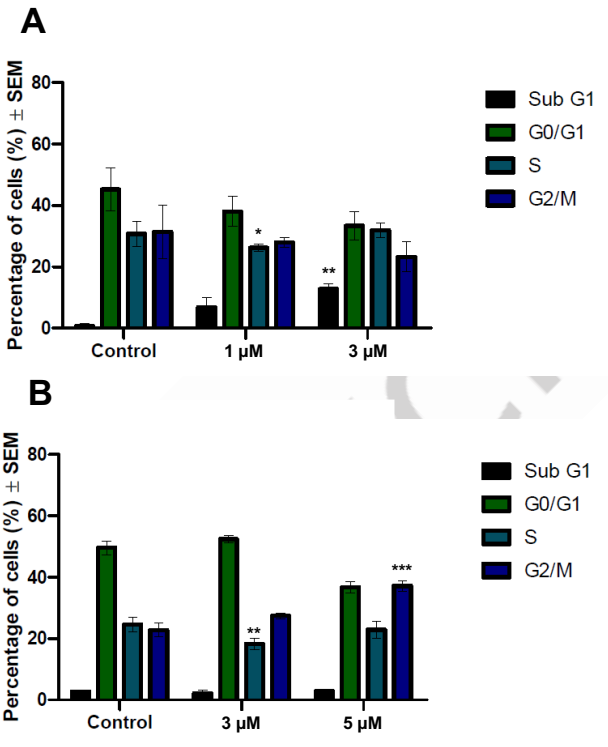


Figure 2. Cell cycle analysis of MDA-MB-231 cells after treatment with compound **2** (**A**) or **8** (**B**) for 24 hours.

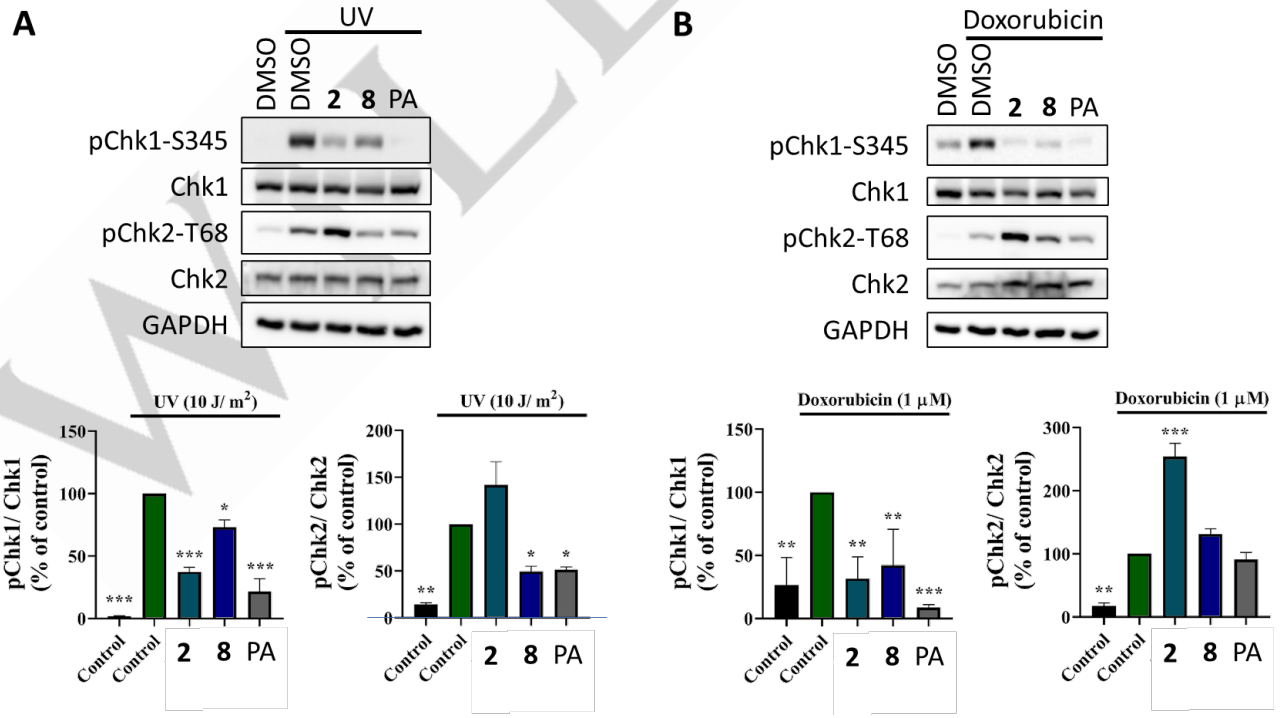


Figure 3. Effects of compounds **2** and **8** on the ATR-mediated phosphorylation of Chk1 and ATM-mediated phosphorylation of Chk2 after induction of DNA damage by UV light (A) or doxorubicin treatment (B) in MCF-7 cells. PA was used as a positive control with a close structural similarity to compounds **2** and **8**; *, ** and ***: $p < 0.05$, 0.01, and 0.001, respectively, by one-way ANOVA followed by Dunnett's multiple comparison test; n=3.

Based on their structural relationship with protoflavonoids that are known to interfere with ATR/ATM-mediated DNA damage response, compounds **2** and **8** were also tested for their ability to influence the activation of serine-threonine checkpoint kinases 1 and 2 (Chk1 and Chk2, respectively) in MCF-7 cells; the results are shown in Figure 3.

It is interesting that compounds **2** and **8** acted as a modulator of DDR induced by UV or doxorubicin through the inhibition of Chk1-S345 phosphorylation, albeit with a decreased potency compared to PA. (Figure 3AB). Chk1 and Chk2 play crucial roles in the DNA damage signaling pathway. When DNA damage occurs, Chk1 becomes active via phosphorylation by ATR, while Chk2's activation is primarily triggered by ataxia telangiectasia mutated kinase (ATM). Chk1 is particularly vital for maintaining the stability of stalled replication forks. In particular, tumor cells with defective DNA repair mechanisms tend to accumulate significant levels of DNA damage. [14] Based on their activity on the ATR-dependent phosphorylation of Chk1, compounds **2** and **8** have a high chance of acting in synergism with DNA-damaging chemotherapeutics, such as cisplatin.

In Figure 3B, our results demonstrate that compound **2** increases Chk2-T68 phosphorylation after the doxorubicin challenge, suggesting that it could induce double-strand DNA breaks and consequentially activate the ATM−Chk2 pathway. This is an interesting difference between compound **2** and the positive control PA, which had no influence on ATM-dependent phosphorylation of Chk2 in this system (Figure 3AB). Compound **2** is therefore similar in this regard to graviquinone (**1**), [13] while compound **8** shares pharmacodynamic similarities with PA, that is, it does not seem to cause double-strand DNA breaks. Compounds capable of interfering with ATR/ATM mediated signaling are of high interest in drug discovery. ATR is considered a 'hot-topic' selective antitumor target and its inhibitors have a good chance to exploit the genomic instability of cancer cells. [26] Currently, several clinical trials (11 running and 23 recruiting patients) are registered at the NIH to evaluate ATR inhibitors alone or in combination with various chemotherapeutics for their antitumor potential.

Conclusion

Herein we report the synthesis of a compound library starting from hydroxycinnamic acid esters. In total, 10 nonsubstituted derivatives of *p*-quinol and substituted *O*-alkyl (**4**–**10**) derivatives were prepared via oxidation with hypervalent iodine reagents. In conclusion, the newly prepared derivatives containing a nonsubstituted *p*-quinol ring (**1**–**3**) demonstrated stronger cytotoxic effect on all cancer cell lines, and compound **2** was the most effective among them. The compounds were able to bypass ABCB1 transporter-mediated multidrug resistance in a mouse lymphoma cell line, suggesting their potential against multi-drug resistant cancers. Among the substituted analogs, butyl ethers (**6**, **8**, **10**) and a propargyl ether (**9**) exerted selective cytotoxicity towards the triple negative MDA-MB-231 cell line as compared with the hormone dependent MCF-7. This suggests our new compounds' potential against gynecological cancers untreatable by estrogen receptor antagonists.

Supporting Information

Supporting information contains the structure elucidation of new compounds, including ^{1}H and ^{13}C NMR, and HR-MS data for compounds **2**–**10**. The authors have cited additional references within the Supporting Information. [13, 27]

Acknowledgements

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Keywords: hydroxycinnamic acid derivative • alkylation • triple-negative breast cancer • multidrug resistance • DNA damage • ATR

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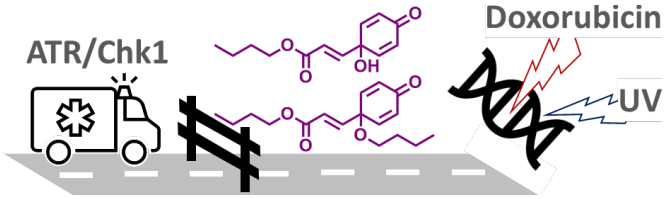

Inspired by an abundant natural antioxidant widely present in cereals, vegetables, fruits, and nuts, we have prepared a set of new antitumor agents interfering with a key mechanism of DNA damage response. This biochemical pathway is an attractive selective antitumor target and the scope of many currently running clinical studies. Two of our compounds show promise for further drug development.