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Synthesis of a Focused Chemical Library Based on Derivatives of Embelin, a Natural Product with Proapoptotic and Anticancer Properties

Guillaume Viault,[a] Danielle Grée,[a] Saibal Das,[b] Jhillu Singh Yadav,[b] and René Grée*[a]

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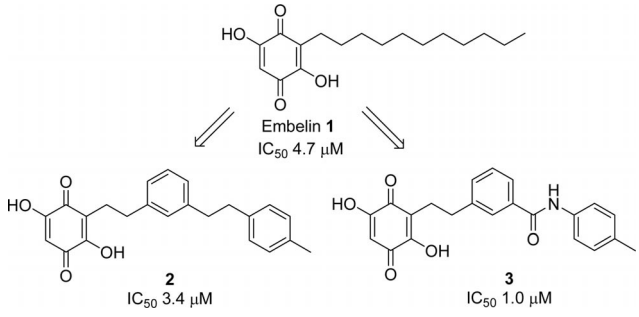
The synthesis of new derivatives of embelin, a natural inhibitor of X-linked inhibitor of apoptosis protein (XIAP) is described. The design of these new molecules involved introduction of aromatic groups directly linked to the benzoquinone core. To allow a large flexibility in the nature and the length of the added chain, the strategy involves first a Suzuki–Miyaura reaction with functionalized aromatics, yielding a first generation of molecules. Then, by appropriate use of the functional groups, a second generation of representative embelin derivatives was prepared.

Introduction

Embelin (**1**) is a natural product known for a very long time in Indian and Chinese pharmacopoeias.[1] It has been extracted from a plant (*Embelia ribes*) used in traditional medicine to treat various diseases and employed as decoction, infusion of roots, aqueous extract, or even directly by application of the seed or dried fruit. Embelin and its derivatives possess analgesic, anti-inflammatory, antioxidant, antitumor and antifertility properties.[2]

It has been demonstrated recently that the inhibitor of apoptosis proteins (IAPs) plays a key role in the regulation of homeostasis in living cells.[3] Furthermore, it is frequently overexpressed in cancer cells, contributing to the gravity of the disease.[4] In this family, X-linked IAP is the most potent inhibitor of apoptosis. Therefore, molecules that can restore apoptosis in cancer cells by inhibition of XIAP would be of much biological interest as well as of therapeutic value.

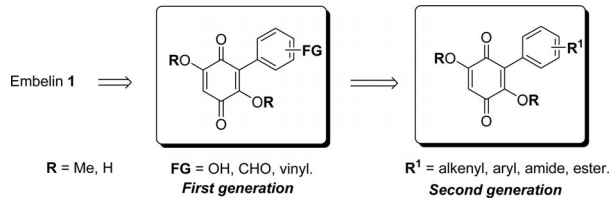
Through *in silico* screening of over 8000 molecules, S. Wang et al. discovered embelin as a potential inhibitor of XIAP protein.[5] They measured an IC_{50} of 4.7 μM for inhibition of XIAP and demonstrated its strong proapoptotic activity on cancer cells. More recently, they prepared a series of new embelin derivatives with aromatic systems incorporated inside the hydrophobic chain. Some of these molecules were even more potent inhibitors of XIAP (up to 1.0 μM) (Scheme 1).[6]



Scheme 1. Embelin and Wang's derivatives.

Several years ago, we started a program for the research of new anticancer compounds through inhibition of anti-apoptotic proteins. We first considered the Bcl-2 family,[7] but more recently, we extended our program to new inhibitors of XIAP, and embelin appeared very attractive as it has a good activity, and, to the best of our knowledge, this natural product is the only non-peptidic inhibitor of XIAP.

As a result, embelin was selected as the starting structure for the development of new derivatives. Our design for new molecules is indicated in Scheme 2. We chose to keep the dihydroxybenzoquinone core and change the nature of the hydrophobic chain by incorporation of aromatic groups in the vicinal position to this core. It has been demonstrated by S. Wang et al. that the length of the hydrophobic chain



Scheme 2. General structures for our designed molecules.

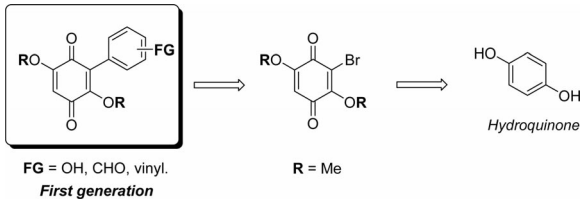
[a] Université de Rennes 1, Laboratoire CPM CNRS UMR 6510 and Laboratoire SCR CNRS UMR 6226,
Avenue du général Leclerc, 35042 Rennes Cedex, France
Fax: +33-2-23236978
E-mail: rene.gree@univ-rennes1.fr
[b] Organic Chemistry Division I, Indian Institute of Chemical Technology, CSIR,
Hyderabad 500607, AP, India

plays an important role in the interaction with XIAP.[6] Therefore, our design involved the preparation of a first generation benzoquinones with functional groups on the new aromatic ring. Further use of these functions should give a good flexibility towards the preparation of a second generation of molecules through variation of the nature and length of the right part (R^1 group).

Finally, our synthetic strategy allowed us to develop automated procedures using a parallel synthesizer towards easy and quick preparation of chemical libraries of designed molecules.

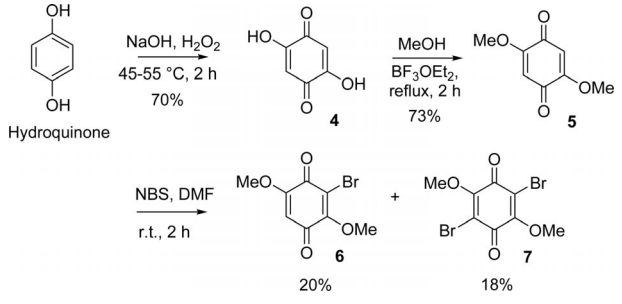
Results and Discussion

Based on a previous design, our synthetic strategy involves Suzuki–Miyaura coupling reactions,[8] as a key step, in order to quickly and efficiently introduce all desired functionalized aromatic substituents in position 3 to afford the first generation analogues (Scheme 3). The first key intermediate is bromodimethoxybenzoquinone derivative **6**, which was envisaged to be obtained from hydroquinone.



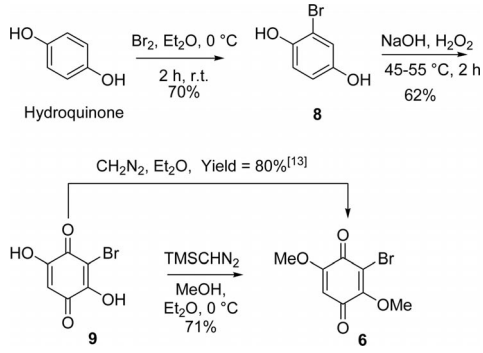
Scheme 3. Retrosynthesis for the preparation of the first generation of embelin derivatives.

The synthesis of bromo compound **6** is described in Scheme 4. Commercial hydroquinone was oxidized with hydrogen peroxide in the presence of a concentrated NaOH solution to give the desired dihydroxybenzoquinone **4** in 70% yield.[9]



Scheme 4. First synthesis of mono- and dibrominated intermediates **6** and **7**.

The two hydroxy groups were then protected by reaction with methanol under acidic conditions to give bis(ether) **5** in 73% yield.[10] Bromination of **5** with *N*-bromosuccinimide (NBS) afforded a mixture of monobrominated and dibrominated intermediates **6** and **7**, respectively, which were easily separated by silica gel column chromatography and isolated in 20% and 18% yields, respectively. Reactions under different conditions (temperature, solvent) or with other brominating agents (Br_2 and HBr) did not improve the selectivity and the yields.[11] Therefore, another synthetic route (Scheme 5) was studied to prepare monobrominated compound **6**. Bromination of hydroquinone in ether afforded bromodiphenol **8** in 70% yield, as described in the literature.[12] The oxidation of **8** with H_2O_2 gave brominated dihydroxybenzoquinone **9** in 62% yield. Bis(ether) **6** can be obtained by reaction of **9** with diazomethane (80% yield) [13] or with trimethylsilyldiazomethane (71% yield).



Scheme 5. Second synthesis of monobrominated intermediates **6** and **9**.

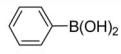
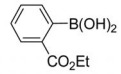
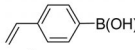
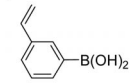
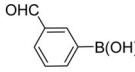
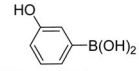
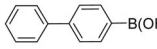
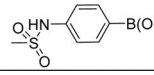
The next step involved Suzuki–Miyaura coupling reactions to introduce the required functionalized aromatic rings linked to the benzoquinone core. It is worth mentioning that we checked various conditions to perform such couplings by starting directly from brominated dihydroxybenzoquinone **9** as such, but all of them failed. Therefore bis(ether) **6** was used as key intermediate for this approach (Scheme 6). Model studies were first performed to optimize the reaction of **6** with phenylboronic acid. Compound **10** was obtained in 60% yield by reaction of **6** with phenylboronic acid, sodium carbonate (2 equiv. each) and palladium dichlorobis(triphenylphosphane) (10 mol-%) in a 4:1 dioxane/water mixture, at 80 °C for 1 h.[14] These conditions were used for a series of representative boronic acids in an automated parallel synthesizer (Chemspeed Accelerator®). They afforded the first generation of our chemical library of embelin analogues in fair to good yields, except for entry 2 (Table 1).

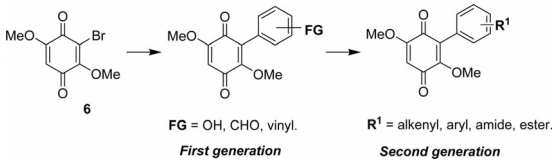
Scheme 6. Synthesis of the first generation of embelin derivatives through Suzuki–Miyaura coupling reactions using automated parallel synthesizer.

To study the structure–activity relationships of the new embelin analogues, it was important also to vary the nature and the length of the side chain. In order to do that, the functions present on the first generation of analogues were used in several ways (Scheme 7).

For instance, in the case of vinylic derivatives, cross-coupling metathesis can be employed.[15] On reaction with ap-

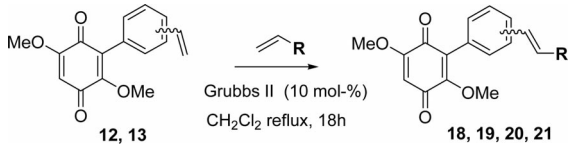
Table 1. Suzuki–Miyaura coupling reactions with **6**.

Entry	Boronic acid	Product	Yield (%)
1		**10**	60
2		**11**	25
3		**12**	53
4		**13**	53
5		**14**	76
6		**15**	69
7		**16**	62
8		**17**	55



Scheme 7. Synthesis of second generation of embelin derivatives.

propriate alkenes and in the presence of a second generation Grubbs catalyst (10 mol-%), compounds **12** and **13** bearing vinyl functions on the aromatic rings afforded the desired products **18** to **21** in 35% to 66% yields (Scheme 8 and Table 2). In all cases, the *E* isomers were obtained exclusively.



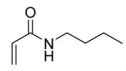
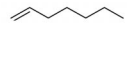
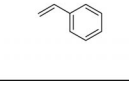
Scheme 8. Cross-coupling metathesis reactions to prepare benzoquinones **18** to **21**.

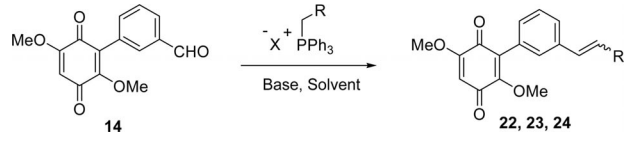
A second alternative to access new analogues was the use of Wittig reactions starting from aldehyde **14** in order to introduce various chains (Scheme 9 and Table 3).

On reaction with the appropriate phosphonium salt in the presence of potassium *tert*-butoxide in THF, aldehyde **14** gave compound **22** in 45% yield. This *Z* alkene is the isomer of product **21** obtained previously. These compounds will allow us to study the effect of the stereochemistry of the double bond on interaction with XIAP protein.

In the same way, by reaction of **14** with the corresponding phosphonium salts and sodium hydride in dichloromethane, the targeted analogues **23** and **24** were obtained in 70% and 53% yields, respectively. Compounds **18** and **23** are regioisomers, and therefore they should allow us to study the effect of the *meta* or *para* position on interaction with the target protein.

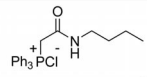
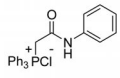
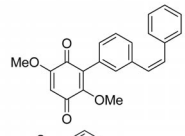
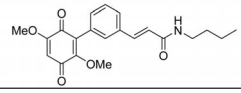
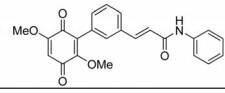
Table 2. Cross-coupling metathesis reactions to prepare benzoquinones **18** to **21**.

Entry	R	Product	Yield (%)
1		**18**	35
2		**19**	66
3		**20**	53
4		**21**	60



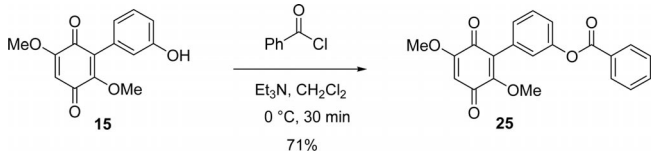
Scheme 9. Wittig reactions to prepare benzoquinones **22** to **24**.

Table 3. Wittig reactions to prepare benzoquinones **22** to **24**.

Entry	Phosphonium salt	Product	Yield (%)
1[a]		 **22**	45
2[b]		 **23**	70
3[b]		 **24**	53

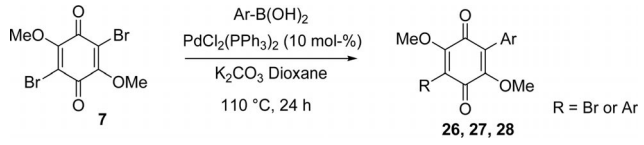
[a] *t*BuOK, THF. [b] NaH, CH_2Cl_2.

Another possibility was to introduce a chain with an ester function in our molecule starting from phenol **15**. Reaction with benzoyl chloride and triethylamine in dichloromethane at 0 °C furnished analogue **25** in 71% yield (Scheme 10).



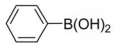
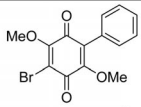
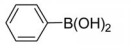
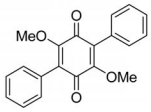
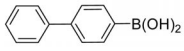
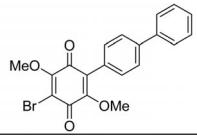
Scheme 10. Esterification reaction to prepare benzoquinone **25**.

These flexible strategies open the route to various types of embelin derivatives. However, in addition to previous studies, it appeared of interest to prepare similar molecules but with bromine in position 6 of the benzoquinone core. Therefore, we also studied the possibility of mono- and dicoupling through Suzuki–Miyaura reactions starting from dibromo intermediate **7** (Scheme 11 and Table 4).



Scheme 11. Mono- and dicoupling by Suzuki–Miyaura reactions on dibromo intermediate **7**.

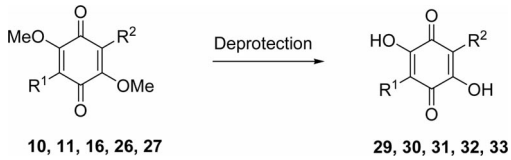
Table 4. Mono- or dicoupling on dibrominated compound **7**.

Entry	Boronic acid	Product		Yield (%)
1[a]			**26**	41
2[b]			**27**	47
3[a]			**28**	62

[a] Boronic acid (1.5 equiv.), K_2CO_3 (2 equiv.). [b] Boronic acid (4 equiv.), K_2CO_3 (5 equiv.).

Dibromo compound **7** was treated with phenylboronic acid (1.5 or 4.0 equiv.), palladium dichlorobis(triphenylphosphane) (10 mol-%), and potassium carbonate (2.0 or 5.0 equiv.) in dioxane at 110 °C for 24 h to give compound **26** and the natural product Betulinan A[16] (**27**) in 41% and 47% yields, respectively. Another molecule, **28**, was synthesized according to the first procedure (entry 3, Table 4) in 62% yield. In agreement with results obtained independently by the group of Hu et al.,[17] it is possible to conduct reactions of mono- or dicoupling by adjusting the number of equivalents of base and boronic acids.

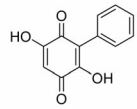
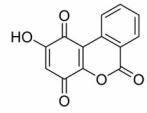
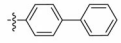
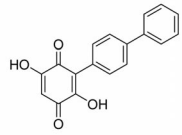
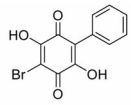
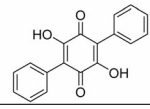
Finally, in order to also obtain molecules closer to embelin, it was necessary to check the possibility for methyl ether deprotection. This was performed on a few selected examples (Scheme 12 and Table 5).



Scheme 12. Model deprotection studies.

The first method involved basic conditions.[18] Compounds **10**, **11**, and **16** reacted with a 1 M potassium hydroxide solution in ethanol at 70 °C for 1 h, and deprotection

Table 5. Model deprotection studies.

Entry	R^1	R^2	Product		Yield (%)
1[a]	H	Ph		**29**	46
2[a]	H			**30**	64
3	H			**31**	28[a] 71[b]
4[b]	Br	Ph		**32**	81
5[b]	Ph	Ph		**33**	72

[a] KOH, EtOH, 70 °C, 1 h. [b] BBr_3, CH_2Cl_2, –78 °C to room temp., 12 h.

products **29**, **30**, and **31** were obtained in 46%, 64%, and 28% yields, respectively. In the case of compound **11**, deprotection followed by intramolecular lactonization afforded **30** under basic conditions. In parallel, a second deprotection method was used in the presence of a Lewis acid.[17] Compounds **26** and **27** were treated with boron tribromide in dichloromethane at –78 °C to afford deprotected products **32** and **33** in 81% and 72% yields, respectively. Starting from bis(ether) **16**, this method afforded dihydroxybenzoquinone derivative **31** in much higher yield (71%) than that under basic conditions (28%).

Conclusions

A flexible strategy has been developed in order to prepare new benzoquinones derived from embelin, a natural product with important proapoptotic and anticancer properties. Our methodology employs bromobenzoquinone **6** as a key intermediate, which is first subjected to Suzuki–Miyaura coupling reactions with various functionalized aromatic boronic acids. This sequence can be easily performed with use of an automated parallel synthesizer (Chemspeed Accelerator®). From the resulting first generation of compounds, new analogues with extended lipophilic chains were obtained by using various types of reaction, such as cross metathesis, Wittig, or esterification reactions. This approach allowed access to a second generation of compounds with a good molecular diversity around the benzoquinone core of embelin. Biological tests are ongoing on these molecules and will be reported in due course.[19] The structure–activity relationships obtained in these studies should help to design more potent analogues of embelin, which in turn should afford a better understanding of bio-

logical mechanisms regulating apoptosis and contribute to the search for new anticancer therapies.

Experimental Section

General: All reagents were obtained commercially and used without further purification. All reactions were carried out under a nitrogen atmosphere and dry conditions. The solvents used were freshly distilled under anhydrous conditions, unless otherwise specified. The reaction mixtures were magnetically stirred with Teflon stirring bars, and the temperatures were measured externally. Reactions that require anhydrous conditions were carried out by using oven-dried (120 °C, 24 h) glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR and ^{13}C NMR) homogeneous materials, and the reactions were monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were pentane (P) and ethyl acetate (EtOAc), with detection by UV light, or a *p*-anisaldehyde staining solution. Acros silica gel (60A, particle size 40–60 μM) was used for column chromatography. NMR spectra were recorded with Bruker Avance 500, 400, and 300 spectrometers. ^{1}H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using [δ (C*H*Cl$_3$) = 7.26 ppm] as internal reference. ^{13}C NMR spectra: δ (C) are given in ppm relative to TMS, using [δ (*C*DCl$_3$) = 77.0 ppm] as internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), or multiplet (m).

Instrumentation: The Suzuki–Miyaura coupling reactions were performed with a Chemspeed Accelerator SLT100 automated synthesizer. The robot was equipped with a four-needle head and an array of 16 parallel 13 mL glass reactors along with a solid dosing unit (SDU) for solid additions. All reactors were connected to a Huber Unistat (heating range: –70 to 300 °C) and were equipped with a cold finger reflux condenser in which the temperature can be fixed from –5 to 40 °C. The inert atmosphere in the glass reactors of Accelerator SLT100 was obtained by flushing with nitrogen for at least 30 min. Before the beginning of the coupling experiments, the reaction vessels were heated to 80 °C, evacuated for 15 min, and then filled with nitrogen. This procedure was repeated twice to perform the reactions under an inert atmosphere with a 1.5 bar flow rate. Different amounts of substrates and reagents were administrated by using the SDU unit, and solvents were transferred from the stock solutions with water and dioxane into the reaction vessels. The reaction mixtures were heated at 80 °C and vortexed at 900 rpm. After 1 h, the reactors were diluted with dichloromethane at 25 °C, and the liquid phase was then filtered through a pad of Celite. After removal of solvents, the compounds were purified by chromatography.

2,5-Dihydroxy-1,4-benzoquinone (4): To an aqueous solution of 50% NaOH (100 g) was added hydroquinone (14 g, 0.13 mol) dropwise at 50 °C. A solution of H_2O_2 (35%, 70 mL) was added slowly for 1.5 h, and the temperature was kept between 45 and 55 °C. The mixture was stirred for 2 h at 45 °C. At 0 °C, a solution of 37% HCl (115 mL) and ice (100 g) were added slowly. At the end of the addition, the solution became yellow and compound **4** precipitated. The solid was filtered and washed with dilute acid solution to give the desired compound as a yellow solid (12 g, 70%). M.p. 210–212 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.11 (s, 2 H, CH), 7.74 (s, 2 H, OH) ppm. IR (neat): $\tilde{\nu}$ = 3297, 3093, 1604 cm^{-1}. HRMS: calcd. for $C_6H_3O_4Na_2$ [M – H + 2Na]$^+$ 184.9827; found 184.9825.

2,5-Dimethoxy-1,4-benzoquinone (5): To a solution of dihydroxybenzoquinone **4** (5.0 g, 36 mmol) in methanol (75 mL) was added BF_3·OEt_2 (12.5 mL). The mixture was stirred at 70 °C for 2 h, and the solid was filtered and washed with cooled methanol to give **5** as a yellow solid (4.25 g, 71%). M.p. 240–242 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.85 (s, 6 H, CH$_3$), 5.87 (s, 2 H, CH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 56.6, 105.5, 159.5, 181.6 ppm.

3-Bromo-2,5-dimethoxy-1,4-benzoquinone (6) and 2,5-Dibromo-3,6-dimethoxy-1,4-benzoquinone (7): To a solution of **5** (1.0 g, 5.95 mmol) in DMF (50 mL) was added a solution of NBS (1.8 g, 20.0 mmol, 1.7 equiv.) in DMF (10 mL). The reaction mixture was stirred at room temperature for 2 h, quenched with water, and extracted with ethyl ether. The organic layers were collected and washed with water then brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. After purification by flash column chromatography on silica gel (pentane/ethyl acetate, 9:1), compound **6** was obtained as an orange solid (310 mg, 20%) and compound **7** was obtained as a red solid (300 mg, 18%). Compound **6**: M.p. 136–138 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.85 (s, 3 H, CH$_3$), 4.26 (s, 3 H, CH$_3$), 5.80 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 56.9, 62.1, 105.3, 114.7, 157.1, 158.6, 175.3, 180.9 ppm. HRMS: calcd. for $C_8H_7O_4{}^{79}BrNa$ [M + Na]$^+$ 268.9425; found 268.9429. Compound **7**: M.p. 168–170 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.24 (s, 6 H, OCH$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 62.3, 114.9, 156.4, 174.7 ppm. HRMS: calcd. for $C_9H_{10}O_5{}^{79}Br_2Na$ [M + Na + CH$_3$OH]$^+$ 378.8792; found 378.8793.

2-Bromobenzene-1,4-diol (8): To a solution of hydroquinone (5.0 g, 45.4 mmol) in ethyl ether (30 mL) was added bromine (2.34 mL, 45.4 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched by using 10% aqueous sodium thiosulfate solution and extracted with ethyl ether. The organic layers were collected and washed with water, then brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. Compound **8** was obtained as a white solid (5.9 g, 70%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 9:1). Compound **8**: M.p. 112 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.40–6.50 (m, 1 H, ArH), 6.60–6.70 (m, 1 H, ArH), 6.75–6.80 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 109.1, 115.1, 116.3, 118.8, 146.2, 150.1 ppm.

3-Bromo-2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (9): To an aqueous solution of NaOH (50%, 12 g) was added compound **8** (1.7 g, 8.9 mmol) dropwise at 50 °C. A solution of H_2O_2 (35%, 12 mL) was added slowly for 1.5 h, and the temperature was kept between 45 and 55 °C. The mixture was then stirred at 45 °C for 2 h. After cooling to 0 °C, a solution of HCl (37%, 15 mL) and ice (10 g) was added slowly. At the end of the addition, the solution turned red, and the product was extracted with ethyl acetate. The organic layers were collected and washed with brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum to furnish compound **9** as a red solid (1.2 g, 62%) Compound **9**: M.p. 100 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 5.98 (s, 1 H), 10.20 (br. s, 2 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 103.2, 105.5, 161.0, 169.4 ppm.

3-Bromo-2,5-dimethoxy-1,4-benzoquinone (6): To a solution of compound **9** (50 mg, 0.23 mmol) in ethyl ether (5 mL) and methanol (1 mL) was added slowly TMSCHN$_2$ (2.0 M in Et$_2$O, 0.75 mL, 1.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and concentrated under vacuum. Compound **6** was obtained (40 mg, 71%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2).

Procedure A. Suzuki Coupling: A mixture of compound **6** (1.0 equiv.), dichlorobis(triphenylphosphane)palladium(II) (0.1 equiv.), sodium carbonate (2.0 equiv.), and boronic acid (2.0 equiv.) in 4:1

dioxane/water mixture was stirred at 80 °C for 1 h. After being cooled down to room temperature, the solution was diluted with CH_2Cl_2 and dried with anhydrous $MgSO_4$. The reaction mixture was filtered through a pad of Celite and concentrated under vacuum.

2,5-Dimethoxy-3-phenyl-1,4-benzoquinone (10): Compound **10** was obtained as an orange solid (150 mg, 60%) by using Procedure A, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 9:1). M.p. 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3), 5.91 (s, 1 H), 7.20–7.40 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 61.6, 105.6, 126.2, 127.9, 128.6, 130.1, 130.6, 155.3, 158.8, 181.6, 183.4 ppm. HRMS: calcd. for $C_{14}H_{12}O_4Na$ [M + Na]$^+$ 267.0633; found 267.0634.

Ethyl 2-(2,5-Dimethoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)benzoate (11): Compound **11** was obtained as an orange oil (105 mg, 25%) by using Procedure A, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3 H), 3.67 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.20 (q, J = 7.0 Hz, 2 H), 5.88 (s, 1 H), 7.15–7.25 (m, 1 H, ArH), 7.40–7.60 (m, 2 H, ArH). 8.00–8.10 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 56.5, 61.0, 61.1, 105.7, 127.8, 128.8, 130.5, 130.6, 131.5, 131.9, 132.0, 153.6, 159.0, 166.3, 181.4, 183.3 ppm. HRMS: calcd. for $C_{17}H_{16}O_6Na$ [M + Na]$^+$ 339.0844; found 339.0844.

2,5-Dimethoxy-3-(4-vinylphenyl)-1,4-benzoquinone (12): Compound **12** was obtained as an orange solid (115 mg, 53%) by using Procedure A, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2). M.p. 120–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 5.30 (dd, J = 0.7, J = 10.9 Hz, 1 H), 5.80 (dd, J = 0.7, J = 17.6 Hz, 1 H), 5.90 (s, 1 H), 6.74 (dd, J = 10.9, J = 17.6 Hz, 1 H), 7.25–7.27 (m, 2 H, ArH), 7.44–7.47 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.5, 61.6, 105.6, 114.7, 125.7, 126.0, 129.4, 130.8, 136.3, 137.8, 155.2, 158.7, 181.6, 183.3 ppm. HRMS: calcd. for $C_{16}H_{14}O_4Na$ [M + Na]$^+$ 293.0789; found 293.0787.

2,5-Dimethoxy-3-(3-vinylphenyl)-1,4-benzoquinone (13): Compound **13** was obtained as an orange solid (230 mg, 53%) by using Procedure A, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2). M.p. 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 5.28 (d, J = 10.9 Hz, 1 H), 5.76 (d, J = 17.6 Hz, 1 H), 5.91 (s, 1 H), 6.72 (dd, J = 10.9, J = 17.6 Hz, 1 H), 7.15–7.20 (m, 1 H, ArH), 7.30–7.47 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 61.6, 105.5, 114.4, 126.0, 126.4, 128.1, 128.4, 129.9, 130.3, 136.4, 137.2, 155.3, 158.7, 181.6, 183.3. HRMS: calcd. for $C_{16}H_{14}O_4Na$ [M + Na]$^+$ 293.07898; found 293.0785.

3-(2,5-Dimethoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)benzaldehyde (14): Compound **14** was obtained as an orange solid (335 mg, 76%) by using Procedure A, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2). M.p. 166–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 5.92 (s, 1 H), 7.53–7.62 (m, 2 H, ArH), 7.80–7.81 (m, 1 H, ArH), 7.89–7.82 (m, 1 H, ArH), 10.03 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 61.8, 105.7, 125.1, 128.6, 129.4, 131.1, 132.1, 136.0, 136.5, 155.5, 158.6, 181.1, 183.0, 191.9 ppm. HRMS: calcd. for $C_{15}H_{12}O_5Na$ [M + Na]$^+$ 295.0582; found 295.0581.

3-(3-Hydroxyphenyl)-2,5-dimethoxy-1,4-benzoquinone (15): Compound **15** was obtained as an orange solid (130 mg, 69%) by using Procedure A, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2). M.p. 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 5.91 (s, 1 H), 6.05 (br. s, 1 H, OH), 6.74–6.88 (m, 3 H, ArH), 7.23–7.29 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 61.5, 105.4, 115.9, 117.6, 122.8, 125.4, 129.2, 131.3, 155.3, 155.5, 158.8, 181.8, 183.3 ppm. HRMS: calcd. for $C_{14}H_{12}O_5Na$ [M + Na]$^+$ 283.0582; found 283.0582.

3-Biphenyl-4-yl-2,5-dimethoxy-1,4-benzoquinone (16): Compound **16** was obtained as an orange solid (80 mg, 62%) by using Procedure A, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2). M.p. 182–184 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 5.92 (s, 1 H, CH), 7.36–7.39 (m, 3 H, ArH), 7.44–7.49 (m, 2 H, ArH), 7.63–7.67 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 61.7, 105.6, 126.1, 126.6, 127.1, 127.5, 128.8, 128.9, 131.0, 140.4, 141.3, 155.3, 158.7, 181.6, 183.3 ppm. HRMS: calcd. for $C_{20}H_{16}O_4Na$ [M + Na]$^+$ 343.0946; found 343.0947.

***N*-[4-(2,5-Dimethoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)phenyl] Methanesulfonamide (17):** Compound **17** was obtained as an orange solid (300 mg, 55%) by using Procedure A, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 2:8). M.p. 204–206 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.10 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3) 5.92 (s, 1 H), 6.80 (br. s, 1 H, NH), 7.25–7.35 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.8, 56.7, 61.7, 105.7, 119.2, 126.2, 126.7, 132.1, 137.0, 155.4, 158.7, 181.6, 183.2 ppm. HRMS: calcd. for $C_{15}H_{15}NO_6SNa$ [M + Na]$^+$ 360.0518; found 360.0518.

Procedure B. Cross Coupling Metathesis: A mixture of compound **12** or **13** (1.0 equiv.), alkene (10.0 equiv.), and Grubbs II catalyst (0.1 equiv.) in CH_2Cl_2 was stirred for 18 h at reflux. The reaction mixture was concentrated under vacuum.

(2*E*)-*N*-Butyl-3-[4-(2,5-dimethoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)phenyl]acrylamide (18): Compound **18** was obtained as a red solid (20 mg, 35%) by using Procedure B, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 7:3). M.p. 188–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.2 Hz, 3 H, CH_3), 1.38 (m, 2 H, CH_2), 1.56 (m, 2 H, CH_2), 3.39 (m, 2 H, CH_2), 3.85 (s, 6 H, OCH_3), 5.84 (br. s, 1 H, NH), 5.90 (s, 1 H), 6.43 (d, J = 15.6 Hz, 1 H, CH), 7.26–7.29 (m, 2 H, ArH), 7.49–7.54 (m, 2 H, ArH), 7.63 (d, J = 15.6 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 20.1, 31.7, 39.5, 56.6, 61.7, 105.6, 121.6, 125.7, 126.0, 127.2, 131.0, 135.1, 140.0, 155.3, 158.7, 165.6, 181.4, 183.1 ppm. HRMS: calcd. for $C_{21}H_{23}NO_5Na$ [M + Na]$^+$ 392.1473; found 392.1476.

3-{3-[(1*E*)-Hept-1-en-1-yl]phenyl}-2,5-dimethoxy-1,4-benzoquinone (19): Compound **19** was obtained (50 mg, 66%) as an oil by using Procedure B, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–0.95 (m, 3 H, CH_3), 1.20–150 (m, 6 H, CH_2), 2.18–2.22 (m, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.91 (s, 1 H), 6.23 (dt, J = 15.8, J = 6.7 Hz, 1 H, CH), 6.38 (d, J = 15.8, 1 H, CH), 7.05–7.35 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.5, 30.0, 31.4, 33.0, 56.6, 61.6, 105.5, 126.1, 126.2, 128.0, 128.1, 128.9, 129.2, 130.2, 132.0, 137.7, 155.3, 158.8, 181.7, 183.3 ppm. HRMS: calcd. for $C_{21}H_{24}O_4Na$ [M + Na]$^+$ 363.1566; found 363.1567.

3-{3-[(1*E*)-Oct-1-en-1-yl]phenyl}-2,5-dimethoxy-1,4-benzoquinone (20): Compound **20** was obtained as an oil (120 mg, 53%) by using Procedure B, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–0.85 (m, 3 H, CH_3), 1.20–1.30 (m, 6 H, CH_2),

1.35–1.45 (m, 2 H, CH_2), 2.11–2.15 (m, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 5.82 (s, 1 H), 6.17 (dt, J = 6.8, J = 15.8 Hz, 1 H, CH), 6.30 (d, J = 15.8, 1 H, CH), 7.01–7.03 (m, 1 H, ArH), 7.16–7.20 (m, 1 H, ArH), 7.25–7.30 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.9, 29.3, 31.8, 33.1, 56.6, 61.6, 105.6, 126.2, 126.3, 128.1, 128.1, 128.9, 129.3, 130.3, 132.0, 137.7, 155.3, 158.8, 181.7, 183.3 ppm. HRMS: calcd. for $C_{22}H_{26}O_4Na$ $[M + Na]^+$ 377.1723; found 377.1726.

2,5-Dimethoxy-3-{3-[(*E*)-2-phenylvinyl]phenyl}-1,4-benzoquinone (21): Compound **21** was obtained as an orange solid (120 mg, 60%) by using Procedure B, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2). M.p. 164–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 5.93 (s, 1 H), 7.12 (s, 2 H), 7.15–7.60 (m, 9 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 61.7, 105.6, 125.9, 126.6, 126.7, 127.7, 128.1, 128.3, 128.7, 128.7, 129.2, 129.7, 130.5, 137.0, 137.1, 155.3, 158.8, 181.6, 183.3 ppm. $C_{22}H_{18}O_4$ (346.38): calcd. C 76.29, H 5.24; found C 75.97, H 5.27.

2,5-Dimethoxy-3-{3-[(*Z*)-2-phenylvinyl]phenyl}-1,4-benzoquinone (22): To a solution of benzyltriphenylphosphonium iodide (560 mg, 1.17 mmol, 2.7 equiv.) in anhydrous THF (6 mL) was added slowly at 0 °C potassium *tert*-butoxide (132 mg, 1.17 mmol, 2.7 equiv.). The mixture was stirred at 0 °C for 30 min. Then, a solution of aldehyde **14** (115 mg, 0.42 mmol, 1.0 equiv.) in THF (3 mL) was added at –78 °C. The reaction mixture was stirred for 1 h until room temperature was attained and then quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The collected organic layers were washed with water, then brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. Compound **22** was obtained as a red solid (90 mg, 45%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 7:3). M.p. 132–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 5.88 (s, 1 H, CH), 6.62 (s, 2 H), 7.15–7.30 (m, 9 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.5, 61.6, 105.5, 125.9, 127.2, 127.9, 128.2, 128.9, 129.0, 129.2, 129.7, 130.2, 130.7, 130.9, 136.9, 137.1, 155.2, 158.7, 181.7, 183.3 ppm. HRMS: calcd. for $C_{22}H_{18}O_4Na$ $[M + Na]^+$ 369.1103; found 369.1099.

Procedure C. Wittig Reaction: To a suspension of sodium hydride (7.0 equiv.) in anhydrous CH_2Cl_2 was added slowly a solution of phosphonium salt (3.0 equiv.) in anhydrous CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then, a solution of compound **14** (1.0 equiv.) in anhydrous CH_2Cl_2 was added at –78 °C. The reaction mixture was stirred 1 h to reach room temperature and then quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were washed with water, then brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum.

(2*E*)-*N*-Butyl-3-[3-(2,5-dimethoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)phenyl]acrylamide (23): Compound **23** was obtained as a red solid (150 mg, 70%) by using Procedure C, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 5:5). M.p. 150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.2 Hz, 3 H, CH_3), 1.30–1.40 (m, 2 H, CH_2), 1.50–1.60 (m, 2 H, CH_2), 3.35–3.45 (m, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.71 (br. s, 1 H, NH), 5.91 (s, 1 H), 6.38 (d, J = 15.5 Hz, 1 H, CH), 7.20–7.52 (m, 4 H, ArH), 7.63 (d, J = 15.5 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 20.1, 31.7, 39.5, 56.6, 61.7, 105.6, 121.4, 125.7, 127.9, 128.4, 129.8, 130.1, 131.6, 134.7, 140.3, 155.4, 158.7, 165.6, 181.4, 183.2 ppm. HRMS: calcd. for $C_{21}H_{23}NO_5Na$ $[M + Na]^+$ 392.1474; found 392.1475.

(2*E*)-3-[3-(2,5-Dimethoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)phenyl]-*N*-phenylacrylamide (24): Compound **24** was obtained as a red solid (120 mg, 53%) by using Procedure C, after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 5:5). M.p. 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.92 (s, 1 H), 6.56 (d, J = 15.5 Hz, 1 H, CH), 7.10–7.62 (m, 9 H, ArH), 7.74 (d, J = 15.5 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 56.7, 61.7, 61.8, 105.6, 105.7, 119.8, 121.5, 124.4, 125.5, 128.1, 128.5, 129.0, 130.0, 130.7, 132.0, 134.4, 138.0, 141.6, 141.7, 155.4, 158.7, 163.8, 181.5, 183.2 ppm. HRMS: calcd. for $C_{23}H_{19}NO_5Na$ $[M + Na]^+$ 412.1161; found 412.1160.

3-(2,5-Dimethoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)phenyl Benzoate (25): To a solution of phenol **15** (130 mg, 0.5 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) were added slowly triethylamine (0.35 mL, 2.5 mmol, 5.0 equiv.) and benzoyl chloride (0.29 mL, 2.5 mmol, 5.0 equiv.) at 0 °C. The mixture was stirred at 0 °C for 30 min. It was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The collected organic layers were washed with water, then brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. Compound **25** was obtained as a red solid (120 mg, 71%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 8:2). M.p. 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 5.91 (s, 1 H), 7.10–7.30 (m, 3 H, ArH), 7.40–7.55 (m, 3 H, ArH), 7.60–7.70 (m, 1 H, ArH), 8.15–8.25 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 61.8, 105.6, 121.9, 124.1, 124.8, 128.2, 128.6, 128.9, 129.4, 130.1, 131.5, 133.6, 150.4, 155.4, 158.7, 165.0, 181.3, 183.1 ppm. $C_{21}H_{16}O_6$ (364.35): calcd. C 69.23, H 4.43; found C 69.05, H 4.51.

2-Bromo-3,6-dimethoxy-5-phenyl-1,4-benzoquinone (26): A mixture of compound **7** (326 mg, 1.0 mmol, 1.0 equiv.), dichlorobis(triphenylphosphane)palladium(II) (70 mg, 0.1 mmol, 0.1 equiv.), potassium carbonate (276 mg, 2.0 mmol, 2.0 equiv.), and phenylboronic acid (200 mg, 1.5 mmol, 1.5 equiv.) in dioxane (10 mL) was stirred at 110 °C for 24 h. The dark solution obtained was diluted with CH_2Cl_2 and dried with anhydrous $MgSO_4$. The mixture was filtered through a pad of Celite and concentrated under vacuum. Compound **26** was obtained as an orange solid (132 mg, 41%) after purification by flash column chromatography on silica gel (pentane/dichloromethane, 4:6). M.p. 210–212 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, CH_3), 4.24 (s, 3 H, CH_3), 7.25–7.45 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.8, 62.0, 114.9, 126.3, 128.0, 128.8, 129.6, 130.4, 154.7, 156.6, 177.0, 181.2 ppm. $C_{14}H_{11}BrO_4$ (323.14): calcd. C 52.04, H 3.43; found C 51.78, H 3.39.

2,5-Dimethoxy-3,6-diphenyl-1,4-benzoquinone (27): A mixture of compound **7** (326 mg, 1.0 mmol, 1.0 equiv.), dichlorobis(triphenylphosphane)palladium(II) (70 mg, 0.1 mmol, 0.1 equiv.), potassium carbonate (690 mg, 5.0 mmol, 5.0 equiv.), and phenylboronic acid (533 mg, 4.0 mmol, 4.0 equiv.) in dioxane (10 mL) was stirred at 110 °C for 24 h. The resulting dark solution was diluted with CH_2Cl_2 and dried with anhydrous $MgSO_4$. The mixture was filtered through a pad of Celite and concentrated under vacuum. Compound **27** was obtained as an orange solid (150 mg, 47%) after purification by flash column chromatography on silica gel (pentane/dichloromethane, 4:6). M.p. 148–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 6 H, CH_3), 7.30–7.50 (m, 10 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.5, 126.6, 127.9, 128.6, 130.1, 130.5, 154.6, 183.4 ppm. HRMS: calcd. for $C_{20}H_{16}O_4Na$ $[M + Na]^+$ 343.0943; found 343.0944.

2-Biphenyl-4-yl-5-bromo-3,6-dimethoxy-1,4-benzoquinone (28): A mixture of compound **7** (260 mg, 0.8 mmol, 1.0 equiv.), dichloro-

bis(triphenylphosphane)palladium(II) (60 mg, 0.08 mmol, 0.1 equiv.), potassium carbonate (220 mg, 1.6 mmol, 2.0 equiv.), and 4–diphenylboronic acid (240 mg, 1.2 mmol, 1.5 equiv.) in dioxane (10 mL) was stirred at 110 °C for 24 h. The resulting dark solution was diluted with CH_2Cl_2 and dried with anhydrous $MgSO_4$. The mixture was filtered through a pad of Celite and concentrated under vacuum. Compound **28** was obtained as an orange solid (200 mg, 62%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate, 9:1). M.p. 170–172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3), 5.91 (s, 1 H), 7.20–7.40 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 61.6, 105.6, 126.2, 127.9, 128.6, 130.1, 130.6, 155.3, 158.8, 181.6, 183.4 ppm. HRMS: calcd. for $C_{20}H_{15}O_4{}^{79}BrNa$ [M + Na]$^+$ 421.0051; found 421.0052.

Procedure D. KOH Deprotection: To a solution of bis(ether) (0.53 mmol) in ethanol (10 mL) was added a KOH solution (1 M, 5 mL) at room temperature. The resulting dark red mixture was then heated whilst stirring at 70 °C for 1 h. The reaction mixture was quenched with HCl solution (1 M) and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum.

2,5-Dihydroxy-3-phenyl-1,4-benzoquinone (29): Compound **29** was obtained as a dark red solid (53 mg, 46%) by using Procedure D, after purification by recrystallization in ethyl acetate. M.p. 218–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.17 (s, 1 H), 7.40–7.50 (m, 5 H, ArH), 7.95 (br. s, 2 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 102.6, 128.2, 128.6, 128.7, 130.1 ppm. HRMS: calcd. for $C_{12}H_8O_4Na$ [M + Na]$^+$ 239.0320; found 239.0324.

2-Hydroxy-1*H*-benzo[*c*]chromene-1,4,6-trione (30): Compound **30** was obtained as a dark red solid (53 mg, 64%) by using Procedure D, after purification by recrystallization in ethyl acetate. M.p.180–182 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 6.03 (s, 1 H), 7.40–7.55 (m, 3 H, ArH), 8.00–8.20 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 103.4, 118.9, 129.1, 131.2, 131.8, 132.7, 132.8, 132.9, 167.8 ppm. HRMS: calcd. for $C_{13}H_6O_5Na$ [M + Na]$^+$ 265.0113; found 265.0116.

3-Biphenyl-4-yl-2,5-dihydroxy-1,4-benzoquinone (31): To a solution of compound **16** (45 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (4.0 mL) was added slowly a solution of BBr_3 in CH_2Cl_2 (1.0 M, 0.50 mL) at –78 °C. The reaction mixture was stirred under argon for 12 h until room temperature was attained. The reaction was quenched with methanol, and the resulting solution was concentrated under vacuum. Compound **31** was obtained as a black solid (29 mg, 71% yield) after recrystallization from dioxane. M.p. 248–250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.20 (s, 1 H), 7.38–7.67 (m, 9 H, ArH), 8.00 (br. s, 2 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 104.0, 125.7, 126.6, 127.4, 128.9, 131.0, 139.9 ppm. HRMS: calcd. for $C_{18}H_{11}O_4Na_2$ [M – H + 2Na]$^+$ 337.0453; found 337.0454.

Compounds **32** and **33** were synthesized by following the same procedure.

2-Bromo-3,6-dihydroxy-5-phenyl-1,4-benzoquinone (32): Compound **32** was obtained as a black solid (43 mg, 81%) after recrystallization from dioxane. M.p. 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.50 (m, 5 H, ArH), 8.13 (br. s, 2 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.2, 129.0, 130.1 ppm. HRMS: calcd. for $C_{12}H_6O_4{}^{79}BrNa_2$ [M – H + 2Na]$^+$ 338.9245; found 338.9247.

2,5-Dihydroxy-3,6-diphenyl-1,4-benzoquinone (33): Compound **33** was obtained as a black solid (53 mg, 72%) after recrystallization from dioxane. M.p. 258–260 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.30–7.60 (m, 10 H, ArH), 10.30 (br. s, 2 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 127.6, 127.8, 130.5, 130.8, 132.5 ppm. HRMS: calcd. for $C_{18}H_{11}O_4Na_2$ [M – H + 2Na]$^+$ 337.0453; found 337.0451.

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[19] Preliminary (unpublished)biological data indicated that molecules with an aromatic group at position 3, such as **10**, had a significant proapoptotic affect against Cal51 cell lines and also a strong synergistic proapoptotic effect in combination with other reagents such as TRAIL or ABT 737.

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