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PII: S0223-5234(18)30322-2

DOI: 10.1016/j.ejmech.2018.03.079

Reference: EJMECH 10344

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 9 January 2018

Revised Date: 27 March 2018

Accepted Date: 29 March 2018

Please cite this article as: T.V. Baiju, R.G. Almeida, S.T. Sivanandan, C.A. de Simone, L.M. Brito, B.C. Cavalcanti, C. Pessoa, I.N.N. Namboothiri, Eufrâ.N. da Silva Júnior, Quinonoid compounds *via* reactions of lawsone and 2-aminonaphthoquinone with α-bromonitroalkenes and nitroallylic acetates: Structural diversity by C-ring modification and cytotoxic evaluation against cancer cells, *European Journal of Medicinal Chemistry* (2018), doi: 10.1016/j.ejmech.2018.03.079.

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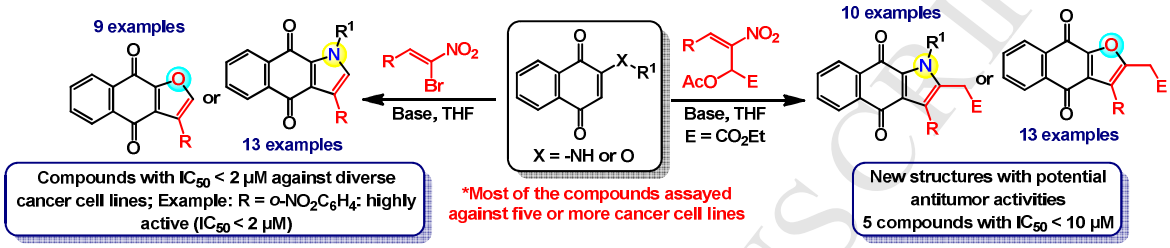
Graphical abstract

Pyrrole and furan fused naphthoquinones were designed and synthesized from corresponding 2-aminonaphthoquinones and 2-hydroxynaphthoquinone on reaction with conjugated nitroalkenes and evaluated against several cancer cell lines showing, in some cases, IC_{50} values below 1.5 µM.



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Quinonoid Compounds *via* Reactions of Lawsone and 2-Aminonaphthoquinone with α-Bromonitroalkenes and Nitroallylic Acetates: Structural Diversity by C-ring Modification and Cytotoxic Evaluation against Cancer Cells

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Abstract. Morita-Baylis-Hillman acetates and α-bromonitroalkenes have been employed in cascade reactions with lawsone and 2-aminonaphthoquinone for the one-pot synthesis of heterocycle fused quinonoid compounds. The reactions reported here utilized the 1,3-binucleophilic potential of hydroxy- and aminonaphthoquinones and the 1,2/1,3-bielectrophilic potential of bromonitroalkenes and Morita-Baylis-Hillman acetates for the synthesis of pyrrole and furan fused naphthoquinones. The synthesized compounds were evaluated against HCT-116 (human colon carcinoma cells), PC3 (human prostate cancer cells), HL-60 (human promyelocytic leukemia cells), SF295 (human glioblastoma cells) and NCI-H460 (human lung cancer cells) and exhibited antitumor activity with IC_{50} values as low as < 2 μM. Selected compounds were also evaluated against OVCAR-8 (ovary), MX-1 (breast) and JURKAT (leukemia) cell lines. The cytotoxic potential of the quinones evaluated was also assayed using non-tumor cells, exemplified by peripheral blood mononuclear (PBMC) and L929 cells.

Introduction

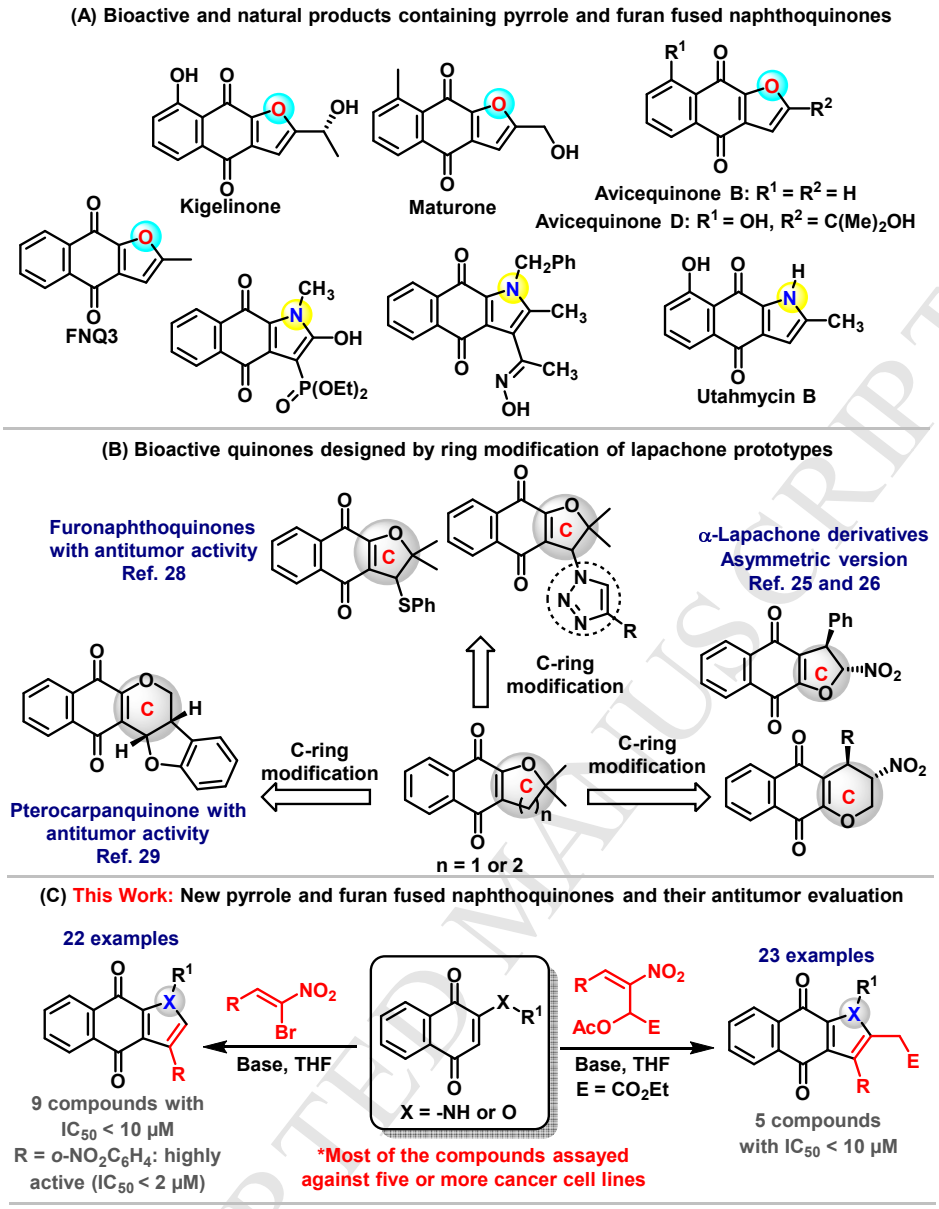
Quinonoids are potent bioactive compounds that are well-known for their medicinal value, particularly, for their excellent cancer chemotherapeutic efficiency. Naphthoquinones are important quinonoid compounds that are abundant in nature and exhibit broad spectrum of biological activities such as anticancer [1], antifungal [2], antibacterial [3], antiviral [4], anti-inflammatory [5], antimalarial [6], antiplatelet [7], antithrombotic and antiallergic activities [7]. Because of these unique biological activities and wide spread applications in pharmaceutical field, the design, synthesis and biological screening of novel naphthoquinone derivatives are at the center stage of research in the biomedical field [8]. Considering the increased mortality rate of tumor patients, recent research has been immensely focused on developing novel antitumor agents from naphthoquinones. Consequently, several reports appeared on the synthesis as well as biological screening of naphthoquinone derivatives [9]. Also, there exists tremendous interest in developing diverse heterocycle fused naphthoquinones owing to their enhanced biological activity compared to the parent naphthoquinone moieties [10]. Heterocycle containing naphthoquinones, especially the pyrrole and furan fused derivatives, are interesting candidates for medicinal chemistry purposes and are well studied [11]. The impact of heterocycle on the naphthoquinone bioactivity was established by structure-activity relationship studies [12]. Some of the bioactive naphthoquinone motifs containing pyrrole and furan skeleton are illustrated in Scheme 1A [11,13].

Pyrrole fused naphthoquinones (*p*-indoloquinones) received great interest in pharmaceutical field due to their applicability in drug release systems [14] and are important precursors of bioactive molecules [15]. The lead role of these heterocycle fused analogues in medicinal chemistry prompted synthetic chemists to develop novel and efficacious synthetic strategies [16] and some of the recently practiced protocols in this direction include ultrasound assisted reaction of 1,4-naphthoquinone and α-aminoacetals [17], Diels-Alder reaction of indole-4,7-dione with conjugated dienes [18], C,N-dialkylation of enaminones by 2,3-dichloronaphthoquinone [19] and various transition metal (Pd, Cu, Au) catalyzed annulation reaction of naphthoquinone derivatives [20]. Additionally, numerous other methods are also available for the preparation of *p*-indoloquinone starting from 2-aminonaphthoquinone derivatives [21]. Even though many elegant protocols exist towards the synthesis of

pyrrolonaphthoquinones, simple and milder methods are still highly desirable in view of their pharmacological activities.

Diverse reactivity exhibited by conjugated nitroalkenes and their derivatives were well-explored for the synthesis of various heterocycles [22]. In particular, the nitroallylic acetate derived from Morita-Baylis-Hillman (MBH) adduct of nitroalkene [23] and α-bromonitroalkene [24] serve as excellent substrates for the synthesis of heterocycles. In 2014, our group reported an efficient and enantioselective method for the synthesis of pyranonaphthoquinones from lawsone and nitroallylic acetate derived MBH-adduct of nitrostyrene and formaldehyde in the presence of a chiral squaramide catalyst [25]. In addition, α-bromonitroalkene was successfully employed to synthesize chiral dihydrofuran and furan fused naphthoquinones (Scheme 1B) [26,27]. These two types of compounds are important examples of C-ring modified lapachone-type molecules with antitumor activities. Our group [28] and others [29] have utilized the strategy of C-ring modification of quinones for preparing potential bioactive compounds in a drug discovery program aiming new antitumor compounds (Scheme 1B).

Methodologies involving transition-metal catalysis [30], organocatalysis [31] and acid catalysis [32] were developed for the synthesis of quinones with diverse biological activities. However, Organic Chemists are often challenged to develop new synthetic strategies for the preparation of new substances with potential bioactivities, and still more, new methods that can be employed in the synthesis of natural bioactive products of this class of compounds. Our continued interest in developing novel synthetic strategies by utilizing nitroalkene derivatives together with synthesis and antitumor evaluation of naphthoquinone derivatives prompted us to investigate the reactivity of 2-aminonaphthoquinones and 2-hydroxynaphthoquinones with conjugated nitroalkene derivatives (Scheme 1C). Thus, taking into account the reasons discussed above, herein, we describe the synthesis of pyrrole and furan fused naphthoquinones from corresponding 2-aminonaphthoquinones and 2-hydroxynaphthoquinone on reaction with conjugated nitroalkenes and their evaluation against diverse cancer and non-tumor cell lines.



Scheme 1. An Overview on Biological and Synthetic Aspects of Heterocycle Fused Naphthoquinone Motifs.

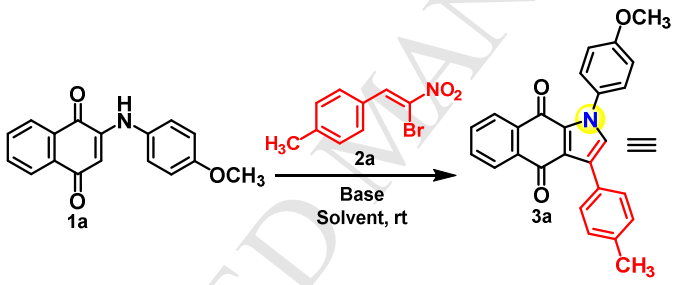
Results and Discussion

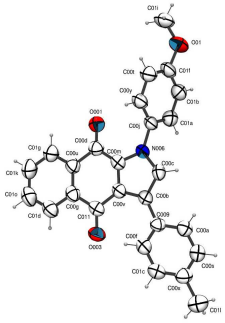
Chemistry

Setting the goal to synthesize heterocycle fused naphthoquinones, we began our investigation by reacting 2-aminonaphthoquinone derivative **1a** and α-bromonitroalkene **2a** in the presence 2 equiv CS_2CO_3 in THF at room temperature (Table 1). Gratifyingly, as expected, pyrrole fused naphthoquinone derivative **3a** was formed in 47% yield (entry 1). The structure of the product **3a** was established by various spectroscopic

analyses and finally unambiguously confirmed by single crystal X-ray analysis (Table 1). After the preliminary experiment, optimization studies were conducted to improve the yield by choosing **1a** and **2a** as model substrates. Initially, different bases were screened to get the best reaction conditions. The organic bases such as DABCO and TMG provided the product **3a** in poor yield (entries 2 and 3). Inorganic bases such as K_2CO_3 (entry 4), and KOH (entry 5), besides Cs_2CO_3 (entry 1) were screened in THF as solvent and among these KOH afforded the product **3a** in 55% yield. Further screening of different solvents revealed that DMF and DMSO are not suitable for our reaction (entries 6-7) and DCM was inferior to THF, especially in terms of reaction rate (entries 5 and 8). However, increasing the amount of α-bromonitroalkene **2a** to 1.5 equiv improved the yield of **3a** to 73% (entry 9) which subsequently reached 86% when silica gel was replaced by neutral alumina for column chromatography (entry 10).

Table 1. Optimization of Reaction Conditions[a]





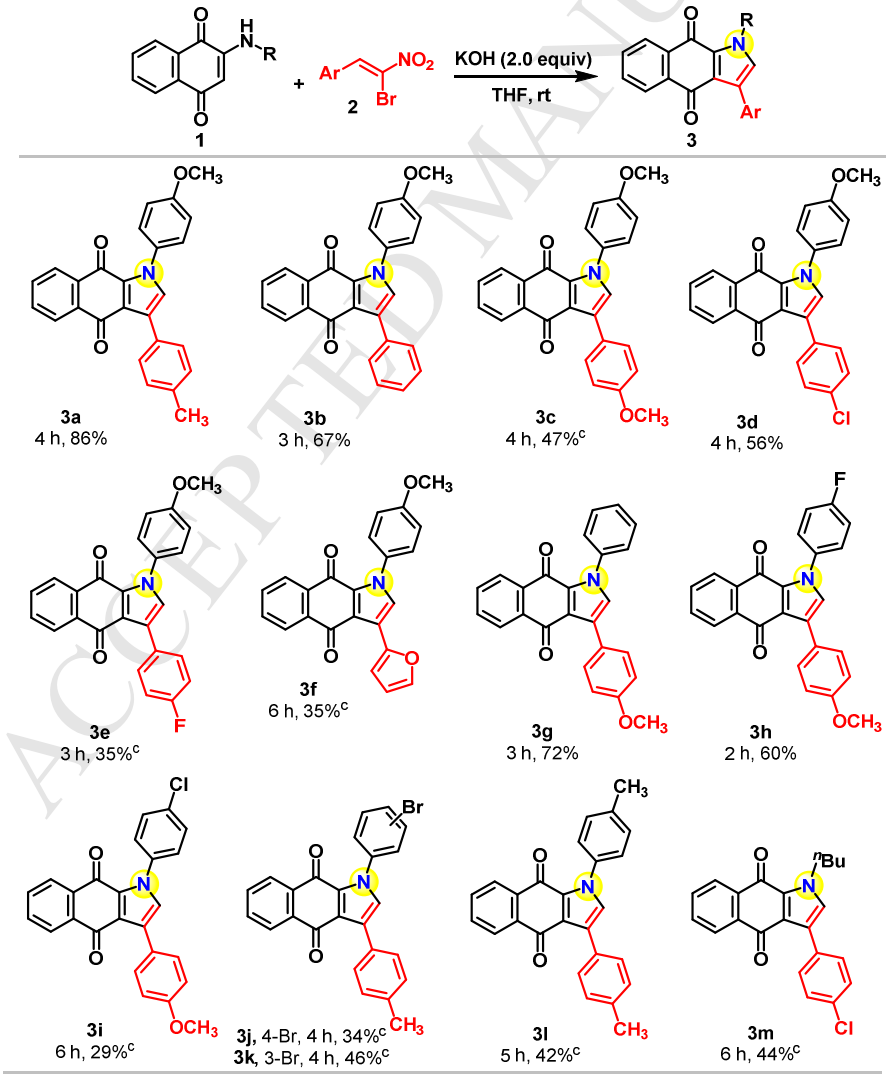
Entry	Base (2.0 equiv)	Solvent	Time (h)	Yield (%)[b]
1	Cs_2CO_3	THF	8	47
2	DABCO	THF	48	9
3	TMG	THF	48	12
4	K_2CO_3	THF	12	31
5	KOH	THF	4	55
6	KOH	DMF	6	--[c]
7	KOH	DMSO	6	--[c]
8	KOH	DCM	12	53
9[d]	KOH	THF	4	73
10[d]	KOH	THF	4	86[e]

[a]Reaction scale: aminonaphthoquinone **1a** (0.5 mmol), α-bromonitroalkene **2a** (0.75 mmol, 1.5 equiv), base (1 mmol, 2 equiv), solvent (2.0 mL). [b]After silica gel column chromatography.[c] Product **3a** was not detected. [d] 1.5 equiv of bromonitroalkene **2a** was added. [e]After neutral alumina column chromatography.

To explore the scope of the reaction, experiments were carried out with differently substituted α-bromonitroalkenes **2** and various *N*-arylated aminonaphthoquinones **1** under the optimized reaction conditions (Table 2). Irrespective of the electronic nature, α-bromonitroalkenes bearing both electron rich and electron

deficient aryl groups tolerated the reaction providing 1,3-diaryl pyrrolonaphthoquinones **3a-e** in moderate to good yields (35-86%). Considering the relevance of heterocycles in the naphthoquinone core, we examined the reactivity of furan containing α-bromonitroalkene with 2-aminonaphthoquinone which also furnished 3-furyl pyrrolonaphthoquinone **3f**, though in moderate yield. Next, the substitution pattern on the *N*-aryl group of 2-aminonaphthoquinone **1** was varied. Regardless of the electronic properties of aryl substituents, various *N*-arylated aminonaphthoquinones **1** smoothly reacted with α-bromonitroalkenes **2** and provided the products **3h-l** in reasonable yields. Furthermore, *N*-alkyl substituted 2-aminonaphthoquinone also participated in the reaction and delivered the corresponding pyrrolonaphthoquinone derivative **3m** in moderate yield.

Table 2. Substrate Scope for the Synthesis of Pyrrolonaphthoquinones[a,b]



[a] Reaction scale: Aminonaphthoquinone **1** (0.5 mmol), bromonitroalkene **2** (0.75 mmol, 1.5 equiv), KOH (1.0 mmol, 2 equiv), THF (2 mL), rt. [b] Yields after neutral alumina column chromatography. [c] 10-20% of Aminonapthoqinone **1** was recovered in these cases.

Encouraged by these results, we decided to examine the reactivity of Morita-Baylis-Hillman (MBH) acetates of nitroalkenes (α-nitroallylic acetates) **4** with 2-aminonaphthoquinones **1**. Similar to α-bromonitroalkenes **2**, nitroallylic acetates **4** also behave as bielectrophiles. Several carbocycles and heterocycles were synthesized by utilizing the 1,2- and 1,3-bielectrophilic nature of nitroallylic acetates **4** by several research groups including ours [23]. Under the established reaction conditions, we investigated the reactivity of various aryl substituted MBH-acetates **4** with 2-aminonaphthouinones **1**. As expected, diverse functionalized pyrrolonaphthoquinones **5** were formed in satisfactory yields and the results are summarized in Table 3. Various *N*-aryl substituents were also tolerated for this reaction to provide 1,2,3-trisubstituted pyrrolonaphthoquinones **5**. Moreover, the reaction was also compatible for heterocylic nitroallylic acetates and produced 3-furyl and 3-thiophene substituted pyrrolonaphthoquinones **5e** and **5f**, respectively, in reasonable yields. The structure of the formed pyrrolonaphthoquinones was characterized by various spectroscopic analyses and the regiochemistry was further confirmed by single crystal X-ray analysis of a representative product **5i** (Table 3). It should be noted that the simple primary 2-aminonaphthoquinone failed to yield the pyrrolonaphthoquinones on reaction with α-bromonitroalkenes **2** and MBH acetates **4**.

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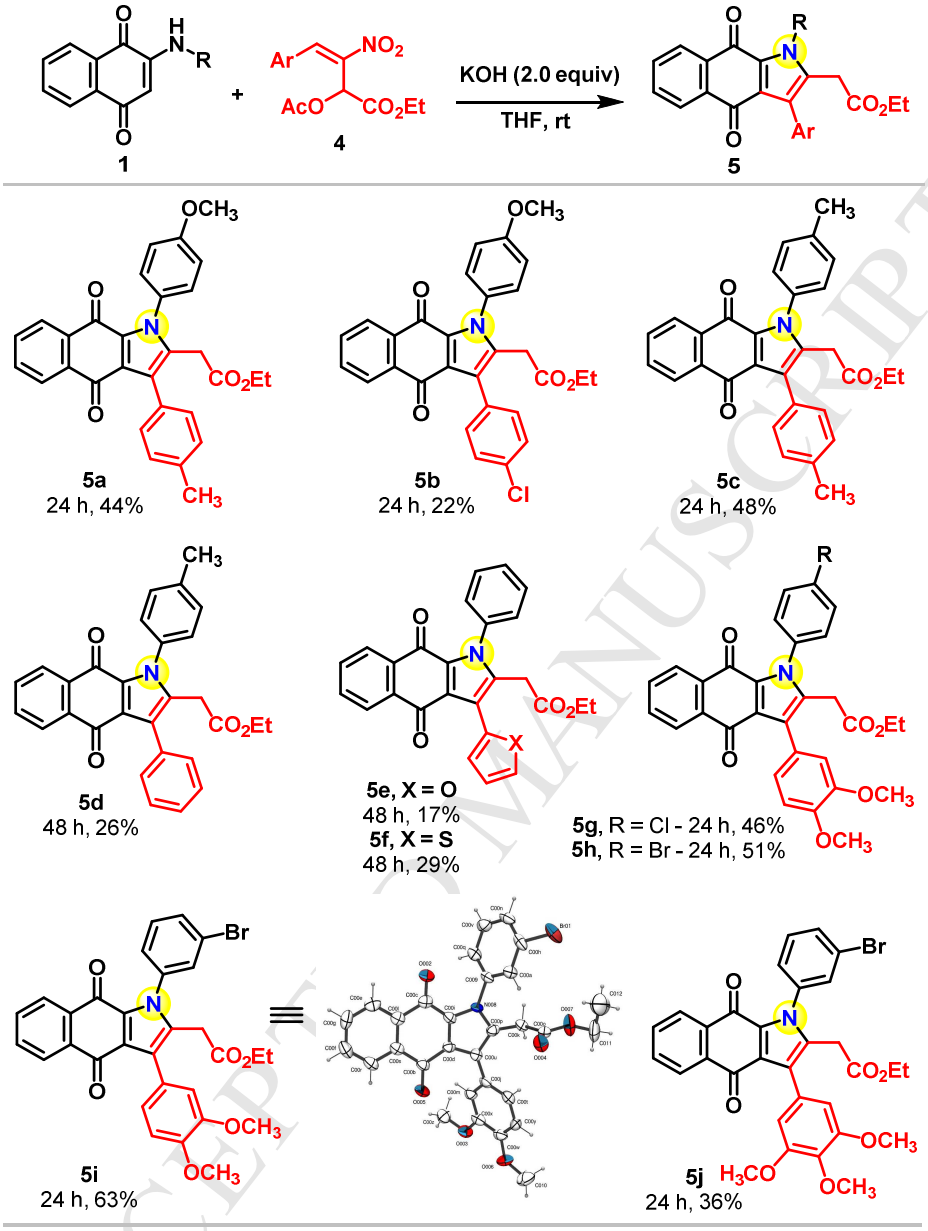
Table 3. Synthesis of Pyrrolonaphthoquinones 5 from 2-Aminonaphthoquinones 1 and MBH-Acetates 4[a,b]

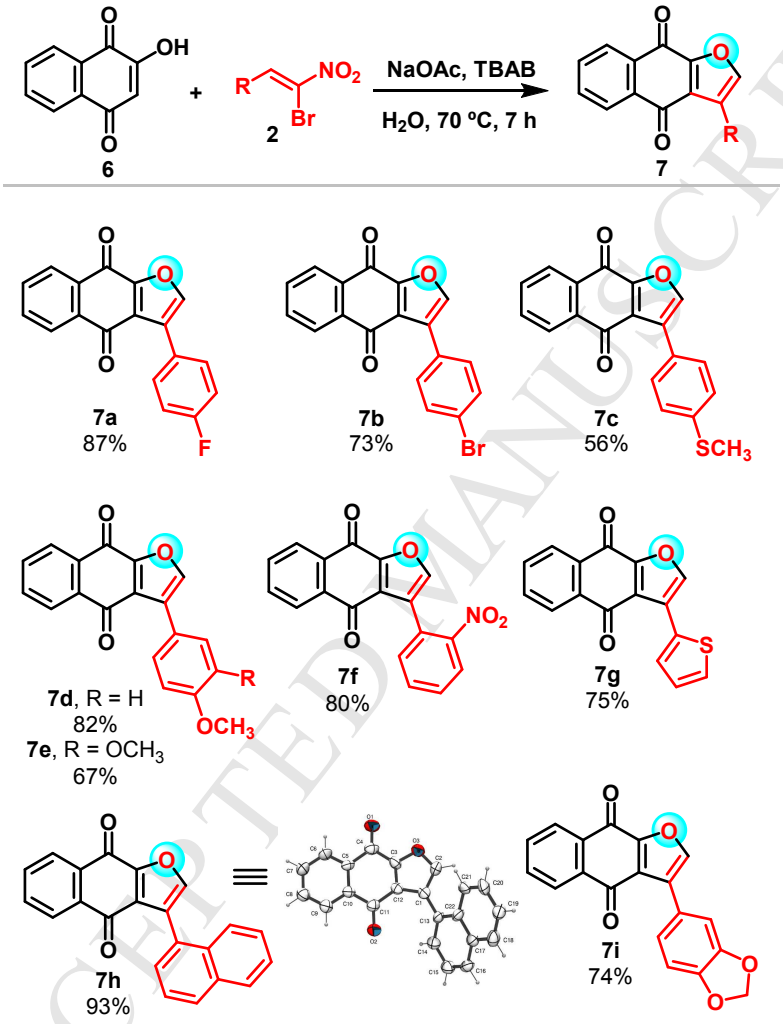


[a] Reaction scale: Aminonaphthoquinone **1** (0.18 mmol), MBH acetate **6** (0.36 mmol, 2 equiv), KOH (0.36 mmol, 2 equiv), THF (5.0 mL). [b] Yields after neutral alumina column chromatography; 10-20% 2-Aminonaphthoquinone was recovered in most cases.

After successful synthesis of pyrrole fused naphthoquinone derivatives, we further proceeded to synthesize the furan fused naphthoquinones **7** by employing 2-hydroxynaphthoquinone **6** (Table 4). The method for the synthesis of furanonaphthoquiones **7** from 2-hydroxynaphthoquinone **6** and α-bromonitroalkenes **2** was previously reported [27]. Considering the biological potential of furan fused naphthoquinones, we have synthesized these furanonaphthoquinone scaffolds **7** under

conditions similar to those reported [27] and subjected them to antitumor evaluation (vide infra). Various 3-aryl furanonaphthoquinones **7** were synthesized in good to excellent yields (56-93%) and the results obtained are summarized in Table 4.

Table 4. Synthesis of Furanonaphthoquinone 7 from 2-Hydroxynaphthoquinone 6 and α-Bromonitroalkenes 2[a,b]



[a] Reaction scale: 2-Hydroxynaphthoquinone **6** (0.15 mmol), α-bromonitroalkene **2** (0.3 mmol, 2 equiv), NaOAc (0.18 mmol, 1.2 equiv), TBAB (0.03 mmol, 20 mol%).
[b] Yields after recrystallization from EtOAc.

The reactivity of MBH-acetates **4** with 2-hydroxynaphthoquinone **6** was then explored towards the synthesis of highly substituted furanonaphthoquinones **8** (Table 5). The initial reaction was performed by reacting 2-hydroxynaphthoquinone **6** with MBH-acetate **4a** in the presence of 1 equiv of DABCO in THF at room temperature. As observed in the case of 2-aminonaphthoquinone **1**, the reaction afforded expected furanonaphthoquinone derivative **8d** in low (12%) yield (entry 1). Upon observation of

this initial reactivity, efforts were made to optimize the reaction conditions to improve the yield. Screening of other different organic bases such as DBU, TMG, DMAP provided the product in inferior yield (entries 2-4). Further, we have screened few inorganic bases such as KOH, Cs_2CO_3 and K_2CO_3 (entries 5-7) of which Cs_2CO_3 provided better yield of 51% (entry 6). Among various solvents screened, the initially employed reaction medium, THF, turned out to be superior to others such as CH_3CN and toluene (entries 6, 8 and 9). Finally, the reaction was performed under microwave irradiation conditions in the presence of Cs_2CO_3 in THF at 40 ^oC. In this case, the yield slightly improved to 54% (entry 10). Changing the solvent from THF to CH_3CN or base from Cs_2CO_3 to KOH and DMAP under the microwave conditions led to unsatisfactory results (entries 11-13). Subsequently, the effect of base loading on the product yield was investigated. While increasing the base loading from 1.0 equiv to 1.5 and 2.0 equiv led to no change and drop in the yield, respectively (entries 14-15), decreasing the base loading from 1.0 equiv to 0.5 equiv caused enhancement in the yield to 65% (entry 16). Further decreasing the base loading or increasing the reaction temperature did not improve the yield (entries 17-18).

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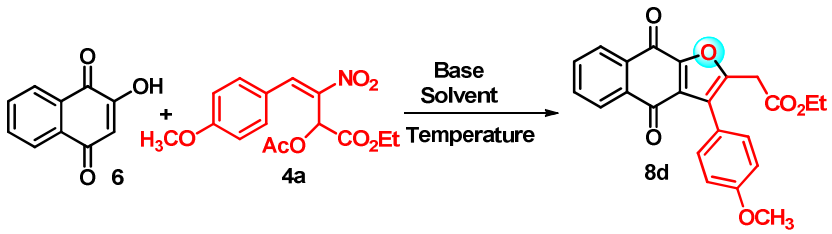
Table 5. Optimization of Reaction Conditions[a,b]

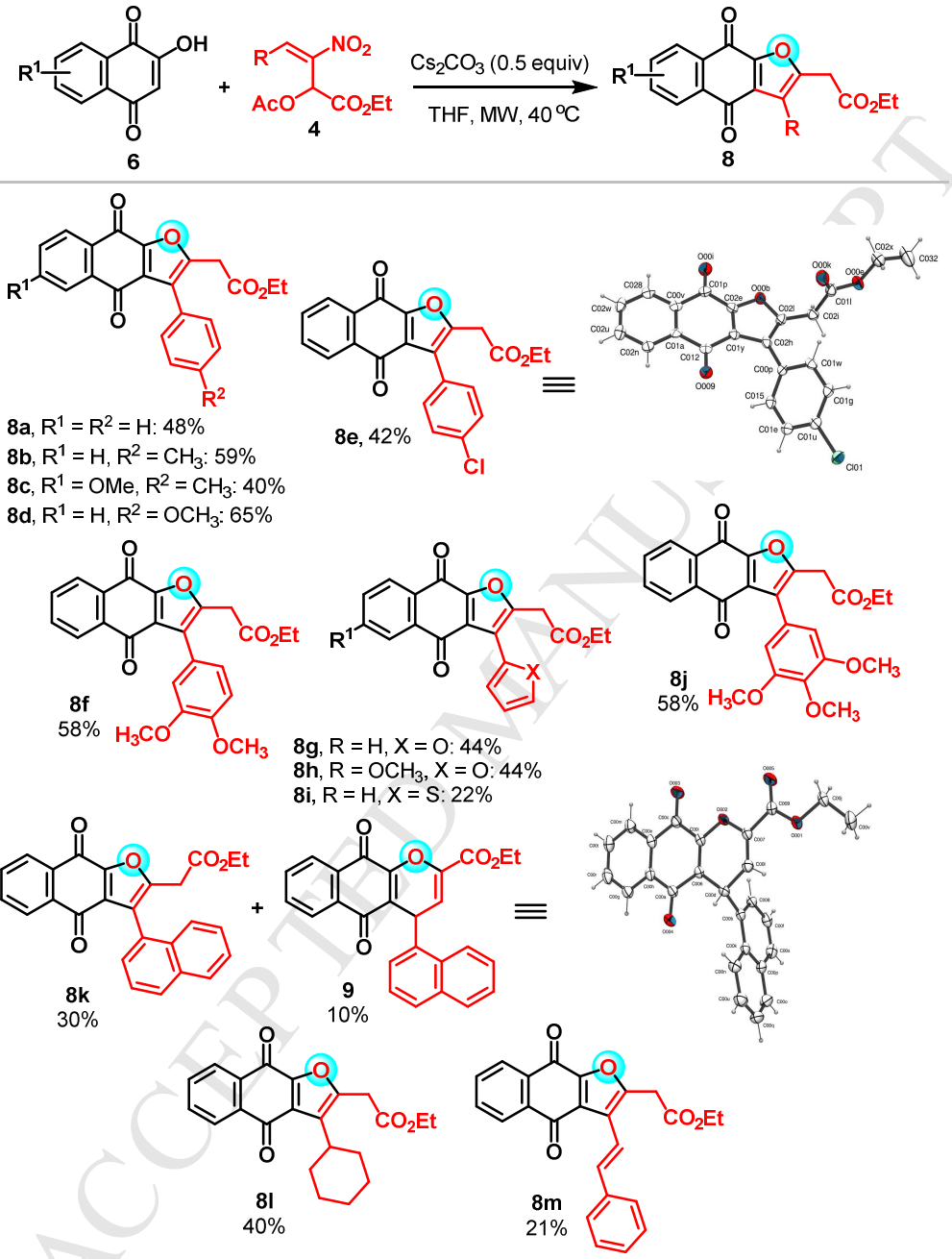


Entry	Base (equiv)	Solvent	Conditions	Time	Yield (%)[b]
1	DABCO (1)	THF	rt	2h	12
2	DBU (1)	THF	rt	2h	No product
3	TMG (1)	THF	0 °C to rt	2h	25
4	DMAP (1)	THF	rt	2h	30
5	KOH (1)	THF	0 °C to rt	2h	46
6	Cs_2CO_3 (1)	THF	rt	2h	51
7	K_2CO_3 (1)	THF	rt	2h	20
8	Cs_2CO_3 (1)	MeCN	0 °C to rt	2h	38
9	Cs_2CO_3 (1)	Toluene	0 °C to rt	2h	trace
10	Cs_2CO_3 (1)	THF	40 °C, MW	10 min	54
11	Cs_2CO_3 (1)	MeCN	40 °C, MW	10 min	45
12	KOH (1)	THF	40 °C, MW	10 min	52
13	DMAP (1)	THF	40 °C, MW	10 min	18
14	Cs_2CO_3 (1.5)	THF	40 °C, MW	20 min	54
15	Cs_2CO_3 (2)	THF	40 °C, MW	20 min	46
16	Cs_2CO_3 (0.5)	THF	40 °C, MW	20 min	65
17	Cs_2CO_3 (0.25)	THF	40 °C, MW	20 min	50
18	Cs_2CO_3 (0.5)	THF	80 °C, MW	60 min	64

[a] Reaction scale: Hydroxynaphthoquinone **6** (0.2 mmol), MBH acetate **4a** (0.2 mmol, 1 equiv), base (0.1 mmol, 0.5 equiv) in solvent (2.0 mL). [b] After neutral alumina column chromatography.

Under the above optimized conditions, the reaction was generalized by varying the MBH acetates **4** and hydroxynaphthoquinones **6** (Table 6). MBH acetates **4** possessing electron donating and electron withdrawing substituents on the aryl ring, heteroaryl and alkyl groups furnished the corresponding furanonaphthoquinones **8** in moderate to good yield. When the reaction was performed by employing α-naphthyl derived MBH-acetate, along with the major product, furanonaphthoquinone derivative **8k**, which was formed in 30% yield, the pyran ring fused naphthoquinone **9** was formed in low (10%) yield.

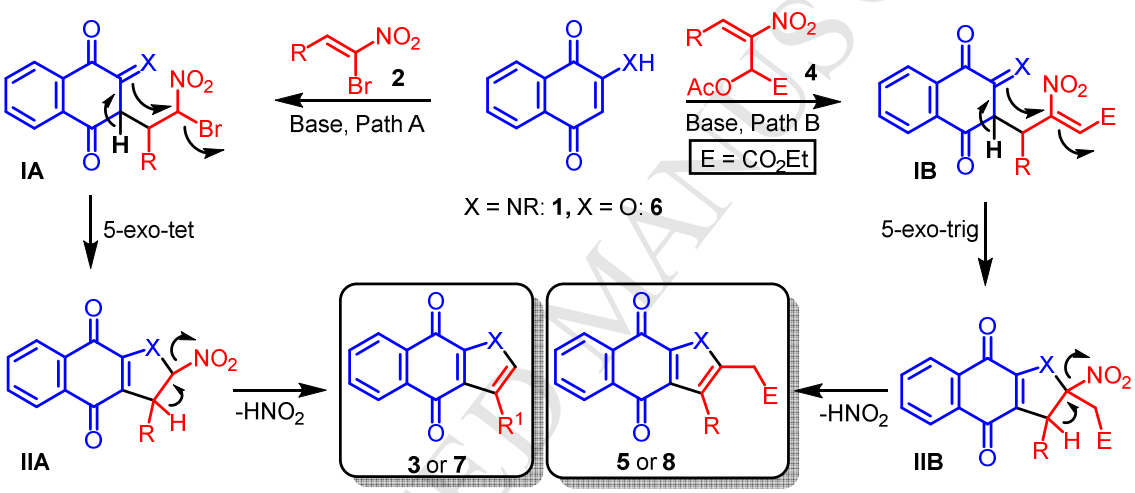
Table 6. Synthesis of Furanonaphthoquinones 8 from 2-Hydroxynaphthoquinones 6 and MBH-acetates 4[a,b]



[a] Reaction scale: Hydroxynaphthoquinone **6** (0.2 mmol), MBH acetate **4a** (0.2 mmol, 1 equiv), base (0.1 mmol, 0.5 equiv) in solvent (2.0 mL). [b] Yields after neutral alumina column chromatography; 10-20% of hydroxynaphthoquinone **6** was recovered in most cases.

Based on our previous reports [23], a possible mechanism for the formation of pyrrole and furan fused naphthoquinones which is outlined in Scheme 2. The base abstracts a proton from lawsone **6** or 2-aminonaphthoquinone **1** and generates corresponding quinonoid anion. The anion reacts with α-bromonitroalkenes **2** in a

Michael fashion to give intermediate **IA** (path A). Intramolecular nucleophilic substitution of bromide in **IA** in a 5-exo-tet fashion provides the cyclized intermediate **IIA** which then undergoes base assisted HNO_2 elimination to afford pyrrole and furan fused naphthoquinones **3** and **7**. Similarly, the bielectrophilic Morita-Baylis-Hillman acetate **4** reacts with quinone in an S_N2' fashion and generates intermediate **IB**. Subsequently, intramolecular aza/oxa-Michael reaction in a 5-exo-trig manner results in the cyclized intermediate **IIB**. Further, base facilitated elimination of HNO_2 from intermediate **IIB** affords the respective heterocycle fused naphthoquinones **5** and **8**. The pyranonaphthoquinone **9** (Table 6) was formed through a 6-*endo*-trig cyclization of intermediate **1B** (not shown).



Scheme 2. Possible Mechanism for the Formation of Pyrrole and Furan Fused Naphthoquinones

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Table 7. Selected Single Crystal X-ray data for compounds **3a**, **5i**, **7i**, **8e** and **9**.

Parameters	**3a**	**5i**	**7h**	**8e**	**9**
CCDC	1570229	1569289	1569291	1570230	1569290
Empirical formula	C_{26} H_{19} N O_3	C_{30} H_{24} Br N O_6	$C_{22}H_{12}$ O_3	C_{88} H_{60} Cl_4 O_{20}	C_{26} H_{18} O_5
Formula weight	393.42	574.41	324.32	1579.16	410.40
Temperature	293(2) K	293(2) K	293(2) K	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å	1.54184 Å
Crystal system	Monoclinic	Triclinic	Monoclinic	Trigonal	Triclinic
Space group	P 1 21/n 1	P -1	P21/c	R -3	P -1
Unit cell dimensions	a = 15.2899(6) Å b = 14.9166(6) Å c = 17.4055(7) Å α = 90° β = 102.107(4)° γ = 90°	a = 7.9504(6) Å b = 10.8078(8) Å c = 15.5154(12) Å α = 81.431(6)°. β = 83.263(6)°. γ = 72.763(7)°.	a = 12.484(5) Å b = 7.767(3) Å c = 15.583(8) Å α = 90° β = 90.83(5)° γ = 90°	a = 59.1248(14) Å b = 59.1248(14) Å c = 10.6783(3) Å α = 90°. β = 90°. γ = 120°.	a = 8.1391(6) Å b = 10.1038(5) Å c = 12.7566(9) Å α = 106.719(6)° β = 90.539(6)° γ = 102.947(5)°
Volume	3881.4(3) Å3	1255.30(17) Å3	1510.8(4) Å3	32327.5(15) Å3	976.09(11) Å3
Z	8	2	4	18	2
Density (calculated)	1.346 Mg/m^3	1.520 Mg/m^3	1.426 Mg/m^3	1.460 Mg/m^3	1.396 Mg/m^3
Absorption coefficient	0.088 mm^{-1}	1.685 mm^{-1}	0.095 mm^{-1}	0.246 mm^{-1}	0.793 mm^{-1}
F(000)	1648	588	672	14688	428
Crystal size	0.144 x 0.204 x 0.206 mm^3	0.057 x 0.162 x 0.239 mm^3	0.30 x 0.24 x 0.16 mm^3	.054 x 0.095 x 0.227 mm^3	0.086 x 0.126 x 0.174 mm^3
Theta range for data collection	2.11 to 25.00°	1.99 to 25.00°	2.6 to 34.3°	1.82 to 25.00°	4.70 to 64.99°
Index ranges	-18<=h<=18, -17<=k<=16, -20<=l<=20	-7<=h<=9, -12<=k<=12, -18<=l<=17	-19≤h1≤18, -11≤k≤11, -24≤l≤23	-70<=h<=39, -68<=k<=70, -12<=l<=7	-9<=h<=9, -11<=k<=7, -14<=l<=14
Reflections collected	38195	8645	21067	39518	6695
Independent reflections	6839 [R(int) = 0.0919]	4398 [R(int) = 0.0416]	6059 [R(int) = 0.06]	12614 [R(int) = 0.0856]	3245 [R(int) = 0.0637]
Completeness	Completeness to theta = 25.00° is 99.9%	Completeness to theta = 25.00° is 99.3 %	Completeness to theta = 25.00° is 98.9%	Completeness to theta = 25.00° is 99.6 %	Completeness to theta = 64.99° is 97.5 %
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	6839 / 0 / 545	4398 / 0 / 346	960/ 0 / 226	12614 / 0 / 1013	3245 / 0 / 280
Goodness-of-fit on F^2	1.052	1.055	0.933	1.019	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0594, wR2 = 0.1375	R1 = 0.0399, wR2 = 0.0842	R1 = 0.14, wR2 = 0.27	R1 = 0.0703, wR2 = 0.1616	R1 = 0.0598, wR2 = 0.1558
R indices (all data)	R1 = 0.0889, wR2 = 0.1636	R1 = 0.0504, wR2 = 0.0903	R1 = 0.29, wR2 = 0.35	R1 = 0.1325, wR2 = 0.2158	R1 = 0.0737, wR2 = 0.1729
Largest diff. peak and hole	0.242 and -0.286 $e.Å^{-3}$	0.422 and -0.590 $e.Å^{-3}$	0.30 and -0.37 $e.Å^{-3}$	0.610 and -0.779 $e.Å^{-3}$	0.335 and -0.244 $e.Å^{-3}$

Biological Studies

The Cytotoxicity of compounds **3a**-**3m**, **5a**-**5j**, **7a**-**7i**, **8a**-**8b**, **8d**-**8g**, **8i**-**8k** and **8m** described above (Tables 2-4 and 6), were evaluated in vitro using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colourimetric assay against five cancer cell lines: HCT-116 (human colon carcinoma cells), PC3 (human prostate cancer cells), HL-60 (human promyelocytic leukemia cells), SF295 (human glioblastoma cells) and NCI-H460 (human lung cancer cells). Non-tumor cells, human peripheral blood mononuclear (PBMC), and murine fibroblast immortalized cell lines (L929) were used to evaluate the selectivity of the compounds (Table 8). As previously described [33], the compounds were classified according to their activity as highly active (IC_{50} < 2 µM), moderately active (2 µM < IC_{50} < 10 µM), or inactive (IC_{50} > 10 µM).

The first class of compounds, pyrrolonaphthoquinones **3a**-**3m**, was considered inactive (IC_{50} > 10 µM) with an exception of compound **3d**. The activity exhibited by compound **3d** may be due to the presence of electron withdrawing chlorine atom. It is important to highlight that **3d** presented low cytotoxicity against the non-tumor cell lines evaluated. For example, the selectivity index calculated for **3d** (represented by the ratio of cytotoxicities between non-tumor cells and different lines of cancer cells), when we have considered NCI-H460 cancer cells was 3.1. In this same direction, the value for doxorubicin, drug used in clinical, is 3.6 considering PBMC as non-tumor cells.

The second class of pyrrolonaphthoquinone derivatives **5a**-**5j** was also evaluated against cancer and healthy cells. Not surprisingly, since the first class of pyrrolonaphthoquinones **3a**-**3m** was inactive, quinones **5a**-**5j** were also not efficient to kill cancer cells. Against HL-60 cancer cells, two compounds **5a** and **5f** have presented moderate activity and compound **5h** was cytotoxic against SF-295 cells. Even with these three compounds active against two different cancer cells, we considered this series not remarkable related to their antitumor potential.

Finally, furanonaphthoquinones **7a-i**, **8a-8b**, **8d-8g**, **8i-8k** and **8m** were also studied. These compounds were active against all cancer cells used in this study. Compounds from the family of type **8** have presented moderate activity with IC_{50} in the range of 3.97 to 10 µM. Among all the compounds evaluated **7a-i** were the most potent with IC_{50} values < 6.33 µM. The quinones **7b**, **7f** and **7i** were the best among the series with IC_{50} in the range 2.23 to 5.39 µM corroborating that the presence of electron withdrawing groups is important for the antitumor activity. As compounds **7a**-**i** were the

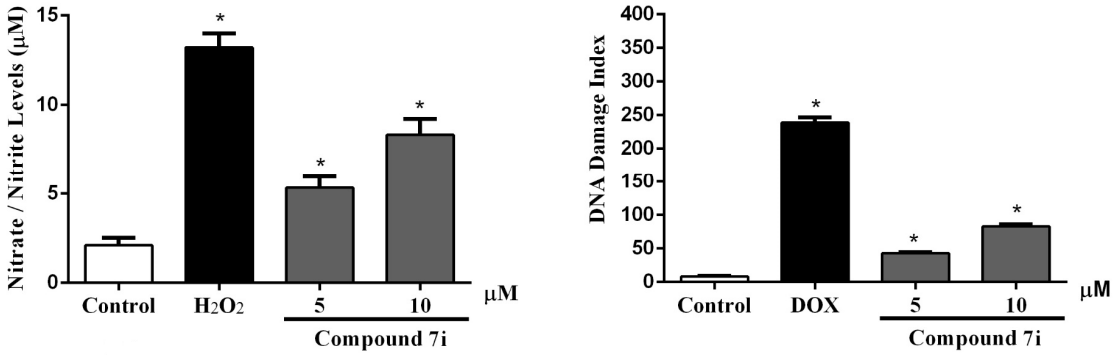
most active derivatives against the five cancer cell lines evaluated (Table 8), we decided to expand the panel of cancer cells used in this study and we also assayed **7a-i** against OVCAR-8 (ovary), MX-1 (breast) and JURKAT (leukemia) cell lines (Table 9). All the compounds in the **7a-i** series were considered moderately active (IC_{50} < 6 µM) of which furanonaphthoquinone **7f** with IC_{50} values in the range of 1.47 to 2.85 µM found to be most active. As these compounds exhibited low cytotoxicity against healthy cells L-929 with IC_{50} > 13 µM, definitely, we have herein identified important structures with potential antitumor activity for further studies.

The mechanism of action of naphthoquinones is intrinsically related to formation of reactive oxygen species (ROS), which cause oxidative stress by oxidizing lipids, proteins and DNA [34]. Recently, our group has described the synthesis of fluorescent quinone-based BODIPY hybrids with potent antitumor activity and some insights about their mechanism of action. Studies involving lipid peroxidation and determination of reduced (GSH) and oxidized (GSSG) glutathione, besides subcellular localization by confocal microscopy were accomplished. Cell imaging experiments indicated that the quinoidal derivatives might preferentially get localized in the lysosomes of cancer cells [35]. These studies represent an important example of the ability of quinones to generate reactive oxygen species and the participation of these species in the mechanism of pharmacological action.

The complexity of biological systems associated with the capacity of quinoidal derivatives to act as multitarget systems become the complete determination of the mechanism of action of such compounds a difficult task which requires a thorough investigation [36]. For instance, β-lapachone (β-lap) is a well-known quinoidal natural product with antitumor activity, also named as ARQ 501. This quinone is currently in advanced clinical trials for the treatment of some types of cancer, as for instance, pancreatic cancer [37]. The mechanism of action is related to destruction of cancer cells with elevated endogenous levels of NAD(P)H:quinone oxidoreductase 1 (NQO1) [38]. This enzyme is considered as an important target associated to the potential cytotoxicity of β-lap. Although its mechanism of action is related to this enzyme, Ohayon and coworkers have demonstrated the hypothesis that β-lap would be able to act nonreversibly for inhibition of deubiquitinases, suggesting that the therapeutic effect could be due to multiple pathways, with USP2 oxidation [39]. These results are important examples of the complexity associated with the mode of action of naphthoquinoidal compounds such as β-lapachone.

Recently, several researchers have shown in independent studies novel quinonoid derivatives as CDC25 inhibitors [40-42]. Known for its function as key regulator of the cell cycle in human cells, the cell division cycle 25 phosphatases (CDC25) are a valuable target for the development of small quinonoid inhibitors of therapeutic importance [41]. This new approach represents another possibility within a wide range of possibilities related to the mechanism of action of naphthoquinones demonstrating the diversity of targets associated with the mode of action of this important class of antitumor compounds.

Bearing in mind, the important aspects associated with the mechanism of action of quinones discussed above, we have selected **7a**-**7i** and accomplished experiments of comet assay and evaluation of nitrate/nitrite levels in relation to oxidative stress parameters to establish preliminary data about the mechanism in HCT-116. Our data (not shown here) suggest that the cytotoxicity of the naphthoquinoidal derivatives may be associated with late apoptosis. To understand important factors and details about the complex mode of action of these compounds, further experiments are underway in our laboratories and will be reported in due course for the compounds **7a**-**7i**. As an illustrative example, in order to determine the oxidative damage triggered by compound **7i**, the production of nitrate/nitrite as a result of NO release after treatment of HCT-116 cells was studied. The treatment of HCT-116 cancer cells with **7i** during 24 h has resulted in a concentration-dependent increase in nitrate/nitrite at all concentrations tested ($p<0.05$) after 24 h exposure. Increase in the levels of NO, oxidative metabolic products, suggests that oxidative damage is involved in the cytotoxic effects of the naphthoquinone studied. Thus, the measured levels (µM) were 5.33 ± 0.64 and 8.33 ± 0.88 after the treatment with 5 and 10 µM of **7i** (Figure 1A). Considering the potential cytotoxic and pro-oxidant properties of **7i**, we have also investigated its ability to induce DNA damage. The *in vitro* alkaline (pH > 13) comet assay, a well-known assay for screening potential genotoxic agents, was used to evaluate DNA damage index (DI) in HCT-116 cells, after 24 h exposure of **7i** according to the comet assay (Figure 1B). Our results clearly show a significant ($p<0.05$) increase in the means of DI values at both concentrations in relation to the negative control group (DI = 8.3 ± 0.88), while for cell cultures treated at 5 and 10 µM, DI values were 42.88 ± 1.97 and 82.77 ± 3.4, respectively.



(**A**) (**B**)

Figure 1. (A) Nitrate/nitrite formation after 24 h treatment of HCT-116 cells with compound **7i.** Data are presented as mean values ± S.E.M. of three independent experiments. *p<0.05 compared to the negative control by ANOVA followed by Tuckey´s test. (B) Effects of **7i** on DNA damage index after 24 h of exposure using alkaline version of comet assay. Data are presented as mean values ± S.E.M. of three independent experiments. *p<0.05 compared to the negative control by ANOVA followed by Tuckey´s test. DOX = Doxorubicin.

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Table 8. Cytotoxic activity of furano- and pyrrolonaphthoquinones expressed by IC_{50} μM (95% CI) of compounds **3a-3m**, **5a-5j**, **7a-i**, **8a-8b**, **8d-8g**, **8i-8k** and **8m** in cancer and non-tumor cell lines after 72 h exposure, obtained by nonlinear regression for all cell lines from three independent experiments.

Compounds	HCT-116	PC3	HL-60	SF-295	NCI-H460	L-929	PBMC
3a	>12.71	>12.71	>12.71	>12.71	>12.71	>12.71	>12.71
3b	>13.18	>13.18	>13.18	>13.18	>13.18	>13.18	>13.18
3c	>12.22	>12.22	>12.22	>12.22	>12.22	>12.22	>12.22
3d	8.88 (8.30-9.24)	8.66 (8.20-8.81)	3.15 (3.09-3.25)	4.28 (4.10-4.39)	3.81 (3.70-3.92)	>12.10	>12.10
3e	>12.59	>12.59	>12.59	>12.59	>12.59	>12.59	>12.59
3f	>13.54	>13.54	>13.54	>13.54	>13.54	>13.54	>13.54
3g	>12.98	>12.98	>12.98	>12.98	>12.98	>12.98	>12.98
3h	>13.18	>13.18	>13.18	>13.18	>13.18	>13.18	>13.18
3i	>12.59	>12.59	>12.59	>12.59	>12.59	>12.59	>12.59
3j	>12.10	>12.10	>12.10	>12.10	>12.10	>12.10	>12.10
3k	>13.25	>13.25	>13.25	>13.25	>13.25	>13.25	>13.25
3l	>11.33	>11.33	>11.33	>11.33	>11.33	>11.33	>11.33
3m	>13.77	>13.77	>13.77	>13.77	>13.77	>13.77	>13.77
5a	>10.43	>10.43	3.36 (2.91-3.88)	>10.43	>10.43	>10.43	>10.43
5b	>10.02	>10.02	>10.02	>10.02	>10.02	>10.02	>10.02
5c	>10.79	>10.79	>10.79	>10.79	>10.79	>10.79	>10.79
5d	>11.13	>11.13	>11.13	>11.13	>11.13	>11.13	>11.13
5e	>11.76	>11.76	>11.76	>11.76	>11.76	>11.76	>11.76
5f	>11.34	>11.34	2.63 (2.29–3.01)	>11.34	>11.34	>11.34	>11.34
5g	>9.45	>9.45	>9.45	>9.45	>9.45	>9.45	>9.45
5h	>17.45	>17.45	>17.45	6.45	>17.45	>17.45	>17.45

				(5.23–7.96)			
5i	>8.72	>8.72	>8.72	>8.72	>8.72	>8.72	>8.72
5j	>8.29	>8.29	>8.29	>8.29	>8.29	>8.29	>8.29
7a	6.02 (5.51-6.43)	3.97 (3.76-4.21)	3.28 (2.97-3.59)	6.33 (5.92-6.77)	4.34 (4.10-4.48)	13.56 (13.11-14.38)	>17.12
7b	5.39 (5.25-5.59)	2.61 (2.41-2.95)	2.64 (2.44-2.81)	3.49 (3.32-3.72)	4.88 (4.65-5.25)	>14.20	>14.20
7c	6.03 (5.84-6.12)	2.49 (2.28-2.74)	3.09 (2.87-3.24)	3.43 (3.21-3.59)	4.68 (4.43-4.84)	>15.62	>15.62
7d	5.78 (5.19-6.38)	4.96 (4.66-5.19)	4.31 (4.14-4.54)	4.99 (4.83-5.22)	6.34 (6.12-6.81)	>16.44	>16.44
7e	5.20 (4.84-5.56)	3.89 (3.62-4.31)	3.41 (3.05-3.74)	3.74 (3.59-4.01)	4.07 (3.86-4.37)	>14.96	>14.96
7f	1.28 (1.03-1.53)	1.59 (1.50-1.66)	1.66 (1.50-1.78)	2.94 (2.75-3.32)	2.53 (2.31-2.75)	>15.67	>15.67
7g	5.17 (4.92-5.53)	4.85 (4.64-5.17)	3.28 (2.92-3.61)	4.96 (4.46-5.28)	5.67 (5.24-6.17)	>17.85	>17.85
7h	6.17 (5.89-6.38)	1.82 (1.57-1.97)	2.37 (2.19-2.62)	4.44 (4.19-4.62)	3.79 (3.67-4.01)	13.02 (12.74-13.42)	>15.42
7i	2.76 (2.60-2.95)	2.54 (2.26-3.01)	2.23 (1.94-2.51)	3.71 (3.48-3.86)	3.61 (3.33-3.99)	>15.72	>15.72
8a	12.50 (11.32–12.82)	>13.89	8.38 (7.48–9.38)	>13.89	8.86 (8.12–9.67)	>13.89	>13.89
8b	>13.36	>13.36	>13.36	>13.36	>13.36	>13.36	>13.36
8d	>12.82	>12.82	>12.82	>12.82	>12.82	>12.82	>12.82
8e	>12.69	>12.69	10.23 (6.83–15.34)	>12.69	>12.69	>12.69	>12.69
8f	6.16 (5.57–6.80)	>11.90	3.97 (3.45–4.57)	>11.90	7.53 (6.47–8.77)	8.47 (7.59–9.45)	>11.90
8g	>14.28	>14.28	>14.28	>14.28	>14.28	>14.28	>14.28
8i	13.67 (12.07–15.48)	>27.32	5.91 (5.04–6.91)	>27.32	9.09 (7.34–11.28)	>27.32	>27.32
8j	>11.11	8.61 (7.13–10.39)	4.01 (3.52–4.57)	10.34 (9.01–11.85)	>11.11	>11.11	>11.11

8k	>12.19	>12.19	6.69 (5.43–8.24)	>12.19	>12.19	>12.19)	>12.19
8m	>12.95	>12.95	10.65 (9.06–12.51)	>12.95	>12.95	>12.95	>12.95
Doxorubicin	0.21 (0.16–0.29)	0.76 (0.59–0.93)	0.02 (0.01–0.02)	0.41 (0.21–0.47)	0.15 (0.13–0.18)	1.72 (1.58–1.87)	0.55 (0.41–0.58)

Table 9. Cytotoxic activity of compounds **7a-i** expressed by IC_{50} µM (95% CI) in cancer cell lines OVCAR-8, MX-1 and JURKAT and non-tumor cells L-929 after 72 h exposure, obtained by nonlinear regression for all cell lines from three independent experiments.

Compounds	OVCAR-8	MX-1	JURKAT	L-929
7a	5.43 (4.75-4.86)	5.20 (5.03-5.47)	3.45 (3.01-3.76)	13.56 (13.11-14.38)
7b	2.98 (2.58-3.32)	3.23 (3.09-3.49)	2.78 (2.61-3.04)	>14.20
7c	4.09 (3.87-4.37)	4.74 (4.37-5.24)	2.18 (2.06-2.59)	>15.62
7d	6.01 (5.32-6.67)	5.59 (5.45-5.75)	3.81 (3.55-3.97)	>16.44
7e	4.69 (4.51-4.84)	5.05 (4.72-5.29)	3.71 (3.56-3.89)	>14.96
7f	2.25 (1.91-2.60)	2.85 (2.53-3.25)	1.47 (1.31-1.66)	>15.67
7g	5.39 (5.21-5.78)	4.92 (4.46-5.32)	4.21 (3.96-4.53)	>17.85
7h	3.88 (3.76-3.98)	3.30 (2.65-3.51)	2.09 (1.88-2.28)	13.02 (12.74-13.42)
7i	3.08 (2.98-3.36)	2.92 (2.76-3.04)	2.04 (1.82-2.20)	>15.72
Doxorubicin	0.45 (0.41-0.49)	0.42 (0.39-0.45)	0.02 (0.01-0.03)	1.72 (1.58–1.87)

Conclusions

An efficient and convenient protocol towards the synthesis of heterocycle fused naphthoquinones has been developed. Base mediated one-pot reaction of α-bromonitroalkenes and nitroallylic acetates as bielectrophiles with 2-amino/hydroxy-1,4-naphthoquinones as binucleophiles produced pyrrole and furan fused naphthoquinones in moderate to good yields. The steps involved an S_N2' reaction followed by an intramolecular nucleophilic substitution in a 5-exo-tet fashion or an intramolecular oxa- or aza-Michael addition in a 5-exo-trig fashion. All the compounds were evaluated against five cancer cell lines and two non-tumor cell lines. We have expanded the panel of cancer cells used in this study for selected compounds which exhibited potent cytotoxicity, thus evaluating a total of eight cancer cell lines. We identified a very promising compound, a furanonaphthoquinone (**7f**) possessing an *o*-nitrophenyl group at position 3, with IC_{50} in the range of 1.28 to 2.94 μM against cancer cells and low cytotoxity against non-tumor cells. Consequently, this compound presented high selectivity index, and we consider it as a promising candidate for subsequent studies. This study represents the application of a simple and efficient synthetic method for developing novel potential drugs against cancer.

Experimental Section

General Experimental Details: The melting points recorded are uncorrected. NMR spectra (^{1}H, ^{1}H decoupled ^{13}C, ^{13}C-APT, ^{1}H- ^{1}H COSY and NOESY) were recorded with TMS as the internal standard. The coupling constants (*J* values are given in Hz). High resolution mass spectra were recorded under ESI Q-TOF conditions. X-ray data were collected on a diffractometer equipped with graphite monochromated Mo Kα radiation. The structures were solved by direct methods shelxs97 and refined by full-matrix least squares against F2 using shelxl97 software. All H atoms were located by geometric considerations placed (C-H = 0.93-0.96 Å; N-H = 0.86 Å) and refined as riding with Uiso(H) = 1.5Ueq(C-methyl) or 1.2Ueq(other). Crystallographic data for the structure was deposited in the Cambridge Crystallographic Data Centre, with numbers CCDC 1570229, 1569289, 1569291, 1570230 and 1569290 for **3a**, **5i**, **7h**, **8e** and **9**, respectively. Starting materials α-bromonitroalkenes **2** [43], Morita-Baylis-Hillman acetates **4** [44], and 2-aminonaphthoquinones **1** [45] were prepared by following

literature methods. 2-Hydroxynaphthoquinone **6** was commercially available (Aldrich) and 6-methoxy-2-hydroxynaphthoquinone was prepared by following the reported literature procedure [46].

General Procedure for the Synthesis of Pyrrolonaphthoquinones 3a-3m. To a stirred solution of 2-aminonaphthoquinone **1** (0.5 mmol, 1.0 equiv) in THF (4 mL), KOH (56 mg, 1.0 mmol, 2 equiv) was added and the reaction mixture was stirred at rt under N_2 atmosphere. After 5 min, α-bromonitroalkene **2** (0.75 mmol, 1.5 equiv) in THF (2 mL) was added dropwise to the reaction mixture and continued stirring at rt. After completion of the reaction (as evidenced by TLC), the solvent was removed *in vacuo* and water (4 mL) was added to the crude residue. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue on purification by column chromatography (neutral alumina) using petroleum ether-ethyl acetate (5:95 to 10:90) yielded pyrrolonaphthoquinones **3**.

1-(4-Methoxyphenyl)-3-(*p*-tolyl)-1*H*-benzo[*f*]indole-4,9-dione (3a). Red solid; Yield 169 mg, 86%; mp 142-146 °C; IR (film, cm^{-1}) 1658 (s), 1592 (w), 1515 (m), 1483 (w), 1383 (w), 1266 (s), 1248 (s), 1170 (w), 1031 (w), 916 (m), 836 (w), 716 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.0, 1.5 Hz, 1H), 8.06 (dd, J = 7.0, 1.5 Hz, 1H), 7.65 (td, J = 7.0, 1.5 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.09 (s, 1H), 7.03 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2, 175.6, 160.0, 137.8, 134.6, 133.8, 133.4, 133.1, 131.9, 131.8, 131.1, 129.6, 129.1, 129.0, 127.3, 127.2, 126.9, 126.4, 124.7, 114.3, 55.7, 21.5; HRMS (ES^+, Ar) calcd for $C_{26}H_{20}NO_3$ (MH^+) 394.1438, found 394.1433.

1-(4-Methoxyphenyl)-3-phenyl-1*H*-benzo[*f*]indole-4,9-dione (3b). Yellow solid; Yield 128 mg, 67%; mp 164-166 °C; IR (film, cm^{-1}) 3062 (w), 2931 (w), 2835 (w), 1659 (vs), 1592 (m), 1514 (s), 1437 (m), 1387 (m), 1265 (s), 1247 (s), 1169 (m), 1029 (m), 915 (s), 834 (m), 761 (m), 717 (m), 696 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, J = 7.0, 1.5 Hz, 1H), 8.07 (dd, J = 7.0, 1.5 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.67 (td, J = 7.0, 1.5 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.40 (d, J = 9.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.11 (s, 1H), 7.03 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 181.3, 175.6, 160.0, 134.5, 133.8, 133.4, 133.2, 132.6, 131.8, 131.2, 129.8, 129.2, 128.3, 128.0, 127.3, 127.2, 126.9, 126.4, 124.6, 114.4, 55.7; HRMS (ES^+, Ar) calcd for $C_{25}H_{17}NO_3Na$ (MNa^+) 402.1101, found 402.1100.

1,3-Bis(4-methoxyphenyl)-1*H*-benzo[*f*]indole-4,9-dione (3c). Orange Solid; Yield 96 mg, 47%; mp 178-180 °C; IR (film, cm^{-1}) 2923 (s), 2852 (m), 1655 (s), 1475 (m), 1248 (vs), 1030 (m), 744 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.0, 1.8 Hz, 1H), 8.07 (dd, J = 7.6, 1.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.64 (td, J = 8.0, 1.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.08 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 175.6, 160.0, 159.6, 134.6, 133.9, 133.4, 133.1, 131.9, 131.7, 130.9, 130.4, 127.3, 127.0, 126.9, 126.4, 124.9, 124.5, 114.4, 113.8, 55.8, 55.5; HRMS (ES^+, Ar) calcd for $C_{26}H_{19}NO_4Na$ (MNa^+) 432.1206, found 432.1205.

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-1*H*-benzo[*f*]indole-4,9-dione (3d). Yellow solid; Yield 117 mg, 56%; mp 173-175 °C; IR (film, cm^{-1}) 3065 (w), 2920 (w), 2838 (w), 1659 (vs), 1591 (m), 1513 (s), 1494 (m), 1266 (vs), 1248 (vs), 1169 (w), 1091 (w), 1031 (w), 915 (w), 834 (m), 736 (w), 715 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.5, 1.5 Hz, 1H), 8.06 (dd, J = 7.5, 1.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.63-7.69 (m, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 9.0 Hz, 2H), 7.09 (s, 1H), 7.02 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 175.5, 160.1, 134.4, 133.9, 133.7, 133.5, 133.3, 132.0, 131.7, 131.1, 131.0, 130.5, 128.5, 127.3, 126.8, 126.4, 125.9, 124.5, 114.4, 55.7; HRMS (ES^+, Ar) calcd for $C_{25}H_{16}ClNNaO_3$ (MNa^+) 436.0711, found 436.0710.

3-(4-Fluorophenyl)-1-(4-methoxyphenyl)-1*H*-benzo[*f*]indole-4,9-dione (3e). Yellow solid; Yield 71 mg, 35%; mp 145-147 °C; IR (film, cm^{-1}) 3069 (w), 2934 (w), 2839 (w), 1659 (vs), 1592 (m), 1549 (w), 1515 (s), 1506 (s), 1443 (m), 1416 (m), 1266 (vs), 1248 (vs), 1169 (m), 1160 (m), 1031 (m), 916 (m), 837 (m), 736 (m), 715 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.0, 2.0 Hz, 1H), 8.06 (dd, J = 6.5, 2.0 Hz, 1H), 7.73-7.64 (m, 4H), 7.39 (d, J = 8.5 Hz, 2H), 7.13 (t, J = 9.0 Hz, 2H), 7.08 (s, 1H), 7.03 (d, J 8.5 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 175.6, 162.7 (J = 246.0 Hz), 160.1, 134.5, 133.8, 133.5, 133.3, 131.9, 131.8, 131.0, 130.9 (d, J = 8.0 Hz), 128.6

(d, *J* = 3.0 Hz), 127.3, 126.9, 126.4, 126.1, 124.5, 115.2 (d, *J* = 21.0 Hz), 114.4, 55.8; HRMS (ES^+, Ar) calcd for $C_{25}H_{16}FNNaO_3$ (MNa^+) 420.1006, found 420.1007.

3-(Furan-2-yl)-1-(4-methoxyphenyl)-1*H*-benzo[*f*]indole-4,9-dione (3f). Yellow solid; Yield 64 mg, 35%; mp 190-192 °C; IR (film, cm^{-1}) 2924 (m), 2850 (w), 1658 (vs), 1592 (m), 1513 (s), 1488 (s), 1390 (m), 1267 (s), 1169 (w), 1030 (w), 923 (w), 834 (w), 716 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 3.5 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.46 (s, 1H), 7.41-7.43 (unresolved m, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.53 (t, *J* = 1.5 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.8, 175.4, 160.1, 147.7, 141.8, 134.3, 133.8, 133.4, 133.2, 131.8, 131.4, 129.7, 127.3, 126.9, 126.4, 122.9, 117.1, 114.4, 112.0, 111.1, 55.8; HRMS (ES^+, Ar) calcd for $C_{23}H_{15}NO_4Na$ (M^+) 392.0893, found 392.0900.

3-(4-Methoxyphenyl)-1-phenyl-1*H*-benzo[*f*]indole-4,9-dione (3g). Red solid; Yield 137 mg, 72%; mp 173-175 °C; IR (film, cm^{-1}) 2923 (m), 2850 (w), 1658 (vs), 1594 (m), 1467 (m), 1383 (m), 1265 (vs), 1249 (vs), 1179 (m), 1029 (m), 915 (m), 716 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.06 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.69-7.63 (m, 2H), 7.56-7.52 (m, 3H), 7.49-7.47 (m, 2H), 7.11 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 175.5, 159.6, 139.0, 134.5, 133.8, 133.4, 133.2, 131.6, 130.7, 130.4, 129.2 (× 2), 127.2, 126.9, 126.4, 126.2, 124.8, 124.7, 113.8, 55.5; HRMS (ES^+, Ar) calcd for $C_{25}H_{17}NNaO_3$ (MNa^+) 402.1101, found 402.1102.

1-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1*H*-benzo[*f*]indole-4,9-dione (3h). Orange solid; Yield 123 mg, 60%; mp 168-170 °C; IR (film, cm^{-1}) 2919 (vs), 2850 (m), 1656 (s), 1591 (w), 1544 (w), 1505 (m), 1467 (w), 1381 (w), 1246 (s), 914 (m), 838 (m), 715 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 6.5, 1.5 Hz, 1H), 8.05 (dd, *J* = 6.5, 1.5 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 2H), 7.70-7.63 (m, 2H), 7.46 (dd, *J* = 8.5, 4.5 Hz, 2H), 7.22 (t, *J* = 8.5 Hz, 2H), 7.07 (s, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2, 175.6, 163.7, 160.70 (d, *J* = 266.3 Hz), 135.0 (d, *J* = 3.8 Hz), 134.5, 133.7, 133.5, 133.2, 131.7, 130.6, 130.4, 128.1 (d, *J* = 8.8 Hz), 127.3, 126.9, 126.3, 124.7, 124.6, 116.2 (d, *J* = 23.8 Hz), 113.8, 55.5; HRMS (ES^+, Ar) calcd for $C_{25}H_{17}FNO_3$ (MH^+) 398.1187, found 398.1185.

1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1*H*-benzo[*f*]indole-4,9-dione (3i). Orange solid; Yield 61 mg, 29%; mp 193-195 °C; IR (film, cm^{-1}) 2923 (w), 2854 (w), 1660 (vs), 1611 (w), 1591 (w), 1495 (m), 1419 (w), 1382 (w), 1278 (m), 1245 (s), 1182 (w), 1091 (w), 1031 (w), 915 (m), 833 (m), 714 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 6.6, 2.0 Hz, 1H), 8.05 (dd, J = 6.6, 2.0 Hz, 1H), 7.70-7.62 (m, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.50, 7.42 (ABq, J = 8.4 Hz, 2H), 7.06 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 175.6, 159.7, 137.5, 135.1, 134.5, 133.6, 133.5, 133.2, 131.6, 130.4, 129.4, 127.6, 127.5, 126.9, 126.4, 124.9, 124.6, 113.8, 55.5; HRMS (ES^+, Ar) calcd for $C_{25}H_{16}ClNNaO_3$ (MNa^+) 436.0711, found 436.0714.

1-(4-Bromophenyl)-3-(*p*-tolyl)-1*H*-benzo[*f*]indole-4,9-dione (3j). Yellow solid; Yield 76 mg, 34%; mp 179-181 °C; IR (film, cm^{-1}) 2923 (s), 2851 (m), 1661 (vs), 1591 (w), 1493 (s), 1470 (m), 1278 (m), 1249 (m), 915 (m), 828 (w), 714 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.0, 2.0 Hz, 1H), 8.05 (dd, J = 7.0, 2.0 Hz, 1H), 7.69-7.63 (m, 2H), 7.66 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.08 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1, 175.6, 138.0, 137.9, 134.4, 133.6 (× 2), 133.2, 132.4, 131.6, 130.5, 129.3, 129.1 (× 2), 127.9, 127.7, 126.9, 126.4, 125.1, 123.1, 21.5; HRMS (ES^+, Ar) calcd for $C_{25}H_{16}BrNO_2Na$ (MNa^+) 464.0257, found 464.0254.

1-(3-Bromophenyl)-3-(*p*-tolyl)-1H-benzo[*f*]indole-4,9-dione (3k). Yellow solid; Yield 103 mg, 46%; mp 153-155 °C; IR (film, cm^{-1}) 3069 (w), 2923 (s), 2853 (m), 1661 (vs), 1593 (s), 1486 (vs), 1384 (m), 1273 (vs), 1171 (m), 1003 (m), 919 (s), 786 (m), 719 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (dd, J = 7.3, 1.8 Hz, 1H), 8.09 (dd, J = 7.3, 1.8 Hz, 1H), 7.72-7.66 (m, 4H), 7.63 (d, J = 8.0 Hz, 2H), 7.46 (dt, J = 8.0, 1.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.11 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0, 175.4, 140.1, 138.0, 134.4, 133.6, 133.2, 132.3, 131.7, 130.5, 130.4, 129.4, 129.2, 129.1, 129.0, 127.7, 126.9, 126.4, 125.2, 125.0, 122.5, 21.5; HRMS (ES^+, Ar) calcd for $C_{25}H_{16}BrNNaO_2$ (MNa^+) 464.0257, found 464.0252.

1,3-Di-*p*-tolyl-1*H*-benzo[*f*]indole-4,9-dione (3l). Orange solid; Yield 79 mg, 42%; mp 134-136 °C; IR (film, cm^{-1}) 3028 (w), 2922 (m), 2862 (w), 1660 (vs), 1593 (m), 1517 (m), 1483 (s), 1266 (s), 1171 (w), 998 (w), 916 (s), 807 (m), 719 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, J = 7.6, 1.8 Hz, 1H), 8.07 (dd, J = 7.6, 1.8 Hz, 1H), 7.69-7.62

(m, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.37, 7.33 (ABq, *J* = 8.4 Hz, 4H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 2.47 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 175.5, 139.2, 137.8, 136.5, 134.5, 133.8, 133.4, 133.1, 131.7, 130.9, 129.8, 129.6, 129.1, 129.0, 127.3, 126.8, 126.3, 125.9, 124.7, 21.5, 21.4; HRMS (ES^+, Ar) calcd for $C_{26}H_{19}NO_2Na$ (MNa^+) 400.1308, found 400.1307.

1-Butyl-3-(4-chlorophenyl)-1*H*-benzo[*f*]indole-4,9-dione (3m). Yellow solid; Yield 81 mg, 44%; mp 90-92 °C; IR (film, cm^{-1}) 3068 (w), 2960 (s), 2931 (m), 2873 (m), 1654 (vs), 1592 (s), 1546 (m), 1488 (s), 1454 (s), 1411 (s), 1380 (s), 1275 (vs), 1214 (s), 1091 (s), 1013 (m), 930 (s), 836 (m), 791 (m), 718 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.09 (m, 2H), 7.66-7.59 (m, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.97 (s, 1H), 4.44 (t, *J* = 7.4 Hz, 2H), 1.85 (quintet, *J* = 7.4 Hz, 2H), 1.41 (sextet, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.8, 176.3, 134.4, 133.6, 133.5, 133.3, 133.0, 131.3, 131.1, 130.3, 129.9, 128.3, 126.7, 126.2, 125.2, 123.9, 49.7, 33.0, 20.0, 13.8; HRMS (ES^+, Ar) calcd for $C_{22}H_{18}ClNO_2Na$ (MNa^+) 386.0918, found 386.0918.

General Procedure for the Synthesis of Pyrrolonaphthoquinones 5a-j. To a stirred solution of 2-aminonaphthoquinone **1** (0.18 mmol, 1.0 equiv) in THF (3 mL) under N_2, was added base KOH (20 mg, 0.36 mmol, 2 equiv) and the reaction mixture was stirred at rt. After 5 min, MBH acetate **4** (0.36 mmol, 2.0 equiv) dissolved in THF (2 mL) was added dropwise and continued stirring till the completion of the reaction (monitored by TLC). The solvent was evaporated *in vacuo* and water (5 mL) was added to the crude reaction mixture. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was further purified by neutral alumina column chromatography by eluting with 5-15% EtOAc-petroleum ether (gradient elution) to afford 2,3-disubstituted pyrrolonaphthoquinones **5**.

Ethyl 2-(1-(4-methoxyphenyl)-4,9-dioxo-3-(*p*-tolyl)-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5a). Yellow solid; Yield 38 mg, 44%; mp 136-138 °C; IR (film, cm^{-1}) 2919 (m), 2849 (w), 1735 (s), 1659 (vs), 1593 (m), 1511 (vs), 1486 (m), 1472 (m), 1444 (m), 1250 (s), 1208 (m), 1184 (m), 1030 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.2, 2.4 Hz, 1H), 8.02 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.65-7.59 (m, 2H), 7.38 (d, *J* = 7.6

Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 3.45 (s, 2H), 2.42 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 175.3, 169.7, 160.3, 137.7, 135.0, 134.3, 133.9, 133.3, 133.1, 131.9, 130.1, 129.9, 129.6, 129.0, 128.7, 126.6, 126.3, 125.9, 124.8, 114.7, 61.5, 55.7, 31.0, 21.5, 14.2; HRMS (ES^+, Ar) calcd for $C_{30}H_{26}NO_5$ (MH^+) 480.1805, found 480.1806.

Ethyl 2-(3-(4-chlorophenyl)-1-(4-methoxyphenyl)-4,9-dioxo-4,9-dihydro-1H-benzo[*f*]indol-2-yl)acetate (5b). Yellow solid; Yield 20 mg, 22%; mp 147-149 °C; IR (film, cm^{-1}) 3065 (w), 2986 (w), 2936 (w), 1734 (s), 1660 (vs), 1592 (m), 1514 (s), 1250 (s), 1208 (s), 1095 (m), 1030 (m), 836 (m), 739 (m), 715 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.02 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.66-7.61 (m, 2H), 7.44-7.41 (unresolved m, 4H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.90 (s, 3H), 3.41 (s, 2H), 1.15 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2, 175.3, 169.6, 160.4, 135.0, 134.1, 134.0, 133.8, 133.4, 133.3, 132.0, 131.6, 131.2, 129.7, 128.7, 128.6, 126.7, 126.4, 124.6, 124.5, 114.8, 61.6, 55.7, 31.0, 14.2; HRMS (ES^+, Ar) calcd for $C_{29}H_{22}ClNO_5Na$ (MNa^+) 522.1079, found 522.1078.

Ethyl 2-(4,9-dioxo-1,3-di-*p*-tolyl-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5c). Red viscous liquid; Yield 40 mg, 48%; IR (film, cm^{-1}) 3065 (w), 2980 (w), 2924 (w), 1735 (s), 1659 (vs), 1594 (m), 1512 (m), 1486 (m), 1439 (m), 1326 (m), 1283 (m), 1208 (s), 1188 (s), 1158 (m), 1046 (m), 1012 (m), 998 (m), 824 (m), 740 (m), 715 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 6.0, 2.4 Hz, 1H), 8.03 (dd, *J* = 6.0, 2.4 Hz, 1H), 7.65-7.58 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 4H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.46 (s, 2H), 2.49 (s, 3H), 2.43 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 175.1, 169.6, 139.6, 137.6, 134.7 (× 2), 134.2, 133.7, 133.1, 133.0, 131.7, 130.1, 130.0, 129.5, 128.9, 127.3, 126.5, 126.2, 125.9, 124.7, 61.4, 31.0, 21.5, 14.1; HRMS (ES^+, Ar) calcd for $C_{30}H_{25}NO_4Na$ (MNa^+) 486.1676, found 486.1671.

Ethyl 2-(4,9-dioxo-3-phenyl-1-(*p*-tolyl)-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5d). Red viscous liquid; Yield 21 mg, 26%; IR (film, cm^{-1}) 2924 (s), 2851 (m), 1736 (s), 1661 (vs), 1594 (m), 1501 (m), 1440 (s), 1282 (m), 1211 (s), 1045 (m), 1024 (m),

726 (m), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 6.8, 2.4 Hz, 1H), 8.01 (dd, J = 6.8, 2.4 Hz, 1H), 7.64-7.57 (m, 2H), 7.49-7.36 (m, 5H), 7.33 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 4.01 (q, J = 7.2 Hz, 2H), 3.43 (s, 2H), 2.46 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 175.2, 169.6, 139.7, 134.8, 134.7, 134.2, 133.8, 133.3, 133.1, 132.7, 131.8, 130.2 (× 2), 128.3, 128.0, 127.3, 126.6, 126.3, 125.9, 124.7, 61.5, 31.0, 21.5, 14.2; HRMS (ES^+, Ar) calcd for $C_{29}H_{23}NO_4Na$ (MNa^+) 472.1519, found 472.1514.

Ethyl 2-(3-(furan-2-yl)-4,9-dioxo-1-phenyl-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5e). Red solid; Yield 13 mg, 17%; mp 177-179 °C; IR (film, cm^{-1}) 3070 (w), 2988 (w), 1734 (s), 1660 (s), 1593 (m), 1492 (s), 1465 (m), 1430 (m), 1227 (m), 1223 (w), 1186 (w), 1155 (m), 1027 (m), 1016 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, J = 7.5, 1.0 Hz, 1H), 7.99 (dd, J = 7.5, 1.0 Hz, 1H), 7.67 (td, J = 7.5, 1.0 Hz, 1H), 7.62 (td, J = 7.5, 1.0 Hz, 1H), 7.59-7.53 (m, 4H), 7.46 (d, J = 1.5 Hz, 1H), 7.36-7.38 (m, 2H), 6.56 (dd, J = 3.5, 1.5 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.75 (s, 2H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 175.0, 169.7, 147.4, 141.9, 137.0, 134.5, 134.2, 133.4, 133.1, 131.9, 129.9, 129.7, 127.7, 126.9, 126.3, 123.2, 115.4, 112.0, 111.6, 61.5, 32.4, 14.3; HRMS (ES^+, Ar) calcd for $C_{26}H_{19}NO_5K$ (MK^+) 464.0895, found 464.0899.

Ethyl 2-(4,9-dioxo-1-phenyl-3-(thiophen-2-yl)-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5f). Yellow solid; Yield 23 mg, 29%; mp 160-162 °C; IR (film, cm^{-1}) 3066 (w), 2979 (w), 2927 (w), 1735 (s), 1661 (vs), 1594 (m), 1497 (s), 1443 (m), 1273 (m), 1206 (s), 1007 (m), 697 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, J = 7.0, 1.5 Hz, 1H), 8.00 (dd, J = 7.0, 1.5 Hz, 1H), 7.67-7.61 (m, 2H), 7.61-7.54 (m, 3H), 7.44 (dd, J = 5.0, 1.0 Hz, 1H), 7.39 -7.36 (m, 2H), 7.26 (dd, J = 3.5, 1.0 Hz, 1H), 7.14 (dd, J = 5.0, 3.5 Hz, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.53 (s, 2H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.9, 175.2, 169.3, 137.2, 135.8, 134.2, 133.6, 133.5, 133.2, 132.9, 131.9, 129.8, 129.7, 128.9, 127.6, 127.1, 126.8, 126.7, 126.4, 125.1, 118.3, 61.7, 31.3, 14.3; HRMS (ES^+, Ar) calcd for $C_{26}H_{20}NO_4S$ (MH^+) 442.1108, found 442.1105.

Ethyl 2-(1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)-4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5g). Yellow solid; Yield 44 mg, 46%; mp 143-145 °C; IR (film, cm^{-1}) 3062 (w), 2985 (w), 2960 (w), 2937 (w), 2837 (w), 1734 (s), 1660 (vs),

1592 (m), 1514 (m), 1494 (vs), 1465 (s), 1436 (s), 1325 (m), 1250 (m), 1206 (m), 1141 (m), 1091 (m), 1045 (m), 1026 (s), 1004 (s), 736 (s), 709 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 6.2, 2.2 Hz, 1H), 8.00 (dd, J = 6.2, 2.2 Hz, 1H), 7.67 -7.60 (m, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 2.0 Hz, 1H), 7.03, 6.95 (ABq, J = 8.0 Hz, the lower half is further split into d, J = 2.0 Hz, 2H), 4.04 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.44 (s, 2H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 175.3, 169.7, 149.0, 148.6, 135.9, 135.8, 134.6, 134.2, 133.6, 133.5, 133.2, 131.7, 129.9, 129.1, 126.8, 126.3, 126.2, 124.9, 124.7, 122.6, 113.6, 111.0, 61.7, 56.0 (× 2), 31.1, 14.2; HRMS (ES^+, Ar) calcd for $C_{30}H_{24}ClNO_6Na$ (MNa^+) 552.1184, found 552.1184.

Ethyl 2-(1-(4-bromophenyl)-3-(3,4-dimethoxyphenyl)-4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5h). Yellow solid; Yield 52 mg, 51%; mp 148-149 °C; IR (film, cm^{-1}) 2919 (w), 1734 (m), 1659 (vs), 1592 (m), 1491 (s), 1436 (m), 1250 (m), 1207 (m), 1025 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 7.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.69-7.61 (m, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.05 (s, 1H), 7.04, 6.96 (ABq, J = 8.0 Hz, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.45 (s, 2H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 175.2, 169.6, 148.9, 148.6, 136.3, 134.4, 134.2, 133.5, 133.4, 133.1, 132.8, 131.6, 129.4, 126.7, 126.2, 126.1, 124.8, 124.7, 123.8, 122.6, 113.6, 111.0, 61.6, 56.0 (× 2), 31.0, 14.2; HRMS (ES^+, Ar) calcd for $C_{30}H_{24}BrNO_6Na$ (MNa^+) 596.0679, found 596.0681.

Ethyl 2-(1-(3-bromophenyl)-3-(3,4-dimethoxyphenyl)-4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5i). Red solid; Yield 65 mg, 63%; mp 171-173 °C; IR (film, cm^{-1}) 3066 (w), 2934 (w), 2834 (w), 1734 (s), 1660 (vs), 1592 (m), 1484 (s), 1323 (m), 1254 (s), 1206 (s), 1027 (m), 731 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, J = 6.5, 2.0 Hz, 1H), 8.01 (dd, J = 6.5, 2.0 Hz, 1H), 7.70 (dt, J = 8.0, 2.0 Hz, 1H), 7.67-7.61 (m, 2H), 7.55 (t, J = 2.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.35 (dt, J = 8.0, 2.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 7.05, 6.96 (ABq, J = 9.0 Hz, the lower half is further split into d, J = 2.0 Hz, 2H), 4.06 (q, J = 7.0 Hz, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.47, 3.41 (ABq, J = 17.4 Hz, 2H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 175.0, 169.6, 148.9, 148.6, 138.5, 134.4, 134.1, 133.5, 133.4, 133.1, 132.8, 131.6, 130.8, 130.7, 126.7, 126.6, 126.2, 126.1, 124.7, 124.6, 122.8, 122.6,

113.6, 111.0, 61.7, 56.0 (× 2), 31.1, 14.2; HRMS (ES^+, Ar) calcd for $C_{30}H_{24}BrNO_6Na$ (MNa^+) 596.0679, found 596.0678.

Ethyl 2-(1-(3-bromophenyl)-4,9-dioxo-3-(3,4,5-trimethoxyphenyl)-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)acetate (5j). Red solid; Yield 39 mg, 36%; mp 217-219 °C; IR (film, cm^{-1}) 3065 (w), 2933 (m), 2833 (w), 2834 (w), 1732 (s), 1661 (vs), 1588 (s), 1484 (vs), 1330 (m), 1244 (m), 1207 (s), 1127 (s), 1006 (s), 788 (m), 710 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.6, 2.0 Hz, 1H), 8.02 (dd, J = 7.6, 2.0 Hz, 1H), 7.71 (dt, J = 8.0, 2.0 Hz, 1H), 7.69-7.62 (m, 2H), 7.54 (t, J = 2.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.35 (dt, J = 8.0, 2.0 Hz, 1H), 6.75 (s, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 6H), 3.47, 3.43 (ABq, J = 17.2 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 175.2, 169.8, 153.0, 138.5, 137.9, 134.6, 134.2, 133.6, 133.5, 133.3, 133.0, 131.8, 130.9, 130.8, 127.7, 126.8, 126.6, 126.4, 124.7, 123.0, 107.5, 61.8, 61.1, 56.3, 31.3, 14.3; HRMS (ES^+, Ar) calcd for $C_{31}H_{27}BrNO_7$ (MH^+) 604.0965, found 604.0966.

General Procedure for the synthesis of furanonaphthoquinones 7a-h: To a stirred solution of lawsone **6** (26 mg, 0.15 mmol) and α-bromonitroalkene **2** (0.3 mmol, 2 equiv) in water (1 mL) were added NaOAc (15 mg, 0.18 mmol, 1.2 equiv) and tetrabutylammonium bromide (TBAB, 10 mg, 0.03 mmol, 20 mol%). The reaction mixture was heated at 70 ℃ for 7 h. After completion of the reaction, the crude product was isolated by filtration and washed with water. The product was further purified by recrystallization from EtOAc.

3-(4-Fluorophenyl)naphtho[2,3-*b*]furan-4,9-dione (7a) [27]. Yellow solid; Yield 38 mg, 87%; mp 226-228 ºC; IR (KBr, cm^{-1}) 3075 (w), 1684 (s), 1584 (w), 1424 (w), 1326 (m), 1295 (s), 808 (m), 708 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 5.2, 3.6 Hz, 1H), 8.18 (dd, J = 5.2, 3.6 Hz, 1H), 7.83 (s, 1H), 7.77 (td, J = 5.2, 3.6 Hz, 2H), 7.69 (dd, J = 8.2, 5.2 Hz, 2H), 7.16 (t, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.9, 174.0, 163.2 (d, J = 247.5 Hz), 154.0, 145.5, 134.3, 134.1, 133.9, 132.2, 130.9 (d, J = 8.8 Hz), 127.4, 127.0, 126.9, 126.8, 124.9, 115.7 (d, J = 22.5 Hz); HRMS (ES^+, Ar) calcd for $C_{18}H_{10}FO_3$ (MH^+) 293.0608, found 293.0605.

3-(4-Bromophenyl)naphtho[2,3-*b*]furan-4,9-dione (7b) [27]. Yellow solid; Yield 39 mg, 73%; mp 243-245 ºC; IR (KBr, cm^{-1}) 2922 (w), 1673 (s), 1586 (w), 1172 (s), 839 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 5.6, 3.2 Hz, 1H), 8.19 (dd, J = 5.6, 3.2 Hz, 1H), 7.86 (s, 1H), 7.77 (td, J = 5.6, 3.2 Hz, 2H), 7.58-7.62 (unresolved m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 174.0, 154.2, 145.6, 134.4, 134.1, 133.9, 132.2, 131.9, 130.7, 127.9, 127.4, 126.9, 126.8, 123.3; HRMS (ES^+, Ar) calcd for $C_{18}H_{10}BrO_3$ (MH^+) 352.9808, found 352.9808.

3-(4-(Methylthio)phenyl)naphtho[2,3-*b*]furan-4,9-dione (7c). Purple solid; Yield 27 mg, 56%; mp 206-208 ºC; IR (KBr, cm^{-1}) 3118 (m), 2926 (w), 1678 (s), 1528 (w), 1408 (w), 1374 (m), 1278 (s), 804 (m), 528 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 6.0, 3.2 Hz, 1H), 8.18 (dd, J = 6.0, 3.2 Hz, 1H), 7.84 (s, 1H), 7.75 (td, J = 6.0, 3.2 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 174.0, 154.1, 145.5, 139.9, 134.2, 134.0 (× 2), 132.3, 129.4, 127.4, 127.3, 127.1, 126.8, 126.4, 125.5, 15.8; HRMS (ES^+, Ar) calcd for $C_{19}H_{12}NaO_3S$ (MNa^+) 343.0399, found 343.0395.

3-(4-Methoxyphenyl)naphtho[2,3-*b*]furan-4,9-dione (7d) [27]. Red solid; Yield 37 mg, 82%; mp 233-235 °C; IR (KBr, cm^{-1}) 3126 (m), 2924 (w), 1678 (s), 1536 (w), 1498 (w), 1378 (m), 1256 (s), 824 (m); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.10 (dd, J = 5.6, 3.3 Hz, 2H), 7.88 (td, J = 5.6, 3.3 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.5, 173.2, 159.4, 153.4, 146.6, 134.2, 134.0, 133.5, 131.7, 130.1, 126.7, 126.4, 126.1, 126.0, 121.0, 113.7, 55.2; HRMS (ES^+, Ar) calcd for $C_{19}H_{13}O_4$ (MH^+) 305.0808, found 305.0806.

3-(3,4-Dimethoxyphenyl)naphtho[2,3-*b*]furan-4,9-dione (7e). Orange solid; Yield 34 mg, 67%; mp 173-175 °C; IR (KBr, cm^{-1}) 3116 (m), 2928 (w), 1662 (s), 1499 (w), 1388 (m), 1232 (s), 802 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 6.0, 3.2 Hz, 1H), 8.19 (dd, J = 6.0, 3.2 Hz, 1H), 7.85 (s, 1H), 7.76 td, J = 6.0, 3.2 Hz, 2H), 7.37 (d, J = 2.0 Hz, 1H), 7.27-7.24 (m, 1H), 6.95 (dd, J = 8.4, 2.0 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 174.0, 154.0, 149.8, 149.0, 145.2, 134.1, 134.0, 133.9, 132.2, 127.7, 127.4, 127.0, 126.7, 121.5, 121.4, 112.7, 111.3, 56.2, 56.1; HRMS (ES^+, Ar) calcd for $C_{20}H_{14}NaO_5$ (MNa^+) 357.0733, found 357.0736.

3-(2-Nitrophenyl)naphtho[2,3-*b*]furan-4,9-dione (7f). Yellow solid; Yield 38 mg, 80%; mp 242-244 °C; IR (KBr, cm^{-1}) 3132 (m), 2924 (w), 1676 (s), 1586 (s), 1524 (w), 1348 (m), 1196 (s), 794 (m); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.27 (t, J = 6.7 Hz, 1H), 8.12 (d, J = 6.7 Hz, 1H), 7.96 (d, J = 6.7 Hz, 1H), 7.82-7.93 (m, 3H), 7.77 (t, J = 7.2 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.6, 173.2, 152.6, 148.0, 147.3, 134.5, 134.4, 134.1, 133.1, 132.5, 131.9, 130.4, 126.5, 126.4, 125.0, 124.1, 122.5; HRMS (ES^+, Ar) calcd for $C_{18}H_9NNaO_5$ (MNa^+) 342.0373, found 342.0377.

3-(Thiophen-2-yl)naphtho[2,3-*b*]furan-4,9-dione (7g). Orange solid; Yield 32 mg, 75%; mp 175-177 °C; IR (KBr, cm^{-1}) 3120 (m), 2920 (w), 1670 (s), 1374 (s), 1248 (m), 1194 (w), 716 (m); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.05-8.12 (unresolved m, 2H), 7.82-7.90 (unresolved m, 3H), 7.60-7.65 (unresolved m, 1H), 7.15-7.20 (unresolved m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.2, 173.0, 153.4, 146.4, 134.2, 134.1, 133.2, 131.6, 129.6, 128.5, 127.6, 127.0, 126.7, 126.0, 125.3, 119.9; HRMS (ES^+, Ar) calcd for $C_{16}H_9O_3S$ (MH^+) 281.0267, found 281.0266.

3-(Naphthalen-1-yl)naphtho[2,3-*b*]furan-4,9-dione (7h). Yellow solid; Yield 45 mg, 93%; mp 204-206 °C; IR (KBr, cm^{-1}) 3146 (m), 2924 (w), 1670 (s), 1400 (s), 1208 (m), 716 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 7.2, 1.2 Hz, 1H), 8.05 (dd, J = 7.2, 1.2 Hz, 1H), 7.98-7.92 (m, 2H), 7.87 (s, 1H), 7.79-7.69 (m, 3H), 7.58-7.50 (m, 3H), 7.44 (td, J = 7.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 174.1, 153.4, 147.1, 134.2, 133.9, 133.8, 133.7, 132.5, 132.2, 129.6, 128.9, 128.7, 128.2, 127.3, 126.9, 126.6, 126.3, 125.4, 125.3, 124.9; HRMS (ES^+, Ar) calcd for $C_{22}H_{13}O_3$ (MH^+) 325.0859, found 325.0860.

3-(Benzo[*d*][1,3]dioxol-4-yl)naphtho[2,3-*b*]furan-4,9-dione (7i). Orange solid; Yield 36 mg, 74%; mp 243-245 °C; IR (KBr, cm-1) ν: 3132 (m), 2922 (w), 1674 (s), 1490 (w), 1400 (s), 1240 (s), 928 (m), 710 (m); ^{1}H NMR (400 MHz, CDCl3) δ 8.27-8.15 (m, 2H), 7.77 (dd, J = 11.8 and 8.5 Hz, 3H), 7.29-7.13 (m, 2H), 6.89 (d, J = 7.9 Hz, 1H), 6.03 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.9, 174.1, 154.0, 148.4, 148.0, 145.4, 134.3, 134.1, 134.0, 132.3, 127.7, 127.5, 127.1, 126.8, 122.9, 122.6, 109.7, 108.6, 101.9.

General procedure for the synthesis of furanonaphthoquinones 8a-m. A dry reaction vial containing 2-hydroxynaphthoquinone **6** (35 mg, 0.2 mmol), Cs_2CO_3 (33 mg, 0.1 mmol, 0.5 equiv) and MBH acetate **4** (0.2 mmol, 1 equiv) in THF (2 mL) was stirred under microwave at 40 ^oC. After completion of the reaction (monitored by TLC), the solvent was evaporated *in vacuo*. The crude residue was directly purified by neutral alumina column chromatography using EtOAc-petroleum ether (5-10% pet ether: ethyl acetate).

Ethyl 2-(4,9-dioxo-3-phenyl-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8a). Yellow solid; Yield 35 mg, 48%; mp 126-128 ^oC; IR (film, cm^{-1}) 3064 (w), 2982 (w), 1739 (s), 1674 (vs), 1593 (m), 1543 (m), 1373 (m), 1204 (s), 978 (m), 718 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.9 Hz, 1H), 8.12 (d, J = 8.9 Hz, 1H), 7.76-7.71 (m, 2H), 7.50-7.43 (m, 5H), 4.20 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 173.8, 168.2, 152.4, 152.3, 134.1, 133.9, 133.8, 132.4, 129.9, 129.2, 128.9, 128.6, 128.3, 127.2, 126.9, 124.8, 62.1, 33.1, 14.3; HRMS (ES^+, Ar) calcd for $C_{22}H_{16}O_5Na$ (MNa^+) 383.0890, found 383.0889.

Ethyl 2-(4,9-dioxo-3-(*p*-tolyl)-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8b). Yellow solid; Yield 44 mg, 59%; mp 167-169 ^oC; IR (film, cm^{-1}) 2986 (w), 2924 (w), 2851 (w), 1739 (vs), 1674 (vs), 1594 (m), 1548 (m), 1510 (m), 1373 (s), 1262 (m), 1203 (s), 717 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.76-7.70 (m, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.82 (s, 2H), 2.42 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 173.6, 168.0, 152.0, 138.6, 133.9, 133.7, 133.6, 132.2, 129.6, 129.2, 128.2, 127.0, 126.7, 126.0, 124.6, 61.8, 32.9, 21.4, 14.1; HRMS (ES^+, Ar) calcd for $C_{23}H_{18}O_5Na$ (MNa^+) 397.1046, found 397.1046.

Ethyl 2-(6-methoxy-4,9-dioxo-3-(*p*-tolyl)-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8c). Yellow solid; Yield 32 mg, 40%; mp 137-139 ^oC; IR (film, cm^{-1}) 2981 (m), 2925 (m), 2849 (w), 1740 (vs), 1670 (vs), 1596 (vs), 1545 (s), 1511 (m), 1372 (s), 1337 (m), 1275 (s), 1248 (s), 1191 (s), 1161 (m), 1030 (s), 1005 (s), 987 (s), 748 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.37 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 8.5 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.80 (s, 2H), 2.41 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

180.7, 173.2, 168.3, 164.4, 152.6, 151.6, 138.7, 136.1, 129.7, 129.3, 128.0, 126.2, 125.6, 124.6, 119.5, 111.5, 62.0, 56.0, 33.0, 21.5, 14.3; HRMS (ES^+, Ar) calcd for $C_{24}H_{20}NaO_6$ (MNa^+) 427.1152, found 427.1149.

Ethyl 2-(3-(4-methoxyphenyl)-4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8d). Yellow solid; Yield 51 mg, 65%; mp 144-146 ^oC; IR (film, cm^{-1}) 3054 (s), 2985 (s), 2935 (m), 1738 (s), 1673 (s), 1264 (s), 1029 (s), 997 (s), 742 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.70 - 7.75 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.0 (d, *J* = 8.8 Hz, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.9, 173.8, 168.3, 160.0, 152.2, 152.1, 134.1, 133.9, 133.8, 132.3, 131.1, 128.3, 127.2, 126.8, 124.6, 121.2, 114.1, 62.0, 55.5, 33.1, 14.3; HRMS (ES^+, Ar) calcd for $C_{23}H_{18}NaO_6$ (MNa^+) 413.0996, found 413.0993.

Ethyl 2-(3-(4-chlorophenyl)-4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8e). Yellow solid; Yield 33 mg, 42%; mp 165-167 ^oC; IR (film, cm^{-1}) 3062 (w), 2981 (m), 2926 (m), 1730 (s), 1679 (m), 1486 (m), 1371 (m), 1262 (s), 1199 (s), 997 (m), 978 (m), 733 (s), 717 (s); ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.22 (d, *J* = 8.9 Hz, 1H), 8.11 (d, *J* = 8.9 Hz, 1H), 7.78-7.72 (m, 2H), 7.42-7.47 (unresolved m, 4H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 180.8, 173.7, 168.0, 152.4, 152.3, 135.0, 134.2, 134.1, 133.7, 132.3, 131.3, 128.9, 128.1, 127.7, 127.2, 126.9, 123.7, 62.2, 33.0, 14.3; HRMS (ES^+, Ar) calcd for $C_{22}H_{15}ClNaO_5$ (MNa^+) 417.0500, found 417.0506.

Ethyl 2-(3-(3,4-dimethoxyphenyl)-4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8f). Orange solid; Yield 48 mg, 58%; mp 129-131^oC; IR (film, cm^{-1}) 3069 (w), 2937 (m), 2838 (w), 1739 (vs), 1674 (vs), 1595 (m), 1544 (m), 1515 (vs), 1465 (m), 1373 (s), 1256 (m), 1027 (s), 989 (s), 719 (m); ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.22 (d, *J* = 8.9 Hz, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 7.79-7.69 (m, 2H), 7.11-7.03 (m, 2H), 6.96 (d, *J* = 8.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.84 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 180.8, 173.8, 168.4, 152.2 (× 2), 149.6, 148.9, 134.1, 133.9, 133.8, 132.3, 128.3, 127.2, 126.8, 124.8, 122.4, 121.5, 113.4, 111.2, 62.1, 56.2, 56.1, 33.2, 14.3; HRMS (ES^+, Ar) calcd for $C_{24}H_{20}O_7Na$ (MNa^+) 443.1101, found 443.1105.

Ethyl 2-(3-(furan-2-yl)-4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8g). Red solid; Yield 31 mg, 44%; mp 146-148 ^{o}C; IR (film, cm^{-1}) 2991 (w), 1726 (s), 1678 (s), 1229 (m), 1189 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23-8.19 (m, 2H), 7.78-7.73 (m, 2H), 7.63 (d, J = 3.5 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 6.54 (dd, J = 3.5, 1.7 Hz, 1H), 4.22 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.3, 173.6, 168.3, 152.2, 151.9, 144.6, 142.8, 134.2, 133.9, 133.7, 132.0, 127.4, 126.8, 126.5, 115.0, 113.2, 111.9, 61.9, 35.0, 14.3; HRMS (ES$^+$, Ar) calcd for $C_{20}H_{15}O_6$ (MH^+) 351.0863, found 351.0865.

Ethyl 2-(3-(furan-2-yl)-6-methoxy-4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8h). Orange solid; Yield 32 mg, 44%; mp 161-163 ^{o}C; IR (film, cm^{-1}) 2928 (w), 1739 (s), 1671 (vs), 1595 (s), 1368 (m), 1274 (m), 1245 (s), 1019 (s), 747 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.6 Hz, 1H), 7.68-7.66 (unresolved m, 1H), 7.60 (d, J = 3.2 Hz, 1H), 7.50-7.48 (unresolved m, 1H), 7.19 (dd, J = 8.6, 3.2 Hz, 1H), 6.58-6.51 (unresolved m, 1H), 4.21 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 173.0, 168.4, 164.6, 152.7, 151.3, 144.8, 142.8, 136.1, 129.3, 126.2, 125.3, 119.6, 114.9, 113.0, 111.8 (× 2), 61.8, 56.1, 34.9, 14.3; HRMS (ES$^+$, Ar) calcd for $C_{21}H_{16}O_7Na$ (MNa^+) 403.0788, found 403.0789.

Ethyl 2-(4,9-dioxo-3-(thiophen-2-yl)-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8i). Yellow solid; Yield 16 mg, 22%; mp 131-133 ^{o}C; IR (film, cm^{-1}) 3106 (w), 2981 (w), 1739 (s), 1675 (vs), 1592 (m), 1552 (m), 1371 (m), 1225 (m), 1205 (s), 715 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.78-7.69 (m, 2H), 7.48-7.41 (m, 2H), 7.15 (dd, J = 5.1, 3.6 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.96 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 173.7, 167.8, 152.8, 152.2, 134.2, 134.0, 133.7, 132.1, 129.7, 129.2, 127.9, 127.5, 127.3 (× 2), 126.8, 118.2, 62.1, 33.6, 14.3; HRMS (ES$^+$, Ar) calcd for $C_{20}H_{15}O_5S$ (MH^+) 367.0635, found 367.0633.

Ethyl 2-(4,9-dioxo-3-(3,4,5-trimethoxyphenyl)-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8j). Brown solid; Yield 52 mg, 58%; mp 173-175 ^{o}C; IR (film, cm^{-1}) 2925 (s), 2851 (m), 1737 (s), 1675 (vs), 1584 (m), 1508 (m), 1375 (m), 1126 (vs), 992 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.78-

7.72 (m, 2H), 6.77 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 6H), 3.85 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.8, 173.8, 168.4, 153.3, 152.3, 152.2, 138.5, 134.2, 134.0, 133.8, 132.3, 128.2, 127.3, 126.9, 125.0, 124.4, 107.3, 62.1, 61.1, 56.4, 33.4, 14.3; HRMS (ES^+, Ar) calcd for $C_{25}H_{22}O_8Na$ (MNa^+) 473.1207, found 473.1202.

Ethyl 2-(3-(naphthalen-1-yl)-4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8k). Yellow solid; Yield 25 mg, 30%; mp 139-141 ^{o}C; IR (film, cm^{-1}) 3059 (m), 2983 (m), 2933 (m), 1739 (vs), 1675 (vs), 1595 (s), 1547 (vs), 1369 (vs), 1206 (vs), 991 (s), 780 (s), 735 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.0 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.75 (td, *J* = 7.7, 1.2 Hz, 1H), 7.69 (td, *J* = 7.7, 1.2 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.59-7.47 (m, 3H), 7.47-7.38 (m, 1H), 4.17-4.03 (m, 2H), 3.70, 3.66 (ABq, *J* = 17.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); Confirmed by ^{1}H-^{1}H COSY experiment; ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 173.9, 167.8, 153.6, 152.4, 134.1, 133.9, 133.8, 133.6, 132.5, 132.3, 130.0, 129.6, 128.7, 128.2, 127.2, 127.0, 126.9, 126.7, 126.4, 125.4 (× 2), 122.4, 61.9, 33.0, 14.2; HRMS (ES^+, Ar) calcd for $C_{26}H_{18}O_5Na$ (MNa^+) 433.1046, found 433.1049.

Ethyl 4-(naphthalen-1-yl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[g]chromene-2-carboxylate (9). Yellow solid; Yield 7 mg, 10%; mp 207-209 ^{o}C; IR (film, cm^{-1}) 2922 (vs), 2851 (s), 1740 (m), 1674 (m), 1263 (m), 738 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.4 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 1H), 7.92 (t, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.0 Hz, 1H), 7.30 (d, *J* = 7.0 Hz, 1H), 6.55 (d, *J* = 4.7 Hz, 1H), 5.67 (d, *J* = 4.7 Hz, 1H), 4.39-4.24 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); Confirmed by ^{1}H-^{1}H COSY experiment; ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.6, 177.9, 160.6, 151.6, 139.7, 139.2, 134.6, 134.1, 134.0, 131.9, 131.0, 130.5, 129.2, 128.5, 127.3, 127.2, 126.9, 126.6, 126.3, 125.9, 122.9, 121.3, 116.0, 62.2, 31.5, 14.3; HRMS (ES^+, Ar) calcd for $C_{26}H_{18}O_5Na$ (MNa^+) 433.1046, found 433.1048.

Ethyl 2-(3-cyclohexyl-4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8l). Yellow solid; Yield 29 mg, 40%; mp 100-102 ^{o}C; IR (film, cm^{-1}) 2929 (s), 2855 (m), 1743 (vs), 1673 (vs), 1538 (m), 1372 (m), 1205 (s), 1028 (m), 983 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.15 (m, 2H), 7.77-7.69 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.88 (s,

2H), 2.85 (tt, *J* = 12.2, 3.4 Hz, 1H), 1.97-1.81 (m, 4H), 1.80-1.68 (m, 4H), 1.43-1.35 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 173.7, 168.2, 152.5, 150.9, 133.9, 133.8, 133.7, 132.2, 129.5, 129.0, 127.2, 126.7, 61.9, 35.4, 33.7, 31.1, 29.9, 26.9, 25.9, 14.3; HRMS (ES^+, Ar) calcd for $C_{22}H_{23}O_5$ (MH^+) 367.1540, found 367.1543.

(*E*)-ethyl 2-(4,9-dioxo-3-styryl-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)acetate (8m). Brown solid; Yield 16 mg, 21%; mp 123-125 ^{o}C; IR (film, cm^{-1}) 2924 (vs), 2855 (s), 1739 (s), 1673 (s), 1594 (m), 1543 (m), 1465 (m), 1370 (m), 1265 (s), 1206 (s), 1024 (m), 990 (m), 739 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.7, 4.2 Hz, 2H), 7.74 (td, *J* = 8.7, 4.2 Hz, 2H), 7.54 (d, *J* = 7.4 Hz, 2H), 7.43-7.33 (m, 3H), 7.33-7.23 (m, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 173.6, 167.8, 152.1, 137.0, 135.2, 134.1, 133.9, 133.7, 132.3, 128.9, 128.5, 128.3, 127.2, 127.0, 126.8, 122.1, 116.1, 62.2, 34.0, 14.3; HRMS (ES+, Ar) calcd for $C_{24}H_{18}O_5Na$ (MNa^+) 409.1046, found 409.1041.

Biological assays: Compounds (0.01-27.32 μM) were tested for cytotoxic activity in cell culture *in vitro* using several human cancer and non-cancer cell lines. The human cancer cell lines used in this work were obtained from the National Cancer Institute (Bethesda, MD, USA), and the mouse fibroblast cell line (L929) was purchased from Rio de Janeiro Cell Bank (Rio de Janeiro, Brazil). The cells were maintained in RPMI 1640 (cancer cell lines) and DMEM (L929 cell line) medium supplemented with 10% (cancer and L929 cells) fetal bovine serum, 2 mM glutamine, 100 U mL^{-1} penicillin, 100 μg mL^{-1} streptomycin at 37 °C with 5% CO_2). Peripheral blood mononuclear cells (PBMC) were isolated from heparinized blood from healthy, non-smoker donors who had not taken any drugs for at least 15 days prior to sampling by a standard method of density-gradient centrifugation over Histopaque-1077 (Sigma-Aldrich Co. St). PBMC were cultivated in a complete RPMI 1640 medium as described above, but supplemented with 20% fetal bovine serum. The cells were plated in 96-well test plates in the following densities: 0.7×10^5 (HCT-116 and MX-1), 0.6×10^5 (SF-295, NCI-H460 and OVCAR-8), 0.1×10^6 (PC-3), 0.3×10^6 (HL-60 and JURKAT), 0.1×10^6 (L929) and 0.1×10^5 (PBMC). For cultured PBMC, phytohemagglutinin (2%) was added at the beginning of culture. The samples were incubated for 72 h in a concentration range of 0.04-5 μg/mL. The cell viability was determined by reduction of

the yellow dye 3-(4,5-dimethyl-2-thiazol)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) to a purple formazan product as described by Mosmann [47]. Doxorubicin (0.001-1.10 µM) was used as the positive control, and negative control groups received the same amount of vehicle (DMSO). 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. Three hours later, the MTT formazan product was dissolved in DMSO (150 µL) and the absorbance was measured using a multiplate reader (Spectra Count, Packard, Ontario, Canada). The influence of the compound on cell toxicity was quantified as the percentage of control absorbance of the reduced dye at 550 nm. The experiments were analyzed using averages and the corresponding confidence intervals based on the non-linear regression generated using GraphPad Prism. Each sample was tested in triplicate in at least three independent experiments. An intensity scale was used to evaluate the cytotoxic potential of the tested samples. All cells were mycoplasma-free.

Measurements of nitrite/nitrate production: The production of nitrate/nitrite as a result of nitric oxide (NO) release was measured according to the procedure reported by Green *et al*. [48]. After cell treatments (24 h), 100 µL of the cell culture supernatant was added to 100 µL of the Griess reagent (1% sulfanilamide in 1% H_3PO_4/0.1% *N*-(1-naphthyl)-ethylenediaminedihydrochloride/1% H_3PO_4/distilled water, 1:1:1:1), and the mixture was incubated at room temperature for 10 min. A standard curve was prepared with several concentrations of $NaNO_2$ (ranging from 0.75 to 100 µM) under the same conditions. Blanks were prepared by adding 100 µL of the Griess reagent to 100 µL of the culture medium. The absorbance was measured using a multiplate reader (Spectra Count, Packard, Ontario, Canada) at 560 nm. The vehicle was used as negative control and H_2O_2 (10 µM) was used as positive control. Experiments were performed in three independent experiments.

Alkaline comet assay: Treated cells (24 h) and controls were trypsinized and kept on ice to inhibit repair. HCT-116 cells were processed in the alkaline version of the comet assay as described by Singh *et al.* [49] with minor modifications [50]. About 10^4 cells in 10 µL were mixed with 120 µL of low-melting point agarose (0.75%) and added to a slide precoated with normal-melting point agarose (1%). Lysis was performed overnight at pH 10.0. After that, cells were placed in an electrophoresis chamber (in an ice bath at

4 ºC), exposed to alkali (pH > 13) for 20 min. Electrophoresis was performed for 20 min at 25 V (0.86 V/cm) and 300 mA. All the above steps were carried out under yellow light or in the dark to prevent additional DNA damage. The slides were neutralized, dried with 100% ethanol, stained with ethidium bromide (20 µg/mL) and analyzed using a fluorescence microscope. Three hundred randomly selected cells (100 cells from each of the three replicate slides) were analyzed for each concentration of tested substance. Cells were scored visually according to tail length into five classes: (1) class 0: undamaged, without a tail; (2) class 1: with a tail shorter than the diameter of the head (nucleus); (3) class 2: with a tail length 1 - 2x the diameter of the head; (4) class 3: with a tail longer than 2x the diameter of the head; (5) class 4: comets with no heads. A value (damage index, DI) was assigned to each comet according to its class, using the formula: $DI = (0 \times n_0) + (1 \times n_1) + (2 \times n_2) + (3 \times n_3) + (4 \times n_4)$, where n = number of cells in each class analyzed. The damage index ranged from 0 (completely undamaged: 100 cells x 0) to 400 (with maximum damage: 100 cells x 4) [51]. The vehicle was used as negative control and doxorubicin (1 µM) was used as positive control. Experiments were performed in triplicate.

Acknowledgements

This research was funded by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 305385/2014-3, PVE 401193/2014-4, 477346/2013-8, PDS, Proc: 110818/2016-4, 305741/2017-9 and 404466/2016-8), FAPEMIG (APQ-02478-14), Programa Pesquisador Mineiro (PPM-00638-16) and Rede de Pesquisa e Inovação para Bioengenharia de Nanossistemas - RED-00282-16, INCT-Catálise, CAPES/DAAD 99999.008126/2015-01 and CAPES. Science and Engineering Research Board (SERB), India to INNN. CAS would like to thank DAIRIX Analytical Equipment, for kindly allowing the use of the Rigaku Mini XtaLAB diffractometer installed at the Institute of Physics of University of São Paulo (São Carlos) for demonstration. BCC and CP would like to thank Janaina S. A. M. Evangelista for her contribution in the studies related to compound 7i.

Supporting Information Available. Copies of NMR spectra for all the new compounds. This material is available free of charge via the internet at doi:.

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Research highlights

1. Pyrrole and furan fused quinones were obtained with potent antitumor activity.

2. α-Bromonitroalkenes and nitroallylic acetates were used for preparing new quinones.

3. Promising antitumor candidates for subsequent studies were discovered.

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