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A new approach for the synthesis of novel naphthoquinone chalcone hybrid compounds

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ABSTRACT

A facile and efficient synthesis of novel naphthoquinone-based chalcone hybrids (**7** and **24**) *via* the microwave-assisted one-pot three-component reactions of 2-substituted-1,4-naphthoquinones, *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA), and acetophenone derivatives has been reported. Whereas the synthesis of hybrids **7** proceeded *via* a condensation, 1,4-addition, rotation, elimination, and [1,3]-H shift sequence of steps, the synthesis of hybrids **24** were formed through a three-step sequence including condensation, 1,4-addition, and elimination reactions.

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Introduction

Chalcones (**1**) consisting of an α,β-unsaturated ketone and two aromatic rings are ubiquitous compounds in Nature (Fig 1) [1]. The α,β-unsaturated ketone functional group acts as a potential Michael acceptor for a variety of biological nucleophiles [2–5]. Due to their small structures and Michael acceptor features, naturally occurring or synthetic chalcones possess a variety of pharmacological properties, such as antibacterial [6,7], anticancer [8,9], antileishmanial [10], antifungal [11], antiviral [12,13], antitubercular [14], and antimalarial activities [15]. Moreover, due to the fact that different pharmacophores can correspond to different mechanisms of action [16], the hybrid compounds of chalcones with heterocycles, for example, anthraquinone – chalcone hybrids (**2**) [17], chalcone-coumarin hybrids (**3**) [18], chalcone-quinoxaline hybrids (**4**) [19], pyranochalcone derivatives (**5**) [20], chalcone-quinoline hybrids (**6**) [21], *β*-carboline – chalcone hybrids [22], indole – chalcone hybrids [23], and chalcone-dihydrobenzofuran hybrids (Fig. 1) [24–26], have attracted considerable interest. A number of literature methods for the synthesis of chalcone derivatives have been developed, for example, Claisen – Schmidt condensation [27], various cross couplings (Suzuki reaction [28], Heck reaction [29], Julia – Kocienski reaction [30], and Wittig reaction [31]), and a one-pot synthesis from alcohols [32].

On the other hand, naphthoquinones with a wide variety of structures based on the naphthalene skeleton possess a broad range of biological activities, for example, atovaquone (**8**) [33], NQ-1 (**9**) [34], vitamin K2 (MK-n) (**10**) [35], and lapachol (**11**) (Fig. 2) [36]. Various naphthoquinone derivatives have also been used as key intermediates for the construction of biologically active compounds with anticancer [37–39], leishmanicidal [40,41], anti-tumor [40,42], anti-inflammatory [43], antibacterial [44,45], antifungal [46,47], antitrypanosomal [48], antineoplastic [49], and apoptotic [50] activities. Although heterocycles containing chalcone and naphthoquinone moieties are of great interest, the hybridization of these moieties into a single molecule have rarely been studied [51]. In that respect, in continuation of our research on the synthesis of bioactive heterocyclic naphthoquinone compounds [52], and multicomponent reactions [52b-d], herein we report a facile and efficient method for the synthesis of novel naphthoquinone-based chalcone hybrids *via* the microwave (MW)-assisted one-pot three-component reactions of 2-substituted-1,4-naphthoquinones, *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA), and acetophenone derivatives under metal-free conditions.

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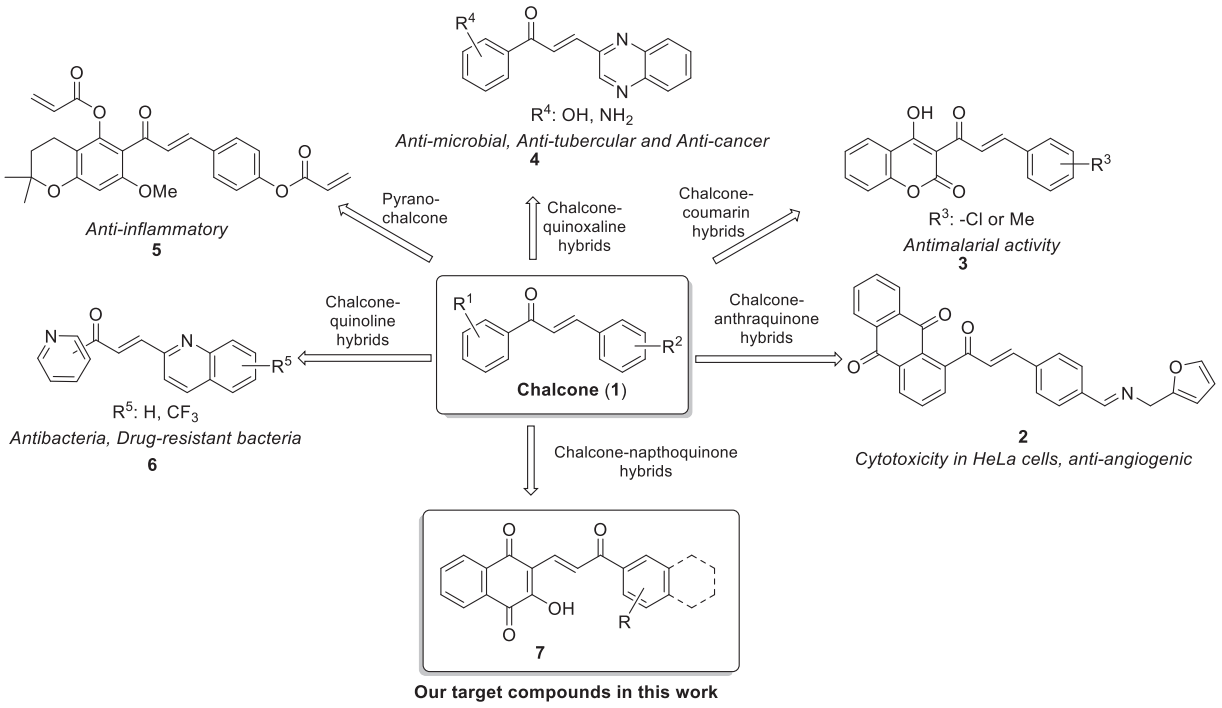


Fig. 1. Hybrid compounds of chalcones with heterocycles.

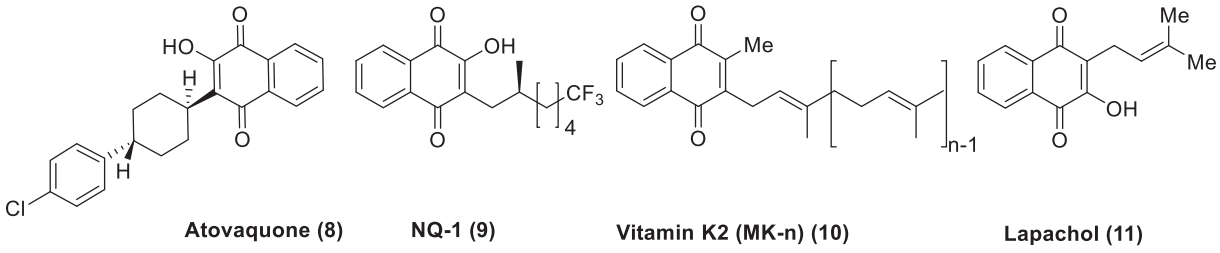


Fig. 2. Selected bioactive naphthoquinones.

Results and discussion

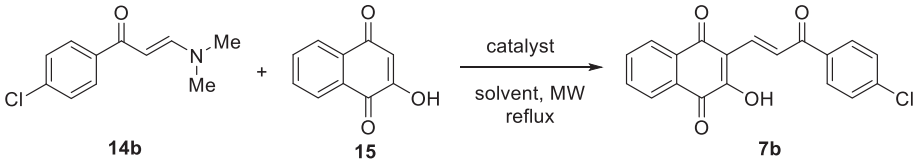
In order to obtain the optimal reaction conditions, the one-pot two-step synthesis of (*E*)-2-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)-3-hydroxynaphthalene-1,4-dione **7b** was studied as a model reaction. In the first step, the reaction between DMF-DMA **12** (1 mmol) and 1-(4-chlorophenyl)ethan-1-one **13b** (1 mmol) was carried out in different organic solvents (*t*-BuOH, *i*-PrOH, toluene, and CH_3CN) under MW irradiation at reflux without a catalyst. In all cases, the reaction proceeded smoothly and compound **13b** was completely converted into the enaminone intermediate **14b** in 60 min.

In the next step, the reaction of 2-hydroxy-1,4-naphthoquinone **15** (1 mmol) with enaminone **14b** was investigated under several different conditions (Table 1). The reactions carried out for 30 min in *t*-BuOH, *i*-PrOH, toluene or CH_3CN under catalyst-free conditions afforded trace amounts of the desired compound **7b** (Entries 1–4). In the cases using 10 mol% of glacial acetic acid, compound **7b** was obtained in 12–23% yield (Entries 5–8). Further increasing the catalyst loading to 20 mol% led to improved yields (Entries 9–12). Notably, when the reaction was performed in CH_3CN at reflux in the presence of 20 mol% of glacial AcOH, the yield increased dramatically to 83% (Entry 12). At the same time, the yield was not improved further when an increased amount of catalyst (30 mol%) was used (Entry 13). Thus, 20 mol% of glacial AcOH was chosen as an effective catalyst for the reaction between enaminone **14b** and 2-hydroxy-1,4-naphthoquinone **15**. Besides that, CH_3CN was chosen as the solvent for the one-pot two-step synthesis of compound **7b** starting from DMF-DMA, 1-(4-chlorophenyl) ethan-1-one **13b** and 2-hydroxy-1,4-naphthoquinone **15**.

Using the optimal conditions, the scope of the microwave-assisted three-component reaction was explored using various acetophenone derivatives **13a–m** containing electron-donating groups or electron-withdrawing groups at different positions (Scheme 1). Novel 3-alkylated-2-hydroxy-1,4-naphthoquinone derivatives **7a–m** were obtained in good yields (76–89%) under the optimized conditions. It worth noting that the electronic effect of the substituents in different positions on the aryl group did not affect the reaction outcome. The structures of all synthesized compounds **7a–m** were fully characterized by 1D and 2D NMR, and mass spectra. Taking a close look at the ^1H NMR spectrum of compound **7c**, two doublets at 8.50 and 8.39 ppm corresponding to H-2′ and H-1′, shared coupling constants of 15.6 Hz, confirming the double bond is in the *trans* configuration (see ESI).

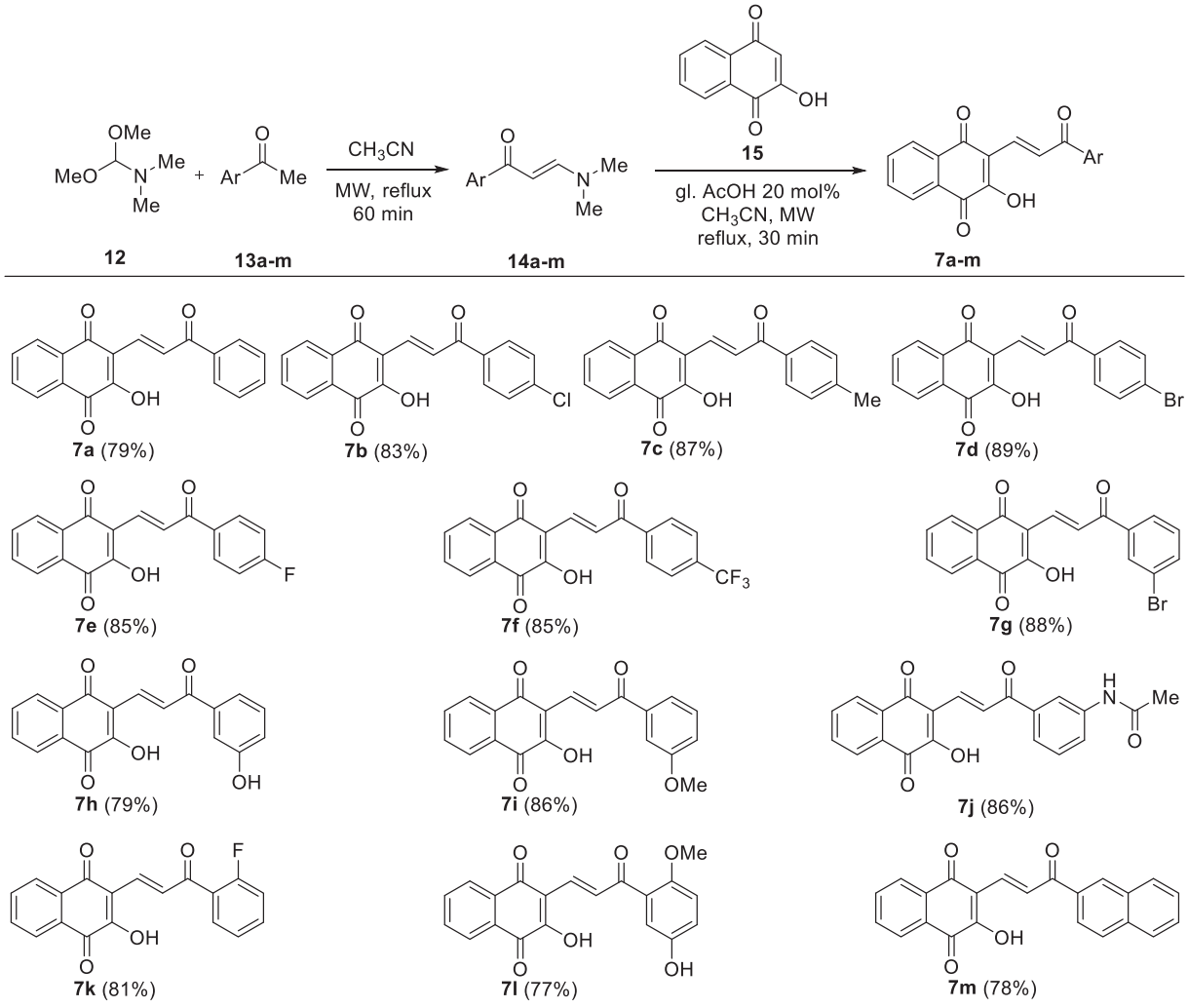
A plausible mechanism is outlined in Scheme 2. In the first step, the condensation between acetophenone derivatives **13** and DMF-DMA affords enaminone intermediates **14**. The 1,4-addition reaction of 1,4-naphthoquinone **15** with enaminones **14** gives intermediates **19**, which then rotates about the carbon–carbon single (sigma) bond. Intermediates **19** undergo elimination of the amine,

Table 1
Optimization of the reaction condition for the second step of the synthesis of compound **7b**.*

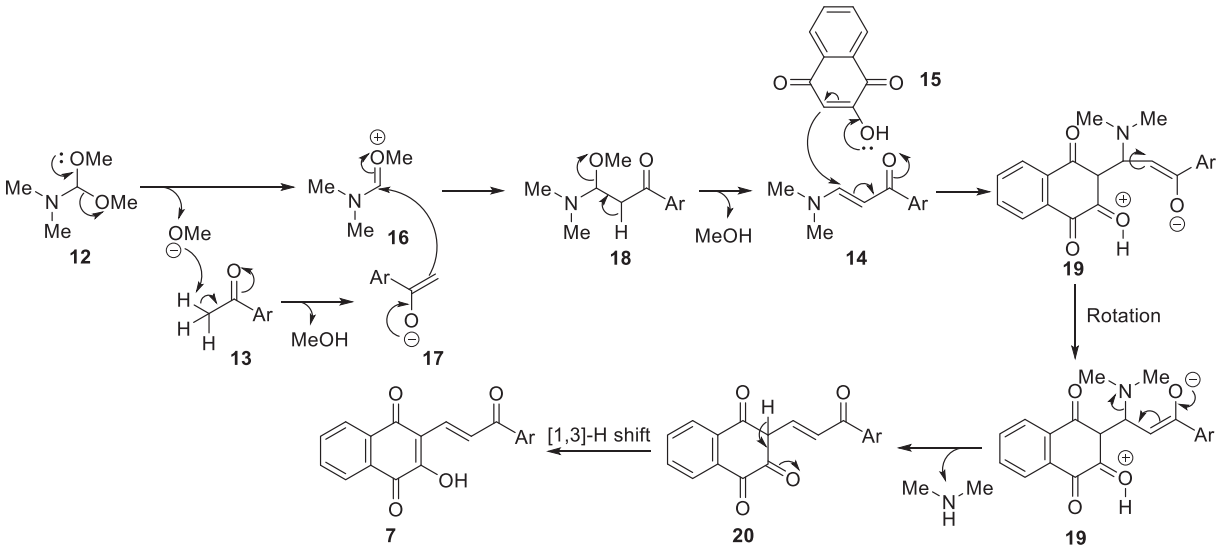


Entry	Solvent	Catalyst	Isolated yield **7b** (%)
1	*t*-BuOH	–	trace
2	*i*-PrOH	–	trace
3	Toluene	–	trace
4	CH_3CN	–	trace
5	*t*-BuOH	gl. AcOH (10 mol%)	14
6	*i*-PrOH	gl. AcOH (10 mol%)	18
7	Toluene	gl. AcOH (10 mol%)	12
8	CH_3CN	gl. AcOH (10 mol%)	23
9	*t*-BuOH	gl. AcOH (20 mol%)	45
10	*i*-PrOH	gl. AcOH (20 mol%)	52
11	Toluene	gl. AcOH (20 mol%)	13
12	**CH_3CN**	**gl. AcOH (20 mol%)**	**83**
13	CH_3CN	gl. AcOH (30 mol%)	83

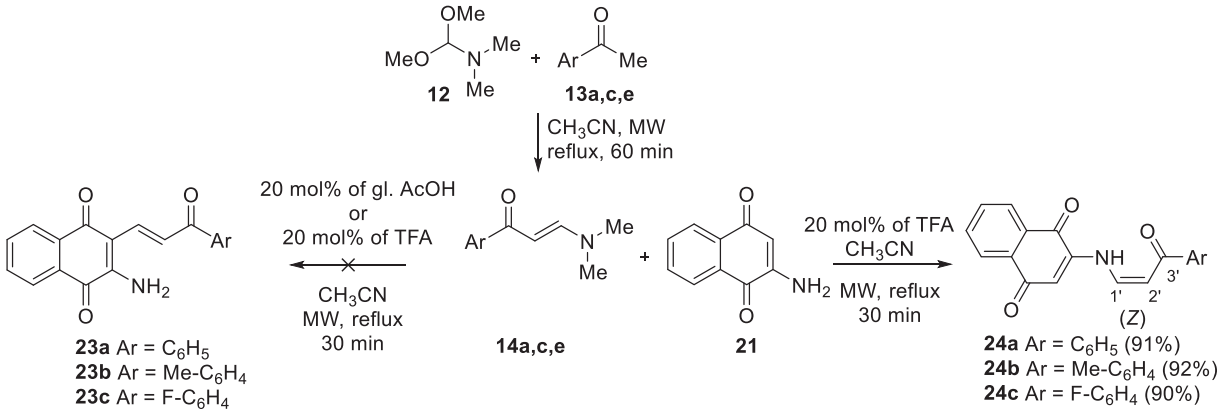
*All reactions were carried out on a 1 mmol scale in 3 mL solvent at reflux for 30 min under MW irradiation using an equimolar ratio of reactants.



Scheme 1. Synthesis of (*E*)-3-alkylated-2-hydroxy-naphthalene-1,4-diones **7a–m**.



Scheme 2. Plausible mechanism for the synthesis of 1,4-naphthoquinone based chalcone hybrids **7a-m**.

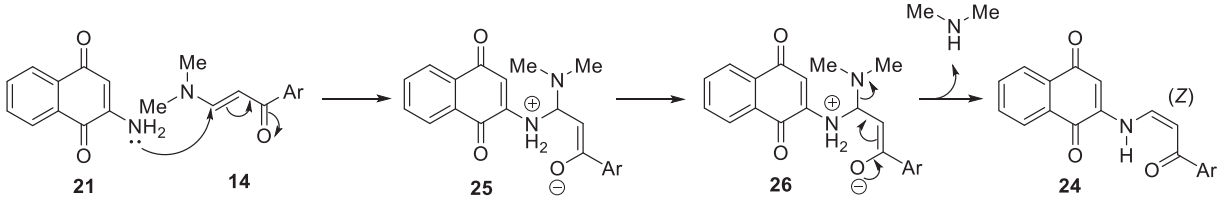


Scheme 3. One-pot two-step reactions of acetophenone derivatives, DMF-DMA and 2-amino-1,4-hydroxy-naphthoquinone.

followed by a [1,3]-hydrogen shift to afford the desired products (*E*)-3-alkylated-2-hydroxy-naphthlene-1,4-diones **7**.

In order to broaden the reaction scope, the one-pot two-step reactions of acetophenone derivatives, DMF-DMA **12**, and 2-amino-1,4-naphthoquinone **21** were carried out under the previously optimized conditions, however, no conversion was observed. Interestingly, replacing glacial acetic acid with trifluoroacetic acid (TFA) furnished (*Z*)-2-((3-oxo-3-(aryl)prop-1-en-1-yl)amino)naphthalene-1,4-dione derivatives **24** instead of compounds **23** (Scheme 3). Compounds **24** were synthesized in excellent yields (90–92%) and their structures were characterized by IR, ^{1}H, ^{13}C NMR, DEBPT and mass spectra. In the ^{1}H NMR spectra, the olefinic protons H-1′ and H-2′ showed a doublet of doublets (J = 8.4, 12.0 Hz) and a doublet (J = 8.4 Hz), respectively, confirming the *cis*-configuration of enaminones **24**. Furthermore, the N—H proton appeared as a doublet (J = 12.0 Hz) at 12.13–12.17 ppm indicating the presence of strong intramolecular hydrogen bonding in the *Z*-isomer of enaminones **24** (see ESI) [53].

Amines are good nucleophiles, readily attacking the carbon β to the carbonyl; therefore enaminones **14** undergo a 1,4-addition of 2-amino-1,4-naphthoquinone **21**, followed by elimination of dimethylamine to afford compounds **24** (Scheme 4) [54].



Scheme 4. Plausible mechanism for the formation of compound **24**.

Conclusion

We have developed a facile and efficient method to synthesize naphthoquinone-based chalcone hybrids **7a-m** *via* the reaction of 2-hydroxy-1,4-naphthoquinone, *N,N*-dimethylformamide dimethyl acetal, and acetophenone derivatives in CH_3CN at reflux in the presence of 20 mol% of glacial AcOH under MW irradiation for 30 min. In addition, the replacement of 2-hydroxy-1,4-naphthoquinone by 2-amino-1,4-naphthoquinone in the reaction with DMF-DMA and acetophenone using 20 mol% of TFA as a catalyst led to hybrids **24** in excellent yields. Plausible reaction mechanisms have also been described to explain the formation of these products. The naphthoquinone-based chalcone hybrid compounds could represent interesting new structures for the development of biologically active compounds as well as versatile synthons in organic synthesis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153337.

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