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Synthesis of novel 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-diones using a domino reaction

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ABSTRACT

A convenient one-pot multicomponent synthetic approach was developed for the synthesis of novel 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-diones using 2-amino-1,4-naphthoquinone, *N*-acylmethylpyridinium bromides and a variety of aromatic aldehydes.

Keywords: Benzo[*f*]indole-4,9-dione, domino reactions, 2-amino-1,4-naphthoquinone

Quinone moieties, especially nitrogen heterocyclic quinones, are important structural units in many natural and unnatural products that possess a wide range of biological activities.[1] Naturally occurring quinones are found in bacteria, fungi and plants, for example; benz[*g*]isoquinoline-5,10-dione **1** (Fig. 1), isolated from *Psychotria camponutans* and *Mitracarpus scaber*, exhibit antimalarial and trypanocidal activities as well as growth inhibition against multi-drug resistant pathogens.[2] 2-Azaanthraquinone **1** and its oxygenated derivatives **2**-**5** interfere with the activity of DNA topoisomerases and have attracted considerable attention in cancer chemotherapy as intercalating DNA binding agents.[3] Moreover, bostrycoidin **2** and 9-*O*-methylbostrycoidin **3** show antibiotic activity against the tubercle bacil and G^+ bacteria, respectively,[4] whilst tolypocladin **4** displays metal-chelating properties.[5] In conjunction with the azaanthraquinones, *p*-indolequinones are important nitrogen heterocyclic quinones, which possess interesting bioactivities such as anticancer activitity[6] as well as the ability to trigger drug release.[7] Examples include 3-ethoxycarbonylbenzoindole-4,9-diones **6**-**8**, which exhibit greater cytotoxic activity against a wide variety of human tumor cell lines than etoposide and doxorubicin.[1e,1f,8,9] Compound **8** (SME-6) induces G2/M cell cycle arrest and apoptosis in cultured human lung cancer cells and results in the inhibition of not only invasion or metastasis-associated protease activities, but also degradation and cellular invasion of the extracellular matrix and basement membrane.[1e,1f] Recently, 3-methyl-1*H*-benzo[*f*]indole-4,9-dione **9**[10] and 2-methyl-8-hydroxy-1*H*-benzo[*f*]indole-4,9-dione **10** (Utahmycin B),[11] isolated from *Goniothalamus tapis Miq* and *Streptomyces albus*, respectively, were found to be promising bioactive compounds.

Due to the broad biological relevance of *p*-indoloquinones, in particular benzo[*f*]indole-4,9-diones, possessing antineoplastic, antibacterial, virustatic, fungicidal, anti-inflammatory

and anticoagulant properties,[1e-g,8,10-12] considerable effort has been devoted to the development of new syntheses of this class of compounds. Reported methods are mostly based on metal-initiated oxidative-free radical reactions between 2-amino-1,4-naphthoquinones and *β*-dicarbonyl or carbonyl compounds,[13] the Diels-Alder reaction of indole-4,7-dione with conjugated dienes,[14] the multicomponent reaction of 2-bromo-1,4-naphthoquinone, primary amines and *β*-dicarbonyl compounds,[15] the transition metal-catalyzed reaction of 1,4-naphthoquinone derivatives[1k,16] and the one-pot sequential *C,N*-dialkylation of enaminones using 2,3-dichloronaphthoquinone.[17]

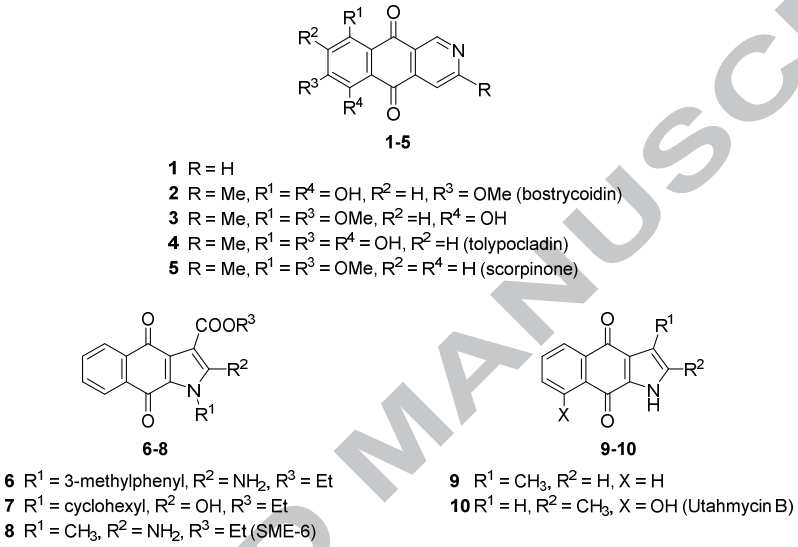
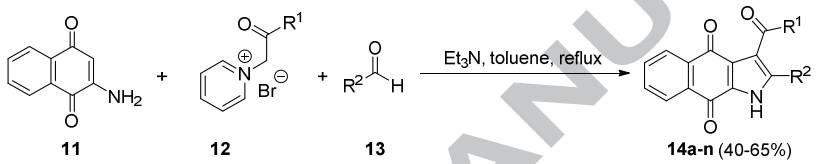


Figure 1. Chemical structures of several biologically active heterocyclic naphthoquinones

In a continuation of our interest in the synthesis of heterocyclic naphthoquinones[18] and domino reactions,[18j,k] herein, we report the synthesis of novel 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-diones from 2-aminonaphthalene-1,4-dione using a one-pot, multicomponent domino reaction (MDR). Multicomponent domino reactions have been widely applied in recent years as they provide high structural diversity through multiple bond-forming reactions in a one-pot approach with high synthetic efficiency.[19] These reactions involve at least three substrates and produce two or more bond-forming transformations, based on functionalities induced in the previous step, without changing the reaction conditions or adding catalysts and/or additional reagents.[19a,20] Furthermore, structure-activity relationships concerning functionalized heterocyclic naphthoquinones have shown that the introduction of chemically diverse side chains to the heterocyclic ring can enhance the bioactivities of these molecules,[21] making the synthesis of new heterocyclic naphthoquinones through MDR an appropriate challenge.

The synthesis of the target naphthoquinones **14a-n** was conducted using a one-pot MDR, starting from simple and readily available substrates, namely 2-amino-1,4-naphthoquinone **11**, *N*-acylmethylpyridinium bromides **12**[18b,i,j,22] and aromatic aldehydes **13**. *N*-Acylmethylpyridinium bromides were obtained in 90-95% yield *via* the reaction of

pyridine (1 equiv.) and 2-bromomethylacetophenone derivatives (1 equiv.) in acetonitrile at room temperature for 12 h. Thus, a solution of 2-amino-1,4-naphthoquinone **11** (1 equiv.), pyridinium bromide **12** (1.2 equiv.) and triethylamine (5 equiv.) in toluene was heated at reflux for 30-60 min, after which aromatic aldehyde **13** (1.2 equiv.) was added. The resulting mixture was further heated at reflux for 24 h. Using this reaction 14 new fused benzo[*f*]indole-4,9-diones **14a-n** were obtained in 45-65% yield after purification by silica gel column chromatography (Scheme 1, Table 1).[23] The proposed molecular structures of the functionalized naphthoquinones **14a-n** were assigned by ^{1}H NMR, ^{13}C NMR, MS and IR analysis. Single crystal X-Ray analysis was performed on compound **14k** to confirm the structure of this molecular framework (Fig. 2). Both electron-donating and electron-withdrawing substituents on the phenyl moieties were selected to assess their influence on the reaction outcome. However, no major effect was observed, leading to comparable yields in all cases.



Scheme 1. Synthesis of 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-diones **14a-n**

Table 1. Synthesis of 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-diones **14a-n**

Entry	R^1	R^2	Compound	Yield (%)
1	C_6H_5	C_6H_5	**14a**	63
2	C_6H_5	3-$MeOC_6H_4$	**14b**	59
3	C_6H_5	4-$MeOC_6H_4$	**14c**	60
4	C_6H_5	3-MeO-4-HOC_6H_3	**14d**	62
5	C_6H_5	3-BrC_6H_4	**14e**	48
6	C_6H_5	4-BrC_6H_4	**14f**	47
7	C_6H_5	4-ClC_6H_4	**14g**	45
8	C_6H_5	4-$Me_2NC_6H_4$	**14h**	45
9	C_6H_5	naphth-2-yl	**14i**	48
10	C_6H_5	3,4-methylenedioxyphenyl	**14j**	47
11	4-FC_6H_4	C_6H_5	**14k**	65
12	4-FC_6H_4	naphth-2-yl	**14l**	40
13	3-HOC_6H_4	C_6H_5	**14m**	47
14	3-HOC_6H_4	4-$MeOC_6H_4$	**14n**	45

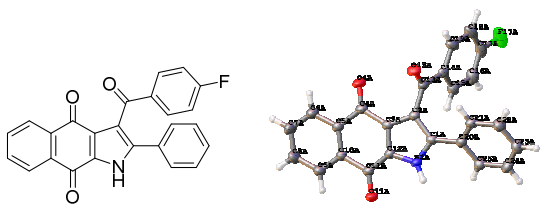
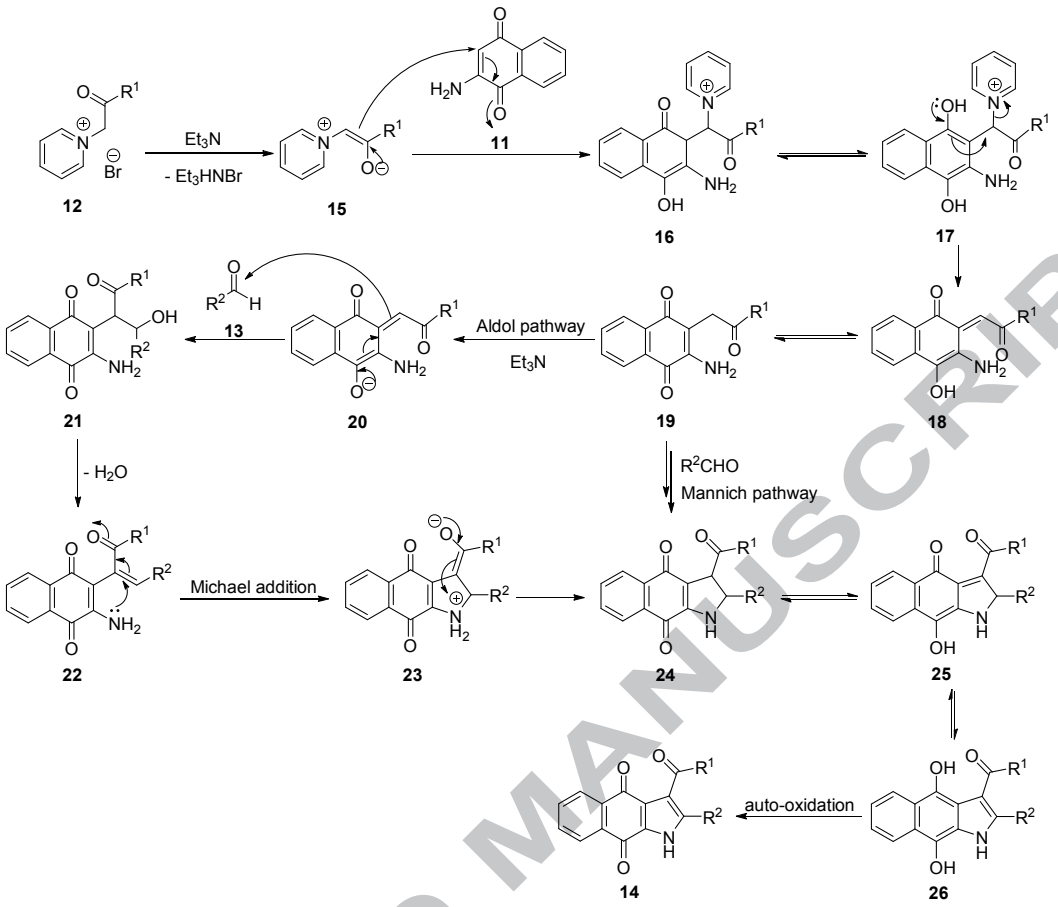


Figure 2. Single crystal X-ray structure of compound **14k**

A possible mechanistic interpretation of this MDR begins with the Michael addition of 2-amino-1,4-naphthoquinone **11** with *N*-acylmethylpyridinium ylides **15**, formed *in situ* by the deprotonation of pyridinium bromides **12** by Et_3N.[18a,b,e] After the elimination of pyridine from intermediates **16**, compounds **18** engage in a base promoted Knoevenagel condensation with aromatic aldehydes **13**, resulting in the formation of naphthoquinones **22**. The latter undergo intramolecular nucleophilic attack of the vinyligous amide nitrogen atom to produce compounds **24**, which undergo keto-enol tautomerization and auto-oxidation to furnish the desired substituted 1*H*-benzo[*f*]indole-4,9-diones **14** (Scheme 2). The reaction could also proceed *via* a Mannich type reaction, in which the condensation of compound **19** with aromatic aldehydes leads to a Schiff base which after a subsequent cyclization sequence provides compound **24**.

In conclusion, the efficient synthesis of novel 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-quinones **14** using a one-pot MDR from 2-amino-1,4-naphthoquinone, pyridinium bromides and aromatic aldehydes has been described. The influence of electron-donating and electron-withdrawing substituents on the phenyl moieties on the reaction outcome was also evaluated. These heterocyclic naphthoquinones could represent interesting new structures for the pursuit of biologically active compounds.



Scheme 2. Proposed mechanism for the formation of compounds **14**

Acknowledgements

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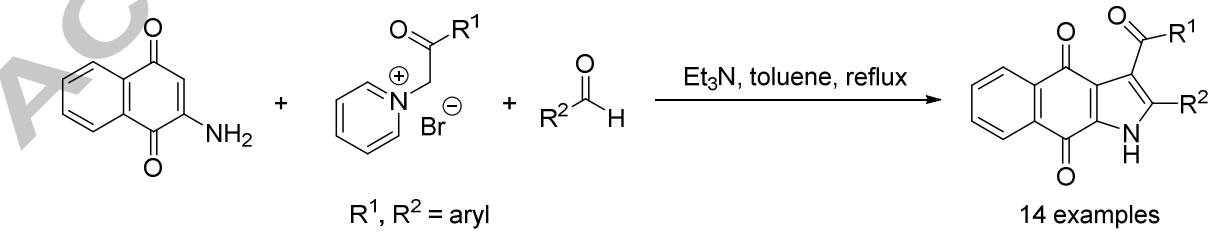
23. *General procedure for the synthesis of 2-aryl-3-benzoyl-1H-benzo[f]indole-4,9-diones* ***14a-n***: A solution of 2-amino-1,4-naphthoquinone **11** (1 equiv.), pyridinium bromide **12** (1.2 equiv.) and Et_3N (5 equiv.) in toluene (5 ml) was heated at reflux for 30-60 min. Aromatic aldehyde **13** (1.2 equiv.) was added and the resulting mixture was further heated at reflux for 24 h. The reation mixture was extracted with EtOAc (20 ml x 3) and the combined organic phases dried with $MgSO_4$ and evaporated *in vacuo*. The reaction mixture was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (8:2). *3-(4-Fluorobenzoyl)-2-phenyl-1H-benzo[f]indole-4,9-dione* **14k**: Orange yellow solid. Yield: 65%. Mp 286-287 ^{o}C. IR (KBr) cm^{-1}: 3219, 1661, 1641, 1594, 1435, 1233, 1146, 967, 904, 766, 708, 685, 615, 510, 441; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.56 (s, 1H, NH), 8.15-8.13 (m, 1H), 8.07-8.05 (m, 1H), 7.98-7.96 (m, 2H), 7.70-7.68 (m, 2H), 7.56-7.54 (m, 2H), 7.39-7.37 (m, 3H), 7.08 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 191.52, 179.71, 176.12, 166.06 (d, J = 253.7 Hz, CF), 139.47, 134.15, 134.12, 133.93, 133.26, 133.00, 132.21, 132.13, 131.89, 129.63, 129.18, 129.06 (2xCH), 127.72 (2xCH), 127.25, 127.21, 126.48, 120.84, 115.90, 115.72; HRMS (ESI): *m/z* $[M-H]^-$ calcd $C_{25}H_{13}FNO_3$: 394.0879; found: 394.0876. Single crystal X-ray structure of compound **14k** has been deposited at the Cambridge Crystallographic Data Center with the following deposition number CCDC 1491059.

GRAPHICAL ABSTRACT

Synthesis of novel 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-diones using a domino reaction



Synthesis of novel 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-diones using a domino reaction

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- One-pot multicomponent synthesis of 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-quinones.
- A mechanism for the transformation has been proposed.
- Single crystal X-ray structure of 2-phenyl-3-(4-fluorobenzoyl)-1*H*-benzo[*f*]indole-4,9-dione is provided.