Synthesis of novel 2-aryl-3-benzoyl-1H-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

Trung Quang Nguyen [a], Thuy Giang Le Nhat [a], Doan Vu Ngoc [a,b], Tuyet Anh Dang Thi [a], Ha Thanh Nguyen [a], Phuong Hoang Thi [a], Hung Huy Nguyen [c], Hai Thuong Cao [b], Kourosch Abbaspour Tehrani [d], Tuyen Van Nguyen [a]

[a] Institute of Chemistry, Vietnam Academy of Science and Technology, 18-Hoang Quoc Viet, Cau Giay, Hanoi, Viet Nam

[b] Le Quy Don Technical University, 236-Hoang Quoc Viet, Cau Giay, Hanoi, Viet Nam

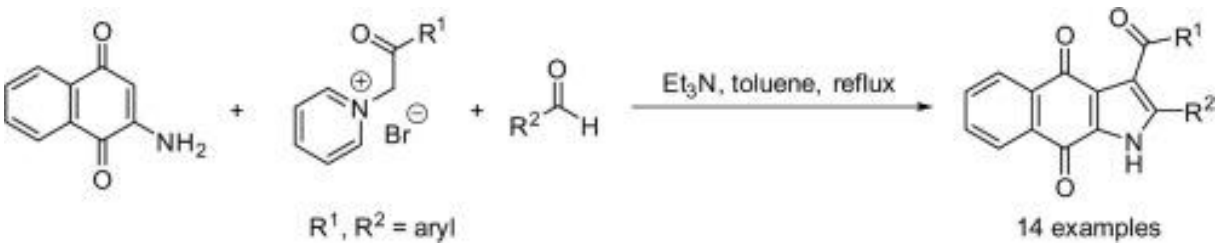
[c] Hanoi University of Science, 19-Le Thanh Tong, Hoan Kiem, Hanoi, Viet Nam

[d] Organic Synthesis, Faculty of Sciences, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium

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.

Graphical abstract

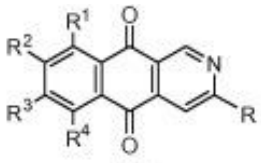


Keywords

Benzo[*f*]indole-4,9-dione; Domino reactions; 2-Amino-1,4-naphthoquinone

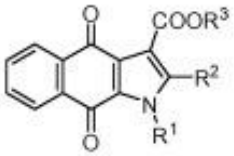
Quinone moieties, especially nitrogen heterocyclic quinones, are important structural units in many natural and unnatural products that possess a wide range of biological activities.[1] Naturally occurring quinones are found in bacteria, fungi, and plants, for example; benz[*g*]isoquinoline-5,10-dione **1** (Fig. 1), isolated from *Psychotria camponutans* and *Mitracarpus scaber*, exhibits 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] while 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,f,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,f] 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.



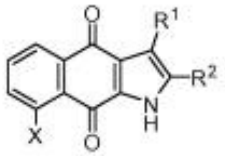
1-5

1 R = H
2 R = Me, $R^1 = R^4 = OH$, $R^2 = H$, $R^3 = OMe$ (bostrycoidin)
3 R = Me, $R^1 = R^3 = OMe$, $R^2 = H$, $R^4 = OH$
4 R = Me, $R^1 = R^3 = R^4 = OH$, $R^2 = H$ (tolypocladin)
5 R = Me, $R^1 = R^3 = OMe$, $R^2 = R^4 = H$ (scorpinone)



6-8

6 R^1 = 3-methylphenyl, $R^2 = NH_2$, R^3 = Et
7 R^1 = cyclohexyl, R^2 = OH, R^3 = Et
8 $R^1 = CH_3$, $R^2 = NH_2$, R^3 = Et (SME-6)



9-10

9 $R^1 = CH_3$, R^2 = H, X = H
10 R^1 = H, $R^2 = CH_3$, X = OH (Utahmycin B)

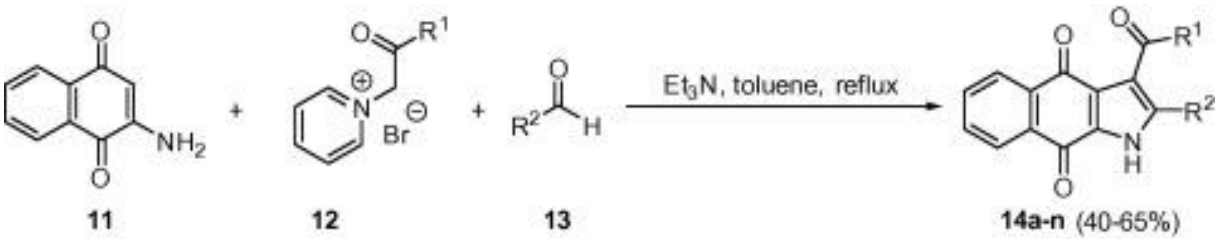
Figure 1. Chemical structures of several biologically active heterocyclic naphthoquinones.

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]

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-1H-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

Entry	R^1	R^2	Compound	Yield (%)
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

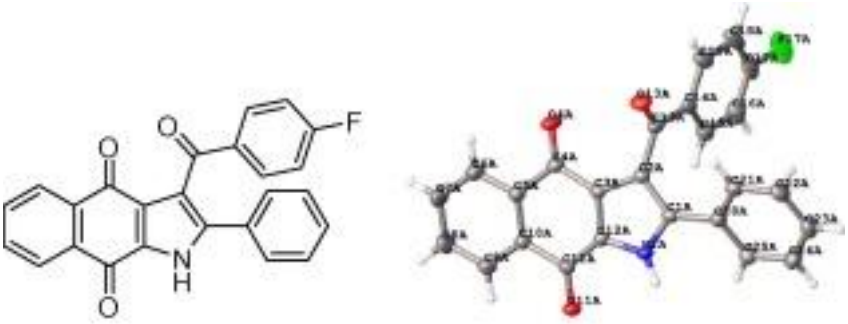
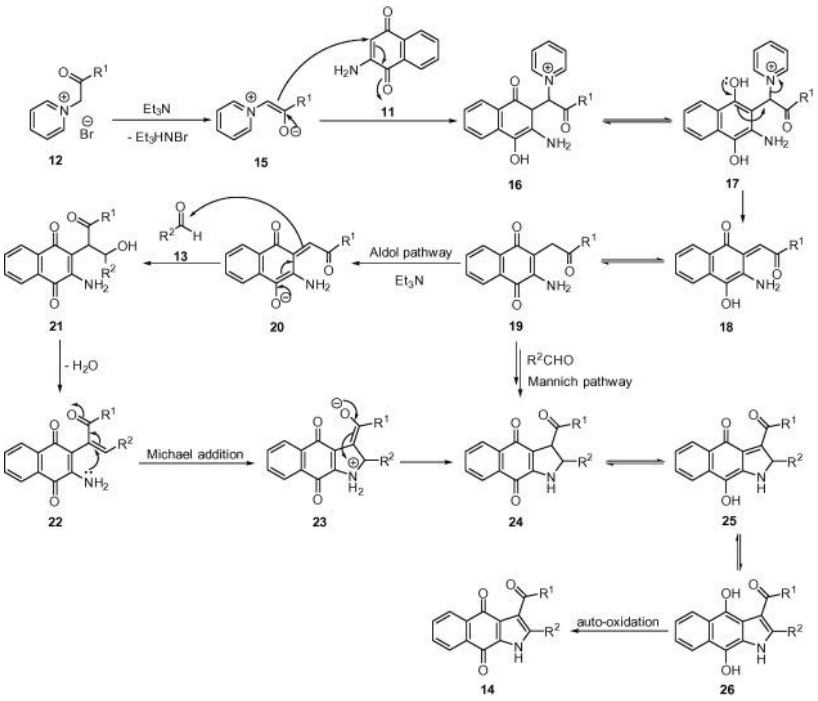


Figure 2. Single crystal X-ray structure of compound **14k**.

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**.



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

In conclusion, the efficient synthesis of novel 2-aryl-3-benzoyl-1*H*-benzo[*f*]indole-4,9-diones **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.

Acknowledgements

The authors are indebted to the Bilateral Scientific Research Cooperation Projects between FWO (Flanders, G005514N) and NAFOSTED (Viet Nam, FWO.104.2013.12) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.042

References and notes

1. (a) Thomson, R. H. Naturally Occurring Quinones, 2nd ed.; Academic Press: London and New York, 1971; (b) Thomson, R. H. Naturally Occurring Quinones III: Recent Advances, 3rd ed.; Chapman and Hall: London and New York, 1987; (c) Sharma, P. S.; Pietrzyk-Le, A.; D'Souza, F.; Kutner, W. Anal. Bioanal. Chem. 2012, 402, 3177–3204; (d) Furstner, A. Angew. Chem., Int. Ed. 2003, 42, 3582– 3603; (e) Lee, E.-J.; Lee, H.-J.; Park, H. J.; Min, H.-Y.; Suh, M.-E.; Chung, H.-J.; Lee, S. K. Bioorg. Med. Chem. Lett. 2004, 14, 5175–5178; (f) Park, H. J.; Lee, H.-J.; Min, H.-Y.; Chung, H.-J.; Suh, M. S.; Park-Choo, H.-Y.; Kim, C.; Kim, H. J.; Seo, E.-K.; Lee, S. K. Eur. J. Pharmacol. 2005, 527, 31–36; (g) Ryu, C.-K.; Lee, J. Y.; Jeong, S. H.; Nho, J.-H. Bioorg. Med. Chem. Lett. 2009, 19, 146–148; (h) Ryu, C.-K.; Yoon, J. H.; Song, A. L.; Im, H. A.; Kim, J. Y.; Kim, A. Bioorg. Med. Chem. Lett. 2012, 22, 497–499; (i) Shchekotikhin, A. E.;

Glazunova, V. A.; Dezhenkova, L. G.; Kaluzhny, D. N.; Luzikov, Y. N.; Buyanov, V. N.; Treshalina, H. M.; Lesnaya, N. A.; Romanenko, V. I.; Balzarini, J.; Agama, K.; Pommier, Y.; Shtil, A. A.; Preobrazhenskaya, M. N. Eur. J. Med. Chem. 2014, 86, 797–805; (j) Nadji-Boukrouche, A. R.; On, S.; Khoumeri, O.; Terme, T.; Vanelle, P. Tetrahedron Lett. 2015, 56, 2272–2275; (k) Guo, S.; Chen, B.; Guo, X.; Zhang, G.; Yu, Y. Tetrahedron 2015, 71, 9371–9375; (l) Gach, K.; Modranka, J.; Szymanski, J.; Pomorska, D.; Krajewska, U.; Mirowski, M.; Janecki, T.; Janecka, A. Eur. J. Med. Chem. 2016, 120, 51–63; (m) Luu, Q. H.; Guerra, J. D.; Castaneda, C. M.; Martinez, M. A.; Saunders, J.; Garcia, B. A.; Gonzales, B. V.; Aidunithula, A. R.; Mito, S. Tetrahedron Lett. 2016, 57, 2253–2256.

2. (a) Krapcho, A. P.; Waterhouse, D. J. Heterocycles 1999, 51, 737–749; (b) Okunade, A. L.; Clark, A. M.; Hufford, C. D.; Oguntimein, B. O. Planta Med. 1999, 65, 447–448; (c) Nok, A. J. Cell Biochem. Funct. 2002, 20, 205–212; (d) Chem. Abstr. Nr. 2002, 636119.

3. Khanapure, S. P.; Biehl, E. R. Heterocycles 1988, 27, 2643–2650.

4. (a) Arsenault, G. P. Tetrahedron Lett. 1965, 45, 4033–4037; (b) Steyn, P. S.; Wessels, P. L.; Marasas, W. O. F. Tetrahedron 1979, 35, 1551–1555.

5. Grafe, U.; Ihn, W.; Tresselt, D.; Miosga, N.; Kaden, U.; Schlegel, B.; Bormann, E.-J.; Sedmera, P.; Novak, J. Biol. Met. 1990, 3, 39–44.

6. (a) Martin, T.; Moody, C. J. J. Chem. Soc., Perkin Trans. 1 1988, 235–240; (b) Matsuo, K.; Ishida, S. Chem. Expr. 1993, 8, 321–324; (c) Moody, C. J.; Swann, E. Tetrahedron Lett. 1993, 34, 1987–1988; (d) Matsuo, K.; Ishida, S. Chem. Pharm. Bull. 1994, 42, 1325–1327; (e) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. Chem. Pharm. Bull. 1998, 46, 1948–1949; (f) Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. Chem. Pharm. Bull. 2001, 49, 881–886; (g) Sofiyev, V.; Lumb, J.-P.; Volgraf, M.; Trauner, D. Chem.-Eur. J. 2012, 18, 4999–5005; (h) Wang, C.; Sperry, J. Tetrahedron 2013, 69, 4563–4577.

7. (a) Huang, B.; Desai, A.; Tang, S.; Thomas, T. P.; Baker, J. R. Org. Lett. 2010, 12, 1384–1387; (b) Ferrer, S.; Naughton, D. P.; Threadgill, M. D. Tetrahedron 2003, 59, 3445–3454; (c) Sharma, K.; Iyer, A.; Sengupta, K.; Chakrapani, H. Organic Lett. 2013, 15, 2636–2639; (d) Schäfer, A.; Burstein, E. S.; Olsson, R. Bioorg. Med. Chem. Lett. 2014, 24, 1944–1947; (e) Skibo, E. B.; Xing, C.; Dorr, R. T. J. Med. Chem. 2001, 44, 3545–3562.

8. Lee, H. J.; Suh, M. E.; Lee, Ch. O. Bioorg. Med. Chem. 2003, 11, 1511–1519.

9. Park, H. J.; Lee, H.-J.; Lee, E.-J.; Hwang, H. J.; Shin, S.-H.; Shu, M.-E.; Kim, Ch.; Kim, H. J.; Seo, E.-K.; Lee, S. K. Biosci. Biotechnol. Biochem 2003, 67, 1944–1949.

10. Efdi, M.; Fujita, S.; Inuzuka, T.; Koketsu, M. Nat. Prod. Res. 2010, 24, 657–662.

11. Bauer, J. D.; King, R. W.; Brady, S. F. J. Nat. Prod. 2010, 73, 976–979.

12. Moharam, B. A.; Jantan, I.; Jalil, J.; Ahmad, F. Phytother Res. 2012, 26, 687–691.

13. (a) Jiang, M. C.; Chuang, C. P. J. Org. Chem. 2000, 65, 5409–5412; (b) Wu, Y. L.; Chuang, C. P. Tetrahedron 2002, 57, 5543–5549; (c) Tseng, C. C.; Wu, Y. L.; Chuang, C. P. Tetrahedron 2004, 60, 12249–12260.

14. (a) Weeratunga, G.; Prasad, G. K. B.; Dilley, J.; Taylor, N. J.; Dmitrienko, G. I. Tetrahedron Lett. 1990, 31, 5713–5716; (b) Mithani, S.; Weeratunga, G.; Taylor, N. J.; Dmitrienko, G. I. J. Am. Soc. Chem. 1994, 116, 2209–2210.

15. Suryavanshi, P. A.; Sridharan, V.; Menendez, J. C. Org. Biomol. Chem. 2010, 8, 3426–3436.

16. (a) Inman, M.; Moody, C. J. J. Org. Chem. 2010, 75, 6023–6026; (b) Inman, M.; Moody, C. J. Eur. J. Org. Chem. 2013, 2179–2187; (c) Shvartberg, M. S.; Kolodina, E. A.; Lebedeva, N. I.; Fedenok, L. G. Tetrahedron Lett. 2009, 50, 6769–6771; (d) Yamashita, M.; Ueda, K.; Sakaguchi, K.; Iida, A. Tetrahedron Lett. 2011, 52, 4665–4670.

17. Hu, H.-Y.; Liu, Y.; Ye, M.; Xu, J.-H. Synlett 2006, 12, 1913–1917.

18. (a) Kesteleyn, B.; Tuyen Nguyen Van, T.; De Kimpe, N. Tetrahedron 1999, 55, 2091–2102; (b) Van Nguyen, T.; Kesteleyn, B.; De Kimpe, N. Tetrahedron 2001, 57, 4213–4219; (c) Van Nguyen, T.; De Kimpe, N. Tetrahedron 2003, 59, 5941–5946; (d) Van Nguyen, T.; De Kimpe, N. Tetrahedron Lett. 2004, 45, 3443–3446; (e) Van Nguyen, T.; Verniest, G.; Claessens, S.; De Kimpe, N. Tetrahedron 2005, 61, 2295–2300; (f) Claessens, S.; Verniest, G.; El Hady, S.; Van Nguyen, T.; Kesteleyn, B.; Van Puyvelde, L.; De Kimpe, N. Tetrahedron 2006, 62, 5152–5158; (g) Van Nguyen, T.; Claessens, S.; Habonimana, P.; Abbaspour Tehrani, K.; Van Puyvelde, L.; De Kimpe, N. Synlett 2006, 2469–2471; (h) Claessens, S.; Verniest, G.; Jacobs, J.; Van Hende, E.; Habonimana, P.; Van Nguyen, T.; Van Puyvelde, L.; De Kimpe, N. Synlett 2007, 829–850; (i) Dang Thi, T. A.; Vu Thi, T. H.; Hoang Thi, P.; Nguyen, T. H.; Pham The, C.; Vu Duc, C.; Depetter, Y.; Van Nguyen, T.; Dhooghe, M. Bioorg. Med. Chem. Lett. 2015, 25, 3355–3358; (j) Dang Thi, T. A.; Depetter, Y.; Mollet, K.; Phuong, H. T.; Vu Ngoc, D.; Pham The, C.; Nguyen, H. T.; Nguyen Thi, T. H.; Nguyen, H. H.; D'hooghe, M.; Van Nguyen, T. Tetrahedron Lett. 2015, 56, 2422–2425; (k) Dang Thi, T. A.; Depetter, Y.; Phuong, H. T.; Vu Ngoc, D.; Nguyen, T. T.; Do Huy, T.; Nguyen, H. H.; D'hooghe, M.; Van Nguyen, T. Tetrahedron Lett. 2015, 56, 5855–5858.

19. (a) Brauch, S.; van Berkel, S. S.; Westermann, B. Chem. Soc. Rev. 2013, 42, 4948–4962; (b) Ramachary, D. B.; Jain, S. Org. Biomol. Chem. 2011, 9, 1277–1300; (c) Rossi, B.; Pastori, N.; Prosperini, S.; Punta, C. Beilstein J. Org. Chem. 2015, 11, 66–73.

20. (a) Tietze, L. F. Chem. Rev. 1996, 96, 115–136; (b) Pellissier, H. Chem. Rev. 2013, 113, 442–524.

21. (a) Perez-Sacau, E.; Estévez-Braun, A.; Ravelo, A. G.; Ferro, E. A.; Tokuda, H.; Mukainaka, T.; Nishino, H. Bioorg. Med. Chem. 2003, 11, 483–488; (b) De Castro, S. L.; Emery, F. S.; Da Silva, E. N., Junior Eur. J. Med. Chem. 2013, 69, 678–700.

22. (a) Aldersley, M. F.; Dean, F. M.; Hamzah, A. S. Tetrahedron Lett. 1986, 27, 255–258; (b) Aldersley, M. F.; Chishti, S. H.; Dean, F. M.; Douglas, M. E.; Ennis, D. S. J. Chem. Soc., Perkin Trans. 1 1990, 2163–2174.

23. General procedure for the synthesis of 2-aryl-3-benzoyl-1*H*-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 reaction mixture was extracted with EtOAc (20 ml × 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-1*H*-benzo[*f*]indole-4,9-dione **14k**: Orange yellow solid. Yield: 65%. Mp 286–287 °C. IR (KBr) cm^{-1}: 3219, 1661, 1641, 1594, 1435, 1233, 1146, 967, 904, 766, 708, 685, 615, 510, 441; 1H 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); 13C 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.