ACS Combinatorial Science

RESEARCH ARTICLE

pubs.acs.org/acscombsci

Multicomponent Synthesis of Poly-Substituted Benzo[*a*]pyrano-[2,3-*c*]phenazine Derivatives under Microwave Heating

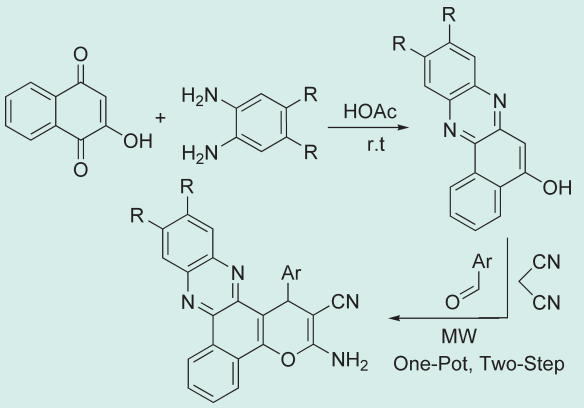
Shu-Liang Wang, Fei-Yue Wu, Chuang Cheng, Ge Zhang, Yin-Ping Liu, Bo Jiang,* Feng Shi, and Shu-Jiang Tu*

School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, 221116, P. R. China

Supporting Information

ABSTRACT: A new one-pot two-step tandem synthesis of highly functionalized benzo[*a*]pyrano[2,3-*c*]phenazine derivatives via microwave-assisted multicomponent reactions of 2-hydroxynaphthalene-1,4-dione, diamines, aldehydes, and malononitrile is reported. The procedures are facile, avoiding time-consuming and costly syntheses, tedious workup, and purifications of precursors, as well as protection/deprotection of functional groups. The method is expected to find application in the combinatorial synthesis of biologically active compounds, since phenazine and chromene motifs have a broad spectrum of biological activities.

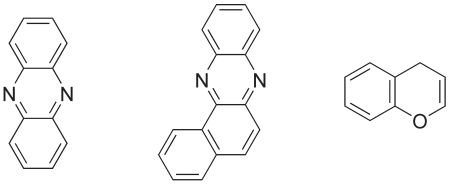
KEYWORDS: 2-hydroxynaphthalene-1,4-dione, tandem synthesis, benzo[*a*]pyrano[2,3-*c*]phenazine, microwave heating, multicomponent reactions



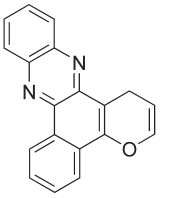
INTRODUCTION

Diversity-oriented synthesis (DOS) is a useful tool at the interface of the fields of organic synthesis and chemical biology.[1] At the heart of DOS are the synthetic means needed for the generation of collections of functionally and regiochemically diverse small molecules, particularly those possessing skeletons resembling those found in natural products or drug-like molecules.[2] An efficient method for generating these collections of molecules is by turns multicomponent reactions (MCRs) with subsequent transformations that further increase molecular complexity and diversity, requiring a minimum of time, labor, cost, and waste production.[3] Therefore, the design of novel MCRs for the synthesis of diverse groups of compounds, especially the ones that are biologically active, have commanded great attention.[4]

Phenazines (I) are present in natural and synthetic products showing a variety of biological functions, including antimalarial,[5] trypanocidal,[6] fungicidal,[7] and antiplatelet[8] activities. By virtue of their DNA intercalating ability, they exhibit antitumor activity in leukemia and solid tumors. For example, some benzophenazines (II) are dual inhibitors of topoisomerase I and II, two key enzymes that affect the topology of DNA at different points in the cell cycle.[9] In addition, chromenes (III) as an important class of compounds, widely present in plants, including edible vegetables and fruits[10] also exhibit remarkable effects as pharmaceuticals,[11] including antifungal[12] and antimicrobial activity.[13] While phenazines[14] and chromenes[15] have attracted great attention, compounds incorporating both phenazine and chromene motifs (IIII) have seldom been described. In 2005, Perez-Sacau and co-workers reported a two-step synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives, requiring harsh conditions, long reaction times, and providing a narrow substrate scope.[16] We therefore sought to develop a facile and versatile method for the combinatorial synthesis of benzo[*a*]-pyrano[2,3-*c*]phenazine library for biological screening.



Phenazine (I) Benzo[a]phenazine (II) Chromene (III)



Benzo[*a*]pyrano[2,3-*c*]phenazine (IV)

As part of our continuing interest in the development of new synthetic methods in heterocyclic compounds[17] and

Received: October 15, 2010
Revised: December 1, 2010
Published: January 10, 2011

naphthoquinone-based multicomponent reactions,[18] in this paper we would like to report new sequence of a four-component reaction for the synthesis of poly substituted benzo[*a*]pyrano-[2,3-*c*]phenazines. This reaction was achieved by reacting simple 2-hydroxynaphthalene-1,4-dione, diamines (Figure 1), aldehydes (Figure 2), and malononitrile under microwave irradiation (MWI in the absence of strong acids, metal catalysts or promoters (Scheme 1).

RESULTS AND DISCUSSION

We began this study by subjecting 2-hydroxynaphthalene-1, 4-dione, benzene-1,2-diamine, and 4-chlorobenzaldehyde to reactions with malononitrile in HOAc under microwave irradiation (Scheme 2). Unfortunately, complex mixtures were observed. To minimize the formation of byproducts, the 2-hydroxynaphthalene-1,4-dione and benzene-1,2-diamine were first stirred at room temperature for 5 min, and orange solid was observed. Next, 4-chlorobenzaldehyde and malononitrile were added and the mixture was heated under microwave irradiation for 15 min at 90 °C. The desired product was obtained as a yellow solid in 67% yield. This two-step procedure allows the one-pot four-component reaction to be controlled, avoiding the separation of intermediates, as well as time-consuming and costly purification processes.

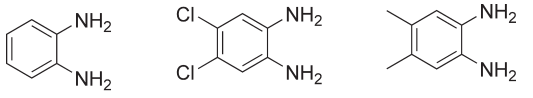


Figure 1. Aromatic diamine components **2**{*1*−*3*}.

The one-pot four-component reactions were examined under different reaction temperatures, with results summarized in Table 1. The yield of product **5**{*1,1,1,4*} was found to increase and the reaction time decrease as the temperature was raised from 90 to 120 °C (Table 1, entries 1−4). No significant improvement in yield was obtained past that point, so 120 °C was chosen as the reaction temperature for all further studies.

Scheme 2. Synthesis of Benzo[*a*]pyrano[2,3-*c*]phenazine Derivatives 5{*1,1,1,4*}

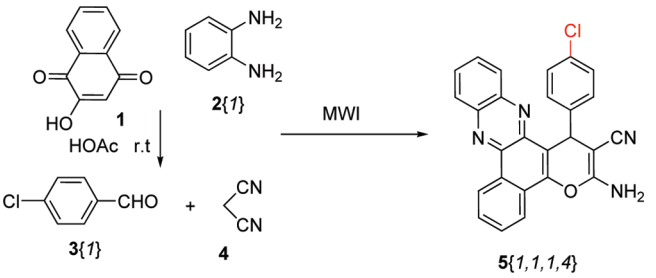


Table 1. Temperature Optimization for the Synthesis of 5{*1,1,1,4*} under Microwave Irradiation

entry	temp/°C	time/min	yield (%)
1	90	15	67
2	100	15	71
3	110	13	79
4	120	10	89
5	130	8	84
6	140	7	81

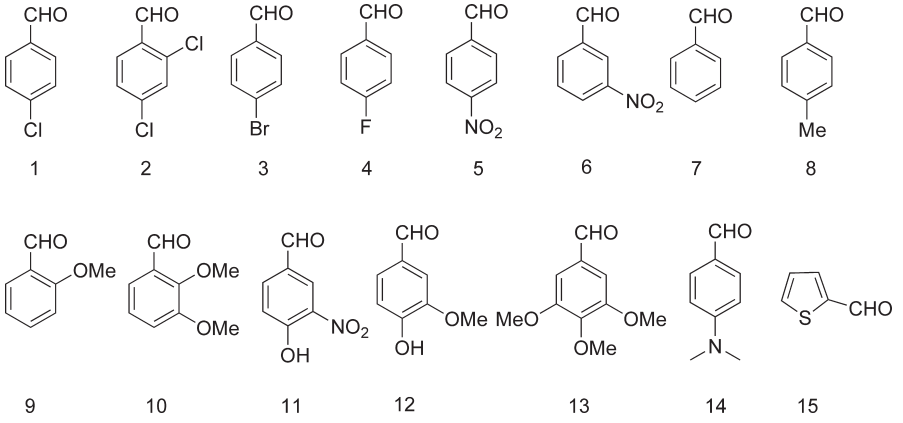
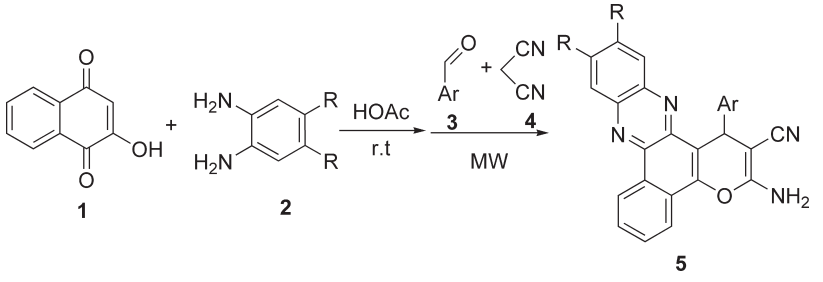


Figure 2. Aromatic aldehyde components **3**{*1*−*15*}.

Scheme 1. One-Pot Two-Step Tandem Synthesis of Benzo[*a*]pyrano[2,3-*c*]phenazine Derivatives



dx.doi.org/10.1021/co1000376 |*ACS Comb. Sci.* 2011, 13, 135–139

Using these optimized conditions, the reaction scope was evaluated by using different diamines and aldehydes (Figure 2). Commercially available aromatic aldehydes bearing either electron-withdrawing or electron-donating functional groups, such as chloro (**3**{*1*}, **3**{*2*}), fluoro (**3**{*4*}), bromo (**3**{*3*}), nitro (**3**{*5*}, **3**{*6*}, **3**{*11*}), methyl (**3**{*8*}), methoxy (**3**{*9*}, **3**{*10*}, **3**{*12*}, **3**{*13*}), or dimethylamino (**3**{*14*}) were all found to be suitable for the reaction with 2-hydroxynaphthalene-1,4-dione **1** benzene-1,2-diamine (**2**{*1*}) and malononitrile **4** to obtain benzo[*a*]pyrano[2,3-*c*]phenazines in very good yields of 85−92% under microwave heating (Table 2, entries 1−13). Even substrate (**3**{*15*}), which contains a 2-thienyl group, was effectively incorporated to give the 1-thienylsubstituted benzo[*a*]pyrano[2,3-*c*]phenazine **5**{*1,1,15,4*} with 87% yield (Table 2, entry 14). We also utilized 4,5-dichlorobenzene-1,2-diamine (**2**{*2*}) and 4,5-dimethylbenzene-1,2-diamine (**2**{*3*}) instead of benzene-1,2-diamine (**2**{*1*}) to afford the corresponding benzo[*a*]pyrano[2,3-*c*]phenazines within 10−14 min in very good yields (81−86%) and excellent regioselectivities (Table 2, entries 15−26). Given the large number of commercially available aldehydes, and the easy access to diamine, the present method should be applicable to the synthesis of libraries with high functional group diversity. We expect this method to find application in the field of combinatorial chemistry, diversity-oriented synthesis and drug discovery.

Similar to our previous four-component reaction process,[17] the present reaction also showed the following attractive characteristics: (1) fast reaction rates which enable the reaction to be completed within 7−14 min, (2) convenient workup requiring only simple filtration since the products precipitate upon dilution of the reaction mixtures with acetone, and (3) readily available starting materials of 2-hydroxynaphthalene-1,4-dione, diamines, aldehydes, and malononitrile. Moreover, regioselectivity is completely

Table 2. Synthesis of Poly-Substituted Benzo[*a*]pyrano[2,3-*c*]-phenazine Derivatives 5

entry	product	time/min	yield/%
1	5{*1,1,1,4*}	10	89
2	5{*1,1,3,4*}	8	87
3	5{*1,1,4,4*}	9	90
4	5{*1,1,5,4*}	9	92
5	5{*1,1,6,4*}	8	91
6	5{*1,1,7,4*}	10	90
7	5{*1,1,8,4*}	10	88
8	5{*1,1,9,4*}	11	86
9	5{*1,1,10,4*}	9	86
10	5{*1,1,11,4*}	10	87
11	5{*1,1,12,4*}	7	86
12	5{*1,1,13,4*}	9	85
13	5{*1,1,14,4*}	10	88
14	5{*1,1,15,4*}	10	87
15	5{*1,2,2,4*}	11	81
16	5{*1,2,4,4*}	11	84
17	5{*1,2,5,4*}	10	84
18	5{*1,2,6,4*}	10	83
19	5{*1,2,11,4*}	12	86
20	5{*1,2,13,4*}	12	86
21	5{*1,3,2,4*}	13	81
22	5{*1,3,3,4*}	12	85
23	5{*1,3,5,4*}	12	82
24	5{*1,3,6,4*}	12	82
25	5{*1,3,7,4*}	13	83
26	5{*1,3,13,4*}	14	86

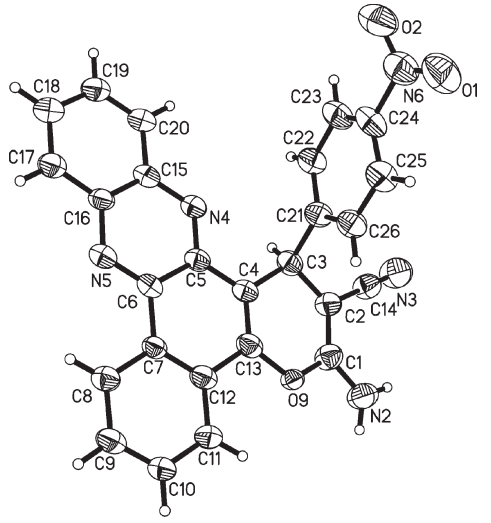
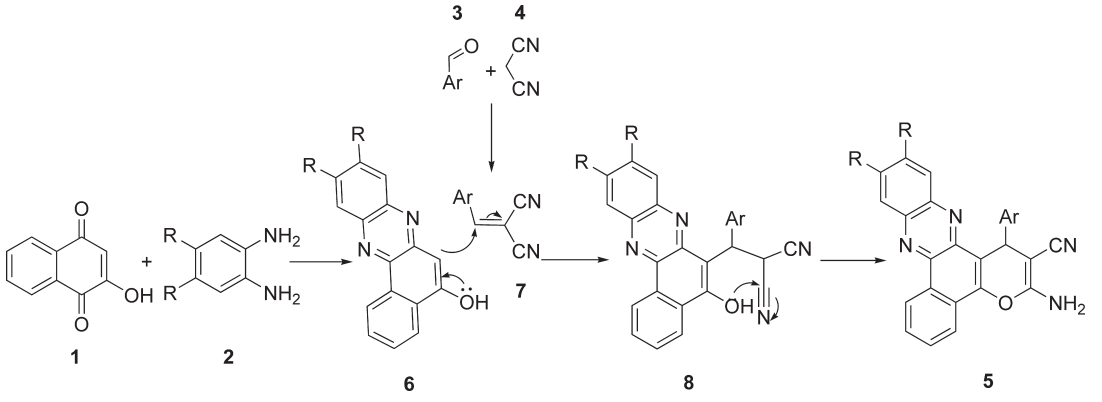


Figure 3. X-ray crystallographic structure of compound **5**{*1,1,5,4*}.

Scheme 3. Possible Mechanism for the Formations of Benzo[*a*]pyrano[2,3-*c*]phenazine Derivatives 5



dx.doi.org/10.1021/co1000376 |*ACS Comb. Sci.* 2011, 13, 135–139

controlled by changing the charging sequence in this one-pot reaction.

Structural assignments of these new compounds have been characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and HRMS (ESI) (see the Supporting Information). Additionally, the structures of **5**{*1,1,5,4*} was confirmed by single-crystal X-ray diffraction analysis (Figure 3).

A reaction mechanism consistent with the above results is shown in Scheme 3. The formation of **5** is expected to proceed via initial condensation of 2-hydroxynaphthalene-1,4-dione **1** and diamine **2** to afford benzo[*a*]phenazin-5-ol **6**, which undergoes in situ Michael addition with 2-benzylidenemalononitrile **7**, formed from condensation of aldehydes with malononitrile, to yield intermediate **8**, which is then cyclized to afford the products **5**.

CONCLUSION

We have demonstrated a simple and efficient route for the one-pot, four-component synthesis of benzo[*a*]pyrano[2,3-*c*]-phenazines and in good to excellent yields. Particularly valuable features of this method included operational simplicity, increased safety for small-scale high-speed synthesis, and broad substrate scope. Furthermore, this series of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives may provide new class of biologically active compounds for biomedical screening, which is in progress in our laboratory.

EXPERIMENTAL SECTION

General. Microwave irradiation was carried out with Biotage microwave synthesizer from Personal Chemistry, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 (100 MHz, ^{13}C NMR) with chemical shift (δ) given in ppm relative to TMS as internal standard. ESI-MS was determined by using the LCQ Advantage HPLC/MS instrument (Thermo Finnigan). HRMS (ESI) was determined by using microTOF-Q‖ HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

Typical Procedure for the Preparation of 3-Amino-1-(4-chloro-phenyl)-1*H*-benzo[*a*]pyrano [2,3-c]phenazine-2-carbonitrile 5{*1,1,1,4*}. In a 10-mL Biotage microwave process vial, the 2-hydroxynaphthalene-1,4-dione (0.17 g, 1 mmol), benzene-1,2-diamine (0.11 g, 1 mmol), and HOAc (2.0 mL) were mixed and stirred at room temperature. After five minutes, 4-chlorobenzaldehyde (0.14 g, 1.0 mmol) and malononitrile (0.10 g, 1.5 mmol) were added into the reaction system and then capped. The mixture was heated for 10 min at 120 °C under microwave irradiation. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was collected by Büchner filtration and subsequently washed with acetone to give the pure yellow solid (0.39 g, yield 89%). mp: 288−291 °C. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.18−9.16 (m, 1H, Ar−H), 8.43−8.41 (m, 1H, Ar−H), 8.24−8.22 (m, 1H, Ar−H), 8.11−8.08 (m, 1H, Ar−H), 8.01−7.89 (m, 4H, Ar−H), 7.43−7.41 (m, 4H, Ar−H), 7.29−7.27 (m, 2H, NH_2), 5.44 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.8, 152.2, 144.3, 140.6, 139.9, 131.0, 130.8, 130.6, 130.3, 130.1, 129.6, 129.2, 128.7, 128.3, 125.6, 124.9, 122.2, 120.0, 113.3, 57.6. IR (KBr, ν, cm^{-1}): 3452, 3309, 3174, 2189, 1660, 1624, 1593, 1488, 1473, 1402, 1385, 1350, 1329, 1291, 1268, 1163, 1105, 1088, 1053, 1015, 848, 759, 749. HRMS (ESI): m/z calcd $C_{26}H_{16}ClN_4O$, 435.1008; found 435.1019.

ASSOCIATED CONTENT

Supporting Information. Representative experimental procedures and characterizations and crystallographic data for **5**{*1,1,5,4*}.This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Tel.: 0086-516-83500065. Fax: 0086-516-83500065. E-mail: laotu@xznu.edu.cn (B.J.) or jxznu07@126.com (S.-J.T).

Author Contributions

B. Jiang and S.-J. Tu conceived and designed the experiments, S. L. Wang and F.-Y Wu performed the experiments, and co-wrote the manuscript. B. Jiang, revised the manuscript. C. Cheng and G. Zhang co-wrote the Supporting Information. Y.-P. Liu and F. Shi checked the references.

Funding Sources

We are grateful for financial support from the National Science Foundation of China (Nos. 21072163 and 21002083), Sci. Foundation in Interdisciplinary Major Res. Project of XZNU (No. 09XKXK01), Qing Lan Project (08QLT001) of Jiangsu Education Committee and Graduate Foundation of XZNU (No. 2010YLB031).

REFERENCES

(1) (a) Burke, M. D.; Schreiber, S. L. A planning strategy for diversity-oriented synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58. (b) Spring, D. R. Diversity-oriented synthesis: A challenge for synthetic chemists. *Org. Biomol. Chem.* **2003**, *1*, 3867–3870. (c) Strausberg, R. L.; Schreiber, S. L. From knowing to controlling: A path from Genomics to drugs using small molecule probes. *Science* **2003**, *300*, 294–295.

(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chem. Rev.* **2003**, *103*, 893–930.

(3) (a) Marcaccini, S.; Torroba, T. Post-condensation modifications of the Passerini and Ugi reactions.*Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Wienheim, Germany, 2005; p 33. (b) Domling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem. Rev.* **2006**, *106*, 17–89.

(4) (a) Orru, R. V. A.; De Greef, M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis* **2003**, 1471–1499. (b) Schreiber, S. L. Target-oriented and diversity-oriented organic synthesis in drug discovery. *Science* **2000**, *287*, 1964–1969. (c) Weber, L. The application of multi-component reactions in drug discovery. *Curr. Med. Chem.* **2002**, *9*, 2085–2093. (d) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing synthetic efficiency: multi-component transformations lead the way. *Chem.—Eur. J.* **2000**, *6*, 3321–3329. (e) Abboub, F.; Amari, M.; Kolli, B. Novel synthesis techniques in the series of condensed heterocyclic compounds. *J. Soc. Alger. Chim.* **2001**, *11*, 223–230.

(5) (a) Makgatho, M.; Anderson, R.; O'Sullivan, J.; Egan, T.; Freese, J.; Cornelius, N.; Van Rensburg, C. Tetramethylpiperidine-substituted phenazines as novel anti-plasmodial agents. *Drug Dev. Res.* **2000**, *50*, 195–202. (b) Andrade-Nieto, V.; Goulart, M.; da Silva, J. F.; da Silva, M. J.; Pinto, M.; Pinto, A.; Zalis, M.; Carvalho, L.; Krettli, A. Antimalarial activity of phenazines from lapachol, β-lapachone and its derivatives

against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1145–1149.

(6) Neves-Pinto, C.; Malta, V.; Pinto, M.; Santos, R.; Castro, S.; Pinto, A. Structure−activity relationships for pyrido-, imidazo-, pyrazolo-, pyrazino-, and pyrrolophenazinecarboxamides as topoisomerase-targeted anticancer agents. *J. Med. Chem.* **2002**, *45*, 740–743.

(7) (a) Cartwright, D.; Chilton, W.; Benson, D. Pyrrolnitrin and phenazine production by *Pseudomonas cepacia*, strain 5.5B, a biocontrol agent of *Rhizoctonia solani*. *Appl. Microbiol. Biotechnol.* **1995**, *43*, 211–216. (b) Ligon, J.; Dwight, S.; Hammer, P.; Torkewitz, N.; Hofmann, D.; Kempf, H.; Pee, K. Natural products with antifungal activity from *Pseudomonas* biocontrol bacteria. *Pest. Manage. Sci.* **2000**, *56*, 688–695.

(8) Muller, M.; Sorrell, T. Inhibition of the human platelet cyclooxygenase response by the naturally occurring phenazine derivative, 1-hydroxyphenazine. *Prostaglandins* **1995**, *50*, 301–311.

(9) (a) Rewcastle, G.; Denny, W.; Baguley, B. Potential antitumor agents. 51. Synthesis and antitumor activity of substituted phenazine-1-carboxamides. *J. Med. Chem.* **1987**, *30*, 843–851. (b) Funayama, S.; Eda, S.; Komiyama, K.; Omura, S. Structure of phenazinomycin, a novel antitumor antibiotic. *Tetrahedron Lett.* **1989**, *30*, 3151–3154. (c) Wang, S.; Miller, W.; Milton, J.; Vicker, N.; Stewart, A.; Charlton, P.; Mistry, P.; Hardick, D.; Denny, W. Structure−activity relationships for analogues of the phenazine-based dual topoisomerase I/II inhibitor XR11576. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 415–418. (d) Vicker, N.; Burgess, L.; Chuckowree, I.; Dodd, R.; Folkes, A.; Hardick, D.; Hancox, T.; Miller, W.; Milton, J.; Sohal, S.; Wang, S.; Wren, S.; Charlton, P.; Dangerfield, W.; Liddle, C.; Mistry, P.; Stewart, A.; Denny, W. Novel angular benzophenazines: Dual topoisomerase I and topoisomerase II inhibitors as potential anticancer agents. *J. Med. Chem.* **2002**, *45*, 721–739. (e) Gamage, S.; Spicer, J.; Rewcastle, G.; Milton, J.; Sohal, S.; Dangerfield, W.; Mistry, P.; Vicker, N.; Charlton, P.; Denny, W. Structure−activity relationships for pyrido-, imidazo-, pyrazolo-, pyrazino-, and pyrrolophenazinecarboxamides as topoisomerase-targeted anticancer agents. *J. Med. Chem.* **2002**, *45*, 740–743.

(10) Curini, M.; Cravotto, G.; Epifano, F.; Giannone, G. Chemistry and biological activity of natural and synthetic prenyloxycoumarins. *Curr. Med. Chem.* **2006**, *13*, 199–222.

(11) (a) Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K.-H. Recent progress in the development of coumarin derivatives as potent anti-HIV agents. *Med. Res. Rev.* **2003**, *23*, 322–345. (b) Abd El-Aziz, A. S.; El-Agrody, A. M.; Bedair, A. H.; Corkery, T. C.; Ata, A. Synthesis of hydroxyquinoline derivatives, aminohydroxychromene, aminocoumarin and their antibacterial activities. *Heterocycles* **2004**, *63*, 1793–1812. (c) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. *Curr. Med. Chem.* **2005**, *12*, 887–916.

(12) (a) Tangmouo, J. G.; Meli, A. L.; Komguem, J.; Kuete, V.; Ngounou, F. N.; Lontsi, D.; Beng, V. P.; Choudhary, M. I.; Sondengam, B. L. Crassiflorone, a new naphthoquinone from *Diospyros crassiflora* (Hien). *Tetrahedron Lett.* **2006**, *47*, 3067–3070. (b) Abd-El-Aziz, A. S.; El-Agrody, A. M.; Bedair, A. H.; Corkery, T. C.; Ata, A. Synthesis of hydroxyquinoline derivatives, aminohydroxychromene, aminocoumarin, and their antibacterial activities. *Heterocycles* **2004**, *63*, 1793–1812.

(13) (a) Kitamura, R. O. S.; Romoff, P.; Young, M. C. M.; Kato, M. J.; Lago, J. H. G. Chromenes from peperomia serpens (Sw.) Loudon (*Piperaceae*). *Phytochemistry* **2006**, *67*, 2398–2402. (b) Iqbal, M. C. M.; Jayasinghe, U. L. B.; Herath, H. M. T. B.; Wijesekara, K. B.; Fujimoto, Y. A fungistatic chromene from ageratum conyzoides. *Phytoparasitica* **2004**, *32*, 119–126. (c) Kraus, G. A.; Kim, I. A direct synthesis of *o*-methyl claussequinone. *J. Org. Chem.* **2003**, *68*, 4517–4518.

(14) Laursen, J. B.; Nielsen, J. Phenazine natural products: Biosynthesis, synthetic analogues, and biological activity. *Chem. Rev.* **2004**, *104*, 1663–1685.

(15) Ellis, G. P. Chromenes, chromanones, and chromones-introduction. *Chem. Heterocycl. Compd.* **1977**, *31*, 1–10.

(16) Elisa, P.-S.; Jorge, S.-D.; Ana, E.-B.; Angel, G. R. Synthesis of 9- and 10-membered macrolactones by selective ozonolysis of 1,4-diazaphenanthrene derivatives. *Tetrahedron* **2005**, *61*, 437–445.

(17) (a) Jiang, B.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. Four-component domino reaction leading to multifunctionalized quinazolines. *J. Am. Chem. Soc.* **2009**, *131*, 11660–11661. (b) Jiang, B.; Li, C.; Shi, F.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. Four-component domino reaction providing an easy access to multifunctionalized tricyclo-[6.2.2.0^{1,6}]dodecane derivatives. *J. Org. Chem.* **2010**, *75*, 2962–2965. (c) Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G. New multicomponent domino reactions (MDRs) in water: highly chemo-, regio- and stereoselective synthesis of spiro{[1,3]dioxanopyridine}-4,6-diones and pyrazolo[3,4-*b*]pyridines. *Green Chem.* **2010**, *12*, 1357–1361.

(18) (a) Wei, P.; Zhang, X.-H.; Tu, S.-J.; Yan, S.; Ying, H.-J.; Ouyang, P.-K. New potential inhibitors of DNA topoisomerase. Part II: Design and synthesis of β-lapachone derivatives under microwave irradiation. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 828–830. (b) Wang, X.-H.; Zhang, X.-H.; Tu, S.-J.; Shi, F.; Zou, X.; Yan, S.; Han, Z.-G; Hao, W.-J.; Cao, X.-D.; Wu, S.-S. A facile route to the synthesis of 1,4-pyranonaphthoquinone derivatives under microwave irradiation without catalyst. *J. Heterocycl. Chem.* **2009**, *46*, 832–836.