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New potential inhibitors of DNA topoisomerase. Part II: Design and synthesis of α-lapachone derivatives under microwave irradiation

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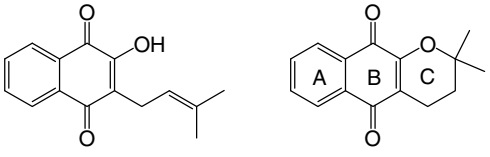
ABSTRACT

A new series of potential inhibitors of DNA topoisomerase II were synthesized from facile materials (aromatic aldehydes, Meldrum's acid and 2-hydroxynaphthalene-1,4-dione) under microwave irradiation. The method provides a valuable tool in designing new and more potent cytotoxic analogues. This procedure is advantageous both economically and environmentally.

Cancer has been proven to be the second most common cause of death after cardiovascular disease in the developed world.[1] Mass screening programs of natural products by the National Cancer Institute have identified the quinone moiety as an important pharmacophoric element for cytotoxic activity.[2]

Naturally occurring naphthoquinones comprise an important class of natural products with a wide range of biological activity[3,4] arising from their ability to cause DNA modification. Among the structurally diverse naphthoquinone natural products, lapachol (**a**) and several 1,4- and 1,2-naphthoquinones are associated with diverse biological activities[5] and are components of antibacterial,[6] fungicidal,[6] antimalarial[7] trypanocidal,[8] antiparasitic,[8] and antitumoral[9] agents.

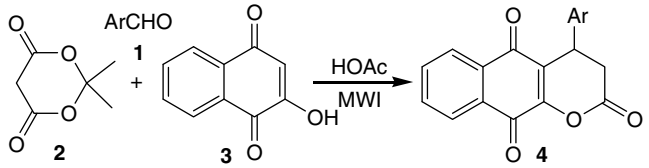
One of the most important lapachol derivatives with antitumoral activity is α-lapachone (**b**). Structure–activity relationship studies in lapachones have shown that the modification to the C-ring[10] leads to significant changes in bioactivities, which are important in searching for possible lead compounds with more potent pharmaceutical activity and less toxicity. On the basis of biological properties, 1,4- and 1,2-naphthoquinones are considered privileged structures in medicinal chemistry,[11] with the 1,4-naphthoquinones having great cancer-preventing potential.[12] In addition, more recent investigations have shown that α-lapachone is an effective DNA topoisomerase II inhibitor and is a potential lead compound for the development of drugs for the treatment of multidrug resistant cell lines with low expressions of topoisomerase II.[13]



a **b**

Lapachones are minor components in plants, therefore they are not readily available in large quantities from natural sources. The needs for large quantities of naturally occurring substances and their analogues demand the new and convenient synthetic methods.

Keeping the availability of the starting materials, the synthetic efficiency, and simplicity of procedures in our minds, we developed an efficient method to prepare a new class of α-lapachone derivatives with diversed structure in one pot by three-component condensation (Scheme 1).



Scheme 1. Synthetic route to α-lapachone derivatives **4**.

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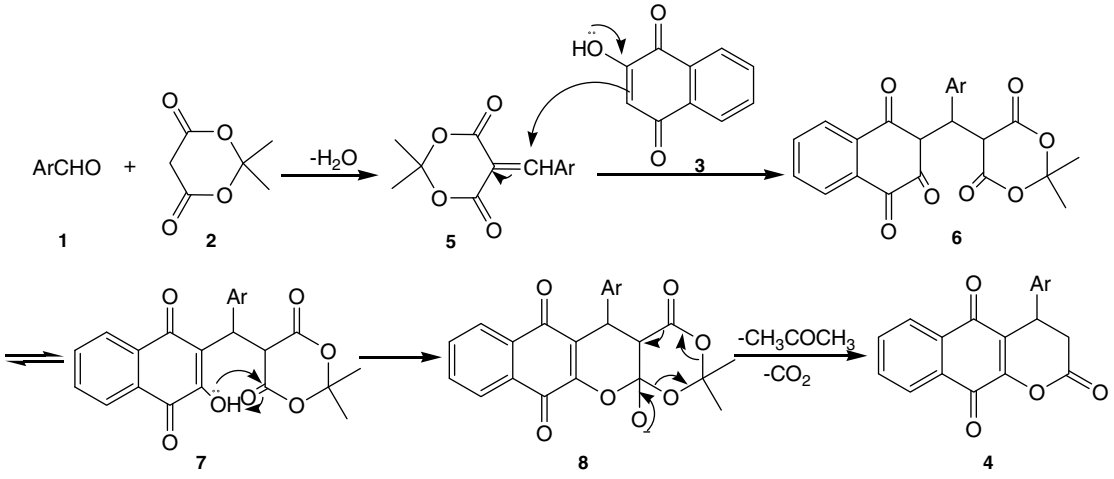
Table 1
Optimization of solvent and temperature for the synthesis of **4b**

Entry	Solvent	*T*/°C	Time/min	Yield/%
1	Glycol	100	8	76
2	EtOH	100	10	80
3	DMF	100	10	73
4	HOAc	100	7	83
5	HOAc	105	6	85
6	HOAc	110	6	88
7	HOAc	115	5	89
8	HOAc	120	5	91
9	HOAc	125	4	93
10	HOAc	130	4	89

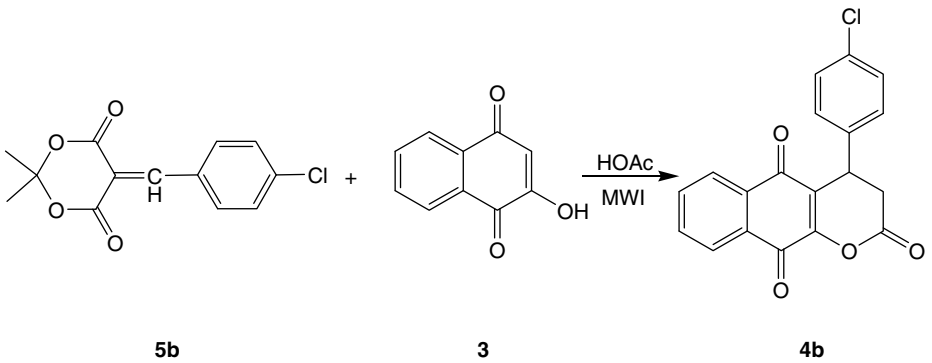
Table 2
Synthesis of product **4** under microwave irradiation

Entry	Product	Ar	Time (min)	Yield (%)	Mp (°C)
1	**4a**	4-FC_6H_4	4	89	210–212
2	**4b**	4-ClC_6H_4	4	93	224–227
3	**4c**	4-BrC_6H_4	3	92	242–244
4	**4d**	4-$CH_3C_6H_4$	5	89	208–210
5	**4e**	3-$NO_2C_6H_4$	3	87	235–238
6	**4f**	3,4-$OCH_2OC_6H_3$	4	89	208–211
7	**4g**	4-$NO_2C_6H_4$	3	91	219–221
8	**4h**	2-ClC_6H_4	4	88	238–242
9	**4i**	2,4-$Cl_2C_6H_3$	4	90	278–282
10	**4j**	4-OH-3-$NO_2C_6H_3$	5	84	231–235
11	**4k**	3,4,5-$(CH_3O)_3C_6H_2$	6	86	203–206
12	**4l**	Thien-2-yl	6	83	212–215

The reaction showed in Scheme 1[14] was employed to optimize the reaction conditions. Different organic solvents, containing glacial acetic acid (HOAc), glycol, EtOH, and *N*,*N*-dimethylformamide (DMF) were examined in the reaction of 4-chlorobenzaldehyde (**1b**, 1.0 mmol), Meldrum's acid (**2**, 1.0 mmol) and 2-hydroxynaphthalene-1,4-dione (**3**, 1.0 mmol) to investigate how the solvents affect the yields. All reactions were carried out at the maximum power of 200 W (initial power 100 W) at 100 °C. The results showed that reaction with HOAc as solvent gave higher yields and shorter reaction time compared with others (Table 1, entries **1–4**). HOAc was thus chosen as the solvent for all further reactions. Moreover, the same reaction was carried out in the range of 100–130 °C in increments of 5 °C each time in HOAc under microwave irradiation. When the temperature was increased from 100 to 125 °C, the yield of product 4b was improved from 83% to 93% (Table 1, entries **4–9**). However, further increase of the temperature to 130 °C did not improve the yield of product **4b**. So the best temperature for the reaction was 125 °C. In order to demonstrate the efficiency and applicability of the methodology, we performed the reaction of a variety of substituted aromatic as well as heteroaromatic aldehydes as reactants using these optimal microwave experimental conditions [solvent, HOAc, 125 °C, 200 W (maximum power)]. The results are summarized in Table 2. Both aromatic aldehydes bearing either electron-donating groups (such as alkoxy and methyl) and electron-withdrawing groups (such as nitro or halide) afforded high yields of α-lapachone derivatives **4**. Moreover, a



Scheme 2.



Scheme 3. Synthetic route of compound 4b yield, 91%; time, 4 min.

heterocyclic aldehyde, thiophene-2-carbaldehyde (Table 2, entry **12**), still showed high reactivity.

The detailed mechanism is still unclear, however a plausible pathway to products **4** is illustrated in Scheme 2. In the initial step, the condensation between aromatic aldehydes **1** and Meldrum's acid **2** gave intermediate **5**. Michael addition between **5** and **3** then furnished the intermediate **6**, which isomerized to **7**, subsequently underwent intramolecular cyclization and then released acetone and carbon dioxide to give compounds **4**.

The observation of compound **4b** in the reaction of **5b** with **3** in the same conditions (Scheme 3) provided the evidence supporting this proposed mechanism.

Structures of all the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. All the data are conformity with the structures.

In conclusion, an efficient MW-assisted multi-component tandem reaction to constitute the α-lapachone derivatives has been developed. The reaction is easy to perform in high yields by using inexpensive starting materials. The operational simplicity, combined with environmental friendly aspect, make this new heterocycle synthetic strategy highly attractive and promising for the development of compounds of potential synthetic interest. Additionally, the newly synthesized α-lapachone analogues may present potential inhibitive ability of DNA topoisomerase II. Further efforts are underway to explore their bioactivity and the results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.12.006.

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14. The general procedure for **4** was as follows: A mixture of aromatic aldehyde **1** (1.0 mmol), Meldrum's acid **2** (1.0 mmol), 2-hydroxynaphthalene-1,4-dione **3** (1.0 mmol), and glacial acetic acid (2.0 mL) was added to the reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to react under microwave irradiation at 200 W power (initial power 100 W) and 125 °C for several minutes. The automatic mode stirred helps in mixing and the uniform heating of the reactants. Upon completion, monitored by TLC, the reaction vessel was cooled to room temperature. The solid compound was collected by filtration, and recrystallized from EtOH (95%) to give pure α-lapachone derivatives **4**. Compound **4c**: mp: 242–244 °C; ^{1}H NMR: δ 8.12–8.10 (m, 1H, ArH), 8.01–7.99 (m, 1H, ArH), 7.93–7.87 (m, 2H, ArH), 7.52 (d, 2H, J = 8.8 Hz, ArH), 7.31 (d, 2H, J = 8.4 Hz, ArH), 4.59 (dd, 1H, J_1 = 1.2 Hz, J_2 = 7.2 Hz, CH), 3.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 16.0 Hz, CH_2), 2.91 (dd, 1H, J_1 = 1.2 Hz, J_2 = 16.0 Hz, CH_2); ^{13}C NMR (100 MHz) (δ, ppm): 182.55, 176.95, 165.19, 152.15, 138.91, 134.49, 134.24, 131.78, 130.95, 130.89, 129.22, 126.05, 125.91, 124.27, 120.68, 35.47, 33.95. IR: (KBr, ν, cm^{-1}): 1792, 1681, 1660. Anal. Calcd for $C_{19}H_{11}BrO_4$: C, 59.55; H, 2.89. Found: C, 59.74; H, 2.92.