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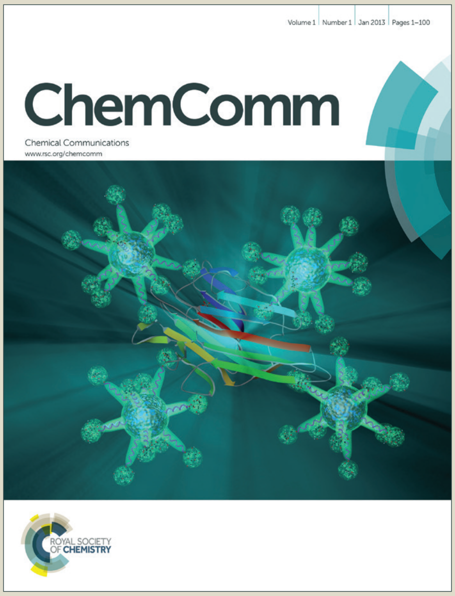

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COMMUNICATION

A one-pot, three-component reaction for the synthesis of novel 7-arylbenzo[*c*]acridine-5,6-diones

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A one pot domino protocol for an efficient synthesis of 7-arylbenzo[*c*]acridine-5,6-diones, with a novel nucleus, has been developed by reacting 2-hydroxy naphthalene-1,4-dione, aromatic aldehydes and aromatic amines using environmentally benevolent *p*-toluene sulphonic acid as a catalyst. An exciting feature of this communication is the reaction mechanism that depends on the reaction solvent.

Naphthoquinone based natural products are known to possess a myriad of biological activities including antibiotic, antiviral, antiproliferative, antibacterial, antifungal, insecticidal, anti-inflammatory, and antipyretic.[1] This pharmacophore is known to impart anticancer activity to a number of drugs like streptonigrin, mitomycins etc.[2] Lapachol and its derivatives have shown a wide spectrum of therapeutic activities.[3] *β*-Lapachone, a naturally occurring *o*-naphthoquinone derived from the lapacho tree (*Tabeuia avellanedae*) is known to possess anti-trypanocidal, antibacterial, anti-fungal, and cytotoxic activities.[4] Quinoline has functioned as a "privileged" scaffold of several FDA approved drugs.[5] The alkaloids derived from 2-alkylquinoline, chimanine B and chimanine D, isolated from the leaves of *Galipea longiflora*, show activity at an IC_{90} of 25 µg/mL against promastigotes of *Leishmania braziliensis*.[6] Skimmianine was found to be active against *L. amazonensis*.[7]

Multi-component and domino reactions being efficient and effective methods in the sustainable and diversity-oriented synthesis of heterocycles provide one of the most powerful platforms to access diversity as well as complexity in a limited number of reaction steps. The development of cheap, novel and green synthetic route for the synthesis of privileged heterocyclic scaffolds of medicinal relevance, a continuing challenge at the forefront of modern chemistry, can be achieved using multi-component protocols. Herein, we report our studies to develop a novel domino protocol for the synthesis of a previously unexplored 7-arylbenzoacridine-5,6-dione nucleus incorporating *o*-naphthoquinone and quinoline moiety (Fig. 1) into a single nucleus through a multicomponent strategy.

Focusing our interest on anti-leishmanial activity of lapachol derivatives, synthesis of hydroxynaphthalene-1,4-dione nucleus (**4**) was attempted by one pot reaction of 2-hydroxynaphthalene-1,4-dione (**1**), benzaldehyde (**2**) and aniline (**3**) as reported (see Scheme 1) and the corresponding product was obtained in reported yield.[8] To our delight, the reaction was observed to yield altogether different products while changing the sequence and time of addition.[9] Addition of benzaldehyde (**2**) to a solution of 2-hydroxynaphthalene-1,4-dione (**1**) and aniline (**3**) in 20 mol% of *p*-TSA that was under reflux in water for 30 minutes, followed by continuous refluxing for 12 h led to unexpected reaction products. The resulting reaction mixture was purified using column chromatography to give a single spot on TLC. However, ^{1}H and ^{13}C NMR data indicated that to be a mixture of at least two compounds. The mixture was subjected to analytical HPLC that clearly indicated two peaks which were analyzed using LCMS (Fig. S1a and S1b, ESI†) and purified using preparative HPLC to obtain **5** and **6**[10] in 10 % and 49 % yields, respectively (Scheme 2) and characterized on the basis of spectral data. The HRMS, 1D and 2D NMR data (Table S1, ESI†) of **5** suggested two possible structures as shown in Fig S2, ESI†. Finally, the structure was confirmed as **5** on the basis of single crystal X-ray crystallography data (Table S2, Figs. S3, S4 and S5).[11-14] An ORTEP diagram of **5** is shown in Fig. 2 while a labelled figure is included in the ESI† (Fig. S3). It forms a 1D linear supramolecular assembly via C--H…O interactions (C15….-O1 3.136 Å, symmetry: 1+x, y, z) and strong π-π interactions (the centroid-centroid distance: 3.612 Å and 3.627 Å) as shown in Figs. S3, S4 and S5, respectively, in the ESI†. These interactions provide extra stability for **5**. In order to confirm whether the single crystal structure represents the bulk material of **5** that will exclusively show its purity and homogeneity, the experimental and simulated powder X-ray diffraction patterns were matched (Fig. S6, ESI†).

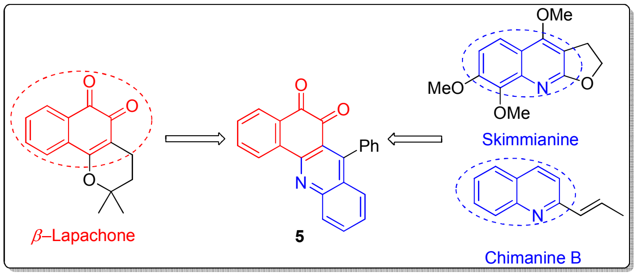


Fig. 1. Design of 7-arylbenzo[*c*]acridine-5,6-dione derivatives based on anti-leishmanial activity of *β*-lapachone, skimmianine and chimanine B.

To the best of our knowledge, condensation of 2-hydroxynaphthelene-1,4-dione, aromatic aldehyde and aniline to generate acridine nucleus has not been investigated yet. The combination of novel skeleton of **5** (containing *o*-naphthoquinone and quinoline moieties) and biological activity of compounds like β-lapachone, chimanine B and skimmianine, prompted us to investigate concise routes to 7-arylbenzo[*c*]acridine-5,6-dione nucleus (Fig. 1).

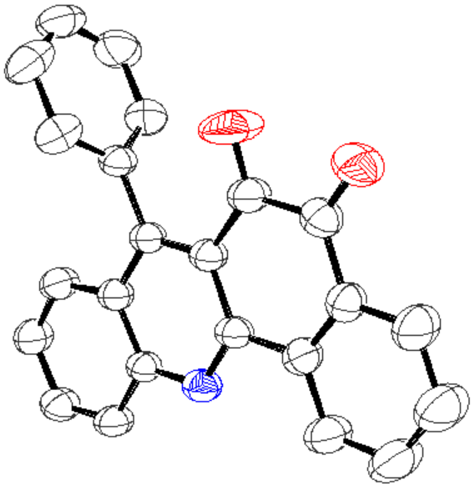
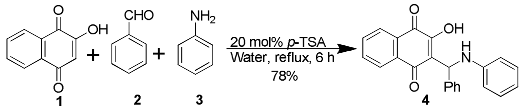
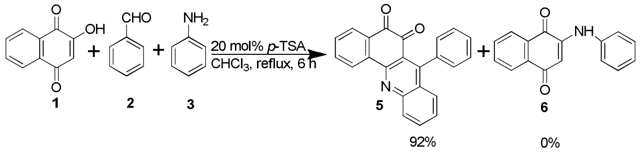


Fig. 2. An ORTEP drawing of 5. Thermal ellipsoids are shown at the 50% probability level.



Scheme 1. Synthesis of 2-hydroxynaphthalene-1,4-dione (4).

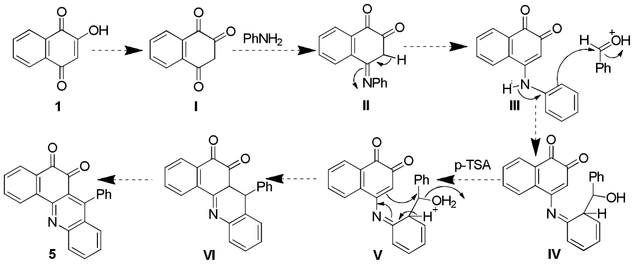


Scheme 2. Optimization of 7-phenylbenzo[*c*]acridine-5,6-diones.

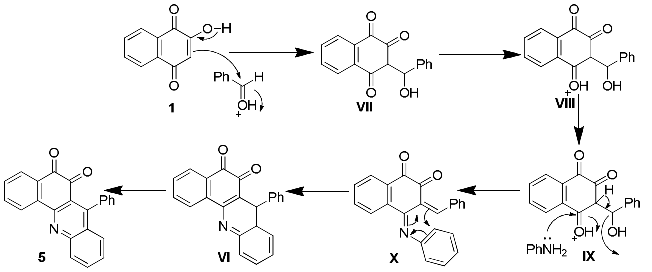
In search of effective reaction conditions, 2-hydroxynaphthalene-1,4-dione (**1**), benzaldehyde (**2**) and aniline (**3**) were used in the model reaction (Scheme 2) to investigate all the variable parameters like solvent, time, catalyst, sequence of addition of reagents and time of addition of reagents and the results are summarized in Table 1.

During initial attempts, various polar protic, polar aprotic and non polar solvents were investigated in presence of catalytic amount of *p*-toluene sulphonic acid. It was observed that a variation in solvents resulted in a complete change in reaction products. Investigational results of polar protic solvent (water) indicated that the reaction was found to yield 10% of the required product **5** (entry 1, Table 1). Using water in combination with other reagents like polyphosphoric acid, PEG 6000, acetic acid did not yield the desired product. Polar aprotic solvent (ethyl acetate) gave 12% of desired product (entry 3, Table 1). Based upon the solvent screening (see ESI† Tables S3, S4 and S5), the maximum yield (16%) was obtained using chloroform.[15]

Considering chloroform as the solvent of choice, we studied the effect of addition sequence of reagents with respect to the time. It was observed that the reaction did not yield the desired product, when **2** was added after 3 h, 2 h, 1 h to the reaction mixture containing **1** and **3** in *p*-TSA under refluxing conditions in chloroform. A continuous decrease in the time of addition of **2** to reaction mixture provides a significant rise in the yield of the required product as summarized in Table S6, ESI†. Here, the best results were obtained when all the three reactants **1**, **2** and **3** were mixed together (entry 7, Table 1)**.**



Scheme 3. Surmised mechanism for the formation of 5.



Scheme 4. Proposed mechanism for the formation of 5.

To study the progress of reaction with time, the reaction was monitored by HPLC every 30 minutes and the results are summarized in Table S7 of ESI†.[16] The optimal reaction time was found to be 6 h. The yield of **5** decreased after 6 h due to the formation of non-polar side products as observed on HPLC. The HPLC analyses revealed the appearance of peak having retention time (t_R) 23 min which could be ascribed to intermediate **VI** on the basis of HRMS data (HRMS-ESI *m/z* calcd for $C_{23}H_{15}NO_2$ $[M+ Na]^+$: 360.1000, found: 360.1001 (Fig. S7 ESI†)) during initial hours, which diminished with time and the peak of desired product (**5**) having t_R 32 min increased to 90% at 6 h (for chromatogram see Figs. S8 and S9 ESI†).

Thereafter, we screened a range of Lewis acids in order to obtain better yields (Table S8 of ESI†). The Lewis acid screening resulted $NbCl_5$ as a surrogate catalyst (entry 15, Table 1) with 78% yield of the required product. Screening with various acidic catalysts (see Table S9, ESI†) showed that *p*-TSA was the most preponderant one. Continuous loading of catalyst did not give significant change in the yield of the reaction indicating 20 mol% as optimal to obtain maximum yield of the product. On the basis of above studies, the most favourable reaction condition for the formation of **5** is as shown for entry 7 in Table 1.

An exciting feature of this work is the postulated mechanism that depends on the reaction solvent. The variation in solvent i.e. water to $CHCl_3$ led to a change in the reaction mechanism, leading to a novel skeleton. Mixing **1**, **2** and **3** in presence of 20 mol% *p*-TSA in water under refluxing for 6 h resulted in **4** (Scheme 1) through formation of Schiff base (Scheme S1, ESI†),[8] whereas use of $CHCl_3$ as solvent gave **5** through the nucleophillic addition of benzaldehyde at the double bond of 2-hydroxynaphthalene-1,4-dione (**1**), followed by reaction with aniline as shown in Scheme 4.

Table 1. Reaction optimization conditions

S. No.	Solvent	Catalyst[a]	Time[b] (min)	Time[c] (h)	Temp[d]	Yield[e]
1	Water	*p*-TSA	30	12	100	10
2	$CHCl_3$	*p*-TSA	30	12	60	16
3	EtOAc	*p*-TSA	30	12	70	12
4	$CHCl_3$	*p*-TSA	15	12	60	57
5	$CHCl_3$	*p*-TSA	10	12	60	64
6	$CHCl_3$	*p*-TSA	0	12	60	75
7	$CHCl_3$	*p*-TSA	0	6	60	92
8	$CHCl_3$	$BF_3.Et_2O$	0	6	60	25
9	Water	$ZnCl_2$	0	6	100	41
11	$CHCl_3$	$ZnCl_2$	0	6	60	35
12	$CHCl_3$	$SnCl_2$	0	6	60	12
13	$CHCl_3$	$TiCl_4$	0	6	60	22
14	$CHCl_3$	$FeCl_3$	0	6	60	50
15	$CHCl_3$	$NbCl_5$	0	6	60	78
16	$CHCl_3$	CsCl	0	6	60	46

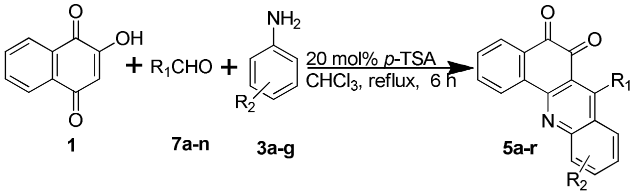
[a]20 mol%, [b]time at which **2** was added to the reaction mixture of **1** and **3** in *p*-TSA; [c]reaction time; [d]reaction temperature (°C); [e]yield (%age of product **5**) determined using HPLC.

It seems reasonable to think that the product **5** is the result of the four distinct events, namely nucleophillic attack of aniline to give intermediate **III**, followed by its acylation at *α*-position and cyclization to **VI**, followed by aerial oxidation to give **5** (Scheme 3). To support the above sequence of events, benzoyl chloride was added to the mixture of **1** and **3** in *p*-TSA after 3 h, in both water and chloroform under refluxing conditions, considering *in situ* benzoylation of intermediate **III**, the results showed no product formation leading to dereliction of the mechanism discussed in Scheme 3.

Further, to gain information on the exact mechanisitic aspect of the reaction some more reactions were examined: (i) activated benzaldehyde[17] was added dropwise to **3**, followed by 3 h refluxing for Schiff base formation and was added dropwise to **1** and refluxed for 6 h; (ii) activated benzaldehyde[17] was added dropwise to **1** for nucleophillic addition of benzaldehyde at the double bond of 2-hydroxynaphthalene-1,4-dione (**1**)**,** followed by 3 h refluxing, which was added dropwise to **3** and refluxed for 6 h; (iii) activated **1**[17] was added dropwise to **3**, followed by 3 h refluxing and was added dropwise to **2** and refluxed for 6 h. Favourable outcome of experiment (ii) led to the conclusion that reaction proceeded through the nucleophillic addition of benzaldehyde at the double bond of 2-hydroxynaphthalene-1,4-dione (**1**), as shown in Scheme 4. Formation of **VI** as principal product under nitrogen atmosphere confirmed the air-oxidation proceeded in the reaction. Based on these results, a reasonable mechanism accounting for the observed transformation was proposed (Scheme 4). As outlined in Scheme 4, the initial condensation of **1** with benzaldehyde (**2)** gave the corresponding intermediate **VII** which subsequently underwent nucleophillic addition of aniline to generate intermediate **X**. Finally, intermediate **X** was cyclized followed by aerial oxidation to afford the product **5**.

The reaction may seem to resemble Doebner-Miller quinoline synthesis (reaction of an α,β-unsaturated carbonyl and aniline) with respect to the substrates 2-hydroxynaphthalene-1,2-dione **1** and aniline **3**, however, as per the suggested mechanism, the substrate bearing the α,β-unsaturated carbonyl scaffold acts as a nucleophile rather than an electrophile as in the conjugate addition step of Doebner-Miller reaction (discussed in ESI, Scheme S2, Table S10). The enol form of 2-hydroxynaphthalene-1,4-dione acts as a nucleophile to attack carbonyl functionality of benzaldehyde to yield aldol-type intermediate that reacts with the aniline. Both the steps involving α,β-unsaturated carbonyl are different from those proposed for Doebner-Miller reaction (Scheme 4). A Doebner-Miller type generation of quinoline would have resulted in a different product (**XV**) as shown (Scheme S3, ESI).

Table 2. Diversity of uniquely decorated 7-arylbenzo[*c*]acridine-5,6-diones



Entry	R_1	R_2	Yield[a]
1	4-Ph-Cl	OCH_3	91
2	4-Ph-Cl	CH_3	87
3	4-Ph-Br	OCH_3	82
4	4-Ph-Br	CH_3	80
5	4-Ph-CN	OCH_3	91
6	4-Ph-CN	CH_3	88
7	4-Ph-CF_3	OCH_3	79
8	4-Ph-CF_3	CH_3	81
9	2-Napthyl	OCH_3	84
10	2-Napthyl	CH_3	73
11	4-Ph-F	OCH_3	76
12	4-Ph-F	CH_3	72
13	4-Ph-NO_2	OCH_3	87
14	4-Ph-NO_2	CH_3	86
15	Ph	3,4-methylenedioxy	90
16	Ph	1-naphthyl	83
17	Ph	3-F	85
18	Ph	3-Cl	82

[a]isolated yield

With the optimized conditions in hand, to delineate this approach, the scope and generality of this protocol was next accessed by employing various aromatic aldehydes (**7a-n**) and anilines (**3a-g**) to synthesize the corresponding 7-arylbenzoacridine-6,11-diones. An assembly of nineteen compounds was synthesized using this protocol (Table 2) and the purity of all the synthesized compounds was confirmed using qNMR (Table S11).[18] The reaction could tolerate various substitutions on aromatic aldehydes. Notably, aromatic aldehydes bearing electron withdrawing substituents e.g. 4-Cl, 4-Br, 4-F, 4-NO_2, 4-CF_3 etc. at the aryl ring, afforded the desired products with excellent efficiency. It was pleasing to find that sterically bulky 2-naphthaldehyde also reacted very efficiently. The failure of reaction with aromatic aldehydes bearing *o*/*p* electron releasing groups (-OCH_3, -OH, substituted amine, morpholine, pyrrolidine, piperidine) can be attributed to the mechanism of the reaction. The result is not surprising in the light of the reduced electrophillicity of the aldehyde due to the effect of electron releasing groups. To further evaluate the substrate scope, differently substituted anilines were investigated. The reaction worked well with anilines bearing electron releasing groups (3-

Me, 3-OMe and 3,4-methylenedioxy) as well as with sterically bulky 1-naphthylamine but not with electron withdrawing groups (F, CF_3, CN, Cl, Br and NO_2) at *o*- and *p*-position. It was pleasing to observe that reaction could tolerate electron withdrawing group at *m*-position. The results are convincing for anilines bearing electron withdrawing groups at *o*- and *p*-position due to the effect of reduced nucleophilicity of the substrate.

In summary, we have developed a novel one pot domino protocol for the efficient synthesis of 7-arylbenzo[*c*]acridine-5,6-diones, a class of previously unreported compounds whose activity deserves more investigation, in 70-90% yields along with the mechanistic details. The simple experimental procedure, utilization of an inexpensive, readily available and environmental friendly catalyst and excellent yields are the advantages of the present methodology. The reaction enriches the toolbox for the synthesis of *o*-naphthoquinone heterocycles which could be applied in medicinal chemistry. Further efforts on the exploration of their biological activities are in progress.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Additional information on this study, detailed experimental procedure and analytical data for all the new compounds. Crystallographic data of the structure **5** in CIF format.] See DOI: 10.1039/b000000x/

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9. Benzaldehyde was added after 30 minutes to the refluxing mixture of aniline and 2-hydroxynaphthalene-1,4-dione in 20 mol% of *p*-TSA and the resulting mixture was refluxed for 12 h. The reported procedure is concomitant mixing of all the reagents and refluxing for 6 h.
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11. Crystal data for **5**: $C_{23}H_{13}NO_2$, M = 335.34, Monoclinic, space group $P2_1/m$, a = 9.638(6) Å, b = 7.105(5) Å, c = 11.862(8) Å, α = 90°, β = 95.858(11)°, γ = 90°, V = 808.0(9) $Å^3$, Z = 2, D_c = 1.378 mg/cm^3, μ (Mo-Kα) = 0.088 mm^{-1}, T = 296 K, 6011 reflections collected. Refinement of 721 reflections (148 parameters) with $I > 2\sigma(I)$ converged at a final $R_1 = 0.0610$, $wR_2 = 0.1451$, gof = 0.959. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary material (CCDC 998127).
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15. *p*-Toluene sulphonic acid was added to 2-hydroxynaphthalene-1,4-dione (**1**), followed by the addition of aniline (**2**). The mixture was dissolved in respective solvents (discussed in Table S1, S2 and S3) and allowed to reflux for 30 minutes, followed by the addition of benzaldehyde (**3**) and refluxed for further 12 h. The reactions were analysed by HPLC.
16. Mobile phase composition used for HPLC gradient program for the analyses was Acetonitrile:Water gradient from 10:90 at 0 min to 100:0 at 40 min.
17. These experiments were performed considering both acid activation (20 mol% *p*-TSA) and metal activation (20 mol% $NbCl_5$) of respective reagent for 10 minutes, to confirm the mechanism as per the two possibilities considered (see Fig. S2, ESI†). All the three cases were explored in both water and chloroform.
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