3,3′-(Arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) as the main product of the Mannich reaction of 2-hydroxy-1,4-naphthoquinone with 4*H*-1,2,4-triazol-4-amine and various aldehydes

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The Mannich reaction of lawsone with various aldehydes and 4*H*-1,2,4-triazol-4-amine gave unexpected 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) derivatives. With 2,4-dihydroxybenzaldehyde under the same conditions, it led to the formation of 3-hydroxy-12-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-6*H*-benzo[*b*]xanthene-6,11(12*H*)-dione instead of various triazolylaminonaphthoquinones.

Keywords: Mannich reaction, 2-hydroxynaphthalene-1,4-dione (lawsone), 4*H*-1,2,4-triazol-4-amine, 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione), benzo[*b*]xanthene-6,11(12*H*)-dione

Interest in the organic synthesis of molecules possessing the quinone structure has increased in recent years because of their biological properties, including antitumour. anti-inflammatory, molluscicidal, leishmanicidal, trypanocidal and antifungal activities.[1–6] 1,4-Naphthoquinones are widely distributed in nature, and many clinically important antitumour drugs having a quinone moiety, such as mitoxantrones, anthracyclines and saintopin, display excellent anticancer activities.[7] 2-Hydroxynaphthalene-1,4-dione (lawsone) is a red-orange dye present in the leaves of the henna plant, which is traditionally used for colouring hair and dying nails and skin and as a starting material for the development of new bioactive compounds.[8]

Some authors have reported the synthesis of aminonaphthoquinone by a one-pot reaction of 2-hydroxynaphthalene-1,4-dione aromatic aldehydes and aromatic amines in the presence of different catalysts and solvents. Dabiri *et al*.[9] reported the synthesis of 2-hydroxy-1,4-naphthoquinone derivatives using the Mannich reaction in water under reflux in the presence of indium chloride as a catalyst. Shaterian *et al*.[10] have recently described the use of ionic liquids as catalysts in the Mannich reaction of lawsone with various aldehydes and amines. Recently, Fiorot *et al*.[11] used *p*-TsOH as a catalyst in the multicomponent Mannich reaction of lawsone with *p*-nitroaniline and of pyrrolidine with some aromatic aldehydes in acetonitrile at room temperature. Saluja *et al*.[12] have also reported the synthesis of naphthoquinone–urazole hybrids *via* a one-pot condensation of lawsone, aldehydes and 4-phenylurazole employing a task-specific ionic liquid (bmim[HSO_4]).

We have designed some triazolylaminonaphthoquinones as anticancer agents, and we have used 4*H*-1,2,4-triazol-4-amine aromatic aldehydes and lawsone to synthesise them *via* the Mannich reaction in ethanol under reflux in the presence of a catalytic amount of trifluoroacetic acid (TFA). The aim of this study was to examine the application of TFA for the one-pot synthesis of our desired triazolylaminonaphthoquinones.

Results and discussion

According to the mechanism of the Mannich reaction of lawsone with aldehydes and amines that Dabiri *et al*.[10] proposed, and also for preventing side reactions, we first allowed 4*H*-1,2,4-triazol-4-amine to combine with various aromatic aldehydes in ethanol under reflux to produce the imines **3**. The formation of these imines was followed by thin-layer chromatography (TLC), and, following completion of imine formation, lawsone was added to the reaction mixture, as shown in Scheme 1. The NMR data showed, however, that the compound thus synthesised was 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) instead. Before characterising the exact structures of our products, we compared the NMR and mass spectra of our compounds with those of Fiorot's compounds.[11] Interestingly, the NMR spectrum of one of our compounds synthesised from 4-methoxybenzaldehyde was the same as the compound that Fiorot *et al*. synthesised using this aldehyde, 4-nitroaniline and lawsone. Also, the mass of the compound they reported is that of the [M-H] of 3′-[(4-methoxyphenyl) methylene]bis(2-hydroxynaphthalene-14-dione) and not of the product they expected. In addition, the melting points of our compound and that of Fiorot and co-workers were identical. The melting points and IR and NMR data of our products are the same as those of the products that Oliveira *et al*.[13] and Tisseh *et al*.[14] reported in their synthesis of 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) or bisnaphthoquinones derivatives.

In order to accomplish the synthesis of the desired triazolylaminonaphthoquinones (Scheme 1), we first allowed 4*H*-1,2,4-triazol-4-amine **1** (1.0 mmol) and 4-hydroxybenzaldehyde **2f** (1.0 mmol) to combine in ethanol under reflux to produce various imines **3**, following the formation of these imines by TLC and, after completion of imine formation, adding lawsone 4 (1.0 mmol) and TFA (20 mol%) to react in ethanol under reflux (Table 1, entry 1) to yield bisnaphthoquinone, or 3,3′-[(4-hydroxyphenyl)methylene] bis(2-hydroxynaphthalene-1,4-dione). The above three-component condensation was then tried with $InCl_3$, *p*-toluenesulfonic acid (*p*-TSA) and AcOH instead of TFA in ethanol, but the desired triazolylaminonaphthoquinone **5** did not result. Saluja *et al*.[12] also reported that a reaction of 4-chlorobenzaldehyde, lawsone and 4-phenylurazole in the presence of $InCl_3$ or other Lewis acid catalyst, such as CAN, $CeCl_3$ or $La(OTf)_3$, in ethanol under reflux gave only the bisnaphthoquinone and not their targeted aminonaphthoquinone. Surprisingly, using 2,4-dihydroxybenzaldehyde under the same conditions led to the formation of 3-hydroxy-12-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-6*H*-benzo[b]xanthene-6,11(12*H*)-dione instead of the symmetric 3,3-[(2,4-dihydroxyphenyl)methylene] bis(2-hydroxynaphthalene-1,4-dione).

The formation of this product probably occurs through nucleophilic addition of 2-hydroxy-1,4-naphthoquinone to the resulting aminonaphthoquinone in the acidic medium. The molecular structure was confirmed by IR and NMR data. We did not investigate the exact mechanism of this reaction, but a possible mechanism for the formation of the

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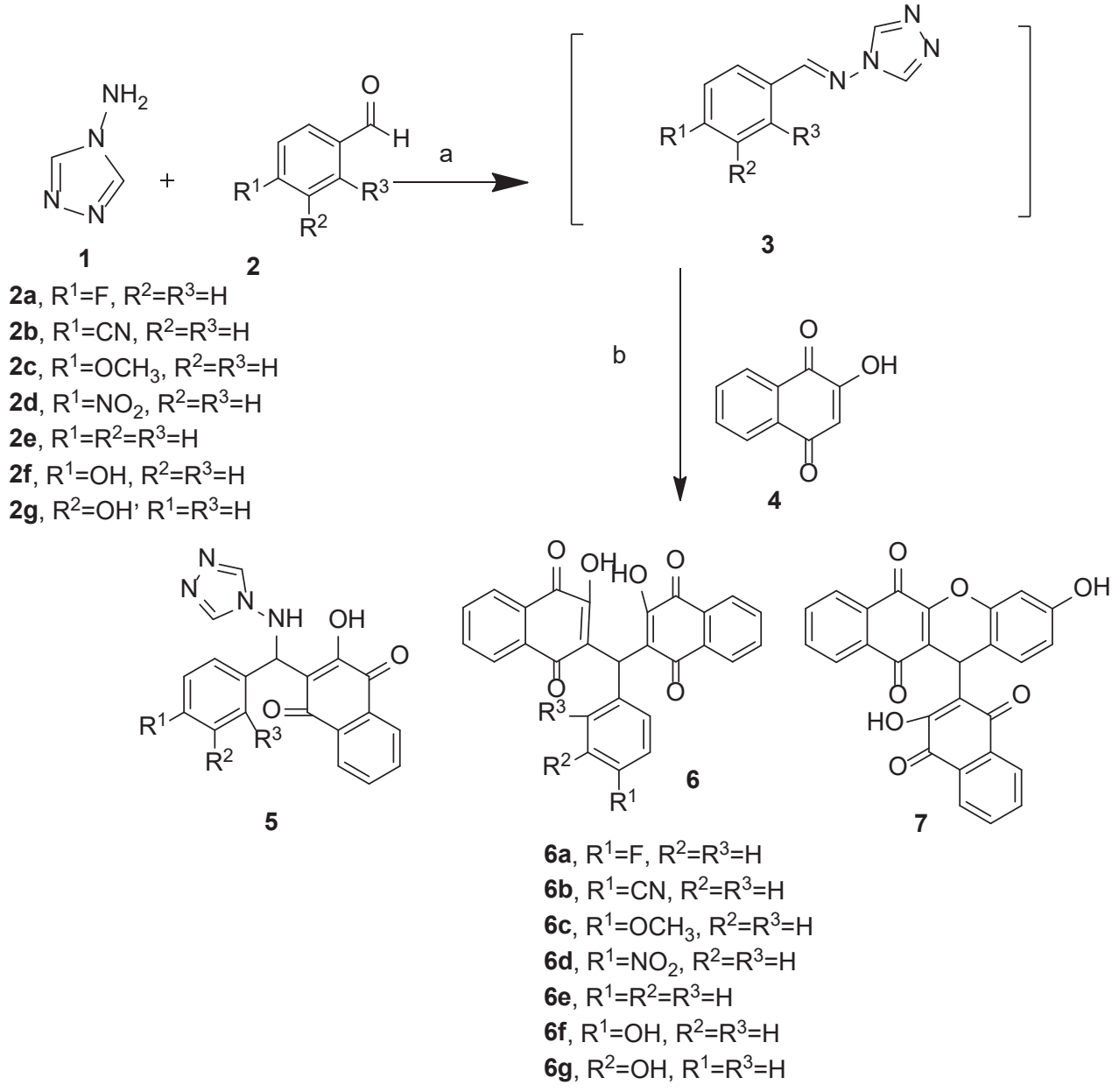
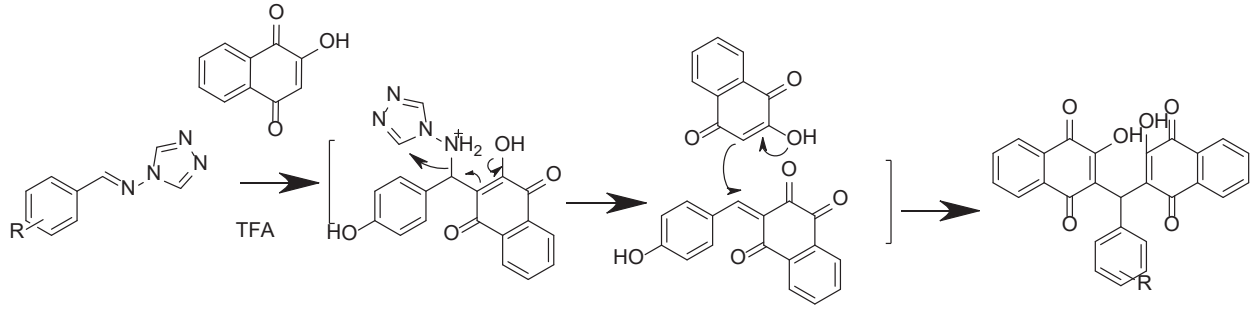


Scheme 1 Reagents and conditions: (a) EtOH, reflux; (b) EtOH, TFA, reflux.



Scheme 2 Proposed mechanism for the formation of bisnaphthoquinone derivatives.

Table 1 Reaction conditions for the synthesis of **6f**

Entry	Catalyst	Catalyst (mol%)	Solvent	Time (h)	Yield of **6f** (%)
1	TFA	20	EtOH	10	75
2	$InCl_3$	20	EtOH	10	85
3	$InCl_3$	20	Water	10	81
4	AcOH	20	EtOH	10	78
5	*p*-TSA	20	EtOH	10	53

3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) is shown in Scheme 2.

Conclusions

In conclusion, 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) is a by-product, or the main product, in the Mannich reaction of 2-hydroxy-1,4-naphthoquinone with different

aldehydes and amines, usually when the amine contains an electron-withdrawing group. With our product, the triazole ring might act as a good leaving group in the acidic environment produced by TFA following nucleophilic attack by 2-hydroxy-1,4-naphthoquinone on the aminonaphthoquinone. The reaction of lawsone with an aromatic aldehyde possessing a hydroxyl group in the *ortho* position gave the novel benzo[*b*]xanthene-6,11-dione scaffold with potential biological activity.

Experimental

All chemical reagents and solvents used in this study were purchased from Merck AG or Aldrich Chemical. Melting points were determined with a Thomas–Hoover capillary apparatus. IR spectra were acquired using a Perkin Elmer Model 1420 spectrometer. A Bruker FT-400 MHz instrument (Brucker Biosciences USA) was used to acquire ^{1}H NMR spectra with tetramethylsilane (TMS) as internal standard. Chloroform-D and DMSO-d_6 were used as solvents. Coupling constant (*J*) values were estimated in hertz (Hz), and spin multiplets are given as s (singlet), d (doublet), t (triplet) or m (multiplet) in parts per million (ppm).

Synthesis of **6a–g** *and* **7***; general procedure*

A mixture of amine (10.0 mmol) and aldehyde (10.0 mmol) was refluxed in ethanol[15]. After completion of the imine synthesis reaction, as monitored by TLC, 2-hydroxynaphthalene-1,4-dione and TFA (20 mol%) were added and the mixture refluxed overnight. The reaction mixture was then filtered and washed with ethanol to give the pure products **6a** and **6c–g.** Compounds **6b** and **7** were purified by column chromatography (chloroform:methanol, 95:5) and recrystallised from ethanol.

3,3′-[(4-Fluorophenyl)methylene]bis(2-hydroxynaphthalene-1,4-dione) (**6a**): Orange powder; m.p. 194–195 °C (same as ref.16); Yield 73%.

3,3′-[(4-Cyanophenyl)methylene]bis(2-hydroxynaphthalene-1,4-dione) (**6b**): Orange-yellow powder; m.p. 195–197 °C (same as ref.17); Yield 63%.

3,3′-[(4-Methoxyphenyl)methylene]bis(2-hydroxynaphthalene-1,4-dione) (**6c**): Yellow powder; m.p. 220–222 °C (same as ref.13); Yield 71%.

3,3′-[(4-Nitrophenyl)methylene]bis(2-hydroxynaphthalene-1,4-dione) (**6d**): Orange powder; m.p. 177–178 °C (same as ref.18); Yield 87%.

3,3′-(Phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione) (**6e**): Yellow powder; m.p. 202–204 °C (same as ref.19); Yield 55%.

3,3′-[(4-Hydroxyphenyl)methylene]bis(2-hydroxynaphthalene-1,4-dione) (**6f**): Red powder; m.p. 175–177 °C (same as ref.19); Yield 62%.

3,3′-[(3-Hydroxyphenyl)methylene]bis(2-hydroxynapthelene-1,4-dione) (**6g**): Brown powder; m.p. 170–172 °C (same as ref.17); Yield 67%.

*3-Hydroxy-12-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-6*H*-benzo[*b*]xanthene-6,11(12*H*)-dione* (**7**): Red-orange solid; m.p. 185–187 °C (decomposed); IR (KBr) (ν_{max}/cm^{-1}): 3070 (OH), 1667, 1639 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.65 (s, 1H, CH), 6.41–6.45 (m, 2H), 6.88 (s, 1H), 7.01–7.04 (d, 1H, *J* = 9 Hz), 7.45–7.50 (t, 1H, *J* = 9 Hz), 7.60–7.65 (t, 1H, *J* = 9 Hz), 7.69–7.72 (d, 1H, *J* = 9 Hz), 7.77–7.87 (m, 4H), 8.02–8.05 (dd, 1H, *J* = 6.6, *J* = 2.4), 9.45 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 67.49, 102.62, 112.79, 123.45, 124.43, 125.20, 125.38, 125.66, 126.0, 126.09, 129.75, 130.69, 130.89, 131.54, 132.02, 133.88, 134.28, 134.69, 135.85, 139.67, 149.82, 151.54, 156.78, 178.74, 188.12, 183.58, 188.35; LC-MS (ESI): 451.1 (M+1)$^+$; Anal. calcd for $C_{27}H_{14}O_7$: C, 72.00; H, 3.13; found: C, 69.92; H, 3.28%.

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