Regioselective synthesis of thiadiazolo[3,2-*a*]benzimidazole-5,8-diones

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Regioselective synthesis of the novel 7-hydroxy-2-(alkylsulfanyl)-6-undecyl[1,3,4]thiadiazolo[3,2-*a*]benzimidazole-5,8-diones was achieved by the reaction of 2,5-dihydroxy-6-undecyl-1,4-bezoquinone (embelin) with 5-(alkyl/aralkyl/phenacylsulfanyl)-1,3,4-thiadiazol-2-amines in refluxing acetic acid.

Keywords: embelin, benzoquinone, thiadiazole, heterocyclic fused

Quinones are ubiquitous in nature. They are implicated in numerous cellular functions and are involved in mechanisms of electron and hydrogen transfers. Quinones form a large class of antitumour agents approved for clinical use, and many other antitumour quinones are in different stages of clinical and preclinical development.[1] The efficiency of the quinones in inhibiting cancer cell growth is believed to stem from their participation in key cellular redox mechanisms with consequent generation of highly reactive oxygen species (ROS). It is found that the ROS modify and degrade nucleic acids and proteins within the cells.[2,3]

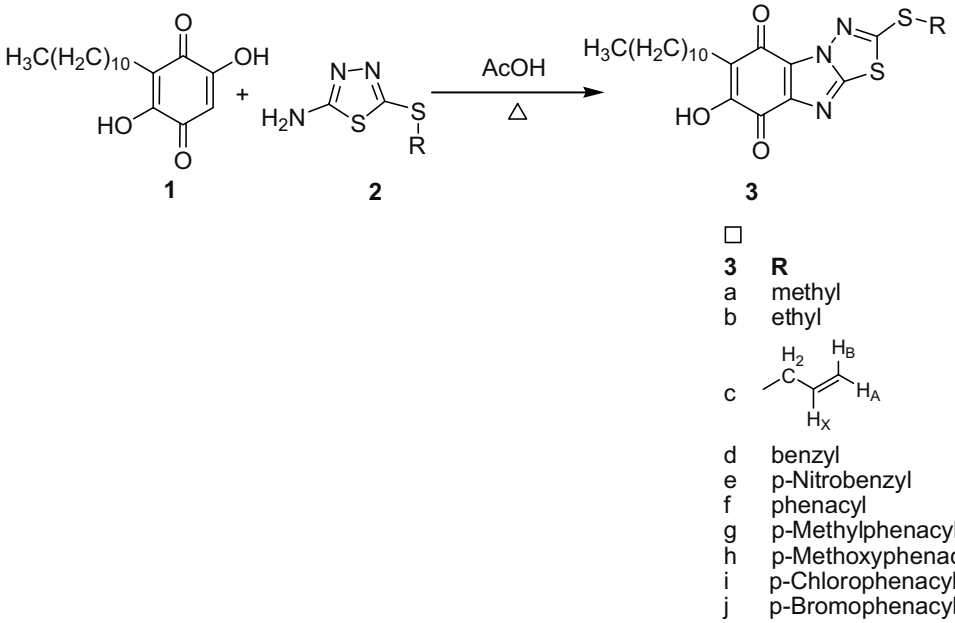
One of the most simple 1,4-benzoquinones isolated from natural sources is embelin (**1**). Embelin (**1**) is isolated as the main secondary metabolite from species of the Myrsinaceae[4,5] and Oxalidaceae[6] families. Compound **1** shows a diversity of relevant biological activities such as chemopreventive effect against DENA/PB-induced hepatocarcinogenesis in Wistar rats,[7] anti-fertility effects,[8] and *in vitro* cytotoxic activity against B16 and XC cell lines.[9] In addition, recent studies have shown that embelin is a fairly potent, nonpeptidic, cell-permeable inhibitor of XIAP (X-linked inhibitor of apoptosis protein), and it represents a promising lead compound for designing an entirely new class of anticancer agents that target the BIR3 domain of XIAP.[10,11] These antecedents justify the interest in evolving newer synthetic methods for the construction of embelin derivatives.

In view of broad biological activities of embelin derivatives, we became interested in developing novel heterocyclic fused embelin derivatives. In continuation of our earlier work,[12-14] on the synthesis of heterocyclics fused quinones from naturally occurring quinones, we now report the synthesis of the novel 7-hydroxy-2-(alkylsulfanyl)-6-undecyl[1,3,4] thiadiazolo[3,2-*a*]benzimidazole-5,8-dione (3) in a single step (Scheme 1).

The embelin (**1**) used in the reactions was obtained from Oxalis erythrorhiza following the procedure described in ref. 4. The various 5-(alkyl/aralkyl/phenacylsulfanyl)-1,3,4-thiadiazol-2-amines **2** were synthesised by the reaction of 2-amino-5-mercapto-1,3,4-thiadiazole with alkyl, aralkyl, phenacyl halides.

5-(Alkyl/aralkyl/phenacylsulfanyl)-1,3,4-thiadiazol-2-amines is believed to exist in two tautomeric structures **2** and **5.** It has been shown that in thiadiazole system, the more nucleophilic site is the cyclic secondary nitrogen at position 3. In the course of the reaction of 5-(alkyl/aralkyl/phenacylsulfanyl)-1,3,4-thiadiazol-2-amines with embelin, the secondary nitrogen with its nonbonding electrons attack on less sterically hindred carbonyl carbon of quinone **4**. Subsequent elimination of water molecule followed by oxidative cyclisation *in situ* furnished the product **3**. Further the disappearance of the characteristic signal of vinylic proton at 5.90 (s, 1H) of embelin (**1**) confirms the structure (**3**).

The possible mechanism for the formation of **3** is proposed in Scheme 2. Compound **3** was shown to have quinone moiety intact by its behaviour towards Zn/AcOH in a reduction and re-aerial oxidation test.



Scheme 1

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In summary, we have described a convenient one-step synthesis of 7-hydroxy-2-(alkylsulfanyl)-6-undecyl[1,3,4] thiadiazolo[3,2-*a*]benzimidazole-5,8-dione **3** *via* hetero-cyclisation of embelin **1** with 5-(alkyl/aralkyl/phenacyl-sulfanyl)-1,3,4-thiadiazol-2-amines **2**.

Experimental

Melting points were determined in open capillaries with a "cintex" melting point apparatus, Mumbai, India. Melting points were uncorrected and CHNS analysis was performed using Carlo Erba EA 1108 automatic elemental analyser. The purity of the compounds was checked by TLC plates (E.Merek, Mumbai, India), IR spectra (KBr) were recorded on a BrukerWM-4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-300 MHz spectrometer in δ ppm using TMS as internal standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API-2000, ESI) at 12.5eV.

Synthesis of 7-hydroxy-2-(alkyl/aralkyl/phenacylsulfanyl)-6-undecyl-[1,3,4]thiadiazolo[3,2-a]benzimidazole-5,8-dione **3***; general procedure*
A mixture of embelin **1** (10 mmol) and 5-(alkyl/aralkyl/phenacylthio)-1,3,4-thiadiazol-2-amines **2** (10 mmol) was dissolved in glacial acetic acid (15 mL) and the solution was refluxed for 4 h, cooled and treated with ice cold water. The solid separated was filtered dried and crystallised from ethanol.

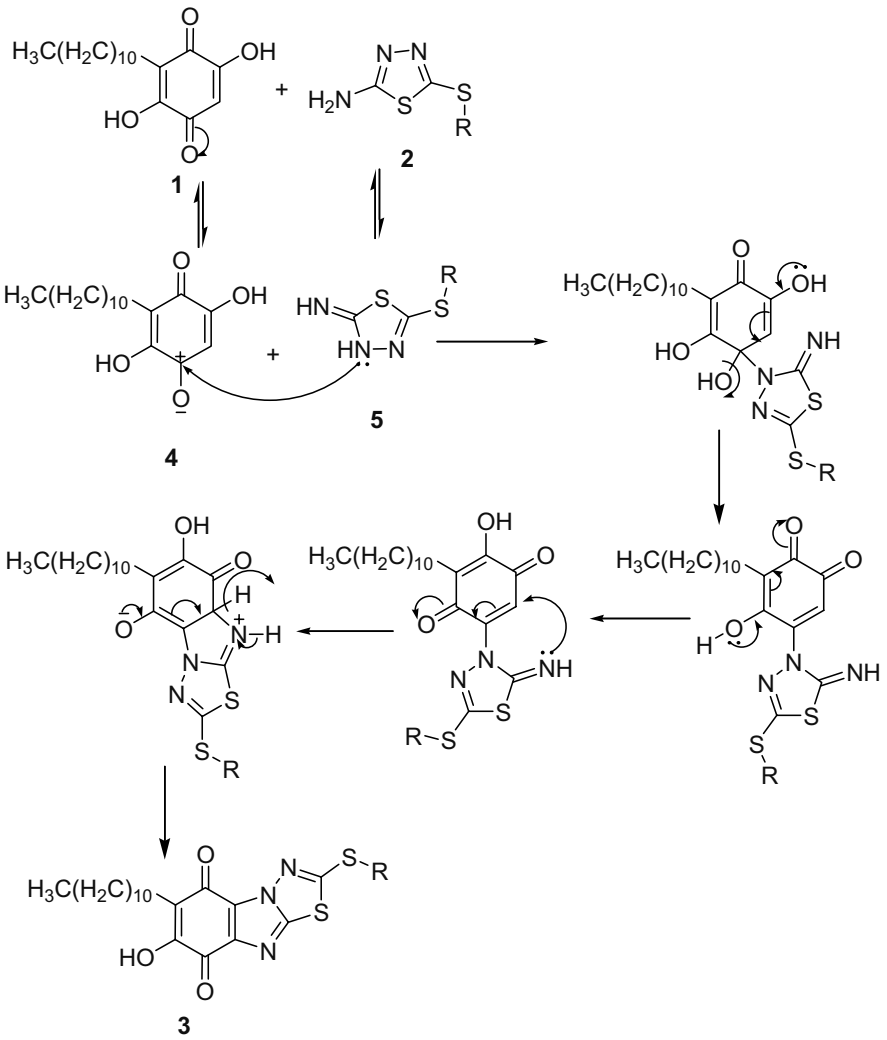
7-Hydroxy-2-(methylsulfanyl)-6-undecyl[1,3,4]thiadiazolo[3,2-a] benzimidazole-5,8-dione (**3a**): Brown solid, yield 95%, m.p. 111–112 °C. IR: ν_{max} 1648 (quinonoid C=O), 2850 (CH) and 3315 (OH) cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 0.87 (t, 3H, end CH_3), 1.20–1.40 (m, 18H, –$(CH_2)_9$-), 2.20 (s, 3H, SCH_3), 2.35 (t, 2H, allylic CH_2), and 11.77 (s, 1H, OH). EI-MS 421 (M^+). Anal. Calcd for $C_{20}H_{27}N_3O_3S_2$: C, 56.98; H, 6.46; N, 9.92; S, 15.21. Found: C, 56.94; H, 6.41; N, 9.89; S, 15.18%.

7-Hydroxy-2-(ethylsulfanyl)-6-undecyl[1,3,4]thiadiazolo[3,2-a] benzimidazole-5,8-dione (**3b**): Brown solid, yield 90%, m.p. 119–120 °C. IR: ν_{max} 1614 (quinonoid C=O), 2852 (CH) and 3313 (OH) cm^{-1}. ^{1}H NMR δ (DMSO-d_6) 0.85 (t, 3H, CH_3), 1.22–1.34 (m, 18H, –$(CH_2)_9$-), 3.35 (q, 2H, SCH_2), 1.40 (t, 3H, CH_3), 2.25 (t, 2H, –CH_2-), and 12.58 (s, 1H, OH). Anal. Calcd for $C_{21}H_{29}N_3O_3S_2$: C, 57.90; H, 6.71; N, 9.65; S, 14.72. Found: C, 57.86; H, 6.67; N, 9.62; S, 14.68%.

7-Hydroxy-2-(allylsulfanyl)-6-undecyl[1,3,4]thiadiazolo[3,2-a] benzimidazole-5,8-dione (**3c**): Brown solid, yield 92%, m.p. 101–102 °C. IR: ν_{max} 1614 (quinonoid C=O), 2848 (CH) and 3317 (OH) cm^{-1}. ^{1}H NMR δ (DMSO-d_6) 0.84 (t, 3H, CH_3), 1.25–1.35 (m, 18H, –$(CH_2)_9$-), 2.25 (t, 2H, –CH_2-), 3.86 (d, J = 5.1 Hz, 2H, S–CH_2), 5.14 (d, J = H_X, H_A, J = 8 Hz, H_A of allyl group), 5.28 (d, J = H_X, H_B, J = 16.8 Hz, H_B of allyl group), 5.90–6.00 (m, 1H, H_X), and 12.60 (s, 1H, OH). Anal. Calcd for $C_{22}H_{29}N_3O_3S_2$: C, 59.03; H, 6.53; N, 9.39; S, 14.33. Found: C, 58.96; H, 6.50; N, 9.35; S, 14.30%.

7-Hydroxy-2-(benzysulfanyll)-6-undecyl[1,3,4]thiadiazolo[3,2-a] benzimidazole-5,8-dione (**3d**): Brown solid, yield 94%, m.p. 113–114 °C. IR: ν_{max} 1614 (quinonoid C=O), 2852 (CH) and 3313 (OH) cm^{-1}. ^{1}H NMR δ (DMSO-d_6) 0.85 (t, 3H, CH_3), 1.23–1.36 (m, 18H, –$(CH_2)_9$-), 2.25 (t, 2H, –CH_2-), 4.47 (s, 2H, SCH_2), 7.27–7.40 (m, 5H, ArH) and 12.58 (s, 1H, OH). Anal. Calcd for $C_{26}H_{31}N_3O_3S_2$: C, 62.75; H, 6.28; N, 8.44; S, 12.89. Found: C, 62.71; H, 6.23; N, 8.41; S, 12.86%.

7-Hydroxy-2-(p-nitrobenzylsulfanyl)-6-undecyl[1,3,4]thiadiazolo-[3,2-a]benzimidazole-5,8-dione (**3e**): Brown solid, yield 91%, m.p. 139–140 °C. IR: ν_{max} 1614 (quinonoid C=O), 2853 (CH) and 3311 (OH) cm^{-1}. ^{1}H NMR δ (DMSO-d_6) 0.85 (t, 3H, CH_3), 1.22–1.34 (m, 18H, –$(CH_2)_9$-), 2.27 (t, 2H, –CH_2-), 5.77 (s, 2H, SCH_2), 7.67 (d, 2H, J = 8.4 Hz, ArH), 8.04 (d, 2H, J = 6.4 Hz, ArH) and 12.61 (s, 1H, OH). Anal. Calcd for $C_{26}H_{30}N_4O_5S_2$: C, 57.54; H, 5.57; N, 10.32; S, 11.82. Found: C, 57.51; H, 5.54; N, 10.30; S, 11.79%.



Scheme 2

7-Hydroxy-2-(phenacylsulfanyl)-6-undecyl[1,3,4]thiadiazolo-[3,2-a]benzimidazole-5,8-dione (**3f**): Brown solid, yield 96%, m.p. 172–173 °C. IR: ν_{max} 1614 (quinonoid C=O), 1694 (ketone C=O), 2852 (CH) and 3313 (OH) cm^{-1}. ^1H NMR δ (DMSO-d_6) 0.85 (t, 3H, CH_3), 1.31–1.46 (m, 18H, $-(CH_2)_9-$), 2.30 (t, 2H, $-CH_2-$), 5.05 (s, 2H, SCH_2), 7.58 (m, 2H, ArH), 7.70 (m, 1H, ArH), 8.05 (m, 2H, ArH) and 12.58 (s, 1H, OH). Anal. Calcd for $C_{27}H_{31}N_3O_4S_2$: C, 61.69; H, 5.94; N, 7.99; S, 12.20. Found: C, 61.64; H, 5.91; N, 7.75; S, 12.00%.

7-Hydroxy-2-(p-methylphenacylsulfanyl)-6-undecyl[1,3,4]thiadiazolo-[3,2-a]benzimidazole-5,8-dione (**3g**): Brown solid, yield 93%, m.p. 140–141 °C. IR: ν_{max} 1613 (quinonoid C=O), 1681 (ketone C=O), 2852 (CH) and 3312 (OH) cm^{-1}. ^1H NMR δ (DMSO-d_6) 0.85 (t, 3H, CH_3), 1.32–1.44 (m, 18H, $-(CH_2)_9-$), 2.31 (t, 2H, $-CH_2-$), 2.40 (s, 3H, p-methyl), 5.00 (s, 2H, SCH_2), 7.38 (m, 2H, ArH), 7.90 (m, 2H, ArH) and 12.58 (s, 1H, OH). Anal. Calcd for $C_{28}H_{33}N_3O_4S_2$: C, 62.31; H, 6.16; N, 7.79; S, 11.88. Found: C, 62.28; H, 6.13; N, 7.75; S, 11.84%.

7-Hydroxy-2-(p-methoxyphenacylsulfanyl)-6-undecyl[1,3,4]-thiadiazolo[3,2-a]benzimidazole-5,8-dione (**3h**): Brown solid, yield 97%, m.p. 159–160 °C. IR: ν_{max} 1612 (quinonoid C=O), 1676 (ketone C=O), 2852 (CH) and 3312 (OH) cm^{-1}. ^1H NMR δ (DMSO-d_6) 0.82 (t, 3H, CH_3), 1.35–1.43 (m, 18H, $-(CH_2)_9-$), 2.30 (t, 2H, $-CH_2-$), 3.80 (s, 3H, OCH_3), 5.00 (s, 2H, SCH_2), 7.10 (d, 2H, J = 8 Hz, ArH), 8.00 (d, 2H, J = 8 Hz ArH) and 12.58 (s, 1H, OH). Anal. Calcd for $C_{28}H_{33}N_3O_5S_2$: C, 60.52; H, 5.99; N, 7.56; S, 11.54. Found: C, 60.50; H, 5.96; N, 7.53; S, 11.50%.

7-Hydroxy-2-(p-chlorophenacylsulfanyl)-6-undecyl[1,3,4]-thiadiazolo[3,2-a]benzimidazole-5,8-dione (**3i**): Brown solid, yield 90%, m.p. 170–171 °C. IR: ν_{max} 1614 (quinonoid C=O), 1680 (ketone C=O), 2853 (CH) and 3313 (OH) cm^{-1}. ^1H NMR δ (DMSO-d_6) 0.85 (t, 3H, CH_3), 1.32–1.46 (m, 18H, $-(CH_2)_9-$), 2.31 (t, 2H, $-CH_2-$), 5.05 (s, 2H, SCH_2), 7.65 (m, 2H, ArH), 8.10 (m, 2H, ArH) and 12.58 (s, 1H, OH). Anal. Calcd for $C_{27}H_{30}ClN_3O_4S_2$: C, 57.90; H, 5.40; N, 7.50; S, 11.45. Found: C, 57.84; H, 5.38; N, 7.47; S, 11.41%.

7-Hydroxy-2-(p-bromophenacylsulfanyl)-6-undecyl[1,3,4]-thiadiazolo[3,2-a]benzimidazole-5,8-dione (**3j**): Brown solid, yield 92%, m.p. 165–166 °C. IR: ν_{max} 1614 (quinonoid C=O), 1680 (ketone C=O), 2852 (CH) and 3312 (OH) cm^{-1}. ^1H NMR δ (DMSO-d_6) 0.85 (t, 3H, CH_3), 1.35–1.44 (m, 18H, $-(CH_2)_9-$), 2.30 (t, 2H, $-CH_2-$), 5.00 (s, 2H, SCH_2), 7.80 (m, 2H, ArH), 8.00 (m, 2H, ArH) and 12.58 (s, 1H, OH). Anal. Calcd for $C_{27}H_{30}BrN_3O_4S_2$: C, 53.64; H, 5.00; N, 6.95; S, 10.61. Found: C, 53.58; H, 4.97; N, 6.93; S, 10.56%.

Conclusion

In conclusion, we have found a novel unexpected product formation of 7-hydroxy-2-(alkylsulfanyl)-6-undecyl[1,3,4] thiadiazolo[3,2-*a*]benzimidazole-5,8-dione **3** *via* heterocyclisation of embelin **1** with 5-(alkyl/aralkyl/phenacylsulfanyl)-1,3,4-thiadiazol-2-amines **2**.

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