

A highly regioselective synthesis of 8-hydroxy-3-sulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione and its derivatives

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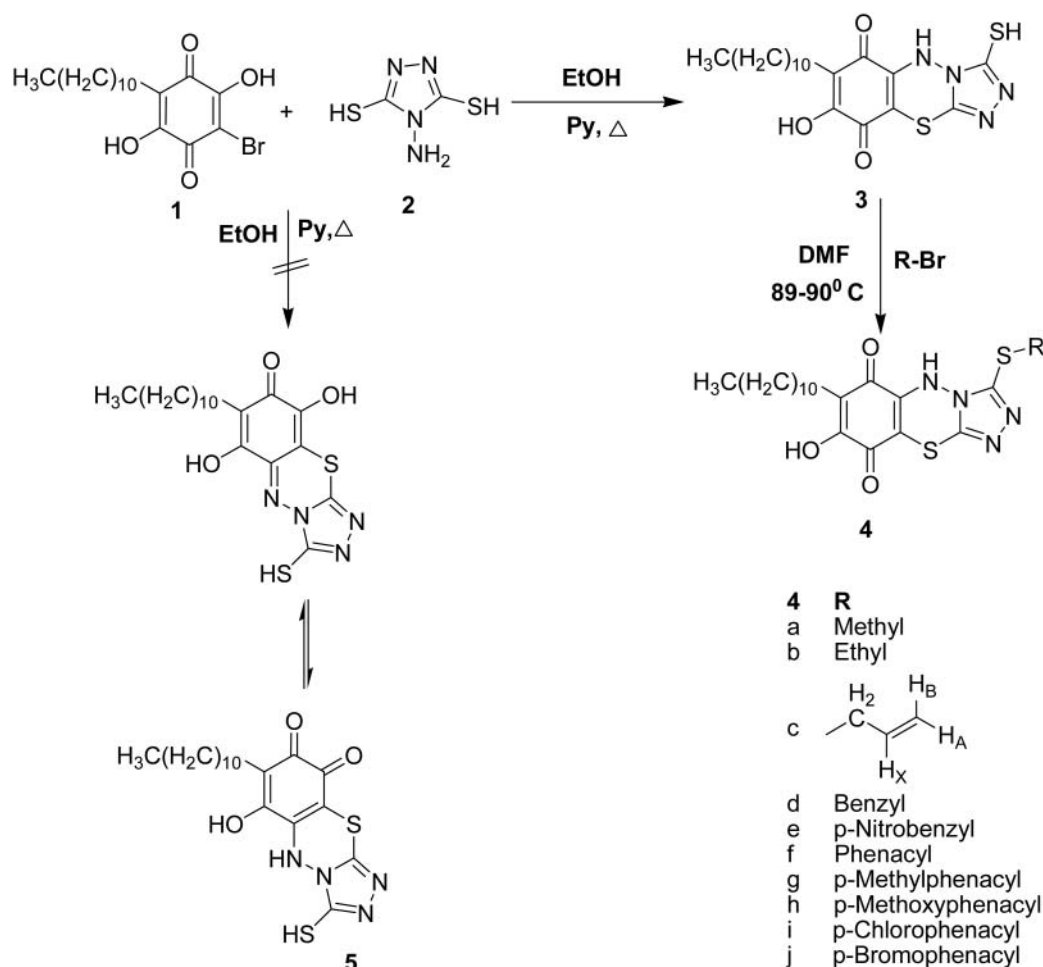
Regioselective synthesis of novel 8-hydroxy-3-sulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**3**) by condensation of 2-bromo-3,6-dihydroxy-5-undecyl-1,4-benzoquinone (bromoembelin) (**1**) with 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**2**) in ethanol. Reaction of **3** with various alkyl, aralkyl and phenacyl halides gave the corresponding thioethers (**4**).

Keywords: regioselective synthesis, 8-hydroxy-3-sulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione

The chemistry of quinones is of considerable interest since this class of compounds include many natural products and numerous important synthetic products.^{1,2} Addition of nitrogen nucleophiles to benzo and naphthoquinones represents a common synthetic route to many fused heterocyclic rings which have been used as synthetic intermediates in medicinal chemistry.^{3–6} Quinone derivatives may be toxic to cells by a number of mechanisms^{7,8} including redox arylation, intercalation, induction of DNA strand breaks, generation of free radicals and alkylation via quinone methide formation.⁹ As a consequence, the molecular framework of a large number of pharmaceuticals and biological important compounds contains a quinone moiety. Nowadays, their important pharmacological activity is also attributed to the inhibition of special proteins,

such as bacterial topoisomerase, II-DNA gyrase (antibacterial),¹⁰ mammalian topoisomerases I and II (antitumor),^{11–12} and HIV-1 integrase and proteinase (antiviral).^{13,14} Representative examples of this class of compounds are well known anticancer drugs of the anthracycline series-doxorubicine and mitoxanthrone. The action of which is believed to occur via topoisomerase II inhibition.¹²

In connection^{15–17} with our research program directed toward the synthesis of novel heterocyclic fused quinones and its derivatives, we now report the regioselective synthesis of novel 8-hydroxy-3-sulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**3**) and its derivatives **4a–j**. (Scheme 1).



Scheme 1

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2-Bromo-3,6-dihydroxy-5-undecyl-1,4-benzoquinone (**1**) has been prepared by the bromination of 2,5-dihydroxy-3-undecyl-1,4-benzoquinone using NBS in CCl_4 .¹⁸ The 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**2**) was prepared by condensation of thiocarbonylhydrazide with carbon disulfide in pyridine.¹⁹

The cyclocondensation reaction between **1** and **2** leading to the formation of **3** is highly regioselective. The reaction between **1** and **2** may also be expected to give *o*-quinonoid structure **5**. Further formation of **5** could be ruled out by the fact that the product failed to condense with *o*-phenylene diamine to give phenazine derivative under different conditions. Both the compounds **3** and **4** on reduction with Zn dust in acetic acid gave a colourless solution which on aerial oxidation regained the original colour providing evidence for the presence of 1,4-quinonoid structure.

Reaction of 2-bromo-3,6-dihydroxy-5-undecyl-1,4-benzoquinone (**1**) with 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**2**) in ethanol afforded the 8-hydroxy-3-sulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**3**). Condensation of **3** with various alkyl, aralkyl and phenacyl halides in DMF yielded the corresponding thioethers (**4**) respectively. The formation of **4** is highly selective *S*-alkylation reaction. The alkylation of **3** with alkyl, aralkyl and phenacyl halides may result in the formation of different types of products like *O*-alkylated, *N*-alkylated and *S*-alkylated. No mixtures of products were formed. In our case, only one product was observed (as evidenced by TLC). This formation of *S*-alkylated products has been explained in preference to the two other alkylated product is due to high nucleophilicity of thiol group. The *S*-alkylated products were confirmed by spectral data.

Experimental

Melting points were determined in open capillaries with a Cintex melting point apparatus, Mumbai, India. Melting points uncorrected and CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyser. The purity of the compounds was checked by TLC plates (E.Merck, Mumbai, India), IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ¹H NMR spectra were recorded on a Bruker WM-400 MHz spectrometer in δ ppm using TMS as internal standard. The NH and OH protons were exchanged with D_2O . Mass spectra (EI-MS) were determined on a Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV.

8-hydroxy-3-sulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione

A mixture of 2-bromo-3,6-dihydroxy-5-undecyl-1,4-benzoquinone (3.73 g, 0.01 mol) and 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (1.48 g, 0.01 mol) in ethanol (20 mL) and few drops of pyridine was refluxed for 4 hours. After completion of reaction the mixture was cooled and poured over crushed ice. The solid thus, separated was filtered, dried and recrystallised from methanol.

8-Hydroxy-3-sulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**3**): Yield 90%, m.p. 197–198 °C. IR: ν_{max} 1486 (C=C), 1522 (C=N), 1603, 1622 (C=O), 2916 (SH), 3305 (OH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.87 (t, 3H, $J = 5.2$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 1.62 (s, 1H, SH), 2.50 (t, 2H, $J = 6.8$ Hz, allylic CH_2), 8.85 (s, 1H, NH), 14.00 (s, 1H, OH). EI-MS 422 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_3\text{S}_2$: C, 54.00; H, 6.20; N, 13.26; S, 15.18. Found: C, 53.94; H, 6.15; N, 12.82; S, 15.12%.

Reaction of **3** with alkyl, aralkyl and phenacyl halides (**4**); general procedure

Compound **3** (0.01 mol) was dissolved in a mixture of dimethyl formamide (10 mL) and anhydrous ethanol (10 mL) and appropriate alkyl, aralkyl and phenacyl halides (0.01 mol) was added. The reaction mixture was refluxed for 3–4 hours at 80–90 °C, and then cooled; the solid separated was filtered, dried and recrystallised from suitable solvent to give the corresponding thioethers.

8-Hydroxy-3-methylsulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4a**): Yield 92%, m.p. 112–113 °C. IR: ν_{max} 1517 (C=C), 1565 (C=N), 1604 (C=O), 3274 (OH) cm^{-1} .

¹H NMR δ (CDCl_3) 0.85 (t, 3H, $J = 5.2$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.43 (t, 2H, $J = 8$ Hz, allylic CH_2), 2.67 (s, 3H, SCH_3), 8.84 (s, 1H, NH), 14.00 (s, 1H, OH). Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_3\text{S}_2$: C, 55.02; H, 6.46; N, 12.83; S, 14.69. Found: C, 55.12; H, 6.49; N, 12.82; S, 14.64%.

3-Ethylsulfanyl-8-hydroxy-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4b**): Yield 89%, m.p. 158–159 °C. IR: ν_{max} 1466 (C=C), 1559 (C=N), 1609 (C=O), 3208 (OH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.84 (t, 3H, $J = 6.4$ Hz, end CH_3), 1.23–1.30 (m, 18H, $-(\text{CH}_2)_9-$), 2.43 (t, 2H, $J = 6.8$ Hz, allylic CH_2), 2.55 (t, 3H, $J = 5.6$ Hz, CH_3 of ethyl), 3.25 (q, 2H, $J = 7.2$ Hz, CH_2 of ethyl), 14.16 (s, 1H, OH). Anal. Calcd for $\text{C}_{21}\text{H}_{30}\text{N}_4\text{O}_3\text{S}_2$: C, 55.97; H, 6.71; N, 12.43; S, 14.23. Found: C, 55.92; H, 6.67; N, 12.40; S, 14.20%.

3-Allylsulfanyl-8-hydroxy-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4c**): Yield 91%, m.p. 127–128 °C. IR: ν_{max} 1459 (C=C), 1558 (C=N), 1616 (C=O), 3268 (OH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.83 (t, 3H, $J = 8$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.42 (t, 2H, $J = 8$ Hz, allylic CH_2), 3.92 (d, $J = 7.2$ Hz, 2H, S- CH_2), 5.14 (d, $J = \text{H}_\text{X}, \text{H}_\text{A}$, $J = 9.6$ Hz, H_A of allyl group), 5.30 (d, $J = \text{H}_\text{X}, \text{H}_\text{B}$, $J = 16.8$ Hz, H_B of allyl group), 5.93–6.04 (m, 1H, H_X). Anal. Calcd for $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_3\text{S}_2$: C, 57.12; H, 6.54; N, 12.11; S, 13.86. Found: C, 57.10; H, 6.51; N, 12.00; S, 13.83%.

3-Benzylsulfanyl-8-hydroxy-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4d**): Yield 93%, m.p. 76–77 °C. IR: ν_{max} 1455 (C=C), 1495 (C=N), 1628 (C=O), 3302 (OH), 3437 (NH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.83 (t, 3H, $J = 8$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.41 (t, 2H, $J = 8$ Hz, allylic CH_2), 4.51 (s, 2H, S- CH_2), 7.25–7.33 (m, 5H, ArH). Anal. Calcd for $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_3\text{S}_2$: C, 60.91; H, 6.29; N, 10.93; S, 12.51. Found: C, 60.87; H, 5.64; N, 12.51; S, 11.46%.

3-*p*-Nitrobenzylsulfanyl-8-hydroxy-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4e**): Yield 90%, m.p. 132–133 °C. IR: ν_{max} 1466 (C=C), 1523 (C=N), 1602 (C=O), 3345 (OH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.83 (t, 3H, $J = 5.2$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.31 (t, 2H, $J = 8$ Hz, allylic CH_2), 4.58 (s, 2H, S- CH_2), 7.65–7.72 (m, 2H, ArH), 8.15–8.18 (m, 2H, ArH). Anal. Calcd for $\text{C}_{26}\text{H}_{31}\text{N}_5\text{O}_3\text{S}_2$: C, 56.00; H, 5.60; N, 12.56; S, 11.50. Found: C, 56.10; H, 5.64; N, 12.51; S, 11.46%.

8-Hydroxy-3-(2-oxo-2-phenyl-ethylsulfanyl)-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4f**): Yield 92%, m.p. 145–146 °C. IR: ν_{max} 1458 (C=C), 1526 (C=N), 1615, 1617 (C=O), 3147 (OH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.83 (t, 3H, $J = 8$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.35 (t, 2H, $J = 8$ Hz, allylic CH_2), 2.93 (s, 2H, S- CH_2), 7.43–7.58 (m, 5H, ArH), 14.00 (s, 1H, OH). Anal. Calcd for $\text{C}_{27}\text{H}_{32}\text{N}_4\text{O}_4\text{S}_2$: C, 59.98; H, 5.97; N, 10.36; S, 11.86. Found: C, 59.94; H, 5.94; N, 10.31; S, 11.89%.

8-Hydroxy-3-(2-oxo-2-*p*-tolyl-ethylsulfanyl)-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4g**): Yield 89%, m.p. 140–141 °C. IR: ν_{max} 1457 (C=C), 1516 (C=N), 1610 (quinonoid C=O), 1654 (C=O), 3412 (OH), 3740 (NH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.83 (t, 3H, $J = 8$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.35 (t, 2H, $J = 8$ Hz, allylic CH_2), 2.77 (s, 3H, *p*- CH_3), 2.89 (s, 2H, S- CH_2), 7.37–7.48 (m, 4H, ArH). Anal. Calcd for $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}_4\text{S}_2$: C, 60.62; H, 6.18; N, 10.10; S, 11.56. Found: C, 60.61; H, 6.14; N, 10.14; S, 11.59%.

8-Hydroxy-3-[2-(4-methoxy-phenyl)-2-oxo-ethylsulfanyl]-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4h**): Yield 93%, m.p. 168–169 °C. IR: ν_{max} 1512 (C=C), 1562 (C=N), 1660 (C=O), 3385 (OH), 3732 (NH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.83 (t, 3H, $J = 8$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.35 (t, 2H, $J = 8$ Hz, allylic CH_2), 3.85 (s, 3H, O- CH_3), 2.89 (s, 2H, S- CH_2), 7.06–7.20 (m, 4H, ArH). Anal. Calcd for $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}_5\text{S}_2$: C, 58.93; H, 6.00; N, 9.82; S, 11.24. Found: C, 58.97; H, 6.10; N, 9.85; S, 11.29%.

3-[2-(4-Chloro-phenyl)-2-oxo-ethylsulfanyl]-8-hydroxy-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4i**): Yield 90%, m.p. 123–124 °C. IR: ν_{max} 1523 (C=C), 1562 (C=N), 1622 (C=O), 3325 (OH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.83 (t, 3H, $J = 5.2$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.35 (t, 2H, $J = 8$ Hz, allylic CH_2), 4.39 (s, 2H, S- CH_2), 7.62–7.68 (m, 4H, ArH), 14.02 (s, 1H, OH). Anal. Calcd for $\text{C}_{27}\text{H}_{31}\text{ClN}_4\text{O}_3\text{S}_2$: C, 56.38; H, 5.43; N, 9.74; S, 11.15. Found: C, 56.34; H, 5.47; N, 9.81; S, 11.18%.

3-[2-(4-Bromo-phenyl)-2-oxo-ethylsulfanyl]-8-hydroxy-7-undecyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]benzothiadiazole-6,9-dione (**4j**): Yield 92%, m.p. 152–153 °C. IR: ν_{max} 1521 (C=C), 1562 (C=N), 1622 (C=O), 3317 (OH), 3601 (NH) cm^{-1} . ¹H NMR δ (CDCl_3) 0.83

(t, 3H, $J = 8$ Hz, end CH_3), 1.23–1.28 (m, 18H, $-(\text{CH}_2)_9-$), 2.35 (t, 2H, $J = 8$ Hz, allylic CH_2), 4.42 (s, 2H, $\text{S}-\text{CH}_2$), 7.76–7.96 (m, 4H, ArH), 14.02 (s, 1H, OH). Anal. Calcd for $\text{C}_{27}\text{H}_{31}\text{BrN}_4\text{O}_4\text{S}_2$: C, 52.34; H, 5.04; N, 9.04; S, 10.35. Found: C, 52.38; H, 5.12; N, 9.14; S, 10.39%.

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