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Regioselective synthesis of 3-sulfanyl-5*H*-naphtho[2,3-*e*][1,3,4]triazino[3,4-*b*][1,3,4]thiadiazole-6,11-dione and its derivatives

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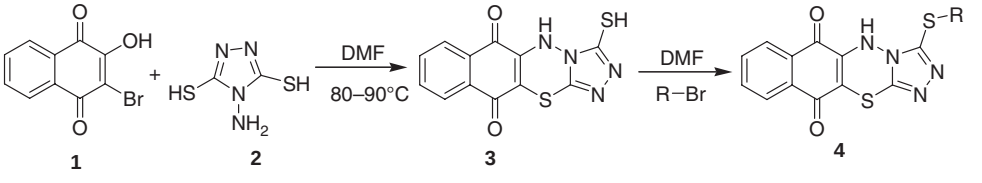
Regioselective synthesis of novel 3-sulfanyl-5*H*-naphtho[2,3-*e*][1,3,4]triazino[3,4-*b*][1,3,4]thiadiazole-6,11-dione (**3**) has been achieved by the condensation of 2-bromo-3-hydroxynaphthalene-1,4-dione (**1**) with 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**2**) in DMF. Condensation of (**3**) with various alkyl, aralkyl, and phenacyl halides gives the corresponding thioethers (**4**). The structures of newly prepared compounds have been confirmed by analytical and spectral (IR, ^{1}H NMR, MS) data.



Keywords: 2-bromo-3-hydroxynaphthalene-1,4-dione; 4-amino-4*H*-1,2,4-triazole-3,5-dithiol; bromolawsone; thiadiazole-6,11-dione; lawsone; 1,4-naphthoquinone

1. Introduction

The naphthoquinone skeleton is found in many natural products and has been employed as a synthetic intermediate for the preparation of numerous heterocyclic compounds with interesting biological properties such as antitumor, antibacterial, antifungal, and anti-inflammatory agents (*1–3*). Compounds containing the heterocyclic quinone group represent an important class of biologically active molecules (*4*). The quinones occupy an important place among the different classes of antitumor agents. The biological processes involved with the antitumoral activity of quinones are DNA intercalation, bioreductive alkylation of biomolecules, and generation of oxy radicals through redox cyclizing (*5–8*). The amino and thioether derivatives of 1,4-naphthoquinones have extremely rich biological activities because of their redox potentials (*9*, *10*). These derivatives have been found to possess marked antiviral (*11*), molluscidal (*12*), antimalarial (*13*), antileishmanial (*14*), antiproliferative (*15*), antibacterial, and antifungal activities (*16–20*).

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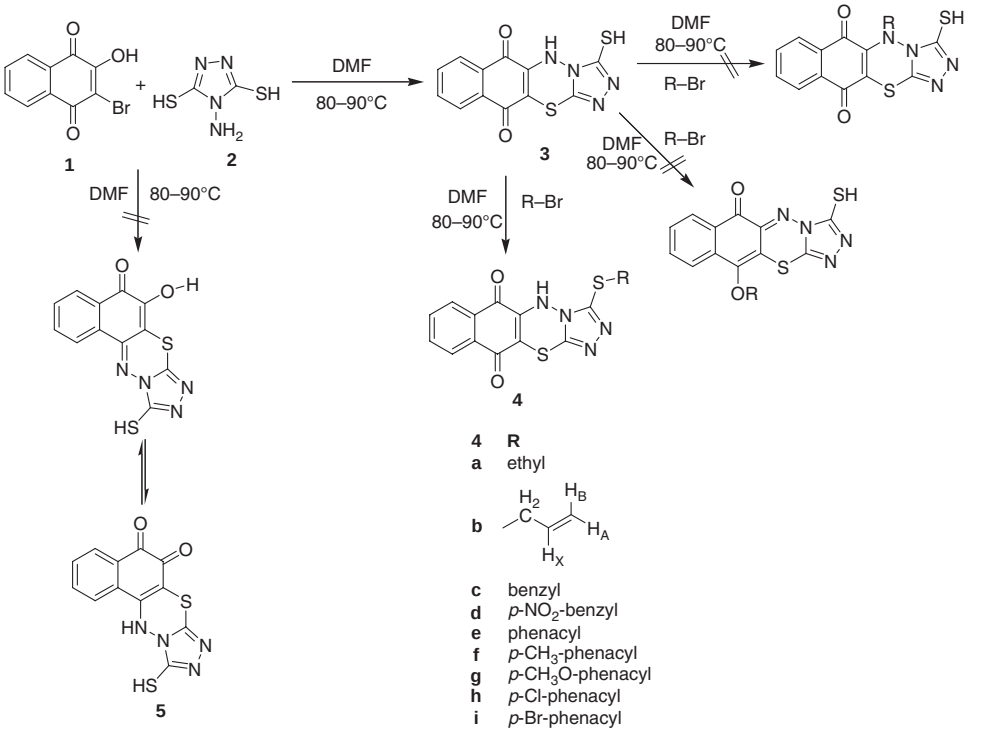
In view of various biological activities of quinones, the present work has been under taken. In continuation of our earlier work (*21, 22*) on the synthesis of heterocyclic fused quinones from naturally occurring quinones, we are now reporting the regioselective synthesis of the novel 3-sulfanyl-5*H*-naphtho[2,3-*e*][1,3,4]triazino[3,4-*b*][1,3,4]thiadiazole-6,11-dione and its derivatives.

2. Results and discussion

2-Bromo-3-hydroxynaphthalene-1,4-dione (**1**) has been prepared by the bromination of 2-hydroxy-1,4-naphthoquinone using NBS in CCl_4 (*23*). The 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**2**) was prepared by the condensation of thiocarbohydrazide with carbon disulfide in pyridine (*24*). Reaction of 2-bromo-3-hydroxynaphthalene-1,4-dione (**1**) with 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**2**) in DMF afforded the regioselective formation of 3-sulfanyl-5*H*-naphtho[2,3-*e*][1,3,4]triazino[3,4-*b*][1,3,4]thiadiazole-6,11-dione (**3**) (Scheme 1).



Scheme 1. 3-sulfanyl-5*H*-naphtho[2,3-*e*][1,3,4]triazino[3,4-*b*][1,3,4]thiadiazole-6,11-diones.

The initial nucleophilic attack of thiol (**2**) on **1** followed by an intramolecular ring closer favors the formation of a six-membered ring (**3**). The cyclocondensation reaction between **1** and **2** leading to the formation of **3** is highly regioselective.

Another possible structure to the product with *o*-quinonoid (**5**) can be proposed for the compound prepared. However, this possibility is eliminated due to the fact that the C_2 of the lawsone (2-hydroxy-1,4-naphthoquinone) moiety is relatively more positively charged than the C_4 carbonyl carbon. This favors the formation of structure **3** only. Further, the formation of **5** could be ruled out by the fact that the product failed to condense with *o*-phenylenediamine in different

conditions. Both compounds **3** and **4** on reduction with Zn dust in acetic acid gave a colorless solution which on aerial oxidation regained the original color providing evidence for the presence of 1,4-quinonoid structure.

Reaction of **3** with different alkyl, aralkyl, and phenacyl halides in a mixture of dry alcohol and DMF under anhydrous conditions yielded the corresponding thioethers (**4**). The formation **4** is a regioselective S-alkylation. The alkylation of **3** with alkyl, aralkyl, and phenacyl halides may result in the formation of different types of products such as O-alkylated, N-alkylated, and S-alkylated and a mixture of all possible alkylated products. In the present investigation, a mixture of products is not formed (as evidenced by TLC). The formation of S-alkylated products has been explained in preference to the two other alkylated products as due to high nucleophilicity of thiol group. The formation of these S-alkylated products was confirmed by spectral data.

Condensation of **3** with various alkyl, aralkyl, and phenacyl halides resulted in the formation of thioethers (**4**). The IR spectrum of **3** displayed bands in the region 1528 (C=C), 1594 (−C=N−), 1638 (−C=O), and 2931 cm^{-1} (SH weak). The ^{1}H NMR (DMSO-d_6) spectrum of **3** displayed a characteristic singlet at δ 13.7 assignable to the SH group, a signal at δ 8.3 for NH and complex multiplet centered at δ 8.0 for the four aromatic protons. In the mass spectrum of **3**, the molecular ion was recorded at m/z 302.

3. Conclusion

In summary, we have developed a concise and efficient regioselective approach for the synthesis of novel 3-sulfanyl-5*H*-naphtho[2,3-*e*][1,3,4]triazino[3,4-*b*][1,3,4]thiadiazole-6,11-dione and its derivatives. Anticancer activity of these compounds is in progress.

4. Experimental

All the reagents and solvents were purchased from commercial sources and were used without further purification unless otherwise stated. Melting points were determined in open capillaries with a "cintex" melting point apparatus, Mumbai, India. All the melting points were uncorrected and CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E. Merek, Mumbai, India), and IR spectra (KBr) were recorded on a BrukerWM-4(X) spectrometer (577model). ^{1}H NMR spectra were recorded on a Bruker WM-300 MHz spectrometer in δ (ppm) using TMS as the internal standard. The NH protons were exchanged with D_2O. Mass spectra (EI-MS) were determined on a Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV.

4.1. *General procedure*

4.1.1. *Synthesis of 3-sulfanyl-5H-naphtho[2,3-e][1,3,4]triazino[3,4-b][1,3,4]thiadiazole-6,11-dione* **3**

A mixture of 2-bromo-3-hydroxynaphthalene-1,4-dione (2.53 g, 0.01 mol) and 4-amino-4H-[1,2,4]triazole-3,5-dithiol (1.48 g, 0.01 mol) in DMF (20 ml) was stirred at 80–90 °C for 8 h. The reaction mixture was cooled and poured over crushed ice. The solid thus, separated was filtered, dried, and recrystallized from methanol.

4.1.1.1. *3-Sulfanyl-5H-naphtho[2,3-e][1,3,4]triazino[3,4-b][1,3,4]thiadiazole-6,11-dione* (**3**). Yield 92%, mp 200–202 °C. IR (KBr, υ_{max} cm^{-1}) 1528 (C=C), 1594 (−C=N−), 1638 (−C=O)

and 2931 (SH weak). ^{1}H NMR (DMSO-d_6, δ ppm): 13.4 (s, 1H, D_2O exchangable SH), 8.30 (s, 1H, NH), 7.70–8.00 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d_6, δ ppm): 126.0, 127.1, 129.8, 131.4, 132.4, 133.0, 135.0, 162.3; MS: m/z 303 $(M + H)^+$. Anal. Calcd. for $C_{12}H_6N_4O_2S_2$: Calcd: C, 47.67; H, 2.00; N, 18.53; S, 21.21%. Found: C, 47.71; H, 2.04; N, 18.57; S, 21.24%.

4.1.2. *Reaction of* **3** *with alkyl, aralkyl and phenacyl halides* **4**

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 h at 80–90 °C, then cooled, the solid separated was filtered, dried, and recrystallized from methanol to give the corresponding thioethers.

4.1.2.1. *3-Ethylsulfanyl-5H-naphtho[2,3-e][1,3,4]triazino[3,4-b][1,3,4]thiadiazole-6,11-dione* (**4a**).

Yield 91%, mp 138–140 °C. IR (KBr, υ_{max}cm^{-1}): 1540 (C=C), 1590 (−C=N−), 1626 (−C=O), 3379 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 1.35 (t, 3H, CH_3 of ethyl), 3.20 (q, 2H, CH_2 of ethyl), 7.50–7.70 (m, 2H, Ar-H), 7.85–7.75 (m, 2H, Ar-H), 8.25 (s, 1H, NH). Anal. Calcd. for $C_{14}H_{10}N_4O_2S_2$: Calcd: C, 50.90; H, 3.05; N, 16.96; S, 19.41%. Found: C, 50.94; H, 3.00; N, 16.91; S, 19.46%.

4.1.2.2. *3-Allylsulfanyl-5H-naphtho[2,3-e][1,3,4]triazino[3,4-b][1,3,4]thiadiazole-6,11-dione* (**4b**).

Yield 88%, mp 198–200 °C. IR (KBr, υ_{max} cm^{-1}): 1540 (C=C), 1593 (−C=N−), 1629 (−C=O), 3386 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 3.90 (d, $J = 6.0$ Hz, 2H, S-CH_2), 5.11 (d, $J = 7.5$ Hz, H_A of allyl group), 5.27 (d, $J = 12$ Hz, H_B of allyl group), 5.90–6.00 (m, 1H, H_X), 7.65–7.80 (m, 2H, Ar-H), 8.05–8.10 (m, 2H, Ar-H) 8.25 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{10}N_4O_2S_2$: Calcd: C, 52.62; H, 2.94; N, 16.36; S, 18.73%. Found: C, 52.66; H, 2.94; N, 16.31; S, 18.76%.

4.1.2.3. *3-Benzylsulfanyl-5H-naphtho[2,3-e][1,3,4]triazino[3,4-b][1,3,4]thiadiazole-6,11-dione* (**4c**).

Yield 87%, mp 190–192 °C. IR (KBr, υ_{max} cm^{-1}): 1541 (C=C), 1593 (C=N), 1627 (−C=O), 3379 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 4.50 (s, 2H, S-CH_2), 7.20–7.35 (m, 5H, Ar-H), 7.70–7.80 (m, 2H, Ar-H), 8.05–8.15 (m, 2H, Ar-H), 8.40 (s, 1H, NH). Anal. Calcd. for $C_{19}H_{12}N_4O_2S_2$: Calcd: C, 58.15; H, 3.08; N, 14.28; S, 16.34%. Found: C, 58.00; H, 3.00; N, 14.23; S, 16.31%.

4.1.2.4. *3-p-Nitrobenzylsulfanyl-5H-naphtho[2,3-e][1,3,4]triazino[3,4-b][1,3,4]thiadiazole-6,11-dione* (**4d**).

Yield 92%, mp 144–146 °C. IR (KBr, υ_{max} cm^{-1}) 1518 (C=C), 1594 (C=N), 1626 (−C=O), 3381 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 5.10 (s, 2H, S-CH_2), 7.40–7.60 (m, 4H, Ar-H), 8.10 (d, $J = 8.2$ Hz, 2H, H_3 and H_5 of *p*-nitrophenyl), 8.20 (d, $J = 8.2$ Hz, 2H, H_2 and H_6 of *p*-nitrophenyl), 8.40 (s, 1H, NH). Anal. Calcd. for $C_{19}H_{11}N_5O_4S_2$: Calcd: C, 52.17; H, 2.53; N, 16.01; S, 14.66%. Found: C, 52.19; H, 2.56; N, 16.10; S, 14.69%.

4.1.2.5. *3-(2-Oxo-2-phenyl-ethylsulfanyl)-5H-naphtho[2,3-e][1,3,4]triazino[3,4-b][1,3,4] thiadiazole-6,11-dione* (**4e**).

Yield 95%, mp 140–142 °C. IR (KBr, υ_{max} cm^{-1}): 1535 (C=C), 1595 (C=N), 1679 (−C=O), 3367 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 5.05 (s, 2H, S-CH_2), 7.30–7.40 (m, 5H, Ar-H), 7.80 (m, 2H, Ar-H), 8.10 (m, 2H, Ar-H), 8.40 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{12}N_4O_3S_2$: Calcd: C, 57.13; H, 2.88; N, 13.32; S, 15.25%. Found: C, 57.15; H, 2.84; N, 13.35; S, 15.28%.

4.1.2.6. *3-(2-Oxo-2-p-tolyl-ethylsulfanyl)-5H-naphtho[2,3-e][1,3,4]triazino[3,4-b][1,3,4] thiadiazole-6,11-dione* (**4f**). Yield 92%, mp 166–168 °C. IR (KBr, υ_{max} cm^{-1}): 1514 (C=C), 1601 (C=N), 1676 (–C=O), 3379 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 2.50 (s, 3H, Ph-CH_3), 4.60 (s, 2H, S-CH_2), 7.60–7.80 (m, 4H, Ar-H), 8.10 (d, $J = 8.2$ Hz, 2H, H_3 and H_5 of tolyl ring) and 8.20 (d, $J = 8.2$ Hz, 2H, H_2 and H_6 of tolyl ring), 8.30 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{14}N_4O_3S_2$: Calcd: C, 58.05; H, 3.25; N, 12.89; S, 14.76%. Found: C, 58.00; H, 3.28; N, 12.92; S, 14.29%.

4.1.2.7. *3-[2-(4-Methoxy-phenyl)-2-oxo-ethylsulfanyl]-5H-naphtho[2,3-e][1,3,4]triazino [3,4-b][1,3,4]thiadiazole-6,11-dione* (**4g**). Yield 88%, mp 178–180 °C. IR (KBr, υ_{max} cm^{-1}): 1572 (C=C), 1595 (C=N), 1669 (−C=O), 3406 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 3.80 (s, 3H, O-CH_3), 5.00 (s, 2H, S-CH_2), 7.81–7.89 (m, 4H, Ar-H), 8.10 (d, $J = 8.2$ Hz, 2H, H_3 and H_5 of *p*-methoxy phenyl), 8.50 (d, $J = 8.2$ Hz, 2H, H_2 and H_6 of *p*-methoxy phenyl), 8.40 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{14}N_4O_4S_2$: Calcd: C, 55.99; H, 3.13; N, 12.44; S, 14.24%. Found: C, 55.96; H, 3.15; N, 12.48; S, 14.28%.

4.1.2.8. *3-[2-(4-Chloro-phenyl)-2-oxo-ethylsulfanyl]-5H-naphtho[2,3-e][1,3,4]triazino [3,4-b][1,3,4]thiadiazole-6,11-dione* (**4h**). Yield 87%, mp 172–174 °C. IR (KBr, υ_{max} cm^{-1}) 1529 (C=C), 1587 (C=N), 1648 (−C=O), 3088 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 5.10 (s, 2H, S-CH_2), 7.60–7.70 (m, 4H, Ar-H), 7.80 (d, $J = 8$ Hz, 2H, H_3 and H_5 of *p*-chlorophenacyl), 7.9 (d, $J = 8$ Hz, 2H, H_2 and H_6 of *p*-chlorophenacyl), 8.50 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{11}ClN_4O_3S_2$: Calcd: C, 52.80; H, 2.44; N, 12.32; S, 14.10%. Found: C, 52.84; H, 2.48; N, 12.34; S, 14.14%.

4.1.2.9. *3-[2-(4-Bromo-phenyl)-2-oxo-ethylsulfanyl]-5H-naphtho[2,3-e][1,3,4]triazino [3,4-b][1,3,4]thiadiazole-6,11-dione* (**4i**). Yield 90%, mp 118–120 °C. IR (KBr, υ_{max} cm^{-1}): 1544 (C=C), 1583, (C=N), 1679 (C=O) 3082 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 5.00 (s, 2H, S-CH_2), 7.60–7.70 (m, 4H, Ar-H), 7.80 (d, $J = 8$ Hz, 2H, H_3 and H_5 of *p*-bromophenacyl), 7.90 (d, $J = 8$ Hz, 2H, H_2 and H_6 of *p*-bromophenacyl), 8.50 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{11}BrN_4O_3S_2$: Calcd: C, 48.10; H, 2.22; N, 11.22; S, 12.84%. Found: C, 48.14; H, 2.24; N, 11.25; S, 12.88%.

Acknowledgements

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