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RESEARCH ARTICLE

Facile synthesis of some novel 4-{3-aryl-3, 4-dihydro-2*H*-benzo[*b*][1,4] thiazin-2-*yl*}-2*H*-chromen-2-one derivatives

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A protocol for chemoselective one pot synthesis of 4-{3-aryl-3, 4-dihydro-2*H*-benzo[b][1,4]thiazin-2-*yl*}-2*H*-chromen-2-ones **4** and 4-{3-aryl-3, 4-dihydro-2*H*-benzo[b][1,4]thiazin-2-*yl*}-2*H*-chromen-2-ones **6** under refluxing conditions has been developed. Starting from 4-bromomethylcoumarin and Schiff base, which is derived from *o*-aminothiophenol and substituted aromatic aldehydes, the intermediate sulfide spontaneously underwent intramolecular carbanion addition across the azomethine carbon.

Keywords: 4-Bromomethylcoumarin; 4-{3-aryl-3, 4-dihydro-2*H*-benzo[b][1,4]thiazin-2-*yl*}-2*H*-chromen-2-ones; Schiff base; Nucleophilicity; Intramolecular; *o*-Aminothiophenol

1. Introduction

Several substituted thieno[2,3-*b*][1,4]-thiazine derivatives are currently of interest due to their therapeutic role as smooth muscle relaxants [1] and as potassium channel-opening agents [2], which make them potentially useful for the treatment of various diseases. Further, thieno[2,3-*b*][1,4]thiazine-2-ones have been patented as urokinase inhibitors [3] while [1,4]benzothiazine derivatives act as calcium antagonists [4–6]. The 4-hydroxycoumarin fragment occurs in many synthetic and natural products, which are used clinically as drugs [7–9], anticoagulants [10–13], and rodenticides [14]. Some of the coumarin derivatives exhibit antimicrobial [15] and antiinflamatory [16] activity.

2. Results and discussion

We have developed interest in the condensed benzo-[1,4]thiazinylcoumarin systems. In particular, we investigated that the hitherto described 4-{3-aryl-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-2*H*-chromen-2-one (**4a–4f**) and 4-{3-aryl-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-2*H*-chromen-2-ones (**6a–6d**), representing a benzo[1,4]thiazine

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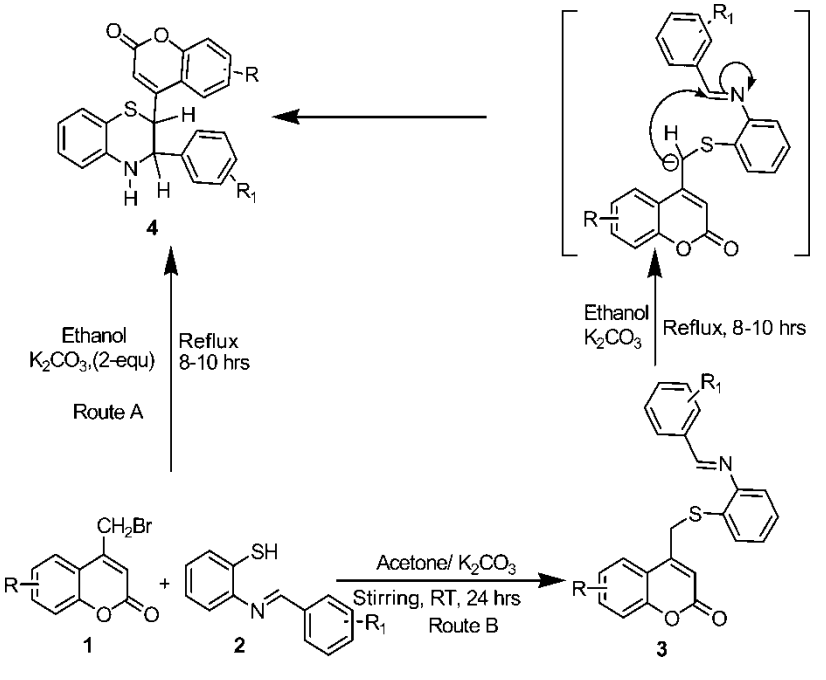
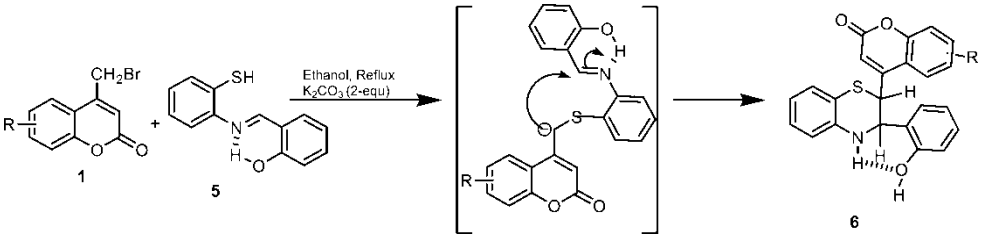
having coumarin heterocycles, as they may exhibit interesting bioproperties. Hence, this work deals with the synthesis and properties of such compounds as outlined in schemes 1 and 2 and detailed in the experimental section. These novel heterocycles (**4a**–**4f**) and (**6a**–**6d**) may be potential bioisosteres of the recently described [1,4]-thiazino-[2,3-*h*]quinoline-8-carboxylic acids [17].

The required 4-bromomethylcoumarins [18] **1** were prepared by the Pechmann cyclization of various phenols with 4-bromoethylacetoacetate [19]. The *o*-*N*-benzylidene thiophenols **2** were prepared by the nucleophilic addition of aromatic aldehydes with *o*-aminothiophenol. The 4-bromomethylcoumarins **1** and the *o*-*N*-benzylidene thiophenols **2** were refluxed in ethanol in the presence of two equivalents of anhydrous potassium carbonate: in route **A**, resulting a high yielding compound that exhibited the characteristic two doublets of **4a** at δ 4.59 (d, 1H, $J = 4.1$ Hz, C_2-H of 1,4-benzothiazine), 5.82 (d, 1H, $J = 4.2$ Hz, C_3-H of benzothiazine), but also peaks at 6.38 (s, 1H, C_3-H of coumarin), 6.46–7.63 (m, 13H Ar−H and NH) in ^{1}H NMR, and NH stretching band at 3373 cm^{-1} in the IR spectrum; in route **B**, the two reactants were stirred at room temperature with an equimolar quantity of anhydrous potassium carbonate in acetone, which led to the sulfide **3** that exhibited a singlet ~4.5 δppm in ^{1}H NMR for two methylene protons. This was again converted to **4** by refluxing in ethanol with anhydrous potassium carbonate, presumably according to the mechanistic pathway presented in scheme 1. The purity was confirmed by LCMS and HPLC.

In view to study the nucleophilicity of phenolic OH and thiol, the reaction of Schiff base **5** derived from salicylaldehyde and *o*-aminothiophenol was used and its reaction was attempted with 4-bromomethylcoumarin **1**. The two reactants **1** and **5** were refluxed in ethanol for 10 h in the presence of two equivalents of anhydrous potassium carbonate to obtain the target molecule **6**, the assignment of which was confirmed by spectral analysis. In the ^{1}H NMR of **8a**, peaks were observed at δ 2.50 (s, 3H, C_6-CH_3, of coumarin), 4.66 (d, 1H, $J = 4.6$ Hz, C_2-H of 1,4-benzothiazine), 5.20 (br, s, 1H, OH), 5.72 (d, 1H, $J = 4.5$ Hz, C_3-H of benzothiazine), 6.53 (s, 1H, C_3-H of coumarin), 6.67–7.74 (m, 11H, Ar−H), and 9.45 (s, 1H, NH). To corroborate,



SCHEME 1



SCHEME 2

the characteristic OH, NH broad-stretching bands were observed at 3367–3300 cm^{-1} in the IR. The intramolecular hydrogen bonding could make the azomethine more electrophilic, thus facilitating the attack of carbanion. The SH in the *o*-aminothiophenol moiety is less stabilized by intramolecular hydrogen bonding via a five-membered ring, and the phenolic OH from the salal ring is better stabilized via six-membered ring **5**, and hence less nucleophilic. The reaction mechanism is presented in scheme 2. The results obtained have led us to conclude the formation of 4-{3-aryl-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-2*H*-chromen-2-ones **6**.

3. Experimental section

Melting points were determined using an electric melting point apparatus (Shital scientific industries, Mumbai, India) and are uncorrected. IR spectra (KBr) were run on a Nicolet impact 410 FT-IR spectrometer (ν_{max} in cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with TMS as an internal standard (chemical shift in δ, ppm and J values in Hz) on a Brucker 300 MHz FTNMR spectrometer. Mass spectra were recorded on Finnigan MAT (Model MAT8200) spectrometer. Electrospray ionization mass spectra (ESI-MS) were recorded on Quattro LCZ (Walters-Micromass, Manchester) and Elemental analyses were carried out on a Heraus CHN rapid analyzer. Purity of the compounds was checked by TLC, LCMS (MPS-SCIEX-API-2000), and HPLC (Agilent 1100 Series). Nomenclature was made using ChemDraw software. All the reagents were of laboratory reagent quality and were used after purification.

Preparation of 4-{3-aryl-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-2*H*-chromen-2-ones (4a–4f and 6a–6d); General procedure. The substituted 4-bromomethylcoumarin (**1**) (0.004 mol) was refluxed with 2-aminothiophenol Schiff base (**2**/**5**) (0.004 mol) and potassium carbonate (0.008 mol) in 20 mL of dry ethanol on a water bath for 10 h. The reaction mixture was filtered to remove potassium carbonate. The filtrate was concentrated and the residue obtained was washed with 1:1 (HCl), finally washed with water and saturated brine solution and crystallized from ethanol.

4-{3-aryl-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-6-methyl-2*H* -chromen-2-one (4a). Colorless solid, crystalized from ethanol, yield 89%, m.p. 208 °C; IR (KBr), 1720, 3373 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 2.51 (s, 3H), 4.59 (d, 1H, $J = 4.1$ Hz), 5.82 (d, 1H, $J = 4.2$ Hz), 6.38 (s, 1H), 6.46–7.63 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.86, 65.09, 85.67, 105.87, 107.83, 109.88, 114.85, 114.97, 117.02, 117.81, 119.94, 120.08, 126.09, 129.89, 130.07, 131.96, 134.01, 135.07, 141.87, 143.90, 146.76, 147.11, 152.05, 161.88; MS (EI) m/z 385.09 (M^+, 100%); Anal. Calcd. for $C_{24}H_{19}NO_2S$; C, 74.78; H, 4.97; N, 3.63%. Found: C, 74.74; H, 5.01; N, 3.68%.

4-{3-(4-methoxyaryl)-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-6-methyl-2*H*-chromen-2-one (4b). Colorless solid, crystalized from ethanol, yield 82%, m.p. 165 °C; IR (KBr) 1731, 3392 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 2.48 (s, 3H), 3.72 (s, 3H), 5.23 (d, 1H, $J = 3.8$ Hz), 5.82 (d, 1H, $J = 3.8$ Hz), 6.45 (s, 1H), 6.47–7.67 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 26.25, 55.01, 62.32, 87.82, 106.41, 108.09, 109.56, 115.21, 115.93, 117.87, 118.95, 120.08, 120.96, 126.87, 130.08, 131.03, 132.07, 134.71, 134.63, 142.83, 143.04, 147.06, 147.62, 151.91, 162.65; MS (EI) *m/z* 415.52 (M^+, 100%); LCMS (*m/z*) 414.9 (M^+, 96.72%); HPLC 98.01%; Anal. Calcd. for $C_{25}H_{21}NO_3S$; C, 72.27; H, 5.09; N, 3.37%. Found: C, 72.32; H, 5.07; N, 3.42%.

4-{3-(4-nitroaryl)-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-6-methyl-2*H*-chromen-2-one (4c). Pale yellow solid, crystalized from ethanol:1,4-dioxane (80:20%), yield 75%, m.p. 202 °C; IR (KBr) 1725, 3363 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), 2.45 (s, 3H), 5.13 (d, 1H, $J = 4.0$ Hz), 5.84 (d, 1H, $J = 4.0$ Hz), 6.48 (s, 1H), 6.52–7.65 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) 25.92, 71.31, 88.76, 106.36, 107.05, 108.93, 115.08, 115.92, 117.79, 118.09, 119.85, 120.87, 127.11, 130.06, 131.17, 132.14, 134. 98, 136.10, 142.74, 143.97, 147.06, 148.01, 158.15, 163.89; MS (EI) *m/z*430.18 (M^+, 100%); Anal. Calcd. for $C_{24}H_{21}N_2O_4S$; C, 66.96; H, 4.21; N, 6.51%. Found: C, 66.92; H, 4.28; N, 6.57%.

4-{3-aryl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-7-methyl-2*H*-chromen-2-one (4d). Colorless solid, crystalized from ethanol, yield 85%, m.p. 115 °C; IR (KBr), 1716, 3368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), 2.54 (s, 3H), 4.56 (d, 1H, $J = 4.2$ Hz), 5.80 (d, 1H, $J = 4.4$ Hz), 6.48 (s, 1H), 6.52–7.67 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.06, 66.11, 85.71, 105.79, 107.02, 109.07, 113.97, 114.88, 117.70, 118.01, 119.24, 121.01, 125.93, 129.67, 131.01, 132.06, 135.12, 135.87, 142.17, 143.95, 147.13, 147.90, 151.79, 162.18; MS (EI) *m/z* 385.13 (M^+, 100%); Anal. Calcd. for $C_{24}H_{19}NO_2S$; C, 74.78; H, 4.97; N, 3.63%. Found: C, 74.81; H, 5.03; N, 3.65%.

4-{3-(4-methoxyaryl)-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-7-methyl-2*H*-chromen-2-one (4e). Colorless solid, crystalized from ethanol, yield 78%, m.p. 121 °C; IR (KBr) 1708, 3378 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), 2.50 (s, 3H), 3.71 (s, 3H), 4.54 (d, 1H, $J = 3.5$ Hz), 5.56 (d, 1H, $J = 3.5$ Hz), 6.53 (s, 1H), 6.57–7.39 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.82, 55.12, 63.03, 86.97, 106.51, 108.43, 108.95, 116.02, 116.43, 117.90, 118.91, 120.12, 120.76, 126.94, 130.19, 131.58, 132.68, 134.73, 134.81, 143.03, 143.54, 147.36, 147.72, 152.01, 162.43; MS (EI) *m/z* 415.43 (M^+, 100%); Anal. Calcd. for $C_{25}H_{21}NO_3S$; C, 72.27; H, 5.09; N, 3.37%. Found: C, 72.36; H, 5.11; N, 3.40%.

4-{3-(4-nitroaryl)-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-7-methyl-2*H*-chromen-2-one (4f). Yellow solid, crystalized from ethanol:1,4-dioxane (80:20%), yield 82%, m.p. 182 °C; IR (KBr) 1712, 3382 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), 2.51 (s, 3H), 5.23 (d, 1H, $J = 3.7$ Hz), 5.86 (d, 1H, $J = 3.6$ Hz), 6.43 (s, 1H), 6.55–7.63 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) 26.02, 71.78, 88.93, 106.26, 107.25, 108.81, 115.34, 115.83, 117.81, 118.11, 120.05, 120.83, 127.61, 130.13, 131.31, 132.27, 135. 11, 136.15, 142.24, 143.79, 147.56, 148.57, 158.29, 163.65; MS (EI) *m/z* 430.08 (M^+, 100%); Anal. Calcd. for $C_{24}H_{21}N_2O_4S$; C, 66.96; H, 4.21; N, 6.51%. Found: C, 66.94; H, 4.26; N, 6.59%.

4-{3-(2-hydroxyaryl)-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-6-methyl-2*H*-chromen-2-one (6a). Colorless solid, crystalized from ethanol:1,4-dioxane (90 : 10%), yield 72%, m.p. 226 °C; IR (KBr) 1716, 3367–3300 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6); 2.50 (s, 3H), 4.66 (d, 1H, $J = 4.6$ Hz), 5.20 (br, s, 1H), 5.72 (d, 1H, $J = 4.5$ Hz), 6.53 (s, 1H), 6.67–7.74 (m, 11H), 9.45 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) 24.85, 59.62, 78.38, 104.53, 105.09, 107.61, 114.65, 114.98, 116.80, 117.85, 119.84, 120.09, 125.92, 130.21, 130.93, 131.43, 132. 71, 132.97, 141.93, 142.09, 146.17, 147.01, 150.08, 160.95; MS (EI) m/z 401.7 (M^+, 100%); LCMS (m/z) 401.9 (M^+, 97.63%); HPLC 98.81%; Anal. Calcd. for $C_{24}H_{19}NO_3S$; C, 71.80; H, 4.77; N, 3.49%. Found: C, 71.85; H, 4.88; N, 3.52%.

4-{3-(2-hydroxyaryl)-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-7-methyl-2*H*-chromen-2-one (6b). Colorless solid, crystalized from ethanol:1,4-dioxane (90:10%), yield 75%, m.p. 117 °C; IR (KBr) 1712, 3352–3309 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), 2.45 (s, 3H), 4.68 (d, 1H, $J = 4.8$ Hz), 5.18 (br, s, 1H), 5.76 (d, 1H, $J = 4.8$ Hz), 6.46 (s, 1H), 6.66–7.78 (m, 11H), 9.53 (s, 1H); MS (EI) m/z 401.5 (M^+, 100%).

4-{3-(2-hydroxyaryl)-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-6-methoxyl-2*H*-chromen-2-one (6c). Colorless solid, crystalized from ethanol: 1,4-dioxane (90:10%), yield 68%, m.p. 182 °C; IR (KBr) 1709, 3348–3313 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), 3.65 (s, 3H), 4.67 (d, 1H, $J = 4.3$ Hz), 5.28 (br, s, 1H), 5.71 (d, 1H, $J = 4.2$ Hz), 6.42 (s, 1H), 6.65–7.75 (m, 11H), 9.48 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) 54.87, 61.74, 81.28, 105.63, 106.11, 108.51, 114.75, 115.38, 116.79, 117.71, 120.04, 120.13, 125.87, 130.63, 131.07, 131.94, 132. 84, 133.17, 142.21, 142.88, 147.47, 148.34, 151.13, 161.82; MS (EI) m/z 417.16 (M^+, 100%); Anal. Calcd. for $C_{24}H_{19}NO_4S$; C, 69.05; H, 4.59; N, 3.36%. Found: C, 69.11; H, 4.65; N, 3.41%.

4-{3-(2-hydroxyaryl)-3, 4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-*yl*}-6-chloro-2*H*-chromen-2-one (6d). Colorless needles, crystalized from ethanol, yield 65%, m.p. 163 °C; IR (KBr) 1714, 3355–3311 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), 4.64 (d, 1H, $J = 4.1$ Hz), 5.31(br, s, 1H), 5.74 (d, 1H, $J = 3.9$ Hz), 6.47 (s, 1H), 6.63–7.71 (m, 11H), 9.43 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) 65.18, 86.38, 106.37, 107.01, 109.73, 113.53, 115.72, 116.08, 118.86, 120.89, 121.22, 124.92, 130.74, 131.57, 132.41, 133.39, 133.27, 143.01, 143.68, 149.58, 150.41, 154.35, 163.53; MS (EI) m/z 422.02 (M^{+1}, 100%); Anal. Calcd. for $C_{23}H_{16}ClNO_3S$; C, 65.48; H, 3.82; N, 3.32%. Found: C, 65.53; H, 3.87; N, 3.39%.

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