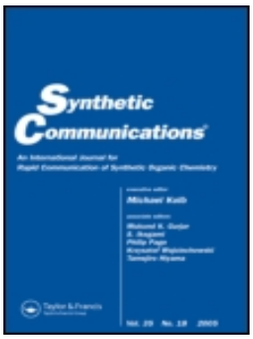

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SYNTHESIS OF COUMARIN-SUBSTITUTED 1,3,4-THIADIZINE-2-THIONES AND 1,3-THIAZOLINE-2-THIONES

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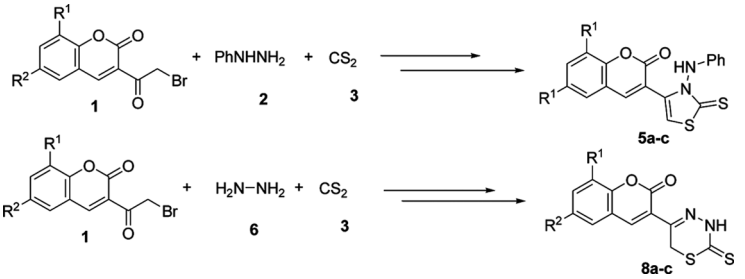
GRAPHICAL ABSTRACT



Abstract *Interaction of phenyl hydrazine / hydrazine with carbon disulfide in the presence of KOH affords the corresponding potassium salts of dithioformates. These in situ generated salts were reacted with different 3-(2-bromoacetyl)coumarins to yield N^1-phenyl-hydrazinecarbodithioic acid 2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl ester **(4a–c)** and hydrazinecarbodithioic acid 2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl ester **(7a–c)** respectively. Cyclocondensation of these compounds in the presence of an acid gave 3-(3-phenylamino-2-thioxo-2,3-dihydro-thiazol-4-yl)-chromen-2-ones **(5a–c)** and 3-(2-thioxo-3,6-dihydro-2-H-[1,3,4]thiadiazin-5-yl)-chromen-2-ones **(8a–c)** respectively.*

Keywords 3-(2-Bromoacetyl)coumarin; one-pot synthesis; thiadiazine-2-thiones; thiazoline-2-thiones

INTRODUCTION

Dithioformates are obtained by the reaction of carbon disulfide with amines or hydrazines. Using dithioformates, various types of N- and S-containing heterocycles have been synthesized. Among these heterocycles, 1,3,4-thiadiazines are biologically active compounds. Many of these derivatives are important matrix metalloproteinase inhibitors.[1] They have shown excellent cardiotonic and hypertensive activities.[2,3] They act as phosphodiesterase IV inhibitors, and these will be used for treatment of tumors and Acquired Immune Deficiency Syndrome (AIDS).[4]

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These derivatives may be used in agriculture as pesticides and insecticides.[5,6] Some of these derivatives act as photographic magenta couplers.[7] Similarly, thiazolines also act as dopamine β-monooxygenase (DBM) inhibitors.[8] They are also used as antimicrobial agents.[9,10]

Coumarins are heterocyclic compounds, which are also known as benzo-2-pyrone derivatives, and constitute an important group of natural products with various biological activities.[11,12] The synthesis of coumarins and their derivatives have attracted considerable attention from organic and medicinal chemists for many years because of their wide range of medicinal applications such as antitumoral, anti-inflammatory, antiviral, CNS active, and antioxidant activities.[13–15] Some of coumarin derivatives have been known for their anti-HIV activities.[16–18] They were also extensively used as photochromes with modulated fluorescence and laser dyes.[19,20]

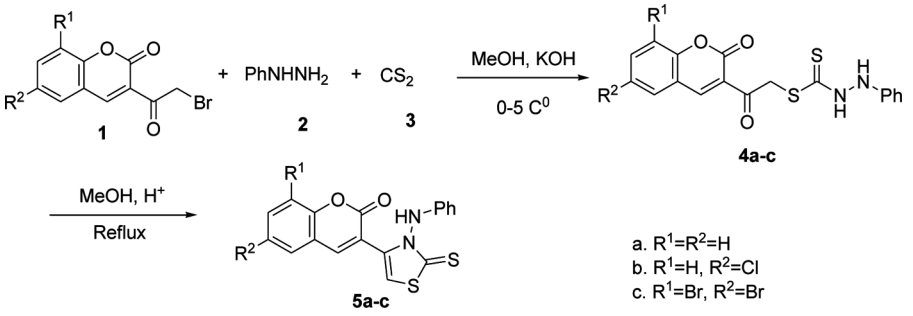
In view of the biological importance of coumarins, thiadiazines, and thiazolidines, and in continuation of our earlier work on the synthesis of novel heterocyclic systems,[21–23] in the present investigation an attempt has been made to synthesize compounds containing coumarin: 1,3,4-thiadiazine-2-thione and 1,3-thiazoline-2-thione. These compounds are expected to have enhanced biological activity and might provide additional lead molecules for use in drug discovery.

RESULTS AND DISCUSSION

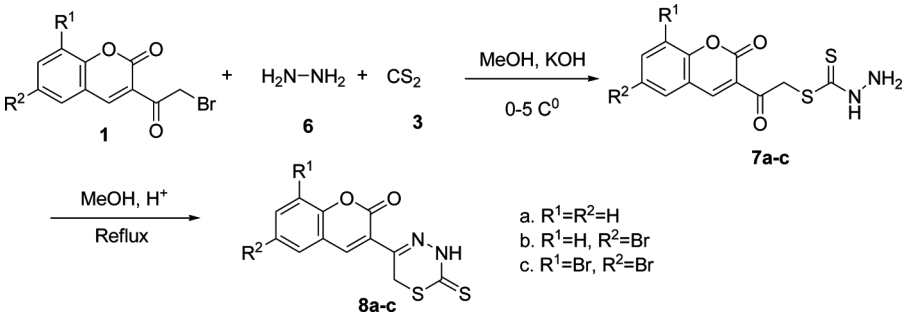
Humphlett et al.[24,25] prepared thiazoline-2-thiones by the reaction of ammonium dithioformate and α -halo ketones. During the formation of thiazoline-2-thiones, the intermediates formed are 4-hydroxy thiazolidine-2-thiones. On subsequent dehydration, these gave thiazoline-2-thione. Later, Ege et al.[26] prepared 3-arylamino-1,3-thiazoline-2-thiones. Reaction of potassium (*N*-arylhydrazino)-dithioformates with phenacyl halides gave the acylmethyl (hydrazino)thioformates. On cyclization in acidic medium, these resulted in the formation of 3-arylamino-1,3-thiazolin-2-thiones.

In this present study, we describe the preparation of 3-comarinyl-1,3-thiazoline-2-thiones and 1,3,4-thiadiazine-2-thiones under mild and efficient conditions. 3-(2-Bromoacetyl)coumarins on reaction with phenyl hydrazine and carbondisulfide gave the corresponding uncyclized compounds N^1-phenyl-hydrazinecarbodithioic acid 2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl esters **(4a–c)**. It is believed that reaction between phenyl hydrazine and carbondisulfide led to the formation of s-potassium (N-arylhydrazino)dithioformate. This salt was not isolated and was formed in situ. On reaction with 3-(2-bromoacetyl)coumarins, the salt gave the uncyclized intermediates **(4a–c)**. These underwent cyclocondensation reaction catalyzed by an acid to yield the 3-(3-phenylamino-2-thioxo-2,3-dihydro-thiazol-4-yl)-chromen-2-ones **(5a–c)** (Scheme 1). On the other hand, reaction of 3-(2-bromoacetyl)coumarins with hydrazine hydrate and carbondisulfide gave the corresponding uncyclized intermediates (7a–c). These intermediates (7a–c) under acidic conditions were cyclized to the six-membered compounds 3-(2-thioxo-3,6-dihydro-2*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-ones **(8a–c)** (Scheme 2).

All the synthesized compounds were characterized by infrared (IR) and NMR. In the ^{1}H NMR spectra of **4** and **7**, the methylene protons adjacent to



Scheme 1. Synthesis of 3-(3-phenylamino-2-thioxo-2,3-dihydro-thiazol-4-yl)-chromen-2-ones.



Scheme 2. Synthesis of 3-(2-thioxo-3,6-dihydro-2*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-ones.

the sulfur atom appeared as two doublets. This nonequivalence can be explained by the anisotropic effect caused by *d* orbitals of the sulfur atom.[27] The hydrogens of CH_2 were not equivalent, indicating the structure existed in the nonplanar conformation. Compound **5** can be readily distinguished from compound **8** by using ^{13}C NMR spectral studies. In broad-band decoupled spectrum of **8a**, there is a characteristic singlet for S-CH_2 carbon of the thiadiazine ring at δ 26.0. This type of singlet was absent in the case of **5**. This clearly confirmed that structure **8** is a six-membered thiadiazine-2-thione derivative and that the structure **5** is a five-membered thiazoline-2-thione. The structures **5** and **8** were further confirmed from the literature.[9,26]

CONCLUSION

In summary, we have prepared a five-membered cyclic product 3-(3-phenylamino-2-thioxo-2,3-dihydro-thiazol-4-yl)-chromen-2-ones and a six-membered cyclic product 3-(2-thioxo-3,6-dihydro-2*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-ones through novel ring-closing reactions. The advantages of this methodology are mild reaction conditions, easy workup, clean reaction profile, shorter reaction time, and wide range of substrate applicability.

EXPERIMENTAL

All the reagents and solvents were pure, purchased from commercial sources, and used without further purification unless otherwise stated. 3-(2-Bromoacetyl)-coumarins[28] were prepared according to literature procedures. Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India) and were uncorrected. CHNS analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by thin-layer chromatographic (TLC) plates (E. Merek Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using tetramethylsilane (TMS) as standard. Mass spectra (EI-MS) were determined on a Perkin-Elmer instrument (SCIEX API- 2000, ESI) at 12.5 eV.

General Procedure for the Synthesis of N^1-Phenyl-hydrazine-, Hydrazinecarbodithioic Acid 2-Oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl Esters 4a–c and 7a–c

Carbon disulfide (2 mmol) was added gradually with stirring to a solution of phenyl hydrazine or hydrazine hydrate (2 mmol) in absolute ethanol (10 mL) at 0 °C, followed by ice-cold potassium hydroxide (2 mmol) in absolute ethanol (5 mL). After stirring at 0–5 °C for 2 h, 3-(2-bromoacetyl)coumarin (2 mmol) was added and stirred for about 1 h at 0–5 °C. The solid obtained was filtered, washed with water, and recrystallized from ethanol.

Data

N^1-Phenyl-hydrazinecarbodithioic acid 2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl ester (4a). Yield 80%, mp 182–184 °C. Color: light yellow; IR (KBr, υ_{max}): 3341, 3297, 1714, 1630, 1601, 1188; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.38 (d, 1H of CH_2, $J = 12.4$ Hz), 4.05 (d, 1H of CH_2, $J = 12$ Hz), 6.65 (t, 1H, $J = 7.2$ Hz, Hz, ArH), 6.77 (d, 2H, $J = 7.6$ Hz, ArH), 7.03 (t, 2H, $J = 8.4$ Hz, ArH), 7.35–7.45 (m, 2H, ArH), 7.65 (t, 1H, $J = 8.4$ Hz, ArH), 7.83 (d, 1H, $J = 8$ Hz, ArH), 8.07 (s, 1H, -NH, D_2O, exchangeable), 8.16 (s, 1H, -NH, D_2O, exchangeable), 8.31 (s, 1H, C-4 of coumarin). EI-MS 393 (100%) $[M + Na]^+$. Anal. calcd. for $C_{18}H_{14}N_2O_3S_2$: C, 58.36; H, 3.81; N, 7.56. Found: C, 58.29; H, 3.88; N, 7.50%.

N^1-Phenyl-hydrazinecarbodithioic acid 2-(6-chloro-2-oxo-2*H*-chromen-3-yl)-2-oxo-ethyl ester (4b). Yield 85%, mp 170–172 °C. Color: light yellow; IR (KBr, υ_{max}): 3325, 3230, 1718, 1625, 1600, 1184; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.37 (d, 1H of CH_2, $J = 12.4$ Hz), 4.05 (d, 1H of CH_2, $J = 12.4$ Hz), 6.65 (t, 1H, $J = 7.2$ Hz, ArH), 6.75 (d, 2H, $J = 8$ Hz, ArH), 7.03 (d, 2H, $J = 8.4$ Hz, ArH) 7.50 (d, 1H, $J = 8.8$ Hz, ArH), 7.67–7.70 (m, 1H, ArH), 8.0 (d, 1H, $J = 2.4$ Hz, ArH), 8.15 (s, 2H, -NH, D_2O, exchangeable), 8.31 (s, 1H, C-4 of coumarin). Anal. calcd. for $C_{18}H_{13}ClN_2O_3S_2$: C, 53.40; H, 3.24; N, 6.92. Found: C, 53.44; H, 3.18; N, 6.98%.

N^1-Phenyl-hydrazinecarbodithioic acid 2-(6,8-dibromo-2-oxo-2*H*-chromen-3-yl)-2-oxo-ethyl ester (4c). Yield 85%, mp 110–112 °C. Color: light

yellow; IR (KBr, υ_{max}): 3426, 1719, 1648, 1606, 1189; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.38 (d, 1H of CH_2, $J = 12.4$ Hz), 4.03 (d, 1H of CH_2, $J = 12$ Hz), 6.66 (t, 1H, $J = 7.2$ Hz, ArH), 6.74 (d, 2H, $J = 7.6$ Hz, ArH), 7.04 (t, 2H, $J = 8.4$ Hz, ArH), 8.16 (s, 2H, ArH), 8.20 (s, 2H, -NH, D_2O, exchangeable), 8.29 (s, 1H, C-4 of coumarin). Anal. calcd. for $C_{18}H_{12}Br_2N_2O_3S_2$: C, 40.93; H, 2.29; N, 5.30. Found: C, 40.98; H, 2.32; N, 5.35%.

Hydrazinecarbodithioic acid 2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl ester (7a). Yield 79%, mp 188–190 °C. Color: light yellow; IR (KBr, υ_{max}): 3311, 3302, 3199, 1716, 1625, 1606, 1199; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.15 (d, 1H of CH_2, $J = 12$ Hz), 3.80 (d, 1H of CH_2, $J = 12$ Hz), 5.07 (s, 2H, -NH_2, D_2O, exchangeable), 7.39–7.47 (m, 2H, ArH), 7.67 (t, 1H, $J = 8.4$ Hz, ArH), 7.84 (s, 1H, -NH, D_2O, exchangeable), 7.90 (d, 1H, $J = 8.4$ Hz, ArH), 8.35 (s, 1H, C-4 of coumarin). EI-MS 317 (75%) $[M + Na]^+$. Anal. calcd. for $C_{12}H_{10}N_2O_3S_2$: C, 48.97; H, 3.42; N, 9.52. Found: C, 48.91; H, 3.47; N, 9.58%.

Hydrazinecarbodithioic acid 2-(6-bromo-2-oxo-2*H*-chromen-3-yl)-2-oxo-ethyl ester (7b). Yield 82%, mp 180–182 °C. Color: light yellow; IR (KBr, υ_{max}): 3340, 3296, 1712, 1629, 1610, 1188; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.15 (d, 1H of CH_2, $J = 12.4$ Hz), 3.79 (d, 1H of CH_2, $J = 12$ Hz), 5.06 (s, 2H, -NH_2, D_2O, exchangeable), 7.51 (d, 1H, $J = 8.8$ Hz ArH), 7.69–7.72 (m, 1H, ArH), 7.90 (s, 1H, -NH, D_2O, exchangeable), 8.08 (d, 1H, $J = 2.8$ Hz, ArH), 8.35 (s, 1H, C-4 of coumarin). Anal. calcd. for $C_{12}H_9BrN_2O_3S_2$: C, 38.61; H, 2.43; N, 7.51. Found: C, 38.65; H, 2.47; N, 7.55%.

Hydrazinecarbodithioic acid 2-(6,8-dibromo-2-oxo-2*H*-chromen-3-yl)-2-oxo-ethyl ester (7c). Yield 83%, mp 190–192 °C. Color: light yellow; IR (KBr, υ_{max}): 3311, 3201, 1734, 1631, 1556, 1178; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.14 (d, 1H of CH_2, $J = 12.4$ Hz), 3.81 (d, 1H of CH_2, $J = 12.4$ Hz), 5.09 (s, 2H, -NH_2, D_2O, exchangeable), 7.94 (s, 1H, -NH, D_2O, exchangeable), 8.21 (s, 1H, ArH), 8.24 (s, 1H, ArH), 8.33 (s, 1H, C-4 of coumarin). Anal. calcd. for $C_{12}H_8Br_2N_2O_3S_2$: C, 31.88; H, 1.78; N, 6.20. Found: C, 31.84; H, 1.73; N, 6.24%.

General Procedure for the Synthesis of 3-(3-Phenylamino-2-thioxo-2,3-dihydro-thiazol-4-yl)-chromen-2-ones 5a–c and 3-(2-Thioxo-3,6-dihydro-2*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-ones 8a–c

Compounds **4a–c** or **7a–c** (1 mmol) was taken in absolute ethanol (10 mL) with one or two drops of concentrated HCl and refluxed for 2–3 h. After completion of the reaction, it was cooled to room temperature, and the yellow solid obtained was filtered and recrystallized from ethanol.

Data

3-(3-Phenylamino-2-thioxo-2,3-dihydro-thiazol-4-yl)-chromen-2-one (5a). Yield 75%, mp 180–182 °C. Color: yellow; IR (KBr, υ_{max}): 3325, 1701, 1604, 1560, 1114; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.47 (d, 2H, $J = 8.4$ Hz, ArH), 6.74

(t, 1H, $J = 7.6$ Hz, ArH), 7.01–7.05 (m, 3H, 2H, ArH and 1H, thiazoline), 7.11–7.17 (m, 2H, ArH), 7.32 (d, 1H, $J = 7.6$ Hz, ArH), 7.39–7.43 (m, 1H, ArH), 8.01 (s, 1H, -NH, D_2O, exchangeable), 8.05 (s, 1H, C-4 of coumarin). ^{13}C NMR (75 MHz, DMSO-d_6): 110.2, 110.9, 113.0, 116.6, 119.2, 120.5, 120.8, 128.9, 130.4, 137.2, 138.0, 142.6, 145.6, 149.2, 157.2, 186.5. EI-MS 391 (100%) $[M + K]^+$. Anal. calcd. for $C_{18}H_{12}N_2O_2S_2$: C, 61.34; H, 3.43; N, 7.95. Found: C, 61.38; H, 3.47; N, 7.91%.

6-Chloro-3-(3-phenylamino-2-thioxo-2,3-dihydro-thiazol-4-yl)-chromen-2-one (5b). Yield 77%, mp 194–196 °C. Color: yellow; IR (KBr, υ_{max}): 3350, 1716, 1600, 1577, 1114; ^1H NMR (400 MHz, $CDCl_3$): δ 6.65 (d, 2H, $J = 7.6$ Hz, ArH), 6.98 (t, 1H, $J = 7.6$ Hz, ArH), 7.22–7.29 (m, 4H, 3H, ArH and 1H, thiazoline), 7.44 (s, 1H, -NH, D_2O, exchangeable), 7.51 (d, 2H, $J = 9.2$ Hz, ArH), 8.22 (s, 1H, C-4 of coumarin). ^{13}C NMR (75 MHz, DMSO-d_6): 110.3, 110.8, 113.1, 115.6, 119.3, 120.5, 121.1, 128.4, 130.6, 136.2, 138.1, 143.6, 145.9, 148.2, 156.2, 186.1. Anal. calcd. $C_{18}H_{11}ClN_2O_2S_2$: C, 55.88; H, 2.87; N, 7.24. Found: C, 55.85; H, 2.86; N, 7.29%.

6,8-Dibromo-3-(3-phenylamino-2-thioxo-2,3-dihydro-thiazol-4-yl)-chromen-2-one (5c). Yield 76%, mp 168–170 °C. Color: yellow; IR (KBr, υ_{max}): 3350, 1716, 1600, 1577, 1116; ^1H NMR (400 MHz, DMSO-d_6): δ 6.51 (d, 2H, $J = 7.6$ Hz, ArH), 6.77 (t, 1H, $J = 7.6$ Hz, ArH), 7.12 (t, 2H, $J = 8.4$ Hz, ArH), 7.39 (s, 1H, thiazoline), 7.96 (s, 1H, ArH), 8.20 (s, 1H, ArH), 8.32 (s, 1H, C-4 of coumarin), 9.37 (s, 1H, -NH, D_2O, exchangeable). Anal. calcd. for $C_{18}H_{10}Br_2N_2O_2S_2$: C, 42.37; H, 1.98; N, 5.49. Found: C, 42.34; H, 1.96; N, 5.45%.

3-(2-Thioxo-3,6-dihydro-2*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-one (8a). Yield 73%, mp 200–202 °C. Color: yellow; IR (KBr, υ_{max}): 3323, 1701, 1620, 1604, 1107; ^1H NMR (400 MHz, DMSO-d_6): δ 3.98 (s, 2H, S-CH_2), 7.71 (d, 2H, $J = 2.4$ Hz, Hz, ArH), 7.91 (d, 2H, $J = 2.4$, ArH), 8.16 (s, 1H, C-4 of coumarin), 10.28 (s, 1H, -NH, D_2O, exchangeable). EI-MS 277 (100%) $[M + H]^+$. ^{13}C NMR (75 MHz, DMSO-d_6): 26.0, 110.1, 116.5, 121.5, 124.7, 131.1, 137.3, 141.2, 145.3, 149.6, 157.7, 189.3. Anal. calcd. for $C_{12}H_8N_2O_2S_2$: C, 52.16; H, 2.92; N, 10.14. Found: C, 52.11; H, 2.96; N, 10.17%.

6-Bromo-3-(2-thioxo-3,6-dihydro-2*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-one (8b). Yield 76%, mp 194–196 °C. Color: yellow; IR (KBr, υ_{max}): 3172, 1728, 1616, 1587, 1116; ^1H NMR (400 MHz, DMSO-d_6): δ 3.98 (s, 2H, S-CH_2), 7.52–7.57 (m, 1H, ArH), 7.73–7.75 (m, 1H, ArH), 8.03 (d, 1H, $J = 2.4$ Hz, ArH), 8.42 (s, 1H, C-4 of coumarin), 13.48 (s, 1H, -NH, D_2O, exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6): 26.3, 116.3, 118.3, 122.1, 124.8, 128.9, 132.9, 143.3, 144.4, 153.9, 159.2, 189.8. Anal. calcd. for $C_{12}H_7BrN_2O_2S_2$: C, 40.57; H, 1.99; N, 7.89. Found: C, 40.54; H, 1.96; N, 7.81%.

6,8-Dibromo-3-(2-thioxo-3,6-dihydro-2*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-one (8c). Yield 76%, mp 216–216 °C. Color: yellow; IR (KBr, υ_{max}): 3172, 1728, 1616, 1587, 1116; ^1H NMR (400 MHz, DMSO-d_6): δ 3.98 (s, 2H, S-CH_2), 8.17 (d, 1H, $J = 2.4$ Hz, ArH), 8.24 (d, 1H, $J = 2$ Hz, ArH), 8.39 (s, 1H, C-4 of coumarin), 13.50 (s, 1H, -NH, D_2O, exchangeable). Anal. calcd. for $C_{12}H_6Br_2N_2O_2S_2$:C, 33.20; H, 1.39; N, 6.45. Found: C, 33.24; H, 1.35; N, 6.49%.

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