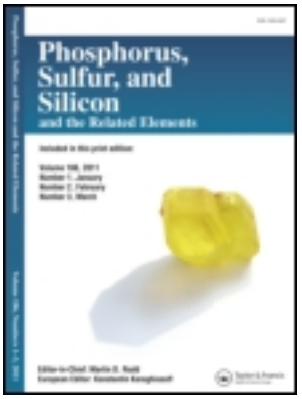

Phosphorus, Sulfur, and Silicon and the Related Elements

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One-Pot Synthesis and Methylation of 3-[2-(1H-Benzimidazol-2-yl-Sulfanyl)-Acetyl]-Chromen-2-Ones

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ONE-POT SYNTHESIS AND METHYLATION OF 3-[2-(1*H*-BENZIMIDAZOL-2-YL-SULFANYL)-ACETYL]-CHROMEN-2-ONES

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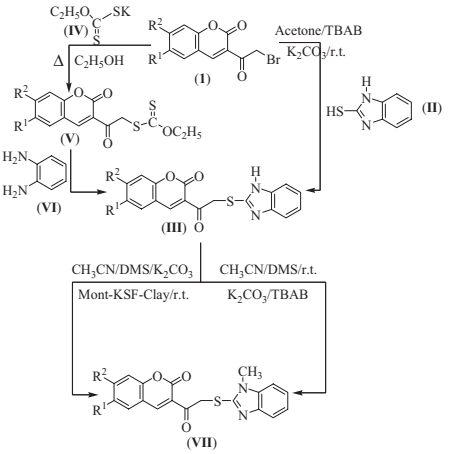
GRAPHICAL ABSTRACT



Abstract *3-(2-Bromoacetyl)coumarins (**I**), when treated with 2-mercatobenzimidazole (**II**) in acetone containing K_2CO_3 (mild base) and tetrabutylammonium bromide (TBAB) as a phase transfer catalyst, at room temperature yielded the title compound 3-[2-(1H-benzimidazole-2-yl-sufanyl)-acetyl]-chromen-2-one (**III**) in a one-pot synthesis. Alternatively, **III** could also be prepared by treating dithiocarbonic acid O-ethyl ester, S-[2-oxo-2-(2-oxo-2H-chromen3-yl)-ethyl] ester (**V**), with o-phenylenediamine (**VI**). The methylation of the title compound **III** was performed with dimethyl sulfate (DMS), in acetonitrile containing TBAB and K_2CO_3 at room temperature, resulting in 3-[2-(N-methyl-benzimidazol-2-yl-sulfanyl)]-acetyl-chromen-2-ones (**VII**). Alternatively, methylation of **III** could also be performed with DMS in acetonitrile containing K_2CO_3 as base and clay as surface catalyst. All the compounds were synthesized in good yields and their structures were confirmed by spectral and analytical data.*

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[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource: [1]H NMR of IIIB, VB and VIIB]*

Keywords 3-(2-Bromoacetyl)coumarins; dithiocarbonic acid *O*-ethyl ester *S*-[2-oxo-2-(2-oxo-2*H*-chromen3-yl)-ethyl] ester; DMS; clay

INTRODUCTION

Literature reports revealed that coumarin derivatives constitute an important class of heterocyclic compounds with anticoagulant (e.g., warfarin, acenocoumarol),[1,2] rodenticide (e.g., brodifacoum, bromadiolone),[3] insecticide (e.g., coumaphos),[4] and antibacterial (e.g., novobiocin, clorobiocin)[5,6] properties. They also possess important biological activities like antitumor,[7] antifungal,[8] antimycobacterial,[9] and anti-inflammatory[10] properties. However, there are other coumarin compounds such as *N*-acetyl-*N*-allylamino-4-thiazolylcoumarins,[11] *N*-chloroacetamido derivatives,[12] and *N*-benzoyl derivatives, which displayed significant analgesic and anti-inflammatory activity.[13] In view of these wide ranges of pharmacological activities of coumarin derivatives, it was thought of interest to synthesize potent coumarin derivatives, which may possess useful biological properties.

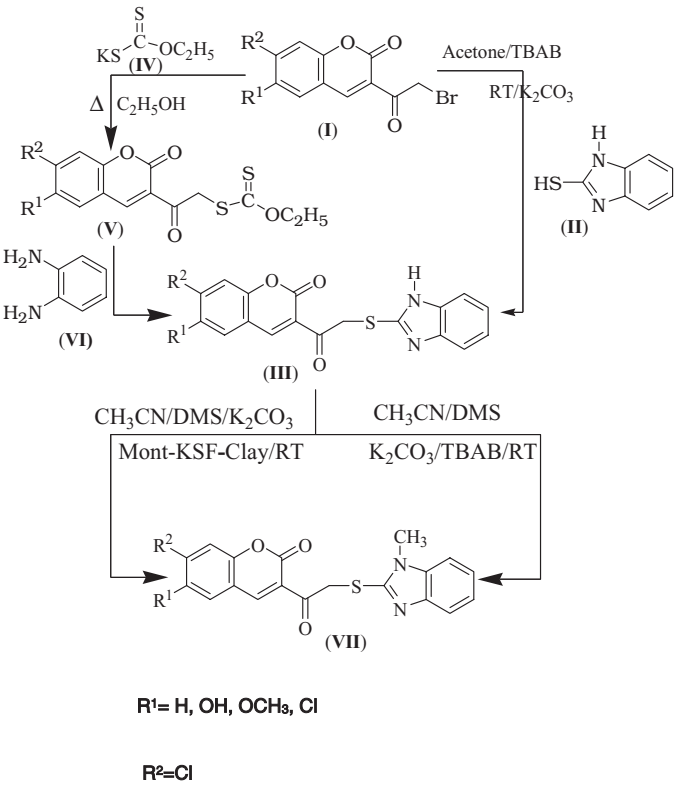
RESULTS AND DISCUSSION

The reaction of 3-(2-bromoacetyl)coumarin,[14] (**Ia**, i.e., **I**, $R^1 = R^2 = H$), with 2-mercaptobenzimidazole[15] (**II**), in acetone containing tetrabutylammonium bromide (TBAB) as phase transfer catalyst and K_2CO_3 as a base at room temperature, gave a product, which has been characterized as 3-[2-(1*H*-benzimidazole-2-yl-sulfanyl)-acetyl]-chromen-2-ones (**IIIa**, i.e., **III**, $R^1 = R^2 = H$), on the basis of its spectral and analytical data.

IIIa (i.e., **III**, $R^1 = R^2 = H$) could also be synthesized by an alternative method. Thus, reaction of **Ia** (i.e., **I**, $R^1 = R^2 = H$) with potassium ethoxydithiocarbamate (**IV**) gave dithiocarbonic acid *O*-ethyl ester *S*-[2-oxo-2-(2-oxo-2*H*-chromen3-yl)-ethyl] ester (**Va**, i.e., **V**, $R^1 = R^2 = H$)**,** which when treated with *o*-phenylenediamine (**VI**), in ethanol under reflux for 2–3 h, followed by a workup, afforded a white crystalline solid identical with **IIIa** (i.e., **III,** $R^1 = R^2 = H$), in all respects (mp, mmp., and co-TLC) (Scheme 1).

The above reaction of **Ia** (i.e., **I**, $R^1 = R^2 = H$) with **II** was found to be a general one and the other compounds, namely, 3-[2-(1H-benzimidazol-2-yl-sulfanyl)-acetyl]-6-hydroxy-[-chromen-2-one] (**IIIb**, i.e., **III**, $R^1 = OH$, $R^2 = H$), 3-[2-(1H-benzimidazol-2-yl-sulfanyl)-acetyl]-6-methoxy-[-chromen-2-one] (**IIIc**, i.e., **III**, $R^1 = OCH_3$, $R^2 = H$), and 3-[2-(1H-benzimidazol-2-yl-sulfanyl)-acetyl]-6,7-dichloro-[-chromen-2-one] (**IIId**, i.e., **III**, $R^1 = R^2 = Cl$), have been synthesized by extending it. All the compounds have been characterized by spectral and analytical data (for details please see experimental data).

Potassium ethoxydithiocarbamate (**IV**) required in the above reaction was prepared by refluxing KOH in ethanol followed by addition of carbon disulfide in ice-cold condition[16] to the preliminary solution. When **Ia** (i.e., **I**, $R^1 = R^2 = H$) was treated with **IV** in ethanol under reflux condition for 1–2 h, dithiocarbonic acid *O*-ethyl ester *S*-[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl] ester (**Va**, i.e., **V**, $R^1 = R^2 = H$) was obtained, which has been characterized by spectral and analytical data.



Scheme 1

The other compounds such as dithiocarbonic acid *O*-ethyl ester, *S*-[2-(6-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-ethyl] ester (**Vb**, i.e., **V**, $R^1 = OH$, $R^2 = H$), dithiocarbonic acid *O*-ethyl ester, *S*-[2-(6-methoxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-ethyl] ester (**Vc**, i.e., **V**, $R^1 = OCH_3$, $R^2 = H$), and dithiocarbonic acid *S*-[2-(6,7-dichloro-2-oxo-2*H*-chromen-3-yl)-2-oxo-ethyl] ester *O*-ethyl ester (**Vd**, i.e., **V**, $R^1 = R^2 = Cl$) have been prepared by extending the above reaction. All the compounds have been characterized by spectral and analytical data. The yields, melting points and spectral data, are given in the Experimental Section.

Treatment of **IIIa** (i.e., **III**, $R^1 = R^2 = H$) with dimethylsulfate (DMS), in CH_3CN containing K_2CO_3 as a base and TBAB as PTC, afforded a pure crystalline solid. The compound has been assigned as 3-[2-(*N*-methyl-benzimidazol-2-yl-sulfanyl)]-acetyl-chromen-2-one (**VIIa**, i.e., **VII**, $R^1 = R^2 = H$), on the basis of spectral and analytical data.

VIIa (i.e., **VII**, $R^1 = R^2 = H$) could also be prepared by treating the suspension of **IIIa** (i.e., **III**, $R^1 = R^2 = H$) in CH_3CN, with DMS and base K_2CO_3, in the presence of clay (montmorillonite-KSF), identical in all respects (mp, mmp, and co-TLC result).

By adopting the same procedure, other compounds, namely, 6-hydroxy-3-[2-(1-methyl-1*H*-benzimidazol-2-yl-sulfanyl)-acetyl-chromen-2-one (**VIIb**, i.e., **VII**, $R^1 = OH$, $R^2 = H$), 6-methoxy-3-[2-(1-methyl-1*H*-benzimidazol-2-yl-sulfanyl)-acetyl-chromen-2-one, (**VIIc**, i.e., **VII**, $R^1 = OCH_3$, $R^2 = H$), and 6,7-dichloro-3-[2-(1-methyl-1*H*-benzimidazol-2-yl-sulfanyl)-acetyl-chromen-2-one (**VIId**, i.e., **VII**, $R^1 = R^2 = Cl$), have

been synthesized. All the compounds have been characterized by spectral and analytical data.

It may be mentioned here that the reactions catalyzed by clays have received great attention in recent years.[17–20] The salient features of the reactions catalyzed by clay supported reagents are that the clay catalyst can be recovered after the completion of reaction by simple filtration.[21] The recovered catalyst is washed thoroughly with diethyl ether and dried at 140 °C for 1 h under vacuum. The recovered catalyst, in the present work, showed consistent activity for five cycles, and then, the activity slowly begins to decrease.

EXPERIMENTAL SECTION

General Conditions

Melting points are uncorrected and were determined in open capillary tubes in sulfuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV-light. IR spectra were recorded with Perkin-Elmer 1000 instrument in KBr phase. ^{1}H NMR was recorded on VARIAN 400 MHz instrument and Mass spectra were recorded on Agilent-LC-MS instrument.

Preparation of 3-[2-(1*H*-Benzimidazole-2-yl-Sulfanyl)-Acetyl]-Chromen-2-Ones (III) (General Procedure)

A mixture of 2-mercaptobenzimidazole **(II)** (0.75 g, 0.005 mol) in dry acetone (50 mL), K_2CO_3 (2.76 g, 0.01 mol), and TBAB (0.05 g) was stirred at room temperature for 0.5 h. To this mixture, 3-(2-bromoacetyl)coumarins **(I)** (1.19 g, 0.005 mol) was added and was continued stirring further for 2–3 h. The completion of the reaction was monitored by TLC analysis. After completion of reaction, the mixture was poured in ice-cold water and neutralized with $NaHCO_3$. The solid obtained was filtered and dried. It was recrystallized from dimethyl formamide (DMF)/methanol (1:1 ratio), yielding a pure crystalline solid.

IIIa: White crystalline solid; Yield 1.4 g (92%); mp 178 °C–79 °C; IR (KBr) 3423 cm^{-1} (medium, broad assignable to –NH–), 1720 cm^{-1} (strong, sharp, due to lactone C=O group) 1640 cm^{-1} (strong, sharp, assignable to C=O of $COCH_2$–). ^{1}H NMR spectrum (DMSO-d_6/TMS), showed signals at δ 5.56 (s, 2H, –C**H**$_2$–), 7.34–8.88 (complex, m, 9H, aryl protons, J = 3–7 Hz) 12.68 (s, br, 1H, –N**H**–). ^{13}C NMR (DMSO-d_6/TMS) δ 65, 116, 119, 121, 125, 127, 129, 134, 145, 151, 168, 172. IMS (CI, M$^{\cdot+}$+1) *m/z* 337 (base peak). Elem. Anal: Found. C 64.27%, H 3.60%, N 8.33%; $C_{18}H_{12}N_2O_3S$ requires C 64.25%, H 3.58%, N 9.15%.

IIIb: White crystalline solid; Yield 1.3 g (88%); mp 263 °C–64 °C; IR (KBr): 3450 cm^{-1} (medium, broad, –NH– stretching); 1740 cm^{-1} (strong, sharp, C=O of coumarin ring); 1628 cm^{-1} (strong, sharp, C=O of $COCH_2$–). ^{1}H NMR (DMSO-d_6/TMS): δ 5.66 (s, 2H, –C**H**$_2$–), 7.14–8.88 (complex, m, 8H, aryl protons) 11.42 (s, 1H, D_2O Exchangeable –O**H**), 12.20 (s, 1H, –N**H**–); MS *m/z* = 353 (M$^{\cdot+}$ + 1). Elem. Anal: Found. C 61.90%, H 4.35%, N 7.31%, S 8.68%; $C_{18}H_{12}N_2O_4S$ requires C 61.94%, H 4.38%, N 7.32%, S 8.71%.

IIIc: White crystalline solid; Yield 1.34 g (84%); mp 243 °C–245 °C; IR (KBr): 3455 cm^{-1} (medium, broad,–NH– stretching), 1730 cm^{-1} (strong, sharp, C=O of coumarin ring), 1660 cm^{-1} (strong, sharp, C=O of $COCH_2$–); ^{1}H NMR (DMSO-d_6/TMS) signals at δ 4.34 (s, 3H, –OC**H**$_3$–), 5.68 (s, 2H, –C**H**$_2$–), 7.12–8.88 (complex, m, 8H, aryl protons) δ 12.20

(s, 1H, –N**H**–); MS *m/z* = 367 ($M^{\cdot+}$ + 1). Element. Anal: Found. C 62.79%, H 4.71%, N 17.31%, S 8.35%; $C_{19}H_{14}N_2O_4S$ requires C 62.81%, H 4.73%, N 7.31%, S 8.38%.

IIId: White crystalline solid; Yield 1.17g (80%); mp 254 °C–255 °C; IR (KBr): 3460 cm^{-1} (medium, broad, –NH– stretching), 1741 cm^{-1} (strong, sharp, C=O of coumarin ring), 1660 cm^{-1} (strong, sharp, C=O of $COCH_2$–); ^{1}H NMR (DMSO-d_6/TMS) signals at δ 5.88(s, 2H, –C**H**$_2$–), 7.22–8.86 (complex, m, 7H, aryl protons) and at δ 12.40 (s, 1H, –N**H**–), MS *m/z* = 405 ($M^{\cdot+}$ + 1). Elem. Anal: Found. C 54.15%, H 3.33%, N 6.63%, S 7.59%; $C_{18}H_{10}Cl_2N_2O_3S$ requires C 54.17%, H 3.35%, N 6.65%, S 7.61%.

Preparation of Dithiocarbonic Acid *O*-Ethyl Ester S-[2-Oxo-2-(2-Oxo-2*H*-Chromen-3-yl)-Ethyl] Ester (V) (General Procedure)

A mixture of 3-(2-bromoacetyl)coumarin (**I**) (0.01 mol), potassium ethoxydithiocarbamate (**IV**) (1.60 g, 0.01 mol), and ethanol (30 mL) was refluxed for 1 h. Then, the reaction mixture was cooled to room temperature and the separated KBr salt was filtered and washed with ethanol (10 mL). The filtrate was distilled off and the residue diluted with water. The separated solid was filtered, washed with water, and dried to give **V.**

Va: Crystalline solid; Yield 1.35 g (88%); mp 154 °C–56 °C; IR (KBr) 1735 cm^{-1} (strong, sharp, assignable to lactone C=O), 1678 cm^{-1} (strong, sharp due to C=O of $COCH_2$–). ^{1}H NMR (DMSO-d_6/TMS), spectrum showed signal at δ 1.24 (t, 3H, –C**H**$_3$), 5.24 (q, 2H, –C**H**$_2$-), 6.66 (s, 2H, –C**H**$_2$–), 7.38–8.88 (complex, m, 5H, aryl protons, *J* = 3–7.5 Hz). Its ^{13}C spectrum (DMSO-d_6/TMS) showed signals at *ca* δ 18, 62, 66, 116, 119, 121, 127, 129, 134, 151, 160, 166, and 177. Its MS (CI) ($M^{\cdot+}$ + 1) *m/z* 309 (base peak). Elem. Anal: Found. C 54.50%, H 3.88%, S 20.78%; $C_{14}H_{12}O_4S_2$ requires C 54.53%, H 3.91%, S 20.80%.

Vb: Crystalline solid; Yield 1.24 g (82%); mp 188 °C–90 °C; IR (KBr): 1745 cm^{-1} (strong, sharp, C=O of coumarin ring), 1681 cm^{-1} (strong, sharp, C=O of $COCH_2$–). ^{1}H NMR (DMSO-d_6/TMS) signal at δ 1.31 (t, 3H, –C**H**$_3$), 4.88 (q, 2H, –C**H**$_2$–), 5.21 (s, 2H, –C**H**$_2$–), 7.31–8.98 (complex, m, 5H, aryl protons). 10.81 (s, 1H, O**H**). MS *m/z* = 325 ($M^{\cdot+}$ + 1). Elem. Anal: Found. C 51.81%, H 3.70%, S 19.74%; $C_{14}H_{12}O_5S_2$ requires C 51.84%, H 3.73%, S 19.78%.

Vc: Crystalline solid; Yield 1.15 g (80%); mp 219 °C–21 °C; IR (KBr): 1748 cm^{-1} (strong, sharp, C=O of coumarin ring), 1677 cm^{-1} (strong, sharp, C=O of $COCH_2$–). ^{1}H NMR (DMSO-d_6/TMS), spectrum showed signal at δ 1.53 (t, 3H, –C**H**$_3$), 4.29 (s, 3H, –OC**H**$_3$–), 5.13 (q, 2H, –C**H**$_2$–), 5.40 (s, 2H, –C**H**$_2$–), 7.11–8.88 (complex, m, 5H, aryl protons); MS *m/z* = 338 ($M^{\cdot+}$ + 1). Elem. Anal: Found. C 53.21%, H 4.15%, S 18.93%; $C_{15}H_{14}O_5S_2$ requires C 53.24%, H 4.17%, S 18.95%.

Vd: Crystalline solid; Yield 1.23 g (80%); mp 227 °C–29 °C; IR (KBr) 1751 cm^{-1} (strong, sharp, C=O of coumarin ring), 1672 cm^{-1} (strong, sharp, C=O of $COCH_2$–). ^{1}H NMR (DMSO-d_6/TMS), signal at δ 1.59 (t, 3H, –C**H**$_3$), 4.83 (q, 2H, –C**H**$_2$–), 5.12 (s, 2H, –C**H**$_2$–), 7.13–8.89 (complex, m, 3H, aryl protons); MS *m/z* = 377 ($M^{\cdot+}$ + 1). Elem. Anal: Found. C 44.55%, H 2.65%, S 16.98%; $C_{14}H_{10}Cl_2O_4S_2$ requires C 44.55%, H 2.67%, S 17.00%.

Alternative Method for the Synthesis of III

Dithiocarbonic acid *O*-ethyl ester, *S*-[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl] ester (**V**) (0.01 mol), was refluxed with *o*-phenylenediamine (**VI**) (0.01 mol), for 8–10 h, in

C_2H_5OH (50 mL). The completion of the reaction was monitored by TLC analysis. At the end, the reaction mixture was poured in ice-cold water, neutralized with conc. HCl and pH was adjusted to neutral with aq. NH_3. The separated solid was filtered, washed with water, and dried to obtain **III**.

Preparation of 3-[2-(*N*-Methyl-Benzimidazol-2-yl-Sulfanyl)]-Acetyl-Chromen-2-One (VII) from III (General Procedure)

A mixture of 3-[2-(1*H*-benzimidazole-2-yl-sulfanyl)-acetyl]-chromen-2-ones (**III**) (0.01 mol), K_2CO_3 (1.63 g, 0.012 mol), TBAB (0.2 g), dimethyl sulfate (1.0mL, 0.01 mol), and acetonitrile (25 mL) was stirred at room temperature for 3 h. On completion of the reaction, the mixture was filtered and the insoluble material washed with CH_3CN (2 × 5 mL); the CH_3CN filtrate was evaporated to dryness and the residue treated with chloroform (25 mL). The chloroform layer was washed with water (3 × 30 mL) and evaporated to dryness, to give crude **VII**. It was recrystallized from methanol-chloroform to obtain pure **VII.**

VIIa. Yellow solid; Yield 1.17 g (90%); mp 219 °C–21 °C; IR (KBr) 3423 cm^{-1} (medium, broad, **NH** group); 1748 cm^{-1} (strong, sharp assignable to lactone C=O group) 1693 cm^{-1} (strong, sharp due to C=O of $COCH_2$– group). ^1H NMR (DMSO-d_6/TMS) δ 5.28 (s, 3H, N–C**H**$_3$), 5.30 (s, 2H, –C**H**$_2$–), 6.98–9.01 (complex, m, 9H, aryl protons, J = 2.5–8 Hz). MS ($M^{\cdot+}$ + 1) *m/z* 351 (base peak) corresponding to a molecular mass of 350. Elem. Anal: Found. C 65.64%, H 4.93%, N 7.62%, S 8.71%; $C_{20}H_{13}N_3O_3S$ requires C 65.66%, 4.95%, N 7.64%, S 8.74%.

VIIb. Yellow solid; Yield 1.1 g (84%); mp 201 °C–03 °C; IR (KBr): 1740 cm^{-1} (strong, sharp, C=O of coumarin ring), 1640 cm^{-1} (strong, sharp, C=O of $COCH_2$-); ^1H NMR (DMSO-d_6/TMS), δ 6.04 (s, 3H, N–C**H**$_3$), 6.28 (s, 2H, –C**H**$_2$–), 7.12–8.88 (complex, m, 8H, aryl protons), 11.22 (s, 1H, –O**H**); MS *m/z* = 367 ($M^{\cdot+}$ + 1). Elem. Anal: Found. C 62.80%, H 4.71%, N 7.31%, S 8.34%; $C_{19}H_{14}N_2O_4S$ requires C 62.81%, H 4.74%, N 7.33%, S 8.38%.

VIIc. Yellow solid; Yield 1.0 g (80%); mp 211 °C–13 °C; IR (KBr) 1738 cm^{-1} (strong, sharp, C=O of coumarin ring), 1648 cm^{-1} (strong, sharp, C=O of $COCH_2$); ^1H NMR (DMSO-d_6/TMS) δ 2.22 (s, 3H, O–**CH$_3$**), 5.68 (s, 3H, N–CH_3), 5.72 (s, 2H, –C**H**$_2$–), 7.27–8.89 (complex, m, 8H, aryl protons); MS *m/z* = 381 ($M^{\cdot+}$ + 1). Elem. Anal: Found. C 63.60%, H 5.05%, N 7.05%, S 8.05%; $C_{20}H_{16}N_2O_4S$ requires C 63.63%, H 5.08%, N 7.07%, S 8.07%.

VIId. Yellow solid; Yield 1.0 g (77%); mp 231 °C–33 °C; IR (KBr) 1742 cm^{-1} (strong, sharp, C=O of coumarin ring), 1652 cm^{-1} (strong, sharp, C=O of $COCH_2$); ^1H NMR (DMSO-d_6/TMS) δ 5.74 (s, 3H, N–CH_3), 5.81 (s, 2H, –CH_2–), 7.21–8.88 (complex, m, 7H, aryl protons); MS *m/z* = 419 ($M^{\cdot+}$ + 1). Elem. Anal: Found. C 55.14%, H 3.04%, N 6.63%, S 7.35%; $C_{19}H_{12}N_2O_4S$ requires C 55.18%, H 3.08%, N 6.66%, S 7.37%.

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