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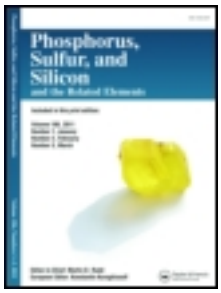

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of 3-(3-(phenacyl/alkyl/benzylthio)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2H-chromen-2-ones

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Synthesis of 3-(3-(phenacyl/alkyl/benzylthio)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-ones

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ABSTRACT

Reaction of coumarin-3-carboxylic acid with 3,5-di mercapto-4-amino-s-triazole in $POCl_3$ to gave 3-(3-mercapto-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-one (**3**). Reaction of **3** with different substituted phenacyl/benzyl/allyl bromides in anhydrous ethanol gave corresponding 3-(3-(phenacyl/alkyl/benzylthio)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-6-yl)-2*H*-chromen-2-ones **5**. The structures of newly prepared compounds were confirmed from their analytical and spectral data.

Graphical Abstract

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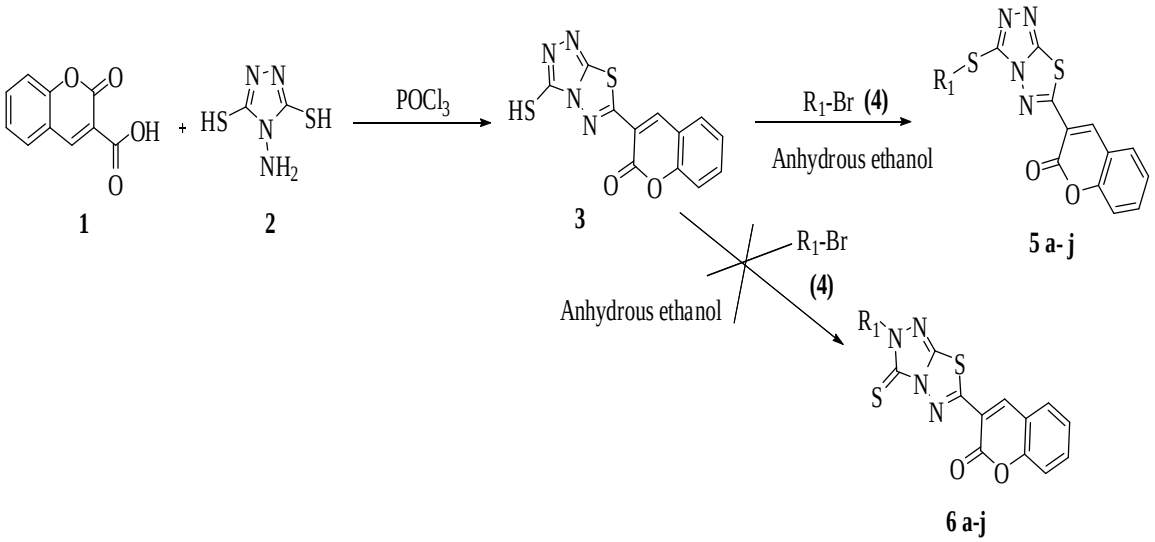

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Keywords: triazole, 1,3,4-thiadiazol, 1,2,4-triazole, phenacyl bromide, coumarin.

INTRODUCTION

The compounds having sulfur and nitrogen in a 5-membered ring system exhibit broad range of biological properties[1]. Thiadiazole and its derivatives have various biological activities such as anti-tuberculosis[2], anticancer[3], carbonicanhydrase-inhibiting effect[4], antioxidant properties[5] and antimycobacterial[6]. When thiadiazole is fused with triazoles show antiviral[7], antitumor[8], anthelmentic[9] activities and the substituted triazolo thiadiazoles exhibit various pharmacological activities such as herbicidal[10], anti-HIV-1 effects[11]. 1,3,4-Thiadiazoles posses various biological activities due to presence of =N–C–S moiety[12].

Coumarins are very important heterocyclic systems used in drugs and dyes [13] . They are usually available from natural sources such as secondary metabolite present in roots and leaves

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of many plant species[14]. Coumarins and their derivatives show a wide range of biological activities such as HIV protease inhibition[15], anticoagulant[16], anti-inflammatory[17] activity.

Prompted by the above observations and in continuation of our search for biologically active nitrogen and sulfur containing heterocycles[18-20], it was decided to synthesize these heterocyclic coumarins.

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RESULTS AND DISCUSSION

We have synthesized 3-(3-(phenacyl/alkyl/benzyl thio)-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-ones via a two-step process. In the first step, coumarin-3-carboxylic acid (**1**) was reacted with 4-amino-4*H*-[1,2,4]triazole-3,5-dithiol (**2**) in $POCl_3$. In the second step the intermediate was further reacted with different substituted phenacyl / benzyl/ alkyl bromides (**4**) in anhydrous ethanol under reflux condition for 4-6 h to gave the corresponding thio ethers (**5**). All the thio ethers prepared were new compounds. This is a regioselective S-alkylation. The alkylation of (**3**) with phenacyl/ benzyl/ alkyl bromides may result in different types of products such as N-alkylated, S-alkylated products and a mixture of both. In the present investigation, a mixture of products is not formed (as evidenced by TLC).

The formation of S-alkylated products have been explained in preference to N-alkylated products as due to high nucleophilicity of thiol group[21]. The formation of these S-alkylated products was confirmed by spectral data.

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Scheme-1

The compound **3** showed in its IR spectrum characteristic peaks for SH at 2922 cm^{-1} and lactone carbonyl at 1710 cm^{-1}. In the ^{1}H-NMR (DMSO-d_6) spectrum , the compound **3** showed a characteristic singlet at δ 2.79 for SH and coumarin C-4 proton appeared as singlet at δ 7.25. The remaining aromatic protons were observed in the usual aromatic region. In the mass spectrum the compound **3** exhibited $[M+H]^+$ ion at m/z 303.

The compound **5a** was characterized by analytical and spectral data. In the IR spectrum it exhibited a lactonyl carbon band at 1720 cm^{-1} , C=O stretching frequency at 1681 cm^{-1}, C=N stretching frequency at 1610 cm^{-1} respectively.

The ^{1}H NMR spectrum of **5a** showed –S- CH_2 protons at δ 4.90, aromatic proton chemical shifts appeared in the region δ 7.46-8.04 as a multiplet and the C-4 proton of coumarin resonated at δ 8.97 as a singlet.

The ^{13}C NMR spectrum of **5a** showed carbon chemical shift for -CH_2- at δ 40.3 , the lactone carbonyl carbon resonated at δ 160.8 and carbonyl carbon signal appeared at most downfield δ 192.8 . The mass spectrum showed a molecular ion peak at m/z 421.

EXPERIMENTAL

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All the reagents and solvents were pure, 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) and were uncorrected. CHN analytical data acquired by Carlo Erba EA 1108 automatic elemental analyzer. The compounds purity was checked by TLC plates (E. Merck, 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 TMS as standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API- 2000, ESI) at 12.5 eV. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for 5a and 5d (Figures S 1 – S 3)

General Procedure for preparation of compound (3)

A mixture of coumarin-3-carboxylic acid **1**(1mmol), 4-amino-4*H*-[1,2,4]triazole-3,5-dithiol **2** (1mmol) and $POCl_3$ (10 mL) was heated under reflux for 4 h. Excess $POCl_3$ was removed under reduced pressure. The concentrated mass was cooled and poured into ice to yield a solid product which on washing with $NaHCO_3$ followed by water and recrystallization from ethanol gave the title compound.

General Procedure for preparation of compounds (5a-j)

A mixture of 3-(3-mercapto-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-one **3** (1mmol) and appropriate phenacyl/ benzyl/ allyl bromide **4** was refluxed for 4-6 h in

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anhydrous ethanol. The reaction mixture was cooled and the solid separated was filtered, washed thoroughly with water and recrystallized from methanol to get the title compounds.

Synthesis of 3-[3-(2-oxo-2-phenyl-ethylsulfanyl)-[1,2,4]triazolo[3,4- b] [1,3,4] thiadiazol-6-yl]-chromen-2-one (5a)

Yellow solid, yield 78%, 4h, m.p. 194-196 ^{o}C. IR (KBr, cm^{-1}): υ 1720 (lactone carbonyl carbon of coumarin), 1681 (C=O), 1610 (C=N), 1567 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.90 (s, 2H, -SCH$_2$CO–), 7.46-7.60 (m, 4H, ArH), 7.67 (t, 1H, J=7.2Hz, ArH), 7.82 (t, 1H, J= 7.8Hz, ArH), 7.99–8.04 (m, 3H, ArH), 8.97 (s, 1H, C-4 of coumarin). ^{13}C NMR (400 MHz, DMSO-d_6 δ ppm): 40.3, 116.3, 117.0, 118.1, 125.3, 125.6, 128.3, 128.7, 130.7, 133.7, 135.1, 143.4, 150.0, 151.7, 154.3, 158.9, 160.9, 193.1. EI-MS 421 [M+H]$^{+}$. Anal. calcd. For $C_{20}H_{12}N_4O_3S_2$: C, 57.13; H, 2.88; N, 13.32; Found: C, 57.10; H, 2.82; N, 13.19.

Synthesis of 3-{3-[2-(4-bromo-phenyl)-2-oxo-ethylsulfanyl]-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazol-6-yl}-chromen-2-one (5b)

Yellow solid, yield 79%, 4h, m.p. 207-209 ^{o}C. IR (KBr, cm^{-1}): υ 1722 (lactone carbonyl carbon of coumarin), 1684 (C=O), 1609 (C=N), 1584 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.85 (s, 2H, -SCH$_2$CO–), 7.47-7.61 (m, 2H, ArH), 7.76 (d, 2H, J=8.4 Hz, ArH), 7.82 (t, 1H, J=7.8 Hz, ArH), 7.93 (t, 1H, J=9 Hz, ArH), 8.03 (d, 2H, J=8 Hz, ArH), 8.96 (s, 1H, C-4 of coumarin). ^{13}C NMR (400 MHz, DMSO-d_6 δ ppm): 40.4, 116.2, 116.8, 118.0, 125.2, 127.8, 130.3, 130.7, 131.7, 134.1, 135.1, 150.0, 151.5, 154.3, 158.8, 160.8, 192.4. EI-MS 499 [M]$^{+}$.

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Anal. calcd. For $C_{20}H_{11}BrN_4O_3S_2$: C, 48.10; H, 2.22; N, 11.22; Found: C, 48.14; H, 2.20; N,11.18

Synthesis of 3-{3-[2-(4-chloro-phenyl)-2-oxo-ethylsulfanyl]-[1,2,4] triazolo[3,4-b] [1,3,4]thiadiazol-6-yl}-chromen-2-one (5c)

Yellow solid, yield 76%, 4h, m.p. 210-212 ^{o}C. IR (KBr, cm^{-1}): υ 1723 (lactone carbonyl carbon of coumarin), 1698 (C=O), 1609 (C=N), 1566 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.86 (s, 2H, -SCH_2CO–), 7.46-7.62 (m, 4H, ArH), 7.82 (t, 1H, J=7.2Hz, ArH), 7.99–8.04 (m, 3H, ArH), 8.96 (s, 1H, C-4 of coumarin). ^{13}C NMR (400 MHz, DMSO-d_6 δ ppm): 40.3, 116.2, 116.8, 118.0, 125.2, 128.8, 130.2, 130.6, 133.8, 135.0, 138.6, 150.0, 151.5, 154.3, 158.8, 160.8, 192.2. EI-MS 455 $[M+H]^{+}$. Anal. calcd. For $C_{20}H_{11}ClN_4O_3S_2$: C, 52.80; H, 2.44; N, 12.32 Found: C, 52.76; H, 2.40; N, 12.28.

Synthesis of 3-(3-(2-(4-nitrophenyl)-2-oxoethylthio)-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-one (5d)

Yellow solid, yield 75%, 5h, m.p. 221-222 ^{o}C. IR (KBr, cm^{-1}): υ 1718 (lactone carbonyl carbon of coumarin), 1698 (C=O), 1608 (C=N), 1566 (C=C), 1347 (NO_2) . ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.92 (s, 2H, -SCH2CO–), 7.48-7.56 (m, 2H, ArH), 7.82 (d, 1H, J=7.6Hz, ArH), 8.03 (d, 1H, J=7.6Hz, ArH), 8.22 (d, 2H, J=8.8Hz ArH), 8.35 (d, 2H, J=8.8Hz ArH) 8.96 (s, 1H,

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C-4 of coumarin). EI-MS 466 $[M+H]^+$. Anal. calcd. For $C_{20}H_{11}N_5O_5S_2$: C, 51.61; H, 2.38; N, 15.05; Found: C, 51.54; H, 2.35; N, 15.12.

Synthesis of 3-(3-(2-oxo-2-p-tolylethylthio)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-6-yl)- chromen-2-one (5e)

Yellow solid, yield 80%, 4h, m.p. 190-192 ^oC. IR (KBr, cm^{-1}): υ 1721 (lactone carbonyl carbon of coumarin), 1698 (C=O), 1605 (C=N), 1564(C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 4.85 (s, 2H, -SCH_2CO–), 7.34 (d, 2H, J=8.0Hz, ArH), 7.46-7.60 (m, 2H, ArH), 7.82–7.93 (m, 3H, ArH), 8.03 (d, 1H, J=8Hz, ArH), 8.96 (s, 1H, C-4 of coumarin). Anal. calcd. For $C_{21}H_{14}N_4O_3S_2$: C, 58.05; H, 3.25; N, 12.89; Found: C, 58.10; H, 3.28; N, 12.85.

Synthesis of 3-(3-(2-(4-methoxyphenyl)-2-oxoethylthio)- [1,2,4]triazolo [3,4-b] [1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-one (5f)

Yellow solid, yield 84%, 4h, m.p. 205-207 ^oC. IR (KBr, cm^{-1}): υ 1723 (lactone carbonyl carbon of coumarin), 1676 (C=O), 1598 (C=N), 1564 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 4.83 (s, 2H, -SCH_2CO–), 7.04-7.06 (d, 2H, J=8.8Hz ArH), 7.46-7.56 (m, 2H, ArH), 7.82 (s, 1H, ArH), 7.96–8.03 (m, 3H, ArH), 8.96 (s, 1H, C-4 of coumarin). Anal. calcd. For $C_{21}H_{14}N_4O_4S_2$: C, 55.99; H, 3.13; N, 12.44; Found: C, 55.91; H, 3.16; N, 12.48.

Synthesis of 3-(3-(2-(biphenyl-4-yl)-2-oxoethylthio)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-6-yl)-2*H*-chromen-2-one (5g)

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Yellow solid, yield 75%, 5h, m.p. 207-209 ^{o}C. IR (KBr, cm^{-1}): υ 1722 (lactone carbonyl carbon of coumarin), 1697 (C=O), 1603 (C=N), 1565 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.92 (s, 2H, -SCH_2CO–), 7.44-7.55 (m, 5H, ArH), 7.75 (d, 2H, J= 8 Hz, ArH), 7.83 (t, 3H, J= 8.6 Hz, ArH), 8.02 (d, 1H, J= 8 Hz, ArH), 8.08 (d, 2H, J= 8.4 Hz, ArH), 8.99 (s, 1H, C-4 of coumarin). ^{13}C NMR (400 MHz, DMSO-d_6 δ ppm): 40.4, 116.2, 116.9, 118.0, 125.2, 126.8, 126.9, 128.4, 129.0, 129.1, 130.6, 133.9, 135.0, 138.6, 150.0, 151.6, 154.3, 158.9, 160.8, 192.7. Anal. calcd. For $C_{26}H_{16}N_4O_3S_2$: C, 62.89; H, 3.25; N, 11.28; Found: C, 62.77; H, 3.28; N, 11.24.

Synthesis of 3-(3-(benzylthio)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-one (5h)

Red solid, yield 73%, 5h, m.p. 225-227 ^{o}C. IR (KBr, cm^{-1}): υ 1705 (lactone carbonyl carbon of coumarin), 1603 (C=N), 1562 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.50 (s, 2H, -SCH_2–), 7.22-7.33 (m, 5H, ArH), 7.53 (d, 1H, J=7.6Hz, ArH), 7.60 (d, 1H J=8.4Hz, ArH), 7.82 (d, 1H, J=7.2Hz, ArH), 8.14 (d, 1H, J=8.0Hz ArH), 9.13 (s, 1H, C-4 of coumarin). Anal. calcd. For $C_{19}H_{12}N_4O_2S_2$: C, 58.15; H, 3.08; N, 14.28; Found: C, 58.18; H, 3.12; N, 14.32.

Synthesis of 3-(3-(3-nitrobenzylthio)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-6-yl)-2*H*-chromen-2-one (5i)

Red solid, yield 70%, 6h, m.p. 232-234 ^{o}C. IR (KBr, cm^{-1}): υ 1708(lactone carbonyl carbon of coumarin), 1606 (C=N), 1563 (C=C), 1344 (NO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ

4.46 (s, 2H, -SCH_2-), 7.53-7.64 (m, 4H, ArH), 7.82 (s, 1H, ArH), 8.02 (d, 1H, J=6.0Hz ArH), 8.12–8.17 (m, 2H, ArH), 9.09 (s, 1H, C-4 of coumarin). Anal. calcd. For $C_{19}H_{11}N_5O_4S_2$: C, 52.17; H, 2.53; N, 16.01; Found: C, 52.14; H, 2.58; N, 16.12.

Synthesis of 3-(3-(allylthio)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2H-chromen-2-one (5j)

Red solid, yield 72%, 6h, m.p. >300 ^oC. IR (KBr, cm^{-1}): υ 1708 (lactone carbonyl carbon of coumarin), 1605 (C=N), 1562 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 3.92 (d, 2H, J=7.2 Hz, -SCH_2-), 5.13 (d, 1H, J=8.8 Hz, CH_2 of allyl proton), 5.23 (d, 1H, J= 8 Hz, CH_2 of allyl proton), 5.99 (m, 1H, CH of allyl proton), 7.99–8.04 (m, 4H, ArH), 8.64 (s, 1H, C-4 of coumarin). EI-MS 343 $[M+H]^+$. Anal. calcd. For $C_{15}H_{10}N_4O_2S_2$: C, 52.62; H, 2.94; N, 16.36; Found: C, 52.58; H, 2.92; N, 16.31.

CONCLUSION

In conclusion we have developed an efficient regioselective approach for the synthesis of 3-(3-(phenacyl/alkyl/benzylthio)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-6-yl)-2*H*-chromen-2-ones in a simple procedure. The yields of the products are good in this synthesis.

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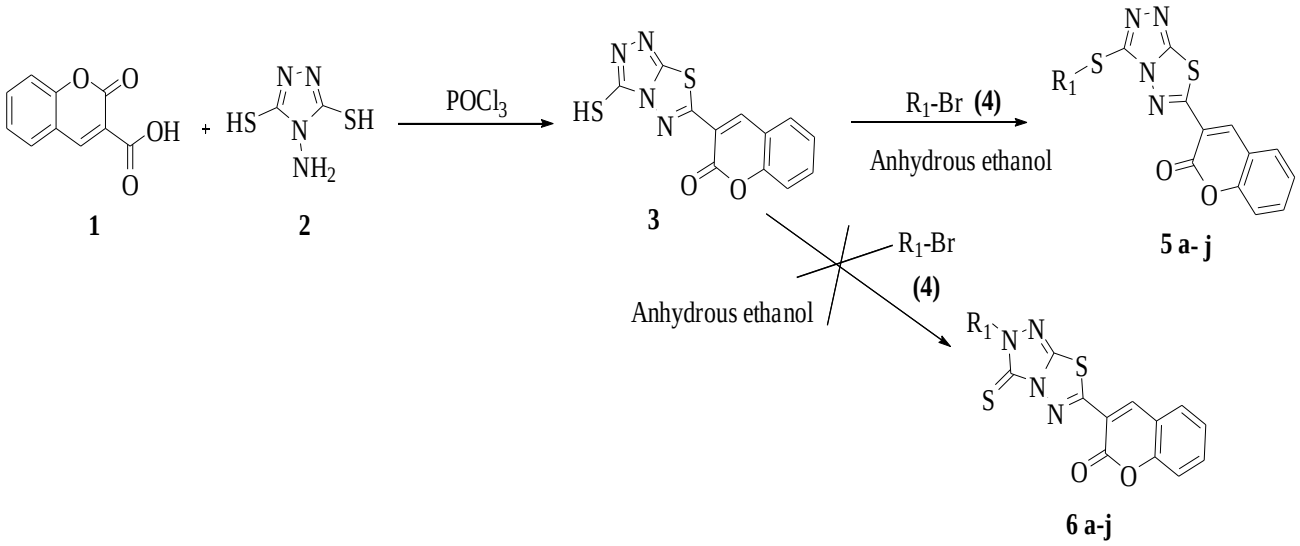

1 **2** **3** **5 a- j** **6 a-j**

	R_1		R_1
5a	Phenacyl	5f	p-Methoxy phenacyl
5b	p-Bromo phenacyl	5g	p-Phenyl phenacyl
5c	p-Chloro phenacyl	5h	Benzyl
5d	p-Nitro phenacyl	5i	m-Nitro benzyl
5e	p-Methyl phenacyl	5j	Allyl

Scheme-1: Synthesis of 3-(3-(phenacyl/alkyl/benzylthio)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-6-yl)-2*H*-chromen-2-ones

Supplemental Materials

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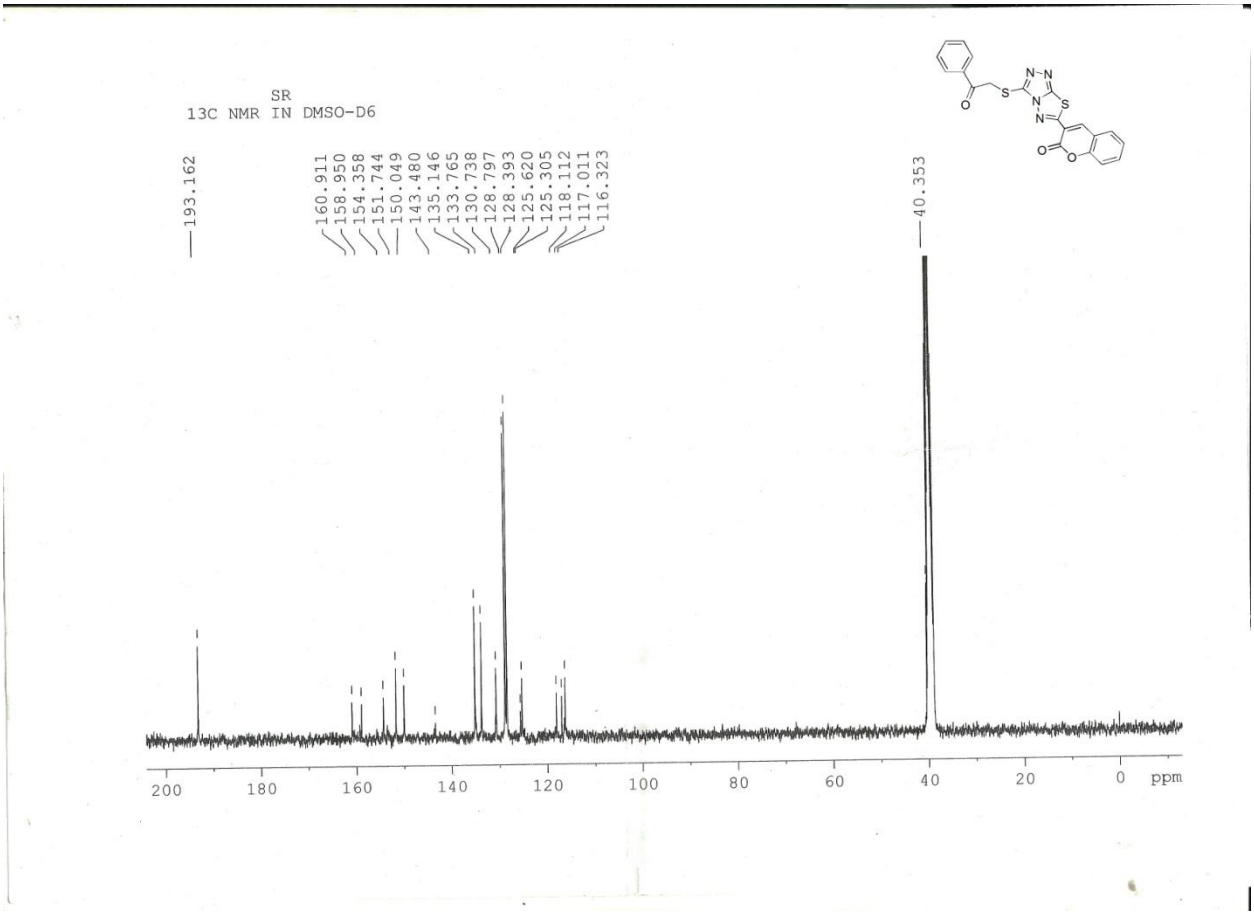

Figure S 1: ^{13}C NMR of 5a

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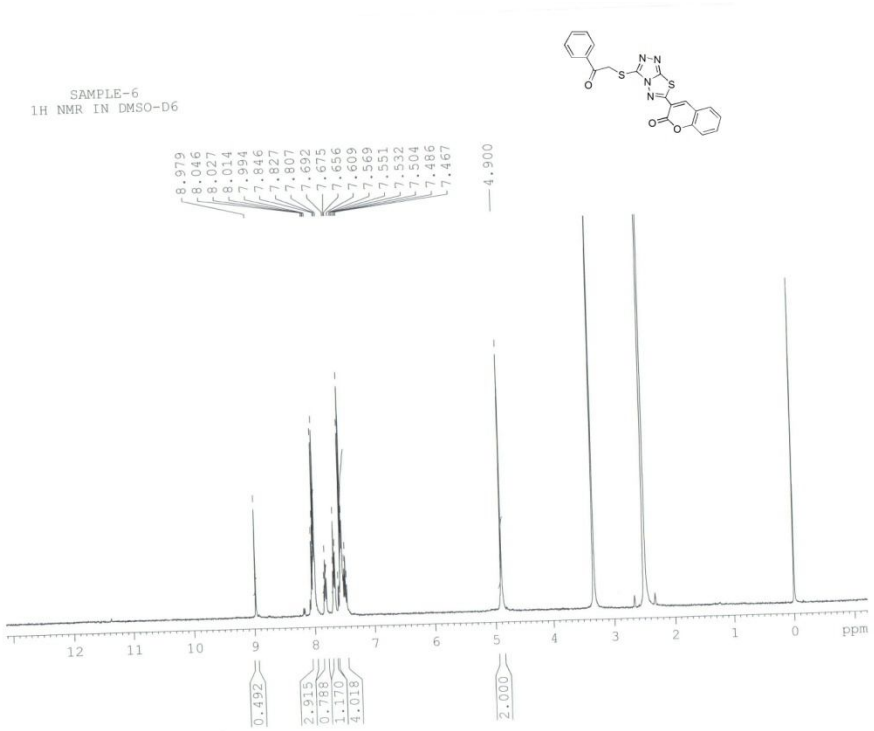

Figure S 2: ^{1}H NMR of 5a

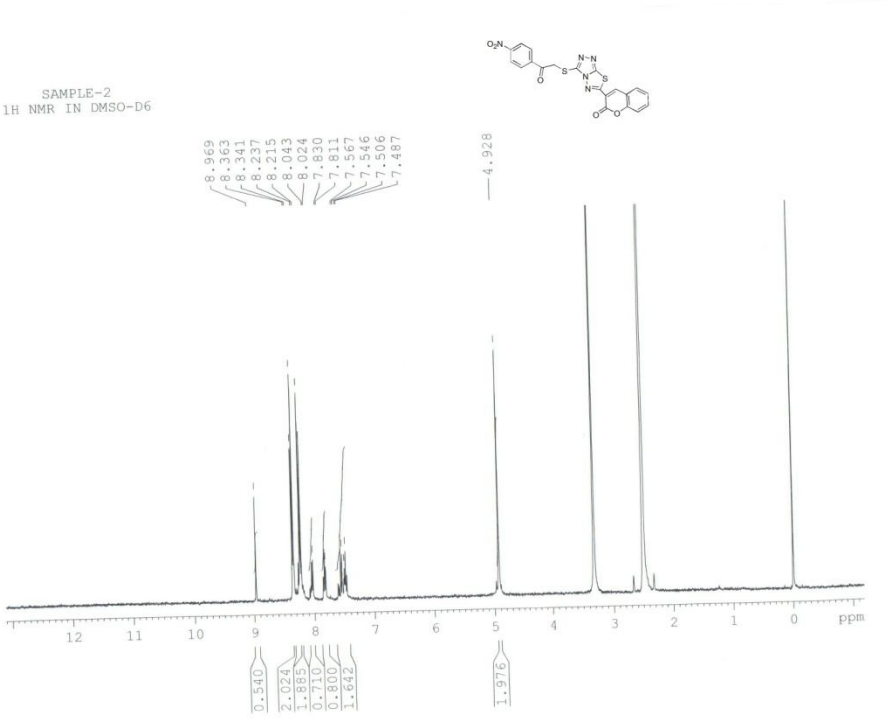

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Figure S 3: ^{1}H NMR of 5d

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