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Synthesis of some 3-(2-substituted sulfanyl-imidazo [2,1-b][1,3,4] thiadiazol-6-yl)-chromen-2-one and its derivatives

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A series of 3-(2-substituted sulfanyl-imidazo [2,1-b][1,3,4] thiadiazol-6-yl)-chromen-2-ones (**3**) have been synthesized from 3-(2-bromo acetyl) chromen-2-ones **1** and 2-amino-5-thio substituted[1,3,4]thiadiazole **2** in anhydrous ethanol. The 7,8-benzo analogs of 3-(2-substituted sulfanyl-imidazo[2,1-*b*][1,3,4] thiadiazol-6-yl)-chromen-2-ones **5** have been synthesized under similar conditions. All the synthesized compounds have been characteriszed by analytical and spectral data.

Keywords: Chromen-2-ones, coumarin, heterocyclic systems, biological activity

The Imidazo[2,1-b][1,3,4]thiadiazoles and their analogs have been used for anticancer[1], antitubercular[2], antibacterial[3], antitumor[4], anti-inflamatory[5] activities. The imidazo[2,1-b][1,3,4]thiadiazole system is present on Levamisole, a well known immuno modulator[6]. The thiazole (sulfathiazole / cerfixime)[7], imidazo[2,1-b]thiazole and their bio-isosteric derivatives of thiadiazole (acetazolamide)[8], imidazo[2,1-b][1,3,4]-thiadiazole[9] are regarded as safer and better drug molecules that are found to possess diversified biological activities[10].

In continuation of our earlier work on the synthesis of heterocyclic systems derived from coumarin[11-13] and also our search for biologically active imidazo [2,1-b][1,3,4] thiadiazoles[14], we report here in the synthesis and preliminary biological evaluation of some 3-(2-substituted sulfanyl-imidazo [2,1-b][1,3,4] thiadiazol-6-yl)-chromen-2-ones and its derivatives.

Results and Discussions

The compounds (**3**) were synthesized by the reaction of various 3-(2-bromacetyl)-chromen-2-ones (**1**) with 2-amino-5-thiomethyl/benzyl [1,3,4] thiadiazole (**2**) in anhydrous ethanol, (Scheme I). The experimental procedure is very simple and products obtained were in good yields (80-90%).

Structures of all the newly synthesized compounds are well supported by spectral data such as IR, NMR, Mass and elemental analysis. The proton NMR spectrum of **3a** showed characteristic peaks at δ 2.75 (s, 3H of SCH_3), C_4-H of coumarin at δ 8.50 (S,1H) and imidazo[2,1-b][1,3,4] thiadiazoles proton at δ 8.62 (s,1H), the remaining aromatic protons were appeared at usual region. The molecular ion peak showed at *m/z* 316.

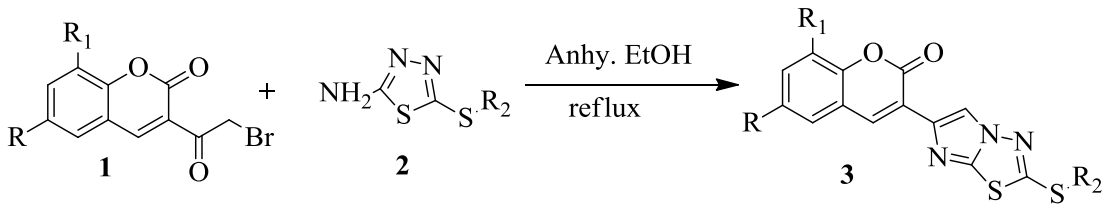
In the first step of the reaction between **1** and **2**, the cyclic secondary nitrogen of the thiadiazole replaces the bromine of the 3-(2-bromo acetyl) coumarin to give the intermediate (**6**). This on subsequent cyclodehydration yields the products (**3** and **5**, Scheme II).

Attempts to isolate the intermediate were futile as the final product was directly obtained under different reaction conditions and media. The prepared final compounds **3** and **5** were tested chemically and proved to have sulphur (Lassigne's test) but no halogen (Beilstein's test and Lassaigne's test).

Another possible isomeric structure (**7**) (Figure 1) can be proposed for the prepared compounds. However this structure (**7**) can be readily discarded basing on the fact that in the thiadiazole system, the most nucleophilic site is the cyclic secondary nitrogen at 3rd position[15, 16]. Hence, the preferential attack starts with this center leading to structure **3** and **5** only.

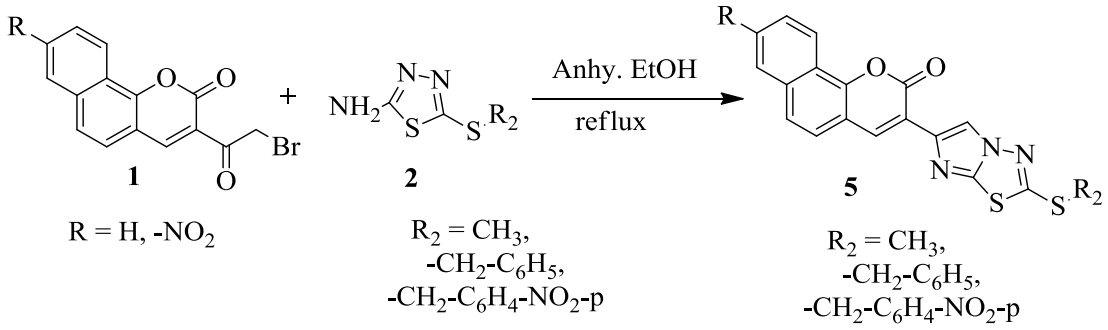
Experimental Section

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The



3a: R = R_1= H, R_2 = -CH_3
b: R = R_1= H, R_2 = -CH_2-C_6H_5
c: R = H, R_1= -OCH_3, R_2 = -CH_2-C_6H_5
d: R = Cl, R_1= H, R_2 = -CH_2-C_6H_5
e: R = R_1= Cl, R_2 = -CH_2-C_6H_5
f: R = Br, R_1= H, R_2 = -CH_2-C_6H_5
g: R = R_1= Br, R_2 = -CH_2-C_6H_5
h: R = R_1= H, R_2 = -CH_2-C_6H_4-NO_2-p
i: R = H, R_1= -OCH_3, R_2 = -CH_2-C_6H_4-NO_2-p
j: R = Cl, R_1= H, R_2 = -CH_2-C_6H_4-NO_2-p
k: R = R_1= Cl, R_2 = -CH_2-C_6H_4-NO_2-p
l: R = Br, R_1= H, R_2 = -CH_2-C_6H_4-NO_2-p
m: R = R_1= Br, R_2 = -CH_2-C_6H_4-NO_2-p

Scheme I



R = H, -NO_2

R_2 = CH_3,
-CH_2-C_6H_5,
-CH_2-C_6H_4-NO_2-p

R_2 = CH_3,
-CH_2-C_6H_5,
-CH_2-C_6H_4-NO_2-p

Scheme II

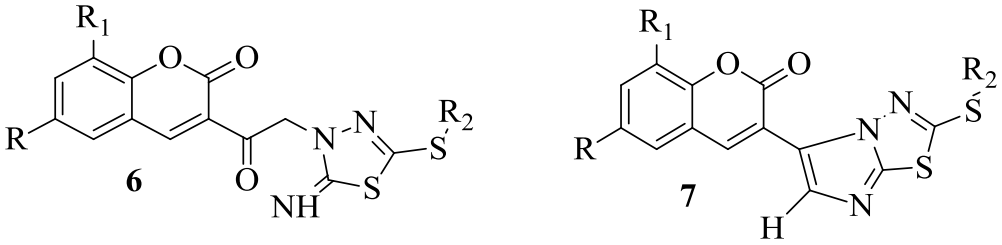


Figure 1

purity of compounds was checked by TLC plates (E. Merck, Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-400 spectrometer. ^{1}H-NMR spectra were recorded on Buckner WM-300 spectrometer (in δ ppm) using TMS as internal standard. Mass Spectra (EI-MS) were determined on Jeol-D-300 Spectrometer at 70 ev. The 3-(2-bromoacetyl)-chromen-2-ones[17] and [1,3,4] thiadiazoles[16] were prepared by reported procedures[17].

General procedure for the synthesis 3-(2-substituted sulfanyl-imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-chromen-2-one (3a-m and 5a-b). Compound 1 (or) 4 (0.001 mole) was dissolved in anhydrous ethanol (10ml) then added compound 2 (0.001 mole). The reaction mixture was refluxed for 3-4 hours. Then the mixture was cooled at room temperature. The solid separated was filtered and washed with cold ethanol, water, dried and recrystallised from

methanol. All the other compounds were synthesized similarly (3b-m and 5a-b).

3-(2-Methyl sulfanyl-imidazo[2,1-b][1,3,4]thiadiazol-5-yl) -chromen-2-one (3a): Brown Solid. Yield 90%. m.p. 228-230°C. IR (KBr): 1725 (lactone, -C=O), 1602 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 2.75 (s, 3H, $-CH_3$), 7.35-7.96 (m, 4H, Ar-H), 8.45 (s, 1H, C_4-H of Coumarin); 8.55 (s, 1H, imidazo thiazole proton); MS: *m/z* 315 (Molecular ion). Anal. calcd. for $C_{14}H_9N_3S_2O_2$: C, 53.32; H, 2.888; N, 13.32. Found: C, 53.27; H, 2.80; N, 13.24.

3-(2-Benzyl sulfanyl-imidazo[2,1-b][1,3,4]thiadiazol-6-yl) -chromen-2-one (3b): Brown Solid. Yield 85%. m.p. 223-225°C. IR (KBr): 1722.28 (lactone, -C=O), 1601 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.56 (s, 2H, benzyl-CH_2-S), 7.35-7.78 (m, 9H, Ar-H), 8.50 (s, 1H, C_4-H of Coumarin); 8.66 (s,1H, imidazo thiazole proton); MS: *m/z* 391 (Molecular ion). Anal. calcd. for $C_{20}H_{13}N_3S_2O_2$: C, 61.36; H, 3.35; N, 10.73, Found: C, 61.25; H, 3.26; N, 10.68.

3-(2-Benzylsulfanyl-imidazo[2,1-b][1,3,4]thiadiazol-6-yl) -8-methoxy-chromen-2-one (3c). Brown Solid. Yield 87%. m.p. 227-229°C. IR (KBr): 1720 (lactone, -C=O), 1602 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.60 (s, 3H, $-OCH_3$), 4.55 (s, 2H, -S-CH_2-), 7.26-7.82 (m, 8H, Ar-H), 8.45 (s, 1H, C_4-H of coumarin); 8.63 (s, 1H, imidazo thiazole proton); MS: *m/z* 421 (Molecular ion). Anal. calcd. for $C_{21}H_{15}N_3S_3O_2$: C, 59.84; H, 3.59; N, 9.97, Found: C, 59.76; H, 3.47; N, 9.83.

3-(2-Benzylsulfanyl-imidazo[2,1-b][1,3,4]thiadiazol-6-yl) -6-chloro-chromen-2-one (3d): Brown Solid. Yield 83%. m.p. 161-163°C. IR (KBr): 1720 (lactone, -C=O), 1601 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.60 (s, 2H, -S-CH_2-for benzyl), 7.27-7.50 (m, 3H, Ar-H), 7.55-7.88 (m, 5H, Ar-H); 8.40 (s, 1H, C_4-H of coumarin); 8.66 (s,1H, imidazo thiazole proton); MS: *m/z* 425 (Molecular ion). Anal. calcd. for $C_{20}H_{12}ClN_3O_2S_2$: C, 56.40; H, 2.84; N, 9.87, Found: C, 56.33; H, 2.76; N, 9.73.

3-(2-Benzyl sulfanyl-imidazo [2,1-b] [1,3,4] thiadiazol-6-yl)-6,8-dichloro-chromen-2-one (3e): Brown Solid. Yield 86%. m.p. 198-200°C. IR (KBr): 1722 (lactone, -C=O), 1606 (-C=N) cm^{-1}; ^1H-NMR (200MHz, DMSO-d_6): δ 4.56 (s, 2H, -S-CH_2-for benzyl), 7.20 (d, 1H, Ar-H, *J* = 3Hz), 7.47 (d, 1H, Ar-H, *J* = 3Hz); 7.50-7.87 (m, 5H, Ar-H), 8.48 (s,1H, C_4-H of coumarin); 8.68 (s, 1H, imidazo thiazole proton); MS: *m/z* 460 (Molecular ion). Anal. calcd. for $C_{20}H_{11}Cl_2N_3O_2S_2$: C, 52.18; H, 2.41; N, 9.13, Found: C, 52.06; H, 2.34; N, 9.08.

3-(2-Benzyl sulfanyl-imidazo [2,1-b] [1,3,4] thiadiazol-6-yl)-6-bromo-chromen-2-one (3f): Brown Solid. Yield 84%. m.p. 216-218°C. IR (KBr): 1726 (lactone, -C=O), 1610 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.56 (s, 2H, -S-CH_2-for benzyl), 7.45 (d, 1H, *J* = 7Hz, C_8-H of coumarin), 7.66 (d, 1H, *J* = 8Hz, C_7 or coumarin); 7.84 (d, 1H, *J* = 2Hz, C_5 of coumarin); 7.88-8.20 (m, 5H, Ar-H); 8.69 (s, 1H, C_4 of coumarin), 8.80 (s, 1H, imidazo thiazole proton); MS: *m/z* 470 (Molecular ion). Anal. calcd. for $C_{20}H_{12}BrN_3O_2S_2$: C, 51.07; H, 2.57; N, 8.93, Found: C, 51.01; H, 2.49; N, 8.86.

3-(2-Benzylsulfanyl-imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-6,8-dibromo-chromen-2-one (3g): Brown Solid. Yield 88%. m.p. 226-228°C. IR (KBr): 1721 (lactone, -C=O), 1606 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.57 (s, 2H, -S-CH_2-for benzyl), 7.33 (d, 1H, C_7 of coumarin, *J* = 8Hz), 7.46 (d, 1H, C_5 of coumarin, *J* = 2 Hz); 7.50-7.99 (m, 5H, Ar-H), 8.5(s, 1H, C_4 of coumarin); 8.65 (s, 1H, imidazo thiazole proton); MS: *m/z* 549 (Molecular ion). Anal. calcd. for $C_{20}H_{11}Br_2N_3O_2S_2$: C, 43.74; H, 2.02; N, 7.65, Found: C, 43.66; H, 1.94; N, 7.54.

3-[2-(4-Nitro-benzylsulfanyl-imidazo[2,1-b][1,3,4] thiadiazol-6-yl)-

chromen-2-one (3h): Brown Solid. Yield 78%. m.p. 206-208°C. IR (KBr): 1726 (lactone, -C=O), 1608 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.56 (s, 2H, -S-CH_2-for benzyl), 7.33-7.64 (m, 4H, Ar-H), 7.88-7.90 (d, d, 2H, Ar-H); 7.98-8.00 (d, d, 2H, Ar-H), 8.51 (s, 1H, C_4 of coumarin); 8.60 (s, 1H, imidazo thiazole proton); MS: *m/z* 436 (Molecular ion). Anal. calcd. for $C_{20}H_{12}N_4O_4S_2$: C, 55.04; H, 2.77; N, 12.84, Found: C, 57.96; H, 2.67; N, 12.75.

3-[2-(4-Nitro-benzylsulfanyl-imidazo[2,1-b][1,3,4] thiadiazol-6-yl)-8-methoxy-chromen-2-one (3i): Brown Solid. Yield 76%. m.p. 210-212°C. IR (KBr): 1725 (lactone, -C=O), 1604 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.6 (s, 3H, $-OCH_3$), 4.50 (s, 2H, -S-CH_2- for benzyl), 7.33-7.60 (m, 3H, Ar-H); 7.71-7.78 (d, d, 2H, Ar-H), 7.80-7.88 (d, d, 2H, Ar-H); 8.55 (s, 1H, Ar-H); 8.60 (s, 1H, imidazo thiazole proton); MS: *m/z* 466 (Molecular ion). Anal. calcd. for $C_{21}H_{14}N_4O_5S_2$: C, 54.07; H, 3.03; N, 12.01, Found: C, 53.96; H, 2.95; N, 11.94.

3-[2-(4-Nitro-benzylsulfanyl-imidazo[2,1-b][1,3,4] thiadiazol-6-yl)-6-chloro-chromen-2-one (3j).

Brown Solid. Yield 76%. m.p. 204-208°C. IR (KBr): 1720 (lactone, -C=O), 1610 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.54 (s, 2H, -S-CH_2-for benzyl), 7.30-7.60 (m, 3H, Ar-H), 7.70-7.76 (d, d, 2H, Ar-H); 7.80-7.98 (d, d, 2H, Ar-H), 8.55 (s, 1H, C_4 coumarin); 8.65 (s, 1H, imidazo thiazole proton); MS: *m/z* 470 (Molecular ion). Anal. calcd. for $C_{20}H_{11}ClN_4O_4S_2$: C, 51.01; H, 2.35; N, 11.90, Found: C, 49.96; H, 2.27; N, 11.87.

3-[2-(4-Nitro-benzylsulfanyl-imidazo [2,1-b] [1,3,4] thiadiazol-6-yl)-6,8-dichloro-chromen-2-one (3k): Brown Solid. Yield 78%. m.p. 242-246°C. IR (KBr): 1723 (lactone, -C=O), 1609 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.56 (s, 2H, -S-CH_2 for benzyl), 7.35 (d, 1H, C_7 of coumarin, J = 3Hz), 7.55 (d, 1H, C_5 of coumarin); 7.60-7.75 (d, d, 2H, Ar-H), 7.80-7.92 (d, d, 2H, Ar-H); 8.54 (s, 1H, C_4 of coumarin); 8.66 (s, 1H, imidazo thiazole proton);); MS: *m/z* 505 (Molecular ion). Anal. calcd. for $C_{20}H_{10}Cl_2N_4O_4S_2$: C, 47.53; H, 47.53; N, 11.09, Found: C, 47.47; H, 1.85; N, 11.02.

3-[2-(4-Nitro-benzylsulfanyl-imidazo[2,1-b][1,3,4] thiadiazol-6-yl)-6-bromo-chromen-2-one (3l): Brown Solid. Yield 76%. m.p. 250-252°C. IR (KBr): 1723 (lactone, -C=O), 1608 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.53 (s, 2H, -S-CH_2 for benzyl), 7.50-7.67 (m, 3H, Ar-H), 7.71-7.83 (d, d, 2H, Ar-H); 7.85-7.88 (d, d, 2H, Ar-H), 8.51 (s, 1H, C_4 of coumarin); 8.66 (s, 1H, imidazo thiazole proton); MS: *m/z* 515 (Molecular ion). Anal. calcd. for $C_{20}H_{11}BrN_4O_4S_2$: C, 46.61; H, 2.15; N, 10.87, Found: C, 46.54; H, 2.09; N, 10.81.

3-[2-(4-Nitro-benzylsulfanyl-imidazo[2,1-b][1,3,4] thiadiazol-6-yl)-6,8-dibromo-chromen-2-one (3m): Brown Solid. Yield 78%. m.p. 264-268°C. IR (KBr): 1720 (lactone, -C=O), 1606 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.56 (s, 2H, -S-CH_2 for benzyl), 7.45 (d, 1H, C_7 of coumarin, J = 8 Hz), 7.69(d, 1H, C_5 of coumarin, J = 2Hz); 7.75-7.78 (d, d, 2H, Ar-H), 7.81-7.96 (d, d, 2H, Ar-H), 8.54 (s, 1H, C_4 of coumarin); 8.67 (s, 1H, imidazo thiazole proton); MS: *m/z* 594 (Molecular ion). Anal. calcd. for $C_{20}H_{10}Br_2N_4O_4S_2$: C, 40.42; H, 1.70; N, 9.43, Found: C, 40.38; H, 1.66; N, 9.37.

3-(2-Benzylsulfanyl-imidazo[2,1-b][1,3,4]thiadiazol -6-yl)-benzo[b]-chromen-2-one (5a). Brown Solid. Yield 80%. m.p. 177-179°C. IR (KBr): 1726 (lactone, -C=O), 1610 (-C=N) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.67 (s, 2H, -S-CH_2-for benzyl), 7.30-7.76 (m, 6H, Ar-H), 7.80-8.00 (m, 5H, Ar-H); 8.45 (s, 1H, C_4 of coumarin), 8.87 (s, 1H, imidazo thiazole proton); MS: *m/z* 441 (Molecular ion). Anal. calcd. for $C_{24}H_{15}N_3O_2S_2$: C, 65.29; H, 3.42; N, 9.52, Found: C, 65.21; H, 3.36; N, 9.45.

Conclusion

In conclusion, we have described a series of sulfanyl-imidazo [2,1-b] [1,3,4]-thiadiazole and their derivatives have been synthesized from easily available starting materials. The title compounds were obtained by the single step, with a simple and convenient method (conventional) in good yields, without any side products.

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