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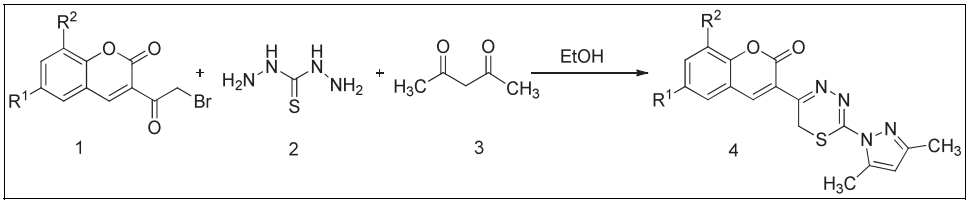

An efficient novel one-pot synthesis of pyrazolyl-thiadiazinyl-2*H*-chromen-2-ones. In this process, an equimolar mixture of substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones, thiocarbohydrazide and pentane-2,4-dione were taken in absolute ethanol. All these synthesized compounds were characterized by their analytical and spectral data.

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INTRODUCTION

In recent years, multicomponent reactions are well known in organic synthesis because of their several applications over traditional reactions because of high efficiency, less reaction time, atom economy and high yields [1]. In continuation to our earlier work on the synthesis of coumarin containing heterocyclic compounds [2,3], now we are reporting an efficient one-pot synthesis of 3-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6*H*-1,3,4-thiadiazin-5-yl)-2*H*-chromen-2-ones.

The literature survey on 1,3,4-thiadiazines clearly reveals that very little work has been carried out. So, we have attempted novel synthesis of the title compounds using MCR approach. The specialty of the present one-pot multicomponent synthesis is that by using simple synthons, we could be able to construct two new rings such as 1,3,4-thiadiazine and pyrazole at a time. No such one-pot preparation was reported in the literature.

The procedure has several advantages such as atom economy, simplicity and easy work up procedure, readily available starting materials, no catalyst usage and usage of no hazardous chemicals. 1,3,4-Thiadiazine type of compounds is an important class of heterocycles, which has paid much attention because of their wide range of biological activities [4]. They act as matrix metalloproteinase inhibitors [5], and they can show cardiotonic and hypertensive activities [6,7]. Compounds with thiadiazine moiety exhibit antimicrobial properties, and some of the thiadiazine derivatives are significant antibacterial and antifungal compounds [8]. 1,3,4-Thiadiazine-containing compounds are used against the bacterium *Helicobacter pylori* and reverse transcriptase inhibitor of human immunodeficiency virus [9]. Coumarins possess pharmalogical activities such as anti-inflammatory, antipyretic [10] and bronchodilator [11] activities. Their derivatives show a broad range of biological activities such as anticoagulant [12] and antitumor [13,14] activity.

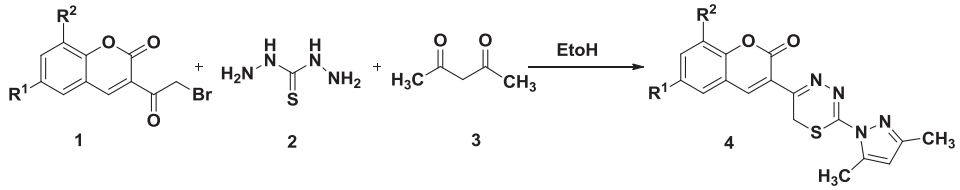
RESULTS AND DISCUSSION

In the present investigation, we have synthesized various novel analogues of 3-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6*H*-1,3,4-thiadiazin-5-yl)-2*H*-chromen-2-ones via one-pot synthesis. As shown in Scheme 1, a mixture of substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones, thiocarbohydrazide and pentane-2,4-dione was taken in absolute ethanol. These components are stirred at RT for 30 min, followed by reflux for 4 h. After completion of reaction, the reaction mixture was filtered, washed with methanol, water and recrystallized from ethanol.

To the formation of these compounds, first bromine atom is substituted by thiol group of thiocarbohydrazide to form alpha thioimidate. This undergoes cyclization with amino group, followed by loss of proton and water molecule to give 3-(2-hydrazinyl-6*H*-1,3,4-thiadiazin-5-yl)-2*H*-chromen-2-one. This further reacts with acetyl acetone to give 3-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6*H*-1,3,4-thiadiazin-5-yl)-2*H*-chromen-2-one.

The compounds were characterized by analytical and spectral data. IR spectrum of **4a** showed lactone carbon frequency at 1729 cm^{-1} and C=N stretching frequency at 1556 cm^{-1}. In ^{1}H-NMR spectrum, the compound **4a** showed two methyl groups of pyrazole at δ 2.19, 2.57, and the thiadiazine proton signal appeared at δ 4.98; the C-4 of coumarin proton signal appeared at δ 8.85, and the aromatic protons appeared at their appropriate regions. In ^{13}C-NMR spectrum, the compound **4a** showed two methyl carbons signals at δ 12.9, 13.0, and thiadiazine carbon showed at δ 44.1; lactone carbonyl carbon of

Scheme 1. One-pot three-component synthesis of pyrazolyl-thiadiazinyl-2*H*-chromen-2-one derivatives.



Entry	R^1	R^2
4a	H	H
4b	H	OCH_3
4c	$N(C_2H_5)_2$	H
4d	5,6-benzo	
4e	Cl	H
4f	Br	H
4g	Cl	Cl
4h	Br	Br
4i	NO_2	H

coumarin appeared at δ 163.6. In mass spectrum, the compound **4a** appeared at $[M+H]^+$ 339.

CONCLUSION

In summary, we have reported an efficient, practical one-pot synthesis of 3-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6*H*-1,3,4-thiadiazin-5-yl)-2*H*-chromen-2-ones. This is a simple, mild, inexpensive and environmentally benign reaction, and the biological activity of these compounds are in progress.

EXPERIMENTAL

All the solvents and chemicals were purchased from commercial sources. 3-(2-Bromo acetyl) coumarins [15] were prepared by the literature procedure. Melting points were determined in open capillaries with a Stuart melting point apparatus Mumbai, India and were uncorrected. IR spectra were recorded on a Perkin Elmer 100S instrument. ^{1}H-NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using TMS as the standard. ESI-MS spectra were recorded on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 ev. Elemental analysis was carried out by Carlo Erba EA 1108 automatic elemental analyser. Compound purity was checked by TLC plates (E.merk, Mumbai, India).

General procedure for synthesis of compounds (4a–i). An equimolar mixture of various 3-(2-bromoacetyl)-2*H*-chromen-2-ones (1 mmol), thiocarbohydrazide (1 mmol) and pentane-2, 4-dione (1 mmol) was taken in 5 mL of absolute ethanol. The reaction mixture was stirred RT for 30 min and then followed by refluxed for 4 h. After completion of the reaction by monitoring TLC, the solid separated was filtered, washed with methanol and recrystallized from ethanol.

***3-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6H-1, 3,4-thiadiazin-5-yl)-2H*-chromen-2-one (4a).** Colour: yellow solid; yield 85%; Mp 176–178°C; IR (KBr, υ max/cm^{-1}): 1729 (lactone C=O), 1608 (C=C), 1556 (C=N). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 2.19 (s, 3*H*, CH_3 of pyrazole), 2.57 (s, 3H, CH_3 of pyrazole), 4.98 (s, 2H, CH_2 of thiadiazine), 6.25 (s, 1H, pyrazole proton), 7.45 (t, 1H, *J* = 7.6 Hz, ArH), 7.52 (d, 1H, *J* = 8.4 Hz, ArH), 7.79 (t, 1H, *J* = 8.2 Hz, ArH), 8.00–8.02 (m, 1H, ArH), 8.85 (s, 1H, C-4 of coumarin). ^{13}C NMR (DMSO-*d*6, δ ppm): 12.9, 13.0, 44.1, 110.3, 116.2, 118.0, 122.7, 125.1, 131.0, 135.0, 141.8, 148.6, 152.6, 154.6, 158.4, 160.9, 163.6. ESI-MS 339 $[M+H]^+$; *Anal*. Calcd. for: $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.16; H, 4.10; N, 16.47.

3-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6H-1, 3,4-thiadiazin-5-yl)-8-methoxy-2H-chromen-2-one (4b). Colour: orange solid; yield 78%; Mp 156–158°C; IR (KBr, υ max/cm^{-1}): 1727 (lactone C=O), 1601 (C=C), 1565 (C=N), 1277 (C-OCH_3). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 2.19 (s, 3H, CH_3 of pyrazole), 2.57 (s, 3H, CH_3 of pyrazole), 3.95 (s, 3H, CH_3 of methoxy), 4.89 (s, 2H, CH_2 of thiadiazine), 6.17 (s, 1H, pyrazole proton), 7.36–7.41 (m, 1H, ArH), 7.47 (d, 1H, *J* = 7.6 Hz, ArH), 7.51–7.55 (m, 1H, ArH), 8.81 (s, 1H, C-4 of coumarin). ^{13}C NMR (DMSO-*d*6, δ ppm): 13.0, 13.0, 44.0, 56.2, 110.4, 117.4, 118.5, 119.6, 121.8, 125.0, 141.9, 144.0, 146.2, 150.7, 153.3, 157.2, 165.7. *Anal*. Calcd. for: $C_{18}H_{16}N_4O_3S$: C, 58.68; H, 4.38; N, 15.21. Found: C, 58.58; H, 4.30; N, 15.18.

6-(Diethyl amino)-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-6H-1,3,4-thiadiazin-5-yl)-2H-chromen-2-one (4c). Colour: yellow solid; yield 75%; Mp 160–162°C; IR (KBr, υ max/cm^{-1}): 1727 (lactone C=O), 1574 (C=N). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 1.25 (t, 6H, CH_3 of $N(C_2H_5)_2$), 2.19 (s, 3H, CH_3 of pyrazole), 2.35 (s, 3H, CH_3 of pyrazole), 3.45–3.50 (q, 4H, CH_2 of $N(C_2H_5)_2$, 4.77 (s, 2H, CH_2 of thiadiazine), 6.18 (s, 1H, pyrazole), 6.47 (d, 1H, *J* = 2 Hz, ArH), 6.63–6.66 (m, 1H, ArH), 7.42 (d, 1H, *J* = 9.2 Hz, ArH), 8.53 (s, 1H, C-4 of coumarin). *Anal*. Calcd. for: $C_{21}H_{23}N_5O_2S$: C, 61.59; H, 5.66; N, 17.10. Found: C, 61.49; H, 5.69; N, 17.19.

2-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6H-1,3,4-thiadiazin-5-yl)-3H-benzo[f]chromen-3-one (4d). Colour: red solid; yield 70%; Mp 164–166°C; IR (KBr, υ max/cm^{-1}): 1720 (lactone C=O), 1624 (C=C), 1559 (C=N). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 2.18 (s, 3H, CH_3 of pyrazole), 2.56 (s, 3H, CH_3 of pyrazole), 4.98 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 7.65–7.69 (m, 2H, ArH), 7.79–7.84 (m, 2H, ArH), 8.12 (d, 1H, J = 8 Hz), 8.38 (d, 1H, *J* = 8.8 Hz), 8.70 (s, 1H, C-4 of coumarin). ^{13}C NMR ($CDCl_3$, δ ppm): 13.0, 13.0, 43.8, 110.1, 112.9, 116.4, 120.0, 120.8, 121.6, 121.7, 137.0, 137.1, 142.4, 145.0, 145.2, 153.0, 156.4, 159.0, 159.3, 160.5, 164.3. ESI-MS 389 [M + 1]. *Anal*. Calcd. for: C, 64.93; H, 4.15; N, 14.42. $C_{21}H_{16}N_4O_2S$: found: C, 64.86; H, 4.22; N, 13.88.

6-Chloro-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-6H-1,3,4-thiadiazin-5-yl)-2H-chromen-2-one (4e). Colour: red solid; yield 70%; Mp 184–86°C; IR (KBr, υ max/cm^{-1}): 1733 (lactone C=O), 1610 (C=C), 1556 (C=N). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 2.19 (s, 3H, CH_3 of pyrazole), 2.57 (s, 3H, CH_3 of pyrazole), 4.97 (s, 2H, CH_2 of thiadiazine), 6.25 (s, 1H, pyrazole proton),

7.57 (d, 1H, $J = 8.4$ Hz, ArH), 7.81–7.84 (m, 1H, ArH), 8.14 (d, 1H, $J = 2.4$ Hz, ArH), 8.79 (s, 1H, C-4 of coumarin). ^{13}C NMR (DMSO-*d*6, δ ppm): 13.0, 13.0, 44.0, 110.4, 118.2, 119.4, 123.8, 128.7, 129.7, 134.4, 141.9, 143.2, 147.2, 152.7, 153.3, 158.0, 160.9. ESI-MS 395 [M + 23]. *Anal*. Calcd. for: C, 54.77; H, 3.51; N, 15.03. $C_{17}H_{13}ClN_4O_2S$: found: C, 54.64; H, 3.48; N, 15.17.

6-Bromo-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-6H-1,3,4-thiadiazin-5-yl)-2H-chromen-2-one (4f). Colour: orange solid; yield 70%; Mp 159–161°C; IR (KBr, υ max/cm^{-1}): 1733 (lactone C═O), 1605 (C═C), 1550 (C═N). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 2.19 (s, 3H, CH_3 of pyrazole), 2.57 (s, 3H, CH_3 of pyrazole), 4.89 (s, 2H, thiadiazine), 6.17 (s, 1H, pyrazole), 7.92–7.95 (m, 2H, ArH), 8.26 (t, 1H, $J = 3.4$ Hz, ArH), 8.78 (s, 1H, C-4 of coumarin). ^{13}C NMR (DMSO-*d*6, δ ppm): 13.0, 13.0, 44.0, 110.4, 118.3, 118.4, 119.8, 120.0, 125.3, 132.1, 132.5, 136.4, 136.5, 145.5, 145.7, 153.5, 157.9. *Anal*. Calcd. for: C, 48.93; H, 3.14; N, 13.43. $C_{17}H_{13}BrN_4O_2S$: found: C, 48.81; H, 3.10; N, 13.36.

6,8-Dichloro-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-6H-1,3,4-thiadiazin-5-yl)-2H-chromen-2-one (4g). Colour: yellow solid; yield 73%; Mp 178–180°C; IR (KBr, υ max/cm^{-1}): 1734 (lactone C═O), 1610 (C═C), 1555 (C═N). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 2.19 (s, 3H, CH_3 of pyrazole), 2.58 (s, 3H, CH_3 of pyrazole), 4.89 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 8.32–8.34 (m, 2H, ArH), 8.76 (s, 1H, C-4 of coumarin). ^{13}C NMR ($CDCl_3$, δ ppm): 13.0, 13.0, 43.4, 117.8, 118.2, 119.0, 119.1, 123.1, 124.1, 142.4, 144.8, 146.6, 147.8, 148.0, 153.1, 153.6, 160.1. *Anal*. Calcd. for: C, 50.13; H, 2.97; N, 13.76. $C_{17}H_{12}Cl_2N_4O_2S$: found: C, 50.18; H, 2.89; N, 13.68.

6,8-Dibromo-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-6H-1,3,4-thiadiazin-5-yl)-2H-chromen-2-one (4h). Colour: orange solid; yield 72%; Mp 180–182°C; IR (KBr, υ max/cm^{-1}): 1738 (lactone C═O), 1599 (C═C), 1542 (C═N). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.57 (s, 3H, CH_3 of pyrazole), 4.89 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 8.27 (d, 1H, $J = 2.4$ Hz, ArH), 8.32 (d, 1H, $J = 2$ Hz, ArH), 8.75 (s, 1H, C-4 of coumarin). ^{13}C NMR ($CDCl_3$, δ ppm): 13.0, 13.2, 43.0, 110.0, 111.0, 117.4, 120.0, 120.1, 123.4, 124.4, 131.4, 147.1, 147.5, 150.7, 152.9, 157.3, 159.7. ESI-MS 497 [M + 1]. *Anal*. Calcd. for: C, 41.15; H, 2.44; N, 11.29. $C_{17}H_{12}Br_2N_4O_2S$: found: C, 41.10; H, 2.37; N, 11.18.

3-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6H-1,3,4-thiadiazin-5-yl)-6-nitro-2H-chromen-2-one (4i). Colour: orange solid; yield 72%; Mp 152–154°C; IR (KBr, υ max/cm^{-1}): 1711 (lactone C═O), 1605 (C═C), 1531 (C═N), 1348 (NO_2). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.59 (s, 3H, CH_3 of pyrazole), 4.90 (s, 2H, thiadiazine), 6.19 (s, 1H, pyrazole), 7.73 (d, 1H, $J = 6.4$ Hz, ArH), 8.53–8.56 (m, 2H, ArH), 8.99 (s, 1H, C-4 of coumarin). *Anal*. Calcd. for: C, 53.26; H, 3.42; N, 18.27. $C_{17}H_{13}N_5O_4S$: found: C, 53.20; H, 3.38; N, 18.20.

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