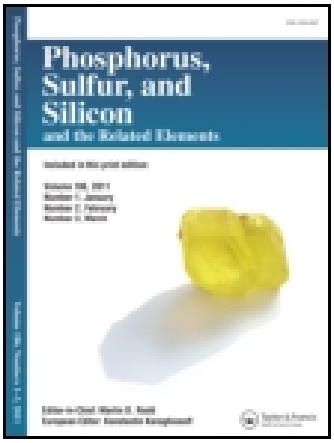

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Synthesis of Some New 3-(5-(Arylamino)-1,3,4-thiadiazol-2-yl)-2H-chromen-2-ones and 3-(4-Aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-YL)-2H-chromen-2-ones

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SYNTHESIS OF SOME NEW 3-(5-(ARYLAMINO)-1,3,4-THIADIAZOL-2-YL)-2H-CHROMEN-2-ONES AND 3-(4-ARYL-5-THIOXO-4,5-DIHYDRO-1H-1,2,4-TRIAZOL-3-YL)-2H-CHROMEN-2-ONES

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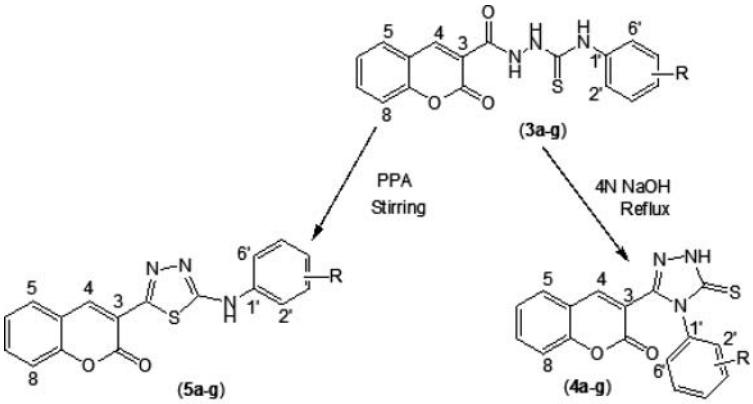
GRAPHICAL ABSTRACT



Abstract *In this study, 2-oxo-2H-chromene-3-carbohydrazide (**1**) was synthesized by the condensation of ethyl 2-oxo-2H-chromene-3-carboxylate with hydrazine hydrate. Thiosemicarbazide derivatives (**3a–g**) were afforded by the treatment of carbohydrazide (**1**) with substituted phenyl isothiocyanates (**2a–g**). The cyclization of compounds (**3a–g**) in the presence of aqueous sodium hydroxide resulted in the formation of compounds **4a–g** containing a 1,2,4-triazole ring. On the other hand, the treatment of compounds **3a–g** with polyphosphoric acid caused the conversion of side chain of **3a–g** into the 1,3,4-thiadiazole ring; thus, compounds **5a–g** were obtained. The structures of the products were established by elemental analyses, IR, ^{1}H, and ^{13}C NMR spectroscopy.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Coumarin; 1; 3; 4-thiadiazole; thiosemicarbazides; 1; 2; 4-triazole

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INTRODUCTION

Coumarins (2*H*-1-benzopyran-2-ones) are natural lactones and among the best known oxygen heterocycles, well represented as a structural motif in numerous natural products.[1] Various coumarin derivatives are known to possess an array of biological activities, including anticancer, anti-HIV, anti-acetylcholinesterase, antifungal, antioxidant, antihelmintic, anticoagulant, antibacterial, antiviral, and anticlotting activities, and find extensive application in pharmaceuticals, fragrances, agrochemicals, and as additives in food, cosmetics, and insecticides.[2–10] Moreover, coumarins find application as dyes in laser technology, fluorescent indicators, optical brighteners, and photosensitizers.[1,11] Introduction of fluorine at the 4-position in the aryloxy and arylamino moieties of coumarin enhances their antimicrobial activities.[12] Scoparone isolated from the hypolipidaemic Chinese herb *Artemisia scoparia* is shown to reduce the proliferative responses of human peripheral mononuclear cells, to relax smooth muscle, to reduce total cholesterol and triglycerides, and to retard the characteristic pathomorphological changes in hypercholesterolaemic diabetic rabbits.[13] Osthole from *Angelica pubescens* causes hypotension in vivo and inhibits platelet aggregation and smooth muscle contraction in vitro.[14]

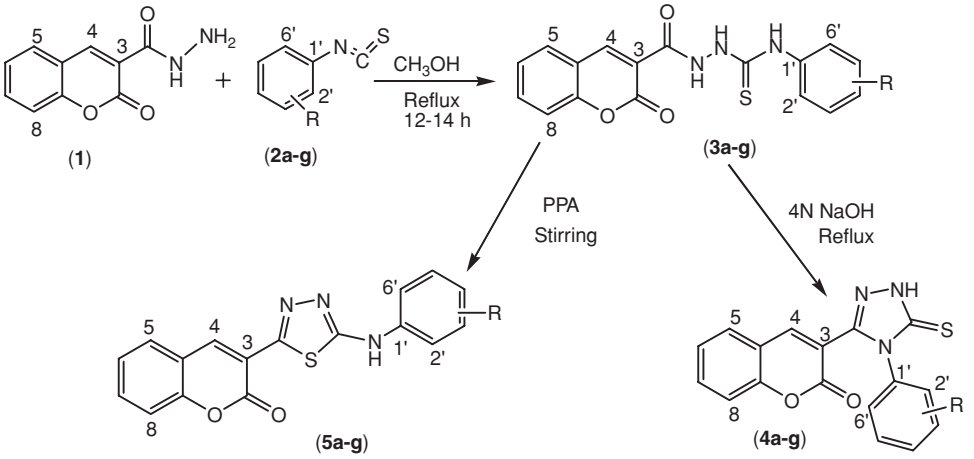
Over the last few decades, the biological and pharmaceutical properties of 1,2,4-triazoles have created considerable interest in their synthesis and characterization. 4,5-Disubstituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and their derivatives are of great importance due to their biological,[15] industrial, and agricultural activities. A well-known example is that of fluconazole, an antifungal agent for the treatment of superficial and systemic infections.[16] Others have diuretic,[17] antibacterial,[18] hypoglycemic,[19] and antitubercular[20] activities. Moreover, they are inhibitors of corrosion of copper, brass, aluminium, and steel in marine environments[21] and inhibitors of fog formation in photographic emulsions.[22]

Similarly the substituted-1,3,4-thiadiazoles are found to exhibit a variety of applications including antibacterial agents,[23] radioprotective agents, investigational antitumor drugs, gastroprotective drugs,[24] corrosion inhibitors,[25] ulcer inhibitors,[26] in photography,[27] and as diuretic drugs.[28]

Keeping in view the biological significance of the aforementioned individual heterocycles, namely triazoles and thiadiazoles on one hand and that of coumarins on other, the aim of the present work was the synthesis of biheterocyclic compounds by coupling of these heterocycles with a coumarin nucleus to combine their useful effects in a single structural unit.

RESULTS AND DISCUSSION

The coumarinyl ester was synthesized by the reaction of salicylaldehyde with diethylmalonate according to the reported procedure.[29] It was converted into the corresponding hydrazide (**1**) by refluxing with hydrazine hydrate (80%) in methanol.[30] The IR spectrum of hydrazide exhibited a characteristic absorption band for primary NH_2 along with a shoulder at 3380 and for the secondary NH at 3287 cm^{-1}. The strong absorptions at 1732 and 1643 cm^{-1} were assigned to the coumarin and amide carbonyls, respectively. In the ^1H NMR spectrum, the characteristic singlets at 7.88 for H-4 of coumarin nucleus and those for N—H and NH_2 protons at 11.11 and 5.45 ppm, respectively, were observed. The ^{13}C NMR spectrum showed characteristic absorption at 157.7 and 165.1 ppm due to coumarin and amide carbonyl groups, respectively (Scheme 1).



Scheme 1 Synthetic pathway of 3-(5-(arylamino)-1,3,4-thiadiazol-2-yl)-2*H*-chromen-2-ones and 3-(4-Aryl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-ones.

Aryl isothiocyanates (**2a–g**) were prepared from the corresponding substituted anilines according to the standard procedure.[31] The thiosemicarbazides (**3a–g**) were synthesized by the condensation of corresponding hydrazide (**1**) and isothiocyanates (**2a–g**) in methanol.[32] The formation of thiosemicarbazides (**3a–g**) was indicated by the IR spectra where (C=O) absorption appeared in the range of 1644–1689 cm^{-1} and that of (C=S) in the range of 1235–1268 cm^{-1}. The characteristic absorption bands for three secondary N−H groups were observed in the region of 3143–3432 cm^{-1}. In the ^{1}H NMR spectrum, the NH proton of amide type linkage appeared in the range of 11.23–11.96 ppm and a signal for two NH protons of thiourea type linkage appeared in the range of 9.99–11.14 ppm. In the ^{13}C NMR spectrum, the appearance of new peaks in aromatic region and carobonyl in the range of 164.7–167.0 and thiocarbonyl in the range of 176.2–181.7 ppm was noted.

The 4,5-disubstituted-1,2,4-triazol-3-thiones (**4a–g**) were synthesized by refluxing the corresponding thiosemicarbazides (**3a–g**) in an aqueous sodium hydroxide (4N) solution.[33,34] The products were purified by recrystallization in aqueous ethanol. The formation of triazoles (**4a–g**) was indicated by the disappearance of broad peaks of NH groups and of a (C=O) group of thiosemicarbazides and by the appearance of (C=N) absorption in the range 1375–1413 cm^{-1}. In ^{1}H NMR, a signal for N−H proton of triazoles appeared in the range of 11.13–13.94 ppm. The disappearance of signals for N−H protons confirmed the formation of the triazoles. In the ^{13}C NMR spectrum, the disappearance of a peak due to amidic (C=O) group and the appearance of a (C=N) peak in the range of 156.3–159.1 ppm was detected.

2,5-Disubstituted-1,3,4-thiadiazoles (**5a–g**) were synthesized by treating the thiosemicarbazide intermediates (**3a–g**) with concentrated polyphosphoric acid at low temperature.[35] The formation of thiadiazoles was indicated by the disappearance of broad peaks of NH groups and amidic (C=O) group of thiosemicarbazides, and appearance of (C=N) absorption in the range 1415–1471 cm^{-1}. In the ^{1}H NMR spectrum, the signal for

the N-H proton of thiadiazoles appeared in the range of 11.14–11.86 ppm, while in the ^{13}C NMR spectrum, the disappearance of a (C=O) group peak and the appearance of a (C=N) peak in the range of 157.0–159.2 ppm indicated the desired conversion.

CONCLUSIONS

In conclusion, 2-oxo-2*H*-chromene-3-carbohydrazide has successfully been used as a molecular handle to generate 1,2,4-triazole and 1,3,4-thiadiazole rings leading to biologically potent biheterocyclic compounds containing a coumarin nucleus to combine their useful effects in a single structural unit.

EXPERIMENTAL

The R_f-values were determined using aluminum precoated silica gel plates Kiesel 60 F_{254} from Merck (Germany). Melting points of the compounds were measured in open capillaries using Stuart melting point apparatus (SMP3) and are uncorrected. The IR spectra were recorded on an FTS 3000 MX, Bio-Rad Merlin (Excalibur Model) spectrophotometer. ^1H NMR spectra were determined as $CDCl_3$ solutions at 300 MHz using a Bruker AM-300 spectrophotometer using TMS as an internal reference, and the ^{13}C NMR spectra were determined at 75 MHz using a Bruker 75 MHz NMR in DMSO-d_6 and $CDCl_3$ solutions using TMS as an internal standard. The elemental analysis was performed on Leco CHNS-932 Elemental Analyzer (Leco Corporation, USA). Figures S1–S4 (Supplemental Materials, available online) include the ^1H and ^{13}C NMR spectra of **3e** and **4f**.

Synthesis of 2-Oxo-2*H*-chromene-3-carbohydrazide (1)

2-Oxo-2*H*-chromene-3-carboxylate (0.02 mol) was dissolved in methanol (100 mL) in a round bottom flask fitted with a reflux condenser and a calcium chloride drying tube. Hydrazine hydrate (80%, 1.94 mL, 0.04 mol) was added slowly, and the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting crude solid was filtered, washed with water, and recrystallized from aqueous ethanol. White solid (87%): mp: 145–148°C; R_f*: 0.13, IR (KBr, cm^{-1}): 3380, 3287 (NH), 1732 (C=O), 1643 (C=O), 1572, 1540 (C=C ring). ^1H NMR (300MHz, $CDCl_3$): δ 11.11 (s, 1H, NH-C=O), 7.88 (s, 1H, C-H, H-4), 7.24 (d, 1H, J = 7.8Hz, H-8), 7.13-7.10 (m, 1H, H-6), 6.98-6.95 (m, 1H, H-7), 6.88 (d, 1H, J = 7.5Hz, H-5), 5.45 (s, 2H, NH_2); ^{13}C NMR (75MHz, $CDCl_3$): δ 165.1 (C=O), 157.7 (NH−C=O), 146.8, 133.5, 130.0, 129.3, 119.8, 119.1, 118.4, 116.5 (Ar-Cs). Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72; Found: C, 58.62; H, 3.81; N, 13.76.

Synthesis of 1,4-Disubstituted Thiosemicarbazides (3a–g): General procedure

The carbohydrazide (**1**) (6.8 mmol) was dissolved in methanol (30 mL), and a solution of substituted isothiocyanate (**2a–g**) (6.6 mmol) separately dissolved in methanol (10 mL) was added dropwise with continuous stirring. The reaction mixture was refluxed for 10–12 h and monitored by TLC. After consumption of the starting materials, the mixture was cooled

to room temperature. The methanol was evaporated on a rotary evaporator leaving behind the crude product as oil that became solidified upon cooling and was recrystallized from a mixture of ethyl acetate and petroleum ether (4:1) to yield thiosemicarbazides (**3a–g**).

4-(2-Chlorophenyl)-1-(2-oxo-2*H*-chromene-3-carbonyl)thiosemicarbazide (3a). Green solid (54%): mp 215–217°C; R_f^* : 0.54; IR (KBr, cm^{-1}): 3296–3163 (NH), 1731 (C=O), 1673 (C=O), 1596, 1512 (C=C), 1268 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.96 (s, 1H, NH−C=O), 10.05 (s, 2H, NH−C=S), 9.01 (s, 1H, C-H, H-4), 8.03 (d, 1H, J = 7.5 Hz, H-8), 7.71–7.69 (m, 1H, H-6), 7.37–7.09 (m, 3H, H-7, H-3′, H-5′), 6.99 (d, 1H, J = 8.1 Hz, H-5), 6.94–6.76 (m, 2H, H-4′, H-6′); ^{13}C NMR (75 MHz, DMSO-d_6): δ 181.2 (C=S), 166.9 (NH−C=O), 159.5 (C=O), 150.2, 135.3, 134.6, 132.1, 129.5, 126.6, 125.5, 124.9, 123.4, 122.4, 120.9, 118.6, 116.2 (Ar-Cs). Anal. Calcd. for $C_{17}H_{12}ClN_3O_3S$: C, 54.62; H, 3.24; N, 11.24, S, 8.58; Found: C, 54.54; H, 3.11; N, 11.09; S, 8.49.

4-(3-Chlorophenyl)-1-(2-oxo-2*H*-chromene-3-carbonyl)thiosemicarbazide (3b). Yellow solid (59%): mp 189–191°C; R_f*: 0.54; IR (KBr, cm^{-1}): 3295–3163 (NH), 1724 (C=O), 1670 (C=O), 1590, 1508 (C=C), 1267 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.35 (s, 1H, NH−C=O), 10.15 (s, 2H, NH−C=S), 9.00 (s, 1H, C−H, H-4), 7.68 (d, 1H, J = 7.8 Hz, H-8), 7.42–7.36 (m, 2H, H-6, H-7), 7.20 (d, J = 7.8Hz, H-5), 6.99–6.89 (m, 2H, H-3′, H-5′), 6.84–6.79 (m, 2H, H-4′, H-6′); ^{13}C NMR (75MHz, DMSO-d_6): δ 181.4 (C=S), 163.1 (NH−C=O), 159.3 (C=O), 156.9, 142.2, 133.6, 131.1, 129.0, 128.6, 125.4, 120.2, 119.8, 119.4, 118.7, 117.1, 116.1 (Ar-Cs). Anal. Calcd. for $C_{17}H_{12}ClN_3O_3S$: C, 54.62; H, 3.24; N, 11.24, S, 8.58; Found: C, 54.71; H, 3.17; N, 11.15; S, 8.43.

4-(4-Chlorophenyl)-1-(2-oxo-2*H*-chromene-3-carbonyl)thiosemicarbazide (3c). Greenish solid (56%): mp 177–179°C; Rf*: 0.57; IR (KBr, cm^{-1}): 3341–3223 (NH), 1732 (C=O), 1670 (C=O), 1558, 1514, 1484 (C=C), 1268 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.23 (s, 1H, NH−C=O), 11.11 (s, 2H, NH−C=S), 9.01 (s, 1H, C−H, H-4), 7.70 (d, 1H, J = 7.5 Hz, H-8), 7.50–7.22 (m, 5H, H-5, H-6, H-7, H-3′, H-5′), 7.00–6.94 (m, 2H, H-2′, H-6′); ^{13}C NMR (75 MHz, DMSO-d_6): δ 181.5 (C=S), 167.0 (NH−C=O), 163.2 (C=O), 149.3, 133.7, 131.3, 131.2, 129.1, 125.3, 124.3, 123.7, 123.4, 118.7, 117.0 (Ar-Cs). Anal. Calcd. for $C_{17}H_{12}ClN_3O_3S$: C, 54.62; H, 3.24; N, 11.24, S, 8.58; Found: C, 54.51; H, 3.32; N, 11.07; S, 8.43.

1-(2-Oxo-2*H*-chromene-3-carbonyl)-4-*m*-tolylthiosemicarbazide (3d). Yellow solid (61%): mp 150–152°C; Rf*: 0.50; IR (KBr, cm^{-1}): 3300–3143 (NH), 1732 (C=O), 1674 (C=O), 1522, 1497 (C=C), 1236 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.76 (s, 1H, NH−C=O), 9.99 (s, 2H, NH−C=S), 8.48 (s, 1H, C−H, H-4), 8.10 (d, 1H, J = 7.5 Hz, H-8), 7.41–7.36 (m, 1H, H-6), 7.25–7.20 (m, 2H, H-7, H-5′), 7.21–7.14 (m, 1H, H-2′), 7.01 (d, 1H, J = 7.5 Hz, H-5), 6.89–6.81 (m, 2H, H-4′, H-6′), 2.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.2 (C=S), 164.7 (NH−C=O), 157.0 (C=O), 149.4, 138.7, 137.7, 131.7, 128.3, 126.6, 126.2, 124.5, 123.3, 122.4, 120.7, 119.7, 116.4 (Ar-Cs), 21.4 (CH_3). Anal. Calcd. for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89, S, 9.07; Found: C, 61.11; H, 4.33; N, 11.75; S, 8.97.

1-(2-Oxo-2*H*-chromene-3-carbonyl)-4-*p*-tolylthiosemicarbazide (3e). White solid (59%): mp 179–181°C; R_f*: 0.51; IR (KBr, cm^{-1}): 3432–3179 (NH), 1718 (C=O), 1689 (C=O), 1573, 1538, 1513 (C=C), 1259 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ

*R_f solvent system (petroleum ether:ethyl acetate, 4:1).

11.73 (s, 1H, NH−C=O), 11.14 (s, 2H, NH−C=S), 9.98 (s, 1H, C−H, H-4), 7.42 (d, 1H, $J = 7.5$ Hz, H-8), 7.26–7.23 (m, 2H, H-7, H-6), 7.21–7.14 (m, 2H, H-2′, H-6′), 6.99 (d, 1H, $J = 7.5$ Hz, H-5), 6.89–6.81 (m, 2H, H-3′, H-5′), 2.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.2 (C=S), 165.4 (NH−C=S), 157.0 (C=O), 148.2, 137.0, 134.8, 131.8, 128.9, 126.2, 123.4, 122.7, 120.7, 119.7, 116.5 (Ar-Cs), 21.1 (CH_3). Anal. Calcd. for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89, S, 9.07; Found: C, 61.02; H, 4.20; N, 11.95; S, 8.92.

4-(2-Methoxyphenyl)-1-(2-oxo-2*H*-chromene-3-carbonyl)thiosemicarbazide (3f). White solid (57%): mp 198–200°C; R_f*: 0.56; IR (KBr, cm^{-1}): 3326–3281 (NH), 1726 (C=O), 1644 (C=O), 1593, 1520 (C=C), 1235 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.90 (s, 1H, NH−C=O), 11.14 (s, 2H, NH−C=S), 9.97 (s, 1H, C-H, H-4), 7.88 (d, 1H, $J = 7.8$Hz, H-8), 7.28–7.25 (m, 1H, H-6), 7.23–7.14 (m, 1H, H-7), 7.09 (d, 1H, $J = 7.2$Hz, H-5), 7.00–6.96 (m, 2H, H-3′, H-6′), 6.93–6.86 (m, 2H, H-4′, H-5′), 3.35 (s, 3H, OCH_3); ^{13}C NMR (75MHz, DMSO-d_6): δ 181.7 (C=S), 166.2 (NH−C=O), 161.2 (C=O), 151.6, 139.1, 136.2, 130.4, 128.2, 126.0, 125.9, 125.7, 124.5, 120.6, 120.3, 119.9, 116.6, 111.6 (Ar-Cs), 55.7 (OCH_3). Anal. Calcd. for $C_{18}H_{15}N_3O_4S$: C, 58.53; H, 4.09; N, 11.38, S, 8.68; Found: C, 58.67; H, 4.21; N, 11.24; S, 8.53.

4-(3-Methoxyphenyl)-1-(2-oxo-2*H*-chromene-3-carbonyl)thiosemicarbazide (3g). Green solid (57%): mp 169–172°C; R_f*: 0.56; IR (KBr, cm^{-1}): 3324–3283 (NH), 1721 (C=O), 1652 (C=O), 1589, 1518 (C=C), 1237 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.70 (s, 1H, NH−C=O), 10.00 (s, 2H, NH−C=S), 9.01 (s, 1H, C-H, H-4), 7.69 (d, 1H, $J = 7.8$Hz, H-8), 7.40–7.37 (m, 1H, H-6), 7.30–7.17 (m, 2H, H-7, H-5), 7.00–6.91 (m, 2H, H-4′, H-5′), 6.90–6.75 (m, 2H, H-2′, H-6′), 3.76(s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 180.7 (C=S), 163.2 (NH−C=O), 159.4 (C=O), 150.4, 140.7, 133.7, 131.3, 129.9, 129.1, 127.5, 125.7, 124.5, 120.7, 120.0, 119.6, 117.0, 111.5 (Ar-Cs), 55.5 (OCH_3). Anal. Calcd. for $C_{18}H_{15}N_3O_4S$: C, 58.53; H, 4.09; N, 11.38, S, 8.68; Found: C, 58.45; H, 4.11; N, 11.29; S, 8.51.

Synthesis of 4,5-Disubstituted-1,2,4-triazol-3(4*H*) thiones (4a–g): General Procedure

The thiosemicarbazides (**3a–g**) (1.4 mmol) were refluxed (4–5 h) in aqueous sodium hydroxide solution (4N, 25 mL). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered. The filtrate was neutralized with hydrochloric acid (4N) to precipitate the triazoles, which were filtered and recrystallized from aqueous ethanol.

3-(4-(2-Chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (4a). Yellow solid (63%): mp 205–207°C; Rf*: 0.61; IR (KBr, cm^{-1}): 3292 (NH), 1730 (C=O), 1555, 1477 (C=C), 1409 (C=N), 1253 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.13 (s, 1H, NH), 9.01 (s, 1H, C-H, H-4), 7.63 (d, 1H, $J = 7.8$ Hz, H-8), 7.42–7.38 (m, 2H, H-6, H-7), 6.93 (d, 1H, $J = 7.5$Hz, H-5), 7.11–7.08 (m, 2H, H-3′, H-5′), 7.03–6.99 (m, 1H, H-6′), 6.88–6.81 (m, 1H, H-4′); ^{13}C NMR (75MHz, DMSO-d_6): δ 165.2 (C=S), 159.5 (C=O), 158.5 (C=N), 148.7, 133.6, 131.8, 131.1, 128.9, 128.6, 127.6, 126.4, 122.2, 121.4, 119.4, 119.1, 117.3, 116.9 (Ar-Cs). Anal. Calcd. for $C_{17}H_{10}ClN_3O_2S$: C, 57.39; H, 2.83; N, 11.81, S, 9.01; Found: C, 57.23; H, 2.71; N, 11.70; S, 8.87.

3-(4-(3-Chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (4b). Yellow solid (61%): mp 207–209°C; Rf*: 0.61; IR (KBr, cm^{-1}): 3282 (NH), 1728 (C=O), 1553, 1482 (C=C), 1383 (C=N), 1267 (C=S); ^{1}H NMR (300 MHz,

DMSO-d_6): δ 11.13 (s, 1H, NH), 9.00 (s, 1H, C-H, H-4), 7.68 (d, 1H, J = 7.8Hz, H-8), 7.43–7.41 (m, 2H, H-6, H-7), 7.38–7.37 (m, 2H, H-4′, H-5′), 7.00 (d, 1H, J = 7.8 Hz, H-5), 6.97–6.95 (m, 2H, H-2′, H-6′); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.2 (C=S), 159.3 (C=O), 157.8 (C=N), 148.4, 133.7, 131.2, 130.5, 129.1, 128.6, 122.2, 120.1, 119.2, 118.6, 117.3, 117.0 (Ar-Cs). Anal. Calcd. for $C_{17}H_{10}ClN_3O_2S$: C, 57.39; H, 2.83; N, 11.81, S, 9.01; Found: C, 57.27; H, 2.69; N, 11.88; S, 8.92.

3-(4-(4-Chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (4c). Green solid (66%): mp 204–206°C; Rf*: 0.62; IR (KBr, cm^{-1}): 3287 (NH), 1728 (C=O), 1571, 1486 (C=C), 1381 (C=N), 1269 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.14 (s, 1H, N*H*), 9.01 (s, 1H, C-H, H-4), 7.69 (d, 1H, J = 7.8 Hz, H-8), 7.43–7.40 (m, 2H, H-6, H-7), 7.39–7.37 (m, 2H, H-3′, H-5′), 6.98 (d, 1H, J = 7.8 Hz, H-5), 6.96–6.94 (m, 2H, H-2′, H-6′); ^{13}C NMR (75MHz, DMSO-d_6): δ 163.3 (C=S), 159.1 (C=O), 157.9 (C=N), 148.6, 133.7, 131.3, 130.4, 129.2, 128.7, 122.6, 120.0, 119.3, 118.7, 117.2, 117.0 (Ar-Cs). Anal. Calcd. for $C_{17}H_{10}ClN_3O_2S$: C, 57.39; H, 2.83; N, 11.81, S, 9.01; Found: C, 57.26; H, 2.69; N, 11.67; S, 8.92.

3-(5-Thioxo-4-*m*-tolyl-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (4d). Yellow solid (59%): mp 217–219°C; Rf*: 0.59; IR (KBr, cm^{-1}): 3281 (NH), 1725 (C=O), 1576, 1541 (C=C), 1413 (C=N), 1235 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.15 (s, 1H, NH), 9.00 (s, 1H, C-H, H-4), 7.71–7.68 (m, 2H, H-8, H-6), 7.43–7.37 (m, 2H, H-7, H-5), 6.99–6.95 (m, 4H, H-2′, H-4′, H-5′, H-6′), 2.21 (s, 3H, CH_3); ^{13}C NMR (75MHz, DMSO-d_6): δ 163.3 (C=S), 160.1 (C=O), 159.1 (C=N), 149.3, 133.7, 131.3, 131.1, 129.2, 128.2, 126.1, 124.6, 122.1, 120.1, 119.3, 118.6, 117.4, 117.0 (Ar-Cs), 24.3 (CH_3). Anal. Calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.46; H, 3.91; N, 12.53, S, 9.56; Found: C, 64.51; H, 3.79; N, 12.42; S, 9.40.

3-(5-Thioxo-4-*p*-tolyl-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (4e). Yellow solid (61%): mp 211–213°C; Rf*: 0.58; IR (KBr, cm^{-1}): 3297 (NH), 1732 (C=O), 1557, 1513 (C=C), 1375 (C=N), 1288 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.14 (s, 1H, NH), 9.01 (s, 1H, C-H, H-4), 7.43–7.25 (m, 4H, H-8, H-7, H-6, H-5), 7.07 (d, 2H, J = 8.1Hz, H-2′, H-6′), 6.99 (d, 2H, J = 7.8 Hz, H-3′, H-5′), 2.23 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.5 (C=S), 159.4 (C=O), 158.6 (C=N), 149.1, 137.7, 133.6, 130.9, 129.6, 128.7, 125.5, 121.0, 119.3, 118.6, 117.0, 116.0, 112.7, 116.8 (Ar-Cs), 20.8 (CH_3). Anal. Calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.46; H, 3.91; N, 12.53, S, 9.56; Found: C, 64.61; H, 3.82; N, 12.39; S, 9.41.

3-(4-(2-Methoxyphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (4f). Yellow solid (64%): mp 214–216°C; Rf*: 0.51; IR (KBr, cm^{-1}): 3275 (NH), 1730 (C=O), 1552, 1475 (C=C), 1410 (C=N), 1233 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.94 (s, 1H, NH), 9.88 (s, 1H, C-H, H-4), 7.36–7.28 (m, 2H, H-8, H-6), 7.22–7.14 (m, 2H, H-5, H-7), 7.00–6.95 (m, 2H, H-3′, H-5′), 6.77–6.72 (m, 2H, H-4′, H-6′), 3.56 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5 (C=S), 159.1 (C=O), 156.3 (C=N), 150.9, 139.7, 132.3, 131.4, 130.7, 126.2, 123.1, 120.5, 119.8, 118.8, 117.7, 116.0, 112.7, 113.7 (Ar-Cs), 56.0 (OCH_3). Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96, S, 9.13; Found: C, 61.43; H, 3.56; N, 11.88; S, 9.01.

3-(4-(3-Methoxyphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (4g). Green solid (60%): mp 218–220°C; Rf*: 0.51; IR (KBr, cm^{-1}): 3273 (NH), 1727 (C=O), 1551, 1477 (C=C), 1412 (C=N), 1237 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.13 (s, 1H, NH), 9.01 (s, 1H, C-H, H-4), 7.71–7.68 (m, 2H, H-8, H-6), 7.43–7.37 (m, 2H, H-5, H-7), 7.01–6.95 (m, 2H, H-4′, H-5′), 6.70–6.36 (m, 2H, H-2′, H-6′), 3.53 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.5 (C=S), 159.1 (C=O),

156.4 (C=N), 150.8, 139.9, 133.7, 131.3, 130.4, 126.6, 123.2, 120.7, 119.7, 118.6, 117.0, 116.1, 113.5, 112.4 (Ar-Cs), 56.7 (OCH_3). Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96, S, 9.13; Found: C, 61.48; H, 3.61; N, 11.81; S, 9.16.

Synthesis of 2,5-Disubstituted-1,3,4-thiadiazoles (5a–g): General Procedure

1,4-Disubstituted thiosemicarbazides (**3a–g**) (1.4 mmol) in polyphosphoric acid (0.5 mL, 2.8 mmol) were stirred overnight at 70°C. After completion of the reaction, the cooled solution was poured onto the crushed ice. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), and the combined extracts were washed with sodium bicarbonate (5%) and water until the washings were neutral. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure to yield the 2,5-disubstituted-1,3,4-thiadiazoles, purified by recrystallization in ethanol.

3-(5-(2-Chlorophenylamino)-1,3,4-thiadiazol-2-yl)-2*H*-chromen-2-one (5a). Yellow solid (45%): mp 212–214°C; R_f*: 0.40; IR (KBr, cm^{-1}): 3278 (NH), 1725 (C=O), 1563, 1529 (C=C), 1415 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.42 (s, 1H, NH), 8.73 (s, 1H, C-H, H-4), 7.44–7.36 (m, 4H, H-6, H-8, H-3′, H-5′), 7.04–6.96 (m, 4H, H-5, H-7, H-4′, H-6′); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.7 (C=O), 159.8 (C=N−NH), 159.2 (C=N), 149.2, 133.5, 132.6, 131.9, 130.7, 129.1, 128.5, 127.8, 127.6, 120.0, 119.8, 117.8, 117.3, 116.8 (Ar-Cs). Anal. Calcd. for $C_{17}H_{10}ClN_3O_2S$: C, 57.39; H, 2.83; N, 11.81, S, 9.01; Found: C, 57.27; H, 2.76; N, 11.72; S, 8.87.

3-(5-(3-Chlorophenylamino)-1,3,4-thiadiazol-2-yl)-2*H*-chromen-2-one (5b). Yellow solid (44%): mp 210–212°C; R_f*: 0.40; IR (KBr, cm^{-1}): 3271 (NH), 1728 (C=O), 1565, 1527 (C=C), 1419 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.15 (s, 1H, NH), 9.01 (s, 1H, C-H, H-4), 7.70–7.61 (m, 4H, H-6, H-8, H-3′, H-5′), 7.50–7.36 (m, 4H, H-5, H-7, H-2′, H-6′); ^{13}C NMR (75MHz, DMSO-d_6): δ 163.7 (C=O), 159.9 (C=N−NH), 159.1 (C=N), 148.2, 135.5, 133.6, 132.9, 130.5, 129.2, 128.6, 127.7, 126.6, 120.2, 119.1, 117.9, 117.1, 116.3 (Ar-Cs). Anal. Calcd. for $C_{17}H_{10}ClN_3O_2S$: C, 57.39; H, 2.83; N, 11.81, S, 9.01; Found: C, 57.23; H, 2.71; N, 11.67; S, 9.09.

3-(5-(4-Chlorophenylamino)-1,3,4-thiadiazol-2-yl)-2*H*-chromen-2-one (5c). Yellow solid (59%): mp 216–218°C; R_f*: 0.45; IR (KBr, cm^{-1}): 3256 (NH), 1728 (C=O), 1543, 1521 (C=C), 1432 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.15 (s, 1H, NH), 9.01 (s, 1H, C-H, H-4), 7.69 (d, 1H, J = 7.5Hz, H-8), 7.65–7.61 (m, 1H, H-6), 7.48 (d, 2H, J = 8.4Hz, H-3′, H-5′), 7.42-7.36 (m, 1H, H-7), 6.98 (d, 1H, J = 8.4Hz, H-5), 6.95 (d, 2H, J = 8.1Hz, H-2′, H-6′); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.3 (C=O), 159.1 (C=N−NH), 157.3 (C=N), 148.6, 133.7, 131.3, 130.7, 129.3, 129.1, 128.3, 127.9, 120.1, 119.3, 118.6, 116.9 (Ar-Cs). Anal. Calcd. for $C_{17}H_{10}ClN_3O_2S$: C, 57.39; H, 2.83; N, 11.81, S, 9.01; Found: C, 57.26; H, 2.96; N, 11.74; S, 8.89.

3-(5-(*m*-Toluidino)-1,3,4-thiadiazol-2-yl)-2*H*-chromen-2-one (5d). Yellow solid (39%): mp 219–221°C; R_f*: 0.47; IR (KBr, cm^{-1}): 3198 (NH), 1730 (C=O), 1600, 1561, 1501 (C=C), 1463 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.14 (s, 1H, NH), 9.01 (s, 1H, C-H, H-4), 7.71–7.68 (m, 2H, H-8, H-6), 7.43–7.37 (m, 2H, H-7, H-5′), 6.99–6.94 (m, 4H, H-5, H-2′, H-4′, H-6′), 2.08 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.2 (C=O), 159.1 (C=N−NH), 157.4 (C=N), 148.8, 133.7, 130.9, 130.2, 128.3, 127.1, 124.3, 121.9, 121.8, 120.1, 119.7, 119.5, 119.1, 118.6, 117.9, 117.3, 117.0,

116.7, 116.3, 116.0 (Ar-Cs), 31.1 (CH_3). Anal. Calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.46; H, 3.91; N, 12.53, S, 9.56; Found: C, 64.34; H, 3.98; N, 12.38; S, 9.41.

3-(5-(*p*-Toluidino)-1,3,4-thiadiazol-2-yl)-2*H*-chromen-2-one (5e). Yellow solid (56%): mp 191–193°C; R_f*: 0.44; IR (KBr, cm^{-1}): 3267 (NH), 1725 (C=O), 1592, 1554 (C=C), 1471 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.14 (s, 1H, NH), 9.70 (s, 1H, C-H, H-4), 7.72–7.64 (m, 2H, H-8, H-6), 7.45–7.24 (m, 2H, H-7, H-5), 7.17–7.13 (m, 2H, H-2′, H-6′), 7.12–7.08 (m, 2H, H-3′, H-5′), 2.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4 (C=O), 163.0 (C=N−NH), 157.0 (C=N), 145.8, 134.0, 131.6, 130.0, 129.0, 124.3, 121.9, 119.7, 119.5, 117.9, 117.0, 116.3 (Ar-Cs), 20.8 (CH_3). Anal. Calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.46; H, 3.91; N, 12.53, S, 9.56; Found: C, 64.32; H, 3.78; N, 12.40; S, 9.45.

3-(5-(2-Methoxyphenylamino)-1,3,4-thiadiazol-2-yl)-2*H*-chromen-2-one (5f). Yellow solid (49%): mp 206–208°C; R_f*: 0.51; IR (KBr, cm^{-1}): 3287 (NH), 1726 (C=O), 1594, 1544 (C=C), 1466 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.86 (s, 1H, NH), 9.96 (s, 1H, C-H, H-4), 7.69 (d, 1H, J = 7.2Hz, H-8), 7.43–7.38 (m, 2H, H-6, H-7), 7.04–6.85 (m, 5H, H-5, H-3′, H-4′, H-5′, H-6′), 3.87 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.2 (C=O), 159.1 (C=N−NH), 157.3 (C=N), 148.6, 147.0, 133.7, 132.0, 129.5, 128.3, 128.0, 121.7, 121.0, 120.1, 118.6, 116.8, 116.4 (Ar-Cs), 56.5 (OCH_3). Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96, S, 9.13; Found: C, 61.41; H, 3.60; N, 11.83; S, 9.04.

3-(5-(3-Methoxyphenylamino)-1,3,4-thiadiazol-2-yl)-2*H*-chromen-2-one (5g). Yellow solid (46%): mp 202–204°C; R_f*: 0.51; IR (KBr, cm^{-1}): 3284 (NH), 1729 (C=O), 1584, 1545 (C=C), 1468 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.15 (s, 1H, NH), 9.79 (s, 1H, C-H, H-4), 7.70 (d, 1H, J = 7.2 Hz, H-8), 7.43–7.37 (m, 2H, H-6, H-7), 7.99–6.85 (m, 5H, H-5, H-2′, H-4′, H-5′, H-6′), 3.56 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.2 (C=O), 159.9 (C=N−NH), 157.7 (C=N), 147.,8 146.3, 133.6, 131.0, 129.2, 128.4, 127.7, 123.7, 121.9, 120.5, 119.6, 118.8, 116.4 (Ar-Cs), 58.6 (OCH_3). Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96, S, 9.13; Found: C, 61.46; H, 3.81; N, 11.85; S, 9.02.

Supplementary Material

^{1}H NMR and ^{13}C NMR spectra of representative compounds are available online as Supplementary Material.

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