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Scientific paper

Synthesis of New of 4-Thiazolidinone and Thiazole Derivatives Containing Coumarin Moiety with Antimicrobial Activity

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Abstract

Synthesizing hybrid molecules is one of the best manners to achieve novel promising agents. Consequently, series of new thiazoles having coumarin nucleus were synthesized from 3-acetylcoumarin thiosemicarbazones. Cyclization of thiosemicarbazone derivatives with ethyl 2-chloroacetate, 1-chloropropan-2-one and 2-bromo-1-phenylethanone afforded the corresponding 4-thiazolidinones, 4-methylthiazoles and 4-phenylthiazoles, respectively. The expected antimicrobial proprieties for the synthesized thiosemicarbazone and thiazole derivatives were investigated. The thiosemicarbazones and thiazolidin-4-ones showed moderate activities against Gram-positive and Gram-negative bacteria.

Keywords: Thiazoles; Coumarin; Benzopyrone; Chromenes; Thiosemicarbazones; Antibacterial and antifungal activities.

1. Introduction

Most of microbial infections are the reason of serious diseases. The microbial resistance against the well known antimicrobial drugs is the most common antimicrobial medication problem. The infections with resistant organisms cannot be treated by using common antibiotic drugs. One of the strategies that was exercised to overcome this problem is design of novel pharmacophores. So, recently the main tasks of medicinal chemists are creation of novel antimicrobial drugs against novel molecular targets. To get powerful synergistic effect, researches were directed to combine different pharmacophores in one structure.[1–4]

Coumarin is family of benzopyrones and it is frequently found in nature. Coumarin is considered to be one of significant members of the family of benzopyrone scaffolds. So, the design and synthesis of coumarins are an attractive developing topic for medicinal chemists. Due to the versatility of the coumarin moiety, it is an amazing material suitable for many applications. Coumarins have been reported as anticoagulant, antioxidant, antimicrobial, anticancer, anti-diabetic, analgesic, antineurodegenerative, and anti-inflammatory agents.[5–11] Coumarin and its derivatives are used in several anticoagulants, including warfarin, acenocoumarin, phenprocoumon, choleraicin A, hymecromone (umbelliferone) and the antibiotic novobiocin.[12] On the other hand, coumarins have a wide range of applications such as perfumes, cosmetics, industrial additives and aroma enhancers in tobaccos and certain alcoholic drinks.[13–15] Coumarin-based ion receptors, fluorescent probes, and biological stains are a quickly growing area and have extensive applications to monitor timely enzyme activity, complex biological events, as well as accurate pharmacological and pharmacokinetic properties in living cells.[16]

Thiazole is a privileged scaffold in medicinal chemistry; so, it has displayed crucial role in the medicinal chemistry research. Thiazole ring appears in many structures of natural compounds and some of the synthesized biologically active agents.[1,17–20] Thiazole nucleus constitutes an interesting class of bioactive molecules where it exhibits broad spectra of biological activities such as anti-HIV,[21] antimicrobial,[1] anticancer,[22] hypnotic,[23] anticonvulsant,[17] analgesic,[24] and anti-inflammatory[24] activities. Moreover, some of the derivatives of thiazole have been reported as potent antimicrobial drugs. Some examples of drugs con-

taining thiazole scaffold that are approved for medical uses are penicillin and its analogous (Figure 1) that were the first successful antibiotic drugs.

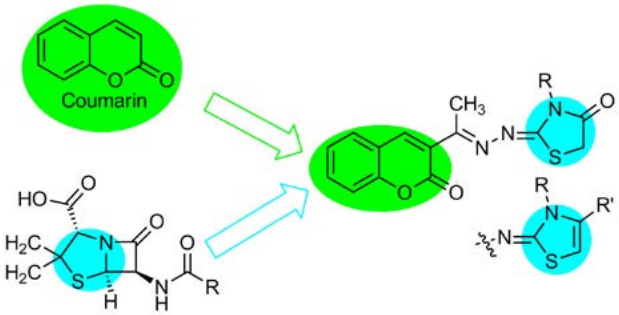


Figure 1. Design of new hybrids of coumarin and thiazole moieties as antimicrobial agents

Penicillins play critical roles in the therapy of the bacterial diseases.[25] Some examples of thiazole-based drugs are ravuconazole (antifungal agent), ritonavir (anti-HIV), tiazofurin (antineoplastic agent), dasatinib (antineoplastic agent), nitazoxanide (antiparasitic agent), thiamethoxam (insecticide), fentiazac (anti-inflammatory agent), fanetizole (anti-inflammatory agent), meloxicam (anti-inflammatory agent) and nizatidine (antiulcer agent).[26]

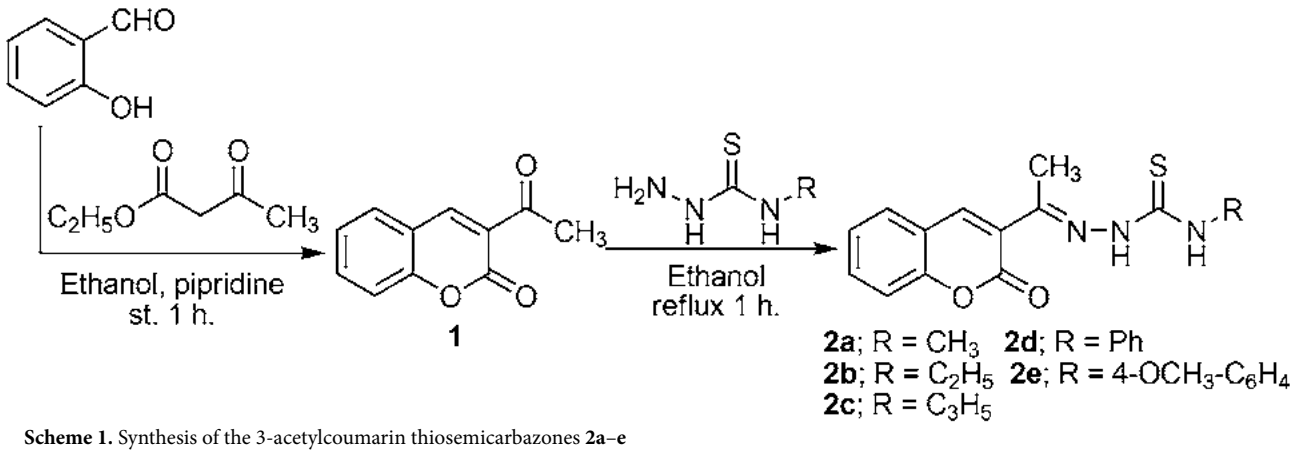
The design of our structures was depended on the validation of coumarins and some of their analogues as drugs. Many studies reported the potency of many thiazole containing compounds. In this direction, previously, we synthesized quinoline derivatives having a thiazole moiety. The thiazole derivative had a potent antimicrobial activity toward eight of the tested strains including Gram-positive and Gram-negative bacteria and fungi.[1]

Moreover, heterocyclic compounds have been reported as a significant class of organic molecules where they are the main scaffolds for the variety of bioactive compounds.[27,28] So, depending on our experience in the synthesis of the thaizole derivatives,[29] we aim to synthesize series of coumarins bearing thiazole nucleus. Thus, the derivatives of thiosemicarbazone will be subjected to ring closure by ethyl chloroacetate, chloroacetone and phenacyl bromide in the hope of obtaining potent antimicrobial thiazole derivatives.

2. Results and Discussion

Coumarins are usually synthesized from salicylaldehyde derivatives *via* tandem condensation Knoevenagel reaction with ester derivatives containing active methylene group in the presence of basic medium to give intermediates that are subjected to intramolecular cyclization.[8] Thus, 3-acetylcoumarin **(1)** was prepared in good yield by using a reported procedure with some modification[14] by treating salicyladehyde with ethyl acetoacetate in ethanol containing piperidine as the catalyst. The 3-acetylcoumarin thiosemicarbazones **2a–e** were prepared as illustrated in Scheme 1.

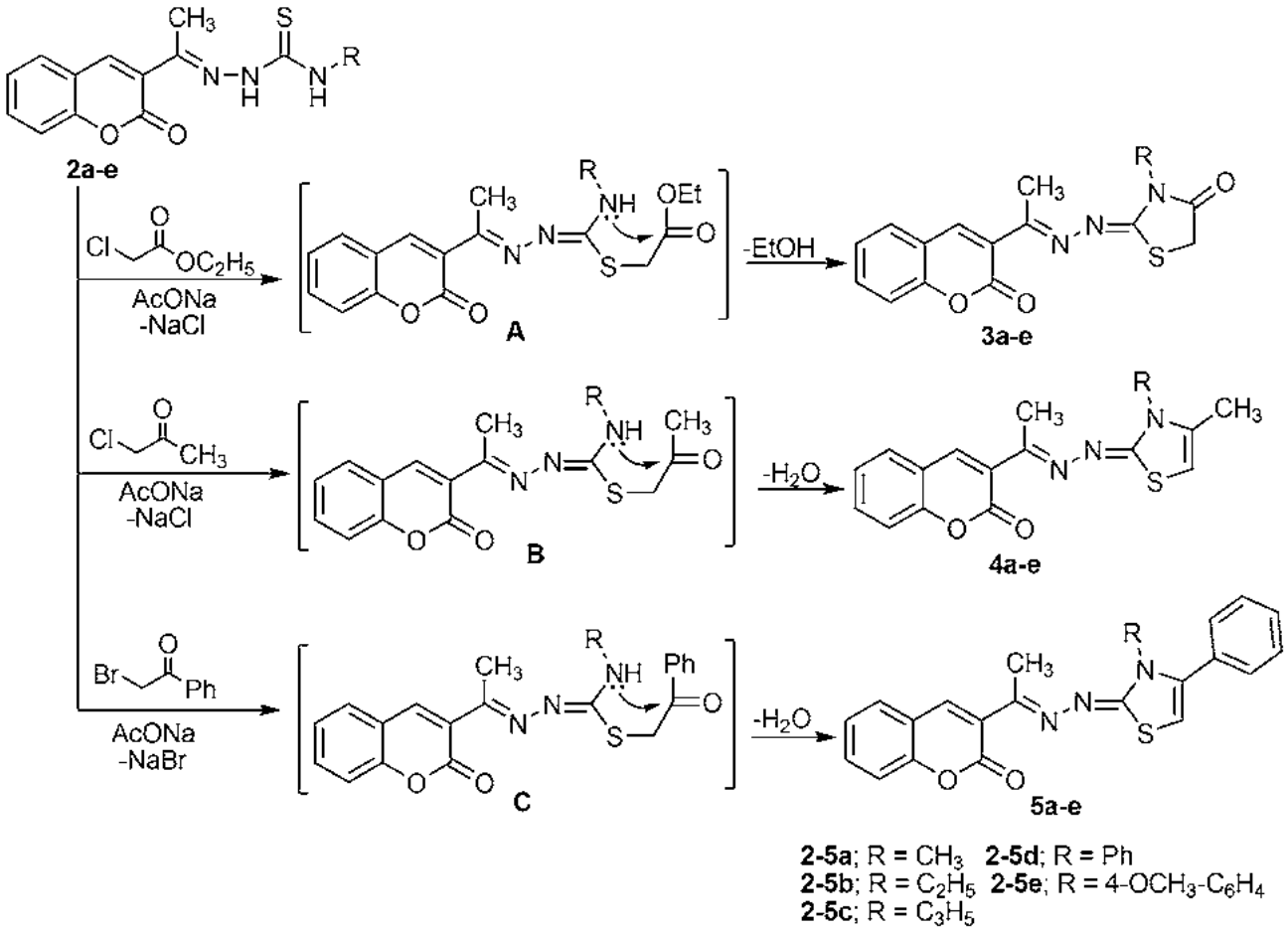
Thiosemicarbazones of 3-acetylcoumarin were prepared through the condensation reactions between 3-acetylcoumarin **(1)** and some selected thiosemicarbazides in ethanol containing catalytic amount of acetic acid under reflux. IR spectrum of thiosemicarbazone **2a**, as an example of the formed thiosemicarbazones **2a–e**, displayed bands at: 3326, 3365, 3312 cm^{-1} for NH groups, and a band at 1708 cm^{-1} for the carbonyl group. Its ^1H NMR spectrum displayed two diagnostic aliphatic signals for two methyl groups at δ 2.26 (CH_3-C=N) and 3.03 ppm ($NHCH_3$). Beside the characteristic signal at δ 8.36 for proton at C-4 of chromene, the other protons of chromene ring appeared as two doublet signals (C_8-H at 7.43 and C_5-H at 7.79 ppm) and two triplet signals (C_6-H at 7.40 and C_7-H at 7.65 ppm). Two signals for NH groups at δ 8.50 ($NHCH_3$) and 10.44 ppm (N-NH-CS) were displayed. ^{13}C NMR spectrum of compound **2a** showed two diagnostic signals in the aliphatic region at δ 16.34 and 31.41 ppm for two methyl groups. The signals resonating in the deshielded region at 153.68, 159.74 and 179.10 ppm were assigned to the carbons of C=N, C=O and C=S, respectively.



Scheme 1. Synthesis of the 3-acetylcoumarin thiosemicarbazones **2a–e**

Thiosemicarbazone derivatives **2a**–**e** were subjected to cyclize with three various halo compounds. The thiosemicarbazones **2a**–**e** reacted with ethyl chloroacetate in tetrahydrofuran under reflux condition resulted in the formation of the 4-thiazolidone derivatives **3a**–**e** in high yields as shown in Scheme 2. The formation of 4-thiazolidones **3a**–**e** initially takes place *via S*-alkylation of the thiosemicarbazones to obtain the intermediate **A**, then intramolecular cyclization occurred through the elimination of ethanol. In IR spectrum of 4-thiazolidone **3a**, a diagnostic band at 1712 cm^{-1} for carbonyl group was observed. Its ^1H NMR spectrum revealed three characteristic aliphatic signals for two methyl groups and CH_2-thiazole at **δ** 2.37, 3.21 and 3.96 ppm, respectively. The chromene protons were assigned at 7.40 (triplet, C_6-H), 7.46 (doublet, C_8-H), 7.68 (triplet, C_7-H), 7.88 (doublet, C_5-H), and 8.21 ppm (singlet, C_4-H). Under the same reaction conditions, cyclocondensation of thiosemicarbazone derivatives **2a**–**e** with 1-chloropropan-2-one furnished the corresponding 4-methylthiazole derivatives **4a**–**e**. The formation of 4-methylthiazoles **4a**–**e** was carried out through *S*-alkylation of thiosemicarbazones to obtain intermediate **B**, then intramolecular cyclization occurred through the elimination of a molecule of water. IR spectrum of **4a** exhibited a diagnostic band at 1716 cm^{-1} for carbonyl group. Its ^1H NMR spectrum exhibited two diagnostic aliphatic singlet signals for methyl protons at δ 2.17 (CH_3-thiazole) and 2.32 ppm (s, 3H, CH_3-C=N). The characteristic H-5 proton of thiazole was found at δ 6.09 ppm. The diagnostic C_4-H of chromene appeared at δ 8.11 ppm.

Moreover, similarly to the above mentioned condition, ring closing of thiosemicarbazones **2a**–**e** by 2-bromo-1-phenylethanone (phenacyl bromide) furnished the corresponding 4-phenylthiazole derivatives **5a**–**e**. Also, the formation of 4-phenylthiazoles **5a**–**e** was carried out through *S*-alkylation of thiosemicarbazones to obtain intermediate **C**, then intramolecular cyclization occurred through the elimination of a molecule of water. IR spectrum of **5a** exhibited diagnostic absorption band for carbonyl group at 1710 cm^{-1}. ^1H NMR spectrum of **5a** displayed two diagnostic signals for two methyl group at **δ** 2.35 (CH_3-C=N), 3.36 ppm (NCH_3). The proton of CH-thiazole was displayed at δ 6.448 ppm. The protons of chromene ring were displayed at 7.38 (C_6-H), 7.44 (C_8-H), 7.63 (C_7-H), 7.86 (C_5-H), 8.15 ppm (C_4-H), while the protons of phenyl ring were displayed at 7.53 ppm. Its ^{13}C



Scheme 2. Syntheses of 4-thiazolidinone derivatives **3a**–**e**, 4-methyl-2,3-dihydrothiazole derivatives **4a**–**e** and 4-phenyl-2,3-dihydrothiazole derivatives **5a**–**e**.

NMR spectrum exhibited four diagnostic signals at δ 16.96 and 33.98 ppm for two methyl carbons. Three signals were observed in the deshielded region at 153.63, 159.91 and 170.44 ppm for carbons of 2 × C=N and C=O.

2. 1. Antibacterial and Antifungal Activities

For all new synthesized thiosemicarbazones **2a**–**e**, 4-thiazolidinones **3a**–**e**, 4-methylthiazoles **4a**–**e** and 4-phenylthiazoles **5a**–**e** were evaluated their antibacterial and antifungal properties. For the screening of antibacterial activity, diffusion agar technique[1] was applied at 5 mg/mL concentration (50 μL was tested), well diameter 6.0 mm. The obtained inhibition zone diameters are given in Table 1. The following three microbial categories were estimated. Category 1: Gram-positive bacteria: *Staphylococcus aureus* (ATCC25923) and *Bacillus subtilis* (RCMB015 NRRL B-543). Category 2: Gram-negative bacteria: *Escherichia coli* (ATCC25922) and *Proteus vulgaris* (RCMB004 ATCC13315). Category 3: Fungi*: Aspergillus fumigates* (RCMB002008) and *Candida albicans* (RCMB005003 ATCC10231).

Few compounds showed good effects towards some bacteria. All of the compounds gave no effects towards fungi. Definite interpretation will be clarified. The 3-acetylcoumarin thiosemicarbazone derivatives **2a**–**e** carried various substituents at terminal nitrogen atom. The prosperity of each substituent was estimated. Changing the substituent on nitrogen atom from methyl to ethyl to allyl to phenyl to 4-methoxyphenyl (**2a** / **2b** / **2c** / **2d** / **2e**) was used to estimate the variation between them. It was noted that there is a moderate variation in antimicrobial property between the thiosemicarbazone derivatives; this suggested that the main antimicrobial activity may be due to the presence of the coumarin and thiosemicarbazone scaffolds. All thiosemicarbazones **2a**–**e** showed moderate activity toward Gram-positive bacteria. Almost all of the thiosemicarbazones **2a**–**e** displayed moderate activity toward Gram-negative bacteria. Ring closure of thiosemicarbazones **2a**–**e** with ethyl chloroacetate to give the 4-thiazolidinones **3a**–**e** does not improve the antimicrobial activity. The thiazolidin-4-ones **3a**–**e** gave nearly the same effects as thiosemicarbazone derivatives **2a**–**e** toward the tested organisms. Ring closure of the thiosemicarbazone derivatives **2a**–**e** with chloroacetone to give the 4-methylthiazoles **4a**–**e** decreased the antimicrobial activity. The 4-methylthiazoles **4a**–**e** gave lesser effects than their thiosemicarbazone derivatives **2a**–**e** against the tested organisms. Ring closure of the thiosemicarbazones **2a**–**e** with phenacyl bromide to give the 4-phenylthiazoles **5a**–**e** gave bad effects where the 4-phenylthiazoles **5a**–**e** gave no effects towards all the tested organisms.

3. Conclusion

To investigate new antimicrobial drugs, five 3-acetylcoumarin thiosemicarbazones **2a**–**e**, five 4-thiazolidinones **3a**–**e**, five 4-methylthiazoles **4a**–**e** and five 4-phenylthiazoles **5a**–**e** were efficiently synthesized. The antibacterial

Table 1. The mean inhibition zones measured for the pathogenic microorganisms (in mm)

Compd. .	Gram-positive bacteria		Gram-negative bacteria		Fungi	
No	*S. aureus*	*B. subtilis*	*E. coli*	*P. vulgaris*	*A. fumigatus*	*C. albicans*
2a	11	22	NA	12	NA	NA
2b	13	20	NA	13	NA	NA
2c	15	21	13	15	NA	NA
2d	13	15	11	14	NA	NA
2e	14	17	12	13	NA	NA
3a	10	9	11	10	NA	NA
3b	11	12	13	12	NA	NA
3c	13	13	10	13	NA	NA
3d	14	18	11	15	NA	NA
3e	15	17	9	12	NA	NA
4a	10	NA	NA	NA	NA	NA
4b	9	10	NA	NA	NA	NA
4c	11	15	NA	12	NA	NA
4d	10	17	NA	13	NA	NA
4e	12	NA	11	NA	NA	NA
5a	NA	NA	10	NA	NA	NA
5b	NA	NA	NA	NA	NA	NA
5c	NA	NA	NA	NA	NA	NA
5d	NA	NA	NA	NA	NA	NA
5e	NA	NA	NA	NA	NA	NA
Gentamycin	24	26	30	25	—	—
Ketoconazole	—	—	—	—	17	20

and antifungal properties were investigated. Few thiosemicarbazone and thiazole derivatives gave good activity against some microorganisms. The thiosemicarbazones **2a–e** and thiazolidin-4-ones **3a–e** showed moderate effect toward Gram-negative and Gram-positive bacteria. The 4-phenylthiazoles **5a–e** gave no effects towards all the tested organisms. None of the derivatives gave any effect toward fungi.

3. 1. Experimental Section

NMR spectra were recorded on Bruker spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 101 MHz) in deuterated dimethylsulfoxide (DMSO-d_6) with chemical shift in δ from internal standard TMS. Elemental analyses were determined on EuroVector apparatus C, H, N analyzer EA3000 Series.

3. 2. Preparation of 3-Acetyl-2*H*-chromen-2-one (1)

To a solution of salicylaldehyde (10 mmol, 1.22 g) in ethanol (20 mL), ethyl acetoacetate (12 mmol, 1.56 g) was added while stirring. After that, piperidine (catalytic amount) was added. The stirring was continued for 1 h at room temperature. The obtained solid product was formed. The pure precipitate was collected by filtration and washed with cold methanol. The obtained 3-acetylcoumarin (**1**) was used for further reactions without purification.

3. 3. Synthesis of 3-Acetylcoumarin Thiosemicarbazone Derivatives 2a–e

A mixture of 3-acetylcoumarin **1** (0.01 mol, 1.88 g) and the selected thiosemicarbazide derivatives (0.01 mol) (namely: *N*-methylthiosemicarbazide (1.05 g), *N*-ethylthiosemicarbazide (1.19 g), *N*-allylthiosemicarbazide (1.31 g), *N*-phenylthiosemicarbazide (1.67 g), or *N*-(4-methoxyphenyl)-thiosemicarbazide) (1.97 g) was heated in a mixture of ethanol (60 mL) and acetic acid (3 mL) for 1 h under reflux. The resultant precipitated products were collected by filtration and recrystallized from dioxane.

***N*-Methyl-2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazinecarbothioamide (2a).** Yield 2.2 g (80%); m.p. 197–198 °C (m.p. lit. 192–194 °C[30]). IR: ν 3365, 3312 (2×NH), 3033 (CH-Ar), 2934, 2989 (CH-aliph.), 1708 (C=O), 1605 cm^{-1} (C=N); ^{1}H NMR: δ 2.26 (s, 3H, CH_3-C=N), 3.03 (d, 3H, *J* = 4.6 Hz, $NHCH_3$), 7.40 (t, 1H, *J* = 7.5 Hz, C_6-H of chromene), 7.43 (d, 1H, *J* = 8.2, C_8-H of chromene), 7.65 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.79 (dd, 1H, *J* = 7.7, 1.3 Hz, C_5-H of chromene), 8.36 (s, 1H, C_4-H of chromene), 8.50 (d, 1H, *J* = 4.4 Hz, $NHCH_3$), 10.44 (s, 1H, N-NH-CS); ^{13}C NMR: δ 16.34 (CH_3), 31.41 (CH_3), 116.52 (C), 119.20 (C), 125.24 (C), 126.30 (CH), 129.54 (CH), 132.87 (CH), 142.30 (CH), 146.11 (CH), 153.68 (C=N), 159.74 (C=O), 179.10 (C=S); MS: *m/z* (%) 275 (M^+; 39.8). Anal. Calcd for $C_{13}H_{13}N_3O_2S$ (275.33): C, 56.71; H, 4.76; N, 15.26. Found: C, 56.66; H, 4.74; N, 15.30.

***N*-Ethyl-2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazinecarbothioamide (2b).** Yield 2.457 g (85%); m.p. 206–208 °C (m.p. lit. 170–172 °C[30]; 293–295 °C[31]). IR: ν 3350, 3157 (2×NH), 2971, 2885 (CH-aliph.), 1722 (C=O), 1607 cm^{-1} (C=N); ^{1}H NMR: δ 1.15 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 2.26 (s, 3H, CH_3-C=N), 3.61 (q, 2H, *J* = 7.0 Hz, $\underline{CH_2}CH_3$), 7.30–7.51 (m, 2H, C_6-H, C_8-H of chromene), 7.64 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.79 (dd, 1H, *J* = 7.7, 1.4 Hz, C_5-H of chromene), 8.34 (s, 1H, C_4-H of chromene), 8.51 (t, 1H, *J* = 5.8 Hz, $NHCH_2$), 10.37 (s, 1H, N-NH-CS); ^{13}C NMR: **δ** 13.96, 16.34, 31.41, 116.36, 119.20, 125.24, 126.28, 129.59, 132.87, 142.30, 146.11, 153.69, 159.74, 179.10; MS: *m/z* (%) 289 (M^+; 71.4). Anal. Calcd for $C_{14}H_{15}N_3O_2S$ (289.35): C, 58.11; H, 5.23; N, 14.52. Found: C, 58.07; H, 5.21; N, 14.47.

***N*-Allyl-2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene) hydrazinecarbothioamide (2c).** Yield 2.559 g (85%); m.p. 138–139 °C. IR: ν 3366, 3209 (NH), 2989 (CH-aliph.), 1716, 1697, 1645 (C=O), 1619, 1606 cm^{-1} (C=N); ^{1}H NMR: δ 2.28 (s, 3H, CH_3-C=N), 4.24 (t, 2H, *J* = 5.6 Hz, $NH\underline{CH_2}$), 5.04–5.24 (m, 2H, CH_2-olefinic), 5.87–5.89 (m, 1H, CH-olefinic), 7.25–7.48 (m, 2H, C_6-H, C_8-H of chromene), 7.65 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.80 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.36 (s, 1H, C_4-H of chromene), 8.63 (t, 1H, *J* = 5.7 Hz, $NHCH_2$), 10.51 (s, 1H, N-NH-CS); ^{13}C NMR: **δ** 16.50 (CH_3), 46.35 (CH_2), 116.19 (=CH_2), 116.43 (C), 119.26 (C), 125.21 (C), 126.42 (CH), 129.56 (CH), 132.85 (CH), 135.17 (CH), 142.2 (CH), 146.40 (CH), 153.77 (C=N), 159.51 (C=O), 178.85 (C=S); MS: *m/z* (%) 301 (M^+; 46.5). Anal. Calcd for $C_{15}H_{15}N_3O_2S$ (301.36): C, 59.78; H, 5.02; N, 13.94. Found: C, 59.81; H, 5.03; N, 13.89.

2-(1-(2-Oxo-2*H*-chromen-3-yl)ethylidene)-*N*-phenylhydrazinecarbothioamide (2d). Yield 3.033 g (90%); m.p. 192–193 °C (m.p. lit. 183–185 °C[31]). IR: ν 3219, 3178 (NH), 3113, 3048 (CH-Ar), 2887, 2292 (CH-aliph.), 1707 (C=O), 1604, 1593 cm^{-1} (C=N); ^{1}H NMR: **δ** 2.35 (s, 3H, CH_3-C=N), 7.19 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.33–7.62 (m, 6H, Ar-H), 7.66 (d, 1H, C_7-H of chromene), 7.80 (d, 1H, C_5-H of chromene), 8.50 (s, 1H, C_4-H of chromene), 10.16 (s, 1H, NHPh), 10.85 (s, 1H, N-NH-CS); MS: *m/z* (%) 337 (M^+; 51.4). Anal. Calcd for $C_{18}H_{15}N_3O_2S$ (337.40): C, 64.08; H, 4.48; N, 12.45. Found: C, 64.08; H, 4.48; N, 12.45.

***N*-(4-Methoxyphenyl)-2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazinecarbothioamide (2e).** Yield 3.303 g (90%); m.p. 183–185 °C (m.p. lit. 285–287 °C[31]). IR: ν 3327, 3282 (NH), 3066 (CH-Ar), 2954, 2847

(CH-aliph.), 1721 cm^{-1} (C=O); ^{1}H NMR: **δ** 2.34 (s, 3H, CH_3-C=N), 3.76 (s, 3H, OCH_3), 6.92 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.21–7.50 (m, 4H, Ar-H), 7.65 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.78 (d, 1H, *J* = 6.7 Hz, C_5-H of chromene), 8.50 (s, 1H, C_4-H of chromene), 10.02 (s, 1H, NH-Ar-H), 10.75 (s, 1H, N-NH-CS); MS: *m/z* (%) 367 (M^+; 55.8). Anal. Calcd for $C_{19}H_{17}N_3O_3S$ (367.42): C, 62.11; H, 4.66; N, 11.44. Found: C, 62.07; H, 4.64; N, 11.38.

3. 4. Synthesis of 4-Thiazolidinone Derivatives 3a–e

To the mixture of 3-acetylcoumarin thiosemicarbazone derivatives **2a–e** (3 mmol) and ethyl chloroacetate (0.61 g; 5 mmol) in 50 mL THF, freshly prepared fused sodium acetate (0.492 g; 6 mmol) was added. The reaction mixture was heated for 4 h under reflux condition and left to cool. The obtained solid products were filtrated and recrystallized from THF.

3-Methyl-2-((1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazono)thiazolidin-4-one (3a). Yield 0.756 g (80%); m.p. 285–287 °C (m.p. lit. 280–282 °C[30]). IR: ν 1712 cm^{-1} (C=O); ^{1}H NMR: δ 2.37 (s, 3H, CH_3-C=N), 3.21 (s, 3H, NCH_3), 3.96 (s, 2H, CH_2-thiazole), 7.40 (t, 1H, *J* = 7.4 Hz, C_6-H of chromene), 7.46 (d, 1H, *J* = 8.3 Hz, C_8-H of chromene), 7.68 (t, 1H, *J* = 7.1 Hz, C_7-H of chromene), 7.88 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.21 (s, 1H, C_4-H of chromene); ^{13}C NMR: **δ** 17.34, 27.65, 32.37, 116.52, 119.25, 125.23, 126.86, 129.82, 133.13, 142.23, 154.13, 159.45, 161.13, 164.11, 172.45; MS: *m/z* (%) 315 (M^+; 72.3). Anal. Calcd for $C_{15}H_{13}N_3O_3S$ (315.35): C, 57.13; H, 4.16; N, 13.33. Found: C, 57.08; H, 4.14; N, 13.26.

3-Ethyl-2-((1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazono)thiazolidin-4-one (3b). Yield 0.839 g (85%); m.p. 220–222 °C (m.p. lit. 213–215 °C[30]). IR: ν 2983, 2951 (CH-aliph.), 1714 (C=O), 1618, 1595 cm^{-1} (C=N); ^{1}H NMR: δ 1.22 (t, 3H, *J* = 7.0 Hz, $CH_2\underline{CH_3}$), 2.36 (s, 3H, CH_3-C=N), 3.79 (q, 2H, *J* = 7.0 Hz, $\underline{CH_2}CH_3$), 3.97 (s, 2H, CH_2-thiazole), 7.30–7.53 (m, 2H, C_6-H,C_8-H of chromene), 7.67 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.87 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.22 (s, 1H, C_4-H of chromene); ^{13}C NMR: **δ** 12.65 (CH_3), 17.34 (CH_3), 32.66 (CH_2), 38.37 (CH_2), 116.50 (C), 119.15 (C), 125.26 (C), 126.86 (CH), 129.81 (CH), 133.13 (CH), 142.18 (CH), 154.00 (CH), 159.44 (C=N), 161.13 (C=N), 163.99 (C=O), 172.40 (C=O); MS: *m/z* (%) 329 (M^+; 38.9). Anal. Calcd for $C_{16}H_{15}N_3O_3S$ (329.37): C, 58.34; H, 4.59; N, 12.76. Found: C, 58.29; H, 4.60; N, 12.81.

3-Allyl-2-((1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazono)thiazolidin-4-one (3c). Yield 0.767 g (75%); m.p. 215–217 °C. IR: ν 1710 cm^{-1} (C=O); ^{1}H NMR: δ 2.31 (s, 3H, CH_3-C=N), 4.57 (m, 2H, NCH_2), 5.17–5.19 (m, 2H, CH_2-olefinic), 5.88–6.05 (m, 1H, CH-olefinic), 3.96 (s, 2H, CH_2-thiazole), 7.30–7.50 (m, 2H, C_6-H, C_8-H of chromene), 7.66 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.88 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.22 (s, 1H, C_4-H of chromene); MS: *m/z* (%) 341 (M^+; 46.5). Anal. Calcd for $C_{17}H_{15}N_3O_3S$ (341.38): C, 59.81; H, 4.43; N, 12.31. Found: C, 59.78; H, 4.41; N, 12.26.

2-((1-(2-Oxo-2*H*-chromen-3-yl)ethylidene)hydrazono)-3-phenylthiazolidin-4-one (3d). Yield 0.905 g (80%); m.p. 175–177 °C. IR: ν 2927 (CH-aliph.), 1711 (C=O), 1589 cm^{-1} (C=N); ^{1}H NMR: δ 2.13 (s, 3H, CH_3-C=N), 4.07 (s, 2H, CH_2-thiazole), 7.36–7.50 (m, 7H, Ar-H, C_6-H of chromene and C_8-H of chromene), 7.67 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.87 (d, 1H, *J* = 7.8 Hz, C_5-H of chromene), 8.20 (s, 1H, C_4-H of chromene); MS: *m/z* (%) 377 (M^+; 41.6). Anal. Calcd for $C_{20}H_{15}N_3O_3S$ (377.42): C, 63.65; H, 4.01; N, 11.13. Found: C, 63.58; H, 3.99; N, 11.20.

3-(4-Methoxyphenyl)-2-((1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazono)thiazolidin-4-one (3e). Yield 1.038 g (85%); m.p. 254–256 °C. IR: ν 2998 (CH-aliph.), 1726 cm^{-1} (C=O); ^{1}H NMR: δ 2.12 (s, 3H, CH_3-C=N), 3.82 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2-thiazole), 7.07 (d, *J* = 8.9 Hz, 2H, Ar-H, AB), 7.33 (d, 2H, *J* = 8.9 Hz, Ar-H, AB), 7.40–7.44 (m, 2H, C_6-H, C_8-H of chromene), 7.67 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.87 (d, 1H, *J* = 7.8 Hz, C_5-H of chromene), 8.20 (s, 1H, C_4-H of chromene); MS: *m/z* (%) 407 (M^+; 54.0). Anal. Calcd for $C_{21}H_{17}N_3O_4S$ (407.44): C, 61.90; H, 4.21; N, 10.31. Found: C, 61.94; H, 4.19; N, 10.26.

3. 5. Synthesis of 4-Methyl-2,3-dihydrothiazole Derivatives 4a–e

To the mixture of 3-acetylcoumarin thiosemicarbazone derivatives **2a–e** (3 mmol) and chloroacetone (0.46 g; 5 mmol) in 50 mL THF, fused sodium acetate (0.492 g; 6 mmol) was added. The reaction mixture was heated for 6 h under reflux condition then the solution was concentrated and left to cool. The obtained products were filtrated and recrystallized from ethanol.

3-(1-((3,4-Dimethylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (4a). Yield 0.563 g (60%); m.p. 156–157 °C (m.p. lit. 210–212 °C[30]). IR: ν 1716 (C=O), 1603 cm^{-1} (C=N); ^{1}H NMR: δ 2.16 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.09 (s, 1H, thiazole-H), 7.23–7.53 (m, 2H, C_6-H, C_8-H of chromene), 7.62 (t, 1H, *J* = 7.2 Hz, C_7-H of chromene), 7.83 (d, 1H, *J* = 7.0 Hz, C_5-H of chromene), 8.11 (s, 1H, C_4-H of chromene); ^{13}C NMR: **δ** 14.96, 16.14, 33.93, 100.57, 116.33, 119.39, 125.21, 127.50, 130.83, 132.51, 140.63, 141.05, 153.29, 153.64, 159.91, 170.44; MS: *m/z* (%) 313 (M^+; 42.4). Anal. Calcd for $C_{16}H_{15}N_3O_2S$ (313.37): C, 61.32; H, 4.82; N, 13.41. Found: C, 61.28; H, 4.80; N, 13.36.

3-(1-((3-Ethyl-4-methylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (4b). Yield 0.638 g (65%); m.p. 133–135 °C (m.p. lit. 232–234 °C[30]). IR: ν 3276 (CH-Ar), 2974 (CH-aliph.), 1726 (C=O), 1605 cm^{-1} (C=N); ^{1}H NMR: δ 1.26 (t, 3H, *J* = 6.9 Hz, $CH_2\underline{CH_3}$), 2.18 (s, 3H, CH_3-thiazole), 2.31 (s, 3H, CH_3-C=N), 3.84 (q, 2H, *J* = 7.0 Hz, $\underline{CH_2}CH_3$), 6.05 (s, 1H, thiazole-H), 7.21–7.51 (m, 2H, C_6-H, C_8-H of chromene), 7.61 (t, 1H, *J* = 7.2 Hz, C_7-H of chromene), 7.82 (d, 1H, *J* = 7.0 Hz, C_5-H of chromene), 8.12 (s, 1H, C_4-H of chromene); ^{13}C NMR: **δ** 12.33, 14.96, 16.21, 38.78, 99.39, 116.36, 119.69, 125.20, 127.56, 129.41, 130.83, 132.56, 140.62, 141.40, 153.62, 160.99, 170.29; MS: *m/z* (%) 327 (M^+; 63.2). Anal. Calcd for $C_{17}H_{17}N_3O_2S$ (327.40): C, 62.36; H, 5.23; N, 12.83. Found: C, 62.42; H, 5.21; N, 12.79.

3-(1-((3-Allyl-4-methylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (4c). Yield 0.661 g (65%); m.p. 115–117 °C. IR: ν 1726 cm^{-1} (C=O); ^{1}H NMR: δ 2.14 (s, 3H, CH_3-thiazole), 2.29 (s, 3H, CH_3-C=N), 4.55 (m, 2H, NCH_2), 5.17–5.19 (m, 2H, CH_2-olefinic), 5.88–6.05 (m, 1H, CH-olefinic), 6.59 (s, 1H, thiazole-H), 7.37–7.43 (m, 2H, C_6-H, C_8-H of chromene), 7.62 (t, 1H, *J* = 7.2 Hz, C_7-H of chromene), 7.83 (d, 1H, *J* = 7.8 Hz, C_5-H of chromene), 8.13 (s, 1H, C_4-H of chromene); ^{13}C NMR: **δ** 13.51, 16.96, 34.98, 100.55, 116.33, 119.39, 125.21, 129.06, 129.31, 129.41, 129.67, 132.51, 140.63, 141.05, 153.29, 153.64, 159.91, 170.44; MS: *m/z* (%) 339 (M^+; 46.5). Anal. Calcd for $C_{18}H_{17}N_3O_2S$ (339.41): C, 63.70; H, 5.05; N, 12.38. Found: C, 63.66; H, 5.03; N, 12.42.

3-(1-((4-Methyl-3-phenylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (4d). Yield 0.788 g (70%); m.p. 198–200 °C. IR: ν 3106, 3069 (CH-Ar), 2918 (CH-aliph.), 1709 (C=O), 1600 cm^{-1} (C=N); ^{1}H NMR: δ 1.87 (s, 3H, CH_3-thiazole), 2.05 (s, 3H, CH_3-C=N), 6.25 (s, 1H, thiazole-H), 7.36–7.50 (m, 5H, Ar-H), 7.54–7.58 (m, 2H, C_6-H, C_8-H of chromene), 7.62 (t, 1H, C_7-H of chromene), 7.84 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.12 (s, 1H, C_4-H of chromene); ^{13}C NMR: **δ** 14.46, 16.96, 100.57, 116.33, 119.39, 125.21, 128.13, 129.06 (2C), 129.31 (2C), 129.41, 129.67, 130.43, 132.51, 140.63, 141.05, 153.29, 153.64, 157.44, 170.44; MS: *m/z* (%) 375 (M^+; 45.7). Anal. Calcd for $C_{21}H_{17}N_3O_2S$ (375.44): C, 67.18; H, 4.56; N, 11.19. Found: C, 67.11; H, 4.55; N, 11.24.

3-(1-((3-(4-Methoxyphenyl)-4-methylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (4e). Yield 0.911 g (75%); m.p. 218–219 °C. IR: ν 2922 (CH-aliph.), 1728 cm^{-1} (C=O); ^{1}H NMR: δ 1.87 (s, 3H, CH_3-thiazole), 2.07 (s, 3H, CH_3-C=N), 3.83 (s, 3H, OCH_3), 6.22 (s, 1H, thiazole-H), 7.07 (d, 2H, *J* = 8.7 Hz, Ar-H, AB), 7.34 (d, 2H, *J* = 8.6 Hz, Ar-H, AB), 7.37–7.42 (m, 2H, C_6-H, C_8-H of chromene), 7.62 (t, 1H, C_7-H of chromene), 7.82 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.11 (s, 1H, C_4-H of chromene); MS: *m/z* (%) 405 (M^+; 36.5). Anal. Calcd for $C_{22}H_{19}N_3O_3S$ (405.47): C, 65.17; H, 4.72; N, 10.36. Found: C, 65.24; H, 4.73; N, 10.26.

3. 6. Synthesis of 4-Phenylthiazole Derivatives 5a–e

To the mixture of 3-acetylcoumarin thiosemicarbazone derivatives **2a–e** (3 mmol) and phenacyl bromide (0.995 g; 5 mmol) in 50 mL THF, fused sodium acetate (0.492 g; 6 mmol) was added. The reaction mixture was heated for 5 h under reflux condition and left to cool. The obtained solid products were filtrated and recrystallized from dioxane.

3-(1-((3-Methyl-4-phenylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (5a). Yield 0.9 g (80%); m.p. 165–167 °C (m.p. lit. 161–163 °C[30]). IR: ν 3086 (CH-Ar), 2946, 2906 (CH-aliph.), 1710 cm^{-1} (C=O); ^{1}H NMR: δ 2.35 (s, 3H, CH_3-C=N), 3.36 (s, 3H, NCH_3), 6.44 (s, 1H, thiazole-H), 7.38 (t, 1H, *J* = 7.5 Hz, C_6-H of chromene), 7.44 (d, 1H, *J* = 8.3 Hz, C_8-H of chromene), 7.53 (m, 5H, Ph-H), 7.63 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.86 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.15 (s, 1H, C_4-H of chromene); ^{13}C NMR: **δ** 16.96 (CH_3), 33.98 (CH_3), 100.56 (C), 116.33 (C), 119.39 (C), 125.20 (C), 127.49 (C), 129.06 (2CH), 129.31 (2CH), 129.42 (CH), 129.67 (CH), 130.82 (CH), 132.51 (CH), 140.63 (CH), 141.05 (CH), 153.28 (CH), 153.63 (C=N), 159.91 (C=N), 170.44 (C=O); MS: *m/z* (%) 375 (M^+; 38.3). Anal. Calcd for $C_{21}H_{17}N_3O_2S$ (375.44): C, 67.18; H, 4.56; N, 11.19. Found: C, 67.23; H, 4.55; N, 11.23.

3-(1-((3-Ethyl-4-phenylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (5b). Yield 0.875 g (75%); m.p. 176–178 °C (m.p. lit. 158–160 °C[30]). IR: ν 3099, 3055 (CH-Ar), 2971, 2936 (CH-aliph.), 1717 (C=O), 1690 cm^{-1} (C=N); ^{1}H NMR: δ 1.16 (t, 3H, *J* = 7.0 Hz, $CH_2\underline{CH_3}$), 2.35 (s, 3H, CH_3-C=N), 3.84 (q, 2H, *J* = 7.0 Hz, $\underline{CH_2}CH_3$), 6.39 (s, 1H, thiazole-H), 7.38 (t, 1H, *J* = 7.5 Hz, C_6-H of chromene), 7.44 (d, 1H, *J* = 8.3 Hz, C_8-H of chromene), 7.48–7.53 (m, 5H, Ph-H), 7.66 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.85 (dd, 1H, *J* = 7.7, 1.2 Hz, C_5-H of chromene), 8.16 (s, 1H, Ar-H at C_4-H of chromene); MS: *m/z* (%) 389 (M^+; 58.1). Anal. Calcd for $C_{22}H_{19}N_3O_2S$ (389.47): C, 67.84; H, 4.92; N, 10.79. Found: C, 67.81; H, 4.94; N, 10.83.

3-(1-((3-Allyl-4-phenylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (5c). Yield 0.962 g (80%); m.p. 168–170 °C. IR: ν 1718 cm^{-1} (C=O); ^{1}H NMR: δ 2.31 (s, 3H, CH_3-C=N), 4.45 (d, 2H, *J* = 4.7 Hz, NCH_2), 4.94 (dd, 1H, *J* = 17.3, 1.4 Hz, CH-olefinic), 5.14 (dd, 1H, *J* = 10.5, 1.3 Hz, CH-olefinic), 5.80–5.89 (m, 1H, CH-olefinic), 6.44 (s, 1H, thiazole-H), 7.40 (t, 1H, *J* = 7.6 Hz, C_6-H of chromene), 7.45 (d, 1H, *J* = 8.4 Hz, C_8-H of chromene), 7.48–7.53 (m, 5H, Ph-H), 7.64 (t, 1H, *J* = 7.8 Hz, C_7-H of

chromene), 7.86 (dd, 1H, *J* = 7.7, 1.2 Hz, C_5-H of chromene), 8.17 (s, 1H, Ar-H at C_4-H of chromene); MS: *m/z* (%) 401 (M^+; 46.5). Anal. Calcd for $C_{23}H_{19}N_3O_2S$ (401.48): C, 68.81; H, 4.77; N, 10.47. Found: C, 68.78; H, 4.75; N, 10.44.

3-(1-((3,4-Diphenylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (5d). Yield 1.049 g (80%); m.p. 210–212 °C. IR: ν 1732 (C=O), 1600, 1589 cm^{-1} (C=N); ^{1}H NMR: δ 2.14 (s, 3H, CH_3-C=N), 6.67 (s, 1H, thiazole-H), 7.18 (m, 2H, Ar-H), 7.21–7.28 (m, 3H, Ar-H), 7.29 (m, 3H, Ar-H), 7.38 (m, 3H, Ar-H), 7.43 (d, 1H, *J* = 8.3 Hz, C_8-H of chromene), 7.66 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.85 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.15 (s, 1H, C_4-H of chromene); MS: *m/z* (%) 437 (M^+; 53.3). Anal. Calcd for $C_{26}H_{19}N_3O_2S$ (437.51): C, 71.38; H, 4.38; N, 9.60. Found: C, 71.42; H, 4.36; N, 9.57.

3-(1-((3-(4-Methoxyphenyl)-4-phenylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-chromen-2-one (5e). Yield a1.191 g (85%); m.p. 291–293 °C. IR: ν 3114, 3068, 3009 (CH-Ar), 2942, 2841 (CH-aliph.), 1726 (C=O), 1603 cm^{-1} (C=N); ^{1}H NMR: δ 2.13 (s, 3H, CH_3-C=N), 3.85 (s, 3H, OCH_3), 6.65 (s, 1H, thiazole-H), 7.15–7.40 (m, 10H, Ar-H), 7.44 (d, 1H, *J* = 8.3 Hz, C_8-H of chromene), 7.67 (t, 1H, *J* = 7.8 Hz, C_7-H of chromene), 7.84 (d, 1H, *J* = 7.7 Hz, C_5-H of chromene), 8.16 (s, 1H, C_4-H of chromene); MS: *m/z* (%) 467 (M^+; 63.0). Anal. Calcd for $C_{27}H_{21}N_3O_3S$ (467.54): C, 69.36; H, 4.53; N, 8.99. Found: C, 69.28; H, 4.51; N, 9.03.

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Povzetek

Priprava hibridnih molekul je eden izmed najboljših načinov izdelave novih biološko aktivnih spojin. Skladno s tem načelom smo iz tiosemikarbazonov 3-acetilkumarina pripravili serijo novih tiazolov, ki vsebujejo kumarinski fragment. S ciklizacijo tiosemikarbazonskih derivatov z etil 2-kloroacetatom, 1-kloropropan-2-onom in 2-bromo-1-feniletanonom smo pripravili ustrezne 4-tiazolidinone, 4-metiltiazole in 4-feniltiazole. Za vse pripravljene tiosemikarbazone in tiazole smo raziskali antimikrobne lastnosti. Tiosemikarbazoni in tiazolidin-4-oni so izkazali zmerne aktivnosti proti Gram-pozitivnim in Gram-negativnim bakterijam.