

Article

## Synthesis and Characterization of Some New 4-Hydroxycoumarin Derivatives

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**Abstract:** Some novel coumarins were synthesized starting from 4-hydroxycoumarin and methyl bromoacetate. The structures of the newly obtained compounds were confirmed by elemental analysis, mass, IR and NMR spectra.

**Keywords:** bromoacetate; 4-hydroxycoumarin; maleic anhydride; mercaptoacetic acid

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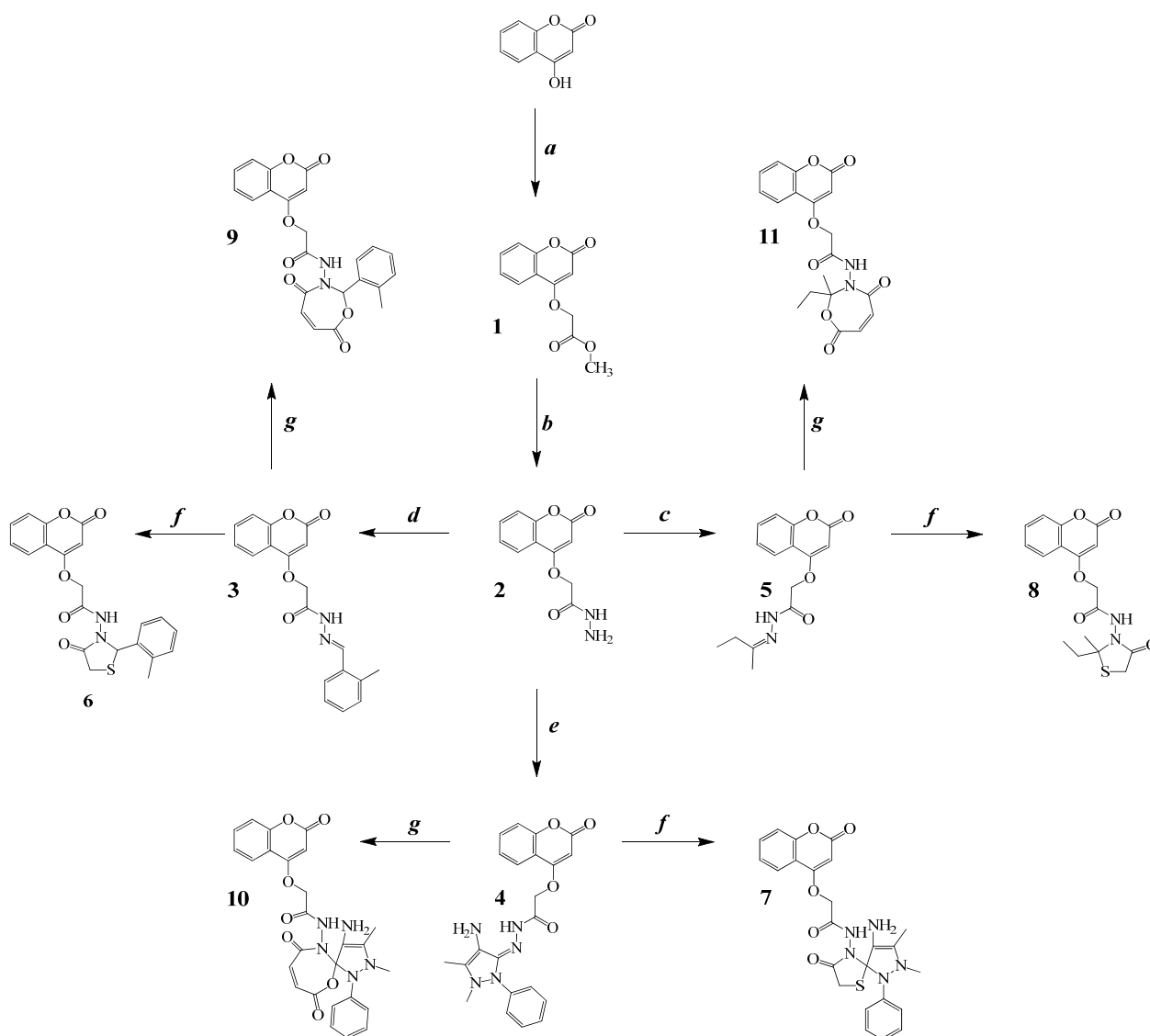
### 1. Introduction

Coumarins or benzo-2-pyrone derivatives are one of the most significant families of natural product compounds and are also important in synthetic organic chemistry. They have been widely used as starting materials or intermediates in the pharmaceutical, perfumery and agrochemical industries. Coumarins are also used as fluorescent brighteners, efficient laser dyes and additives in food and cosmetics [1]. The coumarins represent a large group of compounds that have been reported to possess a wide range of biological activities [2–4], including anticoagulant and antithrombotic properties [5–7]. Many coumarin derivatives, especially 4-hydroxycoumarin, show significant anticoagulant action by antagonizing the action of vitamin K. [8,9]. Recently, coumarins have attracted considerable attention for electronic and photonic applications [10,11] due to their inherent photochemical characteristics, reasonable stability and solubility in various organic solvents. Many coumarin derivatives have been

commercialized as blue-green lasers for fluorescent labels, fluorescent probes [12–14] and enzymatic measurements [15]. They exhibit intense fluorescence upon substitution with various functional groups at different positions [16,17].

In view of the high degree of bioactivity shown by 4-aminoantipyrene, thiazolidinones and hydroxycoumarin heterocyclic analogs, and in continuation of previous studies [18–23], we focus herein on the design of some novel structural entities that incorporate both of these moieties in a single molecular scaffold. We first report the synthesis of methyl 2-(coumarin-4-yloxy)acetate (**1**), which was then used as starting material for the synthesis of new molecules **2–11** (Scheme 1).

**Scheme 1.** Reaction sequences of the synthesized compounds.



*Reagents and Conditions:* *a* = Ethyl bromoacetate/reflux; *b* = hydrazine hydrate/refluxed; Ethylmethylketone/refluxed in ethanol; *d* = 2-methyl benzaldehyde/refluxed in ethanol; *e* = 4-aminoantipyrene/refluxed in ethanol; *f* = mercaptoacetic acid/refluxed in benzene; *g* = maleic anhydride/refluxed in benzene.

## 2. Results and Discussion

### 2.1. Chemistry

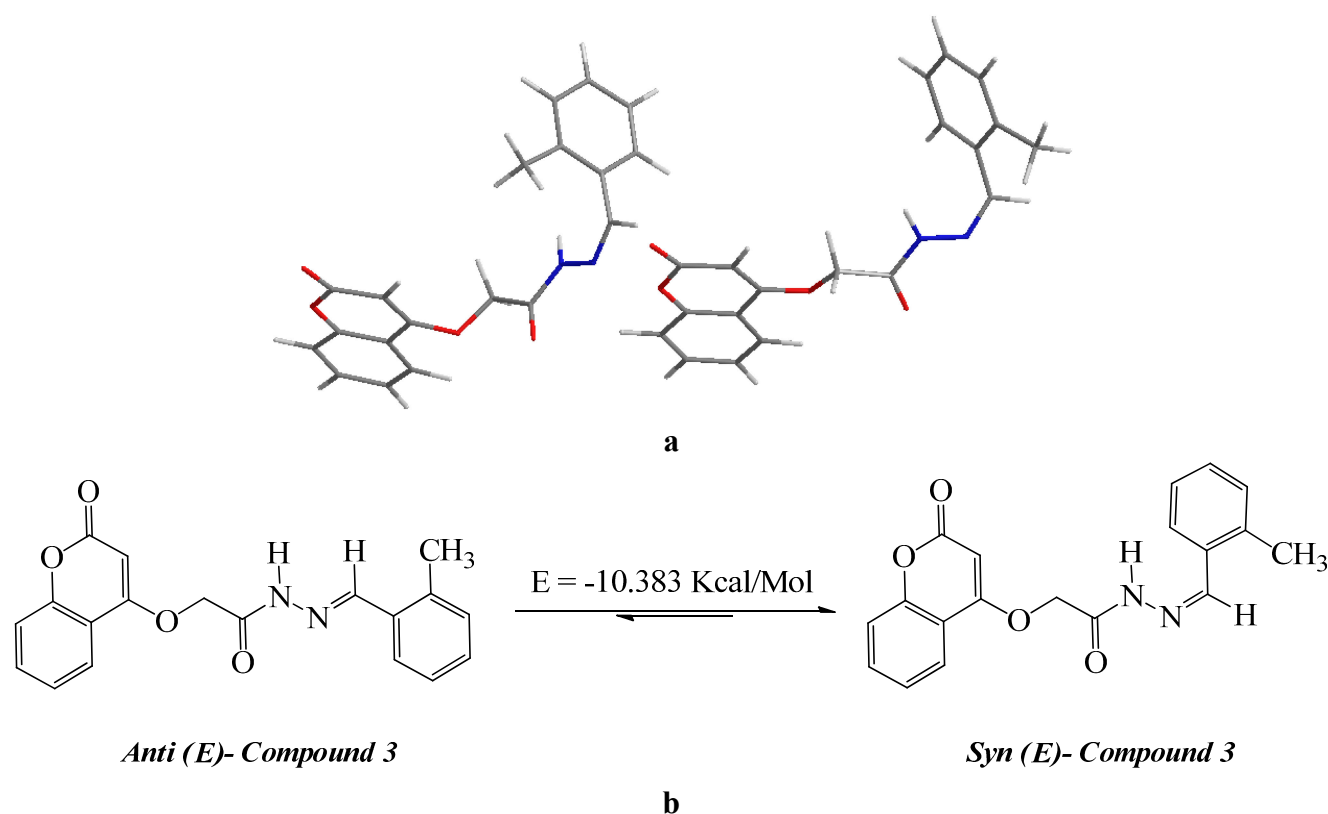
The reaction sequences for the synthesis of coumarins **2–11** starting from 4-hydroxycoumarin are outlined in Scheme 1. Methyl 2-(coumarin-4-yloxy)acetate (**1**) was obtained by refluxing methyl bromoacetate with 4-hydroxycoumarin in anhydrous acetone in the presence of anhydrous potassium carbonate. The FT-IR spectrum of this compound showed an absorption band at  $1,723.1\text{ cm}^{-1}$  (ester C=O carbonyl stretching). The  $^1\text{H-NMR}$  spectrum exhibited a singlet at  $\delta\ 3.63$  ppm due to the three  $\text{CH}_3$  protons. The reaction of **1** with hydrazine hydrate afforded hydrazide **2** in good yield. The FT-IR spectrum of compound **2** showed absorption bands at  $3,233.3$  and  $3,210.0\text{ cm}^{-1}$  (hydrazide  $\text{NH-NH}_2$ ). The  $^1\text{H-NMR}$  spectrum exhibited a singlet at  $\delta\ 4.45$  ppm due to the two  $\text{CH}_2$  protons and a singlet due to the single NH proton at  $\delta\ 8.21$  ppm. The reaction of compound **2** with various carbonyl compounds (2-methylbenzaldehyde, 4-aminoantipyrine and ethyl methyl ketone) yielded the new Schiff bases *N'*-(2-methylbenzylidene)-2-[(coumarin-4-yl)oxy]acetohydrazide (**3**), *N'*-[4-amino-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-ylidene]-2-[(coumarin-4-yl)oxy]acetohydrazide (**4**) and *N'*-(butan-2-ylidene)-2-[(coumarin-4-yl)oxy]acetohydrazide (**5**), respectively. Schiff bases **3**, **4** and **5** were cyclized by reaction with mercaptoacetic acid to yield novel coumarin compounds *N*-[4-oxo-2-(*O*-tolyl)thiazolidin-3-yl]-2-[(coumarin-4-yl)oxy]acetamide (**6**), *N*-(4-amino-2,3-dimethyl-8-oxo-1-phenyl-6-thia-1,2,9-triazaspiro[4.4]non-3-en-9-yl)-2-[(coumarin-4-yl)oxy]acetamide (**7**) and *N*-(2-ethyl-2-methyl-4-oxothiazolidin-3-yl)-2-[(coumarin-4-yl)oxy]acetamide (**8**), respectively. The FT-IR spectrum of compound **6** showed absorption bands at  $3,191.4\text{ cm}^{-1}$  (NH) and  $1,715.6\text{ cm}^{-1}$  (C=O, lactone) as well as  $1,695$  and  $1,677\text{ cm}^{-1}$  (C=O, amide). The  $^1\text{H-NMR}$  spectrum exhibited a singlet due to the (S-CH) proton at  $\delta\ 4.88$  ppm and another singlet due to the O- $\text{CH}_2$  proton at  $\delta\ 5.11$  ppm (2H). For compound **7**, the FT-IR spectrum showed absorption bands at  $3,388.3\text{ cm}^{-1}$  for  $\text{NH}_2$  and  $3,189.1\text{ cm}^{-1}$  for N-H, and the C=N bands disappeared due to cyclization. The  $^1\text{H-NMR}$  spectrum exhibited a doublet due to the two protons at  $\delta\ 4.89$  and  $\delta\ 4.12$  ppm and singlet due to the single S-CH proton at  $\delta\ 3.89$  ppm. For compound **8**, the FT-IR spectrum showed absorption bands at  $3,199.0\text{ cm}^{-1}$  (NH) as well as  $1,691$  and  $1,685\text{ cm}^{-1}$  (C=O, amide); the C=N bands disappeared due to cyclization. The  $^1\text{H-NMR}$  spectrum exhibited a doublet due to the S- $\text{CH}_2$  proton at  $\delta\ 3.86$  and  $\delta\ 8.02$  ppm, and a singlet due to the NH proton. Another three novel compounds were synthesized by the cyclization of Schiff bases **3**, **4** and **5** with maleic anhydride to yield *N*-[4,7-dioxo-2-(*O*-tolyl)-1,3-oxazepin-3(2*H*,4*H*,7*H*)-yl]-2-[(coumarin-4-yl)oxy] acetamide (**9**), *N*-[2-(4-amino-1,5-dimethyl-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl)4,7-dioxo-1,3-oxazepin-3(2*H*,4*H*,7*H*)-yl]-2-[(coumarin-4-yl)oxy] acetamide (**10**) and *N*-[2-ethylmethyl-4,7-dioxo-1,3-oxazepin-3(2*H*,4*H*,7*H*)-yl]-2-[(coumarin-4-yl)oxy] acetamide (**11**), respectively. For compound **9**, the FT-IR spectrum showed absorption bands at  $3,196.2\text{ cm}^{-1}$  (NH) and  $1,667.9\text{ cm}^{-1}$  for the amide as well as  $1,755$  and  $1,745\text{ cm}^{-1}$  for carbonyls. The  $^1\text{H-NMR}$  spectrum exhibited a singlet at  $\delta\ 5.38$  ppm due to the two O- $\text{CH}_2$  protons. For compound **10**, the FT-IR spectrum of showed absorption bands at  $2,981.4\text{ cm}^{-1}$  (C-H, aliphatic),  $1,765$  and  $1,734\text{ cm}^{-1}$  for the carbonyls, and  $1,678\text{ cm}^{-1}$  for the amide. The  $^1\text{H-NMR}$  spectrum exhibited a singlet  $\delta\ 4.89$  ppm due to the two O- $\text{CH}_2$  protons at. For compound **11**, the FT-IR spectrum of showed absorption bands at  $3,199\text{ cm}^{-1}$  (NH) and

1,669.2  $\text{cm}^{-1}$  for the amides as well as 1,758 and 1,733  $\text{cm}^{-1}$  for the carbonyls. The  $^1\text{H-NMR}$  spectrum exhibited a singlet due to the two O-CH<sub>2</sub> protons at  $\delta$  4.65 ppm.

## 2.2. Geometrical Isomers of the Acylhydrazone of Coumarins 3–5

With respect to the C=N double bond, *N*-acylhydrazones (NAHs) may exist as *Z/E* geometrical isomers and *syn/anti* amide conformers [24,25]. In a study involving compounds 3, 4 and 5, energy calculations performed on the selected conformers according to the density functional theory (DFT) B3LYP method using the 6–31G basis set by means of the Gaussian 09, revision A.02 method indicated a slight difference in energy ( $\Delta E = -10.383$  Kcal/mol,  $-2.350$  Kcal/mol and  $-13.918$  Kcal/mol) respectively, between the *syn*-periplanar and *anti*-periplanar conformers in the favor of the former (Figure 1). Therefore, we concluded that the new derivatives 3, 4 and 5 were obtained as single *E* geometrical isomers.

**Figure 1.** Probable conformational isomers of the *N*-acylhydrazone of compound 3. (a) = 3dimetional structures; (b) = *geometrical Isomers*).



## 3. Experimental Section

### 3.1. General Information

The chemicals used during synthesis were supplied by Sigma-Aldrich (Selangor, Malaysia). The IR spectra were obtained on a Nicolet 6700 FT-IR spectrophotometer (Thermo Nicolet Corp., Madison, WI, USA), and the values are expressed in  $\text{cm}^{-1}$ . Nuclear magnetic resonance (NMR) spectra were recorded using an AVANCE III 600 MHz spectrometer (Bruker, Billerica, MA, USA), using DMSO as an internal

standard and the values are expressed in  $\delta$  ppm. Elemental microanalysis was performed on an Elementar Vario El III Carlo Erba 1108 elemental analyzer (Carlo Erba Reagenti SpA, Rodano, Italy).

### 3.2. Methyl 2-(coumarin-4-yloxy)acetate (1)

A suspension of 4-hydroxycoumarin (0.999 g, 6.17 mmol) in acetone (30 mL) was refluxed with methyl bromoacetate (9.15 mmol) and  $K_2CO_3$  (4.69 g, 33.91 mmol) for 12 h. After cooling, the mixture was evaporated to dryness and the residue was partitioned between  $CHCl_3$  (50 mL) and water (50 mL). The organic phase was dried using  $Na_2SO_4$ , filtered and evaporated to dryness. The residue was recrystallized from acetone; yield 85%; m.p. 84–85 °C;  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  3.6 (s, 3H,  $CH_3$ ), 4.79 (s, 2H,  $CH_2$ ) and 5.58 (s, 1H,  $-C=C-H$ ), 7.3111, 7.555, 7.896 (three s, 1H each, aromatic ring); IR ( $cm^{-1}$ ): 2,960 (C-H, aliphatic), 3,083.4 (C-H, aromatic), 1,760.3 (C=O, ester), 1,723.1 (C=O, lactone), 1,624.5 (C=C, alkene), 1,567.2 (C=C, aromatic).

### 3.3. 2-(Coumarin-4-yloxy)acetohydrazide (2)

A solution of compound **2** (2.34 g, 10 mmol) in ethanol 25 mL was refluxed with hydrazine hydrate (15 mmol) for 4 h. After concentrating the reaction mixture an oily mass separated out and was recrystallized using ethanol, yield 55%;  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  4.45 (s, 2H,  $CH_2$ ), 4.75 (s, 2H,  $NH_2$ ), 5.43 (s, 1H,  $-C=C-H$ ), 7.41–7.78 (m, 4H, aromatic ring), 8.21 (s, 1H,  $NH$ ); IR ( $cm^{-1}$ ): 3,233.3, 3,210 (N-H), 2,959.0 (C-H, aliphatic), 3,083.9 (C-H, aromatic), 1,721.4 (C=O, lactone), 1,624.2 (C=O, amide).

### 3.4. Synthesis of Schiff bases 3–5

A solution of compound **2** (0.2 mmol) in ethanol (25 mL) was refluxed with 2-methyl benzaldehyde, 4-aminoantipyrine or ethyl methyl ketone (0.2 mmol) for 20 h. After cooling to room temperature, a solid mass was filtered and the solid was recrystallized from ethanol.

*N'*-(2-Methylbenzylidene)-2-(coumarin-4-yloxy)acetohydrazide (**3**). Yield 50%;  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  2.891 (s, 3H,  $CH_3$ ), 4.19 (s, 2H,  $CH_2$ ), 5.355 (s, 2H, O- $CH_2$ ), 5.57 (s, 1H,  $-C=C-H$ ), 7.270–7.75 (m, 4H, aromatic ring); 8.31 (s, 1H,  $N=CH$ ), 8.01 (s, 1H,  $NH$ ); IR ( $cm^{-1}$ ): 3,199.3 (N-H), 2,965.4 (C-H, aliphatic), 3,067.2 (CH, aromatic), 1,730.3 (C=O, lactone), 1,683.7 (C=O, amide), 1,627.7 (C=C).

*N'*-(4-Amino-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-ylidene)-2-(coumarin-4-yloxy)acetohydrazide (**4**). Yield 60%; m.p 162–163 °C;  $^1H$ -NMR ( $CDCl_3$ ): 4.05 (s, 2H, assignment?), 4.67 (s, 2H, O- $CH_2$ ), 5.23 (s, 1H,  $-C=C-H$ ), 3.21 (s, 3H,  $CH_3$ ), 2.83 (s, 3H,  $CH_3$ ), 7.11–7.34 (m, 4H, aromatic ring), 8.0 (s, 1H,  $NH$ ), 8.41 (s, 1H,  $N=CH$ ); IR ( $cm^{-1}$ ): 3,432.8 ( $NH_2$ ), 3,328.0.3 (N-H), 2,989.9 (C-H, aliphatic), 3,077.3 (C-H, aromatic), 1,725.8 (C=O, lactone), 1,651.9 (C=O, amide), 1,616.3 (C=N), 1,6229 (C=C); Analysis: Calc. for  $C_{21}H_{21}N_5O_4$ : C 61.91%, H 5.20%, N 17.19%. Found: C 60.057%, H 5.641%, N 16.685%.

*N'*-(Butan-2-ylidene)-2-(coumarin-4-yloxy)acetohydrazide (**5**). Yield 50%; m.p 71–72 °C;  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  0.81 (t, 3H,  $CH_3$ ), 1.49 (q, 2H,  $CH_2$ ), 2.01 (s, 3H,  $CH_3$ ), 4.64 (s, 2H, O- $CH_2$ ), 5.21 (s, 1H,  $-C=C-H$ ), 6.95 (s, 1H,  $N=CH$ ), 7.38–7.79 (m, 4H, aromatic ring); IR ( $cm^{-1}$ ): 3,198.2 (N-H),

2,922.9 (C-H, aliphatic), 3,068.4 (C-H, aromatic), 1,732.2 (C=O, lactone), 1,673.1 (C=O, amide), 1,615.3 (C=N), 1,621.5 (C=C); Analysis: Calc. for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C 62.49%, H 5.59%, N 9.72%. Found: C 61.70%, H 4.89%, N 9.11%.

### 3.5. Cyclization with Mercaptoacetic Acid: Synthesis of Compounds 6–8

A mixture of compound (3 or 4 or 5) (0.01 mole) with mercaptoacetic acid (0.01 mole) in dry benzene (50 mL) was refluxed in a water bath for 20 h, filtered off, washed with water, dried and recrystallized from dichloromethane.

*N*-[4-Oxo-2-(*o*-tolyl)thiazolidin-3-yl]-2-(coumarin-4-yloxy)acetamide (6). Yield 45%; oil; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.920 (s, 3H, CH<sub>3</sub>), 4.88 (s, S-CH), 4.67 (s, 1H, CH), 5.11 (s, 2H, O-CH<sub>2</sub>), 5.73 (s, 1H, -C=C-H), 7.270–7.820 (m, 4H, aromatic ring), 8.12 (s, 1H, NH); IR (cm<sup>-1</sup>): 3,191.4 (N-H), 2,930 (C-H, aliphatic), 3,043 (C-H, aromatic), 1,715.6 (C=O, lactone), 1,695, 1677 (C=O, amide), 1,631.5 (C=C, aromatic).

*N*-{2-[(*S*)-4-Amino-1,5-dimethyl-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl]-4-oxothiazolidin-3-yl}-2-(coumarin-4-yloxy)acetamide (7). Yield 45%; oil; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.24 (s, 3H, CH<sub>3</sub>), 3.06 (s, 3H, N-CH<sub>3</sub>), 3.89 (s, S-CH<sub>2</sub>), 4.67 (s, 2H, CH<sub>2</sub>), 4.69 (s, 2H, O-CH<sub>2</sub>), 5.26 (s, 1H, -C=C-H), 7.31, 7.52, 7.81 (s, 1H, aromatic ring), 6.84, 7.11, 7.29 (s, 1H, aromatic ring) 8.02 (s, 1H, NH), 8.32 (s, NH<sub>2</sub>); IR (cm<sup>-1</sup>): 3,388.3 (NH<sub>2</sub>), 3,189.1 (N-H), 2,928 (C-H, aliphatic), 3,057.7 (C-H, aromatic), 1,719.5 (C=O, lactone), 1,685, 1667 (C=O, amide), 1,633.7 (C=C, aromatic); Analysis: Calc. for C<sub>25</sub>H<sub>25</sub>N<sub>5</sub>O<sub>5</sub>S: C 59.16%, H 4.96%, N 13.80%. Found: C 58.91%, H 4.11%, N 12.92%.

*N*-(2-Ethyl-2-methyl-4-oxothiazolidin-3-yl)-2-(coumarin-4-yloxy)acetamide (8). Yield 45%; oil; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 0.89 (t, 3H, CH<sub>3</sub>), 1.59 (s, 3H, CH<sub>3</sub>), 1.78 (q, 2H, CH<sub>2</sub>), 3.86 (s, S-CH), 4.68 (s, 2H, O-CH<sub>2</sub>), 5.21 (s, 1H, -C=C-H), 7.36, 7.54, 7.71 (s, 1H, aromatic ring) 8.02 (s, 1H, NH); IR (cm<sup>-1</sup>): 3,199.0 (N-H), 2,931.3 (C-H, aliphatic), 3,040.5 (C-H, aromatic), 1,719 (C=O, lactone), 1,691, 1,685 (C=O, amide), 1,632 (C=C, aromatic).

### 3.6. Cyclization with Maleic Anhydride; Synthesis of Compounds 9–11

A mixture of compound (3, 4 or 5) (1 mmol) and maleic anhydride (1 mmol) in dry benzene (50 mL) was refluxed in a water bath for 20 h. The solvent was removed and the precipitate was recrystallized from tetrahydrofuran.

*N*-[4,7-Dioxo-2-(*o*-tolyl)-1,3-oxazepin-3(2*H*,4*H*,7*H*)-yl]-2-(coumarin-4-yloxy) acetamide (9). Yield 40%; m.p. 128–130 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.784 (s, 3H, CH<sub>3</sub>), 3.012 (d, 1H, CH), 3.69 and 4.02 (dd, 1H, CH=CH), 5.38 (s, 2H, O-CH<sub>2</sub>), 6.281 (s, 1H, -C=C-H), 7.329, 7.446, 7.964 (s, 1H, aromatic ring) 9.14 (s, 1H, NH); IR (cm<sup>-1</sup>): 3,196.2 (N-H), 2,970.5 (C-H, aliphatic), 3,087.2 (C-H, aromatic), 1,755, 1,745 (C=O), 1,667.9 (C=O, amide), 1,630.1 (C=C, aromatic).

*N*-[2-(4-Amino-1,5-dimethyl-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl)4,7-dioxo-1,3-oxazepin-3(2*H*,4*H*,7*H*)-yl]-2-(coumarin-4-yloxy) acetamide (10). Yield 35%; m.p. 120–121 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.24 (s,

3H, CH<sub>3</sub>), 3.01 (s, 3H, CH<sub>3</sub>), 4.89 (s, 2H, O-CH<sub>2</sub>), 5.38 (s, 1H, -C=C-H), 6.89 and 6.39 (dd, 1H, CH=CH), 6.99, 7.11, 7.29 (s, 1H, aromatic ring); 8.14 (s, 1H, NH), 8.45 (s, NH<sub>2</sub>); IR (cm<sup>-1</sup>): 3,391.8 (NH<sub>2</sub>), 3,284.1 (N-H), 2,981.4 (C-H, aliphatic), 3,081.2.2 (C-H, aromatic), 1,765, 1,734 (C=O), 1,678 (C=O, amide), 1,629.6 (C=C, aromatic); Analysis: Calc. for C<sub>27</sub>H<sub>25</sub>N<sub>5</sub>O<sub>7</sub>: C 61.01%, H 4.74%, N 13.18%. Found: C 60.73%, H 4.01%, N 12.65%.

*Synthesis of N-[2-Ethylmethyl-4,7-dioxo-1,3-oxazepin-3(2H,4H,7H)-yl]-2-(coumarin-4-yloxy) acetamide (11).* Yield 40%; m.p. 118–120 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 0.89 (t, 3H,CH<sub>3</sub>), 1.69 (s, 3H, CH<sub>3</sub>), 1.505 (q, 2H, CH<sub>2</sub>), 4.65 (s, 2H, O-CH<sub>2</sub>), 5.23 (s, 1H, -C=C-H), 6.82 and 6.41 (dd, 1H, HC=CH), 7.41, 7.453, 7.81 (s, 1H, aromatic ring), 8.12 (s, 1H, NH); IR (cm<sup>-1</sup>): 3,199.0 (N-H), 2,973.1 (C-H, aliphatic), 3,091.0 (C-H, aromatic), 1,758, 1,733 (C=O), 1,669.2 (C=O, amide), 1,630.3 (C=C, aromatic); Analysis: Calc. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>7</sub>: C 59.07%, H 4.70%, N 7.25%. Found: C 58.81%, H 4.12%, N 6.88%.

#### 4. Conclusions

A series of new cyclic compounds based 4-hydroxycoumarin were successfully synthesized in high to acceptable yields (35%–85%). The proposed structures of the new coumarins were confirmed by spectral analysis performed by IR, UV-Vis, <sup>1</sup>H-NMR and elemental analysis. Coumarins **6**, **7** and **8** were synthesized by the cyclization of Schiff bases **3**, **4** and **5** using mercaptoacetic acid. The cyclization of Schiff bases **3–5** with maleic anhydride yielded new coumarins **9–11**.

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#### Author Contributions

Yasameen K. Al-Majedy was a second year PhD. student where she synthesis all the compounds, this work was a part of her project. Ahmed A. Al-Amiery was the principle investigator while Abu Bakar Mohamad and Abdul Amir H. Kadhum were co-investigators of the project. All authors are aware of this manuscript and have agreed for its publication.

#### Conflicts of Interest

The authors confirm that this paper content has no conflict of interests.

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*Sample Availability:* Samples of the compounds 1–6 are available from the authors.

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