Molecules **2009**, *14*, 2501-2513; doi:10.3390/molecules14072501

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

Design and Synthesis of Some Thiazolidin-4-ones Based on (7-Hydroxy-2-oxo-2*H*-chromen-4-yl) Acetic Acid

Milan Cacic [1,*], Maja Molnar [1], Tomislav Balic [2], Nela Draca [1] and Valentina Rajkovic [3]

[1] Department of Applied Chemistry and Ecology, Faculty of Food Technology, J. J. Strossmayer University, Franje Kuhaca 20, 31 000 Osijek, Croatia

[2] Department of Chemistry, J. J. Strossmayer University, Franje Kuhaca 20, 31 000 Osijek, Croatia

[3] Department of Biology, J. J. Strossmayer University, Trg Ljudevita Gaja 6, 31 000 Osijek, Croatia

* Author to whom correspondence should be addressed; E-mail: mcacic@ptfos.hr

Received: 27 May 2009; in revised form: 7 July 2009 / Accepted: 8 July 2009 / Published: 10 July 2009

Abstract: (7-Hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid methyl ester (**1**) upon reaction with ethyl bromoacetate furnishes (7-ethoxycarbonylmethoxy-2-oxo-2*H*-chromen-4-yl)-acetic acid methylester (**2**), which on treatment with 100% hydrazine hydrate yields (7-hydrazinocarbonylmethoxy-2-oxo-2*H*-chromen-4-yl)-acetic acid hydrazide (**3**). The condensation of compound **3** with different aromatic aldehydes afforded a series of [7-(arylidenehydrazinocarbonylmethoxy)-2-oxo-2*H*-chromen-4-yl]-acetic acid arylidene-hydrazide Schiff's bases **4a-k.** Cyclo-condensation of compounds **4a-k** with 2-mercapto-acetic acid in *N*,*N*-dimethylformamide in the presence of anhydrous $ZnCl_2$ affords *N*-(2-aryl-4-oxothiazolidin-3-yl)-2-(4-(2-aryl-4-oxothiazolidin-3-ylcarbamoyl)-methyl)-2-oxo-2*H*-chromen-7-yloxy)-acetamides **5a-k**. Structure elucidation of the products has been accomplished on the basis of elemental analysis, IR, ^{1}H-NMR and ^{13}C-NMR data. Compounds **4a-k** and **5a-k** will be screened for their antibacterial activity against both Gram-positive and Gram-negative bacteria and the results reported elsewhere in due course.

Keywords: coumarin; dihydrazides; aromatic Schiff's bases; *N*-(2-aryl-4-oxo-thiazolidin-3-yl)-2-((4-(2-aryl-4-oxo-thiazolidin-3-ylcarbamoyl)-methyl)-2-oxo-2*H*-chromen-7-yl-oxy)-acetamides; biological activity

Introduction

Coumarin (2-oxo-2*H*-chromene) and its derivatives represent one of the most active classes of heterocyclic compounds, possessing a wide spectrum of biological activities [1-9] as many of these compounds posses antitumor [1-2], antibacterial [3-4], antifungal [5-7], anticoagulant [8] and anti-inflammatory [9] properties. They have also shown to be useful as anti-HIV agents and as CNS active compounds [10]. In addition, these compounds are used as additives to food and cosmetics [11], dispersed fluorescence and lasers [12]. Coumarins are present in remarkable amounts in plants, although their presence has also been detected in microorganisms and animal sources [10].

Thiazolidinones are derivatives of thiazolidine and they also constitute an important group of heterocyclic compounds. Thiazolidinones, with a carbonyl group in positions 2,4- or just 4-, have been subject of extensive study in the recent past [13,14] and literature surveys show that thiazolidin-4-ones are important compounds due to their broad range of biological activities [15-21]. 4-Thiazolidinones substituted in the 2-position, its derivatives and analogues exhibit unusually high *in vitro* activity against *Mycobacterium tuberculosis* [22]. Overviews of their synthesis, properties, reactions and applications have been published [13,14].

Thiazolidine compounds are formed by condensation of either aliphatic or aromatic moieties, containing a formyl group (-CHO), with different aminothiols [23]. It should be noted that the thiazolidine ring is the core building unit of penicillin antibiotics. A novel synthesis of thiazolidine-2-thione and thiazolidine-2-one derivatives is described with the iodo-cyclothiocarbamation reaction as the key step for the heterocyclic ring formation. The new method has been applied to the synthesis of thiazolidinones as bioisosteric analog of Linezolid [24]. In recent years several new methods for preparing thiazolidinone derivatives have been reported in the literature [25, 26].

As part of our aim in search of biologically active heterocyclic compounds with one, two or three coumarin cores and thiazolidinone moieties, we have previously reported the synthesis of some of these compounds [27, 28]. Since 4-thiazolidinones show a wide range of biological activities [15-21], we extended our work on the synthesis of novel compounds formed by cyclocondensation from compounds (Schiff's bases) **4a-k** and mercaptoacetic acid in *N,N*-dimethylforamide in the presence of anhydrous $ZnCl_2$, to afford *N*-(2-aryl-4-oxothiazolidin-3-yl)-2-(4-(2-aryl-4-oxothiazolidin-3-yl-carbamoyl)-methyl)-2-oxo-2*H*-chromen-7-yloxy)-acetamides **5a-k** (Scheme 1).

Thiazolidinone coumarin derivatives have been proven to have significant biological activity, like anticonvulsant activity [29], cytotoxic activity [30] and antioxidant activity [31]. Therefore, our aim in this work was to prepare thiazolidinone derivatives using (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid as starting compound.

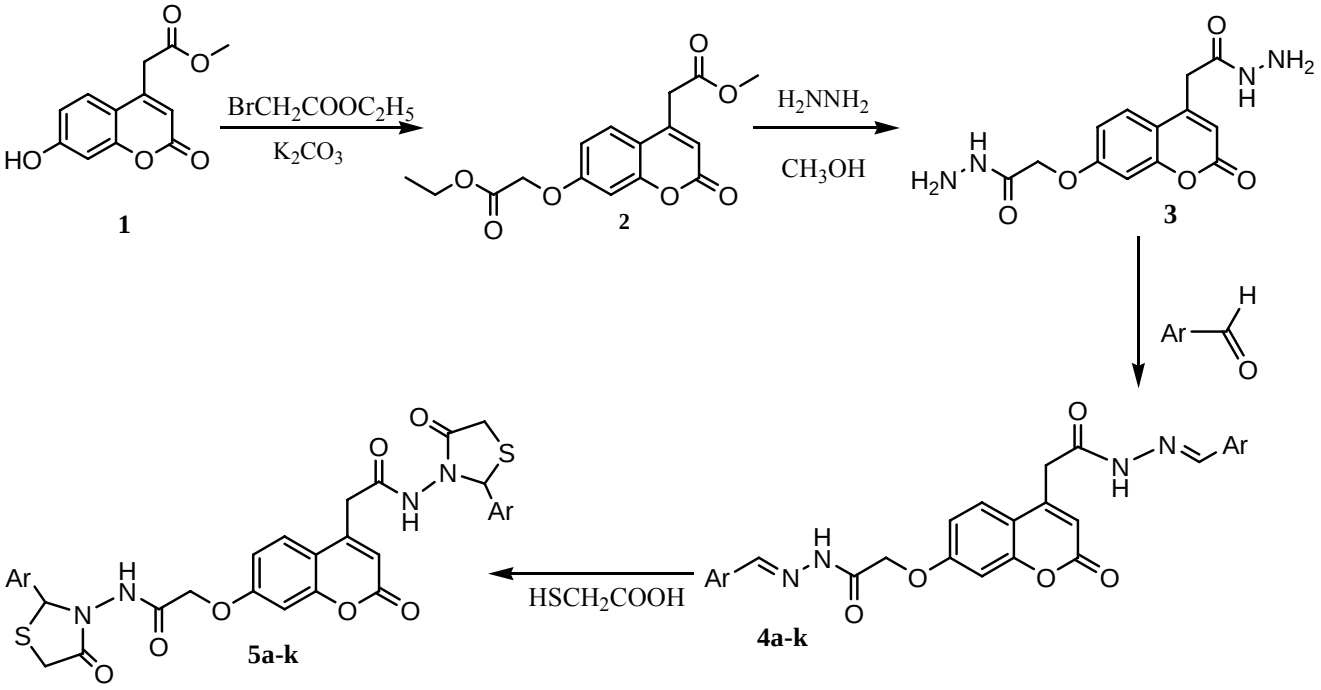
Results and Discussion

Synthesis

The synthesis of the target compounds was carried out as outlined in Scheme 1. The starting compound (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid methyl ester (**1**) was prepared in 92% yield by esterification of (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid [28]. We have previously

reported the preparation of (7-ethoxycarbonylmethoxy-2-oxo-2*H*-chromen-4-yl)-acetic acid methyl ester (**2**) in 82% yield by direct condensation of **1** with bromoacetic acid ethyl ester [28].

Scheme 1. Synthetic route for thiazolidinones **5a-k.**



Entry	Ar	Entry	Ar
a	Phenyl	**g**	4-Hydroxy-3-methoxyphenyl
b	2-Chlorophenyl	**h**	3-Phenoxyphenyl
c	3-Chlorophenyl	**i**	4-*N*,*N*-Dimethylaminophenyl
d	2,4-Dihydroxyphenyl	**j**	2-Hydroxy-5-nitrophenyl
e	3,4-Dihydroxyphenyl	**k**	Styryl
f	2,5-Dihydroxyphenyl		

Hydrazinolysis of **2** with 86% hydrazine hydrate in methanol at room temperature afforded dihydrazide **3** in good yield. The FT-IR spectra of carbohydrazide **3** showed absorption bands in the 3,317 cm^{-1} (hydrazide NH-NH_2), 3,269 cm^{-1}(aromatic C-H), 1,711 cm^{-1}(-C=O carbonyl stretching) and 1,621-1,640 cm^{-1}(-CO-NH-NH_2 groups) regions, respectively. The ^{1}H-NMR spectrum exhibited a singlet due to the –CO-NH-NH_2 NH proton at δ 9.32 ppm. Methylene protons –CH_2 and –OCH_2 resonated as singlets at 4.23 and 4.85 ppm, respectively.

A new series of compounds **4a-k** was prepared similarly to those previously described [28] by refluxing a solution of suitable different aromatic aldehydes and dihydrazide **3** in absolute ethanol for 2 to 4 hours, in a presence of a catalytic amount of glacial acetic acid. The structures of compounds **4a-k** were inferred from their analytical and spectral data.

Thus, their IR spectra showed characteristic bands at 3,448-3,278 cm^{-1}(NH), 1,709 cm^{-1}, 1,672 cm^{-1} (C=O, lactone) and 1,620 cm^{-1}(C=O, amide, -HC=N- azomethine). The ^{1}H-NMR spectra did not only show the absence of NH_2 protons at 3.38, but also the presence of the N=CH proton at 8.30 ppm.

N-(2-aryl-4-oxo-thiazolidin-3-yl)-2-(4-(2-aryl-4-oxo-thiazolidin-3-ylcarbamoyl)-methyl)-2-oxo-2H-chromen-7-yloxy)-acetamides **5a-k** were obtained by refluxing a solution of compounds **4a-k** and thioglicolic acid in *N,N*-dimethylformamide for 6-8 hours in the presence of anhydrous $ZnCl_2$.

Experimental

General

Melting points were determined on Electrothermal Capillary melting point apparatus and are uncorrected. Thin-layer chromatography was performed with fluorescent silica gel plates HF_{254} Merck, which were checked under UV 254 and 365 nm light. The elemental analysis for C, H and N was done on a Perkin-Elmer Analyzer 2440. Infrared spectra (ν_{max}-cm^{-1}) were recorded on a Beckmann FT-IR 3303, using KBr disks. ^{1}H-NMR spectra were recorded on JEOL EX-270 MHz NMR Spectrometer at 293 K in DMSO-d_6. ^{13}C-NMR spectra were recorded on a Varian Gemini at 50 MHz in DMSO-d_6. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS.

(7-Ethoxycarbonylmethoxy-2-oxo-2H-chromen-4-yl)-acetic acid methylester (**2**)

A mixture of (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid methylester (**1,** 25.74 g, 0.11 mole), anhydrous potassium carbonate (15.20 g, 0.11 mole) and ethyl bromoacetate (18.37 g, 0.11 mole) in dry acetone (200 mL) was refluxed with continuous stirring for 12 hours. After filtration, the solution was concentrated under reduced pressure, vacuum dried and the solid product was recrystallized from ethanol.M.p.185-186°C, yield 64%; IR: ν_{max} 3,429, 2,986, 2,941, 1,753, 1,724, 1,619, 1,439, 1,393, 1,341, 1,221, 1,198, 1,089 cm^{-1}; ^{1}H-NMR: δ 7.76 (d, 1H, H-5), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.92 (s, 2H, -OCH_2), 4.19 (q, 2H, CH_2, -CH_2CH_3), 4.02 (s, 2H, CH_2), 3.65 (s, 3H, OCH_3), 1.22 (t, 3H, CH_3, -CH_2CH_3); ^{13}C-NMR: δ 14.2 ($CH_2\underline{CH_3}$), 34.8 ($\underline{CH_2}CO$), 52.1 (OCH_3), 61.3 ($\underline{CH_2}CH_3$), 65.5 ($COCH_2O$), 109.6 (C-8), 112.8 (C-6), 113.8 (C-3), 114.8 (C-10), 128.3 (C-5), 151.2 (C-9), 155.2 (C-4), 160.3 (C-7), 160.9 (C-2), 168.9 (CO-O), 169.3 (C-CO-C); Anal. Calcd. for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04; Found: C, 59.98; H, 5.01%.

(7-Hydrazinocarbonylmethoxy-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide (**3**)

To a solution of methanol (120 mL) and 86% hydrazine hydrate (12 mL) (7-ethoxycarbonylmethoxy-2-oxo-2*H*-chromen-4-yl)-acetic acid methylester (**2**, 3.2 g, 0.01 mole) was added, and the mixture was left to stand overnight at 5°C. The product precipitated and was collected by suction filtration, washed with methanol (petrolether) and recrystallized from dil. acetic acid. M.p.> 300°C, yield 70%; IR: ν_{max} 3,461, 3,325 (NH), (NH_2), 1,707 (lactone C=O), 1,623 (C=O, amide), 1,516 (C=C, arom.), 1,430, 1,298, 1,277 and 1,153 cm^{-1}; ^{1}H-NMR: δ 9.41 (s, 1H, NH), 9.34 (s, 1H, NH), 7.76 (d, 1H, H-5), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.94 (s, 2H, -OCH_2), 4.34 (s, 2H, NH_2), 4.08 (s, 2H, CH_2), 3.38 (s, 2H, NH_2); ^{13}C-NMR: δ 45.8 (CH_2), 68.9 (CH_2O-), 108.0 (C-8), 111.8 (C-6), 112.9 (C-3), 114.1 (C-10), 128.3 (C-5), 152.2 (C-9), 155.2 (C-4), 160.4 (C-7), 160.9 (C-2), 166.8 ($COCH_2O$), 169.6 ($COCH_2$); Anal. Calcd. for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29; Found: C, 51.02; H, 4.58; N, 18.25%.

General procedure for preparation of (7-(arylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl)-acetic acid aryilidene-hydrazides **4a-k**

A mixture of (7-Hydrazinocarbonylmethoxy-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide (**3,** 3.06 g, 0.01 mole) and appropriate aromatic aldehyde (**Ar/a-k**, 0.01 mole) was refluxed in absolute ethanol (30 mL) in the presence of a catalytic amount of glacial acetic for 2 to 4 hours. The reaction mixture was cooled, the solid separated was filtered and recrystallized from methanol to give compounds **4a-k**.

[7-(Benzylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]-acetic acid benzylidene hydrazide (**4a**). M.p. 268-269°C; yield 74%; IR: ν_{max} 3,418, 3,313 (NH), 1,712, 1,682 (C=O, lactone), 1,666 (C=O, amide), 1,613 (C=C, arom., C=N, azomet.), 1,550, 1,378, 1,269 and 1,153 cm^{-1}; ^{1}H-NMR: δ 8.30 (s, 1H, HC=N-), 8.24 (s, 1H, HC=N-), 8.06 (s, 1H, NH), 8.02 (s, 1H, NH), 7.76 (d, 1H, H-5), 7.72-7.31 (m, 10H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.83 (s, 2H, -OCH_2), 4.28 (s,2H,CH_2); ^{13}C-NMR: δ 45.7 (CH_2), 69.2 (CH_2O-), 108.1 (C-8), 111.6 (C-6), 112.5 (C-3), 114.4 (C-10), 127.9 (C-5), 128.4 (C-3,5, Ar-), 129.0 (C-2,6, Ar-), 131.4 (C-4, Ar-), 133.9 (C-1, Ar-), 143.6 (N=CH-), 151.8 (C-9), 155.2 (C-4), 160.4 (C-7), 160.9 (C-2), 166.9 ($COCH_2O$), 170.0 (CONH-); Anal. Calcd. for $C_{27}H_{22}N_4O_5$: C, 67.21; H, 4.60; N, 11.61; Found: C, 67.19; H, 4.61; N, 11.58%.

[7-(2-Chlorobenzylidenehydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]-acetic acid (2-chloro-benzylidene)- hydrazide (**4b**). M.p. 225-226°C, yield (76%); IR: ν_{max} 3,428, 3,283 (NH), 1,710, 1,692 (C=O, lactone), 1,656 (C=O, amide), 1,612 (C=C, arom., C=N, azomet.), 1,542, 1,398, 1,264 and 1,155 cm^{-1}; ^{1}H-NMR: δ 8.73 (s, 1H, -HC=N-), δ 8.62 (s, 1H, -HC=N-), δ 8.48 (s, 1H, NH), 8.45 (s, 1H, NH), 7.72 (d, 1H, H-5), 7.60-7.30 (m, 8H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.84 (s, 2H, -OCH_2), 4.30 (s, 2H, CH_2); ^{13}C-NMR: δ 45.6 (CH_2), 68.9 (CH_2O-), 107.8 (C-8), 111.5 (C-6), 112.7 (C-3), 113.9 (C-10), 127.8 (C-5), 129.4 (C-3, Ar-), 130.6 (C-6, Ar-), 132.7 (C-4, Ar-), 133.8 (C-1, Ar-), 134.3 (C-2, Ar-), 143.5 (N=CH-), 151.7 (C-9), 155.0 (C-4), 160.3 (C-7), 160.9 (C-2), 166.4 ($COCH_2O$), 169.9 (CONH-); Anal. Calcd. For $C_{27}H_{20}Cl_2N_4O_5$: C, 58.81; H, 3.66; N, 10.16; Found: C, 58.79; H, 3.69; N, 10.12%.

[7-(3-Chlorobenzylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]-acetic acid (3-chloro-benzylidene)-hydrazide (**4c**). M.p. 259-261°C, yield 72%; IR: ν_{max} 3,408, 3,188 (NH), 1,727, 1,683 (C=O, lactone), 1,616 (C=O, amide, C=N, azomet.), 1,561 (C=C, arom.), 1,394, 1,262 and 1,138 cm^{-1}; ^{1}H-NMR: δ 8.31 (s, 1H, -HC=N-), 8.22 (s, 1H, -HC=N-), 8.48 (s, 1H, NH), 8.45 (s, 1H, NH), 7.76 (d, 1H, H-5), 7.67-7.30 (m, 8H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.84 (s, 2H, -OCH_2), 4.28 (s, 2H, CH_2); ^{13}C-NMR: δ 45.5 (CH_2), 69.1 (CH_2O-), 107.9 (C-8), 111.4 (C-6), 112.5 (C-3), 113.4 (C-10), 127.3 (C-6, Ar-), 127.9 (C-5), 129.3 (C-2, Ar-), 130.3 (C-5, Ar-), 131.2 (C-4, Ar-), 135.2 (C-1, Ar-), 134.4 (C-3, Ar-), 143.4 (N=CH-), 151.6 (C-9), 155.2 (C-4), 160.6 (C-7), 160.9 (C-2), 166.7 ($COCH_2O$), 169.8 (CONH-); Anal. Calcd. For $C_{27}H_{20}Cl_2N_4O_5$: C, 58.81; H, 3.66; N, 10.16; Found: C, 58.80; H, 3.68; N, 10.13%.

[7-(2,4-Dihydroxy-benzylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]-acetic acid (2,4-dihydroxybenzylidene)-hydrazide (**4d**). M.p. 273-275°C, yield 52%; IR: ν_{max} 3,434 (OH), 3,366, 3,092 (NH), 1,712, 1,672 (C=O, lactone), 1,623 (C=O, amide, C=N, azomethine), 1,612 (C=C, arom., C=N), 1,559, 1,509, 1,395, 1,265 and 1,153 cm^{-1}; ^{1}H-NMR: δ 11.80 (s, 1H, OH), 11.17 (s, 1H, OH), 8.42 (s, 1H, -HC=N-), 8.30 (s, 1H, -HC=N-), 8.23 (s, 1H, NH), 8.19 (s, 1H, NH), 7.76 (d, 1H, H-5), 7.61-7.30 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.82 (s, 2H, -OCH_2), 4.28 (s, 2H, CH_2); ^{13}C-NMR: δ 45.6 (CH_2), 69.2 (CH_2O-), 103.8 (C-3, Ar-), 107.6 (C-8), 108.7 (C-5, Ar-), 111.3 (C-6), 112.7 (C-3), 113.4 (C-10), 127.2 (C-6, Ar-), 127.9 (C-5), 135.2 (C-1, Ar-), 143.0 (N=CH-), 151.2 (C-9), 155.1 (C-4), 160.5 (C-7), 160.9 (C-2), 162.4 (C-2, Ar-), 162.6 (C-4, Ar-), 166.5 ($COCH_2O$), 169.4 (CONH-); Anal. Calcd. For $C_{27}H_{22}N_4O_9$: C, 59.34; H, 4.06; N, 10.25; Found: C, 59.30; H, 4.07; N, 10.29%.

[7-(3,4-Dihydroxy-benzylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]- acetic acid (3,4-dihydroxybenzylidene)-hydrazide (**4e**). M.p. 205°C, yield 62%; IR: ν_{max} 3,408, 2,922 (NH), 1,725, 1,664 (C=O, lactone), 1,619 (C=O, amide, C=N, azomethine), 1,593 (C=C, arom.), 1,444, 1,393, 1,284 and 1,152 cm^{-1}; ^{1}H-NMR: δ 11.98 (s, 1H, OH), 11.45 (s, 1H, OH), 8.41 (s, 1H, -HC=N-), 8.30 (s, 1H, -HC=N-), 8.12 (s, 1H, NH), 8.03 (s, 1H, NH), 7.76 (d, 1H, H-5), 7.65-7.41 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.77 (s, 2H, -OCH_2), 4.22 (s, 2H, CH_2); ^{13}C-NMR: δ 45.5 (CH_2), 69.3 (CH_2O-), 107.6 (C-8), 111.4 (C-6), 112.5 (C-3), 113.5 (C-10), 116.4 (C-2, Ar-), 117.5 (C-5, Ar-), 123.3 (C-6, Ar-), 127.8 (C-5), 127.9 (C-1, Ar-), 143.1 (N=CH-), 147.4 (C-3, Ar-), 149.6 (C-4, Ar-), 151.3 (C-9), 155.0 (C-4), 160.4 (C-7), 160.9 (C-2), 166.6 ($COCH_2O$), 169.5 (CONH-); Anal. Calcd. For $C_{27}H_{22}N_4O_9$: C, 59.34; H, 4.06; N, 10.25; Found: C, 59.13; H, 4.03; N, 10.04%.

[7-(2,5-Dihydroxybenzylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]- acetic acid (2,5-dihydroxybenzylidene)-hydrazide (**4f**). M.p. 275-276°C, yield 76%; IR: ν_{max} 3,369, 3,286 (NH), 1,717, 1,681, 1,667 (C=O, lactone), 1,624 (C=O, amide, C=N, azomethine), 1,585 (C=C arom.), 1,492, 1,396, 1,267 and 1,156 cm^{-1}; ^{1}H-NMR: δ 11.95 (s, 1H,OH), 11.56 (s,1H,OH), 8.48 (s, 1H, -HC=N-), 8.34 (s, 1H, -HC=N-), 8.30 (s, 1H, NH), 8.25 (s, 1H, NH), 7.76 (d, 1H, H-5), 7.68-7.30 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.82 (s, 2H, -OCH_2), 4.24 (s, 2H, CH_2); ^{13}C-NMR: δ 45.6 (CH_2), 69.3 (CH_2O-), 107.8 (C-8), 111.4 (C-6), 112.7 (C-3), 113.8 (C-10), 116.4 (C-6, Ar-), 117.4 (C-3, Ar-), 119.6 (C-4, Ar-), 119.9 (C-1, Ar-), 127.8 (C-5), 143.5 (N=CH-), 151.4 (C-9), 151.3 (C-5, Ar-), 153.7 (C-2, Ar-), 155.2 (C-4), 160.4 (C-7), 160.9 (C-2), 166.7 ($COCH_2O$), 169.4 (CONH-); Anal. Calcd. For $C_{27}H_{22}N_4O_9$: C, 59.34; H, 4.06; N, 10.25; Found: C, 59.32; H, 4.04; N, 10.20%.

[7-(4-Hydroxy-3-methoxybenzylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4yl]-acetic acid(4-hydroxy-3-methoxybenzylidene)-hydrazide (**4g**). M.p. 232-233°C, yield 84%; IR: ν_{max} 3,430, 3,224 (NH), 1,711, 1,671 (C=O, lactone), 1,622 (C=O, amide, C=N, azomethine), 1,605 (C=C, arom.), 1,429, 1,394, 1,272 and 1,164 cm^{-1}; ^{1}H-NMR: δ 11.96 (s, 1H, OH), δ 11.50 (s, 1H, OH), 8.19 (s, 1H, -HC=N-), 8.10 (s, 1H, -HC=N-), 7.99 (s, 1H, NH), 7.97 (s, 1H, NH), 7.77 (d, 1H, H-5), 7.40-7.21 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.78 (s, 2H, -OCH_2), 4.24 (s, 2H, CH_2), 3.80 (s, 6H, -OCH_3); ^{13}C-NMR: δ 45.6 (CH_2), 56.0 (OCH_3), 69.2 (CH_2O-), 107.6 (C-8), 111.2 (C-6), 112.5 (C-3), 113.6(C-10), 114.8 (C-2, Ar-), 117.0 (C-5, Ar-), 122.9 (C-6, Ar-), 127.4 (C-1,Ar-), 127.8 (C-5), 143.3 (N=CH-), 148.1 (C-4, Ar-), 151.4 (C-9), 151.5 (C-3, Ar-), 155.1 (C-4), 160.4 (C-7),

160.9 (C-2), 166.8 ($COCH_2O$), 169.8 (CONH-); Anal. Calcd. For $C_{29}H_{26}N_4O_9$: C, 60.62; H, 4.56; N, 9.75; Found: C, 60.59; H, 4.75; N, 9.70%.

[7-(3-Phenoxybenzylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]-acetic acid 3-phenoxybenzylidene)-hydrazide (**4h**). M.p. 236-237°C, yield 57%; IR: ν_{max} 3,409, 3,071 (NH), 1,726, 1,685 (C=O, lactone), 1,624 (C=O, lactone, C=N, azomethine), 1,597 (C=C, arom.), 1,490, 1,394, 1,261 and 1,156 cm^{-1}; ^{1}H-NMR: δ 8.30 (s, 1H, -HC=N-), 8.21 (s, 1H, -HC=N-), 8.03 (s, 1H, NH), 7.99 (s, 1H, NH), 7.76 (d, 1H, H-5), 7.70-7.10 (m, 18H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.79 (s, 2H, $-OCH_2$), 4.18 (s, 2H, CH_2); ^{13}C-NMR: δ 45.5 (CH_2), 56.1 (OCH_3), 69.1 (CH_2O-), 107.8 (C-8), 111.4 (C-6), 112.7 (C-3), 113.5 (C-10), 116.6 (C-2, Ar-), 117.5 (C-2,6, Ar-PhO), 119.8 (C-4, Ar-), 121.9 (C-4, Ar- PhO), 122.3 (C-2, Ar-), 127.8 (C-5), 128.5 (C-3,5 Ar- PhO), 128.9 (C-5 Ar-), 133.5 (C-1 Ar-), 143.4 (N=CH-), 151.3 (C-9), 155.4 (C-4), 157.1 (C-1 Ar- PhO), 157.1 (C-3 Ar-), 160.4 (C-7), 160.9 (C-2), 166.8 ($COCH_2O$), 170.0 (CONH-); Anal. Calcd. For $C_{39}H_{30}N_4O_7$: C, 70.26; H, 4.54; N, 8.40; Found: C, 70.23; H, 4.55; N, 8.37%.

[7-(4-N,N-Dimethylaminobenzylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]-acetic acid (4-N,N-dimethylaminobenzylidene)-hydrazide (**4i**). M.p. 207-209°C, yield 63%; IR: ν_{max} 3,408, 3,082 (NH), 1,724, 1,679 (C=O, lactone), 1,623 (C=O, amide, C=N, azomethine), 1,604 (C=C, arom.), 1,554, 1,525, 1,364, 1,269 and 1,181cm^{-1}; ^{1}H-NMR: δ 8.49 (s, 1H, -HC=N-), 8.44 (s, 1H, -HC=N-), 8.17 (s, 1H, NH), 8.07 (s, 1H, NH), 7.66 (d, 1H, H-5), 7.24-7.52 (m, 8H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.74 (s, 2H, $-OCH_2$), 4.18 (s, 2H, CH_2), 3.32 (s, 6H, $-N(CH_3)_2$), 2.99 (s, 6H, $-N(CH_3)_2$); ^{13}C-NMR: δ 40.3 (CH_3N-), 45.6 (CH_2), 69.1 (CH_2O-), 107.6 (C-8), 111.3 (C-6), 112.7 (C-3), 113.8 (C-10), 114.4 (C-3,5 Ar-), 123.3 (C-1, Ar-), 127.8 (C-5), 130.2 (C-2,6 Ar-), 143.3 (N=CH-), 151.4 (C-9), 151.0 (C-4, Ar-), 155.5 (C-4), 160.6 (C-7), 160.9 (C-2), 166.7 ($COCH_2O$), 169.8 (CONH-); Anal. Calcd. For $C_{31}H_{32}N_6O_5$: C, 64.97; H, 5.45; N, 15.15; Found: C, 65.89; H, 5.58; N, 15.11 %.

[7-(2-Hydroxy-5-nitrobenzylidenehydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]-acetic acid (2-hydroxy-5-nitrobenzylidene)-hydrazide (**4j**). M.p. 204°C, yield 82%; IR: ν_{max} 3,367, 3,272 (NH), 1,706, 1,689 (C=O, lactone), 1,616 (C=O, C=N, azomethine), 1,600 (C=C, arom.), 1,577, 1,517, 1,481, 1,342, 1,287 and 1,150 cm^{-1}; ^{1}H-NMR: δ 12.02 (s, 2H, OH), 8.71 (s, 1H, -HC=N-), 8.59 (s, 1H, -HC=N-), 8.36 (s, 1H, NH), 8.31 (s, 1H, NH), 7.67 (d, 1H, H-5), 7.32-7.54 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 4.84 (s, 2H, $-OCH_2$), 4.08 (s, 2H, CH_2); ^{13}C-NMR: δ 45.7 (CH_2), 69.2 (CH_2O-), 107.8 (C-8), 111.5 (C-6), 112.4 (C-3), 113.8 (C-10), 116.9 (C-3, Ar-), 119.4 (C-1, Ar-), 124.8 (C-4, Ar-), 125.5 (C-2, Ar-), 127.8 (C-5), 141.6 (C-5, Ar-), 143.4 (N=CH-), 151.4 (C-9), 155.4 (C-4), 160.8 (C-7), 160.9 (C-2), 166.2 (C-2, Ar-), 166.8 ($COCH_2O$), 170.0 (CONH-); Anal. Calcd. For $C_{27}H_{20}N_6O_{11}$: C, 53.65; H, 3.33; N, 13.90; Found: C, 53.63; H, 3.35; N, 13.91%.

[2-Oxo-7-(3-phenylallylidenehydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl]-acetic acid (3-phenylallylidene)-hydrazide (**4k**). M.p. 290-292°C, yield 68%; IR: ν_{max} 3,428, 3,256 (NH), 1,718 (C=O, lactone), 1,624 (C=O, amide, C=N, azomethine), 1,613 (C=C, arom.), 1,560, 1,509, 1,393, 1,266 and 1,151 cm^{-1}; ^{1}H-NMR: δ 8.38 (s, 1H, -HC=N-), 8.24 (s, 1H, -HC=N-), 8.15 (s, 1H, NH), 8.08 (s, 1H, NH), 7.78 (2d, 4H, -HC=CH-), 7.64 (d, 1H, H-5), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s,

1H, H-3), 4.77 (s, 2H, -OCH_2), 4.08 (s, 2H, CH_2); ^{13}C-NMR: δ 45.6 (CH_2), 69.1 (CH_2O-), 107.8 (C-8), 111.4 (C-6), 112.8 (C-3), 113.4 (C-10), 126.3 (C-2, Ar-), 126.4 (C-2,6, Ar-), 127.8 (C-5), 128.0 (C-4, Ar-), 128.9 (C-3,5, Ar-), 135.1 (C-1, Ar-), 139.0 (C-3, Ar-), 143.3 (N=CH-), 151.2 (C-9), 155.4 (C-4), 160.5 (C-7), 160.9 (C-2), 166.7 ($COCH_2O$), 169.8,(CONH-); Anal. Calcd. For $C_{31}H_{26}N_4O_5$: C, 69.65; H, 4.90; N, 10.48; Found: C, 69.67; H, 4.88; N, 10.45%.

General procedure for the preparation of N-(2-aryl-4-oxo-thiazolidin-3-yl)-2-(4-(2-aryl-4-oxo-thiazolidin-3-ylcarbamoyl)-methyl)-2-oxo-2H-chromen-7-yloxy)-acetamides **5a-k**

A mixture of (7-(arylidene-hydrazinocarbonylmethoxy)-2-oxo-2H-chromen-4-yl)-acetic acid aryilidenehydrazide **4a-k** (0.01 mole) and mercaptoacetic acid (1.82 g, 0.02 mole) in DMF (30 mL) containing a pinch of anhydrous $ZnCl_2$ was refluxed 6-8 hours. The reaction mixture was cooled and poured onto crushed ice. The solid thus obtained was filtered, washed with water and recrystallized from DMF yielding **5a-k**.

2-{2-Oxo-7-[(4-oxo-2-phenylthiazolidin-3-ylcarbamoyl)-methoxy]-2H-chromen-4-yl}-N-(4-oxo-2-phenylthiazolidin-3-yl)acetamide (**5a**). M.p. 202-204°C, yield 40%; IR: ν_{max} 3,418, 3,313 (NH), 1,712, 1,682 (C=O, lactone), 1,666 (C=O, amide), 1,613 (C=C, arom.), 1,550, 1,378, 1,269 and 1,153 cm^{-1}; ^{1}H-NMR: δ 8.22 (s, 1H, -NH), 8.12 (s, 1H, -NH), 7.76 (d,1H,H-5), 7.71-7.23 (m, 10H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, -SCHN-), 4.83 (s, 2H, -OCH_2), 4.28 (s, 2H, CH_2), 3.38 (s, 2H, $COCH_2S$-); ^{13}C-NMR: δ 35.8 ($CO\underline{C}H_2S$), 45.5 (CH_2), 57.4 ($N\underline{C}HS$), 69.1 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 127.2 (C-4, Ar-), 127.8 (C-5), 128.7 (C-3,5, Ar-), 128.8 (C-2,6 Ar-), 139.2 (C-1, Ar-), 151.2 (C-9), 155.0 (C-4), 160.3 (C-7), 160.9 (C-2), 166.4 ($\underline{C}OCH_2O$), 168.8 ($SCH_2\underline{C}O$-N), 173.3 (CONH-); Anal. Calcd. For $C_{31}H_{26}N_4O_7S_2$: C, 59.94; H, 4.16; N, 8.88; S, 10.17; Found: C, 60.05; H, 4.14; N, 8.91; S, 10.14%.

N-[2-(2-Chlorophenyl)-4-oxo-thiazolidin-3-yl]-2-(7-{[2-(2-chlorophenyl)-4-oxo-thiazolidin-3-ylcarbamoyl]-methoxy}-2-oxo-2H-chromen-4-yl)-acetamide (**5b**). M.p. 184°C, yield 76%; IR: ν_{max} 3,425, 3,283 (NH), 1,692 (C=O, lactone), 1,656 (C=O, amide), 1,612 (C=C, arom.), 1,542, 1,398, 1,264 and 1,155 cm^{-1}; ^{1}H-NMR: δ 8.73 (s, 1H, NH-), 8.62 (s, 1H, NH-), 7.76 (d, 1H, H-5), 7.60-7.30 (m, 8H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, $N\underline{CH}S$), 4.84 (s, 2H, -OCH_2), 4.30 (s, 2H, CH_2), 3.38 (s, 2H, $CO\underline{CH_2}S$); ^{13}C-NMR: δ 35.7 ($CO\underline{C}H_2S$), 45.5 (CH_2), 57.4 ($N\underline{C}HS$), 69.10 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 127.0 (C-5), 129.0 (C-3, Ar-), 130.6 (C-6, Ar-), 132.5 (C-4, Ar-), 133.4 (C-1, Ar-), 134.0 (C-2, Ar-), 143.0 (N=CH-), 151.2 (C-9), 155.0 (C-4), 160.3 (C-7), 160.9 (C-2), 166.4 ($COCH_2O$), 173.0 (CONH-); Anal. Calcd. For $C_{31}H_{24}Cl_2N_4O_7S_2$: C, 53.22; H, 3.46; N, 8.01; S, 9.17; Found: C, 53.18; H, 3.44; N, 7.89; S, 9.20%.

N-[2-(3-Chlorophenyl)-4-oxo-thiazolidin-3-yl]-2-(7-{[2-(3-chlorophenyl)-4-oxo-thiazolidin-3-ylcarbamoyl]-methoxy}-2-oxo-2H-chromen-4-yl)-acetamide (**5c**). M.p. 240-241°C, yield 72%; IR: ν_{max} 3,450, 3,188 (NH), 1,727, 1,683 (CO, lactone), 1,616 (C=O, amide), 1,598 (C=C, arom.), 1,394, 1,262 and 1,138 cm^{-1}; ^{1}H-NMR: δ 8.31 (s, 1H, NH-), 8.22,(s, 1H, NH-), 7.76 (d, 1H, H-5), 7.67-7.30 (m, 8H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, $N\underline{CH}S$), 4.84 (s, 2H, -OCH_2), 4.28 (s, 2H, CH_2), 3.38 (s, 2H, $CO\underline{CH_2}S$); ^{13}C-NMR: δ 35.7 ($CO\underline{C}H_2S$), δ 45.5 (CH_2),

57.4 (NCHS), 69.10 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 127.3 (C-6, Ar-), 127.8 (C-5), 129.3 (C-2, Ar-), 130.3 (C-5, Ar-), 131.2 (C-4, Ar-), 135.2 (C-1, Ar-), 134.4 (C-3, Ar-), 143.0 (N=CH-), 151.2 (C-9), 155.0 (C-4), 160.3 (C-7), 160.9 (C-2), 173.0 ($COCH_2O$), 173.0 (CONH-); Anal. Calcd. For $C_{31}H_{24}Cl_2N_4O_7S_2$: C, 53.22; H, 3.46; N, 8.01; S, 9.17; Found: C, 53.18; H, 3.44; N, 7.89; S, 9.20%.

N-[2-(2,4-Dihydroxyphenyl)-4-oxo-thiazolidin-3-yl]-2-(4-{[2-(2,4-dihydroxyphenyl)-4-oxo-thiazolidin-3-ylcarbamoyl]-methyl}-2-oxo-2H-chromen-7-yloxy)-acetamide (**5d**). M.p. 239-241°C, yield 52%; IR: ν_{max} 3,266 (OH), 3,092 (NH), 1,712, 1,672 (C=O, lactone), 1,624 (C=O, amide), 1,612 (C=C, arom.), 1,559, 1,509, 1,395, 1,265 and 1,153 cm^{-1}; ^{1}H-NMR: δ 11.80 (s, 1H, OH), 11.17 (s, 1H, OH), 8.42 (s, 1H, NH-), 8.30 (s, 1H, NH-), 7.76 (d, 1H, H-5), 7.61-7.30 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, NCHS), 4.82 (s, 2H, -OCH_2), 4.28 (s, 2H, CH_2), 3.38 (s, 2H, COCH_2S); ^{13}C-NMR: δ 35.7 (COCH_2S), δ 45.5 (CH_2), 47.4 (NCHS), 69.10 (CH_2O-), 103.7 (C-3, Ar-), 107.6 (C-8), 108.4 (C-5, Ar-), 110.1 (C-1, Ar-), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 127.8 (C-5), 131.3 (C-6, Ar-), 151.2 (C-9), 157.2 (C-2, Ar-), 158.2 (C-4), 160.3 (C-7), 160.9 (C-2), 166.4 (CONH), 168.8 (NCOCH_2), 173.3 (CH_2CONH); Anal. Calcd. For $C_{31}H_{26}N_4O_{11}S_2$: C, 53.60; H, 3.77; N, 8.07; S, 9.23; Found: C, 53.58; H, 3.79; N, 7.98; S, 9.20%.

N-[2-(3,4-Dihydroxyphenyl)-4-oxo-thiazolidin-3-yl]-2-(7-{[2-(3,4-dihydroxyphenyl)-4-oxo-thiazolidin-3-ylcarbamoyl]-methoxy}-2-oxo-2H-chromen-4-yl)-acetamide (**5e**). M.p. 198-200°C, yield 47%; IR: ν_{max} 3,388 (NH), 2,922 (OH), 1,725, 1,694 (C=O, lactone), 1,619 (C=O, amide), 1,523, 1,444, 1,393, 1,284 and 1,152 cm^{-1}; ^{1}H-NMR: δ 11.98 (s, 1H, OH), 11.45 (s, 1H, OH), 8.41 (s, 1H, NH), 8.30 (s, 1H, NH-), 7.76 (d, 1H, H-5), 7.65-7.41 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, NCHS), 4.77 (s, 2H, -OCH_2), 4.22 (s, 2H, CH_2), 3.38 (s, 2H, COCH_2S); ^{13}C-NMR: δ 35.7 (COCH_2S), δ 45.5 (CH_2), 57.4 (NCHS), 69.10 (CH_2O-), 103.7 (C-3, from Ph), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 115.4 (C-2, Ar-), 117.4 (C-5, Ar-), 122.2 (C-6, Ar-), 117.8 (C-5), 133.8 (C-1, Ar-), 143.0 (N=CH-), 147.4 (C-3, Ar-), 145.6 (C-4, Ar-), 151.2 (C-9), 155.0 (C-4), 160.3 (C-7), 160.9 (C-2), 166.4 (CONH-), 168.8 ($COCH_2S$), 173.3 (CH_2CONH-); Anal. Calcd. For $C_{31}H_{26}N_4O_{11}S_2$: C, 53.60; H, 3.77; N, 8.07; S, 9.23; Found: C, 53.58; H, 3.79; N, 7.98; S, 9.20%.

N-[2-(2,5-Dihydroxyphenyl)-4-oxo-thiazolidin-3-yl]-2-(7-{[2-(2,5-dihydroxyphenyl)-4-oxo-thiazolidin-3-ylcarbamoyl]-methoxy}-2-oxo-2H-chromen-4-yl)-acetamide (**5f**). M.p. 221-223°C, yield 46%; IR: ν_{max} 3,369 (OH), 3,286 (NH), 1,717, 1,681 (C=O, lactone), 1,667 (C=O, amide), 1,624 (C=C, arom.), 1,585, 1,492, 1,396, 1,267 and 1,156 cm^{-1}; ^{1}H-NMR: δ 11.95 (s, 1H, OH), 11.56 (s, 1H, OH), 8.48 (s, 1H, NH-), 8.34 (s, 1H, NH-), 7.76 (d, 1H, H-5), 7.68-7.30 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, NCHS), 4.82 (s, 2H, -OCH_2), 4.24 (s, 2H, CH_2), 3.38 (s, 2H, COCH_2S); ^{13}C-NMR: δ 35.7 (COCH_2S), δ 45.5 (CH_2), 47.4 (NCHS), 69.1 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 115.4 (C-6, Ar-), 117.4 (C-3, Ar-), 115.6 (C-4, Ar-), 119.6 (C-1, Ar-), 127.8 (C-5), 143.0 (N=CH-), 148.7 (C-2, Ar-), 151.2 (C-9), 151.2 (C-5, Ar-), 155.0 (C-4), 160.2 (C-7), 160.9 (C-2), 166.4 (CONH-), 168.8 ($COCH_2S$), 173.3 (CONH-); Anal. Calcd. For $C_{31}H_{26}N_4O_{11}S_2$: C, 53.60; H, 3.77; N, 8.07; S, 9.23; Found: C, 53.58; H, 3.79; N, 7.98; S, 9.20%.

N-[2-(4-Hydroxy-3-methoxyphenyl)-4-oxo-thiazolidin-3-yl]-2-(7-{[2-(4-hydroxy-3-methoxyphenyl-4-oxo-thiazolidin-3-ylcarbamoyl]-methoxy}-2-oxo-2H-chromen-4-yl)-acetamide (**5g**). M.p. 217-218°C, yield 84%; IR: ν_{max} 3,434, 3,224 (NH), 1,711, 1,671 (C=O, lactone), 1,632 (C=O, amide), 1,603 (C=C, arom.), 1,529, 1,394, 1,272 and 1,164 cm^{-1}; ^{1}H-NMR: δ 11.96 (s, 1H, OH), 8.19 (s, 1H, NH-), 8.10 (s, 1H, NH-), 7.77 (d, 1H, H-5), 7.40-7.21 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, NCHS), 4.78 (s, 2H, -OCH_2), 4.24 (s, 2H, CH_2), 3.80 (s, 6H, -OCH_3), 3.38 (s, 2H, COCH_2S); ^{13}C-NMR: δ 35.7 (COCH_2S), δ 45.5 (CH_2), 56.2 (OCH_3), 57.8 (NCHS), 69.1 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 114.8 (C-2, Ar-), 117.0 (C-5, Ar-), 122.9 (C-6, Ar-), 132.4 (C-1, Ar-), 144.1 (C-4, Ar-), 151.2 (C-9), 151.5 (C-3, Ar-), 155.0 (C-4), 160.3 (C-7), 160.9 (C-2), 166.4 (CONH-), 168.8 ($COCH_2S$), 173.0 (CONH-), Anal. Calcd. For $C_{33}H_{30}N_4O_{11}S_2$: C, 54.84; H, 4.18; N, 7.75; S, 8.87; Found: C, 54.79; H, 4.19; N, 7.71; S, 8.82%.

2-(2-Oxo-7-{[4-oxo-2-(3-phenoxyphenyl)-thiazolidin-3-ylcarbamoyl]-methoxy}-2H-chromen-4-yl)-N-[4-oxo-2-(3-phenoxyphenyl)-thiazolidin-3-yl]-acetamide (**5h**). M.p. 221-222°C, yield 57%; IR: ν_{max} 3,389, 3,071 (NH), 1,726, 1,685 (C=O, lactone), 1,628 (C=O, amide), 1,614 (C=C, arom.), 1,577, 1,490, 1,394, 1,261 and 1,156 cm^{-1}; ^{1}H-NMR: δ 8.30 (s, 1H, NH-), 8.21 (s, 1H, NH-), 7.76 (d, 1H, H-5), 7.70-7.10 (m, 18H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, NCHS), 4.79 (s, 2H, -OCH_2), 4.18 (s, 2H, CH_2), 3.38 (s, 2H, COCH_2S); ^{13}C-NMR: δ 35.7 (COCH_2S), δ 45.5 (CH_2), 56.2 (OCH_3), 57.6 (NCHS), 69.10 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 115.4 (C-4, Ar-), 116.1 (C-2, Ar-), 117.5 (C -2,6, Ar- PhO), 121.4 (C-4, Ar- PhO), 121.9 (C-6, Ar-), 127.8 (C-5), 128.5 (C-3,5 Ar- PhO), 128.6 (C-5 Ar-), 139.1 (C-1 Ar-), 151.2 (C-9), 155.0 (C-4), 156.8 (C-3, Ar-), 157.6 (C-1, Ar-PhO), 160.3 (C-7), 160.9 (C-2), 166.4 (CONH-), 168.9 ($COCH_2S$), 173.3 (CH_2CONH-); Anal. Calcd. For $C_{43}H_{34}N_4O_9S_2$: C, 63.38; H, 4.21; N, 6.88; S, 7.87; Found: C, 63.34; H, 4.19; N, 6.86; S, 7.84%.

N-[2-(4-N,N-Dimethylaminophenyl)-4-oxo-thiazolidin-3-yl]-2-(7-{[2-(4-N,N-dimethylaminophenyl)-4-oxo-thiazolidin-3-ylcarbamoyl]-methoxy}-2-oxo-2H-chromen-4-yl)-acetamide (**5i).** M.p. 198-201°C, yield 71%; IR: ν_{max} 3,398, 3,082 (NH), 1,724, 1,679 (C=O, lactone), 1,623 (C=O, amide), 1,604 (C=C, arom.), 1,554, 1,525, 1,364, 1,269 and 1,181 cm^{-1}; ^{1}H-NMR: δ 8.49 (s, 1H, NH-), 8.44 (s, 1H, NH-), 7.66 (d, 1H, H-5), 7.24-7.52 (m, 8H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s,1H,H-3), 5.92 (s, 1H, NCHS), 4.74 (s, 2H, -OCH_2), 4.18 (s, 2H, CH_2), 3.38 (s, 2H, COCH_2S), 3.32 (s, 6H, -$N(CH_3)_2$), 2.99 (s, 6H, -$N(CH_3)_2$); ^{13}C-NMR: δ 35.7 (COCH_2S), δ 40.3 (CH_3N-), 45.5 (CH_2), 57.6 (NCHS), 69.10 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 114.4 (C-3,5, Ar-), 127.8 (C-5), 128.9 (C-1, Ar-), 130.1 (C-2,6 Ar-), 148.2 (C-4, Ar-), 151.2 (C-9), 155.0 (C-4), 160.3 (C-7), 160.9 (C-2), 166.4 (CONH-), 168.9 ($COCH_2S$), 173.3 (CH_2CONH-); Anal. Calcd. For $C_{35}H_{36}N_6O_7S_2$: C, 58.64; H, 5.06; N, 11.72; S, 8.95; Found: C, 58.60; H, 4.98; N, 11.70; S, 8.90%.

N-[2-(2-Hydroxy-5-nitrophenyl)-4-oxo-thiazolidin-3-yl]-2-(4-{[2-(2-hydroxy-5-nitrophenyl)-4-oxo-thiazolidin-3-ylcarbamoyl]-methyl}-2-oxo-2H-chromen-7-yloxy)-acetamide (**5j**). M.p. 240-242°C, yield 82%; IR: ν_{max} 3,367, 3,272 (NH), 1,689 (C=O), 1,618 (C=O, amide), 1,598 (C=C, arom.), 1,577, 1,517, 1,481, 1,342, 1,287 and 1,150 cm^{-1}; ^{1}H-NMR: δ 12.02 (s, 2H, OH), 8.71 (s, 1H, NH-), 8.59 (s, 1H, NH-), 7.67 (d, 1H, H-5), 7.32-7.54 (m, 6H, arom.), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, NCHS), 4.84 (s, 2H, -OCH_2), 4.08 (s, 2H, CH_2), 3.38 (s, 2H, COCH_2S); ^{13}C-

NMR: δ 35.7 (CO<u>C</u>H_2S), δ 45.5 (CH_2), 47.6 (N<u>CH</u>S), 69.10 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10), 116.9 (C-3, Ar-), 119.4 (C-1, Ar-), 121.8 (C-4, Ar-), 125.5 (C-6, Ar-), 127.8 (C-5), 141.1 (C-5, Ar-), 151.2 (C-9), 155.0 (C-4) 160.3 (C-7), 160.9 (C-2), 163.2 (C-2 Ar-), 166.4 (<u>C</u>ONH-), 168.9 (COCH_2S), 173.3 (CH_2CONH-); Anal. Calcd. For $C_{31}H_{24}N_6O_{13}S_2$: C, 49.47; H, 3.21; N, 11.17; S, 8.52; Found: C, 49.45; H, 3.19; N, 11.12; S, 8.50%.

2-{2-Oxo-7-[(4-oxo-2-styrylthiazolidin-3-ylcarbamoyl)-methoxy]-2H-chromen-4-yl}-N-(4-oxo-2-styrylthiazolidin-3-yl)-acetamide (**5k**). M.p. 221-224°C, yield 48%; IR: ν_{max} 3,424, 3,276 (NH), 1,718 (C=O, lactone), 1,628 (C=O, amide), 1,613 (C=C, arom.), 1,560, 1,509, 1,393, 1,266 and 1,151 cm^{-1}; ^{1}H-NMR: δ 8.38 (s, 1H, NH-), 8.24 (s, 1H, NH-), 7.78 (2d, 4H, -HC=CH-), 7.64 (d, 1H, H-5), 7.04 (d, 1H, H-6), 7.02 (s, 1H, H-8), 6.34 (s, 1H, H-3), 5.92 (s, 1H, N<u>CH</u>S), 4.77 (s, 2H, -OCH_2), 4.08 (s, 2H, CH_2), 3.38 (s, 2H, CO<u>CH_2</u>S); ^{13}C-NMR: δ 36.3 (CO<u>C</u>H_2S), δ 45.5 (CH_2), 56.9 (N<u>CH</u>S), 69.10 (CH_2O-), 107.6 (C-8), 111.0 (C-6), 112.5 (C-3), 113.4 (C-10) 123.8 (C-1, ethenyl-Ar)), 126.4 (C-2,6, Ar-), 128.0 (C-4, Ar-), 128.7 (C-3,5, Ar-), 129.6 (C-2, ethenyl-Ar), 135.2 (C-1, Ar-), 137.3 (N=CH-), 139.0 (C-3 Ar-), 151.2 (C-9), 155.0 (C-4), 160.2 (C-7), 160.9 (C-2), 166.4 (<u>C</u>ONH-), 168.9 (COCH_2S), 173.3 (CH_2CONH-); Anal. Calcd. For $C_{35}H_{30}N_4O_7S_2$: C, 61.57; H, 4.43; N, 8.21; S, 9.39;Found: C, 61.56; H, 4.41; N, 8.19; S, 9.40%.

References

1. Raev, L.; Voinov, E.; Ivanov, I.; Popov, D. Antitumor activity of some coumarin derivatives. *Pharmazie* **1990**, *45*, 696-698.
2. Nofal, Z.M.; El-Zahar, M.; Abd El-Karim, S. Novel coumarin derivatives with expected biological activity. *Molecules* **2000**, *5*, 99-113.
3. El-Agrody, A.M.; Abd El-Latif, M.S.; El-Hady, N.A.; Fakery, A.H.; Badair, A.H. Heteroaromatisation with 4-hydroxycoumarin part 2. *Molecules* **2001**, *6*, 519-527.
4. Patibha, S.; Shreeya, P. Synthesis, Characterization and antimicrobial studies of some novel 3-arylazo-7-hydroxy-4-methylcoumarin. *Indian J. Chem.* **1999**, *38B*, 1139-1142.
5. Patonay, T.; Litkei, G.Y.; Bognar, R.; Erdei, J.; Misztic, C. Synthesis, antimicrobial and antifungal activity of 4-hydroxycoumarin derivatives, Analogues of Novobiocin. *Pharmazie* **1984**, *39*, 86-91.
6. Shaker, R.M. Synthesis and reactions of some new 4H-pyrano[3,2-c]benzopyran-5-one derivatives and their potential biological activities. *Pharmazie* **1996**, *51*, 148.
7. El-Farargy, A.F. Synthesis and some reactions of 8-tert-butyl-6-hydroxy-4-methylcoumarin. *Egypt J. Pharm. Sci.* **1991**, *32*, 625.
8. Manolov, I.; Danchev, N. D. Synthesis, toxicological and pharmacological assessment of some 4-hydroxycoumarin. *Eur. J. Med. Chem. Chim. Ther.* **1995**, *30*, 531-536.
9. Emmanuel-Giota, A. A.; Fylaktakidou, K.C.; Hadjipavlou-Latina, D.J.; Litinas, K.E.; Nicolaides, D.N. Synthesis and biological evaluation of several 3-(coumarin-4-yl)tetrahydroisoxazole and 3-(coumarin-4-yl)dihydropyrazole derivatives. *J. Heterocycl. Chem*. **2001**, *38*, 717-722.
10. Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. *Curr. Med. Chem.* **2005**, *12*, 887-916.

11. Kennedy, R.O.; Thornes, R.D. *Coumarins: Biology, Applications and Mode of Action*; Wiley & Sons: Chichester, UK, 1997.
12. Zahradnik, M. *The Production and Applications of Fluorescent Brightening Agent*; Wiley & Sons: Chichester, UK, 1992.
13. Brown, F.C. 4-Thiazolidinones. *Chem. Rev.* **1961**, *61*, 463.
14. Singh, S.P.; Parmar, S.S.; Raman, K.; Stenberg, V.I. Chemistry and Biological Activity of Thiazolidinones. *Chem. Rev*. **1981**, *81*, 175-203.
15. Doran, W.J.; Shonle, H.A. Dialkyl thiazolidinones. *J. Org. Chem*. **1938**, *3*, 193-197.
16. Troutman, H.D.; Long, L.M. The synthesis of 2,3-disubstituted-4-thiazolidinones. *J. Am. Chem. Soc*. **1948**, *70*, 3436-3439.
17. Rout, M.K.; Mahapatra, G.N. 2-β-Naphtylamino-4-thiazolidinone and its derivatives. *J. Am. Chem. Soc.* **1955**, *77*, 2427-2428.
18. Gaikwad, N. J.; Tripude, R.N. Substituted 4-thiazolidinones as anticonvulsants. *Indian Drugs* **1994**, *31*, 593-594.
19. El-Gendy, Z.; Abdel-Rahman, R.M.; Fawzy, M.M.; Mahmoud, M.B. Biologically active thiazolidinone derived from thiosemicarbazones. *J. Ind. Chem. Soc.* **1990**, *67*, 927-929.
20. Diumo, M.V.; Mazzoni, O.; Piscopo, E.; Calignano, A; Giordano, F.; Bolognese, A. Synthesis and antihistaminic activity of some thiazolidin-4-ones. *J. Med. Chem.* **1992**, *35*, 2910-2912.
21. Shah, V.; Pant, C.K.; Joshi, P.C. Synthesis and antifungal activity of some bis(2-arylimino-3-yl-thiazolidinones) and bis(1-aryl-3-yl-thiohydantoins). *Asian J. Chem*. **1993**, *5*, 83-88.
22. Mukhatar, S.; Mujeebur, R.V.P.; Ansari, W.H.; Lemiere,G.; De Groot, A. and Dommisse, R. Bifunctional Derivative of p,p'-Dichlorochalcone. Part II. Synthesis of a Novel Compound 2-[2-Carboxymethylthio-2-(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-4-thiazolidinone. *Molecules* **1999**, *4*, 232-237.
23. Sattigeri, V.J.; Soni, A.; Singhal, S.; Khan, S.; Pandya, M.; Bhateja, P.; Mathur. T.; Rattan, A.; Khanna, J.M.; Mehta, A. Synthesis and antimicrobial activity of novel thiazolidinones. *ARKIVOC* **2005,** *ii*, 46-59.
24. Iyengar, D.S.; Kamalah, J.; Anandalwar, S.M.; Rangappa, K.S.; Prasad, J. Synthesis and Crystal Structure of 2-(3-pyridyl)-3-(4-methylphenyl)-1,3-thiazolidin-4-one. *Anal. Sci.* **2005**, *21*, 217-218.
25. Moawad, E.B. Synthesis of some new heterocyclic compounds with expected potential biological activity. *J. Islam. Acad. Sci.* **1989**, *2-4*, 237-240.
26. Čačić, M.; Trkovmik, M., Čačić, F.; Has-Schon, E. Synthesis of N_1-Substituted Coumarino[4,3-c]pyrazoles. *J. Heterocycl. Chem.* **2002**, *40*, 833-836.
27. Cacic, M.; Trkovnik, M.; Cacic, F.; Has-Schon, E. Synthesis and Antimicrobial Activity of Some Derivatives of (7-Hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic Acid Hydrazide. *Molecules* **2006**, *11*, 134-147.
28. Čačić, M.; Trkovnik, M.; Čačić, F.; Has-Schon, E. Synthesis of [2-aryl-6-oxo-6*H*-chromeno[6,7-d]oxazol-8-yl]-acetic acid ethyl esters. *J. Heterocycl. Chem*. **2006**, *43*, 261-266.
29. Amin, K.M.; Rahman, D.E.A.; Al-Eryani, Y.A. Synthesis and preliminary evaluation of some substituted coumarins as anticonvulsant agents. *Bioorg. Med. Chem.* **2008**, *16*, 5377-5388.

30. Elhafez, O.M.A.; El Khrisy, E.E.; Badria, F.; Fathy, A.E.D.M. Synthesis and biological investigations of new thiazolidinone and oxadiazoline coumarin derivatives. *Arch. Pharm. Res*. **2003**, *26*, 686-696.
31. Manojkumar, P.; Ravi, T.K.; Subbuchettiar, G. Synthesis of coumarin heterocyclic derivatives with antioxidant activity and *in vitro* cytotoxic activity against tumour cells. *Acta Pharm.* **2009**, 59, 159-170.

Sample Availability: Samples of the compounds are available from the authors.