Design, Synthesis and Characterization of Some Novel 3-Coumarinyl-5-aryliden-1,3-thiazolidine-2,4-diones and Their Antioxidant Activity

Milan Čačić and Maja Molnar

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

Reprint requests to Dr. Milan Čačić. Fax: 00385 31 207 115. E-mail: mcacic@ptfos.hr

Z. Naturforsch. **2011**, *66b,* 177 – 183; received September 29, 2010

In our effort to obtain biologically active compounds, new 3,5-disubstituted 1,3-thiazolidine-2,4-diones (**5a** – **r**) were synthesized. A series of 5-arylmethylidene-1,3-thiazolidine-2,4-diones (**3a** – **r**) were prepared by Knoevenagel reaction from 1,3-thiazolidine-2,4-dione (**2**) and appropriate aromatic aldehydes. Condensation of **3a** – **r** with 7-hydroxy-4-bromomethyl-2-oxo-2*H*-chromene (**1**) afforded novel 3-(7-hydroxy-2-oxo-2*H*-chromen-4-ylmethyl)-5-arylidene-1,3-thiazolidine-2,4-diones **5a** – **r**. Compounds **3a** – **r** and **5a** – **r** were evaluated for their antioxidant activity (DPPH free radical scavenging activity).

Key words: 1,3-Thiazolidine-2,4-diones, 7-Hydroxy-4-bromomethyl-2-oxo-2*H*-chromene, Knoevenagel Reaction, N-Substitution, Antioxidant Activity

Introduction

1,3-thiazolidine-2,4-dione is used as a starting material for the synthesis of drugs. In heterocyclic chemistry, the class of 1,3-thiazolidine-2,4-diones is particularly important as therapeutic agents and have been thoroughly investigated as peroxisome proliferator-activated receptor-γ-antagonists (PPAR-γ-antagonists), leading to the development of several insulin-sensitizing drugs for the treatment of diabetes type-2.

Extensive interest has been focused on 1,3-thiazolidine-2,4-dione derivatives which have been shown to possess a broad spectrum of biological activities. The most important of these are antidiabetic [1, 2], analgesic [3], cardiotonic [4], antibacterial, antifungal [5–8], antimicrobial [9], anticonvulsant [10], and cyclooxygenase and lipoxygenase inhibitory [11] activities. 1,3-thiazolidine-2,4-dione derivatives were investigated as templates for the design and synthesis of novel and safe anti-inflammatory compounds [12, 13]. Multi-substituted benzylidenethiazolidine-2,4-diones have also been proven to be potent antioxidants [14]. Hossain and Bhattacharya [15] have synthesized a series of 5-arylidene-2,4-thiazolidinediones and their geranyloxy or prenyloxy derivatives; all compounds scavenged the DPPH (1,1-diphenyl-2-picryhydrazyl) radical significantly in a concentration-dependent manner.

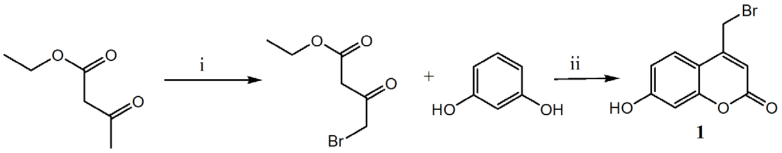
Natural coumarins affect the formation and scavenging of reactive oxygen species (ROS) and influence free radical-mediated oxidative damage [16]. The styryl carbonyl moiety in the coumarin skeleton is expected to affect scavenging of reactive substances derived from oxygen and to influence the process involving free radical-mediated injury [17].

Based upon the above considerations, it seemed worthy to design and synthesize certain new heterocyclic compounds containing the 1,3-thiazolidine-2,4-dione moiety and the coumarin unit in one frame.

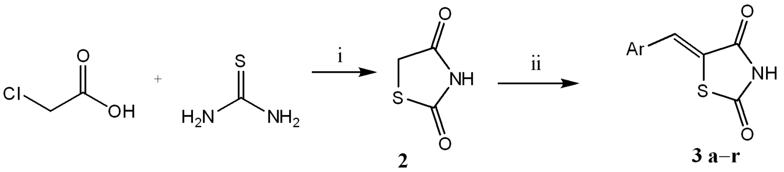
Results and Discussion

The synthetic routes followed in the preparation of the new compounds are illustrated in Schemes 1 – 3. The products are listed in Table 1. Compound **1** was synthesized from ethyl 4-bromoacetoacetate and resorcinol in conc. sulfuric acid at −10 °C, according to the literature method [18] (Scheme 1). 1,3-thiazolidine-2,4-dione (**2**) was obtained from monochloroacetic acid and thiourea in hot water [7], and yielded up on Knoevenagel condensation [19] with substituted aromatic aldehydes the 5-arylmethylidene-1,3-thiazolidine-2,4-diones **3a** – **r** (Scheme 2). A series of novel 3,5-disubstituted 1,3-thiazolidin-2,4-diones **5a** – **r** was

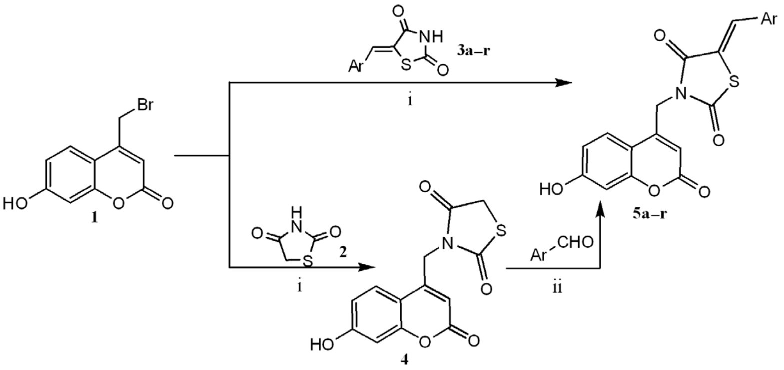
0932–0776 / 11 / 0200–0177 $ 06.00 © 2011 Verlag der Zeitschrift für Naturforschung, Tübingen · http://znaturforsch.com



Scheme 1. Reagents and conditions: (i) Br_2, $CHCl_3$ or CH_2Cl_2, 0 °C, stirring, 15 h, r. t.; (ii) H_2SO_4 conc., −10 °C, 2 to 4 d, r. t.



Scheme 2. Reagents and conditions: (i) HCl conc., reflux, 10 h; (ii) aromatic aldehydes, piperidine, ethanol, reflux, 24 h.



Scheme 3. Reagents and conditions: (i) K_2CO_3, DMF, r. t., 6 h; (ii) aromatic aldehydes, piperidine, ethanol, reflux, 24 h.

Table 1. Compounds **3** and **5** synthesized.

3, 5	Ar
a	phenyl
b	2-hydroxyphenyl
c	3-hydroxyphenyl
d	4-hydroxyphenyl
e	2-methoxyphenyl
f	3-methoxyphenyl
g	4-methoxyphenyl
h	2-chlorophenyl
i	3-bromophenyl
j	4-bromophenyl
k	4-fluorophenyl
l	3-phenoxyphenyl
m	4-N,N-dimethylaminophenyl
n	styryl
o	2,4-dihydroxyphenyl
p	3,4-dihydroxyphenyl
q	4-hydroxy-3-methoxyphenyl
r	3,4,5-trimethoxyphenyl

obtained by condensation of compounds **3a – r** with **1** (Scheme 3). N-Substitution [20] of 1,3-thiazolidin-2,4-diones **2** with 7-hydroxy-4-bromomethyl-2-oxo-2*H*-chromene (**1**) in DMF/K_2CO_3 furnished thiazolidine-2,4-dione derivative **4**, which on Knoevenagel condensation with substituted aromatic aldehydes yielded the same compounds **5a – r** (Scheme 3).

The constitution of the synthesized compounds was elucidated by elemental analysis, FT IR, ^{1}H NMR and mass spectral data. The IR spectra of compounds **5a – r** showed bands at 3300 – 3420 (7-OH coum. and arom. stretching), 3120 (CH aromatic stretching), 3002 (CH stretching, vinyl), 2925 and 2785 (aliphatic asymmetric and symmetric stretching, respectively), 1726 – 1670 (α-pyrone C=O stretching), 1587, 1608 – 1654 (C=C stretching), 1313 (C–N stretching), 1253 – 1270 (C–O–C stretching), and 748 – 783 cm^{-1} (C–S–C stretching).

The ^{1}H NMR spectrum for compound **4** shows singlet signals for the NCH_2 protons at δ = 4.86 ppm and for the ring-CH_2 protons at 4.37 ppm. After Knoevenagel condensation, compounds **5a – r** were obtained. In the ^{1}H NMR spectra of these products the signal for the ring-CH_2 protons is absent. In the mass spectra, all the compounds gave $[M–H]^+$ ion peaks.

Antioxidant assay

The DPPH free radical, bearing an odd electron, gives a strong absorption maximum at λ = 517 nm and is purple in color. When the odd electron of the DPPH radical pairs with a hydrogen atom from a free radical scavenging antioxidant, the reduced form DPPH-H is created, and the color turns from purple to yellow. The method used in our work applies to the overall antioxi-

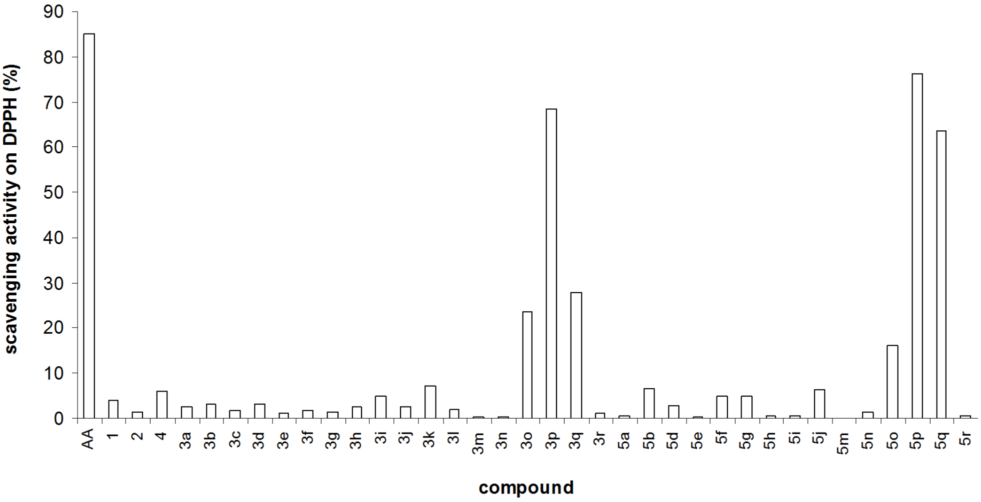


Fig. 1. Scavenging activity on DPPH (%) of the tested compounds, compared to the scavenging activity of ascorbic acid (AA).

dant capacity of the sample after 30 min of incubation. The DPPH-scavenging activity was determined against ascorbic acid as the standard compound.

Antioxidant activity

The data given in Fig. 1 show that substituents on the phenyl ring have a great influence on the antioxidant activity. The DPPH-scavenging activity of the compounds showing the best results in descending order was found to be: **5p** > **3p** > **5q** > **3q** > **3o**.

The compound showing the best DPPH scavenging activity was **5p** with a 3,4-$(OH)_2$-substitued phenyl ring, followed by **3p** with the same substituents on the phenyl ring. Compounds **5q** and **3q** with 3-OCH_3-4-OH substituents on the phenyl ring also showed very good antioxidant activity. All of these compounds possess a free hydroxyl group in *p*-position of the phenyl ring, which can donate a hydrogen atom, and another electron-donating group in *m*-position, the presence of which obviously enhances the scavenging activity. Lin *et al.* [21] showed that radical-scavenging effects of coumarins were correlated with the number of hydroxyl groups, the presence of a free hydroxyl group in a phenyl ring influencing the scavenging activity [22]. Substituents on the phenyl ring, as well as their position, had a greater influence on the free radical scavenging activity than the presence of the coumarin moiety attached to the 5-arylmethylidene-1,3-thiazolidine-2,4-dione core. However, in a comparison of compounds with the same substituent pattern in the series **3a – r** *vs*. **5a – r**, the latter ones showed a better scavenging activity, with the exception of **3o**. These compounds also possess an olefinic bond and an NH group in the thiazolidinedione moiety, which can also contribute to the radical scavenging activity [15].

Conclusion

In this study antioxidant properties of the 5-arylmethylidene-1,3-thiazolidine-2,4-diones **3a – r** and of the novel 3-(7-hydroxy-2-oxo-2*H*-chromen-4-ylmethyl)-5-arylidene-1,3-thiazolidine-2,4-diones **5a – r** were examined. Some of the compounds show excellent DPPH scavenging properties.

Experimental Section

General information

The melting points were taken on an Electrothermal Capillary melting point apparatus and are uncorrected. Thin-layer chromatographies were performed using fluorescent silica gel plates HF_{254} Merck, which were examined under UV light (254 and 365 nm), using benzene / acetone / acetic acid (8 : 1 : 1) as eluent. Silica gel (230 – 400 mesh) was used for flash chromatography separations. The elemental analyses for C, H and N were carried out on a Perkin-Elmer Analyzer 2440. Infrared spectra (ν in cm^{-1}) were recorded on a Shimadzu FT-IR 8400 S instrument, using KBr disks. ^1H NMR spectra were recorded on a Jeol EX-270 MHz NMR spectrometer at 293 K in $[D_6]$DMSO. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS. The mass spectra were recorded on an LC/MS/MS (API 2000) Applied Biosystems instrument. The absorbance was measured on a UV/Vis spectrophotometer Helios γ (Thermo Spectronic, Cambridge UK).

*General procedure for preparation of 5-arylidene-1,3-thiazolidine-2,4-diones **3a – r*** [19]

An appropriate aromatic aldehyde (5 mmol) was added to a stirred mixture of 1,3-thiazolidine-2,4-dione (**2**) (5 mmol) and piperidine (4 mmol) in ethanol (8.5 mL). The reaction mixture was refluxed for 24 h until the starting compounds had completely disappeared as monitored by TLC using benzene / acetone / acetic acid (8 : 1 : 1). The reaction mixture was poured into water, and acetic acid was added dropwise till acidic to litmus paper. The precipitated product was filtered, washed with water, and crystallized from the appropriate solvent to give pure compounds **3a – r**.

*General procedure for preparation of 3-(7-hydroxy-2-oxo-2H-chromen-4-ylmethyl)-5- arylidene-1,3-thiazolidine-2,4-diones **5a – r*** [20]

An equimolar mixture of 5-arylidene-1,3-thiazolidine-2,4-diones **3a – r** (10.0 mmol), 7-hydroxy-4-bromomethyl-2-oxo-2*H*-chromene (**1**), (10.0 mmol) and anhydrous K_2CO_3 (10.0 mmol) was stirred at room temperature in DMF (10 mL) for 6 h. The reaction mixture was poured into crushed ice/water. The precipitated product was filtered, washed with water and crystallized from methanol. Pure compounds **5a – r** were obtained.

*(Z)-5-Benzylidene-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)-methyl]thiazolidine-2,4-dione (**5a**)*

M. p. 270 °C. – R_f = 0.52. – Yield 61 %. – FT-IR (KBr): ν_{max} = 3398, 3082, 1689, 1595, 1414, 1384, 1323, 1282, 1124, 981 and 769 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.90 – 7.54 (m, 5H, arylidene), 7.71 (d, 1H, 6-H, coum.), 7.94 (s, 1H, -HC=C-), 10.03 (s, 1H, OH, coum.). – MS: m/z = 377.9 [M–H]$^+$. – Anal. for $C_{20}H_{13}NO_5S$ (379.05): calcd. C 63.32, H 3.45, N 3.69, S 8.45; found C 63.30, H 3.47, N 3.71, S 8.40 %.

*(Z)-5-(2-hydroxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5b**)*

M. p. 229 °C. – R_f = 0.46. – Yield 74 %. – FT-IR (KBr): ν_{max} = 3412, 3315, 3082, 2922, 1724, 1701, 1676, 1612, 1572, 1458, 1379, 1313, 1257, 1145 and 750 cm^{-1}. – ^{1}H NMR: δ = 5.01 (s, 2H, CH_2, coum.), 5.95 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.93 – 7.55 (m, 4H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.90 (s, 1H, -HC=C-), 10.05 (s, 1H, OH, coum.), 13.34 (s, 1H, OH, arylidene). – MS: m/z = 394.7 [M–H]$^+$. – Anal. for $C_{20}H_{13}NO_6S$ (395.05): calcd. C 60.75, H 3.31, N 3.54, S 8.11; found C 60.71, H 3.29, N 3.50, S 8.14 %.

*(Z)-5-(3-hydroxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5c**)*

M. p. 287 °C. – R_f = 0.48. – Yield 76 %. – FT-IR (KBr): ν_{max} = 3282, 3082, 2820, 1737, 1678, 1604, 1575, 1494, 1415, 1381, 1315, 1276, 1143 and 769 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.77 (s, 1H, 8-H, coum.), 6.84 (d, 1H, 5-H, coum.), 6.92 – 7.51 (m, 4H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.91 (s, 1H, -HC=C-), 10.08 (s, 1H, OH, coum.), 13.33 (s, 1H, OH, arylidene). – MS: m/z = 394.1 [M–H]$^+$. – Anal. for $C_{20}H_{13}NO_6S$ (395.05): calcd. C 60.75, H 3.31, N 3.54, S 8.11; found C 60.72, H 3.34, N 3.57, S 8.08 %.

*(Z)-5-(4-hydroxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5d**)*

M. p. 295 °C. – R_f = 0.52. – Yield 78 %. – FT-IR (KBr): ν_{max} = 3350, 3203, 2929, 2816, 1720, 1685, 1598, 1512, 1415, 1379, 1327, 1284, 1149, 1089, 985 and 731 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.93 (d, 2H, arylidene), 7.54 (d, 2H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.90 (s, 1H, -HC=C-), 10.05 (s, 1H, OH, coum.), 13.38 (s, 1H, OH, arylidene). – MS: m/z = 394.0 [M–H]$^+$. – Anal. for $C_{20}H_{13}NO_6S$ (395.05): calcd. C 60.75, H 3.31, N 3.54, S 8.11; found C 60.74, H 3.33, N 3.50, S 8.13 %.

*(Z)-5-(2-Methoxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5e**)*

M. p. 306 °C. – R_f = 0.51. – Yield 74 %. – FT-IR (KBr): ν_{max} = 3367, 3080, 2926, 2839, 1722, 1705, 1678, 1612, 1592, 1570, 1485, 1417, 1377, 1313, 1257, 1143, 1020, 840 and 748 cm^{-1}. – ^{1}H NMR: δ = 3.85 (s, 3H, OCH_3), 5.03 (s, 2H, CH_2, coum.), 6.02 (s, 1H, 3-H, coum.), 6.77 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 7.12 – 7.66 (m, 4H, arylidene), 7.74 (d, 1H, 6-H, coum.), 7.97 (s, 1H, -HC=C-), 10.35 (s, 1H, OH, coum.). – MS: m/z = 408.1 [M–H]$^+$. – Anal. for $C_{21}H_{15}NO_6S$ (409.06): calcd. C 61.61, H 3.69, N 3.42, S 7.83; found C 61.59, H 3.71, N 3.40, S 7.81 %.

*(Z)-5-(3-Methoxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5f**)*

M. p. 279 °C. – R_f = 0.56. – Yield 81 %. – FT-IR (KBr): ν_{max} = 3298, 3082, 2972, 2928, 1737, 1705, 1678, 1608, 1560, 1489, 1379, 1417, 1381, 1307, 1274, 1145, 1003 and 784 cm^{-1}. – ^{1}H NMR: δ = 3.85 (s, 3H, OCH_3), 5.03 (s, 2H, CH_2, coum.), 6.02 (s, 1H, 3-H, coum.), 6.77 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 7.12 – 7.66 (m, 4H, arylidene), 7.74 (d, 1H, 6-H, coum.), 7.97 (s, 1H, -HC=C-), 10.35 (s, 1H, OH, coum.). – MS: m/z = 408.1 [M–H]$^+$. – Anal.

for $C_{21}H_{15}NO_6S$ (409.06): calcd. C 61.61, H 3.69, N 3.42, S 7.83; found C 61.60, H 3.70, N 3.44, S 7.80 %.

*(Z)-5-(4-Methoxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5g**)*

M. p. 287 °C. – R_f = 0.62. – Yield 78 %. – FT-IR (KBr): ν_{max} = 3412, 3068, 3014, 2933, 2640, 1726, 1680, 1593, 1551, 1413, 1379, 1332, 1253, 1182, 1149, 1022 and 769 cm^{-1}. – ^{1}H NMR: δ = 3.85 (s, 3H, OCH_3), 5.03 (s, 2H, CH_2, coum.), 6.00 (s, 1H, 3-H, coum.), 6.77 (s, 1H, 8-H, coum.), 6.84 (d, 1H, 5-H, coum.), 7.12 (d, 2H, arylidene), 7.65 (d, 2H, arylidene), 7.74 (d, 1H, 6-H, coum.), 7.96 (s, 1H, -HC=C-), 10.66 (s, 1H, OH, coum.). – MS: m/z = 408.0 $[M–H]^+$. – Anal. for $C_{21}H_{15}NO_6S$ (409.06): calcd. C 61.61, H 3.69, N 3.42, S 7.83; found C 61.61, H 3.60, N 3.41, S 7.82 %.

*(Z)-5-(2-Chlorobenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5h**)*

M. p. 265 °C. – R_f = 0.55. – Yield 54 %. – FT-IR (KBr): ν_{max} = 3412, 3070, 2928, 1687, 1608, 1417, 1375, 1323, 1271, 1138, 1041, 852 and 758 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.94 – 7.56 (m, 4H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.94 (s, 1H, -HC=C-), 10.55 (s, 1H, OH, coum.). – MS: m/z = 411.8 $[M–H]^+$. – Anal. for $C_{20}H_{12}ClNO_5S$ (413.01): calcd. C 58.05, H 32.92, N 3.38, S 7.75; found C 58.00, H 32.94, N 3.39, S 7.71 %.

*(Z)-5-(4-Fluorobenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5i**)*

M. p. 252 °C. – R_f = 0.53. – Yield 65 %. – FT-IR (KBr): ν_{max} = 3398, 3064, 2935, 1724, 1678, 1595, 1512, 1418, 1383, 1323, 1282, 1151 and 740 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.96 (d, 2H, arylidene), 7.58 (d, 2H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.90 (s, 1H, -HC=C-), 10.35 (s, 1H, OH, coum.). – MS: m/z = 395.9 $[M–H]^+$. – Anal. for $C_{20}H_{12}FNO_5S$ (397.04): calcd. C 60.45, H 3.04, N 3.52, S 8.07; found C 60.47, H 3.03, N 3.50, S 8.09 %.

*(Z)-5-(3-Bromobenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5j**)*

M. p. 276 °C. – R_f = 0.54. – Yield 82 %. – FT-IR (KBr): ν_{max} = 3396, 3305, 3066, 2929, 1718, 1680, 1606, 1560, 1419, 1381, 1315, 1136 and 783 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.93 – 7.58 (m, 4H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.90 (s, 1H, -HC=C-), 10.45 (s, 1H, OH, coum.). – MS: m/z = 457.8 $[M–H]^+$. – Anal. for $C_{20}H_{12}BrNO_5S$ (456.96): calcd. C 52.42, H 2.64, N 3.06, S 7.00; found C 52.40, H 2.65, N 3.02, S 7.02 %.

*(Z)-5-(4-Bromobenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5k**)*

M. p. 284 °C. – R_f = 0.59. – Yield 80 %. – FT-IR (KBr): ν_{max} = 3433, 3088, 2937, 2703, 1720, 1691, 1649, 1604, 1423, 1373, 1336, 1273, 1151, 1072 and 762 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.94 (d, 2H, arylidene), 7.64 (d, 2H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.90 (s, 1H, -HC=C-), 10.38 (s, 1H, OH, coum.). – MS: m/z = 457.8 $[M–H]^+$. – Anal. for $C_{20}H_{12}BrNO_5S$ (456.96): calcd. C 52.42, H 2.64, N 3.06, S 7.00; found C 52.41, H 2.65, N 3.08, S 6.98 %.

*(Z)-5-(3-Phenoxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5l**)*

M. p. 200 °C. – R_f = 0.64. – Yield 84 %. – FT-IR (KBr): ν_{max} = 3434, 3267, 3135, 3062, 2931, 1724, 1608, 1487, 1414, 1375, 1317, 1257, 1141, 997 and 777 cm^{-1}. – ^{1}H NMR: δ = 5.01 (s, 2H, CH_2, coum.), 5.98 (s, 1H, 3-H, coum.), 6.75 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.93 – 7.58 (m, 9H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.92 (s, 1H, -HC=C-), 10.25 (s, 1H, OH, coum.). – MS: m/z = 470.0 $[M–H]^+$. – Anal. for $C_{26}H_{17}NO_6S$ (471.08): calcd. C 66.23, H 3.63, N 2.97, S 6.80; found C 66.20, H 3.65, N 2.98, S 6.81 %.

*(Z)-5-[4-(Dimethylamino)benzylidene]-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5m**)*

M. p. > 300 °C. – R_f = 0.50. – Yield 79 %. – FT-IR (KBr): ν_{max} = 3435, 3088, 2926, 2813, 1726, 1678, 1606, 1575, 1525, 1444, 1408, 1371, 1151, 1097 and 713 cm^{-1}. – ^{1}H NMR: δ = 2.84 (s, 6H, $N(CH_3)_2$), 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.95 (d, 2H, arylidene), 7.56 (d, 2H, arylidene), 7.73 (d, 1H, H-6, coum.), 7.95 (s, 1H, -HC=C-), 10.55 (s, 1H, OH, coum.). – MS: m/z = 421.1 $[M–H]^+$. – Anal. for $C_{22}H_{18}N_2O_5S$ (422.09): calcd. C 62.55, H 4.29, N 6.63, S 7.59; found C 62.53, H 4.31, N 6.60, S 7.60 %.

*(Z)-5-(4-hydroxy-3-methoxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5n**)*

M. p. 257 °C. – R_f = 0.51. – Yield 80 %. – FT-IR (KBr): ν_{max} = 3365, 3080, 2924, 1701, 1687, 1610, 1570, 1516, 1417, 1377, 1284, 1139 and 794 cm^{-1}. – ^{1}H NMR: δ = 3.73 (s, 3H, OCH_3), 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.92 – 7.55 (m, 3H, arylidene), 7.74 (d, 1H, 6-H, coum.), 7.94 (s, 1H, -HC=C-), 10.05 (s, 1H, OH, coum.), 10.48 (s, 1H, OH, arylidene). – MS: m/z = 424.1 $[\mathrm{M{-}H}]^+$. – Anal. for $C_{21}H_{15}NO_7S$ (425.06): calcd. C 59.29, H 3.55, N 3.29, S 7.54; found C 59.28, H 3.54, N 3.30, S 7.57 %.

*(Z)-5-(2,4-Dihydroxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5o**)*

M. p. > 300 °C. – R_f = 0.47. – Yield 62 %. – FT-IR (KBr): ν_max = 3412, 3315, 3082, 2922, 2853, 1724, 1701, 1676, 1612, 1572, 1458, 1379, 1417, 1313, 1257, 1145 and 750 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.90 – 7.57 (m, 4H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.95 (s, 1H, -HC=C-), 10.45 (s, 1H, OH, coum.), 10.68 (s, 2H, OH, arylidene). – MS: m/z = 410.1 $[\mathrm{M{-}H}]^+$. – Anal. for $C_{20}H_{13}NO_7S$ (411.04): calcd. C 58.39, H 3.19, N 3.40, S 7.79; found C 58.40, H 3.17, N 3.42, S 7.81 %.

*(Z)-5-(3,4-Dihydroxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5p**)*

M. p. 235 °C. – R_f = 0.42. – Yield 55 %. – FT-IR (KBr): ν_max = 3367, 3091, 3022, 2924, 1734, 1676, 1610, 1585, 1518, 1415, 1381, 1300, 1205, 1145 and 733 cm^{-1}. – ^{1}H NMR: δ = 5.01 (s, 2H, CH_2, coum.), 5.97 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.87 (d, 1H, 5-H, coum.), 6.93 – 7.55 (m, 4H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.95 (s, 1H, -HC=C-), 10.45 (s, 1H, OH, coum.), 10.58 (s,. 2H, OH, arylidene). – MS: m/z = 410.0 $[\mathrm{M{-}H}]^+$. – Anal. for $C_{20}H_{13}NO_7S$ (411.04): calcd. C 58.39, H 3.19, N 3.40, S 7.79; found C 58.38, H 3.21, N 3.41, S 7.81 %.

*(Z)-5-(3,4,5-Trimethoxybenzylidene)-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5q**)*

M. p. 185 °C. – R_f = 0.59. – Yield 86 %. – FT-IR (KBr): ν_max = 3379, 3084, 2972, 1737, 1689, 1607, 1466, 1413, 1373, 1323, 1143, 972 and 732 cm^{-1}. – ^{1}H NMR: δ = 3.76 (s,9H, OCH_3), 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.77 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.98 (s, 2H, arylidene), 7.72 (d,1H, 6-H, coum.), 7.96 (s, 1H, -HC=C-), 10.15 (s, 1H, OH, coum.). – MS: m/z = 468.1 $[\mathrm{M{-}H}]^+$. – Anal. for $C_{23}H_{19}NO_8S$ (469.08): calcd. C 58.84, H 4.08, N 2.98, S 6.83; found C 58.83, H 4.09, N 2.96, S 6.84 %.

*(Z)-5-[(E)-3-Phenylallylidene]-3-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methyl]thiazolidine-2,4-dione (**5r**)*

M. p. 244 °C. – R_f = 0.50. – Yield 48 %. – FT-IR (KBr): ν_max = 3412, 3315, 3082, 2922, 2853, 1724, 1701, 1676, 1612, 1572, 1458, 1379, 1417, 1313, 1257, 1145 and 750 cm^{-1}. – ^{1}H NMR: δ = 5.02 (s, 2H, CH_2, coum.), 5.96 (s, 1H, 3-H, coum.), 6.76 (s, 1H, 8-H, coum.), 6.86 (d, 1H, 5-H, coum.), 6.92 – 7.56 (m, 5H, arylidene), 7.72 (d, 1H, 6-H, coum.), 7.94 – 8.01 (m, 3H, -HC=CH-CH=), 10.55 (s, 1H, OH, coum). – MS: m/z = 404.0 $[\mathrm{M{-}H}]^+$. – Anal. for $C_{22}H_{15}NO_5S$ (405.42): calcd. C 65.18, H 3.73, N 3.45, S 7.91; found C 65.16, H 3.75, N 3.46, S 7.90 %.

Scavenging of the 1,1-diphenyl-2-picrylhydrazyl radical

Determination of the antioxidant activity was performed according to the procedure described in the literature [24,25] with some modifications. DMSO was used as a solvent [23], due to the low solubility of the synthesized compounds in ethanol and methanol.

0.75 mL of a DMSO solution of a synthesized compound (0.2 mM) was added to a DMSO solution of the DPPH radical (0.2 mM), so that the final concentration of DPPH radical and the synthesized compound was 0.1 mM. The mixture was shaken and allowed to stand at r. t. After 30 min the absorbance at λ = 517 nm was determined, and the scavenging activity was calculated according to the formula below. Ascorbic acid was used as a reference compound.

$$scavenging\ activity\ (\%) = \frac{Ab + As - Am}{Ab} \times 100$$

Ab – absorbance of a 0.1 mM DMSO solution of the DPPH radical at λ= 517 nm; As – absorbance of a 0.1 mM DMSO solution of the test compound at λ = 517 nm; Am – absorbance of the DMSO mixture of the test compound and the DPPH radical at λ = 517 nm.

---

[1] B. C. C. Cantello, M. A. Cawthorne, G. P. Cottam, P. T. Duff, D. Haigh, R. M. Hindley, C. A. Lister, S. A. Smith, P. L. Thurlby, *J. Med. Chem.* **1994**, *37*, 3977 – 3985.

[2] C. S. T. Hii, S. L. Howell, *J. Endocrinol.* **1985**, *107*, 1 – 8.

[3] J. G. de Lima, M. Perrissin, J. Chantegrel, C. Luu-Duc, A. Rousseau, G. Narcisse, *Arzneim. Forsch. Drug Res.* **1994**, *44*, 831 – 834.

[4] A. Andreani, M. Rambaldi, A. Locatelli, A. Leoni, R. Bossa, M. Chiericozzi, I. Galatulas, G. Salvatore, *Eur. J. Med. Chem.* **1993**, *28*, 825 – 829.

[5] I. M. Labouta, H. M. Salama, N. H. Eshba, O. Kader, E. El-Chrbini, *Eur. J. Med. Chem.* **1987**, *22*, 485 – 489.

[6] A. J. S. Goes, M. C. A. de Lima, S. L. Galdino, I. R. Pitta, C. Luu-Duc, *Ann. Pharm. Fracaises*. **1991**, *49*, 92 – 98.

[7] M. C. A. Lima, D. L. B. Costa, A. J. S. Goes, S. L. Galdino, I. R. Pitta, C. Luu-Duc, *Pharmazie* **1992**, *47*, 182 – 184.

[8] A. Mori, C. Nishino, N. Enoki, S. Tawata, *Phytochemistry* **1987**, *26*, 2231 – 2234.

[9] H. M. Salama, I. M. Labouta, M. A. Moustafa, *Alex. J. Pharm. Sci.* **1990**, *4*, 44 – 46.

[10] S. A. H. El-Feky, *Pharmazie* **1993**, *48*, 894 – 896.

[11] D. H. Boschelli, D. T. Connor, P. J. Kuipers, C. D. Wright, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 705 – 708.

[12] J. S. Seehra, Y. Xiang, J. E. Bemis, J. McKew, N. Kaila, L. Chen, *WO Patent* 9943672, **1999a**.

[13] J. S. Seehra, J. McKew, F. Lovering, J. E. Bemis, Y. Xiang, L. Chen, J. L. Knopf, *WO Patent* 9943654, **1999b**.

[14] T.-S. Jeong, J.-R. Kim, K. S. Kim, K. H. Cho, K. H. Bae, W. S. Lee, *Bioorg. Med. Chem.* **2004**, *12*, 4017 – 4023.

[15] S. U. Hossain, S. Bhattacharya, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1149 – 1154.

[16] K. C. Fylaktakidou, D. J. Hadjipavlou-Litina, K. E. Litinas, D. N. Nikolaides, *Curr. Pharm. Des.* **2004**, *10*, 3813 – 3833.

[17] D. N. Nicolaides, K. C. Fylaktakidou, K. E. Litinas, D. Hadjipavlou-Litina, *Eur. J. Med. Chem.* **1998**, *33*, 715 – 724.

[18] M. Cacic, M. Trkovnik, F. Cacic, E. Has-Schon, *Molecules* **2006**, *11*, 134 – 147.

[19] S. R. Mahalle, P. D. Netankar, S. P. Bondge, R. A. Mane, *Green Chem. Lett. Rev.* **2008**, *1*, 103 – 106.

[20] H. S. Yathirajan, K. M. L. Rai, S. L. Gaonkar, R. S. Narasegowda, B. Prabhuswamy, M. Bolte, *Acta Cryst. Sect. E* **2005**, *61*, o245 – o246.

[21] H. C. Lin, S. H. Tsai, C. S. Chen, Y. C. Chang, C. M. Lee, Z. Y. Lai, C. M. Lin, *Biochem. Pharmacol.* **2008**, *75*, 1416 – 1425.

[22] H. Tominaga, Y. Kabayashi, T. Goto, K. Kasemura, M. Nomura, *Yakugaku Zasshi*. **2005**, *125*, 371 – 375.

[23] R. Taskova, M. Mitova, B. Mikhova, H. Duddeck, *Z. Naturforsch.* **2003**, *58c*, 704 – 707.

[24] P. Manojkumar, T. K. Ravi, S. Gopalakrishnan, *Eur. J. Med. Chem.* **2009**, *44*, 4690 – 4694.

[25] C.-R. Wu, M.-Y. Huang, Y.-T. Lin, H.-Y. Ju, H. Ching, *Food Chem.* **2007**, *104*, 1464 – 1471.