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Synthesis and NMR spectroscopy investigations of functionalized 8,8,10-trimethyl-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-diones and their spirothiadiazole derivatives

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Abstract New functionalized derivatives of 8,8,10-trimethyl-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*]-chromene-2,6-dione – analogues of the natural compound graveolone – possessing hydrazine, hydroxylamine, and thiosemicarbazide residues were synthesized and their reactions with acetic anhydride were studied. The structure of the obtained compounds was confirmed by NMR spectroscopy.

Keywords Heterocycles; Natural products; NMR spectroscopy; Neoflavones; 8,8,10-Trimethyl-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-dione.

Introduction

Derivatives of 4-phenyl-2*H*-chromen-2-ones, or neoflavones, are widespread in nature. By today, more than 130 corresponding compounds have been extracted from natural sources [1]. These neoflavones exhibit bactericidal [2], insecticidal [3], hypoglycemic [4], antitumor [5], antimalarial [6], cytotoxic [7] activities, and possess HIV-1 reverse transcriptase inhibition properties. At the same time, neoflavones are suitable targets for chemical modification [8]. Their synthetic derivatives show antioxidant [9], antiatheroscletoric [10], cytotoxic [11], and antibacterial [12, 13] properties. Also, it is rather common for natural neoflavones to contain a pyran or furan ring annulated with the benzopyran-2-one system.

This work is devoted to the synthesis of such natural compounds through modification of dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-dione at the exocyclic oxygen atom, which leads to the formation of nitrogen-containing derivatives functionalized at position 6.

Results and discussion

The starting linear 8,8,10-trimethyl-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-dione (**1**, Fig. 1) – a modified analogue of graveolone (Formulae) – was synthesized by *Kabbe* cyclization of 6-acetyl-7-hydroxy-8-methyl-4-phenyl-2*H*-chromene-2-one with acetone in the presence of pyrrolidine, which resulted in the 2,2-dimethylpyranone ring formation [14, 15].

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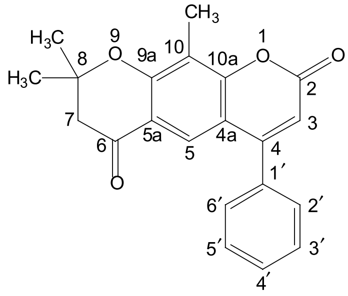
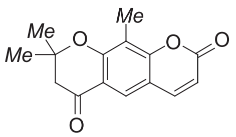
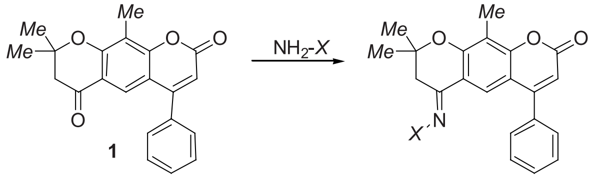


Fig. 1 8,8,10-Trimethyl-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-dione and its numbering scheme



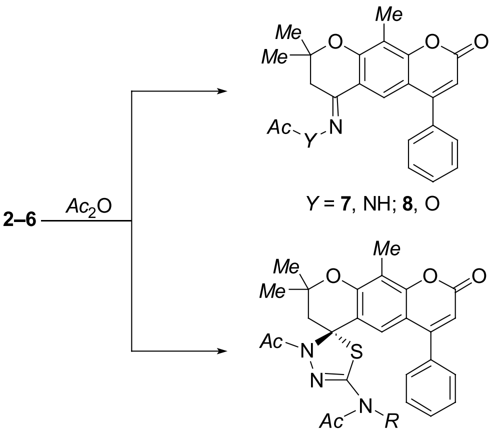
graveolone

Further treatment of dihydropyrano[3,2-*g*]chromene-2,6-dione **1** with several nucleophilic reagents, such as hydrazine hydrate, hydroxylamine, thiosemicarbazide, *N*-methylthiosemicarbazide, and *N*-phenylthiosemicarbazide led to 8,8,10-trimethyl-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-dione 6-hydrazone (**2**), 6-oxime (**3**), 6-thiosemicarbazone (**4**), 6-(*N*-methylthiosemicarbazone) (**5**) and 6-(*N*-phenylthiosemicarbazone) (**6**) (Scheme 1). Only the exocyclic oxygen atom of the 2,2-dimethyl-2,3-dihydropyran-4-one ring, and not the oxygen atom of the benzopyran-2-one ring, was attacked by



X = **2**, NH_2; **3**, OH; **4**, NH-CS-NH_2; **5**, NH-CS-NH-CH_3; **6**, -NH-CS-NH-*Ph*

Scheme 1



R = **9**, H; **10**, CH_3; **11**, *Ph*

Scheme 2

the nucleophiles, even when a three-fold excess of the latter was used.

Subsequent acylation of **2**–**6** led to *N*- and *O*-acyl derivatives of hydrazone **2** and oxime **3** – *N*′-[8,8,10-trimethyl-2-oxo-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano-

Table 1 ^1H chemical shifts (δ/ppm) of **2–11** in *DMSO*-d_6

No.	H-3[a]	H-5[a]	7-CH_2	8-CH_3 (×2)[a]	10-CH_3[a]	H-2′, 6′[b]	H-3′, 4′, 5′[c]	Other signals
2	6.04	7.69	2.50[a]	1.42	2.29	7.39	7.44	5.07 (wide s, 6-NNH_2)
3	6.12	7.73	2.77[a]	1.38	2.26	7.45	7.54	11.16 (s, 6-NOH)
4	6.17	7.95	2.90[a]	1.39	2.26	7.51	7.54	7.05 (s, NH), 8.18 (s, NH), 10.44 (s, NH)
5	6.19	7.97	2.89[a]	1.39	2.26	7.46	7.56	3.01 (s, N-CH_3), 7.74 (s, NH), 10.50 (s, NH)
6	6.18	8.17	2.93[a]	1.42	2.28	7.43	7.58	6.74 (H-2″,4″,6″), 7.17 (m, H-3″,H-5″), 9.76 (s, NH), 10.76 (s, NH)
7	6.17	7.93	2.75[a]	1.40	2.27	7.51	7.56	10.47 (s, NH), 2.01 (s, N*Ac*)
8	6.19	7.89	2.96[a]	1.43	2.28	7.49	7.56	2.15 (s, NO*Ac*)
9	6.23	7.26	2.51[d], 3.25[e,f]	1.31[e], 1.47[d]	2.19	7.39	7.53	2.07 (s, *Ac*N-*TDA*), 1.99 (s, *Ac*NH-*TDA*), 11.66 (s, NH)
10	6.19	7.32	2.54[d], 3.34[e,f]	1.39[e], 1.48[d]	2.10	7.47	7.56	1.89 (s, *Ac*N-*TDA*), 2.26 (s, *Ac*NCH_3-*TDA*), 3.01 (s, *Ac*N*CH*$_3$-*TDA*)
11	6.18	7.28	2.85[d], 3.15[e,f]	1.42[e], 1.48[d]	2.11	7.42	7.59	1.86 (s, *Ac*N-*TDA*), 2.24 (s, *Ac*N*Ph*), 7.17, 6.79 (m, *Ac*N*Ph*)

[a] s.; [b] d., $J = 8.8$ Hz; [c] m.; [d] *pro-S*; [e] *pro-R*; [f] 2 × d., $J = 14.0$ Hz

[3,2-*g*]chromen-6-ylidene]acetohydrazide (**7**) and 8,8,10-trimethyl-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-dione 6-(*O*-acetyloxime) (**8**); in case of thiosemicarbazides **4**–**6** cyclization of the thiosemicarbazide residue into the 1,3,4-thiadiazoline ring occurred, leading to the formation of the corresponding *N*-[3′-acetyl-2,2,10-trimethyl-8-oxo-6-phenyl-2,3-dihydro-3′*H*,8*H*-spiro[pyrano[3,2-*g*]chromene-4,2′-[1,3,4]thiadiazol]-5′-yl]acetamide (**9**), -*N*-methylacetamide (**10**), and -*N*-phenylacetamide (**11**) (Scheme 2).

^{1}H and ^{13}C NMR data confirmed the structures of **2**–**11**. ^{1}H NMR spectra (Table 1) of **2**–**11** corresponded to the proposed structures; however, since the skeleton of the molecules is complex and lactone derivatives are known to be unstable in the presence of nucleophilic reagents, ^{13}C NMR spectra were measured to prove the structure of the compounds (Table 2).

The ^{13}C NMR absorption of C-6 in compounds **2**–**8** occurs at 136.1–151.4 ppm, whereas it is observed at $\delta = 74.7$–76.9 ppm for **9**–**11**. For comparison, the chemical shift of the C-6 in dihydropyrano[3,2-*g*]-chromene-2,6-dione **1** is 196.8 ppm. The substitution affects not only the C-6 atom, but more distant atoms as well. For example, the C-7 signal of compound **1** is observed at 49.5 ppm and, upon the substitution of the oxygen atom at C-6 with nitrogen atom in hydrazone **2**, oxime **3** and thiosemicarbazides **4**–**6**, experiences an upfield shift (31.7–33.8 ppm). A lesser effect of the substituent at C-6 on the chemical shift of C-8 is also observed. ^{1}H and ^{13}C NMR signals of other atoms of molecules **2**–**6** are insensitive to changes at C-6. The ^{1}H and ^{13}C NMR peaks in the spectra of acyl derivatives of hydrazone and oxime (**7** and **8**) can be reliably assigned; in the case of **9**–**11** a more detailed discussion is required.

Table 2 ^{13}C chemical shifts (δ/ppm) of **1**–**11** in *DMSO*-d$_6$

No.	C-2	C-3	C-4	C-4a	C-5	C-5a	C-6	C-7	C-8	C-9a
1	160.8	112.7	155.4	111.6	123.2	116.9	196.8	49.5	78.3	156.4
2	159.9	112.4	154.5	111.8	128.5	113.5	136.1	33.8	96.1	156.1
3	159.6	112.5	155.8	112.1	128.5	113.9	146.1	33.4	96.1	155.1
4	160.8	112.7	155.3	111.9	126.9	113.7	146.5	31.7	94.8	156.3
5	159.9	112.6	155.4	111.8	127.6	113.9	146.5	31.7	96.1	156.8
6	159.9	112.7	155.3	111.6	126.9	112.9	145.8	32.9	95.8	155.4
7	160.8	112.7	155.4	111.8	123.6	113.9	146.5	30.1	96.3	156.8
8	160.8	112.5	155.4	111.6	123.8	113.7	151.4	34.2	97.3	156.8
9	160.4	112.4	155.3	112.9	123.4	122.7	74.7	44.8	77.1	154.2
10	160.8	112.7	155.4	111.5	123.7	121.7	76.8	45.6	68.0	153.2
11	160.8	112.7	155.4	111.5	123.7	121.7	76.9	44.6	75.4	153.2

No.	C-10	C-10a	8-CH$_3$ (×2)	10-CH$_3$	C-1′	C-2′,6′	C-3′,5′	C-4′	Other signals
1	119.0	155.4	26.7	8.6	140.0	126.4	128.7	128.0	–
2	118.5	152.5	27.3	8.4	128.2	129.5	116.3	128.9	–
3	119.1	153.5	27.1	9.6	129.1	129.7	115.1	128.3	–
4	119.2	152.8	27.3	9.8	130.3	128.9	116.5	128.6	181.4 (C=S)
5	119.2	153.4	27.1	9.6	127.9	129.7	115.6	128.0	176.8 (C=S), 34.3 (NH–CH$_3$)
6	119.1	153.3	27.3	9.8	128.7	129.6	115.4	127.8	178.0 (C=S), 137.6, 126.3, 129.3, 123.9 (NH–*Ph*)
7	119.2	153.3	27.0	10.2	134.2	126.4	123.9	128.3	25.3, 173.4 (6-NNH-*Ac*)
8	119.1	153.6	27.7	9.6	136.1	126.4	125.3	128.4	18.3, 168.3 (6-NO-*Ac*)
9	113.4	152.7	25.8^a, 30.3^b	8.9	135.6	129.1	129.6	130.6	23.0, 168.2 (*Ac*), 22.7, 171.5 (*Ac*NH), 143.6 (*TDA*-C-5)
10	115.6	148.2	24.6^a, 29.4^b	9.4	136.3	126.4	128.7	130.1	23.0, 168.2 (*Ac*), 20.2, 173.0 ($\underline{Ac}$NCH$_3$), 26.2 (*Ac*N$\underline{CH_3}$), 145.8 (*TDA*-C-5)
11	118.9	148.2	26.3^a, 31.0^b	9.2	140.0	126.4	128.7	128.0	23.0, 168.2 (*Ac*), 20.1, 174.1 ($\underline{Ac}$N*Ph*), 121.6, 124.4, 129.0, 135.3, (*Ac*N$\underline{Ph}$), 148.3 (*TDA*-C-5)

[a] *pro-R*; [b] *pro-S*

The NMR spectra of **9–11** correspond to their expected structures, but an unequivocal assignment of all signals cannot be done using ^{1}H and ^{13}C NMR spectra data alone. The assignment becomes possible only be means of two-dimensional ^{1}H–^{13}C shift correlation *via* one bond (HMQC) and long-range (HMBC) experiments. Table 3 summarizes the coordinates of cross-peaks observed in HMQC and HMBC spectra of corresponding compounds

Table 3 Heteronuclear correlation data for **9–11**

No.	^{1}H NMR signal, δ/ppm	13C NMR signals which correlate with ^{1}H NMR signal, δ/ppm	
		HMQC	HMBC
9	1.31	25.8	30.3, 44.8, 77.1
	1.47	30.3	25.8, 44.8, 74.7, 77.1, 154.2
	1.99	22.7	143.6, 171.5
	2.07	23.0	168.2
	2.19	8.9	113.4, 123.4, 152.7, 154.2
	2.51	44.8	74.7, 122.7
	3.25	44.8	25.8, 30.3, 74.7, 77.1
	6.23	112.4	112.9, 135.6, 160.4
	7.26	123.4	74.7, 113.4, 122.7, 152.7, 154.2, 155.3
	7.36	129.1	129.1, 130.6, 155.3
	7.53	129.6, 130.6	129.1, 129.6, 135.6
	11.66	–	143.6, 171.5
10	1.39	24.6	29.4, 45.6, 68.0
	1.48	29.4	24.6, 45.6, 76.8, 68.0, 153.2
	1.89	23.0	168.2
	2.10	9.4	115.6, 123.7, 148.2, 153.2
	2.26	20.2	145.8, 173.0
	2.54	45.6	76.8, 121.7
	3.01	26.2	145.8, 173.0
	3.34	45.6	24.6, 29.4, 68.0, 76.8
	6.19	112.7	111.5, 136.3, 160.8
	7.32	123.7	76.8, 115.6, 121.7, 148.2, 153.2, 155.4
	7.47	126.4	126.4, 130.1, 155.4
	7.56	128.7, 130.1	126.4, 128.7. 136.3
11	1.42	26.3	31.0, 44.6, 75.4
	1.48	31.0	26.3, 44.6, 75.4, 76.9, 153.2
	1.86	23.0	168.2
	2.11	9.2	118.9, 123.7, 148.2, 153.2
	2.24	20.1	148.3, 174.1
	2.85	44.6	76.9, 121.7
	3.15	44.6	26.3, 31.0, 75.4, 76.9
	6.18	112.7	111.5, 140.0, 160.8
	6.79	124.4, 129.0	121.6, 129.0, 135.3
	7.17	121.6	121.6, 124.4, 148.3, 174.1
	7.28	123.7	76.9, 118.9, 121.7, 148.2, 153.2, 155.4
	7.42	126.4	126.4, 128.0, 155.4
	7.59	128.0, 128.7	126.4, 128.7, 140.0

A more detailed explanation of the spectra of **9** is provided to clarify the obtained results. Two singlets with chemical shifts of 7.26 and 6.23 ppm (which corresponds to aromatic protons absorption region) are observed in the ^{1}H NMR spectra; these two signals are assigned to H-5 and H-3 protons. The H-3 signal correlates with a low-field ^{13}C NMR signal at $\delta = 160.4$ ppm. This allows to assign this signal to the C-2 atom, which is separated from the H-3 by two chemical bonds. The presence of H-3–H-3′ correlation signals with a ^{13}C signal at 135.6 ppm lets us to assign the latter signal to the C-1′ atom. The assignment of a ^{13}C NMR signal at 155.3 ppm to the C-4 follows from its correlations with H-2′ and H-5 proton signals. The nodal C-9a and C-10a atoms can be assigned based on correlations of their signals with C-10 methyl proton signals; the correlations also identify the ^{13}C signal of the mentioned methyl group. Signals of methyl residues of *N*-acetyl groups are assigned from their correlations with corresponding carbonyl C atoms. Bearing in mind that the signal of the NH-proton correlates with a ^{13}C NMR signal of one of the carbonyls (at 171.5 ppm), all the signals of acetyl fragments may be reliably assigned. A scheme which shows the assignments and the most important HMBC correlations upon which the assignments were based is shown in (Fig. 2).

HMBC correlations also allow to draw conclusions regarding orientation of hydrogen atoms in conformationally unrestricted pyran ring of the compound. Two doublets of two nonequivalent protons with chemical shifts at $\delta = 3.25$ and 2.51 ppm are observed in the ^{1}H NMR spectra. The latter of the signals is correlated with the ^{13}C-signal of the C-5a atom, while the signal at $\delta = 3.25$ ppm is not; a lack of HMBC correlation means that a corresponding spin–spin coupling constant ^{3}J(H,C) is close to zero, which is possible only when dihedral angle between H – C-7 and C-6–C-5a bonds is close to 90°. This implies that the H-7 proton with a chemical shift of 3.25 ppm assumes axial (*pro-R*) orientation, while the signal at 2.51 ppm corresponds to an equatorial (*pro-S*) hydrogen atom. Similarly, it can be shown that a methyl group 8-CH_3, which gives a ^{1}H NMR signal at $\delta = 1.47$ ppm, is oriented equatorially (*pro-S*), based on the presence of correlation of the signal of its protons with the ^{13}C NMR signal of the nodal

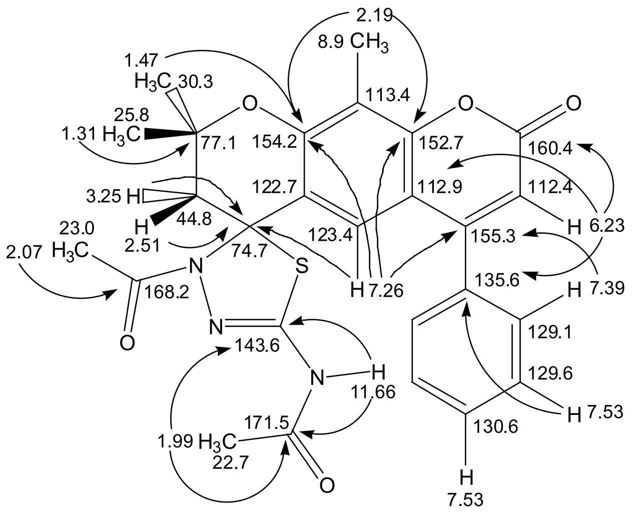


Fig. 2 Heteronuclear correlations in compound **9**

C-9a atom *via* four bonds. The fact that ^4J(H,C) between these atoms is visible can be explained by the *zig-zag* conformation of chemical bonds between them (*W*-conformation). The structure of **10** and **11** was confirmed similarly.

Therefore, it was shown that among the two possibilities (C-2 and C-6), the nitrogen-containing nucleophilic reagents used selectively attack the 8,8,10-trimethyl-4-phenyl-7,8-dihydro-2*H*,6*H*-pyrano-[3,2-*g*]chromene-2,6-dione at position 6. In this way, a series of nitrogen-containing functionalized derivatives of neoflavones was obtained; these compounds are of great interest regarding their physicochemical properties and biological activity.

Experimental

Reaction flow and identity of obtained compounds was controlled with TLC on Merck F_{254} plates using chloroform: methanol (9/1, *v*/*v*) and (95/5, *v*/*v*) systems as eluents. Melting points were determined using a *Kofler*-type Leica Galen III micro hot stage microscope. NMR spectra were recorded on a Mercury-400 spectrometer (spectrometer frequency for ^{1}H: 400 MHz, ^{13}C: 100 MHz) from *DMSO*-d_6 solutions. The *TMS* signal was used as an internal standard. HMQC spectra were acquired as 128 × 32 data matrices with spectral ranges: for ^{1}H–4 kHz, for 13C–21 kHz; mixing time corresponds to $^1I_{CH} = 140$ Hz. HMBC spectra were acquired as 400 × 32 data matrices with spectral ranges: for ^{1}H–4 kHz, for ^{13}C–21 kHz; mixing time corresponds to $^{2-3}I_{CH} = 8$ Hz. Spectra were measured with detection on protons and gradient selection of signals. Elemental analyses for C, H, and N were conducted using a Perkin-Elmer C, H, and N Analyzer, their results were found to be in good agreement (±0.2%) with the calculated values. Mass spectra were recorded on an Agilent 1100 LC/MSD instrument with chemical ionization (CI).

6-Acetyl-7-hydroxy-8-methyl-4-phenyl-2*H*-chromene-2-one, which was used to obtain 8,8,10-trimethyl-4-phenyl-7,8-dihydropyrano[3,2-*g*]chromene-2,6-dione (**1**), was synthesized from a corresponding 7-hydroxy-8-methyl-4-phenylcoumarin by acylation followed by a *Fries* rearrangement [16].

8,8,10-Trimethyl-4-phenyl-7,8-dihydropyrano[3,2-g]-chromene-2,6-dione (**1**, $C_{21}H_{18}O_4$)
To a solution of 5.89 g 6-acetyl-7-hydroxy-8-methyl-4-phenyl-2*H*-chromene-2-one (20 mmol) in 40 cm^3 acetonitrile, 5.1 cm^3 pyrrolidine (50 mmol) and 10.3 cm^3 acetone (14 mmol) were added. The reaction mixture was kept at 45°C for 8 h (the reaction completeness was monitored with TLC). The resulting solution was diluted with ice H_2O, acidified to *pH* 5 and filtered. Recrystallization from acetonitrile afforded 3.76 g (56%) **1**. Mp 185–186°C; ^{1}H NMR: $\delta = 1.47$ (s, CH_3-8), 2.30 (CH_3-10), 2.77 (s, CH_2-7), 6.21 (s, H-3), 7.46 (m, H-2′, H-6′), 7.56 (m, H-3′, H-4′, H-5′), 7.70 (s, H-5) ppm; MS: $m/z = 335.4$ ([MH]$^+$).

8,8,10-Trimethyl-4-phenyl-7,8-dihydropyrano[3,2-g]-chromene-2,6-dione 6-hydrazone (**2**, $C_{21}H_{20}N_2O_3$)
To a solution of 0.33 g **1** (1 mmol) in 5 cm^3 anhydr. pyridine 1.5–3 mmol of hydrazine hydrate were added. The reaction mixture was boiled for 1 h (the reaction completeness was monitored with TLC). After the reaction was complete, the mixture was poured in 50 cm^3 of ice-H_2O, acidified to neutral *pH* and filtered. Recrystallization from propan-2-ol afforded 0.28 g (82%) **2**. Mp 228–229°C; MS: $m/z = 349.4$ ([MH]$^+$).

8,8,10-Trimethyl-4-phenyl-7,8-dihydropyrano[3,2-g]-chromene-2,6-dione 6-oxime (**3**, $C_{21}H_{19}NO_4$)
To a solution of 0.33 g **1** (1 mmol) in 5 cm^3 anhydr. pyridine 1.5–3 mmol of hydroxylamine hydrochloride were added. The reaction mixture was kept on an oil bath at 120–150°C for 1 h (the reaction completeness was monitored with TLC). After the reaction was complete, the mixture was poured in 50 cm^3 of 5% acetic acid and filtered. Recrystallization from propan-2-ol afforded 0.3 g (88%) **3**. Mp 284–285°C; MS: $m/z = 350.4$ ([MH]$^+$).

General procedure for the preparation of 8,8,10-trimethyl-4-phenyl-7,8-dihydropyrano[3,2-g]chromene-2,6-dione thiosemicarbazones (***4–6***)
To a solution of 1.1 g **1** (3 mmol) in 10 cm^3 ethanol an alcoholic solution of 3.5 mmol of a corresponding thiosemicarbazide with 1 cm^3 HCl was added dropwise. The reaction mixture was kept on a water bath for 3–5 h. The formed precipitate was filtered off and crystallized from propan-2-ol.

8,8,10-Trimethyl-4-phenyl-7,8-dihydropyrano[3,2-g]-chromene-2,6-dione 6-thiosemicarbazone (**4**, $C_{22}H_{21}N_3O_3S$)
Yield 1.14 g (85%); mp 257–259°C; MS: $m/z = 408.5$ ([MH]$^+$).

8,8,10-Trimethyl-4-phenyl-7,8-dihydropyrano[3,2-g]-chromene-2,6-dione 6-(N-methylthiosemicarbazone)
(**5**, $C_{23}H_{23}N_3O_3S$)
Yield 0.98 g (61%); mp 268–270°C; MS: $m/z = 422.5$ ($[MH]^+$).

8,8,10-Trimethyl-4-phenyl-7,8-dihydropyrano[3,2-g]-chromene-2,6-dione 6-(N-phenylthiosemicarbazone)
(**6**, $C_{28}H_{25}N_3O_3S$)
Yield 0.98 g (61%); mp 254–256°C; MS: $m/z = 484.6$ ($[MH]^+$).

*General procedure for the preparation of acyl derivatives of 8,8,10-trimethyl-4-phenyl-7,8-dihydropyrano[3,2-g]-chromene-2,6-dione 6-hydrazone **7** and 6-oxime **8***
A suspension of 1 mmol of hydrazone **2** or oxime **3** in 0.2 cm^3 acetic anhydride (2 mmol) was heated in the presence of catalytic quantities of pyridine (2–3 drops) until complete dissolution. The reaction solution was then kept at room temperature until a precipitate was formed, then the reaction mixture was introduced into 50 cm^3 of ice H_2O. The precipitate was filtered off and crystallized from methanol.

N′-[8,8,10-Trimethyl-2-oxo-4-phenyl-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-6-ylidene]acetohydrazide
(**7**, $C_{23}H_{22}N_2O_4$)
Yield 0.32 g (84%); mp 307–309°C; MS: $m/z = 391.4$ ($[MH]^+$).

8,8,10-Trimethyl-4-phenyl-7,8-dihydro-2H,6H-pyrano[3,2-g]-chromene-2,6-dione 6-(O-acetyloxime) (**8**, $C_{23}H_{21}NO_5$)
Yield 0.29 g (76%); mp 210–211°C; MS: $m/z = 392.4$ ($[MH]^+$).

*General procedure for the preparation of N-[3′-acetyl-2,2,10-trimethyl-8-oxo-6-phenyl-2,3-dihydro-3′H,8H-spiro[pyrano-[3,2-g]chromene-4,2′-[1,3,4]thiadiazol]-5′-yl]acetamides (**9–11**)*
A solution of 1 mmol of a corresponding thiosemicarbazone **4–6** in 10 cm^3 acetic anhydride was refluxed at a water bath for 6–7 h. The reaction mixture was left to cool to room temperature and then poured on ice. The formed precipitate was filtered off and crystallized from aqueous propan-2-ol (20/80, *v/v*).

N-[3′-Acetyl-2,2,10-trimethyl-8-oxo-6-phenyl-2,3-dihydro-3′H,8H-spiro[pyrano[3,2-g]chromene-4,2′-[1,3,4]-thiadiazol]-5′-yl]acetamide (**9**, $C_{26}H_{25}N_3O_5S$)
Yield 0.29 g (60%); mp 241–243°C; MS: $m/z = 492.6$ ($[MH]^+$).

N-[3′-Acetyl-2,2,10-trimethyl-8-oxo-6-phenyl-2,3-dihydro-3′H,8H-spiro[pyrano[3,2-g]chromene-4,2′-[1,3,4]-thiadiazol]-5′-yl]-N-methylacetamide (**10**, $C_{27}H_{27}N_3O_5S$)
Yield 0.26 g (52%); mp 256–258°C; MS: $m/z = 506.6$ ($[MH]^+$).

N-[3′-Acetyl-2,2,10-trimethyl-8-oxo-6-phenyl-2,3-dihydro-3′H,8H-spiro[pyrano[3,2-g]chromene-4,2′-[1,3,4]-thiadiazol]-5′-yl]-N-phenylacetamide (**11**, $C_{32}H_{29}N_3O_5S$)
Yield 0.23 g (41%); mp 239–240°C; MS: $m/z = 568.7$ ($[MH]^+$).

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References

1. Garazd MM, Garazd YaL, Khilya VP (2003) Chem Nat Compounds 39:54
2. Cakraborty DP, Chatterji D (1969) J Org Chem 34:3784
3. Finnegan RA, Morris MP, Djerassi C (1961) J Org Chem 26:1180
4. Korec R, Sensch KH, Zoukas T (2000) Arzneim Forsch 50:122
5. Itoigawa M, Ito C, Tan HTW, Kuchide M, Tokuda H, Nishino H, Furukawa H (2001) Cancer Lett 169:15
6. Kohler I, Jenett-Siems K, Mockenhaupt FP, Siems K, Jakupovic J, Gonzalez JC, Hernandez MA, Ibarra RA, Berendsohn WG, Bienzle U, Eich E (2001) Planta Med 67:89
7. Guilet D, Helesbeux JJ, Seraphin D, Sevenet T, Richomme P, Bruneton J (2001) J Nat Prod 64:563
8. Garazd MM, Garazd YaL, Khilya VP (2005) Chem Nat Compounds 41:245
9. Lee JM, Tseng TH, Lee YJ (2001) Synthesis:2247
10. Meguro K, Tawada H, Ikeda H (1991) Pat WO 9112249; Chem Abstr 115:279815
11. Bailly C, Bal C, Babier P, Combes S, Finet JP, Hildebrand MP, Peyrot V, Wattez N (2003) J Med Chem 46:5437
12. Shah S, Vyas R, Mehta RH (1991) J Indian Chem Soc 68:411
13. Desai P, Mehta R (1996) Indian J Heterocycl Chem 5:319
14. Kabbe HJ (1978) Synthesis:886
15. Kabbe HJ, Widdig A (1982) Angew Chem 94:254
16. Moskvina VS, Khilya VP (2008) Chem Nat Compounds 44:15