REACTIONS OF SUBSTITUTED FURO[3,2-*b*]PYRROLE-5-CARBOHYDRAZIDES UNDER CLASSICAL AND MICROWAVE CONDITIONS

Renata GAŠPAROVÁ[a1], Margita LÁCOVÁ[b] and Alžbeta KRUTOŠÍKOVÁ[a2,*]

[a] *Department of Chemistry, Faculty of Natural Sciences, University of St. Cyril and Methodius, Námestie Jozefa Herdu 2, Sk-917 01 Trnava, Slovak Republic; e-mail: [1] renata.gasparova@ucm.sk, [2] alzbeta.krutosikova@ucm.sk*

[b] *Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Mlynská dolina CH-2, Sk-842 15 Bratislava, Slovak Republic; e-mail: lacova@fns.uniba.sk*

Received September 21, 2004
Accepted July 8, 2005

Substituted hydrazones **5** and **6** were synthesized by the reaction of the corresponding furo[3,2-*b*]pyrrole-5-carboxyhydrazides **1** with 6-substituted 4-oxochromene-3-carbaldehydes **2** and methyl 2-formylfuro[3,2-*b*]pyrrole-5-carboxylates **3** under microwave irradiation as well as by the classical method. The beneficial effect of the microwave irradiation on these reactions was a shortening of the reaction time and an increase in the yields. The reactions of **1** with 4-[(4-oxochromen-3-yl)methylidene]-2-phenyloxazol-5(4*H*)-one (**4**) were also studied. Compounds **7** or **8** were obtained, depending on the reaction temperature.

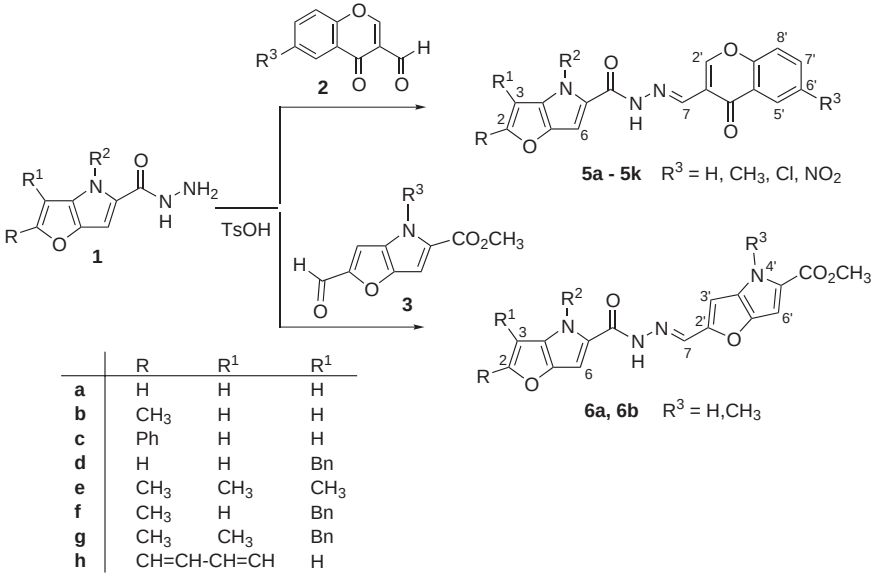
Keywords: 4-Oxochromene-3-carbaldehydes; Furo[3,2-*b*]pyrrole-5-carbohydrazides; Methyl 2-formylfuro[3,2-*b*]pyrrole-5-carboxylates; Hippuric acid; Fused heterocycles; Hydrazones; Microwave irradiation.

N-Aroyl and *N*-heteroaroyl hydrazones have been described as useful building blocks for various heterocyclic rings[1–3]. A large number of hydrazones have exhibited a wide variety of biological activities, e.g. antibacterial[4], analgesic and anti-inflammatory[5], antimycobacterial[6] and the reduction of the fatigue of skeletal muscles[7]. Synthesis and study of physical and chemical properties of heterocyclic compounds containing furan ring fused with various heterocycles, including furo[3,2-*b*]pyrrole derivatives, attracted a great interest during the recent decades[8]. The benzopyrane moiety is known as the structural unit of many natural products and pharmaceuticals[9–11], and has been widely used as a synthetic intermediate[12–14].

In continuation of our program aimed at developing efficient syntheses of fused oxygen-nitrogen containing heterocycles, we have reported the use of substituted furo[3,2-*b*]pyrroles and their derivatives in synthesis[15–19]. 4-Oxochromene-3-carbaldehyde and its derivatives have also played an important role in our research[20–23] because of their biological activity as well as their synthetic potential.

The use of microwave irradiation in organic synthesis has become highly valued for its remarkable influence on the rate enhancement of a wide variety of reactions as well as on the purity and yields of products[24–27].

The aim of this study was to synthesize some new hydrazones **5a**–**6b** derived from furo[3,2-*b*]pyrrole-5-carbohydrazides **1** by their reactions with substituted 4-oxochromene-3-carbaldehydes **2** and methyl 2-formylfuro-[3,2-*b*]pyrrole-5-carboxylates **3** (Scheme 1). Our goal was to obtain new compounds with potential biological activity and to compare the classical method with the effect of microwave irradiation, with a view to finding conditions under which the yield or the rate of reaction would increase.



	R	R^1	R^1
a	H	H	H
b	CH_3	H	H
c	Ph	H	H
d	H	H	Bn
e	CH_3	CH_3	CH_3
f	CH_3	H	Bn
g	CH_3	CH_3	Bn
h	CH=CH-CH=CH		H

SCHEME 1

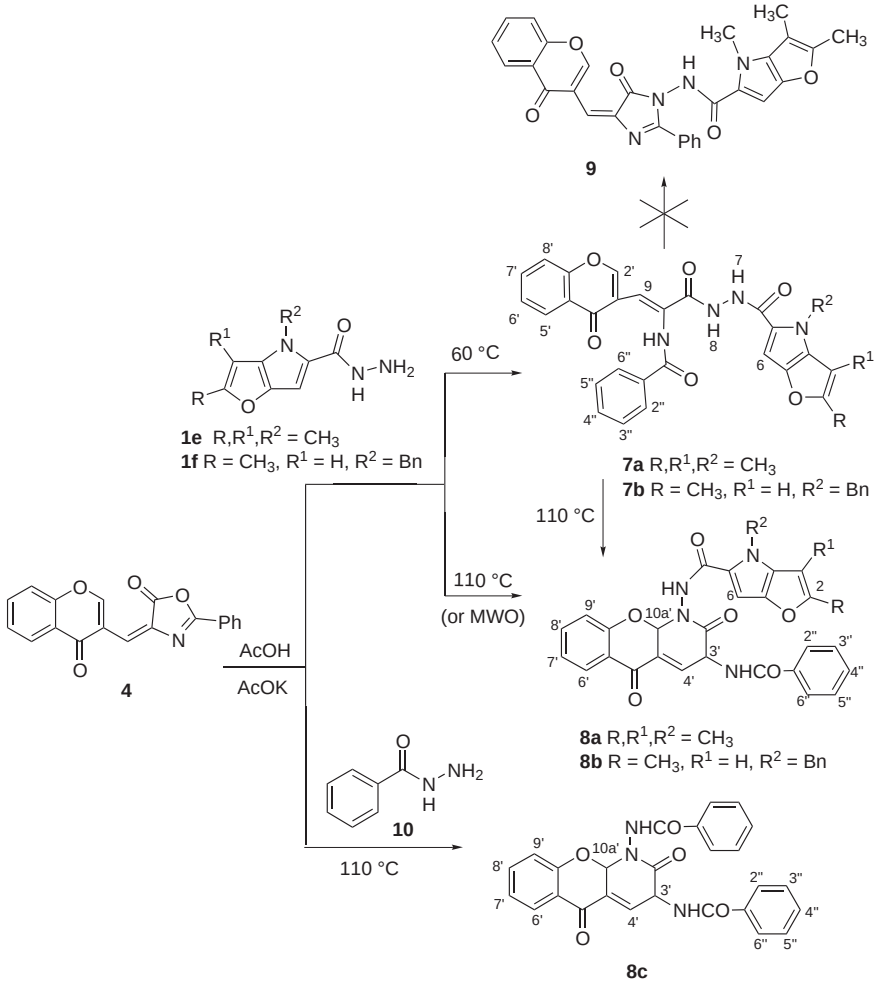
Another goal of this study was to investigate the reactions of **1** with 5-oxo-4,5-dihydrooxazole derivatives **4** which constitute an efficient method of the synthesis of *N*-heterocycles (Scheme 2).

RESULTS AND DISCUSSION

N'-[(6-R^3-4-Oxochromen-3-yl)methylidene]-2-R^1-3-R^2-4-R-furo[3,2-*b*]-pyrrole-5-carbohydrazides **5a**–**5k** and *N'*-{[(4-R^3-5-methoxycarbonyl)furo-[3,2-*b*]pyrrol-2-yl]methylidene}-2-R^1-3-R^2-4-R-furo[3,2-*b*]pyrrole-5-carbohydrazides **6a**, **6b** were synthesized in high yields (72–83%) by the reaction

of **1** with **2** and **3**, respectively, in ethanol in the presence of 4-methylbenzene-1-sulfonic acid by heating at 50–60 °C over 1–4.5 h.

Microwave-assisted synthesis of **5a**–**6b** was performed using an output of 90 W. The reaction times were only 4–9 min, while the yields were comparable or slightly higher (73–94%) than those achieved under the classical conditions (Table I). The ^{1}H NMR spectra of compounds **5a**–**6b** displayed the signals of H-6 pyrrole protons in the 6.47–7.23 ppm range, and the signals of H-7 of the double bond in 8.10–8.70 ppm range. The resonance signals and their multiplicity confirmed the proposed structures.



SCHEME 2

It is known that the reactions of aldehydes with hippuric acid lead to oxazol-5(4*H*)-one derivatives[28,29], which can serve as precursors of amino acids[30] or as convenient reagents for the synthesis of new heterocycles[31]. Thus, Nálepa and co-workers[32] described the synthesis of 1-(arylamino)-substituted imidazol-5(4*H*)-ones by the treatment of substituted 4-aryliden-2-phenyloxazol-5(4*H*)-ones with substituted phenylhydrazines. Therefore, we investigated the reaction of 4-[(4-oxochromen-3-yl)methylidene]-2-phenyloxazol-5(4*H*)-one (**4**) with 2,3,4-trimethylfuro[3,2-*b*]pyrrole-5-carbohydrazide (**1e**) with the intention to obtain compound **9**, as this process would offer a convenient synthetic route to furo[3,2-*b*]pyrrole derivatives, bearing the chromone as well as imidazolone moieties.

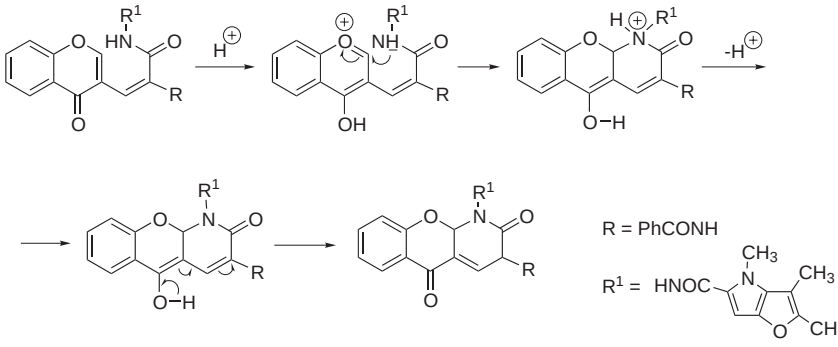
TABLE I
Yields and reaction times of compounds **5a**–**8c** in microwave method (MW) and classical method (C)

Comp.	R	R^1	R^2	R^3	Yield, %		Rection time min	Rection time h
					MW	C	MW	C
5a	C_6H_5	H	H	H	86	80	8	4
5b	C_6H_5	H	H	Cl	83	80	5	4
5c	H	H	$CH_2C_6H_5$	NO_2	80	72	4	2
5d	CH_3	H	H	Cl	86	83	5	4
5e	CH_3	H	$CH_2C_6H_5$	H	85	74	7	2.5
5f	CH_3	CH_3	$CH_2C_6H_5$	NO_2	79	73	4.5	1
5g	H	H	H	H	77	76	7	1.5
5h	H	H	H	NO_2	81	72	5	1
5i	H	H	H	CH_3	79	75	6.5	1.5
5j	CH_3	CH_3	CH_3	Cl	77	73	9	3
5k	CH=CH–CH=CH		H	H	83	81	6.5	3
6a	CH_3	CH_3	H	H	94	81	8.5	3
6b	CH=CH–CH=CH		H	CH_3	79	77	6	1.5
7a	CH_3	CH_3	CH_3	–	–	76	–	2
7b	CH_3	H	$CH_2C_6H_5$	–	–	78	–	2
8a	CH_3	CH_3	CH_3	–	72	70	11	4
8b	CH_3	H	C_6H_5	–	–	75	–	5
8c	–	–	–	–	68	71	8	6

When 4-[(4-oxochromen-3-yl)methylidene]-2-phenyloxazol-5(4*H*)-one (**4**) was treated with 2,3,4-trimethylfuro[3,2-*b*]pyrrol-5-carbohydrazide (**1e**) in acetic acid in the presence of a catalytic amount of fused potassium acetate either under reflux for 4 h or with microwave irradiation for 11 min, unexpected pyranopyridone **8a** was obtained in 72% yield (Scheme 2). On the other hand, *N*′-{2-benzamido-[3-(oxochromen-3-yl)]propenoyl}-2,3,4-trimethylfuro[3,2-*b*]pyrrole-5-carbohydrazide (**7a**) was obtained in 76% yield, when the reaction mixture was heated at lower temperature (60 °C) for 2 h. Subsequently, **7a** was cyclized either under 2 h reflux in acetic acid–potassium acetate medium or upon irradiation in a microwave oven for 9 min to give 65% yield of **8a**. The formation of **7a** in the microwave oven was not observed (Scheme 2). Similar results were obtained by the classical reaction of 4-benzyl-2-methylfuro[3,2-*b*]pyrrole-5-carbohydrazide (**1f**) with oxazolone **4** to give either **7b** in 78% yield after heating at 60 °C for 2 h or **8b** in 75% yield after heating at 110 °C for 5 h. Compound **8c** was obtained by the reaction of **4** with benzohydrazide (**10**) in 71% yield after irradiation in the microwave oven for 8 min, while classical heating for 6 h led to 68% yield of **8c**. The ^{1}H NMR spectra of compounds **7a** and **7b** displayed the signals of three NH protons at 9.90–10.16 ppm, pyrrole H-6 at 6.88 or 6.30 ppm, and the signals of H-9 on the double bond at 7.02 or 7.09 ppm. Protons H-2′ of the chromene ring showed a singlet at 8.64 ppm. The ^{1}H NMR spectra confirmed structures of **8a**–**8c**, based on missing H-2′ signals and the resonances of two NH protons, which can serve as a good indication of the addition reaction. The signals of the two NH protons were at 9.82–9.88 and 11.11–11.79 ppm. The singlet signals of H-10a′ protons appeared in the 7.41–7.44 ppm range, and the signals of H-6 protons in compounds **8a** and **8b** were at 6.36 and 6.95 ppm, respectively. The formation of pyranopyridone ring system of **8a**–**8c** could be explained by an acid catalyzed 1,6-addition, with a possible mechanism outlined in Scheme 3. To the best of our knowledge, chromone derivatives are usually readily ring-opened via nucleophilic attack at C-2, but in the presence of suitable groups, e.g. 3-(aryliminomethyl)[33], the reactivity towards nucleophiles is altered and nucleophilic 1,4-addition rather than the ring cleavage can be preferred. However, the reaction with hydrazine or its derivatives led to the pyrane ring cleavage, and a number of pyrazole derivatives were obtained[34]. In our case, a hitherto undescribed 1,6-addition took place.

In summary, we have shown that the conversion of the starting hydrazones **1** into substituted compounds **5** and **6** can be substantially improved upon using microwave irradiation, which led to the reduction of the reaction times from hours to seconds and, in a number of cases, to an increase

of the yields as well. We have also demonstrated that the reaction of hydrazones **1e** and **1f** with oxazolone **4** gave rise, depending on the conditions, either to the cleavage of the oxazolone moiety and the formation of substituted hydrazones **7a** and **7b** or to a tandem sequence, in which the above oxazolone ring fragmentation was followed by an unexpected, formal 1,6-addition to yield pyranopyridones of type **8**.



SCHEME 3

EXPERIMENTAL

Melting points were determined on a Kofler hot plate and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer Varian Gemini 200 in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. Chemical shifts are given in ppm, coupling constants (*J*) in Hz. The course of the reaction was monitored by TLC in ethyl acetate–hexane. All microwave experiments were performed in a Whirlpool M401 home microwave oven in an apparatus, adapted for laboratory applications; hexane was used as a cooling medium for the condenser. Elemental analyses were determined using a Carlo Erba CHNS-OEA 1108-Elemental Analyser.

Furo[3,2-*b*]pyrrole-5-carbohydrazides **1** were prepared according to ref.[37], 4-oxochromene-3-carbaldehydes **2** according to ref.[36], methyl 2-formylfuro[3,2-*b*pyrrole-5-carboxylates **3** according to ref.[35] and 4-[(4-oxochromen-3-yl)methylidene]-2-phenyloxazol-5(4*H*)-one (**4**) was prepared according to ref.[29] Benzohydrazide **10** was prepared by the reaction of benzoyl chloride with sodium methanolate and subsequent heating of methyl benzoate with hydrazine hydrate under reflux for 12 h.

N′-[(6-R^3-Oxochromen-3-yl)methylidene]-2-R-3-R^1-4-R^2-furo[3,2-*b*]pyrrole-5-carbohydrazides (**5a**–**5k**) and *N*′-[(4-R^3-5-carboxymethylfuro[3,2-*b*]pyrrole-2-yl)-methylidene]-2-R^1-3-R^2-4-R-furo[3,2-*b*]pyrrole-5-carbohydrazides (**6a**, **6b**)

Classical Method

A mixture of furo[3,2-*b*]pyrrole-5-carbohydrazide **1** (1 mmol) and 4-oxochromene-3-carbaldehyde **2** or methyl 2-formylfuro[3,2-*b*]pyrrole-5-carboxylate **3** (1 mmol) was heated

for 1–4 h at 50–60 °C in ethanol (3 ml) in the presence of 4-methylbenzene-1-sulfonic acid. The solid products were filtered off, dried and crystallized from ethanol.

Microwave Method

The mixture of the same composition as above was irradiated in the microwave oven at 90 W output over the period, given in Table I. The products were isolated and purified in the same manner as above.

N′-[(Oxochromen-3-yl)methylidene]-2-phenylfuro[3,2-b]pyrrole-5-carbohydrazide (**5a**). Yield 86% (MW), 80% (C), time 8 min (MW), 4 h (C), m.p. 260–263 °C (ethanol). ^{1}H NMR (DMSO-d_6): 6.92 s, 1 H (H-3); 7.17 s, 1 H (H-6); 7.28–7.59 m, 5 H (C_6H_5); 7.74–7.91 m, 4 H (H-5′, H-6′, H-7′, H-8′); 8.18 s, 1 H (H-7); 8.87 s, 1 H (H-2′); 11.65 bs, 1 H (NH); 11.76 br, 1 H (NH). For $C_{23}H_{15}N_3O_4$ (397.4) calculated: 69.52% C, 3.80% H, 10.57% N; found: 69.73% C, 3.80% H, 10.52% N.

N′-[(6-Chloroxochromen-3-yl)methylidene]-2-phenylfuro[3,2-b]pyrrole-5-carbohydrazide (**5b**). Yield 83% (MW), 80% (C), time 5 min (MW), 4 h (C), m.p. 239–242 °C (ethanol). ^{1}H NMR (DMSO-d_6): 6.93 s, 1 H (H-3); 7.10 s, 1 H (H-6); 7.18–7.50 m, 5 H (C_6H_5); 7.80–7.92 m, 3 H (H-5′, H-7′, H-8′); 8.11 s, 1 H (H-7); 8.89 s, 1 H (H-2′); 11.66 br, 1 H (NH); 11.85 br, 1 H (NH). For $C_{23}H_{14}ClN_3O_4$ (431.8) calculated: 63.97% C, 3.27% H, 8.21% Cl, 9.73% N; found: 63.91% C, 3.23% H, 8.17% Cl, 9.55% N.

N′-[(6-Nitrooxochromen-3-yl)methylidene]-4-benzylfuro[3,2-b]pyrrole-5-carbohydrazide (**5c**). Yield 80% (MW), 72% (C), time 4 min (MW), 2 h (C), m.p. 181–185 °C (ethanol). ^{1}H NMR ($CDCl_3$): 5.73 s, 2 H (CH_2); 6.18 s, 1 H (H-3); 6.73 s, 1 H (H-6); 7.15–7.31 m, 6 H (H-2, C_6H_5); 7.59–7.84 m, 3 H (H-5′, H-7′, H-8′); 8.25 s, 1 H (H-7); 8.96 s, 1 H (H-2′); 11.32 br, 1 H (NH). For $C_{24}H_{16}N_4O_6$ (456.4) calculated: 63.16% C, 3.53% H, 12.28% N; found: 63.71% C, 3.65% H, 12.10% N.

N′-[(6-Chlorooxochromen-3-yl)methylidene]-2-methylfuro[3,2-b]pyrrole-5-carbohydrazide (**5d**). Yield 86% (MW), 83% (C), time 5 min (MW), 4 h (C), m.p. 232–235 °C (ethanol). ^{1}H NMR (DMSO-d_6): 2.39 s, 3 H (CH_3); 6.20 s, 1 H (H-3); 7.00 s, 1 H (H-6); 7.79–7.93 m, 3 H (H-5′, H-7′, H-8′); 8.10 s, 1 H (H-7); 8.86 s, 1 H (H-2′); 11.48 bs, 1 H (NH); 11.56 bs, 1 H (NH). For $C_{28}H_{12}ClN_3O_4$ (369.9) calculated: 58.47% C, 3.27% H, 9.59% Cl, 11.36% N; found: 58.36% C, 3.28% H, 9.57% Cl, 11.29% N.

N′-[(Oxochromen-3-yl)methylidene]-4-benzyl-2-methylfuro[3,2-b]pyrrole-5-carbohydrazide (**5e**). Yield 85% (MW), 74% (C), time 7 min (MW), 2.5 h (C), m.p. 238–240 °C (ethanol). ^{1}H NMR (DMSO-d_6): 2.35 s, 3 H (CH_3); 5.66 s, 2 H (CH_2); 6.23 s, 1 H (H-3); 7.02 s, 1 H (H-6); 7.17–7.29 m, 5 H (C_6H_5); 7.51–7.56 m, 1 H (H-6′); 7.66, 7.69 d, 1 H, J(7′,8′) = 8.1 (H-8′); 7.81–7.83 m, 1 H (H-7′); 8.12, 8.15 d, 1 H, J(5′, 6′) = 8.1 (H-5′); 8.49 s, 1 H (H-7); 8.71 s, 1 H (H-2′); 11.34 bs, 1 H (NH). For $C_{25}H_{19}N_3O_4$ (425.5) calculated: 70.58% C, 4.50% H, 9.88% N; found: 70.74% C, 4.73% H, 10.14% N.

N′-[(6-Nitrooxochromen-3-yl)methylidene]-4-benzyl-2,3-dimethylfuro[3,2-b]pyrrole-5-carbohydrazide (**5f**). Yield 79% (MW), 73% (C), time 4.5 min (MW), 1 h (C), m.p. 240–243 °C (ethanol). ^{1}H NMR (DMSO-d_6): 2.08 s, 3 H (CH_3); 2.27 s, 3 H (CH_3); 5.79 s, 2 H (CH_2); 7.02 s, 1 H (H-6); 7.26–7.28 m, 5 H (C_6H_5); 7.93–8.26 m, 3 H (H-5′, H-7′, H-8′); 8.46 s, 1 H (H-7); 8.81 s, 1 H (H-2′); 11.43 bs, 1 H (NH). For $C_{26}H_{20}N_4O_6$ (484.5) calculated: 64.40% C, 4.13% H, 11.56% N; found: 64.27% C, 4.25% H, 11.59% N.

N′-[(Oxochromen-3-yl)methylidene]furo[3,2-b]pyrrole-5-carbohydrazide (**5g**). Yield 77% (MW), 76% (C), time 7 min (MW), 1.5 h (C), m.p. 249–252 °C (ethanol). ^{1}H NMR (DMSO-d_6): 6.58,

6.59 d, 1 H, *J*(3,2) = 2 (H-3); 7.03 s, 1 H (H-6); 7.55, 7.57 d, 1 H, *J*(2,3) = 2.1 (H-2); 7.68–7.71 m, 2 H (H-6′, H-8′); 7.81–7.85 m, 1 H (H-7′); 8.16, 8.19 d, 1 H, *J*(5′, 6′) = 9.3 (H-5′); 8.38 s, 1 H (H-7); 8.78 s, 1 H (H-2′); 11.37 bs, 1 H (NH); 11.46 bs, 1 H (NH). For $C_{17}H_{11}N_3O_4$ (321.3) calculated: 63.55% C, 3.45% H, 13.08% N; found: 63.52% C, 3.59% H, 13.06% N.

N′-[(6-Nitrooxochromen-3-yl)methylidene]furo[3,2-b]pyrrole-5-carbohydrazide (**5h**). Yield 81% (MW), 72% (C), time 5 min (MW), 1 h (C), m.p. 261–263 °C (ethanol). ^{1}H NMR (DMSO-d_6): 6.59, 6.60 d, 1 H, *J*(3,2) = 2.2 (H-3); 7.05 s, 1 H (H-6); 7.70, 7.71 d, 1 H, *J*(2,3) = 2.2 (H-2); 7.95, 7.98 d, 1 H, *J*(8′,7′) = 9 (H-8′); 8.38 s, 1 H (H-7); 8.56–8.60 m, 1 H (H-7′); 8.84–8.87 m, 2 H (H-2′, H-5′); 11.33 bs, 1 H (NH); 11.44 bs, 1 H (NH). For $C_{17}H_{10}N_4O_6$ (366.3) calculated: 55.74% C, 2.75% H, 15.30% N; found: 55.54% C, 3.01% H, 15.16% N.

N′-[(6-Methyloxochromen-3-yl)methylidene]furo[3,2-b]pyrrole-5-carbohydrazide (**5i**). Yield 79% (MW), 75% (C), time 6.5 min (MW), 1.5 h (C), m.p. 232–235 °C (ethanol). ^{1}H NMR ($CDCl_3$): 2.35 s, 3 H (CH_3); 6.57, 6.59 d, 1 H, *J*(3,2) = 2.2 (H-3); 7.04 s, 1 H (H-6); 7.71–7.72 d, 1 H, *J*(2,3) = 2.2 (H-2); 7.76–7.87 m, 2 H (H-7′, H-8′); 8.32 s, 1 H (H-7); 8.59–8.61 m, 1 H (H-5′); 8.77 s, 1 H (H-2′); 11.35 bs, 1 H (NH); 11.42 bs, 1 H (NH). For $C_{18}H_{13}N_3O_4$ (335.3) calculated: 60.48% C, 3.91% H, 12.53% N; found: 60.55% C, 4.16% H, 12.22% N.

N′-[(6-Chloroxochromen-3-yl)methylidene]-2,3,4-trimethylfuro[3,2-b]pyrrole-5-carbohydrazide (**5j**). Yield 77% (MW), 73% (C), time 9 min (MW), 3 h (C), m.p. 215–219 °C (ethanol). ^{1}H NMR ($CDCl_3$): 2.19 s, 3 H (CH_3); 2.32 s, 3 H (CH_3); 4.08 s, 3 H (CH_3); 6.55 s, 1 H (H-6); 7.45, 7.48 d, 1 H, *J*(8′,7′) = 9 (H-8′); 7.63, 7.66 d, 1 H, *J*(7′,8′) = 9 (H-7′); 8.21, 8.22 d, 1 H, *J*(5′,7′) = 2.4 (H-5′); 8.70 s, 1 H (H-7); 8.91 s, 1 H (H-2′); 10.97 bs, 1 H (NH). For $C_{20}H_{16}ClN_3O_4$ (397.8) calculated: 60.38% C, 4.05% H, 8.91% Cl, 10.56% N; found: 60.41% C, 4.08% H, 8.88% Cl, 10.51% N.

N′-[(Oxochromen-3-yl)methylidene]benzo[4,5]furo[3,2-b]pyrrole-5-carbohydrazide (**5k**). Yield 83% (MW), 81% (C), time 6.5 min (MW), 3 h (C), m.p. 251–255 °C (ethanol). ^{1}H NMR (DMSO-d_6): 7.13 s, 1 H (H-6); 7.32–7.35 m, 4 H (H-5′, H-6′, H-7′, H-8′); 7.71–8.16 m, 4 H (H_{benzo}); 8.54 s, 1 H (H-7); 8.81 s, 1 H (H-2′); 11.71 bs, 2 H (NH). For $C_{21}H_{13}N_3O_4$ (371.4) calculated: 67.92% C, 3.53% H, 11.32% N; found: 67.89% C, 3.51% H, 11.27% N.

N′-{[5-(Methoxycarbonyl)furo[3,2-b]pyrrol-2-yl]methylidene}-2,3-dimethylfuro[3,2-b]pyrrole-5-carbohydrazide (**6a**). Yield 94% (MW), 81% (C), time 8.5 min (MW), 3 h (C), m.p. 302–305 °C (ethanol). ^{1}H NMR (DMSO-d_6): 2.06 s, 3 H (CH_3); 2.30 s, 3 H (CH_3); 3.82 s, 3 H (CH_3); 6.81 s, 1 H (H-3); 7.00 s, 2 H (H-6, H-6′); 11.48 bs, 2 H (NH); 11.91 s, 1 H (NH). For $C_{18}H_{16}N_4O_5$ (368.3) calculated: 58.69% C, 4.38% H, 15.21% N; found: 58.64% C, 4.33% H, 15.19% N.

N′-{[5-(Methoxycarbonyl)-4-methylfuro[3,2-b]pyrrol-2-yl]methylidene}benzo[4,5]furo[3,2-b]pyrrole-5-carbohydrazide (**6b**). Yield 79% (MW), 77% (C), time 6 min (MW), 1.5 h (C), m.p. 282–286 °C (ethanol). ^{1}H NMR (DMSO-d_6): 3.95 s, 3 H (CH_3); 4.24 s, 3 H (CH_3); 6.85 s, 1 H (H-3′); 7.07 s, 1 H (H-6′); 7.23 s, 1 H (H-6); 7.33–7.96 m, 4 H (H_{benzo}); 8.26 s, 1 H (H-7); 11.67 bs, 2 H (NH). For $C_{21}H_{16}N_4O_5$ (404.4) calculated: 62.37% C, 3.99% H, 13.86% N; found: 62.31% C, 3.94% H, 13.82% N.

N′-{2-Benzamido-[3-(oxochromen-3-yl)]propenoyl}-2-R-3-R^1-4-R^2-furo[3,2-*b*]pyrrole-5-carbohydrazides (**7a**, **7b**)

A mixture of furo[3,2-*b*]pyrrole-5-carbohydrazide **1e** or **1f** (1 mmol) and 4-[(4-oxochromen-3-yl)methylidene]-2-phenyloxazol-5(4*H*)-one (**4**; 1 mmol) was heated in acetic acid (5 ml) in the presence of freshly fused potassium acetate at 60 °C for 2 h. The solid product was filtered off, dried and crystallized from ethanol.

N′-{2-Benzamido-[3-(oxochromen-3-yl)]propenoyl}-2,3,4-trimethylfuro[3,2-b]pyrrole-5-carbohydrazide (**7a**). Yield 76%, m.p. 237–241 °C (ethanol). ^{1}H NMR (DMSO-d_6): 2.17 s, 3 H (CH_3); 2.29 s, 3 H (CH_3); 3.97 s, 3 H (CH_3); 6.88 s, 1 H (H-6); 7.09 s, 1 H (H-9); 7.49–7.62 m, 5 H (C_6H_5); 7.82–8.17 m, 4 H (H-5′, H-6′, H-7′, H-8′); 8.64 s, 1 H (H-2′); 9.90 s, 1 H (NH); 10.12, 10.15 d, 2 H, *J*(7,8) = 9 (NH). For $C_{29}H_{24}N_4O_6$ (524.5) calculated: 66.40% C, 4.61% H, 10.68% N; found: 66.28% C, 4.58% H, 10.71% N.

N′-{2-Benzamido-[3-(oxochromen-3-yl)]propenoyl}-4-benzyl-2-methylfuro[3,2-b]pyrrole-5-carbohydrazide (**7b**). Yield 78%, m.p. 220–221 °C (ethanol). ^{1}H NMR (DMSO-d_6): 2.34 s, 3 H (CH_3); 5.65 s, 2 H (CH_2); 6.30 s, 1 H (H-6); 7.02 s, 1 H (H-3); 7.09 s, 1 H (H-9); 7.16–7.33 m, 5 H (C_6H_5); 7.48–7.62 m, 4 H (H-6′, H-3″, H-4″, H-5″); 7.64, 7.65 d, 1 H, *J*(8′,7′) = 7.9 (H-8′); 7.81, 7.84 tt, 1 H, *J*(7′,8′) = 8.5, *J*(7′,5′) = 1.6 (H-7′); 7.77, 8.09 dd, 2 H, *J*(2″,6″) = 7.1, (H-2″, H-6″); 8.14, 8.19 d, 1 H, *J*(5′,6′) = 7.9 (H-5′); 8.64 s, 1 H (H-2′); 10.01 s, 1 H (NH); 10.13, 10.16 d, 2 H, *J*(7,8) = 9 (NH). For $C_{34}H_{26}N_4O_6$ (586.6) calculated: 69.62% C, 4.47% H, 9.55% N; found: 69.89% C, 4.54% H, 9.68% N.

3-Benzamido-1-(2-R-3-R^1-4-R^2-furo[3,2-*b*]pyrrole-5-carboxamido)-2,5-dioxo-3,10a-dihydro-2*H*-chromeno[2,3-*b*]pyridines (**8a**, **8b**) and 1,3-Dibenzamido-2,5-dioxo-3,10a-dihydro-2*H*-chromeno[2,3-*b*]pyridine (**8c**)

Classical Method

Method A: A mixture of a furo[3,2-*b*]pyrrole-5-carbohydrazide (**1e**, **1f**) or benzohydrazide (**10**; 1 mmol) and 4-[(4-oxochromen-3-yl)methylidene]-2-phenyloxazol-5(4*H*)-one (**4**; 1 mmol) was heated at reflux in acetic acid (5 ml) in the presence of freshly fused potassium acetate for 4–6 h. The yellow solid products **8a**–**8c** were filtered off, dried and crystallized from ethanol.

Method B: Carbohydrazide **7a** (1 mmol) was heated at reflux in acetic acid (5 ml) in the presence of freshly fused potassium acetate for 2 h. The isolation and purification of the product **8a** was the same as described above.

Microwave Method

Method A: A mixture of 2,3,4-trimethylfuro[3,2-*b*]pyrrole-5-carbohydrazide (**1e**) or benzohydrazide (**10**; 1 mmol) and 4-[(4-oxochromen-3-yl)methyl]-2-phenyloxazol-5(4*H*)-one (**4**; 1 mmol) in acetic acid (5 ml) was irradiated in microwave oven at 90 W output in the presence of freshly fused potassium acetate for 8–11 min (see Table I). Compounds **8a** or **8c** were isolated and purified in the same manner as in the classical method.

Method B: Carbohydrazide **7a** (1mmol), acetic acid (5 ml) and a catalytic amount of freshly fused potassium acetate were irradiated in the microwave oven for 9 min. Work-up was the same as in the classical method.

3-Benzamido-1-(2,3,4-trimethylfuro[3,2-b]pyrrole-5-carboxamido)-2,5-dioxo-3,10a-dihydro-2H-chromeno[2,3-b]pyridine (**8a**). Method *A*: Yield 72% (MW), 70% (C), time 11 min (MW), 4 h (C). Method *B*: Yield 65% (MW), 65% (C), time 9 min (MW), 2 h (C), m.p. 293–295 °C. ^{1}H NMR (DMSO-d_6): 2.15 s, 3 H (CH_3); 2.30 s, 3 H (CH_3); 3.85 s, 3 H (CH_3); 6.95 s, 1 H (H-6); 7.41 s, 1 H (H-10a′); 7.53–7.65 m, 5 H (H-3′, H-4′, H-7′, H-3″, H-5″); 7.75, 7.77 d, 1 H, *J*(9′,8′) = 7.9 (H-9′); 7.87–7.93 m, 1 H (H-8′); 8.12, 8.15 dd, 3 H, *J*(2″,3″) = 8.5 (H-2″, H-4″, H-6″); 8.18, 8.22 d, 1 H, *J*(6′,7′) = 7.9 (H-6′); 9.82 s, 1 H (NH); 11.11 s, 1 H (NH). For

$C_{29}H_{24}N_4O_6$ (524.5) calculated: 66.40% C, 4.61% H, 10.68% N; found: 66.68% C, 4.60% H, 10.41% N.

3-Benzamido-1-(4-benzyl-2-methylfuro[3,2-b]pyrrole-5-carboxamido)-2,5-dioxo-3,10a-dihydro-2H-chromeno[2,3-b]pyridine (**8b**). Method *A*: Yield 71% (C), time 5 h (C), m.p. 279–280 °C. ^{1}H NMR (DMSO-d_6): 2.36 s, 3 H (CH_3); 5.49–5.60 q, 2 H, *J* = 15 (CH_2); 6.36 s, 1 H (H-6); 6.99–7.10 m, 3 H (H-3, H-3′, H-4′); 7.18–7.23 m, 3 H (H-8, H-9, H-10); 7.44 s, 1 H (H-10a′); 7.50–7.60 m, 5 H (H-3″, H-4″, H-5″, H-7, H-11); 7.64–7.66 dd, 1 H, *J*(7′,6′) = 7.9 (H-7′); 7.78 d, 1 H, *J*(9′,8′) = 8.2 (H-9′); 7.90, 7.92 tt, 1 H, *J*(8′,9′) = 8.5, *J*(8′,6′) = 1.4 (H-8′); 8.07, 8.14 dd, 2 H, *J*(2″,6″) = 7.5, (H-2″, H-6″); 8.18, 8.20 d, 1 H, *J*(6′,7′) = 7.9 (H-6′); 9.88 s, 1 H (NH); 11.31 s, 1 H (NH). For $C_{34}H_{26}N_4O_6$ (586.6) calculated: 69.62% C, 4.47% H, 9.55% N; found: 69.91% C, 4.24% H, 9.61% N.

1,3-Dibenzamido-2,5-dioxo-3,10a-dihydro-2H-chromeno[2,3-b]pyridine (**8c**). Method *A*: Yield 71% (MW), 68% (C), time 8 min (MW), 6 h (C), m.p. 276–279 °C. ^{1}H NMR (DMSO-d_6): 7.43 s, 1 H (H-10a′); 7.55–7.69 m, 8 H (H-3′, H-4′, H-7′, C_6H_5); 7.74, 7.77 d, 1 H, *J*(9′,8′) = 8.4 (H-9′); 7.83–7.98 m, 4 H (H-8′, H-3″, H-4″, H-5″); 8.12, 8.14 d, 2 H, *J*(2″,3″) = *J*(6″,5″) = 7.25 (H-2″, H-6″); 8.15, 8.20 d, 1 H (H-6′); 9.83 s, 1 H (NH); 11.79 s, 1 H (NH). For $C_{26}H_{19}N_3O_5$ (453.5) calculated: 68.87% C, 4.22% H, 9.27% N; found: 69.17% C, 4.23% H, 9.46% N.

The authors R. Gašparová and A. Krutošíková are grateful to the VEGA Grant Agency of the Slovak Ministry of Education for financial support of project No. 1/0069/03.

REFERENCES

1. Jedlovská E., Gavláková E.: *Collect. Czech. Chem. Commun.* **1994**, *59*, 1892.
2. Jedlovská E., Leško J.: *Synth. Commun.* **1994**, *24*, 1879.
3. Cao H. L., Cui J. P. Y.: *J. Chin. Chem. Soc.* **2003**, *50*, 903.
4. Foltínová P., Lácová M., Loos D.: *Farmaco* **2000**, *55*, 21.
5. Santos M. R. L., Barreiro E. J., Braz-Filho R., Miranda A. L. P.: *J. Braz. Chem. Soc.* **1997**, *8*, 471.
6. El-Shaaer H. M., Lácová M., Odlerová Ž., Furdík M.: *Chem. Pap.* **1994**, *48*, 344.
7. Gonzales-Serratos H., Chang R., Pereira E. F. R., Castro N. G., Aracava Y., Melo P. A., Lima P. C., Fraga C. A. M., Barreiro E. G., Albuquerque E. X.: *J. Pharmacol. Exp. Ther.* **2001**, *299*, 588.
8. Krutošíková A. in: *Comprehensive Heterocyclic Chemistry II* (C. A. Ramsden, Ed.), Vol. 7, p. 1. Pergamon, Oxford 1996.
9. Huttrer C. P., Dale E.: *Chem. Rev.* **1951**, *48*, 543.
10. Dann O., Illing G.: *Arch. Pharm.* **1956**, *289*, 18.
11. Groundwater P. W., Hibbs D. E., Hursthouse M. B., Nyerges M.: *J. Chem. Soc., Perkin Trans. 1* **1997**, 163.
12. Ghosh C. K.: *J. Heterocycl. Chem.* **1983**, *20*, 1437.
13. Abass M., Hassan A.: *Chem. Pap.* **2003**, *57*, 267.
14. Pinto D. C. G. A., Silva A. M. S., Almeida L. M. P. M., Carrillo J. R., Diaz-Ortiz A., de la Hoz A., Cavaleiro J. A. S.: *Synlett* **2003**, *10*, 1415.
15. Krutošíková A., Kováč J., Kráľovičová E.: *Collect. Czech. Chem. Commun.* **1983**, *48*, 1878.
16. Krutošíková A., Kováč J., Dandárová M.: *Collect. Czech. Chem. Commun.* **1984**, *49*, 65.

17. Koreňová A., Krutošíková A., Dandárová M., Kováč J.: *Collect. Czech. Chem. Commun.* **1984**, *49*, 1529.
18. Krutošíková A., Kováč J., Banák P.: *Chem. Zvesti* **1984**, *38*, 707.
19. Krutošíková A., Mastik S., Dandárová M., Lyčka A.: *Collect. Czech. Chem. Commun.* **1997**, *62*, 1612.
20. Lácová M., El-Shaaer H. M., Loos D., Matulová M., Chovancová J., Furdík M.: *Molecules* **1998**, *3*, 120.
21. Gašparová R., Lácová M.: *Collect. Czech. Chem. Commun.* **1995**, *60*, 1178.
22. Stankovičová H., Gašparová R., Lácová M., Chovancová J.: *Collect. Czech. Chem. Commun.* **1997**, *62*, 781.
23. Lácová M., Gašparová R., Loos D., Liptay T., Pronayová N.: *Molecules* **2000**, *5*, 167.
24. Loupy A., Petit A., Hamelin J., Texier-Boullet F., Jacquault P., Mathé D.: *Synthesis* **1998**, 1213.
25. Toma Š.: *Chem. Listy* **1993**, *87*, 627.
26. Galema S. A.: *Chem. Soc. Rev.* **1997**, *26*, 233.
27. Varma R. S.: *Pure Appl. Chem.* **2001**, *73*, 193.
28. Puterová Z., Sterk H., Krutošíková A.: *Molecules* **2004**, *9*, 11.
29. Fitton A. O., Frost J. R., Sushitzky H., Houghton P. G.: *Synthesis* **1977**, 133.
30. Kidwai M. M., Khan N. H., Ali M.: *Synth. Commun.* **1979**, *9*, 363.
31. Cativiela C., de Villegas M. D., Mayoral J., Avenoza A., Roy M. A.: *J. Heterocycl. Chem.* **1988**, *25*, 851.
32. Nálepa K., Zedníková G.: *Acta Univ. Palacki. Olomuc., Fac. Rerum Nat., Chem.* **1999**, *38*, 53; and references therein.
33. Fitton A. O., Frost J. R., Houghton P. G., Suschitzky H.: *J. Chem. Soc., Perkin Trans. 1* **1978**, 1691.
34. Ghosh C. K., Mhukopadhyay K. K.: *J. Indian Chem. Soc.* **1978**, *55*, 386.
35. Krutošíková A., Dandárová M., Alföldi J.: *Chem. Pap.* **1994**, *48*, 268.
36. Nohara A., Umetani T., Sanno Y.: *Tetrahedron* **1974**, *30*, 3553.
37. Krutošíková A., Dandárová M., Bobošík V.: *Collect. Czech. Chem. Commun.* **1994**, *59*, 473.