ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2006, Vol. 32, No. 3, pp. 277–279. © Pleiades Publishing, Inc., 2006.
Original Russian Text © A.A. Poyarkov, M.S. Frasinyuk, V.K. Kibirev, S.A. Poyarkova, 2006, published in Bioorganicheskaya Khimiya, 2006, Vol. 32, No. 3, pp. 308–310.

# The Synthesis of Arginine Derivatives of Chromone and Azauracil

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Received March 3, 2005; in final form, November 20, 2005

**Abstract**—The coupling of *N*-succinimide esters of 3-[7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-6-ethyl-4-oxo-4*H*-chromen-2-yl]propanoic acid and 5-carboxymethyl-6-azauracil with free arginine yielded the corresponding arginine derivatives, which were purified by crystallization. The structures of the compounds were confirmed by $^1$H NMR spectroscopy

*Key words: arginine, azauracil, 7-hydroxychromone*

**DOI:** 10.1134/S1068162006030095

## INTRODUCTION

Natural and synthetic derivatives of chromones [1] and azauracil [2] exhibit a wide spectrum of biological activities. They display cerebroprotective, antispasmodic, antitumor, and cardiostimulating properties [3]. Chromone derivatives are agonists of γ-aminobutyric acid receptors and, therefore, strong tranquilizers devoid of side effects, such as amnesia, myorelaxation, and sedative effect. *L*-Arginine is a very interesting amino acid with a clearly pronounced biological activity. Arginine stimulates in organism the insulin and somatostatin release, displays vasodilating properties at hypercholesteremia, and regulates metabolism of nitrogen monoxide [4]. The introduction of an arginine residue into the chromone molecule may essentially alter its hydrophilic–lipophilic properties and affect in this way its transport in biological systems. It was shown that the modification of a hydrophobic compound with arginine allows the preparation of reverse inhibitors of thrombin, a therapeutic target for potential anticoagulants, which may be used for therapy of cardiovascular disorders [5].

## RESULTS AND DISCUSSION

We used a classical method of peptide chemistry for coupling arginine with chromone derivatives and azauracil, namely, the method of active esters [6] (Scheme 1). An advantage of these active agents is their high reactivity along with hydrolytic stability, which enables their coupling in aqueous dioxane or DMF and the use of *N*-succinimide esters for the synthesis of peptides with *C*-terminal free arginine [7].

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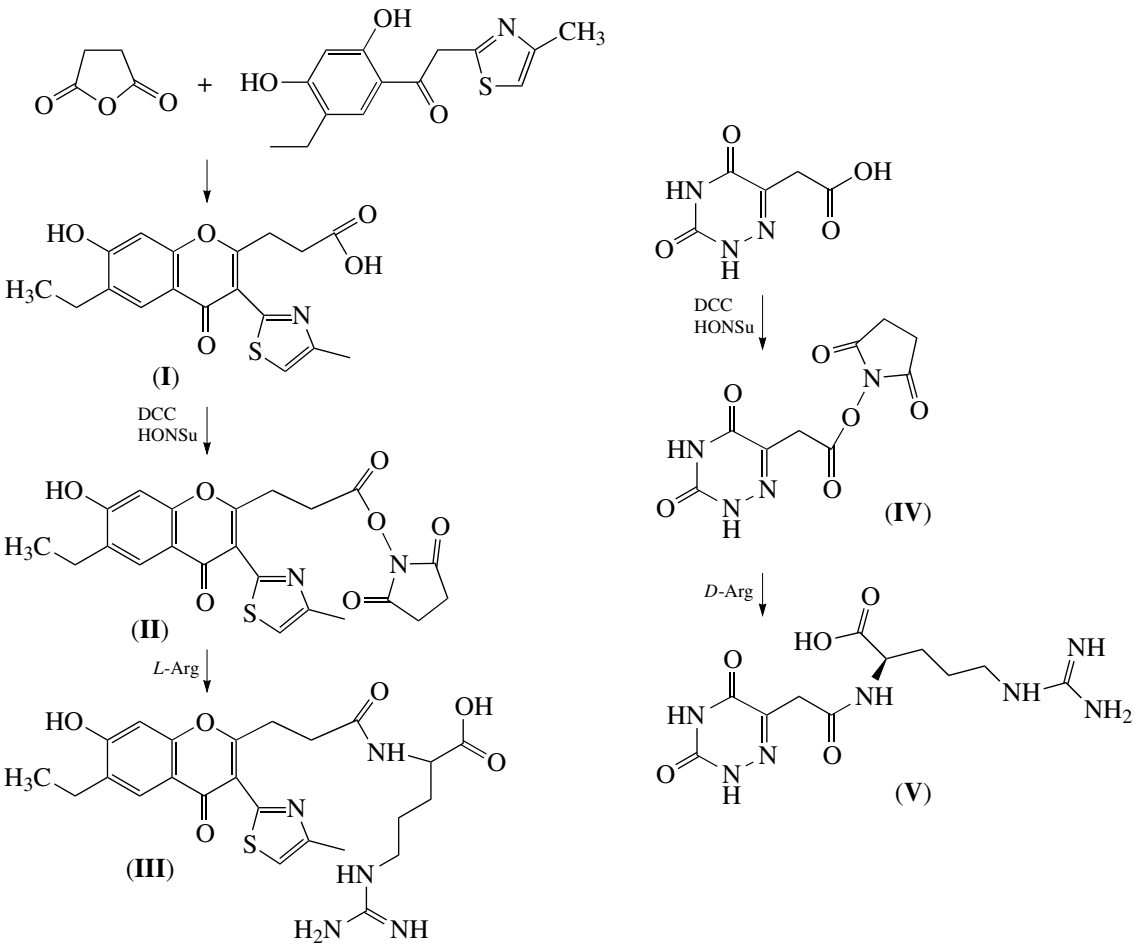
Flavones can enter the guanidine-induced recyclization reactions [8]; therefore, we were not sure that the chromone core would not be damaged in the presence of *L*-arginine containing a guanidine group. However, we did not observe in our experiments the processes described in [8]. The *L*-arginine derivative (**III**) of 2,3,6,7-substituted chromone (**I**) we synthesized [9] contained a small admixture of the starting compound. The purification of the reaction product by adsorption chromatography on alumina with methanol as eluent did not result in homogeneous compounds. It turned out that the usual crystallization from 50% ethanol gives a good result. A *D*-arginine derivative of 5-carboxymethyl-6-azauracil (**V**) was prepared in a high yield via the corresponding *N*-succinimide ester (**IV**) in a similar way. The structures and the purity of the resulting compounds were confirmed by $^1$H NMR spectroscopy.

## EXPERIMENTAL

We used *D*- and *L*-arginines from Reanal (Hungary), 5-carboxymethyl-6-azauracil kindly presented by S.S. Tarnavsky (Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine), and domestic solvents and chemicals of the special purity grade. Melting points were determined on a Boetius hot plate (Germany). Monitoring of the reaction and the analysis of product purity were carried out by TLC on precoated silica gel 60 $F_{254}$ plates (Merck, Germany) in (A) 4 : 1 : 1 *n*-butanol–acetic acid–water and (B) 5 : 4 benzene–ethyl acetate. The syntheses were carried out according to the given scheme.

**3-[7-Hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-6-ethyl-4-oxo-4*H*-chromen-2-yl]propanoic acid (I).** A suspension of 1-(2,4-dihydroxy-5-ethylphenyl)-2-(4-methyl-1,3-thiazol-2-yl)ethanone (1.55 g, 5 mmol) [9],




**Scheme 1.**

succinic anhydride (3.03 g, 30 mmol), and dry pyridine (10 ml) was heated at 40°C under stirring and kept for 72 h. The reaction mixture was poured onto ice, acidified with concentrated HCl to pH 2–3, and allowed to be heated to room temperature. The solution was adjusted to pH 6–7 with 5% sodium hydroxide, and the resulting crystals were filtered, washed with cold water, and reprecipitated from an alkaline solution with dilute HCl. The precipitate was filtered and crystallized from a water–DMF mixture to give (**I**), yield 85%, mp >300°C (dec.)

***N*-Succinimide ester of 3-[7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-6-ethyl-4-oxo-4*H*-chromen-2-yl]propanoic acid (II).** *N*-Succinimide (0.12 g, 1.01 mmol) and dicyclohexylcarbodiimide (0.21 g, 1.01 mmol) were added to a solution of (**I**) (0.4 g, 1 mmol) in dry DMF (20 ml) at 4°C. The reaction mixture was stirred at 4°C for 4 h and at room temperature for 18 h. After the reaction was over, dicyclohexylurea was filtered off, DMF was evaporated in a vacuum at 40°C, and the residue was crystallized from isopropanol to give 0.6 g (80%) of (**II**), mp 110°C, $R_f$ 0.6 (B).

***N*$^1$-{3-[7-Hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-6-ethyl-4-oxo-4*H*-chromen-2-yl]propionyl}-*L*-arginine (III).** A solution of *L*-arginine (0.46 g, 2.6 mmol) in water (10 ml) was added to a solution of (**II**) (0.6 g, 1.3 mmol) in dry DMF (20 ml), the mixture was stirred for 48 h at room temperature, and evaporated in a vacuum at 40°C. The oil-like residue was recrystallized from 50% ethanol to give (**III**); yield 0.38 g (60%); mp 238°C (dec.); $R_f$ 0.45 (A); $^1$H NMR spectra were registered on a Varian VXC-400 (Germany) with a working frequency of 400 MHz in DMSO-$d_6$ (99.9%) relative to residual solvent protons (δ, ppm, *J*, Hz)[2]: 8.80 (1 H, br. s, II, Arg), 7.78 (1 H, s, H5, Chr), 7.69 (1 H, s, 7-OH, Chr), 7.42 (5 H, 4 NH + $NH_2$); 7.40 (1 H, s, H5, Thia), 6.93 (1 H, s, H8, Chr), 4.01 (1 H, q, *J* 6.0, CI, Arg), 3.60 (2 H, m, $CH_2$-NH)), 3.45 (2 H, m, $CH_2$, propionyl), 2.85 (2 H, m, $CH_2$, Et); 2.60 (2 H, m, $CH_2$, propionyl), 2.40 (3 H, s, $CH_3$, Et), 1.35–1.75 (4 H, m, 2 $CH_2$, Arg), and 1.25 (3 H, t, *J* 8.9, $CH_3$, Thia).

[2] Chr, Thia, and AzU are chromone, thiazoline, and 6-azauracil residues, respectively.

***N*-Succinimide ester of 5-carboxymethyl-6-azauracil (IV).** *N*-Hydroxysuccinimide (0.59 g, 5.1 mmol) was added to a stirred solution of 5-carboxymethyl-6-azauracil (0.86 g, 5 mmol) in dry THF (20 ml). The reaction mixture was cooled to 0°C, and DCC (1.05 g, 5.1 mmol) was added under vigorous stirring. After 2 h at 4°C and then 18 h at room temperature, the precipitated dicyclohexylurea was filtered, THF was evaporated in a vacuum at 40°C, and the residue was crystallized from isopropanol to give (**IV**), yield 1.06 g (79%).

***N*$^1$-[(6-Azauracil-5-yl)methylcarbonyl]-*D*-arginine (V).** A solution of *D*-arginine (0.53 g, 3 mmol) in water (7 ml) was added to a solution of *N*-succinimide ester of 5-carboxymethyl-6-azauracil (0.5 g, 1.86 mmol) in dioxane (14 ml) under vigorous stirring. The mixture was stirred at room temperature and evaporated in a vacuum at 40°C, and the residue was crystallized from 50% ethanol to give 0.50 g (80%) of (**V**); mp 214°C (dec); $R_f$ 0.43 (A); $^1$H NMR (δ, ppm, *J*, Hz): 12.06 (1 H, m, H4, AzU), 9.04 (1 H, m, H2, AzU), 7.67 (1 H, d, *J* 7.4, CONH), 7.50 (5 H, m, 3NH + $NH_2$), 4.01 (H, q, *J* 6.2, CH, Arg), 3.37 (2 H, d, *J* 7.5, $CH_2$–N–); 3.3 (2 H, m, $CH_2$, Arg), and 1.4–1.7 (4 H, m, 2 $CH_2$, Arg).

## REFERENCES


1. Yishai Karton., Ji-long Jiang., Xiao-duo Ji., Melman, N., Olah, M.E., Stiles, G., Jacobson, K.A., *J. Med. Chem.*, 1996, vol. 39, pp. 2293–2301.
2. Mikhailov, S.N., *Bioorg. Khim.*, 1992, vol. 18, pp. 1033–1066.
3. Xiaoqin Huang, Tong Liu, Jiande Gu, Xiaomin Luo, Ruyun Ji, Yang Cao, Hong Xue, J. Tze-Fei Wong, Bing L. Wong, Gang Pei, Hualiang Jiang, and Kaixian Chen K., *J. Med. Chem.*, 2001, vol. 44, pp. 1883–1891.
4. Granik, V.G., *Khim.–Farm. Zh.*, 2003, vol. 37, pp. 3–20.
5. Butenas, S. and Mann, K.G., *Biokhimiya* (Moscow), 2002, vol. 67, pp. 5–15.
6. Anderson, G.H., Zimmerman, J.E., and Collahan, F.M., *J. Am. Chem. Soc.*, 1964, vol. 86, pp. 1839–1842.
7. Filatova, M.P., Krit, N.A., Suchkova, G.S., Ravdel', G.A., and Ivanov, V.T., *Bioorg. Khim.*, 1975, vol. 1, pp. 437–441.
8. Aitmambetov, A. and Menlimuratova, Z., *Russ. J. Bioorg. Chem.*, 2003, vol. 29, pp. 175–176.
9. Frasinyuk, M.S., Gorbulenko, N.V., and Khilya, V.P., *Khim. Geterotsikl. Soedin.*, 1997, no. 10, pp. 1237–1244.