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SYNTHESIS OF AMINO-ACID DERIVATIVES OF CHRYSIN

M. V. Veselovskaya,[1*] M. M. Garazd,[1] A. S. Ogorodniichuk,[1] Ya. L. Garazd,[2] and V. P. Khilya[2]

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Various conjugates of amino acids with chrysin in which the amino acid was bonded through the C- *or* N-*terminus to the flavone were prepared using peptide chemistry methods (symmetric anhydrides and activated esters).*

Key words: flavonoids, flavones, chrysin, amino-acid derivatives.

Flavonoids are the most widely distributed compounds of natural origin. They can be found in practically all plant species. At present, flavonoids comprise about 6500 natural compounds [1]. The study of flavonoids is becoming increasingly interesting because of the important role that they play in the metabolism of plants and animals and their high and diversified biological activity [2]. Chrysin (5,7-dihydroxyflavone) is one of the most common flavonoids, has been isolated from various plant families [3, 4], and possesses, like its derivatives, a broad spectrum of biological activity. Thus, chrysin exhibits anticancer [5, 6], antioxidant [7, 8], anti-inflammatory [9, 10], vasodilating [11, 12], immunomodulating [13, 14], antibacterial [15, 16], antifungal [16], antiprotozal [17], neuroprotective [18], hypotensive [19], and anti-allergy [20] activity. Chrysin derivatives possess hypoglycemic [21], anticancer [22-25], anti-inflammatory [26, 27], and antibacterial [15] action.

Considering the importance to the metabolism of all animals of amino acids and their derivatives, our goal was to synthesize chrysin derivatives with pharmacophores containing amino acids.

The amino-acid derivatives of chrysin were synthesized via two modification pathways. The first was based on formation of the ester of *N*-protected amino acid and phenolic compounds. The most suitable and convenient method for synthesizing 7-*O*-amino-acid chromone derivatives is the reaction of 7-hydroxychromones and symmetric anhydrides of *N*-substituted amino acids because the reaction proceeds under mild conditions and is not complicated by side reactions [28]. It has been used successfully to synthesize similar types of compounds [29, 30].

The hydroxyls of 5,7-dihydroxychromones have different reactivities because of the different influence of electron-donors, steric factors, and intramolecular H-bonds. Therefore, the 7-hydroxyl of the chromone system is acylated exclusively under mild conditions [31, 32].

Symmetric anhydrides of *N*-protected amino acids were prepared by reaction of dicyclohexylcarbodiimide (DCC) with two equivalents of the corresponding *N*-protected amino acid in anhydrous dioxane at 0°C. The amines of the amino acids were blocked with *t*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and *p*-toluenesulfonic acid (Tos). Chrysin was acylated by the resulting amino-acid anhydrides at 0°C in anhydrous dioxane in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) to produce *N*-protected 7-*O*-aminoacyl-5-hydroxy-2-phenylchromen-4-ones **2**-**20**. The products contained glycine (**2**, **8**), L-alanine (**3**, **9**), L-valine (**4**, **10**), L-leucine (**5**, **11**), L-isoleucine (**6**, **12**), L-methionine (**13**), L-phenylalanine (**7**, **14**), β-alanine (**15**, **17**, **19**), and 6-aminohexanoic acid (**16**, **18**, **20**).

The selective acylation of the chromone 7-hydroxyl was confirmed by PMR spectroscopy. The spectra of **2**-**20** contained resonances for the flavone ring, an amino-acid moiety, and the protecting group. The resonance of the 5-OH, which was involved in an intramolecular H-bond, appeared in the range 12.72-12.95 ppm. Derivatives **2**-**20** gave an intense brown color with alcoholic $FeCl_3$ due to formation of an intramolecular chelate complex.

1) Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, 02094, Ukraine, Kiev, ul. Murmanskaya, 1, e-mail: gmm@i.com.ua; 2) Taras Shevchenko Kiev National University, 01033, Ukraine, Kiev, ul. Vladimirskaya, 64. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 569-574, November-December, 2008. Original article submitted January 14, 2008.

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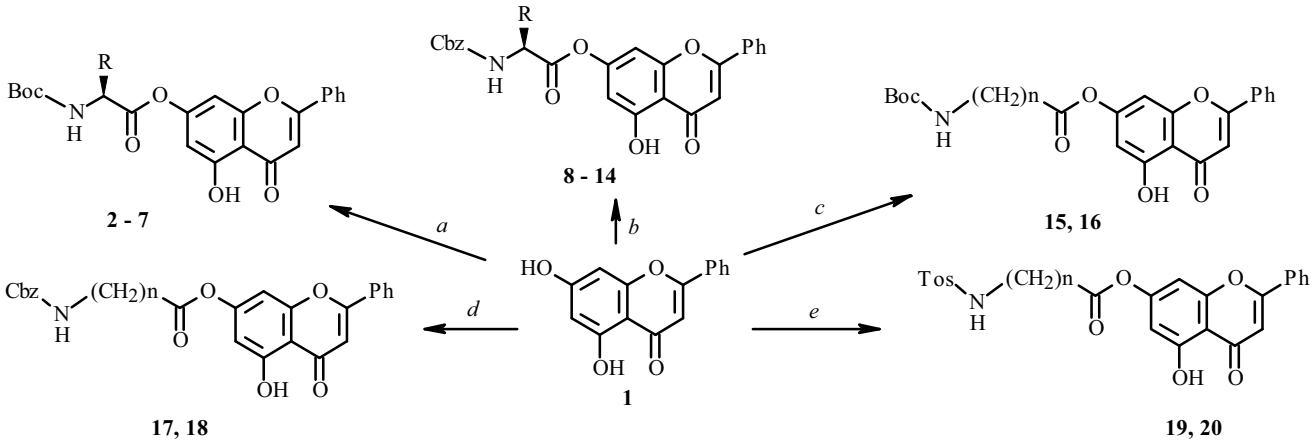
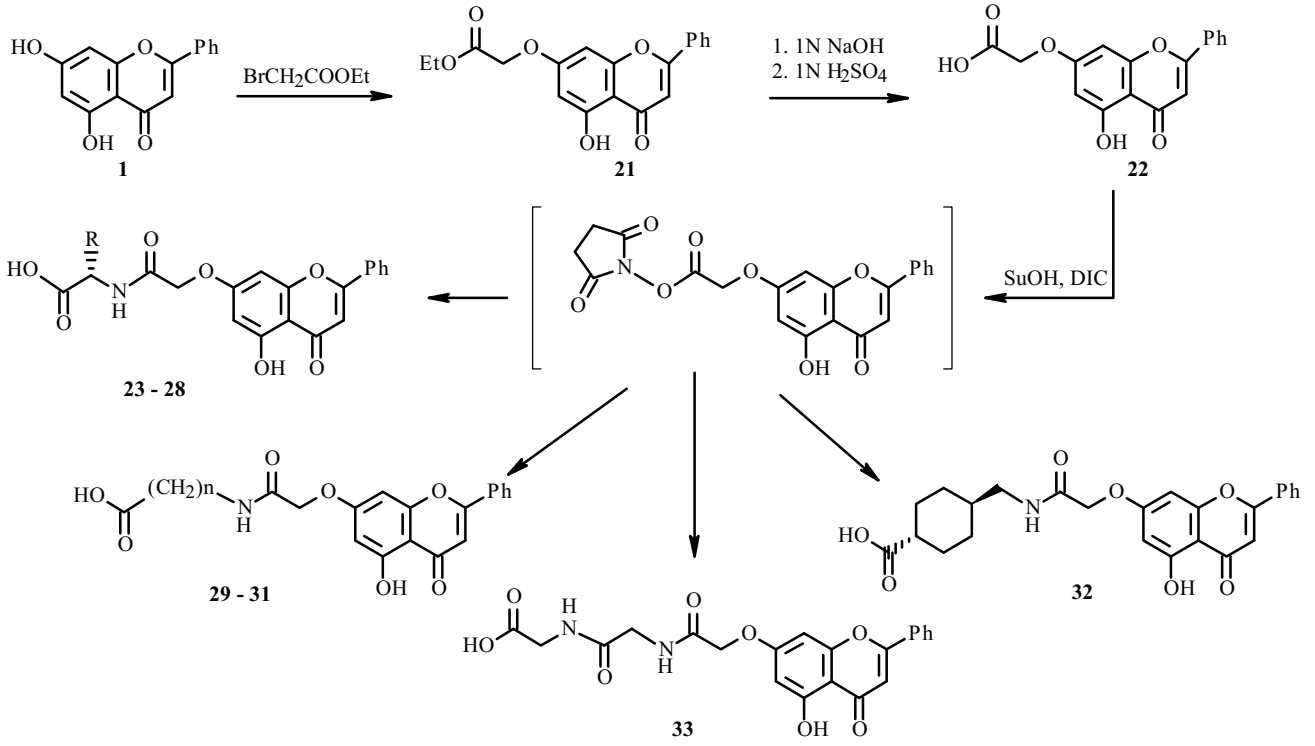


a. $(BocNHCHRCO)_2O$, DMAP; *b.* $(CbzNHCHRCO)_2O$, DMAP; *c.* $(BocNH(CH_2)_nCO)_2O$, DMAP;
d. $(CbzNH(CH_2)_nCO)_2O$, DMAP; *e.* $(TosNH(CH_2)_nCO)_2O$, DMAP

2, 8: R = H; **3, 9:** R = CH_3; **4, 10:** R = $CH(CH_3)_2$; **5, 11:** R = $CH_2CH(CH_3)_2$; **6, 12:** R = $CH_2CH(CH_3)CH_2CH_3$
7, 14: R = CH_2Ph; **13:** R = $CH_2CH_2SCH_3$; **15, 17, 19:** n = 2; **16, 18, 20:** n = 5

The second approach to modifying chrysin with amino acids was based on the method of activated esters, which is widely used in peptide chemistry. Selective alkylation of the chrysin 7-hydroxyl under Williamson reaction conditions by ethylbromoacetate produced ethyl ester **21**, saponification of which by NaOH in aqueous propanol-2 and subsequent acidolysis of the reaction mixture formed [(5-hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetic acid (**22**).



23: R = H; **24:** R = CH_3; **25:** R = $CH(CH_3)_2$; **26:** R = $CH_2CH_2SCH_3$; **27:** R = CH_2Ph; **28:** R = Ph; **30:** n = 2; **31:** n = 5

The carboxylic acid was activated using *N*-hydroxysuccinimide to form highly reactive esters without racemizing the reaction products [33]. This method was used successfully to synthesize similar types of compounds [30, 34]. The activated ester was prepared by reacting starting acid **22** and *N*-hydroxysuccinimide (SuOH) in anhydrous DMF with diisopropylcarbodiimide (DIC) as the condensing agent. Reaction of the activated ester and sodium salts of the amino acids in

DMF:H_2O at room temperature with subsequent acidolysis of the resulting salts gave in high yields **23**-**33** with a free carboxylic acid.

The synthesis gave chrysin derivatives modified with glycine (**23**), L-alanine (**24**), L-valine (**25**), L-methionine (**26**), L-phenylalanine (**27**), L-α-phenylglycine (**28**), and β-alanine (**29**) and 4-aminobutanoic (**30**), 6-aminohexanoic (**31**), and *trans*-4-aminomethylcyclohexanecarboxylic (**32**) acids in addition to glycylglycine (**33**). PMR spectra of **23**-**33** contained resonances for chrysin, the amino-acid moiety, the amide bond at 8.12-8.93 ppm, and the free carboxylic acid at 11.90-12.65 ppm.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck 60 F254 plates with elution by $CHCl_3$:CH_3OH (9:1). Melting points were determined on a Kofler block. PMR spectra were recorded on Varian VXR-300 and Mercury 400 spectrometers at 300 and 400 MHz, respectively, vs. TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

5,7-Dihydroxyflavone was prepared as before [35].

***N*-Substituted 7-*O*-Aminoacyl-5-hydroxy-2-phenylchromen-4-ones 2-20.** A cooled (0°C) solution of the appropriate *N*-substituted amino acid (9 mmol) in anhydrous dioxane (20 mL) was treated with DCC (0.93 g, 4.5 mmol) and stirred vigorously for 20-30 min at 0°C. The precipitate of dicyclohexylurea was filtered off. The resulting symmetric anhydride was treated with chrysin (1.02 g, 4 mmol) in anhydrous dioxane (20 mL) and DMAP (20 mg), held for 1-2 h at room temperature, and stirred vigorously (finish of the reaction was determined using TLC). Solvent was removed in vacuo. The solid was dissolved in ethylacetate (50 mL) and washed successively with $NaHCO_3$ solution (2 × 50 mL), water (50 mL), and saturated NaCl solution (50 mL). The organic phase was dried over anhydrous $MgSO_4$. Solvent was removed in vacuo. The solid was crystallized from propanol-2.

7-*O*-(*N*-*t*-Butyloxycarbonylglycyl)-5-hydroxy-2-phenylchromen-4-one (2), yield 69%, mp 218-219°C, $C_{22}H_{21}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.44 [9H, s, $(CH_3)_3C$], 4.14 (2H, d, J = 5.7, CH_2-2″), 6.54 (1H, br.m, CONH), 6.61 (1H, d, J = 2.1, H-6), 6.92 (1H, s, H-3), 7.01 (1H, d, J = 2.1, H-8), 7.56-7.68 (3H, m, H-3′, H-4′, H-5′), 8.11 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.91 (1H, s, OH-5).

7-*O*-(*N*-*t*-Butyloxycarbonyl-L-alanyl)-5-hydroxy-2-phenylchromen-4-one (3), yield 78%, mp 192-193°C, $C_{23}H_{23}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.45 [9H, s, $(CH_3)_3C$], 1.55 (3H, d, J = 7.5, CH_3-3″), 4.44 (1H, m, H-2″), 6.59 (1H, d, J = 7.2, CONH), 6.61 (1H, d, J = 2.1, H-6), 6.93 (1H, s, H-3), 7.01 (1H, d, J = 2.1, H-8), 7.56-7.68 (3H, m, H-3′, H-4′, H-5′), 8.12 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.90 (1H, s, OH-5).

7-*O*-(*N*-*t*-Butyloxycarbonyl-L-valyl)-5-hydroxy-2-phenylchromen-4-one (4), yield 73%, mp 188-189°C, $C_{25}H_{27}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.11 (6H, d, J = 6.6, CH_3-4″, CH_3-3″), 1.45 [9H, s, $(CH_3)_3C$], 2.34 (1H, m, H-3″), 4.29 (1H, t, J = 6.0, H-2″), 6.52 (1H, d, J = 7.5, CONH), 6.60 (1H, d, J = 2.1, H-6), 6.95 (1H, s, H-3), 7.02 (1H, d, J = 2.1, H-8), 7.60-7.70 (3H, m, H-3′, H-4′, H-5′), 8.13 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.94 (1H, s, OH-5).

7-*O*-(*N*-*t*-Butyloxycarbonyl-L-leucyl)-5-hydroxy-2-phenylchromen-4-one (5), yield 68%, mp 181-182°C, $C_{26}H_{29}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.03 (6H, d, J = 5.7, CH_3-5″, CH_3-4″), 1.45 [9H, s, $(CH_3)_3C$], 1.82-1.87 (3H, m, CH_2-3″, H-4″), 4.41 (1H, m, H-2″), 6.61 (1H, d, J = 2.1, H-6), 6.65 (1H, d, J = 7.2, CONH), 6.96 (1H, s, H-3), 7.01 (1H, d, J = 2.1, H-8), 7.56-7.69 (3H, m, H-3′, H-4′, H-5′), 8.14 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.95 (1H, s, OH-5).

7-*O*-(*N*-*t*-Butyloxycarbonyl-L-isoleucyl)-5-hydroxy-2-phenylchromen-4-one (6), yield 73%, mp 176-177°C, $C_{26}H_{29}NO_7$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.04 (3H, t, J = 5.7, CH_3-5″), 1.09 (3H, d, J = 6.9, CH_3-3″), 1.44 (1H, m, CH_2-4″a), 1.45 [9H, s, $(CH_3)_3C$], 1.66 (1H, m, CH_2-4″b), 2.10 (1H, m, H-3″), 4.49 (1H, m, H-2″), 5.06 (1H, m, CONH), 6.59 (1H, d, J = 2.1, H-6), 6.74 (1H, s, H-3), 6.87 (1H, d, J = 2.1, H-8), 7.50-7.60 (3H, m, H-3′, H-4′, H-5′), 7.95 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.75 (1H, s, OH-5).

7-*O*-(*N*-*t*-Butyloxycarbonyl-L-phenylalanyl)-5-hydroxy-2-phenylchromen-4-one (7), yield 83%, mp 208-209°C, $C_{29}H_{27}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.46 [9H, s, $(CH_3)_3C$], 3.21-3.45 (2H, m, CH_2-3″), 4.63 (1H, q, J = 7.2, H-2″), 6.50 (1H, d, J = 2.1, H-6), 6.62 (1H, d, J = 7.2, CONH), 6.90 (1H, d, J = 2.1, H-8), 6.93 (1H, s, H-3), 7.25-7.45 (5H, m, Ph-3″), 7.58-7.69 (3H, m, H-3′, H-4′, H-5′), 8.12 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.93 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxyglycyl)-5-hydroxy-2-phenylchromen-4-one (8), yield 85%, mp 224-225°C, $C_{25}H_{19}NO_7$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.27 (2H, d, J = 5.7, CH_2-2″), 5.17 (2H, s, PhC$\underline{H}_2$CO), 5.39 (1H, m, CONH), 6.59 (1H, d, J = 2.1, H-6), 6.73 (1H, s, H-3), 6.89 (1H, d, J = 2.1, H-8), 7.37 (5H, s, $\underline{Ph}CH_2CO$), 7.51-7.62 (3H, m, H-3′, H-4′, H-5′), 7.89 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.74 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxy-L-alanyl)-5-hydroxy-2-phenylchromen-4-one (9), yield 79%, mp 209-210°C, $C_{26}H_{21}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.59 (3H, d, J = 7.5, CH_3-3″), 4.52 (1H, m, H-2″), 5.15 (2H, s, PhC$\underline{H}_2$CO), 6.59 (1H, d, J = 2.1, H-6), 6.78 (1H, d, J = 7.2, CONH), 6.92 (1H, s, H-3), 6.95 (1H, d, J = 2.1, H-8), 7.28-7.44 (5H, m, $\underline{Ph}CH_2CO$), 7.55-7.69 (3H, m, H-3′, H-4′, H-5′), 8.11 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.90 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxy-L-valyl)-5-hydroxy-2-phenylchromen-4-one (10), yield 76%, mp 195-196°C, $C_{28}H_{25}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.13 (6H, d, J = 6.6, CH_3-4″, CH_3-3″), 2.41 (1H, m, H-3″), 4.38 (1H, t, J = 6.0, H-2″), 5.14 (2H, s, PhC$\underline{H}_2$CO), 6.60 (1H, d, J = 2.1, H-6), 6.92 (1H, d, J = 7.5, CONH), 6.95 (1H, s, H-3), 7.01 (1H, d, J = 2.1, H-8), 7.28-7.44 (5H, m, $\underline{Ph}CH_2CO$), 7.58-7.68 (3H, m, H-3′, H-4′, H-5′), 8.14 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.95 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxy-L-leucyl)-5-hydroxy-2-phenylchromen-4-one (11), yield 83%, mp 187-188°C, $C_{29}H_{27}NO_7$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.03 (6H, d, J = 5.7, CH_3-5″, CH_3-4″), 1.68-1.83 (3H, m, CH_2-3″, H-4″), 4.60 (1H, m, H-2″), 5.16 (2H, s, PhC$\underline{H}_2$CO), 5.26 (1H, d, J = 7.2, CONH), 6.57 (1H, d, J = 2.1, H-6), 6.72 (1H, s, H-3), 6.81 (1H, d, J = 2.1, H-8), 7.30-7.44 (5H, m, $\underline{Ph}CH_2CO$), 7.54-7.65 (3H, m, H-3′, H-4′, H-5′), 7.91 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.73 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxy-L-isoleucyl)-5-hydroxy-2-phenylchromen-4-one (12), yield 77%, mp 184-185°C, $C_{29}H_{27}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.00 (3H, t, J = 5.7, CH_3-5″), 1.11 (3H, d, J = 6.9, CH_3-3″), 1.48 (1H, m, CH_2-4″a), 1.69 (1H, m, CH_2-4″b), 2.12 (1H, m, H-3″), 4.43 (1H, m, H-2″), 5.14 (2H, s, PhC$\underline{H}_2$CO), 6.60 (1H, d, J = 2.1, H-6), 6.93 (1H, m, CONH), 6.95 (1H, s, H-3), 7.01 (1H, d, J = 2.1, H-8), 7.28-7.45 (5H, m, $\underline{Ph}CH_2CO$), 7.58-7.70 (3H, m, H-3′, H-4′, H-5′), 8.15 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.95 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxy-L-methionyl)-5-hydroxy-2-phenylchromen-4-one (13), yield 76%, mp 194-195°C, $C_{28}H_{25}NO_7S$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.14 (3H, s, SCH_3), 2.15-2.42 (2H, m, CH_2-4″), 2.67 (2H, m, CH_2-3″), 4.76 (1H, m, H-2″), 5.16 (2H, s, PhC$\underline{H}_2$CO), 5.54 (1H, d, J = 7.2, CONH), 6.58 (1H, d, J = 2.1, H-6), 6.75 (1H, s, H-3), 6.86 (1H, d, J = 2.1, H-8), 7.30-7.40 (5H, m, $\underline{Ph}CH_2CO$), 7.50-7.60 (3H, m, H-3′, H-4′, H-5′), 7.89 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.76 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxy-L-phenylalanyl)-5-hydroxy-2-phenylchromen-4-one (14), yield 86%, mp 228-229°C, $C_{32}H_{25}NO_7$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.20-3.35 (2H, m, CH_2-3″), 4.89 (1H, q, J = 7.2, H-2″), 5.14 (2H, s, PhC$\underline{H}_2$CO), 5.32 (1H, d, J = 7.2, CONH), 6.44 (1H, d, J = 2.1, H-6), 6.74 (1H, s, H-3), 6.78 (1H, d, J = 2.1, H-8), 7.18-7.35 (5H, m, $\underline{Ph}$-3″), 7.50-7.60 (3H, m, H-3′, H-4′, H-5′), 7.91 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.75 (1H, s, OH-5).

7-*O*-(*N*-*t*-Butyloxycarbonyl-*β*-alanyl)-5-hydroxy-2-phenylchromen-4-one (15), yield 68%, mp 193-194°C, $C_{23}H_{23}NO_7$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.47 [9H, s, $(CH_3)_3C$], 2.83 (2H, t, J = 7.2, CH_2-2″), 3.54 (2H, m, CH_2-3″), 5.01 (1H, m, CONH), 6.59 (1H, d, J = 2.1, H-6), 6.74 (1H, s, H-3), 6.88 (1H, d, J = 2.1, H-8), 7.52-7.61 (3H, m, H-3′, H-4′, H-5′), 7.92 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.74 (1H, s, OH-5).

7-*O*-(*N*-*t*-Butyloxycarbonyl-6-aminohexanoyl)-5-hydroxy-2-phenylchromen-4-one (16), yield 64%, mp 176-177°C, $C_{26}H_{29}NO_7$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.42-1.78 (6H, m, CH_2-3″, CH_2-4″, CH_2-5″), 1.45 [9H, s, $(CH_3)_3C$], 2.60 (2H, t, J = 7.2, CH_2-2″), 3.16 (2H, m, CH_2-6″), 4.56 (1H, m, CONH), 6.57 (1H, d, J = 2.1, H-6), 6.74 (1H, s, H-3), 6.85 (1H, d, J = 2.1, H-8), 7.52-7.60 (3H, m, H-3′, H-4′, H-5′), 7.90 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.72 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxy-β-alanyl)-5-hydroxy-2-phenylchromen-4-one (17), yield 76%, mp 208-209°C, $C_{26}H_{21}NO_7$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.86 (2H, t, J = 7.2, CH_2-2″), 3.60 (2H, m, CH_2-3″), 5.14 (2H, s, PhCH_2CO), 5.30 (1H, m, CONH), 6.57 (1H, d, J = 2.1, H-6), 6.75 (1H, s, H-3), 6.86 (1H, d, J = 2.1, H-8), 7.30-7.40 (5H, m, Ph-3″), 7.50-7.60 (3H, m, H-3′, H-4′, H-5′), 7.89 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.72 (1H, s, OH-5).

7-*O*-(*N*-Carbobenzyloxy-6-aminohexanoyl)-5-hydroxy-2-phenylchromen-4-one (18), yield 81%, mp 192-193°C, $C_{29}H_{27}NO_7$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 1.42-1.65 (4H, m, CH_2-3″, CH_2-4″), 1.72-1.80 (2H, m, CH_2-5″), 2.66 (2H, t, J = 7.2, CH_2-2″), 3.21 (2H, m, CH_2-6″), 5.06 (2H, s, PhCH_2CO), 6.38 (1H, m, CONH), 6.60 (1H, d, J = 2.1, H-6), 6.93 (1H, s, H-3), 7.02 (1H, d, J = 2.1, H-8), 7.25-7.42 (5H, m, PhCH_2CO), 7.56-7.68 (3H, m, H-3′, H-4′, H-5′), 8.12 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.91 (1H, s, OH-5).

7-*O*-(*N*-*p*-Tosyl-β-alanyl)-5-hydroxy-2-phenylchromen-4-one (19), yield 81%, mp 203-204°C, $C_{25}H_{21}NO_7S$.

PMR spectrum (300 MHz, CD_3COCD_3, δ, ppm, J/Hz): 2.43 (3H, s, CH_3-4‴), 2.89 (2H, t, J = 7.2, CH_2-2″), 3.35 (2H, m, CH_2-3″), 6.61 (1H, d, J = 2.1, H-6), 6.68 (1H, t, J = 7.2, SO_2NH), 6.92 (1H, s, H-3), 7.01 (1H, d, J = 2.1, H-8), 7.42 (2H, d, J = 8.1, H-3‴, H-5‴), 7.55-7.65 (3H, m, H-3′, H-4′, H-5′), 7.82 (2H, d, J = 8.1, H-2‴, H-6‴), 8.11 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.89 (1H, s, OH-5).

7-*O*-(*N*-*p*-Tosyl-6-aminohexanoyl)-5-hydroxy-2-phenylchromen-4-one (20), yield 76%, mp 195-196°C, $C_{28}H_{27}NO_7S$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.42 (2H, m, CH_2-4″), 1.55 (2H, m, CH_2-3″), 1.72 (2H, m, CH_2-5″), 2.43 (3H, s, CH_3-4‴), 2.56 (2H, t, J = 7.2, CH_2-2″), 2.99 (2H, m, CH_2-6″), 4.55 (1H, t, J = 7.2, SO_2NH), 6.54 (1H, d, J = 2.1, H-6), 6.75 (1H, s, H-3), 6.85 (1H, d, J = 2.1, H-8), 7.32 (2H, d, J = 8.1, H-3‴, H-5‴), 7.50-7.61 (3H, m, H-3′, H-4′, H-5′), 7.76 (2H, d, J = 8.1, H-2‴, H-6‴), 7.89 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.73 (1H, s, OH-5).

Ethyl-[(5-hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetate (21). A hot solution of chrysin (25.42 g, 100 mmol) in anhydrous acetone (150 mL) was treated with freshly calcined potash (41.40 g, 0.3 mol), stirred vigorously, heated (50-56°C) for 1 h, treated dropwise with ethylbromoacetate (12.2 mL, 110 mmol), and heated for 2 h with vigorous stirring (course of reaction monitored by TLC). When the reaction was finished, the mixture was poured into H_2SO_4 solution (1 L, 1 N). The resulting precipitate was filtered and crystallized from propanol-2. Yield 86%, mp 164-165°C (lit. [36] mp 157°C), $C_{19}H_{16}O_6$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.24 (3H, t, J = 7.2, CH_3-2′), 4.21 (2H, q, CH_2-1′), 4.96 (2H, s, OCH_2-7), 6.44 (1H, d, J = 2.1, H-6), 6.86 (1H, d, J = 2.1, H-8), 7.06 (1H, s, H-3), 7.54-7.68 (3H, m, H-3′, H-4′, H-5′), 8.10 (2H, dd, J = 2.1, 8.4, H-2′, H-6′), 12.82 (1H, s, OH-5).

[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetic Acid (22). A solution of **21** (23.82 g, 70 mmol) in propanol-2 (150 mL) was treated with NaOH solution (150 mL, 1 N), stirred vigorously, and refluxed for 2 h (course of reaction monitored by TLC). When the reaction was finished, the mixture was treated with H_2SO_4 solution (400 mL, 1 N). The resulting precipitate was filtered and crystallized from propanol-2 (50%). Yield 91%, mp 261-262°C (lit. [37] mp 266-268°C), $C_{17}H_{21}O_6$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 4.84 (2H, s, OCH_2-7), 6.39 (1H, d, J = 2.0, H-6), 6.79 (1H, d, J = 2.0, H-8), 7.01 (1H, s, H-3), 7.52-7.67 (3H, m, H-3′, H-4′, H-5′), 8.07 (2H, dd, J = 2.0, 8.4, H-2′, H-6′), 12.15 (1H, br.s, OH-5), 12.79 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetylamino Acids 23-33.** A cooled solution of acid **22** (1.25 g, 4 mmol) and *N*-hydroxysuccinimide (0.51 g, 4.4 mmol) in anhydrous DMF (10 mL) was treated with DIC (0.69 mL, 4.4 mmol) and stirred vigorously for 2 h (course of reaction monitored by TLC). The resulting *N*-hydroxysuccinimide ester was treated with a solution of the appropriate amino acid (4.4 mmol) and NaOH (0.18 g, 4.4 mmol) in water (10 mL) and stirred for 3-4 h (course of reaction monitored by TLC). After the reaction was finished, water (100 mL) was added. The pH was adjusted to 4. The precipitate was filtered and crystallized from propanol-2.

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetylglycine (23)**, yield 72%, mp 264-265°C, $C_{19}H_{15}NO_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.85 (2H, d, J = 6.0, CH_2-2″), 4.72 (2H, s, OCH_2-7), 6.47 (1H, d, J = 2.0, H-6), 6.85 (1H, d, J = 2.0, H-8), 7.07 (1H, s, H-3), 7.58-7.64 (3H, m, H-3′, H-4′, H-5′), 8.10 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.53 (1H, d, J = 5.6, CONH), 12.35 (1H, br.s, COOH), 12.82 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-L-alanine (24)**, yield 81%, mp 249-250°C, $C_{20}H_{17}NO_7$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.33 (3H, d, J = 7.2, CH_3-2″), 4.29 (1H, m, H-2″), 4.80 (2H, q, J = 8.0, OCH_2-7), 6.43 (1H, d, J = 2.0, H-6), 6.79 (1H, d, J = 2.0, H-8), 7.06 (1H, s, H-3), 7.58-7.65 (3H, m, H-3′, H-4′, H-5′), 8.09 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.37 (1H, d, J = 7.2, CONH), 12.40 (1H, br.s, COOH), 12.79 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-L-valine (25)**, yield 77%, mp 254-255°C, $C_{22}H_{21}NO_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.92 (6H, d, J = 7.2, CH_3-4″, CH_3-3″), 2.13 (1H, m, H-3″), 4.24 (1H, m, H-2″), 4.80 (2H, q, J = 8.0, OCH_2-7), 6.43 (1H, d, J = 2.0, H-6), 6.79 (1H, d, J = 2.0, H-8), 7.06 (1H, s, H-3), 7.58-7.65 (3H, m, H-3′, H-4′, H-5′), 8.09 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.33 (1H, d, J = 8.4, CONH), 12.48 (1H, br.s, COOH), 12.79 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-L-methionine (26)**, yield 74%, mp 232-233°C, $C_{22}H_{21}NO_7S$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.95-2.08 (2H, m, CH_2-4″), 2.02 (3H, s, SCH_3), 2.45 (2H, m, CH_2-3″), 4.42 (1H, m, H-2″), 4.74 (2H, q, J = 8.0, OCH_2-7), 6.45 (1H, d, J = 2.0, H-6), 6.81 (1H, d, J = 2.0, H-8), 7.07 (1H, s, H-3), 7.57-7.64 (3H, m, H-3′, H-4′, H-5′), 8.09 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.42 (1H, d, J = 7.6, CONH), 12.64 (1H, br.s, COOH), 12.81 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-L-phenylalanine (27)**, yield 88%, mp 268-269°C, $C_{26}H_{21}NO_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.99 (1H, dd, J = 12.0, 16.4, CH_2-3″a), 3.10 (1H, dd, J = 2.8, 16.4, CH_2-3″b), 4.52 (1H, m, H-2″), 4.65 (2H, q, J = 8.8, OCH_2-7), 6.41 (1H, d, J = 2.0, H-6), 6.72 (1H, d, J = 2.0, H-8), 7.08 (1H, s, H-3), 7.13-7.21 (5H, m, Ph-3″), 7.57-7.64 (3H, m, H-3′, H-4′, H-5′), 8.09 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.44 (1H, d, J = 8.0, CONH), 12.60 (1H, br.s, COOH), 12.82 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-L-phenylglycine (28)**, yield 78%, mp 276-277°C, $C_{25}H_{19}NO_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 4.81 (2H, q, J = 8.8, OCH_2-7), 5.43 (1H, d, J = 7.2, H-2″), 6.44 (1H, d, J = 2.0, H-6), 6.79 (1H, d, J = 2.0, H-8), 7.06 (1H, s, H-3), 7.25-7.45 (5H, m, Ph-2″), 7.56-7.64 (3H, m, H-3′, H-4′, H-5′), 8.09 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.93 (1H, d, J = 7.6, CONH), 12.65 (1H, br.s, COOH), 12.81 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-*β*-alanine (29)**, yield 83%, mp 252-253°C, $C_{20}H_{17}NO_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.44 (2H, t, J = 6.8, CH_2-2″), 3.36 (2H, m, CH_2-3″), 4.64 (2H, s, OCH_2-7), 6.44 (1H, d, J = 2.0, H-6), 6.82 (1H, d, J = 2.0, H-8), 7.06 (1H, s, H-3), 7.58-7.64 (3H, m, H-3′, H-4′, H-5′), 8.11 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.23 (1H, d, J = 5.2, CONH), 12.35 (1H, br.s, COOH), 12.82 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-4-aminobutanoic acid (30)**, yield 76%, mp 248-249°C, $C_{21}H_{19}NO_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.69 (2H, m, CH_2-3″), 2.24 (2H, t, J = 6.8, CH_2-2″), 3.17 (2H, m, CH_2-4″), 4.64 (2H, s, OCH_2-7), 6.45 (1H, d, J = 2.0, H-6), 6.82 (1H, d, J = 2.0, H-8), 7.05 (1H, s, H-3), 7.57-7.64 (3H, m, H-3′, H-4′, H-5′), 8.09 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.22 (1H, d, J = 5.2, CONH), 12.10 (1H, br.s, COOH), 12.81 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-6-aminohexanoic acid (31)**, yield 81%, mp 225-226°C, $C_{23}H_{23}NO_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.22 (2H, m, CH_2-4″), 1.44 (4H, m, CH_2-3″, CH_2-5″), 2.16 (2H, t, J = 7.2, CH_2-2″), 3.14 (2H, m, CH_2-6″), 4.63 (2H, s, OCH_2-7), 6.45 (1H, d, J = 2.0, H-6), 6.83 (1H, d, J = 2.0, H-8), 7.07 (1H, s, H-3), 7.57-7.64 (3H, m, H-3′, H-4′, H-5′), 8.10 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.18 (1H, d, J = 5.2, CONH), 11.90 (1H, br.s, COOH), 12.82 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetyl-*trans*-4-aminomethylcyclohexane carboxylic acid (32)**, yield 86%, mp 264-265°C, $C_{25}H_{25}NO_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.88 and 1.18 (4H, two m, CH_2-3″, CH_2-5″), 1.25 (1H, m, H-4″), 1.73 and 1.87 (4H, two m, CH_2-3″, CH_2-5″), 2.10 (1H, m, H-1″), 3.00 (2H, t, J = 7.2, CH_2-1″), 4.66 (2H, s, OCH_2-7), 6.45 (1H, d, J = 2.0, H-6), 6.81 (1H, d, J = 2.0, H-8), 7.06 (1H, s, H-3), 7.57-7.64 (3H, m, H-3′, H-4′, H-5′), 8.10 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.15 (1H, d, J = 5.6, CONH), 12.05 (1H, br.s, COOH), 12.81 (1H, s, OH-5).

***N*-[(5-Hydroxy-4-oxo-2-phenylchromen-7-yl)oxy]acetylglycylglycine (33)**, yield 69%, mp 235-236°C, $C_{21}H_{18}N_2O_7$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.80 and 3.85 (4H, two d, J = 6.0, CH_2-2″, CH_2-2‴), 4.72 (2H, s, OCH_2-7), 6.48 (1H, d, J = 2.0, H-6), 6.89 (1H, d, J = 2.0, H-8), 7.07 (1H, s, H-3), 7.57-7.64 (3H, m, H-3′, H-4′, H-5′), 8.12 (2H, dd, J = 2.0, 8.0, H-2′, H-6′), 8.18, 8.20 (two t, J = 5.6, two CONH), 12.45 (1H, br.s, COOH), 12.82 (1H, s, OH-5).

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