DOI 10.1007/s10600-019-02821-5
Chemistry of Natural Compounds, Vol. 55, No. 5, September, 2019

SYNTHESIS OF ISOFLAVONE–AMINO-ACID CONJUGATES

M. M. Garazd[1] and M. S. Frasinyuk[2*]

Conjugates of natural and synthetic amino acids and 7-hydroxyisoflavone in which the amino-acid residue was bonded to the isoflavone through a hydroxyacetate linker were prepared using the activated ester method.

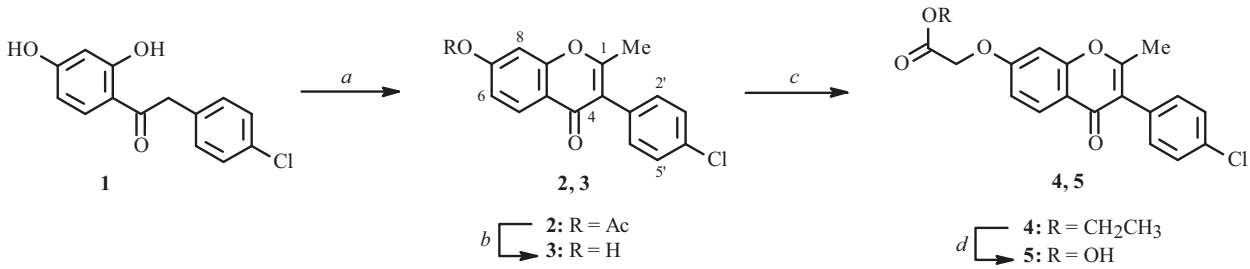
Keywords: flavonoids, isoflavone, amino acids, amino-acid derivatives, conjugates.

Isoflavones comprise a group of natural flavonoids that play important roles by affecting *in vivo* biochemical processes [1]. On the other hand, the huge significance of amino acids in metabolic processes stimulated a search for novel biologically active natural amino acids, their synthetic analogs, and various compounds containing amino acids. In this respect, conjugation of flavonoids and amino acids is interesting for both the theory of organic synthesis and targeted preparation of new biologically active compounds. Flavonoids with amino acids in their structures are known to act as cyclin-dependent kinase 2 (CDK2) inhibitors [2, 3] and antitumor agents [4, 5].

The goal of the present work was to functionalize an isoflavonoid by introducing an additional pharmacophore, i.e., a natural or synthetic amino acid. Such modification is an important tool for increasing the bioavailability of biologically active flavonoids [6].

Derivatives of 4′-chloroisoflavone are promising from a pharmacological aspect as analogs of natural compounds [7]. Also, we recently showed that 4′-chloroisoflavone derivatives containing cytisine are inhibitors of hydroxysteroid 17β-dehydrogenase-4 (HSD17B4) [8], an enzyme playing an important role in carcinogenesis [9].

Cyclization of 1-(2,4-dihydroxyphenyl)-2-(4-chlorophenyl)ethanone (**1**) by an Ac_2O–Et_3N mixture gave acetoxyisoflavone **2**, which was converted by NaOH in EtOH into 7-hydroxy-2-methylisoflavone (**3**). Alkylation of isoflavone **3** by ethyl bromoacetate in the presence of potash in Me_2CO afforded ester **4**, further heating of which in AcOH in the presence of H_2SO_4 synthesized chromonoxyacetic acid **5**, the synthon required to construct isoflavone–amino-acid conjugates.

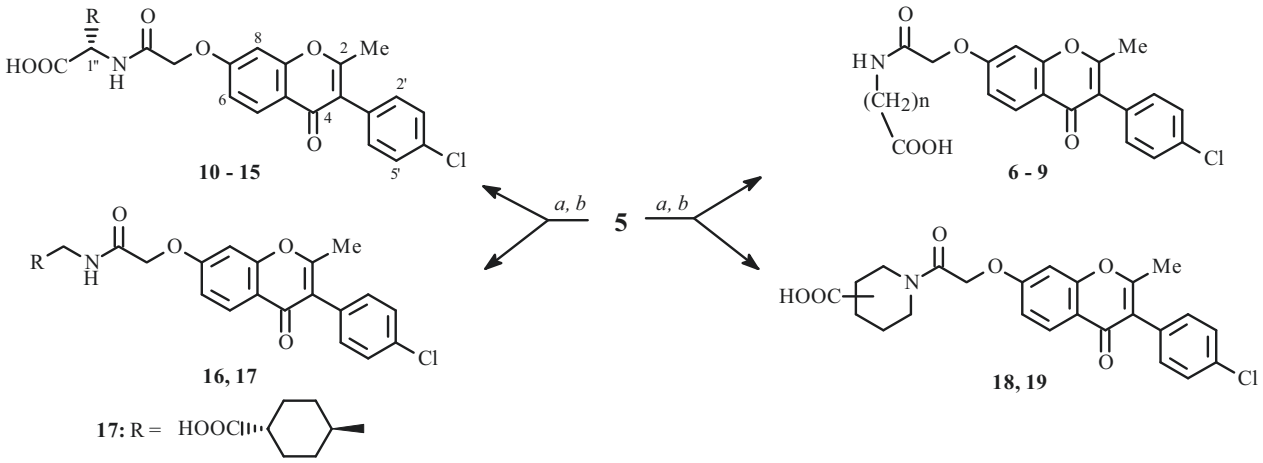


a. Ac_2O, Et_3N, 140°C; *b*. NaOH, EtOH, 78°C; *c*. $BrCH_2COOEt$, K_2CO_3, Me_2CO, 78°C; *d*. H_2SO_4, AcOH, 100–110°C

The carboxylic acids were activated using *N*-hydroxysuccinimide esters, which were highly reactive and did not racemize the synthetic products [10], which could also be used successfully to synthesize such compounds [11, 12].

The intermediate activated ester was produced by treating acid **5** with *N*-hydroxysuccinimide (SuOH) in anhydrous dioxane using diisopropylcarbodiimide (DIC). Reaction of the activated ester and amino-acid sodium salts in dioxane–H_2O (1:1) at room temperature followed by acidolysis of the resulting salts gave in high yields (61–89%) amino-acid derivatives **6**–**19** containing free carboxylic acids.

1) Eximed, 50 Kharkovskoe Shosse, Kiev, 02160, Ukraine; 2) V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, 1 Murmanskaya St., Kiev, 02094, Ukraine; e-mail: mykhaylo.frasinyuk@ukr.net. Translated from *Khimiya Prirodnykh Soedinenii*, No. 5, September–October, 2019, pp. 702–705. Original article submitted March 5, 2019.



n = 1 (**6**), 2 (**7**), 3 (**8**), 4 (**9**)

10: R = Me; **11:** R = *i*Pr; **12:** R = *sec*-Bu; **13:** R = *i*-Bu; **14:** R = CH_2CH_3SMe; **15:** R = Ph; **16:** R = $CONHCH_2COOH$; **18:** 3-COOH; **19:** 4-COOH

a. SuOH, 1,4-dioxane, DIC, room temp.; *b*. 1. amino acid, $NaHCO_3$, 2. HCl

Derivatives of 4′-chloroisoflavone containing glycine (**6**), *β*-alanine (**7**), L-alanine (**10**), L-valine (**11**), L-isoleucine (**12**), L-leucine (**13**), L-methionine (**14**), and L-phenylglycine (**15**) and 4-aminobutanoic (**8**), 6-aminohexanoic (**9**), *trans*-4-aminomethylcyclohexanecarboxylic (**17**), piperidine-3-carboxylic (**18**), and piperidine-4-carboxylic acids (**19**) in addition to glycylglycine (**16**) were synthesized.

NMR spectra of **6**–**19** showed resonances for isoflavone and amino-acid protons in addition to the protons of the resulting amide bond at 8.20–8.95 ppm and the free carboxylic acid at 12.01–13.10 ppm.

Thus, isoflavone–amino-acid conjugates were prepared using activated esters and did not require protection and subsequent deprotection of the carboxylic acids. This method could be expanded for targeted synthesis and increased bioavailability of biologically active flavonoids.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck plates (Germany). The eluents were CH_2Cl_2–MeOH mixtures (100:1 and 50:1). PMR spectra were measured on the δ-scale vs. TMS (internal standard) using an M-400 instrument (Varian, 400 MHz). Elemental analyses of all compounds agreed with those calculated.

1-(2,4-Dihydroxyphenyl)-2-(4-chlorophenyl)ethanone (1). A mixture of 4-chlorophenylacetonitrile (15.1 g, 0.1 mol) and resorcinol (11.0 g, 0.1 mol) in $BF_3 \cdot Et_2O$ (50 mL) was stirred for 4–6 h with purging by dry HCl, poured after 12 h with stirring into H_2O heated to 80°C, refluxed for 1.5–2 h, and cooled. The resulting precipitate was filtered off, rinsed with cold H_2O, and crystallized from MeOH. Yield 20.5 g (78 %), mp 153–154°C, $C_{14}H_{11}ClO_3$. ^{1}H NMR spectrum (400 MHz., DMSO-d_6, δ, ppm, J/Hz): 4.33 (2H, s, $COCH_2$), 6.27 (1H, d, J = 2.4, H-3), 6.41 (1H, dd, J = 8.8, 2.4, H-5), 7.31 (2H, d, J = 8.8, H-3′, 5′), 7.38 (2H, d, J = 8.8, H-2′, 6′), 7.94 (1H, d, J = 8.8, H-6), 10.72 (1H, s, 4-OH), 12.42 (1H, s, 2-OH).

2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl Acetate (2). A solution of **1** (13.1 g, 50 mmol) in a mixture of Ac_2O (23 mL, 250 mmol) and NEt_3 (28 mL, 200 mmol) was heated at 120–130°C for 6–10 h. The reaction mixture was poured into cold H_2O (500 mL). The resulting precipitate was filtered off and crystallized from *i*-PrOH. Yield 11.1 g (68%), mp 162–164°C, $C_{18}H_{13}ClO_4$. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.31 (3H, s, CH_3COO-7), 2.36 (3H, s, CH_3-2), 7.13 (1H, dd, J = 8.8, 2.4, H-6), 7.22 (2H, d, J = 8.8, H-3′, 5′), 7.28 (1H, d, J = 2.4, H-8), 7.42 (2H, d, J = 8.8, H-2′, 6′), 8.23 (1H, d, J = 8.8, H-5).

7-Hydroxy-2-methyl-3-(4-chlorophenyl)-4*H*-chromen-4-one (3). A hot solution of **2** (3.3 g, 10 mmol) in EtOH (20 mL) was treated with NaOH solution (10 mL, 1 N), refluxed for 5 min, diluted with H_2O (20 mL), refluxed for another 10 min, and neutralized with dilute HCl to pH 7. The resulting precipitate was filtered off and crystallized from DMF–MeOH. Yield 2.34 g (82%), mp 295–297°C, $C_{16}H_{11}ClO_3$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.45 (3H, s, CH_3-2), 6.85 (1H, d, J = 2.0, H-8), 6.92 (1H, dd, J = 8.8, 2.0, H-6), 7.31 (2H, d, J = 8.3, H-3′, 5′), 7.49 (2H, d, J = 8.3, H-2′, 6′), 7.84 (1H, d, J = 8.8, H-5), 10.81 (1H, s, 7-OH).

Ethyl {[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetate (4). A hot solution of **3** (2.86 g, 10 mmol) in anhydrous Me_2CO (30 mL) was treated with freshly calcined potash (2.1 g, 15 mmol), stirred, refluxed, treated with ethyl bromoacetate (1.32 mL, 12 mmol), held at 50°C for 1–4 h (end of reaction determined by TLC), and poured into acidified ice water (100 mL). The resulting precipitate was filtered off and recrystallized from EtOH. Yield 3.20 g (86%), mp 134–136°C, $C_{20}H_{17}ClO_5$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.24 (3H, t, J = 7.1, CH_3-2″), 2.28 (3H, s, CH_3-2), 4.19 (2H, q, J = 7.1, CH_2-1″), 5.00 (2H, s, 7-OCH_2), 7.10 (1H, dd, J = 8.8, 2.4, H-6), 7.18 (1H, d, J = 2.4, H-8), 7.33 (2H, d, J = 8.8, H-3′, 5′), 7.51 (2H, d, J = 8.8, H-2′, 6′), 7.96 (1H, d, J = 8.8, H-5).

{[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetic Acid (5). A solution of **4** (3.72 g, 10 mmol) in AcOH (20 mL) was treated with conc. H_2SO_4 (1 mL), heated at 100–110°C for 8–12 h, and poured into cold H_2O (100 mL). The resulting precipitate was filtered off and recrystallized from DMF–H_2O. Yield 2.58 g (75%), mp 227–229°C, $C_{18}H_{13}ClO_5$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, s, CH_3-2), 4.89 (2H, s, 7-OCH_2), 7.08 (1H, dd, J = 8.8, 2.4, H-6), 7.12 (1H, d, J = 2.4, H-8), 7.32 (2H, d, J = 8.8, H-3′, 5′), 7.50 (2H, d, J = 8.8, H-2′, 6′), 7.95 (1H, d, J = 8.8, H-5), 13.18 (1H, br.s, COOH).

General Method for Synthesizing *N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)amino Acids 6–19. A solution of **5** (1.03 g, 3 mmol) and SuOH (0.38 g, 3.3 mmol) in anhydrous dioxane (20 mL) was stirred vigorously, treated with DIC (0.52 mL, 3.3 mol), and stirred for 2 h (course of reaction monitored by TLC). The resulting activated ester was treated with a solution of the appropriate amino acid (3.3 mmol) and $NaHCO_3$ (0.28 g, 3.3 mmol) in H_2O (20 mL), and stirred vigorously for 2–4 h (course of reaction monitored by TLC). When the reaction was finished, the precipitate of diisopropylurea was filtered off. The filtrate was treated with H_2O (200 mL) and acidified to pH 5–6. The resulting precipitate was filtered off and crystallized from aqueous *i*-PrOH.

***N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)glycine (6).** Yield 0.87 g (72%), mp 221–222°C, $C_{20}H_{16}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.28 (3H, s, CH_3-2), 3.83 (2H, d, J = 5.6, CH_2-1″), 4.72 (2H, s, 7-OCH_2), 7.11–7.17 (2H, m, H-6, 8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.97 (1H, d, J = 8.8, H-5), 8.52 (1H, t, J = 5.6, NH).

***N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)-*β*-alanine (7).** Yield 1.11 g (89%), mp 217–218°C, $C_{21}H_{18}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, s, CH_3-2), 2.45 (2H, t, J = 7.0, CH_2-2″), 3.35 (2H, m, CH_2-1″), 4.66 (2H, s, 7-OCH_2), 7.07–7.15 (2H, m, H-6, 8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.97 (1H, d, J = 8.8, H-5), 8.29 (1H, t, J = 5.4, NH).

4-[({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)amino]butanoic Acid (8). Yield 0.95 g (74%), mp 202–203°C, $C_{22}H_{20}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.62–1.73 (2H, m, CH_2-2″), 2.19–2.25 (2H, m, CH_2-3″), 2.27 (3H, s, CH_3-2), 3.12–3.21 (2H, m, CH_2-1″), 4.67 (2H, s, 7-OCH_2), 7.10–7.15 (2H, m, H-6, 8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.97 (1H, d, J = 8.8, H-5), 8.27 (1H, t, J = 5.8, NH), 12.13 (br.s, COOH).

6-[({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)amino]hexanoic Acid (9). Yield 1.12 g (82%), mp 195–196°C, $C_{24}H_{24}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.19–1.55 (6H, m, CH_2-2″, 3″, 4″), 2.12–2.20 (2H, m, CH_2-5″), 2.27 (3H, s, CH_3-2), 3.09–3.18 (2H, m, CH_2-1″), 4.66 (2H, s, 7-OCH_2), 7.08–7.16 (2H, m, H-6, 8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.97 (1H, d, J = 8.8, H-5), 8.20 (1H, t, J = 5.6, NH), 12.01 (br.s, COOH).

***N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)-L-alanine (10).** Yield 1.02 g (82%), mp 209–210°C, $C_{21}H_{18}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.34 (3H, d, J = 7.1, CH_3-2″), 2.27 (3H, s, CH_3-2), 4.27–4.38 (1H, m, CH-1″), 4.70, 4.75 (1H each, d, J = 14.9, 7-OCH_2), 7.10–7.17 (2H, m, H-6, 8), 7.32 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.96 (1H, d, J = 8.8, H-5), 8.52 (1H, d, J = 7.6, NH), 12.73 (br.s, COOH).

***N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)-L-valine (11).** Yield 1.01 g (76%), mp 201–202°C, $C_{23}H_{22}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.92 (6H, d, J = 6.8, CH_3-2″), 2.07–2.20 (1H, m, CH-2″), 2.27 (3H, s, CH_3-2), 4.18 (1H, dd, J = 9.0, 5.6, CH-1″), 4.79, 4.84 (1H each, d, J = 14.9, 7-OCH_2), 7.07–7.14 (2H, m, H-6, 8), 7.32 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.95 (1H, d, J = 9.0, H-5), 8.33 (1H, d, J = 9.0, NH), 12.82 (br.s, COOH).

***N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)-L-isoleucine (12).** Yield 1.20 g (88%), mp 188–189°C, $C_{24}H_{24}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.80–0.95 (6H, m, CH_3-2″, 4″), 1.14–1.30, 1.36–1.52 (1H each, m, CH_2-3″), 1.79–1.92 (1H, m, CH-2″), 2.27 (3H, s, CH_3-2), 4.12–4.28 (1H, dd, J = 6.6, 7.8, CH-1″), 4.78, 4.82 (1H each, d, J = 14.9, 7-OCH_2), 7.07–7.14 (2H, m, H-6, 8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.95 (1H, d, J = 9.0, H-5), 8.34 (1H, d, J = 7.8, NH), 12.80 (br.s, COOH).

***N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)-L-leucine (13).** Yield 1.15 g (84%), mp 196–197°C, $C_{24}H_{24}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.85, 0.90 (3H each, d, J = 5.6, CH_3-4″, 5″), 1.52–1.72 (3H, m, CH_2-2″, CH-3″), 2.27 (3H, s, CH_3-2), 4.28–4.37 (1H, m, CH-1″), 4.72, 4.79 (1H each, d, J = 14.9, 7-OCH_2), 7.06–7.16 (2H, m, H-6, 8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.96 (1H, d, J = 9.0, H-5), 8.48 (1H, d, J = 7.6, NH), 12.68 (br.s, COOH).

***N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)-L-methionine (14).** Yield 0.91 g (64%), mp 167–168°C, $C_{23}H_{22}ClNO_6S$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.88–2.01 (2H, m, CH_2-2″), 2.03 (3H, s, SCH_3), 2.27 (3H, s, CH_3-2), 2.40–2.50 (2H, m, CH_2-3″), 4.38–4.47 (1H, m, CH-1″), 4.74, 4.79 (1H each, d, J = 15.0, 7-OCH_2), 7.09–7.16 (2H, m, H-6, 8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.97 (1H, d, J = 9.0, H-5), 8.52 (1H, d, J = 7.6, NH), 12.81 (br.s, COOH).

(2*S*)-[({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)amino](phenyl)acetic Acid (15). Yield 1.22 g (85%), mp 239–240°C, $C_{26}H_{20}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, s, CH_3-2), 4.81, 4.86 (1H each, d, J = 14.9, 7-OCH_2), 5.42 (1H, d, J = 7.6, CH-1″), 7.06–7.13 (2H, m, H-6, 8), 7.32 (2H, d, J = 8.5, H-3′, 5′), 7.34–7.46 (5H, m, Ph-1″), 7.51 (2H, d, J = 8.5, H-2′, 6′), 7.95 (1H, d, J = 8.5, H-5), 8.95 (1H, d, J = 7.6, NH), 13.10 (br.s, COOH).

***N*-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)glycylglycine (16).** Yield 1.12 g (81%), mp 211–212°C, $C_{22}H_{19}ClN_2O_7$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.28 (3H, s, CH_3-2), 3.79, 3.84 (2H each, d, J = 5.9, CH_2-1″, 1‴), 4.74 (2H, s, 7-OCH_2), 7.11–7.20 (2H, m, H-6, 8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.51 (2H, d, J = 8.5, H-2′, 6′), 7.98 (1H, d, J = 8.8, H-5), 8.27, 8.48 (1H each, t, J = 5.9, 2 NH), 12.63 (br.s, COOH).

***trans*-4-{[({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)amino]methyl} cyclohexanecarboxylic Acid (17).** Yield 1.15 g (79%), mp 197–198°C, $C_{26}H_{26}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.81–0.96, 1.14–1.45, 1.64–1.74, 1.82–1.92, 2.02–2.15 (2H, 3H, 2H, 2H, 1H, 5m, cyclohexane protons), 2.27 (3H, s, CH_3-2), 2.95–3.05 (2H, m, CH_2-1″), 4.69 (2H, s, 7-OCH_2), 7.09 (1H, d, J = 2.2, H-8), 7.12 (1H, dd, J = 8.8, 2.2, H-6), 7.32 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.97 (1H, d, J = 8.8, H-5), 8.21 (1H, t, J = 5.3, NH), 12.02 (br.s, COOH).

1-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)piperidine-3-carboxylic Acid (18). Yield 0.83 g (61%), mp 174–175°C, $C_{24}H_{22}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.33–1.80, 1.90–2.03, 2.31–2.38, 2.58–2.66, 2.79–2.92, 3.03–3.17, 3.36–3.45, 3.68–3.81, 4.28–4.39 (3H, 1H, 0.5H, 0.5H, 0.5H, 1H, 0.5H, 1.5H, 0.5H, 9m, piperidine protons), 2.27 (3H, s, CH_3-2), 5.04, 5.11 (1H each, s, 7-OCH_2), 7.07 (1H, dd, J = 8.8, 2.2, H-6), 7.13 (1H, d, J = 2.2, H-8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.94 (1H, d, J = 8.8, H-5), 12.52 (br.s, COOH).

1-({[2-Methyl-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl]oxy}acetyl)piperidine-4-carboxylic Acid (19). Yield 1.16 g (85%), mp 192–193°C, $C_{24}H_{22}ClNO_6$. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.33–1.48, 1.54–1.68, 1.79–1.94, 2.49–2.59, 2.73–2.85, 3.08–3.18, 3.71–3.83, 4.13–4.24 (1H, 1H, 2H, 1H, 1H, 1H, 1H, 1H, 8m, piperidine protons), 2.27 (3H, s, CH_3-2), 5.02, 5.07 (1H each, d, J = 14.9, 7-OCH_2), 7.07 (1H, dd, J = 8.8, 2.2, H-6), 7.14 (1H, d, J = 2.2, H-8), 7.33 (2H, d, J = 8.5, H-3′, 5′), 7.50 (2H, d, J = 8.5, H-2′, 6′), 7.94 (1H, d, J = 8.8, H-5), 12.34 (br.s, COOH).

REFERENCES

1. O. M. Andersen and K. R. Markham, *Flavonoids: Chemistry Biochemistry Applications*, CRC Press, Boca Raton, 2006, 1197 pp.
2. J. Kim, Y. Lee, H. Kim, S.-Y. Kang, K.-S. Park, J.-H. Cho, Y.-Y. Lee, B.-S. Kim, Y. Lim, and Y. Chong, *Bull. Korean Chem. Soc.*, **26**, 2065 (2005).
3. H. Kim, E. Lee, J. Kim, J. Kim, H. Lim, C.-H. Lee, J.-H. Ahn, Y. Chong, and Y. Lim, *Bull. Korean Chem. Soc.*, **28**, 1413 (2007).
4. X. Song, Y. Liu, J. Ma, J. He, X. Zheng, X. Lei, G. Jiang, and L. Zhang, *Med. Chem. Res.*, **24**, 1789 (2015).
5. D. Liu, Y. Li, H. Shen, Y. Li, J. He, Q. Zhang, and Y. Liu, *Chin. Herb. Med.*, **10**, 323 (2018).
6. M. Ninomiya, K. Tanaka, Y. Tsuchida, Y. Muto, M. Koketsu, and K. Watanabe, *J. Med. Chem.*, **54**, 1529 (2011).

7. S. Wetzel, W. Wilk, S. Chammaa, B. Sperl, A. G. Roth, A. Yektaoglu, S. Renner, T. Berg, C. Arenz, A. Giannis, T. I. Oprea, D. Rauh, M. Kaiser, and H. Waldmann, *Angew. Chem., Int. Ed.*, **49**, 3666 (2010).
8. M. S. Frasinyuk, W. Zhang, P. Wyrebek, T. Yu, X. Xu, V. M. Sviripa, S. P. Bondarenko, Y. Xie, H. X. Ngo, A. J. Morris, J. L. Mohler, M. Fiandalo, D. S. Watt, and C. Liu, *Org. Biomol. Chem.*, **15**, 7623 (2017).
9. H.-K. Ko, M. Berk, Y.-M. Chung, B. Willard, R. Bareja, M. Rubin, A. Sboner, and N. Sharifi, *Cell Rep.*, **22**, 809 (2018).
10. G. W. Anderson, J. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **85**, 3039 (1963).
11. M. M. Garazd, Ya. L. Garazd, and V. P. Khilya, *Chem. Nat. Compd.*, **37**, 32 (2001).
12. M. V. Veselovskaya, M. M. Garazd, A. S. Ogorodniichuk, Ya. L. Garazd, and V. P. Khilya, *Chem. Nat. Compd.*, **44**, 704 (2008).