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SYNTHESIS OF DIPEPTIDE DERIVATIVES OF 3,4-SUBSTITUTED 7-HYDROXYCOUMARINS

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Coumarins modified with dipeptides were prepared by condensation of N-*hydroxysuccinimide esters of 2-(3,4,8-substituted-2-oxo-2*H-*7-chromenyloxy)- and 2-(3,4-substituted-7-methyl-2-oxo-2*H-*5-chromenyloxy)acetic and -propionic acids with amino acids and dipeptides.*

Key words: coumarins, amino-acid derivatives, dipeptides, activated esters, synthesis.

We have previously reported the preparation of several coumarins and furocoumarins modified with amino acids. In continuation of this work, we investigated the synthesis of substances in which a dipeptide would be added to the benzopyran core.

Starting 3,4-disubstituted 7-hydroxycoumarins were synthesized by Pechmann condensation of the corresponding resorcinols and esters of substituted β-ketoacids in the presence of H_2SO_4 as condensing agent [3, 4]. PMR spectra of the starting coumarins contained resonances typical of the coumarin system and its substituents.

Williamson reaction of the 7-hydroxycoumarins with methylchloroacetate using potash as the base produced the corresponding esters of substituted 2-oxo-2*H*-7-chromenyloxyacetic acids. The esters were hydrolyzed by heating with sodium bicarbonate solution (5%). The structures of the resulting acids were confirmed by PMR spectroscopy. The spectra of the products (**11**-**20**) lacked a resonance for the hydroxyl proton of the starting 7-hydroxycoumarins and contained resonances for the acetic acid as a very broad singlet for the carboxyl at 12.0-12.5 ppm and a resonance for the α-CH_2 protons at 4.5-5.0 ppm.

Dipeptide derivatives of **11**-**20** could be prepared by two routes, addition of the dipeptide or successive elongation of the peptide chain. We used activated esters to synthesize the amino-acid derivatives. These are used widely in peptide synthesis [5] to activate the carboxyl using the *N*-hydroxysuccinimide (NHS) ester, which is highly reactive and does not racemize the products.

Reaction of **11**-**20** with NHS in absolute dioxane using diisopropylcarbodiimide as the condensing agent produced the corresponding NHS esters. Compounds **21**-**36** were synthesized by reaction of the NHS esters with sodium salts of glycylglycine (**21**-**30**), norleucine (**31**), leucine (**32**), and β-alanine (**33**) in dioxane:water (1:1) with subsequent acidolysis of the resulting salts. The isolated amino-acid derivatives had a free carboxylic acid that could be activated analogously for addition of the next amino acid. Compounds **34**-**36** were prepared this way. PMR spectra of the isolated compounds contained resonances for the coumarin ring, the dipeptide, amide bonds at 8.02-8.46 ppm, and the carboxylic acid at 12.11-12.69 ppm.

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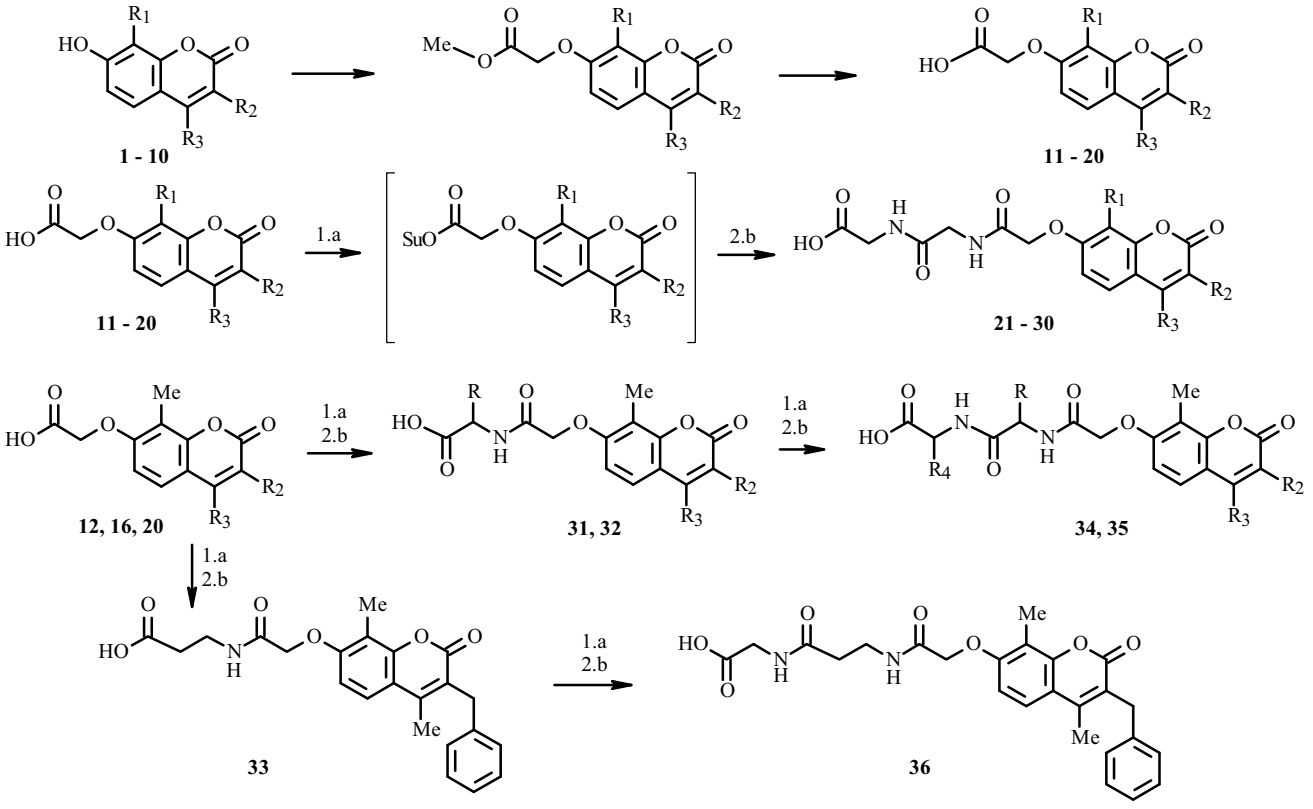

a. *N*-hydroxysuccinimide, diisopropylcarbodiimide; *b*. amino-acid (dipeptide) sodium salt

1, 11, 21: $R_1 = R_2 = H$, $R_3 = CH_2CH_3$; **2, 12, 22:** $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_2CH_3$; **3, 13, 23:** $R_1 = R_2 = H$, $R_3 = (CH_2)_2CH_3$
4, 14, 24: $R_1 = CH_3$, $R_2 = H$, $R_3 = (CH_2)_2CH_3$; **5, 15, 25:** $R_1 = R_2 = H$, $R_3 = (CH_2)_3CH_3$
6, 16, 26: $R_1 = CH_3$, $R_2 = H$, $R_3 = (CH_2)_3CH_3$; **7, 17, 27:** $R_1 = H$, $R_2 = R_3 = CH_3$; **8, 18, 28:** $R_1 = R_2 = R_3 = CH_3$
9, 19, 29: $R_1 = H$, $R_2 = (CH_2)_5CH_3$, $R_3 = CH_3$; **10, 20, 30:** $R_1 = R_3 = CH_3$, $R_2 = CH_2C_6H_5$
31: $R = (CH_2)_3CH_3$, $R_2 = H$, $R_3 = CH_2CH_3$; **32:** $R = CH_2CH(CH_3)_2$; $R_2 = H$, $R_3 = (CH_2)_3CH_3$
34: $R = (CH_2)_3CH_3$, $R_2 = H$, $R_3 = CH_2CH_3$, $R_4 = (CH_2)_2SCH_3$; **35:** $R = CH_2CH(CH_3)_2$, $R_2 = H$, $R_3 = (CH_2)_3CH_3$, $R_4 = CH(CH_3)_2$

EXPERIMENTAL

The course of reactions and the purity of products were monitored using TLC on Merck 60 F254 plates and $CHCl_3$:CH_3OH (9:1 and 95:5). Melting points were determined on a Kofler block. PMR spectra were measured on Varian VXR-300 and Varian Mercury-400 spectrometers relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

General Method for Synthesizing 2-(3,4,8-Substituted-2-oxo-2*H*-7-chromenyloxy)acetic Acids (11-20). A hot solution of the starting coumarin (0.05 mol) in absolute acetone (100 mL) was treated with potash (20.7 g, 0.15 mol), stirred vigorously, heated (50-56°C), treated with methylchloroacetate (4.75 mL, 0.055 mol) and a catalytic amount of KI, and stirred vigorously for 1-2 h (course of reaction monitored by TLC). The inorganic solid was filtered off. The acetone was evaporated in vacuo. The solid was dissolved in isopropanol (150 mL), treated with aqueous $NaHCO_3$ (175 mL, 5%, 0.1 mol), refluxed for 3-4 h (course of reaction monitored by TLC), diluted with water (400 mL), and acidified with HCl until the pH was 4. The solid was filtered off and crystallized from aqueous isopropanol.

General Method for Synthesizing *N*-[7-(Carbonyl-*R*-methoxy)-3,4,8-substituted]coumarinylamino Acids (31-33) and Dipeptides (21-30, 34-36). A solution of acid (3 mmol) and *N*-hydroxysuccinimide (0.38 g, 3.3 mmol) in absolute dioxane (20 mL) was stirred vigorously, treated with diisopropylcarbodiimide (0.52 mL, 3.3 mmol), and stirred for 2 h (course of reaction

monitored by TLC). The resulting activated ester was treated with the appropriate amino acid or glycylglycine (3.3 mmol) and $NaHCO_3$ (0.28 g, 3.3 mmol) in water (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 diluted with water (200 mL) and acidified until the pH was 5-6. The resulting solid was filtered off and crystallized from aqueous ethanol.

4-Butyl-7-hydroxy-2*H*-2-chromenone (5). Yield 91%, $C_{13}H_{14}O_3$, mp 141-142°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.94 (3H, t, J = 7.5, $C\underline{H}_3CH_2CH_2CH_2$-4), 1.41 (2H, m, $CH_3C\underline{H}_2CH_2CH_2$-4), 1.60 (2H, m, $CH_3CH_2C\underline{H}_2CH_2$-4), 2.68 (2H, t, J = 7.5, $CH_3CH_2CH_2C\underline{H}_2$-4), 5.93 (1H, s, H-3), 6.64 (1H, s, H-8), 6.71 (1H, d, J = 8, H-6), 7.46 (1H, d, J = 8, H-5), 10.22 (1H, s, OH).

4-Butyl-7-hydroxy-8-methyl-2*H*-2-chromenone (6). Yield 94%, $C_{14}H_{16}O_3$, mp 152-153°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.89 (3H, t, J = 7.5, $C\underline{H}_3CH_2CH_2CH_2$-4), 1.35 (2H, m, $CH_3C\underline{H}_2CH_2CH_2$-4), 1.63 (2H, m, $CH_3CH_2C\underline{H}_2CH_2$-4), 2.44 (3H, s, CH_3-8), 2.75 (2H, t, J = 7.5, $CH_3CH_2CH_2C\underline{H}_2$-4), 5.98 (1H, s, H-3), 6.87 (1H, d, J = 8, H-6), 7.56 (1H, d, J = 8, H-5), 10.35 (1H, s, OH).

2-(4-Ethyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (11). Yield 88%, $C_{13}H_{12}O_5$, mp 192-194°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.19 (3H, t, J = 7, $C\underline{H}_3CH_2$-4), 2.81 (2H, q, J = 7, $CH_3C\underline{H}_2$-4), 4.55 (2H, s, CH_2O-7), 6.15 (1H, s, H-3), 6.94 (2H, m, H-6, H-8), 7.64 (1H, d, J = 8, H-5), 12.54 (1H, br.s, COOH).

2-(4-Ethyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (12). Yield 90%, $C_{14}H_{14}O_5$, mp 237-239°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.29 (3H, t, J = 7.5, $C\underline{H}_3CH_2$-4), 2.33 (3H, s, CH_3-8), 2.80 (2H, q, J = 7.5, $CH_3C\underline{H}_2$-4), 4.58 (2H, s, CH_2O-7), 6.07 (1H, s, H-3), 6.88 (1H, d, J = 9, H-6), 7.53 (1H, d, J = 9, H-5), 12.48 (1H, br.s, COOH).

2-(4-Propyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (13). Yield 78%, $C_{14}H_{14}O_5$, mp 187-189°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.96 (3H, t, J = 7.5, $C\underline{H}_3CH_2CH_2$-4), 1.65 (2H, m, $CH_3C\underline{H}_2CH_2$-4), 2.75 (2H, t, J = 7.5, $CH_3CH_2C\underline{H}_2$-4), 4.66 (2H, s, CH_2O-7), 6.17 (1H, s, H-3), 7.00 (2H, m, H-6, H-8), 7.76 (1H, d, J = 8, H-5), 12.48 (1H, br.s, COOH).

2-(4-Propyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (14). Yield 79%, $C_{15}H_{16}O_5$, mp 220-221°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.02 (3H, t, J = 8, $C\underline{H}_3CH_2CH_2$-4), 1.71 (2H, m, $CH_3C\underline{H}_2CH_2$-4), 2.32 (3H, s, 8-CH_3), 2.73 (2H, t, J = 8, $CH_2CH_2C\underline{H}_2$-4), 4.65 (2H, s, CH_2O-7), 6.07 (1H, s, H-3), 6.91 (1H, d, J = 9, H-6), 7.54 (1H, d, J = 9, H-5), 12.51 (1H, br.s, COOH).

2-(4-Butyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (15). Yield 81%, $C_{15}H_{16}O_5$, mp 154-156°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.90 (3H, t, J = 7.5, $C\underline{H}_3CH_2CH_2CH_2$-4), 1.39 (2H, m, $CH_3C\underline{H}_2CH_2CH_2$-4), 1.60 (2H, m, $CH_3CH_2C\underline{H}_2CH_2$-4), 2.76 (2H, t, J = 7.5, $CH_3CH_2CH_2C\underline{H}_2$-4), 4.67 (2H, s, CH_2O-7), 6.18 (1H, s, H-3), 6.99 (2H, m, H-6, H-8), 7.76 (1H, d, J = 8, H-5), 12.52 (1H, br.s, COOH).

2-(4-Butyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (16). Yield 83%, $C_{16}H_{18}O_5$, mp 205-206°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.92 (3H, t, J = 7.5, $C\underline{H}_3CH_2CH_2CH_2$-4), 1.45 (2H, m, $CH_3C\underline{H}_2CH_2CH_2$-4), 1.67 (2H, m, $CH_3CH_2C\underline{H}_2CH_2$-4), 2.39 (3H, s, CH_3-8), 2.77 (2H, t, J = 7.5, $CH_3CH_2CH_2C\underline{H}_2$-4), 4.59 (2H, s, CH_2O-7), 6.01 (1H, s, H-3), 6.99 (1H, d, J = 8, H-6), 7.51 (1H, d, J = 8, H-5), 12.50 (1H, br.s, COOH).

2-(3,4-Dimethyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (17). Yield 92%, $C_{13}H_{12}O_5$, mp 175-177°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.09 (3H, s, CH_3-3), 2.38 (3H, s, 4-CH_3), 4.63 (2H, s, CH_2O-7), 6.95 (1H, d, J = 2.5, H-8), 6.99 (1H, dd, J = 8.5, 2.5, H-6), 7.66 (1H, d, J = 8.5, H-5), 12.56 (1H, br.s, COOH).

2-(3,4,8-Trimethyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (18). Yield 84%, $C_{14}H_{14}O_5$, mp 210-211°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.09 (3H, s, CH_3-3), 2.32 (3H, s, CH_3-8), 2.35 (3H, s, CH_3-4), 4.61 (2H, s, CH_2O-7), 6.88 (1H, d, J = 8.5, H-6), 7.47 (1H, d, J = 8.5, H-5), 12.52 (1H, br.s, COOH).

2-(*H*-3-Hexyl-4-methyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (19). Yield 68%, $C_{18}H_{22}O_5$, mp 158-160°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.84 [3H, m, $C\underline{H}_3(CH_2)_5$-3], 1.26-1.41 [8H, m, $CH_3(C\underline{H}_2)_4CH_2$-3], 2.38 (3H, s, CH_3-4), 2.51 [2H, m, $CH_3(CH_2)_4C\underline{H}_2$-3], 4.64 (2H, s, CH_2O-7), 6.94 (1H, d, J = 2, H-8), 6.98 (1H, dd, J = 8, 2, H-6), 7.70 (1H, d, J = 8, H-5), 12.50 (1H, br.s, COOH).

2-(3-Benzyl-4,8-dimethyl-2-oxo-2*H*-7-chromenyloxy)acetic Acid (20). Yield 78%, $C_{20}H_{18}O_5$, mp 191-192°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, s, CH_3-8), 2.41 (3H, s, CH_3-4), 3.94 (2H, s, $PhC\underline{H}_2$-3), 4.62 (2H, s, CH_2O-7), 6.94 (1H, d, J = 8, H-6), 7.14-7.26 (5H, m, $\underline{Ph}CH_2$-3), 7.60 (1H, d, J = 8, H-5), 12.53 (1H, br.s, COOH).

***N*-[2-(4-Ethyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetyl]norleucine (31).** Yield 81%, $C_{20}H_{25}NO_6$, mp 196-198°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.75 [3H, t, J = 8, $C\underline{H}_3(CH_2)_3CHNHCOCH_2O$-7], 1.24 (7H, m, CH_3CH_2-4, $CH_3C\underline{H}_2C\underline{H}_2CH_2CHNHCOCH_2O$-7), 1.71 (2H, m, $CH_3CH_2CH_2C\underline{H}_2CHNHCOCH_2O$-7), 2.79 (3H, s, CH_3-8), 2.79 (2H, q,

J = 7.5, CH_3CH_2-4), 4.18 [1H, m, $CH_3(CH_2)_3C\underline{H}NHCOCH_2O$-7], 4.63 (2H, s, CH_2O-7), 6.17 (1H, s, H-3), 6.90 (1H, d, J = 9, H-6), 7.58 (1H, d, J = 9, H-5), 8.28 (1H, d, J = 8, NH), 12.66 (1H, br.s, COOH).

***N*-[2-(4-Butyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetyl]leucine (32).** Yield 59%, $C_{22}H_{29}NO_6$, mp 147-148°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.82-0.93 [9H, m, $C\underline{H}_3CH_2CH_2CH_2$-4, $(C\underline{H}_3)_2CHCH_2NHCOCH_2O$-7], 1.38-1.56 [6H, m, $CH_3C\underline{H}_2C\underline{H}_2CH_2$-4, $(CH_3)_2C\underline{H}_2CHNHCOCH_2O$-7], 2.31 (3H, s, 8-$CH_3$), 2.76 (2H, t, J = 7.5, $CH_3CH_2CH_2C\underline{H}_2$-4), 4.29 [1H, m, $(CH_3)_2CH_2C\underline{H}NHCOCH_2O$-7], 4.69 (2H, s, CH_2O-7), 6.18 (1H, s, H-3), 6.95 (1H, d, J = 8, H-6), 7.73 (1H, d, J = 8, H-5), 8.41 (1H, d, J = 8, NH), 12.66 (1H, br.s, COOH).

***N*-[2-(3-Benzyl-4,8-dimethyl-2-oxo-2*H*-7-chromenyloxy)acetyl]-β-alanine (33).** Yield 64%, $C_{23}H_{23}NO_6$, mp 208-210°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, s, CH_3-8), 2.42 (2H, t, J = 7, $CH_2C\underline{H}_2NHCOCH_2O$-7), 2.50 (3H, s, CH_3-4), 3.39 (2H, t, J = 7, $C\underline{H}_2CH_2NHCOCH_2O$-7), 3.96 (2H, s, $PhC\underline{H}_2$-3), 4.62 (2H, s, CH_2O-7), 6.96 (1H, d, J = 8, H-6), 7.21-7.26 (5H, m, $\underline{Ph}CH_2$-3), 7.61 (1H, d, J = 8, H-5), 8.02 (1H, d, J = 7, NH), 12.13 (1H, br.s, COOH).

***N*-[2-(4-Ethyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (21).** Yield 75%, $C_{17}H_{18}N_2O_7$, mp 227-229°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.23 (3H, t, J = 7, $C\underline{H}_3CH_2$-4), 2.81 (2H, q, J = 7, $CH_3C\underline{H}_2$-4), 3.77 (2H, d, J = 6, $CH_2NHCOC\underline{H}_2NHCOCH_2O$-7), 3.82 (2H, d, J = 6, $C\underline{H}_2NHCOCH_2NHCOCH_2O$-7), 4.67 (2H, s, CH_2O-7), 6.17 (1H, s, H-3), 7.01-7.04 (2H, m, H-6, H-8), 7.76 (1H, d, J = 7, H-5), 8.20 (1H, t, J = 6, $CH_2NHCOCH_2N\underline{H}COCH_2O$-7), 8.38 (1H, t, J = 6, $CH_2N\underline{H}COCH_2NHCOCH_2O$-7), 12.54 (1H, br.s, COOH).

***N*-[2-(4-Ethyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (22).** Yield 67%, $C_{18}H_{20}N_2O_7$, mp 197-198°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.29 (3H, t, J = 7.5, $C\underline{H}_3CH_2$-4), 2.33 (3H, s, CH_3-8), 2.80 (2H, q, J = 7.5, $CH_3C\underline{H}_2$-4), 3.78 (2H, d, J = 8, $CH_2NHCOC\underline{H}_2NHCOCH_2O$-7), 3.84 (2H, d, J = 8, $C\underline{H}_2NHCOCH_2NHCOCH_2O$-7), 4.65 (2H, s, CH_2O-7), 6.08 (1H, s, H-3), 6.92 (1H, d, J = 9, H-6), 7.55 (1H, d, J = 9, H-5), 8.12-8.18 (2H, m, 2NH), 12.50 (1H, br.s, COOH).

***N*-[2-(4-Propyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (23).** Yield 64%, $C_{18}H_{20}N_2O_7$, mp 191-192°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.98 (3H, t, J = 7, $C\underline{H}_3CH_2CH_2$-4), 1.64 (2H, m, $CH_3C\underline{H}_2CH_2$-4), 2.45 (2H, t, J = 7, $CH_3CH_2C\underline{H}_2$-4), 3.76-3.80 (4H, m, $C\underline{H}_2NHCOC\underline{H}_2NHCOCH_2O$-7), 4.68 (2H, s, CH_2O-7), 6.19 (1H, s, H-3), 7.01 (2H, m, H-6, H-8), 7.75 (1H, d, J = 7, H-5), 8.26 (1H, t, J = 6, $CH_2NHCOCH_2N\underline{H}COCH_2O$-7), 8.41 (1H, t, J = 6, $CH_2N\underline{H}COCH_2NHCOCH_2O$-7), 12.60 (1H, br.s, COOH).

***N*-[2-(4-Propyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (24).** Yield 78%, $C_{19}H_{22}N_2O_7$, mp 195-197°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.04 (3H, t, J = 7, $C\underline{H}_3CH_2CH_2$-4), 1.71 (2H, m, $CH_3C\underline{H}_2CH_2$-4), 2.32 (3H, s, CH_3-8), 2.73 (2H, t, J = 7, $CH_3CH_2C\underline{H}_2$-4), 3.78 (4H, m, $C\underline{H}_2NHCOC\underline{H}_2NHCOCH_2O$-7), 4.66 (2H, s, CH_2O-7), 6.07 (1H, s, H-3), 6.92 (1H, d, J = 8.5, H-6), 7.55 (1H, t, J = 8.5, H-5), 8.16 (2H, m, 2NH), 12.48 (1H, br.s, COOH).

***N*-[2-(4-Butyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (25).** Yield 73%, $C_{19}H_{22}N_2O_7$, mp 133-135°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.93 (3H, t, J = 7.5, $C\underline{H}_3CH_2CH_2CH_2$-4), 1.39 (2H, t, $CH_3C\underline{H}_2CH_2CH_2$-4), 1.59 (2H, m, $CH_3CH_2C\underline{H}_2CH_2$-4), 2.77 (2H, t, J = 7.5, $CH_3CH_2CH_2C\underline{H}_2$-4), 3.74-3.84 (4H, m, $C\underline{H}_2NHCOC\underline{H}_2NHCOCH_2O$-7), 4.68 (2H, s, CH_2O-7), 6.19 (1H, s, H-3), 7.01 (2H, m, H-6, H-8), 7.77 (1H, d, J = 8.5, H-5), 8.28 (1H, t, J = 6, $CH_2NHCOCH_2N\underline{H}COCH_2O$-7), 8.46 (1H, t, J = 6, $CH_2N\underline{H}COCH_2NHCOCH_2O$-7), 12.69 (1H, br.s, COOH).

***N*-[2-(4-Butyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (26).** Yield 81%, $C_{20}H_{24}N_2O_7$, mp 198-199°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.97 (3H, t, J = 8, $C\underline{H}_3CH_2CH_2CH_2$-4), 1.45 (2H, m, $CH_3C\underline{H}_2CH_2CH_2$-4), 1.64 (2H, m, $CH_3CH_2C\underline{H}_2CH_2$-4), 2.29 (3H, s, CH_3-8), 2.75 (2H, t, J = 7.5, $CH_3CH_2CH_2C\underline{H}_2$-4), 3.77-3.84 (4H, m, $C\underline{H}_2NHCOC\underline{H}_2NHCOCH_2O$-7), 4.65 (2H, s, CH_2O-7), 6.06 (1H, s, H-3), 6.92 (1H, d, J = 8.5, H-6), 7.54 (1H, d, J = 8.5, H-5), 8.16 (2H, m, 2NH), 12.51 (1H, br.s, COOH).

***N*-[2-(3,4-Dimethyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (27).** Yield 85%, $C_{17}H_{18}N_2O_7$, mp 230-232°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.06 (3H, s, CH_3-3), 2.42 (3H, s, CH_3-4), 3.82 (4H, m, $C\underline{H}_2NHCOC\underline{H}_2NHCOCH_2O$-7), 4.66 (2H, s, CH_2O-7), 6.97-7.03 (2H, m, H-6, H-8), 7.73 (1H, d, J = 8.5, H-5), 8.27 (1H, t, J = 6, $CH_2NHCOCH_2N\underline{H}COCH_2O$-7), 8.44 (1H, m, $CH_2N\underline{H}COCH_2NHCOCH_2O$-7), 12.63 (1H, br.s, COOH).

***N*-[2-(3,4,8-Trimethyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (28).** Yield 84%, $C_{18}H_{20}N_2O_7$, mp 203-205°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.10 (3H, s, CH_3-3), 2.34 (3H, s, CH_3-8), 2.36 (3H, s, CH_3-4), 3.77-3.85 (4H, m, $C\underline{H}_2NHCOC\underline{H}_2NHCOCH_2O$-7), 4.63 (2H, s, CH_2O-7), 6.91 (1H, d, J = 8.5, H-6), 7.50 (1H, d, J = 8.5, H-5), 8.12-8.19 (2H, m, 2NH), 12.44 (1H, br.s, COOH).

***N*-[2-(*H*-3-Hexyl-4-methyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (29).** Yield 59%, $C_{22}H_{28}N_2O_7$, mp 186-188°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.85 [3H, t, J = 6.5, $C\underline{H}_3(CH_2)_5$-3], 1.26-1.42 [8H, m,

$CH_3(C\underline{H}_2)_4CH_2$-3], 2.43 (3H, s, CH_3-4), 2.52 [2H, t, $CH_3(CH_2)_4C\underline{H}_2$-3], 3.8-3.84 (4H, m, $C\underline{H}_2NHCOC\underline{H}_2NHCOCH_2O$-7), 4.65 (2H, s, CH_2O-7), 6.96 (1H, d, J = 2.5, H-8), 7.01 (1H, d, J = 8.5, H-6), 7.71 (1H, d, J = 8.5, H-5), 8.26 (1H, t, J = 6, $CH_2NHCOCH_2N\underline{H}COCH_2O$-7), 8.46 (1H, t, J = 6, $CH_2N\underline{H}COCH_2NHCOCH_2O$-7), 12.57 (1H, br.s, COOH).

***N*-[2-(3-Benzyl-4,8-dimethyl-2-oxo-2*H*-7-chromenyloxy)acetyl]glycylglycine (30).** Yield 78%, $C_{24}H_{24}N_2O_7$, mp 217-219°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.29 (3H, s, CH_3-8), 2.42 (3H, s, CH_3-4), 3.78-3.82 (4H, m, $C\underline{H}_2NHCOC\underline{H}_2NHCOCH_2O$-7), 3.96 (2H, s, $PhC\underline{H}_2$-3), 4.71 (2H, s, OCH_2-7), 7.01 (1H, d, J = 8.5, H-6), 7.19-7.25 (5H, m, $\underline{Ph}CH_2$-3), 7.65 (1H, d, J = 8.5, H-5), 8.23-8.27 (2H, m, 2NH), 12.54 (1H, br.s, COOH).

***N*-[2-(4-Ethyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetyl]norleucinylmethionine (34).** Yield 48%, $C_{25}H_{34}N_2O_7S$, mp 126-128°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.82 (3H, t, J = 7, $C\underline{H}_3CH_2CH_2CH_2$), 1.22 (7H, m, $C\underline{H}_3CH_2$-4, $CH_3C\underline{H}_2C\underline{H}_2CH_2$), 1.58 (2H, t, $CH_3CH_2CH_2C\underline{H}_2$), 1.98 (2H, t, $CH_3SC\underline{H}_2CH_2$), 2.02 (3H, s, $C\underline{H}_3SCH_2CH_2$), 2.26 (3H, s, CH_3-8), 2.40 (2H, t, $CH_3SCH_2C\underline{H}_2$), 2.79 (2H, t, J = 7, $CH_3SC\underline{H}_2CH_2$), 4.36 [2H, m, $C\underline{H}(CH_2CH_2SCH_3)NHCOC\underline{H}((CH_2)_3CH_3)NHCOCH_2O$-7), 4.74 (2H, s, CH_2O-7), 6.18 (1H, s, H-3), 6.94 (1H, d, J = 9, H-6), 7.63 (1H, d, J = 9, H-5), 8.06 [1H, m, $CH(CH_2CH_2SCH_3)N\underline{H}COCH((CH_2)_3CH_3)NHCOCH_2O$-7], 8.31 [1H, m, $CH(CH_2CH_2SCH_3)NHCOCH((CH_2)_3CH_3)N\underline{H}COCH_2O$-7), 12.69 (1H, br.s, COOH).

***N*-[2-(4-Butyl-8-methyl-2-oxo-2*H*-7-chromenyloxy)acetyl]leucylvaline (35).** Yield 42%, $C_{27}H_{38}N_2O_7$, mp 169-170°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.86 [12H, m, $(C\underline{H}_3)_2CHCH_2$, $(C\underline{H}_3)_2CHCH_2CH$), 1.23 (3H, t, $C\underline{H}_3CH_2CH_2CH_2$-4), 1.40 [3H, m, $CH_3C\underline{H}_2CH_2CH_2$-4, $(CH_3)_2C\underline{H}CH_2CH$], 1.58 [4H, m, $CH_3CH_2C\underline{H}_2CH_2$-4, $(CH_3)_2CHC\underline{H}_2CH$], 2.05 [1H, m, $(CH_3)_2C\underline{H}CH_2$], 2.26 (3H, s, CH_3-8), 2.77 (2H, t, J = 7, $CH_3CH_2CH_2C\underline{H}_2$-4), 4.17 [1H, m, $CH(CH(CH_3)_2)NHCOC\underline{H}(CH_2CH(CH_3)_2)NHCOCH_2O$-7], 4.48 [1H, m, $C\underline{H}(CH(CH_3)_2)NHCOCH(CH_2CH(CH_3)_2)NHCOCH_2O$-7], 4.73 (2H, br.s, CH_2O-7), 6.18 (1H, s, H-3), 6.95 (1H, d, J = 8, H-6), 7.63 (1H, d, J = 8, H-5), 8.03 (2H, m, 2NH), 12.66 (1H, br.s, COOH).

***N*-[2-(3-Benzyl-4,8-dimethyl-2-oxo-2*H*-7-chromenyloxy)acetyl]-β-alanylglycine (36).** Yield 44%, $C_{26}H_{26}N_2O_7$, mp 192-194°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.40 (3H, s, CH_3-8), 2.42 (2H, t, J = 7, $CH_2NHCH_2C\underline{H}_2NHCOCH_2O$-7), 2.42 (3H, s, CH_3-4), 3.39 (2H, m, $CH_2NHC\underline{H}_2CH_2NHCOCH_2O$-7), 3.73 (2H, d, J = 7, $C\underline{H}_2NHCH_2CH_2NHCOCH_2O$-7), 3.96 (2H, s, $PhC\underline{H}_2$-3), 4.62 (2H, m, CH_2O-7), 6.96 (1H, d, J = 8.5, H-6), 7.22-7.26 (5H, m, $\underline{Ph}CH_2$-3), 7.61 (1H, d, J = 8.5, H-5), 8.02 (1H, d, J = 7, $CH_2NHCH_2CH_2N\underline{H}COCH_2O$-7), 8.23 (1H, d, J = 7, $CH_2N\underline{H}CH_2CH_2NHCOCH_2O$-7), 12.11 (1H, br.s, COOH).

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