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AMINO-ACID AND DIPEPTIDE DERIVATIVES OF 2-(6-ETHYL-4-OXO-3-(4-PHENYL-4*H*-1,2,4-TRIAZOL-3-YL)-4*H*-CHROMEN-7-YLOXY)ACETIC ACID

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Chromones modified by triazole, amino acids, and dipeptides were prepared by condensation of the N-hydroxysuccinimide ester of 2-(6-ethyl-4-oxo-3-(4-phenyl-4H-1,2,4-triazol-3-yl)-4H-chromen-7-yloxy)acetic acid with salts of amino acids or dipeptides. The dipeptide derivatives were also synthesized by extending the chain of amino acids.

Key words: chromones, isoflavones, triazoles, amino-acid derivatives, dipeptides, activated esters, synthesis.

Natural and synthetic isoflavonoids possess a broad spectrum of biological activity, for example, growth inhibition of pathogenic microbes and fungi, inhibition of certain enzymes, anti-inflammatory activity, etc. [1, 2]. At present 3-hetarylchromones are widely used because introduction of a heteroaromatic core can impart valuable biological properties to these compounds.

Introducing an amino acid or peptide into a hetaryl-substituted isoflavone can increase the hydrophilicity or lipophilicity, increase or decrease the toxicity, and prolong its action. Furthermore, such modification can change the selectivity of its action.

Methods for modifying chromones include those in which the 7-hydroxychromone is bound to an amino acid at the C-terminus by aminoacylation of N-substituted amino acids [3-8] and at the N-terminus by Mannich aminomethylation [9, 10]. Activated esters are also used [7, 11, 12]. There is only a single report [4] on the synthesis of amino-acid derivatives of 3-hetarylchromones, namely 7-O-aminoacyl-3-(1-methyl-2-benzimidazolyl)chromones.

Triazoles themselves [13] and 2,3-dihydro-3-(1*H*-1,2,4-triazol-1-yl)chromones [14] have already exhibited biological activities. Therefore, our goal was to synthesize amino-acid derivatives of triazole analogs of isoflavone.

Alkylation of starting 7-hydroxy-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-6-ethyl-4*H*-chromen-4-one (**1**) with ethylchloroacetate and subsequent acid hydrolysis of the resulting ester **2** produced **3**, which then was used to acylate natural and synthetic amino acids.

We used activated N-hydroxysuccinimide esters to activate the carboxylic group. The esters were prepared in high yields, are active acylating agents, and do not racemize the chiral amino acids [15, 16]. This method was not used previously to modify 3-hetarylchromones. N-Hydroxysuccimide ester **4** was prepared by reacting **3** with N-hydroxysuccinimide in DMF:dioxane. The condensing agent was diisopropylcarbodiimide because diisopropylurea is soluble in water. This enabled the reaction products to be easily purified and the reactions to be carried out in a single flask.

Activated ester **4** was reacted without purification with amino-acid salts in DMF:dioxane:water at room temperature. After the reaction was finished, the desired compounds were isolated by acidolysis.

Thus, **5-18** were synthesized with glycine (**5**), β-alanine (**6**), γ-aminobutyric acid (GABA) (**7**), ε-aminocaproic acid (**8**), L-valine (**9**), L-methionine (**10**), L-phenylalanine (**11**), L-leucine (**12**), L-isoleucine (**13**), L-aspargic acid (**14**), DL-norvaline (**15**), DL-norleucine (**16**), DL-α-aminobutyric acid (**17**), and L-tryptophan (**18**).

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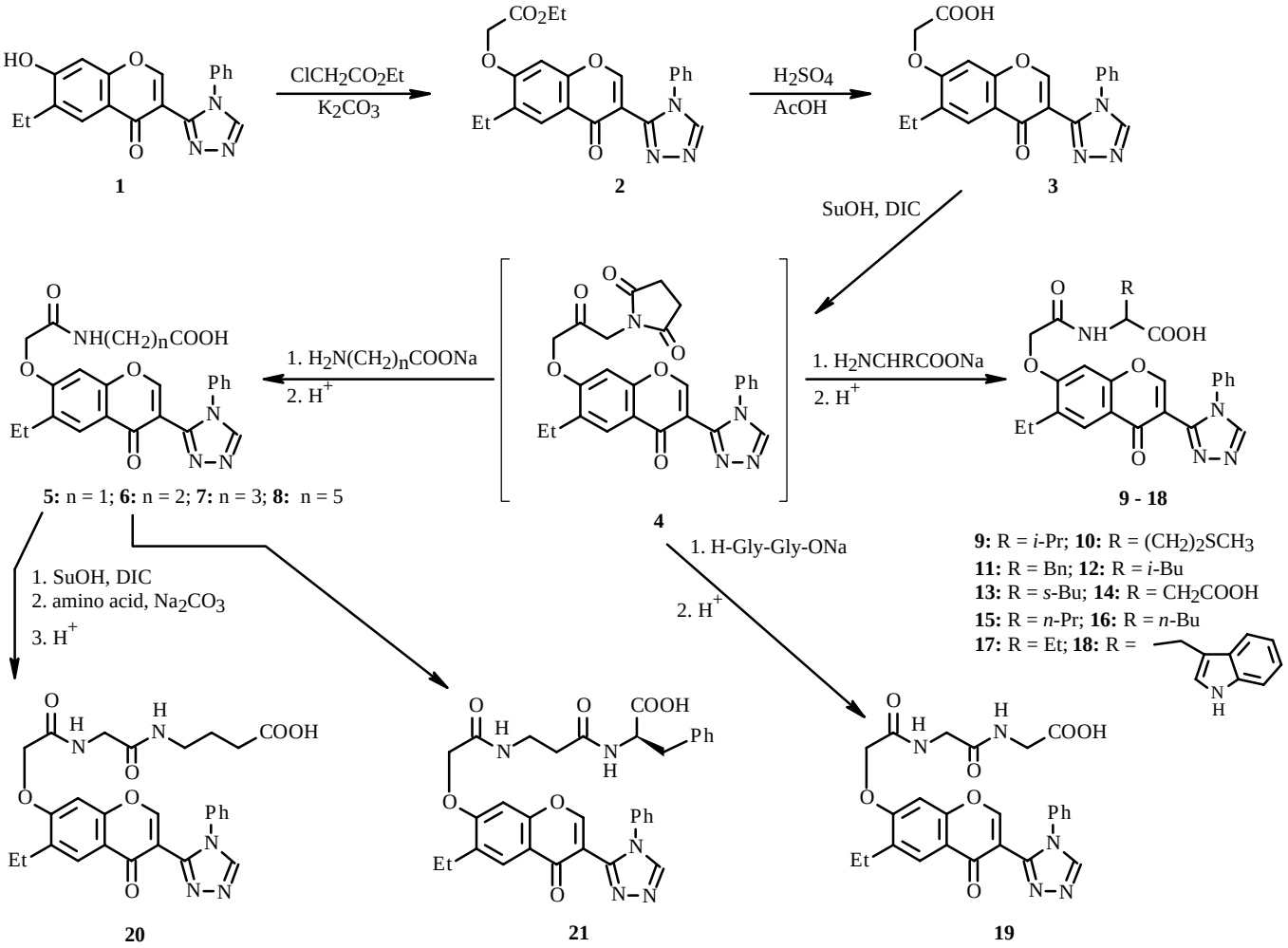

1 **2** **3** **4** **5** **19** **20** **21**

Dipeptide derivatives of 2-(6-ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetic acids (**19-21**) were synthesized by two methods. Product **19** was prepared from **3** and glycylglycine analogously to amino-acid derivatives **5-18**; **20** and **21**, from amino-acid derivatives **5** and **6**, respectively, by stepwise extension of the amino-acid chain.

The formation of **5-21** was confirmed as follows. Their PMR spectra contain characteristic signals for the triazole ring (1H singlet at 8.75-8.79 ppm for H-5), the chromone system (1H singlets at 6.88-7.10 ppm for H-8, 7.60-7.64 ppm for H-5, and 8.59-8.63 ppm for H-2), the amino-acid (see Experimental section), and the amide N–H (**9-18**, 1H doublet at 8.02-8.29; **5-8**, 1H triplet at 7.91-8.23 ppm). Signals for free carboxylic groups appeared at 11.81-12.81 ppm. Signals for OCH_2CO groups of all compounds were 2H singlets at 4.62-4.76 ppm with the exception of **11** and **12**, where they appeared as two doublets with SSCC 14-15 Hz, i.e., these protons became nonequivalent. For **10**, **11**, **13**, and **15-18**, the methylene protons of the amino-acid moieties became nonequivalent. The differences in their chemical shifts were 0.1-0.2 ppm, SSCC 7-9 Hz. For **9** and **12**, the methyls of the amino acids (CMe_2) were also nonequivalent with differences in their chemical shifts of 0.2-0.3 ppm.

The COSY spectrum of **18** was recorded in order to assign accurately the aromatic signals. As it turned out, the field strength of the indole system increased the same as in tryptophan. The assignments for the signals are given in the Experimental section.

COSY spectra of **19-21** were recorded in order to identify signals of the dipeptides. The signal of one of the methylenes in **20** fell in the water-absorption region. Signals of the amides and methylenes were accurately assigned from the appearance of cross peaks between signals at 7.90 and 3.1 and between those at 8.10 and 3.76 ppm. The signal of one methylene of *β*-alanine in **21** fell in the DMSO-absorption region; the signal of another at 2.31 ppm was a multiplet. The COSY spectrum exhibited a cross peak between signals of the amide proton and a signal at 3.33 ppm. We note that the signal of the methylene bound to the amide N in **6** was also found at weaker field than the methylene bound to the carboxylate.

Thus, activated esters were used to prepare a series of amino-acid and dipeptide derivatives of 2-(6-ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetic acid.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using $CHCl_3$:CH_3OH (9:1 and 4:1). PMR spectra were recorded in DMSO-d_6 on a Varian Mercury 400 spectrometer relative to TMS internal standard. Elemental analyses of all compounds agreed with those calculated.

Ethyl 2-(6-ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetate (2). A solution of **1** (15.4 g, 46 mmol) in DMF (40 mL) was treated with freshly calcined potash (12.7 g, 92 mmol), stirred, and treated dropwise with ethylchloroacetate (15 mL, 92 mmol). The mixture was stirred for 2 h at 60-70°C and for 18 h without heating. The reaction mixture was poured into water. The resulting precipitate was filtered off and recrystallized from CCl_4. Yield 15.44 g (80%), mp 171-172°C, $C_{23}H_{21}N_3O_5$.

PMR spectrum (δ, ppm, J/Hz): 1.21 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.29 (3H, t, J = 7.5, $\underline{CH_2}CH_2CO_2$), 2.67 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 4.20 (2H, q, J = 7.5, $CH_3\underline{CH_2}CO_2$), 4.91 (2H, s, OCH_2CO_2), 7.09 (1H, s, H-8), 7.40 (5H, s, Ph), 7.65 (1H, s, H-5), 8.63 (1H, s, H-2), 8.77 (1H, s, H-5″$_{triazole}$).

2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetic Acid (3). Compound **2** (15.44 g, 37 mmol) was dissolved in acetic acid (73.5 mL, 780 mmol) and H_2SO_4 (18.4 mL, 380 mmol) and boiled for 10 min. On the next day,it was poured into water (1.5 L). The resulting solid was filtered off and recrystallized from DMF. Yield 11.87 g (82%), mp 266-267°C, $C_{21}H_{17}N_3O_5$.

PMR spectrum (δ, ppm, J/Hz): 1.21 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.68 (2H, t, J = 7.5, $CH_3\underline{CH_2}$-6), 4.82 (2H, s, $O\underline{CH_2}COOH$), 7.05 (1H, s, H-8), 7.41 (5H, s, Ph), 7.64 (1H, s, H-5), 8.62 (1H, s, H-2), 8.78 (1H, s, H-5′$_{triazole}$), 13.06 (1H, br.s, COOH).

General Method for Synthesizing Amino-acid Derivatives of 2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetic Acid 5-18. A solution of **3** (1.17 g, 3 mmol) and N-hydroxysuccinimide (0.46 g, 3.9 mmol) in dioxane (absolute, 15 mL) and DMF (absolute, 7 mL) was stirred and treated with diisopropylcarbodiimide (0.6 mL, 3.9 mmol) and stirred vigorously for 2 h (TLC monitoring). The resulting ester (**4**) was treated with a solution of amino acid (3.6 mmol) and Na_2CO_3 (0.19 g, 1.8 mmol) in water (22 mL) (0.38 g, 3.6 mmol of Na_2CO_3 for aspartic acid). The reaction mixture was stirred for 2-4 h (TLC monitoring). After the reaction was finished, the mixture was poured into water (200 mL) and acidified with HCl until the pH was 2-3. The solid was filtered off on the following day and dried. It was crystallized from aqueous alcohol if necessary.

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)acetic Acid (5). Yield 88%, mp 139-140°C, $C_{23}H_{20}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 1.21 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.72 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 3.83 (2H, d, J = 5.6, $NH\underline{CH_2}COOH$), 4.72 (2H, s, OCH_2CO), 7.06 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.23 (1H, t, J = 5.6, NH), 8.63 (1H, s, H-2), 8.79 (1H, s, H-5′$_{triazole}$), 12.57 (1H, br.s, COOH).

3-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)propanoic Acid (6). Yield 83%, mp 121-122°C, $C_{24}H_{22}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 1.21 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.43 (2H, t, J = 6.4, $\underline{CH_2}COOH$), 2.71 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 3.39 (2H, m, $NH\underline{CH_2}CH_2COOH$), 4.63 (2H, s, OCH_2CO), 7.02 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 7.98 (1H, t, J = 5.6, NH), 8.62 (1H, s, H-2), 8.78 (1H, s, H-5′$_{triazole}$), 12.18 (1H, br.s, COOH).

4-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)butanoic Acid (7). Yield 86%, mp 109-110°C, $C_{25}H_{24}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 1.21 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.17 (2H, m, $CH_2\underline{CH_2}CH_2$), 2.23 (2H, m, $NH\underline{CH_2}CH_2$), 2.72 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 3.18 (2H, m, $CH_2\underline{CH_2}COOH$), 4.63 (2H, s, OCH_2CO), 7.00 (1H, s, H-8), 7.40 (5H, s, Ph), 7.63 (1H, s, H-5), 7.99 (1H, t, J = 5.6, NH), 8.61 (1H, s, H-2), 8.78 (1H, s, H-5′$_{triazole}$), 11.91 (1H, br.s, COOH).

6-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)hexanoic Acid (8). Yield 80%, mp 103-104°C, $C_{27}H_{28}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 1.21 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.32 (2H, m, $NHCH_2CH_2CH_2\underline{CH_2}CH_2$), 1.54 (4H, m, $NHCH_2\underline{CH_2}\underline{CH_2}CH_2CH_2$), 2.17 (2H, m, $NH\underline{CH_2}CH_2$), 2.71 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 3.14 (2H, m, $\underline{CH_2}COOH$), 4.62 (2H, s, OCH_2CO), 6.99 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 7.91 (1H, t, J = 5.6, NH), 8.61 (1H, s, H-2), 8.78 (1H, s, H-5′$_{triazole}$), 11.81 (1H, br.s, COOH).

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)-3-methylbutanoic Acid (9). Yield 58%, mp 135-136°C, $C_{26}H_{26}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 0.94 and 0.95 [6H, t, J = 6.8, CH($\underline{CH_3}$)$_2$], 1.22 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.16 [1H, m, $\underline{CH}(CH_3)_2$], 2.70 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 4.28 [1H, dd, $J_{CH,CH}$ = 5.6, $J_{CH,NH}$ = 8.8, NH$\underline{CH}$(COOH)CH], 4.76 (2H, s, OCH_2CO), 7.02 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.02 (1H, d, J = 8.8, NH), 8.61 (1H, s, H-2), 8.77 (1H, s, H-5′$_{triazole}$), COOH exchanged with D_2O.

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)-4-(methylthio)butanoic Acid (10). Yield 69%, mp 115-116°C, $C_{26}H_{26}N_4O_6S$.

PMR spectrum (δ, ppm, J/Hz): 1.23 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.95 (1H, m, SCH_2-*β*), 2.04 (4H, m, SCH_3 and SCH_2-*α*), 2.47 [2H, m, CH(COOH)$\underline{CH_2}CH_2S$), 2.72 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 4.41 [1H, m, NH$\underline{CH}$(COOH)CH_2], 4.73 (2H, s, OCH_2CO), 7.03 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.29 (1H, d, J = 7.2, NH), 8.61 (1H, s, H-2), 8.78 (1H, s, H-5′$_{triazole}$), COOH exchanged with D_2O.

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)-3-phenylpropanoic Acid (11). Yield 79%, mp 150-151°C, $C_{30}H_{26}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 1.16 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.64 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 2.99 and 3.13 (1H each, m, $\underline{CH_2}$Ph), 4.55 [1H, m, NH$\underline{CH}$(COOH)CH_2], 4.68 and 4.62 (1H each, 2d, J = 14.8, OCH_2CO), 6.88 (1H, s, H-8), 7.17 (5H, s, $CH_2\underline{Ph}$), 7.41 (5H, s, Ph$_{triazole}$), 7.62 (1H, s, H-5), 8.11 (1H, d, J = 7.2, NH), 8.63 (1H, s, H-2), 8.78 (1H, s, H-5′$_{triazole}$), 12.81 (1H, br.s, COOH).

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)-4-methylpentanoic Acid (12). Yield 66%, mp 134-135°C, $C_{27}H_{28}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 0.90 and 0.93 [3H each, d, J = 6.5, CH($\underline{CH_3}$)$_2$], 1.22 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.60 [2H, pt, $J_{CH_2,CH(COOH)}$ = $J_{CH_2,CHC(Me_2)}$ = 6.6, CH(COOH)$\underline{CH_2}$CH], 1.66 [1H, m, $CH_2\underline{CH}(CH_3)_2$], 2.70 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 4.31 (1H, m, NH$\underline{CH}$), 4.69 and 4.75 (2H, 2d, J = 14.8, OCH_2CO), 7.00 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.20 (1H, d, J = 8.0, NH), 8.61 (1H, s, H-2), 8.76 (1H, s, H-5′$_{triazole}$), 12.60 (1H, br.s, COOH).

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)-3-methylpentanoic Acid (13). Yield 80%, mp 132-133°C, $C_{27}H_{28}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 0.92 [6H, m, CH($\underline{CH_3}$)$CH_2\underline{CH_3}$], 1.22 [4H, t, J = 7.5, $\underline{CH_3}CH_2$-6 and CH(CH_3)*α*-$\underline{CH_2}CH_3$], 1.48 [1H, d, J = 7.0, CH(CH_3)*β*-$\underline{CH_2}CH_3$), 1.87 (1H, m, $CH_3\underline{CH}CH_2$), 2.70 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 4.30 [1H, dd, $J_{CH,CH}$ = 5.2, $J_{CH,NH}$ = 8.8, NH$\underline{CH}$(COOH)CH], 4.74 (2H, s, OCH_2CO), 7.02 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.01 (1H, d, J = 8.8, NH), 8.60 (1H, s, H-2), 8.75 (1H, s, H-5′$_{triazole}$), COOH exchanged with D_2O.

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)succinic Acid (14). Yield 57%, mp 137-138°C, $C_{25}H_{22}N_4O_8$.

PMR spectrum (δ, ppm, J/Hz): 1.21 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.70 [4H, m, $CH_3\underline{CH_2}$-6 and CH(COOH)$\underline{CH_2}$COOH], 4.64 [1H, m, NH$\underline{CH}$(COOH)CH_2], 4.72 (2H, s, OCH_2CO), 7.05 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.21 (1H, d, J = 8.4, NH), 8.61 (1H, s, H-2), 8.76 (1H, s, H-5′$_{triazole}$), 12.57 (0.5H, br.s, COOH), the other COOH exchanged with D_2O.

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)pentanoic Acid (15). Yield 85%, mp 181-182°C, $C_{26}H_{26}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 0.92 (3H, t, J = 7.5, $CH_2\underline{CH_3}$), 1.21 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.36 (2H, m, $CH_2\underline{CH_2}CH_3$), 1.67 and 1.75 [1H each, 2d, J = 8.8, CH(COOH)$\underline{CH_2}CH_2$], 2.70 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 4.30 [1H, m, NH$\underline{CH}$(COOH)CH], 4.71 (2H, s, OCH_2CO), 7.02 (1H, s, H-8), 7.40 (5H, s, Ph), 7.63 (1H, s, H-5), 8.17 (1H, d, J = 7.2, NH), 8.61 (1H, s, H-2), 8.78 (1H, s, H-5′$_{triazole}$), 12.53 (1H, br.s, COOH).

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)hexanoic Acid (16). Yield 86%, mp 112-113°C, $C_{27}H_{28}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 0.89 (3H, t, J = 7.5, $CH_2CH_2\underline{CH_3}$), 1.22 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.31 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), 1.68 and 1.80 [1H each, m, CH(COOH)$\underline{CH_2}CH_2$], 2.71 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 4.28 [1H, m, NH$\underline{CH}$(COOH)CH], 4.71 (2H, m, OCH_2CO), 7.01 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.14 (1H, d, J = 8.0, NH), 8.59 (1H, s, H-2), 8.74 (1H, s, H-5′$_{triazole}$), 12.60 (1H, br.s, COOH).

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)butanoic Acid (17). Yield 85%, mp 133-134°C, $C_{25}H_{24}N_4O_6$.

PMR spectrum (δ, ppm, J/Hz): 0.94 [3H, t, J = 7.5, CH(COOH)$CH_2$$\underline{CH_3}$], 1.22 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.74 and 1.85 [1H each, m, CH(COOH)$\underline{CH_2}CH_3$], 2.70 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 4.25 [1H, m, NH$\underline{CH}$(COOH)CH], 4.73 (2H, s, OCH_2CO), 7.03 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.17 (1H, d, J = 8.0, NH), 8.62 (1H, s, H-2), 8.79 (1H, s, H-5′$_{triazole}$), 12.68 (1H, br.s, COOH).

2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)-3-(1*H*-indol-3-yl)propanoic Acid (18). Yield 86%, mp 161-162°C, $C_{32}H_{27}N_5O_7$.

PMR spectrum (δ, ppm, J/Hz): 1.12 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.58 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 3.20 and 3.26 [1H each, m, CH(COOH)$\underline{CH_2}_{indole}$], 4.62 [1H, m, NH$\underline{CH}$(COOH)$CH_2$], 4.67 (2H, s, OCH_2CO), 6.92 (1H, m, H-5′), 6.94 (1H, m, H-6′), 7.01 (1H, m, H-2′), 7.10 (1H, s, H-8), 7.30 (1H, d, J = 8.0, H-7′), 7.40 (5H, s, Ph), 7.51 (1H, d, J = 8.8, H-4′), 7.60 (1H, s, H-5), 8.03 (1H, d, J = 8.8, NH), 8.62 (1H, s, H-2), 8.77 (1H, s, H-5″$_{triazole}$), 10.74 (1H, br.s, NH_{indole}), COOH exchanged with D_2O.

2-(2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)acetamido)acetic Acid (19) was synthesized from **3** and glycylglycine by the method used for **5-18**. Yield 64%, mp 146-147°C, $C_{25}H_{23}N_5O_7$.

PMR spectrum (δ, ppm, J/Hz): 1.22 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.73 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 3.78 and 3.84 (2H each, d, J = 5.6, NH$\underline{CH_2}$), 4.73 (2H, s, OCH_2CO), 7.07 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 8.20 and 8.23 (1H each, t, J = 5.6, $\underline{NH}$), 8.63 (1H, s, H-2), 8.78 (1H, s, H-5′$_{triazole}$), 12.45 (1H, br.s, COOH).

4-(2-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)acetamido)butanoic Acid (20). A solution of **5** (1.3 g, 2.9 mmol) and *N*-hydroxysuccinimide (0.46 g, 3.9 mmol) in dioxane (20 mL) and DMF (5 mL) was treated with diisopropylcarbodiimide (0.6 mL, 3.9 mmol). The mixture was stirred vigorously for 2 h (TLC monitoring). The resulting activated ester was treated with a solution of GABA (0.37 g, 3.6 mmol) and Na_2CO_3 (0.19 g, 1.8 mmol) in water (25 mL). The reaction mixture was stirred for 2.5 h and poured into water (200 mL) after the reaction was finished. On the following day the oil that appeared in the water was ground. The water was decanted. The oil was filtered and ground in ethylacetate. White crystals were filtered off.

Yield 77%, mp 115-116°C, $C_{27}H_{27}N_5O_7$.

PMR spectrum (δ, ppm, J/Hz): 1.23 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 1.69 (2H, m, $CH_2\underline{CH_2}$NH), 2.22 (2H, t, J = 7.2, $CH_2\underline{CH_2}$COOH), 2.72 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 3.1 (s, NH$\underline{CH_2}CH_2$), 3.76 (2H, d, J = 5.2, NH$\underline{CH_2}$CO), 4.72 (2H, s, OCH_2CO), 7.07 (1H, s, H-8), 7.40 (5H, s, Ph), 7.64 (1H, s, H-5), 7.90 (1H, t, J = 5.6, CO$\underline{NH}CH_2CH_2$), 8.10 (1H, t, J = 5.2, CO$\underline{NH}CH_2CO$), 8.61 (1H, s, H-2), 8.75 (1H, s, H-5′$_{triazole}$), 11.90 (1H, br.s, COOH).

2-(3-(2-(6-Ethyl-4-oxo-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-7-yloxy)acetamido)propanamido)-3-phenylpropanoic Acid (21) was synthesized from **6** and L-phenylalanine by the method used for **20**.

Yield 42%, mp 123-124°C, $C_{33}H_{31}N_5O_7$.

PMR spectrum (δ, ppm, J/Hz): 1.20 (3H, t, J = 7.5, $\underline{CH_3}CH_2$-6), 2.31 (2H, br.m, $CH_2\underline{CH_2}$CO), 2.71 (2H, q, J = 7.5, $CH_3\underline{CH_2}$-6), 2.88 and 3.05 (1H each, m, $\underline{CH_2}$Ph), 3.33 (2H, br.m, NH$\underline{CH_2}CH_2$), 4.48 [1H, m, NH(COOH)$\underline{CH}CH_2$Ph], 4.59 (2H, s, OCH_2CO), 7.01 (1H, s, H-8), 7.14 (2H, m, H_{Ph}-2′,6′), 7.21 (3H, s, H_{Ph}-3′,4′,5′), 7.41 (5H, s, $Ph_{triazole}$), 7.64 (1H, s, H-5), 7.93 (1H, t, J = 5.2, CO$\underline{NH}CH_2CH_2$), 8.17 [1H, d, J = 8.4, CO$\underline{NH}$CH(COOH)CH_2], 8.61 (1H, s, H-2), 8.79 (1H, s, H-5′$_{triazole}$), COOH exchanged with D_2O.

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