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MODIFIED COUMARINS. 9. SYNTHESIS OF AMINO-ACID DERIVATIVES OF 3-(2,3,5-TRIMETHYL-7-OXOFURO-[3,2-*g*]CHROMEN-6-YL)PROPANOIC ACID

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Furocoumarins modified by amino acids were prepared by condensation of the N-hydroxysuccinimide ester of 3-(2,3,5-trimethyl-7-oxofuro[3,2-g]chromen-6-yl)propanoic acid with amino acids.

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

Natural bioregulators with the coumarin and furocoumarin structures have a broad spectrum of physiological activity and provide a platform for chemical modification. Owing to the important role of amino acids in life processes, new biologically active compounds have been sought for a long time among natural amino acids, their synthetic analogs, and various compounds containing amino-acid fragments. In our opinion, functionalization of benzopyran bioregulators by pharmacophores of amino-acid nature is promising. Our goal was to modify the furocouomarin ring with amino-acid substituents.

We prepared ethyl-3-(7-hydroxy-4-methyl-2-oxo-2*H*-3-chromenyl)propanoate (**1**), which was necessary for further reactions, in 56% yield by Pechmann condensation of resorcinol and diethyl-2-acetylglutarate in the presence of dry HCl as a condensing agent. The PMR spectrum of **1** contains signals characteristic of the coumarin system and signals for alkyl substituents on the coumarin ring. The IR spectrum has a signal at 1735 cm^{-1} that also proves the coumarin ring was formed.

The MacLeod method was used to fuse the furan ring to the benzopyran-2-one system. This method is based on cyclization in basic medium of 1-(7-coumarinyloxy)acetone derivatives [1]. The cyclization produces linear furocoumarins because the 6-position of the coumarin ring is less reactive than the 8-position [1].

Williamson reaction of **1** and 3-chlorobutan-2-one in the presence of potash as the base forms the correspondingly substituted ketone ethyl-3-[4-methyl-7-(1-methyl-2-oxopropoxy)-2-oxo-2*H*-3-chromenyl]propanoate (**2**). The PMR spectrum of **2** contains signals characteristic of a coumarin ring and a 7-alkoxy group.

Heating **2** with NaOH solution (1 N) readily cyclizes it into the corresponding psoralen furocoumarin **3** with simultaneous hydrolysis of the ester. Fusion of the furan ring to the 6,7-positions of the coumarin was confirmed by PMR spectroscopy. The PMR spectrum of **3** exhibits a broad splitting pattern for the aromatic protons because H-6 of the coumarin ring is decoupled, as a result of which H-4 and H-9 of the intact furoocoumarin resonate as singlets at 7.72 and 7.35 ppm, respectively. The PMR spectrum also has a characteristic signal of the free carboxylic proton as a broad singlet at 12.20 ppm. The UV spectrum of acid **3**, in contrast with that of ketone **2**, has a strong absorption at 254 nm that is stronger than the long-wavelength band at 299 nm. This also proves that the furan ring is fused [2].

The amino-acid derivatives of the furocoumarin were synthesized using the activated-ester method that is commonly used in peptide synthesis [3]. The carboxylic acids were functionalized using the N-hydroxysuccinimide ester, which is highly reactive and does not racemize the product [4].

The N-hydroxysuccinimide ester of **3** was prepared by reacting starting **3** and N-hydroxysuccinimide (SuOH) in absolute dioxane using diisopropylcarbodiimide (DIC) as a condensing agent. The amino-acid derivatives of furocoumarin **4**-**20** with a free carboxylic acid were synthesized in 61-94% yields by reacting the activated ester and the sodium salts of the amino

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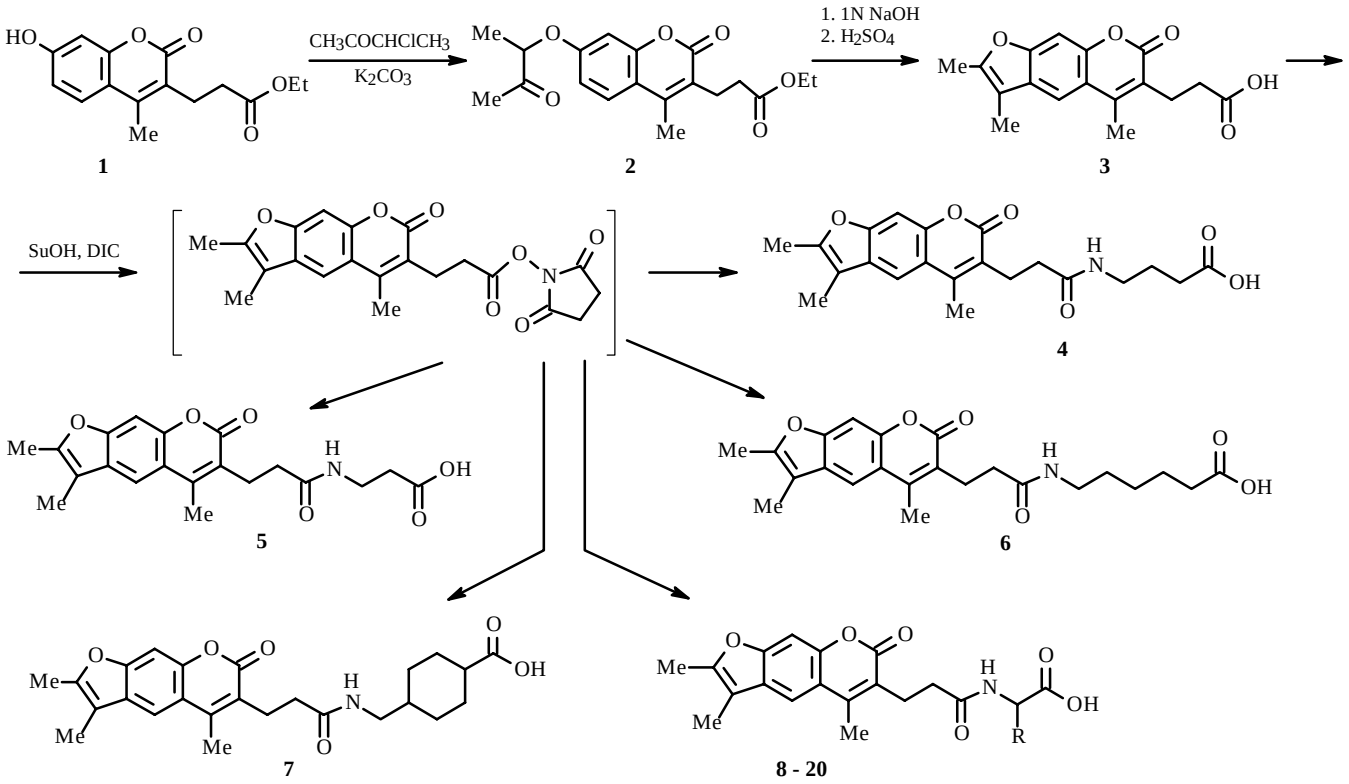
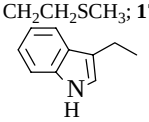
acids in dioxane—water at room temperature with subsequent acidolysis of the salts. We prepared furocoumarin derivatives containing glycine (**8**), *β*-alanine (**5**), L-alanine (**9**), L-valine (**11**), DL-norvaline (**12**), L-leucine (**13**), L-isoleucine (**14**), DL-norleucine (**15**), L-methionine (**16**), DL-phenylglycine (**17**), L-citrulline (**18**), L-phenylalanine (**19**), L-tryptophan (**20**), DL-2-aminobutanoic (**10**), 4-aminobutanoic (**4**), 6-aminohexanoic (**6**), and *trans*-4-aminomethylcyclohexanecarboxylic (**7**) acids. The PMR spectra of **4**-**20** contain signals of the coumarin ring, amino-acid fragment, amide bond at 7.71-8.59 ppm, and free carboxylic acid at 11.68-12.55 ppm.



1 **2** **3** **4** **5** **6** **7** **8 - 20**

8: R = H; **9:** R = CH_3; **10:** R = CH_2CH_3; **11:** R = $CH(CH_3)_2$; **12:** R = $CH_2CH_2CH_3$;
13: R = $CH_2CH(CH_3)_2$; **14:** R = $CH(CH_3)CH_2CH_3$; **15:** R = $CH_2CH_2CH_2CH_3$;
16: R = $CH_2CH_2SCH_3$; **17:** R = Ph; **18:** R = $CH_2CH_2CH_2NHCONH_2$; **19:** R = CH_2Ph;
20: R =



EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by TLC on Merck 60 F254 plates using $CHCl_3$—CH_3OH (9:1 and 95:5). Melting points were determined on a Kofler block. IR and UV spectra were measured on a Nicolet FTIR Nexus 475 spectrometer and Specord M40 spectrophotometer, respectively. PMR spectra were recorded on Varian VXR-300 and Mercury-400 spectrometers relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

Ethyl-3-(7-hydroxy-4-methyl-2-oxo-2*H*-3-chromenyl)propanoate (1). A cooled (0°C) solution of resorcinol (22.0 g, 0.2 mol) and diethyl-2-acetylglutarate (49.4 mL, 0.2 mol) in absolute ethanol (50 mL) was vigorously stirred and cooled. Dry HCl was passed through the solution for 3 h. The reaction mixture was left overnight at room temperature and poured into icewater (500 mL). The precipitate was filtered off and crystallized from ethanol (50%). Yield 30.95 g (56%), empirical formula $C_{15}H_{16}O_5$, mp 116-117°C. IR spectrum (KBr, cm^{-1}): 3250, 1735, 1675, 1615, 1568, 1513, 1468, 1388, 1360, 1324, 1299, 1237, 1181, 1149, 1095, 853. UV (EtOH, λ_{max}, nm, log ε): 204 (4.65), 222 (4.28), 326 (4.24). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.17 (3H, t, J = 7.2, CH_3-2′), 2.37 (3H, s, CH_3-4″), 2.47 (2H, t, J = 7.2, CH_2-2), 2.80 (2H, t, J = 7.2,

CH_2-3), 4.04 (2H, q, CH_2-1′), 6.68 (1H, d, J = 2.4, H-8″), 6.81 (1H, dd, J = 2.4, J = 8.4, H-6″), 7.58 (1H, d, J = 8.4, H-5″), 10.43 (1H, s, OH).

Ethyl-3-[4-methyl-7-(1-methyl-2-oxopropoxy)-2-oxo-2*H*-3-chromenyl]propanoate (2). A hot solution of **1** (27.63 g, 0.1 mol) in absolute acetone (300 mL) was treated with freshly calcined potash (41.4 g, 0.3 mol), stirred vigorously, heated (50-56°C), treated with 3-chloro-2-butanone (11.1 mL, 0.11 mol), held for 3 h with heating and vigorous stirring (course of the reaction monitored by TLC), and poured into H_2SO_4 solution (600 mL, 1 N). The precipitate was filtered off and crystallized from aqueous ethanol. Yield 27.36 g (79%), empirical formula $C_{19}H_{22}O_6$, mp 76-77°C. IR spectrum (KBr, cm^{-1}): 1728, 1694, 1614, 1563, 1435, 1377, 1349, 1330, 1298, 1193, 1160, 1123, 1099, 863. UV spectrum (dioxane, λ_{max}, nm, log ε): 211 (4.55), 223 (4.37), 291 (4.03), 321 (4.24). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.19 (3H, t, J = 7.2, CH_3-2′), 1.48 (1H, d, J = 7.2, CH_3-1‴), 2.18 (3H, s, CH_3-3‴′), 2.40 (3H, s, CH_3-4″), 2.47 (2H, t, J = 7.2, CH_2-2), 2.78 (2H, t, J = 7.2, CH_2-3), 4.06 (2H, q, CH_2-1′), 5.04 (1H, q, H-1‴), 6.83 (1H, d, J = 2.4, H-8″), 6.88 (1H, dd, J = 2.4, J = 8.4, H-6″), 7.66 (1H, d, J = 8.4, H-5″).

3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoic Acid (3). A solution of **2** (26.0 g, 75 mmol) in propan-2-ol (200 mL) was treated with NaOH solution (400 mL, 1 N), heated for 3 h (course of the reaction monitored by TLC), and poured into H_2SO_4 solution (100 mL, 1 N). The precipitate was filtered off and crystallized from propan-2-ol. Yield 17.78 g (79%), empirical formula $C_{17}H_{16}O_5$, mp 219-220°C. IR spectrum (KBr, cm^{-1}): 3506, 2925, 1721, 1707, 1671, 1642, 1627, 1579, 1440, 1400, 1294, 1209, 1177, 1159, 1128, 871. UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.12), 254 (4.10), 299 (3.78), 336 (3.64). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.19 (3H, s, CH_3-3′), 2.39 (3H, s, CH_3-2′), 2.41 (2H, t, J = 7.2, CH_2-2), 2.51 (3H, s, CH_3-5′), 2.81 (2H, t, J = 7.2, CH_2-3), 7.35 (1H, s, H-9′), 7.72 (1H, s, H-4′), 12.08 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]amino Acids 4-20. General Method. A solution of **3** (0.85 g, 3 mmol) and N-hydroxysuccinimide (0.38 g, 3.3 mmol) in absolute dioxane (20 mL) was stirred vigorously, treated with DIC (0.52 mL, 3.3 mmol), and stirred for 2 h (course of the 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). The mixture was stirred vigorously for 2-4 h (course of the reaction monitored by TLC). After the reaction was finished, the diisopropylurea was filtered off. The filtrate was diluted with H_2O (200 mL) and acidified until the pH was 5-6. The resulting precipitate was filtered off and crystallized from aqueous ethanol.

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-4-aminobutanoic Acid (4). Yield 89%, empirical formula $C_{21}H_{23}NO_6$, mp 219-220°C. IR spectrum (KBr, cm^{-1}): 3312, 2936, 1704, 1696, 1684, 1660, 1640, 1584, 1552, 1400, 1152. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.33), 254 (4.33), 299 (3.98), 338 (3.83). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.60 (2H, m, CH_2-3), 2.14 (2H, t, J = 7.2, CH_2-2), 2.20 (3H, s, CH_3-3″), 2.26 (2H, t, J = 7.2, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.51 (3H, s, CH_3-5″), 2.81 (2H, t, J = 7.2, CH_2-2′), 3.02 (2H, m, CH_2-4), 7.35 (1H, s, H-9″), 7.73 (1H, s, H-4″), 7.81 (1H, t, J = 5.2, CONH), 11.88 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-*β*-alaninie(5). Yield 94%, empirical formula $C_{20}H_{21}NO_6$, mp 208-209°C. IR spectrum (KBr, cm^{-1}): 3336, 2920, 1708, 1696, 1684, 1656, 1584, 1552, 1400, 1160. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.37), 254 (4.36), 299 (4.02), 338 (3.85). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.20 (3H, s, CH_3-3″), 2.26 (2H, t, J = 7.2, CH_2-1′), 2.34 (2H, t, J = 7.2, CH_2-2), 2.40 (3H, s, CH_3-2″), 2.49 (3H, s, CH_3-5″), 2.80 (2H, t, J = 7.2, CH_2-2′), 3.23 (2H, m, CH_2-3), 7.28 (1H, s, H-9″), 7.65 (1H, s, H-4″), 7.87 (1H, t, J = 5.2, CONH), 12.01 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-6-aminohexanoic Acid (6). Yield 86%, empirical formula $C_{23}H_{27}NO_6$, mp 212-213°C. IR spectrum (KBr, cm^{-1}): 3352, 2928, 1688, 1656, 1632, 1584, 1552, 1460, 1400, 1348, 1152, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.46), 254 (4.47), 299 (4.13), 338 (3.94). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.22 (2H, m, CH_2-4), 1.34 (2H, m, CH_2-3), 1.45 (2H, m, CH_2-5), 2.08 (2H, t, J = 7.2, CH_2-2), 2.20 (3H, s, CH_3-3″), 2.26 (2H, t, J = 7.2, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.51 (3H, s, CH_3-5″), 2.81 (2H, t, J = 7.2, CH_2-2′), 2.99 (2H, m, CH_2-6), 7.32 (1H, s, H-9″), 7.69 (1H, s, H-4″), 7.71 (1H, t, J = 5.2, CONH), 11.76 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-*trans*-4-aminomethylcyclohexanecarboxylic Acid (7). Yield 85%, empirical formula $C_{25}H_{29}NO_6$, mp 119-120°C. IR spectrum (KBr, cm^{-1}): 3384, 2928, 1700, 1672, 1652, 1584, 1400, 1152, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.38), 254 (4.38), 299 (4.03), 338 (3.89). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.82 (2H, m, CH_2-3*α*, CH_2-5*α*), 1.17 (2H, m, CH_2-3*β*, CH_2-5*β*), 1.27 (1H, m, H-4), 1.64 (2H, m, CH_2-2*α*, CH_2-6*α*), 1.87 (2H, m, CH_2-2*β*, CH_2-6*β*), 1.96 (1H, m, H-1), 2.20 (3H, s, CH_3-3″), 2.28 (2H, t, J = 7.2,

CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.50 (3H, s, CH_3-5″), 2.83 (4H, m, CH_2-4, CH_2-2′), 7.32 (1H, s, H-9″), 7.69 (1H, s, H-4″), 7.71 (1H, t, J = 5.6, CONH), 11.68 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-glycine (8). Yield 91%, empirical formula $C_{19}H_{19}NO_6$, mp 255-256°C. IR spectrum (KBr, cm^{-1}): 3296, 2928, 1688, 1656, 1640, 1584, 1552, 1400, 1160, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.37), 255 (4.37), 301 (4.01), 342 (3.87). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.21 (3H, s, CH_3-3″), 2.34 (2H, t, J = 7.2, CH_2-1′), 2.41 (3H, s, CH_3-2″), 2.52 (3H, s, CH_3-5″), 2.83 (2H, t, J = 7.2, CH_2-2′), 3.70 (2H, d, J = 5.2, CH_2-2′), 7.36 (1H, s, H-9″), 7.74 (1H, s, H-4″), 8.14 (1H, t, J = 5.2, CONH), 12.37 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-L-alanine (9). Yield 72%, empirical formula $C_{20}H_{21}NO_6$, mp 224-225°C. IR spectrum (KBr, cm^{-1}): 3283, 2926, 1734, 1687, 1641, 1622, 1581, 1458, 1400, 1347, 1227, 1154, 1126. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.42), 254 (4.40), 298 (4.06), 338 (3.88). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.23 (3H, d, J = 7.2, CH_3-2), 2.20 (3H, s, CH_3-3″), 2.31 (2H, t, J = 7.2, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.50 (3H, s, CH_3-5″), 2.82 (2H, t, J = 7.2, CH_2-2′), 4.16 (1H, m, H-2), 7.52 (1H, s, H-9″), 7.83 (1H, s, H-4″), 8.23 (1H, d, J = 7.2, CONH), 12.45 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-DL-2-aminobutanoic Acid (10). Yield 94%, empirical formula $C_{21}H_{23}NO_6$, mp 212-213°C. IR spectrum (KBr, cm^{-1}): 3296, 2968, 1696, 1656, 1644, 1584, 1460, 1400, 1152. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.23), 254 (4.23), 299 (3.88), 338 (3.74). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.84 (3H, t, J = 7.2, CH_3-4), 1.58 (1H, m, CH_2-3α), 1.70 (1H, m, CH_2-3β), 2.20 (3H, s, CH_3-3″), 2.35 (2H, t, J = 7.2, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.50 (3H, s, CH_3-5″), 2.82 (2H, t, J = 7.2, CH_2-2′), 4.10 (1H, m, H-2), 7.35 (1H, s, H-9″), 7.75 (1H, s, H-4″), 8.05 (1H, d, J = 7.2, CONH), 12.28 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-L-valine (11). Yield 89%, empirical formula $C_{22}H_{25}NO_6$, mp 189-190°C. IR spectrum (KBr, cm^{-1}): 3290, 2962, 2924, 1700, 1641, 1581, 1551, 1460, 1398, 1347, 1271, 1153, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.40), 254 (4.39), 299 (4.04), 338 (3.88). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.82 (6H, d, J = 6.4, two CH_3-3), 2.00 (1H, m, H-3), 2.20 (3H, s, CH_3-3″), 2.40 (3H, s, CH_3-2″), 2.42 (2H, t, J = 7.2, CH_2-1′), 2.51 (3H, s, CH_3-5″), 2.81 (2H, t, J = 7.2, CH_2-2′), 4.11 (1H, dd, J = 6.4, J = 6.4, H-2), 7.52 (1H, s, H-4″), 7.83 (1H, d, H-9″), 8.06 (1H, d, J = 8.0, CONH), 12.50 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-DL-norvaline (12). Yield 77%, empirical formula $C_{22}H_{25}NO_6$, mp 101-102°C. IR spectrum (KBr, cm^{-1}): 3320, 2960, 1712, 1696, 1688, 1584, 1548, 1464, 1400, 1152, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.39), 254 (4.40), 298 (4.05), 338 (3.87). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.81 (3H, t, J = 7.6, CH_2-5), 1.24 (2H, m, CH_2-4), 1.56 (1H, m, CH_2-3α), 1.68 (1H, m, CH_2-3β), 2.20 (3H, s, CH_3-3″), 2.34 (2H, t, J = 7.2, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.50 (3H, s, CH_3-5″), 2.82 (2H, t, J = 7.2, CH_2-2′), 4.14 (1H, m, H-2), 7.33 (1H, s, H-9″), 7.71 (1H, s, H-4″), 8.00 (1H, d, J = 7.6, CONH), 12.22 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-L-leucine (13). Yield 75%, empirical formula $C_{23}H_{27}NO_6$, mp 213-214°C. IR spectrum (KBr, cm^{-1}): 3432, 2960, 1710, 1680, 1656, 1628, 1596, 1580, 1464, 1400, 1348, 1276, 1208, 1156, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.34), 254 (4.33), 296 (4.00), 338 (3.95). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.72, 0.74 (6H, two d, J = 5.6, two CH_3-4), 1.41 (3H, m, H-3, CH_2-3), 2.19 (3H, s, CH_3-3″), 2.34 (2H, t, J = 7.2, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.51 (3H, s, CH_3-5″), 2.81 (2H, t, J = 7.2, CH_2-2′), 4.17 (1H, m, H-2), 7.51 (1H, s, H-4″), 7.83 (1H, s, H-9″), 8.13 (1H, d, J = 8.0, CONH), 12.46 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-L-isoleucine (14). Yield 62%, empirical formula $C_{23}H_{27}NO_6$, mp 157-158°C. IR spectrum (KBr, cm^{-1}): 3352, 2964, 1704, 1650, 1580, 1544, 1460, 1400, 1348, 1260, 1156. UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.35), 253 (4.37), 298 (4.02), 338 (3.86). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.76 (3H, t, J = 7.2, CH_3-5), 0.79 (3H, d, J = 6.8, CH_3-3), 1.10 (1H, m, CH_2-4α), 1.31 (1H, m, CH_2-4β), 1.70 (1H, m, H-3), 2.19 (3H, s, CH_3-3″), 2.40 (3H, s, CH_3-2″), 2.49 (2H, t, J = 7.2, CH_2-1′), 2.51 (3H, s, CH_3-5″), 2.80 (2H, t, J = 7.2, CH_2-2′), 4.14 (1H, dd, J = 6.4, J = 6.4, H-2), 7.51 (1H, s, H-4″), 7.82 (1H, s, H-9″), 8.08 (1H, d, J = 8.0, CONH), 12.52 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-DL-norleucine (15). Yield 61%, empirical formula $C_{23}H_{27}NO_6$, mp 127-128°C. IR spectrum (KBr, cm^{-1}): 3344, 2960, 1704, 1596, 1584, 1460, 1400, 1152, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.42), 254 (4.42), 299 (4.07), 338 (3.90). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.80 (3H, t, J = 7.2, CH_2-6), 1.22 (4H, m, CH_2-4, CH_2-5), 1.52 (1H, m, CH_2-3α), 1.63 (1H, m, CH_2-3β), 2.20 (3H, s, CH_3-3″), 2.35 (2H, t, J = 7.2, CH_2-1′), 2.41 (3H, s, CH_3-2″), 2.51 (3H, s, CH_3-5″), 2.83 (2H, t, J = 7.2, CH_2-2′), 4.12

(1H, m, H-2), 7.32 (1H, s, H-9″), 7.70 (1H, s, H-4″), 7.98 (1H, d, J = 8.0, CONH), 12.20 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-L-methionine (16). Yield 92%, empirical formula $C_{22}H_{25}NO_6S$, mp 140-141°C. IR spectrum (KBr, cm^{-1}): 3428, 2924, 1700, 1686, 1650, 1625, 1580, 1496, 1400, 1364, 1348, 1252, 1156. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.46), 253 (4.44), 299 (4.09), 338 (3.92). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.81 (1H, m, CH_2-4α), 1.91 (1H, m, CH_2-4β), 1.94 (3H, s, CH_3-6), 2.20 (3H, s, CH_3-3″), 2.37 (4H, m, CH_2-4, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.82 (2H, t, J = 7.2, CH_2-2′), 4.26 (1H, m, H-2), 7.51 (1H, s, H-4″), 7.82 (1H, s, H-9″), 8.20 (1H, d, J = 7.6, CONH), 12.55 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-DL-phenylglycine (17). Yield 73%, empirical formula $C_{25}H_{23}NO_6$, mp 223-224°C. IR spectrum (KBr, cm^{-1}): 3416, 2968, 1700, 1688, 1596, 1584, 1528, 1456, 1400, 1156. UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.52), 254 (4.41), 299 (4.06), 338 (3.89). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.21 (3H, s, CH_3-3″), 2.39 (2H, t, J = 7.2, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.83 (2H, t, J = 7.2, CH_2-2′), 5.35 (1H, d, J = 7.2, H-2), 7.24 (3H, m, H-3, H-4, H-5 Ph-2), 7.31 (2H, m, H-2, H-6 Ph-2), 7.33 (1H, s, H-4″), 7.64 (1H, s, H-9″), 8.59 (1H, d, J = 7.6, CONH), 12.10 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-L-citrulline (18). Yield 77%, empirical formula $C_{23}H_{27}N_3O_7$, mp 160-161°C. IR spectrum (KBr, cm^{-1}): 3344, 2936, 1704, 1660, 1596, 1584, 1464, 1400, 1348, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.47), 254 (4.46), 299 (4.11), 338 (3.92). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.38 (2H, m, CH_2-4), 1.55 (1H, m, CH_2-3α), 1.68 (1H, m, CH_2-3β), 2.19 (3H, s, CH_3-3″), 2.35 (2H, t, J = 7.2, CH_2-1′), 2.40 (3H, s, CH_3-2″), 2.50 (3H, s, CH_3-5″), 2.82 (2H, t, J = 7.2, CH_2-2′), 2.93 (2H, m, CH_2-5), 4.16 (1H, m, H-2), 5.23 (2H, br.s, $CONH_2$), 5.86 (1H, br.s, –NHCO–), 7.31 (1H, s, H-9″), 7.69 (1H, s, H-4″), 8.10 (1H, d, J = 8.0, CONH), 12.20 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-L-phenylalanine (19). Yield 73%, empirical formula $C_{26}H_{25}NO_6$, mp 102-104°C. IR spectrum (KBr, cm^{-1}): 3320, 2928, 1708, 1969, 1684, 1640, 1584, 1536, 1456, 1400, 1348, 1272, 1152, 1128. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.62), 254 (4.49), 299 (4.14), 338 (4.02). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.21 (3H, s, CH_3-3″), 2.30 (2H, t, J = 7.2, CH_2-1′), 2.41 (3H, s, CH_3-2″), 2.50 (3H, s, CH_3-5″), 2.75 (2H, t, J = 7.2, CH_2-2′), 2.86 (1H, m, CH_2-3α), 3.03 (1H, m, CH_2-3β), 4.41 (1H, m, H-2), 7.08-7.22 (5H, m, Ph), 7.33 (1H, s, H-9″), 7.68 (1H, s, H-4″), 8.10 (1H, d, J = 8.4, CONH), 12.48 (1H, br.s, COOH).

N-[3-(2,3,5-Trimethyl-7-oxo-7*H*-furo[3,2-*g*]chromen-6-yl)propanoyl]-L-tryptophan (20). Yield 68%, empirical formula $C_{28}H_{26}N_2O_6$, mp 200-202°C. IR spectrum (KBr, cm^{-1}): 3312, 3280, 2920, 1700, 1672, 1664, 1580, 1456, 1400, 1344, 1228, 1152, 1128, 1096. UV spectrum (EtOH, λ_{max}, nm, log ε): 214 (4.67), 222 (4.66), 255 (4.47), 284 (4.18), 292 (4.23), 338 (4.00). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.20 (3H, s, CH_3-3″), 2.32 (2H, t, J = 7.2, CH_2-1′), 2.41 (3H, s, CH_3-2″), 2.49 (3H, s, CH_3-5″), 2.77 (2H, t, J = 7.2, CH_2-2′), 3.02 (1H, m, CH_2-3α), 3.14 (1H, m, CH_2-3β), 4.47 (1H, m, H-2), 6.94 (1H, t, J = 7.2, H-5‴), 7.01 (1H, t, J = 7.2, H-6‴), 7.07 (1H, br.s, H-2‴), 7.27 (1H, d, J = 7.2, H-7‴), 7.33 (1H, s, H-9″), 7.50 (1H, d, J = 7.2, H-4‴), 7.67 (1H, s, H-4″), 8.04 (1H, d, J = 8.0, CONH), 10.67 (1H, br.s, NH-1‴), 12.48 (1H, br.s, COOH).

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