SYNTHESIS OF CYTISINE DERIVATIVES OF COUMARINS

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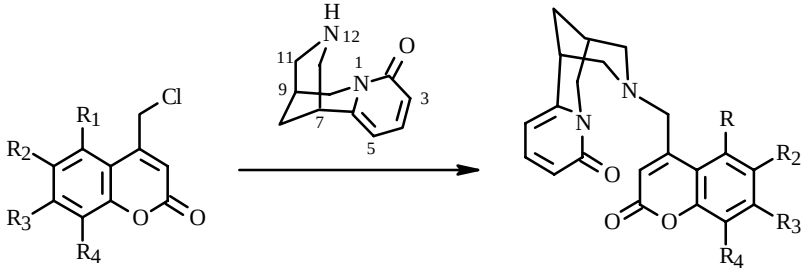
New substituted 4-chloromethylcoumarins that were used as alkylating agents to modify cytisine were synthesized by Pechmann condensation. A series of 4-(12-cytisylmethyl)coumarins containing pharmacophores of the natural heterocycles coumarin and cytisine in a single molecule was prepared. The alkylation gave the best results if diisopropylethylamine was used as the base.

Key words: cytisine, 4-chloromethylcoumarin, alkylation, diisopropylethylamine.

In continuation of research on the modification of natural compounds, we decided to investigate the alkaloid (-)-cytisine from seeds of *Cytisus laburnum* L. and *Thermopsis lanceolata* R.Br. Cytisine is of great interest to many researchers because of its effect on the ganglionic nervous system and its use in medicine as a respiratory analeptic [1]. A variety of *N*-alkyl derivatives of cytisine has been synthesized [2-4], among which are compounds with analgesic, antihypertensive, and inotropic activities [3]. According to the patent literature [5], *N*-methyl derivatives also possess anti-inflammatory and hypoglycemic activities.

Therefore, the search for methods of modifying cytisine is very timely. The combination into one molecule of two natural heterocyclic compounds can lead to the production of compounds with new types of physiological activity. Considering this, we selected substituted 4-chloromethylcoumarins, which are used to synthesize compounds with antimicrobial [6] and anti-inflammatory [7] properties, as alkylating agents for modifying cytisine.



1 - 11 **12 - 22**

1, 12: $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$; **2, 13:** $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$; **3, 14:** $R_1 = R_2 = H$, $R_3 = OH$, $R_4 = CH_3$
4, 15: $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$; **5, 16:** $R_1 = R_4 = H$, $R_2 = Cl$, $R_3 = CH_3$; **6, 17:** $R_1 = R_4 = H$, $R_2 = OH$, $R_3 = CH_3$
7, 18: $R_1 = R_3 = CH_3$, $R_2 = R_4 = H$; **8,19:** $R_1 = R_3 = H$, $R_2 = R_4 = CH_3$; **9, 20:** $R_1 = R_3 = R_4 = H$, $R_3 = CH_2CH_3$
10, 21: $R_1 = R_4 = H$, $R_2R_3 = CH_2CH_2CH_2$; **11, 22:** $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$

Several synthetic methods for 4-chloromethylcoumarins are known. These include the reaction of phenols with 4-chloroacetoacetic ester in H_2SO_4 (Pechmann condensation) [8-10], chlorination of coumarin-4-acetic acid in AcOH [11], and reaction of 4-hydroxymethylcoumarins with PCl_5 in benzene [8, 12]. Based on the literature, we selected the Pechmann condensation for preparing 4-chloromethylcoumarins **1-11**.

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Our challenge was to find the optimal conditions for carrying out the reaction because of the instability of the 4-chloromethylcoumarins to base [13] and the structural features of cytisine. Alkylation of cytisine by substituted 4-chloromethylcoumarins occurs only in the presence of bases. We used K_2CO_3 and tertiary amines {triethylamine, *N*-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine} as the base to synthesize 4-(12-cytisylmethyl)coumarins **12-22**.

As it turned out, using K_2CO_3 did not give the desired result in either alcohol or acetonitrile as solvent. If triethylamine or *N*-methylmorpholine was used, the principal reaction products were quaternary *bis*-alkyl derivatives of the cytisine *N*-12 and quaternary alkyl derivatives of the amines. According to TLC, the main reaction pathway using the stronger base DBU was recyclization of the 4-chloromethylcoumarins into 3-benzofurylacetic acid derivatives.

The best results were obtained if diisopropylethylamine (Hunig's base) in ethanol was used. Thus, alkylation of cytisine by 4-chloromethylcoumarins **1-11** occurred with heating for 5-10 h in the presence of Hunig's base. Under these conditions, cytisine was monoalkylated exclusively at the *N*-12 atom and gave 4-(12-cytisylmethyl)coumarins **12-22** in high yields.

For the reaction of hydroxyl derivatives of 4-chloromethylcoumarins **3** and **6**, use of a sterically hindered base prevents alkylation of the hydroxyls and gives a reaction that is selective for cytisine *N*-12 to form phenols **14** and **17**.

Thus, we developed the optimal conditions for alkylation of cytisine using 4-chloromethylcoumarins. This enabled the synthesis of compounds containing the pharmacophores coumarin and cytisine in a single molecule and provided new potential for chemical modification of cytisine.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck (Germany) plates with elution by $CHCl_3$ and $CHCl_3$:CH_3OH (19:1). NMR spectra in DMSO-d_6 were measured on a Varian VXR-300 (300 MHz) instrument relative TMS (internal standard) on the δ-scale. Analytical data for all compounds agreed with those calculated.

Synthesis of 4-Chloromethylcoumarins 5-11. A mixture of 4-chloroacetoacetic ester (0.1 mol) and the corresponding phenol (0.1 mol) was added to H_2SO_4 (50 mL, 73%), stirred for 18-24 h at room temperature, and poured onto ice. The resulting precipitate was filtered off and crystallized from dioxane.

7-Methyl-6-chloro-4-(chloromethyl)-2*H*-chromen-2-one (5). Yield 64%, $C_{11}H_8Cl_2O_2$, mp 219-220°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 2.40 (3H, s, Me-7), 5.02 (2H, s, CH_2-4), 6.65 (1H, s, H-3), 7.44 (1H, s, H-8), 7.86 (1H, s, H-5).

6-Hydroxy-7-methyl-4-(chloromethyl)-2*H*-chromen-2-one (6). Yield 56%, $C_{11}H_9ClO_3$, mp 223-225°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 2.21 (3H, s, Me-7), 4.91 (2H, s, CH_2-4), 6.58 (1H, s, H-3), 7.11 (1H, s, H-8), 7.21 (1H, s, H-5), 9.82 (1H, s, OH-6).

5,7-Dimethyl-4-(chloromethyl)-2*H*-chromen-2-one (7). Yield 73%, $C_{12}H_{11}ClO_2$, mp 176-177°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 2.35 (3H, s, Me-7), 2.75 (3H, s, Me-5), 5.10 (2H, s, CH_2-4), 6.63 (1H, s, H-3), 7.04 (1H, s, H-8), 7.12 (1H, s, H-6).

6,8-Dimethyl-4-(chloromethyl)-2*H*-chromen-2-one (8). Yield 69%, $C_{12}H_{11}ClO_2$, mp 150-151°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 2.35, 2.36 (6H, 2s, Me-6 and Me-8), 5.01 (2H, s, CH_2-4), 6.66 (1H, s, H-3), 7.37 (1H, s, H-7), 7.50 (1H, s, H-5).

4-(Chloromethyl)-6-ethyl-2*H*-chromen-2-one (9). Yield 57%, $C_{12}H_{11}ClO_2$, mp 145-146°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 1.23, 2.70 (3H, t, 2H, q, ^3J = 8, CH_3CH_2-6), 5.05 (2H, s, CH_2-4), 6.67 (1H, s, H-3), 7.37 (1H, d, ^3J = 8, H-8), 7.52 (1H, dd, ^3J = 8, ^4J = 2, H-7), 7.68 (1H, d, ^4J = 2, H-5).

4-(Chloromethyl)-7,8-dihydrocyclopenta[*g*]chromen-2(6*H*)-one (10). Yield 77%, $C_{13}H_{11}ClO_2$, mp 240-241°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 2.07 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.94 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$), 5.00 (2H, s, CH_2-4), 6.59 (1H, s, H-3), 7.30 (1H, s, H-8), 7.67 (1H, s, H-5).

6,7-Dimethyl-4-(chloromethyl)-2*H*-chromen-2-one (11). Yield 82%, $C_{12}H_{11}ClO_2$, mp 215-217°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 2.30, 2.32 (6H, 2s, Me-6 and Me-7), 4.96 (2H, s, CH_2-4), 6.54 (1H, s, H-3), 7.20 (1H, s, H-8), 7.58 (1H, s, H-5).

4-Chloromethylcoumarins agreed with literature data for **1**, **2** [8, 14], **3** [9], and **4** [10].

General Method for Preparing 4-(Cytisyl-12)-methylchromones 12-22. A mixture of 4-chloromethylcoumarin **1-11** (2 mmol), cytisine (2 mmol), and diisopropylethylamine (2.5 mmol) in ethanol (20 mL) was stirred for 5-10 h at 70°C

(completion of reaction monitored by TLC), cooled, mixed with water (20 mL), and left overnight. The resulting precipitate was filtered off, washed with water, and crystallized from ethanol.

(1*R*,5*S*)-3-[(7-Methyl-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]-diazocin-8-one (12). Yield 68%, $C_{22}H_{22}N_2O_3$, mp 176-178°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.67-1.90 (2H, m, CH_2-8), 2.30-2.45 (3H, m, H-9, H-11, H-13), 2.80 (1H, m, H-11), 2.95 (1H, m, H-13), 3.02 (1H, m, H-7), 3.60-3.82 (2H, 2d, ^{2}J = 15.5, CH_2-10), 5.99 (1H, dd, ^{3}J = 6.9, ^{4}J = 1.2, H-5), 6.21 (1H, dd, ^{3}J = 8.7, ^{4}J = 1.2, H-3), 7.25 (1H, dd, ^{3}J = 6.9, ^{3}J = 8.7, H-4); coumarin protons: 2.35 (3H, s, CH_3-7), 3.59 (2H, s, CH_2-4), 6.06 (1H, s, H-3), 6.85 (1H, dd, ^{3}J = 8, ^{4}J = 2, H-6), 7.12 (1H, d, ^{4}J = 2, H-8), 7.42 (1H, d, ^{3}J = 8, H-5).

(1*R*,5*S*)-3-[(6-Methyl-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (13). Yield 80%, $C_{22}H_{22}N_2O_3$, mp 149-151°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.69-1.88 (2H, m, CH_2-8), 2.30-2.46 (3H, m, H-9, H-11, H-13), 2.85 (1H, m, H-11), 2.96 (1H, m, H-13), 3.03 (1H, m, H-7), 3.62-3.80 (2H, 2d, ^{2}J = 15.5, CH_2-10), 6.02 (1H, dd, ^{3}J = 6.9, ^{4}J = 1.2, H-5), 6.18 (1H, dd, ^{3}J = 8.7, ^{4}J = 1.2, H-3), 7.26 (1H, dd, ^{3}J = 6.9, ^{3}J = 8.7, H-4); coumarin protons: 2.20 (3H, s, CH_3-6), 3.58 (2H, s, CH_2-4), 6.12 (1H, s, H-3), 7.20 (1H, d, ^{3}J = 8, H-8), 7.32 (1H, dd, ^{3}J = 8, ^{4}J = 2, H-7), 7.37 (1H, d, ^{4}J = 2, H-5).

(1*R*,5*S*)-3-[(7-Hydroxy-8-methyl-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (14). Yield 45%, $C_{22}H_{22}N_2O_4$, mp 212-214°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.65-1.92 (2H, m, CH_2-8), 2.29-2.45 (3H, m, H-9, H-11, H-13), 2.81 (1H, m, H-11), 2.91 (1H, m, H-13), 3.03 (1H, m, H-7), 3.56-3.81 (2H, 2d, ^{2}J = 15.5, CH_2-10), 6.02 (1H, dd, ^{3}J = 6.9, ^{4}J = 1.2, H-5), 6.22 (1H, dd, ^{3}J = 8.7, ^{4}J = 1.2, H-3), 7.27 (1H, dd, ^{3}J = 6.9, ^{3}J = 8.7, H-4); coumarin protons: 2.09 (3H, s, CH_3-8), 3.52 (2H, s, CH_2-4), 5.91 (1H, s, H-3), 6.56 (1H, d, ^{3}J = 8, H-6), 7.25 (1H, d, ^{3}J = 8, H-5), 10.3 (1H, s, HO-7).

(1*R*,5*S*)-3-[(7,8-Dimethyl-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (15). Yield 63%, $C_{23}H_{24}N_2O_3$, mp 198-200°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.69-1.89 (2H, m, CH_2-8), 2.35-2.45 (3H, m, H-9, H-11, H-13), 2.82 (1H, m, H-11), 2.92 (1H, m, H-13), 3.03 (1H, m, H-7), 3.60-3.80 (2H, 2d, ^{2}J = 15.5, CH_2-10), 6.02 (1H, dd, ^{3}J = 6.9, ^{4}J = 1.2, H-5), 6.23 (1H, dd, ^{3}J = 8.7, ^{4}J = 1.2, H-3), 7.27 (1H, dd, ^{3}J = 6.9, ^{3}J = 8.7, H-4); coumarin protons: 2.23 (3H, s, CH_3-8), 2.30 (3H, s, CH_3-7), 3.58 (2H, s, CH_2-4), 6.05 (1H, s, H-3), 6.86 (1H, d, ^{3}J = 8, H-6), 7.29 (1H, d, ^{3}J = 8, H-5).

(1*R*,5*S*)-3-[(7-Methyl-6-chloro-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (16). Yield 76%, $C_{22}H_{21}ClN_2O_3$, mp 207-208°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.69-1.88 (2H, m, CH_2-8), 2.36-2.45 (3H, m, H-9, H-11, H-13), 2.87 (1H, m, H-11), 2.95 (1H, m, H-13), 3.04 (1H, m, H-7), 3.68-3.79 (2H, 2d, ^{2}J = 15.5, CH_2-10), 6.04 (1H, dd, ^{3}J = 6.9, ^{4}J = 1.2, H-5), 6.19 (1H, dd, ^{3}J = 8.7, ^{4}J = 1.2, H-3), 7.27 (1H, dd, ^{3}J = 6.9, ^{3}J = 8.7, H-4); coumarin protons: 2.36 (3H, s, CH_3-7), 3.56, 3.63 (2H, 2d, ^{2}J = 15, CH_2-4), 6.07 (1H, s, H-3), 7.34 (1H, s, H-8), 7.58 (1H, s, H-5).

(1*R*,5*S*)-3-[(6-Hydroxy-7-methyl-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (17). Yield 68%, $C_{22}H_{22}N_2O_4$, mp 293-295°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.70-1.92 (2H, m, CH_2-8), 2.33-2.48 (3H, m, H-9, H-11, H-13), 2.84 (1H, m, H-11), 2.96 (1H, m, H-13), 3.06 (1H m, H-7), 3.68-4.00 (2H, 2d, ^{3}J = 15.5, CH_2-10), 6.08 (1H, dd, ^{3}J = 6.9, ^{4}J = 1.2, H-5), 6.24 (1H, dd, ^{3}J = 8.7, ^{4}J = 1.2, H-3), 7.32 (1H, dd, ^{3}J = 6.9, ^{3}J = 8.7, H-4); coumarin protons: 2.19 (3H, s, CH_3-7), 3.45, 3.60 (2H, 2d, ^{2}J = 16, CH_2-4), 5.75 (1H, s, H-3), 6.91 (1H, s, H-8), 7.09 (1H, s, H-5), 9.44 (1H, s, HO-7).

(1*R*,5*S*)-3-[(5,7-Dimethyl-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (18). Yield 72%, $C_{23}H_{24}N_2O_3$, mp 200-202°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.68-1.88 (2H, m, CH_2-8), 2.23-2.45 (3H, m, H-9, H-11, H-13), 2.79 (1H, m, H-11), 2.90 (1H, m, H-13), 3.03 (1H, m, H-7), 3.59-3.75 (2H, 2d, ^{2}J = 15.5, CH_2-10), 6.01 (1H, dd, ^{3}J = 6.9, ^{4}J = 1.2, H-5), 6.21 (1H, dd, ^{3}J = 8.7, ^{4}J = 1.2, H-3), 7.25 (1H, dd, ^{3}J = 6.9, ^{3}J = 8.7, H-4); coumarin protons: 2.28 (3H, s, CH_3-7), 2.36 (3H, s, CH_3-5), 3.55, 3.66 (2H, 2d, ^{2}J = 15, CH_2-4), 6.09 (1H, s, H-3), 6.79, 6.97 (2H, 2s, H-6 and H-8).

(1*R*,5*S*)-3-[(6,8-Dimethyl-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (19). Yield 75%, $C_{23}H_{24}N_2O_3$, mp 120-122°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.68-1.88 (2H, m, CH_2-8), 2.31-2.45 (3H, m, H-9, H-11, H-13), 2.85 (1H, m, H-11), 2.93 (1H, m, H-13), 3.03 (1H, m, H-7), 3.60-3.80 (2H, 2d, ^{2}J = 15.5, CH_2-10), 6.03 (1H, dd, ^{3}J = 6.9, ^{4}J = 1.2, H-5), 6.18 (1H, dd, ^{3}J = 8.7, ^{4}J = 1.2, H-3), 7.27 (1H, dd, ^{3}J = 6.9, ^{3}J = 8.7, H-4); coumarin protons: 2.16 (3H, s, CH_3-8), 2.28 (3H, s, CH_3-6), 3.53, 3.60 (2H, 2d, ^{3}J = 15, CH_2-4), 6.12 (1H, s, H-3), 7.22 (2H, s, H-5 and H-7).

(1*R*,5*S*)-3-[(2-Oxo-6-ethyl-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (20). Yield 91%, $C_{23}H_{24}N_2O_3$, mp 155-156°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.70-1.88 (2H, m, CH_2-8), 2.34-2.45 (3H, m, H-9, H-11, H-13), 2.88 (1H, m, H-11), 2.97 (1H, m, H-13), 3.04 (1H, m, H-7), 3.63-3.80 (2H, 2d, ^2J = 15.5, CH_2-10), 6.04 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.18 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.27 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); coumarin protons: 1.12, 2.53 (3H, t, 2H, q, ^3J = 8, CH_3CH_2-6), 3.57, 3.64 (2H, 2d, ^2J = 15, CH_2-4), 6.08 (1H, s, H-3), 7.24 (1H, d, ^3J = 8, H-8), 7.38 (1H, dd, ^3J = 8, ^4J = 2, H-7), 7.40 (1H, d, ^4J = 2, H-5).

(1*R*,5*S*)-3-[(2-Oxo-2,6,7,8-tetrahydrocyclopenta[*g*]chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (21). Yield 85%, $C_{24}H_{24}N_2O_3$, mp 223-225°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.67-1.88 (2H, m, CH_2-8), 2.30-2.45 (3H, m, H-9, H-11, H-13), 2.70, 2.98 (6H, m, H-11, H-13, coumarin CH_2-6 and CH_2-7), 3.02 (1H, m, H-7), 3.61-3.78 (2H, 2d, ^2J = 15.5, CH_2-10), 5.99 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.16 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.24 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); coumarin protons: 2.02 (3H, m, $CH_2C\underline{H}_2CH_2$), 3.56 (2H, s, CH_2-4), 6.09 (1H, s, H-3), 7.15 (1H, s, H-8), 7.37 (1H, s, H-5).

(1*R*,5*S*)-3-[(5,6-Dimethyl-2-oxo-2*H*-chromen-4-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (22). Yield 83%, $C_{23}H_{24}N_2O_3$, mp 237-239°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.68-1.88 (2H, m, CH_2-8), 2.31-2.44 (3H, m, H-9, H-11, H-13), 2.85 (1H, m, H-11), 2.94 (1H, m, H-13), 3.03 (1H, m, H-7), 3.60-3.78 (2H, 2d, ^2J = 15.5, CH_2-10), 6.02 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.18 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.26 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); coumarin protons: 2.09 (3H, s, CH_3-6), 2.25 (3H, s, CH_3-7), 3.56 (2H, s, CH_2-4), 6.03 (1H, s, H-3), 7.10 (1H, s, H-8), 7.32 (1H, s, H-5).

REFERENCES

1. M. D. Mashkovskii, *Medicinal Preparations* [in Russian], Vol. 1, Torsing, Khar′kov (1997).
2. C. C. Boido and F. Sparatore, *Farmaco*, **54**, 7, 438 (1999).
3. a) O. Nicolotti, C. Boido, S. Canu, F. Sparatore, and A. Carotti, *Farmaco*, **57**, 6, 469 (2002); b) C. C. Boido, B. Tasso, V. Boido, and F. Sparatore, *Farmaco*, **58**, 3, 265 (2003).
4. a) K. A. Krasnov, V. G. Kartsev, and A. S. Gorovoi, *Khim. Prir. Soedin.*, 152 (2000); b) K. A. Krasnov, V. G. Kartsev, A. S. Gorovoi, and V. N. Khrustalev, *Khim. Prir. Soedin.*, 367 (2002); c) S. Ohmiya, H. Otomasu, and I. Murakoshi, *Chem. Pharm. Bull.*, **32**, 2, 815 (1984).
5. a) I. Murakoshi, Y. Fujii, S. Takedo, and I. Arai, Jpn. Kokai Tokkyo Koho, Jpn. Pat. No. 04-295480, Oct. 20, 1992; *Chem. Abstr.*, **118**, 45733 (193); b) I. Murakoshi, Y. Fujii, H. Kawamura, and H. Maruyama, Jpn. Kokai, Tokkyo Koho, Jpn. Pat. No. 04-295479, Oct. 20, 1992; *Chem. Abstr.*, **118**, 45734 (1993).
6. R. Singh, R. P. Singh, and O. P. Malik, *Indian J. Chem., Sect. B*, **28**, 996 (1989).
7. M. Ghate, D. Manohar, V. Kulkarni, R. Shobha, and S. Y. Kattimani, *Eur. J. Med. Chem.*, **38**, 297 (2003).
8. S. D. Joshi and R. N. Usgaonkar, *Indian J. Chem., Sect. B*, **21**, 5, 399 (1982).
9. G. V. M. Sharma, J. J. Reddy, P. S. Lakshmi, P. R. Krishna, *Tetrahedron Lett.*, **46**, 36, 6119 (2005).
10. a) R. P. Singh, R. V. Singh, and O. P. Malik, *Indian J. Chem., Sect. B*, **27**, 1-12, 1031 (1988); b) R. Singh, S. Sharma, and O. P. Malik, *J. Indian Chem. Soc.*, **69**, 6, 338 (1992); c) P. Kele, J. Orbulescu, T. L. Calhoun, R. E. Gawley, and R. M. Leblanc, *Tetrahedron Lett.*, **43**, 25, 4413 (2002); d) R. G. Hanshaw, S. M. Hilkert, H. Jiang, and B. D. Smith, *Tetrahedron Lett.*, **45**, 47, 8721 (2004); e) H. Valizadeh and A. Shockravi, *Tetrahedron Lett.*, **46**, 20, 3501 (2005); f) A. M. Piloto, S. P. G. Costa, and M. S. T. Goncalves, *Tetrahedron Lett.*, **46**, 28, 4757 (2005); g) Y. Ma, W. Luo, P. J. Quinn, Z. Liu, and R. C. Hider, *J. Med. Chem.*, **47**, 25, 6349 (2004); h) F. Leonetti, A. Favia, A. Rao, R. Aliano, A. Paluszcak, R. W. Hartmann, and A. Carotti, *J. Med. Chem.*,, **47**, 27, 6792 (2004); i) J. Einhorn, G. Lamotte, J.-P. Buisson, P. Demerseman, and R. Royer, *Eur. J. Med. Chem.*, **19**, 2, 143 (1984); j) M. Campos-Toimil, F. Orallo, L. Santana, and E. Uriarte, *Bioorg. Med. Chem. Lett.*, **12**, 5, 783 (2002); k) N.-H. Nam, Y. Kim, Y.-J. You, D.-H. Hong, H.-M. Kim, and B.-Z. Ahn, *Bioorg. Med. Chem. Lett.*, **12**, 17, 2345 (2002); l) A. Chilin, G. Pastorini, A. Castellin, F. Bordin, P. Rodighiero, and A. Guiotto, *Synthesis*, 1190 (1995); m) S. Akita, N. Umezawa, and T. Higuchi, *Org. Lett.*, **25**, 5565 (2005); n) A. L. James, J. D. Perry, and S. P. Stanforth, *J. Heterocycl. Chem.*, **43**, 2, 515 (2006); o) G. Smitha and C. S. Reddy, *Synth. Commun.*, **34**, 21, 3997 (2004).
11. R. Dey, *J. Indian Chem. Soc.*, **11**, 635 (1934).
12. P. Waykole and R. N. Usgaonkar, *Indian J. Chem., Sect. B*, **21**, 8, 707 (1982).
13. Y. Fall, L. Santana, M. Teijeira, and E. Uriarte, *Heterocycles*, **41**, 4, 647 (1995).