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MODIFIED COUMARINS. 22. SYNTHESIS OF *N*-COUMARINYLOXYACETYL DERIVATIVES OF CYTISINE

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N-*Acetyl derivatives of cytisine modified by coumarins were synthesized.*

Key words: cytisine, coumarins, acylation, activated esters.

Adding a natural alkaloidal fragment to organic molecules leads in most instances to the appearance of new biological properties. Cytisine possesses potent pharmacological activity [1, 2]. On the other hand, coumarins form a group of structurally varied natural bioregulators of plant origin that are based on the benzopyran-2-one skeleton [3]. Depending on the structure, natural coumarins and their synthetic analogs possess a wide spectrum of biological activity [4]. We synthesized a series of cytisine derivatives that contain the coumarin moiety, a heterocycle that is widely distributed in nature.

Hydroxycoumarins **1**-**8** that were required for further transformations were prepared by Pechmann condensation of polyphenols (resorcinol, 2-methylresorcinol, orcine) and ethyl-2-oxocyclopentanecarboxylate or ethyl-2-oxocyclohexanecarboxylate in the presence of conc. H_2SO_4 [5, 6].

Alkylation of **1**-**8** in acetone in the presence of potash by ethylchloroacetate produced ethyl esters **9**-**16**, saponification of which by NaOH in aqueous propan-2-ol with subsequent acidolysis gave the corresponding acids **17**-**24**.

Cytisine was modified by two methods. The first method of cytisine *N*-acylation was based on the method of activated esters that is widely applied in peptide synthesis [7]. We used the highly reactive *N*-hydroxysuccinimide ester to activate the carboxylic function [8]. Activated esters were prepared by reacting corresponding acids **17**-**24** and *N*-hydroxysuccinimide (SuOH) in absolute dioxane using diisopropylcarbodiimide (DIC) as the condensing agent. Condensation of the resulting esters with cytisine in dioxane at room temperature formed in high yields the *N*-acyl cytisine derivatives **25**-**32**, which contain coumarin moieties.

The second method was based on activation of the carboxylic function of coumarinyloxyacetic acids using *N*,*N*-carbonyldiimidazole (CDI) [9, 10]. Reaction of acids **17**-**24** and CDI in absolute DMF formed *N*-acylimidazoles, which were converted in high yields and smoothly by cytisine to the corresponding *N*-acyl cytisine derivatives **25**-**32**.

Analysis of PMR spectra revealed that a doubled set of signals was found for all prepared compounds. Obviously formation of amide bonds in such systems produces invertomers with hindered rotation around the N–C bond that can be considered to be *Z*- and *E*-isomers. The presence of amide conjugation was confirmed by temperature experiments. Thus, heating samples of the prepared compounds to 100°C caused signals in the PMR spectrum to coalesce because of free rotation of the substituents around the N–C bond.

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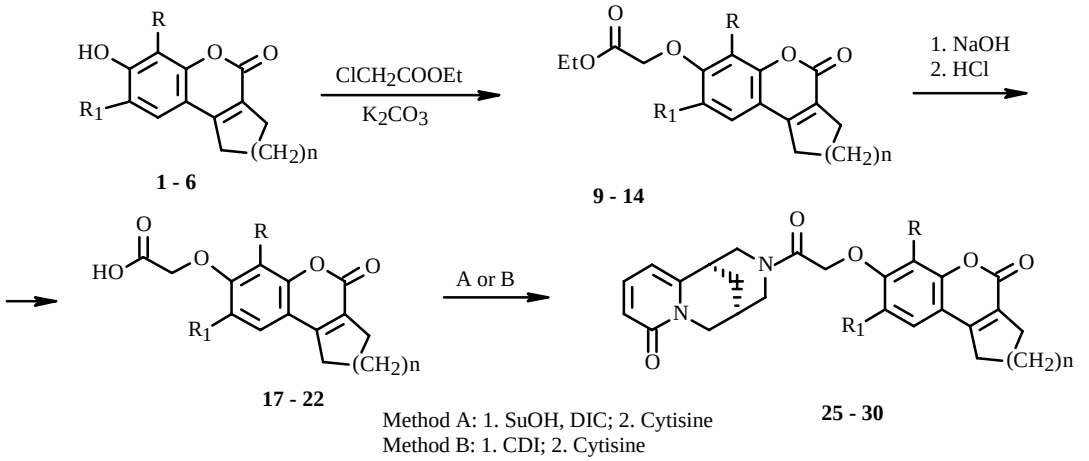
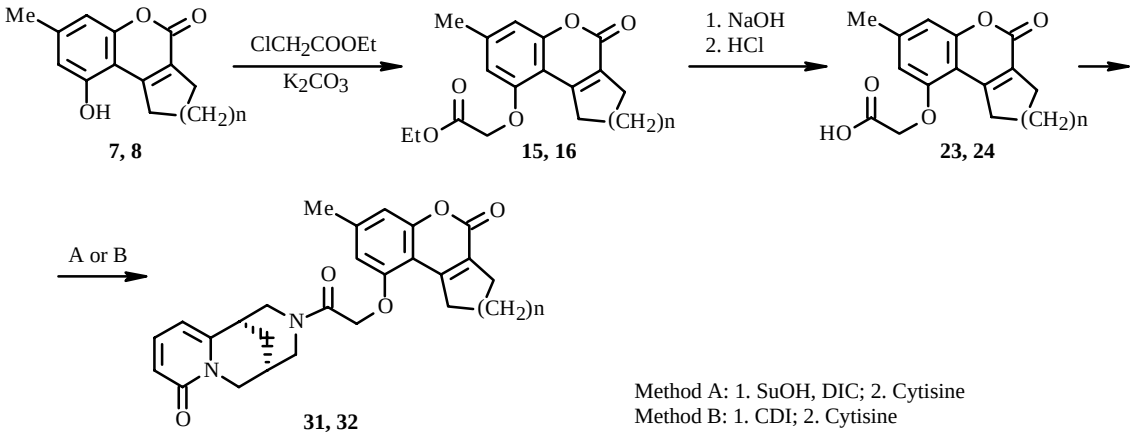


Method A: 1. SuOH, DIC; 2. Cytisine
Method B: 1. CDI; 2. Cytisine

1, 9, 17, 25: R = R_1 = H, n = 1; **2, 10, 18, 26:** R = Me, R_1 = H, n = 1; **3, 11, 19, 27:** R = H, R_1 = Cl, n = 1;
4, 12, 20, 28: R = R_1 = H, n = 2; **5, 13, 21, 29:** R = Me, R_1 = H, n = 2; **6, 14, 22, 30:** R = H, R_1 = Cl, n = 2



Method A: 1. SuOH, DIC; 2. Cytisine
Method B: 1. CDI; 2. Cytisine

7, 15, 23, 31: n = 1; **8**, **16, 24, 32:** n = 2

EXPERIMENTAL

The course of reactions and purity of compounds were monitored by TLC on Merck 60 F254 plates with elution by $CHCl_3$:CH_3OH (9:1 and 19:1). Melting points were determined on a Kofler block. PMR spectra were recorded on a Varian VXR-300 spectrometer at 300 MHz relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated. Hydroxycoumarins **1-8** were synthesized as before [5, 6]; **12** and **20**, by the literature method [11]. Pharmacopoeic cytisine isolated from *Thermopsis alterniflora* was used.

Ethylcoumarinyloxyacetates 9-16. A hot solution of **1-8** (10 mmol) in absolute acetone (50 mL) was treated with freshly calcined potash (4.14 g, 30 mmol), stirred vigorously, heated (50-56°C), treated with ethylchloroacetate (1.2 mL, 11 mmol), and stirred vigorously for 2-4 h (course of reaction monitored by TLC). After the reaction was complete, the mixture was cooled, transferred into icewater (500 mL), and acidified to pH 5-6. The resulting precipitate was filtered off and crystallized from propan-2-ol (75%).

Ethyl[(4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl)oxy]acetate (9). Yield 86%, $C_{16}H_{16}O_5$, mp 148-149°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.26 (3H, t, J = 7.2, CH_3-2′), 2.14 (2H, m, CH_2-2), 2.76 (2H, m, CH_2-1), 3.06 (2H, m, CH_2-3), 4.17 (2H, q, J = 7.2, CH_2-1′), 4.87 (2H, s, CH_2O-7), 6.88 (1H, dd, J = 2.4, 8.7, H-8), 6.97 (1H, d, J = 2.4, H-6), 7.49 (1H, d, J = 8.7, H-9).

Ethyl[(6-methyl-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl)oxy]acetate (10). Yield 91%, $C_{17}H_{18}O_5$, mp 169-170°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.26 (3H, t, J = 7.2, CH_3-2′), 2.10 (2H, m, CH_2-2), 2.26 (3H, s, CH_3-6), 2.74 (2H, m, CH_2-1), 3.04 (2H, m, CH_2-3), 4.17 (2H, q, J = 7.2, CH_2-1′), 4.97 (2H, s, CH_2O-7), 6.98 (1H, d, J = 8.7, H-8), 7.39 (1H, d, J = 8.7, H-9).

Ethyl[(8-chloro-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl)oxy]acetate (11). Yield 89%, $C_{16}H_{15}ClO_5$, mp 181-182°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.26 (3H, t, J = 7.2, CH_3-2′), 2.14 (2H, m, CH_2-2), 2.76 (2H, m, CH_2-1), 3.05 (2H, m, CH_2-3), 4.19 (2H, q, J = 7.2, CH_2-1′), 4.98 (2H, s, CH_2O-7), 7.17 (1H, s, H-6), 7.62 (1H, s, H-9).

Ethyl[(4-methyl-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl)oxy]acetate (13). Yield 83%, $C_{18}H_{20}O_5$, mp 158-159°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.26 (3H, t, J = 7.2, CH_3-2′), 1.77 (4H, m, CH_2-8, CH_2-9), 2.26 (3H, s, CH_3-4), 2.41 (2H, m, CH_2-10), 2.74 (2H, m, CH_2-7), 4.18 (2H, q, J = 7.2, CH_2-1′), 4.87 (2H, s, CH_2O-7), 6.86 (1H, d, J = 8.7, H-2), 7.44 (1H, d, J = 8.7, H-1).

Ethyl[(2-chloro-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl)oxy]acetate (14). Yield 86%, $C_{17}H_{17}ClO_5$, mp 183-184°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.23 (3H, t, J = 7.2, CH_3-2′), 1.72 (4H, m, CH_2-8, CH_2-9), 2.40 (2H, m, CH_2-10), 2.75 (2H, m, CH_2-7), 4.18 (2H, q, J = 7.2, CH_2-1′), 5.04 (2H, s, CH_2O-3), 7.17 (1H, s, H-4), 7.75 (1H, s, H-1).

Ethyl[(7-methyl-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-9-yl)oxy]acetate (15). Yield 85%, $C_{17}H_{18}O_5$, mp 166-167°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.25 (3H, t, J = 7.2, CH_3-2′), 2.04 (2H, m, CH_2-2), 2.35 (3H, s, CH_3-7), 2.67 (2H, m, CH_2-1), 3.24 (2H, m, CH_2-3), 4.18 (2H, q, J = 7.2, CH_2-1′), 4.89 (2H, s, CH_2O-9), 6.74 (1H, s, H-8), 6.84 (1H, s, H-6).

Ethyl[(3-methyl-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-1-yl)oxy]acetate (16). Yield 79%, $C_{18}H_{20}O_5$, mp 151-152°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.28 (3H, t, J = 7.2, CH_3-2′), 1.70 (4H, m, CH_2-8, CH_2-9), 2.34 (3H, s, CH_3-3), 2.42 (2H, m, CH_2-10), 3.14 (2H, m, CH_2-7), 4.18 (2H, q, J = 7.2, CH_2-1′), 4.83 (2H, s, CH_2O-1), 6.67 (2H, s, H-2), 6.74 (2H, s, H-4).

Coumarinyloxyacetic Acids 17-24. A solution or suspension of ester **9-16** (5 mmol) in propan-2-ol (10 mL) was treated with NaOH solution (1 M, 20 mL, 20 mmol) and heated with stirring for 0.5-1 h (course of reaction monitored by TLC). After the reaction was complete, the mixture was cooled, transferred into icewater (100 mL) and acidified to pH 5-6. The resulting precipitate was filtered off and crystallized from aqueous propan-2-ol.

[(4-Oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl)oxy]acetic Acid (17). Yield 86%, $C_{14}H_{12}O_5$, mp 206-207°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.13 (2H, m, CH_2-2), 2.74 (2H, m, CH_2-1), 3.06 (2H, m, CH_2-3), 4.87 (2H, s, CH_2O-7), 6.88 (1H, dd, J = 2.4, 8.7, H-8), 6.97 (1H, d, J = 2.4, H-6), 7.48 (1H, d, J = 8.7, H-9), 12.45 (1H, br.s, COOH).

[(6-Methyl-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl)oxy]acetic Acid (18). Yield 88%, $C_{15}H_{14}O_5$, mp 228-229°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.11 (2H, m, CH_2-2), 2.25 (3H, s, CH_3-6), 2.74 (2H, m, CH_2-1), 3.04 (2H, m, CH_2-3), 4.84 (2H, s, CH_2O-7), 6.94 (1H, d, J = 8.7, H-8), 7.38 (1H, d, J = 8.7, H-9), 12.18 (1H, br.s, COOH).

[(8-Chloro-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl)oxy]acetic Acid (19). Yield 92%, $C_{14}H_{11}ClO_5$, mp 213-214°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.13 (2H, m, CH_2-2), 2.75 (2H, m, CH_2-1), 3.05 (2H, m, CH_2-3), 4.89 (2H, s, CH_2O-7), 7.12 (1H, s, H-6), 7.62 (1H, s, H-9), 12.05 (1H, br.s, COOH).

[(4-Methyl-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl)oxy]acetic Acid (21). Yield 86%, $C_{16}H_{16}O_5$, mp 223-224°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.75 (4H, m, CH_2-8, CH_2-9), 2.25 (3H, s, CH_3-4), 2.41 (2H, m, CH_2-10), 2.76 (2H, m, CH_2-7), 4.82 (2H, s, CH_2O-7), 6.84 (1H, d, J = 8.7, H-2), 7.44 (1H, d, J = 8.7, H-1), 12.54 (1H, br.s, COOH).

[(2-Chloro-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl)oxy]acetic Acid (22). Yield 88%, $C_{15}H_{13}ClO_5$, mp 231-232°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.74 (4H, m, CH_2-8, CH_2-9), 2.41 (2H, m, CH_2-10), 2.74 (2H, m, CH_2-7), 4.93 (2H, s, CH_2O-3), 7.08 (1H, s, H-4), 7.71 (1H, s, H-1), 12.20 (1H, br.s, COOH).

[(7-Methyl-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-9-yl)oxy]acetic Acid (23). Yield 84%, $C_{15}H_{14}O_5$, mp 227-228°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.04 (2H, m, CH_2-2), 2.35 (3H, s, CH_3-7), 2.67 (2H, m, CH_2-1), 3.30 (2H, m, CH_2-3), 4.78 (2H, s, CH_2O-9), 6.72 (1H, s, H-8), 6.83 (1H, s, H-6), 13.04 (1H, br.s, COOH).

[(3-Methyl-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-1-yl)oxy]acetic Acid (24). Yield 86%, $C_{16}H_{16}O_5$, mp 214-215°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.67 (4H, m, CH_2-8, CH_2-9), 2.33 (3H, s, CH_3-3), 2.40 (2H, m, CH_2-10), 3.12 (2H, m, CH_2-7), 4.79 (2H, s, CH_2O-1), 6.71 (2H, s, H-2), 6.78 (2H, s, H-4), 12.42 (1H, br.s, COOH).

General Method of Cytisine *N*-Acylation. Method A. A solution of **17-24** (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 reaction monitored by TLC). The resulting activated ester was treated with cytisine (0.63 g, 3.3 mmol). The mixture was stirred vigorously for 4-6 h (course of reaction monitored by TLC). After the reaction was complete the mixture was diluted with water (200 mL) and acidified to pH 5-6. The resulting precipitate was filtered off and crystallized from propan-2-ol.

Method B. A solution of **17-24** (3 mmol) in absolute DMF (5 mL) was treated with CDI (0.54 g, 3.3 mmol), stirred vigorously at room temperature for 2 h, and treated with cytisine (0.63 g, 3.3 mmol). The mixture was stirred vigorously at room temperature for 4-6 h. After the reaction was complete the mixture was diluted with water (100 mL) and acidified to pH 5-6. The resulting precipitate was filtered off and crystallized from propan-2-ol.

***N*-[([-Oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl]oxy)acetyl]cytisine (25).** Yield 82%, $C_{25}H_{24}N_2O_5$, mp 255.5-257°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.90-2.08 (2H, m, CH_2-8), 2.10-2.18 (2H, m, CH_2-2′), 2.54 (1H, m, H-9), 2.75 (2H, m, CH_2-1′), 2.90 (1H, m, H-11_{ax}), 3.04 (2H, m, CH_2-3′), 3.14 (1H, m, H-7), 3.35 and 3.44 (1H, 2d, J = 13.2, H-13_{ax}), 3.60-3.70 (1H, m, H-10_{ax}), 3.83-4.02 (2H, m, H-10_{eq}, H-13_{eq}), 4.43 and 4.62 (1H, 2d, J = 13.2, H-11_{eq}), 4.22 (2d, J = 13.2), 4.65 (dd, J = 6.3, 13.2) and 4.89 (2H, d, J = 13.2, $COCH_2O$-7′), 6.11 and 6.25 (1H, 2d, J = 6.3, H-5), 6.21 (1H, d, J = 6.3, H-3), 6.52 and 6.76 (1H, 2dd, J = 2.4, 8.7, H-8′), 6.73 and 6.88 (1H, d, J = 2.4, H-6′), 7.20-7.30 (1H, m, H-4), 7.35 and 7.38 (1H, 2d, J = 8.7, H-9′).

***N*-[([6-Methyl-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl]oxy)acetyl]cytisine (26).** Yield 89%, $C_{26}H_{26}N_2O_5$, mp 254-255°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.90-2.08 (2H, m, CH_2-8), 2.11 (2H, m, CH_2-2′), 2.16 and 2.18 (3H, 2s, CH_3-6′), 2.54 (1H, m, H-9), 2.73 (2H, m, CH_2-1′), 2.90 (1H, m, H-11_{ax}), 3.03 (2H, m, CH_2-3′), 3.18 (1H, m, H-7), 3.34 and 3.48 (1H, 2d, J = 13.2, H-13_{ax}), 3.60-3.70 (1H, m, H-10_{ax}), 3.80-4.05 (2H, m, H-10_{eq}, H-13_{eq}), 4.25 and 4.47 (1H, 2d, J = 13.2, H-11_{eq}), 4.26 (2d, J = 13.2), 4.82 (dd, J = 6.3, 13.2) and 5.09 (2H, d, J = 13.2, $COCH_2O$-7′), 6.10-6.50 (3H, m, H-3, H-5, H-8′), 7.18-7.40 (2H, m, H-4, H-9′).

***N*-[([8-Chloro-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl]oxy)acetyl]cytisine (27).** Yield 78%, $C_{25}H_{23}ClN_2O_5$, mp 256.5-258°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.90-2.08 (2H, m, CH_2-8), 2.13 (2H, m, CH_2-2′), 2.54 (1H, m, H-9), 2.76 (2H, m, CH_2-1′), 2.91 (1H, m, H-11_{ax}), 3.04 (2H, m, CH_2-3′), 3.18 (1H, m, H-7), 3.35 and 3.49 (1H, 2d, J = 13.2, H-13_{ax}), 3.60-3.70 (1H, m, H-10_{ax}), 3.80-4.02 (2H, m, H-10_{eq}, H-13_{eq}), 4.33 and 4.52 (1H, 2d, J = 13.2, H-11_{eq}), 4.20 (2d, J = 13.2), 4.82 (dd, J = 6.3, 13.2) and 5.04 (2H, d, J = 13.2, $COCH_2O$-7′), 6.08-6.25 (2H, m, H-3, H-5), 6.78 and 6.92 (1H, 2s, H-6′), 7.20-7.35 (1H, m, H-4), 7.56 (1H, s, H-9′).

***N*-[([6-Oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl]oxy)acetyl]cytisine (28).** Yield 84%, $C_{26}H_{26}N_2O_5$, mp 157-159°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.70-1.85 (4H, m, CH_2-8′, CH_2-9′), 1.90-2.08 (2H, m, CH_2-8), 2.41 (2H, m, CH_2-10′), 2.54 (1H, m, H-9), 2.75 (2H, m, CH_2-7′), 2.90 (1H, m, H-11_{ax}), 3.18 (1H, m, H-7), 3.32 and 3.47 (1H, 2d, J = 13.2, H-13_{ax}), 3.62-3.71 (1H, m, H-10_{ax}), 3.80-4.02 (2H, m, H-10_{eq}, H-13_{eq}), 4.36 and 4.52 (1H, 2d, J = 13.2, H-11_{eq}), 4.21 (2d, J = 13.2), 4.67 (dd, J = 6.3, 13.2) and 4.91 (2H, d, J = 13.2, $COCH_2O$-3′), 6.10 and 6.28 (1H, 2d, J = 6.3, H-5), 6.22 (1H, d, J = 6.3, H-3), 6.47 and 6.76 (1H, 2dd, J = 2.4, 8.7, H-2′), 6.67 and 6.81 (1H, d, J = 2.4, H-4′), 7.24-7.36 (1H, m, H-4), 7.43 and 7.48 (1H, 2d, J = 8.7, H-9′).

***N*-[([4-Methyl-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl]oxy)acetyl]cytisine (29).** Yield 83%, $C_{27}H_{28}N_2O_5$, mp 219-220.5°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.70-1.85 (4H, m, CH_2-8′, CH_2-9′), 1.90-2.08 (2H, m, CH_2-8), 2.17 and 2.20 (3H, 2s, CH_3-4′), 2.41 (2h, m, CH_2-10′), 2.54 (1H, m, H-9), 2.74 (2H, m, CH_2-7′), 2.89 (1H, m, H-11_{ax}), 3.18 (1H, m, H-7), 3.35 and 3.47 (1H, 2d, J = 13.2, H-13_{ax}), 3.65-3.76 (1H, m, H-10_{ax}), 3.80-4.09 (2H, m, H-10_{eq}, H-13_{eq}), 4.35 and 4.51 (1H, 2d, J = 13.2, H-11_{eq}), 4.26 (2d, J = 13.2), 4.72 (dd, J = 6.3, 13.2) and 5.03 (2H, d, J = 13.2, $COCH_2$O-3′), 6.05-6.41 (3H, m, H-3, H-5, H-8′), 7.22-7.32 (2H, m, H-4, H-9′).

***N*-[([2-Chloro-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl]oxy)acetyl]cytisine (30).** Yield 84%, $C_{26}H_{25}ClN_2O_5$, mp 275.5-277°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.68-1.85 (4H, m, CH_2-8′, CH_2-9′), 1.90-2.08 (2H, m, CH_2-8), 2.41 (2H, m, CH_2-10′), 2.54 (1H, m, H-9), 2.73 (2H, m, CH_2-7′), 2.91 (1H, m, H-11_{ax}), 3.18 (1H, m, H-7), 3.38 and 3.47 (1H, 2d, J = 13.2, H-13_{ax}), 3.65-3.76 (1H, m, H-10_{ax}), 3.82-3.99 (2H, m, H-10_{eq}, H-13_{eq}), 4.35 and 4.51 (1H, 2d, J = 13.2, H-11_{eq}), 4.26 (2d, J = 13.2), 4.72 (dd, J = 6.3, 13.2) and 5.01 (2H, d, J = 13.2, $COCH_2$O-3′), 6.08-6.26 (3H, m, H-3, H-5), 6.72 and 6.85 (1H, 2s, H-6′), 7.22-7.36 (2H, m, H-4), 7.61 (1H, s, H-9′).

***N*-[([7-Methyl-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-9-yl]oxy)acetyl]cytisine (31).** Yield 78%, $C_{26}H_{26}N_2O_5$, mp 207-209°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.90-2.08 (4H, m, CH_2-8, CH_2-2′), 2.31 (3H, br.s, CH_3-7′), 2.54 (1H, m, H-9), 2.65 (2H, m, CH_2-1′), 2.90 (1H, m, H-11_{ax}), 3.20 (3H, m, H-7, CH_2-3′), 3.34 and 3.48 (1H, 2d, J = 13.2, H-13_{ax}), 3.60-3.70 (1H, m, H-10_{ax}), 3.80-4.05 (2H, m, H-10_{eq}, H-13_{eq}), 4.31 and 4.48 (1H, 2d, J = 13.2, H-11_{eq}), 4.18 (2d, J = 13.2), 4.77 (dd, J = 6.3, 13.2) and 4.98 (2H, d, J = 13.2, $COCH_2$O-9′), 6.11-6.22 (2H, m, H-3, H-5), 6.26 and 6.50 (1H, 2d, H-8′), 6.79 (1H, s, H-6′), 7.26-7.35 (1H, m, H-4).

***N*-[([3-Methyl-6-oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-1-yl]oxy)acetyl]cytisine (32).** Yield 74%, $C_{27}H_{28}N_2O_5$, mp 148-150°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.60-1.80 (4H, m, CH_2-8′, CH_2-9′), 1.90-2.05 (2H, m, CH_2-8), 2.28 and 2.30 (3H, 2s, CH_3-3′), 2.39 (2H, m, CH_2-10′), 2.54 (1H, m, H-9), 2.90-3.15 (3H, m, H-11_{ax}, CH_2-7′), 3.20 (1H, m, H-7), 3.34 and 3.46 (1H, 2d, J = 13.2, H-13_{ax}), 3.60-3.72 (1H, m, H-10_{ax}), 3.80-4.05 (2H, m, H-10_{eq}, H-13_{eq}), 4.35 and 4.53 (1H, 2d, J = 13.2, H-11_{eq}), 4.18 (d, J = 13.2), 4.73 (dd, J = 6.3, 13.2) and 4.96 (2H, d, J = 13.2, $COCH_2$O-1′), 6.08-6.18 (2H, m, H-3, H-5), 6.19 and 6.41 (1H, 2s, H-2′), 6.66 (1H, s, H-4′), 7.22-7.31 (1H, m, H-4).

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