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SYNTHESIS OF FLAVONOID DERIVATIVES OF CYTISINE. 5. AMINOMETHYLATION OF 6-HYDROXYAURONES

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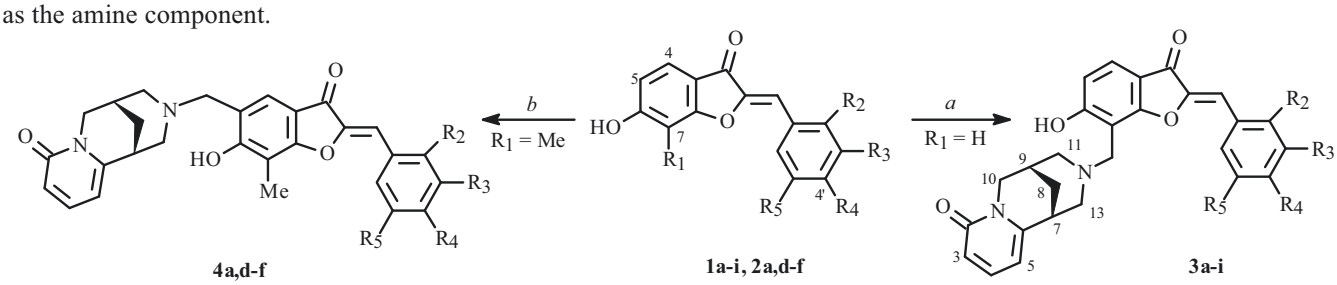
Aminomethylation of 6-hydroxy- and 6-hydroxy-7-methylaurones by the alkaloid cytisine was studied. It was shown that the aminomethylation of the 6-hydroxyaurones occurred at the 7-position of the benzofuran ring and at the 5-position if the 7-position was occupied.

Keywords: cytisine, aurone, aminomethylation, Mannich base.

Cytisine is a quinolizidine alkaloid with various types of biological activity [1, 2] including a high affinity for nicotine acetylcholine receptors (nAChR), especially α4β2, which represents a promising target for chemical design of nAChR subtype-selective ligands [3]. In continuation of research on the conjugation of cytisine and benzopyrone moieties through a methylene linker [4–8], we modified aurones, 2-benzylidenebenzofuran-3(2*H*)-ones, which are known for their valuable pharmacological properties [9].

The goal of the present research was to study the possibility of using cytisine as the amine in Mannich aminomethylation of 6-hydroxyaurones. The fact that flavonoid-methyl cytisine derivatives tonkinensines A and B that possessed cytotoxicity against cancer cells were isolated from roots of *Sophora tonkinensis* L. played an important role in selecting the type of conjugation of the cytisine and flavonoid components [10].

Previously, we took two approaches to the synthesis of Mannich bases of benzopyrones, i.e., aminomethylation involving methylene-*bis*-cytisine [5, 6] and reaction of cytisine and formalin [7, 8]. The advisability of using one method or the other was determined by the nature of the benzopyrone substituents. The syntheses of cytisine-containing aminomethyl derivatives of barbituric acid [11, 12], benzimidazole-2-thione [13], 3,4-dihydropyrimidine-2-thione [14], and 1,4-dihydropyridine [15] were also reported. In our opinion, formalin was synthetically more attractive for Mannich aminomethylation of 6-hydroxy-2-benzylidenebenzofuran-3-ones because it allowed the cytisine to be used more efficiently as the amine component.



a: $R_2 = R_3 = R_5 = H$, $R_4 = OMe$; **b:** $R_2 = R_3 = R_5 = H$, $R_4 = OEt$; **c:** $R_2 = R_3 = R_5 = H$, $R_4 = COOMe$
d: $R_2 = R_4 = R_5 = H$, $R_3 = OMe$; **e:** $R_2 = R_5 = H$, $R_3 = R_4 = OMe$; **f:** $R_2 = H$, $R_3 = R_4 = R_5 = OMe$
g: $R_2 = OCHF_2$, $R_3 = R_4 = R_5 = H$; **h:** $R_2 = Cl$, $R_3 = R_4 = R_5 = H$; **i:** $R_2 = R_3 = R_4 = OMe$, $R_5 = H$
1a – i: $R_1 = H$, **2a, d-f:** $R_1 = CH_3$

a. Cytisine, $(CH_2O)_n$, *i*-PrOH; *b.* cytisine, $(CH_2O)_n$, 1,4-dioxane

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The search for aminomethylation conditions for 6-hydroxyaurones **1a**–**i** showed that the most suitable solvent for the Mannich reaction was propanol-2. Like for aminomethylation of isoflavone and 3-arylcoumarins [7, 8], use of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as the catalyst turned out to be convenient. Moreover, the paraformaldehyde form of formaldehyde was optimal because it allowed an undesired excess of H_2O in the reaction mixture to be avoided.

Aminomethylation of cytisine and paraformaldehyde under the proposed conditions produced only one regioisomer despite the fact that the electrophilic substitution could occur at the benzofuran-3-one C-7 and C-5 positions during Mannich reactions of 6-hydroxyaurones **1a**–**i**. The structures of the aminomethyl 6-hydroxyaurone derivatives were chosen based on PMR spectra of the synthesized compounds. Thus, spectra of **3a**–**i** showed simplified spin–spin coupling of the aurone A-ring protons. Doublets for protons at 6.61–6.64 and 7.50–7.53 ppm with SSCC 8.4–8.5 Hz confirmed that the benzofuran moiety reacted at the 7-position.

Aminomethylation of 6-hydroxy-7-methylaurones **2a** and **2d**–**f** by cytisine occurred under harsher conditions. In these instances, 1,4-dioxane solvent and an excess of cytisine had to be used.

Thus, the ability to use cytisine as the amine component in Mannich aminomethylation of 6-hydroxyaurones was demonstrated. Conditions for preparing regioisomeric 7-(N^{12}-cytisinyl)methyl- and 5-(N^{12}-cytisinyl)methyl-derivatives of 6-hydroxyaurones were proposed. This opened new approaches for modifying cytisine.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254_f plates (Merck, Germany). The eluents were CH_2Cl_2–MeOH mixtures (9:1, 95:5). PMR and ^{13}C NMR spectra were recorded in DMSO-d_6 relative to TMS (internal standard) on the δ-scale on Varian M400 (400 and 100 MHz, respectively) and Bruker 500 instruments (500 and 125 MHz, respectively). LC-MS were recorded using a system with an Agilent 1100 Series HPLC equipped with an Agilent LC\MSD SL diode array mass-selective detector and chemical ionization at atmospheric pressure (APCI). Analyses of all compounds agreed with those calculated.

General Method for Synthesizing 6-Hydroxyaurones 1a–i and 6-Hydroxy-7-methylaurones 2a and 2d–f. A solution of 6-hydroxybenzofuran-3(2*H*)-one (1.50 g, 10 mmol) or 6-hydroxy-7-methylbenzofuran-3(2*H*)-one (1.64 g, 10 mmol) in a mixture of EtOH (10 mL) and DMF (10 mL) was treated with the appropriate aldehyde (10 mmol) and aqueous KOH solution (2.3 mL, 50%), stirred at room temperature for 4–6 h (end of reaction monitored by TLC), stirred vigorously, poured into hot H_2O (50 mL), and neutralized with conc. HCl to pH 4–5. The resulting precipitate was filtered off, rinsed with H_2O, dried, and recrystallized from DMF–MeOH (1:1).

(2*Z*)-6-Hydroxy-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (1a). $C_{16}H_{12}O_4$, yield 85%, mp 268–270°C (lit. [16]: 256–258°C). MS(CI): 269.1 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.81 (3H, s, 4′-OCH_3), 6.70 (1H, dd, J = 8.5, 2.0, H-5), 6.77–6.81 (2H, m, H-2a, 7), 7.06 (2H, d, J = 8.4, H-3′, 5′), 7.60 (1H, d, J = 8.5, H-4), 7.89 (2H, d, J = 8.4, H-2′, 6′), 11.17 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-2-(4-ethoxybenzylidene)-1-benzofuran-3(2*H*)-one (1b). $C_{17}H_{14}O_4$, yield 83%, mp 264–266°C. MS(CI): 283.2 $[M + H]^+$ (100 %). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.36 (3H, t, J = 7.0, 4′-$OCH_2C\underline{H}_3$), 4.10 (2H, q, J = 7.0, 4′-$OC\underline{H}_2CH_3$), 6.73 (1H, dd, J = 8.5, 2.0, H-5), 6.78 (1H, s, H-2a), 6.80 (1H, d, J = 2.0, H-7), 7.05 (2H, d, J = 8.8, H-3′, 5′), 7.63 (1H, d, J = 8.5, H-4), 7.91 (2H, d, J = 8.9, H-2′, 6′), 11.18 (1H, s, 6-OH).

Methyl 4-[(2*Z*)-(6-Hydroxy-3-oxo-1-benzofuran-2(3*H*)-ylidene)methyl]benzoate (1c). $C_{17}H_{12}O_5$, yield 76%, mp 295–296°C. MS(CI): 297.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.84 (3H, s, 4′-$COOCH_3$), 6.54–6.90 (3H, m, H-5, 7, 2a), 7.60 (1H, d, J = 8.4, H-4), 7.84–8.15 (4H, m, H-2′, 3′, 5′, 6′), 11.32 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-2-(3-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (1d). $C_{16}H_{12}O_4$, yield 79%, mp 261–263°C. MS(CI): 269.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.83 (3H, s, 3′-OCH_3), 6.74 (1H, dd, J = 8.5, 2.0, H-5), 6.78 (1H, s, H-2a), 6.83 (1H, d, J = 2.0, H-7), 6.99–7.06 (1H, m, H-4′), 7.42 (1H, t, J = 8.0, H-5′), 7.50–7.53 (1H, m, H-2′), 7.57 (1H, d, J = 8.0, H-6′), 7.65 (1H, d, J = 8.5, H-4), 11.26 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-2-(3,4-dimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (1e). $C_{17}H_{14}O_5$, yield 87%, mp 224–226°C (lit. [17]: 118–120°C). MS(CI): 299.1 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.82 and 3.83 (each 3H, s, 3′, 4′-OCH_3), 6.68 (1H, dd, J = 8.5, 1.8, H-5), 6.74 (1H, s, H-2a), 6.75 (1H, d, J = 1.8, H-7), 7.09 (1H, d, J = 8.5, H-5′), 7.54–7.60 (3H, m, H-4, 2′, 6′), 11.15 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (1f). $C_{18}H_{16}O_6$, yield 81%, mp 254–256°C (lit. [18]: 264–266°C). MS(CI): 329.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.72 (3H, s, 4′-OCH_3), 3.85 (6H, s, 3′, 5′-OCH_3), 6.72 (1H, dd, J = 8.5, 2.0, H-5), 6.75 (1H, s, H-2a), 6.82 (1H, d, J = 2.0, H-7), 7.32 (2H, s, H-2′, 6′), 7.61 (1H, d, J = 8.5, H-4), 11.19 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-2-[2-(difluoromethoxy)benzylidene]-1-benzofuran-3(2*H*)-one (1g). $C_{16}H_{10}F_2O_4$, yield 68%, mp 237–239°C. MS(CI): 305.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.75 (1H, dd, J = 8.5, 1.9, H-5), 6.82 (1H, d, J = 1.9, H-7), 6.90 (1H, s, H-2a), 7.31–7.34 (1H, m, H-3′), 7.36 (1H, t, J_{CF} = 73.5, 2′-$OCHF_2$), 7.38–7.47, 7.49–7.57 (each 1H, m, H-4′, 5′), 7.66 (1H, d, J = 8.5, H-4), 8.29 (1H, dd, J = 7.8, 1.7, H-6′), 11.31 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-2-(2-chlorobenzylidene)-1-benzofuran-3(2*H*)-one (1h). $C_{15}H_9ClO_3$, yield 91%, mp 270–272°C. MS(CI): 273.2 $[M + H]^+$ (100%), 275.2 $[M + H]^+$ (31%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.71 (1H, dd, J = 8.5, 1.5, H-5), 6.76 (1H, d, J = 1.5, H-7), 6.90 (1H, s, H-2a), 7.35–7.49 (2H, m, H-4′, 5′), 7.53 (1H, d, J = 7.9, H-6′), 7.60 (1H, d, J = 8.5, H-4), 8.21 (1H, d, J = 7.8, H-3′), 11.35 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-2-(2,3,4-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (1i). $C_{18}H_{16}O_6$, yield 78%, mp 249–251°C. MS(CI): 329.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.79, 3.88, 3.89 (each 3H, s, 2′, 3′, 4′-OCH_3), 6.72 (1H, dd, J = 8.4, 1.8, H-5), 6.78 (1H, d, J = 1.8, H-7), 6.91 (1H, s, H-2a), 7.01 (1H, d, J = 8.9, H-5′), 7.63 (1H, d, J = 8.4, H-4), 7.95 (1H, d, J = 8.9, H-6′), 11.17 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-7-methyl-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (2a). $C_{17}H_{14}O_4$, yield 89%, mp > 300°C. MS(CI): 283.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.21 (3H, s, 7-CH_3), 3.81 (3H, s, 4′-OCH_3), 6.72–6.80 (2H, m, H-5, 2a), 7.07 (2H, d, J = 8.9, H-3′, 5′), 7.45 (1H, d, J = 8.3, H-4), 7.92 (2H, d, J = 8.9, H-2′, 6′), 11.01 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-7-methyl-2-(3-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (2d). $C_{17}H_{14}O_4$, yield 86%, mp 263–265°C. MS(CI): 283.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.17 (3H, s, 7-CH_3), 3.80 (3H, s, 3′-OCH_3), 6.70 (1H, s, H-2a), 6.74 (1H, d, J = 8.4, H-5), 6.92–7.01 (1H, m, H-4′), 7.31–7.60 (4H, m, H-4, 2′, 5′, 6′), 11.05 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-2-(3,4-dimethoxybenzylidene)-7-methyl-1-benzofuran-3(2*H*)-one (2e). $C_{18}H_{16}O_5$, yield 83%, mp 235–237°C. MS(CI): 313.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.19 (3H, s, 7-CH_3), 3.82 and 3.84 (each 3H, s, 3′, 4′-OCH_3), 6.68–6.80 (2H, m, H-5, 2a), 7.06 (1H, d, J = 8.4, H-5′), 7.39–7.52 (2H, m, H-4, 6′), 7.66 (1H, d, J = 1.9, H-2′), 10.99 (1H, s, 6-OH).

(2*Z*)-6-Hydroxy-7-methyl-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (2f). $C_{19}H_{18}O_6$, yield 93%, mp 249–251°C. MS(CI): 343.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.18 (3H, s, 7-CH_3), 3.75 (3H, s, 4′-OCH_3), 3.86 (6H, s, 3′, 5′-OCH_3), 6.71 (1H, s, H-2a), 6.76 (1H, d, J = 8.4, H-5), 7.33 (2H, s, H-2′, 6′), 7.44 (1H, d, J = 8.4, H-4), 11.04 (1H, s, 6-OH).

General Method for Synthesizing 6-Hydroxy-7-[(cytisin-12-yl)methyl]aurones 3a–i. A hot solution of the appropriate 6-hydroxyaurone **1a–i** (2 mmol) in *i*-PrOH (15 mL) was treated with cytisine (380 mg, 2 mmol), paraformaldehyde (75 mg, 2.5 mmol), and DMAP (2–3 mg); refluxed for 4–6 h (end of reaction monitored by TLC), cooled, and diluted with hexane (15–20 mL). The resulting precipitate was filtered off and crystallized from *i*-PrOH–hexane (1:1).

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-2-(4-methoxybenzylidene)-3-oxo-2,3-dihydro-1-benzofuran-7-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3a). $C_{28}H_{26}N_2O_5$, yield 76%, mp 140–142°C. MS(CI): 471.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.69–1.86 (2H, m, H-8), 2.40–2.60 (3H, m, H-9, 11a, 13a), 2.96–3.11 (3H, m, H-7, 11b, 13b), 3.67–3.89 (4H, m, H-10, N(12)-CH_2-Ar), 6.07 (1H, d, J = 6.7, H-5), 6.19 (1H, d, J = 9.0, H-3), 7.27 (1H, dd, J = 9.0, 6.7, H-4); aurone protons: 3.84 (3H, s, 4′-OCH_3), 6.61 (1H, d, J = 8.4, H-5), 6.75 (1H, s, H-2a), 7.07 (2H, d, J = 8.4, H-3′, 5′), 7.50 (1H, d, J = 8.4, H-4), 7.88 (2H, d, J = 8.4, H-2′, 6′). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 24.66, 27.09, 34.27, 49.31, 50.60, 55.34, 58.77, 59.73, 103.98, 105.67, 110.78, 112.62, 112.65, 114.61, 115.70, 124.36, 124.63, 132.96, 138.71, 146.11, 151.11, 160.41, 162.14, 165.56, 165.59, 181.40.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-3-oxo-2-(4-ethoxybenzylidene)-2,3-dihydro-1-benzofuran-7-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3b). $C_{29}H_{28}N_2O_5$, yield 53%, mp 177–178°C. MS(CI): 485.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.69–1.85 (2H, m, H-8), 2.41–2.58 (3H, m, H-9, 11a, 13a), 2.95–3.11 (3H, m, H-7, 11b, 13b), 3.67–3.87 (4H, m, H-10, N(12)-CH_2-Ar), 6.08 (1H, d, J = 6.8, H-5), 6.20 (1H, d, J = 9.0, H-3), 7.27 (1H, dd, J = 9.0, 6.8, H-4); aurone protons: 1.36 (3H, t, J = 7.0, 4′-$OCH_2C\underline{H}_3$), 4.11 (2H, q, J = 7.0, 4′-$OC\underline{H}_2CH_3$), 6.61 (1H, d, J = 8.5, H-5), 6.75 (1H, s, H-2a), 7.04 (2H, d, J = 9.1, H-3′, 5′), 7.50 (1H, d,

J = 8.5, H-4), 7.87 (2H, d, J = 9.1, H-2′, 6′). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 14.57, 24.67, 27.10, 34.28, 49.35, 50.59, 58.79, 59.74, 63.34, 104.02, 105.70, 110.87, 112.64, 112.68, 115.03, 115.71, 124.38, 124.49, 133.02, 138.75, 146.09, 151.15, 159.74, 162.18, 165.57, 165.61, 181.43.

Methyl 4-{(*Z*)-[6-Hydroxy-3-oxo-7-{[(1*R*,5*S*)-8-oxo-1,5,6,8-tetrahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-3(4*H*)-yl]methyl}-1-benzofuran-2(3*H*)-ylidene]methyl}benzoate (3c). $C_{29}H_{26}N_2O_6$, yield 65%, mp 196–198°C. MS(CI): 499.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.69–1.85 (2H, m, H-8), 2.40–2.60 (3H, m, H-9, 11a, 13a), 2.95–3.11 (3H, m, H-7, 11b, 13b), 3.66–3.91 (4H, m, H-10, N(12)-CH_2-Ar), 6.06 (1H, d, J = 6.8, H-5), 6.16 (1H, d, J = 9.0, H-3), 7.23 (1H, dd, J = 9.0, 6.8, H-4); aurone protons: 3.89 (3H, s, 4′-$COOCH_3$), 6.64 (1H, d, J = 8.4, H-5), 6.81 (1H, s, H-2a), 7.53 (1H, d, J = 8.4, H-4), 7.96–8.07 (4H, m, H-2′, 3′, 5′, 6′). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 24.69, 27.10, 34.28, 49.36, 50.32, 52.32, 58.79, 59.72, 103.97, 106.15, 108.68, 112.10, 112.96, 115.53, 115.65, 124.80, 124.86, 129.61, 131.06, 136.81, 138.70, 148.44, 151.23, 162.16, 165.79, 166.20, 181.58.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-2-(3-methoxybenzylidene)-3-oxo-2,3-dihydro-1-benzofuran-7-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3d). $C_{28}H_{26}N_2O_5$, yield 68%, mp 207–209°C. MS(CI): 471.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.66–1.84 (2H, m, H-8), 2.37–2.57 (3H, m, H-9, 11a, 13a), 2.95–3.11 (3H, m, H-7, 11b, 13b), 3.64–3.86 (4H, m, H-10, N(12)-CH_2-Ar), 6.06 (1H, dd, J = 6.9, 1.4, H-5), 6.19 (1H, dd, J = 9.0, 1.4, H-3), 7.28 (1H, dd, J = 9.0, 6.8, H-4); aurone protons: 3.84 (3H, s, 3′-OCH_3), 6.65 (1H, d, J = 8.4, H-5), 6.76 (1H, s, H-2a), 6.99–7.07 (1H, m, H-4′), 7.42 (1H, t, J = 7.9, H-5′), 7.47–7.57 (3H, m, H-4, 2′, 6′). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 24.61, 27.09, 34.27, 49.32, 50.35, 55.15, 58.77, 59.70, 103.95, 105.81, 110.33, 112.27, 112.81, 115.61, 115.67, 115.87, 123.72, 124.66, 130.01, 133.36, 138.70, 147.40, 151.20, 159.40, 162.14, 165.88, 166.04, 181.61.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-2-(3,4-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1-benzofuran-7-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3e). $C_{29}H_{28}N_2O_6$, yield 65%, mp 227–229°C. MS(CI): 501.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.66–1.85 (2H, m, H-8), 2.37–2.48 (3H, m, H-9, 11a, 13a), 2.95–3.09 (3H, m, H-7, 11b, 13b), 3.66–3.88 (4H, m, H-10, N(12)-CH_2-Ar), 6.07 (1H, d, J = 6.8, H-5), 6.20 (1H, d, J = 9.1, H-3), 7.29 (1H, dd, J = 9.0, 6.8, H-4); aurone protons: 3.84, 3.85 (each 3H, s, 3′, 4′-OCH_3), 6.63 (1H, d, J = 8.4, H-5), 6.76 (1H, s, H-2a), 7.09 (1H, d, J = 8.4, H-5′), 7.48 (1H, d, J = 1.9, H-2′), 7.51 (1H, d, J = 8.4, H-4), 7.62 (1H, d, J = 1.9, H-6′). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 24.66, 27.09, 34.25, 49.36, 50.50, 55.42, 55.61, 58.91, 59.74, 104.01, 105.63, 111.26, 111.92, 112.62, 112.68, 113.46, 115.73, 124.48, 124.79, 125.54, 138.75, 146.14, 148.71, 150.38, 151.22, 162.19, 165.50, 165.62, 181.39.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-3-oxo-2-(3,4,5-trimethoxybenzylidene)-2,3-dihydro-1-benzofuran-7-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3f). $C_{30}H_{30}N_2O_7$, yield 81%, mp 206–207°C. MS(CI): 531.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.65–1.83 (2H, m, H-8), 2.35–2.47 (3H, m, H-9, 11a, 13a), 2.92–3.09 (3H, m, H-7, 11b, 13b), 3.67–3.89 (4H, m, H-10, N(12)-CH_2-Ar), 6.05 (1H, d, J = 6.9, H-5), 6.20 (1H, d, J = 8.9, H-3), 7.30 (1H, dd, J = 8.9, 6.9, H-4); aurone protons: 3.74 (3H, s, 4′-OCH_3), 3.85 (6H, s, 3′, 5′-OCH_3), 6.65 (1H, d, J = 8.3, H-5), 6.76 (1H, s, H-2a), 7.32 (2H, s, H-2′, 6′), 7.52 (1H, d, J = 8.3, H-4). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 24.65, 27.08, 34.24, 49.34, 50.29, 55.91, 58.93, 59.70, 60.19, 103.92, 105.70, 108.61, 110.82, 112.27, 112.82, 115.69, 124.61, 127.56, 138.68, 139.00, 146.82, 151.27, 152.94, 162.16, 165.75, 165.87, 181.43.

(1*R*,5*S*)-3-({(2*Z*)-6-Hydroxy-2-[2-(difluoromethoxy)benzylidene]-3-oxo-2,3-dihydro-1-benzofuran-7-yl}methyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3g). $C_{28}H_{24}F_2N_2O_5$, yield 53%, mp 214–216°C. MS(CI): 507.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.67–1.87 (2H, m, H-8), 2.40–2.58 (3H, m, H-9, 11a, 13a), 2.93–3.09 (3H, m, H-7, 11b, 13b), 3.64–3.86 (4H, m, H-10, N(12)-CH_2-Ar), 6.06 (1H, dd, J = 6.9, 1.4, H-5), 6.17 (1H, dd, J = 9.0, 1.4, H-3), 7.25 (1H, dd, J = 9.0, 6.6, H-4); aurone protons: 6.65 (1H, d, J = 8.5, H-5), 6.86 (1H, s, H-2a), 7.30–7.34 (1H, m, H-3′), 7.35 (1H, t, J_{CF} = 73.5, 2′-$OCHF_2$), 7.39–7.48, 7.48–7.58 (1H, 2H, m, H-4, 4′, 5′), 8.21 (1H, dd, J = 7.9, 1.7, H-6′). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 24.65, 27.10, 34.29, 49.35, 50.30, 58.77, 59.71, 101.89, 103.96, 106.13, 112.09, 112.97, 115.63, 116.58 (t, J_{CF} = 259.0), 118.83, 123.56, 124.82, 125.95, 131.22, 131.41, 138.74, 148.17, 149.61 (t, J_{CF} = 2.7), 151.22, 162.16, 166.20, 181.49.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-3-oxo-2-(2-chlorobenzylidene)-2,3-dihydro-1-benzofuran-7-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3h). $C_{27}H_{23}ClN_2O_4$, yield 57%, mp 238–240°C. MS(CI): 475.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.67–1.84 (2H, m, H-8), 2.39–2.58 (3H, m, H-9, 11a, 13a), 2.91–3.10 (3H, m, H-7, 11b, 13b), 3.65–3.83 (4H, m, H-10, N(12)-CH_2-Ar), 6.05 (1H, d,

J = 6.8, H-5), 6.16 (1H, d, J = 8.9, H-3), 7.24 (1H, dd, J = 8.9, 6.8, H-4); aurone protons: 6.66 (1H, d, J = 8.4, H-5), 6.93 (1H, s, H-2a), 7.42–7.63 (4H, m, H-4, 3′, 4′, 5′), 8.20 (1H, dd, J = 7.9, 1.8, H-6′). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 24.64, 27.10, 34.30, 49.36, 50.20, 58.75, 59.71, 103.95, 104.23, 106.21, 111.96, 113.02, 115.60, 124.87, 127.94, 129.65, 129.96, 131.02, 131.67, 134.16, 138.73, 148.37, 151.24, 162.15, 166.30, 181.46.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-3-oxo-2-(2,3,4-trimethoxybenzylidene)-2,3-dihydro-1-benzofuran-7-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3i). $C_{30}H_{30}N_2O_7$, yield 64%, mp 147–149°C. MS(CI): 531.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.68–1.86 (2H, m, H-8), 2.40–2.58 (3H, m, H-9, 11a, 13a), 2.95–3.10 (3H, m, H-7, 11b, 13b), 3.67–3.92 (4H, m, H-10, N(12)-CH_2-Ar), 6.08 (1H, d, J = 6.8, 1.4, H-5), 6.19 (1H, dd, J = 9.0, 1.4, H-3), 7.27 (1H, dd, J = 9.0, 6.8, H-4); aurone protons: 3.78, 3.88, 3.90 (each 3H, s, 2′, 3′, 4′-OCH_3), 6.60 (1H, d, J = 8.5, H-5), 6.88 (1H, s, H-2a), 7.00 (1H, d, J = 9.0, H-5′), 7.49 (1H, d, J = 8.5, H-4), 7.89 (1H, d, J = 9.0, H-6′). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 24.70, 27.12, 34.30, 49.38, 50.60, 56.09, 58.85, 59.77, 60.51, 61.71, 104.10, 105.76, 108.74, 112.56, 112.75, 115.73, 118.38, 124.49, 126.36, 138.80, 141.68, 146.87, 151.17, 152.98, 155.11, 162.22, 165.63, 165.75, 181.42.

General Method for Synthesizing 6-Hydroxy-8-[(cytisin-12-yl)methyl]aurones 4a and 4d–f. A hot solution of the appropriate 6-hydroxy-7-methylaurone (**2a** or **2d–f**, 2 mmol) in 1,4-dioxane (15 mL) was treated with cytisine (475 mg, 2.5 mmol), paraformaldehyde (75 mg, 2.5 mmol), and DMAP (2–3 mg); refluxed for 4–6 h (end of reaction monitored by TLC), cooled, and diluted with hexane (15–20 mL). The resulting precipitate was filtered off and crystallized from *i*-PrOH–hexane (1:1).

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-7-methyl-2-(4-methoxybenzylidene)-3-oxo-2,3-dihydro-1-benzofuran-5-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (4a). $C_{29}H_{28}N_2O_5$, yield 70%, mp 213–215°C. MS(CI): 485.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.76–1.93 (2H, m, H-8), 2.40–2.55 (3H, m, H-9, 11a, 13a), 2.79–2.87, 3.02–3.15 (1H, 2H, 2m, H-7, 11b, 13b), 3.60–3.78, 3.88–3.96 (3H, 1H, 2m, H-10, N(12)-CH_2-Ar), 6.05 (1H, d, J = 6.8, H-5), 6.30 (1H, d, J = 9.0, H-3), 7.33 (1H, dd, J = 9.0, 6.8, H-4); aurone protons: 2.03 (3H, s, 7-CH_3), 3.82 (3H, s, 4′-OCH_3), 6.73 (1H, s, H-2a), 7.07 (2H, d, J = 8.8, H-3′, 5′), 7.30 (1H, s, H-4), 7.90 (2H, d, J = 8.8, H-2′, 6′). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 7.31, 24.65, 26.99, 33.91, 49.13, 55.34, 58.60, 59.24, 59.27, 104.29, 107.41, 110.50, 111.97, 114.66, 116.17, 117.98, 121.50, 124.75, 132.91, 138.68, 146.23, 150.27, 160.38, 162.33, 164.28, 165.05, 181.68.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-7-methyl-2-(3-methoxybenzylidene)-3-oxo-2,3-dihydro-1-benzofuran-5-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (4d). $C_{29}H_{28}N_2O_5$, yield 83%, mp 162–164°C. MS(CI): 485.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.75–1.93 (2H, m, H-8), 2.42–2.49 (3H, m, H-9, 11a, 13a), 2.77–2.87, 3.01–3.14 (1H, 2H, 2m, H-7, 11b, 13b), 3.59–3.78, 3.88–3.98 (3H, 1H, 2m, H-10, N(12)-CH_2-Ar), 6.05 (1H, d, J = 6.5, H-5), 6.31 (1H, d, J = 9.2, H-3), 7.33 (1H, m, H-4); aurone protons: 2.01 (3H, s, 7-CH_3), 3.81 (3H, s, 3′-OCH_3), 6.71 (1H, s, H-2a), 6.97–7.02 (1H, m, H-4′), 7.30 (1H, s, H-4), 7.36–7.58 (3H, m, H-2′, 5′, 6′). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 7.20, 24.64, 27.00, 33.89, 49.12, 55.02, 58.61, 59.18, 66.35, 104.30, 107.45, 109.99, 111.57, 115.54, 115.71, 116.19, 118.15, 121.69, 123.61, 129.98, 133.51, 138.67, 147.54, 150.23, 159.38, 162.34, 164.76, 165.33, 181.79.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-2-(3,4-dimethoxybenzylidene)-7-methyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (4e). $C_{30}H_{30}N_2O_6$, yield 67%, mp 157–159°C. MS(CI): 515.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.77–1.91 (2H, m, H-8), 2.40–2.53 (3H, m, H-9, 11a, 13a), 2.76–2.84, 3.02–3.14 (1H, 2H, 2m, H-7, 11b, 13b), 3.58–3.78, 3.88–3.96 (3H, 1H, 2m, H-10, N(12)-CH_2-Ar), 6.04 (1H, d, J = 6.9, H-5), 6.30 (1H, d, J = 9.1, H-3), 7.32 (1H, dd, J = 9.1, 6.9, H-4); aurone protons: 2.00 (3H, s, 7-CH_3), 3.82, 3.83 (each 3H, s, 3′, 4′-OCH_3), 6.69 (1H, s, H-2a), 7.06 (1H, d, J = 8.4, H-5′), 7.26 (1H, s, H-4), 7.46 (1H, d, J = 8.4, H-6′), 7.62 (1H, s, H-4′). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 7.10, 24.65, 27.01, 33.90, 49.13, 55.18, 55.55, 58.64, 59.17, 59.25, 104.26, 107.32, 110.85, 111.85, 111.91, 113.45, 116.17, 117.95, 121.44, 124.92, 125.24, 138.65, 146.27, 148.65, 150.21, 150.25, 162.33, 164.23, 164.94, 181.54.

(1*R*,5*S*)-3-{[(2*Z*)-6-Hydroxy-7-methyl-3-oxo-2-(3,4,5-trimethoxybenzylidene)-2,3-dihydro-1-benzofuran-5-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (4f). $C_{31}H_{32}N_2O_7$, yield 80%, mp 246–248°C. MS(CI): 545.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.76–1.93 (2H, m, CH_2-8), 2.41–2.55 (3H, m, H-9, 11a, 13a), 2.75–2.84, 3.03–3.14 (1H, 2H, 2m, H-7, 11b, 13b), 3.55–3.96 (4H, m, H-10, N(12)-CH_2-Ar), 6.03 (1H, d, J = 6.9, H-5), 6.30 (1H, d, J = 9.1, H-3), 7.32 (1H, dd, J = 9.1, 6.8, H-4); aurone protons: 1.99 (3H, s, 7-CH_3), 3.73 (3H, s, 4′-OCH_3), 3.84 (6H, s, 3′, 5′-OCH_3), 6.68 (1H, s, H-2a), 7.27 (1H, s, H-4), 7.31 (2H,

s, H-2′, 6′). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 6.98, 24.63, 27.01, 33.87, 49.11, 55.70, 58.66, 59.10, 59.19, 60.14, 104.25, 107.36, 108.48, 110.52, 111.67, 116.17, 118.08, 121.56, 127.66, 138.64, 138.81, 146.92, 150.21, 152.85, 162.32, 164.47, 165.08, 181.60.

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