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SYNTHESIS OF 7-(*N*-12-CYTISINYLPROPOXY)ISOFLAVONES

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The reactions of cytisine with isoflavone glycidyl ethers were investigated. A series of cytisine–isoflavone conjugates were regioselectively synthesized via opening the oxirane ring by cytisine.

Keywords: cytisine, isoflavone, propanolamine, glycidyl ether.

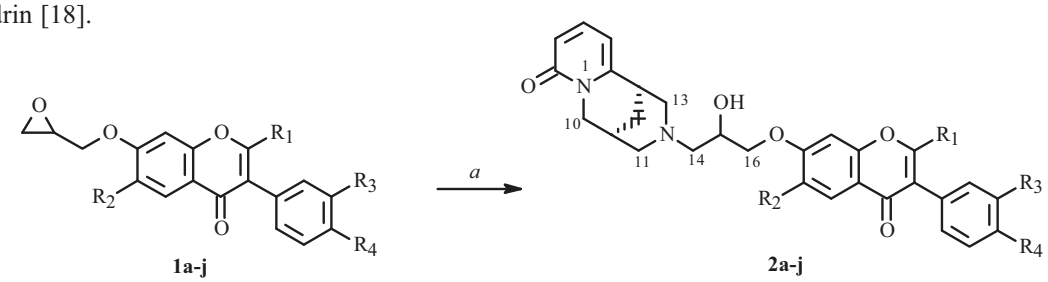
The alkaloid cytisine possesses high affinity for nicotinic acetylcholine receptors (nAChRs), especially the neuronal $\alpha4\beta2$ subtype [1, 2]. Also, cytisine and its derivatives exhibit antidepressant, neuroprotective, nootropic, antiviral, antiparasitic, insecticidal, and anticancer activity [3].

Cytisine is a promising platform for discovering new compounds with potential therapeutic applications. One of the key directions of cytisine chemistry is the synthesis of 12-*N*-alkyl derivatives [4–15]. This structural modification can expand the spectrum of pharmacological action of cytisine derivatives and produce compounds affecting H-choline receptors and possessing spasmolytic, hemostatic [6], and antileishmanial properties [9] and antiarrhythmic, analgesic [15], and antineoplastic activity [16, 17].

The present research was aimed at developing a novel efficient method for conjugation of cytisine and isoflavone fragments through an alkoxy linker. The potential of this type of cytisine conjugation for designing biologically active molecules was confirmed by our previous research that found compounds affecting carcinogenesis and revealing their mechanism of action among cytisine–isoflavone conjugates [17].

The phenolic compounds for conjugation to cytisine that were used to develop the method for synthesizing 7-(*N*-12-cytisinylpropoxy)isoflavones were 7-*O*-glycidyl ethers of 4′-chloroisoflavone **1a**,**b** [17]; the natural isoflavones formononetin (**1c**), 2-methylformononetin (**1d**), cladrin (**1e**), afromosin (**1f**), cladrastin (**1g**), pseudobaptigenin (**1h**); and isoflavones **1i**,**j**.

The isoflavone glycidyl ethers were synthesized via alkylation of the phenol hydroxyl by epichlorohydrin without involving the oxirane ring in the reaction in dimethylacetamide (DMA) in the presence of potash by using an excess of epichlorohydrin [18].



1a-j **2a-j**

a: $R_1 = R_2 = R_3 = H$, $R_4 = Cl$; **b:** $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = Cl$; **c:** $R_1 = R_2 = R_3 = H$, $R_4 = OMe$; **d:** $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = OMe$
e: $R_1 = R_2 = H$, $R_3 = R_4 = OMe$; **f:** $R_1 = R_3 = H$, $R_2 = R_4 = OMe$; **g:** $R_1 = H$, $R_2 = R_3 = R_4 = OMe$; **h:** $R_1 = R_2 = H$, $R_3R_4 = OCH_2O$
i: $R_1 = R_2 = R_3 = H$, $R_4 = F$; **j:** $R_1 = R_2 = H$, $R_3R_4 = 3'\text{-}OCH_2CH_2O\text{-}4'$

a. Cytisine, MeCN, $(C_4H_9)_4N^+I^-$

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The reactions of cytisine glycidyl ethers were studied to prepare new vicinal aminoalcohol derivatives and to diversify the cytisine derivatives. Known methods for aminolysis of epoxides had to be slightly adapted to use cytisine as the nucleophile for opening the oxirane ring. Studies of the effects of temperature, solvent nature, and ratio of starting compounds on the course of the reaction enabled development of the optimal conditions for synthesizing the vicinal aminoalcohol derivatives with isoflavone fragments and cytisine. The glycidyl ethers of 7-hydroxyisoflavones reacted with cytisine to give satisfactory yields in MeCN in the presence of catalytic amounts of Bu_4NI [$(C_4H_9)_4N^+I^-$] in a 1:1:1 ratio.

The oxirane ring opened regiospecifically under the proposed conditions through the action of cytisine at the least substituted C atom according to NMR spectral data. Thus, PMR spectra of the cytisine–isoflavone conjugates lacked characteristic resonances of the oxirane ring and exhibited resonances for the cytisine fragment. The synthesized compounds were mixtures of epimers in a 1:1 ratio. PMR and ^{13}C NMR spectra showed doubled resonances for the cytisine and aminoalcohol fragments and for the chromone core atoms positioned close to the alcohol fragment. This feature prevented observation of the spin–spin fine structure in PMR spectra. Resonances of C atoms in ^{13}C NMR spectra appeared as two closely positioned singlets (chemical shifts of the second peak are given in parentheses in the Experimental part), which was also confirmed by HSQC and HMBC spectra of **2a**,**b**.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck plates (Germany) using CH_2Cl_2–MeOH mixtures (100:1, 50:1) as eluents. PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on the δ-scale vs. TMS (internal standard) on Varian M400 (400 and 100 MHz, respectively) and Bruker 500 instruments (500 and 125 MHz). GC-MS used an Agilent 1100 Series liquid-chromatograph–mass-spectrometer system equipped with an Agilent LC/MSD SL diode-array and mass-selective detector and chemical ionization at atmospheric pressure (APCI). Analyses of all compounds agreed with those calculated. Glycidyl ethers of 7-hydroxyisoflavones **1a**–**j** were synthesized as before [18].

General Method for Synthesizing 2a–j. A solution of glycidyl ether **1a**–**j** (1 mmol) in MeCN (20 mL) was treated with cytisine (0.21 g, 1.1 mmol) and Bu_4NI (10 mg) and stirred under reflux for 10–12 h (end of reaction determined by TLC). The precipitate that formed upon cooling was filtered off and crystallized from EtOH.

(1*S*,5*R*)-3-(3-{[3-(4-Chlorophenyl)-4-oxo-4*H*-chromen-7-yl]oxy}-2-hydroxypropyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2a). $C_{29}H_{27}ClN_2O_5$, yield 405 mg (78%), mp 180–182°C. APCI MS: 519.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.59–1.86 (2H, m, CH_2-8), 2.24–2.70 (6H, m, H-9, 11a, 13a, 14, OH), 2.71–3.02 (3H, m, H-7, 11b, 13b), 3.63–4.06 (5H, m, H-10, 15, 16), 5.75–5.91 (1H, m, H-5), 6.27 (1H, d, J = 9.0, H-3), 7.02–7.12 (1H, m, H-4), protons of the isoflavone fragment: 6.57–6.66 (1H, m, H-8), 6.74–6.83 (1H, m, H-6), 7.25 (2H, d, J = 8.4, H-3′, 5′) (2H, m), 7.35 (2H, d, J = 8.4, H-2′, 6′), 7.80 (1H, s, H-2), 7.95–8.06 (1H, m, H-5). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 25.7, 27.9 (28.2), 35.6 (35.3), 50.0 (49.9), 59.3 (59.7), 60.0 (59.9), 62.0 (61.5), 66.1 (65.9), 70.4 (70.3), 100.9 (100.8), 104.7 (104.6), 115.0, 116.9, 118.4 (118.4), 124.2, 127.7, 128.6, 130.2, 130.3, 134.1, 138.8 (138.8), 150.8 (150.6), 152.6 (152.6), 157.8 (157.8), 163.0, 163.3 (163.0), 175.3.

(1*S*,5*R*)-3-(3-{[3-(4-Chlorophenyl)-2-methyl-4-oxo-4*H*-chromen-7-yl]oxy}-2-hydroxypropyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2b). $C_{30}H_{29}ClN_2O_5$, yield 394 mg (74%), mp 165–167°C. APCI MS: 533.0 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.73–1.96 (2H, m, H-8), 2.37–2.80 (6H, m, H-9, 11a, 13a, 14, OH), 2.82–3.10 (3H, m, H-7, 11b, 13b), 3.63–4.18 (5H, m, H-10, 15, 16), 5.87–6.03 (1H, m, H-5), 6.32–6.45 (1H, m, H-3), 7.18–7.23 (1H, m, H-4), protons of the isoflavone fragment: 2.27 (3H, s, CH_3-2), 6.66–6.78 (1H, m, H-8), 6.81–6.89 (1H, m, H-6), 7.19 (2H, d, J = 8.6, H-3′, 5′) (2H, m), 7.37 (2H, d, J = 8.6, H-2′, 6′), 8.00–8.11 (1H, m, H-5). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 19.6, 25.9, 28.0 (28.3), 35.7 (35.4), 50.1 (50.2), 59.5 (60.1), 60.0, 62.1 (61.7), 66.3 (66.0), 70.4, 100.8 (100.8), 104.7 (104.8), 114.6, 117.0, 117.5, 122.4, 127.7, 128.7, 131.7, 132.0, 133.8, 138.9 (138.9), 151.0 (150.7), 157.5, 162.9 (163.0), 163.0, 163.4 (163.5), 176.1.

(1*S*,5*R*)-3-(2-Hydroxy-3-{[3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl]oxy}propyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2c). $C_{30}H_{30}N_2O_6$, yield 324 mg (63%), mp 169–171°C. APCI MS: 515.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.74–1.98 (2H, m, H-8), 2.38–2.70 (6H, m, H-9, 11a, 13a, 14, OH), 2.85–3.14 (3H, m, H-7, 11b, 13b), 3.84–4.18 (5H, m, H-10, 15, 16), 5.94–6.01 (1H, m, H-5), 6.40–6.47 (1H, m, H-3), 7.19–7.27 (1H, m, H-4), protons of the isoflavone fragment: 3.84 (3H, s, 4′-OCH_3),

6.72–6.78 (1H, m, H-8), 6.89–6.94 (1H, m, H-6), 6.97 (2H, d, J = 8.7, H-3′, 5′), 7.50 (2H, d, J = 8.7, H-2′, 6′), 7.93 (1H, s, H-2), 8.17 (1H, d, J = 8.9, H-5).

(1*S*,5*R*)-3-(2-Hydroxy-3-{[3-(4-methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-yl]oxy}propyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2d). $C_{31}H_{32}N_2O_6$, yield 328 mg (62%), mp 223–225°C. APCI MS: 529.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.79–2.00 (2H, m, H-8), 2.40–2.77 (6H, m, H-9, 11a, 13a, 14, OH), 2.87–3.14 (3H, m, H-7, 11b, 13b), 3.85–4.18 (5H, m, H-10, 15, 16), 5.93–6.04 (1H, m, H-5), 6.41–6.46 (1H, m, H-3), 7.22–7.26 (1H, m, H-4), protons of the isoflavone fragment: 2.31 (3H, s, CH_3-2), 3.84 (3H, s, 4′-OCH_3), 6.69–6.77 (1H, m, H-8), 6.84–6.92 (1H, m, H-6), 6.97 (2H, d, J = 8.3, H-3′, 5′), 7.21 (2H, d, J = 8.3, H-2′, 6′), 8.09 (1H, d, J = 8.8, H-5).

(1*S*,5*R*)-3-(3-{[3-(3,4-Dimethoxyphenyl)-4-oxo-4*H*-chromen-7-yl]oxy}-2-hydroxypropyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2e). $C_{31}H_{32}N_2O_7$, yield 414 mg (76%), mp 190–192°C. APCI MS: 545.1 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.78–1.99 (2H, m, H-8), 2.44–2.71 (6H, m, H-9, 11a, 13a, 14, OH), 2.85–3.14 (3H, m, H-7, 11b, 13b), 3.81–4.21 (5H, m, H-10, 15, 16), 5.90–6.04 (1H, m, H-5), 6.43 (1H, d, J = 9.1, H-3), 7.22–7.26 (1H, m, H-4), protons of the isoflavone fragment: 3.92 (3H, s, 3′-OCH_3), 3.93 (3H, s, 4′-OCH_3), 6.74–6.79 (1H, m, H-8), 6.90–6.96 (2H, m, H-5′, 6′), 7.06 (1H, dd, J = 8.3, 2.0, H-6), 7.21 (1H, d, J = 2.0, H-2′), 7.93–8.00 (1H, m, H-2), 8.13–8.24 (1H, m, H-5).

(1*S*,5*R*)-3-(2-Hydroxy-3-{[6-methoxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl]oxy}propyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2f). $C_{31}H_{32}N_2O_7$, yield 261 mg (48%), mp 115–117°C. APCI MS: 545.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.81–2.01 (2H, m, H-8), 2.37–2.73 (6H, m, H-9, 11a, 13a, 14, OH), 2.90–3.20 (3H, m, H-7, 11b, 13b), 3.78–4.21 (5H, m, H-10, 15, 16), 5.94–5.99 (1H, m, H-5), 6.40 –6.45 (1H, m, H-3), 7.18–7.26 (1H, m, H-4), protons of the isoflavone fragment: 3.85, 3.94 (3H each, s, 6, 4′-OCH_3), 6.76–6.80 (1H, m, H-8), 6.98 (2H, d, J = 8.8, H-3′, 5′), 7.52 (2H, d, J = 8.8, H-2′, 6′), 7.59–7.61 (1H, m, H-2), 7.93–8.00 (1H, m, H-5).

(1*S*,5*R*)-3-(3-{[3-(3,4-Dimethoxyphenyl)-6-methoxy-4-oxo-4*H*-chromen-7-yl]oxy}-2-hydroxypropyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2g). $C_{32}H_{34}N_2O_8$, yield 264 mg (46%), mp 121–123°C. APCI MS: 575.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.74–2.06 (2H, m, H-8), 2.38–2.70 (6H, m, H-9, 11a, 13a, 14, OH), 2.84–3.12 (3H, m, H-7, 11b, 13b), 3.76–4.17 (5H, m, H-10, 15, 16), 5.92–6.00 (1H, m, H-5), 6.38–6.46 (1H, m, H-3), 7.17–7.22 (1H, m, H-4), protons of the isoflavone fragment: 3.91, 3.92, 3.93 (3H, each, s, 6, 3′, 4′-OCH_3), 6.71–6.78 (1H, m, H-8), 6.93 (1H, d, J = 8.3, H-5′), 7.06 (1H, dd, J = 8.3, 1.8, H-6′), 7.22–7.26 (1H, m, H-2′), 7.55–7.62 (1H, m, H-2), 7.95–8.02 (1H, m, H-5).

(1*S*,5*R*)-3-(3-{[3-(1,3-Benzodioxol-5-yl)-4-oxo-4*H*-chromen-7-yl]oxy}-2-hydroxypropyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2h). $C_{30}H_{28}N_2O_7$, yield 275 mg (52%), mp 228–230°C. APCI MS: 529.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.78–2.00 (2H, m, H-8), 2.41–2.74 (6H, m, H-9, 11a, 13a, 14, OH), 2.86–3.18 (3H, m, H-7, 11b, 13b), 3.80–4.23 (5H, m, H-10, 15, 16), 5.95–5.99 (1H, m, H-5), 6.43 (1H, d, J = 9.0, H-3), 7.20–7.26 (1H, m, H-4), protons of the isoflavone fragment: 5.99 (2H, s, OCH_2O), 6.74–6.79 (1H, m, H-8), 6.87 (1H, d, J = 8.0, H-7′), 6.90–6.95 (1H, m, H-6), 6.98 (1H, d, J = 8.0, H-6′), 7.10 (1H, s, H-4′), 7.92 (1H, s, H-2), 8.17 (1H, d, J = 8.9, H-5).

(1*S*,5*R*)-3-(3-{[3-(4-Fluorophenyl)-4-oxo-4*H*-chromen-7-yl]oxy}-2-hydroxypropyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2i). $C_{29}H_{27}FN_2O_5$, yield 437 mg (87%), mp 164–166°C. APCI MS: 503.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.81–1.99 (2H, m, H-8), 2.40–2.76 (6H, m, H-9, 11a, 13a, 14, OH), 2.86–3.12 (3H, m, H-7, 11b, 13b), 3.78–4.21 (5H, m, H-10, 15, 16), 5.93–6.03 (1H, m, H-5), 6.40–6.46 (1H, m, H-3), 7.21–7.26 (1H, m, H-4), protons of the isoflavone fragment: 6.72–6.80 (1H, m, H-8), 6.90–6.96 (1H, m, H-6), 7.12 (2H, t, J = 8.7, H-3′, 5′), 7.54 (2H, dd, J = 8.8, 5.4, H-2′, 6′), 7.94 (1H, s, H-2), 8.17 (1H, d, J = 8.9, H-5).

(1*S*,5*R*)-3-(3-{[3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4-oxo-4*H*-chromen-7-yl]oxy}-2-hydroxypropyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (2j). $C_{31}H_{30}N_2O_7$, yield 396 mg (73%), mp 217–219°C. APCI MS: 543.1 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): protons of the 3-(12-cytisinyl)-2-hydroxypropyl fragment: 1.77–2.03 (2H, m, H-8), 2.42–2.71 (6H, m, H-9, 11a, 13a, 14, OH), 2.85–3.13 (3H, m, H-7, 11b, 13b), 3.79–4.21 (5H, m, H-10, 15, 16), 5.93–6.03 (1H, m, H-5), 6.44 (1H, d, J = 9.1, H-3), 7.21–7.27 (1H, m, H-4), protons of the isoflavone fragment: 4.25–4.36 (4H, m, H-2, 3), 6.76 (1H, d, J = 2.1, H-8), 6.90–6.95 (2H, m, H-7′, 8′), 7.03 (1H, dd, J = 8.3, 2.0, H-6), 7.11 (1H, d, J = 2.0, H-5′), 7.92 (1H, s, H-2), 8.18 (1H, d, J = 9.0, H-5).

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