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NEW ALOPERINE–ISOFLAVONE CONJUGATES

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The reaction of aloperine with isoflavone glycidyl ethers was investigated. A series of alkaloid–isoflavonoid conjugates were synthesized via regioselective opening of the oxirane ring by aloperine.

Keywords: aloperine, isoflavone, propanolamine, isoflavone glycidyl ether.

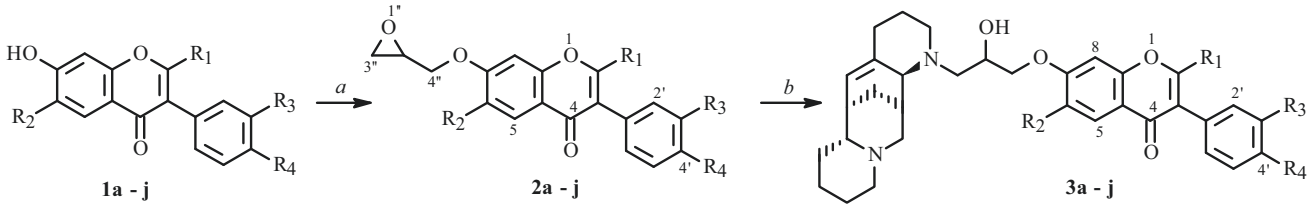
β-Adrenoblockers play an important role in the treatment of cardiovascular diseases. Their anti-ischemic, anti-arrhythmic, and antihypertensive properties have been used in clinical medicine for many years. Derivatives of phenylpropanolamine and phenoxypropanolamine are typical β-adrenoreceptor blockers [1, 2]. Chromone and flavone derivatives containing a propanolamine fragment are also known to be capable of blocking β-adrenoreceptors [3, 4]. Furthermore, several 7-(3-amino-2-hydroxypropoxy) flavonoid derivatives exhibited antihypertensive [5–7], antihyperglycemic [8], and antiproliferative [9] activity. Isoflavones containing an aminopropanol fragment showed anti-osteoporosis activity, an estrogen effect [10], and anticancer activity [11].

In continuation of research on the synthesis of alkaloid–flavonoid conjugates, it seemed interesting to study the possibility of using a hydroxypropane linker to conjugate 7-hydroxyisoflavones and aloperine, which was isolated as a minor constituent from seeds and leaves of *Sophora alopecuroides* L. [12–16].

Modification of this alkaloid was interesting because of its valuable biological properties. Aloperine exhibits anti-inflammatory, anti-allergic [17, 18], and antiviral activity [19]; inhibits proliferation of HCT116 cancer cells; initiates apoptosis; and interrupts the cell cycle [20].

The phenols for conjugation with aloperine were the natural isoflavones formononetin **1a** [21], 2-methylformononetin **1b** [22], cladrin **1c** [23], afromorsin **1d** [24], cladrastin **1e** [23], pseudobaptigenin **1f** [25], and their derivatives **1g**–**j**.

Oxiranes are widely used to synthesize phenoxypropanolamines. Their cyclic system can be opened highly regioselectively by *N*-nucleophiles. Thus, the most common method for synthesizing phenol glycidyl ethers uses attack of the phenols at the oxirane ring of 1-chloro-2,3-epoxypropane (epichlorohydrin) to give the chlorohydrin ethers followed by dehydrochlorination by base to close the epoxide ring [4, 5, 26, 27].



1a - j **2a - j** **3a - j**

a: $R_1 = R_2 = R_3 = H$, $R_4 = OMe$; **b:** $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = OMe$; **c:** $R_1 = R_2 = H$, $R_3 = R_4 = OMe$; **d:** $R_1 = R_3 = H$, $R_2 = R_4 = OMe$
e: $R_1 = H$, $R_2 = R_3 = R_4 = OMe$; **f:** $R_1 = R_2 = H$, $R_3R_4 = OCH_2O$; **g:** $R_1 = R_2 = R_3 = H$, $R_4 = F$; **h:** $R_1 = R_2 = R_3 = H$, $R_4 = Cl$
i: $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = Cl$; **j:** $R_1 = R_2 = H$, $R_3R_4 = OCH_2CH_2O$

a. epichlorohydrin, K_2CO_3, DMA, 70°C; *b*. aloperine, CH_3CN, $(C_4H_9)_4N^+I^-$

Scheme 1

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Isoflavone glycidyl ethers should be synthesized in the absence of strong bases because isoflavone derivatives are unstable to basic reagents. In our opinion, direct alkylation of the isoflavone phenol hydroxyl by alkylhalide without involving the oxirane ring in the reaction would be the most effective approach to synthesizing their glycidyl ethers. For this, we studied the reaction of 7-hydroxyisoflavones with epichlorohydrin in various solvents in the presence of bases. Dimethylacetamide (DMA) turned out to be the most convenient solvent for using epichlorohydrin as an alkylating agent. High yields of the glycidyl ethers without side products were obtained by using an excess of epichlorohydrin in the presence of potash. The proposed conditions for alkylating isoflavone 7-hydroxy groups avoided opening the chromone ring to form phenoxychlorohydrin and diphenoxypropanol derivatives. They produced high yields of 7-hydroxyisoflavone glycidyl ethers **2a**–**j**.

The known methods required some adjustment in order to use aloperine as a nucleophile to open the oxirane ring. 7-Hydroxyisoflavone glycidyl ethers **2a**–**j** were reacted with aloperine in MeCN with a catalytic amount of tetrabutylammonium iodide [$(C_4H_9)_4N^+I^-$]. Classical attack at the least substituted C atom (S_N2 mechanism) occurred. These conditions gave high yields of isoflavonoid 7-(3-amino-2-hydroxypropoxy) derivatives **3a**–**j** with an aloperine fragment (Scheme 1).

The structures of the synthesized compounds were elucidated using PMR spectra. Thus, PMR spectra of the aloperine–isoflavone conjugates lacked peaks characteristic of an oxirane ring and exhibited resonances for an aloperine fragment as unresolvable multiplets.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck plates (Germany) using CH_2Cl_2–MeOH (100:1, 50:1). PMR spectra were measured on the δ-scale vs. TMS (internal standard) on an M-400 instrument (Varian, 400 MHz). Elemental analyses of all compounds agreed with those calculated. Starting natural 7-hydroxyisoflavones and their analogs **1a**–**j** were synthesized earlier by us [28–30].

General Method for Preparing 7-Hydroxyisoflavone Glycidyl Ethers 2a–j. A solution of **1a**–**j** (10 mmol) in DMA (20 mL) was treated with potash (5.56 g, 40 mmol) and epichlorohydrin (20 mL) and stirred at 70°C for 5–10 h (end of reaction determined by TLC). The potash was filtered off. The solvent was evaporated. The solid was crystallized from *i*-PrOH.

3-(4-Methoxyphenyl)-7-(oxiran-2-ylmethoxy)-4*H*-chromen-4-one (2a). $C_{19}H_{16}O_5$, yield 78%, mp 139–141°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.81 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.96 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.38–3.44 (1H, m, H-2″), 3.84 (3H, s, OCH_3-4′), 4.02 (1H, dd, ^{2}J = 11.1, ^{3}J = 5.9, H-4″α), 4.37 (1H, dd, ^{2}J = 11.1, ^{3}J = 2.9, H-4″β), 6.89 (1H, d, J = 2.4, H-8), 6.97 (2H, d, J = 8.9, H-3′, 5′), 7.02 (1H, dd, J = 8.9, 2.4, H-6), 7.50 (2H, d, J = 8.9, H-2′, 6′), 7.92 (1H, s, H-2), 8.22 (1H, d, J = 8.9, H-5).

2-Methyl-3-(4-methoxyphenyl)-7-(oxiran-2-ylmethoxy)-4*H*-chromen-4-one (2b). $C_{20}H_{18}O_5$, yield 51%, mp 102–104°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.30 (3H, s, CH_3-2), 2.81 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.97 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.38–3.44 (1H, m, H-2″), 3.84 (3H, s, OCH_3-4′), 4.02 (1H, dd, ^{2}J = 11.1, ^{3}J = 5.9, H-4″α), 4.37 (1H, dd, ^{2}J = 11.1, ^{3}J = 2.8, H-4″β), 6.87 (1H, d, J = 2.4, H-8), 6.95–7.00 (3H, m, H-6, 3′, 5′), 7.18–7.23 (2H, J = 8.9, H-2′, 6′), 8.14 (1H, d, J = 8.9, H-5).

3-(3,4-Dimethoxyphenyl)-7-(oxiran-2-ylmethoxy)-4*H*-chromen-4-one (2c). $C_{20}H_{18}O_6$, yield 75%, mp 151–153°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.82 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.97 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.38–3.42 (1H, m, H-2″), 3.92 (3H, s, OCH_3-3′), 3.94 (3H, s, OCH_3-4′), 4.04 (1H, dd, ^{2}J = 11.1, ^{3}J = 5.9, H-4″α), 4.39 (1H, dd, ^{2}J = 11.1, ^{3}J = 2.8, H-4″β), 6.90 (1H, d, J = 2.4, H-8), 6.93 (1H, d, J = 8.3, H-5′), 7.00–7.05 (2H, m, H-6, 6′), 7.21 (1H, d, J = 2.0, H-2′), 7.96 (1H, s, H-2), 8.23 (1H, d, ^{3}J = 8.9, H-5).

6-Methoxy-3-(4-methoxyphenyl)-7-(oxiran-2-ylmethoxy)-4*H*-chromen-4-one (2d). $C_{20}H_{18}O_6$, yield 68%, mp 153–154°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.83 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.98 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.43–3.50 (1H, m, H-2″), 3.85 (3H, s, OCH_3-4′), 3.99 (3H, s, OCH_3-6), 4.10 (1H, dd, ^{2}J = 11.4, ^{3}J = 5.8, H-4″α), 4.43 (1H, dd, ^{2}J = 11.4, ^{3}J = 3.0, H-4″β), 6.95–7.00 (3H, m, H-6, 3′, 5′), 7.51 (2H, d, J = 8.8, H-2′, 6′), 7.64 (1H, s, H-2), 7.94 (1H, s, H-5).

3-(3,4-Dimethoxyphenyl)-6-methoxy-7-(oxiran-2-ylmethoxy)-4*H*-chromen-4-one (2e). $C_{21}H_{20}O_7$, yield 85%, mp 159–161°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.82 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.97 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.42–3.49 (1H, m, H-2″), 3.91 (3H, s, OCH_3-3′), 3.93 (3H, s, OCH_3-4′), 3.98 (3H, s, OCH_3-6), 4.09

(1H, dd, ^{2}J = 11.5, ^{3}J = 5.9, H-4″α), 4.43 (1H, dd, ^{2}J = 11.5, ^{3}J = 3.0, H-4″β), 6.93 (1H, d, J = 8.3, H-5′), 6.97 (1H, s, H-8), 7.04 (1H, dd, ^{3}J = 8.3, ^{4}J = 2.0, H-6′), 7.24 (1H, d, J = 2.0, H-2′), 7.64 (1H, s, H-2), 7.97 (1H, s, H-5).

3-(1,3-Benzodioxol-5-yl)-7-(oxiran-2-ylmethoxy)-4*H*-chromen-4-one (2f). $C_{19}H_{14}O_6$, yield 87%, mp 150–152°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.81 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.97 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″b), 3.37–3.46 (1H, m, H-2″), 4.02 (1H, dd, ^{2}J = 11.1, ^{3}J = 5.9, H-4″α), 4.38 (1H, dd, ^{2}J = 11.1, ^{3}J = 2.8, H-4″β), 5.99 (2H, s, 3′, 4′-OCH_2O), 6.87 (1H, d, J = 8.0, H-5′), 6.89 (1H, d, J = 2.4, H-8), 6.97 (1H, dd, ^{3}J = 8.0, ^{4}J = 1.7, H-6′), 7.02 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 7.09 (1H, d, ^{4}J = 1.7, H-2′), 7.91 (1H, s, H-2), 8.21 (1H, d, J = 8.9, H-5).

7-(Oxiran-2-ylmethoxy)-3-(4-fluorophenyl)-4*H*-chromen-4-one (2g). $C_{18}H_{13}FO_4$, yield 76%, mp 155–157°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.81 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.96 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.39–3.45 (1H, m, H-2″), 4.03 (1H, dd, ^{2}J = 11.1, ^{3}J = 6.0, H-4″α), 4.39 (1H, dd, ^{2}J = 11.1, ^{3}J = 2.8, H-4″β), 6.90 (1H, d, J = 2.4, H-8), 7.04 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 7.13 (2H, t, $^3J_{H,H}$ = 8.9, $^3J_{H,F}$ = 8.9, H-3′, 5′), 7.53 (2H, dd, $^3J_{H,H}$ = 8.9, $^4J_{H,F}$ = 5.5, H-2′, 6′), 7.94 (1H, s, H-2), 8.22 (1H, d, ^{3}J = 8.9, H-5).

7-(Oxiran-2-ylmethoxy)-3-(4-chlorophenyl)-4*H*-chromen-4-one (2h). $C_{18}H_{13}ClO_4$, yield 73%, mp 164–166°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.81 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.97 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.38–3.45 (1H, m, H-2″), 4.03 (1H, dd, ^{2}J = 11.1, ^{3}J = 5.9, H-4″α), 4.39 (1H, dd, ^{2}J = 11.1, ^{3}J = 2.8, H-4″β), 6.91 (1H, d, J = 2.4, H-8), 7.04 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 7.40 (2H, d, J = 8.9, H-3′, 5′), 7.51 (2H, d, J = 8.9, H-2′, 6′), 7.95 (1H, s, H-2), 8.22 (1H, d, J = 8.9, H-5).

2-Methyl-7-(oxiran-2-ylmethoxy)-3-(4-chlorophenyl)-4*H*-chromen-4-one (2i). $C_{19}H_{15}ClO_4$, yield 70%, mp 160–162°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.29 (3H, s, CH_3-2), 2.81 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.95 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.38 –3.44 (1H, m, H-2″), 4.03 (1H, dd, ^{2}J = 11.1, ^{3}J = 5.9, H-4″α), 4.38 (1H, dd, ^{2}J = 11.1, ^{3}J = 2.8, H-4″β), 6.88 (1H, d, ^{4}J = 2.4, H-8), 6.99 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 7.23 (2H, d, J = 8.9, H-3′, 5′), 7.41 (2H, d, J = 8.9, H-2′, 6′), 8.13 (1H, d, J = 8.9, H-5).

3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-7-(oxiran-2-ylmethoxy)-4*H*-chromen-4-one (2j). $C_{20}H_{16}O_6$, yield 83%, mp 146–148°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.81 (1H, dd, ^{2}J = 4.8, ^{3}J = 2.6, H-3″α), 2.96 (1H, t, ^{2}J = 4.8, ^{3}J = 4.8, H-3″β), 3.38–3.44 (1H, m, H-2″), 4.02 (1H, dd, ^{2}J = 11.1, ^{3}J = 5.9, H-4″α), 4.28 (4H, s, 3′, 4′-OCH_2CH_2O), 4.37 (1H, dd, ^{2}J = 11.1, ^{3}J = 2.8, H-4″β), 6.88 (1H, d, J = 2.5, H-8), 6.92 (1H, d, J = 8.3, H-5′), 7.00–7.05 (2H, m, H-6, 6′), 7.10 (1H, d, J = 2.1, H-2′), 7.90 (1H, s, H-2), 8.21 (1H, d, J = 8.9, H-5).

General Method for Preparing 3a–j. A solution of **2a–j** (1 mmol) in MeCN (20 mL) was treated with aloperine (0.25 g, 1.1 mmol) and $(C_4H_9)_4N^+I^-$ (10 mg), stirred, refluxed for 10–15 h (end of reaction determined by TLC), and cooled. The resulting precipitate was filtered off and crystallized from *i*-PrOH.

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-3-(4-methoxyphenyl)-4*H*-chromen-4-one (3a). $C_{34}H_{40}N_2O_5$, yield 68%, mp 161–163°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.17–1.94, 1.96–2.47, 2.56–2.90, 2.96–3.23, 5.51–5.66 (12H, 7H, 4H, 2H, 1H, 5m, aloperine protons and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 3.85 (3H, s, OCH_3-4′), 4.00–4.24 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.88 (1H, d, J = 2.4, H-8), 6.97 (2H, d, J = 8.9, H-3′, 5′), 7.02 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 7.50 (2H, d, J = 8.9, H-2′, 6′), 7.92 (1H, s, H-2), 8.22 (1H, d, J = 8.9, H-5).

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-2-methyl-3-(4-methoxyphenyl)-4*H*-chromen-4-one (3b). $C_{35}H_{42}N_2O_5$, yield 69%, mp 93–95°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.19–1.93, 1.95–2.48, 2.60–2.90, 2.95–3.22, 5.51–5.65 (12H, 10H, 4H, 2H, 1H, 5m, aloperine protons, CH_3-2 and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 3.85 (3H, s, OCH_3-4′), 3.98–4.24 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.86 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 6.93–7.01 (3H, m, H-8, 3′, 5′), 7.21 (2H, d, J = 8.9, H-2′, 6′), 8.13 (1H, d, J = 8.9, H-5).

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-3-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one (3c). $C_{35}H_{42}N_2O_6$, yield 82%, mp 94–96°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20–1.92, 1.95–2.46, 2.58–2.89, 2.95–3.21, 5.51–5.63 (12H, 7H, 4H, 2H, 1H, 5m, aloperine protons and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 3.91, 3.93 (each 3H, s, OCH_3-3′, 4′), 4.00–4.26 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.81–6.96 (2H, m, H-8, 5′), 6.99–7.09 (2H, m, H-6, 6′), 7.18–7.23 (1H, m, H-2′), 7.95 (1H, s, H-2), 8.21 (1H, d, J = 8.9, H-5).

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-6-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (3d). $C_{35}H_{42}N_2O_6$, yield 84%, mp 103–105°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.18–1.91, 1.96–2.45, 2.58–2.89, 2.97–3.18, 5.52–5.62 (12H, 7H, 4H,

2H, 1H, 5m, aloperine protons and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 3.85, 3.97 (each 3H, s, OCH_3-4′, 6), 3.98–4.31 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.92 (1H, s, H-8), 6.97 (2H, d, J = 8.9, H-3′, 5′), 7.51 (2H, d, J = 8.9, H-2′, 6′), 7.62 (1H, s, H-2), 7.94 (1H, s, H-5).

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-3-(3,4-dimethoxyphenyl)-6-methoxy-4*H*-chromen-4-one (3e). $C_{36}H_{44}N_2O_7$, yield 75%, mp 102–104°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.19–1.91, 1.94–2.45, 2.56– 2.89, 2.95–3.19, 5.50–5.62 (12H, 7H, 4H, 2H, 1H, 5m, aloperine protons and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 3.91, 3.93, 3.97 (each 3H, s, OCH_3-3′, 4′, 6), 4.02–4.30 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.91 (1H, d, J = 8.3, H-5′), 6.94 (1H, s, H-8), 7.05 (1H, dd, ^{3}J = 8.3, ^{4}J = 2.0, H-6′), 7.25 (1H, d, J = 2.0, H-2′), 7.62 (1H, s, H-2), 7.97 (1H, s, H-5).

3-(1,3-Benzodioxol-5-yl)-7-{2-hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-4*H*-chromen-4-one (3f). $C_{34}H_{38}N_2O_6$, yield 77%, mp 170–172°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20–1.93, 1.98–2.46, 2.58–2.90, 2.96–3.21, 5.50–5.64 (12H, 7H, 4H, 2H, 1H, 5m, aloperine protons and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 4.00–4.24 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.00 (2H, s, 3′, 4′-OCH_2O), 6.85–6.91 (2H, m, H-8, 5′), 6.96–7.06 (2H, m, H-6, 6′), 7.11 (1H, d, J = 1.7, H-2′), 7.92 (1H, s, H-2), 8.21 (1H, d, J = 8.9, H-5).

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-3-(4-fluorophenyl)-4*H*-chromen-4-one (3g). $C_{33}H_{37}FN_2O_4$, yield 73%, mp 177–179°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.18–1.92, 1.96–2.45, 2.58–2.90, 2.96–3.20, 5.50–5.64 (12H, 7H, 4H, 2H, 1H, 5m, aloperine protons and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 4.00–4.25 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.89 (1H, d, J = 2.4, H-8), 7.04 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 7.13 (2H, t, $^3J_{H,H}$ = 8.9, $^3J_{H,F}$ = 8.9, H-3′, 5′), 7.54 (2H, dd, $^3J_{H,H}$ = 8.9, $^4J_{H,F}$ = 5.5, H-2′, 6′), 7.94 (1H, s, H-2), 8.21 (1H, d, J = 8.9, H-5).

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-3-(4-chlorophenyl)-4*H*-chromen-4-one (3h). $C_{33}H_{37}ClN_2O_4$, yield 52%, mp 157–159°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.19–1.90, 1.94–2.45, 2.56–2.90, 2.93–3.20, 5.50–5.64 (12H, 7H, 4H, 2H, 1H, 5m, aloperine protons and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 4.00–4.26 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.89 (1H, d, J = 2.4, H-8), 7.05 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 7.40 (2H, d, J = 8.9, H-3′, 5′), 7.51 (2H, d, J = 8.9, H-2′, 6′), 7.59 (1H, s, H-2), 8.21 (1H, d, J = 8.9, H-5).

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-2-methyl-3-(4-chlorophenyl)-4*H*-chromen-4-one (3i). $C_{34}H_{39}ClN_2O_4$, yield 68%, mp 89–91°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.22–1.92, 1.95–2.44, 2.57–2.87, 2.91–3.22, 5.43–5.64 (12H, 10H, 4H, 2H, 1H, 5m, aloperine protons, CH_3-2 and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 3.98–4.26 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 6.87 (1H, d, J = 2.4, H-8), 6.99 (1H, dd, ^{3}J = 8.9, ^{4}J = 2.4, H-6), 7.32 (2H, d, J = 8.9, H-3′, 5′), 7.41 (2H, d, J = 8.9, H-2′, 6′), 8.12 (1H, d, J = 8.9, H-5).

7-{2-Hydroxy-3-[(6*S*,6a*R*,13a*S*)-3,4,6,7,8,9,10,12,13,13a-decahydro-2*H*-6,13-methanopyrido[1,2-*a*:3′,2′-*e*]azocin-1(6a*H*)-yl]propoxy}-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-4*H*-chromen-4-one (3j). $C_{35}H_{40}N_2O_6$, yield 77%, mp 138–140°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20–1.92, 1.97–2.44, 2.58–2.88, 2.96–3.18, 5.51–5.63 (12H, 7H, 4H, 2H, 1H, 5m, aloperine protons and $NC\underline{H}_2C\underline{H}(OH)CH_2O$-7), 4.00–4.24 (3H, m, $NCH_2CH(O\underline{H})C\underline{H}_2O$-7), 4.29 (4H, s, OCH_2CH_2O-3′, 4′), 6.85–6.94 (2H, m, H-8, 5′), 6.99–7.06 (2H, m, H-6, 6′), 7.11 (1H, d, J = 1.7, H-2′), 7.90 (1H, s, H-2), 8.21 (1H, d, J = 8.9, H-5).

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