LAPPAKONITIN ALKALOIDINI GIDROLIZLANISHI

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Annotatsiya. Diterpen alkaloid lappakonitinni kislotali sharoitda gidrolizlab N-dezatsetillappakonitin olindi. Ushbu gidroliz reaksiya mahsulotining biologik faolligi PASS dasturi orqali bashorat qilindi. Ajratib olingan moddaning tuzilishi fizik - kimyoviy (YaMR, IQ, Mass, RTT) usullar yordamida to‘liq isbotlandi.

Kalit so‘zlar: Diterpen alkaloidi, N-dezatsetillappakonitin, gidroliz, terapevtik, antiaritmik, geterosiklik, lappakonitin

Аннотация. N-дезацетиллаппаконитин был получен путем гидролиза дитерпенового алкалоида лаппаконитина в кислых условиях. Биологическая активность этого продукта реакции гидролиза была предсказана с помощью программы PASS. Структура выделенного вещества полностью доказана с использованием физико-химических (ЯМР, ИК, масс-спектроскопия, ОТ-ПЦР) методов.

Ключевые слова: Дитерпеновый алкалоид, N-дезацетиллаппаконитин, гидролиз, терапевтический, антиаритмический, гетероциклический, лаппаконитин

Abstract. N-desacetyllappaconitine was obtained by hydrolysis of the diterpene alkaloid lappaconitine under acidic conditions. The biological activity of this hydrolysis reaction product was predicted using the PASS program. The structure of the isolated substance was fully proven using physical and chemical (NMR, IR, Mass, RTD) methods.

Keywords: Diterpene alkaloid, N-desacetyllappaconitine, hydrolysis, therapeutic, antiarrhythmic, heterocyclic, lappaconitine

Kirish

Dunyo olimlarning diterpen alkaloidlariga bo‘lgan qiziqishiga sabab bu alkaloidlarning har xil faolligi, tuzilish jihatidan murakkabligi, sintezi hamda dorivor xususiyati bilan bog‘liq. 1998 - 2008 yillar oralig‘ida tabiiy o‘simlik manbaalaridan 300 tadan ko‘proq yangi diterpen alkaloidlar ajratib olingan [1]. Lappakonitindan keyin uchta eng muhim C_{18}-diterpen alkaloidlaridan

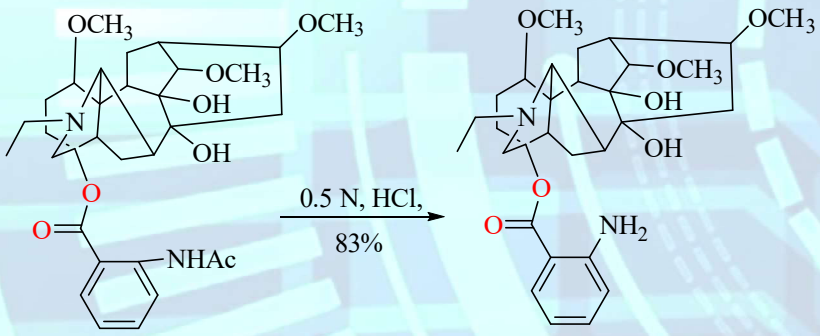
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lappakonidin aniqlandi. Bu alkaloidlar oxirgi 40 yil davomida “bisnorditerpen alkaloidlar”ning rivojlanishi uchun asos bo‘ldi [2]. *Aconitum* turkum o‘simlik ekstraktlari asosan hayvonlarini ovlash maqsadida o‘qlarning uchlarini tayyorlashda foydalangan. [3]. Allapinin (lappakonitinin alkaloididan olingan) dori sifatida tasdiqlangan.

ADABIYOTLAR TAHLILI. Kardiologlarning fikricha, allapinin o‘zining noyob xususiyatlari tufayli yurak aritmiyasining ayrim turlarini davolashda birinchi darajali dori sifatida qo‘llanilib kelinmoqda [4]. *Aconitum* va *Delphinium* turkum o‘simliklaridan ajratib olingan diterpen alkaloidlari (DA) antiaritmik, kuraresimon, aritmogen, psixostimulyatorlik, neyrotoksik, ganglioblokloychi, mahalliy anesteziya chaqiruvchi, gipotenziv va boshqa turdagi biologik faolliklarga ega birikmalar aniqlangan [5-28]. Lappakonitin alkaloidi birinchi martta *Aconitum septentrionale* o‘simligidan ajratib olingan diterpen alkaloidi hisoblanadi, hozirgi kunda u *A. orientale, A. åxcelsum, A. barbatum, A. nasutum, A. netianum, A. leucostomum, A. ranunculaefolium, A. sinomontanum, A. talassicum è Delphinium cashmerianum* kabi o‘simliklardan ajratib olingan [29].

OLINGAN NATIJALARNING MUHOKAMASI.

Lappakonitin alkaloidini kislotali sharoitda gidrolizlab N-dezatsetillappakonitin olindi (1-sxema). Mahsulotning tuzilishi IQ, YaMR ^{1}H va ^{13}C spektroskopik hamda RTT usullar yordamida isbotlandi.



1 2

Sxema 1. Lappakonitin alkaloidini kislotali sharoitda gidrolizlab N-dezatsetillappakonitinni olinishi

Lappakonitin alkaloidning kislotali gidrolizlanishi natijasidan hosil bo‘lgan N-dezatsetillappakonitin alkaloidining (**2**) tuzilishi fizik-kimyoviy tadqiqot usullar yordamida isbotlandi. N-dezatsetillappakonitin (**2**) ning IQ spektriga e’tibor qaratadigan bo‘lsak, molekula tarkibidagi -OH guruhiga -3539 sm^{-1} va $-NH_2$ guruhiga xos valent tebranishlar 3376 sm^{-1} sohalarda, 1684 sm-1 sohada esa karbonil guruhiga C=O xos valent va diformatsion tebranishlar, hamda 1073-750 sm^{-1} sohalarda tebranishlar aniqlandi. Qolgan barcha funksional guruhlardagi bog‘larga mansub bo‘lgan valent va diformatsion tebranishlar ham IQ spektrlarida

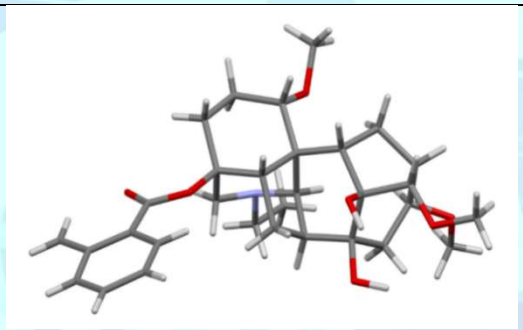
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tegishli sohalarida namoyon bo‘ldi. 2-Moddaning mass spektrometrdagi signallari shuni ko‘rsatdiki, ESI-MS m/z 543.5137 $[M+H]^+$ ushbu ion molekulasi barqaror ekanligi isbotlandi.

2-Birikmaning tuzilishi ^1H va ^{13}C YaMR spektrlari va HSQC, HMBC tajribalarini tahlil qilish orqali aniqlandi. 2-Birikmaning ^1H YaMR spektrining kuchli maydon qismida ya’ni 1.10 m.u. sohasida molekula tarkibidagi metil guruhi protonlariga xos triplet (J =7.1) signal aniqlandi. 1.62-3.17 m.u. gacha bo‘lgan sohalarda siklik alifatik protonlarga xos bo‘lgan dubletli-dubletlar va multplet ko‘rinishdagi signallarni kuzatish mumkin. Bundan tashqari spektrning o‘rta 3.28-3.40 m.u. sohalarida (1-OCH_3, 16-OCH_3, 14-OCH_3) uchta metoksil guruhiga xos singlet signallar, hamda 6.59-7.75 m.u. sohalarda (3′-6′) aromatik protonlarga mansub spin-spin o‘zaro ta’sirlashuv qiymati, J = 8.0, 1.6 (6′) Gs bo‘lgan dubletli-dubleti kabi signallar aniqlandi.

^{13}C YaMR spektrining kuchsiz maydon qismida δ 167.5 (C=O) karbonil guruhi uglerod atomiga tegishli signalni, δ 150.5 (C-2′) m.u. da aromatik to‘rtlamchi uglerod atomiga, δ 133.9-116.4 m.u. sohalarda molekula tarkibidagi protonlangan (6′-1′) aromatik halqaga tegishli uglerod atomlariga xos signallar aniqlandi. Kuchliroq maydon δ 56.2-58.0 m.u. sohada kislorod bilan bog‘langan C atomlariga xos bo‘lgan uchta metoksil guruhi (16-OCH_3, 1-OCH_3, 14-OCH_3) uglerodlariga xos rezonanslashgan signallar kuzatildi. Keyinchalik δ 47.6 (C-13), δ 26.9 (C-3) va δ 13.7 (C-19) m.u. sohalarda metin, metilen, metil guruhlari uglerodlariga va boshqa alifatik C atomlarining rezonanslariga tegishli signallar aniqlandi. Uchta metoksil va bitta metilning joylashgan o‘rinlari HMBC tajribasidan aniqlandi. HMBC spektrida 1-OCH_3/C-1, 14-OCH_3/C-14, 16-OCH_3/C-16 va H-19(H-18)/C-18, H-1′/C=O o‘zaro cho‘qqilarining mavjudligi metoksillarning joylashishini ko‘rsatdi. Ular mos ravishda C-1, C-14 va C-16 da uchta metoksil hamda C-18 da esa metil guruhi joylashganligini ko‘rsatdi. Bundan tashqari molekula tuzilishi rentgen tuzilish tahlili usuli yordamida to‘liq isbotlandi va quyidagicha nomlandi 1-etil-7a,11a-digidroksi-6,8,10-trimetoksidodekagidro-2H-3,6a,12-(epietan[1,1,2]triil)-7,9-metanonaft[2,3-b]azotsin-3(4H)-il 2-aminobenzoat.

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N-dezatsetillappakonitin (2) kristalidagi tuzilishi

Tajribaviy qismi. IQ spektrlari ATR tizimidan foydalangan holda FT-IR/NIT Spectrum 3 spektrometri yordamida qayd etilgan. Mass spektrlari Waters ACQUITY® QDa™ spektrometrda qayd etildi. YaMR spektrlari JNM-ECZ400R va JNM-ECZ600R (Jeol, Yaponiya) 400 va 600 MHz ish chastotalarida, CDCl3 eritmalarida 1H uchun qayd etilgan. TMS (0 m.d.) 1H YaMR spektrlarida ichki standart sifatida ishlatilgan. 13C YaMR spektrlarida ichki standart sifatida erituvchining kimyoviy siljishi (CDCl3, TMSga nisbatan 77,16 m.d.) ishlatilgan. YaMR spektrlari MestReNova 14.2.0 (Mestrelab Research S.L., Santiago de Compostela, Spain) bilan qayta ishlandi. Reaksiyaning borishi va olingan birikmalarning tozaligi Sigma-Aldrich, silufol L/W 10×20sm, 254 nm (Germaniya) YuQX plastinkasida nazorat qilindi, sistema sifatida benzol: xloroform: tirietilamin 4:1:0.3, ishlatildi. Ochiltirish uchun yodli kamera va Dragendorf reaktividan foydalanildi. Barcha sintezlangan moddalarning suyuqlanish harorati BOETIUS asbobida aniqlandi.

1-Etil-7a,11a-digidroksi-6,8,10-trimetoksidodekagidro-2H-3,6a,12-(epietan[1,1,2]triil)-7,9-metanonaft[2,3-b]azotsin-3(4H)-il 2-aminobenzoat (2).

2 g (3.4 mmol) lappakonitin 9.38 ml diss suvda eritildi va 1 N 0.884 ml (30.7 mmol) HCl solindi (1:3). Reaksiya suv hammomida qayta sovutish bilan 2 soat davomida olib borildi. Reaksiyaning borishi YuQX usulida tekshirilib turildi. Hosil bo‘lgan N-dezatsetillappakonitin $NaHCO_3$ to‘yingan eritmasi ishtirokida pH 8-9 ga o‘tkazildi va xloroformda ekstraksiya qilindi. Xloroform qismi Na_2SO_4 bilan quritildi va xloroform haydaldi. Hosil bo‘lgan cho‘kma metanolda qayta kristallandi. 1.545 g 83% unum bilan N-dezatsetillappakonitin (**2**) hosil bo‘ldi. $C_{30}H_{42}N_2O_7$ rangsiz kristall, suyuqlanish harorati 215-217°C (metanol), Rf 0.45 (sistema benzol:xloroform:trietilamin, 4: 1 :0.3).

IQ spektr (sm-1): 3539, 3376, 2927, 2821, 1684, 1616, 1558, 1245, 1105, 1073, 750, 526.

Mass-spektr ESI-MS m/z 543.5137 $[M-H]^{+}$, (hisoblangan 543.6738, $C_{30}H_{42}N_2O_7$).

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^{1}H YaMR (600 MGs, CDCl3, δ, m.u., J/Gs): 7.75 (1H dd, J = 8.0, 1.6, H-6'), 7.21 (1H,ddd, J = 8.4, 7.0, 1.6, H-4'), 6.57 – 6.61 (2H,m, H-3',H-5'), 3.61 (1H, d, J = 3.6, H-17), 3.54 (1H, s, H-16), 3.43 (4H, dd, J = 4.8-1.1, H-14), 3.40 (3H, s, 14-OCH3), 3.30 (3H, s, 16-OCH3), 3.28 (3H, s, 1-OCH3), 3.17 (1H, dd, J = 10.5, 6.9, H-1), 2.62-2.70 (2H, m, H-5,H-15), 2.48-2.54 (4H, m, H-3, H-6, H-7, H-13), 2.27 (2H,m, H-10), 2.14 (2H,d, J=8.1,H-3,H-12), 2.08 (1H,dd, J = 12.5, 4.8, H-12), 1.98 (2H, tdd,J= 14.9, 12.5, 7.6, H-2, H-6),1.74 (1H,dddd, J = 14.5, 12.1, 4.9, 2.2, H-2), 1.63 (2H,dd, H-10), 2.42 – 2.38 (1H m, H-7), 1.1 (3H, t , J=7.1 H-19).

^{13}C YaMR (150 MGs, CDCl3, δ, m. u., J/Gs): 167.48 (OCO), 150.5 (C-2′), 133.92 (C-19), 131.66 (C-4′), 116.74 (C-3′), 116.36 (C-5′), 112.05 (C-1′), 90.28 (C-14), 84.51 (C-4), 83.04 (C-16), 83.00 (C-1), 78.67. (C-9), 75.79 (C-17), 61.73 (C-8), 58.02 (C-14-OCH3), 56.63 (C-1-OCH3), 56.22 (C-16-OCH3),55.75 (C-11),50.94 (C-10),49.94 (C-15),49.11(C-5),47.64 (C-13), 26.92 (C-3),26.34 (C-6) 24.16 (C-2).

Xulosa

Diterpen alkaloidi Lappokonitinni turli xil molyarli kislotali sharoitda gidroliz qilindi. Tadqiqot natijasida N-dezatsetillappokonitin (**2**) olishning optimal usuli topildi. Ajratib olingan moddalar keyingi reaksiyalar uchun dastlabki modda sifatida foydalanish reja qilingan. Ajratib olingan moddalarning tuzilishi fizik - kimyoviy (YaMR, IQ, Mass, RTT) usullar yordamida to‘liq isbotlandi.

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