O‘SIMLIK MODDALARI KIMYOSI INSTITUTI HUZURIDAGI ILMIY DARAJALAR BERUVCHI DSc.02/30.01.2020. K/T. 104.01 RAQAMLI ILMIY KENGASH

O‘SIMLIK MODDALARI KIMYOSI INSTITUTI

BO ZHAO

MARKAZIY OSIYODA O‘SADIGAN *ACONITUM* VA *DELPHINIUM* TURKUM O‘SIMLIKLARINING DITERPENOID ALKALOIDLARI VA ULARNING BIOLOGIK FAOLLIGINI O‘RGANISH

02.00.10 – Bioorganik kimyo

KIMYO FANLARI DOKTORI (DSc) DISSERTATSIYASI AVTOREFERATI

TOSHKENT – 2025

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Fan doktori (DSc) dissertatsiyasi mavzusi O‘zbekiston Respublikasi Oliy ta’lim, fan va innovatsiyalar vazirligi huzuridagi Oliy attestatsiya komissiyasida B2025.2.DSc/K.... raqam bilan ro‘yxatga olingan.

Dissertatsiya ishi O‘zR FA O‘simlik moddalari kimyosi instituti va Xitoy Fanlar akademiyasi Shinjon fizika va kimyo texnika institutida bajarilgan.

Dissertatsiya avtoreferati uch tilda (o‘zbek, rus va ingliz (rezyume)) (www.uzicps.uz) va «Ziyonet» axborot-ta’lim portalida (www.ziyonet.uz) joylashtirilgan.

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Yetakchi tashkilot:	**Toshkent Farmatsevtika instituti**

Dissertatsiya himoyasi O‘simlik moddalari kimyosi instituti huzuridagi DSc.02/30.01.2020.K/T.104.01 raqamli Ilmiy kengashning 2025-yil «___» _____ soat ____ dagi majlisida bo‘lib o‘tadi (Manzil: 100170, Toshkent sh., Mirzo Ulug‘bek ko‘ch., 77. Tel.: (+99871) 262-59-13, faks: (+99871) 262-73-48, e-mail plant.inst@icps.org.uz, ixrv@mail.ru.

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KIRISH (fan doktori (DSc) dissertatsiyasi annotatsiyasi)

Dissertatsiya mavzusining dolzarbligi va zarurati. Dunyoda farmatsevtika sanoatida tabiiy moddalar asosida yaratilayotgan yangi dori vositalari har tomonlama afzalligi jihatidan doim muhim o‘rin tutib kelgan, shuning uchun o‘simlik xom ashyolaridan olinadigan fiziologik faol moddalarga bo‘lgan qiziqish yildan yilga ortib bormoqda. Bugungi kunda tarkibida turli xil moddalar saqlagan o‘simliklardan individual moddalarni ajratib olish, ularning biologik faolliklari, fizik-kimyoviy hususiyatlarini aniqlash va ularni ishlab chiqarishga tadbiq etish bo‘yicha bir qancha ilmiy-tadqiqotlar olib borilmoqda.

Ular tuzilishining xilma xilligi, kimyoviy polifunksionalligi, yuqori fiziologik faolligi va ular asosida dorivor vositalar yaratishda katta imkoniyatga ega ekanligi bilan diterpen alkaloidlari kimyogarlar va farmakologlarning diqqatini jalb etib kelmoqda.

Markaziy Osiyoda o‘sadigan *Aconitum* va *Delphinium* turkumiga xos ba’zi turlarining quritilgan ildizlari an’anaviy Xitoy tabobatida antiaritmiyaga qarshi, og‘riq qoldiruvchi yoki o‘smaga qarshi vosita sifatida ko‘p kasalliklarni davolashda keng qo‘llaniladi.

Xitoy florasida o‘suvchi *Delphinium* turkum o‘simligini fitokimyoviy tadqiqotlari natijasida diterpen alkaloidlari ajratilgan va ularning biologik faolliklarini o‘rganish natijasida yallig‘lanishga qarshi, og‘riq qoldiruvchi, aritmiyaga qarshi, shuningdek, insektitsid va antifeedant kabi xususiyatlari tekshirilgan.

O‘simlik moddalari kimyosi institutida olib borilgan tadqiqotlar natijasida Xitoy florasida o‘suvchi *Aconitum barbatum* var. *puberulum* va *Delphinium iliense* o‘simliklarining kimyoviy tarkibi bir biriga o‘xshamasligi, *Aconitum barbatum* var. *puberulum* dan ajratib olingan diterpen alkaloid - *N*-acetylsepaconitin va *N*-deacetyllappaconitin ning antiaritmik xususiyatga ega ekanligi aniqlandi. Shuningdek, *Delphinium iliense* o‘simligidan ajratib olingan Sinchianidin C va D lar analgetik ta’sirga egaligi namoyon bo‘ldi. Bu esa mahaliy xom ashyo asosida import o‘rnini bosuvchi dori vositalarini yaratish, aholini arzon, sifatli dori vositalari bilan ta’minlash imkonini beradi.

Mazkur dissertatsiya tadqiqoti O‘zbekiston Respublikasi Prezidentining 2022 yil 21 yanvardagi PF-55-son “2022-2026 yillarda Respublikaning farmatsevtika tarmog‘ini jadal rivojlantirishga oid qo‘shimcha chora-tadbirlar to‘g‘risida” gi Farmoni, 2018 yil 14 fevraldagi PQ-3532-son “Farmatsevtika tarmog‘ini jadal rivojdantirish bo‘yicha qo‘shimcha chora-tadbirlar to‘g‘risida” gi, 2019 yil 6 maydagi PQ-4310-son “Tibbiyot va Farmatsevtika ta’limi va ilm fani tizimini yanada rivojlantirish chora-tadbirlari tug‘risida” [1] gi Qarorlari hamda mazkur faoliyatga tegishli boshqa me’yoriy-huquqiy hujjatlarda belgilangan vazifalarni amalga oshirishga muayyan darajada xizmat qiladi..

Mazkur dissertatsiya tadqiqoti O‘zbekiston va Xitoy davlat dasturlari doirasida Markaziy Osiyodagi endemik *Aconitum* va *Delphinium* o‘simliklaridan yangi tuzilishli diterpenoid alkaloidlarini izlab topish, antiaritmiya, og‘riq qoldiruvchi va

[1] O‘zbekiston Respublikasi Prezidentining 2022 yil 28 yanvardagi PF-60-son “2022-2026” yillarga mo‘ljallangan yangi O‘zbekistonning Taraqqiyot strategiyasi” to‘g‘risidagi Farmoni.

o‘smaga qarshi ta’sirlarni tekshirish kabi dolzarb vazifalarni bajarishga bag‘ishlangan. Ushbu tadqiqotlar samarali va kam zaharli diterpenoid alkaloid innovatsion dori vositalarini yanada rivojlantirish hamda Markaziy Osiyoda o‘ziga xos o‘simlik manbalaridan barqaror foydalanish va rivojlantirish uchun ilmiy asos bo‘lib xizmat qiladi hamda inson salomatligi uchun foydali bo‘lgan yangi faol tabiiy mahsulotlarni topishda muhim ahamiyat kasb etadi.

Tadqiqotning O‘zbekiston va Xitoy fan va texnologiyalari rivojlanishining ustuvor yo‘nalishlariga bog‘liqligi. Ushbu tadqiqot Xitoy Xalq Respublikasi Fan va texnologiyalar sohasidagi hamkorlik bo‘limi va O‘zbekiston Respublikasi Hukumati hamkorlik qo‘mitasining ikkinchi majlisini o‘tkazish to‘g‘risidagi 2014-yil 17-iyulda imzolangan hukumatlararo bitimlar to‘g‘risidagi memorandumga muvofiq bajarilgan. Shuningdek, tadqiqot Xitoy Xalq Respublikasi Fan va texnologiyalar sohasidagi hamkorlik bo‘limi va O‘zbekiston Respublikasi Hukumati hamkorlik qo‘mitasining 2017-yil 15-fevralda imzolangan uchinchi majlisi; 2019-yil 24-iyulda imzolangan to‘rtinchi majlisi; va 2021-yil 28-iyun kungi beshinchi majlisi kelishuvlariga muvofiq bajarilgan. Bundan tashqari, ushbu tadqiqot yaqinda bo‘lib o‘tgan Oliy darajadagi ikki tomonlama uchrashuvlarda e’lon qilingan “Yangi davrda Xitoy-O‘zbekiston” keng qamrovli Strategik sheriklik doirasida belgilangan maqsadlarni to‘liq qo‘llab-quvvatlaydi. Ushbu hamkorlik innovatsiyalar, biotexnologiyalar, an’anaviy tibbiyot va yashil rivojlanish kabi sohalarda har tomonlama hamkorlikni, shu bilan birga tabiiy mahsulotlar va farmatsevtika kashfiyoti bo‘yicha hamkorlikda tadqiqotlar uchun kuchli siyosat poydevori va o‘zaro manfaatdorlikni ta’minlaydi.

Dissertatsiya mavzusi bo‘yicha xorijiy ilmiy-tadqiqotlar sharhi. Diterpenoid alkaloidlarini o‘rganishga qaratilgan ilmiy tadqiqotlar dunyoning yetakchi ilmiy markazlari va universitetlarida olib borilgan, shu jumladan: Georgia universitetining Tabiiy mahsulotlar tadqiqot instituti va kimyo bo‘limi (AQSh); G‘arbiy Xitoy farmatsiya, Sichuan universitetining Dorivor tabiiy mahsulotlar kimyosi kafedrasi (Xitoy); O‘zbekiston Respublikasi Fanlar akademiyasi akad. S.Yu.Yunusov nomidagi O‘simlik moddalari kimyosi instituti (O‘zbekiston); Rossiya Fanlar akademiyasining Ural bo‘limi Organik kimyo instituti (Rossiya); Xokkaydo farmatsevtika universitetining Farmatsevtika maktabi (Yaponiya); Xitoy Fanlar Akademiyasining Kunming Botanika instituti (Xitoy); Janubi-g‘arbiy Jiaotong universitetining Hayot fanlari va muhandislik maktabi (Xitoy); Xitoy Fanlar akademiyasining Shinjon fizika va kimyo texnika instituti (Xitoy) va boshqalar tomonidan o‘simlik xom ashyosidan diterpenoid alkaloidlari asosida dori vositalari yaratish bilan bog‘liq nazariy va amaliy tadqiqotlar sohasida chuqur ilmiy izlanishlar olib borilgan.

Tadqiqotlar mazmuni diterpen alkaloidlarini *Aconitum*, *Delphinium* va boshqa o‘simliklardan ajratib olish, tuzilishini aniqlash, biofaolliklarini skrining qilish, tuzilish-biologik faollik munosabatlarini tadqiq qilish, alkaloidlar, farmakologik, farmakodinamik va toksikologik tadqiqotlar va boshqalarni qamrab oladi.

Diterpenoid alkaloidlarini tadqiq qilish deyarli 100 yildan buyon davom etib kelayotgan, hozir ham dolzarb bo‘lgan mavzudir. Bir tomondan, o‘zining murakkab va o‘zgaruvchan tuzilishi sababli turli xil biologik faollikka ega; boshqa tomondan, ularning faolligi va zaharliligi ko‘pincha birga namoyon bo‘ladi. Shuning uchun nafaqat ularning strukturasining o‘zgarishiga e’tibor berish, tuzilishi va faolligi

o‘rtasidagi bog‘liqlikni aniqlash, balki tadqiqot jarayonida ularning zaharliligiga ham e’tibor qaratish, qo‘shimcha qiymati yuqori bo‘lgan yuqori samarali va kam zaharli dori birikmalarini topish lozim.

Muammoning o‘rganilganlik darajasi. Diterpenoid alkaloidlari birinchi marta 1830-yillarda kashf etilgan bo‘lsa-da, ularning murakkab tuzilishi sababli mutlaq konfiguratsiyasi 1950-yillarga kelibgina, rentgen monokristal difraksiyasi va boshqa usullar bilan aniqlandi. Spektral texnologiyalar, xususan, massa-spektrometriya va yadro magnit rezonansining keng tatbiq etilishi natijasida diterpenoid alkaloidlarini tadqiq qilish, ayniqsa, Jorjiya universitetining Tabiiy mahsulotlar ilmiy-tadqiqot instituti va kimyo kafedrasi professori S.W. Pelletier, O‘zbekiston Respublikasi Fanlar akademiyasi O‘simlik moddalari kimyosi instituti professori S.Y. Yunusov va Sichuan universiteti G‘arbiy Xitoy farmatsiyasi Dorivor tabiiy mahsulotlar kimyosi kafedrasi professori F.P. Wang tadqiqotlari natijasida jadal rivojlandi.

Diterpenoid alkaloidlarning yallig‘lanishga qarshi, og‘riq qoldiruvchi, antiaritmik, kardiotonik, yurak etishmovchiligiga qarshi va hasharotlarga chidamli ta’sirga ega ekanligi aniqlaganidan keyin, tobora ko‘proq olimlar diterpenoid alkaloidlarini tadqiq qilishga kirishdilar, shu jumladan, o‘zbek va rus olimi M.S. Yunusov, yapon olimi K. Wada, Xitoylik olimlar X.J. Hao, X.L. Zhou, H.A. Aisa va boshqalar. Ko‘pgina olimlarning birgalikdagi sa’y-harakatlari bilan hozirgi vaqtda o‘simliklardan 1600 dan ortiq tabiiy diterpenoid alkaloidlar topilgan bo‘lib, ulardan 4 ta diterpenoid alkaloidi: lappakonitin, bulleyakonitin A, 3-atsetilakonitin va guan-fu asosi A ni klinik amaliyotdagi antiaritmik yoki analgetik preparatlarga aylantirilgan.

O‘zbekistonda ilk bor diterpenoid alkaloidlarining tuzilishi va faolligini o‘rganish akademik S.Y. Yunusov rahbarligida O‘zR FA O‘simlik moddalari kimyosi institutida boshlangan. Yangi tuzilishdagi va yaxshi biologik faollikka ega ko‘plab diterpenoid alkaloidlari *Aconitum, Delphinium* va *Consolida* turlaridan ajratilgan. O‘MKI da akademik Sh.Sh. Sagdullaev rahbarligida lappakonitin alkaloidi asosida antiaritmik xossaga ega Allapinin preparatini yaratildi, u Rossiya va O‘zbekistonda ro‘yxatga olingan va 2007 yilda O‘zbekiston Fan va texnologiya Milliy mukofotiga sazovor bo‘lgan.

Aconitum va *Delphinium* turkumiga mansub bo‘lgan o‘simliklarning ekstraktlari va alohida birikmalarining farmakologik faolligi keng qamrovli bo‘lib, hozirga qadar to‘liq o‘rganilmaganligi ushbu yo‘nalishda ilmiy amaliy tadqiqotlar olib borish qanchalik dolzarb ekanligini ko‘rsatadi.

Ushbu dissertatsiya ishi muallifi tomonidan Markaziy Osiyoda o‘suvchi *Aconitum* va *Delphinium* turkumiga mansub bo‘lgan o‘simliklarning diterpen alkaloidlari va boshqa biologik faol komponentlarini o‘rganish bo‘yicha olib borilayotgan tizimli tadqiqotlarning davomi hisoblanadi.

Dissertatsiya mavzusining dissertatsiya bajarilgan ilmiy tadqiqot muassasasining ilmiy-tadqiqot ishlari bilan bog‘liqligi. Dissertatsiya ishi Xitoy Fan va texnologiyalar vazirligining “Madaniy *Consolida sp.* o‘simligining C_{20}-diterpenoid alkaloidlari: ajratib olsih, tuzilishi, biologik xossalari” (№ 2016YFE0120700, 2017-2018) nomli Milliy asosiy tadqiqot va ishlanmalar dasturiga (Xitoy va O‘zbekiston hukumatlari o‘rtasidagi xalqaro ilmiy-texnikaviy innovatsion hamkorlik) muvofiq amalga oshirildi. “Analgetik va mahalliy anestetik ta’sirga ega

(faolliklari) yangi antiaritmik preparatlarni tadqiq qilish va ishlab chiqish” (№ 2021YFE0104000, 2021-2023); Xitoy Fan va texnologiyalar vazirligining “Yangi dori vositalari va innovatsion dori vositalarini tadqiq qilish bo‘yicha Xitoy-O‘zbekiston “Kamar va yo‘l” qo‘shma laboratoriyasini qurish” nomli Milliy asosiy tadqiqot va ishlanmalar dasturi (№ 2020YFE0205600, 2020-2023); Shinjon-Uyg‘ur Muxtor viloyati Fan va texnologiya boshqarmasining “Diterpenoid alkaloidlarini ajratish va tahlil qilish va ularning dori-darmonliligini o‘rganish” nomli Xalqaro fan va texnologiya hamkorlik loyihasi (№ 20166014, 2016-2018); Xitoy Milliy Tabiatshunoslik Fondining Yoshlar jamg‘armasi “LC-DAD-MS asosida ikkita Markaziy Osiyoga xos bo‘lgan o‘simliklardan yangi diterpenoid alkaloidlarni kashf qilish va ularning biologik faolligini tadqiq qilish” (№ 32000277, 2021-2023) nomli loyihalari doirasida bajarilgan.

Tadqiqotning maqsadi. Markaziy Osiyoda o‘sadigan *Aconitum* va *Delphinium* turkumlariga mansub 7 tur o‘simliklarning ikkilamchi metabolitlarini ajratib olish, kimyoviy tarkibi va tuzilishini aniqlash hamda ular asosida samarali dori vositalarini yaratishdan iborat.

Tadqiqotning vazifalari:

1. *Aconitum* va *Delphinium* turkumiga mansub o‘simlik turlari xom ashyolarini turli organik erituvchilar yordamida ekstraksiya qilish va fraksiyalarga ajratish, alkaloidlar yig‘indisini ajratib olish;
2. Yuqoridagi o‘simliklardan olingan alkaloidlar yig‘indisidan sof birikmalarni ajratib olish va tozalash;
3. Ajratilgan birikmalarning birlamchi tuzilishi va yangi birikmalarning absolyut konfiguratsiyasini aniqlash;
4. Individual birikmalarining biologik ta’sirini, shu jumladan, antiaritmik, ion kanallarini ingibirlovchi, og‘riq qoldiruvchi, o‘smaga qarshi va mikroblarga qarshi faolliklarini baholash;
5. *Delphinium naviculare var. lasiocarpum* tarkibidagi lappakonitin miqdorini aniqlash;
6. Allapinin substansiyasidagi aralashmalarni ajratish jarayonini ishlab chiqish.

Tadqiqotning ob’ekti sifatida *Aconitum* va *Delphinium* turkumiga oid 7 ta tur o‘simlik turlari tanlangan: *Aconitum barbatum* var. *puberulum* Ledeb, *Aconitum smirnovii* Steinb, *Aconitum sinchiangense* W. T. Wang, *Delphinium pseudoaemulans* C. Y. Yang et B. Wang, *Delphinium naviculare* var. *lasiocarpum* W. T. Wang, *Delphinium aemulans* Navski, *Delphinium iliense* Huth o‘simliklari va Allapinin substansiyasi hisoblanadi.

Tadqiqotning predmeti. Markaziy Osiyoda o‘sadigan *Aconitum* va *Delphinium* turlarining diterpenoid alkaloidlari va boshqa komponentlari va ularning biologik faolliklari; Allapinin substansiyasi aralashmalaridan iborat.

Tadqiqotning usullari. Tadqiqotlar jarayonida texnologik (erituvchi yordamida ekstraksiya, dekompression konsentrlash, xromatografik ajratish, spektral tahlil), xromatografik (silika gel, sefadeks LH-20 va ODS kolonkali xromatografiya, Flesh, YuQX, YuSSX), fizik-kimyoviy va spektral tahlil (UB, IQ, Optik burilish, ESI-MS, 1D va 2D YaMR, experimental va hisoblash ESD) usullaridan foydalanildi. Antiaritmik faollikni aniqlashda aritmiya modeli, analgetik faollikni sinash uchun *in*

vivo modeli, hEGR va CaV3.1 kanallari ion kanallarini ingibirlash faolligini aniqlashda, o‘smaga qarshi faollikni (sitotoksiklikni) tekshirish uchun MTT (3-(4,5-dimetiltiazol-2-il)2,5-difeniltetrazoliy bromid) usuli, mikroblarga qarshi faollikni aniqlash uchun agar qudug‘ida diffuziya usuli qo‘llanildi.

Tadqiqotning ilmiy yangiligi quyidagilardan iborat:

birinchi marta Markaziy Osiyoda o‘sadigan *Aconitum* va *Delphinium* turkumining yetti turdagi o‘simliklari tarkibidan jami 176 ta birikma, shu jumladan, 26 ta yangi va 107 ta ma’lum diterpenoid alkaloidlar, shuningdek, 43 ta boshqa sinf birikmalari ajratilgan;

ajratib olingan diterpenoid alkaloidlarining fizikaviy va kimyoviy xossalari hamda, antiaritmik, analgetik, o‘smaga qarshi va mikroblarga qarshi biologik faolligi tizimli ravishda tadqiq qilingan;

ilk bor *Aconitum barbatum var. puberulum* (N-acetylsepaconitin va N-deacetyllappaconitin) va *Delphinium iliense* (Sinchianidin C va D) o‘simliklari tarkibidan yangi birikmalar ajratib olingan;

Aconitum barbatum var. puberulum dan C20-diterpenoid alkaloidlarining yangi uglerod skeletli vakili barpuberudin (AB-1), qayta guruhlangan yangi C18-diterpenoid alkaloidlari barpubeninlar A-B (AB-6 va AB-7) ilk bora aniqlangan;

birinchi marotaba *Delphinium naviculare var. lasiocarpum* o‘simligining kimyoviy tarkibi tadqiq qilingan va lappakonitin mavjudligi aniqlangan;

ilk marotaba *Aconitum smirnovii* o‘simligidan ajratilgan smirnotin A ning antiaritmik faolligi, shuningdek, *Delphinium iliense* o‘simligidan ajratib olingan sinchianidin C va D larining analgetik ta’sir ko‘rsatishi isbotlangan;

birinchi marta yarim-preparativ YuSSX va preparativ YuSSX texnologiyalarini birlashtirilgan holda foydalanib, Allapinnin substansiyasidan oltita standart alkaloidlar ajratilgan, bu esa Allapinin substansiyasi sifatini nazorat qilishda tozalik standartlarini ta’minlash imkonini bergan.

Tadqiqotning amaliy natijalari quyidagilardan iborat:

Aconitum barbatum var. *puberulum* dan ajratilgan *N*-deasetillappakonitin va *N*-asetilsepakonitin sezilarli antiaritmik faollik ko‘rsatgan, *Aconitum barbatum* var. *puberulum* dan ajratilgan sepakonitin va *Aconitum smirnovii* dan ajratilgan smirnotin A o‘rtacha antiaritmik faollikni ko‘rsatgan. Antiaritmikning dastlabki tuzilish-faollik munosabatlari ushbu tadqiqot natijalari va adabiyot ma’lumotlari asosida muhokama qilingan. Bu topilmalar endemik dorivor o‘simlik resurslarini barqaror rivojlantirish va ulardan foydalanishga yordam beradi va tabiiy mahsulotlardan olingan yangi dori nomzodlarini klinika-oldi baholash zaruratini tasdiqlaydi.

Delphinium iliense-dan ajratilgan sinchianidin C va D lar zaharli bo‘lmagan 5 mg/kg dozada mos ravishda 78.16% va 72.54% burishishni kamaytirish bilan potensial og‘riq qoldiruvchi ta’sir ko‘rsatishi aniqlangan. *Delphinium iliense* dan diterpenoid alkaloidlarini tayyorlash usuli va ularni potensial analgetik sifatida qo‘llash mumkinligi ishlab chiqilgan.

Delphinium aemulans dan diterpenoid alkaloidlarini tayyorlash usuli va ularning kuchlanish bilan bog‘liq kaliy kanali oqimlarini (IKv) ingibirlovchi potensiali ishlab chiqilgan. *Delphinium pseudoaemulans* dan diterpenoid alkaloidlarini tayyorlash usuli va ularning potensial o‘smaga qarshi qo‘llanilishi ishlab chiqilgan.

Allapinin substansiyasidan oltita standart alkaloidlar muvaffaqiyatli ajratildi va ajratish usullari ishlab chiqildi, bu Allapinin substansiyasining sifatini nazorat qilishda tozalik standartlarini ta’minlash uchun ishonchli yondashuvni ta’minlaydi.

D. naviculare var. *lasiocarpum* o‘simligida lappakonitin (0.25%) borligi topilgan bo‘lib, bu lappakonitinning yangi potensial zaxira manbasini ta’minlagan.

Tadqiqot natijalarining ishonchliligi xromatografik (silikagel, sefadeks LH-20 va ODS kolonnali xromatografiya, Flash, YuQX, YuSSX va PYuSSX), texnologik (erituvchi ekstraktsiya, dekompressiya kontsentratsiyasi, xromatografik ajratish va spektral tahlil), fizik-kimyoviy va spektral analitik (UB, IQ, Optik aylanish, ESI-MS, 1D, 2D YaMR) va eksperimental hisoblash, va hisoblash usullari hamda biologik usullarni qo‘llanganligi bilan isbotlandi. Natijalarning haqqoniyligi ularning xalqaro va respublika miqyosidagi ilimiy konferensiyalarda muhokama qilinganligi hamda taqriz qilinuvchi xorijiy va mahalliy ilmiy nashrlarda chop etganligi, Xitoyning Shinjon va Qinghai provinsiyalarida lappakonitinni ishlab chiqarish uchun xom ashyo manbasi sifatida foydalanish bilan izohlanadi.

Tadqiqot natijalarining ilmiy va amaliy ahamiyati. Tadqiqot natijalarining ilmiy ahamiyati shundan iboratki, Markaziy Osiyo hududida o‘suvchi *Aconitum* va *Delphinium* turkumi o‘simliklari yer ustki qismidan tabiiy yangi diterpen alkaloidlari ajratilganligi va ularning kimyoviy tuzilishi aniqlanganligi tabiiy birikmalar kimyosini boyitishi bilan izohlanadi. Jami 176 ta birikma, shu jumladan 26 ta yangi va 107 ta ma’lum bo‘lgan diterpenoid alkaloidlar, shuningdek, 43 ta boshqa birikmalar ajratilgan. Ularning strukturalari spektroskopik tahlillar (HR-ESI-MS, 1D NMR va 2D NMR) va adabiyotda keltirilgan ma'lumotlar bilan taqqoslash orqali aniqlandi, yangi birikmalarning mutlaq konfiguratsiyasi esa kvant ECD hisobi bilan aniqlandi. Aconitum barbatum var. puberulum dan ajratilgan barpuberudin C_{20}-diterpenoid alkaloid uglerod skeletiga ega bo‘lsa, barpubeninlar A-B qayta guruhlangan birinchi tipdagi C_{18}-diterpenoid alkaloidlari hisoblanadi. Ushbu uchta birikma biogenezining ehtimoliy yo‘llari taklif qilingan. Monomer birikmalarining biologik faolligi, jumladan, antiaritmik, analgetik, ion kanallarini ingibirlovchi faolligi, sitotoksikligi va mikroblarga qarshi faolligi baholangan. Tadqiqot natijalari va adabiyot ma'lumotlariga ko'ra, antiaritmik va og'riq qoldiruvchi vositalarning dastlabki tuzilish-faollik munosabatlari muhokama qilingan. *Aconitum barbatum* var. *puberulum* va *Delphinium iliense* o‘simliklaridan olingan *N*-atsetilsepaconitin va *N*-deatsetillappaconitin, Sinchianidin C va D lar farmakologik tekshiruvlar natijasida antiaritmik, analgetik xususiyatga ega vositalar yaratish uchun asos bo‘lishi mumkinligi bilan izohlanadi.

Tadqiqot natijalarining amaliy ahamiyati shundaki, lappakonitin Delphinium naviculare var. lasiokarpum butun o'simlikda 0,25% ni tashkil qiladi, o‘simlik lappakonitinning manbai ekanligi aniqlangan. Allapinin substansiyasi tarkibidagi oltita alkaloid ajratilib, standart sifatida foydalanishga tavsiya etildi. Ushbu tadqiqot Markaziy Osiyodagi Aconitum va Delphinium turlarining fitokimyoviy va farmakologik tadqiqotlarini rivojlantiradi va mintaqani biofaol tabiiy moddalar uchun muhim manba sifatida joylashtiradi. Strukturaviy kashfiyotlar, biofaollik profili va barqaror manbalarni rivojlantirish integratsiyasi kelajakda diterpenoid alkaloidlarga asoslangan terapevtik vositalar uchun mustahkam poydevor yaratadi.

Tadqiqot natijalarining joriy qilinishi. “Markaziy Osiyoda o‘sadigan Aconitum va Delphinium turkum o‘simliklarining diterpenoid alkaloidlari va ularning biologik faolligini o‘rganish” bo‘yicha olib borilgan tadqiqotlarning natijalari asosida:

Delphinium pseudoaemulans o‘simligi diterpenoid alkaloidlarini ajratish va tozalash, shuningdek, ularning in vitro inson saratoni A549 va HeLa hujayralariga sitotoksikligi natijalari asosida o‘smaga qarshi vosita yaratish ixtirosiga Xitoy Xalq respublikasi patenti (№ ZL201810714295.7, 2018 yil) olingan. Natijada o‘simlik alkaloidlari asosida ekologik toza, samarali dori vositasi yaratish imkonini bergan;

Delphinium aemulans o‘simligi diterpenoid alkaloidlari asosida kaliy kanali (IKv) toklarini ingibirlash ixtirosi uchun Xitoy Xalq respublikasi patenti olingan (№ 2024100199358, 2024 y). Natijada o‘simlik alkaloidlari asosida kaliy kanalini ingibirlovchi yangi vosita yaratish imkonini bergan;

Delphinium iliense Huth osimligi diterpenoid alkaloidlaridan potensial analgetik vosita ishlab chiqish ixtirosiga Xitoy Xalq respublikasi patenti olingan (№ 2025103304327, 2025 y). Natijada o‘simlik diterpenoid alkaloidlari asosida samarali analgetik vositalar yaratish imkonini bergan;

Shinjon Shafei Ya Biological Technology Co., Ltd (Xitoy X.R.) va Xitoy Fanlar Akademiyasi Shinjon Fizika va kimyo texnika instituti (XTIPC) bilan xamkorlik bitimiga asosan ko‘p miqdorda lappakonitin ishlab chiqarish uchun Delphinium naviculare var. lasiocarpum o‘simligi xomashyosi bilan ta’minlashni kafolatlab Xitoyning Shinjon va Sinxay viloyatlarida madaniylashtirish bo‘yicha tadqiqot ishlarini boshlagan (Xitoy Xalq Respublikasi Shinjon Shafei Ya Biological Technology Co., Ltd ma’lumotnomasi15.05.2025y). Natijada o‘simlik diterpenoid alkaloidlari asosida samarali dori vositasi islab chiqarish uchun xomashyo bilan ta’minlash kafolatlangan;

Allapinin substansiyasininig farmakologik faol qo‘shimchasi (FFQ) sifatini nazorat qilish uchun O‘simlik moddalari kimyosi institutining GMP korxonasida tozalik standartlari sifatida ajratilgan to‘rtta birikmadan foydalanilgan (O‘simlik moddalari kimyosi institutining 23.06.2025y., 01-02/499-son malumotnomasi). Natijada Allapinin substansiyasini ishlab chiqarish sifatini nazorat qilish tizimini yaxshilash, me’yoriy hujjatlarga muvofiqligini ta’minlash va klinik sharoitlarda qo‘llashni kengaytirish imkonini bergan.

Tadqiqot natijalarining aprobatsiyasi. Mazkur tadqiqot ishi natijalari 7 ta, jumladan 4 ta halqaro va 3 ta Respublika ilmiy-amaliy anjumanlarida ma’ruza qilingan va muhokamadan o‘tkazilgan.

Tadqiqot natijalarining e’lon qilinganligi. Dissertatsiya mavzusi bo‘yicha 24 ta ilmiy ish chop etilgan, shulardan, O‘zbekiston Respublikasi Oliy ta’lim, fan va innovatsiyalar vazirligi huzuridagi OAK ning kimyo fanlari doktori (DSc) dissertatsiyalarining asosiy ilmiy natijalarini chop etishga tavsiya etilgan ilmiy nashrlarida 14 ta maqola xalqaro jurnallarda nashr etilgan va 3 ta Xitoy Xalq Respublikasi patenti olingan.

Dissertatsiyaning tuzilishi va hajmi. Dissertatsiya tarkibi kirish, uchta bob, xulosalar, foydalanilgan adabiyotlar ro‘yxati va ilovalardan iborat. Dissertatsiyaning hajmi 229 betni tashkil etadi.

DISSERTATSIYANING ASOSIY MAZMUNI

Kirish qismida dissertatsiya mavzusining dolzarbligi va zaruriyligi asoslangan, maqsad va vazifalar, tadqiqot ob'ektlari va predmetlari ifodalangan, tadqiqotning Xitoy va O‘zbekiston fan va texnologiyalarni rivojlantirishning ustuvor yo‘nalishlariga mosligi ko‘rsatilgan, tadqiqotning ilmiy yangiligi va amaliy natijalari bayon qilingan, olingan natijalarning ishonchliligi asoslangan, nazariy va amaliy ahamiyati ochib berilgan, tadqiqot natijalarining amaliyotga joriy etish istiqbollari bo‘yicha xulosa qilingan hamda chop etilgan patentlar va maqolalar va dissertatsiyaning tuzilishi bo‘yicha ma'lumotlar keltirilgan.

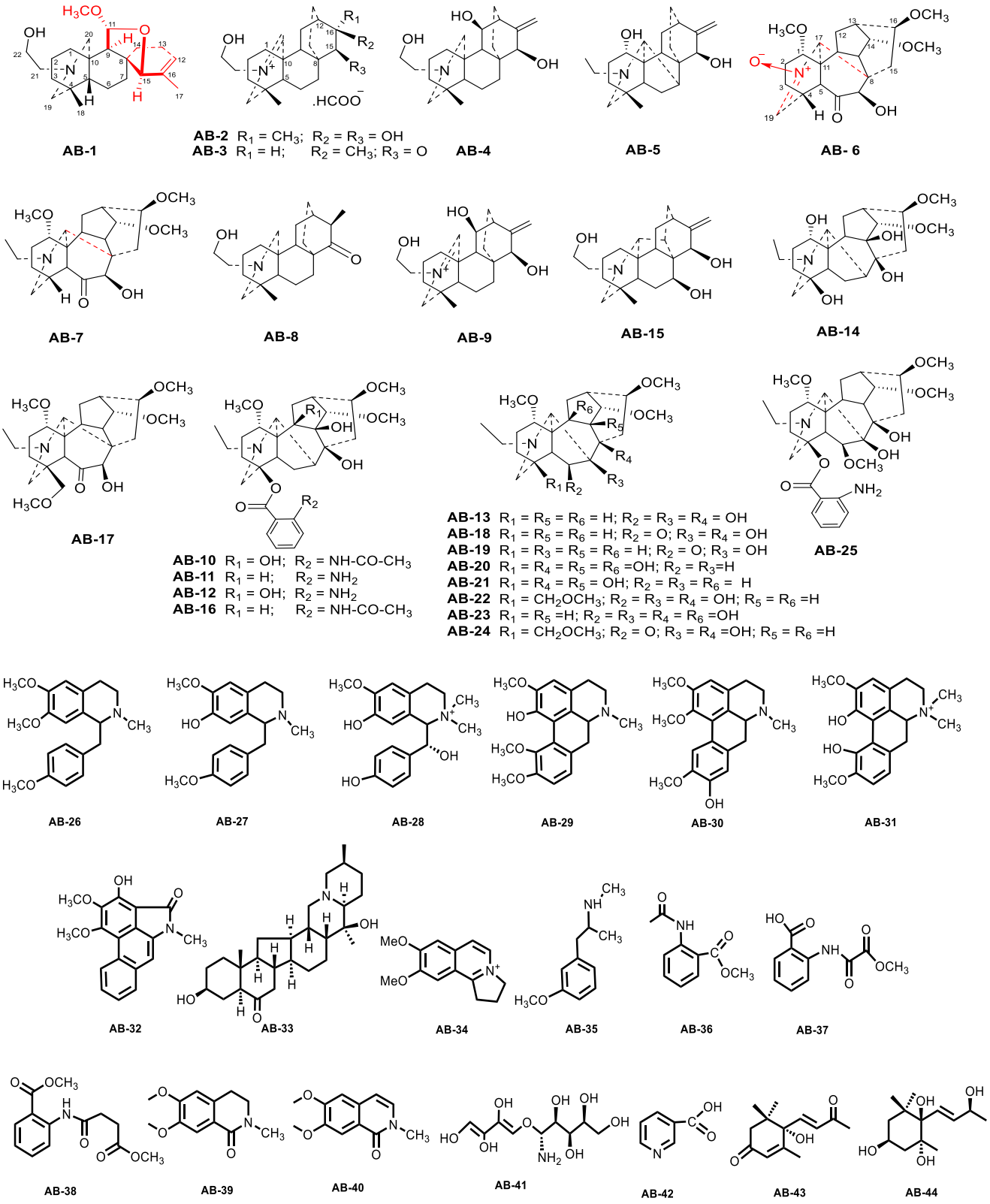
Dissertatsiyaning **"*Aconitum* va *Delphinium* turkum o‘simliklari diterpen alkaloidlari sharhi"** deb nomlangan **birinchi bobida** adabiyotlar tahlili keltirilgan. Diterpenoid alkaloidlarning klassifikatsiyasi, tuzilish xususiyatlari, biologik faollik xususiyatlari, struktura-faollik munosabatlari va amaliy qo‘llash imkoniyatlari haqida so‘z yuritilgan. Shuningdek, O‘zbekiston va Xitoyning Shinjon viloyatida yetishtiriladigan *Aconitum* va *Delphinium* turkumlari ham o‘rganilib, umumlashtirilgan.

Dissertatsiyaning "**Markaziy Osiyoda o‘sadigan *Aconitum* va *Delphinium* turkumlaridan kimyoviy birikmalarni ajratib olish, tozalash va biofaolligini tekshirish jarayonlari (Materiallar va usullar)**" deb nomlangan **ikkinchi bobida** umumiy tajribaviy amaliyotlar, jumladan *Aconitum barbatum* var. *puberulum*, *Aconitum smirnovii*, *Aconitum sinchiangense*, *Delphinium pseudoaemulans*, *Delphinium naviculare* var. *lasiocarpum*, *Delphinium aemulans* va *Delphinium iliense* o‘simliklaridan kimyoviy birikmalarni ajratib olish, tozalash va biologik faolligini sinovdan o‘tkazish jarayonlari; *Delphinium naviculare* var. *lasiocarpum* dagi lappokonitin miqdorini aniqlash; shuningdek, Allapinin substansiyasidan notoza qo‘shimchalarni ajratish va tozalash keltirilgan. Mazkur tadqiqotda texnologik (erituvchili ekstraksiya, decompression konsentrlash, xromatografik ajratish, spekt tahlillari), xromatografik (silika gel, sefadeks LH-20 va ODS kolonkali xromatografiya, Flesh, YuQX, YuSSC) usullardan foydalanilgan.

Dissertatsiyaning "**Natijalar va ularning muhokamasi (dissertatsiyaning asosiy mazmuni)**" deb nomlangan uchinchi bobida *Aconitum barbatum* var. *puberulum*, *Aconitum smirnovii*, *Aconitum sinchiangense*, *Delphinium pseudoaemulans*, *Delphinium naviculare* var. *lasiocarpum*, *Delphinium aemulans* va *Delphinium iliense* o‘simliklaridan kimyoviy birikmalarni ajratish, tozalash va biologik sinovlardan o‘tkazishda olingan natijalar muhokama qilingan; *Delphinium naviculare* var. *lasiocarpum* tarkibidagi lappakonitin miqdorini aniqlash; shuningdek, Allapinin substansiyasidan qo‘shimchalarni ajratish va tozalash ishlari olib borilgan. Mazkur tadqiqotda fizik-kimyoviy va spektral tahlil (UB, IQ, Optik burilish, ESI-MS, 1D va 2D YaMR, eksperimental va hisoblash ESD) usullari qo‘llanilgan. Antiaritmik faollikni aniqlash uchun akonitin tomonidan qo‘zg‘atilib behush qilingan sichqonlarning aritmiya modeli ishlatilgan; analgetik faollikni sinash uchun sirka kislota bilan qo‘zg‘atadigan sichqonlarning burishishining *in vivo* modeli ishlatilgan; hEGR va CaV3.1 kanallari ion kanallarini ingibirlash faolligi uchun ishlatilgan; 3-(4,5-dimetiltiazol-2-il)2,5-difeniltetrazoliy bromid (MTT) usuli o‘smaga qarshi

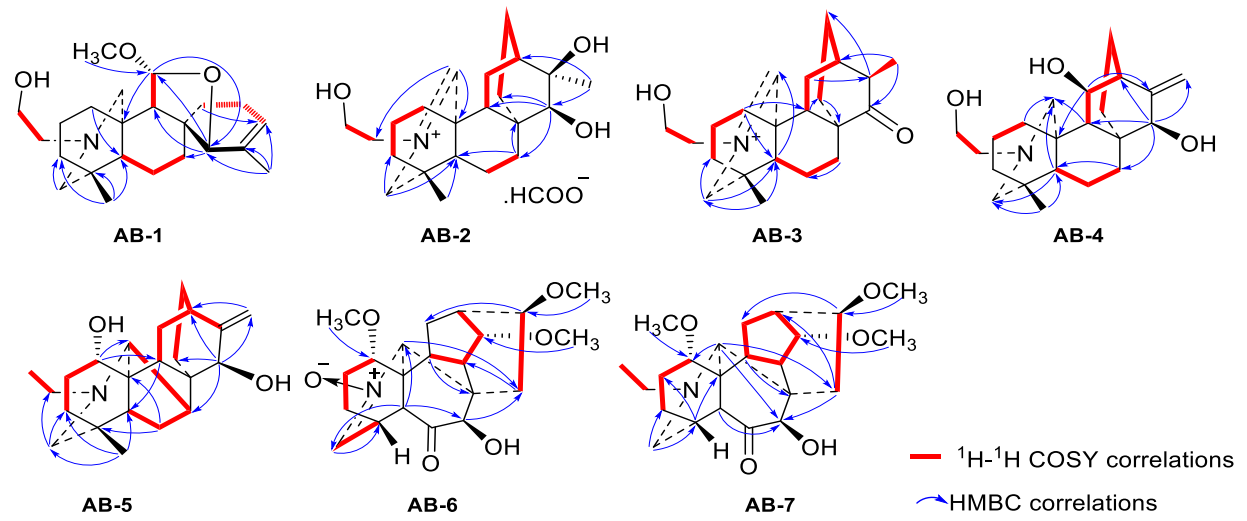
faollikni (sitotoksiklikni) tekshirish uchun, mikroblarga qarshi faollikni aniqlash uchun agar quduq diffuziya usuli qo‘llanilgan.

***Aconitum barbatum* var. *puberulum* tarkibidagi kimyoviy birikmalar tadqiqoti.** Markaziy Osiyo o‘simlik manbalaridan noyob tuzilish va kuchli biofaollikka ega birikmalarni topish bo‘yicha uzluksiz tadqiqotlar doirasida O‘rta Osiyodan to‘plangan *A. barbatum* var. *puberulum* o‘simligini fitokimyoviy tekshirish o‘tkazildi. Natijada ilgari adabiyotlarda ma’lum bo‘lmagan ettita diterpenoid alkaloidlari: barpuberudin (**AB-1**), barpubezinlar A-D (**AB-2~AB-5**), barpubeninlar A-B (**AB-6~AB-7**), va 37ta ma’lum birikmalar, 15-Ketotetrogidroatizin (**AB-8**), leukoztomin A (**AB-9**), *N*-atcetilsepakonitin (**AB-10**), *N*-deatcetillappakonitin (**AB-11**), sepakonitin (**AB-12**), akoseptisin (**AB-13**), lappakonidin (**AB-14**), trabzonin (**AB-15**), lappakonitin (**AB-16**), puberulin C (**AB-17**), leukostin (**AB-18**), leukonin (**AB-19**), sepakonitin aminospirti (**AB-20**), lappakonin (**AB-21**), akozanin (**AB-22**), akoseptrin (**AB-23**), 6-degidroakozanin (**AB-24**), antranoillikoktonin (**AB-25**), O-metilarmepavin (**AB-26**), (S)-6-Metoksi-1-(4-metoksibenzil)-2-metil-1,2,3,4-tetragidroizoxinolin-7-ol (**AB-27**), (+)-(1R,laR)-la-gidroksimagnokurarin (**AB-28**), (6R,6aS,P)-(+)-koridin (**AB-29**), (+)-*N*-metillaurotetanin (**AB-30**), magnoflorin (**AB-31**), 3-gidroksi-1,2-dimetoksi-5-metil-5H-dibenzoindol-4-on (**AB-32**), imperialin (**AB-33**), krispin B (**AB-34**), (S)-1-(3-Metoksifenil)-*N*-metilpropan-2-amin (**AB-35**), metil 2-(atsetamino)benzoat (**AB-36**), 2-karboksioksanilin kislotasi metil efiri (**AB-37**), 4-[2-(metoksikarbonil) anilin]-4-oksobutan kislota metil efiri (**AB-38**), *N*-metilkoridaldin (**AB-39**), *N*-metil-6,7-dimetoksiizoqinolon (**AB-40**), (5*S*,6*R*,7*S*,8*R*)-5-amino-(2Z,4Z)-1,2,3-trigubuta-2,4-dieniloksi-pentan-6,7,8,9-tetraol (**AB-41**), nicotinic acid (**AB-42**), S(+)-dehydrovomifoliol (**AB-43**) va megastigman (**AB-44**), va 19ta ma’lum diterpenoid alkaloidlar ajratildi. Ularning tuzilishi (**1-rasm**) keng qamrovli spektroskopik HR-ESIMS va 1D va 2D NMR ma’lumotlar tahlili asosida aniqlandi, shu jumladan (**2-rasm** va **3-rasm**).

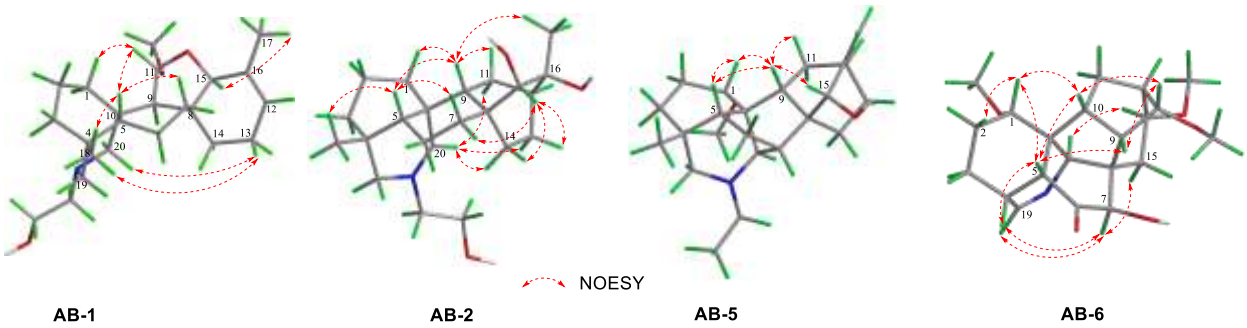


1-Rasm. *Aconitum barbatum* var. *puberulum* o‘simligidan ajratilgan **AB-1**~**AB-44** birikmalar tuzilishi

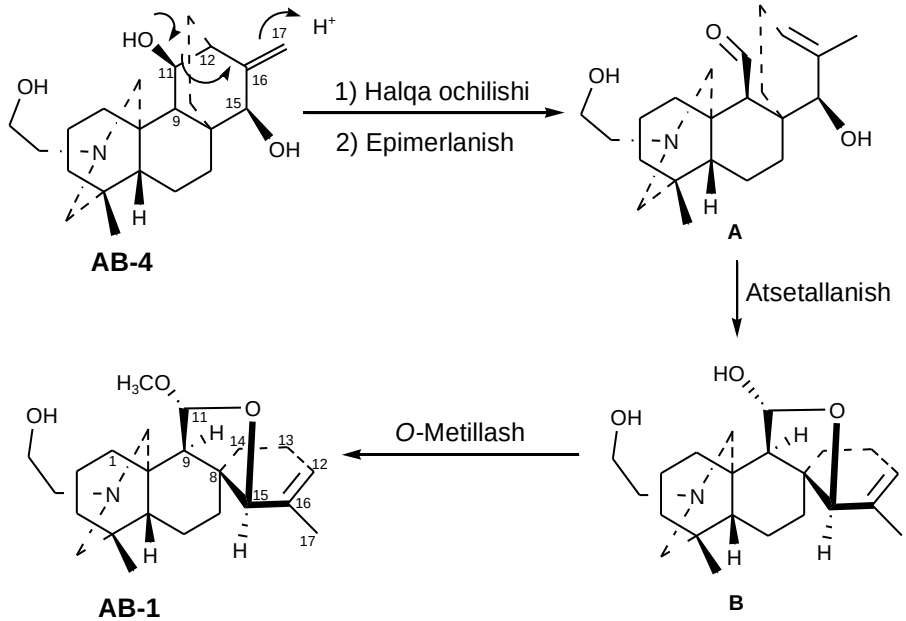
Barpuberudin (**AB-1**) yangi turdagi C_{20}-diterpenoid alkaloidi uglerod skeletiga ega bo‘lsa, A-B barpubeninlar (**AB-6 ~ AB-7**) esa qayta guruhlangan C_{18}-diterpenoid alkaloidlarilarning birinchi namunasi hisoblanadi. Barpuberudin va A-B barpubeninlar biogenezining ehtimoliy yo‘li muhokama qilindi (**4-rasm** va **5-rasm**).



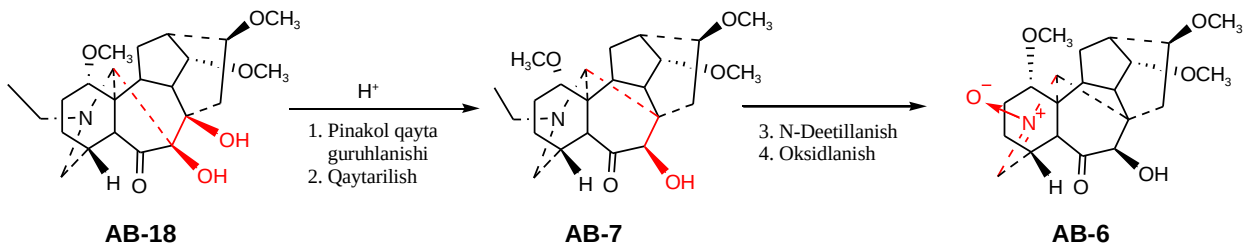
2-Rasm. AB-1~AB-7 birikmalarning asosiy HMBC va ^{1}H-^{1}H COSY korrelyatsiyalari



3-Rasm. AB-1, **AB-2**, **AB-5** va **AB-6** birikmalarining NOESY korrelyatsiyalari



4-Rasm. Barpuberudin (**AB-1**) biosintezining taxminiy yo‘li



5-Rasm. Barpubeninlar A-B (**AB-6~AB-7**) biosintezining taxminiy yo‘li

N-atsetilsepakonitin (**AB-10**) va *N*-deatsetillappakonitin (**AB-11**) akonitin bilan qo‘zg‘atilgan aritmiya sichqoncha modelida 8 mg/kg dozada sezilarli antiaritmik faollik ko‘rsatdi (**1-jadval**). Sepakonitininning (**AB-12**) ma’lum antiaritmik faolligi bor bo‘lsa-da, *N*-detasetillappakonitin (**AB-11**) dan sezilarli darajada zaif. Barpubenin B (**AB-7**), leukostomin A (**AB-9**) va trabzonin (**AB-15**) birikmalarini potensial antiaritmik birikmalar deb hisoblash mumkin emas. Ushbu tadqiqot adabiyotda keltirilgan antiaritmik tuzilishi - faollik munosabatini tasdiqladi: eng faollari C_{18}-diterpenoid alkaloidlari, masalan, lappakonitin. Ushbu birikmalarning umumiy xususiyati C-4 da atsetilantranil yoki antranil kislota fragmentining mavjudligi; C-1, C-14 va C-16 da metoksil guruhlari; va C-8 da gidroksi guruhi. Farqlar C-7, C-9 va C-10 da qo‘shimcha gidroksi guruhlari mavjudligidan iborat. C-6, C-7 va C-10 da gidroksi guruhlari, C-6 da metoksil guruhi va C-6 da atsetil guruhini kiritish orqali molekulaning keyingi o‘zgarishlari antiaritmik ta’sir darajasini sezilarli darajada kamaytiradi. Ko‘p ionli kanallarning ingibitorlari bo‘lgan diterpenoid alkaloidlar sababli ushbu funksional guruhlarning faollikka bevosita ta’sirini to‘liq aniqlash oson emas.

1-Jadval. **AB-7**, **AB-9**~**AB-12**, **AB-15** and **AB-16** birikmalarining antiaritmik faolligi

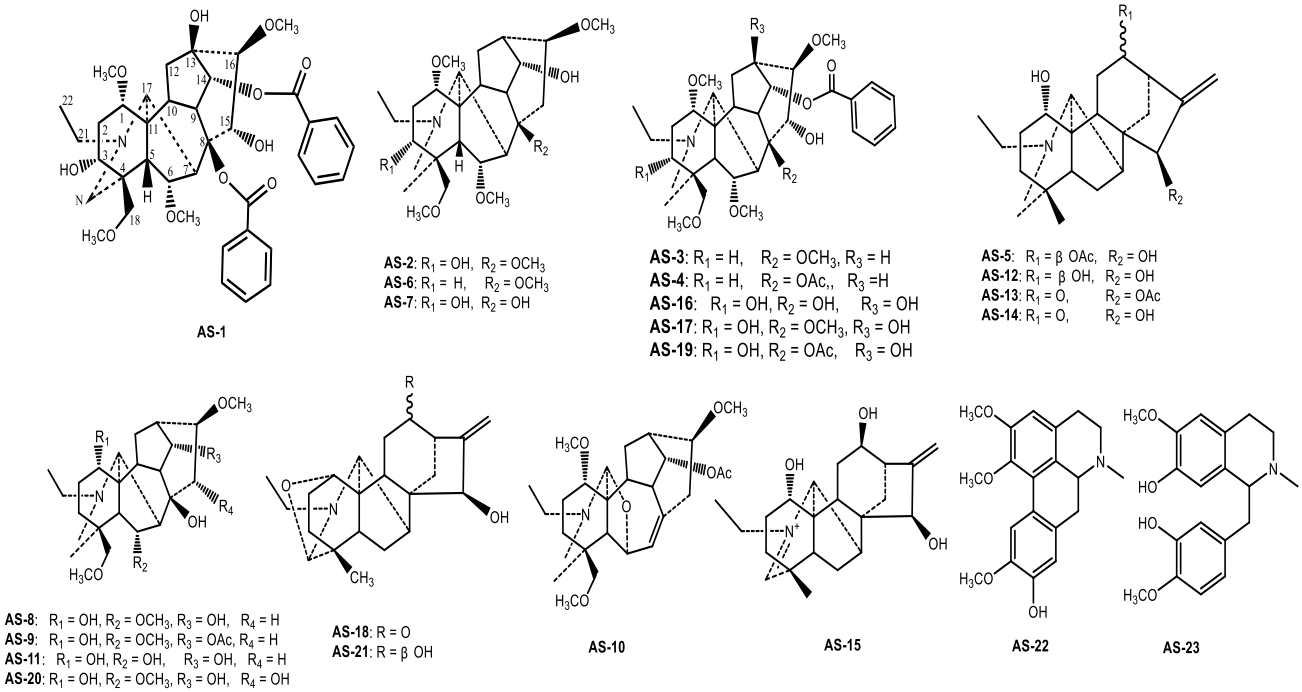
Namuna [a]	EKG o‘zgarishi uchun akonitin dozasi (μg/kg)				Akonitinning o‘lim dozasi (μg/kg)
	VP	VT	VFL	VFib	
Model guruhi	47.10±9.86	90.55 ±12.25	120.83 ±28.58	227.34 ±44.52	287.82 ±46.77
AB-16 Lappakonitin	68.89 ±11.35 [b]**	152.70 ±21.39**	239.98 ±39.69**	346.11 ±53.51**	395.82 ±44.96**
AB-7 Barpubenin B	44.79 ±9.66	134.10 ±6.74**	204.79 ±12.21**	261.89 ±25.42	325.91 ±23.56
AB-9 Leukostomin A	48.15 ±4.20	140.27 ±20.59**	228.04 ±38.83**	305.99 ±46.80*	328.12 ±23.33
AB-10 N-atcetilsepakonitin	93.57 ±16.71**	146.63 ±25.27**	242.86 ±60.24**	318.66 ±26.04**	371.29 ±42.11*
AB-11 N-deatcetillappakonitin	89.59 ±11.40**	183.47 ±26.57**	272.49 ±49.97**	331.26 ±35.92**	403.08 ±46.63**
AB-12 Sepakonitin	58.74 ±18.21	93.21 ±17.43	208.43 ±26.31**	295.93 ±65.47	339.84 ±54.54
AB-15 Trabzonin	45.73 ±12.17	132.65 ±23.36*	222.97 ±27.71**	315.05 ±41.32*	364.22 ±40.93

[a] Birikmalar 8 mg/kg dozada qo‘llanilgan, qo‘llash usuli 0.4 ml/20g qorin bo‘shlig‘iga yuborish. [b] ** P<0.01, * P<0.05, namuna guruhlari model guruhi bilan solishtirildi.

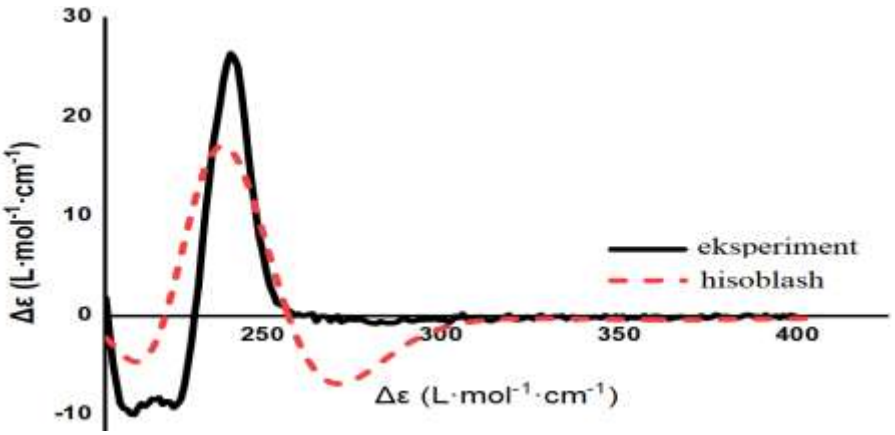
AB-30 birikmasi IC_{50} qiymati 13.69 μM bo‘lgan HeLa hujayra liniyalariga nisbatan kuchli sitotoksiklikni ko‘rsatdi, **AB-26** va **AB-31** birikmalari esa *S. aureus*ga qarshi kuchli ingibirlovchi faollik ko‘rsatdi. **AB-41** birikmasi *E. coli* va **AB-1**, **AB-7**, **AB-13**, **AB-25**, **AB-27**, **AB-29**, **AB-37**, **AB-38**, va **AB-41** birikmalari *S. aureus*ga qarshi o‘rtacha ingibirlovchi faollik ko‘rsatdi.

***Aconitum smirnovii* o’simligining kimyoviy birikmalari.** Ikkita yangi C_{19}-diterpenoid alkaloidlari, smirnotin A (**AS-1**) va smirnotin B (**AS-2**), shu bilan birga 21 ta ma’lum alkaloid, 14α-benzoiloksi-*N*-etil-15α-gidroksi-1α,6α,8β,16β,18-

tametoksiakonitan formiat (**AS-3**), pendulin formiat (**AS-4**), 12-atsetil-12-epi-napellin (**AS-5**), gomoxasmanin (**AS-6**), ezoxasmanin (**AS-7**), neolin (**AS-8**), bullatin C (14-atsetilneolin; **AS-9**), vilmorizin (**AS-10**), senbuzin A (**AS-11**), 12-epi-napellin (**AS-12**), 15-atsetilzongorin (**AS-13**), zongorin (**AS-14**), akonikarmixiniy A (**AS-15**), benzoilakonin (**AS-16**), 14-benzoil-8-O-metilakonin (**AS-17**), zongoramin (**AS-18**), akonitin (**AS-19**), 15*α*-gidroksineolin (**AS-20**), 12-epi-degidronapellin (**AS-21**), *N*-metillaurotetanin (**AS-22**) va retikulin (**AS-23**), Xitoy X.R.ning Shinjon-Uyg‘ur muxtor viloyati Oltoy prefekturasining Qinghe shahridan to‘plangan *A. smirnovii* ning yer ustki qismidan ajratildi. Ularning tuzilishi (**6-rasm**) spektroskopik (HR-ESI-MS, 1D va 2D NMR) tahlillar yordamida va adabiyot ma’lumotlari bilan solishtirish orqali aniqlandi. **AS-1** ning absolyut konfiguratsiyasi esa ESD qvant hisoblashlar asosida 1S, 3R, 4R, 5S, 6R, 7R, 8R, 9R, 10R, 11S, 13R, 14R, 16S, va 17R sifatida o‘rnatildi tasdiqlandi (**7-rasm**). Yuqorida keltirilgan barcha birikmalar mazkur o‘simlikdan birinchi marta ajratilgan.



6-Rasm. *Aconitum smirnovii* dan ajratilgan birikmalar tuzilishi



7-Rasm. AS-1 ning eksperimental va hisoblangan ESD spektri

Smirnotin A (**AS-1**) noyob diterpenoid alkaloid bo‘lib, ikkita benzoil guruhi saqlaydi va antiaritmik ta’sir ko‘rsatdi (**2-jadval**). Bu diterpenoid alkaloidlarning

antiaritmik tuzilishi va faolligi orasidagi bog‘liqlikni tasdiqladi, ya’ni C_{18} yoki C_{19}-diterpenoid alkaloidining ikkita aromatik murakkab efiri bitta efir yoki efir guruhi bo‘lmagan alkaloidga nisbatan yuqori faollik namoyon qiladi. Ammo shuni qayd etish lozimki, aromatik murakkab efir guruhining ortishi ularning zaharliligini oshirishi mumkin.

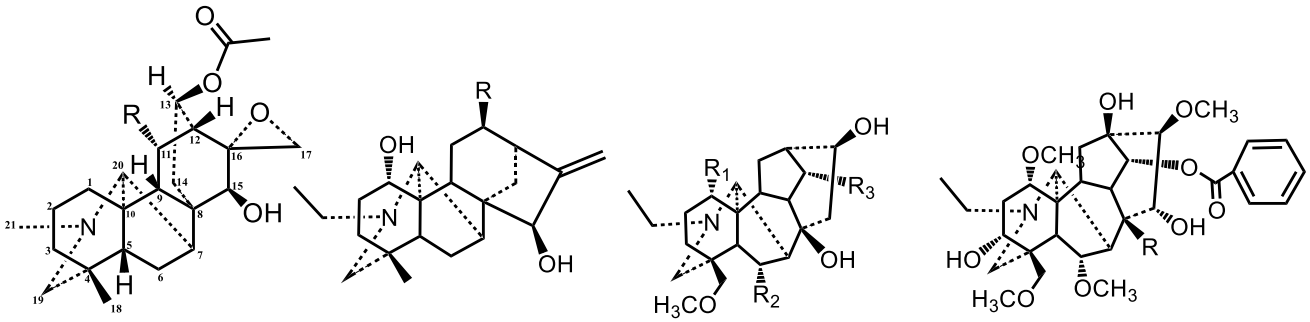
AS-1 ~ AS-5 uchun A549 va HeLa saraton hujayralari qatoriga nisbatan sezilarli sitotoksiklik kuzatilmadi. Ushbu ma’lumotlar diterpenoid alkaloidlarning tuzilishi-faollik munosabatlarini yanada aniqlashtirish uchun foydali bo‘ladi.

2-Jadval. **AS-1** ning EKG o‘zgarishi va sichqonlarda o‘lim uchun akonitin dozasiga ta’siri (x ±s, n = 6)

Guruhlar	Doza (mg/kg)	EKG o‘zgarish uchun Akonitin dozasi (μg/kg)				Akonitinning o‘lim dozasi (μg/kg)
		Ventrikulyar erta tug‘ilish	Ventrikulyar taxikardiya	Ventrikulyar chayqalish	Qorincha fibrilatsiyasi	
Nazorat		47.1 ±9.9	90.6 ±12.3	120.8 ±28.6	227.3 ±44.5	287.8 ±46.8
AS-1	8	46.9 ±10.7	128.5 ±25.3 *	234.3 ±35.5 **	321.8 ±51.2	396.1 ±60.3
	16	46.2 ±11.0	146.3 ±43.1	265.8 ±57.2 **	362.9 ±96.1*	413.6 ±95.9*

Eslatma: ** P < 0.01, * P < 0.05, test guruhi va nazorat guruhi o‘rtasidagi taqqoslash.

***Aconitum sinchiangense* ning kimyoviy tarkibi.** Yangi C_{20}-diterpenoid alkaloidi, sinxianin (**ASW-1**), sakkizta ma’lum diterpenoid alkaloidlar, uchta ma’lum C_{20}-diterpenoid alkaloidlar, 12-atsetil-12-epi-napellin (**ASW-2**), 12-epi-napellin (**ASW-3**) va zongorin (**ASW-8**), va beshta ma’lum C_{19}-diterpenoid alkaloidlar, neolin (**ASW-4**), talatizamin (**ASW-5**), 14-O-atseilzenbuzin A (**ASW-6**), benzoilakonin (**ASW-7**) va akonitin (**ASW-9**), Xitoy X.R.ning Shinjon, Yili viloyatining Gongliu shahridan yig'ilgan *A. sinchiangense* o‘simligidan ajratildi. Ularning tuzilishi (**8-rasm**) spektoskopik (HR-ESI-MS, 1D NMR va 2D NMR) tahllillar yordamida va adabiyot ma’lumotlari bilan solishtirish orqali aniqlandi. **ASW-1** - 16,17-epoksi guruhiga ega bo‘lgan noyob denudatin tipidagi C_{20}-diterpenoid alkaloid hisoblanadi. **ASW-2 ~ ASW-7** birikmalari ushbu o‘simlikdan birinchi marta ajratilgan.



ASW- 1 R = OH
ASW-1a R = H

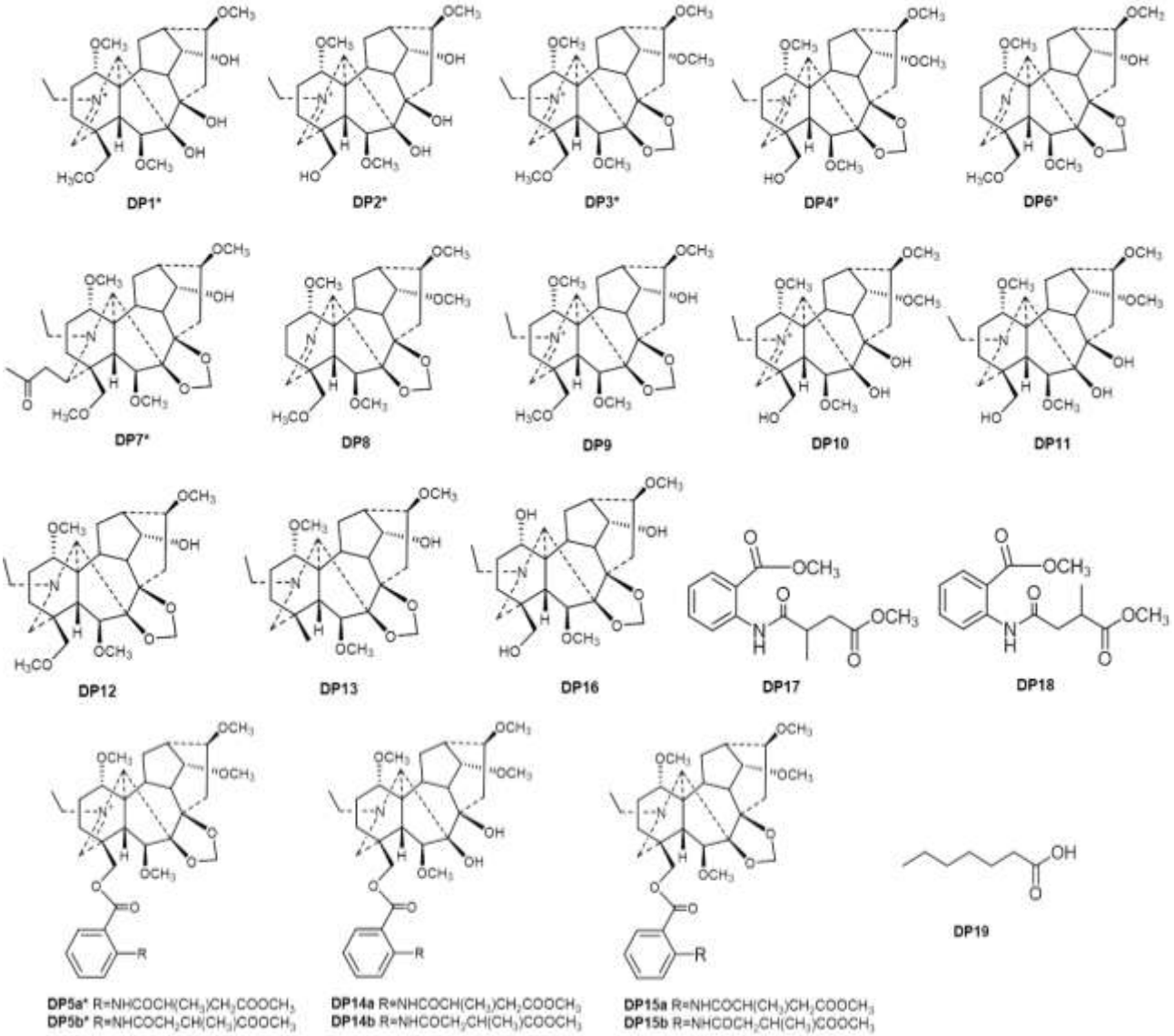
ASW-2 R = OAc **ASW-4** R_1 = OH R_2 = OCH_3 R_3 = OH
ASW-3 R = OH **ASW-5** R_1 = OCH_3 R_2 = H R_3 = OH
ASW-8 R = O **ASW-6** R_1 = OH R_2 = OH R_3 = OAc

ASW-7 R = OH
ASW-9 R = OAc

8-Rasm. ASW1~ASW9 birikmalar tuzilishi

***Delphinium pseudosemulans* ning kimyoviy tarkibini o‘rganish.** Sakkizta ilgari tavsiflanmagan likoktonin turi C_{19}-diterpenoid alkaloidlari, pseudofninlar A–D (**DP1-DP4**), pseudoreninlar A–B (**DP5a, DP5b**), pseudonidinlar A–B (**DP6-DP7**),

va o‘n bitta ma’um likoktonin tipidagi C_{19}-diterpenoid alkaloidlari, tianshanizin E (**DP8**), sharvufinin B (**DP9**), potanizin A (**DP10**), likoktonin (**DP11**), delbrulin (**DP12**), izondelfelin (**DP13**), delavainlar A–B (**DP14a, DP14b**), shavureninlar A–B (**DP15a, DP15b**), kampilotin (**DP16**), va uchta ma’lum boshqa birikmalar, metil 2-(4-metoksi-2-metil-4-oksobutanamid)benzoat (**DP17**), metil 2-(4-metoksi-3-metil-4-oksobutanamid)benzoat (**DP18**) va geptan kislota (**DP19**) Xitoy X.R Shinjon Uyg‘ur muxtor viloyatiga xos endemik tur *D. pseudosemulans* o‘simligidan ajratildi. Ularning tuzilishi (**9-rasm**) spektoskopik (HR-ESI-MS, 1D NMR va 2D NMR) tahllillar yordamida va adabiyot ma’lumotlari bilan solishtirish orqali aniqlandi. **DP-1 ~ DP-5** kamdan-kam uchraydigan C_{19}-diterpenoid alkaloidlari bo‘lib, iminiy spirtiga ega. **DP5 (DP5a** va **DP5b), DP14 (DP14a** va **DP14b)** va **DP15 (DP15a** va **DP15b)** birikmalari *Delphinium*da keng tarqalgan uch juft regioizomerik C_{19}-diterpenoid alkaloidlardir. Tekshirilgan barcha birikmalar sitotoksiklik ko‘rsatmadi. Adabiyot ma’lumotlari bilan birgalikda, C_{19}-diterpenoid alkaloidlarida likoktonin tipidagi birikmalarning sitotoksik faolligi akonitin turiga qaraganda zaifroq degan xulosaga kelish mumkin.



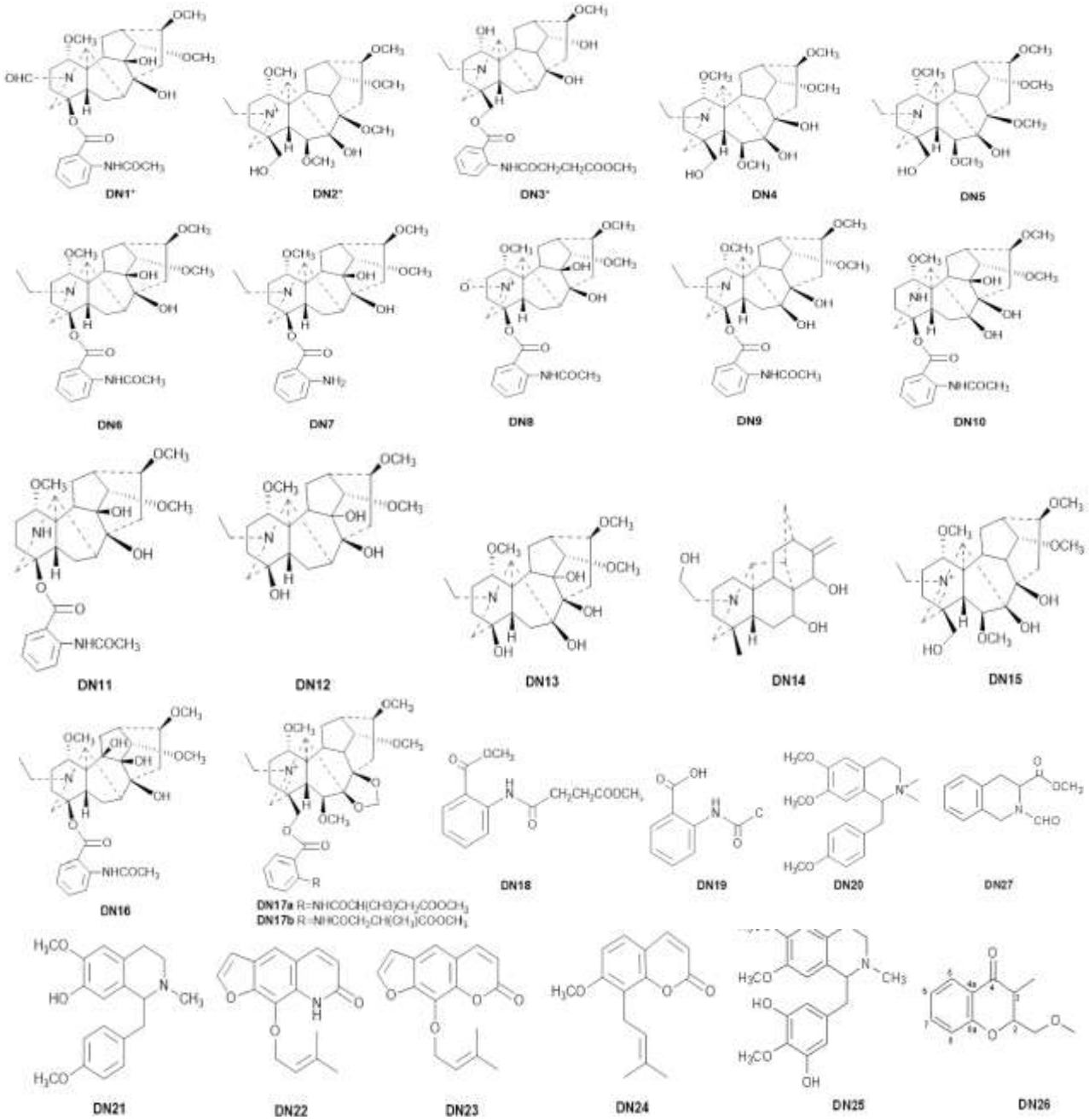
9-Rasm. DP1~DP19 birikmalar tuzilishi

***Delphinium naviculare* var. *lasiocarpum* ning kimyoviy birikmalarining tadqiqoti.** Uchta yangi diterpenoid alkaloidi, navikonin, navikulin va navikonitin (**DN1**-**DN3**), 15ta ma'lum diterpenoid alkaloid bilan birga, likoktonin (**DN4**), 8-O-Metil likoktonin **(DN5**), lappakonitin **(DN6**), *N*-deatsetillappakonitin **(DN7**), *N*-deetillappakonitin **(DN8**), izolappakonitin **(DN9**), sinomontanin F **(DN10**), sinomontanin A **(DN11**), lappakonin (**DN12**), ranakonin (**DN13**), trabzonin **(DN14**), potanizin A **(DN15**), *N*-atsetilsepakonitin **(DN16**) va pseudoreninlar A-B **(DN17a** va **DN17b**), 3ta benzil izoquinolin alkaloidlar, izoquinoliniy (**DN20**), 1,2,3,4-tetragidro-6-metoksi-1-[(4-metoksifenil)metil]-2-metil-7-izoquinolinol/7-isoquinolinol (**DN21**) va 2-metoksi-5-[(1,2,3,4-tetragidro-6,7-dimetoksi-2-metil-1-izoquinolinil)metil]-1,3-benzoldiol (**DN25**), 4 ta boshqa alkaloid, benzoy kislota 2-[(4-metoksi-1,4-dioksobutil)amino]-meti efiri **(DN18**), 2-atsetamidobenzoy kislota (**DN19**), giemalin/furo[3,2-*g*]quinolin-7(*8H*)-on,9-[(3-metil-2-buten-1-il)oksi] (**DN22**) va metil 2-formil-1,2,3,4-tetragidroizoquinolin-3-karboksilat (**DN27**), shuningdek, 3ta boshqa birikma, 8-izopenteniloksipsoralen (**DN23**), 7-metoksi-8-izopentenilkumarin (**DN24**) va 2*H*-1-benzopiran-2-on,3-(atsetiloksi)-3,4-digidro-,(3*R*) (**DN26**) *D. naviculare* var. *lasiocarpum* W. T. Wang o'simligidan ajratildi. Ularning tuzilishi (**10-rasm**) spektoskopik (HR-ESI-MS, 1D NMR va 2D NMR) tahllillar yordamida va adabiyot ma'lumotlari bilan solishtirish orqali aniqlandi.

Ajratib olingan diterpenoid alkaloidlar jami 3ta skelet va 5 ta subskelet turini, shu jumladan, 7ta lappakonitin tipidagi C_{18}-diterpenoid alkaloidini, 3ta ranakonitin tipidagi C_{18}-diterpenoid alkaloidini, 1ta akonitin tipidagi C_{19}-diterpenoid alkaloidini, 6ta likoktonin tipidagi C_{19}-diterpenoid alkaloid va 1ta getidin tipidagi C_{20}-diterpenoid alkaloidini o'z ichiga oladi.

Ajratilgan birikmalarning *in vitro* o'smaga sitotoksikligi MTT usuli bilan tekshirildi. Natijalar shuni ko'rsatdiki, bu birikmalar inson yo'g'on ichak saratoni HT-29 hujayrasi, ko'krak saratoni MDA-MB-231 hujayrasi va inson bachadon bo'yni saratoni HeLa hujayralarini ingibirlovchi faollikka ega emas. Antibakterial faollik skrining natijalari shuni ko'rsatdiki, faqat **DN24** birikmasi *Staphylococcus aureus*ga qarshi kuchsiz antibakterial faollik namoyon qildi. Qolgan birikmalar *Candida albicans*, *Escherich coli* va *Staphylococcus aureus*ga qarshi antibakterial faollikni ko'rsatmadi.

D. naviculare var. *lasiocarpum* tarkibidagi lappakonitin (**DN6**) miqdori YuSSC usulida aniqlandi. Natijalar *D. naviculare* var. *lasiocarpum* o'simligidagi lappakonitin miqdori 0.25% ekanligini ko'rsatdi. Diterpenoid alkaloid birikmalar vakili sifatida lappakonitin asosan *Aconitum* turlarida, jumladan, *Aconitum sinomontanum* da uchraydi va *Delphinium* turlarida juda kam uchraydi. Olingan natija *D. naviculare* var *lasiocarpum* lappakonitininng yangi zahira manbai sifatida ishlatilishi uchun nazariy asos yaratadi.

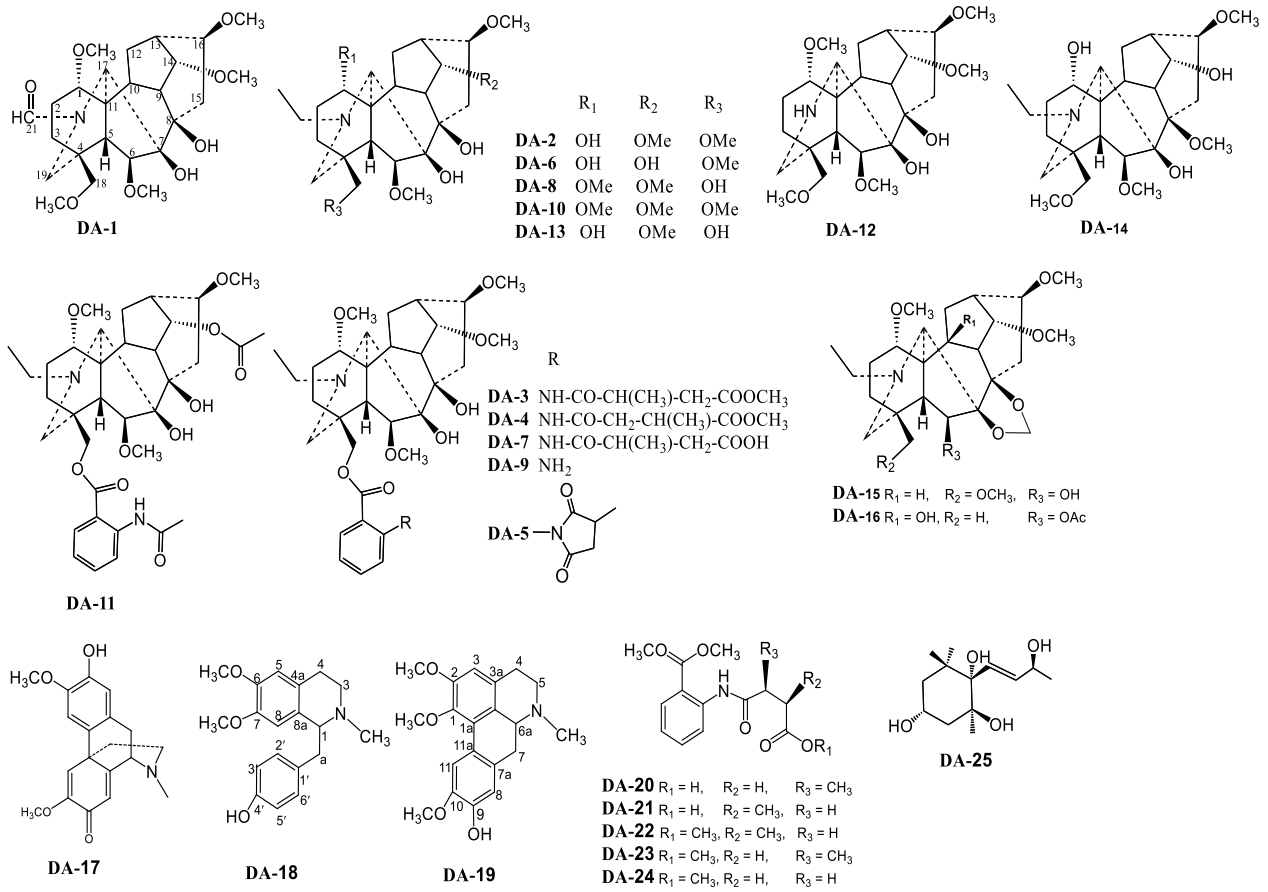


10-Rasm. DN1-DP27 birikmalar tuzilishi

***Delphinium aemulans* kimyoviy birikmalarining tadqiqoti.** Bitta yangi tabiiy tarqalgan likoktonin tipidagi C_{19}-diterpenoid alkaloid aemulansin (**DA-1**), 15ta ma'um C_{19}-diterpenoid alkaloidi, delsolin (**DA-2**), delavain A (**DA-3**), delavain B (**DA-4**), metillikakonitin (**DA-5**), delkozin (**DA-6**), shavurenzin (**DA-7**), likoktonin (**DA-8**), antranoillikoktonin (**DA-9**), delfatin (**DA-10**), ajadin (**DA-11**), *N*-deetildelfatin (**DA-12**), gigaktonin (**DA-13**), deltatsin (**DA-14**), delkorin (**DA-15**), deltalin (**DA-16**), 9ta boshqa birikma, (–)-pallidin (**DA-17**), armepavin (**DA-18**), (+)-*N*-Metillaurotetanin (**DA-19**), 4-[2-(metoksikarbonil)anilino]-3-metil-4-ooksbutan kislota (**DA-20**), 4-[2-metoksikarbonilanilino]-2-metil-4-oksobutan kislota (**DA-21**), 4-[2-(metoksikarbonil)anilino]-2-metil-4-oksobutan kislota metil efiri (**DA-22**), 4-[2-(metoksikarbonil)anilino]-3-metil-4-oksobutan kislota metil efiri (**DA-23**), 4-[2-(metoksikarbonil)anilino]-4-oksobutan kislota metil efiri (**DA-24**) va euscaphin B

(**DA-25**) bilan birga *D. aemulans* o‘simligidan ajratildi. Ularning tuzilishi (**11-rasm**) spektoskopik (HR-ESI-MS, 1D NMR va 2D NMR) tahllillar yordamida va adabiyot ma’lumotlari bilan solishtirish orqali aniqlandi.

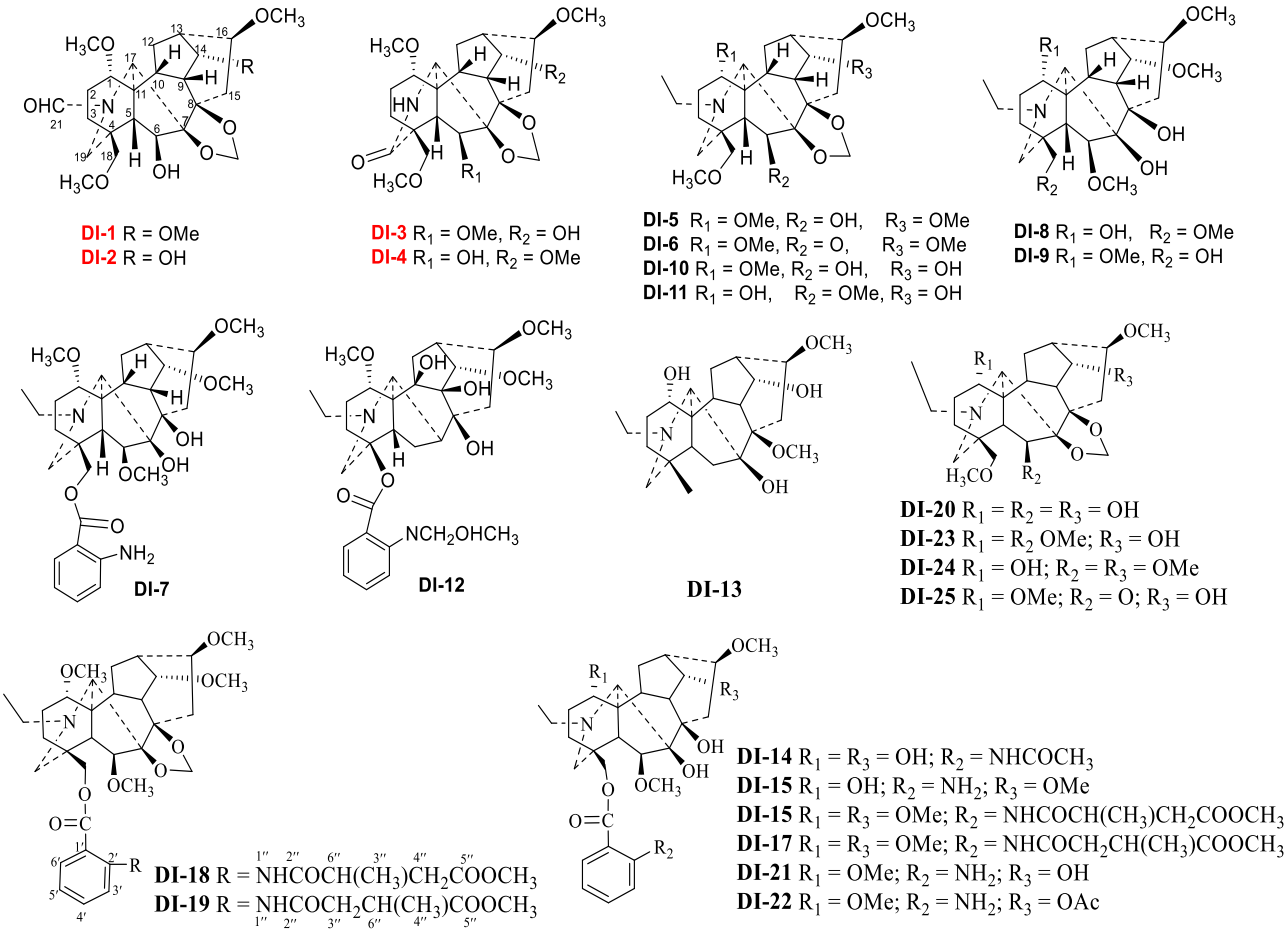
Ajratilgan birikmalarning *in vitro* saratonga qarshi sitotoksikligi MTT usulida tekshirildi. **DA-19** IC_{50} qiymatlari 13.69 μM bo‘lgan HeLa hujayralariga nisbatan o‘rtacha sitotoksiklik ko‘rsatdi. Diterpenoid alkaloidlarning hech biri sezilarli sitotoksiklik namoyon qilmadi. Ajratilgan birikmalarning mikroblarga qarshi faolligi agar qudug‘ini diffuziya qilish usuli bilan tekshirildi. Natijalar shuni ko‘rsatdiki, faqat **DA-19** birikmasi *S. aureus*ga qarshi zaif ingibitor faollik namoyon qiladi.



11-Rasm. *Delphinium aemulans* dan ajratilgan **DA-1~DA-25** birikmalarning kimyoviy tuzilishi

***Delphinium iliense* kimyoviy birikmalarining tadqiqoti.** To‘rtta yangi likoktonin tipidagi C_{19}-diterpenoid alkaloid, sinxianidinlar A-D (**DI-1~DI-4**), va 21ta ma’lum C_{19}-diterpenoid alkaloid, delkorin (**DI-5**), 6-degidrodelkorin (**DI-6**), antranoillikoktonin (**DI-7**), delsolin (**DI-8**), likoktonin (**DI-9**), delkoridin (**DI-10**), delbrunin (**DI-11**), *N*-atsetilsepakonitin (**DI-12**), blaknidin (**DI-13**), majuzin A (**DI-14**), izodelektin (**DI-15**), delavain A (**DI-16**), delavain B (**DI-17**), shavurenin A (**DI-18**), shavurenin B (**DI-19**), delbruninol (**DI-20**), delektin (**DI-21**), andersonidin (**DI-22**), delbrulin (**DI-23**), 7,8-Metilenedioksidelkolin (**DI-24**), va ilidin (**DI-25**) *D. iliense* Huth o‘simligidan ajratildi va identifikatsiya qilindi.

Ularning tuzilishi (**12-rasm**) HR-ESI-MS, 1D NMR va 2D NMR spektoskopik tahllillar yordamida o‘rnatilgan bo‘lsa, sinxianidin A (**DI-1**) va sinxianidin C (**DI-3**) larning absolyut konfiguratsiyasi eksperimental elektron sirkulyar dixroizm (ESD) spektrlarini taqqoslash orqali aniqlandi.



12-Rasm. DI-1~DI-25 birikmalar tuzilishi

Sinxianidinlar C-D (**DI-3** va **DI-4**) sirka kislotasi qo‘zg‘atgan sichqonlar burishishining *in vivo* modeli orqali ularning analgetik faolligi sinovdan o‘tkazildi. Natijalar shuni ko‘rsatdiki, zaharli bo‘lmagan 5 mg/kg dozada ikkita birikma mos ravishda 78.16% va 72.54% ingibirlash bilan sezilarli analgetik ta’sir ko‘rsatdi. Bundan tashqari, **DI-3** birikmasi 55.91% ingibirlash bilan 1 mg/kg zaharli bo‘lmagan dozada qayta sinovdan o‘tkazildi (3-jadval).

3-Jadval. DI-3 va **DI-4** sinov birikmalarining burishishni ingibirlovchi ta’siri

Guruh	Doza (mg/kg)	Burishishlar soni	Burishishning ingibirlanishi (%)
Nazorat	0	60.10 ±3.57	0
lappakonitin	5	8.37 ±1.25	86.06
DI-3 (yuqori-doza guruhi)	5	13.12 ±1.99	78.16
DI-3 (past-doza guruhi)	1	26.5 ±4.38	55.91
DI-4 (yuqori-doza guruhi)	5	16.50 ±1.99	72.54

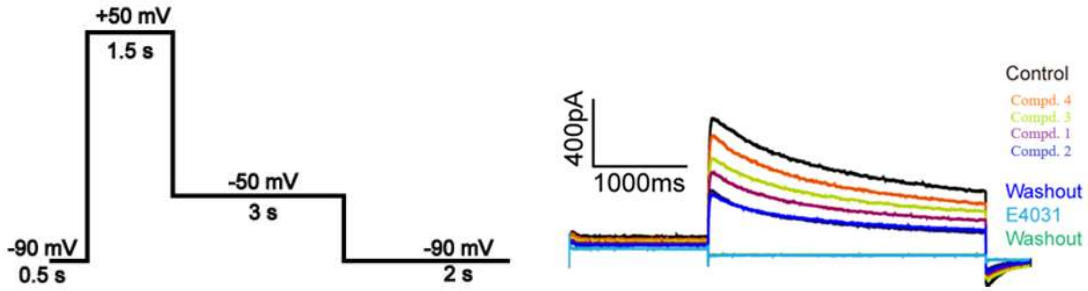
2010 yilda Fengpeng Wang C_{18}- va C_{19}-diterpenoid alkaloidlari o‘rtasidagi analgetik tuzilish-faollik munosabatlarini o’rganishi natijasida A halqasida *N*-etil o‘rinbosari uchlamchi amin, C-14 yoki C-4 da aromatik efir [OBz yoki 4-metoksibenzoil esteri (OAs)] va D halqaning to‘yinganligi C_{18}- va C_{19}-diterpenoid alkaloidlarining analgetik faolligining namoyon bo‘lishi uchun zarur ekanligini aniqladi. Qizig‘i shundaki, sinxianidinlar C-D (**DI-3** va **DI-4**) *N*-etil o‘rinbosarli

uchlamchi amin va aromatik efirga ega emas, lekin yaxshi analgetik faollik potensialini namoyish etadi. Biz uning faolligi C_{19}=O bilan bog‘liq bo‘lishi mumkinligini taxmin qilamiz. Albatta, bu taxminni tasdiqlash uchun keyingi tizimli tadqiqotlar talab qilinadi.

Yangi **DI-1~DI-4** birikmalari hEGR va CaV3.1 kanallarida ion kanallarini ingibirlovchi faolligiga tekshirildi. **DI-1~DI-4** birikmalarning hEGR va CaV3.1 kanallariga ingibirlovchi ta’sirini ko‘rsatuvchi I/I_0 qiymatlari 4-jadval va 13-rasmda keltirilgan. Afsuski, hech bir birikma sezilarli ingibitor faolligini namoyon qilmadi (I/I_0 > musbat nazorat). Natijalar shuni ko‘rsatdiki, bu ikki birikma antiaritmik faollik uchun potensialga ega emas. Ushbu natija antiaritmik faollik uchun C_{19}-diterpenoid alkaloidlarining tuzilishi-faollik munosabatlari hisobotini yana bir bor tasdiqladi.

4-Jadval. *D. iliense* dan ajratilgan **DI-1~DI-4** birikmalarining hEGR va CaV3.1 kanallarini ingibirlovchi ta’siri

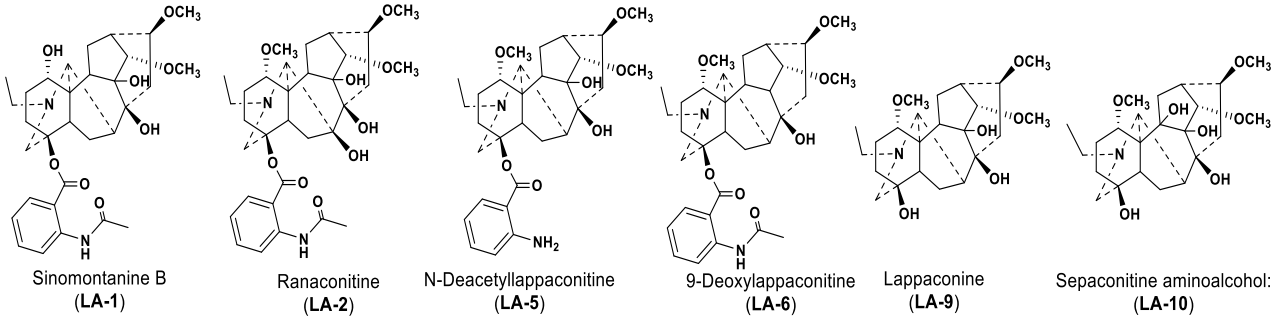
hEGR			**CaV3.1**		
Birikma	I/I_0(o‘rtacha ± SEM)	n	Birikma	I/I_0(o‘rtacha ± SEM)	n
Digidroxlorid	0.007 ±0.003	6	Uliksakaltamid	0.1776 ±0.01067	10
DI-1	0.947 ±0.041	4	**DI-1**	0.9446 ±0.06961	3
DI-2	0.889 ±0.044	4	**DI-2**	1.1450 ±0.09581	3
DI-3	0.926 ±0.041	4	**DI-3**	0.9530 ±0.02832	3
DI-4	0.918 ±0.017	4	**DI-4**	1.0290 ±0.05818	3



13-Rasm. Kuchlanish qisqichi parametrlarini o‘rnatish diagrammasi (chapda) va **DI-1 ~ DI-4** birikmalarining odatdagi grafigi hERG oqimiga ingibirlovchi ta’siri (o‘ngda)

Allapinin substansiyasidan aralashmalarni ajratish va tozalash. Allapinin substansiyasi tarkibida lappakonitin miqdorining ko‘pligi qo‘shimchalarni ajratib olishda qiyinchiliklar tug‘diradi. Ushbu tadqiqotda sanoat preparativ YuSSX texnologiyasi lappakonitinni ajratish uchun qo‘llanildi, so‘ngra yarim-preparativ YuSSX texnologiyasi qo‘shimchalarni ajratish ucun qo‘llanildi. Natijada 6 ta qo‘shimcha, sinomontanin B (**LA-1**), ranakonitin (**LA-2**), *N*-deatsetillappakonitin (**LA-5**), 9-dezoksilappakonitin (**LA-6**), lappakonin (**LA-9**) va sepakonitin aminospirti (**AL-10**) ajratib olindi va Allapinin substansiyasidan tozalandi. Ularning tuzilishi (**14-rasm**) spektoskopik (HR-ESI-MS, 1D NMR va 2D NMR) tahllillar yordamida va adabiyot ma’lumotlari bilan solishtirish orqali aniqlandi. Ushbu tadqiqot natijalari muhim amaliy ahamiyatga ega bo‘lgan Allapinin substansiyasining sifatini nazorat

qilish uchun notozalik standartlarini taqdim etdi.



14-Rasm. LA1, LA2, LA5, LA6, LA9 va **LA10** birikmalari tuzilishi

XULOSALAR

1. Markaziy Osiyoda o‘suvchi *Aconitum* va *Delphinium* turkumlarining yetti turi, jumladan, *A. barbatum* var. *puberulum*, *A. smirnovii*, *A. sinchiangense*, *D. pseudoaemulans*, *D. naviculare* var. *lasiocarpum*, *D. aemulans* va *D. iliense* bo‘yicha kompleks fitokimyoviy tadqiqot o‘tkazilgan.

2. Jami 176 ta birikma, shu jumladan, 26 ta yangi va 107 ta ma’lum bo‘lgan diterpenoid alkaloidlar, 43 ta boshqa birikma ajratildi. Ularning tuzilishi HR-ESI-MS, 1D va 2D NMR spektroskopiyasi va adabiyot ma’lumotlari bilan taqqoslash orqali aniqlandi; yangi birikmalarning mutlaq konfiguratsiyasi kvant ECD hisoblashlari bilan tasdiqlangan.

3. Barpuberudin (**AB-1**), yangi uglerod skeletiga ega C_{20}-diterpenoid alkaloidi va yangi qayta guruhlangan C_{18}-diterpen alkaloidlari barpubenin A va B lar (**AB-6** va **AB-7**) *A. barbatum* var. *puberulum* dan ajratildi. Ularning ishonchli biosintetik yo‘llari taklif qilingan.

4. *Delphinium naviculare* var. *lasiocarpum* kimyoviy tarkibi tizimli ravishda tadqiq etilgan va YuSSX yordamida o‘simlik tarkibida 0.25% lappakonitin borligi aniqlangan, bu ushbu turning fitokimyoviy ma’lumotlarini boyitadi va lappakonitin ishlab chiqarish uchun barqaror zaxira manbai sifatida potensial rivojlanishini ta’minlaydi.

5. Allapinin substansiyasidan oltita qo‘shimcha ajratilgan va tozalangan, bu sifat nazorati uchun mos havola standartlarini ta’minlaydi. Ushbu yutuq nafaqat klinikada qo‘llaniladigan antiaritmik vositani ishlab chiqarish jarayonlarini standartlashtirishni qo‘llab-quvvatlaydi, balki uning sifat xususiyatlarini yaxshilaydi va Allapininni mahalliy va xalqaro farmatsevtika bozorlarida qo‘llash doirasini kengaytirishga yordam beradi.

6. Bir qator monomer diterpenoid alkaloidlarning biologik faolliklari, jumladan, antiaritmik, analgetik, sitotoksik, ion kanallarini ingibirlovchi va mikroblarga qarshi ta’sirlarga baholangan.

7. *A. barbatum* var. *puberulum* dan ajratilgan *N*-deatsetillappakonitin va *N*-atsetilsepakonitin sezilarli antiaritmik faollikni, *A. barbatum* var. *puberulum* dan ajratilgan sepakonitin va *A. smirnovii* dan ajratilgan smirnotin A o‘rtacha faollikni

namoyon qildi, bu yurak-qon tomir preparatlari ishlab chiqish uchun ularning potensiali yuqoriligini ko 'rsatadi.

8. *D. iliense* dan ajratilgan sinchianidin C va D lar zagarli bo‘lmagan 5 mg/kg dozada mos ravishda 78.16% va 72.54% burishishni ingibirlashi bilan istiqbolli og‘riq qoldiruvchi ta’sir ko‘rsatgan, bu og‘riq qoldiruvchi vositalar yaratish imkoniyatlarini kengaytiradi.

9. Tanlangan diterpenoid alkaloidlarning *in vitro* sitotoksikligi A549, HCT8, MCF7, HT-29, MDA-MB-231 va HeLa hujayra liniyalariga nisbatan baholangan. Barcha birikmalar zaif sitotoksiklikni ko‘rsatgan (IC_{50} > 50 μM), bu likoktonin tipidagi alkaloidlar past sitotoksik potensialga ega degan xulosani tasdiqlaydi.

10. Tanlangan birikmalarning mikroblarga qarshi faolligi baholangan. Natijalar selektiv, ammo cheklangan faollikni namoyon qilgan, bu mikroblarga qarshi samaradorlikni oshirish uchun strukturani keyinchalik optimallashtirish zarurligini ko‘rsatadi.

11. *D. iliense* dan ajratilgan sinchianidin A-D lar hEGR va CaV3.1 kanallarida ion kanallarini ingibirlovchi faolligi uchun baholandi, ammo barcha birikmalar sezilarli ingibirlovchi ta’sir ko‘rsatmadi (I/I_0 > ijobiy nazorat). Ushbu natija salbiy bo‘lsa-da, diterpenoid alkaloidlardagi ion kanallari bilan bog‘liq biofaolliklarning kelajakdagi skrining strategiyalari uchun qimmatli ma’lumot bazasini taqdim etadi va struktura-faollik munosabatlari modellarini takomillashtirishda qo‘llash tavsiya qilinadi.

12. Ushbu tadqiqot Markaziy Osiyoda *Aconitum* va *Delphinium* turlarini barqaror rivojlantirish va ulardan foydalanishning ilmiy asoslarini beradi. Tuzilish tahlili, biofaollikni baholash va amaliy qo‘llash integratsiyasi diterpenoid alkaloidlari asosidagi innovatsion terapevtik vositalarning kelajakdagi rivojlanishi uchun mustahkam poydevor yaratadi.

SCIENTIFIC COUNCIL ON AWARDING SCIENTIFIC DEGREES DSc. 02/30.01.2020.K/T.104.01 AT THE INSTITUTE OF THE CHEMISTRY OF PLANT SUBSTANCES

INSTITUTE OF THE CHEMISTRY OF PLANT SUBSTANCES

BO ZHAO

STUDY ON THE DITERPENOID ALKALOIDS OF GENERA *ACONITUM* AND *DELPHINIUM* GROWING IN CENTRAL ASIA AND THEIR BIOLOGICAL ACTIVITIES

02.00.10 - Bioorganic chemistry

THESIS ABSTRACT OF THE DOCTOR OF CHEMICAL SCIENCES (DSc)

TASHKENT – 2025

The title of the research (DSc) has been registered by the Supreme Attestation Commission of the Cabinet of Ministers of the Republic of Uzbekistan under the number B2025.2.DSc/K…..

Doctoral thesis was carried out at the Acad. S.Yu.Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan and Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences.

The abstract of dissertation in three languages (Uzbek, English, Russian (resume)) is available on the website at www.ik-kimyo.nuu.uz and on the website of «ZiyoNET» information-educational portal www.ziyonet.uz.

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The defense of thesis will take place on «____» _____ 2025 at _____ at the meeting of the Scientific Council №. DSc.02/30.01.2020.K/T.104.01 at the Institute of the Chemistry of Plant Substances (address: 100170, Tashkent, 77 M. Ulugbek street. Tel.: 71 262-59-13, Fax: (99871) 262-73-48, e-mail: plant.inst@icps.org.uz; ixrv@mail.ru).

The thesis can be reviewed at the Informational Resource Centre of the Institute of the Chemistry of Plant Substances (registration №. _____)(address: 100170, Tashkent, 77 M. Ulugbek street. Tel.: 71 262-59-13, Fax: (99871) 262-73-48, e-mail: nhidirova@yandex.ru).

The abstract of the thesis has been distributed on «___»_____ 2025.

(Protocol at the registtation № _____dated «____» _____ 2025.)

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INTRODUCTION (Abstract of DSc thesis)

Topicality and relevance of the theme of the thesis. In the global pharmaceutical industry, new drugs derived from natural substances have consistently held a significant position due to their comprehensive advantages. Consequently, interest in physiologically active compounds obtained from plant materials has been steadily increasing. Currently, numerous scientific studies are underway to isolate specific compounds from plants, assess their biological activity, determine their physicochemical properties, and explore their applications in production.

Diterpenoid alkaloids, with their diverse structures, chemical multifunctionality, high physiological activity, and potential for developing medicinal products, have particularly captured the attention of chemists and pharmacologists.

The dried roots of certain species from the *Aconitum* and *Delphinium* genera, found in Central Asia, are widely utilized in traditional Chinese medicine for their antiarrhythmic, analgesic, and antitumor properties in treating various diseases. Phytochemical studies of *Delphinium* species native to China have led to the isolation of diterpenoid alkaloids, whose biological activities have been investigated, revealing their anti-inflammatory, analgesic, antiarrhythmic, insecticidal, and antifeedant properties.

Research conducted at the Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, revealed that the chemical compositions of *Aconitum barbatum* var. *puberulum* and *Delphinium iliense*, found in the Chinese flora, are distinct. Diterpenoid alkaloids such as *N*-acetylsepaconitine and *N*-deacetyllappaconitine, isolated from *Aconitum barbatum* var. *puberulum*, exhibit antiarrhythmic properties. Additionally, sinchianidines C and D, isolated from *Delphinium iliense*, demonstrate analgesic effects. This research opens the possibility for the development of import-substituting medications based on local raw materials, providing the population with affordable, high-quality medicines.

This thesis research will to a certain extent serve the implementation of the tasks set out in the Decree of the President of the Republic of Uzbekistan No. B3-55 dated January 21, 2022 “On additional measures for the accelerated development of the Pharmaceutical Industry of the Republic in 2022-2026”, Resolutions No. RP-3532 dated February 14, 2018 “On additional measures for the accelerated development of the Pharmaceutical Industry”, Resolutions No. RP-4310 dated May 6, 2019 “On measures for the further development of the system of Medical and Pharmaceutical Education and Science”, as well as other regulatory legal acts related to this activity.

This thesis research is dedicated to addressing urgent tasks such as the search for novel structural diterpenoid alkaloids from endemic *Aconitum* and *Delphinium* speices of Central Asia, and the investigation of their antiarrhythmic, analgesic, and antitumor effects within the framework of state programs of Uzbekistan and China. These studies provide a scientific foundation for the further development of effective and low-toxicity innovative drugs based on diterpenoid alkaloids, as well as for the sustainable utilization and development of unique plant resources in Central Asia.

They are of great significance in the discovery of new bioactive natural products beneficial to human health.

Conformity of research to priority directions of development of science and technologies in the Republic of Uzbekistan and China. This research aligns with the priority areas of bilateral scientific and technological development between the Republic of Uzbekistan and the People's Republic of China. It corresponds to the frameworks and strategic objectives defined in: The Memorandum of Intergovernmental Agreements signed during the second session (July 17, 2014), the third session (February 15, 2017), the fourth session (July 24, 2019) and the fifth session (June 28, 2021) of the Science and Technology Cooperation Subcommittee under the China–Uzbekistan Intergovernmental Cooperation Committee. Furthermore, this research fully supports the goals set under the China–Uzbekistan Comprehensive Strategic Partnership in the New Era, announced during recent high-level bilateral meetings. This partnership emphasizes all-weather, all-dimensional cooperation in areas such as innovation, biotechnology, traditional medicine, and green development, thereby providing a strong policy foundation and mutual interest for collaborative research in natural products and pharmaceutical discovery.

A review of international research on the topic of thesis. Scientific research aimed at studying diterpenoid alkaloids has been conducted at leading scientific centers and universities around the world, including: Institute for Natural Products Research and Department of Chemistry, University of Georgia (USA); Department of Chemistry of Medicinal Natural Products, West China of Pharmacy, Sichuan University (China); the Acad. S.Yu.Yunusov Institute of the Chemistry of Plant Substances， Academy of Sciences of the Republic of Uzbekistan (Uzbekistan); Institue of Organic Chemistry, Ural Department of the Russian Academy of Sciences (Russia); School of Pharmacy, Hokkaido Pharmaceutical University (Japan); Kunming Istitute of Botany, Chinese Academy of Sciences (China); School of Life Science and Engineering, Southwest Jiaotong University (China); The Xinjiang Technical Institue of Physics and Chemistry, Chinese Academy of Sciences (China); and others conducted in-depth scientific researches on theoretical and practical studies related to the creation of drugs based on diterpenoid alkaloids from plant raw materials, the research contents include the separation of diterpenoid alkaloids from *Aconitum*, *Delphinium* and other plants, the structural identification, bioactivity screening, structure-activity relationship research, source pathway research, structural modification of diterpenoid alkaloids, pharmacological, pharmacodynamic and toxicological studies, among others.

The study of diterpenoid alkaloids has been ongoing for nearly 100 years and remains highly relevant today. On one hand, their complex and variable structures confer diverse biological activities; on the other hand, their activity and toxicity often coexist. Therefore, it is essential not only to focus on structural modifications and to determine the relationship between structure and activity but also to address toxicity during the research process, in order to discover highly effective and low-toxic drug compounds with high added value.

Problem development status. Although diterpenoid alkaloids were first discovered in the 1830s, their absolute configurations were not determined until the

1950s through X-ray single-crystal diffraction and other methods due to their complex structures. With the widespread application of spectroscopic technologies, particularly mass spectrometry and nuclear magnetic resonance, the study of diterpenoid alkaloids has progressed rapidly - especially as a result of research by Professor S.W. Pelletier of the Natural Products Research Institute and Department of Chemistry at the University of Georgia, Professor S.Y. Yunusov of the Institute of the Chemistry of Plant Substances of the Academy of Sciences of the Republic of Uzbekistan, and Professor F.P. Wang of the Department of Chemistry of Medicinal Natural Products at the West China School of Pharmacy, Sichuan University.

After the discovery that diterpenoid alkaloids possess anti-inflammatory, analgesic, antiarrhythmic, cardiotonic, anti-heart failure, and insecticidal properties, an increasing number of scientists began to study them - among them Uzbek and Russian scientist M.S. Yunusov, Japanese scientist K. Wada, and Chinese scientists X.J. Hao, X.L. Zhou, and H.A. Aisa. Through the joint efforts of many researchers, more than 1,600 natural diterpenoid alkaloids have been identified in plants. Of these, four - lappaconitine, crassiculine A, 3-acetylaconitine, and guan-fu base A - have been developed into clinically used antiarrhythmic or analgesic drugs.

For the first time in Uzbekistan, research into the structure and biological activity of diterpenoid alkaloids began at the Institute of the Chemistry of Plant Substances of the Academy of Sciences of the Republic of Uzbekistan under the leadership of Academician S.Y. Yunusov. Numerous diterpenoid alkaloids with novel structures and promising biological activities were isolated from *Aconitum*, *Delphinium*, and *Consolida* species. Under the leadership of Academician Sh.Sh. Sagdullaev, the Institute also developed the antiarrhythmic drug Allapinin, based on the alkaloid lappaconitine. This drug was registered in Russia and Uzbekistan and was awarded the National Prize of Uzbekistan for Science and Technology in 2007.

The pharmacological activity of extracts and individual compounds from plants of the *Aconitum* and *Delphinium* genera is extensive but not yet fully explored, highlighting the urgency and importance of continued scientific and practical research in this area.

This thesis continues the author's systematic study of diterpenoid alkaloids and other biologically active components from *Aconitum* and *Delphinium* speices native to Central Asia.

Connection of the thesis work to the state programs or plans for scientific research. The thesis work has been performed in accordance with the National Key Research and Development Program (International Scientific and Technological Innovation Cooperation between the Governments of China and Uzbekistan) of the Ministry of Science and Technology of China entitled, "C_{20}-diterpenoid alkaloids of cultivated plant *Consolida sp.*: isolation, structure, biological properties" (No. 2016YFE0120700, 2017-2018) and "Research and development of new antiarrhythmic drugs with analgesic and local anesthetic effects (activities)" (No. 2021YFE0104000, 2021-2023); the National Key Research and Development Program of the Ministry of Science and Technology of China entitled "Construction of China-Uzbekistan Belt and Road Joint Laboratory on New Drug and Research of Innovative Drug" (2020YFE0205600, 2020-2023); the International Science

&Technology Cooperation Project of the Science and Technology Department of Xinjiang Uygur Autonomous Region entitled, “Study on separation and analysis of diterpenoid alkaloids and their druggability” (No. 20166014, 2016-2018); Youth Fund of the National Natural Science Foundation of China entitled, “LC-DAD-MS guided discovery of new diterpenoid alkaloids from two Central Asian characteristic plants and their biological activities research” (No. 32000277, 2021-2023).

The purpose of the study is to isolate secondary metabolites of 7 species of plants belonging to the *Aconitum* and *Delphinium* genera growing in Central Asia, determine their chemical composition and structure, and create effective medicines based on them.

Tasks of research work:

1. Extraction and fractionation of total alkaloids from plant species belonging to the *Aconitum* and *Delphinium* genera using various organic solvents;
2. Isolation and purification of pure compounds from the total alkaloids obtained from the above plants;
3. Determination of the primary structure of the isolated compounds and the absolute configuration of new compounds;
4. Evaluation of the biological effects of individual compounds, including antiarrhythmic, ion channel inhibitory, analgesic, antitumor and antimicrobial activities;
5. Determination of the amount of lappaconitine in *Delphinium naviculare* var. *lasiocarpum*;
6. Development of a process for the separation of impurities in the substance allapinin.

Object of the study are 7 species of plants belonging to the *Aconitum* and *Delphinium* genera: *Aconitum barbatum* var. *puberulum* Ledeb, *Aconitum smirnovii* Steinb, *Aconitum sinchiangense* W. T. Wang, *Delphinium pseudoaemulans* C. Y. Yang et B. Wang, *Delphinium naviculare* var. *lasiocarpum* W. T. Wang, *Delphinium aemulans* Navski and *Delphinium iliense* Huth; as well as Allapinin substance.

Subject of the study are diterpenoid alkaloids and other components of *Aconitum* and *Delphinium* species growing in Central Asia and their biological activities; impurities of allapinin substance.

Methods of experimental research. During the research technological (solvent extraction, decompression concentration, chromatographic separation and spectral analysis), chromatographic (silica gel, sephadex LH-20 and ODS column chromatography, Flash, TLC and HPLC), physic-chemical and spectral analytical (UV, IR, Optical rotation, ESI-MS, 1D and 2D NMR, experimental and calculated ECD) methods were used. Arrhythmia model of anesthetized mice induced by aconitine was used for determination of antiarrhythmic activity; in *vivo* model of acetic acid-induced mice writhing was used for test of analgesic activity; the hEGR and CaV3.1 channels were used for determination of ion channel inhibitory activity; MTT [3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide] method was used for testing of antitumor activity (cytotoxicity), the agar well diffusion method was were used for determination of antimicrobial activity.

The scientific novelty of the research is as follows:

for the first time, a total of 176 compounds, including 26 new and 107 known diterpenoid alkaloids, as well as 43 compounds from other classes, were isolated from seven species of plants of the *Aconitum* and *Delphinium* genera growing in Central Asia;

The physical and chemical properties of the isolated diterpenoid alkaloids, as well as their antiarrhythmic, analgesic, antitumor and antimicrobial biological activities, were systematically studied;

for the first time, new compounds were isolated from the plants *Aconitum barbatum var. puberulum* (N-acetylsepaconitin and N-deacetyllappaconitin) and *Delphinium iliense* (Sinchianidin C and D);

A new carbon skeleton representative of C20-diterpenoid alkaloids, barpuberudin (AB-1), and new rearranged C18-diterpenoid alkaloids, barpubenins A-B (AB-6 and AB-7), were identified for the first time from *Aconitum barbatum var. puberulum*;

for the first time, the chemical composition of *Delphinium naviculare var. lasiocarpum* was studied and the presence of lappaconitine was revealed;

Practical values of the present research. *N*-deacetyllappaconitine and *N*-acetylsepaconitine isolated from *Aconitum barbatum* var. *puberulum* showed significant antiarrhythmic activity, while sepaconitine isolated from *Aconitum barbatum* var. *puberulum*, and smirnotine A isolated from *Aconitum smirnovii* showed moderate antiarrhythmic activity. The preliminary structure-activity relationship of anti-arrhythmic was discussed according to this research results and literature reports, these finding contribute to the sustainable development and utilization of endemic medicinal plant resources, and support the preclinical evaluation of novel drug candidates derived from natural products.

Sinchianidines C and D, isolated from *Delphinium iliense* were found to display potential analgesic effects with 78.16% and 72.54% writhing reduction at a nontoxic dose of 5 mg/kg, respectively. A preparation method for diterpenoid alkaloids from *Delphinium iliense* and their potential analgesic applications were developed.

A preparation method for diterpenoid alkaloids from *Delphinium aemulans* and their potential inhibiting voltage-gated potassium channel currents (IKv) applications were developed. A preparation method for diterpenoid alkaloids from *Delphinium pseudoaemulans* and their potential antitumor applications were developed.

Six standard alkaloids were successfully isolated from the Allapinin substance, and the isolation methods were developed, providing a reliable approach for ensuring purity standards in the quality control of Allapinin substance.

The lappaconitine (0.25%) in whole plant of *D. naviculare* var. *lasiocarpum* was found, providing a new potential reserve source of lappaconitine.

Verification of the obtained data was proven by the use of chromatographic (silica gel, Sephadex LH-20 and ODS column chromatography, Flash, TLC, HPLC and PHPLC), technological (solvent extraction, decompression concentration, chromatographic separation and spectral analysis), physicochemical and spectral analytical (UV, IR, Optical rotation, ESI-MS, 1D, 2D NMR) and experimental,

computational methods, as well as biological methods. The validity of the results is explained by their discussion at international and republican scientific conferences and publication in peer-reviewed foreign and domestic scientific publications, as well as their use as a source of raw materials for the production of lappaconitin in the Xinjiang and Qinghai provinces of China.

Theoretical and practical value of the research results. The scientific significance of the research results is that the isolation of natural new diterpenoid alkaloids from the aerial parts of plants of the *Aconitum* and *Delphinium* genera growing in Central Asia and the determination of their chemical structure enriches the Chemistry of Natural Compounds. As a result, a total of 176 compounds, including 26 new and 107 known diterpenoid alkaloids, as well as 43 other compounds were isolated. Their structures were elucidated by means of spectroscopic analyses (HR-ESI-MS, 1D NMR and 2D NMR), and comparison with data reported in the literature, while the absolute configuration of new compounds was determined by quantum ECD calculation. Barpuberudine isolated from *Aconitum barbatum* var. *puberulum* was an unprecedented carbon skeleton of C_{20}-diterpenoid alkaloid, while barpubenines A-B isolated from *Aconitum barbatum* var. *puberulum* were the first example of rearranged types in C_{18}-diterpenoid alkaloids. The probable pathways of biogenesis of these three compounds were proposed. Biological activities of monomer compounds, including antiarrhythmic, analgesic, ion channel inhibitory activity, cytotoxicity and antimicrobial were selectively evaluated.

N-deacetylappaconitine and *N*-acetylsepaconitine, sincianidines C and D, obtained from *Aconitum barbatum* var. *puberulum* and *Delphinium iliense*, as a result of pharmacological studies, can serve as the basis for creating agents with antiarrhythmic and analgesic properties. The preliminary structure-activity relationships of anti-arrhythmic and analgesic were also discussed according to this research results and literature reports. The practical significance of the research results is that lappaconitine was isolated from *Delphinium naviculare* var. *Lasiocarpum* with content of 0.25% in the whole plant, which was found to be a source of lappaconitine. Six alkaloids contained in the substance allapinin were isolated and recommended for use as standards. This study advances the phytochemical and pharmacological understanding of *Aconitum* and *Delphinium* species from Central Asia, highlighting the region as a significant reservoir of bioactive natural products. The integration of structural elucidation, bioactivity profiling, and sustainable resource development provides a solid foundation for the future development of diterpenoid alkaloid-based therapeutics.

Implementation of research results. Based on the results of the research on "Study of diterpenoid alkaloids of plants of the genera *Aconitum* and *Delphinium* growing in Central Asia and their biological activity":

A patent of the People's Republic of China (No. ZL201810714295.7, 2018) was obtained for the invention of isolating and purifying diterpenoid alkaloids of the *Delphinium pseudoaemulans* plant, as well as creating an antitumor agent based on the results of their in vitro cytotoxicity to human cancer A549 and HeLa cells. As a result, it allowed the creation of an environmentally friendly, effective drug based on plant alkaloids;

A patent of the People's Republic of China was obtained for the invention of inhibiting potassium channel (IKv) currents based on diterpenoid alkaloids of the *Delphinium aemulans* plant (No. 2024100199358, 2024). As a result, it was possible to create a new agent that inhibits potassium channels based on plant alkaloids;

A patent of the People's Republic of China was obtained for the invention of developing a potential analgesic agent from diterpenoid alkaloids of the *Delphinium iliense Huth* plant (No. 2025103304327, 2025). As a result, it was possible to create effective analgesic agents based on plant diterpenoid alkaloids;

Xinjiang Shafei Ya Biological Technology Co., Ltd (PRC) and the Xinjiang Institute of Physics and Chemistry Technology (XTIPC), Chinese Academy of Sciences, have started research on cultivation in Xinjiang and Xinhai provinces of China, guaranteeing the supply of raw materials for the production of lappaconitin in large quantities (Report of Xinjiang Shafei Ya Biological Technology Co., Ltd, People's Republic of China, 15.05.2025). As a result, the supply of raw materials for the production of effective medicines based on plant diterpenoid alkaloids is guaranteed;

To control the quality of the pharmacologically active additive of the Allapinin substance, four compounds isolated as purity standards were used at the GMP enterprise of the Institute of Chemistry of Plant Substances (Reference of the Institute of Chemistry of Plant Substances dated 23.06.2025, No. 01-02/499). As a result, it was possible to improve the quality control system for the production of the Allapinin substance, ensure compliance with regulatory documents, and expand its use in clinical settings.

Approbation of the research results. The results of this research were presented and discussed at 7 scientific and practical conferences, including 4 international and 3 national events.

Publications of research results. Twenty-four scientific works have been published related to the thesis topic, including 14 articles in international journals recognized for the publication of key scientific results of Doctor of Chemical Sciences (DSc) thesiss by the PAK under the Ministry of Higher Education, Science, and Innovation of the Republic of Uzbekistan. Additionally, three patents have been obtained in the P.R. China.

The outline of the thesis. The thesis comprises an introduction, three chapters, conclusions, a list of references, and appendices, totaling 229 pages.

MAIN CONTENTS OF THE THESIS

The introduction justifies the topicality and relevance of the conducted research, outlines the aim and objectives of the study, characterizes the research object and subject, and demonstrates the alignment of the study with global scientific priorities as well as the key areas of science and technology in both China and Uzbekistan. The section also highlights the scientific novelty and practical outcomes of the investigation, elaborates on the scientific and practical significance of the results, and discusses the practical applications of the research findings. Furthermore,

information on granted patents, published papers, and the structure of the thesis is presented.

The **first chapter** of the thesis, which entitled "**Overview of Diterpenoid Alkaloids from *Aconitum* and *Delphinium* Genera**" provides a literature review. The classification, structural characteristics, biological activity characteristics, structure-activity relationship of diterpenoid alkaloids, and the possibility of practical application were discussed. As well as the genera of *Aconitum* and *Delphinium* grown in Uzbekistan and Xinjiang province of China were also investigated and summarized.

The **second chapter** of the thesis, which entitled "**Processes for the Isolation, Purification, and Bioactivity Testing of Chemical Compounds from *Aconitum* and *Delphinium* Genera in Central Asia (Materials and Methods)**" presents general experimental procedures; plant materials; the processes for isolation, purification and bioactivity test of chemical compounds from *Aconitum barbatum* var. *puberulum*, *Aconitum smirnovii*, *Aconitum sinchiangense*, *Delphinium pseudoaemulans*, *Delphinium naviculare var. lasiocarpum*, *Delphinium aemulans* and *Delphinium iliense*. This chapter also describes the quantification of lappaconitine content in *D. naviculare* var. *lasiocarpum*, as well as the isolation and purification of impurities from the allapinin substance. The study employed a range of technological methods, including solvent extraction, vacuum concentration, chromatographic separation, and spectral analysis. Chromatographic techniques used include silica gel, Sephadex LH-20, ODS column chromatography, flash chromatography, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC).

The **third chapter** of the thesis entitled "**Results and Discussions (main content of thesis)**" presents the outcomes of the isolation, purification, and bioactivity testing of chemical compounds from *Aconitum barbatum* var. *puberulum*, *Aconitum smirnovii*, *Aconitum sinchiangense*, *Delphinium pseudoaemulans*, *Delphinium naviculare* var. *lasiocarpum*, *Delphinium aemulans*, and *Delphinium iliense*. It also includes the quantification of lappaconitine content in *D. naviculare* var. *lasiocarpum* and the isolation and purification of impurities from allapinin substance. A range of physicochemical and spectral analytical methods were employed, including UV, IR, optical rotation, ESI-MS, 1D and 2D NMR, and both experimental and calculated ECD. The pharmacological evaluation involved various bioassays: the antiarrhythmic activity was assessed using an aconitine-induced arrhythmia model in anesthetized mice; analgesic activity was evaluated using the acetic acid-induced writhing test in mice; ion channel inhibitory activity was tested against hERG and CaV3.1 channels; antitumor (cytotoxic) activity was assessed via the MTT assay; and antimicrobial activity was determined using the agar well diffusion method.

Study on the chemical compounds from *Aconitum barbatum* var. *puberulum*. A phytochemical investigation of the whole plants of *A. barbatum* var. *puberulum* collected from Central Asia was thus performed as part of our continuous work on the discovery of compounds with unique structures and strong bioactivities from Central Asia plant resources. This led to isolation of seven previously undescribed

diterpenoid alkaloids, barpuberudine (**AB-1**), barpubesines A-D (**AB-2~AB-5**), barpubenines A-B (**AB-6~AB-7**), and 37 known compounds, 15-ketotetrohydroatisine (**AB-8**), leucostomine A (**AB-9**), *N*-acetylsepaconitine (**AB-10**), *N*-deacetyllappaconitine (**AB-11**), sepaconitine (**AB-12**), acosepticine (**AB-13**), lappaconidine (**AB-14**), trabzonine (**AB-15**), lappaconitine (**AB-16**), puberuline C (**AB-17**), leucostine (**AB-18**), leuconine (**AB-19**), sepaconitine aminoalcohol (**AB-20**), lappaconine (**AB-21**), acosanine (**AB-22**), acoseptrine (**AB-23**), 6-dehydroacosanine (**AB-24**), anthranoyllycoctonine (**AB-25**), O-methylarmepavine (**AB-26**), (S)-6-Methoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (**AB-27**), (+)-(1R,laR)-la-hydroxymagnocurarin (**AB-28**), (6R,6aS,P)-(+)-corydine (**AB-29**), (+)-*N*-methyllaurotetanine (**AB-30**), magnoflorine (**AB-31**), 3-hydroxy-1,2-dimethoxy-5-methyl-5H-dibenzoindol-4-one (**AB-32**), imperialine (**AB-33**), crispine B (**AB-34**), (S)-1-(3-Methoxyphenyl)-*N*-methylpropan-2-amine (**AB-35**), methyl-2-(acetamino)benzoate (**AB-36**), 2-carboxyoxanilic acid methylester (**AB-37**), 4-[2-(methoxycarbonyl) anilino]-4-oxobutanoic acid methyl ester (**AB-38**), *N*-methylcorydaldine (**AB-39**), *N*-methyl-6,7-dimethoxyisoquinolone (**AB-40**), (5*S*,6*R*,7*S*,8*R*)-5-amino-(2Z,4Z)-1,2,3-trihybuta-2,4-dienyloxy-pentane-6,7,8,9-tetraol (**AB-41**), nicotinic acid (**AB-42**), S(+)-dehydrovomifoliol (**AB-43**) and megastigmane (**AB-44**), including 19 known diterpenoid alkaloids. Their structures (**Fig. 1**) were elucidated based on a comprehensive spectroscopic data analysis including HR-ESIMS and 1D and 2D NMR (**Fig. 2** and **Fig. 3**).

Barpuberudine (**AB-1**) was an unprecedented carbon skeleton of C_{20}-diterpenoid alkaloid, while barpubenines A-B (**AB-6~AB-7**) were the first example of rearranged types in C_{18}-diterpenoid alkaloids. The probable pathway of biogenesis of barpuberudine and barpubenines A-B were discussed (**Fig. 4** and **Fig. 5**).

N-acetylsepaconitine (**AB-10**) and *N*-deacetyllappaconitine (**AB-11**) showed significant antiarrhythmic activity at a dose of 8 mg/kg in a mouse model of aconitine induced arrhythmia (**Table 1**). Sepaconitine (**AB-12**) had a certain antiarrhythmic activity, but it was significantly weaker than *N*-deacetyllappaconitine (**AB-11**). Compounds barpubenine B (**AB-7)**, leucostomine A (**AB-9**) and trabzonine (**AB-15)** could not be regarded as potential antiarrhythmic compounds. This study confirmed the structure-activity relationship of anti-arrhythmic as literature report: the most active are the C_{18}-diterpenoid alkaloids, such as lappaconitine. A common feature of these compounds is the presence of an acetylanthranilic or anthranilic acid moiety at C-4; methoxyl groups at C-1, C-14, and C-16; and a hydroxy group at C-8. Differences consist in the presence of additional hydroxy groups at C-7, C-9, and C-10. Further enhancements of the molecule by the introduction of hydroxy groups at C-6, C-7, and C-10, a methoxyl group at C-6, and an acetyl group at C-6 significantly lowers the degree of antiarrhythmic action. It is not easy to fully define the direct action of these functional groups on the activity due to diterpenoid alkaloids are inhibitors of multi-ion channels.

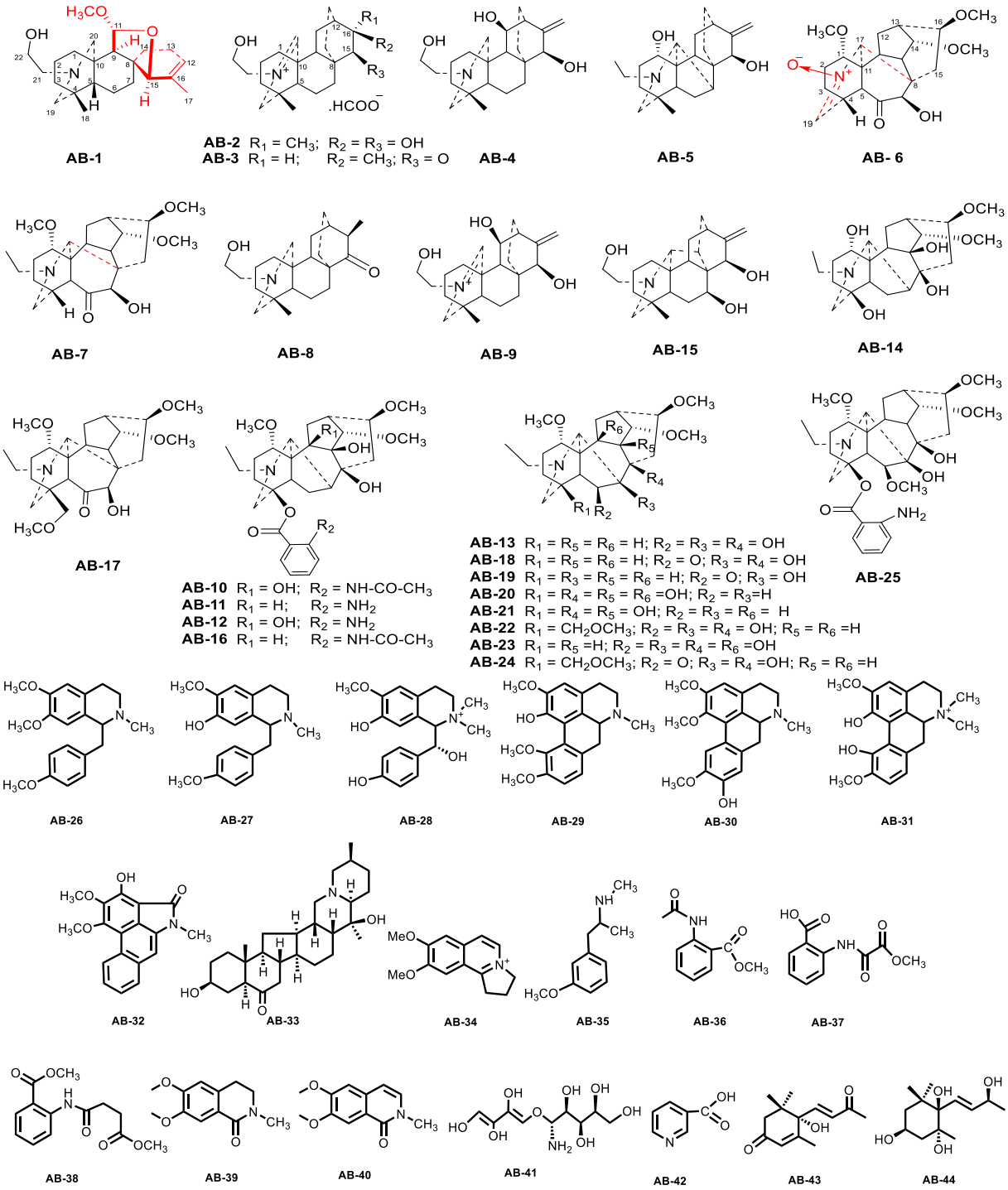

Fig. 1 Structures of compounds **AB-1~AB-44** isolated from *Aconitum barbatum* var. *puberulum*

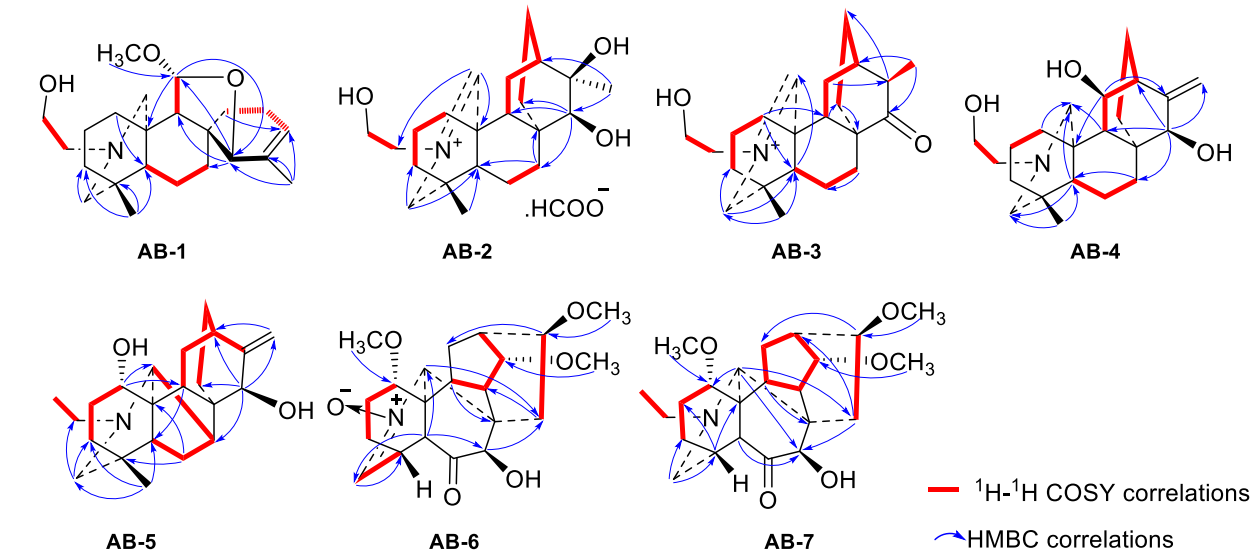

Fig. 2 Key HMBC and ^{1}H-^{1}H COSY correlations of compounds **AB-1**~**AB-7**

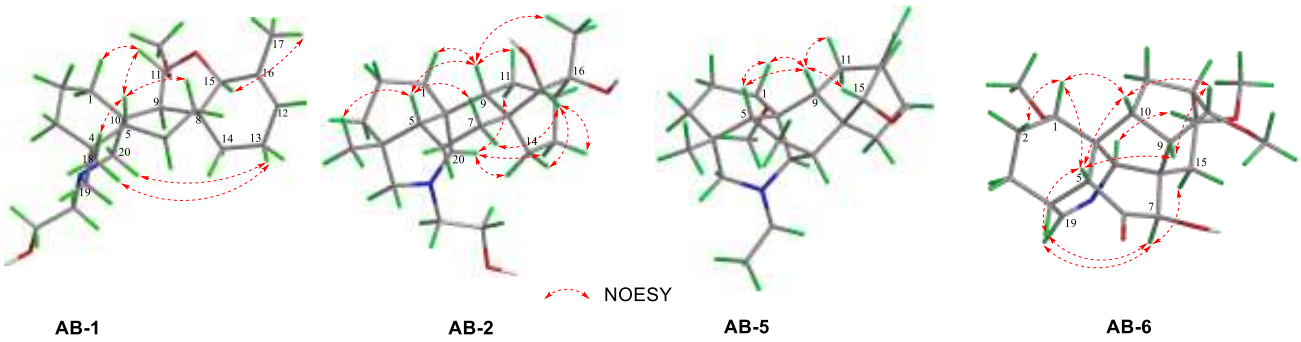

Fig. 3 Key NOESY correlations of compounds **AB-1**, **AB-2**, **AB-5** and **AB-6**

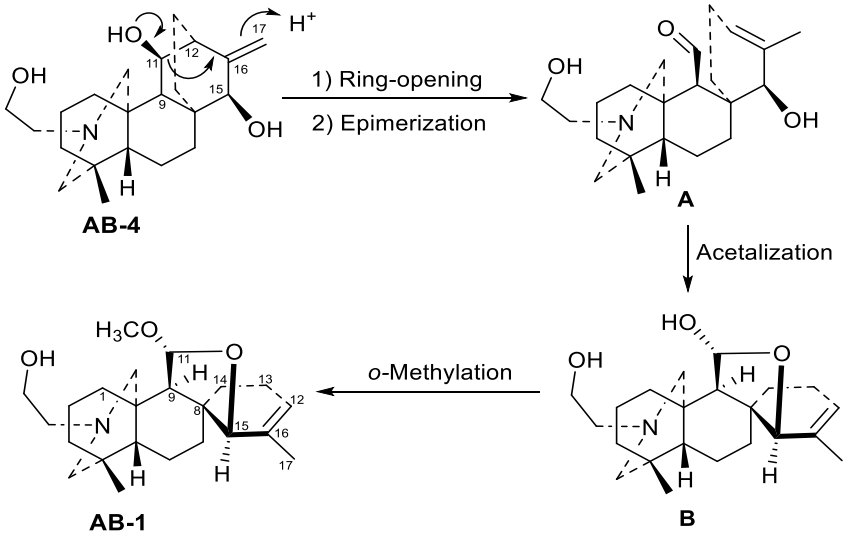

Fig. 4 Plausible biosynthetic pathway of barpuberudine (**AB-1**)

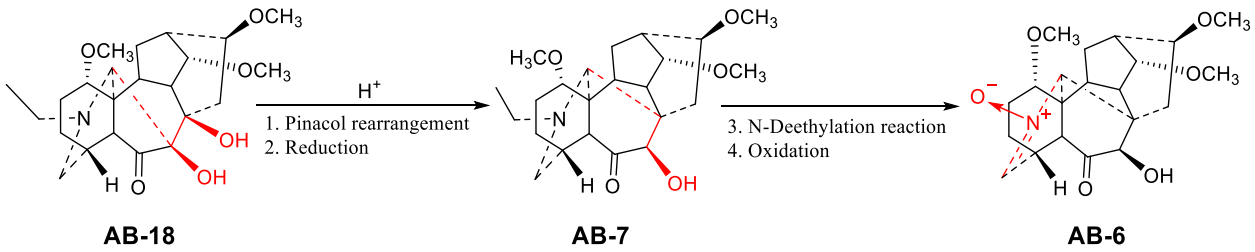

Fig. 5 Plausible biosynthetic pathway of barpubenines A-B (**AB-6~AB-7**)

Table 1 Antiarrhythmic activity of compounds **AB-7**, **AB-9**~**AB-12**, **AB-15** and **AB-16**

Sample [a]	Aconitine dosage in ECG change (μg/kg)				Aconitine dosage for death (μg/kg)
	Ventricular premature	Ventricular tachycardia	Ventricular flutter	Ventricular fibrillation	
Model group	47.10±9.86	90.55 ±12.25	120.83 ±28.58	227.34 ±44.52	287.82 ±46.77
AB-16 Lappaconitine	68.89 ±11.35 [b]**	152.70 ±21.39**	239.98 ±39.69**	346.11 ±53.51**	395.82 ±44.96**
AB-7 Barpubenine B	44.79 ±9.66	134.10 ±6.74**	204.79 ±12.21**	261.89 ±25.42	325.91 ±23.56
AB-9 Leucostomine A	48.15 ±4.20	140.27 ±20.59**	228.04 ±38.83**	305.99 ±46.80*	328.12 ±23.33
AB-10 N-acetylsepaconitine	93.57 ±16.71**	146.63 ±25.27**	242.86 ±60.24**	318.66 ±26.04**	371.29 ±42.11*
AB-11 N-deacetyllappaconitine	89.59 ±11.40**	183.47 ±26.57**	272.49 ±49.97**	331.26 ±35.92**	403.08 ±46.63**
AB-12 Sepaconitine	58.74 ±18.21	93.21 ±17.43	208.43 ±26.31**	295.93 ±65.47	339.84 ±54.54
AB-15 Trabzonine	45.73 ±12.17	132.65 ±23.36*	222.97 ±27.71**	315.05 ±41.32*	364.22 ±40.93

[a] The dosage of the compounds was 8 mg/kg, the method of administration was intraperitoneal administration at 0.4 ml/20 g. [b] ** P<0.01, * P<0.05, the sample groups were compared with the model group.

Compound **AB-30** exhibited moderate cytotoxicity against the Hela cell lines with the IC_{50} values of 13.69 μM, while compounds **AB-26** and **AB-31** showed strong inhibitory activity against the *S. aureus*, Compound **AB-41** showed moderate inhibitory activity against the *E. coli* and compounds **AB-1**, **AB-7**, **AB-13**, **AB-25**, **AB-27**, **AB-29**, **AB-37**, **AB-38**, and **AB-41** presented moderate inhibitory activity against the *S. aureus.* This research provided important scientific support for the sustainable utilization and development of characteristic plant resources in Central Asia.

Study on the chemical compounds from *Aconitum smirnovii*. Two new C_{19}-diterpenoid alkaloids, smirnotine A (**AS-1**) and smirnotine B (**AS-2**), as well as 21 known alkaloids, 14α-benzoyloxy-*N*-ethyl-15α-hydroxy-1α,6α,8β,16β,18-tamethoxyaconitane formate (**AS-3**), penduline formate (**AS-4**), 12-acetyl-12-epi-napelline (**AS-5**), homochasmanine (**AS-6**), ezochasmanine (**AS-7**), neoline（**AS-8**）, bullatine C (14-acetylneoline; **AS-9**), vilmorisine (**AS-10**), senbusine A (**AS-11**), 12-epi-napelline (**AS-12**), 15-acetylsongorine (**AS-13**), songorine (**AS-14**), aconicarmichinium A (**AS-15**), benzoylaconine (**AS-16**), 14-benzoyl-8-O-methylaconine (**AS-17**), songoramine (**AS-18**), aconitine (**AS-19**), 15α-hydroxyneoline (**AS-20**), 12-epi-dehydronapelline (**AS-21**), N-methyllaurotetanine (**AS-22**) and reticuline (**AS-23**), were isolated from the aerial part of *A. smirnovii*, which was collected from the Qinghe of Altay Prefecture of Xinjiang Uyghur Autonomous Region, P. R. China. Their structures (**Fig. 6**) were elucidated by means

of spectroscopic analyses (HR-ESI-MS, 1D and 2D NMR), and comparison with data reported in the literature, while the absolute configuration of **AS-1** was determined as 1S, 3R, 4R, 5S, 6R, 7R, 8R, 9R, 10R, 11S, 13R, 14R, 16S, and 17R by quantum ECD calculation (**Fig. 7**). All the compounds were isolated from this plant for the first time.

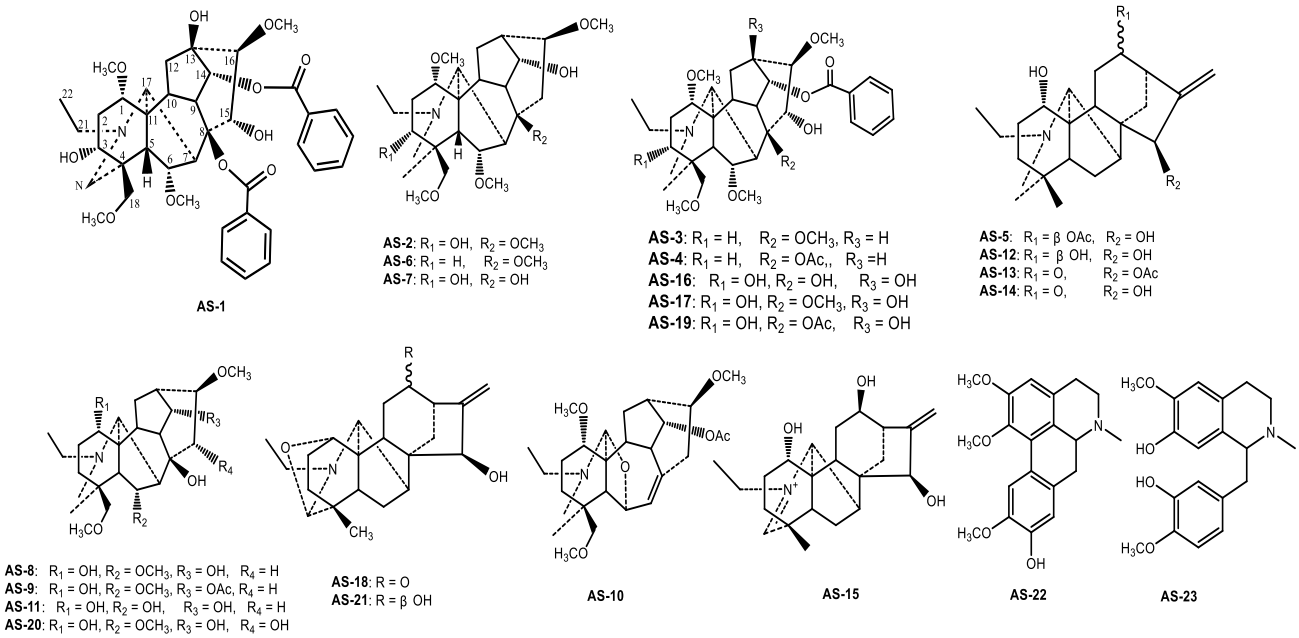

Fig. 6 Structures of compounds isolated from *Aconitum smirnovii*

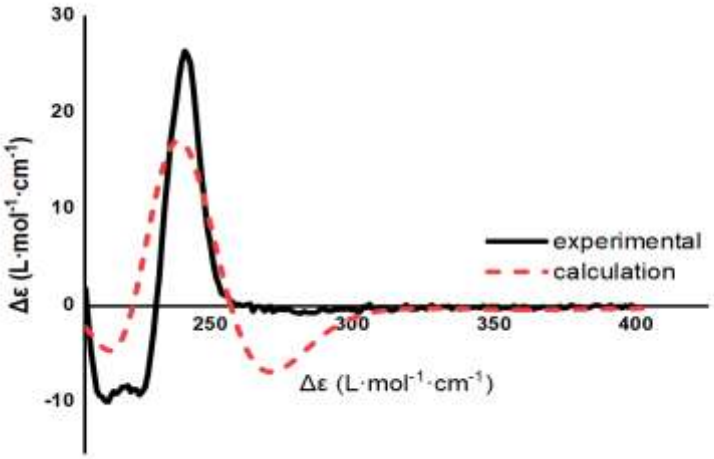

Fig. 7 Experimental and calculated ECD spectra of **AS-1**

Smirnotine A (**AS-1**) was a rare diterpenoid alkaloid contains two benzoyl groups, and showed certain preventive effect of antiarrhythmic activity (**Table 2**), which confirmed the report of structure-activity relationship of antiarrhythmic of diterpenoid alkaloids, that is, C_{18}- or C_{19}-diterpenoid alkaloid with two aromatic esters have stronger activity than one or no aromatic ester, but it should be noted that increasing aromatic ester may increases its toxicity.

Smirnotine A (**AS-1**) showed weak antimicrobial activity against *S. aureus*, and smirnotine B (**AS-2**) exhibited weak antimicrobial activity against *C. albicans* and *S. aureus*. No significant cytotoxicity against A549 and HeLa human cancer cell lines was observed for **AS-1**~**AS-5**. This report will be helpful to further clarify the structure-activity relationship of diterpenoid alkaloids.

Table 2 Effect of **AS-1** on aconitine dosage for ECG changes and death on mice (x ± s, n = 6)

Groups	Dosage (mg/kg)	Aconitine dosage for ECG changes (μg/kg)				Aconitine dosage for death (μg/kg)
		Ventricular premature	Ventricular tachycardia	Ventricular flutter	Ventricular fibrillation	
Control		47.1 ±9.9	90.6 ±12.3	120.8 ±28.6	227.3 ±44.5	287.8 ±46.8
AS-1	8	46.9 ±10.7	128.5 ±25.3 *	234.3 ±35.5 **	321.8 ±51.2	396.1 ±60.3
	16	46.2 ±11.0	146.3 ±43.1	265.8 ±57.2 **	362.9 ±96.1*	413.6 ±95.9*

Note: ** P < 0.01, * P < 0.05, comparison between the test group and the control group.

Study on the chemical compounds from *Aconitum sinchiangense*. A new C_{20}-diterpenoid alkaloid, sinchianine (**ASW-1**), together with eight known diterpenoid alkaloids, together with three known C_{20}-diterpenoid alkaloids, 12-acetyl-12-epi-napelline (**ASW-2**), 12-epi-napelline (**ASW-3**) and songorine (**ASW-8**), and five known C_{19}-diterpenoid alkaloids, neoline (**ASW-4**), talatisamine (**ASW-5**), 14-O-acetylsenbusine A (**ASW-6**), benzoylaconine (**ASW-7**) and aconitine (**ASW-9**), were isolated from the whole herb of *A. sinchiangense* which was collected from the Gongliu of Yili Region, Xinjiang of P. R. China. Their structures (**Fig. 8**) were elucidated by means of spectroscopic analyses (HR-ESI-MS, 1D NMR and 2D NMR) and comparison with data reported in the literature. **ASW-1** is a rare denudatine-type C_{20}-diterpenoid alkaloid bearing a 16,17-epoxy group. Compounds **ASW-2**~**ASW-7** were isolated from this plant for the first time.

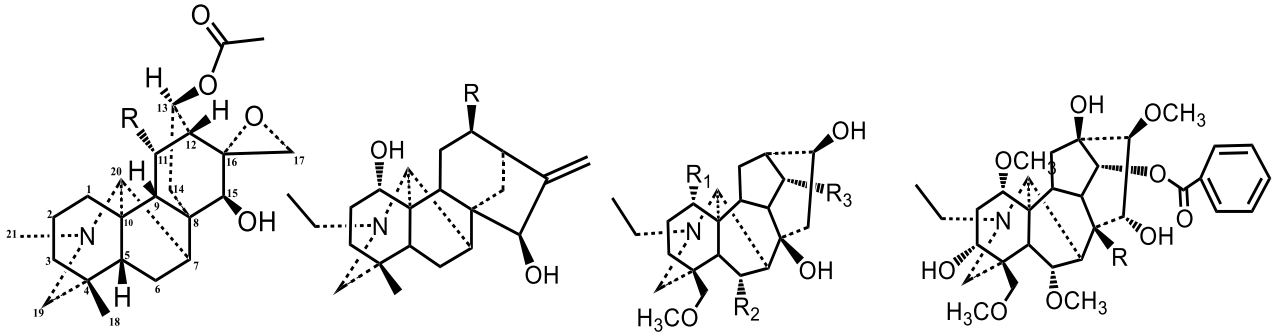

Fig. 8 Structures of compounds **ASW1**~**ASW9**

Study on the chemical compounds from *Delphinium pseudosemulans*. Eight previously undescribed lycoctonine-type C_{19}-diterpenoid alkaloids, pseudophnines A–D (**DP1**-**DP4**), pseudorenines A–B (**DP5a, DP5b**), pseudonidines A–B (**DP6**-**DP7**), and eleven known lycoctonine-type C_{19}-diterpenoid alkaloids, tianshanisine E (**DP8**), sharwuphinine B (**DP9**), potanisine A (**DP10**), lycoctonine (**DP11**), delbruline (**DP12**), isondelpheline (**DP13**), delavaines A–B(**DP14a, DP14b**), shawurenines A–B (**DP15a, DP15b**), campylotine (**DP16**), and three known other compounds, methyl 2-(4-methoxy-2-methyl-4-oxobutanamido)benzoate (**DP17**), methyl 2-(4-

methoxy-3-methyl-4-oxobutanamido)benzoate (**DP18**) and heptanoic acid (**DP19**) were isolated from the whole plant of *D. pseudosemulans* , which was a species endemic to Xinjiang Uygur Autonomous region of P. R. China. Their structures (**Fig. 9**) were elucidated by means of spectroscopic analyses (HR-ESI-MS, 1D NMR and 2D NMR), and comparison with data reported in the literature. **DP-1~DP-5** were rare C_{19}-diterpenoid alkaloids with alcohol iminium. Compounds **DP5** (**DP5a** and **DP5b**), **DP14** (**DP14a** and **DP14b**) and **DP15** (**DP15a** and **DP15b**) were three pairs of regioisomeric C_{19}-diterpenoid alkaloids which are common in *Delphinium*. All the compounds showed no cytotoxicity. Combined with the literature reports, it can be concluded that the cytotoxic activities of lycoctonine-type compounds are weaker than aconitine-type ones in C_{19}-diterpenoid alkaloids.

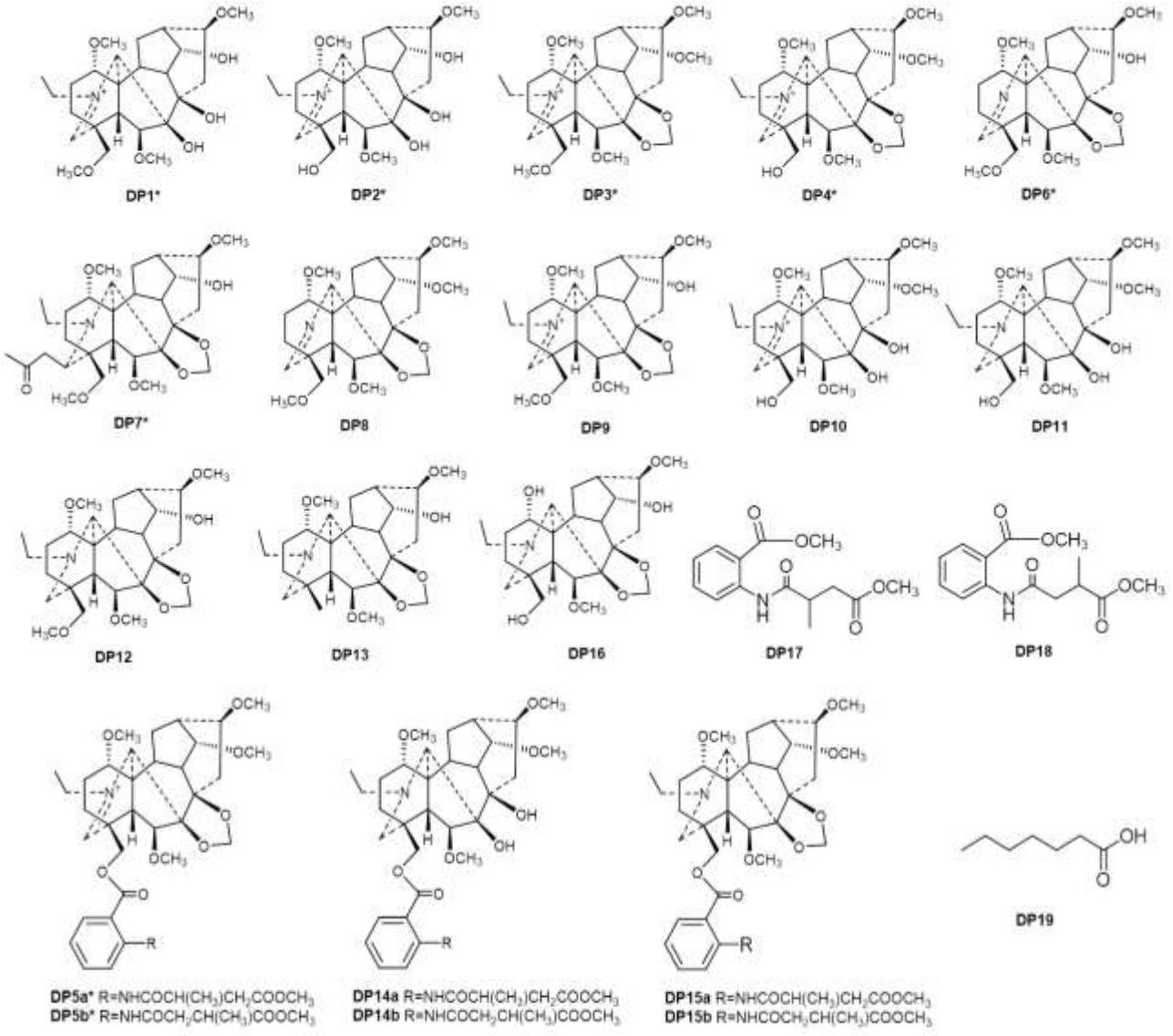

Fig. 9 Structures of compounds **DP1~DP19**

Study on the chemical compounds from *Delphinium naviculare* var. *lasiocarpum*. Three new diterpenoid alkaloids, naviconine, naviculine and naviconitine (**DN1**-**DN3**), together with 15 known diterpenoid alkaloids, lycoctonine (**DN4**), 8-O-methyllycoctonine **(DN5**), lappaconitine **(DN6**), N-deacetyllappaconitine **(DN7**), N-deethyllappaconitine **(DN8**), isolappaconitine **(DN9**), sinomontanine F

(DN10), sinomontanine A **(DN11**), lappaconine (**DN12**), ranaconine (**DN13**), trabzonine **(DN14**), potanisine A **(DN15**), N-acetylsepaconitine **(DN16**) and pseudorenines A-B **(DN17a** and **DN17b**), 3 benzyl isoquinoline alkaloids, isoquinolinium (**DN20**), 1,2,3,4-tetrahydro-6-methoxy-1-[(4-methoxyphenyl)methyl]-2-methyl-7-isoquinolinol/7-Isoquinolinol (**DN21**) and 2-methoxy-5-[(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolinyl)methyl]-1,3-benzenediol (**DN25**), 4 other alkaloids, benzoic acid, 2-[(4-methoxy-1,4-dioxobutyl)amino]-methyl ester **(DN18**), 2-acetamidobenzoic acid (**DN19**), hyemaline/furo[3,2-*g*]quinolin-7(*8H*)-one,9-[(3-methyl-2-buten-1-yl)oxy] (**DN22**) and methyl 2-formyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**DN27**), as well as 3 other compounds, 8-isopentenyloxypsoralene (**DN23**), 7-methoxy-8-isopentenylcoumarin (**DN24**) and 2*H*-1-benzopyran-2-one,3-(acetyloxy)-3,4-dihydro-,(3*R*) (**DN26**), were isolated from the whole plant of *D. naviculare* var. *lasiocarpum*. Their structures (**Fig. 10**) were elucidated by means of spectroscopic analyses (HR-ESI-MS, 1D NMR and 2D NMR), and comparison with data reported in the literature. The isolated diterpenoid alkaloids involved a total of 3 skeletons and 5 sub-skeleton types, including 7 lappaconitine type C_{18}-diterpenoid alkaloids, 3 ranaconitine type C_{18}-diterpenoid alkaloids, 1 aconitine type C_{19}-diterpenoid alkaloids, 6 lycoctonine type C_{19}-diterpenoid alkaloids and 1 hetidines type C_{20}-diterpenoid alkaloids.

The in *vitro* tumor cytotoxicity of isolates was screened by MTT method. The results showed that these compounds had no inhibitory activity on human colon cancer cell line HT-29, breast cancer cell line MDA-MB-231 and human cervical cancer cell line Hela. Antibacterial activity screening results showed that only compound **DN24** showed weak antibacterial activity against *Staphylococcus aureus*. The remaining compounds did not show certain antibacterial activity against *Candida albicans*, *Escherich coli* and *Staphylococcus aureus*.

The content of lappaconitine (**DN6**) in *D. naviculare* var. *lasiocarpum* was determined using HPLC. The results showed that the content of lappaconitine in the whole plant of *D. naviculare* var. *lasiocarpum* reached 0.25%. As a representative compound of diterpenoid alkaloids, lappaconitine is mainly distributed in *Aconitum* species, such as *Aconitum sinomontanum*, and is extremely rare in *Delphinium* species. This finding provides a theoretical foundation for developing *D. naviculare* var. *lasiocarpum* as a new reserve source of lappaconitine.

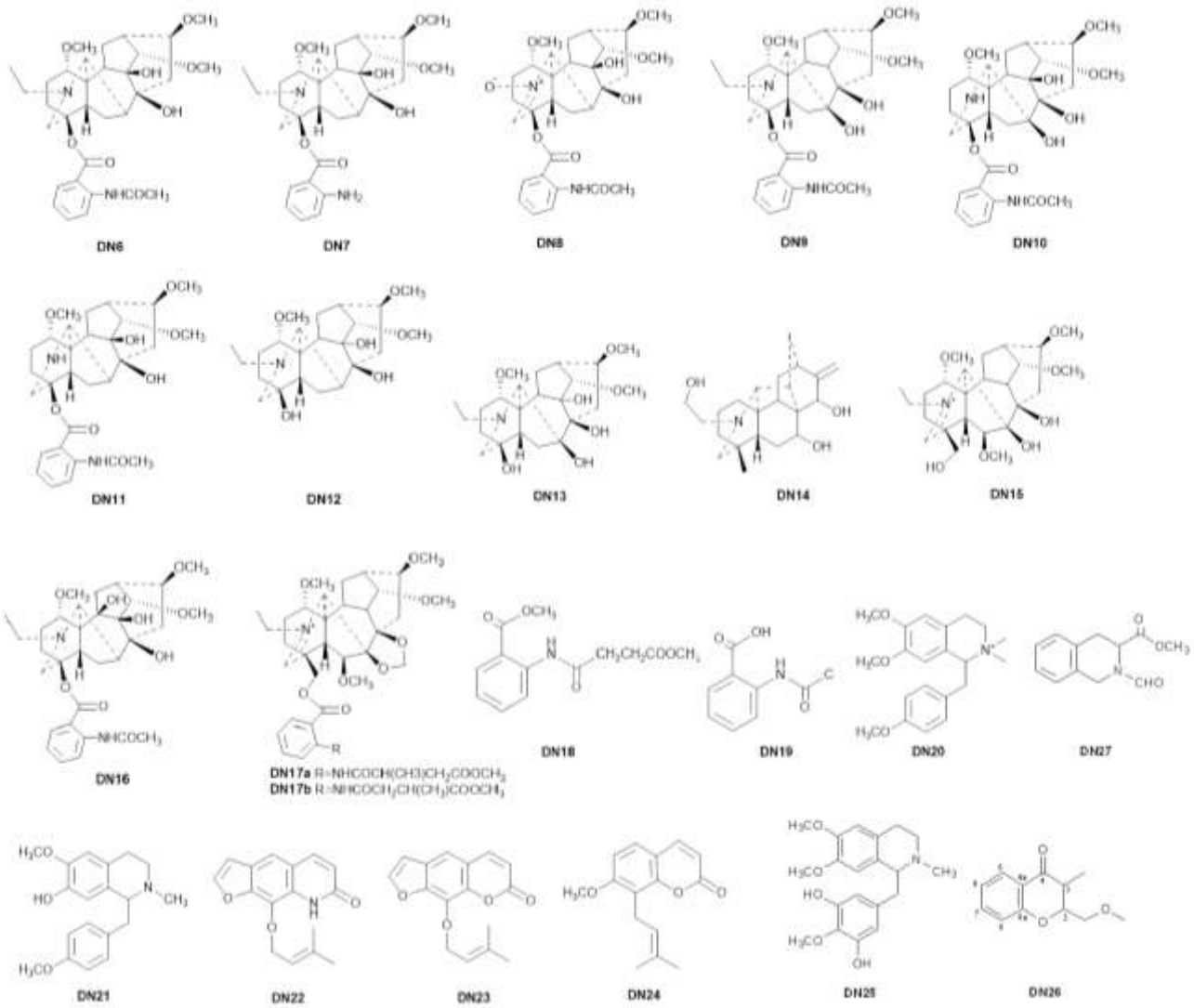

Fig. 10 Structures of compounds **DN1-DP27**

Study on the chemical compounds from *Delphinium aemulans*. One new naturally occurring lycoctonine-type C_{19}-diterpenoid alkaloid aemulansine (**DA-1**), together with 15 known C_{19}-diterpenoid alkaloids, delsoline (**DA-2**), delavaine A (**DA-3**), delavaine B (**DA-4**), methyllycaconitine (**DA-5**), delcosine (**DA-6**), shawurensine (**DA-7**), lycoctonine (**DA-8**), anthranoyllycoctonine (**DA-9**), delphatine (**DA-10**), ajadine (**DA-11**), *N*-deethyldelphatine (**DA-12**), gigactonine (**DA-13**), deltatsine (**DA-14**), delcorine (**DA-15**), deltaline (**DA-16**), as well as 9 other compounds, (–)-pallidine (**DA-17**), armepavine (**DA-18**), (+)-*N*-methyllaurotetanine (**DA-19**), 4-[2-(methoxycarbonyl)anilino]-3-methyl-4-oxobutanoic acid (**DA-20**), 4-[2-(methoxycarbonyl)anilino]-2-methyl-4-oxobutanoic acid (**DA-21**), 4-[2-(methoxycarbonyl)anilino]-2-methyl-4-oxobutanoic acid methyl ester (**DA-22**), 4-[2-(methoxycarbonyl)anilino]-3-methyl-4-oxobutanoic acid methyl ester (**DA-23**), 4-[2-(methoxycarbonyl)anilino]-4-oxobutanoic acid methyl ester (**DA-24**) and euscaphin B (**DA-25**), were isolated from the whole herb of *D. aemulans*. Their structures (**Fig. 11**) were elucidated by means of spectroscopic analyses (HR-ESI-MS, 1D NMR and

2D NMR) and comparison with data reported in the literature.

The in *vitro* tumor cytotoxicity of isolates was screened by MTT method. **DA-19** exhibited moderate cytotoxicity against the HeLa cell lines with the IC_{50} values of 13.69 μM. None of the diterpenoid alkaloids showed significant cytotoxicity. The antimicrobial activity of isolates was screened the agar well diffusion method. The results showed that only compound **DA-19** showed weak inhibitory activity against the *S. aureus*. This research provided important scientific support for the sustainable utilization and development of characteristic plant resources in Central Asia.

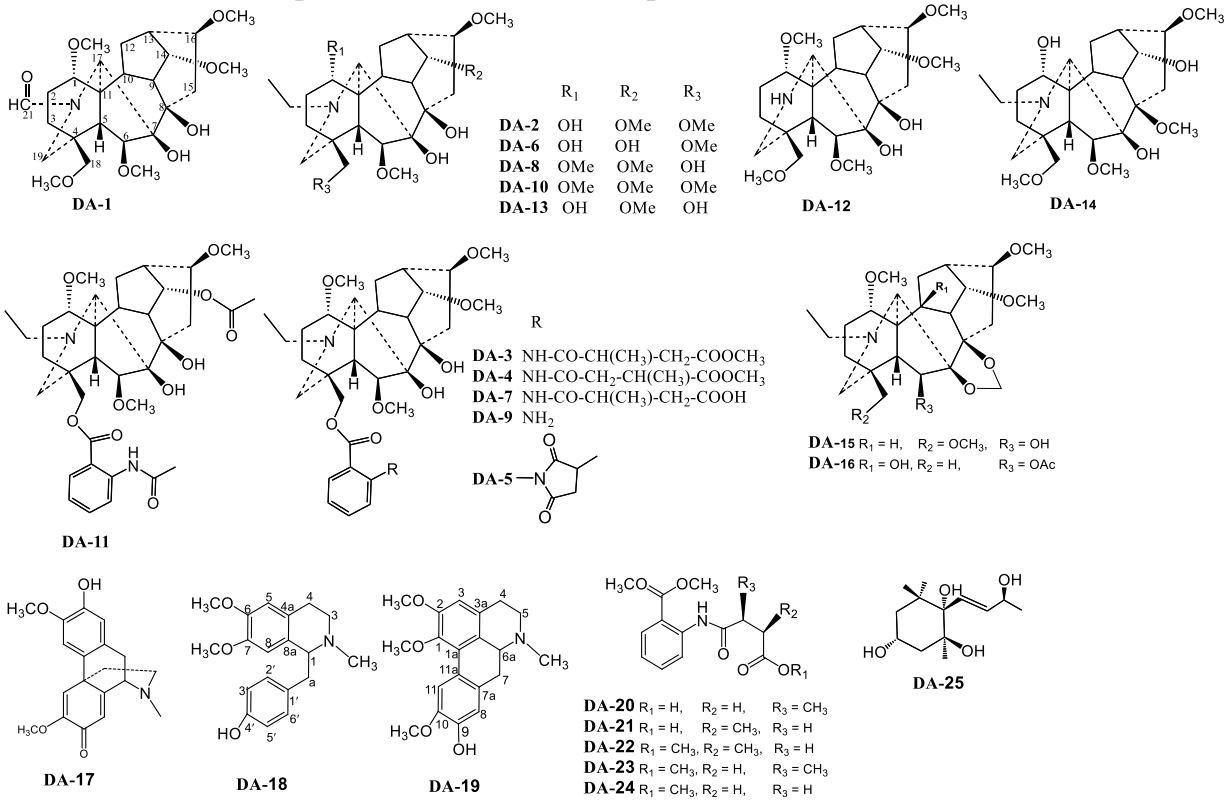

Fig. 11 Structure of compounds **DA-1~DA-25** isolated from *Delphinium aemulans*

Study on the chemical compounds from *Delphinium iliense*. Four new lycoctonine-type C_{19}-diterpenoid alkaloids, sinchianidines A-D (**DI-1~DI-4**), and twenty-one known C_{19}-diterpenoid alkaloids, delcorine (**DI-5**), 6-dehydrodelcorine (**DI-6**), anthranoyllycoctonine (**DI-7**), delsoline (**DI-8**), lycoctonine (**DI-9**), delcoridine (**DI-10**), delbrunine (**DI-11**), *N*-acetylsepaconitine (**DI-12**), blacknidine (**DI-13**), majusine A (**DI-14**), isodelectine (**DI-15**), delavaine A (**DI-16**), delavaine B (**DI-17**), shawurenine A (**DI-18**), shawurenine B (**DI-19**), delbruninol (**DI-20**), delectine (**DI-21**), andersonidine (**DI-22**), delbruline (**DI-23**), 7,8-methylenedioxydelcoline (**DI-24**), and ilidine (**DI-25**) were isolated and identified from the whole plant of *D. iliense*. Their structures were elucidated on the basis of HR-ESI-MS, 1D and 2D NMR spectroscopic data (**Fig. 12**), while the absolute configurations of sinchianidine A (**DI-1**) and sinchianidine C (**DI-3**) were determined by experimental electronic circular dichroism (ECD) spectra comparison.

Sinchianidines C-D (**DI-3** and **DI-4)** were tested for their analgesic activity through *in vivo* model of acetic acid-induced mice writhing. The results showed that at a nontoxic dose of 5 mg/kg, two compounds exhibited significant analgesic effect

with 78.16% and 72.54% inhibition, respectively. Furthermore, compound **DI-3** was tested again at a nontoxic dose of 1 mg/kg with 55.91% inhibition (Table 3). In 2010, Fengpeng Wang proposed in an analgesic structure-activity relationship between C_{18}- and C_{19}- diterpenoid alkaloids that an N-ethyl substituted tertiary amine in ring A, an aromatic ester [OBz or 4-methoxybenzoyl ester (OAs)] at C-14 or C-4, and the saturation state of the ring Da are necessary for the manifestation of the analgesic activity of the C_{18}- and C_{19}-diterpenoid alkaloids. Interestingly, sinchianidines C-D (**DI-3** and **DI-4**) have neither N-ethyl substituted tertiary amine nor aromatic ester, but exhibits good analgesic activity potential. We speculate that its activity may be related to C_{19}=O. Of course, further systematic research is needed to confirm this speculation.

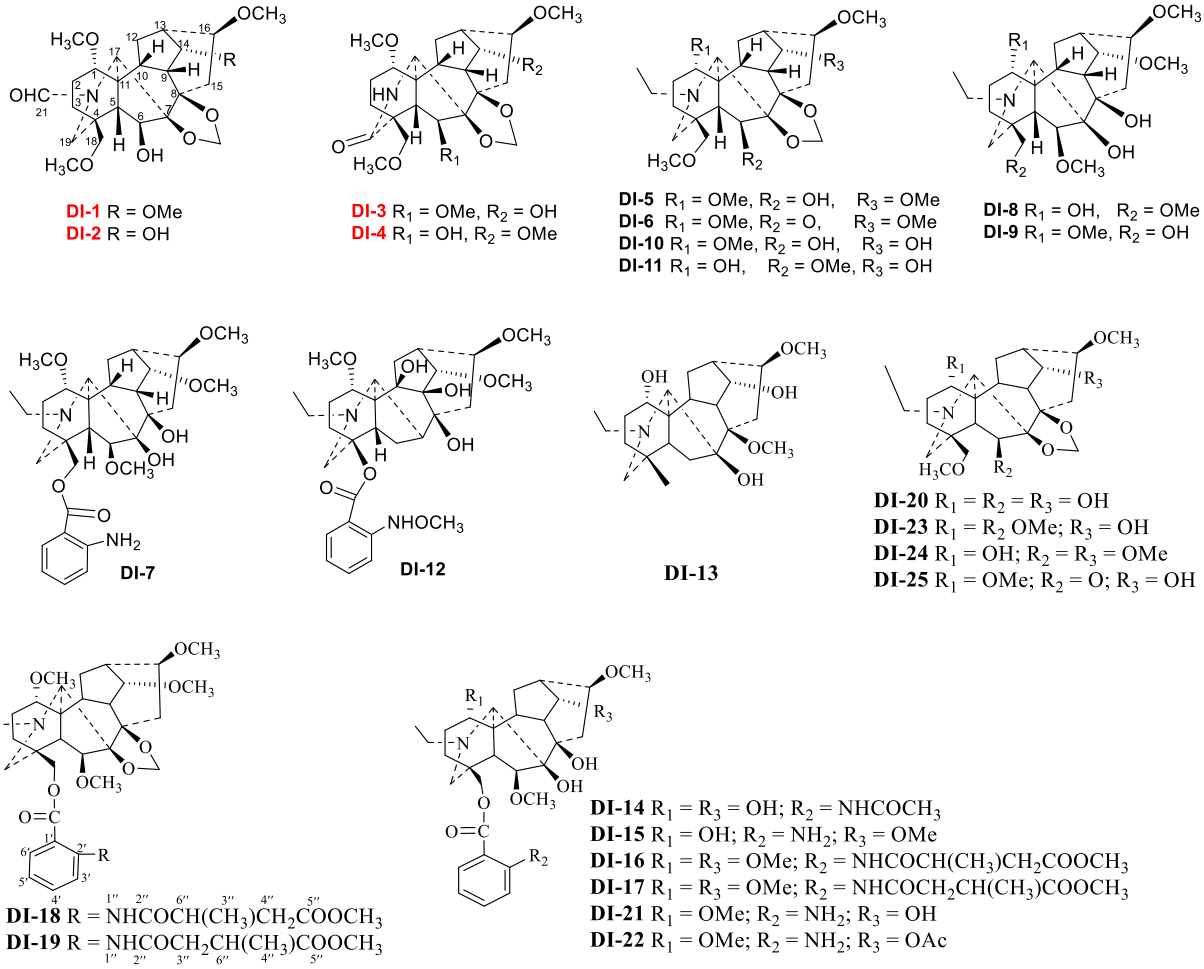

Fig. 12 The structures of compounds **DI-1~DI-25**

New compounds **DI-1~DI-4** were evaluated for their ion channel inhibitory activity on the hEGR and CaV3.1 channels. The I/I_0 values which show the inhibitory effect of the compounds **DI-1~DI-4** on hEGR and CaV3.1 channels are listed in Table 4 and Fig. 13. Unfortunately, all the compounds showed no significant inhibitory activity (I/I_0 > positive control). The results indicated that these four compounds have no potential for anti arrhythmic activity. This further confirmed the structure-activity relationship report of C_{19}-diterpenoid alkaloids for antiarrhythmic activity. This research provided scientific support for the sustainable utilization and development of characteristic plant resources in Central Asia.

Table 3. Writhing inhibition effect of the test compounds **DI-3** and **DI-4**

Group	Dose (mg/kg)	Number of writhes	Writhing inhibition (%)
control group	0	60.10 ±3.57	0
lappaconitine	5	8.37 ±1.25	86.06
DI-3 (high-dose group)	5	13.12 ±1.99	78.16
DI-3 (low-dose group)	1	26.5 ±4.38	55.91
DI-4 (high-dose group)	5	16.50 ±1.99	72.54

Table 4. Inhibitory activity of the **DI-1~DI-4** isolated from *D. iliense* on hEGR and CaV3.1 channel

hEGR			**CaV3.1**		
Compd.	I/I_0(Mean ±SEM)	n	Compd.	I/I_0(Mean ±SEM)	n
Dihydrochloride	0.007 ±0.003	6	Ulixacaltamide	0.1776 ±0.01067	10
DI-1	0.947 ±0.041	4	**DI-1**	0.9446 ±0.06961	3
DI-2	0.889 ±0.044	4	**DI-2**	1.1450 ±0.09581	3
DI-3	0.926 ±0.041	4	**DI-3**	0.9530 ±0.02832	3
DI-4	0.918 ±0.017	4	**DI-4**	1.0290 ±0.05818	3

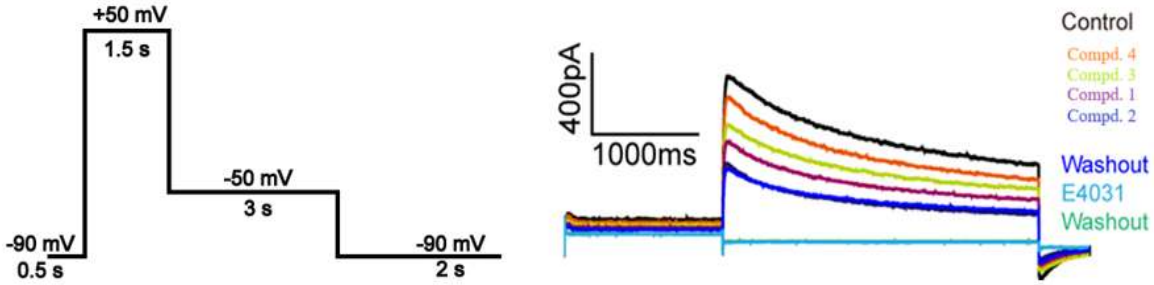

Fig. 13 Voltage clamp parameter setting diagram (L) and Typical graph of compounds **DI-1~DI-4** inhibition effect on hERG current (R)

Study on the isolation and purification of impurities from substance of Allapinin. The high content of lappaconitine in Allapinin substance makes it difficult to separate impurities. In this study, industrial preparative HPLC technology was used to remove lappaconitine, and then semipreparative HPLC technology was used to separate impurities. As a result, six impurities, sinomontanine B (**LA-1**), ranaconitine (**LA-2**), N-deacetyllappaconitine (**LA-5**), 9-deoxylappaconitine (**LA-6**), lappaconine (**LA-9**) and sepaconitine aminoalcohol (**AL-10**), were islolated and purification from the Allapinin substance. Their structures were elucidated by means of spectroscopic analyses (ESI-MS, 1D NMR and 2D NMR), and comparison with data reported in the literature (Fig. 14). The results of this study provided impurity standards for the quality control of Allapinin substance, which have important practical significance.

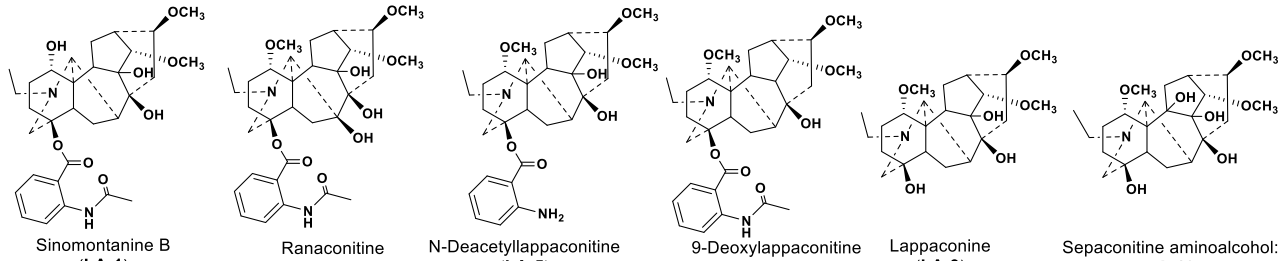

Fig. 14 The structures of compounds **LA1, LA2, LA5, LA6, LA9** and **LA10**

CONCLUSIONS

1. A comprehensive phytochemical investigation was conducted on seven species from the genera *Aconitum* and *Delphinium* growing in Central Asia, including *A. barbatum* var. *puberulum*, *A. smirnovii*, *A. sinchiangense*, *D. pseudoaemulans*, *D. naviculare* var. *lasiocarpum*, *D. aemulans*, and *D. iliense*.

2. A total of 176 compounds were isolated, including 26 new and 107 known diterpenoid alkaloids, along with 43 other compounds. Their structures were elucidated by HR-ESI-MS, 1D and 2D NMR spectroscopy, and comparison with literature data; the absolute configurations of new compounds were confirmed by quantum ECD calculations.

3. Barpuberudine (**AB-1**), a new C_{20}-diterpenoid alkaloid with an unprecedented carbon skeleton, and barpubenines A and B (**AB-6** and **AB-7**), representing novel rearranged C_{18}-diterpenoid alkaloids, were isolated from *A. barbatum* var. *puberulum*. Their plausible biosynthetic pathways were proposed.

4. The chemical composition of *Delphinium naviculare* var. *lasiocarpum* was systematically investigated, and the content of lappaconitine was determined to be 0.25% in the whole plant using HPLC, enriching the phytochemical data of this species and supporting its potential development as a sustainable reserve resource for lappaconitine production.

5. Six impurities were isolated and purified from the Allapinin substance, providing reference standards for quality control. This advancement not only supports the standardization of production processes for this clinically used antiarrhythmic agent but also improves its quality specifications, thereby facilitating the expansion of Allapinin's application scope in both domestic and international pharmaceutical markets.

6. A series of monomeric diterpenoid alkaloids were evaluated for biological activities, including antiarrhythmic, analgesic, cytotoxic, ion channel inhibitory, and antimicrobial effects.

7. N-deacetyllappaconitine and N-acetylsepaconitine isolated from *A. barbatum* var. *puberulum* demonstrated significant antiarrhythmic activity, while sepaconitine isolated from *A. barbatum* var. *puberulum* and smirnotine A isolated from *A. smirnovii* showed moderate activity, supporting their potential as lead compounds for cardiovascular drug development.

8. Sinchianidines C and D isolated from *D. iliense* showed promising analgesic effects, with 78.16% and 72.54% inhibition of writhing at a nontoxic dose of 5 mg/kg, respectively, suggesting potential for further development as pain-relieving agents.

9. *In vitro* cytotoxicity of selected diterpenoid alkaloids was assessed against A549, HCT8, MCF7, HT-29, MDA-MB-231 and HeLa cell lines. All compounds exhibited weak cytotoxicity (IC_{50} > 50 μM), supporting the conclusion that these lycoctonine-type alkaloids possess low inherent cytotoxic potential.

10. Antimicrobial activity of selected compounds was also evaluated. The results revealed selective but limited activity, indicating the need for further structural optimization to enhance antimicrobial efficacy.

11. Sinchianidines A–D isolated from *D. iliense* were evaluated for their ion channel inhibitory activity on hEGR and CaV3.1 channels, but all compounds exhibited no significant inhibitory effects (I/I_0 > positive control). This outcome, while negative, provides a valuable reference framework for future screening strategies of ion channel-related bioactivities in diterpenoid alkaloids, contributing to the refinement of structure–activity relationship models.

12. This study provides a scientific basis for the sustainable development and utilization of *Aconitum* and *Delphinium* species from Central Asia. The integration of structural elucidation, bioactivity evaluation, and practical applications lays a solid foundation for future development of innovative diterpenoid alkaloid-based therapeutics.

НАУЧНЫЙ СОВЕТ DSc.02/30.01.2020. K/T. 104.01
ПО ПРИСУЖДЕНИЮ УЧЕНЫХ СТЕПЕНЕЙ
ПРИ ИНСТИТУТЕ ХИМИИ РАСТИТЕЛЬНЫХ ВЕЩЕСТВ
ИНСТИТУТ ХИМИИ РАСТИТЕЛЬНЫХ ВЕЩЕСТВ

BO ZHAO

ИЗУЧЕНИЕ ДИТЕРПЕНОИДНЫХ АЛКАЛОИДОВ РАСТЕНИЙ РОДОВ *ACONITUM* И *DELPHINIUM*, ПРОИЗРАСТАЮЩИХ В ЦЕНТРАЛЬНОЙ АЗИИ И ИХ БИОЛОГИЧЕСКИЕ АКТИВНОСТИ

02.00.10 – Биоорганическая химия

АВТОРЕФЕРАТ ДИССЕРТАЦИИ
ДОКТОРА ХИМИЧЕСКИХ НАУК (DSc)

Ташкент – 2025

Тема докторской диссертации (DSc) зарегистрирована в Высшей аттестационной комиссии при Министерстве высшего образования, науки и инноваций Республики Узбекистан за номером B2025.2.DSc/K.....

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ВВЕДЕНИЕ (аннотация диссертации доктора наук (DSc))

Актуальность и востребованность темы диссертации. В мировой фармацевтической промышленности новые лекарственные препараты, созданные на основе природных веществ, всегда занимали важное место благодаря своим комплексным преимуществам, поэтому интерес к физиологически активным веществам, полученным из растительного сырья, растёт с каждым годом. В настоящее время проводится ряд научных исследований, посвящённых выделению индивидуальных веществ из растений, содержащих различные соединения, изучению их биологической активности, физико-химических свойств и применению в производстве.

Дитерпеновые алкалоиды привлекают внимание химиков и фармакологов благодаря своему структурному разнообразию, химической полифункциональности, высокой физиологической активности и большому потенциалу для создания лекарственных препаратов на их основе.

Высушенные корни некоторых видов родов *Aconitum* и *Delphinium*, произрастающих в Центральной Азии, широко используются в традиционной китайской медицине в качестве антиаритмических, обезболивающих и противоопухолевых средств при лечении многих заболеваний. В результате фитохимических исследований рода *Delphinium*, произрастающего во флоре Китая, были выделены дитерпеновые алкалоиды, а в результате изучения их биологической активности выявлены противовоспалительные, анальгезирующие, антиаритмические, а также инсектицидные и антифидантные свойства.

В результате исследований, проведенных в Институте химии растительных веществ, установлено, что химический состав растений *Aconitum barbatum* var. *puberulum* и *Delphinium iliense*, произрастающих во флоре Китая, не совпадает, а дитерпеновые алкалоиды – *N*-ацетилсепаконитин и *N*-дезацетиллаппаконитин, выделенные из *Aconitum barbatum* var. *puberulum*, – обладают антиаритмическими свойствами. Также было показано, что синцианидин C и D, выделенные из *Delphinium iliense*, обладают анальгезирующим действием. Это позволяет создавать импортозамещающие лекарственные средства на основе местного сырья и обеспечивать население дешевыми и качественными лекарствами.

Настоящее диссертационное исследование в определенной мере послужит реализации задач, обозначенных в Указе Президента Республики Узбекистан от 21 января 2022 года № УП-55 «О дополнительных мерах по ускоренному развитию фармацевтической отрасли республики в 2022-2026 годах», [2] Постановлениях № ПП-3532 от 14 февраля 2018 года «О дополнительных мерах по ускоренному развитию фармацевтической отрасли», Постановлениях № ПП-4310 от 6 мая 2019 года «О мерах по дальнейшему развитию системы медицинского и фармацевтического образования и науки», а также других нормативно-правовых актах, касающихся данной деятельности.

[2] Указ Президента Республики Узбекистан от 28 января 2022 года № УФ-60 «О новой Стратегии развития Республики Узбекистан на 2022-2026 годы».

Настоящее диссертационное исследование посвящено выполнению таких актуальных задач, как поиск новых структурных дитерпеновых алкалоидов из эндемичных растений рода *Aconitum* и *Delphinium* Средней Азии, изучение их антиаритмического, анальгезирующего и противоопухолевого действия в рамках государственных программ Узбекистана и Китая. Эти исследования служат научной основой для дальнейшей разработки эффективных и малотоксичных инновационных лекарственных препаратов на основе дитерпеновых алкалоидов, рационального использования и освоения уникальных растительных ресурсов Средней Азии и имеют важное значение для открытия новых активных природных продуктов, полезных для здоровья человека.

Целью исследования является выделение вторичных метаболитов 7 видов растений родов *Aconitum* и *Delphinium*, произрастающих в Средней Азии, определение их химического состава и структуры, создать на их основе эффективные лекарственные препараты.

Задачи исследования:

1. Экстракция и фракционирование сырья видов растений родов *Aconitum* и *Delphinium* с использованием различных органических растворителей, выделение суммы алкалоидов;
2. Выделение и очистка чистых соединений из суммы алкалоидов, полученного из указанных растений;
3. Определение первичной структуры выделенных соединений и абсолютной конфигурации новых соединений;
4. Оценка биологического действия отдельных соединений, включая антиаритмическую, ингибирующую ионные каналы, анальгетическую, противоопухолевую и антимикробную активность;
5. Определение количества лаппаконитина в *Delphinium naviculare* var. *lasiocarpum*;
6. Разработка способа разделения примесей в субстанции аллапинин.

Объектом исследования послужили 7 видов растений, принадлежащих к родам *Aconitum* и *Delphinium*: растения *Aconitum barbatum* var. *puberulum* Ledeb, *Aconitum smirnovii* Steinb, *Aconitum sinchiangense* W.T. Wang, *Delphinium pseudoaemulans* C.Y. Yang et B. Wang, *Delphinium naviculare* var. *lasiocarpum* W.T. Wang, *Delphinium aemulans* Navski, *Delphinium iliense* Huth и субстанция аллапинин.

Предметом исследования являются дитерпеновые алкалоиды и другие компоненты видов *Aconitum* и *Delphinium*, произрастающих в Центральной Азии, и их биологическая активность; смеси субстанции аллапинин.

Научная новизна исследования заключается в следующем:

Впервые из семи видов растений родов *Aconitum* и *Delphinium*, произрастающих в Центральной Азии, выделено 176 соединений, в том числе 26 новых и 107 известных дитерпеновых алкалоидов, а также 43 соединения из других классов;

Систематически изучены физико-химические свойства выделенных дитерпеновых алкалоидов, их антиаритмическая, анальгезирующая, противоопухолевая и антимикробная биологическая активность;

Впервые выделены новые соединения из растений *Aconitum barbatum var. puberulum* (N-ацетилсепаконитин и N-дезацетиллаппаконитин) и *Delphinium iliense* (синчианидин C и D);

В *Aconitum barbatum var. puberulum* впервые идентифицирован новый представитель углеродного скелета C20-дитерпеноидных алкалоидов барпуберудин (AB-1) и новые перегруппированные C18-дитерпеноидные алкалоиды барпубенины A-B (AB-6 и AB-7);

Впервые изучен химический состав *Delphinium naviculare var. lasiocarpum* и определено наличие лаппаконитина;

Впервые доказана антиаритмическая активность смирнотина A, выделенного из *Aconitum smirnovii*, а также анальгезирующее действие синхианидинов C и D, выделенных из *Delphinium iliense*;

Впервые из субстанции Аллапинин с использованием комбинации полупрепаративных и препаративных ВЭЖХ-технологий выделены шесть стандартных алкалоидов, что позволило обеспечить стандарты чистоты при контроле качества субстанции Аллапинин.

Внедрение результатов исследования.

По результатам исследований на тему «Изучение дитерпеноидных алкалоидов растений родов *Aconitum* и *Delphinium*, произрастающих в Средней Азии, и их биологической активности»:

Получен патент Китайской Народной Республики (№ ZL201810714295.7, 2018) на изобретение способа выделения и очистки дитерпеноидных алкалоидов из растения *Delphinium pseudoaemulans*, а также создание противоопухолевого средства на основе результатов исследования их цитотоксичности in vitro в отношении клеток рака человека A549 и HeLa. В результате был создан экологически безопасный, эффективный лекарственный препарат на основе растительных алкалоидов;

Получен патент Китайской Народной Республики на изобретение ингибитора калиевых каналов (IKv) на основе дитерпеноидных алкалоидов растения *Delphinium aemulans* (№ 2024100199358, 2024). В результате удалось создать новый ингибитор калиевых каналов на основе растительных алкалоидов;

Получен патент Китайской Народной Республики на изобретение «Разработка потенциального анальгетического средства из дитерпеновых алкалоидов растения *Delphinium iliense Huth*» (№ 2025103304327, 2025 г.). В результате удалось создать эффективные анальгетические средства на основе дитерпеновых алкалоидов растения;

Компания Xinjiang Shafei Ya Biological Technology Co., Ltd (КНР) и Синьцзянский институт физико-химических технологий (XTIPC) Китайской академии наук начали исследования по выращиванию лаппаконитина в

провинциях Синьцзян и Синьхай Китая, гарантируя поставку сырья для производства лаппаконитина в больших количествах (Отчёт компании Xinjiang Shafei Ya Biological Technology Co., Ltd, Китайская Народная Республика, 15.05.2025). В результате гарантирована поставка сырья для производства эффективных лекарственных препаратов на основе растительных дитерпеноидных алкалоидов;

Для контроля качества фармакологически активной добавки (ФАД) субстанции «Аллапинин» использованы четыре соединения, выделенные в качестве стандартов чистоты на GMP-предприятии Института химии растительных веществ (ИХРВ) (Справка Института химии растительных веществ от 23.06.2025 г. № 01-02/499). В результате удалось усовершенствовать систему контроля качества производства субстанции «Аллапинин», обеспечить соответствие требованиям нормативной документации и расширить возможности ее применения в клинической практике.

Апробация результатов исследования. Результаты исследования были представлены и обсуждены на 7 научно-практических конференциях, в том числе на 4 международных и 3 республиканских.

Опубликованность результатов исследования. По теме диссертации опубликовано 24 научные работы, в том числе 14 статей в международных журналах, признанных ПАК при Министерстве высшего образования, науки и инноваций Республики Узбекистан для публикации основных научных результатов диссертаций докторов химических наук. Кроме того, получены три патента Китайской Народной Республики.

Структура и объем диссертации. Диссертация состоит из введения, трёх глав, заключения, списка литературы и приложений общим объёмом 229 страницы.

ЭЪЛОН ҚИЛИНГАН ИШЛАР РЎЙХАТИ
СПИСОК ОПУБЛИКОВАННЫХ РАБОТ
LIST OF PUBLISHED WORKS

I бўлим (I часть; I part)

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